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Robert J. Sharpe

Stereoselective Desymmetrization Methods in the Assembly of Complex Natural Molecules

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Stereoselective Desymmetrization Methods in the Assembly of Complex Natural Molecules

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To my wife in honor of her love, patience, encouragement, and support during these past four years.
I can't wait for our next adventure together, and I wouldn't want to do it with anyone else but you!

Supervisor's Foreword

The design and implementation of new chemical reactions is central to the advancement of the chemical and pharmaceutical industries. Whether these processes provide more efficient access to known compounds or entry into heretofore underexplored structural motifs, synthetic organic chemistry remains a critical facet in the betterment of global health. These goals have remained at the core of our research program in designing and implementing novel reaction methodologies for rapid introduction of structural and stereochemical complexity from relatively simple starting materials.

In pursuing these challenges, our most fruitful source for inspiration is nature itself, which for centuries has been the source of architecturally complex and biologically interesting small molecules. These molecular scaffolds charge the organic chemist with extending the limits of known reaction space, and it is often the case that endeavors in natural product synthesis lead simultaneously (and perhaps out of necessity!) to new reaction development. Each of the total synthetic endeavors in our group have been made possible by or ultimately resulted in new reaction development.

One of the most fruitful reaction methodologies in our laboratory in recent years has been the manipulation of molecular symmetry elements for rapidly introducing stereochemical information that would otherwise require multiple stepwise transformations. It may come as no surprise to the reader that this strategy was initially borne out of desperation with a challenging total synthesis! When Robert Sharpe, the author of this thesis, joined our group in 2011, we were "knee deep" in the synthesis of the aminocyclitol natural product pactamycin. While this molecule's biological profile has made it an attractive target for biological investigation, the inherent cytotoxicity of the parent structure has, to date, precluded its use in chemotherapy. Thus, the value of an expedient total synthesis of pactamycin (vis-à-vis, structure–activity relationship investigations) is obvious. However, for 50 years since its discovery, this molecule had remained impervious to total synthesis until a 32-step synthesis was reported in 2011. In revising our original approach to pactamycin, Robert, in cooperation with another student in our group, came upon a

symmetry-breaking diketone monoreduction strategy which completed assembly of the entire carbon skeleton of the molecule within the first three steps of the synthesis. Additionally, the discovery of a fortuitous "stereochemical correction" downstream in the synthesis ultimately yielded the natural product in 15 steps from commercial starting materials. This work challenged the limits of synthetic creativity and provided expedient access to further exploration of the biological space in which pactamycin participates. Robert then went on to prepare 25 unique structural analogs of the parent structure via this synthetic route and demonstrated its effectiveness in modifying biological activity of the parent structure.

Our studies in implementing stereoselective desymmetrization reactions then continued with the preparation of the indole-diterpene alkaloid natural product paspaline, the parent member of a now extensive family of natural products. While the synthesis of steroid and steroid-like molecules has been extensively studied, the recent discovery of new molecules bearing unique deviations from the classical steroid design has reignited investigations in this arena. In Robert's hands, paspaline again served as the breeding ground for new reaction development, as a biocatalytic enantioselective desymmetrization rapidly assembled core features of the molecule. As the synthesis progressed, however, a second avenue for stereoselective desymmetrization presented itself; in this iteration, an oxime-directed symmetry-breaking C–H activation/acetoxylation delivered the necessary stereochemical information at a critical all-carbon quaternary center near the end of the synthesis. Robert's work on this molecule continued to demonstrate the viability of desymmetrization analysis in planning for complex molecule synthesis.

This thesis is outstanding, not just for the quality of the science described, but also for delineating that science in a narrative that effectively tells the entire story of each total synthesis. In each chapter, Robert describes in detail the initial results that, while ultimately unfruitful in our routes, represent quality contributions to the synthetic toolbox and guided our thinking as we arrived at the final, successful approach in each project. This thesis is the final product of an incredible amount of hard work and sheer determination and should be inspirational to future graduate students undertaking challenging total syntheses. The work described herein served as an inspiration to UNC faculty and students alike. I hope this document will motivate you in your future endeavors to continue to challenge the limits of known space to create knowledge that will likewise inspire another generation of scientists.

February 2016 Jeffrey Johnson

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My success in this program has been primarily the result of contributions and encouragement from so many others outside of myself during these past four years. I would first like to thank my advisor, Jeff Johnson, for the teaching, mentorship, patience, and support he has provided me since I began in his program in 2011. Jeff, even going back to when I was crowding your inbox with emails as a prospective student, your kindness to me has been far more than I deserve. Because of your research program, I feel equipped for success in any future scientific endeavor, not just because of your training in synthesis, but also for your training in effectively communicating scientific discoveries, devising creative approaches to hard problems, and managing time effectively. I am especially grateful for your help and referrals during my job search: one interviewer, when asked by me why I was brought on-site for an interview, simply stated, "I have a high respect for Jeff, and he wrote you a strong recommendation." Thank you for taking me on four years ago, and I am grateful to have been a part of your program and to have worked on some really fun projects.

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although our collaboration has been short, it is already evident that you are going to be really successful in this laboratory and will be able to complete tetrodotoxin in no time after my departure. Special thanks also to Blane for engaging college football discussions, Will for engaging early morning conversations on a variety of topics, and Scott Krabbe for career advice as he went through his job search process a year before I did.

I would also like to thank my friends and family from home who have been so loving and understanding during this period of intense work in my life. My parents (Ed and Anna Sharpe) have been so supportive during these past four years. I love you both and am excited to move closer back to home! To my brother and sister-in-law (Grayson and Holly Sharpe) and my niece (Josie Sharpe), thank you guys for always being there when Alden and I needed advice (or a weekly college football reprieve). To my in-laws (Pat and Darlene Jones, Pres, Peyton, Barrett), thank you for supporting me and loving Alden and I so well since we have been here. I would finally like to thank Jeffrey Bolan, whose weekly accountability discussions have been a huge source of encouragement and prayer each week. I really appreciate your continued friendship, even through great distance for many years.

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Abbreviations and Symbols

A549	Human lung cancer cell
p-ABSA	*para*-acetamidobenzenesulfonyl azide
Ac	Acetate
Ar	Aryl
aq	Aqueous
atm	Atmospheres
9-BBN	9-Borabicyclo[3.3.1]nonane
BINAP	binapthyl
Bn	Benzyl
Boc	Benzyloxycarbonyl
Boc_2O	Di-*tert*-butylcarbonate
br	Broad
br s	Broad singlet
^{n}Bu	*normal*-butyl
^{t}Bu	*tert*-butyl
^{t}BuOH	*tert*-butanol
^{t}BuOK	Potassium *tert*-butoxide
Bz	Benzoyl
CSA	Camphorsulfonic acid
^{13}C NMR	Carbon nuclear magnetic resonance spectroscopy
Cbz	Carboxybenzyl
CbzCl	Benzyl chloroformate
cat	Catalytic amount or catalyst
COSY	Correlated spectroscopy
m-CPBA	*meta*-chloroperoxybenzoic acid
d	Doublet or days
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N′*-dicyclohexylcarbodiimide
dd	Doublet of doublet
ddt	Doublet of doublet of triplets
DFT	Density functional theory

DIBAL-H	Diisobutylaluminum hydride
DIC	Diisopropylcarbodiimide
DIPEA	Ethyldiisopropylamine
DLS	Dynamic light scattering
DMA	Dimethylacetamide
DMAP	4-*N,N*-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMP	Dess–Martin periodinane
DMSO	Dimethyl sulfoxide
dq	Doublet of quartet
d.r.	Diastereomeric ratio
dt	Doublet of triplet
DU-145	Prostate cancer cell line
EC_{50}	Half maximal effective concentration
ent	Enantiomer
equiv	Equivalents
e.r.	Enantiomeric ratio
ESI	Electrospray ionization
Et	Ethyl
EtLi	Ethyllithium
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EWG	Electron withdrawing group
FDA	Food and Drug Administration
GII	Grubbs' second-generation catalyst
GGDP	Geranylgeranyl diphosphate
h	Hour
^{1}H NMR	Proton nuclear magnetic resonance spectroscopy
HCT-15	Colon cancer cell line
HeLa	Human epithelial
n-hexylMgBr	*normal* hexyl magnesium bromide
HOAc	Acetic acid
HMDS	Hexamethyldisilazane
$HNMe_2$	Dimethylamine
HMPA	Hexamethylphosphoramide
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectroscopy
HT-1080	Human fibrosarcoma cell line
Hz	Hertz
IC_{50}	Half maximal inhibitory concentration
IR	Infrared spectroscopy
J	Coupling constant
KDS	Known drug space
LA	Lewis acid
LDA	Lithium diisopropylamide

LDBBA	Lithium diisobutyl(*tert*-butoxy)aluminum hydride
LiHMDS	Lithium hexamethyldisilazide
LTBA	Lithium tri-*tert*-butoxyaluminum hydride
M	Metal or molarity
m	Multiplet
M14	Melanoma
MCF7	Breast cancer cell line
MDA-MB-231	Human breast cancer cell
Me	Methyl
MeLi	Methyllithium
MeMgBr	Methylmagnesium bromide
MeMgCl	Methylmagnesium chloride
MeOH	Methanol
Me_2S	Dimethylsulfide
Me_2S_2	Dimethyldisulfide
mg	Milligram
MHz	Megahertz
MIC	Macrophage inhibitory cytokine
min	Minutes
mL	Milliliter
mmol	Millimole
mol	Mole
MOLT-4	Leukemia cell line
mp	Melting point
MRC-5	Human lung fibroblast cell
MS	Molecular sieves
MsCl	Methanesulfonyl chloride
MsOH	Methanesulfonic acid
MVK	Methyl vinyl ketone
n	Number of atoms or counterions
NaHMDS	Sodium hexamethyldisilazide
NaOAc	Sodium acetate
NaO^{t}Bu	Sodium *tert*-butoxide
NaOMe	Sodium methoxide
NCI-H322M	Non-small cell lung cancer cell line
nd	Not determined
NEt_3	Triethylamine
NME	New molecular entity
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine *N*-oxide
nOe	Nuclear Overhauser enhancement
NOESY	Nuclear Overhauser enhancement spectroscopy
NP	Nanoparticle
p-NPBA	*p*-nitroperbenzoic acid
Nu	Nucleophile

[O]	Oxidation
OVCAR-3	Ovarian cancer cell line
Oxone®	Potassium peroxymonosulfate
P.f. K1	*Plasmodium falciparum* K1
PCC	Pyridinium chlorochromate
PET	Poly(ethylene terephthalate)
Ph	Phenyl
PhMgBr	Phenylmagnesium bromide
PhSeBr	Phenylselenyl bromide
Phth	Phthalimide
Piv	Pivaloyl
PLA	Poly(D,L-lactide)
PMB	*p*-methoxybenzyl
PMBz	*p*-methoxybenzoyl
PMP	*p*-methoxyphenyl
ppm	Parts per million
PPTS	Pyridinium *p*-toluenesulfinate
^{i}Pr	*iso*-propyl
PRINT©	Particle replication on non-wetting templates
PTSA	*p*-toluenesulfonic acid
q	Quartet
R	Substituent
R_f	Retention factor
rac	Racemic
Red-Al®	Sodium bis(2-methoxyethoxy)aluminumhydride
RNA	Ribonucleic acid
rt	Room temperature
RXF 393	Renal cancer cell line
s	Singlet
SAR	Structure–activity relationship
Sec	secondary
SEM	Scanning electron microscopy
SFC	Supercritical fluid chromatography
SK-OV-3	Human ovarian cancer cell
S_N2	Bimolecular nucleophilic substitution
SNB-19	CNS tumor cell lines
Super Hydride	Lithium triethylborohydride
t	Triplet
tert	Tertiary
t_r	Retention time
TBAF	Tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBDPSCl	*tert*-butyldiphenylsilyl chloride
TBS	*tert*-butyldimethylsilyl
TBSCl	*tert*-butyldimethylsilyl chloride

TBSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
Tf_2O	Trifluoromethanesulfonic anhydride
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMS	Trimethylsilyl
$TMSCHN_2$	(trimethylsilyl)methyldiazomethane
TMSCl	Trimethylsilyl chloride
TMSI	Trimethylsilyl iodide
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TPAP	Tetrapropylammonium perruthenate
triflate	Trifluoromethanesulfonate
Ts	*para*-toluenesulfonyl
UV	Ultraviolet
X	Anionic ligand, halide, substituent, or number
[α]	Optical rotation
δ	Chemical shift or partial charge
μL	Microliter
YSC-2	*Saccharomyces cerevisiae*

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Chapter 1
Asymmetric Synthesis of the Aminocyclitol Pactamycin, A Universal Translocation Inhibitor

1.1 Introduction

The value of the continued advancement of natural products synthesis cannot be understated. The arena of preparing complex molecules serves as the ideal breeding (and proving) ground for innovation in organic synthesis, and successful total synthetic endeavors of biologically active "privileged" natural scaffolds have played a vital role in the betterment of global health. In this chapter, we report the expedient total synthesis of the natural product pactamycin, a complex aminocyclitol alkaloid with a promising biological profile. Key to this approach was the implementation of a complex symmetry-breaking reduction reaction for rapid incorporation of core stereochemistry. The synthetic route provides the functionally and stereochemically dense natural product in fifteen steps from commodity chemicals, notably, in the absence of non-strategic downstream functional group or oxidation state manipulations. These studies were completed as part of a cooperative effort with Justin Malinowski of these laboratories and constitute the shortest synthesis of pactamycin reported to date.

1.2 Background

1.2.1 Introduction, History, and Biological Activity of Pactamycin

Nature continues to test the state of the art in organic synthesis by providing chemists with both structurally complex, biologically relevant molecules. Construction of these

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DOI 10.1007/978-3-319-39025-3_1

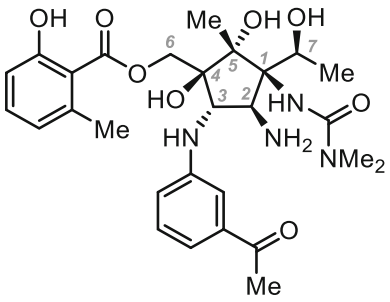


Fig. 1.1 Structure and atom numbering of pactamycin

natural products often requires the expansion of known synthetic methods to previously unreported substrate classes or the development of new approaches for the assembly of natural frameworks [1, 2]. Isolated in 1961 from *Streptomyces pactum* by scientists at the former UpJohn Chemical Co., pactamycin (**1.1**, Fig. 1.1) remains one of the most complex aminocyclopentitol antibiotics known, bearing a remarkable array of unique functionality and exceptional bioactivity [3].

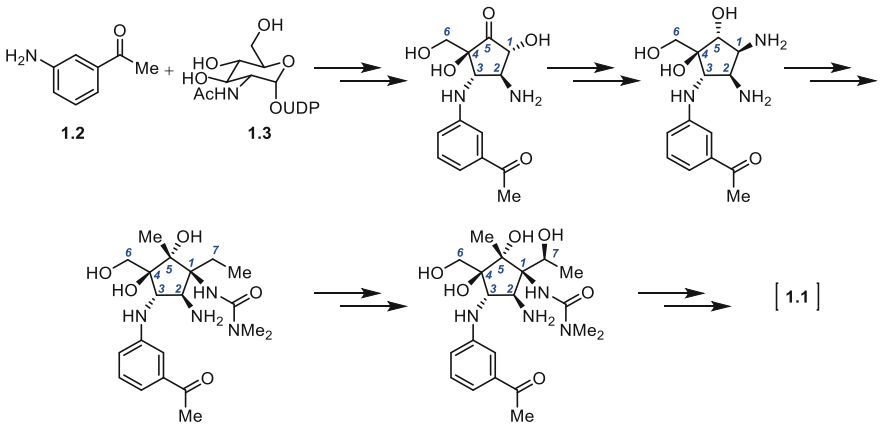
Pactamycin exhibits activity against both Gram-positive and Gram-negative bacteria and is a powerful antitumor agent [4, 5]. More recent biological studies have demonstrated **1.1** to have potent antiviral (complete inhibition of polio-infected HeLa cells at 10^{-7} M) and antiprotozoal qualities (P.f. K1: IC_{50} = 14.2 nM) [6, 7]. However, despite the obvious application of these qualities to medicinal development, pactamycin's known cytotoxicity against certain human eukaryotic cell lines (MRC-5: IC_{50} = 95 nM) have to date precluded its use in human disease treatments [6, 7]. The source of these activities was elucidated by Ramakrishnan and co-workers via X-ray crystallographic studies [8–10]. These investigations showed that pactamycin inhibits protein synthesis via its action as an RNA dinucleotide mimic, employing its unique aromatic appendages (C3 aniline, C6 salicylate) in H-bonding interactions with the 30S ribosomal subunit. This activity prevents translocation and leads ultimately to cell death.

Given the above facts, it is evident that if the promising biological traits of this molecule are ever to probed further for the betterment of global health, they will be explored not in the environment of the parent structure but in the structural congeners derived thereof. In support of this claim, a number of biosynthetically engineered congeners of the parent pactamycin structure have been recently reported which display diminished cytotoxicity relative to **1.1** [11, 12]. These data will be described in detail in Chap. 2 and have reignited promise for structure-activity relationship (SAR) investigations of **1.1** toward the goal of obtaining a useful drug molecule. In order to further investigate the medicinal development of **1.1** through chemical approaches, the necessity of a practical and flexible synthesis of the target molecule is paramount for the success of such endeavors.

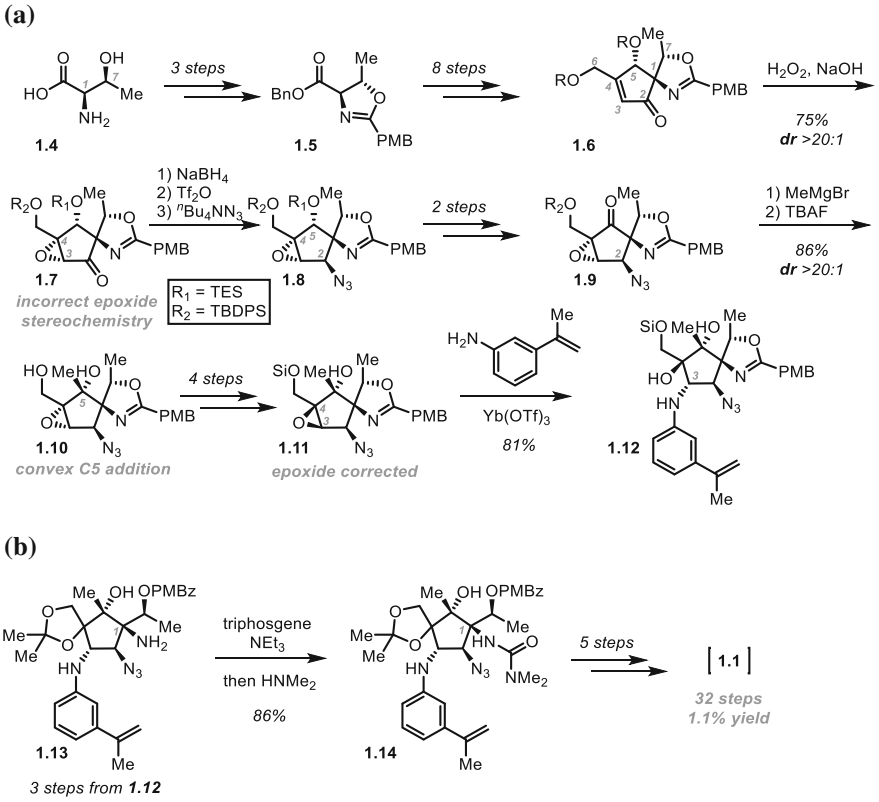
1.2.2 Pactamycin Structural Features, Biosynthesis, and Previous Synthetic Endeavors

Pactamycin bears a densely-functionalized cyclopentane core featuring six contiguous stereogenic centers, three of which are fully substituted [13]. Additionally, unusual dimethylurea, aniline, and salicylate moieties adorn the core structure, presenting numerous synthetic challenges. The biosynthesis of pactamycin has been proposed by Mahmud and co-workers to originate from *m*-acetylaniline **1.2** and UDP-*N*-acetyl-α-D-glucosamine **1.3** [14]; a subsequent series of enzymatic functional group and oxidation state transformations ensue to efficiently produce the title compound. This sequence is summarized in Scheme 1.1.

The unique challenges presented by pactamycin's architecture have been addressed in a number of approaches as synthetic interest in **1.1** has flourished over the past decade. Synthetic efforts by Isobe [15], Knapp [16], Looper [17], Nishikawa [18], and our group [19] have been recently disclosed. While our studies were underway, the Hanessian group disclosed the landmark first total synthesis of pactamycin [20, 21]. Their approach was comprised of a thirty-two-step manipulation of L-threonine (**1.4**) and is summarized in Scheme 1.2. From L-threonine, a three-step sequence provided the known oxazoline **1.5**, setting the stage for the assembly of cyclopentenone **1.6** in eight manipulations. The C3 and C4 stereocenters were initially established via nucleophilic epoxidation of the alkene in **1.6** to provide epoxyketone **1.7**, and the C2 amine functionality was incorporated via S_N2 addition of NaN_3 to the triflate electrophile derived from ketone **1.7**. It is important to note that the epoxide stereochemistry in **1.8** corresponds to the incorrect C4 stereochemistry needed for pactamycin at this juncture. Following deprotection and oxidation of the C5 alcohol in **1.8**, the "incorrect" epoxide was then leveraged to enable stereoselective introduction of the C5 methyl group via convex surface



Scheme 1.1 Summary of proposed pactamycin biosynthesis



Scheme 1.2 Summary of Hanessian total synthesis of pactamycin. **a** Hanessian synthesis: core functionalization. **b** Urea installation and synthesis completion

addition to the bicyclic ketone **1.9** to afford alcohol **1.10**. A four-step protocol was employed from **1.10** to "correct" the epoxide stereochemistry and afford **1.11**, giving thence the *m*-propenyl aniline **1.12** after a Lewis acid mediated epoxide addition.

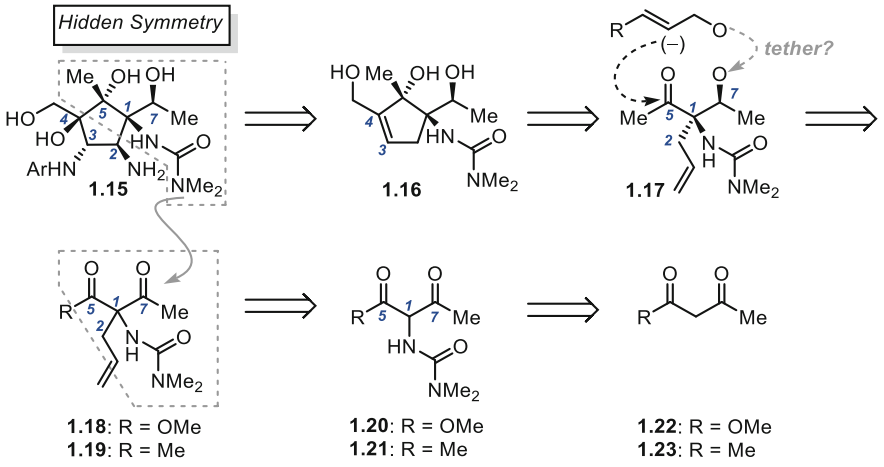
A significant challenge Hanessian faced in synthesis completion was introduction of the C1 dimethylurea functionality via acylation of a primary amine bound to the fully-substituted C1 atom. After extensive experimentation, acylation of **1.13** (prepared in three steps from aniline addition product **1.12**) was accomplished upon generation of a transient isocyanate intermediate, which subsequently underwent trapping with dimethylamine to furnish urea **1.14**. Oxidation of the *m*-propenyl aniline to the acetophenone, salicylate introduction, and deprotection afforded pactamycin in thirty-two steps and 1.1 % overall yield.

A close inspection of this route and the published partial synthetic studies reveals two challenges one faces in assembling the core structure of pactamycin: (i) execution of chemo- and stereoselective reactions in a highly congested chemical

environment and (ii) the method by which the unusual functionality of **1.1** is introduced. In their total synthesis, the Hanessian group observed numerous side reactions due to functional group propinquity [20, 21]. Looper and Hanessian also noted the importance of the order in which functional group manipulations were executed [17, 20, 21]. Regarding the dimethylurea, Hanessian relied on an oxazoline protecting group at C1 from the outset, necessitating the challenging deprotection and acylation previously described. In the development of a synthesis plan, we took note of these issues and sought to develop a synthesis of **1.1** that rapidly assembled the core structure and incorporated all unique functionality in its final form, precluding the use of nonstrategic redox and protecting group manipulations [22]. This flexible route, we surmised, would provide access to the title compound in a manner amenable to the synthesis of analogs for biological examination.

1.2.3 Initial Retrosynthetic Analysis and Summary of Preliminary Route

Our original retrosynthetic disconnection began with simplification of **1.1** to functionalized cyclopentane **1.15** (Scheme 1.3). C2 (allylic) functionalization, C4 hydroxylation, and C3 aniline installation might be possible from a C3–C4 alkene in **1.16**, accessed by a ring-closing metathesis (RCM) reaction. The requisite precursor would be derived from nucleophilic addition to methyl ketone **1.17**. We surmised that this addition could occur either by intermolecular or intramolecular nucleophile delivery, the latter facilitated by the C7 secondary carbinol. Two approaches to β-hydroxyketone **1.17** were envisioned, dependent upon the identity



Scheme 1.3 Initial retrosynthetic analysis of pactamycin

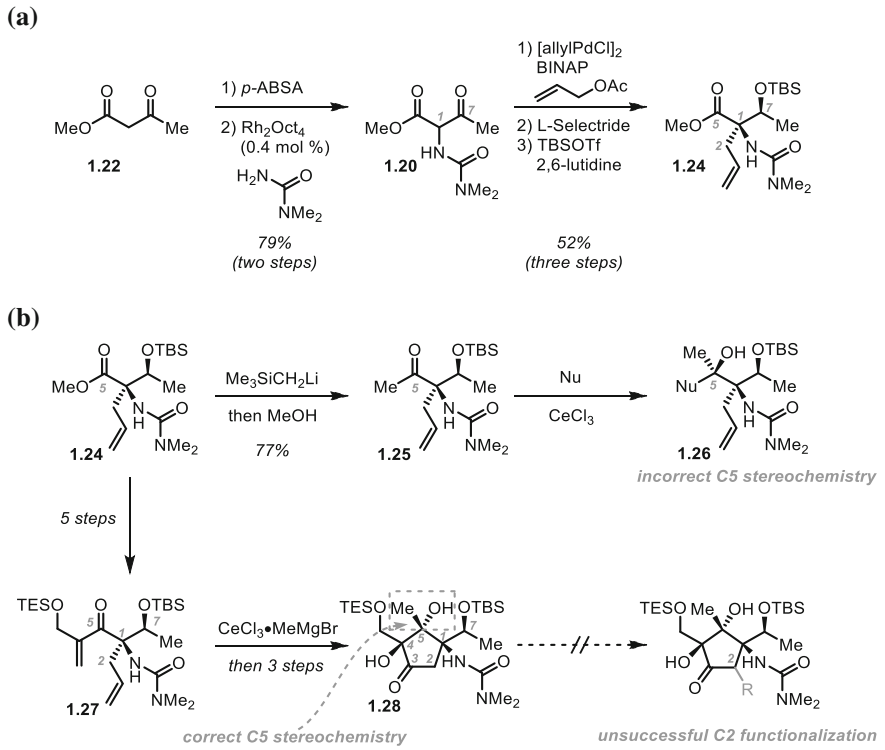
of the R-substituent. If R = OMe (**1.18**), we proposed an enantioselective Tsuji–Trost allylation of ketoester **1.20** followed by diastereoselective ketone reduction and ester → ketone conversion [22]. Alternatively, if R = Me (**1.19**), we would invoke an enantioselective, symmetry-breaking reduction strategy via diketone monoreduction, exploiting the hidden symmetry (see outlined region) in the northeast quadrant of **1.1** [23]. Critical to our strategy in either case was the early-stage installation of the dimethylurea functionality in its final, native form, an approach divergent from those previously reported. α-Ureidodicarbonyls **1.20** or **1.21** would serve as our points of origin, synthesized from commodity chemicals (methyl acetoacetate **1.22** or 2,4-pentanedione **1.23**, respectively).

In pursuit of this approach, our group published a preliminary synthetic study that provided a highly advanced intermediate for pactamycin core assembly and synthesis completion [19]; the results and challenges that this synthesis faced are summarized in Scheme 1.4. Using methyl acetoacetate **1.22** as the point of origin, diazo transfer followed by a Rh-catalyzed N–H insertion reaction provided urea **1.20** in 79 % yield [24]. The C1 carbon atom was further functionalized via Tsuji–Trost allylation to install an allyl group; stereoselective reduction of the ketone followed by silyl protection furnished β-silyloxyester **1.24** in 52 % yield. From **1.24**, C5 carbinol installation became the next challenge. Thus, the C1 ester was converted to its methyl ketone upon treatment with Me_3SiCH_2Li to afford β-silyloxyketone **1.25** poised for nucleophilic addition. From **1.25**, a screen of nucleophiles and conditions were investigated for access to the requisite C5 carbinol; however, while addition of a model 2-propenylmetal nucleophile mediated by $CeCl_3$ proceeded in good yield, this reaction gave consistent preference for epimeric C5 stereochemistry (**1.26**). This stereoerror necessitated synthesis of ketone **1.27**, which upon methide addition mediated by $CeCl_3$, provided the desired C5 stereochemistry with >20:1 dr. This intermediate was then elaborated to **1.28** in three steps, setting the stage for leveraging the C3 ketone to install the critical C2 amine functionality; however, attempts to introduce the amine (or a suitable surrogate) at C2 from **1.28** failed under a variety of conditions examined.

1.3 Results and Discussion

1.3.1 C2 Unfunctionalized Desymmetrization Approach: Strategy Development

While the route described in Scheme 1.4 was scalable and effective for accessing advanced intermediate **1.28**, the synthesis of ketone **1.27** required a number of nonstrategic redox and protecting group manipulations and lacked efficiency. As a result, we sought a streamlined approach to its synthesis in parallel to the C2 functionalization studies described above. Cognizant of the undesired stereoselectivity encountered in intermolecular addition to methyl ketone **1.25**, we envisaged

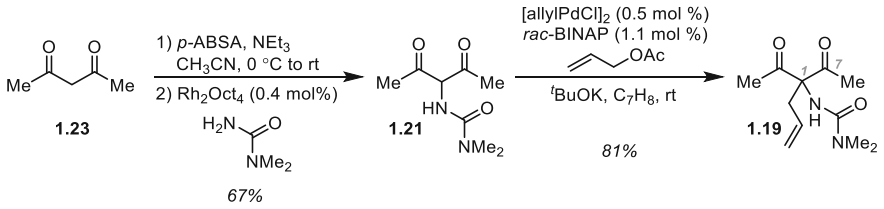


Scheme 1.4 Previously reported approach to pactamycin by our laboratory. **a** C1-urea and C7-hydroxyl installation. **b** C5-addition approaches and challenging late-stage C2 functionalization

that an intramolecular addition might provide the opposite facial preference. Delivery of a tethered nucleophile from the C7 hydroxyl followed by reduction and RCM would intercept our previous intermediate **1.28**. This intermediate could be synthesized from our proposed enantioselective desymmetrization strategy from urea **1.19**, the diketone analog of **1.18**.

1.3.2 Substrate Preparation for Symmetry-Breaking Reduction

The diketone reduction precursor **1.19** was prepared in three steps (Scheme 1.5). We were pleased to find that the sequence used to synthesize ketoester **1.20** could be directly applied to 2,4-pentanedione **1.23** with minimal reoptimization [19]. In practice, the reaction of 2,4-pentanedione **1.23** with p-ABSA and NEt_3 afforded the corresponding diazoketone in nearly quantitative yield. An N–H insertion reaction



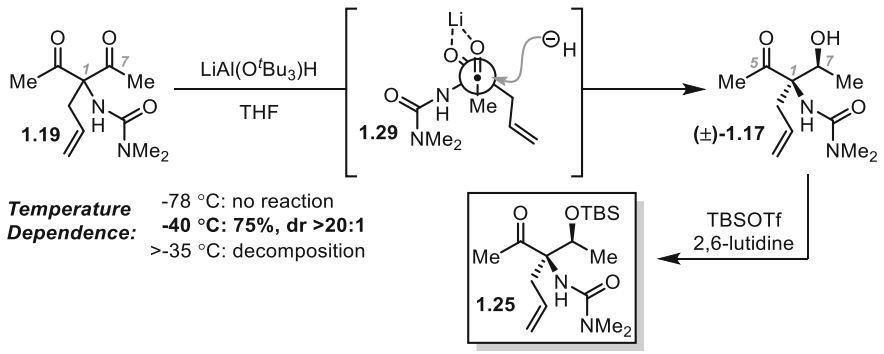
Scheme 1.5 Synthesis of C2 unfunctionalized desymmetrization precursor

analogous to that used in our previous studies delivered the desired ureidodiketone **1.21** in 67 % yield, and a Tsuji–Trost allylation provided the necessary diketone precursor **1.19** in 81 % yield.

1.3.3 Symmetry-Breaking Reduction and Stereochemical Analysis

Having diketone **1.19** in our possession set the stage for development of the proposed symmetry-breaking reduction (Scheme 1.6). Working first to optimize the racemic reaction, we began screening reducing agents and conditions for selectivity. Gratifyingly, $LiAl(O^tBu_3)H$ (LTBA) emerged early in our evaluation, providing β-hydroxyketone (±)-**1.17** in 75 % yield with >20:1 diastereoselection. The desired stereochemistry was confirmed via TBS protection of the ketoalcohol and direct ^1H NMR comparison with **1.25** (see Scheme 1.4), which had been independently synthesized our in laboratory via our previous route [19].

We speculate that this reduction proceeds via chelated structure **1.29**, in which steric demand of the dimethyl urea functionality directs hydride addition to the least hindered diastereoface of the enantiotopic ketones, delivering (±)-**1.17** in high selectivity. Also of note in this reaction is the temperature required for successful reduction to occur; when the reduction is carried out at −78 °C, no reaction is



Scheme 1.6 Racemic diketone desymmetrization and stereochemical confirmation

observed, and if the reaction is warmed past the ideal temperature of −40 °C, retroaldol fragmentation ensues, presumably via instability of the alkoxide anion derived from hydroxyketone **1.17**.

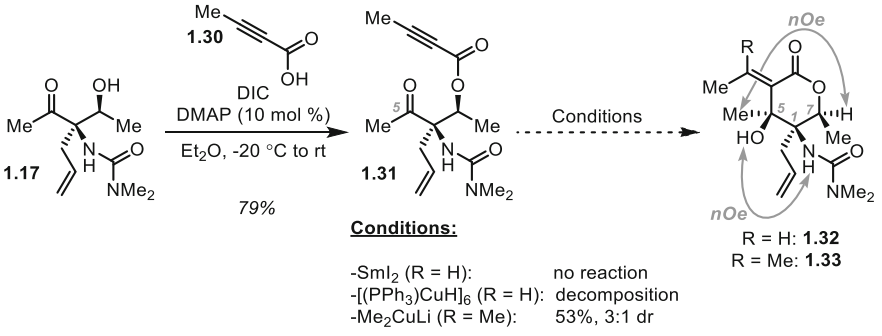
1.3.4 Intramolecular C5 Addition

From β-hydroxyketone **1.17**, we began investigating intramolecular additions to the C5 ketone (Scheme 1.7). Specifically, we were motivated by extant methods reported for reductive (or alkylative) cyclizations of ynoates to carbonyls and hoped that the same protocol might be applied to our system. Thus, acylation of monoalcohol **1.17** with 2-butynoic acid **1.30** cleanly delivered ynoate **1.31** in 79 % yield. **1.30** was selected over the corresponding propiolate ester due to a significant decrease in yield observed in the analogous esterification with propiolic acid.

From ester **1.31**, we began screening known conditions for allenoate generation. Reducing agents such as SmI_2 failed to promote any desired reactivity, returning only recovered starting material [25]. Soft hydride reducing agents also gave little promise as starting material decomposition was observed [26]. We were encouraged, however, by the work of Crimmins and co-workers in the use of organocuprate nucleophiles for initiating intramolecular, alkylative cyclizations and hoped this reaction manifold might be more compatible [27]. Indeed, treatment of **1.31** with Me_2CuLi delivered lactone **1.33** in 53 % yield and 3:1 dr. The desired relative configuration of the C1/C5/C7 stereotriad in **1.33** was confirmed by nuclear Overhauser effect spectroscopy (nOesy) analysis.

1.3.5 Attempts at Lactone Reduction

At this juncture, only reduction of lactone **1.33** remained to provide triol **1.34**; this intermediate would effectively intercept the synthesis of cyclopentanone **1.28** (Table 1.1).



Scheme 1.7 Attempts at intramolecular carbon delivery to C5 ketone

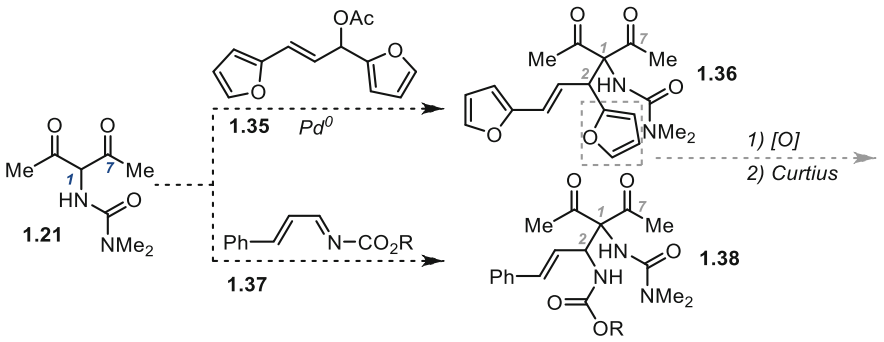
Table 1.1 Failed attempts at lactone reduction

Reductant	Conditions	Result
DIBAL-H	CH_2Cl_2, 0 °C to rt	No reaction
DIBAL-H	C_7H_8, 0 °C to rt	Urea reduced
$LiBH_4$	Et_2O, 0 °C to rt	No reaction
LTBA	THF, rt	No reaction
$LiAlH_4$	Et_2O, 0 °C to rt	Urea reduced
$LiBEt_3H$	THF, −78 to 0 °C	Lactol isolated
$LiBEt_3H$	THF, 0 °C to rt	Urea reduced

However, an exhaustive screen of reducing agents and conditions failed to provide triol **1.34**. Hindered reducing agents such as LTBA displayed no reactivity even at elevated temperatures, while stronger reducing agents ($LiAlH_4$, $LiBEt_3H$, DIBAL-H) resulted only in complex mixtures or reduction of the dimethylurea functionality. Additionally, attempts at ring opening of **1.33** via transesterification to its corresponding ester or thioester failed to show any desired reactivity. These failed attempts led to the conclusion that intramolecular addition/ring–opening strategies to establish the C5 stereochemistry might not be viable in providing access to **1.1**, and as a result, this approach was abandoned.

1.3.6 Revision of Strategy and Early Stage Incorporation of C2 Functionality

At this impasse, we began to form conclusions regarding our original and revised strategies. First, early-stage incorporation of the dimethylurea functionality, while a strategic risk at the onset of this work, had proven useful in directing desirable stereochemical outcomes in each of our initial routes. The impressive diastereoselectivity accessed from symmetry-breaking reduction of diketone **1.19** gave us cause to incorporate this strategy again in future routes to **1.1**. However, neither our previously reported approach nor the above strategy addressed a major problem facing the endgame of our synthesis, namely, late-stage installation of the primary amine at C2. In devising a new approach, we determined that this issue would need to be addressed in any future iteration of our synthetic strategy. Consequently, we envisioned enantioselective installation of C2 functionality on ureidodiketone **1.21** prior to the symmetry-breaking reduction (Scheme 1.8). Monoreduction of this



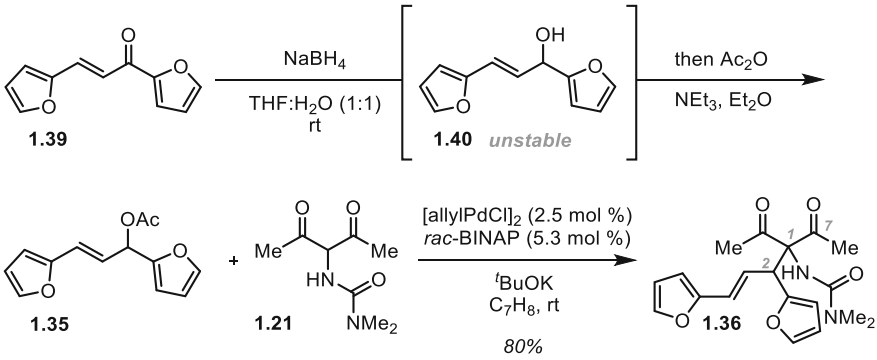
Scheme 1.8 Proposed routes to C2-functionalized desymmetrization precursors

substrate would provide access to the C1/C2/C7 stereotriad within the first four steps of the synthesis, from which strategic manipulation of the available functional handles might give expedient access to **1.1**. Beginning from the previously synthesized α-ureidodiketone **1.21**, an enantioselective Tsuji–Trost allylation with difurylidene acetate **1.35** would install a 2-furyl group at the C2 center (**1.36**); we felt that this group could function as an amine surrogate via downstream oxidative cleavage and Curtius rearrangement [28]. Since the ideal functionality at C2 would be the amine itself, a catalytic, asymmetric Mannich reaction of **1.21** with a strategically configured imine such as **1.37** was projected to deliver diketone **1.38** with carbamate-protected amine installed directly at C2 [29, 30].

In both the allylation and Mannich scenarios, enantioselective formation of the C2 asymmetric center would be the lone initial challenge. The ensuing diastereoselective symmetry-breaking monoreduction of a chiral diketone would be the key for controlling the C1/C7 configurations and would require effective guidance from the initially-installed C2 stereocenter. The identities of the alkene termini in the generic structures **1.36** and **1.38** can be disregarded since downstream operations would purge these functionalities. Both of these proposed pathways would deliver the entire core skeleton of **1.1** within the first three steps, providing all carbons necessary for cyclopentane assembly. Equipped with these new hypotheses, we began pursuing each in parallel.

1.3.7 C2 Furan Approach—Substrate Preparation and Desymmetrization Studies

Our first challenge in realizing the Tsuji–Trost allylation strategy was the synthesis of the allylic acetate **1.35**, which surprisingly had not been previously reported (Scheme 1.9). To this end, reduction of difurylpropenone **1.39** afforded the corresponding alcohol **1.40**; however, upon concentration of the crude mixture, this product rapidly decomposed. The observed decomposition was unexpected since



Scheme 1.9 Synthesis of diarylketone for Tsuji–Trost allylation

this compound had been previously reported, although no notes had been made regarding its instability [31, 32]. A screen of conditions designed to circumvent this problem revealed that $NaBH_4$ reduction of **1.39** followed by immediate acylation using ethereal solvents provided **1.35** in crude form. Acetate **1.35** was also found to be unstable, but could be stored in solution for up to thirty days at 0 °C.

With the desired electrophile in our possession, the reaction of diketone **1.21** with difurylidene acetate **1.35** under the previously optimized allylation conditions afforded C2-functionalized diketone (±)-**1.36** in 80 % yield. From this compound, we began to examine conditions by which we might effect symmetry-breaking reduction (Fig. 1.2). Monoreduction of the chiral diketone **1.36** presented a complicated scenario, however, since four diastereomeric products could result. In the first case, exposure of diketone **1.36** to our previously optimized desymmetrization

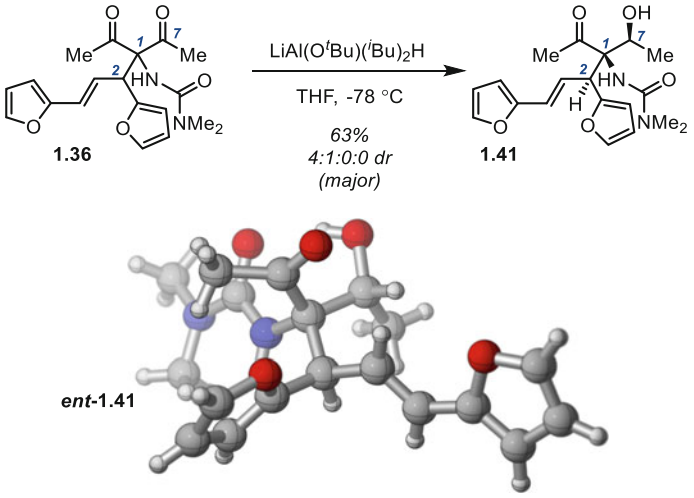
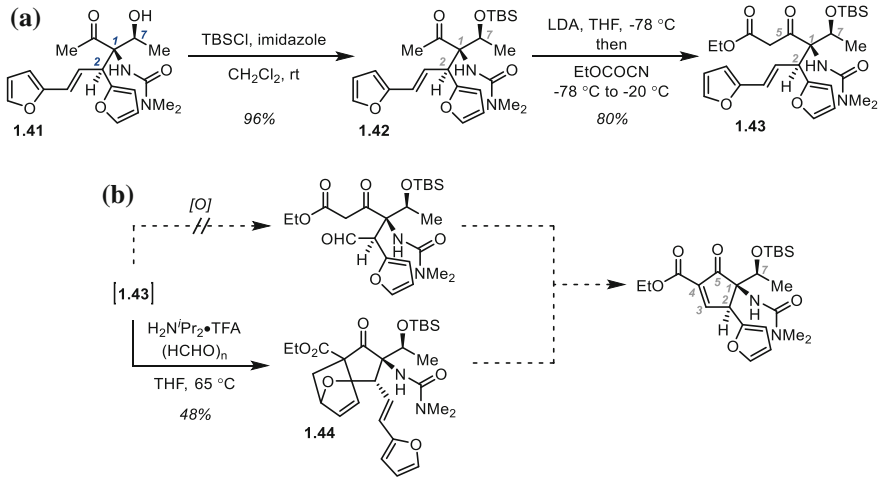


Fig. 1.2 Symmetry-breaking reduction of diarylketone and X-ray analysis

conditions (LTBA, −40 °C) resulted only in retro-aldol decomposition. A brief screen of reducing agents revealed that the reaction of **1.36** with the recently reported LiAl(O^{t}Bu)(^{i}Bu)$_2$H (LDBBA) afforded mono-alcohol (±)-**1.41** with moderate diastereoselectivity (4:1 **1.41**:Σ other diastereomers) [33]. While the reduction of diketone **1.19** (lacking any C2 substituent) required warmer temperatures and extended reaction times, reduction of **1.36** was complete within ten minutes at −78 °C. An X-ray diffraction study of the major diastereomer confirmed the *exact relative configuration* needed for elaboration to **1.1**. While we envision a chelation mode similar to transition structure **1.29** might be taking place in this reduction, the involvement of the C2 furan in directing the C1/C7 relative configuration and dramatically affecting the reactivity is not well understood.

1.3.8 Advancement of Desymmetrization Product to Pactamycin

Having accessed this key intermediate, we proceeded to test conditions for functionalization of the C5 methyl ketone (Scheme 1.10). Based on our previous studies [19], we anticipated potential stereoselectivity and reactivity problems associated with nucleophilic addition to the C5 carbonyl and accordingly decided initially to invoke the ability of **1.41** to participate in enolate chemistry. To this end, silyl protection of β-hydroxyketone **1.41** proceeded smoothly to deliver ketone **1.42** in 96 % yield. The reaction of the lithium enolate derived from **1.42** with ethyl cyanoformate provided β-ketoester **1.43** in 80 % yield [34].



Scheme 1.10 Advancement of furan reduction product toward pactamycin

To access the cyclic core of **1.1** from this functionality, we proposed two parallel strategies: (i) alkene oxidative cleavage followed by aldol condensation or (ii) α-methylenation with subsequent RCM. As these routes were pursued, however, it was quickly found that the furan functionality in **1.43** was not compatible with standard oxidative cleavage conditions (O_3, Johnson-Lemieux, $RuCl_3$, etc.), giving only complex mixtures or starting material decomposition. Turning to the metathesis strategy, we began investigating α-methylenation protocols. Using the conditions recently reported by Connell and co-workers, treatment of **1.43** with $(HCHO)_n$ and diisopropylammonium trifluoroacetate afforded the undesired Diels–Alder adduct **1.44**, effectively rendering our RCM approach unfeasible [35]. These results caused doubt as to whether our proposed C2-furan approach would provide access to pactamycin. In addition, the problems encountered in attempted oxidative cleavage of ketoester **1.43** gave us concern as to whether a late-stage unmasking of C2-furan (via oxidation and Curtius rearrangement) could be realized. With these data points in hand, we abandoned this route and turned our attention toward developing a route to **1.1** from an early-stage Mannich reaction.

1.3.9 C2 Mannich Reaction Development

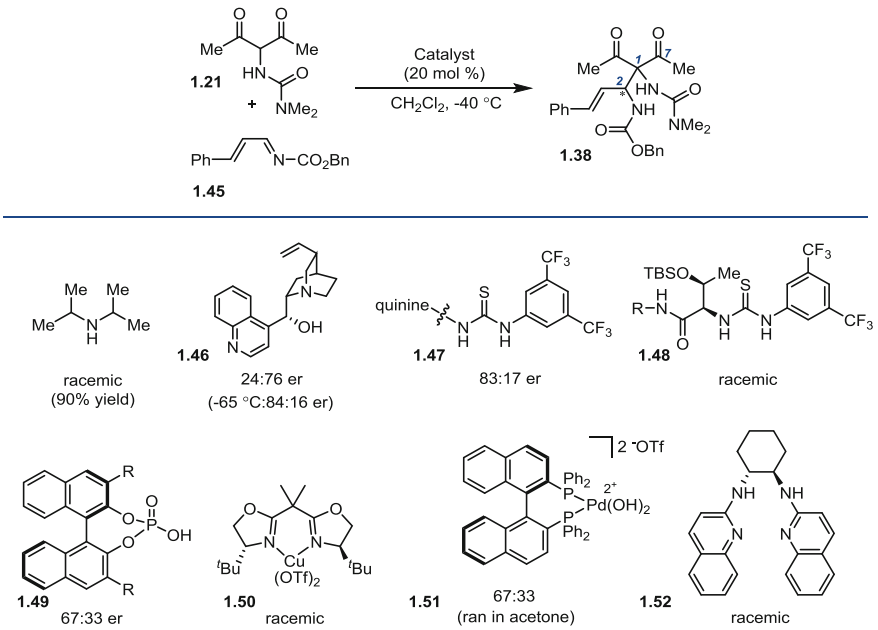
Our strategy for direct installation of a protected amine at C2 required an expansion of the work of Schaus and co-workers to *N*-substituted dicarbonyls (Table 1.2) [29, 30]. Also crucial to the success of this approach would be selection of the appropriately-protected imine electrophile. In the event, we proceeded with Cbz-protected cinnamyl imine **1.45** and began testing conditions for the Mannich reaction. Working first to develop the racemic reaction, the union of α-ureidodiketone **1.21** with imine **1.45** in the presence of catalytic quantities of Hunig's base delivered Mannich product (±)-**1.38** in 90 % yield. With the feasibility of this bond construction established, focus turned to finding a suitable chiral catalyst for the reaction.

In order to develop the corresponding asymmetric reaction, we initially applied Schaus's unmodified conditions to the union of **1.21** and **1.45** (cinchonidine [20 mol%], CH_2Cl_2, −35 °C, 24 h). We were pleased to obtain the crude Mannich adduct **1.38** in 24:76 er. An extensive screen of known Mannich reaction promotors then ensued. These findings are summarized in Table 1.2 and detailed in Sect. 1.5 of this Chapter. Toward these aims, quinine thiourea **1.47** gave increased levels of induction (83:17 er), although these selectivities were still below desirable levels [36, 37].

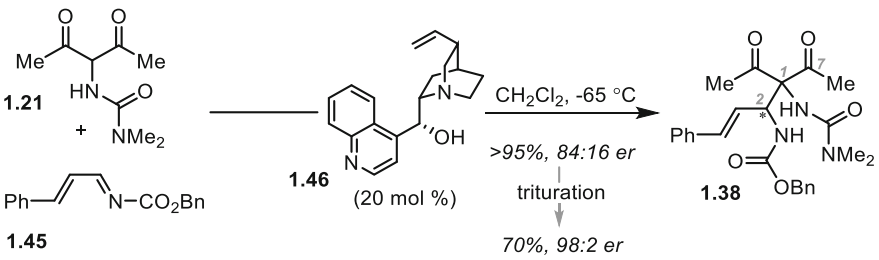
Thioureas of class **1.48** gave no enantioinduction. BINOL-derived phosphoric acid catalysts **1.49** showed no improvement in selectivity, and the same was true for copper (box) **1.50** [38], Pd-BINAP **1.51** [39] and the free base of Johnston's organocatalyst (**1.52**) [40]. The results led to the conclusion that cinchonidine **1.46**, the catalyst originally examined, might be the best promoter for this transformation.

After optimizing the reaction further for cinchonidine by lowering the reaction temperature (−65 °C), an initial 84:16 er was obtained. We then began examining

Table 1.2 Development of an asymmetric C2 Mannich reaction



conditions for recrystallizing this crude enantioselectivity up to suitable levels for advancement to **1.1** (Scheme 1.11). However, upon trituration of crude **1.38** (84:16 er) for purposes of purification, we found that crystalline racemic product could be removed by filtration, leaving highly enantioenriched (+)-**1.38** (98:2 er) in 70 % yield. The simplicity and scalability of this protocol allowed for large scale material throughput. Unsure of the absolute configuration of (+)-**1.38**, we proceeded in our studies with racemic material assuming that the Mannich catalyst enantiomer could be inverted if necessary to access the correct antipode of pactamycin.



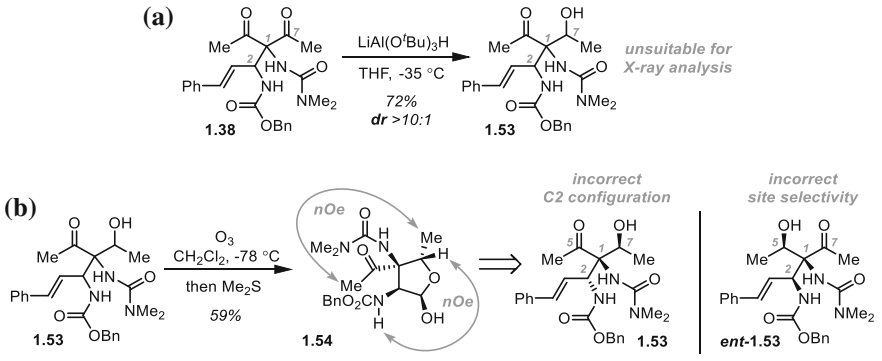
Scheme 1.11 Optimized protocol for asymmetric Mannich reaction

1.3.10 C2 Mannich Product Symmetry-Breaking Reduction Studies

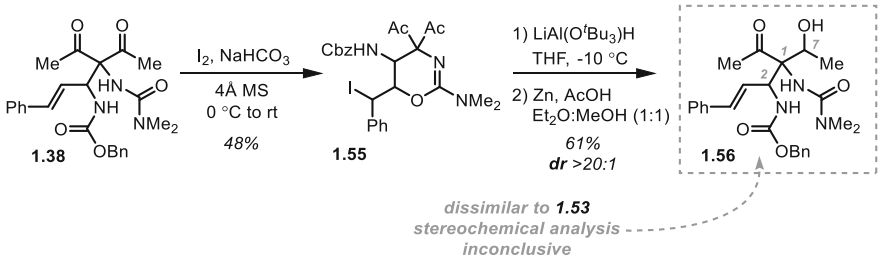
From functionalized dicarbonyl **1.38**, we turned towards assembly of the C1/C2/C7 stereotriad via symmetry-breaking reduction (Scheme 1.12). Referring to our previously optimized conditions in the C2-unsubstituted case, monoreduction of **1.38** with LiAl(O^{t}Bu$_3$)H at −35 °C provided β-hydroxy ketone **1.53** in 72 % yield with high diastereoselectivity (>10:1 **1.53**:Σ other diastereomers). Efforts to determine the relative configuration of this monoalcohol became challenging, however, when initial studies toward accessing a crystalline derivative proved fruitless. Turning to spectroscopic methods, ozonolysis of the styrene moiety provided lactol derivative **1.54** in 59 % yield from which nOesy analysis suggested the relative configuration of the C1/C2/C7 stereotriad illustrated in Scheme 1.12. Alternatively, when viewed as its enantiomer, the reduction product may be depicted as *ent*-(**1.53**).

With this result in hand, we began to analyze the stereochemical outcome, considering the two illustrated product enantiomers. β-Hydroxyketone **1.53** is epimeric at C2 relative to pactamycin (**1.1**), a stereochemical error for which a solution was not immediately obvious given our projected synthetic plan. Alternatively, the enantiomeric form (*ent*-**1.53**) presents C1 and C2 in the correct pactamycin configuration, but is a product resulting from incorrect diastereotopic ketone site selectivity in the desymmetrization. Although this was a discouraging initial result, we remained confident in our symmetry-breaking approach to **1.1** and began pursuing myriad strategies in parallel for the elaboration of diketone **1.38** to our desired reduction diastereomer.

We first pursued an exhaustive screen of reducing agents and conditions in hopes that reagent control would provide stereoselectivity opposite to that observed using LiAl(O^{t}Bu$_3$)H. Monoreduction with a number of bulky hydride sources (L-Selectride®, LDBBA, Red-Al®, DIBAL-H) resulted only in the formation of stereoisomer **1.53** in lower yields. Unhindered hydride sources (LiAlH$_4$, Super



Scheme 1.12 Symmetry-breaking reduction and initial stereochemical analysis



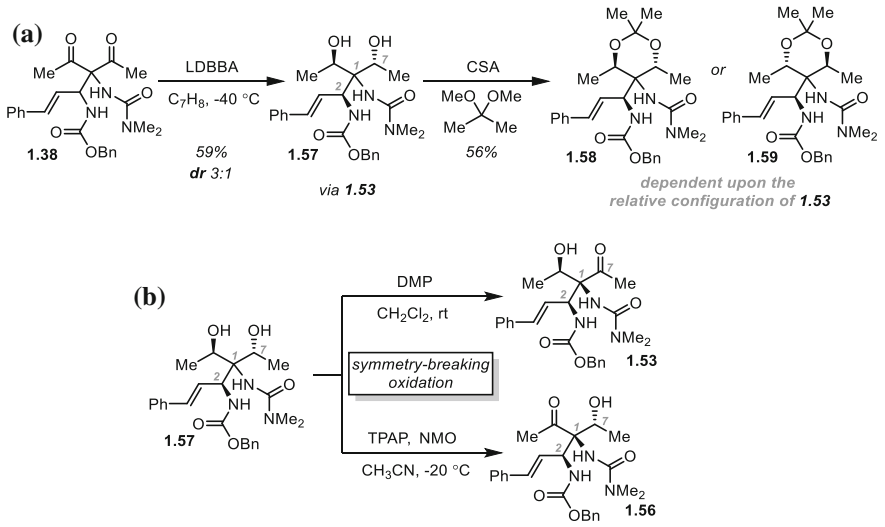
Scheme 1.13 Iodoimidate synthesis and symmetry-breaking reduction

Hydride, $NaBH_4$), gave only minimal amounts of **1.53** accompanied with retro-aldol decomposition pathways. Finally, alternative reduction pathways (enzymatic reduction, transfer hydrogenation) gave no promise for delivering diastereoselectivity opposite to that observed in LTBA reduction of diketone **1.38**. These unsuccessful efforts led us to the conclusion that this reduction was proceeding with virtually complete substrate control, and as a result, direct reduction strategies of **1.38** towards the desired diastereomer were abandoned.

In an effort to alter the apparent conformational bias associated with the acyclic structure **1.38**, the diketone was engaged as its derived cyclic iodoimidate **1.55** through the action of I_2 and $NaHCO_3$ (Scheme 1.13). Subsequent monoreduction of diketone **1.55** followed by retrocyclization (mediated by Zn/HOAc) gave the acyclic hydroxy ketone **1.56** in 61 % yield over two steps as a single diastereomer. Ketone **1.56** is a diastereomer different from that accessed via $LiAl(O^tBu_3)H$ reduction of **1.38**. We immediately began work in establishing its stereochemical identity; however, nOesy analysis in a strategy analogous to that used for **1.53** was inconclusive.

Concurrent with these studies, we pursued an alternate strategy from the perspective of *ent*-**1.53**. Namely, if the original monoreduction product could be further reduced to its corresponding diol (*syn* or *anti*), a site selective oxidation might deliver the desired C1/C2/C7 configuration (Scheme 1.14). To this end, a screen of conditions revealed that direduction of **1.38** with excess LDBBA afforded diol **1.57** as a 3:1 mixture of separable diastereomers. The major isomer was determined to be the 1,3-*trans* diol via nOesy and ^{13}C NMR analysis of the derived acetonide **1.58** [41]. Control experiments revealed that this reduction proceeds via the intermediacy of β-hydroxyketone **1.53**. Consequently, the relative stereochemistry at C2 was assigned according to that shown in alcohol **1.57**.

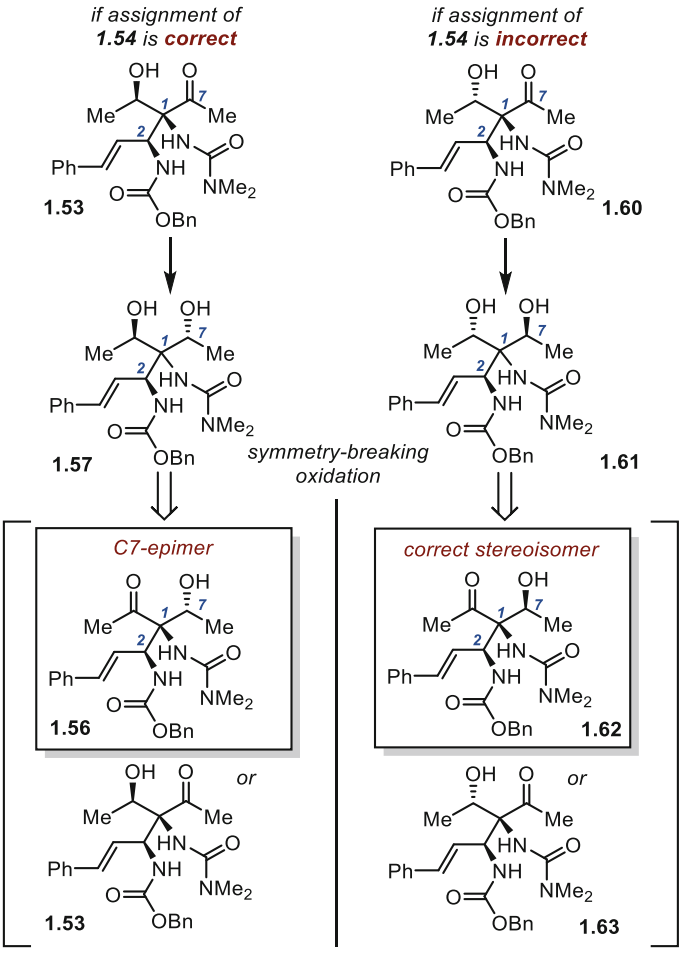
With this diol in hand, we began evaluating oxidants for symmetry-breaking oxidation. Treating diol **1.57** with Dess-Martin periodinane (DMP) showed complete selectivity for oxidation of a single site, returning the original hydroxyketone **1.53**. Alternatively, tetrapropylammonium perruthenate (TPAP) gave preference for the opposite alcohol, delivering monoalcohol **1.56** whose spectral characteristics matched those of the compound prepared via the iodoimidate reduction. The ability to access **1.56** from this route enabled us to assign its relative stereochemistry, which had previously remained ambiguous via nOesy analysis of its derivatives.



Scheme 1.14 Bis-ketone reduction and symmetry-breaking oxidation studies

1.3.11 Stereochemical Analysis: Conclusions

The stereochemical analysis that follows provides the context for the experimental plan that we elected to pursue (Scheme 1.15). It is germane to emphasize at the outset that all of our conclusions thus far hinged on the nOesy analysis of lactol derivative **1.54**, which was suggestive of its illustrated structure, but not unambiguous. Thus, while two of the four possible monoreduction diastereomers (**1.53**, **1.56**) had been accessed, we sought crystallographic evidence for conclusive stereochemical assignment. Diastereoselective oxidation of *trans*-diol **1.57** gives access to two (of the four possible) monoreduction diastereomers of diketone **1.38** (the identities depending on assignment of **1.54**). Should our nOesy analysis of lactol **1.54** prove correct, then the identity of the *trans*-diol would be **1.57**, giving access to the C7-epimeric diastereomer **1.56** (via symmetry-breaking oxidation), which could potentially be inverted downstream in the synthesis. Alternatively, should our assignment of **1.54** be incorrect, the configuration of the *trans*-diol would be **1.61**, enabling access to the desired C1/C2/C7 stereotriad **1.62**. With this information in hand, we concluded that this selective oxidation pathway could provide entry to a useful monoreduction diastereomer for elaboration to **1.1** regardless of the stereochemical identity of **1.53**. Because it was so easily accessible, we moved forward with keto alcohol **1.53** to explore the viability of our remaining synthetic plan. It was our hope that unambiguous stereochemical assignment would be realized via a suitable crystalline derivative later in the route and that the chemistry developed during those studies could be translated to whatever diastereomer was needed.

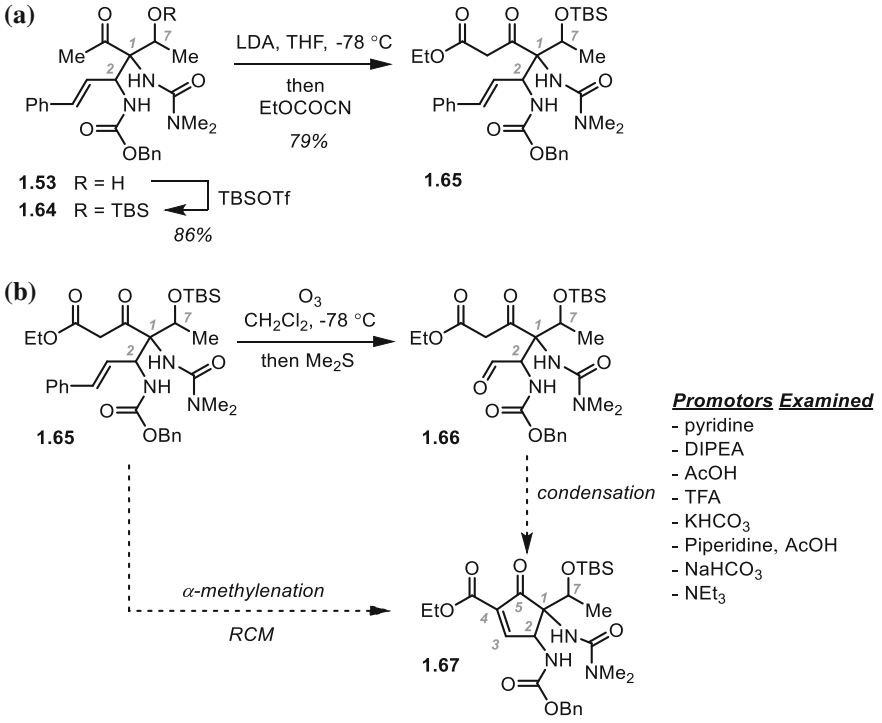


Conclusion: selective oxidation of trans diol by choice of oxidation protocol gives access to two of the four possible monoreduction diastereomers

Scheme 1.15 Stereochemical possibilities arising from diketone monoreduction

1.3.12 Attempted Acylation/Cyclocondensation Route

Silyl protection of **1.53** under typical conditions proceeded smoothly, delivering β-silyloxy ketone **1.64** in 86 % yield (Scheme 1.16). Some trepidation accompanied the subsequent enolate acylation in light of the possibility for undesired side reactions associated with deprotonation of the NHCbz group (i.e. retro-Mannich cleavage), but carboalkoxylation of the lithium enolate derived from **1.64** with ethyl cyanoformate cleanly delivered β-ketoester **1.65** in 79 % yield. Hoping to access cyclopentenone **1.67** via our two previous strategies in the C2 furan approach, we began testing α-methylenation protocols to set the stage for RCM.

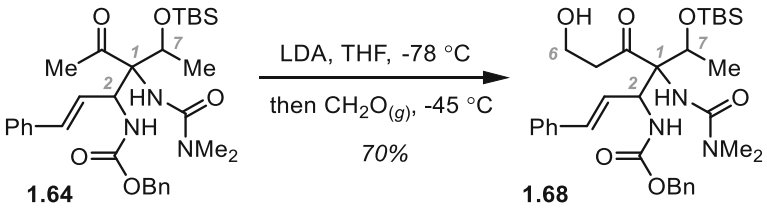


Scheme 1.16 Ring closure strategies examined from Mander's acylation adduct

Unfortunately, treatment of **1.65** with known conditions for α-methylenation (diisopropylammonium trifluoroacetate/$(HCHO)_n$, Eschenmoser salt, etc.) failed to give any promise as only starting material decomposition was observed. However, ozonolysis of **1.65** followed by reductive workup delivered reactive α-aminoaldehyde **1.66** which could not be isolated by chromatography. We then began an extensive screen of conditions with which to effect an intramolecular condensation. Treatment of the crude aldehyde **1.66** with amine bases (NEt_3, DIPEA, pyridine) gave rise only to complex mixtures, while carbonate bases and typical Knoevenagel conditions resulted in starting material decomposition. Furthermore, exposure of **1.66** to mild bicarbonate bases resulted in the formation of a single product; however, this product could never be identified nor manipulated into a useful intermediate.

1.3.13 Formaldehyde Aldol/Cyclocondensation Approach

From these results, we concluded that our desired cyclization from **1.66** could not proceed via the β-ketoester moiety, and we began to investigate routes by which we might directly install the requisite C4 hydroxymethylene in its correct oxidation

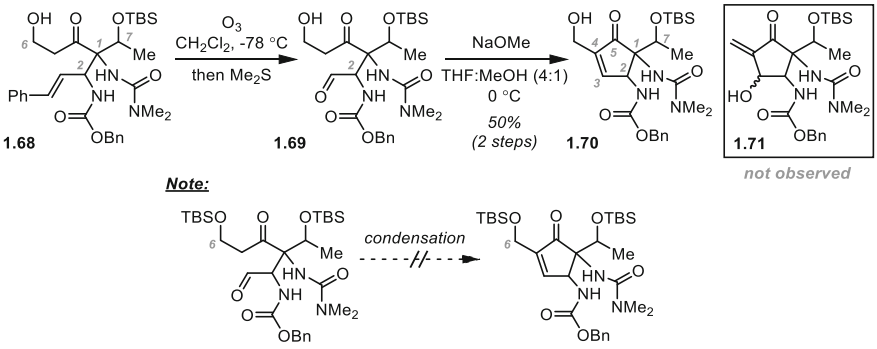


Scheme 1.17 Development of a formaldehyde aldol hydroxymethylation

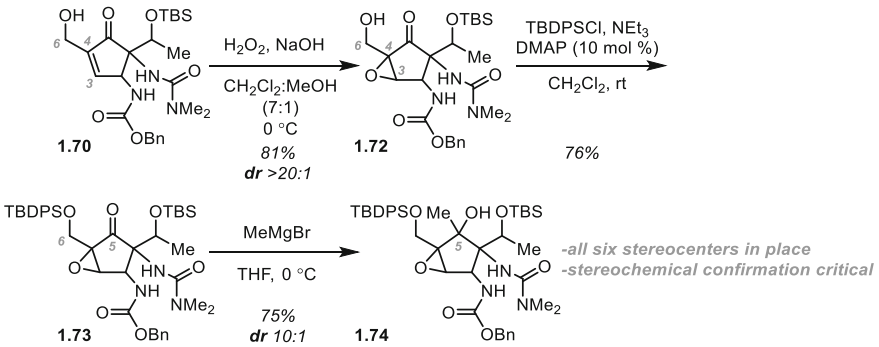
state for elaboration to **1.1** (Scheme 1.17). This route would deliver the less activated β-hydroxyketone for subsequent intramolecular condensation. Although few examples exist in the literature for the use of formaldehyde as an aldol electrophile in complex synthesis, Trost and co-workers have demonstrated its use in their synthesis of corianin [42]. The Cao group, likewise, has shown the use of CH_2O in aldol reactions en route to a total synthesis of malyngamide U [43]. After significant experimentation in our system, we found that by bubbling gaseous CH_2O (generated by the pyrolysis of paraformaldehyde) through a solution of the lithium enolate of **1.64** at −45 °C, the desired primary alcohol **1.68** was isolated in 70 % yield.

Ozonolysis of the styrene in **1.68** delivered the corresponding crude α-aminoaldehyde **1.69** poised for intramolecular condensation (Scheme 1.18). NaOMe emerged early as a superior promoter from our screen of conditions, delivering cyclopentenone **1.70** in 50 % yield from **1.68**. Enone **1.70** contains all of the core carbon atoms necessary for synthesis completion and is ideally functionalized at C2 for late stage revelation of the requisite primary amine.

Interestingly, the condensation of **1.69**–**1.70** was rendered ineffective if the C6 hydroxyl group was protected [44]. Fortunately, elimination of H_2O strongly favors the formation of the endocyclic alkene (**1.70**) over its constitutional isomer, the α-methylidene cyclopentanone (**1.71**).



Scheme 1.18 Intramolecular aldol condensation for access to cyclopentane core



Scheme 1.19 Installation of remaining core stereocenters

1.3.14 Installation of C3, C4, C5 Stereocenters

With cyclopentenone **1.70** in hand, only C5 nucleophilic addition, C4 hydroxylation, and installation of the C3 aniline remained to complete the core structure of **1.1**. We were still without stereochemical confirmation at C1, C2, and C7 at this juncture; however, given the promising access to cyclopentenone **1.70** and its obvious potential for elaboration to **1.1**, we continued to move forward in exploring these remaining core functionalizations (Scheme 1.19). An epoxidation/nucleophilic aniline ring-opening sequence was pursued to access the C3,C4 *trans*-anilinoalcohol, inspired by a related approach by Hanessian and co-workers [20, 21]. We surmised that addition of a suitable methide nucleophile to the C5 ketone would install the final stereogenic center. Our experiments revealed that the order of these steps and the identity of the C6 hydroxymethylene protecting group were critical.

In the permutation of these reactions that ultimately proved successful, we found epoxidation of **1.70** to be the most viable initial transformation. Thus, treatment of enone **1.70** with $NaOH/H_2O_2$ delivered epoxy-alcohol **1.72** in 81 % yield and >20:1 dr. Notably, as in the case of the intramolecular aldol condensation (**1.69** → **1.70**), this reaction was ineffective if the C6 hydroxyl was protected. Further experimentation led to the conclusion that functionalization of the C5 ketone would be the most feasible next step in the sequence. However, treatment of epoxide **1.72** with MeMgBr returned only recovered starting material (even when the reaction was warmed to rt). Surmising that the unprotected C6 hydroxyl might be reducing the electrophilicity of the ketone, the C6 hydroxyl in **1.72** was protected as its sterically-demanding TBDPS derivative **1.73** in 76 % yield [45]. With silyl ether **1.73** in our possession, treatment with MeMgBr at 0 °C proceeded smoothly to provide carbinol **1.74** in 75 % yield and excellent diastereoselection (>10:1).

1.3.15 *Unambiguous Assignment of Stereochemical Identity*

Having arrived at an intermediate bearing all six stereocenters of **1.1**, we were aware that unambiguous confirmation of the relative stereochemistry of **1.74** was essential before any further chemical manipulations could be probed (Fig. 1.3). Consequently, we began aggressively pursuing recrystallization of **1.74** (or derived compounds thereof) to confirm or disprove our earlier stereochemical analyses. Fortunately, carboxybenzyl deprotection of **1.74** occurred readily under hydrogenolysis conditions to deliver the corresponding C2 primary amine **1.75**, which crystallized readily. X-ray analysis of this derivative confirmed the *desired relative stereochemistry at all six centers*. This surprising confirmation prompted us to examine this result further. Two points were of interest and will be discussed in the following sections: (i) the apparent concave-selective C5 ketone methylation (**1.73** → **1.74**) and (ii) the apparent disproval of our originally determined stereochemistry of **1.53**.

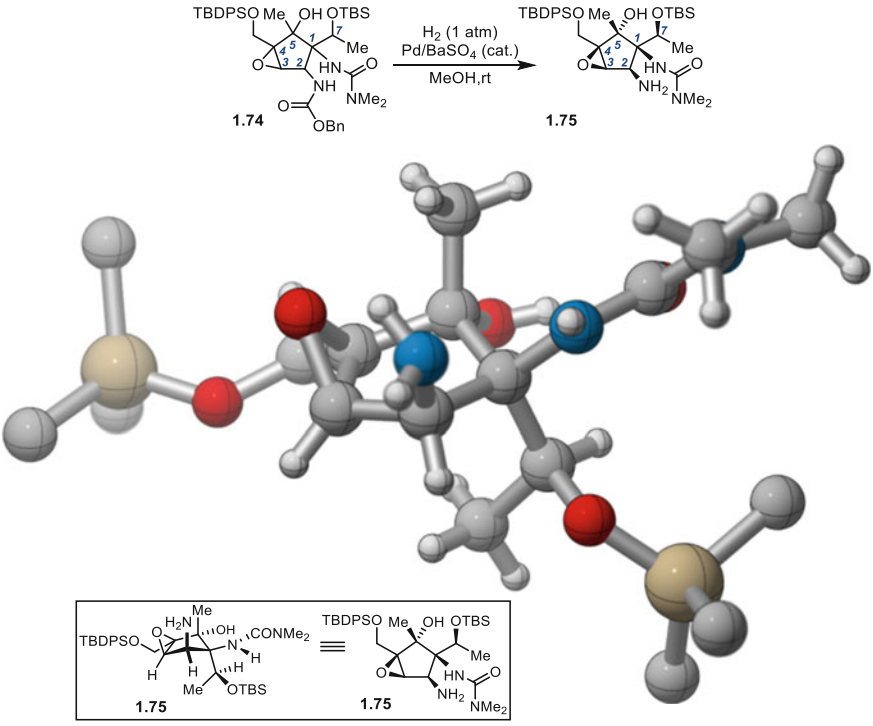


Fig. 1.3 Cbz deprotection and critical X-ray diffraction study

1.3.16 Implications of C5 Ketone Methylation

With regard to the C5 ketone methylation, nucleophile addition to the convex surface of similar oxabicyclo[3.1.0]hexanone systems is well documented; in our system, this trajectory would have delivered the incorrect C5 configuration in the conversion of **1.73**–**1.74** (Fig. 1.4).

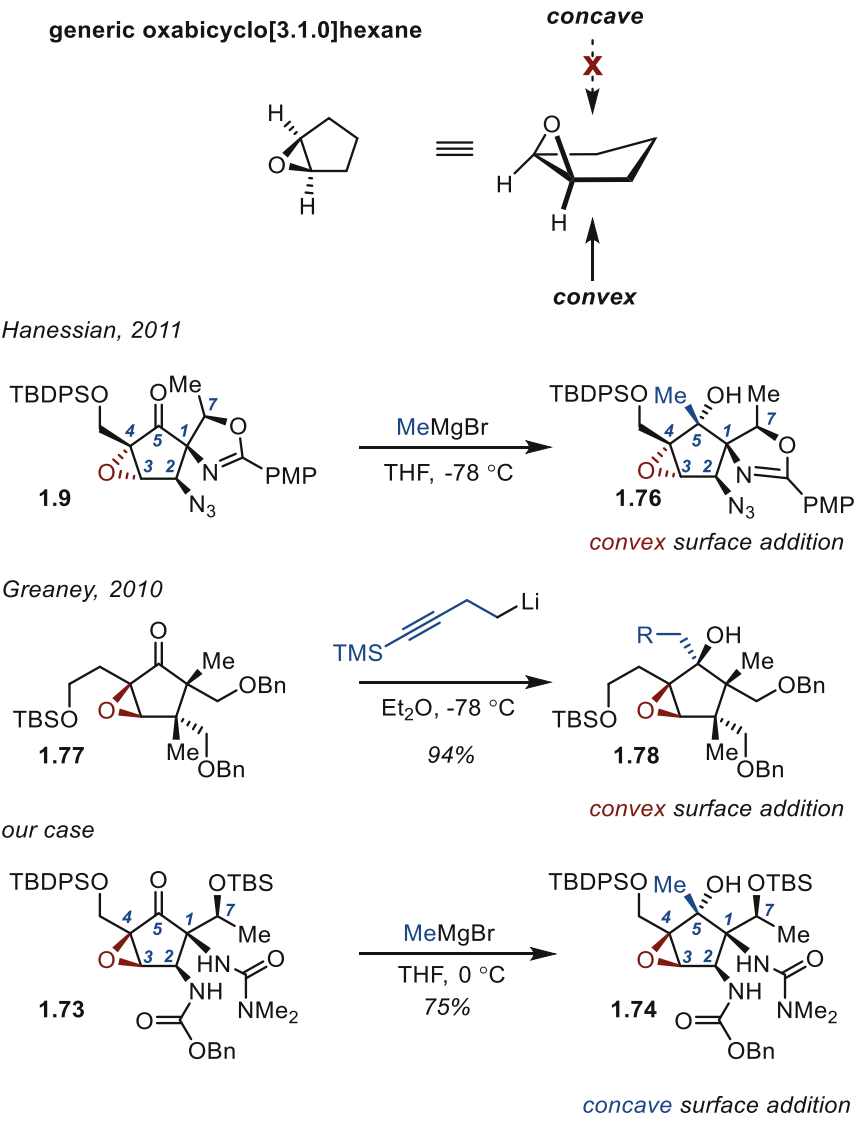
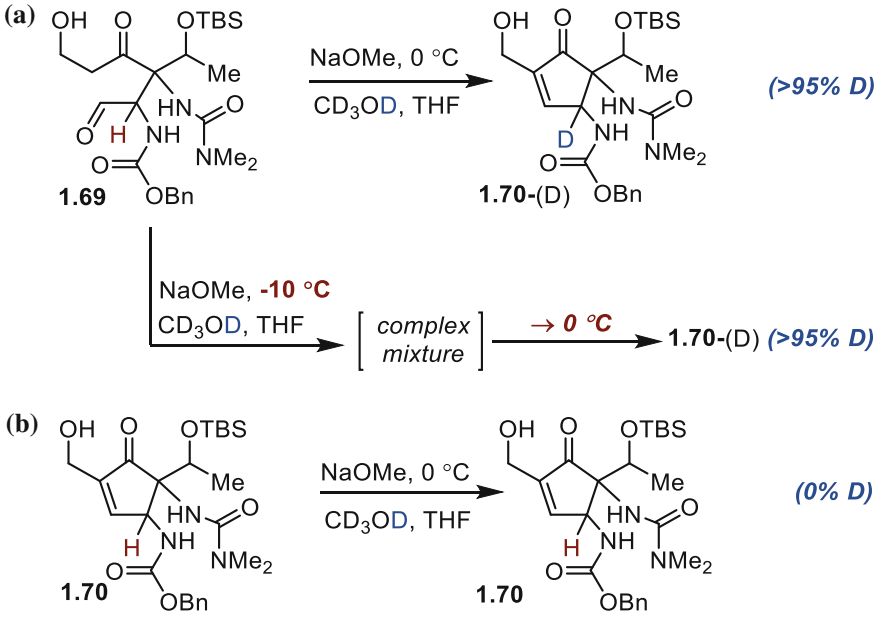


Fig. 1.4 Analysis of addition to oxabicyclo[3.1.0]hexanes

As was discussed in Sect. 1.2.2, Hanessian and co-workers witnessed exclusively convex surface addition of a methide nucleophile to ketone **1.9** in their total synthesis of **1.1** [20, 21]. Greaney and co-workers, likewise, observed this facial preference in the addition of an alkyllithium nucleophile to ketone **1.77** in their syntheses of merrilactone A and anislactone A [46]. In our system, however, this inherent preference was seemingly overridden, delivering the desired stereochemistry at C5 (**1.73** → **1.74**). In the present case, we surmise this selectivity is observed at least in part due to direction by the C1-dimethylurea, providing additional support to the decision to incorporate this functionality in its native form early in the synthesis. Furthermore, the presence of two large silyl groups on the convex face of epoxide **1.73** might serve to block the undesired facial approach.

1.3.17 Implications of X-Ray Study to the Symmetry Breaking Reduction

The presence of the desired C1/C2/C7 stereotriad in **1.74** seemed to refute our original stereochemical determination of hydroxyketone **1.53** based on nOesy analysis of lactol derivative **1.54**; however, in employing an intramolecular condensation to access the cyclopentane core or **1.1**, the C2 stereocenter had become configurationally labile upon ozonolysis of styrene **1.68** to aldehyde **1.69**. This would leave an acidic aminomethine proton at C2 during the aldol condensation reaction (**1.69** → **1.70**). This led us to consider the possibility of epimerization in the conversion of **1.69**–**1.70** during base-promoted condensation to deliver the desired C2 configuration. We devised a deuterium labeling experiment to examine the possibility of this pathway (Scheme 1.20). Treating α-carbamoyl aldehyde **1.69** with NaOMe in CD_3OD using the optimized conditions afforded enone **1.70**–(D) with complete incorporation of deuterium at C2. When this experiment was conducted at −10 °C for the same time duration, a complex mixture of products was observed by ^1H NMR spectroscopy. Resubmission of this unpurified mixture to the reaction conditions at 0 °C afforded enone **1.70**–(D) with complete D-incorporation. Finally, submission of the product enone **1.70**–d_0 to NaOMe in CD_3OD returned the starting material with no deuterium incorporation. These results indicate that the C2 methine undergoes proton exchange prior to the condensation.



Scheme 1.20 Deuterium labeling studies on the intramolecular aldol condensation

1.3.18 Absolute Confirmation of Symmetry-Breaking Reduction Stereochemistry, Desymmetrization Analysis, and a Fortuitous Stereochemical Correction

In order to unambiguously confirm an epimerization event in the intramolecular aldol condensation, X-ray diffraction analysis of an intermediate upstream of aldehyde **1.69** would be required (Fig. 1.5). Returning to our previous attempts at derivatization of hydroxyketone **1.53**, we found that acylation of the previously-synthesized lactol **1.54** with *p*-nitrobenzoyl chloride provided benzoate derivative **1.79**, which crystallized readily. X-ray analysis of **1.79** (derived from enantioenriched **1.38**) established the sense of enantioinduction in the asymmetric Mannich addition and confirmed the existence of the *incorrect C2 configuration in the desymmetrization product* ***1.53***.

In light of this result, we became interested in the origin of the selectivity afforded in the symmetry-breaking reduction of **1.38**. A survey of the literature led to the discovery of a stereochemical model devised by Davis and co-workers for the selective reduction of 1,3-aminoketones [47]. An application of this model to the reduction of **1.38** is given in Fig. 1.6. As predicted by Davis, preferential *re*-face addition of hydride to pseudochair conformer **1.80** gives rise to the observed monoreduction diastereomer.

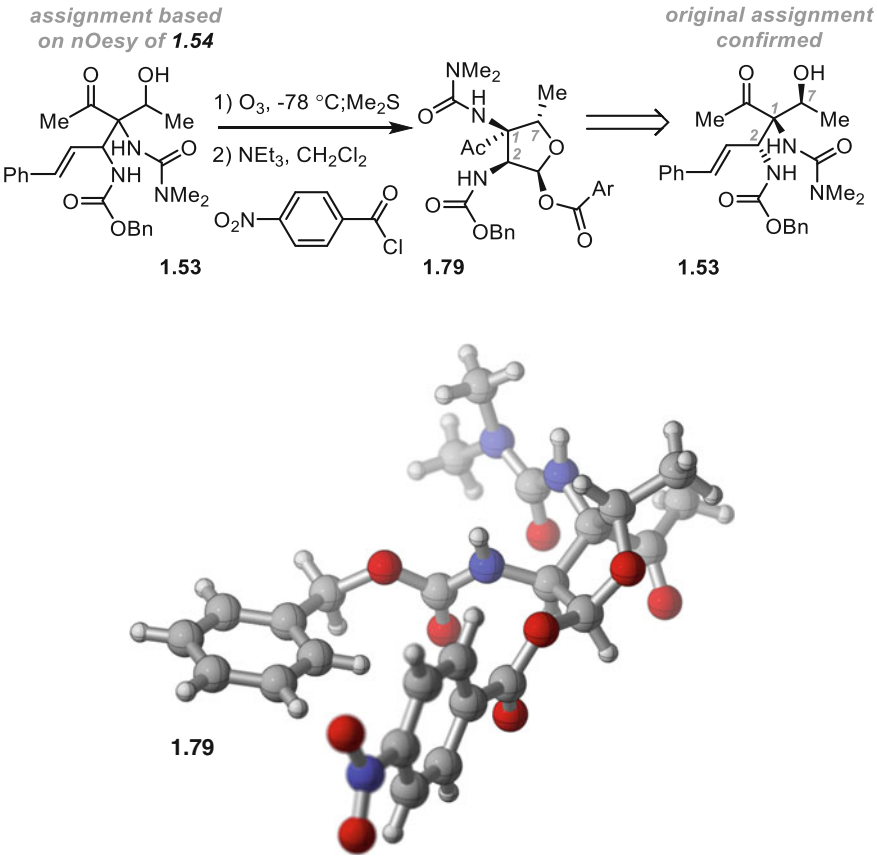


Fig. 1.5 Absolute confirmation of symmetry-breaking reduction stereochemistry

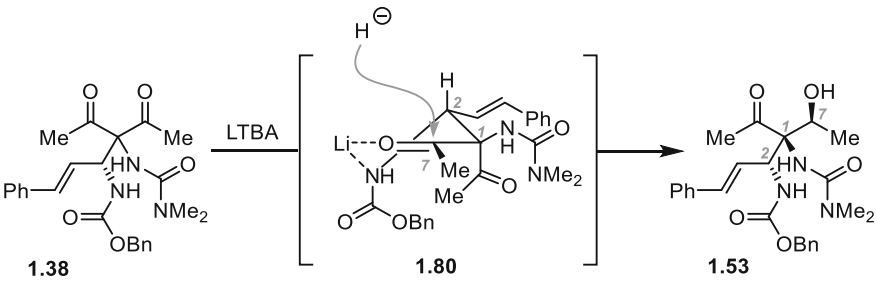


Fig. 1.6 Proposed model for stereoinduction in the symmetry-breaking reduction

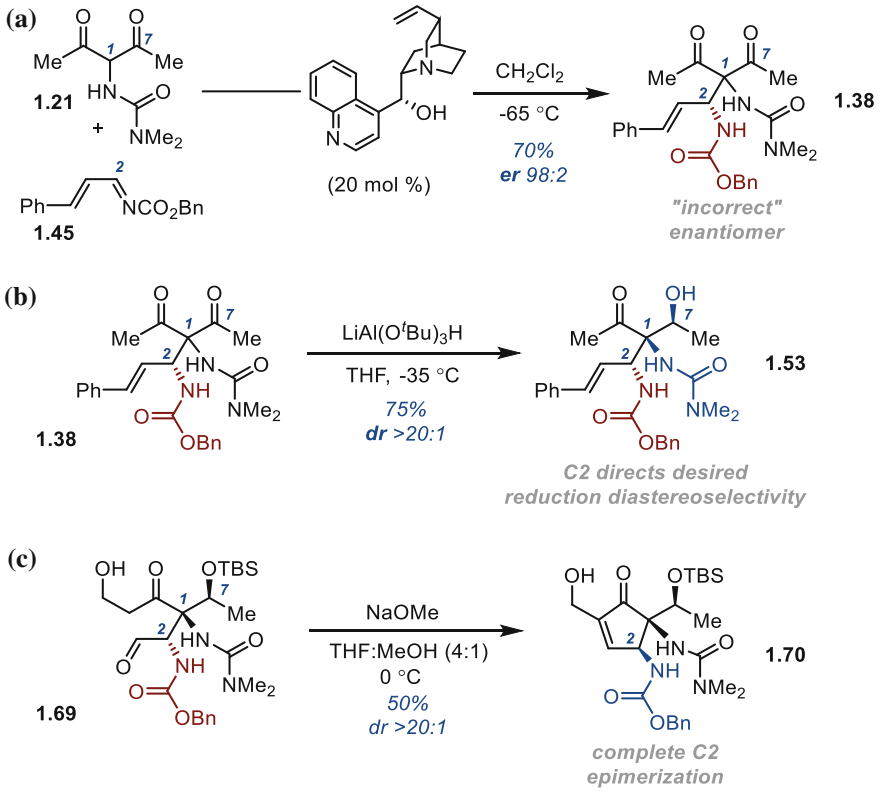
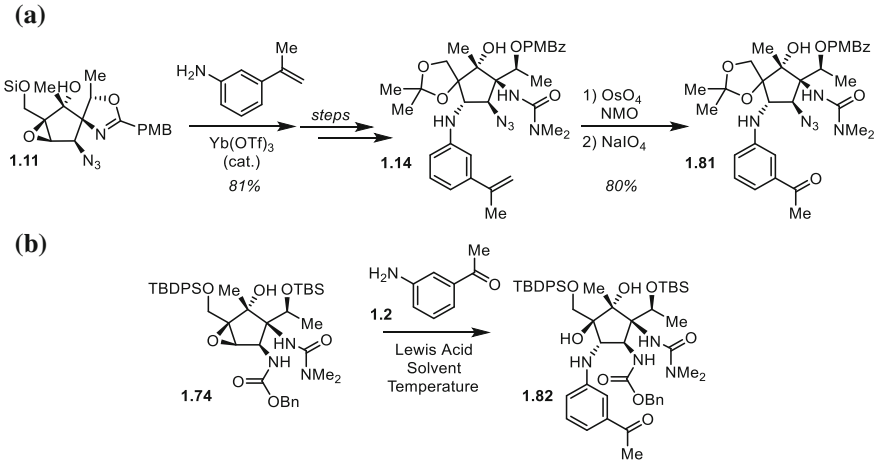


Fig. 1.7 A fortuitous stereochemical correction: conclusions

These results collectively led us to deduce the following (Fig. 1.7): (i) our original stereochemical assignment of hydroxyketone **1.53** via nOesy analysis of **1.54** was correct; (ii) the enantioselective Mannich addition (**1.21** → **1.38**) had yielded the *incorrect* enantiomer nominally required for elaboration to **1.1**; and (iii) this stereochemical "mistake", compulsory for directing the correct C1/C7 stereochemistry in the symmetry-breaking reduction (**1.38** → **1.53**), was later corrected via epimerization in the aldol condensation (**1.69** → **1.70**). Incredibly, this series of events had taken place unbeknownst to us until crystallographic evidence of a much later intermediate led us to suspect the validity of our original stereochemical analysis. Having arrived at these conclusions, we moved forward in our endgame strategy towards synthesis completion.

1.3.19 Endgame and Synthesis Completion

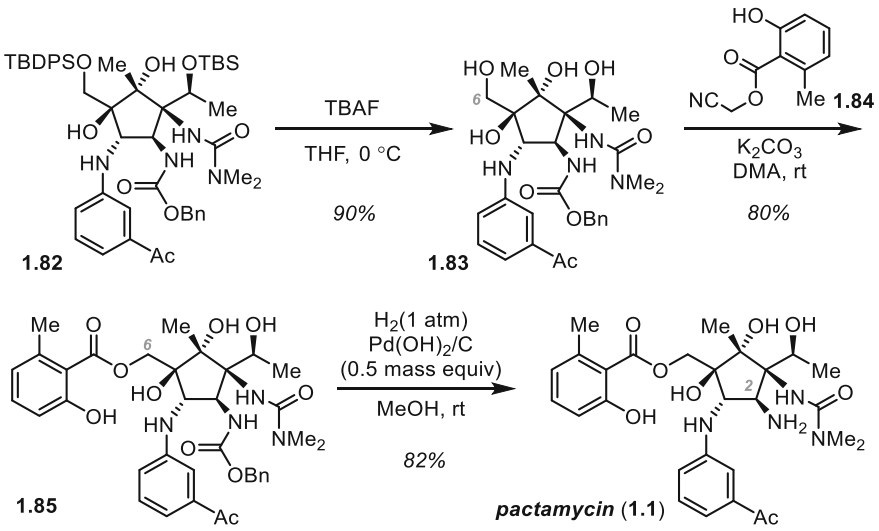
Our plan to complete the synthesis began with the development of a Lewis acid-promoted aniline epoxide opening to install the required *m*-acetylaniline in **1.1**



Lewis Acid (equiv)	Conditions	Result
$Yb(OTf)_3$ (3.5)	C_7H_8, 80 °C	45% conversion, 29% yield
$Dy(OTf)_3$ (5.0)	C_7H_8, 80 °C	100% conversion, 35% yield
$Pm(OTf)_3$	C_7H_8, 80 °C	<50% conversion
$Sc(OTf)_3$ (3.5)	C_7H_8, 80 °C	100% conversion, 27% yield
$Sc(OTf)_3$ (1.0)	C_7H_8, 80 °C	75% conversion
$Sc(OTf)_3$ (1.5)	C_7H_8, 65 °C	70% conversion, 48% yield
$Sc(OTf)_3$ (3.0)	C_7H_8, 60 °C	80% conversion, 65% yield

Scheme 1.21 Development of a lewis acid catalyzed aniline epoxide opening. **a** Hanessian Aniline installation. **b** Direct Aniline installation

(Scheme 1.21). A similar approach had been employed by Hanessian and co-workers for introduction of the C3/C4 *trans*-anilinoalcohol whereupon the requisite aniline was incorporated via its *m*-propenyl derivative (**1.14**) [20, 21]. The necessary acetophenone was later revealed via oxidative cleavage of the olefin (**1.14** → **1.81**). By contrast, we hoped that the required *m*-acetylaniline **1.2** could be installed in its native form, obviating downstream introduction of the ketone. An extensive screen of conditions ensued, and these results are briefly summarized in Scheme 1.19. We found that the conversion of **1.74**–**1.82** was promoted by a variety of Lewis acids, although stoichiometric amounts of promoter were necessary to achieve suitable levels of conversion (presumably due to the Lewis basic ketone on **1.2**). Highest conversions were achieved when $Sc(OTf)_3$ was employed, albeit yields decreased at 80 °C. Determining that three equivalents of the Lewis acid were optimal, we probed lowering of the reaction temperature. This feature



Scheme 1.22 Salicylate installation and total synthesis completion

resulted in decreased product decomposition and elevated yields, leading to our optimized conditions ($Sc(OTf)_3$ [3.0 equiv], C_7H_8, 60 °C) which consistently provided aniline **1.82** in 66 % yield with ~18 % recovery of unreacted **1.74**. It is important to note that while this transformation proceeds in moderate yield, the use of more electron-rich anilines in the reaction delivers the corresponding epoxide-opened products in high yield, a valuable result as this step is a crucial branch point for analog synthesis.

From **1.82**, we set out to install the remaining salicylate functionality and eliminate all protecting groups (Scheme 1.22). Fortunately, global silyl deprotection proceeded readily upon treatment with tetrabutylammonium fluoride (TBAF), providing tetraol **1.83** in 90 % yield. To incorporate the salicylate moiety, we employed the method developed by Porco and later employed by Hanessian wherein the requisite electrophile is generated via deprotonation/elimination of cyanomethyl ester **1.84**, providing a ketene electrophile selective for the C6 primary hydroxyl [48]. Execution of this protocol on **1.83** occurred with minimal optimization, providing ester **1.85** in 80 % yield. This left only removal of the C2 protecting group to complete our synthesis. Cbz-deprotection was effected readily upon hydrogenolysis of **1.85** in the presence of Pearlman's catalyst to deliver pactamycin (**1.1**) in 82 % yield [49].

A survey of our completed synthesis of **1.1** demonstrates the immediate applicability of this route to modular incorporation of functional diversity towards future SAR studies (Fig. 1.8). Late stage ketone intermediate **1.74** (which can be prepared in gram scale in a single pass) is considered to be a valuable branch point for synthetic diversification at the C5, C3, and C6 positions. Additionally, based on

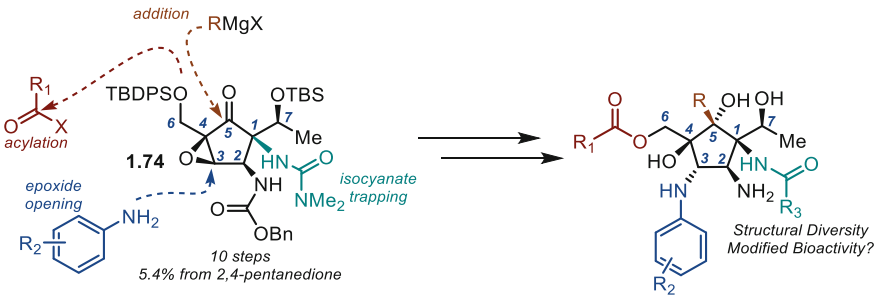


Fig. 1.8 Synthetic plan for preparation of pactamycin structural congeners

Hanessian's strategy for late stage C1 functionalization, it is envisioned that even the C1 dimethylurea may be modulated via a transiently-generated isocyanate intermediate. These studies will be further detailed in Chap. 2.

1.4 Conclusion

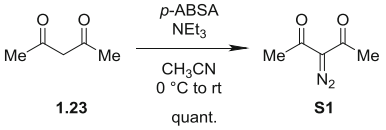
In summary, we have detailed a fifteen-step total synthesis of pactamycin in 1.9 % overall yield from commodity chemical 2,4-pentanedione. Emphasis was placed on incorporation of all unique functionality (dimethylurea, aniline, salicylate) in its native form for minimization of protecting group manipulations. Revision of our originally published strategy [19] led to the development of a novel alkylative cyclization for intramolecular delivery of C5 stereochemistry. A need to incorporate C2 functionality early-stage gave rise to the synthesis of a new difurylidene acetate reagent which was employed in a complex Tsuji–Trost allylation, and an enantioselective Mannich addition of α-ureidodicarbonyls was developed via an adaptation of the Schaus conditions [29, 30]. A symmetry-breaking reduction was employed for rapid delivery of the C1/C2/C7 stereotriad in **1.1**, and proposed stereochemical models for these reductions are presented. In the case of the C2-carbamate approach, a thorough analysis of monoreduction stereochemical outcomes is presented. These studies culminated with the conclusion that selective oxidation of *trans*-diol **1.57** could allow access to a suitable monoreduction diastereomer of **1.38** for elaboration to **1.1**. This deduction directed the decision to move forward in our strategy without unambiguous stereochemical confirmation of alcohol **1.53** with the assumption that the necessary relative configuration of **1.1** could be realized later in the synthesis. The stereochemical identity of **1.53** was later unambiguously determined to be incorrect at C2, although this "stereochemical error" was corrected via epimerization during a downstream aldol condensation. This fortuitous turn of events allowed facile access to **1.1** in the absence of non-strategic stereochemical manipulations. This route is flexible and immediately amenable to the synthesis of structural analogs as major functional groups (aniline, salicylate) are incorporated in a late-stage fashion.

1.5 Experimental Details

Methods: General. Infrared (IR) spectra were obtained using a Jasco 460 Plus Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker model Avance 400 (^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz) or a Bruker Avance III 600 (^{1}H NMR at 600 MHz and ^{13}C NMR at 150 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, br d = broad doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Mass spectra were obtained using a Micromass Quattro-II triple quadrupole mass spectrometer in combination with an Advion NanoMate chip-based electrospray sample introduction system and nozzle or a Thermo LTqFT mass spectrometer with electrospray introduction and external calibration. All samples were prepared in methanol. Analytical thin layer chromatography (TLC) was performed on Sorbent Technologies 0.20 mm Silica Gel TLC plates. Visualization was accomplished with UV light, $KMnO_4$, and/or aqueous ceric ammonium nitrate solution followed by heating. Purification of the reaction products was carried out by flash chromatography using Siliaflash-P60 silica gel (40–63 μm) purchased from Silicycle. Supercritical fluid chromatography was performed on a Berger SFC system equipped with a Chiralcel OD column. Samples were eluted with SFC grade CO_2 at the indicated percentage of MeOH. Unless otherwise noted, all reactions were carried out under an atmosphere of dry nitrogen in oven-dried glassware with magnetic stirring. Yield refers to isolated yield of analytically pure material unless otherwise noted. Yields are reported for a specific experiment and as a result may differ slightly from those found in figures, which are averages of at least two experiments.

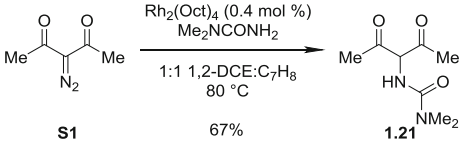
Materials: General. Tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), and toluene (C_7H_8) were dried by passage through a column of neutral alumina under nitrogen prior to use. Acetonitrile (CH_3CN), Triethylamine (NEt_3) and diisopropylamine were freshly distilled from calcium hydride prior to use. Cinnamaldehyde was distilled under reduced pressure and elevated temperature immediately prior to use. LiAl(^{i}Bu)$_2$(O^{t}Bu)H [33], Imine **1.45** [50] and cyanomethyl ester **1.84** [51] were prepared by known procedures. All other reagents were purchased from commercial sources and were used as received unless otherwise noted.

Experimental Procedures:

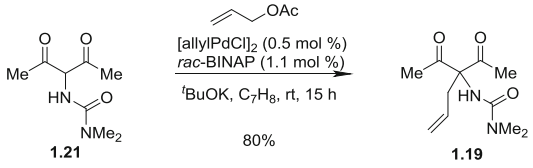


3-diazopentane-2,4-dione (S1): A 1-L round-bottomed flask was charged with acetylacetone (**1.23**) (10.25 mL, 100 mmol, 1.0 equiv) and acetonitrile (600 mL).

p-Acetamidobenzene sulfonyl azide (*p*-ABSA) (24.0 g, 100 mmol, 1.0 equiv) was added and the reaction was cooled to 0 °C. Triethylamine (NEt_3) (41.8 mL, 300 mmol, 3 equiv) was added dropwise and the reaction was warmed to rt for 1 h. The resulting suspension was filtered through a fritted funnel and concentrated. The obtained residue was triturated with 1:1 ether:petroleum ether and the precipitated white soilds were removed via filtration. Solvents were removed in vacuo providing analytically pure **S1** as a yellow oil in quantitative yield. Spectral data matched those reported in the literature [51].

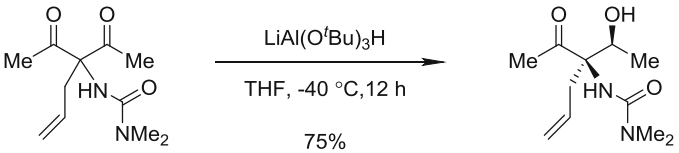


3-(2,4-dioxopentan-3-yl)-1,1-dimethylurea (1.21): A 1-L round-bottomed flask was charged with finely ground 1,1-dimethylurea (21.0 g, 237.0 mmol, 1.5 equiv). C_7H_8 (400 mL) and 1,2-dichlorethane (400 mL) were added, followed by diazodiketone **S1** (20 g, 158.0 mmol, 1.0 equiv). The suspension was heated to 80 °C in a sand bath with magnetic stirring and gradually became homogeneous. $Rh_2(Oct)_4$ (0.492 g, 0.632 mmol, 0.004 equiv) suspended in C_7H_8 (10 mL) was added in four portions over 30 min. The reaction temperature was maintained at 80 °C and stirred until complete consumption of **S1** was indicated by TLC analysis, typically 1 h. The reaction was allowed to cool to rt whereupon the excess 1,1-dimethylurea precipitated from solution. Solids were removed by vacuum filtration and the filtrate was concentrated in vacuo. The crude product was purified via flash chromatography (70:30 to 60:40 petroleum ether/acetone) to provide the title compound as a yellow solid (19.8 g, 67 %). Note: NMR analyses typically showed a ~2:1 mixture of enol: keto tautomers. Analytical data: **mp** 105–109 °C; **^{1}H NMR** (600 MHz, $CDCl_3$): **keto-tautomer**: δ 5.92 (br s, 1H), 5.03 (d, J = 4.8 Hz, 1H), 2.92 (s, 6H), 2.20 (s, 6H); **enol-tautomer**: δ 15.77 (s, 1H), 5.99 (s, 1H), 2.94 (s, 6H), 2.03 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 201.7, 191.8, 157.5, 157.2, 112.3, 72.8, 36.5, 36.3, 36.2, 27.2, 23.9, 21.9; **HRMS (ESI$^+$)** Calcd. for $C_8H_{14}N_2O_3$ + H, 187.1084; Found, 187.1091; **IR** (thin film, cm^{-1}) 3419, 2360, 2126, 1636, 1317, 1315, 1022, 914, 889; **TLC** (60:40 petroleum ether/acetone): R_f = 0.30.



3-(3-acetyl-2-oxohex-5-en-3-yl)-1,1-dimethylurea (1.19). In a nitrogen-filled glove box a flame-dried 100-mL round-bottomed flask was charged with allylpalladium chloride dimer (0.02 g, 0.05 mmol, 0.005 equiv) and *rac*-BINAP (0.07 g, 0.11 mmol, 0.0106 equiv). C_7H_8 (10 mL) was added and the suspension was stirred

for 10 min, capped with a rubber septum, and removed from the glove box. Allyl acetate (1.75 mL, 16.1 mmol, 1.50 equiv) was added and the catalyst solution was stirred for an additional 10 min. A separate flame-dried 250-mL round-bottomed flask was charged with diketone **1.21** (2.0 g, 10.7 mmol, 1.00 equiv) and ^{t}BuOK (1.27 g, 11.31 mmol, 1.05 equiv). C_7H_8 (54 mL) was added and the suspension was stirred under a nitrogen atmosphere. The catalyst solution was introduced via cannula transfer, and the reaction was stirred for 12 h at room temperature. The reaction was quenched with 1 M HCl (30 mL) and extracted with EtOAc (3 × 40 mL). The combined organic extracts were washed with brine (30 mL), dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (70:30 petroleum ether/acetone) to give the desired product (1.93 g, 80 %) as a pale yellow oil. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.22 (s, 1H), 5.39 (m, 1H), 5.04 (m, 2H), 3.07 (dd, J = 1.2, 6.6 Hz, 2H), 2.92 (s, 6H), 2.06 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 202.0, 155.8, 131.3, 119.3, 78.9, 36.0, 24.7; **HRMS (ESI^{+})** Calcd. for $C_{11}H_{18}N_2O_3$ + H, 227.1396; Found, 227.1407; **IR** (thin film, cm^{-1}) 3146, 2979, 2925, 1707, 1638, 1519, 1369, 1227, 1119, 923; **TLC** (75:25 petroleum ether:acetone): R_f = 0.30.

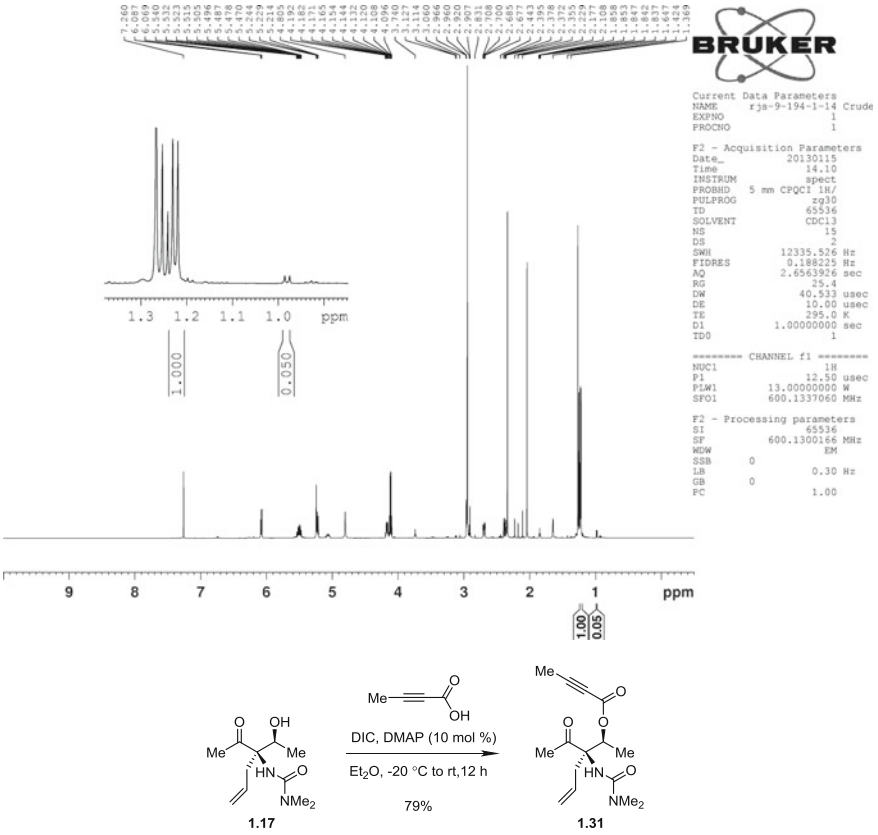


1.19 **1.17**

3-(3-acetyl-2-hydroxyhex-5-en-3-yl)-1,1-dimethylurea (1.17). A flame-dried 250-mL round-bottomed flask was charged with diketone **1.19** (6.8 g, 30.1 mmol, 1.00 equiv) and THF (232 mL). The solution was cooled to −78 °C, and lithium tri-*tert*-butoxyaluminum hydride (1.1 M in THF, 43.8 mL, 48.2 mmol, 1.60 equiv) was added slowly. The resulting mixture was warmed to −40 °C and stirred until complete consumption of diketone **1.19** was indicated by TLC analysis, typically 12 h. The reaction was quenched by the addition of saturated $NH_4Cl_{(aq)}$ (100 mL) and the mixture was extracted with EtOAc (3 × 60 mL). The combined organic extracts were washed with brine (70 mL), dried with magnesium sulfate, and concentrated in vacuo. The crude product was purified via flash chromatography (80:20 to 70:30 petroleum ether:acetone) to afford alcohol 17 (5.16 g, 75 %) as a yellow viscous oil with >20:1 ratio of diastereomers. The stereochemical relationship of **1.17** was confirmed via TBS protection and direct ^{1}H NMR comparison with the corresponding TBS ether **1.25** that has previously been reported [19]. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.03 (d, J = 9.0 Hz, 1H), 5.44 (m, 1H), 4.88 (s, 1H), 4.13 (t, J = 8.4 Hz, 1H), 2.86 (s, 6H), 2.62 (ddd, J = 1.2, 4.2, 7.8 Hz, 1H), 2.40 (dd, J = 4.8, 9.6 Hz, 1H), 2.25 (s, 3H), 1.12 (dd, J = 1.8, 7.2 Hz, 3H);

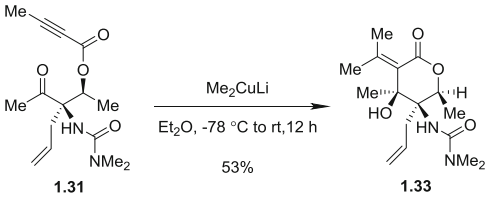
^{13}C NMR (150 MHz, $CDCl_3$): δ 206.7, 158.6, 120.6, 72.2, 70.3, 38.8, 36.5, 36.4, 25.8, 18.2; **HRMS (ESI$^+$)** Calcd. for $C_{11}H_{20}N_2O_3$ + Na, 251.1371; Found, 251.1367; **IR** (thin film, cm^{-1}) 3410, 2979, 2932, 1711, 1639, 1526, 1378, 1229, 1118, 920; **TLC** (70:30 petroleum ether:acetone): R_f = 0.25.

Crude ^{1}H NMR Spectrum of 1.17



3-acetyl-3-(3,3-dimethylureido)hex-5-en-2-yl but-2-ynoate (1.31). A flame-dried 100 mL round-bottomed flask was charged with alcohol **1.17** (0.82 g, 3.6 mmol, 1.00 equiv), 2-butynoic acid (0.60 g, 7.1 mmol, 2.00 equiv), and Et_2O (30 mL). The resulting mixture was cooled to −20 °C, and a solution of diisopropylcarbodiimide (1.1 mL, 7.1 mmol, 2.00 equiv) and DMAP (0.04 g, 0.36 mmol, 0.10 equiv) in Et_2O (6 mL) was added dropwise. The reaction mixture was allowed to slowly warm to rt overnight. The resulting solution was filtered, and the filtrate was washed with Et_2O (15 mL). The resulting solution was washed with 0.5 M $HCl_{(aq)}$ (15 mL) and Brine

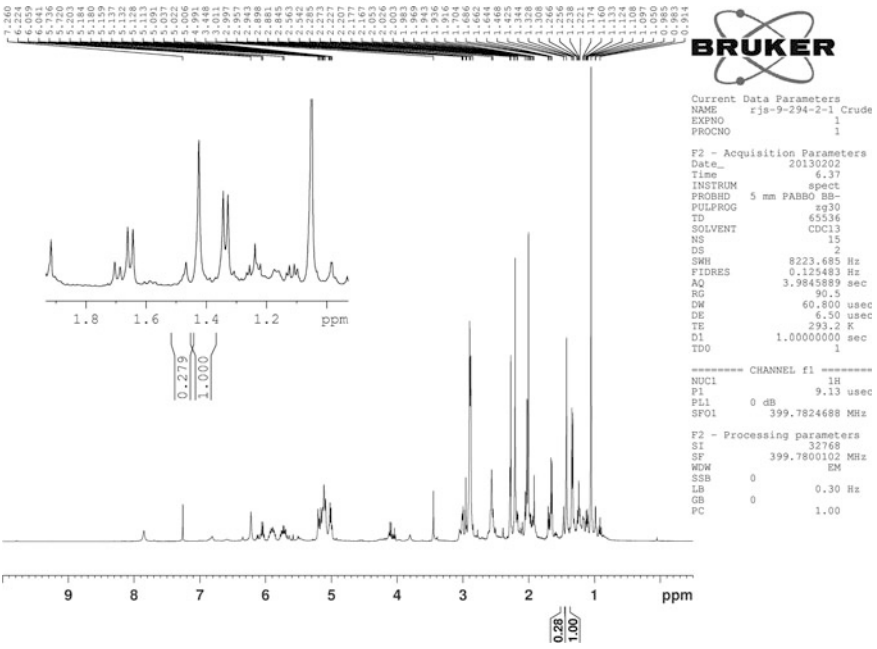
(15 mL), dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (65:35 hexanes:EtOAc) to afford ynoate **1.31** (0.82 g, 79 %) as a clear, viscous oil. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.80 (s, 1H), 5.76 (q, *J* = 6.6 Hz, 1H), 5.46 (m, 1H), 5.05 (dd, *J* = 1.8, 13.8 Hz, 1H), 5.01 (dd, *J* = 1.8, 15.0 Hz, 1H), 3.36 (dd, *J* = 6.6, 7.8 Hz, 1H), 2.85 (s, 6H), 2.62 (dd, *J* = 8.4, 6.6 Hz, 1H), 2.28 (s, 3H), 1.95 (s, 3H), 1.11 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 206.6, 156.2, 152.3, 131.8, 118.7, 86.3, 72.5, 72.4, 72.0, 69.8, 36.1, 36.0, 35.9, 34.3, 26.4, 15.2, 3.7; **HRMS (ESI$^+$)** Calcd. for $C_{15}H_{22}N_2O_4$ + Na, 317.1477; Found, 317.1508; **IR** (thin film, cm^{-1}) 3411, 1978, 2937, 2240, 1711, 1657, 1513, 1371, 1258, 1063, 923; **TLC** (65:45 EtOAc:hexanes): R_f = 0.65.

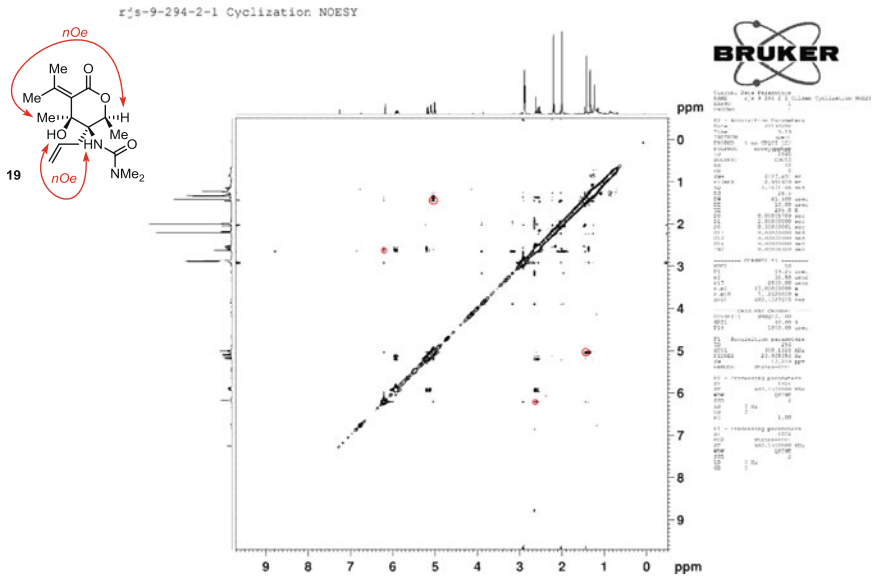


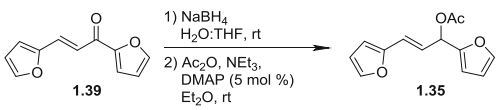
1.31 **1.33**

3-(3-allyl-4-hydroxy-2,4-dimethyl-6-oxo-5-(propan-2-ylidene)tetrahydro-2H-pyran-3-yl)-1,1-dimethylurea (1.33). A flame-dried, 10 mL round-bottomed flask was charged with CuI (0.39 g, 2.00 mmol, 5.00 equiv) and Et_2O (5 mL). The resulting suspension was cooled to −20 °C, and MeLi (1.6 M, 2.55 mL, 10 equiv) was added dropwise. The solution was allowed stir at −20 °C for 1 h, cooled to −78 °C, and a solution of ynoate **1.31** (0.12 g, 0.81 mmol, 1.00 equiv.) in Et_2O (1 mL) was added dropwise. The resulting mixture was allowed to slowly warm to rt overnight, quenched with 10 % AcOH (5 mL), and poured into a separatory funnel containing saturated $NaHCO_{3(aq)}$ (15 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organics were washed with saturated $NaHCO_{3(aq)}$, dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (60:40 to 70:30 EtOAc:hexanes) to afford lactone **1.33** (0.07 g, 53 %) as a clear, viscous oil in a 3:1 ratio of separable diastereomers. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.18 (s, 1H), 5.90 (m, 1H), 5.18 (d, *J* = 16.8 Hz, 1H), 5.10 (d, *J* = 9.6 Hz, 1H), 5.01 (q, *J* = 6.0 Hz, 1H), 2.89 (s, 3H), 2.88 (s, 3H), 2.59 (dd, *J* = 5.4, 9.0 Hz, 1H), 2.53 (dd, *J* = 5.4, 9.0 Hz, 1H), 2.20 (s, 3H), 2.00 (s, 3H), 1.42 (s, 3H), 1.33 (d, *J* = 6.0 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 169.4, 155.4, 147.4, 134.8, 131.6, 118.5, 80.2, 73.7, 65.4, 36.6, 29.7, 23.6, 21.3, 16.6; **HRMS (ESI$^+$)** Calcd. for $C_{16}H_{26}N_2O_4$ + Na, 333.1790; Found, 333.1786; **IR** (thin film, cm^{-1}) 3399, 2923, 2853, 1688, 1642, 1442, 1186, 1054, 909; **TLC** (65:45 EtOAc:hexanes): R_f = 0.35.

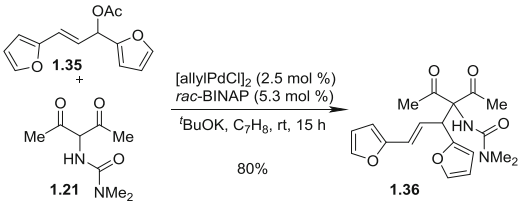
Crude ^{1}H NMR Spectrum of 1.33





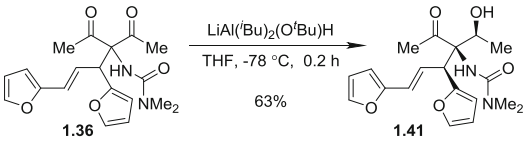


(*E*)-1,3-di(furan-2-yl)allyl acetate (1.35). A 250 mL round-bottomed flask was charged with $NaBH_4$ (1.21 g, 31.9 mmol, 6.00 equiv), THF (27 mL) and H_2O (27 mL). The mixture was cooled to 0 °C and ketone **1.39** (1.0 g, 5.32 mmol, 1.00 equiv) was added as a solution in THF (3 mL). The reaction mixture was allowed to warm to rt and stirred until TLC analysis confirmed complete consumption of the starting material, typically 2 h. The resulting mixture was diluted with brine (30 mL), and the aqueous layer was extracted with Et_20 (3 × 30 mL). The combined organic extracts were dried with magnesium sulfate. The crude solution was concentrated on a rotary evaporator to a volume of *ca.* 5 mL and immediately redissolved in anhydrous Et_2O (27 mL). A stir bar was added followed by NEt_3 (2.22 mL, 15.95 mmol, 3.00 equiv), DMAP (0.03 g, 0.27 mmol, 0.05 equiv.) and lastly Ac_2O (0.88 mL, 9.30 mmol, 1.75 equiv) at rt. The resulting mixture was allowed to stir for 4 h whereupon the reaction was quenched via addition of saturated $NaHCO_{3(aq.)}$ (20 mL). The resulting mixture was transferred to a separatory funnel, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo to afford crude difurylidine acetate **1.35** (1.10 g) as a reddish brown viscous oil. This material was dissolved in anhydrous C_7H_8 and was used in the next step without further purification.



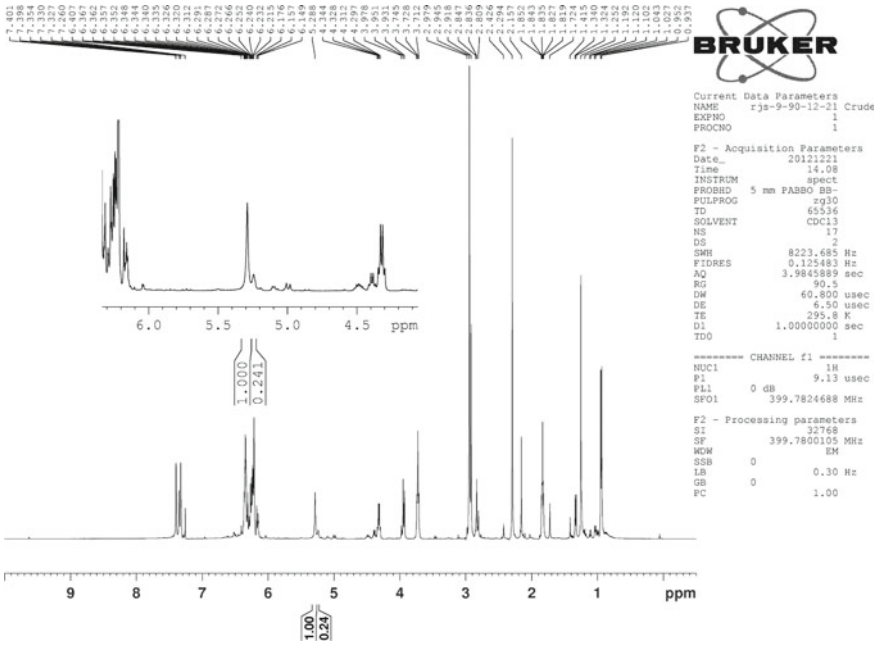
(*E*)-3-(3-acetyl-4,6-di(furan-2-yl)-2-oxohex-5-en-3-yl)-1,1-dimethylurea (1.36). In a nitrogen-filled glove box a flame-dried 100-mL round-bottomed flask was charged with allylpalladium chloride dimer (0.04 g, 0.11 mmol, 0.025 equiv) and *rac*-BINAP (0.14 g, 0.23 mmol, 0.053 equiv). C_7H_8 (5 mL) was added and the suspension was stirred for 10 min, capped with a rubber septum, and removed from the glove box. To this mixture was added crude difurylidine acetate **1.35** (1.49 g, 6.44 mmol, 1.50 equiv) as a solution in C_7H_8, and the catalyst solution was stirred for an additional 10 min upon which a reddish brown color was observed. A separate flame-dried 250-mL round-bottomed flask was charged with diketone **1.21** (0.80 g, 4.29 mmol, 1.00 equiv) and ^{t}BuOK (0.51 g, 4.51 mmol, 1.05 equiv). C_7H_8 (25 mL) was added and the suspension was stirred under a nitrogen atmosphere. The catalyst solution was introduced via cannula transfer, and the reaction was stirred for 12 h at room temperature. The reaction was quenched with 1 M HCl (25 mL) and extracted with EtOAc

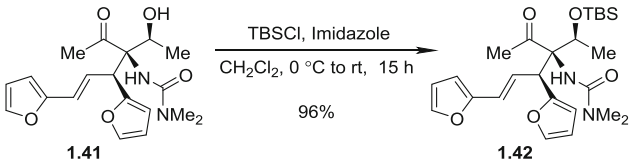
(3 × 20 mL). The combined organic extracts were washed with brine (200 mL), dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (50:50 hexanes:EtOAc) to give the desired product (1.22 g, 80 %) as a dark brown, viscous oil. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.31 (dd, J = 1.2, 7.2 Hz, 1H), 6.36 (dd, J = 7.2, 8.4 Hz, 1H), 6.30 (m, 2H), 6.22 (d, J = 3.0 Hz, 1H), 6.17–6.15 (m, 2H), 6.03 (s, 1H), 4.85 (d, J = 8.4 Hz, 1H), 2.86 (s, 6H), 2.13 (s, 3H), 2.03 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 201.8, 201.5, 156.6, 152.3, 151.6, 141.9, 123.7, 121.3, 111.1, 110.5, 108.8, 107.8, 79.4, 46.3, 36.1, 26.8, 26.1; **HRMS (ESI$^+$)** Calcd. for $C_{19}H_{22}N_2O_5$ + Na, 381.1426; Found, 381.1424; **IR** (thin film, cm^{-1}) 3414, 3118, 2929, 1708, 1656, 1511, 1357, 1196, 1012, 735; **TLC** (65:45 EtOAc: hexanes): R_f = 0.63.



(*E*)-3-(3-acetyl-4,6-di(furan-2-yl)-2-hydroxyhex-5-en-3-yl)-1,1-dimethylurea (1.41). A flame dried 100 mL round-bottomed flask was charged with diketone **1.36** (0.84 g, 2.17 mmol, 1.0 equiv) and THF (31 mL). The resulting mixture was cooled to −78 °C and LiAl(^{i}Bu)$_2$(O^{t}Bu)H (0.9 M in THF:hexanes, 6.02 mL, 5.42 mmol, 2.5 equiv) was added dropwise. TLC analysis of the resulting mixture showed remaining starting material, at which point an additional 2.89 mL (1.2 equiv) of LiAl(^{i}Bu)$_2$(O^{t}Bu)H was added. At this point, TLC analysis confirmed complete consumption of the starting material and the reaction was quenched via addition of saturated $HCl_{(aq)}$ (15 mL). The mixture was warmed to rt and extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo. The product was purified via flash chromatography (60:40 EtOAc:hexanes) afforded alcohol **1.41** (0.54 g, 63 %) as a brown solid in a 4:1 ratio of separable diastereomers. Slow evaporation (CH_2Cl_2) at room temperature provided crystals suitable for X-ray analysis. Analytical data: **mp**: 155–156 °C **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.4 (d, J = 0.9 Hz, 1H), 7.33 (d, J = 1.8 Hz, 1H), 6.35–6.33 (m, 3H), 6.30–6.18 (m, 4H), 5.28 (s, 1H), 4.32 (m, 1H), 3.93 (d, J = 8.4 Hz, 1H), 2.94 (s, 6H), 2.29 (s, 3H), 0.94 (d, J = 6.0 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 206.2, 159.2, 151.4, 150.9, 142.5, 142.4, 122.6, 122.0, 111.3, 110.7, 109.2, 108.9, 76.1, 70.1, 47.7, 36.7, 28.0, 18.1; **HRMS (ESI$^+$)** Calcd. for $C_{19}H_{24}N_2O_5$ + H, 361.1763; Found, 361.1762; **IR** (thin film, cm^{-1}) 3403, 3125, 2930, 1709, 1641, 1529, 1376, 1256, 1013, 766; **TLC** (65:45 EtOAc:hexanes): R_f = 0.40.

Crude ^{1}HNMR Spectrum of 1.41

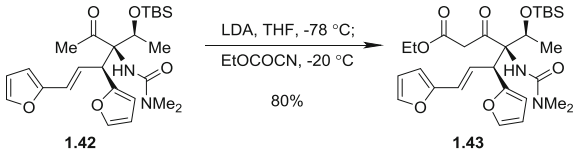




1.41 **1.42**

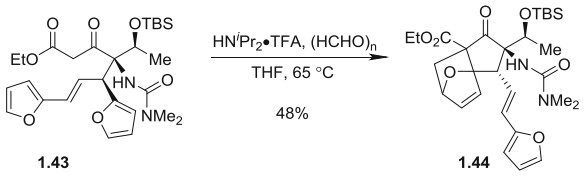
3-(*E*)-3-acetyl-2-((*tert*-butyldimethylsilyl)oxy)-4,6-di(furan-2-yl)hex-5-en-3-yl)-1,1-dimethylurea (1.42). A flame dried 25 mL round-bottomed flask was charged with alcohol **1.41** (0.54 g, 1.49 mmol, 1.00 equiv) and CH_2Cl_2 (7 mL). The resulting mixture was cooled to 0 °C and imidazole (0.41 g, 5.96 mmol, 4.00 equiv) was added followed by TBSCl (0.56 g, 3.73 g, 2.50 equiv). The reaction was warmed to rt and stirred until TLC analysis confirmed complete consumption of the starting material, typically 15 h. The reaction was quenched via addition of saturated $NaHCO_{3(aq)}$ (5 mL), and the resulting mixture was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with 1 M $HCl_{(aq)}$ (10 mL) and brine, dried with magnesium sulfate, and concentrated in vacuo.

The product was purified via flash chromatography (70:30 hexanes:EtOAc) to afford silyl ether **1.42** (0.67 g, 96 %) as a pale brown, viscous oil. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.30 (dd, *J* = 1.2, 9.0 Hz, 2H), 6.54 (dd, *J* = 7.8, 8.4 Hz, 1H), 6.31 (dd, *J* = 1.2, 1.8 Hz, 1H), 6.28 (dd, *J* = 1.2, 1.8 Hz, 1H), 6.13 (t, *J* = 3.6 Hz, 2H), 6.06 (d, *J* = 16.2 Hz, 1H), 5.79 (s, 1H), 4.85 (d, *J* = 8.4 Hz, 1H), 4.66 (q, *J* = 6.0 Hz, 1H), 2.85 (s, 6H), 2.30 (s, 3H), 1.16 (d, *J* = 6.6 Hz, 3H), 0.86 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 206.2, 157.4, 153.3, 152.7, 141.7, 141.2, 126.4, 120.5, 111.1, 110.2, 108.2, 107.4, 73.4, 70.7, 43.8, 36.3, 36.2, 27.7, 25.8, 19.1, 18.0, −3.9, −4.9; **HRMS (ESI$^+$)** Calcd. for $C_{25}H_{38}N_2O_5Si$ + H, 475.2628; Found, 475.2627; **IR** (thin film, cm^{-1}) 3434, 2953, 2856, 1711, 1658, 1503, 1361, 1253, 1149, 1011, 835, 732; **TLC** (65:45 EtOAc: hexanes): R_f = 0.90.



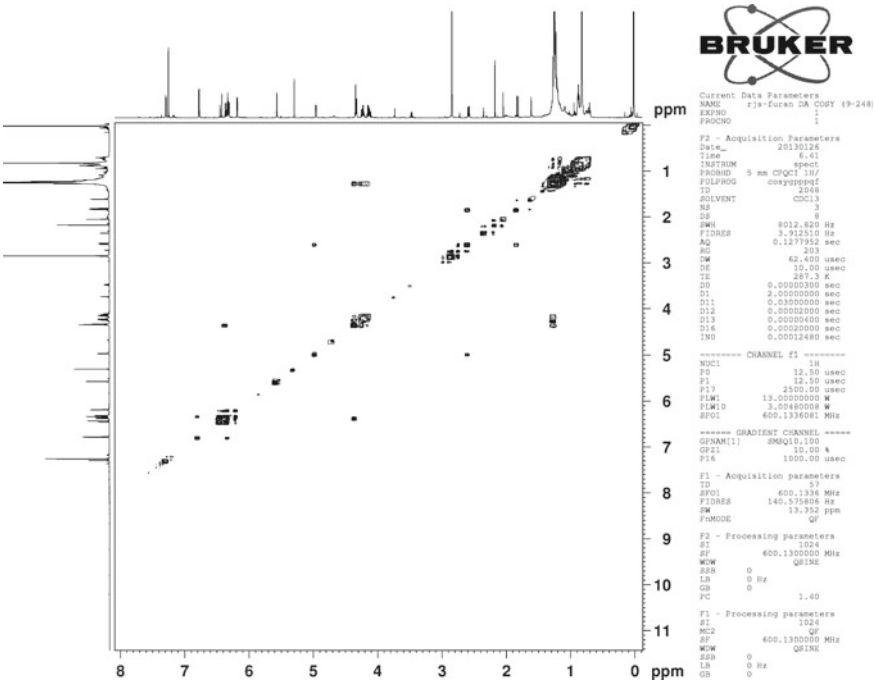
Ethyl (*tert*-butyldimethylsilyl)oxy)ethyl)-4-(3,3-dimethylureido)-5,7-di(furan-2-yl)-3-oxohept-6-enoate (1.43). A flame-dried 250-mL round-bottomed flask was charged with diisopropylamine (0.16 mL, 1.11 mmol, 3.50 equiv) and THF (2.5 mL). The resulting solution was cooled to 0 °C and *n*-butyllithium (1.72 M in hexanes, 0.65 mL, 1.11 mmol, 3.50 equiv) was added dropwise. The solution was stirred at 0 °C for 30 min and then cooled to −78 °C. A solution of ketone **1.42** (0.15 g, 0.32 mmol, 1.0 equiv) in THF (1 mL) was added dropwise, and the resulting solution was stirred at −78 °C for 45 min whereupon ethyl cyanoformate (0.05 mL, 0.52 mmol, 1.7 equiv) was added dropwise. The reaction was allowed to slowly warm to −20 °C over 2 h and quenched via addition of saturated $NH_4Cl_{(aq.)}$ (4 mL). The mixture was warmed to rt and extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo. The product was purified via flash chromatography (80:20 to 70:30 hexanes:EtOAc) to afford ketoester **1.43** (0.14 g, 80 %) as a pale brown, viscous oil. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.30 (d, *J* = 1.2, Hz, 1H), 7.27 (d, *J* = 1.2 Hz, 1H), 6.46 (dd, *J* = 7.8, 8.4 Hz, 1H), 6.29 (m, 2H), 6.16 (d, *J* = 3.0 Hz, 1H), 6.11 (d, *J* = 3.6 Hz, 1H), 5.99 (d, *J* = 15.6 Hz, 1H), 5.79 (s, 1H), 4.73 (d, *J* = 7.8 Hz, 1H), 4.57 (q, *J* = 6.0 Hz, 1H), 4.11 (m, 2H), 3.80 (d, *J* = 15.6 Hz, 1H), 3.72 (d, *J* = 15.6 Hz, 1H), 2.86 (s, 6H), 1.21 (t, *J* = 7.2 Hz, 3H),

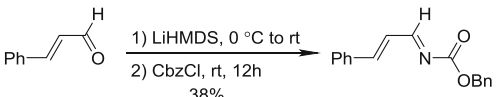
1.17 (d, J = 6.0 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 200.3, 167.8, 157.4, 153.1, 152.8, 141.6, 141.2, 126.4, 120.3, 111.0, 110.3, 108.3, 107.2, 73.0, 70.1, 61.0, 45.5, 43.6, 36.3, 36.2, 29.6, 25.8, 18.5, 17.9, 14.0, −4.2, −4.9; **HRMS (ESI$^+$)** Calcd. for $C_{28}H_{42}N_2O_7Si$ + Na, 569.2659; Found, 569.2657; **IR** (thin film, cm^{-1}) 3432, 2929, 2856, 1744, 1711, 1657, 1502, 1367, 1256, 1150, 1012, 836, 734; **TLC** (65:45 EtOAc:hexanes): R_f = 0.95.



Ethyl (*tert*-butyldimethylsilyl)oxy)ethyl)-2-(3,3-dimethylureido)-3-((*E*)-2-(furan-2-yl)vinyl)-1-oxo-2,3,6,7-tetrahydro-3a,6-epoxyindene-7a(1H)-carboxylate (1.44). A 5 mL dram vial was charged with ketoester **1.43** (0.035 g, 0.064 mmol, 1.00 equiv) and THF (1.5 mL). To the resulting solution was added diisopropylammonium trifluoroacetate (0.014 g, 0.064 mmol, 1.00 equiv), and lastly $(HCHO)_n$ (0.009 g, 0.26 mmol, 4.00 equiv), and the reaction was warmed to 65 °C for 15 h. The resulting solution was cooled to rt and diluted with H_2O (10 mL) and Et_2O (10 mL). The resulting mixture was extracted with Et_2O (3 × 10 mL), and the combined organic extracts were washed with 1 M $HCl_{(aq.)}$ (5 mL), 1 M $NaOH_{(aq.)}$ (5 mL), and brine (5 mL), washed with magnesium sulfate and concentrated in vacuo. The product was purified via flash chromatography (80:20 to 70:30 hexanes: EtOAc) to afford tricycle **1.44** (0.017 g, 48 %) as a clear, viscous oil. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.30 (d, J = 1.8 Hz, 1H), 6.78 (d, J = 6.0 Hz, 1H), 6.44 (d, J = 15,6 Hz, 1H), 6.38–6.31 (m, 3H), 6.19 (d, J = 3.0 Hz, 1H), 5.57 (s, 1H), 4.96 (dd, J = 6.0, 3.0 Hz, 1H), 4.34 (m, 2H), 4.24 (m, 1H), 4.14 (m, 1H), 2.85 (s, 6H), 2.59 (dd, J = 4.8, 7.2 Hz, 1H), 1.83 (d, J = 12.0 Hz, 1H), 1.27–1.21 (m, 6H), 0.83 (s, 9H), 0.02 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 206.8, 169.4, 156.8, 152.8, 141.6, 137.1, 135.0, 123.9, 121.0, 111.0, 107.2, 94.0, 78.2, 72.8, 71.7, 66.4, 61.3, 48.2, 39.8, 36.2, 29.7, 25.7, 21.8, 17.8, 14.1, 14.0, −4.0, −4.7; **HRMS (ESI$^+$)** Calcd. for $C_{29}H_{42}N_2O_7Si$ + H, 559.2840; Found, 559.2881; **IR** (thin film, cm^{-1}) 3438, 2956, 2925, 2853, 1759, 1655, 1508, 1463, 1254, 1088, 836, 733; **TLC** (65:45 EtOAc:hexanes): R_f = 0.95.

^{1}H COSY Spectrum of 1.44

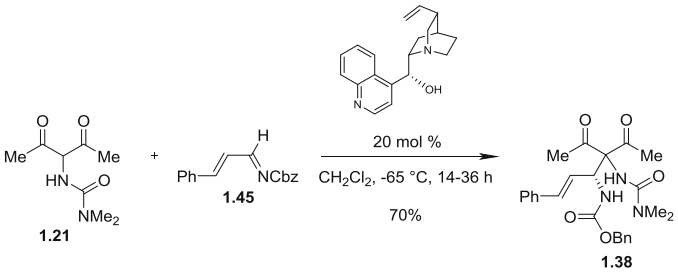




1.45

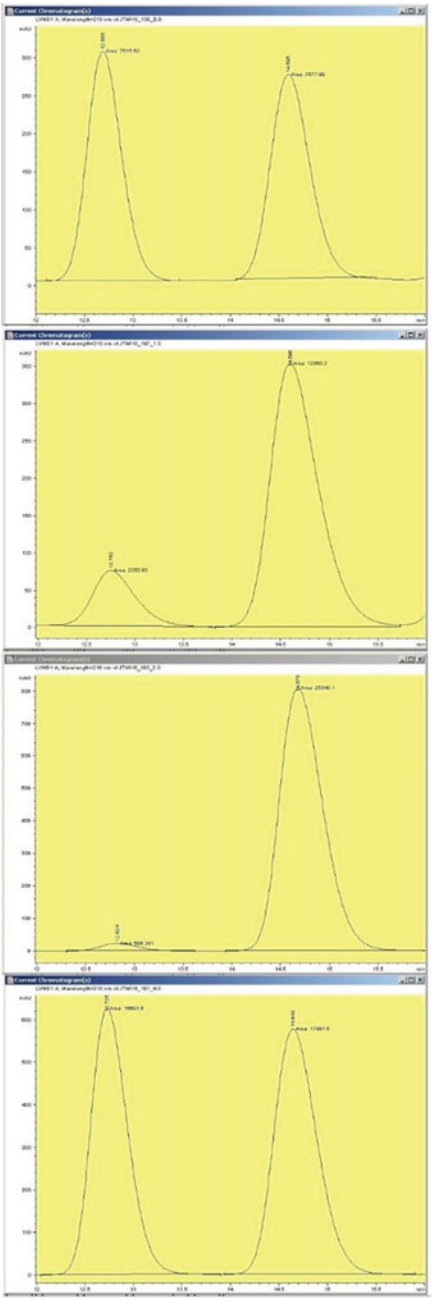
Benzyl ((E)-3-phenylallylidene)carbamate (1.45): A 500-mL round-bottomed flask was charged with N, N-hexamethyldisilazane (20.6 mL, 98.4 mmol, 1.3 equiv) and was cooled to 0 °C under a nitrogen atmostphere. nBuLi (60 mL, 99 mmol, 1.654 M in Hexanes, 1.3 equiv) was added dropwise, and the resulting mixture was warmed to rt and stirred for 30 min. The freshly prepared LiHMDS solution was cooled to 0 °C, and freshly distilled trans-cinnamaldehyde (9.5 mL, 75.7 mmol, 1.0 equiv) was added dropwise. The resulting mixture was warmed to rt and stirred for 45 min. The reaction mixture was concentrated in vacuo to remove hexanes, and the residue was redissolved in CH_2Cl_2 (96 mL) under a nitrogen atmosphere. The reaction mixture was cooled to 0 °C, and CbzCl (14.2 mL, 99 mmol, 1.3 equiv) was added dropwise. The resulting mixture was warmed to rt and stirred overnight. The reaction was diluted with hexanes (75 mL), filtered

through Celite, and concentrated in vacuo. The resulting orange residue was triturated (90:10 Hexanes:EtOAc) and the filtrate removed to give aldimine **1.45** as a pale orange solid. Analytical data matched those reported in the literature [50].



(*R*,*E*)-benzyl (4-acetyl-4-(3,3-dimethylureido)-5-oxo-1-phenylhex-1-en-3-yl) carbamate (1.38): A flame-dried 250-mL round-bottomed flask was charged with urea **1.21** (2.38 g, 12.28 mmol, 1.0 equiv), cinchonidine (0.72 g, 2.46 mmol, 0.2 equiv), and CH_2Cl_2 (65 mL). The resulting suspension was cooled to −78 °C and a cold solution of imine **1.45** (5.1 g, 19.24 mmol, 1.5 equiv) in CH_2Cl_2 (35 mL) was added via cannula transfer. The reaction was warmed to −65 °C and stirred until complete consumption of urea **1.21** was indicated by TLC analysis, typically 14–36 h (scale-dependent). The crude reaction was filtered through a short silica plug and rinsed with EtOAc (300 mL). The filtrate was concentrated in vacuo to give a pale yellow foam with a 84:16 enantiomeric ratio. Crystalline *racemic* product was isolated via trituration with 60:40 (v/v) hexanes:EtOAc (300 mL). The analytically-pure white solid was removed by filtration (1.33 g, 24 %) and the filtrate was concentrated in vacuo to give a yellow oil. The crude oil was purified by flash chromatography (60:40 to 50:50 hexanes:EtOAc) affording diketone **1.38** as a pale yellow foam (3.87 g, 70 %, 97:3 er). The enantiomeric ratio was determined by SFC analysis (Chiralcel, OD, 9.0 % MeOH, 1.5 mL/min, 150 bar, 210 nm; t_R-minor 12.8 min, t_R-major 14.7 min). Analytical data: $[\alpha]_D^{19}$ +16.5 (*c* = 1.00, $CHCl_3$); **mp** (*racemate*) 130–134 °C; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.37–7.21 (m, 10H), 7.07 (br d, *J* = 6.0 Hz, 1H), 6.59 (d, *J* = 16.2 Hz, 1H), 6.50 (s, 1H), 5.96 (dd, *J* = 7.2, 16.2 Hz, 1H), 5.40 (t, *J* = 7.2 Hz, 1H), 5.14 (d, *J* = 12.0 Hz, 1H), 5.11 (d, *J* = 12.0 Hz, 1H), 2.97 (s, 6H), 2.28 (s, 3H), 2.14 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 200.9, 200.4, 157.6, 156.7, 136.9, 136.5, 133.2, 128.7, 128.6, 128.2, 128.2, 128.1, 126.9, 124.6, 81.7, 67.0, 57.2, 36.8, 26.2, 25.4; **HRMS (ESI$^+$)** Calcd. For $C_{25}H_{29}N_3O_5$ + H, 452.2187; Found, 452.2212; **IR** (thin film, cm^{-1}) 3418, 2243, 1702, 1635, 1507, 1371, 1249, 1066, 912, 693; **TLC** (60:40 hexanes:EtOAc): R_f = 0.20.

Enantioselectivity Assays of Mannich Reaction (1.21 → 1.38):



Enantioselective Mannich Reaction - SFC Traces

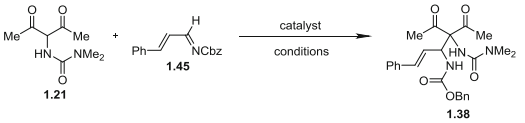
Racemate: 50:50 er

Crude Reaction: 16:84 er

Purified Reaction (after trituration): 2:98 er

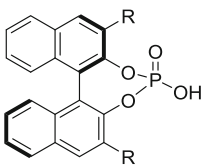
Residual Solid (trituration): 48:52 er

Enantioselectivitiy Screenings for Asymmetric Mannich Reaction

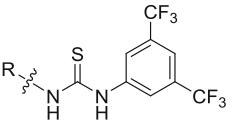


1.21 1.45 1.38

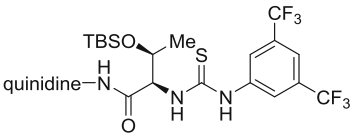
Entry	Urea (equiv)	Imine (equiv)	Catalyst (mol%)	Conditions	Result (er)
1	1.0	2.5	Cinchonidine (20)	CH_2Cl_2, 1d, −35 °C	24:76
2	1.0	2.5	Cinchonidine (20)	CH_2Cl_2, 4d, −40 °C	20:80
3	1.0	2.5	Cinchonidine (20)	CH_2Cl_2, 1d, rt	30:70
4	1.0	2.5	Cinchonine (20)	CH_2Cl_2, 4d, −40 °C	75:25
5	1.0	2.5	Quinine (20)	CH_2Cl_2, 4d, −40 °C	37:63
6	1.0	2.5	Quinidine (20)	CH_2Cl_2, 4d, −40 °C	66:34
7	1.0	2.5	$(DHQ)_2PHAL$ (20)	CH_2Cl_2, 4d, −40 °C	60:40
8	1.0	2.5	$(DHQD)_2PHAL$ (20)	CH_2Cl_2, 4d, −40 °C	rac.
9	1.0	2.5	**1.49a** (20)	CH_2Cl_2, 1d, −40 °C	44:56
10	1.0	2.5	**1.49b** (20)	CH_2Cl_2, 1d, −40 °C	33:67
11	1.0	2.5	**1.47a** (20)	CH_2Cl_2, 1d, −40 °C	83:17
12	1.0	2.5	**1.47b** (20)	CH_2Cl_2, 1d, −40 °C	20:80
13	1.0	2.5	**1.47c** (20)	CH_2Cl_2, 1d, −40 °C	39:61
14	1.0	2.5	**1.47d** (20)	CH_2Cl_2, 1d, −40 °C	72:28
15	1.0	1.0	**1.48** (20)	CH_2Cl_2, 1d, −40 °C	rac.
16	1.0	1.0	**S2** (20)	CH_2Cl_2, 1d, 0 °C	49:51
17	1.0	1.0	**S2** (20)	THF, 1d, 0 °C	54:46
18	1.0	1.0	**S2** (20)	toluene, 1d, 0 °C	rac.
19	1.0	1.0	**S3** (20)	CH_2Cl_2, 1d, 0 °C	49:51
20	1.0	1.0	**S3** (20)	THF, 1d, 0 °C	46:54
21	1.0	1.0	**S3** (20)	toluene, 1d, 0 °C	47:53
22	1.0	1.5	**1.52** (20)	CH_2Cl_2, 1d	rac.
23	1.0	1.5	**S4** (20)	THF, 1d, −20 °C	rac.
24	1.0	1.0	**1.51** (5)	acetone, 3 h	67:33
25	1.0	1.0	**S5**(20)	toluene, 2d, −78 °C	52:48
26	1.0	1.0	**S6** (20)	THF, 8 h	rac.
27	1.0	1.5	**1.50** (10)	CH_2Cl_2, 1d, −78 °C	rac.
28	1.0	1.0	Cinchonidine (20)	CH_2Cl_2, 1d, −65 °C	18:82
29	1.0	1.0	Cinchonidine (20)	Et_2O, 1d, −40 °C	35:65
30	1.0	1.0	Cinchonidine (20)	toluene, 1d, −40 °C	36:64
31	1.0	1.0	Cinchonidine (20)	THF, 1d, −40 °C	33:67
32	1.0	1.0	Cinchonidine (20)	CH_2Cl_2, 17 h, −45 °C	23:77
33	2.0	1.0	Cinchonidine (20)	CH_2Cl_2, 17 h, −45 °C	23:77
34	1.0	1.5	Cinchonidine (20)	CH_2Cl_2, 14 h, −78 to −65 °C	16:84



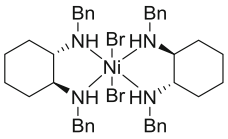
R = H 1.49a
biphenyl 1.49b



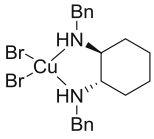
R = quinine 1.47a
quinidine 1.47b
cinchonine 1.47c
cinchonidine 1.47d



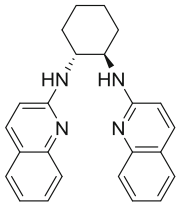
1.48



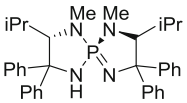
S2



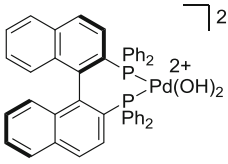
S3



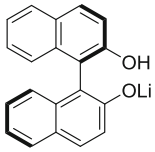
1.52



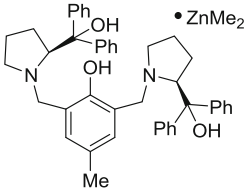
S4



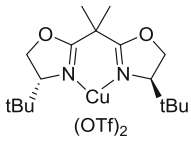
1.51



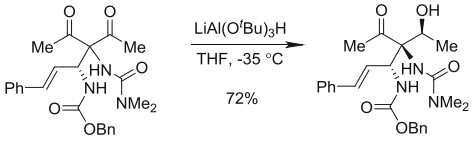
S5



S6



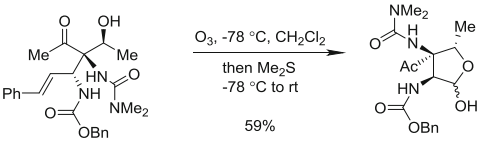
1.50



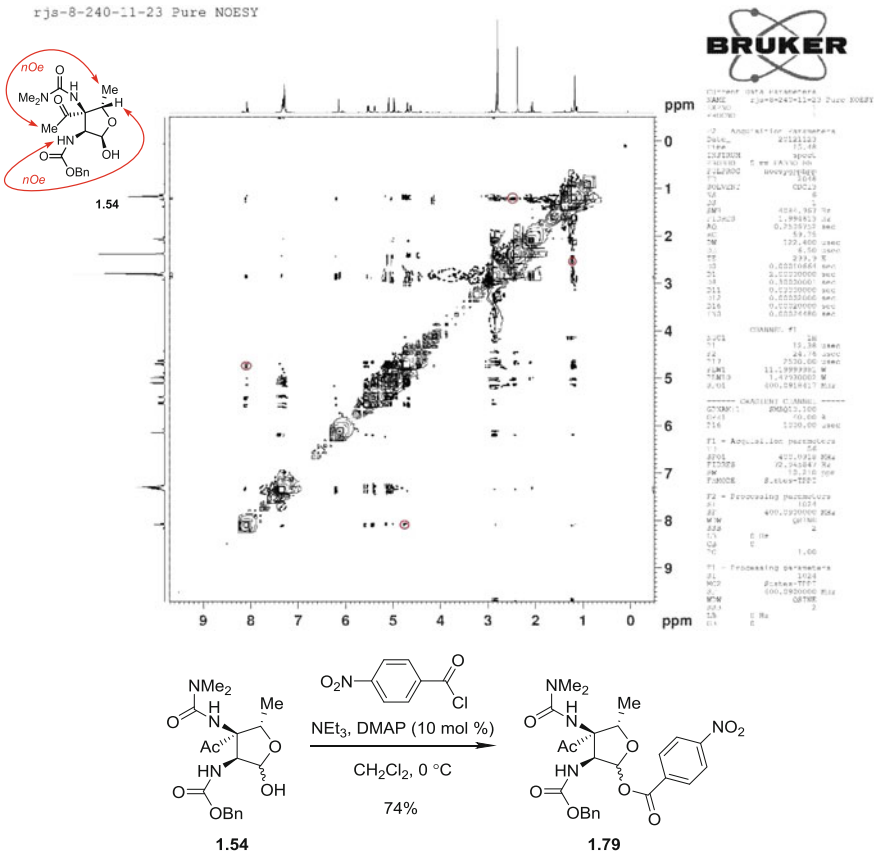
1.38 1.53

Benzyl ((3*R*,4*R*,5*S*,*E*)-4-acetyl-4-(3,3-dimethylureido)-5-hydroxy-1-phenylhex-1-en-3-yl) carbamate (1.53): A flame-dried 250-mL round-bottomed flask was charged with diketone **1.38** (8.5 g, 18.8 mmol, 1.0 equiv) and THF (188 mL). The solution was cooled to −78 °C, and lithium tri-*tert*-butoxyaluminum hydride (1.1 M in THF, 25.7 mL, 28.2 mmol, 2.0 equiv) was added dropwise. The resulting mixture was warmed to −35 °C and stirred until complete consumption of diketone **1.38** was indicated by TLC analysis, typically 12 h. The reaction was quenched by

the addition of 1 M $HCl_{(aq)}$ (50 mL) and the biphasic mixture was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried with magnesium sulfate, and concentrated in vacuo. The crude product was purified via flash chromatography (50:50 to 60:40 EtOAc/hexanes) to afford alcohol **1.53** as a yellow viscous oil with >10:1 ratio of **1.53**:Σ(other diastereomers) (6.2 g, 72 %). Analytical data: $[\alpha]_D^{19}$ +19.5 (*c* = 1.00, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.36–7.25 (m, 10H), 6.67 (d, *J* = 16.2 Hz, 1H), 6.59 (br s, 1H), 6.17 (dd, *J* = 9.0, 15.6 Hz, 1H), 5.47 (s, 1H), 5.11 (d, *J* = 12.0 Hz, 1H), 5.07 (d, *J* = 12.0 Hz, 1H), 4.70 (t, *J* = 9.0 Hz, 1H), 4.60 (br s, 1H), 4.30 (br s, 1 H), 2.90 (s, 6H), 2.28 (s, 3H), 1.23 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 207.9, 158.4, 156.1, 136.2, 135.9, 133.8, 128.5, 128.3, 128.0, 127.9, 127.8, 126.5, 125.5, 73.7, 69.8, 66.8, 57.2, 36.5, 27.6, 18.6; **HRMS (ESI$^+$)** Calcd. for $C_{25}H_{31}N_3O_5$ + H, 454.2344; Found, 454.2368; **IR** (thin film, cm^{-1}) 3410, 2938, 2359, 2248, 1700, 1637, 1520, 1235, 909, 731; **TLC** (50:50 hexanes:EtOAc): R_f = 0.20.

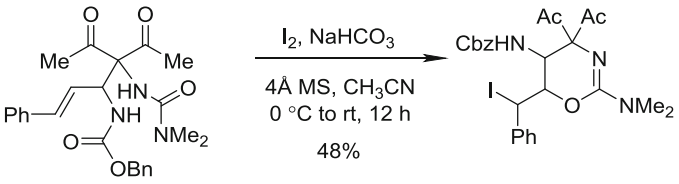


Benzyl ((3*S*,4*R*,5*S*)-4-acetyl-4-(3,3-dimethylureido)-2-hydroxy-5-methyl tetrahydro- furan-3-yl)carbamate (1.54): A 250-mL round-bottomed flask was charged with alcohol **1.53** (1.4 g, 3.1 mmol, 1.0 equiv) and CH_2Cl_2 (62 mL). The resulting solution was cooled to −78 °C, and a stream of O_3 was bubbled through the solution until a blue color was observed, typically 5 min. The mixture was sparged with O_2 for 5 min, and Me_2S (0.9 mL, 12.4 mmol, 4.0 equiv) was added. The resulting mixture was warmed to rt and stirred for 12 h and concentrated in vacuo. Flash chromatography (60:40 EtOAc:hexanes) afforded an inseparable ∼5:1 diastereomeric mixture of lactols (**1.54**) (0.69 g, 58 %) as a viscous oil. Analytical data: $[\alpha]_D^{19}$ +18.3 (*c* = 1.00, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.08 (d, *J* = 12.0 Hz, 1H), 7.37–7.28 (m, 5H), 6.15 (br s, 1H), 5.53 (dd, *J* = 6.0, 6.6 Hz, 1H), 5.39 (d, *J* = 8.4 Hz, 1H), 5.10 (d, *J* = 12.6 Hz, 1H), 4.98 (d, *J* = 12.6 Hz, 1H), 4.70 (q, *J* = 7.2 Hz, 1H), 4.63 (dd, *J* = 3.0, 6.0 Hz, 1H), 2.83 (s, 1H), 2.80 (s, 6H), 2.38 (s, 3H), 1.17 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 204.6, 157.0, 156.2, 136.1, 128.4, 128.1, 127.9, 95.9, 71.4, 66.7, 59.3, 36.0, 26.6, 14.1; **LRMS (ESI$^+$)** Calcd. for $C_{18}H_{25}N_3O_6$ + H, 380.18; Found, 380.17; **IR** (thin film, cm^{-1}) 3390, 2938, 2066, 1700, 1636, 1522, 1351, 1230, 1063, 752; **TLC** (60:40 EtOAc:hexanes): R_f = 0.35.



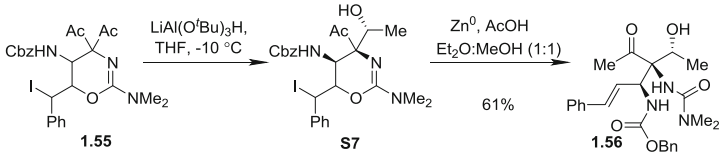
(3*S*,4*R*,5*S*)-4-Acetyl-3-(((benzyloxy)carbonyl)amino)-4-(3,3-dimethylureido)-5-methyl- tetrahydrofuran-2-yl 4-nitrobenzoate (1.79): A flame-dried, 50-mL round-bottomed flask was charged with diastereomeric lactols (**1.54**) (0.69 g, 1.8 mmol, 1.0 equiv) and CH_2Cl_2 (18 mL). The resulting solution was cooled to 0 °C and NEt_3 (0.76 mL, 5.4 mmol, 3.0 equiv), DMAP (0.02 g, 0.18 mmol, 0.1 equiv), and 4-nitrobenzoyl chloride (0.51 g, 2.7 mmol, 1.5 equiv) were added sequentially. The reaction was stirred at 0 °C until TLC analysis indicated complete consumption of the lactol, typically 30 min. H_2O (10 mL) was added to the reaction and the resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo. The crude residue was purified by flash chromatography (30:70 hexanes:EtOAc) afforded a ~5:1 diasteromeric mixture of 4-nitrobenzoate **1.79** (0.71 g, 74 %) as a yellow powder. Slow evaporation (MeOH) at room temperature afforded crystals suitable for X-ray analysis. (Note: to obtain analytically pure **1.79**, a small portion of the fractions were collected from column chromatography, resulting in a discrepancy in the diastereomeric ratio.) Analytical data: $[\alpha]_D^{19}$ −11.8 (c = 1.00, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.42

(d, J = 9.0 Hz, 2H), 8.27 (d, J = 9.0 Hz, 2H), 7.31–7.24 (m, 5H), 6.82 (d, J = 6.0 Hz, 1H), 6.66 (d, J = 9.0 Hz, 1H), 5.94 (br s, 1H), 5.13 (q, J = 6.6 Hz, 1H), 5.06 (d, J = 12.0 Hz, 1H), 5.02 (d, J = 16.2 Hz, 1H), 4.99 (m, 1H), 2.90 (s, 6H), 2.38 (s, 3H), 1.17 (d, J = 6.6 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 203.8, 163.5, 157.4, 156.6, 150.6, 136.1, 135.0, 131.2, 128.4, 128.3, 128.1, 127.9, 123.5, 95.4, 72.5, 66.7, 57.9, 36.2, 26.4, 14.4; **LRMS (ESI$^+$)** Calcd. for $C_{25}H_{28}N_4O_9$ + H, 529.19; Found, 529.20; **IR** (thin film, cm^{-1}) 3393, 3113, 2944, 1715, 1637, 1526, 1349, 1271, 1081, 1011, 736; **TLC** (70:30 EtOAc:Hexanes): R_f = 0.30.



1.38 **1.55**

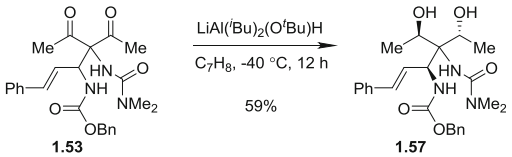
Benzyl (4,4-diacetyl-2-(dimethylamino)-6-(iodo(phenyl)methyl)-5,6-dihydro-4H-1,3-oxazin-5-yl)carbamate (1.55). A flame dried 100 mL round-bottomed flask was charged with diketone **1.38** (0.20 g, 0.44 mmol, 1.00 equiv), 4Å molecular sieves (4.0 g), $NaHCO_3$ (0.74 g, 8.86 mmol, 20 equiv), and CH_3CN (24.6 mL). The resulting mixture was cooled to 0 °C and I_2 (0.35 g, 1.37 mmol, 3.1 equiv) was added. The reaction mixture was warmed to rt and stirred until TLC analysis confirmed complete consumption of the starting material, typically 12 h. The reaction was quenched via addition of saturated $NaHCO_{3(aq.)}$ (20 mL), and the resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with saturated $Na_2S_2O_{3(aq.)}$ (30 mL) and brine (20 mL), dried with magnesium sulfate, and concentrated in vacuo. The product was purified by flash chromatography (60:40 hexanes:EtOAc) to afford imidate **1.55** (0.12 g, 48 %) as a clear viscous oil in a 5:1 ratio of inseparable diastereomers. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.39–7.29 (m, 10H), 5.71 (d, J = 10.2 Hz, 1H), 5.18 (d, J = 12.6 Hz, 1H), 5.08 (d, J = 12.6 Hz, 1H), 4.94 (t, J = 11.4 Hz, 1H), 4.80 (d, J = 10.8 Hz, 1H), 4.18 (t, J = 10.8 Hz, 1H), 2.98 (s, 1H), 2.17 (s, 3H), 1.53 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 209.8, 162.2, 155.14, 139.0, 136.4, 128.8, 128.6, 128.4, 128.3, 128.2, 128.1, 127.5, 109.0, 83.4, 80.0, 66.9, 56.6, 37.3, 34.3, 28.2, 20.5; **HRMS (ESI$^+$)** Calcd. for $C_{25}H_{28}IN_3O_5$ + Na, 600.0971; Found, 600.0971; **IR** (thin film, cm^{-1}) 3407, 3033, 2942, 1724, 1661, 1497, 1239, 1085, 915, 877; **TLC** (65:45 EtOAc:hexanes): R_f = 0.75.



1.55 **S7** **1.56**

Benzyl (4-acetyl-4-(3,3-dimethylureido)-5-hydroxy-1-phenylhex-1-en-3-yl) carbamate (1.56). A flame dried 10 mL round-bottomed flask was charged with imidate **1.55** (0.13 g, 0.22 mmol, 1.00 equiv), and THF (2.3 mL). The resulting mixture was cooled to −78 °C and lithium tri-*tert*-butoxyaluminum hydride (1.1 M in THF, 0.51 mL, 0.56 mmol, 2.50 equiv) was added dropwise. The resulting mixture was slowly warmed to −10 °C and stirred overnight at that temperature. The reaction was then quenched via addition of saturated $NH_4Cl_{(aq.)}$ (4 mL), and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried with magnesium sulfate, and concentrated in vacuo to afford the crude intermediate monoalcohol **S7**, which was used in the next step without further purification.

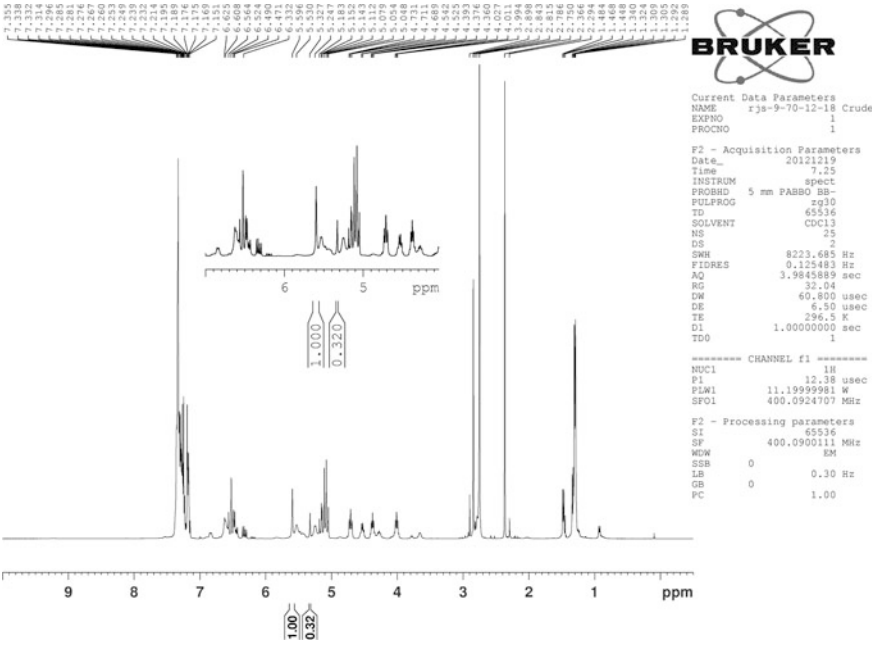
The requisite alcohol was dissolved in Et_2O (1.6 mL) and MeOH (1.6 mL) and transferred to a 25 mL round-bottomed flask. Zinc powder (0.07 g, 1.09 mmol, 5.00 equiv) and AcOH (0.075 mL, 1.32 mmol, 6.00 equiv) were added sequentially, and the reaction was allowed to stir for 1 h at rt. The resulting mixture was filtered through a pad of Celite and concentrated in vacuo. The product was purified via flash chromatography (50:50 to 60:40 EtOAc:hexanes) to afford monoalcohol **1.56** (0.061 g, 61 %) as clear viscous oil as a single diastereomer. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.36–7.23 (m, 10H), 6.57 (d, J = 16.2 Hz, 1H), 6.52 (d, J = 7.2 Hz, 1H), 6.43 (dd, J = 5.4, 10.2 Hz, 1H), 6.20 (s, 1H), 5.2 (t, J = 7.2 Hz, 1H), 5.14 (d, J = 12.6 Hz, 1H), 5.07 (d, J = 12.0 Hz, 1H), 4.54 (t, J = 7.8 Hz, 1H), 2.83 (s, 6H), 2.29 (s, 3H), 1.10 (d, J = 6.6 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 205.5, 158.1, 156.0, 136.3, 136.1, 131.9, 128.6, 128.5, 128.2, 128.2, 127.9, 126.6, 125.8, 75.9, 68.2, 67.0, 56.2, 36.5, 36.4, 29.7, 27.1, 19.2; **HRMS (ESI$^+$)** Calcd. for $C_{25}H_{31}N_3O_5$ + Na, 476.2161; Found, 476.2176; **IR** (thin film, cm^{-1}) 3390, 2925, 2097, 1709, 1631, 1563, 1528, 1501, 1244, 1051; **TLC** (65:45 EtOAc:hexanes): R_f = 0.55.



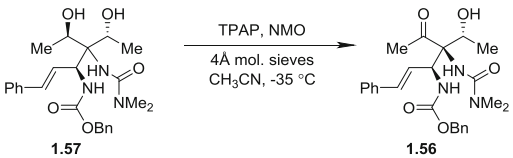
Benzyl (*E*)-(4-(3,3-dimethylureido)-5-hydroxy-4-(1-hydroxyethyl)-1-phenylhex-1-en-3-yl)carbamate (1.57). A flame dried, 50 mL round-bottomed flask was charged with diketone **1.53** (0.50 g, 1.11 mmol, 1.00 equiv) and C_7H_8 (8.6 mL). The resulting solution was cooled to −78 °C, and LiAl(^{i}Bu)$_2$(O^{t}Bu)H (0.9 M in THF:Hexanes, 7.38 mL, 6.66 mmol, 6.0 equiv) was added dropwise. The reaction was then warmed to −40 °C and stirred until TLC analysis confirmed complete consumption of the starting material, typically 12 h. The reaction was quenched via addition of 1 M $HCl_{(aq.)}$ (10 mL), and the resulting mixture was extracted with Et_2O (3 × 15 mL). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo. The product was purified via flash chromatography (60:40 EtOAc:hexanes) to afford diol **1.57** (0.30 g, 59 %) as a clear, viscous

oil with a 3:1 ratio of diastereomers. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.34–7.21 (m, 10H), 6.60 (s, 1H), 6.53 (d, *J* = 16.2 Hz, 1H), 6.46 (dd, *J* = 7.8, 7.8 Hz, 1H), 5.58 (s, 1H), 5.47 (d, *J* = 16.2 Hz, 1H), 5.26 (br s, 1H), 5.11 (d, *J* = 12.6 Hz, 1H), 5.06 (d, *J* = 12.6 Hz, 1H), 4.69 (t, *J* = 8.4 Hz, 1H), 4.37 (t, *J* = 6.6 Hz, 1H), 4.00 (t, *J* = 6.6 Hz, 1H), 2.74 (s, 6H), 1.29 (dd, *J* = 2.4, 4.2 Hz, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 158.6, 156.4, 136.3, 136.2, 132.2, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 126.4, 70.0, 67.7, 66.9, 66.8, 57.2, 36.4, 18.5, 18.0; **HRMS (ESI$^+$)** Calcd. for $C_{25}H_{33}N_3O_5$ + Na, 478.2318; Found, 478.2322; **IR** (thin film, cm^{-1}) 3408, 2090, 1691, 1630, 1545, 1378, 1234, 1066; **TLC** (65:45 EtOAc:hexanes): R_f = 0.50.

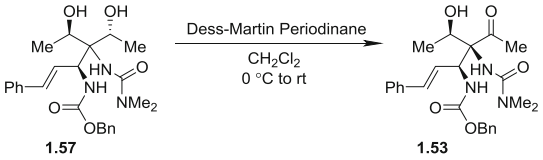
Crude ^{1}H NMR Spectrum of 1.57



Synthesis of monoalcohols 1.56 and 1.53 from selective oxidation of *trans*-diol 1.57.

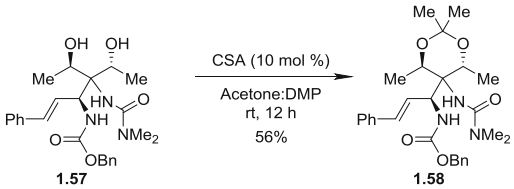


A flame dried 5 mL dram vial was charged with diol **1.57** (0.025 g, 0.06 mmol, 1.00 equiv), CH_3CN (0.8 mL), and 4 Å molecular sieves (0.027 g). The resulting mixture was cooled to −40 °C and NMO (0.012 g, 0.1 mmol, 1.80 equiv) was added followed by a single flake of tetra-*N*-propylammonium perruthenate. The reaction was allowed to stir at −40 °C for 12 h then diluted with CH_2Cl_2 (2 mL) and filtered through a 1-in. Monstr-Pette plug of silica gel with EtOAc (5 mL) and concentrated. The product was purified via flash chromatography (50:50 hexanes: EtOAc) to afford monoalcohol **1.56** (0.012 g, 48 %) as a clear viscous oil. Spectral data were identical with the monoalcohol isolated from reduction of **1.55**.



1.57 **1.53**

A 5 mL dram vial was charged with diol **1.57** (0.02 g, 0.044 mmol, 1.00 equiv) and CH_2Cl_2 (1 mL). The resulting solution was cooled to 0 °C and Dess-Martin Periodinane (0.016 g, 0.04 mmol, 0.9 equiv) was added. The reaction was allowed to stir for 2 h upon which TLC analysis confirmed no reaction had taken place. The reaction was then slowly warmed to room temperature and stirred for 1 h. A 1:1 mixture of saturated $NaHCO_{3(aq.)}$:saturated $Na_2S_2O_{3(aq.)}$ (2 mL) was added, and the mixture was extracted with Et_2O (3 × 5 mL), dried with magnesium sulfate, and concentrated in vacuo. ^{1}H NMR analysis showed ∼80 % conversion of the starting material exclusively to monoalochol **1.53,** matching spectral data to that of the reduction of **1.38**. Arriving at this result, no further optimization of this reaction was attempted.

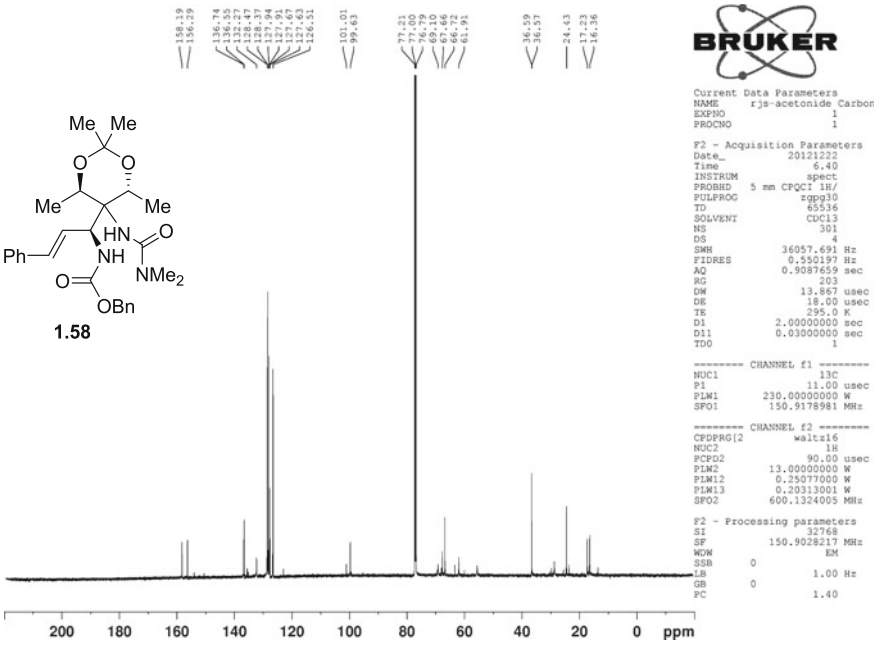


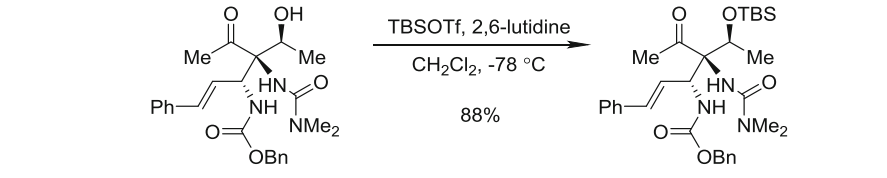
1.57 **1.58**

Benzyl (*E*)-(1-(5-(3,3-dimethylureido)-2,2,4,6-tetramethyl-1,3-dioxan-5-yl)-3-phenylallyl)carbamate (1.58). A 20 mL scintillation vial was charged with diol **1.57** (0.07 g, 0.16 mmol, 1.00 equiv), acetone (1 mL) and 2,2-dimethoxypropane (1 mL) with stirring. Camphorsulfonic acid (0.005 g, 0.016 g, 0.1 equiv) was added, and the reaction was allowed to stir until TLC analysis confirmed complete consumption of the starting material, typically 12 h. The reaction mixture was quenched with saturated $NaHCO_{3(aq.)}$ (2 mL) and the resulting mixture was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo. The product was purified via flash chromatography (50:50 hexanes:EtOAc) to afford acetonide **1.58** (0.04 g, 56 %) as a clear, viscous oil.

Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.38–7.22 (m, 10H), 6.19 (d, J = 16.2 Hz, 1H), 6.53 (dd, J = 7.2, 8.4 Hz, 1H), 5.25 (s, 1H), 5.14 (d, J = 12.0 Hz, 1H), 5.06 (d, J = 12.0 Hz, 1H), 4.71 (d, J = 5.4 Hz, 1H), 4.38 (t, J = 8.4 Hz, 1H), 4.22 (q, J = 6.0 Hz, 1H), 2.92 (s, 6H), 1.43 (s, 3H), 1.41 (s, 3H), 1.38 (d, J = 7.2 Hz, 3H), 1.21 (d, J = 6.0 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 158.2, 156.3, 136.7, 136.6, 132.3, 128.5, 128.4, 127.9, 127.7, 127.6, 126.5, 101.0, 99.6, 67.7, 66.7, 36.6, 24.4, 17.2, 16.4; **HRMS (ESI$^+$)** Calcd. for $C_{28}H_{37}N_3O_5$ + Na, 518.2631; Found, 518.2636; **IR** (thin film, cm^{-1}) 3421, 3305, 3057, 2987, 1709, 1650, 1524, 1380, 1225, 1067, 736; **TLC** (65:45 EtOAc:hexanes): R_f = 0.60.

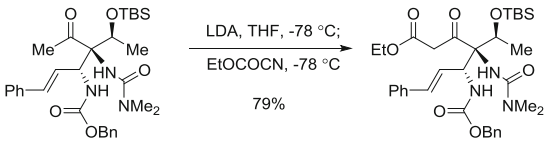
^{13}C NMR Spectrum of 1.58





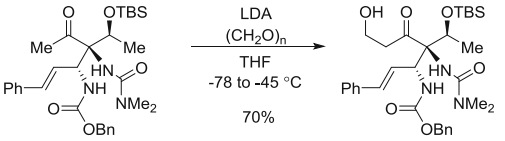
1.58 **1.53** **1.64**

Benzyl ((3*R*,4*R*,5*S*,*E*)-4-acetyl-5-((*tert*-butyldimethylsilyl)oxy)-4-(3,3-dimethylureido)-1-phenylhex-1-en-3-yl)carbamate (1.64): A flame-dried 100-mL round-bottomed flask was charged with alcohol **1.53** (6.2 g, 13.6 mmol, 1.0 equiv) and CH_2Cl_2 (68 mL). 2,6-Lutidine (4.7 mL, 40.7 mmol, 3.0 equiv) was added and the solution was cooled −78 °C. TBSOTf (3.7 mL, 16.3 mmol, 1.2 equiv) was added dropwise and the reaction was stirred for 30 min at −78 °C. Saturated $NaHCO_{3(aq.)}$ (30 mL) and EtOAc (30 mL) were added and the reaction was allowed to warm to rt. The layers were separated and the aqueous portion was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with 1 M HCl (30 mL) and brine (30 mL), and dried with magnesium sulfate. The crude product was concentrated in vacuo and purified via flash chromatography (20:80 to 30:70 EtOAc:hexanes) to give the title compound as a pale yellow oil (6.8 g, 88 %). Analytical data: $[\alpha]_D^{19}$ −1.5 (*c* = 1.00, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.37–7.27 (m, 10H), 7.22 (t, *J* = 7.2 Hz, 1H), 6.63 (d, *J* = 16.2 Hz, 1H), 6.32 (dd, *J* = 7.8, 16.2 Hz, 1H), 5.31 (s, 1H), 5.11 (d, *J* = 12.6 Hz, 1H), 5.06 (d, *J* = 12.6 Hz, 1H), 5.03 (t, *J* = 8.4 Hz, 1H), 4.48 (q, *J* = 6.0 Hz, 1H), 2.96 (s, 6H), 2.22 (s, 3H), 1.22 (d, *J* = 6.0 Hz, 3H), 0.88 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 205.2, 158.8, 155.7, 136.8, 136.6, 132.2, 128.2, 128.1, 127.7, 127.6, 127.3, 127.1, 126.4, 71.2, 66.3, 54.8, 36.5, 26.5, 25.5, 19.1, 17.7, −3.9, −5.2; **HRMS (ESI$^+$)** Calcd. for $C_{31}H_{45}N_3O_5Si$ + H, 568.3208; Found, 568.3237; **IR** (thin film, cm^{-1}) 3417, 2954, 1857, 1714, 1651, 1517, 1253, 1128, 1063, 837, 737; **TLC** (75:25 hexanes/EtOAc): R_f = 0.30.



Ethyl ((((benzyloxy)carbonyl)amino)-4-(1-((tert-butyldimethylsilyl)oxy)ethyl)-4-(3,3-dimethylureido)-3-oxo-7-phenylhept-6-enoate (1.65). A flame-dried 250-mL round-bottomed flask was charged with diisopropylamine (0.21 mL, 1.46 mmol, 3.50 equiv) and THF (4 mL). The resulting solution was cooled to 0 °C and *n*-butyllithium (1.72 M in hexanes, 0.85 mL, 1.46 mmol, 3.50 equiv) was added dropwise. The solution was stirred at 0 °C for 30 min and then cooled to −78 °C. A solution of ketone **1.64** (0.24 g, 0.42 mmol, 1.0 equiv) in THF (0.5 mL) was added dropwise, and the resulting solution was stirred at −78 °C for 45 min upon which ethyl cyanoformate (0.1 mL, 1.04 mmol, 2.5 equiv) was added dropwise. The reaction was allowed to stir for 2 h and quenched via addition of saturated $NH_4Cl_{(aq.)}$ (4 mL). The mixture was warmed to rt and extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo.

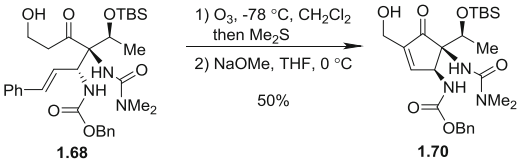
The product was purified via flash chromatography (80:20 to 70:30 hexanes:EtOAc) to afford ketoester **1.65** (0.21 g, 79 %) as clear, viscous oil. Analytical data: Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.35–7.25 (m, 10H), 7.21–7.17 (m, 1H), 6.60 (d, *J* = 15.6 Hz, 1H), 6.33 (dd, *J* = 6.6, 9.0 Hz, 1H), 5.38 (s, 1H), 5.13 (m, 2H), 5.07 (d, *J* = 12.6 Hz, 1H), 4.48 (q, *J* = 6.0 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.74 (d, *J* = 16.2 Hz, 1H), 3.71 (d, *J* = 16.2 Hz, 1H), 2.92 (s, 6H), 1.26–1.22 (m, 6H), 0.9 (s, 9H), 0.12 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 200.7, 167.3, 158.3, 156.0, 136.8, 136.6, 132.0, 128.3, 128.2, 127.9, 127.8, 127.5, 126.9, 126.5, 74.3, 70.7, 66.6, 61.1, 54.9, 45.7, 36.6, 25.7, 19.0, 17.8, 14.1, −3.8, −5.0; **HRMS (ESI$^+$)** Calcd. for $C_{34}H_{49}N_3O_7Si$ + Na, 662.3238; Found, 662.3242; **IR** (thin film, cm^{-1}) 3424, 2954, 2931, 2857, 2249, 1745, 1650, 1513, 1259, 1128, 1060, 911; **TLC** (65:45 EtOAc: hexanes): R_f = 0.70.



1.64 **1.68**

Benzyl ((3*R*,4*R*,*E*)-4-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-(3,3-dimethylureido)-7-hydroxy-5-oxo-1-phenylhept-1-en-3-yl)carbamate (1.68): A flame-dried 250-mL round-bottomed flask was charged with diisopropylamine (5.8 mL, 41.3 mmol, 3.5 equiv) and THF (100 mL). The resulting solution was cooled to 0 °C and *n*-butyllithium (1.65 M in hexanes, 25.0 mL, 41.3 mmol, 3.5 equiv) was added dropwise. The reaction was stirred at 0°C for 30 min and then cooled to −78°C. A solution of ketone **1.64** (6.8 g, 11.8 mmol, 1.0 equiv) in THF (25 mL) was added dropwise, and the resulting mixture was stirred for 45 min and warmed to −45 °C. Formaldehyde gas ($CH_2O_{(g)}$, prepared by heating paraformaldehyde ($(CH_2O)_n$, 5.0 g, 166.7 mmol, 14.1 equiv) to 145 °C under a positive pressure of nitrogen) was bubbled through the reaction. The reaction was stirred at −45 °C until full conversion to product was indicated by TLC analysis, typically 1 h. The reaction was quenched by the addition of a saturated $NH_4Cl_{(aq.)}$ (30 mL), and the resulting mixture was extracted with Et_2O (3 × 30 mL). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo. The crude product was purified via flash chromatography (50:50 to 60:40 EtOAc:hexanes) to give alcohol **1.68** as a clear, viscous oil (4.9 g, 70 %). Analytical data: $[\alpha]_D^{19}$ +11.2 (*c* = 1.00, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.35–7.26 (m, 10H), 7.21 (t, *J* = 7.0 Hz, 1H), 6.59 (d, *J* = 16.0 Hz, 1H), 6.28 (dd, *J* = 9.0, 16.0 Hz 1H), 5.32 (s, 1H), 5.11 (d, *J* = 12.0 Hz, 1H), 5.02 (d, *J* = 12.0 Hz, 1H), 4.98 (t, *J* = 8.5 Hz, 1H), 4.40 (q, *J* = 6.5 Hz, 1H), 3.85–3.82 (m, 1H), 3.73–3.71 (m, 1H), 2.93 (s, 6H), 2.82–2.70 (m, 2H), 1.23 (d, *J* = 6.5 Hz, 3H), 0.87 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 208.5,

158.7, 155.9, 136.8, 136.6, 132.3, 128.4, 128.3, 128.1, 127.9, 127.5, 127.1, 126.6, 74.2, 71.7, 66.6, 58.1, 55.2, 40.7, 36.6, 25.7, 19.2, 17.8, −3.7, −5.0; **HRMS (ESI$^+$)** Calcd. for $C_{32}H_{47}N_3O_6Si$ + H, 598.3314; Found, 598.3345; **IR** (thin film, cm^{-1}) 3429, 2954, 1716, 1646, 1507, 1252, 966, 695, 530; **TLC** (50:50 hexanes:EtOAc): R_f = 0.20.

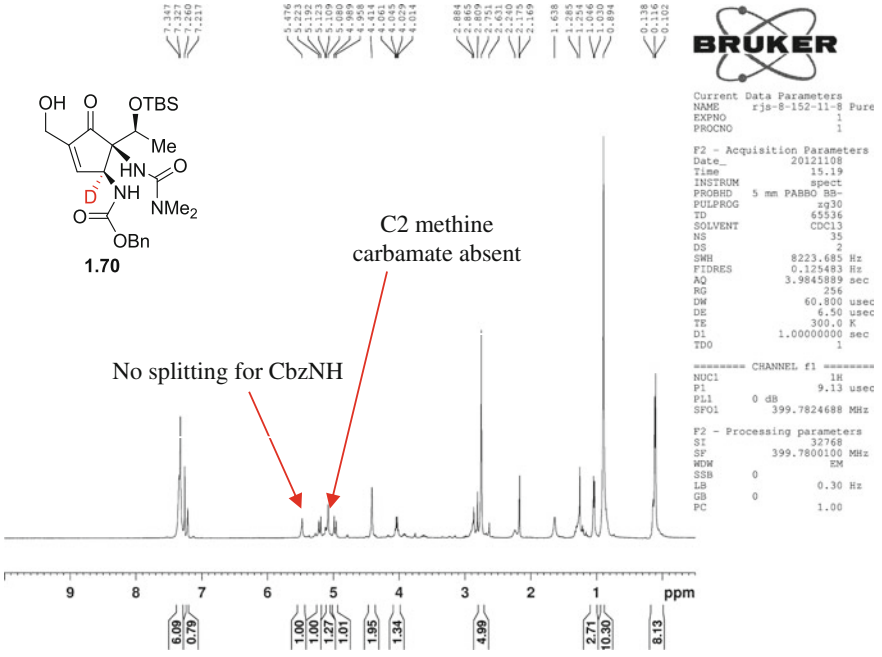


Benzyl ((1*S*,5*R*)-5-((*S*)-1-((tert-butyldimethylsilyl)oxy)ethyl)-5-(3,3-dimethylureido)-3-(hydroxymethyl)-4-oxocyclopent-2-en-1-yl)carbamate (1.70): A 250-mL round-bottomed flask was charged with alcohol **1.68** (2.5 g, 4.1 mmol, 1.0 equiv) and CH_2Cl_2 (82 mL). The resulting solution was cooled to −78 °C, and a stream of ozone (O_3) was bubbled through the solution until a blue color was observed, typically 5–15 min (scale dependent). The mixture was sparged with N_2 for 5 min or until the full disappearance of blue color, and Me_2S (6.0 mL, 82.0 mmol, 20.0 equiv) was added. The reaction was warmed to rt, stirred for 12 h, and concentrated in vacuo affording the crude aldehyde (**1.69**) as a yellow oil. The unpurified product was taken on directly to the next step.

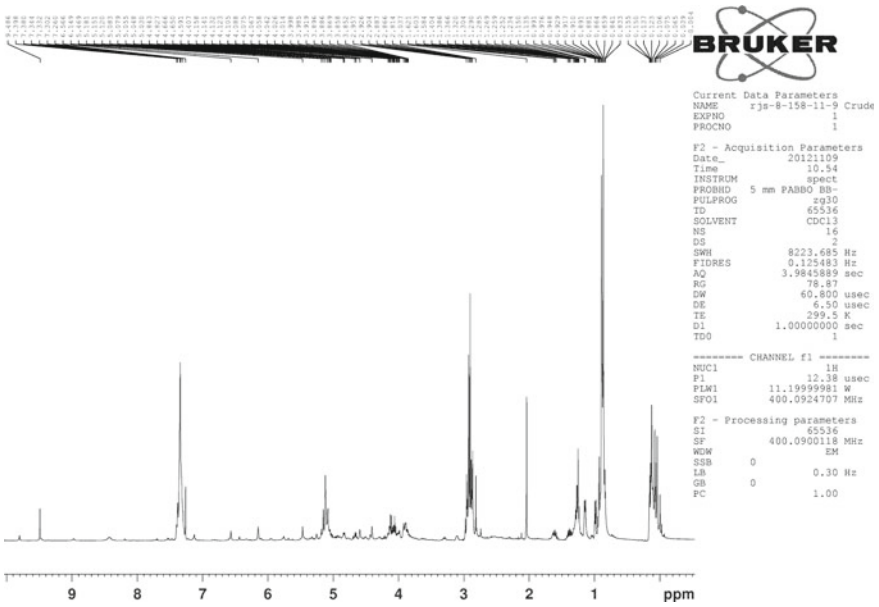
Aldehyde **1.69** was dissolved in THF (103 mL) and cooled to 0 °C. Sodium methoxide (NaOMe) (0.5 M in MeOH, 24.6 mL, 12.3 mmol, 3.0 equiv) was added dropwise. The reaction was stirred at 0 °C until TLC analysis indicated complete consumption of the aldehyde, typically 30 min. The reaction was quenched by the addition of saturated $NaHCO_{3(aq.)}$ (30 mL), and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried with magnesium sulfate, and concentrated in vacuo. The product was purified by flash chromatography (70:30 to 60:40 petroleum ether:acetone) to afford enone **1.70** as a pale yellow, viscous oil with >20:1 diastereoselection (1.02 g, 50 %). When this experiment was conducted replacing NaOMe in MeOH with a CD_3OD solution of $NaOCD_3$, complete D-incorporation was observed at the carbamate methine (C2 in pactamycin numbering; C1 in the IUPAC name given as the title for this experimental). When this experiment is conducted for the same time duration at −10 °C, a complex product mixture is observed. When this mixture is resubmitted to the reaction conditions at 0 °C, complete conversion to **1.70** is observed. Further evidence for inversion of the carbamate methine during this condensation was found in X-ray analysis analysis of nitrobenzoate **1.79** and by

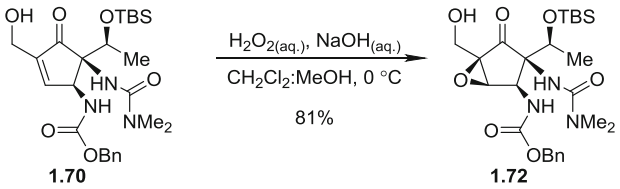
ultimate conversion of **1.70** to pactamycin. (Note: complete epimerization of C2 was confirmed based on crude ^{1}HNMR analysis; however the reaction is generally low-yielding). Analytical data: $[\alpha]_D^{19}$ −25.9 (c = 1.00, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.35–7.29 (m. 5H), 7.22 (d, J = 1.2, 1H), 5.47 (d, J = 10.2 Hz, 1H), 5.21 (d, J = 12.0 Hz, 1H), 5.08 (s, 1H), 5.06 (d, J = 10.2 Hz, 1H), 4.97 (d, J = 12.0 Hz, 1H), 4.41 (s, 2H), 4.03 (q, J = 6.6 Hz, 1H), 2.75 (s, 6H), 1.04 (d, J = 6.6 Hz, 3H), 0.89 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 203.3, 158.3, 155.9, 151.8, 146.5, 136.8, 128.4, 128.0, 128.0, 71.9, 68.5, 66.3, 57.3, 54.1, 36.3, 25.5, 18.1, 17.8, −3.7, −4.9; **HRMS (ESI^{+})** Calcd. for $C_{25}H_{39}N_3O_6Si$ + H, 506.2688; Found, 506.2715; **IR** (thin film, cm^{-1}) 3431, 2953, 2857, 2125, 1715, 1634, 1514, 1220, 928, 830; **TLC** (35:65 Hexanes:EtOAc): R_f = 0.20.

^{1}H NMR Spectrum of 1.70 Showing D-Incorporation



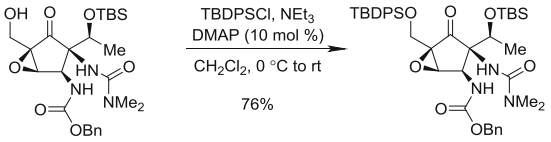
Crude ^{1}H NMR Spectrum of $NaOCD_3$ condensation in CD_3OD when conducted for 0.5 h at −10 °C





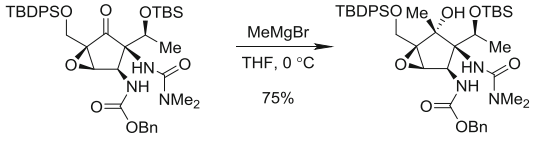
Benzyl ((1*R*,2*R*,3*R*,5*R*)-3-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(3,3-dimethylureido)-5-(hydroxymethyl)-4-oxo-6-oxabicyclo[3.1.0]hexan-2-yl)carbamate (1.72): A 200-mL round-bottomed flask was charged with enone **1.70** (1.1 g, 2.2 mmol, 1.0 equiv) and MeOH:CH_2Cl_2 (7:1, 32 mL). The resulting solution was cooled to 0 °C, and a cooled solution of H_2O_2 (30 % aq., 20 mL) and NaOH (20 % aq., 5 mL) was added dropwise. The reaction was stirred at 0 °C for 2 h, and diluted with Et_2O (30 mL). The layers were separated and the aqueous was extracted with Et_2O (3 × 15 mL). The combined organics were washed with H_2O (3 × 30 mL), brine (20 mL), dried with magnesium sulfate, and concentrated in vacuo. The crude product was purified via flash chromatography (70:30 petroleum ether:acetone) affording the title compound as a clear, viscous oil with >20:1 diastereoselection (0.91 g, 81 %). Analytical data: $[\alpha]_D^{19}$ −22.4 (c = 1.00, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.32–7.26 (m, 5H), 5.66 (d, J = 9.6 Hz, 1H), 5.20

(d, J = 12.0 Hz, 1H), 4.93 (d, J = 12.6 Hz, 1H), 4.68 (s, 1H), 4.68–4.66 (m, 1H), 4.07–4.04 (m, 2H), 4.02–3.98 (m, 2H), 2.64 (s, 6H), 1.15 (d, J = 6.6 Hz, 3H), 0.89 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 204.4, 156.9, 156.0, 136.6, 128.3, 128.1, 128.0, 74.0, 69.3, 66.4, 65.9, 60.7, 56.0, 52.3, 36.1, 25.5, 18.2, 17.7, −3.9, −4.8; **HRMS (ESI$^+$)** Calcd. for $C_{25}H_{39}N_3O_7Si$ + H, 522.2637; Found, 522.2663; **IR** (thin film, cm^{-1}) 3402, 2954, 2857, 2359, 2249, 2125, 1650, 1519, 1227, 830, 732; **TLC** (70:30 petroleum ether/acetone): R_f = 0.30.



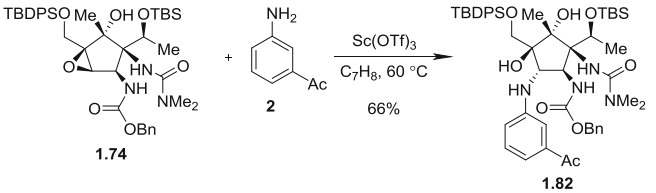
1.72 **1.73**

Benzyl ((1*R*,2*R*,3*R*,5*R*)-3-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-(3,3-dimethylureido)-4-oxo-6-oxabicyclo[3.1.0]hexan-2-yl)carbamate (1.73): A flame-dried 25-mL round-bottomed flask was charged with alcohol **1.72** (1.0 g, 1.9 mmol, 1.0 equiv) and CH_2Cl_2 (9.5 mL). NEt_3 (0.8 mL, 5.7 mmol, 3.0 equiv) and DMAP (0.023 g, 0.19 mmol, 0.1 equiv) were added and the solution was cooled 0 °C. TBDPSCl (1.47 mL, 5.7 mmol, 3.0 equiv) was added dropwise and the reaction was warmed to rt and stirred for 8 h. Saturated $NH_4Cl_{(aq.)}$ (10 mL) was added and the mixture was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried with magnesium sulfate, and concentrated in vacuo. The crude product was purified via flash chromatography (70:30 hexanes:EtOAc) to give the title compound as a pale yellow oil (1.1 g, 76 %). Analytical data: $[\alpha]_D^{19}$ −4.4 (c = 0.70, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.67 (d, J = 7.2 Hz, 2H), 7.62 (d, J = 7.2 Hz, 2H), 7.44–7.30 (m, 11H), 5.68 (d, J = 10.2 Hz, 1H), 5.23 (d, J = 12.0 Hz, 1H), 4.97 (d, J = 12.6 Hz, 1H), 4.74 (dd, J = 3.0, 7.2 Hz, 1H), 4.70 (br s, 1H), 4.26 (d, J = 12.6 Hz, 1H), 4.11 (d, J = 3.0 Hz, 1H), 4.03 (q, J = 6.0 Hz, 1H), 3.92 (d, J = 12.0 Hz, 1H), 2.68 (s, 6H), 1.19 (d, J = 6.0 Hz, 3H), 1.01 (s, 9H), 0.92 (s, 9H), 0.13 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 203.9, 156.8, 156.0, 136.7, 135.5, 135.4, 132.6, 132.3, 129.8, 129.7, 128.3, 128.1, 127.9, 127.8, 127.7, 74.1, 69.4, 66.4, 66.2, 60.8, 57.5, 52.2, 36.1, 26.6, 25.6, 19.1, 18.3, 17.8, −3.8, −4.8; **HRMS (ESI$^+$)** Calcd. for $C_{41}H_{57}N_3O_7Si_2$ + H, 760.3815; Found, 760.3862; **IR** (thin film, cm^{-1}) 3419, 2931, 2857, 2359, 1716, 1651, 1507, 1226, 1113, 828, 733; **TLC** (70:30 hexanes/EtOAc): R_f = 0.30.



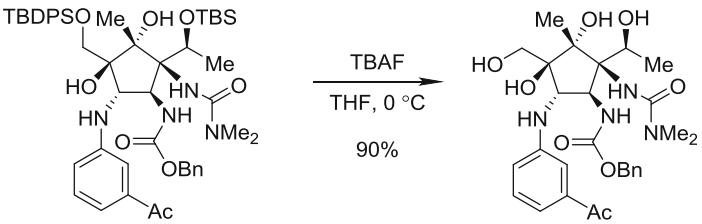
1.73 **1.74**

Benzyl ((1*R*,2*R*,3*R*,4*R*,5*R*)-3-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-(3,3-dimethylureido)-4-hydroxy-4-methyl-6-oxabicyclo [3.1.0]hexan-2-yl)carbamate (1.74): A flame-dried 25-mL round-bottomed flask was charged with ketone **1.73** (1.7 g, 2.3 mmol, 1.0 equiv) and THF (23 mL). The solution was cooled to 0 °C and MeMgBr (3 M in THF, 7.6 mL, 22.9 mmol, 10.0 equiv) was added dropwise. The reaction was stirred at 0 °C until TLC analysis indicated complete ketone consumption, typically 2 h. Saturated $NH_4Cl_{(aq.)}$ (20 mL) was carefully added dropwise and the resulting mixture was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (20 mL), dried with magnesium sulfate, and concentrated in vacuo. The crude product was purified via flash chromatography (90:10 to 70:30 hexanes:EtOAc) to afford carbinol **1.74** as a clear, viscous oil with >10:1 diastereoselection (1.3 g, 75 %). The enantiomeric ratio was assayed at this intermediate and was found to be 95:5. This composition was determined by SFC analysis (Chiralcel, OD, 4.0 % MeOH, 1.5 mL/min, 150 bar, 210 nm; t_R-minor 34.4 min, t_R-major 37.6 min). Analytical data: $[\alpha]_D^{19}$ +7.2 (c = 0.70, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.73 (d, J = 7.8 Hz, 2H), 7.70 (d, J = 7.2 Hz, 2H), 7.45–7.30 (m, 12H), 5.55 (br s, 1H), 5.21 (d, J = 12.6 Hz, 1H), 5.17 (br s, 1H), 5.07 (d, J = 12.0 Hz, 1H), 4.77 (br s, 1H), 4.64 (dd, J = 3.6, 8.4 Hz, 1H), 4.21 (d, J = 12.6 Hz, 1H), 4.12 (d, J = 12.6 Hz, 1H), 3.90 (s, 1H), 2.75 (s, 6H), 1.30 (s, 3H), 1.25 (d J = 6.0 Hz, 3H), 1.07 (s, 9H), 0.97 (s, 9H), 0.11 (s, 3H), −0.01 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 158.8, 156.5, 136.3, 135.6, 135.5, 134.7, 133.3, 132.9, 129.6, 129.4, 128.4, 128.2, 128.1, 127.7, 127.6, 127.6, 67.1, 66.8, 62.1, 58.3, 36.1, 26.7, 26.5, 25.7, 23.8, 19.6, 19.2, 17.8, −4.2, −5.5; **HRMS (ESI$^+$)** Calcd. for $C_{42}H_{61}N_3O_7Si_2$ + H, 776.4128; Found, 776.4179; **IR** (thin film, cm^{-1}) 3430, 2429, 2359, 1716, 1635, 1506, 1456, 1112, 831, 700; **TLC** (90:10 hexanes/EtOAc): R_f = 0.35.



Benzyl ((1*S*,2*R*,3*R*,4*S*,5*S*)-5-((3-acetylphenyl)amino)-2-((*S*)-1-((*tert*-butyldimethylsilyl)oxy) ethyl)-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-(3,3 dimethyl ureido)-3,4-dihydroxy-3-methylcyclopentyl)carbamate (1.82): In a nitrogen-filled glove box, a flame-dried 100-mL round-bottomed flask was charged with $Sc(OTf)_3$ (0.38 g, 0.77 mmol, 3.0 equiv). The flask was capped with a rubber septum and removed from the glove box. C_7H_8 (20 mL) was added and to the resulting suspension were added aniline **2** (0.35 g, 2.6 mmol, 10.0 equiv) and a C_7H_8 solution (1.5 mL) of epoxide **1.74** (0.20 g, 0.26 mmol, 1.0 equiv). The reaction was heated to 60 °C with vigorous stirring and maintained for 14 h. (Note: increased reaction times led to product decomposition). The reaction was cooled to

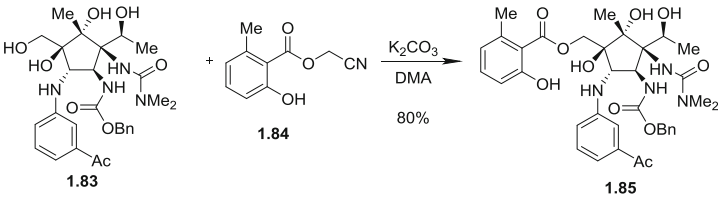
rt, diluted with H_2O (10 mL) and EtOAc (10 mL), and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with 0.5 M $HCl_{(aq.)}$ (2 × 20 mL), saturated $NaHCO_{3(aq.)}$ (15 mL), dried with magnesium sulfate, and concentrated in vacuo. The crude product was purified via flash chromatography (90:10 to 80:20 hexanes:EtOAc) to afford anilino-alcohol **1.82** as a yellow, viscous oil (0.16 g, 66 %) with recovery of the unreacted epoxide **1.74** (0.04 g, 18 %). Analytical data: $[\alpha]_D^{19}$ −39.3 (*c* = 0.70, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.21 (d, *J* = 6.6 Hz, 1H), 7.70 (d, *J* = 6.6 Hz, 2H), 7.51 (d, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.28–7.22 (m, 8H), 7.16 (t, *J* = 7.2 Hz, 2H), 7.12 (t, *J* = 7.8 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 6.13 (s, 1H), 5.88 (s, 1H), 5.39–5.36 (m, 1H), 5.36 (s, 1H), 5.04 (d, *J* = 12.0 Hz, 1H), 5.01 (d, *J* = 12.0 Hz, 1H), 4.78 (dd, *J* = 4.6, 6.6 Hz, 1H), 4.37 (d, *J* = 10.2 Hz, 1H), 4.13 (s, 1H), 3.68 (dd, *J* = 3.0, 4.6 Hz, 1H), 3.48 (d, *J* = 10.8 Hz, 1H), 2.96 (s, 6H), 2.49 (s, 3H), 1.69 (s, 3H), 1.41 (d, *J* = 6.6 Hz, 3H), 0.98 (s, 9H), 0.92 (s, 9H), 0.12 (s, 3H), 0.02 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 198.7, 158.6, 158.4, 149.5, 137.7, 136.6, 135.6, 135.4, 132.4, 132.0, 129.6, 128.8, 128.2, 128.1, 127.8, 127.6, 118.2, 117.0, 112.6, 83.6, 81.0, 70.3, 68.4, 66.9, 66.5, 63.0, 59.3, 36.6, 26.7, 26.7, 25.7, 21.2, 19.4, 19.0, 17.7, −4.3, −6.1; **HRMS (ESI$^+$)** Calcd. for $C_{50}H_{70}N_8Si_2$ + H, 911.4812; Found, 911.4867; **IR** (thin film, cm^{-1}) 3361, 2953, 2358, 1716, 1698, 1652, 1539, 1488, 1472, 1243, 1041, 829, 701; **TLC** (80:20 hexanes:EtOAc): R_f = 0.35.



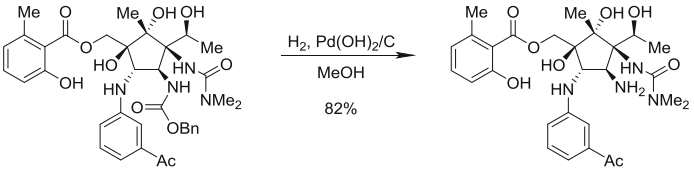
1.82 **1.83**

Benzyl ((1*S*,2*R*,3*R*,4*S*,5*S*)-5-((3-acetylphenyl)amino)-2-(3,3-dimethylureido)-3,4-dihydroxy-2-((*S*)-1-hydroxyethyl)-4-(hydroxymethyl)-3-methylcyclopentyl) carbamate (1.83): A 20-mL scintillation vial was charged with silyl ether **1.82** (0.25 g, 0.28 mmol, 1.0 equiv) and THF (5.5 mL). The resulting solution was cooled to 0 °C, and TBAF (1 M solution in THF, 1.1 mL, 1.1 mmol, 4.0 equiv) was added. The reaction was allowed to stir at 0 °C until TLC analysis indicated consumption of the starting material, typically 30 min. The reaction was diluted with brine (3 mL) and EtOAc (3 mL) and extracted with EtOAc (3 × 7 mL). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo. The crude product was purified via flash chromatography (60:40 petroleum ether:acetone) to afford tetraol **1.83** as a pale yellow, viscous oil (0.14 g, 90 %). Analytical data: $[\alpha]_D^{19}$ +26.0 (*c* = 0.70, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.36 (s, 4H), 7.29 (br s, 1H), 7.23 (br s, 1H), 7.12 (br s, 1H), 6.99 (d, *J* = 7.8 Hz,

1H), 6.75 (d, J = 6.6 Hz, 1H), 6.02 (d, J = 7.2 Hz, 1H), 5.80 (br s, 1H), 5.48 (d, J = 7.8 Hz, 1H), 5.27 (br s, 1H), 5.13 (br s, 2H), 4.14–4.10 (m, 1H), 4.06 (br s, 2H), 3.80 (br s, 2H), 3.74–3.68 (m, 1H), 3.55 (m, 1H), 2.87 (s, 6H), 2.52 (s, 3H), 1.42 (s, 3H), 1.25 (br s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 198.7, 158.7, 155.8, 146.6, 138.3, 136.0, 129.7, 128.6, 128.4, 118.4, 112.0, 88.2, 83.9, 73.2, 71.7, 67.4, 66.9, 64.2, 61.8, 61.2, 36.7, 29.7, 26.7, 22.7, 21.2, 18.0, 14.1; **HRMS (ESI$^+$)** Calcd. For $C_{28}H_{38}N_4O_8$ + H, 559.2770; Found, 559.2800; **IR** (thin film, cm^{-1}) 3392, 2938, 1716, 1684, 1652, 1635, 1540, 1507, 1473, 1456, 1361, 1243, 739; **TLC** (60:40 petroleum ether/acetone): R_f = 0.30.



((1*S*,2*R*,3*R*,4*S*,5*S*)-5-((3-acetylphenyl)amino)-4-(((benzyloxy)carbonyl)amino)-3-(3,3-dimethylureido)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)-2-methylcyclopentyl)methyl 2-hydroxy-6-methylbenzoate (1.85): A flame-dried 20-mL scintillation vial was charged with cyanomethyl ester **1.84** (0.0075 g, 0.044 mmol, 1.1 equiv) and dimethylacetamide (DMA) (0.3 mL). K_2CO_{3-} (0.005 g, 0.04 mmol, 1.0 equiv) was added, and the resulting mixture was stirred for 1 h. The in situ generated ketene solution was transferred to a stirred solution of tetraol **1.83** (0.02 g, 0.04 mmol, 1.0 equiv) in DMA (0.7 mL). The reaction was stirred until TLC analysis indicated full consumption of the tetraol starting material, typically 3 h. The reaction was cooled to 0 °C and quenched by the dropwise addition of saturated $NH_4Cl_{(aq.)}$ (1.5 mL). The resulting mixture was extracted with EtOAc (3 × 5 mL), washed with H_2O (10 ml), brine (10 mL), dried with magnesium sulfate, and concentrated in vacuo. The crude product was purified via flash chromatography (50:50 hexanes:EtOAc) to afford an inseparable mixture of salicylate **1.85** (0.02 g, 80 %) and an unknown impurity (15 % by NMR analysis) as a pale yellow, viscous oil. Analytical data: $[\alpha]_D^{19}$ +33.6 (c = 0.70, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 10.87 (s, 1H), 7.52 (br s, 1H), 7.36 (br s, 5H), 7.30–7.22 (m, 4H), 7.10 (s, 1H), 6.81 (d, J = 8.4 Hz, 1H), 6.63 (d, J = 7.2 Hz, 1H), 6.13 (s, 1H), 5.79 (d, J = 9.0 Hz, 1H), 5.72 (d, J = 9.6 Hz, 1H), 5.23–5.10 (m, 3H), 4.91–4.84 (m, 2H), 4.06 (br s, 2H), 3.80 (d, J = 9.6 Hz, 1H), 3.69 (s, 1H), 2.85 (s, 7H), 2.30 (s, 3H), 1.42 (s, 3H), 1.26 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 198.3, 173.4, 162.9, 158.5, 155.3, 146.0, 141.6, 138.3, 135.0, 129.7, 128.6, 128.5, 123.2, 119.4, 118.4, 115.8, 111.9, 111.6, 99.7, 88.6, 85.0, 73.9, 72.3, 67.5, 66.8, 66.6, 65.4, 62.7, 36.7, 23.9, 21.0, 18.0, 17.4; **HRMS (ESI$^+$)** Calcd. For $C_{36}H_{44}N_4O_{10}$ + H, 693.3137; Found, 693.3172; **IR** (thin film, cm^{-1}) 3392, 2965, 1867, 1698, 1670, 1541, 1456, 1374, 1249, 874, 737; **TLC** (50:50 EtOAc:Hexanes): R_f = 0.30.



Pactamycin (1.1): A 4-mL vial was charged with salicylate **1.85** (0.0075 g, 0.01 mmol, 1.0 equiv), and $Pd(OH)_2/C$ (20 wt%, 0.005 g). MeOH (1 mL) was added and the vial was sealed with a Teflon cap. The atmosphere was replaced by H_2 (balloon, ~1 atm.) and stirred until TLC analysis indicated complete consumption of the starting material, typically 20 min. The resulting suspension was filtered through a pad of Celite and washed with MeOH. The homogeneous solution was concentrated in vacuo. The crude residue was purified by flash chromatography (98:2 CH_2Cl_2:MeOH) affording pactamycin (0.005 g, 82 %) as a pale yellow solid. Analytical data: $[\alpha]_D^{19}$ +27.4 (c = 0.40, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 10.98 (br s, 1H), 7.91 (d, J = 10.8 Hz, 1H), 7.26–7.23 (m, 4H), 7.18–7.16 (m, 2H), 6.81–6.78 (m, 2H), 6.64 (d, J = 7.2 Hz, 1H), 5.78 (br s, 1H), 5.67 (d, J = 10.8 Hz, 1H), 4.84 and 4.79 (ABq, J = 12.6 Hz, 2H), 3.93 (m, 1H), 3.80 (d, J = 10.2 Hz, 1H), 2.99 (s, 6H), 2.95 (s, 1H), 2.55 (s, 3H), 2.38 (s, 3H), 1.55 (s, 3H), 1.04 (d, J = 6.0 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 198.5, 172.6, 162.8. 159.2, 146.6, 141.2, 138.3, 134.6, 129.6, 123.0, 118.7, 118.4, 115.7, 112.0, 110.8, 88.8, 84.9, 74.3, 71.5, 68.7, 65.4, 63.2, 36.9, 29.7, 26.7, 24.1, 21.1, 18.1; **HRMS (ESI$^+$)** Calcd. for $C_{28}H_{38}N_4O_8$ + H, 559.2762; Found, 559.2763; **IR** (thin film, cm^{-1}) 3393, 2938, 2359, 2341, 1698, 1652, 1520, 1473, 1418, 1338, 873, 668; **TLC** (95:5 CH_2Cl_2/MeOH): R_f = 0.30.

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Chapter 2
Preparation and Biological Evaluation of Synthetic and Polymer-Encapsulated Congeners of the Antitumor Agent Pactamycin: Insight into Functional Group Effects and Biological Activity

2.1 Introduction

An expeditious total synthesis of the aminocyclitol antibiotic pactamycin was described in Chap. 1, enabling fifteen-step preparation of the natural product from commercially available materials. Pactamycin, while bearing a remarkable array of valuable biological traits, is hindered in medicinal development by its high cytotoxicity. For this molecule to achieve its full potential as a therapuetic, chemical modifications to the parent structure must be enabled for structure-activity relationship (SAR) investigations to be possible. Accordingly, our synthesis of pactamycin was designed with the goal of late-stage structural modification toward the preparation of heretofore inaccessible synthetic analogs of pactamycin. This chapter will describe our successful efforts in the synthesis and biological analysis of twenty-five unique structural analogs of pactamycin. Additionally, as part of a collaboration with the DeSimone group (UNC Chapel Hill), the encapsulation of pactamycin and select derivatives into the PRINT® nanoparticle technology is demonstrated as proof-of-concept.

2.2 Background

2.2.1 Importance of Natural Products in Pharmaceutical Development

Pharmaceutical development through organic synthesis remains a critical feature of the drug discovery process [1]. Upon identification of an initial hit via

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Robert J. Sharpe, *Stereoselective Desymmetrization Methods in the Assembly of Complex Natural Molecules*, Springer Theses,
DOI 10.1007/978-3-319-39025-3_2

high-throughput screening, a significant amount of structural modification is often required before a lead candidate can be advanced to clinical trials. Natural molecules are frequently identified as initial hits in these screenings; a recent survey study showed that natural products and their derivatives comprise over one-third of all FDA-approved new molecular entities (NMEs) [2]. Furthermore, Reynisson and co-workers reported that of the 39 % of known drug space (KDS) that is comprised of natural products and their derivatives, 74 % of this subset is made up of natural product derivatives [3]. Figure 2.1 illustrates a selection of natural product-derived structures (and their corresponding parent structures) approved for use by the FDA in the past decade [4]. The morphine-derived methylnaltrexone is currently in use for the treatment of opiod-induced constipation. Fingolimod, derived from myriocin, is being employed as a treatment for multiple sclerosis. Zucapsaicin and dapagliflozin (derived from the natural products capsaicin and phlorizin, respectively) are also in use as analgesic and diabetic medicines. These examples speak to the power of natural product scaffolds in the continued development of the pharmaceutical industry.

2.2.1.1 Medicinal Development of Pactamycin to Date

Despite these demonstrated successes, efficient modification of complex natural product structures toward the preparation of useful drug molecules can often be hindered by the deficiency of a practical and flexible chemical synthesis [5]. As a result, the continued advancement of synthetic organic methodology is critical for facile and flexible drug discovery and development. Pactamycin (**2.1**, Fig. 2.2) is an example of a valuable natural target that has yet to reach its full medicinal potential due to both its inherent cytotoxicity and challenges associated with preparation of structurally-distinct analogs.

Its impressive biology has attracted the attention of a multidisciplinary field in hopes of transforming pactamycin into a suitable therapeutic. In addition to **2.1**, a number of naturally-occurring structural congeners have been isolated from related *Streptomyces* bacteria, displaying varied bioactivities (Fig. 2.3). Among these, 7-deoxypactamycin (**2.2**) and jogyamycin (**2.3**) have shown increased antiprotozoal activity relative to **2.1**, albeit with increased cytotoxicity [6]. Additionally, natural derivatives including pactamycate **2.4** (bearing an oxazolidinone ring in place of the dimethylurea) and the 8″-hydroxypactamycin series have also been recently reported [7, 8].

Alternatively, biosynthetic engineering studies pioneered by Mahmud and co-workers have provided researchers with the first series of unnatural structural analogs (Fig. 2.4). An initial report disclosed the preparation of TM-025 (**2.7**) and TM-026 (**2.8**). In contrast to **2.2**, these compounds demonstrated an increase in activity against *Plasmodium falciparum* relative to pactamycin in combination with a decrease in cytotoxic effects [8]. In 2013, Mahmud described the preparation of biosynthetically-generated fluorinated analogs (**2.9**, **2.10**) displaying comparable antimalarial activity to **2.1** [9]. These findings have renewed promise for pactamycin analogs in drug development.

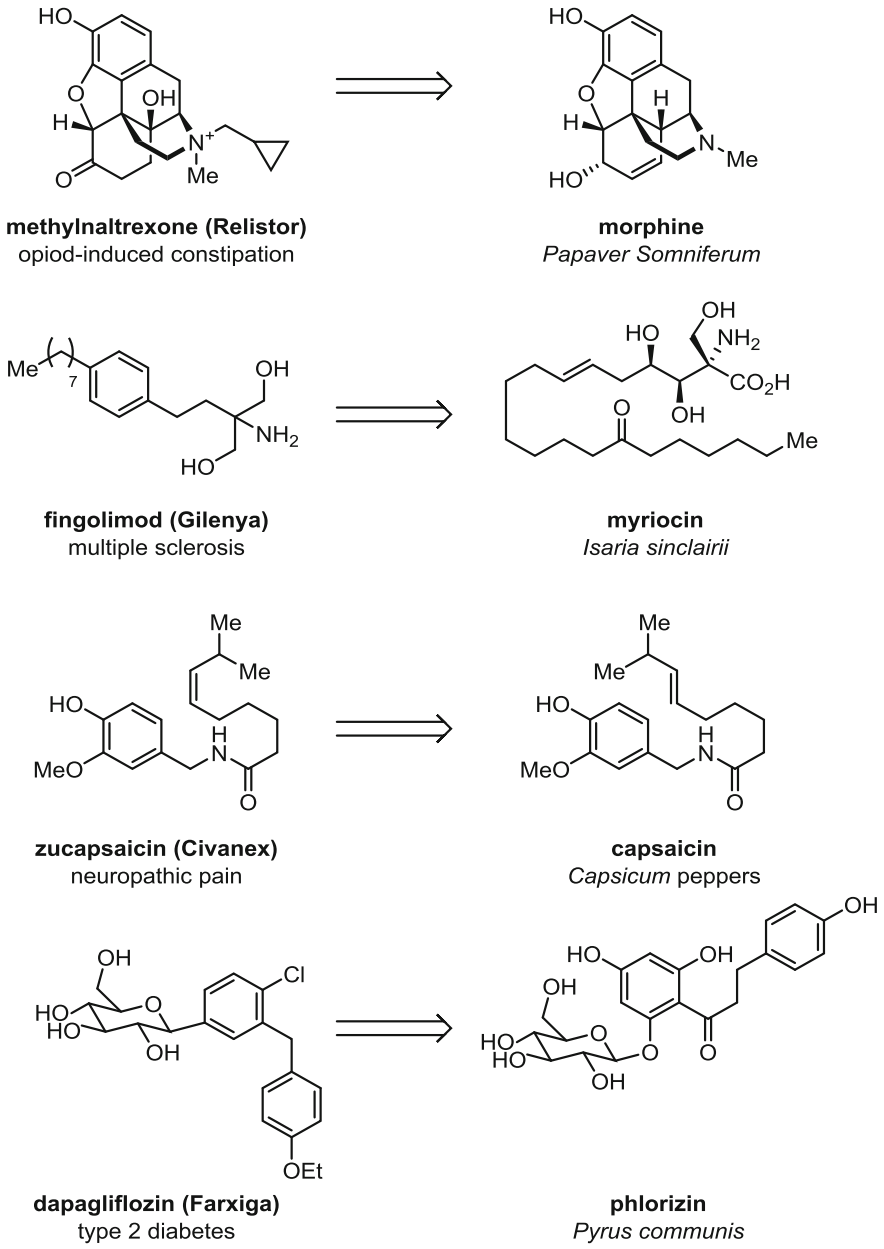


Fig. 2.1 Natural product derivatives approved by FDA in the past ten years

Moreover, encapsulation of natural cytotoxic agents into nanoparticles (NPs) has also shown improved clinical benefits, the most germane of these being reduction of undesired toxic side effects and increased therapeutic delivery to the target of

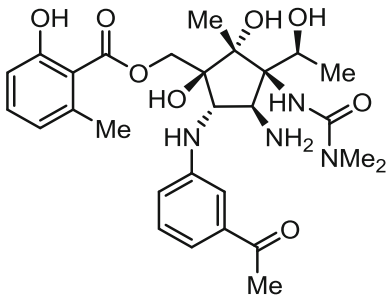


Fig. 2.2 Pactamycin

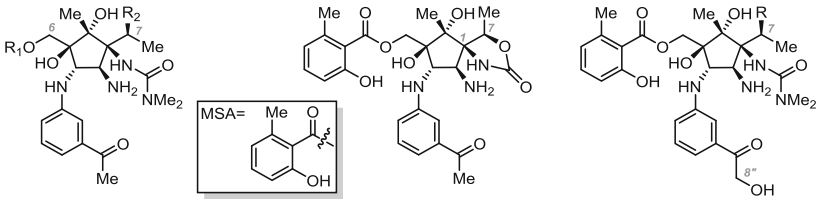


Fig. 2.3 Naturally-occurring pactamycin congeners

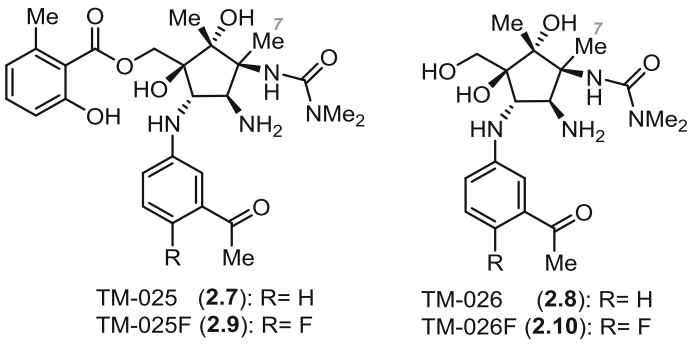


Fig. 2.4 Biosynthetically-engineered derivatives produced by Mahmud

interest. This approach has been successfully implemented in the case of doxorubicin (Doxil©) [10], paclitaxel (Abraxane©) [11] and others [12–14]. More recently, Bind Therapeutics [15] and Cerulean [16, 17] have ongoing clinical trials in NP formulations of cancer therapeutics (docetaxel, irinotecan, and camptothecin). DeSimone and co-workers have demonstrated the use of the Particle Replication in Non-Wetting Templates (PRINT®) technology to modulate the

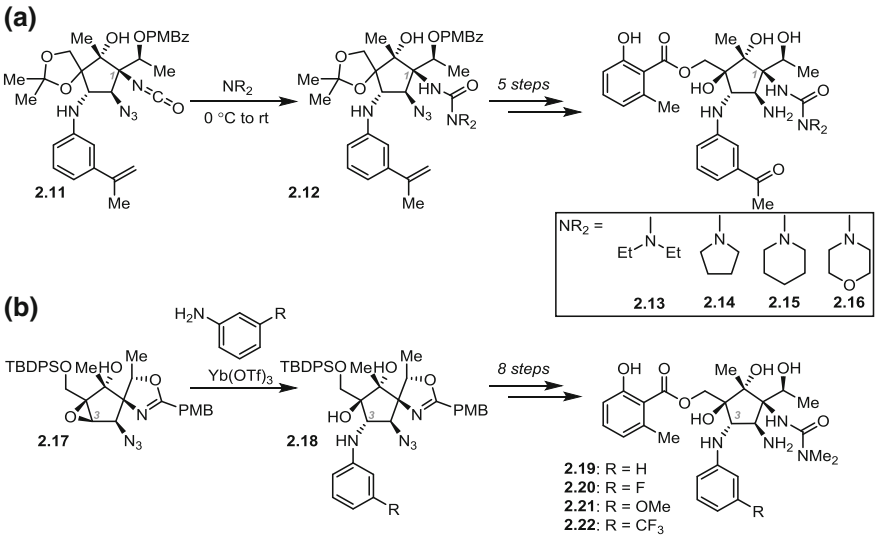


Fig. 2.5 Hanessian approach to pactamycin derivatives

activity of cytotoxic agents such as docetaxel, reducing unwanted side-effects and increasing therapeutic activity in vivo [18–21]. To the best of our knowledge, however, the incorporation of pactamycin or its congeners into NPs of any type with the goal of bioactivity attenuation has not yet been explored.

While an efficient chemical synthesis of **2.1** might provide the most flexibility in structural derivatization, the inherent complexity of the molecule has rendered this a difficult undertaking. Indeed, one researcher went so far as to argue that a chemical approach to derivatives of **2.1** was "inaccessible by synthetic organic chemistry [8]." The heavily-compacted and heteroatom-rich functionality in pactamycin presents a number of challenges toward selective structural modification. Additionally, while the unique functional groups present in the molecule (salicylate, dimethylurea, aniline) offer novel branch points for structural diversification, methods with which to install these moieties are underexplored in the literature.[1] As discussed in Chap. 1, a number of groups have undertaken this endeavor [30–34], most notably the landmark Hanessian total synthesis in 2011 [35, 36]. Since this initial publication, Hanessian has demonstrated the efficacy of his route in producing pactamycin derivatives (Fig. 2.5) [37, 38]. Entry into derivatives at the C1 position was accomplished via amine addition to late stage isocyanate **2.11**. These analogs were carried through the remaining sequence to provide C1 derivatives **2.13–2.16**. In addition, C3-aniline derivatives were accessed via a Lewis acid catalyzed epoxide opening strategy (**2.17** → **2.18**), which ultimately provided aniline

[1]Summary methods for synthesis of unsymmetrical dialkylureas: [22–29].

derivatives **2.19**–**2.22**. These compounds have provided the medicinal community with the first library of synthetically-generated pactamycin analogs to date.

2.2.1.2 Application of the Johnson Synthesis to Structural Analog Preparation

Our work on the synthesis of pactamycin culminated in 2013 with a fifteen-step, asymmetric synthesis from commercially available 2,4-pentanedione [39, 40]. Critical to our approach was to assemble the molecule in a fashion such that key functional groups were installed both in their native form and in a late-stage fashion; we surmised that this approach would provide our synthesis platform with the greatest possible flexibility, facilitating investigations of structure-activity relationships at all critical branch points (Fig. 2.6). To this end, we envisaged a

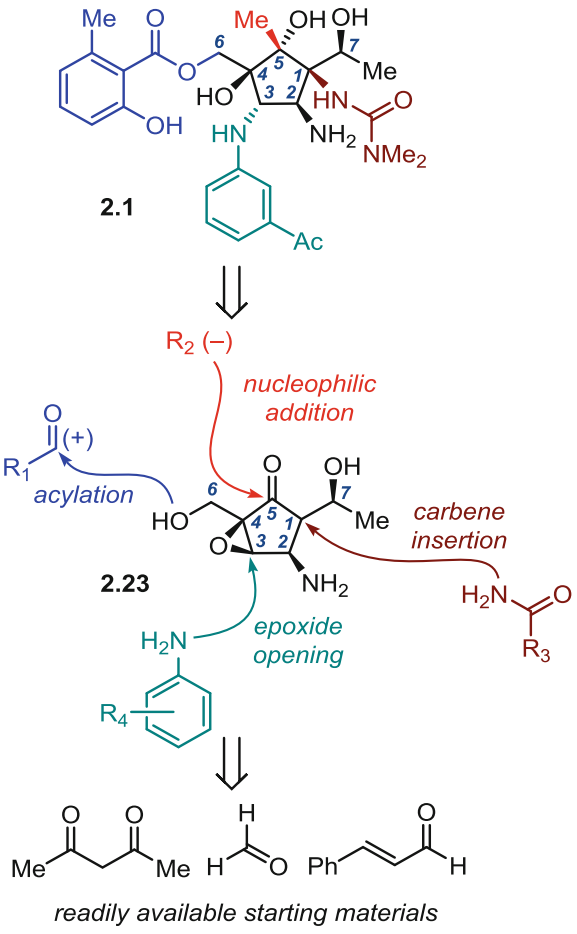
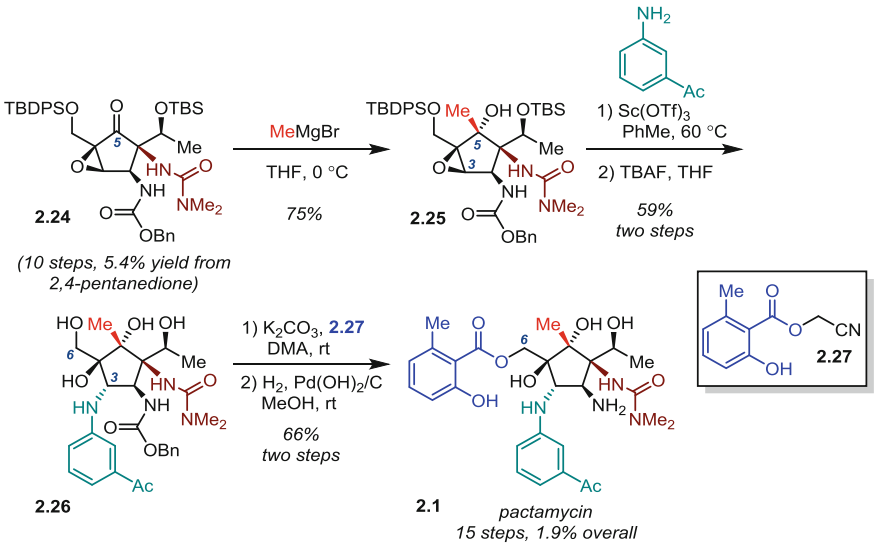


Fig. 2.6 Synthon analysis of pactamycin with branch points for structural derivatization



Scheme 2.1 Pactamycin synthesis Endgame: Summary

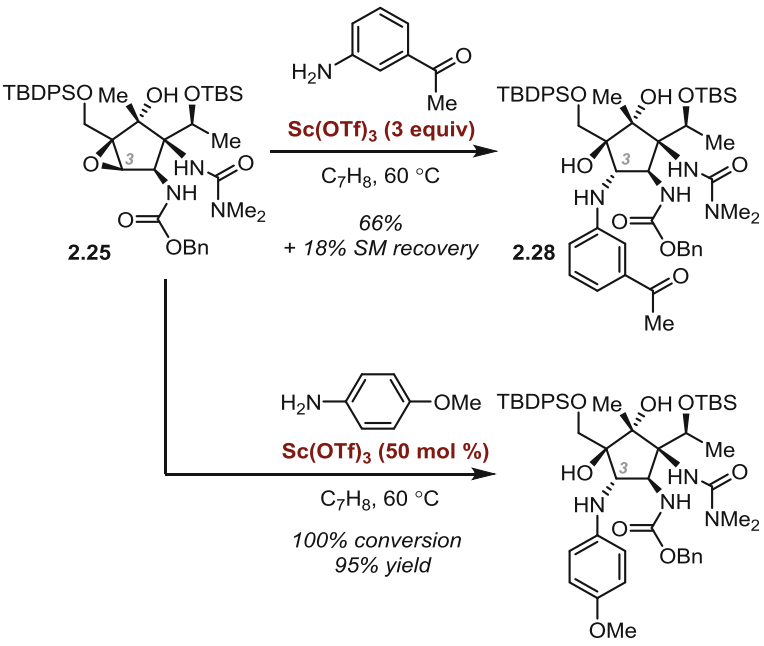
synthon such as **2.23** in which exploitation of the appropriate functional handles at the correct stage would install the requisite functionalities.

Our synthesis endgame was described in detail in Chap. 1 and is summarized in Scheme 2.1. Ketone intermediate **2.24** (synthesized in ten steps in gram quantities) would serve as our first point of derivatization. Nucleophilic methylation of **2.24** provided carbinol **2.25** in 75 % yield of a single diastereomer at C5. $Sc(OTf)_3$-promoted addition of *m*-acetylaniline installed the substituted C3-aniline necessary for elaboration to **2.1**, upon which silyl deprotection afforded tetraol **2.26**. Introduction of the remaining salicylate moiety to the C6-hydroxymethylene of **2.26** was accomplished via reaction with the reported acyl electrophile **2.27**, which upon hydrogenative removal of the Cbz protecting group, delivered pactamycin in fifteen steps and 1.9 % overall yield. These late stage introductions of core functionality (and in their final forms for elaboration to pactamycin) would enable direct access to synthetic diversity at the indicated positions.

2.3 Results and Discussion

2.3.1 C3 Aniline Derivative Preparation

We first pursued the preparation of pactamycin congeners at the C3-aniline position, inspired by the related epoxide-opening strategy by Hanessian and co-workers [35, 36]. At this juncture, it is valuable to recall from Chap. 1 that the union of



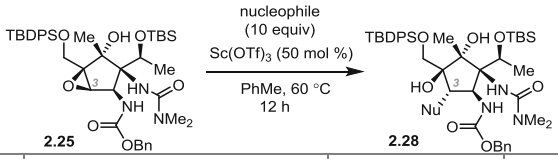
Scheme 2.2 Reactivity difference of *m*-acetylaniline and *p*-anisidine in epoxide opening

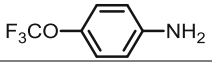
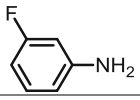
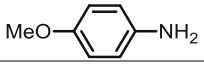
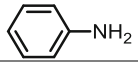
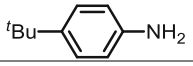
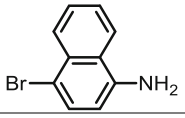
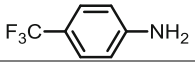
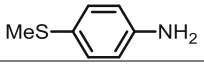
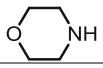
epoxide **2.25** with *m*-acetylaniline requisite for pactamycin synthesis suffered from incomplete starting material conversion, poor solubility of the aniline, and the requirement of superstoichiometric Lewis acid promoter (Scheme 2.2). We initially surmised that this poor reactivity was a function of the electron-poor aniline employed and that the use of varied anilines in this reaction would proceed more readily. Indeed, we were pleased to find that when *p*-anisidine was substituted for *m*-acetylaniline in the epoxide opening, the reaction proceeded in 100 % conversion and 95 % yield. Additionally, the stoichiometry of $Sc(OTf)_3$ could be lowered to catalytic amounts with no decrease in reaction efficiency.

With the aniline tolerance established, we turned our attention towards incorporation of a variety of anilines and nitrogen nucleophiles (Table 2.1). In the event, epoxide **2.25** reacted readily with a variety of electron-rich and electron-poor aniline nucleophiles. Even sterically-demanding fluorenyl (entry 6) and 4-bromo-1-naphthyl anilines (entry 7) proceeded in 59 and 87 % yields, respectively. We surprised to find, however, that extension of the epoxide opening reaction to aliphatic amines (entries 10–11) resulted in no reaction. Additionally, NaN_3 failed to react with **2.25**, giving only cleavage of the TBS protecting group.

Although we were disappointed by the lack of reactivity observed in the use of non-aromatic amines, we moved forward with aniline addition products **2.28a–i** towards preparation of their corresponding pactamycin analogs (Fig. 2.7). In general, this operation proceeded uneventfully to afford pactamycin derivatives **2.29a–h** over the three-step sequence. However, thioether substrate **2.28i** failed to undergo

Table 2.1 Scope of addition of nitrogen nucleophiles in epoxide opening reaction



Entry	Nucleophile	Product	% Yield[a]
1		**2.28a**	83
2		**2.28b**	43
3		**2.28c**	95
4		**2.28d**	71
5		**2.28e**	86
6	2-aminofluorene	**2.28f**	59
7		**2.28 g**	87
8		**2.28 h**	47
9		**2.28i**	77
10		–	TBS deprotection
11	$BnNH_2$	–	No reaction
12[b]	NaN_3	–	TBS deprotection

[a]Isolated yields
[b]Conditions: NaN_3 (1.1 equiv), Oxone (0.5 equiv), CH_3CN:H_2O (9:1), rt

Cbz deprotection in the final step (presumably due to poisoning of the catalyst by the substrate), rendering this derivative inaccessible via this route. In the case of bromonaphthyl addition product **2.28 g**, reduction of the aryl bromide was observed during Cbz deprotection, providing naphthylaniline **2.29 g** in decreased yield as the final derivative.

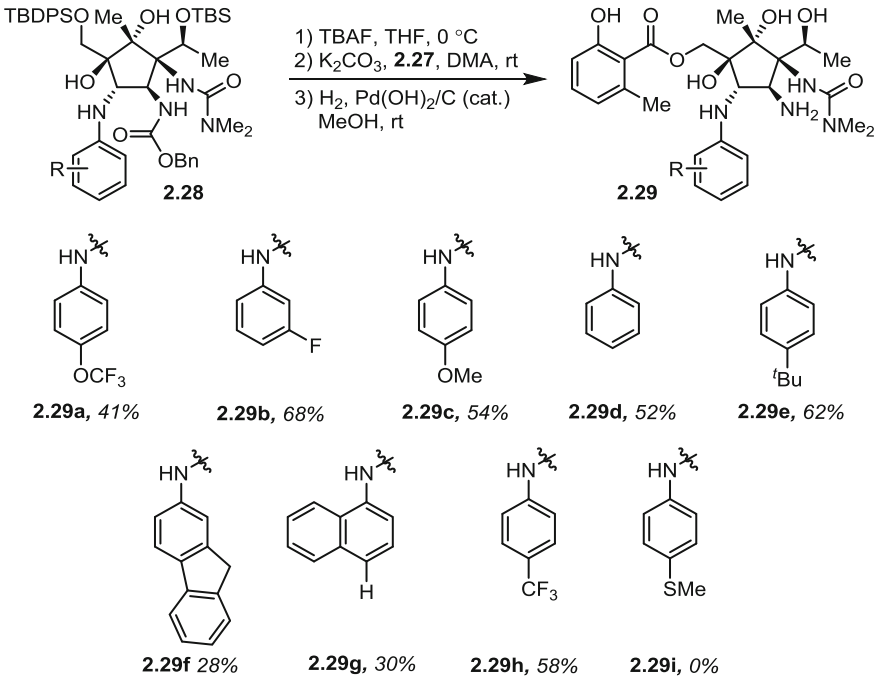
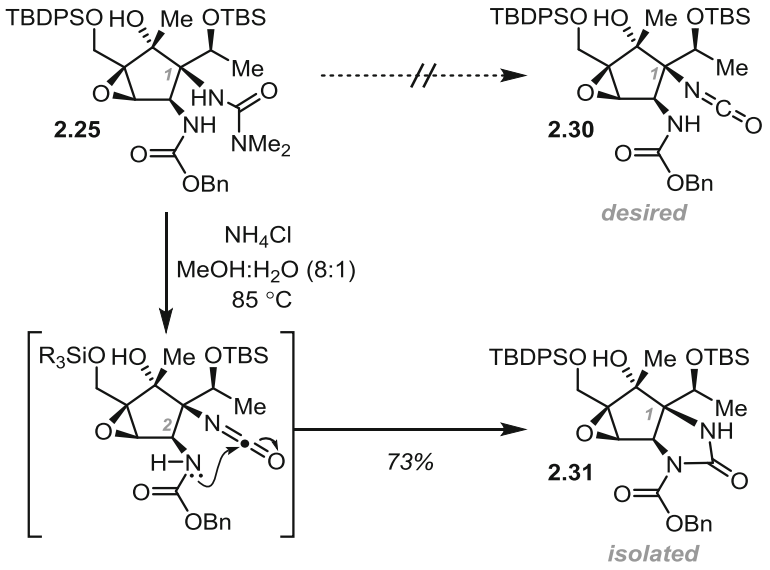


Fig. 2.7 Synthesis completion of C3 aniline pactamycin derivatives

2.3.2 *Derivatization at the C1 Dimethyl Urea: A Surprising Ring Closure*

Hanessian's approach toward preparation of pactamycin analogs at the C1 dimethylurea position substituent relied on the trapping of an in situ generated isocyanate electrophile late in the synthesis (**2.11**) [35, 36]. This tactic proved effective in the preparation of a series of functionalized ureas in good yields. By contrast, our synthesis of **2.1** utilized an early-stage N–H insertion reaction to install the urea [39, 40]. Synthetic diversification from this early intermediate would be a significant challenge. Consequently, we envisaged a similar isocyanate formation/trapping strategy from carbinol intermediate **2.25** via the acid-catalyzed elimination of dimethylamine (Scheme 2.3). The literature showed that isocyanate generation from ureas could be readily accomplished via treatment with mildly acidic conditions [41]; in a first pass, epoxide **2.25** was treated with NH_4Cl in refluxing MeOH. Upon observing clean conversion to a single product, we were surprised to isolate imidazolidinone **2.31** and not the desired isocyanate **2.30**. Imidazolidinone **2.31** arises from intramolecular trapping of the in situ generated isocyanate with the C2 amine carbamate functionality.

Considering that the facility of this intramolecular process might preclude all attempts at intermolecular isocyanate addition, focus shifted to other avenues of

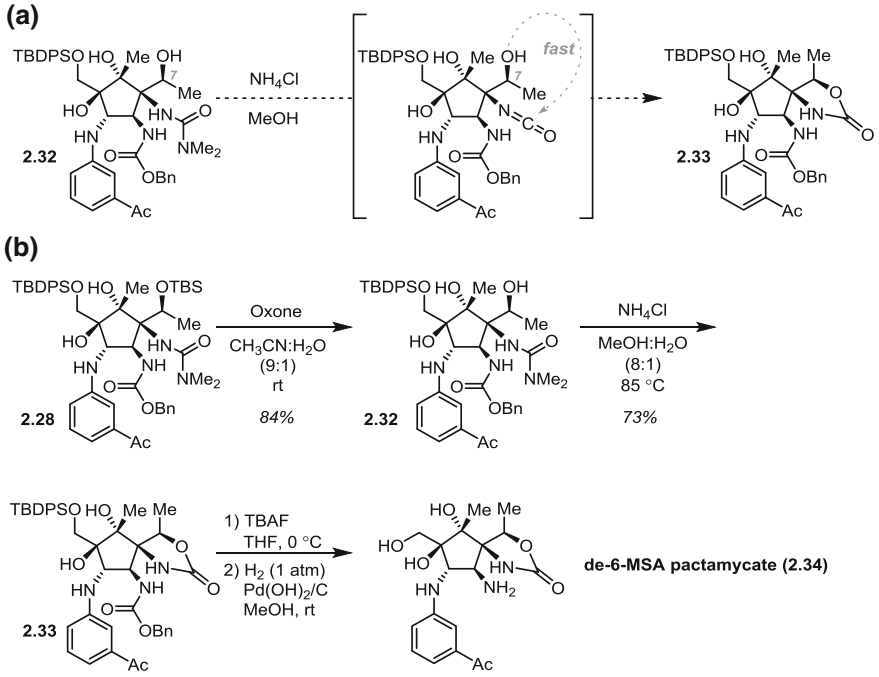


Scheme 2.3 Surprising imidazolidinone formation

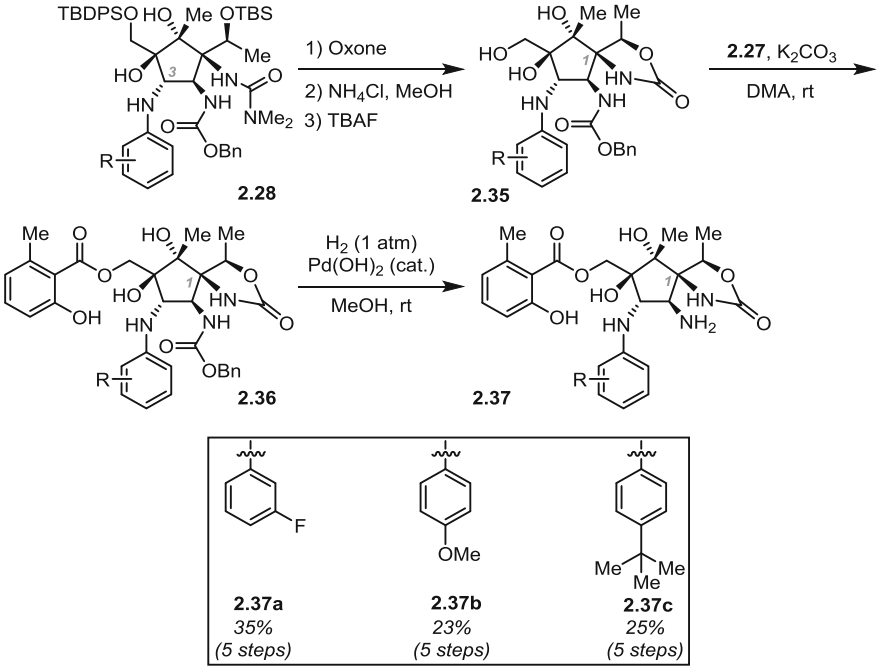
trapping isocyanate **2.30** (Scheme 2.4). We surmised that if the isocyanate were generated in the presence of an unprotected C7-hydroxyl (**2.32**), then intramolecular trapping would result preferentially in formation of the corresponding oxazolidinone **2.33** (and not the undesired imidazolidinone). This reactivity pattern would enable access to analogs of the naturally-occurring congener pactamycate (**2.4**), for which no synthetic derivatives had been previously reported. In practice, we selected the aniline addition product **2.28** for investigation. A screen of deprotection conditions revealed that treatment of **2.28** with Oxone® in aqueous CH_3CN furnished alcohol **2.32** in 84 % yield. Submission of this compound to the conditions developed for isocyanate generation resulted in the formation of a single product **2.33** in 73 % yield, although we were unsure of whether **2.32** had undergone oxazolidinone or imidazolidinone formation. To ascertain this structural confirmation, we subjected **2.33** to silyl deprotection and Cbz hydrogenation, whereupon we isolated de-6-MSA pactamycate **2.34**, whose spectral data had been previously reported [36]. This result confirmed the identity of **2.33** as the product illustrated.

2.3.3 Preparation of Pactamycate Derivatives

With the feasibility of this sequence established, we set out to prepare a series of C3-aniline pactamycate derivatives (Scheme 2.5). Initiating with anilines **2.28b**, **2.28c**, and **2.28e** already in our possession, TBS deprotection followed by oxazolidinone formation proceeded smoothly to give the corresponding oxazolidinones,



Scheme 2.4 Investigating access to pactamycate derivatives. **a** Hypothesis. **b** Application



Scheme 2.5 Preparation of pactamycate derivatives

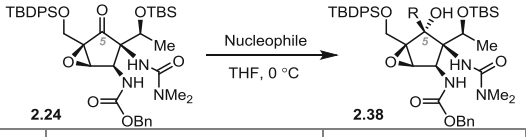
which upon desilylation, acylation, and hydrogenolysis, provided pactamycate derivatives **2.37a–c** in 35, 23, and 25 % yields, respectively, over the five-step sequence.

2.3.4 C5 Derivatization

Access to pactamycin derivatives at C5 was envisioned via addition of alternative carbon nucleophiles to ketone **2.24**. We were concerned, however, that the steric encumbrance of ketone **2.24** might preclude the application of nucleophiles with elevated complexity relative to MeMgBr (Table 2.2). Fortunately, we found that ketone **2.24** reacted efficiently with nucleophiles EtMgBr, *n*-hexylMgBr, and H_2C = CHMgBr to give the corresponding carbinols in 75, 73, and 43 % yields, respectively. Unfortunately, larger aliphatic nucleophiles (^{i}Pr, isopropenyl) failed to react with **2.24**, returning only recovered starting material. As an additional example, the ketone was also reduced with $NaBH_4$ to give the *seco*-alcohol **2.38d** in 88 % yield.

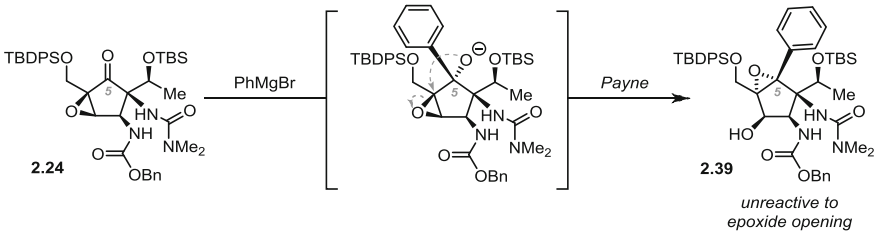
When a sterically-demanding aryl nucleophile (PhMgBr) was employed, complete conversion to a single product **2.39** matching the desired mass spectrum was observed (Scheme 2.6), although the ^{1}H NMR spectrum was significantly different from that expected. Additionally, this product was unreactive in the subsequent epoxide opening stage. On the basis of these facts, we speculate that the most probable identity of **2.39** is the result of an in situ Payne rearrangement in order to relieve the additional strain associated with the encumbering nucleophile [42]. Unfortunately, this unexpected side reaction was observed in the addition of all larger nucleophiles, precluding the further exploration of C5 ketone diversity.

Table 2.2 Addition of nucleophiles to advanced ketone intermediate



Entry	Nucleophile	Product	% Yield[a]
1	Me MgBr	**2.38a**	75
2	Me (CH2)4 MgBr	**2.38b**	73
3	MgBr	**2.38c**	43
4	Me Me MgBr	–	No reaction
5	Me MgBr	–	No reaction
6[b]	$NaBH_4$	**2.38d**	88

[a]Isolated yields
[b]Conditions: $NaBH_4$, MeOH, −45 °C

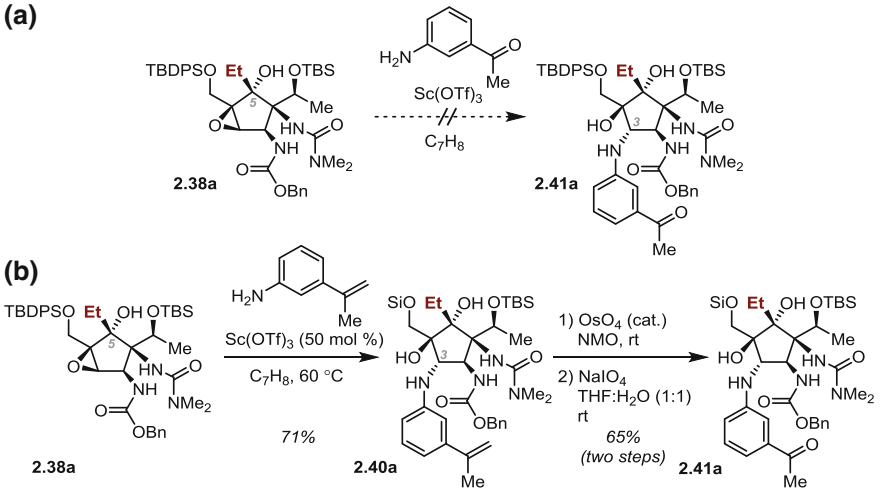


Scheme 2.6 Rearrangement observed in the case of Aryl Nucleophiles

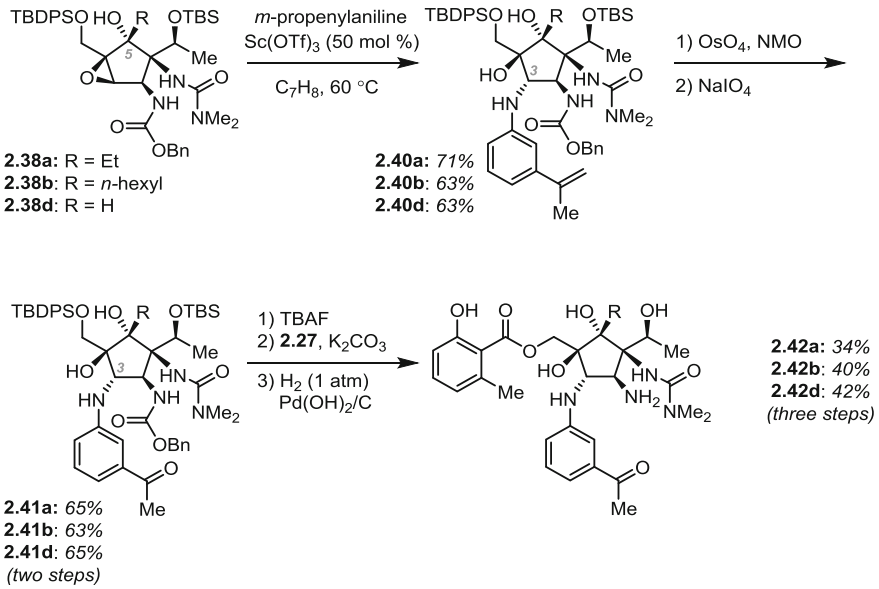
2.3.5 *Elaboration of C5 Addition Products to Pactamycin Derivatives*

With addition products **2.38a–d** in hand, we proceeded in our studies to complete C5 analog preparation (Scheme 2.7). However, upon subjection of ethyl derivative **2.38a** to the previously optimized conditions for *m*-acetylaniline addition, no reaction was observed. Increasing the loading of $Sc(OTf)_3$ or the reaction time/temperature had seemingly no effect. We reasoned at this impasse that the added steric encumbrance about C5 hinders addition of the electron-poor *m*-acetylaniline, either due to poor coordination of the Lewis acid or by an unfavorable substrate conformation for addition relative to the parent C5-methyl compound.

In order to circumvent this issue, we looked to the strategy of Hanessian and co-workers wherein the required *m*-acetylaniline was first incorporated as an *m*-isopropenyl derivative [35, 36]. The ketone was then revealed via Johnson-Lemieux oxidation of the olefin. Fortunately, epoxide opening of **2.38a** with *m*-isopropenyl aniline afforded aniline **2.40a** in 71 % yield. Alkene **2.40a** was then subjected to Johnson-Lemieux conditions, revealing acetophenone **2.41a** in 53 % yield over two steps. With this reactivity established, C5 addition products **2.38a**, **2.38b**, and **2.38d**



Scheme 2.7 Native aniline installation to pactamycin C5 derivatives



Scheme 2.8 Synthesis of C5 pactamycin derivatives

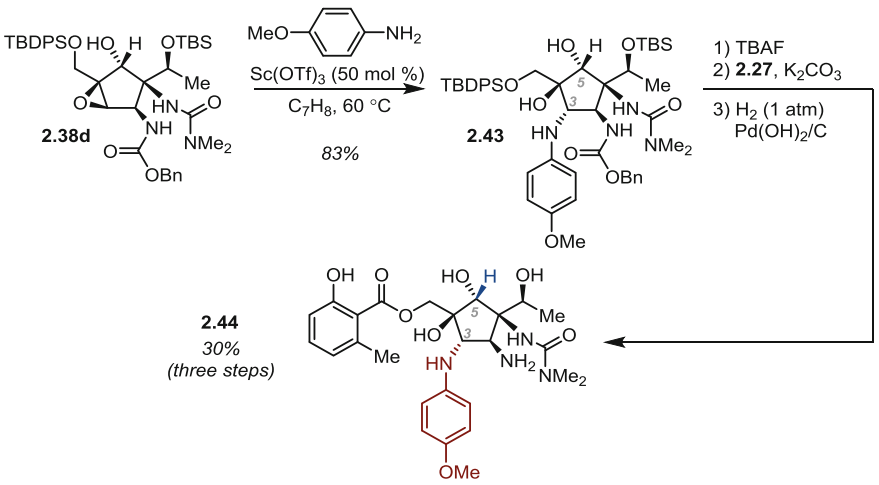
were carried through the revised aniline addition sequence (Scheme 2.8). Elaboration of vinyl addition product **2.38c** to the corresponding pactamycin derivative was not attempted as reduction of the alkene was expected to occur during the final hydrogenation stage.

Finally, in order to probe the activity profile of a C5 derivative bearing an alternate functional group at the aniline position, a second C5-hydrido analog was prepared via addition of *p*-methoxyaniline to **2.38d** in the epoxide opening stage (Scheme 2.9).

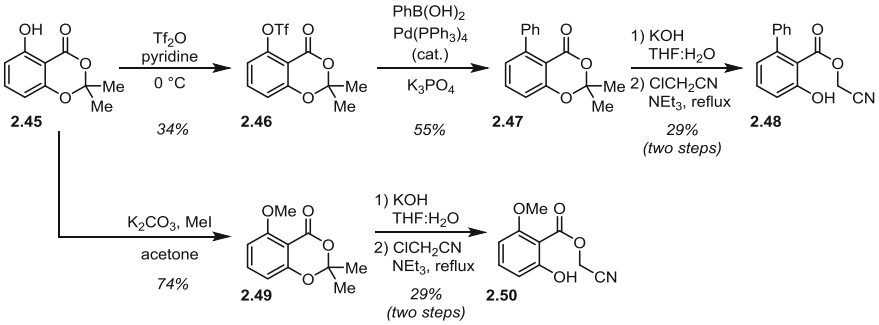
As anticipated based on the above studies, addition of this aniline proceeded uneventfully under the optimized conditions to give anisidine **2.43** in 83 % yield. Elaboration of this material through the remaining sequence provided derivative **2.44** in 30 % yield over the three-step sequence.

2.3.6 Derivative Preparation at the C6 Hydroxymethylene Position

The next point of synthetic diversification centered on manipulation of the salicylate-bearing C6 ester in **2.1**. The esters we hoped to prepare included both simple esters as well as "salicylate-like" esters to examine the importance of this functional group in the key binding event of **2.1** (Scheme 2.10). Accordingly, we employed a modified procedure for that reported in the synthesis of **2.27** [43] to prepare electrophiles **2.48** and **2.50**. Phenyl-substituted salicylate **2.48** was synthesized via Suzuki reaction of triflate **2.46** followed by hydrolysis and



Scheme 2.9 Preparation of a C5, C3 pactamycin derivative

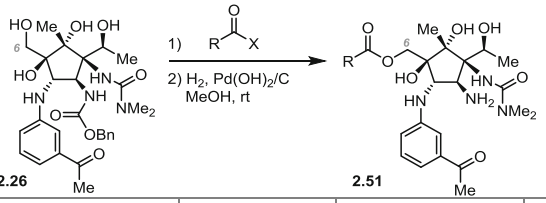


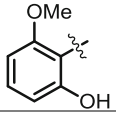
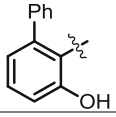
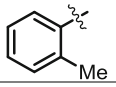
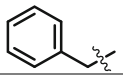
Scheme 2.10 Synthesis of varied Salicylate Electrophiles

esterification. Differentiated methoxyphenol was prepared from the known phenol **2.45** via etherification and hydrolysis/esterification.

With these electrophiles in hand, we began screening esters in the acylation of tetraol **2.26** (Table 2.3). Gratifyingly, efficient monoacylation was accomplished with a variety of the electrophiles examined in good yields. Modified salicylates **2.50** (entry 1) and **2.48** (entry 2) both underwent esterification under the conditions optimized for esterification with **2.27**. An *o*-toluyl ester was also tolerated (entry 3). Esterification of **2.26** with aliphatic electrophiles performed well (entries 4–5), and the corresponding mesylate ester could also be prepared (entry 6). The resulting monoesters were then submitted to the optimized conditions for Cbz hydrogenolysis, affording C6 derivatives **2.51b–e**. Unfortunately, in the case of the methoxyphenol **2.51a** and mesylate **2.51f**, only starting material decomposition was observed at this stage.

Table 2.3 Synthesis of C6 hydroxymethylene pactamycin derivatives

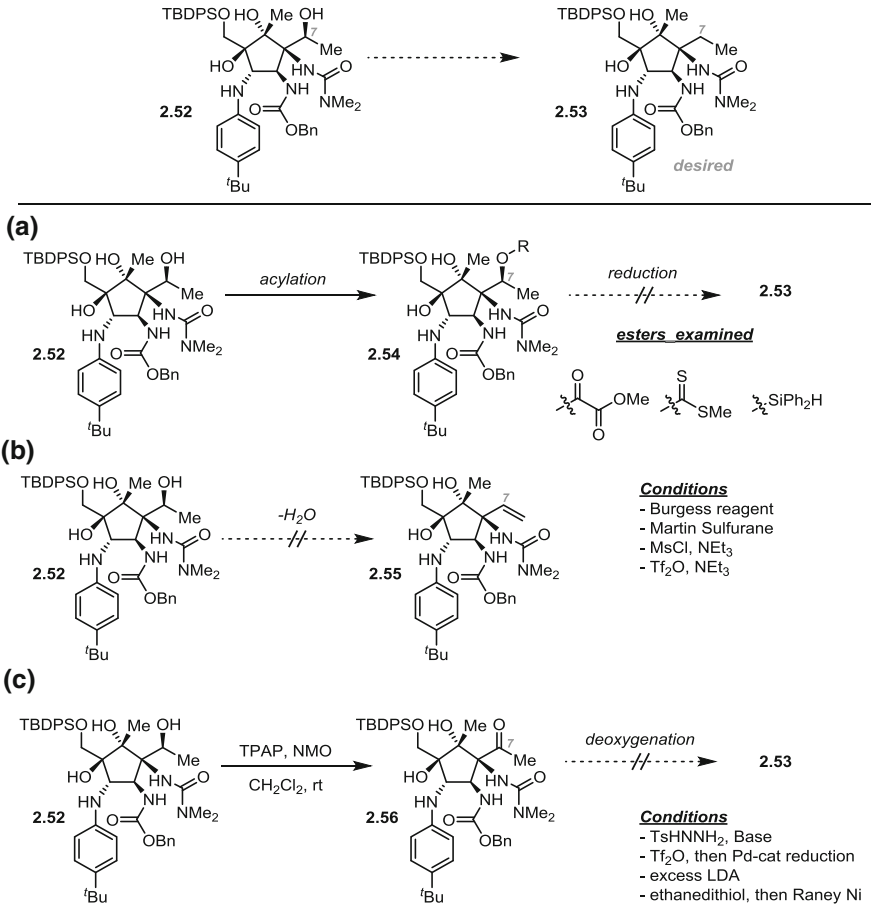


Entry	R	Product	% Yield 1[a]	% Yield 2[a]
1		**2.51a**[b]	57	Decomposition
2		**2.51b**[b]	43	62
3		**2.51 c**[c]	60	73
4		**2.51d**[c]	83	76
5		**2.51e**[c]	87	61
6	MsCl	**2.51f**[c]	54	Decomposition

[a]Isolated yields
[b]Conditions: K_2CO_3, DMA, rt
[c]Conditions: 2,4,6-collidine, CH_2Cl_2, −78 °C to rt

2.3.7 *Attempts to Prepare C7-Deoxypactamycin Derivatives*

The next series of derivatives we sought to prepare were those in which the C7 hydroxyl was removed. Cognizant of the known bioactivity differences between **2.1** and its 7-deoxy congener (**2.2**) [7, 8], we began probing selective reduction of the C7 hydroxyl to its corresponding methylene. Scheme 2.11 summarizes the approaches we elected to pursue. Because it was easily accessible and obviated potential issues associated with the reactive C3 acetophenone functionality, we selected aniline addition product **2.52** as a model substrate for examination (prepared via Oxone® deprotection of **2.28e**). We first pursued radical reduction of a suitable C7 ester such as **2.54**. To this end, we prepared the corresponding xanthate, oxalate, and diphenylsilyl ether. Unfortunately, all conditions examined towards radical reduction of these compounds ($SnBu_3H$, AIBN/Et_3B/$(TMS)_3SiH$) failed to provide **2.53**. In most cases, only deacylation was obtained to return **2.52**. A second

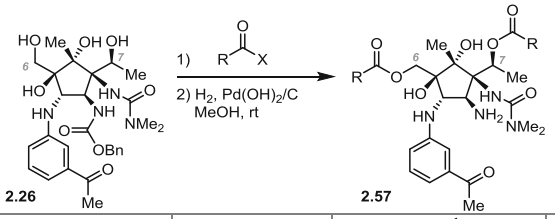


Scheme 2.11 Attempts directed at reduction of the C7-Hydroxyl. **a** Radical reduction. **b** Dehydration/hydrogenation. **c** Oxidation/deoxygenation

approach envisioned dehydration of the C7 hydroxyl followed by hydrogenation to arrive at **2.53**. This approach was also unsuccessful, as even the Burgess reagent and the Martin sulfurane showed no reactivity towards alcohol **2.52**. In a final case, oxidation of the C7 hydroxyl (TPAP, NMO) furnished the resulting ketone **2.56**. From this compound, we investigated deoxygenation of the ketone via its derived enol triflate or dithiolane. However, this route also gave no promise for yielding access to **2.53**.

As an alternative strategy, we envisaged masking of the C7 hydroxyl as its ester might serve the same purpose as deoxygenation (i.e. removal of the H-bonding interaction at C7) [44, 45]. From tetraol **2.26**, this would take the form of bis-acylation of the C6 and C7 hydroxyl groups (Table 2.4). In practice, we were pleased to find that tetraol **2.26** underwent clean bis-acylation with Ac_2O, PivCl,

Table 2.4 Synthesis of C6,C7 Bis-Acylated pactamycin derivatives



Entry	R	Product	% Yield 1[a, b]	% Yield 2[a, b]
1		**2.57a**	86	38
2		**2.57b**	92	53
3		**2.57c**	76	72

[a]Isolated yields
[b]Conditions: electrophile (2.2 equiv), NEt_3, DMAP (10 mol%), CH_2Cl_2, 0 °C to rt

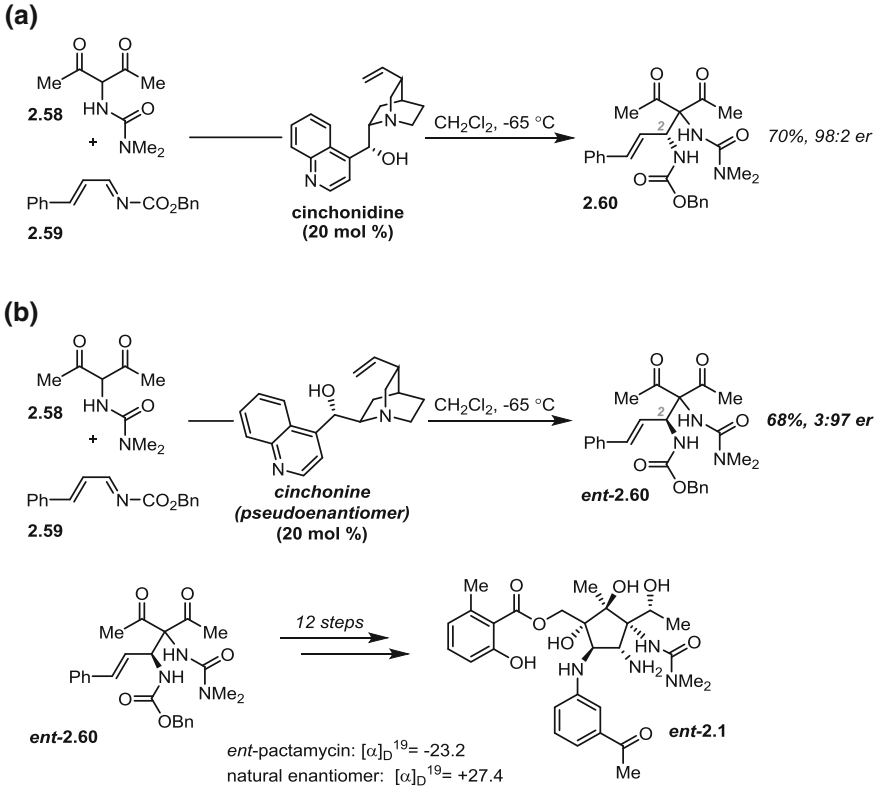
and cyclohexoyl chloride to give the corresponding diesters in 86, 92 %, and 76 % yields, respectively.

The ester identities were selected on the basis of varying levels of steric encumbrance about C7. Cbz hydrogenolysis of these compounds provided the diesters **2.57a–c**.

2.3.8 Synthesis of Ent-*Pactamycin*

In order to better understand the effects of chirality on the parent pactamycin structure, we investigated the preparation of *ent*-**2.1** (Scheme 2.12). As described in Chap. 1, the enantiomer identity in our total synthesis was established via an early-stage asymmetric Mannich addition (**2.58** → **2.60**) [39, 40]. To translate this chemistry to the synthesis of *ent*-**2.1**, cinchonine, the pseudoenantiomer of cinchonidine, would need to be employed. To this end, we were pleased to find that the asymmetric Mannich addition proceeded smoothly when cinhonine was used (**2.58** → *ent*-**2.60**) with a yield and selectivity comparable to that of the parent reaction (68 %, 3:97 er).

This material was advanced through the remaining steps of the synthesis to provide *ent*-**2.1**, the optical activity of which was confirmed via comparison of the specific rotation with natural pactamycin.

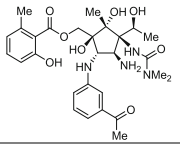
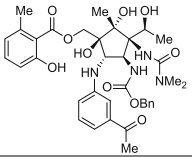
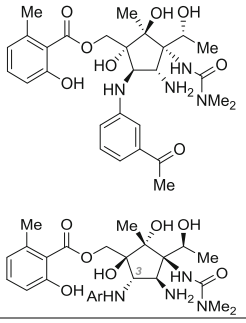
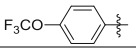
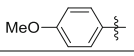
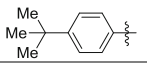
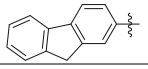
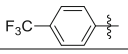


Scheme 2.12 Synthesis of *ent*-Pactamycin. **a** Pactamycin mannich addition. **b** *ent*-Pactamycin synthesis

2.3.9 Carcinoma *in Vitro Biological Evaluation*

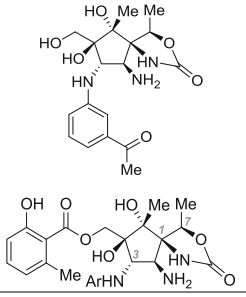
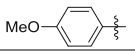
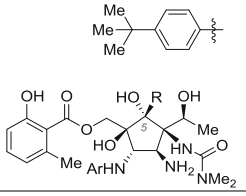
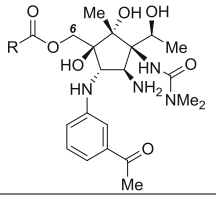
Having prepared a library of novel compounds, we set out to examine their varied biological profiles. Specifically, compounds were tested against human breast (MDA-MB-231), ovarian (SK-OV-3), and lung (A549) *carcinoma* cell lines. Additionally, the human embryonic cell line for which pactamycin's toxicity has been established (MRC-5) was assayed for comparison [46]. The results for all derivatives are summarized in Table 2.5. As anticipated, pactamycin (**2.1**, entry 1) displayed exceptional potency, showing nanomolar inhibition against all three *carcinoma* cell lines. For comparison, the penultimate intermediate in our synthesis of pactamycin (**2.61**, entry 2) bearing Cbz protection at the C2-aminomethine (entry 2) showed a dramatic decrease in activity relative to **2.1.** *ent*-Pactamycin (*ent*-**2.1**, entry 3) displayed a threefold order of magnitude decrease in bioactivity, illustrating the impact of the natural enantiomer of pactamycin to effective cell-growth inhibition.

Table 2.5 *Carcinoma* biological evaluation of pactamycin derivatives[a]

Entry	Structure	Code Number	A549 EC_{50}	MDA-MB-231 EC_{50}	SK-OV-3 EC_{50}	MRC-5 EC_{50}
1		**2.1**	160 nM	124 nM	129 nM	53 nM
2		**2.61**	11.8 μM	10.4 μM	12 μM	n.d.[b]
3		***ent*-2.1**	2.1 μM	1.2 μM	1.6 μM	933 nM
4	Ar = 	**2.29a**	800 nM	659 nM	1.4 μM	380 nM
5		**2.29b**	141 nM	556 nM	434 nM	314 nM
6		**2.29c**	1.0 μM	n.d.	600 nM	582 nM
7		**2.29d**	777 nM	4.0 μM	4.0 μM	682 nM
8		**2.29e**	884 nM	3.3 μM	1.6 μM	2.3 μM
9		**2.29f**	324 nM	376 nM	145 nM	431 nM
10		**2.29 g**	2.21 μM	1.84 μM	2.44 μM	860 nM
11		**2.29 h**	760 nM	800 nM	436 nM	366 nM

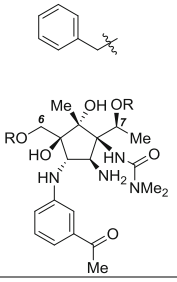
(continued)

Table 2.5 (continued)

Entry	Structure	Code Number	A549 EC_{50}	MDA-MB-231 EC_{50}	SK-OV-3 EC_{50}	MRC-5 EC_{50}
12		**2.34**	6.0 μM	n.d.	3.8 μM	2.9 μM
13	Ar = 	**2.37a**	n.d.	n.d.	n.d.	n.d.
14		**2.37b**	n.d.	n.d.	n.d.	n.d.
15		**2.37c**	n.d.	n.d.	n.d.	n.d.
16	R = C_2H_5 Ar = *m*-acetyl	**2.42a**	n.d.	n.d.	n.d.	2.1 μM
17	R = C_6H_{14} Ar = *m*-acetyl	**2.42b**	n.d.	n.d.	n.d.	11 μM
18	R = H Ar = *m*-acetyl	**2.42d**	32 nM	50 nM	7 nM	6.5 nM
19	R = H Ar = *p*-methoxy 	**2.44**	83 nM	356 nM	91 nM	49 nM
20		**2.51b**	88 nM	203 nM	103 nM	129 nM
21		**2.51c**	114 nM	79 nM	80 nM	105 nM

(continued)

Table 2.5 (continued)

Entry	Structure	Code Number	A549 EC_{50}	MDA-MB-231 EC_{50}	SK-OV-3 EC_{50}	MRC-5 EC_{50}
22		**2.51d**	118 nM	300 nM	75 nM	100 nM
23		**2.51e**	194 nM	352 nM	436 nM	366 nM
24	R = Ac	**2.57a**	137 nM	458 nM	123 nM	132 nM
25	R = Piv	**2.57b**	175 nM	1.93 μM	86 nM	396 nM
26	R = $CO(C_6H_{11})$	**2.57c**	588 nM	2.44 μM	593 nM	778 Nm

[a]Assays were carried out as triplicates

[b]Not determined

Generally, all C3-aniline derivatives (entries 4–11) showed a marginal to significant decrease in activity relative to **2.1** across all cell lines, although **2.29b** (entry 5) showed comparable activity against A549 (EC_{50} = 141 nM) with a marginal decrease in MRC5 activity. With regard to the pactamycate series of analogs, De-6-MSA pactamycate **2.34** (entry 12) showed only minor cell-growth inhibition. This was not an unexpected result, however, as biological assays of **2.34** conducted by Hanessian and co-workers also showed little promising activity [37, 38]. Altering the C3 aniline position of the pactamycate parent structure (entries 13–15) resulted in complete loss of biological activity. These results, in combination with those of the pactamycin C3 analogs, speak to the importance of the *m*-acetyl functionality in pactamycin to its bioactivity [47, 48].

The results of compounds bearing diversity at C5 are shown in entries 16–19. Extending the length of the carbon chain at C5 (entries 16–17) had significantly deleterious effects to bioactivity as a complete loss of *carcinoma* activity was observed, leaving only low inhibition of MRC-5. However, removing alkyl functionality altogether at C5 (entries 18–19) had the opposite effect, as these C5 hydrido analogs (**2.42d**, **2.44**) displayed the greatest activity across all cell lines of any compound tested in our study (including pactamycin). We speculate that these results are primarily a function of adjusting the lipophilicity of the structure relative to **2.1** [49]. As further evidence to the importance of the *m*-acetyl functionality, **2.44** (entry 19) showed less potency across all cell lines in comparison to **2.42d** (entry 18).

The results of our diversification of the C6 hydroxymethylene (entries 20–23) are in agreement with Hanessian's earlier findings. Namely, no significant gain (or loss) of biological activity was observed when the salicylate ester was altered relative to the parent pactamycin structure. These results further support the hypothesis that the C6 ester side chain has a limited role in the key binding event of **2.1** in the 30S ribosome [37, 38]. The three prepared C6,C7 bis-acylated derivatives (entries 24–26) showed a linear decrease in activity with steric encumbrance of the ester group. These results suggest that the C7 hydroxyl in **2.1** plays a larger role in the bioactivity of the structure than the C6 hydroxymethylene.

2.3.10 Analysis of Pactamycin Derivatives via NCI 60-Cell Line Screen

Upon collection of these initial data, derivatives *ent*-(**2.1**), **2.42d**, **2.51c**, **2.29f**, and **2.57a** were identified as the most promising lead compounds and assayed via the NCI-60 human tumor cell line screen. Upon initial one-dose screening, all five compounds were found to have sufficient activity to merit the subsequent five-dose assay. These derivatives were evaluated to determine GI_{50} (50 % growth inhibition) values. The results of these assays are described in detail in the Sect. 2.5 and summarized in Table 2.6. Additionally, the previously documented cell data for **2.1** is shown for comparison.

As expected based on our initial screen, *ent*-(**2.1**) showed multiple orders of magnitude loss in activity across the entire assay. By contrast, compound **2.42d** bearing a secondary hydroxyl at C5 demonstrated exceptional activity, showing nM inhibition throughout the screen and outperforming pactamycin in multiple cell lines. Derivatives **2.51c** (modified salicylate ester) and **2.57a** (C6,C7 diacetoxy-pactamycin) also demonstrated general nM activity in the assay. The final derivative **2.29f** bearing a fluorenyl aniline at C3 showed a general decrease in biological activity relative to **2.1** by factors of 10–100.

2.3.11 Pactamycin Nanoparticle Fabrication and Biological Evaluation

With these studies completed, we set out to examine the efficacy of pactamycin and select analogs to activity modulation via nanoparticle encapsulation. Polymeric PRINT® nanoparticles were fabricated by encapsulating compounds **2.1**, **2.29e**, and **2.42d**, in poly(*d*,*l*-lactide) using previously described methods [19, 50]. Compounds **2.29e** and **2.42d** were selected on the basis of observing the effect of nanoformulation on derivatives both more and less active than **2.1**. PRINT® NPs containing **2.1** and derivatives **2.29e** and **2.42d** all showed similar hydrodynamic

Table 2.6 Summary GI_{50} values from NCI-60 cell line screening[a]

GI_{50} (μM)	2.1[b]	*ent*-2.1	2.42d	2.51c	2.29f	2.57a
MOLT-4	<0.10	1.19	0.046	0.12	0.78	0.33
NCI-H322 M	0.12	3.72	0.016	0.33	1.07	0.48
HCT-15	0.03	20.0	0.16	0.65	1.46	10.2
SNB-19	<0.10	3.07	0.52	0.19	1.40	0.57
M14	0.12	3.01	0.10	0.19	0.88	0.68
OVCAR-3	<0.10	2.50	0.041	0.20	0.73	0.53
RXF 393	<0.10	1.50	0.064	0.12	0.61	0.61
DU-145	<0.01	7.26	0.15	0.26	1.37	0.34
MCF7	<0.01	2.04	0.051	0.17	0.73	7.31

[a]Data obtained from NCI-60 screening. See Sect. 2.5 for comprehensive results. MOLT-4, leukemia cell line; NCI-H322 M, nonsmall-cell lung cancer cell line; HCT-15, colon cancer cell line; SNB-19, CNS tumor cell lines; M14, melanoma; OVCAR-3, ovarian cancer cell line; RXF 393, renal cancer cell line; DU-145, prostate cancer cell line; MCF7, breast cancer cell line
[b]Data can be accessed from the CAS: 23668-11-3 at the following website: http://dtp.cancer.gov/dtpstandard/dwindex/index.jsp

radii and PDI as determined by dynamic light scattering (DLS) [51]. Scanning electron microscopy (SEM) analysis confirmed uniform particle size and shape regardless of compound identity, and drug loading of each sample was found to be ~10 % as determined by HPLC [52]. NP-encapsulated compounds **NP-2.1**, **NP-2.29e**, and **NP-2.42d**, were then examined in our assay, and the results are given in Table 2.7 where the baseline toxicity values for each compound are restated for comparison.

In vitro analysis of the derivative NP formulations showed bimodal effects on therapeutic activity. In the A549 assay, nanoparticle delivery increased the cytotoxicity of the therapeutic cargo. **NP-2.1** demonstrated an EC_{50} threefold more potent than pactamycin itself (52 to 160 nm, respectively). **NP-2.42d** showed a near fivefold increase in potency when compared to the unadulterated small molecule (6.5 to 32 nM, respectively). Even compound **2.29e**, a less active drug in

Table 2.7 Cell-Based Assay Comparison for Pactamycin Derivatives and NP Counterparts[a]

Compound	A549 EC_{50}	MDA-MB-231 EC_{50}	MRC-5 EC_{50}
2.1	160 nM	124 nM	53 nM
NP-**2.1**	52 nM	117 nM	52 nM
2.29e	884 nM	3.3 μM	2.3 μM
NP-**2.29e**	693 nM	5.5 μM	1.8 μM
2.42d	32 nM	50 nM	6.5 nM
NP-**2.42d**	6.5 nM	724 nM	18 nM

[a]Assays were carried out as triplicates

comparison to **2.1**, showing a nominal reduction in EC_{50} value for the A549 cell line. Of significant interest was the increase in selectivity observed for **2.42d**, wherein the EC_{50} for A549 decreased while the EC_{50} for MDA-MB-231 and MRC5 increased.

2.4 Conclusion

In summary, we have demonstrated the efficacy of our synthesis of pactamycin to efficient and modular production of structural derivatives with a range of varied bioactivities. Enabled branch points for derivatization include the C3 aniline, C5 carbinol, and the C6 hydroxymethylene position. Additionally, this route has enabled unprecedented access to derivatives of the natural congener pactamycate and the enantiomeric series of pactamycin. These results have provided additional insight into the roles that each functional group plays in providing the observed activity of the parent structure. Additionally, we have established a heretofore undocumented proof-of-concept for modulation of pactamycin bioactivities via the use of the PRINT® nanoparticle delivery vehicle.

2.5 Experimental Details

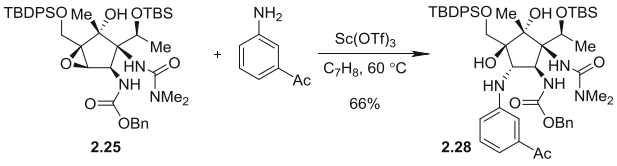
Methods: **General**. Infrared (IR) spectra were obtained using a Jasco 460 Plus Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker Avance 400 (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz), Bruker Avance III 500 (^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz) or a Bruker Avance III 600 (^{1}H NMR at 600 MHz and ^{13}C NMR at 150 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm, ^{1}H NMR: CD_3OD at 3.34 ppm; ^{13}C NMR: CD_3OD at 49.8 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, br d = broad doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Mass spectra were obtained using a Micromass Quattro-II triple quadrupole mass spectrometer in combination with an Advion NanoMate chip-based electrospray sample introduction system and nozzle or a Thermo LTqFT mass spectrometer with electrospray introduction and external calibration. All samples were prepared in methanol. Analytical thin layer chromatography (TLC) was performed on Sorbent Technologies 0.20 mm Silica Gel TLC plates. Visualization was accomplished with UV light, $KMnO_4$, and/or aqueous ceric ammonium nitrate solution followed by heating. Purification of the reaction products was carried out by flash chromatography using Siliaflash-P60 silica gel (40–63 μm) purchased from Silicycle. Supercritical fluid chromatography was performed on a Berger SFC system

equipped with a Chiralcel OD column. Samples were eluted with SFC grade CO_2 at the indicated percentage of MeOH. Unless otherwise noted, all reactions were carried out under an atmosphere of dry nitrogen in oven-dried glassware with magnetic stirring.

Materials: **General**. Tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), and toluene (C_7H_8) were dried by passage through a column of neutral alumina under nitrogen prior to use. Acetonitrile (CH_3CN), Triethylamine (NEt_3) and diisopropylamine were freshly distilled from calcium hydride prior to use. All other reagents were purchased from commercial sources and were used as received unless otherwise noted. Poly(D,L-lactide) (lactide: 75,000–120,000; 0.55–0.75 dL/g Inherent Viscosity) (PLA) was purchased from Sigma-Aldrich. Chloroform and solvents (acetonitrile and water) for high performance liquid chromatography (HPLC) were purchased from Fisher Scientific. Poly(ethylene terephthalate) (PET) sheets (6″ width) were purchased from KRS plastics. Fluorocur®, diameter (d) = 80 nm; height (h) = 320 nm; (80 × 320 nm) prefabricated molds were provided by Liquidia Technologies.

Experimental Procedures

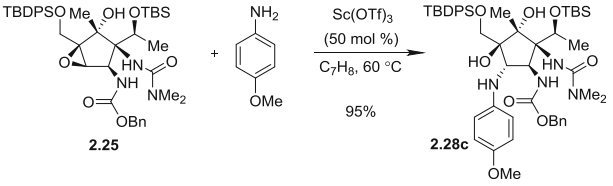
General procedure A for the addition of *m*-acetylaniline to epoxide 2.25.



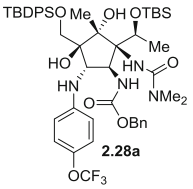
Benzyl ((1*S*,2*R*,3*R*,4*S*,5*S*)-5-((3-acetylphenyl)amino)-2-((*S*)-1-((*tert*-butyldimethylsilyl) oxy) ethyl)-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-(3,3 dimethyl ureido)-3,4-dihydroxy-3-methylcyclopentyl)carbamate (2.28): In a nitrogen-filled glove box, a flame-dried 100-mL round-bottomed flask was charged with $Sc(OTf)_3$ (0.38 g, 0.77 mmol, 3.0 equiv). The flask was capped with a rubber septum and removed from the glove box. Toluene (20 mL) was added and to the resulting suspension were added *m*-acetylaniline (0.35 g, 2.6 mmol, 10.0 equiv) and a toluene solution (1.5 mL) of epoxide **2.25** (0.20 g, 0.26 mmol, 1.0 equiv). The reaction was heated to 60 °C with vigorous stirring and maintained for 14 h. (Note: increased reaction times led to product decomposition). The reaction was cooled to rt, diluted with H_2O (10 mL) and EtOAc (10 mL), and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with 0.5 M $HCl_{(aq.)}$ (2 × 20 mL), saturated $NaHCO_{3(aq.)}$ (15 mL), dried with magnesium sulfate, and concentrated in vacuo. The crude product was purified via flash chromatography (90:10 to 80:20 hexanes:EtOAc) to afford anilino-alcohol **2.28** as a yellow, viscous oil (0.16 g, 66 %) with recovery of the unreacted epoxide **2.25** (0.04 g, 18 %). Analytical data: $[\alpha]_D^{19}$ −39.3 (c = 0.70, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.21 (d, J = 6.6 Hz, 1H), 7.70 (d, J = 6.6 Hz, 2H), 7.51 (d, J = 7.2 Hz, 2H), 7.39 (t, J = 7.2 Hz, 1H), 7.32 (t, J = 7.2 Hz, 2H), 7.28–7.22 (m, 8H), 7.16 (t, J = 7.2 Hz,

2H), 7.12 (t, J = 7.8 Hz, 1H), 6.79 (d, J = 7.8 Hz, 1H), 6.13 (s, 1H), 5.88 (s, 1H), 5.39–5.36 (m, 1H), 5.36 (s, 1H), 5.04 (d, J = 12.0 Hz, 1H), 5.01 (d, J = 12.0 Hz, 1H), 4.78 (dd, J = 4.6, 6.6 Hz, 1H), 4.37 (d, J = 10.2 Hz, 1H), 4.13 (s, 1H), 3.68 (dd, J = 4.6, 3.0 Hz, 1H), 3.48 (d, J = 10.8 Hz, 1H), 2.96 (s, 6H), 2.49 (s, 3H), 1.69 (s, 3H), 1.41 (d, J = 6.6 Hz, 3H), 0.98 (s, 9H), 0.92 (s, 9H), 0.12 (s, 3H), 0.02 (s, 3H); **MS (ESI$^+$)** Calcd. for $C_{50}H_{70}N_8Si_2$ + H, 911.4812; Found, 911.4867.

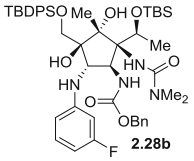
General procedure B for the addition of varied anilines to epoxide 2.25.



(Benzyl ((1*S*,2*R*,3*R*,4*S*,5*S*)-2-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-(3,3-dimethylureido)-3,4-dihydroxy-5-((4-methoxyphenyl)amino)-3-methylcyclopentyl)carbamate) (2.28c): In a nitrogen-filled glove box, a flame-dried 100-mL round-bottomed flask was charged with $Sc(OTf)_3$ (0.035 g, 0.065 mmol, 0.5 equiv). The flask was capped with a rubber septum and removed from the glove box. Toluene (9 mL) was added and to the resulting suspension were added *p*-anisidine (0.160 g, 1.29 mmol, 10 equiv) and a toluene solution (2 mL) of epoxide **2.25** (0.10 g, 0.129 mmol, 1.0 equiv). The reaction was heated to 60 °C with vigorous stirring and maintained for 14 h. (Note: increased reaction times led to product decomposition). The reaction was cooled to rt, diluted with H_2O (15 mL) and EtOAc (15 mL), and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with 0.5 M $HCl_{(aq.)}$ (2 × 20 mL), saturated $NaHCO_{3(aq.)}$ (15 mL), dried with magnesium sulfate, and concentrated in vacuo. The crude product was purified via flash chromatography (90:10 to 80:20 hexanes:EtOAc) to afford anilino-alcohol **2.28c** as a yellow, viscous oil (0.110 g, 95 %). Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.10 (d, J = 6.4 Hz, 1H); 7.71 (d, J = 6.4 Hz, 2H); 7.56 (d, J = 6.8 Hz, 2H); 7.40–7.30 (m, 12H); 6.67 (d, J = 8.8 Hz, 2H); 6.56 (d, J = 8.8 Hz, 2H); 6.17 (s, 1H); 5.83 (s, 1H); 5.37 (q, J = 6.8 Hz, 1H); 5.02 (br s, 2H); 4.96 (s, 1H); 4.75–4.73 (m, 1H); 4.39 (d, J = 10.8 Hz, 1H); 3.74 (s, 3H); 3.61–3.54 (m, 2H); 2.95 (s, 2H); 1.67 (s 3H); 1.40 (d, J = 6.4 Hz, 3H); 1.01 (s, 9H); 0.92 (s, 9H); 0.11 (s, 3H); 0.02 (s, 3H). **MS (ESI$^+$)** Calcd. For $C_{49}H_{70}N_4O_8Si_2$ + H, 899.48; Found, 899.47.

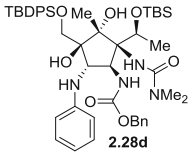


Benzyl ((1*S*,2*R*,3*R*,4*S*,5*S*)-2-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-(3,3-dimethylureido)-3,4-dihydroxy-3-methyl-5-((4-(trifluoromethoxy)phenyl)amino)cyclopentyl)carbamate (2.28a): Isolated from **2.25** via general procedure B using 4-trifluoromethoxyaniline as the nucleophile in 83 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 6.8 Hz, 1H); 7.71 (d, *J* = 6.4 Hz, 2H); 7.56 (d, *J* = 6.8 Hz, 2H); 7.55–7.44 (m, 6H); 7.03 (d, *J* = 8.0 Hz, 2H); 6.92 (d, *J* = 8.4 Hz, 2H); 6.66 (d, *J* = 8.8 Hz, 2H); 5.56 (d, *J* = 8.8 Hz, 2H); 6.14 (s, 1H); 5.90 (s, 1H); 5.38 (q, *J* = 6.4 Hz, 1H); 5.30 (d, *J* = 3.2 Hz, 1H); 5.08 (d, *J* = 12.4 Hz, 1H); 5.02 (d, *J* = 12.0 Hz, 1H);4.78 (dd, *J* = 6.4, 10.0 Hz, 1H); 4.39 (d, *J* = 10.8 Hz, 1H); 4.13 (s, 1H); 3.75 (br s, 1H); 3.59 (dd, *J* = 2.8, 9.8, 1H); 3.48 (d, *J* = 10.8 Hz, 1H); 2.97 (s, 6H); 1.71 (s, 3H); 1.44 (d, J = 6.4 Hz, 3H); 1.04 (s, 9H); 0.95 (s, 9H); 0.14 (s, 3H); 0.04 (s, 3H); **MS (ESI$^+$)** Calcd. For $C_{49}H_{67}F_3N_4O_8Si_2$ + H, 953.45; Found, 953.22.



2.28b

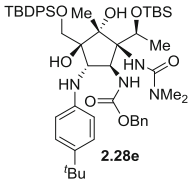
Benzyl ((1*S*,2*R*,3*R*,4*S*,5*S*)-2-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-(3,3-dimethylureido)-5-((3-fluorophenyl)amino)-3,4-dihydroxy-3-methylcyclopentyl)carbamate (2.28b): Isolated from **2.25** via general procedure B using 3-fluoroaniline as the nucleophile in 43 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.18 (d, *J* = 6.6 Hz, 1H); 7.73 (d, *J* = 7.1 Hz, 2H); 7.36 (d, *J* = 6.6, 2H); 7.42 (d, *J* = 7.6 Hz, 1H); 7.39–7.25 (m, 11H); 6.96 (d, *J* = 7.2 Hz, 1H); 6.42–6.31 (m, 3H); 6.12 (s, 1H); 5.86 (s, 1H); 5.38 (q, *J* = 6.8 Hz, 1H); 5.32 (br s, 1H); 4.75 (dd, *J* = 9.8, 6.8 Hz, 1H); 4.35 (d, *J* = 10.4 Hz, 1H); 4.13 (s, 1H); 3.6 (dd, *J* = 9.8, 3.6 Hz, 1H); 3.52 (d, *J* = 10.8 Hz, 1H) 2.97 (s, 6H); 1.68 (s, 3H); 1.42 (d, *J* = 6.8 Hz, 1H), 3H); 1.01 (s, 9H); 0.93 (s, 9H); 0.12 (s, 3H); 0.02 (s, 3H); **MS (ESI$^+$)** Calcd. For $C_{48}H_{67}FN_4O_7Si_2$ + H, 887.46; Found, 887.32.



2.28d

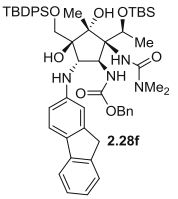
Benzyl ((1*S*,2*R*,3*R*,4*S*,5*S*)-2-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-(3,3-dimethylureido)-3,4-dihydroxy-3-methyl-5-(phenylamino)cyclopentyl)carbamate (2.28d): Isolated from **2.25** via general procedure B using aniline as the nucleophile in 71 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.09 (d, *J* = 6.8 Hz, 1H); 7.71 (d, *J* = 8.0 Hz, 2H); 7.55 (d, *J* = 7.6 Hz, 2H); 7.41–7.21 (m, 12H); 7.09–7.05 (m, 2H); 6.65–6.62 (m, 3H); 6.17 (s, 1H); 5.85 (s, 1H); 5.37 (q, *J* = 6.8 Hz, 1H); 5.14 (br s, 1H); 5.02 (s, 2H); 4.76

(dd, J = 9.8, 6.4 Hz, 1H); 4.37 (d, J = 10.8 Hz, 1H); 3.63 (d, J = 10.4 Hz, 1H); 3.60 (d, J = 10.8 Hz, 1H); 2.96 (s, 6H); 1.67 (s, 3H); 1.40 (d, J = 6.8 Hz, 3H); 1.00 (s, 9H); 0.92 (s, 9H); 0.11 (s, 3H); 0.02 (s, 3H); **MS (ESI$^+$)** Calcd. For $C_{48}H_{68}N_4O_7Si_2$ + H, 869.47; Found, 869.61.



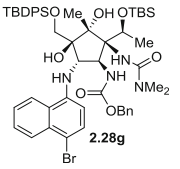
2.28e

Benzyl ((1*S*,2*R*,3*R*,4*S*,5*S*)-5-((4-(tert-butyl)phenyl)amino)-2-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-(3,3-dimethylureido)-3,4-dihydroxy-3-methylcyclopentyl)carbamate (2.28e): Isolated from **2.25** via general procedure B using 4-*tert*-butylaniline as the nucleophile in 86 % yield. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.11 (d, J = 6.6 Hz, 1H); 7.73 (d, J = 7.2 Hz, 2H); 7.56 (d, J = 7.2 Hz, 2H); 7.40 (d, J = 6.6 Hz, 1H); 7.36–7.31 (m, 5H); 7.27–7.23 (m, 5H); 7.20 (d, J = 8.4 Hz, 2H); 6.60 (d, J = 8.4 Hz, 2H); 6.20 (s, 1H); 5.83 (s, 1H); 5.38 (q, J = 6.6 Hz, 1H); 5.12 (s, 1H); 5.05 (d, J = 12.6 Hz, 1H); 5.00 (d, J = 12.0 Hz, 1H); 4.77 (m, 1H); 4.37 (d, J = 10.8 Hz, 1H); 4.16 (s, 1H); 4.14 (d, J = 7.2 Hz, 1H); 3.64–3.60 (m, 2H); 2.96 (s, 6H); 1.68 (s, 3H); 1.42 (d, J = 6.6 Hz, 3H); 1.29 (s, 9H); 1.01 (s, 9H); 0.93 (s, 9H); 0.12 (s, 3H); 0.02 (s, 3H); **MS (ESI$^+$)** Calcd. For $C_{52}H_{76}N_4O_7Si_2$ + H, 925.53; Found, 925.45.

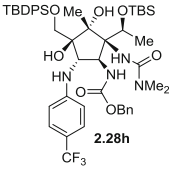


2.28f

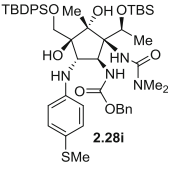
Benzyl ((1*S*,2*R*,3*R*,4*S*,5*S*)-5-((9H-fluoren-2-yl)amino)-2-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-(3,3-dimethylureido)-3,4-dihydroxy-3-methylcyclopentyl)carbamate (2.28f): Isolated from **2.25** via general procedure B using 2-fluorenyl aniline as the nucleophile in 59 % yield. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.17 (d, J = 6.7 Hz, 1H); 7.72 (d, J = 7.1 Hz, 2H); 7.67 (t, J = 7.0 Hz, 1H); 7.56 (br s, 2H); 7.50 (br s, 2H); 7.39 (t, J = 7.1 Hz, 1H); 7.37–7.32 (m, 5H); 7.26–7.35 (m, 3H); 7.21 (t, J = 8.1 Hz, 1H); 7.15 (br s, 3H); 6.82 (s, 1H); 6.68 (d, J = 5.6 Hz, 1H); 6.22 (s, 1H); 5.92 (s, 1H); 5.43 (d, J = 4.4 Hz, 1H); 5.07 (s, 2H); 4.83–4.80 (m, 1H); 4.44 (d, J = 7.2 Hz, 1H); 4.21 (s, 1H); 3.84(s, 1H); 3.76–3.65 (m, 3H); 3.64 (d, J = 7.2 Hz, 1H); 3.01 (s, 6H); 1.73 (s, 3H); 1.45 (d, J = 4.4 Hz, 3H); 1.042 (s, 9H); 0.98 (s, 9H); 0.16 (s, 3H); 0.07 (s, 3H); **MS (ESI$^+$)** Calcd. For $C_{55}H_{72}N_4O_7Si_2$ + H, 957.50; Found, 957.42.



Benzyl ((1*S*,2*R*,3*R*,4*S*,5*S*)-5-((4-bromonaphthalen-1-yl)amino)-2-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-(3,3-dimethylureido)-3,4-dihydroxy-3-methylcyclopentyl)carbamate (2.28 g): Isolated from **2.25** via general procedure B using 4-bromonaphthalen-1-amine as the nucleophile in 87 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.24 (d, *J* = 6.4 Hz, 1H); 8.15 (d, *J* = 8.4 Hz, 1H); 7.95 (d, *J* = 8.4 Hz, 1H); 7.67 (d, *J* = 6.9 Hz, 2H); 7.54 (t, *J* = 7.1 Hz, 1H); 7.52–7.07 (m, 15H); 6.61 (d, *J* = 8.4 Hz, 1H); 6.18 (d, *J* = 12.4 Hz, 2H); 5.97 (s, 1H); 5.45 (d, *J* = 6.8 Hz, 1H); 5.04–4.93 (m, 3H); 4.44 (d, *J* = 10.4 Hz, 1H); 4.20 (s, 1H); 3.83 (d, *J* = 10.0 Hz, 1H); 3.49 (d, *J* = 10.8 Hz, 1H); 3.00 (s, 6H); 1.74 (s, 3H); 1.46 (d, *J* = 6.8 Hz, 3H); 1.01 (s, 9H); 0.99 (s, 9H); 0.17 (s, 3H); 0.11 (s, 3H); **MS (ESI$^+$)** Calcd. For $C_{52}H_{69}BrN_4O_7Si_2$ + H, 997.40; Found, 997.48.

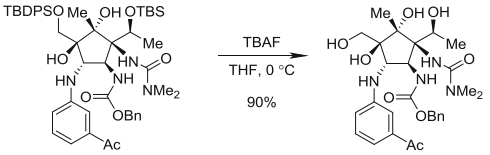


Benzyl ((1*S*,2*R*,3*R*,4*S*,5*S*)-2-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-(3,3-dimethylureido)-3,4-dihydroxy-3-methyl-5-((4-(trifluoromethyl)phenyl)amino)cyclopentyl)carbamate (2.28 h): Isolated from **2.25** via general procedure B using 4-trifluoromethylaniline as the nucleophile in 47 % yield. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.25 (d, *J* = 6.6 Hz, 1H); 7.73 (d, *J* = 7.2 Hz, 2H); 7.53 (d, *J* = 7.8 Hz, 2H); 7.44–7.21 (m, 11H); 6.71 (d, *J* = 7.8 Hz, 2H); 6.61 (d, *J* = 8.4 Hz, 2H); 6.14 (s, 1H); 5.94 (s, 1H); 5.52 (s, 1H); 5.40 (q, *J* = 6.6 Hz, 1H); 5.05 (s, 2H); 4.81–4.78 (m, 1H); 4.39 (d, *J* = 10.8 Hz, 1H); 3.98 (s, 1H); 3.69–3.67 (m, 1H); 3.41 (d, *J* = 10.8 Hz, 1H); 2.99 (s, 6H); 1.72 (s, 3H); 1.44 (d, *J* = 6.6 Hz, 3H); 1.04 (s, 9H); 0.95 (s, 9H); 0.15 (s, 3H); 0.04 (s, 3H); **MS (ESI$^+$)** Calcd. For $C_{49}H_{67}F_3N_4O_7Si_2$ + H, 937.46; Found, 937.36.



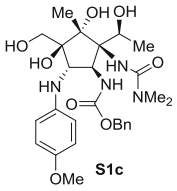
Benzyl ((1S,2R,3R,4S,5S)-2-((S)-1-((tert-butyldimethylsilyl)oxy)ethyl)-4-(((tert-butyldiphenylsilyl)oxy)methyl)-2-(3,3-dimethylureido)-3,4-dihydroxy-3-methyl-5-((4-(methylthio)phenyl)amino)cyclopentyl)carbamate (2.28i): Isolated from **2.25** via general procedure B using 4-thiomethylaniline as the nucleophile in 77 % yield. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.15 (d, *J* = 6.6 Hz, 1H); 7.71 (d, *J* = 7.2 Hz, 2H); 7.55 (d, *J* = 7.2 Hz, 2H); 7.41 (t, *J* = 7.2 Hz, 1H); 7.36–7.23 (m, 10H); 7.13 (d, *J* = 9.0 Hz, 2H); 6.57 (d, *J* = 7.8 Hz, 2H); 6.14 (s, 1H); 5.86 (s, 1H); 5.37 (d, *J* = 6.6 Hz, 1H); 5.23 (s, 1H); 5.02 (s, 2H); 4.75 (dd, *J* = 9.6, 6.6 Hz, 1H); 4.36 (d, *J* = 10.8 Hz, 1H); 4.13 (s, 1H); 3.61 (d, *J* = 9.6 Hz, 1H); 3.52 (d, *J* = 10.8 Hz, 1H); 2.96 (s, 6H); 2.39 (s, 3H); 1.67 (s, 3H); 1.14 (d, *J* = 6.6 Hz, 3H); 1.01 (s, 9H); 0.92 (s, 9H); 0.11 (s, 3H); 0.01 (s, 3H); **MS (ESI$^+$)** Calcd. For $C_{49}H_{70}N_4O_7SSi_2$ + Na, 937.46; Found, 937.36.

General procedure C for global silyl deprotection.



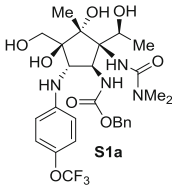
2.28 **2.26**

Benzyl ((1*S*,2*R*,3*R*,4*S*,5*S*)-5-((3-acetylphenyl)amino)-2-(3,3-dimethylureido)-3,4-dihydroxy-2-((*S*)-1-hydroxyethyl)-4-(hydroxymethyl)-3-methylcyclopentyl)-carbamate (2.26): A 20-mL scintillation vial was charged with silyl ether **2.28** (0.25 g, 0.28 mmol, 1.0 equiv) and THF (5.5 mL). The resulting solution was cooled to 0 °C, and TBAF (1 M solution in THF, 1.1 mL, 1.1 mmol, 4.0 equiv) was added. The reaction was allowed to stir at 0 °C until TLC analysis indicated consumption of the starting material, typically 30 min. The reaction was diluted with brine (3 mL) and EtOAc (3 mL) and extracted with EtOAc (3 × 7 mL). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo. The crude product was purified via flash chromatography (60:40 petroleum ether:acetone) to afford tetraol **2.26** as a pale yellow, viscous oil (0.14 g, 90 %). Analytical data: $[\alpha]_D^{19}$ +26.0 (*c* = 0.70, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.36 (s, 4H); 7.29 (br s, 1H); 7.23 (br s, 1H); 7.12 (br s, 1H); 6.99 (d, *J* = 7.8 Hz, 1H); 6.75 (d, *J* = 6.6 Hz, 1H); 6.02 (d, *J* = 7.2 Hz, 1H); 5.80 (br s, 1H); 5.48 (d, *J* = 7.8 Hz, 1H); 5.27 (br s, 1H); 5.13 (br s, 2H); 4.14–4.10 (m, 1H); 4.06 (br s, 2H); 3.80 (br s, 2H); 3.74–3.68 (m, 1H); 3.55 (m, 1H); 2.87 (s, 6H); 2.52 (s, 3H); 1.42 (s, 3H); 1.25 (br s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 198.7, 158.7, 155.8, 146.6, 138.3, 136.0, 129.7, 128.6, 128.4, 118.4, 112.0, 88.2, 83.9, 73.2, 71.7, 67.4, 66.9, 64.2, 61.8, 61.2, 36.7, 29.7, 26.7, 22.7, 21.2, 18.0, 14.1; **MS (ESI$^+$)** Calcd. For $C_{28}H_{38}N_4O_8$ + H, 559.2770; Found, 559.2800; **IR** (thin film, cm^{-1}) 3392, 2938, 1716, 1684, 1652, 1635, 1540, 1507, 1473, 1456, 1361, 1243, 739; **TLC** (60:40 petroleum ether/acetone): R_f = 0.30.



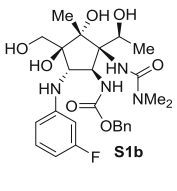
S1c

(Benzyl ((1*S*,2*R*,3*R*,4*S*,5*S*)-2-(3,3-dimethylureido)-3,4-dihydroxy-2-((*S*)-1-hydroxyethyl)-4-(hydroxymethyl)-5-((4-methoxyphenyl)amino)-3-methylcyclopentyl)carbamate) (S1c): Isolated from **2.28** via general procedure C in 94 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34–7.26 (m, 5H); 6.85 (br s, 1H); 6.73 (d, *J* = 8.4 Hz, 2H); 6.5 (d, *J* = 8.0 Hz, 2H); 6.06 (br s, 1H); 5.73 (br s, 1H); 5.28 (s, 1H); 5.13–5.10 (m, 2H); 4.95 (br s, 1H); 4.15 (br s, 1H); 4.04 (d, *J* = 11.2 Hz, 2H); 3.72 (s, 3H); 3.66 (br s, 2H); 2.84 (s, 6H); 1.38 (s, 3H); 1.24 (br s, 3H). **MS (ESI$^+$)** Calcd. For $C_{27}H_{38}N_4O_8$ + H + H, 547.28; Found, 547.28.



S1a

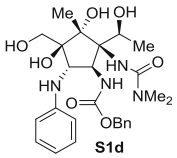
Benzyl ((1*S*,2*R*,3*R*,4*S*,5*S*)-2-(3,3-dimethylureido)-3,4-dihydroxy-2-((*S*)-1-hydroxyethyl)-4-(hydroxymethyl)-3-methyl-5-((4-(trifluoromethoxy)phenyl) amino)cyclopentyl) carbamate H(S1a): Isolated from **2.28a** via general procedure C in 68 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34–7.26 (m, 5H); 7.00 (d, *J* = 8.0 Hz, 2H); 6.71 (br s, 1H); 6.50 (d, *J* = 8.4 Hz, 2H); 6.05 (br s, 1H); 5.72 (br s, 1H); 5.31 (br s, 1H); 5.26 (s, 1H); 5.12 (s, 2H); 4.17 (br s, 1H); 4.05 (br s, 1H); 4.01 (d, J = 12.0 Hz, 1H); 3.82 (d, *J* = 11.6 Hz, 1H); 3.69 (dd, *J* = 2.8, 9.0 Hz, 1H); 3.52 (s, 1H); 2.87 (s, 6H); 1.41 (s, 3H); 1.25 (br s, 3H); **MS (ESI$^+$)** Calcd. For $C_{27}H_{35}F_3N_4O_8$ + Na, 623.33; Found, 623.19.



S1b

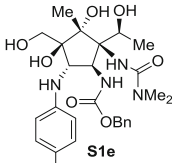
Benzyl ((1*S*,2*R*,3*R*,4*S*,5*S*)-2-(3,3-dimethylureido)-5-((3-fluorophenyl)amino)-3,4-dihydroxy-2-((*S*)-1-hydroxyethyl)-4-(hydroxymethyl)-3-methylcyclopentyl)-carbamate (S1b): Isolated from **2.28b** via general procedure C in 85 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34–7.26 (m, 5H); 7.07 (d, *J* = 7.2 Hz, 1H); 6.85 (br s, 1H); 6.42–6.38 (m, 1H); 6.32–6.26 (m, 2H); 6.07 (br s,

1H); 5.76 (br s, 1H); 5.39 (d, J = 8.0 Hz, 1H); 5.26 (s, 1H); 5.13 (d, J = 12.4 Hz, 1H); 5.10 (d, J = 12.4 Hz, 1H); 4.17 (br s, 1H); 4.06 (br s, 1H); 3.98 (d, J = 11.2 Hz, 1H); 3.80 (d, J = 11.2 Hz, 1H); 3.68 (dd, J = 2.4, 9.0 Hz, 1H); 3.6 (br s, 1H); 2.86 (s, 6H); 1.40 (s, 3H); 1.25 (d, J = 3.2 Hz, 3H); **MS (ESI$^+$)** Calcd. For $C_{26}H_{35}FN_4O_7$ + H, 535.26; Found, 535.19.



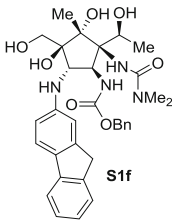
S1d

Benzyl ((1*S*,2*R*,3*R*,4*S*,5*S*)-2-(3,3-dimethylureido)-3,4-dihydroxy-2-((*S*)-1-hydroxyethyl)-4-(hydroxymethyl)-3-methyl-5-(phenylamino)cyclopentyl)carbamate (S1d): Isolated from **2.28d** via general procedure C in 91 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34 (br s, 5H); 7.16–7.13 (m, 2H); 6.90 (br s, 1H); 6.72 (br s, 1H); 6.56 (br s, 2H); 6.05 (br s, 1H); 5.78 (s, 1H); 5.28 (br s, 1H); 5.10 (s, 2H); 4.18 (br s, 1H); 4.02 (br s, 2H); 3.78 (br s, 2H); 3.63 (s, 1H); 2.85 (s, 6H); 2.61 (br s, 1H); 1.85 (br s, 1H); 1.39 (s, 3H); 1.24 (br s, 3H); **MS (ESI$^+$)** Calcd. For $C_{26}H_{36}N_4O_7$ + Na, 539.25; Found, 539.32.



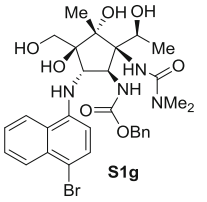
S1e

Benzyl ((1*S*,2*R*,3*R*,4*S*,5*S*)-5-((4-(*tert*-butyl)phenyl)amino)-2-(3,3-dimethylureido)-3,4-dihydroxy-2-((*S*)-1-hydroxyethyl)-4-(hydroxymethyl)-3-methylcyclopentyl)carbamate (S1e): Isolated from **2.28e** via general procedure C in 93 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ7.35 (br s, 5H); 7.18 (d, J = 8.4 Hz, 2H); 6.84 (br s, 1H); 6.51 (d, J = 8.0 Hz, 2H); 6.06 (br s, 1H); 5.78 (br s, 1H); 5.28 (br s, 1H); 5.15–5.08 (m, 3H); 4.21 (br s, 1H); 4.06–4.03 (m, 2H); 3.75 (d, J = 11.6 Hz, 1H); 3.70 (d, J = 8.8 Hz, 1H); 3.69 (br s, 1H); 2.86 (s, 6H); 1.39 (s, 3H); 1.27 (s, 9H); 1.25 (br s, 3H); **MS (ESI$^+$)** Calcd. For $C_{30}H_{44}N_4O_7$ + H, 573.33; Found, 573.33.



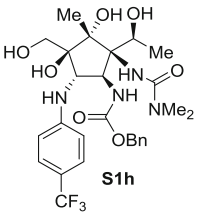
S1f

Benzyl ((1*S*,2*R*,3*R*,4*S*,5*S*)-5-((9H-fluoren-2-yl)amino)-2-(3,3-dimethylureido)-3,4-dihydroxy-2-((*S*)-1-hydroxyethyl)-4-(hydroxymethyl)-3-methylcyclopentyl)-carbamate (S1f): Isolated from **2.28f** via general procedure C in 85 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 7.3 Hz, 1H); 7.55 (br s, 1H); 7.45 (d, *J* = 7.3 Hz, 1H); 7.42–7.26 (m, 6H); 7.20–7.17 (m, 1H); 6.97 (br s, 1H); 6.76 (s, 1H); 6.59 (br s, 1H); 6.06 (br s, 1H); 5.84 (br s, 1H); 5.35 (br s, 1H); 5.29 (br s, 1H); 5.12 (s, 2H); 4.18–4.06 (m, 3H); 3.82–3.75 (m, 4H); 3.64 (br s, 1H); 2.86 (s, 6H); 1.41 (s, 3H); 1.24 (s, 3H); **MS (ESI$^+$)** Calcd. For $C_{33}H_{40}N_4O_7$ + H, 605.30; Found, 605.23.



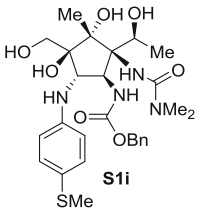
S1g

Benzyl ((1*S*,2*R*,3*R*,4*S*,5*S*)-5-((4-bromonaphthalen-1-yl)amino)-2-(3,3-dimethylureido)-3,4-dihydroxy-2-((*S*)-1-hydroxyethyl)-4-(hydroxymethyl)-3-methylcyclopentyl) carbamate (S1 g): Isolated from **2.28 g** via general procedure C in 65 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.4 Hz, 1H); 7.70 (d, *J* = 7.6 Hz, 1H); 7.59–7.55 (m, 2H); 7.48–7.45 (m, 1H); 7.27–7.21 (m, 5H); 7.20 (br s, 1H); 6.42 (br s, 1H); 6.32 (br s, 1H); 6.06 (br s, 2H); 5.25 (s, 1H); 5.14–5.12 (m, 2H); 4.15–4.12 (m, 3H); 3.89–3.82 (m, 2H); 3.64 (br s, 1H); 2.85 (s, 6H); 1.25 (br s, 3H); **MS (ESI$^+$)** Calcd. For $C_{30}H_{37}BrN_4O_7$ + H, 645.19; Found, 645.25.



S1h

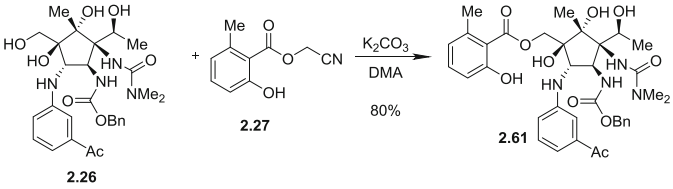
Benzyl ((1*S*,2*R*,3*R*,4*S*,5*S*)-2-(3,3-dimethylureido)-3,4-dihydroxy-2-((*S*)-1-hydroxyethyl)-4-(hydroxymethyl)-3-methyl-5-((4-(trifluoromethyl)phenyl) amino) cyclopentyl) carbamate (S1 h): Isolated from **2.28 h** via general procedure C in 60 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35–7.26 (m, 8H); 6.87 (br s, 2H); 6.10 (br s, 1H); 5.77 (br s, 1H); 5.62 (s, 1H); 5.12 (br s, 2H); 4.17 (s, 1H); 4.06 (s, 1H); 3.97 (d, *J* = 10.4 Hz, 1H); 3.83 (d, *J* = 10.4 Hz, 1H); 3.75 (d, *J* = 6.8 Hz, 1H); 2.86 (s, 6H); 1.41 (s, 3H); 1.25 (d, *J* = 4.0 Hz, 3H); **MS (ESI$^+$)** Calcd. For $C_{27}H_{35}F_3N_4O_7$ + H, 585.25; Found, 585.24.



S1i

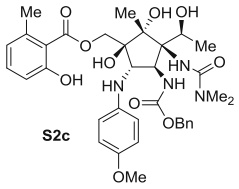
Benzyl ((1S,2R,3R,4S,5S)-2-(3,3-dimethylureido)-3,4-dihydroxy-2-((S)-1-hydroxyethyl)-4-(hydroxymethyl)-3-methyl-5-((4-(methylthio)phenyl)amino) cyclopentyl)carbamate (S1i): Isolated from **2.28i** via general procedure C in 89 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.33 (bs, 5H); 7.16 (d, *J* = 7.6 Hz, 2H); 6.90 (bs, 1H); 6.49 (d, *J* = 7.2 Hz, 2H); 6.11 (bs, 1H); 5.74 (bs, 1H); 5.27 (bs, 2H); 5.11 (d, *J* = 12.4 Hz, 1H); 5.07 (s, *J* = 12.4 Hz, 1H); 4.15 (bs, 1H); 4.03 (bs, 1H); 3.97 (d, *J* = 11.6 Hz, 1H); 3.76 (d, *J* = 12.0 Hz, 1H); 3.69 (d, *J* = 8.8 Hz, 1H); 2.84 (s, 6H); 2.39 (s, 3H); 1.38 (s, 3H); 1.24 (d, *J* = 5.6 Hz, 13H); **MS (ESI$^+$)** Calcd. For $C_{27}H_{38}N_4O_7S$ + H, 563.25; Found, 563.27.

General procedure D for salicylate ester formation.

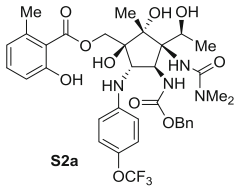


((1*S*,2*R*,3*R*,4*S*,5*S*)-5-((3-acetylphenyl)amino)-4-(((benzyloxy)carbonyl)xamino)-3-(3,3-dimethylureido)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)-2-methylcyclopentyl) methyl 2-hydroxy-6-methylbenzoate (2.61): A flame-dried 20-mL scintillation vial was charged with cyanomethyl ester **2.27** (0.0075 g, 0.044 mmol, 1.1 equiv) and dimethylacetamide (DMA) (0.3 mL). K_2CO_{3-} (0.005 g, 0.04 mmol, 1.0 equiv) was added, and the resulting mixture was stirred for 1 h. The in situ generated ketene solution was transferred to a stirred solution of tetraol **2.26** (0.02 g, 0.04 mmol, 1.0 equiv) in DMA (0.7 mL). The reaction was stirred until TLC analysis indicated full consumption of the tetraol starting material, typically 3 h. The reaction was cooled to 0 °C and quenched by the dropwise addition of saturated $NH_4Cl_{(aq.)}$ (1.5 mL). The resulting mixture was extracted with EtOAc (3 × 5 mL), washed with H_2O (10 ml), brine (10 mL), dried with magnesium sulfate, and concentrated in vacuo. The crude product was purified via flash chromatography (50:50 hexanes:EtOAc) to afford an inseparable mixture of salicylate **2.61** (0.02 g, 80 %) and an unknown impurity (15 % by NMR analysis) as a pale yellow, viscous oil. Analytical data: $[\alpha]_D^{19}$ +33.6 (*c* = 0.70, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 10.87 (s, 1H), 7.52 (br s, 1H), 7.36 (br s, 5H), 7.30–7.22 (m, 4H), 7.10 (s, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 6.63 (d, *J* = 7.2 Hz, 1H), 6.13 (s, 1H), 5.79 (d, *J* = 9.0 Hz, 1H), 5.72 (d, *J* = 9.6 Hz, 1H), 5.23–5.10 (m, 3H),

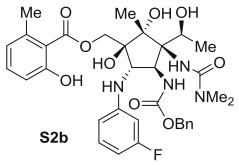
4.91–4.84 (m, 2H), 4.06 (br s, 2H), 3.80 (d, J = 9.6 Hz, 1H), 3.69 (s, 1H), 2.85 (s, 7H), 2.30 (s, 3H), 1.42 (s, 3H), 1.26 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 198.3, 173.4, 162.9, 158.5, 155.3, 146.0, 141.6, 138.3, 135.0, 129.7, 128.6, 128.5, 123.2, 119.4, 118.4, 115.8, 111.9, 111.6, 99.7, 88.6, 85.0, 73.9, 72.3, 67.5, 66.8, 66.6, 65.4, 62.7, 36.7, 23.9, 21.0, 18.0, 17.4; **MS (ESI$^+$)** Calcd. For $C_{36}H_{44}N_4O_{10}$ + H, 693.3137; Found, 693.3172; **IR** (thin film, cm^{-1}) 3392, 2965, 1867, 1698, 1670, 1541, 1456, 1374, 1249, 874, 737; **TLC** (50:50 EtOAc:hexanes): R_f = 0.30.



(((1*S*,2*R*,3*R*,4*S*,5*S*)-4-(((benzyloxy)carbonyl)amino)-3-(3,3-dimethylureido)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)-5-((4-methoxyphenyl)amino)-2-methylcyclopentyl) methyl 2-hydroxy-6-methylbenzoate) (S2c): Isolated from **S1c** via general procedure D in 80 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.95 (s, 1H); 7.58 (d, J = 7.2 Hz, 1H); 7.36 (br s, 4H); 7.28 (d, J = 8.8 Hz, 1H); 6.82 (d, J = 8.4 Hz, 1H); 6.74 (d, J = 8.8 Hz, 2H); 6.66 (d, 7.6 Hz, 1H); 6.48 (d, J = 8.8 Hz, 2H); 6.04 (s, 1H); 5.90 (d, J = 8.0 Hz, 1H); 5.27 (d, J = 10.4 Hz, 1H); 5.23 (s, 1H); 5.17 (d, J = 12.0 Hz, 1H); 5.11 (d, J = 12.0 Hz, 1H); 4.88 (d, J = 12.8 Hz, 1H); 4.84 (d, J = 12.0 Hz, 1H); 4.07 (br s, 2H); 3.75 (s, 3H); 2.86 (s, 6H); 2.44 (s, 3H); 1.50 (s, 3H); 1.27 (br s, 3H). **MS (ESI$^+$)** Calcd. For $C_{35}H_{44}N_4O_{10}$ + H, 681.31; Found, 681.26.

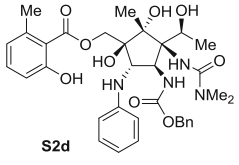


((1*S*,2*R*,3*R*,4*S*,5*S*)-4-(((benzyloxy)carbonyl)amino)-3-(3,3-dimethylureido)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)-2-methyl-5-((4-(trifluoromethoxy)phenyl)amino) cyclopentyl)methyl 2-hydroxy-6-methylbenzoate (S2a): Isolated from **S1a** via general procedure D in 63 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.90 (br s, 1H); 7.37–7.28 (m, 8H); 7.01 (d, J = 8.4 Hz, 2H); 6.84 (d, J = 8.4 Hz, 1H); 6.67 (d, J = 7.6 Hz, 1H); 6.48 (d, J = 8.8 Hz, 2H); 5.84 (d, J = 8.0 Hz, 1H); 5.64 (br s, 1H); 5.22–5.51 (m, 2H); 4.93 (d, J = 12.4 Hz, 1H); 4.05 (d, J = 7.6 Hz, 1H); 3.82 (br s, 1H); 3.72 (s, 1H); 3.00 (s, 1H); 2.88 (s, 6H); 2.31 (s, 3H); 1.52 (s, 3H); 1.29 (d, J = 6.8 Hz, 3H); **MS (ESI$^+$)** Calcd. For $C_{35}H_{41}F_3N_4O_{10}$ + H, 735.29; Found, 735.20.



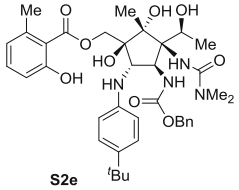
S2b

((1*S*,2*R*,3*R*,4*S*,5*S*)-4-(((benzyloxy)carbonyl)amino)-3-(3,3-dimethylureido)-5-((3-fluorophenyl)amino)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)-2-methylcyclopentyl)methyl 2-hydroxy-6-methylbenzoate (S2b): Isolated from **S1b** via general procedure D in 80 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 11.91 (s, 1H); 7.54 (br s, 1H); 7.34 (br s, 4H); 7.27 (d, *J* = 8.0 Hz, 1H); 7.25 (d, *J* = 6.4 Hz, 1H); 7.07 (q, *J* = 7.2 Hz, 1H); 6.81 (d, *J* = 8.0 Hz, 1H); 6.65 (d, *J* = 7.6 Hz, 1H); 6.39 (dd, *J* = 2.0, 8.0 Hz, 1H); 6.29 (dd, *J* = 1.6, 8.0 Hz, 1H); 6.21 (d, *J* = 11.6 Hz, 1H); 6.12 (s, 1H); 5.79 (d, *J* = 8.8 Hz, 1H); 5.69 (d, *J* = 10.0 Hz, 1H); 5.17–5.10 (m, 3H); 4.90 (d, *J* = 12.4 Hz, 1H); 4.80 (d, *J* = 12.4 Hz, 1H); 4.03 (d, *J* = 8.4 Hz, 1H); 3.74 (s, 1H); 3.70 (d, *J* = 9.6 Hz, 1H); 2.84 (s, 6H); 2.33 (s, 3H); 1.48 (s, 3H); 1.24 (d, *J* = 7.2 Hz, 3H); **MS (ESI$^+$)** Calcd. For $C_{34}H_{41}FN_4O_9$ + H, 669.15; Found, 669.15.



S2d

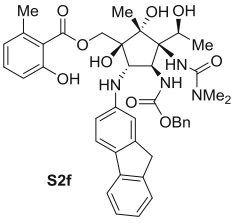
((1*S*,2*R*,3*R*,4*S*,5*S*)-4-(((benzyloxy)carbonyl)amino)-3-(3,3-dimethylureido)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)-2-methyl-5-(phenylamino)cyclopentyl)methyl 2-hydroxy-6-methylbenzoate (S2d): Isolated from **S1d** via general procedure D in 69 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.93 (s, 1H); 7.57 (br s, 1H); 7.35 (br s, 4H); 7.27–7.20 (m, 2H); 7.14 (t, *J* = 7.6 Hz, 2H); 6.80 (d, *J* = 8.4 Hz, 1H); 6.72 (t, *J* = 7.2 Hz, 1H); 6.65 (d, *J* = 7.2 Hz, 1H); 6.52 (d, *J* = 7.6 Hz, 2H); 6.05 (s, 1H); 5.84 (d, *J* = 9.6 Hz, 1H); 5.50 (d, *J* = 10.0 Hz, 1H); 5.21 (s, 1H); 5.17–5.07 (m, 2H); 4.91–4.81 (m, 2H); 4.28 (s, 1H); 4.05 (d, *J* = 8.0 Hz, 1H); 3.75 (br s, 2H); 2.83 (s, 6H); 2.34 (s, 3H); 1.48 (s, 3H); 1.13 (br s, 3H); **MS (ESI$^+$)** Calcd. For $C_{34}H_{42}N_4O_9$ + H, 651.30; Found, 651.39.



S2e

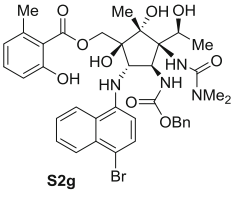
((1*S*,2*R*,3*R*,4*S*,5*S*)-4-(((benzyloxy)carbonyl)amino)-5-((4-(*tert*-butyl)phenyl)amino)-3-(3,3-dimethylureido)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)-2-methyl-

cyclopentyl)methyl 2-hydroxy-6-methylbenzoate (S2e): Isolated from **S1e** via general procedure D in 76 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.95 (br s, 1H); 7.49 (br s, 1H); 7.54 (br s, 5H); 7.27–7.24 (m, 2H); 7.15 (d, *J* = 8.4 Hz, 2H); 6.81 (d, *J* = 8.4 Hz, 1H) 6.65 (d, *J* = 7.6 Hz, 1H); 6.06 (s, 1H); 5.83 (d, *J* = 8.4 Hz, 1H); 5.37 (d, *J* = 10.4 Hz, 1H); 5.20–5.15 (m, 2H); 5.09 (d, *J* = 12.0 Hz, 1H); 4.85–4.80 (m, 2H); 4.31 (s, 1H); 4.05 (d, *J* = 7.6, 1H); 3.75 (d, *J* = 9.2 Hz, 1H); 3.66 (br s, 1H); 2.83 (s, 6H); 2.33 (s, 3H); 1.47 (s, 3H); 1.27–1.23 (m, 12H); **MS (ESI$^+$)** Calcd. For $C_{38}H_{50}N_4O_9$ + H, 707.37; Found, 707.24.



S2f

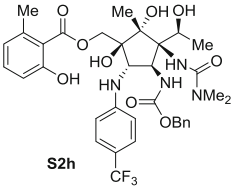
((1*S*,2*R*,3*R*,4*S*,5*S*)-5-((9H-fluoren-2-yl)amino)-4-(((benzyloxy)carbonyl)amino)-3-(3,3-dimethylureido)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)-2-methylcyclopentyl)methyl 2-hydroxy-6-methylbenzoate (S2f): Isolated from **S1f** via general procedure D in 83 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.92 (s, 1H); 7.61 (d, *J* = 7.2 Hz, 1H); 7.54 (d, *J* = 8.0 Hz, 2H); 7.45 (d, *J* = 7.2 Hz, 1H); 7.42 (m, 4H); 7.31 (t, *J* = 7.5 Hz, 2H); 7.26–7.18 (m, 3H); 6.79 (d, *J* = 8.4 Hz, 1H); 6.71 (s, 1H); 6.61 (d, *J* = 7.6 Hz, 1H); 6.54 (d, *J* = 8.0 Hz, 1H); 6.16 (s, 1H); 5.82 (d, *J* = 8,4 Hz, 1H); 5.63 (d, *J* = 10.0 Hz, 1H); 5.21–5.14(m, 3H); 4.91–4.88 (m, 2H); 3.82 (br s, 1H); 3.71 (br s, 2H); 2.85 (s, 6H); 2.32 (s, 3H); 1.50 (s, 3H); 1.24 (br s, 3H); **LRMS (ESI$^+$)** Calcd. For $C_{41}H_{46}N_4O_9$ + H, 739.33; Found, 739.21.



S2g

((1*S*,2*R*,3*R*,4*S*,5*S*)-4-(((benzyloxy)carbonyl)amino)-5-((4-bromonaphthalen-1 - y l)amino)-3-(3,3-dimethylureido)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)-2-methylcyclopentyl) methyl 2-hydroxy-6-methylbenzoate (S2 g): Isolated from **S1 g** via general procedure D in 97 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.88 (br s, 1H); 8.21 (d, *J* = 8.4 Hz, 1H); 7.73 (d, *J* = 8.0 Hz, 1H); 7.62–7.58 (m, 2H); 7.50 (t, *J* = 7.2 Hz, 2H); 7.36 (br s, 5H); 7.27–7.23 (m, 2H); 6.80 (d, *J* = 8.0 Hz, 1H); 6.64–6.59 (m, 2H); 6.36 (s, 1H); 6.20 (d, *J* = 8.0 Hz, 1H); 5.81 (br s, 1H); 5.20–5.18 (m, 3H); 5.00–4.98 (m, 2H); 4.05 (br s, 1H); 3.89

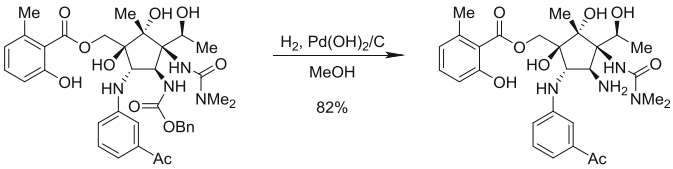
(d, J = 9.2 Hz,1H); 3.81 (s, 1H); 2.86 (s, 6H); 2.21(s, 3H); 1.65 (s, 3H) 1.22 (br s, 3H); **MS (ESI$^+$)** Calcd. For $C_{38}H_{43}BrN_4O_9$ + H, 779.23; Found, 779.20.



S2h

((1*S*,2*R*,3*R*,4*S*,5*S*)-4-(((benzyloxy)carbonyl)amino)-3-(3,3-dimethylureido)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)-2-methyl-5-((4-(trifluoromethyl) phenyl)amino) cyclopentyl)methyl 2-hydroxy-6-methylbenzoate (S2 h): Isolated from **S1 h** via general procedure D in > 99 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.89 (br s, 1H); 7.52 (br s, 1H); 7.36–7.26 (m, 8H); 6.82 (d, J = 8.4 Hz,1H); 6.65 (d, J = 7.6 Hz, 1H); 6.51 (d, J = 8.0 Hz, 2H); 6.16 (s, 1H); 5.92 (d, J = 9.6 Hz, 1H); 5.81 (br s, 1H); 5.17–5.11(m, 3H); 4.93 (d, J = 12.4 Hz, 1H); 4.81 (d, J = 12.8 Hz, 1H); 2.27 (s, 3H); 1.50 (s, 3H); 1.26 (br s, 3H); **MS (ESI$^+$)** Calcd. For $C_{35}H_{41}F_3N_4O_9$ + H, 719.29; Found, 719.23.

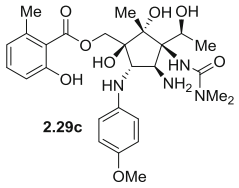
General procedure E for Carboxybenzyl group hydrogenolysis.



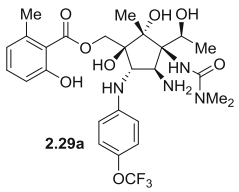
2.61 pactamycin, 2.1

Pactamycin (2.1): A 4-mL vial was charged with salicylate **2.61** (0.0075 g, 0.01 mmol, 1.0 equiv), and $Pd(OH)_2$/C (20 wt%, 0.005 g). MeOH (1 mL) was added and the vial was sealed with a Teflon cap. The atmosphere was replaced by H_2 (balloon, ∼1 atm.) and stirred until TLC analysis indicated complete consumption of the starting material, typically 20 min. The resulting suspension was filtered through a pad of Celite and washed with MeOH. The homogeneous solution was concentrated in vacuo. The crude residue was purified by flash chromatography (98:2 CH_2Cl_2:MeOH) affording pactamycin (0.005 g, 82 %) as a pale yellow solid. Analytical data: $[\alpha]_D^{19}$ +27.4 (c = 0.40, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 10.98 (br s, 1H), 7.91 (d, J = 10.8 Hz, 1H), 7.26–7.23 (m, 4H), 7.18–7.16 (m, 2H), 6.81–6.78 (m, 2H), 6.64 (d, J = 7.2 Hz, 1H), 5.78 (br s, 1H), 5.67 (d, J = 10.8 Hz, 1H), 4.84 and 4.79 (ABq, J = 12.6 Hz, 2H), 3.93 (m, 1H), 3.80 (d, J = 10.2 Hz, 1H), 2.99 (s, 6H), 2.95 (s, 1H), 2.55 (s, 3H), 2.38 (s, 3H), 1.55 (s, 3H), 1.04 (d, J = 6.0 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 198.5, 172.6, 162.8. 159.2, 146.6, 141.2, 138.3, 134.6, 129.6, 123.0, 118.7, 118.4, 115.7, 112.0, 110.8, 88.8, 84.9, 74.3, 71.5, 68.7, 65.4, 63.2, 36.9, 29.7, 26.7, 24.1, 21.1, 18.1; **MS (ESI$^+$)**

Calcd. for $C_{28}H_{38}N_4O_8$ + H, 559.2762; Found, 559.2763; **IR** (thin film, cm^{-1}) 3393, 2938, 2359, 2341, 1698, 1652, 1520, 1473, 1418, 1338, 873, 668; **TLC** (95:5 CH_2Cl_2/MeOH): R_f = 0.30.

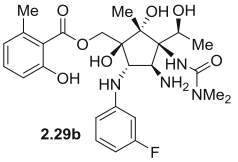


(((1*S*,2*R*,3*R*,4*S*,5*S*)-4-amino-3-(3,3-dimethylureido)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)-5-((4-methoxyphenyl)amino)-2-methylcyclopentyl)methyl 2-hydroxy-6-methylbenzoate) (2.29c): Isolated from **S2c** via general procedure E in 72 % yield. Analytical data: $[\alpha]_D^{19}$ +20.9 (*c* = 0.63, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.80 (br s, 1H); 7.93 (br s, 1H); 7.28–7.24 (m, 2H); 7.21–7.18 (m, 2H); 6.83 (d, *J* = 8.4 Hz, 1H); 6.78 (d, *J* = 8.8 Hz, 2H); 6.68 (d, *J* = 7.2 Hz, 1H); 6.57 (d, *J* = 8.4 Hz, 2H); 5.68 (br s, 1H); 5.18 (br s, 1H); 4.85 (d, *J* = 12.4 Hz, 1H); 4.80 (d, *J* = 12.0 Hz, 1H); 3.97 (br s, 1H); 3.76 (s, 3H); 3.00 (s, 7H); 2.91 (s, 1H); 2.47 (s, 3H); 2.38 (s, 1H); 1.55 (s, 3H); 1.06 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 172.3, 162.5, 159.2, 152.1, 141.3, 140.5, 134.3, 129.0, 128.2, 125.2, 122.9, 115.6, 115.1, 114.5, 112.40, 88.7, 84.7, 74.0, 71.3, 69.9, 65.4, 62.6, 55.7, 36.80, 23.9, 21.4, 18.1; **MS (ESI$^+$)** Calcd. for $C_{27}H_{38}N_4O_8$ + H, 547.28; Found, 547.22; **IR** (thin film, cm^{-1}) 3774, 3406, 2935, 2359, 2069, 1610, 1511, 1377, 1251, 1105, 943; **TLC** (95:5 CH_2Cl_2:MeOH): R_f = 0.30.



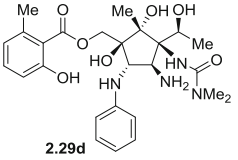
((1*S*,2*R*,3*R*,4*S*,5*S*)-4-amino-3-(3,3-dimethylureido)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)-2-methyl-5-((4-(trifluoromethoxy)phenyl)amino)cyclopentyl) methyl 2-hydroxy-6-methylbenzoate (2.29a): Isolated from **S2a** via general procedure E in 96 % yield. Analytical data: $[\alpha]_D^{19}$ +34.4 (*c* = 0.70, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 11.02 (br s, 1H); 7.94 (d, *J* = 11.4 Hz, 1H); 7.31–7.27 (m, 2H); 7.17 (br s, 1H); 7.05 (d, *J* = 9.0 Hz, 2H); 6.85 (d, *J* = 7.8 Hz, 1H); 6.69 (d, *J* = 7.2 Hz, 1H); 6.58 (d, *J* = 8.4 Hz, 1H); 5.84 (br s, 1H); 5.62 (d, *J* = 10.2 Hz,1H); 4.87 (d, *J* = 12.6 Hz, 1H); 4.83 (d, *J* = 12.6 Hz, 1H); 3.99 (br s, 1H); 3.74 (d, *J* = 10.2 Hz, 1H); 3.02 (s, 6H); 2.40 (s, 3H); 1.58 (s, 3H); 1.10 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 172.7, 162.8, 159.2, 145.2, 141.4, 140.6, 134.7, 123.1, 122.8, 115.7, 113.3, 112.1, 84.9, 65.4, 36.9, 24.0, 21.1, 18.1; **MS (ESI$^+$)** Calcd. For $C_{27}H_{35}F_3N_4O_8$ + H, 601.25; Found, 601.28; **IR**

(thin film, cm^{-1}) 3774, 3398, 2935, 2359, 2056, 1723, 1612, 1513, 1378, 1253, 1163, 1106, 1044, 977, 805; **TLC** (95:5 CH_2Cl_2:MeOH): R_f = 0.29.



2.29b

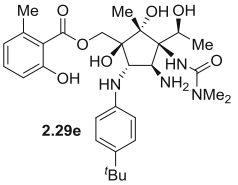
((1*S*,2*R*,3*R*,4*S*,5*S*)-4-amino-3-(3,3-dimethylureido)-5-((3-fluorophenyl)amino)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)-2-methylcyclopentyl)methyl 2-hydroxy-6-methyl benzoate (2.29b): Isolated from **S2b** via general procedure E in > 99 % yield. Analytical data: $[\alpha]_D^{19}$ +34.8 (*c* = 0.90, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 11.04 (br s, 1H); 7.99 (d, *J* = 5.2 Hz, 1H); 7.30–7.28 (m, 2H); 7.27–7.18 (m, 2H); 7.12 (dd, *J* = 5.2, 10.0 Hz, 1H); 6.85 (d, *J* = 5.2 Hz, 1H); 6.70 (d, *J* = 5.2 Hz, 1H); 6.43 (dd, *J* = 1.2, 5.6 Hz, 1H); 6.39 (dd, *J* = 1.2, 11.6 Hz, 1H); 6.29 (d, *J* = 7.6 Hz, 1H); 5.83 (s, 1H); 5.69 (d, *J* = 6.8 Hz, H); 4.87 (d, *J* = 7.2 Hz, 1H); 4.82 (d, *J* = 8.4 Hz, 1H); 3.95 (br s, 1H); 3.72 (d, *J* = 7.2 Hz, 1H); 3.01 (s, 6H); 2.97 (s,1H); 2.43 (s, 3H); 1.57 (s, 3H); 1.07 (d, *J* = 4.0 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 172.7, 162.8, 159.2, 148.1, 141.3, 134.6, 130.7, 129.0, 128.2, 123.1, 115.7, 112.0, 109.4, 104.1, 99.4, 88.7, 84.8, 74.2, 71.4, 68.7, 65.2, 63.0, 36.8, 24.0, 21.1, 18.1; **MS (ESI$^+$)** Calcd. For $C_{26}H_{37}FN_4O_7$ + H, 535.26; Found, 535.19; **IR** (thin film, cm^{-1}) 3397, 2933, 2359, 1724, 1655, 1617, 1513, 1495, 1377, 1291, 1213, 1091, 943; **TLC** (95:5 CH_2Cl_2: MeOH): R_f = 0.29.



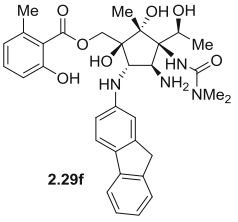
2.29d

((1*S*,2*R*,3*R*,4*S*,5*S*)-4-amino-3-(3,3-dimethylureido)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)-2-methyl-5-(phenylamino)cyclopentyl)methyl 2-hydroxy-6-methyl benzoate (2.29d): Isolated from **S2d** via general procedure E in 83 % yield. Analytical data: $[\alpha]_D^{19}$ −8.9 (*c* = 0.40, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 10.94 (br s, 1H); 7.90 (dd, *J* = 5.4 Hz, 1H); 7.26 (t, *J* = 7.8 Hz, 2H); 7.22–7.16 (m, 3H); 6.82 (d, *J* = 8.4 Hz, 1H); 6.71 (t, *J* = 7.8 Hz, 1H); 6.66 (d, *J* = 7.2 Hz,1H); 6.59 (d, *J* = 7.8 Hz, 2H); 5.76 (s, 1H); 5.47 (d, *J* = 11.4 Hz, 1H); 4.84 (d, *J* = 12.6 Hz, 1H); 4.82 (d, *J* = 12.0 Hz, 1H); 3.94 (dd, *J* = 6.0, 10.2 Hz, 1H); 3.76 (d, *J* = 10.8 Hz, 1H); 2.98 (s, 6H); 2.94 (s, 1H); 2.42 (s, 3H); 1.54 (s, 3H); 1.03 (d, *J* = 6. Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 172.7, 162.8, 159.2, 146.3, 141.4, 134.5, 129.5, 123.0, 117.7, 115.7, 113.2, 112.1, 89.8, 88.8, 84.9, 74.2, 71.5, 68.9, 65.3, 63.0, 36.8, 36.8, 29.7, 24.1, 21.2, 18.1; **MS (ESI$^+$)** Calcd. For $C_{26}H_{38}N_4O_7$ + H, 517.27; Found, 517.29; **IR** (thin film, cm^{-1})

3876, 3846, 3774, 3398, 2929, 2359, 1724, 1603, 1460, 1305, 1213, 977; **TLC** (95:5 CH_2Cl_2:MeOH): $R_f = 0.26$.

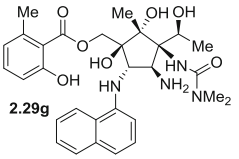


((1*S*,2*R*,3*R*,4*S*,5*S*)-4-amino-5-((4-(*tert*-butyl)phenyl)amino)-3-(3,3-dimethyl ureido)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)-2-methylcyclopentyl)methyl 2-hydroxy-6-methylbenzoate (2.29e): Isolated from **S2e** via general procedure E in 88 % yield. Analytical data: $[\alpha]_D^{19}$ +35.9 (*c* = 0.50, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 11.03 (br s, 1H);7.89 (d, *J* = 10.8 Hz, 1H); 7.28 (t, *J* = 6.0 Hz, 2H); 7.22–7.19 (m, 4H); 6.84 (d, *J* = 8.4 Hz, 1H); 6.69 (d, *J* = 7.6, 1H); 6.56 (d, *J* = 8.4 Hz, 2H); 5.70 (s, 1H); 5.33 (d, *J* = 11.2 Hz, 1H); 4.85 (d, *J* = 12.0 Hz, 1H); 4.81 (d, *J* = 12.4 Hz, 1H); 3.98 (dd, *J* = 6.4, 1.2 Hz, 1H); 3.76 (d, *J* = 10.8 Hz, 1H); 3.01 (s, 6H); 2.46 (s, 3H); 2.38 (s, 1H); 1.56 (s, 3H); 1.29 (s, 9H) 1.06 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 172.5, 167.7, 159.2, 143.8, 141.3, 140.4, 134.4, 126.2, 122.9, 115.7, 112.9, 112.2, 88.7, 84.8, 74.0, 71.4, 69.3, 65.3, 63.2, 36.8, 33.8, 31.5, 29.7, 24.1, 21.2, 18.1; **MS (ESI$^+$)** Calcd. For $C_{30}H_{44}N_4O_7$ + H, 573.33; Found, 573.33; **IR** (thin film, cm^{-1}) 3379, 3204, 2961, 2360, 1723, 1607, 1518, 1364, 1255, 1082; **TLC** (90:10 CH_2Cl_2/MeOH): $R_f = 0.92$.

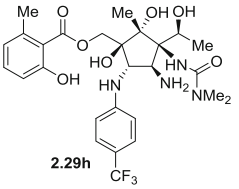


((1*S*,2*R*,3*R*,4*S*,5*S*)-5-((9H-fluoren-2-yl)amino)-4-amino-3-(3,3-dimethyl-ureido)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)-2-methylcyclopentyl)methyl 2-hydroxy-6-methylbenzoate (2.29f): Isolated from **S2f** via general procedure E in 40 % yield. Analytical data: $[\alpha]_D^{19}$ +21.4 (*c* = 0.23, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ (400 MHz, $CDCl_3$): δ 11.02 (br s, 1H); 7.95 (d, *J* = 10.8 Hz, 1H); 7.64 (d, *J* = 7.6 Hz, 1H); 7.59 (d, *J* = 8.4 Hz, 1H); 7.48 (d, *J* = 7.6 Hz, 1H); 7.33 (t, *J* = 7.2 Hz, 1H); 7.29–7.19 (m, 3H); 6.81 (d, *J* = 8.0 Hz, 2H); 6.66–6.63 (m, 2H); 5.83 (s, 1H); 5.60 (d, *J* = 10.8 Hz, 1H); 4.90 (d, *J* = 12.4 Hz, 1H); 4.86 (d, *J* = 12.4 Hz, 1H); 4.01 (dd, *J* = 6.4, 10.4 Hz, 1H); 3.85 (d, *J* = 10.8 Hz, 2H); 3.81 (d, *J* = 7.6 Hz, 1H); 3.06

(s, 1H); 3.02 (s, 6H); 2.44 (s, 3H); 1.59 (s, 3H); 1.07 (d, J = 6.4 Hz, 3H); **^{13}C NMR** (150 MHz, CDCl3): δ 172.6, 162.7, 159.2, 145.8, 145.4, 142.1, 142.1, 141.3, 134.5, 132.3, 126.6, 125.0, 124.7, 123.0, 120.9, 118.4, 115.6, 122.1, 110.0, 88.8, 85.0, 74.2, 71.4, 69.2, 65.4, 65.1, 36.9, 36.8, 24.1, 21.2, 18.1; **MS (ESI$^+$)** Calcd. For $C_{33}H_{40}N_4O_7$ + H, 605.30; Found, 605.29. **IR** (thin film, cm^{-1}) 3397, 2925, 1653, 1616, 1519, 1457, 1375, 1290, 1256, 1096, 804; **TLC** (95:5 CH_2Cl_2:MeOH): R_f = 0.37.



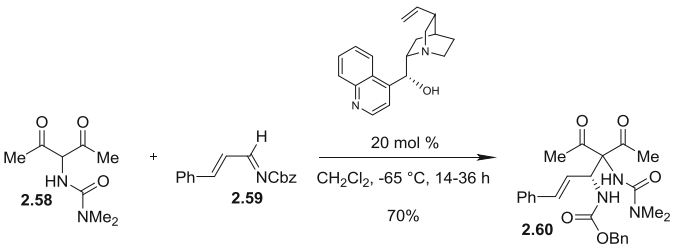
((1*S*,2*R*,3*R*,4*S*,5*S*)-4-amino-3-(3,3-dimethylureido)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)-2-methyl-5-(naphthalen-1-ylamino)cyclopentyl)methyl 2-hydroxy-6-methylbenzoate (2.29 g): Isolated from **S2 g** via general procedure E in 48 % yield. Analytical data: $[\alpha]_D^{19}$ +28.1 (c = 0.82, $CHCl_3$) **^{1}H NMR** (600 MHz, $CDCl_3$): δ 10.98 (s, 1H); 7.97 (br s, 1H); 7.79 (d, J = 6.0 Hz, 1H); 7.74 (d, J = 12.0 Hz, 1H); 7.46 (m, 2H); 7.31 (t, J = 6.0 Hz, 1H); 7.27–7.21 (m, 4H); 6.79 (d, J = 8.4 Hz, 1H); 6.61 (d, J = 7.2 Hz, 1H); 6.51 (m, 2H); 5.98 (s, 1H); 4.95 (dd, J = 12.0, 7.2 Hz, 2H); 3.97 (m, 2H); 3.06 (br s, 1H); 2.98 (s, 6H); 2.96 (m, 2H); 2.33 (s, 3H); 1.61 (s, 3H); 0.98 (d, J = 6.6 Hz, 3H); **^{13}C NMR** (100 MHz, CDCl3): δ 172.7, 162.7, 159.3, 141.7, 141.4, 134.6, 134.5, 128.5, 126.3, 126.1, 125.2, 123.7, 123.0, 120.1, 117.3, 115.6, 122.1, 103.3, 88.9, 85.1, 74.5, 71.6, 68.5, 65.4, 62.9, 36.8, 23.9, 21.2, 18.0; **MS (ESI$^+$)** Calcd. For $C_{30}H_{38}N_4O_7$ + H, 567.28; Found, 567.28; **IR** (thin film, cm^{-1}) 3756, 3398, 3053, 2984, 2935, 2410, 2304, 1949, 1725, 1656, 1582, 1486, 1265, 1120, 943; **TLC** (95:5 CH_2Cl_2:MeOH): R_f = 0.33.



((1*S*,2*R*,3*R*,4*S*,5*S*)-4-amino-3-(3,3-dimethylureido)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)-2-methyl-5-((4-(trifluoromethyl)phenyl)amino)cyclopentyl) methyl 2-hydroxy-6-methylbenzoate (2.29 h): Isolated from **S2 h** via general procedure E in 96 % yield. Analytical data: $[\alpha]_D^{19}$ +30.0 (c = 0.15, $CHCl_3$) **^{1}H NMR** (600 MHz, $CDCl_3$): δ 10.98 (br s, 1H); 7.93 (d, J = 10.8 Hz, 1H); 7.39 (d, J = 8.4 Hz, 2H); 7.27 (m, 2H); 7.16 (s, 1H); 6.82 (d, J = 8.4 Hz, 1H); 6.66 (d, J = 7.2 Hz, 1H); 6.59 (d, J = 8.4 Hz, 2H); 5.91 (d, J = 9.6 Hz, 1H); 5.84 (s, 1H); 4.85 (d, J = 12.0 Hz, 1H); 4.79 (d, J = 12.0 Hz, 1H); 3.91 (m, 1H); 3.76

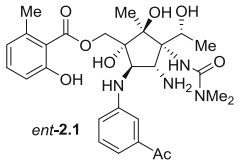
(d, J = 12.0 Hz, 1H); 2.99 (s, 6H); 2.36 (s, 3H); 2.17 (s, 3H); 2.07 (s, 3H); 1.55 (s, 3H); 1.05 (d, J = 6.0 Hz, 3H); **^{13}C NMR** (100 MHz, CDCl3): δ 172.5, 170.7, 162.7, 159.2, 148.5, 141.2, 134.6, 126.9, 126.9, 123.0, 115.7, 112.2, 112.1, 88.9, 84.7, 74.3, 71.5, 68.3, 65.3, 63.4, 38.0, 36.8, 35.2, 23.9, 21.5, 21.1, 18.1; **MS (ESI$^+$)** Calcd. For $C_{27}H_{35}F_3N_4O_7$ + H, 585.25; Found, 585.18; **IR** (thin film, cm^{-1}) 3413, 2359, 1617, 1524, 1457, 1375, 1321, 1255, 1213, 1160, 1106, 1064, 737; **TLC** (95:5 CH_2Cl_2:MeOH): R_f = 0.17.

Enantioselective Mannich reaction to provide enantioenriched material.



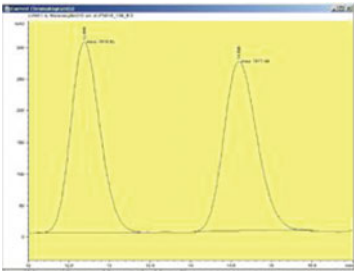
(***R***,***E***)**-benzyl (4-acetyl-4-(3,3-dimethylureido)-5-oxo-1-phenylhex-1-en-3-yl)carbamate (2.60)**: A flame-dried 250-mL round-bottomed flask was charged with urea **2.58** (2.38 g, 12.28 mmol, 1.0 equiv), cinchonidine (0.72 g, 2.46 mmol, 0.2 equiv), and CH_2Cl_2 (65 mL). The resulting suspension was cooled to −78 °C and a cold solution of imine **2.59** (5.1 g, 19.24 mmol, 1.5 equiv) in CH_2Cl_2 (35 mL) was added via cannula transfer. The reaction was warmed to −65 °C and stirred until complete consumption of urea **2.58** was indicated by TLC analysis, typically 14–36 h (scale-dependent). The crude reaction was filtered through a short silica plug and rinsed with EtOAc (300 mL). The filtrate was concentrated in vacuo to give a pale yellow foam with a 84:16 enantiomeric ratio. Crystalline *racemic* product was isolated via trituration with 60:40 (v/v) hexanes:EtOAc (300 mL). The analytically-pure white solid was removed by filtration (1.33 g, 24 %) and the filtrate was concentrated in vacuo to give a yellow oil. The crude oil was purified by flash chromatography (60:40 to 50:50 hexanes:EtOAc) affording diketone **2.60** as a pale yellow foam (3.87 g, 70 %, 97:3 er). The enantiomeric ratio was determined by SFC analysis (Chiralcel, OD, 9.0 % MeOH, 1.5 mL/min, 150 bar, 210 nm; t_R-minor 12.8 min, t_R-major 14.7 min). Analytical data: $[\alpha]_D^{19}$ +16.5 (c = 1.00, $CHCl_3$); **mp** (*racemate*) 130–134 °C; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.37–7.21 (m, 10H), 7.07 (br d, J = 6.0 Hz, 1H), 6.59 (d, J = 16.2 Hz, 1H), 6.50 (s, 1H), 5.96 (dd, J = 16.2 Hz, 7.2, 1H), 5.40 (t, J = 7.2 Hz, 1H), 5.14 (d, J = 12.0 Hz, 1H), 5.11 (d, J = 12.0 Hz, 1H), 2.97 (s, 6H), 2.28 (s, 3H), 2.14 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 200.9, 200.4, 157.6, 156.7, 136.9, 136.5, 133.2, 128.7, 128.6, 128.2, 128.2, 128.1, 126.9, 124.6, 81.7, 67.0, 57.2, 36.8, 26.2, 25.4; **MS**

(ESI$^+$) Calcd. For $C_{25}H_{29}N_3O_5$ + H, 452.2187; Found, 452.2212; **IR** (thin film, cm^{-1}) 3418, 2243, 1702, 1635, 1507, 1371, 1249, 1066, 912, 693; **TLC** (60:40 hexanes:EtOAc): R_f = 0.20.



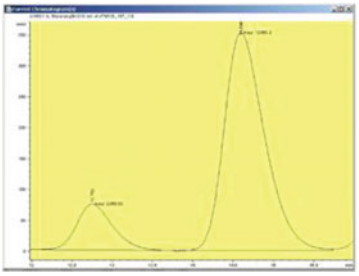
***ent*-pactamycin (*ent*-2.1)**: When cinchonidine is replaced by cinchonine in the above reaction, a crude enantiomeric ratio of 84:16 is obtained. Upon the analogous trituration protocol, *ent*-**2.60** is isolated in 68 % yield and 96.5:3.5 er (See SFC assay comparison below). When this material is carried forward in the synthesis, *ent*-pactamycin is obtained. The optical rotation was measured: $[\alpha]_D^{19}$ −23.2 (c = 0.40, $CHCl_3$).

SFC analysis of racemic Mannich product 2.60 (20 mol % $NIPr_2Et$)

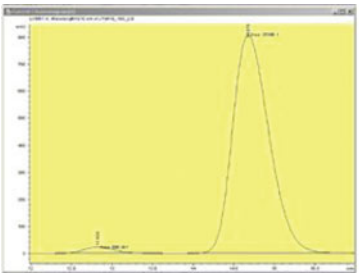


Mannich product for natural pactamycin enantiomer synthesis

Cinchonidine: Crude reaction mixture (16:84 e.r.)

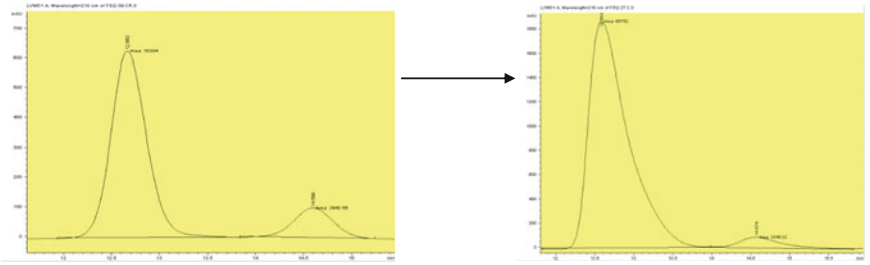


after purification/trituration (2:98 er)

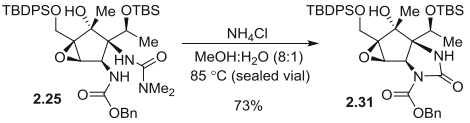


Mannich product for *ent*-pactamycin synthesis

Cinchonine: Crude reaction mixture (84:16 e.r.) after trituration/purification (96.5:3.5 e.r.)

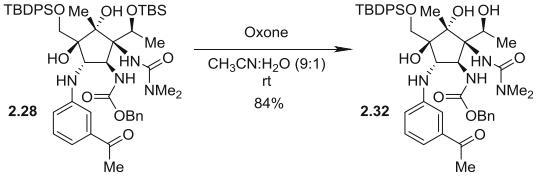


General procedure F for isocycanate formation/trapping.

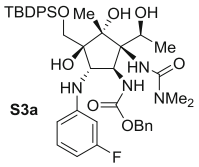


Benzyl (1a*R*,1b*R*,4a*R*,5*R*,5a*R*)-4a-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-5a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5-hydroxy-5-methyl-3-oxohexahydro oxireno [2′,3′:3,4]cyclopenta[1,2-d]imidazole-2(1aH)-carboxylate (2.31). A 20-mL scintillation vial was charged with urea **2.25** (0.06 g, 0.077 mmol, 1.00 equiv) and an 8:1 mixture of MeOH:H_2O (6.0 mL), and NH_4Cl (0.123 g, 2.31 mmol, 30.0 equiv) was added. The vial was sealed with a screw-cap and the mixture was heated to 85 °C with vigorous stirring until TLC analysis indicated full conversion of the starting material, generally 16 h. The resulting mixture was concentrated and the remaining residue was dissolved in water (10 mL). The solution was extracted with EtOAc (3 × 8 mL) and the combined organics were washed with brine (10 mL), dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (70:30 hexanes:EtOAc), obtaining **2.31** as a pale yellow solid (0.056 g, 73 %). Analytical Data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.67–7.65 (m, 4H); 7.44–7.33 (m, 12H); 5.35 (s, 1H); 5.30 (s, 2H); 4.23 (br s, 2H); 3.99 (br s, 2H); 3.75 (s, 1H); 1.60 (s, 3H); 1.17 (d, J = 6.0 Hz, 3H); 1.16 (s, 9H); 0.87 (s, 9H); 0.10 (s, 3H); 0.08 (s, 3H); **MS (ESI$^+$)** Calcd. For $C_{40}H_{54}N_2O_7Si_2$ + H, 731.35; Found, 731.23.

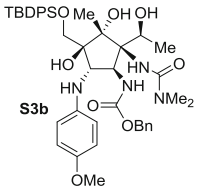
General procedure G for selective TBS deprotection of C7 alcohol.



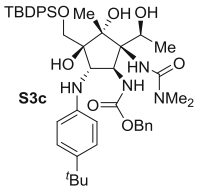
Benzyl ((1*R*,2*R*,3*R*,4*R*,5*R*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-(3,3-dimethylureido)-4-hydroxy-3-((S)-1-hydroxyethyl)-4-methyl-6-oxabicyclo [3.1.0]hexan-2-yl)carbamate (2.32) A 20-mL scintillation vial was charged with silyl ether **2.28** (0.067 g, 0.073 mmol, 1.00 equiv), and a 9:1 mixture of CH_3CN: H_2O (5 mL). To the resulting solution was added Oxone ® (0.022 g, 0.15 mmol, 2.00 equiv), and the reaction was vigorously stirred until full conversion of **2.28** was observed by TLC analysis, typically 3 h. The mixture was diluted with H_2O (3 mL) and EtOAc (3 mL), and the layers were partitioned in a separatory funnel and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (70:30 hexanes: EtOAc) to afford triol **2.32** (0.049 g, 84 %) as a clear, viscous oil. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 6.4 Hz, 2H); 7.50 (d, *J* = 8.0 Hz, 2H); 7.43–7.30 (m, 11H); 7.25 (d *J* = 8.4 Hz,2H); 7.19 (t, *J* = 7.2 Hz, 2H); 7.05 (s, 1H); 6.66 (d, *J* = 7.2 Hz, 1H); 5.92 (d, *J* = 9.6 Hz, 1H); 5.55 (br s, 1H); 5.22–5.13 (m, 3H); 4.02–3.99 (m, 3H); 3.92 (d, *J* = 10.0 Hz,1H); 3.74 (d, *J* = 9.6 Hz, 1H); 2.87 (s, 6H); 2.53 (s, 3H); 1.43 (s, 3H); 1.25 (d, *J* = 8.4 Hz, 3H); 1.02 (s, 9H); **MS (ESI$^+$)** Calcd. For $C_{44}H_{56}N_4O_8Si$ + H, 797.39; Found, 797.34.



Benzyl ((1*S*,2*R*,3*R*,4*S*,5*S*)-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-(3,3-dimethylureido)-5-((3-fluorophenyl)amino)-3,4-dihydroxy-2-((S)-1-hydroxyethyl)-3-methylcyclopentyl)carbamate (S3a): Isolated from **2.28b** via general procedure G in 87 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 6.8 Hz, 2H); 7.51 (d, *J* = 7.2 Hz, 2H); 7.46–7.37 (m, 9H); 7.23–7.19 (m, 2H); 7.10 (br s, 1H); 6.44–6.41 (m, 1H); 6.25 (d, *J* = 8.0 Hz, 1H); 6.18 (d, *J* = 11.6 Hz, 1H); 5.95 (br s, 2H); 5.55 (d, *J* = 9.6 Hz,1H); 5.20–5.17 (m, 3H); 4.12 (br s, 3H); 4.01 (d, *J* = 10.4 Hz, 1H); 3.69 (br s, 2H); 2.87 (s, 6H); 1.41 (s, 3H); 1.25 (br s, 3H); 1.03 (s, 9H); **MS (ESI$^+$)** Calcd. For $C_{42}H_{53}FN_4O_7Si$ + H, 773.37; Found, 773.46.

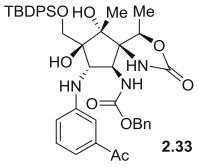


Benzyl ((1*S*,2*R*,3*R*,4*S*,5*S*)-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-(3,3-dimethylureido)-3,4-dihydroxy-2-((S)-1-hydroxyethyl)-5-((4-methoxyphenyl)-amino)-3-methylcyclopentyl)carbamate (S3b): Isolated from **2.28c** via general procedure G in 62 % yield. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.8 Hz, 2H); 7.58 (br s, 1H); 7.55 (d, *J* = 7.8 Hz, 2H); 7.44–7.34 (m, 8H); 7.22 (t, *J* = 7.8 Hz, 2H); 6.76 (d, *J* = 8.4 Hz, 2H); 6.42 (d, *J* = 7.8 Hz, 2H); 5.95 (s, 1H); 5.89 (br s, 1H); 5.20–5.18 (m, 2H); 5.14–5.11 (m, 2H); 4.00 (br s, 2H); 3.92 (d, *J* = 9.6 Hz, 1H); 3.76 (s, 3H); 3.68 (s, 1H); 3.64 (d, *J* = 6.6 Hz, 1H); 2.86 (s, 6H); 1.41 (s, 3H); 1.25 (br s, 3H); 1.03 (s, 9H); **MS (ESI$^+$)** Calcd. For $C_{43}H_{56}N_4O_8Si$ + H, 785.39; Found, 785.49.



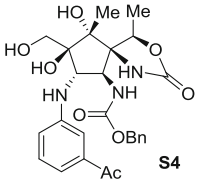
Benzyl ((1*S*,2*R*,3*R*,4*S*,5*S*)-5-((4-(*tert*-butyl)phenyl)amino)-4-(((*tert*-butyldiphenylsilyl) oxy)methyl)-2-(3,3-dimethylureido)-3,4-dihydroxy-2-((S)-1-hydroxyethyl)-3-methylcyclopentyl)carbamate (S3c): Isolated from **2.28e** via general procedure G in 77 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 6.8 Hz, 2H); 7.58 (d, *J* = 9.8 Hz, 1H); 7.51 (d, *J* = 6.8 Hz, 2H); 7.43–7.32 (m, 9H); 7.20–7.17 (m, 4H); 6.42 (d, *J* = 8.4 Hz, 2H); 5.96–5.92 (m, 2H); 5.27 (dd, *J* = 4.4, 14.4 Hz, 1H); 5.23–5.20 (m, 2H); 5.13 (d, *J* = 12.0 Hz, 1H); 4.15–4.10 (m, 3H); 3.72 (s, 1H); 3.67 (d, *J* = 8.8 Hz, 1H); 2.87 (s, 6H); 1.43 (s, 3H); 1.29 (s, 9H); 1.27 (d, *J* = 7.2 Hz, 3H); 1.03 (s, 9H); **MS (ESI$^+$)** Calcd. For $C_{46}H_{62}N_4O_7Si$ + H, 811.45; Found, 811.53.

Synthesis of De 6-MSA Pactamycate:



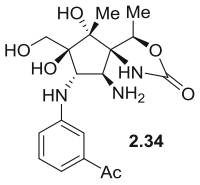
Benzyl ((4*R*,5*R*,6*S*,7*S*,8*S*,9*R*)-7-((3-acetylphenyl)amino)-8-(((*tert*-butyldiphenylsilyl) oxy)methyl)-8,9-dihydroxy-4,9-dimethyl-2-oxo-3-oxa-1-azaspiro[4.4] nonan-6-yl)carbamate (2.33): Isolated from **2.32** via general procedure F in 73 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 6.8 Hz, 2H); 7.45–7.44 (m, 3H); 7.37–7.34 (m, 4H); 7.28–7.26 (m, 6H); 7.14–7.10(m, 3H); 6.68 (d, *J* = 6.4 Hz, 1H); 5.69 (s, 1H); 5.34 (d, *J* = 6.4 Hz, 1H); 5.69 (s, 1H); 5.34 (d, *J* = 10,4 Hz, 1H); 5.07 (d, *J* = 12,4 Hz, 1H); 5.00 (d, *J* = 12.4 Hz, 1H); 4.80 (q, *J* = 6.4 Hz, 1H); 3.51–3.47 (m, 1H), 3.34 (s, 1H); 2.46 (s, 3H); 2.45(s, 1H);

2.04 (s, 1H); 1.45 (s, 3H); 143 (br s, 3H); 1.02 (s, 9H); **MS (ESI$^+$)** Calcd. For $C_{42}H_{49}N_3O_8Si$ + H, 752.34; Found, 752.48.



S4

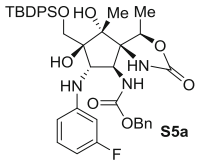
Benzyl ((4*R*,5*R*,6*S*,7*S*,8*S*,9*R*)-7-((3-acetylphenyl)amino)-8,9-dihydroxy-8-(hydroxymethyl)-4,9-dimethyl-2-oxo-3-oxa-1-azaspiro[4.4]nonan-6-yl)carbamate (S4): Isolated from **2.33** via general procedure C in > 95 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.26–7.03 (m, 7H); 6.49 (br s, 2H); 6.30 (d, *J* = 8.0 Hz, 1H); 5.04 (d, *J* = 12.8 Hz, 1H); 4.95 (d, *J* = 12.4 Hz, 1H); 8.21 (br s, 1H); 4.53 (br s, 1H); 4.45 (s, 1H); 4.32 (br s, 1H); 4.24 (br s, 1H); 4.04 (d, *J* = 12.0 Hz, 1H); 3.59–3.56 (m, 3H); 2.35 (s, 1H); 2.27 (s, 3H); 1.39 (d, J = 6.0, 3H); 1.36 (s, 3H); **MS (ESI$^+$)** Calcd. For $C_{26}H_{31}N_3O_8$ + H, 514.22; Found, 514.27.



2.34

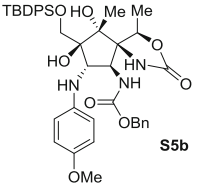
De-6-MSA Pactamycate (2.34): Isolated from **S4** via general procedure E in 46 % yield. Analytical data: $[\alpha]_D^{19}$ +4.4 (*c* = 0.11, $CHCl_3$); **^{1}H NMR** (400 MHz, MeOD): δ 7.38 (br s, 1H); 7.21–7.19 (m, 2H); 7.01 (dt, *J* = 2.0, 6.8 Hz, 1H); 4.82 (q; *J* = 6.4 Hz, 1H); 3.91 (d, *J* = 11.6 Hz, 1H); 3.58–3.56 (m, 2H); 3.53 (m, 2H); 3.53 (d, *J* = 7.6 Hz; 1H); 2.55 (s, 3H); 1.54 (d, *J* = 6.8 Hz, 3H); 1.35 (s, 3H); **^{13}C NMR** (150 MHz, MeOD): δ 201.5, 161.0, 150.9, 139.2, 130.3, 119.2, 118.0, 113.2, 84.1, 83.1, 78.4, 72.5, 70.7, 63.5, 60.7, 26.9, 17.5, 17.3; **MS (ESI$^+$)** Calcd. For $C_{18}H_{25}N_3O_6$ + H, 380.18; Found, 380.23; **IR** (thin film, cm^{-1}) 2921, 2846, 2359, 1861, 1785, 1738, 1710, 1641, 1598, 1512, 1409, 1380, 1252, 1095; **TLC** (95:5 CH_2Cl_2:MeOH): R_f = 0.13.

Synthesis of Pactamycate Derivatives:



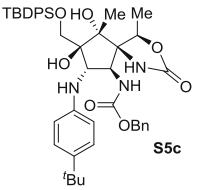
S5a

Benzyl ((4*R*,5*R*,6*S*,7*S*,8*S*,9*R*)-8-(((*tert*-butyldiphenylsilyl)oxy)methyl)-7-((3-fluorophenyl)amino)-8,9-dihydroxy-4,9-dimethyl-2-oxo-3-oxa-1-azaspiro[4.4]nonan-6-yl)carbamate (S5a): Isolated from **S3a** via general procedure F in 88 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.55 (dd, *J* = 1.27, 8.31 Hz, 2H); 7.50 (dd, *J* = 1.21, 8.29, 2H); 7.36–7.10 (m, 11H); 6.93 (dd, *J* = 7.6, 14.8 Hz, 1H); 6.35–6.30 (m,1H); 6.24 (d, *J* = 8.8 Hz, 2H); 6.08 (s, 1H); 5.57 (d, *J* = 10.0 Hz, 1H); 5.05 (d, *J* = 12.4 Hz, 1H); 4.92 (d, *J* = 12.0 Hz, 1H); 4.79 (q, *J* = 6.4 Hz, 1H); 4.49–4.45 (m, 1H); 4.31 (d, *J* = 6.8 Hz, 1H); 4.02 (d, *J* = 11.2 Hz, 1H); 3.67 (d, *J* = 11. Hz, 1H) 3.48–3.44 (m, 1H); 3.43 (s, 1H); 2.91 (s, 1H); 1.42 (s, 3H); 1.39 (d, *J* = 6.0 Hz, 3H); 1.03 (s, 9H); **MS (ESI$^+$)** Calcd. For $C_{40}H_{46}FN_3O_7Si$ + H, 728.32; Found, 728.35.



S5b

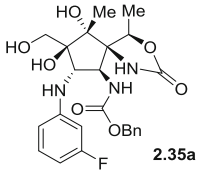
Benzyl ((4*R*,5*R*,6*S*,7*S*,8*S*,9*R*)-8-(((*tert*-butyldiphenylsilyl)oxy)methyl)-8,9-dihydroxy-7-((4-methoxyphenyl)amino)-4,9-dimethyl-2-oxo-3-oxa-1-azaspiro[4.4]nonan-6-yl)carbamate (S5b): Isolated from **S3b** via general procedure F in 73 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 7.2 Hz, 2H); 7.51 (d, *J* = 7.2 Hz, 2H); 7.45.7.22 (m, 12H); 6.62 (d, *J* = 8.8 Hz, 2H); 6.45 (d, *J* = 8.8 Hz, 2H); 5.83 (s, 1H); 5.34 (d, *J* = 10.4 Hz, 1H); 5.05 (d, *J* = 12.0 Hz, 1H); 4.97 (d, *J* = 12.0 Hz, 1H); 4.78 (q, *J* = 6.4 Hz, 1H); 4.45–4.40 (m, 1H); 4.06 (d, *J* = 11.6 Hz, 1H); 3.81 (br s, 1H); 3.71 (s, 3H); 3.36 (d, *J* = 7.2 Hz, 1H); 3.26 (s, 1H); 2.56 (s, 1H); 1.41 (br s, 6H); 0.87 (s, 9H); **MS (ESI$^+$)** Calcd. For $C_{41}H_{49}N_3O_8Si$ + H, 740.34; Found, 740.38.



S5c

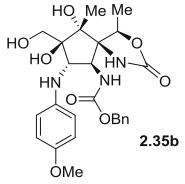
Benzyl ((4*R*,5*R*,6*S*,7*S*,8*S*,9*R*)-7-((4-(*tert*-butyl)phenyl)amino)-8-(((*tert*-butyldiphenylsilyl)oxy)methyl)-8,9-dihydroxy-4,9-dimethyl-2-oxo-3-oxa-1-azaspiro[4.4]nonan-6-yl)carbamate (S5c): Isolated from **S3c** via general procedure F in 80 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 6.8 Hz, 2H); 7.49 (d, *J* = 6.8 Hz, 2H); 7.42–7.22 (m, 12H); 7.06 (d, *J* = 8.4 Hz, 2H); 6.46 (d, *J* = 8.4 Hz, 2H); 5.93 (s, 1H); 5.39 (d, *J* = 10.0 Hz, 1H); 5.02 (d, *J* = 12.0 Hz, 1H); 4.98 (d, *J* = 12.4 Hz, 1H); 4.80 (dd, *J* = 6.4, 13.2 Hz, 1H); 4.50–4.77 (m, 1H); 4.05 (br s, 1H); 3.74 (d, *J* = 11.2 Hz, 1H); 3.47 (br s, 1H); 3.42 (s, 1H); 2.75

(s, 1H); 1.42 (d, J = 9.2 Hz, 1H); 1.30 (s, 3H); 1.27 (s, 9H); 1.03 (s, 9H); **MS (ESI$^+$)** Calcd. For $C_{44}H_{55}N_3O_7Si$ + H, 766.39; Found, 766.42.



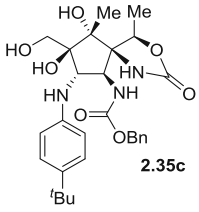
2.35a

Benzyl ((4*R*,5*R*,6*S*,7*S*,8*S*,9*R*)-7-((3-fluorophenyl)amino)-8,9-dihydroxy-8-(hydroxymethyl)-4,9-dimethyl-2-oxo-3-oxa-1-azaspiro[4.4]nonan-6-yl)carbamate (2.35a): Isolated from **S5a** via general procedure C in 78 % yield. Analytical data: **^{1}H NMR** (400 MHz, d_6-Acetone): δ 7.26 (br s, 5H); 7.05 (d, J = 8.0 Hz, 1H); 6.65 (d, J = 10.4 Hz, 1H); 6.57 (d, J = 8.4 Hz, 2H); 6.52 (s, 1H); 6.33–6.29 (m, 1H); 6.08 (s, 1H); 5.15 (d, J = 8.8 Hz, 1H); 5.08 (d, J = 12.4 Hz, 1H); 5.00 (d, J = 12.4 Hz, 1H); 4.78 (q, J = 6.4 Hz, 1H); 4.74 (s, 1H); 4.57–4.52 (m, 1H); 4.45 (s, 1H); 4.05 (d, J = 11.2 Hz, 1H); 3.85 (t, J = 8.8 Hz, 1H); 3.67 (d, J = 11.2 Hz, 1H); 1.44–1.43 (m, 6H); **MS (ESI$^+$)** Calcd. For $C_{24}H_{28}FN_3O_7$ + H, 490.20; Found, 490.26.



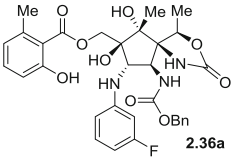
2.35b

Benzyl ((4*R*,5*R*,6*S*,7*S*,8*S*,9*R*)-8,9-dihydroxy-8-(hydroxymethyl)-7-((4-methoxyphenyl)amino)-4,9-dimethyl-2-oxo-3-oxa-1-azaspiro[4.4]nonan-6-yl)carbamate (2.35b): Isolated from **S5b** via general procedure C in 76 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29 (br s, 2H); 7.26 (br s, 3H); 6.77 (d, J = 8.4 Hz, 2H); 6.70 (d, J = 8.4 Hz, 2H); 5.72 (s, 1H); 5.32 (d, J = 9.6 Hz, 1H); 5.09 (d, J = 12.4 Hz, 1H); 5.02 (d, J = 12.4 Hz, 1H); 4.86 (q, J = 6.4 Hz, 1H); 4.60–4.56 (m, 1H); 3.94 (d, J = 12.0 Hz, 1H); 3.88 (br s, 1H); 3.81 (d, J = 12.4 Hz, 1H); 3.75 (s, 3H); 3.44 (d, J = 8.4 Hz, 1H); 2.63 (s, 1H); 1.47 (d, J = 6.8 Hz, 3H); 1.38 (s, 3H); **MS (ESI$^+$)** Calcd. For $C_{25}H_{31}N_3O_8$ + H, 502.22; Found, 502.17.



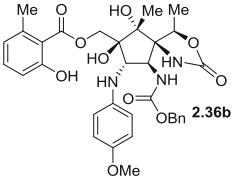
2.35c

Benzyl ((4*R*,5*R*,6*S*,7*S*,8*S*,9*R*)-7-((4-(*tert*-butyl)phenyl)amino)-8,9-dihydroxy-8 -(hydroxymethyl)-4,9-dimethyl-2-oxo-3-oxa-1-azaspiro[4.4]nonan-6-yl)carbamate (2.35c): Isolated from **S5c** via general procedure C in 80 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.28–7.26 (m, 5H); 7.22 (d, *J* = 8.4 Hz, 2H); 6.69 (d, *J* = 8.4 Hz, 2H); 5.77 (br s, 1H); 5.33 (d, *J* = 9.2 Hz, 1H); 5.10 (d, *J* = 12.4 Hz, 1H); 5.04 (d, *J* = 12.4 Hz, 1H); 4.86 (d, *J* = 6.4 Hz, 1H); 4.35 (br s, 1H); 3.98 (d, *J* = 12.0 Hz, 1H); 3.85 (br s, 1H); 3.78 (d, *J* = 12.4 Hz, 1H); 3.50 (d, *J* = 7.2 Hz, 1H); 3.35 (s, 1H); 3.11 (br s, 1H); 1.46 (d, *J* = 6.8 Hz, 3H); 1.38 (s, 3H); 1.28 (s, 9H); **MS (ESI$^+$)** Calcd. For $C_{28}H_{37}N_3O_7$ + H, 528.27; Found, 528.34.



2.36a

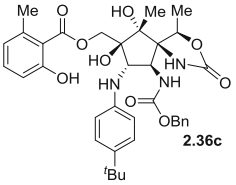
((4*R*,5*R*,6*R*,7*S*,8*S*,9*S*)-9-(((benzyloxy)carbonyl)amino)-8-((3-fluorophenyl)amino)-6,7-dihydroxy-4,6-dimethyl-2-oxo-3-oxa-1-azaspiro[4.4]nonan-7-yl)methyl 2-hydroxy-6-methylbenzoate (2.36a): Isolated from **2.35a** via general procedure D in 89 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.33 (br s, 1H); 7.26–7.17 (m, 5H); 7.05 (br s, 1H); 6.92 (q, *J* = 7.6 Hz, 1H); 6.78 (d, *J* = 8.4 Hz, 1H); 6.66 (d, *J* = 7.2 Hz, 1H); 6.37–6.29 (m, 3H); 5.78 (d, *J* = 10.0 Hz, 1H); 5.05 (d, *J* = 12.0 Hz, 1H); 4.92 (d, *J* = 11.6 Hz,1H); 4.8 (d, *J* = 6.0 Hz, 1H); 4.57 (t, *J* = 8.8 Hz, 1H); 4.53 (d, *J* = 12.0 Hz, 1H); 4.43 (d, *J* = 12.4 Hz, 1H); 4.02 (s, 1H); 3.76 (s, 1H); 3.65 (br s, 1H); 2.37 (s, 3H); 1.43 (d, *J* = 6.0 Hz, 3H); 1.24 (br s, 3H); **MS (ESI$^+$)** Calcd. For $C_{32}H_{34}FN_3O_9$ + H, 624.24; Found, 624.30.



2.36b

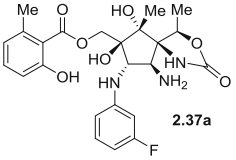
((4*R*,5*R*,6*R*,7*S*,8*S*,9*S*)-9-(((benzyloxy)carbonyl)amino)-6,7-dihydroxy-8-((4-methoxyphenyl)amino)-4,6-dimethyl-2-oxo-3-oxa-1-azaspiro[4.4]nonan-7-yl)methyl 2-hydroxy-6-methylbenzoate (2.36b): Isolated from **2.35b** via general procedure D in 76 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.46 (s, 1H); 7.31–7.23 (m, 6H); 6.83 (d, *J* = 8.0 Hz, 1H); 6.70–6.68 (m, 3H); 6.62 (d, *J* = 8.4 Hz, 2H); 5.96 (s, 1H); 5.48 (d, *J* = 10.8 Hz, 1H); 5.08 (d, *J* = 12.4 Hz, 1H); 5.00 (d, *J* = 12.4 Hz, 1H); 4.80 (br s1H); 4.60–4.56 (m, 1H); 4.45 (d, *J* = 12.4 Hz, 1H); 4.08 (br s, 1H); 3.76 (s, 1H); 3.69 (s, 3H); 3.55 (br s, 1H);

2.45 (s, 3H); 1.45 (d, J = 6.4 Hz, 3H); 1.26 (s, 3H); **MS (ESI$^+$)** Calcd. For $C_{33}H_{37}N_3O_{10}$ + H, 636.26; Found, 636.27.



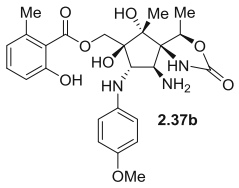
2.36c

((4*R*,5*R*,6*R*,7*S*,8*S*,9*S*)-9-(((benzyloxy)carbonyl)amino)-8-((4-(tert-butyl)phenyl)amino)-6,7-dihydroxy-4,6-dimethyl-2-oxo-3-oxa-1-azaspiro[4.4]nonan-7-yl) methyl 2-hydroxy-6-methylbenzoate (2.36c): Isolated from **2.35c** via general procedure D in 95 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.42 (s, 1H); 7.23 (br s, 6H); 7.09 (d, J = 8.0 Hz, 2H); 6.81 (d, J = 8.0 Hz, 1H); 6.67 (d, J = 7.2 Hz, 1H); 6.60 (d, J = 8.4 Hz, 1H); 6.24 (s, 1H); 5.66 (d, J = 9.6 Hz, 1H); 5.07–4.97 (m, 2H); 4.82 (br s, 1H); 4.61 (m, 1H); 4.46 (d, J = 12.8 Hz, 1H); 4.28 (s, 1H); 4.10 (s, 1H); 3.67 (s, 1H); 3.36 (d, J = 6.8 Hz, 1H); 2.40 (s, 3H); 1.46 (d, J = 6.4 Hz, 3H); 1.28 (br s, 3H); 1.23 (s, 9H); **MS (ESI$^+$)** Calcd. For $C_{36}H_{43}N_3O_9$ + H, 662.31; Found, 662.38.

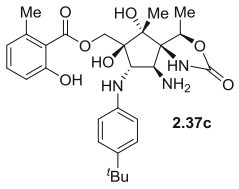


2.37a

((4*R*,5*R*,6*R*,7*S*,8*S*,9*S*)-9-amino-8-((3-fluorophenyl)amino)-6,7-dihydroxy-4,6-dimethyl-2-oxo-3-oxa-1-azaspiro[4.4]nonan-7-yl)methyl 2-hydroxy-6-methyl benzoate (2.37a): Isolated from **2.36a** via general procedure E in 66 % yield. Analytical data: $[\alpha]_D^{19}$ +37.3 (c = 0.8, $CHCl_3$); **^{1}H NMR** (600 MHz, MeOD): δ 7.16 (t, J = 7.8 Hz, 1H), 6.94 (q, J = 7.2 Hz, 1H), 6.69 (m, 2H), 6.51 (m, 2H), 6.17 (m, 1H), 4.81 (q, J = 6.6 Hz, 1H), 4.55 (d, J = 11.4 Hz, 1H), 4.50 (d, J = 11.4 Hz, 1H), 3.54 (s, 2H), 2.29 (s, 3H), 1.55 (d, J = 6.6 Hz, 3H), 1.35 (s, 3H); **^{13}CNMR** (150 MHz, CDCl3): δ 170.6, 164.7, 161.0, 158.4, 152.0, 140.3, 133.0, 131.1, 123.1, 119.3, 114.9, 109.9, 103.9, 103.7, 100.5, 100.4, 83.9, 82.7, 78.5, 72.7, 71.4, 67.1, 21.3, 17.2; **IR** (thin film, cm^{-1}) 3895, 3582, 3388, 3054, 2986, 2520, 2410, 2305, 1736, 1550, 1422, 1333, 1265, 1115; **MS (ESI$^+$)** Calcd. For $C_{24}H_{28}FN_3O_7$ + H, 490.20; Found, 490.26; **TLC** (95:5 CH_2Cl_2:MeOH): R_f = 0.08.

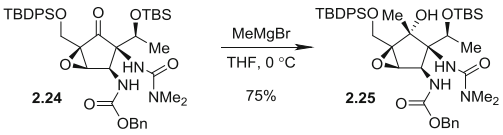


((4*R*,5*R*,6*R*,7*S*,8*S*,9*S*)-9-amino-6,7-dihydroxy-8-((4-methoxyphenyl)amino)-4,6-dimethyl-2-oxo-3-oxa-1-azaspiro[4.4]nonan-7-yl)methyl 2-hydroxy-6-methylbenzoate (2.37b): Isolated from **2.36b** via general procedure E in 85 % yield. Analytical data: $[\alpha]_D^{19}$ +18.8 (*c* = 0.95, $CHCl_3$); **^{1}H NMR** (500 MHz, MeOD): δ 7.17 (t, *J* = 8.0 Hz, 1H); 6.69–6.68 (m, 4H); 6.62 (t, *J* = 3.5 Hz, 1H); 6.60 (t, *J* = 2.0 Hz, 1H); 4.82 (q, *J* = 7.0 Hz, 1H); 4.57 (d, *J* = 12.0 Hz, 1H); 4.51 (d, *J* = 12.0 Hz, 1H); 3.63 (s, 3H); 3.54 (s, 2H); 2.31 (s, 3H); 1.52 (d, *J* = 6.5 Hz, 3H); 1.41 (s, 3H); **^{13}C NMR** (150 MHz, CD_3OD): δ 170.7, 160.9, 158.9, 153.2, 143.8, 140.6, 133.2, 123.1, 118.8, 115.6, 115.5, 115.0, 84.2, 82.8, 78.5, 72.9, 72.3, 66.9, 61.3, 56.1, 21.6, 17.4, 17.0, 15.4; **MS (ESI$^+$)** Calcd. For $C_{25}H_{31}N_3O_8$ + H, 502.22; Found, 502.22; **IR** (thin film, cm^{-1}) 3828, 3740, 3389, 3054, 2986, 2521, 2359, 2305, 1735, 1550, 1441, 1265, 1114; **TLC** (95:5 CH_2Cl_2:MeOH): R_f = 0.07.

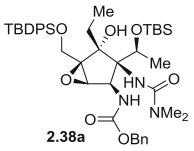


((4*R*,5*R*,6*R*,7*S*,8*S*,9*S*)-9-amino-8-((4-(*tert*-butyl)phenyl)amino)-6,7-dihydroxy-4,6-dimethyl-2-oxo-3-oxa-1-azaspiro[4.4]nonan-7-yl)methyl 2-hydroxy-6-methylbenzoate (2.37c): Isolated from **2.36c** via general procedure E in 48 % yield. Analytical data: $[\alpha]_D^{19}$ +27.0 (*c* = 0.85, $CHCl_3$); **^{1}H NMR** (400 MHz, MeOD): δ 7.17 (t, *J* = 7.6 Hz, 1H); 7.05 (d, *J* = 8.4 Hz, 2H); 6.71–6.67 (m, 4H); 4.82 (q, *J* = 6.8 Hz, 1H); 4.54 (s, 2H); 3.57 (d, *J* = 6.8 Hz, 1H); 3.52 (d, *J* = 6.8 Hz, 1H); 2.29 (s, 3H); 1.53 (d, *J* = 6.8 Hz, 3H); 1.35 (s, 3H); 1.20 (s, 9H); **^{13}C NMR** (100 MHz, MeOD): δ 170.7, 161.0, 158.8, 147.3, 140.7, 140.6, 133.1, 126.7, 123.1, 119.0, 115.0, 114.0, 84.1, 82.8, 78.6, 72.9, 72.00, 67.0, 61.4, 34.5, 32.0, 21.5, 17.4, 17.1; **IR** (thin film, cm^{-1}) 3390, 2960, 2359, 1707, 1649, 1552, 1482, 1385, 1303, 1198, 1071, 737; **MS (ESI$^+$)** Calcd. For $C_{28}H_{37}N_3O_7$ + H, 528.27; Found, 528.34; **TLC** (95:5 CH_2Cl_2:MeOH): R_f = 0.13.

General procedure H for addition of nucleophiles to ketone 2.24.

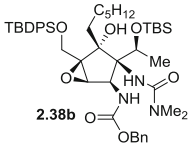


Benzyl ((1*R*,2*R*,3*R*,4*R*,5*R*)-3-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-5-((*tert*-butyldiphenylsilyl)oxy)methyl)-3-(3,3-dimethylureido)-4-hydroxy-4-methyl-6-oxabicyclo [3.1.0]hexan-2-yl)carbamate (2.25): A flame-dried 25-mL round-bottomed flask was charged with ketone **2.24** (1.7 g, 2.3 mmol, 1.0 equiv) and THF (23 mL). The solution was cooled to 0 °C and MeMgBr (3 M in THF, 7.6 mL, 22.9 mmol, 10.0 equiv) was added dropwise. The reaction was stirred at 0 °C until TLC analysis indicated complete ketone consumption, typically 2 h. Saturated $NH_4Cl_{(aq.)}$ (20 mL) was carefully added dropwise and the resulting mixture was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (20 mL), dried with magnesium sulfate, and concentrated in vacuo. The crude product was purified via flash chromatography (90:10 to 70:30 hexanes:EtOAc) to afford carbinol **2.25** as a clear, viscous oil with > 10:1 diastereoselection (1.3 g, 75 %). Analytical data: $[\alpha]_D^{19}$ +7.2 (c = 0.70, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.73 (d, J = 7.8 Hz, 2H), 7.70 (d, J = 7.2 Hz, 2H), 7.45–7.30 (m, 12H), 5.55 (br s, 1H), 5.21 (d, J = 12.6 Hz, 1H), 5.17 (br s, 1H), 5.07 (d, J = 12.0 Hz, 1H), 4.77 (br s, 1H), 4.64 (dd, J = 8.4, 3.6 Hz, 1H), 4.21 (d, J = 12.6 Hz, 1H), 4.12 (d, J = 12.6 Hz, 1H), 3.90 (s, 1H), 2.75 (s, 6H), 1.30 (s, 3H), 1.25 (d J = 6.0 Hz, 3H), 1.07 (s, 9H), 0.97 (s, 9H), 0.11 (s, 3H), −0.01 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 158.8, 156.5, 136.3, 135.6, 135.5, 134.7, 133.3, 132.9, 129.6, 129.4, 128.4, 128.2, 128.1, 127.7, 127.6, 127.6, 67.1, 66.8, 62.1, 58.3, 36.1, 26.7, 26.5, 25.7, 23.8, 19.6, 19.2, 17.8, −4.2, −5.5; **MS (ESI$^+$)** Calcd. for $C_{42}H_{61}N_3O_7Si_2$ + H, 776.4128; Found, 776.4179; **IR** (thin film, cm^{-1}) 3430, 2429, 2359, 1716, 1635, 1506, 1456, 1112, 831, 700; **TLC** (90:10 hexanes/EtOAc): R_f = 0.35.



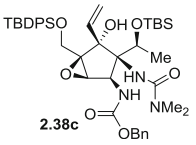
2.38a

Benzyl ((1*R*,2*R*,3*R*,4*R*,5*R*)-3-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-(3,3-dimethylureido)-4-ethyl-4-hydroxy-6-oxabicyclo[3.1.0]hexan-2-yl)carbamate (2.38a): Isolated from **2.24** via general procedure H using EtMgBr as the nucleophile in 75 % yield. Analytical data: **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.66–7.63 (m, 4H); 7.42–7.33 (m, 11H); 5.31 (br s, 1H); 5.24 (br s, 1H); 5.16 (d, J = 12.0 Hz, 1H); 5.04 (d, J = 12.5 Hz, H); 4.66 (s, 1H); 4.61–4.57 (m, 2H); 4.33 (d, J = 12.5 Hz, 1H); 3.98 (s, 1H); 3.95–3.94 (m, 1H); 2.68 (s, 6H); 1.44–1.41 (m, 1H); 1.36–1.32(m, 1H); 1.27–1.25 (m, 3H); 1.01 (s, 9H); 0.95 (s, 9H); 0.81 (t, J = 7.5 Hz, 3H); 0.08 (s, 3H); 0.07 (s, 3H); **MS (ESI$^+$)** Calcd. For $C_{43}H_{63}N_3O_7Si_2$ + H, 790.43; Found, 790.43.

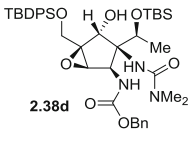


2.38b

Benzyl ((1*R*,2*R*,3*R*,4*R*,5*R*)-3-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-(3,3-dimethylureido)-4-hexyl-4-hydroxy-6-oxabicyclo[3.1.0]hexan-2-yl)carbamate (2.38b): Isolated from **2.24** via general procedure H using (^{n}Hexyl)MgBr as the nucleophile in 73 % yield. Analytical data: **^{1}HNMR** (400 MHz, $CDCl_3$): δ 7.67–7.63 (m, 4H), 7.40–7.31 (m, 12H), 5.32 (d, *J* = 6.8 Hz, 1H), 5.23 (br s, 1H), 5.18 (d, *J* = 12.4 Hz, 1H), 5.07 (d, *J* = 12.4 Hz, 1H), 4.72 (s, 1H), 4.59 (m, 2H), 4.34 (d, *J* = 13.2 Hz, 1H), 3.97 (m, 2H), 2.70 (s, 6H), 1.26 (m, 4H), 1.30–1.26 (m, 8H), 1.18 (m, 4H), 1.02 (s, 9H), 0.96 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); **MS (ESI$^+$)** Calcd. For $C_{47}H_{71}N_3O_7Si_2$ + H, 846.49; Found, 846.59.

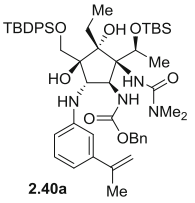


Benzyl ((1*R*,2*R*,3*R*,4*R*,5*R*)-3-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-(3,3-dimethylureido)-4-hydroxy-4-vinyl-6-oxabicyclo[3.1.0]hexan-2-yl)carbamate (2.38c): Isolated from **2.24** via general procedure H using (vinyl)MgBr as the nucleophile in 43 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.65–7.64 (m, 4H); 7.40–7.35 (m, 11H); 5.93 (dd, *J* = 10.8, 17.20 Hz, 1H); 5.70 (br s, 1H); 5.35 (d, *J* = 17.2 Hz, 1H); 5.19 (d, *J* = 12.0 Hz, 1H); 5.11–5.06 (m, 3H); 4.93 (br s, 1H); 4.19 (d, *J* = 12.8 Hz, 1H); 4.02 (s, 1H); 3.97 (d, *J* = 12.4 Hz, 1H); 2.72 (s, 6H); 1.23 (d, *J* = 6.4 Hz, 3H); 1.01 (s, 9H); 0.93 (s, 9H); 0.09 (s, 3H); 0.01 (s, 3H); **MS (ESI$^+$)** Calcd. For $C_{43}H_{61}N_3O_7Si_2$ + Na, 810.39; Found, 810.24.



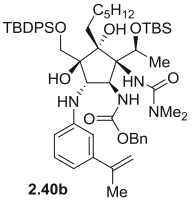
Benzyl ((1*R*,2*R*,3*S*,4*R*,5*S*)-3-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-(3,3-dimethylureido)-4-hydroxy-6-oxabicyclo[3.1.0]hexan-2-yl)carbamate (2.38d): A flame-dried 100 mL round bottomed flask was charged with ketone **2.24** (0.280 g, 0.369 mmol, 1.0 equiv) and MeOH (20 mL) under an atmosphere of nitrogen. The solution was cooled to −45 °C and $NaBH_4$ (0.056 g, 1.47 mmol, 4.0 equiv) was added in one portion. The reaction was allowed to stir at this temperature until TLC analysis indicated full conversion of the starting material, generally 1 h. Saturated $NH_4Cl_{(aq.)}$ (10 mL) was added slowly followed by EtOAc (20 mL) and the mixture was allowed to warm to r.t. The mixture was partitioned and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with H_2O (2 × 20 mL), brine (15 mL), dried with magnesium sulfate and concentrated in vacuo. The crude product was purified via flash chromatography (90:10

hexanes:EtOAc) to obtain the title compound as a white foam (249 mg, 88 %). Analytical Data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.67–7.64 (m, 4H); 7.39–7.34 (m, 11H); 5.49 (br s, 1H); 5.28 (br s, 1H); 5.20 (d, *J* = 12.0 Hz, 1H); 5.02 (d, *J* = 12.0 Hz, 1H); 4.97 (s, 1H); 4.61(dd, *J* = 2.8, 8.8 Hz, 1H); 4.48 (bs, 1H); 4.16 (s, 1H); 4.15 (d, *J* = 12.4 Hz, 1H); 4.09 (d, *J* = 12.4 Hz, 1H); 3.92 (br s, 1H); 2.70 (s, 6H); 1.18 (d, *J* = 6.4 Hz, 3H); 1.02 (s, 9H); 0.92 (s, 9H); 0.06 (s, 3H); −0.07 (s, 3H); **MS (ESI$^+$)** Calcd. For $C_{41}H_{59}N_3O_7Si_2$ + Na, 784.38; Found, 784.44.



2.40a

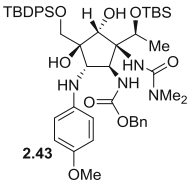
Benzyl ((1*S*,2*R*,3*R*,4*S*,5*S*)-2-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-(3,3-dimethylureido)-3-ethyl-3,4-dihydroxy-5-((3-(prop-1-en-2-yl)phenyl)amino)cyclopentyl)carbamate (2.40a): Isolated from **2.38a** via general procedure B using 3-isopropenylaniline as the nucleophile in 71 % yield. Analytical data: **^{1}HNMR** (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 6.8 Hz, 1H), 7.66 (d, *J* = 6.8 Hz, 2H), 7.47 (d, *J* = 6.8 Hz, 2H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.34–7.19 (m, 10H), 7.05 (t, *J* = 8.0 Hz, 1H), 6.80 (m, 2H), 6.57 (d, *J* = 7.6 Hz, 1H), 6.15 (s, 1H), 5.47 (s, 1H), 5.36 (s, 1H), 5.27 (q, *J* = 6.4 Hz, 1H), 5.17 (d, *J* = 3.6 Hz, 1H), 5.02 (br s, 3H), 4.72 (dd, *J* = 7.2, 2.8 Hz, 1H), 4.36 (s, 1H), 4.13 (d, *J* = 10.8 Hz, 1H), 3.75 (d, *J* = 10.8 Hz, 1H), 3.66 (dd, *J* = 4.0, 6.0 Hz, 1H), 2.95 (s, 6H), 2.12 (s, 3H), 1.88 (m, 1H), 1.35 (d, *J* = 6.8 Hz, 3H), 0.96 (s, 9H), 0.898 (br s, 12H), 0.09 (s, 3H), 0.01 (s, 3H); **MS (ESI$^+$)** Calcd. For $C_{52}H_{74}N_4O_7Si_2$ + H, 923.52; Found, 923.54.



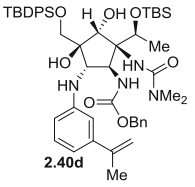
2.40b

Benzyl ((4*S*,5*S*)-2-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-(((*tert*-butyldiphenyl silyl)oxy)methyl)-2-(3,3-dimethylureido)-3-hexyl-3,4-dihydroxy-5-((3-(prop-1-en-2-yl)phenyl)amino)cyclopentyl)carbamate (2.40b): Isolated from **2.38b** via general procedure B using 3-isopropenylaniline as the nucleophile in 63 % yield. Analytical data: **^{1}HNMR** (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 6.8 Hz, 1H), 7.66 (d, *J* = 6.4 Hz, 2H), 7.48 (d, *J* = 6.8 Hz, 2H), 7.40(m, 1H), 7.35–7.19 (m, 10H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.79 (m, 2H), 6.57 (d, *J* = 7.6 Hz, 1H), 6.18 (s, 1H), 5.49 (s, 1H), 5.37 (s, 1H), 5.28 (q, *J* = 6.4 Hz, 1H), 5.16 (s, 1H), 5.01 (s, 3H), 4.73 (dd, *J* = 7.2, 2.4 Hz, 1H), 4.38 (s, 1H), 4.13 (d, *J* = 10.8 Hz, 1H), 3.76 (d,

J = 10.8 Hz, 1H), 3.67 (dd, *J* = 3.6, 2 Hz, 1H), 2.96 (s, 6H), 2.12 (s, 3H), 1.75 (m, 1H), 1.45 (m, 1H), 1.34 (d, *J* = 6.4 Hz 3H), 1.22 (br s, 4H), 0.97 (s, 9H), 0.91 (s, 11H), 0.10 (s, 3H), 0.01 (s, 3H); **MS (ESI$^+$)** Calcd. for $C_{56}H_{82}N_4O_7Si_2$ + H, 979.58; Found, 979.58.

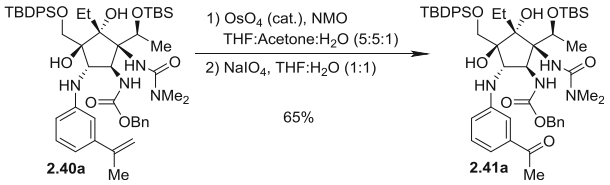


Benzyl ((1*S*,2*S*,3*R*,4*S*,5*S*)-2-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-(3,3-dimethylureido)-3,4-dihydroxy-5-((4-methoxyphenyl)amino)cyclopentyl)carbamate (2.43): Isolated from **2.38d** via general procedure B using *p*-anisidine as the nucleophile in 83 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.27 (d, *J* = 6.0 Hz, 1H); 7.74 (d, *J* = 6.8 Hz, 2H); 7.68(d, *J* = 6.8 Hz, 2H); 7.40–7.26 (m, 12H); 6.69 (d, *J* = 8.8 Hz, 2H); 6.60 (d, *J* = 8.40 Hz, 2H); 6.02 (s, 1H); 5.33 (s, 1H); 5.31 (d, *J* = 6.8 Hz, 1H); 5.02 (s, 2H); 4.67 (dd, *J* = 6.4, 9.6 Hz, 1H); 4.38 (d, *J* = 10.8 Hz, 1H); 3.92 (s, 1H); 3.83 (s, 1H); 3.74 (s, 3H); 3.64 (d, *J* = 10.0 Hz, 1H); 3.59 (d, *J* = 10.8 Hz, 1H); 2.93 (s, 6H); 1.39 (d, *J* = 6.0 Hz, 3H); 1.04 (s, 9H); 0.91 (s, 9H); 0.12 (s, 3H); 0.01 (s, 3H); **MS (ESI$^+$)** Calcd. For $C_{48}H_{68}N_4O_8Si_2$ + H, 885.47; Found, 885.53.



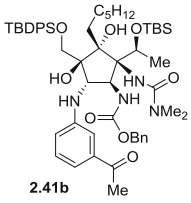
Benzyl ((1*S*,2*S*,3*R*,4*S*,5*S*)-2-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-(3,3-dimethylureido)-3,4-dihydroxy-5-((3-(prop-1-en-2-yl)phenyl)amino)cyclopentyl)carbamate (2.40d): Isolated from **2.38d** via general procedure B using *m*-isopropenylaniline as the nucleophile in 63 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.28 (d, J = 6.4 Hz, 1H); 7.75 (d, J = 6.8 Hz, 2H); 7.60 (d, J = 6.8 Hz, 2H); 7.38 (d, *J* = 7.2 Hz, 2H); 7.33–7.25 (m, 8H); 7.12 (t, *J* = 7.6 Hz, 1H); 7.05 (t, *J* = 7.6 Hz, 1H); 6.88 (d, *J* = 7.6 Hz, 1H); 6,84 (s, 1H); 6.80 (br s, 1H); 6.61 (d, *J* = 8.0 Hz, 1H); 6.58 (d, *J* = 8.0 Hz, 1H); 6.03 (s, 1H); 5.37–5.29 (m, 3H); 5.04–5.01 (m, 2H); 4.69 (dd, *J* = 6.4,10.0 Hz, 1H); 4.40 (d, *J* = 10.8 Hz, 1H); 3.93 (s, 1H); 3.84 (s, 1H); 3.74(d, *J* = 8.0 Hz, 1H); 3.58 (d, *J* = 10.8 Hz, 1H); 2.94 (s, 6H); 2.12 (s, 3H); 1.40 (d, *J* = 6.4 Hz, 3H); 1.02 (s, 9H); 0.91 (s, 9H); 0.13 (s, 3H); 0.00 (S, 3H); **MS (ESI$^+$)** Calcd. For $C_{50}H_{70}N_4O_7Si_2$ + H, 895.49; Found, 895.59.

General procedure I for isopropenyl group oxidative cleavage:

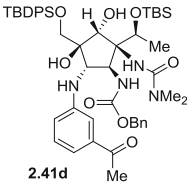


Benzyl ((4*S*)-5-((3-acetylphenyl)amino)-2-((*S*)-1-((*tert*-butyldimethylsilyl) oxy)ethyl)-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-(3,3-dimethylureido)-3-ethyl-3,4-dihydroxycyclopentyl)carbamate (2.41a). A 20 mL scintillation vial was charged with olefin **2.40a** (0.154 g, 0.17 mmol, 1.00 equiv) and THF (2 mL), Acetone (2 mL), and H_2O (0.4 mL) were added. The solution was cooled to 0 °C and NMO (0.101 g, 0.860 mmol, 5.00 equiv) was added followed by two flakes of OsO_4. The resulting mixture and stirred for 1 h at r.t. Saturated $NaHSO_3$ $_{(aq)}$ (3 mL) was added, and the mixture was stirred 30 min. The mixture was then extracted with EtOAc (3 × 30 mL) and the combined organic layers were washed with water (10 mL), brine (10 mL), dried with magnesium sulfate and concentrated in vacuo. The crude diol was judged clean by ^{1}H NMR spectroscopy and was submitted to the next step without further purification.

The crude diol was added to a 20 mL scintillation vial and dissolved in THF (3 mL) and water (3 mL). $NaIO_4$ (0.065 g, 0.30 mmol, 2.40 equiv) was added at rt and the reaction was allowed to stir for 3 h. The reaction mixture was partitioned between EtOAc (5 mL) and H_2O (5 mL), and the mixture was extracted with EtOAc (3 × 30 mL) and the combined organic layers were washed with water (10 mL), brine (10 mL), dried with magnesium sulfate and concentrated in vacuo. The crude product was purified via flash chromatography (90:10 to 80:20 hexanes:EtOAc) to give acetophenone **2.41a** as a pale yellow foam (98 mg, 65 % over two steps) Analytical data: **^{1}HNMR** (400 MHz, $CDCl_3$): δ 8.18 (d, *J* = 6.8 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 6.8 Hz, 2H), 7.38 (d, *J* = 7.2 Hz, 1H), 7.33–7.12 (m, 13H), 6.81 (d, *J* = 8.8 Hz, 1H), 6.11 (s, 1H), 5.45 (s, 1H), 5.33 (d, *J* = 4.0 Hz, 1H), 5.26 (q, *J* = 6.8 Hz, 1H), 5.02 (d, *J* = 1.2 Hz, 2H), 4.72 (dd, *J* = 6.8, 2.8 Hz, 1H), 4.32 (s, 1H), 4.06 (d, *J* = 10.8 Hz, 1H), 6.68 (d, *J* = 10.8 Hz, 1H), 3.64 (d, *J* = 4.0 Hz, 1H), 2.96 (s, 6H), 2.50 (s, 3H), 2.09 (m, 1H), 2.05 (s, 3H), 1.85 (m, 1H), 1.34 (d, *J* = 6.8 Hz, 3H), 0.92 (br s, 11H), 0.89 (br s, 10H), 0.09 (s, 3H), 0.00 (s, 3H); **MS (ESI$^+$)** Calcd. for $C_{51}H_{72}N_4O_8Si_2$ + H, 925.50; Found, 925.52.

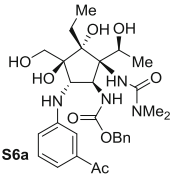


Benzyl ((4*S*,5*S*)-5-((3-acetylphenyl)amino)-2-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-(3,3-dimethylureido)-3-hexyl-3,4-dihydroxycyclopentyl)carbamate (2.41b): Isolated from **2.40b** via general procedure I in 63 % yield. Analytical data: **^{1}HNMR** (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 6.4 Hz, 1H), 7.62 (d, *J* = 6.8 Hz, 2H), 7.43 (d, *J* = 6.8 Hz, 2H), 7.38 (d, *J* = 7.2 Hz, 1H), 7.33–7.12 (m, 13H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.13 (s, 1H), 5.47 (s, 1H), 5.31 (d, *J* = 3.6 Hz, 1H), 5.26 (q, *J* = 6.4 Hz, 1H), 5.02 (s, 1H), 4.34 (s, 1H), 4.07 (*J* = 10.8 Hz, 1H), 3.69 (d, *J* = 10.8 Hz, 1H), 3.65 (dd, *J* = 4.0, 6.0 Hz, 1H), 2.96 (s, 6H), 2.50 (s, 3H), 1.74 (m, 1H), 1.42 (br s, 2H), 1.33 (d, *J* = 6.4 Hz, 3H), 1.20 (br s, 4H), 0.95–0.86 (m, 24H), 0.09 (s, 3H), 0.00 (s, 3H); **MS (ESI$^+$)** Calcd. for $C_{55}H_{80}N_4O_8Si_2$ + H, 981.56; Found, 981. 55.



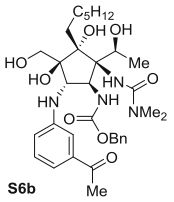
2.41d

Benzyl ((1*S*,2*S*,3*R*,4*S*,5*S*)-5-((3-acetylphenyl)amino)-2-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-(3,3-dimethylureido)-3,4-dihydroxycyclopentyl)carbamate (2.41d): Isolated from **2.40d** via general procedure I in 65 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.36 (br s, 1H); 7.72 (d, *J* = 7.2 Hz, 2H); 7.56 (d, *J* = 6.8 Hz, 2H); 7.38 (d, *J* = 7.6 Hz, 1H); 7.33–7.20 (m 12H); 5.99 (s, 1H); 5.46 (s, 1H); 5.39 (s, 1H); 5.05 (d, *J* = 12.0 Hz, 1H); 4.99 (d, *J* = 12.0 Hz, 1H); 4.69 (dd, *J* = 6.4, 10.0 Hz, 1H); 4.34 (d, *J* = 10.4 Hz, 1H), 3.94 (s, 1H); 3.86 (s, 1H); 3.74 (d, *J* = 10.4 Hz, 1H); 3.47 (d, *J* = 10.8 Hz, 1H); 2.94 (s, 6H); 2.50 (S, 3 h); 1.4 (d, *J* = 6.4 Hz, 3H); 1.00 (s, 9H); 0.93 (s, 9H); 0.13 (s, 3H); 0.00 (s, 3H); **MS (ESI$^+$)** Calcd. For $C_{49}H_{68}N_4O_8Si_2$ + H, 897.47; Found, 897.56.



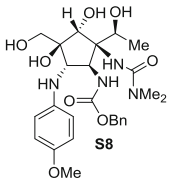
S6a

Benzyl ((4*S*)-5-((3-acetylphenyl)amino)-2-(3,3-dimethylureido)-3-ethyl-3,4-dihydroxy-2-((*S*)-1-hydroxyethyl)-4-(hydroxymethyl)cyclopentyl)carbamate (S6a): Isolated from **2.41a** via general procedure C in 88 % yield. Analytical data: **^{1}HNMR** (400 MHz, $CDCl_3$): δ 7.33–7.15 (m, 5H), 6.96 (br s, 1H), 6.78 (d, *J* = 7.2 Hz, 2H), 6.56 (br s, 2H), 6.06 (br s, 1H), 5.58 (s, 1H), 5.47 (br s, 1H), 5.37–5.25 (m, 3H), 5.11 (br s, 2H), 4.33 (br s, 1H), 4.07 (br s, 1H), 3.85 (s, 2H), 3.71 (s, 1H), 2.87 (s, 6H), 2.50 (s, 3H), 1.86 (m, 2H), 1.25 (br s, 5H); **MS (ESI$^+$)** Calcd. for $C_{29}H_{40}N_4O_8$ + H, 573.29; Found, 573.27.



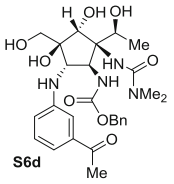
S6b

Benzyl ((4*S*,5*S*)-5-((3-acetylphenyl)amino)-2-(3,3-dimethylureido)-3-hexyl-3,4-dihydroxy-2-((*S*)-1-hydroxyethyl)-4-(hydroxymethyl)cyclopentyl)carbamate (S6b): Isolated from **2.41b** via general procedure C in 78 % yield. Analytical data: **^{1}HNMR** (400 MHz, $CDCl_3$): δ 7.32–7.05 (m, 10H), 6.94 (br s, 1H), 6.77 (br s, 2H), 6.14 (d, *J* = 7.6 Hz, 1H), 5.43 (br s, 1H), 5.25 (s, 1H), 5.10 (br s, 2H), 4.23 (br s, 1H), 4.10 (br s, 1H), 3.86–3.73 (m, 3H), 2.87 (s, 6H), 2.49 (s, 3H), 1.93 (br s, 2H), 1.56 (t, *J* = 12.0 Hz, 1H), 1.50 (br s, 1H), 1.26 (br s, 9H), 1.00 (br s, 1H); **MS (ESI$^+$)** Calcd. for $C_{33}H_{48}N_4O_8$ + H, 629.36; Found, 629.36.



S8

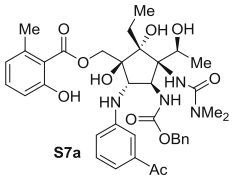
Benzyl ((1*S*,2*R*,3*R*,4*S*,5*S*)-2-(3,3-dimethylureido)-3,4-dihydroxy-2-((*S*)-1-hydroxyethyl)-4-(hydroxymethyl)-5-((4-methoxyphenyl)amino)cyclopentyl)carbamate (S8): Isolated from **2.43** via general procedure C in 73 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.33–7.26 (m, 8H); 6.72 (d, *J* = 8.4 Hz, 2H); 6.64 (br s, 2H); 6.00 (br s, 1H); 5.72 (br s, 1H); 5.61 (br s, 1H); 5.10 (d, *J* = 11.2 Hz, 1H); 5.04 (d, *J* = 12.0 Hz, 1H); 4.40 (s, 1H); 4.10 (br s, 1H); 4.04–3.97 (m, 3H); 3.80 (d, *J* = 11.8 Hz, 1H); 3.73 (s, 3H); 3.59 (br s, 1H); 2.90 (s, 6H); 1.19 (d, *J* = 4.4 Hz, 3H); **MS (ESI$^+$)** Calcd. For $C_{26}H_{36}N_4O_8$ + H, 533.26; Found, 533.26.



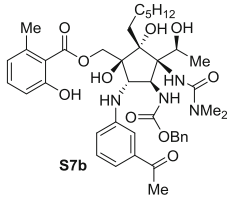
S6d

Benzyl ((1*S*,2*R*,3*R*,4*S*,5*S*)-5-((3-acetylphenyl)amino)-2-(3,3-dimethylureido)-3,4-dihydroxy-2-((*S*)-1-hydroxyethyl)-4-(hydroxymethyl)cyclopentyl)carbamate (S6d): Isolated from **2.41d** via general procedure C in 91 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29–7.22 (m, 7H); 7.15 (t, *J* = 8.0 Hz, 1H); 6.84 (d, *J* = 6.4 Hz, 1H); 6.32 (d, *J* = 8.4 Hz, 1H); 5.85 (s, 1H); 5.60 (br s, 1H); 5.04 (d, *J* = 12.0 Hz, 1H); 4.97 (d, *J* = 12.4 Hz, 1H); 4.78 (br s, 1H); 4.43 (s, 1H); 4.22–4.15 (m, 2H); 4.03–3.97 (m, 2H); 3.73 (d, *J* = 11.6 Hz, 1H); 2.87 (s, 6H);

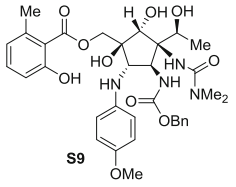
2.47 (s, 3H); 1.16 (d, J = 5.2 Hz, 3H); **MS (ESI$^+$)** Calcd. For $C_{27}H_{36}N_4O_8$ + H, 545.26; Found, 545.31.



((1*S*,5*S*)-5-((3-acetylphenyl)amino)-4-(((benzyloxy)carbonyl)amino)-3-(3,3-dimethylureido)-2-ethyl-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)cyclopentyl) methyl 2-hydroxy-6-methylbenzoate (S7a): Isolated from **S6a** via general procedure D in 80 % yield. Analytical data: **^{1}HNMR** (400 MHz, $CDCl_3$): δ 10.89 (s, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.35 (br s, 4H), 7.27–7.20 (m, 4H), 7.05 (s, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.68 (d, J = 6.8 Hz, 1H), 6.58 (d, J = 7.2 Hz, 1H), 5.88 (s, 1H), 5.83 (m, 1H), 5.16 (s, 2H), 5.107–5.063 (m, 2H), 4.88 (d, J = 12.8 Hz, 1H), 4.04 (br s, 2H), 3.71 (d, J = 9.2 Hz, 1H), 2.84 (s, 6H), 2.49 (s, 3H), 2.19 (s, 3H), 2.12 (m, 1H), 1.97 (m, 1H), 1.24 (d, J = 7.2 Hz, 3H), 1.04 (t, J = 7.6 Hz, 3H); **MS (ESI$^+$)** Calcd. for $C_{37}H_{46}N_4O_{10}$ + H, 707.33; Found, 707.36.

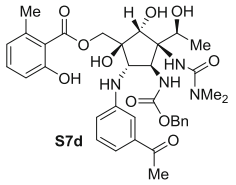


((1*S*,5*S*)-5-((3-acetylphenyl)amino)-4-(((benzyloxy)carbonyl)amino)-3-(3,3-dimethylureido)-2-hexyl-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)cyclopentyl) methyl 2-hydroxy-6-methylbenzoate (S7b): Isolated from **S6b** via general procedure D in 84 % yield. Analytical data: **^{1}HNMR** (400 MHz, $CDCl_3$): δ 10.90 (s, 1H), 7.44–7.18 (m, 9H), 7.06 (s, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.69, (d, J = 7.6 Hz, 1H), 6.59 (d, J = 7.2 Hz, 1H), 5.90 (s, 2H), 5.78 (d, J = 9.6 Hz, 1H), 5.16–5.04 (m, 4H), 4.87 (d, J = 12.8 Hz, 1H), 4.03 (s, 2H), 2.85 (s, 6H), 2.49 (s, 3H), 2.20 (s, 3H), 1.83 (m, 1H), 1.61 (m, 2H), 1.28 (br s, 12H); **MS (ESI$^+$)** Calcd. for $C_{41}H_{54}N_4O_{10}$ + H, 763.39; Found, 763.46.

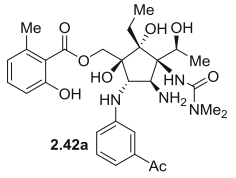


((1*S*,2*R*,3*R*,4*S*,5*S*)-4-(((benzyloxy)carbonyl)amino)-3-(3,3-dimethylureido)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)-5-((4-methoxyphenyl)amino)cyclopentyl) methyl 2-hydroxy-6-methylbenzoate (S9): Isolated from **S8** via general

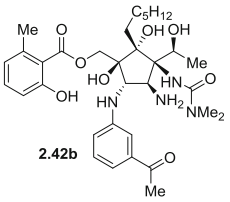
procedure D in 56 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.78 (br s, 1H); 7.34–7.24 (m, 5H); 7.17 (d, *J* = 7.6 Hz, 1H); 6.83 (d, *J* = 8.4 Hz, 2H); 6.75–6.69 (m, 4H); 6.53 (br s, 2H); 5.88 (br s, 2H); 5.50 (s, 1H); 5.15–5.09 (m, 3H); 4.93 (d, *J* = 12.0 Hz, 1H); 4.75 (d, *J* = 12.4 Hz, 1H); 4.31 (s, 1H); 4.09 (br s, 1H); 3.88 (br s, 1H); 3.74 (s, 3H); 2.96 (s, 1H); 2.86 (s, 6H); 2.47 (s,3H); 1.21 (br s, 1H); **MS (ESI$^+$)** Calcd. For $C_{34}H_{42}N_4O_{10}$ + H, 667.30; Found, 667.31.



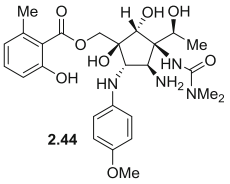
((1*S*,2*R*,3*R*,4*S*,5*S*)-5-((3-acetylphenyl)amino)-4-(((benzyloxy)carbonyl)amino)-3-(3,3-dimethylureido)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)cyclopentyl) methyl 2-hydroxy-6-methylbenzoate (S7d): Isolated from **S6d** via general procedure D in 66 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.61 (br s, 1H); 7.29 (m, 10H); 6.77 (d, *J* = 8.4 Hz, 2H); 6.64 (d, *J* = 7.2 Hz, 1H); 6.37 (br s, 1H); 6,21 (br s, 1H); 5.64 (br s, 2H); 5.19–4.09 (m, 3H); 4.86 (d, *J* = 12.0 Hz, 1H); 4.67 (d, *J* = 12.0 Hz, 1H); 4.41 (s, 1H); 4.13–4.08 (m, 1H); 3.86 (br s, 1H); 2.85 (s, 6H); 2.46 (s, 3H); 1.18 (br s, 3H); **MS (ESI$^+$)** Calcd. For $C_{35}H_{42}N_4O_{10}$ + H, 679.30; Found, 679.35.



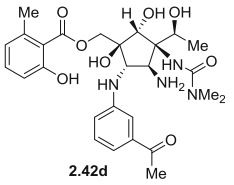
((1*S*,5*S*)-5-((3-acetylphenyl)amino)-4-amino-3-(3,3-dimethylureido)-2-ethyl-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)cyclopentyl)methyl 2-hydroxy-6-methyl benzoate (2.42a): Isolated from **S7a** via general procedure E in 48 % yield. Analytical data: $[\alpha]_D^{19}$ +39.3 (*c* = 0.25, $CHCl_3$); **^{1}HNMR** (400 MHz, $CDCl_3$): δ 10.99 (s, 1H), 7.84 (d, *J* = 10.8 Hz, 1H), 7.25–7.21 (m, 5H), 7.11 (s, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.75 (m, 1H), 6.60 (d, *J* = 7.6 Hz, 1H), 5.75 (d, *J* = 10.0 Hz, 1H), 5.63 (s, 1H), 4.99 (d, *J* = 12.8 Hz, 1H), 4.88 (d, *J* = 12.4 Hz, 1H), 3.98 (m, 1H), 3.76 (d, *J* = 10.4 Hz, 1H), 2.99 (s, 6H), 2.91 (s, 1H), 2.53(s, 3H), 2.29 (s, 3H), 2.16 (m, 1H), 2.05 (m, 1H), 1.05 (m, 6H). **^{13}C NMR** (150 MHz, CDCl3): δ 198.5, 173.0, 162.8, 159.2, 146.5, 141.5, 138.2, 134.6, 129.6, 129.0, 128.2, 125.3, 123.0, 118.2, 115.6, 111.9, 90.4, 86.0, 73.8, 72.8, 68.4, 66.8, 62.2, 36.90, 26.7, 25.8, 23.8, 18.1, 8.6; **IR** (thin film, cm^{-1}) 3381, 2926, 1724, 1667, 1604, 1522, 1485, 1464, 1389, 1253, 1115, 1074, 735; **MS (ESI$^+$)** Calcd. for $C_{29}H_{40}N_4O_8$ + H, 573.29; Found, 573.33; **TLC** (95:5 CH_2Cl_2:MeOH): R_f = 0.18.



((1*S*,5*S*)-5-((3-acetylphenyl)amino)-4-amino-3-(3,3-dimethylureido)-2-hexyl-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)cyclopentyl)methyl 2-hydroxy-6-methylbenzoate (2.42b): Isolated from **S7b** via general procedure E in 61 % yield. Analytical data: $[\alpha]_D^{19}$ +28.8 (*c* = 0.15, $CHCl_3$); **^{1}HNMR** (400 MHz, $CDCl_3$): δ 10.98 (br s, 1H), 7.85 (br s, 1H), 7.25–7.11 (m, 5H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.75 (m, 1H), 6.60 (d, *J* = 7.2 Hz, 1H), 5.73 (d, *J* = 10.0 Hz, 1H), 5.67 (s, 1H), 4.94 (d, *J* = 12.4 Hz, 1H), 4.86 (d, *J* = 12.4 Hz, 1H), 3.98 (br s, 1H), 3.76 (d, *J* = 10.0 Hz, 1H), 3.64 (s, 1H), 2.99 (s, 6H), 2.95 (s, 1H), 2.53 (s, 3H), 2.29 (s, 3H), 2.07 (m, 1H), 1.93 (m 2H), 1.62 (m, 2H), 1.31 (br s, 7H), 1.04 (d, *J* = 6.0 Hz, 3H). **^{13}C NMR** (150 MHz, CDCl3): δ 198.59, 172.88, 162.73, 159.17, 146.49, 141.47, 138.15, 134.52, 129.58, 122.98, 118.46, 118.20, 115.61, 111.96, 110.52, 90.22, 86.00, 73.67, 72.82, 68.23, 66.68, 62.31, 36.93, 33.40, 31.84, 30.51, 29.68, 26.68, 24.05, 23.84, 22.66, 18.13, 14.15; **IR** (thin film, cm^{-1}) 3413, 2928, 2359, 1653, 1604, 1509, 1438, 1378, 1252, 1213, 1095, 736; **MS (ESI$^+$)** Calcd. for $C_{33}H_{48}N_4O_8$ + H,629.36; Found, 629.42; **TLC** (95:5 CH_2Cl_2:MeOH): R_f = 0.21.



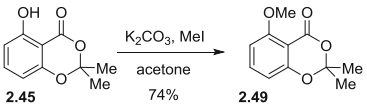
((1*S*,2*R*,3*R*,4*S*,5*S*)-4-amino-3-(3,3-dimethylureido)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)-5-((4-methoxyphenyl)amino)cyclopentyl)methyl 2-hydroxy-6-methylbenzoate (2.44): Isolated from **S9** via general procedure E in 67 % yield. Analytical data: $[\alpha]_D^{19}$ +4.4 (*c* = 0.25, $CHCl_3$); **^{1}HNMR** (400 MHz, $CDCl_3$): δ 10.92 (br s, 1H); 7.46 (br s, 1H); 7.29–7.25 (m, 2H); 6.99 (br s, 1H); 6.82 (d, *J* = 8.0 Hz, 1H); 6.79 (d, *J* = 8.8 Hz, 2H);6.70 (d, *J* = 7.2 Hz, 1H); 6.60 (d, *J* = 8.8 Hz, 2H); 5.52 (br s, 1H); 4.87 (d, *J* = 12.4 Hz, 1H); 4.75 (d, *J* = 12.0 Hz, 1H); 4.70 br s, 1H); 4.32 (s, 1H); 3.84 (br s, 1H); 3.74 (s, 3H); 3.13 (br s, 1H); 2.96 (s, 6H); 2.51 (s, 3H); 1.06 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (150 MHz, CDCl3): δ 171.5, 158.6, 152.4, 141.1, 140.7, 134.2, 122.9, 115.6, 115.0, 114.5, 64.4, 55.7, 50.9, 36.7, 31.9, 29.7, 29.6, 24.8, 23.6, 22.7, 17.7, 14.1; **IR** (thin film, cm^{-1}) 3939, 3389, 3054, 2931, 2359, 2054, 1640, 1512, 1442, 1382, 1265, 1119, 736; **MS (ESI$^+$)** Calcd. for $C_{26}H_{36}N_4O_8$ + H, 533.26; Found, 533.26; **TLC** (95:5 CH_2Cl_2:MeOH): R_f = 0.05.



2.42d

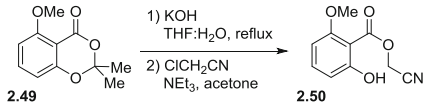
((1*S*,2*R*,3*R*,4*S*,5*S*)-5-((3-acetylphenyl)amino)-4-amino-3-(3,3-dimethylureido)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)cyclopentyl)methyl 2-hydroxy-6-methylbenzoate (2.42d): Isolated from **S7d** via general procedure E in 72 % yield. Analytical data: $[\alpha]_D^{19}$ +39.3 (*c* = 0.25, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.86 (br s, 1H); 7.55 (br s, 1H); 7.52–7.54 (m, 4H); 7.20 (s, 1H); 7.10 (s, 1H); 6.83–6.79 (m, 2H); 6.67 (d, *J* = 7.6 Hz, 1H); 5.61 (br s, 1H); 5.11 (s, 1H); 4.84 (d, *J* = 12.4 Hz, 1H); 4.76 (d, *J* = 12.4 Hz, 1H); 4.81 (s, 1H); 3.85 (d, *J* = 10.4 Hz, 1H); 3.80 (br s, 1H); 3.48 (s, 1H); 3.07 (s, 6H); 2.55 (s, 3H); 2.47 (s, 3H); 1.04 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (150 MHz, CDCl3): δ 198.6, 171.7, 162.3, 159.0, 146.6, 141.2, 138.2, 134.3, 129.7, 123.0, 118.7, 118.6, 115.6, 112.5, 111.0, 83.9, 82.9, 74.1, 69.7, 68.5, 65.9, 63.4, 36.6, 29.7, 26.7, 23.9, 17.9; **IR** (thin film, cm^{-1}) 3381, 2926, 1724, 1667, 1604, 1522, 1485, 1464, 1389, 1253, 1115, 1074, 735; **MS (ESI$^+$)** Calcd. For $C_{27}H_{36}N_4O_8$ + H, 545.26; Found, 545.32; **TLC** (90:10 CH_2Cl_2:MeOH): R_f = 0.90.

C6 Hydroxymethylene Derivatives



2.45 2.49

5-methoxy-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (2.49): A flame dried 250-mL round bottomed flask was charged with **2.45** (0.50 g, 2.57 mmol, 1.00 equiv), acetone (70 mL) and anhydrous K_2CO_3 (0.53 g, 3.85 mmol, 1.50 equiv). The mixture was cooled to 0 °C and MeI (0.239 mL, 3.85 mmol, 1.50 equiv) was added slowly, and then warmed slowly to rt. After 1 h the reaction was poured into H_2O (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (15 mL), dried with magnesium sulfate, and concentrated in vacuo. The crude product was purified via flash chromatography (60:40 hexanes:EtOAc), affording ether **2.49** (400 mg, 74 % yield) as a pale yellow solid. Analytical Data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.45 (t, *J* = 8.4 Hz, 1H); 6.63 (d, *J* = 8.4 Hz, 1H); 6.56 (d, *J* = 9.6 Hz, 1H); 3.96 (s, 3H); 1.70 (s, 6H).

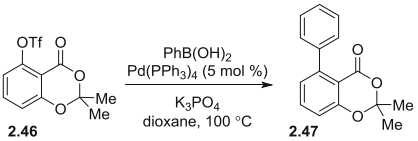


2.49 2.50

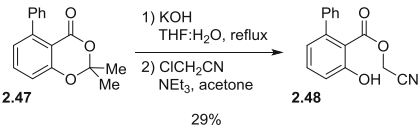
cyanomethyl 2-hydroxy-6-methoxybenzoate (2.50): Methyl ether **2.49** (0.40 g, 1.90 mmol, 1.00 equiv) was dissolved in THF (2 mL) and a solution of KOH (0.53 g, 9.50 mmol, 5.00 equiv) in 2 mL of H_2O was added. The mixture was

refluxed overnight, subsequently cooled to rt, acidified to pH 1 with 6 M $HCl_{(aq.)}$ (10 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried with magnesium sulfate, and concentrated in vacuo, to afford the crude acid, which was carried on to the next step without further purification.

The crude product was dissolved distilled acetone (7 mL). Et_3N (379 µl, 2.85 mmol, 1.50 equiv) and chloroacetonitrile (181 µl, 2.85 mmol, 1.50 equiv) were added to the solution and the mixture was refluxed for 3 h. The solvent was removed via rotary evaporator and pH 4 buffer (10 mL) was added. The aqueous layer was extracted with EtOAc (3 × 15 mL). The organic layers were combined, washed with brine (10 mL), dried with magnesium sulfate, and concentrated in vacuo. The crude product was purified with flash chromatography (80:20 Hexane: EtOAc) to afford ester **2.50** as a pale yellow solid (113 mg, 29 % yield). Analytical Data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.86 (s, 1H); 3.40 (t, *J* = 8.4 Hz, 1H); 6.62 (d, *J* = 9.2 Hz, 1H); 6.44 (d, *J* = 8.4 Hz, 1H); 4.96 (s, 2H); 3.87 (s, 3H).



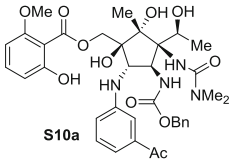
2,2-Dimethyl-5-phenyl-4H-benzo[d][1,3]dioxin-4-one (2.47): A 100-mL round-bottomed flask was charged with **2.46** (0.948 g, 2.91 mmol, 1.00 equiv), phenyl boronic acid (0.531 g, 4.36 mmol, 1.5 equiv), KBr (0.346 g, 2.91 mmol, 1equiv), K_3PO_4 (0.928 g, 4.36 mmol, 1.50 equiv) and dioxane (12 mL). $Pd(PPh_3)_4$ (0.169 g, 0.15 mmol, 0.05 equiv) was added as a suspension in dioxane (3 mL) and the mixture was stirred at 100 °C for 12 h. The mixture was cooled to room temperature, diluted with H_2O (10 mL), and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (60:40 hexanes:EtOAc), affording the desired product **2.47** (413 mg, 55 %) as a pale yellow solid. Analytical Data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.52 (t, *J* = 8.0 Hz, 1H); 7.42–7.37 (m, 3H); 7.34–7.32 (m, 2H); 7.01 (d, *J* = 6.4 Hz, 1H); 6.98 (d, *J* = 7.2, 1H); 1.79 (s, 6H). **MS (ESI$^+$)** Calcd. For $C_{16}H_{14}O_3$ + Na, 277.08; Found, 277.11.



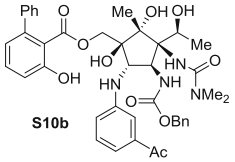
Cyanomethyl 3-hydroxybiphenyl-2-carboxylate (2.48): **2.47** (0.40 g, 1.90 mmol, 1.00 equiv) was dissolved in THF (2 mL), and a solution of KOH (0.53 g, 9.50 mmol, 5.00 equiv) in 2 mL H_2O was added. The mixture was heated at reflux for 12 h. The resulting mixture was cooled to room temperature and acidified with 6 M $HCl_{(aq.)}$ (10 mL) and extracted with EtOAc (3 × 10 mL). The

combined organic layers were washed with brine, dried with magnesium sulfate and concentrated in vacuo to afford crude the crude acid, which was used in the next step without further purification.

The crude acid was dissolved in acetone (7 mL), and triethylamine (379 μL, 2.85 mmol, 1.50 equiv) and chloroacetonitrile (181 μL, 2.85 mmol, 1.50 equiv) were added to the solution. The mixture was refluxed for 3 h, upon which the solvent was removed in vacuo. A pH = 4 buffer solution (10 mL) was then added to the residue, and the mixture was extracted with EtOAc (3 × 15 mL). The organic layers were combined, washed with brine, dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (80:20 hexanes:EtOAc) to afford ester **2.48** as a pale yellow solid (113 mg, 29 %). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.11 (br s, 1H); 7.50–7.40 (m, 1H); 7.39–7.37 (m, 3H); 7.36–7.23 (m, 2H); 7.05 (d, *J* = 9.6 Hz, 1H); 6.86 (d, *J* = 8.4 Hz, 1H); 4.52 (s, 2H). **MS (ESI$^+$)** Calcd. For $C_{15}H_{11}NO_3$ + Na, 276.06; Found, 276.49.

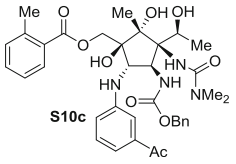


((1*S*,2*R*,3*R*,4*S*,5*S*)-5-((3-acetylphenyl)amino)-4-(((benzyloxy)carbonyl)amino)-3-(3,3-dimethylureido)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)-2-methylcyclopentyl)methyl 2-hydroxy-6-methoxybenzoate (S10a): Isolated from **2.26** via general procedure D using cyanomethyl ester **2.50** as the electrophile in 57 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 11.08 (s, 1H); 7.37–7.20 (m, 8H); 7.12 (s, 1H); 6.73 (d, *J* = 6.4 Hz, 1H); 6.59 (d, *J* = 6.0 Hz, 1H); 6.39 (d, *J* = 8.4 Hz, 1H); 6.04 (s, 1H); 5.89 (br s, 1H); 5.59 (d, *J* = 7.9 Hz, 1H); 5.27 (s, 1H); 5.20 (d, *J* = 13.5 Hz, 1H); 5.14 (d, *J* = 11.8 Hz, 1H); 4.72 (d, *J* = 12.0 Hz, 1H); 4.66 (d, *J* = 11.6 Hz, 1H); 4.07 (br s, 1H); 3.84 (d, *J* = 9.6 Hz, 1H); 3.79 (s, 1H); 3.75 (s, 3H); 2.88 (s, 6H); 2.50 (s, 3H); 1.48 (s, 3H); 1.23 (br s, 3H); **MS (ESI$^+$)** Calcd. For $C_{36}H_{44}N_4O_{11}$ + H, 709.31; Found, 709.15.



((1*S*,2*R*,3*R*,4*S*,5*S*)-5-((3-acetylphenyl)amino)-4-(((benzyloxy)carbonyl)amino)-3-(3,3-dimethylureido)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)-2-methylcyclopentyl)methyl 3-hydroxy-[1,1′-biphenyl]-2-carboxylate (S10b): Isolated from **2.26** via general procedure D using **S17** as the electrophile in 43 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 11.04 (s, 1H); 7.51–7.46 (m, 6H); 7.40–7.32 (m, 3H); 7.26–7.23 (m, 4H); 7.19–7.17 (m, 1H); 7.04 (s, 1H); 6.98 (d, *J* = 8.0 Hz, 1H); 6.61 (t, *J* = 8.4 Hz, 2H); 5.86 (s, 1H); 5.38–5.34 (m, 1H); 5.30 (s, 1H); 5.20 (d, *J* = 11.2 Hz,

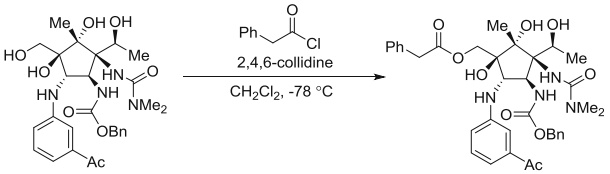
1H); 5.05 (d, J = 8.0 Hz, 1H); 5.00 (s, 1H); 4.56 (d, J = 11.6 Hz, 1H); 4.08 (d, J = 12.0 Hz, 1H); 3.91 (br s, 1H); 3.82 (d, J = 8.4 Hz, 1H); 2.91 (d, J = 10.4 Hz, 1H); 2.85 (s, 6H); 2.25 (s, 3H); 1.261.22 (m, 6H); **MS (ESI$^+$)** Calcd. For $C_{41}H_{46}N_4O_{10}$ + H, 755.33; Found, 755.19.



S10c

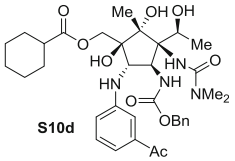
((1*S*,2*R*,3*R*,4*S*,5*S*)-5-(3-acetylphenylamino)-4-(benzyloxycarbonylamino)-3-(3,3-dimethylureido)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)-2-methylcyclopentyl)methyl 2-methylbenzoate (S10c): A flame-dried 20-mL scintillation vial was charged with tetraol **2.26** (0.041 g, 0.073 mmol, 1.00 equiv) and CH_2Cl_2 (3.3 mL) was added under an atmosphere of N_2. The solution was cooled to −78 °C and 2,4,6-collidine (0.02 mL, 0.47 mmol, 2.00 equiv) and DMAP (0.001 g, 0.01 mmol, 0.10 equiv) were added sequentially. The mixture was stirred for 30 min, and 2-methylbenzoyl chloride was added. The reaction was allowed to stir for 1 h, warmed to room temperature and stirred until TLC analysis indicated full conversion of the starting material, generally 8 h. A 1:1 mixture of saturated $NH_4Cl_{(aq.)}$: 1 M $HCl_{(aq.)}$ (3 mL) was added, followed by EtOAc (4 mL). The mixture was partitioned in a separatory funnel, and the aqueous layer was extracted with EtOAc (3 × 6 mL), and the combined organic layers were washed with saturated $NaHCO_{3(aq.)}$ (5 mL), water (5 mL), brine (5 mL) and dried with magnesium sulfate. The crude product was concentrated in vacuo and purified via flash chromatography (60:40 to 50:50 hexanes:EtOAc) to give the ester **S10c** (0.03 g, 60 %) as a pale yellow foam. Analytical Data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.31 (d, J = 7.6 Hz, 1H); 7.51 (br s, 1H); 7.38–7.12 (m, 11H); 6.74 (d, J = 7.6 Hz, 1H); 6.07 (s, 1H); 5.87 (d, J = 9.2 Hz, 1H); 5.74 (d, J = 10.0 Hz, 1H); 5.20 (s, 1H); 5.16 (d, J = 12.4 Hz, 1H); 5.10 (d, J = 12.0 Hz, 1H); 4.8 (d, J = 12.8 Hz, 1H); 4.73 (d, J = 12.4 Hz, 1H); 4.12–4.05 (m, 2H); 3.97 (s, 1H); 3.81 (d, J = 9.6 Hz, 1H); 2.85 (s, 6H); 2.50 (s, 3H); 2.49 (s, 3H); 1.51 (s, 3H); 1.25 (br s, 3H); **MS (ESI$^+$)** Calcd. For $C_{36}H_{44}N_4O_9$ + H, 677.32; Found, 677.25.

General Procedure J for primary alcohol esterification using aliphatic electrophiles.



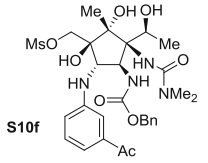
2.26 **S10e**

((1*S*,2*R*,3*R*,4*S*,5*S*)-5-((3-acetylphenyl)amino)-4-(((benzyloxy)carbonyl)amino)-3-(3,3-dimethylureido)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)-2-methylcyclopentyl) methyl 2-phenylacetate (S10e): A flame-dried scintillation vial was charged with tetraol **2.26** (0.032 g, 0.056 mmol, 1.00 eq.) and CH_2Cl_2 (2.5 mL) under an atmosphere of N_2. The solution was cooled to −78 °C and 2,4,6-collidine (15 μL, 0.112 mmol, 2.00 eq.) was added. The resulting mixture was stirred for 30 min, and phenylacetyl chloride was added. The reaction was allowed to stir at this temperature until TLC analysis indicated full conversion of the starting material, typically 1 h. A mixture of saturated $NH_4Cl_{(aq.)}$:1 M $HCl_{(aq.)}$ (1:1) (3 mL) was added followed by EtOAc (4 mL) and the reaction was allowed to warm to rt. The mixture was partitioned in a separatory funnel and the aqueous layer was extracted with EtOAc (3 × 6 mL). The combined organic layers were washed with saturated $NaHCO_{3(aq.)}$ (5 mL), water (5 mL), brine (5 mL), dried with magnesium sulfate, and concentrated in vacuo. The crude product was purified via flash chromatography (60:40 to 50:50 hexanes:EtOAc) to give the title compound **S10e** as a pale yellow foam (0.033 g mg, 87 %). Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.39–7.34 (m, 5H); 7.32 (d, *J* = 7.6 Hz, 1H); 7.26–7.23 (m, 5H); 7.17 (d, *J* = 6.4 Hz, 2H); 6.67 (d, *J* = 7.6 Hz, 1H); 5.98 (s, 1H); 5.65 (d, *J* = 9.2 Hz, 1H); 5.59 (d, *J* = 10.4 Hz, 1H); 5.15–5.13 (m, 3H); 4,53 (s, 2H); 4.01 (br s, 1H); 3.96 (d, *J* = 8.4 Hz; 1H); 3.59 (s, 2H); 3.55 (d, *J* = 9.6 Hz, 1H); 3.21 (s, 1H); 2.84 (s, 6H); 2.54 (s, 3H); 1.37 (s, 3H); 1.20 (d, *J* = 7.2 Hz, 3H); **MS (ESI$^+$)** Calcd. For $C_{36}H_{44}N_4O_9$ + H, 677.32; Found, 677.31.



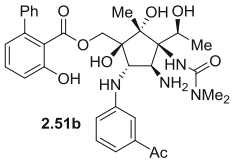
S10d

((1*S*,2*R*,3*R*,4*S*,5*S*)-5-((3-acetylphenyl)amino)-4-(((benzyloxy)carbonyl)amino)-3-(3,3-dimethylureido)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)-2-methylcyclopentyl)methyl cyclohexanecarboxylate (S10d): Isolated from **2.26** via general procedure J using cyclohexoyl chloride as the electrophile in 83 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37 (br s, 1H); 7.31–7.23 (m, 6H); 7.10 (s, 1H); 6.71 (d, *J* = 6.4 Hz, 1H); 6.02 (s, 1H); 5.82 (d, *J* = 8.0 Hz, 1H); 5.64 (d, *J* = 10.0 Hz, 1H); 5.16–5.10 (m, 3H); 4.52 (d, *J* = 12.0 Hz, 1H); 4.51 (d, *J* = 12.4 Hz, 1H); 4.02 (br s, 1H); 3.72–3.68 (m, 2H); 2.85 (s, 6H); 2.54 (s, 3H); 2.29–2.35 (m, 1H); 1.83–1.74 (m, 2H): 1.67–1.63 (m, 4H); 1.44 (s, 3H); 1.36–1.27 (m, 2H); 1.25–1.18 (m, 5H); **MS (ESI$^+$)** Calcd. For $C_{35}H_{48}N_4O_9$ + H, 669.35; Found, 669.35.



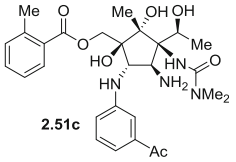
S10f

((1S,2R,3R,4S,5S)-5-((3-acetylphenyl)amino)-4-(((benzyloxy)carbonyl)amino)-3-(3,3-dimethylureido)-1,2-dihydroxy-3-((S)-1-hydroxyethyl)-2-methylcyclopentyl) methyl methanesulfonate (S10f): Isolated from **2.26** via general procedure J using cyclohexoyl chloride as the electrophile in 54 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34–7.24 (m, 7H); 7.14 (s, 1H); 6.75 (d, *J* = 7.6 Hz; 1H); 5.96 (d, *J* = 9.6 Hz, 1H); 5.55 (bs, 1H); 5.25 (s, 1H); 5.12 (bs, 2H); 4.65 (d, *J* = 11.2 Hz, 1H); 4.53 (d, *J* = 11.2 Hz, 1H); 4.09 (bs, 1H); 3.85 (bs, 1H); 2.90 (s, 3H); 2.85 (s, 6H); 2.53 (s, 3H); 1.46 (s, 3H); 1.25 (bs, 3H); **MS (ESI$^+$)** Calcd. For $C_{29}H_{40}N_4O_{10}S$ + H, 637.25; Found, 669.14.



2.51b

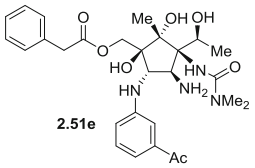
((1*S*,2*R*,3*R*,4*S*,5*S*)-5-((3-acetylphenyl)amino)-4-amino-3-(3,3-dimethylureido)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)-2-methylcyclopentyl)methyl 3-hydroxy-[1,1′-biphenyl]-2-carboxylate (2.51b): Isolated from **S10b** via general procedure E in 62 % yield. Analytical data: $[\alpha]_D^{19}$ +8.4 (*c* = 0.3, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 11.05 (br s, 1H); 7.85 (d, *J* = 10.8 Hz, 1H); 7.57 (t, *J* = 7.4 Hz, 2H); 7.44–7.33 (m, 5H); 7.18–7.15 (m, 2H); 7.10 (s, 1H); 7.02 (s, 1H); 6.97 (d, J = 8.4 Hz, 1H); 6.67 (d, *J* = 7.2 Hz, 1H); 6.62 (d, *J* = 7.6 Hz, 1H); 5.48 (s, 1H); 5.32 (d, *J* = 10.4 Hz, 1H); 5.11 (br s, 1H); 4.09 (d, *J* = 12.0 Hz, 1H); 3.80 (br s, 1H); 2.98 (s, 6H); 2.95 (s, 1H); 2.91–2.83 (m, 2H); 2.75 (s, 1H); 2.54 (s, 3H); 1.30 (s, 3H): 0.97 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (150 MHz, CDCl3): δ 198.6, 170.7, 162.4, 159.1, 146.7, 144.6, 143.8, 137.9, 133.9, 130.9, 129.5, 128.8, 128.7, 128.5, 127.1, 123.1, 119.8, 118.7, 117.3, 110.7, 110.00, 88.5, 83.1, 74.0, 71.2, 68.2, 68.2, 66.3, 65.9, 65.4, 36.8, 31.9, 29.7, 28.9, 26.7, 23.7, 21.0, 18.1, 15.3, 14.2, 11.00; **IR** (thin film, cm^{-1}) 3376, 2925, 2853, 2359, 1727, 1672, 1602, 1520, 1438, 1267, 1216; **MS (ESI$^+$)** Calcd. For $C_{33}H_{40}N_4O_8$ + H, 621.29; Found, 621.22; **TLC** (95:5 CH_2Cl_2:MeOH): R_f = 0.24.



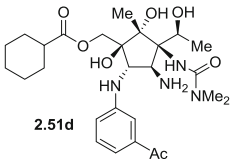
2.51c

((1*S*,2*R*,3*R*,4*S*,5*S*)-5-((3-acetylphenyl)amino)-4-amino-3-(3,3-dimethylureido)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)-2-methylcyclopentyl)methyl 2-methyl benzoate (2.51c): Isolated from **S10c** via general procedure E in 73 % yield. Analytical data: $[\alpha]_D^{19}$ +9.9 (*c* = 0.28, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.0 Hz, 1H); 7.39 (t, *J* = 7.6 Hz, 1H); 7.26–7.25 (m, 6H); 6.83 (d, *J* = 6.8 Hz, 1H); 5.8 (br s, 1H); 5.68 (d, *J* = 10.4 Hz, 1H): 4.74 (s, 2H); 4.01 (br s, 1H); 3.86 (d, *J* = 10.4 Hz, 1H); 3.01 (s, 6H); 2.55 (s, 3H); 2.52 (s, 3H); 1.58 (s, 3H); 1.08 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (150 MHz, CDCl3): δ 198.6, 168.7, 159.2, 146.8, 140.4,

138.2, 132.3, 131.7, 131.5, 130.7, 129.6, 128.8, 125.7, 118.7, 118.1, 110.7, 89.8, 88.6, 85.1, 84.9, 64.7, 36.8, 29.7, 26.7, 21.7, 21.1, 18.1; **IR** (thin film, cm^{-1}) 3408, 2925, 2360, 1716, 1636, 1520, 1375, 1252, 1082; **MS (ESI$^+$)** Calcd. For $C_{28}H_{38}N_4O_7$ + H, 543.28; Found, 543.21; **TLC** (95:5 CH_2Cl_2:MeOH): R_f = 0.32.

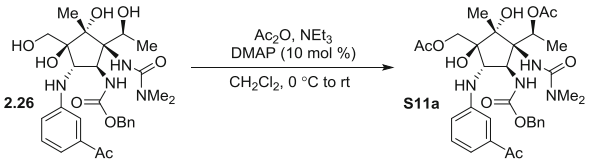


((1*S*,2*R*,3*R*,4*S*,5*S*)-5-((3-acetylphenyl)amino)-4-amino-3-(3,3-dimethylureido)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)-2-methylcyclopentyl)methyl 2-phenyl acetate (2.51e): Isolated from **S10e** via general procedure E in 61 % yield. Analytical data: $[\alpha]_D^{19}$ +48.9 (*c* = 0.45, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 11.2 Hz, 1H); 7.29–7.24 (m,6H); 7.18–7.24 (m, 4H); 6.74 (d, *J* = 7.6 Hz, 1H); 5.55 (d, *J* = 10.4 Hz, 1H); 4.53 (d, *J* = 12.4 Hz, 1H); 4.44 (d, *J* = 12.4 Hz, 1H); 3.87 (br s, 1H); 3.58 (s, 2H); 3.55 (s, 1H); 2.96 (s, 6H); 2.85 (s, 1H); 1.41 (s, 3H); 1.01 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR** (150 MHz, CDCl3): δ 198.7, 172.4, 159.2, 146.6, 138.3, 133.7, 129.6, 129.2, 129.1, 128.6, 127.2, 118.9, 118.2, 110.5, 88.5, 84.6, 74.2, 71.4, 68.3, 64.6, 63.1, 41.3, 36.8, 29.7, 26.8, 21.0, 18.1; **IR** (thin film, cm^{-1}) 3398, 2928, 2359, 1733, 1671, 1602, 1519, 1455, 1373, 1327, 1266, 1094, 780; **MS (ESI$^+$)** Calcd. For $C_{28}H_{38}N_4O_7$ + H, 543.28; Found, 543.21; **TLC** (95:5 CH_2Cl_2: MeOH): R_f = 0.15.

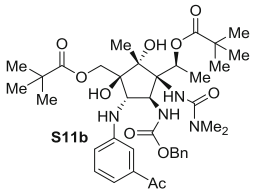


((1*S*,2*R*,3*R*,4*S*,5*S*)-5-((3-acetylphenyl)amino)-4-amino-3-(3,3-dimethylureido)-1,2-dihydroxy-3-((*S*)-1-hydroxyethyl)-2-methylcyclopentyl)methyl cyclohexanecarboxylate (2.51d): Isolated from **S10d** via general procedure E in 76 % yield. Analytical data: $[\alpha]_D^{19}$ +22.3 (*c* = 0.3, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.86 (br s, 1H); 7.24–7.21 (m, 3H); 7.16–7.13 (m, 2H); 6.77 (d, *J* = 6.8 Hz, 1H); 5.69 (br s, 1H); 5.57 (d, *J* = 10.4 Hz, 1H); 4.48 (d, *J* = 12.0 Hz, 1H); 4.43 (d, *J* = 12.0 Hz, 1H); 3.95 (br s, 1H); 3.72 (d, *J* = 10.4 Hz, 1H); 2.98 (s, 6H); 2.57 (br s, 1H); 1.83–1.60 (m, 5H); 1.49 (s, 3H); 1.36–1.15 (m, 5H); 1.03 (d, *J* = 6.0 Hz, 3H); **^{13}C NMR** (150 MHz, CDCl3): δ 198.7, 177.3, 159.2, 146.8, 138.2, 129.6, 118.8, 118.2, 110.5, 84.6, 65.9, 64.2, 43.0, 36.8, 29.0, 28.8, 26.7, 25.6, 25.3, 25.2, 21.1, 18.1, 15.3; **IR** (thin film, cm^{-1}) 3380, 3054, 2986, 2935, 2410, 1727, 1679, 1603, 1514, 1440, 1265, 738; **MS (ESI$^+$)** Calcd. For $C_{27}H_{42}N_4O_7$ + H, 535.31; Found, 535.37; **TLC** (95:5 CH_2Cl_2:MeOH): R_f = 0.36.

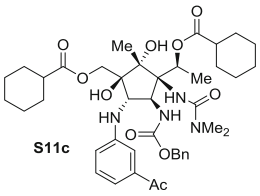
General Procedure K for C6,C7 bis acylation:



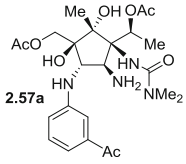
((1*S*,2*R*,3*R*,4*S*,5*S*)-3-((*S*)-1-acetoxyethyl)-5-((3-acetylphenyl)amino)-4-(((benzyloxy) carbonyl)amino)-3-(3,3-dimethylureido)-1,2-dihydroxy-2-methylcyclopentyl)methyl acetate (S11a): A flame-dried 20-mL scintillation vial was charged with tetraol **2.26** (0.020 g, 0.036 mmol, 1.00 equiv) and CH_2Cl_2 (1 mL) under an atmosphere of N_2. The solution was cooled to 0 °C and NEt_3 (0.01 mL, 0.07 mmol, 2.00 equiv) and DMAP (0.001 g, 0.01 mmol, 0.27 equiv) were added followed lastly by Ac_2O (0.01 mL, 0.11 mmol, 3.00 equiv). The mixture was allowed to warm to rt and stirred until full conversion of the starting material was observed by TLC analysis, typically 12 h. The reaction was quenched via addition of saturated $NaHCO_{3(aq.)}$ (5 mL), and the layers were partitioned in a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organics were washed with brine (5 mL), dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (70:30 to 60:40 petroleum ether:acetone) to afford diester **S11a** (0.02 g, 86 %) as a colorless foam. Analytical Data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.0 Hz, 1H), 7.25–7.23 (m, 8H), 6.20 (q, *J* = 6.4 Hz, 1H), 5.57 (s, 1H), 5.07 (d, *J* = 12.4 Hz, 1H), 5.00 (d, *J* = 12.8 Hz, 1H), 4.82 (d, *J* = 5.2 Hz, 1H), 4.59 (m, 3H), 4.21 (d, *J* = 12.4 Hz, 1H), 3.85 (m, 1H), 3.62 (s, 1H), 2.96 (s, 6H), 2.55 (s, 3H), 2.06 (s, 3H), 1.91 (s, 3H), 1.48 (s, 3H), 1.37 (d, *J* = 6.4 Hz, 3H); **MS (ESI$^+$)** Calcd. For $C_{32}H_{42}N_4O_{10}$ + Na, 665.28; Found, 665.34.



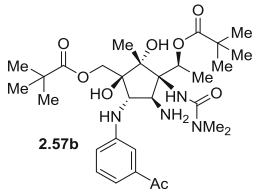
((1*S*,2*R*,3*R*,4*S*,5*S*)-5-((3-acetylphenyl)amino)-4-(((benzyloxy)carbonyl) amino)-3-(3,3-dimethylureido)-1,2-dihydroxy-2-methyl-3-((*S*)-1-(pivaloyloxy)ethyl)cyclopentyl)methyl pivalate (S11b): Isolated from **2.26** via general procedure K using pivaloyl chloride as the electrophile in 92 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.0 Hz, 1H), 7.25–7.19 (m, 8H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.16 (q, *J* = 8.0 Hz, 1H), 5.61 (s, 1H), 5.03 (dd, *J* = 4.8, 12.0 Hz, 2H), 4.95 (d, *J* = 5.2 Hz, 1H), 4.66 (m, 2H), 4.57 (t, *J* = 12.5 Hz, 1H), 4.17 (d, *J* = 12.4 Hz, 1H), 3.86 (m, 1H), 3.64 (s, 1H), 2.96 (s, 6H), 2.55 (s, 3H), 2.17 (s, 3H), 1.46 (s, 3H), 1.38 (d, *J* = 6.8 Hz, 3H), 1.19 (s, 9H), 1.14 (s, 9H); **MS (ESI$^+$)** Calcd. For $C_{38}H_{54}N_4O_{10}$ +Na, 749.37; Found, 749.45.



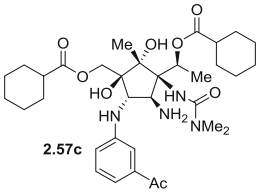
((1*S*,2*R*,3*R*,4*S*,5*S*)-5-((3-acetylphenyl)amino)-4-(((benzyloxy)carbonyl)amino)-3-((*S*)-1-((cyclohexanecarbonyl)oxy)ethyl)-3-(3,3-dimethylureido)-1,2-dihydroxy-2-methylcyclopentyl)methyl cyclohexanecarboxylate (S11c): Isolated from **2.26** via general procedure K using cyclohexylacetyl chloride as the electrophile in 76 % yield. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.0 Hz, 1H), 7.28–7.20 (m, 8H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.23 (q, *J* = 6.8 Hz, 1H), 5.64 (s, 1H), 5.04 (dd, *J* = 5.6, 12.4 Hz, 2H), 4.96 (d, *J* = 5.2 Hz, 1H), 4.64 (m, 3H), 4.22 (d, *J* = 12.4 Hz, 1H), 3.84 (dd, *J* = 4.0, 5.2 Hz, 1H), 3.79 (s, 1H), 2.97 (s, 6H), 2.56 (s, 3H), 2.27 (m, 1H), 2.16 (t, *J* = 10.8 Hz, 1H), 1.96–1.62 (m, 11H), 1.48 (s, 3H), 1.38 (d, *J* = 6.4 Hz, 3H), 1.32–1.13 (m, 9H); **MS (ESI$^+$)** Calcd. For $C_{42}H_{58}N_4O_{10}$ + H, 801.41; Found, 801.54.



((1*S*,2*R*,3*R*,4*S*,5*S*)-3-((*S*)-1-acetoxyethyl)-5-((3-acetylphenyl)amino)-4-amino-3-(3,3-dimethylureido)-1,2-dihydroxy-2-methylcyclopentyl)methyl acetate (2.57a): Isolated from **S11a** via general procedure E in 38 % yield. Analytical data: $[\alpha]_D^{19}$ +5.6 (*c* = 0.17, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.27–7.21 (m, 4H), 6.95 (d, *J* = 6.6 Hz, 1H), 6.10 (q, *J* = 6.6 Hz, 1H), 5.54 (s, 1H), 4.51 (d, *J* = 12.0 Hz, 2H), 4.21 (d, *J* = 12.0 Hz, 1H), 4.06 (br s, 1H), 3.44 (br s, 1H), 2.99 (s, 7H), 2.55 (s, 3H), 2.11 (s, 1H), 1.82 (s, 1H), 1.44 (m, 6H); **^{13}C NMR** (150 MHz, CDCl3): δ 198.9, 172.2, 169.7, 158.7, 148.2, 138.0, 129.3, 117.8, 112.1, 85.7, 81.7, 72.1, 69.3, 65.6, 36.7, 29.7, 26.8, 21.5, 20.8, 20.2, 16.6, 1.0; **IR** (thin film, cm^{-1}) 3421, 2926, 2846, 1637, 1541, 1246, 1066; **MS (ESI$^+$)** Calcd. For $C_{24}H_{36}N_4O_8$ + H; Found, 509.33; **TLC** (98:2 CH_2Cl_2:MeOH): R_f = 0.10.



((1*S*,2*R*,3*R*,4*S*,5*S*)-5-((3-acetylphenyl)amino)-4-amino-3-(3,3-dimethylureido)-1,2-dihydroxy-2-methyl-3-((*S*)-1-(pivaloyloxy)ethyl)cyclopentyl)methyl pivalate (2.57b): Isolated from **S11b** via general procedure E in 53 % yield. Analytical data: $[\alpha]_D^{19}$ +21.8 (*c* = 0.45, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.29–7.22 (m, 4H), 6.95 (d, *J* = 6.6 Hz, 1H), 6.08 (q, *J* = 6.6 Hz, 1H), 5.55 (s, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.33 (br s, 1H), 4.17 (d, *J* = 12.0 Hz, 1H), 4.04 (t, *J* = 7.8 Hz, 1H), 3.34 (d, *J* = 6.8 Hz, 1H), 2.98 (s, 6H), 2.55 (s, 3H), 1.43 (d, *J* = 6.6 Hz, 3 H), 1.38 (s, 3H), 1.23 (s, 9H), 1.09 (s, 9H); **^{13}C NMR** (150 MHz, CDCl3): δ 198.7, 179.9, 177.0, 158.6, 148.2, 138.1, 129.5, 117.7, 117.4, 112.2, 85.5, 81.5, 69.6, 66.0, 38.9, 38.8, 36.7, 27.1, 26.8, 20.2, 16.6; **IR** (thin film, cm^{-1}) 3895, 3399, 2972, 2359, 1710, 1642, 1530, 1461, 1367, 1284, 1165; **MS (ESI$^+$)** Calcd. For $C_{30}H_{48}N_4O_8$ + H, 593.36; Found, 593.38; **TLC** (90:10 CH_2Cl_2:MeOH): R_f = 0.34.



((1*S*,2*R*,3*R*,4*S*,5*S*)-5-((3-acetylphenyl)amino)-4-amino-3-((*S*)-1-((cyclohexane carbonyl) oxy)ethyl)-3-(3,3-dimethylureido)-1,2-dihydroxy-2-methylcyclo pentyl)methyl cyclohexanecarboxylate (2.57c): Isolated from **S11c** via general procedure E in 72 % yield. Analytical data: $[\alpha]_D^{19}$ +22.6 (*c* = 0.85, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.28–7.20 (m, 4H), 6.93 (d, *J* = 7.2 Hz, 1H), 6.14 (q, *J* = 6.6 Hz, 1H), 5.55 (s, 1H), 4.53 (d, *J* = 12.6 Hz, 1H), 4.34 (s, 1H), 4.18 (d, *J* = 16.2 Hz, 1H), 3.98 (t, *J* = 7.8 Hz, 1H), 3.30 (d, *J* = 7.2 Hz, 1H), 2.98 (s, 6H), 2.55 (s, 3H) 2.30 (m, 1H), 2.05 (m, 1H), 1.91 (m, 2H), 1.76 (m, 3H), 1.66–1.57 (m, 5H), 1.42 (d, *J* = 6.6 Hz, 3H), 1.38 (s, 3H), 1.28–1.10 (m, 10H); **^{13}C NMR** (150 MHz, CDCl3): δ 198.7, 177.4, 174.5, 158.5, 148.4, 138.0, 129.3, 117.6, 117.5, 112.2, 85.6, 81.6, 69.5, 65.5, 43.4, 43.1, 36.7, 28.7, 26.8, 25.8, 25.6, 25.5, 25.4, 25.3, 20.3, 16.6; **IR** (thin film, cm^{-1}) 3390, 3055, 2935, 2857, 2305, 2054, 1723, 1642, 1538, 1450, 1332, 1247, 1132, 737; **MS (ESI$^+$)** Calcd. For $C_{34}H_{52}N_4O_8$ + H, 645.39; Found, 645.47; **TLC** (90:10 CH_2Cl_2:MeOH): R_f = 0.36.

Nanoparticle Fabrication and Characterization

PRINT-pactamycin NPs were fabricated with solutions of P(d,l-lactide) and docetaxel dissolved in chloroform as previously described [19, 50]. Particle size and shape were determined by Dynamic Light Scattering (DLS, Malvern Instruments) and confirmed by Scanning Electron Microscopy (SEM; Hitachi model 2-4700). Drug loadings were determined by dissolving the NPs and analyzing solutions by reverse-phase HPLC using validated concentration curves. NP fabrication was conducted, molds were filled with a pre-particle polymer solution prepared with 2 % by weight PLGA and quantum dots (28:1) in chloroform as previously described [19, 50]. Particle size and shape were determined by DLS and SEM. Particle concentration was determined using Thermogravimetric Analysis

correcting for the supernatant (TA Instruments). Excitation, emission, and absorbance wavelength scans of PLGA Quantum Dot NPs were performed on a 96 well plate reader (Molecular Devices SpectraMax M5). QD concentrations were determined by inductively coupled plasma mass spectroscopy (ICP-MS).

High Pressure Liquid Chromatography Analysis and Drug Loading

HPLC analysis of PRINT-therapeutics was performed with an analytical Agilent 1200 HPLC system equipped with a variable wavelength absorbance detector using a reverse phase C18 column (Agilent, Zorbax Eclipse XDB-C18, 5 Å, 4.6 × 150 mm). A binary gradient of water (10 % isopropyl alcohol), acetonitrile (10 % isopropyl alcohol), 1 mL min^{-1} was used and the eluent was monitored by UV absorbance at 205 and 210 nm.

In vitro cytotoxicity assays

A549 (ATCC® CCL-185™), MDAMB231 (ATCC® HTB-26™), SK-OV-3 (ATCC® HTB-77™), MRC-5 (ATCC® CCL-171™), were purchased directly from and authenticated by ATCC immediately prior to initiation of these studies. All cell-based assays were performed utilizing passage number for each cell line ranging from 6–16. Each cell line was seeded in 200 μL of media [RPMI1640 (A549), Leibovitz's L-15 medium (MDAMB231), McCoy's 5A (SK-OV-3), and EMEM (MRC-5) with 10 % fetal bovine serum] at a density of 5000 cells per cm^2 into a 96-well microtiter plate. Cells were allowed to adhere for 24 h and subsequently incubated with PRINT particles at drug concentrations ranging from 4 uM to 0.05 nM for 72 h at 37 °C in a humidified 5 % CO_2 atmosphere. After the incubation period, all medium/particles were aspirated off cells. 100 μL fresh medium was added back to cells followed by the addition of 100 μL CellTiter-Glo® Luminescent Cell Viability Assay reagent. Plates were placed on a microplate shaker for 2 min, then incubated at room temperature for 10 min to stabilize luminescent signal. The luminescent signal was recorded on a SpectraMax M5 plate reader (Molecular Dynamics). The viability of the cells exposed to PRINT particles was expressed as a percentage of the viability of cells grown in the absence of particles (Figs. 2.8, 2.9, 2.10, 2.11, 2.12 and 2.13, Table 2.8).

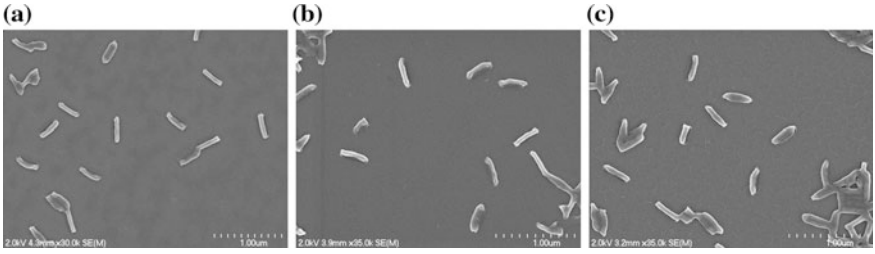


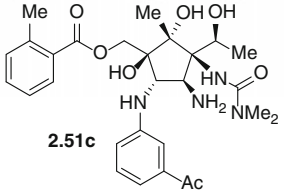
Fig. 2.8 Scanning electron microscope (SEM) images of 80 × 320 nm PRINT-therapeutic NPs containing derivative (**a**) **2.1**, (**b**) **2.29e**, and (**c**) **2.42d**, show that the particles are monodisperse and uniform in size and shape despite containing different therapeutics

National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

NSC : D - 778754 / 1	Experiment ID : 1405RS75	Test Type : 08	Units : Molar
Report Date : October 06, 2014	Test Date : May 05, 2014	QNS :	MC :
COMI : JSJ135759 (135759)	Stain Reagent : SRB Dual-Pass Related	SSPL : 0YLQ	

Log10 Concentration

Panel/Cell Line	Time Zero	Mean Optical Densities Ctrl	-8.0	-7.0	-6.0	-5.0	-4.0	Percent Growth -8.0	-7.0	-6.0	-5.0	-4.0	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.454	2.190	1.567	0.785	0.529	0.530	0.544	64	19	4	4	5	2.06E-8	> 1.00E-4	> 1.00E-4
HL-60(TB)	0.721	2.843	2.171	0.662	0.697	0.672	0.736	68	-8	-3	-7	1	1.74E-8	.	> 1.00E-4
K-562	0.310	2.450	1.472	0.635	0.520	0.405	0.424	54	15	10	4	5	1.29E-8	> 1.00E-4	> 1.00E-4
MOLT-4	0.810	3.169	2.056	1.120	0.881	0.921	1.031	53	13	3	5	9	1.18E-8	> 1.00E-4	> 1.00E-4
RPMI-8226	0.887	2.948	2.113	0.768	0.728	0.627	0.632	59	-13	-18	-29	-29	1.35E-8	6.54E-8	> 1.00E-4
SR	0.497	2.506	1.610	0.688	0.573	0.546	0.681	55	9	4	2	9	1.31E-8	> 1.00E-4	> 1.00E-4
Non-Small Cell Lung Cancer															
A549/ATCC	0.338	1.758	1.225	0.586	0.333	0.257	0.278	62	17	-2	-24	-18	1.89E-8	8.22E-7	> 1.00E-4
EKVX	0.834	2.337	2.120	1.328	0.852	0.704	0.648	86	33	1	-16	-22	4.72E-8	1.18E-6	> 1.00E-4
HOP-62	0.546	1.394	1.036	0.615	0.467	0.426	0.416	58	8	-15	-22	-24	1.44E-8	2.28E-7	> 1.00E-4
HOP-92	1.383	1.891	1.706	1.415	1.048	0.950	0.978	63	6	-24	-31	-29	1.72E-8	1.61E-7	> 1.00E-4
NCI-H226	0.814	2.149	1.582	0.858	0.559	0.447	0.494	57	3	-31	-45	-39	1.37E-8	1.24E-7	> 1.00E-4
NCI-H23	0.591	1.625	1.213	0.624	0.437	0.383	0.334	60	3	-26	-35	-44	1.51E-8	1.28E-7	> 1.00E-4
NCI-H322M	0.922	2.264	1.909	1.292	0.944	0.761	0.680	74	28	2	-18	-26	3.25E-8	1.22E-6	> 1.00E-4
NCI-H460	0.221	2.637	1.154	0.401	0.237	0.202	0.174	39	7	1	-9	-21	< 1.00E-8	1.17E-6	> 1.00E-4
NCI-H522	0.555	1.749	1.382	0.640	0.296	0.256	0.254	69	7	-47	-54	-54	2.04E-8	1.36E-7	2.90E-6
Colon Cancer															
COLO 205	0.519	2.325	1.519	0.708	0.310	0.254	0.263	55	10	-40	-51	-49	1.32E-8	1.61E-7	.
HCC-2998	0.684	2.073	1.285	0.543	0.435	0.363	0.343	43	-21	-36	-47	-50	< 1.00E-8	4.75E-8	> 1.00E-4
HCT-116	0.160	1.485	0.948	0.244	0.190	0.122	0.087	59	6	2	-24	-46	1.51E-8	1.22E-6	> 1.00E-4
HCT-15	0.206	1.437	1.244	0.723	0.287	0.186	0.115	84	42	7	-10	-44	6.45E-8	2.50E-6	> 1.00E-4
HT29	0.117	0.846	0.342	0.138	0.093	0.082	0.049	31	3	-21	-30	-58	< 1.00E-8	1.33E-7	5.10E-5
KM12	0.478	2.753	1.938	0.926	0.565	0.457	0.372	64	20	4	-4	-22	2.08E-8	2.91E-6	> 1.00E-4
SW-620	0.242	1.983	1.264	0.557	0.297	0.260	0.174	59	18	3	1	-28	1.64E-8	1.08E-5	> 1.00E-4
CNS Cancer															
SF-268	0.666	2.100	1.622	0.931	0.591	0.532	0.484	67	18	-11	-20	-27	2.22E-8	4.18E-7	> 1.00E-4
SF-295	0.400	2.461	1.679	0.798	0.438	0.361	0.314	62	19	2	-10	-22	1.92E-8	1.44E-6	> 1.00E-4
SF-539	1.236	2.961	1.655	1.020	0.715	0.554	0.447	24	-18	-42	-55	-64	< 1.00E-8	3.81E-8	3.99E-6
SNB-19	0.626	2.067	1.494	0.948	0.657	0.612	0.544	60	22	2	-2	-13	1.86E-8	3.06E-6	> 1.00E-4
SNB-75	0.970	1.850	1.334	1.062	0.569	0.017	0.031	41	10	-41	-98	-97	< 1.00E-8	1.59E-7	1.42E-6
U251	0.340	1.624	1.168	0.589	0.312	0.286	0.255	64	19	-8	-16	-25	2.09E-8	5.03E-7	> 1.00E-4
Melanoma															
LOX IMVI	0.221	1.516	0.298	0.091	0.098	0.103	0.128	6	-59	-56	-53	-42	< 1.00E-8	1.24E-8	.
MALME-3M	0.606	1.184	0.915	0.659	0.552	0.272	0.203	54	9	-9	-55	-67	1.20E-8	3.18E-7	7.75E-6
M14	0.473	2.102	1.504	0.704	0.127	0.079	0.103	63	14	-73	-83	-78	1.86E-8	1.45E-7	5.42E-7
MDA-MB-435	0.477	2.567	1.812	0.809	0.345	0.015	0.017	64	16	-28	-97	-96	1.94E-8	2.32E-7	2.10E-6
SK-MEL-2	0.810	1.807	1.261	0.640	0.399	0.289	0.269	45	-21	-51	-64	-67	< 1.00E-8	4.81E-8	9.40E-7
SK-MEL-28	0.720	1.943	1.522	0.799	0.572	0.455	0.373	66	6	-21	-37	-48	1.83E-8	1.73E-7	> 1.00E-4
SK-MEL-5	0.506	2.343	1.616	0.812	0.224	0.095	0.071	60	17	-56	-81	-86	1.73E-8	1.70E-7	8.33E-7
UACC-257	0.723	1.504	1.297	0.833	0.571	0.488	0.449	73	14	-21	-33	-38	2.49E-8	2.51E-7	> 1.00E-4
UACC-62	0.909	2.759	2.138	1.087	0.525	0.186	0.182	66	10	-42	-80	-80	1.95E-8	1.53E-7	1.61E-6
Ovarian Cancer															
IGROV1	0.752	2.272	1.752	1.130	0.716	0.638	0.600	66	25	-5	-15	-20	2.43E-8	6.87E-7	> 1.00E-4
OVCAR-3	0.502	1.791	1.309	0.777	0.494	0.449	0.409	63	21	-2	-11	-19	2.02E-8	8.44E-7	> 1.00E-4
OVCAR-4	0.859	1.820	1.554	1.066	0.837	0.742	0.797	72	21	-3	-14	-7	2.75E-8	7.79E-7	> 1.00E-4
OVCAR-5	0.660	1.556	1.282	0.840	0.595	0.525	0.506	69	20	-10	-21	-23	2.47E-8	4.68E-7	> 1.00E-4
OVCAR-8	0.483	1.847	1.412	0.701	0.420	0.362	0.353	68	16	-13	-25	-27	2.22E-8	3.53E-7	> 1.00E-4
NCI/ADR-RES	0.538	1.636	1.516	1.183	0.722	0.466	0.392	89	59	17	-13	-27	1.61E-7	3.60E-6	> 1.00E-4
SK-OV-3	0.689	1.690	1.173	0.845	0.658	0.569	0.558	48	16	-4	-17	-19	< 1.00E-8	5.96E-7	> 1.00E-4
Renal Cancer															
786-0	0.780	2.512	1.882	1.353	0.818	0.623	0.592	64	33	2	-20	-24	2.79E-8	1.25E-6	> 1.00E-4
A498	1.361	2.067	1.645	1.164	0.702	0.291	0.636	40	-14	-48	-79	-53	< 1.00E-8	5.43E-8	1.13E-6
ACHN	0.591	2.161	1.428	0.822	0.541	0.476	0.457	53	15	-8	-20	-23	1.22E-8	4.31E-7	> 1.00E-4
CAKI-1	0.667	3.138	2.832	1.711	0.784	0.612	0.543	88	42	5	-8	-19	6.75E-8	2.31E-6	> 1.00E-4
RXF 393	1.000	1.899	1.489	1.043	0.624	0.432	0.367	54	5	-38	-57	-63	1.23E-8	1.30E-7	4.42E-6
SN12C	1.014	3.096	2.284	1.270	0.980	0.888	0.913	61	12	-3	-12	-10	1.68E-8	6.07E-7	> 1.00E-4
TK-10	0.422	1.114	0.821	0.588	0.388	0.372	0.306	58	24	-8	-12	-27	1.69E-8	5.57E-7	> 1.00E-4
UO-31	0.631	2.072	1.577	1.078	0.678	0.540	0.460	66	31	3	-15	-27	2.82E-8	1.53E-6	> 1.00E-4
Prostate Cancer															
PC-3	1.043	2.891	2.060	1.251	0.884	0.783	0.747	55	11	-15	-25	-28	1.30E-8	2.66E-7	> 1.00E-4
DU-145	0.390	1.668	1.275	0.677	0.378	0.322	0.309	69	22	-3	-17	-21	2.58E-8	7.50E-7	> 1.00E-4
Breast Cancer															
MCF7	0.408	2.211	1.521	0.620	0.424	0.389	0.328	62	12	1	-5	-20	1.72E-8	1.43E-6	> 1.00E-4
MDA-MB-231/ATCC	0.774	1.685	1.432	1.105	0.738	0.582	0.530	72	36	-5	-25	-32	4.15E-8	7.70E-7	> 1.00E-4
HS 578T	1.111	2.227	1.874	1.511	1.065	0.946	0.887	68	36	-4	-15	-20	3.67E-8	7.86E-7	> 1.00E-4
BT-549	1.169	2.348	1.785	0.989	0.883	0.829	0.714	52	-15	-25	-29	-39	1.08E-8	5.91E-8	> 1.00E-4
MDA-MB-468	0.696	1.419	0.970	0.659	0.483	0.478	0.429	38	-5	-31	-31	-38	< 1.00E-8	7.50E-8	> 1.00E-4



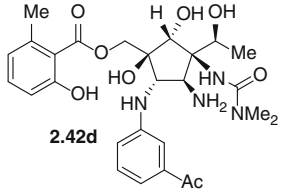
2.51c

Fig. 2.9 NCI-60 screening results for derivative **2.51c**

National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

NSC : D - 778755 / 1	Experiment ID : 1405RS75	Test Type : 08	Units : Molar
Report Date : October 06, 2014	Test Date : May 05, 2014	QNS :	MC :
COMI : JSJ135760 (135760)	Stain Reagent : SRB Dual-Pass Related	SSPL : 0YLQ	

		Log10 Concentration												
	Time	Mean Optical Densities					Percent Growth							
Panel/Cell Line	Zero	Ctrl	-10.0	-9.0	-8.0	-7.0	-6.0	-10.0	-9.0	-8.0	-7.0	-6.0	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.454	2.190	2.134	2.069	0.999	0.516	0.525	97	93	31	4	4	4.98E-9	> 1.00E-6	> 1.00E-6
HL-60(TB)	0.721	2.843	2.789	2.893	1.724	0.627	0.574	97	102	47	-13	-20	8.92E-9	6.07E-8	> 1.00E-6
K-562	0.310	2.450	2.499	2.448	0.863	0.401	0.379	102	100	26	4	3	4.72E-9	> 1.00E-6	> 1.00E-6
MOLT-4	0.810	3.169	3.120	3.098	1.422	0.895	0.739	98	97	26	4	-9	4.59E-9	1.96E-7	> 1.00E-6
RPMI-8226	0.887	2.948	2.964	2.933	1.431	0.683	0.658	101	99	26	-23	-26	4.74E-9	3.42E-8	> 1.00E-6
SR	0.497	2.506	2.444	2.399	1.221	0.529	0.460	97	95	36	2	-7	5.78E-9	1.49E-7	> 1.00E-6
Non-Small Cell Lung Cancer															
A549/ATCC	0.338	1.758	1.767	1.763	1.091	0.345	0.249	101	100	53	.	-26	1.14E-8	1.04E-7	> 1.00E-6
EKVX	0.834	2.337	2.164	2.217	1.756	0.883	0.722	88	92	61	3	-13	1.57E-8	1.56E-7	> 1.00E-6
HOP-62	0.546	1.394	1.201	1.208	0.767	0.431	0.361	77	78	26	-21	-34	3.47E-9	3.57E-8	> 1.00E-6
HOP-92	1.383	1.891	1.830	1.773	1.451	1.129	0.933	88	77	13	-18	-33	2.64E-9	2.63E-8	> 1.00E-6
NCI-H226	0.814	2.149	2.034	1.873	1.159	0.634	0.405	91	79	26	-22	-50	3.53E-9	3.45E-8	9.75E-7
NCI-H23	0.591	1.625	1.629	1.580	0.973	0.386	0.298	100	96	37	-35	-50	5.99E-9	3.27E-8	> 1.00E-6
NCI-H322M	0.922	2.264	2.272	2.259	1.785	0.857	0.815	101	100	64	-7	-12	1.59E-8	7.96E-8	> 1.00E-6
NCI-H460	0.221	2.637	2.607	2.375	0.563	0.253	0.201	99	89	14	1	-9	3.33E-9	1.34E-7	> 1.00E-6
NCI-H522	0.555	1.749	1.650	1.613	0.955	0.384	0.286	92	89	33	-31	-49	5.01E-9	3.31E-8	> 1.00E-6
Colon Cancer															
COLO 205	0.519	2.325	2.137	2.117	0.963	0.296	0.233	90	88	25	-43	-55	4.00E-9	2.31E-8	3.80E-7
HCC-2998	0.684	2.073	2.060	1.929	0.885	0.441	0.340	99	90	14	-36	-50	3.36E-9	1.94E-8	9.55E-7
HCT-116	0.160	1.485	1.543	1.526	0.735	0.148	0.137	104	103	43	-8	-14	7.75E-9	7.04E-8	> 1.00E-6
HCT-15	0.206	1.437	1.323	1.310	1.251	0.652	0.242	91	90	85	36	3	5.21E-8	> 1.00E-6	> 1.00E-6
HT29	0.117	0.846	0.854	0.753	0.244	0.096	0.075	101	87	17	-18	-36	3.41E-9	3.06E-8	> 1.00E-6
KM12	0.478	2.753	2.697	2.775	1.471	0.547	0.394	98	101	44	3	-18	7.74E-9	1.40E-7	> 1.00E-6
SW-620	0.242	1.983	2.047	1.875	0.742	0.298	0.254	104	94	29	3	1	4.71E-9	> 1.00E-6	> 1.00E-6
CNS Cancer															
SF-268	0.666	2.100	2.006	1.986	1.318	0.595	0.492	93	92	45	-11	-26	7.99E-9	6.46E-8	> 1.00E-6
SF-295	0.400	2.461	2.259	2.278	1.276	0.434	0.407	90	91	43	2	.	7.02E-9	> 1.00E-6	> 1.00E-6
SF-539	1.236	2.961	2.827	2.672	1.313	0.831	0.647	92	83	4	-33	-48	2.64E-9	1.32E-8	> 1.00E-6
SNB-19	0.626	2.067	1.947	1.847	1.118	0.604	0.585	92	85	34	-4	-7	4.86E-9	8.03E-8	> 1.00E-6
SNB-75	0.970	1.850	1.650	1.738	1.185	0.781	0.033	77	87	24	-19	-97	3.92E-9	3.60E-8	2.49E-7
U251	0.340	1.624	1.642	1.582	0.798	0.287	0.250	101	97	36	-16	-27	5.82E-9	4.94E-8	> 1.00E-6
Melanoma															
LOX IMVI	0.221	1.516	1.467	1.200	0.197	0.041	0.035	96	76	-11	-82	-84	1.97E-9	7.45E-9	3.56E-8
MALME-3M	0.606	1.184	1.163	1.116	0.748	0.516	0.226	96	88	25	-15	-63	3.98E-9	4.18E-8	5.42E-7
M14	0.473	2.102	1.964	1.907	1.307	0.381	0.097	92	88	51	-20	-79	1.04E-8	5.29E-8	3.22E-7
MDA-MB-435	0.477	2.567	2.371	2.406	1.153	0.508	0.122	91	92	32	1	-75	5.07E-9	1.05E-7	4.76E-7
SK-MEL-2	0.810	1.807	1.811	1.747	0.977	0.485	0.315	100	94	17	-40	-61	3.71E-9	1.97E-8	2.96E-7
SK-MEL-28	0.720	1.943	1.860	1.807	1.173	0.599	0.483	93	89	37	-17	-33	5.62E-9	4.87E-8	> 1.00E-6
SK-MEL-5	0.506	2.343	2.299	2.139	1.200	0.344	0.112	98	89	38	-32	-78	5.76E-9	3.47E-8	2.46E-7
UACC-257	0.723	1.504	1.501	1.516	1.140	0.559	0.498	100	102	53	-23	-31	1.11E-8	5.03E-8	> 1.00E-6
UACC-62	0.909	2.759	2.694	2.549	1.797	0.778	0.212	96	89	48	-14	-77	8.94E-9	5.87E-8	3.73E-7
Ovarian Cancer															
IGROV1	0.752	2.272	2.313	2.267	1.352	0.743	0.673	103	100	39	-1	-11	6.68E-9	9.34E-8	> 1.00E-6
OVCAR-3	0.502	1.791	1.913	1.897	0.677	0.494	0.389	109	108	14	-2	-23	4.12E-9	7.74E-8	> 1.00E-6
OVCAR-4	0.859	1.820	1.725	1.716	1.295	0.812	0.750	90	89	45	-6	-13	7.83E-9	7.79E-8	> 1.00E-6
OVCAR-5	0.660	1.556	1.458	1.455	0.984	0.590	0.555	89	89	36	-11	-16	5.45E-9	5.93E-8	> 1.00E-6
OVCAR-8	0.483	1.847	1.845	1.853	1.232	0.401	0.366	100	100	55	-17	-24	1.17E-8	5.79E-8	> 1.00E-6
NCI/ADR-RES	0.538	1.636	1.695	1.661	1.663	1.413	0.679	105	102	102	80	13	2.78E-7	> 1.00E-6	> 1.00E-6
SK-OV-3	0.689	1.690	1.550	1.546	0.898	0.574	0.577	86	86	21	-17	-16	3.55E-9	3.59E-8	> 1.00E-6
Renal Cancer															
786-0	0.780	2.512	2.215	2.222	1.689	0.884	0.651	83	83	52	6	-17	1.13E-8	1.85E-7	> 1.00E-6
A498	1.361	2.067	1.903	1.860	1.595	0.872	0.301	77	71	33	-36	-78	3.56E-9	3.02E-8	2.16E-7
ACHN	0.591	2.161	2.106	2.066	1.559	0.626	0.498	96	94	62	2	-16	1.57E-8	1.33E-7	> 1.00E-6
CAKI-1	0.667	3.138	2.921	2.978	2.914	1.939	0.717	91	94	91	51	2	1.07E-7	> 1.00E-6	> 1.00E-6
RXF 393	1.000	1.899	1.820	1.730	1.381	0.918	0.615	91	81	42	-8	-39	6.37E-9	6.89E-8	> 1.00E-6
SN12C	1.014	3.096	3.005	2.936	1.520	0.911	0.963	96	92	24	-10	-5	4.19E-9	5.06E-8	> 1.00E-6
TK-10	0.422	1.114	1.078	1.045	0.756	0.408	0.361	95	90	48	-3	-14	9.04E-9	8.62E-8	> 1.00E-6
UO-31	0.631	2.072	1.904	1.950	1.793	0.917	0.624	88	92	81	20	-1	3.19E-8	8.78E-7	> 1.00E-6
Prostate Cancer															
PC-3	1.043	2.891	2.882	2.743	1.654	0.897	0.758	99	92	33	-14	-27	5.15E-9	5.04E-8	> 1.00E-6
DU-145	0.390	1.668	1.718	1.673	1.190	0.375	0.284	104	100	63	-4	-27	1.54E-8	8.71E-8	> 1.00E-6
Breast Cancer															
MCF7	0.408	2.211	2.025	2.027	1.015	0.366	0.378	90	90	34	-10	-7	5.12E-9	5.80E-8	> 1.00E-6
MDA-MB-231/ATCC	0.774	1.685	1.731	1.666	1.231	0.731	0.594	105	98	50	-6	-23	1.01E-8	7.93E-8	> 1.00E-6
HS 578T	1.111	2.227	2.161	2.091	1.673	1.144	0.984	94	88	50	3	-11	1.02E-8	1.61E-7	> 1.00E-6
BT-549	1.169	2.348	2.218	2.175	1.452	0.883	0.865	89	85	24	-24	-26	3.76E-9	3.12E-8	> 1.00E-6
MDA-MB-468	0.696	1.419	1.322	1.260	0.741	0.542	0.446	87	78	6	-22	-36	2.45E-9	1.65E-8	> 1.00E-6



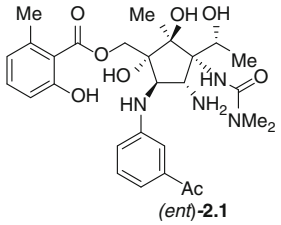
2.42d

Fig. 2.10 NCI-60 screening results for derivative **2.42d**

National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

NSC : D - 778756 / 1	Experiment ID : 1402NS30	Test Type : 08	Units : Molar
Report Date : October 06, 2014	Test Date : February 18, 2014	QNS :	MC :
COMI : JSJ135762 (135762)	Stain Reagent : SRB Dual-Pass Related	SSPL : 0YLQ	

		Log10 Concentration												
	Time	Mean Optical Densities					Percent Growth							
Panel/Cell Line	Zero	Ctrl	-8.0	-7.0	-6.0	-5.0	-4.0	-8.0	-7.0	-6.0	-5.0	-4.0	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.364	1.672	1.564	1.124	0.597	0.321	0.326	92	58	18	-12	-11	1.59E-7	3.99E-6	> 1.00E-4
HL-60(TB)	0.610	1.886	1.927	1.496	0.570	0.477	0.464	103	69	-7	-22	-24	1.80E-7	8.18E-7	> 1.00E-4
K-562	0.133	0.752	0.694	0.448	0.273	0.151	0.135	91	51	23	3	.	1.07E-7	> 1.00E-4	> 1.00E-4
MOLT-4	0.893	2.657	2.321	1.826	1.168	0.833	0.894	81	53	16	-7	.	1.19E-7	.	> 1.00E-4
RPMI-8226	0.676	1.948	1.933	1.251	0.416	0.357	0.358	99	45	-38	-47	-47	8.13E-8	3.47E-7	> 1.00E-4
SR	0.273	0.806	0.759	0.593	0.335	0.266	0.230	91	60	12	-3	-16	1.61E-7	6.44E-6	> 1.00E-4
Non-Small Cell Lung Cancer															
A549/ATCC	0.450	1.923	1.884	1.633	1.042	0.501	0.366	97	80	40	3	-19	5.69E-7	1.43E-5	> 1.00E-4
HOP-62	0.770	1.751	1.641	1.395	0.978	0.572	0.430	89	64	21	-26	-44	2.10E-7	2.83E-6	> 1.00E-4
HOP-92	1.093	1.534	1.496	1.381	1.199	0.974	0.841	91	65	24	-11	-23	2.34E-7	4.88E-6	> 1.00E-4
NCI-H226	0.854	1.587	1.517	1.346	1.021	0.816	0.698	90	67	23	-4	-18	2.42E-7	6.86E-6	> 1.00E-4
NCI-H23	0.556	1.679	1.586	1.343	0.747	0.362	0.286	92	70	17	-35	-49	2.39E-7	2.12E-6	> 1.00E-4
NCI-H322M	0.797	1.891	1.799	1.626	1.132	0.753	0.609	92	76	31	-6	-24	3.72E-7	7.04E-6	> 1.00E-4
NCI-H460	0.268	2.579	2.626	1.646	0.673	0.244	0.173	102	60	18	-9	-35	1.69E-7	4.59E-6	> 1.00E-4
NCI-H522	0.919	2.022	2.023	1.677	1.037	0.602	0.499	100	69	11	-35	-46	2.10E-7	1.72E-6	> 1.00E-4
Colon Cancer															
COLO 205	0.507	1.337	1.282	1.079	0.619	0.268	0.126	93	69	13	-47	-75	2.19E-7	1.67E-6	1.25E-5
HCC-2998	0.609	2.013	1.960	1.522	0.919	0.492	0.383	89	65	22	-19	-37	2.24E-7	3.42E-6	> 1.00E-4
HCT-116	0.237	1.748	1.732	1.328	0.489	0.250	0.173	99	72	17	1	-27	2.51E-7	1.07E-5	> 1.00E-4
HCT-15	0.265	1.664	1.551	1.563	1.179	0.470	0.196	92	93	65	15	-26	2.00E-6	2.28E-5	> 1.00E-4
HT29	0.212	1.169	1.085	0.704	0.343	0.177	0.151	91	51	14	-17	-29	1.09E-7	2.82E-6	> 1.00E-4
KM12	0.483	2.443	2.424	1.916	1.116	0.515	0.349	99	73	32	2	-28	3.68E-7	1.14E-5	> 1.00E-4
SW-620	0.272	1.909	1.945	1.335	0.699	0.339	0.222	102	65	26	4	-19	2.42E-7	1.51E-5	> 1.00E-4
CNS Cancer															
SF-268	0.543	1.924	1.827	1.616	0.991	0.544	0.375	93	78	32	.	-31	4.09E-7	1.01E-5	> 1.00E-4
SF-295	0.850	2.935	2.778	2.342	1.526	0.871	0.543	92	72	32	1	-36	3.55E-7	1.06E-5	> 1.00E-4
SF-539	0.924	2.420	2.304	1.449	0.883	0.619	0.510	92	35	-4	-33	-45	5.48E-8	7.72E-7	> 1.00E-4
SNB-19	0.543	1.855	1.806	1.467	0.917	0.568	0.451	96	70	28	2	-17	3.07E-7	1.26E-5	> 1.00E-4
SNB-75	0.696	1.293	1.230	1.001	0.813	0.480	0.171	89	51	20	-31	-75	1.08E-7	2.43E-6	2.67E-5
U251	0.521	1.918	1.798	1.568	0.976	0.556	0.416	91	75	33	3	-20	3.88E-7	1.29E-5	> 1.00E-4
Melanoma															
LOX IMVI	0.229	1.791	1.541	0.288	0.103	0.070	0.098	84	4	-55	-70	-57	2.65E-8	1.16E-7	8.15E-7
MALME-3M	0.571	1.082	1.038	0.934	0.658	0.442	0.329	91	71	17	-23	-42	2.45E-7	2.69E-6	> 1.00E-4
M14	0.441	1.340	1.283	1.097	0.667	0.229	0.061	94	73	25	-48	-86	3.01E-7	2.20E-6	1.12E-5
MDA-MB-435	0.452	2.033	2.009	1.545	0.895	0.337	0.100	98	69	28	-25	-78	2.92E-7	3.34E-6	2.94E-5
SK-MEL-2	1.184	2.371	2.269	1.844	0.823	0.285	0.249	91	56	-30	-76	-79	1.16E-7	4.42E-7	2.69E-6
SK-MEL-28	0.605	1.703	1.672	1.364	0.839	0.527	0.382	97	69	21	-13	-37	2.51E-7	4.20E-6	> 1.00E-4
SK-MEL-5	0.842	3.000	2.775	2.700	1.364	0.442	0.188	90	86	24	-48	-78	3.83E-7	2.17E-6	1.21E-5
UACC-257	1.119	2.289	2.216	2.183	1.574	1.039	0.794	94	91	39	-7	-29	6.11E-7	6.98E-6	> 1.00E-4
UACC-62	0.838	2.623	2.562	2.239	1.156	0.575	0.273	97	79	18	-31	-67	2.95E-7	2.30E-6	3.27E-5
Ovarian Cancer															
IGROV1	0.641	2.099	2.089	1.698	1.221	0.780	0.517	99	72	40	9	-19	4.87E-7	2.13E-5	> 1.00E-4
OVCAR-3	0.459	1.415	1.162	1.097	0.695	0.405	0.299	74	67	25	-12	-35	2.50E-7	4.76E-6	> 1.00E-4
OVCAR-4	0.536	1.056	1.036	0.896	0.684	0.472	0.330	96	69	28	-12	-39	2.96E-7	5.06E-6	> 1.00E-4
OVCAR-5	0.647	1.703	1.655	1.397	0.980	0.655	0.500	95	71	32	1	-23	3.40E-7	1.08E-5	> 1.00E-4
OVCAR-8	0.612	2.223	2.201	1.838	1.144	0.637	0.479	99	76	33	2	-22	4.03E-7	1.17E-5	> 1.00E-4
NCI/ADR-RES	0.643	2.030	2.049	2.025	1.793	1.097	0.584	101	100	83	33	-9	4.52E-6	6.02E-5	> 1.00E-4
SK-OV-3	0.642	1.106	1.101	0.941	0.787	0.630	0.521	99	64	31	-2	-19	2.71E-7	8.78E-6	> 1.00E-4
Renal Cancer															
786-0	0.602	1.907	1.890	1.497	0.927	0.504	0.307	99	69	25	-16	-49	2.66E-7	4.01E-6	> 1.00E-4
A498	1.389	2.307	2.306	1.784	0.993	0.691	0.675	100	43	-29	-50	-51	7.54E-8	4.00E-7	9.74E-6
ACHN	0.502	1.599	1.550	1.298	0.870	0.517	0.369	96	73	34	1	-27	3.79E-7	1.12E-5	> 1.00E-4
CAKI-1	0.609	1.521	1.452	1.219	0.868	0.516	0.377	92	67	28	-15	-38	2.74E-7	4.47E-6	> 1.00E-4
RXF 393	0.786	1.363	1.233	1.123	0.848	0.526	0.255	78	58	11	-33	-68	1.50E-7	1.75E-6	3.08E-5
SN12C	0.861	2.492	2.336	2.151	1.182	0.715	0.720	90	79	20	-17	-16	3.09E-7	3.44E-6	> 1.00E-4
TK-10	0.870	1.919	1.830	1.630	1.390	0.993	0.680	91	72	50	12	-22	9.53E-7	2.23E-5	> 1.00E-4
UO-31	0.884	2.566	2.345	2.241	1.716	1.128	0.678	87	81	49	14	-23	9.59E-7	2.42E-5	> 1.00E-4
Prostate Cancer															
PC-3	0.565	2.110	2.103	1.624	0.984	0.585	0.453	100	69	27	1	-20	2.80E-7	1.15E-5	> 1.00E-4
DU-145	0.409	1.733	1.687	1.492	1.003	0.485	0.227	97	82	45	6	-44	7.26E-7	1.30E-5	> 1.00E-4
Breast Cancer															
MCF7	0.429	2.297	2.168	1.626	0.775	0.401	0.326	93	64	18	-7	-24	2.04E-7	5.49E-6	> 1.00E-4
HS 578T	0.885	1.782	1.785	1.587	1.220	0.802	0.562	100	78	37	-9	-37	4.89E-7	6.30E-6	> 1.00E-4
BT-549	0.934	1.798	1.654	1.352	0.869	0.689	0.583	83	48	-7	-26	-38	8.96E-8	7.47E-7	> 1.00E-4
MDA-MB-468	0.773	1.706	1.539	1.234	0.670	0.436	0.377	82	49	-13	-44	-51	9.58E-8	6.12E-7	6.90E-5



(ent)-**2.1**

Fig. 2.11 NCI-60 screening results for derivative *ent*-Pactamycin

National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

NSC : D - 778757 / 1	Experiment ID : 1402NS30	Test Type : 08	Units : Molar
Report Date : October 06, 2014	Test Date : February 18, 2014	QNS :	MC :
COMI : JSJ135763 (135763)	Stain Reagent : SRB Dual-Pass Related	SSPL : 0YLQ	

			Log10 Concentration											
	Time		Mean Optical Densities					Percent Growth						
Panel/Cell Line	Zero	Ctrl	-8.3	-7.3	-6.3	-5.3	-4.3	-8.3	-7.3	-6.3	-5.3	-4.3	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.364	1.964	1.871	1.402	0.531	0.359	0.231	94	65	10	-2	-37	9.37E-8	3.74E-6	> 5.00E-5
HL-60(TB)	0.610	1.995	2.005	1.352	0.553	0.521	0.458	101	54	-9	-15	-25	5.70E-8	3.55E-7	> 5.00E-5
K-562	0.133	0.751	0.704	0.405	0.204	0.126	0.118	92	44	11	6	-12	3.75E-8	2.33E-6	> 5.00E-5
MOLT-4	0.893	2.650	2.405	1.946	1.055	0.868	0.549	86	60	9	-3	-39	7.84E-8	2.92E-6	> 5.00E-5
RPMI-8226	0.676	2.037	2.040	1.435	0.466	0.422	0.454	100	56	-31	-38	-33	5.82E-8	2.19E-7	> 5.00E-5
SR	0.273	0.855	0.800	0.550	0.293	0.204	0.195	91	48	3	-25	-29	4.39E-8	6.59E-7	> 5.00E-5
Non-Small Cell Lung Cancer															
A549/ATCC	0.450	1.926	1.836	1.391	0.587	0.348	0.300	94	64	9	-23	-33	8.94E-8	9.76E-7	> 5.00E-5
HOP-62	0.770	1.722	1.631	1.306	0.716	0.386	0.231	90	56	-7	-50	-70	6.29E-8	3.87E-7	5.07E-6
HOP-92	1.093	1.472	1.411	1.295	1.070	0.871	0.529	84	53	-2	-20	-52	5.74E-8	4.57E-7	4.43E-5
NCI-H226	0.854	1.601	1.509	1.415	0.876	0.733	0.723	88	75	3	-14	-15	1.11E-7	7.38E-7	> 5.00E-5
NCI-H23	0.556	1.664	1.579	1.286	0.567	0.312	0.221	92	66	1	-44	-60	8.77E-8	5.25E-7	1.17E-5
NCI-H322M	0.797	1.924	1.888	1.579	0.915	0.718	0.398	97	69	10	-10	-50	1.07E-7	1.63E-6	4.96E-5
NCI-H460	0.268	2.571	2.562	1.439	0.364	0.219	0.055	100	51	4	-18	-79	5.21E-8	7.63E-7	1.64E-5
NCI-H522	0.919	2.040	1.998	1.650	0.839	0.472	0.134	96	65	-9	-49	-85	8.03E-8	3.81E-7	5.43E-6
Colon Cancer															
COLO 205	0.507	1.306	1.221	0.971	0.413	0.119	0.036	89	58	-19	-77	-93	6.37E-8	2.86E-7	1.74E-6
HCC-2998	0.609	2.070	2.060	1.593	0.644	0.317	0.058	99	67	2	-48	-91	9.25E-8	5.58E-7	5.59E-6
HCT-116	0.237	1.699	1.573	1.137	0.274	0.172	0.078	91	62	3	-28	-67	7.85E-8	6.07E-7	1.84E-5
HCT-15	0.265	1.645	1.575	1.430	0.408	0.197	0.158	95	84	10	-26	-41	1.46E-7	9.65E-7	> 5.00E-5
HT29	0.212	1.210	1.150	0.755	0.266	0.092	0.071	94	54	5	-57	-67	6.15E-8	6.10E-7	3.88E-6
KM12	0.483	2.436	2.335	1.766	0.692	0.377	0.009	95	66	11	-22	-98	9.65E-8	1.06E-6	1.16E-5
SW-620	0.272	1.869	1.966	1.379	0.429	0.236	0.019	106	69	10	-13	-93	1.06E-7	1.33E-6	1.44E-5
CNS Cancer															
SF-268	0.543	1.837	1.774	1.555	0.690	0.418	0.348	95	78	11	-23	-36	1.32E-7	1.07E-6	> 5.00E-5
SF-295	0.850	2.908	2.753	2.253	1.137	0.553	0.096	92	68	14	-35	-89	1.08E-7	9.64E-7	9.53E-6
SF-539	0.924	2.433	2.398	1.557	0.709	0.534	0.246	98	42	-23	-42	-73	3.58E-8	2.19E-7	8.86E-6
SNB-19	0.543	1.950	1.892	1.604	0.805	0.559	0.304	96	75	19	1	-44	1.40E-7	5.30E-6	> 5.00E-5
SNB-75	0.696	1.231	1.158	0.922	0.660	0.308	0.189	86	42	-5	-56	-73	3.34E-8	3.88E-7	3.85E-6
U251	0.521	1.843	1.730	1.364	0.665	0.416	0.096	91	64	11	-20	-82	9.11E-8	1.12E-6	1.53E-5
Melanoma															
LOX IMVI	0.229	1.761	1.480	0.259	0.129	0.086	0.038	82	2	-44	-62	-84	1.25E-8	5.51E-8	1.07E-6
MALME-3M	0.571	1.120	1.039	0.927	0.606	0.405	0.219	85	65	6	-29	-62	8.94E-8	7.53E-7	2.20E-5
M14	0.441	1.272	1.205	0.982	0.470	0.129	0.105	92	65	3	-71	-76	8.78E-8	5.56E-7	2.62E-6
MDA-MB-435	0.452	2.028	1.918	0.902	0.510	0.212	0.010	93	29	4	-53	-98	2.32E-8	5.80E-7	4.41E-6
SK-MEL-2	1.184	2.248	2.301	1.853	0.696	0.362	0.246	105	63	-41	-69	-79	6.65E-8	2.01E-7	1.02E-6
SK-MEL-28	0.605	1.717	1.641	1.305	0.627	0.438	0.071	93	63	2	-28	-88	8.15E-8	5.83E-7	1.17E-5
SK-MEL-5	0.842	3.052	2.884	2.581	0.666	0.174	0.037	92	79	-21	-79	-96	9.70E-8	3.08E-7	1.57E-6
UACC-257	1.119	2.154	2.094	2.024	1.078	0.721	0.200	94	87	-4	-36	-82	1.29E-7	4.56E-7	1.02E-5
UACC-62	0.838	2.622	2.549	2.355	0.994	0.590	0.138	96	85	9	-30	-84	1.44E-7	8.45E-7	1.19E-5
Ovarian Cancer															
IGROV1	0.641	2.108	2.090	1.682	0.899	0.622	0.406	99	71	18	-3	-37	1.23E-7	3.59E-6	> 5.00E-5
OVCAR-3	0.459	1.445	1.126	1.033	0.541	0.351	0.224	68	58	8	-24	-51	7.29E-8	9.12E-7	4.53E-5
OVCAR-4	0.536	1.016	0.965	0.847	0.586	0.364	0.310	89	65	10	-32	-42	9.35E-8	8.74E-7	> 5.00E-5
OVCAR-5	0.647	1.749	1.756	1.381	0.713	0.569	0.245	101	67	6	-12	-62	9.40E-8	1.07E-6	2.86E-5
OVCAR-8	0.612	2.104	2.093	1.708	0.701	0.462	0.357	99	73	6	-25	-42	1.11E-7	7.84E-7	> 5.00E-5
NCI/ADR-RES	0.643	2.029	1.984	1.822	1.001	0.562	0.489	97	85	26	-13	-24	1.95E-7	2.35E-6	> 5.00E-5
SK-OV-3	0.642	1.084	1.093	0.731	0.608	0.499	0.237	102	20	-5	-22	-63	2.16E-8	3.07E-7	2.39E-5
Renal Cancer															
786-0	0.602	1.933	1.834	1.474	0.701	0.395	0.184	93	66	7	-34	-69	9.25E-8	7.53E-7	1.39E-5
A498	1.389	2.328	2.216	2.054	0.883	0.632	0.094	88	71	-36	-55	-93	7.81E-8	2.29E-7	2.81E-6
ACHN	0.502	1.610	1.509	1.061	0.454	0.373	0.237	91	50	-10	-26	-53	5.08E-8	3.46E-7	3.92E-5
CAKI-1	0.609	1.519	1.450	1.092	0.623	0.433	0.245	92	53	1	-29	-60	5.72E-8	5.59E-7	2.41E-5
RXF 393	0.786	1.410	1.327	1.129	0.784	0.436	0.246	87	55	.	-45	-69	6.14E-8	4.93E-7	8.37E-6
SN12C	0.861	2.634	2.437	1.993	1.009	0.725	0.544	89	64	8	-16	-37	8.88E-8	1.11E-6	> 5.00E-5
TK-10	0.870	1.852	1.740	1.503	0.933	0.698	0.278	89	64	6	-20	-68	8.88E-8	8.78E-7	2.11E-5
UO-31	0.884	2.577	2.342	1.963	1.110	0.769	0.605	86	64	13	-13	-32	9.36E-8	1.60E-6	> 5.00E-5
Prostate Cancer															
PC-3	0.565	2.042	1.975	1.521	0.636	0.471	0.201	95	65	5	-17	-65	8.80E-8	8.36E-7	2.49E-5
DU-145	0.409	1.665	1.643	1.375	0.601	0.301	0.108	98	77	15	-26	-74	1.37E-7	1.16E-6	1.58E-5
Breast Cancer															
MCF7	0.429	2.246	2.069	1.498	0.515	0.327	0.070	90	59	5	-24	-84	7.28E-8	7.31E-7	1.37E-5
HS 578T	0.885	1.834	1.807	1.582	0.903	0.688	0.543	97	73	2	-22	-39	1.06E-7	5.96E-7	> 5.00E-5
BT-549	0.934	1.757	1.585	1.466	0.791	0.641	0.182	79	65	-15	-31	-81	7.62E-8	3.21E-7	1.20E-5
MDA-MB-468	0.773	1.703	1.544	1.179	0.637	0.383	0.258	83	44	-18	-51	-67	3.44E-8	2.58E-7	4.82E-6

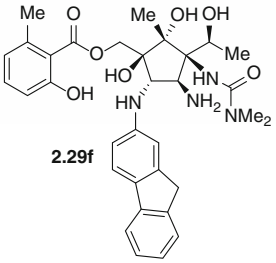


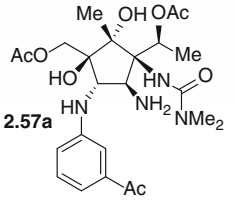
Fig. 2.12 NCI-60 screening results for derivative **2.29f**

National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

NSC : D - 778758 / 1	Experiment ID : 1405RS75	Test Type : 08	Units : Molar
Report Date : October 06, 2014	Test Date : May 05, 2014	QNS :	MC :
COMI : JSJ135764 (135764)	Stain Reagent : SRB Dual-Pass Related	SSPL : 0YLQ	

Log10 Concentration

Panel/Cell Line	Time Zero	Mean Optical Densities Ctrl	-8.3	-7.3	-6.3	-5.3	-4.3	Percent Growth -8.3	-7.3	-6.3	-5.3	-4.3	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.454	2.045	2.013	1.355	0.641	0.494	0.520	98	57	12	3	4	7.02E-8	> 5.00E-5	> 5.00E-5
HL-60(TB)	0.721	3.138	3.060	1.545	0.696	0.647	0.764	97	34	-3	-10	2	2.79E-8	.	> 5.00E-5
K-562	0.310	2.477	2.269	1.397	0.623	0.451	0.403	90	50	14	7	4	5.04E-8	> 5.00E-5	> 5.00E-5
MOLT-4	0.810	3.218	3.057	1.784	1.014	0.901	1.017	93	40	8	4	9	3.30E-8	> 5.00E-5	> 5.00E-5
RPMI-8226	0.887	2.874	2.805	1.730	0.790	0.677	0.643	96	42	-11	-24	-28	3.62E-8	3.11E-7	> 5.00E-5
SR	0.497	2.467	2.226	1.238	0.626	0.627	0.697	88	38	7	7	10	2.83E-8	> 5.00E-5	> 5.00E-5
Non-Small Cell Lung Cancer															
A549/ATCC	0.338	1.892	1.767	1.090	0.463	0.303	0.290	92	48	8	-11	-14	4.59E-8	1.35E-6	> 5.00E-5
EKVX	0.834	2.235	2.225	1.871	1.078	0.785	0.691	99	74	17	-6	-17	1.33E-7	2.78E-6	> 5.00E-5
HOP-62	0.546	1.468	1.343	1.016	0.602	0.447	0.434	86	51	6	-18	-21	5.26E-8	8.86E-7	> 5.00E-5
HOP-92	1.383	1.772	1.690	1.507	1.206	1.017	0.906	79	32	-13	-27	-35	2.05E-8	2.58E-7	> 5.00E-5
NCI-H226	0.814	2.042	1.921	1.269	0.665	0.500	0.389	90	37	-18	-39	-52	2.85E-8	2.33E-7	3.41E-5
NCI-H23	0.591	1.559	1.458	1.025	0.502	0.363	0.342	90	45	-15	-39	-42	3.83E-8	2.79E-7	> 5.00E-5
NCI-H322M	0.922	2.235	2.045	1.571	0.894	0.774	0.656	86	49	-3	-16	-29	4.81E-8	4.37E-7	> 5.00E-5
NCI-H460	0.221	2.679	2.500	1.135	0.354	0.255	0.207	93	37	5	1	-6	2.94E-8	7.52E-6	> 5.00E-5
NCI-H522	0.555	1.874	1.684	1.121	0.468	0.321	0.289	86	43	-16	-42	-48	3.40E-8	2.70E-7	> 5.00E-5
Colon Cancer															
COLO 205	0.519	2.373	2.152	1.130	0.316	0.265	0.257	88	33	-39	-49	-51	2.45E-8	1.43E-7	2.22E-5
HCC-2998	0.684	2.076	1.910	1.098	0.507	0.414	0.358	88	30	-26	-40	-48	2.24E-8	1.71E-7	> 5.00E-5
HCT-116	0.160	1.563	1.412	0.707	0.200	0.168	0.135	89	39	3	1	-16	3.01E-8	5.40E-6	> 5.00E-5
HCT-15	0.206	1.380	1.388	1.299	0.970	0.395	0.158	101	93	65	16	-24	1.02E-6	1.27E-5	> 5.00E-5
HT29	0.117	0.928	0.743	0.268	0.126	0.093	0.054	77	19	1	-21	-54	1.45E-8	5.61E-7	3.82E-5
KM12	0.478	2.704	2.510	1.477	0.683	0.504	0.399	91	45	9	1	-17	3.88E-8	5.80E-6	> 5.00E-5
SW-620	0.242	2.004	1.857	1.166	0.436	0.277	0.191	92	52	11	2	-21	5.72E-8	6.07E-6	> 5.00E-5
CNS Cancer															
SF-268	0.666	2.129	1.963	1.579	0.823	0.590	0.542	89	62	11	-11	-19	8.68E-8	1.52E-6	> 5.00E-5
SF-295	0.400	2.429	2.218	1.442	0.705	0.397	0.391	90	51	15	-1	-2	5.44E-8	4.48E-6	> 5.00E-5
SF-539	1.236	3.031	2.752	1.771	0.991	0.709	0.514	84	30	-20	-43	-58	2.14E-8	1.99E-7	1.46E-5
SNB-19	0.626	2.031	1.893	1.357	0.850	0.600	0.532	90	52	16	-4	-15	5.68E-8	3.10E-6	> 5.00E-5
SNB-75	0.970	1.862	1.652	1.194	0.931	0.528	0.236	77	25	-4	-46	-76	1.64E-8	3.62E-7	6.99E-6
U251	0.340	1.757	1.660	1.250	0.524	0.316	0.273	93	64	13	-7	-20	9.47E-8	2.20E-6	> 5.00E-5
Melanoma															
LOX IMVI	0.221	1.583	1.175	0.176	0.108	0.109	0.139	70	-20	-51	-37	8.33E-9	2.98E-8	.	.
MALME-3M	0.606	1.112	1.043	0.841	0.554	0.439	0.303	86	46	-9	-28	-50	4.08E-8	3.49E-7	4.96E-5
M14	0.473	1.975	1.852	1.324	0.569	0.142	0.152	92	57	6	-70	-68	6.78E-8	6.06E-7	2.74E-6
MDA-MB-435	0.477	2.569	2.336	1.370	0.520	0.280	0.081	89	43	2	-41	-83	3.47E-8	5.57E-7	8.08E-6
SK-MEL-2	0.810	1.868	1.838	1.234	0.512	0.307	0.315	97	40	-37	-62	-61	3.35E-8	1.66E-7	1.66E-6
SK-MEL-28	0.720	1.961	1.848	1.380	0.730	0.556	0.488	91	53	1	-23	-32	5.74E-8	5.41E-7	> 5.00E-5
SK-MEL-5	0.506	2.314	2.059	1.322	0.394	0.146	0.082	86	45	-22	-71	-84	3.80E-8	2.34E-7	1.85E-6
UACC-257	0.723	1.571	1.488	1.161	0.673	0.527	0.470	90	52	-7	-27	-35	5.33E-8	3.81E-7	> 5.00E-5
UACC-62	0.909	2.709	2.587	2.091	0.956	0.479	0.216	93	66	3	-47	-76	8.85E-8	5.63E-7	6.20E-6
Ovarian Cancer															
IGROV1	0.752	2.149	2.065	1.587	0.850	0.646	0.533	94	60	7	-14	-29	7.66E-8	1.07E-6	> 5.00E-5
OVCAR-3	0.502	1.825	1.773	1.180	0.614	0.473	0.434	96	51	8	-6	-14	5.34E-8	1.96E-6	> 5.00E-5
OVCAR-4	0.859	1.780	1.671	1.228	0.882	0.733	0.697	88	40	2	-15	-19	3.10E-8	6.99E-7	> 5.00E-5
OVCAR-5	0.660	1.619	1.603	1.251	0.771	0.575	0.525	98	62	12	-13	-21	8.54E-8	1.49E-6	> 5.00E-5
OVCAR-8	0.483	1.908	1.849	1.188	0.550	0.409	0.370	96	49	5	-15	-23	4.86E-8	8.56E-7	> 5.00E-5
NCI/ADR-RES	0.538	1.684	1.653	1.634	1.501	0.984	0.536	97	96	84	39	.	2.83E-6	4.87E-5	> 5.00E-5
SK-OV-3	0.689	1.775	1.693	1.099	0.824	0.642	0.617	92	38	12	-7	-10	2.98E-8	2.21E-6	> 5.00E-5
Renal Cancer															
786-0	0.780	2.548	2.337	1.902	1.372	0.778	0.612	88	63	33	.	-22	1.40E-7	4.89E-6	> 5.00E-5
A498	1.361	2.123	1.839	1.687	1.182	0.852	0.473	63	43	-13	-37	-65	2.16E-8	2.91E-7	1.42E-5
ACHN	0.591	2.140	1.998	1.505	0.785	0.523	0.474	91	59	13	-12	-20	7.81E-8	1.66E-6	> 5.00E-5
CAKI-1	0.667	3.146	3.068	2.923	2.408	0.924	0.598	97	91	70	10	-10	1.09E-6	1.58E-5	> 5.00E-5
RXF 393	1.000	1.858	1.715	1.473	0.958	0.659	0.504	83	55	-4	-34	-50	6.10E-8	4.25E-7	> 5.00E-5
SN12C	1.014	3.138	2.977	2.078	1.225	0.982	0.940	92	50	10	-3	-7	5.02E-8	2.85E-6	> 5.00E-5
TK-10	0.422	1.222	1.133	0.941	0.575	0.398	0.320	89	65	19	-6	-24	1.05E-7	2.92E-6	> 5.00E-5
UO-31	0.631	1.951	1.782	1.683	1.168	0.679	0.441	87	80	41	4	-30	2.89E-7	6.40E-6	> 5.00E-5
Prostate Cancer															
PC-3	1.043	2.745	2.660	1.724	0.962	0.795	0.760	95	40	-8	-24	-27	3.29E-8	3.44E-7	> 5.00E-5
DU-145	0.390	1.631	1.543	0.905	0.433	0.349	0.319	93	41	3	-11	-18	3.41E-8	8.80E-7	> 5.00E-5
Breast Cancer															
MCF7	0.408	2.350	2.275	1.541	0.559	0.375	0.322	96	58	8	-8	-21	7.31E-8	1.55E-6	> 5.00E-5
MDA-MB-231/ATCC	0.774	1.570	1.551	1.247	0.748	0.540	0.526	98	59	-3	-30	-32	7.07E-8	4.42E-7	> 5.00E-5
HS 578T	1.111	2.213	2.056	1.827	1.147	0.978	0.883	86	65	3	-12	-21	8.74E-8	8.19E-7	> 5.00E-5
BT-549	1.169	2.420	2.389	1.745	1.035	0.871	0.818	98	46	-12	-25	-30	4.19E-8	3.16E-7	> 5.00E-5
MDA-MB-468	0.696	1.295	1.175	0.803	0.507	0.384	0.368	80	18	-27	-45	-47	1.51E-8	1.24E-7	> 5.00E-5



2.57a

Fig. 2.13 NCI-60 screening results for derivative **2.57a**

Table 2.8 Physical Characteristics of 80 × 320 nm PRINT-Therapeutic NPs as Measured by DLS and ζ-Potential

NP containing therapeutic#	Hydrodynamic size (nm)	Polydisdersity Index	Zetapotential (mV)	Drug Loading (wt%)
1	253 ± 8	0.07 ± 0.02	−9	10
2.29e	262 ± 5	0.09 ± 0.02	−9	9
2.42dc	243 ± 2	0.09 ± 0.02	−9	9

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51. See Table 2.8 in Section 2.5 of this Chapter
52. See Figure 2.8 in Section 2.5 of this Chapter

Chapter 3
Inception and Development of a Global and Local Desymmetrization Approach to the Synthesis of Steroidal Alkaloids: Stereocontrolled Total Synthesis of Paspaline

3.1 Introduction

The total synthesis of terpene alkaloid natural products has received significant attention from the synthetic community in the last half-century. In recent years, however, synthetic interest in these targets has been reignited, in no small part due to the continued discovery of natural molecules bearing deviations from the classical steroid architecture. These findings have challenged the organic chemist toward new innovations in the preparation of these molecules. In this final chapter, we detail the design and implementation of a series of new synthetic disconnetions in the arena of terpene alkaloid synthesis, specifically applied to the total synthesis of paspaline. These studies culminated in the further application of symmetry-breaking techniques (both "global" and "local") in the rapid assembly of stereochemical information, providing the title compound with exceptional stereochemical fidelity.

3.2 Background

3.2.1 Historical Perspective on Ergot Alkaloids

Production of novel metabolites by the ergot fungus has been well-documented [1]. Most notably, those produced by *Claviceps purpurea* have long been implicated in the contamination of various grains [2]. *Claviceps paspali*, another species in this genus, has been linked to "paspalum stagger" poisoning, most commonly in livestock [3–7]. This infection is typically marked by sustained tremors,

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Robert J. Sharpe, *Stereoselective Desymmetrization Methods in the Assembly of Complex Natural Molecules*, Springer Theses,
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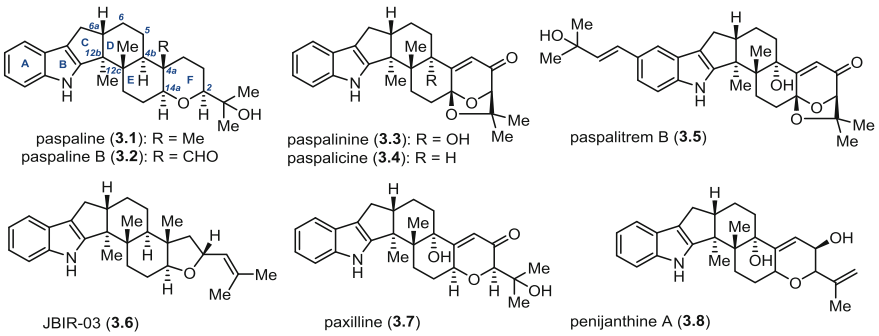


Fig. 3.1 Paspaline and related indole diterpenoid natural products

discoordination, limb weakness, and severe convulsions, which may ultimately result in death. Near the middle of the twentieth century, the source of these toxins was identified in a series of alkaloid small molecules [8–10]. Among these compounds were the tremorgenic indole diterpenoid family of structures (Fig. 3.1).

Arigoni and co-workers first reported the isolation of paspaline (**3.1**) and paspalicine (**3.4**) in 1966 [8–10], the first of what has become an extensive family of natural products. Since this initial report, the related structures including paspaline B (**3.2**) [11], paspalinine (**3.3**) [12, 13], JBIR-03 (**3.6**) [14], paxilline (**3.7**) [15, 16], and others have also been reported [17, 18].

The varied biological profiles of these compounds have rendered them particularly attractive targets. The recently discovered JBIR-03 has displayed significant inhibition of *V. ceratosperma* (MIC = 128 μg/mL) while showing no cytotoxic effects to the human fibrosarcoma cell line HT-1080 at 100 μM [14]. Moreover, paspalinine and its derivatives have demonstrated marked activity as Maxi-K channel antagonists, and as a result, are under examination as treatments for Alzheimer's disease and other neurological disorders [19–21]. Paxilline is currently under study for its properties as a BK-channel antagonist toward the suppression of seizures in postnatal mammals [22]. From a standpoint of structure-activity, prior work by Cole has underscored the significance of the axial *tert*-hydroxyl functionality (C4b, paspaline numbering) as an important source of activity for these structures, evidenced by the lack of tremorgenicity demonstrated by paspaline and paspalicine [23, 24].

3.2.2 *Structure Analysis and Biosynthetic Proposal for Paspaline*

The absolute structure of **3.1** was confirmed in 1980 by Springer and Clardy on the basis of X-ray diffraction studies [23]. Paspaline and its related compounds are characterized principally by their unique departures from the classical steroid

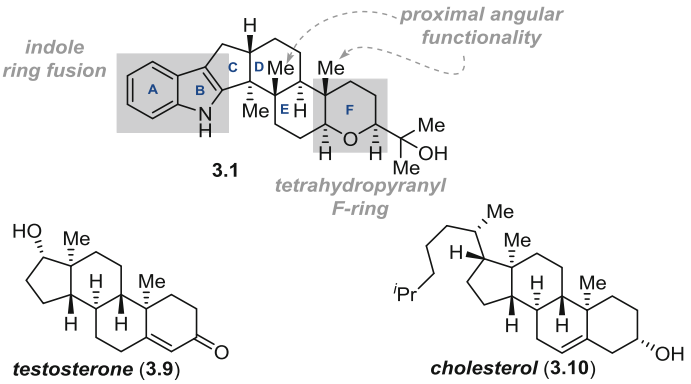


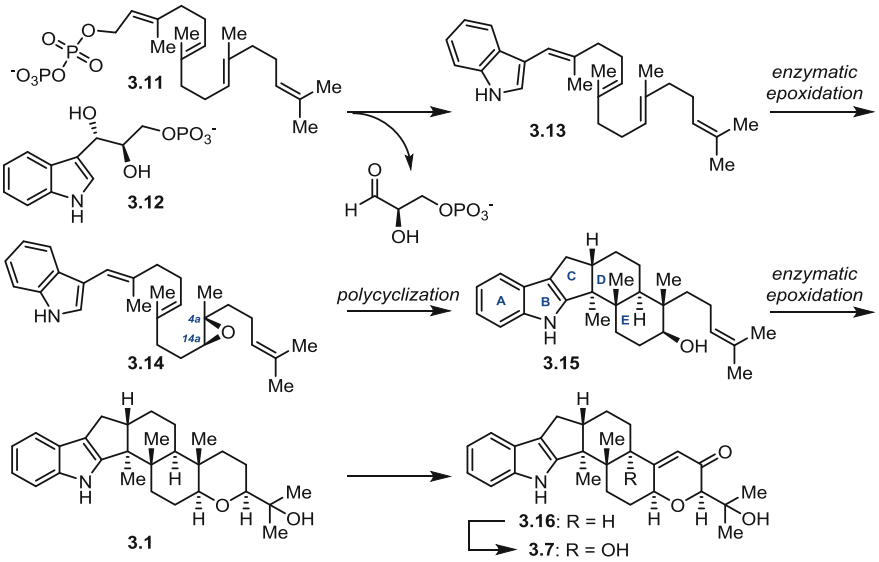
Fig. 3.2 Divergence of paspaline from classical steroidal structures

architecture; these features are contrasted with the archetypal steroid motif in Fig. 3.2. While the core 6,6,6,5 ring system is retained in **3.1**, the presence of a fused indole functional group (A,B rings) replaces the more standard oxygenation pattern observed in steroids such as testosterone (**3.9**) and cholesterol (**3.10**). Additional oxygenation is present in the terminal 6-ring in the form of a tetrahydropyran (or derivatives thereof). Furthermore, grafted onto the D/E decalin core one encounters three all-carbon quaternary carbons. This so-called "angular functionality," while non-distinct from classical steroid architecture, is of note due to its proximal arrangement in paspaline, particularly the vicinal C12b, C12c methyl groups and the *syn*-diaxial C12c, C4a methyl groups.

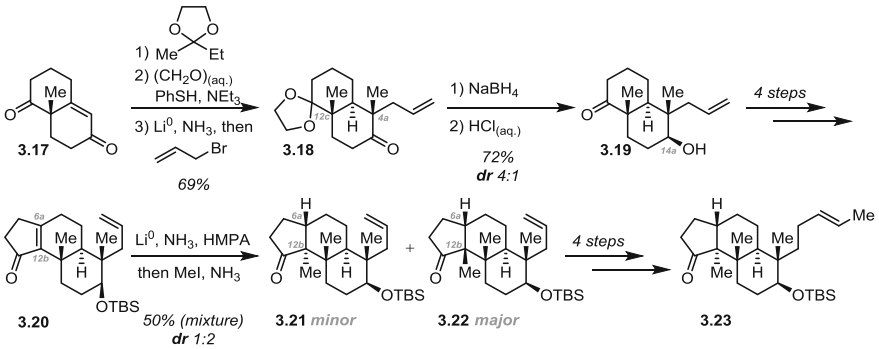
The biosynthesis for paspaline was first proposed by Arigoni in 1977 [25] and has since been confirmed by Hull and Oikawa (Scheme 3.1) [26, 27]. Synthesis of **3.1** arises from building blocks geranylgeranyl diphosphate (GGDP, 3.11) and indole phosphate 3.12 [28]. A prenyltransferase enzyme facilitates the union of **3.11** and **3.12** to install the needed carbon skeleton. Stereoselective epoxidation of the C4a, C14a double bond in **3.13** and subsequent polycyclization ensues to construct rings A–E, and a second epoxidation/etherification sequence affords paspaline. **3.1** is also a biosynthetic intermediate to a number of its related structures including paxilline (**3.7**) as illustrated [28]. While an approach such as this one would be challenging in a laboratory setting, this synthesis provides insight into how nature addresses the preparation of the indole, tetrahydropyran, and angular methyl groups.

3.2.3 Smith Synthesis of Paspaline

The salient features of **3.1** necessitate careful planning for endeavors in total synthesis; outside of significant contributions from the Smith laboratory [29–37],



Scheme 3.1 Biosynthetic pathway for paspaline



Scheme 3.2 Smith synthesis of paspaline: angular methyl group installation

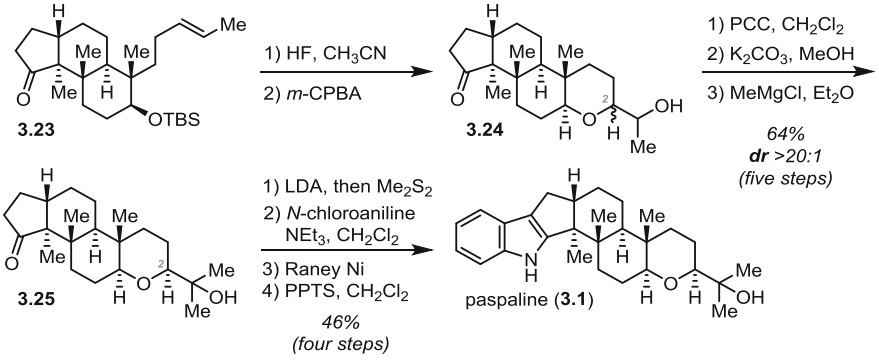
whose thirty-year research program in this field has defined the state of the art for this class of molecule, synthetic interest in this subset of alkaloids has been limited [38–49][1]. Smith's twenty-three-step synthesis of **3.1**, the single published total synthesis of paspaline prior to our work, was reported in 1985 [29]. His approach to the core stereochemistry is described in Scheme 3.2. Beginning from Wieland-Miescher ketone **3.17**, ketalization, thiomethylation, and reductive alkylation installed the C4a, C12c diaxyl methyl groups in 69 % yield (**3.18**). Reduction of the

[1]Partial and total synthetic studies on terpene alkaloids.

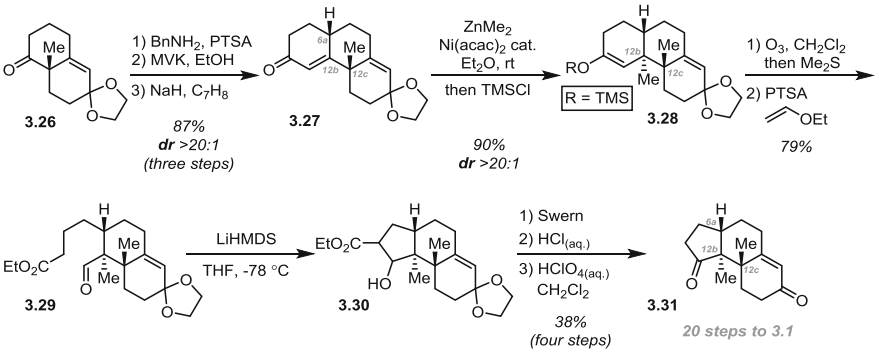
ketone in **3.18** with preferential hydride approach opposite the C12c and C4a axial methyl groups delivered alcohol **3.19** in 72 % yield and 4:1 dr following removal of the dioxolane protecting group. A four-step sequence provided access to enone **3.20**. As the centerpiece to their strategy, Smith envisioned stereoselective reductive alkylation of the enone to give the desired *trans*-hydrindanone **3.21**. However, treatment of **3.20** with Li^0, NH_3, and MeI furnished exclusively the undesired *cis* adduct **3.22** in 50 % yield. An extensive screen of conditions for this reaction resulted in only marginal improvement in diastereoselectivity as modification of the reaction temperature and order of addition of the enolate furnished a 50 % yield of the diastereomeric ketones with the desired isomer **3.21** isolated in 17 % yield. The allyl group was then extended in a four-step sequence to provide advanced ketone intermediate **3.23** poised for synthesis completion.

From ketone **3.23**, two challenges remained: (i) installation of the tetrahydropyran and C2 stereocenter, and (ii) incorporation of the indole moiety (Scheme 3.3). Toward this goal, Smith elected to perform a nonstereoselective epoxidation on alkene **3.23**, which upon silyl deprotection and ring closure gave the secondary alcohol **3.24**. Oxidation of the alcohol provided a configurationally-labile C2 methine proton, wherein base mediated epimerization installed the final stereocenter in **3.1**. Addition of a methyl nucleophile gave tertiary alcohol **3.25** in 64 % over five steps. While at first a Fisher indolization of ketone **3.25** to paspaline seemed obvious, this indolization proved to be a significant issue in synthesis completion, primarily due to the steric encumbrance associated with the ketone in **3.25** (a problem that will be further elaborated upon in Sect. 3.3.20) [32]. Ultimately, the Gassman four-step indolization protocol proved successful in incorporating the indole moiety and completing their synthesis [50].

In a second generation approach, Smith looked to circumvent the problematic reductive alkylation protocol (**3.20** → **3.21**) [30, 31]. Beginning from dioxolane **3.26**, Robinson annulation delivered enone **3.27** with complete control of the C6a stereocenter (Scheme 3.4). This set the stage for an alternative reductive alkylation in which electrophile approach was projected to occur opposite the C12c angular



Scheme 3.3 Smith synthesis of paspaline: tetrahydropyran and indole synthesis



Scheme 3.4 Second generation approach to paspaline and C12b stereocenter

methyl group. Treatment of enone **3.27** with $ZnMe_2$ and $Ni(acac)_2$ followed by trapping with TMSCl afforded enol-silane **3.28** with complete selectivity for the desired *trans*-fused bicycle in 90 % yield. The cyclohexene was then cleaved via ozonolysis, which after esterification and intramolecular aldol cyclization, gave alcohol **3.30**. Oxidation of the alcohol, elimination of the ester, and cleavage of the dioxolane gave diketone **3.31** in 38 % yield from **3.29**. Diketone **3.31** is converted to paspaline in twenty steps using the previously described route [33]. In addition, Smith demonstrated the applicability of **3.31** as a common intermediate in the synthesis of diterpenoids paspalinine and paspalicine.

In summary, the Smith work illustrates marked creativity in the midst of a highly rigid chemical environment but also highlights the major challenges we were led to anticipate at the genesis of our endeavors. Namely, stereocontrolled incorporation of the three angular methyl groups and the tetrahydropyranyl D-ring would require a well-designed approach in which the 3-D environment of each synthetic intermediate is carefully planned and manipulated.

3.2.4 Desymmetrization Analysis for Paspaline

Following our successful use of symmetry-breaking transformations applied to the pactamycin problem (described in Chap. 1) [51, 52], we identified paspaline and its family of compounds for further investigation in this area (Fig. 3.3). Specifically, we noted the applicability of stereoselective desymmetrizations in the remote stereocontrol of highly congested quaternary atoms. In the symmetry-breaking transformation used for pactamycin (**3.32** → **3.33**), a diketone monoreduction was employed. This reaction established the identity of the C7 secondary alcohol with indirect stereochemical assignment of the C1 fully-substituted carbon. As applied to paspaline, we envisioned that this mode of stereocontrol could be employed to quaternary carbons C12b and C4a via the manifolds of ketone reduction and C–H

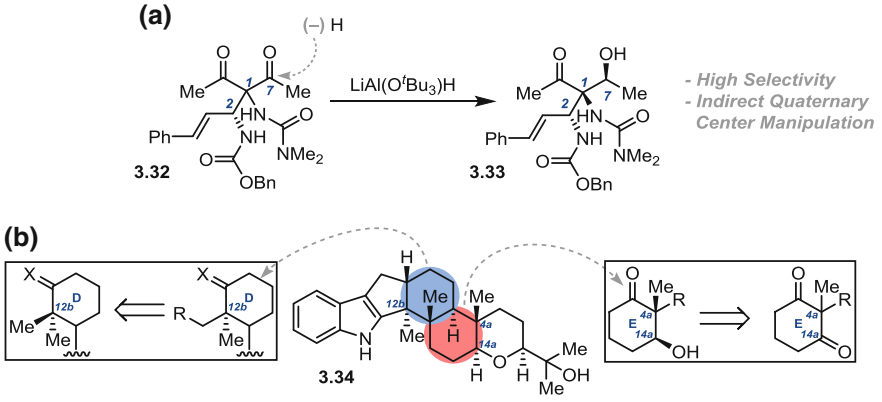


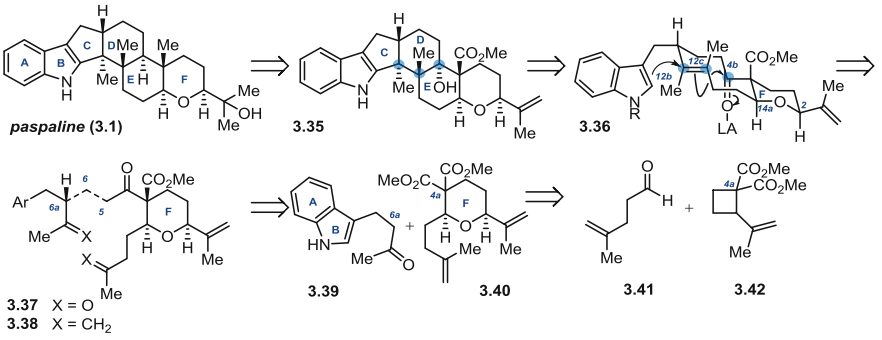
Fig. 3.3 Desymmetrization applied to pactamycin and paspaline. **a** Pactamycin desymmetrization. **b** Theoretical desymmetrization possibilities for paspaline

activation (**3.34**). It is important to note, however, that while this synthetic analysis proved fruitful in the end, it was not the strategy we envisioned for paspaline at the outset. The discussion that follows details chronologically the foundation and evolution of this approach in route to a highly stereocontrolled preparation of paspaline and its core architecture.

3.3 Results and Discussion

3.3.1 Transannular Cyclization Strategy

Our preliminary synthetic plan for paspaline identified the C,D,E ring fusion as the product of a complex transannular cyclization (Scheme 3.5) [53, 54]. Accordingly,

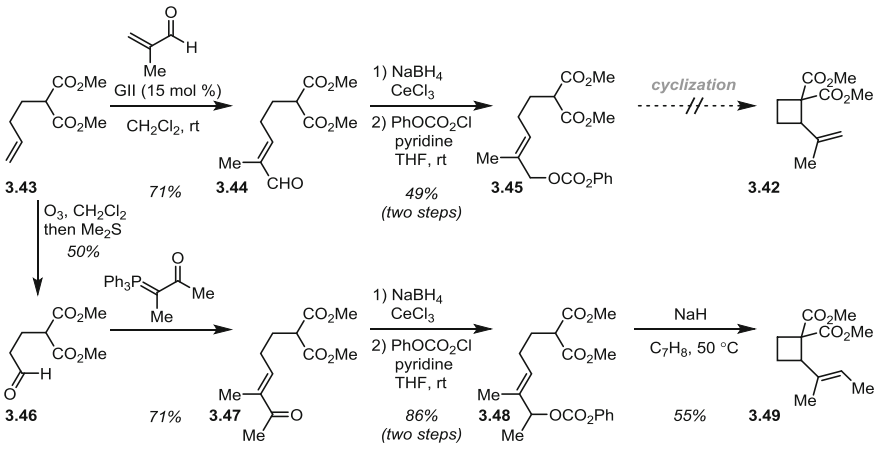


Scheme 3.5 Initial retrosynthetic analysis for paspaline

we envisioned simplification of **3.1** to hydroxyalkene **3.35**. This intermediate could arise from a Lewis acid mediated cyclization of cyclodecenone **3.36**, establishing the vicinal C12b, C12c quaternary centers in a single operation. Enone **3.36** presented a particularly stimulating challenge in that stereoselective construction of *trans*-tetrasubstituted alkene within a ten-membered ring would be required. At the outset, we proposed that this alkene could be prepared via a complex ring-closing metathesis from diene **3.38** [55, 56] or McMurry coupling reaction from dicarbonyl **3.37** [57], both of which would provide avenues for new methods development. Synthesis of this ketone would rely on the union of fragments **3.39** and **3.40** to assemble the C6a, C6, and C5 carbon carbon bonds. This left only preparation of pyran **3.40**, for which we initially hoped to construct via a Lewis acid catalyzed donor-acceptor cyclobutane annulation according to chemistry previously developed in our laboratory [58].

3.3.2 Donor-Acceptor Cyclobutane Annulation Studies

Initial focus was placed on probing the feasibility of uniting the known aldehyde **3.41** [59] and cyclobutane **3.42** (Scheme 3.6). Prior art suggested that vinyl cyclobutane **3.42** could be prepared via S_N2' cyclization of the appropriately-selected allylic electrophile [60]. Accordingly, cross metathesis of alkene **3.43** with methacrolein proceeded in 71 % yield. Reduction of the resulting aldehyde **3.44** and acylation afforded carbonate **3.45** in 49 % yield over the two-step sequence. However, upon subjection of **3.45** to a variety of basic conditions, only starting material recovery or decomposition was observed. It seems reasonable that this poor reactivity is the result of an undesirable conversion of trisubstituted alkene

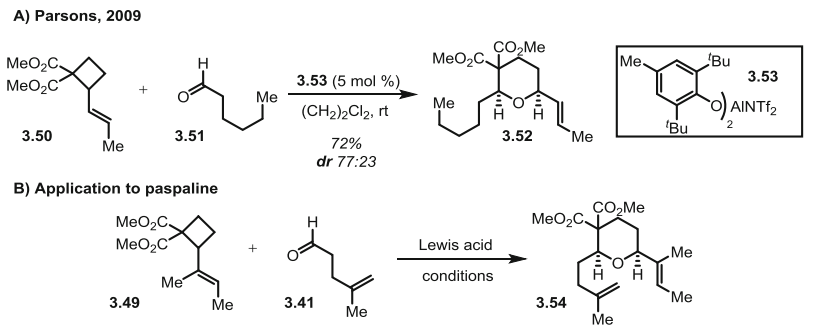


Scheme 3.6 Synthesis of cyclobutane [4 + 2] annulation precursor

3.45 to a less substituted form; consequently, we set out to prepare cyclobutane **3.49**, which was also viable in our synthetic approach and would obviate the alkene substitution problem. Carbonate **3.48** was prepared in three steps in a manner similar to **3.45**. Gratifyingly, subjection of the secondary carbonate **3.48** to NaH in C_7H_8 furnished cyclobutane **3.49** in 55 % yield.

With both coupling partners in hand, we began screening conditions for our proposed cycloaddition (Table 3.1). Previous work in our laboratory had demonstrated the applicability of strained ring cycloadditions to stereoselective tetrahydropyran synthesis [58]. Specifically, vinyl cyclobutane **3.50** was reacted with aliphatic aldehyde **3.51** using catalytic $MADNTf_2$ [61] (**3.53**) to give pyran **3.52** in 72 % yield and 77:23 dr. When we applied these conditions to aldehyde **3.41** and our prepared cyclobutane **3.49**, we were disappointed to observe only decomposition of the cyclobutane and recovery of the aldehyde. Screening other Lewis acids such as $Sc(OTf)_3$ and $Hf(OTf)_2$ resulted in complex mixtures or decomposition of **3.49**. In a final case, we employed the conditions used in our previously reported annulation of cyclopropanes and aldehydes ($Sn(OTf)_2$, MgI_2(pybox)) [62, 63]; however, these reactions also failed to provide any amounts of **3.54**. In light of the observed instability of **3.49** to the reaction conditions examined, we began to doubt the applicability of this protocol in our synthesis and proceeded to evaluate contingency plans with which to prepare pyran **3.40**.

Table 3.1 Summary of attempted strained ring cycloaddition for paspaline



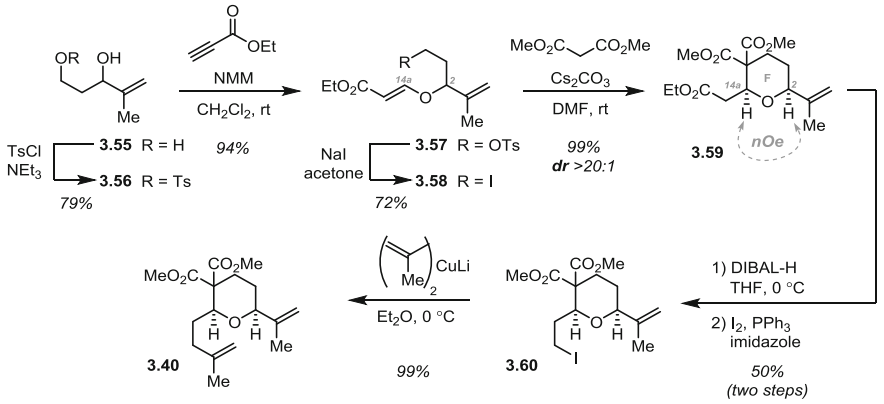
Lewis acid (mol%)	Conditions	Result
$MADNTf_2$ (5)	$(CH_2)_2Cl_2$, rt	Decomposition of **3.49**
$MADNTf_2$ (20)	CH_2Cl_2, rt	Decomposition of **3.49**
$Sc(OTf)_3$ (20)	CH_2Cl_2, rt	Complex mixture
$Hf(OTf)_4$ (20)	CH_2Cl_2, rt	Decomposition of **3.49**
$Sn(OTf)_2$ (20)	$(CH_2)_2Cl_2$, rt	Complex mixture
MgI_2(pybox) (10)	CCl_4, rt	No reaction

3.3.3 Tetrahydropyran Synthesis via Tandem Alkylation/Michael Addition

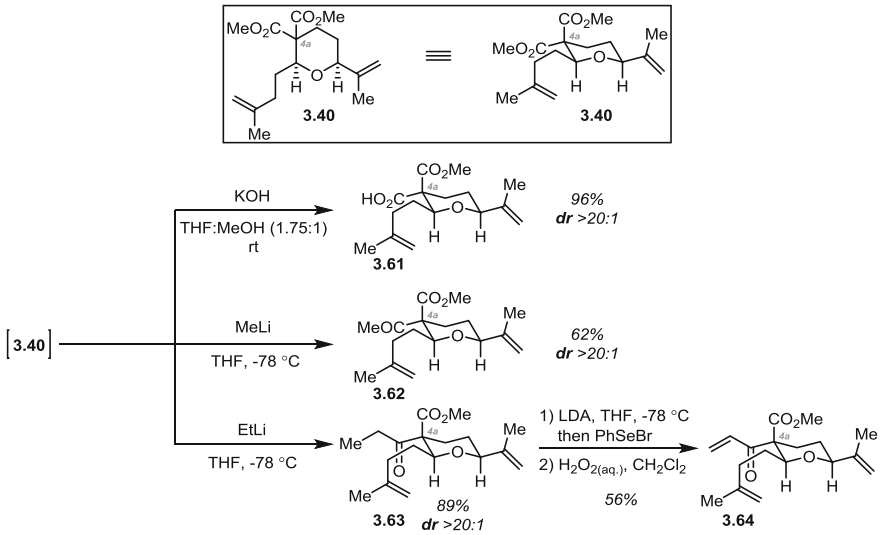
A survey of the literature led to the identification of a protocol by Gharpure for stereoselective tetrahydropyran synthesis derived from malonates and vinylogous esters bearing a tethered primary iodide [64]; a tandem alkylation/Michael addition reaction provided products bearing exactly the substitution pattern needed for our synthetic strategy, although our required substrate was not reported (Scheme 3.7). In our hands, tosylation of diol **3.55** proceeded uneventfully (79 % yield) [65], and a subsequent oxy-Michael addition reaction gave vinyl ether **3.57**. Iodination of the tosylate gave the key precursor **3.58** in 72 % yield, and subjection of this material to Gharpure's conditions (dimethylmalonate, Cs_2CO_3) furnished pyran **3.59** in 99 % yield and >20:1 dr, completing F-ring synthesis for **3.1**. The desired *cis*-pyran configuration was confirmed on the basis of nOesy analysis. To intercept intermediate **3.40** required for our strategy, the ethyl ester in **3.59** was selectively reduced with DIBAL-H, giving thence the iodide **3.60** upon treatment with I_2 and PPh_3. Finally, alkylation of the iodide **3.60** was accomplished upon treatment with $(isopropenyl)_2CuLi$ to give diene **3.40** in 99 % yield.

3.3.4 Access to the C4a Stereocenter

With pyran **3.40** in our possession, we sought to further elaborate the available functional handles towards preparation of cyclodecenone **3.36**. Access to the C4a stereocenter was envisioned via desymmetrization of the *gem*-diester (Scheme 3.8). Previous work by Deslongchamps had shown that equatorial-selective manipulations of cyclohexane diesters were feasible [66]; in our system, this selectivity



Scheme 3.7 Tandem alkylation/cyclization approach to tetrahydropyran synthesis



Scheme 3.8 Desymmetrization of the C14a stereocenter

would deliver exactly the relative configuration needed for synthesis completion. In a first trial, monohydrolysis of **3.40** (KOH, THF:MeOH) gave exclusively the carboxylic acid diastereomer **3.61** in 96 % yield (as determined by nOesy analysis). Anticipating that this selectivity might be general for other addition reactions, we next examined incorporation of carbon nucleophiles. Toward this aim, careful addition of MeLi to **3.40** also proceeded with complete stereoselectivity to give methyl ketone **3.62** in 62 % yield. In a final case, **3.40** was treated with EtLi, giving the ethyl ketone **3.63** in 89 % yield and >20:1 dr. This compound provided entry into a valuable unsaturated ketone handle **3.64** via α-selenide addition/elimination. Since an approach could be devised for synthesis completion using any of the three illustrated products, we envisioned these compounds would give us maximum flexibility in construction of the remaining carbon skeleton of **3.1**.

3.3.5 Indole/Pyran Fragment Coupling: A Non-trivial Operation

With the pyran stereochemistry in place, the next challenge was assembly of the C5/C6/C6a carbon skeleton concomitant with incorporation of the indole fragment. This transformation could take many forms depending on the identities of the reactive functional groups employed on both the pyran and indole segments However; we found this union to be a significantly greater challenge than first expected. A brief summary of these screenings is given in Fig. 3.4 (see Sect. 3.5 for

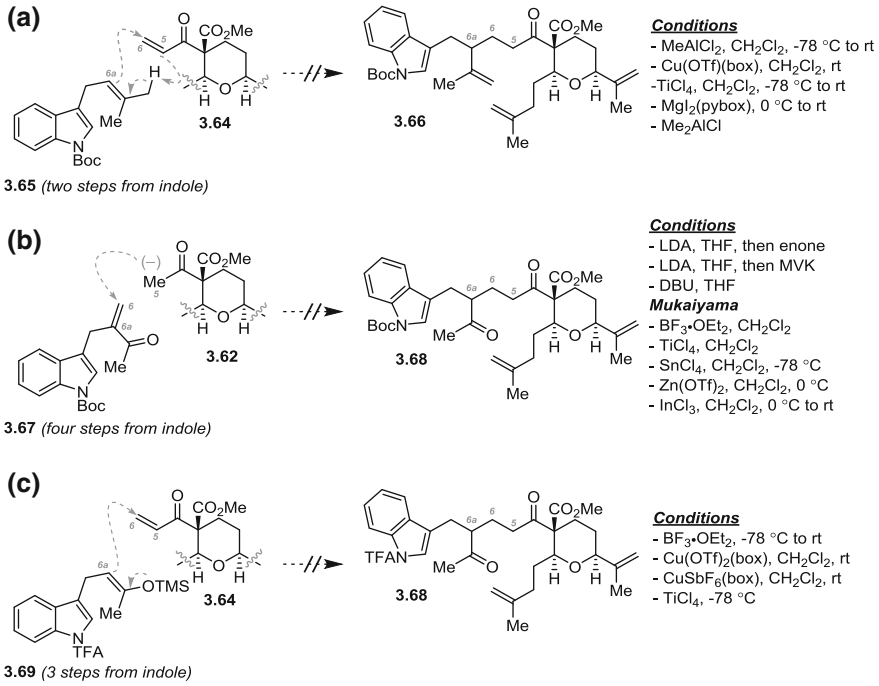


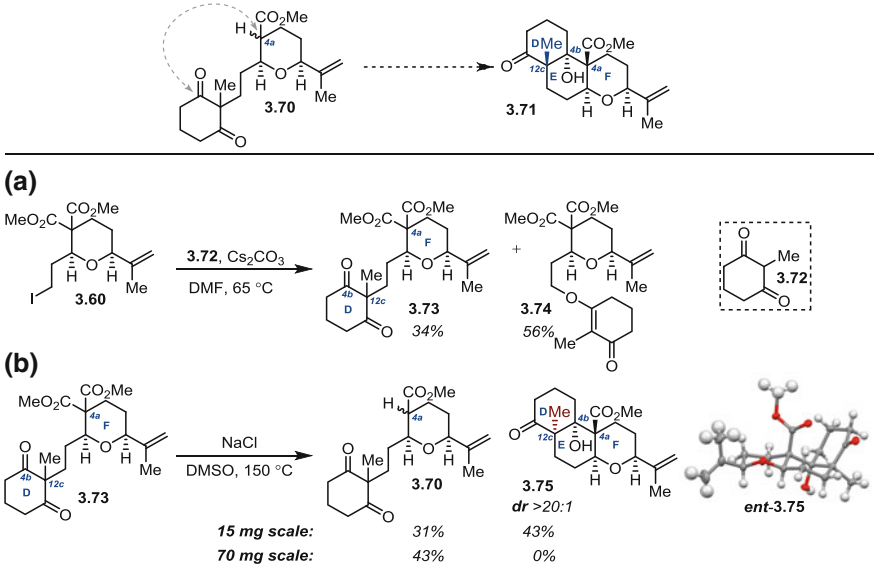
Fig. 3.4 Attempts at coupling of the indole and pyran fragments. **a** One coupling. **b** (Mukaiyama) Michael addition. **c** Mukaiyama Michael—reveresed polarity

synthesis of the indole fragments). At the outset, we envisioned a stereocontrolled ene reaction of unsaturated ketone **3.64** and prenylated indole **3.65**. Unfortunately, this approach failed to deliver triene **3.66** as strong Lewis acids such as $MeAlCl_2$ and $TiCl_4$ quickly resulted in decomposition of enone **3.64**. Milder Lewis acids gave only starting material recovery. In our first contingency, we attempted the reaction of methyl ketone **3.62** and indole enone **3.67** via a Michael addition reaction. This addition could occur either via an anionic pathway or under Mukaiyama conditions using the enol-silane of **3.62**; however, enone **3.67** lacked sufficient reactivity to interact with the enolate of **3.62** under any basic conditions examined as only recovered starting material was observed in all cases. Notably, ketone **3.62** was unreactive to methyl vinyl ketone under basic conditions during a model study. Mukaiyama conditions also failed to produce sufficient reactivity, primarily due to premature deprotection of the enol-silane of **3.62**. A final contingency examined the reversal of nucleophile and electrophile identities in a Mukaiyama addition of enol-silane **3.69** to the enone **3.64**. This approach, perhaps expectedly, was also met with failure due to the previously described instability of enone **3.64** to acidic conditions and premature deprotection of enol-silane **3.69**. Collectively, these failed efforts led us to conclude that direct intermolecular coupling methodologies of these fragments to **3.1** from the C4a functionality were

prohibitively challenging. Furthermore, the inability to access diene **3.38** or diketone **3.37** thus far had prevented us from even attempting the critical cyclodecenone synthesis (**3.36**). Concluding that the route in its current formed lacked feasibility, this approach was abandoned.

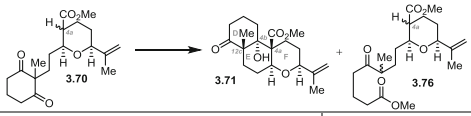
3.3.6 *Decarboxylative Annulation Approach to D,E Rings*

In an effort to circumvent the issues associated with the above strategy, we postulated that an intramolecular approach to the critical bond disconnection might be more facile (Scheme 3.9). This process would be enabled via appendage of the appropriate functionality to the iodide **3.60.** We selected 2-methyl-1,3-cyclohexanedione **3.72** as this nucleophile anticipating that an intramolecular aldol addition process might result from Krapcho product **3.70** to assemble the D,E-ring decalin moiety in **3.1** as well as the C12c and C4b stereocenters (**3.71**). In practice, alkylation of iodide **3.60** with **3.72** gave a ~1:2 mixture of diketone **3.73** and the undesired *O*-alkylation product **3.74** in 34 and 56 % yields, respectively. While this issue of regiochemistry rendered material throughput challenging, we carried on in the interest of validating the proposed downstream reactivity. Operating first on small scale (15 mg), treatment of diketone **3.73** with NaCl in DMSO afforded a ~1:1 ratio of the diastereomeric Krapcho product **3.70** and tricycle **3.75** as a single diastereomer. However, a single crystal X-ray diffraction study revealed **3.75** to be the undesired *cis*-decalinone product



Scheme 3.9 Cyclohexanedione alkylation and decarboxylative annulation strategy

Table 3.2 Intramolecular aldol reaction screenings

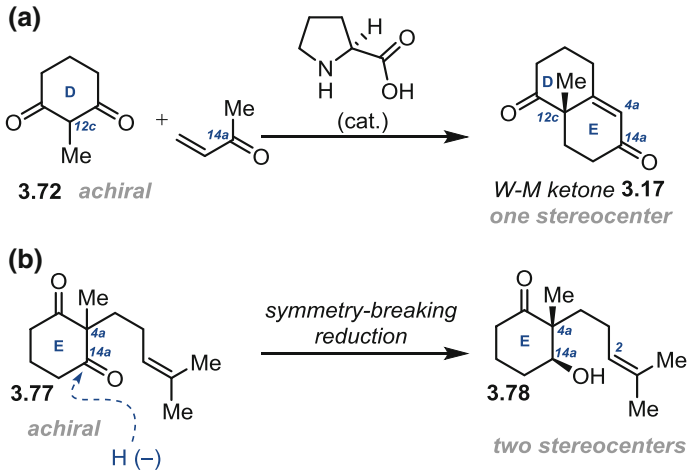


Conditions	Result
$Yb(OTf)_3$, C_7H_8, rt to 70 °C	No reaction
$Sc(OTf)_3$, C_7H_8, rt to 70 °C	Decomposition
TMSI, CH_2Cl_2, −78 °C to rt	Decomposition
TMSOTf, CH_2Cl_2, 0 °C	Decomposition
BF_3•OEt_2, CH_2Cl_2, 0 °C	Decomposition
CSA, C_7H_8, rt to 70 °C	No reaction
TFA, CH_2Cl_2, rt	No reaction
NEt_3, DMSO, rt to 80 °C	No reaction
K_2CO_3, DMSO, rt to 80 °C	Decomposition
DBU, THF, rt to 80 °C	Decomposition
DMAP, DMF, rt to 70 °C	No reaction
K_2CO_3, MeOH, rt	**3.76**
NaO^{t}Bu, MeOH, rt	**3.76**
NaO^{t}Bu, THF, rt	Decomposition
$CeCl_3$•NaI, CH_3CN, rt to 80 °C	No reaction

(e.g. epimeric at C12c). Fortunately, formation of **3.75** was suppressed when the reaction was further scaled (70 mg), giving exclusively the monoester **3.70** in 43 % yield. In hopes that a stepwise Krapcho/aldol process might proceed with selectivity orthogonal to **3.75**, we began an extensive screen of conditions in an attempt to access **3.71**. A summary of our screenings is given in Table 3.2. Exposure of diketone **3.70** to Brønsted or Lewis acidic conditions failed to produce any observable amounts of **3.71**, often giving starting material recovery or decomposition when the reaction temperature was increased. Basic conditions also failed promote any desirable reactivity. When **3.70** was treated with bases in protic media, only conversion to the retro-Dieckmann adduct **3.76** was observed as a diastereomeric mixture.

3.3.7 Development of an Enantioselective Desymmetrization Strategy

Having arrived at another impasse, we began to question the viability of this initial route in providing access to **3.1**. While the alkylation/Michael cascade sequence (**3.58** → **3.59**) provided expedient access to the F-ring tetrahydropyran stereochemistry and desymmetrization of the C4a stereocenter proceeded as planned,

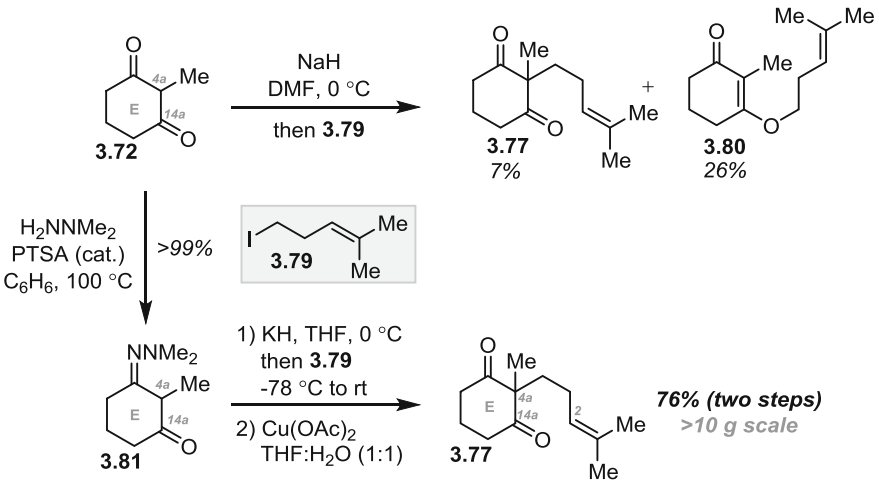


Scheme 3.10 Revised approach to paspaline via enantioselective desymmetrization. **a** Smith paspaline synthesis. **b** Revised approach

further elaboration of this material to **3.1** seemed an unlikely venture. At this stage in our studies, we began to examine alternative points of initiation for our synthesis (Scheme 3.10). Guided by our previous work in developing symmetry-breaking processes to enable rapid construction of complex natural products [51, 52], we surmised that a synthesis beginning from desymmetrization of a paspaline E-ring precursor might circumvent the problems associated with our initial strategy. It is important to note at this juncture that Smith's synthesis of **3.1** also commences via a symmetry-breaking process [29]; namely, the Wieland-Miescher ketone synthesis (**3.72** → **3.17**) assembles the D–E ring fusion of paspaline concomitant with the C12c quaternary stereocenter. While this reaction is a classic "single stereocenter" desymmetrization, we envisioned an alternative E-ring desymmetrization arising from stereoselective mono-reduction of functionalized diketone **3.77**. Reduction of this compound would establish the stereochemical identity of C4a and C14a in **3.78** in a single operation while supplying the needed functional handles for tetrahydropyran assembly and synthesis completion. Armed with this new hypothesis, we refocused our efforts in the synthesis of **3.1** via this approach.

3.3.8 Enantioselective Desymmetrization: Substrate Preparation

The first challenge in our revised synthesis plan was preparation of the desymmetrization precursor **3.77** via alkylation of dione **3.72** or its derivatives (Scheme 3.11). In practice, deprotonation of **3.72** with NaH followed by addition of

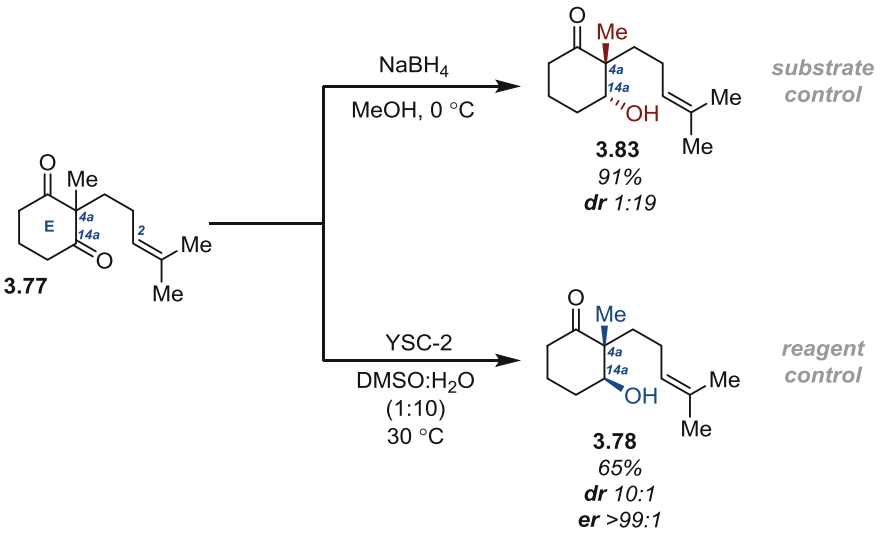


Scheme 3.11 Scalable preparation of diketone desymmetrization precursor

iodide **3.79** provided the desired cycloalkanone **3.77** in 7 % yield along with 26 % of the undesired *O*-alkylation product **3.80**. A screen of alternative bases and conditions provided no enhancement in the yield or selectivity of this reaction. These results were not entirely unexpected: challenges associated with regioselective *C*-alkylation of cyclic α-dicarbonyls have been well-documented [67–69]. In hopes of enhancing the *C*-nucleophilicity of this structure, we prepared hydrazone **3.81** [70]. A screen of conditions revealed that enolization of **3.81** with KH followed by addition of iodide **3.79** provided exclusively the corresponding *C*-alkylation adduct which, following hydrazone deprotection, afforded functionalized diketone **3.77** in 76 % yield over two steps. Of particular importance is the scalability of this process: diketone **3.77** can be prepared using this route in >10 g scale in a single batch.

3.3.9 Development of a "Global" Enantioselective Desymmetrization

With the key desymmetrization precursor in our possession, we began investigating selective monoreduction of **3.77** to access the C4a/C14a stereodiad (Scheme 3.12). Operating first in a racemic sense, treatment of **3.77** with $NaBH_4$ in MeOH provided the monoreduction product **3.83** with excellent yield and diastereoselectivity (19:1). However, nOesy analysis revealed that **3.83** was the opposite diastereomer to that required. It is reasonable to expect formation of this diastereomer under strictly substrate-controlled conditions, although we were surprised by the magnitude of selectivity for this diastereomer. We were encouraged, however, by the

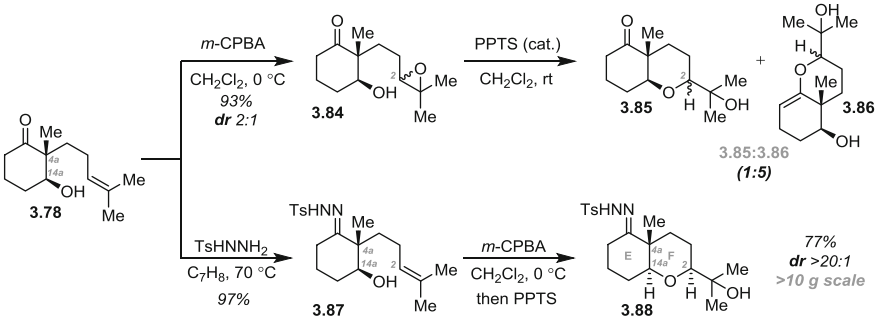


Scheme 3.12 Enantioselective desymmetrization studies

recent reports of Nakada [71] and Node [72, 73] which demonstrated access to the diastereomer needed for our synthesis on similar cyclic diketones using biocatalytic reducing conditions. In experimenting with our compound, we were pleased to find monoreduction of **3.77** with *Saccharomyces cerevisiae* (YSC-2) proceeded with virtually complete reagent control, giving the desired alcohol diastereomer **3.78** in 10:1 dr and >99:1 er. While only minimal optimization was required to achieve suitable levels of selectivity and conversion in this reaction, the chemical yield initially suffered (~10–20 %) due to material loss from the workup procedure. A series of modifications to this protocol (see Sect. 3.5 for the optimized workup procedure) improved the yield to suitable levels of **3.78** for material throughput (65 %). The success of this transformation provided encouragement to the viability of our revised synthesis plan and set the stage for further manipulation to paspaline.

3.3.10 F-Ring Synthesis and C2 Stereocenter: An Unexpected Stereocontrol Element

From hydroxy olefin **3.78**, we anticipated assembly of the tetrahydropyranyl F-ring via an oxidative cyclization sequence (Scheme 3.13). With this goal in mind, treating the alkene in **3.78** with *m*-CPBA provided the corresponding epoxide **3.84** in 93 % yield and poor diastereoselectivity (2:1). While any number of asymmetric epoxidation methods could likely enhance this selectivity, of greater concern was that treatment of this diastereomeric mixture **3.84** with conditions requisite for ring closure (PPTS) gave an inseparable 5:1 mixture of products with the desired



Scheme 3.13 Unexpected stereoselective access to tetrahydropyran and C2 stereocenter

tetrahydropyran **3.85** as the minor product. The major material was identified as alcohol **3.86**, the result of epoxide trapping by the enol tautomer of the ketone in **3.84**. To circumvent this issue, we envisaged that masking the ketone in **3.78** would preclude this undesired mode of ring closure. Since it translated well to our downstream strategy for D-ring construction, **3.78** was converted to the corresponding tosyl hydrazone **3.87** in 97 % yield. To our surprise, the reaction of this compound with *m*-CPBA followed by PPTS initiated an epoxidation/cyclization cascade, providing the desired tetrahydropyran **3.88** directly in 77 % yield and >20:1 dr. This reaction gave expedient preparation of the paspaline F-ring in a single operation. Notably, the cyclization step in the conversion of **3.87**–**3.88** takes place in the absence of PPTS; in the optimized system, this additive was included as it promoted formation of **3.88** in the absence of hydrazone hydrolysis decomposition, which was found to be competitive with the desired ring closure event when promoters were not employed.

We were unaware of any previously reported directing effects of tosyl hydrazones on analogous systems (Fig. 3.5). To provide understanding to this difference in reactivity between hydroxyketone **3.78** and hydrazone **3.87**, we carried out the following experiments. First, the alkene in hydrazone **3.87** was removed via hydrogenation to give alcohol **3.89**. Treatment of **3.89** with the exact reaction conditions used in the epoxidation of **3.87** resulted in quantitative starting material recovery. This datum excluded the possibility of intramolecular oxygen delivery in the reaction via a transient oxazidirine such as **3.90**.

Concluding that the reactivity may be a consequence of underlying conformational differences between **3.78** and **3.87**, we calculated both structures using density functional theory (DFT) at the level of B3LYP/6-311G(d) [74–77]. Interestingly, the optimized structures of **3.78** and **3.87** showed a significant difference in the dihedral angle about the C14a C–OH bond and the C4a C–CH_2R bond (69° for **3.78** and 85° for **3.87**). On the basis of these facts, we hypothesize that the observed selectivity is a consequence of the hydrazone in **3.87** imposing a favorable reactive conformation (**3.91**) on the cyclohexane such that the C14a hydroxyl is in close proximity to the alkene during the oxidation. It follows that this

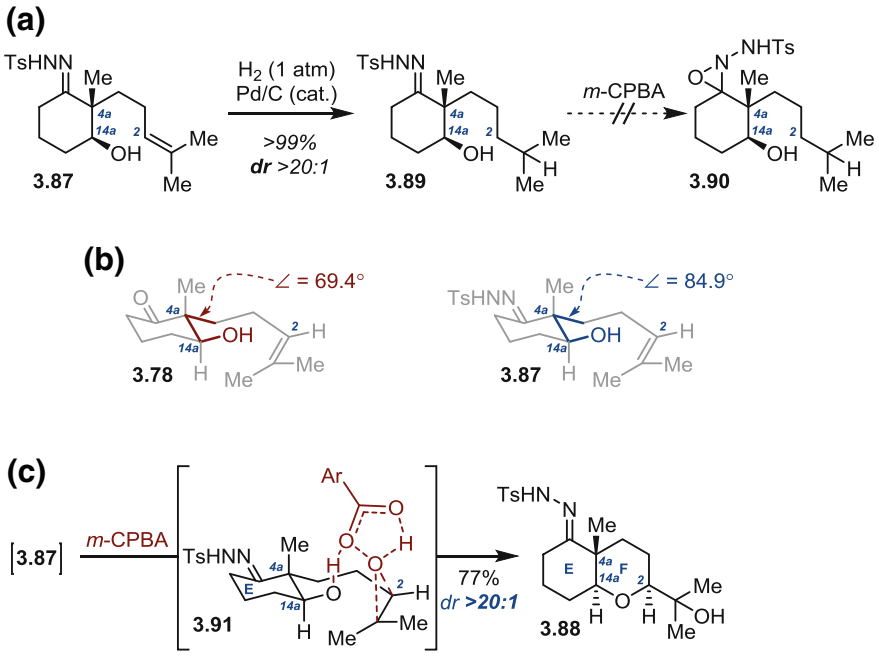
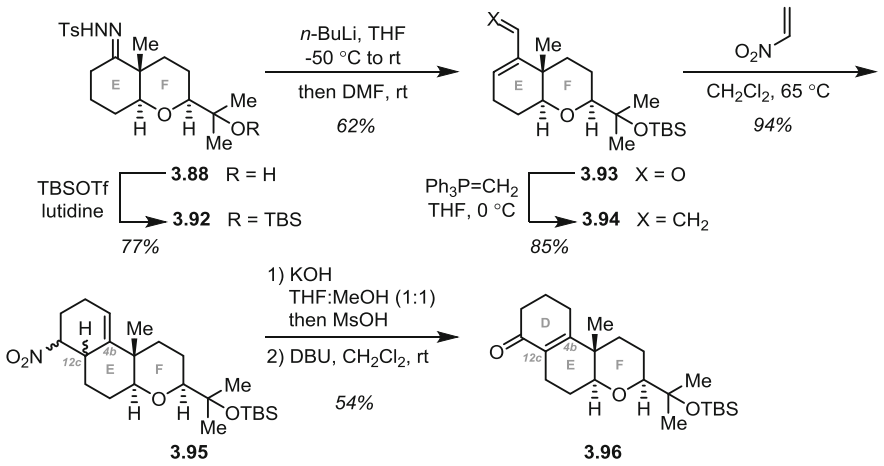


Fig. 3.5 Mechanistic investigations in the "hydrazone directed" epoxidation. **a** Examining feasibility of intramolecular epoxidation via **3.89**. **b** Calculated structures of **3.78** and **3.87**. **c** Mechanistic hypothesis for the conversion of **3.87**–**3.88**

would enhance transfer of the substrate's chiral information to C2 during the oxidation, giving the observed pyran **3.88** following ring closure. To the best of our knowledge, this reaction is the first example of an alkene epoxidation stereoselectivity being influenced by the presence of a tosyl hydrazone [78, 79].

3.3.11 Synthesis of Paspaline via "D-Ring First" Approach

With assembly of the E- and F-rings complete, attention was directed toward construction of the sterically congested D-ring and C12c stereocenter (Scheme 3.14). A critical decision we faced at this juncture was whether to install the C12c methyl group first followed by cyclization (D-ring in paspaline) or vice versa. Either option would invariably have a significant impact on downstream stereochemical outcomes. At the outset, we elected to pursue installation of the D-ring first followed by a downstream C12c methylation. We believed that the tosyl hydrazone in **3.88** would be engaged via the Shapiro reaction to produce a transient vinyllithium which, upon trapping with the appropriate electrophile, would provide the functionality required to incorporate the remaining paspaline core [80, 81].



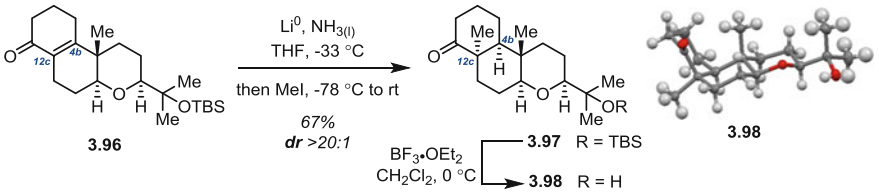
Scheme 3.14 Synthesis of paspaline D-ring via Diels-Alder reaction/isomerization

Thus, TBS protection of the *tert*-alcohol in **3.88** proceeded to give silyl ether **3.92** in 77 % yield. Shapiro reaction of **3.92** followed by DMF trapping furnished unsaturated aldehyde **3.93** in 62 % yield, which upon olefination, gave diene **3.94** poised for a Diels-Alder cycloaddition.

To be compatible in our synthesis manifold, a ketene surrogate would be needed in this transformation. Gratifyingly, nitroethylene proved to be an excellent dienophile in this reaction, giving the annulation product **3.95** in 94 % yield and with complete regioselectivity under thermal conditions. Subsequent Nef reaction and alkene isomerization afforded the ketone **3.96**. We surmised that the enone functional handle in **3.96** would allow for the investigation of multiple approaches for installing the C12c methyl group and C4b methine stereocenter.

3.3.12 Attempts to Install C12c Quaternary Stereocenter

We first pursued manipulation of the alkene functional handle in **3.96** via a Birch alkylation, simultaneously establishing both the C4b and C12c stereocenters (Scheme 3.15). Accordingly, Birch reduction (Li^0, liq. NH_3) of **3.96** followed by electrophilic trapping with MeI furnished decalinone **3.97** in 67 % yield and high stereoselectivity (>20:1). We immediately set out to determine the stereochemical identity of this compound, whereupon TBS deprotection of **3.97** afforded a derivative that crystallized readily. Unfortunately, X-ray diffraction analysis of **3.98** identified the product as the undesired *cis*-decalinone (bearing desired C4b stereochemistry and undesired C12c stereochemistry). A subsequent screen of reducing metals, solvents, and addition methods gave no promise for overriding this selectivity. It is rational to expect that this diastereomer might be formed as prior art by

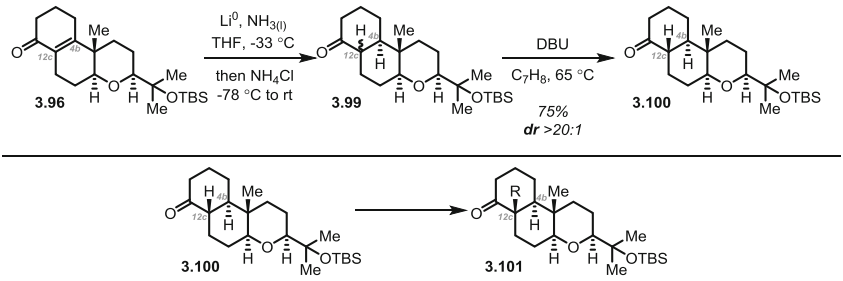


Scheme 3.15 Attempted Birch alkylation approach to C12c and C4b stereocenters

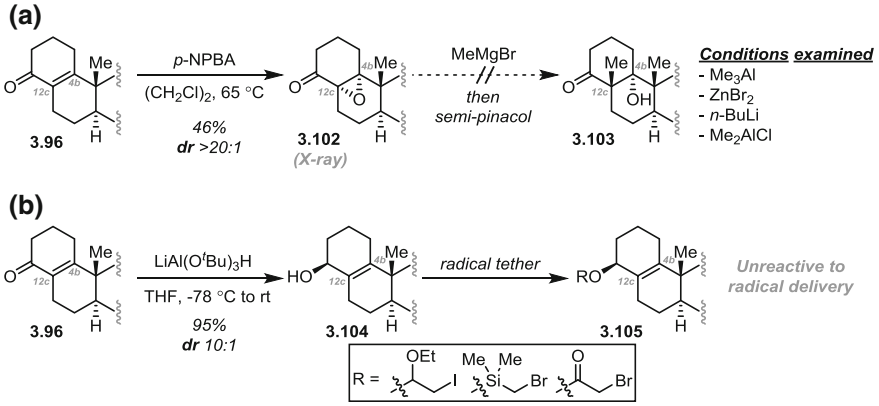
Stork suggests that the kinetically-favored *cis* decalin is preferentially generated in related systems [82, 83].

We then began investigating auxiliary methods for stereoselective introduction of the C12c methyl group. First, we surmised that if the Birch reduction product could be isolated and exposed to thermodynamic methylation conditions, the stereochemical outcome might differ from that observed in **3.97** (Table 3.3). To this end, Birch reduction of **3.96** followed by protic quenching gave a 1:1 mixture of crude diastereomeric ketones **3.99**. Subjection of this mixture to thermodynamic enolization conditions (DBU, C_7H_8) provided exclusively *trans*-decalinone **3.100** in 75 % yield over the two-step sequence. We then screened a variety of conditions for thermodynamic introduction of the requisite carbon functionality. In the first case, typical conditions for thermodynamic methylation (^{t}BuOK, THF:^{t}BuOH, then MeI) failed to give any desired product as polymethylated products were isolated as

Table 3.3 Birch reduction and thermodynamic methylation studies



Conditions	Result
^{t}BuOK, ^{t}BuOH:THF, MeI, 60 °C	Polymethylation
NaO^{t}Bu, THF, MeI, rt to 60 °C	No reaction
LDA, THF, then MeI	No reaction
NaHMDS, THF, then MeI	No reaction
KOH, THF:MeOH, $CH_2O_{(aq.)}$	Decomposition
NaOMe, THF, $CH_2O_{(aq.)}$	Polymethylation
^{t}BuOK, 18-crown-6, then CH_2I_2 THF, rt	No reaction
K_2CO_3, $(HCHO)_n$, DMF, 90 °C	No reaction
^{t}BuOK, THF, 18-crown-6 MeI, 60 °C	Polymethylation



Scheme 3.16 C12c incorporation attempts via semi-pinacol and radical cyclization

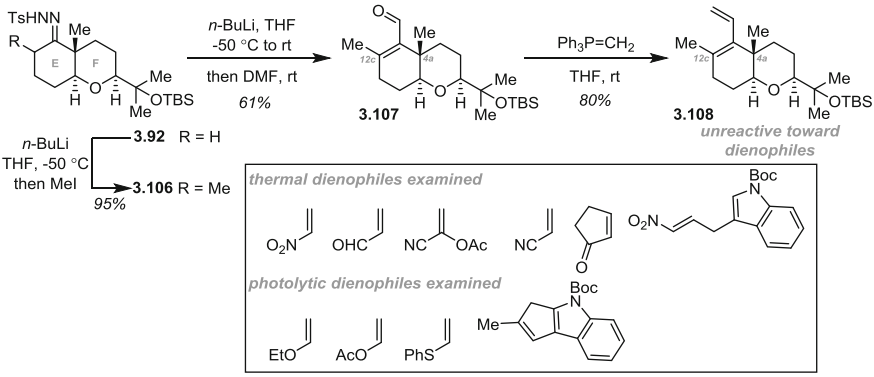
the major material. Kinetic deprotonation and treatment with MeI resulted only in starting material recovery. Additionally, attempts at thermodynamic hydroxymethylation with $CH_2O_{(aq.)}$ or $(HCHO)_n$ gave either no reaction or alkylation at the less-substituted α-position.

Met with these failures in delivering the methyl group directly, we next examined whether the C12c methyl group could be introduced stereospecfically via an epoxidation/semipinacol reaction sequence (Scheme 3.16). This would be enabled by a stereoselective epoxidation of the alkene in **3.96**. Toward this aim, epoxidation of **3.96** with the electrophilic *p*-NPBA [84] afforded ketoepoxide **3.102** in 46 % yield as a single diastereomer. X-ray diffraction analysis indicated that the correct epoxide had been formed for semi-pinacol studies. Ketone **3.102** was then treated with MeMgBr to provide the carbinol envisioned to undergo rearrangement; unfortunately, all conditions examined failed to initiate the desired semi-pinacol process.

In a final attempt to install the methyl group from this route, the ketone in **3.96** was reduced upon treatment with $LiAl(O^tBu)_3H$ to give alcohol **3.104** in 95 % yield and 10:1 dr. From this compound, we pursued radical delivery of the C12c methyl group via tethering from the secondary hydroxyl [85, 86]. However, while functionalization of the alcohol was realized with a number of known radical precursors, the alkene in **3.105** failed to engage all of these radical tethers, ultimately returning starting material or unidentified reduction products.

3.3.13 Paspaline "Methyl Group-First" Approach via Diels Alder Reaction

Collectively, these reactions indicated that the inherent bias of enone **3.96** for the α-face of the D–E-ring fusion (presumably influenced by the C4a angular methyl

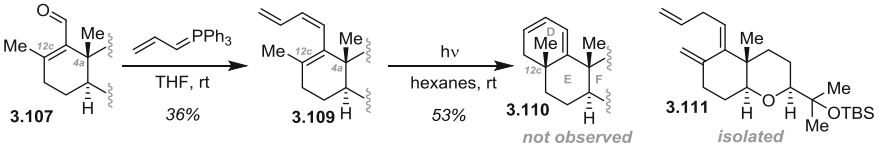


Scheme 3.17 Attempts to install D-ring and C12c methyl group via Diels-Alder reaction

group) would preclude all attempts at late-stage introduction of the C12c methyl group. At this juncture in our studies, we decided that if D-ring assembly was preceded by introduction of this methyl group, then the subsequent annulation step might also proceed with α-face selectivity to give the needed *syn*-diaxial methyl group relationship. Thus, methylation of hydrazone **3.92** upon treatment with *n*-BuLi and MeI proceeded smoothly to give the monomethylated product **3.106** in 95 % yield (Scheme 3.17). In accordance with our Diels-Alder strategy, Shapiro reaction of **3.106** followed by trapping with DMF afforded aldehyde **3.107** in 61 % yield, giving thence the diene **3.108** upon olefination. While we at first anticipated that the [4 + 2] annulation of **3.108** with nitroethylene would proceed in a manner similar to the previously-described des-methyl cycloaddition (**3.94** → **3.95**), we quickly found the steric impact of the newly-introduced methyl group to be much greater than expected. In our initial trials, the reaction of **3.108** with nitroethylene failed to produce the desired cycloadduct under both thermal and Lewis acidic conditions. An extensive screen of thermal dienophiles including acrolein, acrylonitriles, enones, and functionalized nitroalkenes also gave no promise for efficient reactivity. Photo-induced Diels-Alder pathways were also pursued using the illustrated dienophiles, although these cycloaddition partners showed no improvement in reactivity with diene **3.108**.

3.3.14 Investigation of Alternative Methyl Group-First Annulation Modes

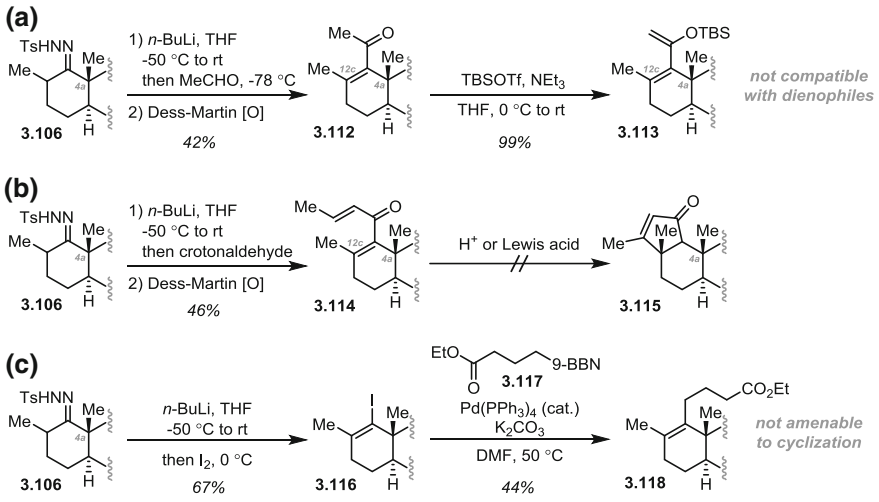
Having encountered this lack of reactivity, we turned to alternative annulation modes, making use of the flexibility of electrophile choice in the Shapiro reaction step and its subsequent intermediates (Scheme 3.18). To bypass an intermolecular cycloaddition, we pursued an electrocyclization pathway to form the requisite



Scheme 3.18 Electrocyclization approach to D-ring synthesis

D-ring. Operating first in the simplest case, olefination of aldehyde **3.107** with the ylide derived from allyltriphenylphosphonium bromide gave the simplified triene **3.109** in 36 % yield. Irradiation of **3.109** (Hg vapour lamp) gave complete conversion to a single product after one hour, although the product did not match the expected ^{1}H NMR spectrum. Further spectroscopic analysis revealed the identity of the material as the sigmatropic rearrangement product **3.111** and not the desired cyclization adduct **3.110**. Suspecting that this rearrangement might predominate using any analog of this triene, this pathway was abandoned.

Having arrived at another impasse, we continued exploring alternative electrophiles in the Shapiro reaction of **3.106** (Scheme 3.19). We first returned to our [4 + 2] cycloaddition strategy, envisioning that a suitable diene bearing additional electron density relative to **3.108** might engage dienophiles more readily. Accordingly, Shapiro reaction of **3.106** followed by trapping with acetaldehyde gave the resulting *sec*-alcohol, which after Dess-Martin oxidation and enol-silane formation gave silyloxydiene **3.113** in 42 % yield over the three-step sequence. The reaction of this diene with nitroethylene (among other dienophiles) was then studied; however, **3.113** showed no improvement in reactivity as a Diels-Alder counterpart over simplified diene **3.108**.



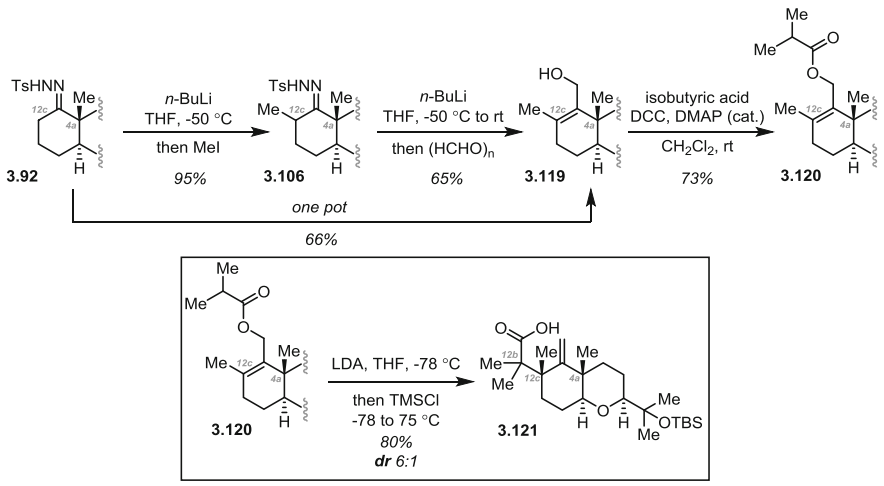
Scheme 3.19 Alternative Shapiro adducts explored in D-ring synthesis. **a** Diels-Alder. **b** Nazarov cyclization. **c** Cross coupling

In another contingency, Shapiro reaction of **3.106** followed by trapping with (*E*)-crotonaldehyde followed by oxidation gave dienone **3.114** in 46 % yield. This substrate could be employed in our synthesis via its action as a Nazarov reaction substrate. A subsequent ozonolysis/condensation sequence from **3.115** would generate the D-Ring. While dienone **3.114** seemed ideally-poised for rearrangement, exposure of this compound to a variety of acidic promoters failed to induce the desired cyclization.

We next employed I_2 as the electrophilic trap in the Shapiro reaction, giving vinyl iodide **3.116** in 67 % yield from which we aimed to incorporate the necessary functionality for ring closure via cross coupling methods. Gratifyingly, iodide **3.116** reacted readily with alkyl borane **3.117** to give the tethered ester **3.118** in 44 % yield. Unfortunately, this ester (or its derivatives) could not be further manipulated to access the D-ring of **3.1**.

3.3.15 *Development of an Ireland-Claisen Rearrangement Approach to Paspaline*

Our options diminishing, we prepared primary alcohol **3.119** via trapping the Shapiro intermediate of **3.106** with $(HCHO)_n$ (Note: this reaction could also be performed in a one pot protocol from des-methyl hydrazone **3.92**, see Scheme 3.20). We surmised that the appropriately-selected ester of **3.119** would participate in an Ireland-Claisen rearrangement [87, 88], influenced by the C4a stereocenter, to install the C12c (and potentially C12b) quaternary methyl group(s) while providing functional handles for D-ring construction. In an initial model case,

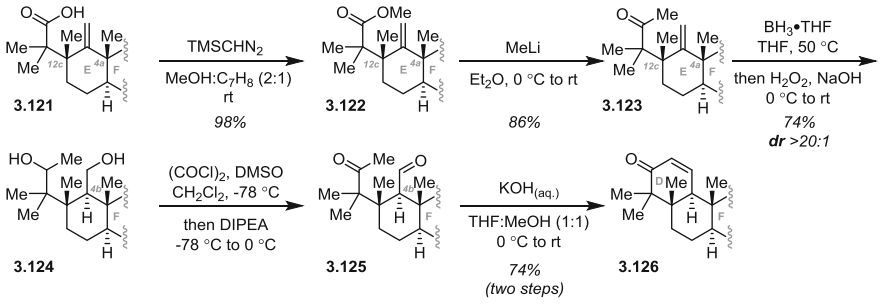


Scheme 3.20 Discovery of an Ireland-Claisen rearrangement for paspaline

acylation of alcohol **3.119** with isobutyric acid (mediated by DCC) gave the corresponding isobutyrate **3.120** in 73 % yield. Gratifyingly (and perhaps also to our relief!), enolization of isobutyrate **3.120** followed by trapping with TMSCl, heating and hydrolysis afforded rearrangement product **3.121** in 80 % yield and 6:1 dr. The presence of the correct C12c relative configuration was confirmed via X-ray crystallographic evidence of a later intermediate (vide infra). While entry into the C12b quaternary stereocenter from α-dimethyl carboxylic acid **3.121** was not immediately clear, access to D-ring synthesis completion from the available functional handles was palpable and subsequently studied from this compound as proof-of-concept.

Esterification of **3.121** proceeded uneventfully to give ester **3.122** in 98 % yield (Scheme 3.21). While we initially imagined conversion of the ester to its methyl ketone might be challenging, we were surprised to find that ketone **3.123** was readily accessed in 86 % yield upon treatment of ester **3.122** with excess MeLi at rt (!). Hydroboration/oxidation of the alkene in **3.123** established the identity of the C4b methine carbon with complete stereofidelity (**3.124**, 74 % yield) concomitant with non-stereoselective reduction of the ketone.

From diol **3.124**, only oxidation of both alcohols and intramolecular condensation remained to complete D-ring construction. This oxidation was complicated, however, by intramolecular interception of the initially-formed aldehyde by the secondary hydroxyl, ultimately forming a lactone upon oxidation of the lactol. Indeed, numerous oxidative conditions (Dess-Martin, TPAP, PCC) gave only starting material decomposition with trace amounts of the lactone side product. Fortunately, global Swern oxidation proved viable in producing the crude ketoaldehyde **3.125** in the absence of unwanted cyclization side products. Exposure of ketoaldehyde **3.125** to basic conditions furnished cyclohexenone **3.126** in 74 % yield from diol **3.124**. This sequence confirmed the viability of this route in completing our synthesis of **3.1**. At this juncture, we returned to the Ireland-Claisen rearrangement stage to find a suitable ester for incorporation of the C12b quaternary stereocenter.

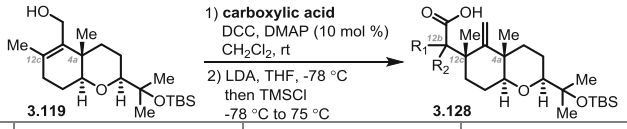


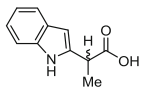
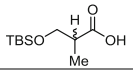
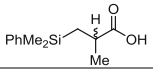
Scheme 3.21 D-ring synthesis completion with model Ireland-Claisen substrate

3.3.16 *Investigation of Higher Order Esters in the Ireland-Claisen Rearrangement*

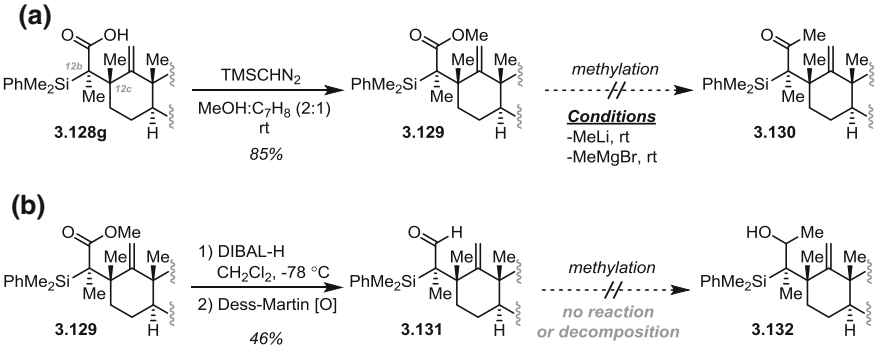
Our goal at the outset of these screenings was to identify an ester of **3.119** that i) participated efficiently in the Ireland-Claisen rearrangement to assemble (at very least) the C12c stereocenter and ii) provided accommodating functionality for immediate or downstream incorporation of the C12b quaternary center (Table 3.4). To these aims, the simplified acetate **3.127a** and propionate **3.127b** (entries 1–2) were prepared and examined in the rearrangement. However, these substrates failed to rearrange as the intermediate silyl ketene acetals of **3.127a–b** were labile to the required reaction temperatures. We subsequently focused our search on more functionalized esters. Indole ester **3.127c** (entry 3) and its protected derivatives, perhaps ideally suited for our synthesis manifold, also failed to rearrange as the additional steric encumbrance precluded any observable silyl ketene acetal generation. Unfortunately, the same issue was true for esters **3.127d–f**. We were pleased to find promising reactivity in the case of silyl functionalized isobutyrate **3.127g** (entry 7), which readily underwent rearrangement to give carboxylic acid **3.128g** in 52 % yield and 6.6:1.1:1 dr. The stereochemistry at C12c of this compound was

Table 3.4 Alternative ester screenings in Ireland-Claisen rearrangement



Entry	Carboxylic acid	Ester (yield)[a]	Acid (yield, dr)[a]
1	Ac_2O	**3.127a** (82 %)[b]	No reaction
2		**3.127b** (83 %)	No reaction
3		**3.127c** (73 %)	No reaction
4		**3.127d** (93 %)	No reaction
5		**3.127e** (74 %)	No reaction
6		**3.127f** (54 %)	No reaction
7		**3.127g** (87 %)	**3.128g** (57 %, 6.6:1.1:1 dr)

[a]Isolated yields
[b]Conditions: Ac_2O, NEt_3, DMAP (10 mol%), CH_2Cl_2, rt
[c]Determined by ^1H NMR analysis of crude mixtures



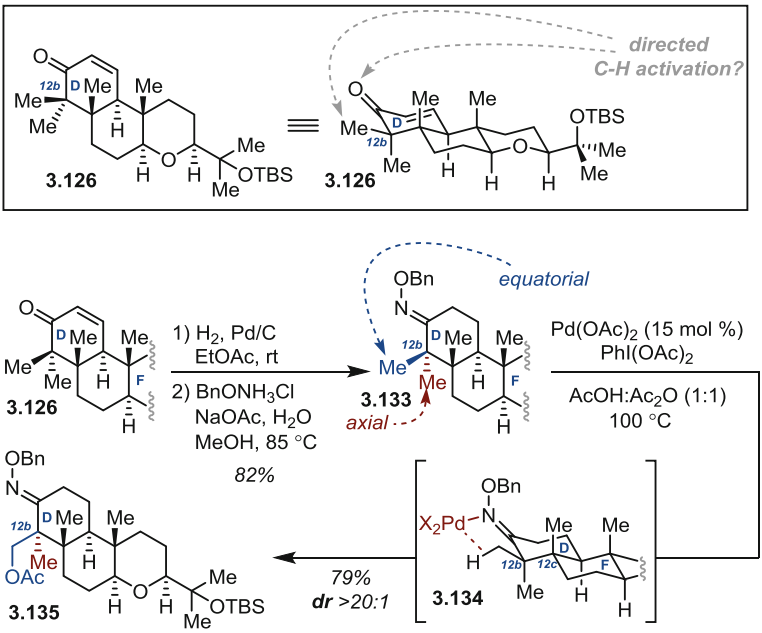
Scheme 3.22 Failed advancement of silyl-functionalized I-C product to paspaline

assigned by analogy to rearrangement product **3.121**. The identity of the C12b stereocenter could not be determined at this juncture.

With carboxylic acid **3.128g** in our possession, we envisioned direct translation of our ring closure strategy (**3.121** → **3.126**) would complete D-ring assembly and set the stage for synthesis completion (Scheme 3.22). The phenyldimethylsilyl group was purposed to be revealed downstream as a primary alcohol via Tamao-Fleming oxidation [89]. Along these lines, esterification of **3.128g** with $TMSCHN_2$ provided ester **3.129** in 85 % yield, setting the stage for conversion to the resulting methyl ketone. However, ester **3.129** was found to be unreactive to all conditions examined for nucleophilic methylation, even at elevated temperatures. In order to circumvent this challenging addition, the ester in **3.129** was reduced with DIBAL-H to give the corresponding alcohol. Dess-Martin oxidation subsequently gave the aldehyde **3.131** in 46 % yield over two steps. We surmised that aldehyde **3.131** would be more accessible to methide nucleophiles. Unfortunately, this approach was also met with failure due to unsuitable reactivity of the aldehyde to nucleophilic addition.

3.3.17 Development of a "Local" Desymmetrization of C12b Dimethyl Group

The studies on carboxylic acid **3.128g** seemed to suggest that further elaboration of this compound to paspaline would be significantly impaired by the challenging manipulation of the carbonyl, a problem that would inevitably be encountered in any variant of this substrate. Moreover, early returns on elaboration of the dimethyl carboxylic acid **3.121** to complete D-ring synthesis (**3.126**) had been successful; elaboration of this compound to **3.1** would require a late-stage C–H activation reaction to desymmetrize the C12b stereocenter for synthesis completion (Scheme 3.23). For a C–H activation of this compound to be successful, a selective functionalization of the equatorial methyl group over its axial counterpart would be



Scheme 3.23 Development of a local desymmetrization for C12b stereocenter

required to achieve the diastereomer needed. We were aware that the lowest energy conformer of **3.126** places the C–O double bond in the same plane as the equatorial methyl group and anticipated that the appropriate catalytic system would operate selectively if a suitable directing group were employed. In the event, we selected the catalytic C–H oxidation reaction developed by Sanford and co-workers [90, 91], which had demonstrated applicability to substituted cyclohexanone oximes. Toward this aim, hydrogenation of enone **3.126** followed by amine condensation provided oxime **3.133** in 82 % yield. In the key experiment, the direct application of Sanford's conditions to oxime **3.133** provided monoacetate **3.135** (via transition structure **3.134**) in 79 % yield and >20:1 dr. This "local" desymmetrization completed assembly of the final quaternary center in **3.1** and provided a functional handle for completion of our synthesis.

The yield and selectivity of this transformation is noteworthy; examples for the successful execution of this reaction as a platform for desymmetrization of achiral quaternary centers are scarce in recent literature (Fig. 3.6). In 2008, Yu and co-workers reported a stoichiometric desymmetrization of dimethyl oxime **3.136**, proceeding in 72 % yield and complete selectivity en route to the synthesis of lobatoside E [92]. Six years later, the Sorenson laboratory described the first symmetry-breaking implementation of Sanford's catalytic reaction in their synthesis of jiadifenolide [93]. In this reaction, treating oxime **3.138** with $Pd(OAc)_2$ and PhI $(OAc)_2$ afforded the desired acetate **3.139** in 22 % yield and 1:1 dr. In our case, exposure of oxime **3.133** to Sanford's conditions provided the desired acetate

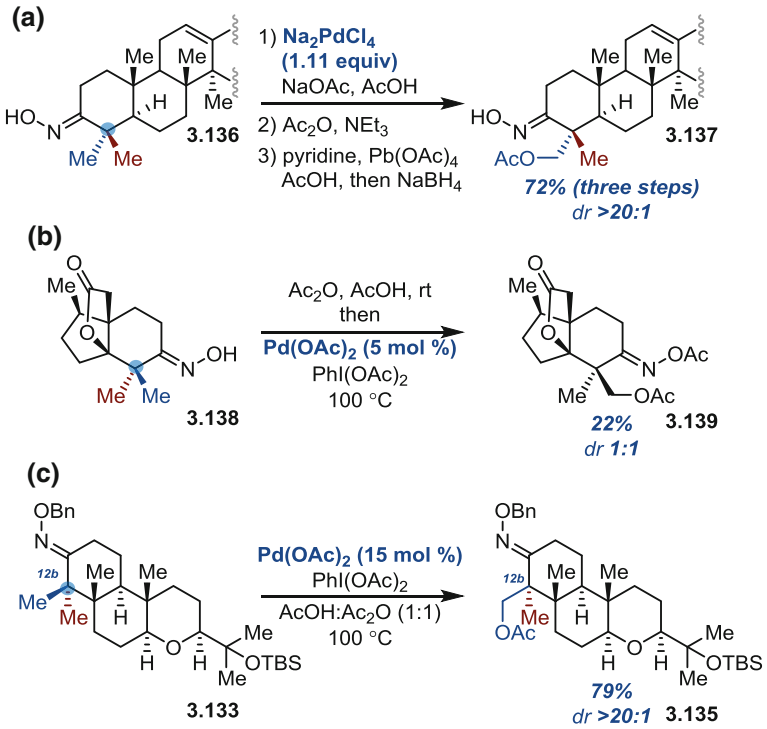
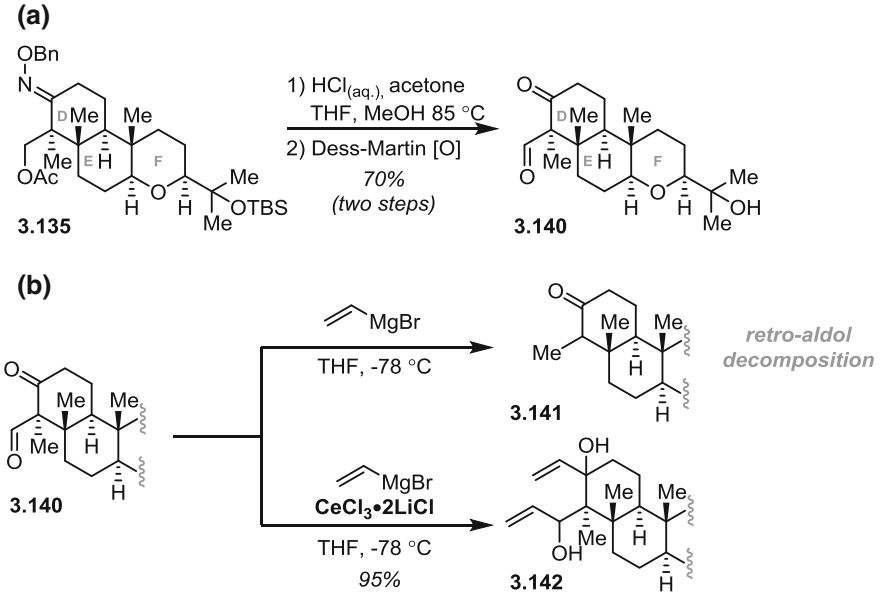


Fig. 3.6 Examples of substrate-directed sp^3 C–H oxidation/desymmetrization. **a** Yu (2008). **b** Sorensen (2014). **c** This work

diastereomer **3.135** in 79 % yield and >20:1 dr. That this reaction (**3.133** → **3.135**) provided the desired product diastereomer in such high yield illustrates the viability of this and related transformations in the late-stage pursuit of challenging quaternary stereocenters.

3.3.18 Synthesis of Paspaline C-Ring and Incorrect C6a Stereocenter

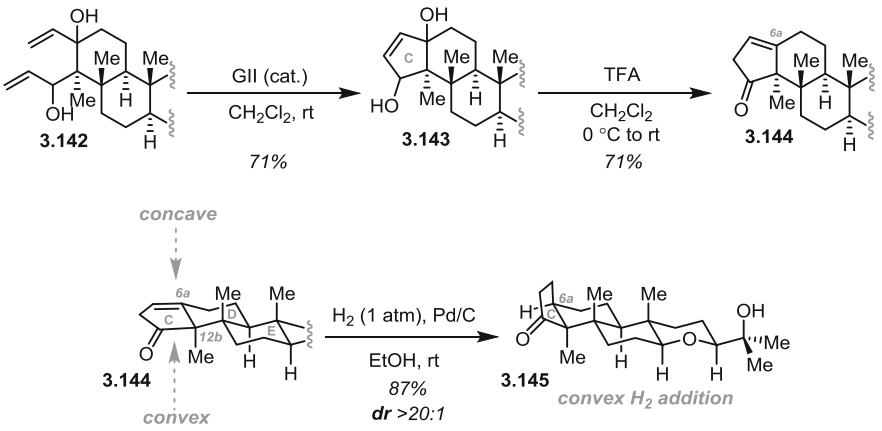
With acetate **3.135** in hand, we faced the remaining challenges of C-ring installation, C6a reduction, and indolization to complete our synthesis (Scheme 3.24). Acetate **3.135** was subjected to global hydrolysis to remove the acetate, oxime, and silyl ether functionalities. The resulting primary alcohol was oxidized with Dess-Martin periodinane (DMP) to give ketoaldehyde **3.140** in 70 % yield over two steps. From **3.140**, we envisioned bis-vinylation followed by ring-closing metathesis (RCM) would install the remaining carbon skeleton. To our surprise, treatment of **3.140** with vinylmagnesium bromide at −78 °C gave predominantly



Scheme 3.24 Access to *bis*-allylic alcohol substrate for ring-closing metathesis

the retro-aldol decomposition product **3.141**. After some experimentation, we found that the $CeCl_3 \cdot 2LiCl$ complex recently reported by Knochel aided in suppressing the retro-aldol product completely [94], giving diol **3.142** in 95 % yield.

Treatment of **3.142** with Grubb's second Generation catalyst provided allylic alcohol **3.143** in 71 % yield (Scheme 3.25). While an alcohol oxidation/hydroxyl elimination pathway was first pursued for the conversion of diol **3.143** to enone **3.144**, we found that simply subjecting **3.143** to acidic conditions (TFA) resulted in

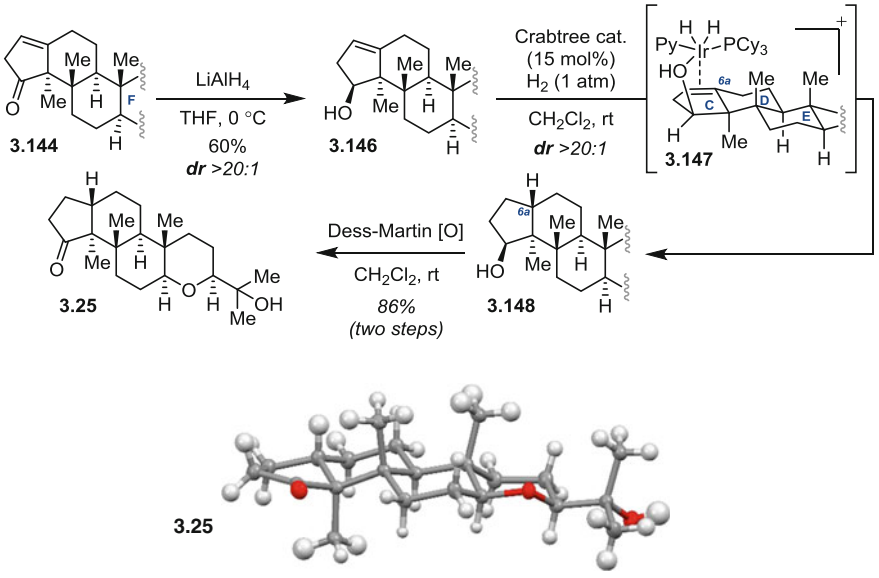


Scheme 3.25 Access to non-conjugated enone and undesired convex-face reduction

direct elimination of the *tert*-hydroxyl to give nonconjugated enone **3.144** in 71 % yield. This set the stage for hydrogenation of the resultant alkene to install the final stereocenter in **3.1**. In the event, catalytic hydrogenation of alkene **3.144** with Pd/C provided ketone **3.145** in 87 % yield and >20:1 dr. However, ^{1}H NMR spectral data of this compound were not consistent with that of the desired compound previously synthesized by Smith and co-workers [32], leading to the conclusion that this hydrogenation had delivered the opposite diastereomer to that required. In order to better rationalize this result, we calculated the structure of non-conjugated enone **3.144**. As anticipated, the DFT-optimized structure of **3.144** revealed a marked puckering of the C–D ring fusion; catalytic hydrogenation of this alkene to give the desired diastereomer at C6a would necessitate approach of H_2 to the concave *Re* face of **3.144**. This result is in accord with prior studies on similar steroidal systems [95] which also describe convex surface hydrogenation on related enones.

3.3.19 Substrate Directed Hydrogenation for Access to C6a Stereocenter

Upon assessing our available functional handles, we surmised that selective reduction of the ketone in **3.144** might alter the outcome of the ensuing alkene hydrogenation by virtue of directing ability of the nascent hydroxyl group (Scheme 3.26). The use of Crabtree's catalyst in alcohol-directed alkene hydrogenations has been well-documented [96, 97] and would presumably engage the alkene on the same face as the hydroxyl. To this end, treatment of ketone **3.144**



Scheme 3.26 Directed alkene hydrogenation and completion of paspaline core

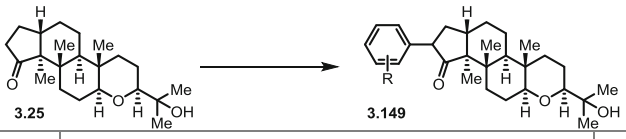
with $LiAlH_4$ afforded the desired (*S*)-alcohol **3.146** in 60 % yield >20:1 dr over two steps from diol **3.143**. The steric impact of the C12c methyl group on the outcome of this reaction cannot be overstated; ketone reduction in analogous steroidal systems not bearing this methyl group generally proceed with the opposite sense of selectivity in ketone reduction [95, 98–101].

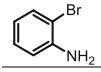
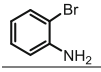
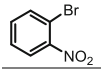
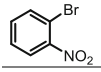
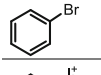
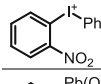
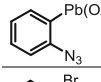
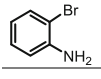
With this alcohol in hand, catalytic hydrogenation of **3.146** using Crabtree's catalyst completely overrode the inherent substrate bias, giving the corresponding alcohol **3.148** (via **3.147**) in >20:1 dr and subsequently the ketone **3.25** in 86 % over two steps after re-oxidation of the alcohol. The stereochemistry of **3.25** was confirmed via ^1H NMR comparison with Smith's intermediate and an X-ray diffraction study [32].

3.3.20 Indolization and Synthesis Completion

With ketone **3.25** in hand, only indolization of the ketone functionality remained to complete our synthesis. As in Smith's synthesis [29], we anticipated significant

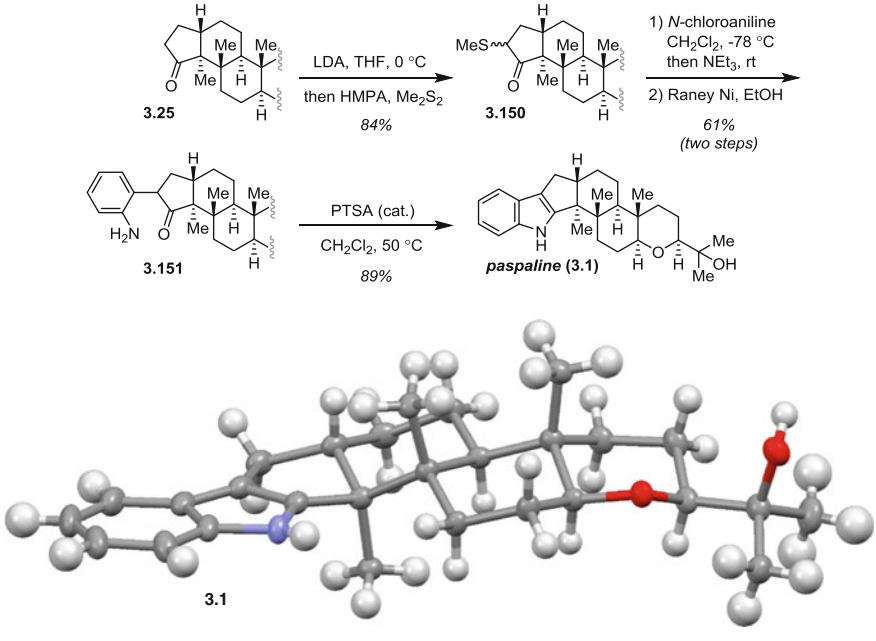
Table 3.5 Summary attempts at ketone indolization via enolate arylation



Aryl electrophile	Conditions	Result
	$Pd(OAc)_2$ (cat.) JohnPhos, Cs_2CO_3, DMF	No reaction
	$Pd(OAc)_2$ (cat.) XantPhos, NaO^tBu, C_7H_8	No reaction
	$Pd(OAc)_2$ (cat.) JohnPhos, Cs_2CO_3, DMF	No reaction
	Pd_2dba_3 (cat.) 4-methoxyphenol, NaHMDS, DavePhos	No reaction
	Pd_2dba_3 (cat.) XantPhos, NaHMDS C_7H_8	No reaction
	LDA, CuCN, then electrophile	No reaction
	LDA, THF, HMPA then electrophile	No reaction
	KNH_2, liq. NH_3, hν	Decomposition

difficulty associated with direct incorporation of the indole via the ketone. In the present case, we envisioned incorporation of the necessary functionality via ketone enolate arylation. A summary of our attempts is given in Table 3.5. Treatment with *o*-amino electrophiles using Pd-catalyzed arylation failed to give any desired product as **3.25** was recovered in all cases. As a control experiment, 2-bromobenzene also failed under these conditions. We then moved on to S_nAr electrophiles such as aryliodonium and aryl lead reagents. Unfortunately, these electrophiles were also unreactive to the ketone enolate **3.25**. In a final iteration, **3.25** was reacted with 2-bromoaniline under conditions suited for radical arylation. This trial only resulted in starting material decomposition.

Determined to complete our synthesis, we turned to the Gassman protocol which proved successful in the hands of Smith and co-workers (Scheme 3.27) [50]. This approach installs the requisite aryl portion **via** an intramolecular [2,3] rearrangement, obviating intermolecular functionalization of the ketone. Thus, enolization of 3.25 followed by addition of Me_2S_2 gave thioether 3.150 in **84 %** yield as a mixture of diastereomers. Treatment of this compound with *N*-chloroaniline led to S_N2 displacement of the chloride by the thioether, which upon treatment with base, initiated a Sommelet-Hauser type rearrangement and assembled the critical C–C bond. The thioether was then reduced with Raney Ni to give ketoaniline 3.151 in **61 %** yield over two steps. Exposure of this compound to acidic conditions (PTSA, 50 °C) resulted in intramolecular condensation to give paspaline in **89 %** yield (**46 %** yield from ketone 3.25). In addition to matching the reported analytical data,



Scheme 3.27 Gassman indole synthesis and completion of the synthesis of paspaline

an X-ray diffraction study of synthetic paspaline provided secondary confirmation of the final structure [13] and the sense of enantioinduction imposed in the biocatalytic desymmetrization of diketone **3.77**.

3.4 Conclusion

In conclusion, we have described a global and local symmetry-breaking approach to the total synthesis of the indole diterpene alkaloid paspaline. After initial approaches for the assembly of **3.1** via a cationic transannular cyclization were unsuccessful, a symmetry-breaking biocatalytic monoreduction was devised to establish the initial C4a/C14a stereocenters. A novel tosyl hydrazone-influenced epoxidation enabled excellent control of the C2 stereocenter (>20:1), and an Ireland-Claisen rearrangement provided access to the D-ring and C12c stereocenter of **3.1**. A substrate-directed symmetry-breaking C–H acetoxylation inspired by Sanford and co-workers provided excellent control of the C12b stereocenter (>20:1). To override the inherent facial bias in the hydrogenation of enone **3.144**, stereoselective reduction of the ketone followed by hydrogenation with Crabtree's catalyst provided the final stereocenter in **3.1** with excellent selectivity at C6a (>20:1) The route and methods described in this work present a number of complimentary conceptual disconnections in the arena of steroid total synthesis.

3.5 Experimental Details

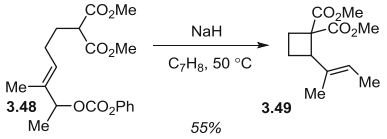
Methods: **General**. Infrared (IR) spectra were obtained using a Jasco 460 Plus Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker model Avance 400 (^{1}H NMR at 400 MHz and ^{19}F NMR at 376 MHz), Bruker Avance III 500 (^{1}H NMR at 500 MHz), Varian INOVA600 (^{1}H NMR at 600 MHz), or a Bruker Avance III 600 (^{1}H NMR at 600 MHz and ^{13}C NMR at 150 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm and C_6D_6 at 7.16 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, br d = broad doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Mass spectra were obtained using a Thermo LTqFT mass spectrometer with electrospray introduction and external calibration. All samples were prepared in methanol. Analytical thin layer chromatography (TLC) was performed on Sorbent Technologies 0.20 mm Silica Gel TLC plates. Visualization was accomplished with UV light, $KMnO_4$, and/or Seebach's stain followed by heating. Purification of the reaction products was carried out by flash chromatography using Siliaflash-P60 silica gel (40–63 μm) purchased from Silicycle. Unless otherwise noted, all reactions were carried out under an atmosphere of dry nitrogen in

flame-dried glassware with magnetic stirring. Yield refers to isolated yield of analytically pure material unless otherwise noted. Yields are reported for a specific experiment and as a result may differ slightly from those found in figures, which are averages of at least two experiments.

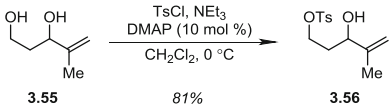
Materials: **General**. Tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), and toluene (C_7H_8) were dried by passage through a column of neutral alumina under nitrogen prior to use. Aniline, Hexamethylphosphoramide (HMPA), and Diisopropylamine were freshly distilled from calcium hydride prior to use. Compounds **3.55** [102], **S2** [103], **S5** [104], **S7** [105], **3.79** [106], nitroethylene [106], *p*-NPBA [84], **S10** [107], **S12** [108], **S13** [109], and **S14** [110] were prepared according to known procedures. All other reagents were purchased from commercial sources and were used as received unless otherwise noted.

Computation Analysis: High-level density functional theory (DFT) calculations using the B3LYP [74, 75] approximate exchange-correlation energy density functional were performed with the standard Pople triple-zeta basis set 6-311G(d) [76, 78] for all elements when stable structures are optimized. Calculations were performed in the gas phase at 0 K with tight SCF convergence and ultrafine integration grids. All calculations were performed with the package of Gaussian 09 version D01 [111]. Cartesian coordinates of the studied systems are provided below.

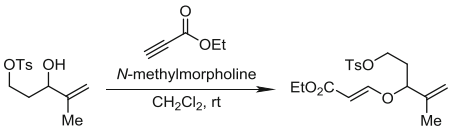
Experimental Procedures



Dimethyl (E)-2-(but-2-en-2-yl)cyclobutane-1,1-dicarboxylate (3.49): NaH (60 % dispersion in oil, 0.084 g, 2.10 mmol, 1.90 equiv) was washed free of oil with hexanes and transferred to a flame-dried 20-mL scintillation vial. C_7H_8 (2 mL) was added followed by a solution of carbonate **3.48** (0.40 g, 1.10 mmol, 1.00 equiv). The resulting mixture was warmed to 50 °C and stirred until complete conversion of **3.48** was observed by TLC analysis, typically 4 h. The mixture was cooled to rt, diluted with H_2O (5 ml), and partitioned in a separatory funnel. The aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic extracts were washed with 1 M $NaOH_{(aq.)}$ (2 × 5 mL), dried with magnesium sulfate, and concentrated *in vacuo*. The product was purified via flash chromatography (95:5 to 90:10 hexanes:EtOAc) to afford volatile cyclobutane **3.49** (0.139 g, 55 % yield) as a clear oil. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.27 (d, *J* = 6.4 Hz, 1H), 3.73 (s, 3H), 3.63 (s, 3H), 2.51 (t, *J* = 9.6 Hz, 1H), 2.29 (m, 1H), 2.08 (m, 1H), 1.79 (m, 1H), 1.62 (s, 3H), 1.59 (d, *J* = 6.8 Hz, 3H).

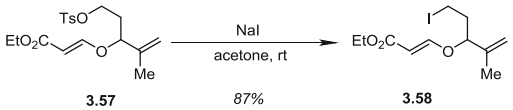


3-hydroxy-4-methylpent-4-en-1-yl 4-methylbenzenesulfonate (3.56): A flame-dried, 1000 mL round bottomed flask was charged with diol **3.55** (4.67 g, 40.2 mmol, 1.00 equiv) and CH_2Cl_2 (300 mL) under an atmosphere of N_2. The solution was cooled to 0 °C and NEt_3 (14.0 mL, 100.5 mmol, 2.50 equiv), DMAP (0.49 g, 4.00 mmol, 0.10 equiv), and lastly TsCl (8.43 g, 44.2 mmol, 1.10 equiv) were added sequentially. The resulting mixture was allowed to stir at this temperature until complete conversion of the starting material was observed by TLC analysis, typically 12 h. The mixture was then diluted with H_2O (150 mL) and partitioned in a separatory funnel. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried with sodium sulfate and concentrated *in vacuo*. The product was purified via flash chromatography (70:30 to 60:40 hexanes:EtOAc) to afford the tosylate **3.56** (8.75 g, 81 % yield) as a pale yellow oil. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 4.91 (s, 1H), 4.82 (s, 1H), 4.22 (m, 1H), 4.16 (m, 1H), 4.09 (m, 1H), 2.44 (s, 3H), 1.91 (m, 1H), 1.79 (m, 1H), 1.75 (br s, 1H), 1.68 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 146.4, 144.8, 132.9, 129.8, 127.9, 111.4, 71.5, 67.6, 34.1, 21.6, 17.6; **HRMS (ESI$^+$)** Calcd. For $C_{13}H_{18}O_4S$ + Na, 293.0824; Found, 293.0815; **IR** (thin film, cm^{-1}) 3545, 3055, 2984, 2686, 1652, 1616, 1456, 1360, 1266, 1189; **TLC** (80:20 hexanes:EtOAc): R_f = 0.14.



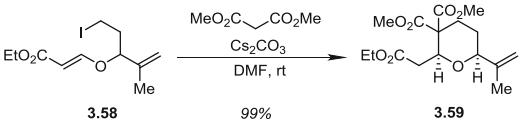
3.56 *97%* **3.57**

Ethyl (*E*)-3-((2-methyl-5-(tosyloxy)pent-1-en-3-yl)oxy)acrylate (3.57): A flame-dried, 500 mL round bottomed flask was charged with alcohol **3.56** (8.75 g, 32.0 mmol, 1.00 equiv) and CH_2Cl_2 (160 mL) under an atmosphere of N_2 at rt. *N*-methylmorpholine (3.60 mL, 35.7 mmol, 1.10 equiv) and ethyl propiolate (3.92 mL, 35.7 mmol, 1.10 equiv) were added sequentially, and the mixture was allowed to stir until complete conversion of the starting material was observed by TLC analysis, typically 4 h. The reaction mixture was concentrated on a rotary evaporator, and the crude product was purified via flash chromatography (80:20 to 70:30 hexanes:EtOAc) to give the vinyl ether **3.57** (11.4 g, 97 % yield) as a clear oil. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 12.6 Hz, 1H), 5.14 (d, *J* = 12.6 Hz, 1H), 4.97 (s, 1H), 4.93 (s, 1H), 4.31 (dd, *J* = 4.8, 4.2 Hz, 1H), 4.16–4.06 (m, 4H), 2.43 (s, 3H), 1.97 (m, 2H), 1.61 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 167.6, 160.5, 145.0, 141.5, 132.6, 129.9, 127.9, 115.4, 98.6, 81.5, 66.2, 59.8, 32.7, 21.6, 16.7, 14.3; **HRMS (ESI$^+$)** Calcd. For $C_{18}H_{24}O_6S$ + Na, 391.1191; Found, 391.1181; **IR** (thin film, cm^{-1}) 2980, 2916, 2849, 1706, 1644, 1488, 1362, 1189, 1097, 923; **TLC** (80:20 hexanes:EtOAc): R_f = 0.32.



3.57 *87%* **3.58**

Ethyl (*E*)-3-((5-iodo-2-methylpent-1-en-3-yl)oxy)acrylate (3.58): To a solution of tosylate **3.57** (11.4 g, 30.8 mmol, 1.00 equiv) in acetone (300 mL) at rt was added NaI (40.0 g, 308.0 mmol, 10.0 equiv) portionwise with vigorous stirring. The resulting suspension was allowed to stir 12 h at which point TLC analysis confirmed complete consumption of the starting material. The reaction mixture was diluted with brine (150 mL) and transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (3 × 60 mL), and the combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo*. The product was purified via flash chromatography (90:10 to 80:20 hexanes:EtOAc) to afford the alkyl iodide **3.58** (8.67 g, 87 % yield) as a pale yellow oil. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.46 (d, *J* = 12.6 Hz, 1H), 5.27 (d, *J* = 12.6 Hz, 1H), 5.05 (s, 1H), 5.04 (s, 1H), 4.39 (dd, *J* = 4.8, 3.0 Hz, 1H), 4.14 (m, 2H), 3.17 (m, 2H), 2.21 (m, 1H), 2.07 (m, 1H), 1.67 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 167.7, 160.8, 141.5, 115.3, 98.6, 85.5, 59.8, 36.7, 17.0, 14.3, 0.9; **HRMS (ESI$^+$)** Calcd. For $C_{11}H_{17}IO_3$ + Na, 347.0120; Found, 347.0111; **IR** (thin film, cm^{-1}) 3078, 2978, 2916, 1707, 1644, 1456, 1322, 1171, 1006, 834; **TLC** (80:20 hexanes:EtOAc): R_f = 0.64.

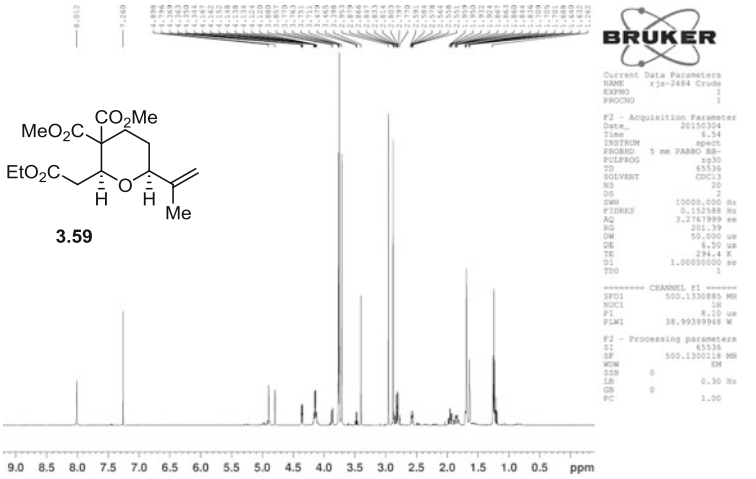


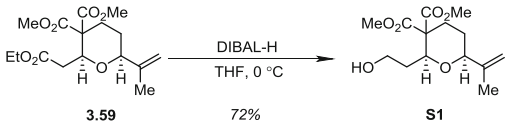
3.58 *99%* *dr >20:1* **3.59**

Dimethyl 2-(2-ethoxy-2-oxoethyl)-6-(prop-1-en-2-yl)dihydro-2H-pyran-3,3 (4H)-dicarboxylate (3.59): A 500 mL round bottomed flask was charged with the iodide **3.58** (8.75 g, 27.00 mmol, 1.00 equiv) and DMF (130 mL) at rt. Dimethyl malonate (6.20 mL, 54.0 mmol, 2.00 equiv) and Cs_2CO_3 (26.4 g, 81.0 mmol, 3.00 equiv) were added sequentially, whereupon a bright orange color was observed. The resulting mixture was allowed to stir for 14 h and was subsequently diluted with H_2O (50 mL) and Et_2O (50 mL). The layers were partitioned in a separatory funnel, and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with brine (40 mL), dried with magnesium sulfate and concentrated *in vacuo* to give the crude pyran as a single diastereomer (as determined by ^{1}H NMR spectroscopic analysis of the crude mixture, which revealed a single compound). The product was purified via flash chromatography (90:10 to 80:20 hexanes:EtOAc) to afford tetrahydropyran **3.59** (8.85 g, 99 % yield) as a clear, viscous oil. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.86 (s, 1H), 4.75 (s, 1H), 4.31 (dd, *J* = 9.0, 6.0 Hz, 1H), 4.11 (m, 2H), 3.83 (d, *J* = 12.0 Hz, 1H),

3.72 (s, 3H), 3.67 (s, 3H), 2.77 (m, 2H), 2.54 (m, 1H), 1.92 (m, 1H), 1.82 (m, 1H), 1.67 (br s, 1H), 1.65 (s, 3H), 1.20 (t, J = 6.6 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 171.4, 170.7, 169.0, 144.6, 110.7, 81.1, 77.3, 60.3, 55.8, 52.5, 52.2, 38.0, 31.7, 26.0, 18.8, 14.1; **HRMS (ESI$^+$)** Calcd. For $C_{16}H_{24}O_7$ + Na, 351.1420; Found, 351.1409; **IR** (thin film, cm^{-1}) 3446, 2955, 2849, 1733, 1652, 1455, 1267, 1186, 1072, 904; **TLC** (80:20 hexanes:EtOAc): R_f = 0.43.

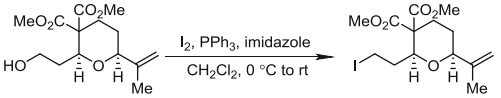
Crude ^{1}H NMR spectrum of 17



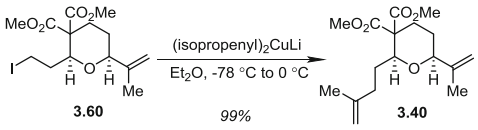


Dimethyl-2-(2-hydroxyethyl)-6-(prop-1-en-2-yl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (S1): A flame-dried, 500 mL round bottomed flask was charged with ester **3.59** (6.00 g, 18.3 mmol, 1.00 equiv) and THF (150 mL) under an atmosphere of N_2. The solution was cooled to 0 °C, and DIBAL-H (1 M solution in hexane, 18.3 mL, 18.3 mmol, 1.00 equiv) was added slowly. The reaction was then analyzed for reaction completion via TLC analysis, which indicated incomplete starting material conversion. Another 1.00 equiv DIBAL-H was added, whereupon TLC analysis indicated incomplete starting material conversion. Another 1.00 equiv DIBAL-H was added, whereupon TLC analysis indicated complete conversion of the starting material. The reaction mixture was quenched via addition of acetone (30 mL), and the mixture was stirred 5 min at 0 °C. Saturated Rochelle's salt$_{(aq.)}$ (40 mL) was then added, and the mixture was transferred to a separatory funnel.

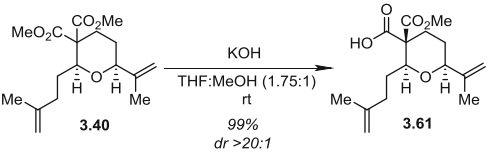
The aqueous layer was extracted with Et_2O (3 × 40 mL), and the combined organic extracts were washed with 1 M $HCl_{(aq.)}$ (40 mL) and brine (40 mL), dried with magnesium sulfate and concentrated *in vacuo*. The product was purified via flash chromatography (60:40 to 50:50 to 40:60 hexanes:EtOAc) to afford alcohol **S1** (3.78 g, 72 % yield) as a clear, viscous oil. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.92 (s, 1H), 4.81 (s, 1H), 4.01 (dd, *J* = 8.4, 1.8 Hz, 1H), 3.88 (m, 1H), 3.79–3.76 (m, 5H), 3.71 (s, 3H), 2.54 (m, 1H), 2.42 (d, *J* = 5.4 Hz, 1H), 2.14 (m, 1H), 1.93–1.88 (m, 3H), 1.70 (s, 3H), 1.67 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 171.2, 169.3, 144.7, 111.1, 81.5, 81.1, 62.1, 56.2, 52.6, 52.1, 34.7, 31.9, 26.6, 18.7; **HRMS (ESI$^+$)** Calcd. For $C_{14}H_{22}O_6$ + Na, 309.1314; Found, 309.1305; **IR** (thin film, cm^{-1}) 3446, 3055, 2954, 2883, 1731, 1455, 1266, 1078, 906, 737; **TLC** (75:25 hexanes:EtOAc): R_f = 0.05.



Dimethyl-2-(2-iodoethyl)-6-(prop-1-en-2-yl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (3.60): A 500 mL round bottomed flask was charged with CH_2Cl_2 (96 mL), and the solution was cooled to 0 °C. Imidazole (3.22 g, 47.4 mmol, 4.96 equiv) and PPh_3 (5.14 g, 19.0 mmol, 2.05 equiv) were added followed by I_2 (4.83 g, 19.0 mmol, 2.00 equiv). The mixture was allowed to stir at 0 °C for 10 min whereupon a pale yellow suspension was observed. The alcohol **S1** (2.73 g, 9.55 mmol, 1.00 equiv) was then added as a solution in CH_2Cl_2 (20 mL), and the mixture was allowed to warm to rt and stirred until complete consumption of the starting material was observed by TLC analysis, typically 12 h. The mixture was then quenched via addition of saturated $Na_2S_2O_{3(aq.)}$ (50 mL) and transferred to a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic extracts were washed with brine (30 mL), dried with magnesium sulfate, and concentrated *in vacuo*. The product was purified via flash chromatography (95:5 to 90:10 hexanes:EtOAc) to afford primary iodide **3.60** (2.64 g, 70 % yield) as a white solid. Analytical data: **mp** 61–65 °C; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.93 (s, 1H), 4.83 (s, 1H), 3.88 (d, *J* = 10.2 Hz, 1H), 3.84 (d, *J* = 11.4 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.36 (m, 1H), 3.28 (m, 1H), 2.56 (dt, *J* = 6.6, 3.0 Hz, 1H), 2.37 (m, 1H), 2.13 (m, 1H), 1.95 (m, 1H), 1.84 (m, 1H), 1.73 (s, 3H), 1.69 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 171.0, 169.3, 144.8, 110.9, 81.4, 80.9, 56.4, 52.6, 52.2, 35.8, 32.0, 26.3, 19.0, 4.3; **HRMS (ESI$^+$)** Calcd. For $C_{14}H_{21}IO_5$ + Na, 419.0326; Found, 419.0320; **IR** (thin film, cm^{-1}) 2917, 2849, 1731, 1652, 1540, 1455, 1265, 1083, 905; **TLC** (75:25 hexanes:EtOAc): R_f = 0.50.



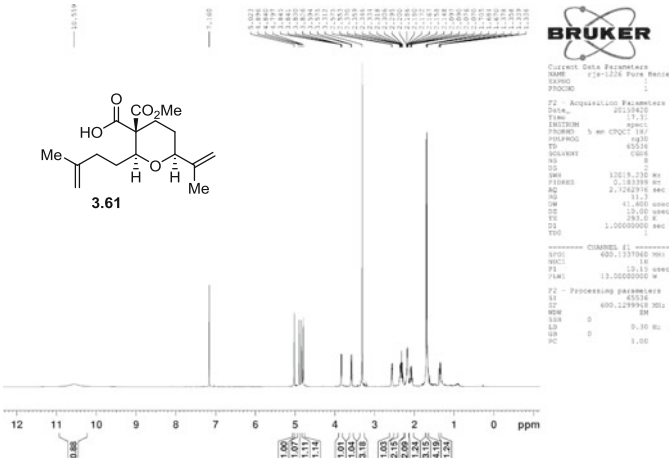
Dimethyl-2-(3-methylbut-3-en-1-yl)-6-(prop-1-en-2-yl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (3.40): A flame-dried, 50 mL round bottomed flask was charged with 2-bromopropene (0.67 mL, 7.57 mmol, 3.00 equiv) and Et_2O (13 mL) under an atmosphere of N_2. The mixture was cooled to −78 °C, and ^{t}BuLi (1.70 M solution in pentane, 8.91 mL, 15.14 mmol, 6.00 equiv) was added dropwise. The reaction mixture was allowed to stir 30 min at −78 °C, then warmed to rt and stirred for 1 h. During this time period, a second flame-dried, 100 mL round bottomed flask was charged with CuI (0.72 g, 3.79 mmol, 1.50 equiv) and Et_2O (12 mL) and was cooled to −78 °C. The isopropenyllithium solution was then cooled to −78 °C and transferred via cannula to the CuI suspension over a period of ∼1 min. The resulting suspension was then warmed to −45 °C and stirred 1 h, upon which a color change from pale brown to dark gray to dark yellow-green was observed. The mixture was cooled to −78 °C, and a solution of iodide **3.60** (1.00 g, 2.52 mmol, 1.00 equiv) in Et_2O (5 mL) was added. The reaction was then warmed to 0 °C and stirred until complete conversion of the starting material was observed by TLC analysis, typically 30 min. The reaction was then quenched via addition of saturated $NH_4Cl_{(aq.)}$ (20 mL), and the mixture was transferred to a separatory funnel. The aqueous layer was extracted with Et_2O (3 × 20 mL), and the combined organic extracts were washed with saturated $NH_4Cl_{(aq.)}$ (20 mL), dried with magnesium sulfate, and concentrated *in vacuo*. The product was purified via flash chromatography (100:0 to 95:5 to 90:10 hexanes:EtOAc) to afford the alkene **3.40** (0.77 g, 99 % yield) as a clear oil. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.93 (s, 1H), 4.81 (s, 1H), 4.72 (s, 1H), 4.69 (s, 1H), 3.75 (br s, 4H), 3.70 (br s, 4H), 2.53 (m, 1H), 2.21 (m, 1H), 2.12 (m, 1H), 1.94–1.78 (m, 4H), 1.74 (s, 3H), 1,72 (s, 3H), 1.67 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 171.6, 169.7, 154.4, 145.1, 110.6, 110.3, 81.0, 80.5, 56.6, 52.4, 52.0, 34.9, 32.2, 30.1, 26.2, 22.2, 19.2; **HRMS (ESI$^+$)** Calcd. For $C_{17}H_{26}O_5$ + Na, 333.1678; Found, 333.1669; **IR** (thin film, cm^{-1}) 3446, 3056, 2953, 2849, 1731, 1669, 1636, 1520, 1455, 1203, 1266; **TLC** (75:25 hexanes:EtOAc): R_f = 0.52.



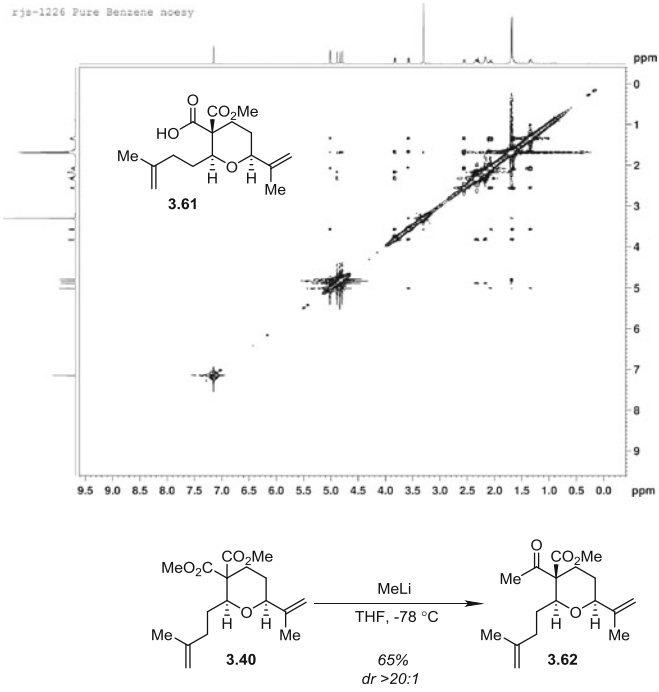
3-(methoxycarbonyl)-2-(3-methylbut-3-en-1-yl)-6-(prop-1-en-2-yl)tetrahydro-2H-pyran-3-carboxylic acid (3.61): A 20 mL scintillation vial was charged with

diester **3.40** (0.10 g, 0.32 mmol, 1.00 equiv) and THF (3 mL) with stirring at rt. KOH (1 M in MeOH, 1.70 mL, 1.70 mmol, 5.27 equiv) was added, and the resulting mixture was allowed to stir at rt until complete consumption of the starting material was observed by TLC analysis. This time period varied widely for each experiment (from 12 h to 6 d dependent on scale; in this iteration, 5 days were required to reach complete conversion). Once complete, the reaction mixture was concentrated on a rotary evaporator. The residue was diluted with H_2O (10 mL), transferred to a separatory funnel, and extracted with Et_2O (2 × 5 mL). The aqueous layer was acidified to pH = 1 with 1 M $HCl_{(aq.)}$ and extracted with EtOAc (3 × 5 mL). The combined EtOAc extracts were dried with magnesium sulfate and concentrated *in vacuo* to afford the crude mono-acid **3.61** (0.094 g, >99 % crude yield) as a pale yellow, viscous oil. The diastereomeric ratio was determined via ^{1}H NMR spectroscopic analysis of this crude material, which revealed a single compound. Analytical data: **^{1}H NMR** (600 MHz, C_6D_6): δ 10.56 (br s, 1H), 5.02 (s, 1H), 4.90 (s, 1H), 4.84 (s, 1H), 4.80 (s, 1H), 3.84 (dd, *J* = 7.2, 1.8 Hz, 1H), 3.58 (d, *J* = 11.4 Hz, 1H), 3.31 (s, 3H), 2.56 (d, *J* = 13.2 Hz, 1H), 2.33 (m, 2H), 2.17 (m, 2H), 2.08 (m, 1H), 1.71 (s, 3H), 1.68–1.67 (m, 4H), 1.34 (d, *J* = 1.8 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 177.1, 169.6, 145.3, 145.0, 110.8, 110.4, 81.1, 80.3, 56.6, 52.2, 34.8, 32.2, 30.1, 26.1, 22.2, 19.2; **HRMS (ESI$^+$)** Calcd. For $C_{16}H_{24}O_5$ + Na, 319.1521; Found, 319.1513; **IR** (thin film, cm^{-1}) 3566, 3074, 2952, 2857, 2633, 1732, 1650, 1438, 1268, 1080, 891; **TLC** (75:25 hexanes:EtOAc): R_f = 0.32.

Crude ^{1}H NMR Spectrum of 3.61



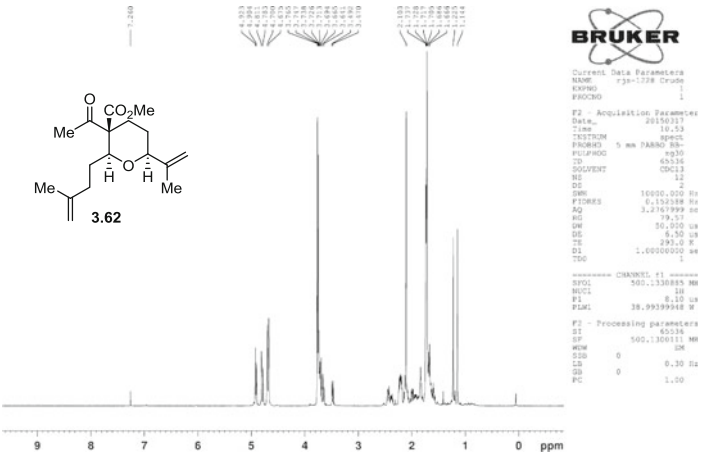
nOesy Spectrum of 3.61 (C_6D_6)



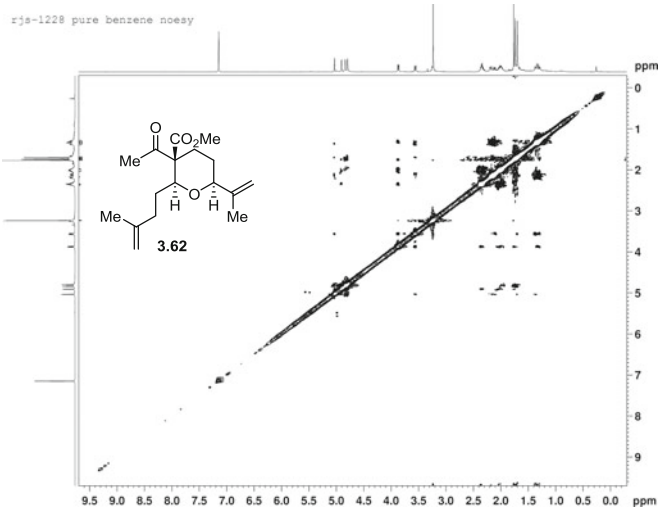
Methyl-3-acetyl-2-(3-methylbut-3-en-1-yl)-6-(prop-1-en-2-yl)tetrahydro-2H-pyran-3-carboxylate (3.62): A flame-dried, 25 mL round bottomed flask was charged with diester **3.40** (0.35 g, 1.13 mmol, 1.00 equiv) and THF (11 mL) under an atmosphere of N_2. The solution was cooled to −78 °C, and MeLi (1.60 M in Et_2O, 0.6 mL, 0.97 mmol, 2.00 equiv) was added over 5 s. The reaction was then checked via TLC analysis, which showed incomplete conversion of the starting material. Another 2.00 equiv MeLi was added, whereupon TLC analysis showed incomplete conversion of the starting material. Another 1.00 equiv MeLi was added, whereupon TLC analysis showed complete conversion of the starting material. The reaction mixture was then quenched via addition of saturated $NH_4Cl_{(aq.)}$ (5 mL) and subsequently warmed to rt. The mixture was transferred to a separatory funnel, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo* to give the crude ketone as a single diastereomer (as determined via ^{1}H NMR spectroscopic analysis of the crude product residue, which revealed a single stereoisomer in combination with over-addition products). The product was purified via flash chromatography (100:0 to 98:2 to 95:5 to 90:10 hexanes:EtOAc) to afford ketone **3.62** (0.22 g, 65 % yield) as a clear, viscous oil. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.94 (s, 1H), 4.82 (s, 1H), 4.71 (s, 1H), 4.69 (s, 1H), 3.78–3.75 (m, 4H), 3.71

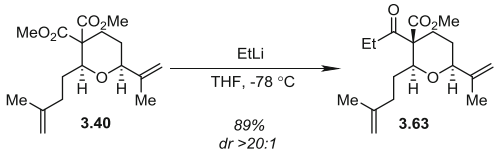
(d, J = 11.4 Hz, 1H), 2.45 (m, 1H), 2.22 (m, 1H), 2.12 (br s, 4H), 1.99 (m, 1H), 1.75 (br s, 4H), 1.73 (br s, 4H), 1.68 (m, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 205.1, 171.0, 145.6, 145.2, 110.6, 110.3, 80.8, 80.3, 62.3, 52.0, 34.9, 31.4, 30.2, 27.1, 26.4, 22.3, 19.3; **HRMS (ESI$^+$)** Calcd. For $C_{17}H_{26}O_4$ + Na, 317.1729; Found, 317.1720; **IR** (thin film, cm^{-1}) 3445, 3072, 2969, 2857, 1708, 1649, 1436, 1356, 1221, 1081; **TLC** (75:25 hexanes:EtOAc): R_f = 0.45.

Crude ^{1}H NMR spectrum of 1.62



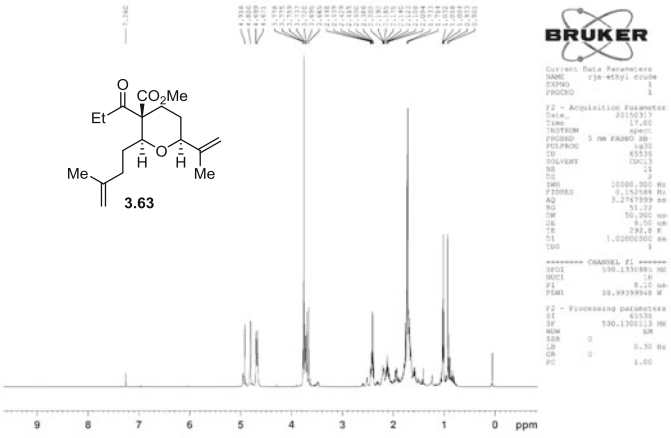
nOesy Spectrum of 3.62 (C_6D_6)



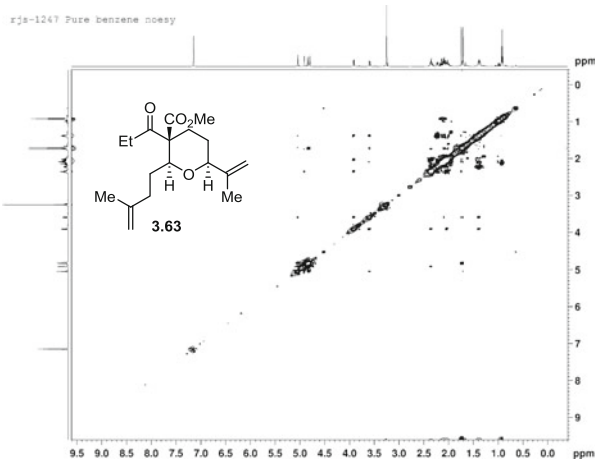


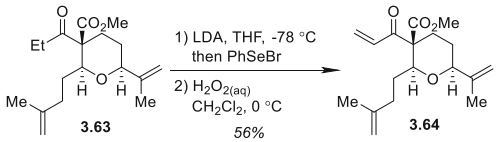
Methyl-2-(3-methylbut-3-en-1-yl)-6-(prop-1-en-2-yl)-3-propionyltetrahydro-2H-pyran-3-carboxylate (3.63): A flame-dried 20 mL scintillation vial was charged with bromoethane (0.13 mL, 1.69 mmol, 3.50 equiv) and THF (5 mL) under an atmosphere of N_2. The solution was cooled to −78 °C, and ^{t}BuLi (1.70 M in pentane, 1.99 mL, 3.38 mmol, 7.00 equiv) was added dropwise. The mixture was allowed to stir 30 min at −78 °C whereupon a solution of the diester **3.40** (0.15 g, 0.48 mmol, 1.00 equiv) was added over ∼10 s. The reaction progress was immediately checked via TLC analysis, which confirmed complete consumption of the starting material. The reaction was then quenched via addition of saturated $NH_4Cl_{(aq.)}$ (5 mL) and warmed to rt. The mixture was transferred to a separatory funnel, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo* to afford the crude ketone as a single diastereomer (as determined via ^{1}H NMR spectroscopic analysis of the crude product residue, which revealed a single stereoisomer in combination with over-addition products). The product was purified via flash chromatography (100:0 to 98:2 to 95:5 to 90:10 hexanes:EtOAc) to afford ketone **3.63** (0.13 g, 89 % yield) as a clear, viscous oil. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.93 (s, 1H), 4.82 (s, 1H), 4.71 (s, 1H), 4.68 (s, 1H), 3.79–3.77 (m, 4H), 3.71 (d, J = 3.6 Hz, 1H), 2.42 (m, 3H), 2.21 (m, 1H), 2.12 (m, 1H), 1.95 (m, 1H), 1.78 (m, 1H), 1.74 (s, 3H), 1.73 (s, 3H), 1.69 (m, 2H), 1.60 (br s, 1H), 1.03 (t, J = 7.2 Hz, H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 208.0, 171.2, 145.6, 145.2, 110.6, 110.3, 80.8, 80.5, 62.4, 51.9, 34.9, 32.6, 31.7, 30.2, 26.4, 22.3, 19.3, 7.9; **HRMS (ESI$^+$)** Calcd. For $C_{18}H_{28}O_4$ + Na, 331.1885; Found, 331.1876; I**R** (thin film, cm^{-1}) 3446, 3073, 2970, 2855, 1739, 1650, 1455, 1342, 1159, 892; **TLC** (75:25 hexanes:EtOAc): R_f = 0.47.

Crude ^{1}H NMR spectrum of 3.63



nOesy Spectrum of 3.63 (C_6D_6)

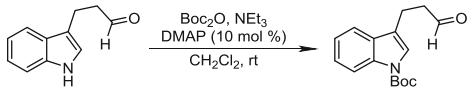




Methyl 3-acryloyl-2-(3-methylbut-3-en-1-yl)-6-(prop-1-en-2-yl)tetrahydro-2H-pyran-3-carboxylate (3.64): A flame-dried, 20 mL scintillation vial was charged with THF (4 mL) and diisopropylamine (0.08 mL, 0.55 mmol, 1.30 equiv) under an atmosphere of N_2. The mixture was cooled to 0 °C, and ^{n}BuLi (1.74 M in hexanes, 0.32 mL, 0.55 mmol, 1.30 equiv) was added dropwise. After stirring 30 min, the mixture was cooled to −78 °C, and a solution of ketone **3.63** (0.13 g, 0.42 mmol, 1.00 equiv) in THF (1 mL) was added. After stirring 45 min at −78 °C, PhSeBr (0.11 g, 0.51 mmol, 1.10 equiv) was added, and the mixture was allowed to stir until complete consumption of the starting material was observed by TLC analysis, typically 45 min. The reaction mixture was diluted with H_2O (10 mL), warmed to rt, and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo* to give the crude α-selenide, which was used in the next step without further purification.

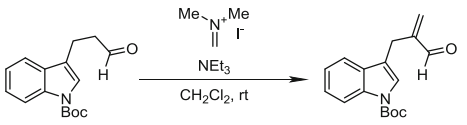
The intermediate selenide was dissolved in CH_2Cl_2 (2 mL), and the mixture was cooled to 0 °C. H_2O_2 (30 % w/w in H_2O, 0.80 mL) was added dropwise, and the mixture was stirred at 0 °C until complete consumption of the starting material was observed by TLC analysis, typically 15 min. The reaction mixture was diluted with H_2O (7 mL) and transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (3 × 7 mL), and the combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo*. The product was purified via flash chromatography (100:0 to 98:2 to 95:5 hexanes:EtOAc) to afford unsaturated

ketone **3.64** (0.079 g, 56 %) as a pale yellow, viscous oil. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.39 (d, *J* = 3.0 Hz, 1H), 6.38 (s, 1H), 5.71 (dd, *J* = 4.2, 3.0 Hz, 1H), 4.95 (s, 1H), 4.84 (s, 1H), 4.72 (s, 1H), 4.70 (s, 1H), 3.84 (d, *J* = 10.2 Hz, 1H), 3.76 (s, 3H), 3.72 (d, *J* = 11.4 Hz, 1H), 2.43 (m, 1H), 2.22 (m, 1H), 2.17 (m, 1H), 2.08 (m, 1H), 1.81 (m, 1H), 1.77 (s, 3H), 1.74 (s, 3H), 1.72–1.66 (m, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 195.6, 170.9, 145.6, 145.2, 131.7, 129.7, 110.7, 110.4, 80.7, 79.9, 60.8, 52.0, 34.8, 31.0, 30.2, 26.2, 22.3, 19.4; **HRMS (ESI$^+$)** Calcd. For $C_{18}H_{26}O_4$ + Na, 329.1729; Found, 329.1720; **IR** (thin film, cm^{-1}) 3420, 3054, 2952, 2852, 1740, 1636, 1455, 1265, 1049, 894; **TLC** (75:25 hexanes:EtOAc): R_f = 0.63.



S2 *42%* **S3**

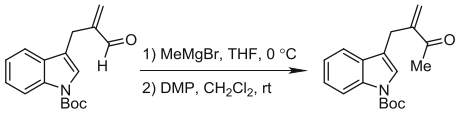
***tert*-butyl 3-(3-oxopropyl)-1H-indole-1-carboxylate (S3)**: A flame-dried, 50 mL round bottomed flask was charged with 3-(1H-indol-3-yl)propanal **S2** (0.37 g, 2.10 mmol, 1.00 equiv), CH_2Cl_2 (14 mL), NEt_3 (0.44 mL, 3.15 mmol, 1.50 equiv), and lastly DMAP (0.005 g, 0.21 mmol, 0.10 equiv) at rt under an atmosphere of N_2. Boc_2O (0.55 g, 2.52 mmol, 1.20 equiv) was added in one porition, and the resulting mixture was allowed to stir until complete consumption of the starting material was observed by TLC analysis, typically 5 h. The mixture was then diluted with H_2O (10 mL) and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo*. The product was purified via flash chromatography (100:0 to 90:10 to 80:20 hexanes:EtOAc) to afford the protected indole **S3** (0.24 g, 42 % yield) as a clear, viscous oil. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 9.87 (s, 1H), 8.13 (br s, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.38 (br s, 1H), 7.33 (t, *J* = 7.2 Hz, 1H), 7.25 (t, *J* = 7.2 Hz, 1H), 3.04 (t, *J* = 7.2 Hz, 2H), 2.87 (t, *J* = 7.8 Hz, 2H), 1.67 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 201.5, 124.5, 122.6, 122.4, 119.1, 118.7, 115.3, 43.1, 28.2, 17.4; **HRMS (ESI$^+$)** Calcd. For $C_{16}H_{19}NO_3$ + Na, 296.1263; Found, 296.1256; **IR** (thin film, cm^{-1}) 3446, 2977, 2916, 1731, 1670, 1636, 1455, 1373, 1256, 1158, 1018, 746; **TLC** (80:20 hexanes: EtOAc): R_f = 0.53.



S3 *45%* **S4**

***tert*-butyl 3-(2-formylallyl)-1H-indole-1-carboxylate (S4)**: A flame-dried, 50 mL round bottomed flask was charged with aldehyde **S3** (0.16 g, 0.60 mmol, 1.00 equiv) and CH_2Cl_2 (12 mL) at rt under an atmosphere of N_2. NEt_3 (0.84 mL, 6.00 mmol, 10.0 equiv) was added followed lastly by dimethylmethylideneiminium

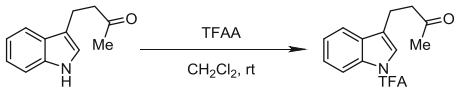
iodide (0.33 g, 1.8 mmol, 3.00 equiv). The mixture was allowed to stir at rt until complete conversion of the starting material was observed by TLC analysis, typically 12 h. The reaction was then concentrated on a rotary evaporator and purified via flash chromatography (95:5 to 90:10 hexanes:EtOAc) to afford unsaturated aldehyde **S4** (0.08 g, 45 % yield) as a yellow, viscous oil. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 9.67 (s, 1H), 8.13 (br s, 1H), 7.42 (br s, 1H), 7.39 (d, J = 7.8 Hz, 1H), 7.32 (t, J = 8.4 Hz, 1H), 7.22 (t, J = 7.8 Hz, 1H), 3.65 (s, 2H), 1.67 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 194.0, 149.7, 147.9, 135.3, 130.1, 124.4, 124.1, 122.5, 119.1, 116.8, 115.3, 83.6, 28.2, 23.3; **HRMS (ESI$^+$)** Calcd. For $C_{17}H_{19}NO_3$ + Na, 308.1263; Found, 308.1255; **IR** (thin film, cm^{-1}) 3446, 2916, 1732, 1685, 1488, 1455, 1370, 1255, 1158, 1083, 959; **TLC** (80:20 hexanes:EtOAc): R_f = 0.60.



S4 *71%* **3.67**

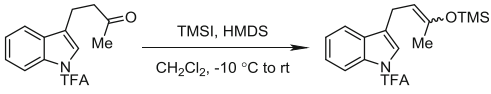
***tert*-butyl 3-(2-methylene-3-oxobutyl)-1H-indole-1-carboxylate (3.67)**: A flame-dried, 20 mL scintillation vial was charged with aldehyde **S4** (0.04 g, 0.12 mmol, 1.00 equiv) and THF (2 mL) under an atmosphere of N_2. The solution was cooled to 0 °C, and MeMgBr (3 M in Et_2O, 0.12 mL, 0.37 mmol, 3.00 equiv) was added over a period of ~1 min. The mixture was allowed to stir until complete consumption of the starting material was observed by TLC analysis, typically 30 min. The reaction was then quenched via addition of saturated $NH_4Cl_{(aq.)}$ (5 mL), and the mixture was transferred to a separatory funnel. The aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo* to give the crude alcohol, which was used in the next step without further purification.

The crude residue was dissolved in CH_2Cl_2 (2 mL) and transferred to a 20 mL scintillation vial. Dess-Martin periodinane (0.10 g, 0.25 mmol, 2.00 equiv) was added to the vial, and the resulting mixture was allowed to stir until complete consumption of the starting material was observed by TLC analysis, typically 20 min. The reaction mixture was then quenched via a 1:1 mixture of saturated $NaHCO_{3(aq.)}$ and saturated $Na_2S_2O_{3(aq.)}$ (5 mL) and allowed to stir 5 min. The mixture was then transferred to a separatory funnel, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo*. The product was purified via flash chromatography (95:5 to 90:10 hexanes:EtOAc) to afford enone **3.67** (0.026 g, 71 % yield) as a yellow viscous oil. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.12 (br s, 1H), 7.41 (d, J = 9.0 Hz, 1H), 7.39 (br s, 1H), 7.31 (t, J = 9.0 Hz, 1H), 7.21 (t, J = 9.0 Hz, 1H), 6.10 (s, 1H), 5.72(s, 1H), 3.67 (s, 2H), 2.39 (s, 3H), 1.67 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 199.4, 146.8, 126.5, 124.3, 124.0, 122.4, 119.2, 117.8, 115.2, 36.6, 28.2, 25.9; **HRMS (ESI$^+$)** Calcd. For $C_{18}H_{21}NO_3$ + Na, 322.1419; Found, 322.1411; **IR** (thin film, cm^{-1}) 3445, 3054, 2980, 2930, 1731, 1680, 1628, 1454, 1368, 1256, 1158, 1082; **TLC** (80:20 hexanes:EtOAc): R_f = 0.60.



S5 *71%* **S6**

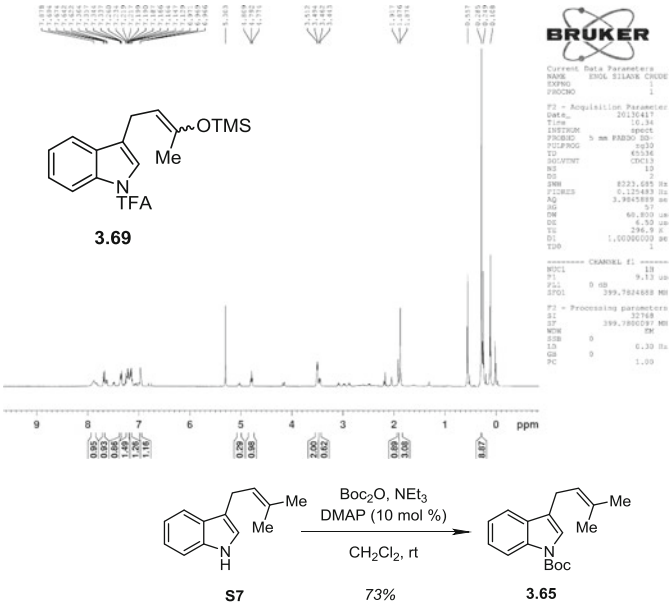
4-(1-(2,2,2-trifluoroacetyl)-1H-indol-3-yl)butan-2-one (S6): A flame-dried, 100 mL round bottomed flask was charged with TFAA (1.51 mL, 10.7 mmol, 4.00 equiv) and CH_2Cl_2 (25 mL) under an atmosphere of N_2. 4-(1H-indol-3-yl) butan-2-one **S5** (0.50 g, 2.67 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (2 mL) and added dropwise to the TFAA solution. Once the addition was complete, the mixture was allowed to stir at rt until complete consumption of the starting material was observed by TLC analysis, typically 12 h. The reaction was quenched via addition of saturated $NaHCO_{3(aq.)}$ (10 mL) and transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried with sodium sulfate and concentrated *in vacuo*. The product was purified via flash chromatography (90:10 to 80:20 hexanes:EtOAc) to afford TFA-protected indole **S6** (0.54 g, 71 % yield) as a pale yellow solid. Analytical data: **mp** 55–58 °C; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.43 (d, J = 7.8 Hz, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.42 (m, 2H), 7.25 (br s, 1H), 2.99 (t, J = 7.8 Hz, 2H), 2.87 (t, J = 7.8 Hz, 2H), 2.20 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 207.0, 136.2, 130.5, 126.4, 125.5, 125.2, 120.3, 120.2, 119.2, 117.0, 42.2, 30.0, 18.6; **HRMS (ESI$^+$)** Calcd. For $C_{14}H_{12}F_3NO_2$ + Na, 306.0718; Found, 306.0709; **IR** (thin film, cm^{-1}) 2917, 1717, 1459, 1419, 1292, 1207, 1155, 880; **TLC** (80:20 hexanes:EtOAc): R_f = 0.48.



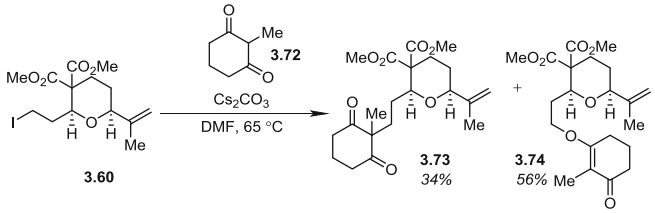
S6 **3.69**

2,2,2-trifluoro-1-(3-(3-((trimethylsilyl)oxy)but-2-en-1-yl)-1H-indol-1-yl) ethan-1-one (3.69): a flame-dried, 20 mL scintillation vial was charged with ketone **S6** (0.05 g, 0.267 mmol, 1.00 equiv) and CH_2Cl_2 (3 mL) under an atmosphere of N_2. The mixture was cooled to −10 °C, and HMDS (0.17 mL, .801 mmol, 3.00 equiv) was added followed by TMSI (0.02 mL, 0.267 mmol, 1.00 equiv) dropwise. The reaction mixture was warmed to rt and stirred until TLC analysis confirmed complete consumption of the starting material, typically 45 min. The reaction mixture was then quenched via addition of saturated $NaHCO_{3(aq.)}$ (5 mL) and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo* to afford the crude enol-silane as a ∼3:1 mixture of alkene isomers as determined by ^{1}H NMR analysis. This material was unstable to further purification and was used directly in reaction screenings. The crude ^{1}H NMR spectrum is included below.

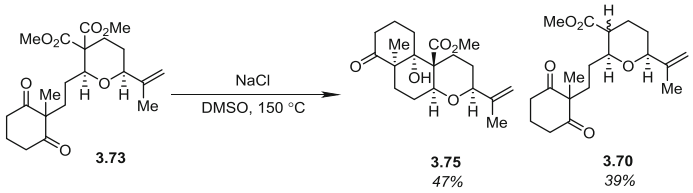
Crude ^{1}H NMR spectrum of 3.69



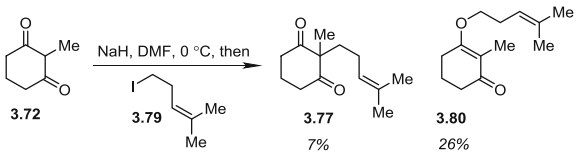
***tert*-butyl 3-(3-methylbut-2-en-1-yl)-1H-indole-1-carboxylate (3.65)**: A flame-dried, 20 mL scintillation vial was charged with 3-(3-methylbut-2-en-1-yl)-1H-indole **S7** (0.05 g, 0.27 mmol, 1.00 equiv), NEt_3 (0.06 mL, 0.41 mmol, 1.50 equiv), DMAP (0.003 g, 0.027 mmol, 0.10 equiv), and CH_2Cl_2 (3 mL) at rt under an atmosphere of N_2. Boc_2O (0.07 mL, 0.32 mmol, 1.20 equiv) was added, and the mixture was allowed to stir at rt until TLC analysis confirmed complete consumption of the starting material, typically 12 h. The mixture was diluted with H_2O (5 mL) and transferred to a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts were washed with H_2O (5 mL), dried with sodium sulfate, and concentrated *in vacuo*. The product was purified via flash chromatography (100:0 to 98:2 hexanes:EtOAc) to afford protected indole **3.67** (0.06 g, 73 % yield) as a yellow viscous oil. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.11 (d, J = 9.0 Hz, 1H), 7.53 (d, J = 7.8 Hz, 1H), 7.35–7.31 (m, 2H), 7.25 (t, J = 7.8 Hz, 1H), 5,41 (t, J = 7.2 Hz, 1H), 3.39 (d, J = 7.2 Hz, 2H), 1.78 (br s, 6H), 1.68 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 133.0, 124.2, 123.1, 122.3, 122.2, 121.5, 120.6, 120.5, 119.1, 115.2, 107.1, 28.2, 25.7, 23.9, 17.8; **HRMS (ESI^{+})** Calcd. For $C_{18}H_{23}NO_2$ + Na, 308.1626; Found, 308.1619; **IR** (thin film, cm^{-1}) 3421, 3053, 2980, 2931, 1730, 1454, 1371, 1265, 1158, 855; **TLC** (80:20 hexanes:EtOAc): R_f = 0.95.



Dimethyl 2-(2-(1-methyl-2,6-dioxocyclohexyl)ethyl)-6-(prop-1-en-2-yl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (3.73): A flame-dried, 20 mL scintillation vial was charged with iodide **3.60** (0.60 g, 1.51 mmol, 1.00 equiv), 2-methyl-1,3-cyclohexanedione (0.27 g, 2.12 mmol, 1.4 equiv), and DMF (3 mL) at rt under an atmosphere of N_2. Cs_2CO_3 (0.74 g, 2.27 mmol, 1.50 equiv) was added, and the mixture was warmed to 65 °C. The reaction was allowed to stir at this temperature until complete consumption of the starting material was observed by TLC analysis, typically 5 h. The reaction mixture was cooled to rt, diluted with H_2O (6 mL) and Et_2O (5 mL), and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried with magnesium sulfate, and concentrated *in vacuo*. The mixture was purified via flash chromatography (70:30 to 60:40 to 50:50 hexanes:EtOAc) to afford diketone **3.73** (0.20 g, 34 % yield) as a clear, viscous oil and enol ether **3.74** (0.34 g, 56 % yield) as a clear, viscous oil. Analytical data: O-alkylation product **3.74**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.90 (s, 1H), 4.79 (s, 1H), 4.09 (m, 2H), 3.92 (d, J = 10.8 Hz, 1H), 3.77 (d, J = 11.4 Hz, 1H), 3.74 (s, 3H), 3.69 (s, 3H), 2.55–2.51 (m, 3H), 2.31 (t, J = 6.6 Hz, 2H), 2.21 (m, 1H), 2.09 (m, 1H), 1.96–1.90 (m, 3H), 1.79 (m, 1H), 1.70 (s, 3H), 1.68 (s, 3H), 1.66 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 198.8, 171.5, 110.9, 169.3, 144.8, 115.0, 110.8, 81.3, 77.1, 64.6, 56.4, 52.6, 52.1, 36.2, 32.7, 31.9, 26.4, 25.3, 20.9, 18.8, 7.3; **HRMS (ESI$^+$)** Calcd. For $C_{21}H_{30}O_7$ + Na, 417.1889; Found, 417.1879; **IR** (thin film, cm^{-1}) 2953, 1731, 1635, 1455, 1377, 1355, 1262, 1095, 921; **TLC** (75:25 hexanes:EtOAc): R_f = 0.10. C-alkylation product **3.73**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.90 (s, 1H), 4.79 (s, 1H), 3.73–3.70 (m, 4H), 3.68 (s, 3H), 3.61 (m, 1H), 2.76 (m, 2H), 2.56–2.48 (m, 3H), 2.12 (m, 1H), 2.04 (m, 1H), 1.85–1.74 (m, 4H), 1.69 (s, 3H), 1.63 (m, 1H), 1.59 (m, 2H), 1.18 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 210.0, 209.8, 171.3, 169.2, 145.0, 110.6, 81.1, 80.9, 66.1, 56.2, 52.5, 52.0, 37.5, 35.5, 32.0, 27.6, 26.4, 18.8, 17.8, 17.0; **HRMS (ESI$^+$)** Calcd. For $C_{21}H_{30}O_7$ + Na, 417.1889; Found, 417.1879; **IR** (thin film, cm^{-1}) 3403, 3057, 2954, 2872, 1729, 1696, 1455, 1266, 1084, 905; **TLC** (75:25 hexanes:EtOAc): R_f = 0.13.

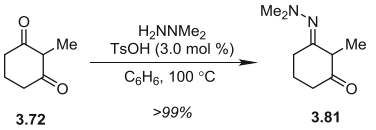


Methyl 10a-hydroxy-6a-methyl-7-oxo-3-(prop-1-en-2-yl)decahydro-1H-benzo [f]chromene-10b(4aH)-carboxylate (3.75): A 5 mL dram vial was charged with diketone **3.73** (0.015 g, 0.04 mmol, 1.00 equiv) and DMSO (2 mL), and NaCl (0.02 g, 0.38 mmol, 10.0 equiv) was added in one portion. The vial was sealed with a screw-cap, and the mixture was warmed to 150 °C and stirred 9 h. The mixture was cooled to rt, diluted with Et_2O (2 mL) and transferred to a separatory funnel containing H_2O (10 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL), and the combined organic extracts were washed with brine (5 mL), dried with magnesium sulfate, and concentrated *in vacuo*. Crude ^{1}H NMR analysis revealed a ~1:1 mixture of the diastereomeric decarboxylation product **3.70** and annulation product **3.75**. This mixture was purified via flash chromatography (70:30 to 60:40 hexanes: EtOAc) to afford annulation product **3.75** (0.006 g, 47 % yield) as a clear, viscous oil and Krapcho adduct **3.70** (0.005 g, 39 % yield) as a clear, viscous oil. Slow evaporation of **3.75** from acetone and hexanes provided crystals suitable for X-ray crystallographic analysis. (Note: when this reaction was conducted on 0.07 g, scale, only the Krapcho adduct **3.70** was isolated in 43 % yield. No cyclization product **3.75** was detected on this scale.) Analytical data: decarboxylation product **3.70**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.94 (s, 2H), 4.82–4.81 (m, 2H), 3.73–3.70 (m, 2H), 3.68–6.67 (m, 3H), 3.47–3.41 (m, 2H), 2.80–2.69 (m, 4H), 2.60–2.54 (m, 4H), 2.24 (m, 1H), 2.14–2.12 (m, 2H), 2.07–1.98 (m, 5H), 1.85–1.77 (m, 3H), 1.74–1.73 (m, 5H), 1.51–1.39 (m, 5H), 1.21 (s, 3H), 1.18 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 210.3, 210.1, 210.0, 209.9, 174.3, 172.8, 145.8, 145.5, 110.6, 110.2, 81.5, 80.0, 78.0, 77.3, 66.1, 65.5, 51.7, 51.3, 46.7, 37.8, 37.7, 37.5, 34.0, 33.5, 29.7, 29.1, 28.9, 28.8, 27.7, 26.2, 25.7, 19.0, 18.8, 18.3, 17.9, 17.7, 16.4; **HRMS (ESI$^+$)** Calcd. For $C_{19}H_{28}O_5$ + Na, 359.1834; Found, 359.1825; **IR** (thin film, cm^{-1}) 3446, 2917, 2849, 1731, 1652, 1540, 1456, 1200, 901; **TLC** (75:25 hexanes:EtOAc): R_f = 0.17. Annulation product **3.75**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.91 (s, 1H), 4.78 (s, 1H), 3.86 (d, *J* = 12.0 Hz, 1H), 3.66 (dd, *J* = 7.8, 4.8 Hz, 1H), 3.59 (s, 3H), 2.47 (m, 2H), 2.31 (m, 2H), 2.16 (dd, *J* = 10.8, 6.0 Hz, 1H), 2.10–2.00 (m, 3H), 1.77 (m, 2H), 1.68 (s, 3H), 1.62 (m, 1H), 1.52 (br s, 1H), 1.45 (m, 1H), 1.35 (m, 1H), 1.18 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 210.0, 172.5, 145.7, 110.9, 82.0, 80.0, 78.2, 53.5, 53.2, 50.5, 34.1, 29.1, 28.1, 27.5, 26.9, 25.9, 25.4, 18.4, 18.1; **HRMS (ESI$^+$)** Calcd. For $C_{19}H_{28}O_5$ + Na, 359.1834; Found, 359.1825; **IR** (thin film, cm^{-1}) 3446, 3055, 2950, 1718, 1456, 1339, 1265, 1073, 899; **TLC** (75:25 hexanes:EtOAc): R_f = 0.07.

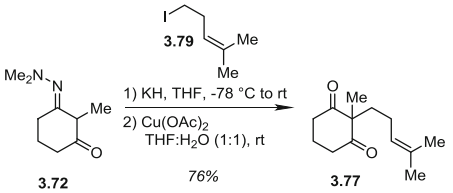


2-methyl-3-((4-methylpent-3-en-1-yl)oxy)cyclohex-2-en-1-one (3.80): A flame-dried, 25 mL round bottomed flask was charged with 2-methyl-1,3-cyclohexane dione **3.72** (1.00 g, 7.93 mmol, 100 equiv) and DMF (8 mL) under an atmosphere of

N_2. The mixture was cooled to 0 °C and NaH (60 % dispersion in oil, 0.39 g, 10.3 mmol, 1.30 equiv) was added portionwise. The mixture was warmed to rt and stirred 10 min whereupon the iodide **3.79** (2.16 g, 10.3 mmol, 1.30 equiv) was added. The mixture was allowed to stir 12 h, and the reaction mixture was poured into a separatory funnel containing H_2O (20 mL). CH_2Cl_2 (20 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried with magnesium sulfate, and concentrated *in vacuo*. The products were purified via flash chromatography (90:10 to 80:20 to 60:40 hexanes:EtOAc) to afford cycloalkanedione **3.77** (0.12 g, 7 % yield) as a yellow oil and vinyl ether **3.80** (0.43 g, 26 % yield) as a clear, viscous oil. Analytical data: O-alkylation product **3.80**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.11 (m, 1H), 3.93 (t, J = 6.6 Hz, 2H), 2.51 (m, 2H), 2.36 (q, J = 7.2 Hz, 2H), 2.30 (t, J = 6.6 Hz, 2H), 1.93 (m, 2H), 1.68 (s, 3H), 1.66 (t, J = 1.2 Hz, 3H), 1.61 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 198.8, 171.4, 134.8, 118.9, 115.0, 67.4, 36.2, 28.7, 25.7, 25.4, 20.9, 17.7, 7.29; **HRMS (ESI$^+$)** Calcd. For $C_{13}H_{20}O_2$ + Na, 231.1361; Found, 231.1354; **IR** (thin film, cm^{-1}) 3446, 2926, 1732, 1646, 1472, 1376, 1238, 1096; **TLC** (70:30 hexanes:EtOAc): R_f = 0.26. C-alkylation product **3.77**: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.99 (br s, 1H), 2.70 (m, 2H), 2.60 (m, 2H), 2.01 (m, 1H), 1.86–1.80 (m, 5H), 1.64 (s, 3H), 1.55 (s, 3H), 1.23 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 210.3, 132.9, 122.9, 65.6, 37.9, 37.5, 25.6, 23.3, 18.9, 17.7, 17.6; **HRMS (ESI$^+$)** Calcd. For $C_{13}H_{20}O_2$ + H, 209.1542; Found, 209.1537; **IR** (thin film, cm^{-1}) 3400, 2967, 2929, 1725, 1695, 1602, 1451, 1280, 1169, 1026; **TLC** (80:20 hexanes: EtOAc): R_f = 0.40.

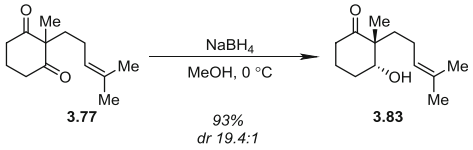


(*E*)-3-(2,2-dimethylhydrazono)-2-methylcyclohexan-1-one (3.81): A 250 mL round bottomed flask was charged with 2-methyl-1,3-cyclohexanedione **3.72** (12.0 g, 95.1 mmol, 1.00 equiv), C_6H_6 (150 mL), H_2NNMe_2 (8.70 mL, 114.2 mmol, 1.20 equiv), and TsOH (0.50 g, 2.63 mmol, 0.03 equiv). A Dean-Stark apparatus was connected to the flask, and the mixture was heated to 100 °C with vigorous stirring for 6 h. The mixture was cooled to rt and concentrated on a rotary evaporator. The crude residue was then recrystallized from C_7H_8 to afford ketohydrazone **3.81** (16.00 g, 99 % yield) as a yellow powder. Analytical data for this compound matched that reported in the literature [70]. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.05 (br s, 1H), 2.64 (m, 2H), 2.53 (s, 6H), 2.32 (t, J = 7.2 Hz, 2H), 1.90 (m, 2H), 1.66 (s, 3H).



2-methyl-2-(4-methylpent-3-en-1-yl)cyclohexane-1,3-dione(3.77): A flame-dried, 500-mL round-bottomed flask was charged with THF (250 mL) under an atmosphere of N_2. KH (10.40 g, 30 % dispersion in oil, 78.50 mmol, 1.20 equiv) was washed free of oil three times with petroleum ether, suspended in THF (20 mL) and added to the flask with stirring. The reaction mixture was cooled to −78 °C, and a solution of ketohydrazone **3.72** (11.00 g, 65.42 mmol, 1.00 equiv) in THF (25 mL) was slowly added. The reaction was warmed to 0 °C and allowed to stir 4.5 h. The resulting dark-brown mixture was re-cooled to −78 °C, and iodide **3.79** (17.3 g, 78.50 mmol, 1.20 equiv) was added. The reaction mixture was allowed to stir while slowly warming to rt overnight, producing a cream-white suspension. The reaction was then quenched with saturated $NH_4Cl_{(aq.)}$ (50 mL), and the resulting mixture was partitioned in a separatory funnel. The aqueous layer was extracted with Et_2O (3 × 50 mL), and the combined organic extracts were washed with brine (40 mL), dried with magnesium sulfate, and concentrated *in vacuo* to give the intermediate alkylation product, which was used in the next step without further purification.

$Cu(OAc)_2 \cdot H_2O$ (26.00 g, 130.9 mmol, 2.00 equiv) was dissolved in H_2O (300 mL) in a 1000-mL round-bottomed flask with vigorous stirring. The crude hydrazone was then dissolved in THF (300 mL) and added to the $Cu(OAc)_2 \cdot H_2O$ solution, and the reaction mixture was allowed to stir until TLC analysis confirmed complete conversion of the starting material, typically 12 h. The resulting mixture was concentrated on a rotary evaporator to remove the THF, and the solution was then diluted with saturated $NH_4Cl_{(aq.)}$ (100 mL) and CH_2Cl_2 (100 mL). This mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried with magnesium sulfate, and concentrated *in vacuo*. The product was purified via flash chromatography (90:10 to 80:20 hexanes:EtOAc) to afford diketone **3.77** (10.34 g, 76 % yield) as an orange, viscous oil.

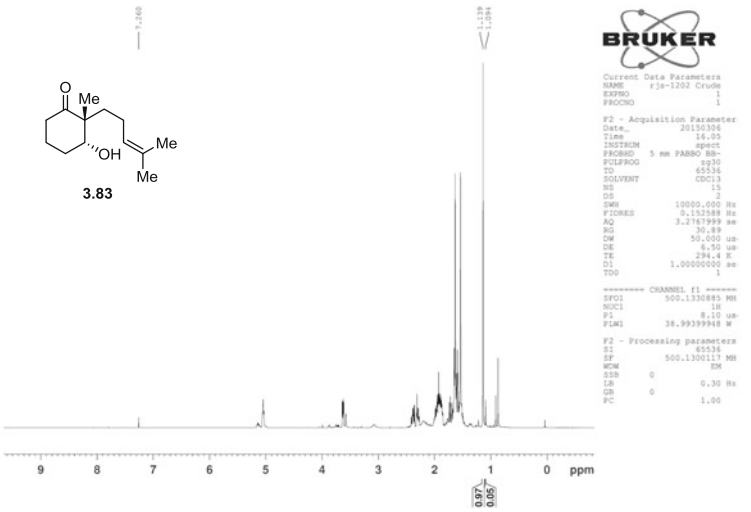


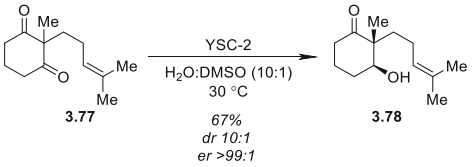
3.77 *93%* *dr 19.4:1* **3.83**

3-hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)cyclohexan-1-one (3.83): A 20 mL scintillation vial was charged with diketone **3.77** (0.1 g, 0.48 mmol, 1.00 equiv) and MeOH (10 mL), and the solution was cooled to 0 °C. $NaBH_4$ (0.005 g, 0.12 mmol, 0.25 equiv) was added, and the mixture was allowed to stir at this temperature until complete consumption of the starting material was observed by TLC analysis, typically 10 min. The reaction was diluted with brine (5 mL) and CH_2Cl_2 (5 mL), and the mixture was transferred to a separatory funnel.

The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts were dried with sodium sulfate and concentrated *in vacuo* to give the crude alcohol as a 19.4:1 mixture of diastereomers. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 1.14 (major diastereomer) and δ 1.09 (minor diastereomer). The product was purified via flash chromatography (80:20 to 70:30 hexanes:EtOAc) to afford hydroxyketone **3.83** (0.093 g, 93 % yield) as a clear, viscous oil. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.05 (t, J = 6.0 Hz, 1H), 3.65 (d, J = 7.8 Hz, 1H), 2.39 (m, 1H), 2.32 (m, 1H), 1.99–1.88 (m, 5H), 1.73 (m, 1H), 1.66–1.63 (m, 4H), 1.55 (br s, 4H), 1.15 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 214.1, 132.1, 123.9, 77.5, 54.7, 37.6, 31.5, 28.7, 25.6, 21.9, 20.7, 18.7, 17.6; **HRMS (ESI$^+$)** Calcd. For $C_{13}H_{22}O_2$ + Na, 233.1518; Found, 233.1510; **IR** (thin film, cm^{-1}) 3420, 2939, 2871, 1698, 1455, 1375, 1161, 1059, 993, 831; **TLC** (70:30 hexanes:EtOAc): R_f = 0.32.

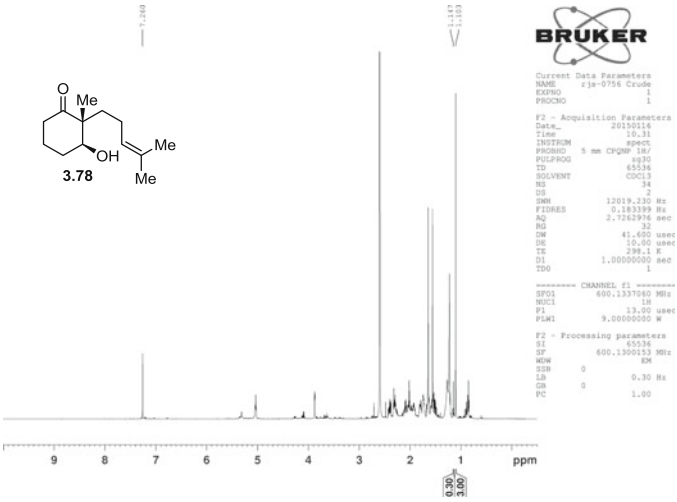
Crude ^{1}H NMR Spectrum of 3.83

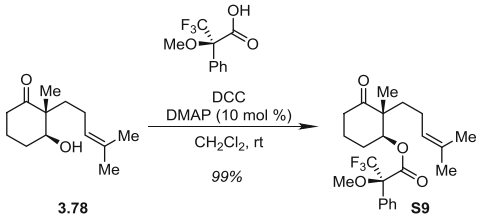




(2*R*,3*S*)-3-hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)cyclohexan-1-one (3.78): A 1000-mL round-bottomed flask was charged with H_2O (320 mL), and YSC-2 (77 g, purchased from Sigma Aldrich) was added portion-wise with vigorous stirring. Diketone **3.77** (2.00 g, 9.60 mmol, 1.00 equiv) was dissolved in DMSO (32 mL) and added to the YSC-2 suspension, and the mixture was warmed to 30 °C and vigorously stirred for 24 h. The reaction mixture was then cooled to rt, diluted with Et_2O (50 mL), and Celite (10 g) was added. The stirring was stopped, and the mixture was allowed to let stand at rt for 12 h. The resulting mixture was then filtered through a pad of Celite in a Buchner funnel. Once the filter cake was dry, the Celite pad was then washed with Et_2O (100 mL), CH_2Cl_2 (100 mL), acetone (100 mL), Et_2O (100 mL), and EtOAc (100 mL), ensuring that the filter cake was loosened with a spatula between each wash. The filtrate was transferred to a separatory funnel, and the organic layer was separated. The aqueous layer was extracted with EtOAc (50 mL), and the combined organic extracts were dried with sodium sulfate and concentrated *in vacuo*, giving crude alcohol **3.78** as a 10:1 mixture of diasteromers. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 1.15 (minor diastereomer) and δ 1.10 (major diastereomer). The product was purified via flash chromatography (80:20 to 70:30 hexanes:EtOAc) to afford alcohol **3.78** (1.32 g, 67 % yield) as a yellow, viscous oil. (Note: for purposes of material throughput, the crude residue may be stored indefinitely with no deleterious effects to yield. In practice, up to 8 iterations of this procedure were carried out, and the crude residues were combined and purified simultaneously). The enantioselectivity (>99:1) was determined via ^{19}F NMR analysis of the resulting Mosher ester **S9** (vide infra). Analytical data: $[\alpha]_D^{28}$ –74.7 (c = 0.30, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.04 (m, 1H), 3.89 (dd, J = 3.0, 2.4 Hz, 1H), 2.41 (m, 1H), 2.31 (m, 1H), 2.08 (m, 1H), 2.02 (m, 1H), 1.93 (m, 1H), 1.87–1.79 (m, 4H), 1.65 (br s, 4H), 1.56 (s, 3H), 1.53 (m, 1H), 1.10 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 214.4, 132.2, 123.7, 76.3, 54.3, 37.8, 36.2, 28.1, 25.6, 22.6, 20.7, 17.6, 17.3; **HRMS (ESI$^+$)** Calcd. For $C_{13}H_{22}O_2$ + Na, 233.1518; Found, 233.1514; **IR** (thin film, cm^{-1}) 3434, 3054, 2985, 2305, 1703, 1630, 1442, 1265, 738; **TLC** (80:20 hexanes:EtOAc): R_f = 0.23.

Crude ^{1}H NMR spectrum of 3.78.

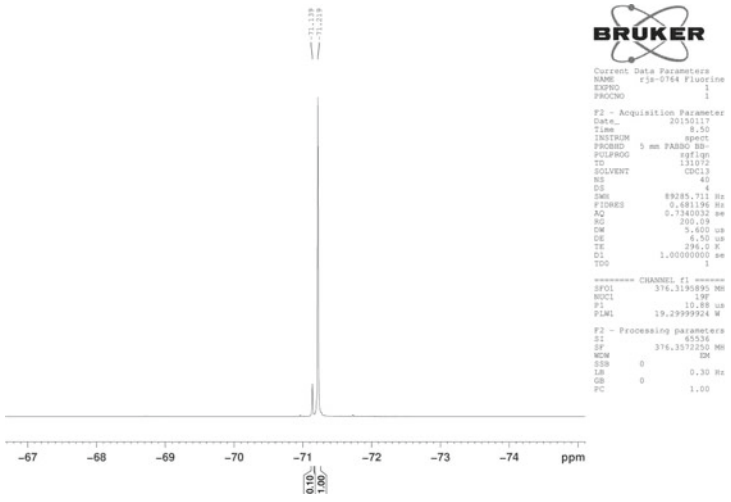


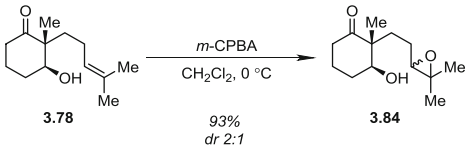


(1*S*,2*R*)-2-methyl-2-(4-methylpent-3-en-1-yl)-3-oxocyclohexyl(*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (S9): A flame-dried, 20 mL scintillation vial was charged with (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (0.45 g, 1.90 mmol, 2.00 equiv) and CH_2Cl_2 (8 mL) with magnetic stirring at rt under an atmosphere of N_2. DCC (0.39 g, 1.90 mmol, 2.00 equiv) was added followed by DMAP (0.01 g, 0.10 mmol, 0.10 equiv) and lastly a 10:1 diastereomeric mixture of alcohol **3.78** (0.20 g, 0.95 mmol, 1.00 equiv) in CH_2Cl_2 (2 mL). The reaction mixture was allowed to stir at rt until complete conversion of the starting material was observed by TLC analysis, typically 12 h. The resulting mixture was filtered through cotton and concentrated *in vacuo*. The product was purified via flash chromatography (95:5 to 90:10 hexanes:EtOAc) to provide Mosher ester **S9** (0.40 g, 99 % yield) as an inseparable 10:1 mixture of diastereomers (as determined by integration of the resonances at dd 5.33 (major diastereomer) and dd 5.06 (minor diastereomer)). ^{19}F NMR analysis revealed only a 10:1 mixture of diastereomers at δ −71.1 ppm (minor diastereomer) and δ −71.2 ppm (major diastereomer). Analytical data: $[\alpha]_D^{28}$

+22.6 (c = 0.50, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.50 (m, 2H), 7.39 (m, 3H), 5.33 (dd, J = 3.0, 3.0 Hz, 1H), 3.50 (s, 3H), 2.45 (m, 1H), 2.35 (m, 1H), 2.22 (m, 1H), 1.96–1.74 (m, 5H), 1.66 (s, 3H), 1.57 (s, 3H), 1.54 (m, 2H), 0.96 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 211.5, 165.8, 132.5, 131.9, 129.6, 128.4, 127.2, 123.2, 80.3, 55.3, 52.6, 37.4, 35.9, 25.6, 25.5, 22.4, 20.4, 17.8, 17.6; **HRMS (ESI$^+$)** Calcd. For $C_{23}H_{29}F_3O_4$ + Na, 449.1916; Found, 449.1923; **IR** (thin film, cm^{-1}) 3423, 2949, 2855, 1746, 1713, 1451, 1270, 1168, 1019, 807, 721; **TLC** (80:20 hexanes:EtOAc): R_f = 0.51.

^{19}F NMR Spectrum of S9

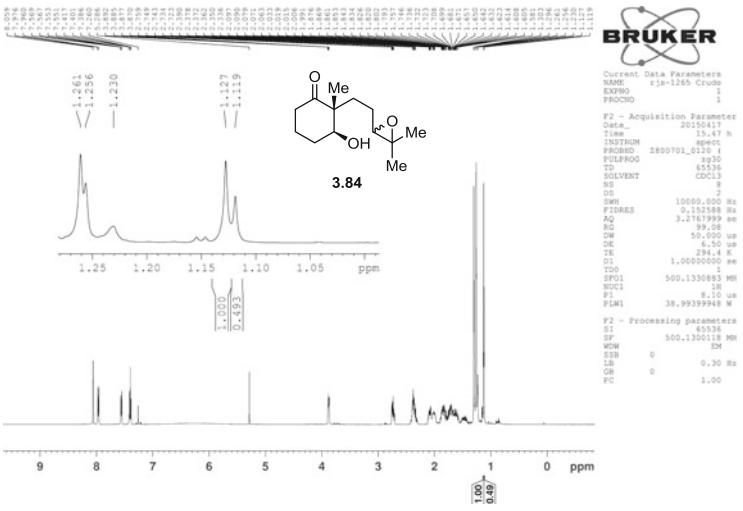


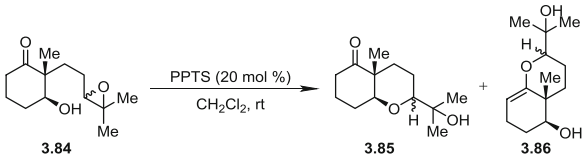


(2*R*,3*S*)-2-(2-(3,3-dimethyloxiran-2-yl)ethyl)-3-hydroxy-2-methylcyclohexan-1-one (3.84): A 20 mL scintillation vial was charged with hydroxyketone **3.78** (0.10 g, 0.48 mmol, 1.00 equiv) and CH_2Cl_2 (5 mL), and the mixture was cooled to 0 °C. *m*-CPBA (70 % dispersion in H_2O, 0.19 g, 0.76 mmol, 1.60 equiv) was added in one portion, and the mixture was stirred until complete consumption of the starting material was observed by TLC analysis, typically 20 min. The reaction was quenched via saturated $Na_2S_2O_3$ (5 mL), and the mixture was transferred to a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts were dried with sodium sulfate and concentrated *in vacuo* to give the crude epoxide as a 2:1 mixture of diastereomers. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude

reaction mixture by comparison of the integration of the resonances at δ 1.13 (major diastereomer) and δ 1.12 (minor diastereomer). The product was purified via flash chromatography (60:40 to 50:50 to 40:60 hexanes:EtOAc) to afford epoxide **3.84** (0.10 g, 93 % yield) as a clear oil in an inseparable mixture of diastereomers. Analytical data: $[\alpha]_D^{25}$ +1.9 (*c* = 1.25, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 3.83 (dd, *J* = 4.2, 3.0 Hz, 1H), 2.68 (m, 1H), 2.33 (m, 2H), 2.01 (m, 2H), 1.84–1.54 (m, 5H), 1.48–1.40 (m, 1H), 1.27 (m, 3H), 1.23 (m, 3H), 1.09 (m, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 214.2, 214.1, 75.6, 74.4, 64.7, 64.3, 59.1, 58.7, 54.3, 54.0, 37.6, 37.5, 32.0, 31.7, 28.4, 28.3, 24.8, 23.6, 23.5, 20.4, 20.3, 18.6, 18.5, 18.0, 17.1; **HRMS (ESI$^+$)** Calcd. For $C_{13}H_{22}O_3$ + Na, 249.1467; Found, 249.1459; **IR** (thin film, cm^{-1}) 3446, 3054, 2982, 2874, 1732, 1702, 1497, 1422, 1266, 1156, 1016, 895; **TLC** (80:20 hexanes:EtOAc): R_f = 0.07.

Crude ^{1}H NMR spectrum of 3.84

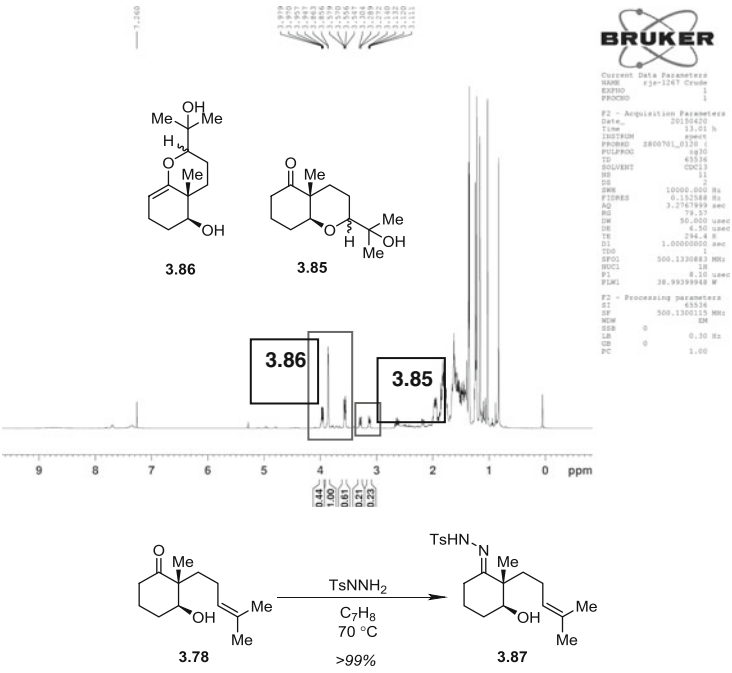




(4a*R*,8a*S*)-2-(2-hydroxypropan-2-yl)-4a-methyloctahydro-5H-chromen-5-one (3.85) and **(4a*R*,5*S*)-2-(2-hydroxypropan-2-yl)-4a-methyloctahydro-2H-chromen-5-ol (3.86)**: A 20 mL scintillation vial was charged with keto-epoxide **3.84** (0.05 g, 0.22 mmol, 1.00 equiv) and CH_2Cl_2 (2 mL), and PPTS (0.01 g, 0.04 mmol, 0.20 equiv) was added. The mixture was allowed to stir at rt until TLC analysis indicated complete consumption of the starting material, typically 30 min.

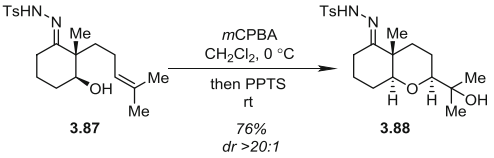
The reaction mixture was diluted with saturated $NaHCO_{3(aq.)}$ (5 mL) and transferred to a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts were dried with sodium sulfate and concentrated *in vacuo*. Crude ^{1}H NMR analysis revealed an inseparable ~1:5 mixture of diastereomeric tetrahydropyrans **3.85** and diastereomeric vinyl ethers **3.86**. The crude ^{1}H NMR spectrum and mass spectral data are included below: **HRMS (ESI$^+$)** Calcd. For +Na, 249.1467; Found, 249.1459.

Crude ^{1}H NMR spectrum of 3.85 and 3.86



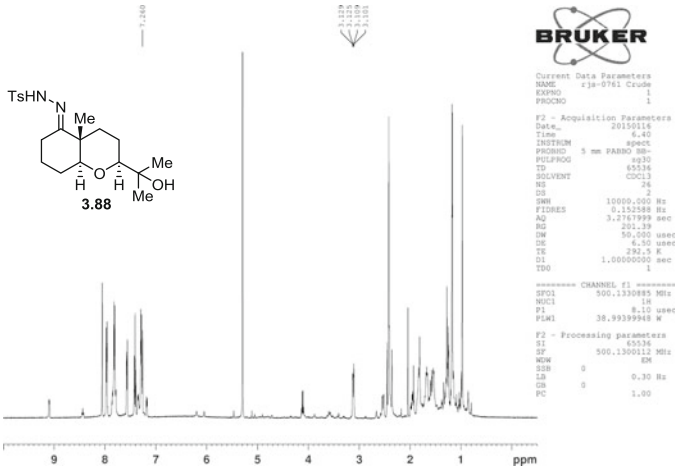
***N*'-((2*S*,3*S*,*E*)-3-hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)cyclohexylidene)-4-methylbenzenesulfonohydrazide(3.87)**: The alcohol **3.78** (8.20 g, 38.99 mmol, 1.00 equiv) was dissolved in wet C_7H_8 (195 mL) in a 500-mL round-bottomed flask, and *p*-toluenesulfonylhydrazine (8.71 g, 46.79 mmol, 1.20 equiv) was added with magnetic stirring. The mixture was placed in a preheated oil bath at 70 °C and allowed to stir for 50 min. (Note: product decomposition was observed if the reaction was allowed to stir for longer than this time period). The resulting mixture was cooled to rt and concentrated on a rotary evaporator. The product was purified via flash chromatography (70:30 to 60:40 to 50:50 hexanes:EtOAc) to provide the hydrazone **3.87** (14.75 g, >99 % yield) as a pale yellow, viscous foam. Analytical data: $[\alpha]_D^{28}$ –144.6 (c = 0.50, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.82 (d, J = 8.4 Hz, 2H), 7.64 (br s, 1H), 7.28 (d, J = 7.8 Hz, 2H), 4.93 (t, J = 6.6 Hz, 1H), 3.63 (dd, J = 3.0, 2.4 Hz,

1H), 2.39 (s, 3H), 2.35 (m, 1H), 2.00 (m, 1H), 1.90 (m, 1H), 1.75–1.66 (m, 3H), 1.64 (s, 3H), 1.57–1.49 (m, 2H), 1.46 (s, 3H), 1.37 (m, 2H), 1.04 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 163.3, 143.9, 135.1, 131.5, 129.3, 128.2, 124.1, 75.4, 47.6, 36.5, 25.6, 22.0, 21.5, 19.8, 19.1, 17.5; **HRMS (ESI$^+$)** Calcd. For $C_{20}H_{30}N_2O_3S$ + Na, 401.1875; Found, 401.1892; **IR** (thin film, cm^{-1}) 3516, 3212, 2933, 2872, 1914, 1725, 1598, 1447, 1329, 1185, 1165, 1091, 736; **TLC** (80:20 hexanes:EtOAc): R_f = 0.17.



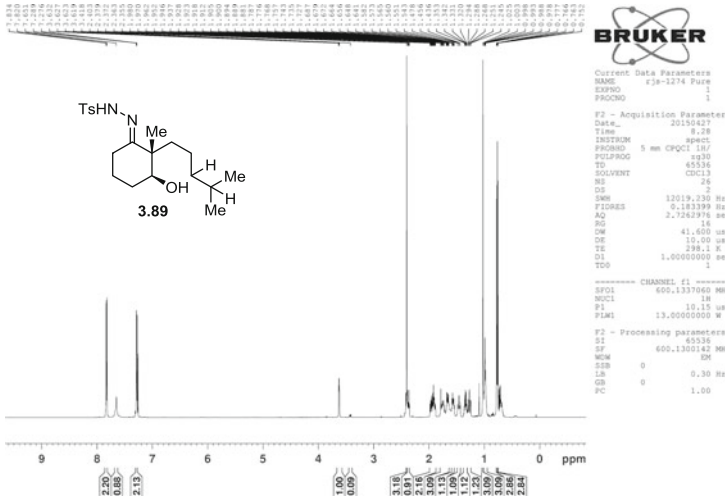
***N′*-((2*S*,4a*S*,8a*S*,*E*)-2-(2-hydroxypropan-2-yl)-4a-methyloctahydro-5H-chromen-5-ylidene)-4-methylbenzenesulfonohydrazide(3.88)**: Hydrazone **3.87** (14.76 g, 38.99 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (320 mL) in a 1000-mL round-bottomed flask with stirring. The mixture was cooled to 0 °C, and *m*-CPBA (14.42 g, 70 % dispersion in H_2O, 58.49 mmol, 1.50 equiv) was added. The reaction was allowed to stir at this temperature until TLC analysis showed full conversion of the starting material, typically 10 min. The reaction was quenched via addition of saturated $Na_2S_2O_{3(aq.)}$ (70 mL), and the mixture was partitioned in a separatory funnel. The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic extracts were washed with brine (50 mL), dried with magnesium sulfate, and concentrated to a volume of ∼300 mL on a rotary evaporator. A stir bar was added followed by PPTS (0.98 g, 3.90 mmol, 0.10 equiv), and the mixture was allowed to stir 12 h at rt. The reaction mixture was then concentrated *in vacuo* to give the crude tetrahydropyran **3.88** as a single diastereomer (as determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture, which revealed a single stereoisomer). The product was purified via flash chromatography (60:40 to 50:50 to 40:60 hexanes:EtOAc) to afford pyran **3.88** (11.63 g, 76 % yield) as a pale yellow, viscous foam. Analytical data: $[\alpha]_D^{28}$ –63.2 (c = 0.40, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.82 (d, J = 7.8 Hz, 2H), 7.73 (br s, 1H), 7.30 (d, J = 7.8 Hz, 2H), 3.11 (t, J = 3.6 Hz, 1H), 3.09 (t, J = 2.4 Hz, 1H), 2.52 (dd, J = 12.0, 3.0 Hz, 1H), 2.45–2.40 (m, 4H), 1.94 (m, 1H), 1.82 (m, 2H), 1.67 (m, 2H), 1.59–1.50 (m, 3H), 1.33–1.26 (m, 2H), 1.15 (s, 3H), 1.14 (s, 3H), 0.96 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 164.5, 143.9, 135.1, 129.3, 128.1, 84.5, 82.0, 71.8, 42.4, 32.1, 26.3, 21.6, 17.2; **HRMS (ESI$^+$)** Calcd. For $C_{20}H_{30}N_2O_4S$ + Na, 417.1824; Found, 417.1840; **IR** (thin film, cm^{-1}) 3451, 3216, 2946, 2870, 1630, 1598, 1450, 1333, 1166, 1089, 925; **TLC** (80:20 hexanes: EtOAc): R_f = 0.11.

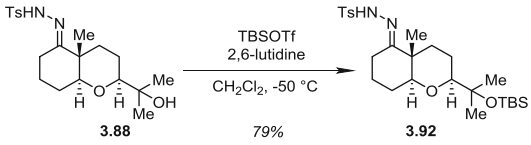
Crude ^{1}H NMR spectrum of 3.88.



***N′*-((2*S*,3*S*,*E*)-3-hydroxy-2-methyl-2-(4-methylpentyl)cyclohexylidene)-4-methylbenzenesulfonohydrazide (3.89)**: A 20-mL scintillation vial was charged with alkene **3.87** (0.05 g, 0.13 mmol, 1.00 equiv) and MeOH (4 mL). Pd/C (0.025 g, 0.50 mass equiv) was added, and the resulting suspension was placed under 1 atm H_2 (balloon) and allowed to stir 1 h whereupon TLC analysis indicated complete consumption of the starting material. The suspension was filtered through a pad of Celite and concentrated on a rotary evaporator to afford hydrazone **3.89** (0.05 g, >99 % crude yield) as a single diastereomer (as determined by ^{1}H NMR analysis of the crude mixture, which revealed a single stereoisomer). When this material was subjected to the reaction conditions used in the conversion of **3.87** to **3.88**, no reaction was observed, and the starting material was recovered quantitatively. Analytical data: $[\alpha]_D^{28}$ 51.9 (c = 1.25, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.83 (d, J = 8.2 Hz, 2H), 7.65 (br s, 1H), 7.28 (d, J = 7.8 Hz, 2H), 3.63 (dd, J = 3.0, 1.8 Hz, 1H), 2.40 (s, 3H), 2.36 (m, 1H), 1.93 (m, 2H), 1.79–1.64 (m, 3H), 1.56 (m, 1H), 1.46 (m, 1H), 1.34 (m, 1H), 1.27 (m, 1H), 1.02 (s, 3H), 1.00–0.98 (m, 3H), 0.77 (d, J = 6.6 Hz, 3H), 0.76 (d, J = 6.6 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 163.5, 143.8, 135.2, 129.3, 128.2, 75.6, 47.6, 39.5, 36.8, 27.7, 27.6, 22.6, 22.5, 21.5, 21.1, 19.7, 19.2; **HRMS (ESI^{+})** Calcd. For $C_{20}H_{32}N_2O_3S$ + Na, 403.2031; Found, 403.2022; **IR** (thin film, cm^{-1}) 3503. 3214, 2951, 2868, 1670, 1470, 1329, 1165, 1092, 1001, 924; **TLC** (80:20 hexanes:EtOAc): R_f = 0.07.

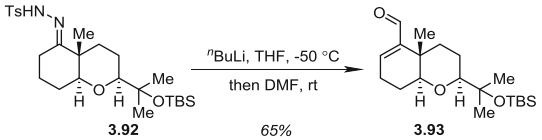
Crude ^{1}H NMR Spectrum of 3.89



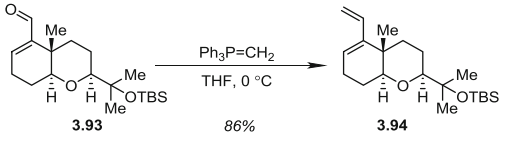


***N′*-((2*S*,4a*S*,8a*S*,*E*)-2-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-4a-methyloctahydro-5H-chromen-5-ylidene)-4-methylbenzenesulfonohydrazide(3.92)**: A flame-dried, 150-mL round-bottomed flask was charged with pyran **3.88** (9.41 g, 23.88 mmol, 1.00 equiv) and CH_2Cl_2 (120 mL) under an atmosphere of N_2. The reaction mixture was cooled to −50 °C ($CO_{2(s)}$/acetonitrile bath), and 2,6-lutidine (5.50 mL, 47.46 mmol, 2.00 equiv) and TBSOTf (9.87 mL, 42.99 mmol, 1.8 equiv) were added sequentially. The reaction was allowed to stir at this temperature until TLC analysis confirmed complete consumption of the starting material, typically 30 min. The reaction was quenched via addition of saturated $NaHCO_{3(aq.)}$ (40 mL), and the mixture was warmed to rt and partitioned in a separatory funnel. The aqueous layer was extracted with EtOAc (3 × 30 mL), and the combined organic extracts were washed with brine (40 mL), dried with magnesium sulfate, and concentrated *in vacuo*. The product was purified via flash chromatography (100:0 to 95:5 to 90:10 to 80:20 hexanes:EtOAc) to remove silanol byproducts then purified a second time (90:10 to 80:20 hexanes:EtOAc) to afford silyl ether **3.92** (9.46 g, 79 % yield) as a pale yellow, viscous foam. Analytical data: $[\alpha]_D^{28}$ –75.5 (c = 0.35, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.84 (d, J = 8.4 Hz, 2H), 7.57 (br s, 1H), 7.31 (d, J = 7.8 Hz, 2H), 3.04 (dd, J = 7.8, 3.6 Hz, 1H), 2.99

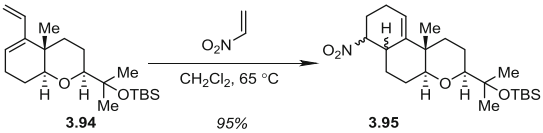
(d, J = 11.4 Hz, 1H), 2.50 (d, J = 14.4 Hz, 1H), 2.43 (s, 3H), 1.93 (m, 1H), 1.83–1.76 (m, 2H), 1.68–1.50 (m, 6H), 1.19 (s, 3H), 1.15 (s, 3H), 0.95 (s, 3H), 0.84 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 165.0, 143.8, 135.2, 129.3, 128.1, 85.3, 82.0, 76.8, 74.7, 42.5, 32.4, 27.2, 25.1, 21.6, 21.3, 17.3, −2.1, −2.2; **HRMS (ESI$^+$)** Calcd. For $C_{26}H_{44}N_2O_4SSi$ + Na, 531.2689; Found, 531.2704; **IR** (thin film, cm^{-1}) 3433, 3054, 2985, 2855, 2305, 1630, 1422, 1167, 1092, 835, 739; **TLC** (80:20 hexanes:EtOAc): R_f = 0.37.



(2*S*,4a*S*,8a*S*)-2-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-4a-methyl-3,4, 4a,7,8,8a-hexahydro-2H-chromene-5-carbaldehyde (3.93): A flame-dried, 100 mL round bottomed flask was charged with hydrazone **3.92** (2.00 g, 3.93 mmol, 1.00 equiv) and THF (39 mL) under an atmosphere of N_2. The mixture was cooled to −50 °C, and ^{n}BuLi (1.64 M in hexane, 12.0 mL, 19.7 mmol, 5.00 equiv) was added dropwise, producing a dark orange color. The mixture was allowed to stir 30 min at −50 °C. The flask was fitted with a venting needle, and the mixture was warmed to 0 °C and stirred 5 min, then warmed to rt and stirred until complete consumption of the starting material was observed by TLC analysis, typically 20 min (scale dependent). The venting needle was removed, and DMF (3.02 mL, 39.3 mmol, 10.0 equiv) was added. Following this addition, the reaction was stirred 20 min, diluted with H_2O (20 mL) and Et_2O (20 mL) and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried with magnesium sulfate, and concentrated *in vacuo*. The product was purified via flash chromatography (100:0 to 95:5 to 90:10 hexanes:EtOAc) to afford unsaturated aldehyde **3.93** (0.92 g, 66 % yield) as a yellow, viscous oil. Analytical data: $[\alpha]_D^{28}$ −138.0 (c = 0.55, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 9.38 (s, 1H), 6.55 (t, J = 3.0 Hz, 1H), 3.22 (dd, J = 8.4, 3.6 Hz, 1H), 3.15 (dd, J = 9.0, 3.0 Hz, 1H), 2.70 (m, 1H), 2.46 (m, 2H), 1.68 (m, 2H), 1.57 (m, 2H), 1.28 (m,1H), 1.23 (s, 3H), 1.18 (s, 3H), 1.14 (s, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 193.8, 151.0, 148.3, 85.9, 80.9, 74.9, 35.4, 32.6, 27.2, 26.4, 25.8, 25.1, 23.2, 21.3, 17.9, −2.2; **HRMS (ESI$^+$)** Calcd. For $C_{20}H_{36}O_3Si$ + Na, 375.2331; Found, 375.2323; **IR** (thin film, cm^{-1}) 3435, 2955, 2855, 1692, 1635, 1472, 1376, 1251, 1173, 1042; **TLC** (90:10 hexanes:EtOAc): R_f = 0.49.



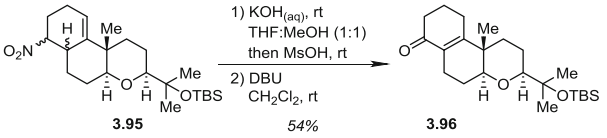
***tert*-butyldimethyl((2-((2*S*,4a*S*,8a*S*)-4a-methyl-5-vinyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-2-yl)propan-2-yl)oxy)silane (3.94)**: A flame-dried, 100 mL round bottomed flask was charged with methyltriphenylphosphonium bromide (4.90 g, 13.7 mmol, 6.00 equiv) and THF (20 mL) under an atmosphere of N_2. The mixture was cooled to 0 °C and ^{n}BuLi (1.65 M in hexanes, 7.63 mL, 12.6 mmol, 5.50 equiv) was added dropwise. The deep yellow mixture was allowed to stir 1 h at 0 °C upon which the aldehyde **3.93** (0.81 g, 2.29 mmol, 1.00 equiv) was added as a solution in THF (3 mL). The reaction was allowed to stir until complete consumption of the starting material was observed by TLC analysis, typically 15 min. The reaction was diluted with H_2O (15 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried with magnesium sulfate, and concentrated *in vacuo*. The product was purified via flash chromatography (100:0 to 99:1 to 97.5:2.5 hexanes:EtOAc) to afford diene **3.94** (0.69 g, 86 % yield) as a clear oil. Analytical data: $[\alpha]_D^{28}$ −167.4 (*c* = 0.35, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.24 (dd, *J* = 10.8, 6.0 Hz, 1H), 5.61 (t, *J* = 3.6 Hz, 1H), 5.26 (d, *J* = 17.4 Hz, 1H), 4.93 (d, *J* = 10.8 Hz, 1H), 3.23 (dd, *J* = 5.4, 4.8 Hz, 1H), 3.12 (m, 1H), 2.20 (m, 1H), 1.93 (dt, *J* = 6.0, 3.0 Hz, 1H), 1.66 (m, 2H), 1.60 (m, 2H), 1.35 (m, 1H), 1.24 (s, 3H), 1.18 (s, 3H), 1.07 (s, 3H), 0.85 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 144.5, 135.4, 121.6, 113.5, 85.5, 81.5, 74.9, 36.1, 34.3, 27.4, 25.9, 25.0, 23.8, 21.8, 18.9, 18.2, −2.1, −2.2; **HRMS (ESI$^+$)** Calcd. For $C_{21}H_{38}O_2Si$ + Na, 373.2539; Found, 373.2529; **IR** (thin film, cm^{-1}) 3053, 2985, 2956, 2854, 2685, 1716, 1636, 1456, 1265, 1143; **TLC** (90:10 hexanes:EtOAc): R_f = 0.91.



3.94 *95%* **3.95**

***tert*-butyldimethyl((2-((3*S*,4a*S*,10b*S*)-10b-methyl-7-nitro-2,3,4a,5,6,6a,7,8,9,10b-decahydro-1H-benzo[f]chromen-3-yl)propan-2-yl)oxy)silane (3.95)**: A 20 mL scintillation vial was charged with diene **3.94** (0.66 g, 1.88 mmol, 1.00 equiv) and CH_2Cl_2 (9 mL). Nitroethylene (10 M solution in CH_2Cl_2, 0.75 mL, 7.50 mmol, 4.00 equiv) was added, and the vial was sealed with a screw-cap. The mixture was heated to 65 °C and stirred until complete conversion of the starting material was observed by TLC analysis, typically 12 h. The mixture was cooled to rt and concentrated on a rotary evaporator. The product was purified via flash chromatography (100:0 to 97.5:2.5 to 95:5 to 90:10 hexanes:EtOAc) to afford alkene **3.95** (0.75 g, 95 % yield) as a clear, viscous oil in an inseparable mixture of diastereomers. Analytical data: $[\alpha]_D^{28}$ −4.7 (*c* = 0.75, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.51 (br s, 1H), 5.45 (d, *J* = 4.8 Hz, 1H), 4.79–4.66 (m, 1H), 4.32–4.20 (m, 1H), 3.45 (dd, *J* = 7.8, 3.0 Hz, 1H), 3.06–3.01 (m, 4H), 2.96–2.87 (m, 3H), 2.27–1.89 (m, 13H), 1.76–1.72 (m, 3H), 1.66–1.37 (m, 17H), 1.25 (m, 2H),

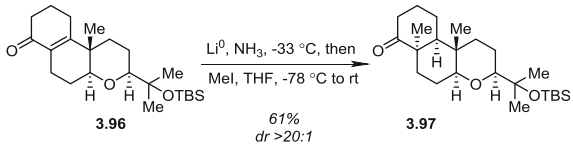
1.21–1.19 (m, 8H), 1.17–1.15 (m, 3H), 1.05–1.03 (m, 8H), 0.84 (br s, 25H), 0.07 (s, 8H), 0.05 (s, 8H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 144.8, 143.9, 143.2, 118.4, 117.9, 117.7, 90.6, 89.8, 85.6, 85.4, 85.1, 84.9, 83.4, 82.2, 74.8, 39.6, 37.5, 36.8, 36.4, 36.1, 34.4, 28.0 27.3, 27.1, 27.0, 25.5, 25.2, 25.0, 24.4, 24.0, 23.0, 22.7, 21.9, 21.8, 21.6, 21.5, 18.1, 17.0, −2.2; **HRMS (ESI$^+$)** Calcd. For $C_{23}H_{41}NO_4Si$ + Na, 446.2703; Found, 446.2692; **IR** (thin film, cm^{-1}) 3054, 2954, 2930, 2855, 1732, 1670, 1546, 1488, 1362, 1265, 1167, 1046; **TLC** (90:10 hexanes:EtOAc): R_f = 0.66.



(*3S,4aS,*10b*S*)-3-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-10b-methyl-1, 2,3,4a,5,6,8,9,10,10b-decahydro-7H-benzo[f]chromen-7-one (3.96): A 100 mL round bottomed flask was charged with alkene **3.95** (0.753 g, 1.78 mmol, 1.00 equiv) and a 1:1 mixture of THF:MeOH (35 mL). The solution was cooled to 0 °C, and KOH (1 M in H_2O, 5.34 mL, 5.34 mmol, 3.00 equiv) was added dropwise, subsequently warming to rt. The mixture was stirred until complete conversion of the starting material was observed by TLC analysis, typically 45 min. The mixture was cooled to 0 °C, and MsOH was added drop-by-drop until the reaction pH reached < 1 (scale dependent, ∼2 mL was required in this iteration), resulting in the formation of a white suspension. The resulting mixture was warmed to rt and stirred vigorously for 1 h whereupon the mixture was neutralized with saturated $NaHCO_{3(aq.)}$ (20 mL). The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried with magnesium sulfate, and concentrated *in vacuo* to give the crude non-conjugated enone, which was used in the next step without further purification.

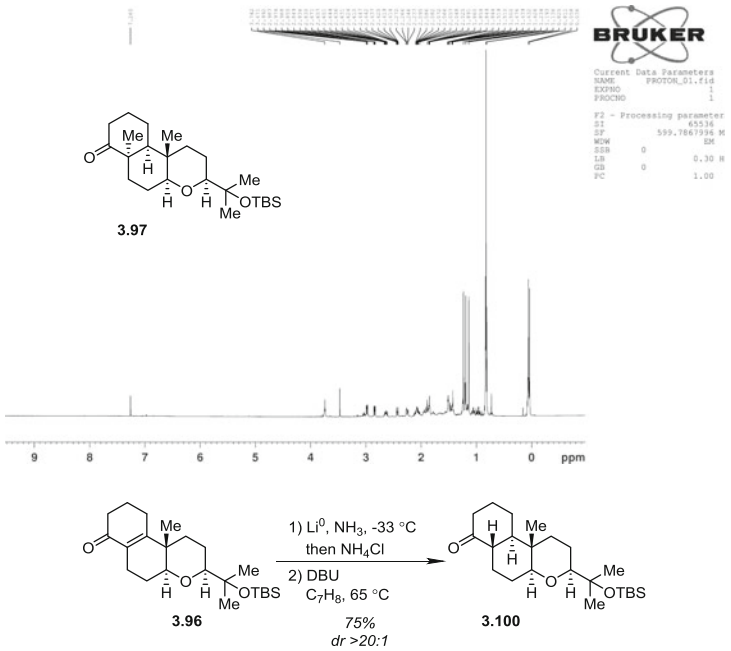
The crude ketone was transferred to a flame-dried, 50 mL round bottomed flask and dissolved in CH_2Cl_2 (18 mL) under an atmosphere of N_2. DBU (0.52 mL, 3.60 mmol, 2.00 equiv) was added, and the mixture was allowed to stir at rt until complete conversion of the starting material was observed by TLC analysis, typically 3 h. The reaction was diluted with H_2O (15 mL) and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried with sodium sulfate and concentrated *in vacuo*. The product was purified via flash chromatography (100:0 to 97.5:2.5 to 95:5 to 90:10 hexanes:EtOAc) to afford conjugated enone **3.96** (0.38 g, 54 % yield) as a yellow solid. Analytical data: **mp**: 85–89 °C; $[\alpha]_D^{28}$ −118.8 (*c* = 0.85, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 3.19 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.08 (dd, *J* = 4.2, 4.2 Hz, 1H), 2.44 (m, 2H), 2.34–2.20 (m, 4H), 2.01 (m, 1H), 1.93 (dt, *J* = 6.0, 3.0 Hz, 1H), 1.84 (m, 1H), 1.76 (m, 1H), 1.65–1.59 (m, 3H), 1.40 (m, 1H), 1.24 (s, 3H), 1.19 (s, 3H), 1.10 (s, 3H), 0.84 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 199.8, 162.7, 129.8, 85.1, 80.4, 74.8, 38.0, 37.7, 33.3, 27.5, 25.8, 25.2, 24.9, 23.3, 22.9, 22.4, 21.4, 18.1,

18.0, −2.1, −2.2; **HRMS (ESI$^+$)** Calcd. For $C_{23}H_{40}O_3Si$ + Na, 415.2644; Found, 415.2636; **IR** (thin film, cm^{-1}) 3053, 2954, 2887, 2855, 1683, 1616, 1576, 1472, 1362, 1265, 1172, 1045; **TLC** (90:10 hexanes:EtOAc): R_f = 0.34.



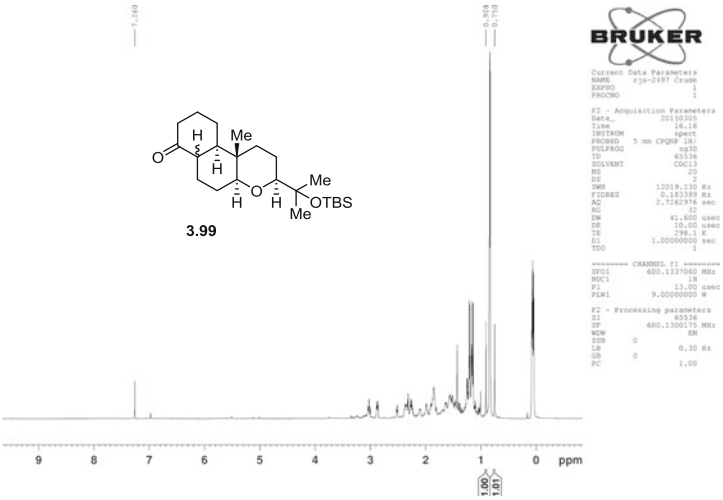
(3*S*,4a*S*,6a*R*,10a*S*,10b*S*)-3-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-6a, 10b-dimethyldodecahydro-7H-benzo[f]chromen-7-one (3.97): An oven-dried, 50 mL two-neck round bottomed flask was fitted with a stir bar and an oven-dried cold finger condenser and placed under an atmosphere of Ar. The flask and condenser were cooled to −78 °C, and liq. NH_3 (5 mL) was allowed to condense into the flask. Freshly cut Li^0 (0.01 g, 1.43 mmol, 14.3 equiv) was washed with hexanes and added to the flask, resulting in the formation of a dark blue color. After stirring 5 min at −78 °C, a solution of ketone **3.96** (0.04 g, 0.10 mmol, 1.00 equiv) in THF (3 mL) was added, and the reaction was warmed to −33 °C and stirred 15 min. The reaction was the cooled to −78 °C, diluted with THF (5 mL), and a solution of MeI (0.38 mL, 6.0 mmol, 60.0 equiv) in THF (2 mL) was added dropwise. The mixture was allowed to warm to rt and stirred until liq. NH_3 had completely evaporated. The residue was quenched with saturated $NH_4Cl_{(aq.)}$ (10 mL), diluted with Et_2O (10 mL) and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo* to give the crude ketone **3.97** as a single diastereomer (as determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture, which revealed a single compound). The product was purified via flash chromatography (100:0 to 98:2 to 95:5 to 90:10 hexanes:EtOAc) to afford ketone **3.97** (0.025 g, 61 % yield) as a clear, viscous oil. Analytical data: $[\alpha]_D^{28}$ −38.2 (*c* = 0.75, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 2.98 (dd, *J* = 8.4, 3.0 Hz, 1H), 2.84 (dd, *J* = 7.8, 3.6 Hz, 1H), 2.64 (m, 1H), 2.44 (dt, *J* = 7.2, 3.0 Hz, 1H), 2.25 (dd, *J* = 10.2, 6.0 Hz, 1H), 2.08 (m, 2H), 1.95–1.87 (m, 3H), 1.52–1.44 (m, 5H), 1.25 (m, 1H), 1.24 (s, 3H), 1.20 (s, 3H), 1.14 (s, 3H), 1.06 (m, 1H), 0.83 (s, 9H), 0.82 (s, 3H) 0.06 (s, 3H), 0.04 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 216.0, 84.9, 84.3, 74.8, 54.4, 47.9, 37.9, 37.3, 36.4, 32.6, 29.9, 27.3, 25.8, 25.1, 25.1, 23.8, 21.5, 19.1, 18.2, 16.0, −2.1, −2.2; **HRMS (ESI$^+$)** Calcd. For $C_{24}H_{44}O_3Si$ + Na, 431.2957; Found, 431.2949; **IR** (thin film, cm^{-1}) 3421, 2954, 2855, 1792, 1698, 1377, 1265, 1215, 1058; **TLC** (90:10 hexanes: EtOAc): R_f = 0.54.

Crude ^{1}H NMR spectrum of 54



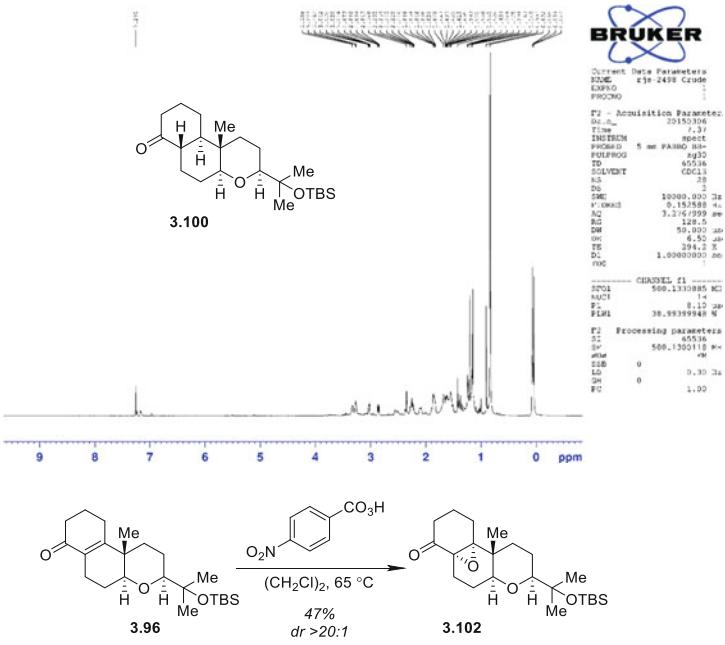
(3*S*,4a*S*,6a*S*,10a*R*,10b*S*)-3-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-10b-methyldodecahydro-7H-benzo[f]chromen-7-one (3.100): An oven-dried, 50 mL two-neck round bottomed flask was fitted with a stir bar and an oven-dried cold finger condenser and placed under an atmosphere of Ar. The flask and condenser were cooled to −78 °C, and liq. NH_3 (5 mL) was allowed to condense into the flask. Freshly cut Li^0 (0.005 g, 0.714 mmol, 14.3 equiv) was washed with hexanes and added to the flask, resulting in the formation of a dark blue color. After stirring 5 min at −78 °C, a solution of ketone **3.96** (0.02 g, 0.05 mmol, 1.00 equiv) in THF (2 mL) was added, and the reaction was warmed to −33 °C and stirred 15 min. The reaction was carefully quenched via portionwise addition of $NH_4Cl_{(s)}$, and the mixture was allowed to warm to rt and stirred until liq. NH_3 had completely evaporated. The residue was diluted with H_2O (10 mL) and Et_2O (10 mL) and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo* to afford the crude ketone as a 1:1 mixture of diastereomers (**3.99**), which was taken on directly to the next step without further purification. A crude ^{1}H NMR spectrum of this reaction is included below.

Crude ^{1}H NMR spectrum of initial Birch reduction product 3.99



This crude residue was transferred to a flame-dried 20 mL scintillation vial and dissolved in C_7H_8 under an atmosphere of N_2. DBU (0.01 mL, 0.05 mmol, 1.00 equiv) was added, and the mixture was warmed to 65 °C and stirred 12 h. The reaction was cooled to rt, diluted with H_2O (10 mL) and CH_2Cl_2 (5 mL) and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo*. At this juncture, crude ^{1}H NMR analysis revealed complete epimerization to a single diastereomer. The product was purified via flash chromatography (100:0 to 97.5:2.5 to 90:10 hexanes: EtOAc) to afford ketone **3.100** (0.015 g, 75 % yield) as a clear, viscous oil. Analytical data: $[\alpha]_D^{28}$ −72.0 (c = 0.75, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 3.03 (dd, J = 7.2, 3.6 Hz, 1H), 2.87 (dd, J = 7.8, 3.6 Hz, 1H), 2.36 (m, 1H), 2.26 (m, 2H), 2.10 (m, 1H), 1.91–1.83 (m, 3H), 1.63 (m, 1H), 1.57–1.52 (m, 4H), 1.43–1.36 (m, 3H), 1.21 (s, 3H), 1.16 (br s, 4H), 0.91 (s, 3H), 0.84 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 213.2, 85.1, 83.2, 74.8, 52.3, 49.2, 41.8, 36.7, 36.6, 27.4, 26.5, 26.2, 25.8, 24.9, 24.3, 23.6, 21.8, 18.1, 12.1, −2.1, −2.2; **HRMS (ESI^{+})** Calcd. For $C_{23}H_{42}O_3Si$ + Na, 417.2801; Found, 417.2793; **IR** (thin film, cm^{-1}) 3420, 2951, 2854, 1715, 1652, 1472, 1376, 1251, 1155, 1051, 835; **TLC** (90:10 hexanes:EtOAc): R_f = 0.40.

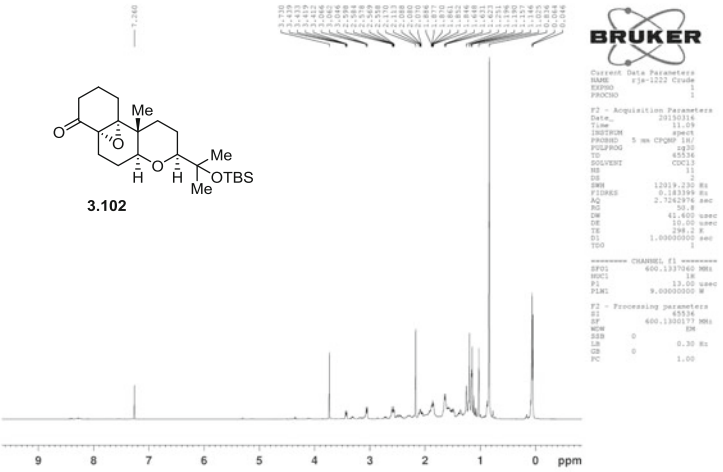
Crude ^{1}H NMR spectrum of 3.100

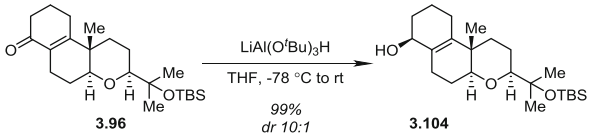


(3*S*,4a*S*,6a*S*,10a*R*,10b*R*)-3-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-10b-methyloctahydro-1H-6a,10a-epoxybenzo[f]chromen-7(8H)-one (3.102): A 20 mL scintillation vial was charged with enone **3.96** (0.10 g, 0.26 mmol, 1.00 equiv) and $(CH_2Cl)_2$ (5 mL). *p*-NPBA (0.19 g, 0.89 mmol, 3.50 equiv) was added, and the vial was sealed with a screw-cap. The mixture was warmed to 65 °C and stirred until complete consumption of the starting material was observed by TLC analysis, typically 3 h. The reaction mixture was warmed to rt, quenched via saturated $Na_2S_2O_{3(aq.)}$ (5 mL), and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 7 mL). The combined organic extracts were dried with sodium sulfate and concentrated *in vacuo* to afford the crude epoxide as a single diastereomer (as determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture, which revealed a single compound). The product was purified via flash chromatography (100:0 to 97.5:2.5 to 95:5 hexanes:EtOAc) to afford keto-epoxide **3.102** (0.05 g, 47 % yield) as a clear, viscous oil. Slow evaporation of **3.102** from HPLC grade methanol afforded crystals suitable for X-ray crystallographic analysis. Analytical data: $[\alpha]_D^{28}$ −105.2 (c = 0.70, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 3.43 (dd, J = 8.4, 4.2 Hz, 1H), 3.06 (m, 1H), 2.58 (m, 1H), 2.08 (m, 2H), 1.91–1.85 (m, 3H), 1.64 (m, 3H), 1.55–1.49 (m, 3H), 1.37 (m, 1H), 1.20 (s, 3H), 1.15 (s, 3H), 1.03 (s, 3H), 0.84 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 207.2, 84.8, 75.4, 74.7, 64.3,

36.4, 36.2, 32.0, 27.4, 25.8, 24.9, 22.3, 21.6, 21.3,18.9, 18.8, 18.1, 15.9, −2.1, −2.2; **HRMS (ESI$^+$)** Calcd. For $C_{23}H_{40}O_4Si$ + Na, 431.2594; Found, 431.2585; **IR** (thin film, cm^{-1}) 3420, 2955, 2856, 1704, 1646, 1488, 1396, 1265, 1173, 1072, 835, 739; **TLC** (90:10 hexanes:EtOAc): R_f = 0.25.

Crude ^{1}H NMR spectrum of 3.102

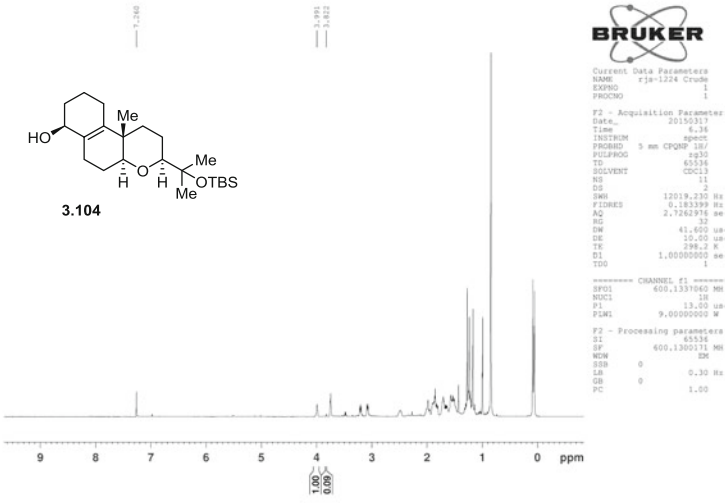


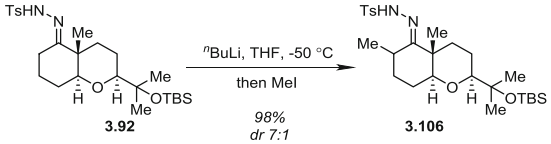


(3*S*,4a*S*,7*S*,10b*S*)-3-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-10b-methyl-2,3,4a,5,6,7,8,9,10,10b-decahydro-1H-benzo[f]chromen-7-ol (3.104): A flame-dried, 20 mL scintillation vial was charged with ketone **3.96** (0.06 g, 0.15 mmol, 1.0 equiv) and THF (2 mL) under an atmosphere of N_2. The reaction mixture was cooled to −78 °C, and LiAl(O^{t}Bu)$_3$H (1 M solution in THF, 0.31 mL, 0.31 mmol, 2.00 equiv) was added in one portion. The reaction mixture was allowed to stir for 12 h, slowly warming to rt during this time period at which point TLC analysis confirmed complete consumption of the starting material. The reaction was quenched via saturated $NH_4Cl_{(aq.)}$ (5 mL) and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 7 mL). The combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo* to give the crude alcohol as a 10:1 mixture of diastereomers.

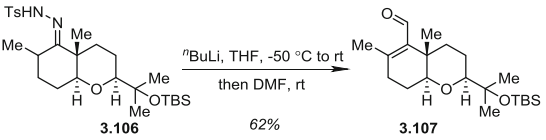
The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 3.99 (major diastereomer) and δ 3.82 (minor diastereomer). The product was purified via flash chromatography (90:10 to 80:20 hexanes:EtOAc) to afford alcohol **3.104** (0.054 g, 90 % yield) as a clear, viscous oil. Analytical data: $[\alpha]_D^{28}$ − 92.7 (*c* = 1.00, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 3.99 (m, 1H), 3.20 (dd, *J* = 8.4, 3.6 Hz, 1H), 3.08 (dd, *J* = 7.2, 3.6 Hz, 1H), 2.49 (m, 1H), 1.98 (m, 2H), 1.88 (m, 2H), 1.82 (m, 1H), 1.71 (m, 2H), 1.65 (m, 2H), 1.57 (m, 2H), 1.52 (m, 2H), 1.29 (m, 1H), 1.23 (s, 3H), 1.17 (s, 3H), 0.99 (s, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 139.7, 128.2, 85.1, 81.2, 74.9, 70.6, 34.5, 34.0, 32.6, 27.3, 26.8, 25.9, 25.1, 24.0, 23.8, 21.8, 19.8, 18.4, 18.2, −2.1, −2.2; **HRMS (ESI$^+$)** Calcd. For $C_{23}H_{42}O_3Si$ + Na, 417.2801; Found, 417.2791; **IR** (thin film, cm^{-1}) 3420, 2930, 2855, 1683, 1636, 1507, 1456, 1361, 1264, 1046, 835; **TLC** (90:10 hexanes: EtOAc): R_f = 0.25.

Crude ^{1}H NMR spectrum of 3.104



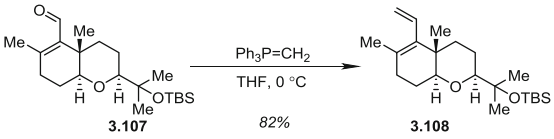


***N'*-((2*S*,4a*S*,8a*S*,*E*)-2-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyloctahydro-5H-chromen-5-ylidene)-4-methylbenzenesulfonohydrazide (3.106)**: A flame-dried, 500 mL round bottomed flask was charged with hydrazone **3.92** (6.21 g, 12.2 mmol, 1.00 equiv) and THF (122 mL) under an atmosphere of N_2. The mixture was cooled to −50 °C, and ^{n}BuLi (2.60 M in hexanes, 16.4 mL, 42.7 mmol, 3.50 equiv) was added over a period of ∼2 min, producing a dark orange color. The reaction mixture was allowed to stir 40 min whereupon MeI (1.90 mL, 30.5 mmol, 2.50 equiv) was added, resulting in a color change from orange to yellow. The reaction was allowed to stir until complete consumption of the starting material was observed by TLC analysis, typically 20 min. The reaction was quenched via saturated $NH_4Cl_{(aq.)}$ (40 mL) and allowed to warm to rt. The mixture was transferred to a separatory funnel, the organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 40 mL). The combined organic extracts were washed with brine (40 mL), dried with magnesium sulfate and concentrated *in vacuo*. The product was purified via flash chromatography (90:10 to 80:20 hexanes:EtOAc) to afford hydrazone **3.106** (6.37 g, 98 % yield) as a white foam in a 7:1 diastereomeric ratio. Analytical data: $[\alpha]_D^{28}$ −121.0 (c = 0.60, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.83 (d, J = 7.2 Hz, 2H), 7.72 (br s, 1H), 7.30 (d, J = 7.8 Hz, 2H), 3.05 (m, 1H), 3.00 (s, 1H), 2.73 (q, J = 7.8 Hz, 1H), 2.43 (s, 3H), 2.01 (d, J = 13.2 Hz, 1H), 1.69 (m, 1H), 1.57–1.54 (m, 5H), 1.45 (m, 1H), 1.34 (m, 1H), 1.20 (s, 3H), 1.15 (s, 3H), 1.07 (d, J = 7.2 Hz, 3H), 0.95 (s, 3H), 0.84 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 167.1, 143.8, 135.3, 129.3, 128.0, 127.9, 85.2, 82.0, 74.7, 41.9, 33.3, 28.3, 27.7, 27.2, 25.8, 25.0, 22.8, 21.6, 21.2, 19.1, 18.3, 18.1, −2.1, −2.2; **HRMS (ESI$^+$)** Calcd. For $C_{27}H_{46}N_2O_4SSi$ + Na, 545.2845; Found, 545.2840; **IR** (thin film, cm^{-1}) 3225, 2954, 2855, 1472, 1396, 1265, 1168, 1090, 1038, 812, 773; **TLC** (90:10 hexanes: EtOAc): R_f = 0.35.



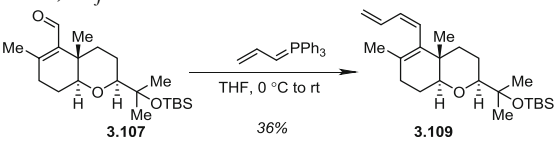
(2*S*,4a*S*,8a*S*)-2-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-3,4,4a,7,8,8a-hexahydro-2H-chromene-5-carbaldehyde (3.107): A flame-dried, 25 mL round bottomed flask was charged with hydrazone **3.106** (0.48 g, 0.92 mmol, 1.00 equiv) and THF (9.5 mL) under an atmosphere of N_2. The solution was cooled to −50 °C, and ^{n}BuLi (1.70 M in hexanes, 3.25 mL, 5.52 mmol, 6.00 equiv) was added over a period of ∼2 min, producing a dark orange color. The reaction was allowed to stir 30 min whereupon a venting needle was added, and the mixture was warmed to 0 °C and stirred 5 min. The reaction was then warmed to rt and stirred until complete consumption of the starting material was observed by TLC analysis, typically 20 min. The venting needle was removed, DMF (0.71 mL, 9.2 mmol, 10.0 equiv) was added, and the reaction was

stirred 20 min. The mixture was diluted with H_2O (15 mL) and Et_2O (10 mL) and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried with magnesium sulfate and concentrated *in vacuo*. The product was purified via flash chromatography (95:5 to 90:10 hexanes:EtOAc) to afford aldehyde **3.107** (0.21 g, 62 % yield) as a yellow, viscous oil. Analytical data: $[\alpha]_D^{28}$ −151.8 (c = 0.80, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 10.05 (br s, 1H), 3.16 (m, 1H), 3.11 (dd, J = 9.0, 3.0 Hz, 1H), 2.65 (m, 1H), 2.38 (m, 1H), 2.28 (m, 1H), 2.06 (s, 3H), 1.69 (m, 2H), 1.62–1.53 (m, 3H), 1.22 (s, 3H), 1.17 (s, 3H), 1.14 (s, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 191.9, 153.9, 140.3, 85.8, 80.6, 74.9, 35.7, 34.3, 33.5, 27.1, 25.8, 25.1, 23.7, 21.6, 18.8, 18.2, 18.1, −2.1, −2.2; **HRMS (ESI$^+$)** Calcd. For $C_{21}H_{38}O_3Si$ + Na, 389.2488; Found, 389.2481; **IR** (thin film, cm^{-1}) 2954, 2928, 2855, 1733, 1674, 1472, 1376, 1251, 1095, 1005, 835; **TLC** (90:10 hexanes:EtOAc): R_f = 0.50.

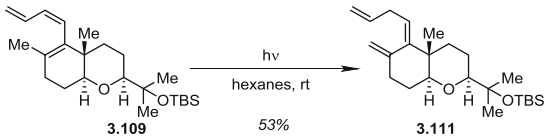


***tert*-butyl((2-((2*S*,4a*S*,8a*S*)-4a,6-dimethyl-5-vinyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-2-yl)propan-2-yl)oxy)dimethylsilane (3.108)**: A flame-dried, 25 mL round bottomed flask was charged with methyltriphenylphosphonium bromide (1.90 g, 5.28 mmol, 8.00 equiv) and THF (7 mL) under an atmosphere of N_2. The mixture was cooled to 0 °C and ^{n}BuLi (1.69 M in hexanes, 2.94 mL, 4.95 mmol, 7.50 equiv) was added dropwise. The deep yellow mixture was allowed to stir 1 h at 0 °C upon which the aldehyde **3.107** (0.24 g, 0.66 mmol, 1.00 equiv) was added as a solution in THF (2 mL). The reaction was allowed to stir until complete consumption of the starting material was observed by TLC analysis, typically 15 min. The reaction was diluted with H_2O (15 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried with magnesium sulfate, and concentrated *in vacuo*. The product was purified via flash chromatography (100:0 to 99:1 to 97.5:2.5 hexanes:EtOAc) to afford diene **3.108** (0.20 g, 82 % yield) as a clear oil. Analytical data: $[\alpha]_D^{28-9}$4.4 (c = 1.50, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.13 (dd, J = 12.0, 6.0 Hz, 1H), 5.23 (dd, J = 8.4, 3.0 Hz, 1H), 4.96 (dd, J = 15.6, 2.4 Hz, 1H), 3.19 (dd, J = 7.2, 4.8 Hz, 1H), 3.08 (dd, J = 6.6, 4.2 Hz, 1H), 2.18 (m, 1H), 2.08 (dd, J = 11.4, 6.6 Hz, 1H), 1.84 (dt, J = 6.0, 4.2 Hz, 1H), 1.66 (br s, 4H), 1.55 (br s, 3H), 1.28 (m, 1H), 1.23 (s, 3H), 1.17 (s, 3H), 1.02 (s, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 138.1, 134.3, 127.5, 118.0, 85.2, 81.4, 75.0, 36.2, 35.2, 31.6, 27.3, 25.9, 25.1, 24.3, 21.8, 20.5, 18.7, 18.2; **HRMS (ESI$^+$)** Calcd. For $C_{22}H_{40}O_2Si$ + Na, 387.2695; Found, 387.2688; **IR**

(thin film, cm^{-1}) 2954, 2855, 1717, 1471, 1376, 1253, 1167, 1039, 880, 741; **TLC** (90:10 hexanes:EtOAc): $R_f = 0.93$.

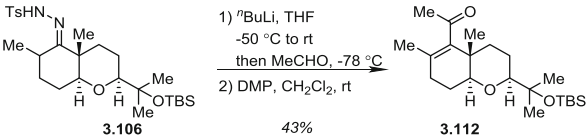


((2-((2*S*,4a*S*,8a*S*)-5-((*Z*)-buta-1,3-dien-1-yl)-4a,6-dimethyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-2-yl)propan-2-yl)oxy)(*tert*-butyl)dimethylsilane (3.109): A flame-dried, 20 mL scintillation vial was charged with allyltriphenylphosphonium bromide (1.31 g, 3.43 mmol, 8.00 equiv) and THF (5 mL) under an atmosphere of N_2. The mixture was cooled to 0 °C and ^{n}BuLi (2.64 M in hexanes, 1.22 mL, 3.21 mmol, 7.50 equiv) was added dropwise. The deep yellow mixture was allowed to stir 1 h at 0 °C whereupon the aldehyde **3.107** (0.16 g, 0.43 mmol, 1.00 equiv) was added as a solution in THF (2 mL). The reaction was allowed to stir until complete consumption of the starting material was observed by TLC analysis, typically 12 h. The reaction was diluted with H_2O (15 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried with magnesium sulfate, and concentrated *in vacuo*. The product was purified via flash chromatography (100:0 to 99:1 to 97.5:2.5 hexanes:EtOAc) to afford triene **3.109** (0.06 g, 36 % yield) as a clear oil. Analytical data: $[\alpha]_D^{28}$ −49.8 (c = 1.25, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.37 (m, 1H), 6.05 (m, 2H), 5.15 (d, J = 16.8 Hz, 1H), 5.03 (d, J = 10.2 Hz, 1H), 3.19 (dd, J = 7.2, 4.8 Hz, 1H), 2.20 (m, 1H), 2.11 (dd, J = 12.6, 5.4 Hz, 1H), 1.88 (dt, J = 6.0, 3.0 Hz, 1H), 1.68 (br s, 5H), 1.56 (m, 2H), 1.27 (m, 1H), 1.23 (s, 3H), 1.17 (s, 3H), 1.04 (s, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 137.7, 137.1, 133.9, 130.7, 128.7, 115.4, 85.2, 81.4, 74.9, 36.6, 35.3, 31.8, 27.3, 25.8, 25.0, 24.2, 21.8, 20.8, 18.9, 18.2, −2.1, −2.2; **HRMS (ESI$^+$)** Calcd. For $C_{24}H_{42}O_2Si$ + Na, 413.2852; Found, 413.2843; **IR** (thin film, cm^{-1}) 3420, 2929, 2855, 1670, 1497, 1457, 1387, 1265, 1165, 1040, 835; **TLC** (90:10 hexanes:EtOAc): $R_f = 0.94$.



((2-((2*S*,4a*S*,8a*S*,*E*)-5-(but-3-en-1-ylidene)-4a-methyl-6-methyleneoctahydro-2H-chromen-2-yl)propan-2-yl)oxy)(*tert*-butyl)dimethylsilane (3.111): The triene **3.109** (0.017 g, 0.043 mmol, 1.00 equiv) was taken up into hexanes and transferred to a toroidal photochemical reactor equipped with a water-cooled Pyrex immersion well. A 450 W Hanovia medium pressure mercury vapor lamp was lowered inside the immersion well, and the triene solution was irradiated for 1 h. The solution was

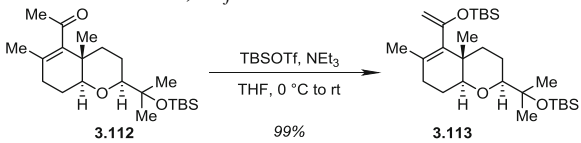
subsequently concentrated *in vacuo*. The product was purified via flash chromatography to give rearrangement product **3.111** (0.009 g, 53 % yield) as a clear, viscous oil. Analytical data: $[\alpha]_D^{28}$ – 11.8 (*c* = 0.10, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.83 (m, 1H), 5.20 (t, *J* = 7.8 Hz, 1H), 5.01 (m, 1H), 4.97 (m, 1H), 4.66 (t, *J* = 1.8 Hz, 1H), 3.10 (dd, *J* = 7.8, 4.2 Hz, 1H), 3.05 (m, 1H), 2.90 (m, 2H), 2.33 (m, 1H), 2.06 (m, 1H), 1.70 (m, 2H), 1.66–1.55 (m, 6H), 1.22 (s, 3H, 1.17 (s, 3H), 0.94 (s, 3H), 0.85 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 148.0, 144.1, 138.3, 119.1, 114.3, 112.8, 85.2, 82.5, 74.9, 39.8, 34.5, 33.8, 33.2, 28.5, 27.2, 25.8, 25.1, 21.9, 18.2, 17.9, −2.1, −2.2; **HRMS (ESI$^+$)** Calcd. For $C_{24}H_{42}O_2Si$ + Na, 413.2852; Found, 413.2843; **IR** (thin film, cm^{-1}) 3053, 2956, 2855, 1749, 1670, 1540, 1456, 1265, 1046, 835; **TLC** (90:10 hexanes:EtOAc): R_f = 0.97.



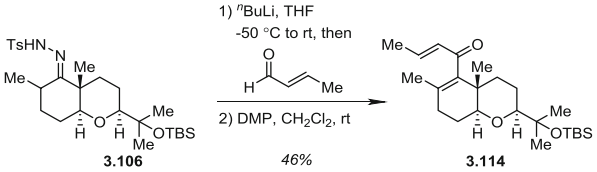
1-((2*S*,4a*S*,8a*S*)-2-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-5-yl)ethan-1-one (3.112): A flame-dried, 25 mL round bottomed flask was charged with hydrazone **3.106** (0.30 g, 0.57 mmol, 1.00 equiv) and THF (6 mL) under an atmosphere of N_2. The solution was cooled to −50 °C, and ^{n}BuLi (2.64 M in hexanes, 1.30 mL, 3.44 mmol, 6.00 equiv) was added over a period of ∼2 min, producing a dark orange color. The reaction was allowed to stir 30 min whereupon a venting needle was added, and the mixture was warmed to 0 °C and stirred 5 min. The reaction was then warmed to rt and stirred until complete consumption of the starting material was observed by TLC analysis, typically 20 min. The venting needle was removed, the mixture was cooled to −78 °C, and acetaldehyde (0.32 mL, 5.74 mmol, 10.0 equiv) was added dropwise. The reaction was allowed to stir 25 min whereupon H_2O (5 mL) and Et_2O (5 mL) were added, and the mixture was warmed to rt and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried with magnesium sulfate, and concentrated *in vacuo* to give the crude alcohol, which was taken on to the next step without further purification.

The crude residue was taken up into CH_2Cl_2 (5 mL) and transferred to a 20 mL scintillation vial. Dess-Martin periodinane (0.29 g, 0.68 mmol, 2.00 equiv) was added to the vial, and the mixture was allowed to stir until TLC analysis indicated complete consumption of the starting material, typically 15 min. The mixture was then quenched via a 1:1 solution of saturated $NaHCO_{3(aq.)}$ and saturated $Na_2S_2O_{3(aq.)}$ (5 mL), and the mixture was stirred 5 min. The reaction mixture was then diluted with Et_2O (10 mL) and partitioned in a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic

extracts were dried with magnesium sulfate and concentrated *in vacuo*. The product was purified via flash chromatography (100:0 to 97.5:2.5 to 95:5 hexanes:EtOAc) to afford ketone **3.112** (0.09 g, 43 % yield) as a yellow, viscous oil. Analytical data: $[\alpha]_D^{28}$ −31.6 (*c* = 0.50, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 3.21 (dd, *J* = 6.0, 3.6 Hz, 1H), 3.09 (dd, *J* = 5.4, 3.6 Hz, 1H), 2.25 (s, 3H), 2.16 (m, 1H), 2.08 (m, 1H), 1.67 (m, 2H), 1.56–1.54 (m, 6H), 1.44 (m, 1H), 1.21 (s, 3H), 1.17–1.15 (m, 6H), 0.83 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 208.2, 143.5, 128.5, 85.4, 80.4, 74.8, 35.4, 34.4, 33.3, 30.6, 27.3, 25.8, 25.0, 23.8, 21.3, 20.1, 19.6, 18.1, −2.1, −2.2; **HRMS (ESI$^+$)** Calcd. For $C_{22}H_{40}O_3Si$ + Na, 403.2644; Found, 403.2636; **IR** (thin film, cm^{-1}) 2955, 2854, 1829, 1686, 1488, 1361, 1249, 1095, 835, 739; **TLC** (90:10 hexanes:EtOAc): R_f = 0.38.

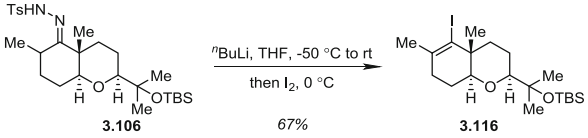


***tert*-butyl((1-((2*S*,4a*S*,8a*S*)-2-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-5-yl)vinyl)oxy)dimethylsilane (3.113)**: A flame-dried, 20 mL scintillation vial was charged with ketone **3.112** (0.06 g, 0.16 mmol, 1.00 equiv) and THF (2 mL) under an atmosphere of N_2. The reaction was cooled to 0 °C and NEt_3 (0.07 mL, 0.47 mmol, 3.00 equiv) and TBSOTf (0.075 mL, 0.32 mmol, 2.00 equiv) were added sequentially. The reaction mixture was warmed to rt and stirred until TLC analysis showed complete consumption of the starting material, typically 3 h. The reaction was quenched via addition of saturated $NaHCO_{3(aq.)}$ (2 mL) and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with pentane (3 × 5 mL). The combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo*. The product was purified via flash chromatography (100:0 to 98:2 to 97.5:2.5 hexanes:EtOAc) to afford silyloxydiene **3.113** (0.077 g, 99 % yield) as a clear, viscous oil. Analytical data: $[\alpha]_D^{28}$ = 20.8 (*c* = 0.33, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.27 (s, 1H), 3.90 (s, 1H), 3.15 (dd, *J* = 7.2, 4.8 Hz, 1H), 3.08 (dd, *J* = 7.8, 3.0 Hz, 1H), 2.15 (m, 1H), 2.06 (dd, *J* = 11.4, 6.6 Hz, 1H), 1.81 (d, *J* = 13.2 Hz, 1H), 1.66 (br s, 5H), 1.54 (m, 2H), 1.39 (m, 1H), 1.23 (s, 3H), 1.16 (s, 3H), 1.07 (s, 3H), 0.92 (s, 9H), 0.84 (s, 9H), 0.20 (s, 3H), 0.17 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 155.6, 138.9, 128.6, 85.3, 81.1, 75.0, 34.7, 30.5, 27.2, 25.9, 25.8, 25.7, 25.2, 24.1, 21.9, 20.8, 18.2, 18.1, −2.1, −2.2, −4.5, −4.6; **HRMS (ESI$^+$)** Calcd. For $C_{28}H_{54}O_3Si_2$ + Na, 517.3509; Found, 517.3499; **IR** (thin film, cm^{-1}) 2930, 2896, 1611, 1497, 1376, 1265, 1165, 1038, 835, 775; **TLC** (90:10 hexanes:EtOAc): R_f = 0.94.

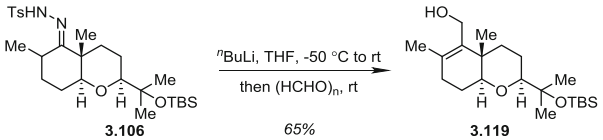


(*E*)-1-((2*S*,4a*S*,8a*S*)-2-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-5-yl)but-2-en-1-one (3.114): A flame-dried, 25 mL round bottomed flask was charged with hydrazone **3.106** (0.30 g, 0.57 mmol, 1.00 equiv) and THF (6 mL) under an atmosphere of N_2. The solution was cooled to −50 °C, and ^{n}BuLi (2.64 M in hexanes, 1.30 mL, 3.44 mmol, 6.00 equiv) was added over a period of ∼2 min, producing a dark orange color. The reaction was allowed to stir 30 min whereupon a venting needle was added, and the mixture was warmed to 0 °C and stirred 5 min. The reaction was then warmed to rt and stirred until complete consumption of the starting material was observed by TLC analysis, typically 20 min. The venting needle was removed, the mixture was cooled to −78 °C, and (*E*)-crotonaldehyde (0.48 mL, 5.74 mmol, 10.0 equiv) was added dropwise. The reaction was allowed to stir 25 min whereupon H_2O (5 mL) and Et_2O (5 mL) were added, and the mixture was warmed to rt and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried with magnesium sulfate, and concentrated *in vacuo* to give the crude alcohol, which was taken on to the next step without further purification

The crude residue was taken up into CH_2Cl_2 (5 mL) and transferred to a 20 mL scintillation vial. Dess-Martin periodinane (0.29 g, 0.68 mmol, 2.00 equiv) was added to the vial, and the mixture was allowed to stir until TLC analysis indicated complete consumption of the starting material, typically 15 min. The mixture was then quenched via a 1:1 solution of saturated $NaHCO_{3(aq.)}$ and saturated $Na_2S_2O_{3\,(aq.)}$ (5 mL), and the mixture was stirred 5 min. The reaction mixture was then diluted with Et_2O (10 mL) and partitioned in a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo*. The product was purified via flash chromatography (100:0 to 97.5:2.5 to 95:5 hexanes:EtOAc) to afford ketone **3.114** (0.10 g, 46 % yield) as a yellow, viscous oil. Analytical data: $[\alpha]_D^{28}$ −72.2 (c = 0.48, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.73 (m, 1H), 6.14 (dd, J = 13.8, 1.8 Hz, 1H), 3.26 (dd, J = 6.6, 5.4 Hz, 1H), 3.09 (dd, J = 7.8, 1.8 Hz, 1H), 2.21 (m, 1H), 2.11 (dd, J = 11.4, 6.6 Hz, 1H), 1.93 (dd, J = 5.4, 1.8 Hz, 3H), 1.74–1.70 (m, 2H), 1.51–1.47 (m, 6H), 1.38 (m, 1H), 1.22 (s, 3H), 1.15 (s, 3H), 1.14 (s, 3H), 0.83 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 200.7, 146.4, 140.2, 134.6, 130.2, 85.4, 80.4, 74.9, 35.7, 34.5, 30.5, 27.2, 25.8, 25.0, 23.9, 21.4, 20.7, 19.7, 18.4, 18.1, −2.1, −2.2; **HRMS (ESI$^+$)** Calcd. For $C_{24}H_{42}O_3Si$ + Na, 429.2801; Found, 429.2792; **IR** (thin film, cm^{-1}) 2955, 2855, 1671, 1472, 1361, 1265, 1165, 1041, 835, 739; **TLC** (90:10 hexanes:EtOAc): R_f = 0.56.



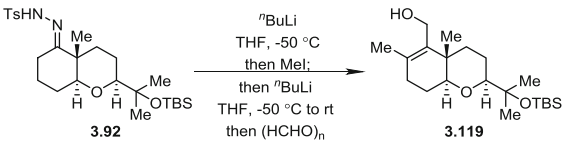
***tert*-butyl((2-((2*S*,4a*R*,8a*S*)-5-iodo-4a,6-dimethyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-2-yl)propan-2-yl)oxy)dimethylsilane (3.116)**: A flame-dried, 20 mL scintillation vial was charged with hydrazone **3.106** (0.30 g, 0.57 mmol, 1.00 equiv) and THF (6 mL) under an atmosphere of N_2. The solution was cooled to −50 °C, and ^{n}BuLi (1.70 M in hexanes, 2.00 mL, 3.42 mmol, 6.00 equiv) was added over a period of ∼2 min, producing a dark orange color. The reaction was allowed to stir 30 min whereupon a venting needle was added, and the mixture was warmed to 0 °C and stirred 5 min. The reaction was then warmed to rt and stirred until complete consumption of the starting material was observed by TLC analysis, typically 20 min. The venting needle was removed, the mixture was cooled to 0 °C, and I_2 (0.43 g, 1.71 mmol, 3.00 equiv) was added portionwise. The reaction was allowed to stir 20 min whereupon H_2O (5 mL) and Et_2O (5 mL) were added, and the mixture was warmed to rt and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL) and saturated $Na_2S_2O_{3(aq.)}$, dried with magnesium sulfate, and concentrated *in vacuo*. The product was purified via flash chromatography (100:0 to 99:1 to 98:2) to afford iodide **3.116** (0.18 g, 67 % yield) containing 17 % of the inseparable vinyl C-H compound (arising from protic quenching of the transient vinyllithium) by ^{1}H NMR analysis. Analytical data: $[\alpha]_D^{28}$ −248.0 (*c* = 1.00, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 3.32 (dd, *J* = 7.8, 4.2 Hz, 1H), 3.07 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.30 (m, 1H), 2.22 (dd, *J* = 11.4, 6.0 Hz, 1H), 1.90 (m, 1H), 185 (s, 3H), 1.70 (m, 1H), 1.60 (br s, 1H), 1.55 (m, 2H), 1.28 (m, 1H), 1.24 (s, 3H), 1.18 (s, 3H), 0.99 (s, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 136.2, 131.2, 114.8, 85.5, 81.1, 74.6, 41.5, 41.3, 32.3, 29.8, 27.4, 25.8, 25.0, 24.2, 22.7, 18.5, 18.1, −2.1, −2.2; **HRMS (ESI$^+$)** Calcd. For $C_{20}H_{37}IO_2Si$ + Na, 487.1505; Found, 487.1497; **IR** (thin film, cm^{-1}) 2954, 2854, 1771, 1670, 1488, 1376, 1264, 1162, 1040, 834; **TLC** (90:10 hexanes: EtOAc): R_f = 0.91.



((2*S*,4a*S*,8a*S*)-2-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-5-yl)methanol (3.119): A flame-dried, 50 mL round bottomed flask was charged with hydrazone **3.106** (0.58 g, 1.10 mmol, 1.00 equiv) and THF (11 mL) under an atmosphere of N_2. The solution was cooled to −50 °C, and ^{n}BuLi (1.55 M in hexanes, 4.27 mL, 6.62 mmol, 6.00 equiv) was added over a period of ∼2 min, producing a dark orange color. The reaction was allowed to stir 30 min whereupon a venting needle was added, and the mixture was warmed to 0 °C and stirred 5 min. The reaction was then warmed to rt

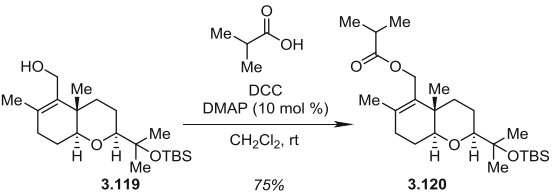
and stirred until complete consumption of the starting material was observed by TLC analysis, typically 20 min. The venting needle was removed, $(HCHO)_n$ (0.35 g, 11.0 mmol, 10.0 equiv) was added to the mixture in one portion, and the reaction was allowed to stir 40 min at rt. H_2O (10 mL) and Et_2O (5 mL) were added, and the mixture was transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried with magnesium sulfate and concentrated *in vacuo*. The product was purified via flash chromatography (100:0 to 95:5 to 90:10 to 80:20 hexanes:EtOAc) to afford alcohol **3.119** (0.26 g, 65 % yield) as a yellow, viscous oil. Analytical data: : $[\alpha]_D^{28}$ –53.7 (c = 0.70, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.20 (d, J = 11.4 Hz, 1H), 4.07 (d, J = 11.4 Hz, 1H), 3.18 (dd, J = 6.0, 4.2 Hz, 1H), 3.09 (dd, J = 6.6, 3.6 Hz, 1H), 2.17 (m, 1H), 2.06 (m, 1H), 1.98 (dt, J = 6.0, 3.6 Hz, 1H), 1.71 (s, 3H), 1.66 (m, 2H), 1.60 (m, 2H), 1.44 (m, 1H), 1.23 (s, 3H), 1.17 (s, 3H), 1.00 (s, 3H), 0.84 (s, 9H), 0.80 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 137.4, 132.2, 85.2, 81.3, 74.9, 58.2, 31.5, 25.8, 25.0, 24.2, 21.7, 19.4, 19.0, 18.1, −2.16, −2.21; **HRMS (ESI$^+$)** Calcd. For $C_{21}H_{40}O_3Si$ + Na, 391.2645; Found, 391.2652; **IR** (thin film, cm^{-1}) 3409, 2953, 2855, 1641, 1461, 1377, 1252, 1168, 1092, 834; **TLC** (85:15 hexanes:EtOAc): R_f = 0.29.

One-pot procedure for the conversion of 3.92 to 3.119



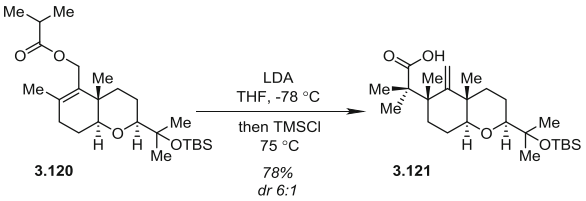
((2*S*,4a*S*,8a*S*)-2-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-5-yl)methanol (3.119): A flame-dried, 250 mL round-bottomed flask was charged with hydrazone **3.92** (1.50 g, 2.95 mmol, 1.00 equiv) and THF (30 mL) under an atmosphere of N_2. The solution was cooled to −50 °C, and ^{n}BuLi (3.97 mL, 2.6 M in hexanes, 10.32 mmol, 3.50 equiv) was added dropwise, producing a dark orange color. The reaction mixture was allowed to stir 40 min at this temperature, then MeI (0.46 mL, 7.37 mmol, 2.50 equiv) was added. The reaction was allowed to stir at −50 °C until TLC analysis confirmed complete conversion of **3.92**, typically 20 min. An additional charge of ^{n}BuLi (9.07 mL, 2.6 M in hexanes, 23.6 mmol, 8.00 equiv) was added to the reaction, and the resulting mixture was stirred 30 min. The flask was fitted with a venting needle, and the reaction mixture was then warmed to 0 °C, stirred 5 min, then warmed to rt and stirred until complete consumption of the intermediate

hydrazone was observed by TLC analysis, typically 15–25 min (scale dependent). The septum was partially removed, and $(HCHO)_n$ (0.89 g, 29.5 mmol, 10.0 equiv) was added in one portion with vigorous stirring. The reaction was allowed to stir 30 min at rt, at which time the mixture was diluted with H_2O (25 mL) and Et_2O (20 mL) and transferred to a separatory funnel. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried with magnesium sulfate, and concentrated *in vacuo*. The product was purified via flash chromatography (100:0 to 95:5 to 90:10 to 80:20 hexanes:EtOAc) to afford alcohol **3.119** (0.76 g, 66 % yield).



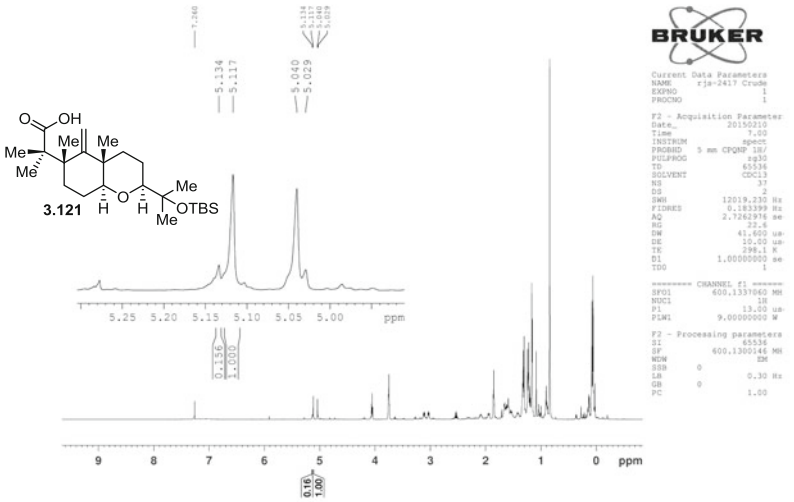
((2*S*,4a*S*,8a*S*)-2-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-5-yl)methyl isobutyrate(3.120): A flame-dried, 500 mL round-bottomed flask was charged with CH_2Cl_2 (110 mL) and isobutyric acid (2.22 mL, 24.47 mmol, 2.00 equiv) at rt under an atmosphere of N_2. DCC (5.05 g, 24.47 mmol, 2.00 equiv) and DMAP (0.15 g, 1.22 mmol, 0.10 equiv) were added followed lastly by a solution of alcohol **3.119** (4.51 g, 12.23 mmol, 1.00 equiv) in CH_2Cl_2 (10 mL), and the reaction was allowed to stir at rt until TLC analysis confirmed complete conversion of the starting material, typically 2.5 h. The reaction mixture was filtered through cotton into a separatory funnel, and H_2O (40 mL) and EtOAc (100 mL) were added. The mixture was extracted with EtOAc (3 × 30 mL), and the combined organic extracts were washed with saturated $NaHCO_{3(aq.)}$ (2 × 30 mL), dried with magnesium sulfate, and concentrated *in vacuo*. The product was purified via flash chromatography (100:0 to 97.5:2.5 to 95:5 hexanes:EtOAc) to afford ester **3.120** (4.01 g, 75 %) as a clear, viscous oil. Analytical data: $[\alpha]_D^{28}$ –73.0 (c = 0.75, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.58 (br s, 2H), 3.19 (dd, J = 5.4, 4.8 Hz, 1H), 3.08 (dd, J = 5.4, 4.2 Hz, 1H), 2.54 (m, 1H), 2.19 (m, 1H), 2.09 (m, 1H), 1.82 (dt, J = 6.0, 3.0 Hz, 1H), 1.67–1.65 (m, 5H), 1.57 (m, 2H), 1.37 (m, 1H), 1.23 (s, 3H), 1.17 (br s, 6H), 1.15 (d, J = 2.4 Hz, 3H), 0.99 (s, 3H), 0.84 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 177.3, 134.5, 132.3, 85.1, 81.0, 74.9, 60.3, 25.8, 24.2, 21.7, 19.3, 19.2, 19.1, 19.0, 18.2, −2.1, −2.2; **HRMS (ESI$^+$)** Calcd. For $C_{25}H_{46}O_4Si$ + Na, 461.3063; Found,

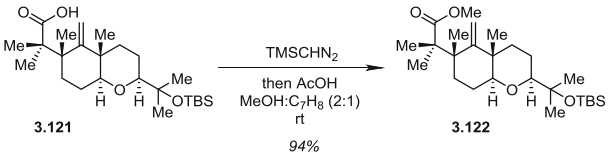
461.3062; **IR** (thin film, cm^{-1}) 2955, 2856, 1721, 1470, 1378, 1215, 1092, 835, 756; **TLC** (85:15 hexanes:EtOAc): $R_f = 0.66$.



2-((2*S*,4a*S*,6*S*,8a*S*)-2-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-5-methyleneoctahydro-2H-chromen-6-yl)-2-methylpropanoic acid (3.121): A flame-dried, 250-mL round-bottomed flask was charged with THF (80 mL) and diisopropylamine (3.84 mL, 27.42 mmol, 3.00 equiv) under an atmosphere of N_2. The mixture was cooled to 0 °C and ^{n}BuLi (1.85 M solution in hexanes, 14.82 mL, 27.42 mmol, 3.00 equiv) was added slowly. After stirring for 30 min at 0 °C, the mixture was cooled to −78 °C, and isobutyrate **3.120** (4.01 g, 9.14 mmol, 1.00 equiv) was added as a solution in THF (15 mL). The mixture was allowed to stir for 45 min at which time TMSCl (3.52 mL, 27.42 mmol, 3.00 equiv) was added. The reaction mixture was then allowed to warm to rt, stirred for 5 min, and subsequently warmed to 75 °C and stirred until TLC analysis indicated complete conversion of the starting material, typically 12 h. The reaction mixture was cooled to rt and quenched via 1 M $HCl_{(aq.)}$ (25 mL). The mixture was then partitioned in a separatory funnel and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with 6 M HCl (2 × 30 mL), dried with magnesium sulfate, and concentrated *in vacuo* to provide the crude acid as a 6:1 mixture of diastereomers. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 5.13 (minor diastereomer) and δ 5.12 (major diastereomer). The product was purified via flash chromatography (100:0 to 90:10 to 80:20 hexanes:EtOAc) to afford acid **3.121** (3.14 g, 78 % yield) as a clear, viscous oil in an inseparable 6:1 diastereomeric ratio. Analytical data: $[\alpha]_D^{28}$ –43.5 (c = 0.70, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.12 (s, 1H), 5.04 (s, 1H), 3.12 (dd, J = 6.6, 2.4 Hz, 1H), 3.04 (m, 1H), 2.09 (m, 1H), 1.95 (m, 1H), 1.66 (m, 2H), 1.59 (m, 2H), 1.54 (m, 1H), 1.41 (m, 1H), 1.33 (s, 3H), 1.31 (s, 3H), 1.25 (s, 3H), 1.23 (s, 3H), 1.17 (s, 3H), 1.09 (s, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 184.5, 161.1, 110.4, 84.7, 81.0, 74.8, 50.2, 44.4, 39.5, 36.9, 33.2, 28.3, 27.4, 25.6, 25.0, 24.6, 23.7, 23.6, 22.4, 22.1, 18.2, −2.2; **HRMS (ESI$^+$)** Calcd. For $C_{25}H_{46}O_4Si$ + Na, 461.3063; Found, 461.3063; **IR** (thin film, cm^{-1}) 3406, 2955, 2856, 1693, 1641, 1471, 1378, 1252, 1170, 1094, 1042, 835, 760; **TLC** (85:15 hexanes:EtOAc): $R_f = 0.40$.

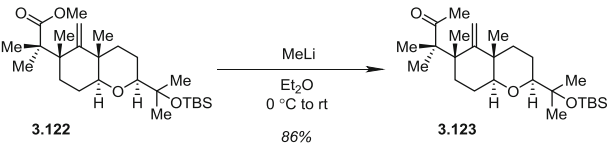
Crude ^{1}H NMR spectrum of 3.121





Methyl 2-((2*S*,4a*S*,6*S*,8a*S*)-2-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-5-methyleneoctahydro-2H-chromen-6-yl)-2-methylpropanoate (3.122): The acid **3.121** (3.14 g, 7.16 mmol, 1.00 equiv) was dissolved in MeOH:C_7H_8 (2:1, 75 mL) in a 250 mL round-bottomed flask with magnetic stirring at rt. $TMSCHN_2$ (2 M in Et_2O, 10.00 mL, 20 mmol, 2.79 equiv) was added dropwise until the yellow color of excess $TMSCHN_2$ in solution persisted. AcOH (1.50 g, 24.98 mmol, 3.50 mmol) was added dropwise, giving a clear solution. The resulting mixture was concentrated *in vacuo* and purified via flash chromatography (100:0 to 97.5:2.5 to 95:5 hexanes:EtOAc) to afford ester **3.122** (3.06 g, 94 % yield) as a clear, viscous oil in an inseparable 6.3:1 diastereomeric ratio (as determined by integration of the resonances at δ 3.64 (minor diastereomer) and δ 3.62 (major diastereomer)). Analytical data: $[\alpha]_D^{28-8}$9.7 (c = 0.60, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.01 (s, 1H), 5.00 (s, 1H), 3.62 (s, 3H), 3.08 (m, 1H),

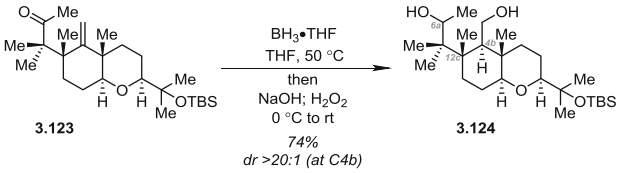
3.03 (dd, J = 6.0, 2.4 Hz, 1H), 2.08 (m, 1H), 1.95 (dt, J = 5.4, 3.6 Hz, 1H), 1.65 (m, 2H), 1.59 (m, 2H), 1.57 (br s, 1H), 1.50 (m, 1H), 1.39 (m, 1H), 1.29 (s, 3H), 1.28 (s, 3H), 1.22 (s, 3H), 1.21 (s, 3H), 1.16 (s, 3H), 1.08 (s, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 178.7, 161.4, 110.0, 84.8, 81.0, 74.9, 51.4, 50.3, 44.3, 39.5, 36.9, 33.1, 28.5, 27.3, 25.6, 25.0, 24.6, 23.9, 23.7, 22.4, 22.1, 18.2, −2.1, −2.2; **HRMS (ESI$^+$)** Calcd. For $C_{26}H_{48}O_4Si$ + Na, 475.3220; Found, 475.3221; **IR** (thin film, cm^{-1}) 2954, 2855, 1722, 1601, 1451, 1378, 1169, 1051, 835, 741; **TLC** (85:15 hexanes:EtOAc): R_f = 0.66.



3.122 **3.123**

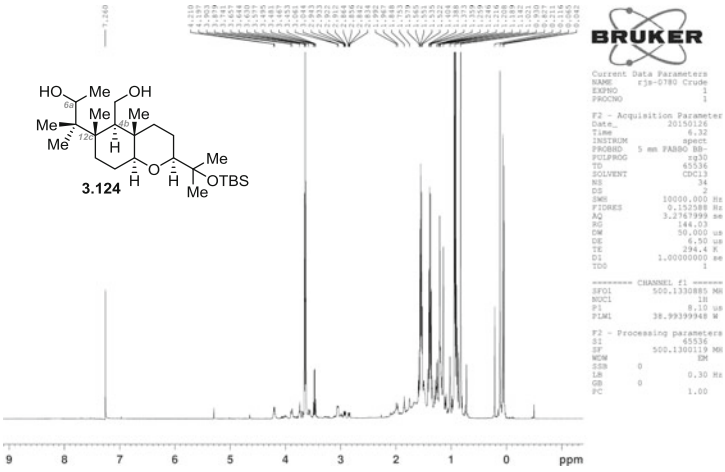
3-((2*S*,4a*S*,6*S*,8a*S*)-2-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-5-methyleneoctahydro-2H-chromen-6-yl)-3-methylbutan-2-one (3.123): A flame-dried, 500-mL round-bottomed flask was charged with ester **3.122** (3.82 g, 8.44 mmol, 1.00 equiv) and Et_2O (84 mL) under an atmosphere of N_2. The mixture was cooled to 0 °C, and MeLi (1.6 M in Et_2O, 21.09 mL, 33.75 mmol, 4.00 equiv) was added. The mixture was warmed to rt whereupon TLC analysis showed incomplete conversion of the starting material. A second addition of MeLi (4.00 equiv) was carried out, upon which TLC analysis showed remaining starting material. A third addition of MeLi (4.00 equiv) was carried out, upon which TLC analysis showed complete conversion of the starting material. The reaction mixture was cooled to 0 °C and quenched carefully with saturated $NH_4Cl_{(aq.)}$ (25 mL). The mixture was partitioned in a separatory funnel, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo*. The product was purified via flash chromatography (100:0 to 97.5:2.5 to 95:5 hexanes:EtOAc) to afford ketone **3.123** (3.52 g, 86 % yield) as a clear, viscous oil in an inseparable 7:1 ratio of diastereomers (as determined by integration of the resonances at δ 5.05 (major diastereomer) and δ 5.03 (minor diastereomer)). Analytical data: $[\alpha]_D^{28-9}$2.2 (c = 0.60, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.05 (s, 1H), 4.90 (s, 1H), 3.15 (dd, J = 5.4, 4.8 Hz, 1H), 3.04 (m, 1H), 2.18 (s, 3H), 1.96 (m, 1H), 1.66 (m, 1H), 1.61–1.59 (m, 3H), 1.53 (m, 1H), 1.44 (m, 1H), 1.30 (s, 3H), 1.23 (s, 3H), 1.22 (s, 3H), 1.16 (br s, 6H), 1.08 (s, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 215.1, 161.4, 111.1, 84.7, 80.5, 74.8, 54.7, 44.9, 39.4, 36.8, 33.0, 29.7, 29.4, 27.4, 25.8, 25.0, 24.6, 23.6, 23.5, 22.7, 22.0, 18.1, −2.1, −2.2; **HRMS (ESI$^+$)** Calcd. For $C_{26}H_{48}O_3Si$ + Na, 459.3271; Found, 459.3267; **IR**

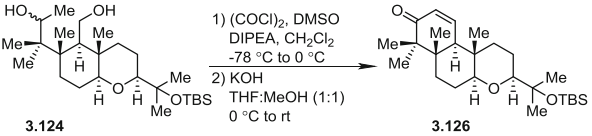
(thin film, cm^{-1}) 2955, 2856, 1694, 1620, 1470, 1377, 1251, 1094, 835; **TLC** (85:15 hexanes:EtOAc): $R_f = 0.54$.



3-((2*S*,4a*S*,5*R*,6*S*,8a*S*)-2-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-5-(hydroxymethyl)-4a,6-dimethyloctahydro-2H-chromen-6-yl)-3-methylbutan-2-ol (3.124): A flame-dried, 250 mL round-bottomed flask was charged with ketone **3.123** (1.63 g, 3.74 mmol, 1.00 equiv) and THF (70 mL) under an atmosphere of N_2. BH_3•THF (1 M in THF, 16.82 mL, 4.50 equiv) was added, and the mixture was warmed to 50 °C and stirred until complete conversion of the starting material was observed by TLC analysis, typically 12 h. The reaction mixture was then cooled to 0 °C, and 3 M $NaOH_{(aq.)}$ (7.5 mL) was added slowly followed by H_2O_2 (30 % w/w in H_2O, 7.5 mL). The resulting mixture was warmed to rt and stirred for 2.5 h, upon which the mixture was partitioned in a separatory funnel, diluted with H_2O (30 mL), and extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo to afford the crude diol as an inseparable mixture of diastereomers at C12c and C6a. The diastereoselection of this reaction at C4b was determined via ^1H NMR analysis of the subsequent intermediate (vide infra). The product was purified via flash chromatography (80:20 to 70:30 hexanes:EtOAc) to afford diol **3.124** (1.27 g, 74 % yield) as a white, viscous foam. This diastereomeric mixture was carried on to the next step without further separation. Analytical data: $[\alpha]_D^{28-8}3.9$ ($c = 0.60$, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.18 (m, 2H), 3.88 (t, $J = 12.6$ Hz, 2H), 3.68 (dd, $J = 9.0$, 3.0 Hz, 1H), 3.56 (d, $J = 12.0$ Hz, 1H), 3.06 (m, 2H), 2.93 (dd, $J = 6.0$, 4.8 Hz, 1H), 2.86 (dd, $J = 7.2$, 4.2 Hz, 1H), 1.98 (m, 3H), 1.76 (s, 1H), 1.59–1.49 (m, 11H), 1.42–1.36 (m, 3H), 1.25 (d, $J = 6.0$ Hz, 5H), 1.21 (s, 6H), 1.15 (s, 7H), 1.01 (s, 2H), 0.95 (br s, 9H), 0.90 (br s, 4H), 0.89 (s, 3H), 0.86 (s, 2H), 0.83 (br s, 22H), 0.07 (s, 7H), 0.05 (s, 7H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 85.1, 84.9, 84.2, 83.7, 74.9, 68.7, 61.5, 61.0, 54.2, 52.9, 45.8, 45.1, 42.5, 42.4, 39.0, 38.5, 37.9, 37.8, 34.0, 33.5, 27.4, 27.3, 25.8, 25.2, 25.0, 24.9, 24.6, 21.5, 21.4, 21.2, 19.8, 18.1, 17.8, 17.5, 14.7, 14.2, −2.1, −2.2; **HRMS (ESI$^+$)** Calcd. For $C_{26}H_{52}O_4Si$ + Na, 479.3533; Found, 479.3549; **IR** (thin film, cm^{-1}) 3320, 2955, 2855, 1471, 1379, 1251, 1172, 1100, 834, 759; **TLC** (85:15 hexanes:EtOAc): $R_f = 0.14$.

Crude ^{1}H NMR spectrum of 3.124.

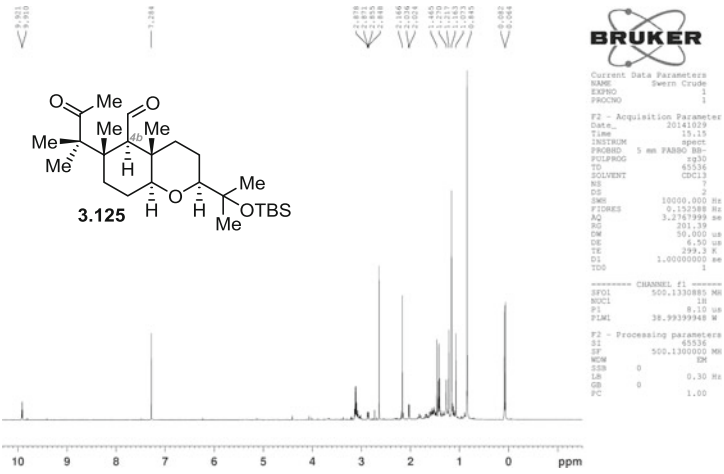




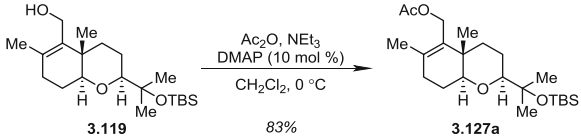
(3*S*,4a*S*,6a*S*,10a*R*,10b*S*)-3-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-6a,7,7,10b-tetramethyl-2,3,5,6,6a,7,10a,10b-octahydro-1H-benzo[f]chromen-8(4aH)-one (3.126): A flame-dried, 250 mL round-bottomed flask was charged with CH_2Cl_2 (70 mL) and $(COCl)_2$ (1.71 mL, 19.92 mmol, 5.00 equiv) under an atmosphere of N_2. The mixture was cooled to −78 °C, and DMSO (2.83 mL, 39.84 mmol, 10.00 equiv) was added slowly. The mixture was allowed to stir 30 min at −78 °C then the diol **3.124** (1.82 g, 3.98 mmol, 1.00 equiv) was added as a solution in CH_2Cl_2 (10 mL). The reaction mixture was stirred at this temperature for 2 h then DIPEA (13.88 mL, 79.69 mL, 20.0 equiv) was added. The reaction was stirred 30 min at −78 °C then warmed to 0 °C and stirred 15 min. At this time TLC analysis confirmed complete conversion of the starting material. The reaction was quenched with saturated $NH_4Cl_{(aq.)}$ (25 mL), and the mixture was partitioned in a separatory funnel. The mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic extracts were washed with brine (20 mL), dried with magnesium sulfate and concentrated in vacuo to afford the crude ketoaldehyde **3.125**, which was

carried to the next step without further purification. (Note: at this stage, a single diastereomer was observed in the ^{1}H NMR spectrum of the crude aldehyde, thereby establishing complete control of the C4b methine stereocenter in the hydroboration/oxidation step. This crude spectrum is provided below.)

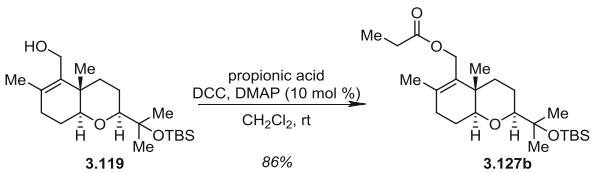
Crude NMR spectrum of 3.125



The crude ketoaldehyde **3.125** was dissolved in MeOH:THF (1:1, 80 mL) in a 250 mL round-bottomed flask and cooled to 0 °C with magnetic stirring. 2 M $KOH_{(aq.)}$ (8 mL) was added, and the reaction was warmed to rt and stirred for 12 h. The resulting mixture was concentrated on a rotary evaporator and partitioned with EtOAc (30 mL) and H_2O (30 mL) in a separatory funnel. The mixture was extracted with EtOAc (3 × 20 mL), and the combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo*. The product was purified via flash chromatography (100:0 to 97.5:2.5 to 95:5 to 90:10 hexanes:EtOAc) to afford the enone **3.126** (1.29 g, 75 % yield) as a yellow, viscous oil. Analytical data: $[\alpha]_D^{28}$ – 109.0 (c = 0.85, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.73 (d, J = 12.6 Hz, 1H), 5.99 (dd, J = 7.0, 3.5 Hz, 1H), 3.14 (dd, J = 9.0, 3.0 Hz, 1H), 2.97 (dd, J = 5.0, 5.0 Hz, 1H), 2.29 (br s, 1H), 1.96 (d, J = 9.0 Hz, 1H), 1.70–1.58 (m, 6H), 1.43 (m, 1H), 1.23 (s, 3H), 1.17 (s, 3H), 1.07 (s, 3H), 1.00 (s, 3H), 0.95 (s, 3H), 0.93 (s, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 204.9, 146.2, 129.0, 85.6, 85.0, 74.8, 51.5, 49.7, 43.8, 37.3, 35.5, 30.5, 27.4, 25.8, 24.9, 23.8, 21.2, 20.3, 18.1, 16.9, 16.6, 14.7, −2.1, −2.2; **HRMS (ESI$^+$)** Calcd. For $C_{26}H_{46}O_3Si$ + Na, 457.3114; Found, 457.3129; **IR** (thin film, cm^{-1}) 2954, 2855, 1677, 1461, 1389, 1251, 1174, 1103, 1041, 834, 756; **TLC** (85:15 hexanes:EtOAc): R_f = 0.43.

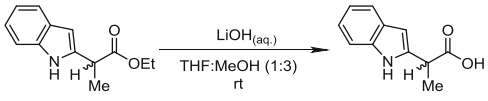


((2*S*,4a*S*,8a*S*)-2-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-5-yl)methyl acetate (3.127a): A flame-dried, 20 mL scintillation vial was charged with alcohol **3.119** (0.05 g, 0.14 mmol, 1.00 equiv) and CH_2Cl_2 under an atmosphere of N_2. The mixture was cooled to 0 °C, and NEt_3 (0.04 mL, 0.27 mmol, 2.00 equiv), DMAP (0.002 g, 0.014 mmol, 0.1 equiv), and lastly Ac_2O (0.03 mL, 0.27 mmol, 2.00 equiv) were added sequentially. The mixture was allowed to stir at this temperature until TLC analysis showed complete consumption of the starting material, typically 3 h. The mixture was diluted with H_2O (7 mL) and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 7 mL), dried with magnesium sulfate, and concentrated *in vacuo*. The product was purified via flash chromatography (100:0 to 98:2 to 95:5 to 90:10 hexanes:EtOAc) to afford acetate **3.127a** (0.046 g, 83 % yield) as a clear, viscous oil. Analytical data: $[\alpha]_D^{28}$ −59.0 (*c* = 1.35, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.59 (dd, *J* = 12.0, 5.4 Hz, 2H), 3.19 (dd, *J* = 6.0, 4.8 Hz, 1H), 3.08 (dd, *J* = 6.0, 4.2 Hz, 1H), 2.20 (m, 1H), 2.11 (m, 1H), 2.05 (s, 3H), 1.82 (m, 1H), 1.67 (br s, 5H), 1.57 (m, 1H), 1.36 (m, 1H), 1.23 (s, 3H), 1.17 (s, 3H), 0.99 (s, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 171.3, 134.8, 132.2, 85.1, 81.0, 74.9, 60.4, 36.3, 33.9, 31.6, 27.3, 25.8, 25.0, 24.1, 21.6, 21.2, 19.3, 19.2, 18.1, −2.1, −2.2; **HRMS (ESI$^+$)** Calcd. For $C_{23}H_{42}O_4Si$ + Na, 433.2750; Found, 433.2741; **IR** (thin film, cm^{-1}) 2955, 2856, 1771, 1730, 1472, 1377, 1249, 1092, 1039, 835, 759; **TLC** (90:10 hexanes:EtOAc): R_f = 0.54.

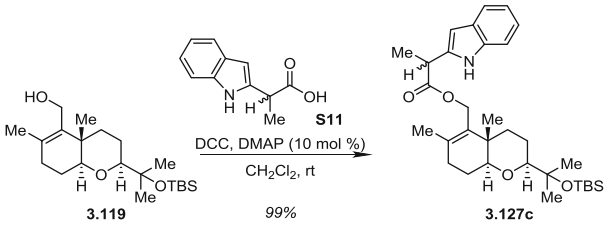


((2*S*,4a*S*,8a*S*)-2-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-5-yl)methyl propionate (3.127b): A flame-dried, 20 mL scintillation vial was charged with CH_2Cl_2 (3 mL) and propionic acid (0.02 g, 0.27 mmol, 2.00 equiv) at rt under an atmosphere of N_2. DCC (0.06 g, 0.27 mmol, 2.00 equiv) and DMAP (0.002 g, 0.014 mmol, 0.10 equiv) were added followed lastly by a solution of alcohol **3.119** (0.05 g, 0.14 mmol, 1.00 equiv) in CH_2Cl_2 (1 mL), and the reaction was allowed to stir at rt until TLC analysis confirmed complete conversion of the starting material, typically 3.5 h. The reaction mixture was filtered through cotton into a separatory funnel, and H_2O (10 mL) and EtOAc (10 mL) were added. The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with saturated $NaHCO_{3(aq.)}$ (10 mL), dried with magnesium sulfate, and concentrated *in vacuo*. The product was purified via flash chromatography (100:0 to 98:2 to 95:5 hexanes: EtOAc) to afford ester **3.127b** (0.05 g, 86 % yield) as a clear, viscous oil. Analytical data: $[\alpha]_D^{28}$ −51.4 (*c* = 1.25, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.60 (dd, *J* = 12.0, 7.8 Hz, 2H), 3.19 (dd, *J* = 5.4, 5.4 Hz, 1H), 3.08 (dd, *J* = 6.0,

4.2 Hz, 1H), 2.32 (q, J = 7.2 Hz, 2H), 2.19 (m,1H), 2.09 (dd, J = 12.6, 4.8 Hz, 1H), 1.82 (dt, J = 6.0, 3.6 Hz, 1H), 1.67 (br s, 5H), 1.56 (m, 1H), 1.37 (m, 1H), 1.23 (s, 3H), 1.17 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H), 0.99 (s, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 174.6, 134.6, 132.3, 85.1, 81.0, 74.9, 60.3, 36.3, 34.0, 27.7, 27.3, 25.8, 25.0, 24.2, 21.7, 19.3, 19.2, 18.2, 9.2, −2.1, −2.2; **HRMS (ESI$^+$)** Calcd. For $C_{24}H_{44}O_4Si$ + Na, 447.2907; Found, 447.2897; **IR** (thin film, cm^{-1}) 3053, 2955, 2855, 1731, 1540, 1472, 1322, 1265, 1179, 1071, 835; **TLC** (90:10 hexanes:EtOAc): R_f = 0.68.

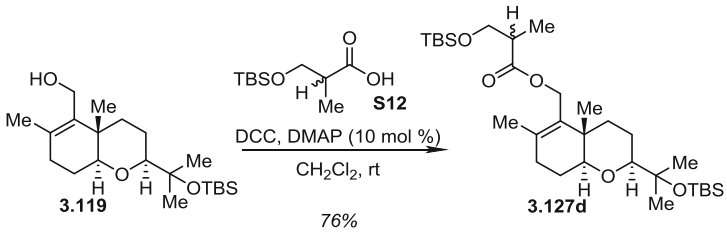


2-(1H-indol-2-yl)propanoic acid (S11): A 20 mL scintillation vial was charged with ethyl 2-(1H-indol-2-yl)propanoate **S10** (0.2 g, 0.92 mmol, 1.00 equiv) and a 3:1 mixture of MeOH:THF (5 mL). LiOH (4 M in H_2O, 0.7 mL, 2.76 mmol, 3.00 equiv) was added, and the mixture was allowed to stir at rt until complete consumption of the starting material was observed by TLC analysis, typically 6 h. The reaction mixture was concentrated on a rotary evaporator, and the residue was diluted with H_2O (10 mL) and transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (2 × 10 mL), and the aqueous layer was then acidified to pH = 0 with 1 M $HCl_{(aq.)}$ and extracted with CH_2Cl_2 (3 × 10 mL). The combined CH_2Cl_2 extracts were dried with magnesium sulfate and concentrated *in vacuo* to give the crude carboxylic acid **S11**. This material could not be isolated due to spontaneous decarboxylation, but could be carried forward directly to the next step without further purification.



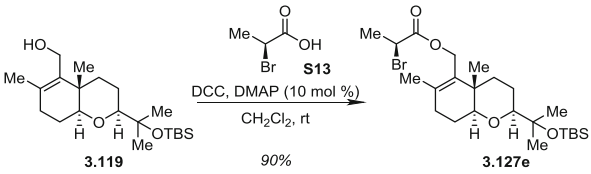
((2*S*,4a*S*,8a*S*)-2-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-5-yl)methyl 2-(1H-indol-2-yl)propanoate (3.127c): The crude acid **S11** (∼ 4.00 equiv) was dissolved in CH_2Cl_2 (3 mL) and transferred to a flame-dried 20 mL scintillation vial under an atmosphere of N_2. DCC (0.095 g, 0.46 mmol, 2.00 equiv) was added followed by DMAP (0.003 g, 0.023 mmol, 0.10 equiv) and lastly a solution of alcohol **3.119** (0.085 g, 0.23 mmol, 1.00 equiv) in CH_2Cl_2 (1 mL). The reaction was allowed to stir until TLC analysis confirmed complete consumption of the starting material, typically 20 min. The reaction mixture was filtered through cotton into a separatory funnel, and H_2O (10 mL) and EtOAc (10 mL) were added. The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with

saturated $NaHCO_{3(aq.)}$ (10 mL), dried with magnesium sulfate, and concentrated *in vacuo*. The product was purified via flash chromatography (100:0 to 95:5 to 90:10 hexanes:EtOAc) to afford an inseparable mixture of diastereomeric esters **3.127c** (0.14 g, 99 % yield) as a brown, viscous oil. Analytical data: $[\alpha]_D^{28}$ −68.4 (*c* = 0.43, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.59 (m, 1H), 7.56 (m, 1H), 7.32 (m, 1H), 7.15 (m, 1H), 7.09 (m, 1H), 6.37 (br s, 1H), 4.66 (m, 2H), 3.95 (m, 1H), 3.17 (m, 1H), 3.06–2.98 (m, 1H), 2.21 (m, 1H), 2.10 (m, 1H), 1.68–1.66 (m, 4H), 1.64–1.62 (m, 4H), 1.46 (m, 2H), 1.32 (m, 2H), 1.23–1.21 (m, 3H), 1.16–1.14 (m, 3H), 0.97–0.96 (m, 3H), 0.86 (s, 9H), 0.10–0.09 (m, 3H), 0.07 (m, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 173.6, 136.7, 136.6, 136.0, 135.4, 131.9, 128.0, 121.7, 120.2, 119.7, 110.6, 100.1, 85.1, 85.0, 80.9, 74.8, 61.3, 61.2, 41.5, 39.3, 39.2, 36.2, 33.9, 31.6, 27.2, 27.1, 26.1, 25.8, 25.2, 25.1, 24.1, 23.3, 21.5, 19.2, 18.1, 17.4, 17.2, 14.1, −2.2, −2.3; **HRMS (ESI$^+$)** Calcd. For $C_{32}H_{49}NO_4Si$ + Na, 562.3329; Found, 562.3320; **IR** (thin film, cm^{-1}) 3392, 2954, 2855, 1716, 1471, 1377, 1250, 1172, 1069, 835; **TLC** (90:10 hexanes:EtOAc): R_f = 0.41.

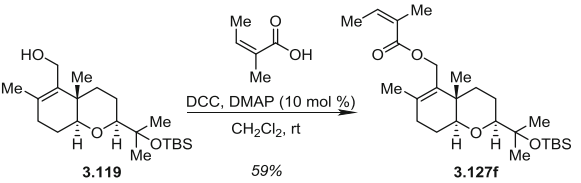


((2*S*,4a*S*,8a*S*)-2-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-5-yl)methyl 3-((tert-butyldimethylsilyl)oxy)-2-methylpropanoate (3.127d): A flame-dried, 20 mL scintillation vial was charged with CH_2Cl_2 (3 mL) and 3-((*tert*-butyldimethylsilyl)oxy)-2-methylpropanoic acid **S12** (0.05 g, 0.22 mmol, 2.00 equiv) at rt under an atmosphere of N_2. DCC (0.04 g, 0.22 mmol, 2.00 equiv) and DMAP (0.002 g, 0.014 mmol, 0.10 equiv) were added followed lastly by a solution of alcohol **3.119** (0.04 g, 0.11 mmol, 1.00 equiv) in CH_2Cl_2 (1 mL), and the reaction was allowed to stir at rt until TLC analysis confirmed complete conversion of the starting material, typically 3.5 h. The reaction mixture was filtered through cotton into a separatory funnel, and H_2O (10 mL) and EtOAc (10 mL) were added. The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with saturated $NaHCO_{3(aq.)}$ (10 mL), dried with magnesium sulfate, and concentrated *in vacuo*. The product was purified via flash chromatography (100:0 to 98:2 to 95:5 hexanes:EtOAc) to afford an inseparable mixture of diastereomeric esters **3.127d** (0.047 g, 76 % yield) as a clear, viscous oil. Analytical data: $[\alpha]_D^{28}$ −42.1 (*c* = 1.20, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.58 (m, 2H), 3.79 (m, 1H), 3.64 (m, 1H), 3.18 (m, 1H), 3.08 (dd, *J* = 7.2, 3.6 Hz, 1H), 2.62 (m, 1H), 2.19 (m, 1H), 2.09 (m, 1H), 1.82 (m, 1H), 1.67–1.66 (m, 5H), 1.57 (m, 2H), 1.37 (m, 1H), 1.23 (s, 3H), 1.17 (s, 3H), 1.14–1.12 (m, 3H),

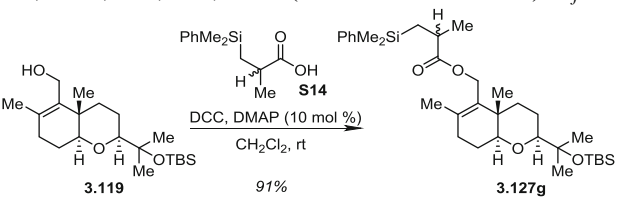
0.99 (m, 3H), 0.87 (s, 9H), 0.84 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H), 0.03 (br s, 6H), **^{13}C NMR** (150 MHz, $CDCl_3$): δ 175.1, 134.6, 134.5, 132.3, 85.1, 81.0, 74.9, 65.3, 65.2, 60.4, 60.3, 42.7, 36.3, 34.1, 34.0, 31.7, 27.4, 27.3, 25.9, 25.8, 25.0, 24.2, 21.7, 21.6, 19.3, 19.2, 18.2, 13.6, −2.1, −2.2, −5.5; **HRMS (ESI$^+$)** Calcd. For $C_{31}H_{60}O_5Si_2$ + Na, 591.3877; Found, 591.3867; **IR** (thin film, cm^{-1}) 3053, 2955, 2884, 2857, 1727, 1471, 1377, 1265, 1179, 1049, 836; **TLC** (90:10 hexanes:EtOAc): R_f = 0.73.



((2*S*,4a*S*,8a*S*)-2-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-5-yl)methyl (*S*)-2-bromopropanoate (3.127e): A flame-dried, 20 mL scintillation vial was charged with CH_2Cl_2 (3 mL) and (*S*)-2-bromopropanoic acid **S13** (0.04 g, 0.27 mmol, 2.00 equiv) at rt under an atmosphere of N_2. DCC (0.06 g, 0.27 mmol, 2.00 equiv) and DMAP (0.002 g, 0.014 mmol, 0.10 equiv) were added followed lastly by a solution of alcohol **3.119** (0.05 g, 0.14 mmol, 1.00 equiv) in CH_2Cl_2 (1 mL), and the reaction was allowed to stir at rt until TLC analysis confirmed complete conversion of the starting material, typically 3.5 h. The reaction mixture was filtered through cotton into a separatory funnel, and H_2O (10 mL) and EtOAc (10 mL) were added. The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with saturated $NaHCO_{3(aq.)}$ (10 mL), dried with magnesium sulfate, and concentrated *in vacuo*. The product was purified via flash chromatography (100:0 to 98:2 to 95:5 hexanes:EtOAc) to afford ester **3.127e** (0.062 g, 90 % yield) as a clear, viscous oil. Analytical data: $[\alpha]_D^{28}$ −49.2 (*c* = 1.50, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.68 (br s, 1H), 4.36 (q, *J* = 6.6 Hz, 1H), 3.19 (dd, *J* = 6.0, 4.2 Hz, 1H), 3.08 (dd, *J* = 6.6, 3.6 Hz, 1H), 2.20 (m, 1H), 2.10 (m, 1H), 1.83–1.81 (m, 5H), 1.69–1.66 (m, 5H), 1.58 (m, 1H), 1.38 (m, 1H), 1.23 (s, 3H), 1.17 (s, 3H), 1.01 (s, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 170.4, 135.7, 131.6, 85.1, 80.9, 74.9, 62.0, 40.3, 36.2, 34.1, 31.7, 27.3, 25.8, 25.0, 24.1, 21.7, 21.6, 19.4, 19.3, 18.1, −2.1, −2.2; **HRMS (ESI$^+$)** Calcd. For $C_{24}H_{43}BrO_4Si$ + Na, 525.2012; Found, 525.2004; **IR** (thin film, cm^{-1}) 2929, 2856, 1732, 1472, 1378, 1329, 1217, 1159, 1070, 835; **TLC** (90:10 hexanes:EtOAc): R_f = 0.62.

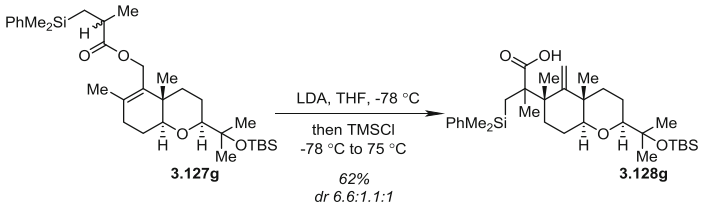


((2*S*,4a*S*,8a*S*)-2-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-5-yl)methyl (*Z*)-2-methylbut-2-enoate (3.127f): A flame-dried, 20 mL scintillation vial was charged with CH_2Cl_2 (3 mL) and angelic acid (0.03 g, 0.27 mmol, 2.00 equiv) at rt under an atmosphere of N_2. DCC (0.06 g, 0.27 mmol, 2.00 equiv) and DMAP (0.002 g, 0.014 mmol, 0.10 equiv) were added followed lastly by a solution of alcohol **3.119** (0.05 g, 0.14 mmol, 1.00 equiv) in CH_2Cl_2 (1 mL), and the reaction was allowed to stir at rt until TLC analysis confirmed complete conversion of the starting material, 30 h. In some cases, an additional 2.00 equiv of angelic acid and DCC were added after 12 h to aide starting material conversion. The reaction mixture was filtered through cotton into a separatory funnel, and H_2O (10 mL) and EtOAc (10 mL) were added. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with saturated $NaHCO_{3(aq.)}$ (10 mL), dried with magnesium sulfate, and concentrated *in vacuo*. The product was purified via flash chromatography (100:0 to 98:2 to 95:5 hexanes:EtOAc) to afford ester **3.127f** (0.040 g, 59 % yield) as a pale yellow, viscous oil. Analytical data: $[\alpha]_D^{28}$ −53.1 (*c* = 1.00, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.83 (q, *J* = 6.6 Hz, 1H), 4.65 (br s, 2H), 3.19 (dd, *J* = 5.4, 5.4 Hz, 1H), 3.09 (dd, *J* = 6.0, 3.6 Hz, 1H), 2.19 (m, 1H), 2.10 (m, 1H), 1.97 (m, 1H), 1.88–1.83 (m, 4H), 1.79 (d, *J* = 6.6 Hz, 3H), 1.67 (br s, 4H), 1.56 (m, 2H), 1.37 (m, 1H), 1.23 (s, 3H), 1.16 (s, 3H), 1.01 (s, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 168.3, 137.4, 136.9, 134.3, 132.4, 128.8, 85.1, 81.0, 74.9, 60.4, 36.2, 34.1, 31.7, 31.6, 27.2, 25.8, 25.0, 24.2, 21.7, 19.4, 19.2, 14.4, 12.1, −2.1, −2.2; **HRMS (ESI$^+$)** Calcd. For $C_{26}H_{46}O_4Si$ + Na, 473.3063; Found, 473.3055; **IR** (thin film, cm^{-1}) 2955, 2855, 1731, 1703, 1636, 1487, 1361, 1263, 1070, 835, 758; **TLC** (90:10 hexanes:EtOAc): R_f = 0.65.



((2*S*,4a*S*,8a*S*)-2-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-5-yl)methyl 3-(dimethyl(phenyl)silyl)-2-methylpropanoate (3.127g): A flame-dried, 20 mL scintillation vial was charged with CH_2Cl_2 (5 mL) and 3-(dimethyl(phenyl)silyl)-2-methylpropanoic acid **S14** (0.18 g, 0.81 mmol, 2.00 equiv) at rt under an atmosphere of N_2. DCC (0.17 g, 0.81 mmol, 2.00 equiv) and DMAP (0.005 g, 0.04 mmol, 0.10 equiv) were added followed lastly by a solution of alcohol **3.119** (0.15 g, 0.41 mmol, 1.00 equiv) in CH_2Cl_2 (2 mL), and the reaction was allowed to stir at rt until TLC analysis confirmed complete conversion of the starting material, 5 h. The reaction mixture was filtered through cotton into a separatory funnel, and H_2O (10 mL) and EtOAc (10 mL) were added. The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with saturated $NaHCO_{3(aq.)}$ (10 mL), dried with magnesium sulfate, and concentrated *in vacuo*. The product was purified via

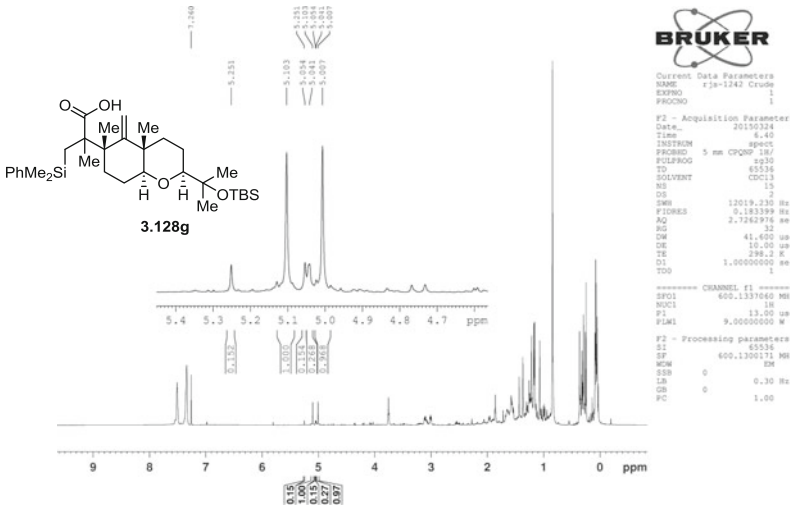
flash chromatography (100:0 to 98:2 to 98:2 to 95:5 hexanes:EtOAc) to afford ester **3.127g** (0.21 g, 91 % yield) as a clear, viscous oil. Analytical data: $[\alpha]_D^{28}$ −42.5 (c = 1.30, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.51 (br s, 2H), 7.36 (br s, 3H), 4.56 (dd, J = 7.8, 4.2 Hz, 1H), 4.50 (d, J = 12.0 Hz, 1H), 3.20 (dd, J = 6.0, 4.2 Hz, 1H), 3.10 (dd, J = 6.0, 3.6 Hz, 1H), 2.54 (m, 1H), 2.20 (m, 1H), 2.10 (m, 1H), 1.79 (d, J = 12.6 Hz, 1H), 1.68–1.66 (m, 5H), 1.58 (m, 2H), 1.32 (m, 2H), 1.25 (s, 3H), 1.19 (s, 3H), 1.15 (d, J = 6.6 Hz, 3H), 1.00 (s, 3H), 0.94–0.89 (m, 2H), 0.87 (s, 9H), 0.31 (br s, 6H), 0.10 (s, 3H), 0.08 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 177.6, 138.8, 134.5, 133.5, 132.3, 129.1, 128.9, 127.9, 127.785.1, 81.0, 74.9, 60.3, 36.6, 36.3, 36.2, 34.1, 31.6, 27.3, 27.2, 25.8, 25.1, 24.1, 21.7, 20.7, 20.6, 20.5, 19.8, 19.3, 19.2, 19.2, 18.1, −2.1, −2.2, −2.3, −2.4, −2.6; **HRMS (ESI$^+$)** Calcd. For $C_{33}H_{56}O_4Si_2$ + Na, 595.3615; Found, 595.3604; **IR** (thin film, cm^{-1}) 3052, 2956, 2856, 1809, 1718, 1487, 1457, 1361, 1265, 1198, 1047, 835; **TLC** (90:10 hexanes:EtOAc): R_f = 0.78.

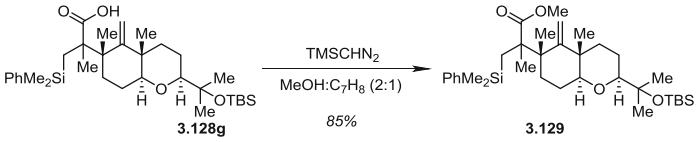


2-((2*S*,4a*S*,6*S*,8a*S*)-2-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-5-methyleneoctahydro-2H-chromen-6-yl)-3-(dimethyl(phenyl)silyl)-2-methylpropanoic acid (3.128g): A flame-dried, 20 mL scintillation vial was charged with THF (2 mL) under an atmosphere of N_2. The mixture was cooled to −78 °C, and a premade solution of LDA (0.5 M in THF:hexanes, 0.52 mL, 0.26 mmol, 3.00 equiv) was added followed by a solution of ester **3.127g** (0.05 g, 0.087 mmol, 1.00 equiv) in THF (1 mL). The reaction was allowed to stir 45 min at this temperature at which point TMSCl (0.04 mL, 0.26 mmol, 3.00 equiv) was added, and the mixture was warmed to rt and stirred 5 min. The septum was replaced with a screw cap, the vial was sealed, and the mixture was warmed to 75 °C and stirred until TLC analysis indicated complete consumption of the starting material, typically 12 h. The mixture was cooled to rt and quenched via addition of 1 M $HCl_{(aq.)}$ (4 mL). The mixture was transferred to a separatory funnel and diluted with Et_2O (10 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL) and concentrated *in vacuo* to give the crude rearrangement product in a 6.6:1.1:1 diastereomeric ratio. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 5.25 (minor diastereomer), δ5.10 (major diastereomer) and δ 5.04 (minor diastereomer, overlapping signals). The product was purified via flash chromatography (100:0 to 95:5 to 90:10 hexanes:EtOAc) to

afford carboxylic acid **3.128g** (0.032 g, 62 % yield) as a clear viscous oil. Analytical data: $[\alpha]_D^{28}$ −18.3 (c = 1.25, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.51 (m, 2H), 7.34 (m, 3H), 5.10 (s, 1H), 5.01 (s, 1H), 3.11 (dd, J = 6.0, 4.8 Hz, 1H), 3.01 (m, 1H), 1.97–1.90 (m, 2H), 1.74 (m, 1H), 1.66–1.54 (m, 6H), 1.38 (s, 3H), 1.27 (m, 2H), 1.22 (s, 3H), 1.17 (s, 3H), 1.16 (s, 3H), 1.15 (m, 1H), 1.07 (s, 3H), 1.05 (m, 1H), 0.84 (s, 9H), 0.37 (s, 3H), 0.29 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 184.0, 160.8, 140.3, 133.5, 128.8, 127.7, 111.7, 84.7, 80.4, 74.8, 52.5, 46.5, 39.3, 36.8, 36.6, 32.7, 30.2, 27.3, 25.9, 25.0, 24.7, 24.5, 23.3, 23.1, 22.1, 22.1, 18.2, −1.2, −1.4, −2.1, −2.2; **HRMS (ESI$^+$)** Calcd. For $C_{33}H_{56}O_4Si_2$ + Na, 595.3615; Found, 595.3605; **IR** (thin film, cm^{-1}) 3420, 3053, 2956, 2956, 2855, 1716, 1689, 1487, 1377, 1265, 1093, 896, 835; **TLC** (90:10 hexanes:EtOAc): R_f = 0.46.

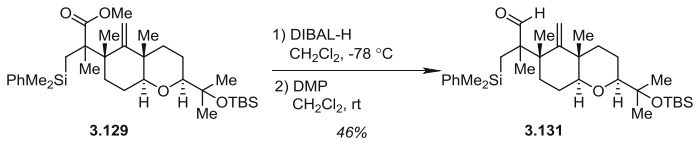
Crude ^{1}H NMR spectrum of 3.128g





methyl 2-((2S,4aS,6S,8aS)-2-(2-((tert-butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-5-methyleneoctahydro-2H-chromen-6-yl)-3-(dimethyl(phenyl)silyl)-2-methyl propanoate (3.129): The acid **3.128g** (0.060 g, 0.11 mmol, 1.00 equiv) was dissolved in MeOH:C_7H_8 (2:1, 2 mL) in a 20-mL scintillation vial with

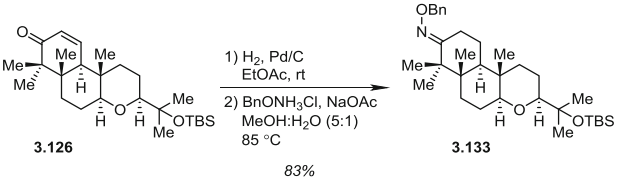
magnetic stirring at rt. $TMSCHN_2$ (2 M in Et_2O, 0.4 mL, 0.80 mmol, 7.30 equiv) was added dropwise until the yellow color of excess $TMSCHN_2$ in solution persisted. AcOH ($\sim$ 10 drops) was added dropwise, giving a clear solution. The resulting mixture was concentrated *in vacuo* and purified via flash chromatography (100:0 to 97.5:2.5 to 95:5 hexanes:EtOAc) to afford ester **3.129** (0.052 g, 85 % yield)) as a clear, viscous oil. Analytical data: **^{1}H NMR** (500 MHz, $CDCl_3$): 7.51–7.49 (m, 4H), 7.35–7.33 (m, 6H), 5.08 (s, 1H), 4.79 (s, 1H), 3.45 (s, 3H), 3.09 (dd, J = 6.0, 4.5 Hz, 1H), 3.00 (m, 1H), 1.59–1.55 (m, 5H), 1.31 (s, 3H), 1.21 (s, 3H), 1.18 (s, 3H), 1.15 (s, 3H), 1.05 (s, 3H), 0.84 (s, 9H), 0.29 (s, 3H), 0.25 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H).



2-((2S,4aS,6S,8aS)-2-(2-((tert-butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-5 methyleneoctahydro-2H-chromen-6-yl)-3-(dimethyl(phenyl) silyl)-2-methylpropanal (3.131): A 20-mL scintillation vial was charged with ester **3.129** (0.03 g, 0.051 mmol, 1.00 equiv) and CH_2Cl_2 (1.5 mL) under an atmosphere of N_2. The mixture was cooled to −78 °C, and DIBAL-H (1 M solution in hexanes, 0.10 mL, 0.10 mmol, 2.00 equiv) was added slowly. TLC analysis showed incomplete conversion of **3.129**, and another charge of DIBAL-H (4.00 equiv) was added. At this juncture, TLC analysis showed complete conversion of the starting material, whereupon the reaction was diluted with acetone (5 mL). After stirring 10 min at −78 °C, the mixture was diluted with a saturated aqueous solution of Rochelle's salt (5 mL). The mixture was transferred to a separatory funnel, the organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo* to give the crude alcohol, which was carried on directly to the next step.

The crude residue was dissolved in CH_2Cl_2 (2 mL) and transferred to a 20-mL scintillation vial. Dess-Martin Periodinane (0.023 g, 0.051 mmol, 1.00 equiv) was added, and the mixture was allowed to stir at rt until complete conversion of the starting material was observed by TLC analysis, typically 10 min. The mixture was then quenched via a 1:1 solution of saturated $NaHCO_{3(aq.)}$ and saturated $Na_2S_2O_{3\,(aq.)}$ (5 mL) and stirred 5 min. The reaction mixture was then diluted with Et_2O (10 mL) and partitioned in a separatory funnel. The aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic extracts were dried with

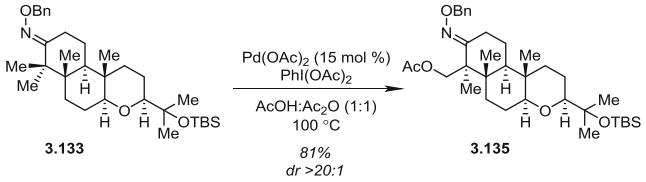
magnesium sulfate and concentrated *in vacuo*. The product was purified via flash chromatography (100:0 to 97.5:2.5 to 95:5 hexanes:EtOAc) to afford aldehyde **3.131** (0.013 g, 46 % yield) as a clear, viscous oil. Analytical data: **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.74 (s, 1H), 7.50–7.49 (m, 4H), 7.36–7.33 (m, 6H), 5.08 (s, 1H), 4.78 (s, 1H), 3.01 (m, 2H), 1.92 (d, J = 10.0 Hz, 1H), 1.63–1.57 (m, 4H), 1.34 (s, 3H), 1.21 (s, 3H), 1.15 (s, 3H), 1.06 (s, 3H), 1.03 (s, 3H), 0.84 (s, 9H), 0.32 (s, 3H), 0.29 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H).



(3*S*,4a*S*,6a*S*,10a*R*,10b*S*,*E*)-3-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-6a,7,7,10b-tetramethyldecahydro-1H-benzo[f]chromen-8(4aH)-one O-benzyl oxime (3.133): The enone **3.126** (1.61 g, 3.70 mmol, 1.00 equiv) was dissolved in EtOAc (60 mL) in a 250 mL round-bottomed flask and charged with Pd/C (2.40 g, 1.50 mass equiv). The reaction mixture was placed under 1 atm (balloon) of H_2 and stirred until full conversion of the starting material was observed by TLC analysis, typically 30 min. The mixture was then filtered through a pad of Celite, and the filter cake was washed with two 20 mL portions of EtOAc. The solution was then concentrated *in vacuo* to afford the crude ketone, which was carried to the next step without further purification.

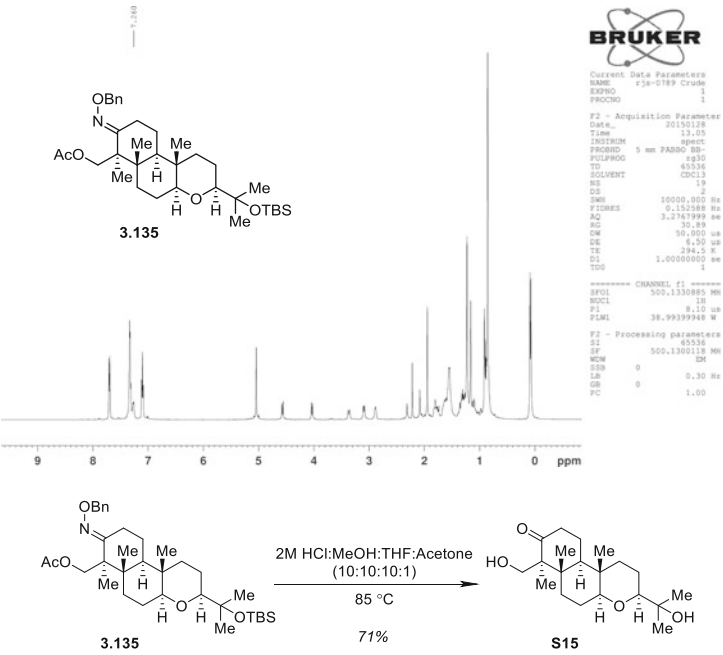
The residue was dissolved in MeOH:H_2O (5:1, 80 mL) in a 250 mL round-bottomed flask. $BnONH_3Cl$ (11.84 g, 74.19 mmol, 20.00 equiv) and NaOAc (4.56 g, 55.64 mmol, 15.00 equiv) were added, and the resulting suspension was fitted with a reflux condenser and heated to 85 °C with stirring until TLC analysis confirmed complete consumption of the starting material, typically 16 h. The reaction mixture was cooled to rt and concentrated on a rotary evaporator. The residue was taken up into H_2O (30 mL) and CH_2Cl_2 (30 mL), and the mixture was partitioned in a separatory funnel and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with H_2O (30 mL), dried with magnesium sulfate, and concentrated *in vacuo*. The product was purified via flash chromatography (100:0 to 98:2 to 97.5:2.5 to 95:5 hexanes:EtOAc) to afford oxime **3.133** (1.66 g, 83 % yield) as a clear, viscous oil. Analytical data: $[\alpha]_D^{28}$ –112.8 (c = 0.45, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.37–7.28 (m, 5H), 5.08 (br s, 2H), 3.35 (dd, J = 9.6, 4.2 Hz, 1H), 3.10 (dd, J = 8.4, 3.0 Hz, 1H), 2.88 (dd, J = 6.0, 4.2 Hz, 1H), 1.82 (m, 2H), 1.66–1.45 (m, 7H), 1.36 (m, 1H), 1.23 (s, 3H), 1.16 (s, 3H), 1.13 (s, 3H), 1.01 (s, 3H), 0.85 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 165.2, 138.7, 128.1, 128.0, 127.4, 85.4, 85.3, 75.1,

74.9, 45.9, 45.5, 41.1, 38.2, 36.2, 31.3, 27.3, 25.8, 25.0, 24.5, 23.3, 21.4, 20.9, 20.0, 19.0, 18.1, 16.8, 13.3, −2.2; **HRMS (ESI$^+$)** Calcd. For $C_{33}H_{55}NO_3Si$ + Na, 564.3849; Found, 564.3862; **IR** (thin film, cm^{-1}) 2951, 2855, 1626, 1470, 1378, 1250, 1173, 1040, 898, 835, 757; **TLC** (85:15 hexanes:EtOAc): R_f = 0.77.

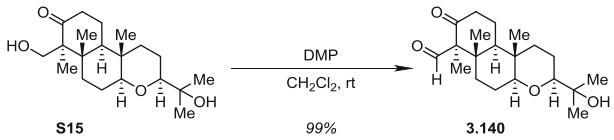


((3*S*,4a*S*,6a*S*,7*R*,10a*R*,10b*S*,*E*)-8-((benzyloxy)imino)-3-(2-((*tert*-butyldimeth ylsilyl)oxy) propan-2-yl)-6a,7,10b-trimethyldodecahydro-1H-benzo[f] chrom en-7-yl)methyl acetate (3.135): A 100 mL round-bottomed flask was charged with oxime **3.133** (1.66 g, 3.06 mmol, 1.00 equiv) and AcOH:Ac_2O (1:1, 31 mL) with magnetic stirring at rt. $Pd(OAc)_2$ (0.10 g, 0.46 mmol, 0.15 equiv) and $PhI(OAc)_2$ (1.48 g, 4.60 mmol, 1.50 equiv) were added sequentially, and the reaction mixture was warmed to 100 °C. This temperature was maintained until TLC analysis showed complete conversion of the starting material, typically 1 h. The mixture was cooled to rt, diluted with pentane (30 mL) and H_2O (20 mL), and transferred to a separatory funnel. Saturated $NaHCO_{3(aq.)}$ (30 mL) was added dropwise into the separatory funnel, and the mixture was allowed to stand 10 min upon completion of the addition. The layers were separated, and the aqueous layer was extracted with pentane (3 × 20 mL). The combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo* to afford the crude acetate **3.135** as a single diastereomer (as determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture, which revealed a single compound). The product was purified via flash chromatography (100:0 to 95:5 to 90:10 hexanes:EtOAc) to afford the acetate **3.135** (1.49 g, 81 % yield) as a reddish-brown, viscous oil. Analytical data: $[\alpha]_D^{28}$ – 66.2 (*c* = 0.70, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.34–7.27 (m, 5H), 5.04 (br s, 2H), 4.55 (d, *J* = 10.8 Hz, 1H), 4.03 (d, *J* = 11.4 Hz, 1H), 3.36 (dd, *J* = 10.8, 13.6 Hz, 1H), 3.09 (dd, *J* = 8.4, 3.0 Hz, 1H), 2.88 (dd, *J* = 5.4, 4.8 Hz, 1H),1.94 (s, 3H), 1.82–1.74 (m, 2H), 1.63–1.52 (m, 8H), 1.35 (m, 1H), 1.22 (s, 3H), 1.21 (s, 3H), 1.15 (s, 3H), 0.91 (s, 3H), 0.84 (s, 12H), 0.08 (s, 3H), 0.06 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 171.1, 161.6, 128.2, 128.0, 127.4, 85.3, 85.1, 75.4, 74.8, 65.6, 48.4, 46.0, 42.1, 38.2, 36.3, 32.0, 27.3, 25.8, 25.0, 24.4, 21.4, 21.1, 20.8, 20.1, 18.1, 17.3, 17.0, 13.5, −2.2; **HRMS (ESI$^+$)** Calcd. For $C_{35}H_{57}NO_5Si$ + Na, 622.3904; Found, 622.3908; **IR** (thin film, cm^{-1}) 2953, 2884, 1732, 1470, 1380, 1249, 1038, 835, 756; **TLC** (60:40 hexanes:EtOAc): R_f = 0.80.

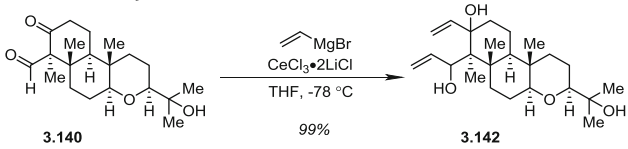
Crude ^{1}H NMR spectrum of 3.135.



(3*S*,4a*S*,6a*S*,7*S*,10a*R*,10b*S*)-7-(hydroxymethyl)-3-(2-hydroxypropan-2-yl)-6a,7,10b-trimethyldecahydro-1H-benzo[f]chromen-8(4aH)-one (S15): A 50 mL round-bottomed flask was charged with acetate **3.135** (0.71 g, 1.18 mmol, 1.00 equiv) and 2 M $HCl_{(aq.)}$:MeOH:THF:acetone (10:10:10:1, 12 mL). The mixture was warmed to 85 °C and stirred until full convergence to a single product was observed by TLC analysis, typically 5 h. The mixture was cooled to rt and concentrated on a rotary evaporator, and the residue was taken up into H_2O (15 mL) and CH_2Cl_2 (15 mL) and partitioned in a separatory funnel. The mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo*. The product was purified via flash chromatography (60:40 EtOAc:hexanes) to afford hydroxy ketone **S15** (0.28 g, 71 % yield) as a reddish-brown, viscous oil. Analytical data: $[\alpha]_D^{28}$ –159.6 (c = 0.30, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 4.12 (dd, J = 8.4, 3.0 Hz, 1H), 3.22 (m, 2H), 3.02 (dd, J = 6.0, 3.0 Hz, 1H), 2.64 (dd, J = 7.2, 3.0 Hz, 1H), 2.59 (br s, 1H), 2.55 (m, 1H), 2.29 (m, 1H), 1.89–1.86 (m, 2H), 1.80 (m, 1H), 1.70–1.60 (m, 6H), 1.46 (m, 1H), 1.40 (dt, J = 6.0, 3.6 Hz, 1H), 1.31 (s, 3H), 1.23 (m, 1H), 1.18 (s, 3H), 1.15 (s, 3H), 0.99 (s, 3H), 0.91 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 219.3, 85.0, 84.6, 71.8, 63.6, 57.4, 45.3, 42.1, 37.9, 37.6. 36.4, 30.7, 26.1, 23.9, 23.7, 21.7, 21.2, 18.2, 16.9, 13.5; **HRMS (ESI^{+})** Calcd. For $C_{20}H_{34}O_4$ + Na, 361.2355; Found, 361.2360; **IR** (thin film, cm^{-1}) 3450, 2950, 1692, 1425, 1166, 1102, 735, 685; **TLC** (60:40 hexanes:EtOAc): R_f = 0.12.

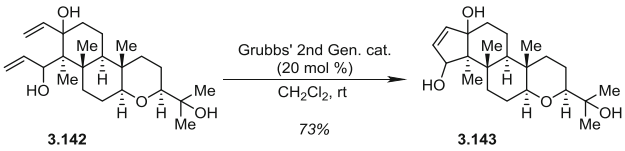


(3*S*,4a*S*,6a*S*,7*S*,10a*R*,10b*S*)-3-(2-hydroxypropan-2-yl)-6a,7,10b-trimethyl-8-oxododecahydro-1H-benzo[f]chromene-7-carbaldehyde (3.140): A 20 mL scintillation vial was charged with alcohol **S15** (0.29 g, 0.84 mmol, 1.00 equiv) and CH_2Cl_2 (8 mL). Dess-Martin periodinane (0.71 g, 1.68 mmol, 2.00 equiv) was added at rt with stirring. The reaction mixture was allowed to stir at room temperature until TLC analysis confirmed complete conversion of the starting material, typically 20 min. The mixture was then quenched via a 1:1 solution of saturated $NaHCO_{3(aq.)}$ and saturated $Na_2S_2O_{3(aq.)}$ (10 mL), and the mixture was stirred 5 min. The reaction mixture was then diluted with Et_2O (15 mL) and partitioned in a separatory funnel. The aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo*. The product was purified via flash chromatography (60:40 to 50:50 hexanes:EtOAc) to afford the ketoaldehyde **3.140** (0.28 g, 99 % yield) as a pale white powder. Analytical data: **mp** 121–125 °C; $[\alpha]_D^{28}$ –223.7 (c = 0.50, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 10.06 (s, 1H), 3.22 (dd, J = 9.0, 3.0 Hz, 1H), 3.02 (dd, J = 6.0, 2.4 Hz, 1H), 2.52–2.46 (m, 2H), 1.94–1.82 (m, 3H), 1.57–1.70 (m, 5H), 1.47 (m, 1H), 1.26 (s, 3H), 1.24 (s, 3H), 1.22 (m, 1H), 1.18 (s, 3H), 1.15 (s, 3H), 0.94 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 214.0, 204.2, 84.9, 84.6, 71.9, 64.7, 45.1, 43.4, 37.8, 37.6, 36.5, 31.6, 26.1, 23.7, 23.5, 21.6, 20.9, 19.5, 14.8, 13.6; **HRMS (ESI$^+$)** Calcd. For $C_{20}H_{32}O_4$ + Na, 359.2199; Found, 359.2198; **IR** (thin film, cm^{-1}) 3019, 2955, 2857, 2400, 1721, 1388, 1265, 1215, 1098; **TLC** (60:40 hexanes:EtOAc): R_f = 0.24.



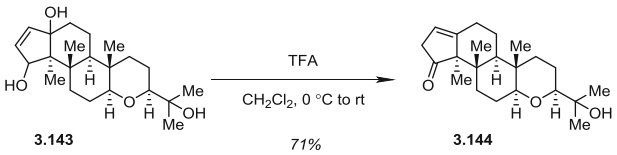
(3*S*,4a*S*,6a*S*,7*S*,10a*R*,10b*S*)-7-(1-hydroxyallyl)-3-(2-hydroxypropan-2-yl)-6a, 7, 10b-trimethyl-8-vinyldodecahydro-1H-benzo[f]chromen-8-ol (3.142): A flame-dried, 20 mL scintillation vial was charged with LiCl (0.30 g, 7.13 mmol, 20.00 equiv equiv), anhydrous $CeCl_3$ (0.88 g, 3.57 mmol, 10.00 equiv), and a stir bar in a nitrogen-filled glove box. The vial was removed from the glove box and placed under an N_2 atmosphere. THF (5 mL) was added, and this mixture was stirred at rt for 2.5 h. A separate flame-dried 20 mL scintillation vial was charged with aldehyde **3.140** (0.12 g, 0.36 mmol, 1.00 equiv) and THF (2 mL) under an atmosphere of N_2. The $CeCl_3$•2LiCl suspension was added to the solution of **3.140** at rt, and the resulting mixture was stirred 2.5 h. The reaction was subsequently cooled to −78 °C, and vinylmagnesium bromide (1 M in THF, 3.57 mL, 3.57 mmol, 10 equiv) was added. The reaction mixture was allowed to stir at this temperature until TLC analysis

confirmed complete consumption of the starting material, typically 20 min. The reaction was quenched with MeOH (3 mL), and the mixture was immediately warmed to rt upon which 5 % $AcOH_{(aq.)}$ (2 mL) and Et_2O (2 mL) were added with stirring. Once the vial had reached rt, the solution was transferred to a separatory funnel, diluted with H_2O (15 mL) and extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with saturated $NaHCO_{3(aq.)}$ (10 mL), dried with magnesium sulfate and concentrated *in vacuo*. The product was purified via flash chromatography (80:20 to 70:30 to 60:40 hexanes:EtOAc) to afford an inseparable 2.6:1 mixture of diol diastereomers **3.142** (0.14 g, 99 % yield) as a pale white, viscous foam. Analytical data: $[\alpha]_D^{28}$ –182.8 (c = 0.25, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.30 (dd, J = 10.8, 6.0 Hz, 1H), 6.14 (m, 1H), 5.24 (d, J = 17.4 Hz, 1H), 5.08 (d, J = 10.8 Hz, 1H), 5.03–4.99 (m, 2H), 4.40 (d, J = 8.4 Hz, 1H), 3.16 (m, 1H), 2.88 (m, 1H), 1.83 (m, 3H), 1.72 (m, 2H), 1.59 (m, 3H), 1.53 (s, 3H), 1.45–1.36 (m, 5H), 1.15 (s, 3H), 1.14 (s, 3H), 1.03 (m, 1H), 0.90 (s, 3H), 0.87 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 145.8, 140.7, 116.4, 112.6, 85.7, 84.5, 80.0, 79.6, 72.0, 49.4, 47.3, 43.1, 38.0, 36.3, 35.9, 32.4, 26.0, 24.3, 23.6, 21.9, 19.5, 18.6, 17.0, 13.3; **HRMS (ESI$^+$)** Calcd. For $C_{24}H_{40}O_4$ + Na, 415.2825; Found, 415.2829; **IR** (thin film, cm^{-1}) 3303, 2949, 2877, 1621, 1461, 1301, 1089, 920, 737; **TLC** (60:40 hexanes:EtOAc): R_f = 0.32.



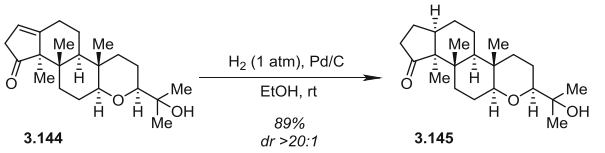
3.142 3.143

(2*S*,4a*S*,4b*R*,9a*S*,9b*S*,11a*S*)-2-(2-hydroxypropan-2-yl)-4a,9a,9b-trimethyl-3,4,4a,4b,5,6,9,9a,9b,10,11,11a-dodecahydroindeno[5,4-f]chromene-6a,9(2H)-diol (3.143): A flame-dried 20 mL scintillation vial was charged with Grubbs' second generation catalyst (0.99 g, 0.12 mmol, 0.20 equiv) and a stir bar in a nitrogen-filled glove box. The vial was removed from the glove box and charged with CH_2Cl_2 (12 mL) under an atmosphere of N_2. Diol **3.142** (0.23 g, 0.59 mmol, 1.00 equiv) was added as a solution in CH_2Cl_2 (3 mL), and the mixture was allowed to stir at rt until complete conversion of the starting material was observed by TLC analysis, typically 3 h. The reaction mixture was concentrated *in vacuo*, and the product was purified via flash chromatography (80:20 to 70:30 to 60:40 hexanes:EtOAc) to afford allylic alcohol **3.143** (0.16 g, 73 % yield) as a pale-brown viscous foam. Analytical data: $[\alpha]_D^{28}$ –62.8 (c = 0.75, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.22 (d, J = 5.4 Hz, 1H), 6.14 (dd, J = 3.0, 2.4 Hz, 1H), 4.42 (br s, 1H), 3.18 (dd, J = 9.0, 3.0 Hz, 1H), 2.95 (dd, J = 7.8, 3.6 Hz, 1H), 2.69 (br s, 1H), 2.26 (d, J = 5.4 Hz, 1H), 2.22 (br s, 1H), 1.83–1.75 (m, 8H), 1.63 (s, 3H), 1.56–1.54 (m, 3H), 1.42 (m, 2H), 1.17 (s, 3H), 1.16 (s, 3H), 0.94 (s, 3H), 0.92 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 143.2, 137.2, 87.3, 86.0, 84.6, 83.3, 71.9, 52.5, 47.9, 41.8, 38.3, 36.3, 32.9, 30.4, 26.8, 26.1, 23.9, 23.6, 21.9, 20.2, 17.7, 13.2; **HRMS (ESI$^+$)** Calcd. For $C_{22}H_{36}O_4$ + Na, 387.2512; Found, 387.2519; **IR** (thin film, cm^{-1}) 3400, 2951, 2675, 1729, 1449, 1384, 1256, 1097, 1023, 910, 754; **TLC** (60:40 hexanes:EtOAc): R_f = 0.25.



3.143 3.144

(2*S*,4a*S*,4b*R*,9a*S*,9b*S*,11a*S*)-2-(2-hydroxypropan-2-yl)-4a,9a,9b-trimethyl-3 4,4a,4b,5,6,8,9a,9b,10,11,11a-dodecahydroindeno[5,4-f]chromen-9(2H)-one (3.144): A flame-dried 20 mL scintillation vial was charged with diol **3.143** (0.15 g, 0.40 mmol, 1.00 equiv) and CH_2Cl_2 (9 mL) under and atmosphere of N_2. The mixture was cooled to 0 °C, and TFA (0.15 mL, 2.02 mmol, 5.00 equiv) was added. The reaction mixture was warmed to rt and allowed to stir until complete conversion of the starting material was observed by TLC analysis, typically 30 min. The reaction was quenched with saturated $NaHCO_{3(aq.)}$ (5 mL), and the mixture was partitioned in a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. The product was purified via flash chromatography (90:10 to 80:20 to 70:30 hexanes:EtOAc) to afford the non-conjugated enone **3.144** (0.10 g, 71 % yield) as a pale brown, viscous oil. Analytical Data: $[\alpha]_D^{28}$ −77.7 (c = 0.50, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.64 (m, 1H), 3.17 (dd, J = 9.0, 2.4 Hz, 1H), 2.95 (dd, J = 5.4, 4.8 Hz, 1H), 2.83 (m, 1H), 2.69 (m, 1H), 2.61 (br s,1H), 2.40 (m, 1H), 2.10 (br s, 1H), 1.84 (m, 2H), 1.64 (m, 3H), 1.55 (m, 2H), 1.43–1.33 (m, 3H), 1.16 (s, 3H), 1.13 (br s, 4H), 1.12 (s, 3H), 0.91 (s, 3H), 0.83 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 223.0, 148.2, 116.3, 85.5, 84.4, 71.8, 59.3, 46.6, 43.0, 41.1, 37.9, 36.5, 30.9, 27.6, 26.1, 24.0, 23.7, 21.8, 21.7, 17.6, 17.4, 13.4; **HRMS (ESI$^+$)** Calcd. For $C_{22}H_{34}O_3$ + Na, 369.2406; Found, 369.2398; **IR** (thin film, cm^{-1}) 3053, 2979, 2977, 1734, 1558, 1472, 1373, 1265, 1139, 1086, 971, 921, 704; **TLC** (80:20 hexanes:EtOAc): R_f = 0.23.

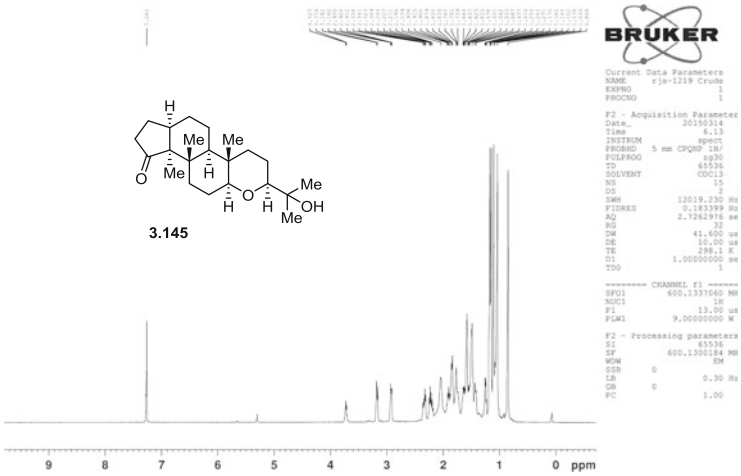


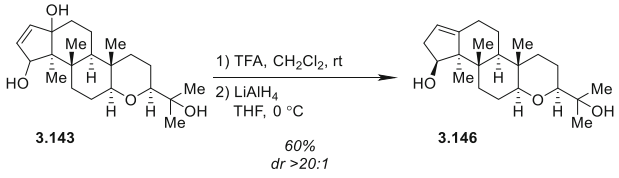
3.144 3.145

(2*S*,4a*S*,4b*R*,6a*R*,9a*S*,9b*S*,11a*S*)-2-(2-hydroxypropan-2-yl)-4a,9a,9b-trimethyltetradecahydroindeno[5,4-f]chromen-9(2H)-one (3.145): A 20 mL scintillation vial was charged with ketone **3.144** (0.008 g, 0.02 mmol, 1.00 equiv) and EtOH (2 mL), and Pd/C (0.013 g, 1.50 mass equiv) was added. The reaction mixture was placed under 1 atm H_2 (balloon), and the mixture was allowed to stir overnight. The reaction was filtered through a Celite plug, and the filtrate was concentrated on a rotary evaporator to give the crude ketone as a single diastereomer (as determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture, which revealed a single compound). The product was purified via flash chromatography (90:10 to 80:20 to 70:30 hexanes:EtOAc) to afford ketone **3.145** as a clear, viscous oil. Analytical data: $[\alpha]_D^{28}$ −45.2 (c = 0.35, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 3.18 (dd, J = 9.0, 3.0 Hz, 1H), 2.92 (d, J = 6.6, 4.2 Hz, 1H), 2.60 (br s, 1H), 2.33 (m, 1H), 2.21 (m, 1H), 2.03 (m, 1H), 1.92–1.82 (m, 3H), 1.74 (m, 2H), 1.64–1.41

(m, 11H), 1.17 (s, 3H), 1.14 (s, 3H), 1.10 (s, 3H), 1.04 (s, 3H), 0.85 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 224.9, 85.4, 84.4, 71.8, 54.5, 47.5, 46.2, 39.3, 38.8, 37.8, 36.3, 32.5, 26.8, 26.2, 26.1, 23.7, 23.5, 21.8, 20.9, 19.5, 17.3, 13.5; **HRMS (ESI$^+$)** Calcd. For $C_{22}H_{36}O_3$ + Na, 371.2562; Found, 371.2554; **IR** (thin film, cm^{-1}) 3446, 2955, 2852, 1731, 1636, 1520, 1473, 1396, 1085, 754; **TLC** (80:20 hexanes: EtOAc): R_f = 0.20.

Crude ^{1}H NMR Spectrum of 3.145



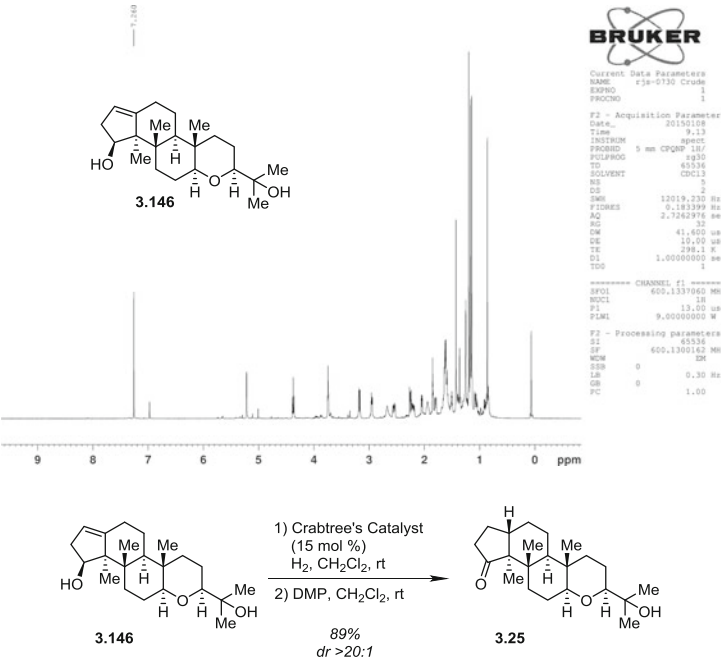


(2*S*,4a*S*,4b*R*,9*S*,9a*S*,9b*S*,11a*S*)-2-(2-hydroxypropan-2-yl)-4a,9a,9b-trimethyl-2,3,4,4a,4b,5,6,8,9,9a,9b,10,11,11a-tetradecahydroindeno[5,4-f]chromen-9-ol (3.146): A flame-dried 20 mL scintillation vial was charged with diol **3.143** (0.16 g, 0.43 mmol, 1.00 equiv) and CH_2Cl_2 (9 mL) under and atmosphere of N_2. The mixture was cooled to 0 °C, and TFA (0.17 mL, 2.14 mmol, 5.00 equiv) was added. The reaction mixture was warmed to rt and allowed to stir until complete conversion of the starting material was observed by TLC analysis, typically 30 min. The reaction was quenched with saturated $NaHCO_{3(aq.)}$ (5 mL), and the mixture was partitioned in a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuo* to afford the crude non-conjugated enone **3.144**, which was carried to the next step without further purification.

A flame-dried 20 mL scintillation vial was charged with the crude ketone **3.144** and THF (5 mL) under an atmosphere of N_2. The reaction mixture was cooled to

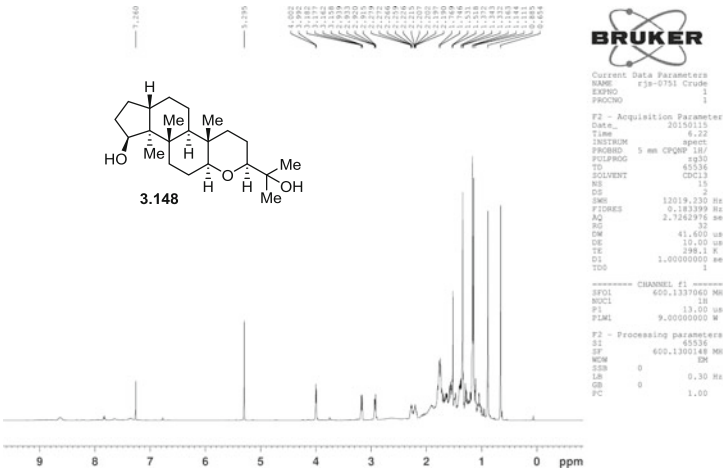
0 °C, and $LiAlH_4$ (1 M in THF, 2.00 mL, 2.00 mmol, 4.70 equiv) was added dropwise. The reaction mixture was allowed to stir at this temperature until TLC analysis indicated complete consumption of the starting material, typically 30 min. The reaction was then carefully quenched with saturated $NH_4Cl_{(aq.)}$ (4 mL) and stirred 5 min at rt. The resulting mixture was partitioned in a separatory funnel and extracted with Et_2O (3 × 5 mL). The combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo* to afford the crude alcohol **3.146** as a single diastereomer (as determined by ^1H NMR spectroscopic analysis of the crude reaction mixture, which revealed a single compound). The crude product was purified via flash chromatography (80:20 to 70:30 to 60:40 hexanes:EtOAc) to afford alcohol **3.146** (0.90 g, 60 % yield) as a pale yellow foam. Analytical data: $[\alpha]_D^{28}$ –116.4 (c = 0.50, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.22 (s, 1H), 4.37 (t, J = 8.4 Hz, 1H), 3.18 (dd, J = 9.0, 3.0 Hz, 1H), 2.95 (m, 1H), 2.68 (br s, 1H), 2.54 (m, 1H), 2.25 (d, J = 10.8 Hz, 1H), 2.20 (m, 1H), 1.94 (br s, 1H), 1.80 (d, J = 2.4 Hz, 1H), 1.69–1.59 (m, 6H), 1.50 (m, 1H), 1.42–1.36 (m, 3H), 1.19 (s, 3H), 1.17 (s, 3H), 1.14 (s, 3H), 0.86 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 148.1, 117.5, 85.8, 85.2, 84.4, 71.9, 55.1, 48.1, 43.9, 40.9, 38.0, 36.7, 31.8, 27.0, 26.1, 24.6, 23.8, 23.6, 22.8, 21.9, 16.7, 13.5; **HRMS (ESI$^+$)** Calcd. For $C_{22}H_{36}O_3$ + Na, 371.2562; Found, 371.2570; **IR** (thin film, cm^{-1}) 3433, 2979, 2678, 2399, 1452, 1373, 1215, 1093, 955, 755, 668; **TLC** (60:40 hexanes:EtOAc): R_f = 0.36

Crude ^{1}H NMR spectrum of 3.146



(2*S*,4a*S*,4b*R*,6a*S*,9a*S*,9b*S*,11a*S*)-2-(2-hydroxypropan-2-yl)-4a,9a,9b-trimethyltetradecahydroindeno[5,4-f]chromen-9(2H)-one (3.25): A flame-dried, 20 mL scintillation vial was charged with Crabtree's catalyst (0.01 g, 0.01 mmol, 0.15 equiv) in a nitrogen-filled glove box. The vial was sealed with a rubber-septum, removed from the glove box, and placed under an atmosphere of N_2. CH_2Cl_2 (4 mL, freshly degassed via N_2 bubbling for 30 min) was added followed by a solution of alcohol **3.146** (0.025 g, 0.07 mmol, 1.00 equiv) in degassed CH_2Cl_2 (2 mL), and the resulting mixture was placed under an atmosphere of H_2 (balloon) and allowed to stir 36 h at rt. The resulting mixture was concentrated *in vacuo* to afford the crude alcohol **3.148**, which was carried forward to the next step without purification. Although this material was not isolated, the diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture, which revealed a single compound. This crude ^{1}H NMR spectrum is included below.

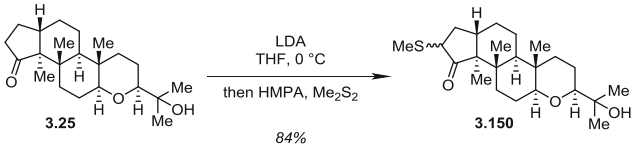
Crude ^{1}H NMR spectrum of 3.148



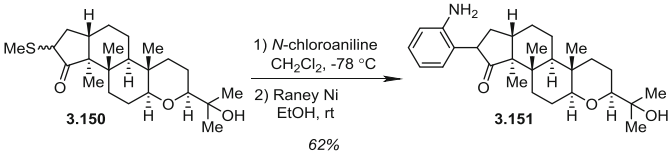
A 20 mL scintillation vial was charged with the crude alcohol **3.148** and CH_2Cl_2 (3 mL) with magnetic stirring. Dess-Martin periodinane (0.045 g, 0.11 mmol, 1.50 equiv) was added, and the reaction mixture was allowed to stir at rt until complete conversion of the starting materal was observed by TLC analysis, typically 20 min. The reaction was then quenched via a 1:1 solution of saturated $NaHCO_{3(aq.)}$ and saturated $Na_2S_2O_{3(aq.)}$ (3 mL), and the mixture was stirred 5 min. The reaction mixture was then diluted with Et_2O (5 mL) and partitioned in a separatory funnel. The aqueous layer was extracted with Et_2O (3 × 5 mL), and the combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo*. The product was purified via flash chromatography (90:10 to 80:20 to 70:30 hexanes:EtOAc) to afford ketone **3.25** (0.022 g, 89 % yield) as a clear semisolid. Slow evaporation from HPLC-grade hexanes provided crystals suitable for X-ray crystallographic

analysis. Analytical data: **mp** 125–130 °C; $[\alpha]_D^{27-8}$9.3 (*c* = 0.85, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.16 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.93 (m, 1H), 2.65 (br s, 1H), 2.32 (dd, *J* = 11.0, 8.5 Hz, 1H), 2.19–2.14 (m, 2H), 2.00 (m, 1H), 1.78–1.23 (m, 15H), 1.16 (s, 3H), 1.14 (s, 3H), 1.02 (s, 3H), 0.92 (s, 3H), 0.83 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 221.2, 85.7, 84.4, 71.8, 56.1, 46.9, 40.2, 39.9, 37.8, 37.5, 36.5, 31.1, 26.1, 25.8, 24.2, 23.8, 23.7, 21.9, 21.2, 18.9, 12.9, 10.3; **HRMS (ESI$^+$)** Calcd. For $C_{22}H_{36}O_3$ + Na, 371.2562; Found, 371.2560; **IR** (thin film, cm^{-1}) 3566, 3446, 2946, 2876, 1772, 1731, 1472, 1385, 1259, 1158, 1098, 974, 735; **TLC** (70:30 hexanes:EtOAc): R_f = 0.60.

Note: The following sequence for conversion of **3.25** to paspaline was adapted from the previously published protocol by Smith and co-workers [32].

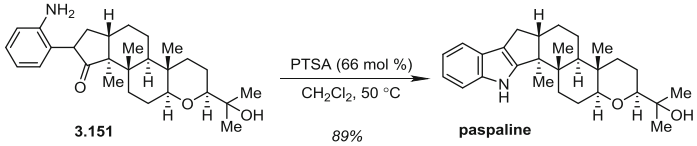


(2*S*,4a*S*,4b*R*,6a*S*,9a*S*,9b*S*,11a*S*)-2-(2-hydroxypropan-2-yl)-4a,9a,9b-trimethyl-8-(methyl thio)tetradecahydroindeno[5,4-f]chromen-9(2H)-one (3.150): A flame-dried, 20 mL scintillation vial was cooled to 0 °C and charged with THF (1 mL) and a freshly-prepared solution of lithium diisopropylamide (0.5 M in THF, 0.57 mL, 0.29 mmol, 5.00 equiv) under an atmosphere of N_2. The resulting solution was then charged with a solution of ketone **3.25** (0.02 g, 0.06 mmol, 1.00 equiv) in THF (0.5 mL), and the reaction mixture was allowed to stir 15 min at 0 °C. HMPA (0.6 mL) was added followed by Me_2S_2 (0.031 mL, 0.34 mmol, 6.00 equiv), and the reaction was allowed to stir until TLC analysis showed complete conversion of the starting material, typically 10 min. The reaction was quenched via addition of H_2O (5 mL). The resulting mixture was transferred to a separatory funnel, and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 × 5 mL), and the combined organic extracts were washed with brine (2 × 10 mL), dried with magnesium sulfate, and concentrated *in vacuo*. The product was purified via flash chromatography (90:10 to 80:20 to 70:30 hexanes:EtOAc) to afford an inseparable, diastereomeric mixture of thioethers **3.150** (0.019 g, 84 % yield) as a yellow, viscous oil. Analytical data: $[\alpha]_D^{27}$ – 57.9 (*c* = 0.70, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 3.16 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.94 (m, 2H), 2.61 (br s, 1H), 2.25 (br s, 3H), 2.22–2.13 (m, 3H), 1.63–1.57 (m, 11H), 1.47 (m, 10H), 1.17 (s, 3H), 1.14 (s, 3H), 1.02 (s, 3H), 1.01 (s, 3H), 0.83 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 218.4, 85.6, 84.4, 71.8, 56.6, 49.8, 46.6, 40.1, 38.1, 37.8, 36.4, 31.8, 31.1, 26.1, 25.2, 24.2, 23.7, 21.8, 21.1, 19.0, 15.4, 12.9, 11.0; **HRMS (ESI$^+$)** Calcd. For $C_{23}H_{38}O_3S$ + Na, 417.2439; Found, 417.2438; **IR** (thin film, cm^{-1}) 3446, 2946, 2874, 1732, 1652, 1519, 1456, 1386, 1232, 1152, 1086, 946; **TLC** (70:30 hexanes:EtOAc): R_f = 0.63.



(2*S*,4a*S*,4b*R*,6a*S*,9a*S*,9b*S*,11a*S*)-8-(2-aminophenyl)-2-(2-hydroxypropan-2-yl)-4a,9a,9b-trimethyltetradecahydroindeno[5,4-f]chromen-9(2H)-one (3.151): A flame-dried, 20 mL scintillation vial was charged with a solution of aniline (0.25 M in CH_2Cl_2, 0.26 mL, 0.07 mmol, 2.00 equiv) under an atmosphere of N_2, and the resulting solution was cooled to −78 °C. The lights in the fume hood were turned off, and a solution of ^{t}BuOCl (0.25 M in CH_2Cl_2, 0.26 mL, 0.07 mmol, 2.00 equiv) was added dropwise. The reaction mixture was allowed to stir 15 min, upon which a solution of thioether **3.150** (0.013 g, 0.03 mmol, 1.00 equiv) in CH_2Cl_2 (1.5 mL) was added. The mixture was allowed to stir 50 min, upon which NEt_3 (0.02 mL, 0.13 mmol, 4.00 equiv) was added. The reaction was then warmed to rt and allowed to stir until a bright orange color was observed, typically 5 min. The resulting solution was diluted with H_2O (5 mL) and Et_2O (10 mL) and partitioned in a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo* to afford a crude mixture of diastereomeric keto-anilines, which was carried directly on to the next step without further purification.

The residue was taken up into EtOH (1 mL) in a 20 mL scintillation vial, and a slurry of Raney Ni in H_2O (150 mg) was added. The reaction mixture was stirred vigorously at rt until complete conversion of the intermediate thioether was observed by TLC analysis, typically 1 h. The reaction mixture was filtered through a Celite plug, and the resulting solution was concentrated *in vacuo*. The crude product was purified via flash chromatography (90:10 to 80:20 to 70:30 to 60:40 hexanes:EtOAc) to afford ketoaniline **3.151** (0.009 g, 62 % yield) as yellow, viscous oil. Analytical data: $[\alpha]_D^{27}$ +26.6 (c = 0.45, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.06 (m, 2H), 6.77 (m, 2H), 4.21 (br s, 2H), 3.54 (t, J = 9.0 Hz, 1H), 3.16 (dd, J = 9.6, 2.4 Hz, 1H), 2.94 (m, 1H), 2.62 (br s, 1H), 2.35 (m, 1H), 2.14–2.04 (m, 3H), 1.84–1.37 (m, 16H), 1.17 (s, 3H), 1.15 (s, 1H), 1.11 (s, 3H), 0.98 (s, 3H), 0.86 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 221.0, 146.0, 127.6, 125.8, 125.4, 119.1, 117.5, 85.6, 84.5, 71.8, 57.0, 51.5, 46.8, 40.1, 38.0, 37.8, 36.5, 31.3, 28.9, 26.1, 25.4, 24.2, 23.7, 21.9, 21.2, 19.2, 12.9, 10.0; **HRMS (ESI$^+$)** Calcd. For $C_{28}H_{41}NO_3$ + Na, 462.2984; Found, 462.2983; **IR** (thin film, cm^{-1}) 3421, 3053, 2984, 2877, 2305, 1732, 1652, 1456, 1362, 1265, 738; **TLC** (70:30 hexanes: EtOAc): R_f = 0.30.



Paspaline (3.1): A 1 mL dram vial was charged with ketone **3.151** (0.007 g, 0.02 mmol, 1.00 equiv), CH_2Cl_2 (1.2 mL), and PTSA (0.002 g, 0.01 mmol, 0.66 equiv). The vial was sealed, and the mixture was warmed to 50 °C and stirred for 16 h. The reaction mixture was cooled to rt, diluted with H_2O (10 mL) and Et_2O (10 mL) and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic extracts were dried with magnesium sulfate and concentrated *in vacuo*. The product was purified via flash chromatography (90:10 to 80:20 hexanes:EtOAc) to afford paspaline (0.006 g, 89 % yield) as a yellow foam. Slow evaporation from HPLC-grade hexanes provided crystals suitable for X-ray crystallographic analysis. Analytical data: $[\alpha]_D^{25}$ –16.4 (c = 0.30, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.72 (br s, 1H), 7.42 (m, 1H), 7.30 (m, 1H), 7.07 (m, 2H), 3.21 (dd, J = 9.6, 2.4 Hz, 1H), 3.03 (dd, J = 8.4, 3.6 Hz, 1H), 2.77–2.65 (m, 3H), 2.32 (dd, J = 10.8, 2.4 Hz, 1H), 1.96 (m, 1H), 1.84–1.77 (m, 3H), 1.70–1.56 (m, 6H), 1.49–1.37 (m, 3H), 1.19 (s, 3H), 1.17 (s, 3H), 1.13 (s, 3H), 1.03 (s, 3H), 0.88 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 150.8, 139.3, 125.1, 120.4, 119.5, 118.4, 118.2, 111.4, 85.7, 84.7, 71.9, 53.0, 48.7, 46.4, 40.0, 37.6, 36.5, 33.9, 27.5, 26.1, 25.2, 24.6, 23.7, 22.0, 21.9, 20.0, 14.6, 12.6; **HRMS (ESI$^+$)** Calcd. For $C_{28}H_{39}NO_2$ + H, 422.3059; Found, 422.3056; **IR** (thin film, cm^{-1}) 3565, 3467, 3053, 2982, 2930, 2855, 1455, 1386, 1375, 1331, 1265, 1158, 1087, 1037; **TLC** (70:30 hexanes:EtOAc): R_f = 0.42.

Comparison of reported analytical data for paspaline

Data type	Data reported in isolation paper [8]	Data reported by Smith and co-workers [32]	Synthetic paspaline
^{1}H NMR ($CDCl_3$)	^{1}H NMR (100 MHz, $CDCl_3$) 7.82 (s, 1H) 7.0–7.5 (m, 4H) 3.68 (q, J = 2.5 Hz, 1H) 3.3–1.4 (m, 18H) 1.18 (s, 6H) 1.13 (s, 3H) 1.02 (s, 3H) 0.88 (s, 3H)	^{1}H NMR (250 MHz, $CDCl_3$) 7.74 (br s, 1H) 7.44–7.40 (m, 1H) 7.31–7.26 (m, 1H) 7.09–7.06 (m, 2H) 3.21 (dd, J = 11.8, 3.0 Hz, 1H) 3.03 (dd, J = 11.3, 4.2 Hz, 1H) 2.85–2.62 (m, 3H) 2.32 (dd, J = 12.7, 10.4 Hz, 1H) 2.04–1.25 (m, 13H) 1.19 (s, 3H)	^{1}H NMR (600 MHz, $CDCl_3$) 7.72 (br s, 1H) 7.42 (m, 1H) 7.30 (m, 1H) 7.07 (m, 2H) 3.21 (dd, J = 9.6, 2.4 Hz, 1H) 3.03 (dd, J = 8.4, 3.6 Hz, 1H) 2.77–2.65 (m, 3H) 2.32 (dd, J = 10.8, 2.4 Hz, 1H) 1.96 (m, 1H) 1.84–1.77 (m, 3H) 1.70–1.56 (m, 6H)

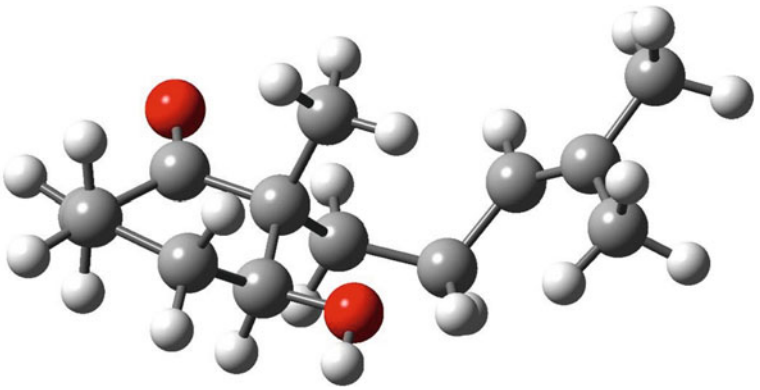
(continued)

(continued)

Comparison of reported analytical data for paspaline			
Data type	Data reported in isolation paper [8]	Data reported by Smith and co-workers [32]	Synthetic paspaline
		1.17 (s, 3H) 1.13 (s, 3H) 1.02 (s, 3H) 0.88 (s, 3H)	1.49–1.37 (m, 3H) 1.19 (s, 3H) 1.17 (s, 3H) 1.13 (s, 3H) 1.03 (s, 3H) 0.88 (s, 3H)
^{13}C NMR ($CDCl_3$)	NA	NA	^{13}C NMR (150 MHz, $CDCl_3$) 150.8, 139.3, 125.1, 120.4, 119.5, 118.4, 118.2, 111.4, 85.7, 84.7, 71.9, 53.0, 48.7, 46.4, 40.0, 37.6, 36.5, 33.9, 27.5, 26.1, 25.2, 24.6, 23.7, 22.0, 21.9, 20.0, 14.6, 12.6
Rotation	−23.0 (c = 0.36, $CHCl_3$)	−42.2 (c = 0.64, C_6H_6)	–16.4 (c = 0.30, $CHCl_3$)
IR	3500, 3450, 2950, 2850, 1440, 1380, 1360, 1320, 1280, 1150, 1090, 1030, 1010, 970, 940, 895, 875	3550, 3470, 3320, 2980, 2950, 2850, 1450, 1385, 1375, 1330, 1300, 1260, 1240, 1160, 1090, 1035	3565, 3467, 3053, 2982, 2930, 2855, 1455, 1386, 1375, 1331, 1265, 1158, 1087, 1037
MS	NA	m/z 421.2997 (M^+, calcd for $C_{28}H_{39}NO_2$, 421.3013)	422.3056 (Calcd. For $C_{28}H_{39}NO_2$ + H, 422.3059)

Computational Details

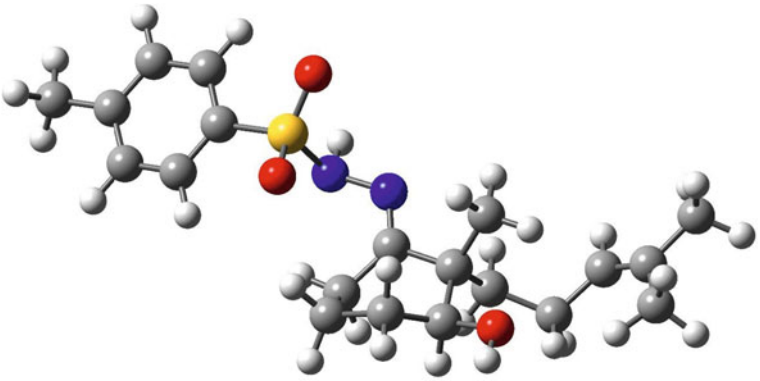
Hydroxyketone **3.78**:



Cartesian Coordinates

C	0.38546	0.90879	−0.16849
C	1.73413	1.58994	−0.51067
C	2.09875	2.70065	0.48898
C	0.95795	3.68809	0.66408
C	−0.46509	3.10881	0.89226
C	−0.37068	1.56788	0.99805
H	−0.27802	0.90915	−1.03680
H	2.54204	0.85495	−0.54461
H	2.32003	2.26173	1.47108
H	0.15664	1.33392	1.93552
H	0.54620	−0.14523	0.08789
H	1.68471	2.02809	−1.51165
H	2.98467	3.25643	0.17773
O	−1.69458	1.02910	1.07655
H	−1.62408	0.06885	1.12912
C	−1.31718	3.53868	−0.32139
H	−2.32521	3.13649	−0.25078
H	−1.37610	4.62651	−0.36428
H	−0.87890	3.19469	−1.26323
C	−0.96615	3.74892	2.22176
H	−0.31676	3.37774	3.02538
H	−0.76610	4.82177	2.15141
C	−2.43226	3.53603	2.66052
H	−2.69977	2.48553	2.57142
H	−2.46197	3.76933	3.73511
C	−3.43397	4.43288	1.98289
H	−3.15545	5.48818	1.97574
C	−4.61612	4.11033	1.44553
C	−5.16718	2.70863	1.36389
H	−4.43947	1.94478	1.63475
H	−6.04066	2.59306	2.01783
H	−5.51464	2.49005	0.34719
C	−5.51843	5.17125	0.86394
H	−5.09080	6.17157	0.95968
H	−5.71319	4.98733	−0.19991
H	−6.49723	5.17512	1.35944
O	1.13979	4.88331	0.61255

Hydrazone **3.87**:



Cartesian Coordinates:

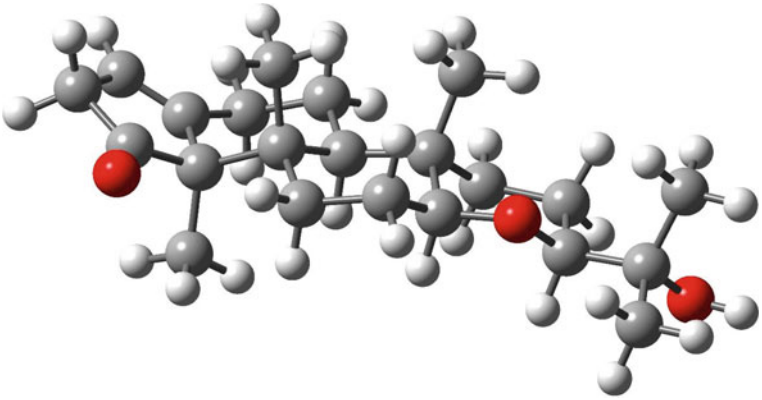
C	−1.58706	2.68188	0.87646
C	−0.26743	2.85482	0.09964
C	−0.04916	1.69871	−0.90540
C	−0.67128	0.41977	−0.41063
C	−2.20054	0.44181	−0.20137
C	−2.62780	1.92617	0.04540
H	−1.41458	2.13073	1.80567
H	−0.26724	3.80193	−0.44877
H	−0.55088	1.94371	−1.84972
N	−0.08880	−0.69814	−0.19218
H	−2.72316	2.42606	−0.93155
H	−1.98677	3.66081	1.16687
H	0.56884	2.88083	0.79751
H	1.00408	1.55438	−1.13081
O	−3.90730	1.92929	0.68252
H	−4.13426	2.84425	0.88421
C	−2.58511	−0.44670	0.99533
H	−3.65727	−0.42029	1.16701
H	−2.27775	−1.47461	0.80986
H	−2.08240	−0.11640	1.90739
C	−2.80907	−0.09244	−1.53598
H	−2.41954	0.52858	−2.35224
H	−2.40338	−1.09527	−1.70547
C	−4.35010	−0.13512	−1.66636

(continued)

(continued)

H	−4.78697	0.77535	−1.25720
H	−4.57100	−0.12038	−2.74339
C	−4.99829	−1.36812	−1.09466
H	−4.55510	−2.30310	−1.44195
C	−6.05066	−1.46034	−0.27384
C	−6.78810	−0.28226	0.31161
H	−6.26749	0.66279	0.16612
H	−7.79241	−0.19426	−0.12177
H	−6.92899	−0.41666	1.39031
C	−6.59302	−2.80687	0.13876
H	−6.04798	−3.62999	−0.32832
H	−6.53780	−2.93926	1.22616
H	−7.65164	−2.90790	−0.13090
N	1.33908	−0.70447	−0.44238
H	1.54340	−1.66076	−0.72908
S	2.24863	−0.47532	1.02527
O	2.16207	−1.63675	1.90726
O	1.88407	0.85262	1.51069
C	3.90198	−0.42842	0.33162
C	4.36514	0.74097	−0.27035
C	4.70968	−1.55737	0.42501
C	5.65236	0.76723	−0.78926
H	3.73039	1.61762	−0.31480
C	5.99748	−1.51255	−0.10374
H	4.33972	−2.44706	0.92043
C	6.48829	−0.35626	−0.71654
H	6.01827	1.67703	−1.25591
H	6.63084	−2.39116	−0.03010
C	7.89322	−0.29966	−1.26135
H	7.92711	0.20612	−2.22970
H	8.55218	0.25497	−0.58500
H	8.31797	−1.29730	−1.38716

Non-conjugated enone **3.144**:



Cartesian Coordinates

C	3.07284	0.27646	−0.57012
C	3.67799	−1.09995	−0.33412
C	2.82409	−2.30537	−0.56760
C	1.47793	−2.15739	0.16950
C	0.80618	−0.80269	−0.13254
C	1.72693	0.41724	0.27484
C	4.21018	1.21207	−0.08036
C	5.41555	0.36053	0.33604
C	4.92366	−1.04576	0.14466
H	2.62477	−2.41512	−1.64246
H	0.82104	−2.97698	−0.13199
H	0.73412	−0.74313	−1.22617
H	5.70226	0.59584	1.36860
H	5.52141	−1.91755	0.39349
O	4.17409	2.41729	−0.07150
C	2.91393	0.56961	−2.08321
H	2.75595	1.63443	−2.25701
H	3.82477	0.28111	−2.61522
H	2.08759	0.01976	−2.53660
H	6.28146	0.62548	−0.28390
H	3.34239	−3.21635	−0.25215
H	1.64100	−2.27515	1.24426
C	1.00547	1.74995	−0.04230

(continued)

(continued)

H	0.93855	1.88386	−1.12596
H	1.60610	2.58474	0.32521
C	−0.42441	1.81937	0.51441
H	−0.44392	1.79995	1.60776
H	−0.89268	2.76195	0.21509
C	−1.23133	0.66890	−0.06110
H	−1.15200	0.74081	−1.16054
C	−0.69253	−0.73173	0.33044
C	2.11980	0.42486	1.77160
H	2.60874	−0.49707	2.08817
H	2.80969	1.24781	1.97288
H	1.26545	0.58321	2.42481
C	−0.90465	−1.03070	1.82758
H	−1.95909	−0.95628	2.09040
H	−0.57522	−2.04465	2.06940
H	−0.37254	−0.35049	2.48794
C	−1.55277	−1.73700	−0.48978
H	−1.31115	−2.76954	−0.22074
H	−1.30244	−1.62837	−1.55333
C	−3.43755	−0.04404	−0.51492
H	−3.27105	0.19837	−1.57742
C	−3.06526	−1.51414	−0.30503
H	−3.62686	−2.12459	−1.01516
H	−3.36993	−1.84061	0.69223
O	−2.60900	0.81362	0.27362
C	−4.90694	0.32004	−0.21075
C	−5.27818	0.11287	1.26157
H	−4.64112	0.70998	1.91633
H	−6.31667	0.41625	1.43321
H	−5.19000	−0.93663	1.54651
C	−5.18335	1.76711	−0.63434
H	−4.96940	1.89756	−1.69806
H	−6.23639	2.02016	−0.46755
H	−4.57178	2.46974	−0.06681
O	−5.65932	−0.57938	−1.04410
H	−6.59468	−0.37199	−0.93630

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