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Robert Doran

Asymmetric Synthesis of Bioactive Lactones and the Development of a Catalytic Asymmetric Synthesis of α-Aryl Ketones

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Robert Doran

Asymmetric Synthesis of Bioactive Lactones and the Development of a Catalytic Asymmetric Synthesis of α-Aryl Ketones

Doctoral Thesis accepted by
the University College Dublin, Ireland

Springer

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"Asymmetric Synthesis of Both Enantiomers of a δ-Lactone Analogue of Muricatacin" Doran, R.; Guiry, P. J., *Synthesis* **2014,** *46*, 761–770.

"Asymmetric Synthesis of (+)-Tanikolide and the β-Methyl-Substituted Analogues of (+)-Tanikolide and (–)-Malyngolide"
Doran, R.; Duggan, L.; Singh, S.; Duffy, C. D.; Guiry, P. J., *Eur. J. Org. Chem.* **2011**, 7097–7106.

To my parents and my sister
In memory of Tony

Supervisor's Foreword

Dr. Doran was awarded a prestigious Irish Research Council Embark Ph.D. Scholarship to work in my group on developing and applying synthetic methodology in total synthesis. He made substantial progress in his Ph.D. research and also contributed intellectually with suggestions for route improvement to analogues of the natural products, e.g. malyngolides and muricatacins. He was the first author on both papers from this section of his thesis [*Eur. J. Org. Chem.* **2011**, 7097–7106 and *Synthesis* **2014**, *46*, 761–770, respectively] and did an excellent job in applying zirconium tetrachloride as a novel catalyst for the preparation of δ-lactone marine natural products. As research can sometimes go against you, some of the initial ideas proved difficult practically and he showed real dedication to circumvent these problems and come out the other end with elegant solutions and good results.

He was keen to extend his Ph.D. research to include synthetic methodology development so he also joined our mini-group on the enantioselective preparation of α-aryl ketones using Pd-catalysed decarboxylative protonation. We had one paper in this area when Robert started and he extended the methodology to include the total synthesis of two naturally occurring isoflavanones. He showed real tenacity and demonstrated his excellent experimental technique to optimise this process up to 97 % ee and also discovered a stereodivergence in the protonation step depending on the proton source employed. This was a very important finding which has inspired us to look, with success, for this phenomenon with related substrates. He was the first author of a paper that reported this work in *Chem. Eur. J.* **2014**, *20*, 15354–15359. This paper, with its remarkable enantioselective switch depending on the acid source employed, has been highlighted as a Science Concentrate by Chemical & Engineering News (**2014**, October 20th, p. 30) and also as a Research Highlight by Chemistry World (**2014**, 11, issue 12, p. 31).

Robert also investigated the substrate scope of this protocol for the enantioselective preparation of α-aryl ketones by extending it to a series of 11 cyclopentanone and 10 cyclohexanone derivatives. This paper, with Robert as the only author responsible for the experimental work, was published in *J. Org. Chem.* **2014**, *79*, 9112–9124.

Robert's findings have inspired further work in the research group where we are currently investigating the enantioselective synthesis of a series of related α-aryl- and α-allyl-α-aryl ketones and lactones.

Robert wrote a superb Ph.D. thesis which is an excellent example of clarity of thought and presentation and is an exceptional piece of scholarly work. He was the deserved recipient of the Royal Irish Academy Ph.D. Prize for 2014 and now the Springer Thesis Award.

Dublin, Ireland
May 2015

Prof. Pat Guiry

Abstract

The total synthesis of natural products continues to be one of the most fascinating and well-studied areas of organic chemistry. The importance of natural products, their synthesis and the design of biologically relevant molecules continues to be the greatest source of potential new pharmaceuticals. The discovery and application of new and interesting methodologies of use in total synthesis is vital to the goals of designing shorter, more elegant and ultimately more reliable syntheses of natural products and analogues.

The asymmetric synthesis of all four diastereomers of β-methyl analogues of the marine natural products (+)-tanikolide, which displays antifungal activity, and (−)-malyngolide, which displays antimicrobial activity, has been successfully completed. The final two diastereomers were synthesised in this Ph.D. project in a 9-step synthesis in 24.9 % and 10.8 % overall yields, respectively. Key steps in the synthetic route included Sharpless asymmetric epoxidation and $ZrCl_4$-catalysed intramolecular acetalisation as the key steps. The β-methyl substituted analogues were designed to probe the effect the β-methyl group change would have on the bioactivity of these compounds. The biological testing of these compounds revealed that these analogues showed no antifungal activity, however, one of the analogues of malyngolide showed promising activity against MRSA with an MIC of 12.5 μg/mL.

The asymmetric synthesis of both enantiomers of the δ-lactone analogue of the anti-tumoral natural product γ-lactone muricatacin has also been carried out in a 9-step sequence with overall yields of 17.8 % and 11.2 %, respectively. Initial attempts to also synthesise the natural product proved unsuccessful due to the poor reactivity of the Grignard reagent derived from 2-(bromomethyl)-1,3-dioxolane. The designed synthetic route enabled us to increase the ring size to generate the δ-lactone analogue employing Sharpless asymmetric epoxidation and $ZrCl_4$-catalysed intramolecular acetalisation as the key steps.

The development of new methods for the synthesis of enantioenriched molecules is a key area of modern organic chemistry. Catalytic asymmetric synthesis is one method by which enantioenriched compounds can be synthesised. A key class of

compounds which are challenging to prepare in an enantioselective manner are tertiary α-aryl ketones, present in isoflavanones and many other bioactive molecules.

A modular, 6-step asymmetric synthesis of 2 naturally occurring and 3 non-natural isoflavanones containing tertiary α-aryl carbonyls was developed. This synthetic route, utilising a Pd-catalysed decarboxylative asymmetric protonation, allows access to isoflavanones in excellent enantioselectivities from 76–97 % *ee*. A switch in the sense of stereoinduction was observed when different H^+ sources were employed showing the first example of dual stereocontrol in an asymmetric protonation reaction whereby the same chiral ligand is used with a different achiral proton donor. The first enantioselective synthesis of the naturally occurring isoflavanones sativanone and 3-*O*-methylviolanone also has been accomplished using this methodology.

To test the substrate scope, the catalytic asymmetric synthesis of a series of tertiary α-aryl cyclopentanones and cyclohexanones has also been achieved *via* a Pd-catalysed decarboxylative protonation of the corresponding α-aryl-β-keto allyl esters. Enantioselectivities of up to 92 % *ee* and 74 % *ee* were achieved for cyclopentanone and cyclohexanone substrates, respectively. The route described gives access to these important structural motifs in moderate to high levels of enantioselectivity. In particular, this is only the second direct approach for the preparation of tertiary α-aryl cyclopentanones. The synthetic approach allows for simple modification of the aryl group and, significantly, substrates containing sterically hindered aryl groups gave the highest levels of enantioselectivity and these aryl groups were readily installed by a Pb-mediated arylation of a β-keto allyl ester.

Acknowledgments

First, I would like to thank my supervisor Prof. Pat Guiry. From the moment I started as a fourth-year undergraduate project student I was treated as part of the research group. He has shown a huge amount of confidence and belief in my abilities, something for which I will always be grateful. He was a constant support throughout my Ph.D., providing me with the research projects and a brilliantly equipped lab in which to conduct research. He gave up huge amounts of his time to help get me to this point and was not only a great source of knowledge and encouragement but also helped put everything in perspective, particularly during difficult periods. Thank you.

I would like to acknowledge the facilities provided by University College Dublin, in particular, the Centre for Synthesis and Chemical Biology (CSCB) which is a world-class research facility where I feel privileged to have conducted research. A huge thank you must also go to the School of Chemistry and Chemical Biology. All of the academic staff were always approachable and happy to help and discuss any chemistry. Particular thanks to Dr. Mike Casey and Prof. Stefan Oscarson as members of my doctoral studies panel and to Dr. Paul Evans for acting as the internal examiner for my viva. Thanks to the technical staff of the school, in particular Dr. Jimmy Muldoon, Dr. Yanick Ortin and Ms. Geraldine Fitzpatrick for endless help with NMR analysis. Thanks also to Mr. Adam Coburn and Mr. Kevin Conboy for HRMS analysis. Thank you to the administrative staff of the school for all of their help throughout my time at UCD.

A massive thank you to all of the members of the Guiry group. There are so many to mention: Surrendra, Christina, Barry, Suribabu, Ramu, Andy, Ludovic, Caroline, Cathal, Xin, Gavin, Michael, Dennis, Caoimhe, Eibhlin, Steven, Claire, Mark, Kieran, Catherine, Chris, Joe, Denise, Cian, Brian, Kevin and Andrea. To start with, I would like to thank Gavin who supervised my fourth-year project and was a big help when I began my Ph.D. and a good friend. In my first year Christina was always there and could answer any question I asked. Thanks to Barry for giving me some extra work to do and for the verbal abuse. Thanks to Michael for his generous help when my Ph.D. branched into asymmetric catalysis. To Eibhlin and Claire for all the Heck chapter fun times and thanks to Claire for her support.

Mark and Kieran are friends for life and great craic. To Ramu for his expertise and support in my final year, a massive thank you. A special thanks to Caoimhe who was such a close friend through all of my Ph.D. and a constant source of entertainment. Finally, the last member of the group I wish to thank is one of my closest friends, Steven. I have been fortunate to know Steven since our first year as undergraduates and I can't thank him enough.

An important thank you must also go to Schering-Plough in Rathdrum and in particular, Dr. Ronan Lockhart, for giving me the opportunity to work there before I started my Ph.D. The guidance given to me by Dr. Robert Collins was invaluable and played a crucial role in my development as a chemist.

The most important thanks of all goes to my family, Mum, Dad and Laura. There are no words to describe how grateful I am to them all. Mum and Dad have supported me every step of the way, I would not have achieved this without them. To my best friend and sister, Laura, simply thanks for being so wonderful.

Collaborations

The biological testing carried out on the β-methyl analogues of tanikolide and malyngolide described in Chap. 2 was carried out by our collaborators in UCD. The antifungal testing was carried out by Dr. Linda Holland in the research group of Prof. Geraldine Butler at the UCD Conway Institute. The antimicrobial testing of the β-methyl tanikolide and malyngolide analogues as well as the isoflavanones prepared in Chap. 5 were conducted by Dr. Marta Martins in the group of Prof. Séamus Fanning at the UCD Centre for Food Science, UCD School of Public Health, Physiotherapy & Population Science. Testing of the δ-muricatacin analogues against a number of tumour cell lines was carried out by Joana Silva and Prof. Pedro V. Baptista, Departamento de Ciências da Vida, Faculdade de Ciências e Tecnologias, Universidade Nova de Lisboa, Caparica, Portugal.

In Chap. 5 the synthesis of the α-aryl-β-keto allyl ester was developed by a former Ph.D. student in our group, Dr. Michael Carroll and a final-year undergraduate student Bryan Hogan. They also carried out the initial catalysis on the three substrates shown in Scheme 5.3.

Contents

Symbols and Abbreviations

ν_{max}	Wavenumbers (IR)
δ	Chemical shift in degrees downfield from TMS
$[\alpha]_D^{20}$	Specific rotation
°	Degrees
°C	Degrees Celsius
^{1}H NMR	Proton nuclear magnetic resonance spectroscopy
^{13}C NMR	Carbon nuclear magnetic resonance spectroscopy
Å	Ångström (10^{-10} m)
Ac	Acetyl
API	Active pharmaceutical ingredient
app. t	Apparent triplet (NMR)
app. d	Apparent doublet (NMR)
app. dd	Apparent doublet of doublets (NMR)
aq.	Aqueous
atm	Atmosphere
Ar	Aryl
Bn	Benzyl
BnBr	Benzyl bromide
br s	Broad singlet (NMR)
c	Concentration in g per 100 mL (optical rotation)
calcd.	Calculated
cm^{-1}	Reciprocal centimetres
conv.	Conversion
cod	Cyclooctadiene
d	Doublet (NMR)
dba	Dibenzylideneacetone
dd	Doublet of doublets (NMR)
ddd	Doublet of doublet of doublets (NMR)
de	Diastereomeric excess
DIAD	Diisopropyl azodicarboxylate
DIBAL	Diisobutylaluminium hydride

DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	Dimethylsulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dt	Doublet of triplets (NMR)
ee	Enantiomeric excess
equiv.	Equivalent(s)
Et	Ethyl
EtOAc	Ethyl acetate
Et_2O	Diethyl ether
EtOH	Ethanol
ESI	Electrospray ionisation (mass spectrometry)
FDA	Food and Drug Administration
g	Gram(s)
h	Hour(s)
HMDS	Hexamethyldisilazane
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz, GHz, MHz	Hertz, gigahertz, megahertz
i-Pr	*iso*-propyl
IR	Infrared spectroscopy
J	Coupling constant
LiHMDS	Lithium hexamethydisilazide
lit.	Literature reference
m	Multiplet (NMR)
M	Molar
Me	Methyl
MeOH	Methanol
MP	Melting point
$[M]^+$	Molecular ion (mass spectrometry)
$[M + H]^+$	Protonated molecular ion (mass spectrometry)
$[M + Na]^+$	Molecular ion plus sodium
μm	Micrometres
mg	Milligram
min	Minute(s)
mL, μL	Millilitre, microlitre
mmol	Millimole
mol	Mole
MW	Microwave irradiation
n-BuLi	*n*-butyllithium
NAP	2-naphtylmethyl
NCE	New chemical entity
n.d.	Not determined
NOE	Nuclear overhauser effect
Nu	Nucleophile

OAc	Acetate
o, *m*, *p*	*Ortho*, *meta*, *para*
PHOX	Phosphinooxazoline
Ph	Phenyl
Ph.D.	*Philosophiae doctor*
PLP	Pyridoxal-phosphate
ppm	Parts per million
qC	Quaternary carbon (NMR)
q	Quartet (NMR)
rac	Racemic mixture
R_f	Retention factor
RBF	Round bottom flask
R_t	Retention time
rt	Room temperature
s	Singlet (NMR)
$scCO_2$	Supercritical CO_2
SFC	Supercritical fluid chromatography
t	Triplet (NMR)
t-Bu	*tert*-butyl
t-BuLi	*tert*-butyllithium
temp.	Temperature
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMEDA	*N,N*-tetramethylethylenediamine
TMS	Tetramethylsilane
TMSBr	Tetramethylsilyl bromide
TOF	Time-of-flight (mass spectrometry)
UV	Ultraviolet irradiation
W	Watts

Chapter 1
Introduction to the Total Synthesis of Lactone-Containing Natural Products Using $ZrCl_4$

1.1 Total Synthesis of Natural Products

> There is excitement, adventure, and challenge, and there can be great art in organic synthesis.
>
> R.B. Woodward

The construction of the molecules of nature in the laboratory from simple molecules or atoms is known as *total synthesis* [1]. The total synthesis of natural products continues to be one of the most fascinating and well-studied areas of organic chemistry. Natural products and designed analogues continues to be the greatest source of potential new pharmaceuticals. The discovery and application of new and interesting methodologies of use in total synthesis is vital to the goals of designing shorter, more elegant and ultimately more reliable syntheses of natural products and analogues.

The total synthesis of complex natural products and designed analogues is still a huge challenge in synthetic chemistry. The ease at which nature can use enzymes to control the orientation and reactivity of organic molecules is astounding and incredibly complex. The ultimate goal in organic synthesis is to someday possess a similar level of control in a synthetic laboratory as nature can already do now. Although this might seem like an unrealistic goal, huge strides have been made over the last century and will continue to be made over the coming ones. The discovery and development of new synthetic reactions, reagents and catalysts is known as *synthetic methodology* and this is fundamental to increasing the power and efficiency of organic synthesis.

The history of organic synthesis is a fascinating one. The first rational synthesis of an organic compound, urea, was carried out by Wöhler in 1828 (Fig. 1.1). This was followed by a number of other landmark syntheses: acetic acid (Kolbe 1845), glucose (Fischer 1890), α-terpinol (Perkin 1904), camphor (Komppa 1903; Perkin 1904), tropinone (Robinson 1917), haemin (Fischer 1929), equilenin (Bachmann

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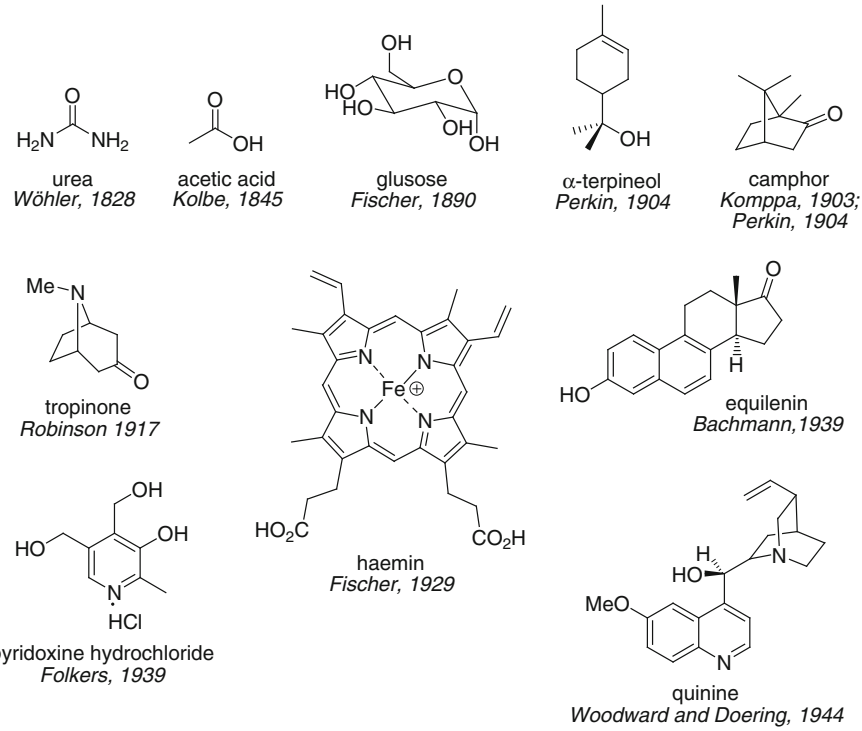


Fig. 1.1 Early achievements in organic synthesis

1939), pyridoxine hydrochloride (Folkers 1939) and quinine (Woodward and Doering 1944).[1]

After this time, rapid advancements were made in the total synthesis of complex natural products. In particular the work of Woodward deserves special mention, his vision and foresight and ability to understand the subtle reactivity of complex systems and ultimately to design and carry out synthetic routes was inspirational. His report on the synthesis of strychnine in 1954 was a remarkable achievement given the beautiful simplicity of the transformations carried out and the difficulties of the characterisation of complex intermediates at that time (Fig. 1.2). Woodward followed this up with the similarly remarkable syntheses of reserpine in 1958 and vitamin B12 with Eschenmoser in 1973.[1]

The contribution to the field by Corey also deserves special mention as someone who systematically developed the idea of retrosynthetic analysis as a tool to design organic synthesis, not to mention a raft of new synthetic methodologies and extraordinary total synthesis including ginkgolide B (Fig. 1.2). One of Corey's former students, Nicolaou also deserves huge recognition for the sheer number of incredibly complex natural products which have been synthesised by his research group, most notably brevetoxin B, containing 11 trans-fused rings and 23 stereocentres, and the key antibiotic vancomycin (Fig. 1.2).

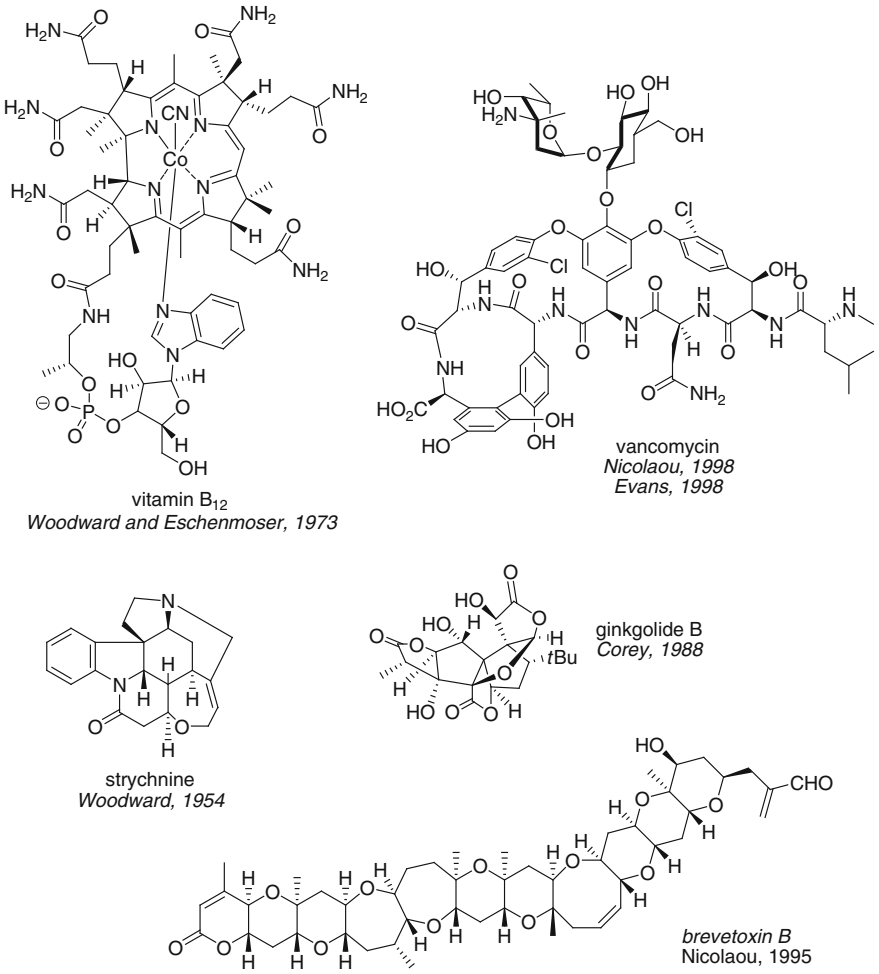


Fig. 1.2 Synthesis of highly complex natural products

1.2 Natural Products as Pharmaceuticals

Natural products have been used as therapeutic agents or medicinal products for millennia in one form or another and a huge number of these, especially prior to the last 50 years, are derived from plants [2]. Today, natural products derived from plant sources continue to play a vital role in the treatment of diseases. There are many examples where the active compound in plant-derived traditional medicines has been used as a pharmaceutical agent. A particularly important example is the discovery and development of anti-malarial drugs such as quinine and artemisinin (Fig. 1.3). Quinine was isolated as early as 1820 and was used extensively until the

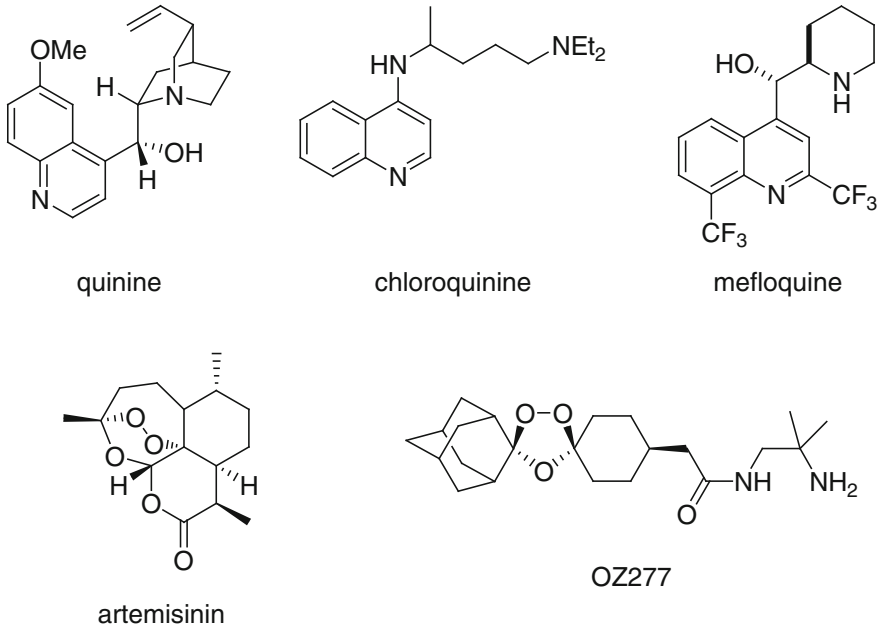


Fig. 1.3 Discovery and development of antimalarial drugs

mid-1900s when it was replaced by the analogues chloroquine and mefloquine. Eventually resistance to these analogues increased and another plant-source was turned to, used in traditional Chinese medicine, which led to the discovery of artemisinin [3]. Importantly, many analogues have been prepared some of which are used in treatment today [4] and others are promising for the future such as a totally synthetic analogue OZ277 [5].

Plants have also provided a key source of potential cancer treatments. A well-known example is paclitaxel (Taxol®), isolated from the bark of the Pacific yew tree, which has become a blockbuster drug and analogues have also been approved for use that demonstrate improved efficacy (Fig. 1.4) [6]. Taxol also provides an excellent example to illustrate the challenges that remain in total synthesis. Numerous examples of the total synthesis of Taxol have been reported [7–13]. However, the overall yield and the number of steps required means it is not economically viable to synthesise the quantities required for its medicinal application. It is therefore obtained industrially via a semi-synthetic route starting from 10-deacetylbaccatin III, a biosynthetic precursor, which can be isolated, in much larger quantities than Taxol itself, from the leaves of a different species of yew tree. More recently however, a plant cell fermentation approach has been developed for the industrial production of Taxol.

Microorganisms have been used as sources of bioactive natural products ever since the serendipitous discovery of penicillin by Fleming in 1929 (Fig. 1.4). To date, microorganisms have been the richest source of active pharmaceutical

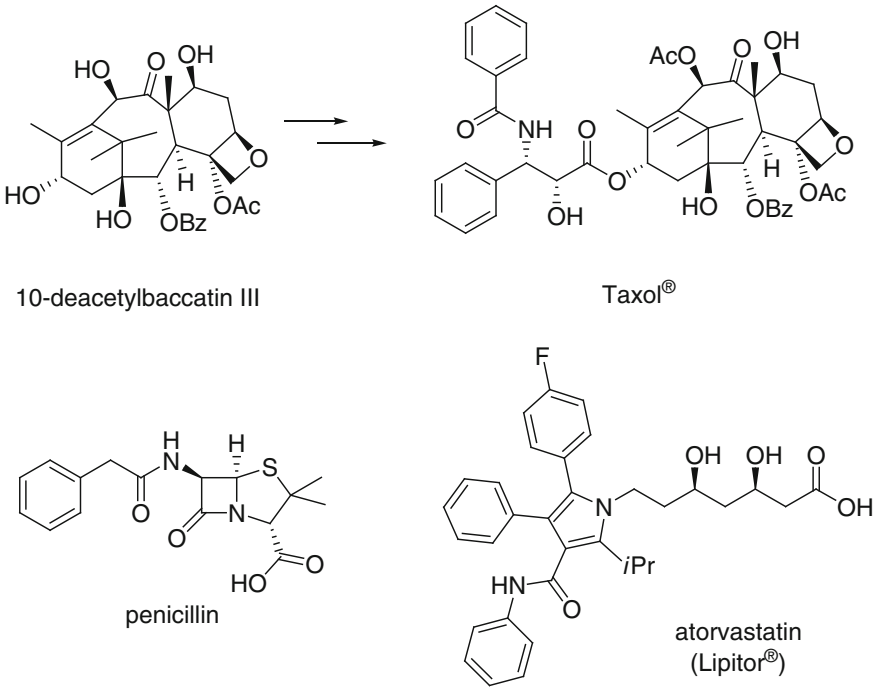


Fig. 1.4 Important pharmaceuticals derived from plant sources and microorganisms

ingredients (APIs) in the form of natural products or more potent or bioavailable derivatives. Other than the key penicillin class of antibiotics, microorganisms have been the source responsible for the discovery of numerous other drug classes. For example, the statin class of drugs, of which Lipitor® is a member, is the biggest selling pharmaceutical in history (Fig. 1.4) [14].

Marine organisms have proved to be another vital source of structurally diverse bioactive metabolites. For example, in a series of review articles by Faulkner, over 840 novel structures from marine sources were published in 1998 alone and this increased to just over 1000 in 2010 [15]. A large number of new classes have been isolated and this environment remains largely untapped, particularly the deep ocean. A key example of a bioactive natural product isolated from a marine source is halichondrin B, a highly complex polyether which was isolated from the sea sponge *Halichondria okadai* Kadota in tiny quantities (12.5 mg from 600 kg of crude sponge) (Fig. 1.5) [16]. It showed promising anti-cancer activity but its structural complexity was beyond industrial scale total synthesis. Fortunately, during laboratory scale total synthesis it was discovered that the right half of the molecule retained much of the biological potency [17]. This analogue, eribulin (Halaven®, E_{7389}), was synthesised in sufficient quantities for clinical trials and was subsequently approved by the United States Food and Drug Administration (FDA) in 2010 as a treatment for breast cancer [18]. Developed by the Eisai Research

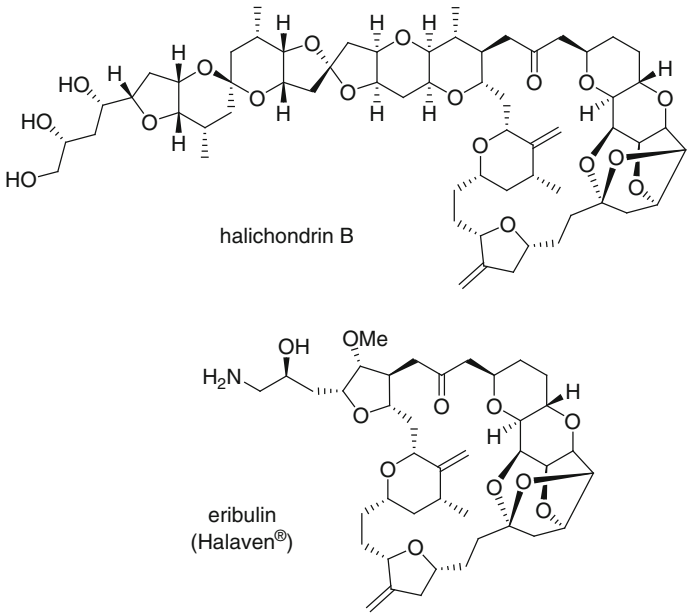


Fig. 1.5 Marine anti-cancer natural product halichondrin B and eribulin analogue

Institute, this analogue is undoubtedly the most difficult and complex total synthesis of a pharmaceutical ever attempted and represents both a milestone and a limitation in the field of industrial scale total synthesis.

In the analysis of natural products as sources of new drugs over the 30 years from 1981 to 2010, Newman and Cragg found that, of the 1073 small molecule new chemical entities (NCEs), 64 % were natural products, derivatives of natural products or modelled on a natural product which inhibits the target of interest [19]. They also pointed out the decline in the number of small molecule NCEs being reported per year from the high point of the late 1980s of over 60/year to an average of 23/year in the 10 years from 2001 to 2010. A major contributing factor is believed to be a result of the declining interest in natural products by the pharmaceutical industry and switching to techniques such as combinatorial chemistry to generate large molecular libraries. This further highlights that the greatest potential of new bioactive molecules is to be found in natural product discovery, identification, analogue design and ultimately organic synthesis.

1.3 Lactone-Containing Natural Products

Lactones are a class of organic compounds which are prevalent in nature and are a key structural motif in many bioactive molecules and pharmaceuticals (Fig. 1.6). For example camptothecin, a cytotoxic quinoline alkaloid, has shown anti-cancer

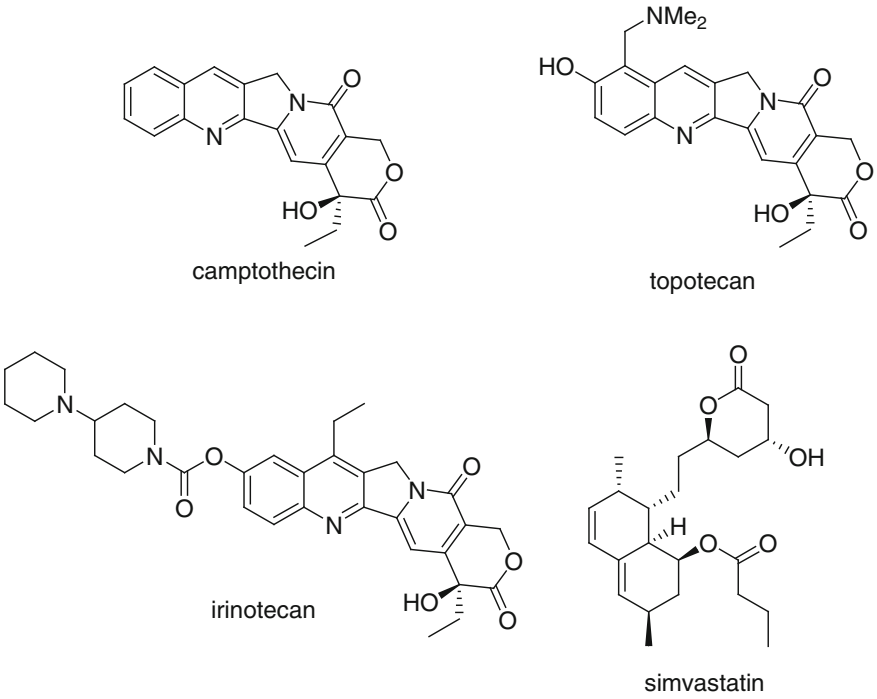
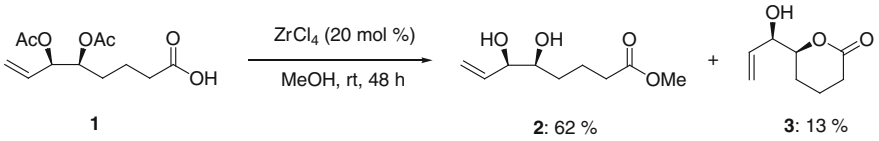


Fig. 1.6 Lactone-containing natural products and pharmaceuticals

activity against a large range of tumours by binding to human DNA to topoisomerase I [20]. Two analogues derived from camptothecin, topotecan (GSK) and irinotecan (Pfizer), have been approved at therapies for ovarian, lung, and colon cancer. Another lactone-containing pharmaceutical is simvastatin, a derivative of a naturally occurring statin isolated from the fermentation of *aspergillus terrus*. Simvastatin, developed by Merck, is used as a treatment for cardiovascular disease by lowering cholesterol and triglyceride levels in the blood [21].

1.4 Synthesis of Lactones Using $ZrCl_4$

The use of zirconium(IV) chloride ($ZrCl_4$) in organic synthesis as a mild Lewis acid catalyst has been widespread and its use has been recently reviewed [22]. Our research group recently discovered a $ZrCl_4$-catalysed formation of δ-lactones, [23] during work on the synthesis of potential anti-inflammatory compounds. Attempts to develop new protection/deprotection methodologies utilising $ZrCl_4$ led to a one-pot esterification and deprotection of (5*S*, 6*R*)-5,6-diacetoxyoct-7-enoic acid (**1**) in good yields (Scheme 1.1).

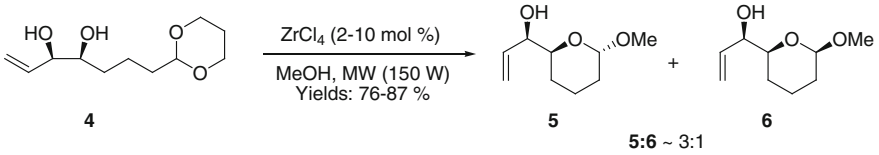


Scheme 1.1 Initial discovery of $ZrCl_4$-catalysis by-product lactone

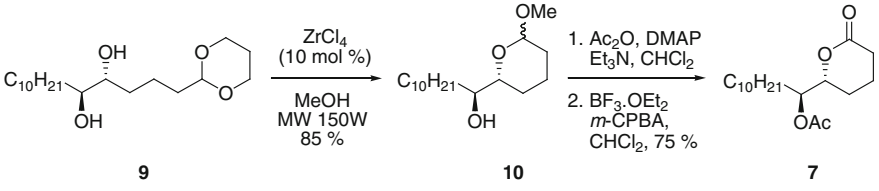
A number of Lewis acid catalysts were screened for the above transformation and it was found that most could not completely deprotect the diacetate and instead formed the methyl ester and mono-deprotected acetate. However, none of the other catalysts tested generated the δ-lactone by-product (**3**), which was formed only when $ZrCl_4$ was employed. The formation of this lactone by-product was the subject of further study due to the importance of lactones, ubiquitous in natural products. Initial investigations found that $ZrCl_4$ successfully catalyses the deprotection of 1,3-dioxane rings in compounds of type **4**, assisted by microwave irradiation, leading to the formation 6-methoxytetrahydropyrans (**5** and **6**) (Scheme 1.2).

We were eager to exploit this methodology in the total synthesis of a lactone-containing natural product. The target chosen was 6-acetoxy-5-hexadecanolide (**7** and **8**) (Fig. 1.7), a major component of mosquito oviposition attractant pheromones.

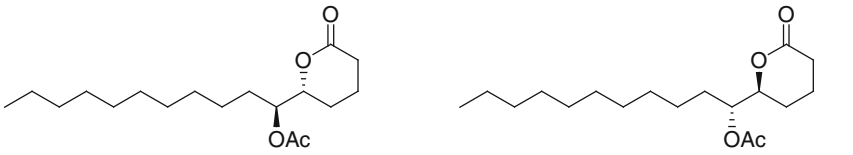
The asymmetric synthesis of both enantiomers of 6-acetoxy-5-hexadecanolide were successfully carried out [24]. This was achieved via initial deprotection of the 1,3-dioxane moiety of compound **9** and subsequent cyclisation, catalysed by $ZrCl_4$, to form 6-methoxytetrahydropyran (**10**) followed by oxidation to form the natural product **7** (Scheme 1.3).



Scheme 1.2 $ZrCl_4$-catalysed formation of 6-methoxytetrahydropyrans

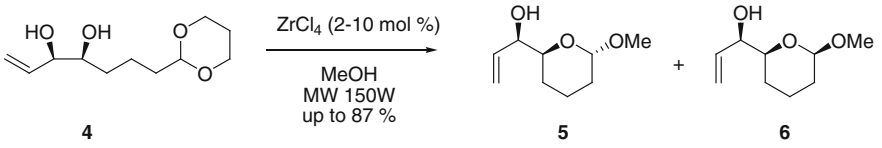


Scheme 1.3 Deprotection/cyclisation sequence to 6-acetoxy-5-hexadecanolide



7: (–)-(5*R*,6*S*)-6-acetoxy-5-hexadecanolide **8**: (+)-(5*S*,6*R*)-6-acetoxy-5-hexadecanolide

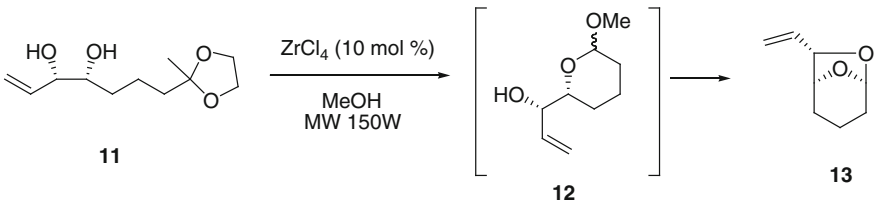
Fig. 1.7 Structures of mosquito attractant pheromone and its enantiomer



Scheme 1.4 Optimisation of $ZrCl_4$-catalysed deprotection/cyclisation

Following on from this successful synthesis, a standard reaction system was set up in order to optimise the conditions for this type of transformation, using diol **4**, varying the temperature range (40–80 °C) and catalyst loadings (2–10 mol %) under constant microwave power for 3 min @ 150 W (Scheme 1.4). A temperature of 50 °C with a catalyst loading of 5 % was found to be optimal with as little as 2 mol % $ZrCl_4$ providing a good yield (76 %). It was also shown that the transformation could be carried out with conventional heating at 40 °C, albeit with much longer reaction times, 2 h versus 3 min. A number of different Lewis acids were screened using this reaction system with only $Sc(OTf)_2$ giving a good yield (65 %). Other Lewis acids, such as ceric ammonium nitrate (CAN), $Cu(OTf)_2$, $SnCl_2$, $Ti(OiPr)_4$, $FeCl_3$ and $InCl_3$, did not form the desired products [25].

Further to this, the strategy was employed in the synthesis of 6,8-dioxabicyclo [3.2.1]octane-containing natural products. This was achieved via a second cyclisation step after initial deprotection and cyclisation (Scheme 1.5).



Scheme 1.5 Second cyclisation to form a 6,8-dioxabicyclo[3.2.1]octane-containing natural product

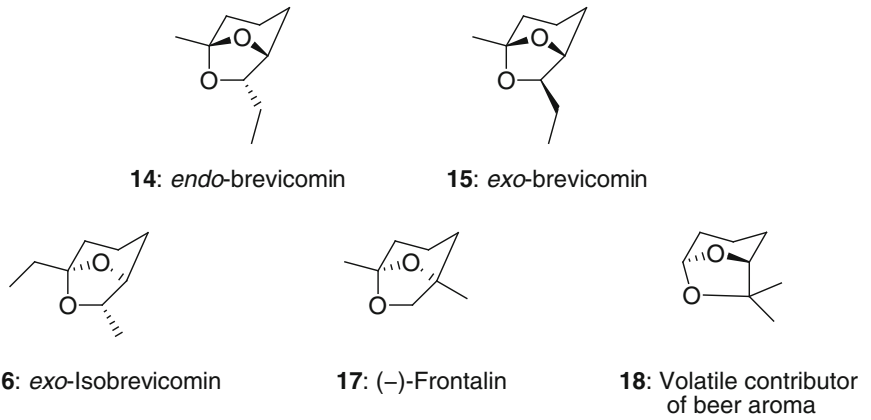


Fig. 1.8 6,8-Dioxabicyclo[3.2.1]octane-containing natural products synthesised using $ZrCl_4$

This was applied to the synthesis of beetle aggregation pheromones; *exo*- and *endo*-brevicomin, *exo*-isobrevicomin and (−)-frontalin (Fig. 1.8). A volatile contributor of beer aroma was also synthesised [25, 26]. The synthesis of these natural products also showed the ability of $ZrCl_4$ to successfully deprotect 1,3-dioxolane groups.

The aim of one section of this Ph.D. project is to further extend the scope of the $ZrCl_4$-catalysed deprotection/cyclisation protocol in the synthesis of analogues of the marine natural products (+)-tanikolide (**19**) and malyngolide (**20**) (Fig. 1.9). It was also hoped to expand the $ZrCl_4$-catalysed deprotection/cyclisation sequence to the synthesis of γ-lactone-containing natural products, namely (+)-muricatacin (**21**) and (−)-muricatacin (**22**).

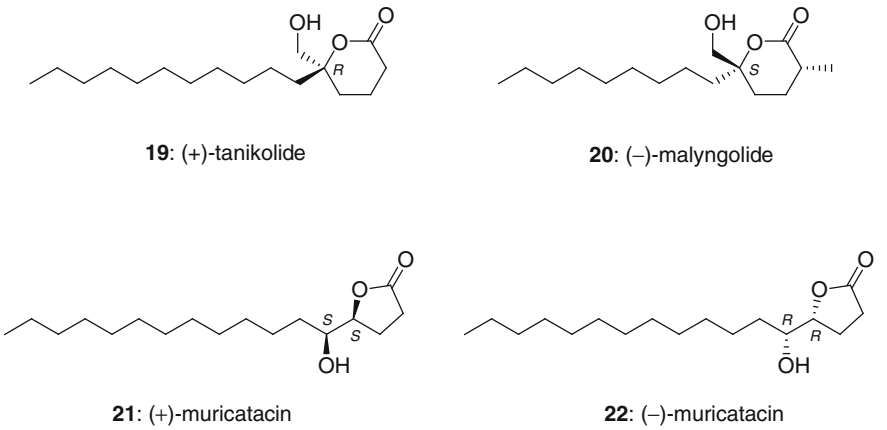


Fig. 1.9 δ- and γ-lactone containing natural products

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Chapter 2
Asymmetric Synthesis of the β-Methyl-Substituted Analogues of (+)-Tanikolide and (–)-Malyngolide

Abstract The asymmetric synthesis of all 4 diastereomers of β-methyl analogues of the marine natural products (+)-tanikolide, which displays antifungal activity, and (−)-malyngolide, which displays antimicrobial activity, has been successfully carried out. The final two diastereomers were synthesised in this Ph.D. project in a 9-step synthesis in 24.9 and 10.8 % overall yields, respectively. Key steps in the synthetic route included Sharpless asymmetric epoxidation and $ZrCl_4$-catalysed intramolecular acetalisation as the key steps. The β-methyl substituted analogues were designed to probe the effect the β-methyl group would have on the bioactivity of these compounds. The biological testing of these compounds revealed that none of these analogues showed any antifungal activity however, one of the analogues of malyngolide showed promising activity against MRSA with an MIC of 12.5 μg/mL.

2.1 Introduction

(+)-Tanikolide (**1**) was isolated from the lipid extract of the marine blue green algae (cyanobacterium) *Lyngbia majuscula*, collected from Tanikeli Island, Madagascar [1]. It has been shown to display strong toxicity against brine shrimp (LD_{50} = 3.6 μg mL^{-1}) and snail (LD_{50} = 9.0 μg mL^{-1}) and antifungal activity against *Candida albicans*. A similar natural product, (−)-malyngolide (**2**), isolated from the shallow water variety of *Lyngbia majuscula*, has a very similar structure with opposite configuration at the quaternary chiral centre, an *n*-nonyl instead of an *n*-undecyl chain and an α-methyl group (Fig. 2.1) [2]. (−)-Malyngolide displays antimicrobial activity against *Mycobacterium smegmatis*, *Staphylococcus*, *Pseudomonas* and *Streptococcus pyogenes*, however, shows no antifungal activity against *C. albicans* as observed with (+)-tanikolide.

R. Doran, *Asymmetric Synthesis of Bioactive Lactones and the Development of a Catalytic Asymmetric Synthesis of α-Aryl Ketones*, Springer Theses,
DOI 10.1007/978-3-319-20544-1_2

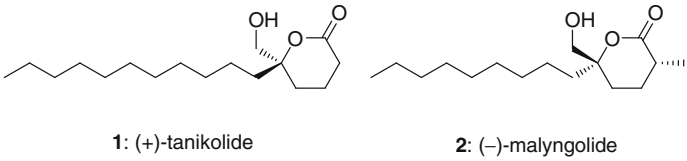


Fig. 2.1 Structures of (+)-tanikolide and (−)-malyngolide

A number of different strategies have been employed in previous syntheses of (+)-tanikolide [3–10] including Sharpless asymmetric epoxidation/dihydroxylation of allylic alcohols [11–14], the use of enantiopure starting materials D-erythrulose [10], and D-erythrose [9], stereospecific C-H insertion of dichlorocarbene with a chiral secondary alcohol [15], an asymmetric α-alkylation of a β-keto ester and subsequent Bayer-Villiger oxidation [16], α-metallation of ketones and ring closing metathesis [10, 12, 17, 18]. Domino reactions of epoxy alcohols with hypervalent iodine reagents [14, 19] and asymmetric dihydroxylation of enamides have also been investigated [20]. The asymmetric synthesis of (−)-malyngolide was first reported by Mukaiyama [21]. A number of different approaches have been utilized since, including chiral auxiliary [22–30], chiral pool [31–41], other asymmetric syntheses [42–44] and catalytic asymmetric syntheses [45–52].

The structures of (+)-tanikolide and (−)-malyngolide were attractive structures to attempt to synthesise using our $ZrCl_4$ methodology and as such the concise asymmetric synthesis of (+)-tanikolide was carried out within this research group in 9 steps with an overall yield of 26.4 % [18]. Following this, a set of analogues of (+)-tanikolide and (−)-malyngolide were envisaged with a methyl group at the β-position of the lactone. The purpose of these analogues was to investigate the effect this structural change would have on the biological activity, considering the contrasting biological activity of (+)-tanikolide and (−)-malyngolide (Fig. 2.2).

Initial work on the synthesis of these analogues was carried out during a final year undergraduate project within our research group, with successful completion of 2 of the 4 analogues (**5** and **6**). The synthesis of the remaining analogues (**3** and **4**) was the initial goal of my Ph.D. project and their synthesis is described herein.

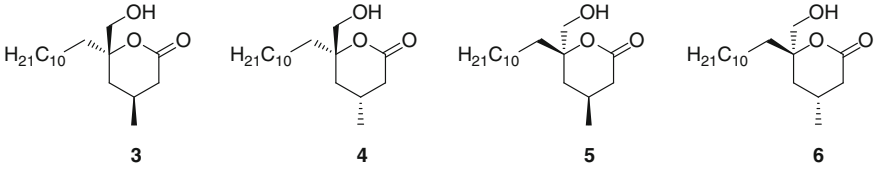
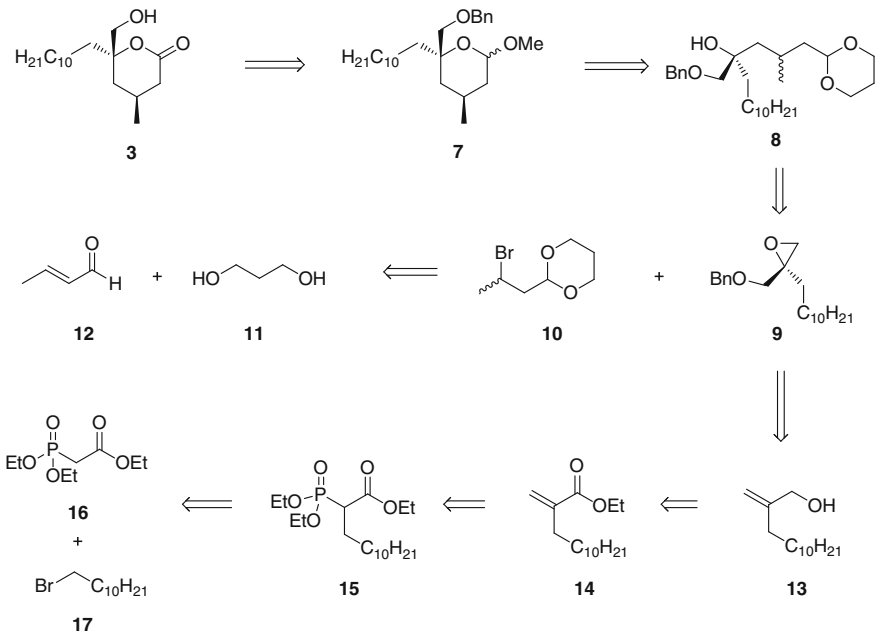


Fig. 2.2 Structures of (+)-tanikolide and (−)-malyngolide analogues

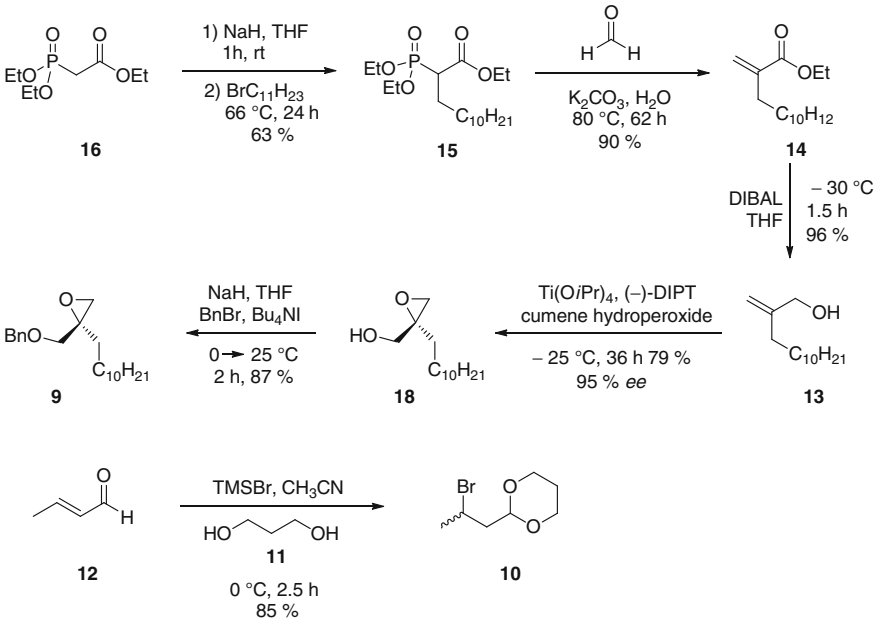
2.2 Results and Discussion

The retrosynthetic analysis of the desired (−)-malyngolide analogue **3** shows it can be formed from the benzyl-protected analogue **7** via oxidation and hydrogenolysis, which in turn can be envisaged to be prepared from a $ZrCl_4$-catalysed deprotection/cyclisation of alcohol **8**. Alcohol **8** could be accessed through an epoxide ring-opening of protected epoxide **9** with the Grignard derivative of the bromo-dioxane **10**. The Grignard precursor could be synthesised via the dioxane protection and bromination of crotonaldehyde **12**. Benzyl-protected epoxide **9** could be generated from allylic alcohol **13** via a Sharpless asymmetric epoxidation (SAE). Allylic alcohol **33** could be obtained from the reduction of its corresponding ester **14**, which in turn could be synthesised from a Horner-Wadsworth-Emmons (HWE) olefination of phosphonate **15**, prepared by alkylation of phosphonoacetate **16** with alkyl bromide **17** (Scheme 2.1).

The first step towards the synthesis of epoxide **9** began with alkylation of phosphonoacetate **16** with 1-bromoundecane using NaH as the base to give alkylated phosphonate **15** with a yield of 63 % and the undesired dialkylated by-product in 27 % yield (Scheme 2.2).[8c] The terminal alkene **14** was prepared in 90 % yield via a HWE olefination using 35 % aqueous formaldehyde and K_2CO_3. The allylic ester **14** was successfully reduced in the presence of DIBAL at −30 °C in 96 % isolated yield to generate allylic alcohol **13**. This alcohol then underwent SAE using Ti(O*i*Pr)$_4$, (−)-diisopropyltartrate and cumene hydroperoxide to yield



Scheme 2.1 Retrosynthesis of β-methyl-malyngolide analogue **3**

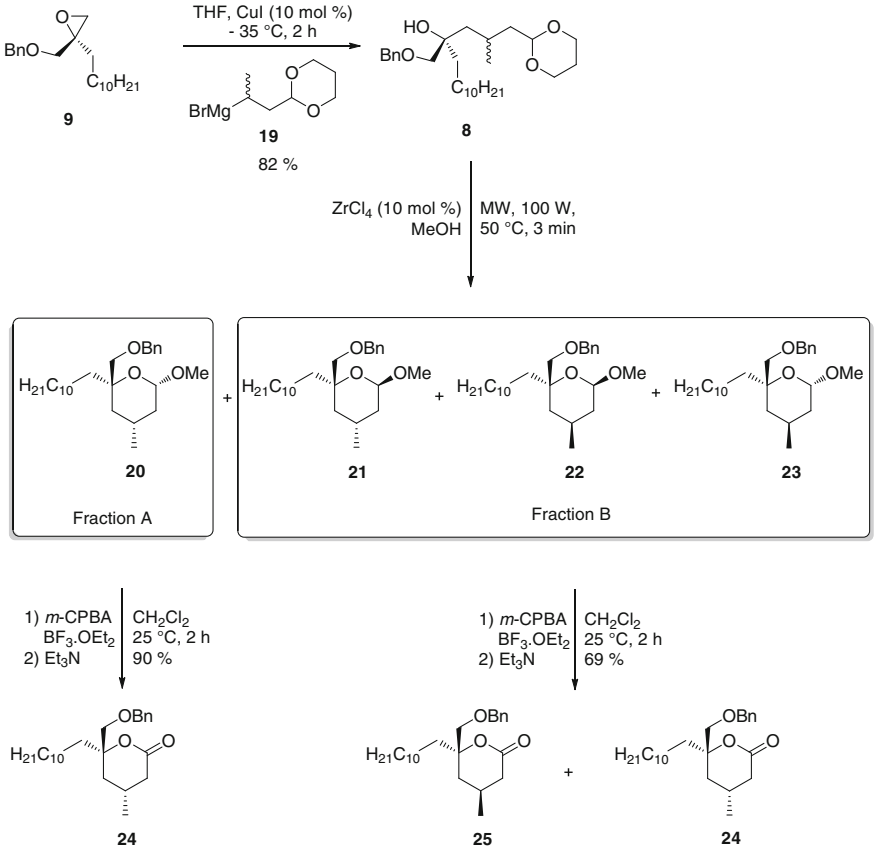


Scheme 2.2 Synthesis of Grignard precursor and protected epoxide

epoxide **17** in a 79 % yield and 95 % *ee*. The primary hydroxy group of epoxide **18** was protected as the benzyl ether **9**,[8c] and this was successfully ring-opened with the Grignard derivative of 2-(2-bromopropyl)-1, 3-dioxane **10**, transmetallated with CuI (10 mol%) to afford tertiary alcohol **8** in 82 % yield (Scheme 2.3) [30]. Grignard precursor **10** was formed via 1, 3-dioxane protection and in situ bromination of crotonaldehyde **12** using propane-1, 3-diol and TMSBr, respectively, in 85 % yield [3].

At this point we were ready to carry out the key step in the synthesis, the $ZrCl_4$-catalysed deprotection/cyclisation reaction. This reaction was carried out, as before in the synthesis of analogues **5** and **6**, to yield two fractions by TLC analysis (Fractions A and B), separable by column chromatography. These fractions were believed to be the mixtures of diastereomers **20/21** and **22/23**. Following lactonisation of the first fraction, we obtained the desired lactone **24**, whereas lactonisation of the second product led only to a 3:1 mixture of **25**:**24** (Scheme 2.3).

Following this unexpected setback, we attempted to separate the diastereomeric mixture prior to the acetalisation step, which was successfully achieved to obtain alcohols **26** and **27** (Scheme 2.4). Subsequent $ZrCl_4$-catalysed acetalisation of **26** showed 2 spots on TLC analysis, as was observed in the epimeric mixture, whereas acetalisation of **27** showed only one spot on TLC. As a result we were able to conclude that one of the undesired diastereomers was co-eluting during our earlier separation of the epimeric cyclisation mixture (Scheme 2.3). Based on nuclear Overhauser effect (NOE) NMR experiments, we can conclude that we originally

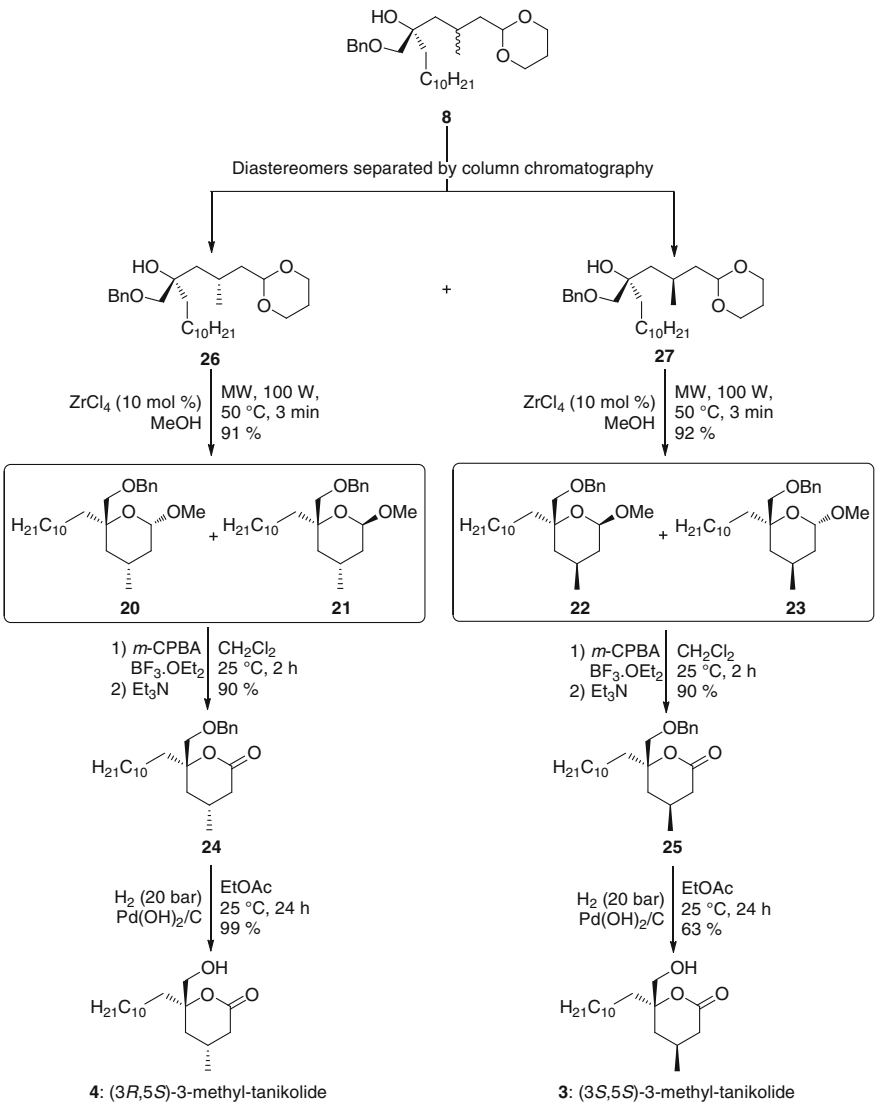


Scheme 2.3 Initial cyclisation and attempted separation of diastereomers

purified diastereomer **20**, (Fraction A, Scheme 2.3). As a result, the second column fraction (Fraction B, Scheme 2.3) contained a mixture of **22** and **23**, as expected, along with the undesired diastereomer **21**. As a consequence, this led to the mixture of diastereomers after the lactonisation step.

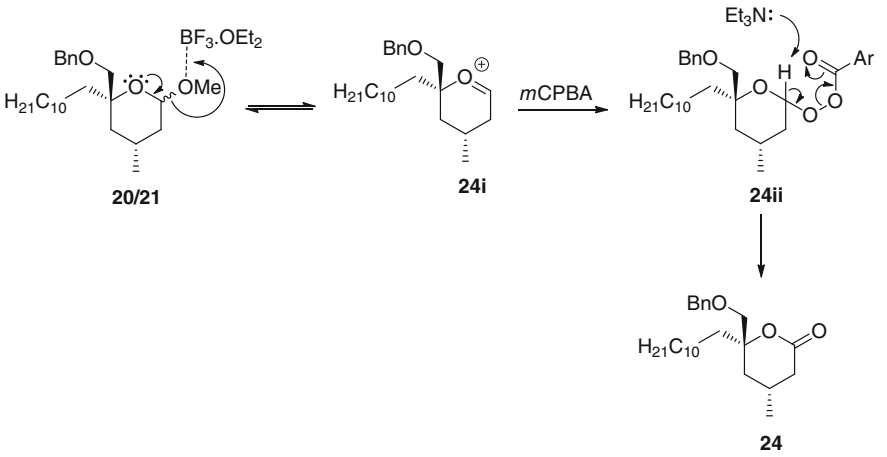
The synthesis was concluded with successful lactonisation of the mixture of **20/21** using *m*-CPBA in the presence of $BF_3.OEt_2$ followed by stirring in Et_3N to form the lactone **24** 91 % yield (Scheme 2.4). Previously, the application of this method, reported by Grieco and co-workers, on protected δ-lactols, i.e. **20/21** gave low yields of the corresponding δ-lactones [53]. A subsequent report by Masaki and co-workers found the addition of Et_3N was necessary after initial oxidation to convert the unstable hemiacetal *m*-chloroperbenzoate (**24ii**) to the δ-lactone [54] (Scheme 2.5).

Following oxidation, hydrogenolysis of the benzyl group carried out at 20 bar H_2 pressure with $Pd(OH)_2/C$ to give (3*R*,5*S*)-3-methyl-tanikolide **3** in 99 % yield. Similarly, lactonisation of the mixture of **22** and **23** (61 % yield) and deprotection yielded (3*S*, 5*S*)-3-methyl-tanikolide **4**, 63 % yield.



Scheme 2.4 Separation of diastereomers and completion of synthesis

Extensive NOE experiments were carried out on the tanikolide analogues, **5** and **6**, and the set of malyngolide analogues **3** and **4** in order to confirm the relative stereochemistry of each (Fig. 2.3). In the case of analogues **4** and **5**, irradiation of the proton signals at 2.24 ppm (C3) led to a positive response from the signal corresponding to the hydroxymethyl protons centered at δ 3.62 ppm, indicating that the C3 methine proton is on the same side as the hydroxymethyl protons, in both



Scheme 2.5 Proposed mechanism for oxidation of protected δ-lactol to δ-lactone

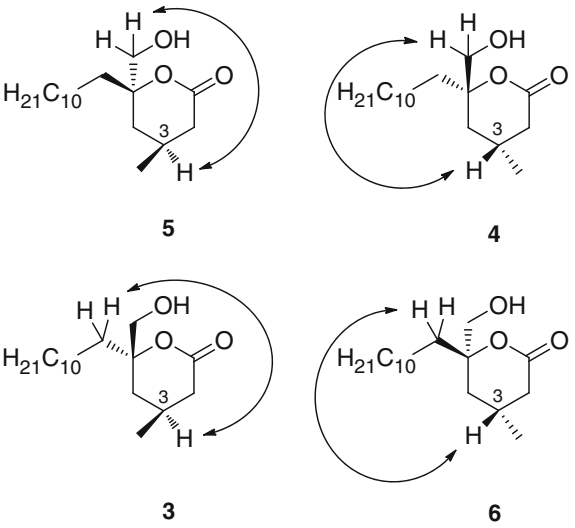
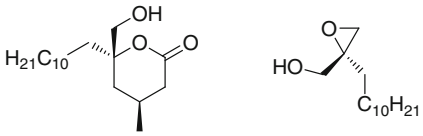


Fig. 2.3 Confirmation of relative configuration of stereocentres

cases. Similarly, irradiation of the hydroxymethyl proton signal at δ 3.62 ppm led to enhancement of the C3 methine proton at δ 2.24 ppm. For the other analogues, **3** and **6**, with the opposite relative stereochemistry to analogues **5** and **4**, irradiation of the C3 methine proton at δ 2.08 ppm showed no response to the hydroxymethyl protons at δ 3.45 and 3.68 ppm, respectively. However, a small positive interaction was observed for one of the protons α-to the quaternary centre on the *n*-undecyl chain [18].



3: (3*S*,5*S*)-3-methyl-tanikolide **18**

Fig. 2.4 Compounds with bioactivity against MRSA

2.3 Biological Testing

The set of β-methyl substituted analogues and a number of intermediates were submitted for biological testing to ascertain if they had any antifungal and antimicrobial activity. The compounds were tested against *Candida albicans* and *Candida parapsilosis*. Unfortunately the compounds did not show any inhibition of growth even at concentrations as high as 800 μg/mL. The series of compounds were also tested for activity against gram-positive and gram-negative bacterial strains, Methicillin-Resistant *Staphylococcus aureus* (MRSA) and *Escherichia coli*. Although the compounds tested showed no activity against *E. coli*, two of the compounds showed activity against the two MRSA strains tested (Fig. 2.4).

One compound, **4** showed excellent activity with an MIC of 12.5 μg/mL. This compound contains the same absolute configuration at the quaternary carbon centre as marine antibiotic (−)-malyngolide (**2**). The configuration of the methyl group in the β-position is opposite to the configuration of the α-methyl group in the natural product. Surprisingly, the other analogue with the (−)-malyngolide configuration did not show any activity. The only other compound which showed activity was epoxide, **18**, with an MIC of 25 μg/mL. Both compounds were shown to be stable for the duration of the assay.

2.4 Conclusions

In summary, we have described the completion of a concise asymmetric synthesis of β-methyl substituted analogues of the marine antifungal (+)-tanikolide and the marine antibiotic (−)-malyngolide. The final pair of β-methyl analogues, comprising of the same configuration of (−)-malyngolide at the quaternary chiral centre, were successfully synthesised by utilizing the $ZrCl_4$-catalysed deprotection/cyclisation as the key transformation in the synthesis. Other key steps involved were Sharpless asymmetric epoxidation and Cu-catalysed epoxide ring-opening with a Grignard reagent. All of the analogues were submitted for biological testing and although none of the analogues displayed any bioactivity against *C. albicans*, one of the analogues showed very promising bioactivity against MRSA with an MIC of 12.5 μg/mL (Tables 2.1 and 2.2).

Table 2.1 UCD Centre for Food Safety strains used for determination of antibacterial activity

	Strain	Type	Hospital/Isolation	Source	ARP (Resistant to)
Gram-negative	*E. coli* 25922	Reference	FDA strain Seattle 1946 [DSM 1103, NCIB 12210]	–	PEN; VAN; AMP; CLI; CL
	E. coli 4	Clinical isolate	UCD Veterinary Hospital	Bovine	AMC; AMP; C; CIP; F; Fc; Gm; N; NAL; S; Su; TET; TMP
Gram-positive	MRSA ATCC 43300	Reference	Kansas	Human	AMP; PEN; OXA; MET; AXO; CIP; LEVO; GAT; ERY; CLI
	MRSA 06/04	Clinical isolate	–	Human	AMP; PEN; OXA; MET; AXO; CIP; LEVO; GAT; ERY

MRSA Methicillin-Resistant *Staphylococcus aureus*; *ARP* Antibiotic Resistance Profile; *AMC* Amoxicillin-Clavulanic acid; C-Chloramphenicol; *F* Furazolidone; *Fc* Florfenicol *Gm* Gentamycin; *N* Neomycin; *NAL* Nalidixic acid; *S* Streptomycin; *Su* Sulfonamides; *TET* Tetracycline; *TMP* Trimetoprim; *AMP* ampicillin; *PEN* penicillin; *OXA* oxacillin; *MET* methicillin; *AXO* ceftriaxone; *CIP* ciprofloxacin; *LEVO* levofloxacin; *GAT* gatifloxacin; *ERY* erythromycin; *CLI* clindamycin; *CL* Cephalexin

Table 2.2 Determination of antibacterial activity—MIC and MBC results (Triplicates)

Compounds	MIC/MBC (mg/L)							
	E. coli ATCC 25922		*E. coli* 4		MRSA ATCC 43300		MRSA 06/04	
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
6	>100	>100	>100	>100	>100	>100	>100**	>100
5	>100	>100	>100	>100	>100	>100	>100**	>100
4	>100	>100	>100	>100	>100	>100	>100**	>100
3	>100	>100	>100	>100	**12.5**	**12.5**	**12.5**	**50**
26	>100	>100	>100	>100	>100	>100	>100	>100
27	>100	>100	>100	>100	>100	>100	>100	>100
22/23	>100	>100	>100	>100	>100	>100	>100	>100
25	>100	>100	>100	>100	>100	>100	>100	>100
24	>100	>100	>100	>100	>100	>100	>100	>100
18	>100	>100	>100	>100	**25**	**25**	**25**	**50**
20	>100	>100	>100	>100	>100	>100	>100	>100

Note * Decreased growth and altered phenotype; ** Change in the strain phenotype; **Bold**—compounds that showed activity against the tested strains

- The maximum concentration of compounds tested was 100 mg/L

2.5 Experimental Section

2.5.1 General Experimental for All Chapters

2.5.1.1 Materials and Methods

Unless otherwise noted, reactions were performed with rigorous exclusion of air and moisture, under an inert atmosphere of nitrogen in flame-dried glassware with magnetic stirring. N_2-flushed stainless steel cannulas or plastic syringes were used to transfer air- and moisture-sensitive reagents. All reagents were obtained from commercial sources and used without further purification unless otherwise stated. Anhydrous tetrahydrofuran (THF), diethyl ether and dichloromethane were obtained from a PureSolv-300-3-MD dry solvent dispenser. All other anhydrous solvents were obtained from commercial sources and used as received. For stated reactions THF was freshly distilled under N_2 from sodium/benzophenone ketyl. Anhydrous 1,4-dioxane was purchased from Sigma Aldrich and dried over molecular sieves (3Å beads, 20 g/100 mL for 3 d). $Pd(OAc)_2$ was purchased from Strem. Powdered activated 4 Å molecular sieves were purchased from Sigma Aldrich and were stored in a desiccator. Tris(dibenzylideneacetone)dipalladium(0) chloroform adduct was prepared via the method of Zalesskiy et al. [55]. Allyl cyanoformate was prepared via a previously reported method [56]. Magnesium turnings were activated at 80 °C under high vacuum for 1 h prior to use. *In vacuo* refers to the evaporation of solvent under reduced pressure on a rotary evaporator. Thin-layer chromatography (TLC) was performed on aluminium plates pre-coated with silica gel F254. They were visualised with UV-light (254 nm) fluorescence quenching, or by charring with an acidic vanillin solution (vanillin, H_2SO_4 in ethanol). Flash column chromatography was carried out using 40–63 μm, 230–400 mesh silica gel.

2.5.1.2 Microwave Irradiation Experiments

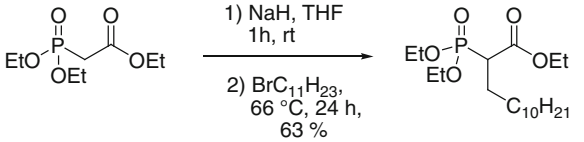
All microwave experiments were performed using the CEM Discover Synthesizer possessing a single-mode microwave cavity producing controlled irradiation at 2.45 GHz. Experiments were carried out in standard microwave process Pyrex vials (capacity 10 mL) using the high-absorbance level. Reaction time reflects time at the set reaction temperature maintained by cycling of irradiation.

2.5.1.3 Instrumentation

^{1}H NMR spectra were recorded on a 300, 400, 500 or 600 MHz spectrometer. ^{13}C NMR spectra were recorded a 400, 500 or 600 MHz spectrometer at 101, 126 or 151 MHz. Chemical shifts (δ) are reported in parts per million (ppm) downfield

from tetramethylsilane and are referenced to residual proton in the NMR solvent ($CDCl_3$ = δ 7.26 ppm, $(CD_3)_2CO$ = δ 2.05 ppm). ^{13}C-NMR are referenced to the residual solvent peak ($CDCl_3$ = δ 77.16 ppm, $(CD_3)_2CO$ = δ 206.26 ppm). All ^{13}C spectra are ^{1}H decoupled. NMR data are represented as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, m = multiplet, app. dd = apparent doublet of doublets, app. t = apparent triplet), coupling constant (*J*) in Hertz (Hz), integration. High resolution mass spectra [electrospray ionisation (ESI-TOF)] (HRMS) were measured on a micromass LCT orthogonal time-of-flight mass spectrometer with leucine enkephalin (Tyr-Gly-Phe-Leu) as an internal lock mass. Infrared spectra were recorded on a Varian 3100 FT-IR spectrometer and are reported in terms wavenumbers (ν_{max}) with units of reciprocal centimetres (cm^{-1}). Optical rotation (α) values were measured at room temperature and specific rotation ($[\alpha]_D^{20}$) values are given in degrees (°). Melting points were determined in open capillary tubes. High-performance liquid chromatography (HPLC) was performed on an Agilent 1200 series instrument. Supercritical fluid chromatography (SFC) was performed on a Waters UPC^2 using a Chiralcel-IA3, IB3, IC3 or ID3 column.

Ethyl 2-(diethoxyphosphoryl)tridecanoate (15)

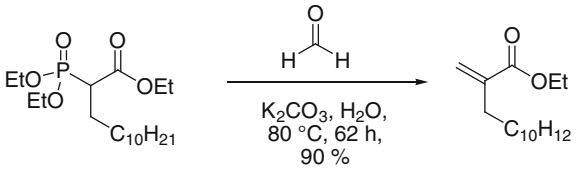


16 **15**

NaH (60 % in mineral oil, 3.0 g, 75.0 mmol) was placed in a dry 250 mL two-neck round bottom flask containing a magnetic stirring bar under inert atmosphere and washed with anhydrous hexanes (2 × 10 mL) and dried under high vacuum. Dry THF (150 mL) was added to the reaction flask and ethyl–2-(diethoxyphosphoryl) acetate **16** (10.1 mL, 50.8 mmol) in dry THF (20 mL) was added drop-wise over 20 min to the reaction mixture with H_2 gas being evolved. 1-Bromoundecane (5.6 mL, 25 mmol) was added dropwise and the reaction mixture refluxed for 24 h. The reaction mixture was quenched with H_2O (50 mL) and aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with H_2O (50 mL), brine (50 mL) and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the crude product was purified by silica gel column chromatography (pentane/ethyl acetate, 5:1) to yield ethyl 2-(diethoxyphosphoryl)tridecanoate **15** as a colourless oil (5.963 g, 63 %).

R_f = 0.36 (pentane/ethyl acetate, 3:1). IR (neat): ν_{max} = 3489, 2926, 2361, 1736, 1467, 1257, 1027 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.30–4.08 (m, 6H), 2.92 (ddd, *J* = 22.5, 11.1, 3.8, 1H), 2.07–1.90 (m, 1H), 1.81 (m, 1H), 1.47–1.17 (m, 27H), 0.88 (t, *J* = 6.9, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.3, 169.2, 62.53 (app. t (dd), $^{2}J_{C\text{-}P}$ = 7.0 Hz, 2C), 45.85 (d, $^{1}J_{C\text{-}P}$ = 131.1 Hz, 1C), 31.8, 29.5, 29.3, 29.0, 28.4, 28.3, 26.9, 22.6, 16.4, 16.3, 14.1, 14.0; HRMS (ESI-TOF): calcd. for $C_{19}H_{39}O_5P$ $[M]^+$ 378.2535, found 378.2547.

Ethyl 2-methylenetridecanoate (14)

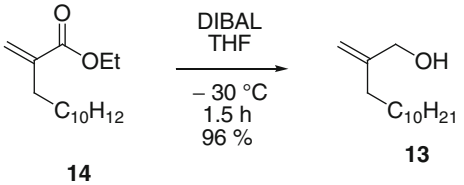


15 **14**

Phosphonate ester **15** (7.482 g, 19.77 mmol) was placed in a 250 mL round bottom flask and deionised water (55 mL) was added along with potassium carbonate (5.464 g, 39.54 mmol) followed by aqueous formaldehyde (5.93 mL, 79.07 mmol). The reaction mixture was stirred at 80 °C for 48 h. A further addition of aqueous formaldehyde (5.93 mL, 79.07 mmol) and potassium carbonate (5.464 g) was made to drive the reaction to completion, as judged by ^{1}H-NMR analysis. The reaction was extracted with diethyl ether (2 × 150 mL) and the combined organic layers were washed with H_2O (75 mL), brine (75 mL) and dried over anhydrous Na_2SO_4. Excess solvent was removed *in vacuo* and the crude product was purified by silica gel column chromatography (pentane/ethyl acetate, 9:1) to yield **14** as a colourless oil (4.550 g, 90 %).

R_f = 0.87 (pentane/ethyl acetate, 4:1). IR (neat): ν_{max} = 2925, 2854, 1455, 1102, 1054 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.12 (d, *J* = 1.5, 1H), 5.50 (d, *J* = 1.5, 1H), 4.20 (q, *J* = 7.1, 2H), 2.29 (dd, *J* = 11.2, 4.1, 2H), 1.46 (m, 2H), 1.38–1.16 (m, 18H), 0.88 (t, *J* = 6.9, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.4, 141.2, 124.0, 60.5, 31.9, 31.8, 29.6, 29.6, 29.6, 29.4, 29.3, 29.2, 28.4, 22.7, 14.2, 14.1. HRMS (ESI-TOF): calcd. for $C_{16}H_{30}O_2$ $[M]^+$ 254.2236, found 254.2246.

2-Methylenetridecan-1-ol (13)



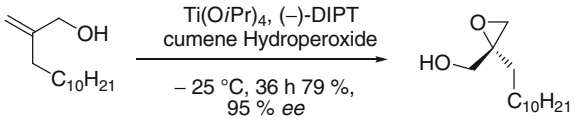
14 **13**

Ethyl 2-methylenetridecanoate **14** (4.535 g, 17.83 mmol) was dissolved in dry THF (50 mL) under inert atmosphere in a dry 100 mL round bottom flask. The reaction mixture was cooled to −30 °C and DIBAL (26.4 mL, 25 wt% in toluene, 39.23 mmol) was added drop-wise over 40 min and the reaction mixture was stirred for 1 h. The reaction mixture was quenched with diethyl ether (5 mL) and a saturated solution of Rochelle's salt (potassium sodium tartrate) (50 mL). The reaction mixture was stirred for 14 h at room temperature. The product was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with H_2O (100 mL), brine (100 mL) and dried over anhydrous Na_2SO_4.

The product was concentrated and purified by silica gel column chromatography (pentane/ethyl acetate, 9:1) to yield alcohol **13** as a colourless oil (3.635 g, 96 %).

R_f = 0.20 (pentane/ethyl acetate, 9:1). IR (neat): ν_{max} = 3326, 2925, 2854, 1655, 1469, 1028 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.07–4.95 (m, 1H), 4.86 (dd, *J* = 2.5, 1.1, 1H), 4.07 (br s, 2H), 2.05 (t, *J* = 8.0, 2H), 1.43 (dd, *J* = 14.8, 7.2, 2H), 1.28 (m, 16H), 0.98–0.82 (t, *J* = 8.0, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.3, 108.9, 65.9, 33.0, 31.9, 29.6, 29.5, 29.4, 29.3, 27.8, 22.7, 14.1. HRMS (ESI-TOF): calcd. for $C_{14}H_{28}O$ $[M]^+$ 212.2140, found 212.2138.

(*S*)-(2-Undecyloxiran-2-yl)methanol (18)

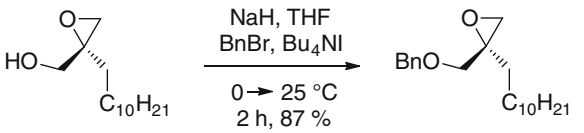


13 **18**

Powdered molecular sieves (4 Å, 0.750 g) and dry CH_2Cl_2 (20 mL) were taken in a 2-neck 50 ml RBF, followed by addition of $Ti(OiPr)_4$ (0.23 mL, 0.76 mmol) and (−)-diisopropyltartrate (0.24 mL, 1.13 mmol) at −35 °C under nitrogen and stirred for 30 min. Alcohol **13** was added (1.605 g, 7.56 mmol) and stirred for 30 min. Cumene hydroperoxide (1.68 mL, 11.34 mmol) was added over 20 min and the reaction temperature was increased to −25 °C. The reaction was complete in 21 h then quenched with saturated sodium sulfate (0.7 mL) and Et_2O (5 mL) and the resulting mixture was stirred for 2 h at rt. The reaction mixture was filtered through the pad of Celite® and concentrated *in vacuo*. The epoxide was purified by silica gel column chromatography (pentane/ethyl acetate, 4:1) to yield epoxide **18** as colourless oil (1.362 g, 79, 95 % *ee*). [The ee value was determined by HPLC analysis of benzyl protected epoxide **9** on an Agilent 1200 series instrument with a Chiracel OJH column using heptane/ethanol, 99.9:0.01 at a flow rate of 0.5 ml/min.

R_f = 0.67 (pentane/ethyl acetate, 4:1). $[\alpha]_D^{20}$ = 13.2 (*c* 1.0, CH_2Cl_2). IR (neat): ν_{max} = 3424, 2925, 2854, 1467, 1048 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.77 (dd, *J* = 12.2, 4.2 Hz, 1H), 3.64 (dd, *J* = 12.2, 8.5 Hz, 1H), 2.88 (d, *J* = 4.7 Hz, 1H), 2.66 (d, *J* = 4.7 Hz, 1H), 1.84–1.71 (m, 1H), 1.64 (dd, *J* = 8.5, 4.4 Hz, 1H), 1.59–1.45 (m, 1H), 1.42–1.20 (m, 18H), 0.88 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 62.8, 59.9, 49.8, 31.9, 31.9, 29.7, 29.6, 29.6, 29.5, 29.5, 29.3, 24.6, 22.6, 14.1. HRMS (ESI-TOF): calcd. for $C_{14}H_{26}O$ $[M—H_2O]^+$ 210.1984, found 210.1990.

(*S*)-2-((Benzyloxy)methyl)-2-undecyloxirane (9)

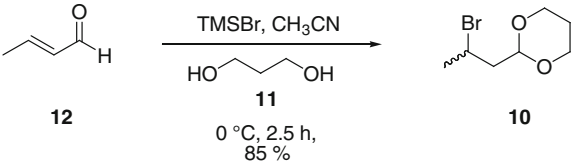


18 **9**

NaH (0.284 g, 7.10 mmol, 60 % dispersion in mineral oil) was washed with anhydrous hexanes (2 × 2.5 mL) and dried under high vacuum. Dry THF (22 mL) was added and the solution was cooled to 0 °C prior to the dropwise addition of epoxide **18** (1.355 g, 5.93 mmol) in THF (2 mL). The reaction was stirred for 30 min and benzyl bromide (0.78 mL, 5.79 mmol) was added dropwise followed by tetra-*n*-butylammonium bromide (1.096 g, 2.98 mmol). The reaction was stirred at 0 °C for 5 min and for a further 2 h at room temperature. The reaction was quenched with H_2O (2.5 mL) followed by Et_2O (5 mL). The aqueous layer was extracted with Et_2O (2 × 40 mL) and the combined organic layers were washed with water (50 mL), brine (50 mL) and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography (pentane/CH_2Cl_2, 1:1) to yield **9** as a very pale yellow oil (1.643 g, 87 %).

R_f = 0.83 (pentane/ethyl acetate, 4:1). $[\alpha]_D^{20} = -3.8$ (*c* 1.0, CH_2Cl_2). IR (neat): ν_{max} = 2925, 2854, 1467, 1098 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–7.24 (m, 5H), 4.56 (q, *J* = 12.0 Hz, 2H), 3.60 (d, *J* = 11.1 Hz, 1H), 3.47 (d, *J* = 11.1 Hz, 1H), 2.70 (d, *J* = 4.9 Hz, 1H), 2.63 (d, *J* = 4.8 Hz, 1H), 1.87–1.74 (m, 1H), 1.62–1.49 (m, 1H), 1.42–1.20 (m, 18H), 0.88 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.1, 128.4, 127.7, 127.6, 73.2, 71.9, 58.6, 50.3, 32.0, 31.9, 29.7, 29.6, 29.6, 29.5, 29.5, 29.3, 24.7, 22.7, 14.1. HRMS (ESI-TOF): calcd. for $C_{21}H_{34}O_2Na$ $[M + Na]^+$ 341.2457, found 341.2443.

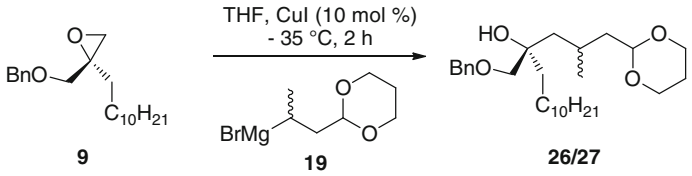
2-(2-Bromopropyl)-1,3-dioxane (10)



Anhydrous acetonitrile (50 ml) was added to a 250 ml round bottom flask under nitrogen and cooled to 0 °C. Crotonaldehyde (4.14 ml, 50.0 mmol) was added followed by the dropwise addition of TMSBr (4.50 ml, 60.0 mmol) and the reaction mixture was stirred for 5 min prior to the dropwise addition of propane-1, 3-diol (9.18 ml, 60.0 mmol). The reaction mixture was stirred for 2.5 h at 0 °C then allowed to warm to room temperature and quenched into a solution of pentane (150 ml) and Na_2CO_3 (50 ml, 10 % solution). The solution was stirred for 5 min and added to a separating funnel. Three layers were observed, top = pentane + product, middle = CH_3CN + product and bottom = aqueous. The aqueous layer was run off and extracted with pentane (10 ml) and sodium thiosulfate (50 ml, 10 % w/v). The organic fractions were combined, washed with water (3 × 60 ml) and dried over anhydrous Na_2SO_4. Excess pentane was removed under moderate vacuum (≈850 mbar, 40 °C) and the remaining yellow solution was purified by high vacuum distillation (bath temperature 120 °C, neck temperature 86 °C) and silica gel column chromatography (pentane/ethyl acetate, 9:1) to yield bromide **10** as a colourless liquid (8.905 g, 85 %).

R_f = 0.83 (pentane/ethyl acetate, 9:1). IR (neat): ν_{max} = 2966, 2856, 1379, 1339 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.74 (dd, *J* = 7.1, 3.5 Hz, 1H), 4.29–4.19 (m, 1H), 4.15–4.05 (m, 2H), 3.84–3.75 (m, 2H), 2.16–1.97 (m, 3H), 1.72 (d, *J* = 6.8 Hz, 3H), 1.39–1.32 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 100.7, 66.9, 66.9, 46.1, 45.6, 26.8, 25.8. HRMS (ESI-TOF): calcd. for $C_7H_{13}O_2^{79}Br$ $[M]^+$ 208.0099 and $C_7H_{13}O_2^{81}Br$ $[M]^+$ 210.0078, found 208.0099 and 210.0079, respectively.

(2*R*,4*S*)-4-((Benzyloxy)methyl)-1-(1,3-dioxan-2-yl)-2-methylpentadecan-4-ol (26) and (2*S*,4*S*)-4-((benzyloxy)methyl)-1-(1,3-dioxan-2-yl)-2-methylpentadecan-4-ol (27)



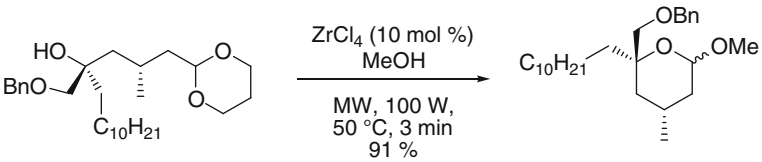
Mg turnings (215 mg, 2.92 mmol) were activated at 80 °C for 1 h under vacuum in a dry 25 mL two-neck round bottom flask. Dry THF (10 mL) was added under N_2 followed by an I_2 crystal and subsequent dropwise addition of 2-(2-bromopropyl)-1, 3-dioxane (1.851 g, 8.77 mmol) with gentle heating to initiate Grignard formation. The reaction was refluxed for 1 h to complete Grignard formation, then cooled and transferred, using a cannula, to a pre-cooled two-neck round bottom flask at – 45 °C containing copper iodide (0.056 g, 0.29 mmol). The solution was stirred for 30 min prior to the dropwise addition of protected epoxide **9** (0.931 g, 2.92 mmol) in THF (3 mL) over 50 min. The reaction was stirred for 2 h and then quenched with ≈0.3 g NH_4Cl and saturated NH_4Cl solution (5 mL). The aqueous layer was extracted with ethyl acetate (6 × 30 mL) and the combined organic layers were washed with water (50 mL), brine (50 mL) and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the residue purified by silica gel column chromatography (pentane/ethyl acetate, 2:1) to yield **26** and **27** as a mixture (1.065 g, 82 % yield) of colourless oils. Subsequent silica gel column chromatography was carried out on 803 mg to yield **26** as a colourless oil (0.233 g, 29 %) and **27** as a colourless oil (0.227 g, 28 %) and a mixture (0.320 g, 43 %).

Spectroscopic analysis of 26: R_f = 0.58 (pentane/ethyl acetate, 4:1). IR (neat): ν_{max} = 3486, 2925, 2853, 1455, 1143, 1100 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37–7.25 (m, 5H), 4.59–4.48 (m, 3H), 4.08 (dd, *J* = 11.7, 4.2 Hz, 2H), 3.72 (td, *J* = 12.2, 2.4 Hz, 2H), 3.32 (q, *J* = 9.0 Hz, 2H), 2.41 (s, 1H), 2.13–1.99 (m, 1H), 1.92–1.80 (m, 1H), 1.68–1.59 (m, 2H), 1.56–1.20 (m, 23H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.3, 128.3, 127.6, 127.6, 101.4, 75.7, 74.3, 73.4, 66.8, 66.8, 43.7, 43.3, 37.5, 31.9, 30.3, 29.7, 29.6,

29.6, 29.3, 25.8, 24.0, 23.6, 22.7, 22.6, 14.1. HRMS (ESI-TOF): calcd. for $C_{28}H_{48}O_4Na$ $[M + Na]^+$ 471.3450, found 471.3460.

Spectroscopic analysis of 27: R_f = 0.58 (pentane/ethyl acetate, 4:1). IR (neat): ν_{max} = 3486, 2925, 2853, 1455, 1143, 1100 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37–7.24 (m, 4H), 4.60–4.49 (m, 3H), 4.07 (dd, *J* = 6.1, 4.7 Hz, 2H), 3.77–3.66 (m, 2H), 3.33 (q, *J* = 9.0 Hz, 2H), 2.41 (s, 1H), 2.13–1.99 (m, 1H), 1.92–1.81 (m, 1H), 1.74–1.65 (m, 1H), 1.61–1.20 (m, 24H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.4, 128.3, 127.6, 127.5, 101.4, 75.9, 74.3, 73.4, 66.8, 66.8, 43.6, 43.5, 37.4, 31.9, 30.3, 29.7, 29.6, 29.3, 25.8, 24.1, 23.6, 22.7, 22.7, 14.1. HRMS (ESI-TOF): calcd. for $C_{28}H_{48}O_4Na$ $[M + Na]^+$ 471.3450, found 471.3453.

(2*S*,4*R*)-2-((Benzyloxy)methyl)-6-methoxy-4-methyl-2-undecyltetrahydro-2H-pyran (20/21)

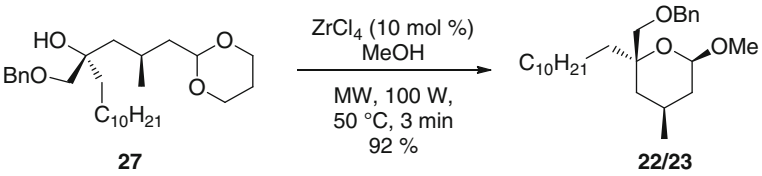


26 **20/21**

Dioxane **26** (0.203 g, 0.452 mmol) and $ZrCl_4$ (0.011 g, 0.047 mmol) were dissolved in anhydrous methanol (0.50 mL) and stirred under microwave irradiation at 50 °C, @ 100 W for 6 min. The crude product was purified directly by silica gel column chromatography (pentane/ethyl acetate, 9:1) to yield **20** and **21** as a mixture (0.167 g, 91 %) of colourless oils.

R_f (**20**) = 0.89 (pentane/ethyl acetate, 9:1). R_f (**21**) = 0.80 (pentane/ethyl acetate, 9:1). IR (neat): ν_{max} = 2925, 2854, 1455, 1100, 1054 cm^{-1}. $[\alpha]_D^{20} = -46.4$ (*c* 1.0, CH_2Cl_2). ^1H NMR (**20**) (500 MHz, $CDCl_3$): δ 7.40–7.20 (m, 5H), 4.73 (d, *J* = 3.5 Hz, 1H), 4.55 (d, *J* = 12.2 Hz, 1H), 4.46 (d, *J* = 12.2 Hz, 1H), 3.70 (d, *J* = 9.0 Hz, 1H), 3.52 (d, *J* = 9.0 Hz, 1H), 3.36 (s, 3H), 1.99–1.87 (m, 1H), 1.79 (d, *J* = 13.4 Hz, 1H), 1.73–1.67 (m, 1H), 1.63–1.49 (m, 2H), 1.37–1.15 (m, 19H), 0.98 (t, *J* = 12.9 Hz, 1H), 0.90–0.84 (m, 6H). ^{13}C NMR (**20**) (126 MHz, $CDCl_3$): δ 138.8, 128.2, 127.4, 127.4, 99.5, 76.2, 73.2, 72.6, 55.3, 39.8, 39.2, 38.7, 31.9, 30.3, 29.7, 29.7, 29.7, 29.6, 29.4, 22.8, 22.7, 22.4, 20.2, 14.1. HRMS (ESI-TOF) (**20**): calcd. for $C_{26}H_{44}O_3Na$ $[M + Na]^+$ 427.3188, found 427.3187.

(2*S*,4*S*)-2-((Benzyloxy)methyl)-6-methoxy-4-methyl-2-undecyltetrahydro-2H-pyran (22/23)

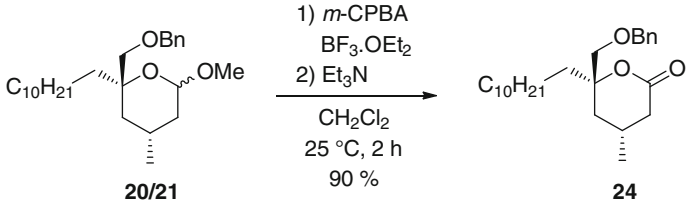


Alcohol (0.219 g, 0.49 mmol) was subjected to the same procedure as for **20/21** using $ZrCl_4$ (11 mg, 0.05 mmol) to yield **22** and **23** as an inseparable mixture (0.197 g, 92 %) of colourless oils.

R_f (**22/23**) = 0.80 (pentane/ethyl acetate, 9:1). IR (neat): ν_{max} = 2925, 2854, 1455, 1102, 1054 cm^{-1}. $[\alpha]_D^{20}$ = −13.4 (*c* 0.8, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.23 (m, 5H), 4.79 (d, J = 3.6 Hz, 1H (minor diastereomer)), 4.61–4.48 (m, 3H), 3.48–3.38 (m, 4H), 3.31–3.24 (m, 1H), 2.11–1.98 (m, 1H), 1.90–1.70 (m, 2H), 1.66–1.47 (m, 2H), 1.43–0.98 (m, 20H), 0.96–0.85 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 138.7 (Ar qC), 128.2, 128.2, 127.6, 127.4, 127.4, 97.7 (O-CHOMe), 77.2 (qC), 76.0 (CH_2OBn), 73.5, 55.8 (OCH_3), 40.3 (O(qC)$CH_2C_{10}H_{21}$), 39.8 (ring CH_2), 31.9, 30.8 (ring CH_2), 30.4, 30.2, 29.7, 29.7, 29.6, 29.3, 25.0 (CH_3CH), 24.4, 22.7, 22.1 (ring CH_3), 14.1 (*n*CH_3) (major diastereomer). ^{13}C NMR (126 MHz, $CDCl_3$): δ 138.7 (Ar qC), 128.2, 128.2, 127.6, 127.4, 127.4, 99.8 (O-CHOMe), 77.2 (qC), 76.4 (CH_2OBn), 73.5, 55.5 (OCH_3), 39.0 (ring CH_2), 38.9 (ring CH_2), 35.2 (O(qC)$CH_2C_{10}H_{21}$), 31.9, 30.4, 30.2, 29.7, 29.7, 29.6, 29.3, 24.4, 22.7, 22.4 (ring CH_3), 19.7 (CH_3CH), 14.1 (minor diastereomer). HRMS (ESI-TOF): calcd. for $C_{26}H_{44}O_3Na$ $[M + Na]^+$ 427.3188, found 427.3183.

(4*R*,6*S*)-6-((Benzyloxy)methyl)-4-methyl-6-undecyltetrahydro-2H-pyran-2-one (24)

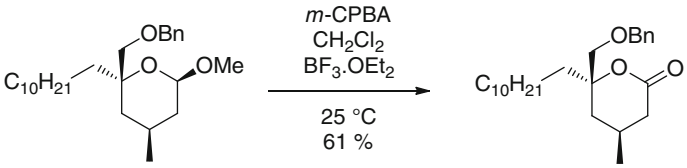


Acetals **20/21** (0.102 g, 0.252 mmol) were dissolved in dichloromethane (12 mL) and cooled to 0 °C. *m*-Chloroperbenzoic acid (0.085 g, <77 %, 0.378 mmol) was added followed by $BF_3 \cdot OEt_2$ (0.047 mL, 0.378 mmol) and the

reaction was stirred at room temperature for 1 h. The reaction mixture was cooled back to 0 °C, Et_3N (0.170 mL, 1.26 mmol) was added slowly and stirred for 1 h. Excess solvent was removed *in vacuo*. The residue was purified by column chromatography (pentane/ethyl acetate, 85:15) to yield **24** (88 mg, 90 %) as a colourless oil [31].

R_f = 0.51 (pentane\ethyl acetate, 85:15). IR (neat): ν_{max} = 2925, 2854, 1739, 1455, 1247, 1092 cm^{-1} $[\alpha]_D^{20}$ = 22.2 (*c* 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.38–7.25 (m, 5H), 4.55–4.47 (m, 2H), 3.44 (s, 2H), 2.57 (ddd, *J* = 17.5, 4.8, 2.1 Hz, 1H), 2.22–2.07 (m, 1H), 2.05–1.97 (m, 1H), 1.88 (dd, *J* = 17.5, 12.1 Hz, 1H), 1.72–1.57 (m, 2H), 1.44–1.19 (m, 19H), 0.96 (d, *J* = 6.4 Hz, 3H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.5, 137.8, 128.4, 127.8, 127.6, 84.6, 73.9, 73.5, 39.2, 38.2, 37.0, 31.9, 29.9, 29.6, 29.6, 29.6, 29.5, 29.3, 23.7, 22.7, 22.7, 21.5, 14.1. HRMS (ESI-TOF): calcd. for $C_{25}H_{40}O_3Na$ $[M + Na]^+$ 411.2875, found 411.2892.

(4*S*,6*S*)-6-((Benzyloxy)methyl)-4-methyl-6-undecyltetrahydro-2H-pyran-2-one (25)

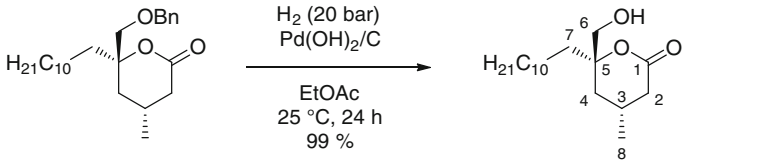


22/23 **25**

Acetals **22/23** as a mixture (0.141 g, 0.348 mmol) were subjected to the procedure described for **24** using *m*-chloroperbenzoic acid (0.117 g, <77 %, 0.522 mmol) and $BF_3{\cdot}OEt_2$ (0.065 mL, 0.527 mmol) to yield **25** (0.082 g, 61 %) as a pale yellow oil.

R_f = 0.51 (pentane/ethyl acetate, 85:15). IR (neat): ν_{max} = 2925, 2854, 1455, 1102, 1054 cm^{-1}. $[\alpha]_D^{20}$ = − 23.6 (*c* 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.37–7.25 (m, 4H), 4.55 (q, *J* = 12.1 Hz, 2H), 3.47–3.41 (m, 2H), 2.60–2.52 (m, 1H), 2.09–1.92 (m, 2H), 1.82–1.75 (m, 1H), 1.73–1.53 (m, 2H), 1.45–1.18 (m, 19H), 1.01 (d, *J* = 6.1 Hz, 2H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.7, 138.0, 128.4, 127.6, 127.6, 85.0, 75.3, 73.6, 38.3, 37.6, 36.4, 31.9, 30.0, 29.6, 29.6, 29.5, 29.4, 29.3, 24.0, 23.3, 22.7, 21.2, 14.1. HRMS (ESI-TOF): calcd. for $C_{25}H_{41}O_3$ $[M + H]^+$ 389.3056, found 389.3061.

(3*R*,5*S*)-3-Methyl-tanikolide (4)

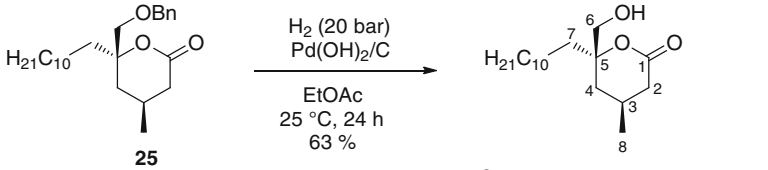


24 **4**: (3*R*,5*S*)-3-methyl-tanikolide

Protected lactone **24** (0.086 g, 0.221 mmol) was dissolved in EtOAc (2 mL) in a 10 mL conical flask. $Pd(OH)_2/C$ (20 wt%) (15.4 mg, 0.022 mmol) was added the flask was placed in a Parr reactor under 20 bar H_2 pressure for 24 h. The reaction mixture was purified directly by silica gel column chromatography (pentane/ethyl acetate, 1:2) to yield **4** (0.065 g, 99 %) as an off-white solid.

R_f = 0.05 (pentane/ethyl acetate, 85:15). IR (neat): ν_{max} = 3426, 2925, 2854, 1710, 1458, 1250, 1072 cm^{-1}. $[\alpha]_D^{20}$ = 34.2 (*c* 1.0, CH_2Cl_2). ^1H NMR (600 MHz, $CDCl_3$): δ 3.65 (dd, *J* = 11.5, 2.8 Hz, 1H, CH_2OH), 3.59 (dd, *J* = 11.5, 5.6 Hz, 1H, CH_2OH), 2.60 (ddd, *J* = 17.4, 4.6, 2.3 Hz, 1H, αCH_a), 2.49 (s, 1H, O*H*), 2.29–2.20 (m, 1H, C*H*), 1.95–1.87 (m, 2H, αCH_b and C(4)H_2), 1.70–1.60 (m, 2H, C(7)H_2), 1.43–1.19 (m, 19H, *n*CH_2), 1.01 (d, *J* = 6.5 Hz, 3H, C(8)H_3), 0.88 (t, *J* = 7.0 Hz, 3H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 171.9 (*C*1), 85.9 (*C*5), 67.9 (*C*6), 38.3 (*C*7), 38.3 (*C*2), 37.0 (*C*4), 31.9, 29.9, 29.6, 29.6, 29.5, 29.5, 29.3, 24.23, 22.9 22.6, 21.5 (*C*8), 14.1 (*C*H_3). HRMS (ESI-TOF): calcd. for $C_{18}H_{34}O_3Na$ $[M + Na]^+$ 321.2406, found 321.2413.

(3*S*,5*S*)-3-Methyl-tanikolide (3)



25 **3**: (3*S*,5*S*)-3-methyl-tanikolide

Protected lactone **25** (0.074 g, 0.190 mmol) was subjected to the same procedure as described for **4** however, required a second addition of catalyst, $Pd(OH)_2/C$ (20 wt%) (13.4 mg, 0.019 mmol), and the reaction was stirred for a further 8 h under 20 bar H_2 pressure. The reaction mixture was purified directly by silica gel column chromatography (pentane/ethyl acetate, 1:2) to yield **3** (0.036 g, 63 %) as a colourless oil. R_f = 0.05 (pentane/ethyl acetate, 85:15). IR (neat): ν_{max} = 3411, 2925, 2854, 1726, 1458, 1249, 1079 cm^{-1}. $[\alpha]_D^{20}$ = − 21.4 (*c* 1.0, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ 3.68 (d, *J* = 11.9 Hz, 1H, CH_2OH), 3.45 (d, *J* = 12.0 Hz, 1H,

CH_2OH), 2.60 (ddd, J = 17.3, 4.5, 2.1 Hz, 1H, αCH_a), 2.42 (s, 1H, OH), 2.15–2.02 (m, 1H, CH), 1.98 (dd, J = 17.3, 12.1 Hz, 1H, αCH_b), 1.78–1.69 (m, 2H, C(4)H_2 and C(7)H_2), 1.65–1.52 (m, 2H, C(4)H_2 and C(7)H_2), 1.44–1.20 (m, 18H), 1.04 (d, J = 6.3 Hz, 3H, C(8)H_3), 0.88 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.8 (*C*1), 86.7 (*C*5), 67.7 (*C*6), 38.0 (*C*2), 36.6 (*C*7), 34.6 (*C*4), 31.9, 30.0, 29.6, 29.6, 29.5, 29.4, 29.3, 23.8, 23.6, 22.6, 21.3 (*C*8), 14.1 (CH_3). HRMS (ESI-TOF): calcd. for $C_{18}H_{34}O_3Na$ $[M + Na]^+$ 321.2406, found 321.2403.

Biological Testing

Antimicrobial Testing

Preparation of compounds. Powders were reconstituted into an appropriate volume of DMSO to achieve a final concentration of 10 mg/mL.

Antibacterial activity testing. Determined using the broth microdilution method. Incubations were performed for 18 h using an Ominolog® automated incubator (Biolog Inc.; 21124 Cabot Boulevard, Hayward, CA 94545, USA).

Results

Antifungal Testing

MIC protocol

Materials needed:

(1) Strains (*C. albicans* and *C. parapsilosis*)
(2) 96 well sterile plates with lids
(3) media [Yeast Dextrose Peptone (YPD)]
(4) Chemical for testing
(5) 15 ml conical tubes

Day 1

(1) Inoculate your overnights of relevant strains (*C. albicans* strain and the *C. parapsilosis* strain CLIB214)

Day 2

(1) Label ten 15 mL conical tubes 1–10. Add 1 mL of media to each tube.
(2) For example: Add another 1 mL of media and 16 μL of the 2 mg/mL stock of analogue to the first tube and mix (this now has a concentration of 16 μg/mL).
(3) Transfer 1 mL from tube 1 to tube 2, mix and transfer 1 ml from tube 2 to tube 3 etc.
(4) Remove 1 mL from tube 10 and dispose, so that all tubes from 1−10 contain 1 mL.
(5) Pipette 100 μL from each tube into each well of the appropriate column (The first tube contains 16 μg/mL of analogue compound but it will be diluted by the inoculum to 8 μg/ml).
(6) Place 100 μL of media in the wells of column 11. Place 200 μL of media into the wells of column 12.

Inoculum preparation

(1) Prepare 1.5 mL of inoculum for each strain/row to be loaded
(2) Dilute your overnight to an OD_{600} of 0.01 or 10^5 cells/mL. [This is then diluted 1/200 (7.5 μL into 1.5 mL of medium)].
(3) Add 100 μL of the diluted inoculum to lanes 1–11 of the prepared plate. This should correspond to 50 cells/well (this may be too little if you do the 1/200 dilution and can be increased)

Incubation and plate reading

(1) Incubate the plate at 30 °C
(2) Visually asses growth at 24 h and 48 h

Results

No growth observed at a concentration of up to 800 μg/mL.

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Chapter 3
Asymmetric Synthesis of Both Enantiomers of a δ-Lactone Analogue of Muricatacin

Abstract The asymmetric synthesis of both enantiomers of the δ-lactone analogue of the anti-tumoral natural product γ-lactone muricatacin has been carried out in a 9-step sequence with overall yields of 17.8 and 11.2 %, respectively. Initial attempts to also synthesise the natural product proved unsuccessful due to the poor reactivity of the Grignard reagent derived from 2-(bromomethyl)-1,3-dioxolane. The designed synthetic route enabled us to increase the ring size to generate the δ-lactone analogue employing Sharpless asymmetric epoxidation and $ZrCl_4$-catalysed intramolecular acetalisation as the key steps.

3.1 Introduction

The γ-lactone natural product muricatacin **1** is a member of the class of biologically active *Annonaceous acetogenin* family. Muricatacin was isolated from the seeds of *Annona muricata L.*, a variety of apple trees grown commercially in the Caribbean and Central America, by McLaughlin and co-workers in 1991 [1, 2]. Muricatacin exists naturally as a mixture of *syn* enantiomers in an approximate ratio of 62:38 (≈24 % *ee*) of (−)-muricatacin (4*R*, 5*R*) versus (+)-muricatacin (4*S*, 5*S*) (Fig. 3.1). These δ-hydroxy-γ-lactones are comprised of adjacent chiral centres, one of which is incorporated into the lactone framework, with a dodecyl alkyl chain extending from the hydroxy bearing carbon atom.

It has been shown to display cytotoxic activity on a number of tumour cell lines: A-549 (lung carcinoma, ED50 = 23.3 μg mL^{-1}), MCF-7 (breast carcinoma, ED50 = 9.8 μg mL^{-1}) and HT-29 (colon carcinoma, ED50 = 14.0 μg mL^{-1}) [1]. As a result of this potent biological activity, a number of total asymmetric syntheses of (+)-muricatacin and/or (−)-muricatacin have been reported employing a variety of approaches including chiral pool [3–25], catalytic asymmetric syntheses [26–38], chiral auxiliary [39–41] and other asymmetric syntheses [42–44]. The various strategies reported include regioselective opening of chiral hydroxy epoxides with a dilithioacetate dianion [27], Sharpless asymmetric dihydroxylation [26, 31, 33, 34,

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36, 38], acetylene-vinylidene rearrangements [5], Lewis acid-catalysed ring-opening of a vinyl epoxide [32], stereoselective addition of a Grignard reagent to a protected α-hydroxy aldehyde [45], α- and α′-C–H bond functionalization of tetrahydrofuran [45], desymmetrisation of dienedioate [19], ring closing metathesis [13], enantioselective 1,2-addition of 2-[(trimethylsilyl)oxy]furan to aldehydes [30] and ruthenium-catalysed cycloisomerization-oxidation of homopropargyl alcohols [37].

The interest in the structure and bioactivity of muricatacin has also led to the synthesis of a number of analogues. The most commonly synthesized analogues are the unnatural diastereomers, known as (+)-*epi*-muricatacin and (−)-*epi*-muricatacin [3, 7, 20, 27, 29, 33, 35, 38, 39]. These were shown to be slightly less active than the *syn* diastereomers of the natural product. The alkyl chain length has also been varied and shown to be critical to the anti-tumoral activity observed [46]. Decreasing the alkyl chain led to a sharp drop-off in activity and increasing the chain length beyond the native chain length also led to a reduction in activity. The synthesis of aza-analogues has also been reported and showed similar activity to the natural product when tested against KB and Vero cell lines [8, 46–49]. To the best of our knowledge, biological testing of any aza-analogue against the tumour cell lines originally tested against the natural product has yet to be disclosed. An 11-methoxy analogue [50] and 7-oxa analogues [16] have also been reported along with heteroannulated mimics [51].

Following the successful application of the $ZrCl_4$-catalysed deprotection/cyclisation protocol in the asymmetric synthesis of the marine natural product (+)-tanikolide along with all four diastereomers of β-methyl analogues of (+)-tanikolide and (−)-malyngolide we were eager to progress this methodology further to the synthesis of both enantiomers of the natural product, muricatacin, a γ-lactone and also more importantly synthesize a δ-lactone analogue (Fig. 3.1). To the best of our knowledge, a six-membered analogue of muricatacin has not been prepared and we believe it important to ascertain any potential effect this structure modification might have on their biological activity.

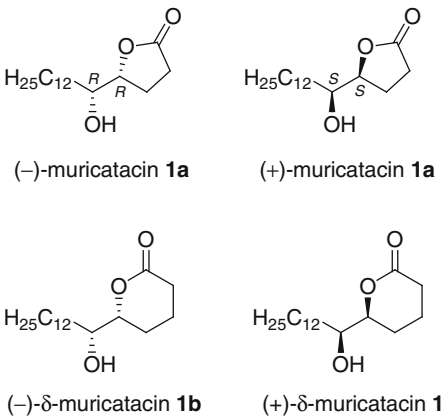
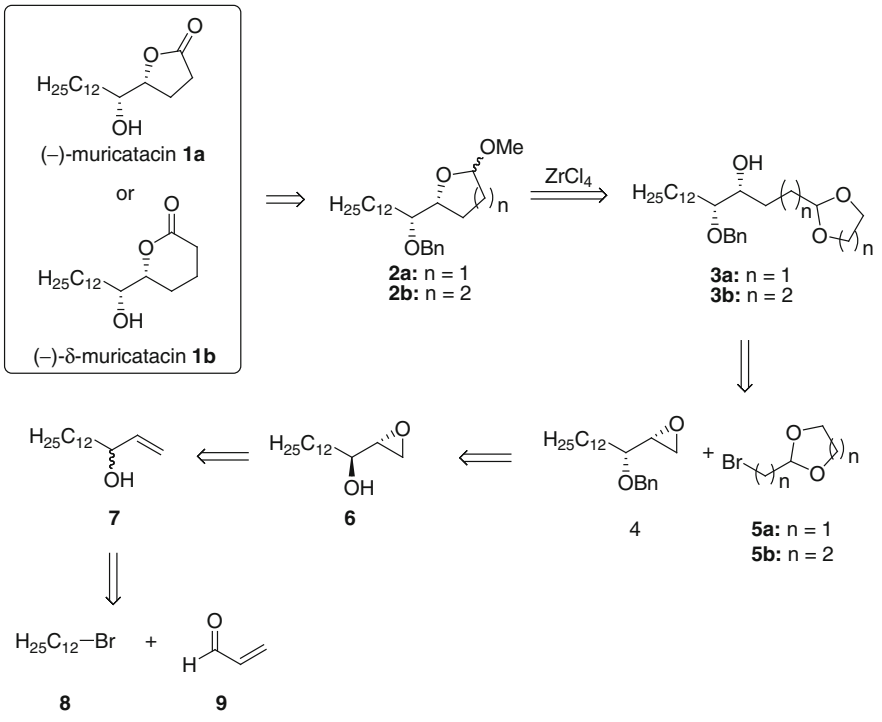


Fig. 3.1 Naturally occurring enantiomers of muricatacin and proposed six-membered muricatacin analogues

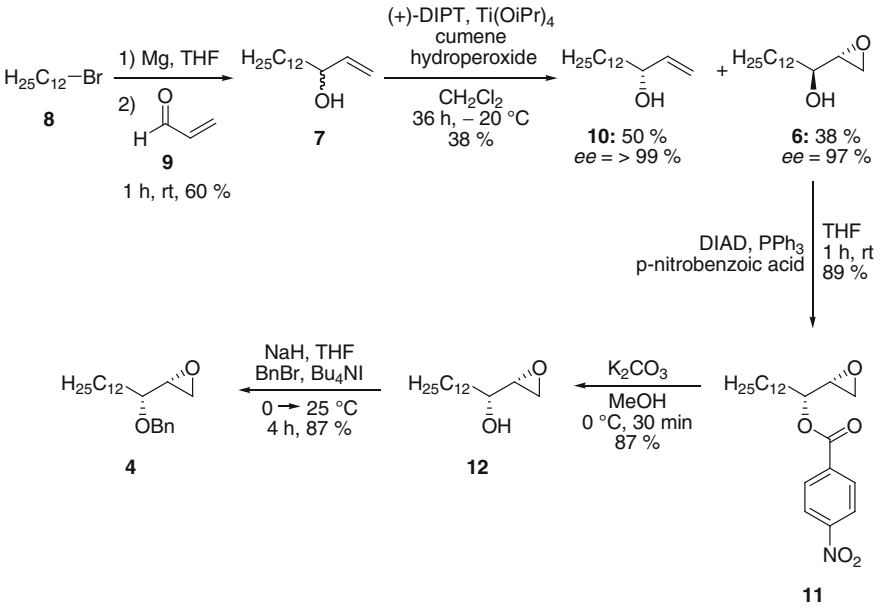
3.2 Results and Discussion

In order to synthesise both the natural product and the six-membered analogue we needed to access both enantiomers of the intermediate epoxide **4** (Scheme 3.1). This intermediate could then be selectively ring-opened with the Grignard derivative of bromo-dioxolane/dioxane **5** in a convergent approach to generate alcohol **3** allowing simple expansion of the lactone ring size [52]. We believed alcohol **3** could successfully be exposed to our $ZrCl_4$-catalysis to generate cyclic acetal **2**, which in turn could be converted into the natural product **1a** and δ-lactone analogue **1b** following oxidation to the lactone before hydrogenolysis of the benzyl group. The key chiral epoxide **4** could be realized via a Mitsonobu inversion of the hydroxy group of **6**, followed by cleavage of the resulting ester and finally protection of the hydroxy group. Epoxide **6** could be formed via a Sharpless asymmetric epoxidation of allylic alcohol **7**, which in turn could be obtained via addition of the Grignard derivative of 1-bromododecane **8** to acrolein **9**.

The first step towards the synthesis of the desired epoxide **4** began with the addition of the Grignard derivative of 1-bromododecane **8** to acrolein **9** to afford racemic allylic alcohol **7** in a moderate yield of 60 % (Scheme 3.2). The next step



Scheme 3.1 Retrosynthetic analysis of (−)-muricatacin (**1a**) and (−)-δ-muricatacin analogue (**1b**)

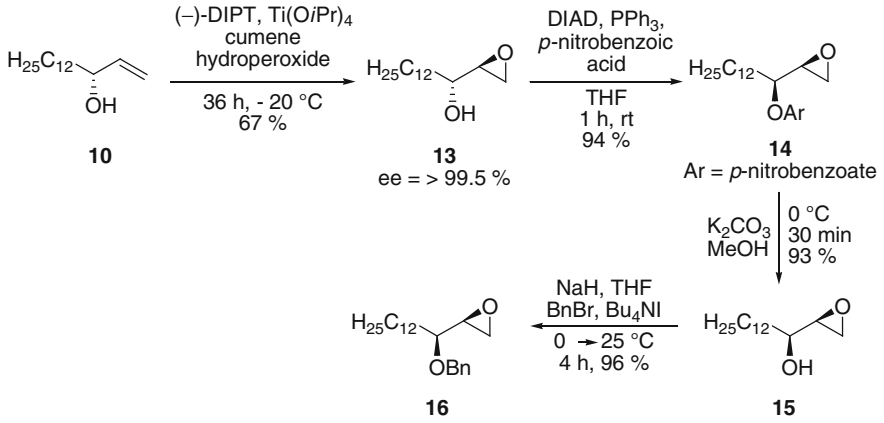


Scheme 3.2 Synthesis of protected epoxide **4**

was the Sharpless asymmetric epoxidation/resolution to yield one enantiomer of the epoxide **6** (38 %) and the unreacted enantiomer of the allylic alcohol **10** (50 %) using Ti(O*i*Pr)$_4$, (+)-diisopropyltartrate and cumene hydroperoxide. The epoxide **6** was then subjected to a Mitsonobu esterification, using diisopropyl azodicarboxylate (DIAD), PPh_3 and *p*-nitrobenzoic acid to invert the configuration of the hydroxy group, successfully yielding benzoate ester **11** in 89 % yield. Following successful cleavage of the ester under basic methanolysis to generate **12** in 87 % yield, the free hydroxy group was protected as the benzyl ether using NaH, benzyl bromide and tetra-*n*-butylammonium bromide to afford one enantiomer of key epoxide **4**, the desired precursor for the Grignard ring-opening reaction, in 87 % yield. This hydroxy group must be protected to prevent a second cyclization occurring during the subsequent $ZrCl_4$-catalysed deprotection/cyclisation sequence.

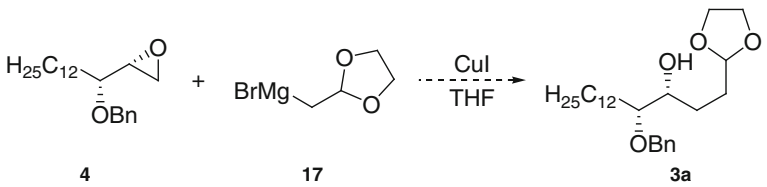
Similarly, the synthesis of the other enantiomer of the benzyl-protected epoxide **16** was carried out starting with the Sharpless asymmetric epoxidation on the recovered unreactive enantiomer of the allylic alcohol **10**, under the same reaction conditions, as before, to obtain epoxy alcohol **13** in 67 % yield (Scheme 3.3).

As before, the hydroxy group of this epoxy alcohol was subjected to a Mitsonobu esterification and subsequent cleavage of the resulting benzoate ester **14** to afford epoxy alcohol **15**, with the desired relative stereochemistry, in 87 % yield over two steps. The free hydroxy group was protected, as previously, with a benzyl group in 96 % yield.

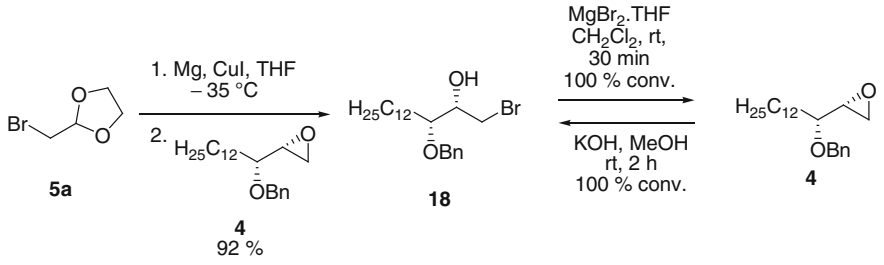


Scheme 3.3 Synthesis of protected epoxide **16**

At this point in the synthesis one more step was required to generate the precursor to the one-pot $ZrCl_4$-catalysed deprotection/cyclisation sequence. Initially we attempted to ring-open epoxide **4** with the Grignard reagent **17** to access **3a** en route to one enantiomer of the natural product **1a** (Scheme 3.4). This Grignard reaction was attempted using catalytic quantities of CuI (10 mol%) at −35 °C, using conditions we previously reported to successfully ring-open epoxides using bromo-ethyl dioxane derivatives [52]. However, in this case none of the desired product was formed. Instead, all of the starting material was consumed and a new product, identified as the β-bromohydrin **18**, was formed (Scheme 3.5).



Scheme 3.4 Attempted ring-opening of epoxide **4**



Scheme 3.5 Unexpected synthesis of β-bromohydrin **18**

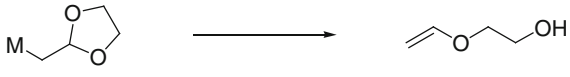
A search of the literature revealed that the ring-opening of epoxides to form β-bromohydrins has been reported [53–56]. It has also been reported when attempting Cu-catalysed ring-opening of epoxides with alkyl Grignard reagents [57]. Therefore we independently prepared **18** by exposing epoxide **4** to $MgBr_2 \cdot THF$ in dichloromethane. We also found that the epoxide could be easily regenerated using a methanolic solution of potassium hydroxide.

We believed the formation of the β-bromohydrin was as a result of the poor reactivity of the Grignard reagent, which has been reported to generally require room temperature and even refluxing THF to enhance its reactivity [58, 59]. Therefore, at −35 °C and following transmetallation to Cu, $MgBr_2$ could be generated in situ in significant enough quantities to ring-open the epoxide and generate the β-halohydrin. Utilising stoichiometric quantities of CuI also resulted in the formation of **18** at −35 °C.

With this in mind we attempted the reaction at room temperature in the hope that the transmetallated Grignard reagent would be more reactive relative to any $MgBr_2$ in solution. Again, no desired product was observed, only the β-bromohydrin. Changing the solvent from THF to diethyl ether, carrying out the reaction at reflux, both in the presence and absence of Cu, led only to β-bromohydrin and/or unreacted starting material. The reaction was also attempted with unprotected epoxide **12**, hoping this epoxide might more favourably undergo epoxide ring-opening with the desired nucleophile but unfortunately this was also unsuccessful.

Failing to ring-open the epoxide with a Grignard reagent we then decided to try to generate the more reactive organolithium derivative of bromo-dioxolane **5** via lithium-halogen exchange with *tert*-butyllithium. The generation of the organolithium derivative would also have the advantage of eliminating the potential to form the β-bromohydrin product. However, only unreacted starting material was recovered. A number of the above conditions were also attempted using benzaldehyde as the electrophile in place of the epoxide and still no desired product was formed, highlighting the remarkably low reactivity of these organometallic reagents. It was also observed that prolonged heating of the organolithium or Grignard derivatives of bromo-dioxolane **5a** led to decomposition and generation of an alkene, particularly with the organolithium reagent (Scheme 3.6). We proposed other potential routes to access intermediate **3a** however, we felt these were too lengthy to pursue.

At this point we decided to attempt to synthesise both enantiomers of the six-membered analogue, (+)-δ-muricatacin **1b** and (−)-δ-muricatacin **1b**, which we also targeted at the outset (Fig. 3.1). Although we were unsuccessful in our attempts



M = Li, MgBr

85 %, M = Li
67 % M = Mg

Scheme 3.6 Degradation of Grignard/organolithium reagent. Yield by ^{1}H-NMR spectroscopy

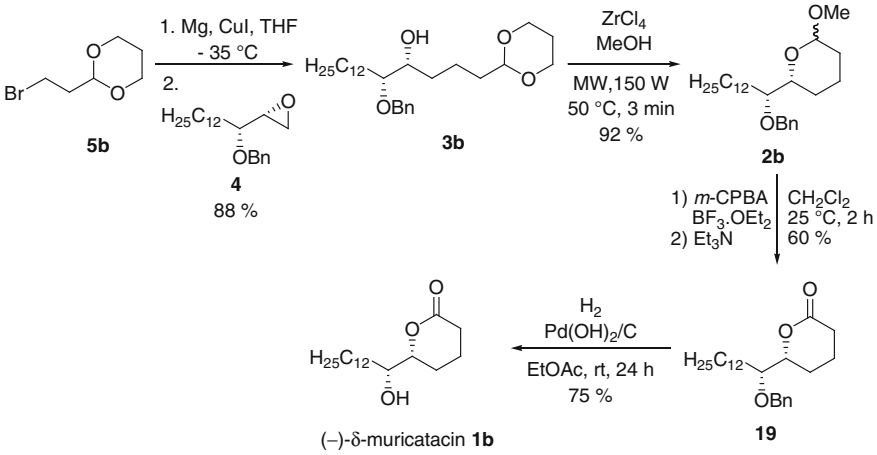
to synthesize the natural product and verify our synthetic strategy, we still believed this route to be viable to access the six-membered analogue, particularly given that we already had gram-quantities of each enantiomer of the chiral epoxides **4** and **16**. Our previous reports have shown the Cu-catalysed ring-opening of epoxides with Grignard derivatives of type **5b** to be very successful [52]. Thus, we believed we could use the Grignard derivative of **5b** to ring open chiral epoxides **4** and **16** to form intermediates **3b** and **20**.

Gratifyingly, the Grignard derivative of **5b** successfully ring-opened epoxide **4** to form alcohol **3b** in 88 % yield in the presence of CuI (10 mol%) at 0 °C (Scheme 3.7). This alcohol was then subjected to $ZrCl_4$-catalysis in the presence of methanol under microwave irradiation at 150 W and 50 °C to generate cyclic acetal **2b** in a high yield of 92 %. This acetal could then be oxidized to the corresponding lactone using *m*CPBA in the presence of $BF_3{\cdot}OEt_2$ to form **19** in 60 % yield [60]. The final step in the synthesis was deprotection of the benzyl group by hydrogenolysis using $Pd(OH)_2/C$ at 15 bar H_2 pressure for 24 h to generate a six-membered muricatacin analogue, (−)-δ-muricatacin **1b**, in an 88 % yield (Scheme 3.7).

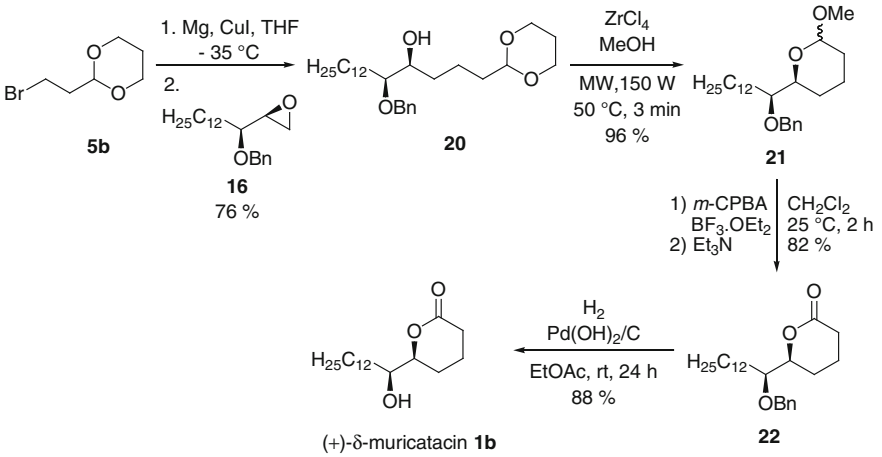
Similarly, the other enantiomer of the epoxide was ring-opened with the Grignard derivative of **5b** to yield alcohol **20** in 76 % yield (Scheme 3.8). Subsequent $ZrCl_4$-catalysed deprotection and cyclization generated cyclic acetal **21** in 96 % yield. Finally, as before, this acetal was oxidized to lactone **22** in an 82 % yield followed by hydrogenolysis of the benzyl group to form (+)-δ-muricatacin **1b** in a 75 % yield.

3.3 Biological Testing

The two six-membered analogues of muricatacin were submitted for biological testing in order to compare any cytotoxicity to the natural product. The analogues were tested against the same tumour cell lines as the natural product, HT-29,



Scheme 3.7 Synthesis of (−)-δ-muricatacin **1b**



Scheme 3.8 Synthesis of (+)-δ-muricatacin **1b**

Table 3.1 Comparison of ED_{50} of muricatacin and IC_{50} values of muricatacin analogues

Cell line	ED_{50}	IC_{50}	
	Muricatacin	(−)-**1b**	(+)-**1b**
HT-29	49	426	75
A-459	82	475	487
MCF-7	35	>500	212

MCF-7 and A-549 [1]. However, neither analogue displayed any significant anti-tumoral activity when compared to the natural product. The IC_{50} values are summarized in Table 3.1 and compared to the ED_{50} values of the natural product [1]. The most active compound was found to be (+)-δ-muricatacin **1b** against a colon carcinoma cell line (HT-29).

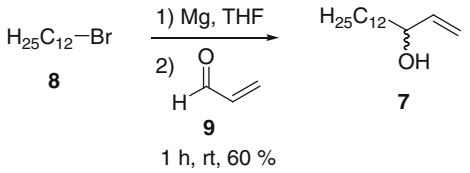
3.4 Conclusions

In conclusion, we have successfully carried out an asymmetric synthesis of both enantiomers of novel δ-lactone analogues of the natural product muricatacin. Key steps in the synthesis of these analogues included Sharpless asymmetric epoxidation, regioselective Cu-catalysed ring-opening of an epoxide with a Grignard reagent and the $ZrCl_4$-catalysed deprotection/cyclisation protocol. The synthetic approach described provides a very reliable, high-yielding route for the asymmetric synthesis of 6-hydroxy-δ-lactone-containing products. These analogues were evaluated for their biological activity against tumour cell lines however they showed no significant bioactivity. This suggests the size of the lactone ring is a

critical aspect of the bioactivity of muricatacin. Attempts to synthesize the natural product were unsuccessful due to the poor reactivity of the Grignard reagent of 2-(bromomethyl)-1,3-dioxolane.

3.5 Experimental

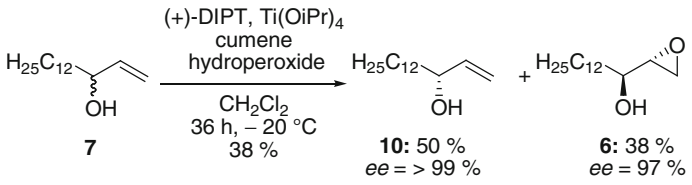
Pentadec-1-en-3-ol (7)



Dry THF (225 mL) was added to a dry two-neck flask containing activated magnesium turnings (4.55 g, 187.17 mmol). 1-Bromododecane (**8**) (44.94 mL, 187.17 mmol) was added slowly with gentle heating to initiate Grignard formation followed by reflux of the solution for 1 h. The solution was cooled to 0 °C prior to the dropwise addition of acrolein (**9**) (6.25 mL, 93.54 mmol). The reaction was stirred at 0 °C for 1 h before quenching with saturated NH_4Cl solution (50 mL) followed by Et_2O (100 mL). The organic layer was separated and the aqueous layer was back extracted with Et_2O (2 × 200 mL), washed with water (100 mL), brine (100 mL) and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the resulting yellow liquid was purified by vacuum distillation followed by silica gel column chromatography (pentane/ethyl acetate, 4:1) to yield **7** as a white solid (8.654 g, 41 %).

R_f = 0.5 (pentane/ethyl acetate, 4:1). IR (neat): ν_{max} = 3340, 2900 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 5.87 (ddd, *J* = 16.7, 10.4, 6.3 Hz, 1H), 5.21 (dt, *J* = 17.2, 1.3 Hz, 1H), 5.09 (dt, *J* = 10.4, 1.3 Hz, 1H), 4.09 (q, *J* = 6.3 Hz, 1H), 1.56–1.46 (m, 2H), 1.42–1.18 (m, 20H), 0.88 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 141.4, 114.4, 73.2, 37.1, 31.9, 29.7, 29.6, 29.6, 29.6, 29.5, 29.3, 25.3, 22.7, 14.1. HRMS (ESI-TOF): calcd. for $C_{15}H_{30}ONa$ $[M + Na]^+$ 249.2194, found 249.2191.

(*S*)-1-((*R*)-Oxiran-2-yl)tridecan-1-ol (6)

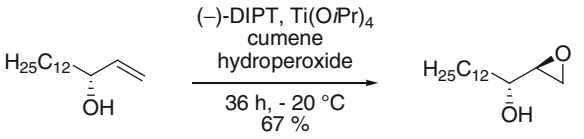


Powered molecular sieves (1.5 g, 4 Å) were dried overnight under high vacuum at 120 °C in a 250 mL two-neck round-bottom flask. Anhydrous CH_2Cl_2 (180 mL) was added and the suspension cooled to −20 °C. Ti(O*i*Pr)$_4$ (1.07 mL, 3.53 mmol) was added followed by L-(+)-diisopropyltartrate (0.96 mL, 4.59 mmol) and the solution was stirred for 30 min. Allylic alcohol (**7**) (8.000 g, 35.34 mmol) was added and the solution was stirred for 30 min. Cumene hydroperoxide was added dropwise over 30 min and the reaction stirred for 41 h at −20 °C. The reaction was quenched with saturated sodium sulfate solution (3 mL) followed by Et_2O (20 mL). The mixture was stirred for 2 h and filtered through a pad of Celite® and washed with Et_2O (3 × 50 mL). Excess solvent was removed in vacuo and the residue was first purified by silica gel column chromatography (pentane/ethyl acetate = 4:1) to recover the unreacted enantiomer of the allylic alcohol **10** and the product epoxide was recovered and further purified by recrystallisation from acetonitrile to yield **6** as a white solid (3.218 g, 38 %, *ee* = 97 %, [flow rate 3 mL/min, 99/1 to 70/30 = $scCO_2$/methanol over 5 min, R_t = 2.9 and 3.1 min]).

R_f = 0.24 (pentane/ethyl acetate = 4:1). IR (neat): ν_{max} = 3380, 2920, 2840, 1464 cm^{-1}. $[\alpha]_D^{20}$ = 11.4 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.86–3.80 (m, 1H), 3.04–2.99 (m, 1H), 2.81 (dd, *J* = 5.1, 2.8 Hz, 1H), 2.73 (dd, *J* = 5.1, 4.0 Hz, 1H), 1.76 (d, *J* = 2.5 Hz, 1H), 1.64–1.46 (m, 4H), 1.28 (d, *J* = 15.5 Hz, 18H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 68.4, 54.5, 43.4, 33.5, 31.9, 29.6, 29.6, 29.6, 29.5, 29.5, 29.3, 25.3, 22.7, 14.1. HRMS (ESI-TOF): calcd. for $C_{15}H_{30}O_2Na$ $[M + Na]^+$ 265.2144, found 265.2152.

The *ee* of the recovered allylic alcohol **10** was obtained by first converting the alcohol group to a *p*-nitrobenzoate [61].

(*R*)-1-((*S*)-Oxiran-2-yl)tridecan-1-ol (13)



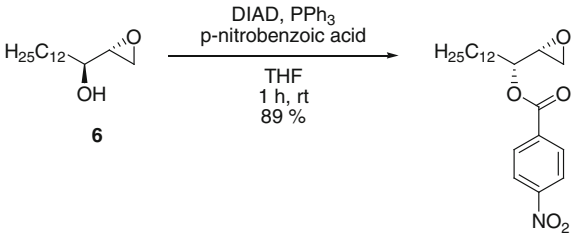
10 **13**
ee = > 99.5 %

Allylic alcohol (**10**) (4.000 g, 17.67 mmol, *ee* > 99 % [flow rate 3 mL/min, 99/1 to 70/30 = $scCO_2$/methanol over 5 min, R_t = 2.2 and 2.4 min]), recovered from the first epoxidation, was subjected to the same procedure as **6** using Ti(O*i*Pr)$_4$ (1.07 mL, 3.53 mmol), D-(−)-diisopropyltartrate (0.96, 4.59 mL) and cumene hydroperoxide (3.92 mL, 26.53 mmol) to yield epoxide **13** (2.889 g, 67 %, *ee* ≥ 99.5 %).

R_f = 0.24 (pentane/ethyl acetate, 4:1). IR (neat): ν_{max} = 3380, 2920, 2840, 1464 cm^{-1}. MP 45.8–46.6 °C. $[\alpha]_D^{20}$ = − 14.4 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.85–3.78 (m, 1H), 3.00 (dd, *J* = 7.0, 2.9 Hz, 1H), 2.80 (dd, *J* = 5.0, 2.9 Hz, 1H), 2.72 (dd, *J* = 5.0, 4.1 Hz, 1H), 1.83 (d, *J* = 2.4 Hz, 1H), 1.63–1.36 (m, 4H), 1.25 (s, 18H), 0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 68.4, 54.5, 43.4, 33.5, 31.9, 29.6, 29.6, 29.6, 29.6, 29.5, 29.3, 25.3, 22.6, 14.1. HRMS (ESI-TOF): calcd. for $C_{15}H_{30}O_2Na$ $[M + Na]^+$ 265.2144, found 265.2146.

The *ee* of the recovered allylic alcohol **10** was obtained by first converting the alcohol group to a *p*-nitrobenzoate [61].

(*R*)-1-((*R*)-Oxiran-2-yl)tridecyl 4-nitrobenzoate (11) [62, 63]

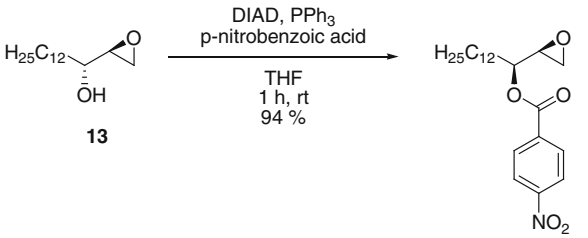


6 **11**

PPh_3 (3.370 g, 12.85 mmol) and *p*-nitrobenzoic acid (2.147 g, 12.85 mmol) were dissolved in dry THF (40 mL) in a 250 mL two-neck round bottom flask and cooled to 0 °C. Diisopropyl azodicarboxylate (DIAD) (2.36 mL, 11.99 mmol) was added dropwise followed by the slow addition of epoxide 6 (2.076 g, 8.56 mmol) in THF (10 mL). The reaction was stirred at 0 °C for 5 min and a room temperature for 55 min. The solvent was removed in vacuo and the resulting oil was dissolved in CH_2Cl_2 and washed with 15 % aq. H_2O_2 (100 mL), sat. Na_2SO_4 (100 mL) and water (100 mL). The water layer was re-extracted with CH_2Cl_2 (50 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed and the residue purified by silica gel column chromatography (pentane/ethyl acetate, 9:1) to yield **11** as a pale yellow oil (2.999 g, 89 %, *ee* > 99 % [flow rate 2 mL/min, 99/1 to 80/20 = $scCO_2$/methanol over 5 min, R_t = 3.8 and 4.3 min]).

R_f = 0.53 (pentane/ethyl acetate, 4:1). IR (neat): ν_{max} = 2926, 2854, 1728, 1531 cm^{-1}. $[\alpha]_D^{20} = -2.6$ (*c* 1.0, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ 8.29 (d, *J* = 9.0 Hz, 2H), 8.23 (d, *J* = 9.0 Hz, 2H), 4.98 (dd, *J* = 13.4, 6.3 Hz, 1H), 3.22 (ddd, *J* = 6.3, 4.0, 2.6 Hz, 1H), 2.89 (t, *J* = 4.5 Hz, 1H), 2.71 (dd, *J* = 4.8, 2.6 Hz, 1H), 1.91–1.76 (m, 2H), 1.46–1.38 (m, 2H), 1.38–1.18 (m, 18H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.0, 150.6, 135.5, 130.8, 123.5, 76.1, 52.9, 45.0, 31.9, 31.4, 29.6, 29.6, 29.6, 29.5, 29.4, 29.4, 29.3, 25.1, 22.6, 14.1. HRMS (ESI-TOF): calcd. for $C_{22}H_{34}NO_5$ $[M + H]^+$ 392.2437, found 392.2441.

(*S*)-1-((*S*)-Oxiran-2-yl)tridecyl 4-nitrobenzoate (14)

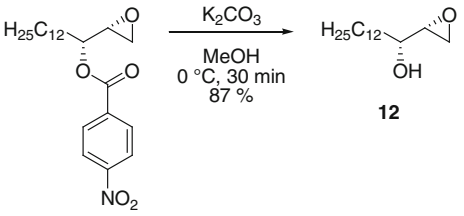


13 **14**

Epoxide **13** (2.575 g, 10.92 mmol) was subjected to the same procedure as for **11** using PPh_3 (3.370 g, 12.85 mmol), *p*-nitrobenzoic acid (2.147 g, 12.85 mmol) and DIAD (2.36 mL, 11.99 mmol) to yield the product as a pale yellow solid (3.91 g, 94 %, *ee* > 99.5 %).

R_f = 0.53 (pentane/ethyl acetate, 4:1). IR (neat): ν_{max} = 2926, 2854, 1728, 1531 cm^{-1}. MP 33.4–34.4 °C. $[\alpha]_D^{20}$ = 0.5 (*c* 1.0, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ 8.29 (d, *J* = 9.0 Hz, 2H), 8.23 (d, *J* = 9.0 Hz, 2H), 4.98 (dd, *J* = 13.4, 6.3 Hz, 1H), 3.22 (ddd, *J* = 6.3, 4.0, 2.6 Hz, 1H), 2.90 (t, *J* = 4.5 Hz, 1H), 2.71 (dd, *J* = 4.8, 2.6 Hz, 1H), 1.92–1.77 (m, 2H), 1.48–1.38 (m, 2H), 1.38–1.20 (m, 18H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.0, 150.6, 135.5, 130.8, 123.5, 76.1, 52.9, 45.0, 31.9, 31.4, 29.6, 29.6, 29.5, 29.5, 29.4, 29.4, 29.3, 25.1, 22.6, 14.0. HRMS (ESI-TOF): calcd. for $C_{22}H_{33}NO_5Na$ $[M + Na]^+$ 414.2256, found 414.2274.

(*R*)-1-((*R*)-Oxiran-2-yl)tridecan-1-ol (12) [62]

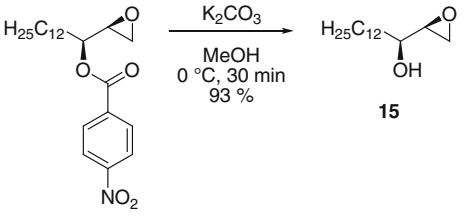


11 **12**

Benzoate (**11**) (2.791 g, 7.13 mmol) in MeOH (20 mL) was cooled to 0 °C in a 250 mL round bottom flask and K_2CO_3 (2.463 g, 17.83 mmol) as a suspension in MeOH (20 mL) was added dropwise and the reaction was stirred at 0 °C for 30 min, then filtered through a pad of silica and washed with Et_2O (100 mL). Excess solvent was removed in vacuo and the residue was purified by silica gel column chromatography (toluene, then pentane/ethyl acetate, 1:1) to yield **12** as a white solid (1.529 g, 88 %).

R_f = 0.51 (pentane/ethyl acetate, 4:1). IR (neat): ν_{max} = 3358, 2918, 2850, 1464 cm^{-1}. MP 49.5–49.9 °C. $[\alpha]_D^{20}$ = −3.2 (*c* 1.0, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ 3.46–3.39 (m, 1H), 2.98 (ddd, *J* = 5.1, 4.2, 2.8 Hz, 1H), 2.82 (dd, *J* = 4.9, 4.2 Hz, 1H), 2.71 (dd, *J* = 4.9, 2.8 Hz, 1H), 2.01 (d, *J* = 5.9 Hz, 1H), 1.65–1.54 (m, 2H), 1.52–1.42 (m, 1H), 1.42–1.21 (m, 19H), 0.88 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 71.7, 55.4, 45.1, 34.4, 31.9, 29.6, 29.6, 29.6, 29.6, 29.5, 29.3, 25.3, 22.7, 14.1. HRMS (ESI-TOF): calcd. for $C_{15}H_{30}O_2Na$ $[M + Na]^+$ 265.2144, found 265.2150.

(*S*)-1-((*S*)-Oxiran-2-yl)tridecan-1-ol (15)

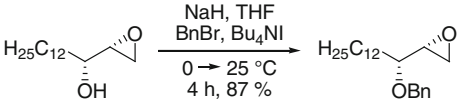


14 **15**

Benzoate (**14**) (3.593 g, 9.18 mmol) was subjected to the same procedure as for **12** using K_2CO_3 (3.171 g, 22.94 mmol) to yield epoxide **15** as a white solid (2.060 g, 93 %).

R_f = 0.51 (pentane/ethyl acetate, 4:1). IR (neat): ν_{max} = 3356, 2917, 2850, 1463 cm^{-1}. MP 48.9–49.5 °C. $[\alpha]_D^{20}$ = 0.5 (*c* 1.0, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ 3.46–3.39 (m, 1H), 2.98 (ddd, *J* = 5.1, 4.2, 2.8 Hz, 1H), 2.82 (dd, *J* = 4.9, 4.2 Hz, 1H), 2.71 (dd, *J* = 4.9, 2.8 Hz, 1H), 1.99 (d, *J* = 5.8 Hz, 1H), 1.66–1.54 (m, 2H), 1.53–1.43 (m, 1H), 1.42–1.21 (m, 19H), 0.88 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 71.7, 55.4, 45.1, 34.4, 31.9, 29.6, 29.6, 29.6, 29.6, 29.5, 29.3, 25.3, 22.7, 14.1, 14.0. HRMS (ESI-TOF): calcd. for $C_{15}H_{30}O_2Na$ $[M + Na]^+$ 265.2144, found 265.2148.

(*R*)-2-((*R*)-1-(Benzyloxy)tridecyl)oxirane (4)



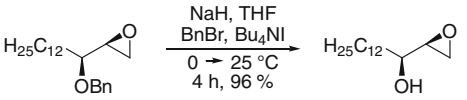
12 **4**

NaH (0.295 g, 7.36 mmol, 60 % dispersion in mineral oil) was washed with anhydrous hexanes (2 × 2.5 mL) and dried under high vacuum. Dry THF (20 mL) was added and the solution was cooled to 0 °C prior to the dropwise addition of epoxide **12** (1.266 g, 5.26 mmol) in THF (3 mL). The reaction was stirred for 30 min and benzyl bromide (0.69 mL, 5.79 mmol) was added dropwise followed by tetra-*n*-butylammonium bromide (0.972 g, 2.63 mmol). The reaction was stirred at 0 °C for 5 min and for a further 4 h at room temperature. The reaction was quenched with H_2O (2.5 mL) followed by Et_2O (5 mL). The aqueous layer was extracted with Et_2O (2 × 40 mL) and the combined organic layers were washed with water (50 mL), brine (50 mL) and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography (pentane/ethyl acetate, 15:1) to yield **4** as a very pale yellow oil (1.666 g, 96 %).

R_f = 0.56 (pentane/ethyl acetate = 9:1). IR (neat): ν_{max} = 2926, 2854, 1466 cm^{-1}. $[\alpha]_D^{20}$ = 20.4 (*c* 1.1, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.40–7.29 (m, 4H), 7.29–7.23 (m, 1H), 4.83 (d, *J* = 11.9 Hz, 1H), 4.58 (d, *J* = 11.9 Hz, 1H), 3.07–2.99

(m, 2H), 2.79–2.75 (m, 1H), 2.48 (dd, J = 4.9, 2.1 Hz, 1H), 1.72–1.60 (m, 1H), 1.56–1.41 (m, 2H), 1.39–1.19 (m, 18H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.7, 128.3, 127.8, 127.4, 80.5, 71.7, 55.1, 43.1, 32.4, 31.9, 29.7, 29.6, 29.6, 29.6, 29.5, 29.4, 25.5, 22.7, 14.1. HRMS (ESI-TOF): calcd. for $C_{22}H_{36}O_2Na$ $[M + Na]^+$ 355.2613, found 355.2626.

(*S*)-2-((*S*)-1-(Benzyloxy)tridecyl)oxirane (16)

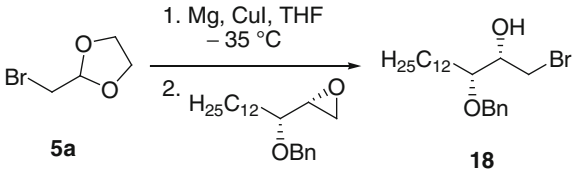


16 **15**

Epoxide **15** (2.010 g, 8.29 mmol) was subjected to the same procedure as **4** using NaH (0.464 g, 8.29 mmol), benzyl bromide (1.09 mL, 9.12 mmol) and tetra-*n*-butylammonium bromide (1.531 g, 4.15 mmol) to yield **16** as a very pale yellow oil (2.400 g, 87 %).

R_f = 0.56 (pentane/ethyl acetate = 9:1). IR (neat): ν_{max} = 2926, 2854, 1466 cm^{-1}. $[\alpha]_D^{20}$ = −20.9 (*c* 1.1, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39–7.29 (m, 4H), 7.25 (dd, J = 11.5, 4.2 Hz, 1H), 4.83 (d, J = 11.9 Hz, 1H), 4.58 (d, J = 11.9 Hz, 1H), 3.06–2.99 (m, 2H), 2.76 (dd, J = 4.9, 4.0 Hz, 1H), 2.47 (dd, J = 4.9, 2.3 Hz, 1H), 1.71–1.61 (m, 1H), 1.57–1.40 (m, 2H), 1.39–1.19 (m, 19H), 0.88 (t, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 138.7, 128.3, 127.8, 127.4, 80.5, 71.7, 55.1, 43.1, 32.4, 31.9, 29.7, 29.6, 29.6, 29.6, 29.5, 29.4, 25.5, 22.7, 14.1. HRMS (ESI-TOF): calcd. for $C_{22}H_{36}O_2Na$ $[M + Na]^+$ 355.2613, found 355.2610.

Attempted synthesis of (3R,4R)-4-(benzyloxy)-1-(1,3-dioxolan-2-yl)hexadecan-3-ol (3a)



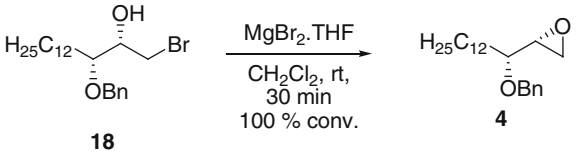
5a **4** 92 % **18**

Activated magnesium turnings (88 mg, 3.62 mmol) were suspended in anhydrous THF (4 mL) and 2-(2-bromoethyl)-1,3-dioxane (0.37 mL, 3.60 mmol) was added slowly. The mixture was heated gently to initiate Grignard formation and then heated to reflux for 1 h. The Grignard solution was transferred to a pre-cooled Schlenk flask containing copper(I) iodide (23 mg, 0.12 mmol) at −35 °C using a cannula and stirred for 15 min prior to the dropwise addition of epoxide **4** (400 mg, 1.20 mmol). The reaction was stirred for 3 h at −35 °C and quenched with saturated NH_4Cl solution. The reaction was stirred for 10 min while warming to room temperature. The aqueous layer was diluted with water (10 mL) and extracted with ethyl acetate

(5 × 30 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous Na_2SO_4. Solvent was removed in vacuo and the resulting oil purified by silica gel column chromatography (pentane/ethyl acetate = 2:1) to yield β-bromohydrin **18** as the sole product as a colourless oil, 474 mg (88 %).

R_f = 0.46 (pentane/ethyl acetate = 9:1). IR (neat): ν_{max} = 3428, 2924, 2854, 1455 cm^{-1}. $[\alpha]_D^{20} = -31.0$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.41–7.28 (m, 5H), 4.68 (d, *J* = 11.3 Hz, 1H), 4.54 (d, *J* = 11.3 Hz, 1H), 3.84–3.76 (m, 1H), 3.68–3.62 (m, 1H), 3.52–3.40 (m, 2H), 2.61 (d, *J* = 6.4 Hz, 1H), 1.70–1.58 (m, 2H), 1.43–1.22 (m, 20H), 0.90 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.1, 128.6, 128.1, 128.0, 79.0, 72.7, 72.5, 34.9, 32.1, 30.4, 29.9, 29.8, 29.8, 29.7, 29.7, 29.5, 25.5, 22.8, 14.3. HRMS (ESI-TOF): calcd. for $C_{22}H_{37}O_2Na^{79}Br$ $[M + Na]^+$ 435.1875 and $C_7H_{13}O_2^{81}Br$ $[M]^+$ 437.1854, found 435.1871 and 437.1881.

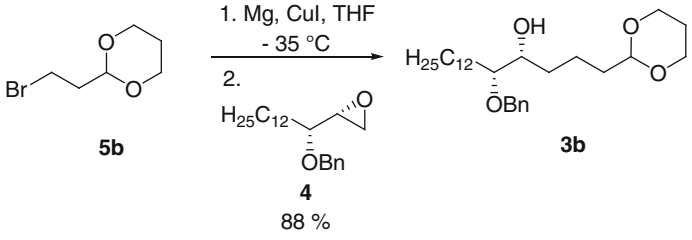
(2*S*,3*R*)-3-(Benzyloxy)-1-bromopentadecan-2-ol (18)



18 **4**

The β-bromohydrin was formed according to the procedure described by Zeng using epoxide **4** (55 mg, 0.15 mmol), $MgBr_2$·THF (0.60 mL, 1.08 mmol, prepared in situ from Mg (88 mg, 3.60 mmol) and 1,2-dibromoethane (0.31 mL, 3.60 mmol) in THF (2.0 mL)). Reaction mixture was stirred at room temperature for 30 min, quenched with saturated NH_4Cl solution, extracted twice with EtOAc, dried over anhydrous Na_2SO_4 and the solvent was removed in vacuo to yield **18** as a colourless oil (68 mg). Pure by crude ^1H-NMR. Analytical data identical to attempted synthesis of **3a**.

(4*R*,5*R*)-5-(Benzyloxy)-1-(1,3-dioxan-2-yl)heptadecan-4-ol (3b)



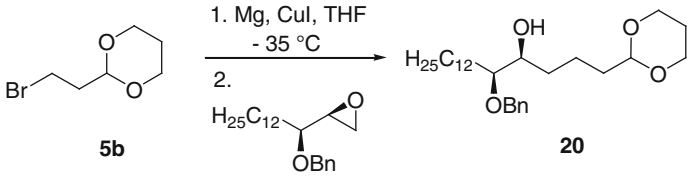
5b **4** 88 % **3b**

Activated magnesium turnings (88 mg, 3.62 mmol) were suspended in anhydrous THF (4 mL) and 2-(2-bromoethyl)-1,3-dioxane (0.49 mL, 3.60 mmol) was added slowly. The mixture was heated gently to initiate Grignard formation and

then heated to reflux for 1 h. The Grignard solution was transferred to a pre-cooled Schlenk flask containing copper(I) iodide (23 mg, 0.12 mmol) at −35 °C using a cannula and stirred for 15 min prior to the dropwise addition of epoxide **4** (400 mg, 1.20 mmol). The reaction was stirred for 3 h at −35 °C and quenched with saturated NH_4Cl solution. The reaction was stirred for 10 min while warming to room temperature. The aqueous layer was diluted with water (10 mL) and extracted with ethyl acetate (5 × 30 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous Na_2SO_4. Solvent was removed in vacuo and the resulting oil purified by silica gel column chromatography (pentane/ethyl acetate = 2:1) to yield **3b** as a colourless oil, 474 mg (88 %).

R_f = 0.32 (pentane/ethyl acetate = 2:1). IR (neat): ν_{max} = 3468, 2924, 2853, 1456 cm^{-1}. $[\alpha]_D^{20}$ = 8.7 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.37–7.25 (m, 5H), 4.63 (d, *J* = 11.3 Hz, 1H), 4.52–4.46 (m, 2H), 4.08 (ddd, *J* = 11.6, 4.9, 1.5 Hz, 2H), 3.77–3.69 (m, 2H), 3.57–3.50 (m, 1H), 3.26 (q, *J* = 5.5 Hz, 1H), 2.36 (d, *J* = 4.8 Hz, 1H), 2.05 (dt, *J* = 13.0, 5.1 Hz, 2H), 1.67–1.40 (m, 8H), 1.26 (s, 20H), 0.88 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.5, 128.4, 127.8, 127.7, 102.3, 82.3, 72.4, 72.4, 66.8, 35.1, 33.2, 31.9, 30.3, 30.0, 29.7, 29.7, 29.6, 29.6, 29.4, 25.8, 25.1, 22.7, 20.3, 14.1. HRMS (ESI-TOF): calcd. for $C_{22}H_{36}O_2Na$ $[M + Na]^+$ 471.3450, found 471.3459.

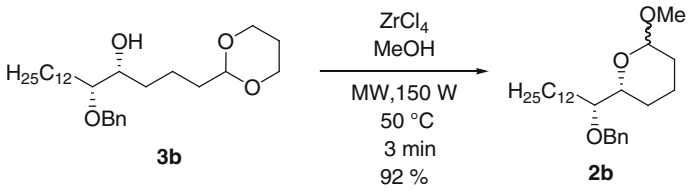
(4*S*,5*S*)-5-(Benzyloxy)-1-(1,3-dioxan-2-yl)heptadecan-4-ol (20)



This reaction was carried in an identical manner to the synthesis of **3b** using epoxide **16** to yield the product **20** as colourless oil, 408 mg (76 %).

R_f = 0.32 (pentane/ethyl acetate = 2:1). IR (neat): ν_{max} = 3474, 2925, 2853, 1456 cm^{-1}. $[\alpha]_D^{20}$ = −6.5 (*c* 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.37–7.25 (m, 5H), 4.64 (d, *J* = 11.3 Hz, 1H), 4.53–4.46 (m, 2H), 4.09 (dd, *J* = 11.5, 4.8 Hz, 2H), 3.79–3.69 (m, 2H), 3.59–3.48 (m, 1H), 3.26 (q, *J* = 5.5 Hz, 1H), 2.31 (d, *J* = 5.0 Hz, 1H), 2.13–2.00 (m, 2H), 1.66–1.41 (m, 8H), 1.26 (s, 20H), 0.88 (t, *J* = 6.7 Hz, 3H). HRMS (ESI-TOF): calcd. for $C_{22}H_{36}O_2Na$ $[M + Na]^+$ 471.3450, found 471.3460.

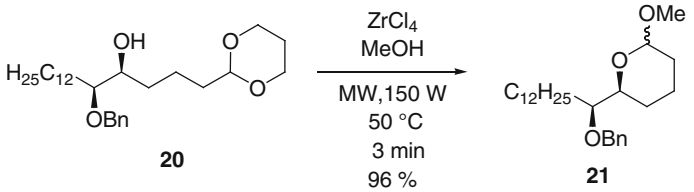
(2*R*)-2-((*R*)-1-(Benzyloxy)tridecyl)-6-methoxytetrahydro-2H-pyran (2b)



$ZrCl_4$ (5 mg, 0.02 mmol, 10 mol%) was added to an oven dry 10 mL microwave flask equipped with a magnetic stirbar. Alcohol **3b** (100 mg, 0.22 mmol) in anhydrous methanol (1 mL) was added under N_2 and the reaction was heated under microwave irradiation at 50 °C, 150 W for 3 min. The reaction mixture was purified directly by silica gel column chromatography (pentane/ethyl acetate = 9:1) to yield cyclic acetal **2b**, as a colourless oil, 83 mg (92 %). Mixture of diastereomers ≈1.8:1.

R_f = 0.44 and 0.51 (pentane/ethyl acetate = 9:1). IR (neat): ν_{max} = 2925, 2854, 1456 cm^{-1}. $[\alpha]_D^{20}$ (mixture) = −13.8 (*c* 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, major diastereomer): δ 7.37–7.28 (m, 4H), 7.28–7.22 (m, 1H), 4.75 (d, *J* = 2.5 Hz, 1H), 4.64 (d, *J* = 11.5 Hz, 1H), 4.58 (d, *J* = 11.5 Hz, 1H), 3.85–3.78 (m, 1H), 3.34 (s, 3H), 3.26 (dt, *J* = 7.6, 4.8 Hz, 1H), 1.84–1.71 (m, 1H), 1.67–1.46 (m, 7H), 1.45–1.37 (m, 1H), 1.24 (s, 19H), 0.91–0.83 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, major diastereomer): δ 139.0, 128.2, 128.0, 127.4, 98.5, 81.4, 72.9, 70.1, 54.5, 31.9, 30.2, 29.8, 29.7, 29.6, 29.6, 29.6, 29.3, 26.5, 25.9, 22.7, 18.1, 14.1, 14.1. ^1H NMR (400 MHz, $CDCl_3$, minor diastereomer): δ 7.37–7.28 (m, 4H), 7.25 (d, *J* = 7.0 Hz, 1H), 4.76 (d, *J* = 11.5 Hz, 1H), 4.59 (d, *J* = 11.5 Hz, 1H), 4.29 (dd, *J* = 9.4, 2.1 Hz, 1H), 3.54–3.46 (m, 4H), 3.43–3.37 (m, 1H), 1.91–1.83 (m, 1H), 1.79–1.72 (m, 1H), 1.62–1.29 (m, 9H), 1.24 (s, 19H), 0.90–0.82 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, minor diastereomer): δ 139.2, 128.2, 127.8, 127.4, 103.5, 81.5, 78.8, 73.4, 56.0, 31.9, 31.1, 30.5, 29.7, 29.7, 29.7, 29.6, 29.6, 29.6, 29.3, 26.2, 25.5, 22.7, 22.1, 14.1. HRMS (ESI-TOF): calcd. for $C_{26}H_{44}O_3Na$ $[M + Na]^+$ 427.3188, found 427.3188.

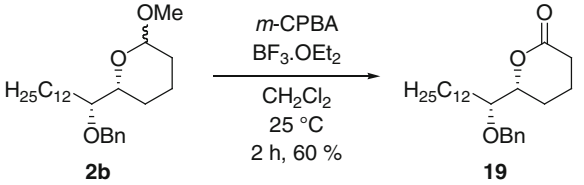
(2*S*)-2-((*S*)-1-(Benzyloxy)tridecyl)-6-methoxytetrahydro-2H-pyran (21)



This reaction was carried in an identical manner to the synthesis of **2b** using alcohol **20** to yield the product **21** (83 mg, 92 %) as a colourless oil. Mixture of diastereomers ≈1.8:1.

R_f = 0.44 and 0.51 (pentane/ethyl acetate = 9:1). IR (neat): ν_{max} = 2925, 2854, 1456 cm^{-1}. $[\alpha]_D^{20}$ (mixture) = 14.2 (*c* 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, major diastereomer): δ 7.37–7.28 (m, 4H), 7.28–7.22 (m, 1H), 4.77–4.72 (m, 1H), 4.64 (d, *J* = 11.5 Hz, 1H), 4.58 (d, *J* = 11.5 Hz, 1H), 3.84–3.77 (m, 1H), 3.34 (s, 3H), 3.26 (dt, *J* = 7.7, 4.7 Hz, 1H), 1.85–1.71 (m, 1H), 1.67–1.45 (m, 7H), 1.44–1.36 (m, 1H), 1.24 (s, 19H), 0.90–0.83 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, major diastereomer): δ 139.0, 128.2, 128.0, 127.4, 98.5, 81.4, 72.9, 70.1, 54.5, 31.9, 30.2, 29.8, 29.7, 29.6, 29.6, 29.6, 29.3, 26.5, 25.9, 22.7, 18.0, 14.1. ^1H NMR (400 MHz, $CDCl_3$, minor diastereomer): δ 7.37–7.27 (m, 3H), 7.27–7.22 (m, 2H), 4.76 (d, *J* = 11.5 Hz, 1H), 4.59 (d, *J* = 11.5 Hz, 1H), 4.29 (dd, *J* = 9.4, 2.1 Hz, 1H), 3.54–3.46 (m, 4H), 3.43–3.37 (m, 1H), 1.91–1.83 (m, 1H), 1.79–1.73 (m, 1H), 1.62–1.30 (m, 9H), 1.24 (s, 19H), 0.90–0.82 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, minor diastereomer): δ 139.2, 128.2, 127.8, 127.4, 103.5, 81.5, 78.8, 73.4, 56.0, 31.9, 31.1, 30.5, 29.7, 29.7, 29.6, 29.6, 29.6, 29.3, 26.2, 25.5, 22.7, 22.1, 14.1. HRMS (ESI-TOF): calcd. for $C_{26}H_{44}O_3Na$ $[M + Na]^+$ 427.3188, found 427.3184.

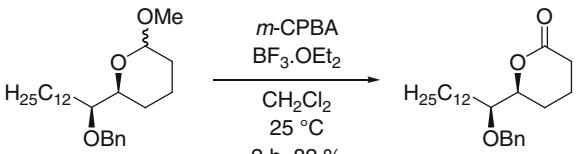
(*R*)-6-((*R*)-1-(Benzyloxy)tridecyl)tetrahydro-2H-pyran-2-one (19)



Acetal **2b** (81 mg, 0.20 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) and cooled to 0 °C. *m*-Chloroperbenzoic acid (<77 %, 68 mg, 0.30 mmol) was added followed by $BF_3.OEt_2$ (38 μL, 0.30 mmol) and the reaction was stirred for 1 h. Et_3N (0.14 mL, 1.00 mmol) was added and the reaction was stirred for a further 1 h. Solvent was removed in vacuo and the residue purified by silica gel column chromatography (pentane/ethyl acetate = 4:1) to yield the product **19** (47 mg, 60 %) as a colourless oil.

R_f = 0.34 (pentane/ethyl acetate = 4:1). IR (neat): ν_{max} = 2925, 2854, 1734, 1456 cm^{-1}. $[\alpha]_D^{20}$ = −2.9 (*c* 1.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.37–7.25 (m, 5H), 4.66 (d, *J* = 11.5 Hz, 1H), 4.60 (d, *J* = 11.5 Hz, 1H), 4.42–4.35 (m, 1H), 3.48 (dt, *J* = 8.6, 4.5 Hz, 1H), 2.64–2.54 (m, 1H), 2.43 (ddd, *J* = 17.6, 9.2, 7.0 Hz, 1H), 1.98–1.75 (m, 3H), 1.72–1.39 (m, 5H), 1.26 (s, 18H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.4, 138.3, 128.4, 127.9, 127.7, 81.1, 80.1, 73.1, 31.9, 29.8, 29.7, 29.7, 29.6, 29.6, 29.6, 29.3, 25.7, 23.2, 22.7, 18.6, 14.1. HRMS (ESI-TOF): calcd. for $C_{25}H_{40}O_3Na$ $[M + Na]^+$ 411.2875, found 411.2864.

(*S*)-6-((*S*)-1-(Benzyloxy)tridecyl)tetrahydro-2H-pyran-2-one (22)

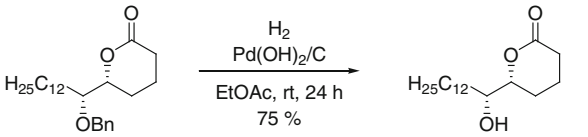


21 **22**

The synthesis of **22** was carried out in an identical manner as the synthesis of **19** using acetal **21** (86 mg, 0.21 mmol), *m*CPBA (<77 %, 72 mg, 0.32 mmol), $BF_3{\cdot}OEt_2$ (40 µL, 0.32 mmol) and Et_3N (0.15 mL, 1.05 mmol) to yield the product **22** (73 mg, 82 %) as a colourless oil.

R_f = 0.34 (pentane/ethyl acetate = 4:1). IR (neat): ν_{max} = 2924, 2854, 1739, 1465 cm^{-1}. $[\alpha]_D^{20}$ = 2.9 (*c* 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.37–7.26 (m, 4H), 4.66 (d, *J* = 11.5 Hz, 1H), 4.61 (d, *J* = 11.5 Hz, 1H), 4.39 (ddd, *J* = 11.1, 4.5, 3.1 Hz, 1H), 3.49 (dt, *J* = 8.6, 4.5 Hz, 1H), 2.64–2.55 (m, 1H), 2.43 (ddd, *J* = 17.6, 9.2, 7.0 Hz, 1H), 1.99–1.74 (m, 3H), 1.73–1.40 (m, 5H), 1.37–1.20 (m, 18H), 0.93–0.85 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.4, 138.3, 128.3, 127.9, 127.7, 81.1, 80.1, 73.1, 31.9, 29.7, 29.7, 29.7, 29.6, 29.6, 29.5, 29.3, 25.7, 23.2, 22.7, 18.6, 14.1. HRMS (ESI-TOF): calcd. for $C_{25}H_{40}O_3Na$ $[M + Na]^+$ 411.2875, found 411.2888.

(*R*)-6-((*R*)-1-Hydroxytridecyl)tetrahydro-2H-pyran-2-one ((−)-1b)

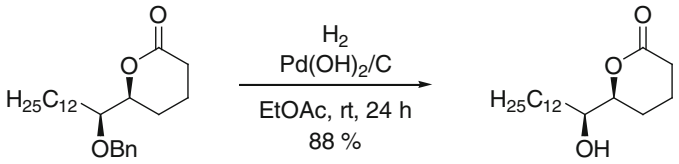


19 (–)-δ-muricatacin **1b**

Protected lactone **19** (43 mg, 0.11 mmol) was dissolved in ethyl acetate (2 mL) and $Pd(OH)_2/C$ (20 wt%, 8 mg, 0.011 mmol) was added. The reaction was stirred under H_2 (17 bar) for 24 h and purified directly by column chromatography (ethyl acetate) to yield (−)-muricatacin analogue (−)-**1b** (24 mg, 75 %) as an off-white solid.

R_f = 0.07 (pentane/ethyl acetate = 4:1). IR (neat): ν_{max} = 3454, 2922, 2850, 1724, 1470 cm^{-1}. $[\alpha]_D^{20}$ = −6.87 (*c* 1.1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 4.19 (ddd, *J* = 11.5, 4.8, 3.2 Hz, 1H), 3.60–3.53 (m, 1H), 2.66–2.57 (m, 1H), 2.46 (ddd, *J* = 17.6, 9.0, 6.9 Hz, 1H), 2.14 (s, 1H), 2.01–1.93 (m, 1H), 1.93–1.82 (m, 2H), 1.79–1.68 (m, 1H), 1.58–1.45 (m, 3H), 1.42–1.21 (m, 19H), 0.88 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.4, 83.2, 73.4, 32.7, 31.9, 29.6, 29.6, 29.6, 29.5, 29.5, 29.3, 25.4, 24.2, 22.7, 18.4, 14.2, 14.1. HRMS (ESI-TOF): calcd. for $C_{18}H_{34}O_3Na$ $[M + Na]^+$ 321.2406, found 321.2395.

(S)-6-((S)-1-Hydroxytridecyl)tetrahydro-2H-pyran-2-one ((+)-1b)



22 (+)-δ-muricatacin **1b**

Protected lactone **22** (66 mg, 0.17 mmol) was dissolved in ethyl acetate (2 mL) and $Pd(OH)_2/C$ (20 wt%, 12 mg, 0.017 mmol) was added. The reaction was stirred under H_2 (17 bar) for 24 h and purified directly by column chromatography (EtOAc) to yield (+)-muricatacin analogue (+)-**1b** (43 mg, 88 %) as an off-white solid. All physical data identical to (−)-enantiomer apart from $[\alpha]_D^{20} = 10.2$ (*c* 1.1, $CHCl_3$).

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Chapter 4
Introduction to the Development of a Catalytic Asymmetric Synthesis of Tertiary α-Aryl Ketones

4.1 Introduction

Biological systems recognise a pair of enantiomers as different substances and thus each enantiomer will trigger a different response. It is possible that one enantiomer could act positively as a therapeutic agent and the other enantiomer might be very harmful or toxic. As a result it is necessary to synthesise target molecules as single enantiomers. It is therefore desirable to develop and discover new methods for the enantioselective synthesis of target molecules, ideally in a catalytic manner.

Numerous pharmaceuticals have shown that only one enantiomer is active against the target of interest whereas the other is completely inactive and in many cases can have a negative effect. Therefore, half of the pharmaceutical ingredient which is synthesised is unnecessary, must be purged by the body, has the potential to cause harm and is also a waste of valuable material. As a result of the potential side effects of the 'other' enantiomer the United States Food and Drug Administration (FDA) introduced new guidelines for the development and approval of chiral drugs in 1992, [1] quickly followed by the equivalent European Union regulatory body for medicinal products (CPMP) in 1993. These new regulations required that the pharmacological activity of the individual enantiomers must be evaluated even if the drug is to be marketed as a racemate. As a result there has been a growing requirement for methods to synthesise chiral pharmaceuticals as single enantiomers.

There are several methods which can be used to obtain enantiomerically pure or enantioenriched compounds including chiral pool synthesis, classical resolution via diastereomers, enzymatic or chemical resolution and asymmetric synthesis. A subcategory of asymmetric synthesis is *catalytic asymmetric synthesis* or *asymmetric catalysis* which is inherently more challenging with the object to use one chiral molecule to potentially synthesise millions of other chiral molecules. This can be achieved, for example, using a transition metal catalyst bound to a chiral ligand or using an organocatalyst.

R. Doran, *Asymmetric Synthesis of Bioactive Lactones and the Development of a Catalytic Asymmetric Synthesis of α-Aryl Ketones*, Springer Theses,
DOI 10.1007/978-3-319-20544-1_4

4.2 Methods for the Synthesis of Enatiomerically Pure Compounds

4.2.1 Chiral Pool

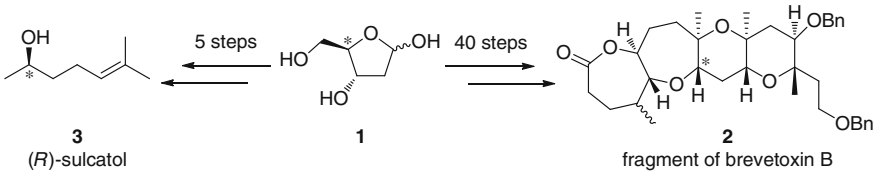
The chiral pool approach for the synthesis of enantiomerically pure compounds uses readily available sources of enantiomerically pure starting materials, usually naturally obtained. The most common sources are amino acids, monosaccharides and terpenes. Using this approach a number of structurally diverse enantiomerically pure compounds have been synthesised by carrying out a series of chemical transformations which will preserve the chiral information. There are both simple and more complex examples of this approach. For example, the insect pheromone (*R*)-sulcatol (**3**) and the more complex fragment of brevetoxin B (**2**) are both prepared from 2-deoxy-D-ribose (Scheme 4.1) [2, 3].

4.2.2 Resolution

The separation of a racemic mixture of enantiomers, or racemate, is a process known as resolution. The first resolution of a pair of enantiomers was achieved by Pasteur in 1848 who observed the racemic conglomerate of a sodium ammonium salt of tartaric acid (**4**, Fig. 4.1). This is an equimolar mechanical mixture of crystals where each crystal only contains a single enantiomer. The enantiomorphous crystals could be observed under magnification and separated manually by hand. Examples of this type are not very common and the separation is labour intensive. However, the principle has been used in the development of *classical resolution*.

4.2.3 Classical Resolution

If the racemic molecule of interest is coupled to, or derivatised with, an enantiomerically pure chiral molecule a pair of diastereomers is formed which can be separated by chromatography or crystallisation. The separation of the benzyl ester



Scheme 4.1 Use of chiral pool reagent 2-deoxy-D-ribose in asymmetric synthesis

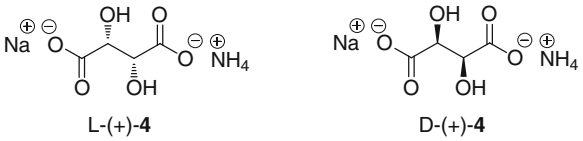
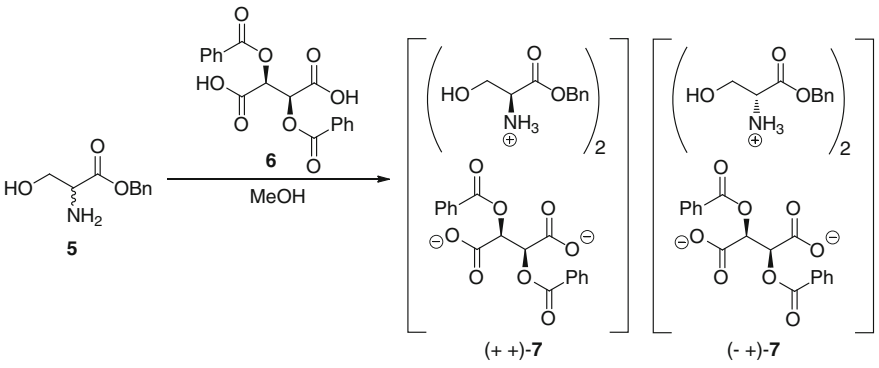


Fig. 4.1 Resolution of tartaric acid from enantiomorphous crystals

of serine (**5**) was accomplished using this concept [4]. The ester was dissolved in MeOH and the addition of the enantiomerically pure 2,3-dibenzoyl-D-tartaric acid resulted in the crystallisation of a single diastereomeric salt (+ +)-**7** which could be isolated by filtration. The other diastereomer remained in solution (Scheme 4.2). The disadvantage of this method is the requirement of a stoichiometric amount of the chiral resolving agent although in some instances this can be recycled.

4.2.4 Kinetic Resolution

Kinetic resolution is the achievement of partial or complete resolution by virtue of unequal rates of reaction of the enantiomers in a racemate with a chiral catalyst [5]. The method usually forms two products; one enantiomer does not react with the chiral catalyst or else it reacts very slowly whilst the other enantiomer reacts with the aid of the chiral catalyst to form a new product which may or may not be chiral. As a result two different compounds now make up the mixture and can be separated by conventional chromatographic techniques. One of the most widely applied examples of this technique is the Sharpless Kinetic Resolution. This asymmetric epoxidation of allylic alcohols was reported by Sharpless in 1980 catalysed by a titanium (IV) tartrate complex in the presence of a hydroperoxide [6] and has been employed in a number of kinetic resolutions [7]. This reaction shows remarkable



Scheme 4.2 Classical resolution of 2,3-dibenzoyl-D-tartaric acid

levels of selectivity for a range of substituted allylic alcohols and it allows both the allylic alcohol and the epoxy alcohol to be obtained with very high levels of enantioselectivity (Scheme 4.3) [8].

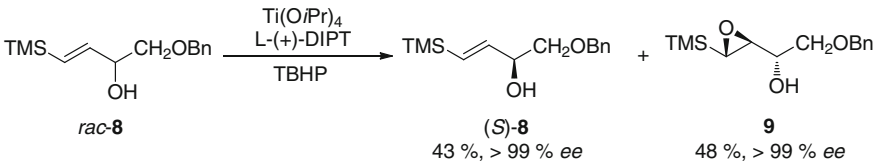
4.2.5 Enzymatic Resolution

Resolution can also be achieved by the use of an enzyme. Much in the way that kinetic resolution works, an enzyme can react selectively with one enantiomer of the racemate and leave the other enantiomer unreacted and resolved. Particularly successful are acylase enzymes which have been applied in a number of synthetically useful transformations [9]. For example, porcine kidney acylase I has been used to prepare unnatural amino acids in almost complete enantiomeric purity (Scheme 4.4) [10].

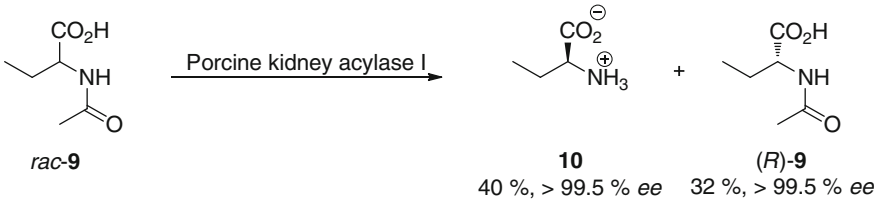
4.2.6 Asymmetric Synthesis

4.2.6.1 Chiral Reagents

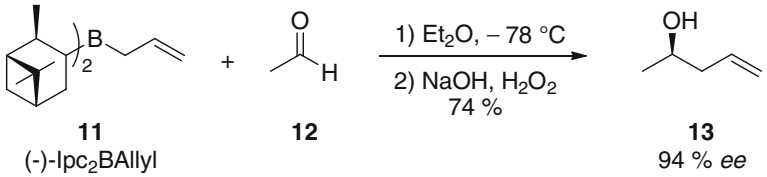
A chiral reagent can also be used as the source of stereoinduction in the synthesis of an enantioenriched compound. They are used in stoichiometric quantities and some typical examples are chiral lithium amide bases to asymmetrically deprotonate a ketone, chiral reducing reagents, such as BINAL-H, to asymmetrically reduce a



Scheme 4.3 Sharpless kinetic resolution of allylic alcohols



Scheme 4.4 Enzymatic resolution using acylase enzymes



11
(-)-Ipc$_2$BAllyl

12

13
94 % *ee*

Scheme 4.5 Brown allylation using a chiral reagent for asymmetric addition to aldehydes

ketone and the use of chiral boron reagents for enantioselective addition to carbonyls. A commonly used example is the Brown crotylation and allylation reagents for asymmetric addition to a prochiral aldehyde. The chiral allylation reagent (**11**) can be easily prepared from (+) or (−)-α-pinene and used to form homoallylic alcohols (**13**) in high *ee* (Scheme 4.5) [11, 12].

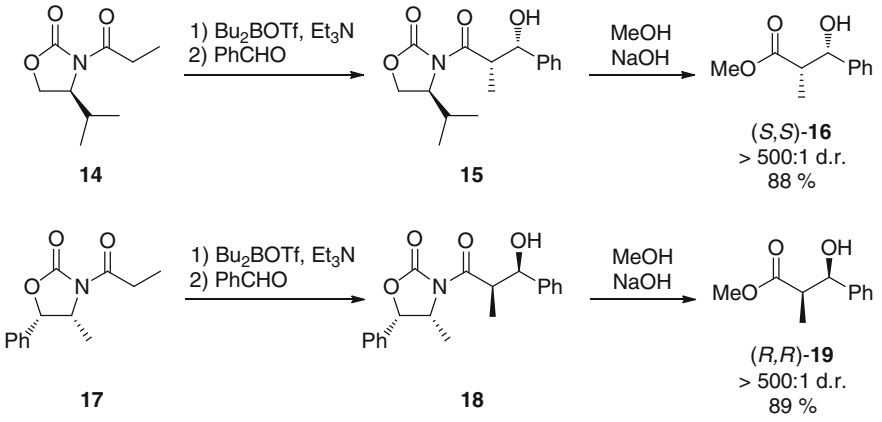
4.2.6.2 Chiral Auxiliaries

A chiral auxiliary is an enantiomerically pure chiral molecule which is attached to a prochiral molecule in order to control the stereoselectivity of a reaction. Following a reaction on the prochiral portion of the molecule a pair of diastereomers is produced which can be separated by conventional chromatographic techniques. Subsequently, the chiral auxiliary can be removed, and recovered in some instances, to yield the enantioenriched product [13]. One of the most successful chiral auxiliaries was developed by Evans. These oxazolidinone-based auxiliaries are formed from amino acids such as valinol in the case of **14** or other chiral pool reagents such as ephedrine as in the case of **17**, each giving access to a different configuration of the newly formed stereocentre [14]. The initial report of these auxiliaries demonstrated their use in a diastereoselective aldol condensation using boron-enolates with exceptionally high levels of selectivity (Scheme 4.6). A number of methods for the removal of the auxiliaries were also developed, including converting the oxazolidinone into carboxylic acids, esters and primary alcohols. These auxiliaries have subsequently been applied in a number of asymmetric transformations including Diels-Alder cycloadditions [15].

4.2.7 Catalytic Asymmetric Synthesis

4.2.7.1 Enzymatic Catalysis

Generally enzymes are highly selective, both in terms of the substrates they can act on and the levels of enantioselectivity that can be induced. In many cases enzymes must be modified for a particular substrate. They are usually only stable in aqueous media and are highly sensitive to pH and temperature. A particular enzyme can be

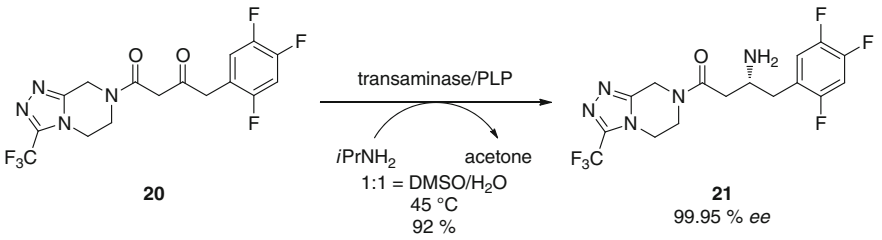


Scheme 4.6 Evans' oxazolidinone-based chiral auxiliaries in diastereoselective aldol condensations

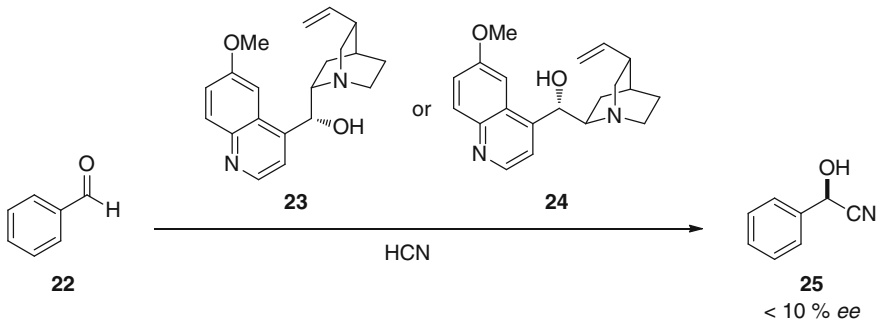
selectively modified to improve recognition of the substrate and selectivity of the asymmetric transformation. Modifications can also improve the stability of the enzyme and its tolerance to organic solvent and pH. The speed of the development of biocatalysis has greatly improved with advances in directed evolution in the 1990s. The blockbuster type II diabetes drug developed by Merck, sitagliptin (**21**), uses a transaminase enzyme to achieve an asymmetric amination of a ketone (Scheme 4.7) [16]. The original large scale industrial synthesis was achieved by asymmetric hydrogenation of an enamine at 250 psi H_2 pressure. The biocatalytic route, developed by a directed evolution approach, requires one fewer step and also eliminates a crystallisation required to increase the enantiomeric purity.

4.2.7.2 Organocatalysis [17]

Organocatalysis can be defined as the acceleration of chemical reactions with a sub-stoichiometric amount of an organic compound which does not contain a metal atom [18]. The first example of an asymmetric organocatalytic reaction was



Scheme 4.7 Asymmetric biocatalytic amination of a pro-sitagliptin ketone

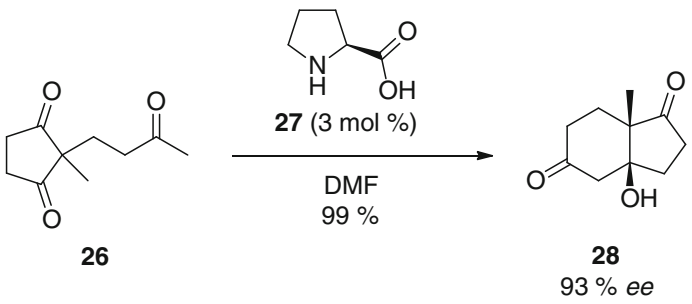


Scheme 4.8 Organocatalytic addition of cyanide to benzaldehyde

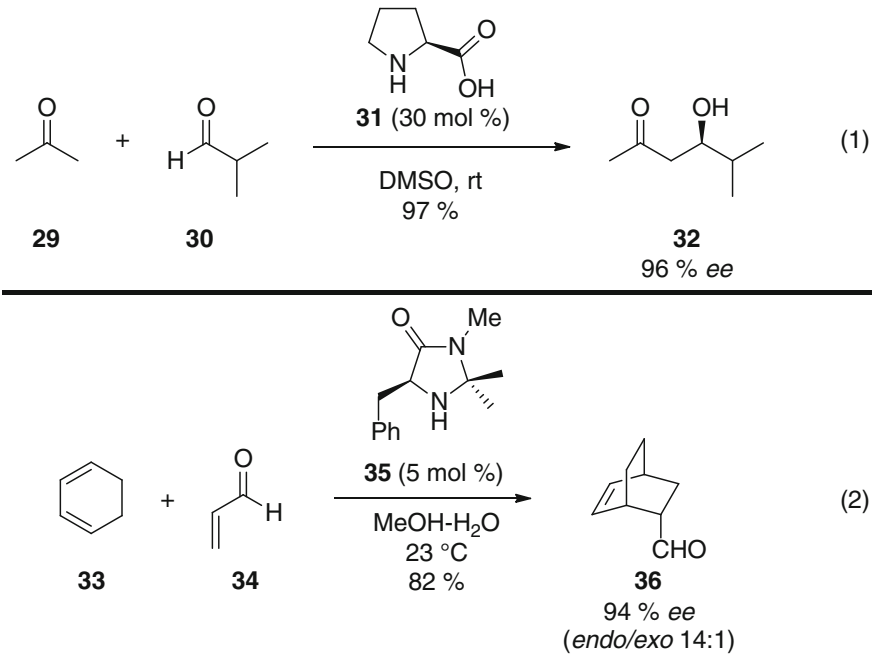
reported by Bredig and Fiske in 1912 using the cinchona alkaloids quinine (**23**) and quinidine (**24**) to catalyse the addition of cyanide to benzaldehyde (**22**) forming mandelonitrile (**25**) with <10 % *ee* (Scheme 4.8) [19].

The next breakthrough was made by Pracejus in 1960 who also used alkaloids as catalysts, namely *O*-acetlyquinine in the addition of methanol to phenylmethylketene in an impressive *ee* of 74 % [20]. Then in 1973 the (*S*)-proline (**27**) catalysed Robinson annulation was discovered by Hajos and Parrish and independently by Wiechert and co-workers [21, 22]. High levels of enantioselectivity of up to 93 % were observed using 3 mol% of catalyst in the transformation which later became known as the Hajos-Parrish-Eder-Sauer-Wiechert reaction (Scheme 4.9).

The first organocatalytic intermolecular asymmetric aldol reaction was reported by List and coworkers in 2000 [23]. The aldol reaction between acetone and a variety of aldehydes was accomplished in excellent yields and high levels of enantioselectivity. For example, the aldol product of the coupling with *iso*-butyraldehyde was formed in 97 % yield and 96 % *ee* ((1), Scheme 4.10). The remarkable levels of selectivity sparked massive interest in the field of proline-catalysed aldol, Michael and Mannich reactions. Later that year MacMillan reported a phenylalanine-derived catalyst (**35**) for the Diels-Alder reaction of α-β-unsaturated aldehydes with up to 94 % *ee* ((2), Scheme 4.10) [24]. Many further applications of



Scheme 4.9 Hajos-Parrish-Eder-Sauer-Wiechert reaction



Scheme 4.10 Organocatalytic aldol (1) and Diels-Alder (2) reactions

catalyst (**35**) were subsequently reported and the field developed into a distinct area of catalysis.

4.2.7.3 Transition Metal Catalysis

Transition metal mediated asymmetric catalysis is a cornerstone of organic chemistry. To emphasise its importance to the field the Nobel Prize in Chemistry was awarded jointly to Knowles and Noyori for their work on chirally catalysed hydrogenation reactions and to Sharpless for his work on chirally catalysed oxidation reactions in 2001 in recognition of their pioneering contributions to the development of transition metal catalysed transformations. The application of these transformations in industrial processes further emphasises their importance [25].

A chiral transition metal catalyst generally consists of a metal atom ligated by a chiral organic molecule. This coordination complex can influence the outcome of a reaction by interacting with a substrate. This interaction involves coordination of the substrate to a vacant site on the metal atom. The ligand is covalently bound to the ligand via donor atoms such as P, N, O or S, typically in a bidentate fashion to form the chiral metal complex (Fig. 4.2). The complex can transfer its chiral information to a substrate when it binds to the metal. The nature of the donor atoms and the backbone through which they are linked can have a profound effect on the

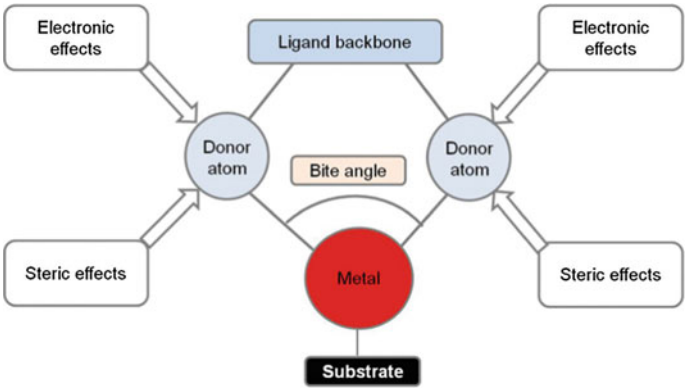


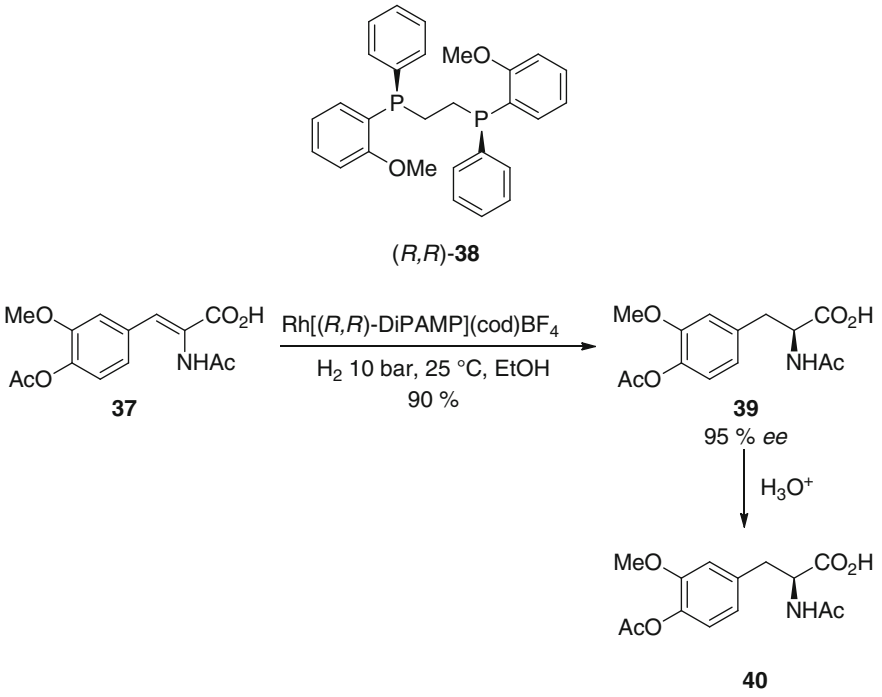
Fig. 4.2 General components of a transition metal bidentate ligand complex [26]

reactivity of the complex and on the outcome of the stereoselective reaction. Therefore, the ligand can be modified both sterically and electronically to improve the levels of enantioselective and/or reactivity of a particular asymmetric transformation.

The first and possibly the most significant reports of transition metal catalysed asymmetric transformations were reported by Nozaki, Noyori, Knowles and Horner in the 1960s. In particular Knowles and Horner independently reported the first homogeneous asymmetric hydrogenation of olefins with chiral monodentate tertiary phosphine-Rh complexes, albeit in low *ee*'s of 3–15 %. Kagan then made a significant breakthrough by developing a C_2 chiral diphosphine ligand, DIOP, derived from tartaric acid. This ligand was used in the Rh-catalysed asymmetric hydrogenation of dehydroamino acids in 80 % *ee*. Knowles and Monsanto then developed the Rh-catalysed asymmetric hydrogenation used for the industrial synthesis of L-DOPA (**40**), a drug used in the treatment of Parkinson's disease, using a DiPAMP ligand (**38**) increasing the *ee* up to 95 % (Scheme 4.11) [27]. These discoveries led to an explosion of research in asymmetric transition metal catalysis which continues apace to this day.

The development of a vast number of chiral ligands has been the key aspect in the development of the field. The potential for variation of these ligands is almost endless by variation of the donor atoms and the ligand backbone. Bidentate chiral ligands which possess central chirality, planar chirality and axial chirality have all been applied in a range of transformations. The most effective donor atoms in these ligands are *P*,*P, N*,*N* and *P*,*N* systems [28].

Other than the L-DOPA, there have been two other significant processes developed for industrial applications. The first of these uses a Sharpless asymmetric epoxidation, one of the most widely applied asymmetric transition metal catalysed transformations, to convert allyl alcohol (**41**) into (*S*)-glycidol (**43**), a valuable chiral building block, developed by ARCO Chemical Company (Scheme 4.12) [29]. Most of the successful applications of transition metal mediated asymmetric



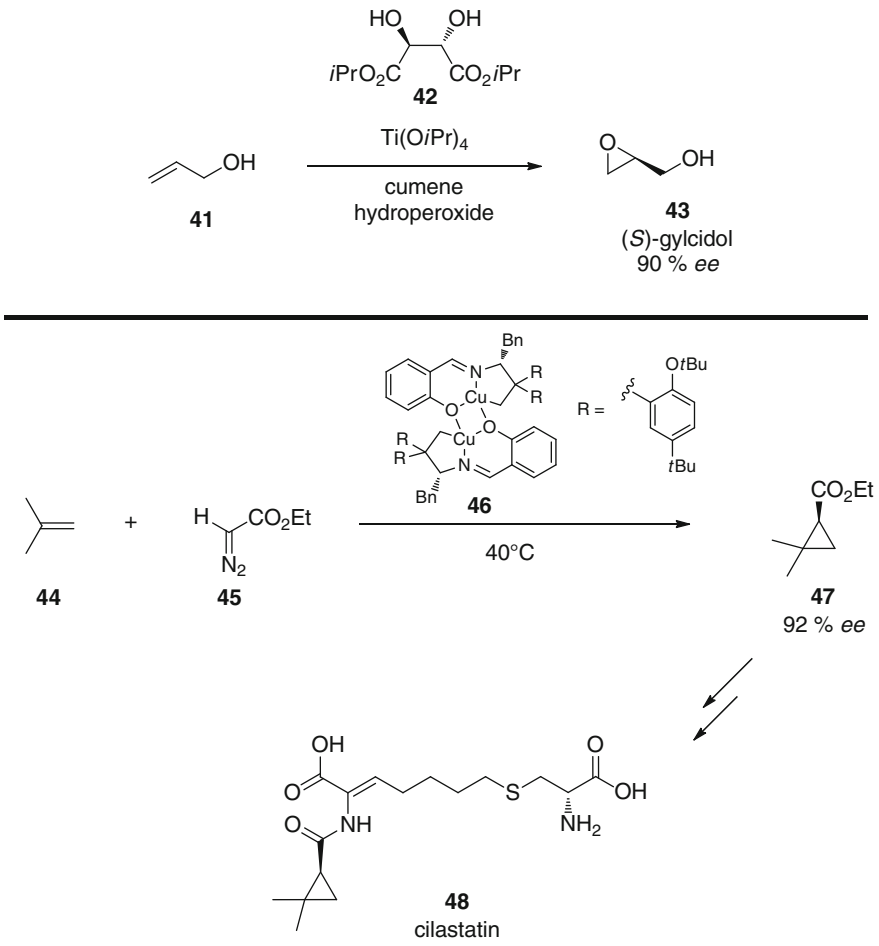
Scheme 4.11 Rh-catalysed asymmetric hydrogenation in the synthesis of L-DOPA

catalysis have been reduction and oxidation processes as illustrated in the previous two examples. An example of a successful carbon-carbon bond forming process is the asymmetric cyclopropanation of 2-methyl propene (**44**) to generate an intermediate in the synthesis of cilastatin (**48**), administered with the antibiotic imipenem to prevent its degradation (Scheme 4.12) [30].

4.3 Palladium-Catalysed Allylic Alkylation

4.3.1 Carroll Rearrangement

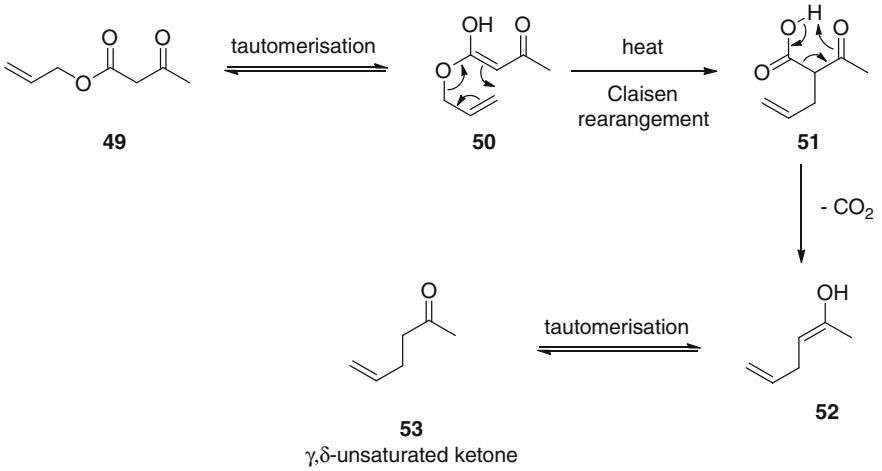
In 1940 Carroll reported the rearrangement of β-keto allyl esters (**49**) followed by decarboxylation to yield γ,δ-unsaturated ketones (**53**) via a [3,3]-sigmatropic (Claisen) rearrangement (Scheme 4.13) [31]. The reaction has found limited scope in organic synthesis due to the harsh conditions required (130–220 °C) to induce the rearrangement.



Scheme 4.12 Industrial applications of asymmetric transition metal catalysis

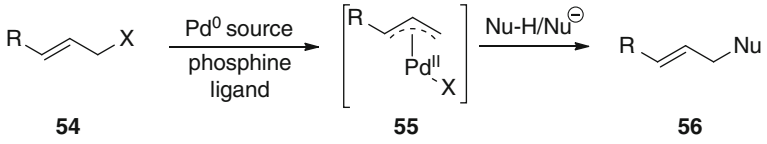
4.3.2 Tsuji-Trost Allylation

The Pd-catalysed allylation of carbon nucleophiles with allylic compounds via π-allylpalladium complexes is called the *Tsuji-Trost reaction* [32]. Typically, an allyl acetate or carbonate (**54**) reacts with a Pd-catalyst resulting in displacement of the leaving group to generate a π-allylpalladium complex (**55**) that can undergo substitution by a nucleophile (**56**) (Scheme 4.14). In 1965, Tsuji reported the reaction of π-allylpalladium chloride with nucleophiles such as enamines and anions of diethyl malonate and ethyl acetoacetate. A catalytic variant was soon reported thereafter in the synthesis of allylic amines [33]. In 1973, Trost described the alkylation of alkyl-substituted π-allylpalladium complexes with methyl methylsulfonylacetate

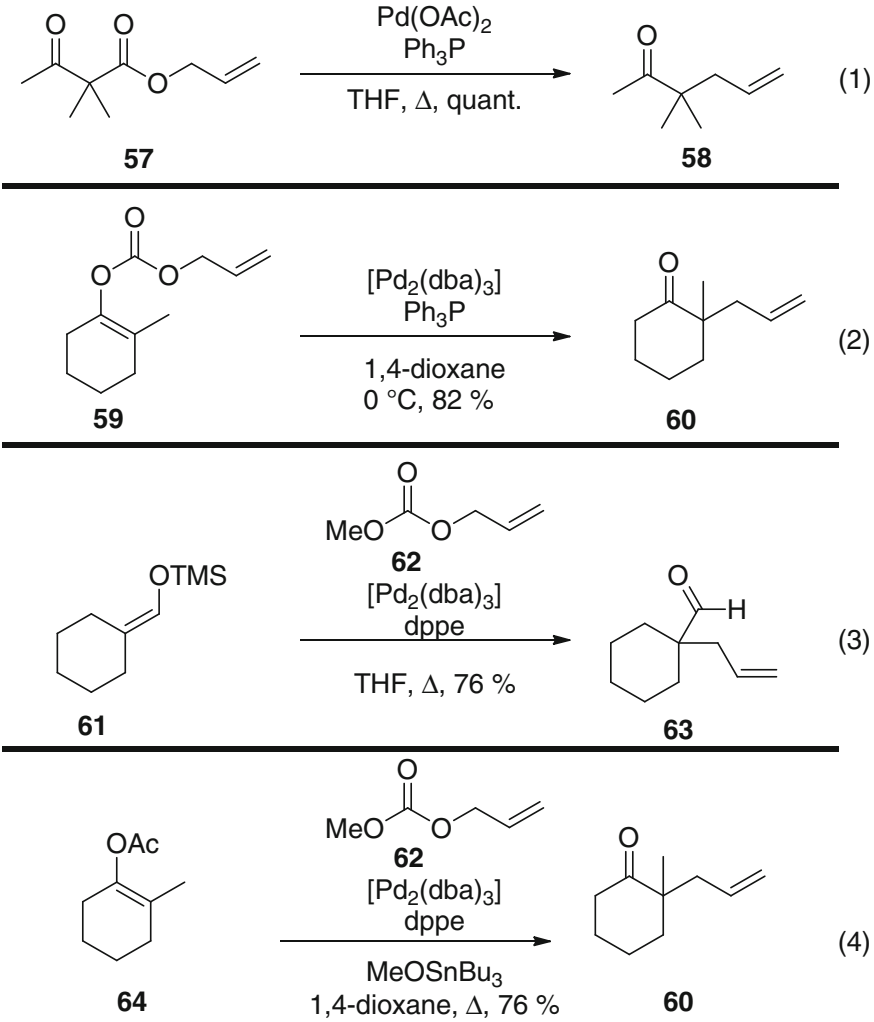


Scheme 4.13 Carroll rearrangement of β-keto allyl esters

with complete regio- and stereoselectivity [34]. The first asymmetric allylic alkylation (AAA) was then reported by Trost in 1977 and since then great strides have been made in increasing the enantioselectivity and applicability of this reaction [35]. Seminal work by Hayashi, Ito, Trost, Hou and Dai led to the extensive development of an asymmetric synthesis of quaternary stereocentres by applying the Pd-catalysed allylic to prochiral stabilised enolates. This was subsequently further extended by Trost, Hou and Dai to unstabilised ketone enolates containing a single acid site. In 1980 Tsuji and Saegusa independently reported the decarboxylative allylation of β-keto allyl esters ((1), Scheme 4.15) wherein the electrophile and nucleophile are generated in situ eliminating the requirement to prepare preformed enolate equivalents. During the 1980s Tsuji extended the viable substrates to allyl enol carbonates ((2), Scheme 4.15), silyl enol ethers ((3), Scheme 4.15) and enol acetates ((4), Scheme 4.15). A key aspect of the decarboxylative variant is the ability to generate quaternary stereocentres when applied to unstabilised enolates or enol equivalents under effectively neutral reaction conditions. As a result it can be applied to substrates containing more than one acidic site without scrambling of the enolate and hence allylation occurs at single site.



Scheme 4.14 The Tsuji-Trost allylation reaction



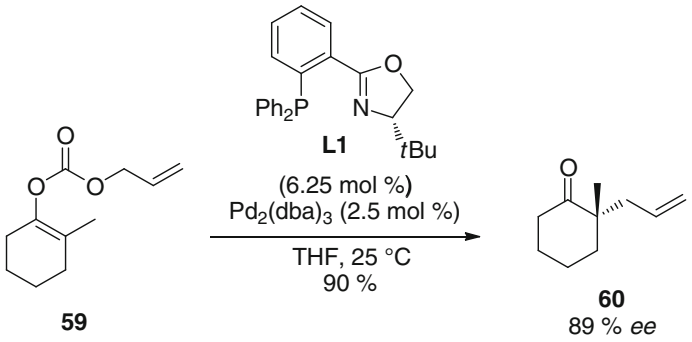
Scheme 4.15 Tsuji allylation reactions from a variety of precursors

4.3.3 Decarboxylative Asymmetric Allylic Allylation (DAAA)

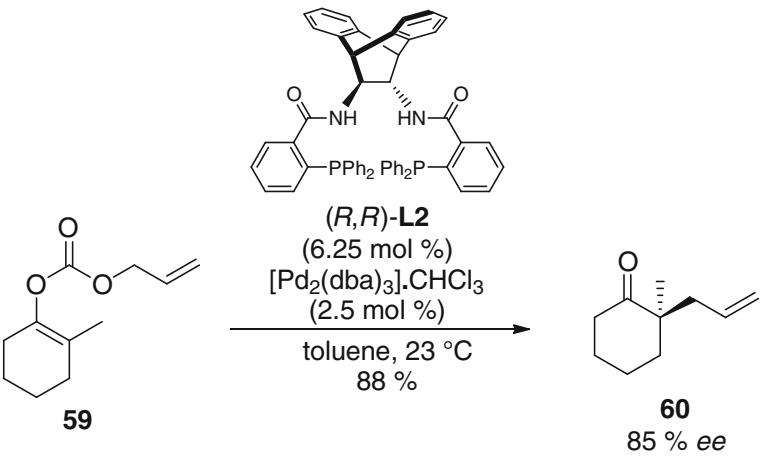
The first decarboxylative asymmetric allylic alkylation (DAAA), also known as the asymmetric Tsuji allylation, was reported by Stoltz in 2004 from allyl enol carbonate substrates (**59**) to generate cyclic α-allyl ketones (**60**) (Scheme 4.16) [36]. Following an initial ligand screening it was found that chelating *P*,*N*-ligands were the most effective at generating the newly formed quaternary stereocentre in high levels of enantioselectivity and yield. In particular, *tert*-butyl phosphinooxazoline ((*S*)-*t*-BuPHOX, **L1**) was the most effective. This ligand class was developed by

Pfaltz, Helmchen and Williams in the 1990s and has repeatedly been shown to be an excellent chiral ligand for a wide variety of asymmetric transformations [37, 38]. Utilising *t*-BuPHOX with Pd_2dba_3 led to the first asymmetric synthesis of 2-allyl-2-methlycyclohexanone in 89 % *ee*, which had not been previously been accessible via AAA due to enolate scrambling in situ. This mild methodology was extended to more complex substrates including ones with a quaternary centre adjacent to the C where the new quaternary centre would be generated with little erosion in *ee* despite the steric encumbrance. Interestingly this protocol showed little effect on the enantioselectivity for a variety of solvents screened such as diethyl ethyl, methyl *tert*-butyl ether, ethyl acetate and toluene.

In 2005 Trost reported a similar system using enol carbonate substrates for the enantioselective allylic alkylation of cyclic ketones (Scheme 4.17) [39]. The best ligand for the transformation was (*R,R*)-ANDEN-Trost ligand (**L2**) which provided



Scheme 4.16 The first decarboxylative asymmetric allylic alkylation



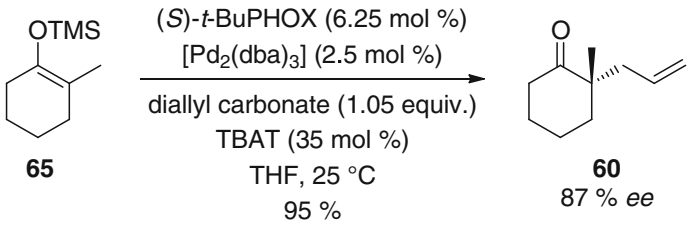
Scheme 4.17 Decarboxylative asymmetric allylic alkylation using (*R,R*)-ANDEN-Trost ligand

the allylic alkylation products in high *ee* and tertiary stereocentres are also accessible. Curiously, this *P*,*P*-ligand gave high levels of enantioselectivity whereas in the system reported by Stoltz it was found that the *P*,*P*-ligands they screened achieved poor to moderate levels of enantioselectivity. Trost also observed that the sense of stereoinduction was the opposite of what was observed for the Pd-catalysed AAA on Li-enolates using the same chiral ligand. The fact that both are the enol carbonate and Li-enolate are presumed to go through the same enolate with Pd as the counterion is suggestive of two different mechanisms such as outer sphere in the Li-enolate versus inner sphere in the enol carbonate.

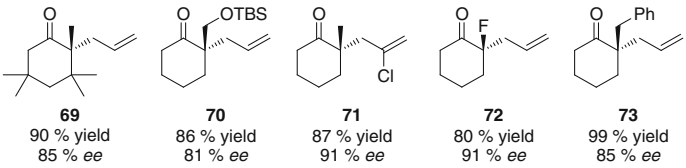
Trost was importantly able to extend this catalyst system to DAAA of acyclic enolate precursors to form a number of α-tertiary ketones using the same catalytic conditions [40]. More significant was the observation that the geometry of the enolate precursor affected both the rate of the reaction and the absolute configuration of the product suggesting that there is no significant geometric isomerisation of the enol carbonate or the Pd-enolate complex.

Stoltz reported the extension of their methodology to silyl enol ether substrates (Scheme 4.18) [36]. In many cases these enolate precursors are easier to prepare compared to their enol carbonate counterpart. The addition of diallyl carbonate was necessitated to generate the enol carbonate in situ. Tetrabutylammonium difluorotriphenylsilicate (TBAT) was also required to activate the cleavage of the enol silane in situ at a temperature for asymmetric induction to occur. Nearly identical levels of enantioselectivity were obtained with this system.

Although both the use of allyl enol carbonates and silyl enol ethers have proved successful in the DAAA reaction, there is a considerable problem in the regioselective preparation of these substrates. If poor selectivity is observed for the desired enol ether formation this will be translated into a mixture of allylated products. To circumvent this problem Stoltz, inspired by the earlier work of Tsuji and Saegusa, looked toward β-keto allyl esters as possible substrates knowing that the enolate generation is regiospecific, they are relatively simple to prepare and quaternary β-keto esters are bench-stable compounds. They found these substrates could in fact be applied in the DAAA reaction in excellent yields and enantioselectivities (Scheme 4.19). Due to the presence of a chiral centre inherent in the β-keto ester substrates this transformation is an example of enantioconvergent catalysis—a synthetic method that converts a racemic stereogenic substrate into an



Scheme 4.18 Decarboxylative asymmetric allylic alkylation using silyl enol ethers



69
90 % yield
85 % *ee*

70
86 % yield
81 % *ee*

71
87 % yield
91 % *ee*

72
80 % yield
91 % *ee*

73
99 % yield
85 % *ee*

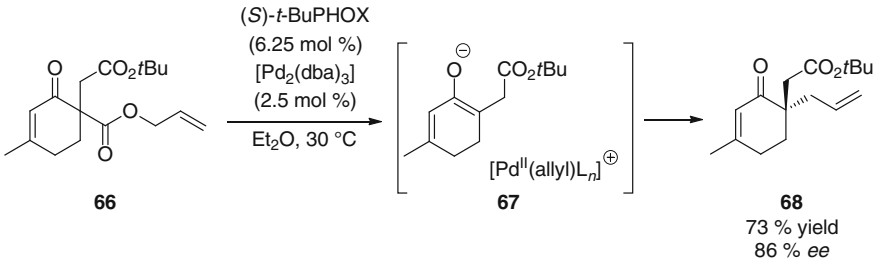
Fig. 4.3 Scope of the decarboxylative asymmetric allylic alkylation using β-keto esters

enantioenriched product. The use of β-keto allyl esters for the DAAA is an example of stereoablative enantioconvergent catalysis wherein the chiral centre is destroyed and converted into an achiral substrate which subsequently reforms the chiral centre with enantioenrichment.

The scope was found to be quite broad with sterically demanding substrates or those that contain a β-leaving group (no elimination) or other α-acidic functionality (no enolate scrambling). An α-fluorine atom could also be tolerated (Fig. 4.3).

Trost and co-workers subsequently reported the use of β-keto allyl esters in the Pd-catalysed DAAA using their (*R,R*)-ANDEN-Trost ligand (**L2**) (Scheme 4.20). In their work they were attempting to develop an asymmetric synthesis of γ,γ-disubstituted cycloalkenones. In order to achieve this they required a vinylogous ester with a heteroatom in the 3-position. They found similar difficulties in the regioselective synthesis of the enol carbonate and so turned to β-keto esters as an alternative. They found that an ether substituent in the 3-position led to poor reactivity when compared to the corresponding enol carbonate. As a result they turned to the corresponding thioether (**74**) as an alternative and this led to improved conversions and they obtained the allylated products in high *ee*'s. Nearby Lewis basic groups, such as alkynes or carbonyls, were found to have a detrimental effect on the *ee* which was proposed to be as a result of coordination to Pd during the enantiodetermining step.

More recently Stoltz has described the application of an electron-deficient PHOX ligand, namely (*S*)-$(CF_3)_3$-*t*-BuPHOX (**L3**) in the DAAA of enolate-stabilised enol carbonates (Scheme 4.21) [41]. The reaction was carried out in a mixture of hexane and toluene and this gave high levels of enantioselectivity. It was proposed that both the low polarity of the solvent and the electron-deficient



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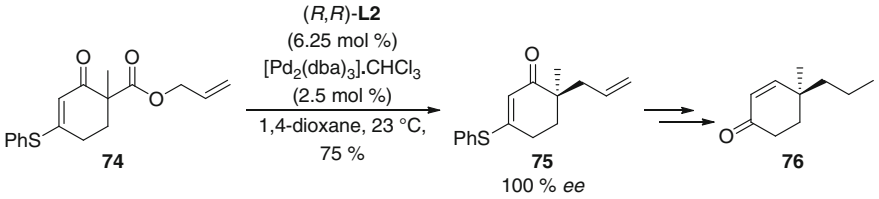
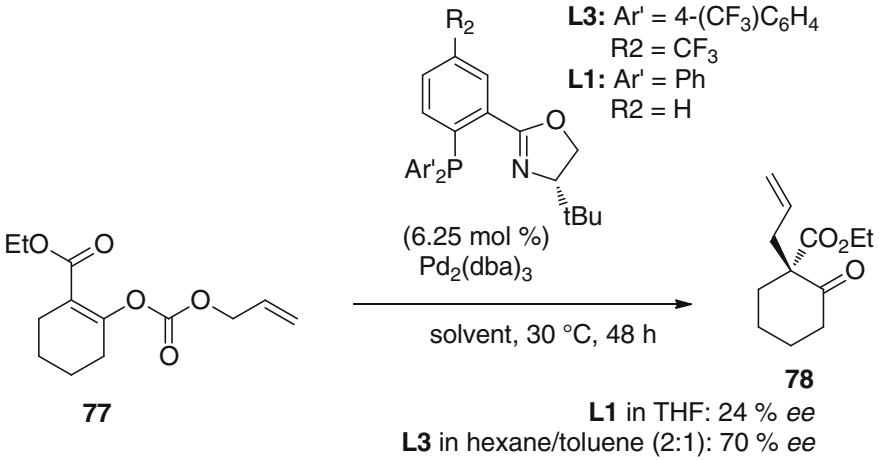
67

68
73 % yield
86 % *ee*

Scheme 4.19 Decarboxylative asymmetric allylic alkylation using β-keto esters



Scheme 4.20 DAAA using β-keto esters to generate γ,γ-disubstituted cyclohexanones



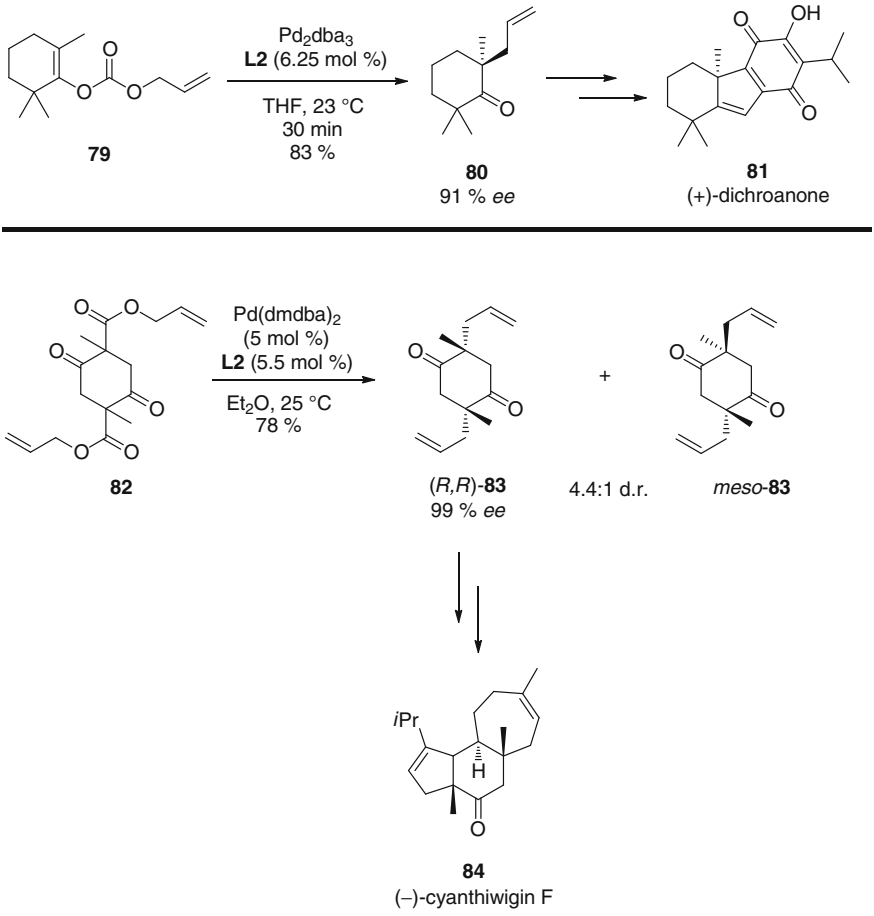
Scheme 4.21 DAAA using an electro-deficient PHOX ligand **L3**

ligand helped to form a tighter Pd-enolate complex leading to improved levels of enantioselectivity.

The DAAA has successfully been applied as a key step in the total synthesis of a number of natural products due to its ability to generate quaternary carbon centres enantioselectively. For example (+)-dichroanone (**81**), [42] oxybutynin, [43] (−)-cyanthiwigin F (**84**) [44] and other examples (Scheme 4.22) [45, 46]. As alluded to above the DAAA has also been extended to the asymmetric synthesis of α-fluorinated cyclohexanones, an important class of compounds for medicinal chemistry [47].

4.3.4 Mechanism of the DAAA

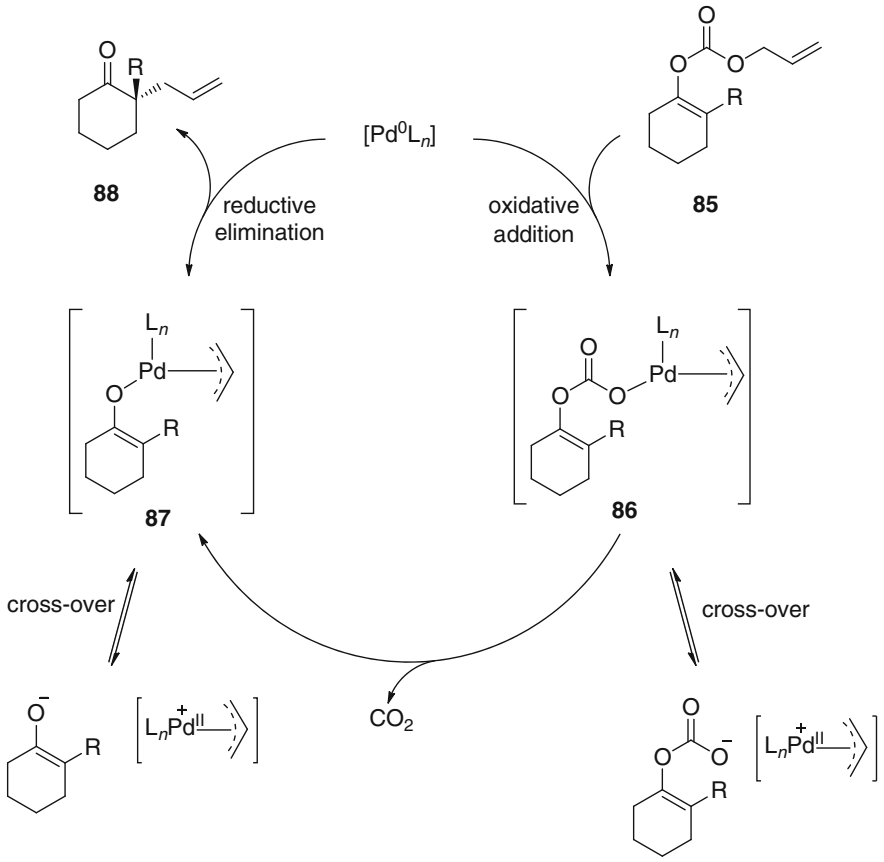
The accepted mechanism involves coordination of the Pd^0 complex to the allyl fragment, subsequent oxidative insertion (**86**) followed by loss of CO_2 to generate a Pd-enolate (**87**) which could then attack the allyl group via reductive elimination to



Scheme 4.22 DAAA in the total synthesis of natural products

form the product (**88**) and regenerate the Pd^0 species (Scheme 4.23). There has been minimal mechanistic evidence proposed to date to prove the mechanism of bond formation or to explain the origin of enantioselectivity.

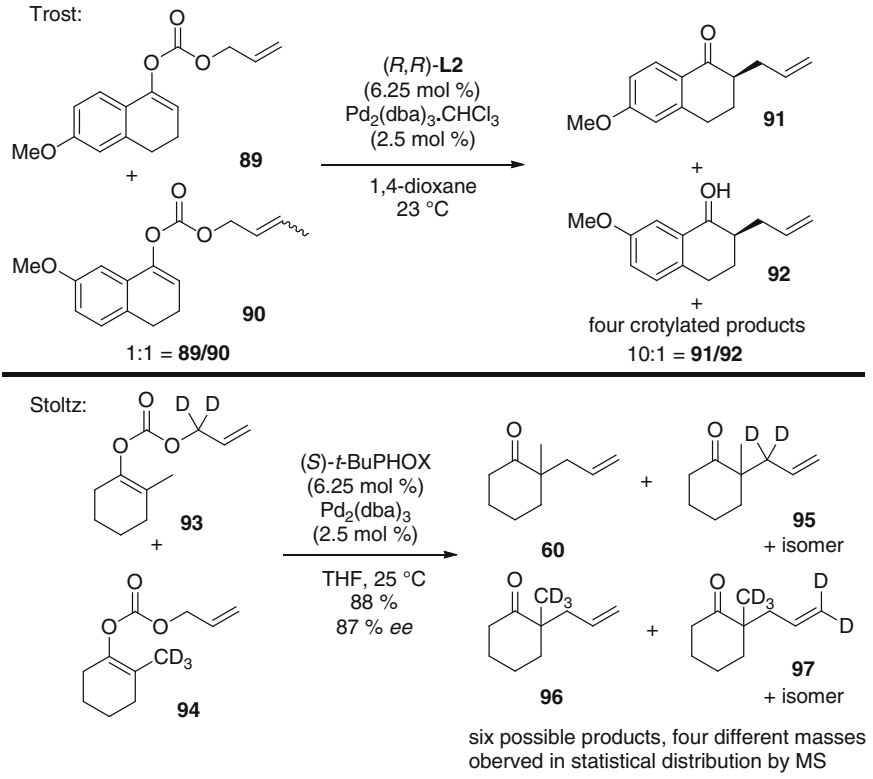
Cross-over experiments were reported by the groups of Stoltz and Trost (Scheme 4.24). The Trost group observed minimal cross-over between the allyl and crotyl fragments in their experiment. It was suggested that this was because the rate of alkylation was faster that the rate of ion diffusion. They believed this was due to solvent caged ion-pairs in dioxane. However, the Stoltz group observed complete cross-over in their deuterium labelling experiment in dioxane, THF and benzene. This highlights the vast different between Stoltz's PHOX and the Trost's bis-phosphine systems. Further evidence of this is the variation on the tolerance of



Scheme 4.23 Proposed mechanism of the decarboxylative asymmetric allylic alkylation

water in both systems. The Trost system is very sensitive to very low levels of water whereas the Stoltz system is considerably more tolerant.

The two plausible mechanisms for the DAAA are either via inner-sphere or outer-sphere attack of the allyl group (Scheme 4.25). As mentioned previously the different selectivity observed by Trost between the Li-enolate and the enol carbonate is suggestive of an inner-sphere mechanism via a Pd-enolate rather than an outer-sphere mechanism as is typically seen in other π-allyl alkylations [48]. The limited enolate scrambling observed in the DAAA would be consistent with an inner-sphere mechanism. A series of computational studies were carried out by Stoltz which suggest that the inner-sphere mechanism is lower in energy that the

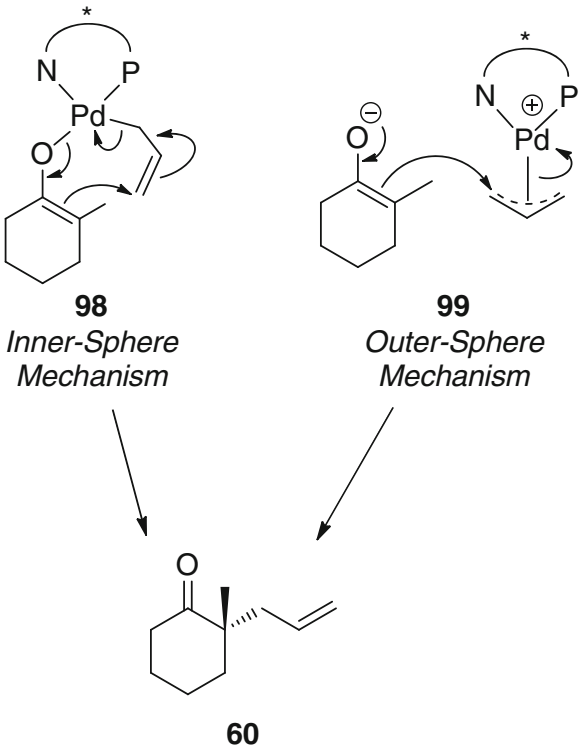


Scheme 4.24 Cross-over experiments performed by Trost and Stoltz

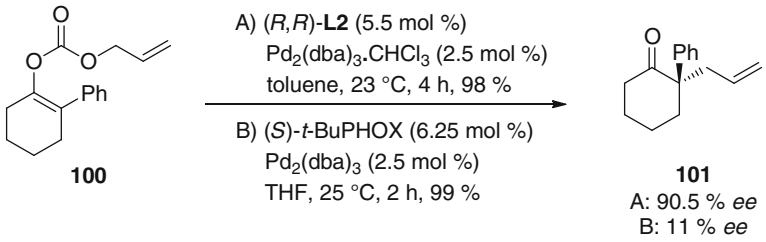
outer-sphere pathway, albeit by a small amount (1.6 kcal/mol) [49]. The most recent study provided rationale for the enantioselectivity via an inner-sphere mechanism involving formation of a 5-coordinate Pd species which undergoes a selective ligand rearrangement followed by reductive elimination to generate the product and a Pd^0 complex [50]. To date this has yet to be verified experimentally.

The rate of the decarboxylative allylic alkylation appears to be limited by the rate of decarboxylation. For example, Ohta and co-workers described the decarboxylative allylic alkylation of α-phenyl substituted malonic ester derivatives which occurred at much lower temperature when compared to its α-alkyl counterpart. Hence the rate of decarboxylation is dependent on the stability of the enolate which is formed in situ. The benzylic enolate has a lower pK_a by around 6–7 units.

The marked differences between the Trost and Stoltz catalytic systems were further illustrated when both systems were applied to an α-phenyl substituted enol carbonate. The Trost system could form the allylated product in 90 % *ee* whereas the Stoltz PHOX system only achieved 11 % *ee*.



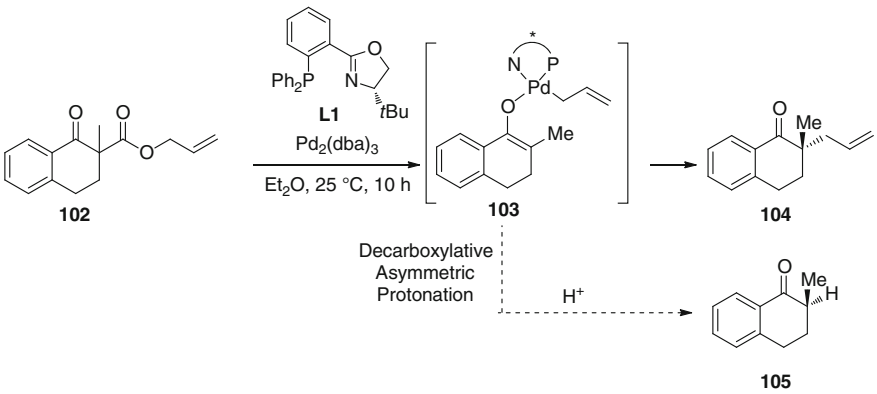
Scheme 4.25 Inner-sphere versus outer-sphere mechanism in the DAAA



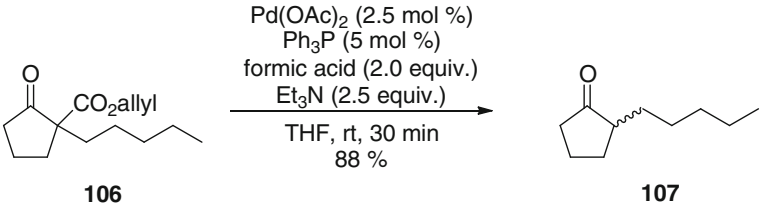
Scheme 4.26 Illustrative example of the differences between the Stoltz and Trost systems

4.4 Palladium-Catalysed Decarboxylative Asymmetric Protonation (DAP)

A key extension of the DAAA was realised by Stoltz and co-workers in 2006 with their seminal report on a stereoablative enantioconvergent decarboxylative asymmetric protonation [51]. This was realised by intercepting the intermediate (**103**)



Scheme 4.27 Concept of a decarboxylative asymmetric protonation reaction

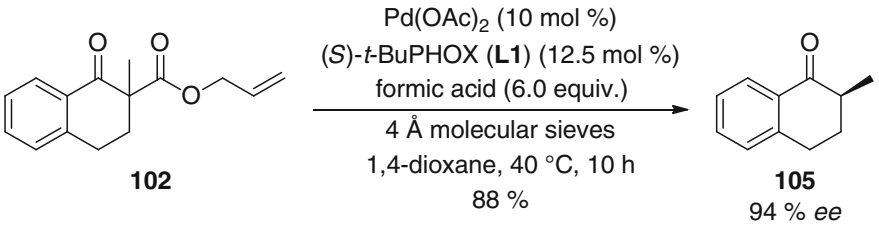


Scheme 4.28 Tsuiji's racemic decarboxylative protonation

generated from a DAAA reaction with a proton source to generate tertiary carbon stereocentres (**105**) (Scheme 4.27). This racemic version of this reaction was first reported by Tsuji using $Pd(OAc)_2$ and Ph_3P in the presence of ammonium formate as the H^+ source, generated from formic acid and Et_3N, to form a number of tertiary α-alkyl ketones (**107**) in good yields (Scheme 4.28).

The enantioselective version developed by Stoltz was optimised using β-keto allyl ester **102**. As in the report by Tsuji, $Pd(OAc)_2$ was used as the Pd source in the presence of (*S*)-*t*-BuPHOX with formic acid in the presence of Et_3N, however, this only led to an *ee* of 7 %. An improvement to 24 % was observed in the absence of Et_3N and, upon the addition of molecular sieves to sequester the small amounts of water present in commercially available formic acid, the *ee* increased drastically to 72 %. Switching the molecular sieves for 3–4 Å and the solvent from THF to 1,4-dioxane and optimisation of the quantity of formic acid and the molecular sieves further increased the *ee* to 94 % (Scheme 4.29).

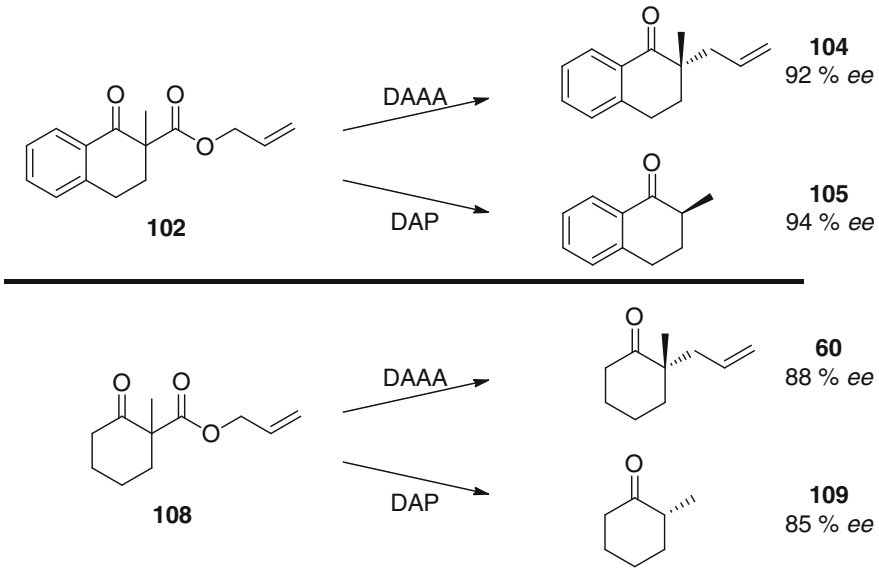
The optimised conditions were then applied to a range of cyclic α-alkyl and α-benzyl substituted β-keto allyl esters to generate the corresponding α-tertiary ketones in good yields and excellent enantioselectivities. Interestingly the fused aromatic substrates such as tetralone **102** gave the opposite sense of stereoinduction in the resulting tertiary product (**105**), compared to the monocyclic compounds such



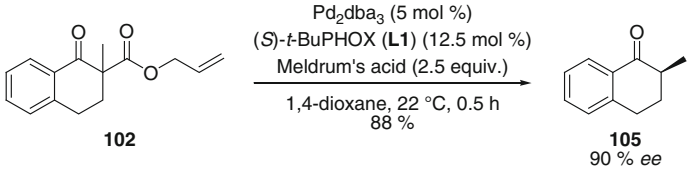
Scheme 4.29 Heterogeneous asymmetric decarboxylative protonation

as cyclohexanone **109**. This result is in stark contrast to the DAAA where consistent enantiofacial selectivity is observed on both fused aromatics (**104**) and monocyclic (**60**) compounds. This further suggests that these two processes proceed via two different pathways.

In 2008 Stoltz and co-workers reported a homogeneous DAP methodology wherein Meldrum's acid was used as the H^+ source (Scheme 4.31) [52]. A number of organic proton donors were screened using Pd_2dba_3 as the Pd source, (*S*)-*t*-BuPHOX as the chiral ligand. Meldrum's acid gave the highest levels of enantioselectivity during the initial screen at 22 °C in 1,4-dioxane. Subsequently a number of Meldrum's acid derivatives were screened varying the steric bulk and electronics of the H^+ source. Although some of these derivatives gave a slightly increased level of enantioselectivity, it was not sufficient to justify replacing the



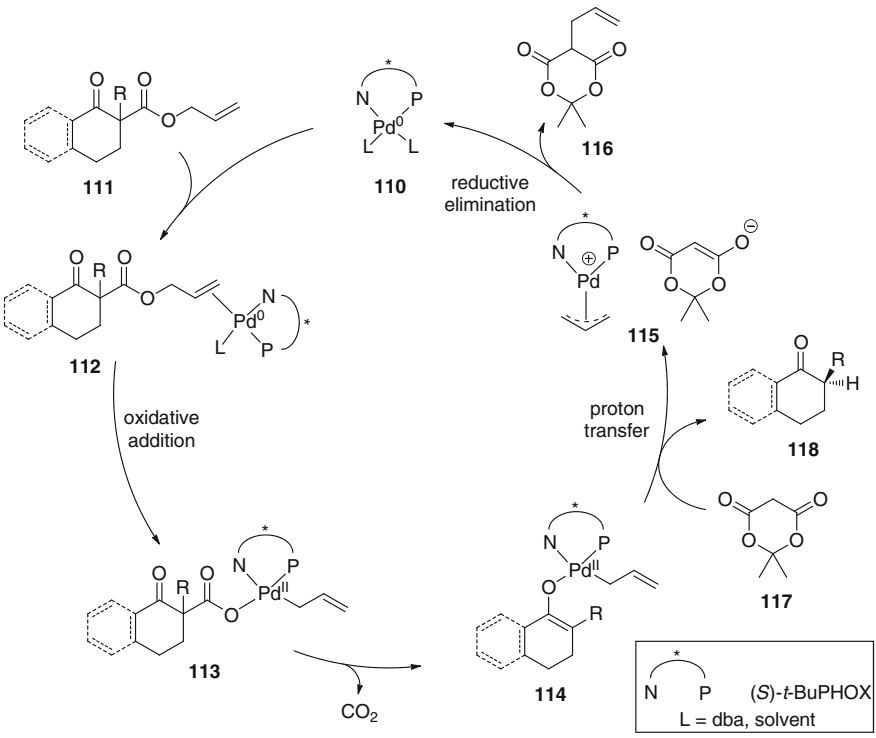
Scheme 4.30 Stereoselectivity differences between decarboxylative asymmetric allylation and protonation



Scheme 4.31 Homogeneous asymmetric decarboxylative protonation

readily available Meldrum's acid as the H^+ source. A similar substrate scope to the heterogeneous conditions was reported to form a number of tertiary α-alkyl/benzyl ketones in high levels of enantioselectivity. Notably the sense of stereoinduction observed was the same as in the heterogeneous conditions, i.e. fused aromatic and monocyclic ketones gave the opposite sense of stereoinduction.

Stoltz and co-workers proposed a catalytic cycle based on observations including the formation of diallylated Meldrum's acid and an understanding of the DAAA process (Scheme 4.32). Kinetic studies suggested the β-keto ester reacts very quickly to generate a Pd-enolate or Pd-carboxylate and this then undergoes asymmetric protonation in a slower second step. The catalytic cycle begins with



Scheme 4.32 Proposed mechanism for the decarboxylative asymmetric protonation

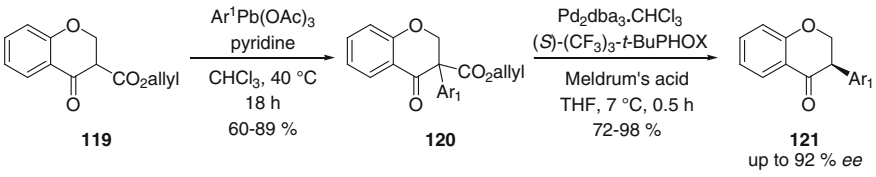
coordination of the Pd^0 complex to the allyl unit of the β-keto ester (**112**). This is followed by oxidative insertion (**113**) and subsequent loss of CO_2 which generates Pd-enolate (**114**). Proton transfer occurs from Meldrum's acid (**117**) to generate the α-tertiary centre (**118**) and the allyl group is transferred to Meldrum's acid to form **116**. This mono-allylated Meldrum's acid was not isolated, only the di-allylated remains after reaction completion.

4.5 Synthesis of Isoflavanones Using DAP

Building on the success of the DAP and the ability of aryllead triacetates to *C*-arylate β-keto esters this research group developed the first catalytic asymmetric synthesis of isoflavanones (Scheme 4.33) [53]. A series of α-aryl-β-keto allyl esters (**120**) were prepared and were converted into a series of isoflavanones (**121**) using the DAP in good to excellent overall yields. Application of the homogeneous conditions developed by Stoltz resulted in poor levels of enantioinduction for this class of substrate. This was unsurprising given the vast difference in pK_a between the enolate of an α-alkyl ketone versus an α-aryl ketone, ≈28 versus 20 in DMSO. Following the screening of a number of ligands it was found that the electron deficient PHOX ligand, (*S*)-*t*-BuPHOX, was by far the best ligand. Further optimisation for the highest level of enantioselectivity was achieved using this ligand with Pd_2dba_3 and Meldrum's acid in THF at 7 °C. This resulted in the formation of the tertiary α-aryl ketone of the isoflavanone in up to 92 % *ee*. The highest levels of enantioselectivity were obtained for aryl groups (Ar_1) that were substituted in the *ortho* position.

4.6 Tertiary α-Aryl Carbonyls

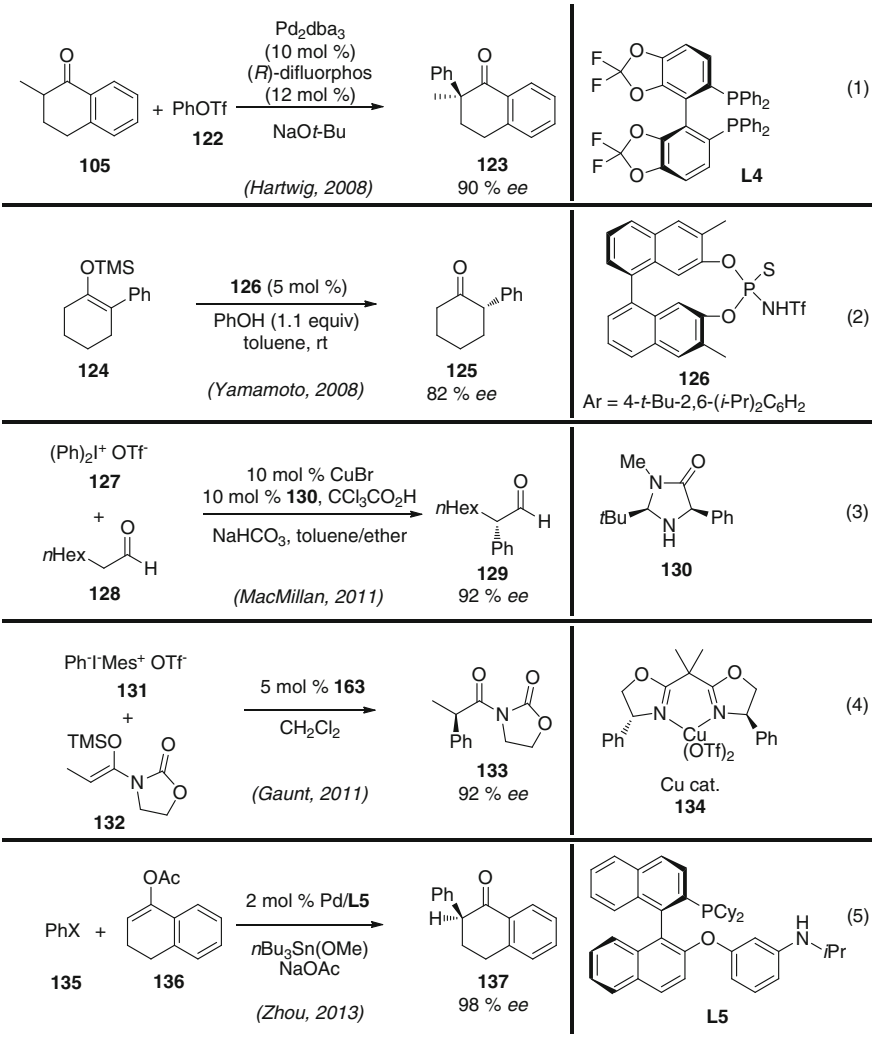
Enantioenriched tertiary α-aryl carbonyls represent an important class of organic compounds. They are prevalent structural motifs in many biologically active molecules and pharmaceuticals such as naproxen and clopidogrel. They are also important intermediates in the synthesis of many medicinally important molecules.



Scheme 4.33 Catalytic asymmetric synthesis of isoflavanones

As a result the asymmetric synthesis of compounds possessing this structural motif has received a great deal of attention, particularly in the last decade.

A number of approaches have been developed for the catalytic asymmetric synthesis of quaternary α-aryl carbonyl containing compounds. However, the basic conditions employed in the vast majority of the reports to date necessitate the use of basic conditions (e.g. (1), Scheme 4.34). Therefore, these methods are unsuitable for the synthesis of tertiary α-aryl carbonyls due to the acidity of a tertiary α-aryl carbonyl proton. Excellent progress has been made in recent years in the realisation of a catalytic asymmetric synthesis of tertiary α-aryl carbonyls (Scheme 4.34).



Scheme 4.34 Selected examples of the synthesis of α-aryl carbonyls

Jørgensen developed an organocatalytic enantioselective α-arylation of aldehydes with quinones [54]. Fu reported Ni-catalysed Kumada and Negishi coupling reactions using bisoxazoline ligands to generate α-aryl ketones [55, 56]. MacMillan described enantioselective α-arylations of aldehydes with diaryliodonium salts in the presence of an organocatalyst ((3), Scheme 4.34) [57]. Also, MacMillan and Gaunt independently reported the enantioselective Cu-catalysed α-arylation of silyl-N-acyloxazolidinones with diaryliodonium salts using bisoxazoline ligands ((4), Scheme 4.34) [58, 59]. Zhou reported the Pd-catalysed α-arylation of silyl ketene acetals to form tertiary α-aryl esters [60] and more recently the arylation of Sn- or Li-enolates to access α-aryl ketones [61] or lactones ((5), Scheme 4.34) [62].

All of the above methods introduce the aryl group during the enantiodetermining step. An alternative strategy would be to already have the aryl group in place and to generate the tertiary stereocentre via an asymmetric protonation of an enolate complex. This was first realised by the pioneering work of Yamamoto in this area with the use of Lewis acid assisted chiral Brønsted acid (LBA) catalysts in the enantioselective synthesis of α-aryl cyclohexanones ((2), Scheme 4.34). Initially developed with the use of stoichiometric quantities of a BINOL-$SnCl_4$ catalyst for the asymmetric protonation of silyl enol ethers, [63] the extensive development of this reaction has resulted in a catalytic variant with an achiral proton donor [64] and expansion of the scope to include tertiary α-aryl carboxylic acids. [65] Further improvement was made with the development of a metal free *N*-triflyl thiophosphoramide BINOL derived proton source (**126**) [66] and more recently a Lewis base-tolerant chiral LBA [67].

A number of other asymmetric enolate protonation reactions have been described using chiral proton sources in the synthesis of α-aryl cyclohexanones. These include the stoichiometric use of chiral diols [68] and α-sulfinyl alcohols [69]. Other catalytic approaches involve the use of a BINAP-AgF complex with MeOH as the achiral proton source, [70] a chiral sulfonamide/achiral sulfonic acid system [71, 72] and a cationic BINAP-Au complex which also was extended to acyclic tertiary α-aryl ketones [73]. Enantioenriched 2-aryl-cyclohexanones have also been accessed by oxidative kinetic resolution of secondary alcohols, kinetic resolution of racemic 2-arylcyclohexanones via an asymmetric Bayer-Villiger oxidation [74] and by arylation with diaryliodonium salts and desymmetrisation with a chiral Li-base [75].

Despite the number of reports of the asymmetric synthesis of tertiary α-aryl cyclohexanones, there have only been three reports which describe the asymmetric synthesis of tertiary α-aryl cyclopentanones. The first of these was reported by Shi via asymmetric epoxidation of benzylidene cyclobutanes and epoxide rearrangement in a subsequent step [76]. Bäckvall used a dynamic kinetic resolution of allylic alcohols-allylic substitution-oxidative cleavage sequence to access 2-phenylcyclopentanone [77]. The first direct catalytic asymmetric synthesis of tertiary α-aryl ketones was recently described by Kingsbury using a series of Sc-catalysed diazoalkane-carbonyl homologations with bis/tris oxazoline ligands [78].

4.7 Aryllead Triacetates

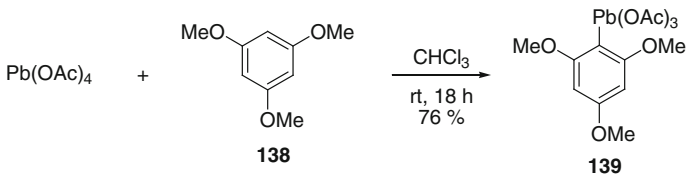
Over the past 40 years aryllead triacetates have been applied as both *N*- and *C*-arylating reagents and cross-coupling partners in organic synthesis. The synthesis and application of aryllead triacetate reagents is a key aspect of this section of this PhD project and an overview of this key class of arylating reagents will now be discussed.

4.7.1 Synthesis of Aryllead Triacetates

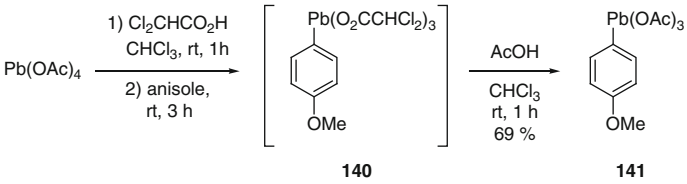
The synthesis of aryllead triacetates has been well developed over the past 40 years [79]. There are two principle methods for the synthesis of aryllead triacetates; direct plumbation and transmetallation. The simplest method is direct plumbation where an arene can be reacted directly with $Pb(OAc)_4$ to form an aryllead triacetate by a highly selective electrophilic aromatic substitution reaction. $Pb(OAc)_4$ can be reacted with 1,3,5-trimethoxybenzene (**138**) in $CHCl_3$ at room temperature to generate 2,4,6-trimethoxyphenyllead triacetate (**139**) in 76 % yield (Scheme 4.35). Although this method is limited to electron rich arenes it is a remarkably selective reaction.

The scope of the arene can by extended by the addition a halogen-substituted acetic acid to replace the acetate groups for haloacetates, thereby making the Pb centre more electrophilic and thus slightly less electron rich arenes can be used. An example which illustrates this also highlights the high degree of selectivity for the most reactive position in the substitution reaction is the preparation of 4-methoxyphenyllead triacetate. Dichloroacetic acid is used to generate $Pb(O_2CCHCl_2)_4$ which, upon plumbation of anisole generates an oligomer of dichloroacetate-substituted 4-methoxyphenyllead (**140**) which can be subjected to metathesis with an excess of acetic acid to give 4-methoxyphenyllead triacetate (**141**) (Scheme 4.36).

The second method for the formation of aryllead triacetates is via transmetallation either from the corresponding aryltrialkylstannane [80] or arylboronoic acid [81] catalysed by $Hg(OAc)_2$. This approach is the more general approach and greatly extends the scope of the aryl group to include different substitution patterns which



Scheme 4.35 Synthesis of 2,4,6-trimethoxyphenyllead triacetate by direct plumbation



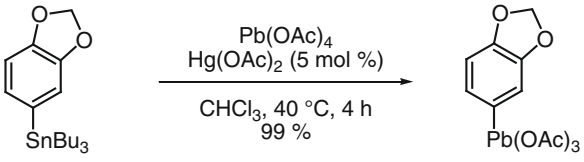
140 **141**

Scheme 4.36 Synthesis of 4-methoxyphenyllead triacetate by direct plumbation

would not be accessible via direct plumbation. This method also enables the synthesis of electron deficient aryllead triacetates such as 4-trifluoromethylphenyllead triacetate.

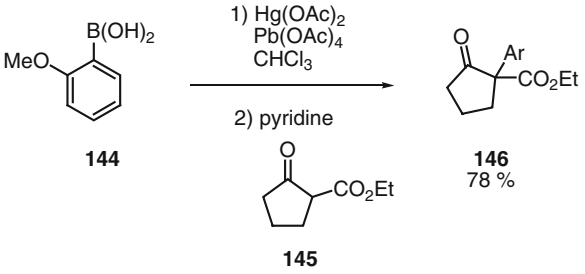
The synthesis of aryllead triacetates via aryltrialkylstannanes was developed by Pinhey [80]. During the study they used another previously reported method for aryllead triacetate synthesis as inspiration, namely the reaction of diarylmercury compounds with $Pb(OAc)_4$. Knowing this to be a rapid reaction they presumed the addition of $Hg(OAc)_2$ might catalyse the transfer of the aryl group from the Sn to the Pb and this was successful. This approach was much more efficient than the corresponding transformation with diarylmercury compounds as the product contained all of the source of the aryl group and was easier to isolate unlike the former reaction where only one aryl group is transferred to Pb. The $Hg(OAc)_2$ is believed to catalyse a sequential Sn-Hg and Hg–Pb exchange. An example is the synthesis of 3,4-methylenedioxyphenyllead triacetate (**143**) in effectively quantitative yield (Scheme 4.37).

Pinhey also pioneered the use of arylboronoic acids in a similar transformation which is also catalysed by $Hg(OAc)_2$ [81]. Although the isolated yields for the aryllead triacetates obtained via this method are generally lower that with aryltrialkylstannanes the commercial availability of a large variety of arylboronoic acids make this a very desirable approach. The lower yields can be circumvented somewhat by generation of the aryllead triacetate in situ which has proved to be a successful approach. For example, the in situ generation of a range of aryllead triacetates such a 4-trifluoromethylphenyl, 2-methoxyphenyl and 3-nitrophenyl derivatives were used in the arylation of a β-keto ester (Scheme 4.38) [81].



142 **143**

Scheme 4.37 Synthesis of 3,4-methylendioxyphenyllead triacetate by Sn–Pb exchange



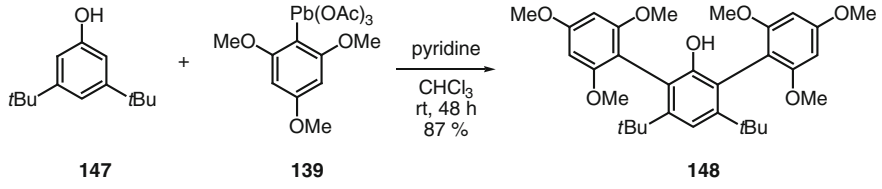
Scheme 4.38 In situ synthesis of arylleadtriacetates by B-Pb exchange and arylation of β-keto esters

4.7.2 Applications of Aryllead Triacetates

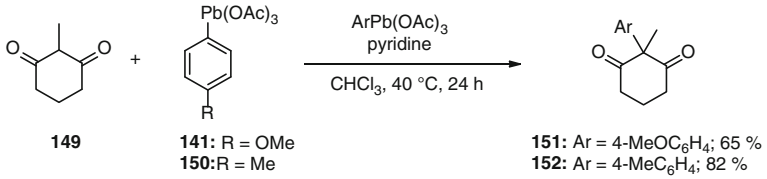
4.7.2.1 C-Arylation

Aryllead triacetates have been applied extensively as—*C*-arylating reagents. One area they have proven very useful is in the arylation of phenols wherein they main product is the *ortho*-arylation product [82]. The mechanism for this type of arylation and indeed the other arylation reactions discussed in this section is believed to be a ligand coupling mechanism and not by a radical process [83]. Originally described by Trost, [84, 85] ligand coupling describes when two groups attached to an atom couple together in a concerted manner without separating into radicals or ions. One particular example was designed to test the limits of the *ortho*-arylation of phenols. Barton and co-workers successfully carried out the di-arylation of 3,5-di-*tert*-butylphenol (**147**) with 2,4,6-trimethoxyphenyllead triacetate (**139**) to generate one of the most sterically hindered phenols (**148**) ever made in 87 % yield under relatively mild conditions (Scheme 4.39) [86].

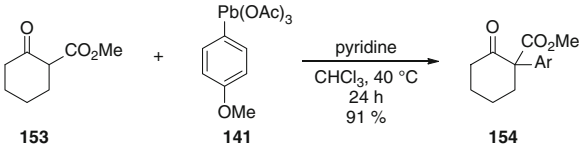
This approach has also been utilised in an enantioselective approach to generate axially chiral diaryl phenols using brucine as the enatiomerically pure amine base at low temperatures of −20 to −40 °C [87]. The phenols could be obtained in up to 83 % *ee*. Aryllead triacetates can also be used to arylate β-diketones. Both linear and cyclic β-diketones with an α-substituent already present could be successfully arylated with a variety of aryllead triacetates. The β-diketone 2-methylcyclohexane-1,3-dione



Scheme 4.39 *Ortho*-arylation of phenols using aryllead triacetates



Scheme 4.40 Arylation of α-substituted β-diketones using aryllead triacetates

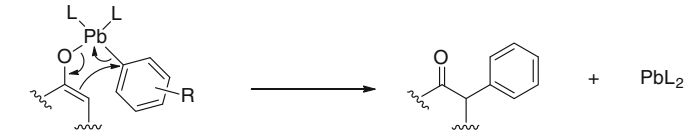


Scheme 4.41 Arylation of α-substituted β-keto esters using aryllead triacetates

(**149**) was arylated with 4-methoxyphenyllead triacetate (**141**) or 4-methylphenyllead triacetate (**150**) to form the arylated products **151** and **152** in 65 and 82 % yields, respectively (Scheme 4.40) [88].

Similarly to β-diketones a number of other β-oxo esters can also be readily arylated with a variety of aryllead triacetates. This was first reported by Pinhey in the arylation of ethyl 2-oxocyclopentanecarboxylate (**153**) with 4-methoxyphenyllead triacetate (**141**) in chloroform and pyridine in high yields (Scheme 4.41). The ideal conditions reported the use of 3.0 equivalents of pyridine to 1.0 equivalent of aryllead triacetate [89]. Moreover this approach could be utilised to generate α-aryl ketones following decarboxylation of the β-ketoester. Other examples include the α-arylation of 3- and 4-hydroxycoumarins [90, 91].

Pyridine was shown in many cases to have a fundamental effect on the success of arylation reactions with aryllead triacetates. As such the effect of pyridine has been studied and it has been concluded that pyridine effectively catalyses the transfer of an aryl group from the Pb to C with concomitant reduction of Pb(IV) to Pb (II), which is the thermodynamic driving force for the reaction (Scheme 4.42) [92]. The



Scheme 4.42 Ligand coupling mechanism of arylation reactions with aryllead triacetates

rate of arylation was investigated for a number of amine bases and it was found there was a large rate enhancement when 4-(dimethylamino)pyridine (DMAP) or 1,10-phenanthroline was used, further suggesting they act as a σ-donor ligand rather than a base.

Other *C*-arylation reactions have been accomplished with vinylogues of β-dicarbonyls [93], malonic acid derivatives [94], α-cyano esters and malonitriles [95]. The α-arylation of ketone enolates/enamines and nitroalkanes has also been achieved [96–98].

In conclusion, aryllead triacetates are versatile and highly selective class of arylating reagents. There are a number of well-established methods for their synthesis giving access to a wide variety of aryl groups, the scope of which is likely to expand over the coming years. These reagents have proven particularly successful as *C*-arylating reagents especially on β-oxo esters. They also have a remarkable ability to generate highly congested quaternary carbon centre in high yields and mild conditions via a ligand coupling mechanism.

4.7.3 Synthesis of Aryllead Triacetates for the C*-Arylation of β-Keto Allyl Esters*

A number of aryllead triacetates were synthesised in this section of the PhD project to be utilised in the *C*-arylation of β-keto allyl esters. In total, 11 aryllead triacetates were prepared according to the synthetic methods described in Sect. 4.7.1. All of the aryllead reagents were prepared using $Pb(OAc)_4$, either by direct plumbation or by transmetallation from the corresponding aryl stannane or aryl boronic acid. The synthesis of all of the aryllead triacetates used in this project has been previously reported, many for the first time by this research group [53, 80, 81, 99].

The range of aryllead triacetates prepared and the method used for their preparation is summarised in Fig. 4.4. The choice of method used depends largely on the aryl group required particularly with regards to the substitution pattern. Aryllead triacetates **138**, **157** and **141** were all accessible by direct plumbation. 1,3,5-Trimethoxybenzene is sufficiently electron rich that it will undergo direct plumbation to form **138** without the addition of a halogen-substituted acetic acid. The direct plumbation of 1,3-dimethoxybenzene required the addition of monochloroacetic acid to increase the electrophilicity of the Pb to enable plumbation to occur, which, after metathesis with acetic acid, formed **157**. Similarly the direction plumbation of anisole required the addition of dichloroacetic acid to form **141**, again after reaction with excess acetic acid.

2,6-Dimethoxyphenyllead triacetate **158**, 2,3,4-trimethoxyphenyllead triacetate (**159**) and 3,4-methylenedioxyphenyllead triacetate (**143**) were synthesised by

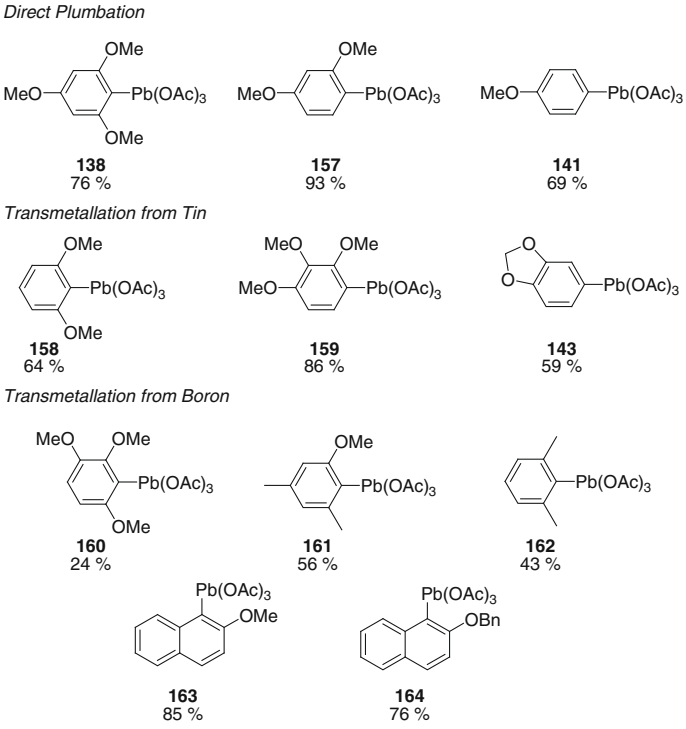


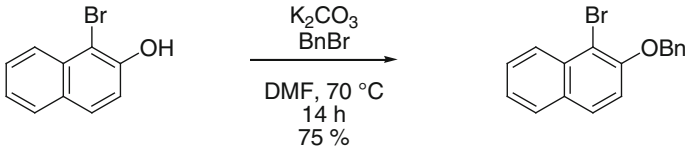
Fig. 4.4 Range of aryllead triacetates prepared by direct plumbation and transmetallation

transmetallation from the corresponding aryltributyl stannane in the presence of catalytic quantities $Hg(OAc)_2$. The aryltributyl stannanes were prepared by *ortho*-lithiation or lithium-halogen exchange from the corresponding aryl bromide followed by quenching with tributyltin chloride.

The remaining aryllead triacetates **160-164** were synthesised by transmetallation from the corresponding boronic acid also catalysed by $Hg(OAc)_2$. This method is the more favourable of the two transmetallation methods due to the toxicity of the organostannanes and lack of commercial availability of many aryltributyl stannanes compared to aryl boronic acids. For example, 2,6-methylphenylboronic acid and 2,3,4-trimethoxyphenylboronic acid are commercially available. The remaining boronic acids were prepared by *ortho*-lithiation or lithium-halogen exchange and subsequent quenching with triisopropyl borate.

4.8 Experimental

2-(Benzyloxy)-1-bromonaphthalene(166) [100]



165 **166**

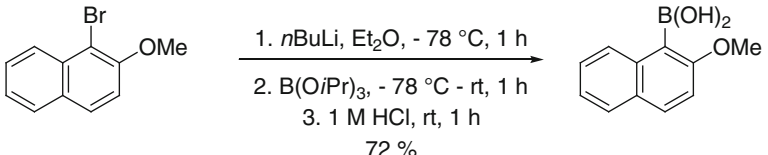
1-Bromo-2-naphthol (15.0 g, 67.2 mmol) was dissolved in anhydrous DMF (100 mL) under N_2 followed by the addition of benzyl bromide (9.6 mL, 74.0 mmol) and potassium carbonate (18.6 g, 134 mmol). The suspension was stirred at 70 °C for 14 h and quenched with H_2O (100 mL). The aqueous layer was extracted with Et_2O (2 × 100 mL) and the combined organic phases were dried over anhydrous Na_2SO_4. The crude off-white solid was recrystallised from Et_2O to yield the product as a white solid (15.8 g, 75 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (d, J = 8.6 Hz, 1H), 7.77–7.72 (m, 2H), 7.55 (ddd, J = 8.3, 6.8, 1.3 Hz, 1H), 7.53–7.50 (m, 2H), 7.41–7.36 (m, 3H), 7.34–7.29 (m, 1H), 7.25 (d, J = 9.0 Hz, 1H), 5.28 (s, 2H). All other physical data was identical to those previously reported [100].

General Procedure for the Preparation of Aryl Boronic Acids

Aryl boronic acid (1.0 equiv. = X; i.e. X g = X mL) was dissolved in Et_2O (0.5 M) and cooled to −78 °C prior to the dropwise addition of *n*-BuLi (1.0 equiv., 1.6 M or 2.5 M in hexanes). The solution was stirred for 1 h at −78 °C and then warmed to room temperature for 30 min and re-cooled to −78 °C. Triisopropyl borate (1.10 equiv.) was added dropwise and the reaction mixture was allowed to warm to room temperature and stirred for 1 h. A solution of 1 M HCl (2.5 equiv.) was then added slowly and the reaction mixture stirred for a further 1 h after which the organic layer was separated and the aqueous layer was extracted twice with Et_2O (2 × 10X). The combined organic layers were washed with water (10X), brine (5X) and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the resulting solid was dissolved in Et_2O (3X) and added dropwise to pentane (10X) to precipitate out the boronic acid which was collected by filtration.

2-Methoxynaphthylboronic acid (168)

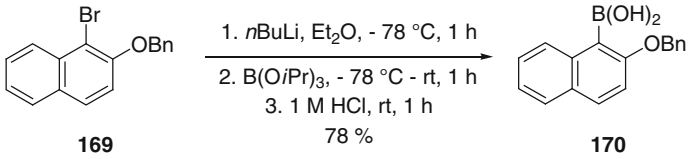


167 **168**

The title compound was prepared according to the general procedure by lithium-halogen exchange using 1-bromo-2-methoxynaphthalene (**167**) (12.00 g, 50.6 mmol) to yield the product as a white solid (7.38 g, 72 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.84 (d, J = 8.6 Hz, 1H), 7.96 (d, J = 9.1 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.53 (ddd, J = 8.6, 6.8, 1.3 Hz, 1H), 7.39 (ddd, J = 8.0, 6.8, 1.3 Hz, 1H), 7.33–7.27 (m, 1H), 6.03 (s, 2H), 4.05 (s, 3H). All other physical data was identical to those previously reported [100].

2-Benzyloxynaphthylboronic acid (170)

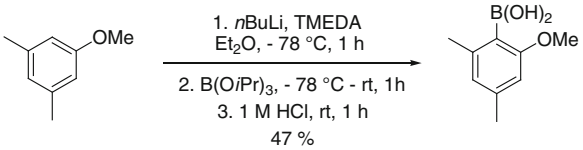


169 **170**

The title compound was prepared according to the general procedure by lithium-halogen exchange using 2-(benzyloxy)-1-bromonaphthalene (**169**) (15.88 g, 50.7 mmol) to yield the product as a white solid (11.04 g, 78 %).

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.34 (s, 2H), 7.91–7.80 (m, 2H), 7.72 (d, J = 8.4 Hz, 1H), 7.57–7.50 (m, 2H), 7.48–7.28 (m, 6H), 5.23 (s, 2H). All other physical data was identical to those previously reported [100].

(2-Methoxy-4,6-dimethylphenyl)boronic acid (172)



171 **172**

The title compound was prepared according to the general procedure by *ortho*-lithiation, which was aided by the addition of TMEDA (16.46 mL, 132 mmol, 1.2 equiv.) to the solution of 3,5-dimethylanisole (15.57 mL, 110 mmol), prior to the addition of *n*-BuLi (53.0 mL, 2.5 M in hexanes, 132 mmol) to yield the product as a white solid (9.3 g, 47 %).

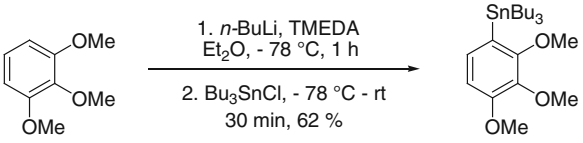
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.72 (s, 1H), 6.60 (s, 1H), 6.36 (s, 2H), 3.89 (s, 3H), 2.56 (s, 3H), 2.35 (s, 3H). All other physical data was identical to those previously reported [101].

General Procedure for the Preparation of Tributylaryl Stannanes

CAUTION *Tributyltin chloride is toxic and the resulting tributylaryl stannane is also potentially toxic. Appropriate safety precautions should be taken during all stages of handling and disposal.*

Aryl bromide or arene (1.0 equiv. = X; i.e. X g = X mL) was dissolved in Et_2O (0.5 M) and cooled to −78 °C prior to the dropwise addition of *n*-BuLi (1.0 equiv., 1.6 M or 2.5 M in hexanes). The solution was stirred for 1 h at −78 °C and then warmed to room temperature for 30 min and re-cooled to −78 °C. Tributyltin chloride (1.2 equiv.) was added dropwise and the reaction mixture was warmed to room temperature and stirred for 30 min. The reaction mixture was quenched with saturated NH_4Cl solution (1X), diluted with water and extracted with Et_2O (2 × 10X). The combined organic layers were washed with water (10X) and brine (5X) and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the resulting oil was purified by high vacuum distillation.

Tributyl(2,3,4-trimethoxyphenyl)stannane (174)

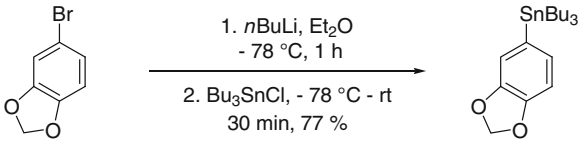


173 **174**

The title compound was prepared according to the general procedure by *ortho*-lithiation which was aided by the addition of TMEDA (12.8 mL, 85.6 mmol, 1.2 equiv.) to the solution of 1,2,3-trimethoxybenzene (12.0 g, 71.4 mmol), prior to the addition of *n*-BuLi (35.7 mL, 85.6 mmol, 2.4 M in hexanes), to yield the product as a colourless oil (20.2 g, 62 %).

b.p. = 138–143 °C at 0.10 mbar; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.01 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 4H), 3.87 (s, 3H), 1.62 – 1.49 (m, 6H), 1.42 – 1.28 (m, 6H), 1.11 – 1.02 (m, 6H), 0.91 (t, J = 7.2 Hz, 9H). All other physical data was identical to those previously reported [102].

(3,4-Methylenedioxyphenyl)tributylstannane (142)

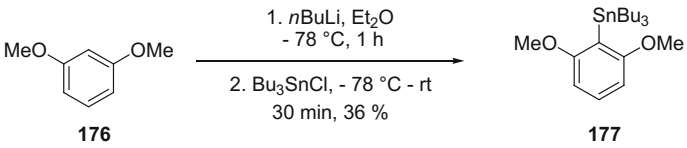


175 **142**

The title compound was prepared according to the general procedure by lithium-halogen exchange using 1-bromo-3,4-(methylenedioxy)benzene (**175**) (6.0 mL, 49.9 mmol) to yield the product as a colourless oil (20.5 g, 77 %).

b.p. = 126–128 °C at 0.09 mbar; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98 – 6.83 (m, 3H), 5.91 (s, 2H), 1.58 – 1.49 (m, 6H), 1.33 (sextet, J = 7.3 Hz, 6H), 1.06 – 0.98 (m, 6H), 0.89 (t, J = 7.4 Hz, 9H). All other physical data was identical to those previously reported [103].

Tributyl(2,6-dimethoxyphenyl)stannane (177)



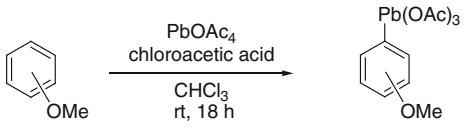
176 **177**

The title compound was prepared according to the general procedure by *ortho*-lithiation of 1,3-dimethoxybenzene (**176**) (10.0 mL, 76.4 mmol) to yield the product as a colourless oil (11.9 g, 36 %).

b.p. = 118–120 °C, 0.11 mbar; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (t, J = 8.1 Hz, 1H), 6.52 (d, J = 8.1 Hz, 2H), 3.77 (s, 6H), 1.60–1.45 (m, 6H), 1.41–1.28 (m, 6H), 1.11–1.02 (m, 6H), 0.91 (t, J = 7.3 Hz, 9H). All other physical data was identical to those previously reported [104].

Preparation of Aryllead Triacetates

General Procedure A for the Preparation of Aryllead Triacetates by Direct Plumbation

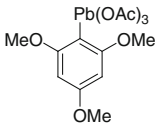


178 **179**

$Pb(OAc)_4$ (1.0 equiv. = X; i.e. X g = X mL) and chloroacetic acid (10.0 equiv.), in the case of 1,3-dimethoxybenzene and anisole, were dissolved in anhydrous $CHCl_3$ (5X) and stirred for 1 h prior to the slow addition of the arene (1.50 equiv.) in $CHCl_3$ (1.5X) and the reaction mixture was stirred for 18 h. The reaction mixture was transferred to a separatory funnel and washed with twice with H_2O (10X). The brown precipitate (PbO_2) was removed by filtration through Celite. The bright yellow or orange solution was concentrated in vacuo and added slowly to pentane (50X) upon which a yellow solid precipitated out. This solid was collected by suction filtration, dissolved in a solution of $CHCl_3$ (4X) and glacial acetic acid (5X) and stirred for 1 h. The solution was then washed with H_2O (2 × 5X) and stirred for a further 1 h in glacial acetic acid (5X). The solution was washed again with H_2O (2 × 5X), the $CHCl_3$ layer was concentrated in vacuo (∼2X) and added dropwise to

pentane (50X). A yellow precipitate forms and is collected by suction filtration, washed with pentane (10X) and stored in a desiccator over KOH in amber glass.

2,4,6-Trimethoxyphenyllead triacetate (138)

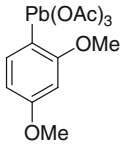


138

The title compound was prepared according to general procedure A from Pb $(OAc)_4$ (8.00 g, 18 mmol) using 1,3,5-dimethoxybenzene (4.54 g, 27 mmol) to yield the product as a bright yellow solid (7.55 g, 76 %). Due to the electron-richness of the arene the addition of chloroacetic acid was not necessitated for direct plumbation to occur. Hence, stirring in glacial acetic acid was not required.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.21 (s, 2H), 3.87 (s, 6H), 3.84 (s, 3H), 2.09 (s, 9H). All other physical data was identical to those previously reported [105].

2,4-Dimethoxyphenyllead triacetate (157)

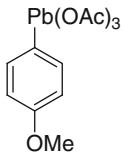


157

The title compound was prepared according to general procedure A from Pb $(OAc)_4$ (9.50 g, 21.4 mmol) using monochloroacetic acid (20.25 g, 210 mmol) and 1,3-dimethoxybenzene (4.21 mL, 32.1 mmol) to yield the product as a bright yellow solid (10.40 g, 93 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, J = 8.9 Hz, 1H), 6.66 (dd, J = 8.9, 2.4 Hz, 1H), 6.55 (d, J = 2.4 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 2.09 (s, 9H). All other physical data was identical to those previously reported [106].

4-Methoxyphenyllead triacetate (141)



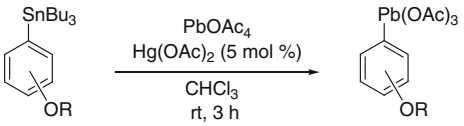
141

The title compound was prepared according to general procedure A from Pb $(OAc)_4$ (2.0 g, 4.51 mmol) using dichloroacetic acid (3.72 mL, 45.10 mmol) and anisole (0.74 mL, 6.77 mmol) to yield the product as a pale yellow solid (1.53 g, 69 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, J = 8.7 Hz, 2H), 7.09 (d, J = 8.7 Hz, 2H), 2.63 (s, 6H), 3.84 (s, 3H), 2.12 (s, 9H). All other physical data was identical to those previously reported [99, 107].

General Procedure B for the Preparation of Aryllead Triacetates by Tin-Lead Exchange

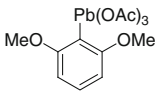
CAUTION *Mercury(II) acetate is highly toxic and may be fatal if ingested or inhaled and moderately toxic by skin contact. Appropriate safety precautions should be taken during all stages of handling and disposal.*



180 **181**

$Pb(OAc)_4$ (1.0 equiv. = X) was dissolved in anhydrous $CHCl_3$ (5X) and mercury (II) acetate (5 mol%) was added followed by aryltributyl stannane (1 equiv.). The reaction mixture was heated to 40 °C, stirred for 3 h and then filtered through Celite. The solvent was removed in vacuo resulting in a yellow solid to which pentane (5X) was added. The bright yellow precipitate was collected by suction filtration, washed with pentane (10X) and stored in a desiccator over KOH in amber glass.

2,6-Dimethoxyphenyllead triacetate (53)

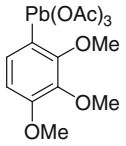


158

The title compound was prepared according to general procedure B using Pb $(OAc)_4$ (11.86 g, 26.8 mmol), mercury (II) acetate (427 mg, 1.34 mmol) tributyl (2,6-dimethoxyphenyl)stannane (11.45 g, 26.8 mmol) to yield the product as a pale yellow solid (8.89 g, 64 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (t, J = 8.1 Hz, 1H), 6.70 (d, J = 8.1 Hz, 2H), 3.89 (s, 6H), 2.09 (s, 9H). All other physical data was identical to those previously reported. All other physical data was identical to those previously reported [53].

2,3,4-Trimethoxyphenyllead triacetate (159)

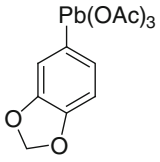


159

The title compound was prepared according to general procedure B using Pb $(OAc)_4$ (20.52 g, 44.0 mmol), mercury (II) acetate (701 mg, 2.20 mmol) and tributyl(2,3,4-trimethoxyphenyl)stannane (20.10 g, 44.0 mmol) to yield the product as a bright yellow solid (20.9 g, 86 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, J = 9.0 Hz, 1H), 6.81 (d, J = 9.0 Hz, 1H), 4.03 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 2.08 (s, 9H). All other physical data was identical to those previously reported [53].

3,4-Methylenedioxyphenyllead triacetate (143)

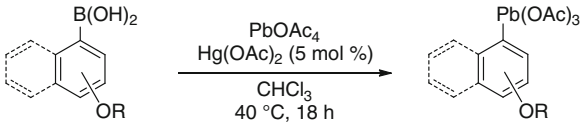


143

The title compound was prepared according to general procedure B using Pb $(OAc)_4$ (13.96 g, 31.5 mmol), mercury (II) acetate (502 mg, 1.58 mmol) and (3,4-methylenedioxyphenyl)tributylstannane (12.62 g, 31.5 mmol) to yield the product as a yellow solid (9.38 g, 59 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17 (d, J = 1.4 Hz, 1H), 7.12 (dd, J = 8.2, 1.4 Hz, 1H), 6.98 (d, J = 8.2 Hz, 1H), 6.04 (s, 2H), 2.12 (s, 9H). All other physical data was identical to those previously reported [103].

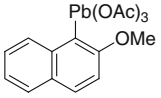
General Procedure C for the Preparation of Aryllead Triacetates by Boron-Lead Exchange



182 **183**

$Pb(OAc)_4$ (1.0 equiv. = X) was dissolved in anhydrous $CHCl_3$ (5X) and mercury (II) acetate (5 mol%) was added followed by arylboronic acid (1.0 equiv.). The reaction mixture was heated to 40 °C, stirred for 18 h and then filtered through Celite. The $CHCl_3$ solution was transferred to a separatory funnel and washed with twice with H_2O (10X). The brown precipitate (PbO_2) was removed by filtration through Celite. The bright yellow or orange solution was concentrated in vacuo and added slowly to pentane (50X) upon which a yellow solid precipitated out (or the solution was stored at −20 °C until crystallisation occurred). The bright yellow precipitate was collected by suction filtration, washed with pentane (10X) and stored in a desiccator over KOH in amber glass.

2-Methoxynaphthyllead triacetate (163)

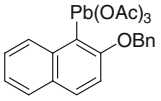


163

The title compound was prepared according to general procedure C using Pb $(OAc)_4$ (6.28 g, 14.2 mmol), mercury (II) acetate (226 mg, 0.71 mmol) and 2-methoxynaphthylboronic acid (2.89 g, 14.2 mmol) to yield the product as a bright yellow solid (6.53 g, 85 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, J = 8.5 Hz, 1H), 7.99 (d, J = 8.8 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.67–7.61 (m, 1H), 7.47–7.42 (m, 1H), 7.34 (d, J = 8.8 Hz, 1H), 4.04 (s, 3H), 2.10 (s, 9H). All other physical data was identical to those previously reported [87].

2-Benzyloxynaphthyllead triacetate (164)

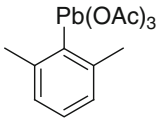


164

The title compound was prepared according to general procedure C using Pb $(OAc)_4$ (20.44 g, 46.1 mmol), mercury (II) acetate (735 mg, 2.31 mmol) and 2-benzyloxynaphthylboronic acid (12.82 g, 46.1 mmol) to yield the product as a yellow solid (21.70 g, 76 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.40 (d, J = 8.3 Hz, 1H), 7.91 (d, J = 8.8 Hz, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.69 – 7.61 (m, 1H), 7.55 – 7.50 (m, 2H), 7.49 – 7.27 (m, 5H), 5.38 (s, 2H), 2.02 (s, 9H). All other physical data was identical to those previously reported [53].

2,6-Dimethylphenyllead triacetate (162)

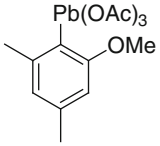


162

The title compound was prepared according to general procedure C using $Pb(OAc)_4$ (28.2 g, 63.6 mmol), mercury (II) acetate (1.013 g, 3.18 mmol) and 2,6-dimethylphenyl boronic acid (9.54 g, 63.6 mmol) to yield the product as a pale yellow solid (13.5 g, 43 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 – 7.23 (m, 1H), 7.20 – 7.16 (m, 2H), 2.63 (s, 6H), 2.11 (s, 9H). All other physical data was identical to those previously reported [53].

2-Methoxy-4,6-dimethylphenyllead triacetate (160)

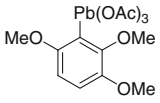


160

The title compound was prepared according to general procedure C using $Pb(OAc)_4$ (20.5 g, 46.1 mmol), mercury (II) acetate (734 mg, 2.31 mmol) and 2-methoxy-4,6-dimethylphenyl boronic acid (8.35 g, 46.1 mmol) to yield the product as an pale yellow solid (13.5 g, 56 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.79 (s, 1H), 6.67 (s, 1H), 3.87 (s, 3H), 2.55 (s, 3H), 2.34 (s, 3H), 2.07 (s, 9H). All other physical data was identical to those previously reported [53].

2,3,6-Trimethoxyphenyllead triacetate (62)



62

The title compound was prepared according to general procedure C from $Pb(OAc)_4$ (12.4 g, 27.9 mmol) using 2,3,6-dimethoxyphenylboronic acid to yield the product as an orange solid (3.65 g, 24 %). All other physical data was identical to those previously reported [53].

^1H NMR (500 MHz, $CDCl_3$): δ 6.96 (d, J = 8.8 Hz, 1H), 6.73 (d, J = 8.8 Hz, 1H), 4.00 (s, 3H), 3.83 (s, 3H), 3.84 (s, 3H), 2.09 (s, 9H).

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Chapter 5
A Stereoselective Switch: Enantiodivergent Approach to the Synthesis of Isoflavanones

Abstract A modular 6 step asymmetric synthesis of 2 naturally occurring and 3 non-natural isoflavanones containing tertiary α-aryl carbonyls has been developed. This synthetic route, utilising a Pd-catalysed decarboxylative asymmetric protonation, allows access to isoflavanones in excellent enantioselectivities from 76–97 % *ee*. A switch in the sense of stereoinduction was observed when different H^+ sources were employed showing the first example of dual stereocontrol in an asymmetric protonation reaction whereby the same chiral ligand is used with a different achiral proton donor. The first enantioselective synthesis of the naturally occurring isoflavanones sativanone and 3-*O*-methylviolanone has also been accomplished using this methodology.

5.1 Introduction

Isoflavanones are a member of the flavonoid class of plant secondary metabolites whose natural occurrence is limited mainly to the *Leguminosae* family of flowering plants [1]. Isoflavanones display a range of biological activity and have been shown to act as immunosuppressive agents, [2] possess anti-bacterial [3] and anti-cancer [4] activity and act as α-glucosidase inhibitors [5]. To the best of our knowledge, the synthesis of any naturally occurring isoflavanones in high enantioselectivity has yet to be reported. A common feature of many isoflavanones isolated from nature is the presence of an oxygen-containing group in the 7-position with additional oxygen-containing groups often found on the 2′ and 4′ positions (Fig. 5.1).

Two examples of these types of isoflavanones are the naturally occurring sativanone **1a** and 3-*O*-methylviolanone **1b** (Fig. 5.2). Sativanone **1a** was first isolated in 1973 by Donnelly from the heart wood of *Dalbergia stevensonii* [6] and has been shown to display activity against human cancer cell lines as well as antibacterial activity [7, 8]. There has been one reported racemic synthesis of sativanone **1a** via a 4 step synthesis involving intramolecular cyclisation to form the B ring of the isoflavanone [9]. 3-*O*-Methylviolanone, first isolated in 1975 from *Dalbergia*

R. Doran, *Asymmetric Synthesis of Bioactive Lactones and the Development of a Catalytic Asymmetric Synthesis of α-Aryl Ketones*, Springer Theses,
DOI 10.1007/978-3-319-20544-1_5

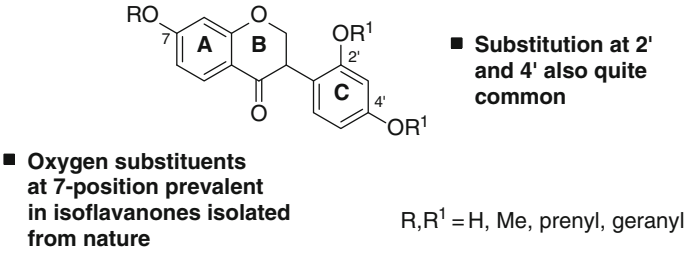


Fig. 5.1 Common substitution patterns in naturally occurring isoflavanones

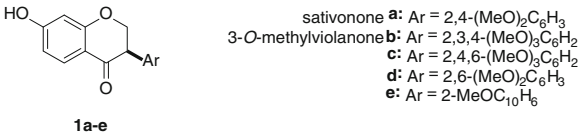
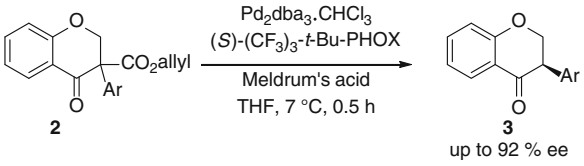


Fig. 5.2 Naturally occurring isoflavanones sativanone (**1a**), 3-*O*-methylviolanone (**1b**) and non-natural isoflavanones targets

cearensis [10] has displayed anti-inflammatory activity and anti-cancer activity [8, 11]. To date a synthesis of 3-*O*-methylviolanone has yet to be reported.

Unsurprisingly due to their potential as medicinal agents there have been many reported synthetic routes to isoflavanones including the reduction of corresponding isoflavones, [12] benzylic oxidation of isoflavans, [13] gold-catalysed annulations, [14] addition of C−O bonds to arynes [15] and palladium catalysed α-arylation [16]. Despite the multitude of syntheses reported over the past 70 years few routes have been shown to be truly modular with respect to substituents on the isoflavanone skeleton and only one route was asymmetric, relying on the use of chiral auxiliaries [17].

Recently we reported the first general catalytic asymmetric synthesis of isoflavanones which featured a Pb-mediated arylation to generate **2** followed by an asymmetric Pd-catalysed decarboxylative asymmetric protonation to generate the chiral centre in **3** (Scheme 5.1) [18]. Having applied this methodology to the construction of several non-natural isoflavanones, we wished to expand its scope to include the asymmetric synthesis of naturally occurring isoflavanones which feature

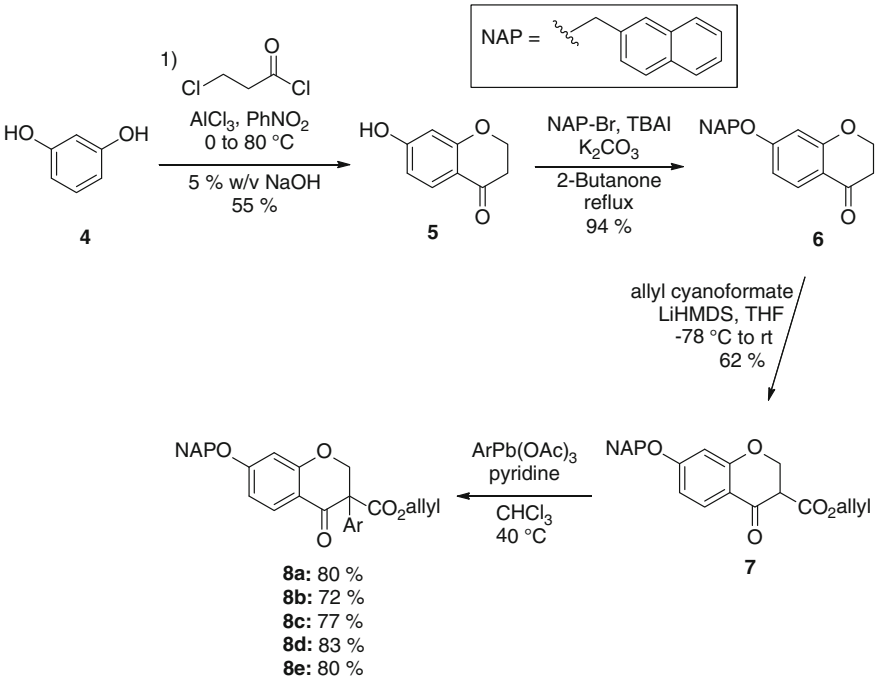


Scheme 5.1 Catalytic asymmetric synthesis of isoflavanones

oxygenation at the 7-position. We aimed to carry out the first asymmetric synthesis of sativanone (**1a**) and the first synthesis of 3-*O*-methylviolanone (**1b**). In addition to the two naturally occurring isoflavanones, we sought to synthesize a number of novel isoflavanones containing a 7-hydroxy substituent and different α-aryl groups: 2′,4′,6′-trimethoxyphenyl (**1c**), 2′,6′-dimethoxyphenyl (**1d**) and 2′-methoxynaphthyl (**1e**) which we felt would be good candidates for biological studies due to their similarities to both **1a** and **1b** (Fig. 5.2).

5.2 Results and Discussion

Our synthesis of the 7-hydroxy-substituted isoflavanones **1a-e** had to take into account protection of hydroxy group due to the likely interference with the synthetic route and in particular the key decarboxylative asymmetric protonation step. The synthesis of **1a-c** could be accomplished by a series of Pb-mediated arylations of allyl-β-keto ester **7**. This was accessed by Friedel-Crafts acylation, cyclization, NAP-protection and subsequent acylation with allyl cyanoformate (Scheme 5.2) [19–21]. We were able to generate isoflavanone precursors **8a-e** from the allyl-β-keto ester (**7**) by introducing various aryl groups through the use of



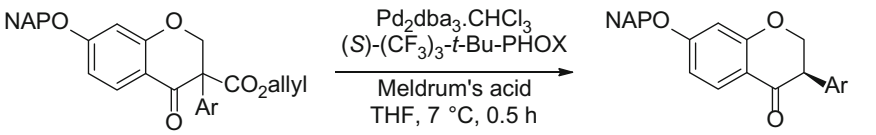
Scheme 5.2 Synthesis of isoflavanone precursors **7a-e**

aryllead triacetates. The use of aryllead triacetates to introduce aromatic groups in the synthesis of natural products and natural product analogues has been well documented, [22–30] and using the standard conditions for arylation [31] common intermediate **7** was arylated with five different aryllead triacetates to provide the isoflavanone precursors **8a-e** in very good yields of 72–83 %.

The isoflavanone precursors **8a-e** were then applied in the decarboxylative asymmetric protonation reaction. Recently Pd-catalysed decarboxylative reactions have emerged as a powerful tool in organic synthesis (see Sects. 4.3 and 4.4) [32, 33]. The often mild reaction conditions employed, coupled with the high yields and enantioselectivities attainable has seen this methodology applied in several syntheses [34–37] and continues to be an area of rapid growth in asymmetric catalysis.

Our previously optimized conditions for the decarboxylative asymmetric protonation of isoflavanones substrates were applied to these substrates [18]. Beginning with the 2′,4′,6′-$(MeO)_3C_6H_2$-substituted β-ketoester (**8c**), the aryl group which gave the highest levels of enantioselectivity in our previous study, we carried out the reaction to yield the *R*-enantiomer in 67 % *ee* (Scheme 5.3). We then observed a sharp drop in enantioselectivity to 25 % for the 2′,3′,4′-$(MeO)_3C_6H_2$ aryl group (**8b**) which was further lowered to effectively racemic using the 2′,4′-$(MeO)_2C_6H_3$ aryl group (**8a**) present in sativanone. At this point, disappointed with the levels of enantioselectivity, we decided to explore different catalysis conditions. Given the 2′,4′-$(MeO)_2C_6H_3$ aryl group gave the poorest results, and that we wished to develop an asymmetric synthesis of sativanone, we chose this as our model substrate in an attempt to improve the enantioselectivity (Table 5.1).

We attempted to carry out the reaction using the same reaction conditions at room temperature. Sampling the reaction after 30 min showed complete conversion of starting material with an *ee* of 21 % of the *S*-enantiomer. However, when the reaction was sampled again after 12 h, the *ee* had changed to 12 % of the (*R*)-enantiomer and this remained unchanged after further reaction time (Table 5.1, entry 2). Following this surprising result we increased the reaction temperature to 40 °C. This time after 30 min an *ee* of 4 % (*S*) was observed. Again, after 12 h this had switched to 20 % (*R*) (Table 5.1, entry 3). Lowering the reaction temperature to 0 °C led to an increase in *ee* to 30 % (*S*), which remained unchanged after warming to room temperature (Table 5.1, entry 4). We then changed the ligand to (*S*)-*t*-

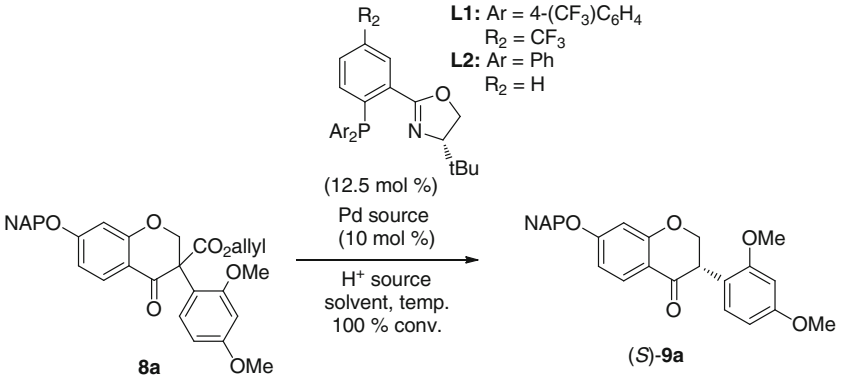


8a: Ar = 2,4-$(MeO)_2C_6H_3$
8b: Ar = 2,3,4-$(MeO)_3C_6H_2$
8c: Ar = 2,4,6-$(MeO)_3C_6H_2$

(*R*)-**9a**: 73 %, ee = 2
(*R*)-**9b**: 90 %, ee = 25
(*R*)-**9c**: 60 %, ee = 67

Scheme 5.3 Catalytic asymmetric synthesis of isoflavanones with oxygenation in 7-position

Table 5.1 Optimization of decarboxylative asymmetric protonation of isoflavanone β-ketoester **8a**



Entry[a]	Ligand	H^+ Source	T (°C)[c]	Time	*ee*(%)
1	**L1**	Meldrum's acid	7	12 h	2 (*R*)
2	**L1**	Meldrum's acid	rt	12 h	12 (*R*)
3	**L1**	Meldrum's acid	40	12 h	20 (*R*)
4	**L1**	Meldrum's acid	0	12 h	30
5	**L2**	Meldrum's acid	rt	12 h	14
6	**L2**	Formic acid	rt	5 d	96[b]
7	**L2**	Formic acid	rt	36 h	92[c]
8	**L2**	Formic acid	40	10 h	84
9	**L1**	**Formic acid**	**40**	**10 h**	**97**

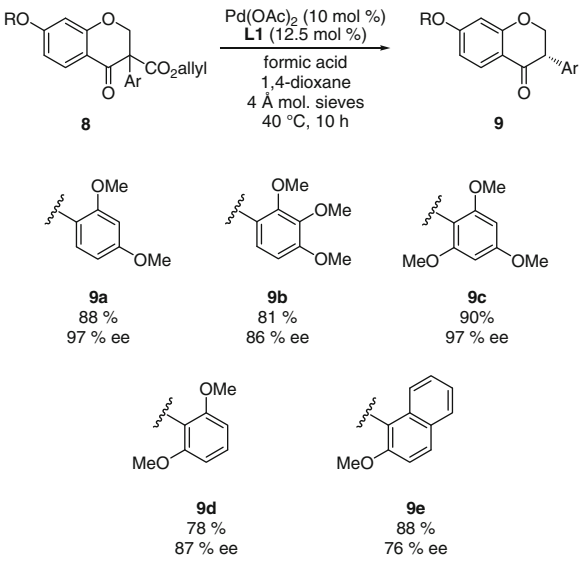
[a]Entries 1–5: $Pd_2dba_3.CHCl_3$ (5 mol% of Pd), THF; Entries 6–9: $Pd(OAc)_2$, 1,4-dioxane, reaction carried out in presence of 4Å powdered molecular sieves
[b]50 % conversion by ^{1}H-NMR
[c]1.0 equiv. of $Pd(OAc)_2$, 1.25 equiv. (*S*)-*t*-Bu-PHOX

Bu-PHOX which gave an *ee* of 26 % (*S*) after 30 min at room temperature, which switched to 14 % (*S*) after 12 h (Table 5.1, entry 5).

At this point, given the difficulty in controlling the enantioselectivity under these conditions, we were eager to test these substrates using the heterogeneous decarboxylative protonation conditions of $Pd(OAc)_2$, (*S*)-*t*-BuPHOX with formic acid as the proton source in the presence of molecular sieves [38]. We initially carried out the reaction at room temperature and we observed a significant increase in *ee* to 96 % (*S*), however, with a low conversion of 50 % after over 5 days (Table 5.1, entry 6). Using a stoichiometric quantity of $Pd(OAc)_2$ led to full conversion after 36 h, albeit with a slightly lower *ee* of 92 %, suggesting the complex will not turn over sufficiently at room temperature (Table 5.1, entry 7). Attempting the reaction at 40 °C led to full conversion in 10 h with an *ee* of 84 % (Table 5.1, entry 8).

Although pleased with this improvement we thought we could improve the enantioselectivity further using the (*S*)-$(CF_3)_3$-*t*-BuPHOX ligand. Gratifyingly this

Scheme 5.4 Decarboxylative asymmetric protonation in the synthesis of 7-substituted isoflavanones

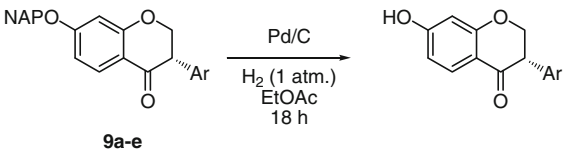


increased the *ee* to 97 % (*S*) with an yield of 87 % (Table 5.1, entry 9). We then applied the optimized conditions to the other four substrates to obtain *ee* values ranging from 76 to 97 % and these results are summarized in Scheme 5.4.

The final step of our synthesis was the removal of the NAP group to yield the free hydroxy group of the isoflavanones. Several conditions were screened in order to find a mild method of deprotection that would leave the stereocentre intact [39]. Ultimately stirring the protected isoflavanones **9a-e** overnight with 10 % Pd/C in ethyl acetate under 1 atmosphere of hydrogen resulted in full deprotection of the isoflavanones without erosion of the enantiomeric excess (Scheme 5.5). The $[\alpha]_D^{20}$ for sativanone **1a** was measured to be + 31.2 (*c* 0.50, acetone), the positive rotation indicating that it was the (*S*)-enantiomer. This was confirmed by obtaining an x-ray crystal structure of NAP-protected sativanone **9a** (Fig. 5.3).

Interestingly, the sense of stereoinduction (*S*) observed following decarboxylative protonation is *opposite* to that observed in our previous report, using Meldrum's acid as the H^+ source, with isoflavanone substrates without oxygenation at the 7-position of type **3** (Scheme 5.1). Intrigued by this finding, we reinvestigated

Scheme 5.5 Deprotection of the NAP-protected isoflavanones



Sativanone **1a:** 70 %, 95 % ee
3-*O*-Methylviolanone **1b:** 99 %, 85 % ee
1c: 85 %, 97 % ee
1d: 85 %, 87 % ee
1e: 87 %, 76 % ee

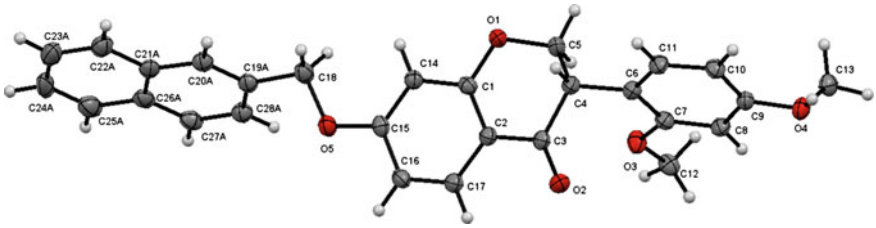
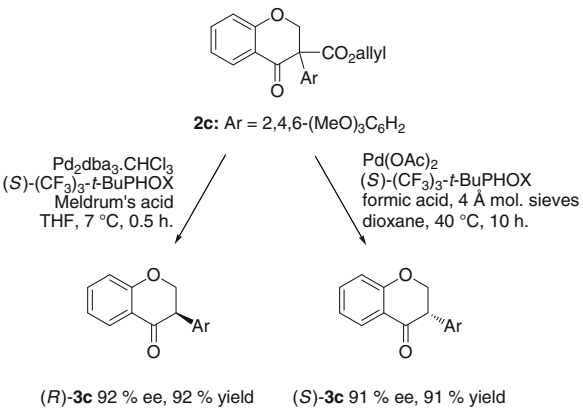


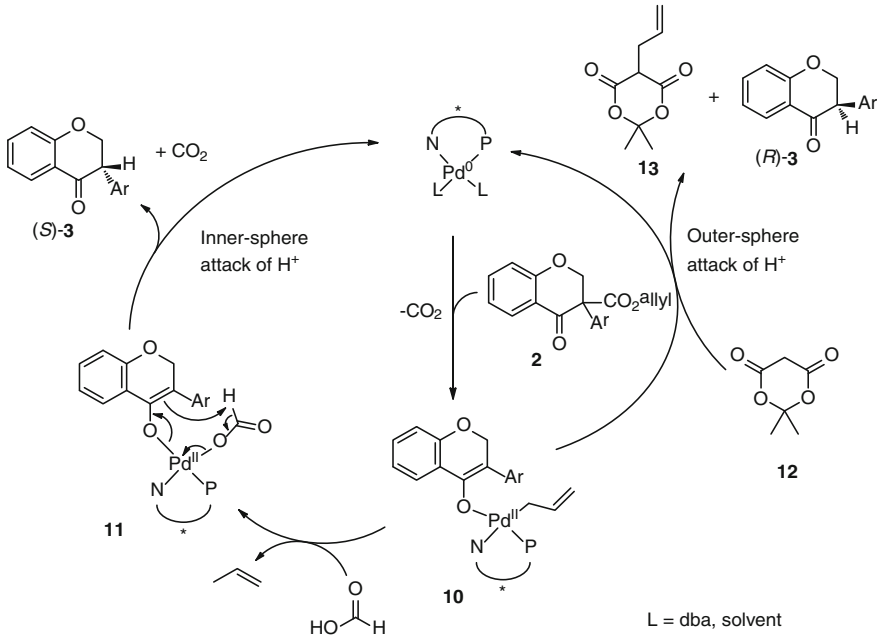
Fig. 5.3 X-ray crystal structure of NAP-protected sativanone (**9a**)



Scheme 5.6 Enantiodivergence observed with different H^+ sources

the reaction of substrate **2c** using formic acid as the H^+ source (Scheme 5.6). This confirmed the enantiodivergence of this process was retained as we observed the formation of (*R*)-**3c** in 91 % *ee* and 91 % yield [40]. This finding shows a remarkable switch in enantioselectivity from 92 % *R* to 91 % *S* as a result of changing the H^+ source. In the previous reports by Stoltz and co-workers, the sense of stereoinduction observed was different for monocyclic substrates versus fused aromatic systems; for example cyclohexanone versus tetralone. This was consistent with both the formic acid and Meldrum's acid methods [38, 41]. However, we have observed the opposite sense of stereoinduction on the same substrate.

The ability to obtain both enantiomers of a particular chiral molecule using the same chiral ligand is a valuable methodology in organic synthesis and represents a significant challenge. Previously, *dual stereocontrol* has been achieved by variation of catalyst substituents, changing of the metal centre or precursor, changing the reaction solvent or temperature. In this instance we have shown that these factors are not the cause of our observed switch in enantioselectivity. We are unaware of any other reports of dual stereocontrol in an asymmetric protonation reaction whereby the same chiral ligand is used with a different achiral proton donor to impart dual stereocontrol [42].



Scheme 5.7 Proposed mechanism for switch in enantioselectivity

The key to the switch most likely is a result of the significantly different proton sources used, an oxo-acid formic acid and the organic acid Meldrum's acid. The catalytic cycle is initiated by coordination of the Pd^0-complex to the allyl group followed by oxidative insertion and decarboxylation to generate a Pd^{II}-enolate (**10**) (Scheme 5.7), as previously proposed by Stoltz [41]. At this point we propose that this enolate attacks the proton source in an outer-sphere mechanism in the case of Meldrum's acid to generate (*R*)-**3**. This results in protonation of the least hindered face opposite to the Pd-PHOX complex. In the case of formic acid as the proton source we believe a formate could coordinate to the Pd^{II}-enolate complex. The enolate could then undergo an inner-sphere attack on the formyl H with loss of CO_2 resulting in the formation of the opposite configuration of the tertiary α-aryl centre ((*S*)-**3**).

The 5 isoflavanones synthesized in this report were assayed to determine the antibacterial activity against *E. Coli* and methicillin-resistant *Staphylococcus aureus* (MRSA) [43]. Unfortunately, none of the compounds showed any significant antibacterial activity(Tables 5.2 and 5.3).

5.3 Conclusions

In conclusion we have developed a modular, 6 step synthetic sequence to construct isoflavanones with a range of substitution on the C ring and a free hydroxy group on the 7-position. Key features of this synthesis are the Pb-mediated arylation to

Table 5.2 UCD Centre for Food Safety strains used for determination of antibacterial activity

	Strain	Type	Hospital/Isolation	Source	ARP (Resistant to)
Gram-negative	*E. coli* 25,922	Reference	FDA strain Seattle 1946 [DSM 1103, NCIB 12,210]	–	PEN; VAN; AMP; CLI; CL
Gram-positive	MRSA ATCC 43,300	Reference	Kansas	Human	AMP; PEN; OXA; MET; AXO; CIP; LEVO; GAT; ERY; CLI

Table 5.3 Determination of antibacterial activity—MIC and MBC results (Duplicates)

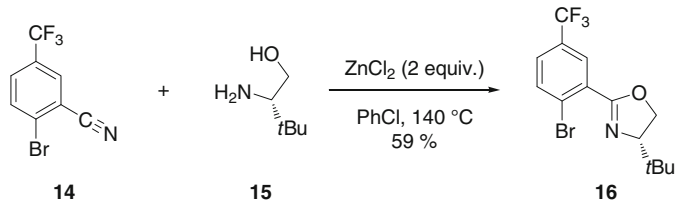
Compound ID	*E. coli* ATCC 25,922		MRSA ATCC 43300	
	MIC	MBC	MIC	MBC
1a	>512*	>512	>512*	>512
1c	512*	>512	>512	>512
1d	>512*	>512	>512	>512
1b	>512*	>512	>512**	>512
1e[@]	>512**	>512	>512**	>512

Note *Decreased growth and altered phenotype
**Changes in the strain phenotype
[@]compound showed some precipitation when transferred into Mueller-Hinton broth

allow a variety of aryl groups to be introduced from a common intermediate and the Pd-catalysed decarboxylative asymmetric protonation to generate a tertiary α-aryl carbonyl. Initial enantioselectivities obtained were poor to moderate. Optimisation of the conditions led to an increase in enantioselectivity up to 97 % *ee*. The first asymmetric isoflavanone synthesis containing oxygenation in the 7-position, a substitution commonly seen in many bioactive isoflavanones isolated from nature, has been achieved resulting in the first asymmetric synthesis of sativanone (**1a**). We have also accomplished the first synthesis of 3-*O*-methylviolanone (**1b**). A switch in enantiomer was observed for the decarboxylative protonation of substrate **8c** when different H^+ sources were employed. This was subsequently confirmed with substrate **2c**. We believe this to be as a result of the inner-sphere attack of a formate bound to Pd when formic acid is used versus outer-sphere attack when Meldrum's acid is used leading to a switch in enantioselectivity. We are currently investigating methods to confirm this mechanistic rationale.

5.4 Experimental

(S)-2-(2-Bromo-5-(trifluoromethyl)phenyl)-4-(tert-butyl)-4,5-dihydrooxazole (16) [44]

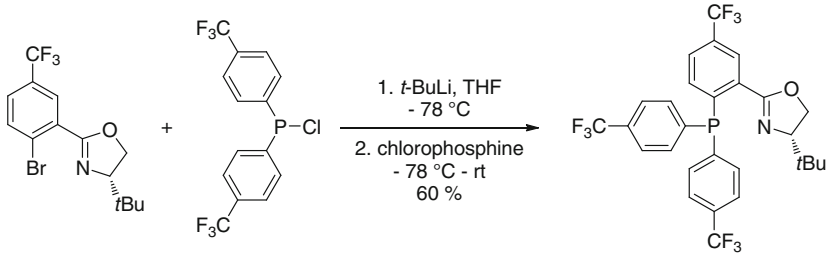


14 **15** **16**

2-Bromo-5-(trifluoromethyl)benzonitrile (**14**) (1.00 g, 4.0 mmol) and (*S*)-*tert*-leucinol (**15**) (469 mg, 4.0 mmol) were dissolved in anhydrous chlorobenzene (4 mL) in a flame dried Schlenk flask (25 mL). The reaction mixture was heated to 60 °C prior to the dropwise addition of $ZnCl_2$ (0.80 mL, 8.0 mmol, 1 M in Et_2O). The reaction was heated to reflux (140 °C) and stirred for 48 h. The reaction was cooled to room temperature and the solvent was removed in vacuo. The resulting orange oil was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 99:1) to yield the product as a pale yellow solid (829 mg, 59 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (d, J = 2.1 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.54 (dd, J = 8.4, 2.1 Hz, 1H), 4.43 (dd, J = 10.3, 8.5 Hz, 1H), 4.30 (t, J = 8.5 Hz, 1H), 4.15 (dd, J = 10.3, 8.0 Hz, 1H), 1.03 (s, 9H). All other physical data was identical to those previously reported [45].

(*S*)-2-(2-(Bis(4-(trifluoromethyl)phenyl)phosphino)-5-(trifluoromethyl) phenyl)-4-(tert-butyl)-4,5-dihydrooxazole [(*S*)-(CF_3)-*t*-BuPHOX] (L1) [46]



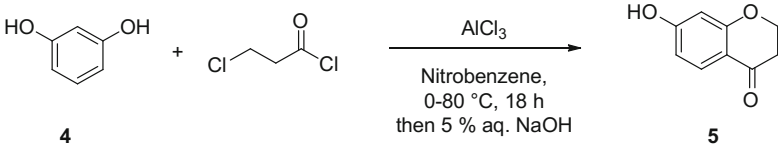
16 **17** **L1**

Bromo-oxazoline (**16**) (738 mg, 2.10 mmol) was dissolved in THF (10 mL) and cooled to −78 °C. *t*-BuLi (2.88 mL, 4.62 mmol, 1.6 M in hexanes) was added dropwise and the reaction mixture was stirred at −78 °C for 1 h prior to the dropwise addition of chlorobis[4-(trifluoromethyl)phenyl)]phosphine (**17**) (1.00 g, 2.80 mmol) in THF (2 mL). The reaction mixture was removed from the cooling bath, allowed to warm to room temperature and stirred for 1 h. The reaction mixture

was transferred to a separatory funnel containing saturated NH_4Cl solution (20 mL). The organic phase was separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The organic layers were combined, washed with brine (50 mL) and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the resulting yellow oil was purified by silica gel column chromatography (short, wide column; pentane/CH_2Cl_2, 4:1) to yield the product as a white solid (742 mg, 60 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.29–8.22 (m, 1H), 7.58 (t, J = 7.4 Hz, 5H), 7.39–7.27 (m, 4H), 6.95 (dd, J = 8.1, 3.2 Hz, 1H), 4.26 (dd, J = 10.1, 8.5 Hz, 1H), 4.11 (t, J = 8.5 Hz, 1H), 3.96 (dd, J = 10.1, 8.5 Hz, 1H), 0.69 (s, 9H); ^{31}P NMR (121 MHz, $CDCl_3$): δ −7.16. All other physical data was identical to those previously reported [45].

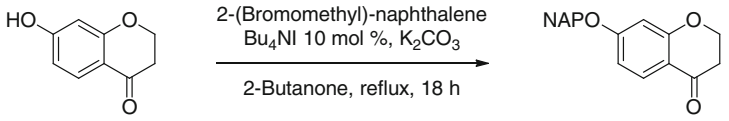
7-Hydroxychromanone (5)



4 **5**

To a suspension of resorcinol **4** (8.00 g, 79.1 mmol), in nitrobenzene (60 mL) at 0 °C, was added dropwise, 3-chloroporpionyl chloride (7.70 mL, 79.1 mmol) over 15 min. The resulting suspension was stirred for 5 min before aluminium chloride (26.30 g, 197.8 mmol) was added to the suspension in portions (5 × 5.26 g) over 30 min. The reaction mixture was then heated at 80 °C for 1 h before being cooled to room temperature and allowed to stir for a further 18 h. After 18 h the solution was then poured onto a mixture of crushed ice (≈200 g) and HCl (10 mL, 37 % w/v). The biphasic mixture was stirred until all the ice had melted and then the phases were separated. The aqueous layer was then extracted with diethyl ether (2 × 80 mL) and the combined organic layers were washed with an aqueous sodium hydroxide solution (5 % w/v) (4 × 150 mL). The organic phase was then extracted with water (2 × 100 mL) and the combined aqueous layers were cooled to 0 °C and acidified to pH ≈ 2 using HCl (≈80 mL, 37 % w/v). The yellow suspension which formed was filtered and recrystallized from toluene/charcoal to give the product as white needles (7.80 g, 55 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (d, J = 8.6 Hz, 1H), 6.57 (dd, J = 8.6, 2.6 Hz, 1H), 6.43 (d, J = 2.6 Hz, 1H), 5.77 (s, 1H), 4.51 (t, J = 6.9 Hz, 2H), 2.75 (t, J = 6.9 Hz, 2H). All other physical and spectroscopic data were in complete agreement with those reported [19].

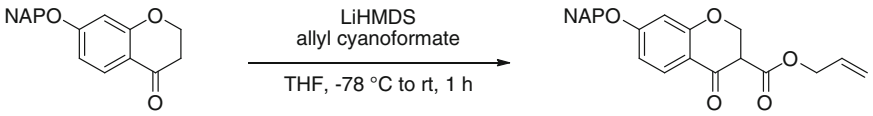
7-(Naphthalen-2-ylmethoxy)chroman-4-one (6)



5 **6**

To a solution of 7-hydroxychromanone (**5**) (6.00 g, 36.5 mmol) and 2-(bromomethyl)naphthalene (9.60 g, 43.8 mmol) in 2-butanone (70 mL) at room temperature was added K_2CO_3 (40.00 g, 292 mmol) and tetra-*n*-butylammonium iodide (1.30 g, 3.6 mmol). The suspension was heated at reflux for 18 h. After this time the reaction mixture was allowed to cool, filtered, and the solvent removed in vacuo to give a pale yellow solid. The solid was dissolved in dichloromethane (≈15 mL) and flushed through a plug of silica to give the product as a white solid (10.40 g, 94 %). $R_f = 0.34$ (cyclohexane/EtOAc, 1.5/1); IR (film) ν_{max} 2361, 2342, 1596, 1256 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (m, 5H), 7.51 (m, 3H), 6.70 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.53 (d, *J* = 2.4 Hz, 1H), 5.26 (s, 2H), 4.51 (t, *J* = 6.4 Hz, 2H), 2.75 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.4, 165.0, 163.7, 133.3, 133.2, 133.1, 128.9, 128.5, 127.9, 127.7, 126.4, 126.3, 126.2, 126.0, 115.5, 110.4, 101.8, 70.4, 67.3, 37.4; HRMS: (ESI-TOF) calculated for $C_{20}H_{16}O_3Na$ ([M + Na^+]) 327.0997, found 327.1009.

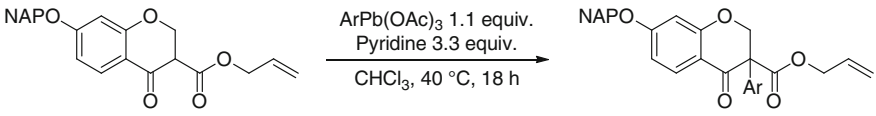
Allyl 7-(naphthalen-2-ylmethoxy)-4-oxochroman-3-carboxylate (7)



6 **7**

n-Butyllithium (6.50 mL, 2.5 M in hexanes, 16.4 mmol) was added dropwise to a well stirred solution of HMDS (3.40 mL, 16.4 mmol) in THF (80 mL) at 0 °C. The solution was stirred for 30 min at this temperature before cooling to –78 °C. 7-(Naphthalen-2-ylmethoxy)chroman-4-one **6** (2.50 g, 8.2 mmol) in THF (56 mL) was then added dropwise. After 1 h allyl cyanoformate (4.55 g, 41 mmol) was added dropwise and the reaction mixture stirred at –78 °C for 1 h. The reaction was then allowed to warm to room temperature and quenched with a saturated aqueous NH_4Cl solution (150 mL). The mixture was then extracted with Et_2O (3 × 70 mL), the combined organic layers dried over $MgSO_4$, filtered and the solvent removed in vacuo. The crude oil was purified via column chromatography to give the title compound as an off white solid (2.00 g, 64 %). $R_f = 0.60$ (pentane/Et_2O, 2.5/3.5); IR (film) ν_{max} 3059, 2939, 2254, 1738, 1686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, keto form): δ 7.87 (m, 4H), 7.51 (m, 2H), 6.73 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.54 (d, *J* = 2.4 Hz, 1H), 5.90 (m, 1H), 5.28 (m, 3H), 4.79 (dd, *J* = 11.6, 8.2 Hz, 1H), 4.69 (m, 2H), 4.60 (dd, *J* = 11.5, 4.5 Hz, 1H), 3.71 (dd, *J* = 8.2, 4.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 185.5, 167.3, 165.6, 163.4, 133.4, 133.3, 131.5, 129.6, 128.8, 128.1, 127.9, 126.7, 126.6, 126.5, 125.2, 118.9, 114.7, 111.3, 102.0, 70.7, 68.6, 66.4, 52.4; HRMS: (ESI-TOF) calculated for $C_{24}H_{21}O_5$ ([M + H^+]) 389.1389, found 389.1379.

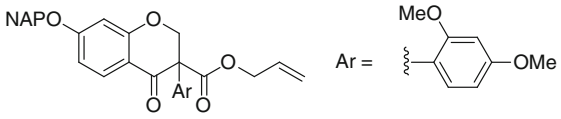
General procedure A for the arylation of allyl 7-(naphthalen-2-ylmethoxy)-4-oxochroman-3-carboxylate (8).



7 **8**

To a stirred solution of allyl 7-(naphthalen-2-ylmethoxy)-4-oxochroman-3-carboxylate **7** (1 equiv. = X, i.e. X g = X mL) and aryllead triacetate (1.1 equiv.) in anhydrous $CHCl_3$ (10X), was added dropwise anhydrous pyridine (3.3 equiv.). The resulting mixture was heated at 40 °C for 18 h, filtered through a plug of Celite® and washed with $CHCl_3$ (30X). The organic layer was washed with 3 M H_2SO_4 (2 × 40X) with vigorous shaking, extracted with $CHCl_3$ (40X) and the combined organic extracts were washed with water (60X) and dried over anhydrous Na_2SO_4. The solvent reduced in vacuo to give an orange oil. The crude oil was then purified via silica gel column chromatography.

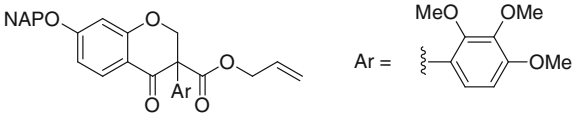
Allyl-3-(2,4-dimethoxyphenyl)-7-(naphthalen-2-methoxy)-4-oxochroman-3-carboxylate (8a)



8a

Prepared according to general procedure A using 0.50 g of **7** and the title compound was isolated as a white solid (0.46 g, 73 %). $R_f = 0.32$ (pentane/EtOAc, 3/1); IR (film) ν_{max} 3154, 2984, 2254, 1816, 1729, 1680, 1607, 1467 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 8.8 Hz, 1H), 7.86 (m, 4H), 7.50 (m, 3H), 6.76 (m, 2H), 6.49 (dd, J = 5.5, 2.4 Hz, 2H), 6.35 (dd, J = 8.6, 2.5 Hz, 1H), 5.87 (m, 1H), 5.22 (m, 4H), 5.10 (d, J = 11.4 Hz, 1H), 4.90 (d, J = 11.4 Hz, 1H), 4.71 (m, 2H), 3.76 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 189.0, 169.2, 165.3, 163.3, 160.9, 158.5, 133.4, 133.33, 133.28, 131.9, 129.7, 129.6, 128.7, 128.1, 127.9, 126.7, 126.5, 126.4, 125.2, 118.3, 116.3, 115.3, 111.2, 104.4, 101.8, 99.9, 72.0, 70.6, 66.2, 60.6, 55.6, 55.4; HRMS: (ESI-TOF) calculated for $C_{32}H_{29}O_7$ ([M + H^+]) 525.1913, found 525.1925.

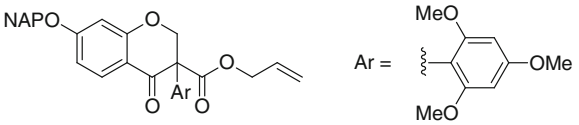
Allyl-3-(2,3,4-trimethoxyphenyl)-7-(naphthalen-2-methoxy)-4-oxochroman-3-carboxylate (8b)



8b

Prepared according to general procedure A using 0.50 g of **7** and the title compound was isolated as a white solid (0.48 g, 72 %). R_f = 0.41 (pentane/EtOAc, 3/1); IR (film) ν_{max} 2975, 2256, 1822, 1734, 1678, 1605, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.8 Hz, 1H), 7.86 (m, 4H), 7.51 (m, 3H), 6.75 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.58 (d, *J* = 8.7 Hz, 1H), 6.51 (m, 2H), 5.87 (m, 1H), 5.26 (m, 3H), 5.17 (m, 1H), 4.98 (d, *J* = 11.3 Hz, 1H), 4.88 (d, *J* = 11.3 Hz, 1H), 4.71 (m, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 187.4, 168.7, 165.0, 163.1, 154.0, 151.8, 141.9, 133.3, 133.2, 133.1, 131.4, 129.6, 128.5, 127.9, 127.7, 126.4, 126.3, 126.2, 125.0, 122.9, 121.0, 118.3, 115.0, 111.0, 106.3, 101.9, 72.6, 70.4, 66.2, 61.1, 60.4, 60.2, 55.8; HRMS: (ESI-TOF) calculated for $C_{33}H_{31}O_8$ ([M + H^+]) 555.2019, found 555.2006.

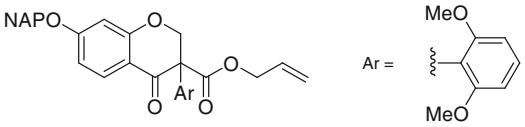
Allyl-3-(2,4,6-trimethoxyphenyl)-7-(naphthalen-2-methoxy)-4-oxochroman-3-carboxylate (8c)



8c

Prepared according to general procedure A using 0.50 g of **7** and the title compound was isolated as a white solid (0.48 g, 77 %). R_f = 0.32 (pentane/EtOAc, 3/1); IR (film) ν_{max} 2941, 2253, 1734, 1685, 1609, 1466 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.8 Hz, 1H), 7.86 (m, 4H), 7.50 (m, 3H), 6.71 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.51 (d, *J* = 2.4 Hz, 1H), 6.11 (s, 2H), 5.87 (m, 1H), 5.24 (m, 3H), 5.14 (m, 1H), 4.89 (s, 2H), 4.67 (dt, *J* = 5.6, 1.5 Hz, 2H), 3.77 (s, 3H), 3.57 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 187.1, 169.2, 164.2, 162.7, 161.1, 159.2, 133.5, 133.2, 133.1, 132.0, 129.3, 128.5, 127.9, 127.7, 126.5, 126.3, 126.2, 125.1, 117.9, 115.9, 110.4, 101.6, 92.5, 72.3, 70.4, 65.9, 58.5, 55.9, 55.2; HRMS: (ESI-TOF) calculated for $C_{33}H_{31}O_8$ ([M + H^+]) 555.2019, found 555.2012.

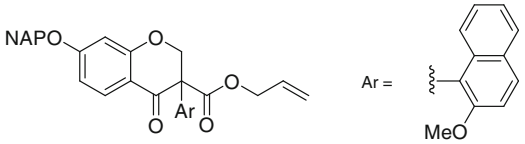
Allyl-3-(2,6-dimethoxyphenyl)-7-(naphthalen-2-ylmethoxy)-4-oxochroman-3-carboxylate (8d)



8d

Prepared according general procedure A using 0.200 g of **7** and the title compound was isolated as a white solid (0.223 g, 83 %). R_f = 0.13 (pentane/EtOAc, 3/1); IR (film) ν_{max} 2938, 2359, 1731, 1687, 1594 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.8 Hz, 1H), 7.86 (m, 4H), 7.51 (m, 3H), 7.23 (t, *J* = 8.3 Hz, 1H), 6.72 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.55 (d, *J* = 8.3 Hz, 2H), 6.51 (d, *J* = 2.3 Hz, 1H), 5.88 (m, 1H), 5.24 (m, 3H), 5.14 (m, 1H), 4.92 (s, 2H), 4.68 (m, 2H), 3.58 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 186.9, 169.0, 164.2, 162.7, 158.5, 133.5, 133.25, 133.15, 132.0, 129.6, 129.3, 128.5, 127.9, 127.7, 126.5, 126.3, 126.2, 125.1, 117.9, 115.9, 113.9, 110.4, 105.8, 101.6, 72.2, 70.4, 66.0, 58.8, 55.9; HRMS: (ESI-TOF) calculated for $C_{32}H_{28}NaO_7$ ([M + Na^+]) 547.1733, found 547.1738.

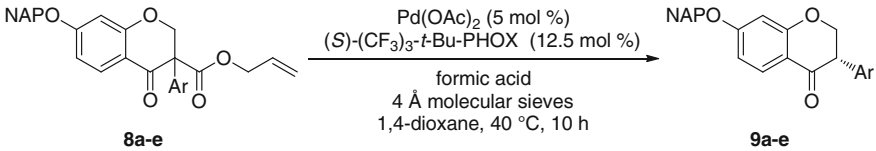
Allyl-3-(2-methoxynaphthalen-1-yl)-7-(naphthalen-2-ylmethoxy)-4-oxochroman-3-carboxylate (8e)



8e

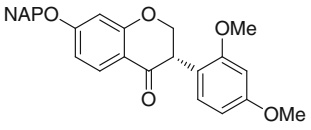
Prepared according to the general procedure using 0.150 g of **7** and the title compound was isolated as a white solid (0.168 g, 80 %). R_f = 0.19 (pentane/EtOAc, 3/1); IR (film) ν_{max} 1722, 1684, 1608 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.8 Hz, 1H), 7.84 (m, 6H), 7.59 (d, *J* = 8.6 Hz, 1H), 7.51 (m, 3H), 7.41 (m, 1H), 7.34 (m, 1H), 7.19 (d, *J* = 9.0 Hz, 1H), 6.78 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.54 (d, *J* = 2.4 Hz, 1H), 5.78 (m, 1H), 5.24 (s, 2H), 5.14 (m, 4H), 4.70 (m, 2H), 3.59 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 186.7, 169.8, 164.6, 162.7, 155.8, 133.4, 133.2, 133.2, 132.3, 131.5, 131.2, 130.6, 129.6, 129.4, 128.6, 128.0, 127.8, 126.6, 126.6, 126.4, 126.3, 125.1, 123.7, 123.5, 118.4, 118.0, 115.59, 115.4, 110.8, 101.7, 72.4, 70.5, 66.5, 60.7, 56.9; HRMS: (ESI-TOF) calculated for $C_{35}H_{28}NaO_6$ ([M + Na^+]) 567.1784, found 567.1784.

General procedure B for the synthesis of 7-Naphthyloxysubstituted Isoflavanones (9a-e)



Powdered 4 Å molecular sieves (180 mg) were added to a flame-dried 10 ml Schlenk flask with a Teflon-coated magnetic stirbar. The flask and molecular sieves were flame dried and back-filled with N_2 three times. Once the flask had cooled to ambient temperature under N_2, $Pd(OAc)_2$ (2.2 mg, 0.010 mmol), (*S*)-$(CF_3)_3$-*t*-Bu-PHOX (7.4 mg, 0.0125 mmol) and anhydrous 1,4-dioxane (1.5 mL) were added. The mixture was stirred vigorously at 40 °C for 30 min prior to the addition of formic acid (0.6 mmol) and followed immediately by a solution of β-ketoester **8** (0.10 mmol) in anhydrous 1,4-dioxane (1.5 mL) [in a flame-dried 2-neck 10 mL round-bottom flask under N_2]. The reaction mixture was stirred at 40 °C for 10 h and filtered through Celite® and the solvent was removed in vacuo. The resulting solid was then purified by silica gel column chromatography.

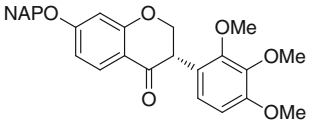
(S)-3-(2,4-Dimethoxyphenyl)-7-(naphthalen-2-ylmethoxy)chroman-4-one (9a)



9a

Prepared according to general procedure B using 52 mg of **8a**. The product was isolated as a white solid (39 mg, 88 %, *ee* = 97 %). R_f = 0.48 (pentane/EtOAc, 3/1); IR (film) ν_{max} 3155, 3019, 2981, 2253, 1794, 1608, 1468 cm^{-1}; $[\alpha]_D^{20}$ = 7.8 (*c* 1.0, $CHCl_3$); M.P. = 127–129 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.8 Hz, 1H), 7.88 (m, 4H), 7.52 (m, 3H), 7.01 (d, *J* = 8.3 Hz, 1H), 6.74 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.57 (d, *J* = 2.4 Hz, 1H), 6.48 (m, 2H), 5.27 (s, 2H), 4.59 (m, 1H), 4.49 (dd, *J* = 11.0, 5.4 Hz, 1H), 4.26 (dd, *J* = 11.5, 5.4 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 191.7, 164.9, 163.8, 160.6, 158.5, 133.6, 133.4, 133.3, 130.8, 129.6, 128.7, 128.1, 127.9, 126.6, 126.5, 126.4, 125.2, 116.1, 115.9, 110.5, 104.7, 102.0, 99.3, 71.4, 70.5, 55.6, 55.5, 47.5; HRMS: (ESI-TOF) calculated for $C_{28}H_{25}O_5$ ([M + H^+]) 441.1702, found 441.1711; SFC (Chiralcel IC-3, $scCO_2$/2-propanol, 70/30, 3 mL/min): R_t = 7.36 (major) and 10.47 min.

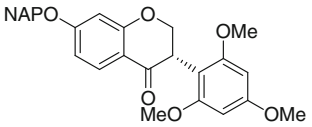
(S)-3-(2,3,4-Trimethoxyphenyl)-7-(naphthalen-2-ylmethoxy)chroman-4-one (9b)



9b

Prepared according to general procedure B using 55 mg of **8b**. The product was isolated as a white solid (38 mg, 81 %, *ee* = 86 %). R_f = 0.28 (pentane/EtOAc, 3/1); IR (film) ν_{max} 2253, 1610, 1496, 1164 cm^{-1}; $[\alpha]_D$ = 3.1 (*c* 1.0, $CHCl_3$); M. P. = 113–117 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.8 Hz, 1H), 7.88 (m, 4H), 7.52 (m, 3H), 6.80 (d, *J* = 8.5 Hz, 1H), 6.75 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.63 (d, *J* = 8.5 Hz, 1H), 6.58 (d, *J* = 2.3 Hz, 1H), 5.27 (s, 2H), 4.60 (m, 1H), 4.49 (dd, *J* = 11.0, 5.5 Hz, 1H), 4.19 (dd, *J* = 11.8, 5.5 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 191.4, 163.8, 163.7, 153.5, 152.0, 142.3, 133.4, 133.2, 133.1, 129.4, 128.5, 127.9, 127.7, 126.3, 125.0, 124.3, 121.4, 115.6, 110.5, 107.3, 106.1, 101.8, 71.5, 70.4, 60.7, 60.6, 55.9, 48.1; HRMS: (ESI-TOF) calculated for $C_{29}H_{27}O_6$ ([M + H^+]) 471.1808, found 471.1815; SFC (Chiralcel IC-3, $scCO_2$/2-propanol, 70/30, 3 mL/min): R_t = 12.31 (major) and 11.00 min.

(S)-3-(2,4,6-Trimethoxyphenyl)-7-(naphthalen-2-ylmethoxy)chroman-4-one (9c)

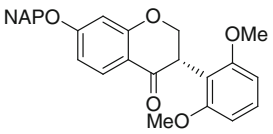


9c

Prepared according to general procedure B using 55 mg of **8c**. The product was isolated as a white solid (42 mg, 90 %, *ee* = 97 %). R_f = 0.33 (pentane/EtOAc, 3/1); IR (film) ν_{max} 2360, 2342, 1654 cm^{-1}; $[\alpha]_D^{20}$ = 13.4 (*c* 1.0, $CHCl_3$); M.P. = 162–165 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.8 Hz, 1H), 7.88 (m, 4H), 7.52 (m, 3H), 6.72 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.57 (d, *J* = 2.4 Hz, 1H), 6.17 (s, 2H), 5.27 (s, 2H), 4.74 (dd, *J* = 13.3, 10.1 Hz, 1H), 4.63 (dd, *J* = 13.3, 5.4 Hz, 1H), 4.35 (dd, *J* = 10.1, 5.4 Hz, 1H), 3.81 (s, 3H), 3.73 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 187.1, 169.2, 164.2, 162.7, 161.1, 159.2, 133.5, 133.2, 133.1, 132.1, 129.3, 128.5, 127.9, 127.7, 126.5, 126.3, 126.2, 125.1, 117.9, 115.9, 110.4, 106.3, 101.6, 92.5, 72.3, 70.4, 66.0, 58.5, 55.9, 55.3; HRMS: (ESI-TOF) calculated for $C_{29}H_{27}O_6$

([M + H^+]) 471.1808, found 471.1816. SFC (Chiralcel IC-3, $scCO_2$/2-propanol, 70/30, 3 mL/min): R_t = 5.76 (major) and 10.24 min.

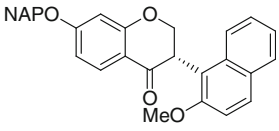
(S)-3-(2,6-Dimethoxyphenyl)-7-(naphthalen-2-ylmethoxy)chroman-4-one (9d)



9d

Prepared according to general procedure B using 52 mg of **8d**. The product was isolated as a white solid (34 mg, 78 %, *ee* = 87 %). R_f = 0.27 (pentane/EtOAc, 3/1); IR (film) ν_{max} 2933, 1684, 1607 cm^{-1}; $[\alpha]_D^{20}$ = 28.7 (*c* 1.0, $CHCl_3$); M.P. = 109–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.8 Hz, 1H), 7.88 (m, 4H), 7.52 (m, 3H), 7.24 (t, *J* = 8.3 Hz, 1H), 6.73 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.58 (m, 3H), 5.27 (s, 2H), 4.76 (m, 2H), 4.37 (dd, *J* = 7.7, 3.1 Hz, 1H), 3.75 (s, 5H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 191.3, 164.5, 163.7, 158.6, 133.59, 133.3, 133.2, 129.4, 129.1, 128.6, 128.0, 127.8, 126.5, 126.4, 126.2, 125.1, 115.8, 111.8, 110.1, 104.5, 101.9, 70.4, 69.7, 55.8, 43.3; HRMS: (ESI-TOF) calculated for $C_{28}H_{25}O_5$ ([M + H^+]) 441.1702, found 441.1718 SFC (Chiralcel IC-3, $scCO_2$/2-propanol, 70/30, 3 mL/min): R_t = 5.29 (major) and 6.21 min.

(*S*)-3-(2-methoxynaphthalen-1-yl)-7-(naphthalen-2-ylmethoxy) chroman-4-one (8e)

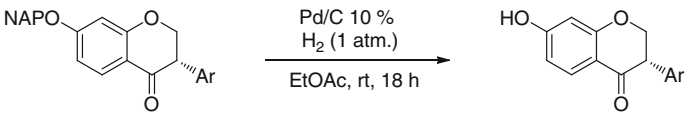


9e

Prepared according to general procedure B using 54 mg of **8e**. The product was isolated as a white solid (44 mg, 96 %, *ee* = 76 %). R_f = 0.34 (pentane/EtOAc, 3/1); IR (film) ν_{max} 2359, 1680, 1609 cm^{-1}; $[\alpha]_D$ = 86.1 (*c* 1.0, $CDCl_3$); M.P. = 133–141 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.8 Hz, 1H), 7.93–7.80 (m, 7H), 7.58–7.43 (m, 4H), 7.36 (t, *J* = 7.3 Hz, 1H), 7.30 (d, *J* = 9.0 Hz, 1H), 6.78 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.62 (d, *J* = 2.4 Hz, 1H), 5.31 (s, 2H), 4.86 (br s, 1H; t, *J* = 11.8 Hz, 1H), 4.46 (q, *J* = 5.5 Hz, 1H), 3.84 (s, 3H), 3.70 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 191.2, 164.7, 163.7, 155.3, 133.5, 133.3, 133.2, 130.0, 129.7, 129.6, 128.9, 128.6, 128.0, 127.8, 127.0, 126.5, 126.4, 126.3, 125.1, 123.6, 116.9,

115.9, 114.1, 110.4, 102.0, 70.4, 69.9, 56.5, 45.5; HRMS: (ESI-TOF) calculated for $C_{31}H_{24}NaO_4$ ([M + Na^+]) 483.1572, found 483.1584. SFC (Chiralcel IC-3, $scCO_2$/2-propanol, 70/30, 3 mL/min): R_t = 9.17 (major) and 8.18 min.

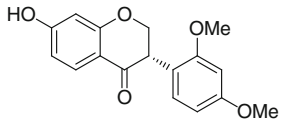
General Procedure C for the deprotection of NAP-protected Isoflavanones



9a-e **1a-e**

To a solution of NAP-protected isoflavanone in ethyl acetate (5 mL) was added 10 wt% palladium on charcoal (10 mol%). The black suspension was then stirred under an atmosphere of hydrogen at room temperature for 18 h. After 18 h the black suspension was filtered through a plug of Celite®. The plug was then washed with ethyl acetate (3 × 10 mL) and the solvent removed in vacuo and the residue was purified via column chromatography.

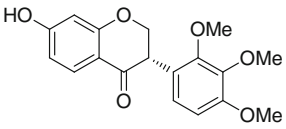
(*S*)-Sativanone (1a)



1a

Prepared according to general procedure C with 50 mg of **9a**. Isolated as a white solid (27 mg, 70 %). R_f = 0.32 (pentane/EtOAc, 2/1); IR (film) ν_{max} 3320, 1664, 1592, 1489 cm^{-1}; $[\alpha]_D^{20}$ = 31.2 (*c* 0.50, acetone); M.P. = 173–176 °C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 9.32 (s, 1H), 7.78 (m, 1H), 7.02 (m, 1H), 6.59 (dq, *J* = 4.8, 2.4 Hz, 2H), 6.48 (d, *J* = 8.3 Hz, 1H), 6.41 (t, *J* = 2.2 Hz, 1H), 4.57 (m, 1H), 4.45 (m, 1H), 4.18 (m, 1H), 3.79 (m, 6H); ^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ 191.0, 164.8, 164.6, 161.5, 159.5, 131.6, 130.0, 117.4, 116.0, 111.2, 105.7, 103.5, 99.6, 71.8, 56.0, 55.6, 48.0, 29.8; HRMS: (ESI-TOF) calculated for $C_{17}H_{16}NaO_5$ ([M + Na^+]) 323.0895, found 323.0884; SFC (Chiralcel IC-3, $scCO_2$/2-propanol, 70/30, 3 mL/min): R_t = 1.23 (major) and 1.43 min.

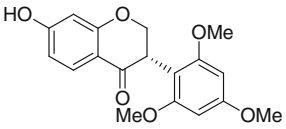
3′-*O*-Methylviolanone (1b)



1b

Prepared according to general procedure C with 29 mg of **9b**. Isolated as a white solid (21 mg, 99 %). R_f = 0.16 (pentane/EtOAc, 2/1); IR (film) ν_{max} 3327, 1677, 1584, 1457 cm^{-1}; $[\alpha]_D^{20}$ = 9.9 (*c* 0.50, acetone); M.P. = 183–186 °C; ^{1}H NMR (500 MHz, $(CD_3)_2CO$): δ 9.40 (s, 1H), 7.78 (d, *J* = 8.6 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 1H), 6.73 (d, *J* = 8.6 Hz, 1H), 6.59 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.42 (d, *J* = 2.3 Hz, 1H), 4.58 (dd, *J* = 11.7, 10.9 Hz, 1H), 4.46 (dd, *J* = 10.9, 5.5 Hz, 1H), 4.15 (dd, *J* = 11.7, 5.5 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (126 MHz, acetone): δ 191.2, 165.0, 164.7, 154.5, 152.9, 143.3, 130.1, 125.4, 122.9, 115.7, 111.3, 108.5, 103.5, 72.0, 61.0, 60.6, 56.3, 48.9; HRMS: (ESI-TOF) calculated for $C_{18}H_{20}NaO_5$ ([M + Na^+]) 339.1208, found 339.1199; SFC (Chiralcel IC-3, $scCO_2$/2-propanol, 80/20, 3 mL/min): R_t = 4.39 (major) and 3.94 min.

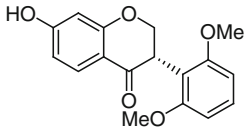
7-Hydroxy-2′,4′,6′-trimethoxyisoflavanone (1c)



1c

Prepared according to general procedure C with 41 mg of **9c**. Isolated as a white solid (24 mg, 85 %). R_f = 0.16 (pentane/EtOAc, 2/1); IR (film) ν_{max} 3250, 1657, 1562, 1472 cm^{-1}; $[\alpha]_D^{20}$ = 9.3 (*c* 0.50, acetone); M.P. = 237–240 °C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 9.28 (s, 1H), 7.77 (d, *J* = 8.6 Hz, 1H), 6.57 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.40 (d, *J* = 2.3 Hz, 1H), 6.26 (s, 2H), 4.67 (dd, *J* = 13.2, 10.4 Hz, 1H), 4.46 (dd, *J* = 13.2, 5.7 Hz, 1H), 4.26 (dd, *J* = 10.4, 5.7 Hz, 1H), 3.81 (s, 3H), 3.74 (s, 6H); ^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ 191.0, 164.6, 164.5, 162.0, 160.3, 130.0, 115.9, 111.0, 105.3, 103.5, 92.2, 70.4, 56.2, 55.7, 43.9, 29.8; HRMS: (ESI-TOF) calculated for $C_{18}H_{18}NaO_6$ ([M—H^+]) 353.1001, found 353.0988; SFC (Chiralcel IC-3, $scCO_2$/2-propanol, 80/20, 3 mL/min): R_t = 3.04 (major) and 4.52 min.

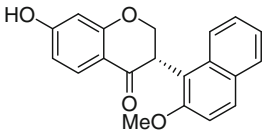
7-Hydroxy-2′,6′-dimethoxyisoflavanone (1d)



1d

Prepared according to general procedure C with 38 mg of **9d**. Isolated as a white solid (24 mg, 85 %). R_f = 0.22 (pentane/EtOAc, 2/1); IR (film) ν_{max} 2936, 1662, 1596 cm^{-1}; $[\alpha]_D^{20}$ = 34.1 (*c* 0.5, acetone); M.P. = 188–193 °C; ^1H NMR (400 MHz, $(CD_3)_2CO$): δ 9.28 (s, 1H), 7.77 (d, *J* = 8.6 Hz, 1H), 7.25 (t, *J* = 8.4 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 2H), 6.58 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.41 (d, *J* = 2.3 Hz, 1H), 4.71 (dd, *J* = 13.1, 10.3 Hz, 1H), 4.58 (dd, *J* = 13.1, 5.6 Hz, 1H), 4.29 (dd, *J* = 10.3, 5.6 Hz, 1H), 3.74 (s, 6H); ^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ 190.7, 164.7, 164.6, 159.8, 130.1, 130.0, 116.0, 113.3, 111.1, 105.6, 103.7, 70.3, 56.4, 44.3; HRMS: (ESI-TOF) calculated for $C_{17}H_{16}NaO_5$ ([M + Na^+]) 323.0895, found 323.0901; SFC (Chiralcel IB-3, $scCO_2$/methanol, 99/1 to 70/30 gradient over 5 min, 3 mL/min): R_t = 3.41 (major) and 3.63 min.

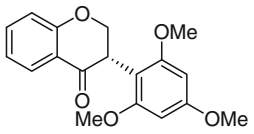
7-Hydroxy-2′-methoxynaphthylisoflavanone (1e)



1e

Prepared according to general procedure C with 70 mg of **9e**. Isolated as a white solid (43 mg, 87 %). R_f = 0.20 (pentane/EtOAc, 2/1); IR (film) ν_{max} 2360, 2339, 1668, 1590 cm^{-1}; $[\alpha]_D^{20}$ = 160.2 (c 0.5, acetone); M.P. = 251–253 °C; ^1H NMR (600 MHz, $(CD_3)_2CO$): δ 9.39 (br s, 1H), 8.07 (br s, 1H), 7.94 (d, *J* = 9.0 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.6 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 9.0 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 6.63 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.47 (d, *J* = 2.3 Hz, 1H), 4.98 (br s, 1H), 4.84 (dd, *J* = 13.1, 10.8 Hz, 1H), 4.46 (dd, *J* = 10.8, 6.0 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (151 MHz, $(CD_3)_2CO$): δ 190.8, 164.8, 164.6, 156.5, 134.3, 130.6, 130.2, 129.6, 127.6, 124.3, 118.6, 116.0, 115.4, 111.2, 103.7, 70.4, 56.9, 46.3; HRMS: (ESI-TOF) calculated for $C_{20}H_{16}NaO_4$ ([M + Na^+]) 343.0946, found 343.0940; SFC (Chiralcel IB-3, $scCO_2$/methanol, 99/1 to 70/30 gradient over 5 min, 3 mL/min): R_t = 4.30 (major) and 4.74 min.

(*S*)-3-(2,4,6-Trimethoxyphenyl)chroman-4-one (3c)



(*S*)-**3c**

Prepared according to general procedure B using 40 mg of **2c** [18]. The product was isolated as a white solid (39 mg, 91 %, *ee* = 91 %). All other physical data was in accordance with those previous reported [18]. $[\alpha]_D^{20}$ = 53.2 (*c* 1.0, $CHCl_3$); SFC (Chiralcel IC-3, $scCO_2$/methanol, 99/1 to 70/30 gradient over 5 min, 3 mL/min): R_t = 3.39 (major) and 4.03 min.
(*R*)-**3c** was prepared in our previous report. $[\alpha]_D^{20}$ = −62.7 (*c* 1.7, $CHCl_3$) [18].

Biological Testing

Compounds tested. Five compounds were tested: **1a. 1b, 1c, 1d** and **1e**.

Preparation of compounds. Powders were reconstituted with 1 mL of DMSO.

Antibacterial activity testing. Determined using the broth microdilution method. Incubations were performed for 18 h using an Ominolog® automated incubator (Biolog Inc.; 21,124 Cabot Boulevard, Hayward, CA 94545, USA). After this period MIC were checked by eye-ball observation and all wells plated to determine the minimum bactericidal concentration (MBC).

Result

- The maximum concentration of compounds tested was 512 mg/L

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40. Using Pd(OAc)2 in place of Pd2dba3 with Meldrum's acid as the H + source in THF formed the R enantiomer albeit in a lower ee of 14 %. Using Pd2dba3 in place of Pd(OAc)2 with formic acid as the H + source formed the S enantiomer albeiit in a lower ee of 44 %. Using Pd(OAc)2 with formic acid in THF instead of 1,4-dioxane also formed the S enantiomer in 85 % ee
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Chapter 6
Asymmetric Synthesis of Tertiary α-Aryl Ketones by Decarboxylative Asymmetric Protonation

Abstract The catalytic asymmetric synthesis of a series of tertiary α-aryl cyclopentanones and cyclohexanones has been accomplished via a Pd-catalysed decarboxylative protonation of the corresponding α-aryl-β-keto allyl esters. Enantioselectivities of up to 92 % *ee* and 74 % *ee* were achieved for cyclopentanone and cyclohexanone substrates, respectively. The route described gives access to these important structural motifs in moderate to high levels of enantioselectivity. In particular, this is only the second direct approach for the preparation of tertiary α-aryl cyclopentanones. The synthetic approach allows for simple modification of the aryl group and, significantly, substrates containing sterically hindered aryl groups gave the highest levels of enantioselectivity and these aryl groups were readily installed by a Pb-mediated arylation of a β-keto allyl ester.

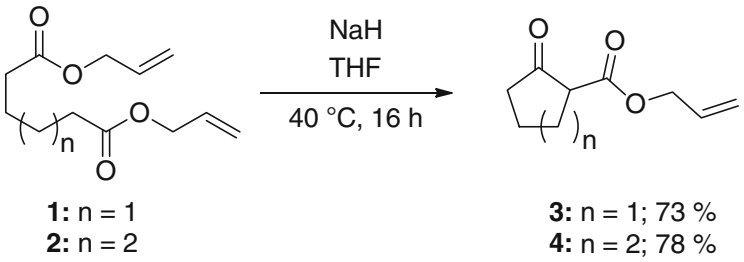
6.1 Introduction

Following the previous successful application of the asymmetric decarboxylative protonation reaction in the catalytic asymmetric synthesis of isoflavanones we hoped to expand the scope of this work to the catalytic asymmetric synthesis of tertiary α-aryl cyclohexanones and, in particular, cyclopentanones given the dearth of reported methods for their direct asymmetric synthesis to date (see Sect. 4.6).

6.2 Results and Discussion

The synthesis of a series of α-aryl-β-keto allyl esters was accomplished by first preparing cyclopentanone- and cyclohexanone-derived β-keto allyl esters **3** and **4** (Scheme 6.1). This was achieved via Dieckmann condensation of commercially available diallyl adipate using NaH as the base to generate cyclopentanone β-keto allyl ester **3** in 73 % yield. Similarly, diallyl pimelate, prepared by transesterification

R. Doran, *Asymmetric Synthesis of Bioactive Lactones and the Development of a Catalytic Asymmetric Synthesis of α-Aryl Ketones*, Springer Theses,
DOI 10.1007/978-3-319-20544-1_6



1: n = 1
2: n = 2

3: n = 1; 73 %
4: n = 2; 78 %

Scheme 6.1 Synthesis of cyclopentanone and cyclohexanone β-keto allyl esters

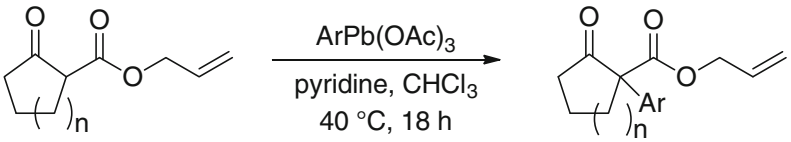
of pimelic acid with allyl alcohol, was cyclised in the same manner to yield cyclohexanone β-keto allyl ester **4** in 74 % yield over 2 steps.

The next step was to generate a series of α-aryl-β-keto allyl esters from the cyclopentanone and cyclohexanone β-keto-allyl esters. This could be achieved by the use of aryllead triacetates under relatively mild conditions of 40 °C in the presence of pyridine. These reagents have shown a remarkable ability for the α-arylation of β-keto esters, particularly impressive is their ability to introduce sterically bulky aryl groups generating a quaternary centre in very high yields (see Sect. 4.7.2).

A total of 11 aryllead triacetates were prepared according to previously reported methods. [1] We chose a number of sterically demanding aryl groups as this was hitherto important to achieve reasonable levels of enantioinduction. These were successfully used in the arylation of the cyclopentanone and cyclohexanone β-keto allyl esters in moderate to excellent yields, with the exception of the 2,6-dimethylphenyl group. The aryl groups utilised and the yields for the various arylation reactions are summarised in Table 6.1.

We chose the cyclopentanone α-aryl-β-keto allyl ester (**5a**) bearing a 2,4,6-trimethoxyphenyl group as the model substrate to assess the viability of our previously optimised conditions for the Pd-catalysed decarboxylative asymmetric protonation protocol on these types of substrates (Table 6.2). Thus, we attempted the reaction using $Pd_2dba_3.CHCl_3$, (*S*)-$(CF_3)_3$-*t*-BuPHOX as the chiral *P*,*N*-ligand and Meldrum's acid as the proton source at 7 °C in THF (Table 6.2, entry 1). Promisingly, the reaction went with full conversion although the level of enantioselectivity was poor at 28 % *ee*. We then lowered the temperature to −20 °C and surprisingly this led to formation of the opposite enantiomer (*R*) of tertiary α-aryl cyclopentanone **7a**, albeit with low enantioselectivity and conversion (Table 6.2, entries 2 and 3). Carrying out the reaction at 23 °C increased the *ee* slightly to 36 % of the *S*-enantiomer (Table 6.2, entry 4). A number of solvents were then screened with 1,4-dioxane leading to an increase in enantioselectivity up to 51 % *ee* (Table 6.2, entry 5). Encouraged by this we decided to increase the temperature to 40 °C as we had seen a slight increase going from 7 to 23 °C. This resulted in further increase in enantioinduction up to 75 % *ee* (Table 6.2, entry 9).

Table 6.1 Synthesis of α-aryl-β-keto allyl esters



3: n = 1
4: n = 2

5a-k: n = 1
6a-j: n = 2

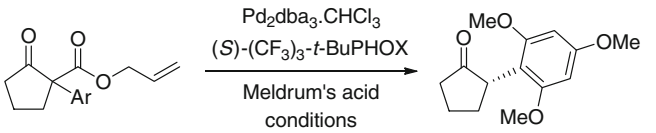
Substrate	Ar	Yield (%) **5**	Yield (%) **6**
a	2,4,6-$(MeO)_3C_6H_2$	80	60
b	2,4-$(MeO)_2C_6H_3$	77	90
c	2,6-$(MeO)_2C_6H_3$	84	61
d	2,3,4-$(MeO)_3C_6H_2$	91	94
e	2,3,6-$(MeO)_3C_6H_2$	91	85
f	4-$MeOC_6H_4$	61	92
g	2-$MeOC_{10}H_6$	62	89
h	3,4-(OCH_2O)-C_6H_3	89	86
i	2-$BnOC_{10}H_6$	67	79
j	2-MeO-4,6-$Me_2C_6H_2$	90	90
k	2,6-$Me_2C_6H_3$	36	n.d.[a]

[a]n.d. = not determined; due to poor yield for arylation and moderate *ee* for the same aryl group in the cyclopentanone series

We then re-examined THF at this higher temperature and this further increased the *ee* to 82 % with an yield of 91 % (Table 6.2, entry 10). For completeness we carried out the reaction at 30 °C and achieved the same level of enantioselectivity albeit with a longer reaction time (Table 6.2, entry 11). At 50 °C the *ee* drops to 73 %, possibly due to the instability of the catalyst at this elevated temperature (Table 6.2, entry 12).

Further attempts were made to improve the level of enantioselectivity. Surprisingly, using only 1.0 equivalent of Meldrum's acid did not result in the formation of the competitive allylation product and had no effect on the enantioselectivity (Table 6.2, entry 14). Increasing this to 5.0 equivalents had a detrimental effect on the enantioselectivity (Table 6.2, entry 15). To ensure complete protonation for both the cyclopentanone and cyclohexanone motifs with the various aryl groups we chose to use 2.5 equivalents of Meldrum's acid in the optimised conditions. Forming the complex in the presence of Meldrum's acid also had a negative effect on enantioselectivity (Table 6.2, entry 19) as did the slow addition of the solution of Meldrum's acid/substrate solution (Table 6.2, entry 20). Also, decreasing the concentration of THF lowered the *ee* whereas increasing the concentration did not have a significant effect (Table 6.2, entries 17 and 18,

Table 6.2 Optimisation of conditions for the decarboxylative asymmetric protonation



5a **7a**

Entry	Solvent	T (°C)	Conv.(%)[a]	ee (%)[b]
1	THF	7	100	28
2	THF	−20	18	20 (R)
3	toluene	−20	60	10 (*R*)
4	THF	23	100(61)	36
5	1,4-dioxane	23	100(69)	51
6	2-Me-THF	23	100(61)	26
7	toluene	23	100	42
8	Et_2O	23	100	17
9	1,4-dioxane	40	100	75
10	**THF**	**40**	**100(91)**	**82 (1.5 h)**
11	THF	30	100	82 (19 h)
12	THF	50	100	73
13	2:1 THF/benzene	40	100	58
14[c]	THF	40	100	62
15[d]	THF	40	100	81
16[e]	THF	40	100	76
17[f]	THF	40	100	70
18 [g]	THF	40	100	80
19 [h]	THF	40	100	70
20[i]	THF	40	100	74
21[j]	THF	40	100	73
22 [k]	THF	40	100	8

Reactions carried out with 5 mol% $Pd_2dba_3.CHCl_3$ and 12.5 mol% ligand in 0.20 M substrate concentration unless otherwise stated

[a]% conversion determined by chiral HPLC analysis. Yields in parentheses

[b]% ee values determined by chiral SFC analysis

[c]Using commercial Pd_2dba_3

[d]1.0 equiv. Meldrum's acid

[e]5.0 equiv. Meldrum's acid

[f]0.025 M THF

[g]0.10 M THF

[h]Meldrum's acid added during complex formation

[I]Meldrum's acid/substrate solution added dropwise

[j]0.10 M THF, 1 equiv. Meldrum's acid

[k]Using (*S*)-*t*-BuPHOX

respectively). The optimum conditions chosen were in THF (0.1 M) at 40 °C with a one-portion addition of the substrate and Meldrum's acid (2.5 equiv.).

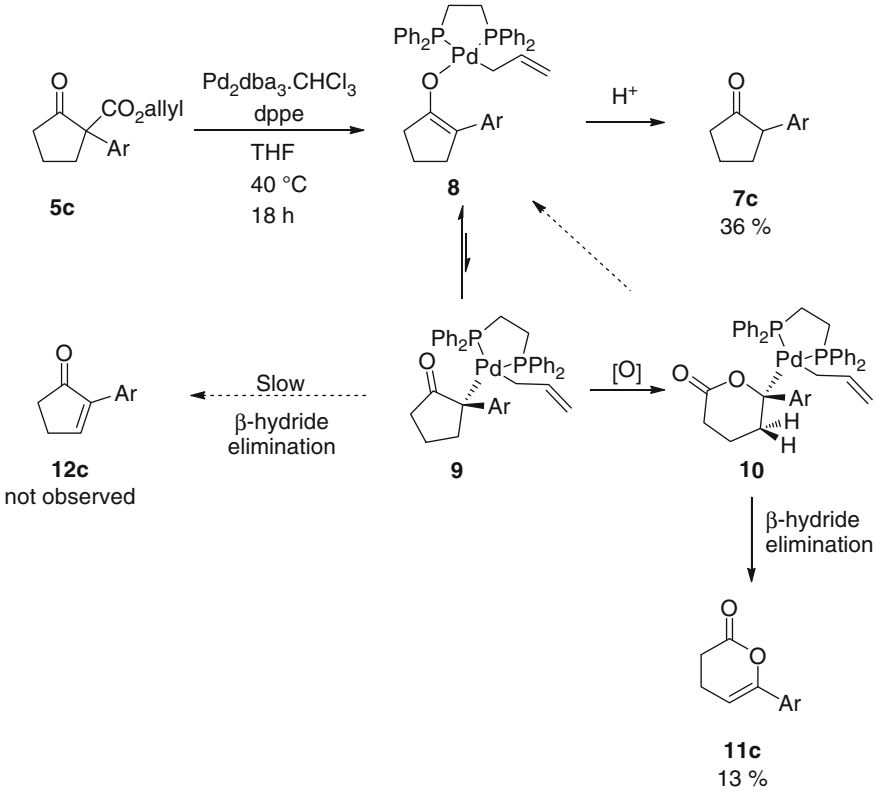
It is worth noting during the course of optimisation of the reaction conditions we found the *ee* values would slowly increase over time when the reaction was carried out at 23 and 7 °C despite complete reaction of all of the starting material upon initial sampling of the reaction. The level of increase in *ee* observed was significantly greater than 10 %, suggesting the intermediate is not a monomeric Pd-bound species. A previous report by Stoltz and co-workers suggested the reaction proceeded via a ligand-bound Pd-enolate complex [2]. For example in Table 6.2, entry 19, the *ee* after 30 min was 30 % with no starting material remaining. When this was sampled after 2 h the *ee* had increased to 70 % and was unchanged thereafter. Previous work carried out during the development of conditions for the catalytic asymmetric synthesis of isoflavanones showed a similar trend [3]. During the course of that study we showed that the process was not dynamic, i.e. the protonated product was not being deprotonated under the reaction conditions. This led us to the conclusion that a long-lived intermediate was being slowly protonated over time. We believed when the reaction was sampled for chromatographic analysis this intermediate was been quenched on silica. In order to prove this we carried out the reaction where we replaced Meldrum's acid with silica gel and this resulted in formation of the racemic protonated product in 78 % yield. Unfortunately we have been unable to establish a potential structure for this postulated intermediate.

This observed increase in *ee* over time might explain why in the case of the cyclopentanone substrate the level of enantioselectivity increased as the temperature was increased. At temperatures lower than 30 °C the intermediate may not have enough reactivity to be asymmetrically protonated by Meldrum's acid and hence the lower *ee* value could be more truly viewed as a lower conversion. It should also be noted that this process is difficult to observe when the THF used for the reaction is of high purity with the asymmetrically protonated product formed in as little as 30 min. The use of dry, degassed and peroxide-free THF is crucial to obtaining good, reproducible levels of enantioselectivity in this reaction.

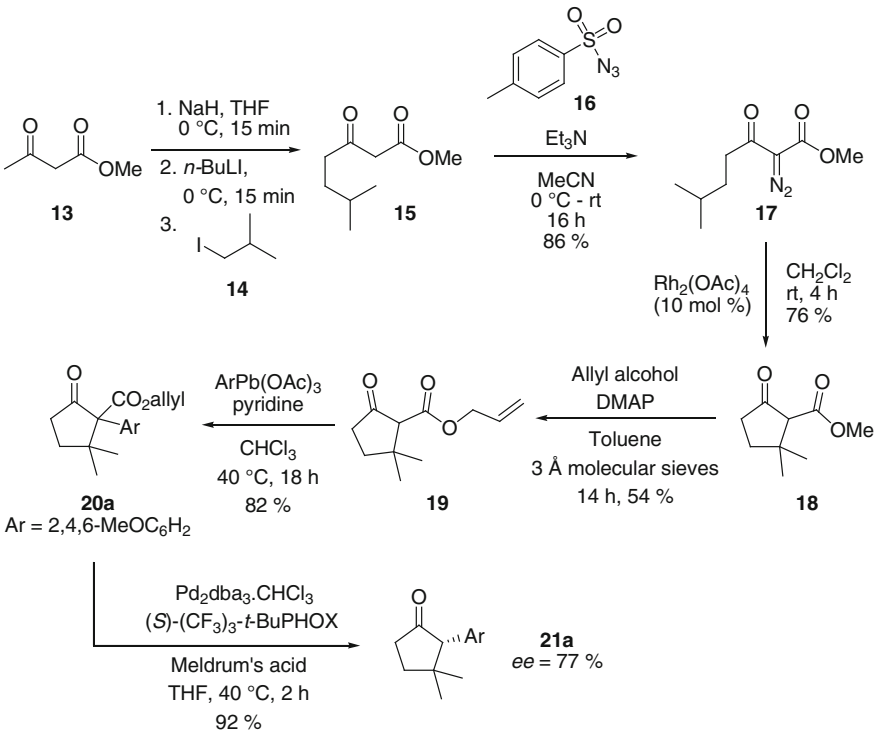
An example of the importance of the solvent purity was the formation of an unexpected impurity during the first few attempts at this reaction. The formation of lactone **11c**, albeit in low yields is likely to have resulted from oxygen insertion (Scheme 6.2) [4]. The only reasonable source of this is dissolved oxygen in the solvent THF or peroxides. It should be noted that this impurity was generated when a Na/benzophenone still was used. The still however, was freshly set-up and had not been refluxed for a sufficient time to allow complete degassing of the solvent, evident by the deep blue colour which indicates the THF is relatively dry, however, a deep purple colour indicates the solvent is also degassed. Perhaps the most significant observation in the formation of this impurity is the unsaturation of the lactone. This is potentially as a result of β-hydride elimination from a carbopalladated species. Against this argument would be the lack of a detectable quantity of cyclopentanone **12c** in any of the reactions carried out. It is perhaps plausible that

there may be equilibrium between a carbopalladated species and a Pd-enolate which may account for the observed product distribution (Scheme 6.2). In order to investigate this further we synthesised a cyclopentanone substrate which contained a *gem*-dimethyl substituent in the β-position (**20a**) (Scheme 6.3). An alkene product, as observed in the formation of **11c**, is not possible with this substrate due to the absence of a β-hydrogen. We have previously exploited this approach in our use of 2,2-dimethyl-2,3-dihydrofuran as a substrate in intermolecular asymmetric Heck reactions to afford one regioisomeric product [5–8]. We did not observe the formation of a lactone by-product with this substrate. We subsequently concluded that degassed and peroxide free THF prevented the formation of lactone **11c**.

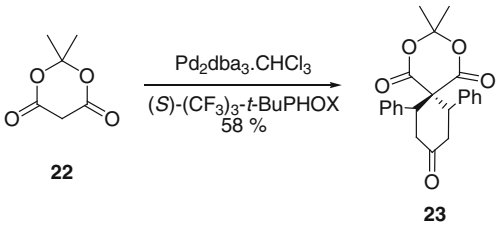
Another minor by-product was also isolated during this study due to a side reaction between dibenzylideneacetone (dba), a ligand from the Pd^0 precursor, and Meldrum's acid (**22**) in the presence of (*S*)-$(CF_3)_3$-*t*-BuPHOX (Scheme 6.4). The double Michael addition of Meldrum's acid to dba formed spirocyclic compound **23**, which is a known reaction, but has not been reported as a by-product from Pd_2dba_3 [9].



Scheme 6.2 Proposed mechanism for the formation of lactone **11c**

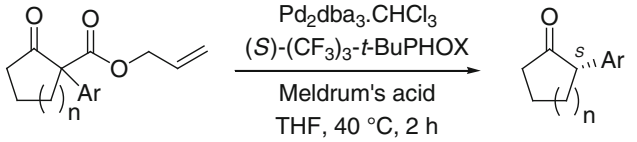


Scheme 6.3 β-g*em*-Dimethyl substituted cyclopentanone analogue



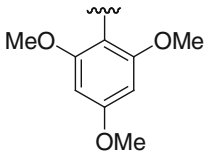
Scheme 6.4 Formation of by-product of Pd_2dba_3 and Meldrum's acid

We then subjected the collection of cyclopentanone and cyclohexanone substrates to the optimised reaction conditions and the enantioselectivities obtained are summarised in Scheme 6.5. The highest level of enantioselectivity was observed for the bulky 2-benzyloxy-napththyl substituted cyclopentanone substrate (**7i**, 92 % *ee*). This high *ee* was unfortunately not transferred to the cyclohexanone substrate (**24i**) which had a more moderate *ee* of 60 %. In most cases the cyclopentanone substrates resulted in a higher level of enantioinduction compared to their cyclohexanone counterpart. The best *ee* achieved in the cyclohexanone series was 74 %

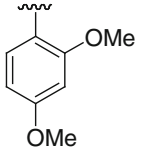


5: n = 1
6: n = 2

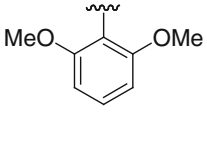
7: n = 1
24: n = 2



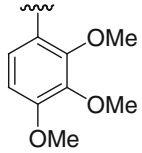
7a: 91 %, *ee* = 82
24a: 88 %, *ee* = 60



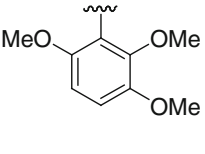
7b: 82 %, *ee* = 60
24b: 97 %, *ee* = 72



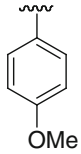
7c: 94 %, *ee* = 80
24c: 93 %, *ee* = 70



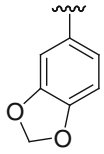
7d: 80 %, *ee* = 70
24d: 83 %, *ee* = 74



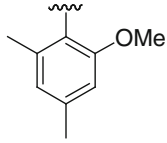
7e: 85 %, *ee* = 71
24e: 87 %, *ee* = 67



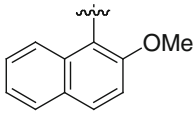
7f: 53 %, *ee* = 29
24f: 59 %, *ee* = 38



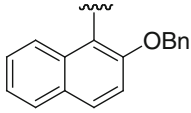
7g: 72 %, *ee* = 24
24g: 82 %, *ee* = 63



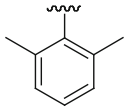
7h: 92 %, *ee* = 77
24h: 63 %, *ee* = 64



7i: 92 %, *ee* = 85
24i: 72 %, *ee* = 74



7j: 95 %, *ee* = 92
24j: 82%, *ee* = 60



7k: 92 %, *ee* = 47

Scheme 6.5 Scope and enantioselectivity of tertiary α-aryl cyclopentanones and cyclohexanones

for both the 2,3,4-trimethoxyphenyl and the 2-methoxynaphthyl substituents, **24d** and **24 g**, respectively. The tertiary α-aryl ketones were obtained in moderate to excellent yields, of 63–97 %. In line with our previous report the presence of substitution in the *ortho*-position of the aryl group is crucial to achieve reasonable levels of stereoselectivity. For example, the 4-methoxyphenyl group gave low *ee* values of 29 and 38 % for the cyclopentanone and cyclohexanone substrates, **7f** and **24f**, respectively. It should also be noted the importance of the presence of an oxygen-containing substituent as evidenced by the drop in enantioselectivity for the 2,6-dimethylphenyl substituted cyclopentanone (**7 k**) to 47 % ee. Comparatively, the 2-methoxy-4,6-dimethylphenyl group (**7j**) gave a much higher *ee* of 77 % with the cyclopentanone substrate. This is likely due to a positive interaction between the

oxygen of the methoxy group and the Pd centre. The presence of steric bulk in the β-position had little effect on the level of enantioselectivity as observed with the β-g*em*-dimethyl-substituted cyclopentanone analogue (**21a**, Scheme 6.3). With a 2,4,6-trimethoxyphenyl group an *ee* of 77 % was observed compared with 82 % in the absence of substitution in the β-position.

The absolute configuration (*S*) of the stereocentre was assigned based on comparison of the optical rotation values of analogous tertiary α-aryl cyclopentanones and cyclohexanones reported in the literature. This was further confirmed by obtaining an X-ray crystal structure of cyclopentanone **7a** and cyclohexanone **24b** (Fig. 6.1).

As noted earlier, a switch in enantioselectivity was observed in our earlier work on isoflavanone substrates (see Scheme 5.6, Sect. 5.3) when the proton source was switched to formic acid. The heterogeneous reaction conditions were also applied to the cyclopentanone and cyclohexanone substrates to ascertain we would observe a

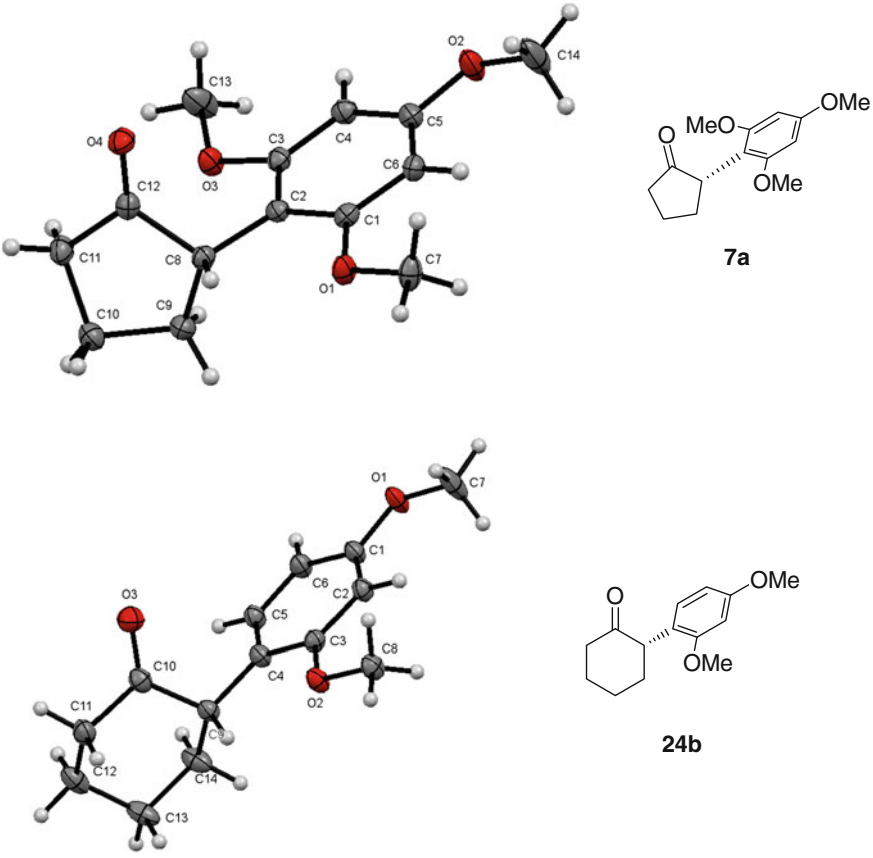
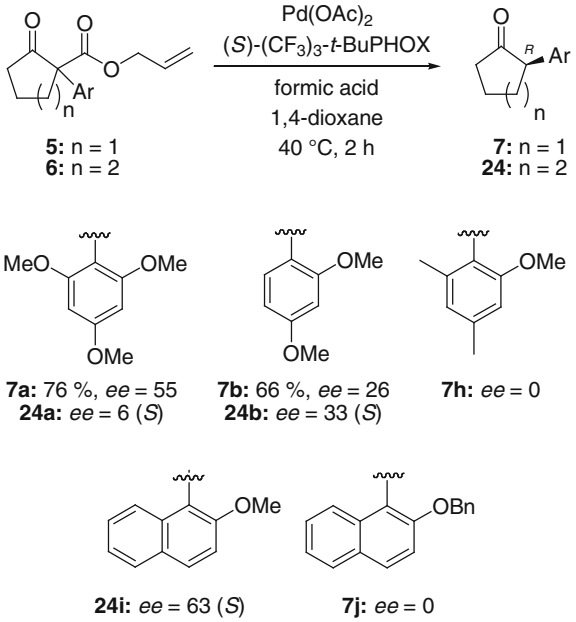


Fig. 6.1 X-ray crystal structure of α-aryl cyclopentanone **7a** and cyclohexanone **24b**



Scheme 6.6 Scope of the switch in enantioselectivity using formic acid

similar switch in enantioselectivity with these substrates (Scheme 6.6). The results obtained showed that only two of the cyclopentanone substrates demonstrated a switch in the sense of enantioinduction with *ee*'s of 55 and 26 % (*R*) for the 2,4,6-trimethoxyphenyl and 2,4-dimethoxyphenyl substrates **7a** and **7b**, respectively. Both the 2-methoxy-4,6-dimethylphenyl and 2-benzyloxynaphthyl substrates, **7h** and **7j**, formed only racemic products. The three cyclohexanone substrates screened did display some enantioinduction, however, preferentially forming the same enantiomer as when Meldrum's acid was used. This goes to underlie the apparent mechanistic differences when using an oxo-acid, formic acid, compared to a carbon acid, Meldrum's acid. It also shows how subtle the interactions are between the substrate, catalyst and proton source given the large changes in selectivity observed.

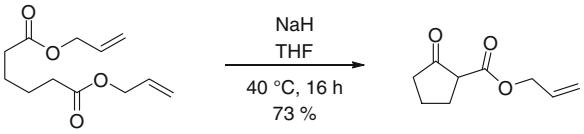
6.3 Conclusions

In conclusion, we have described the catalytic asymmetric synthesis of a series of tertiary α-aryl cyclopentanones and cyclohexanones. This offers a new route to access these important structural motifs with moderate to good levels of enantioselectivity. This is only the second report of the direct catalytic asymmetric synthesis of tertiary α-aryl cyclopentanones. A major advantage of this methodology is the ability to insert a number of different aryl groups prior to the enantiodetermining

step by Pb-mediated α-arylation of a β-keto allyl ester. In particular this allows the insertion of bulky aryl groups where the new stereocentre is generated. Furthermore, the conditions developed for the decarboxylative asymmetric protonation reaction achieved good levels of enantioselectivity for mono- and di-ortho substituted aryl groups.

6.4 Experimental

Allyl 2-oxocyclopentanecarboxylate (3) [10]

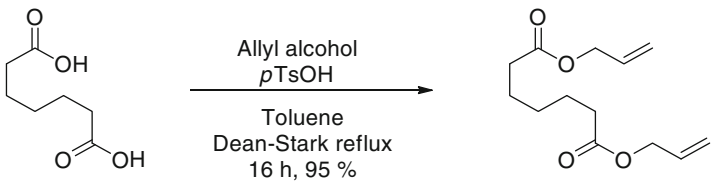


1 3

NaH (793 mg, 19.84 mmol, 60 % dispersion in mineral oil) was suspended in anhydrous THF (15 mL) in a flame dried Schlenk flask. Diallyl adipate (**1**) (4.0 mL, 18.04 mmol) in THF (3 mL) was added dropwise to the stirred suspension and the reaction mixture was stirred at 40 °C for 16 h. The reaction mixture was allowed to cool to room temperature, quenched by the slow addition of 1 M HCl (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the resulting oil was purified by silica gel column chromatography (20 % EtOAc in pentane) to yield the product as a pale pink oil (2.21 g, 73 %).

^{1}H NMR (300 MHz, $CDCl_3$, mixture of keto and enol tautomers; 90 % keto): δ 10.34 (s, 0.1H, enol), 5.92 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.34 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.24 (dq, *J* = 10.4, 1.5 Hz, 1H), 4.71 – 4.58 (m, 2H), 3.19 (t, *J* = 9.2 Hz, 1H), 2.58 – 2.48 (m, 0.3H), 2.37 – 2.25 (m, 4H), 2.22 – 2.08 (m, 1H), 1.97 – 1.80 (m, 1H). All other physical data was identical to those previously reported [11].

Diallyl pimelate (2) [10]

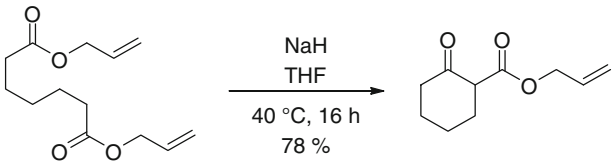


25 2

Pimelic acid (**25**) (10.0 g, 62.6 mmol) and allyl alcohol (12.8 mL, 187.8 mmol) were dissolved in toluene (30 mL) in a 100 mL round bottom flask equipped with a stirbar. *p*-Toluene sulfonic acid monohydrate (59 mg, 0.31 mmol) was added and a Dean-Stark apparatus was attached. The reaction mixture was heated to reflux until no further H_2O was collected in the Dean-Stark trap (16 h). The reaction mixture was allowed to cool to room temperature and transferred to a separatory funnel where it was washed with saturated $NaHCO_3$ solution (3 × 5 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo to yield the product as a pale yellow oil (14.32 g, 95 %) without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.03 – 5.83 (m, 2H), 5.38 – 5.28 (m, 2H), 5.28 – 5.21 (m, 2H), 4.63 – 4.55 (m, 4H), 2.36 (t, J = 7.5 Hz, 4H), 1.68 (quintet, J = 7.5 Hz, 4H), 1.46 – 1.32 (m, 2H). All other physical data was identical to those previously reported [10].

Allyl 2-oxocyclohexanecarboxylate (4) [10]

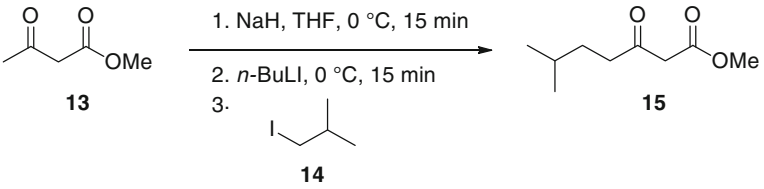


2 **4**

NaH (2.62 g, 65.5 mmol, 60 % dispersion in mineral oil) was suspended in THF (50 mL) in a round bottom flask (250 mL, 3-neck). A solution of crude diallyl pimelate (14.3 g, 59.5 mmol) in THF (10 mL) was added dropwise to the stirred suspension and the reaction mixture was stirred at 40 °C for 16 h. The reaction mixture was allowed to cool to room temperature, quenched by the slow addition of 1 M HCl (60 mL) and extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with brine (200 mL) and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the resulting oil was purified by Kügelrohr distillation (150 °C, 2 mbar) to yield the product as a colourless oil (8.44 g, 78 %).

^{1}H NMR (300 MHz, $CDCl_3$, mixture of keto and enol tautomers, ≈70 % keto): δ 12.16 (s, 0.3H, enol), 6.06 – 5.86 (m, 1H), 5.43 – 5.21 (m, 2H), 4.72 – 4.63 (m, 2H), 2.33 – 2.24 (m, 4H), 1.77 – 1.57 (m, 4H). All other physical data was identical to those previously reported [10].

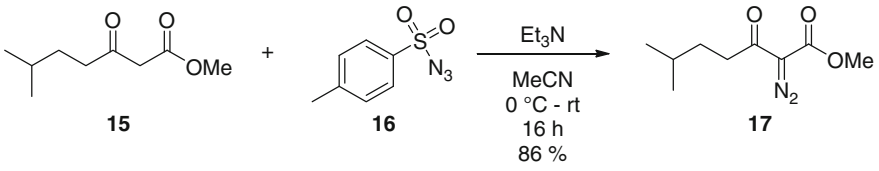
Methyl 6-methyl-3-oxoheptanoate (17) [12]



NaH (1.76 g, 44.0 mmol, 60 % dispersion in mineral oil) was suspended in THF (80 mL) in a flame-dried round bottom flask (250 mL, 3-neck) with a stirbar and cooled to 0 °C. Methyl acetoacetate (4.32 mL, 40.0 mmol) was added dropwise and the reaction was stirred at 0 °C for 15 min. *n*-BuLi (16.8 mL, 42.0 mmol, 2.5 M in hexanes) was added dropwise and the reaction was stirred at 0 °C for a further 15 min. 1-Iodo-2-methylpropane (6.9 mL, 60 mmol) in THF (10 mL) was added dropwise and the reaction mixture was warmed to room temperature and stirred for 30 min. The reaction mixture was quenched by pouring it slowly into a separatory funnel containing 1 M HCl (100 mL). The funnel was inverted several times with venting and the organic layer was separated. The aqueous layer was extracted with Et_2O (2 × 100 mL) and the combined organic layers were washed with water (2 × 100 mL), brine (100 mL) and dried over anhydrous Na_2SO_4. Solvent was removed in vacuo and the resulting oil was purified by Kügelrohr distillation (35 °C, 1 mbar) and then silica gel column chromatography (9:1, pentane/EtOAc) to yield the product as a colourless oil (2.545 g, 37 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.74 (s, 3H), 3.45 (s, 2H), 2.54 (t, J = 7.5 Hz, 2H), 1.62 – 1.44 (m, 3H), 0.90 (s, *3*H; s, 3H). All other physical data was identical to those previously reported [12].

Methyl 2-diazo-6-methyl-3-oxoheptanoate (17) [12]

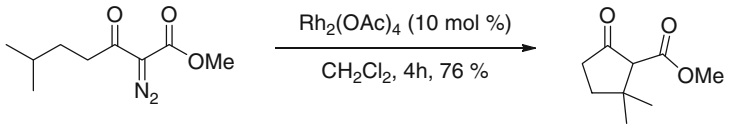


p-Amidobenzenesulfonyl azide (3.55 g, 14.8 mmol) was added to a solution of methyl 6-methyl-3-oxoheptanoate (**15**) (2.55 g, 14.8 mmol) in acetonitrile (75 mL) and cooled to 0 °C in an ice/water bath. Et_3N (6.2 mL, 44.3 mmol) was added in one portion and the reaction mixture was stirred overnight in the ice/water bath allowing it to warm slowly to room temperature. The solvent was removed in vacuo and the residue was triturated with Et_2O/pentane (1:1) to precipitate the sulfonamide by-product which was removed by filtration through Celite. The filtrate was

concentrated in vacuo and purified by silica gel column chromatography (20 % Et_2O in pentane) to yield the product as a yellow oil (2.51 g, 86 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83 (d, J = 1.2 Hz, 3H), 2.84 (d, J = 7.7 Hz, 2H), 1.67 – 1.46 (m, 3H), 0.92 (s, 3H), 0.89 (s, 3H). All other physical data was identical to those previously reported [12].

Methyl 2,2-dimethyl-5-oxocyclopentanecarboxylate (18) [12]

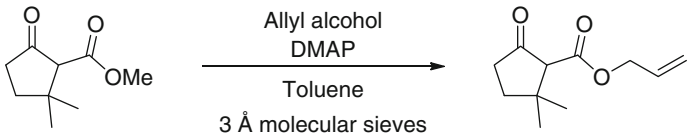


17 **18**

A slurry of $Rh_2(OAc)_4$ (56 mg, 1.27 mmol) in anhydrous CH_2Cl_2 (35 mL) was cooled to 0 °C and a solution of methyl 2-diazo-6-methyl-3-oxoheptanoate (**17**) (2.509 g, 12.66 mmol) in CH_2Cl_2 (10 mL) was added. The reaction was removed from the cooling bath and stirred at room temperature for 4 h. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography (20 % Et_2O in pentane) to yield the product as a colourless oil (1.643 g, 76 %).

^{1}H NMR (300 MHz, $CDCl_3$, mixture of keto and enol tautomers, keto ∼85 %): δ 10.72 (s, 0.15H), 3.73 (s, 3H), 2.93 (s, 1H), 2.56 – 2.37 (m, 2H), 2.07 – 1.95 (m, 1H), 1.83 – 1.69 (m, 1H), 1.22 (s, 3H), 1.10 (s, 3H). All other physical data was identical to those previously reported [12].

Allyl 2,2-dimethyl-5-oxocyclopentanecarboxylate (19) [13]

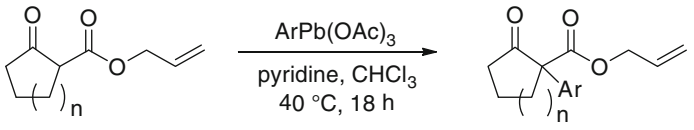


18 **19**

Allyl alcohol (0.60 mL, 8.81 mmol) and DMAP (538 mg, 4.41 mmol) were successively added to a solution of the β-keto methyl ester (**18**) (500 mg, 2.94 mmol) suspended in toluene (5 mL) and 3 Å molecular sieves (500 mg). The reaction mixture was heated to reflux and stirred for 14 h. The reaction mixture was allowed to cool to room temperature, quenched by the slow addition of 1 M HCl (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (40 mL) and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the resulting oil was purified by silica gel column chromatography (20 % EtOAc in pentane) to yield the product as a colourless oil (311 mg, 54 %).

R_f = 0.38 (40 % Et_2O in pentane); IR (thin film) ν_{max} 2963, 1735, 1726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, mixture of keto and enol tautomers, keto ≈85 %): δ 10.70 (s, 0.15H), 5.98 – 5.82 (m, 1H), 5.36 – 5.27 (m, 1H), 5.25 – 5.19 (m, 1H), 4.65 – 4.55 (m, 2H), 2.90 (s, 1H), 2.52 – 2.33 (m, 2H), 2.04 – 1.94 (m, 1H), 1.80 – 1.71 (m, 1H), 1.19 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 212.9, 168.5, 131.9, 118.9, 65.8, 65.6, 41.0, 36.8, 36.1, 29.1, 24.1

General Procedure for the Preparation of α-Aryl-β-keto Allyl Esters (5 and 6)

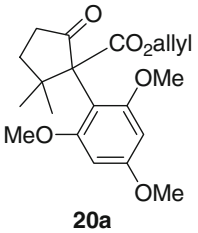


3: n =1
4: n=2

5: n =1
6: n=2

Aryllead triacetate (1.2 equiv.) and β-keto allyl ester (1.0 equiv., X) were dissolved in anhydrous $CHCl_3$ (10X) in a flame-dried Schlenk flask. Anhydrous pyridine (3.6 equiv.) was added dropwise and the reaction mixture was stirred at 40 °C for 18 h. The reaction mixture was then filtered through Celite to remove Pb $(OAc)_2$ precipitate and washed with $CHCl_3$ (30X). The filtrate was transferred to a separatory funnel and washed twice with 3 M H_2SO_4 (40X) with vigorous shaking to quench unreacted aryllead triacetate. The aqueous layers were re-extracted with $CHCl_3$ (40X) and the combined organic layers were washed with water (60X), dried over anhydrous Na_2SO_4 and filtered. The solvent was removed in vacuo and the resulting oil was purified by silica gel column chromatography (pentane/Et_2O or EtOAc).

Allyl 2,2-dimethyl-5-oxo-1-(2,4,6-trimethoxyphenyl)cyclopentanecarboxylate (20a)

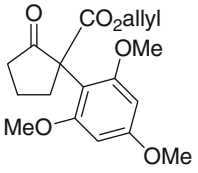


20a

The title compound was prepared according to the general procedure using β-keto allyl ester (**19**) (291 mg, 1.48 mmol) and 2,4,6-trimethoxyphenyllead triacetate (979 mg, 1.78 mmol) to yield the product as a white solid (439 mg, 82 %).

R_f = 0.22 (40 % Et_2O in pentane); IR (thin solid film) ν_{max} 2940, 1748, 1715, 1608 cm^{-1}; M.P. = 92–93 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 6.10 (s, 2H), 5.82 (ddt, *J* = 17.2, 10.5, 5.8 Hz, 1H), 5.22 – 5.15 (m, 1H), 5.15 – 5.07 (m, 1H), 4.56 (ddt, *J* = 13.2, 5.8, 1.4 Hz, 1H), 4.45 (ddt, *J* = 13.2, 5.9, 1.4 Hz, 1H), 3.78 (s, 3H), 3.65 (s, 6H), 2.71 (ddd, *J* = 20.0, 14.8, 9.3 Hz, 1H), 2.45 – 2.34 (m, 2H), 1.72 – 1.63 (m, 1H), 1.41 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 211.9, 169.1, 160.4, 159.5, 158.3, 132.6, 117.8, 109.8, 92.0, 91.9, 68.6, 65.8, 55.6, 55.4, 55.2, 45.9, 37.4, 35.3, 27.1, 25.2; HRMS: (ESI-TOF) calculated for $C_{20}H_{26}O_6Na$ [M + Na^+] 385.1627, found 385.1614.

Allyl 2-oxo-1-(2,4,6-trimethoxyphenyl)cyclopentanecarboxylate (5a)

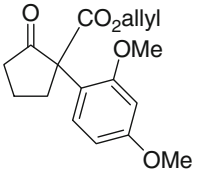


5a

The title compound was prepared according to the general procedure using β-keto allyl ester (**3**) (600 mg, 3.57 mmol) and 2,4,6-trimethoxyphenyllead triacetate (2.361 g) to yield the product as a white solid (951 mg, 80 %).

R_f = 0.15 (40 % Et_2O in pentane); IR (thin solid film) ν_{max} 2942, 1748, 1722, 1608, 1588 cm^{-1}; M.P. = 74–75 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 6.10 (s, 2H), 5.93 – 5.80 (m, 1H), 5.28 – 5.20 (m, 1H), 5.16 – 5.11 (m, 1H), 4.67 – 4.54 (m, 2H), 3.77 (s, 3H), 3.67 (s, 6H), 2.98 – 2.87 (m, 1H), 2.61 – 2.50 (m, 1H), 2.33 – 2.21 (m, 1H), 2.10 – 1.92 (m, 2H), 1.91 – 1.79 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 212.8, 170.7, 160.5, 158.1, 132.5, 117.9, 112.1, 92.2, 66.1, 61.4, 55.9, 55.5, 38.7, 36.0, 20.4; HRMS: (ESI-TOF) calculated for $C_{18}H_{22}O_6Na$ [M + Na^+] 357.1314, found 357.1326.

Allyl 1-(2,4-dimethoxyphenyl)-2-oxocyclopentanecarboxylate (5b)

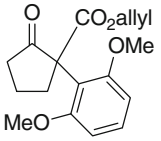


5b

The title compound was prepared according to the general procedure using β-keto allyl ester (**3**) (250 mg, 1.49 mmol) and 2,4-dimethoxyphenyllead triacetate (932 mg, 1.79 mmol) to yield the product as a white solid (349 mg, 77 %).

R_f = 0.30 (40 % Et_2O in pentane); IR (thin solid film) ν_{max} 2958, 1751, 1724, 1613 cm^{-1}; M.P. = 74–76 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 6.85 (d, *J* = 8.5 Hz, 1H), 6.46 (d, *J* = 2.5 Hz, 1H), 6.41 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.91 – 5.79 (m, 1H), 5.24 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.17 (dd, *J* = 10.5, 1.3 Hz, 1H), 4.71 – 4.56 (m, 2H), 3.78 (s, 3H), 3.73 (s, 3H), 2.91 (dt, *J* = 13.5, 6.8 Hz, 1H), 2.46 (t, *J* = 7.5 Hz, 2H), 2.29 (dt, *J* = 13.4, 6.8 Hz, 1H), 2.06 – 1.94 (m, 1H), 1.90 – 1.78 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 214.1, 170.4, 160.4, 157.8, 132.1, 128. 1, 121.1, 118.3, 104.0, 99.9, 66.2, 64.3, 55.5, 55.5, 38.7, 35.4, 19.9; HRMS: (ESI-TOF) calculated for $C_{17}H_{20}O_5Na$ [M + Na^+] 327.1208, found 327.1197.

Allyl 1-(2,6-dimethoxyphenyl)-2-oxocyclopentanecarboxylate (5c)

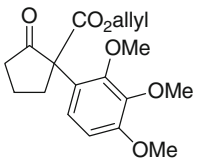


5c

The title compound was prepared according to the general procedure using β-keto allyl ester (**3**) (320 mg, 1.90 mmol) and 2,6-dimethoxyphenyllead triacetate (932 mg, 1.79 mmol) to yield the product as a white solid (511 mg, 88 %).

R_f = 0.32 (40 % Et_2O in pentane); IR (thin solid film) ν_{max} 2957, 1750, 1723, 1613 cm^{-1}; M.P. = 74–75 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.18 (t, *J* = 8.3 Hz, 1H), 6.54 (d, *J* = 8.3 Hz, 1H), 5.93 – 5.80 (m, 1H), 5.23 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.14 (dd, *J* = 10.5, 1.4 Hz, 1H), 4.67 – 4.56 (m, 2H), 3.70 (s, 6H), 2.97 (ddd, *J* = 13.3, 8.4, 6.8 Hz, 1H), 2.65 – 2.54 (m, 1H), 2.35 – 2.23 (m, 1H), 2.14 – 1.95 (m, 2H), 1.94 – 1.81 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 212. 6, 170.5, 157.5, 132.5, 128.7, 119.6, 117.9, 105.6, 66.2, 61.6, 55.9, 38.7, 35.9, 20.5; HRMS: (ESI-TOF) calculated for $C_{17}H_{20}O_5Na$ [M + Na^+] 327.1208, found 327.1201.

Allyl 2-oxo-1-(2,3,4-trimethoxyphenyl)cyclopentanecarboxylate (5d)

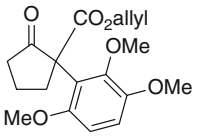


5d

The title compound was prepared according to the general procedure using β-keto allyl ester (**3**) (250 mg, 1.49 mmol) and 2,3,4-trimethoxyphenyllead triacetate (986 mg, 1.79 mmol) to yield the product as a white solid (453 mg, 91 %).

R_f = 0.27 (40 % Et_2O in pentane); IR (thin solid film) ν_{max} 2947, 1753, 1724 cm^{-1}; M.P. = 50–52 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 6.62 (d, *J* = 8.7 Hz, 1H), 6.53 (d, *J* = 8.7 Hz, 1H), 5.93 – 5.79 (m, 1H), 5.25 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.17 (dq, *J* = 10.4, 1.5 Hz, 1H), 4.70 – 4.57 (m, 2H), 3.80 (s, 6H), 3.78 (s, 3H), 2.92 – 2.82 (m, 1H), 2.48 – 2.39 (m, 2H), 2.23 (ddd, *J* = 13.0, 8.2, 6.9 Hz, 1H), 2.03 – 1.83 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 213.3, 170.0, 153.5, 151.2, 142.2, 131.8, 126.0, 122.0, 118.5, 106.3, 66.2, 64.5, 60.5, 60.0, 56.0, 38.2, 36.2, 19.8; HRMS: (ESI-TOF) calculated for $C_{18}H_{22}O_6Na$ [M + Na^+] 357.1314, found 357.1310.

Allyl 2-oxo-1-(2,3,6-trimethoxyphenyl)cyclopentanecarboxylate (5e)

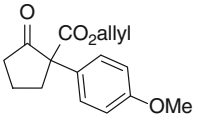


5e

The title compound was prepared according to the general procedure using β-keto allyl ester (**3**) (250 mg, 1.49 mmol) and 2,3,6-trimethoxyphenyllead triacetate (986 mg, 1.79 mmol) to yield the product as a colourless oil (454 mg, 91 %).

R_f = 0.23 (40 % Et_2O in pentane); IR (thin film) ν_{max} 2944, 1746, 1724 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.78 (d, *J* = 8.9 Hz, 1H), 6.56 (d, *J* = 8.9 Hz, 1H), 5.88 (ddt, *J* = 17.2, 10.5, 5.5 Hz, 1H), 5.25 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.15 (dq, *J* = 10.5, 1.5 Hz, 1H), 4.71 – 4.57 (m, 2H), 3.81 (s, 3H), 3.68 (s, 3H), 3.65 (s, 3H), 2.93 (ddd, *J* = 13.0, 9.6, 6.5 Hz, 1H), 2.62 (dddd, *J* = 18.1, 8.5, 4.87, 1.8 Hz, 1H), 2.26 (dt, *J* = 18.1, 8.5 Hz, 1H), 2.13 (dddd, *J* = 13.0, 6.5, 4.7, 1.8 Hz, 1H), 2.02 – 1.93 (m, 1H), 1.90 – 1.78 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 211.6, 170.3, 151.0, 147.0, 147.0, 132.4, 125.2, 117.5, 111.3, 110.0, 106.4, 66.0, 62.1, 59.9, 56.1, 55.8, 38.5, 36.0, 20.1; HRMS: (ESI-TOF) calculated for $C_{18}H_{22}O_6Na$ [M + Na^+] 357.1314, found 357.1305.

Allyl 1-(4-methoxyphenyl)-2-oxocyclopentanecarboxylate (5f)

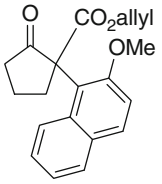


5f

The title compound was prepared according to the general procedure using β-keto allyl ester (**3**) (250 mg, 1.49 mmol) and 4-methoxyphenyllead triacetate (879 mg, 1.79 mmol) to yield the product as a colourless oil (247 mg, 61 %).

R_f = 0.41 (40 % Et_2O in pentane); IR (thin film) ν_{max} 2957, 1749, 1730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.36 – 7.32 (m, 2H), 6.90 – 6.86 (m, 2H), 5.88 – 5.78 (m, 1H), 5.22 (dq, *J* = 17.2, 1.4 Hz, 1H), 5.18 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.60 (dt, *J* = 5.5, 1.4 Hz, 2H), 3.78 (s, 3H), 2.89 – 2.80 (m, 1H), 2.58 – 2.43 (m, 2H), 2.38 – 2.30 (m, 1H), 2.06 – 1.87 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 212.0, 170.6, 159.1, 131.5, 128.6, 127.6, 118.3, 113.9, 66.1, 64.2, 55.2, 37.6, 34.7, 19.3; HRMS: (ESI-TOF) calculated for $C_{16}H_{18}O_4Na$ [M + Na^+] 297.1103, found 297.1100.

Allyl 1-(2-methoxynaphthalen-1-yl)-2-oxocyclopentanecarboxylate (5 g)

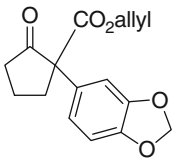


5g

The title compound was prepared according to the general procedure using β-keto allyl ester (**3**) (250 mg, 1.49 mmol) and 2-methoxynaphthyllead triacetate (968 mg, 1.79 mmol) to yield the product as a white solid (303 mg, 62 %).

R_f = 0.32 (40 % Et_2O in pentane); IR (thin solid film) ν_{max} 2948, 1744, 1716 cm^{-1}; M.P. = 83–85 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 – 7.74 (m, 2H), 7.54 (d, *J* = 8.7 Hz, 1H), 7.45 – 7.36 (m, 1H), 7.39 – 7.30 (m, 1H), 7.22 (d, *J* = 9.0 Hz, 1H), 5.66 (ddt, *J* = 17.3, 10.0, 5.6 Hz, 1H), 5.08 – 4.97 (m, 2H), 4.63 – 4.51 (m, 2H), 3.76 (s, 3H), 3.19 (ddd, *J* = 13.0, 11.2, 6.7 Hz, 1H), 2.73 (dddd, *J* = 18.0, 8.4, 3.3, 2.1 Hz, 1H), 2.48 – 2.31 (m, 2H), 2.12 – 2.02 (m, 1H), 1.94 – 1.79 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 211.8, 172.4, 154.0, 132.6, 131.8, 130.9, 130.2, 129.1, 126.7, 124.0, 123.9, 123.8, 118.1, 116.0, 66.5, 63.9, 57.3, 57.3, 39.0, 36.7, 20.5; HRMS: (ESI-TOF) calculated for $C_{20}H_{20}O_4Na$ [M + Na^+] 347.1259, found 347.1265.

Allyl 1-(benzo[*d*] [1, 3] dioxol-5-yl)-2-oxocyclopentanecarboxylate (5 h) [14]

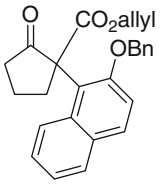


5h

The title compound was prepared according to the general procedure using β-keto allyl ester (**3**) (250 mg, 1.49 mmol) and 3,4-methylenedioxyphenyllead triacetate (902 mg, 1.79 mmol) to yield the product as a colourless oil (382 mg, 89 %).

R_f = 0.45 (40 % Et_2O in pentane); IR (thin film) ν_{max} 2890, 1751, 1730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.94 (d, *J* = 1.9 Hz, 1H), 6.84 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 5.92 (q, *J* = 1.5 Hz, 2H), 5.83 (ddt, *J* = 17.2, 10.5, 5.5 Hz, 1H), 5.23 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.18 (dq, *J* = 10.5, 1.5 Hz, 1H), 4.59 (dt, *J* = 5.5, 1.5 Hz, 2H), 2.86 – 2.78 (m, 1H), 2.52 – 2.42 (m, 2H), 2.38 – 2.28 (m, 1H), 2.03 – 1.87 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 211.6, 170.4, 147.1, 147.1, 131.5, 129.4, 120.7, 118.4, 108.3, 108.1, 101.2, 66.2, 64.4, 37.6, 34.9, 19.2; HRMS: (ESI-TOF) calculated for $C_{16}H_{16}O_5Na$ [M + Na^+] 311.0895, found 311.0903.

Allyl 1-(2-(benzyloxy)naphthalen-1-yl)-2-oxocyclopentanecarboxylate (5i)

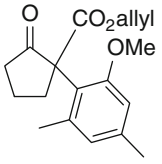


5i

The title compound was prepared according to the general procedure using β-keto allyl ester (**3**) (250 mg, 1.49 mmol) and 2-benzyloxynaphthyllead triacetate (1.104 g, 1.79 mmol) to yield the product as a white solid (399 mg, 67 %).

R_f = 0.56 (40 % Et_2O in pentane); IR (thin solid film) ν_{max} 2948, 1743, 1715 cm^{-1}; M.P. = 121–123 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.79 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.75 (d, *J* = 8.9 Hz, 1H), 7.57 (dd, *J* = 8.6, 1.0 Hz, 1H), 7.50 – 7.45 (m, 2H), 7.45 – 7.33 (m, 5H), 7.27 (d, *J* = 8.9 Hz, 1H), 5.68 (dddt, *J* = 16.5, 10.9, 8.6, 5.6 Hz, 1H), 5.11 – 4.97 (m, 4H), 4.67 – 4.52 (m, 2H), 3.20 (ddd, *J* = 12.7, 10.9, 6.7 Hz, 1H), 2.44 (dddd, *J* = 12.7, 5.9, 3.4, 2.0 Hz, 1H), 2.34 (dddd, *J* = 18.0, 8.2, 3.4, 2.0 Hz, 1H), 2.19 (ddd, *J* = 18.0, 9.9, 8.2 Hz, 1H), 2.06 – 1.96 (m, 1H), 1.92 – 1.79 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 211.9, 172.3, 153.3, 136.4, 132.7, 131.8, 130.8, 130.1, 129.1, 128.7, 128.3, 128.3, 126.7, 124.1, 123.9, 123.9, 118.1, 116.7, 72.8, 66.5, 64.1, 39.0, 36.7, 20.5; HRMS: (ESI-TOF) calculated for $C_{26}H_{24}O_4Na$ [M + Na^+] 423.1572, found 423.1567.

Allyl 1-(2-methoxy-4,6-dimethylphenyl)-2-oxocyclopentanecarboxylate (5j)

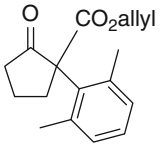


5j

The title compound was prepared according to the general procedure using β-keto allyl ester (**3**) (250 mg, 1.49 mmol) and 2-methoxy-4,6-dimethylphenyllead triacetate (929 mg, 1.79 mmol) to yield the product as a colourless oil (404 mg, 90 %).

R_f = 0.43 (40 % Et_2O in pentane); IR (thin film) ν_{max} 2971, 1748, 1720 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.63 (s, 1H), 6.56 (s, 1H), 5.94 – 5.83 (m, 1H), 5.27 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.18 (dt, *J* = 10.5, 1.4 Hz, 1H), 4.71 – 4.58 (m, 2H), 3.65 (s, 3H), 3.06 – 2.99 (m, 1H), 2.68 – 2.58 (m, 1H), 2.35 – 2.24 (m, 4H), 2.14 – 1.99 (m, 5H), 1.94 – 1.84 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 211.9, 171.2, 156.4, 137.8, 137.7, 131.9, 127.3, 126.1, 118.6, 111.9, 66.5, 64.0, 55.9, 38.7, 36.4, 21.2, 20.7, 20.4; HRMS: (ESI-TOF) calculated for $C_{18}H_{22}O_4Na$ [M + Na^+] 325.1416, found 325.1420.

Allyl 1-(2,6-dimethylphenyl)-2-oxocyclopentanecarboxylate (5k)

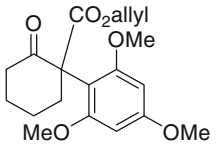


5k

The title compound was prepared according to the general procedure using β-keto allyl ester (**3**) (250 mg, 1.49 mmol) and 2,6-dimethylphenyllead triacetate (875 mg, 1.79 mmol) to yield the product as a colourless oil (146 mg, 36 %).

R_f = 0.63 (40 % Et_2O in pentane); IR (thin film) ν_{max} 2969, 1748, 1716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.04 (dd, *J* = 8.5, 6.4 Hz, 1H), 6.99 – 6.94 (m, 2H), 5.85 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.25 (dq, *J* = 17.2, 1.4 Hz, 1H), 5.18 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.70 – 4.55 (m, 2H), 3.24 – 3.14 (m, 1H), 2.78 – 2.67 (m, 1H), 2.56 – 2.46 (m, 1H), 2.33 – 2.14 (m, 8H), 2.09 – 1.97 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 214.0, 170.8, 139.3, 136.4, 131.4, 130.1, 126.9, 118.9, 67.9, 66.8, 39.1, 36.4, 23.1, 19.8; HRMS: (ESI-TOF) calculated for $C_{17}H_{20}O_3Na$ [M + Na^+] 295.1310, found 295.1323.

Allyl 2-oxo-1-(2,4,6-trimethoxyphenyl)cyclohexanecarboxylate (6a)

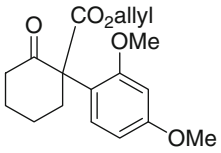


6a

The title compound was prepared according to the general procedure using β-keto allyl ester (**4**) (450 mg, 2.47 mmol) and 2,4,6-trimethoxyphenyllead triacetate (1.635 g, 2.96 mmol) to yield the product as a colourless oil (518 mg, 60 %).

R_f = 0.10 (40 % Et_2O in pentane); IR (thin film) ν_{max} 2940, 1729, 1718, 1607 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.13 (s, 2H), 5.91 – 5.81 (m, 1H), 4.66 (dd, *J* = 13.7, 5.4 Hz, 1H), 4.56 (dd, *J* = 13.7, 5.4 Hz, 1H), 3.78 (s, 3H), 3.68 (s, 6H), 2.66 – 2.51 (m, 2H), 2.48 – 2.40 (m, 1H), 2.37 – 2.29 (m, 1H), 1.89 – 1.74 (m, 3H), 1.66 – 1.57 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 205.6, 170.8, 160.4, 158.6, 132.3, 117.5, 111.2, 92.4, 65.7, 62.6, 55.9, 55.3, 40.5, 34.8, 25.6, 21.9; HRMS: (ESI-TOF) calculated for $C_{19}H_{24}O_6Na$ [M + Na^+] 371.1471, found 371.1480.

Allyl 1-(2,4-dimethoxyphenyl)-2-oxocyclohexanecarboxylate (6b)

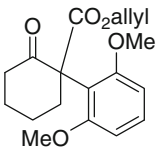


6b

The title compound was prepared according to the general procedure using β-keto allyl ester (**4**) (250 mg, 1.37 mmol) and 2,4-dimethoxyphenyllead triacetate (857 mg, 1.64 mmol) to yield the product as a colourless oil (394 mg, 90 %).

R_f = 0.23 (40 % Et_2O in pentane); IR (thin film) ν_{max} 2940, 1732, 1715, 1612 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.08 – 7.00 (m, 1H), 6.52 – 6.46 (m, 2H), 5.84 (ddt, *J* = 17.1, 10.7, 5.5 Hz, 1H), 5.22 – 5.13 (m, 2H), 4.68 – 4.55 (m, 2H), 3.80 (s, 3H), 3.71 (s, 3H), 2.65 – 2.43 (m, 4H), 1.95 – 1.79 (m, 2H), 1.78 – 1.63 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 206.74, 171.52, 160.45, 158.70, 132.00, 127.98, 120.18, 117.97, 104.68, 99.96, 65.70, 64.26, 55.69, 55.41, 40.50, 35.44, 27.80, 21.86; HRMS: (ESI-TOF) calculated for $C_{18}H_{22}O_5Na$ [M + Na^+] 341.1365, found 341.1375.

Allyl 1-(2,6-dimethoxyphenyl)-2-oxocyclohexanecarboxylate (6c)

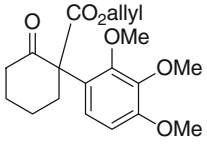


6c

The title compound was prepared according to the general procedure using β-keto allyl ester (**4**) (250 mg, 1.37 mmol) and 2,4-dimethoxyphenyllead triacetate (857 mg, 1.64 mmol) to yield the product as a colourless oil (268 mg, 61 %).

R_f = 0.19 (40 % Et_2O in pentane); IR (thin film) ν_{max} 2940, 1719, 1736, 1587 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.19 (t, *J* = 8.3 Hz, 1H), 6.56 (d, *J* = 8.3 Hz, 2H), 5.86 (ddt, *J* = 17.2, 10.5, 5.5 Hz, 1H), 5.20 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.13 (dq, *J* = 10.5, 1.5 Hz, 1H), 4.67 (ddt, *J* = 13.5, 5.5, 1.5 Hz, 1H), 4.56 (ddt, *J* = 13.5, 5.5, 1.5 Hz, 1H), 3.69 (s, 6H), 2.69 – 2.58 (m, 1H), 2.55 – 2.43 (m, 2H), 2.39 – 2.30 (m, 1H), 1.90 – 1.77 (m, 3H), 1.68 – 1.57 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 205.2, 170.6, 157.8, 132.3, 128.8, 119.0, 117.7, 106.0, 65.8, 62.7, 56.0, 40.6, 34.7, 25.2, 21.9; HRMS: (ESI-TOF) calculated for $C_{18}H_{22}O_5Na$ [M + Na^+] 341.1365, found 341.1353.

Allyl 2-oxo-1-(2,3,4-trimethoxyphenyl)cyclohexanecarboxylate (6d)

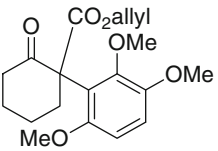


6d

The title compound was prepared according to the general procedure using β-keto allyl ester (**4**) (250 mg, 1.37 mmol) and 2,3,4-trimethoxyphenyllead triacetate (907 mg, 1.64 mmol) to yield the product as a colourless oil (447 mg, 94 %).

R_f = 0.24 (40 % Et_2O in pentane); IR (thin film) ν_{max} 2945, 1733, 1712 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.83 (d, *J* = 8.8 Hz, 1H), 6.64 (d, *J* = 8.8 Hz, 1H), 5.84 (ddt, *J* = 17.1, 10.4, 5.6 Hz, 1H), 5.23 – 5.11 (m, 2H), 4.67 – 4.56 (m, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.77 (s, 3H), 2.60 – 2.52 (m, 3H), 2.50 – 2.42 (m, 1H), 1.89 – 1.81 (m, 2H), 1.70 – 1.63 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 206.5, 171.4, 153.6, 152.4, 142.4, 132.0, 125.0, 121.4, 118.3, 106.8, 65.9, 64.4, 60.6, 56.0, 56.0, 40.6, 35.7, 28.0, 21.7; HRMS: (ESI-TOF) calculated for $C_{19}H_{24}O_6Na$ [M + Na^+] 371.1471, found 371.1480.

Allyl 2-oxo-1-(2,3,6-trimethoxyphenyl)cyclohexanecarboxylate (6e)

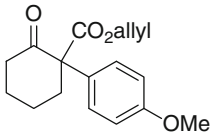


6e

The title compound was prepared according to the general procedure using β-keto allyl ester (**4**) (250 mg, 1.37 mmol) and 2,3,6-trimethoxyphenyllead triacetate (907 mg, 1.64 mmol) to yield the product as a white solid (405 mg, 85 %).

R_f = 0.21 (40 % Et_2O in pentane); IR (thin solid film) ν_{max} 2942, 1736, 1731 cm^{-1}; M.P. = 74–75 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 6.82 (d, *J* = 9.0 Hz, 1H), 6.61 (d, *J* = 9.0 Hz, 1H), 5.88 (ddt, *J* = 17.2, 10.5, 5.5 Hz, 1H), 5.22 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.14 (dq, *J* = 10.5, 1.5 Hz, 1H), 4.71 (ddt, *J* = 13.4, 5.5, 1.5 Hz, 1H), 4.57 (ddt, *J* = 13.4, 5.5, 1.5 Hz, 1H), 3.82 (s, 3H), 3.68 (s, 3H), 3.64 (s, 3H), 2.74 – 2.63 (m, 2H), 2.47 (ddd, *J* = 13.9, 7.9, 3.7 Hz, 1H), 2.43 – 2.34 (m, 1H), 1.88 – 1.72 (m, 3H), 1.63 – 1.54 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 204.9, 170.6, 151.6, 147.8, 147.5, 132.3, 124.6, 117.7, 111.8, 107.3, 66.0, 63.4, 60.8, 56.2, 56.2, 40.8, 34.7, 25.4, 21.8; HRMS: (ESI-TOF) calculated for $C_{19}H_{24}O_6Na$ [M + Na^+] 371.1471, found 341.1472.

Allyl 1-(4-methoxyphenyl)-2-oxocyclohexanecarboxylate (6f)

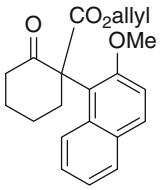


6f

The title compound was prepared according to the general procedure using β-keto allyl ester (**4**) (250 mg, 1.37 mmol) and 4-methoxyphenyllead triacetate (808 mg, 1.64 mmol) to yield the product as a colourless oil (362 mg, 92 %).

R_f = 0.41 (40 % Et_2O in pentane); IR (thin film) ν_{max} 2941, 1735, 1713 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.18 – 7.13 (m, 2H), 6.91 – 6.86 (m, 2H), 5.85 (ddt, *J* = 17.0, 10.2, 5.6 Hz, 1H), 5.25 – 5.15 (m, 2H), 4.67 – 4.58 (m, 2H), 3.78 (s, 3H), 2.80 – 2.71 (m, 1H), 2.54 (app. t, *J* = 6.6 Hz, 2H), 2.41 – 2.33 (m, 1H), 2.02 – 1.90 (m, 1H), 1.88 – 1.71 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 206.8, 171.2, 159.0, 131.6, 129.0, 128.5, 118.5, 113.9, 66.0, 66.0, 55.2, 40.6, 35.1, 27.8, 22.1; HRMS: (ESI-TOF) calculated for $C_{17}H_{20}O_4Na$ [M + Na^+] 311.1259, found 311.1264.

Allyl 1-(2-methoxynaphthalen-1-yl)-2-oxocyclohexanecarboxylate (6g)

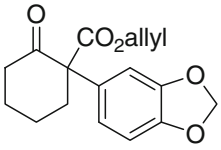


6g

The title compound was prepared according to the general procedure using β-keto allyl ester (**4**) (250 mg, 1.37 mmol) and 2-methoxynaphthyllead triacetate (890 mg, 1.64 mmol) to yield the product as a colourless oil (412 mg, 89 %).

R_f = 0.29 (40 % Et_2O in pentane); IR (thin film) ν_{max} 2940, 1734, 1710 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.8 Hz, 2H), 7.56 (dd, *J* = 8.8, 1.2 Hz, 1H), 7.42 – 7.33 (m, 1H), 7.36 – 7.30 (m, 1H), 7.23 (d, *J* = 9.0 Hz, 1H), 5.79 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.19 – 5.06 (m, 2H), 4.73 (ddt, *J* = 13.4, 5.6, 1.4 Hz, 1H), 4.58 (ddt, *J* = 13.4, 5.6, 1.5 Hz, 1H), 3.78 (s, 3H), 2.87 – 2.73 (m, 2H), 2.73 – 2.64 (m, 1H), 2.55 (ddd, *J* = 14.9, 8.4, 5.9 Hz, 1H), 1.99 – 1.78 (m, 3H), 1.50 – 1.38 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 205.8, 171.9, 154.7, 132.0, 131.9, 130.8, 130.4, 129.2, 126.0, 124.4, 123.6, 123.2, 118.1, 115.9, 77.4, 77.2, 76.9, 66.2, 64.6, 57.5, 40.7, 35.3, 25.0, 21.3; HRMS: (ESI-TOF) calculated for $C_{21}H_{22}O_4Na$ [M + Na^+] 361.1416, found 361.1416.

Allyl 1-(benzo[*d*] [1, 3] dioxol-5-yl)-2-oxocyclohexanecarboxylate (6h)

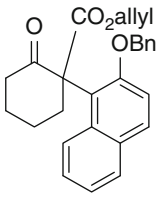


6h

The title compound was prepared according to the general procedure using β-keto allyl ester (**4**) (250 mg, 1.37 mmol) and 3,4-methylenedioxyphenyllead triacetate (828 mg, 1.64 mmol) to yield the product as a white solid (356 mg, 86 %).

R_f = 0.47 (40 % Et_2O in pentane); IR (thin solid film) ν_{max} 2944, 1733, 1713 cm^{-1}; M.P. = 76–78 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 6.79 (d, *J* = 8.2 Hz, 1H), 6.75 (d, *J* = 1.9 Hz, 1H), 6.70 (dd, *J* = 8.2, 1.9 Hz, 1H), 5.95 (s, 2H), 5.87 (ddt, *J* = 17.3, 10.4, 5.6 Hz, 1H), 5.29 – 5.18 (m, 2H), 4.68 – 4.59 (m, 2H), 2.79 – 2.69 (m, 1H), 2.55 (app. t, *J* = 6.6 Hz, 2H), 2.37 – 2.28 (m, 1H), 2.01 – 1.91 (m, 1H), 1.88 – 1.68 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 206.7, 171.1, 147.9, 147.1, 131.6, 130.2, 121.2, 118.8, 108.7, 108.2, 101.3, 66.2, 66.1, 40.7, 35.3, 27.7, 22.2; HRMS: (ESI-TOF) calculated for $C_{17}H_{18}O_5Na$ [M + Na^+] 325.1052, found 325.1046.

Allyl 1-(2-(benzyloxy)naphthalen-1-yl)-2-oxocyclohexanecarboxylate (6i)

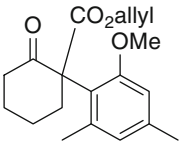


6i

The title compound was prepared according to the general procedure using β-keto allyl ester (**4**) (250 mg, 1.37 mmol) and 2-benzyloxynaphthyllead triacetate (1.015 g, 1.64 mmol) to yield the product as a white solid (448 mg, 79 %).

R_f = 0.52 (40 % Et_2O in pentane); IR (thin solid film) ν_{max} 2942, 1732, 1718 cm^{-1}; M.P. = 84–87 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.77 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.74 (d, *J* = 8.9 Hz, 1H), 7.58 (d, *J* = 8.6 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.40 – 7.35 (m, 3H), 7.35 – 7.29 (m, 2H), 7.23 (d, *J* = 8.9 Hz, 1H), 5.75 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.15 – 5.05 (m, 2H), 5.02 (s, 2H), 4.65 (ddt, *J* = 13.3, 5.6, 1.4 Hz, 1H), 4.46 (ddt, *J* = 13.3, 5.6, 1.4 Hz, 1H), 2.82 – 2.74 (m, 1H), 2.74 – 2.66 (m, 1H), 2.62 (dt, *J* = 15.4, 6.0 Hz, 1H), 2.46 – 2.36 (m, 1H), 1.87 – 1.70 (m, 3H), 1.47 – 1.37 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 205.7, 171.9, 154.1, 136.6, 132.1, 131.9, 130.9, 130.3, 129.2, 128.6, 128.2, 128.1, 126.1, 124.4, 123.8, 123.7, 118.3, 117.3, 73.3, 66.3, 64.8, 40.9, 35.4, 24.7, 21.3; HRMS: (ESI-TOF) calculated for $C_{27}H_{26}O_4Na$ [M + Na^+] 437.1729, found 437.1707.

Allyl 1-(2-methoxy-4,6-dimethylphenyl)-2-oxocyclohexanecarboxylate (6j)

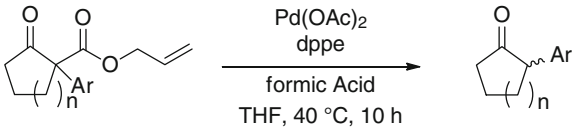


6j

The title compound was prepared according to the general procedure using β-keto allyl ester (**4**) (250 mg, 1.37 mmol) and 2-methoxy-4,6-dimethylphenyllead triacetate (854 mg, 1.64 mmol) to yield the product as a colourless oil (390 mg, 90 %).

R_f = 0.37 (40 % Et_2O in pentane); IR (thin film) ν_{max} 2935, 1721, 1711, 1612 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.60 (s, 1H), 6.58 (s, 1H), 5.84 (ddt, *J* = 17.2, 10.6, 5.5 Hz, 1H), 5.20 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.13 (dq, *J* = 10.6, 1.4 Hz, 1H), 4.69 (ddt, *J* = 13.5, 5.5, 1.4 Hz, 1H), 4.55 (ddt, *J* = 13.5, 5.5, 1.4 Hz, 1H), 3.66 (s, 3H), 2.68 – 2.57 (m, 1H), 2.51 – 2.40 (m, 2H), 2.40 – 2.30 (m, 1H), 2.26 (s, 3H), 2.16 (s, 3H), 1.91 – 1.81 (m, 3H), 1.66 – 1.56 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 205.4, 171.0, 157.1, 137.3, 137.3, 117.9, 111.9, 65.9, 64.7, 55.9, 40.4, 35.5, 25.9, 22.2, 21.7, 21.1, 14.1; HRMS: (ESI-TOF) calculated for $C_{19}H_{24}O_4Na$ [M + Na^+] 339.1572, found 339.1576.

General Procedure for the Racemic Decarboxylative Protonation Reaction (7 and 24)

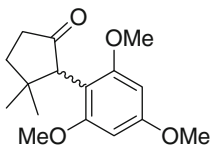


5: n = 1
6: n = 2

7: n = 1
24: n = 2

$Pd(OAc)_2$ (3.4 mg, 0.015 mmol) and dppe (7.5 mg, 0.019 mmol) were added to a flame dried Schlenk flask (10 mL) and 1,4-dioxane (1.5 mL) was added. The suspension was stirred at 40 °C for 90 min and formic acid (34 μL, 0.90 mmol) was added followed immediately by α-aryl-β-keto allyl ester (0.15 mmol) in 1,4-dioxane (1.5 mL) from a flame dried round bottom flask (10 mL, 2-neck). The reaction mixture was stirred at 40 °C for 10 h, cooled to room temperature and filtered through a plug of Celite and washed with Et_2O. The solvent was removed in vacuo and the resulting residue was purified by silica gel column chromatography (pentane/Et_2O).

3,3-Dimethyl-2-(2,4,6-trimethoxyphenyl)cyclopentanone (*rac*-21a)

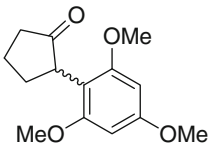


rac-**21a**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**20a**) to yield the product as an pale yellow oil (14.5 mg, 35 %).

R_f = 0.15 (40 % Et_2O in pentane); IR (thin film) ν_{max} 2953, 1739, 1608 cm^{-1}; M.P. = 87–89 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 6.11 (d, *J* = 2.3 Hz, 1H), 6.08 (d, *J* = 2.3 Hz, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.64 (s, 3H), 3.50 (d, *J* = 1.4 Hz, 1H), 2.55 – 2.43 (m, 1H), 2.35 (dddd, *J* = 18.1, 8.4, 5.0, 1.4 Hz, 1H), 1.90 (ddd, *J* = 12.4, 8.4, 5.0 Hz, 1H), 1.77 – 1.66 (m, 1H), 1.13 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 220.4, 160.4, 159.9, 158.5, 107.7, 91.4, 91.1, 55.8, 55.7, 55.5, 55.4, 55.4, 41.7, 37.7, 37.0, 30.9, 24.1; HRMS: (ESI-TOF) calculated for $C_{16}H_{22}O_4Na$ [M + Na^+] 301.1416, found 301.1405.

2-(2,4,6-Trimethoxyphenyl)cyclopentanone (*rac*-7a)

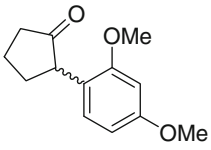


rac-**7a**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**5a**) to yield the product as an off-white solid (24 mg, 64 %).

R_f = 0.15 (40 % Et_2O in pentane); IR (thin solid film) ν_{max} 2960, 1738, 1609 cm^{-1}; M.P. = 87–89 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 6.12 (s, 2H), 3.78 (s, 3H), 3.73 (s, 6H), 3.71 – 3.64 (m, 1H), 2.44 – 2.31 (m, 2H), 2.28 – 2.18 (m, 1H), 2.17 – 2.00 (m, 2H), 1.90 – 1.77 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 220.8, 160.4, 158.7, 109.5, 91.3, 55.7, 55.5, 45.2, 38.2, 30.0, 21.9; HRMS: (ESI-TOF) calculated for $C_{14}H_{18}O_4Na$ [M + Na^+] 273.1103, found 273.1111.

2-(2,4-Dimethoxyphenyl)cyclopentanone (*rac*-7b)

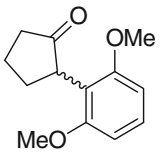


rac-**7b**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**5b**) to yield the product as a pale yellow oil (24 mg, 67 %).

R_f = 0.26 (40 % Et_2O in pentane); IR (thin film) ν_{max} 2960, 1739, 1614 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.97 (d, *J* = 7.9 Hz, 1H), 6.47 – 6.42 (m, 2H), 3.78 (s, 3H), 3.74 (s, 3H), 3.30 (dd, *J* = 10.9, 9.0 Hz, 1H), 2.45 – 2.28 (m, 3H), 2.17 – 2.04 (m, 2H), 1.92 – 1.80 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 219.8, 160.2, 157.9, 130.9, 120.8, 104.6, 99.4, 55.5, 55.4, 52.0, 38.3, 31.3, 21.5; HRMS: (ESI-TOF) calculated for $C_{13}H_{16}O_3Na$ [M + Na^+] 243.0997, found 243.0990.

2-(2,6-Dimethoxyphenyl)cyclopentanone (*rac*-7c)

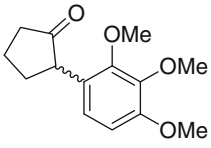


rac-**7c**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**5c**) to yield the product as an off-white solid (28 mg, 78 %).

R_f = 0.29 (40 % Et_2O in pentane); IR (thin solid film) ν_{max} 2961, 1739, 1594 cm^{-1}; M.P. = 52–54 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.16 (t, *J* = 8.3 Hz, 1H), 6.54 (d, *J* = 8.3 Hz, 2H), 3.84 – 3.70 (m, 7H), 2.49 – 2.31 (m, 2H), 2.30 – 2.21 (m, 1H), 2.19 – 2.06 (m, 2H), 1.92 – 1.81 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 220.4, 158.1, 128.2, 117.0, 104.5, 55.8, 45.4, 38.2, 29.9, 22.1; HRMS: (ESI-TOF) calculated for $C_{13}H_{16}O_3Na$ [M + Na^+] 243.0997, found 243.0997.

2-(2,3,4-Trimethoxyphenyl)cyclopentanone (*rac*-7d)

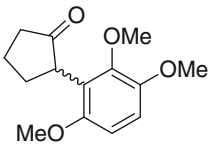


rac-**7d**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**5d**) to yield the product as a pale yellow oil (32 mg, 85 %).

R_f = 0.24 (40 % Et_2O in pentane); IR (thin film) ν_{max} 2960, 1739, 1602 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.74 (d, *J* = 8.5 Hz, 1H), 6.59 (d, *J* = 8.5 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.32 – 3.23 (m, 1H), 2.47 – 2.29 (m, 3H), 2.17 – 2.00 (m, 2H), 1.93 – 1.79 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 219.7, 153.2, 151.5, 142.3, 126.2, 124.4, 107.2, 60.7, 60.2, 56.1, 52.2, 38.3, 32.3, 21.4; HRMS: (ESI-TOF) calculated for $C_{14}H_{18}O_4Na$ [M + Na^+] 273.1103, found 273.1104.

2-(2,3,6-Trimethoxyphenyl)cyclopentanone (*rac*-7e)

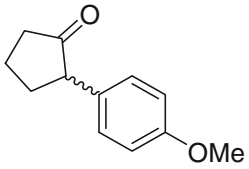


rac-**7e**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**5e**) to yield the product as a pale yellow oil (32 mg, 86 %).

R_f = 0.24 (40 % Et_2O in pentane); IR (thin film) ν_{max} 2959, 1739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.75 (d, *J* = 8.9 Hz, 1H), 6.54 (d, *J* = 8.9 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.74 – 3.67 (m, 1H), 3.70 (s, 3H), 2.48 – 2.33 (m, 2H), 2.32 – 2.22 (m, 1H), 2.19 – 2.07 (m, 2H), 1.94 – 1.80 (m, 1H); HRMS: (ESI-TOF) calculated for $C_{14}H_{18}O_4Na$ [M + Na^+] 273.1103, found 273.1104.

2-(4-Methoxyphenyl)cyclopentanone (*rac*-7f) [15]

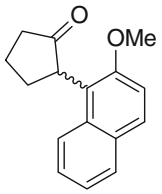


rac-**7f**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**5f**) to yield the product as a pale yellow oil (22 mg, 77 %).

R_f = 0.37 (40 % Et_2O in pentane); IR (thin film) ν_{max} 2927, 1706, 1668, 1601, 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.15 – 7.08 (m, 2H), 6.90 – 6.85 (m, 2H), 3.79 (s, 3H), 3.31 – 3.22 (m, 1H), 2.52 – 2.41 (m, 2H), 2.34 – 2.22 (m, 1H), 2.16 – 2.02 (m, 2H), 1.99 – 1.87 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 218.5, 158.6, 130.6, 129.2, 114.2, 55.4, 54.7, 38.4, 31.9, 20.9; HRMS: (ESI-TOF) calculated for $C_{12}H_{14}O_2Na$ [M + Na^+] 213.0891, found 213.0901.

2-(2-Methoxynaphthalen-1-yl)cyclopentanone (*rac*-7g)

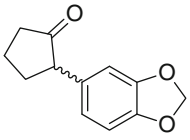


rac-**7g**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**5g**) to yield the product as an off-white solid (24 mg, 65 %).

R_f = 0.26 (40 % Et_2O in pentane); IR (thin solid film) ν_{max} 2962, 1740 cm^{-1}; M.P. = 115-118 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.84 (br s, 1H), 7.81 – 7.74 (m, 2H), 7.49 – 7.43 (m, 1H), 7.35 – 7.31 (m, 1H), 7.25 (d, *J* = 9.0 Hz, 1H), 3.92 (br s, 1H), 3.84 (s, 3H), 2.66 – 2.52 (m, 1H), 2.52 – 2.37 (m, 2H), 2.29 – 2.15 (m, 2H), 2.05 – 1.90 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 219.9, 129.7, 129.1, 128.8, 126.8, 123.6, 122.6, 114.2, 56.2, 47.9, 38.3, 30.9, 22.2; HRMS: (ESI-TOF) calculated for $C_{16}H_{16}O_2Na$ [M + Na^+] 263.1048, found 263.1058.

2-(Benzo[*d*] [1, 3] dioxol-5-yl)cyclopentanone (*rac*-7h) [14]

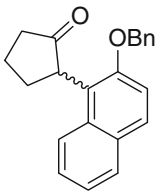


rac-**7h**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**5h**) to yield the product as a pale yellow oil (29 mg, 95 %).

R_f = 0.14 (40 % Et_2O in pentane); IR (thin film) ν_{max} 2922, 1733, 1674 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.77 (d, *J* = 8.0 Hz, 1H), 6.70 – 6.66 (m, 1H), 6.66 – 6.62 (m, 1H), 5.93 (s, 2H), 3.30 – 3.17 (m, 1H), 2.53 – 2.38 (m, 2H), 2.33 – 2.21 (m, 1H), 2.20 – 2.10 (m, 1H), 2.10 – 1.99 (m, 1H), 1.97 – 1.85 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 218.2, 148.0, 146.6, 132.2, 132.2, 121.4, 108.7, 108.5, 101.1, 55.2, 38.4, 32.0, 20.8; HRMS: (ESI-TOF) calculated for $C_{12}H_{13}O_3$ [M + H^+] 205.0865, found 205.0867.

2-(2-(Benzyloxy)naphthalen-1-yl)cyclopentanone (*rac*-7i)

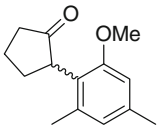


rac-**7i**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**5i**) to yield the product as an off-white solid (44 mg, 93 %).

R_f = 0.41 (40 % Et_2O in pentane); IR (thin solid film) ν_{max} 2958, 1739, 1593 cm^{-1}; M.P. = 114–116 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.86 (br s, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.50 – 7.25 (m, 8H), 5.12 (d, *J* = 11.0 Hz, 1H), 5.04 (d, *J* = 11.0 Hz, 1H), 3.90 (br s, 1H), 2.43 – 2.30 (m, 1H), 2.29 – 2.15 (m, 2H), 2.11 – 1.94 (m, 2H), 1.92 – 1.78 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 219.8, 153.1, 136.6, 133.7, 129.7, 129.0, 128.8, 128.7, 128.4, 128.3, 126.8, 123.6, 122.6, 114.6, 71.4, 48.1, 38.2, 30.7, 22.0; HRMS: (ESI-TOF) calculated for $C_{22}H_{20}O_2Na$ [M + Na^+] 339.1361, found 339.1356.

2-(2-Methoxy-4,6-dimethylphenyl)cyclopentanone (*rac*-7j)

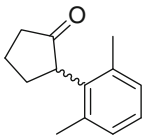


rac-**7j**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**5j**) to yield the product as a pale yellow oil (28 mg, 88 %).

R_f = 0.33 (40 % Et_2O in pentane); IR (thin film) ν_{max} 2958, 1739, 1612, 1581 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.63 (s, 1H), 6.55 (s, 1H), 3.70 (s, 3H), 3.34 (br s, 1H), 2.53 – 2.04 (m, 11H), 1.94 – 1.79 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 220.2, 156.6, 137.8, 137.5, 124.0, 110.4, 55.3, 49.0, 38.0, 29.9, 22.0, 21.5, 20.1; HRMS: (ESI-TOF) calculated for $C_{14}H_{18}O_2Na$ [M + Na^+] 241.1204, found 204.1215.

2-(2,6-Dimethylphenyl)cyclopentanone (*rac*-7k)

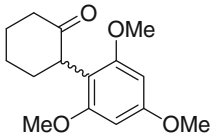


rac-**7k**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**5k**) to yield the product as a pale yellow oil (26 mg, 92 %).

R_f = 0.44 (40 % Et_2O in pentane); IR (thin film) ν_{max} 2960, 1738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.08 – 7.00 (m, 3H), 3.66 – 3.59 (m, 1H), 2.56 – 2.05 (m, 11H), 2.03 – 1.90 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 218.9, 135.8, 127.0, 52.8, 38.1, 29.6, 21.6, 21.4; HRMS: (ESI-TOF) calculated for $C_{13}H_{16}ONa$ [M + Na^+] 211.1099, found 211.1107.

2-(2,4,6-Trimethoxyphenyl)cyclohexanone (*rac*-24a) [16]

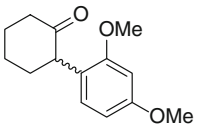


rac-**24a**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**6a**) to yield the product as an off-white solid (17 mg, 45 %).

R_f = 0.17 (40 % Et_2O in pentane); IR (thin solid film) ν_{max} 2939, 1710, 1608 cm^{-1}; M.P. = 109–111 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 6.14 (s, 2H), 3.89 (dd, *J* = 12.3, 6.6 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 6H), 2.62 – 2.55 (m, 1H), 2.37 – 2.26 (m, 1H), 2.18 – 2.08 (m, 1H), 2.07 – 2.01 (m, 1H), 2.00 – 1.89 (m, 2H), 1.85 – 1.74 (m, 1H), 1.74 – 1.63 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 209.92, 160.12, 158.54, 110.29, 91.35, 55.81, 55.39, 46.19, 41.56, 31.29, 25.40, 25.30; HRMS: (ESI-TOF) calculated for $C_{15}H_{20}O_4Na$ [M + Na^+] 287.1259, found 287.1266.

2-(2,4-Dimethoxyphenyl)cyclohexanone (*rac*-24b)

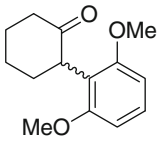


rac-**24b**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**6b**) to yield the product as an off-white solid (34 mg, 97 %).

R_f = 0.30 (40 % Et_2O in pentane); IR (thin solid film) ν_{max} 2937, 1712, 1613, 1588 cm^{-1}; M.P. = 92–93 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.00 (d, *J* = 8.2 Hz, 1H), 6.51 – 6.44 (m, 2H), 3.85 (dd, *J* = 13.0, 5.4 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 2.55 – 2.42 (m, 2H), 2.22 – 2.10 (m, 2H), 2.05 – 1.93 (m, 2H), 1.87 – 1.71 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 210.4, 159.8, 157.9, 129.1, 120.4, 104.2, 98.7, 55.5, 55.4, 50.6, 42.4, 33.7, 27.7, 25.9; HRMS: (ESI-TOF) calculated for $C_{14}H_{18}O_3Na$ [M + Na^+] 257.1154, found 257.1162.

2-(2,6-Dimethoxyphenyl)cyclohexanone (*rac*-24c)

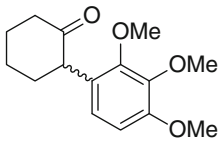


rac-**24c**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**6c**) to yield the product as a pale yellow oil (33 mg, 94 %).

R_f = 0.43 (40 % Et_2O in pentane); IR (thin film) ν_{max} 2938, 1711, 1594 cm^{-1}; M.P. = 79–81 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.18 (t, *J* = 8.3 Hz, 1H), 6.56 (d, *J* = 8.3 Hz, 2H), 4.00 (dd, *J* = 11.9, 6.8 Hz, 1H), 3.76 (s, 6H), 2.65 – 2.57 (m, 1H), 2.39 – 2.30 (m, 1H), 2.19 – 2.09 (m, 1H), 2.09 – 1.97 (m, 2H), 1.97 – 1.91 (m, 1H), 1.88 – 1.77 (m, 1H), 1.77 – 1.63 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 209.7, 157.9, 128.0, 125.6, 117.9, 104.5, 55.8, 46.3, 41.5, 31.0, 25.2, 25.2; HRMS: (ESI-TOF) calculated for $C_{14}H_{18}O_3Na$ [M + Na^+] 257.1154, found 257.1157.

2-(2,3,4-Trimethoxyphenyl)cyclohexanone (*rac*-24d) [17]

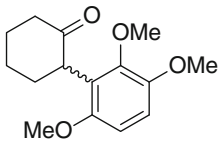


rac-**24d**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**6d**) to yield the product as a pale yellow oil (39 mg, 98 %).

R_f = 0.23 (40 % Et_2O in pentane); IR (thin film) ν_{max} 2936, 1711, 1604 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.78 (d, *J* = 8.6 Hz, 1H), 6.65 (d, *J* = 8.6 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 4H), 3.83 – 3.80 (m, 1H), 3.80 (s, 3H), 2.57 – 2.43 (m, 2H), 2.21 – 2.12 (m, 2H), 2.03 – 1.93 (m, 2H), 1.86 – 1.73 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 210.4, 152.7, 151.6, 142.0, 125.5, 123.4, 107.2, 60.9, 60.7, 56.0, 51.2, 42.3, 34.2, 27.6, 25.8, 15.4; HRMS: (ESI-TOF) calculated for $C_{15}H_{20}O_4Na$ [M + Na^+] 287.1259, found 287.1253.

2-(2,3,6-Trimethoxyphenyl)cyclohexanone (*rac*-24e)

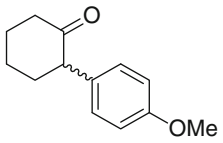


rac-**24e**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**6e**) to yield the product as a pale yellow oil (37 mg, 93 %).

R_f = 0.23 (40 % Et_2O in pentane); IR (thin film) ν_{max} 2939, 1709 cm^{-1}; M.P. = 97–100 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 6.76 (d, *J* = 8.9 Hz, 1H), 6.58 (d, *J* = 8.9 Hz, 1H), 3.93 (dd, *J* = 12.1, 6.7 Hz, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 3.71 (s, 3H), 2.65 – 2.58 (m, 1H), 2.35 (dddd, *J* = 16.3, 13.1, 6.2, 1.2 Hz, 1H), 2.22 – 2.09 (m, 1H), 2.10 – 1.98 (m, 2H), 1.98 – 1.90 (m, 1H), 1.88 – 1.76 (m, 1H), 1.75 – 1.65 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 209.8, 151.6, 147.7, 147.2, 124.2, 111.2, 106.3, 60.7, 56.3, 56.1, 47.3, 41.4, 31.5, 25.2, 25.1; HRMS: (ESI-TOF) calculated for $C_{15}H_{20}O_4Na$ [M + Na^+] 287.1259, found 287.1255.

2-(4-Methoxyphenyl)cyclohexanone (*rac*-24f) [18]

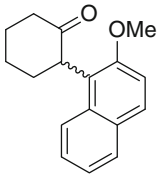


rac-**24f**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**6f**) to yield the product as an off-white solid (30 mg, 97 %).

R_f = 0.36 (40 % Et_2O in pentane); IR (thin solid film) ν_{max} 2926, 1704 cm^{-1}; M.P. = 86–88 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.06 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 3.79 (s, 3H), 3.56 (dd, *J* = 12.4, 5.4 Hz, 1H), 2.56 – 2.48 (m, 1H), 2.48 – 2.39 (m, 1H), 2.29 – 2.20 (m, 1H), 2.18 – 2.09 (m, 1H), 2.04 – 1.93 (m, 2H), 1.87 – 1.75 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 210.8, 158.5, 131.0, 129.5, 113.9, 56.7, 55.3, 42.3, 35.4, 28.0, 25.5; HRMS: (ESI-TOF) calculated for $C_{13}H_{16}O_2Na$ [M + Na^+] 227.1048, found 227.1041.

2-(2-Methoxynaphthalen-1-yl)cyclohexanone (*rac*-24g)

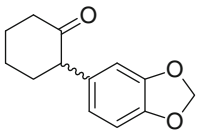


rac-**24g**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**6g**) to yield the product as an off-white solid (33 mg, 87 %).

R_f = 0.28 (40 % Et_2O in pentane); IR (thin solid film) ν_{max} 2937, 1708, 1596 cm^{-1}; M.P. = 116–118 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.81 – 7.75 (m, 2H), 7.71 (d, *J* = 8.6 Hz, 1H), 7.45 – 7.40 (m, 1H), 7.33 – 7.29 (m, 1H), 7.27 (d, *J* = 9.0 Hz, 1H), 4.27 (dd, *J* = 12.4, 6.6 Hz, 1H), 3.87 (s, 3H), 2.77 – 2.70 (m, 1H), 2.52 – 2.41 (m, 1H), 2.28 – 2.17 (m, 1H), 2.17 – 2.10 (m, 2H), 2.05 – 1.89 (m, 2H), 1.84 – 1.73 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 209.8, 154.1, 132.4, 129.8, 129.0, 128.9, 126.4, 123.3, 123.1, 114.0, 56.5, 48.4, 41.5, 31.8, 25.2, 25.1; HRMS: (ESI-TOF) calculated for $C_{17}H_{18}O_2Na$ [M + Na^+] 277.1204, found 277.1196.

2-(Benzo[*d*] [1, 3] dioxol-5-yl)cyclohexanone (*rac*-24h)

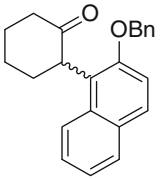


rac-**24h**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**6h**) to yield the product as an off-white solid (12 mg, 37 %).

R_f = 0.37 (40 % Et_2O in pentane); IR (thin solid film) ν_{max} 2930, 1710 cm^{-1}; M.P. = 88–90 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 6.76 (d, *J* = 8.0 Hz, 1H), 6.64 (d, *J* = 1.7 Hz, 1H), 6.57 (dd, *J* = 8.0, 1.7 Hz, 1H), 5.93 (s, 2H), 3.56 – 3.50 (m, 1H), 2.55 – 2.49 (m, 1H), 2.48 – 2.39 (m, 1H), 2.28 – 2.21 (m, 1H), 2.19 – 2.10 (m, 1H), 2.04 – 1.91 (m, 2H), 1.87 – 1.73 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 210.6, 147.7, 146.6, 132.7, 121.7, 109.1, 108.3, 101.1, 57.3, 42.3, 35.5, 27.9, 25.6; HRMS: (ESI-TOF) calculated for $C_{13}H_{15}O_3$ [M + H^+] 219.1021, found 219.1019.

2-(2-(Benzyloxy)naphthalen-1-yl)cyclohexanone (*rac*-24i)

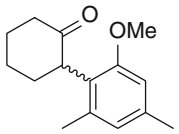


rac-**24i**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**6i**) to yield the product as an off-white solid (26 mg, 52 %).

R_f = 0.40 (40 % Et_2O in pentane); IR (thin solid film) ν_{max} 2937, 1707, 1595 cm^{-1}; M.P. = 129–130 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.84 – 7.74 (m, 3H), 7.49 – 7.32 (m, 8H), 5.19 (d, *J* = 11.2 Hz, 1H), 5.11 (d, *J* = 11.2 Hz, 1H), 4.32 – 4.18 (m, 1H), 2.59 – 2.49 (m, 1H), 2.43 – 2.31 (m, 1H), 2.30 – 2.17 (m, 1H), 2.16 – 2.05 (m, 1H), 2.00 – 1.89 (m, 2H), 1.79 – 1.66 (m, 1H), 1.65 – 1.52 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 209.7, 153.4, 137.1, 132.6, 129.9, 129.0, 128.9, 128.6, 128.2, 128.2, 126.5, 123.5, 123.4, 123.1, 115.0, 71.5, 48.7, 41.6, 31.6, 25.1, 24.7; HRMS: (ESI-TOF) calculated for $C_{23}H_{23}O_2$ [M + H^+] 331.1698, found 331.1693.

2-(2-Methoxy-4,6-dimethylphenyl)cyclohexanone (*rac*-24j)

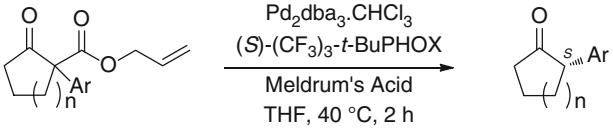


rac-**24j**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**6j**) to yield the product as a pale yellow oil (28 mg, 80 %).

R_f = 0.37 (40 % Et_2O in pentane); IR (thin film) ν_{max} 2935, 1710, 1580 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.63 (s, 1H), 6.58 (s, 1H), 3.73 (s, 3H), 3.66 – 3.58 (m, 1H), 2.65 (dddd, *J* = 16.5, 4.6, 2.7, 1.8 Hz, 1H), 2.40 – 2.31 (m, 1H), 2.30 (s, 3H), 2.22 (s, 3H), 2.11 – 1.93 (m, 4H), 1.90 – 1.79 (m, 1H), 1.74 – 1.63 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 209.9, 156.8, 137.3, 136.9, 125.6, 124.0, 110.4, 55.5, 49.5, 41.3, 31.1, 25.1, 25.0, 21.5, 20.3; HRMS: (ESI-TOF) calculated for $C_{15}H_{21}O_2$ [M + H^+] 233.1542, found 233.1544.

General Procedure for the Decarboxylative Asymmetric Protonation (7 and 24)

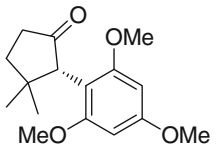


5: n = 1
6: n = 2

7: n = 1
24: n = 2

$Pd_2dba_3{\cdot}CHCl_3$ (7.8 mg, 0.0075 mmol) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (11.1 mg, 0.0188 mmol) were dissolved in freshly distilled THF in a flame dried Schlenk flask and stirred at 40 °C for 30 min. α-Aryl-β-keto allyl ester (0.15 mmol) and Meldrum's acid (0.375 mmol) were dissolved in THF in a flame dried round bottom flask (10 mL, 2-neck) and added to the Pd-complex solution, maintained at 40 °C, in one portion. The reaction mixture was stirred at 40 °C for 2 h, filtered through a bed of charcoal on a plug of Celite and washed with EtOAc. The filtrate was concentrated in vacuo and purified by silica gel column chromatography (pentane/Et_2O).

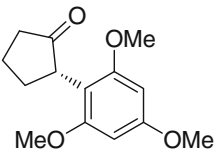
(*S*)-3,3-Dimethyl-2-(2,4,6-trimethoxyphenyl)cyclopentanone ((*S*)-21a)



(*S*)-**21a**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**20a**) to yield the product as a pale yellow oil (38 mg, 92 %, 77 % *ee*), identical in all respects to the previously prepared racemic sample, with the exception of $[\alpha]_D^{20} = -33.4$ (*c* 1.0, $CHCl_3$); SFC (Chiralcel IA-3, $scCO_2$/2-propanol, 99/1 to 70/30 gradient over 5 min, 3 mL/min): R_t = 2.67 (major) and 3.70 min.

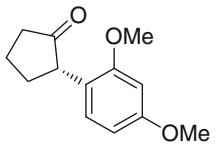
(*S*)-2-(2,4,6-Trimethoxyphenyl)cyclopentanone ((*S*)-7a)



(*S*)-**7a**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**5a**) to yield the product as an off-white solid (34 mg, 91 %, 82 % *ee*), identical in all respects to the previously prepared racemic sample, with the exception of $[\alpha]_D^{20} = -53.3$ (*c* 1.7, CH_2Cl_2); SFC (Chiralcel IC-3, $scCO_2$/MeOH, 99/1 to 60/40 gradient over 4 min, 3 mL/min): R_t = 2.78 (major) and 2.43 min.

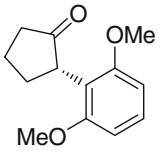
(*S*)-2-(2,4-Dimethoxyphenyl)cyclopentanone ((*S*)-7b)



(*S*)-**7b**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**5b**) to yield the product as an off-white solid (27 mg, 82 %, 60 % *ee*), identical in all respects to the previously prepared racemic sample, with the exception of $[\alpha]_D^{20} = -51.0$ (*c* 1.0, $CHCl_3$); SFC (Chiralcel IC-3, $scCO_2$/MeOH, 99/1 to 60/40 gradient over 4 min, 3 mL/min): R_t = 2.56 (major) and 2.44 min.

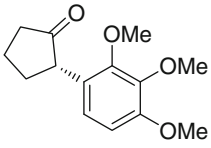
(*S*)-2-(2,6-Dimethoxyphenyl)cyclopentanone ((*S*)-7c)



(*S*)-**7c**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**5c**) to yield the product as an off-white solid (31 mg, 94 %, 80 % *ee*), identical in all respects to the previously prepared racemic sample, with the exception of $[\alpha]_D^{20} = -70.0$ (*c* 1.0, $CHCl_3$); SFC (Chiralcel IC-3, $scCO_2$/MeOH, 99/1 to 70/30 gradient over 5 min, 3 mL/min): R_t = 3.88 (major) and 3.75 min.

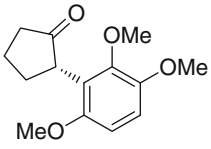
(*S*)-2-(2,3,4-Trimethoxyphenyl)cyclopentanone ((*S*)-7d)



(*S*)-**7d**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**5d**) to yield the product as an off-white solid (30 mg, 80 %, 70 % *ee*), identical in all respects to the previously prepared racemic sample, with the exception of $[\alpha]_D^{20} = -60.5$ (*c* 1.0, $CHCl_3$); SFC (Chiralcel IC-3, $scCO_2$/MeCN, 99/1 to 70/30 gradient over 5 min, 3 mL/min): R_t = 3.92 (major) and 4.51 min.

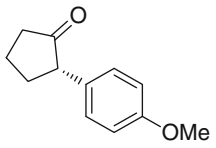
(*S*)-2-(2,3,6-Trimethoxyphenyl)cyclopentanone ((*S*)-7e)



(*S*)-**7e**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**5e**) to yield the product as an off-white solid (32 mg, 85 %, 71 % *ee*), identical in all respects to the previously prepared racemic sample, with the exception of $[\alpha]_D^{20} = -52.3$ (*c* 1.0, $CHCl_3$); SFC (Chiralcel IB-3, $scCO_2$/MeCN, 99/1 to 70/30 gradient over 5 min, 3 mL/min): R_t = 2.74 (major) and 3.07 min.

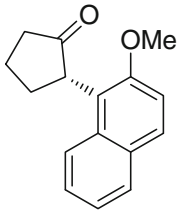
(*S*)-2-(4-Methoxyphenyl)cyclopentanone ((*S*)-7f)



(*S*)-**7f**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**5f**) to yield the product as an off-white solid (15 mg, 53 %, 29 % *ee*), [19] identical in all respects to the previously prepared racemic sample, with the exception of SFC (Chiralcel IC-3, $scCO_2$/2-propanol, 99/1 to 70/30 gradient over 5 min, 3 mL/min): R_t = 3.25 (major) and 2.88 min.

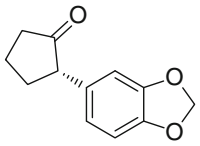
(*S*)-2-(2-Methoxynaphthalen-1-yl)cyclopentanone ((*S*)-7g)



(*S*)-**7g**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**5g**) to yield the product as an off-white solid (33 mg, 92 %, 85 % *ee*), identical in all respects to the previously prepared racemic sample, with the exception of $[\alpha]_D^{20} = -92.2$ (*c* 1.0, $CHCl_3$); SFC (Chiralcel IB-3, $scCO_2$/MeOH, 99/1 to 70/30 gradient over 5 min, 3 mL/min): R_t = 2.86 (major) and 3.17 min.

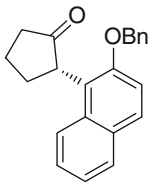
(*S*)-2-(Benzo[*d*] [1, 3] dioxol-5-yl)cyclopentanone ((*S*)-7h)



(*S*)-**7h**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**5h**) to yield the product as an off-white solid (22 mg, 72 %, 24 % *ee*), identical in all respects to the previously prepared racemic sample, with the exception of $[\alpha]_D^{20} = -2.2$ (*c* 1.0, $CHCl_3$); SFC (Chiralcel IC-3, $scCO_2$/2-propanol, 99/1 to 70/30 gradient over 5 min, 3 mL/min): R_t = 2.93 (major) and 2.72 min.

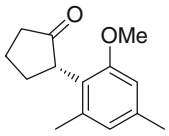
(*S*)-2-(2-(Benzyloxy)naphthalen-1-yl)cyclopentanone ((*S*)-7i)



(*S*)-**7i**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**5i**) to yield the product as an off-white solid (45 mg, 95 %, 92 % *ee*), identical in all respects to the previously prepared racemic sample, with the exception of $[\alpha]_D^{20} = 30.6$ (*c* 1.0, $CHCl_3$); SFC (Chiralcel IC-3, $scCO_2$/MeOH, 99/1 to 70/30 gradient over 5 min, 3 mL/min): R_t = 5.73 (major) and 6.64 min.

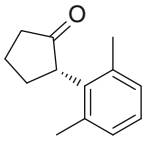
(*S*)-2-(2-Methoxy-4,6-dimethylphenyl)cyclopentanone ((*S*)-7j)



(*S*)-**7j**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**5j**) to yield the product as an off-white solid (30 mg, 92 %, 77 % *ee*), identical in all respects to the previously prepared racemic sample, with the exception of $[\alpha]_D^{20} = -88.4$ (*c* 1.0, $CHCl_3$); SFC (Chiralcel IC-3, $scCO_2$/MeOH, 99/1 to 70/30 gradient over 5 min, 3 mL/min): R_t = 2.83 (major) and 2.61 min.

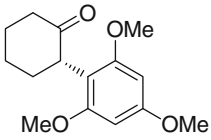
(*S*)-2-(2,6-Dimethylphenyl)cyclopentanone ((*S*)-7k)



(*S*)-**7k**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**5k**) to yield the product as an off-white solid (26 mg, 92 %, 47 % *ee*), identical in all respects to the previously prepared racemic sample, with the exception of $[\alpha]_D^{20} = -88.4$ (*c* 1.0, $CHCl_3$); SFC (Chiralcel IC-3, $scCO_2$/MeCN, 99/1 to 70/30 gradient over 5 min, 3 mL/min): R_t = 2.52 (major) and 2.39 min.

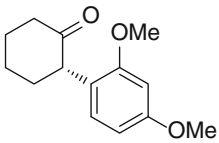
(*S*)-2-(2,4,6-Trimethoxyphenyl)cyclohexanone ((*S*)-24a)



(*S*)-**24a**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**6a**) to yield the product as an off-white solid (35 mg, 88 %, 60 % *ee*), identical in all respects to the previously prepared racemic sample, with the exception of $[\alpha]_D^{20} = -19.6$ (*c* 0.5, $CHCl_3$); SFC (Chiralcel IC-3, $scCO_2$/MeOH, 99/1 to 70/30 gradient over 5 min, 3 mL/min): R_t = 3.85 (major) and 3.62 min.

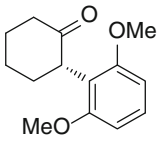
(*S*)-2-(2,4-Dimethoxyphenyl)cyclohexanone ((*S*)-24b)



(*S*)-**24b**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**6b**) to yield the product as an off-white solid (34 mg, 97 %, 72 % *ee*), identical in all respects to the previously prepared racemic sample, with the exception of $[\alpha]_D^{20} = -20.9$ (*c* 1.0, $CHCl_3$); SFC (Chiralcel IB-3, $scCO_2$/MeCN, 99/1 to 70/30 gradient over 5 min, 3 mL/min): R_t = 2.90 (major) and 3.29 min.

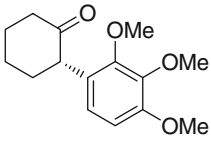
(*S*)-2-(2,6-Dimethoxyphenyl)cyclohexanone ((*S*)-24c)



(*S*)-**24c**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**6c**) to yield the product as an off-white solid (33 mg, 93 %, 70 % *ee*), identical in all respects to the previously prepared racemic sample, with the exception of $[\alpha]_D^{20} = -21.3$ (*c* 1.0, $CHCl_3$); SFC (Chiralcel IB-3, $scCO_2$/MeCN, 99/1 to 70/30 gradient over 5 min, 3 mL/min): R_t = 3.64 (major) and 4.10 min.

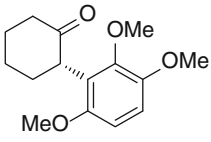
(*S*)-2-(2,3,4-Trimethoxyphenyl)cyclohexanone ((*S*)-24d)



(*S*)-**24d**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**6d**) to yield the product as an off-white solid (33 mg, 83 %, 74 % *ee*), identical in all respects to the previously prepared racemic sample, with the exception of $[\alpha]_D^{20} = -25.1$ (*c* 1.0, $CHCl_3$); SFC (Chiralcel IC-3, $scCO_2$/2-propanol, 99/1 to 70/30 gradient over 5 min, 3 mL/min): R_t = 2.86 (major) and 3.28 min.

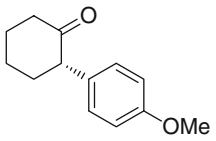
(*S*)-2-(2,3,6-Trimethoxyphenyl)cyclohexanone ((*S*)-24e)



(*S*)-**24e**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**6e**) to yield the product as an off-white solid (34 mg, 87 %, 67 % *ee*), identical in all respects to the previously prepared racemic sample, with the exception of $[\alpha]_D^{20} = -36.7$ (*c* 0.25, $CHCl_3$); SFC (Chiralcel IB-3, $scCO_2$/MeCN, 99/1 to 70/30 gradient over 5 min, 3 mL/min): R_t = 4.12 (major) and 5.55 min.

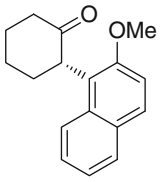
(*S*)-2-(4-Methoxyphenyl)cyclohexanone ((*S*)-24f)



(*S*)-**24f**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**6f**) to yield the product as an off-white solid (18 mg, 59 %, 38 % *ee*), identical in all respects to the previously prepared racemic sample, with the exception of $[\alpha]_D^{20} = -49.3$ (*c* 1.0, $CHCl_3$); SFC (Chiralcel IB-3, $scCO_2$/MeCN, 99/1 to 70/30 gradient over 5 min, 3 mL/min): R_t = 3.25 (major) and 3.40 min.

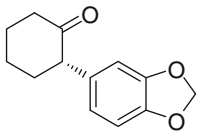
(*S*)-2-(2-Methoxynaphthalen-1-yl)cyclohexanone ((*S*)-24g)



(*S*)-**24g**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**6g**) to yield the product as an off-white solid (28 mg, 72 %, 74 % *ee*), identical in all respects to the previously prepared racemic sample, with the exception of $[\alpha]_D^{20} = -36.8$ (*c* 1.0, $CHCl_3$); SFC (Chiralcel IC-3, $scCO_2$/MeCN, 99/1 to 70/30 gradient over 5 min, 3 mL/min): R_t = 4.94 (major) and 5.30 min.

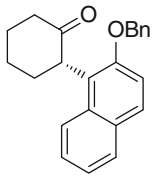
(*S*)-2-(Benzo[*d*] [1, 3] dioxol-5-yl)cyclohexanone ((*S*)-24h)



(*S*)-**24h**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**6h**) to yield the product as an off-white solid (27 mg, 82 %, 63 % *ee*), identical in all respects to the previously prepared racemic sample, with the exception of $[\alpha]_D^{20} = -49.3$ (*c* 1.0, $CHCl_3$); SFC (Chiralcel ID-3, $scCO_2$/MeCN, 70/30, 3 mL/min): R_t = 2.52 (major) and 2.74 min.

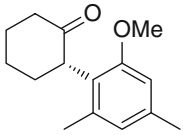
(*S*)-2-(2-(Benzyloxy)naphthalen-1-yl)cyclohexanone ((*S*)-24i)



(*S*)-**24i**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**6i**) to yield the product as an off-white solid (40 mg, 82 %, 60 % *ee*), identical in all respects to the previously prepared racemic sample, with the exception of $[\alpha]_D^{20} = -6.6$ (*c* 1.0, $CHCl_3$); SFC (Chiralcel IC-3, $scCO_2$/ 2-propanol, 70/30, 3 mL/min): R_t = 5.84 (major) and 7.39 min.

(*S*)-2-(2-Methoxy-4,6-dimethylphenyl)cyclohexanone ((*S*)-24j)

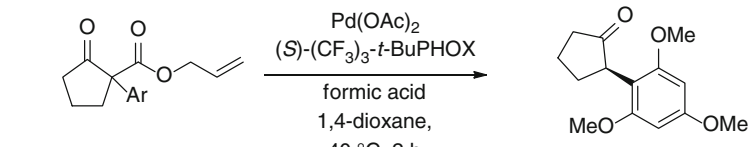


(*S*)-**24j**

The title compound was prepared according to the general procedure using α-aryl-β-keto allyl ester (**6j**) to yield the product as an off-white solid (22 mg, 63 %, 64 % *ee*), identical in all respects to the previously prepared racemic sample, with

the exception of $[\alpha]_D^{20} = -30.6$ (*c* 1.0, $CHCl_3$); SFC (Chiralcel IC-3, $scCO_2$/2-propanol, 80/20, 3 mL/min): $R_t = 1.69$ (major) and 1.54 min.

(*R*)-2-(2,4,6-Trimethoxyphenyl)cyclopentanone ((*R*)-7a)



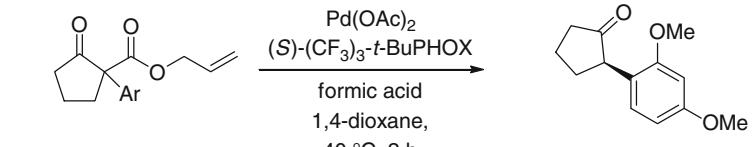
5a
Ar = 2,4,6-$(MeO)_3C_6H_2$

(*R*)-7a

Powdered 4 Å molecular sieves (270 mg) were added to a flame-dried 10 ml Schlenk flask with a Teflon-coated magnetic stirbar. The flask and molecular sieves were flame dried and back-filled with N_2 three times. Once the flask had cooled to ambient temperature under N_2, $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), (*S*)-$(CF_3)_3$-*t*-Bu-PHOX (11.1 mg, 0.0188 mmol) and anhydrous 1,4-dioxane (1.5 mL) were added. The mixture was stirred vigorously at 40 °C for 30 min prior to the addition of formic acid (34 μL, 0.90 mmol) and followed immediately by a solution of β-ketoester **5a** (50 mg, 0.15 mmol) in anhydrous 1,4-dioxane (1.5 mL) [in a flame-dried 2-neck 10 mL round-bottom flask under N_2]. The reaction mixture was stirred at 40 °C for 10 h and filtered through Celite® and the solvent was removed in vacuo. The resulting solid was then purified by silica gel column chromatography (40 % Et_2O in pentane) to yield the product as a white solid (29 mg, 76 %, 55 % *ee*).

All physical data identical in all respects to the previously prepared racemic sample, with the exception of $[\alpha]_D^{20} = 45.4$ (*c* 1.0, $CHCl_3$); SFC (Chiralcel IA-3, $scCO_2$/2-propanol, 99/1 to 70/30 gradient over 5 min, 3 mL/min): $R_t = 2.39$ (major) and 2.71 min.

(*R*)-2-(2,4-Dimethoxyphenyl)cyclopentanone ((*R*)-7b)



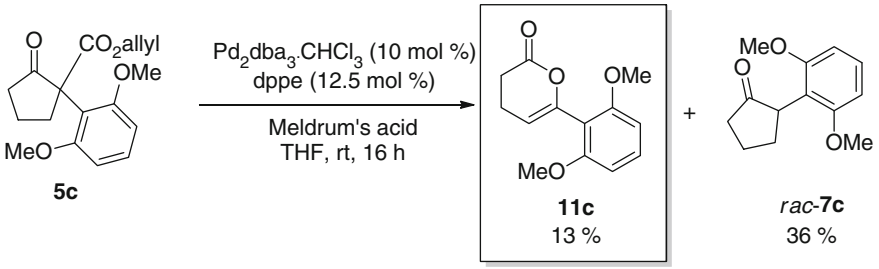
5b
Ar = 2,4-$(MeO)_2C_6H_2$

(*R*)-7b

Reaction carried out according to the same procedure as for (*R*)-**7a** using $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), (*S*)-$(CF_3)_3$-*t*-Bu-PHOX (11.1 mg, 0.0188 mmol), formic acid (34 μL, 0.90 mmol) and β-ketoester **5b** (46 mg, 0.15 mmol) to yield the product as a white solid (22 mg, 66 %, 26 % *ee*).

All physical data identical in all respects to the previously prepared racemic sample, with the exception of $[\alpha]_D^{20}$ = 22.2 (*c* 1.0, $CHCl_3$); SFC (Chiralcel IC-3, $scCO_2$/MeOH, 99/1 to 60/40 gradient over 4 min, 3 mL/min): R_t = 2.41 (major) and 2.54 min.

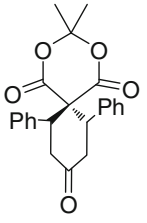
6-(2,6-Dimethoxyphenyl)-3,4-dihydro-2H-pyran-2-one (11c)



$Pd_2dba_3{\cdot}CHCl_3$ (8.5 mg, 0.0082 mmol) and dppe (8.2 mg, 0.0205 mmol) were dissolved THF (2 mL, fresh Na/benzophenone still, indicator blue) in a flame dried Schlenk flask and stirred at 40 °C for 30 min. α-Aryl-β-keto allyl ester (50 mg, 0.164 mmol) and Meldrum's acid (59 mg, 0.410 mmol) were dissolved in THF (2 mL) in a flame dried round bottom flask (10 mL, 2-neck) and added to the Pd-complex solution, maintained at 40 °C, in one portion. The reaction mixture was stirred at 40 °C for 2 h, filtered through a bed of charcoal on a plug of Celite and washed with EtOAc. The filtrate was concentrated in vacuo and purified by silica gel column chromatography (pentane/Et_2O).

IR (thin film) ν_{max} 2925, 1704, 1594 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.27 (t, *J* = 8.4 Hz, 1H), 6.55 (d, *J* = 8.4 Hz, 2H), 5.34 (t, *J* = 4.6 Hz, 1H), 3.80 (s, 6H), 2.71 (t, *J* = 7.6 Hz, 2H), 2.50 (td, *J* = 7.6, 4.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.99, 158.97, 145.13, 130.82, 112.34, 106.68, 104.01, 56.19, 28.69, 19.57. HRMS: (ESI-TOF) calculated for $C_{13}H_{15}O_4$ [M + H^+] 235.0970, found 235.0971.

3,3-Dimethyl-7,11-diphenyl-2,4-dioxaspiro[5.5]undecane-1,5,9-trione (23)



23

$Pd_2dba_3.CHCl_3$ (39 mg, 0.038 mmol) and Meldrum's acid (270 mg, 1.87 mmol) were dissolved in THF (7.5 mL) and stirred at 40 °C for 12 h. The solvent was removed in vacuo and the resulting residue was purified by silica gel column chromatography (10 % Et_2O in pentane) to yield the product as a white solid (25 mg, 58 %).

^{1}H NMR (500 MHz, cdcl$_3$) δ 7.37 – 7.22 (m, 10H), 4.02 (dd, J = 14.4, 4.3 Hz, 2H), 3.73 (t, J = 14.4 Hz, 2H), 2.65 (dd, J = 14.4, 4.3 Hz, 2H), 0.55 (s, 6H). All other physical data was identical to those previously reported [20].

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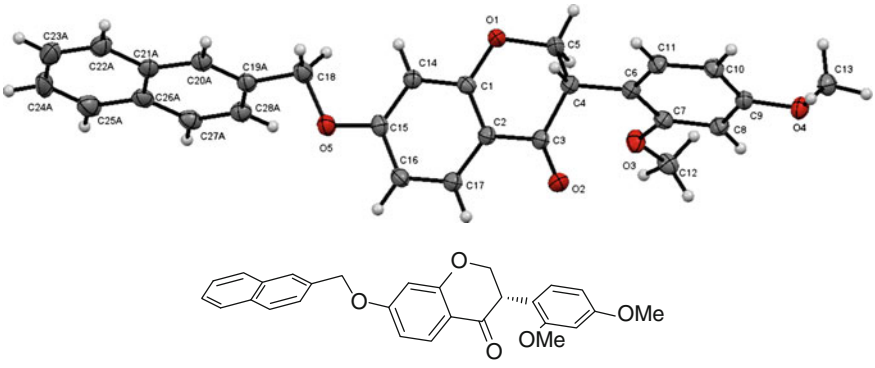
Appendix A
X-Ray Crystal Structure Data

A.1 NAP-Protected Sativanone

See Tables A.1, A.2, A.3, A.4, A.5 and A.6.



1

R. Doran, *Asymmetric Synthesis of Bioactive Lactones and the Development of a Catalytic Asymmetric Synthesis of α-Aryl Ketones*, Springer Theses,
DOI 10.1007/978-3-319-20544-1

Table A.1 Crystal data and structure refinement for **9a**

Identification code	gui80
Empirical formula	C28 H24 O5
Formula weight	440.47
Temperature	100(2) K
Wavelength	1.54184 Å
Crystal system	Orthorhombic
Space group	P212121 (#19)
Unit cell dimensions	a = 7.03460(4) Å, α = 90°
	b = 13.8306(1) Å, β = 90°
	c = 22.6020(2) Å, γ = 90°
Volume	2199.01(3) $Å^3$
Z	4
Density (calculated)	1.330 Mg/m^3
Absorption coefficient	0.737 mm^{-1}
F(000)	928
Crystal size	0.4399 × 0.2558 × 0.1392 mm^3
Theta range for data collection	3.75–76.85°
Index ranges	$-8 \leq h \leq 8$, $-17 \leq k \leq 16$, $-28 \leq l \leq 28$
Reflections collected	51,588
Independent reflections	4615 [R(int) = 0.0554]
Completeness to theta = 76.85°	99.6 %
Absorption correction	Analytical
Max. and min. transmission	0.920 and 0.804
Refinement method	Full–matrix least–squares on F2
Data/restraints/parameters	4615/25/341[a]
Goodness–of–fit on F2	1.070
Final R indices [I > 2 sigma(I)]	R1 = 0.0292, wR2 = 0.0769
R indices (all data)	R1 = 0.0302, wR2 = 0.0779
Absolute structure parameter	0.00(11)
Largest diff. peak and hole	0.150 and –0.197 e $Å^{-3}$

[a]The two disorder parts were restrained to have the same shape using SAME

Table A.2 Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **1**

Atom	x	y	z	U(eq)
O(1)	2512(1)	1367(1)	10253(1)	27(1)
O(2)	–2626(1)	1127(1)	11122(1)	28(1)
O(3)	–183(1)	–522(1)	11475(1)	28(1)
O(4)	619(1)	–72(1)	13549(1)	27(1)
O(5)	–668(1)	1610(1)	8401(1)	28(1)
C(1)	845(2)	1348(1)	9948(1)	22(1)
C(2)	–919(2)	1203(1)	10219(1)	22(1)
C(3)	–1097(2)	1194(1)	10867(1)	23(1)
C(4)	765(2)	1363(1)	11196(1)	24(1)
C(5)	2420(2)	955(1)	10841(1)	29(1)
C(6)	751(2)	999(1)	11827(1)	24(1)
C(7)	226(2)	40(1)	11956(1)	24(1)
C(8)	153(2)	–289(1)	12535(1)	24(1)
C(9)	705(2)	328(1)	12992(1)	23(1)
C(10)	1313(2)	1258(1)	12877(1)	26(1)
C(11)	1305(2)	1583(1)	12292(1)	26(1)
C(12)	–407(2)	–1534(1)	11575(1)	27(1)
C(13)	1080(2)	540(1)	14037(1)	29(1)
C(14)	996(2)	1503(1)	9339(1)	24(1)
C(15)	–636(2)	1468(1)	8997(1)	23(1)
C(16)	–2419(2)	1277(1)	9255(1)	25(1)
C(17)	–2544(2)	1163(1)	9858(1)	24(1)
C(18)	1115(2)	1866(1)	8124(1)	30(1)
C(19A)[a]	775(2)	1878(1)	7467(1)	24(1)
C(20A)[a]	1062(2)	2715(1)	7156(1)	26(1)
C(21A)[a]	846(2)	2731(1)	6528(1)	28(1)
C(22A)[a]	1173(2)	3589(1)	6197(1)	35(1)
C(23A)[a]	928(3)	3593(2)	5599(1)	43(1)
C(24A)[a]	322(4)	2744(3)	5300(1)	44(1)
C(25A)[a]	28(3)	1913(2)	5608(1)	39(1)
C(26A)[a]	289(2)	1874(1)	6233(1)	29(1)
C(27A)[a]	–4(2)	1019(1)	6564(1)	29(1)
C(28A)[a]	241(2)	1019(1)	7166(1)	28(1)
C(19B)[b]	958(14)	2347(8)	7482(4)	18(2)
C(20B)[b]	426(12)	1709(7)	7069(4)	20(2)
C(21B)[b]	344(19)	2033(9)	6455(5)	30(3)
C(22B)[b]	–252(16)	1321(8)	6030(4)	33(2)
C(23B)[b]	–340(20)	1592(10)	5471(5)	35(3)
C(24B)[b]	210(70)	2532(19)	5300(10)	96(16)

(continued)

Table A.2 (continued)

Atom	x	y	z	U(eq)
C(25B)[b]	730(20)	3207(11)	5702(6)	44(4)
C(26B)[b]	867(16)	2996(9)	6322(5)	20(2)
C(27B)[b]	1368(14)	3615(7)	6766(4)	28(2)
C(28B)[b]	1458(13)	3320(7)	7343(4)	22(2)

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor
[a]s.o.f. = 0.878(2)
[b]s.o.f. = 0.122(2), only isotropic refinement possible (s.o.f.: site occupation factor; the sum of the s.o.f.'s *a* and *b* is constrained to be 1)

Table A.3 Bond lengths [Å] and angles [°] for **1**

O(1)–C(1)	1.3602(14)
O(1)–C(5)	1.4475(13)
O(2)–C(3)	1.2225(14)
O(3)–C(7)	1.3677(13)
O(3)–C(12)	1.4258(15)
O(4)–C(9)	1.3749(12)
O(4)–C(13)	1.4273(14)
O(5)–C(15)	1.3625(12)
O(5)–C(18)	1.4453(15)
C(1)–C(14)	1.3977(15)
C(1)–C(2)	1.3978(16)
C(2)–C(17)	1.4063(16)
C(2)–C(3)	1.4706(15)
C(3)–C(4)	1.5247(15)
C(4)–C(6)	1.5109(14)
C(4)–C(5)	1.5225(17)
C(4)–H(4)	1.0000
C(5)–H(5A)	0.9900
C(5)–H(5B)	0.9900
C(6)–C(11)	1.3816(16)
C(6)–C(7)	1.4082(16)
C(7)–C(8)	1.3850(15)
C(8)–C(9)	1.3958(16)
C(8)–H(8)	0.9500
C(9)–C(10)	1.3800(17)
C(10)–C(11)	1.3965(16)
C(10)–H(10)	0.9500
C(11)–H(11)	0.9500
C(12)–H(12A)	0.9800

(continued)

Table A.3 (continued)

C(12)–H(12B)	0.9800
C(12)–H(12C)	0.9800
C(13)–H(13A)	0.9800
C(13)–H(13B)	0.9800
C(13)–H(13C)	0.9800
C(14)–C(15)	1.3844(16)
C(14)–H(14)	0.9500
C(15)–C(16)	1.4081(17)
C(16)–C(17)	1.3745(16)
C(16)–H(16)	0.9500
C(17)–H(17)	0.9500
C(18)–C(19A)	1.5046(17)
C(18)–C(19B)	1.600(10)
C(18)–H(18A)	0.9900
C(18)–H(18B)	0.9900
C(18)–H(18C)	0.9900
C(18)–H(18D)	0.9900
C(19A)–C(20A)	1.369(2)
C(19A)–C(28A)	1.420(2)
C(20A)–C(21A)	1.428(2)
C(20A)–H(20A)	0.9500
C(21A)–C(26A)	1.416(2)
C(21A)–C(22A)	1.421(2)
C(22A)–C(23A)	1.364(2)
C(22A)–H(22A)	0.9500
C(23A)–C(24A)	1.419(5)
C(23A)–H(23A)	0.9500
C(24A)–C(25A)	1.358(4)
C(24A)–H(24A)	0.9500
C(25A)–C(26A)	1.426(2)
C(25A)–H(25A)	0.9500
C(26A)–C(27A)	1.415(2)
C(27A)–C(28A)	1.3706(18)
C(27A)–H(27A)	0.9500
C(28A)–H(28A)	0.9500
C(19B)–C(20B)	1.337(11)
C(19B)–C(28B)	1.426(12)
C(20B)–C(21B)	1.461(12)
C(20B)–H(20B)	0.9500
C(21B)–C(26B)	1.413(13)
C(21B)–C(22B)	1.439(12)

(continued)

Table A.3 (continued)

C(22B)–C(23B)	1.320(13)
C(22B)–H(22B)	0.9500
C(23B)–C(24B)	1.411(19)
C(23B)–H(23B)	0.9500
C(24B)–C(25B)	1.354(18)
C(24B)–H(24B)	0.9500
C(25B)–C(26B)	1.435(14)
C(25B)–H(25B)	0.9500
C(26B)–C(27B)	1.365(11)
C(27B)–C(28B)	1.367(11)
C(27B)–H(27B)	0.9500
C(28B)–H(28B)	0.9500
C(1)–O(1)–C(5)	114.73(9)
C(7)–O(3)–C(12)	117.04(9)
C(9)–O(4)–C(13)	117.26(9)
C(15)–O(5)–C(18)	116.67(9)
O(1)–C(1)–C(14)	115.49(10)
O(1)–C(1)–C(2)	123.15(9)
C(14)–C(1)–C(2)	121.35(10)
C(1)–C(2)–C(17)	118.26(10)
C(1)–C(2)–C(3)	120.85(10)
C(17)–C(2)–C(3)	120.59(10)
O(2)–C(3)–C(2)	122.96(10)
O(2)–C(3)–C(4)	122.54(10)
C(2)–C(3)–C(4)	114.30(9)
C(6)–C(4)–C(5)	112.28(10)
C(6)–C(4)–C(3)	113.80(9)
C(5)–C(4)–C(3)	110.05(9)
C(6)–C(4)–H(4)	106.8
C(5)–C(4)–H(4)	106.8
C(3)–C(4)–H(4)	106.8
O(1)–C(5)–C(4)	111.89(10)
O(1)–C(5)–H(5A)	109.2
C(4)–C(5)–H(5A)	109.2
O(1)–C(5)–H(5B)	109.2
C(4)–C(5)–H(5B)	109.2
H(5A)–C(5)–H(5B)	107.9
C(11)–C(6)–C(7)	117.76(10)
C(11)–C(6)–C(4)	121.44(10)
C(7)–C(6)–C(4)	120.77(10)
O(3)–C(7)–C(8)	123.83(10)

(continued)

Table A.3 (continued)

O(3)–C(7)–C(6)	115.14(9)
C(8)–C(7)–C(6)	121.03(10)
C(7)–C(8)–C(9)	119.23(11)
C(7)–C(8)–H(8)	120.4
C(9)–C(8)–H(8)	120.4
O(4)–C(9)–C(10)	124.12(10)
O(4)–C(9)–C(8)	114.81(10)
C(10)–C(9)–C(8)	121.06(10)
C(9)–C(10)–C(11)	118.50(10)
C(9)–C(10)–H(10)	120.7
C(11)–C(10)–H(10)	120.7
C(6)–C(11)–C(10)	122.29(11)
C(6)–C(11)–H(11)	118.9
C(10)–C(11)–H(11)	118.9
O(3)–C(12)–H(12A)	109.5
O(3)–C(12)–H(12B)	109.5
H(12A)–C(12)–H(12B)	109.5
O(3)–C(12)–H(12C)	109.5
H(12A)–C(12)–H(12C)	109.5
H(12B)–C(12)–H(12C)	109.5
O(4)–C(13)–H(13A)	109.5
O(4)–C(13)–H(13B)	109.5
H(13A)–C(13)–H(13B)	109.5
O(4)–C(13)–H(13C)	109.5
H(13A)–C(13)–H(13C)	109.5
H(13B)–C(13)–H(13C)	109.5
C(15)–C(14)–C(1)	118.80(11)
C(15)–C(14)–H(14)	120.6
C(1)–C(14)–H(14)	120.6
O(5)–C(15)–C(14)	124.12(11)
O(5)–C(15)–C(16)	114.92(10)
C(14)–C(15)–C(16)	120.96(10)
C(17)–C(16)–C(15)	119.23(11)
C(17)–C(16)–H(16)	120.4
C(15)–C(16)–H(16)	120.4
C(16)–C(17)–C(2)	121.28(11)
C(16)–C(17)–H(17)	119.4
C(2)–C(17)–H(17)	119.4
O(5)–C(18)–C(19A)	106.96(10)
O(5)–C(18)–C(19B)	115.8(4)
O(5)–C(18)–H(18A)	110.3

(continued)

Table A.3 (continued)

C(19A)–C(18)–H(18A)	110.3
O(5)–C(18)–H(18B)	110.3
C(19A)–C(18)–H(18B)	110.3
H(18A)–C(18)–H(18B)	108.6
O(5)–C(18)–H(18C)	108.3
C(19B)–C(18)–H(18C)	108.3
O(5)–C(18)–H(18D)	108.3
C(19B)–C(18)–H(18D)	108.3
H(18C)–C(18)–H(18D)	107.4
C(20A)–C(19A)–C(28A)	120.00(13)
C(20A)–C(19A)–C(18)	119.53(14)
C(28A)–C(19A)–C(18)	120.41(14)
C(19A)–C(20A)–C(21A)	120.55(14)
C(19A)–C(20A)–H(20A)	119.7
C(21A)–C(20A)–H(20A)	119.7
C(26A)–C(21A)–C(22A)	119.73(16)
C(26A)–C(21A)–C(20A)	118.98(17)
C(22A)–C(21A)–C(20A)	121.29(15)
C(23A)–C(22A)–C(21A)	120.30(18)
C(23A)–C(22A)–H(22A)	119.9
C(21A)–C(22A)–H(22A)	119.9
C(22A)–C(23A)–C(24A)	120.4(2)
C(22A)–C(23A)–H(23A)	119.8
C(24A)–C(23A)–H(23A)	119.8
C(25A)–C(24A)–C(23A)	120.16(16)
C(25A)–C(24A)–H(24A)	119.9
C(23A)–C(24A)–H(24A)	119.9
C(24A)–C(25A)–C(26A)	121.3(2)
C(24A)–C(25A)–H(25A)	119.3
C(26A)–C(25A)–H(25A)	119.3
C(27A)–C(26A)–C(21A)	119.40(16)
C(27A)–C(26A)–C(25A)	122.53(18)
C(21A)–C(26A)–C(25A)	118.07(17)
C(28A)–C(27A)–C(26A)	120.42(15)
C(28A)–C(27A)–H(27A)	119.8
C(26A)–C(27A)–H(27A)	119.8
C(27A)–C(28A)–C(19A)	120.63(14)
C(27A)–C(28A)–H(28A)	119.7
C(19A)–C(28A)–H(28A)	119.7
C(20B)–C(19B)–C(28B)	122.5(9)
C(20B)–C(19B)–C(18)	112.2(8)

(continued)

Table A.3 (continued)

C(28B)–C(19B)–C(18)	125.1(7)
C(19B)–C(20B)–C(21B)	118.2(9)
C(19B)–C(20B)–H(20B)	120.9
C(21B)–C(20B)–H(20B)	120.9
C(26B)–C(21B)–C(22B)	125.4(9)
C(26B)–C(21B)–C(20B)	118.7(10)
C(22B)–C(21B)–C(20B)	115.9(10)
C(23B)–C(22B)–C(21B)	117.3(10)
C(23B)–C(22B)–H(22B)	121.3
C(21B)–C(22B)–H(22B)	121.3
C(22B)–C(23B)–C(24B)	120.7(14)
C(22B)–C(23B)–H(23B)	119.7
C(24B)–C(23B)–H(23B)	119.7
C(25B)–C(24B)–C(23B)	121.8(18)
C(25B)–C(24B)–H(24B)	119.1
C(23B)–C(24B)–H(24B)	119.1
C(24B)–C(25B)–C(26B)	122.2(15)
C(24B)–C(25B)–H(25B)	118.9
C(26B)–C(25B)–H(25B)	118.9
C(27B)–C(26B)–C(21B)	120.2(10)
C(27B)–C(26B)–C(25B)	127.4(12)
C(21B)–C(26B)–C(25B)	112.4(9)
C(26B)–C(27B)–C(28B)	121.7(10)
C(26B)–C(27B)–H(27B)	119.2
C(28B)–C(27B)–H(27B)	119.2
C(27B)–C(28B)–C(19B)	118.7(9)
C(27B)–C(28B)–H(28B)	120.6
C(19B)–C(28B)–H(28B)	120.6

Symmetry transformations used to generate equivalent atoms

Table A.4 Anisotropic displacement parameters ($Å^2 \times 10^3$) for **1**

Atom	U11	U22	U33	U23	U13	U12
O(1)	20(1)	39(1)	22(1)	7(1)	–2(1)	–2(1)
O(2)	23(1)	34(1)	27(1)	5(1)	2(1)	–1(1)
O(3)	39(1)	25(1)	21(1)	–1(1)	–4(1)	–5(1)
O(4)	35(1)	27(1)	19(1)	2(1)	0(1)	–3(1)
O(5)	27(1)	38(1)	20(1)	1(1)	–1(1)	2(1)
C(1)	21(1)	21(1)	24(1)	1(1)	–3(1)	1(1)
C(2)	22(1)	21(1)	23(1)	3(1)	–2(1)	–1(1)
C(3)	24(1)	21(1)	24(1)	4(1)	–1(1)	0(1)

(continued)

Table A.4 (continued)

Atom	U11	U22	U33	U23	U13	U12
C(4)	25(1)	26(1)	22(1)	4(1)	–2(1)	–5(1)
C(5)	24(1)	40(1)	22(1)	9(1)	–2(1)	–1(1)
C(6)	23(1)	26(1)	23(1)	4(1)	–1(1)	–3(1)
C(7)	23(1)	25(1)	22(1)	–1(1)	–2(1)	–2(1)
C(8)	25(1)	22(1)	25(1)	2(1)	–1(1)	–3(1)
C(9)	22(1)	26(1)	20(1)	3(1)	0(1)	1(1)
C(10)	28(1)	26(1)	24(1)	–1(1)	–4(1)	–3(1)
C(11)	29(1)	24(1)	26(1)	4(1)	–3(1)	–6(1)
C(12)	30(1)	24(1)	27(1)	–3(1)	–4(1)	1(1)
C(13)	32(1)	34(1)	21(1)	–2(1)	0(1)	–2(1)
C(14)	23(1)	25(1)	23(1)	2(1)	1(1)	1(1)
C(15)	28(1)	21(1)	21(1)	1(1)	–2(1)	3(1)
C(16)	24(1)	26(1)	26(1)	2(1)	–6(1)	–1(1)
C(17)	23(1)	25(1)	26(1)	2(1)	–2(1)	–1(1)
C(18)	26(1)	43(1)	21(1)	1(1)	1(1)	5(1)
C(19A)[a]	20(1)	31(1)	22(1)	0(1)	1(1)	4(1)
C(20A)[a]	22(1)	30(1)	26(1)	0(1)	2(1)	4(1)
C(21A)[a]	18(1)	35(1)	29(1)	6(1)	4(1)	6(1)
C(22A)[a]	26(1)	40(1)	37(1)	11(1)	5(1)	4(1)
C(23A)[a]	30(1)	61(1)	39(1)	20(1)	6(1)	4(1)
C(24A)[a]	32(1)	83(2)	18(1)	12(1)	4(1)	8(1)
C(25A)[a]	27(1)	60(1)	29(1)	–5(1)	1(1)	–1(1)
C(26A)[a]	18(1)	42(1)	26(1)	–2(1)	2(1)	3(1)
C(27A)[a]	23(1)	36(1)	28(1)	–7(1)	0(1)	1(1)
C(28A)[a]	24(1)	31(1)	27(1)	0(1)	1(1)	2(1)

The anisotropic displacement factor exponent takes the form: $-2\pi^2[\,h^2\,a*^2\,U^{11}+\cdots+2\,h\,k\,a*\,b*\,U^{12}\,]$

[a]s.o.f. = 0.878(2)

[b]s.o.f. = 0.122(2), only isotropic refinement possible (s.o.f.: site occupation factor; the sum of the s.o.f.'s *a* and *b* is constrained to be 1)

Table A.5 Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for **1**

Atom	x	y	z	U(eq)
H(4)	956	2078	11,216	29
H(5A)	3624	1090	11,052	34
H(5B)	2279	244	10,810	34
H(8)	–267	–927	12,619	29
H(10)	1727	1668	13,189	31
H(11)	1694	2227	12,211	32
H(12A)	–590	–1864	11,195	40
H(12B)	–1516	–1644	11,828	40

(continued)

Table A.5 (continued)

Atom	x	y	z	U(eq)
H(12C)	733	–1788	11,769	40
H(13A)	2401	758	14,000	43
H(13B)	924	181	14,407	43
H(13C)	232	1103	14,037	43
H(14)	2196	1629	9163	28
H(16)	–3523	1227	9015	30
H(17)	–3752	1055	10,034	29
H(18A)[a]	2107	1386	8225	36
H(18B)[a]	1540	2511	8261	36
H(18C)[b]	1902	1275	8092	36
H(18D)[b]	1794	2321	8388	36
H(20A)[a]	1408	3289	7360	31
H(22A)[a]	1563	4163	6394	42
H(23A)[a]	1163	4167	5380	52
H(24A)[a]	123	2756	4885	53
H(25A)[a]	–360	1348	5402	47
H(27A)[a]	–372	441	6368	35
H(28A)[a]	53	439	7383	33
H(20B)[b]	110	1063	7173	24
H(22B)[b]	–567	681	6147	39
H(23B)[b]	–791	1150	5180	42
H(24B)[b]	223	2695	4892	115
H(25B)[b]	1016	3842	5569	53
H(27B)[b]	1661	4267	6672	34
H(28B)[b]	1845	3755	7645	27

[a]s.o.f. = 0.878(2)
[b]s.o.f. = 0.122(2) (s.o.f.: site occupation factor; the sum of the s.o.f.'s *a* and *b* is constrained to be 1)

Table A.6 Torsion angles [°] for **1**

C(5)–O(1)–C(1)–C(14)	–164.02(10)
C(5)–O(1)–C(1)–C(2)	17.07(16)
O(1)–C(1)–C(2)–C(17)	–177.73(11)
C(14)–C(1)–C(2)–C(17)	3.42(17)
O(1)–C(1)–C(2)–C(3)	8.57(17)
C(14)–C(1)–C(2)–C(3)	–170.28(11)
C(1)–C(2)–C(3)–O(2)	175.51(11)
C(17)–C(2)–C(3)–O(2)	1.96(18)
C(1)–C(2)–C(3)–C(4)	0.50(16)
C(17)–C(2)–C(3)–C(4)	–173.05(10)

(continued)

Table A.6 (continued)

O(2)–C(3)–C(4)–C(6)	26.32(16)
C(2)–C(3)–C(4)–C(6)	–158.66(10)
O(2)–C(3)–C(4)–C(5)	153.33(11)
C(2)–C(3)–C(4)–C(5)	–31.64(13)
C(1)–O(1)–C(5)–C(4)	–50.06(14)
C(6)–C(4)–C(5)–O(1)	–175.30(9)
C(3)–C(4)–C(5)–O(1)	56.84(13)
C(5)–C(4)–C(6)–C(11)	105.05(14)
C(3)–C(4)–C(6)–C(11)	–129.10(12)
C(5)–C(4)–C(6)–C(7)	–72.97(14)
C(3)–C(4)–C(6)–C(7)	52.88(15)
C(12)–O(3)–C(7)–C(8)	–9.98(17)
C(12)–O(3)–C(7)–C(6)	169.67(10)
C(11)–C(6)–C(7)–O(3)	–175.74(11)
C(4)–C(6)–C(7)–O(3)	2.36(16)
C(11)–C(6)–C(7)–C(8)	3.93(17)
C(4)–C(6)–C(7)–C(8)	–177.98(11)
O(3)–C(7)–C(8)–C(9)	176.33(11)
C(6)–C(7)–C(8)–C(9)	–3.31(17)
C(13)–O(4)–C(9)–C(10)	3.99(16)
C(13)–O(4)–C(9)–C(8)	–177.11(10)
C(7)–C(8)–C(9)–O(4)	–178.74(10)
C(7)–C(8)–C(9)–C(10)	0.20(17)
O(4)–C(9)–C(10)–C(11)	–179.02(11)
C(8)–C(9)–C(10)–C(11)	2.15(18)
C(7)–C(6)–C(11)–C(10)	–1.52(18)
C(4)–C(6)–C(11)–C(10)	–179.60(11)
C(9)–C(10)–C(11)–C(6)	–1.46(18)
O(1)–C(1)–C(14)–C(15)	178.25(10)
C(2)–C(1)–C(14)–C(15)	–2.82(18)
C(18)–O(5)–C(15)–C(14)	–3.69(17)
C(18)–O(5)–C(15)–C(16)	176.35(10)
C(1)–C(14)–C(15)–O(5)	179.77(10)
C(1)–C(14)–C(15)–C(16)	–0.27(17)
O(5)–C(15)–C(16)–C(17)	–177.37(11)
C(14)–C(15)–C(16)–C(17)	2.66(18)
C(15)–C(16)–C(17)–C(2)	–2.03(18)
C(1)–C(2)–C(17)–C(16)	–0.95(18)
C(3)–C(2)–C(17)–C(16)	172.76(11)
C(15)–O(5)–C(18)–C(19A)	174.02(11)
C(15)–O(5)–C(18)–C(19B)	–161.5(4)
O(5)–C(18)–C(19A)–C(20A)	119.80(13)

(continued)

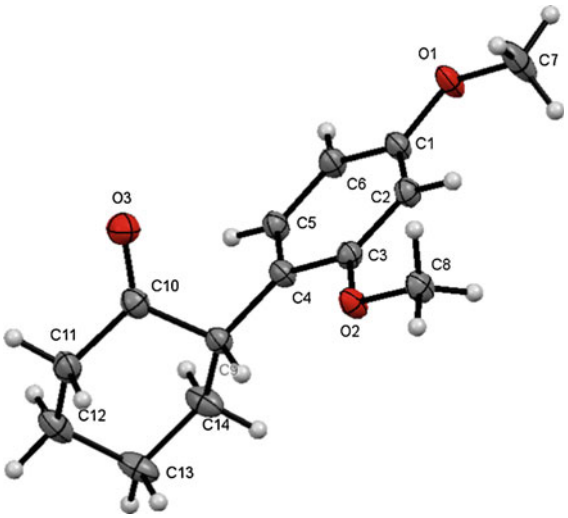
Table A.6 (continued)

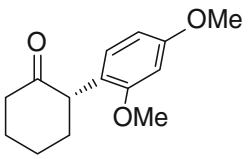
O(5)–C(18)–C(19A)–C(28A)	–62.96(15)
C(28A)–C(19A)–C(20A)–C(21A)	–0.5(2)
C(18)–C(19A)–C(20A)–C(21A)	176.70(12)
C(19A)–C(20A)–C(21A)–C(26A)	1.4(2)
C(19A)–C(20A)–C(21A)–C(22A)	–178.82(13)
C(26A)–C(21A)–C(22A)–C(23A)	0.9(2)
C(20A)–C(21A)–C(22A)–C(23A)	–178.93(15)
C(21A)–C(22A)–C(23A)–C(24A)	0.7(3)
C(22A)–C(23A)–C(24A)–C(25A)	–1.6(3)
C(23A)–C(24A)–C(25A)–C(26A)	0.9(3)
C(22A)–C(21A)–C(26A)–C(27A)	178.96(13)
C(20A)–C(21A)–C(26A)–C(27A)	–1.2(2)
C(22A)–C(21A)–C(26A)–C(25A)	–1.6(2)
C(20A)–C(21A)–C(26A)–C(25A)	178.23(14)
C(24A)–C(25A)–C(26A)–C(27A)	–179.85(18)
C(24A)–C(25A)–C(26A)–C(21A)	0.7(3)
C(21A)–C(26A)–C(27A)–C(28A)	0.3(2)
C(25A)–C(26A)–C(27A)–C(28A)	–179.16(14)
C(26A)–C(27A)–C(28A)–C(19A)	0.6(2)
C(20A)–C(19A)–C(28A)–C(27A)	–0.4(2)
C(18)–C(19A)–C(28A)–C(27A)	–177.66(12)
O(5)–C(18)–C(19B)–C(20B)	–71.3(8)
O(5)–C(18)–C(19B)–C(28B)	113.2(8)
C(28B)–C(19B)–C(20B)–C(21B)	–0.5(15)
C(18)–C(19B)–C(20B)–C(21B)	–176.1(8)
C(19B)–C(20B)–C(21B)–C(26B)	1.3(16)
C(19B)–C(20B)–C(21B)–C(22B)	–179.5(10)
C(26B)–C(21B)–C(22B)–C(23B)	–1(2)
C(20B)–C(21B)–C(22B)–C(23B)	179.9(11)
C(21B)–C(22B)–C(23B)–C(24B)	3(3)
C(22B)–C(23B)–C(24B)–C(25B)	–5(5)
C(23B)–C(24B)–C(25B)–C(26B)	4(5)
C(22B)–C(21B)–C(26B)–C(27B)	178.5(11)
C(20B)–C(21B)–C(26B)–C(27B)	–2.4(18)
C(22B)–C(21B)–C(26B)–C(25B)	0.4(19)
C(20B)–C(21B)–C(26B)–C(25B)	179.5(11)
C(24B)–C(25B)–C(26B)–C(27B)	–180(3)
C(24B)–C(25B)–C(26B)–C(21B)	–2(3)
C(21B)–C(26B)–C(27B)–C(28B)	2.8(17)
C(25B)–C(26B)–C(27B)–C(28B)	–179.5(12)
C(26B)–C(27B)–C(28B)–C(19B)	–1.9(15)
C(20B)–C(19B)–C(28B)–C(27B)	0.8(15)
C(18)–C(19B)–C(28B)–C(27B)	175.8(8)

Symmetry transformations used to generate equivalent atoms

A.2 (*S*)-2-(2,4-Dimethoxyphenyl)cyclohexanone

See Tables A.7, A.8, A.9, A.10, A.11 and A.12.





2

Table A.7 Crystal data and structure refinement for **2**

Identification code	gui83
Empirical formula	C14 H18 O3
Formula weight	234.28
Temperature	100(2) K
Wavelength	1.54184 Å
Crystal system	Monoclinic
Space group	P21 (#4)
Unit cell dimensions	a = 8.9801(1) Å, α = 90°
	b = 6.8503(1) Å, β = 102.746(2)°
	c = 10.1338(2) Å, γ = 90°
Volume	608.033(16) $Å^3$
Z	2
Density (calculated)	1.280 Mg/m^3
Absorption coefficient	0.718 mm^{-1}
F(000)	252

(continued)

Table A.7 (continued)

Identification code	gui83
Crystal size	0.1919 × 0.1348 × 0.0779 mm^3
Theta range for data collection	4.47°–76.78°.
Index ranges	–11 ≤ h ≤ 11, –8 ≤ k ≤ 8, –12 ≤ l ≤ 12
Reflections collected	25,286
Independent reflections	2555 [R(int) = 0.0237]
Completeness to theta = 76.78°	99.9 %
Absorption correction	Analytical
Max. and min. transmission	0.951 and 0.897
Refinement method	Full–matrix least–squares on F2
Data/restraints/parameters	2555/1/156
Goodness–of–fit on F2	1.068
Final R indices [I > 2 sigma(I)]	R1 = 0.0434, wR2 = 0.1223
R indices (all data)	R1 = 0.0441, wR2 = 0.1234
Absolute structure parameter	–0.1(2)
Largest diff. peak and hole	0.418 and –0.209 e $Å^{-3}$

Table A.8 Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **2**

Atom	x	y	z	U(eq)
C(1)	7544(2)	2026(2)	1298(1)	22(1)
O(1)	8953(1)	2003(2)	980(1)	28(1)
C(7)	9001(2)	2029(5)	–414(2)	42(1)
C(2)	6158(2)	2045(3)	342(1)	21(1)
C(3)	4795(2)	2024(2)	795(1)	20(1)
O(2)	3387(1)	2018(2)	–67(1)	23(1)
C(8)	3328(2)	2021(3)	–1490(1)	24(1)
C(4)	4793(2)	2010(2)	2180(1)	20(1)
C(9)	3327(2)	1960(3)	2675(1)	20(1)
C(10)	3026(2)	–61(2)	3206(2)	23(1)
O(3)	3848(1)	–1456(2)	3186(1)	31(1)
C(11)	1599(2)	–198(3)	3770(2)	27(1)
C(12)	1599(2)	1394(3)	4834(2)	31(1)
C(13)	1783(2)	3400(3)	4261(2)	31(1)
C(14)	3266(2)	3523(3)	3759(2)	29(1)
C(5)	6205(2)	2010(3)	3097(1)	22(1)
C(6)	7569(2)	2017(3)	2677(1)	23(1)

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor

Table A.9 Bond lengths [Å] and angles [°] for **2**

C(1)–O(1)	1.3731(16)
C(1)–C(6)	1.3924(19)
C(1)–C(2)	1.3986(19)
O(1)–C(7)	1.4227(18)
C(7)–H(7A)	0.9800
C(7)–H(7B)	0.9800
C(7)–H(7C)	0.9800
C(2)–C(3)	1.3986(18)
C(2)–H(2)	0.9500
C(3)–O(2)	1.3691(16)
C(3)–C(4)	1.4042(19)
O(2)–C(8)	1.4320(16)
C(8)–H(8A)	0.9800
C(8)–H(8B)	0.9800
C(8)–H(8C)	0.9800
C(4)–C(5)	1.3969(19)
C(4)–C(9)	1.5083(17)
C(9)–C(10)	1.531(2)
C(9)–C(14)	1.543(2)
C(9)–H(9)	1.0000
C(10)–O(3)	1.210(2)
C(10)–C(11)	1.517(2)
C(11)–C(12)	1.534(3)
C(11)–H(11A)	0.9900
C(11)–H(11B)	0.9900
C(12)–C(13)	1.515(3)
C(12)–H(12A)	0.9900
C(12)–H(12B)	0.9900
C(13)–C(14)	1.529(2)
C(13)–H(13A)	0.9900
C(13)–H(13B)	0.9900
C(14)–H(14A)	0.9900
C(14)–H(14B)	0.9900
C(5)–C(6)	1.3834(19)
C(5)–H(5)	0.9500
C(6)–H(6)	0.9500
O(1)–C(1)–C(6)	115.06(12)
O(1)–C(1)–C(2)	124.25(12)
C(6)–C(1)–C(2)	120.69(12)
C(1)–O(1)–C(7)	117.67(11)
O(1)–C(7)–H(7A)	109.5

(continued)

Table A.9 (continued)

O(1)–C(7)–H(7B)	109.5
H(7A)–C(7)–H(7B)	109.5
O(1)–C(7)–H(7C)	109.5
H(7A)–C(7)–H(7C)	109.5
H(7B)–C(7)–H(7C)	109.5
C(1)–C(2)–C(3)	118.80(12)
C(1)–C(2)–H(2)	120.6
C(3)–C(2)–H(2)	120.6
O(2)–C(3)–C(2)	122.87(12)
O(2)–C(3)–C(4)	115.63(12)
C(2)–C(3)–C(4)	121.50(12)
C(3)–O(2)–C(8)	117.76(10)
O(2)–C(8)–H(8A)	109.5
O(2)–C(8)–H(8B)	109.5
H(8A)–C(8)–H(8B)	109.5
O(2)–C(8)–H(8C)	109.5
H(8A)–C(8)–H(8C)	109.5
H(8B)–C(8)–H(8C)	109.5
C(5)–C(4)–C(3)	117.64(12)
C(5)–C(4)–C(9)	120.60(11)
C(3)–C(4)–C(9)	121.75(11)
C(4)–C(9)–C(10)	111.83(13)
C(4)–C(9)–C(14)	113.08(13)
C(10)–C(9)–C(14)	109.87(13)
C(4)–C(9)–H(9)	107.2
C(10)–C(9)–H(9)	107.2
C(14)–C(9)–H(9)	107.2
O(3)–C(10)–C(11)	121.75(15)
O(3)–C(10)–C(9)	123.54(14)
C(11)–C(10)–C(9)	114.71(13)
C(10)–C(11)–C(12)	110.57(14)
C(10)–C(11)–H(11A)	109.5
C(12)–C(11)–H(11A)	109.5
C(10)–C(11)–H(11B)	109.5
C(12)–C(11)–H(11B)	109.5
H(11A)–C(11)–H(11B)	108.1
C(13)–C(12)–C(11)	111.01(13)
C(13)–C(12)–H(12A)	109.4
C(11)–C(12)–H(12A)	109.4
C(13)–C(12)–H(12B)	109.4
C(11)–C(12)–H(12B)	109.4
H(12A)–C(12)–H(12B)	108.0

(continued)

Table A.9 (continued)

C(12)–C(13)–C(14)	110.74(15)
C(12)–C(13)–H(13A)	109.5
C(14)–C(13)–H(13A)	109.5
C(12)–C(13)–H(13B)	109.5
C(14)–C(13)–H(13B)	109.5
H(13A)–C(13)–H(13B)	108.1
C(13)–C(14)–C(9)	111.70(13)
C(13)–C(14)–H(14A)	109.3
C(9)–C(14)–H(14A)	109.3
C(13)–C(14)–H(14B)	109.3
C(9)–C(14)–H(14B)	109.3
H(14A)–C(14)–H(14B)	107.9
C(6)–C(5)–C(4)	122.05(12)
C(6)–C(5)–H(5)	119.0
C(4)–C(5)–H(5)	119.0
C(5)–C(6)–C(1)	119.31(12)
C(5)–C(6)–H(6)	120.3
C(1)–C(6)–H(6)	120.3

Symmetry transformations used to generate equivalent atoms

Table A.10 Anisotropic displacement parameters ($Å_2 \times 10^3$) for **2**

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	18(1)	28(1)	21(1)	1(1)	8(1)	0(1)
O(1)	17(1)	48(1)	19(1)	3(1)	7(1)	1(1)
C(7)	23(1)	85(2)	22(1)	5(1)	11(1)	2(1)
C(2)	22(1)	26(1)	16(1)	1(1)	6(1)	0(1)
C(3)	19(1)	22(1)	18(1)	1(1)	3(1)	0(1)
O(2)	18(1)	34(1)	15(1)	–1(1)	3(1)	0(1)
C(8)	23(1)	33(1)	15(1)	–1(1)	3(1)	0(1)
C(4)	18(1)	24(1)	19(1)	–1(1)	6(1)	–1(1)
C(9)	17(1)	26(1)	17(1)	0(1)	5(1)	0(1)
C(10)	23(1)	28(1)	20(1)	–2(1)	5(1)	–1(1)
O(3)	31(1)	28(1)	36(1)	0(1)	11(1)	1(1)
C(11)	23(1)	33(1)	28(1)	5(1)	9(1)	–2(1)
C(12)	22(1)	51(1)	21(1)	–3(1)	8(1)	1(1)
C(13)	21(1)	39(1)	34(1)	–16(1)	9(1)	–1(1)
C(14)	22(1)	31(1)	36(1)	–13(1)	11(1)	–5(1)
C(5)	21(1)	28(1)	16(1)	2(1)	5(1)	1(1)
C(6)	19(1)	31(1)	19(1)	3(1)	3(1)	0(1)

The anisotropic displacement factor exponent takes the form: $-2\pi^2[\, h^2\, a*^2\, U^{11} + \cdots +\ 2\ h\ k\ a\ *\ b*\ U^{12}\,]$

Table A.11 Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for **2**

Atom	x	y	z	U(eq)
H(7A)	8465	882	–865	63
H(7B)	10,066	2005	–501	63
H(7C)	8504	3218	–836	63
H(2)	6142	2071	–598	25
H(8A)	3880	3161	–1721	35
H(8B)	2262	2078	–1989	35
H(8C)	3804	827	–1736	35
H(9)	2475	2245	1880	24
H(11A)	1552	–1499	4185	33
H(11B)	685	–50	3026	33
H(12A)	628	1341	5143	37
H(12B)	2446	1153	5626	37
H(13A)	1794	4400	4969	37
H(13B)	905	3674	3503	37
H(14A)	4145	3344	4532	35
H(14B)	3350	4835	3372	35
H(5)	6228	2005	4039	26
H(6)	8514	2015	3322	27

Table A.12 Torsion angles [°] for **2**

C(6)–C(1)–O(1)–C(7)	–179.42(19)
C(2)–C(1)–O(1)–C(7)	1.0(3)
O(1)–C(1)–C(2)–C(3)	178.61(16)
C(6)–C(1)–C(2)–C(3)	–1.0(3)
C(1)–C(2)–C(3)–O(2)	–179.25(16)
C(1)–C(2)–C(3)–C(4)	0.8(2)
C(2)–C(3)–O(2)–C(8)	0.4(2)
C(4)–C(3)–O(2)–C(8)	–179.64(13)
O(2)–C(3)–C(4)–C(5)	179.84(15)
C(2)–C(3)–C(4)–C(5)	–0.2(2)
O(2)–C(3)–C(4)–C(9)	0.9(2)
C(2)–C(3)–C(4)–C(9)	–179.18(16)
C(5)–C(4)–C(9)–C(10)	–74.1(2)
C(3)–C(4)–C(9)–C(10)	104.80(16)
C(5)–C(4)–C(9)–C(14)	50.5(2)
C(3)–C(4)–C(9)–C(14)	–130.53(16)
C(4)–C(9)–C(10)–O(3)	–2.2(2)
C(14)–C(9)–C(10)–O(3)	–128.65(16)

(continued)

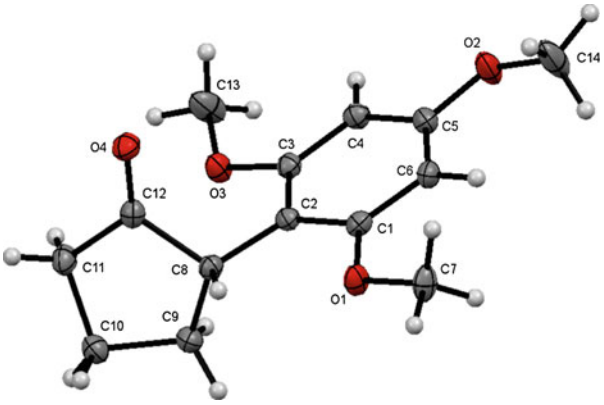
Table A.12 (continued)

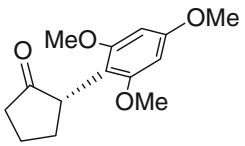
C(4)–C(9)–C(10)–C(11)	177.83(12)
C(14)–C(9)–C(10)–C(11)	51.40(17)
O(3)–C(10)–C(11)–C(12)	127.33(17)
C(9)–C(10)–C(11)–C(12)	–52.71(18)
C(10)–C(11)–C(12)–C(13)	55.15(18)
C(11)–C(12)–C(13)–C(14)	–58.43(17)
C(12)–C(13)–C(14)–C(9)	57.80(19)
C(4)–C(9)–C(14)–C(13)	–178.65(14)
C(10)–C(9)–C(14)–C(13)	–52.93(19)
C(3)–C(4)–C(5)–C(6)	–0.2(3)
C(9)–C(4)–C(5)–C(6)	178.74(15)
C(4)–C(5)–C(6)–C(1)	0.1(3)
O(1)–C(1)–C(6)–C(5)	–179.07(16)
C(2)–C(1)–C(6)–C(5)	0.5(3)

Symmetry transformations used to generate equivalent atoms

A.3 (S)-2-(2,4,6-trimethoxyphenyl)cyclopentanone

See Tables A.13, A.14, A.15, A.16, A.17 and A.18.





3

Table A.13 Crystal data and structure refinement for **3**

Identification code	gui85
Empirical formula	C14 H18 O4
Formula weight	250.28
Temperature	100(2) K
Wavelength	1.54184 Å
Crystal system	Monoclinic
Space group	P21 (#4)
Unit cell dimensions	a = 8.15690(7) Å, α = 90°
	b = 9.74184(8) Å, β = 101.4282(7)°
	c = 8.33981(6) Å, γ = 90°
Volume	649.569(9) $Å^3$
Z	2
Density (calculated)	1.280 Mg/m^3
Absorption coefficient	0.766 mm^{-1}
F(000)	268
Crystal size	0.1735 × 0.1501 × 0.1229 mm^3
Theta range for data collection	5.41–76.72°
Index ranges	$-10 \leq h \leq 10$, $-12 \leq k \leq 12$, $-10 \leq l \leq 10$
Reflections collected	13,437
Independent reflections	2700 [R(int) = 0.0236]
Completeness to theta = 76.72°	99.6 %
Absorption correction	Analytical
Max. and min. transmission	0.933 and 0.912
Refinement method	Full–matrix least–squares on F2
Data/restraints/parameters	2700/1/167
Goodness–of–fit on F2	1.058
Final R indices [I >2 sigma(I)]	R1 = 0.0267, wR2 = 0.0700
R indices (all data)	R1 = 0.0277, wR2 = 0.0710
Absolute structure parameter	0.09(12)
Extinction coefficient	0.0117(11)
Largest diff. peak and hole	0.205 and –0.130 e $Å^{-3}$

Table A.14 Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **3**

Atom	x	y	z	U(eq)
O(1)	4380(1)	–1219(1)	8791(1)	22(1)
O(2)	–834(1)	895(1)	9457(1)	30(1)
O(3)	1948(1)	2195(1)	5178(1)	22(1)
O(4)	2455(1)	–617(1)	3523(1)	23(1)
C(1)	3055(1)	–344(1)	8353(1)	17(1)
C(2)	3071(1)	439(1)	6954(1)	17(1)
C(3)	1797(1)	1415(1)	6513(1)	18(1)
C(4)	505(1)	1568(1)	7361(1)	19(1)
C(5)	507(1)	720(1)	8711(1)	20(1)
C(6)	1774(2)	–222(1)	9243(1)	20(1)
C(7)	4374(2)	–2128(1)	10133(2)	25(1)
C(8)	4378(1)	252(1)	5931(1)	17(1)
C(9)	5682(1)	1405(1)	6006(1)	22(1)
C(10)	6255(2)	1306(1)	4361(2)	24(1)
C(11)	4639(2)	978(1)	3137(2)	24(1)
C(12)	3627(1)	108(1)	4099(1)	19(1)
C(13)	588(2)	3038(2)	4454(2)	35(1)
C(14)	–1057(2)	–114(2)	10649(2)	44(1)

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor

Table A.15 Bond lengths [Å] and angles [°] for **3**

O(1)–C(1)	1.3684(14)
O(1)–C(7)	1.4282(14)
O(2)–C(5)	1.3717(14)
O(2)–C(14)	1.4349(17)
O(3)–C(3)	1.3733(13)
O(3)–C(13)	1.4152(15)
O(4)–C(12)	1.2088(15)
C(1)–C(2)	1.3959(15)
C(1)–C(6)	1.4020(16)
C(2)–C(3)	1.4028(16)
C(2)–C(8)	1.5025(15)
C(3)–C(4)	1.3885(16)
C(4)–C(5)	1.3964(16)
C(4)–H(4)	0.9500
C(5)–C(6)	1.3877(17)
C(6)–H(6)	0.9500
C(7)–H(7A)	0.9800

(continued)

Table A.15 (continued)

C(7)–H(7B)	0.9800
C(7)–H(7C)	0.9800
C(8)–C(12)	1.5354(15)
C(8)–C(9)	1.5394(16)
C(8)–H(8)	1.0000
C(9)–C(10)	1.5382(16)
C(9)–H(9A)	0.9900
C(9)–H(9B)	0.9900
C(10)–C(11)	1.5320(17)
C(10)–H(10A)	0.9900
C(10)–H(10B)	0.9900
C(11)–C(12)	1.5189(16)
C(11)–H(11A)	0.9900
C(11)–H(11B)	0.9900
C(13)–H(13A)	0.9800
C(13)–H(13B)	0.9800
C(13)–H(13C)	0.9800
C(14)–H(14A)	0.9800
C(14)–H(14B)	0.9800
C(14)–H(14C)	0.9800
C(1)–O(1)–C(7)	118.06(9)
C(5)–O(2)–C(14)	116.82(10)
C(3)–O(3)–C(13)	118.59(10)
O(1)–C(1)–C(2)	115.22(10)
O(1)–C(1)–C(6)	122.92(10)
C(2)–C(1)–C(6)	121.86(10)
C(1)–C(2)–C(3)	117.40(10)
C(1)–C(2)–C(8)	122.24(10)
C(3)–C(2)–C(8)	120.36(10)
O(3)–C(3)–C(4)	123.51(10)
O(3)–C(3)–C(2)	114.01(10)
C(4)–C(3)–C(2)	122.48(10)
C(3)–C(4)–C(5)	117.88(10)
C(3)–C(4)–H(4)	121.1
C(5)–C(4)–H(4)	121.1
O(2)–C(5)–C(6)	123.19(11)
O(2)–C(5)–C(4)	114.75(10)
C(6)–C(5)–C(4)	122.06(11)
C(5)–C(6)–C(1)	118.21(11)
C(5)–C(6)–H(6)	120.9
C(1)–C(6)–H(6)	120.9
O(1)–C(7)–H(7A)	109.5
O(1)–C(7)–H(7B)	109.5

(continued)

Table A.15 (continued)

H(7A)–C(7)–H(7B)	109.5
O(1)–C(7)–H(7C)	109.5
H(7A)–C(7)–H(7C)	109.5
H(7B)–C(7)–H(7C)	109.5
C(2)–C(8)–C(12)	112.83(9)
C(2)–C(8)–C(9)	116.76(10)
C(12)–C(8)–C(9)	104.08(9)
C(2)–C(8)–H(8)	107.6
C(12)–C(8)–H(8)	107.6
C(9)–C(8)–H(8)	107.6
C(10)–C(9)–C(8)	104.33(10)
C(10)–C(9)–H(9A)	110.9
C(8)–C(9)–H(9A)	110.9
C(10)–C(9)–H(9B)	110.9
C(8)–C(9)–H(9B)	110.9
H(9A)–C(9)–H(9B)	108.9
C(11)–C(10)–C(9)	103.54(10)
C(11)–C(10)–H(10A)	111.1
C(9)–C(10)–H(10A)	111.1
C(11)–C(10)–H(10B)	111.1
C(9)–C(10)–H(10B)	111.1
H(10A)–C(10)–H(10B)	109.0
C(12)–C(11)–C(10)	104.48(10)
C(12)–C(11)–H(11A)	110.9
C(10)–C(11)–H(11A)	110.9
C(12)–C(11)–H(11B)	110.9
C(10)–C(11)–H(11B)	110.9
H(11A)–C(11)–H(11B)	108.9
O(4)–C(12)–C(11)	125.86(10)
O(4)–C(12)–C(8)	125.23(10)
C(11)–C(12)–C(8)	108.87(10)
O(3)–C(13)–H(13A)	109.5
O(3)–C(13)–H(13B)	109.5
H(13A)–C(13)–H(13B)	109.5
O(3)–C(13)–H(13C)	109.5
H(13A)–C(13)–H(13C)	109.5
H(13B)–C(13)–H(13C)	109.5
O(2)–C(14)–H(14A)	109.5
O(2)–C(14)–H(14B)	109.5
H(14A)–C(14)–H(14B)	109.5
O(2)–C(14)–H(14C)	109.5
H(14A)–C(14)–H(14C)	109.5
H(14B)–C(14)–H(14C)	109.5

Table A.16 Anisotropic displacement parameters ($Å^2 \times 10^3$) for **3**

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	24(1)	24(1)	19(1)	8(1)	6(1)	7(1)
O(2)	23(1)	43(1)	27(1)	12(1)	12(1)	9(1)
O(3)	22(1)	22(1)	22(1)	9(1)	7(1)	5(1)
O(4)	25(1)	24(1)	20(1)	–1(1)	3(1)	–5(1)
C(1)	19(1)	17(1)	16(1)	–1(1)	1(1)	0(1)
C(2)	17(1)	17(1)	16(1)	–1(1)	3(1)	–1(1)
C(3)	19(1)	17(1)	16(1)	1(1)	3(1)	–2(1)
C(4)	18(1)	19(1)	20(1)	1(1)	3(1)	2(1)
C(5)	18(1)	24(1)	19(1)	–1(1)	5(1)	–1(1)
C(6)	21(1)	24(1)	15(1)	2(1)	4(1)	–1(1)
C(7)	37(1)	21(1)	18(1)	6(1)	8(1)	7(1)
C(8)	17(1)	17(1)	16(1)	2(1)	3(1)	1(1)
C(9)	19(1)	26(1)	20(1)	1(1)	4(1)	–3(1)
C(10)	22(1)	27(1)	24(1)	2(1)	8(1)	–2(1)
C(11)	29(1)	25(1)	18(1)	2(1)	7(1)	–5(1)
C(12)	22(1)	17(1)	17(1)	1(1)	5(1)	3(1)
C(13)	24(1)	40(1)	42(1)	24(1)	8(1)	9(1)
C(14)	28(1)	68(1)	41(1)	29(1)	20(1)	15(1)

The anisotropic displacement factor exponent takes the form: $-2\pi^2[\, h^2\, a*^2\, U^{11} + \cdots + 2\, h\, k\, a*\, b*\, U^{12}\,]$

Table A.17 Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for **3**

Atom	x	y	z	U(eq)
H(4)	–351	2230	7034	23
H(6)	1773	–770	10,185	24
H(7A)	4366	–1592	11,126	37
H(7B)	5377	–2706	10,298	37
H(7C)	3375	–2710	9898	37
H(8)	4996	–616	6294	20
H(9A)	5175	2312	6131	26
H(9B)	6633	1260	6931	26
H(10A)	6744	2185	4087	29
H(10B)	7091	566	4382	29
H(11A)	4031	1831	2739	28
H(11B)	4883	463	2187	28
H(13A)	–396	2465	4060	52
H(13B)	881	3543	3534	52
H(13C)	339	3690	5268	52
H(14A)	–1014	–1035	10,184	66
H(14B)	–2145	23	10,956	66
H(14C)	–166	–20	11,620	66

Table A.18 Torsion angles [°] for **3**

C(7)–O(1)–C(1)–C(2)	–175.12(10)
C(7)–O(1)–C(1)–C(6)	5.47(16)
O(1)–C(1)–C(2)–C(3)	–176.06(10)
C(6)–C(1)–C(2)–C(3)	3.35(16)
O(1)–C(1)–C(2)–C(8)	4.61(15)
C(6)–C(1)–C(2)–C(8)	–175.97(11)
C(13)–O(3)–C(3)–C(4)	–11.00(17)
C(13)–O(3)–C(3)–C(2)	169.07(11)
C(1)–C(2)–C(3)–O(3)	176.61(10)
C(8)–C(2)–C(3)–O(3)	–4.05(15)
C(1)–C(2)–C(3)–C(4)	–3.32(16)
C(8)–C(2)–C(3)–C(4)	176.02(11)
O(3)–C(3)–C(4)–C(5)	–179.27(10)
C(2)–C(3)–C(4)–C(5)	0.65(17)
C(14)–O(2)–C(5)–C(6)	–11.23(19)
C(14)–O(2)–C(5)–C(4)	168.83(13)
C(3)–C(4)–C(5)–O(2)	–177.90(11)
C(3)–C(4)–C(5)–C(6)	2.15(17)
O(2)–C(5)–C(6)–C(1)	177.96(11)
C(4)–C(5)–C(6)–C(1)	–2.11(18)
O(1)–C(1)–C(6)–C(5)	178.62(10)
C(2)–C(1)–C(6)–C(5)	–0.75(17)
C(1)–C(2)–C(8)–C(12)	130.54(11)
C(3)–C(2)–C(8)–C(12)	–48.77(14)
C(1)–C(2)–C(8)–C(9)	–108.93(12)
C(3)–C(2)–C(8)–C(9)	71.76(13)
C(2)–C(8)–C(9)–C(10)	–154.08(10)
C(12)–C(8)–C(9)–C(10)	–29.02(12)
C(8)–C(9)–C(10)–C(11)	38.89(12)
C(9)–C(10)–C(11)–C(12)	–33.12(13)
C(10)–C(11)–C(12)–O(4)	–162.40(12)
C(10)–C(11)–C(12)–C(8)	15.32(13)
C(2)–C(8)–C(12)–O(4)	–46.20(16)
C(9)–C(8)–C(12)–O(4)	–173.74(12)
C(2)–C(8)–C(12)–C(11)	136.06(11)
C(9)–C(8)–C(12)–C(11)	8.52(13)