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Alkaloid Synthesis

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309

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Aims and Scope

The series *Topics in Current Chemistry* presents critical reviews of the present and future trends in modern chemical research. The scope includes all areas of chemical science, including the interfaces with related disciplines such as biology, medicine, and materials science.

The objective of each thematic volume is to give the non-specialist reader, whether at the university or in industry, a comprehensive overview of an area where new insights of interest to a larger scientific audience are emerging.

Thus each review within the volume critically surveys one aspect of that topic and places it within the context of the volume as a whole. The most significant developments of the last 5–10 years are presented, using selected examples to illustrate the principles discussed. A description of the laboratory procedures involved is often useful to the reader. The coverage is not exhaustive in data, but rather conceptual, concentrating on the methodological thinking that will allow the non-specialist reader to understand the information presented.

Discussion of possible future research directions in the area is welcome.

Review articles for the individual volumes are invited by the volume editors.

In references *Topics in Current Chemistry* is abbreviated *Top Curr Chem* and is cited as a journal.

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Preface

Natural product chemistry very often stimulates the development of novel pharmaceutical drugs. In fact, the vast majority of new lead structures in medicinal chemistry are derived from frameworks of naturally occurring compounds. In this respect alkaloids lead the way and consequently a breathtaking progress in the chemistry of alkaloids has taken place over the last century. Especially over the past decades, we can follow the evolution of numerous novel synthetic methodologies for the total synthesis of biologically active alkaloids. Due to space limitation, of course only a few aspects of some recent developments in "Alkaloid Synthesis" could be highlighted in the present volume of *Topics in Current Chemistry*. In six contributions, different research teams from Austria, Australia, Canada, Japan and Germany have summarized important achievements of the past decade.

In the first chapter, Mariko Kitajima and Hiromitsu Takayama from the Graduate School of Pharmaceutical Sciences at Chiba University in Japan describe the isolation and asymmetric synthesis of *Lycopodium* alkaloids. The following chapter is a joint contribution by Uwe Rinner from the Institute of Organic Chemistry at the University of Vienna in Austria and Tomas Hudlicky from the Department of Chemistry and Centre of Biotechnology at Brock University in St. Catharines, Canada. They discuss recent developments in the synthesis of morphine alkaloids and derivatives. Thomas Lindel, Nils Marsch and Santosh Kumar Adla from the Institute of Organic Chemistry at the Technical University of Braunschweig describe important aspects of indole prenylation in alkaloid synthesis. Yasuyuki Kita from the College of Pharmaceutical Sciences at Ritsumeikan University in Shiga, Japan, and Hiromichi Fujioka from the Graduate School of Pharmaceutical Sciences at Osaka University in Japan compiled in their joint chapter the synthesis of marine pyrroloiminoquinone alkaloids. The penultimate chapter by Martin G. Banwell, Nadia Gao, Brett D. Schwarz and Lorenzo V. White from the Research School of Chemistry and Institute of Advanced Studies at The Australian National University in Canberra, Australia, report on *Amaryllidaceae* and other terrestrially-derived alkaloids. Finally, an article with Ingmar Bauer as co-author from our own laboratories of the Department of Chemistry at the Technical University of Dresden

in Germany outlines recent developments in the synthesis of pyrrole and carbazole alkaloids.

I am very grateful to all authors and co-authors of this special volume of *Topics in Current Chemistry* for their contributions and for their efforts to meet the timelines. I am convinced that the present compilation of recent developments in "Alkaloid Synthesis" represents a useful and stimulating reference source not only for researchers active in this field but also for young scientists and students.

Dresden Hans-Joachim Knölker
August 2011

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Lycopodium Alkaloids: Isolation and Asymmetric Synthesis

Mariko Kitajima and Hiromitsu Takayama

Abstract *Lycopodium* alkaloids have attracted the attention of many natural product chemists and synthetic organic chemists due to their important biological activities and unique skeletal characteristics. In this review we describe isolation and asymmetric syntheses of several new alkaloids such as lycoposerramines-C, -V, -W, and cernuine, and show that asymmetric total synthesis played a key role in elucidating the structures of these complex natural products.

Keywords Alkaloid · Asymmetric synthesis · Isolation · *Lycopodium* · Structure elucidation

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Abbreviations

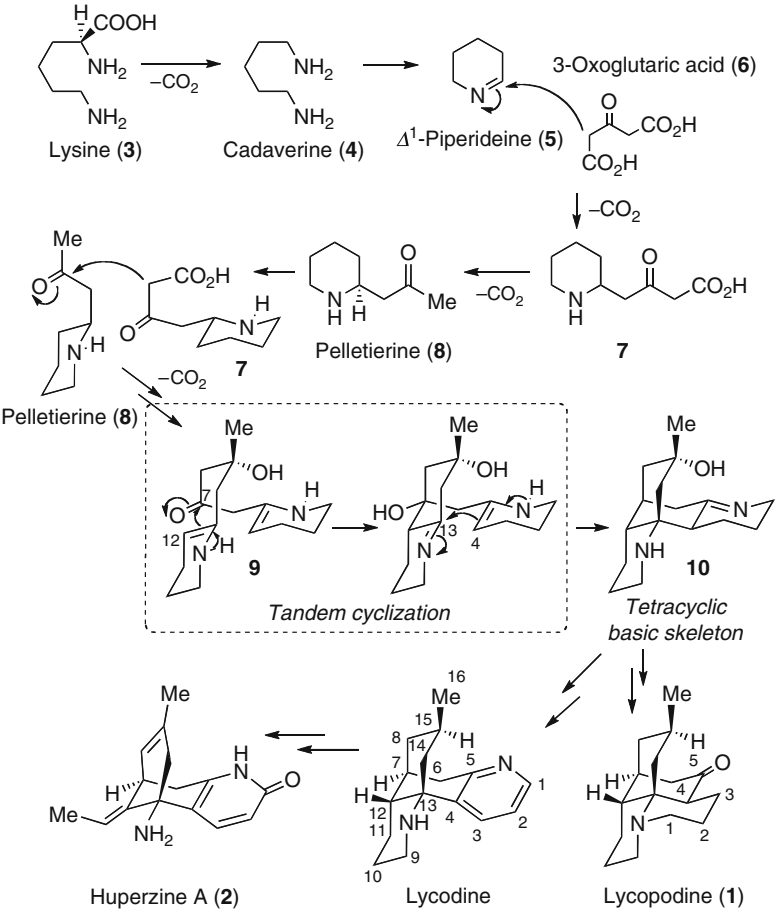
AChE	Acetylcholine esterase
CBS	Corey–Bakshi–Shibata
CDI	Carbonyl diimidazole
DIAD	Diisopropyl azodicarboxylate
DMP	Dess–Martin periodinane
DPPA	Diphenylphosphinyl azide
dppf	1,1′-Bis(diphenylphosphino)ferrocene
DTAD	Di-*tert*-butyl azodicarboxylate
IBX	2-Iodoxybenzoic acid
Ipc	Isopinocampheyl
NMO	*N*-Methylmorpholine oxide
Ns	Nosyl
TASF	Tris(dimethylamino)sulfonium difluorotrimethylsilicate
Teoc	2-(Trimethylsilyl)ethoxycarbonyl

1 Introduction

Plants belonging to the genus *Lycopodium*, Family Lycopodiaceae, are widely distributed all over the world. More than 500 species exist and many of them thrive in tropical regions. Since Bödeker isolated lycopodine (**1**) from *Lycopodium complanatum* in 1881 [1], chemical investigations of the constituents of *Lycopodium* plants have been energetically carried out by many groups [2–12].

Among the alkaloids in *Lycopodium* plants, huperzine A (**2**) was isolated from *Lycopodium serratum* Thunb. in 1986 and has been shown to have acetylcholine esterase (AChE) inhibitory activity and to improve memory disorders in Alzheimer's disease [13–15]. In addition to these unique activities, it was recently reported that some *Lycopodium* alkaloids possessing skeletons different from that of huperzine A (**2**) are able to enhance nerve growth factor (NFG) mRNA expression and production in human glial cells [16, 17]. Because of their useful biological activities, *Lycopodium* alkaloids are an attractive target in natural product chemistry, synthetic chemistry, and medicinal chemistry.

Hemscheidt and Spenser conducted feeding experiments and found that *Lycopodium* alkaloids are secondary metabolites of lysine (**3**) [18] (Scheme 1). The decarboxylation of lysine (**3**) yields cadaverine (**4**), which consists of five carbons, and this, in turn, is converted into Δ^1-piperideine (**5**). The condensation of Δ^1-piperideine (**5**) with 3-oxoglutaric acid (**6**) produces 4-(2-piperidyl)acetoacetic acid (**7**) and this is converted into pelletierine (**8**) after a decarboxylation reaction. The biosynthetic process from this point to structurally complex *Lycopodium* alkaloids, such as lycopodine (**1**) and huperzine A (**2**), is deduced from the structures of the isolated alkaloids. The condensation of pelletierine (**8**) with 4-(2-piperidyl)



Scheme 1 Hypothetical biogetetic route of *Lycopodium* alkaloids

acetoacetic acid (**7**) and the successive oxidation would afford intermediate **9** having two enamine functions in the molecule. Intramolecular tandem cyclization would produce plausible biosynthetic intermediate **10** having a tetracyclic basic skeleton. From this key intermediate, more than 250 *Lycopodium* alkaloids would be derived by further re-cyclization, oxidation, and/or rearrangement. Huperzine A (**2**) mentioned above belongs to the lycodine-type alkaloids.

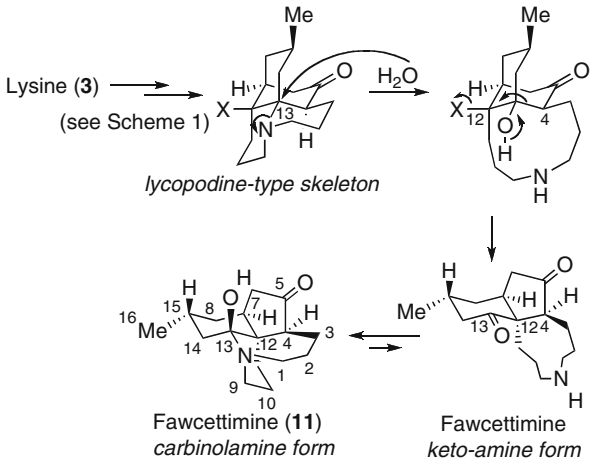
The highly diverse and unique skeletal characteristics of *Lycopodium* alkaloids have inspired many groups to design total syntheses of these alkaloids. However, there are very few reports of their biological activities. Recently, we have initiated a chemical investigation of *Lycopodium* plants, including structure elucidation and total syntheses, to find seed and lead molecules for drug development. In this review we describe the results of our chemical investigation of some new alkaloids isolated from *L. serratum* Thunb. and *Lycopodium cernuum* L., both of which were collected in Japan.

2 Fawcettimine-Type Alkaloids

Fawcettimine-type alkaloids possess a $C_{16}N_1$ skeleton and are considered to be derived from the lycopodine skeleton (Scheme 2). Initially, the nucleophilic attack of water on C-13 of the lycopodine skeleton, followed by C-13–N bond scission, would occur. Next, the Wagner–Meerwein rearrangement would proceed to form the fawcettimine skeleton. Fawcettimine (**11**) exists as an equilibrium mixture of the carbinolamine form and the keto-amine form. A number of fawcettimine-type alkaloids derived from each form have been isolated from nature.

2.1 Lycoposerramine-A

New alkaloid **12**, named lycoposerramine-A [19], was found to have the molecular formula $C_{18}H_{29}N_3O_2$. In its ^{13}C NMR spectra, the chemical shift of the carbonyl carbon signal (δ_C 157.0) indicated the existence of a novel urethane function in the molecule. Furthermore, the characteristic signal at δ_C 88.6 implied the presence of an sp^3 carbon that had an aminoacetal function. ^1H-^1H COSY, HMQC, and HMBC spectral data (Fig. 1) enabled us to construct the basic skeleton of **12**, which consists of a fused tricyclic ring system with five- and six-membered cycloalkanes and 1-azacyclononane, retaining the fundamental backbone of the known alkaloid, fawcettimine (**11**) with the keto-amine form, as shown in Scheme 2. To construct the final structure of **12** by incorporating the remaining elements, i.e., one carbonyl, two nitrogens, and one oxygen atom, several candidates having the spectroscopic data mentioned above could be nominated. Finally, X-ray crystallographic analysis of **12** showed that lycoposerramine-A (**12**) is the first example of a natural product that contains a novel 1,2,4-oxadiazolidin-5-one residue in the molecule.



Scheme 2 Hypothetical biogenesis of fawcettimine

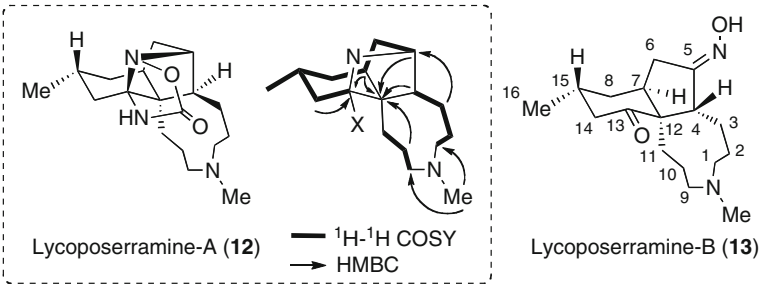
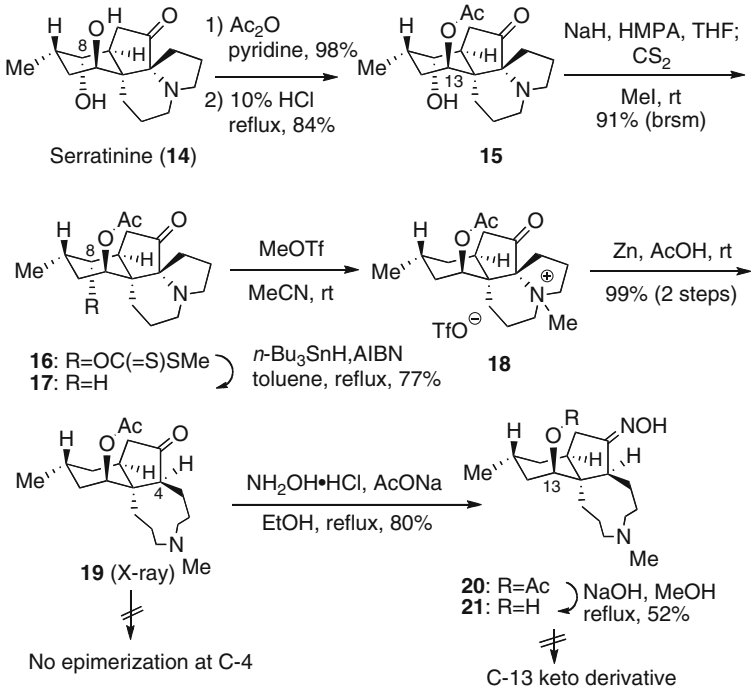


Fig. 1 Structures of lycoposerramines-A and -B

2.2 *Lycoposerramine-B*

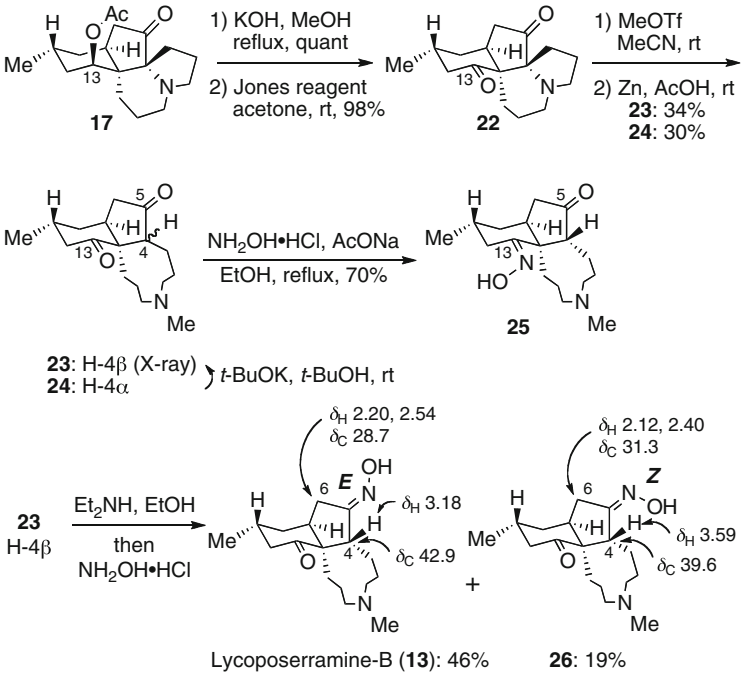
The new alkaloid **13**, named lycoposerramine-B [20], was deduced from NMR and MS data to have a fundamental skeleton of the fawcettimine keto-amine form with a ketone and an oxime function. The stereochemistry at C-7, C-12, and C-15 was assumed to be the same as those in fawcettimine (**11**) based on biogenetic speculation. The configuration at C-4 was inferred from *J*-resolved HMBC spectral data; an *anti* relationship between H-4 and C-7 and a *gauche* relationship between H-4 and C-13. To confirm the structure of **13** that was inferred by spectroscopic analysis, we attempted its synthesis from serratinine (**14**) [21–24], the structure and absolute configuration of which had been proven by X-ray analysis. Initially, according to the procedure reported in the literature [21–24], monoacetate **15** was prepared from serratinine (**14**) (Scheme 3). Then the free secondary hydroxyl group in **15** was removed according to Barton's procedure. Xanthate derivative **16** was exposed to radical conditions by using *n*-Bu_3SnH in the presence of AIBN to afford deoxy derivative **17**. Quaternary ammonium derivative **18**, which was prepared from **17**, was treated with Zn powder in AcOH to give ring-opening product **19** in high yield. The structure of **19** was established by X-ray crystallographic analysis, revealing that the stereochemistry at C-4 was (*S*), which was opposite to that of lycoposerramine-B (**13**). The epimerization at C-4 in **19** did not occur under basic conditions. On the other hand, **19** was converted into alcohol **21** by oximation and this was followed by deacetylation of resulting oxime **20**. The conversion of the hydroxy group at C-13 into the ketone failed in **21** due to a labile oxime function under the attempted oxidation conditions.

Therefore, we adopted an alternative strategy that featured regioselective oximation (Scheme 4). Initially, diketone derivative **22** was prepared from 8-deoxy compound **17** via removal of the acetyl group followed by oxidation of the resulting secondary alcohol, and then **22** was subjected to the reductive ring-opening reaction developed above. The conversion of **22** into a quaternary ammonium intermediate and the subsequent treatment with Zn powder in AcOH afforded two C-4 epimeric ring-opening compounds **23** and **24**. More polar compound **23** showed the desired



Scheme 3 Conversion of serratinine to tricyclic compounds

(*R*) configuration on C-4 (H-4β) by X-ray crystallographic analysis. On the other hand, **24** could be epimerized at C-4 under basic conditions, enabling the convergence of **24** having H-4α into desired **23** having H-4β. The oximation of diketone **23** with 1 equiv. of NH_2OH•HCl under conventional conditions gave undesired regioisomer **25** with an oxime function at C-13. This result suggested that the carbonyl function at C-13 in **23** was more reactive than that at C-5 toward the addition reaction of amine. On the basis of the difference in their reactivities, **23** was treated with Et_2NH in EtOH, followed by the addition of NH_2OH•HCl, to give lycoposerramine-B (**13**) as expected. All of the spectroscopic data, including the optical rotation of synthetic **13**, were identical with those of natural lycoposerramine-B. In this reaction, the geometrical isomer on the oxime function was also obtained in 19% yield. The *E/Z* geometry of the oxime function was estimated by comparing the chemical shifts of both protons and carbons. In the ^{1}H NMR spectra, the *syn* proton to the oxime hydroxy group showed a low-field shift compared to the *anti* proton due to the anisotropy effect of the oxime oxygen. In addition, the *syn* carbon showed a high-field shift compared to the *anti* carbon because of the γ-gauche effect of the oxime oxygen. According to this general rule, the *E/Z* geometry of the oxime function in **13** and **26** was decided by comparing the chemical shifts of the protons and carbons at C-4 and C-6.



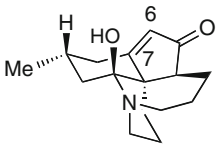
Scheme 4 Synthesis of lycoposerramine-B

2.3 *Lycoposerramine-C*

The structure of the new alkaloid **27**, named lycoposerramine-C [25], was deduced to be a fawcettimine-type alkaloid possessing a double bond at the C-6 and C-7 positions of fawcettimine (**11**), and was finally established by X-ray crystallographic analysis (Fig. 2). Although our preliminary biological screening indicated that **27** possesses potent AChE inhibitory activity, further examination of the activity has been restricted by its limited availability in nature. In order to develop an efficient synthetic route to **27** for further examination, we planned the asymmetric total synthesis of **27**.

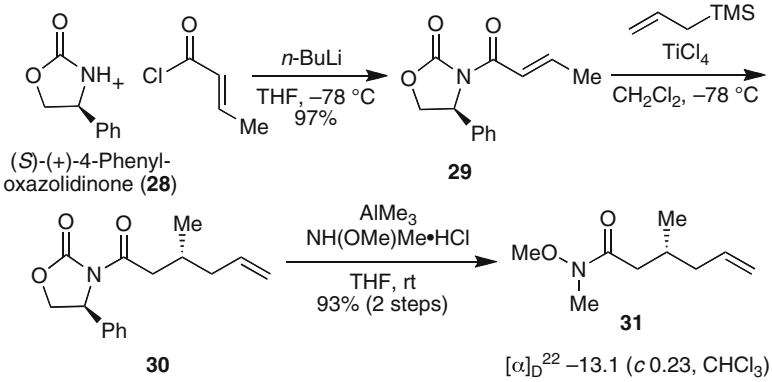
(*S*)-(+)-4-Phenyloxazolidinone (**28**) was acylated with crotonoyl chloride to give crotonamide **29** (Scheme 5). Diastereoselective Hosomi–Sakurai allylation of **29** with allyltrimethylsilane in the presence of $TiCl_4$ afforded compound **30** in a sufficient yield with a diastereomeric ratio of ca. 8:1. Next, the direct conversion of the oxazolidinone **30** into the Weinreb amide **31** was achieved using *N*,*O*-dimethylhydroxylamine.

The absolute configuration of the stereogenic center in Weinreb amide **31** ($[\alpha]_D^{22}$ −13.1 (*c* 0.23, $CHCl_3$)) was confirmed to be (*R*) by direct comparison with **31** ($[\alpha]_D^{22}$ −16.3 (*c* 0.08, $CHCl_3$)) prepared from (*R*)-(+)-citronellic acid (**32**) in six steps (Scheme 6).

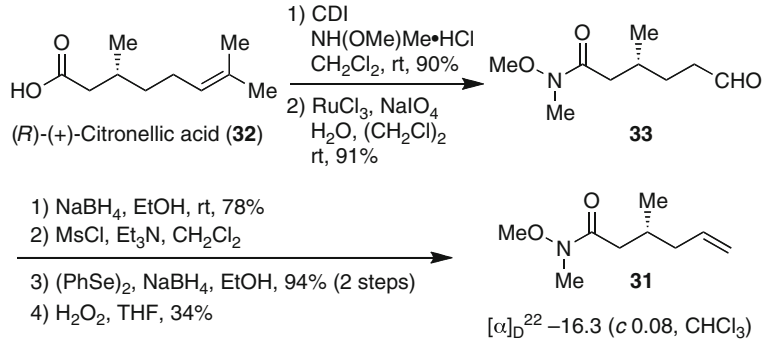


Lycoposerramine-C (**27**)

Fig. 2 Structure of lycoposerramine-C

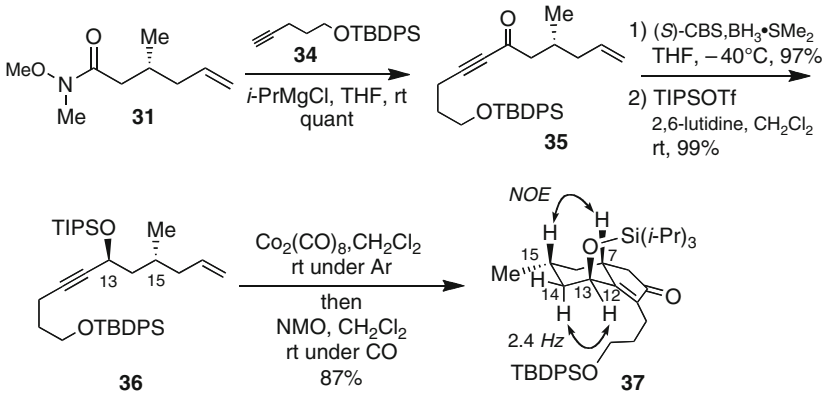


Scheme 5 Preparation of Weinreb amide **31**



Scheme 6 Alternative synthesis of Weinreb amide **31**

The coupling reaction of Weinreb amide **31** with alkyne **34** using *i*-PrMgCl as a base produced 1,7-enyne compound **35** in a quantitative yield (Scheme 7). The diastereoselective reduction of alkynyl ketone **35** with (*S*)-Corey–Bakshi–Shibata (CBS) reagent gave a propargyl alcohol and then the resulting secondary hydroxyl group was protected with a TIPS group to afford substrate **36** for the Pauson–Khand reaction [26–28]. After several attempts to use the intramolecular Pauson–Khand reaction to construct a tetrahydroindenone core, we finally found that pretreatment



Scheme 7 Synthesis of bicyclic compound **37** by Pauson-Khand reaction

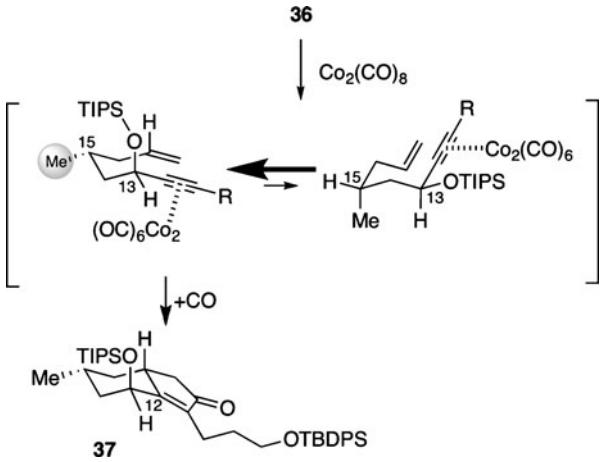
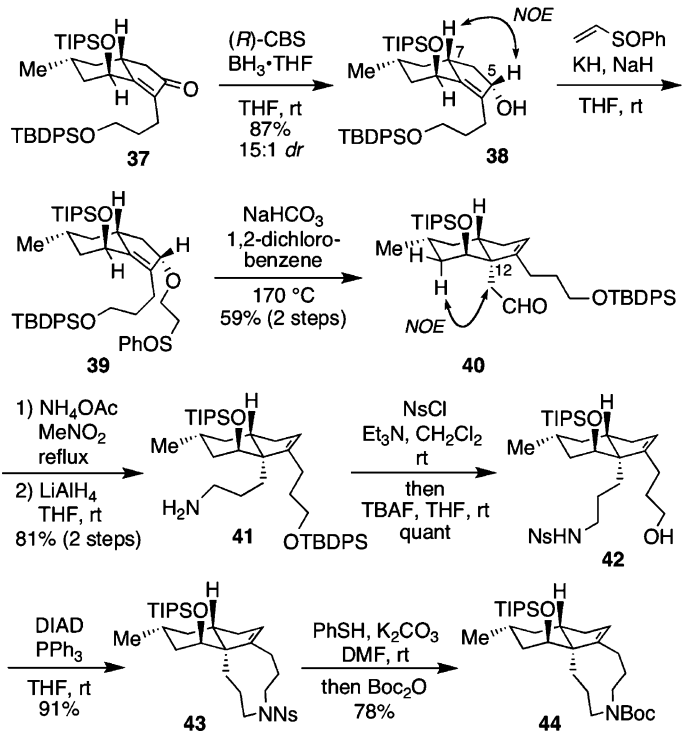


Fig. 3 Mechanistic consideration of Pauson-Khand reaction of **36**

of **36** with $Co_2(CO)_8$ in CH_2Cl_2 at room temperature under Ar atmosphere, followed by manipulation of the resulting coordination product with 4-methylmorpholine *N*-oxide (NMO) in CH_2Cl_2 at room temperature under CO atmosphere, produced desired bicyclo compound **37** having H-7β in 87% yield as the major product. The configuration at C-7 was determined from the NOE correlation between H-7 and H-15. Major product **37** would be obtained via a pseudo-chair transition state in which the methyl group took an equatorial orientation (Fig. 3).

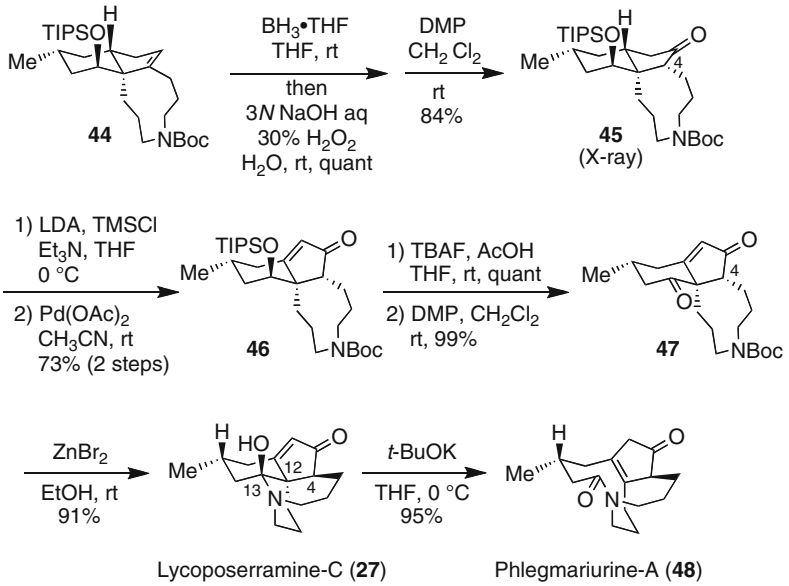
Next, we turned our attention to the construction of a quaternary center at C-12 in the fawcettimine skeleton. For this purpose, we employed the vinyl Claisen rearrangement providing an aldehyde functionality useful for extension of the side chain (Scheme 8). Reduction of enone **37** with (*R*)-CBS reagent gave allyl alcohol **38** in good yield with excellent selectivity (5H-α:5H-β = 1:15).



Scheme 8 Synthesis of tricyclic compound **44**

The stereochemistry of the resulting secondary alcohol was demonstrated by the NOE correlation of H-7 to H-5. Allyl alcohol **38** was treated with phenyl vinyl sulfoxide in the presence of NaH and a catalytic amount of KH to give sulfoxide **39** in quantitative yield [29]. Then **39** was heated at 170 °C in 1,2-dichlorobenzene in the presence of excess $NaHCO_3$ to produce aldehyde **40** having an expected (12*S*) quaternary carbon center. Synthesis of the tricyclic compound containing an azonane ring from aldehyde **40** was achieved by applying the nosyl (Ns) strategy [30–32]. Conversion of **40** into α,β-unsaturated nitro compound by the nitro-aldol reaction, followed by reduction with $LiAlH_4$, gave primary amine **41**. Substrate **42** for the intramolecular Mitsunobu reaction was obtained via a one-pot operation from **41**, i.e., installation of the Ns group onto the primary amine and subsequent removal of the TBDPS group. Under highly diluted conditions, azonane ring compound **43** was obtained in excellent yield by treating **42** with diisopropyl azodicarboxylate (DIAD). The protecting group on the secondary amine was switched to the Boc group to afford desired tricyclic compound **44**.

Then **44** was converted into ketone **45** by the conventional hydroboration-oxidation procedure and the subsequent Dess–Martin oxidation (Scheme 9). At this stage, X-ray crystallographic analysis of **45** enabled us to determine the configuration of the stereogenic center at C-4 as (*S*). By applying the Ito–Saegusa



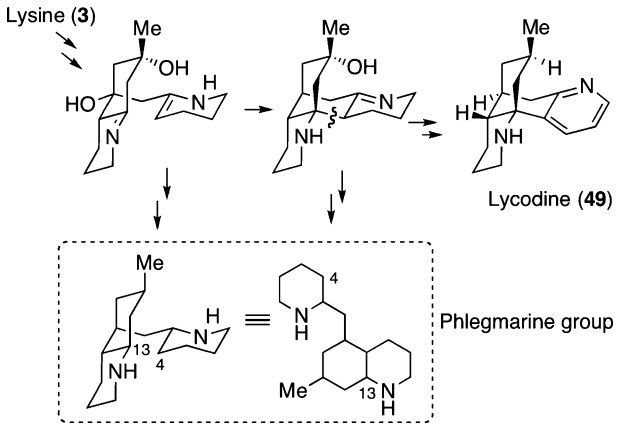
Scheme 9 Completion of the total synthesis of lycoporerramine-C and phlegmariurine-A

oxidation, **45** was regioselectively converted into α,β-unsaturated ketone **46**. Removal of the TIPS group in **46** and subsequent Dess–Martin oxidation of the resulting alcohol gave desired diketone **47**, which was a precursor of lycoposerramine-C. Removal of the Boc group in **47** and simultaneous isomerization at C-4 [33, 34] to form the hemiaminal function were accomplished by treating **47** with excess $ZnBr_2$ in EtOH to give lycoposerramine-C (**27**) in high yield. Synthetic **27** was identical in all respects with the natural product, including the optical rotation, thereby establishing its structure including its absolute configuration [35].

Phlegmariurine-A (**48**) isolated from *L. serratum* would be biogenetically generated by a C-12–C-13 bond scission in lycoposerramine-C (**27**). In accordance with this idea, we treated **27** with *t*-BuOK in THF to form **48** selectively in excellent yield, as expected. This result supported the possibility that lycoposerramine-C (**27**) might be a biogenetic precursor of phlegmariurine-type alkaloids.

3 Phlegmarine-Type Alkaloids

Phlegmarine-type alkaloids possess a $C_{16}N_2$ skeleton that consists of a piperidine ring and a (decahydro)quinoline ring that are connected via a methylene group (Scheme 10). They might be the biogenetic intermediates of lycodine (**49**). We next describe the structure elucidation of this new class of alkaloids based on asymmetric total syntheses.



Scheme 10 Hypothetical biogenesis of lycodine and phlegmarine-type alkalooids

3.1 Lycoposerramine-V

New compound **50**, named lycoposerramine-V [36], had a phlegmarine skeleton with the 5,6,7,8-tetrahydroquinoline moiety, the first of such to be discovered among *Lycopodium* alkaloids, in contrast with common phlegmarine-type alkaloids possessing a decahydroquinoline ring. The relative stereochemistry at H-7 and H-15 was found to be *cis* by NOE analysis. However, it was not possible to elucidate the relative stereochemistry between C-7 in the decahydroquinoline ring and C-5 in the piperidine ring by spectroscopic analyses. Then we attempted the asymmetric total synthesis of lycoposerramine-V to reveal its relative and absolute configurations. The absolute configuration at C-15 was deduced to be (*R*) based on the biogenesis of common *Lycopodium* alkaloids and, therefore, C-7 could be (*R*) from the NOE data. As the asymmetric center at C-5 could not be determined from spectroscopic analyses, we planned the synthesis of both stereoisomers with (5*S*) (**50**) or (5*R*) (**51**) configuration (Fig. 4).

Initially, cyclohexenone **53** was prepared from commercially available (*R*)-3-methylcyclohexanone (**52**) via a three-step operation in 49% yield (Scheme 11). α-Iodination of cyclohexenone **53** with I_2/pyridine gave iodide **54** in 85% yield. Next, the installation of a 3-hydroxypropane side chain onto **54** was accomplished with a tandem sequence involving the regioselective hydroboration of alkene **55** with 9-BBN, followed by coupling of the resulting borane under Pd-catalyzed Suzuki–Miyaura conditions [37] in 83% yield. Regio- and stereoselective reduction of thus obtained enone **56** under Luche conditions gave allyl alcohol **57** as a single isomer in 98% yield. Allyl alcohol **57** was subjected to the Johnson–Claisen rearrangement to construct a C-7 stereogenic center by taking advantage of the stereochemistry of the allyl alcohol function to yield **58**.

By a conventional hydroboration-oxidation procedure [38], **58** was converted into alcohol **59** as the major product in 75% yield with 82% de. Removal of the

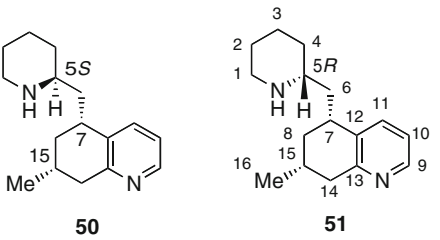
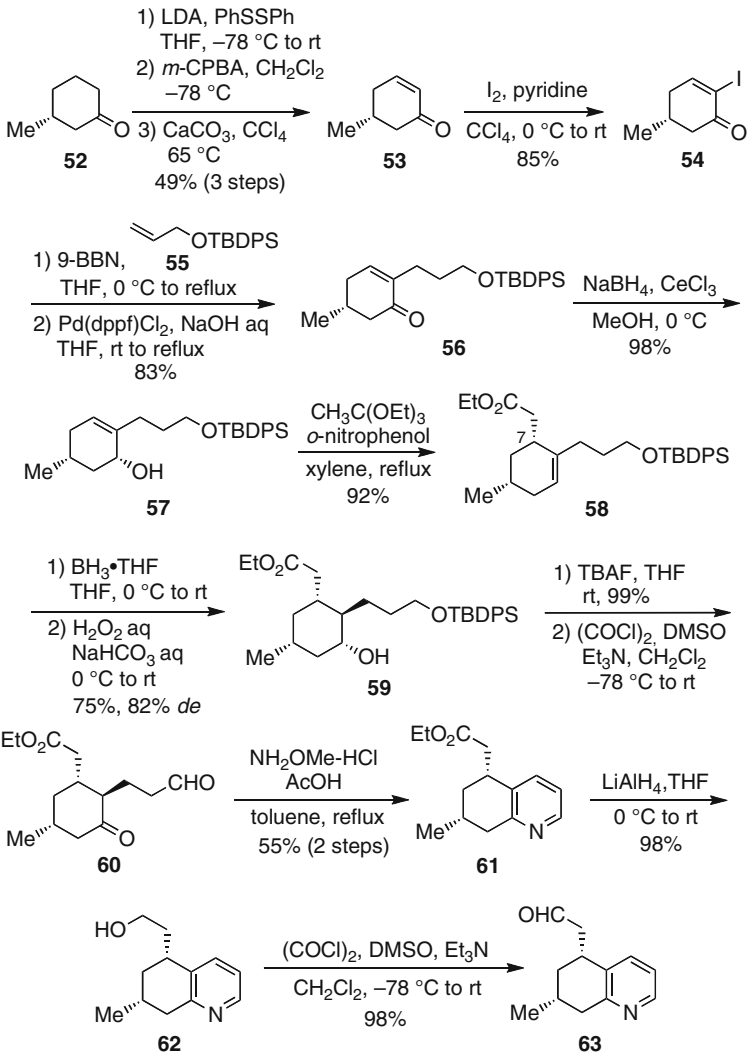


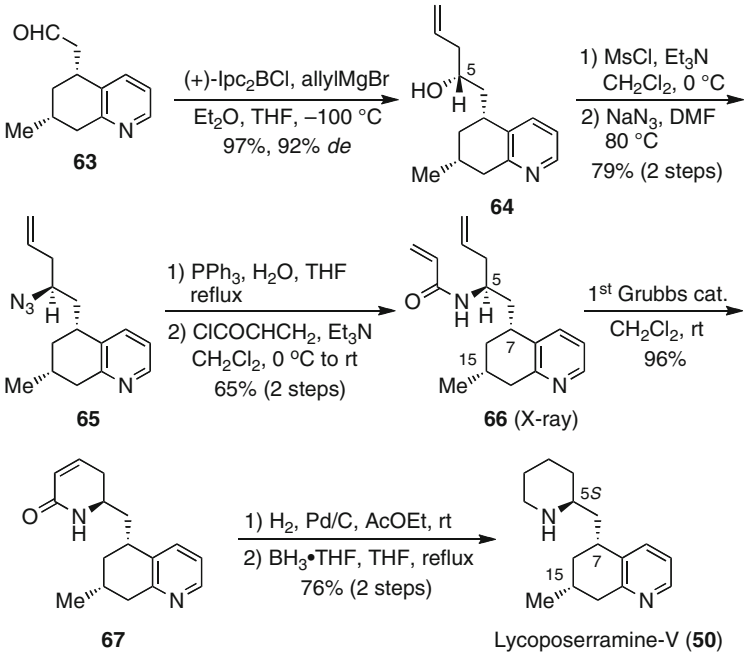
Fig. 4 Structures of lycoposerramine-V and its C-5 epimer



Scheme 11 Synthesis of key intermediate **63**

TBDPS group by TBAF and subsequent Swern oxidation of the resulting diol gave keto-aldehyde **60**. Next, **60** was subjected to Knoevenagel conditions with slight modification using NH_2OMe•HCl to afford 5,6,7,8-tetrahydroquinoline **61**. Reduction of the ester group in **61** with $LiAlH_4$ and subsequent oxidation under Swern conditions gave aldehyde **63**.

Next, we employed Brown's asymmetric allylation with *B*-allyldiisopinocampheylborane [39, 40] to construct the C-5 stereogenic center (Scheme 12). Treatment of aldehyde **63** with *B*-allyldiisopinocampheylborane prepared from (+)-*B*-chlorodiisopinocampheylborane and allylmagnesium bromide furnished homoallylic alcohol **64** in 97% yield with good diastereoselectivity (92% de). The absolute configuration of the newly generated stereogenic center was assigned as (*R*) based on a well-established reaction mechanism and confirmed later by X-ray crystallographic analysis. The alcohol thus obtained was converted into azide **65** in 79% yield in two steps accompanying the stereoinversion at C-5 position via an *O*-mesylated derivative. Using the Staudinger reaction, azide **65** was transformed into primary amine, which, in turn, was directly acylated with acryloyl chloride to give substrate **66** for RCM in 65% yield in two steps. X-ray crystallographic analysis of **66** enabled the unambiguous assignment of all stereogenic centers as (5*S*),(7*R*),(15*R*) configuration. RCM of **66** using first-generation Grubbs' ruthenium catalyst proceeded smoothly to generate unsaturated lactam **67** in 96% yield.



Scheme 12 Completion of the total synthesis of lycoporerramine-V

Finally, reduction of the double bond with H_2/Pd/C and subsequent reduction of lactam with BH_3•THF to construct the piperidine ring afforded the desired compound **50** with the (5*S*),(7*R*),(15*R*) configuration.

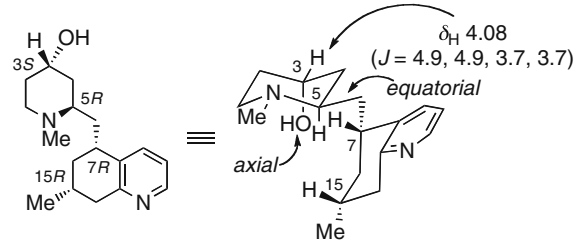
Starting from common intermediate **52**, we achieved the asymmetric synthesis of compound **51** possessing the (5*R*),(7*R*),(15*R*) configuration in 22% yield in seven steps by using a sequence similar to that described above via a homoallyl alcohol having the (5*S*) configuration, which was prepared by the asymmetric allylation reaction of **63** using (−)-*B*-chlorodiisopinocampheylborane.

Having both target compounds (**50** and **51**) in hand, we compared their physicochemical data with those of the natural product. As a result, compound **50** was completely identical in all respects with natural lycoposerramine-V. Therefore, the structure, including the absolute configuration of the stereogenic center, was established to be **50** possessing the (5*S*),(7*R*),(15*R*) configuration [36].

3.2 Lycoposerramine-W

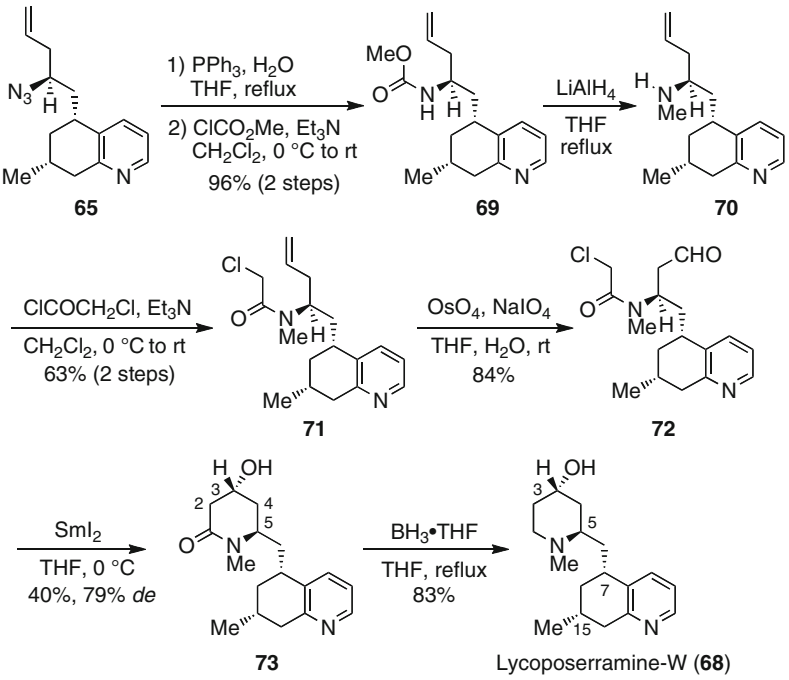
Compound **68**, named lycoposerramine-W, was deduced to be an N_a-methyl-3-hydroxy derivative of lycoposerramine-V (**50**) from spectroscopic analyses (Fig. 5). Its relative configuration between C-5 and C-7 and the absolute configuration at C-5, C-7, and C-15 would be the same as those of **50** based on biogenetic consideration. Furthermore, the remaining stereogenic center (C-3) would be (*S*), that is, the hydroxy group is in an α-axial orientation, based on the coupling constant of the proton on C-3 (δ 4.08, dddd, J = 4.9, 4.9, 3.7, 3.7 Hz). Then we focused on the asymmetric synthesis of compound **68** having the 3(*S*),5(*R*),7(*R*),15(*R*) configuration to elucidate the structure of lycoposerramine-W.

Azide **65**, an intermediate of the synthesis of lycoposerramine-V, was converted into primary amine by the Staudinger reaction and the resulting amine was directly treated with methyl chloroformate to give methyl carbamate derivative **69** (Scheme 13). Reduction of the carbamate with $LiAlH_4$ gave *N*-methyl derivative **70** and then the resulting secondary amine was acylated with chloroacetylchloride



Lycoposerramine-W (**68**)

Fig. 5 Structure of lycoposerramine-W



Scheme 13 Completion of the total synthesis of lycoporerramine-W

to yield amide **71**. Oxidative cleavage of the terminal double bond in **71** under Johnson–Lemieux conditions produced β-chloroacetamide-aldehyde **72**. Next, the samarium(II)-promoted stereoselective intramolecular Reformatsky reaction was investigated. As far as we know, this reaction has been applied only to β-halo acetoxy carbonyl substrates [41, 42], forming a lactone ring. None of the studies that employed the intramolecular Reformatsky reaction used a β-haloacetamide-carbonyl compound. After several attempts, we found that the use of samarium(II) iodide freshly prepared from samarium metal and diiodomethane in THF gave the best result, producing lactam **73** in 40% yield as the major product with good diastereoselectivity (79% de). Careful analysis of the coupling constants of H-2 to H-5 demonstrated that H-3 was in an equatorial orientation and the relative stereochemistry between C-3 and C-5 was *trans*. Having considered the reaction mechanism [42], the stereochemistry of C-3 in **73** was determined to be (*S*), as expected. Finally, the construction of a 4-hydroxy-2-substituted piperidine ring by the reduction of lactam **73** with BH_3•THF afforded target compound **68** having the (3*S*),(5*R*),(7*R*),(15*R*) configuration. Synthetic **68** was completely identical in all respects, including the optical rotation, with natural lycoposerramine-W {synthetic $[\alpha]_D^{25}$ +21.5 (*c* 0.07, $CHCl_3$)/natural $[\alpha]_D^{25}$ +22.4 (*c* 0.14, $CHCl_3$)}, thereby establishing the absolute configuration of the natural compound as (3*S*),(5*R*),(7*R*),(15*R*) [36].

3.3 *Lycoposerramines-X and -Z*

New alkaloids lycoposerramines-X (**74**) and -Z (**75**) are phlegmarine-type alkaloids consisting of a piperidine ring with a novel nitrone residue and a decahydroquinoline ring with four stereogenic centers [43] (Fig. 6). From spectroscopic analyses, **74** and **75** were found to be diastereomers at the C-13 position, but their absolute configuration could not established. Then we planned the asymmetric total syntheses of **74** and **75** to confirm their structures, including the absolute stereochemistry.

The relative stereochemistry at C-7, C-12, and C-15 in the decahydroquinoline ring in lycoposerramines-X (**74**) and -Z (**75**) is the same as that in compound **59**, the synthetic intermediate of lycoposerramines-V (**50**) and -W (**68**). Therefore, compound **59** having four stereogenic centers in the cyclohexane ring was expected to be a common intermediate for the divergent synthesis of lycoposerramines-X (**74**) and -Z (**75**). Furthermore, we considered that a *cis*- or *trans*-decahydroquinoline ring could be constructed by manipulating the hydroxy group at C-13. Based on biogenetic consideration, the absolute configuration at C-15 in **74** and **75** was deduced to be (*R*), similar to that of lycoposerramines-V (**50**) and -W (**68**). Initially, the construction of a *cis*-decahydroquinoline ring in lycoposerramine-Z (**75**) was carried out from common synthetic intermediate **59**.

Acetylation of the secondary alcohol and deprotection of the silyl group of the primary alcohol in **59**, followed by replacement of the resulting hydroxy group at C-9 with 2-nitrobenzenesulfonamide under Mitsunobu conditions and removal of the acetyl group of the secondary hydroxy group at C-13, afforded sulfonamide **76** (Scheme 14). Compound **76** was subjected to the intramolecular Mitsunobu reaction with di-*tert*-butyl azodicarboxylate (DTAD) and PPh_3 in THF to give *cis*-decahydroquinoline **77**.

After switching of the protecting group on the amine function in **77** from Ns to 2-(trimethylsilyl)ethoxycarbonyl (Teoc), reduction of the ester group afforded alcohol **78** (Scheme 15). Oxidation of **78** with 2-iodoxybenzoic acid (IBX) gave aldehyde **79**. The installation of a C4 unit at C-5 was accomplished by treating **79** with an alkynyl anion that was prepared from 3-butyn-1-ol, producing diol **80** in 90% yield as a diastereomeric mixture. Selective oxidation of the hydroxy group on the propargyl position with MnO_2 gave α,β-unsaturated ketone **81**. Mesylation of the primary alcohol and subsequent reduction of the alkyne function afforded keto-mesylate **82**. Next, compound **82** was treated with 1.5 equiv. of NH_2OH•HCl

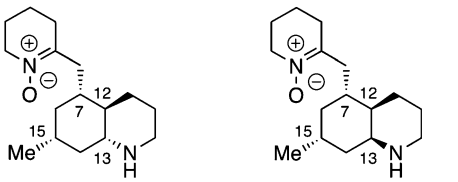
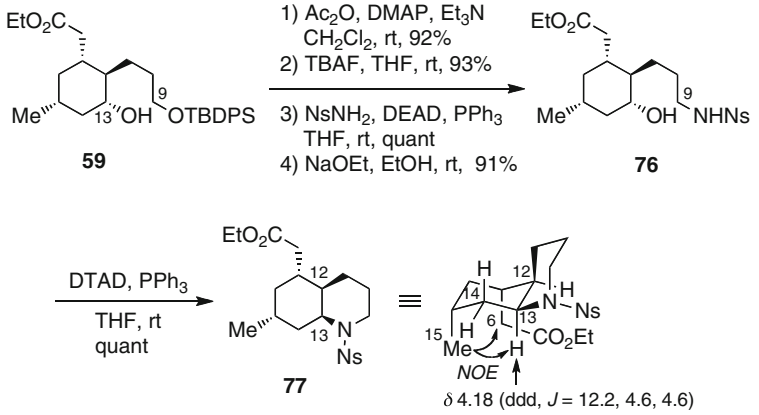
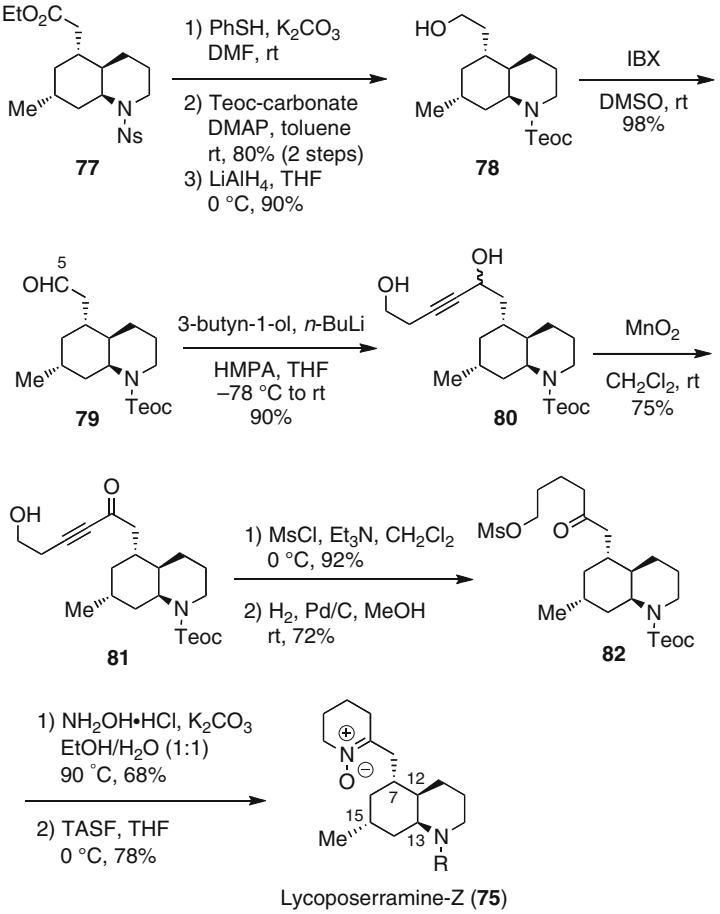


Fig. 6 Structures of lycoposerramines-X and -Z



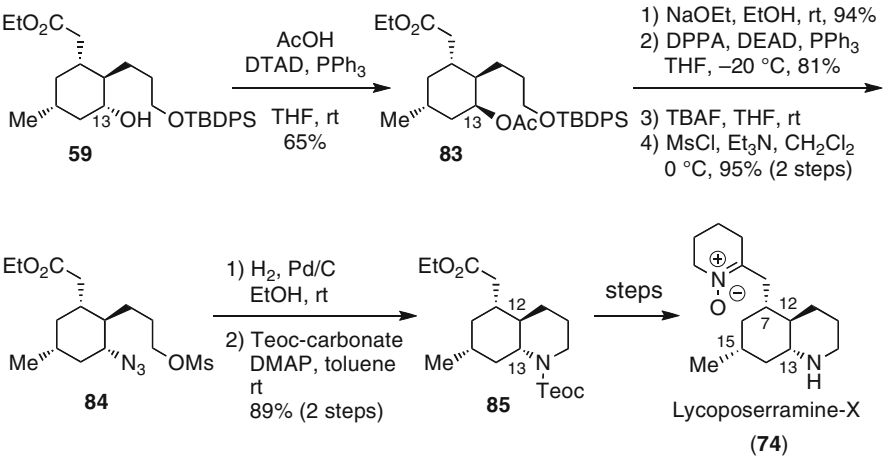
Scheme 14 Synthesis of decahydroquinoline intermediate **77**



Scheme 15 Completion of the total synthesis of lycoporerramine-Z

in the presence of 0.5 equiv. of K_2CO_3 in EtOH/H_2O (1:1) to yield the expected cyclic nitrone in 68% yield. Finally, removal of the Teoc group with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) in THF afforded lycoposerramine-Z (**75**) in 78% yield. Synthetic **75** was identical in all respects with natural lycoposerramine-Z, thereby establishing its structure as well as its absolute configuration as (7*R*),(12*R*),(13*S*),(15*R*) [44].

Next, we examined the construction of a *trans*-decahydroquinoline ring to accomplish the synthesis of lycoposerramine-X (**74**) (Scheme 16). A nitrogen function was introduced at C-13α in secondary alcohol **59** utilizing the Mitsunobu reaction twice. After removal of the TBDPS group on the side chain, the resulting primary alcohol was mesylated to yield substrate **84** for cyclization. Reduction of the azide group in **84** led to the spontaneous cyclization. This was followed by protection of the resulting secondary amine by the Teoc group to give *trans*-decahydroquinoline **85** in 89% yield (two steps). According to the method for the synthesis of **75** described above, *trans*-decahydroquinoline **85** was converted into **74**. Synthetic **74** was identical in all respects with natural lycoposerramine-X, thereby establishing its absolute configuration as (7*R*),(12*R*),(13*R*),(15*R*) [44].



Scheme 16 Completion of the total synthesis of lycoporerramine-X

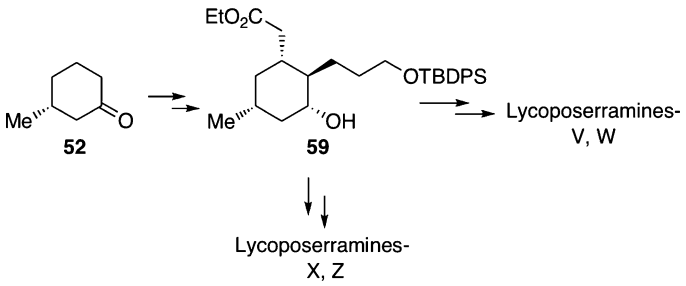


Fig. 7 Common intermediate **59** for the syntheses of lycoposerramines-V, -W, -X, and -Z

As described above, we have achieved the asymmetric total syntheses of lycoposerramines-V (**50**), -W (**68**), -X (**74**), and -Z (**75**) using cyclohexanol **59** as the common intermediate, which has enabled us to determine unambiguously the structures, including the absolute configurations, of the four new phlegmarine-type alkaloids (Fig. 7).

4 Cernuine and Related Alkaloids

From *L. cernuum* collected in Okinawa Prefecture, cernuine (**86**) and a new alkaloid, cermizine C *N*-oxide (**88**), were isolated. Cernuine (**86**) is a representative of cernuane-type *Lycopodium* alkaloids. It was isolated by Marion and Manske in 1948 and its structure was elucidated by Ayer et al. in 1967 [45, 46] (Fig. 8). Its structure features a fused-tetracyclic ring system containing an aminal moiety that is rare among *Lycopodium* alkaloids. The relative configuration of **86** was determined from the coupling constants in the ^{1}H NMR spectra, but its absolute configuration was deduced from CD spectra by comparison with those of related alkaloids. Furthermore, the total synthesis of cernuane-type alkaloids has not been reported to date, although those of various types of *Lycopodium* alkaloids have been achieved. In 2004, Kobayashi et al. reported the isolation of cermizines possessing a quinolizidine skeleton related to cernuine (**86**), in which some compounds exhibited cytotoxicity to murine lymphoma L1210 cells [47]. However, the absolute configuration of cermizines has not been clarified. Then, we attempted to accomplish the first synthesis of cernuine (**86**) and to establish an efficient synthetic route to these cernuane-type and quinolizidine-type alkaloids. Our endeavor has enabled us to confirm their structures and absolute configurations. We focused on the structure similarities between cernuane- and quinolizidine-type *Lycopodium*

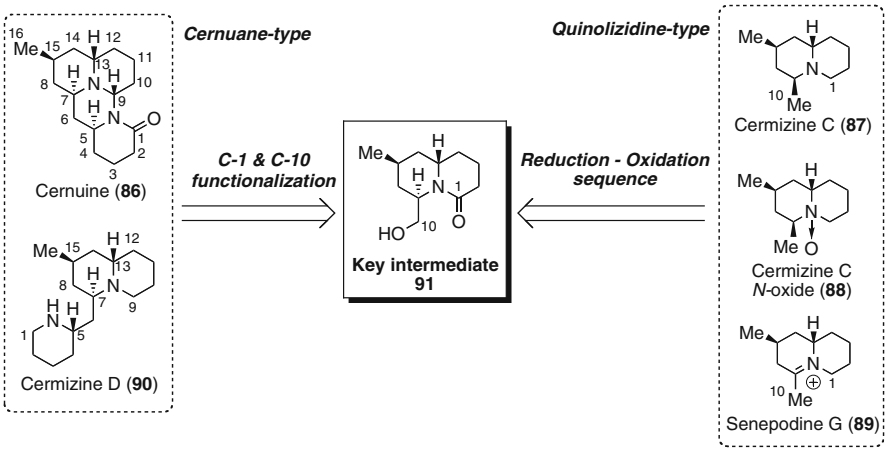
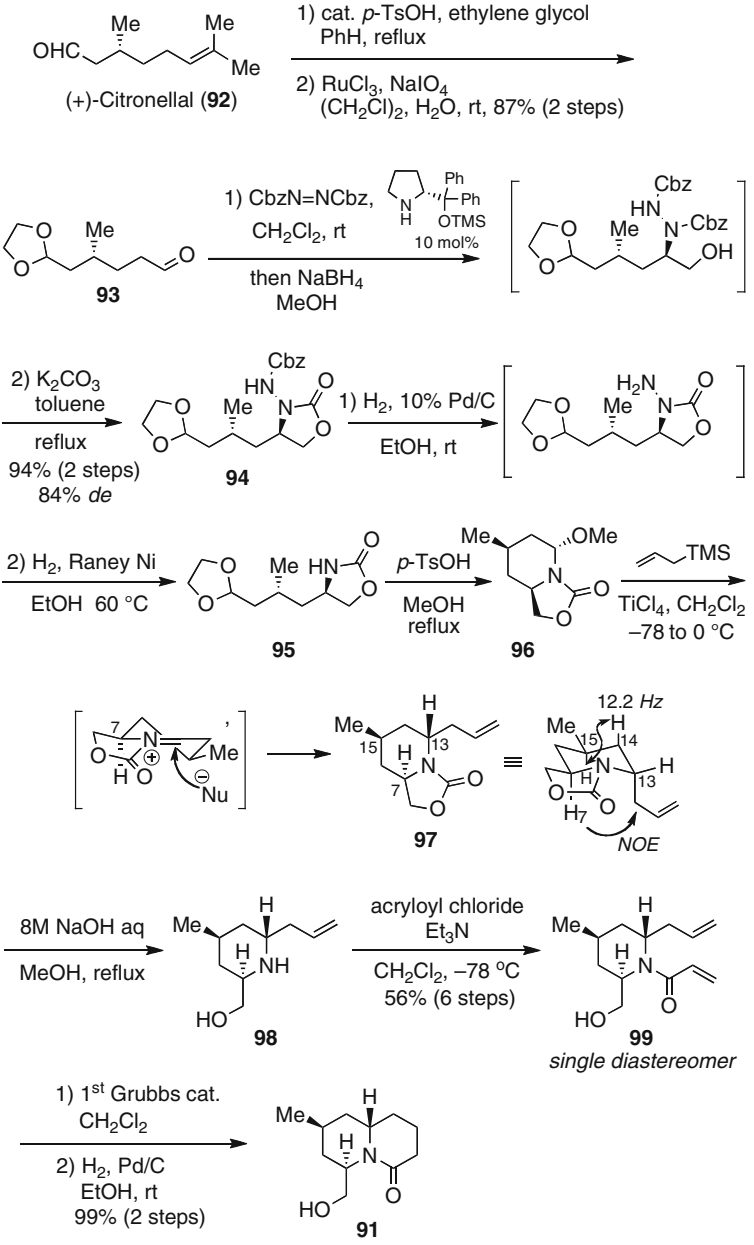


Fig. 8 Divergent strategy for the total syntheses of cernuane-type and quinolizidine-type *Lycopodium* alkaloids

alkaloids. As the target compounds have the same quinolizidine structure, we envisioned that both cernuane- and quinolizidine-type alkaloids could have originated from a key intermediate that has the common quinolizidine core bearing appropriate functional groups. Following a divergent strategy, we designed compound **91** as the common key intermediate possessing the skeleton of cermizine C (**87**) that was oxygenated at C-1 and C-10 positions.

4.1 Establishment of an Efficient Route to a Common Synthetic Intermediate

The aldehyde in (+)-citronellal (**92**) was protected as an acetal function, and this was followed by the Ru-catalyzed oxidative cleavage of the residual olefin function to give aldehyde **93** (Scheme 17). Next, the organocatalytic α-amination of aldehyde **93** was investigated [48–50]. First we carried out the amination of **93** with dibenzyl azodicarboxylate in the presence of a catalytic amount of an (*S*)-proline derivative as organocatalyst. This was followed by in situ reduction to produce oxazolidinone **94** under anhydrous conditions using K_2CO_3 in 94% yield with 84% de. Next, reductive N–N bond cleavage in **94** was attempted. Sequential reduction involving removal of the Cbz group under mild conditions (H_2/Pd/C), followed by hydrogenation of the resulting hydrazine with Raney Ni, gave cyclic carbamate **95** in good yield. Upon treatment of **95** with a catalytic amount of *p*-TsOH in refluxing MeOH, cyclization occurred to give aminoacetal **96** as an allylation precursor. Treatment of aminoacetal **96** with allyltrimethylsilane in the presence of $TiCl_4$ at low temperature gave **97** as the sole isomer at C-13, which would be formed by stereoselective allylation of the acyliminium intermediate. The NOE correlation between H-7 and the proton of the allyl group in **97** revealed that the allyl group was introduced in an axial orientation. The stereoselectivity would be interpreted by the axial attack of a nucleophile on the acyliminium intermediate that had a rigid conformation defined by oxazolidinone. Hydrolysis of oxazolidinone in **97** under basic conditions and subsequent acryloylation of resulting secondary amine **98** gave acrylamide **99**. The synthesis of key intermediate **91** was accomplished by RCM with first-generation Grubbs catalyst, followed by hydrogenation of olefin. At this stage, it was found that the conversion of hydrazine **94** into acrylamide **99** proceeded smoothly without purification, that is, the desired diastereomer of **99** was obtained in pure form from **94** in six steps after a single chromatographic separation from a concomitant diastereomer derived from the organocatalytic reaction of aldehyde **93**. Furthermore, it was found that the RCM reaction of **99** proceeded in the presence of 1 mol% of catalyst to give **91**. It is noteworthy that the present procedure for the preparation of **91** required only two purification steps throughout the eight-step conversion from **94** to **91** in 56% total yield. As described above, we succeeded in the development of an efficient and practical synthetic route to pivotal intermediate **91** in our divergent synthesis.



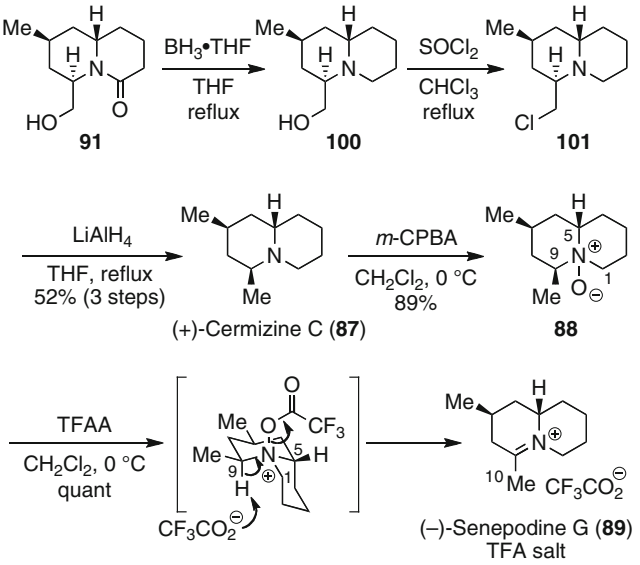
Scheme 17 Synthesis of key intermediate **91**

4.2 Quinolizidine-Type Alkaloids

Having developed an efficient route to the common intermediate **91**, we next turned our attention to the further transformation of **91** into quinolizidine-type alkaloids (Scheme 18). The amido group in **91** was reduced with BH_3•THF in THF under reflux to give amine **100**. Without purification, **100** was treated with $SOCl_2$ to yield chloride **101**, which was subjected to the next reaction without purification because of instability on SiO_2 gel. Reductive dehalogenation of chloride **101** with $LiAlH_4$ afforded cermizine C (**87**) [51].

Next, cermizine C (**87**) was converted into cermizine C *N*-oxide (**88**) by *m*-CPBA oxidation of **87**. Synthetic **88** was identical in all respects with the new alkaloid isolated from *L. cernuum* by us, thereby establishing its structure [51].

To synthesize senepodine G (**89**) [47], regioselective oxidation at C-9 position in cermizine C (**87**) was required. We anticipated that cermizine C (**87**) and cermizine C *N*-oxide (**88**) having a *cis*-quinolizidine skeleton would be suitable for the regioselective oxidation to senepodine G (**89**). This is because among the protons on C-1, C-5, and C-9, only the proton H-9 is situated at an *anti*-position to the N–O bond in the activated intermediate that was prepared from cermizine C *N*-oxide (**88**) in the Polonovski–Potier reaction. In fact, *N*-oxide **88** was treated with TFAA in CH_2Cl_2 to give regioselectively senepodine G (**89**) in quantitative yield

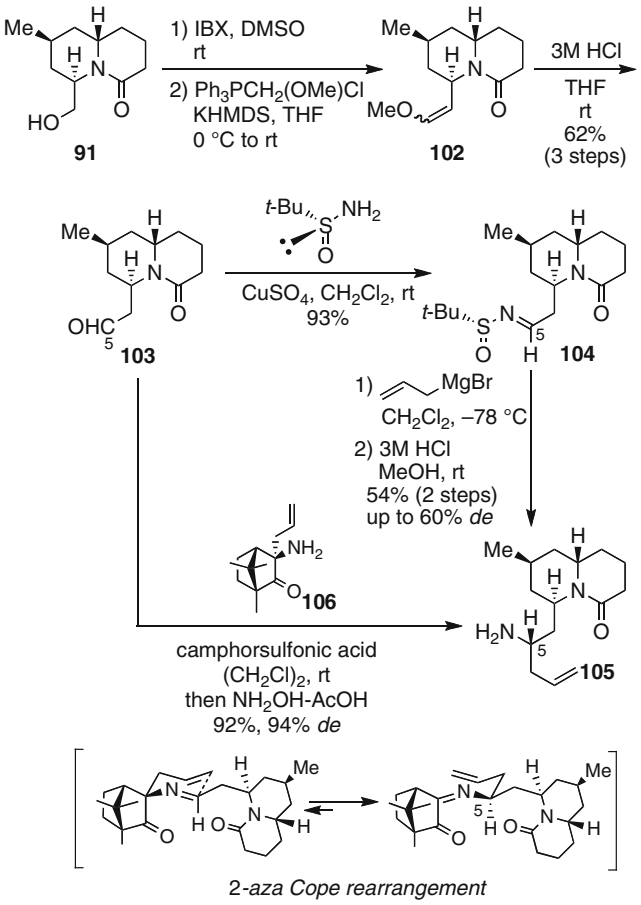


Scheme 18 Completion of the total synthesis of quinolizidine-type alkaloids

(Scheme 18). In the ^{1}H NMR spectra of synthetic **89**, the signal for methyl protons on C-10 was observed at δ 2.45 (3H, s), confirming that the desired oxidation at C-9 position occurred. All of the spectroscopic data of synthetic **89** were identical with the reported data of natural senepodine G in all respects [51].

4.3 Cernuane-Type Alkaloids

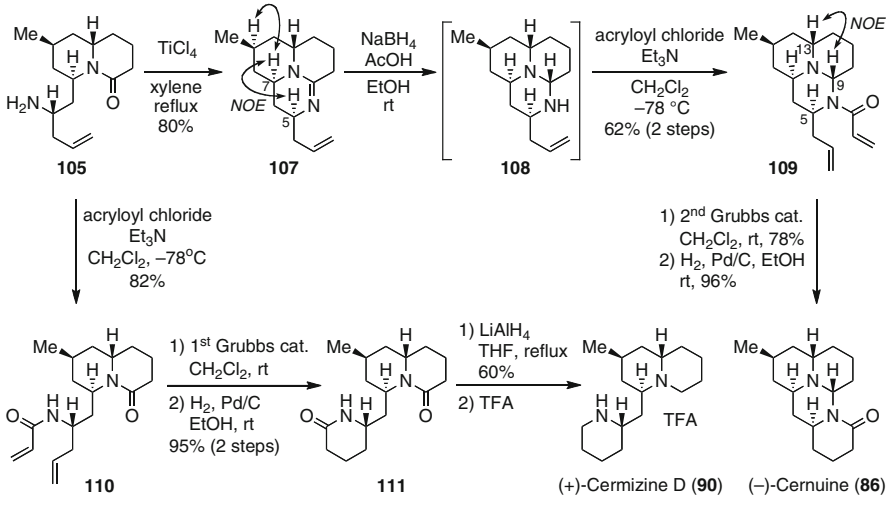
Next, we performed the syntheses of cernuane-type alkaloids, cermizine D (**90**) and cernuine (**86**), from common key intermediate **91** (Scheme 19). The primary alcohol in **91** was oxidized with IBX to give the aldehyde, which, in turn, was subjected to the Wittig reaction without purification to afford **102**. Mild acid



Scheme 19 Stereoselective synthesis of homoallylamine **105**

hydrolysis of the enol ether in **102** using 3M aq. HCl in THF gave carbon-elongated aldehyde **103**. To install allyl and amino groups onto aldehyde **103**, we initially adopted the Ellman protocol using a chiral sulfinimine [52]. Condensation of aldehyde **103** and (*R*)-*tert*-butanesulfinamide in the presence of $CuSO_4$ in CH_2Cl_2 afforded sulfinimine **104** in high yield. The addition of allylmagnesium bromide, followed by the removal of the sulfinyl auxiliary, furnished desired homoallylamine **105** in good yield but with poor stereoselectivity (up to 60% de). In order to improve the stereoselectivity, the transfer aminoallylation via the aza-Cope rearrangement developed by Kobayashi and coworkers [53] was adopted for the synthesis of homoallylamine **105**. Treatment of aldehyde **103** with reagent **106** derived from (1*R*)-camphorquinone in the presence of a catalytic amount of CSA in $(CH_2Cl)_2$, followed by treatment with NH_2OH to liberate amine group, resulted in the simultaneous and highly stereoselective installation of allyl and amine functions onto C-5 in **103** to provide homoallylamine **105** in 92% yield and 94% de. The de value of **105** was determined by HPLC analysis of its benzoylated products.

After examination of the conditions required to construct the aminal ring system, amidine **107** was obtained by treating amine **105** with $TiCl_4$ in refluxing xylene (Scheme 20). The absolute configuration at C-5, which was constructed by the transfer aminoallylation described above, was determined to be (*S*) from the NOE correlation between H-7 and H-5. Amidine **107** was treated with 1 equiv. of AcOH in EtOH and then the imine moiety in the resulting acetate was stereoselectively reduced with $NaBH_4$ to give aminal **108**. Obtained aminal **108** was directly acylated with acryloyl chloride and Et_3N to provide acrylamide **109**. The stereochemistry at C-9 was confirmed by NOE experiment in which significant NOE between H-9 and H-13 was observed. This stereoselectivity can be expected from the attack of hydride from the convex face of **107**. Thus, the characteristic cyclic aminal moiety



Scheme 20 Completion of the total synthesis of cermizine D and cernuine

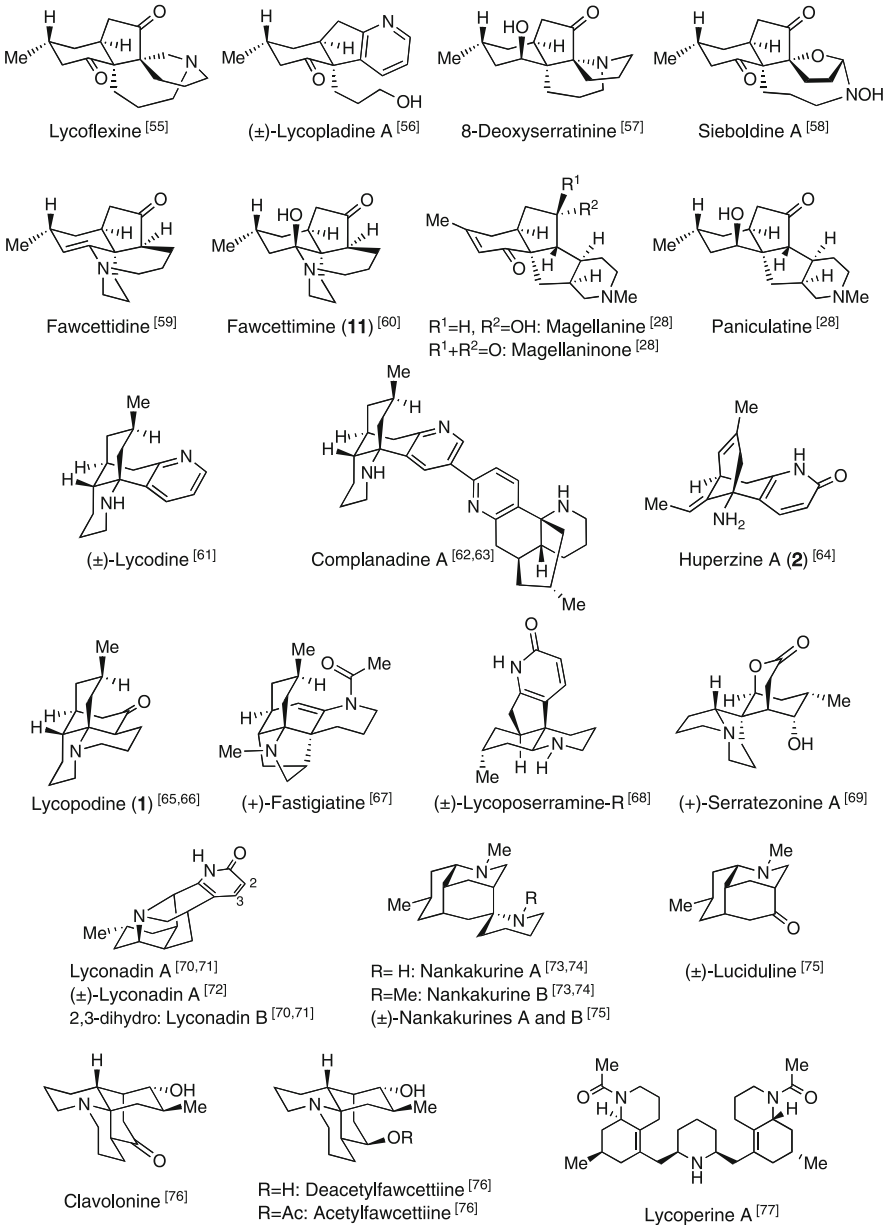


Fig. 9 Structures of some *Lycopodium* alkaloids synthesized in recent years

of cernuine (**86**) could be stereoselectively constructed. Finally, RCM of **109** with second-generation Grubbs catalyst in CH_2Cl_2 to construct the piperidone ring and subsequent hydrogenation completed the first total synthesis of cernuine (**86**).

The spectroscopic data of synthetic **86** were in agreement with those of the natural product in all respects. Therefore, the structure of cernuine (**86**), including the absolute configuration, was confirmed [54].

Next, we investigated the synthesis of cermizine D (**90**) from homoallylamine **105**. According to the synthesis of cernuine (**86**) described above, **105** was acylated with acryloyl chloride to give acrylamide **110**. RCM with first-generation Grubbs catalyst and subsequent hydrogenation afforded bisamide **111**. Reduction of bisamide **111** with $LiAlH_4$ in THF completed the synthesis of cermizine D (**90**).

As described above, the divergent asymmetric total syntheses of cernuane- and quinolizidine-type *Lycopodium* alkaloids were accomplished. The first asymmetric total synthesis of cernuine (**86**) was achieved starting from the easily available (+)-citronellal in 9.6% overall yield in 21 steps. Furthermore, we have succeeded in the syntheses of cermizine D (**90**), cermizine C (**87**), cermizine C *N*-oxide (**88**), and senepodine G (**89**) from common key intermediate **91**, and have established an efficient synthetic route to cernuane- and quinolizidine-type *Lycopodium* alkaloids.

5 Conclusion

Lycopodium alkaloids have attracted the attention of many natural product chemists and synthetic organic chemists due to their important biological activities and unique skeletal characteristics. A number of elegant total syntheses of many kinds of *Lycopodium* alkaloids have been reported in recent years (Fig. 9) (selected reports on the total synthesis of *Lycopodium* alkaloids by other researchers in recent years [28, 55–78]). In this review, we have shown that asymmetric total synthesis played a key role in elucidating the structures of these complex natural products.

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Synthesis of Morphine Alkaloids and Derivatives

Uwe Rinner and Tomas Hudlicky

Abstract This review summarizes recent developments in the total synthesis of morphine alkaloids and some of the semisynthetic derivatives. The literature is covered for the period of 5 years after the publication of the last review in 2005. The syntheses that appeared in this period are covered in detail and are placed in the context of all syntheses of opiate alkaloids since the original one published by Gates in 1952. The introduction covers the historical aspects of total synthesis of these alkaloids. The synthesis of some of the medicinally useful derivatives is reviewed in the last section along with some of the methodology required for their preparation.

Keywords Alkaloids · Analgesia · Codeine · Demethylation · Morphine · Total synthesis

Contents

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Abbreviations

2,4-DNPH	2,4-Dinitrophenylhydrazine
BHT	Butylated hydroxytoluene
CSA	Camphorsulfonic acid
DDQ	Dichloro dicyano benzoquinone
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DMAP	4-Dimethylaminopyridine
DNsCl	2,4-Dinitrobenzene-sulfonyl chloride
dpa	Dibenzylidenacetone
dppf	1,1′-*Bis*(diphenylphosphino)ferrocene
dppp	1,3-*Bis*(diphenylphosphino)propane
EDCI	1-Ethyl-3-(3-dimetylaminopropyl)carbodiimide
IBX	2-Iodoxybenzoic acid
KHMDS	Potassium *bis*(trimethylsilyl)amide
LiHMDS	Lithium *bis*(trimethylsilyl)amide
MCPBA	3-Chloroperbenzoic acid
NaHMDS	Sodium *bis*(trimethylsilyl)amide
NBS	*N*-Bromosuccinimide
PAD	Potassium azodicarboxylate
PPTS	Pyridinium *p*-toluenesulfonate
TBAF	*tetra-n*-Butylammonium fluoride
TCDI	Imidazole 1,1′-thiocarbonyldiimidazole
TFA	Trifluoroacetic acid

1 Introduction

Morphine (**1**) and its congeners, codeine (**2**), thebaine (**3**), and oripavine (**4**), Fig. 1, as well as other minor constituents of the opium poppy latex, continue to garner interest of the chemical community for a number of reasons. The focus on the total synthesis of these alkaloids in the academic sector has not waned and now spans almost 60 years since the seminal disclosure of the first synthesis by Gates in 1952 [1, 2].

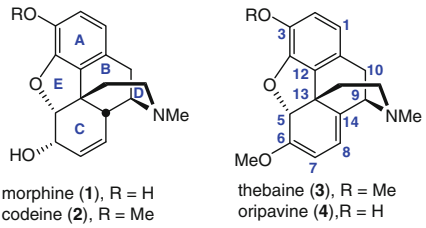

Fig. 1 Morphine and congeners

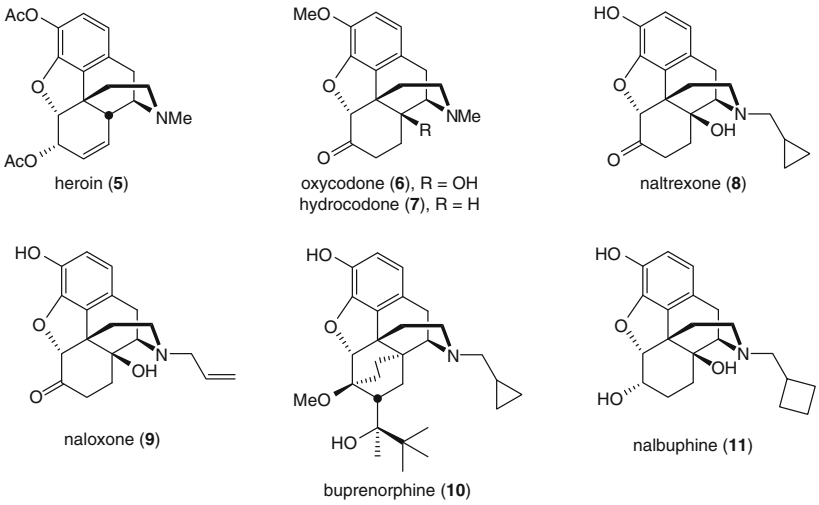

Fig. 2 Opiate-derived agonists and antagonists for legal and illicit (i.e., heroin) use

The medical community requires a constant supply of morphine and other analgesic agents for pain control. The unnatural derivatives of morphine, whether agonists or antagonists, are all derived by semisynthesis from the naturally occurring alkaloids harvested primarily in Asia and Tasmania for legal consumption. The extent of illicit use of morphine and other derivatives, such as heroin (**5**), Fig. 2, can only be estimated but likely exceeds $800 billion annually. Some opiate-derived products, such as the analgesics oxycodone (**6**) and hydrocodone (**7**), enjoy a widespread legal as well as illicit use. The antagonists and mixed agonists, all derived by semisynthesis, include naltrexone (**8**) for treatment of alcohol addiction [3], naloxone (**9**) for treatment of opiate overdose [4], buprenorphine (**10**), and nalbuphine (**11**), Fig. 2.

Naltrexone is an opioid receptor antagonist used primarily in the management of alcohol and/or opioid dependence. It is marketed in generic form as its hydrochloride salt, naltrexone hydrochloride, and sold under the trade names Revia™ and Depade™. Naltrexone and its active metabolite 6-β-naltrexol are competitive antagonists at μ- and κ-opioid receptors, and to a lesser extent at δ-opioid receptors [5]. Naloxone is a drug used to counter the effects of opioid

overdose, for example, heroin or morphine overdose. Naloxone is specifically used to counteract life-threatening depression of the central nervous system and respiratory system. It is also used in combination drugs such as Suboxone™ (buprenorphine and naloxone, 4:1). Nalbuphine is a synthetic opioid used commercially as an analgesic under a variety of trade names, including Nubain™. It is a mixed agonist/antagonist, noteworthy in part for the fact that at low dosages it is much more effective in women than in men, and may even increase pain in men [6], leading to its discontinuation in the UK in 2003. Nalbuphine is indicated for the relief of moderate to severe pain. It can also be used as a supplement to balanced anesthesia, for preoperative and postoperative analgesia, and for obstetrical analgesia during labor and delivery.

It is difficult to estimate accurately the worldwide requirements for these compounds. In the US, the DEA manufacturing quota in 2007 for oxymorphone for conversion to other medicinally important derivatives was 12 tons, compared to 1.8 tons for sale. Total consumption may be as high as 16.8 tons.[1] Estimates for combined naltrexone and naloxone production worldwide might therefore be around 10 tons for 2007. The worldwide demand for the compounds, shown in Figs. 1 and 2, whether legal or illicit, is tremendous and depends entirely on the supply of natural opiates. The estimates for the production of opiates worldwide are shown below in Tables 1 and 2.[2]

To date there is no practical source of morphine, either by chemical synthesis or through fermentation, that would compete with the cost of isolation. Of course, part of the reason that natural morphine is so inexpensive is the low-wage investment in harvesting it, mostly in Afghanistan, Turkey, and India. Were the workers there paid "western" wages, the price could never be as low as it is today (~$400–700/kg). It is very likely that in the event of a natural or a political emergency in those regions that produce morphine and other opiates the price of the medicinal derivatives would climb sharply, and, at that time, the synthetic approaches would receive enhanced credibility. The use of morphine and derivatives in medicine is permanently entrenched in our society and the pricing of "synthetic" morphine, however formidable, would not lead to a decrease in legal use.

Table 1 Worldwide production of raw materials. Designated as alkaloids contained in poppy straw (tons) (see footnote 1)

Opiate	2003	2004	2005	2006	2007
Morphine (**1**)	349.9	300.8	333.4	333.8	287.5
Codeine (**2**)	13.1	12.9	10.9	14.7	23.7
Thebaine (**3**)	65.4	77.0	94.4	92.2	125.5
Oripavine (**4**)	19.1	21.8	24.7	22.0	23.6

[1] http://www.incb.org/pdf/technical-reports/narcotic-drugs/2008/tables_of_reported_statistics.pdf.

[2] The authors thank Dr. Phil Cox, Noramco, Inc. for providing the information in Tables 1 and 2.

Table 2 Worldwide production of opiates in tons (numbers in *brackets* represent production in the US) (see footnote 1)

Opiate	2003	2004	2005	2006	2007
Morphine (**1**)[a]	376.7 (99.0)	354.7 (88.0)	397.6 (96.0)	415.8 (102.0)	440.0 (112.2)
Codeine (**2**)[a]	288.7 (67.9)	298.9 (63.7)	309.8 (70.4)	317.5 (73.4)	349.3 (77.0)
Oxycodone (**6**)	51.5 (41.1)	52.5 (40.3)	56.5 (40.3)	66.9 (49.7)	75.2 (55.7)
Hydrocodone (**7**)	29.8 (29.7)	32.1 (31.9)	35.6 (35.5)	39.7 (39.6)	38.2 (37.9)

[a]Includes morphine/codeine for conversion to other products

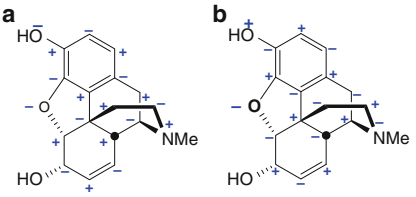

Fig. 3 Dissonant relationship in morphine connectivity (**a** = phenol priority, **b** = amine priority)[3,4]

Morphine has a fascinating history that can be gleaned by reading a number of sources [7, 8], that discuss its pharmacology [9, 10] and societal and historical impact on humans. The isolation of morphine precedes by some 25 years the "official" beginning of organic chemistry, the synthesis of urea by Wöhler. Its isolation from opium by Sertürner in 1805 [11–13] led to more than a century of effort before the final structure elucidation was completed [14]. Sertürner was also the first person to document "animal and human trials" with the newly isolated natural product [15]. Morphine, with its impact on chemists as well as on society in general, is likely one of the very few chemical entities that everyone recognizes.

Morphine's synthesis remains a serious challenge to this day. Until recently, the formal synthesis published by Kenner Rice [16] was its most efficient preparation. In 2009, Magnus reported a route to codeine with a reported overall yield of approximately 17% [17]. All academic syntheses reported in the literature, creative as these may be, suffer from lack of practicality, with the sole exception of Rice's disclosure, which has potential for scale-up.

Morphine, although not particularly complex, suffers from a complete "dissonant connectivity" (shown in Fig. 3) (Evans, 1972, Consonant and dissonant relationships. An organizational model, unpublished manuscript) [20], as we have previously

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[4]Hudlicky T, Reed, JW: the Way of Synthesis. Evolution of Design and Methods. Page 732. Publication year 2007. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.

pointed out on several occasions [18, 19]. Starting from either the phenolic oxygen (a) or the tertiary amine (b), it is not possible to draw a polarization assignment in which all electronegative atoms avoid an incorrect positive charge or in which alternating charges match. Because of this fact almost any strategy applied to the construction of morphine skeleton will, sooner or later, require major tactical maneuvers leading to an increase in the step-count and hence a decrease in practicality.

These issues have been addressed in detail in many previous reviews [18, 21–26]. Since our update on morphine synthesis was published 5 years ago in *Synlett* [18], several new approaches have appeared in the literature. This review summarizes the recent accomplishments and also provides for an update in methods used to approach some of the semisynthetic opiates.

The summary of accomplishments in the total synthesis of morphine alkaloids is depicted in Table 3. Most authors target codeine as the ultimate synthetic target; its attainment represents a formal total synthesis of morphine as Rice demonstrated its conversion to morphine by *O*-demethylation with BBr_3 [55]. Such a strategy has

Table 3 Summary of syntheses of morphine and derivatives

Principal author	Year	Target	Steps	Overall yield (as reported)
Gates [1, 2]	1952	Morphine	31	0.06
Ginsburg [27, 28]	1954	*rac*-Dihydrothebainone	21	8.9
Grewe [29, 30]	1967	*rac*-Dihydrothebainone	9	0.81
Rice [16]	1980	Dihydrocodeinone	14	29.7
Evans [31]	1982	*rac*-*O*-Me-thebainone A	12	16.7
White [32]	1983	Codeine	8[a]	1.8
Rapoport [33]	1983	*rac*-Codeine	26	1.2
Fuchs [34, 35]	1987	*rac*-Codeine	23	1.3
Tius [36]	1992	*rac*-Thebainone-A	24	1.1
Parker [37, 38]	1992	*rac*-Dihydrocodeinone	11	11.1
Overman [39]	1993	Dihydrocodeinone	14	1.9
Mulzer [40]	1996	Dihydrocodeinone	15	9.1
Parsons [41]	1996	Morphine	5[b]	1.8
White [42]	1997	*ent*-Morphine	28	3.0
Mulzer [43]	1997	Dihydrocodeinone	18	5.7
Ogasawara [44, 45]	2001	Dihydrocodeineone ethylene ketal	21	1.5
Taber [46]	2002	Morphine	27	0.51
Trost [47, 48]	2002	Codeine	15	6.8
Fukuyama [49]	2006	*rac*-Morphine	25	6.7
Hudlicky [50]	2007	*ent*-Codeine	15	0.23
Iorga/Guillou [51]	2008	*rac*-Codeine	17	0.64
Chida [52]	2008	*rac*-Dihydroisocodeine	24	3.8
Hudlicky [15]	2009	Codeine	18	0.19
Magnus [17]	2009	*rac*-Codeine	13	20.1
Stork [53]	2009	*rac*-Codeine	22	2.0
Fukuyama [54]	2010	Morphine	18	4.8

[a]*N*-Norreticuline was used as advanced starting material

[b]Only the last five steps of the synthesis have been published in the cited journal

a historical basis as, in the early days of structure elucidation, chemists found it easier to perform degradation on codeine because it was air stable. Morphine is more difficult to handle for several reasons. First, it has the properties of an amino acid, and, second, it is easily oxidized by air (hence the dark color of raw opium). Once it was established that morphine and codeine differ only by the absence or presence of the *O*-methyl group, all subsequent work was carried out with codeine.

Modern approaches no doubt subscribe to a similar strategy for the same reasons and thus most published syntheses stop at the stage of codeine. The syntheses are listed chronologically, with the yields "as reported." It is impossible to validate the claimed yields, especially overall yields, in cases where the reactions are performed on very small scales. Claims of reaction product yields above 94% are clearly erroneous in nature and should be viewed with suspicion. Similarly, the credibility of overall yields above 2 or 3% is questionable, as explained in a recent treatise on accuracy in reporting isolated product yields [56]. An exception to this statement are the yields reported in the synthesis of Rice [16], which was performed on a multigram scale.

2 Early Syntheses of Morphine

The following section highlights two milestone achievements in morphine synthesis. In 1952, Gates published the first total synthesis of the title alkaloid [1, 2] and was thus able to prove the structure of morphine proposed by Robinson in 1925 to be correct [57]. In addition, both enantiomers of morphine can be accessed following the published route as Gates performed a resolution of an advanced intermediate (see Scheme 2, compound **20**). Although Gates did not benefit from modern synthetic methods and structure elucidation techniques such as NMR spectroscopy, he was able to determine the identity of synthetic intermediates by derivatization and degradation studies of natural morphine. Written almost 60 years ago, the original report demonstrates the amazing knowledge of reactions, purification, and structure determination abilities of early synthetic chemists. Gates's full paper, as well as the earlier papers dealing with model studies, should be recommended reading assignment for all students of organic synthesis.

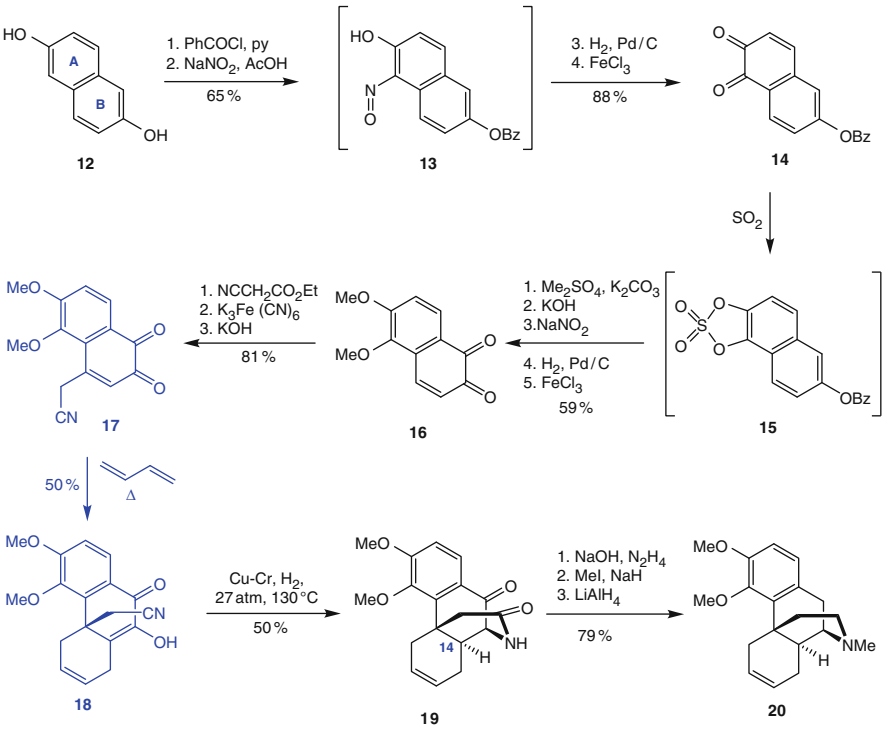
The very short and highly efficient biomimetic synthesis of morphine [16, 32] by Rice stands out in terms of overall yield and brevity; no subsequent contribution to this area exceeds this milestone achievement. The route follows the biosynthetic pathway and delivers dihydrocodeinone in almost 30% overall yield.

Although the syntheses of morphine by Gates and Rice have been reviewed on several occasions [14, 19, 24], they are included in this review as they constitute important highlights in the history of morphine research against which all other approaches should be judged. (For clarity and better understanding, the key transformations in featured syntheses are depicted in blue color within the schemes).

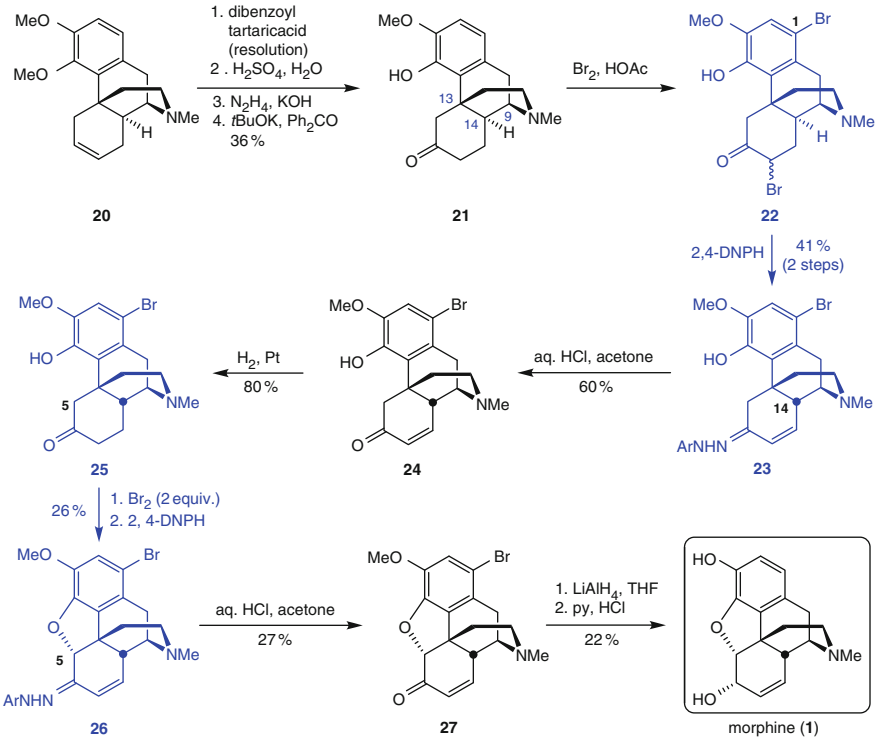
2.1 Gates (1952)

Gates utilized 2,6-dihydroxynaphthalene (**12**) as starting material and synthon for the A,B-ring system of morphine [58]. As outlined in Scheme 1, monoprotection to the corresponding benzoyl naphthol was followed by nitrosation (**13**) and formation of ortho quinone **14**. When treated with sulfur dioxide, cyclic sulfate **15** was formed which upon exposure to dimethyl sulfate provided the methylated catechol. An identical second nitrosation protocol delivered the B-ring of the alkaloid (**16**) for conjugate addition of ethyl cyanoacetate and subsequent reoxidation ($K_3Fe(CN)_6$). Decarboxylation under basic conditions gave nitrile **17**, which served as precursor for the key cycloaddition reaction. Diketone **18** (shown as enol) was obtained when nitrile **17** was heated with butadiene and the material was subjected to a copper chromite reduction, which provided amide **19**. A sequence involving Wolff–Kishner reduction, methylation, and $LiAlH_4$ reduction then afforded morphinan **20**.

With morphinan **20** in hand, the stage was set for the deracemization and functionalization of the D ring of the alkaloid. Resolution of racemic amine **20** with dibenzoyl tartrate (Scheme 2) afforded the isomer with correct configuration at C9 and C13 but epimeric at C14. The identity of the synthetic material was unambiguously confirmed



Scheme 1 Gates's synthesis of morphine – part 1

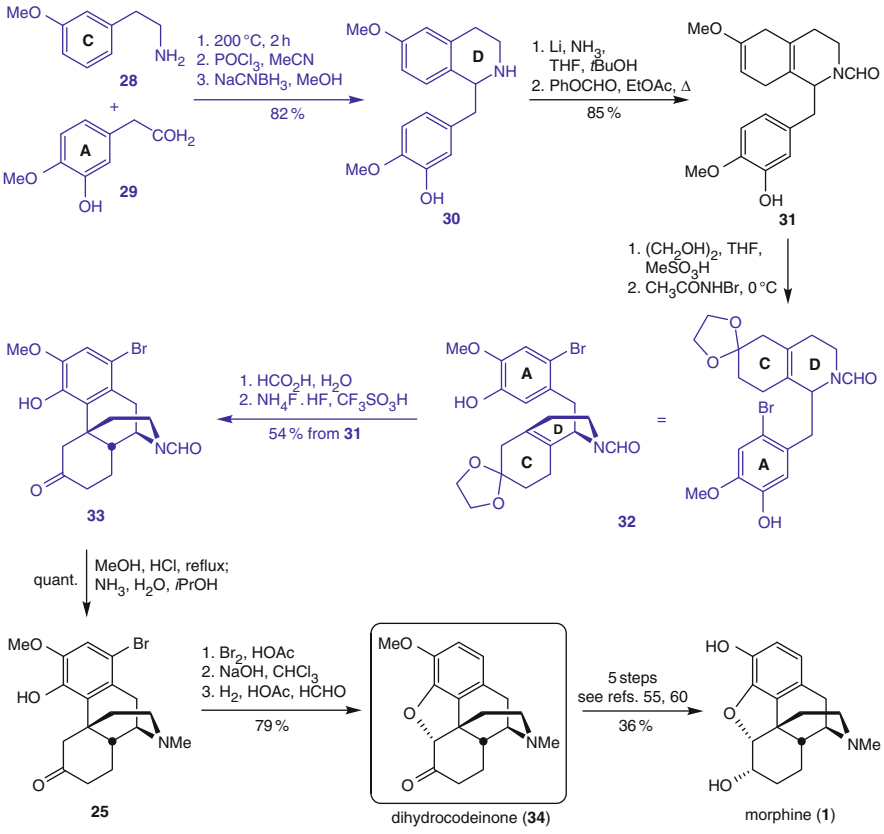


Scheme 2 Gates's synthesis of morphine – part 2

by direct comparison with degradation products obtained from natural codeine, thus confirming the structure of the morphinan skeleton as postulated by Robinson [57]. Furthermore, the remaining steps in the forward synthesis were facilitated by access to larger amounts of material from natural sources. Regioselective hydration and selective monodemethylation with hydrazine and KOH in ethylene glycol were followed by a modified Oppenauer oxidation and ketone **21** was obtained. α-Bromination (along with bromination of the aromatic ring) afforded **22**, which, upon reaction with 2,4-dinitrophenylhydrazine (2,4-DNPH), gave **23** with concomitant epimerization at C14 to the thermodynamically more favored natural configuration. Hydrolysis of the hydrazone and hydration gave **25**, which was brominated and treated with 2,4-DNPH, resulting in the closure of the dihydrofuran ring (**26**). Hydrolysis of the hydrazone delivered the α,β-unsaturated ketone **27**, which was converted into codeine via hydrogenation and reduction of the ketone and the aryl bromide. The use of the unsaturated hydrazone for both epimerization and α-bromination of the C5 position was indeed ingenious and attests to the level of thought that Gates had given to this protocol. Demethylation with hydrochloric acid in pyridine as described by Rapoport [59] concluded the first total synthesis and the final structure proof of morphine (**1**).

2.2 *Rice (1980)*

Rice achieved the shortest and the most efficient formal synthesis of morphine via a biomimetic approach with a Grewe cyclization as the key step (Scheme 3). Condensation of amine **28** and acid **29** is followed by a Bischler–Napieralski reaction and sodium cyanoborohydride reduction to establish the C,D-ring of the alkaloid (**30**). Birch reduction and subsequent N-formylation with phenyl formate gave the methyl enol ether **31**. Ketalization and bromination of the aromatic ring, to protect the para position, afforded **32** as the precursor for the key electrophilic cyclization reaction as described previously by Grewe [29]. This reaction was achieved via treatment of **32** with formic acid to release the β,γ-unsaturated ketone and subsequent exposure to $NH_4F \cdot HF$ in TfOH. Morphinan **33** was deformylated and converted into **25** by reductive amination before the dihydrofuran ring was established via bromination of the α-position of the ketone and deprotonation of the phenol. The aryl bromide was removed by hydrogenation in the presence

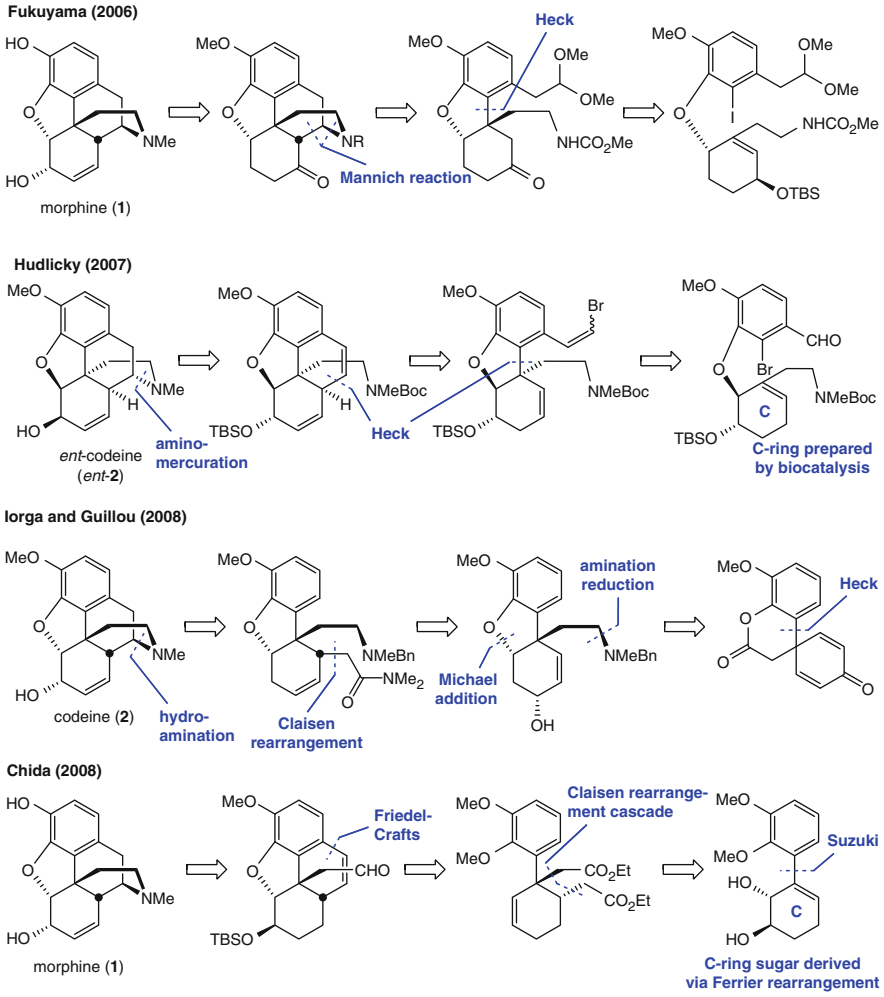


Scheme 3 Rice's biomimetic synthesis of morphine

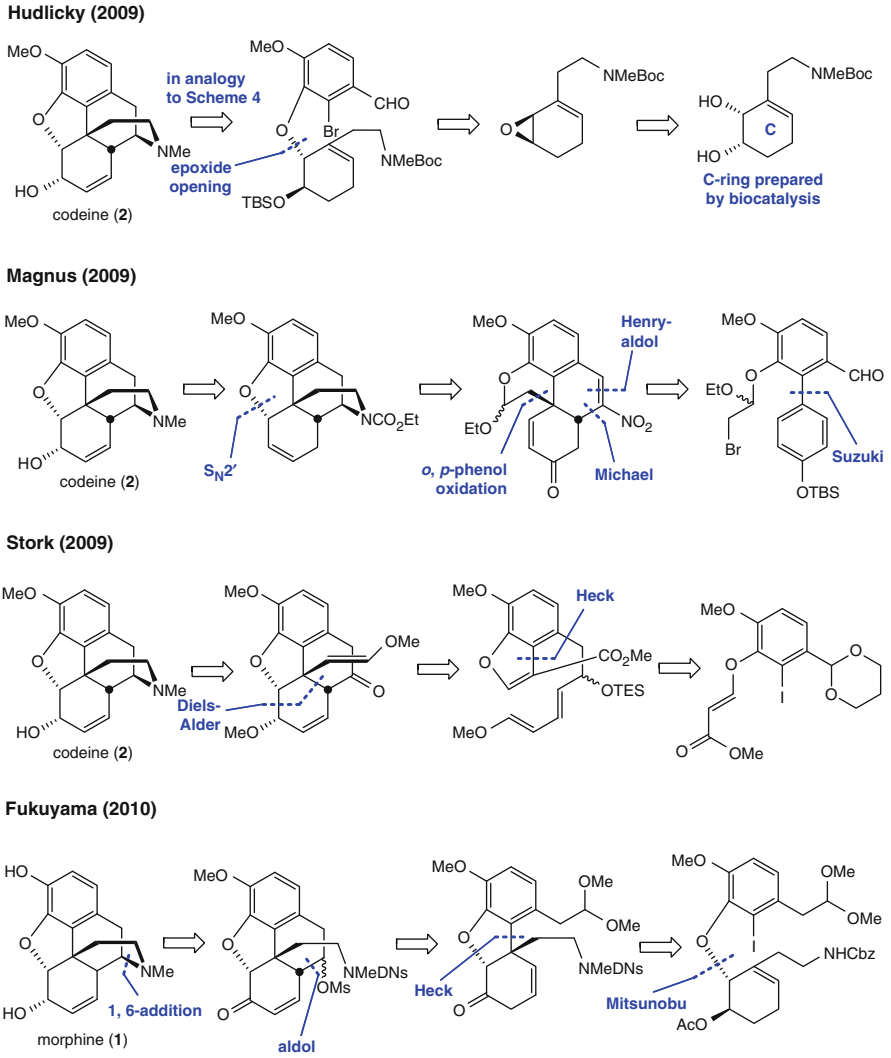
of formaldehyde and dihydrocodeinone (**34**) was isolated. The conversion of this material to morphine has been described before [55, 60] and the preparation of dihydrocodeinone (**34**) constituted the formal synthesis of codeine and/or morphine.

3 Recent Syntheses of Morphine and/or Codeine

This section summarizes all syntheses of morphine and codeine published since the last major review in this area was published in 2005 [18]. A general overview of the key strategic elements in all syntheses discussed within this section is provided in Schemes 4 and 5.



Scheme 4 Overview of strategies in the recent syntheses of morphinans – part 1



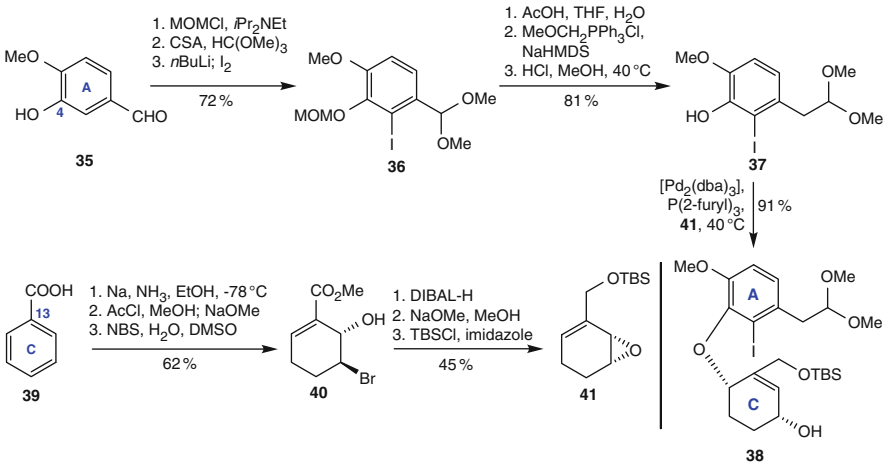
Scheme 5 Overview of strategies in the recent syntheses of morphinans – part 2

3.1 Fukuyama (2006)

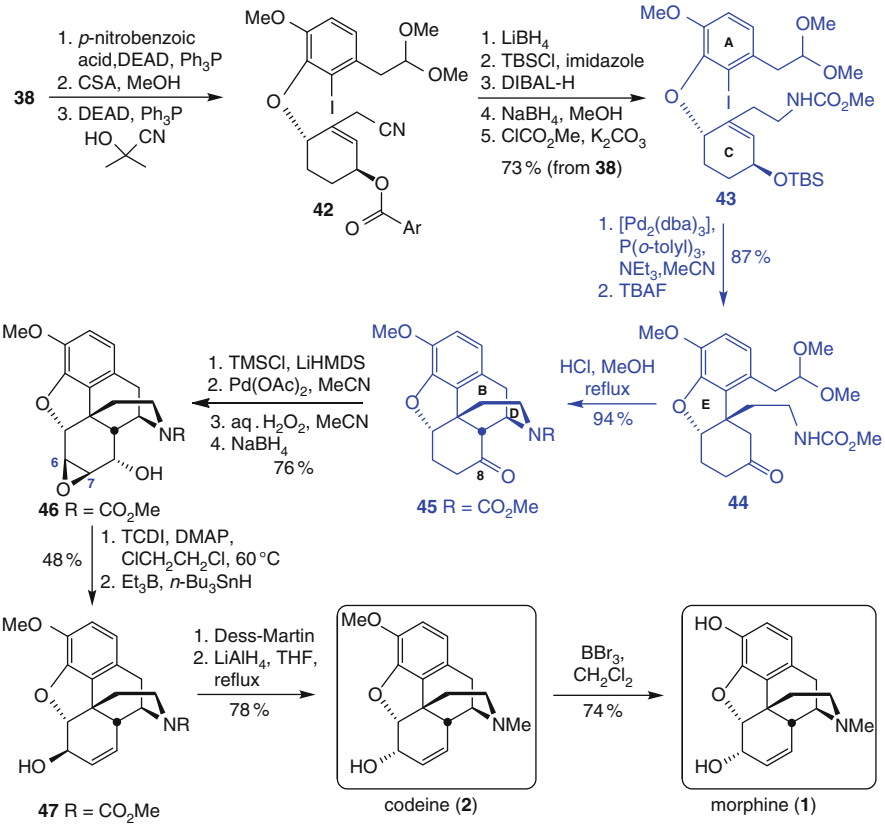
In 2006, Fukuyama presented an approach to codeine and morphine based on a Tsuji–Trost coupling and intramolecular Heck reaction as key steps [49, 61]. The synthesis was carried out in the racemic manifold; however, by devising an alternative stereoselective route to epoxide **41**, access to either the natural or the enantiomeric form of morphine could be achieved.

As outlined in Scheme 6, isovanillin (**35**) was converted to aryl iodide **36** via MOM-protection, protection of the aldehyde, and subsequent iodination. Hydrolysis of the acetal and Wittig olefination delivered phenol **37** after exposure of the intermediate aldehyde to methanolic hydrochloric acid. Epoxide **41**, the coupling partner of phenol **37** in the key Tsuji–Trost-reaction, was synthesized from benzoic acid following a procedure developed by Fukuyama for the synthesis of strychnine [62]. Birch reduction of benzoic acid with subsequent isomerization of one double bond into conjugation was followed by esterification and bromohydrin formation (**40**). The ester was reduced and the bromohydrin was treated with base to provide the epoxide. Silylation concluded the preparation of epoxide **41**, the coupling partner for iodide **37**, and both fragments were reacted in the presence of palladium to attain iodide **38**.

The configuration of the secondary alcohol in **38** (Scheme 7) was inverted by means of a Mitsunobu reaction with *p*-nitrobenzoic acid, and the silyl ether was cleaved under acidic conditions. The primary alcohol was converted into nitrile **42** under Mitsunobu conditions utilizing the cyanohydrin derived from acetone. Reductive cleavage of the *p*-nitrobenzyl ester was followed by TBS protection of the resulting secondary alcohol and the installation of a methyl carbamate (**43**) before the key Heck cyclization was achieved in excellent yield. The silyl enol ether obtained after this crucial transformation was cleaved and ketone **44** was obtained as single isomer. Next, the B and D rings were closed, presumably via an intramolecular Mannich-type reaction, by heating carbamate **44** to reflux in methanolic hydrogen chloride. With morphinan **45** in hand, Fukuyama turned his attention to the functionalization of the C-ring of the alkaloid. Epoxidation of the α,β-unsaturated ketone obtained after a Segusa-oxidation protocol furnished alcohol **46** after sodium borohydride reduction. The hydroxy moiety was converted into a thiocarbonate and subjected to radical reaction conditions resulting in epoxide



Scheme 6 Fukuyama's synthesis of morphine – part 1

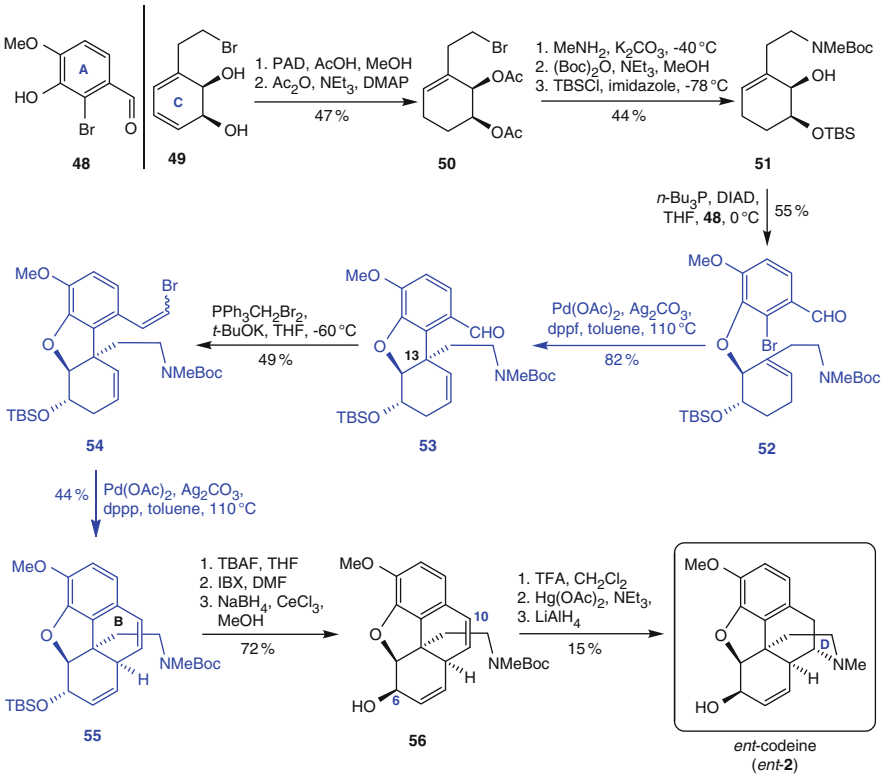


Scheme 7 Fukuyama's synthesis of morphine – part 2

opening and formation of allylic alcohol **47**. The synthesis of codeine (**2**) was accomplished after inversion of the alcohol via the known oxidation/reduction sequence [46, 60]. Morphine (**1**) was obtained after cleavage of the methyl ether following a procedure published by Rice in 1977 [55].

3.2 Hudlicky (2007)

In 2007, Hudlicky and co-workers reported the preparation of *ent*-codeine (*ent*-**2**) with the enzymatically derived cyclohexadiene diol **49** as the starting material (Scheme 8) [50]. Key steps in this synthesis involve the introduction of the aryl moiety via a Mitsunobu reaction, a Heck reaction to establish the carbon bond between the aromatic ring and C13 followed by a second Heck reaction to close



Scheme 8 Hudlicky's synthesis of *ent*-codeine

the B-ring with concomitant shift of the double bond into the position present in the natural product and final closure of the D-ring.

Whole cell oxidation of β-bromoethylbenzene with recombinant *Escherichia coli* JM109 (pDTG601A) [63] afforded cyclohexadiene-*cis*-diol **49**, which was selectively reduced with potassium azodicarboxylate (PAD) before the hydroxy functionalities were protected as acetate **50**. The *bis*-acetate was reacted with methylamine and the corresponding secondary amine was obtained with concomitant cleavage of the acetate functionalities. N-Boc-protection and silylation of the distal hydroxy functionality resulted in allylic alcohol **51**, which served as coupling partner in a Mitsunobu reaction with phenol **48**. Intramolecular Heck cyclization of aryl bromide **52** afforded aldehyde **53** in excellent yield as a single isomer. A Wittig reaction was then used to introduce a vinyl bromide moiety and served to prepare the substrate for the second Heck cyclization reaction to close the B-ring and simultaneously shift the double bond in the position present in the natural product. The configuration of the C6 hydroxy group in **55** was corrected via the known oxidation/reduction sequence [46, 60] after the cleavage of the silyl ether and **56** was isolated. The closure of the

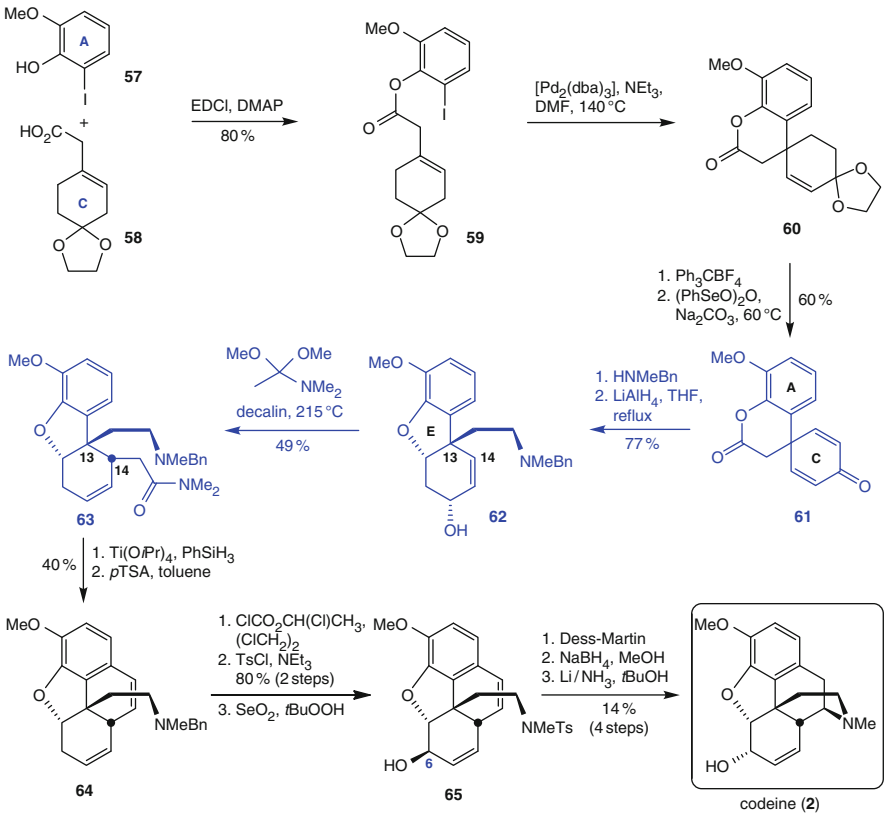
D-ring concluded the synthesis of *ent*-codeine. All attempts to repeat the hydroamination protocol published by Trost for the same synthetic intermediate [47, 48] failed and a different strategy for this operation had to be devised. The D-ring was established by removal of the Boc-protecting group followed by aminomercuration of the benzylic double bond and intramolecular trapping of the resulting organomercurial species by the ethylamino sidechain. The final steps required the reduction ($LiAlH_4$) of the organomercury compounds formed during the aminomercuration protocol.

Two years after the publication of *ent*-codeine, Hudlicky also presented a route towards codeine (natural series) employing the same enzymatically derived starting material (**49**) [15]. The synthesis of the natural isomer is outlined in Sect. 3.5.

3.3 Iorga and Guillou (2008)

Iorga and Guillou presented a route to racemic codeine with a lactone opening/Michael addition sequence and an Eschenmoser–Claisen rearrangement as key steps (Scheme 9) [51]. Acid **58**, accessible by Birch reduction of *p*-methoxyphenylacetic acid and subsequent ketalization with ethylene glycol, was esterified with 2-iodo-6-methoxyphenol (**57**). Subsequent Heck cyclization of ester **59** delivered spirocyclic lactone **60**. Hydrolysis of the ketal and oxidation of the corresponding α,β-unsaturated ketone delivered lactone **61**, which was allowed to react with *N*-methylbenzylamine, resulting in lactone opening and amide formation. Upon reduction with $LiAlH_4$ in refluxing THF, the amine **62** was obtained. During the course of this reaction the deprotonated phenol acted as the nucleophile in a Michael-type addition with concomitant formation of the E-ring. Thus, the exocyclic two-carbon chain in **58** served a dual purpose: it was used as a convenient tether for the intramolecular Heck cyclization of **59** and later provided the ethylamino bridge to complete ring D of morphine.

The allylic alcohol was subjected to an Eschenmoser–Claisen rearrangement with dimethylacetamide dimethylacetal to introduce the C14 substituent in a stereoselective manner. Reduction of the amide to the corresponding aldehyde with phenyl silane in the presence of $Ti(OiPr)_4$ was followed by an acid-promoted closure of the C-ring of codeine. In order to prevent N-oxidation, the amine was converted to the corresponding tosylamide, via debenzylation and treatment with tosyl chloride, before the allylic alcohol was introduced by the reaction of the alkene with selenium dioxide (**65**). The stereochemistry of the C6 hydroxy functionality was corrected by applying the well-known oxidation/reduction protocol [46, 60] before the benzylic double bond was reductively removed under Birch conditions. Codeine (**2**) was obtained in 17 steps with an overall yield of approximately 0.6%.



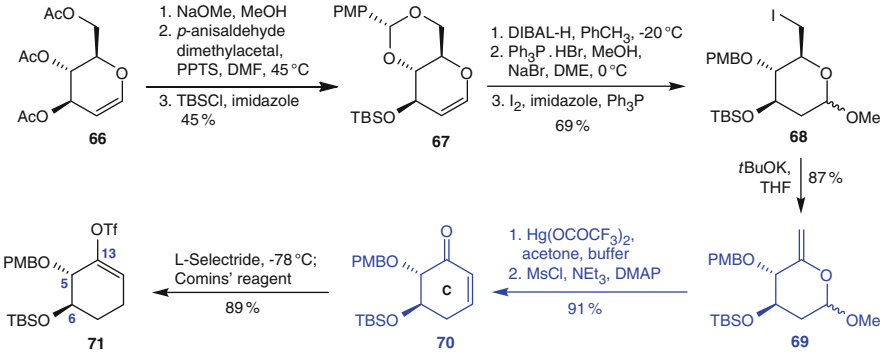
Scheme 9 Iorga and Guillou's synthesis of codeine

3.4 Chida (2008)

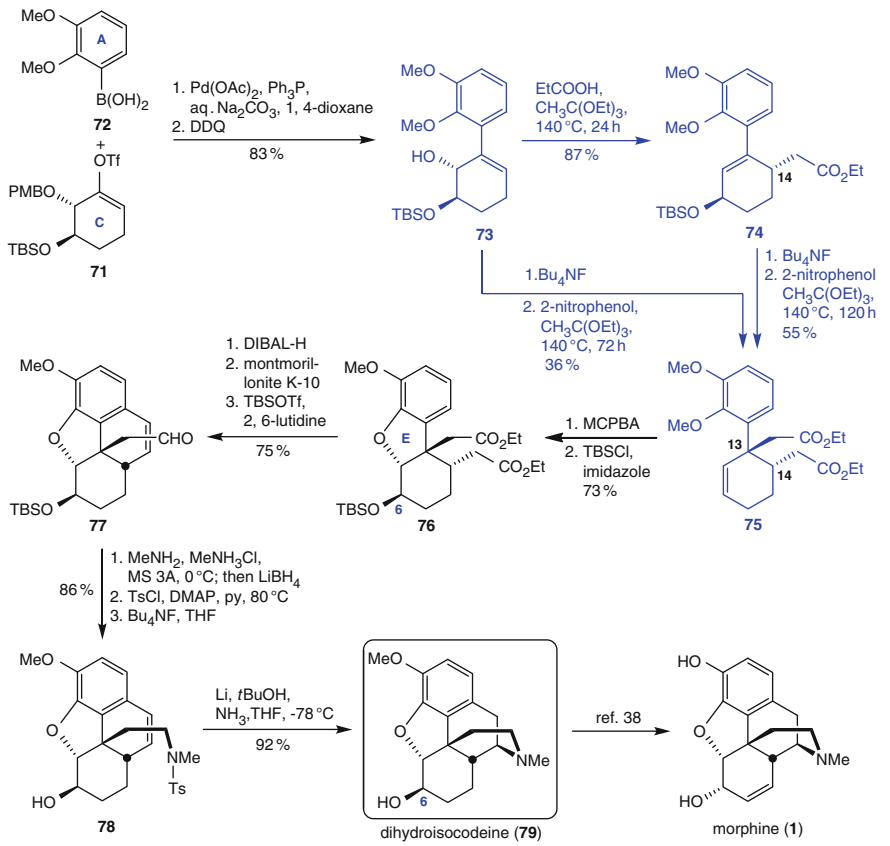
With the preparation of racemic dihydroisocodeine (**79**), Chida reported a formal synthesis of morphine [52]. The synthesis is based on a cascade of sequential Claisen rearrangements of an allylic vicinal diol derivative as key steps. The Claisen rearrangement protocol, as an efficient strategy for the installation of the C13 quaternary carbon, was successfully employed in the preparation of the Amaryllidaceae alkaloid galanthamine, published 1 year before the synthesis of dihydroisocodeinone [64].

With commercially available tri-*O*-acetyl-D-glucal (**66**) as the requisite chiral starting material, dihydroisocodeine was obtained in 24 synthetic operations. The route to the alkaloid is outlined in Schemes 10 and 11.

The C-ring of morphine was prepared from tri-*O*-acetyl-D-glucal (**66**) as shown in Scheme 10. Saponification of the acetate moieties in **66** under basic conditions was followed by treatment with *p*-anisaldehyde dimethylacetal before the C6 hydroxy functionality (morphine numbering) was protected as its silyl ether (**67**).



Scheme 10 Chida's synthesis of dihydroisocodeine – part 1



Scheme 11 Chida's synthesis of dihydroisocodeine – part 2

Reductive cleavage of the *para*-methoxyphenyl (PMP-) group released the primary alcohol and the compound was converted into the corresponding methyl glycoside upon reaction with methanol in the presence of $Ph_3P.HBr$ [65]. Subsequently, the primary alcohol was replaced by iodine to yield **68** to pave the way for the introduction of the exomethylene functionality required for the key Ferrier's carbocyclization reaction. Carbocycle **70** was obtained after exposure of 5-enopyranoside **69** to $Hg(OCOCF_3)_2$ in acetone/acetate buffer and the subsequent β-elimination. The synthesis of the C-ring of the alkaloid was completed by 1,4-reduction and formation of the vinyl triflate **71** with the Comins' reagent.

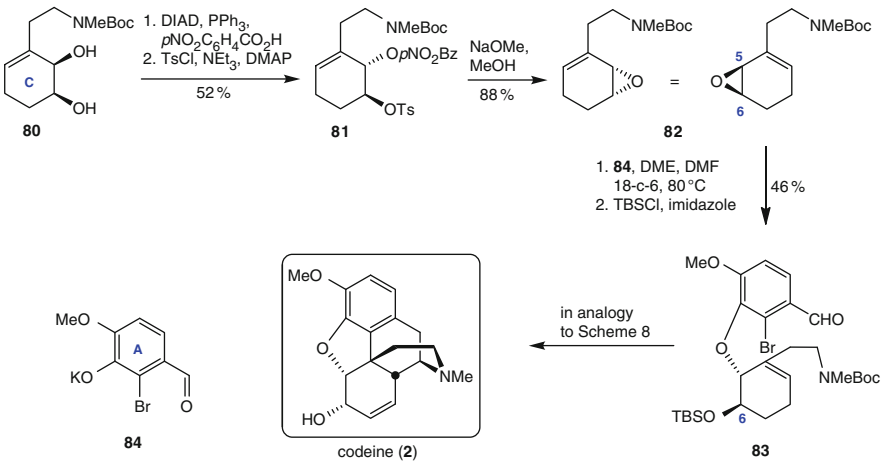
Suzuki coupling of vinyl triflate **71** with boronic acid **72** (Scheme 11) was followed by the cleavage of the PMB ether by means of a dichloro dicyano benzoquinone (DDQ) oxidation to afford allylic alcohol **73** in good yield. When treated with triethyl orthoacetate, the first Claisen rearrangement of **73** took place and ester **74** was obtained in nearly 90% yield as a single stereoisomer. The silyl ether was then cleaved and the corresponding alcohol was used in a second Claisen rearrangement, which delivered the *bis*-ester **75** in 55% yield. *Bis*-ester **75** could also be obtained in a cascade Claisen sequence as shown in Scheme 11. To this end the silyl group in **73** was cleaved to afford the corresponding diol which was then treated with triethyl orthoacetate and heated to 140 °C for 72 h in the presence of 2-nitrophenol, allowing the product of the double Claisen rearrangement, namely compound **75**, to be isolated in 36% yield.

The E-ring of morphine was installed via epoxidation of the C5–C6 double bond and simultaneous dealkylating/epoxide opening sequence using MCPBA as oxidant. Silylation of the secondary alcohol at C6 (**76**) was followed by elaboration of the B-ring of the alkaloid. This was accomplished by DIBAL-H reduction of both ester functionalities in **76** to the corresponding aldehydes and subsequent Friedel-Crafts type cyclization reaction. Elimination of the resulting hydroxyl group afforded alkene **77**. Reductive amination and tosylation of the nitrogen gave **78** after cleavage of the C6 silyl ether. The D-ring was finally established upon treatment of **78** under Birch conditions and dihydroisocodeine **79** was obtained. As this material was previously successfully converted into morphine [38] this achievement formalized the synthesis.

3.5 Hudlicky (2009)

Two years after the synthesis of *ent*-codeine [50], Hudlicky published a route to the natural enantiomer of the alkaloid [15]. With biocatalytically-derived cyclohexadiene-*cis*-diol **49** (Scheme 8), the same starting material in the synthesis of the enantiomer of the natural product was utilized. The strategic difference between the two syntheses is based on the preparation of epoxide **82** obtained via a Mitsunobu inversion/elimination protocol of the diol **80** (Scheme 12).

The cyclohexadiene-*cis*-diol **49**, derived enzymatically from β-bromoethylbenzene, was converted into Boc-protected amine **80** as described previously and



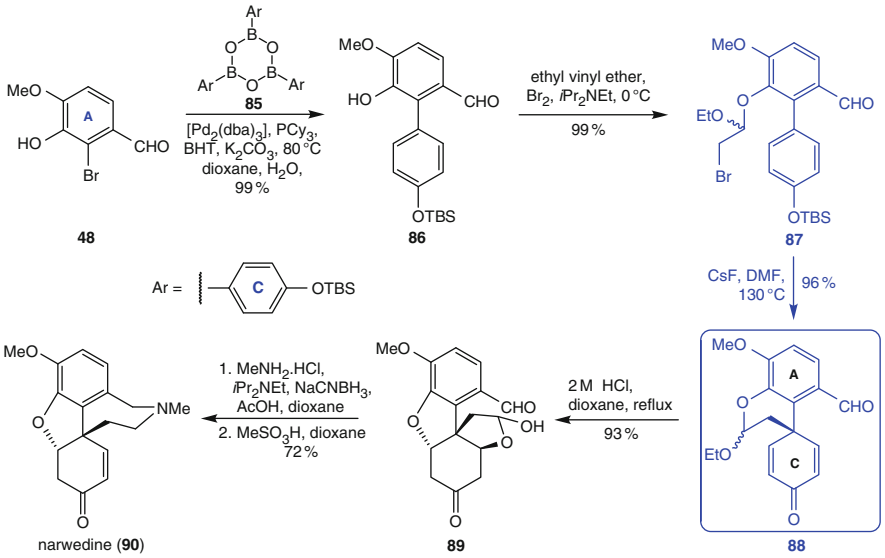
Scheme 12 Hudlicky's synthesis of codeine

outlined in Scheme 8. Inversion of the allylic alcohol by means of a Mitsunobu reaction was followed by tosylation of the remaining hydroxyl functionality (**81**). Basic hydrolysis of the *p*-nitrobenzoate afforded epoxide **82**, which served as the electrophile in the reaction with the potassium salt of bromoisovanillin (**84**). Silylation of the C6 hydroxy group (morphine numbering) afforded aryl bromide **83** and the remaining steps in the route to codeine were carried out in analogy to the preparation of the enantiomer published in 2007. With this slight modification of the synthetic strategy, the natural product and the enantiomeric series of the target compound become available utilizing the same biocatalytically-derived starting material.

3.6 Magnus (2009)

In 2009, Magnus published an approach towards codeine that also constitutes a formal synthesis of the Amaryllidaceae alkaloid galanthamine by the preparation of narwedine (**90**) via a common precursor [17]. Key step in the reaction sequence is an *o*-*p*-phenolic oxidation resulting in the aforementioned common precursor of galanthamine and codeine.

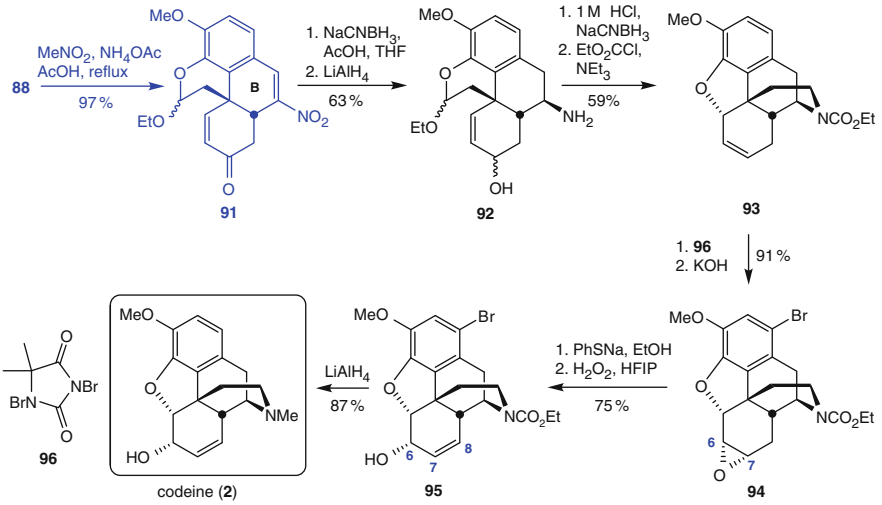
Commercially available bromoisovanillin (**48**) was reacted with the triarylboroxine **85** in a Suzuki cross-coupling to afford biphenyl **86** as outlined in Scheme 13. Reaction of this phenol with ethyl vinyl ether in the presence of bromine afforded ether **87** which was converted into spirocycle **88** by treatment with cesium fluoride in DMF at 130 °C. Spirocycle **88** served as common intermediate in the syntheses of both natural products mentioned above.



Scheme 13 Magnus's synthesis of codeine – part 1

Acid-catalyzed hydrolysis of **88** afforded **89**, which upon reductive amination conditions followed by treatment with methanesulfonic acid gave narwidine (**90**). Racemic narwidine is known to yield enantiomerically pure galanthamine – the corresponding allylic alcohol – by spontaneous resolution and subsequent L-selectride reduction [66]. Thus, the preparation of narwidine concludes the formal synthesis of the Amaryllidaceae alkaloid galanthamine.

The synthesis of codeine from the common intermediate **88** is shown in Scheme 14. Reaction of enone **88** with nitromethane gave **91** via a Henry-aldol/Michael addition cascade with *cis*-relationship between the newly formed B-ring and the C-ring. The benzylic double bond in **91** was reductively removed with sodium cyanoborohydride before the compound was treated with $LiAlH_4$ to afford allylic alcohol **92**. Reductive amination established the morphinan skeleton and the secondary amine was protected as carbamate (**93**). With the morphinan skeleton in hand, the remaining operations were devoted to the functionalization of the C-ring of the alkaloid. The double bond was shifted to the position present in the natural product with concomitant installation of the hydroxy functionality, with the correct stereochemical relationship, via epoxide **94**. Treatment of alkene **93** with 5,5-dimethyl-1,3-dibromohydantoin (**96**) resulted in the formation of the corresponding bromohydrin, which, upon exposure to base, delivered the epoxide. As the bromohydrin formation step also resulted in the bromination of the aromatic A-ring of codeine, an additional reduction step had to be added to the reaction sequence. Treatment of epoxide **94** with thiophenolate and subsequent oxidation with hydrogen peroxide in hexafluoroisopropanol (HFIP) completed the functionalization of the C-ring (**95**) and codeine (**2**) was obtained after a final $LiAlH_4$ reduction to remove the aryl bromide.

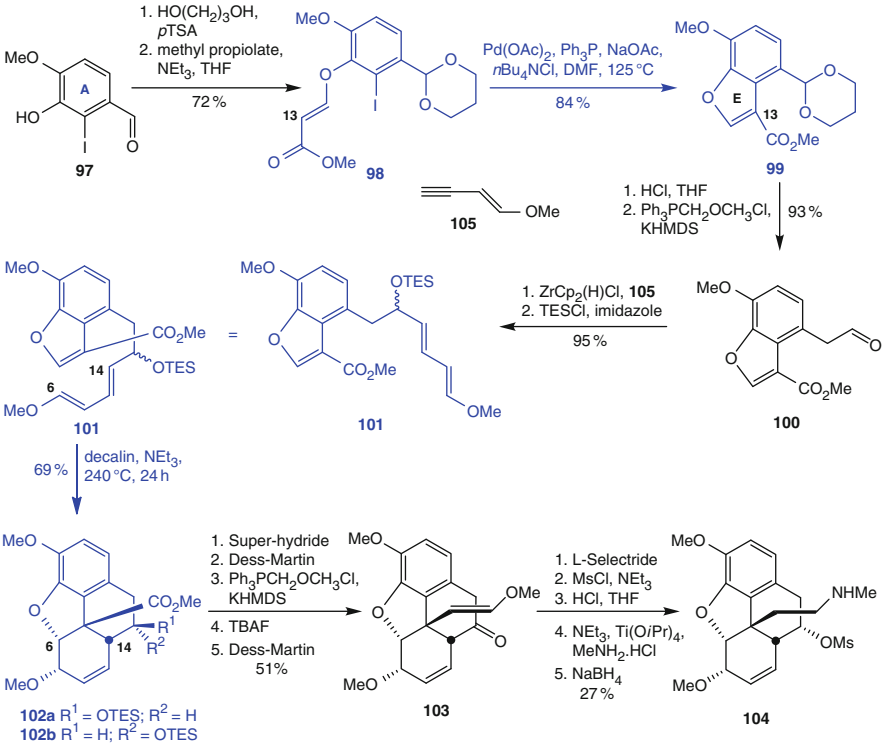


Scheme 14 Magnus's synthesis of codeine – part 2

3.7 Stork (2009)

Stork's strategy towards racemic morphine comprises a Diels–Alder cycloaddition reaction of a benzofuran to establish the B- and C-ring of morphine as the key step [53]. The reaction sequence started with the ketalization of iodoisovanillin **97** (Scheme 15). Subsequently, the phenol was reacted with methyl propiolate to afford **98** as precursor for the installation of the benzofuran moiety via a palladium-catalyzed Heck cyclization (**99**). Next, the key intermediate was prepared for the Diels–Alder reaction. Hydrolysis of the acetal under acidic conditions and Wittig homologation afforded aldehyde **100**, which was converted to diene **101** via hydrozirconation of acetylene **105** employing the Schwartz reagent and subsequent reaction with aldehyde **100** followed by silylation of the secondary alcohol.

When heated to 240 °C in decalin, Diels–Alder precursor **101** underwent the desired cycloaddition reaction and afforded **102a** as the major product. It is noteworthy that four contiguous stereocenters in the correct relative configuration required for the preparation of the natural product were established in this operation and only a minor amount of **102b**, diastereomeric at C9, was formed during the course of the reaction. As the closure of the D-ring was envisaged to proceed via mesylate **104**, the diastereomeric mixture of **102a** and **102b** was not separated, as the C9 alcohol had to be oxidized to the corresponding carbonyl at a later stage. Before this oxidation was carried out, the ester was converted into an aldehyde as precursor for a Wittig reaction to form the corresponding enol ether. Desilylation and subsequent Dess-Martin oxidation of the C9-hydroxy moiety resulted in ketone **103**, which was reduced and mesylated to afford selectively the required stereoisomer for the formation of the D-ring. The methylamino functionality was introduced via a reductive amination protocol after hydrolysis of the enol ether (**103**).



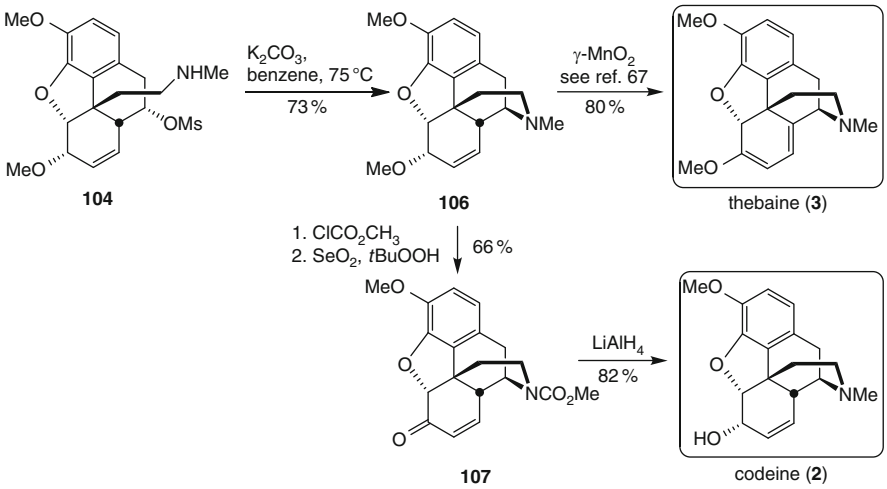
Scheme 15 Stork's synthesis of thebaine and codeine – part 1

The closure of the D-ring succeeded under basic conditions via an S_N2 displacement of the mesylate by the secondary amine (Scheme 16). Morphinan **106** was then successfully converted into thebaine (**3**) via manganese dioxide mediated oxidation following a procedure by Rapoport [67].

Direct cleavage of the allylic methyl ether in **106** with boron tribromide afforded codeine in only minor amounts. Better yields were obtained when **106** was converted to the corresponding carbamate before a selenium dioxide mediated oxidation delivered ketone **107**. Stereoselective reduction of the ketone and concomitant generation of the *N*-methyl group concluded the synthesis of codeine [60, 68]. This synthesis reported by Stork and co-workers provided a closure to several years of research, some of which has been reported in Ph.D. dissertations [69].

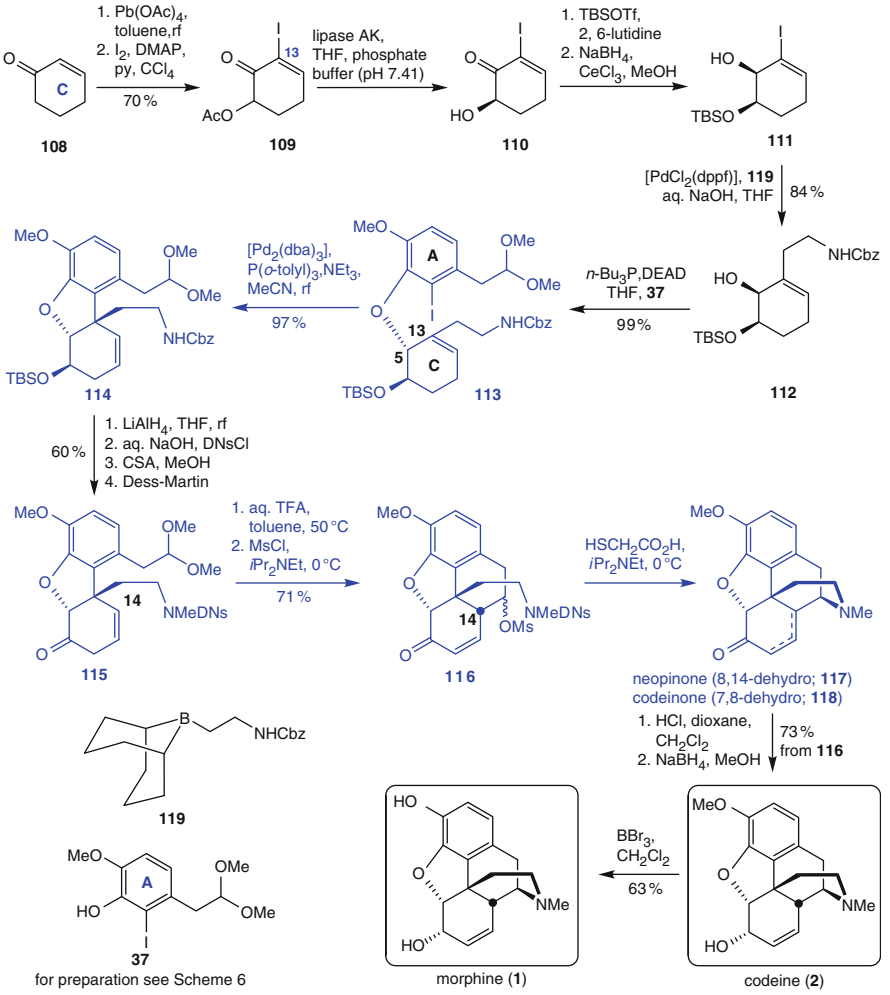
3.8 Fukuyama (2010)

In 2006, Fukuyama reported his first synthesis of morphine [49], followed 4 years later by an improved route [54]. As shown in Scheme 17, cyclohexenone (**108**) was



Scheme 16 Stork's synthesis of thebaine and codeine – part 2

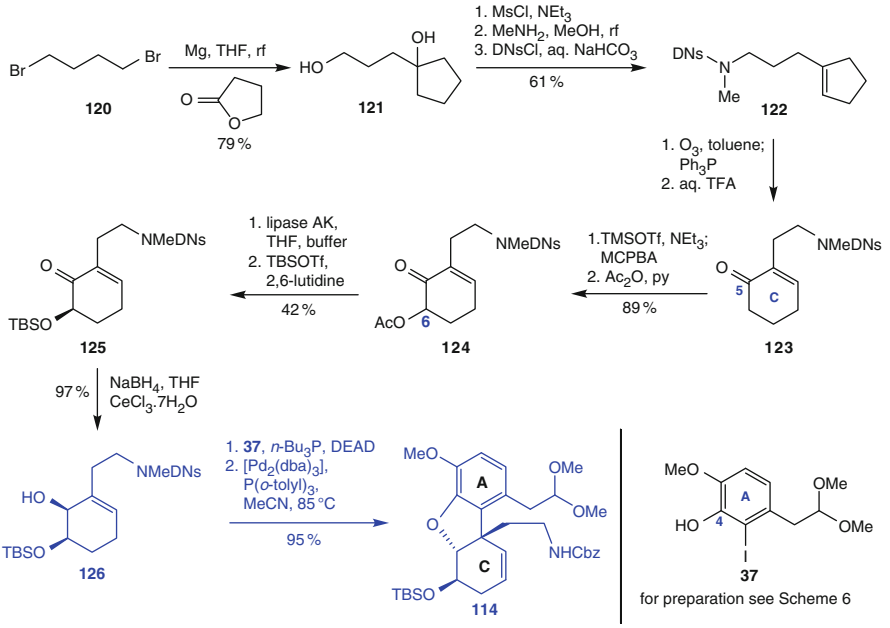
subjected to α-acetoxylation and subsequent iodination to afford iodoketone **109**. Enzymatic resolution of the racemic material with lipase AK yielded alcohol **110**, which was silylated before the α,β-unsaturated ketone was converted to allylic alcohol **111** via Luche reduction. Palladium-catalyzed Suzuki-Miyaura coupling of iodide **111** with boron reagent **119** afforded alcohol **112**, which was used in a Mitsunobu reaction with phenol **37** (for the preparation of this compound see Sect. 3.1 of this review) to give the precursor for the intramolecular Heck reaction with the requisite stereochemistry at C5 (**113**). The cyclization proceeded in high yield and afforded **114**. Reduction of the carbamate was followed by protection of the secondary amine with 2,4-dinitrobenzene-sulfonyl chloride (DNsCl) before the silyl group was cleaved and the resulting alcohol oxidized to the corresponding ketone **115**. Exposure of this β,γ-unsaturated ketone to TFA resulted in hydrolysis of the acetal and subsequent closure of the B-ring via an intramolecular aldol reaction. Mesylation of the secondary hydroxy moiety furnished **116** and prepared the compound for the elimination reaction and subsequent construction of the D-ring of the alkaloid. Treatment of mesylate **116** with base resulted only in the elimination of the β-epimer while the α-epimer remained unchanged and harsher reaction conditions led to decomposition of the starting material. Therefore, the 2,4-dinitrobenzene-sulfonyl group in **116** was cleaved with mercaptoacetic acid and Hünig's base resulting in elimination of both epimeric mesylates with subsequent closure of the D-ring and a mixture of neopinone (**117**) and codeinone (**118**) was obtained. Presumably, this closure proceeds via 1,6-addition of the amine to the dienone **128** (Scheme 19) formed by the elimination of the mesylates. Such strategy was used previously by Fuchs in his morphine synthesis [34, 35]. The synthesis of morphine was completed by acid mediated conversion of the mixture of neopinone and codeinone to pure codeinone [35] and subsequent sodium borohydride



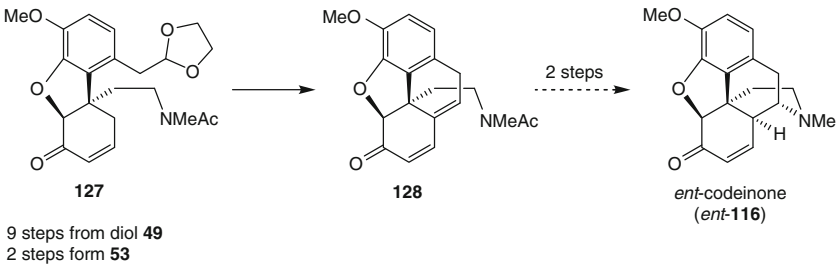
Scheme 17 Fukuyama's synthesis of codeine and morphine

reduction to yield codeine. Morphine was obtained by reaction with boron tribromide following the procedure first reported by Rice [55].

Fukuyama also presented an alternative route to the advanced intermediate **114** as shown in Scheme 18 with an early introduction of the protected amino functionality. Reaction of γ-butyrolactone with the Grignard reagent derived from 1,4-dibromobutane (**120**) afforded diol **121**. Mesylation of the primary hydroxyl functionality with concomitant elimination of the tertiary one was followed by reaction with methylamine and protection of the resulting secondary amine to give alkene **122**. Ozonolysis of the double bond in **122** and subsequent intramolecular aldol condensation of the resulting ketoaldehyde afforded cycohexenone **123**. Rubottom oxidation and acetylation gave **124**, which served as substrate in the lipase-



Scheme 18 Fukuyama's synthesis of codeine and morphine – alternative route to intermediate **114**



Scheme 19 Hudlicky's approach to *ent*-codeinone

catalyzed resolution in close analogy to the approach discussed above. Silylation (**125**) and Luche reduction delivered allylic alcohol **126**, which was used in a Mitsunobu reaction with previously described phenol **37**. The preparation of intermediate **114** was achieved by intramolecular Heck cyclization forming the E-ring of morphine.

At the time of Fukuyama's publication a virtually identical approach was nearing completion in the Hudlicky group. Enone **127** (Scheme 19), analogous to **115**, was synthesized in the *ent*-series in nine steps from diol **49**, previously used in the synthesis of *ent*-codeine, Scheme 8. Cyclization of **127** to dienone **128** leaves only two steps to complete *ent*-codeinone (*ent*-**116**) [70, 71].

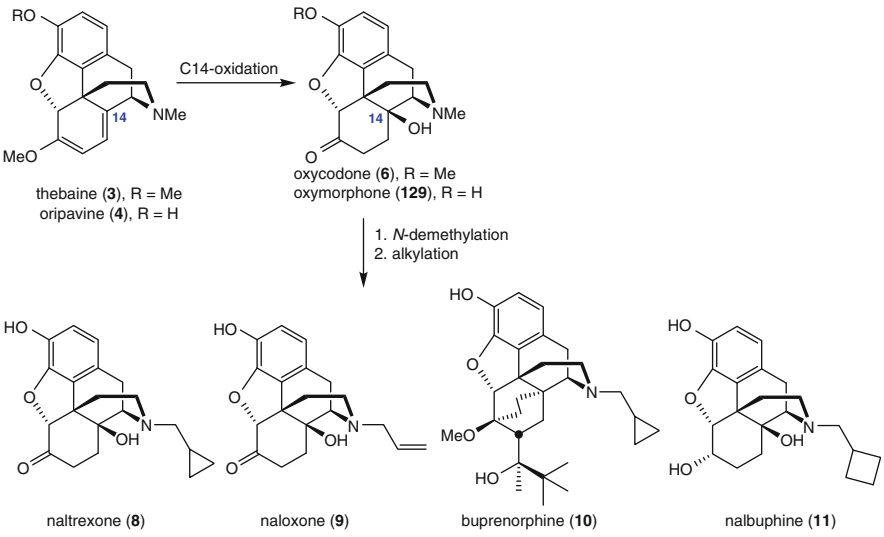
4 Medicinally Important Derivatives of Morphine

The preparation of medicinally important derivatives of morphine has recently been summarized in a review article [72]. Therefore, this section only provides a general outline.

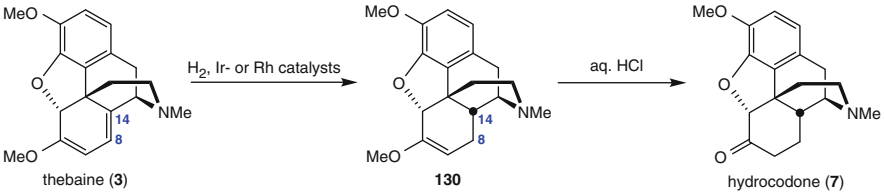
The commercial production of medicinally useful opiate-derived products is faced with two major challenges. The first of these is the introduction of the C14 hydroxy group and the second is the formal exchange of the *N*-methyl group for another alkyl group such as allyl (naloxone, **9**), methylcyclopropyl (naltrexone, **8**, buprenorphine, **10**) or methylcyclobutyl groups (nalbuphine, **11**) as outlined in Scheme 20 [72–77].

The oxidation of C14 is best accomplished by oxidation of either thebaine (**3**) or oripavine (**4**) and the large-scale production of the corresponding ketones has been adequately solved. Such methods include, for example, the addition of singlet oxygen to thebaine (**3**) and subsequent reduction of the resulting endoperoxide [78, 79] or treatment of (**3**) with formic acid and hydrogen peroxide [80]. The preparation of hydrocodone, hydromorphone, and related derivatives can be accomplished via hydrogenation utilizing transition metal catalysts [81–83]. In 2007, Hudlicky reported studies on regioselective hydrogenation of thebaine (**3**) with rhodium and iridium catalysts to form 8,14-dihydrothebaine (**130**), which can be converted to hydrocodone (**7**) via acidic hydrolysis of the enolether as shown in Scheme 21 [84].

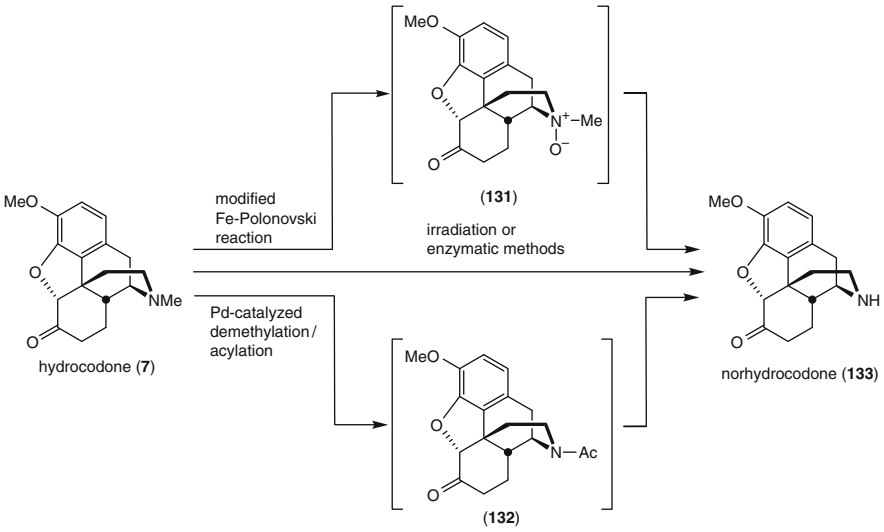
The second issue, the exchange of the *N*-alkyl group, is much more challenging. The current methods include the use of reagents such as cyanogen bromide (von Braun demethylation) [85, 86] or methyl chloroformate [87–91]. Neither is



Scheme 20 Preparation of medicinally important morphine derivatives



Scheme 21 Hudlicky's transition metal catalyzed conversion of thebaine to hydrocodone



Scheme 22 *N*-Demethylation strategies of hydrocodone

particularly environmentally sound or efficient and the actual exchange of a methyl group for any other alkyl group requires multiple steps. Demethylation under irradiation was reported by Scammells [92]. Despite promising results on simple substrates, the method fails to deliver demethylated derivatives of the more complex alkaloids or derivatives in good yield. Once the N-demethylation is accomplished the secondary amine in *O*-protected noroxymorphone is alkylated with the particular alkyl halide.

Among the more modern methods of N-demethylation of hydrocodone are palladium-catalyzed N-demethylation/acylation as reported by Hudlicky [93, 94], or iron-mediated reduction of *N*-oxides published by Scammells [95]. Scammells developed different modifications of this variation of the Polonovski protocol and the reaction can be carried out via a two step procedure (oxidation and in situ demethylation of the activated alkaloid) [96] or under very mild conditions in acetate buffer [97]. Quite recently, a protocol was reported utilizing ferrocene as demethylation catalyst [98].

Alternative methods for the demethylation include biocatalytic protocols mediated by fungal cytochromes [99, 100]. Scheme 22 summarizes the methods discussed above.

5 Conclusion and Outlook

Eight total syntheses of morphine or congeners have been reported in the last 5 years, attesting to no shortage of new ideas or strategies. The interest in this fascinating molecule will no doubt continue, yet a truly practical synthesis of the title alkaloid still remains a distant dream. In order even to approach the current price per kilogram, a synthesis would have to be five to six steps long starting with commodity chemicals. A potential for a practical synthesis may exist in the realm of fermentation provided the biosynthetic pathway could be coded into a single plasmid and used to over-express the required enzymes in a robust bacterial carrier. A proof of principle has been attained through the work of Kutchan with the cloning and expression of codeinone reductase in *E. coli* [101].

Another possibility for practical synthesis could come from the combination of fermentation for attaining specific steps with semisynthesis to complete the preparation. Currently, we are fully dependent on natural sources of morphine and all medicinally useful derivatives are made by semisynthesis. Perhaps more important goals for the future generations of chemists would be to focus on the de novo total synthesis of the derivatives themselves rather than morphine or codeine. Perhaps we will see some effort devoted to this most worthwhile task in the near future.

Addition

After the manuscript has been accepted for publication, a synthesis of codeine was published featuring a Claisen-rearrangement and a 1,3-dipoloar nitrone cycloaddition as key steps: Erhard T, Ehrlich G, Metz, P (2011) A Total Synthesis of (+/−)-codeine by 1,3-Dipolar Cycloaddition. Angew Chem Int Ed doi: 10.1002/anie.201007448.

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Indole Prenylation in Alkaloid Synthesis

Thomas Lindel, Nils Marsch, and Santosh Kumar Adla

Abstract Important biologically active indole alkaloids are decorated with prenyl (3,3-dimethylallyl) and *tert*-prenyl (1,1-dimethylallyl) groups. Covering the literature until the end of 2010, this review article comprehensively summarises and discusses the currently available technologies of prenylation and *tert*-prenylation of indoles, which have been applied in natural products total syntheses or could be applied there in the near future. We focus on those procedures which introduce the C_5 units in one step, organised according to the indole position to be functionalised. Key strategies include electrophilic and nucleophilic prenylation and *tert*-prenylation, prenyl and *tert*-prenyl rearrangements, transition metal-mediated reactions and enzymatic methods.

Keywords Alkaloids · Indole · Prenylation · Regioselectivity · Total synthesis

Contents

Dedicated to Professor Gerhard Bringmann on the occasion of his 60th birthday.

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1 Introduction

Indole alkaloids carrying 3,3-dimethylallyl (prenyl) or 1,1-dimethylallyl (*tert*-prenyl) substituents constitute prominent secondary metabolites found in microbial fungi, cyanobacteria, but also in marine bryozoans. A review on the structures and chemoenzymatic syntheses of prenylated indole alkaloids has been published recently by Li [1]. For earlier review articles, see Williams [2] and Winterfeldt [3]. Given the importance of prenylated indole alkaloids for chemistry and beyond, we thought it would be interesting to comprehensively summarise and discuss the approaches employed for their total synthesis, aiming at identifying established, investigated, and undeveloped areas of indole prenylation. Since natural product synthesis drives and is driven by new synthetic methodology, this review also includes recent advances in indole prenylation, even if no natural products have been synthesised. The literature is covered until 2010.

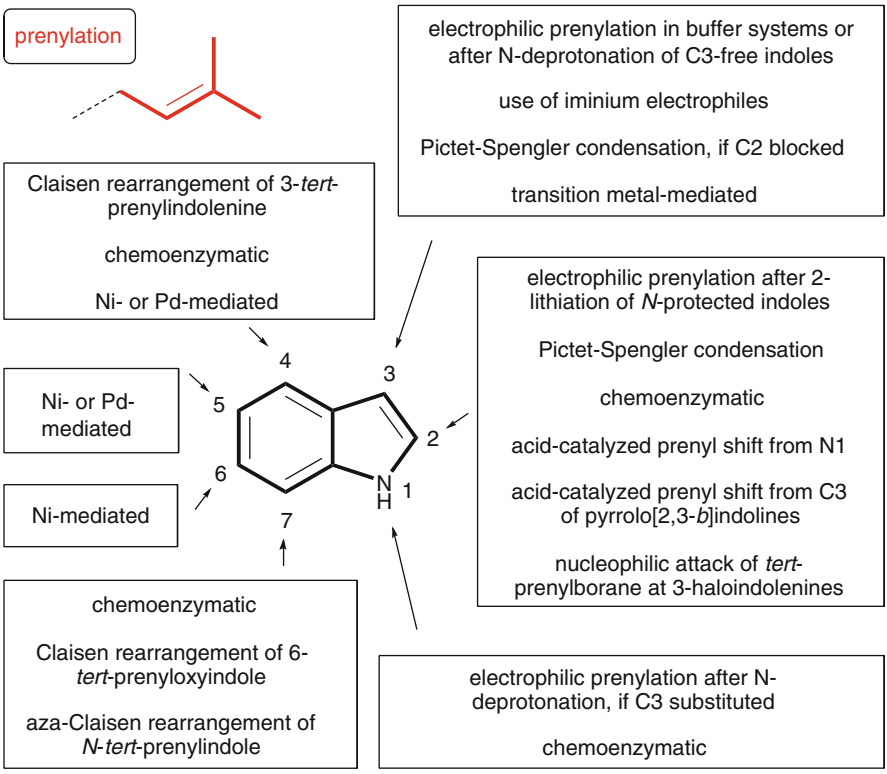


Fig. 1 Major possibilities of one-step indole prenylation

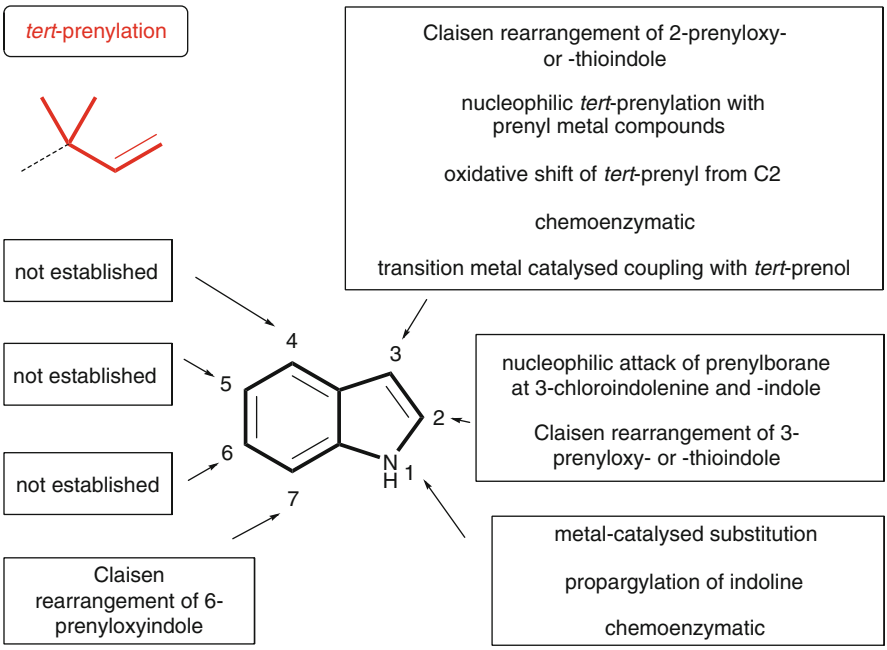


Fig. 2 Major possibilities of one-step indole *tert*-prenylation

Prenylations and *tert*-prenylations of indole most frequently occur at positions N1, C2 and C3 (Sects. 2–4), with fewer indole alkaloids prenylated in the benzene section (Sect. 5). There are no indole derivatives with prenylated or *tert*-prenylated bridge head positions C3a or C7a. Regioselective introduction of prenyl or *tert*-prenyl groups at the indole ring can be challenging, depending on the position. Certain cases are simple, such as N-prenylation, others are still not reported, such as 6-*tert*-prenylation. Figures 1 and 2 give overviews of the major possibilities of synthesising prenylated or *tert*-prenylated indoles, respectively, in one step.

We decided to sort the material according to the indole positions that are prenylated or *tert*-prenylated. Methodology or natural product oriented section headings would also have been possible. With a few exceptions, only those approaches have been included in this review, which incorporate the entire C_5 unit within a single operation. Syntheses building up the indole systems are only briefly mentioned, as are approaches constructing the prenyl or *tert*-prenyl unit stepwise.

2 N-Prenylation and N-*tert*-Prenylation

2.1 N-*Prenylation*

Electrophilic N-prenylation. Synthesis of *N*-prenylindole derivatives is usually facile by deprotonation of *N*-unsubstituted indoles with NaH or, more rarely KH, in DMF [4–17], DMSO [17], THF [18] or acetone [19], followed by reaction with prenyl

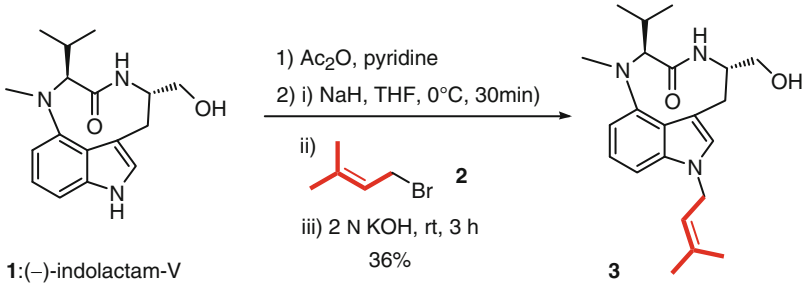
bromide or chloride. Yields normally reach more than 80%. Alkali hydroxides in the presence of crown ethers, phase transfer catalysts [8, 20–23] or K_2CO_3 [24, 25] have also been used as bases, if electron withdrawing groups (Ac, CHO) were present at C3. N-Unsubstituted diketopiperazines and phthalimide-protected tryptophan derivatives underwent partial epimerisation when working with NaH/DMF. As an alternative, it was possible to N-prenylate unprotected tryptophan selectively by treatment with prenyl bromide/Na in liquid ammonia *via* the disodium salt of tryptophan [16, 26]. N-Prenylation of 3-alkylindole can be combined *in situ* with Vilsmeier formylation of the 2-position [27]. However, if the indole is not deprotonated prior to prenylation, e.g. by working in slightly acidic buffer systems instead of using NaH/DMF, other positions than the indole nitrogen are prenylated (see below).

Electrophilic N-prenylation of indole has, for instance, been employed in the synthesis of *N*-prenylindolactam-V (**3**, Scheme 1) [18], where the yield is only moderate, probably due to the simultaneous presence of the amide moiety. The natural product (−)-indolactam V (**1**) is a potent inhibitor of protein kinase C isozymes [28]. Other examples include the total syntheses of deformylflustrabromine B [11], of derivatives of physostigmine and debromoflustramine B [22], or of vulcanine and borrerine [24]. The key step of the synthesis of N-prenyltryprostatin B features N-prenylation with concomitant 3-prenylation (see Sect. 3.1) [29]. As a side reaction, prenylation of diketopiperazines, a frequent structural motif in prenylated indole alkaloids, was observed.

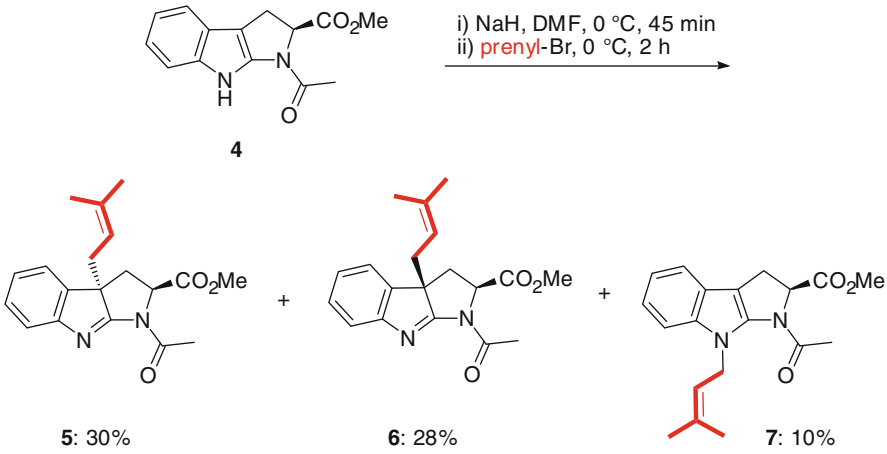
There are only a few cases in which the standard procedure did not work. One of them concerns the behaviour of pyrroloindole **4** on treatment with NaH and then prenyl bromide (Scheme 2). Prabhakar, Lobo and co-workers obtained mostly the 3-prenylated products **5** (30%) and **6** (28%) with minor amounts of **7** (10%) [30, 31]. Perhaps in this special case Na^+ is chelated by the deprotonated indole nitrogen and the oxygen of the acetyl side chain, forming a six-membered ring, thereby shielding N1 and paving the way for C3a to attack at prenylbromide.

As the other important exception to the applicability of the standard procedure, N-prenylation is only the minor reaction if an alkylmercapto group is located at C2. Via S-prenylation, a thia-Claisen rearrangement to the 3-position becomes the major reaction, affording 3-*tert*-prenylindoles [4, 32], as exploited in the total synthesis of amauromine [33–35] (see Chap. 4.2).

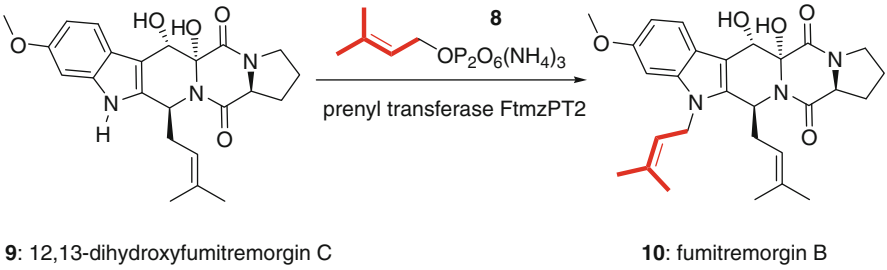
Chemoenzymatic synthesis. The synthesis of the *Aspergillus fumigatus* mycotoxin fumitremorgin B (**10**) from 12,13-dihydroxyfumitremorgin C (**9**) is one of the early, still recent, applications of enzyme-catalysed N-prenylation (Scheme 3).



Scheme 1 *N*-Prenylation of (−)-indolactam-V (**1**) [18]



Scheme 2 Non-regioselective prenylation of an *N*-acetyl pyrrolo[2,3-*b*]indole [30]

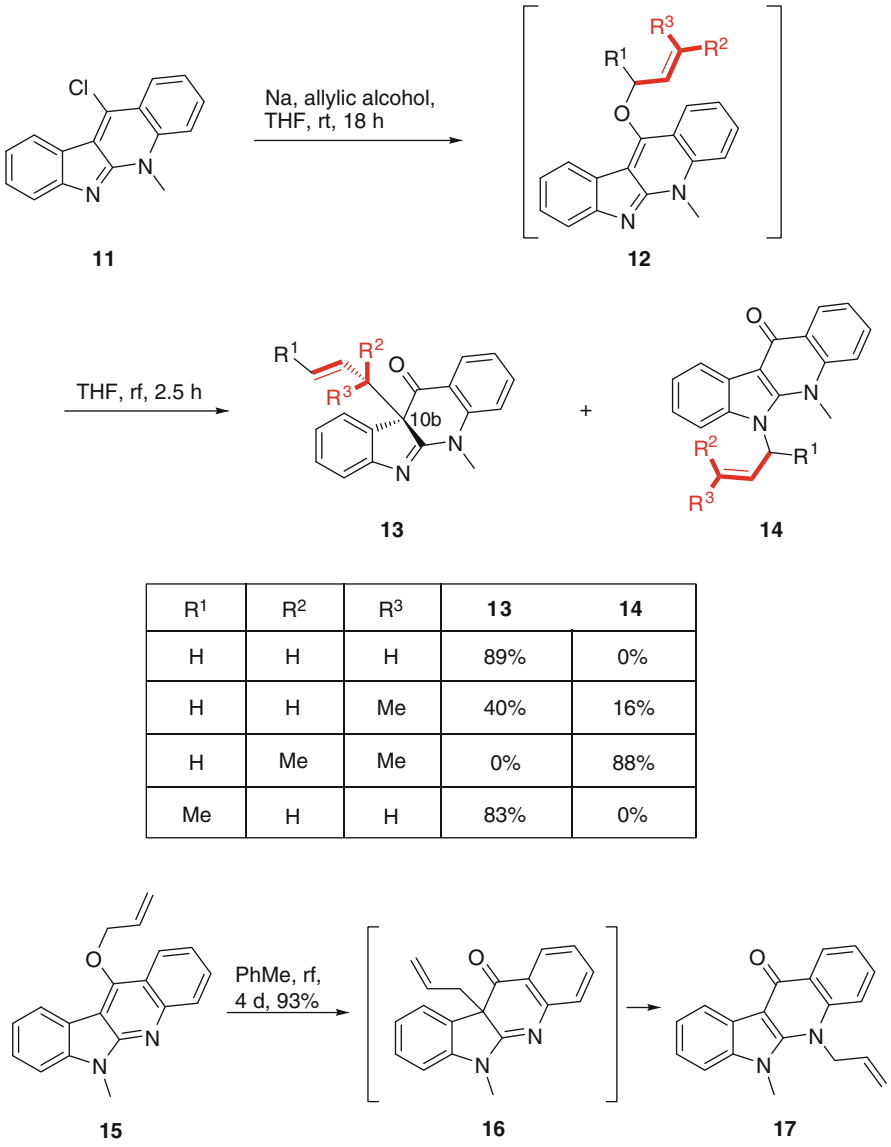


Scheme 3 Enzymatic synthesis of fumitremorgin B (**10**) by Li and co-workers [36]

Li and co-workers expressed the prenyltransferase His_6-FtmPT2 from *Aspergillus fumigatus* (2 mg/L culture) [36], which uses ammonium prenylpyrophosphate (**8**) as prenyl source. After 2 h at 37 °C, about one third of **9** had been converted to **10**. Since then, the Li group has contributed many more and higher yielding examples of enzymatic indole prenylation (see below).

*N-Prenylation of an indolo[2,3-*b*]quinoline*. Working on the synthesis of the communesins, Westwood and co-workers studied the possibility of introducing a prenyl group on the indolo[2,3-*b*]quinoline system *via* a Claisen-Cope sequence starting from the chlorinated precursor **11** (Scheme 4) [37]. Nucleophilic substitution by allylic sodium alkoxides led to formation of intermediate **12**, which could not be isolated in any of the cases shown in Scheme 4 due to rapid Claisen rearrangement. The prenol derivative afforded only N-prenyl product **14** in 88% yield, and it was not possible to isolate the primary rearrangement product **13** with a *tert*-prenyl group at C10b. The rate of the initial Claisen rearrangement is known to be increased by alkyl substituents [38–40]. Product **13** experiences steric strain, which is released by formation of the N-prenylated product **14**. However, if allyl or 1-methylallyl groups are used instead of a prenyl group, quaternised primary products were isolated exclusively.

Interestingly, [3,3] sigmatropic rearrangement of an allyl group did not stop at C10b and proceeded through to product **17** when starting from regioisomer



R^1	R^2	R^3	**13**	**14**
H	H	H	89%	0%
H	H	Me	40%	16%
H	Me	Me	0%	88%
Me	H	H	83%	0%

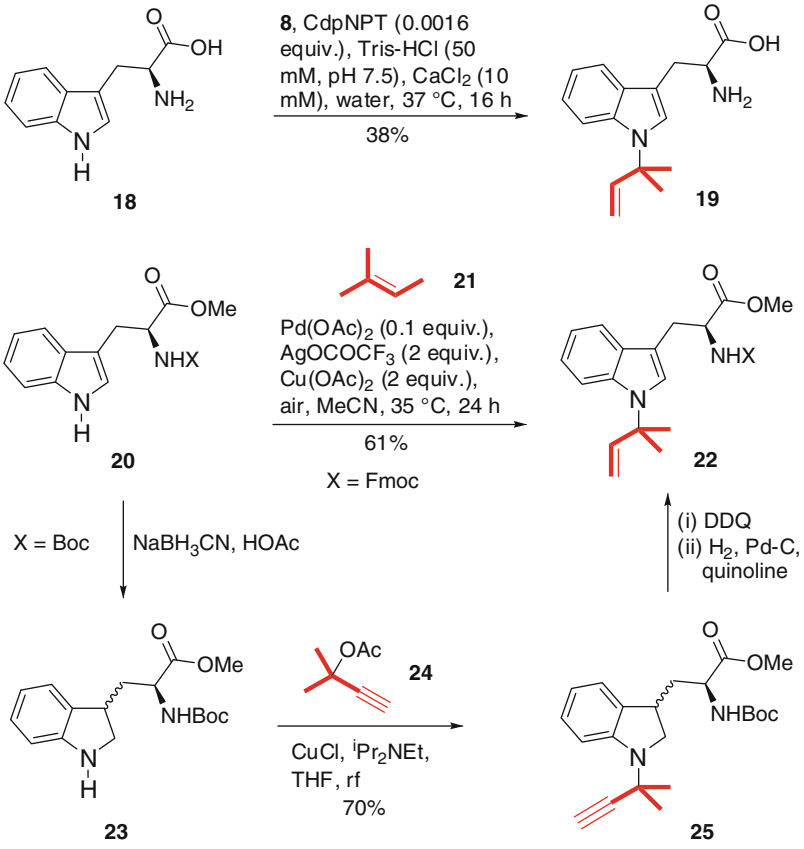
Scheme 4 Sequential Claisen and aza-Claisen rearrangements on the indolo[2,3-*b*]quinoline system [37]

15, which is N-methylated at the indole instead of the quinoline moiety. Allylation of the benzene section of the indole system was observed only as a very minor reaction. By calculation, Westwood was able to confirm that when starting from **12** the barrier of the initial Claisen rearrangement is about 18 kJ/mol higher than that of the subsequent *aza*-Claisen rearrangement, making it impossible to stop at the 10b-allylated intermediate. In the case of **15**, the second barrier is about 7 kJ/mol higher than the first.

2.2 N-tert-*Prenylation*

Chemoenzymatic synthesis. Enzymatic prenylation of indole will probably soon become practical in a chemical sense with general availability of indole prenyltransferases. N-*tert*-Prenylation of L-tryptophan (**18**) was possible employing the cyclic dipeptide prenyltransferase CdpNPT from *Aspergillus fumigatus* affording N-*tert*-prenyltryptophan **19** (38%, Scheme 5) [41]. A prenyl transferase from *Aspergillus oryzae* catalysed the simultaneous N-*tert*-prenylation and 7-prenylation of the diketopiperazine cyclo-L-Trp-L-Trp [43].

Moore and co-workers recently reported the identification of the prenyl transferase CymD from the marine actinobacterium *Salinispora arenicola*, which catalysed N-*tert*-prenylation of L-tryptophan prior to its incorporation into the cyclic

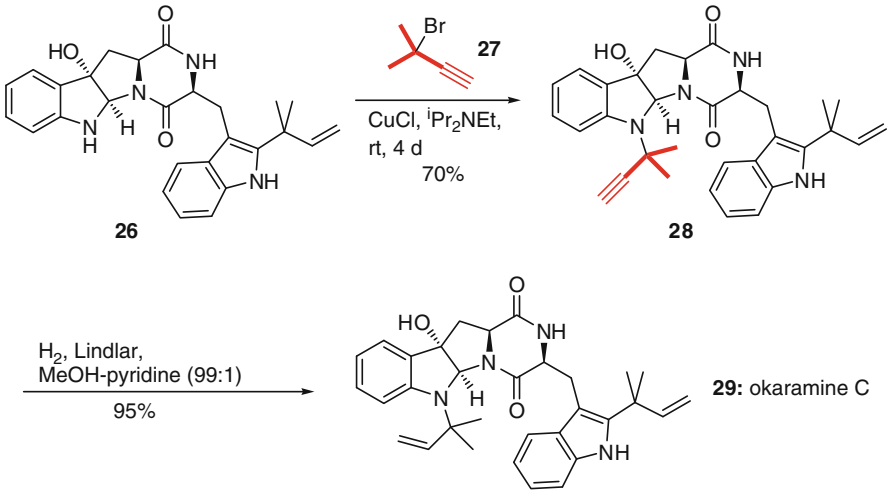


Scheme 5 One-step *N-tert*-prenylation of tryptophan and derivatives, enzyme-catalysed (CdpNPT: cyclic dipeptide *N*-prenyl transferase from *Aspergillus fumigatus*) [41] and Pd-catalysed [42], compared with an earlier pathway

peptide cyclomarin A [44]. For comparison, a sample of *N-tert*-prenyltryptophan had to be synthesised chemically.

Transition metal catalysed prenylation. There is a new one-step N-*tert*-prenylation of indole developed by Baran and co-workers [42] which still outcompetes the chemoenzymatic approach (Scheme 5). Isobutene (**21**) as prenyl source is reacted with side-chain Fmoc-protected tryptophan methyl ester **20** in the presence of catalytic amounts of $Pd(OAc)_2$ and superstoichiometric amounts of Ag(I) trifluoroacetate and Cu(II) acetate. The protocol also requires the presence of oxygen. After about 1 day at 35°C, the N-*tert*-prenylated indole is obtained in a yield of about 60%. The mechanism has not been elucidated, but may involve a π-allyl-Pd(II) complex which is coordinated by the indole nitrogen or by C3. In the latter case, a Pd-Claisen rearrangement of a 3-palladated indole would follow. Ag (I) functions as reoxidant of Pd(0).

Propargylation of indoline. Until 2009, N-*tert*-prenylation of tryptophan derivatives at the indole nitrogen required four steps, beginning with the reduction of **20** to the indoline **23** with $NaBH_3CN$, followed by Cu(I)-catalysed N-propargylation with propargyl acetate **24** [45–47], reoxidation to the indole (DDQ or MnO_2 [48]) and hydrogenation of the alkyne affording **22**. The propargyl pathway may still be the method of choice if indoline moieties instead of indoles are to be N-*tert*-prenylated. The synthesis of the insecticidal indole alkaloid okaramine C (**29**) from *Penicillium simplicissimum* [49] by the Ley group [50] (Scheme 6, endgame shown) features a late stage introduction of the N-*tert*-prenyl group on an indoline moiety, which would otherwise have been in danger of Claisen rearrangement to the indole 7-position, as observed by Ganesan and co-workers (Sect. 5.2). For N-propargylation of **26**, propargyl bromide **27** was used, whereas treatment with the corresponding propargyl acetate/CuCl did not give satisfactory results. The indoline propargylation



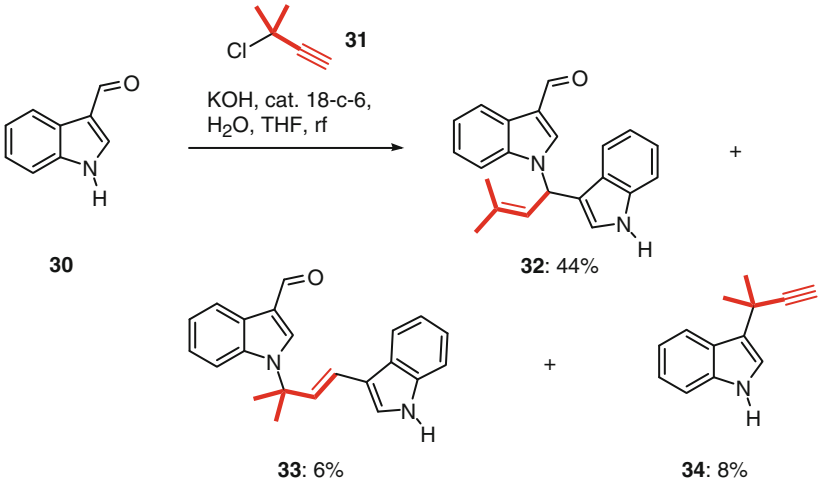
Scheme 6 Endgame of the Ley group synthesis of okaramine C (**29**) [50]

approach has also been used in the Corey synthesis of okaramine N (see Sect. 3.2) [51] and in the Ganesan synthesis of okaramine J (see Sect. 5.2) [52].

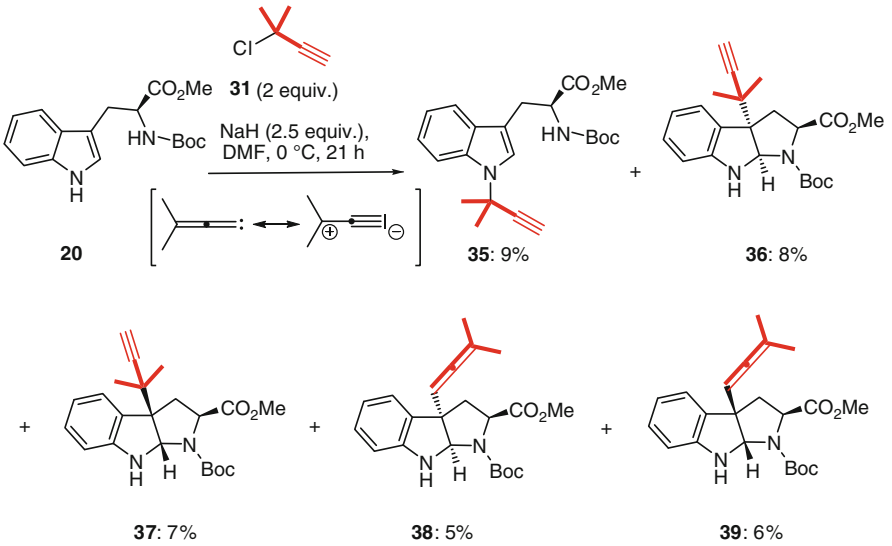
Except for 3-bromoindole, it is necessary to proceed *via* the indoline, because treatment of indole with 1,1-dimethylpropargyl chloride (**31**) in the presence of base leads to product mixtures resulting from reaction of in situ formed dimethylvinylidene carbene. Sheu and co-workers isolated the three products **32**, **33** and **34** on reaction of indole-3-carbaldehyde (**30**) (Scheme 7) [53]. In the main reaction, indole C3 attacks at dimethylvinylidene carbene forming a vinyl anion, which is protonated to give the 3-allenylindolenine. Hydroxide then attacks the carbaldehyde moiety with loss of formic acid and formation of a 3-allenylindole. Addition of a second equivalent of indole-3-carbaldehyde (**30**) affords **32** and **33**.

After treatment of Boc-protected tryptophan methyl ester (**20**) with 1,1-dimethylpropargyl chloride (**31**) / NaH in DMF, we isolated the five products **35**, **36**, **37**, **38** and **39** (Scheme 8) [54]. Both the indole nitrogen and C3 had reacted as nucleophiles towards C1 and C3 of the intermediate dimethylvinylidene carbene, followed by cyclisation to the pyrrolo[2,3-*b*]indoles. Earlier, Hino and co-workers had obtained a similar result when starting from achiral N_b-methoxycarbonyltryptamin [55]. With 3-unsubstituted indoles, Wenkert and co-workers observed formation of quinolines as side products, presumably *via* cyclopropanation of the indole 2,3-double bond by dimethylvinylidenecarbene [56].

Pirrung and co-workers found that direct 1,1-dimethylpropargylation of 3-bromoindole at the indole nitrogen is possible in about 50% yield without prior reduction to the indoline, simply by treatment of 3-bromoindole and 1,1-dimethylpropargyl chloride with NaH in DMF [57]. Joullié and co-workers found that N-propargylation of indoline in boiling THF affords **40**, followed by cyclisation to tricycle **41**, which can be prevented by carefully monitoring the reaction (Scheme 9) [58]. It was also possible to fully convert **40** to **41** at higher

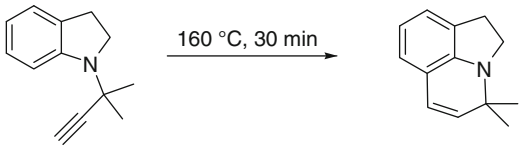


Scheme 7 Treatment of indole with propargylic halides [53]



Scheme 8 Product mixture obtained on reaction of tryptophan derivative **20** with propargylchloride **31**/NaH [54]

Scheme 9 Behaviour of *N*-(1,1-dimethylpropargyl) indoline (**40**) on heating [58]



temperature under microwave conditions. The cyclisation probably proceeds in the same manner as for phenol derivatives, commencing with a thermal Claisen rearrangement to the 7-allenylindole, followed by hydrogen shift and 6π electrocyclisation.

Other approaches. There is also a less efficient multistep procedure first introducing a C_3 substituent at N1 by reaction of the deprotonated indole with ethyl α-bromopropionate, followed by α-methylation and reduction to the hydroxy *tert*-butyl group, oxidation to the aldehyde and elongation to the *tert*-prenyl group by methylenation. This strategy was employed by Yao and co-workers in their synthesis of the marine bacterial natural product cyclomarin C [59, 60] and by Spinella and co-workers for obtaining *N*-*tert*-prenyl-3-methoxycarbonylindole [61].

By building up the indole ring, *N*-*tert*-prenylindole is also accessible. Willis and co-workers synthesised demethylasterriquinone A, isolated from the Congo fungus *Pseudomassaria* sp., from *N*-*tert*-prenyl indole which had been constructed *via* Pd-catalysed condensation of 1,1-dimethylpropargylamine and a dihalogenated styrene derivative [62]. *Ortho*-chlorinated alkynylbenzenes have been employed by Ackermann and co-workers in a Pd-catalysed N-arylation-hydroamination

sequence [63, 64]. Indole assembly was also used by Karchava and co-workers who condensed methyl α-formyl-(*o*-bromophenyl)acetate with 1,1-dimethyl propargylamine, followed by Cu(I)-catalysed cyclisation to *N-tert*-prenylindole [65].

3 Prenylation and *tert*-Prenylation at C2

3.1 Prenylation at C2

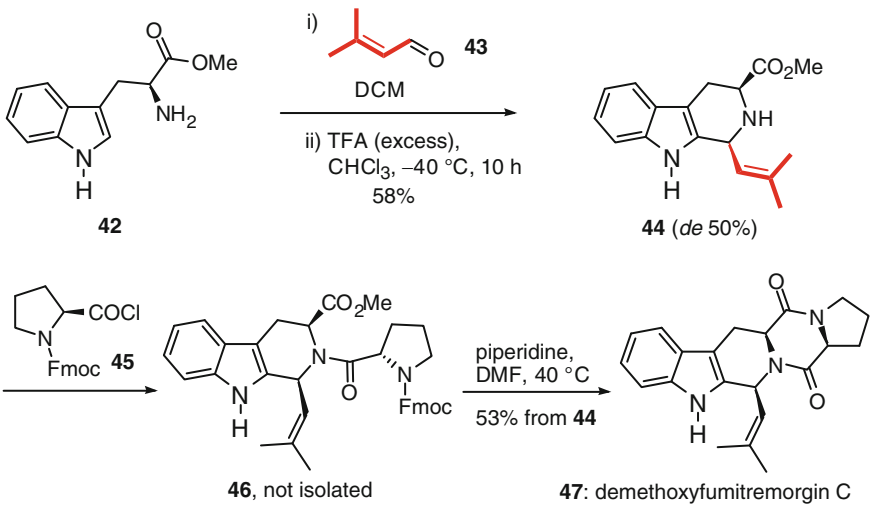
Electrophilic prenylation. By electrophilic prenylation with allyl halides, it is quite difficult to access the indole 2-position, because the 3-position reacts faster if unsubstituted. Westermaier and Mayr quantified the electrophilic prenylation of excess indole or *N*-methylindole (5 equiv.) in 80% aqueous acetone in the presence of NH_4HCO_3 which predominantly affords 3-prenylindole with minor amounts of 2-prenylindole (9:1) [66]. If substoichiometric amounts of indole were employed, 2,3-diprenylindole became the major product. On reaction of 3-methylindole with prenyl bromide in acetate buffer, Casnati and co-workers obtained the 2-prenylated product in 61% yield [67].

It is possible to lithiate the 2-position of N-protected indoles exploiting the *ortho* effect employing LDA, as shown by Wenkert and co-workers, who obtained 1-benzenesulfonyl-2-prenylindole in 76% yield [56], which could be deprotected by reduction with sodium amalgam.

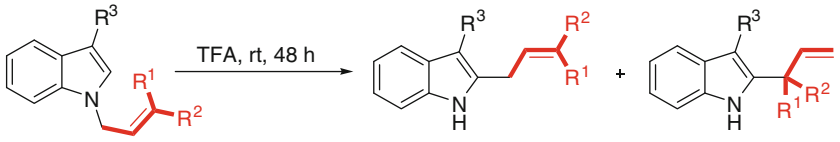
Introduction of a 2-prenyl group as an electrophile can also be achieved *via* Pictet–Spengler condensation of indoles with suitable C_5 aldehydes. The cell cycle inhibitor 6-demethoxyfumitremorgin C (**47**), isolated from *Aspergillus fumigatus*, can be synthesised by condensation of L-tryptophan methyl ester (**42**) and prenal (**43**) as the initial step [68–70]. It is possible to isolate the intermediate imine, which reacts to a mixture of diastereomeric β-carbolines (**44**) under acidic conditions. A problem is always the low diastereoselectivity of the cyclisation step, as observed for **44** by the Ganesan and Bailey groups in their very similar three-step syntheses of **47** (Scheme 10).

Use of α,β-unsaturated aldehydes such as prenal (**43**) tends to diminish the yield of Pictet–Spengler condensations. Therefore, the Nakagawa group used 3-methyl-3-(phenylthio)butanal in their total synthesis of fumitremorgin B [8, 21]. A similar strategy was applied by the Danishefsky group in their synthesis of spirotryprostatin A (see Chap. 4.1) [71, 72]. Thermal dehydrosulfenylation is possible after oxidation to the sulfoxide. Analogues of demethoxyfumitremorgin C (**47**) have been synthesised on the solid phase [73]. The de Meijere group assembled cyclopropanated analogues of demethoxyfumitremorgin C (**47**) [74].

Chemoenzymatic synthesis. Enzymatically, Li and co-workers converted brevianamide F to tryprostatin B [41], employing recombinant FtmPT1 and prenyl pyrophosphate as prenyl source. However, when changing the substrate to L-tryptophan, regioisomeric 1-*tert*-prenylation occurred exclusively, pointing to significant promiscuity of FtmPT1. There are still more substrates to be investigated.



Scheme 10 Synthesis of demethoxyfumitremorgin C (**47**) [69, 70]



R^1	R^2	R^3	% (**48**)	% (**49**)	% (**50**)	ratio **49**:**50**
H	H	Me	100	-	-	-
Me	H	Me	36	14	35	27 : 73
Me	Me	Me	-	50	50	50 : 50
Me	Me	Pr	3	52	45	56 : 44

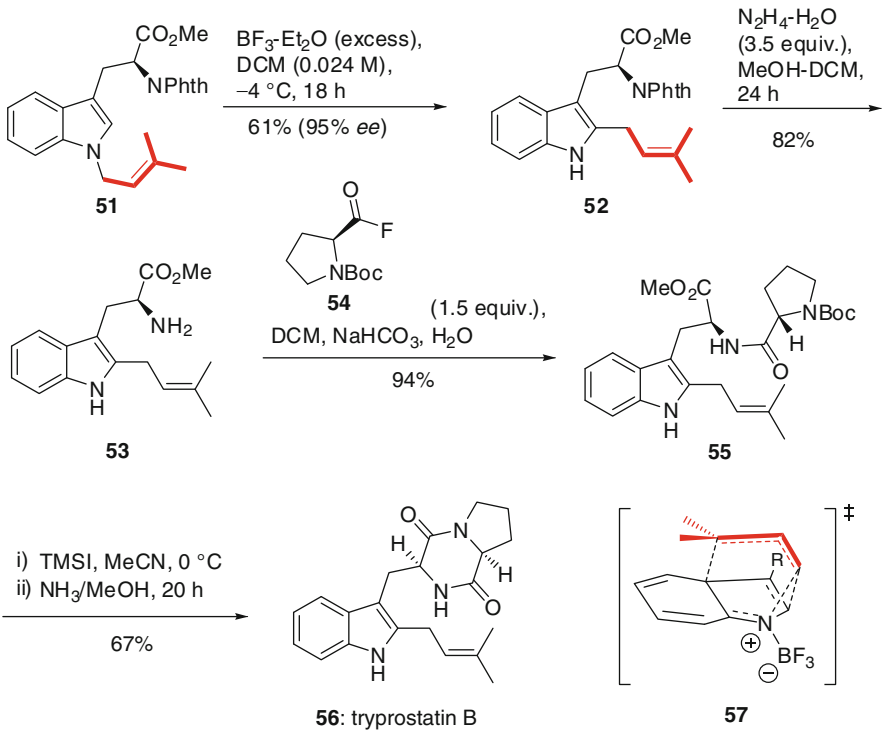
Scheme 11 TFA-mediated allyl shifts of *N*-allylindoles [75]

Prenyl rearrangement. It is possible to access the indole-2-position by prenyl migration either from the indole-1- or from the indole 3-position. In early publications, Casnati and co-workers reported on the behaviour of N-allylated 3-methylindoles (**48**) in TFA [75, 76]. It was found that the N-allyl group itself does not migrate, whereas the prenyl group migrated quantitatively, affording 2-prenylated and 2-*tert*-prenylated indoles (**49**, **50**) in roughly equal amounts (Scheme 11). Furthermore, the product ratio proved to be rather invariant (70:30 to 30:70) against reaction time and temperature. N-Crotyl groups afforded the corresponding regioisomeric products together with recovered starting material. Casnati also used other Lewis acids (BF_3-Et_2O, $AlCl_3$-hexane, $SnCl_4$-hexane)

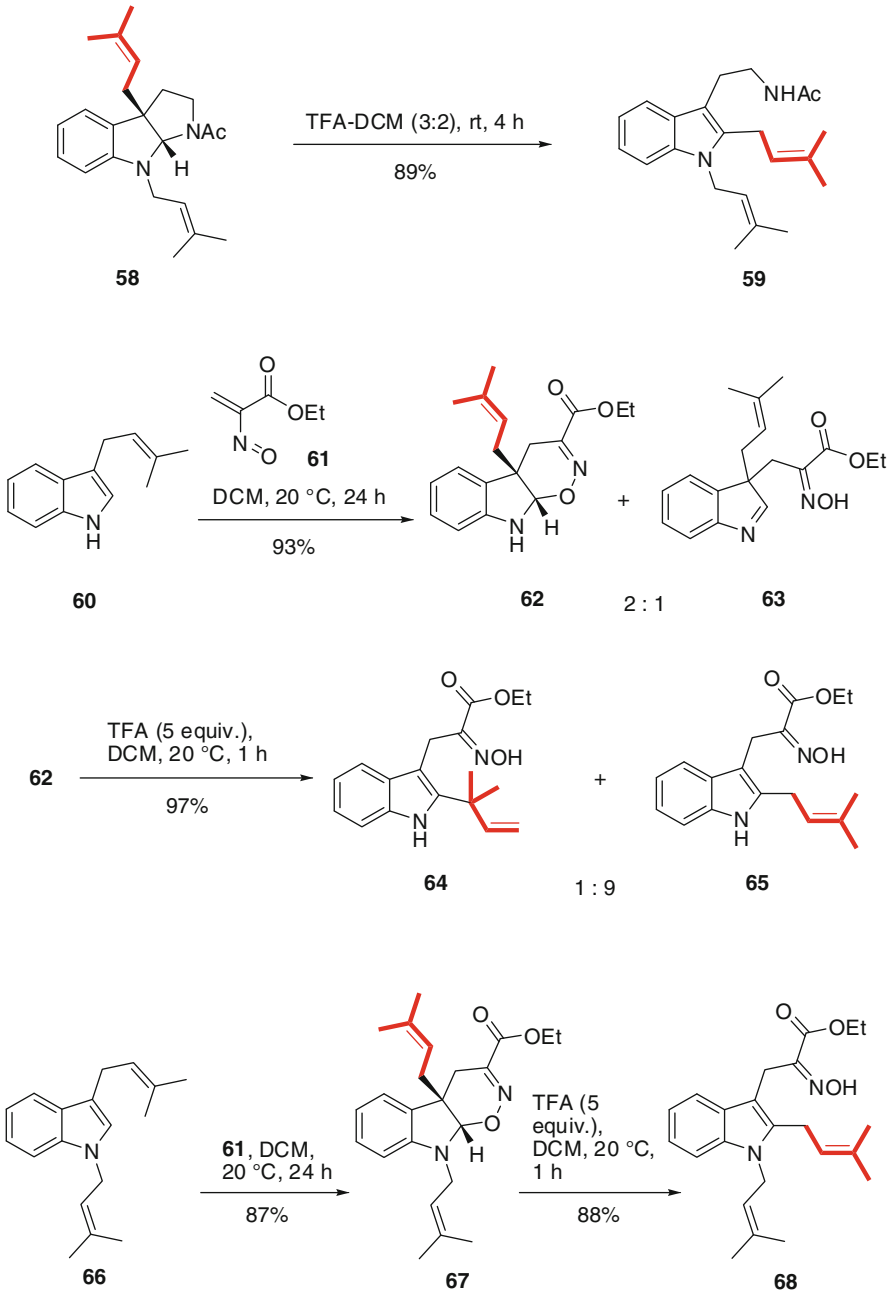
obtaining similar product mixtures when starting from 3-methyl-*N*-prenylindole. Migration of the unsubstituted allyl group was achieved in the presence of $AlCl_3$ in boiling benzene [77], whereas nothing happened when using $ZnCl_2$.

Prabhakar, Lobo and co-workers have been able to catalyse a regioselective prenyl shift from N1 to C2 by BF_3-Et_2O (>20-fold excess) [16, 78]. Phthalimide-protected *N*-prenyl tryptophan methylester **51** was converted to the corresponding 2-prenyl tryptophan derivative **52** at −4 °C in the convincing yield of 61% without epimerisation, paving the way for an efficient formal total synthesis of the *Aspergillus fumigatus* alkaloid tryprostatin B (**56**, Scheme 12). According to DFT calculations (B3LYP), BF_3 coordinates to the indolic nitrogen (**57**) and renders ionic character to the rearrangement. The authors favour a direct [1,5]-shift over two consecutive [3,3] sigmatropic rearrangements with double inversion of the prenyl group. The favoured transition state **57** exhibits an *endo* conformation with the prenyl group being situated on top of the pyrrole section of the indole. The barrier corresponds to those of facile thermal rearrangements.

In 1983, Nakagawa showed that 3a-prenylated pyrrolo[2,3-*b*]indoles rearrange in high yield to 2-prenylindoles (**59**) with concomitant opening of the pyrrolidine ring when exposed to TFA in DCM (Scheme 13) [79]. In acetate buffer (pH 2.7),



Scheme 12 Total synthesis of tryprostatin B (**56**) via BF_3-mediated prenyl shift by Prabhakar, Lobo and co-workers [16]



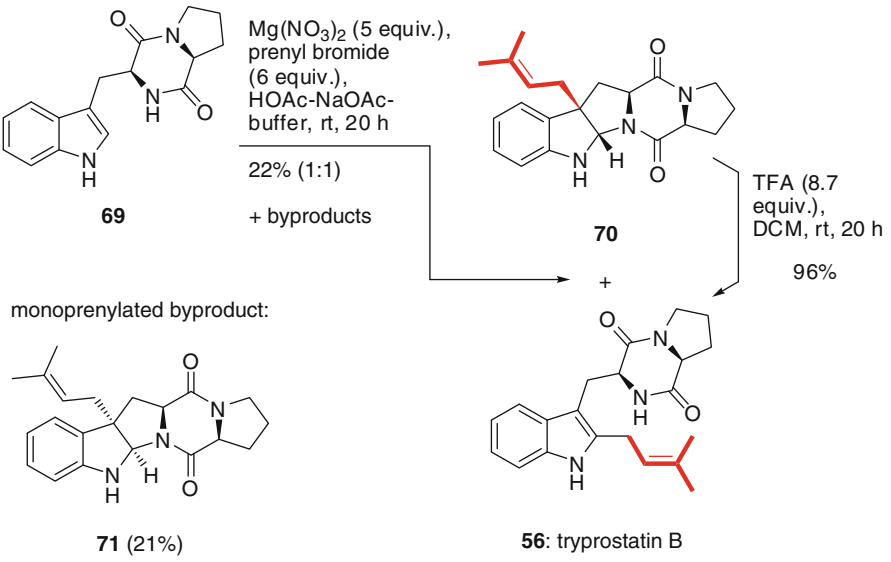
Scheme 13 Studies on prenyl migration from the indole-3- to the -2-position by the Nakagawa [79] and Ottenheijm [80] groups

nothing happens. As an example, the bisprenylated pyrrolo[2,3-*b*]indole **58** was chosen with the N-prenyl group left untouched in the rearrangement reaction.

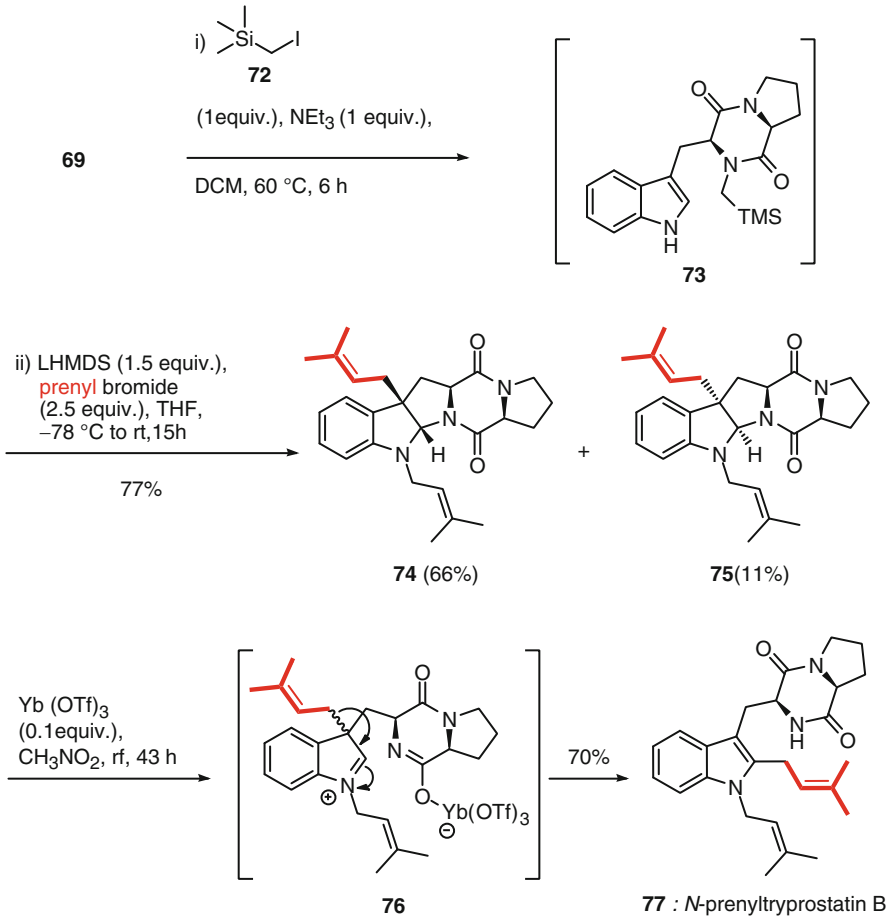
Plate and Ottenheijm published the efficient migration of a prenyl group from C3 to C2 in the presence of TFA (Scheme 13) [80]. 3-Prenylindole (**60**) reacted as a nucleophile with nitrosoacrylic ester **61** affording a 1:2 mixture of the Michael alkylation product **63** and of the further cyclised tricycle **62**. Compound **62** reacted to a mixture of 2-*tert*-prenyl- and 2-prenylindoles **64** and **65** (1:9). The reaction was also carried out starting from 1,3-diprenylindole (**67**) and provided 1,2-diprenylindole **68** in high 88% yield. The N-prenyl group of **67** did not migrate.

The Menéndez first generation synthesis of tryprostatin B (**56**) utilises the shift of a 3-prenyl group to C2 (Scheme 14) [81]. Starting material *cyclo*-(L-Trp-L-Pro) (**69**) was subjected to prenyl bromide in the presence of magnesium nitrate, a method which had been applied to the synthesis of pseudophrynaminol [82]. Menéndez isolated six products of which 22% was a mixture of tryprostatin B (**56**) and the prenylated pentacycle **70**. On treatment of **70** with TFA, additional tryprostatin B was obtained in 96% yield by prenyl shift from C3 to C2 with opening of the anellated pyrrolidine ring. Presumably, ring opening of **70** occurs first, followed by [1,5] sigmatropic shift of the prenyl group.

In the second version of the synthesis, Menéndez and co-workers protected the diketopiperazine nitrogen of **69** by a trimethylsilylmethyl group, before adding prenyl bromide and LHMDS (Scheme 15) [29]. Diastereomers **74** and **75** were now obtained in satisfying yields (66% and 11%, respectively). The authors propose that deprotonation of intermediate **73** takes place at the methylene group leading to



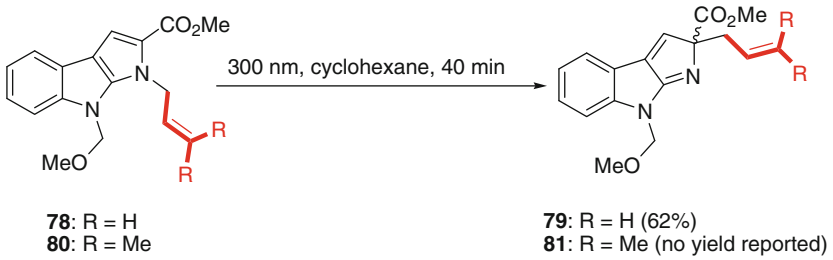
Scheme 14 Tandem-prenylation-cyclisation of the diketopiperazine *cyclo*-(L-Trp-L-Pro) (**69**) by Menéndez and co-workers [81]



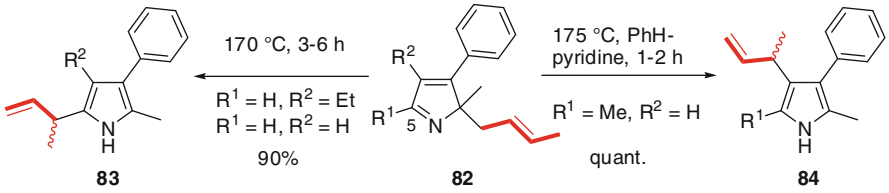
Scheme 15 Second generation synthesis of *N*-prenyltryprostatin B (**77**) by Menéndez and co-workers [29]

liberation of trimethylsilylcarbene and the anion of the amide. Prenylation at C3 would be accompanied by nucleophilic attack of the amide anion at C2. Ytterbium triflate-induced rearrangement of the prenyl group of both diastereomers **74** and **75** afforded *N*-prenyltryprostatin B (**77**). In the presence of Yb(III), the pyrrolidine ring is assumed to re-open, paving the way for the [1,5] prenyl shift.

It is interesting to take a look at the synthesis of 2-prenylpyrroles by prenyl rearrangement. Moody and Ward irradiated the *N*-allylpyrrolo[2,3-*b*]indoles **78** and **80** (Scheme 16) [83]. The major products **79** and **81**, respectively, contain a 2*H*-pyrrole moiety and result from 1,2- (or 1,5-)migration of the allyl group without regioinversion. When the indole nitrogen was allylated and the pyrrole nitrogen methylated instead, no products could be isolated after irradiation.



Scheme 16 Photochemical 1,2-allyl shifts on pyrrolo[2,3-*b*]indole [83]



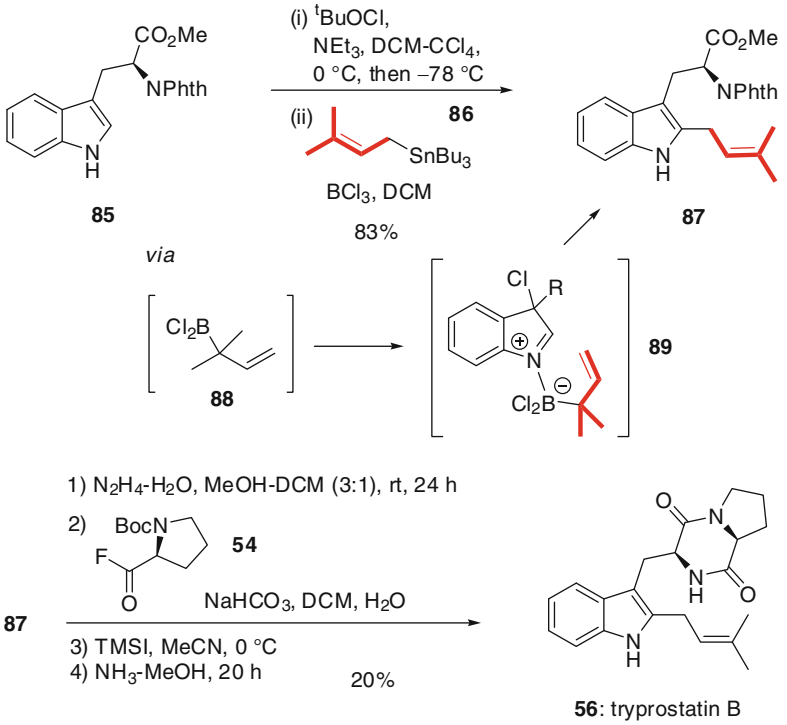
Scheme 17 Thermally induced crotyl migrations starting from 2*H*-pyrrole **82** [84]

Allyl rearrangements on 2*H*-pyrroles (**82**) have also been described. For instance, *aza*-Claisen reactions to **83** take place, if C5 is not substituted, whereas Cope rearrangement to **84** is favoured if C5 is substituted (Scheme 17) [84, 85]. Padwa and co-workers also induced the shift of prenyl groups on oxazolinone systems [86].

Nucleophilic prenylation. Nucleophilic 2-prenylation of indoles was introduced by Danishefsky and co-workers for the synthesis of tryprostatin B (**56**, Scheme 18) [87, 88]. The key idea was to use double regioinversion of prenylstannane **86** *via* conversion to the *tert*-prenylborane **88**, which forms an N–B bond with the in situ-generated 3-chloroindolenine **89**. A second regioinversion affords 2-prenylindole **87**. The reaction was only possible when employing BCl_3 for transmetalation, whereas 9-BBN derivatives did not work. Danishefsky proposes an ate-like six-membered transition state derived form **89**. Danishefsky's general approach became particularly useful for 2-*tert*-prenylations (see Sect. 3.2).

Attempts of Sakurai-type couplings employing prenyltrimethylsilane have been made with indole-3-carbaldehyde, but gave only low yields due to competing addition to the aldehyde carbon atom [89].

Other approaches. It is also possible to obtain 2-prenylindoles by Pd-catalysed cyclisation of *ortho*-alkynylanilines with the prenyl unit situated at the other terminus of the alkyne, as utilised by the Wood group in their work on the total synthesis of the securines and securamines [90].

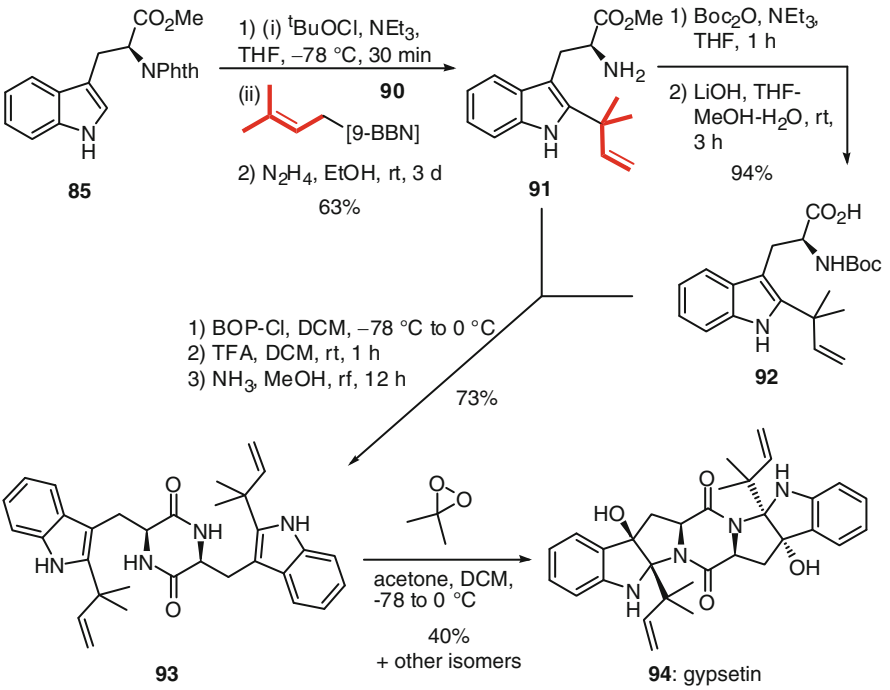


Scheme 18 Synthesis of tryprostatin B (**56**) via double regioinversion of a prenylstannane by Danishefsky and co-workers [87]

3.2 *tert*-Prenylation at C2

Nucleophilic tert-*prenylation*. When using prenylboranes instead of *tert*-prenylboranes, *tert*-prenylation of 3-chloroindolenines becomes possible. The Danishefsky *tert*-prenylation has also been extensively used for the synthesis of 3-*tert*-prenylindoles which can be obtained from 2-*tert*-prenylated precursors (see Sect. 4). The 1995 synthesis of the acyl-CoA-cholesterol acyltransferase inhibitor gypsetin (**94**) [91, 92] was the first occasion to publish that elegant reaction (Scheme 19) [88, 93]. On treatment of phthalimide-protected tryptophan methyl ester (**85**) with *tert*-BuOCl, the 3-chloroindolenine is formed in situ, which is nucleophilically attacked by prenyl-9-BBN with regioinversion of the prenyl group. Hydrazinolysis afforded 2-*tert*-prenyltryptophan methyl ester (**91**).

The gypsetin synthesis features another interesting step, which is the oxidative cyclisation of diketopiperazine **93** employing dimethyldioxirane, affording gypsetin (**94**) as major stereoisomer in a yield of 40%. Interestingly, the *tert*-prenyl group does not migrate to the 3-position, whereas the Davis oxaziridine has induced *tert*-prenyl rearrangements after cyclisation (Sect. 4.2).

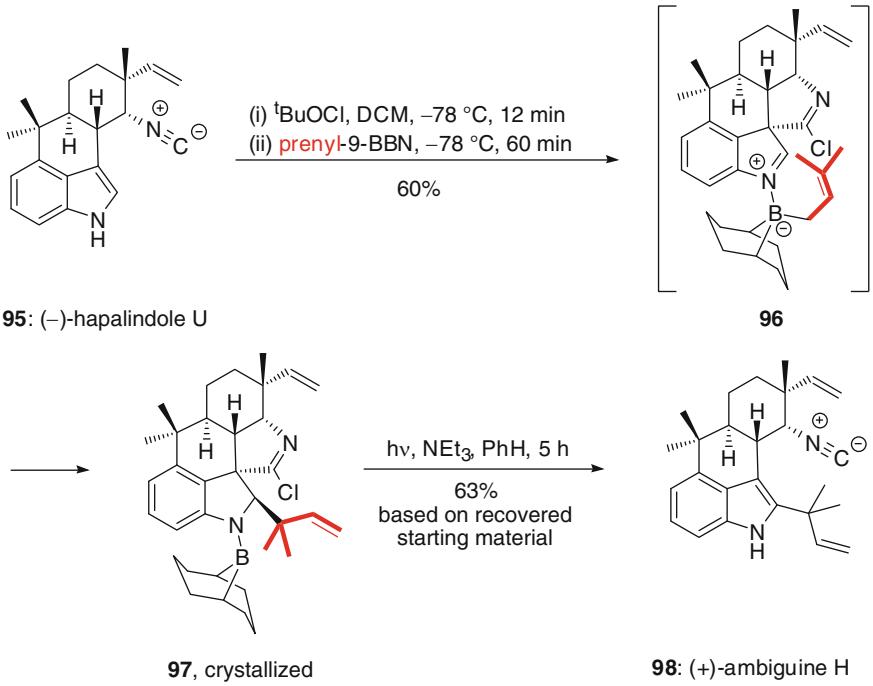


Scheme 19 Synthesis of gypsetin by Danishefsky prenylation and oxidative cyclisation by DMDO [88]

In course of their elegant conversion of (−)-hapalindole U (**95**) to (+)-ambiguine H (**98**), both isolated from the cyanobacterium *Fischerella* sp., Baran and co-workers were able to crystallise the 9-BBN adduct **97** featuring the earlier proposed N–B bond (Scheme 20) [94]. On treatment with *tert*-BuOCl, the isonitrile (−)-hapalindole U (**95**) was not converted to the 3-chloroindolenine, but to the pentacyclic spiro intermediate **96**, in which the former isonitrile carbon is chlorinated and then attacked by the indole 3-position. Isonitriles are more nucleophilic than indoles. Prenyl rearrangement afforded the 2-*tert*-prenylindole **97** with the *tert*-prenyl group located *trans* to the chloropyrroline ring (X-ray analysis). On irradiation of **97** in the presence of base, (+)-ambiguine H (**98**) was formed. Baran proposes a Norrish-type cleavage of the chloroimidate, followed by hydrogen migration to the imine carbon with reconstitution of the indole 2,3-double bond, and heterolysis of the N–B bond after intramolecular attack by chloride.

Remarkably, Zhun and Ignatenko used triprenylborane as prenyl source and were able to attack indole in the 2-position without prior oxidation to the chloroindolenine. The 2-*tert*-prenylindoline was obtained, which was then oxidised to the marine natural product debromoflustrabromine [95].

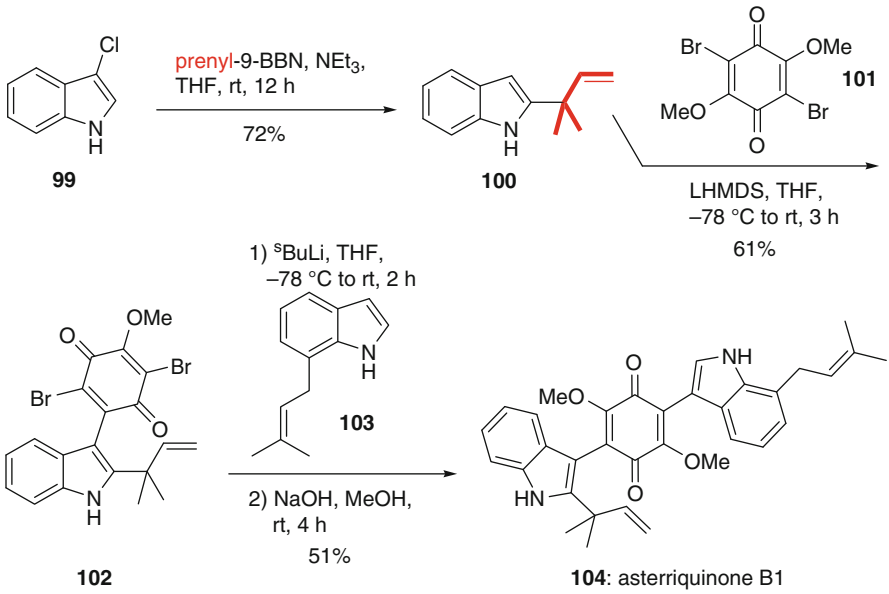
When treating 3-unsubstituted indoles with *tert*-BuOCl, the resulting 3-chloroindoles such as **99** are usually isolated. Subsequent treatment with prenyl-9-BBN affords the 2-*tert*-prenylated product (**100**). Examples are the syntheses of



Scheme 20 Protecting group-free conversion of (−)-hapalindole (**95**) to (+)-ambiguine H (**98**) by Baran and co-workers [94]

asterriquinone B1 (**104**) by Tatsuta and co-workers (Scheme 21) [96] and of malbrancheamide by Williams and co-workers [97]. Recently, a prenyl borane has also been produced in situ from 1,1-dimethylallene and 9-BBN [98]. Pirrung and co-workers assembled various methylated derivatives of the asterriquinones in a similar manner, starting from indoles synthesised following the Fischer or Bartoli pathways [99]; see also [100]. The anti-diabetic asterriquinone B1 (**104**) has also been synthesised *via* Danishefsky *tert*-prenylation by Liu and co-workers [101]. There is also earlier work starting from aniline [102].

A creative strategy of *tert*-prenylation at C2 was applied by Corey and co-workers in their synthesis of okaramine N (**111**, Scheme 22) [51]. After having assembled the peptide **106** from the tryptophan-derived building blocks **22** and **105**, treatment of **106** with $Pd(OAc)_2$ in the presence of oxygen under acidic conditions led to formation of the dihydroindolo azocine **107**. Presence of HOAc and water was necessary [103]. For the cyclisation of the remaining ring, the Corey group had to protect the N-unsubstituted indole unit, which was accomplished by taking the indole 3-position temporarily out of the game by addition to *N*-methyltriazolinedione (**109**, MTAD). Photooxidation of the remaining indole unit became possible and led to cyclisation to intermediate **110**, which lost MTAD on heating.

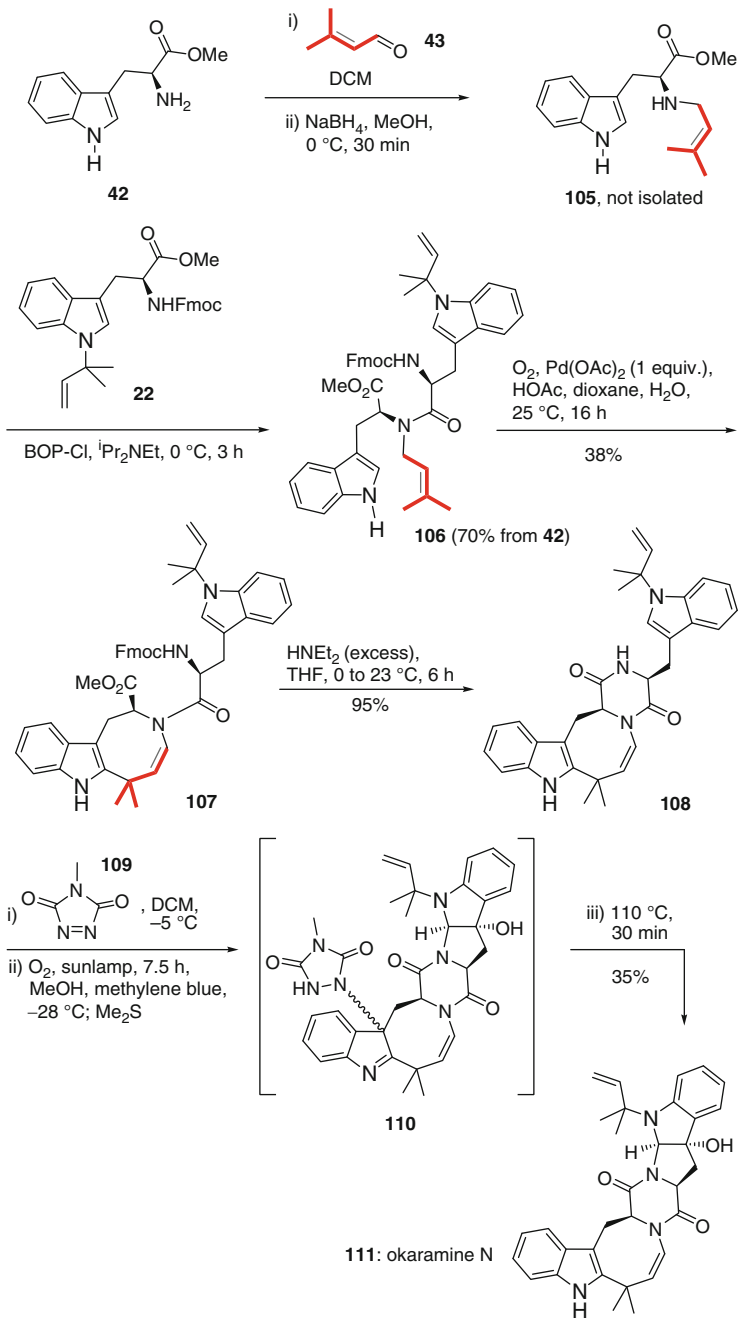


Scheme 21 Synthesis of asterriquinone B1 (**104**) via 2-*tert*-prenylation of 3-chloroindole by Tatsuta and co-workers [96]

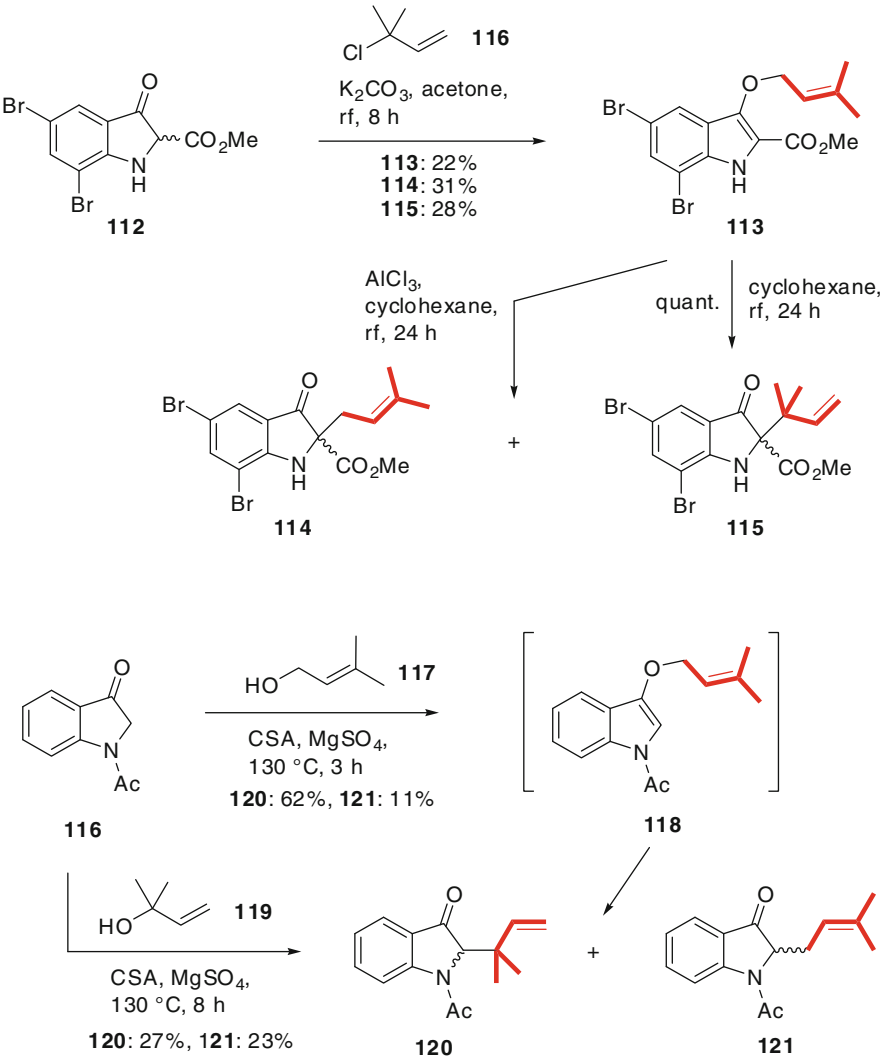
Prenyl rearrangement. Prenyl rearrangements constitute the second general approach to 2-*tert*-prenylindoles. The first example was published by Casnati and co-workers (see Sect. 3) who obtained 2-*tert*-prenyl- together with 2-prenylindoles by treatment of *N*-prenylindole in TFA [75, 76]. Similar results were obtained by Grundon and co-workers [4].

There are several examples of Claisen-type rearrangements starting from prenylated heteroatoms attached to the indole system. In 1971, Plieninger and co-workers reported a study reacting 2-methoxycarbonyl-3-oxindole **112** with *tert*-prenyl chloride in the presence of K_2CO_3 (Scheme 23) [104]. Three products were obtained in similar amounts, of which the *O*-prenyl compound **113** could be converted to the 2-*tert*-prenylated oxindole **115** simply by heating in cyclohexane. Interestingly, addition of $AlCl_3$ led to concomitant formation of 2-prenyloxindole **114** in equal amounts, pointing to an ionic process competing with the Claisen rearrangement. For the corresponding allyl case, Plieninger experimentally determined an activation enthalpy of about 95 kJ/mol and an activation entropy of about -55 J mol^{-1} K^{-1}, which is in good agreement with the values of the classical Claisen rearrangement of allyl phenyl ether.

Similarly, Sakamoto and co-workers treated *N*-acetyl-3-oxindole (**116**) with prenol (**117**) in the presence of CSA forming in situ compound **118** which underwent Claisen rearrangement to a mixture of 2-*tert*-prenylated and 2-prenylated 3-oxindoles **120** and **121** with **120** being the major product (Scheme 23) [105]. After 10 h, *tert*-prenylated compound **120** was the only product, pointing at the interconversion



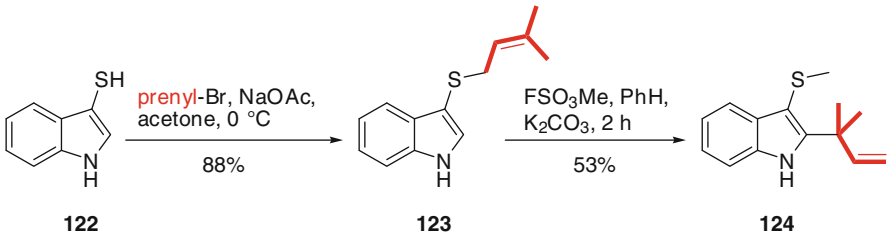
Scheme 22 Efficient synthesis of okaramine N (**111**) by Corey and co-workers [51]



Scheme 23 Claisen rearrangements of 3-prenyloxyindoles [104, 105]

of **121** to **120**. The prenylated compound **121** appears to be formed from **118** by [1,3] sigmatropic rearrangement. When *tert*-prenol (**119**) was used instead, the same products **120** and **121** were obtained in almost equal yields. Ireland–Claisen 2-*tert*-prenylation has been achieved by Dunkerton and co-workers starting from N-protected indoline 2-prenylcarboxylates on treatment with LDA in THF at −78 °C [106].

Plieninger also found that 3-mercaptoindoles (**122**) can be 2-*tert*-prenylated (**124**) *via* thia-Claisen rearrangement after S-prenylation to **123** at 0°C [107].



Scheme 24 Thia-Claisen approach to 2-*tert*-prenylindoles [107]

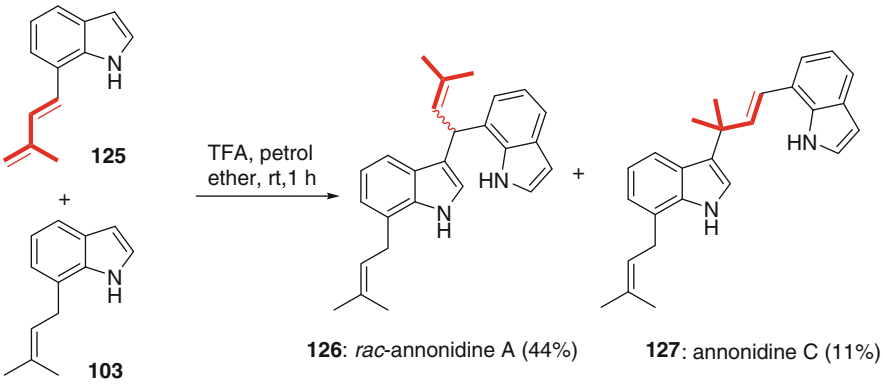
At higher temperatures N-prenylated products were also obtained. The thia-Claisen reaction itself was initiated by S-methylation of **123** employing methyl fluorosulfonate (Scheme 24).

4 Prenylation and *tert*-Prenylation at C3

4.1 Prenylation at C3

Electrophilic prenylation. Electrophilic prenylation of C3-unsubstituted indole occurs predominantly at C3 and can be carried out in good yield in aqueous buffer systems (NH_4HCO_3) [66]. As far as 2-prenylated products were also obtained, this has already been discussed in Sect. 3.1. For another example, see [108]. Use of prenyl diisopropyl phosphate as biomimetic electrophile in the presence of BF_3-Et_2O has afforded 3-prenylindole in a yield of only 21%, accompanied with minor amounts of 3-*tert*-prenylindole [109]. Wenkert and co-workers treated indole with *tert*-prenol in the presence of stoichiometric amounts of MeMgI and catalytic amounts of $[Ni(PPh_3)_2Cl_2]$ and obtained a mixture of 3-prenylated and 3-*tert*-prenylated indoles in 29% combined yield [56] *via* the Mg salt of indole. Later, Yadav and co-workers have treated several N-unsubstituted indoles with prenylZnBr, forming the indole Zn salt and obtaining 3-prenylindoles in more than 80% yield [110]. Zhu and Ganesan found that unsubstituted indole is 3-prenylated by prenyl bromide in the presence of $Zn(OTf)_2$ [111] in moderate yield and, as a drawback, excess of precious indole. One may also try bromine/lithium exchange at N-TBS-protected 3-bromoindole, followed by quenching with prenyl bromide [112], which appears to be a little complicated.

Although not exactly being an installation of a free prenyl group, it should be included here that Achenbach and co-workers reacted 7-prenylindole (**103**) with its oxidised analogue, the butadienylindole **125** in the presence of catalytic amounts of TFA (Scheme 25), obtaining the regioisomeric natural products annonidine A (**126**) and C (**127**), isolated from the tropical plant *Annonidinium manni*, in good yield [113]. The 3-methylbutadienyl group can also be generated in situ from the



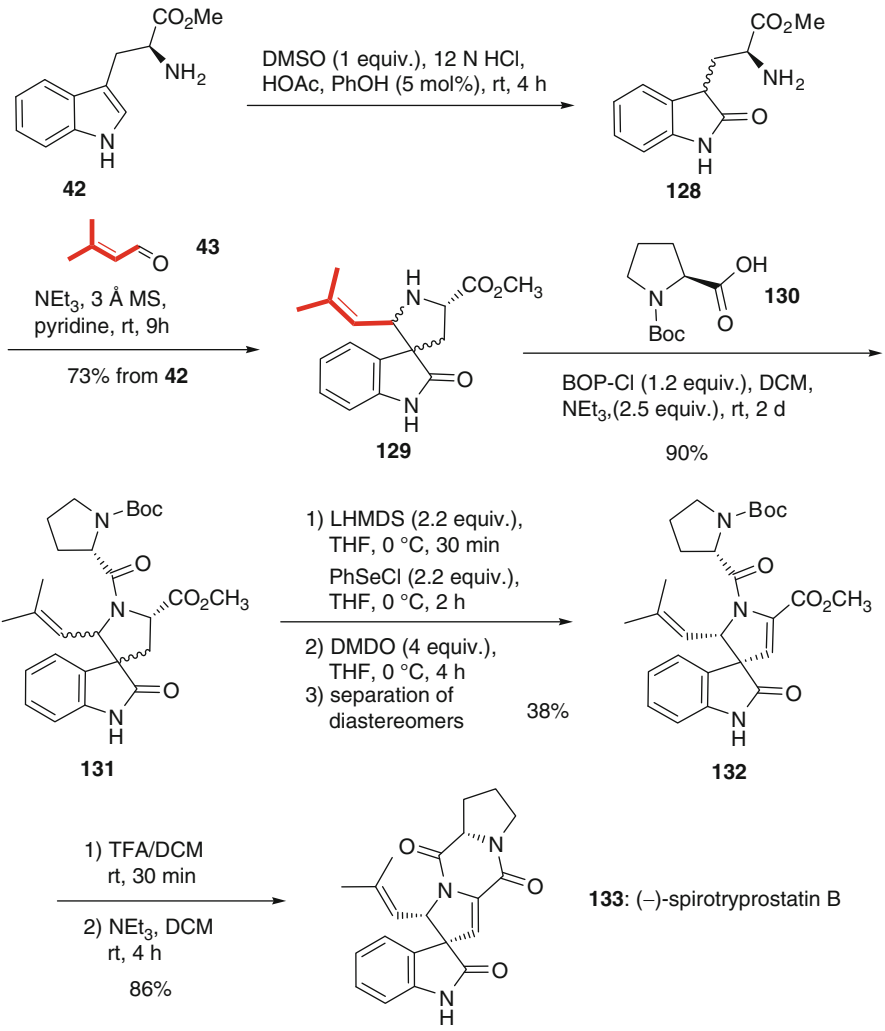
Scheme 25 Biomimetic formation of *rac*-annonidine A (**126**) and annonidine C (**127**) by Achenbach and co-workers [108]

corresponding tertiary alcohol in the presence of HCl, which was exploited by Ohta and co-workers in their synthesis of annonidine A (**126**) [114].

Pictet-Spengler condensation of C2-blocked indoles. Several syntheses of the spirotryprostatins from the fungus *Aspergillus fumigatus* have been published. For a review covering the literature until 2003, see [115]. (−)-Spirotryprostatin B (**133**) inhibits the G2/M phase of the mammalian cell cycle at micromolar concentrations. Similar to a Pictet-Spengler condensation, but at C3 instead of C2, von Nussbaum and Danishefsky utilised the condensation of prenal (**43**) and the tryptophan-derived oxindole **128** (Scheme 26) [116]. This was possible due to the blocking oxo substituent at C2, which at the same time enhances electron density at C3. The spiro system **129** was obtained and elaborated further to (−)-spirotryprostatin B (**133**), although with the necessity to separate four diastereomers of peptide coupling product **131**. The double bond of the pyrroline unit of (−)-spirotryprostatin B (**133**) was introduced by phenylselenation of **131**, oxidation with DMDO and immediate elimination.

Horne and co-workers showed in their synthesis of spirotryprostatin A that indole-2-chlorinated or -brominated tryptophan derivatives also undergo a "spiro-Pictet-Spengler condensation" with participation of the indole 3-position [117, 118]. Imine formation with prenal proceeded quantitatively. However, acid-induced spirocyclisation afforded, as in the other syntheses of spirotryprostatins, a mixture of diastereomeric spiro products in only moderate yield.

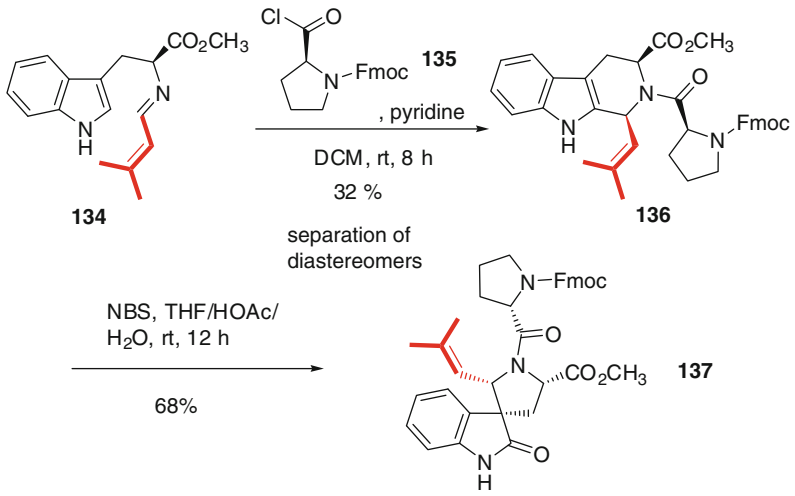
The Danishefsky group also developed a pathway to the spirotryprostatins *via* ring contracting rearrangement of 2-dihydroprenylated indoles obtained by regular Pictet-Spengler condensation [71, 72]. This approach was also chosen by Wang and Ganesan who utilised a ring contracting prenyl rearrangement of compound **136**, which was constructed by the low yielding Pictet-Spengler condensation of L-tryptophan methyl ester **42** and prenal **43** *via* imine **134** (Scheme 27) [119]. The oxidative ring contraction is, as in the case of the notoamides (see below), biomimetic and was induced by treatment of β-carboline **136** with NBS in



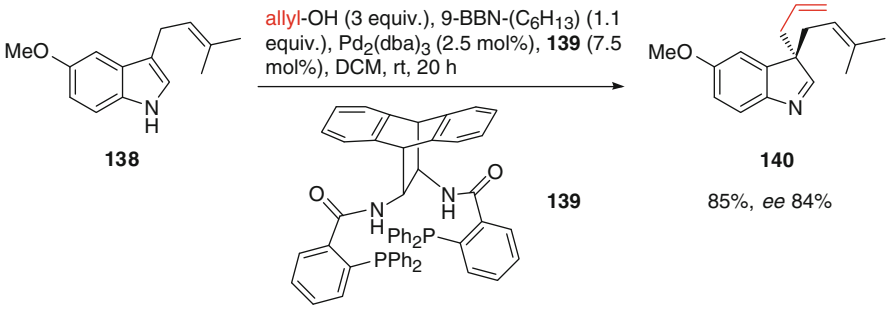
Scheme 26 Synthesis of (−)-spirotryprostatin B (**133**) via "spiro-Pictet–Spengler condensation" by von Nussbaum and Danishefsky [116]

THF-HOAc-H_2O. Spiro compound **137** had been obtained as the Boc analogue by Danishefsky who devised the further pathway to spirotryprostatin B (**133**).

Transition metal-mediated prenylation. Use of transition metals allows prenylation of indole in the 3-position starting from *tert*-prenol. In a stoichiometric application, Nicholas and co-workers prenylated 2-methylindole at C3 with isolable $[(\eta^3\text{-prenyl})Fe(CO)_4]BF_4$ (in $MeNO_2$), which had been obtained from *tert*-prenol and $Fe_2(CO)_9$/CO in Et_2O [120]. 3-Prenylindole was obtained in 70% yield, accompanied by only traces of 3-*tert*-prenylindole. In a Mo(VI)-catalysed reaction, a 4:1 mixture of 3-prenyl- and 3-*tert*-prenylindoles was obtained by Zhu and



Scheme 27 Oxidative ring contraction of Pictet–Spengler product **136** [119]



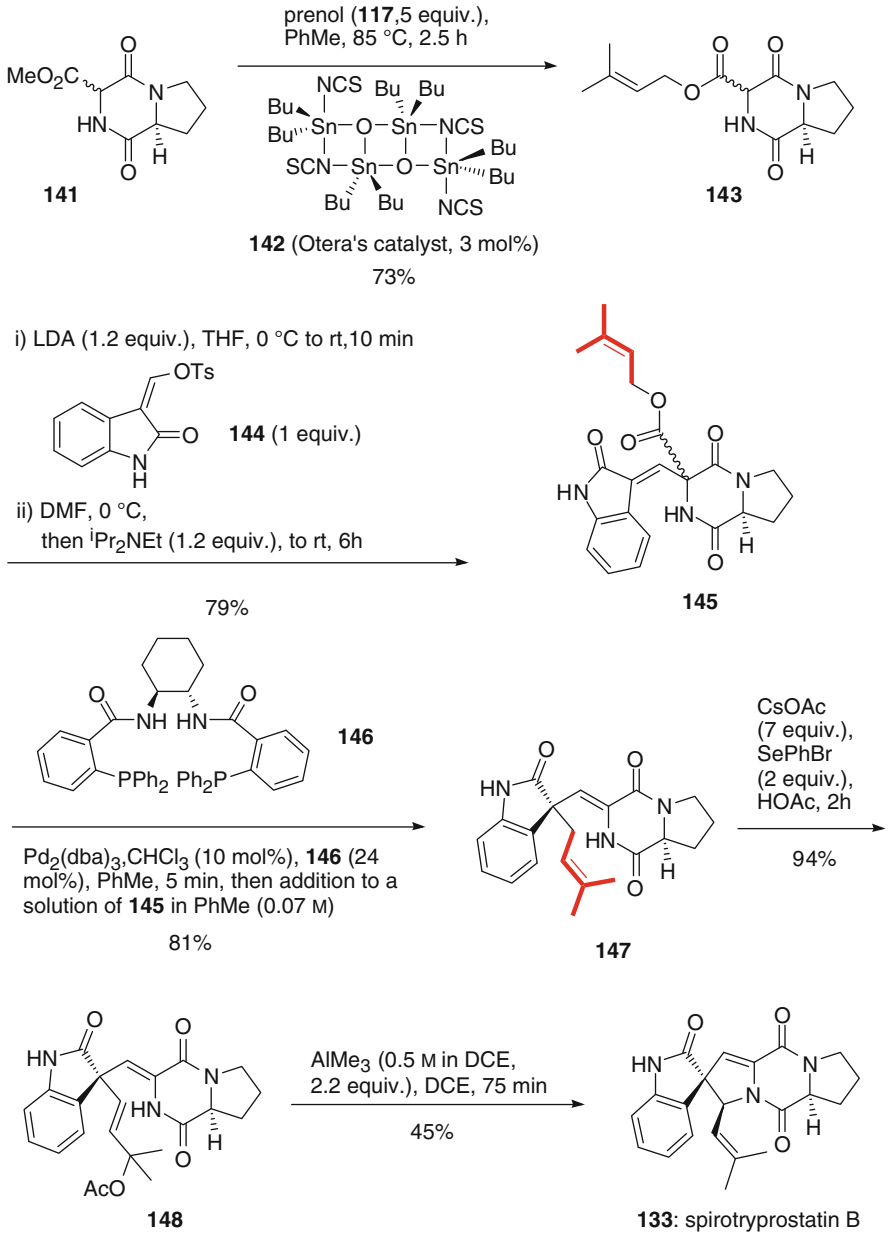
Scheme 28 Enantioselective allylation of a 3-prenylindole by Trost and Quancard [122]

co-workers on reaction of indole and prenol in the presence of $MoO_2(acac)_2$ (10 mol%)/NH_4PF_6 in MeCN [121].

C3-quaternised 3-prenyl indolenines are accessible in an enantioselective manner by Pd-catalysed 3-allylation of 3-prenylindoles, as reported by Trost and Quancard in 2006 (Scheme 28) [122]. In addition to the Pd-source and the anthracene-derived chiral ligand **139**, an optimised bulky tertiary borane (9-BBN-C_6H_{13}) is added, which coordinates to the indole nitrogen, prevents N-allylation and also enhances the enantioselectivity of the reaction. The reaction from **138** to **140** is especially suitable for electron-rich indoles and could be tried with prenol as allylic alcohol.

Echavarren and co-workers reported the Au(I)-catalysed introduction of oxygenated prenyl groups at C3 by treating indole with isoprenoid *tert*-propargyl esters [123], obtaining double bond regioisomers in part. Propargylation of indole derivatives has also led to the formation of bisindoles [53] and allenylated products and quinoline derivatives [56].

The key step of the synthesis of spirotryprostatin B (**133**) by Trost and Stiles is an enantioselective Pd-catalysed decarboxylation-allylation reaction starting from the prenyl β-oxoester **145**, which serves as a pre-nucleophile (Scheme 29) [124].



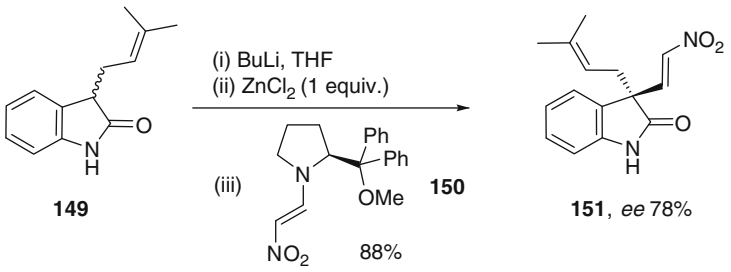
Scheme 29 Synthesis of spirotryprostatin B (**133**) by Trost and Stiles [124]

Originally, this reaction type was carried out under thermal conditions (Carroll rearrangement). Saegusa [125] and Tsuji [126] discovered the possibility of using Pd catalysts, Williams [127], Pfaltz and Helmchen [128] developed chiral Pd ligands for that reaction. The Trost synthesis is the first example of submitting prenyl groups to the key reaction and employed the C_2-symmetrical bisphosphane ligand **146**. Initially, a β-oxocarboxylate is formed, subsequently undergoing decarboxylation to the enolate, which nucleophilically attacks the chiral η^3-Pd complex of the prenyl group. The starting material **143** was synthesised from diketopiperazine **141** (Scheme 29), which was transesterified with prenol (**117**) employing Otera's tin catalyst (**142**) [129]. After enolisation of **143**, tosylated oxindole **144** was added as electrophile affording **145**. The endgame of the synthesis converts the prenyl group of **147** to the allylic acetate **148** by treatment with in situ-produced PhSeOAc. Allylic acetate **148** underwent cyclisation to **133** after the rare conversion to the aluminium amide on treatment with $AlMe_3$.

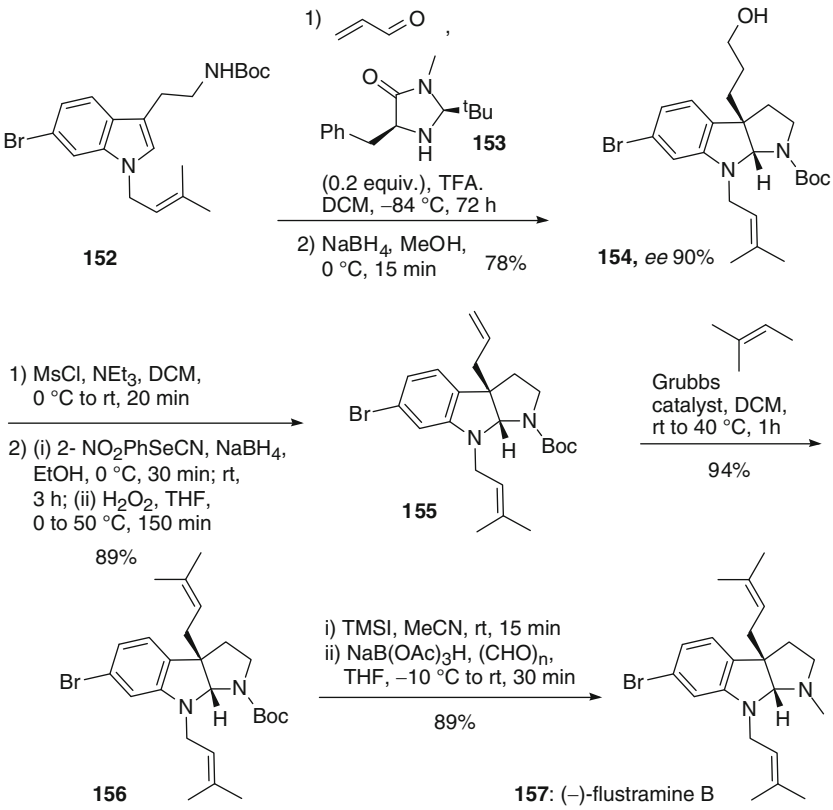
There are also excellent total syntheses of spirotryprostatins which do not apply intermolecular functionalisation of the indole 3-position with a C_5 prenyl-type precursor and are, therefore, not discussed in detail. Carreira and co-workers started from 3-diazo-2-oxindole, which was used in a Rh(I)-catalysed cyclopropanation of 1,3-pentadiene. The resulting cyclopropane was subjected to MgI_2-catalysed ring expansion and added to an imine affording the spiro[5.5] partial structure [130, 131]. Overman and Rosen built up the indole system by intramolecular Heck reaction of a functionalised iodoaniline [132, 133]. In a model study building up the indole system, Cacchi and co-workers synthesised 3-prenylindoles *via* Pd-catalysed cyclisation of *ortho*-alkynyltrifluoroacetanilides with prenyl esters [134].

Use of enamine or iminium electrophiles. In their synthesis of spirotryprostatin B (**133**), Fuji and co-workers started from *rac*-3-prenyl-2-oxindole (**149**) with an interesting enantioconvergent nitroolefination affording the C3-quaternised product **151** (*ee* 78%, Scheme 30). The proline-derived nitroenamine **150** was used with the pyrrolidine section functioning as auxiliary [135, 136].

Iminium organocatalysis was key to the enantioselective total synthesis of (−)-flustramine B (**157**) from the marine bryozoan *Flustra foliacea* by MacMillan and co-workers (Scheme 31) [137], which is discussed here despite not incorporating the entire C_5 unit in one step. On treatment of the Boc-protected



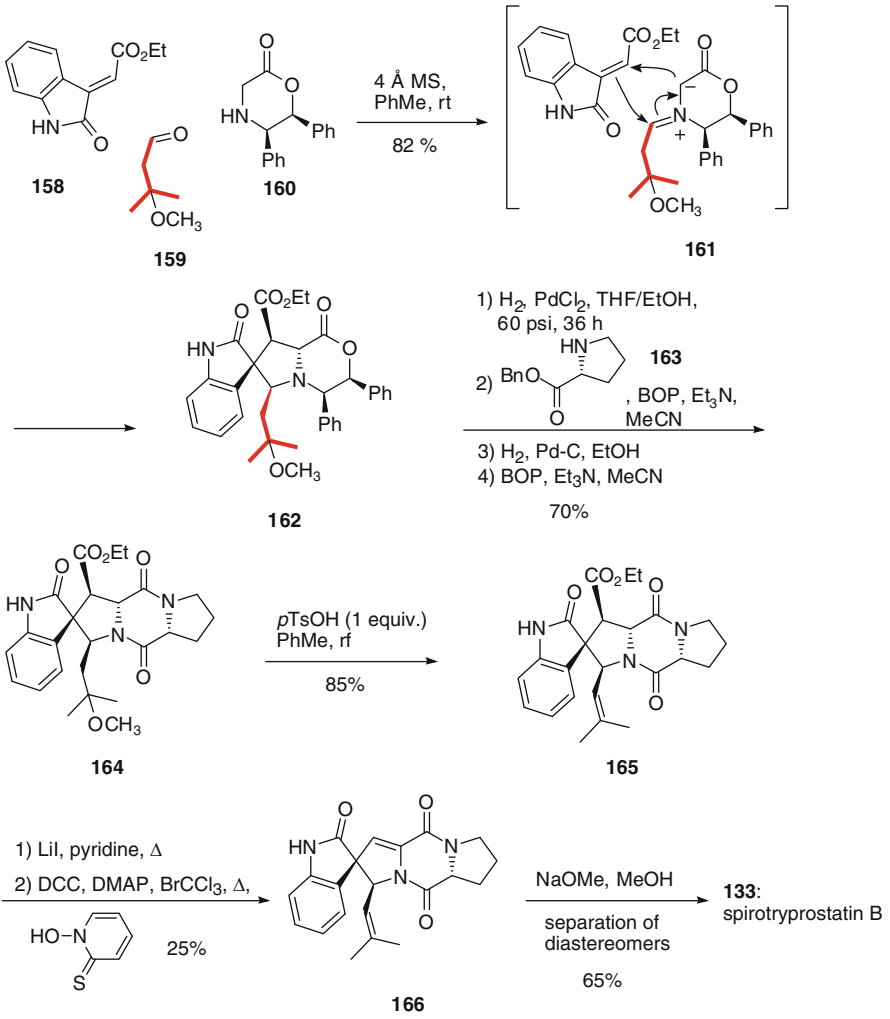
Scheme 30 Enantioconvergent step of Fuji's synthesis of spirotryprostatin B (**133**) [135]



Scheme 31 Enantioselective total synthesis of (−)-flustramine B (**157**) by MacMillan and co-workers [137]

tryptamine derivative **152** with acrolein in the presence of 20 mol% of the imidazolidinone **153**, the tricycle **154** was formed in high yield (78%) and enantiomeric excess (90%). As intermediate, a reactive chiral iminium cation with a lower LUMO than acrolein is formed by nucleophilic attack of the free imidazolidinone nitrogen at the aldehyde carbonyl carbon, which is attacked in the β-position by the indole C3 with subsequent cyclisation to the pyrrolo[2,3-*b*]indole tricycle. After reduction to the alcohol **154**, mesylation, conversion to the selenide and oxidative elimination the allyl compound **155** was obtained, which was submitted to Grubbs metathesis with isobutene completing the prenyl group. Deprotection and reductive methylation afforded (−)-flustramine B (**157**).

The Williams group published a three-component condensation reaction starting from oxindolidene acetate **158** which reacted with the azomethine ylide **161** formed in situ from the diphenylmorpholinone **160** and the isoprenoid aldehyde **159** (Scheme 32) [138–140]. The spiro compound **162** was obtained by 1,3-dipolar cycloaddition and converted further to the pentacyclic diketopiperazine **164**.

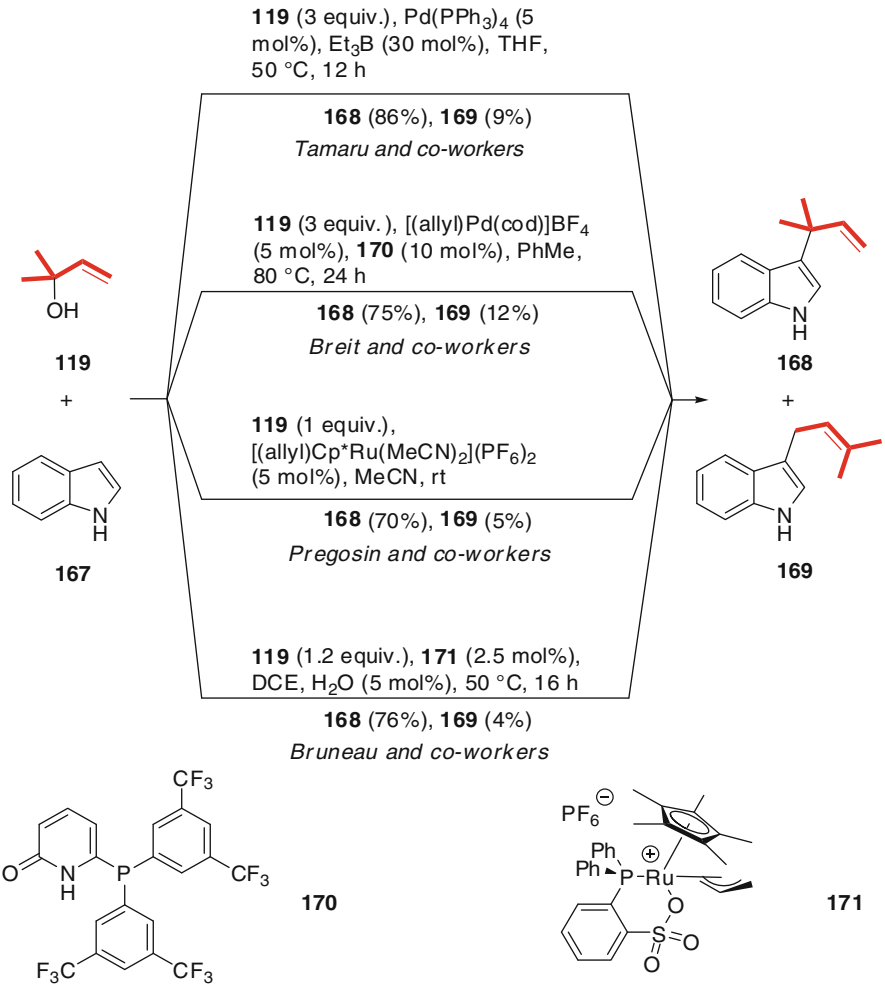


Scheme 32 Three component condensation of the spirocyclic core structure of the spirotryprostatins by Williams and co-workers [138]

Elimination of methanol generated the double bond of the prenyl unit. As in the other syntheses, introduction of the double bond of the pyrroline system proved to be difficult and gave only moderate yields. Diastereomers of **133** had to be separated.

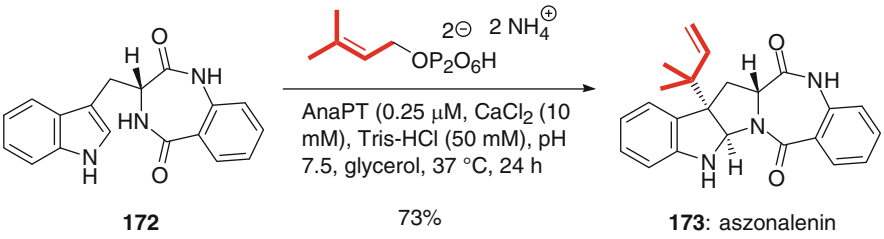
4.2 tert-*Prenylation at C3*

Transition metal catalysed coupling with tert-*prenol*. Recently, several Pd- and Ru-catalysed 3-*tert*-prenylations of indole have been published, all of which start



Scheme 33 Pd- and Ru-catalysed 3-*tert*-prenylations of indole

from 3-unsubstituted indole and thereby do not generate a stereogenic centre at C3. In every case (Scheme 33), yields between 70% and 80% of 3-*tert*-prenylindole (**168**) were obtained and 3-prenylindole (**169**) was formed as minor side product, whereas N-prenylated products have not been observed. Tamaru and co-workers reported a Pd-catalysed reaction employing Et_3B as an in situ auxiliary, which did not prenylate *N*-methylindole, pointing to the necessity of forming an N–B bond [141]. In the case of allylation, Tamaru was also able to convert tryptophan methyl ester to the corresponding 3a-allyl pyrrolo[2,3-*b*]indole. Breit and co-workers utilise pyridone-containing, self-assembling Pd-catalysts. Ligand **170** proved to be very effective for 3-*tert*-prenylation of indole [142]. A π-allylpalladium intermediate was suggested. Pregosin and co-workers [143] and Bruneau and



Scheme 34 Enzymatic synthesis of aszonalenin (**173**) by Li and co-workers [147]

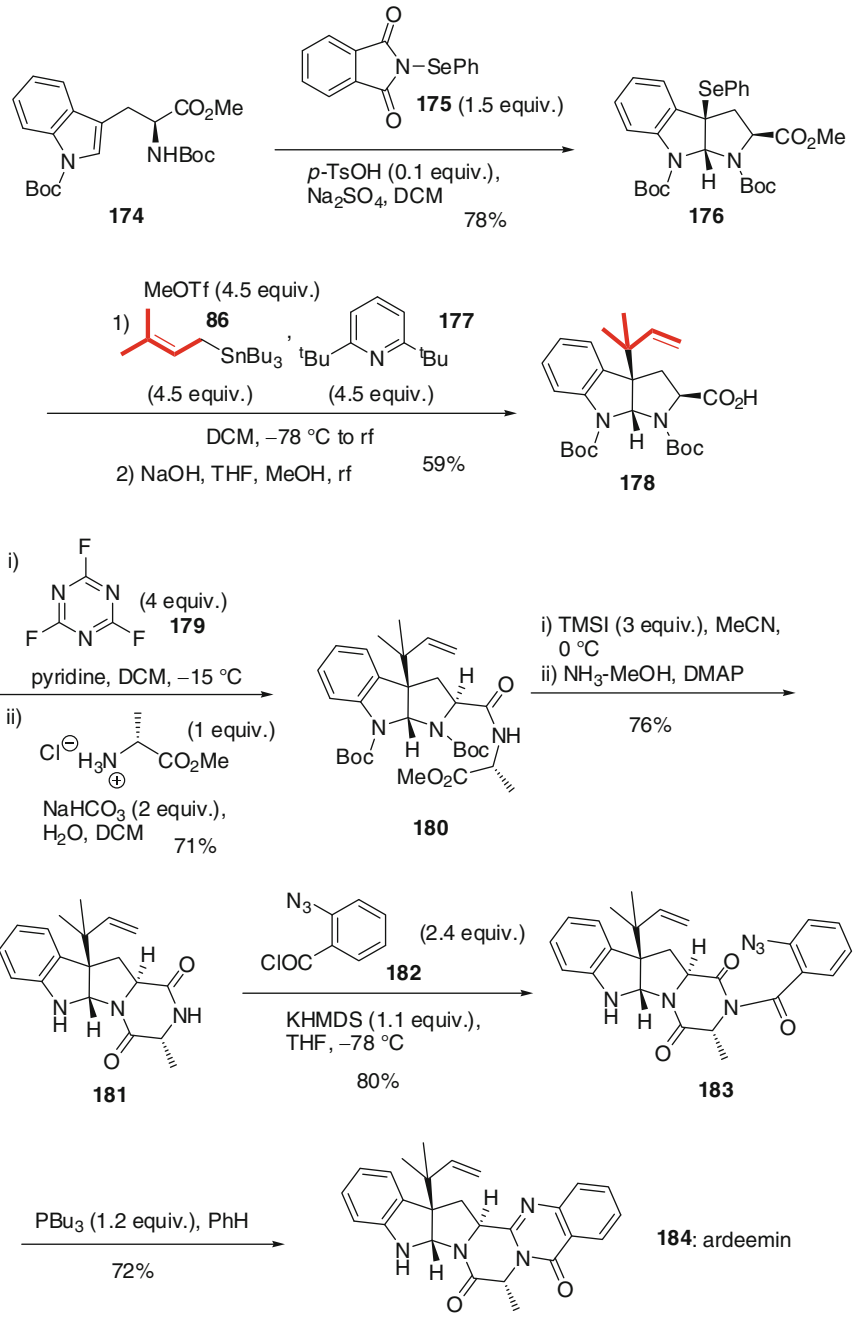
co-workers [144] employed Cp*Ru(IV) complexes to achieve 3-*tert*-prenylation of indole in good yield and regioselectivity.

Chemoenzymatic synthesis. The transition metal-catalysed *tert*-prenylations of indole will have to compete with enzymatic reactions. For instance, several pyrrolo [2,3-*b*]indoles have been synthesised by *tert*-prenylation of tryptophan-derived diketopiperazines employing the recombinant prenyltransferases AnaPT [145] and CdpC3PT [146], respectively, from the fungus *Neosartorya fischeri*. Using the enzyme AnaPT it was also possible to 3-*tert*-prenylate the benzodiazepindione **172**, with subsequent cyclisation to the natural product aszonalenin (**173**) (Scheme 34). When *epi*-**172** was used as substrate, a mixture of the corresponding *epi*-aszolenin and 2-*tert*- and 1-*tert*-prenylated products was obtained [147].

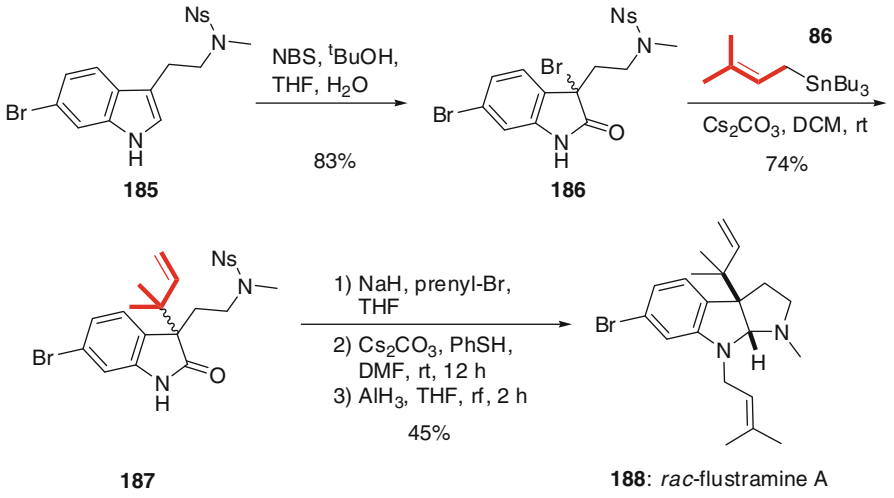
Nucleophilic tert-prenylation. The tert-prenyl group can also be introduced as a nucleophile at the indole 3-position. Danishefsky and co-workers developed a route *via* 3a-phenylseleno pyrrolo[2,3-*b*]indoles which were synthesised by treating N_a,N_b-bis-Boc-protected tryptophan methyl ester (**174**) with *N*-phenylselenophthalimide (**175**, Scheme 35) [148, 149], a reagent introduced by the Nicolaou group [150]. In the presence of pyridinium *p*-toluenesulfonate or *p*-TsOH, the desired diastereomer **176** was formed almost exclusively, probably due to kinetic reasons. For the synthesis of amauromine and ardeemin (**184**), **176** was treated with methyl triflate and prenyl-$SnBu_3$ in the presence of 2,6-di-*tert*-butylpyridine, introducing the *tert*-prenyl group with inversion of regiochemistry. After peptide coupling with an alanine unit, cyclisation of **180** to the diketopiperazine was carried out. The remaining anthranilic acid-derived unit was introduced by acylation with *ortho*-azidobenzoyl chloride (**182**), followed by Staudinger reduction to the amine and cyclising condensation. The phenylselenide pathway for installing the 3-*tert*-prenyl group was also employed by Joullié and co-workers in their synthesis of roquefortine C [151, 152] and, with a less diastereoselective phenylselenation step, by Omura and co-workers [153].

Tributylprenylstannane can also attack 3-brominated 2-oxindoles, as exploited by Fuchs and Funk in their synthesis of *rac*-flustramine A (**188**, Scheme 36) [154]. After preparation of 3-bromoindolin-2-one **186** from the tryptamine derivative **185**, prenylstannane **86** acts as a nucleophile introducing the *tert*-prenyl group at C3 affording **187**. After three more steps, *rac*-flustramine A (**188**) was obtained.

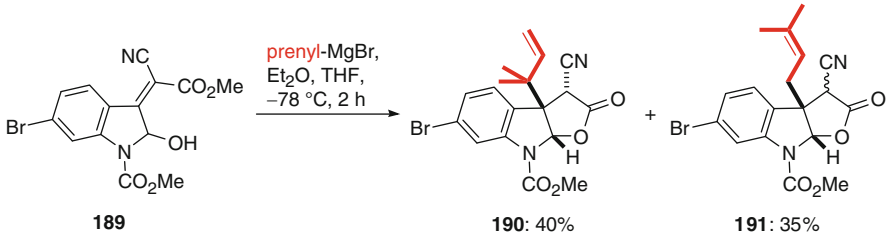
Joseph-Nathan and co-workers converted the indole-3-position into the β-position of an α-cyanoacrylate (Scheme 37) [155–157]. Starting material **189**



Scheme 35 Synthesis of ardeemin (**184**) via nucleophilic *tert*-prenylation by Danishefsky and co-workers [148]



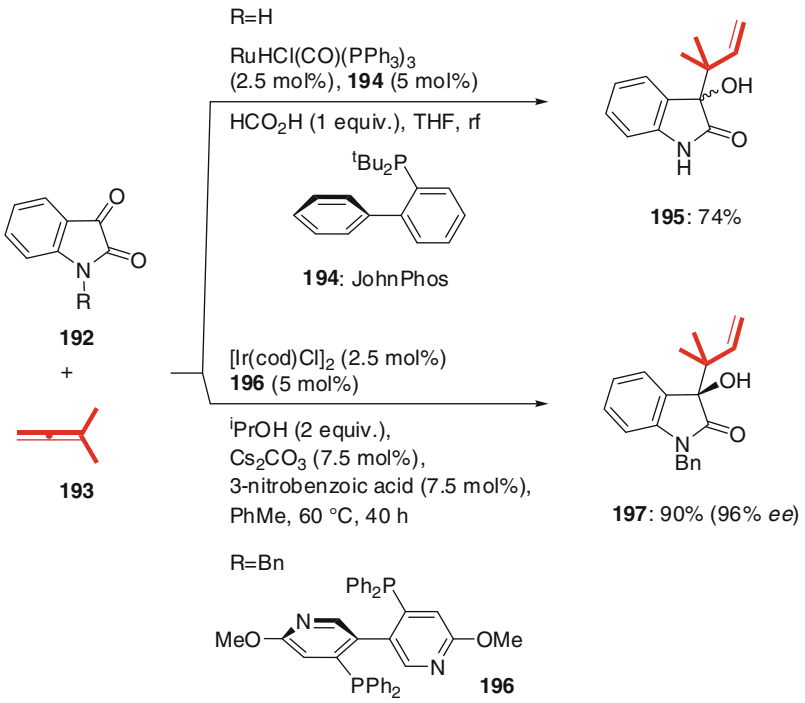
Scheme 36 Synthesis of *rac*-flustramine A (**188**) by Fuchs and Funk [154]



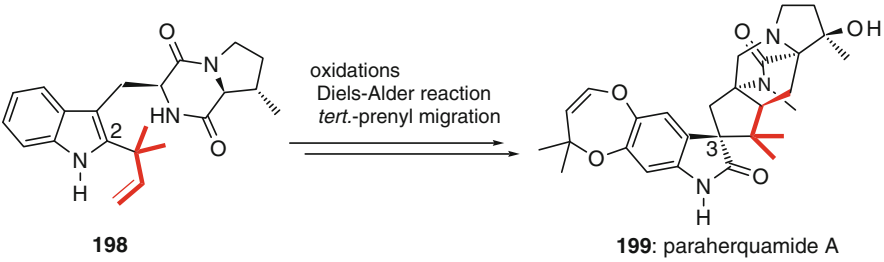
Scheme 37 Key step of Joseph-Nathan's synthesis of several flustramines [155]

was obtained from 3-cyanomethylindole and dimethylcarbonate, followed by oxidation with HNO_3/HOAc. In the key step, treatment of **189** with prenylmagnesium bromide led to both *tert*-prenylation and prenylation in roughly equal amounts with concomitant cyclisation to the oxofuro[2,3-*b*]indoles **190** and **191**. No regiocontrol was possible by the Grignard reaction in Et_2O/THF. *Rac*-flustramine A (**188**) was obtained after further steps (not shown).

Use of isatin (**192**) is another option. Prenylindium species attack isatin derivatives at C3 as γ-nucleophiles and in yields above 80% [158], even in aqueous media [159]. Iminoisatins have also been employed as electrophiles, resulting in the formation of quaternary 3-aminooxindoles [160]. Krische and co-workers achieved interesting reductive Ru- or Ir-catalysed *tert*-prenylations of isatin (Scheme 38) [161, 162], employing 1,1-dimethylallene (**193**) as prenyl source. As reducing hydrogen sources, formic acid or isopropanol are used. Biaryl ligands such as JohnPhos (**194**) proved to be suitable. The reaction has potential to be applied in natural product synthesis, because the generated tertiary alcohol can be elaborated further to a carbon side chain *via* substitution of the hydroxy group by chloride, followed



Scheme 38 Krische's 3-*tert*-prenylation of isatin [161]



Scheme 39 Biosynthetic origin of paraherquamide A (**199**) with *tert*-prenyl migration according to Williams and co-workers [164]

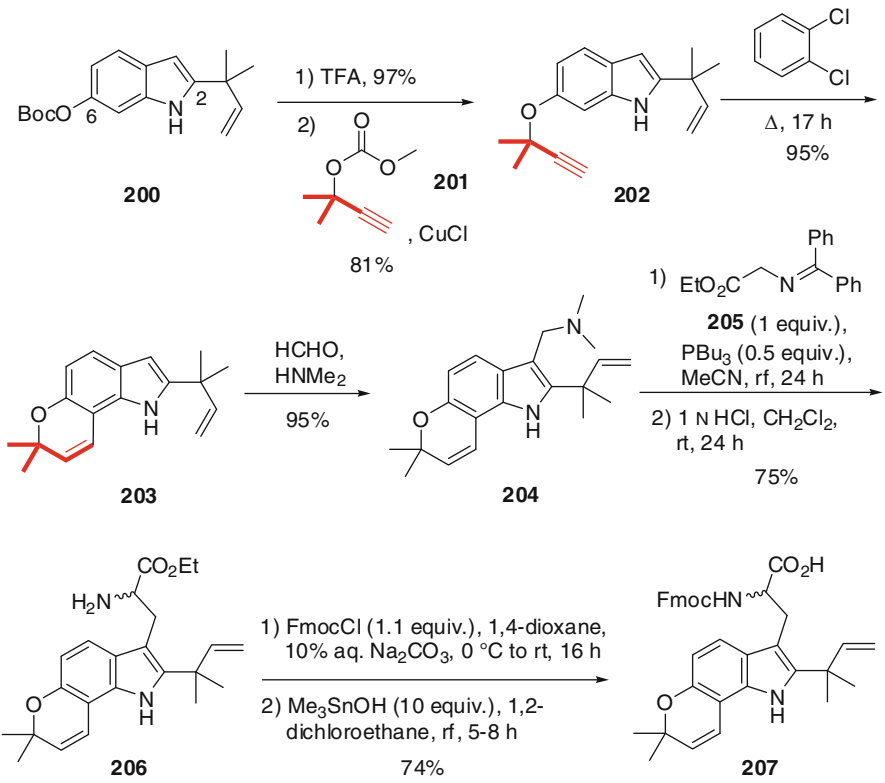
by C-nucleophiles such as cyanide, but also indole. Recently, an enantioselective version has been reported reaching yields and *ee* values above 90% [163].

Prenyl rearrangement. Efficient total syntheses of 3-*tert*-prenylated indole alkaloids employ prenyl shifts from C2, which can be considered biomimetic, since it was shown by Williams that the biosynthesis of paraherquamide A (**199**) from *Penicillium* sp. proceeds *via tert*-prenyl shift from C2 to C3 starting from precursors like **198** (Scheme 39) [2, 165], in agreement with earlier proposals by Barrow [166] and by Gorst-Allman [167] for the biosynthesis of roquefortine.

The 2-*tert*-prenyl group itself stems from the mevalonate pathway and is introduced in a non-stereospecific manner, as shown by isotope labelling studies [164]. The order of oxidations, of Diels–Alder reactions and of the *tert*-prenyl migration is still a subject of research on the individual alkaloids.

Williams and co-workers reported the non-enantioselective total syntheses of the heptacyclic indole alkaloids notoamide B (**227**) and stephacidin A (**225**) (Scheme 43) [168], and of their probable biogenetic precursor, notoamide C (**213**) (Scheme 41) [169]. The notoamides are fungal indole alkaloids from *Aspergillus* species collected from the common mussel *Mytilus edulis* off Noto Island in the Sea of Japan [170, 171]. There is also a synthesis of the closely related notoamide J (**217**) (Scheme 42) [172].

As advanced precursors in all syntheses, racemic 2-*tert*-prenylated tryptophan derivatives were synthesised, which had to be oxygenated at C6 of the indole ring. Batcho–Leimgruber synthesis afforded 6-OBoc-indole **200** in four steps from 4-methyl-3-nitrophenol employing the Danishefsky *tert*-prenylation (Scheme 40) [88]. This procedure did not work for indoles substituted by electron donating



Scheme 40 Conversion of *O*-Boc-protected 2-*tert*-prenyl-6-hydroxyindole **200** to the strategic tryptophan derivative **207** [173]

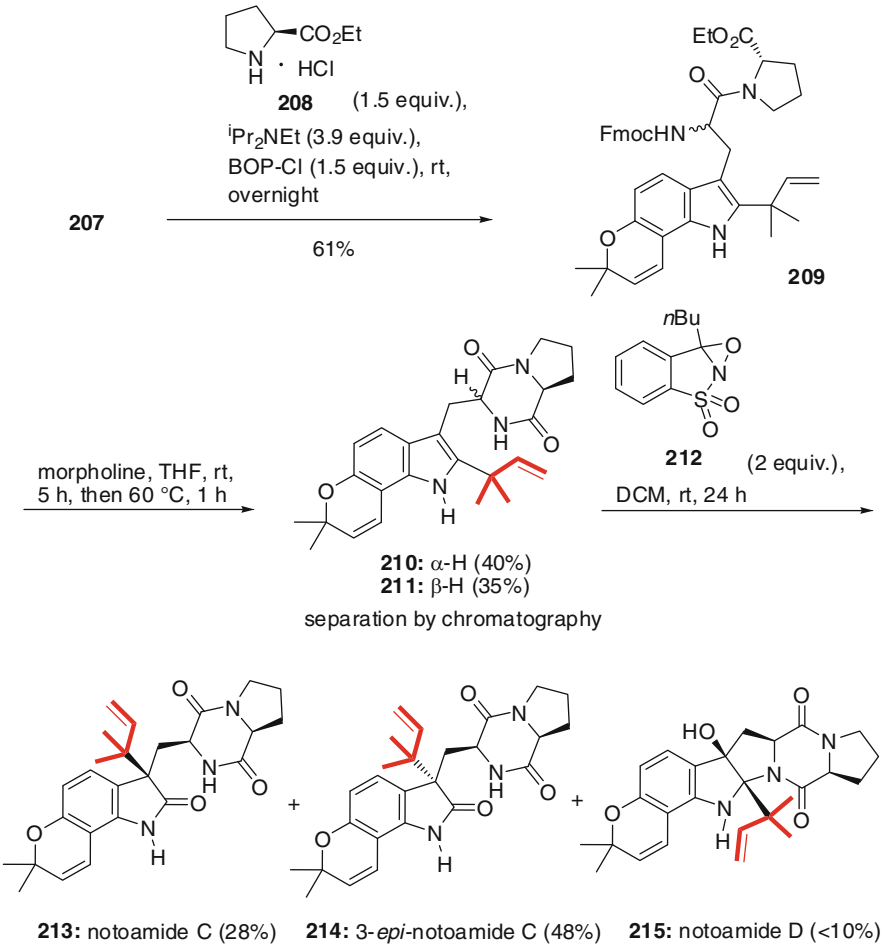
alkoxy or silyloxy groups [174]. Towards notoamides B (**227**), C (**213**) and D (**215**), the 6-oxy substituent was transformed further to the anellated pyran ring. Deprotection and O-propargylation of the N-unsubstituted indole **200** with 1,1-dimethylpropargyl carbonate **201** in the presence of CuCl afforded aryl propargyl ether **202** [173], which underwent thermal Claisen rearrangement in dichlorobenzene under reflux [100, 175]. It can be assumed that initial allene formation is followed by hydrogen shift and 6π electrocyclisation. For the installation of the racemic amino acid functionality, a method developed by Somei and Kametani [176, 177] was modified, which proceeds by coupling of the gramine **204** with the benzophenone imine **205** of glycine ethyl ester in the presence of tributylphosphane, followed by hydrolysis under acidic conditions. Amino acid ethyl ester **206** was Fmoc-protected and hydrolysed to the free acid **207** in high yield by treatment with trimethyltin hydroxide, following a mild procedure developed by the Mascaretti [178] and Nicolaou [179] groups.

The racemic tryptophan derivative **207** was condensed with optically pure proline derivatives following the BOP-Cl protocol. For the synthesis of notoamides C (**213**) and D (**215**), proline ethyl ester was used as coupling partner (Scheme 41), whereas the synthesis of stephacidin A (**225**) and notoamide B (**227**) employed hydroxyproline ethyl ester **219** (Scheme 43). Towards notoamides C (**213**) and D (**215**), the diastereomeric diketopiperazines **210** and **211** had to be separated by chromatography. The Fmoc can be replaced by a Boc protecting group and BOP-Cl by HATU [172].

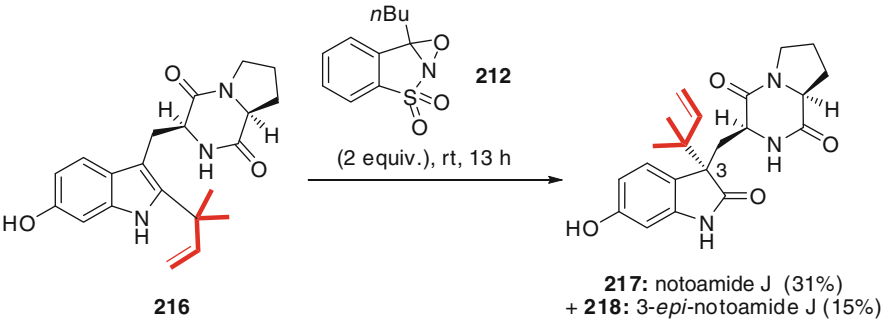
The biomimetic key step of the synthesis of notoamides C (**213**) and J (**217**) treats 2-*tert*-prenylated indoles with Davis' oxaziridine (**212**) [180], which induces oxidative rearrangement of the *tert*-prenyl group from the indole-2- to the -3-position (Schemes 41 and 42). Formation of notoamides C (**213**) and J (**217**) was accompanied by the corresponding 3-*epi*-compounds **214** (48%) and **218** (15%), respectively, because the Davis' reagent epoxidised the indole C2=C3 double bond with low facial selectivity. Epoxide opening appears to occur preferably at C3, setting the stage for a [1,5] sigmatropic rearrangement of the *tert*-prenyl group and thereby generating the oxo group at C2. The electron donating substituent at C6 probably stabilises the intermediate benzylic cation.

Formation of notoamide D (**215**), which was also formed together with its 3-epimer (10% combined yield), can be explained by cyclisation *via* nucleophilic attack of the neighbouring diketopiperazine nitrogen at the intermediate indole epoxide, retaining oxygenation of C3 and preventing migration of the 2-*tert*-prenyl group. Williams and co-workers were able to selectively synthesise notoamide D analogues starting from 6-OBoc-indoles by irradiation in the presence of molecular oxygen and methylene blue [169].

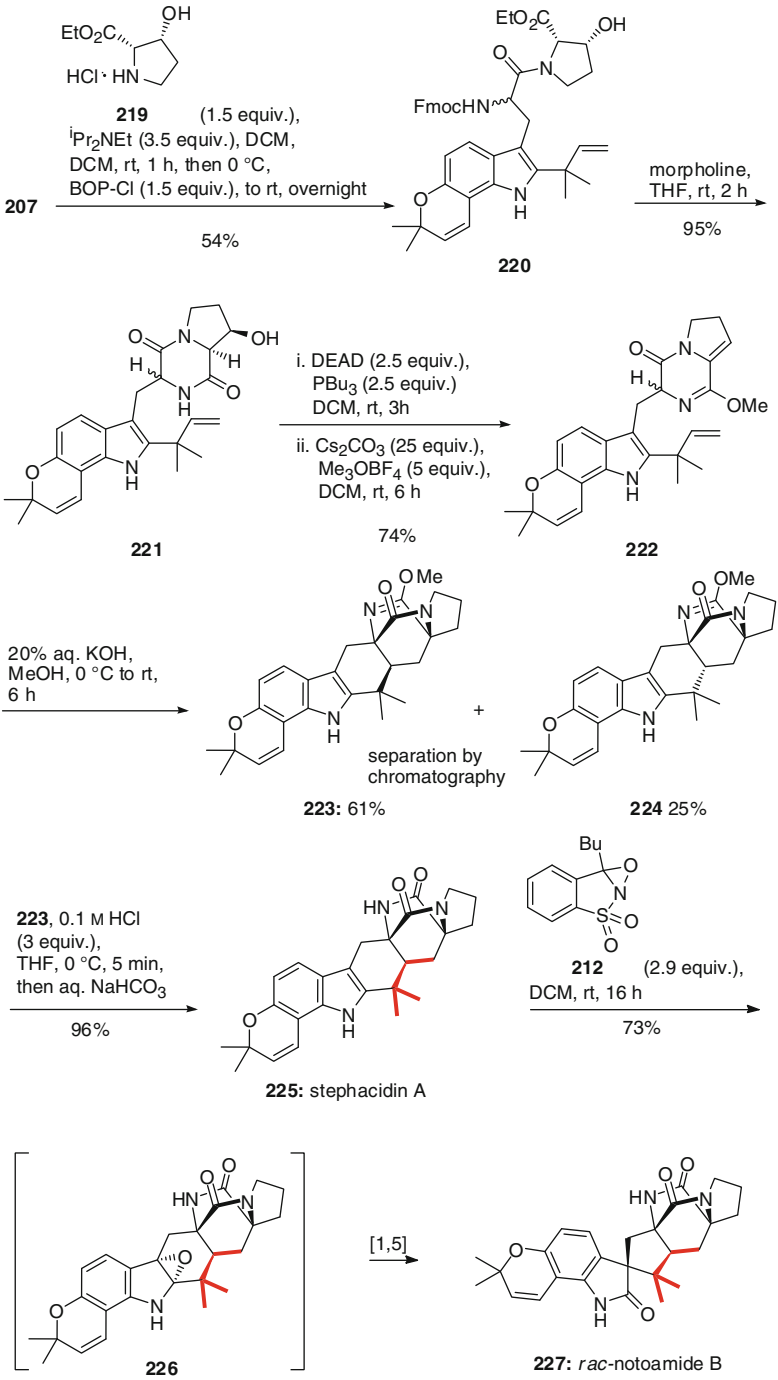
It should be noted that ring contracting migration of the C_5 unit is not restricted to inverse prenyl systems, but also works if the double bond of the *tert*-prenyl group has been removed. For the synthesis of the more complex natural products notoamide B (**227**) and stephacidin A (**225**), the 2-*tert*-prenyl group underwent intramolecular [4+2]-cycloaddition to a dehydrogenated diketopiperazine unit, before its rearrangement to the 3-*tert*-prenylated oxindole was induced by treatment with Davis' reagent (Scheme 43). Hydroxyproline-derived diketopiperazine **221**



Scheme 41 Conversion of protected tryptophan derivative **207** to notoamides C (**213**) and D (**215**) by Williams and co-workers [168, 169]



Scheme 42 Conversion of 2-*tert*-prenyl-6-hydroxyindole **216** to notoamide J (**217**) by Williams and co-workers [172]

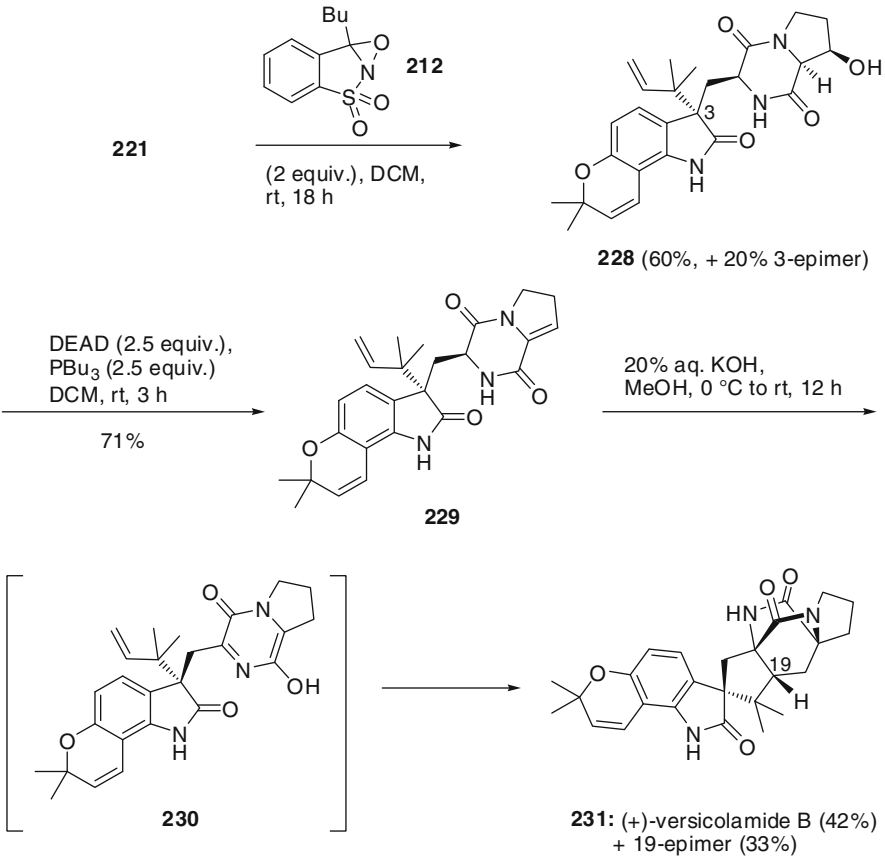


Scheme 43 Conversion of tryptophan derivative **207** to stephacidin A (**225**) and further to notoamide B (**227**) by Williams and co-workers [168]

was subjected to Mitsunobu dehydration (DEAD, PBu_3) affording the pyrroline. It turned out to be possible to convert selectively only the α,β-unsaturated amide partial moiety to the conjugated lactim ether **222**. On treatment of **222** with base, tautomerisation to an azadiene occurred which served as diene component of the subsequent intramolecular hetero Diels–Alder reaction affording a separable mixture of diastereomeric heptacycles **223** and **224**. Acidic hydrolysis of the lactim ether **223** provided the natural product stephacidin A (**225**).

Ring contraction of stephacidin A (**225**) to notoamide B (**227**) was possible by treatment with Davis' reagent (**212**) in high yield (73%). Diastereoselectivity of the initial indole epoxidation was complete, presumably due to the less flexible structure of **225**, when compared to the precursors of notoamides C (**213**), D (**215**) and J (**217**).

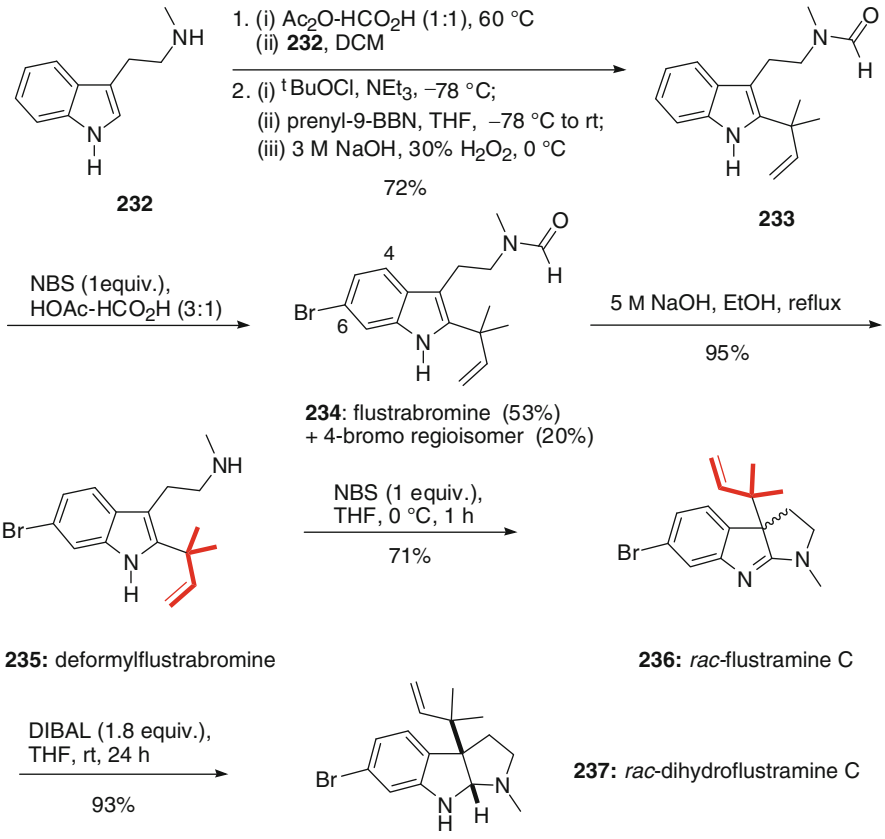
The 2009 synthesis of (+)-versicolamide B (**231**) by Williams and co-workers revealed that the order of Diels–Alder reaction and oxidative *tert*-prenyl shift can be reversed (Scheme 44) [181]. This is important, because racemic intermediates



Scheme 44 Synthesis of (+)-versicolamide B (**231**) carrying out the Diels–Alder reaction after the *tert*-prenyl migration by Williams and co-workers [181]

are avoided and the total synthesis can be conducted enantioselectively, although separation of diastereomers is still necessary on two occasions. Moreover, a lactim ether such as **222** was not required for the intramolecular Diels–Alder reaction, which also runs starting from the amide **229**, which is obtained from **228** *via* Mitsunobu dehydration. Treatment of **229** with aqueous KOH apparently forms the azadiene intermediate **230** followed by cycloaddition of the double bond of the *tert*-prenyl group. Versicolamide B (**231**) is a diastereomer of notoamide B (**227**) and occurs in both enantiomeric forms in *Aspergillus* species.

The discovery of 2-*tert*-prenylated deformylflustrabromine (**235**) as a major metabolite of *Flustra foliacea* collected near Helgoland [182–184] prompted us to investigate its presumably biomimetic conversion to the pyrrolo[2,3-*b*]indole flustramine C (**236**) [185], which is *tert*-prenylated at the bridgehead C3a (Scheme 45). For the synthesis of deformylflustrabromine (**235**), N_b-methyltryptamine (**232**) was converted to N_b-formyl-N_b-methyltryptamine which cleanly underwent



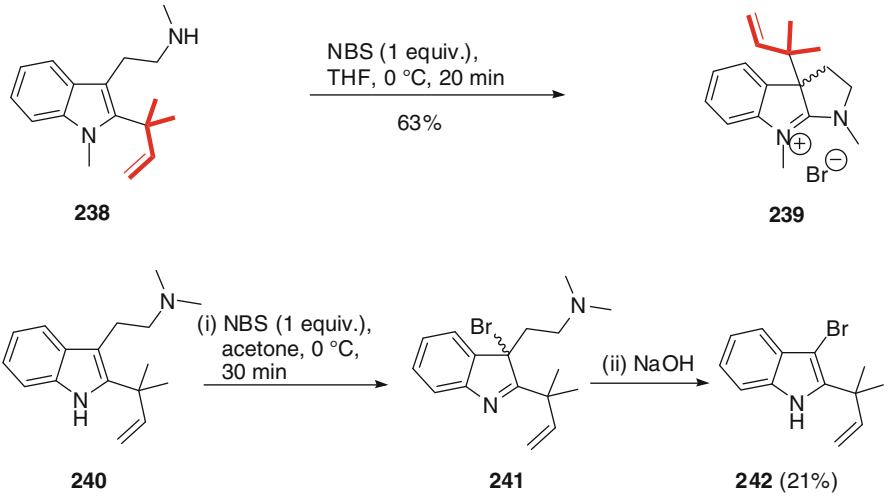
Scheme 45 Synthesis of *rac*-dihydroflustramine C (**237**) by us [185]

Danishefsky's inverse prenylation [93] on treatment with *tert*-BuOCl and freshly prepared prenyl-9-BBN [186] affording 2-*tert*-prenylindole **233** in 72% yield over two steps.

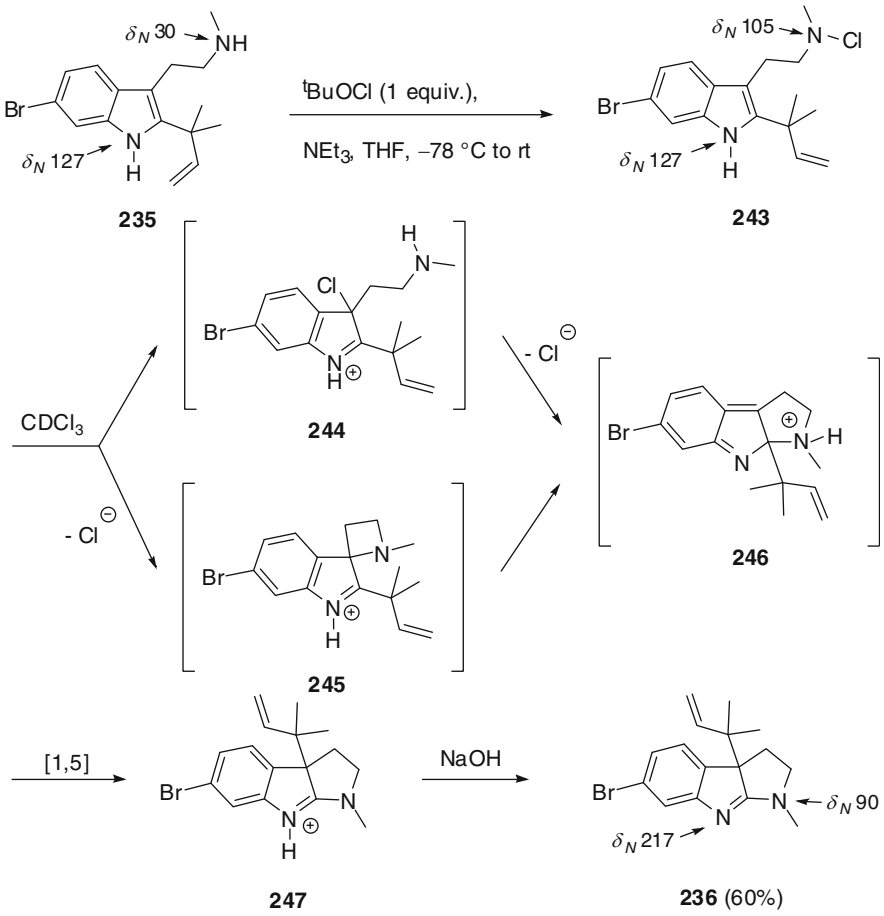
Monobromination of **233** proceeded on treatment with one equivalent of *N*-bromosuccinimide (NBS) in HOAc/HCO_2H (3:1) [187] affording the natural product flustrabromine (**234**) in 53% isolated yield. As side product, the 4-brominated analogue was obtained (20%). Alkaline hydrolysis of flustrabromine (**234**) afforded deformylflustrabromine (**235**), which afforded *rac*-flustramine C (**236**) in one single step on treatment with NBS (1 equiv.). *Rac*-flustramine C (**236**) was reduced diastereoselectively to *rac*-dihydroflustramine C (**237**) with DIBAL-H [188].

Non-brominated indoles also underwent the 2-*tert*-prenyl migration induced by NBS and methylation of the side chain nitrogen was not necessary. N_a,N_b-Dimethyl-2-*tert*-prenyltryptamine (**238**) afforded the *N*,*N*′-dimethylamidinium salt **239**, which precipitated from EtOAc (63% yield, Scheme 46). When the side chain was monoformylated, no cyclisation was observed. In the case of N_b,N_b-dimethyl-2-*tert*-prenyltryptamine (**240**), oxidation with NBS was carried out in acetone for solubility reasons affording 3-bromoindole **242** (21%) *via* bromoindolenine **241**, which was observed on NMR control. Loss of the side chain of the 3-bromoindolenine on alkaline work-up can be explained by nucleophilic attack of hydroxide at the imine β-position.

Deformylflustrabromine (**235**) can also be converted to flustramine C (**236**) on treatment with *tert*-BuOCl (1 equiv.) in the presence of NEt_3 in THF at −78°C. Here, it was possible to identify the first intermediate **243** of the reaction sequence, which was N-chlorinated in the side chain (Scheme 47). The reaction could proceed with intramolecular chlorination of the indole 3-position affording chloroindolenine **244**. Alternatively, azetidine **245** could be formed by nucleophilic attack



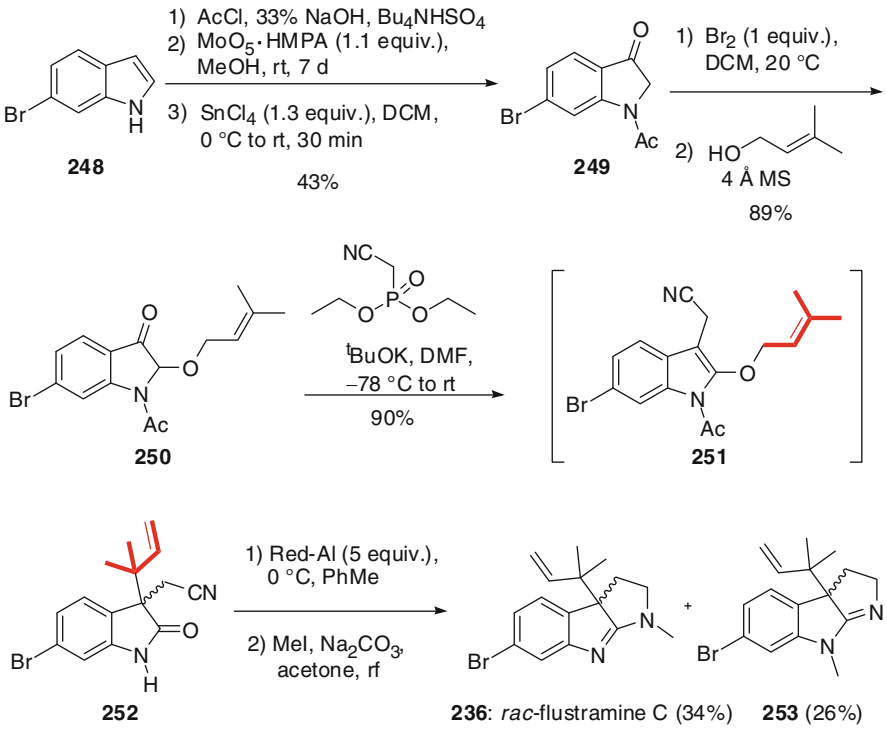
Scheme 46 Effect of methyl substitution on the NBS-induced *tert*-prenyl shift [188]



Scheme 47 Possible mechanisms of the *tert*-BuOCl-induced *tert*-prenyl shift. ^{15}N NMR shifts are referenced to ammonia [185]

of C3 at the chlorinated side chain nitrogen, since the polarity of an N–Cl bond is not pronounced. Ring expansion of **245** would afford pyrroloindole **246** which would then undergo [1,5] sigmatropic *tert*-prenyl rearrangement to form protonated flustramine C (**247**), which was observed in the NMR spectrum.

Claisen rearrangement of 2-prenyloxy- or -thioindole. A viable strategy to synthesise 3-*tert*-prenylindoles employs Claisen rearrangement starting from 2-prenyloxyindoles. The Sakamoto group published a total synthesis of *rac*-flustramine C (**236**) featuring a domino olefination-isomerisation-Claisen rearrangement as the key step (Scheme 48) [189, 190]. Starting from 6-bromoindole (**248**), 6-bromoindolin-3-one **249** was obtained in three steps by N-acetylation, oxidation to the 2-methoxy-3-hydroxyindoline with MoO_5-HMPA and elimination of methanol on treatment with $SnCl_4$. The prenyloxy group was introduced at C2



Scheme 48 Total synthesis of *rac*-flustramine C (**236**) by the Sakamoto group [189]

affording **250** after C2-bromination of **249** and nucleophilic substitution at C2 with prenol in the presence of molecular sieves in high yield.

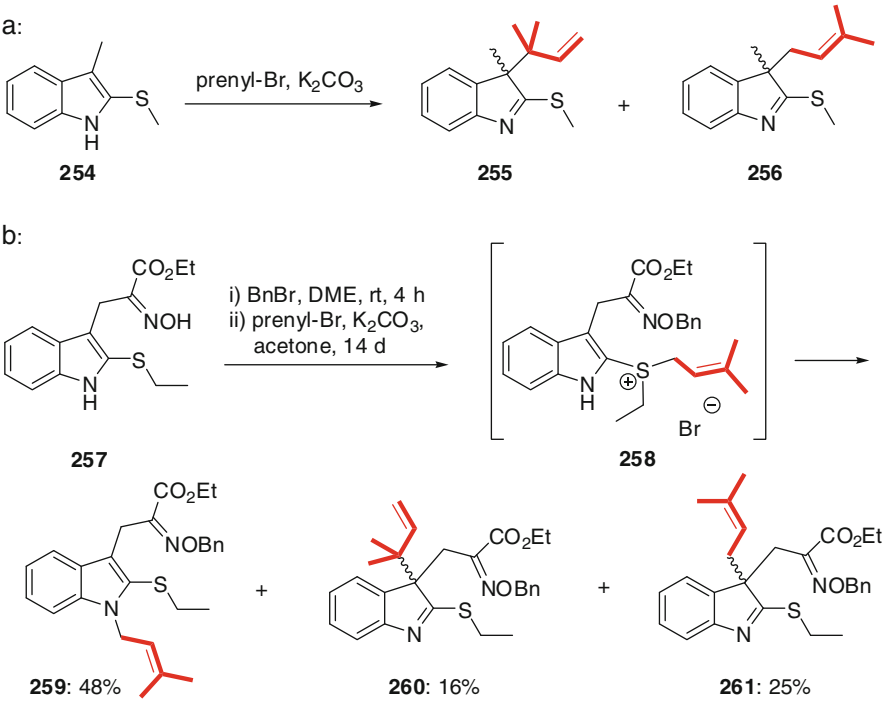
Horner–Wadsworth–Emmons reaction afforded 3-cyanomethylindole **251** as reaction intermediate which underwent Claisen rearrangement under mild conditions affording 3-*tert*-prenylindol-2-one **252** with concomitant deacetylation. The nitrile group was chemoselectively reduced to the amine with Red-Al at 0 °C, followed by cyclisation to the pyrrolo[2,3-*b*]indole. The last step of the total synthesis afforded the N-methylated regioisomers **236** and **253**, substantially diminishing the overall yield of *rac*-flustramine C (**236**). Regioselective introduction of the N-methyl group was achieved by Kawasaki and co-workers following the indole N-prenylation after the Claisen rearrangement. The nitrile was then converted to an N-methylated secondary amide paving the way for the total synthesis of flustramide A and flustramine A (**188**) [191].

A similar Claisen rearrangement starting from 2-prenyloxyindolin-3-ones was induced by treatment with DBU in toluene at 40 °C [192]. The corresponding reaction with the crotyl compound confirmed that a chair-like transition state is favoured. The reaction is also possible in EtOH/KOH with decarboxylation if an additional ethoxycarbonyl group is present at C2 [193]. Booker-Milburn and co-workers started from 3-methoxycarbonylindole, which was first converted to the

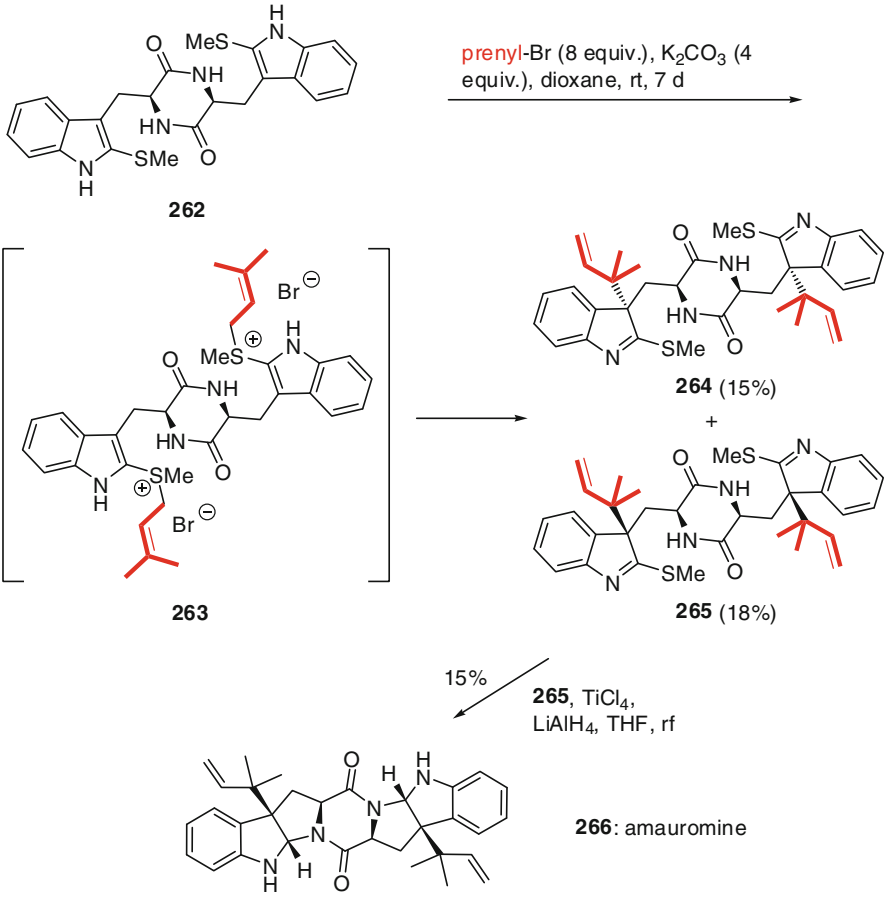
chloroindolenine, followed by nucleophilic attack of prenol and subsequent Claisen rearrangement to the 3-*tert*-prenylindole in trichloroacetic acid-DCM (89% yield) [194].

Lower yields and more byproducts have in most cases been obtained by the corresponding thia-Claisen rearrangement. Bycroft and Landon were the first to report a thia-Claisen rearrangement starting from 2-methylthioxy-3-methylindole **254** (Scheme 49) [195], which was treated with prenyl bromide in the presence K_2CO_3 affording 3-*tert*-prenylindole **255** as major product (no yield given) *via* the indolylprenylmethylsulfonium cation. However, Ottenheijm and co-workers published a less clean reaction of 2-ethylthio α-oximinoester **257**, which, after O-benzylation, afforded a mixture of three products on treatment with prenyl bromide and base. The thia-Claisen product **260** was formed in only 16% yield with N-prenylated indole **259** (48%) being the major product, together with the 3-prenylindolenine **261** (25%, Scheme 49) [32].

Takase and co-workers applied this reaction to the corresponding indolylacetic acid methyl ester and synthesised *rac*-debromodihydroflustramine C with the thia-Claisen step proceeding in about 30% yield and very good regioselectivity in favour of the 3-*tert*-prenylindole [34]. A thia-Claisen rearrangement was also employed for the synthesis of amauromine (**266**) [33, 35], originally isolated from the fungus *Amauroascus* sp. (Scheme 50). Starting material **262** is thiomethylated in both



Scheme 49 Thia-Claisen rearrangements starting from 2-alkylmercaptoindoles [32, 195]



Scheme 50 Synthesis of amauromine (**266**) via bis-thia-Claisen rearrangement by Takase and co-workers [35]

indole 2-positions and was reacted with prenyl bromide in the presence of base, which probably leads to formation of the bis-sulfonium salt **263** as intermediate. A [3,3] sigmatropic rearrangement of the prenyl groups results in the installation of *tert*-prenyl groups in the indole 3-positions. Takase isolated diastereomers **264** (15%) and **265** (18%) in relatively low yields, of which **265** was reduced and cyclised to amauromine (**266**) employing $TiCl_4/LiAlH_4$ in THF [196], again in low yield (15%).

Other approaches. The construction of a *tert*-prenyl group at C3 may also proceed stepwise and finish with the introduction of the terminal carbon by methylenation of an aldehyde. Kawasaki and co-workers followed that strategy in their total synthesis of (−)-flustramine A (**188**) [197], and Sabahi and Rainier in their synthesis of debromodihydroflustramine C [198]. Qin and co-workers assembled (−)-ardeemin (**184**) in the same manner, after having installed an acetic acid

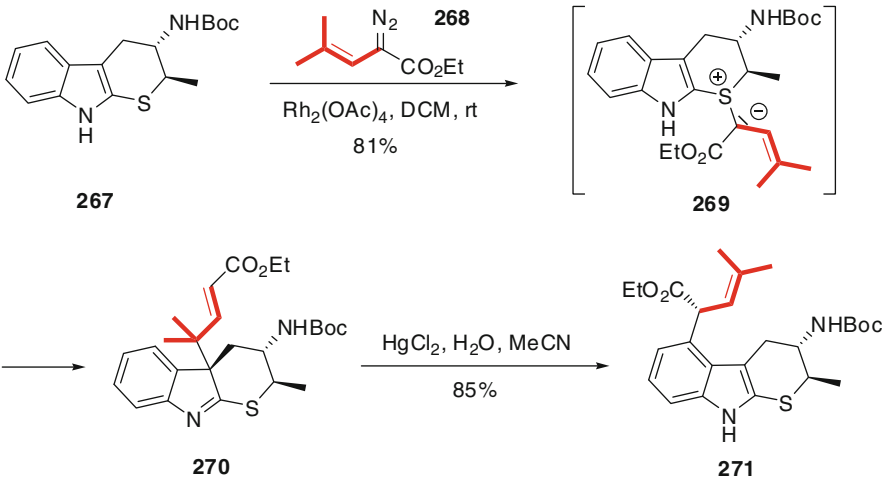
side chain at C3 by reaction of a tryptamine derivative with diazoacetate in the presence of a CuOTf-toluene complex [199]. The indole ring itself can also be assembled after having installed a *tert*-prenyl group in the 3-position, as shown by Viswanathan and co-workers [200].

5 Prenylation and *tert*-Prenylation in the Benzene Section of Indole

5.1 4- and 5-Prenylindoles

Prenyl rearrangement. To date, only 4-prenyl-, but no 4-*tert*-prenylindoles have been synthesised. Rainier and co-workers exploited an interesting sequence of sulphur ylide Claisen rearrangement and Cope rearrangement to achieve C4-prenylation of 2-thioindoles (Scheme 51) [201]. Sulphur ylide intermediate **269** was generated by reaction of the thiane moiety of **267** with the rhodium carbene complex formed from α-diazoester **268** and $Rh_2(OAc)_4$. The following [3,3] sigmatropic rearrangement proceeded with high diastereoselectivity (21:1) affording indolenine **270** with a substituted *tert*-prenyl group at C3. By treatment of **270** with $HgCl_2$, Rainier and co-workers were able to induce a second [3,3] sigmatropic rearrangement to the 4-prenylindole derivative **271**.

Transition metal-mediated prenylation. The earliest example was reported in 1971 by Plieninger and Sirowej who were able to react 4-bromoindole with stoichiometric amounts of preformed η^3-(3,3-dimethylallyl)-nickel bromide at



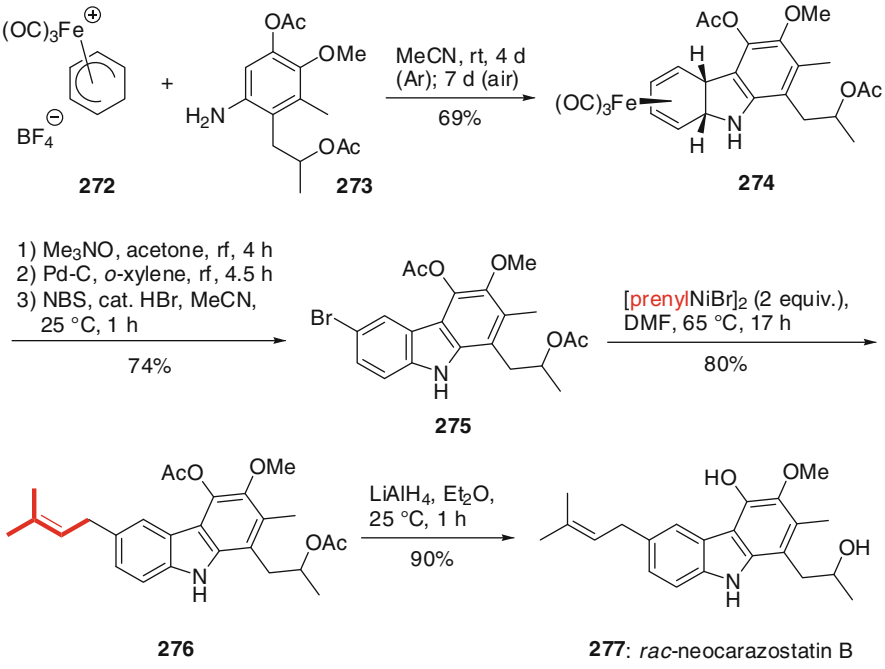
Scheme 51 Sequential sulphur ylide Claisen and Cope rearrangements leading to C4-prenylation of indole [201]

60°C accomplishing 4-prenylation in 67% yield. In the same manner and similar yields 5- and 6-prenylindoles were synthesised [202].

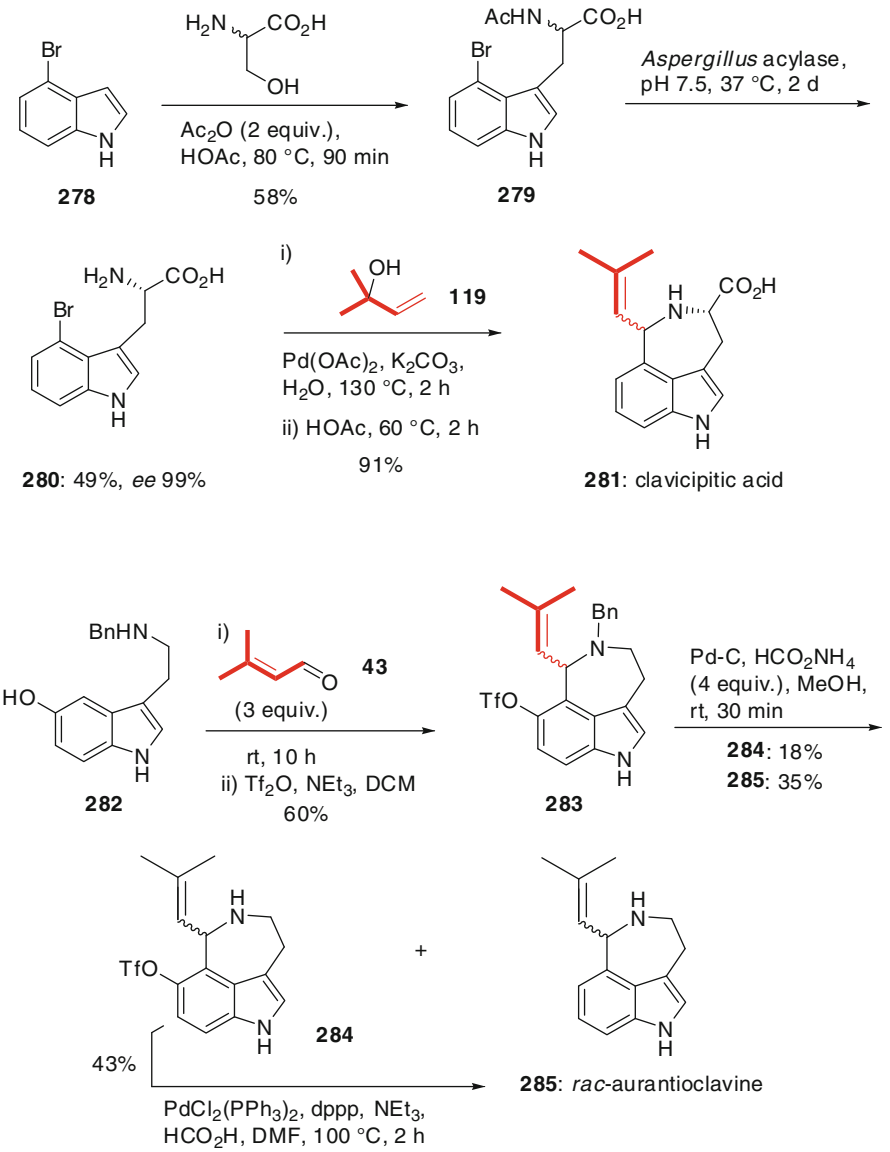
In an in situ version of that reaction, Knölker and co-workers prenylated bromocarbazoles by treatment with excess prenyl bromide and $Ni(cod)_2$, obtaining the natural products glycomaurrol and micromeline [203]. Utilising Ni-based prenylation methodology, Knölker also synthesised the carbazole alkaloid *rac*-neocarazostatin B (**277**) from *Streptomyces* sp. carrying a prenyl group in the indole 5-position (Scheme 52) [204]. The carbazole system itself had been assembled by Knölker's iron-mediated CC and CN bond formation affording iron complex **274**, which was demetalated and regioselectively brominated to **275**. Treatment of **275** with $[prenylNiBr]_2$ (2 equiv.) provided **276** which was reduced to the natural product **277**. The synthesis of carbazole alkaloids has been comprehensively reviewed in an excellent article by Knölker and Reddy [205].

Very recently, She and co-workers reported the total synthesis of the 5-prenylated indole alkaloids tardioxopiperazine A, isoechinulin A and variecolorin C, *via* Pd-catalysed coupling of an in situ-produced prenylindium reagent with a 5-triflyloxytryptophan derivative in DMF at 100°C [206].

Yokoyama and co-workers installed a 4-prenyl group by Heck reaction of *tert*-prenol (**119**) with 4-bromotryptophan (**280**), which was synthesised from 4-bromoindole (**278**) by reaction with *rac*-serine/Ac_2O in HOAc (Scheme 53). An *Aspergillus* acylase was employed for kinetic resolution of the racemic mixture



Scheme 52 Synthesis of *rac*-neocarazostatin B (**277**) by Knölker and co-workers [204]

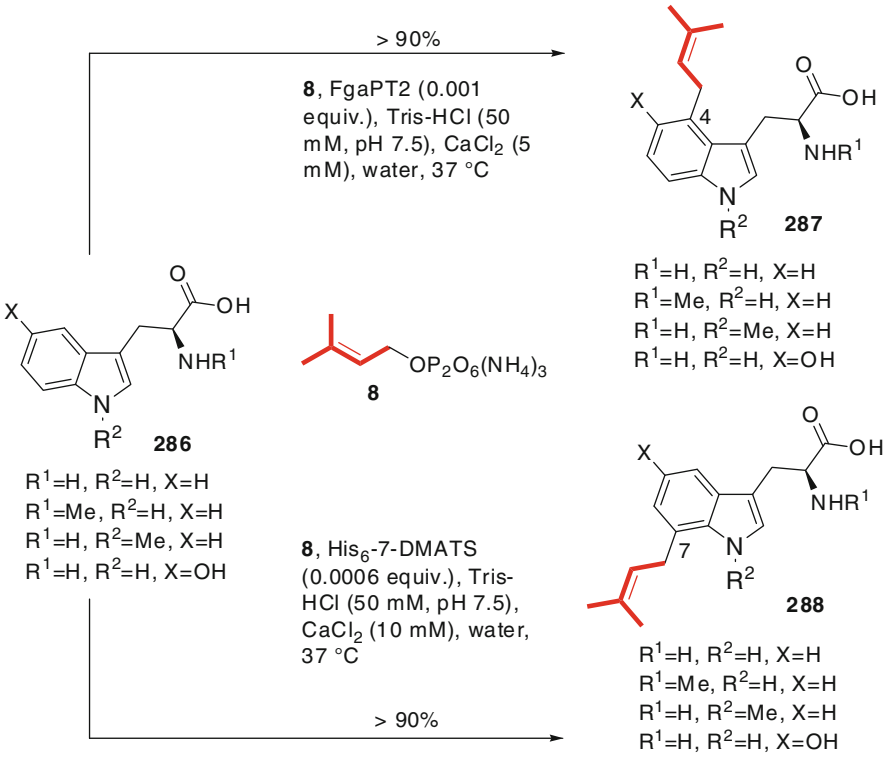


Scheme 53 Synthesis of diastereomeric clavicipitic acids (**281**) by Yokoyama and co-workers [207] and of *rac*-aurantioclavin (**285**) by Ishikura and co-workers [208]

with only the enantiomer (*S*)-**279** being deacetylated. Acid-catalysed cyclisation afforded diastereomeric clavicipitic acids (**281**) [207, 209], originally isolated from *Claviceps* sp. A similar approach *via* a 4-iodoindole with a *de* of 60% in favour of *trans*-clavipitic acid was published by Jia and co-workers [210].

Ishikura and co-workers achieved the same without having to brominate the indole 4-position because of the presence of a 5-hydroxy group in their starting indole **282** and of the tryptamine side chain which probably participates *via* imine formation (Scheme 53) [208]. Pictet–Spengler-type condensation of **282** with prenal (**43**) afforded the azepinoindole **283** which was N-debenzylated with HCO_2NH_4/Pd-C leading to the ergot alkaloid *rac*-aurantioclavine (**285**) from *Penicillium aurantiovirens*, together with the oxygenated compound **284**. Side product **284** could be converted to further amounts of the natural product **285**.

Chemoenzymatic synthesis. As for other indole positions, enzymatic prenylation appears to become competitive. Li employed the 4-dimethylallyltryptophan synthase FgaPT2 [211] and the 7-dimethylallyltryptophan synthase DMATS [212] (both from *Aspergillus fumigatus*) to prenylate tryptophan derivatives (**286**) on the 100 nanomolar scale. In all cases shown in Scheme 54, yields >90% were obtained overnight, based on recovered starting material. As coupling partner, ammonium prenylpyrophosphate (**8**) was used as always.



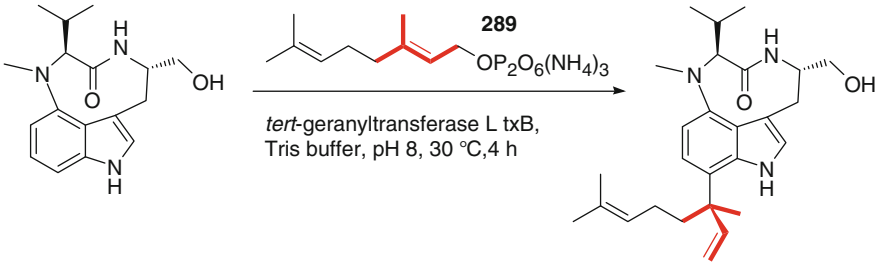
Scheme 54 Chemoenzymatic 4- and 7-prenylations of tryptophan derivatives **286** (FgaPT2: 4-dimethylallyltryptophan synthase, DMATS: 7-dimethylallyltryptophan synthase from *Aspergillus fumigatus*) by Li and co-workers [211, 212]

The exact mechanism of enzymatic prenylations is still subject to debate. On the basis of isotopic labelling, Luk and Tanner recently provided evidence that the reaction proceeds *via* an allylic cation intermediate, rather than *via* an S_N2-type mechanism [213]. The ergot alkaloid producing fungus *Claviceps purpurea* was the source of the first characterised prenyltransferase, isolated by the Floss group [214], followed by identification of its gene [215]. Since then several new members of the family have been characterised [216]. 4-*tert*-Prenylated indoles have not been synthesised. However, the partial structure occurs in the natural product alfatrem [217]. A 6-*tert*-prenylindole moiety occurs in the natural products sulpinine A and B from *Aspergillus sulphureus* [218]. Surprisingly, there are no one-step syntheses of 6-*tert*-prenylated indoles.

5.2 *7-Prenyl- and 7-*tert*-Prenylindoles*

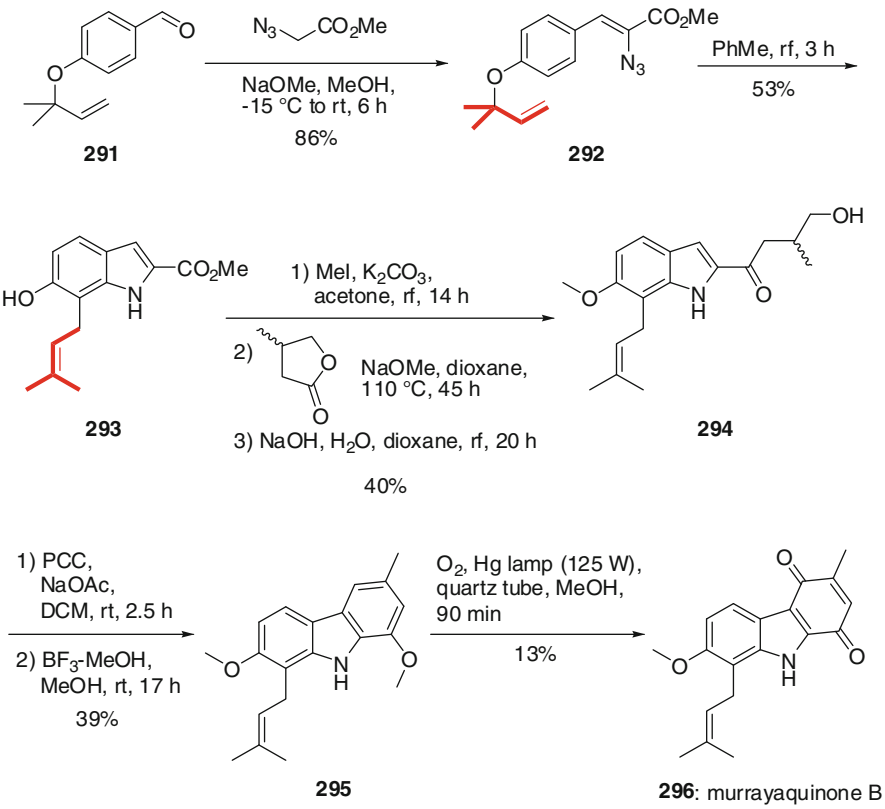
Chemoenzymatic synthesis. In parallel to the work of the Li group on C7 [43, 219], Edwards and co-workers recently identified, expressed and characterised the bacterial *tert*-prenyltransferase LtxB from the marine cyanobacterium *Lyngbya majuscula* [28]. It was possible to catalyse the 7-*tert*-geranylation of indolactam V (**1**) with geranylpyrophosphate (**289**) affording the natural product lyngbyatoxin (**290**) (Scheme 55).

Prenyl rearrangement. By boiling 6-geranyloxyindoles in *N*,*N*-dimethylaniline/Ac_2O, Moody introduced the *tert*-geranyl substituent in the indole-7-position *via* Claisen rearrangement [220, 221]. Similarly, boiling a 6-prenyloxyindole in bromobenzene (156°C) afforded a 7-*tert*-prenylindole (60%). In the presence of water-containing Montmorillonite KSF, refluxing of 6-prenylindole derivatives in toluene afforded 7-prenylindoles without regioinversion [222]. Prenylations of the indole 7-position have also been achieved by Claisen rearrangement of 6-*tert*-prenyloxyindoles and by *aza*-Claisen rearrangement from N-*tert*-prenylindoles. Key step of Moody's synthesis of murrayaquinone B (**296**) from the Rutaceae plant *Murraya euchrestifolia* is a sequential indole formation and



1: (–)-indolactam-V **290**: lyngbyatoxin

Scheme 55 C7-*tert*-geranylation of (−)-indolactam-V (**1**) affording lyngbyatoxin (**290**) [28]

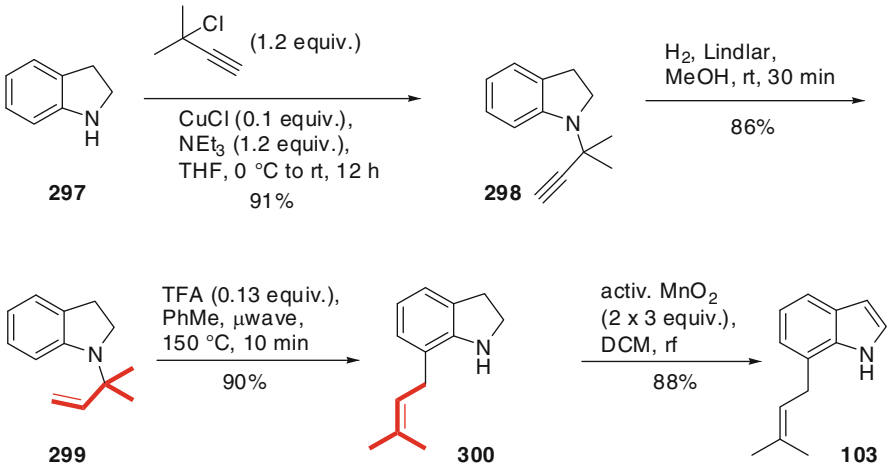


Scheme 56 Synthesis of murrayaquinone B (**296**) by 7-prenylation via Claisen rearrangement by Moody and co-workers [223]

regioselective Claisen rearrangement of azide **292**, prepared by condensation of benzaldehyde derivative **291** with methyl azidoacetate in refluxing toluene affording 7-prenylindole **293** (Scheme 56) [223, 224]. If the *tert*-prenyl group was replaced by allyl, boiling in bromobenzene was necessary to achieve the analogous reaction. The endgame annulates the missing benzene ring, finishing with a low yielding photochemical oxidation of **295**.

Simple treatment of 6-hydroxyindole derivatives with *tert*-prenol in the presence of BF_3-Et_2O does not appear to be selective, since mixtures of prenylated and *tert*-prenylated products were obtained [225].

Xiong and Pirrung found that, when treating N-*tert*-prenylindoline (**299**) with catalytic amounts of TFA under microwave conditions, 7-prenylindoline (**300**) is formed by *aza*-Claisen rearrangement in 90% yield (Scheme 57) [226]. The N-propargylated starting material **298** itself has been synthesised following a protocol by Hennion and Hanzel [45]. Still, the synthesis of 7-prenylindole (**103**) requires four steps from indoline (**297**).



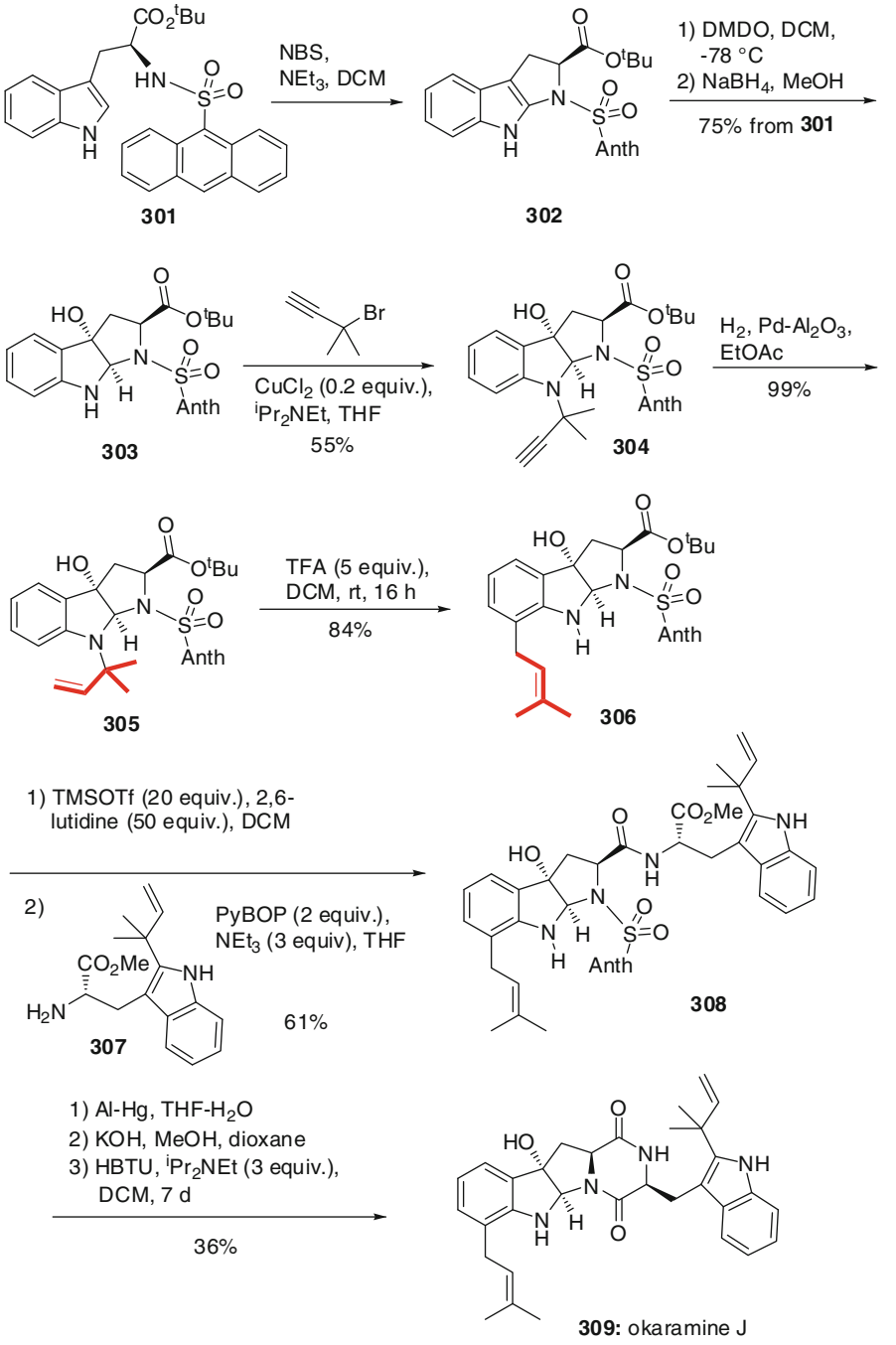
Scheme 57 Synthesis of 7-prenylindole (**103**) by Xiong and Pirrung [226]

In 2003, Ganesan and co-workers reported the total synthesis of the fungal natural product okaramine J (**309**, Scheme 58) from *Penicillium simplicissimum* and *Aspergillus aculeatus*, which for the first time featured an N1 to C7 *aza*-Claisen rearrangement of a *tert*-prenyl group with regioinversion [52]. Following a route developed by Danishefsky and co-workers [227], treatment of the protected tryptophan derivative **301** with NBS afforded the unstable dihydropyrroloindole **302**, which was converted to the hydroxylated pyrroloindole **303** by DMDO oxidation and subsequent $NaBH_4$ reduction. The anthracene sulfonyl protecting group was chosen because it was to be removed later under reductive conditions without dehydrating the hydroxyindolenine **308**.

Installation of the *N*-*tert*-prenyl group was accomplished *via* $CuCl_2$-catalysed propargylation of the indoline **303** in moderate yield (55%), followed by Lindlar hydrogenation of **304**. The key *aza*-Claisen rearrangement proceeded in the high yield of 84% simply by treating the N-*tert*-prenylindoline **305** with TFA in DCM, leading to the presumably charge-accelerated [3,3] sigmatropic rearrangement of the *tert*-prenyl group affording 7-prenylindoline **306**. Ganesan and co-workers propose that the required conformation of the N–C bond is preferred only in the case of **306** because of steric interaction with the bulky anthracenesulfonyl group (Thorpe–Ingold effect).

The endgame of the synthesis features the intermolecular amide coupling with 2-*tert*-prenyltryptophan methyl ester (**307**) employing PyBOP/NEt_3 and the cyclisation to the diketopiperazine **309** employing HBTU/$^{i}Pr_2NEt$. Building block **307** was synthesised by Danishefsky and co-workers in course of their total syntheses of gypsetin (**94**) and brevianamide E.

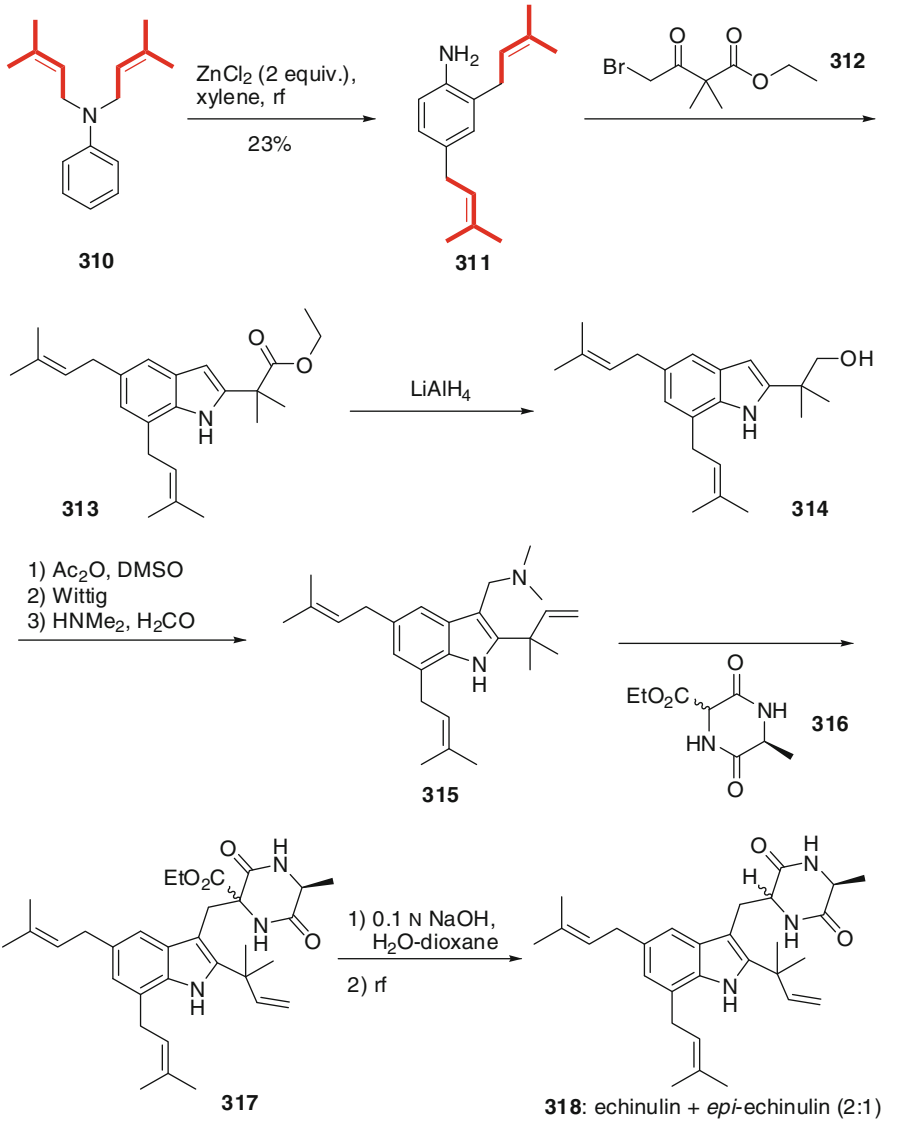
Other approaches. Treatment of an analogue of (−)-indolactam V (**1**) with prenyl bromide in HOAc/NaOAc afforded 7-prenylated, 7-*tert*-prenylated and 2-prenylated products [228]. It was also possible to build up the indole ring of



Scheme 58 Synthesis of the fungal natural product okaramine J (**309**) by aza-Claisen rearrangement by Ganesan and co-workers [52]

7-*tert*-prenylindole starting from suitably functionalised pyrroles, as employed in the total syntheses of pendolmycin [229, 230].

We thought this chapter could finish with one of the earliest total syntheses reported in the field, which made a threefold prenylated indole alkaloid available, admittedly by building up the heterocycle. The key step of the Kishi synthesis of echinulin (**318**) from *Aspergillus echinulatus* is the double prenyl migration starting from *N*,*N*-diprenylaniline (**310**) affording 2,4-diprenylaniline (**311**, Scheme 59)



Scheme 59 Kishi's echinulin synthesis [231]

[231, 232]. The rearrangement is achieved in 23% yield in boiling xylene in the presence of zinc chloride and probably proceeds by *aza*-Claisen–Cope sequences for both prenyl groups. *Tert*-Prenylated intermediates have not been identified. Prior to that work, only one publication on aromatic *aza*-Claisen rearrangements starting from *N*-allylanilines had been published by Hurd and Jenkins [233]. The synthesis of echinulin (**318**) continues with the assembly of the indole ring of **313** by condensation with bromoketone **312**, followed by $LiAlH_4$ reduction to alcohol **314**. Oxidation to the aldehyde was carried out by Ac_2O-DMSO. Wittig methylenation and Mannich reaction afforded the gramine **315**, which was condensed with diketopiperazine **316**. Decarboxylation became possible after saponification of **317** affording a mixture of epimeric echinulins with the correct absolute configuration in the L-alanine-derived portion.

6 Conclusion

A major development in the past 5 years has been the identification and biotechnological production of fungal enzymes catalysing prenylations and *tert*-prenylations of tryptophan derivatives, including diketopiperazines, with ammonium prenylpyrophosphate. Currently, conversions of milligram amounts of substrates are possible, addressing all indole positions except C5, C6 and the bridgeheads. Substantial progress has also been made in the field of transition-metal catalysed *tert*-prenylation of indole N1 and C3. A third important sector is defined by prenyl or *tert*-prenyl shifts around the indole nucleus. This field has been worked on for about four decades, but still delivers most competitive, often biomimetic strategies.

Still, there remain many open problems. It would be efficient to be able to prenylate or *tert*-prenylate indole regioselectively at the benzene positions 4, 5 and 6 without having to rely on pre-functionalisation such as halogenation or hydroxylation. Here, deeper investigation of prenyl shifts and of CH functionalisation on indole is required. Enantioselective catalysis has to be explored further towards the synthesis of optically pure 3-prenylated or -*tert*-prenylated alkaloids. A chiral version of NBS would be helpful. In the case of conformationally flexible starting materials, the diastereoselectivity of oxidative cyclisations of tryptophan-derived diketopiperazines is still not convincing. In the area of chemoenzymatic synthesis, the number and availability of enzymes has to be enhanced and their substrate tolerance has to be elucidated in more detail.

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Marine Pyrroloiminoquinone Alkaloids

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Abstract Recent reports on the synthetic studies of marine pyrroloiminoquinone alakloids and their analogs are reviewed.

Keywords Bispyrroloiminoquinone· Discorhabdin· Isobatzelline· Makaluvamine· Pyrroloiminoquinone alakloid· Prianosin B

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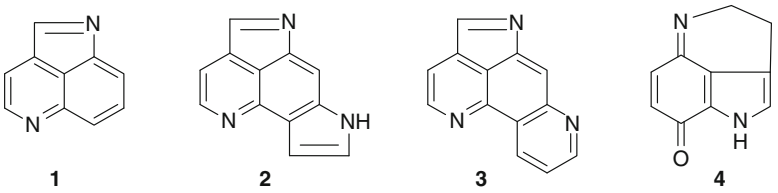
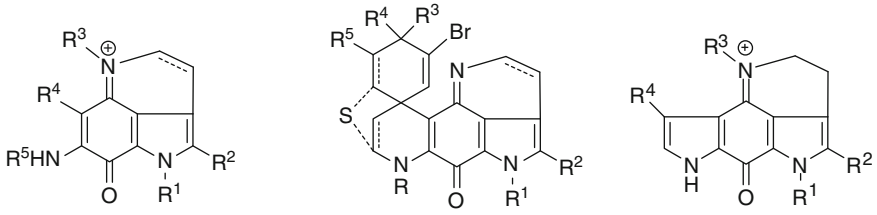
1 Introduction

Marine organisms contain various compounds which are useful for their life and relation with other organisms, and are getting much attention because the natural products isolated from them hopefully have potential as new medicinally valuable agents, agricultural chemicals, cosmetics, and health foods [1–5]. Among them, the marine sponges of the genera *Latrunculia*, *Batzella*, *Prianos*, and *Zyzzya* are a rich source of alkaloid metabolites containing either the tetra-, hexa-, or octahydrogenated variants of pyrrolo[4,3,2-*de*]quinoline **1**, pyrrolo[4,3,2-*de*]pyrrolo[2,3-*h*]quinoline **2**, pyrido[2,3-*h*]pyrrolo[4,3,2-*de*]quinoline **3**, and pyrroloiminoquinone **4** skeletons.

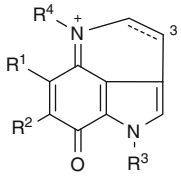


Among these alkaloid metabolites, the alkaloids containing the pyrroloiminoquinone **4** core skeletons comprise about 60 metabolites including makaluvamines, isobatzellines, discorhabdins, tsitsikammamines, and wakayin. There are several reviews of the structures, biological activities, and synthesis of the pyrroloiminoquinone alkaloids and their analogs [6–9].

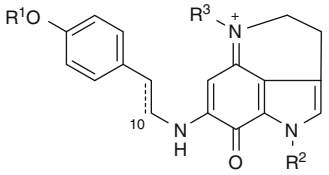


The representative makaluvamine alkaloids having the pyrroloiminoquinone skeleton are shown in Fig. 1. They were isolated from marine sponges collected in Fiji, Micronesia, Australia's Great Barrier Reef, Indonesia, the Philippines, and the Vanuatu area [10–15]. The stereogenic center of makaluvamine F has not been determined. *N*-1-β-D-Ribofuranosylmakaluvamine I, which has a sugar moiety, was also isolated from a South African sponge [16].

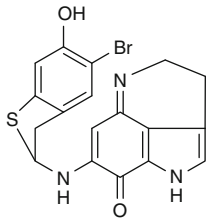
Figure 2 shows the isobatzelline alkaloids. They were isolated from the sponge *Batzella* sp. and an Indopacific collection of *Zyzzya* fuliginosa. Their structures are very close to makaluvamines and they have the 7-aminopyrroloiminoquinone skeleton [17, 18].



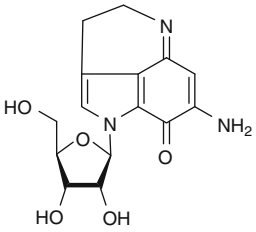
	R1	R2	R3	R4
makaluvamine A	H	NH_2	Me	H
makaluvamine B	H	H	Me	H, Δ^3
makaluvamine C	H	NH_2	H	Me
makaluvamine H	H	H	Me	Me
makaluvamine I	H	NH_2	H	H
makaluvamine N	Br	NH_2	H	H



	R1	R2	R3
makaluvamine D	H	H	H
makaluvamine E	H	Me	H, Δ^{10}
makaluvamine G	H	Me	Me, Δ^{10}
makaluvamine J	H	H	Me
makaluvamine K	H	Me	H
makaluvamine L	H	H	Me, Δ^{10}
makaluvamine M	H	H	H, Δ^{10}
makaluvamine P	H	Me	Me
makaluvamine V	OMe	H	H

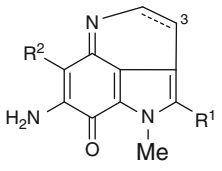


makaluvamine F



N-1-β-D-ribofuranosylmakaluvamine I

Fig. 1 Representative makaluvamine alkaloids



	R1	R2
isobatzelline A	SMe	Cl
isobatzelline B	SMe	H
isobatzelline C	H	H
isobatzelline D	SMe	Cl, Δ^3
isobatzelline E	H	Cl, Δ^3

Fig. 2 Isobatzelline alkaloids

Figure 3 shows the alkaloids with the pyrrolo[4,3,2-*de*]pyrrolo[2,3-*h*]quinoline skeleton, i.e., wakayin and tsitsikammamines. Wakayin was isolated from a Fijian ascidian and is the first pyrroloiminoquinone alkaloid not isolated from a marine sponge [19]. Tsitsikammamines A and B were isolated from a South African latrunculid sponge *Latrunculiidae* in 1996 [20]. They are reported to exhibit a cytotoxicity and topoisomerase I inhibition. Furthermore, reinvestigation of the extracts of the same sponge led to isolation of minor pyrroloiminoquinone

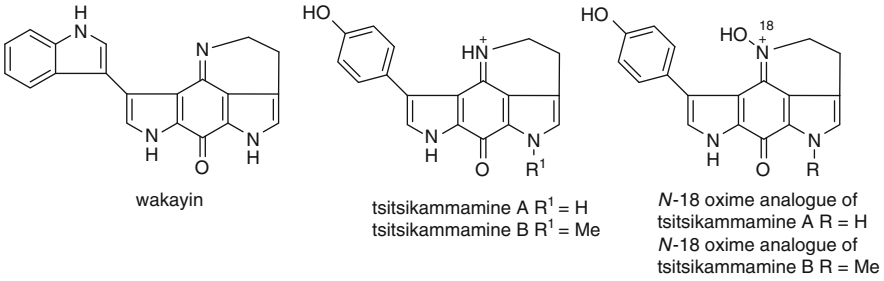
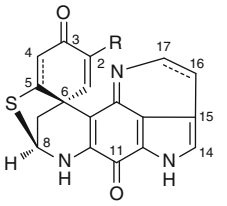


Fig. 3 Wakayin and tsitsikammamines

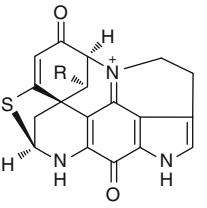
metabolites, i.e., the N-18 oxim analogs of tsitsikammamines A and B. These compounds, however, exhibited a significantly reduced cytotoxicity against human colon tumor (HCT-116) when compared to their parent alkaloids [21].

The discorhabdin alkaloids were isolated from marine sponges such as the New Zealand sponges of the genus *Latrunculia*, the Okinawan sponge *Prianos melanos*, the Fijian sponge *Zyzzya* cf. *Marsailis*, etc. Figure 4 shows some representative discorhabdin alkaloids. Among the various isolated discorhabdins (A–X), discorhabdins A [22, 23], B [22, 23], D [24], H [21], I [25], J [6], L [25], M [6], N [6], Q [26], R [27], and X [28], and prianosins B and D [29] have a sulfur-containing fused ring system. Discorhabdins S, T, and U [30] have a methyl sulfide moiety. Discorhabdin W [31] is a dimeric structure with a disulfide bond, while the others have no sulfur atom. Furthermore, discorhabdins F [32], Q, S, and T and prianosin B contain the 16,17-dehydropyrroloiminoquinone moiety. The enantiomeric pairs of discorhabdins B, G*/I, L, and W were also isolated from *Latrunculia* species sponges [33]. A study on the absolute stereochemistry of several discorhabdins was reported by Copp et al. [34]. Discorhabdin Z was isolated from the Korean marine sponge *Sceptrella* sp. [35] and dihydrodiscorhabdin B and discorhabdin Y were isolated from a deep-water Alaskan sponge of the genus *Latrunculia* [36].

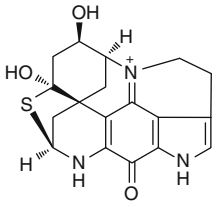
In 1995, Munro et al. reported the putative biosynthetic sequence linking the marine pyrroloiminoquinone and related metabolites (Scheme 1) [6, 37]. Thus, the oxidation of tryptamine first introduces the hydroxyl functions at the 4 and 7 positions, and the successive oxidation affords a quinone, which produces the iminoquinone by imine formation between the carbonyl group and the amine in the side chain. Further oxidation gives makaluvamines, and isobatzellines (Path A). On the other hand, the route in which thyrosine adds to the iminoquinone gives makaluvamines D, E, G, J–M, and P (Path B). The tsitsikammamines can then be biosynthesized. Furthermore, two routes are possible to give the discorhabdins. One is the route via makaluvamine F by early sulfur introduction followed by phenol coupling to give discorhabdins A, B, I, Q, D, and L with sulfur-containing fused



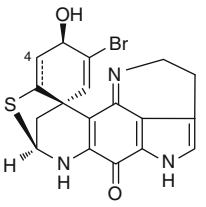
discorhabdin A R = Br
prianosin B R = Br, Δ^{16}
discorhabdin B R = Br, Δ^{4}
discorhabdin I R = H, Δ^{4}
discorhabdin Q R = Br, Δ^{4}, Δ^{16}
debromodiscorhabdin A R = H



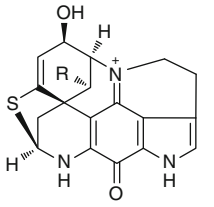
discorhabdin D R = H
discorhabdin L R = OH



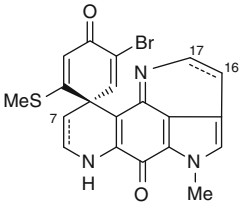
discorhabdin X



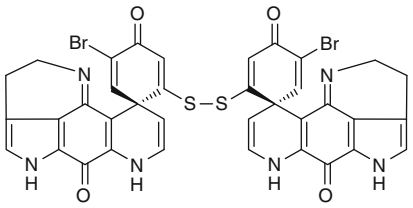
dihydrodiscorhabdin A
dihydrodiscorhabdin B Δ^{4}



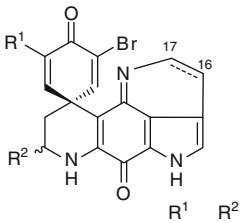
dihydrodiscorhabdin D R = H
dihydrodiscorhabdin L R = OH



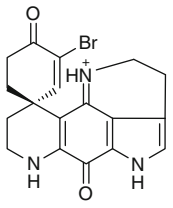
discorhabdin S Δ^{16}
discorhabdin T Δ^{7}, Δ^{16}
discorhabdin U Δ^{7}



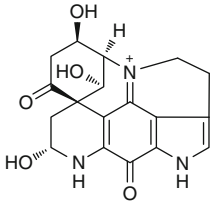
discorhabdin W



	R^1	R^2
discorhabdin C	Br	H
discorhabdin E	H	H
discorhabdin F	H	H, Δ^{16}
discorhabdin O	H	OMe

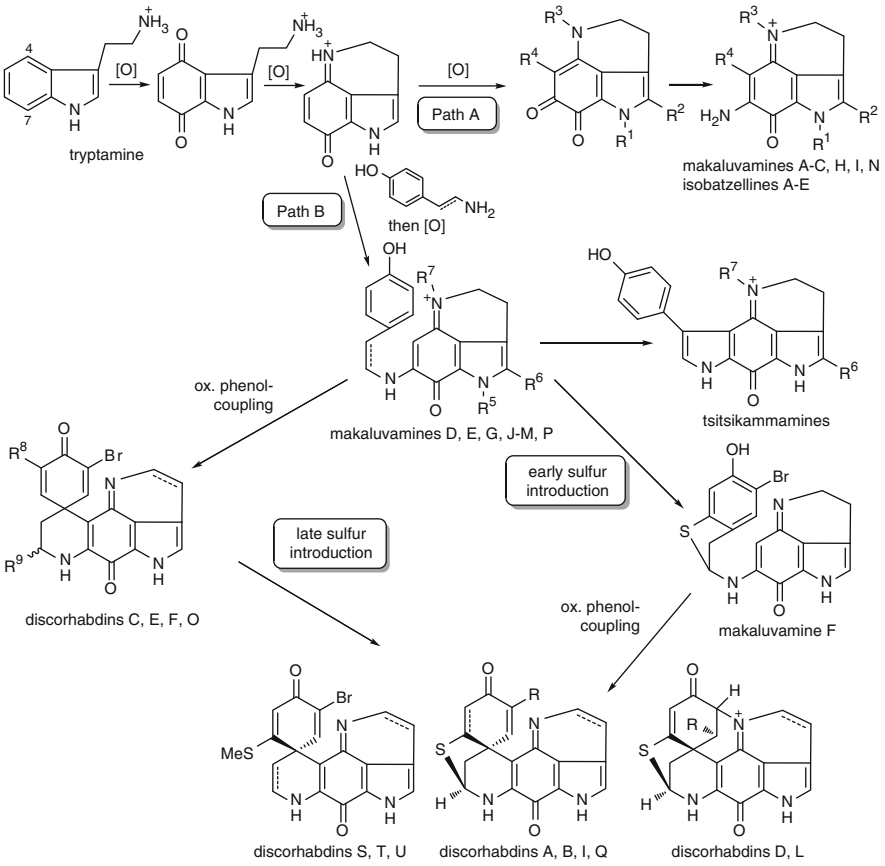


discorhabdin Y



discorhabdin Z

Fig. 4 Discorhabdin alkaloids



Scheme 1 Proposed biosynthesis of pyrroloiminoquinone alkaloids

ring system. The other is the route via discorhabdins C, E, F, and O, which were obtained by the preliminary phenol coupling. Further sulfur introduction then gives discorhabdins S, T, U, A, B, I, Q, D, and L.

Most of the pyrroloiminoquinone alkaloids described above exhibit a strong cytotoxicity towards human tumor cell lines, they are recognized to be the lead compounds for developing new anticancer drugs, and they have attracted the synthetic interest of many groups.

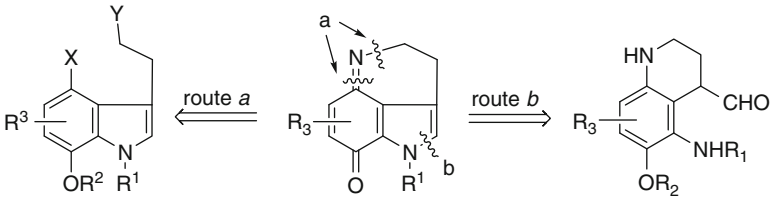
Our group accomplished the total syntheses of discorhabdin C in 1992 [38], makaluvamine F in 1999 [39, 40], and discorhabdin A in 2002 [41, 42]. We also accomplished the first total synthesis of prianosin B in 2009 [43]. We now report the progress towards the synthesis of pyrroloiminoquinone alkaloids, mainly since 2000 including our studies, in this chapter.

2 Construction of the Pyrroloiminoquinone Skeleton

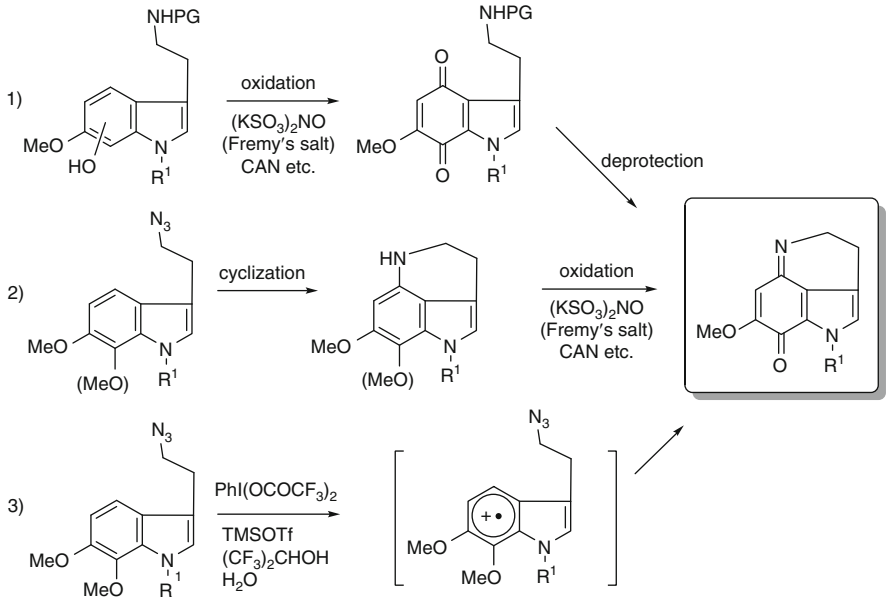
Two routes are currently known to construct the pyrroloiminoquinone skeleton (Scheme 2). One is route *a*, in which the indole ring is first synthesized followed by imine formation. The other is route *b*, in which the dihydroquinoline ring is first formed followed by the five-membered ring formation.

Route *a* is similar to biosynthesis shown in Scheme 1, and many total syntheses have been described using this route. Route *a* is divided into three methods (Scheme 3): 1) first formation of the quinone moiety followed by imine formation, 2) first formation of the cyclic amine followed by oxidation, and 3) the direct iminoquinone formation of the substrates having an azide side chain developed by us (see Schemes 24 and 27).

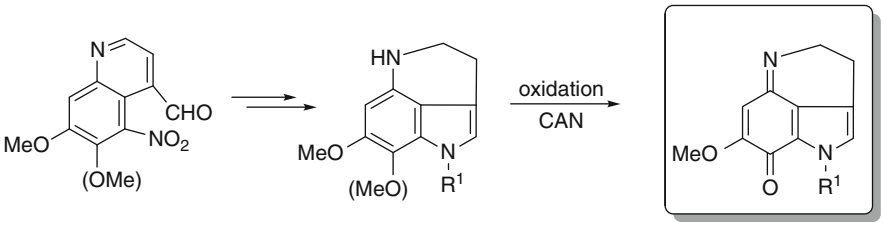
On the other hand, in route *b*, the quinoline ring is first formed, then the pyrrole ring is closed followed by oxidation of the cyclic amine to give the pyrroloiminoquinone skeleton (Scheme 4).



Scheme 2 Two routes for constructing the pyrroloiminoquinone skeleton



Scheme 3 General methods for the pyrroloiminoquinone skeleton by route *a*



Scheme 4 General methods for the formation of the pyrroloiminoquinone skeleton by route *b*

3 Synthetic Works by Other Groups

3.1 Makaluvamines

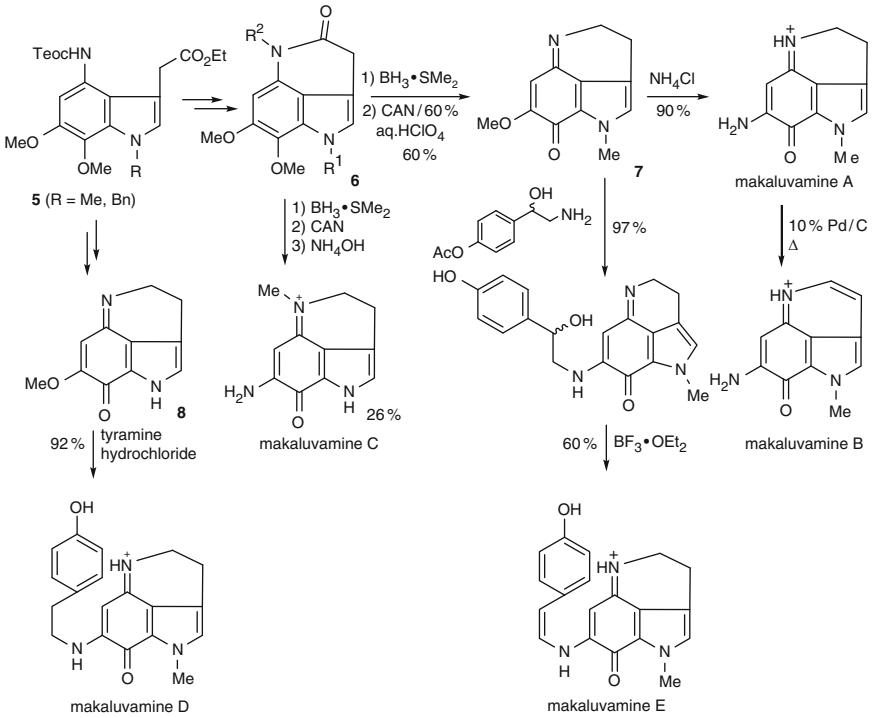
Makaluvamines A [44–48], B [44, 48], C [44, 48, 49], D [44, 47, 48, 50–52], E [44, 46], I [47, 52], and K [47], and *N*-1-*β*-D-ribofuranosylmakaluvamine I [52] have already been synthesized. Most of these syntheses were reported before 2000. Since 2000, there have been few synthetic works of natural products, while the studies of the synthesis of their analogs and their biological activity are receiving much attention.

For the synthesis of the makaluvamine family, most of the synthetic studies have been done through route *a* in Schemes 2 and 3 for the construction of the pyrroloiminoquinone skeleton. As an example of the synthesis of the makaluvamines by route *a*, Yamamura and Nishiyama's synthesis is shown in Scheme 5. Thus, Yamamura et al. reported the total synthesis of makaluvamines A–E (Scheme 5). They started from the indole **5**, which was converted to the lactam **6**. Makaluvamines A, B, and E were synthesized from pyrroloiminoquinone **7**, obtained from **6** (R^1=Me, R^2=H) by reduction and oxidation, and by the attack of the proper amino functions. Makaluvamine C was synthesized from **6** (R^1=H, R^2=Me). Makaluvamine D was synthesized from the iminoquinone **8**, obtained from **5** (R=Bn) [44].

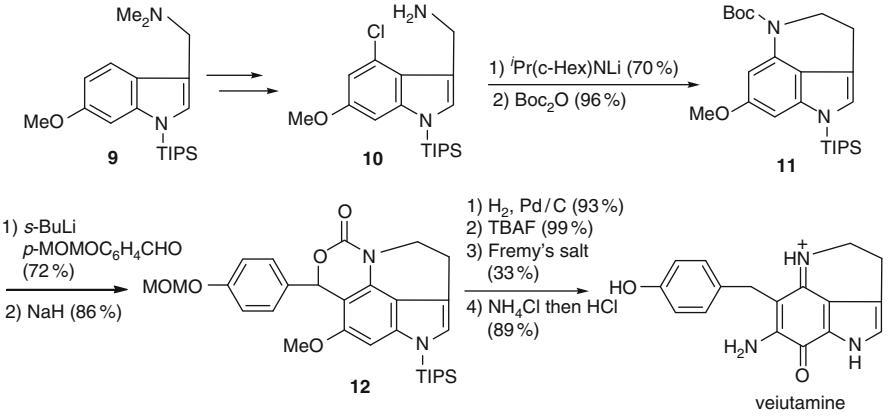
The total synthesis of veiutamine [53], which has a carbon side chain and a structure similar to makaluvamine D, has also been achieved via route *a* (Scheme 6). The 6-methoxyindole derivative **9** was converted to the Boc compound **11**. Regioselective ortholithiation at 6-position using the Boc group as a directing group and coupling with an aldehyde followed by intramolecular cyclization afforded the tetracyclic compound **12**, which was converted to veiutamine [54].

On the other hand, the synthesis of the makaluvamine family by route *b* shown in Schemes 2 and 4 has rarely been reported. Kraus et al. reported the total synthesis of makaluvamine C (Scheme 7). In their synthesis, the 6,6-bicyclic compound **14** was formed first. The reduction of **14** then gave the indole **15**, which was converted to makaluvamine C by demethylation and in situ oxidation with Fremy's salt [49].

We have discovered the inter- and intramolecular nucleophilic addition of aromatic compounds mediated by hypervalent iodine reagent in CF_3CH_2OH or

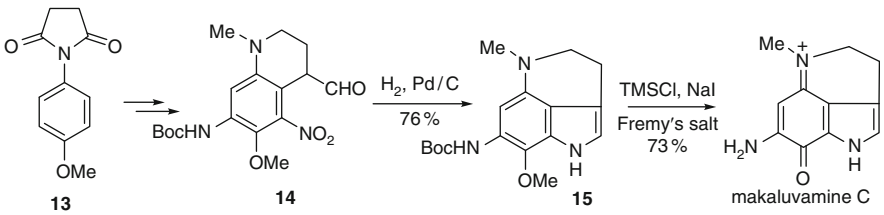


Scheme 5 Total synthesis of makaluvamines A–E

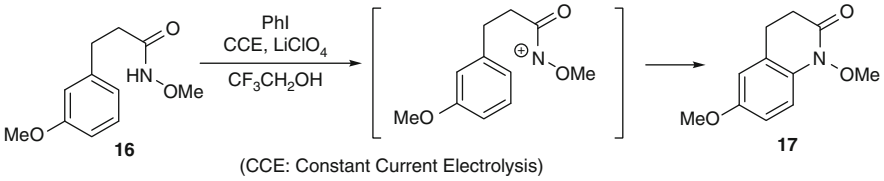


Scheme 6 Total synthesis of veiutamine

$(CF_3)_2CHOH$ in 1994 (For details, see Scheme 23). In 2006, Nishiyama et al. also used the hypervalent iodine reagent prepared from iodobenzene under electrolytic conditions and developed a new method for the synthesis of tetrahydroquinolines (Scheme 8). Thus, the reaction of the methoxyamide **16** with the active species



Scheme 7 Kraus's synthesis of makaluvamine C



Scheme 8 Synthesis of tetrahydroquinolines using hypervalent iodine reagent

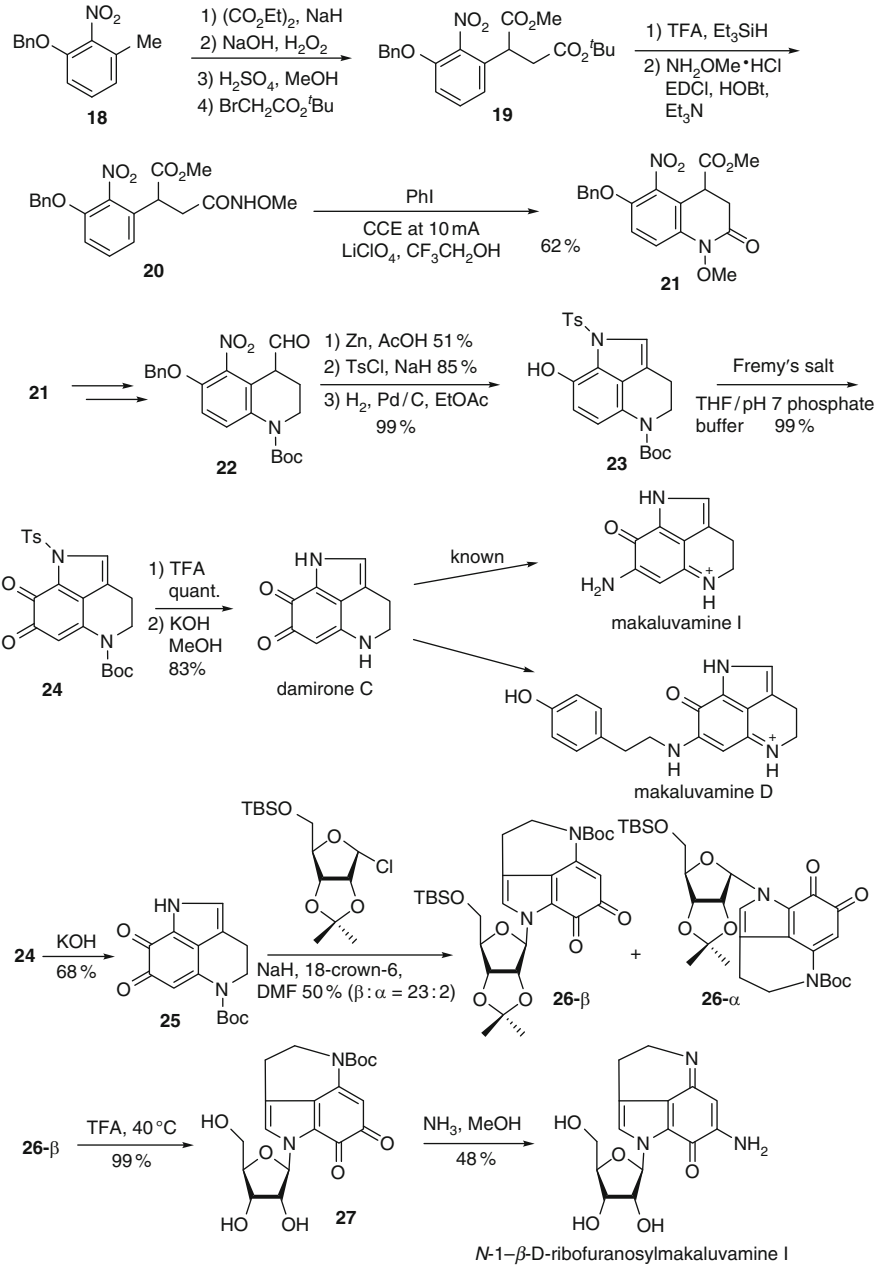
derived from iodobenzene under electrolytic conditions afforded the quinolone-type product **17** [55].

The reaction was applied to the syntheses of the pyrroloiminoquinones, makaluvamines D and I and *N*-1-*β*-D-ribofuranosylmakaluvamine I (Scheme 9). The arylpropionamide **20** was prepared from 3-benzyloxy-2-nitrotoluene (**18**). Compound **20** produced the quinolinone **21** when subjected to either the electrochemically generated hypervalent iodine or PIFA. Quinolinone **21** was converted to the aldehyde **22**, which gave **23** by the reaction with Zn/AcOH, followed by treatment with TsCl–NaH and catalytic hydrogenolysis. The oxidation of **23** with Fermy's salt produced an α-diketone **24**. Exhaustive deprotection of **24** afforded damirone C. Furthermore, the amination of damirone C provided makaluvamine I. The coupling of damirone C with tyramine hydrochloride yielded makaluvamine D. The coupling of **25**, which was obtained from **24**, with a chloro sugar produced the desired glycosides **26**-β and **26**-α in 50% yield as a 23:2 mixture. Removal of the TBS-protecting group in **26**-β afforded **27**. *N*-1-*β*-D-ribofuranosylmakaluvamine I was obtained by the ammonolysis of **27** [52].

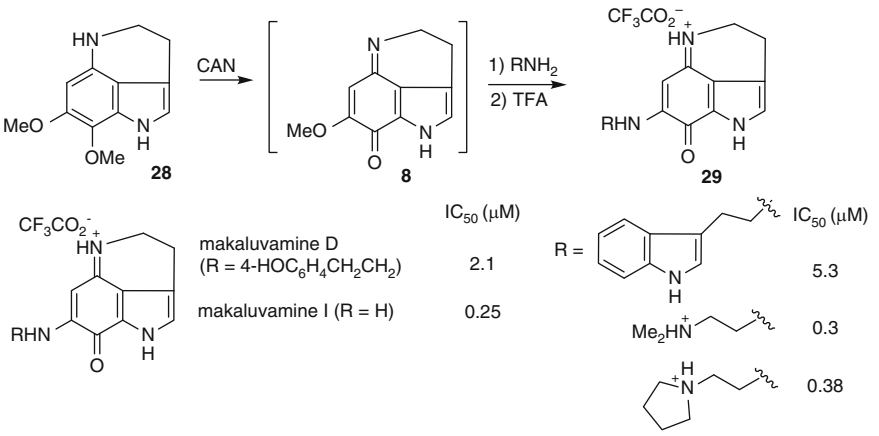
In 2000, Besson et al. reported the biological activity of several makaluvamine analogs, which were synthesized by the reaction of five amines and the 7-methoxy-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline core. Evaluation of the cytotoxic activity on the murine L1210 cells afforded IC_{50} values in the 0.25–5.3 μM range (Scheme 10) [56].

Since the previously reported 6-acetamidopyrrolo[1,2-*a*]benzimidazole (APBI) has a structure similar to the makaluvamines and showed a similar topoisomerase activity. Skibo et al. prepared the imidazoquinoxaline analogs, which possess the ethylene tether and an amidine moiety, and are similar to the makaluvamines (Scheme 11). However, they showed a weaker activity than makaluvamine H [57, 58].

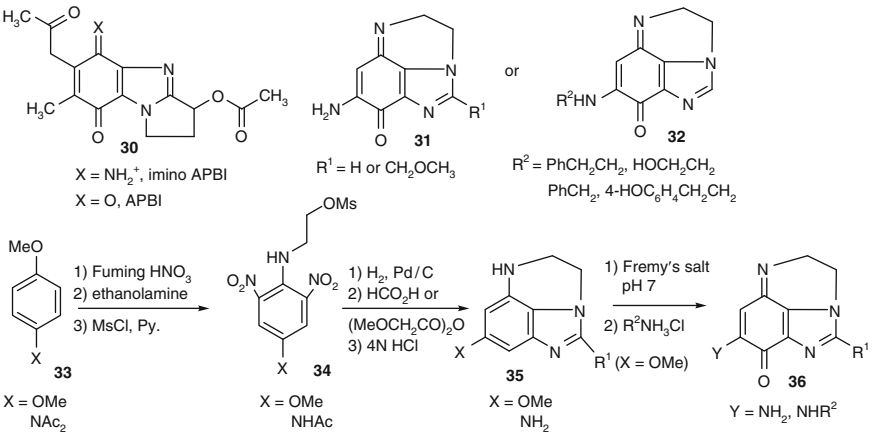
Recently, Velu et al. studied the biological activity of various makaluvamine analogs with benzylamine- or phenethylamine-type side chains, and revealed that



Scheme 9 Syntheses of the pyrroloiminoquinones, makaluvamines D and I and *N*-1-*β*-D-ribofuranosylmakaluvamine I



Scheme 10 Makaluvamine analogs by Besson



Scheme 11 Imidazoquinoxaline analogs by Skibo

compounds having small side chains with an electron-withdrawing group showed a high anticancer activity against various cancer cell lines (Fig. 5) [59–62]. In 2008, Passarella et al. carried out a similar study using N1–Me analogs [63].

3.2 Isobatzellines

Isobatzellines A [64], B [64], and C [48, 65] have already been synthesized. Most of the syntheses of the isobatzellines were reported before 2000. After 2000, few synthetic studies of the natural products have been carried out.

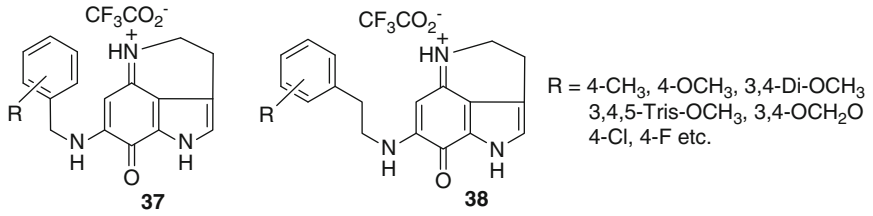
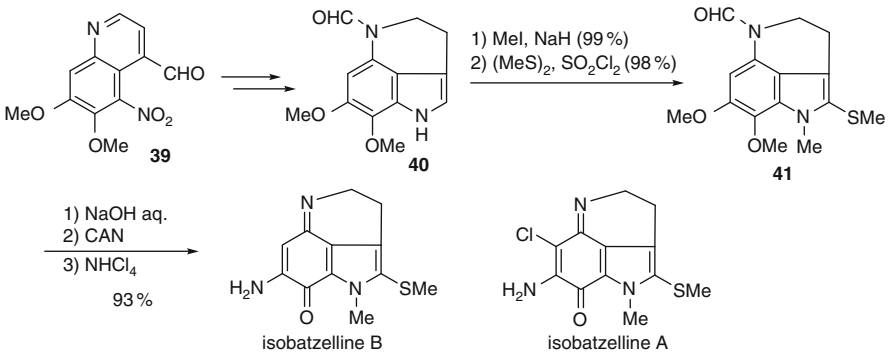


Fig. 5 Makaluvamine analogs by Velu



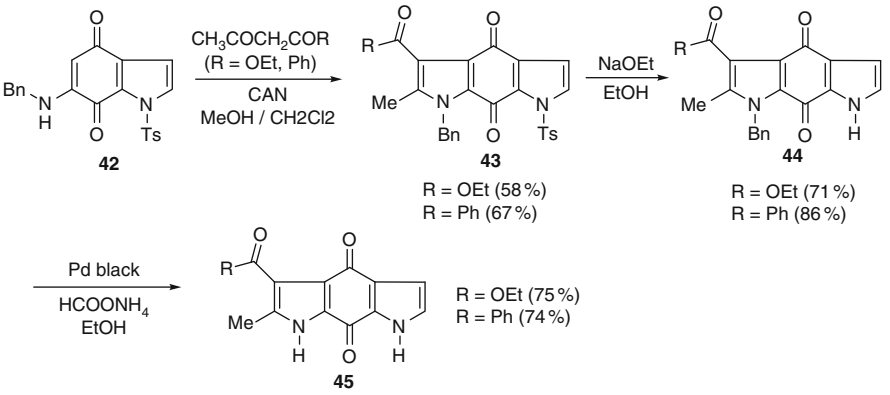
Scheme 12 Synthesis of isobatzellines B and A

Scheme 12 shows the synthesis of isobatzellines A and B, having a sulfur function, by Alvarez and Joule et al. in 1999. After *N*-1-methylation of the tricyclic indole **40**, the crucial electrophilic substitution by dimethyl disulfide afforded **41**. The hydrolysis of **41** followed by CAN oxidation, then replacement of the 7-methoxy group with an amino group, gave isobatzelline B. By a similar procedure, they also synthesized isobatzelline A [64].

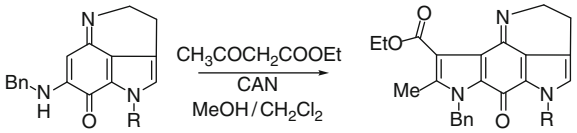
3.3 Bispyrroloiminoquinones

There have been few synthetic studies of the wakayin and tsitsikammamine alkaloids. Model synthetic studies of them were reported by Cave [66] and Barret [67] more than 10 years ago and, recently, several new synthetic studies have appeared.

Velu et al. reported the regioselective synthesis of the bispyrroloquinone and bispyrroloiminoquinone ring system found in the wakayin and tsitsikammamine alkaloids. First, they accomplished the synthetic route to the bispyrroloquinone system (Scheme 13). The treatment of *N*-tosyl-6-(benzylamino)-1*H*-indole-4,7-dione **42** with ethyl acetoacetate or 1-phenylbutane-1,3-dione in the presence of ceric ammonium nitrate (CAN) in MeOH/CH_2Cl_2 resulted in the formation of the



Scheme 13 Synthesis of bispyrroloquinone ring system

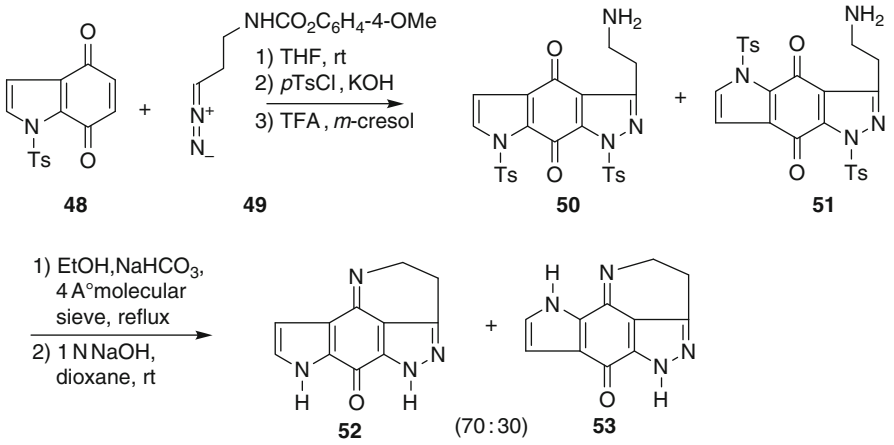


Scheme 14 Synthesis of bispyrroloiminoquinone ring system

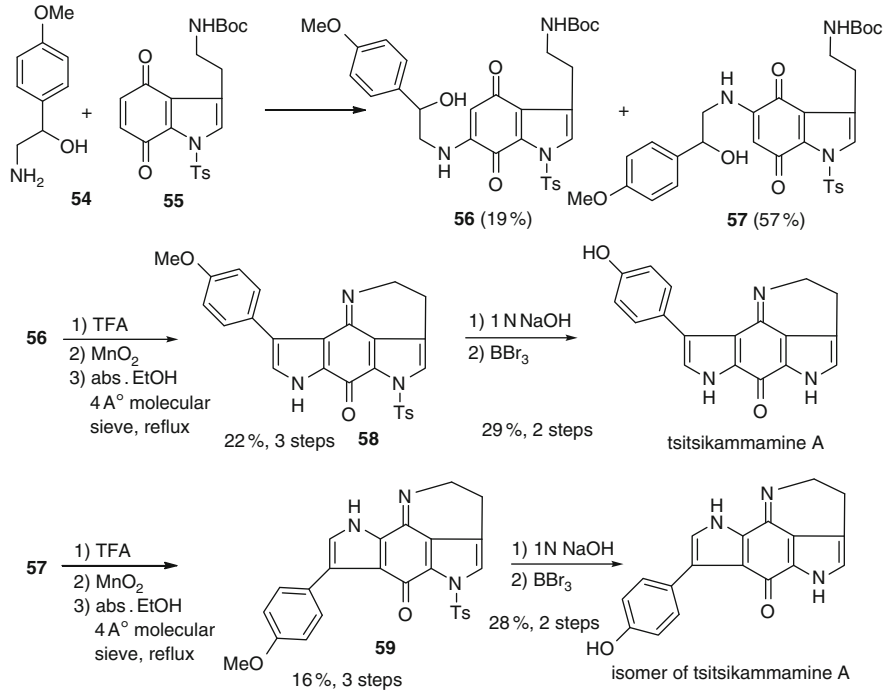
bispyrroloquinone derivative **43**. This cyclization reaction proceeded via an oxidative free radical mechanism. Removal of the tosyl group in **43** and debenzylation then afforded the bispyrroloquinone **45**. The same synthetic methodology afforded the bispyrroloquinone ring system present in wakayin and the tsitsikammamines (Scheme 14) [68].

In 2006, Delfourne et al. reported the syntheses of two aza-analogs of wakayin and tsitsikammamines A and B based on a 1,3-dipolar cycloaddition reaction between the indole-4,7-dione **48** and a diazo-aminopropane derivative **49** (Scheme 15). One of the two analogs partially inhibits human topoisomerase I, whereas the synthetic intermediates inhibit the enzyme DNA cleavage activity at a concentration comparable to that of the control drug camptothecin [69, 70].

In 2009, Delfourne et al. reported the first total synthesis of tsitsikammamine A [71]. The reaction of **54** with a quinone **55** gave two regioisomers **56** and **57**. The treatment of **56** with trifluoroacetic acid caused the formation of the second five-membered nitrogen ring and the cleavage of the Boc protective group, then oxidation with MnO_2 gave the bispyrroloquinone derivative, and the subsequent cyclization gave the corresponding iminoquinone **58**. The tosyl group of **58** was



Scheme 15 Synthesis of aza-analogs of wakayin and tsitsikammamines A and B



Scheme 16 Synthesis of tsitsikammamines A

removed by 1 N NaOH treatment, and demethylation using BBr_3 afforded the free base of tsitsikammamine A. A similar procedure gave the nonnatural regioisomer from compound **57** (Scheme 16).

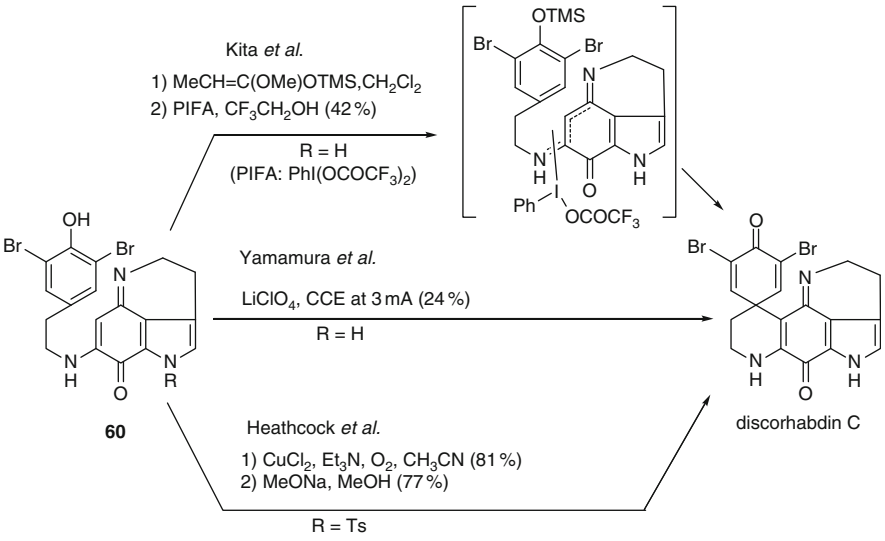
3.4 Discorhabdins

Discorhabdin alkaloids have the richest structure-diversity among the marine pyrroloiminoquinone alkaloids, and new discorhabdins are still being discovered. Although many synthetic studies have been carried out, only a few total syntheses of the natural discorhabdins have been reported. The total synthesis of discorhabdin C was accomplished by our group and Yamamura's group at almost the same time, and later by the Heathcock group. Heathcock et al. also synthesized discorhabdin E at the same time. Those discorhabdins are rather simple. The more complex discorhabdins, discorhabdin A and prianosin B, were synthesized only by us.

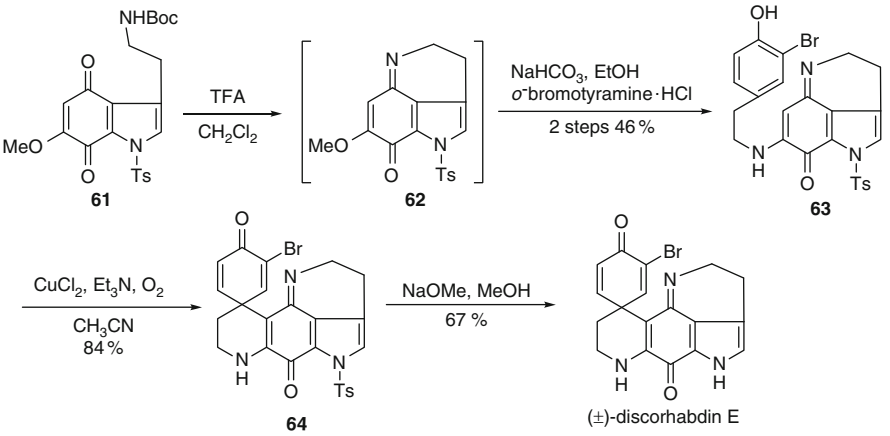
Scheme 17 shows the final steps of each synthesis of (±)-discorhabdin C. For the details of our synthesis, see Sect. 4. In Yamamura's synthesis, discorhabdin C was obtained in 24% yield upon anodic oxidation of the bromophenol derivative **60** (R=H) [72, 73]. In Heathcock's synthesis, discorhabdin C was obtained by a phenolic coupling reaction of **60** (R=Ts) with $CuCl_2$ and Et_3N under bubbling O_2 followed by detosylation [74].

Scheme 18 shows Heathcock's total synthesis of (±)-discorhabdin E by the same procedure as discorhabdin C [74]. The reaction of the imine **62**, derived from **61**, and *o*-bromotyramine furnished **63**. The treatment of **63** with three equivalents of $CuCl_2$ and four equivalents of Et_3N under bubbling O_2 gave the *N*-tosyldiscorhabdin E **64**, the detosylation of which with NaOMe resulted in the formation of (±)-discorhabdin E.

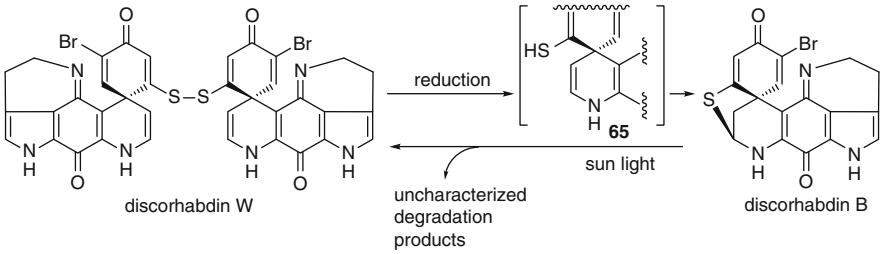
In 2005, Munro et al. discovered discorhabdin W, the dimer of discorhabdin B. At the time, they correlated discorhabdin W with discorhabdin B. Thus, reduction of discorhabdin W with dithiothreitol gave the expected thiol **65**, which was



Scheme 17 Final steps of the synthesis of (±)-discorhabdin C



Scheme 18 Total synthesis of (±)-discorhabdin E



Scheme 19 Correlation of discorhabdin W and discorhabdin B

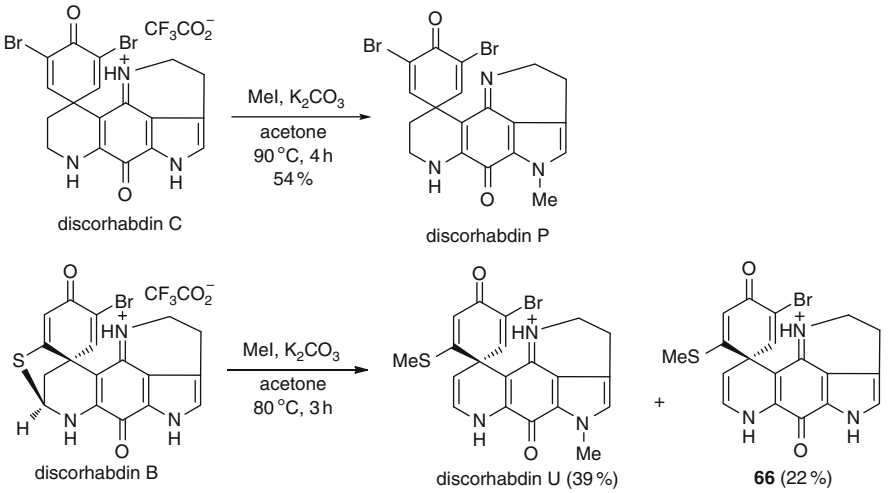
spontaneously converted to discorhabdin B. Conversely, irradiation of discorhabdin B with sunlight afforded discorhabdin W (Scheme 19) [31].

In 2006, Copp et al. reported the semi-synthesis of discorhabdins P and U from the natural discorhabdins C and B (Scheme 20). Discorhabdin C was reacted with CH_3I in dry acetone to yield discorhabdin P in 54% yield. Discorhabdin B was reacted with CH_3I in dry acetone to yield two products, discorhabdin U and **66**. The order of the methylation of discorhabdin B preferentially favors the thio group, and a large excess of CH_3I enables the methylation at the *N*-13 pyrrole position [75].

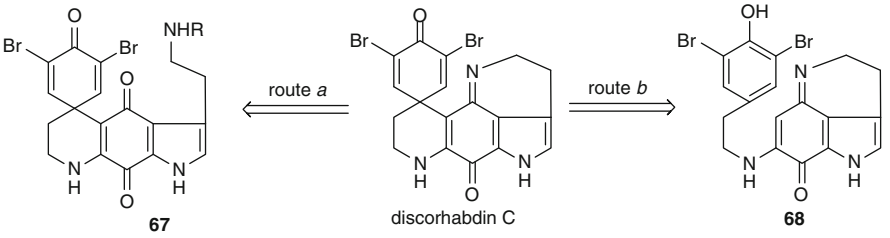
4 Our Synthetic Studies

4.1 Discorhabdin C

We synthesized discorhabdin C in 1992 [38]. For the total synthesis of discorhabdin C, two approaches were studied (Scheme 21). One approach involves the imine



Scheme 20 Semi-synthesis of discorhabdin P and U

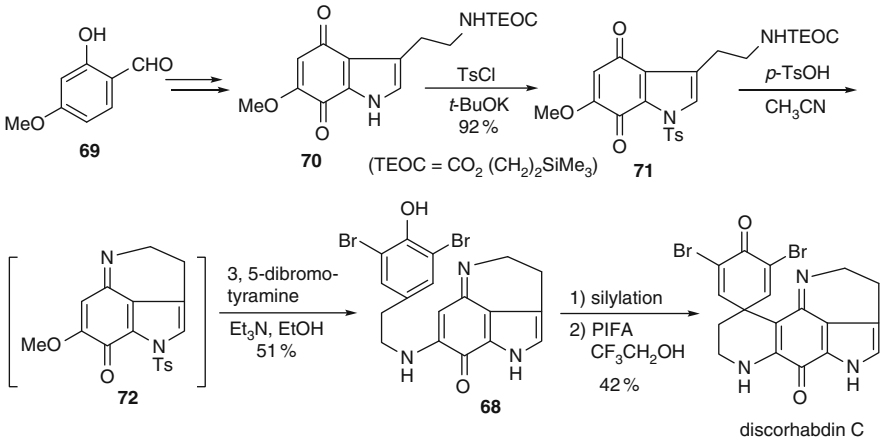


Scheme 21 Two retrosynthetic analysis for discorhabdin C

formation as the final step of the synthesis (route *a*). Another approach involves the oxidative coupling of the indoloquinone imine as the final step (route *b*).

Unfortunately, all attempts to effect the final imine formation between the tryptamine nitrogen and the indoloquinone carbonyl in these types of intermediates failed (route *a* in Scheme 21). We then studied an alternative approach (route *b*), in which the phenolic coupling of the previously produced aminoindoloquinone imine is employed in the final step, to accomplish the first total synthesis of discorhabdin C. The benzaldehyde derivative **69** was converted to the indoloquinone **70**. The direct imine formation from the indoloquinone was achieved by protection of the indoloquinone nitrogen of **70** with the tosyl group followed by an acidic dehydrative treatment to yield an unstable indoloquinone imine **72**, which was subjected to the following one-pot transformation without further purification.

The reaction of the indoloquinone imine **72** with 3,5-dibromotyramine hydrobromide caused a facile substitution reaction and subsequent detosylation to give the



Scheme 22 Total synthesis of discorhabdin C via route *b*

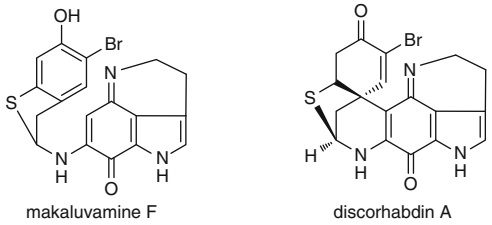


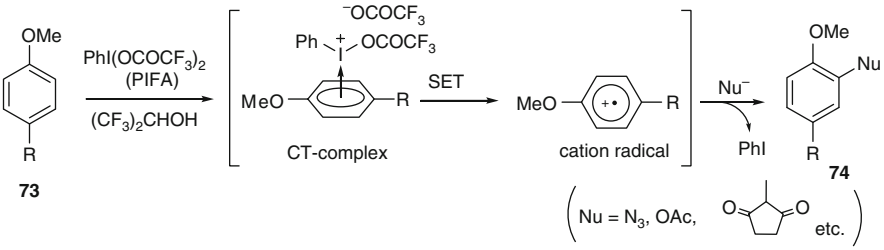
Fig. 6 Makaluvamine F and discorhabdin A

phenolic aminoindoloquinone imine **68**. The conversion of **68** into its corresponding silyl ether and the subsequent oxidative coupling reaction using PIFA gave rise to discorhabdin C (Scheme 22) [38].

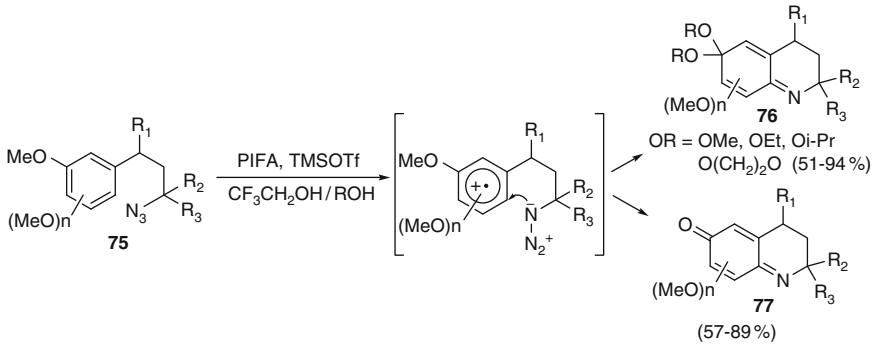
4.2 Development of Methods for the Synthesis of Complex Pyrroloiminoquinone Alkaloids

Among the makaluvamines, makaluvamine F exhibits the most potent biological activity (e.g., cytotoxicity towards the human colon tumor cell line HCT-116 (IC_{50} = 0.17 mM) and inhibition of topoisomerase II). It has a labile *N*, *S*-acetal moiety for oxidation, etc. Synthetic efforts by several groups then resulted in only diverse preparations of the pyrroloiminoquinone unit. For the synthesis of more complex pyrroloiminoquinone alkaloids such as makaluvamine F and discorhabdin A (Fig. 6), we intended to develop several mild reactions.

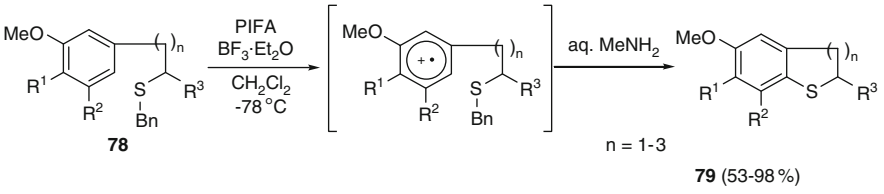
The new methods (Schemes 23–25) valuable for the synthesis of complex pyrroloiminoquinone alkaloids are based on the hypervalent iodine-induced nucleophilic substitution of *p*-substituted phenol ethers via reactive cation radical intermediates. Thus, we found a novel hypervalent iodine induced nucleophilic substitution of *p*-substituted phenol ethers in the presence of a variety of nucleophiles, such as $TMSN_3$, TMSOAc, and β-diketones, etc., in 1994. For this reaction the reaction solvent was quite important, and CF_3CH_2OH and $(CF_3)_2CHOH$ worked very well (Scheme 23) [76].



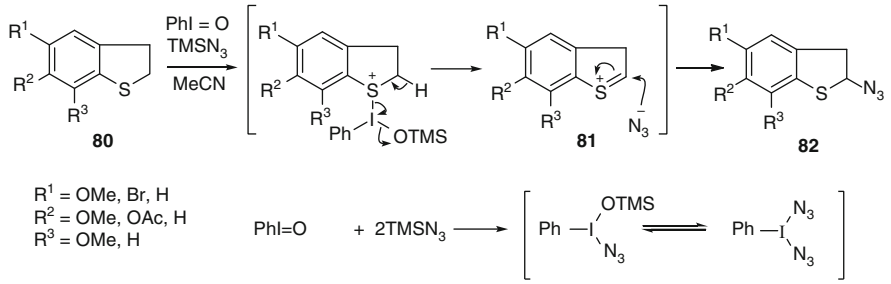
Scheme 23 Hypervalent iodine-induced nucleophilic substitution of *p*-substituted phenol ethers



Scheme 24 Synthesis of quinone imine dimethylacetals and quinone imines



Scheme 25 Intramolecular cyclization of phenyl ethers bearing an alkyl sulfide side chain



Scheme 26 Synthesis of α-azidodihydrobenzothiophene derivatives

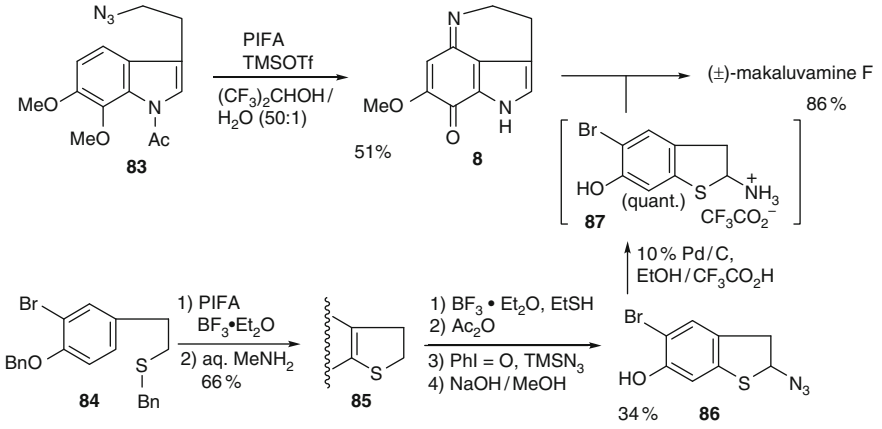
The treatment of phenyl ethers **75** with an alkylazido group in the presence of PIFA–TMSOTf in $(CF_3)_2CHOH/ROH$ or CF_3CH_2OH/ROH gave the corresponding quinone imine dimethylacetals **76**, which in $(CF_3)_2CHOH/H_2O$ or CF_3CH_2OH/H_2O gave the corresponding quinine imines **77** (Scheme 24) [77, 78].

We next attempted to synthesize the α-azidodihydrobenzothiophenes, which can serve as an *N*,*S*-acetal equivalent, by the introduction of an azido group to the dihydrobenzothiophene derivatives. We first developed the new intramolecular cyclization of phenyl ethers **78** bearing an alkylsulfide group using PIFA in $(CF_3)_2CHOH$ and PIFA–$BF_3{\cdot}Et_2O$ in CH_2Cl_2 that specifically proceeded to give the corresponding sulfur-containing heterocycles **79** via the radical cation (Scheme 25) [79].

After considerable effort, the sulfonium cation initially formed by the reaction of the sulfide **80** with PhI=O/Me_3SiN_3 is then deprotonated to give a cation intermediate **81**. The azide anion attacks the α-position of **81** to produce the α-azide sulfide **82** (Scheme 26) [80].

4.3 Makaluvamine F

Having new mild reactions for synthesizing makaluvamine F in hand, we tried to synthesize makaluvamine F (Scheme 27). The reactions of the *N*-protected indoles **83** with PIFA–TMSOTf in the presence of H_2O afforded the corresponding *N*-deprotected pyrroloiminoquinones **8**. The treatment of the phenol ether **84** bearing an alkyl sulfide side chain with PIFA–$BF_3{\cdot}Et_2O$ followed by the treatment with aq. $MeNH_2$ provided 5-bromo-6-benzyloxydihydrobenzothiophene **85**. Although azidation of **85** gave only a trace amount of the expected α-azido compound, treatment of the acetylated compound with PhI=O and Me_3SiN_3 followed by hydrolytic deprotection provided the 2-azido-5-bromo-6-hydroxydihydrobenzothiophene **86**. Catalytic hydrogenation of **86** using 10% Pd-C in the presence of four equivalents of trifluoroacetic acid (TFA) resulted in complete reduction leading to a TFA salt **87** in quantitative yield. The final coupling reaction in MeOH between both synthetic



Scheme 27 Total synthesis of (±)-makaluvamine F

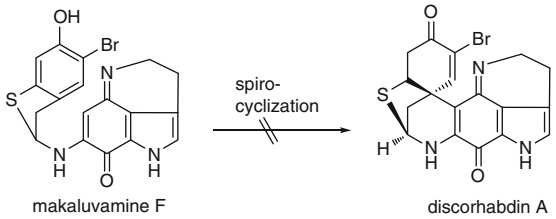
precursors, **87** and **8**, proceeded to give the TFA salt of makaluvamine F (Scheme 27) [39, 40].

4.4 Total Synthesis of Discorhabdin A

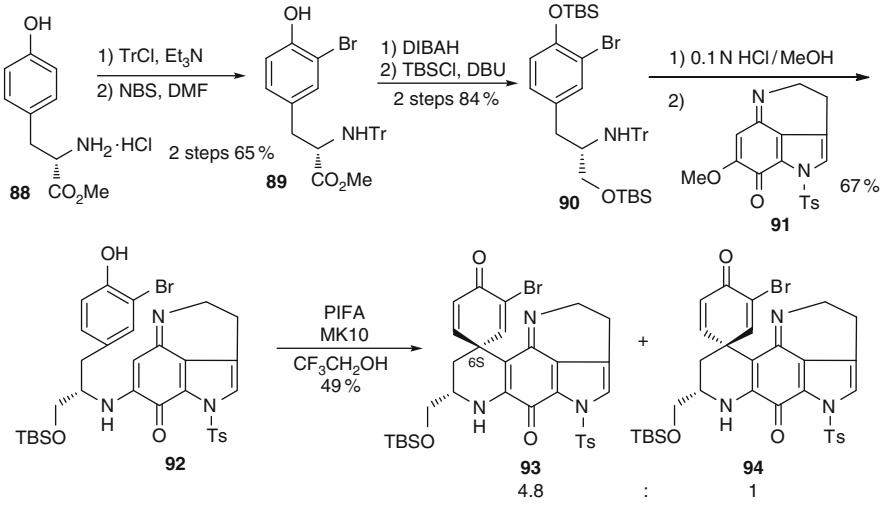
In 1987, prianosin A [22] was isolated from the Okinawan sponge *Prianos melanos* by Kobayashi et al. and, in 1988, discorhabdin A [23] was isolated from New Zealand sponges of the genus *Latrunculia* by Munro et al. Some years later, it was found that prianosin A and discorhabdin A were the same compound. Discorhabdin A (prianosin A) has a strong cytotoxicity (IC_{50} values of 37, 14, 40, and 13 ng/mL against L1210, L5178Y, P388, and xrs-6 in vitro, respectively, and ED_{50} values of 50 ng/mL against P388) and shows antimicrobial activity. Discorhabdin A has a unique sulfur-containing fused ring system incorporating azacarbocyclic spirocyclohexanone and pyrroloiminoquinone systems, and shows the most powerful cytotoxic activity among the isolated discorhabdins.

First, on the basis of the hypothesis by Munro and co-workers shown in Scheme 1, we examined the biosynthetically plausible route from makaluvamine F using our previously developed oxidative spirocyclization reaction with PIFA. As a result, the oxidative cyclization of makaluvamine F as well as the trimethylsilylated makaluvamine F using PIFA under various conditions yielded a complex mixture, probably due to the high reactivity of the iodine(III) reagent toward the sulfide (Scheme 28).

We then altered the synthetic strategy. The new strategy included the preconstruction of the spirodienone system using the hypervalent iodine(III) reagent and the final introduction of the sulfur group to the cross-linked system. Scheme 29 shows the synthesis of the spirodienone in discorhabdin A. The tritylation of the



Scheme 28 Synthetic approach to discorhabdin A from makaluvamine F



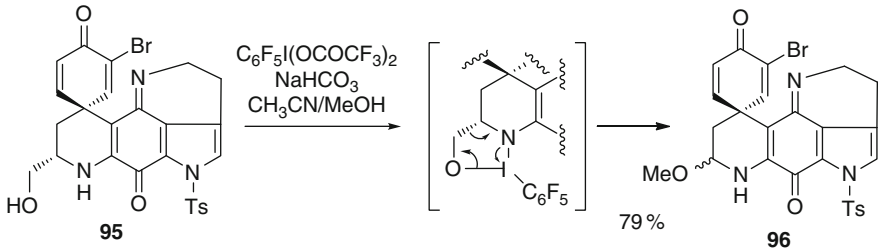
Scheme 29 Synthesis of spirodienone

L-tyrosine methyl ester hydrochloride **88** with TrCl and Et_3N followed by monobromination with NBS yielded **89** (two steps, 65% yield). The reduction of **89** with DIBAH followed by silylation of the resulting alcohol with TBSCl gave the *bis*-silylated compound **90**, and a coupling reaction with pyrroloiminoquinone **91**, which was prepared by our previously developed PIFA-induced pyrroloiminoquinone formation (see Scheme 27), yielded **92**. The spirodienone formation of **92** using PIFA effectively proceeded in the presence of montmorillonite K10 (MK10) to give a diastereomeric mixture of **93** and **94**. Both diastereomers were readily separated by column chromatography on silica gel. The major isomer **93** has the same absolute stereochemistry (*S* configuration) of the spirocenter (C-6) as that of the natural discorhabdin A (Scheme 29).

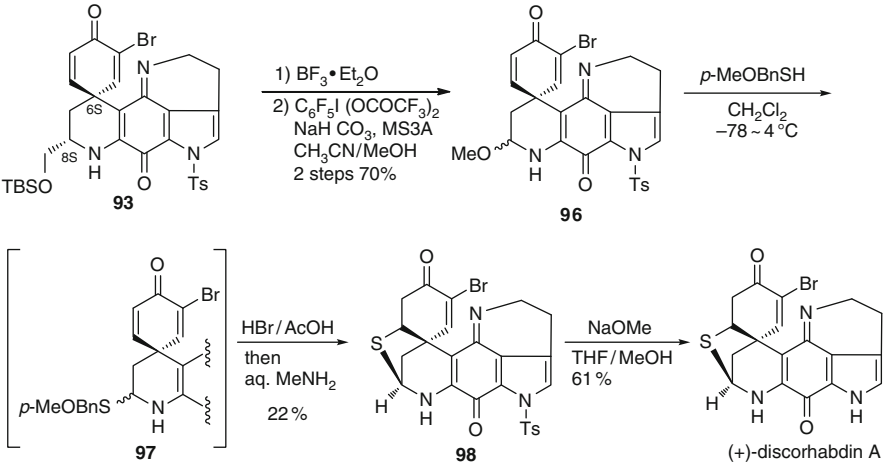
In our total synthesis of discorhabdin A, the *N*,*O*-acetal compound **96** acted as a key compound for the construction of the *N*,*S*-acetal compound (see Scheme 31), and was prepared by the oxidative fragmentation reaction of an α-amino alcohol **95** initially using the highly toxic lead tetraacetate. We then developed a new method using the low toxic hypervalent iodine(III) reagent. Thus, the reaction of the

α-amino alcohol **95**, obtained from **93** by desilylation (see Scheme 31) and bis-(trifluoroacetoxy)iodo(III) pentafluorobenzene ($C_6F_5I(OCOCF_3)_2$) in the presence of $NaHCO_3$, afforded the *N*,*O*-acetal compound **96** in 79% yield, maybe through the five-membered ring intermediate (Scheme 30) [81].

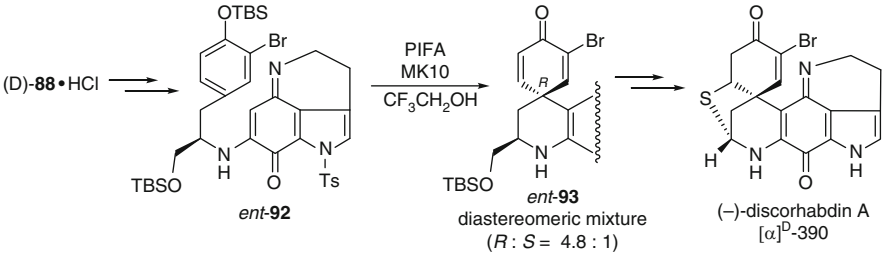
Desilylation of **93** followed by an oxidative fragmentation reaction with $C_6F_5I(OCOCF_3)_2$ and MeOH gave the *N*,*O*-acetal intermediate **96**. The *p*-methoxybenzylthio group was efficiently introduced in the presence of $BF_3{\cdot}Et_2O$ to give the unstable *N*,*S*-acetal **97** as a diastereomeric mixture. The treatment of **97** with 30% HBr–AcOH followed by aqueous work up with $MeNH_2$ produced the *N*-tosylated discorhabdin A **98**. Ultimately, we developed an efficient one-pot transformation procedure yielding **98** from **96**. Finally, removal of the tosyl group of **98** with NaOMe in THF gave discorhabdin A in the optically pure form. The synthetic product as its HCl salt was identical in all respects with the natural discorhabdin A including its optical rotation (Scheme 31).



Scheme 30 Facial formation of *N*,*O*-acetal 68



Scheme 31 Total synthesis of (+)-discorhabdin A

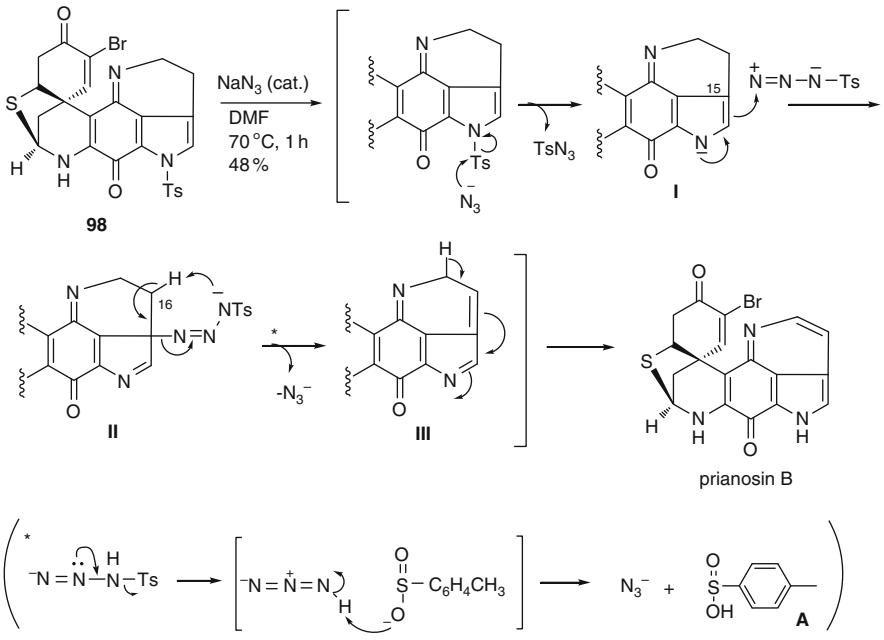


Scheme 32 Total synthesis of (−)-discorhabdin A

We also completed the total synthesis of the unnatural discorhabdin A, (−)-discorhabdin A, starting from the D-tyrosine methyl ester by the same route as described for (+)-discorhabdin A (Scheme 32).

4.5 Prianosin B

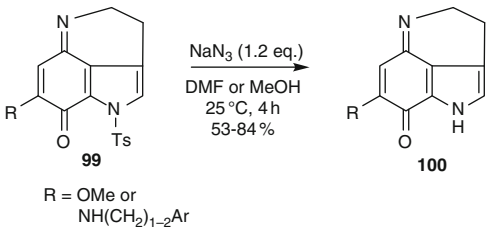
Prianosin B is the oxidized discorhabdin A, whose C16–17 bond is double bond. We found that the detosylation and dehydrogenation reaction of the pyrroloiminoquinone unit proceeded using a catalytic amount of NaN_3 in good yield. We then applied the reactions to the total synthesis of prianosin B (Scheme 33). Thus, the treatment of **98**



Scheme 33 Total synthesis of (+)-prianosin B

(see Scheme 31) with NaN_3 in DMF at 70 °C caused detosylation and dehydrogenation to produce prianosin B in 48% yield. The reaction mechanism for the dehydrogenation reaction of pyrroloiminoquinone using NaN_3 may be as follows. The nucleophilic attack of N_3^- on the tosyl residue followed by the addition of metallated enamine to TsN_3 produces the intermediate **II**. Dehydrogenation would proceed by the intramolecular elimination via a six-membered transition state to produce the intermediate **III** and isomerization to produce prianosin B. Regeneration of the azide anion during the reaction makes possible the use of catalytic amount of NaN_3. The reproduction of the azide anion was deduced from the presence of the toluenesulfinic acid observed in the ^{1}H-NMR spectrum [43].

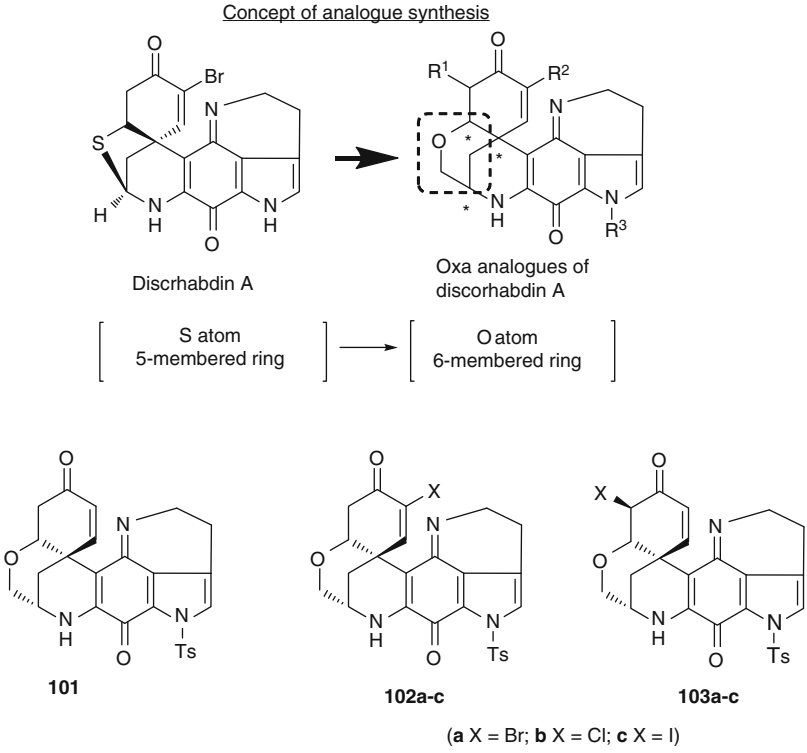
However, Velu et al. reported that treatment of the pyrroloiminoquinone under the same reaction conditions except for the reaction temperature gave only the detosylated product. This shows that the reaction temperature is very important for the dehydrogenation (Scheme 34) [82].



Scheme 34 Detosylation by N_3

4.6 Discorhabdin A Analogs

We recently prepared several discorhabdin A analogs aiming at more stable compounds, because discorhabdin A exhibits a strong cytotoxic activity in vitro, but it shows no activity in vivo due to the instability of its highly strained *N*, *S*-acetal structure. We then designed analogs of discorhabdin A which have a strong cytotoxic activity and stability. We prepared various stable discorhabdin A oxa analogs **101** with the oxygen cross-linked spiro fused ring system, and examined their antitumor activities in vitro against five kinds of tumor model cells, WiDr, HCT-116, DU-145, P388, and L1210. As a result, all the oxa analogs exhibited good IC_{50} values. Especially **102a** and its regioisomer **103a** gave the best results. Their IC_{50} values against HCT-116 (0.04 μM, 0.05 μM) are almost the same as those of discorhabdin A (0.03 μM). To our surprise, their IC_{50} values against L1210 (0.01 μM, 0.02 μM) are stronger than that of discorhabdin A (0.06 μM) (Scheme 35) [83].



Scheme 35 Discorhabdin A oxa analogs

5 Conclusion

Marine organisms produce many types of biologically active compounds. As shown here, sponges give us pyrroloiminoquinone and related metabolites, most of which exhibit strong cytotoxicity towards tumor human cell lines. Furthermore, they have unique structures different from the biological compounds isolated from land-dwelling creatures. Then they are recognized as lead compounds for developing new anticancer drugs. Although synthetic studies of rather simple pyrroloiminoquinones such as makaluvamines, isobatzellines, and their analogs have already been carried out by many groups, only a few total syntheses of more complex ones such as discorhabdins, tsitsikammamines, and wakayin have appeared over the past decade. However, many synthetic studies of such alkaloids have also been reported. We hope that the studies of the structure–activity relationship and the mode of action of alkaloids here and their analogs would reach good anticancer drugs.

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Synthetic Studies on Amaryllidaceae and Other Terrestrially Derived Alkaloids

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Abstract The total syntheses of a wide range of terrestrially derived alkaloids, especially ones isolated from members of the Amaryllidaceae family, are described. Two recurring themes associated with these syntheses are the use of two types of building blocks, namely ring-fused cyclopropanes, especially geminally-dihalogenated ones, and enzymatically derived *cis*-1,2-dihydrocatechols. These have often served as precursors to 2- or 3-halogenated 2-cyclohexen-1-ols that are themselves engaged in cross-coupling reactions, radical addition-elimination processes and/or Claisen- or Overman-type rearrangements so as to construct the highly functionalized six-membered rings associated with the target alkaloids.

Keywords Alkaloids · Amabiline · Amaryllidaceae · Aspidospermidine · Brunsvigine · Colchicine · Corey-Winter reaction · Cross-coupling · Cyclopropane · Erythramine · Eschenmoser-Claisen rearrangement · *epi*-Maritinamine · Galanthamine · Grandirubrine · Haemultine · Imerubrine · Ireland-Claisen rearrangement · γ-Lycorane · Lycoricidine · Maritinamine · Mitsunobu reaction · Nangustine · Narciclasine · Overman rearrangement · Pancracine · Pictet-Spengler reaction · Radical cyclisation · Rhazinal · Rhazinilam · Suzuki-Miyaura reaction · Ullmann reaction · Wittig reaction

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Contents

1 Introduction

In 1819 the German chemist Carl F.W. Meissner introduced the term alkaloid (or "alkali-like") but its widespread application as a descriptor of natural products containing a basic nitrogen only occurred in the 1880s and after the publication of a review article by O. Jacobsen in Albert Ladenburg's Chemical Dictionary (see [1]). Alkaloids, many of which are heterocyclic in nature and the by-products of amino acid metabolism, occur most commonly in the peripheral parts of plants such as the leaves, roots, bark and/or fruit and less so in the wood. Interestingly, significantly reduced concentrations of alkaloids are encountered in terpene- and resin-rich plants. In addition, because many alkaloids are neurotoxic they are not normally encountered in large quantities in the terrestrially based animal kingdom [2]. In contrast, the marine environment appears to contain many alkaloid-producing animals including sponges, tunicates and nudibranchs (for useful points-of-entry into the literature on marine alkaloids see [3, 4]).

Alkaloids and their derivatives, especially those of the morphinan class, have a long history of therapeutic use and remain some of the most heavily prescribed drugs on the market today. Such features, together with issues of supply and the broad range of remarkable structural variations encountered amongst the more than 15,000 alkaloids described thus far, have made them attractive targets for synthesis [5]. Indeed, the development of the discipline of chemical synthesis has been profoundly influenced by the manifold challenges that these natural products have presented (and continue to present) to the practitioners in the field. There are some key milestones in the area worth highlighting to the reader. In 1886 Landenburg reported the first complete synthesis of an alkaloid, namely coniine [(*R*)-2-propylpiperidine] (see [6]). This involved condensing 2-methylpyridine with acetaldehyde

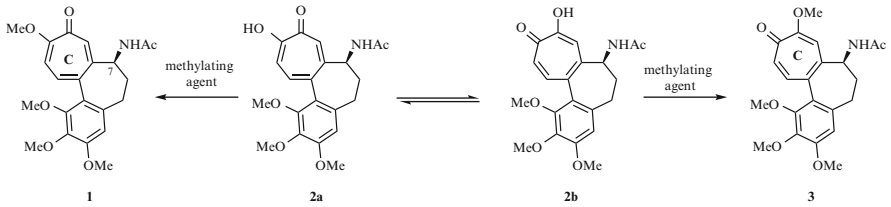
followed by reduction of the ensuing 2-propenylpyridine with sodium to give the racemic modification of the natural product. Robinson's one-step synthesis of the alkaloid tropinone under near-physiological conditions was reported in 1917 [7] and is regarded as one of the most important developments in the discipline, not least because it served to inspire many other biogenetically patterned syntheses. The Woodward–Doering synthesis of quinine, reported in 1944 [8] and at a time when there was a severe shortage of this anti-malarial agent, served to highlight the emerging power of rational synthetic design and the increasing array of chemical methodologies available for the purposes of constructing some of Nature's most challenging and important compounds. Gates' synthesis of morphine followed in the 1950s [9] and emphasised these points, as did reports on, inter alia, the assembly of lysergic acid (Woodward 1954) [10], reserpine (Woodward 1958) [11], colchicine (Eschenmoser 1959; van Tamelen 1961; Scott 1963; Woodward 1963) [12–18] and strychnine (Woodward 1963) [19]. The development, in the mid- to late-1970s, of biomimetic protocols for the synthesis of the dimeric and clinically significant indole alkaloids such as vinblastine and vincristine represents another major development in the field (see [20]). Of course, many beautiful syntheses of alkaloids have emerged since this time and the current state-of-play is emphasised by, for example, Overman's preparation actinophyllic acid [21] as well as Reissig's and Vanderwal's exceptionally concise syntheses of (±)-strychnine [22, 23].

The present chapter is focussed on the contributions of the lead author's group to the synthesis of terrestrially derived alkaloids. The chapter is idiosyncratic in nature insofar as the emphasis has been placed on work (both published and unpublished) carried out by the group.

2 Colchicine, Imerubrine, Grandirubrine, Salimine and Jerusalemine

2.1 Colchicine

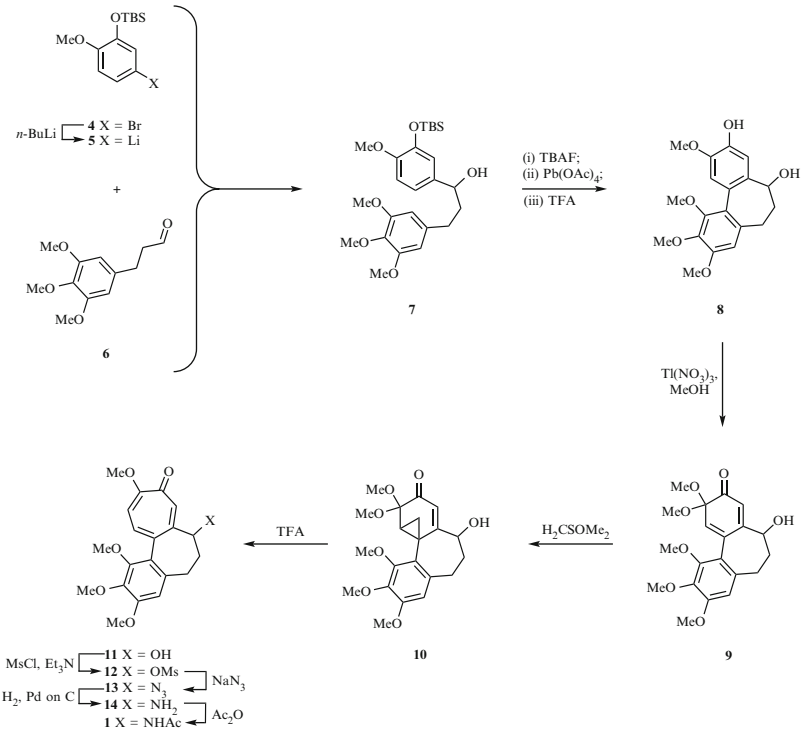
Colchicine (**1**, see Scheme 1 – associated axis of chirality not shown), which embodies a tropolone ring system, is a phenethyltetrahydroisoquinoline-derived alkaloid that was originally isolated from the meadow saffron *Colchicum autumnale* [24]. It is a highly potent anti-mitotic agent that is used in the treatment of liver cirrhosis and gout while its *N*-deacetyl congener, demecolcine, is a clinically effective antineoplastic agent [25]. Its novel structural features and potent biological activities have prompted numerous synthetic studies. However, a fully regiocontrolled synthesis remained elusive for some time. The first synthesis of the alkaloid, described by Eschenmoser and Schreiber in 1959 [12], highlighted two key problems that were not solved simultaneously within the one reaction sequence until our report in 1992. Site-selective introduction of the C-7 acetamido group associated with target **1** had proven somewhat problematic although Nakamura,



Scheme 1 Formation of colchicine (**1**) and isocolchicine (**3**) *via O*-methylation of colchiceine (**2**)

Woodward and Evans [14, 17, 18] advanced solutions to this matter during the course of their studies. The second difficulty stemmed from the rapid equilibrium between the two tautomeric forms, **2a** and **2b**, of colchiceine (10-demethylcolchicine), the free tropolone that is the final intermediate in all pre-1992 syntheses (Scheme 1). As a result of this equilibrium, O-methylation of colchiceine affords a ca. 1:1 mixture of colchicine and isocolchicine (**3**), the latter product differing from **1** in that the positions of the methoxy and carbonyl moieties (as well as the associated double-bonds) in ring-C are reversed.

Our solution to these longstanding problems involved implementing a synthetic sequence ([26, 27]; for a summary of more recent syntheses of colchicine see [28]) that mimicked the proposed biogenesis [29] of the troponoid C-ring of colchicine (Scheme 2). Thus, the aryl bromide **4** was converted into the corresponding lithio-species **5** under standard conditions and this was then treated with the aldehyde **6** to give the alcohol **7**. Deprotection of this last compound with tetra-*n*-butylammonium fluoride (TBAF) and subjection of the resulting phenol (61% yield from **4**) to a Wessely-type oxidation with lead(IV) acetate afforded a diastereoisomeric mixture of the expected *o*-benzoquinone monoketals that upon treatment with trifluoroacetic acid (TFA) engaged in a cyclization reaction to form the dibenzocycloheptane **8** (42% overall yield from **7**). Treatment of compound **8** with thallium (III) nitrate in the presence of methanol afforded the *o*-benzoquinone monoketal **9** (97%) that was subjected to nucleophilic cyclopropanation using the Corey–Chaykovsky ylide and thus affording, in a completely regioselective manner, the ring-fused cyclopropane **10** (75%). In the pivotal and presumably biomimetic step of the reaction sequence, compound **10**, a σ-homo-*o*-benzoquinone monoketal, was treated with TFA in dichloromethane at room temperature. This induced fragmentation of the three-membered ring and accompanying loss of the elements of methanol so as to generate the troponoid **11** in 89% yield (at 53% conversion). Clearly compound **11** embodies the required regiochemical arrangement of the methoxy and carbonyl moieties within the C-ring and all that remained was to convert the C-7 alcohol into the corresponding acetamido group. This was readily effected by the illustrated sequence wherein the alcohol was transformed into the corresponding mesylate **12** (100%) which was displaced with sodium azide to give the azide **13** (85%). Reduction of the latter with dihydrogen in the presence of palladium on carbon then gave the corresponding amine **14** that was immediately subjected to reaction with acetic anhydride and so affording the racemic modification of colchicine (**1**) in 73% overall yield from the precursor azide.



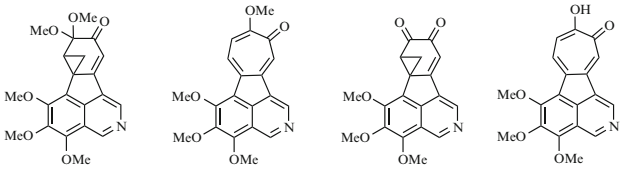
Scheme 2 First fully regiocontrolled total synthesis of colchicine (**1**)

A relatively straightforward modification to the latter parts of this sequence allowed for the synthesis of enantiomerically enriched colchicine [28]. Specifically, a ketone arising from oxidation of a derivative of alcohol **8** could be reduced in an enantioselective manner using the CBS reagent and the resulting enantiomerically enriched form of compound **8** was then carried forward in the same manner as described above and thus providing colchicine (**1**) in >81% ee.

2.2 Imerubrine and Grandirubrine

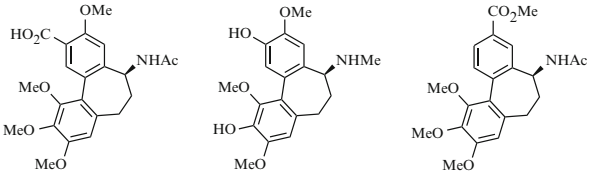
The protocols detailed above have proven effective in the regiospecific construction of other natural products incorporating a tropolone *O*-methyl ether unit. For example, treatment of the σ-homo-*o*-benzoquinone monoketal **15** with TFA gave the tropoloisoquinoline natural product imerubrine (**16**) in 70% yield ([27, 30, 31]; for more recent syntheses of these alkaloids see [32]). Furthermore, the α-diketone, **17**, arising from hydrolysis of compound **15** underwent thermal rearrangement to afford the related natural product grandirubrine (**18**) (87% from **15**). Interestingly, when

compounds **16** and **18** were tested as tubulin binding agents only the former showed any activity and this was much weaker than that observed for colchicine [30–32].



2.3 *Salimine and Jerusalemine*

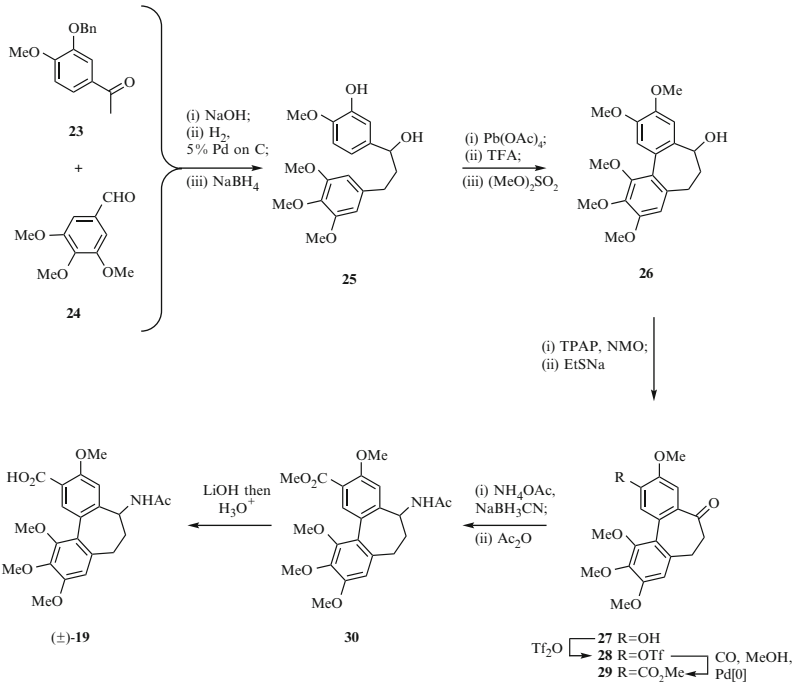
In 1991 Abu Zarga et al. described the isolation of the alkaloids salimine, jerusalemine and suhailamine from the Middle Eastern species *Colchicum decaisnei* Boiss. (Liliaceae) [33]. On the basis of various spectroscopic studies structures **19**–**21**, respectively,[1,2] were assigned to these compounds. Given the resemblance of these structures to the intermediate **8** associated with our biomimetic synthesis of colchicine (Scheme 2) we sought to adapt this work so as to prepare compounds **19** and **20**, on the basis that these might display the same types of anti-mitotic properties shown by allocolchicine (**22**) (see footnote 2), a compound that is readily obtained by the methoxide ion-induced ring-contraction of the C-ring of colchicine and which is also encountered in nature.



The route we employed in obtaining the racemic modification of the structure assigned to salimine (**19**) is shown in Scheme 3 and started with the Claisen–Schmidt condensation of acetophenone **23** with aldehyde **24** [34]. The resulting chalcone (92%) was subjected to simultaneous reduction of the carbon–carbon double bond

[1] Each of these compounds presumably possesses an axis of chirality but the configurations of these were not reported.

[2] Abu Zarga et al. [33] assigned structure **21** to the alkaloid suhailamine without recognising that this is also the structure of the well known colchicine derivative allocolchicine. Since the spectral data derived from suhailamine do not match those recorded for allocolchicine, the structure proposed for the former compound is presumed to be incorrect.



Scheme 3 Total synthesis of the structure, **19**, assigned to the alkaloid salimine

and hydrogenolysis of the benzyl ether using dihydrogen in the presence of Pd on C and this was followed by reduction of the carbonyl unit with sodium borohydride. The ensuing alcohol **25** (96% from the chalcone) was subjected to an oxidative coupling sequence using $Pb(OAc)_4$ and then TFA as described earlier and after O-methylation of the free phenol the dibenzocycloheptane **26** was obtained in 96% yield. Oxidation of the benzylic hydroxyl group within this last compound using the Ley–Griffith reagent was followed by selective demethylation of the required methoxy group within the resulting ketone using the ethanethiolate anion. The phenol **27** (17%) so formed was converted into the corresponding triflate **28** (46%) under standard conditions and this was subjected to Pd[0]-catalysed carbomethoxylation and, thereby affording keto-ester **29** in 43% yield. The structure of this last compound was confirmed by single-crystal X-ray analysis. Reductive amination of the keto group within compound **29** followed by acetylation of the resulting primary amine and saponification of the ester unit within product **30** (45%) gave, after acid work-up, the racemic form of the target **19** in 75% yield. A related sequence of reactions was used to prepare, in racemic form, the structure **20** assigned to jerusalemine. However, the spectral data recorded on both of these synthetically-derived materials did not match those reported for the natural products thus suggesting that their structures have been assigned incorrectly.

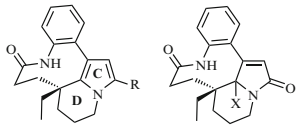
Interestingly, when the synthetically-derived "allocolchicinoids" (±)-**19** and (±)-**20** were subjected to the relevant binding assay they did not show inhibitory effects on tubulin polymerisation. Furthermore, they were not cytotoxic to L1210 (murine lymphocytic leukaemia) cells [34].

3 The Amaryllidaceae Alkaloids

The title alkaloids are a structurally diverse class of natural products that display a remarkable range of biological properties. As a consequence, enormous effort has been devoted to the synthesis of such compounds and the work reported in this area over the last three to four decades has served as something of an indicator of the state-of-the-art of synthesis at any given time.

3.1 Rhazinilam and Rhazinal

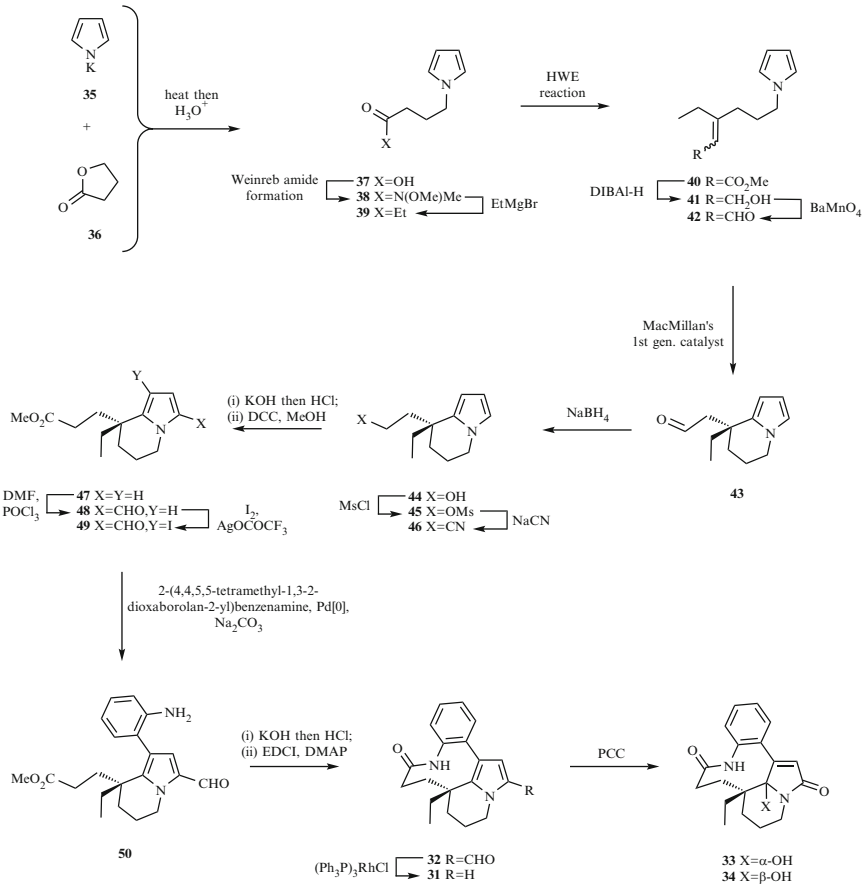
Our own interest in the synthesis of the Amaryllidaceae alkaloids arose when we recognised that, in common with colchicine (**1**), (−)-rhazinilam (**31**) and (−)-rhazinal (**32**) are both spindle toxins although their mode of action is different in that, like Taxol™, they exert their biological effects by inhibiting the depolymerisation of microtubules. This prompted us to develop syntheses of these compounds and certain biogenetically related ones such as (+)-*epi*-leuconolam (**33**) and (−)-leuconolam (**34**) ([35, 36]; for an excellent and very recent review on all of the reported syntheses of rhazinilam see [37]).



31 R=H
32 R=CHO

33 X=α-OH
34 R=β-OH

The pivotal step associated with our approach to compounds **31**–**34** was an organocatalysed, enantioselective and intramolecular Michael addition reaction of the nucleophilic C-2 carbon of a pyrrole to an *N*-tethered α,β-unsaturated aldehyde residue and thereby establishing the required CD-ring system. Full details of the reaction sequence are shown in Scheme 4 and this involves initial reaction of the potassium salt, **35**, of pyrrole with butyrolactone (**36**) to give, after acidic work-up, compound **37** (60–90%). Conversion of this last species into the corresponding Weinreb amide **38** (87%) followed by its reaction with ethylmagnesium bromide then afforded the ethyl ketone **39** (95%) that was subjected to standard Horner–Wadsworth–Emmons (HWE) conditions and thereby generating the



Scheme 4 Total syntheses of (−)-rhazinal (**32**), (−)-rhazinilam (**31**), (+)-*epi*-leuconolam (**33**) and (−)-leuconolam (**34**)

α,β-unsaturated ester **40** which was obtained as a 1:1 mixture of diastereoisomers in 77% yield. Reduction of these esters with DIBAl-H gave the corresponding mixture of allylic alcohols **41** (91%) which were immediately oxidised to the aldehydes **42** (76%) with barium permanganate. Treatment of this mixture with MacMillan's first generation organocatalyst [38] effected the anticipated intramolecular Michael addition reaction and gave the required cyclisation product **43** in 81% chemical yield and ca. 74% ee. A standard homologation sequence was then applied to this aldehyde. Thus, it was reduced with $NaBH_4$ to the corresponding alcohol **44** (84%) that was immediately converted into the corresponding mesylate **45** (95%) under standard conditions. Reaction of the latter compound with sodium cyanide followed by hydrolysis of the resulting nitrile **46** (91%) and esterification of the ensuing acid with methanol in the presence of DCC afforded compound **47** (63%). Vilsmeier–Haack formylation of pyrrole **47** gave the aldehyde **48** (78%)

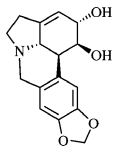
that reacted, in an entirely regioselective manner, with molecular iodine in the presence of silver trifluoroacetate to give the iodinated pyrrole **49** (quant.). Suzuki–Miyaura cross-coupling of this last compound with the commercially available 2-(4,4, 5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenamine provided the expected compound **50** (64%) that was engaged in a two-step macrolactamisation sequence and thereby affording (−)-rhazinal (**32**) in 68% yield and ca. 74% ee as judged by chiral HPLC analysis.

Treatment of compound **32** with stoichiometric quantities of Wilkinson's "catalyst" effected decarbonylation of the substrate and thus gave, without any erosion in optical purity, (−)-rhazinilam (**31**) in 89% yield. Following protocols established earlier within the group, compound **31** was treated with an excess of PCC in the presence of 4 Å molecular sieves to give a chromatographically separable mixture of (+)-*epi*-leuconolam (**33**) (46%) and (−)-leuconolam (**34**) (28%).

We have employed a related reaction sequence to prepare a lower homologue of rhazinal and then shown that this retains many of the potent anti-mitotic properties of the natural product [39].

3.2 Lycorane and Lycorinine-Type Alkaloids

The lycorine alkaloids, of which lycorine (**51**) is the parent member [40], as well as the biogenetically related lycorinine alkaloids, as represented by clividine (**52**) [41] and narseronine (**53**) [42], constitute two further types of Amaryllidaceae alkaloids that have attracted our attention. They display an extraordinary range of biological effects including a pronounced capacity to selectively inhibit the growth of various cancer cells, DNA binding properties, anti-viral activity, anti-fungal behaviour and insect anti-feedant activity [42]. Despite this, there has been remarkably little effort to develop syntheses of members of either of these two classes or analogues thereof. Accordingly, we sought to establish practical routes to these systems and two distinct approaches emerged from our studies in the area. The first of these is highlighted in our syntheses of the (±)-, (−)-, and (+)-forms of the γ-lycorane [**54** – representing (+)-form] [43], the latter two having been obtained through degradation of lycorine as part of the work associated with establishing its structure.



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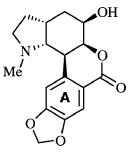

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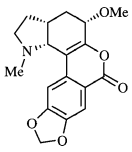

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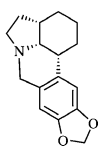
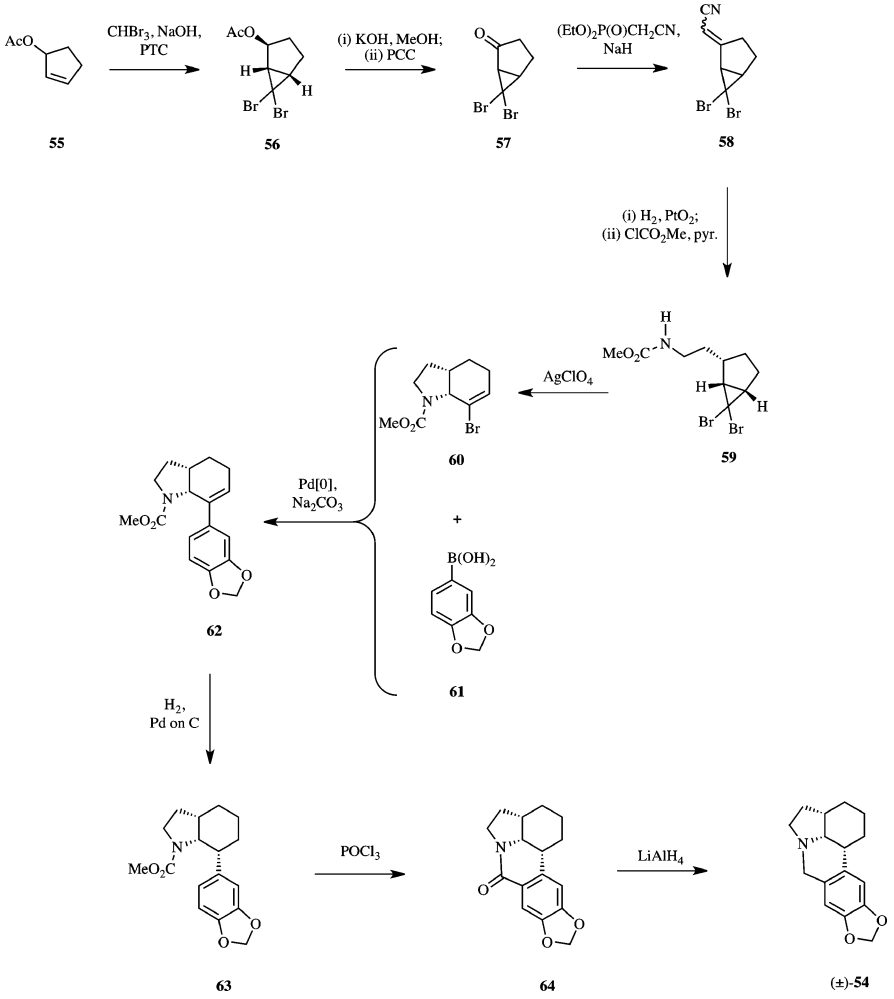


54

The details of our syntheses of these three forms of γ-lycorane are presented in Scheme 5. Thus, the known allylic acetate **55** was reacted with bromoform and sodium

hydroxide in the presence of a phase-transfer catalyst to give the ring-fused *gem*-dibromocyclopropane **56**. This was, in turn, converted, via a standard reaction sequence, into the ketone **57**. Subjection of this last species to an HWE reaction with the anion derived from diethyl cyanomethylphosphonate then gave a ca. 2:1 mixture of the *E*- and *Z*-isomeric forms of the α,β-unsaturated nitrile **58**. Treatment of this mixture with dihydrogen in the presence of PtO_2 and chloroform resulted in the stereoselective formation of the hydrochloride salt of the expected amine that was immediately converted into the corresponding methyl carbamate **59** (32% overall yield from **55**) under standard conditions. In the pivotal step of the reaction sequence, this last compound was treated with silver perchlorate in the weakly nucleophilic solvent trifluoroethanol, resulting in the electrocyclic ring opening of the three-membered

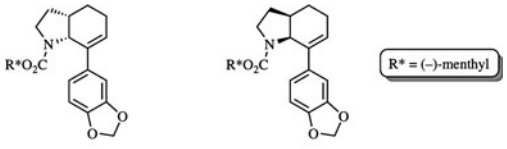


Scheme 5 Total synthesis of (±)-γ-lycorane [(±)−**54**]

ring and intramolecular trapping of the ensuing π-allyl cation by the nitrogen of the pendant carbamate. In this way the hexahydroindole **60** was obtained in 95% yield. Compound **60** readily engaged in a Suzuki–Miyaura cross-coupling reaction with arylboronic acid **61** and thereby affording the expected product **62** in 87% yield.

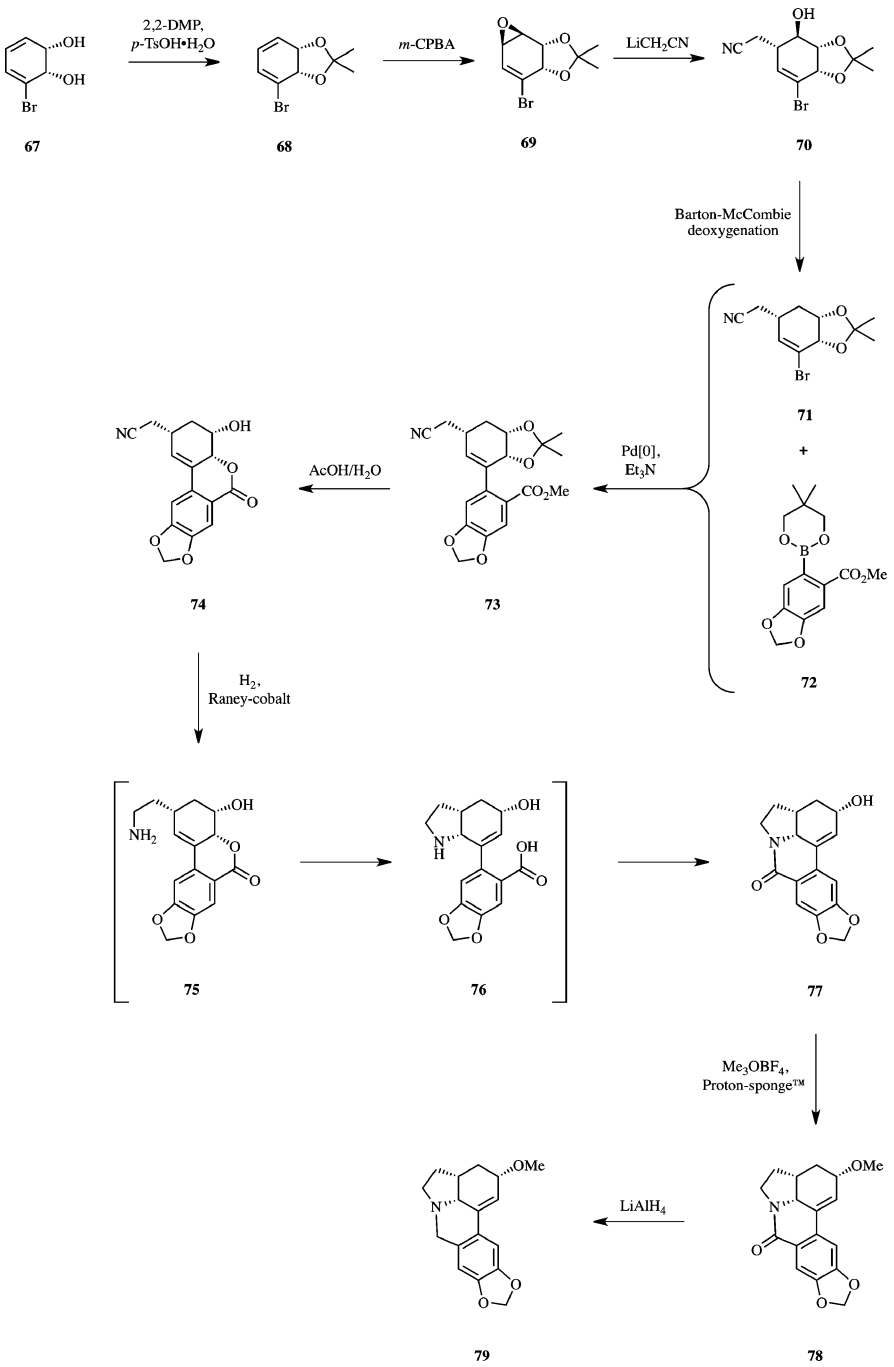
Catalytic hydrogenation of alkene **62** proceeded in a completely facially selective manner to give the C7-arylated perhydroindole **63** (quant.) that was then subjected to treatment with phosphorus oxytrichloride and so effecting a Bischler–Napieralski cyclisation reaction to give the lactam **64** (81%). Upon reduction with lithium aluminium hydride this lactam provided (±)-γ-lycorane [(±)-**54**] in 84% yield.

This reaction sequence was readily modified so as to allow for the synthesis of the (+)- and (−)-forms of γ-lycorane. Thus, by reacting the amine arising from the reduction of the α,β-unsaturated nitriles **58** with (−)-menthyl chloroformate, treating the resulting diastereoisomeric carbamates with silver acetate and cross-coupling the ensuing mixture of hexahydroindoles with aryl boronic acid **61**, the chromatographically separable C7-arylated hexahydroindoles **65** and **66** could be obtained. These were then readily elaborated, using the same protocols as specified in Scheme 5, to the (+)- and (−)-enantiomeric forms, respectively, of the target compound **54**.



65 **66**

A chemoenzymatic approach to the lycorine framework is shown in Scheme 6 [44]. This involved using the enzymatically-derived and enantiomerically pure *cis*-1,2-dihydrocatechol **67** as starting material. Thus, this diol was converted into the corresponding acetonide **68** (93%) under standard conditions and the latter compound subjected to a completely regio- and stereo-controlled epoxidation reaction with *m*-CPBA to give the epoxide **69** in 95% yield. Treatment of oxirane **69** with the acetonitrile anion resulted in a completely regio-selective ring-opening reaction and formation of the γ-hydroxynitrile **70** (96%) that was subjected to a Barton–McCombie deoxygenation reaction and thereby affording compound **71** in 77% yield over the two steps involved. Suzuki-Miyaura cross-coupling of bromoalkene **71** the readily prepared aryl boronate ester **72** gave the expected arylated cyclohexene **73** (75%) that, upon treatment with acetic acid in water at 80 °C, underwent cleavage of the acetonide group and subsequent lactonisation to give the tetracyclic compound **74** (89%). Subjection of nitrile **74** to reaction with dihydrogen in the presence of Raney-cobalt in ammoniacal methanol resulted in formation of the lactam **77** (65%), presumably via a pathway in which the initially generated primary amine **75** engages in an S_N' reaction to give the amino acid **76** that, in turn, undergoes lactamisation to give product **77**. The structure of the last compound was secured by single-crystal X-ray analysis. Treatment of lactam **77** with trimethyloxonium tetrafluoroborate in the presence of Proton-sponge™



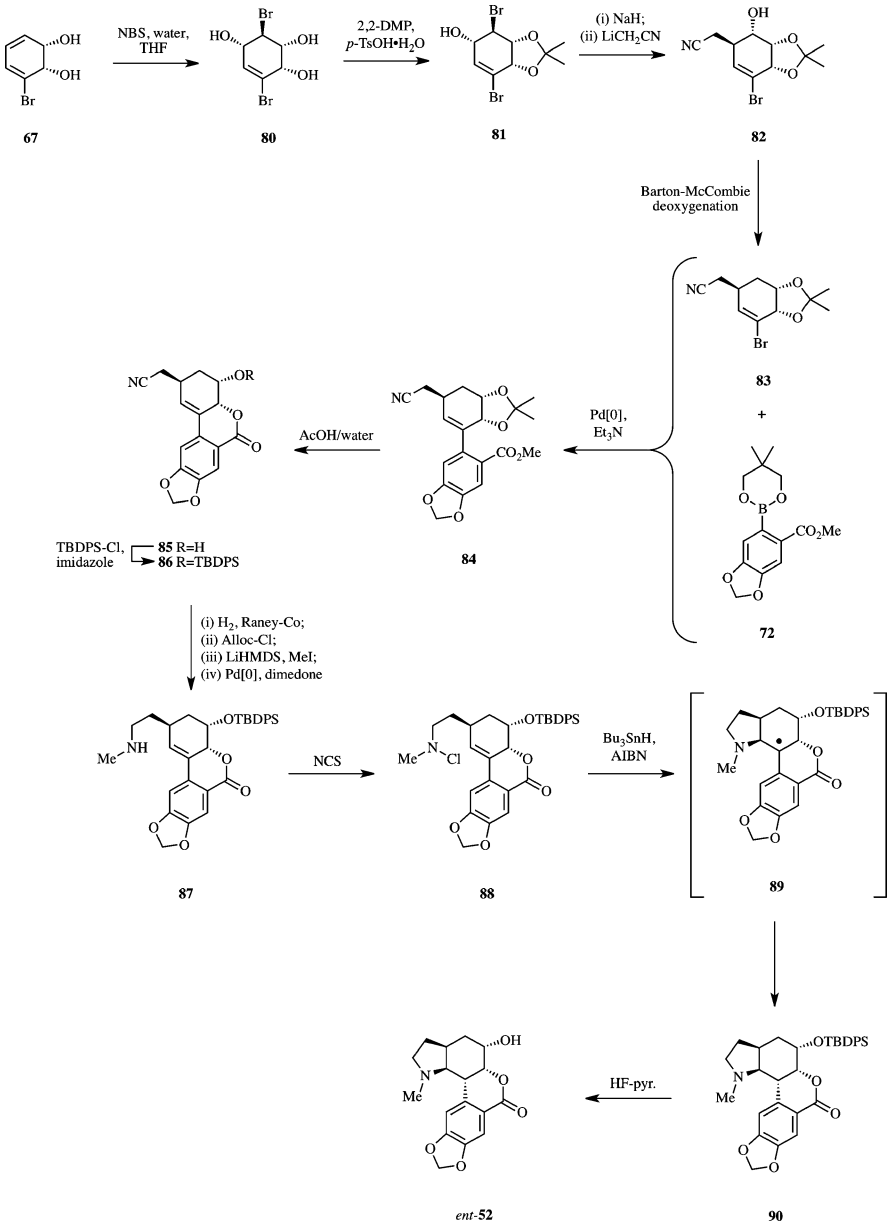
Scheme 6 Synthesis of compound **79**, a degradation product of (−)-lycorine (**51**)

effected O-methylation and reduction of compound **78** so formed (95%) using lithium aluminium hydride then gave target compound **79** (89%) which had been obtained previously by degradation of (−)-lycorine (**51**).

A related strategy has been employed in developing a synthesis of the non-natural enantiomeric form, *ent*-**52**, of the lycorinine alkaloid clividine in which a nitrogen-centred radical cyclisation reaction is used in the key step (Scheme 7) (White et al., unpublished work) (for a summary of the limited number of other synthetic endeavours in this area see [45]). Thus, starting with the same *cis*-1,2-dihydrocatechol (**67**) as used previously but now treating it with NBS in wet THF and then converting the ensuing bromohydrin **80** into the corresponding acetonide **81** (92%) provided a material that upon successive treatment with sodium hydride and $LiCH_2CN$ afforded the γ-hydroxynitrile **82** (87%). Subjection of this last compound to a Barton–McCombie deoxygenation reaction then gave nitrile **83** (81%) that is epimeric with that involved as an intermediate in the synthesis of the lycorine degradation product **79** as detailed immediately above. Suzuki–Miyaura cross-coupling of compound **83** with aryl boronate **72** gave the arylated cyclohexene **84** (95%) that upon treatment with acetic acid/water afforded hydroxy-lactone **85** (84%), the OH group of which was protected, under standard conditions, as the corresponding TBDPS ether **86** (80% yield). Treatment of compound **86** with dihydrogen in the presence of Raney-cobalt, protection of the resulting amine as the Alloc-carbamate, N-methylation of this using LiHMDS and methyl iodide followed by removal of the Alloc group using Pd[0] in the presence of an excess of dimedone then gave the secondary amine **87** (62% over four steps) that was immediately N-chlorinated using NCS to give compound **88**, the substrate required for the foreshadowed and pivotal radical cyclisation process. In the event, treatment of the *N*-chloroamine **88** with tri-*n*-butyltin hydride in the presence of AIBN gave, presumably via the intermediate benzylic radical **89** that accepts a hydrogen atom at the β-face, the pentacyclic lactone **90** (82% yield). Treatment of this last compound with HF•pyridine then afforded *ent*-clividine (*ent*-**52**) in 99% yield. The structure of this last compound was confirmed through a single-crystal X-ray analysis of the corresponding picrate salt. Since the enantiomer of the starting material **67** is known, the route shown also provides access to the natural enantiomeric form, **52**, of clividine.

The stereochemical outcome of the nitrogen-centred radical cyclisation **88** → **90** is strongly influenced by steric effects and the manipulation of these offers considerable potential in the preparation of diastereoisomeric forms of the lycorinine alkaloids. Thus, for example, cyclisation of the non-TBDPS-protected form, **91**, of compound **88** results in the generation of C11b-*epi*-*ent*-clividine (**92**) (67%) (Scheme 8) (White et al., unpublished work) [45].

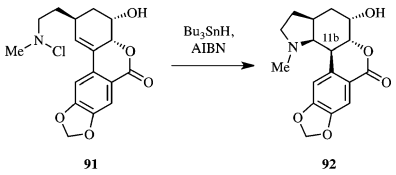
A synthesis of the alkaloid narseronine **53** that highlights yet another novel mode of cyclisation of arylated cyclohexenes derived from compound **67** is shown Scheme 9 (White et al., unpublished work; [45]). Thus, nitrile **73** (generated from precursor **67** during the course of our synthesis of the lycorine degradation product **79** as shown in Scheme 6) was reduced with dihydrogen in the presence of Raney-cobalt and the resulting primary amine was then protected as the corresponding



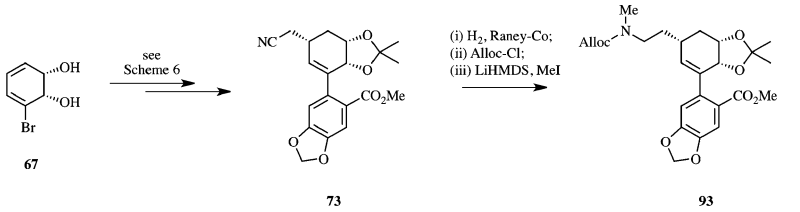
Scheme 7 Total synthesis of *ent*-clividine [*ent*-**52**]

Alloc-carbamate which was, in turn, N-methylated using methyl iodide in the presence of LiHMDS, thus affording compound **93** in 86% yield. Successive treatment of carbamate **93** with acetic acid/water (to effect cleavage of the acetonide ring) and LiHMDS (to lactonise the initially formed diol) and Ag_2O/MeI (to effect a

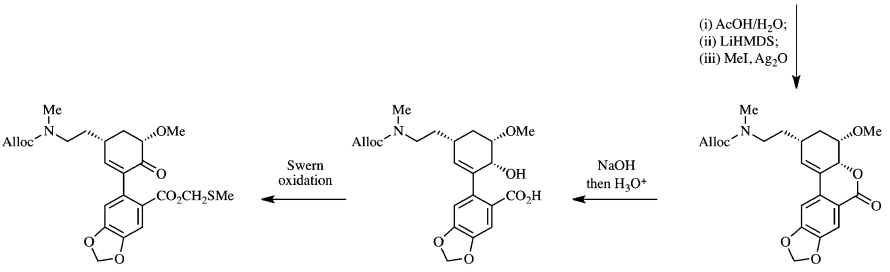
Scheme 8 Final step associated with the synthesis of C11b-*epi-ent*-clividine (**92**)



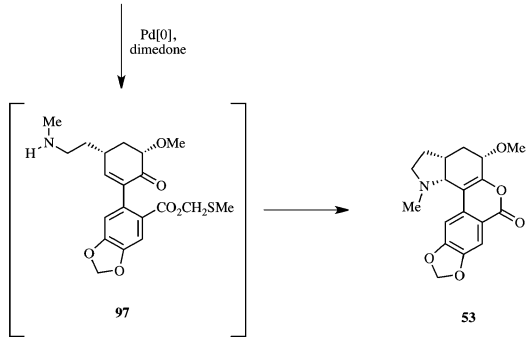
91 **92**



67 **73** **93**



96 **95** **94**



97 **53**

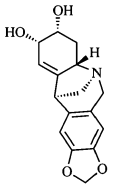
Scheme 9 Total synthesis of narseronine (**53**)

Purdie–Irvine methylation of the residual hydroxyl group) afforded compound **94** (59%) that was treated with sodium hydroxide and then mineral acid to give the hydroxyacid **95**. This last compound was prone to relactonisation and, thereby, regeneration of precursor **94**. Nevertheless, when compound **95** was subjected to

Swern oxidation conditions, using an excess of DMSO and oxalyl chloride, the keto-ester **96** was obtained in 48% yield. The formation of the methylthiomethyl ester moiety in this reaction is presumably the result of the intervention of a Pummerer-type rearrangement reaction. Treatment of compound **96** with Pd $(PPh_3)_4$ and an excess of dimedone resulted in the removal of the Alloc protecting group and formation of the secondary amine **97** which underwent a spontaneous intramolecular hetero-Michael addition to the pendant enone moiety with the ensuing enolate attacking the adjacent ester carbonyl and, after the usual addition/elimination reaction, delivering the unsaturated lactone **53** in 67% yield. The spectral data obtained on compound **53** were in full accord with the assigned structure that was eventually confirmed by a single-crystal X-ray analysis. Furthermore, there was excellent agreement between the spectral data recorded for compound **53** and those reported for naturally-derived narseronine.

3.3 The Montanine Alkaloids

The use of enzymatically-derived *cis*-1,2-dihydrocatechols in conjunction with radical cyclisation processes has also provided useful new routes to certain members of the montanine alkaloid class, members of which have been isolated from various Amaryllidaceae species and incorporate the 5,11-methanomorphanthridine framework bearing hydroxy or methoxy groups in varying configurations at C2 and C3 [46]. (−)-Brunsvigine (**98**) and (−)-nangustine (**99**) are representative members of the class and the non-natural enantiomeric forms of both have been prepared by us from the chloro-analogue of *cis*-1,2-dihydrocatechol **67** ([47]; for a summary of the limited number of other synthetic endeavours in this area see [48]; [49]).



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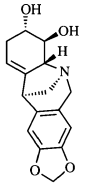
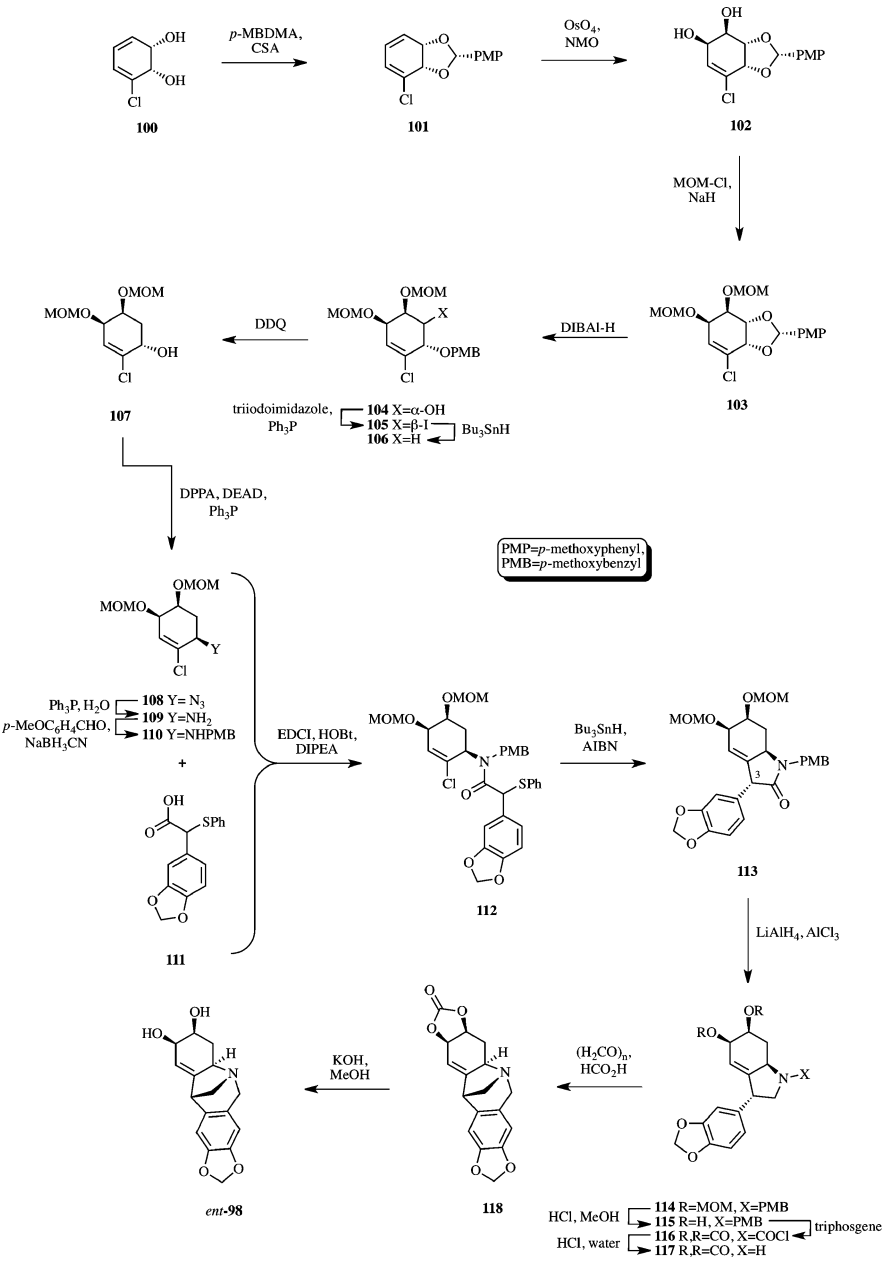


99

The route used in the conversion **100** → *ent*-**98** is shown in Scheme 10 and begins with the conversion of the former compound into the acetal **101** under standard conditions. Dihydroxylation of the non-chlorinated double-bond within the latter compound using the Upjohn conditions [50] provided the diol **102** (66%) in a completely diastereoselective fashion and this was protected as the corresponding di-MOM ether **103** (88%) using MOM chloride in the presence of sodium hydride. Reductive cleavage of the acetal unit within compound **103** was readily effected in a regioselective manner with DIBAl-H and the ensuing alcohol

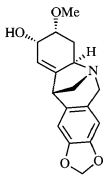


Scheme 10 Total synthesis of *ent*-brunsvigine (*ent*-**98**)

104 (60%) was then converted into the corresponding (inverted) iodide **105** (66%) using triiodoimidazole in the presence of triphenylphosphine. Reductive deiodination of this last compound with tri-*n*-butyltin hydride (to give tris-ether

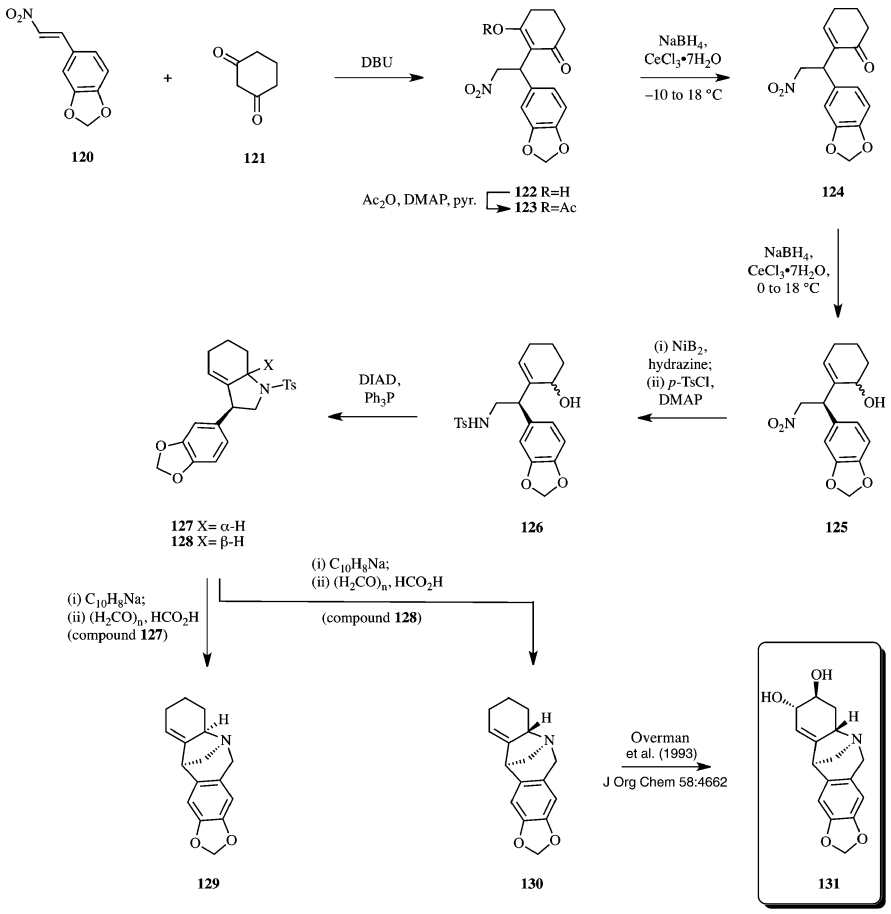
106) followed by selective cleavage of the PMB ether with DDQ then gave alcohol **107** (83% from **105**) that was converted into the epimeric azide **108** (75%) under Mitsunobu conditions. Subjection of compound **108** to a Staudinger reaction then gave the corresponding amine **109** (98%) which participated in a reductive amination reaction with *p*-methoxybenzaldehyde in the presence of sodium cyanoborohydride. The resulting secondary amine **110** (56%) was coupled with the racemic modification of the readily prepared acid **111** and the diastereoisomeric forms of amide **112** (74%) so produced were subjected to reaction with tri-*n*-butyltin hydride. This resulted in homolytic cleavage of the PhS group and the ensuing benzylic radical then added, in an intramolecular fashion, to the nearer terminus of the chlorinated double bond, thereby generating a new radical that "collapses" with ejection of a chlorine radical, so as to produce the annulated and β,γ-unsaturated lactam **113** in 60% yield. Compound **113** was accompanied by smaller amounts (7%) of its C3-epimer. Treatment of lactam **113** with a combination of $LiAlH_4$ and $AlCl_3$ resulted in the reductive removal of the carbonyl group and formation of tertiary amine **114** (94%), the MOM groups within which were removed on treatment with acidic methanol. The ensuing diol **115** (73%) was treated with triphosgene, resulting in the simultaneous generation of a cyclic carbonate unit and cleavage of the PMB group, thus leading to the carbamoyl chloride **116**. Exposure of this last compound to aqueous acid then afforded the secondary amine **117** (42% from **115**) that readily engaged in a Pictet–Spengler reaction on treatment with paraformaldehyde in formic acid, thereby generating compound **118** (65%) that embodies the polycyclic framework associated with the target alkaloid. Indeed, simply treating this cyclic carbonate with potassium hydroxide in methanol gave *ent*-brunsvigine (*ent*-**98**) in 87% yield that, save for the sign of the specific rotation, was spectroscopically identical, in all respects, with the natural product.

We have extended the chemistry shown in Scheme 10 to the preparation of *ent*-nangustine (*ent*-**99**) and to the synthesis of compound **119** that corresponds to the structure assigned to montabuphine [51]. Montabuphine has attracted considerable attention because its isolation suggested that both enantiomeric forms of the montanine alkaloid framework occur in nature. In the event, and by employing a reaction sequence similar to that shown above, we were able to prepare target **119** from *cis*-1,2-dihydrocatechol **100**. However, a comparison of the physical and spectral data recorded on the synthesised form of amine **119** with those reported for (+)-montabuphine suggests that they are different compounds.



119

An alternate approach to the basic pentacyclic framework of the montanine alkaloids is shown in Scheme 11 [52] and involves an initial base-promoted Michael addition reaction between the β-nitrostyrene **120** and cyclohexane-1, 3-dione (**121**). The resulting adduct, β-hydroxyenone **122** (quant.), was O-acylated and the ensuing β-acetoxyenone **123** (74%) subjected to Luche reduction followed by a basic work-up and, thereby affording enone **124** (67%). Subjection of the last compound to a second Luche reduction followed by reduction of the nitro group to the corresponding amine (using NiB_2 in the presence of hydrazine) and conversion of this into the corresponding *p*-toluenesulfonamide gave a ca. 1:1 and chromatographically separable mixture of the two diastereoisomeric forms of allylic alcohol **126** (78% from **125**). Independent treatment of each of these with diisopropyl azodicarboxylate (DIAD) in the presence of triphenylphosphine resulted in an



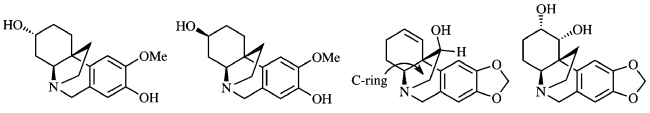
Scheme 11 Synthesis of the basic pentacyclic framework, **103**, associated with the montanine alkaloids

intramolecular Mitsunobu reaction and formation of the corresponding 3-arylhexahydroindole, **127** or **128**, as the major product (70–85% yield) of reaction. Reductive cleavage of the sulfonamide residue within the former product using sodium naphthalenide followed by immediate subjection of the product amine to a Pictet–Spengler reaction then gave compound **129** (56%), the structure of which was established by single-crystal X-ray analysis. Subjection of diastereoisomer **128** to an analogous reaction sequence afforded congener **130** (59%), the acquisition of which constitutes a formal total synthesis of the racemic modification of the montanine alkaloid pancracine (**131**).

3.4 The Crinine Alkaloids

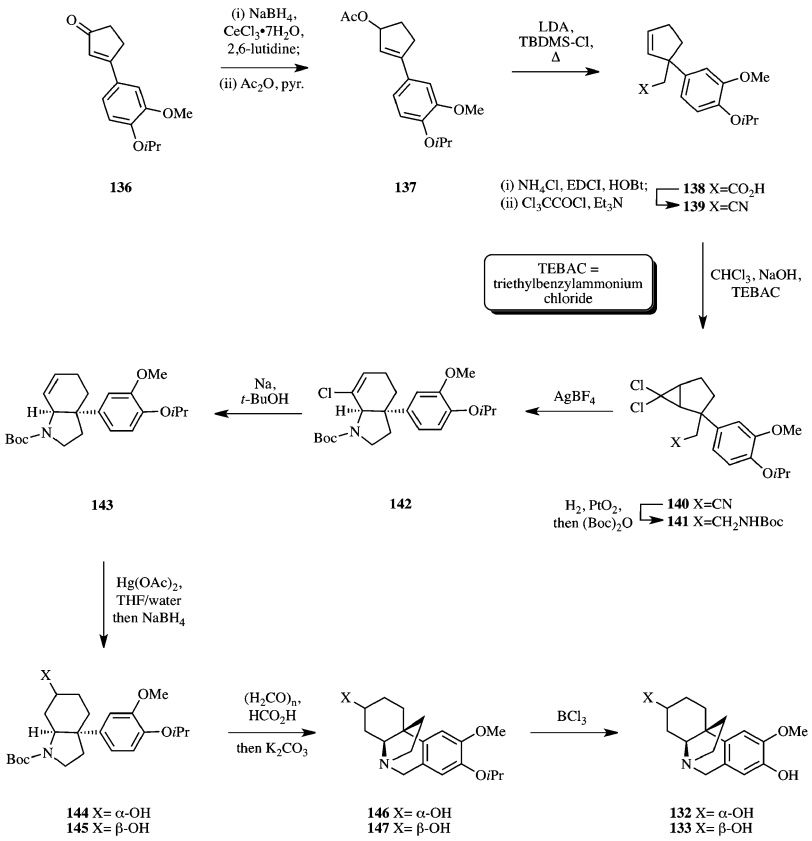
The crinine alkaloids, which can embody either enantiomeric form of the 2,3,4,4a-tetrahydro-1*H*-6*H*-5,10b-ethanophenanthridine framework, represent an important sub-class within the Amaryllidaceae alkaloid family [53]. Many members of this subclass display interesting biological properties including immuno-stimulatory, cytotoxic and anti-malarial activities. As a consequence, they have been the subject of numerous synthetic studies [53].

The key substructure associated with such systems is a C3a-arylpolyhydroindole residue and, as shown in the three examples presented below, upon subjection of such species to a Pictet–Spengler reaction the full tetracyclic framework of the crinine alkaloids is established. Accordingly, this approach has been widely adopted in establishing total syntheses of such natural products. Our syntheses of the racemic modifications of maritinamine (**132**), *epi*-maritinamine (**133**) and haemultine (**134**) as well as *ent*-amabiline (**135**) (Gao et al., unpublished work; [54], [55]) serve to highlight three quite distinct approaches to the C3a-arylpolyhydroindole substructure. Two of these approaches exploit ring-fused *gem*-dihalogenocyclopropanes as early or mid-stage intermediates.



132 **133** **134** **135**

The synthetic route used to access the alkaloids **132** and **133** is shown in Scheme 12 [54] and begins with conversion of the readily available β-arylated cyclopentenone **136** into the corresponding allylic acetate **137** (98%) that was subjected to an Ireland–Claisen rearrangement reaction, thereby affording the propionic acid derivative **138** (83%). Conversion of this last compound, via dehydration of the derived primary amine, into the corresponding nitrile **139** provided the substrate for a dichlorocarbene addition reaction that delivered a ca. 1:1 diastereoisomeric mixture of the ring-fused cyclopropane **140** (38%). Reduction of the nitrile group within the last compound, protection of the resulting

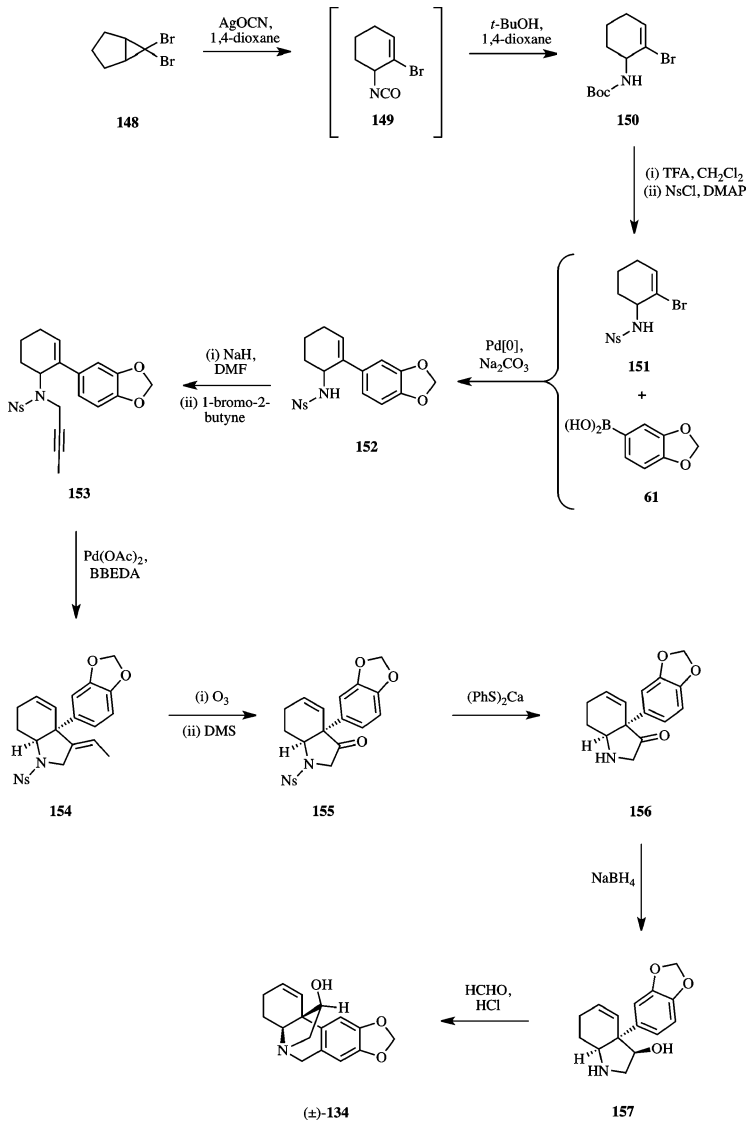


Scheme 12 Total syntheses of (±)-maritinamine [(±)-**132**] and (±)-*epi*-maritinamine [(±)-**133**]

primary amine as the corresponding *tert*-butyl carbamate **141** (75%) and treatment of this with silver tetrafluoroborate resulted in electrocyclic ring-opening of the three-membered ring followed by intramolecular trapping of the ensuing π-allyl cation by the pendant nitrogen and thus generating the desired C3a-arylated hexahydroindole **142** (65–75%). Treatment of compound **142** under Bouveault–Blanc-type reduction conditions and subjection of the ensuing dechlorinated olefin **143** (98%) to a regio- but non-stereocontrolled oxymercuration/demercuration protocol provided a chromatographically separable mixture of alcohols **144** (25%) and **145** (71%). Independent subjection of each of compounds **144** and **145** to reaction with paraformaldehyde in the presence of formic acid resulted in cleavage of the carbamate residues and a subsequent Pictet–Spengler reaction gave, after work-up with potassium carbonate (of the resulting secondary amine), the required pentacyclic species **146** (72%) and **147** (58%), respectively. Treatment of each of these with boron trichloride resulted in selective cleavage of the isopropyl ether residues and the formation of the target crinines **132** (70%) and **133** (70%), respectively.

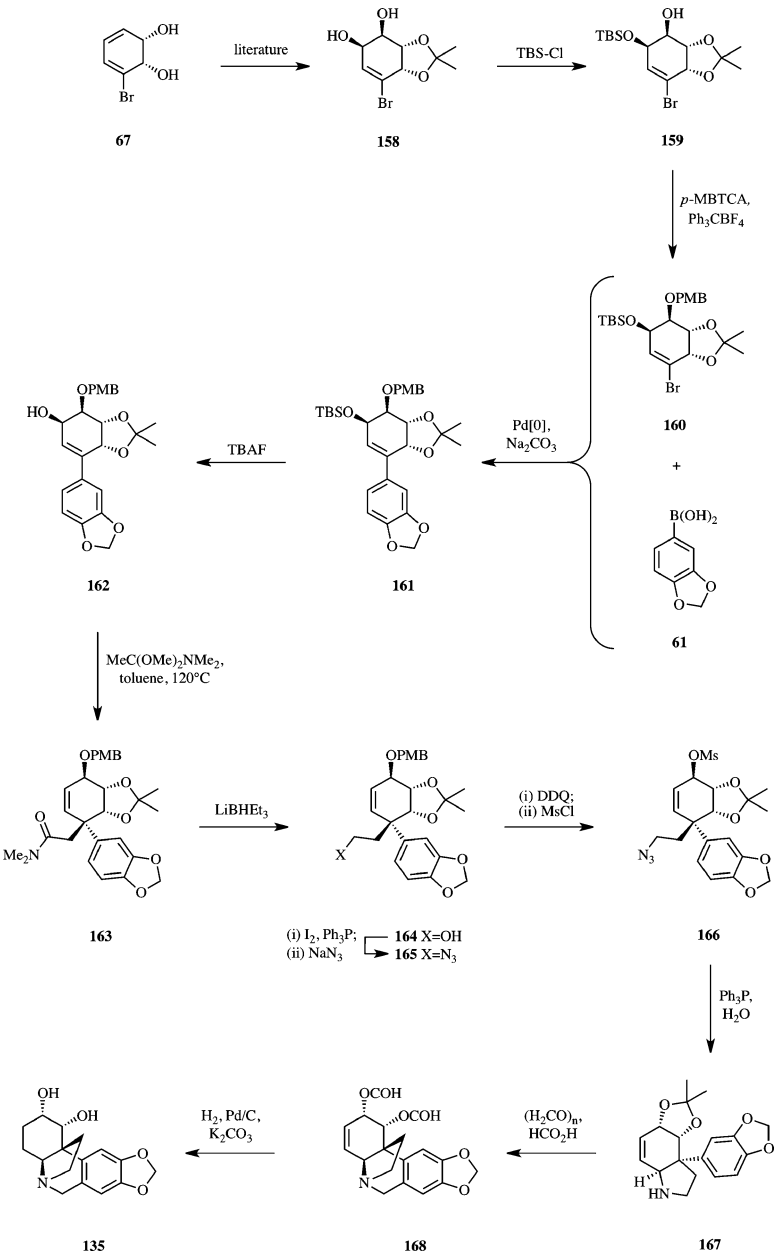
We have employed another cyclopropane-based approach to the synthesis of the crinine alkaloids in seeking to prepare the natural product haemultine that, somewhat controversially, has been assigned structure **134**. Haemultine has not been the subject of any total synthesis studies and this is probably because the preparation of systems containing oxygenation in the C-ring has been rather challenging. The reaction sequence used in accessing the racemic form of compound **134** is shown in Scheme 13 (Gao et al., unpublished work) and involves, as the first step, treatment of the readily available, ring-fused cyclopropane **148** with silver cyanate and thereby affording and after cleavage of the three-membered ring and trapping of the resulting π-allyl cation, the isocyanate **149**. This was not isolated but intercepted with added *tert*-butanol to give the carbamate **150** (79%). Acid-catalysed cleavage of the Boc group followed by reaction of the resulting primary amine with nosyl chloride afforded the sulfonamide **151** (87%) that was subjected to a Suzuki–Miyaura cross-coupling reaction with the aryl boronic acid **61** and so affording the cyclohexene **152** (77%). Sequential treatment of the last compound with sodium hydride and then 1-bromobut-2-yne afforded the secondary amine-based sulfonamide **153** (86%) that readily participated in an intramolecular Alder-ene reaction on treatment with 5 mol% $Pd(OAc)_2$ in refluxing benzene and in the presence of the strong σ-donating ligand *N*,*N*′-bis(benzylidene)ethylenediamine (BBEDA) [56]. As a result the C3a-arylhexahydroindole derivative **154** was obtained in 94% yield. Brief exposure of this compound to ozonolysis followed by a work-up with dimethylsulfide (DMS) then gave the ketone **155** (33%), the structure of which was confirmed by single-crystal X-ray analysis. Treatment of the latter compound with thiophenolate anion resulted in cleavage of the nosyl group and formation of the rather unstable amino-ketone **156**. As a consequence it was immediately subjected to reduction with sodium borohydride and this gave the amino-alcohol **157** in 56% yield and as a single diastereoisomer. Treatment of compound **157** with formaldehyde in the presence of hydrochloric acid then delivered, via a Pictet–Spengler reaction, the target compound (±)-**134** (70%) the structure of which was confirmed by single-crystal X-ray analysis. Efforts are now underway to resolve this material into its constituent enantiomers and once this is achieved and the specific rotations of these are determined it should be possible to establish whether one of them matches the natural product haemultine.

A quite distinct approach to C3a-arylhexahydroindoles, and thence crinanes, is highlighted in a synthesis of (+)-amabiline (**135**), the non-natural form of the alkaloid, that we reported in 2009 [55]. Thus, as shown in Scheme 14, the enantiomerically pure *cis*-1,2-dihydrocatechol **67** was converted, over two standard steps, into the known diol **158** (85%) that was, in turn, subjected to selective mono-O-silylation with TBS-Cl to give the homoallylic alcohol **159** (95%). Treatment of compound **159** with *p*-methoxybenzyl trichloroacetimidate (*p*-MBTCA) in conjunction with trityl tetrafluoroborate effected protection of the remaining hydroxyl group without inducing loss of the TBS group and thereby affording the cyclohexenyl bromide **160** (98%). This last compound engaged in a Suzuki–Miyaura cross-coupling reaction with boronic acid **61** to give the arylated cyclohexene **161** (90%) that upon treatment with tetra-*n*-butylammonium fluoride



Scheme 13 Total synthesis of the racemic form of the structure assigned to haemultine (**134**)

(TBAF) gave the allylic alcohol **162** (94%). Subjection of compound **162** to an Eschenmoser–Claisen rearrangement using *N*,*N*-dimethylacetamide dimethylacetal in toluene afforded the expected amide **163** (95%) that upon treatment with lithium triethylborohydride gave the primary alcohol **164** (94%) which was transformed, by standard methods, into the corresponding azide **165** (85%). Conversion of the PMB ether moiety within compound **165** into the corresponding mesylate **166** followed by Staudinger reduction of the azide residue within this last compound presumably



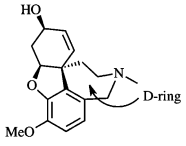
Scheme 14 Total synthesis of (+)-amabiline (**135**)

gave the corresponding primary amine but this immediately engaged in an intramolecular S_N' reaction and thereby affording the C3a-arylhexahydroindole **167** (64%). Treatment of the last compound treatment with paraformaldehyde in the

presence of formic acid effected a Pictet–Spengler reaction and thus forming the (bis)-formate ester **168**. The target **135** was finally generated, in 65% overall yield from **167**, by treating compound **168** with dihydrogen in the presence of palladium on carbon and potassium carbonate, thereby effecting both ester hydrolysis and hydrogenation of the D-ring double bond.

3.5 Galanthamine

The alkaloid galanthamine (**169**) has been obtained from various Amaryllidaceae species including daffodils, the red spider lily (*Lycoris radiata*) and the Caucasian snowdrop (*Galanthus woronowii*). Its effectiveness as a centrally acting, selective, reversible and competitive inhibitor of acetylcholinesterase has resulted in galanthamine being introduced into the clinic in both the USA and Europe for the symptomatic treatment of mild to moderate forms of Alzheimer's disease [57]. These and various other intriguing features of this alkaloid have prompted extensive synthetic studies of it [57].



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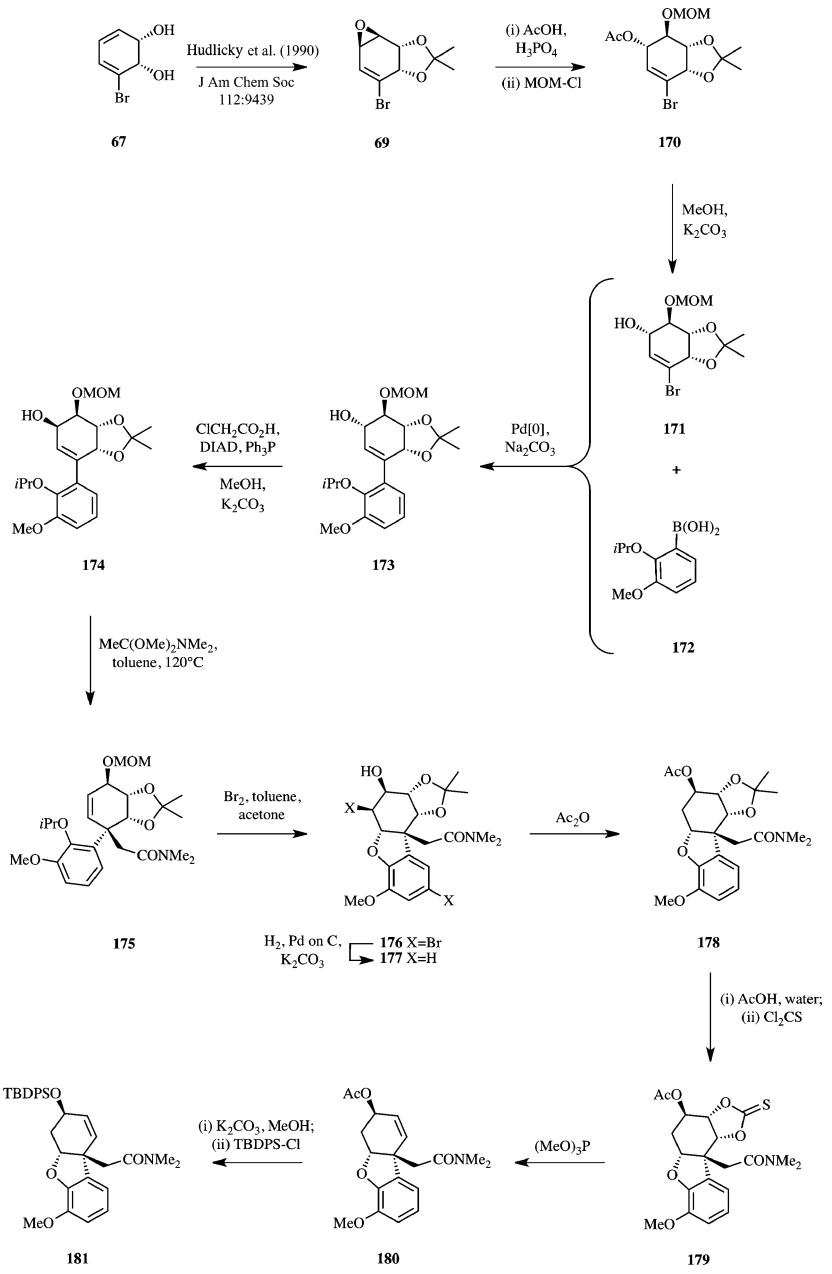
The outcomes of our own efforts in the area [58], which have led to a synthesis of the non-natural enantiomeric form of galanthamine (i.e. *ent*-**169**), are shown in Schemes 15 and 16. Once again, the reaction sequence starts with the versatile *cis*-1,2-dihydrocatechol **67** which is converted, using the well-established two-step protocol shown in the first part of Scheme 6, into epoxide **69**. Treatment of the latter compound with acetic acid in the presence of phosphoric acid gave a *trans*-diol mono-acetate that upon treatment with MOM-Cl afforded the anticipated and fully protected compound **170** (74% from **69**). Suzuki–Miyaura cross-coupling of the product of acetate hydrolysis, namely cyclohexenyl bromide **171**, with the readily prepared arylboronic acid **172** afforded the expected cross-coupling product **173** (94%) that was subjected to a Mitsunobu inversion process, thus delivering, after hydrolysis of the intermediate α-chloroacetate, the epimeric alcohol **174** (93%). The latter compound readily participated in the same type of Eschenmoser–Claisen rearrangement reaction used in the conversion **162** → **163** (Scheme 14), thereby affording amide **175** (89%) incorporating the critical quaternary carbon-centre associated with the target natural product. Treatment of compound **175** with molecular bromine in a mixture of toluene and acetone afforded, via a bromonium ion-mediated cyclisation, the furannulated compound **176** (93%) that was readily debrominated upon exposure to dihydrogen in the presence of palladium on carbon and potassium carbonate. Acetylation of the ensuing alcohol **177** (68%)

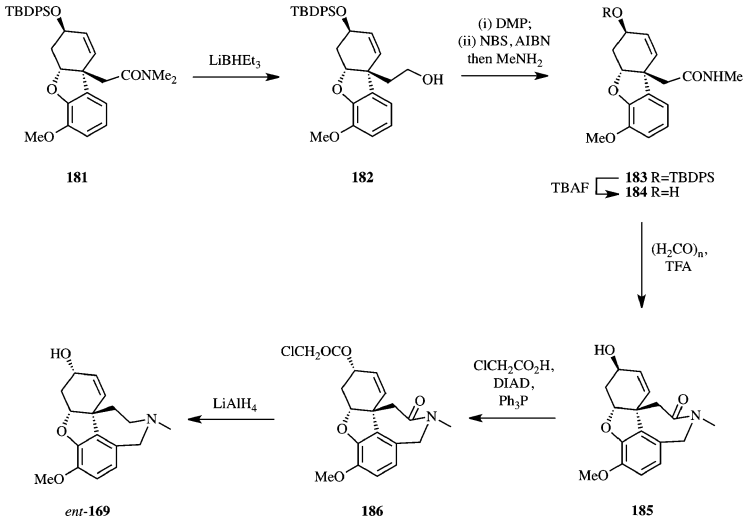


Scheme 15 Synthesis of the ABC-ring system associated with *ent*-galanthamine (*ent*-**169**)

under standard conditions afforded ester **178** (90%) that was subjected to acetonide hydrolysis using aqueous acetic acid. The ensuing diol was converted into the corresponding thiocarbonate **179** (94%) that was, in turn, subjected to a Corey–Winter

reaction using trimethylphosphite and thereby delivering the cyclohexene **180** (72%). In anticipation of the manipulation of the amide unit within this last system, the acetate was converted into the corresponding TBDPS ether **181** (81%) by standard methods.

The completion of the synthesis of (+)-galanthamine from ether **181** clearly requires construction of the D-ring of the target. To that end, compound **181** (Scheme 16) was treated with lithium triethylborohydride and thus providing the 1°-alcohol **182** (95%). Successive treatment of this last compound with Dess–Martin periodinane (DMP) and *N*-bromosuccinimide (NBS) in the presence of AIBN gave an intermediate acyl bromide that was intercepted with added methylamine and thus affording amide **183** (78%). Removal of the TBDPS group within this last compound and subjection of the resulting alcohol **184** to a Pictet–Spengler reaction conditions gave, after work-up under basic conditions, the lactam **185** (75%). Subjecting this compound to reaction with α-chloroacetic acid under Mitsunobu conditions gave the expected ester **186** (93%) that upon treatment with lithium aluminium hydride afforded the final target (+)-galanthamine (*ent*-**169**) in 85% yield.



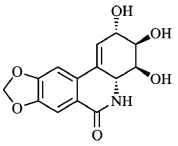
181 182 183 R=TBDPS 184 R=H 185 186 *ent*-169

Scheme 16 Completion of a total synthesis of ent-galanthamine (*ent*-**169**)

This first generation synthesis of (+)-galanthamine should be capable of considerable refinement, especially in regards to the protecting group regimes employed and the manner in which the heterocyclic D-ring is constructed. Furthermore, since the enantiomer of the starting material **67** is available, the illustrated chemistry also allows access to (−)-galanthamine (**169**). As such, a plethora of galanthamine analogues is available in either enantiomeric form and these will be subjected to evaluation as inhibitors of acetylcholinesterase. In addition, the application of this chemistry to the synthesis of the structurally related morphine alkaloids is now under investigation.

3.6 The Narcissus Alkaloids

The *Narcissus* "alkaloids" lycoricidine (**187**), narciclasine (**188**) and pancratistatin (**189**) have attracted considerable attention because of their intriguing range of properties including a capacity to inhibit protein synthesis and, thence, serve as anti-viral as well as selective cytotoxic agents [59, 60]. These compounds also display potent growth regulating and/or insect antifeedant activities. Such features, coupled with the limited availability of these compounds from their natural sources, have prompted extensive studies concerned with their synthesis. We have developed two distinct approaches to lycoricidine, narciclasine and various analogues and these are now described [61–63]. Once again, one of these relies on cyclopropane chemistry while the other exploits enantiomerically pure *cis*-1,2-dihydrocatechols as starting materials.



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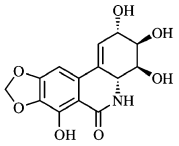

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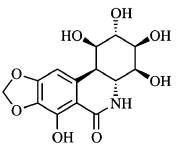
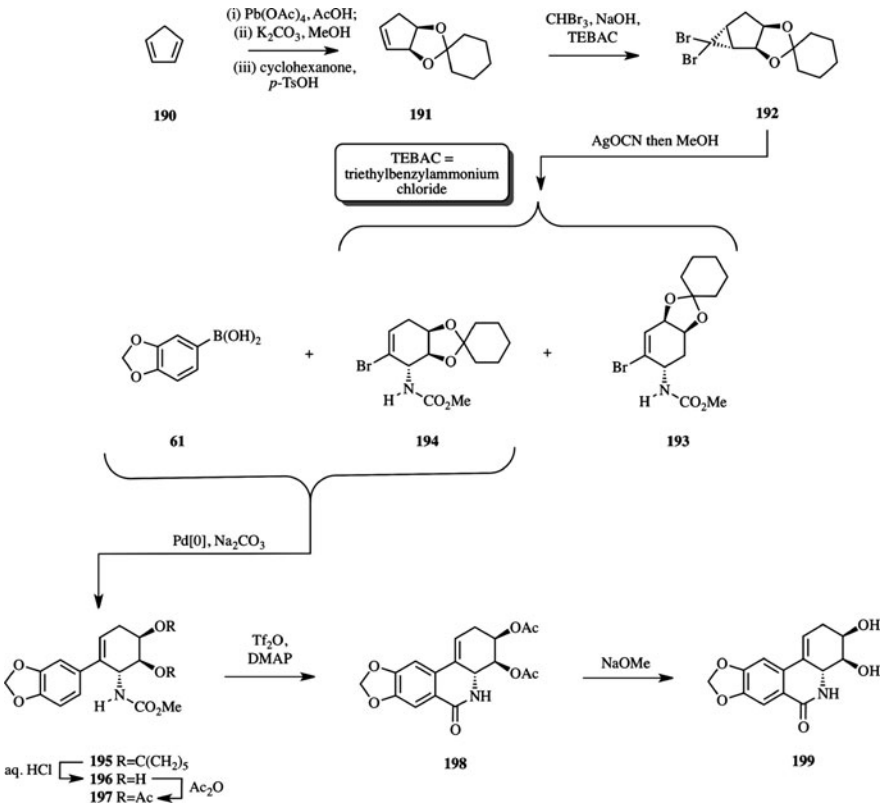


189

The cyclopropane-based route [61] to various lycorine and pancratistatin analogues is shown in Scheme 17 and starts with the conversion of cyclopentadiene (**190**) into the ketal **191** (70%) via sequential treatment of the former compound with lead tetraacetate in acetic acid, methanolic potassium carbonate and then cyclohexanone in the presence of *p*-TsOH. Addition of dibromocarbene to cyclopentene **191** afforded the *gem*-dibromocyclopropane **192** (84%) that upon treatment with silver cyanate and then methanol gave a chromatographically separable mixture of the allylic carbamates **193** (28%) and **194** (40%). Suzuki–Miyaura cross-coupling of the latter product with aryl boronic acid **61** afforded the expected arylated cyclohexene **195** (82%) that was subjected to acid-catalysed ketal group hydrolysis and the ensuing diol **196** was then reprotected as the corresponding diacetate **197** (89%). Treatment of this last compound with a combination of triflic anhydride and DMAP in dichloromethane at 0–15 °C effected a Bischler–Napieralski cyclisation reaction under remarkably mild conditions, thus affording, after acid-catalysed hydrolysis of resulting imidates, lactam **198** (85%), the structure of which was established by single-crystal X-ray analysis. Treatment of compound **198** with sodium methoxide in THF/methanol then gave the racemic modification of 2-deoxylycoricidine (**199**) (96%).

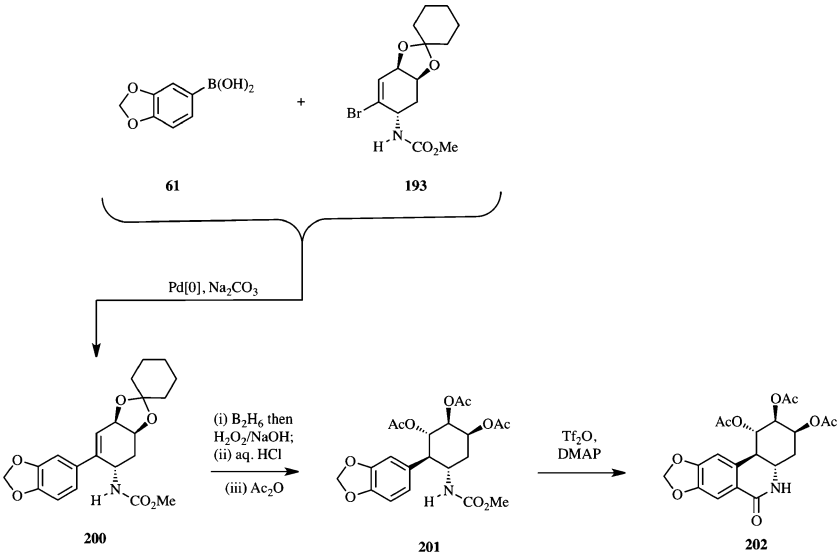
The allylic carbamate **193** formed as shown in Scheme 17 can be exploited in the synthesis of a pancratistatin analogue. Thus, Suzuki–Miyaura cross-coupling of this carbamate with aryl boronic acid **61** (Scheme 18) afforded the expected arylated cyclohexene **200** (87%) that upon sequential treatment with diborane, alkaline hydrogen peroxide, aqueous acid then acetic anhydride gave the triacetate **201** (42%). Subjecting this last compound to the Bischler–Napieralski reaction



Scheme 17 Synthesis of the racemic modification of 2-deoxylycoricidine (**199**)

conditions used for the conversion **197** → **198** then afforded the second targeted analogue, namely the triacetate **202** (59%).

A distinctly different approach to the *Narcissus* alkaloids is shown in Scheme 19 [62, 63] and started with the ever-useful *cis*-1,2-dihydrocatechol **67** that was first converted into the PMP-acetal **203** (85%) under standard conditions. Dihydroxylation of diene **203** under the Upjohn [50] conditions afforded diol **204** that was then converted into the (bis)-MOM ether **205** (59% from **203**). Reductive cleavage of the acetal moiety within the last compound could be accomplished using DIBAl-H and the alcohol **206** (84%) so formed was protected as the corresponding MOM ether **207** (90%). DDQ-mediated cleavage of the PMB ether unit within this last compound then gave the mono-ol **208** (95%) that was subjected to an Overman rearrangement reaction and thereby giving the corresponding acetamide (65%). This was then cleaved to the corresponding amine **209** (89%) by treatment with DIBAl-H. Suzuki–Miyaura cross-coupling of this last compound with the readily available arylboronic acid **210** afforded, after spontaneous lactamisation of the intermediate amino-ester, the (tris)-MOM ether **211** (83%) of the non-natural enantiomer of lycoricidine. Treatment of compound **211** with



Scheme 18 Synthesis of the lycoricidine analogue **202**

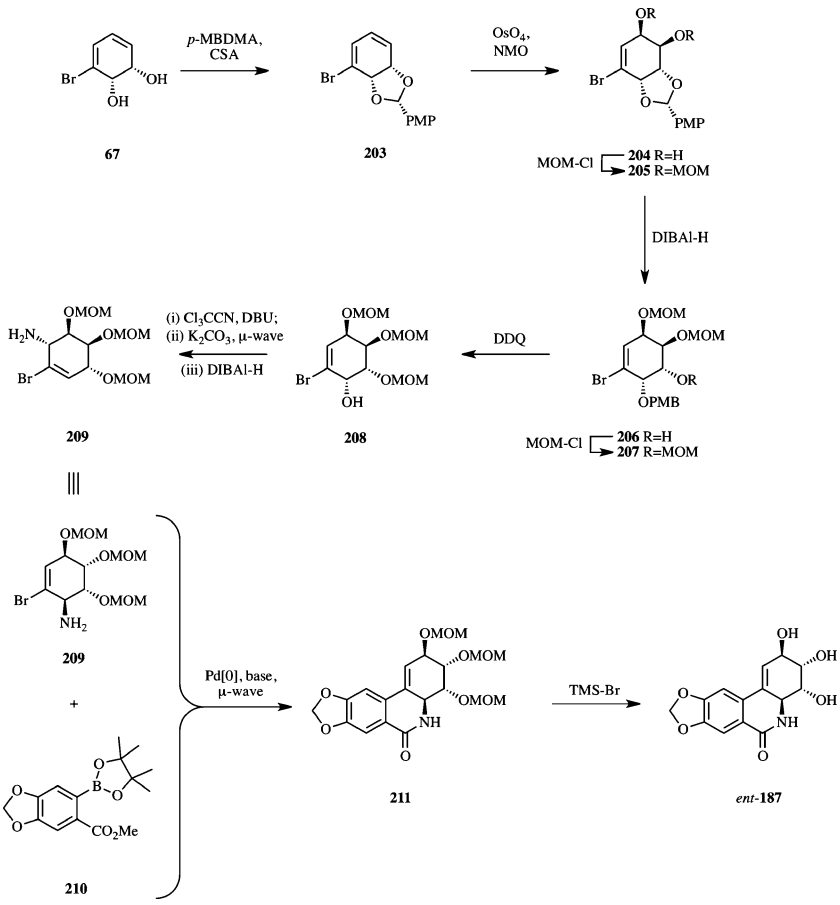
TMS-Br effected exhaustive cleavage of MOM ethers and thus afforded *ent*-lycoricidine (*ent*-**187**) (62%) the structure of which was confirmed through a single-crystal X-ray analysis of the derived triacetate.

A simple modification of the reaction sequence shown above has allowed for the synthesis of *ent*-narciclasine (*ent*-**188**). Thus, as shown in Scheme 20, Suzuki–Miyaura cross-coupling of the previously prepared 2-bromocyclohex-2-enamine **209** with the readily synthesised aryl boronic acid **212** afforded the expected lactam **213** (63%). Once again, treatment of the last compound with TMS-Br resulted in exhaustive cleavage of the MOM ether residues and, this time, the formation of the target compound *ent*-**188** (48%).

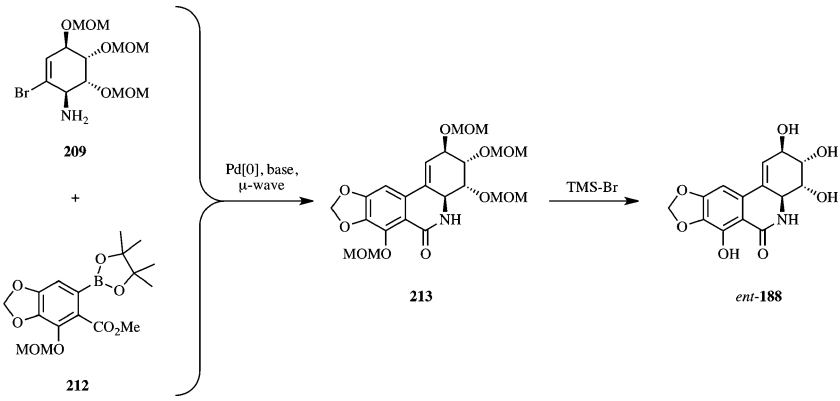
Compounds *ent*-**187** and *ent*-**188**, as well as several analogues available using chemistry similar to that shown in Schemes 19 and 20, have been evaluated for their cytotoxic effects in a 13-member human cancer cell-line panel and found to be only weakly active [64]. In contrast, an authentic sample of the natural enantiomeric form of narciclasine (**188**) was found to be highly active in the same screens.

4 The Erythrina Alkaloids

The *Erythrina* alkaloids represent a group of natural products isolated from various species of plants of the same name and found in tropical and sub-tropical regions of the world. They are all spirocyclic isoquinoline alkaloids and found in all parts of

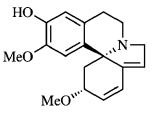


Scheme 19 Total synthesis of *ent*-lycoricidine (*ent*-**187**)



Scheme 20 Total synthesis of *ent*-narciclasine (*ent*-**188**)

the source plants. Various substructural types are encountered within the class, the most common of which are represented by erysodine (**214**) (an erythrinadiene) and erythratine (**215**) (an erythrinene) that differ, inter alia, in the degrees and arrangements of unsaturation within the five-membered and cyclohexane rings [65]. These types of alkaloids exhibit a range of fascinating properties including curare-like activities, as well as hypotensive, diuretic, laxative, sedative and CNS-depressive properties. Not surprisingly, then, they have been the subjects of numerous synthetic studies. Our own efforts in the area have focussed on the synthesis of the non-natural enantiomer of erythramine (**216**) ([66]; for a summary of other synthetic endeavours in this area see [67]). As with a number of the studies described above, the underpinning technology used in obtaining *ent*-erythramine is the electrocyclic ring-opening of a ring-fused *gem*-dihalocyclopropane and trapping of the ensuing π-allyl cation by a pendant nucleophile.



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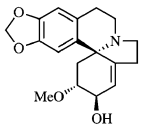

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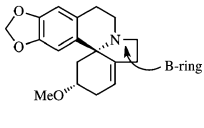
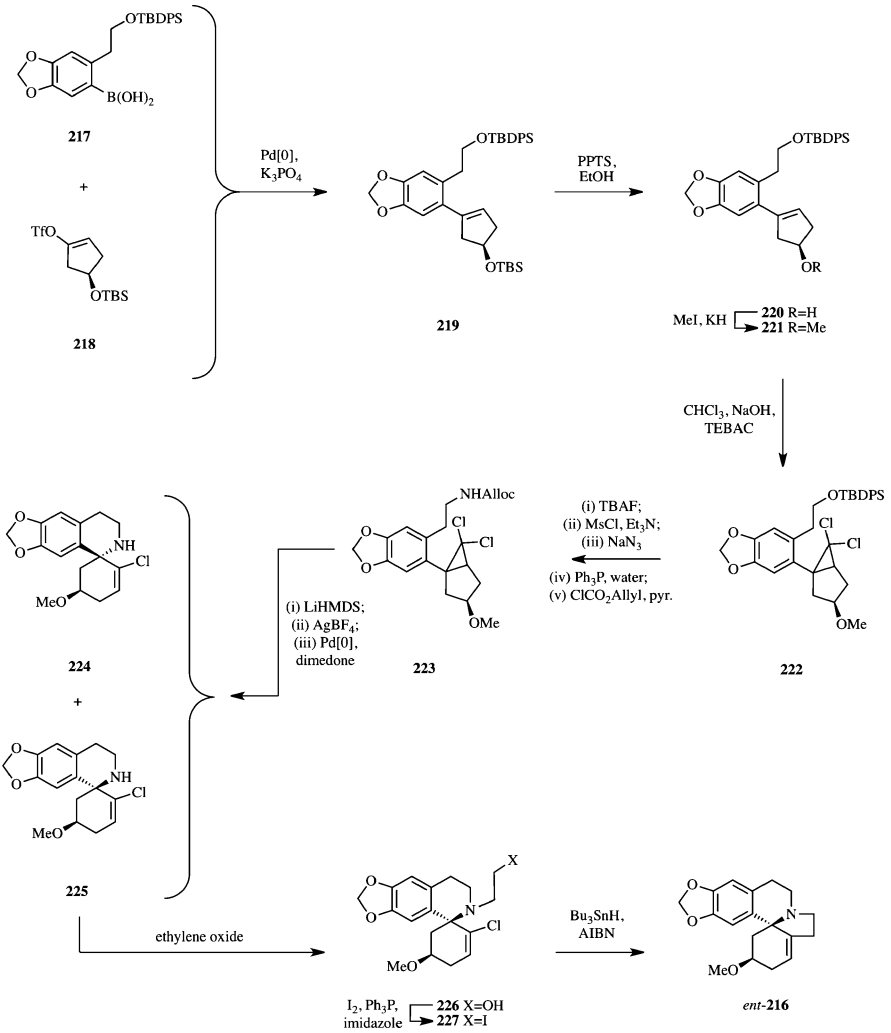


216

The reaction sequence used in obtaining *ent*-erythramine (*ent*-**216**) is shown in Scheme 21 and begins with the Suzuki–Miyaura cross-coupling of the readily available aryl boronic acid **217** with the enantiomerically pure cyclopentene **218** that is generated, using chemoenzymatic techniques, from cyclopentadiene. Selective cleavage of the TBDMS ether within the coupling product **219** (92%) could be accomplished using pyridinium *p*-toluenesulfonate (PPTS) in ethanol and the ensuing alcohol **220** (71%) was O-methylated with methyl iodide in the presence of potassium hydride to give ether **221** (quant.). Subjection of this last compound to reaction with dichlorocarbene gave ca. 2:1 mixture of diastereoisomeric forms of the *gem*-dichlorocyclopropane **222** (91%). A five-step reaction sequence was used to convert the side-chain TBDPS ether within this last compound into the corresponding Alloc-protected primary amine. Thus, compound **222** was desilylated using TBAF and the ensuing alcohol converted into the corresponding mesylate that was treated with sodium azide, thereby affording the expected azido-compound. Staudinger reduction of this last species and reaction of the ensuing primary amine with allyl chloroformate afforded the key sub-target **223** (87% overall yield from **222**). In the first of two key reactions associated with the synthesis, compound **223** was first treated with LiHMDS and then silver tetrafluoroborate. By such means the required ring-cleavage/spirocyclisation process took place and after treatment of the resulting product mixture with Pd[0] in the presence of dimedone (to effect cleavage of the Alloc-protecting group) a chromatographically separable mixture of the diasteroisomeric spirocycles **224** (30%) and **225** (26%) was obtained. For the purpose of installing the B-ring of the target alkaloid, compound **225** was treated

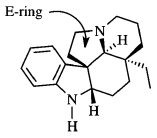


Scheme 21 Total synthesis of *ent*-erythramine (*ent*-**216**)

with ethylene oxide and the resulting amino-alcohol, the structure of which was confirmed by X-ray analysis, was treated with molecular iodine triphenylphosphine and imidazole. The iodide **226** (44%) so formed was reacted with tri-*n*-butyltin hydride and AIBN and thereby inducing a radical addition/elimination sequence analogous to that involved during the conversion **112** → **113** (Scheme 10) with the result that *ent*-erythramine (*ent*-**216**) was generated in 89% yield. The biological evaluation of this compound and related ones is currently underway.

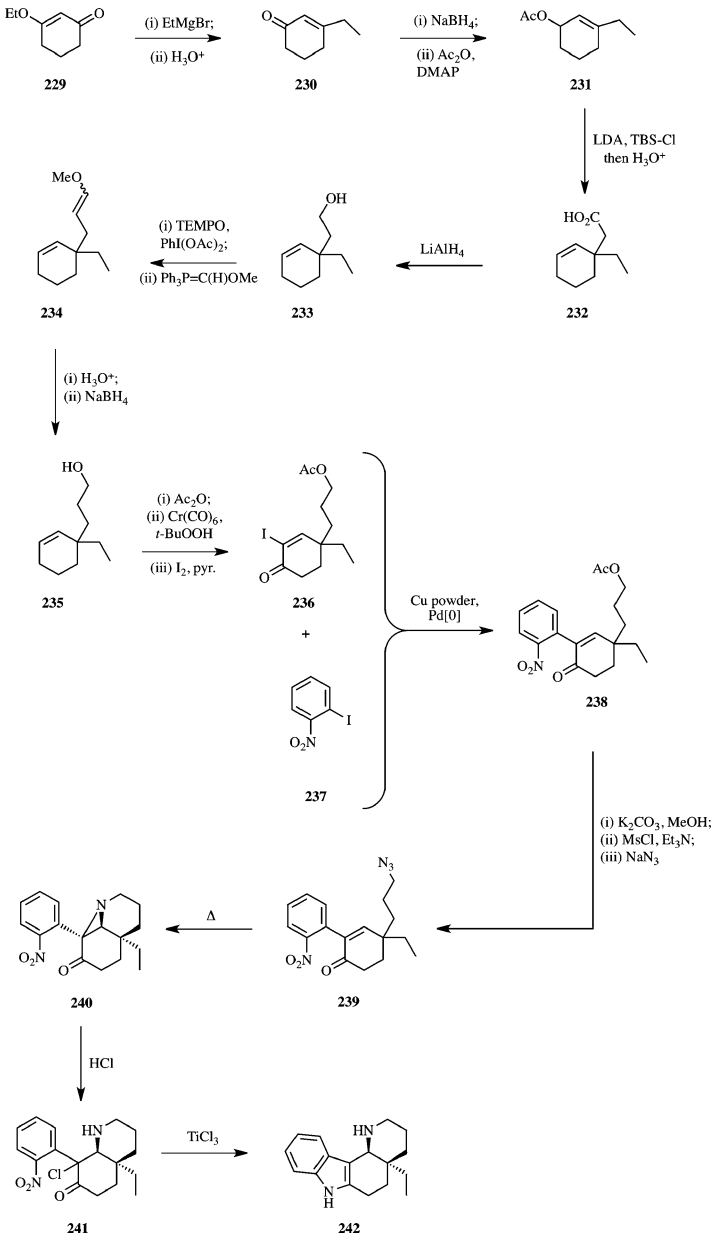
5 Aspidospermidine

The *Aspidosperma* alkaloids are a group of more than 100 monomeric and dimeric monoterpene indole alkaloids with aspidospermidine (**228**) representing a key member of the class and sometimes considered to be the parent [68]. Numerous total syntheses of this pentacyclic compound have been reported. Our own contributions in the area were prompted by the discovery of a new method for preparing indoles via a palladium-catalysed Ullmann cross-coupling reaction that proceeds especially efficiently at close to room temperature [69] and which we felt could serve as the centrepiece in developing a new synthesis of compound **228** and, in the longer term, syntheses of dimeric members of the indole alkaloid class such as the clinically significant alkaloids vinblastine and vincristine.



228

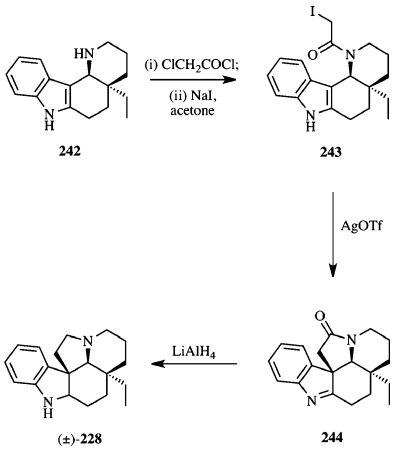
The early to middle stages of the route that we have used in synthesising target **228** are shown in Scheme 22 ([70]; for a summary of other synthetic endeavours in this area see [71]) and involve the initial conversion of commercially available 3-ethoxycyclohexenone (**229**) into 3-ethylcyclohexenone (**230**) (89%) by standard methods. Sodium borohydride-mediated reduction of the latter compound and acetylation of the resulting allylic alcohol gave the allylic acetate **231** (96%) that readily engaged in an Ireland–Claisen rearrangement to give the carboxylic acid **232** (62%) incorporating the quaternary carbon centre required in the final target. Chain extension of compound **232** was achieved by first reducing the carboxylic acid residue to the corresponding alcohol **233** (96%), oxidising this to the aldehyde followed by engaging that in a Wittig reaction with (methoxymethylene)triphenylphosphorane to give the enol ether **234** (92%). Compound **234** was then converted, over two simple steps, into the alcohol **235** (84%) representing the higher homologue of compound **233**. Acetylation of compound **235** followed by an allylic oxidation using a mixture of $Cr(CO)_6$ and *t*-BuOOH gave the corresponding enone (65%) that, in anticipation of the foreshadowed Pd[0]-catalysed Ullmann reaction, was subjected to a Johnson-type α-iodination reaction using molecular iodine in the presence of pyridine. The α-iodoenone **236** (quant.) so formed was subjected to reaction with *o*-nitroiodobenzene (**237**) in the presence of copper powder and Pd[0]. This afforded the cross-coupled product **238** (75%). The acetate residue within compound **238** was converted, over three very conventional and reliable steps, into the corresponding azide **239** (87%) and heating of this in refluxing benzene resulted in the intramolecular 1,3-dipolar cycloaddition of the azide residue onto the pendant enone followed by extrusion of dinitrogen from the resulting triazoline to give the ring-fused aziridine **240** (72%). Treatment of this last



Scheme 22 Synthesis of the ABCD-ring system associated with aspidospermidine (**228**)

compound with HCl then afforded the α-chloroenone **241** (as its hydrochloride salt). Reaction of compound **241** with titanium trichloride (in the form of its THF solvate) resulted in reductive dechlorination and reductive cyclisation reactions and thereby generating indole **242** (46% from **240**).

The completion of the synthesis of aspidospermidine relied on a protocol introduced by Heathcock [72] for annulating the E-ring to the ABCD-framework of **228**. Thus, as shown in Scheme 23, acylation of target compound **242** with α-chloroacetyl chloride followed by a Finkelstein reaction afforded the α-iodoacetamide **243** that upon treatment with silver triflate effected an intramolecular alkylation reaction and the formation of the isoindole-based lactam **244**. Finally, reduction of this last compound with lithium aluminium hydride gave the racemic modification of aspidospermidine (**228**) (32%).



242 243 (±)-228 244

Scheme 23 Completion of a total synthesis of (±)-aspidospermidine [(±)-**228**]

Given that the *S-enantiomer* of compound **233** is readily available in essentially enantiomerically pure form the work shown above constitutes a formal total synthesis of the unnatural or (−)-enantiomer of the title alkaloid. Since the alcohol *R*-**233** will almost certainly be available by closely related means, the chemistry presented here should also allow access to the naturally occurring enantiomeric forms of various *Aspidosperma* alkaloids.

6 Conclusion

An underpinning feature associated with many of the reaction sequences described above is the generation of a 2- or 3-halogenated 2-cyclohexen-1-ol moiety from a ring-fused *gem*-dihalocyclopropane or a *cis*-1,2-dihydrocatechol. This emphasis arises because of the exceptional synthetic utility of this moiety. In particular, the capacity to engage it (or its derivatives) in cross-coupling reactions, radical addition-elimination processes and/or Claisen- or Overman-type rearrangements means that it can be exploited in an extraordinarily diverse range of settings and thus serve as a precursor to a remarkable range of structures. In this context the

α-iodocyclohexenone **236** (Scheme 22), a pivotal precursor to aspidospermidine, can be viewed as a 2-halogeno-2-cyclohexen-1-ol derivative and one that readily engages in cross-coupling reactions. It is also worth noting that the double bond embedded within such cross-coupling products (e.g. **238**, Scheme 22) has, by virtue of the attachment of the strongly electron-withdrawing carbonyl and nitrophenyl groups at the same end of it, some potentially very useful electrophilic properties that should be capable of exploitation in various contexts.

On the face of it, the utilisation of cyclohexane-1,3-dione (**121**) as shown in Scheme 11 does not appear to fit the analysis presented immediately above. However, by virtue of its participation in the illustrated Michael addition reaction (**120** + **121** → **122**) and the subsequent manipulation of adduct **122** (equivalent to a cross-coupling product) compound **121** could legitimately be viewed as a synthetic equivalent for a 2-halogeno-2-cyclohexen-1-ol. The chemical efficiency of the Michael addition reaction is notable and suggests a greater utility for this process than has been realised so far.

The availability of the *cis*-1,2-dihydrocatechols in enantiomerically pure form has meant that, thus far, they have proven somewhat more useful as precursors to alkaloids than the *gem*-dihalocyclopropanes. However, that situation could well change if such systems were also available in scalemic form. Addressing this matter is the subject of ongoing work in our laboratories.

7 Notes Added in Proof

1. MacMillan has recently described concise and enantioselective syntheses of strychnine and several related alkaloids (S. B. Jones, B. Simmons, A. Mastracchio and D. W. C. MacMillan, *Nature*, 2011, **475**, 183);
2. Details of the synthesis of *ent*-clividine [*ent*-**52**] shown in Scheme 7 have now been published (L. V. White, B. D. Schwartz, M. G. Banwell and A. C. Willis, *J. Org. Chem.,* 2011, **76**, 6250)
3. Details of the synthesis of narseronine (**53**) shown in Scheme 9 have now been published (B. D. Schwartz, M. G. Banwell and I. A. Cade, *Tetrahedron Lett.,* 2011, **52**, 4526)

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Synthesis of Pyrrole and Carbazole Alkaloids

Ingmar Bauer and Hans-Joachim Knölker

Abstract An overview of recent transition metal-catalyzed syntheses of pyrroles and carbazoles is presented. The focus is on methods which have been applied to the preparation of biologically active naturally occurring pyrrole and carbazole alkaloids. For pyrroles, special attention is paid to silver(I)-catalyzed cyclization reactions. For carbazoles, iron(0)-mediated and palladium(0/II)-catalyzed cyclization reactions are highlighted and their broad range of applications is discussed.

Keywords Carbazoles · Iron · Oxidative cyclization · Palladium · Pyrroles · Silver

Contents

Abbreviations

ADP	Adenosine diphosphate
ATP	Adenosine triphosphate
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl

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CDK5	Cyclin-dependent kinase 5
DIBAL-H	Diisobutylaluminum hydride
DMDO	Dimethyldioxirane
dppp	1,3-Bis(diphenylphosphino)propane
ent	Enantiomeric
HIV	Human immunodeficiency virus
MTPA-Cl	α-Methoxy-α-trifluoromethylphenylacetyl chloride
NHC	*N*-Heterocyclic carbene
rac	Racemic
S-Phos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
TB	Tuberculosis
TBAF	Tetrabutylammonium fluoride
TON	Turnover number
TPS	*tert*-Butyldiphenylsilyl
X-Phos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

1 Introduction

Pyrroles represent an important class of biologically active heterocyclic compounds which are also of pharmacological interest. A large number of structurally diverse pyrrole, pyrroline, and pyrrolidine alkaloids is known [1–7]. As a subunit of the porphyrin framework, pyrroles are abundant in all aerobic organisms. Classical approaches to pyrroles include the Hantzsch, Knorr, and Paal–Knorr synthesis [8]. The biological importance of pyrroles prompted many research groups to develop new methods for their construction. In recent years, metal-mediated routes to pyrroles have been covered in several reviews [9–16]. Even though many elegant new pyrrole syntheses have been described, only a few have found broader application to the synthesis of naturally occurring pyrrole, pyrroline, and pyrrolidine alkaloids. Section 2 of the present review provides an outline of recent progress in metal-mediated pyrrole synthesis.

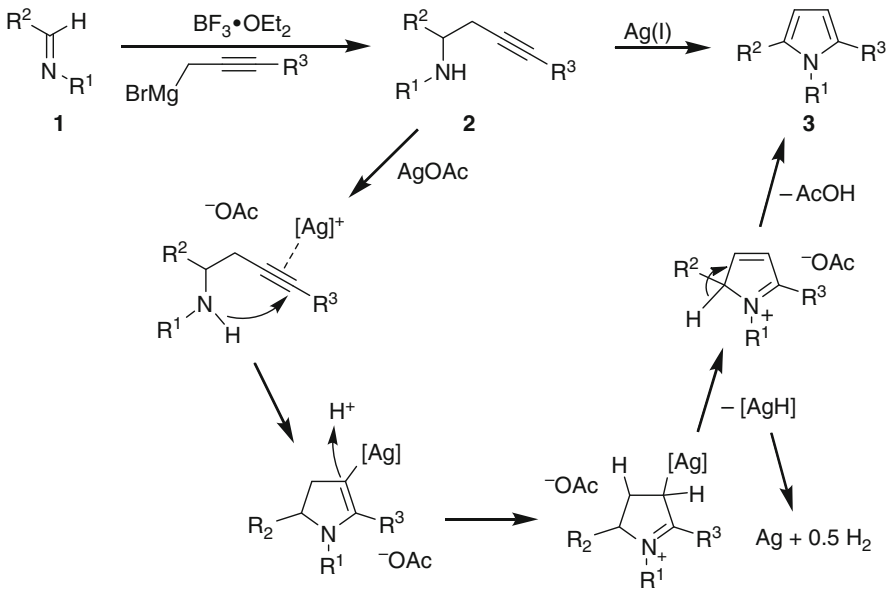
The pyrrole ring is also the central core of the carbazole framework. During the last four decades an increasing number of naturally occurring carbazole alkaloids has been described [17–20]. The majority of carbazoles originates from higher plants of the genera *Murraya*, *Glycosmis*, *Clausena*, and *Micromelum*, all from the family Rutaceae. Other sources are bacteria (e.g., *Streptomyces*), algae (e.g., *Hyella caespitosa*), and fungi (e.g., *Aspergillus* species). Due to their versatile biological activity, carbazoles have been the subject of extensive biological and chemical investigations during recent years. The range of their pharmacological effects includes anti-HIV, anti-TB, anti-malarial, anti-tumor, and neuronal cell protective activity. Our study of the anti-TB activity of carbazoles revealed that some compounds may be considered to be new lead structures for anti-TB agents [21–23]. Beyond classical approaches (for example the Fischer–Borsche, Graebe–Ullmann, and Cadogan syntheses), a variety of transition metal-catalyzed routes to carbazoles

has been developed. The present chapter also summarizes recent progress and applications from our laboratories as an update of previous reviews [19, 24, 25].

2 Synthesis of Pyrrole Alkaloids

2.1 Silver-Catalyzed Cyclization

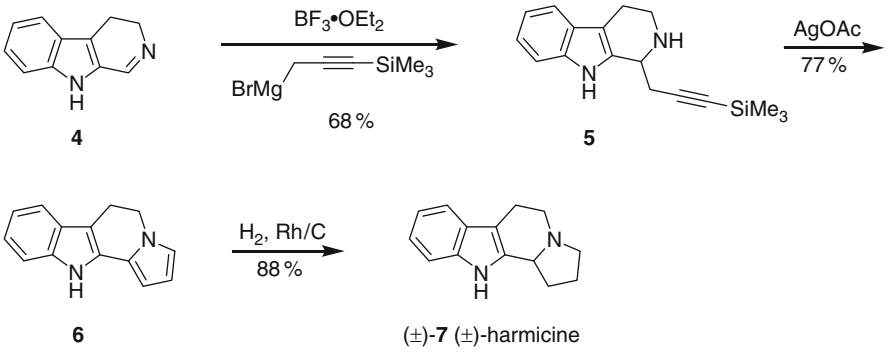
In 2004 we reported a novel silver-mediated oxidative cyclization of homopropargylamines **2** to pyrroles **3** (Scheme 1) [26]. The substrates **2** are easily available by addition of propargyl Grignard reagents to Schiff bases **1** (R^2 = aryl). If R^1 is not an acceptor group, silver(I) functions as an oxidant in the course of this reaction. Thus, stoichiometric amounts of silver(I) salts are consumed in the aromatization to the pyrroles **3**. The reaction is presumably induced by coordination of the alkyne to the silver(I) cation followed by an amino-argentation of the alkyne moiety, protonation of a vinylsilver(I) complex, β-hydride elimination to generate metallic silver and hydrogen, and a final deprotonation of the intermediate pyrrolium ion. For trimethylsilyl-substituted propargyl Grignard reagents (R^3 = $SiMe_3$), the trimethylsilyl group is lost by protodesilylation in the course of the cyclization process.



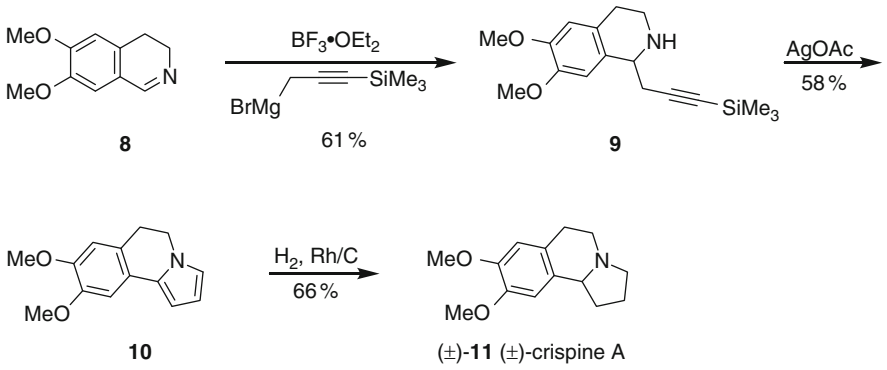
Scheme 1 Synthesis of pyrroles **3** from Schiff bases **1** by silver(I)-mediated oxidative cyclization of the homopropargylamines **2**

Using this method, we have synthesized the indolizino[8,7-*b*]indole alkaloid (±)-harmicine [(±)-**7**] [27]. (*R*)-(+)-Harmicine (**7**) was isolated in 1998 from the ethanol extract of the leaves of the Malaysian plant *Kopsia griffithii*, which shows anti-leishmania activity [28]. Our synthesis started from 3,4-dihydro-*β*-carboline (**4**) (Scheme 2). Addition of trimethylsilylpropargylmagnesium bromide afforded 1-(3-trimethylsilylpropargyl)-1,2,3,4-tetrahydro-*β*-carboline (**5**). Silver(I)-mediated oxidative cyclization of compound **5** afforded 5,6-dihydro-11*H*-indolizino[8,7-*b*]indole (**6**) with concomitant loss of the trimethylsilyl group. Finally, rhodium-catalyzed hydrogenation provided (±)-harmicine [(±)-**7**] in three steps and 46% overall yield.

Zhang et al. isolated the pyrrolo[2,1-*a*]isoquinoline alkaloid crispine A (**11**) from the extracts of the plant *Carduus crispus* [29]. Extracts of this plant have been used in traditional Chinese folk medicine for the treatment of cold, stomach ache, and rheumatism. In a screening assay, Zhang et al. found that the extracts of *C. crispus* inhibit the growth of some human cancer cell lines and show cytotoxic activity [29]. The silver(I)-promoted oxidative cyclization of homopropargylamines opened up simple access to racemic crispine A [(±)-**11**] (Scheme 3) [30]. Addition of



Scheme 2 Silver(I)-mediated synthesis of (±)-harmicine [(±)-**7**]



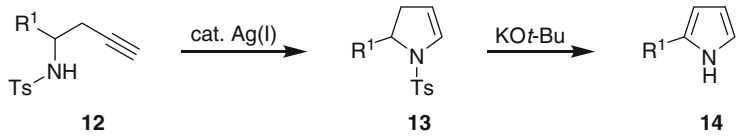
Scheme 3 Silver(I)-mediated synthesis of (±)-crispine A [(±)-**11**]

trimethylsilylpropargylmagnesium bromide to 3,4-dihydro-6,7-dimethoxyisoquinoline (**8**) led to the homopropargylamine **9**. Oxidative cyclization of **9** with concomitant protodesilylation in the presence of silver(I) acetate afforded the pyrrolo[2,1-*a*]isoquinoline **10**. Subsequent catalytic hydrogenation using rhodium on charcoal provided (±)-crispine A [(±)-**11**] in three steps and 23% overall yield.

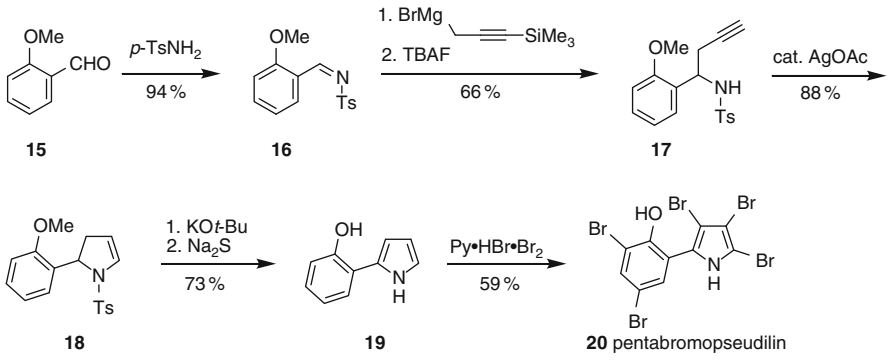
In extension of our silver(I)-mediated synthesis of pyrroles, we have developed a catalytic version which could be realized by using a tosyl function as acceptor at the nitrogen atom. Thus, cyclization of *N*-tosyl-substituted homopropargylamines **12** to Δ^2-pyrrolines **13** has been achieved with catalytic amounts of the silver(I) salt. Aromatization by subsequent elimination of *ρ*-toluenesulfinic acid on treatment with potassium *tert*-butoxide as base afforded the pyrroles **14** (Scheme 4) [31].

This procedure was applied to the syntheses of pentabromo- and pentachloropseudilin. Pentabromopseudilin (**20**) was isolated from *Pseudomonas bromoutilis* [32, 33] and a marine species of *Chromobacterium* [34]. Pentabromopseudilin (**20**) is a highly active antibiotic and also shows anti-tumor and phytotoxic activity [34, 35]. Pentachloropseudilin (**23**) was first isolated from an *Actinoplanes* strain (ATCC 33002) [36]. Pentachloropseudilin (**23**) has a lower antibiotic potency than pentabromopseudilin (**20**).

Our synthesis of pentabromopseudilin (**20**) started from 2-methoxybenzaldehyde (**15**) (Scheme 5) [31]. Treatment with *p*-toluenesulfonamide provided the *N*-tosylimine **16**. Reaction of compound **16** with trimethylsilylpropargylmagnesium bromide and subsequent protodesilylation with tetrabutylammonium fluoride (TBAF) afforded the homopropargylamine **17**. Catalytic amounts of silver(I)



Scheme 4 Pyrroles **14** by silver(I)-catalyzed cyclization of *N*-tosyl-homopropargylamines **12**



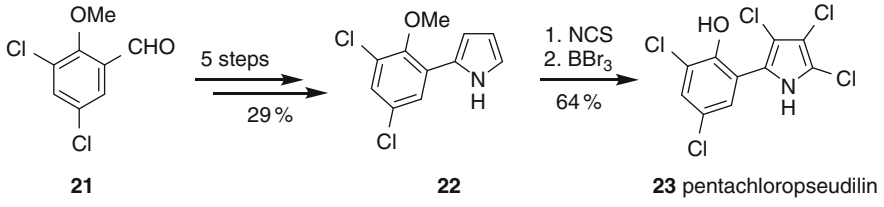
Scheme 5 Silver(I)-catalyzed synthesis of pentabromopseudilin (**20**)

acetate induced a cyclization by intramolecular hydroamination of **17** to the 2,3-dihydropyrrole **18**. Subsequent aromatization and cleavage of the methyl ether provided pseudilin (**19**). Pentabromination of **19** with pyridinium tribromide afforded pentabromopseudilin (**20**) in seven steps and 24% overall yield.

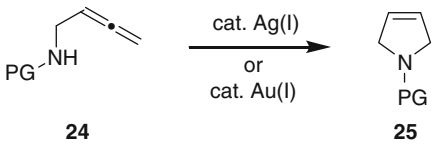
The analogous route to pentachloropseudilin (**23**) was not successful due to an insufficient electrophilic pentachlorination of pseudilin (**19**). The problem was solved by using 3,5-dichloro-2-methoxybenzaldehyde (**21**) as starting material (Scheme 6). Thus, two of the five chlorine atoms are already present at an early stage. For the synthesis of *O*-methyldichloropseudilin **22**, compound **21** was subjected to the same sequence of synthetic steps as described above for pentabromopseudilin (**20**). Electrophilic chlorination using *N*-chlorosuccinimide (NCS) followed by cleavage of the methyl ether provided pentachloropseudilin (**23**) which was obtained in seven steps and 19% overall yield. Moreover, intermediate **22** opens up the access to non-natural pseudilin derivatives containing different halogens in the phenolic and the pyrrole ring as shown by the synthesis of tribromodichloropseudilin. Using 3,5-difluoro-2-methoxybenzaldehyde as starting material, the reaction sequence described above led to tribromodifluoropseudilin [31].

The pentahalogenated pseudilins have been studied in terms of their ability to inhibit skeletal muscle myosin-2 ATPase. This property can be potentially exploited for the treatment of a broad range of diseases such as cancer, malaria, and muscle malfunctions. It turned out that pentabromopseudilin (**20**) was as efficient as the known myosin-2 ATPase inhibitor (−)-blebbistatin. An X-ray crystallographic analysis of pentabromopseudilin (**20**) with the myosin-2 motor-domain complex and Mg^{2+}−ADP-*meta*-vanadate led to the discovery of a new allosteric binding site of this motor protein. Thus, halogenated pseudilins can be regarded as a new class of myosin ATPase inhibitors [31].

In analogy to homopropargylamines, dihomopropargylamines can also be subjected to a silver-catalyzed hydroamination. Messerle et al. evaluated a number of different catalytic systems for the cyclization of 4-pentyn-1-amine to give 2-methyl-Δ^1-pyrroline. As catalysts they used silver(I) complexes which were generated from silver(I) salts and different P- and N-containing bidentate ligands. The best catalyst was obtained from 1-[2-(diphenylphosphino)ethyl]pyrazole and silver(I) triflate and achieved a turnover rate of 129 h^{-1} [37]. Phenanthroline silver complexes are efficient and recyclable catalysts for the intramolecular hydroamination of dihomopropargylamines to 2-substituted Δ^1-pyrrolines [38].



Scheme 6 Silver(I)-catalyzed synthesis of (±)-pentachloropseudilin (**23**)



24 **25**

Scheme 7 Cyclization of buta-2,3-dien-1-amines **24** to Δ^3-pyrrolines **25**

The cyclization of buta-2,3-dien-1-amines **24** to form Δ^3-pyrrolines **25** can be achieved with silver(I) salts as catalysts (Scheme 7) [39–41]. Reissig et al. utilized this strategy for the synthesis of the pyrrolidine alkaloid (±)-codonopsinine [42] and to the azaspirane core of the fungal immunosuppressant FR 901483 [43].

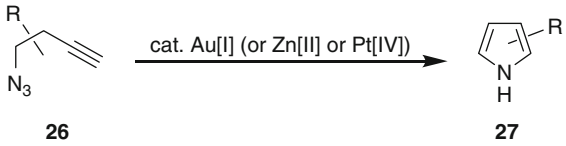
Further silver(I)-catalyzed syntheses of pyrroles include the cycloisomerization of *N*-allyl-*N*-propargylamines to afford 3-vinylidenepyrrolidines, which can be isomerized to 3-vinyl-3-pyrrolines [44]. The reaction of *β*-alkynylketones with primary amines in the presence of silver(I) or gold(I) catalysts provides functionalized pyrroles in good yields [45].

2.2 Gold-Catalyzed Cyclization

Gold has become very popular as catalyst in organic synthesis in recent years (for reviews, see [10, 12, 15, 46]). Gold catalysis has also been investigated for construction of the pyrrole ring system. In analogy to the silver(I)-catalyzed process described above, the hydroamination of α-aminoallenes **24** to substituted Δ^3-pyrrolines **25** has also been catalyzed by gold(I) salts (Scheme 7). The active catalyst in this process is probably a gold(I) species, even when gold(III) salts are employed as precatalysts [47]. The cycloisomerization of *N*-allyl-*N*-propargylamines, which can be achieved with silver(I) catalysts (see above) [44], has also been studied using gold(I) catalysis. This gold-catalyzed process provided 3-alkylidene-4-vinylpyrrolidines which can potentially be transformed to pyrroles [48]. The gold(I)-catalyzed ring expansion of 2-alkynyl-3-aryl-1-tosylaziridines afforded 2,5-disubstituted 1-tosylpyrroles [49, 50]. Pale et al. carried out this reaction with cyclohexane-fused aziridines to furnish 4,5,6,7-tetrahydroindoles [51]. 1-Aminopent-4-en-2-ynes undergo a gold(I)-catalyzed cyclization to give 2-substituted 4-methylpyrroles [52]. Cyclization of 1-amino-3-alkyn-2-ols using a combination of (triphenylphosphane)gold(I) chloride with either silver(I) bis(trifluoromethanesulfonyl)imide or silver(I) triflate as catalytic system provided substituted pyrroles [53]. Toste et al. reported a gold(I)-catalyzed cyclization of homopropargyl azides **26** to substituted pyrroles **27** (Scheme 8) [54].

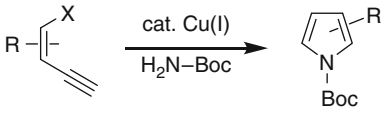
2.3 Copper-Catalyzed Cyclization

Buchwald et al. reported a Cu(I)-catalyzed domino amidation/hydroamidation procedure of 1-halobut-1-en-3-ynes **28** with *tert*-butyl carbamate to form substituted *N*-Boc-protected pyrroles **29** (Scheme 9) [55].



26 **27**

Scheme 8 Synthesis of pyrroles **27** by cyclization of homopropargyl azides **26**



28 **29**

Scheme 9 Synthesis of *N*-Boc-pyrroles **29** from 1-halobut-1-en-3-ynes **28** and *tert*-butyl carbamate

The same group has also developed an efficient Cu-catalyzed method for the reaction of 1,4-dihalo-1,3-dienes with *tert*-butyl carbamate to afford *N*-Boc-pyrroles [56]. A similar cyclizing amidation of 1,4-diiodo-1,3-dienes with primary amides led to di- or trisubstituted *N*-acylpyrroles in good yields using copper(I) iodide as catalyst [57]. A double copper(I)-catalyzed vinylation of *N*,*N*′-bis-Boc-hydrazine afforded *N*,*N*′-bis-Boc-*N*,*N*′-divinylhydrazines. Thermally induced [3,3] sigmatropic rearrangement of these intermediates followed by cyclization provided unsymmetrically substituted pyrroles [58]. 1,2,5-Triarylpyrroles have been obtained by copper(I) chloride-catalyzed addition of arylamines to 1,4-diarylbuta-1,3-diynes [59]. Oxidative cyclization of *β*-amino-*a*,*β*-enones or *β*-amino-*a*,*β*-enoates with dialkyl acetylenedicarboxylates catalyzed by copper(I) iodide in the presence of oxygen afforded a variety of persubstituted pyrroles [60]. Cu(II)-catalyzed 1,4-addition of ethyl acetoacetate or acetylacetone to α-ethoxycarbonylvinyl azides and subsequent cyclocondensation provided 2,3,4,5-tetrasubstituted pyrroles [61].

2.4 Cyclizations Catalyzed by Other Metals

This section covers cyclizations to the pyrrole nucleus catalyzed by other metals (Ti, Mn, Ru, Pd, Pt, Zn, In). Dembinski and co-workers used zinc(II) chloride as ligand-free catalyst for the microwave-assisted cyclization of homopropargyl azides **26** to afford substituted pyrroles **27** (Scheme 8) [62]. A similar methodology for the synthesis of 2,4,5-trisubstituted pyrroles was described by Driver et al. employing substituted 1-azidobuta-1,3-dienes in a cyclization reaction using catalytic amounts of zinc(II) iodide [63]. A three-component zinc-catalyzed one-pot cyclization of aromatic and aliphatic propargylic acetates, silyl enol ethers, and primary amines to substituted pyrroles has been described by Zhan et al. The reaction sequence includes propargylation of the silyl enol ether, amination, 5-*exo*-*dig*-cyclization, and isomerization [64]. Hiroya and co-workers have shown

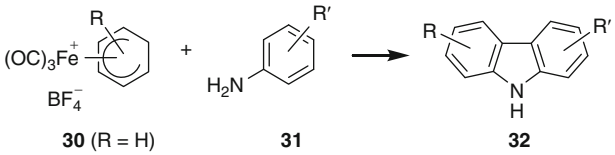
that platinum(IV) efficiently catalyzes the cyclization of homopropargyl azides **26** to give functionalized pyrroles **27** in good yields (Scheme 8) [65]. Platinum(II) has been proven to be less effective in this process. The platinum-catalyzed ring expansion of 2-alkynyl-1-benzylaziridines in aqueous media provided substituted pyrroles in good yields [66]. This method corresponds to the similar gold-catalyzed process employing 2-alkynyl-1-tosylaziridines (cf. Sect. 2.2, [49, 50]). Highly substituted pyrroles have become accessible in a one-pot indium(III)-catalyzed three-component reaction of propargylic alcohols, 1,3-dicarbonyl compounds, and primary amines [67]. A variety of alkyne-1,4-diols has been subjected to a ruthenium(II)-catalyzed isomerization leading to 1,4-diketones. In the presence of primary amines, a spontaneous cyclization occurs to provide 1,2,5-trisubstituted pyrroles [68]. Starting from α-haloalkynols, Ackermann et al. obtained mixtures of diastereoisomeric 1-halobut-1-en-3-ynes. In the presence of a primary amine, titanium tetrachloride-catalyzed intermolecular hydroamination of these compounds led to di-, tri-, tetra-, and pentasubstituted pyrroles [69]. Müller and co-workers reported a one-pot three-component reaction of acid chlorides, *N*-Boc-protected propargylamines, and sodium iodide to afford 2-substituted *N*-Boc-4-iodopyrroles [70]. An initial palladium-catalyzed Sonogashira coupling led to the intermediate ynones. Subsequent addition of iodide followed by cyclocondensation afforded the pyrroles. As the palladium catalyst was still active after this reaction sequence, it could be exploited for another Sonogashira-coupling at the *N*-Boc-4-iodopyrrole to generate 4-alkynyl-*N*-Boc-pyrroles [70]. Starting from vinyl azides and 1,3-dicarbonyl compounds, Mn(III)-catalyzed cyclization provided 2,3,5-trisubstituted and 2,3,4,5-tetrasubstituted pyrroles [71]. This reaction is related to the corresponding Cu(II)-catalyzed process reported by the same group (cf. Sect. 2.3, [61]). In contrast to the latter, a radical mechanism has been proposed for the Mn(III)-catalyzed reaction [71].

3 Synthesis of Carbazole Alkaloids

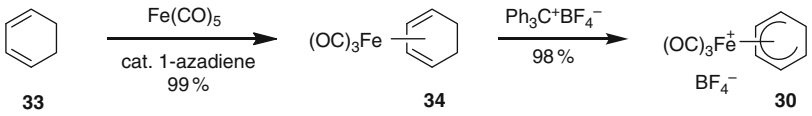
3.1 Iron-Mediated Synthesis of Carbazoles

In 1989 we reported an iron-mediated route for the construction of the tricyclic carbazole skeleton [72, 73]. This convergent method was applied to the total synthesis of the naturally occurring alkaloid carbazomycin A [72]. Key steps of our iron-mediated approach are the consecutive C−C bond formation and oxidative cyclization (formation of the C−N bond) between an electrophilic tricarbonyl(η^5-cyclohexadienylium)iron complex salt **30** and an arylamine **31** (Scheme 10). Subsequent oxidation and demetalation provides the aromatized carbazole **32**.

Starting material for this synthetic strategy is tricarbonyl(η^5-cyclohexadienylium)iron tetrafluoroborate **30**, which can be prepared from cyclohexa-1,3-diene (**33**) and pentacarbonyliron in two steps [74, 75]. Using catalytic amounts of a



Scheme 10 General principle of the iron-mediated carbazole synthesis



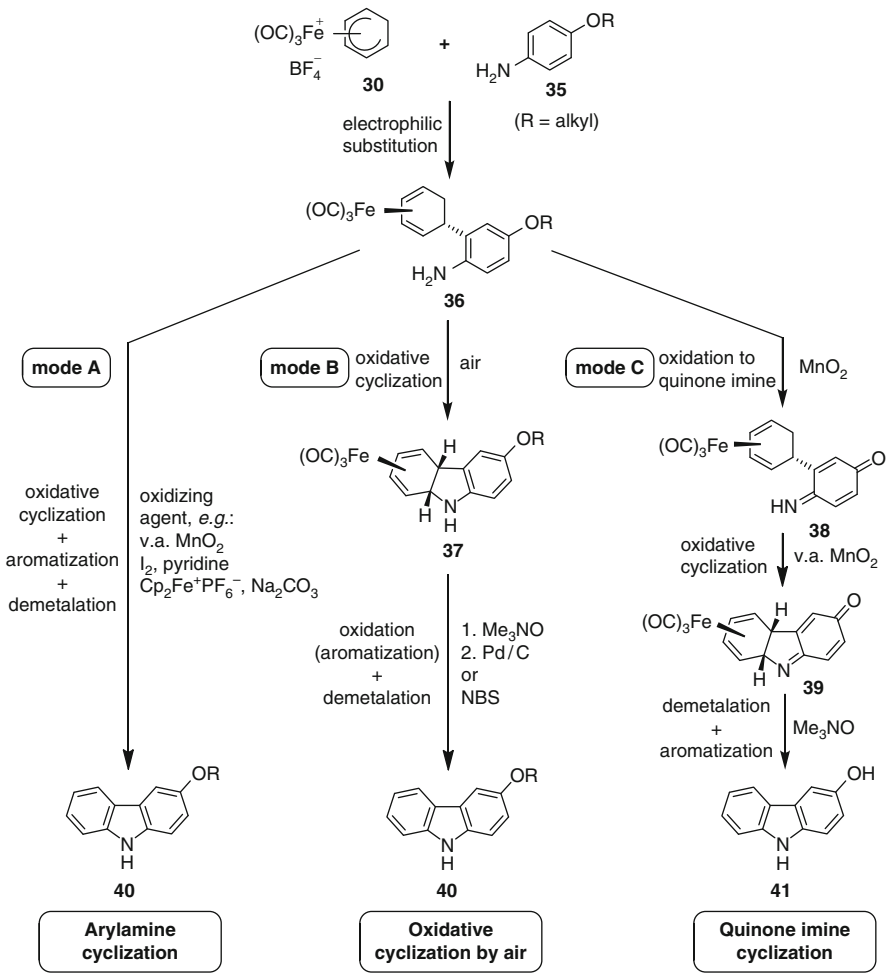
Scheme 11 Preparation of tricarbonyl(η^5-cyclohexadienylium)iron tetrafluoroborate (**30**)

1-azabuta-1,3-diene, the complexation of **33** with pentacarbonyliron provided tricarbonyl(η^4-cyclohexadiene)iron (**34**) in excellent yield (Scheme 11) [76–78]. The modified reactivity of the diene system in this complex has been exploited for many applications [79–88]. Hydride abstraction at complex **34** using triphenylcarbenium tetrafluoroborate afforded the iron complex salt **30** [89, 90].

Tricarbonyl(η^5-cyclohexadienylium)iron complex salts represent versatile electrophiles which readily react with a broad range of nucleophiles [81–83, 85, 87, 88]. According to the Davies–Green–Mingos rules, attack of nucleophiles occurs at the terminus of the tricarbonyliron-coordinated cyclohexadienylium system [91]. Electrophilic substitution of arylamines **35** by the iron complex salt **30** afforded 5-aryl-substituted tricarbonyl(η^4-cyclohexadiene)iron complexes **36** (Scheme 12). Oxidative cyclization of the iron complexes **36** generated the tricyclic carbazole ring system. Depending on the oxidizing agent, three different reaction modes for the oxidative cyclization leading to C−N bond formation have been observed.

The iron-mediated arylamine cyclization (mode A in Scheme 12) proceeds via the steps cyclodehydrogenation, aromatization, and concomitant demetalation, and can be achieved with various oxidizing agents (e.g., very active manganese dioxide [92, 93], iodine in pyridine [94–96], and ferrocenium hexafluorophosphate [92, 97, 98]). Applications of this procedure to the total synthesis of carbazole alkaloids include for example hyellazole [97] and carazostatin [98]; for reviews, see [18–20, 83]. More recent applications of this route to natural product synthesis are described in Sect. 3.1.1.

Alternatively, a mild and efficient one-pot electrophilic aromatic substitution/oxidative cyclization without isolation of the intermediate complexes **36** has been achieved using air as oxidizing agent (mode B in Scheme 12). Thus, reaction via mode B leads to tricarbonyl(η^4-4a,9a-dihydrocarbazole)iron complexes **37**, which on demetalation with trimethylamine *N*-oxide and subsequent catalytic dehydrogenation provide the carbazoles **40**. The naturally occurring carbazole



Scheme 12 Cyclization modes of the iron-mediated carbazole synthesis

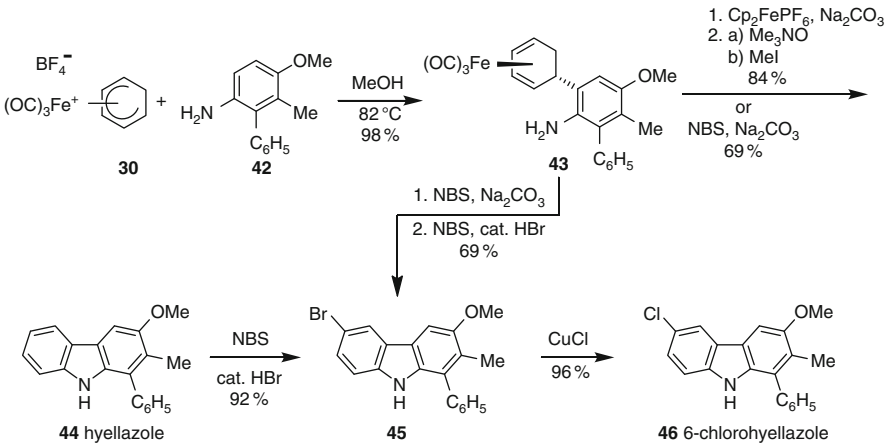
alkaloids carbazoquinocin C [99], carbazomycin A and B [100], (*R*)-carquinostatin A [101–104], (*R*)-lavanduquinocin [105, 106], and (*R*)-(−)-neocarazostatin B [103, 107] have been synthesized using this procedure. A more recent example is presented in Sect. 3.1.2.

A third pathway leads via the quinone imine intermediates **38** to 3-hydroxycarbazoles **41** (mode C in Scheme 12) [97, 98, 108, 109]. Oxidation of the complexes **36** with manganese dioxide afforded the quinone imines **38**, which on treatment with very active manganese dioxide undergo oxidative cyclization to the tricarbonyl(η^4-4b,8a-dihydrocarbazol-3-one)iron complexes **39**. Demetalation of **39** with trimethylamine *N*-oxide and subsequent aromatization lead to the 3-hydroxycarbazoles **41**. The isomerization providing the aromatic carbazole system is a

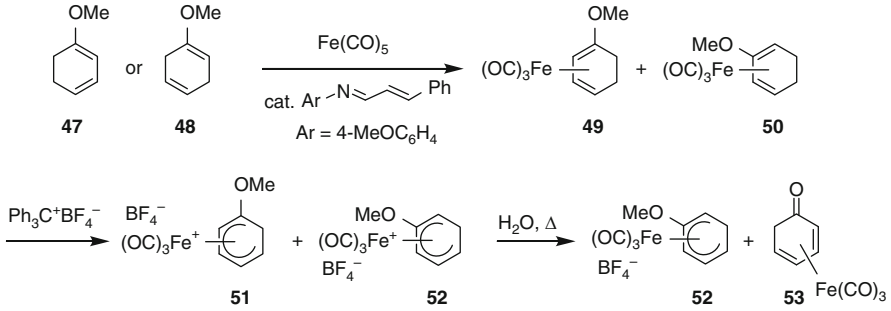
consequence of enolization followed by a [1,5] hydride shift. The quinone imine cyclization has been applied to the syntheses of carbazomycin C and D [108], hyellazole (**44**) [97], and carazostatin [98].

3.1.1 Arylamine Cyclization

Hyellazole (**44**) and 6-chlorohyellazole (**46**) were isolated from the blue-green alga *Hyella caespitosa* [110]. They represent the first carbazole alkaloids obtained from marine sources. Hyellazole (**44**) and 6-chlorohyellazole (**46**) were both synthesized starting from the iron complex salt **30** and arylamine **42** (Scheme 13) [111]. The arylamine **42** is available from 2,6-dimethoxytoluene in five steps and 76% overall yield. Complex salt **30** and arylamine **42** react in an electrophilic substitution to complex **43**. Three different reagents have been found to accomplish the oxidative cyclization of complex **43**. The quinone imine cyclization of **43** by sequential application of manganese dioxide, very active manganese dioxide, and trimethylamine *N*-oxide followed by *O*-methylation provided hyellazole (**44**) in five steps and 57% yield based on **30** [97]. A more efficient oxidative cyclization of complex **43** was achieved with ferrocenium hexafluorophosphate in the presence of sodium carbonate to give hyellazole (**44**) in 59% yield along with 29% of the corresponding tricarbonyliron-complexed dihydrocarbazol-3-one. The latter could be transformed to hyellazole (**44**) on treatment with trimethylamine *N*-oxide and subsequent methylation to contribute to an overall yield of 83% based on **30** [97]. More recently, a third strategy has been reported for the oxidative cyclization of **43** using *N*-bromosuccinimide (NBS) to give hyellazole (**44**) in 69% yield [111]. Electrophilic bromination with the same reagent in the presence of catalytic amounts of hydrobromic acid provides 6-bromohyellazole (**45**) in 92% yield.



Scheme 13 Synthesis of 6-chlorohyellazole (**46**)

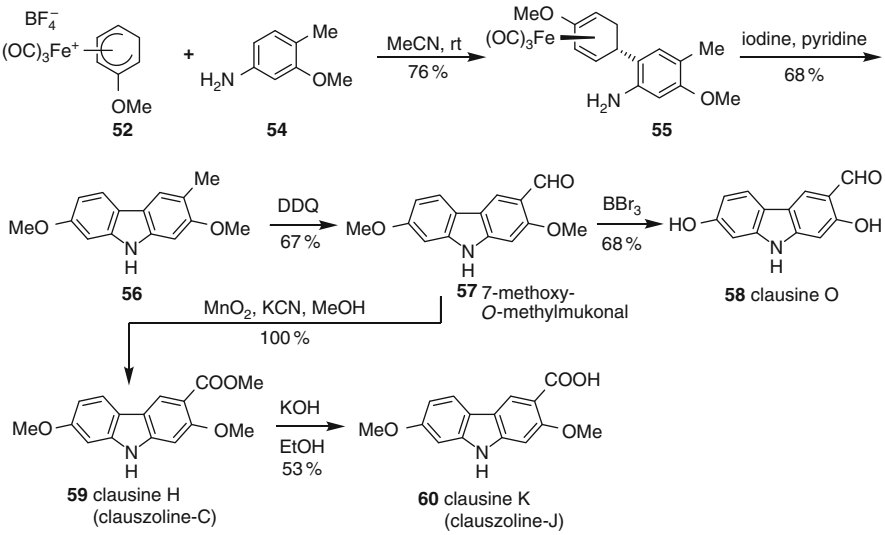


Scheme 14 Synthesis of the 2-methoxycyclohexadienyliron complex salt **52**

These two steps can be combined to a one-pot procedure affording 6-bromohyellazole (**45**) in 69% yield. Compound **45** can be readily transformed into 6-chlorohyellazole (**46**) in 96% yield using copper(I) chloride in dimethylformamide. Direct chlorination of **44** with *N*-chlorosuccinimide (NCS) occurs at C-4 and, thus, provides no access to the naturally occurring 6-chlorohyellazole (**46**) [111].

The synthesis of 7-oxygenated carbazoles via the iron-mediated route requires the 2-methoxy-substituted iron complex salt **52** (Scheme 14). Complexation of the methoxycyclohexadienes **47** and **48** with pentacarbonyliron in the presence of catalytic amounts of 1-(*p*-anisyl)-4-phenyl-1-azabuta-1,3-diene affords a mixture of the regioisomeric 1-methoxy- and 2-methoxy-η^4-cyclohexadieneiron complexes **49** and **50** [77, 78, 84]. Hydride abstraction by triphenylcarbenium tetrafluoroborate provides a mixture of regioisomeric η^5-cyclohexadienyliron complexes **51** and **52**. Separation of the 1-methoxy- and 2-methoxy-substituted complex salts **51** and **52** can be achieved by selective hydrolysis of **51** to the cyclohexadienone−tricarbonyliron complex **53** [74].

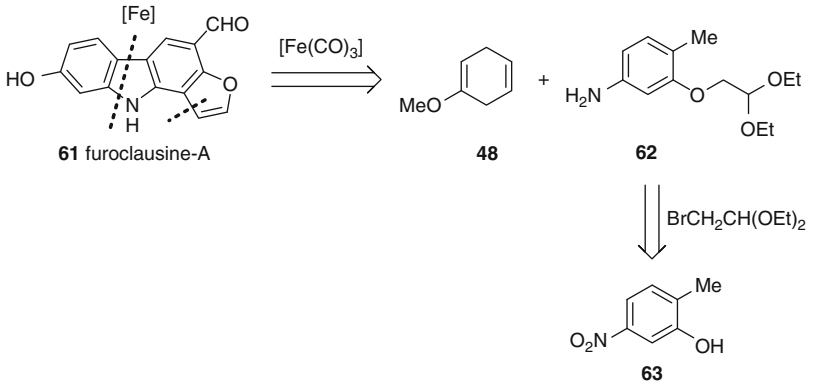
Following our iron-mediated approach, 2,7-dioxygenated carbazole alkaloids became readily available. Several members of this family of natural products show promising pharmacological effects. 7-Methoxy-*O*-methylmukonal (**57**) was isolated from the roots of *Murraya siamensis* [112]. Clausine H (**59**) and clausine K (**60**) were obtained from the stem bark of *Clausena excavata* collected in Taiwan by Wu et al. [113]. Ito and co-workers isolated clauszoline-C (**59**), identical to Wu's clausine H (**59**), from *C. excavata* collected in Singapore [114]. Clauszoline-J (**60**), with the same structure as clausine K (**60**), was obtained from *C. excavata* Burm. f. grown in a greenhouse in Shizuoka [115]. Clausine O (**58**) was isolated from the root bark of *C. excavata* [116]. Clausine K (clauszoline-J) (**60**) was also obtained from the roots of *Clausena harmandiana* by Kittakoop and co-workers [117]. Clausine H (clauszoline-C) (**59**) shows antiplasmodial activity [117]. Clausine K (clauszoline-C) (**60**) exhibits activity against *Mycobacterium tuberculosis* [118]. Using iron complex salt **52** as starting material, the 2,7-dioxygenated carbazole alkaloids **57**–**60** have been synthesized (Scheme 15) [119]. We used 7-methoxy-*O*-methylmukonal (**57**) as relay compound which provides access to clausine H



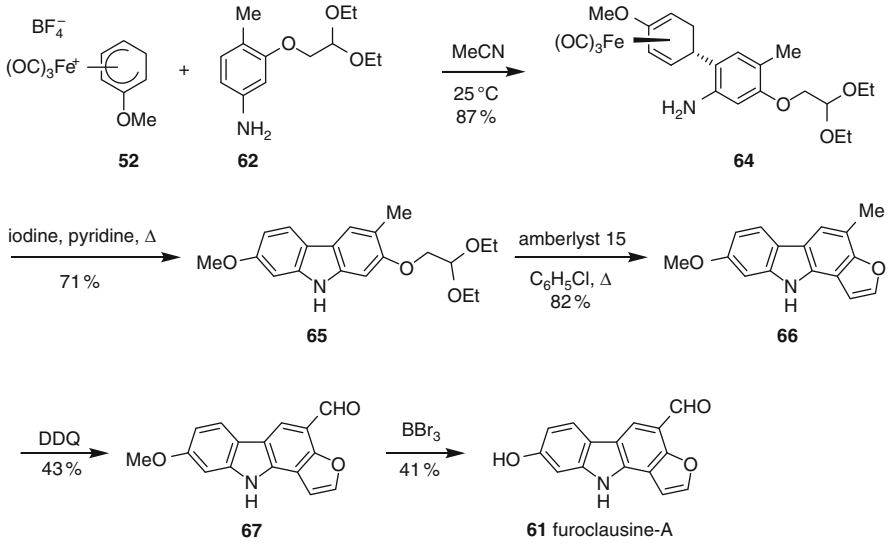
Scheme 15 Iron-mediated synthesis of 2,7-dioxygenated carbazole alkaloids

(clauszoline-C) (**59**), clausine K (clauszoline-J) (**60**), and clausine O (**58**). Reaction of complex salt **52** with 3-methoxy-4-methylaniline (**54**) afforded by an electrophilic substitution the iron complex **55**. Using iodine in pyridine, oxidative cyclization of complex **55** with concomitant aromatization and demetalation led to 2,7-dimethoxy-3-methylcarbazole (**56**). Compound **56** has the appropriate substitution pattern to provide access to the naturally occurring 2,7-dioxygenated carbazole alkaloids mentioned above. Oxidation of the methyl group at C-3 with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) afforded 7-methoxy-*O*-methylmukonal (**57**). Double ether cleavage of **57** with boron tribromide leads to clausine O (**58**) in 68% yield. Application of Corey's methyl ester synthesis [120] by oxidation of aldehydes with manganese dioxide in the presence of potassium cyanide in methanol converted 7-methoxy-*O*-methylmukonal (**57**) quantitatively to clausine H (clauszoline-C) (**59**). Saponification of **59** with potassium hydroxide in methanol provides clausine K (clauszoline-J) (**60**) [119].

Furoannulated carbazole alkaloids represent a relatively new class of natural products which have been isolated from terrestrial plants [121, 122]. The number of members of this family known to date is rather limited. Furoclausine-A (**61**) along with furoclausine-B was isolated first by Wu and co-workers from the root bark of *C. excavata* [122]. We have developed an efficient and convergent access to furo[3,2-*a*]carbazoles via our iron-mediated arylamine cyclization [123, 124]. Retrosynthetic analysis of furoclausine-A (**61**) suggests 1-methoxycyclohexa-1,4-diene (**48**) and the arylamine **62** as building blocks (Scheme 16). The latter was obtained by alkylation of 2-methyl-5-nitrophenol (**63**) with 2-bromo-1,1-diethoxyethane



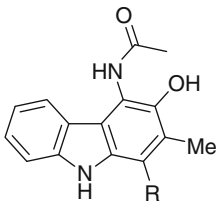
Scheme 16 Retrosynthetic analysis of furoclausine-A (**61**)

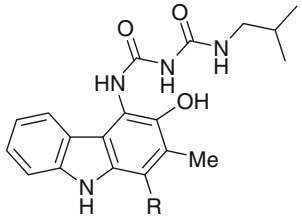


Scheme 17 Synthesis of furoclausine-A (**61**)

followed by catalytic hydrogenation (80% overall yield). Annulation of the furan was carried out after construction of the carbazole framework.

Reaction of the arylamine **62** with the complex salt **52** in acetonitrile at room temperature afforded complex **64** in 87% yield (Scheme 17) [125]. Subsequent oxidative cyclization, aromatization and demetalation using iodine in pyridine provided carbazole **65** in 71% yield. Heating of compound **65** in chlorobenzene in the presence of the acidic cation exchange resin amberlyst 15 led to ring closure with formation of the furo[3,2-*a*]carbazole **66**. Oxidation of the methyl group at C-3 to a formyl group using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)





68a antiostatin A_1 R = $(CH_2)_4CH_3$
68b antiostatin A_2 R = $(CH_2)_2CH(CH_3)CH_2CH_3$
68c antiostatin A_3 R = $(CH_2)_4CH(CH_3)_2$
68d antiostatin A_4 R = $(CH_2)_6CH_3$

69a antiostatin B_2 R = $(CH_2)_5CH_3$
69b antiostatin B_3 R = $(CH_2)_4CH(CH_3)_2$
69c antiostatin B_4 R = $(CH_2)_6CH_3$
69d antiostatin B_5 R = $(CH_2)_5CH(CH_3)_2$

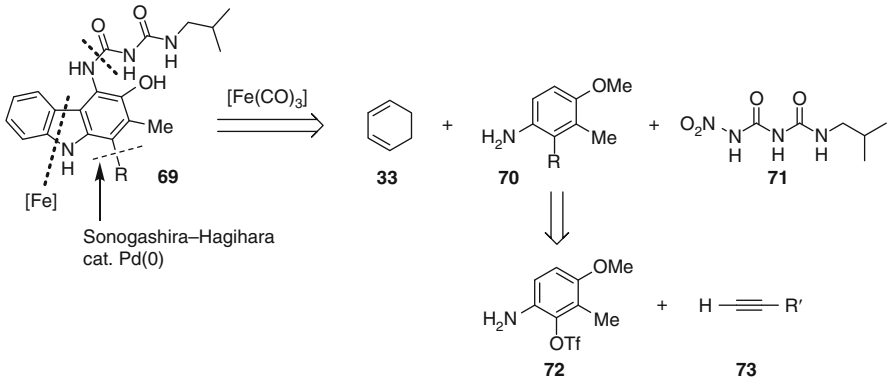
Fig. 1 Antiostatins A_1-A_4 (**68a–d**) and B_2-B_5 (**69a–d**)

afforded *O*-methylfuroclausine-A (**67**). Finally, cleavage of the methyl ether with boron tribromide led to furoclausine-A (**61**) which was obtained in seven steps and 7% overall yield based on 2-methyl-5-nitrophenol (**63**).

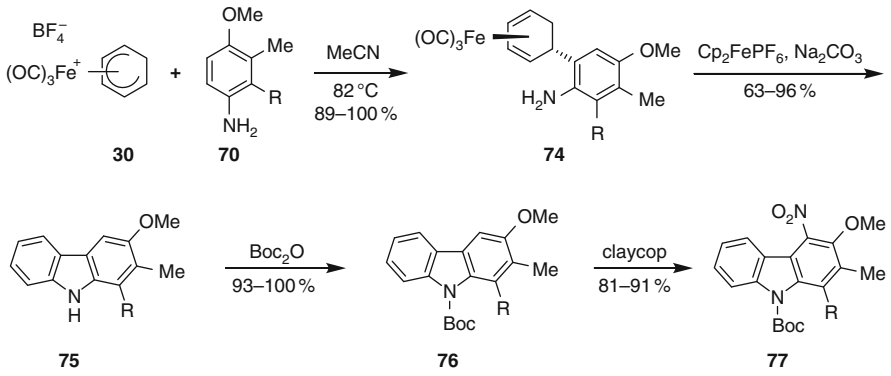
The antiostatins, a unique class of carbazole alkaloids, are characterized by a 3-hydroxy- and a 4-acylamino group. They have been isolated from *Streptomyces cyaneus* 2007-SV_1 [126]. Depending on the side chain at C-4, the antiostatins are classified as antiostatins A (**68a–d**) with an acetamide and antiostatins B (**69a–d**) with an isobutylbiuret moiety (Fig. 1). The antiostatins strongly inhibit the radical induced lipid peroxidation by acting as scavengers of oxygen-derived free radicals. These species are known to promote diseases such as cerebral and myocardial ischemia [127–130], inflammation, autoimmune diseases, diabetes, rheumatism, and cancer [131–133]. Therefore, radical scavengers are under extensive investigation as potential drugs for treatment of these diseases.

Our convergent approach to this class of natural products utilizes the iron-mediated arylamine cyclization for construction of the carbazole framework. The retrosynthetic analysis of the antiostatins B (**69a–d**) leads to cyclohexa-1,3-diene (**33**) and the arylamines **70** as building blocks (Scheme 18) [134]. The different side chains at C-1 are introduced by a palladium(0)-catalyzed Sonogashira–Hagihara coupling. The amino group at C-4 is attached to the preformed carbazole skeleton. For introduction of the biuret side chain, we have developed 5-isobutyl-1-nitrobiuret (**71**) as reagent to access the antiostatins of the B-series.

The anilines **70** were obtained in five steps and 62–88% overall yield from 2,6-dimethoxytoluene (Scheme 19) [134]. The different alkyl side chains, characterizing the antiostatins within each series, were introduced by Sonogashira–Hagihara coupling with the appropriate terminal alkyne. Electrophilic substitution using the iron complex salt **30** afforded the complexes **74**. Subsequent oxidative cyclization with concomitant aromatization and demetalation by treatment of **74** with an excess of ferrocenium hexafluorophosphate provided the carbazoles **75**. Initial protection of the carbazole nitrogen as *tert*-butyl carbamate followed by regioselective nitration at C-4 using claycop led to the 4-nitrocarbazoles **77**. These



Scheme 18 Retrosynthetic analysis of the antiostatins B (**69a–d**); R = R'CH_2CH_2

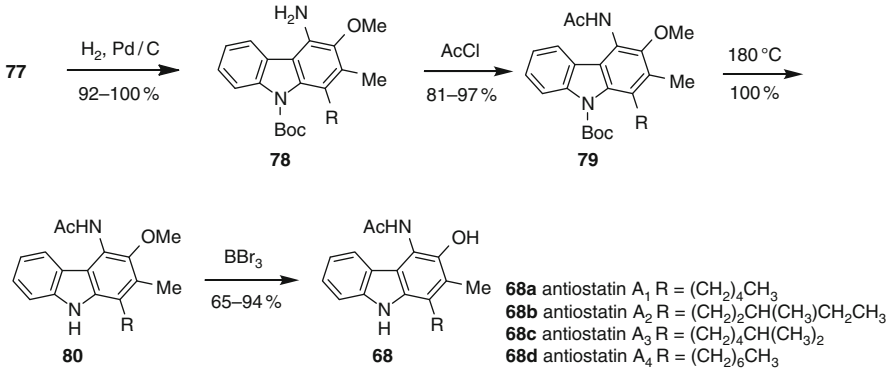


Scheme 19 Synthesis of the antiostatin precursors **77**

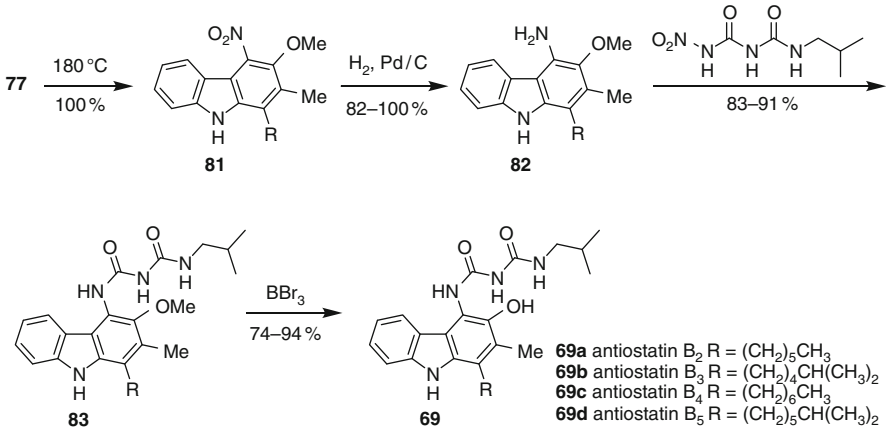
intermediates served as precursors for the antiostatins of the A (**68a–d**) and B (**69a–d**) series [134].

Catalytic hydrogenation of **77** to the 4-aminocarbazoles **78** followed by acetylation of the amino group afforded the acetamides **79** (Scheme 20). Thermal removal of the Boc protecting group and ether cleavage using boron tribromide led in excellent overall yields to all four members of the antiostatin A series (**68a–d**) [134].

The antiostatins B_2-B_5 (**69a–d**) were also obtained from the advanced precursor **77** (Scheme 21). Thermal removal of the Boc group and subsequent catalytic hydrogenation provided the 4-aminocarbazoles **82**. The unusual biuret side chain was attached by reaction with 5-isobutyl-1-nitrobiuret, which proved to be an efficient reagent for this purpose. Finally, the methyl ether was cleaved by reaction with boron tribromide to afford the four antiostatins of the B series (**69a–d**) [134].



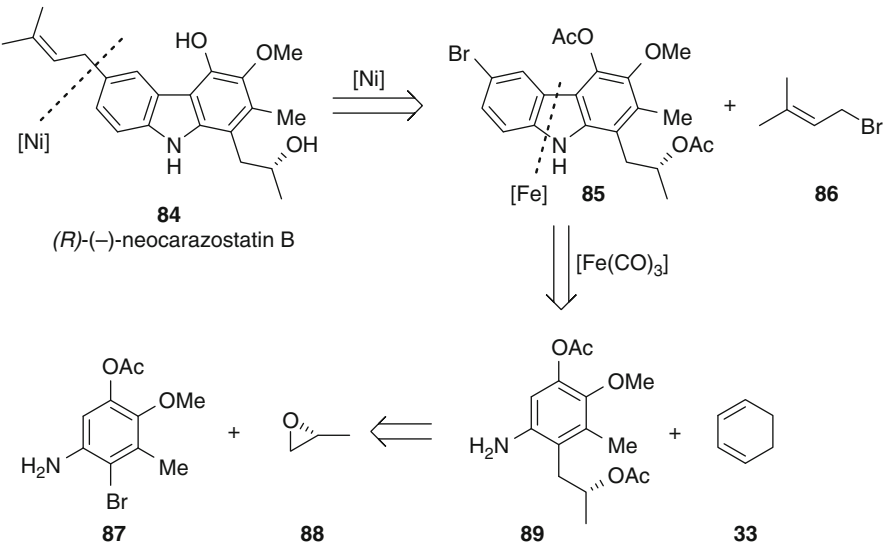
Scheme 20 Synthesis of antiostatins A_1 – A_4 (**68a**–**d**)



Scheme 21 Synthesis of antiostatins B_2–B_5 (**69a**–**d**)

3.1.2 Oxidative Cyclization by Air

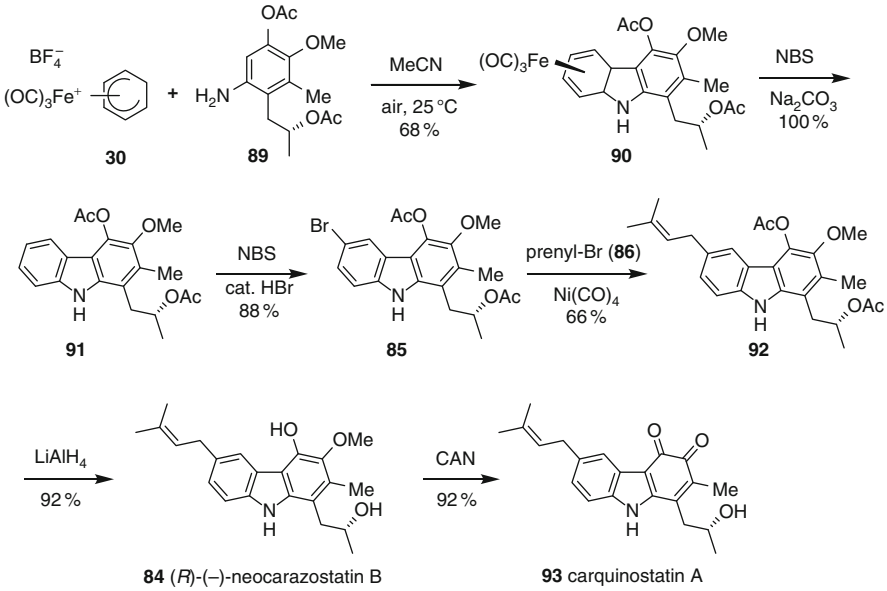
In analogy to the antiostatins, the 3,4-dioxygenated carbazole alkaloids neocarazostatin B (**84**) and carquinostatin A (**93**) also display a pronounced antioxidative activity. Neocarazostatin B (**84**) was isolated first from the culture of *Streptomyces* sp. strain GP 38 [135]. The related *o*-quinone derivative, carquinostatin A (**93**), was obtained by Seto et al. from *Streptomyces exfoliates* 2419-SVT2 [136]. The absolute stereochemistry of neocarazostatin B (**84**) was not reported. In analogy to the known absolute configuration of carquinostatin A (**93**), we assumed an (*R*)-configuration for the 2-hydroxypropyl side chain. We developed the first enantioselective synthesis of neocarazostatin B (**84**), which can be further



Scheme 22 Retrosynthetic analysis of neocarazostatin B (**84**)

transformed into carquinostatin A (**93**) [103]. Thus, we could prove our assumption by comparison of the optical rotation value of our synthetic compound with that of the natural product. The synthetic strategy is related to our previous syntheses of carquinostatin A (**93**) [101, 102, 104] and lavanduquinocin [106]. We projected to introduce the prenyl side chain at the carbazole framework by a nickel-mediated prenylation (Scheme 22). The carbazole skeleton should derive from the arylamine **89** and cyclohexa-1,3-diene (**33**) by an iron-mediated oxidative coupling under air. The 2-hydroxypropyl side chain should be attached to the aromatic amine **87** by lithiation and subsequent reaction with (*R*)-propene oxide (**88**).

The arylamine **89** was obtained in eight steps and 65% overall yield starting from guaiacol. This precursor enables one to differentiate between the oxy substituents at C-3 and C-4 of the carbazole. The chiral side chain is introduced by regioselective bromination, halogen−metal exchange, and subsequent reaction with (*R*)-propene oxide (**88**). Reaction of the highly functionalized arylamine **89** with the iron complex salt **30** in acetonitrile in air afforded complex **90** in 68% yield (Scheme 23) [103]. This transformation combines electrophilic aromatic substitution and oxidative cyclization (mode B in Scheme 12). The oxidative cyclization of similar systems by air in acidic medium was reported by us previously for the synthesis of the carbazole alkaloids mukonine and mukonidine [137, 138]. The one-pot electrophilic substitution and oxidative cyclization was reported first in the course of the synthesis of carbazoquinocin C [99]. In this case, the acidic conditions are provided by tetrafluoroboric acid, which is released during the electrophilic substitution. Aromatization and concomitant demetalation of **90** was achieved by treatment with *N*-bromosuccinimide (NBS) under basic reaction conditions to furnish



Scheme 23 Enantioselective synthesis of (*R*)-(−)-neocarazostatin B (**84**) and carquinostatin A (**93**)

carbazole **91** quantitatively. NBS under acidic conditions is used for regioselective aromatic bromination at C-6. Treatment of the 6-bromocarbazole **85** with an in situ prepared dimeric π-prenylnickel complex afforded the 6-prenylcarbazole **92**. Removal of both acetyl protecting groups of **92** by treatment with lithium aluminum hydride provided (*R*)-(−)-neocarazostatin B (**84**). Based on comparison of the values for the specific rotation, the absolute configuration proved to be identical with that of natural neocarazostatin B. (*R*)-(−)-Neocarazostatin B (**84**) is air sensitive and is slowly oxidized to carquinostatin A (**93**). Smooth oxidation was achieved with ceric ammonium nitrate (CAN) to give carquinostatin A (**93**) in 92% yield. The present route via neocarazostatin B (**84**) constitutes a new access to carquinostatin A (**93**) which complements our previous syntheses [101, 102, 104].

3.2 Palladium-Catalyzed Synthesis of Carbazoles

Palladium appears to be the most versatile metal for catalytic reactions in organic synthesis. Most prominent are cross-coupling reactions between compounds with sp^2 or sp^3 C–X bonds and metal organyls. Moreover, a large number of palladium-mediated reactions for C–H bond activation has been described. In most cases, palladium(0) displays the catalytically active species. However,

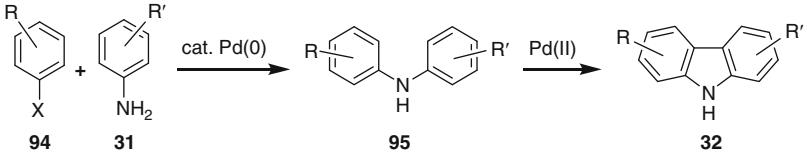
palladium(II)-catalyzed reactions (e.g., the Wacker process) are also well-known. Palladium also plays a major role in diverse approaches to the carbazole ring system which are summarized below. Only a few of them have been widely used for the synthesis of naturally occurring carbazole alkaloids.

3.2.1 Buchwald–Hartwig Amination Followed by Oxidative Cyclization (Pd[0]/Pd[II])

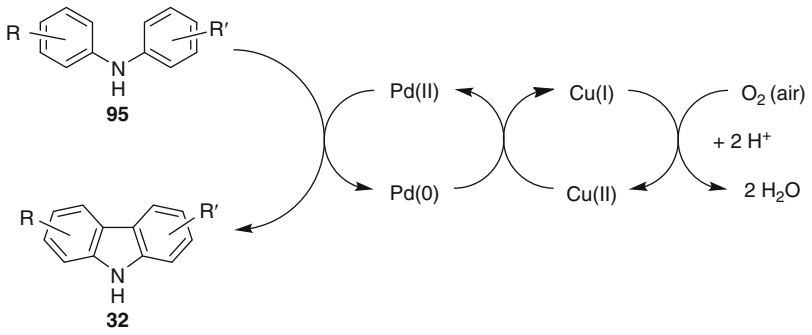
One of the most versatile approaches to highly functionalized carbazoles is the sequential palladium-catalyzed C–N/C–C coupling for assembly of the central pyrrole moiety. Many total syntheses of naturally occurring carbazole alkaloids are following this route. The initial C–N bond formation by a palladium(0)-catalyzed Buchwald–Hartwig amination of aryl halides or triflates **94** with arylamines **31** affords the diarylamines **95** (Scheme 24) [139, 140]. Oxidative cyclization of the diarylamines **95** to the carbazoles **32** proceeds via a double C–H bond activation and is achieved in the presence of palladium(II) compounds.

The oxidative cyclization step has been improved over the years. The first report on the palladium(II)-promoted cyclization of diarylamines to carbazoles dates back to the year 1975. Åkermark required stoichiometric amounts of palladium to achieve an oxidative C–C bond coupling by double sp^2-C–H bond activation [141]. We improved this reaction considerably by using for the first time only catalytic amounts of palladium(II) as originally reported in 1994 [142–152]. Further fine-tuning of the reaction conditions has led to a redox cascade that links three redox systems resembling the Wacker process (Scheme 25). Electrons are transferred from the diarylamine **95** to palladium(II) to afford the carbazole **32** and palladium(0). The latter donates two electrons to copper(II) regenerating palladium(II) under formation of copper(I). Finally, copper(I) transfers one electron to oxygen. Copper(II) is regenerated and molecular oxygen is transformed to water. Thus, palladium(II) and copper(II) can be employed in catalytic amounts and air represents the effective oxidant.

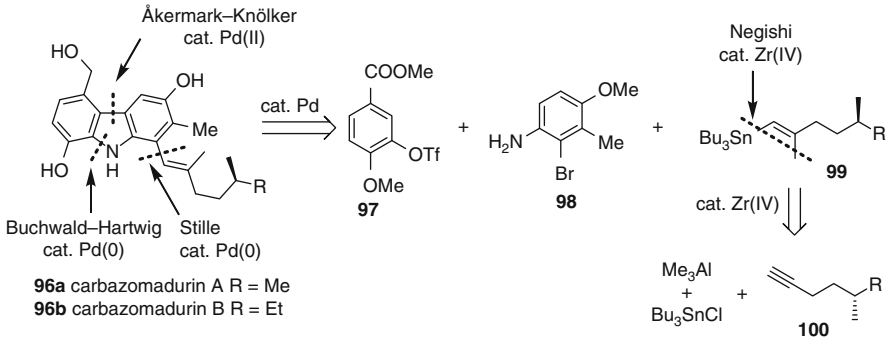
The palladium(II)-catalyzed oxidative cyclization has been applied to the total synthesis of a broad range of naturally occurring carbazole alkaloids. Earlier examples have been presented in our previous review in this series [19]. Herein, we describe recent progress in this area from our laboratories and other research groups.



Scheme 24 Synthesis of carbazoles **32** by Buchwald–Hartwig amination and subsequent oxidative cyclization of the diarylamines **95**



Scheme 25 Redox cascade of the palladium(II)-catalyzed oxidative cyclization of diarylamines **95** to carbazoles **32**

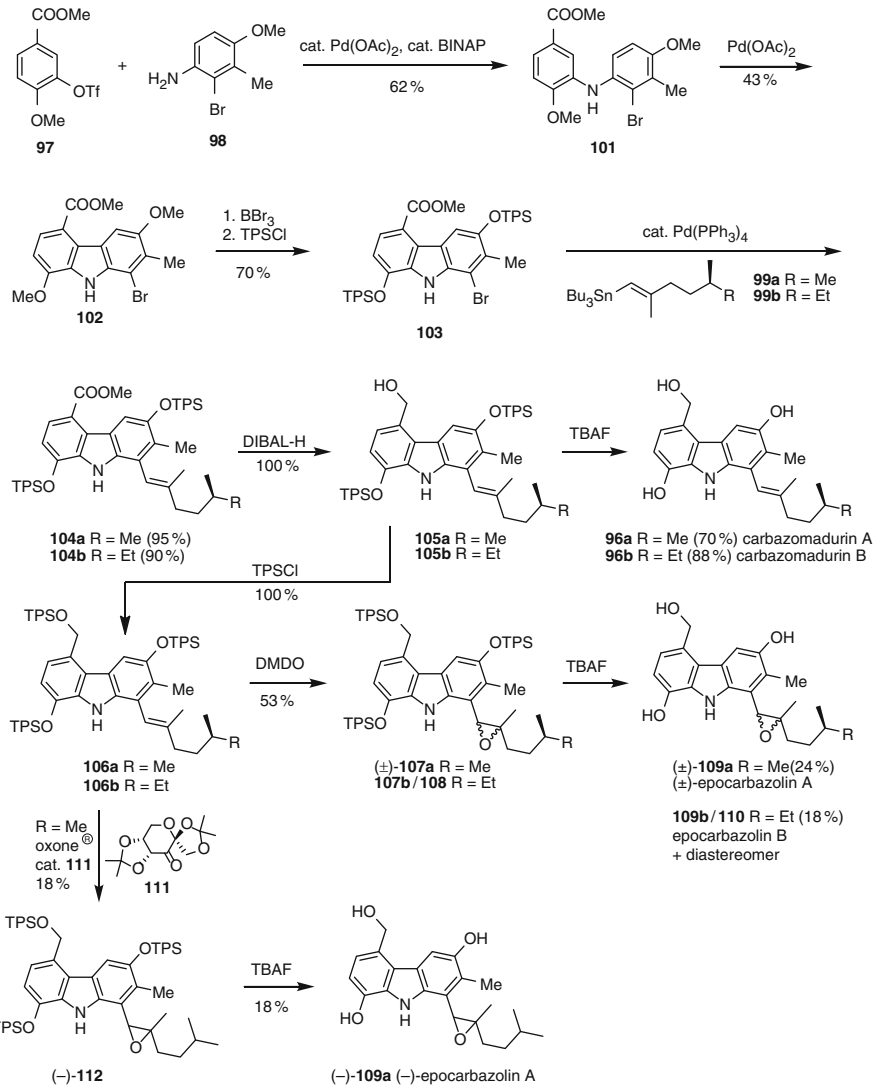


Scheme 26 Retrosynthetic analysis of carbazomadurin A (**96a**) and B (**96b**)

Carbazomadurin A (**96a**) and B (**96b**) were isolated from the microorganism *Actinomadura madurae* by Seto et al. in 1997. They display a strong neuronal cell protecting activity against L-glutamate induced cell death which is ascribed to their antioxidative effect [153]. We accomplished the first synthesis of carbazomadurin A (**96a**) using the sequential aryl amination and oxidative cyclization according to Scheme 24 [154]. Carbazomadurin B (**96b**) can be synthesized following the same route [154, 155]. Retrosynthetic analysis of the carbazomadurins displays the extensive use of palladium-catalyzed reactions following our approach (Scheme 26). The carbazole framework is constructed by Buchwald–Hartwig amination and subsequent oxidative cyclization of the diarylamine using catalytic amounts of palladium(II). The side chain at C-1 is introduced by Stille coupling. Key step for the synthesis of the vinylstannane **99** is the zirconium(IV)-catalyzed carboalumination developed by Negishi.

The palladium-catalyzed approach to carbazomadurin A (**96a**) and B (**96b**) requires the aryl triflate **97** and arylamine **98** as precursors. The former was

obtained from isovanillic acid in two steps and 91% overall yield. Arylamine **98** can be prepared in five steps and 44% overall yield starting from commercially available 2-bromo-6-nitrotoluene. Buchwald–Hartwig coupling of the two components using 5 mol% of palladium(II) acetate and 7.5 mol% of 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) in the presence of cesium carbonate afforded the diarylamine **101** (Scheme 27). Subsequent oxidative cyclization provided the



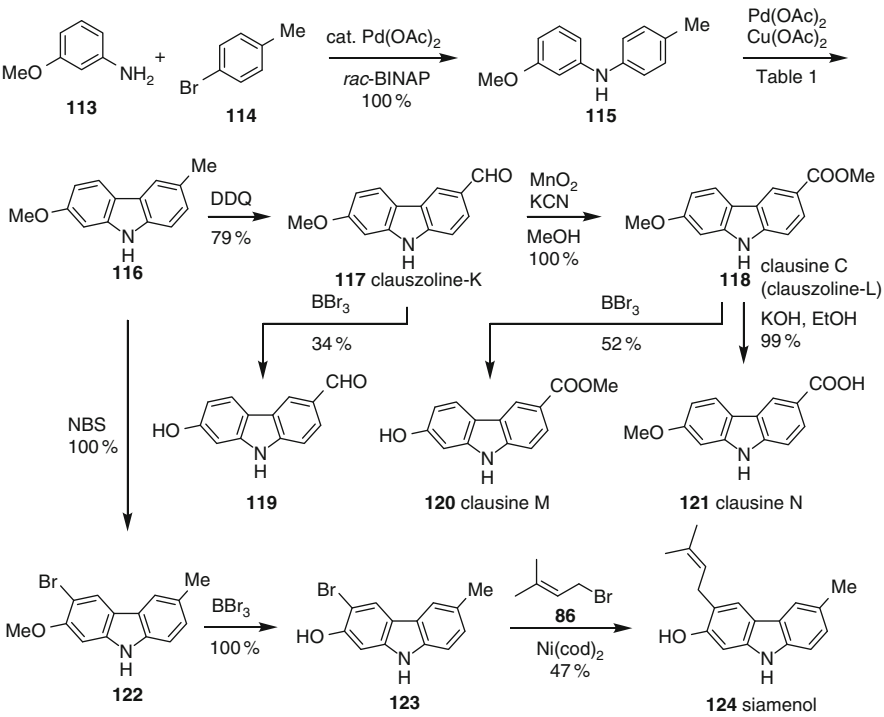
Scheme 27 Palladium-catalyzed synthesis of the carbazomadurins A (**96a**) and B (**96b**), and the epocarbazolins A (**109a**) and B (**109b**)

carbazole **102**. In the present case, stoichiometric amounts of palladium(II) acetate have been employed for this step without further optimization. Ether cleavage and protection of the two hydroxy groups provided the disilyl ether **103**. This key intermediate represents a relay compound for the syntheses of carbazomadurin A (**96a**) and B (**96b**). Stille coupling with the vinylstannanes **99a** and **99b** introduces the two different side chains of the natural products. The *E*-vinylstannane **99a** is conveniently prepared from 5-methyl-1-hexyne (**100a**) via consecutive zirconium(IV)-catalyzed carboalumination, iodation, halogen–metal exchange, and transmetalation using tributyltin chloride. The *E*-vinylstannane **99b** can be obtained in six steps starting from commercially available (*S*)-(−)-2-methyl-1-butanol. The (S)-configuration assumed for the stereogenic center of natural carbazomadurin B (**96b**) was later on shown to be correct. The syntheses of carbazomadurin A (**96a**) and B (**96b**) were completed by ester reduction using diisobutylaluminum hydride (DIBAL-H) and removal of the silyl protecting groups. The nine-step synthesis starting from isovanillic acid afforded carbazomadurin A (**96a**) in 11% and carbazomadurin B (**96b**) in 13% overall yield [154, 155].

The structurally related carbazole alkaloids epocarbazolin A (**109a**) and epocarbazolin B (**109b**) were isolated from *Streptomyces anulatus* T688-8. These compounds show a potent rat 5-lipoxygenase inhibitory activity [156]. We envisaged the synthesis of **109a** and **109b** from the carbazomadurin precursors **105a** and **105b**. Protection of the free hydroxy group provided quantitatively the trisilylated carbazoles **106a** and **106b** (Scheme 27) [157]. Epoxidation of the achiral derivative **106a** with dimethyldioxirane (DMDO) and subsequent removal of the silyl groups afforded *rac*-epocarbazolin A [(±)-**109a**]. The same procedure using the chiral intermediate **106b** provided a mixture of epocarbazolin B (**109b**) and its diastereoisomer **110** [157]. An asymmetric approach using a modified Shi epoxidation has been employed for the synthesis of the unnatural (−)-epocarbazolin A [(−)-**109a**] (Scheme 27). The absolute configuration of this product is still unknown. Epoxidation of the trisilyl-protected carbazomadurin A **106a** using Shi catalyst **111** afforded the (−)-tri-*O*-silylepocarbazolin A (−)-**112**. Removal of the protecting groups led to (−)-epocarbazolin A [(−)-**109a**] with a specific rotation of $[a]_D^{26} = -55$. The natural product was reported to have a specific rotation of $[a]_D^{26} = +75$. Thus, the non-natural enantiomer of epocarbazolin A [(−)-**109a**] was obtained with an enantiomeric excess of approximately 73% [157].

A series of 7-oxygenated carbazole alkaloids has been synthesized by us for the first time, including clauszoline-K (**117**), 3-formyl-7-hydroxycarbazole (**119**), clausine M (**120**), clausine N (**121**), and siamenol (**124**) [148]. Clauszoline-K (**117**) and clauszoline-L (**118**) have been isolated by Ito et al. from the stem bark of *C. excavata* [115]. Wu and co-workers had isolated the same compound **118** one year earlier from the same source and named it clausine C (**118**) [158]. 3-Formyl-7-hydroxycarbazole (**119**) was obtained from the root bark of *Murraya euchrestifolia* [159]. Clausine M (**120**) and clausine N (**121**) were isolated from the root bark of *C. excavata* by Wu et al. [116]. Siamenol (**124**) was isolated from an extract of *M. siamensis* and proved to have anti-HIV activity [160].

Our approach to the 7-oxygenated carbazoles starts with a Buchwald–Hartwig amination of *m*-anisidine (**113**) and *p*-bromotoluene (**114**) to give the diarylamine **115** in quantitative yield (Scheme 28) [148]. For the oxidative cyclization of **115** we investigated different conditions (Table 1). The best yield was obtained using 0.1 equiv. of palladium(II) acetate and 2.5 equiv. of copper(II) acetate as co-oxidant in glacial acetic acid under air. Smaller amounts of palladium(II) acetate decrease the yield slightly but lead to rather high turnover numbers up to 26.5. 7-Methoxy-3-methylcarbazole (**116**) constitutes the crucial compound leading to six different 7-oxygenated carbazole alkaloids. Oxidation of the methyl group at C-3 in **116** to a formyl group using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) affords



Scheme 28 Palladium-catalyzed synthesis of 7-oxygenated carbazole alkaloids

Table 1 Optimization of the palladium(II)-catalyzed oxidative cyclization to 7-methoxy-3-methylcarbazole (**116**)

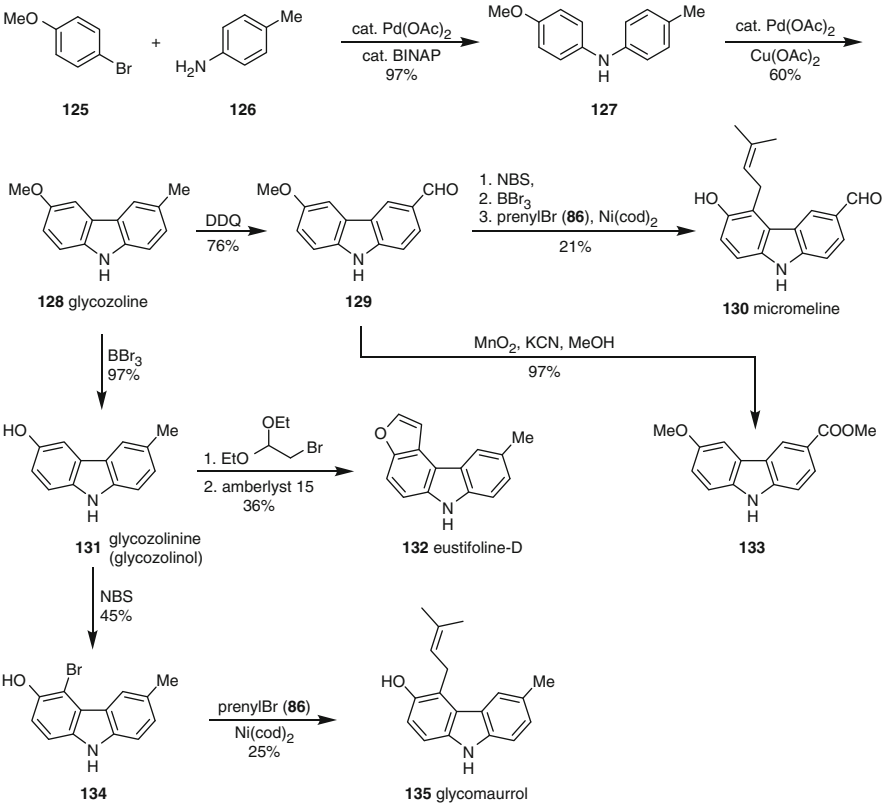
$Pd(OAc)_2$ (equiv.)	$Cu(OAc)_2$ (equiv.)	Reaction conditions	**116**, Yield (%)	TON[a]
1.2	–	AcOH, reflux, argon, 2 h	36	–
0.1	2.5	AcOH, reflux, air, 23 h	64	6.4
0.1	2.5	AcOH, reflux, air, 2 days	72	7.2
0.05	2.5	AcOH, reflux, air, 40 h	61	12.2
0.02	2.5	AcOH, reflux, air, 6 days	53	26.5

[a]TON = turnover number

clauszoline-K (**117**) in 79% yield. Ether cleavage of **117** with boron tribromide provides the naturally occurring alkaloid 3-formyl-7-hydroxycarbazole (**119**). Treatment of clauszoline-K (**117**) with manganese dioxide in the presence of potassium cyanide in methanol converts the formyl group to a methyl ester function and thus, affords clausine C (**118**). Clausine C (**118**) can be further transformed to clausine M (**120**) or clausine N (**121**) by ether cleavage or saponification of the methyl ester. Quantitative and regioselective electrophilic bromination of intermediate **116** at C-6 was achieved using *N*-bromosuccinimide (NBS). Ether cleavage followed by coupling with a dimeric π-prenylnickel bromide complex, generated in situ from prenyl bromide (**86**) and bis(1,5-cyclooctadiene)nickel(0), provided siamenol (**124**) [148].

A wide range of 6-oxygenated carbazole alkaloids has been isolated from natural sources. Glycozoline (**128**) was originally isolated from the root bark of *Glycosmis pentaphylla* [161, 162]. It shows antibiotic and antifungal properties [163]. The related 3-methyl-6-hydroxycarbazole (**131**) was obtained first from *G. pentaphylla* and named glycozolinine (**131**) [164]. Bhattacharyya isolated the same compound one year later and named it glycozolinol (**131**) [165]. Glycomaurrol (**135**) was found in the extract of the stem bark of *Glycosmis mauritiana* [166]. Franzblau isolated 3-formyl-6-methoxycarbazole (**129**) and micromeline (**130**) from the stem bark extract of *Micromelum hirsutum* [167]. Both compounds showed anti-TB activity. The furo[2,3-*c*]carbazole alkaloid eustifoline-D (**132**) (Scheme 29) was isolated from the root bark of *M. euchrestifolia* Hayata [168], a plant that has been traditionally used in Chinese folk medicine.

Our palladium-catalyzed approach for the construction of the carbazole framework led to the 6-oxygenated tricyclic carbazole alkaloids glycozoline (**128**), methyl 6-methoxycarbazole-3-carboxylate (**133**), glycomaurrol (**135**) and micromeline (**130**), as well as to the furo[2,3-*c*]carbazole alkaloid eustifoline-D (**132**) (Scheme 29) [149]. Palladium-catalyzed coupling of *p*-bromoanisole (**125**) and *p*-toluidine (**126**) as the first step led almost quantitatively to the diarylamine **127**. Oxidative cyclization of intermediate **127** using 0.1 equiv. of palladium(II) acetate in the presence of an excess of copper(II) acetate provided glycozoline (**128**) in 60% yield, which corresponds to a turnover number of TON = 6 for the palladium(II) catalyst. Glycozoline (**128**) represents a central intermediate of this approach. Oxidation of the 3-methyl group to a formyl moiety with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) provided 3-formyl-6-methoxycarbazole (**129**). Further oxidation of the formyl group using Corey's conditions by treatment with manganese dioxide and potassium cyanide in methanol afforded methyl 6-methoxycarbazole-3-carboxylate (**133**), which is a naturally occurring carbazole alkaloid. Alternatively, compound **129** can be regioselectively brominated at the 5-position. Subsequent cleavage of the methyl ether and prenylation at C-5 with the dimeric π-prenylnickel bromide complex afforded micromeline (**130**). Ether cleavage of glycozoline (**128**) with boron tribromide provided the 6-hydroxycarbazole glycozolinine (**131**). Annulation of the furan ring by reaction with 2-bromo-1,1-diethoxyethane and subsequent cyclization under acidic conditions using catalytic amounts of amberlyst 15 led to eustifoline-D (**132**) and its

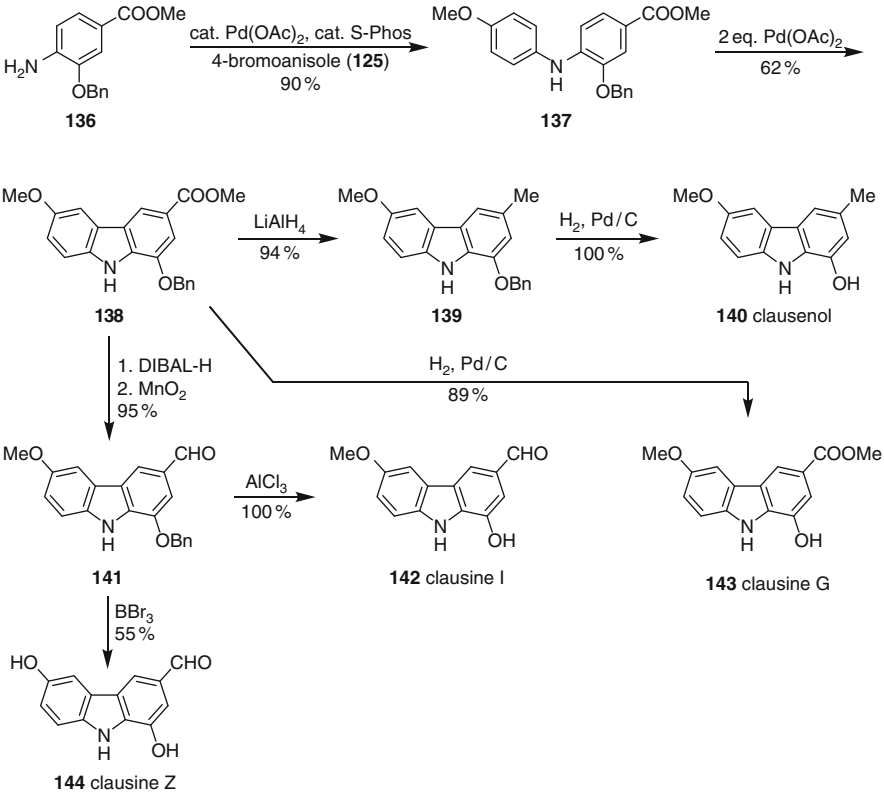


Scheme 29 Palladium-catalyzed synthesis of 6-oxygenated carbazole alkaloids and the furo[2,3-*c*]carbazole alkaloid eustifoline-D (**132**)

regioisomer in a ratio of 4.3:1. In analogy to 3-formyl-6-methoxycarbazole (**129**), glycozolinine (**131**) was brominated at C-5. Coupling of the resulting 5-bromocarbazole **134** with the dimeric π-prenylnickel bromide complex provided glycomaurrol (**135**) [149].

1,6-Dioxygenated carbazole alkaloids have been obtained from several species of the genus *Clausena*. The first 1,6-dioxygenated carbazole alkaloid from natural sources was 6-methoxymurrayanine which has been isolated from the roots of *Clausena lansium* by El-Feraly et al. in 1991 [169]. This report was followed four years later by the isolation of clausenine and clausenol (**140**) from the dried stem bark of *Clausena anisata* by Chakraborty and co-workers [170]. Both compounds show antibiotic activity. In 1996, Wu et al. isolated clausine I (**142**) and clausine G (**143**) from *C. excavata* [113, 158]. Clausine I (**142**) inhibits blood platelet aggregation. Clausine Z (**144**) was obtained from the stem and leaves of *C. excavata* by Potterat et al. in 2005 [171]. It is active against cyclin-dependent kinase 5 (CDK5) and protects cerebral granule neurons against free radical induced cell death.

We achieved the first total synthesis of the 1,6-dioxygenated carbazole alkaloids clausine G (**143**), clausine I (**142**), and clausine Z (**144**) using our palladium-catalyzed approach (Scheme 30) [172]. Methyl 4-amino-3-benzyloxybenzoate (**136**) was obtained in three steps from commercially available 3-hydroxy-4-nitrobenzoic acid. Buchwald–Hartwig coupling of the arylamine **136** with *p*-bromoanisole (**125**) using catalytic amounts of palladium(0) and S-Phos (2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl) as ligand afforded the diarylamine **137**. For the oxidative cyclization to carbazole **138**, application of over-stoichiometric amounts of palladium(II) acetate provided the best results, which has been ascribed to the presence of an electron-withdrawing group [141]. Clausine G (**143**) is readily prepared by catalytic debenzylation of the central intermediate **138**. Reduction of **138** with lithium aluminum hydride converted the ester function into a methyl group and gave compound **139**. Subsequent removal of the benzyl protecting group led to clausenol (**140**). Reduction of intermediate **138** with diisobutylaluminum hydride (DIBAL-H) and subsequent oxidation of the benzylic alcohol with manganese dioxide afforded the 3-formylcarbazole **141**. This product was

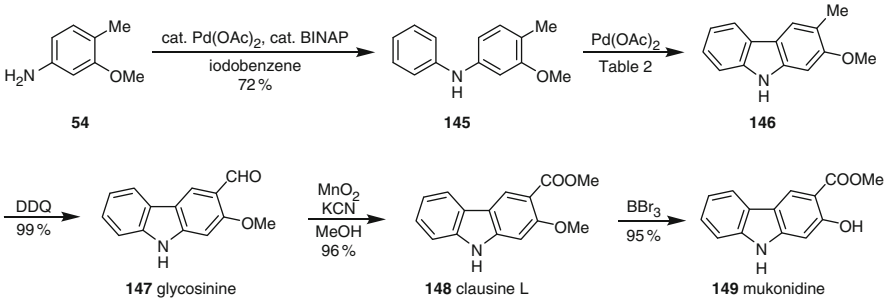


Scheme 30 Palladium-catalyzed synthesis of 1,6-dioxygenated carbazole alkaloids

either selectively debenzylated using aluminum trichloride to give clausine I (**142**), or treated with boron tribromide to provide clausine Z (**144**) by cleavage of both ether groups (Scheme 30) [172]. Moreover, the naturally occurring carbazole alkaloids clausenine and 6-methoxymurrayanine have been synthesized via a similar reaction sequence starting from methyl 4-amino-3-methoxybenzoate [172].

A large number of 2-oxygenated carbazoles has been isolated from natural sources [18, 20]. Mukonidine (**149**) and clausine L (*O*-methylmukonidine) (**148**) have been isolated by Wu et al. from the Chinese medicinal plant *C. excavata* [173]. 2-Methoxy-3-methylcarbazole (**146**) was obtained first from the seeds of the Indian medicinal plant *Murraya koenigii* by Bhattacharyya and co-workers [174]. The isolation of *O*-methylmukonal (**147**) was reported by Lange et al. from *M. siamensis* [112]. Two years later, Bhattacharyya found the same compound in the roots of *G. pentaphylla* and renamed it glycosinine (**147**) [175]. Clausine V (**151**), a 2,7-dioxygenated carbazole alkaloid, was extracted from the root bark of *C. excavata* by Wu and co-workers [116].

Naturally occurring 2-oxygenated carbazole alkaloids are easily accessible via our palladium-catalyzed route. Thus, 2-methoxy-3-methylcarbazole (**146**), glycosinine (**147**), clausine L (**148**), and mukonidine (**149**) became available via one synthetic sequence (Scheme 31) [150]. Buchwald–Hartwig coupling of 3-methoxy-4-methylaniline (**54**) with iodobenzene provided the diarylamine **145**. The subsequent oxidative cyclization of **145** has been investigated using different sets of reaction conditions (Table 2). The best result was obtained using 0.3 equiv. of



Scheme 31 Palladium-catalyzed synthesis of 2-oxygenated carbazole alkaloids

Table 2 Optimization of the palladium(II)-catalyzed oxidative cyclization of the diarylamine **145** to 2-methoxy-3-methylcarbazole (**146**)

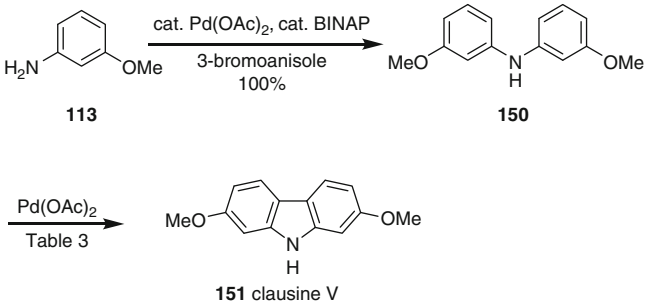
$Pd(OAc)_2$ (equiv.)	$Cu(OAc)_2$ (equiv.)	Reaction conditions	**146**, Yield (%)	**145** (%)[a]	TON[b]
1.2	–	AcOH, reflux, Ar, 1.5 h	48	9	–
0.3	2.5	AcOH, reflux, Ar, 15 h	58	–	1.9
0.3	2.5	AcOH, 90°C, Ar, 21 h	56	33	1.9
0.3	2.5	PivOH, 90°C, Ar, 3 h	63	26	2.1

[a]Reisolated starting material
[b]TON = turnover number

palladium(II) acetate and 2.5 equiv. of copper(II) acetate in pivalic acid under argon atmosphere. The use of pivalic acid instead of acetic acid proved to be advantageous [176]. However, the turnover number of 2.1 for this reaction was rather poor. The product, 2-methoxy-3-methylcarbazole (**146**), represents a naturally occurring carbazole alkaloid. Oxidation of the methyl group at C-3 with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) led to glycosinine (**147**). Further oxidation to the methyl ester using manganese dioxide and potassium cyanide in methanol provided clausine L (**148**). Finally, ether cleavage of **148** with boron tribromide afforded mukonidine (**149**) [150].

Clausine V (**151**) was prepared in two steps (Scheme 32) [150]. Buchwald–Hartwig coupling of *m*-anisidine (**113**) with 3-bromoanisole afforded the diarylamine **150**. Different reaction conditions have been tried for the subsequent palladium(II)-catalyzed oxidative cyclization to clausine V (**151**) (Table 3). Application of 0.1 equiv. of palladium(II) acetate and 0.1 equiv. of copper(II) acetate in glacial acetic acid under an oxygen atmosphere gave the best result for the catalytic process (49% yield). The turnover number of almost 5 confirmed that the system works in a catalytic mode. However, in this case the best yield (67%) was obtained using stoichiometric amounts of palladium(II) acetate in air without co-oxidant.

Pityriazole (**152**) represents an unusual example of a 2-oxygenated carbazole alkaloid since it has an additional indol-3-yl substituent at C-1. This natural product was isolated along with other tryptophan metabolites by Steglich and co-workers from a culture of the human pathogenic yeast *Malassezia furfur*, which is believed to be responsible for the skin disease pityriasis versicolor [177]. Due to the structural similarity of pityriazole (**152**) to mukonidine (**149**) and clausine L (**148**), we



Scheme 32 Synthesis of clausine V (**151**)

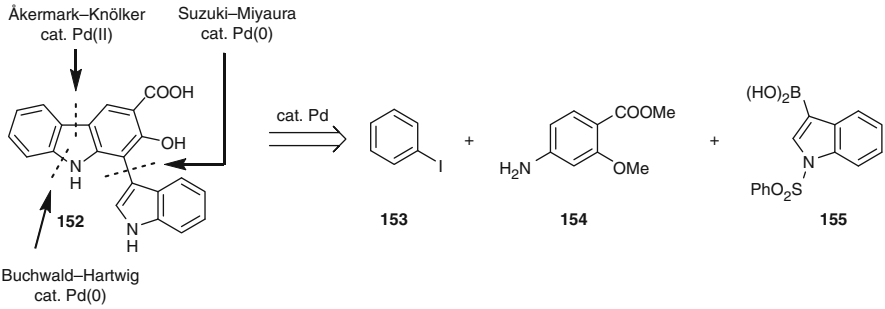
Table 3 Optimization of the palladium(II)-catalyzed oxidative cyclization of the diarylamine **150** to clausine V (**151**)

$Pd(OAc)_2$ (equiv.)	Co-oxidant (equiv.)	Reaction conditions	**151**, Yield (%)	TON[a]
1.2	–	AcOH, reflux, air, 50 min	67	–
0.1	0.1 $Cu(OAc)_2$	AcOH, reflux, air, 9 h	37	3.7
0.1	0.1 $Cu(OAc)_2$	AcOH, reflux, O_2, 9 h	49	4.9
0.1	0.1 $Mn(OAc)_3 \cdot 2\ H_2O$	AcOH, reflux, O_2, 6 h	47	4.7

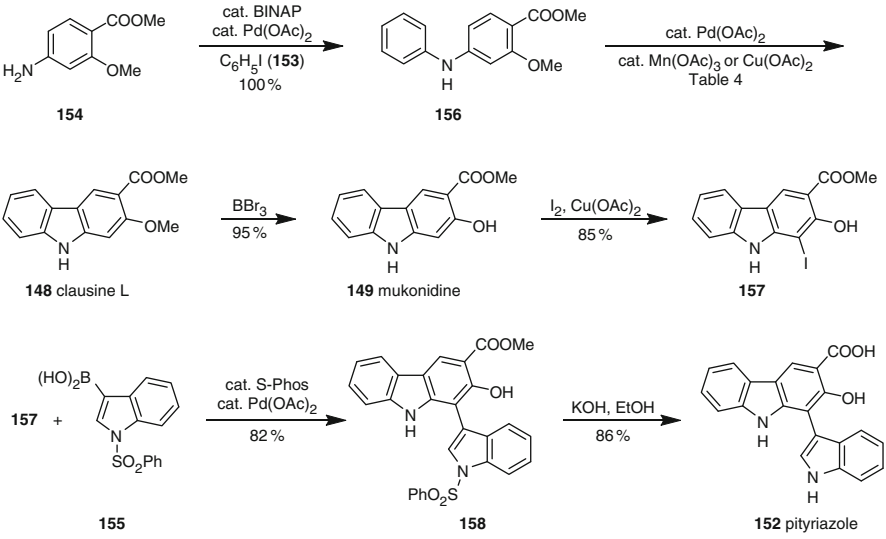
[a]TON = turnover number

envisaged a common synthetic strategy for all three natural products [178]. Our synthetic strategy for pityriazole (**152**) involved construction of the central pyrrole ring of the carbazole framework by palladium(0)-catalyzed Buchwald–Hartwig amination and subsequent palladium(II)-catalyzed oxidative cyclization (Scheme 33). The indol-3-yl group at C-1 should be introduced by palladium(0)-catalyzed Suzuki–Miyaura coupling with the *N*-protected indol-3-ylboronic acid **155**.

Palladium(0)-catalyzed coupling of iodobenzene (**153**) and the commercial arylamine **154** afforded quantitatively the diarylamine **156** (Scheme 34) [178]. The oxidative cyclization of the diarylamine **156** to clausine L (**148**) is catalytic in palladium(II) and copper(II) acetate (or manganese(III) acetate, respectively). Thus, air is the actual oxidizing agent in this process. For example, employing only 0.05 equiv. of palladium(II) acetate and 0.1 equiv. of copper(II) acetate provided



Scheme 33 Retrosynthetic analysis of pityriazole (**152**)

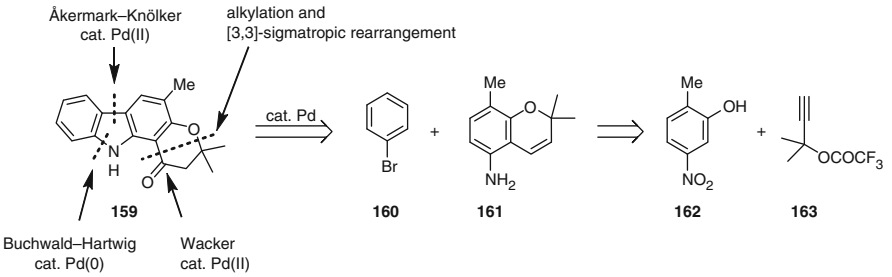


Scheme 34 Synthesis of clausine L (**148**), mukonidine (**149**), and pityriazole (**152**)

Table 4 Optimization of the palladium(II)-catalyzed oxidative cyclization of the diarylamine **156** to clausine L (**148**)

$Pd(OAc)_2$ (equiv.)	Co-oxidant (equiv.)	Reaction conditions	**148**, Yield (%)	**156**, (%)[a]	TON[b]
0.1	2.5 $Cu(OAc)_2$	PivOH, 100°C, air, 1 day	44	55	4.4
0.1	0.1 $Cu(OAc)_2$	PivOH, 100°C, air, 17 h	55	38	5.5
0.05	0.1 $Cu(OAc)_2$	PivOH, 100°C, air, 3.5 days	61	24	12.2
0.12	0.1 $Mn(OAc)_3$	PivOH, 100°C, air, 3 days	62	15	5.2

[a]Reisolated starting material
[b]TON = turnover number for Pd(II)



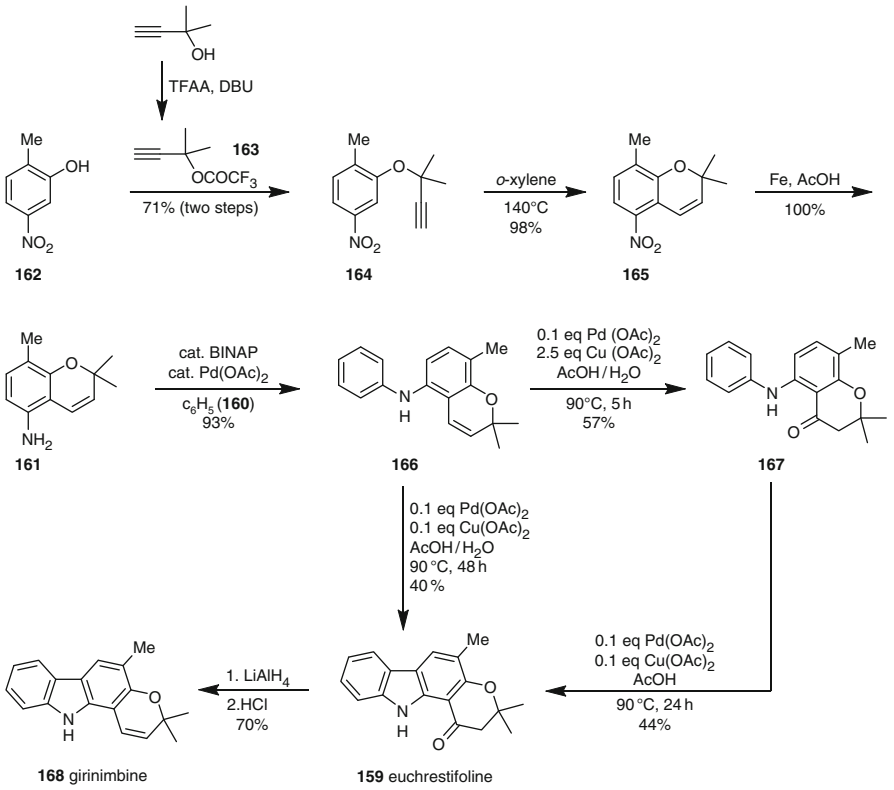
Scheme 35 Retrosynthetic analysis of euchrestifoline (**159**)

clausine L (**148**) in 61% yield which corresponds to a turnover number (TON) of 12.2 for this reaction (Table 4). It is interesting to note that in all cases remaining starting material could be recovered. Ether cleavage of clausine L (**148**) using boron tribromide afforded mukonidine (**149**) and opened up a highly efficient access to this alkaloid (three steps and 59% overall yield). Electrophilic iodination of mukonidine (**149**) at C-1 led to 1-iodomukonidine (**157**). The subsequent Suzuki–Miyaura coupling with the indolylboronic acid **155** was carried out with microwave heating using moist potassium phosphate as base and S-Phos (2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl) as ligand to give the 1-indolylcarbazole **158** in 82% yield. Saponification of the methyl ester with concomitant removal of the protecting group provided pityriazole (**152**). Using our route, pityriazole is available in six steps and an overall yield of 35%. Moreover, this approach provided the first synthetic access to clausine L (**148**) [178].

Euchrestifoline (**159**) was isolated from the leaves of the Chinese medicinal plant *M. euchrestifolia* by Wu and co-workers [179]. The structurally related compound girinimbine (**168**) was obtained and characterized first by Chakraborty and co-workers from the stem bark of *M. koenigii* [180]. Retrosynthetic analysis of the tetracyclic ring system leads to bromobenzene (**160**) and 2,2,8-trimethyl-2*H*-chromen-5-amine (**161**) as appropriate starting materials for application of our methodology (Scheme 35). The keto function was thought to be introduced via a regioselective Wacker oxidation of the chromene moiety. Compound **161**

should be obtained from 2-methyl-4-nitrophenol (**162**) and the propargyl trifluoroacetate **163**.

The propargyl ether **164** was prepared by alkylation of 2-methyl-5-nitrophenol (**162**) with the propargyl trifluoroacetate **163**, which was prepared in situ from the corresponding propargyl alcohol and trifluoroacetic anhydride (TFAA) (71% yield over both steps) (Scheme 36) [181]. [3,3]-Sigmatropic rearrangement of **164** with subsequent cyclization afforded the nitrochromene **165**, which on reduction of the nitro group with iron powder in acetic acid led to the aminochromene **161**. Buchwald–Hartwig coupling of **161** and bromobenzene (**160**) provided the diarylamine **166**. Using catalytic amounts of palladium(II) acetate in the presence of copper(II) acetate in a 10:1 mixture of acetic acid and water initiates both, Wacker oxidation of the double bond and oxidative cyclization by double aryl C–H bond activation. A detailed study of this transformation revealed that the activation of the vinylic C–H bond proceeds faster. Thus, after a reaction time of only 5 h, Wacker oxidation of **166** led to the chromanone **167** (TON = 5.7). Resubmission of compound **167** to the conditions for palladium(II)-catalyzed oxidation for an extended period of time (24 h) resulted in cyclization to euchrestifoline (**159**)



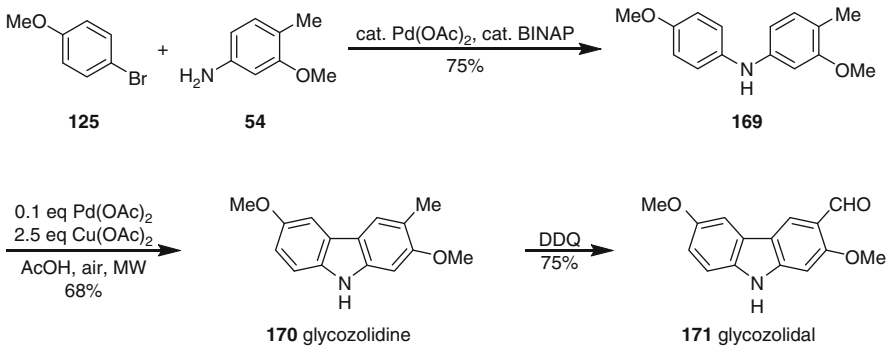
Scheme 36 Synthesis of euchrestifoline (**159**) and girinimbine (**168**)

(TON = 4.4). Under optimized conditions compound **166** can be directly converted to euchrestifoline (**159**) by reaction with 0.1 equiv. of palladium(II) acetate and 0.1 equiv. of copper(II) acetate for 2 days. The turnover number for the one-pot triple C–H bond activation (TON of 4.0) is in the same order of magnitude as for the individual reactions (Wacker oxidation and oxidative cyclization). Euchrestifoline (**159**) was further transformed into girinimbine (**168**) by reduction of the ketone using lithium aluminum hydride followed by elimination under acidic conditions.

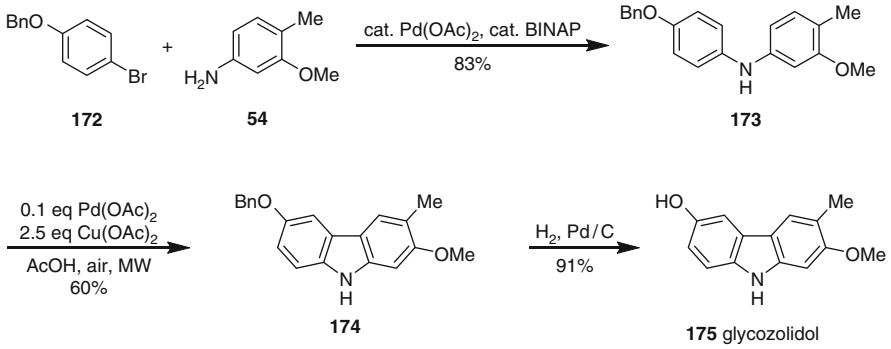
The 2,6-dioxygenated carbazole alkaloid glycozolidine (**170**) was isolated first by Chakraborty et al. from the root bark of *G. pentaphylla* in 1966 [182]. Glycozolidal (**171**) and glycozolidol (**175**) were obtained from the same natural source by Bhattacharyya et al. [183, 184]. Carbalexin C (**179**) represents a stress-induced phytoalexin generated in the leaves of *G. pentaphylla* and *Glycosmis parviflora* [185]. Lansine (**181**) was isolated by Kapil et al. from the leaves of *C. lansium* [186]. Glycozolidal (**171**) and lansine (**181**) were also isolated by Wu and coworkers from the stem bark of the Chinese medicinal plant *C. excavata* [113].

Glycozolidine (**170**) was synthesized via a straightforward two-step reaction sequence. Buchwald–Hartwig coupling of 4-bromoanisol (**125**) with 3-methoxy-4-methylaniline (**54**) afforded the diarylamine **169** (Scheme 37) [152]. Oxidative cyclization of **169** using 0.1 equiv. of palladium(II) acetate and 2.5 equiv. of copper(II) acetate under microwave irradiation provided glycozolidine (**170**) (TON = 6.8). Oxidation of the methyl group of **170** using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) afforded glycozolidal (**171**).

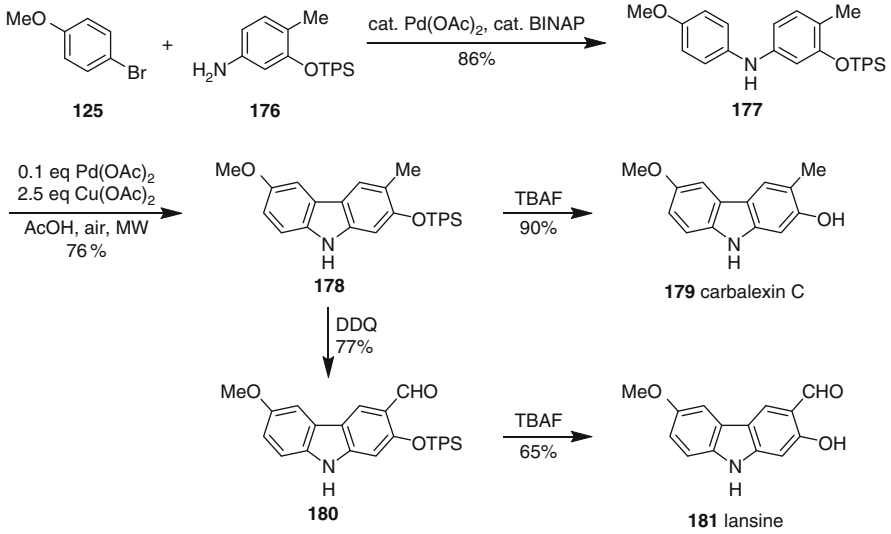
The hydroxy-methoxycarbazoles glycozolidol (**175**), carbalexin C (**179**), and lansine (**181**) were prepared using protecting groups for the hydroxy groups at the 2- or 6-position, respectively. Thus, the synthesis of glycozolidol (**175**) starts with Buchwald–Hartwig amination of the benzyl-protected *p*-bromophenol **172** and 3-methoxy-4-methylaniline (**54**) (Scheme 38) [152]. The palladium(II)-catalyzed oxidative cyclization provided the benzyl-protected glycozolidol **174** (TON = 6.0) under the same conditions as described above for the synthesis of glycozolidine (**170**) (cf. Scheme 37). Finally, removal of the benzyl group led to glycozolidol (**175**).



Scheme 37 Synthesis of glycozolidine (**170**) and glycozolidal (**171**)

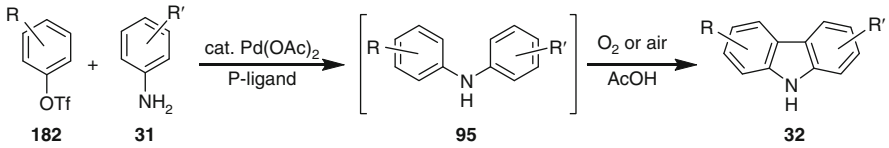


Scheme 38 Synthesis of glycozolidol (**175**)



Scheme 39 Synthesis of carbalexin C (**179**) and lansine (**181**)

For the synthesis of carbalexin C (**179**) and lansine (**181**) the protecting group strategy was reversed. The TPS-protected 2-methyl-5-aminophenol **176** had to be employed to enable a release of the free hydroxy group at C-2 in the final step of the synthesis. Buchwald–Hartwig coupling of compound **176** with *p*-bromoanisole (**125**) afforded the diarylamine **177** (Scheme 39) [152]. The palladium(II)-catalyzed oxidative cyclization in the presence of copper(II) acetate as co-oxidant under microwave irradiation gave the carbazole **178** (TON = 7.6). Desilylation of compound **178** led to carbalexin C (**179**). This first total synthesis provided the phytoalexin carbalexin C (**179**) in five steps and 59% overall yield based



Scheme 40 Synthesis of carbazoles **32** by a one-pot Buchwald–Hartwig amination/oxidative cyclization

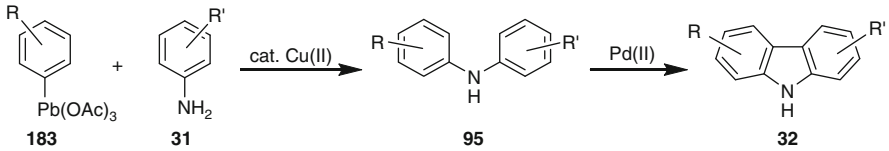
on 2-methyl-5-nitrophenol (**162**). Oxidation of the methyl group at C-3 of the carbazole **178** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave compound **180** and subsequent removal of the silyl protecting group afforded lansine (**181**).

The palladium(II)-catalyzed oxidative cyclization of diarylamines in pivalic acid as solvent has been applied to the synthesis of murrayafoline A (**188**), mukonine (**201**) and clausenine [187]. Ohno et al. combined the palladium(0)-catalyzed N-arylation of arylamines and the palladium(II)-catalyzed oxidative cyclization of the resulting diarylamines to a one-pot procedure (Scheme 40) [188, 189]. Buchwald–Hartwig coupling of aryl triflates **182** with the arylamines **31** using 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (X-Phos) as ligand led to the intermediate diarylamines **95**. Subsequent addition of acetic acid and exposure to air or oxygen atmosphere initiated the oxidative cyclization to carbazoles **32**. This procedure has been applied to the synthesis of a variety of substituted non-natural carbazoles. The alkaloid clausine L (**148**) which displays anti-platelet aggregation activity could be prepared in 74% yield by direct coupling of methyl 4-amino-2-methoxybenzoate (**154**) with phenyl trifluoromethanesulfonate.

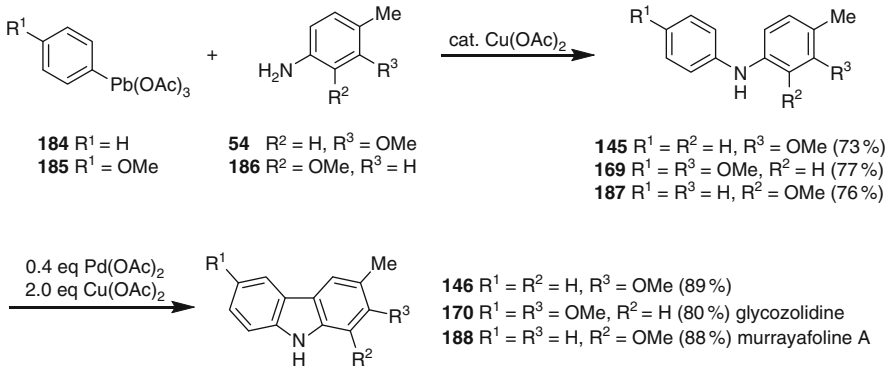
3.2.2 Copper-Catalyzed N-Arylation Followed by Oxidative Cyclization (Cu[II]/Pd[II])

A construction of the carbazole framework involving copper(II)-catalyzed arylamine arylation and palladium(II)-mediated oxidative cyclization has been reported by Menéndez et al. (Scheme 41) [190, 191]. The diarylamines **95** were obtained by copper(II) acetate-catalyzed N-arylation of arylamines **31** with phenyllead triacetate (**183**) using Barton's conditions [192]. Subsequent oxidative cyclization using palladium(II) acetate under microwave irradiation afforded the carbazoles **32**. This procedure was applied to the synthesis of murrayafoline A (**188**) [190].

Subsequently, these authors also used the palladium(II)-catalyzed version with copper(II) acetate as co-oxidant, originally reported by Knölker et al. [142–152], for the synthesis of murrayafoline A (**188**), 2-methoxy-3-methylcarbazole (**146**), and glycozolidine (**170**) (Scheme 42), as well as some non-natural carbazoles [191].



Scheme 41 Synthesis of carbazoles **32** by Cu(II)-catalyzed N-arylation of the arylamines **31** and subsequent oxidative cyclization of the diarylamines **95**



184 R^1 = H
185 R^1 = OMe

54 R^2 = H, R^3 = OMe
186 R^2 = OMe, R^3 = H

145 $R^1 = R^2$ = H, R^3 = OMe (73 %)
169 $R^1 = R^3$ = OMe, R^2 = H (77 %)
187 $R^1 = R^3$ = H, R^2 = OMe (76 %)

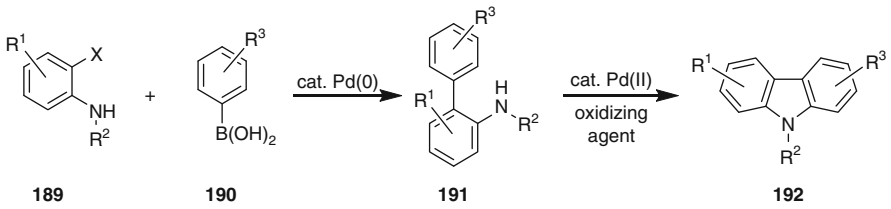
146 $R^1 = R^2$ = H, R^3 = OMe (89 %)
170 $R^1 = R^3$ = OMe, R^2 = H (80 %) glycozolidine
188 $R^1 = R^3$ = H, R^2 = OMe (88 %) murrayafoline A

Scheme 42 Synthesis of 2-methoxy-3-methylcarbazole (**146**), glycozolidine (**170**), and murrayafoline A (**188**)

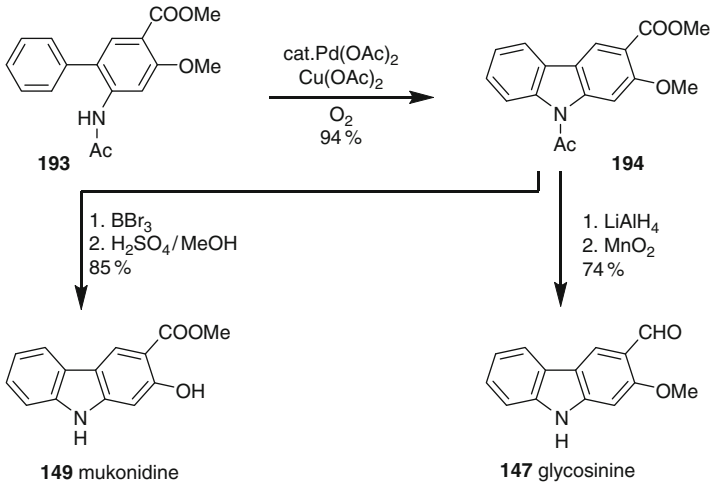
3.2.3 Suzuki–Miyaura Coupling Followed by Oxidative C–H Bond Amination or Amidation (Pd[0]/Pd[II])

In contrast to the synthetic approaches described in Sects. 3.2.1 and 3.2.2, the N-arylation and C–C coupling steps can also be reversed. Suzuki–Miyaura coupling of *N*-substituted 2-haloarylamines **189** with arylboronic acids **190** provides *N*-substituted 2-aminobiaryls **191** (Scheme 43). A palladium(II)-catalyzed oxidative cyclization of the latter forms the tricyclic carbazole framework. Different from the first reaction step in Scheme 24, this is an oxidative C–N coupling which requires N–H and C–H activation, whereas the C–C bond is formed in a cross-coupling process.

Oxidative cyclization of 2-phenylacetanilides in the presence of catalytic amounts of palladium(II) acetate and copper(II) acetate as co-oxidant in an oxygen atmosphere affords *N*-acetylcarbazoles. Subsequent hydrolysis or reduction of the *N*-acetylcarbazoles leads to the corresponding 9*H*-carbazoles [193]. For the synthesis of mukonidine (**149**) and glycosinine (**147**) oxidative cyclization of the *N*-acetylated 2-aminobiphenyl **193** afforded the *N*-acetylcarbazole **194** (Scheme 44) [194]. Demethylation of **194** and amide cleavage led to mukonidine (**149**). Alternatively, reduction of compound **194** with lithium aluminum hydride



Scheme 43 Synthesis of carbazoles **192** by Suzuki–Miyaura coupling and subsequent oxidative cyclization of the 2-aminobiaryl compounds **191**



Scheme 44 Synthesis of mukonidine (**149**) and glycosinine (**147**)

followed by oxidation of the resulting benzylic alcohol with manganese dioxide provided glycosinine (**147**). Analogously, mukonine (**201**) was obtained starting from an appropriate 2-phenylacetanilide.

Using 0.2 equiv. of palladium(II) acetate and (diacetoxy)iodobenzene as co-oxidant, Gaunt et al. achieved an oxidative cyclization of *N*-alkylbiphenyl-2-amines including C–H activation at the 2′-position to give *N*-alkylcarbazoles [195]. The potential of this method was demonstrated by the synthesis of an *N*-glycosylcarbazole.

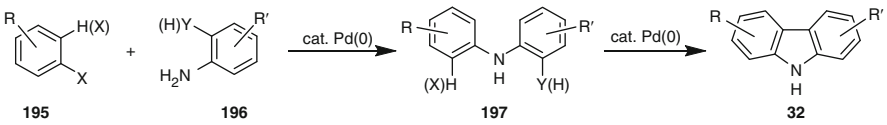
3.2.4 Buchwald–Hartwig Amination Followed by Heck-Type Coupling (Pd[0]/Pd[0])

Carbazoles can be obtained by a sequence of Buchwald–Hartwig amination and intramolecular Heck-type biaryl coupling. Depending on the distribution of

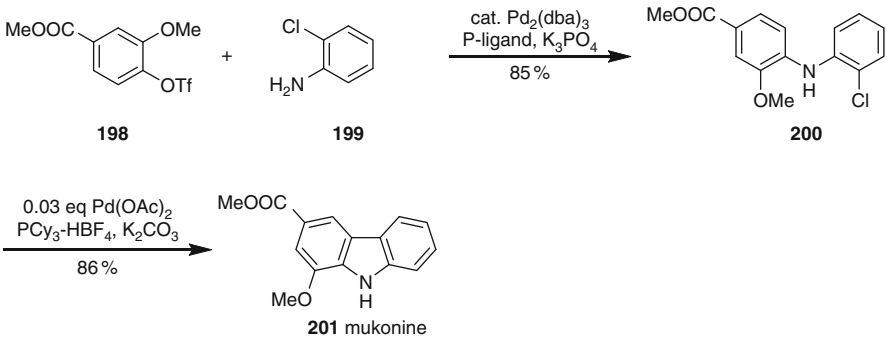
the functional groups in the substrates, two procedures can be distinguished for this approach. The two leaving groups can be placed in one ring as given for the 1,2-dihalo(triflyloxy)arenes **195**. Buchwald–Hartwig coupling with a non-halogenated arylamine **196** followed by Heck-type diaryl coupling of the intermediate monohalodiarylamines **197** provides the carbazoles **32**. Alternatively, the leaving groups can be located in different rings, one in the arene **195** and the other *ortho* to the amino group of the arylamine **196** as shown first by Sakamoto et al. [196]. On palladium(0)-catalyzed coupling the carbazoles **32** are formed via an intermediate diarylamine **197** by the same reaction sequence (Scheme 45).

Buchwald–Hartwig coupling of 2-chloroaniline (**199**) and aryl bromides was used as the first step by Bedford and co-workers [197]. Subsequent palladium(0)-catalyzed cyclization by C–H bond activation afforded the carbazole ring system. For a few examples the transformations could be carried out in one pot. Carbazole natural products, including clausine P and glycozolidine (**170**) [197], and a number of fluorocarbazoles [198] are available by this procedure. Starting from simple *o*-substituted iodoarenes and *N*-sulfonated or *N*-acetylated *o*-bromoanilines, Catellani et al. described a palladium(0)- and norbornene-catalyzed synthesis of substituted carbazoles by sequential C–C and C–N cross coupling [199]. This methodology has been used for the synthesis of carbazomycin A.

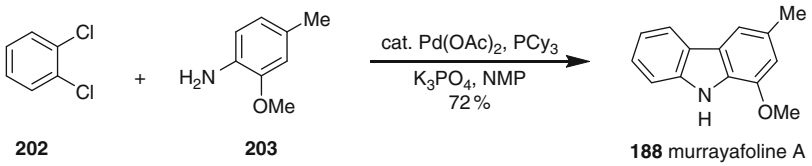
Fagnou et al. applied the intramolecular arylation to the synthesis of mukonine (**201**) (Scheme 46) [200]. Buchwald–Hartwig coupling of 2-chloroaniline (**199**)



Scheme 45 Synthesis of carbazoles **32** by Buchwald–Hartwig amination and subsequent cyclization by intramolecular Heck-type coupling of the intermediate diarylamines **197**



Scheme 46 Synthesis of mukonine (**201**)



202 **203** **188** murrayafoline A

Scheme 47 Synthesis of murrayafoline A (**188**)

with the aryl triflate **198** led to the diarylamine **200**. Subsequent Heck-type cyclization afforded mukonine (**201**).

Chlorinated diarylamines have also been successfully cyclized using *N*-heterocyclic carbene (NHC) palladium catalysts. It has been demonstrated that the turnover number of the catalytic system is substantially improved by using imidazolium salt additives along with a mono-NHC–palladium(II) pre-catalyst [201].

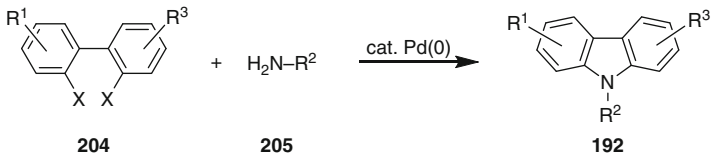
A potential homo-coupling of the halogenated arylamines is avoided by having the halogen leaving groups attached to the same arene. Guided by this idea, Ackermann et al. reported a palladium-catalyzed domino synthesis of substituted carbazoles with readily available anilines and 1,2-dihaloarenes (Scheme 47) [202]. The procedure has been applied to the synthesis of murrayafoline A (**188**) by coupling of 1,2-dichlorobenzene (**202**) with the arylamine **203**.

3.2.5 Suzuki–Miyaura Coupling Followed by Double Buchwald–Hartwig Amination (Pd[0]/Pd[0])

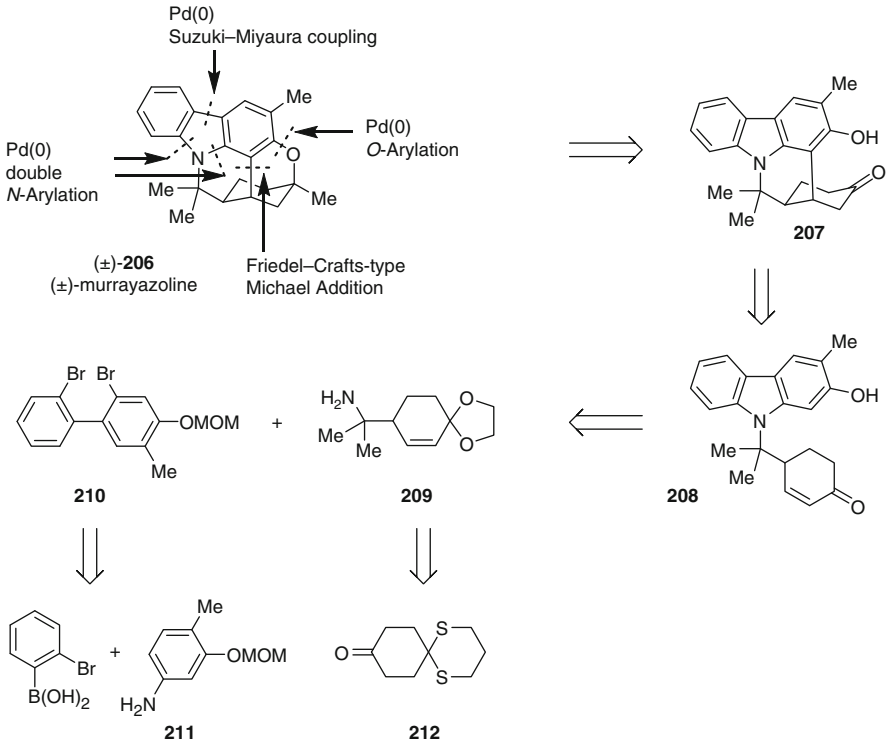
N-Substituted carbazoles **192** are available by double Buchwald–Hartwig amination of 2,2′-dihalobiaryl compounds or biaryl bistriflates **204** with primary amines **205** in the presence of catalytic amounts of palladium(0) (Scheme 48) [203–205].

Chida et al. used this strategy for the total synthesis of murrastifoline A [204, 205]) and (±)-murrayazoline [(±)-**206**] [206]. In addition to the double Buchwald–Hartwig amination generating the carbazole framework, two further palladium(0)-catalyzed couplings have been applied to construct the hexacyclic skeleton of (±)-murrayazoline [(±)-**206**], an O-arylation and a Suzuki–Miyaura coupling. Retrosynthetic analysis of (±)-murrayazoline [(±)-**206**] led to 2-bromophenylboronic acid, the arylamine **211**, and the monoprotected cyclohexane-1,4-dione **212** as precursors (Scheme 49).

2,2′-Dibromobiphenyl **210** and the amine **209** were prepared in five and ten steps, respectively. The double Buchwald–Hartwig coupling of **209** and **210** using 0.2 equiv. of tris(dibenzylideneacetone)dipalladium, 0.6 equiv. of 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (X-Phos), and 3 equiv. of sodium *tert*-butoxide in toluene at 130°C in a sealed tube afforded the carbazole **213** in 59% yield (Scheme 50) [206]. Subsequent treatment with scandium(III) triflate resulted in removal of the MOM group, cleavage of the ketal, and subsequent Friedel–Crafts-



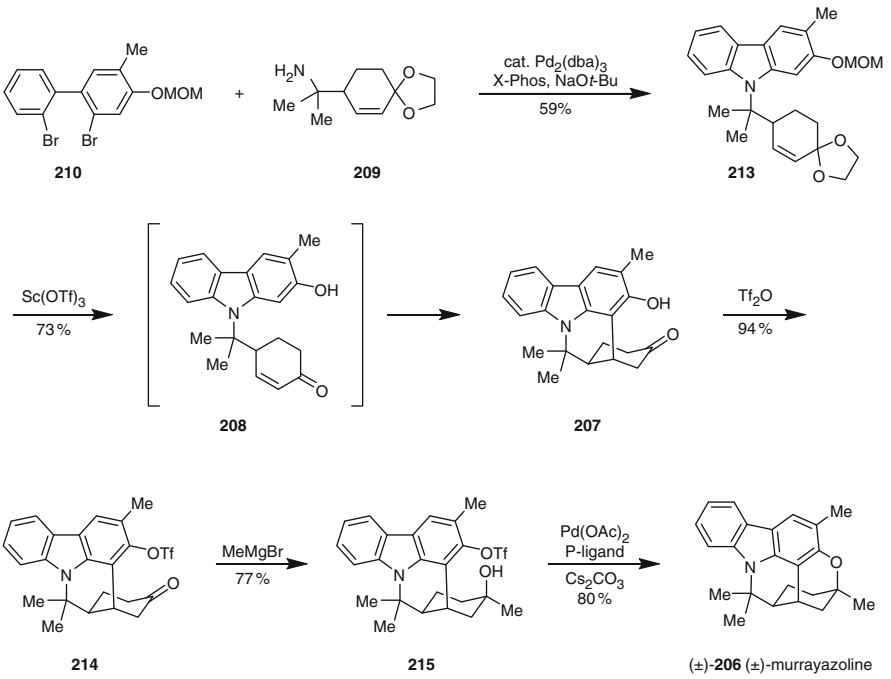
Scheme 48 Synthesis of carbazoles **192** by double Buchwald–Hartwig amination of biaryl compounds **204**



Scheme 49 Retrosynthetic analysis of (±)-murrayazoline [(±)-**206**]

type Michael addition to give the pentacyclic carbazole **207**. Conversion of the hydroxy group into the triflate and diastereoselective methylation of the ketone led to the carbinol **215**. Finally, cyclization by O-arylation using stoichiometric amounts of palladium(II) acetate, 2-di-*tert*-butylphosphinobiphenyl, and cesium carbonate provided (±)-murrayazoline [(±)-**206**].

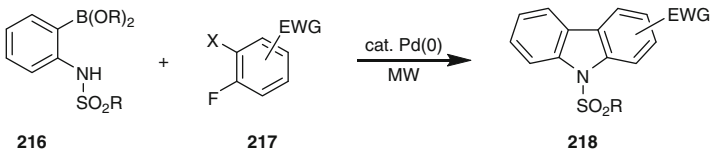
Further applications of the double N-arylation to the synthesis of carbazoles include the natural products ellipticine [207] and mukonine (**201**) [208], and various non-natural 11-phenylbenzofuro[3,2-*b*]carbazoles [209].



Scheme 50 Synthesis of (±)-murrayazoline [(±)-**206**]

3.2.6 Suzuki–Miyaura Coupling Followed by S_NAr-Reaction (Pd[0])

A tandem Suzuki–Miyaura coupling/nucleophilic aromatic substitution to carbazoles was developed by St. Jean et al. (Scheme 51) [210]. Reaction of *N*-sulfonyl-protected 2-aminophenylboronates **216** with 1-bromo-2-fluorobenzenes **217** under palladium(0)-catalysis provides the *N*-sulfonyl-protected carbazoles **218**. This annulation is compatible with a variety of electron-withdrawing groups (e.g., aldehydes, esters, and sulfones) and has been applied to an efficient synthesis of glycosinine (**147**) (four steps, 50% overall yield).

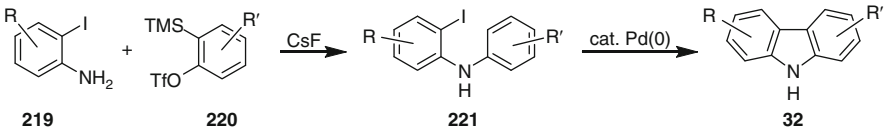


Scheme 51 Synthesis of carbazoles **218** by tandem Suzuki–Miyaura cross-coupling and S_NAr-reaction

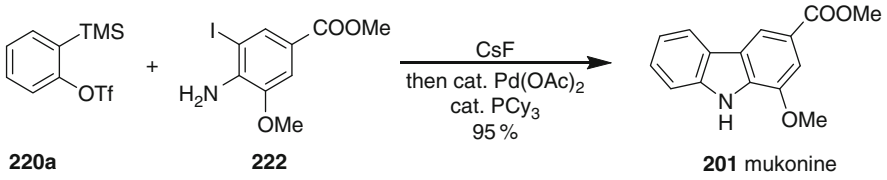
3.2.7 Nucleophilic Addition to Arynes Followed by Heck-Type Coupling (Pd[0])

In a one-pot procedure, the reaction of *o*-iodoanilines **219** with silylaryl triflates **220** in the presence of cesium fluoride affords via an aryne intermediate the *o*-iododiarylamines **221** which are subsequently cyclized to carbazoles **32** by an in situ generated palladium(0) catalyst (Scheme 52) [211, 212].

This procedure has been applied to the synthesis of mukonine (**201**) (Scheme 53) [212]. The *o*-iodoaniline **222** was prepared in two steps from commercially available 4-amino-3-methoxybenzoic acid. Reaction of compound **222** with the silylaryl triflate **220a** in the presence of cesium fluoride leads to an intermediate diarylamine, which is cyclized in situ by addition of catalytic amounts of palladium(II) acetate and tricyclohexylphosphane to afford mukonine (**201**) (three steps and 76% overall yield).



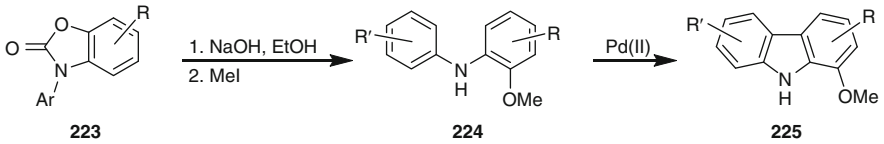
Scheme 52 Synthesis of carbazoles **32** by nucleophilic addition to arynes and subsequent cyclization by intramolecular Heck-type coupling of the diarylamines **221**



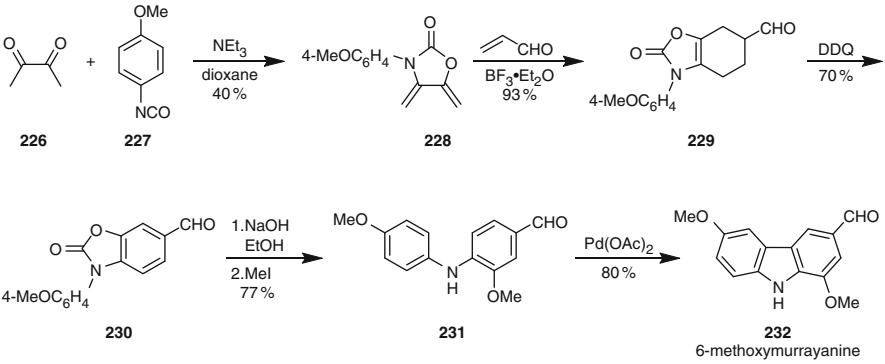
Scheme 53 Synthesis of mukonine (**201**)

3.2.8 Hydrolysis of Benzoxazol-2-ones Followed by Oxidative Cyclization (Pd[II])

Tamariz et al. developed an access to 1-methoxycarbazoles **225** via hydrolysis of 3-arylbenzoxazol-2-ones **223** and subsequent palladium(II)-mediated oxidative cyclization of the resulting diarylamines **224** (Scheme 54) [213, 214]. The required benzoxazol-2-ones **223** are obtained by regioselective Lewis acid-catalyzed Diels–Alder reaction of 4,5-dimethylene-3-aryl-1,3-oxazolidin-2-ones with alkenes followed by aromatization using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).



Scheme 54 Synthesis of 1-methoxycarbazoles **225** by hydrolysis of the benzoxazol-2-ones **223** and subsequent palladium(II)-mediated oxidative cyclization of the diarylamines **224**



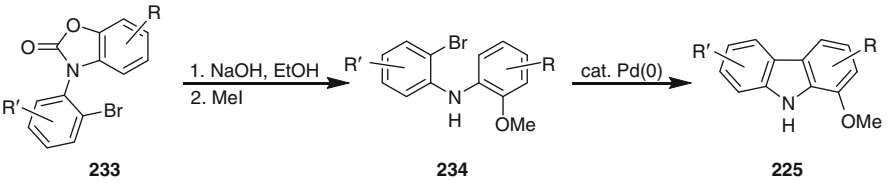
Scheme 55 Synthesis of 6-methoxymurrayanine (**232**)

This sequence has been used for the synthesis of 6-methoxymurrayanine (**232**) (Scheme 55) [214]. Reaction of butane-2,3-dione (**226**) with 4-methoxyphenyl isocyanate (**227**) to 4,5-dimethylene-3-(4-methoxyphenyl)-1,3-oxazolidin-2-one (**228**) followed by regioselective boron trifluoride-catalyzed Diels–Alder reaction with acrolein afforded the oxazolone **229**. Only minor amounts of the undesired regioisomer were formed. Aromatization using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) afforded the benzoxazol-2-one **230**. Saponification of the cyclic carbamate and subsequent O-methylation led to the diarylamine **231**. Finally, oxidative cyclization using stoichiometric amounts of palladium(II) acetate provided 6-methoxymurrayanine (**232**).

This method has also been applied to the synthesis of murrayanine, murrayafoline A (**188**) [213], and clausenine [214] using stoichiometric amounts of palladium (II) actetate for the oxidative cyclization of the intermediate diarylamines.

3.2.9 Hydrolysis of Benzoxazol-2-ones Followed by Heck-Type Coupling (Pd[0])

More recently, a variation of the method described above (cf. Scheme 54) has been reported (Scheme 56) [215]. Hydrolytic cleavage of the 3-(2-bromophenyl)

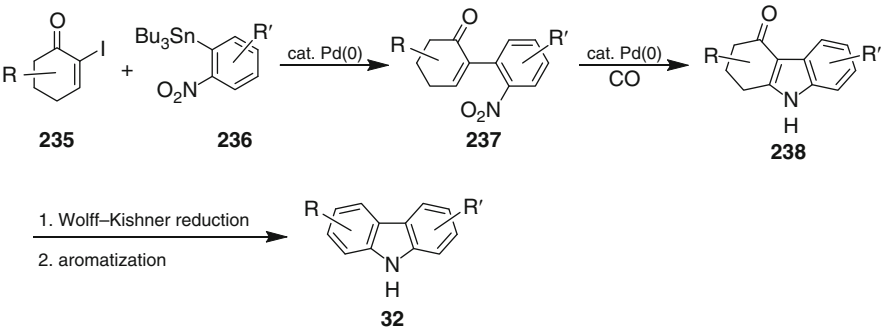


Scheme 56 Synthesis of 1-methoxycarbazoles **225** by hydrolysis of the benzoxazol-2-ones **233** and subsequent cyclization by intramolecular Heck-type coupling of the diarylamines **234**

benzoxazol-2-ones **233** followed by methylation of the hydroxy group provides the diarylamines **234**. Subsequent cyclization by palladium(0)-catalyzed intramolecular Heck-type biaryl coupling leads to the 1-methoxycarbazoles **225**. Following this approach, murrayanine has been synthesized in four steps and 45% overall yield [215].

3.2.10 Stille Coupling Followed by Reductive Annulation (Pd[0]/Pd[0])

Söderberg et al. have developed a sequence of Stille coupling followed by palladium (0)-catalyzed reductive N-heteroannulation for the synthesis of tetrahydrocarbazolones **238** (Scheme 57) [216, 217]. Palladium(0)-catalyzed coupling of 2-nitroarylstannanes **236** with 2-iodo-2-cyclohexenones **235** afforded the 2-(2-nitrophenyl)-2-cyclohexenones **237**. Cyclization with carbon monoxide in the presence of catalytic amounts of bis(dibenzylideneacetone)palladium, 1,3-bis(diphenylphosphino)propane (dppp), and 1,10-phenanthroline led to the corresponding tetrahydrocarbazolones **238** which can be transformed to the carbazoles **32** by Wolff–Kishner reduction and subsequent aromatization. This approach has been applied to the formal synthesis of murrayaquinone A [216].



Scheme 57 Synthesis of carbazoles **32** by Stille coupling and subsequent reductive annulation

4 Conclusion

Transition metal-mediated and -catalyzed coupling reactions can be exploited for selective C–C and/or C–N bond formations. Thus, this chemistry opens up the way to highly efficient routes for the synthesis of heterocyclic ring systems, like pyrroles and carbazoles which are frequently found as frameworks of biologically active naturally occurring alkaloids. The silver(I)-mediated oxidative cyclization of homopropargylamines to pyrroles can be converted to a catalytic process by using the corresponding *N*-tosylhomopropargylamines as substrates. Both versions of this procedure have been applied successfully to natural product synthesis and applications include (±)-harmicine, (±)-crispine A, pentabromopseudilin, and pentachloropseudilin. A range of different methodologies has been developed for the synthesis of carbazoles. The iron-mediated synthesis of carbazoles represents a very useful procedure and has been applied to the total synthesis of hyellazole, 6-chlorohyellazole, 2,7-dioxygenated carbazole alkaloids, furoclausine A, the antiostatin A and B series, (*R*)-(−)-neocarazostatin B, and (*R*)-carquinostatin A. Diverse palladium-catalyzed routes have been developed for the synthesis of carbazole alkaloids. Among these, the sequence of Buchwald–Hartwig amination followed by palladium(II)-catalyzed oxidative cyclization of the intermediate diarylamine has proven to be the most versatile method and superior to the alternative procedures. Recent applications include the total syntheses of the carbazomadurins, epocarbazolins, 7-oxygenated carbazole alkaloids, 6-oxygenated carbazole alkaloids, 1,6-dioxygenated carbazole alkaloids, 2-oxygenated carbazole alkaloids, 2,6-dioxygenated carbazole alkaloids, clausine V, pityriazole, euchrestifoline, and girinimbine.

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