Recent Advances in the Total Synthesis of Piperidine and Pyrrolidine Natural Alkaloids with Ring-Closing Metathesis as a Key Step

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Dedicated, with admiration, to Professor Eric Brown

Keywords: Alkaloids / Cyclization / Metathesis / Total synthesis

This microreview focuses on recent applications of the ring-closing metathesis reaction (RCM) to construct piperidine and pyrrolidine cores for the total synthesis of natural alkaloids. The most recent examples are described, from simple piperidine alkaloids to complex pentacyclic structures such as (+)-tabersonine.

1. Introduction

The last five years have witnessed considerable development of metathesis reactions and an explosion of their application in organic synthesis.[1] Among them, ring-closing metathesis (RCM) has emerged as one of the most powerful tools for the construction of carbo- and heterocyclic compounds, as demonstrated by the numerous total syntheses of complex molecules and natural products that include this versatile technique as the key synthetic step.[2]

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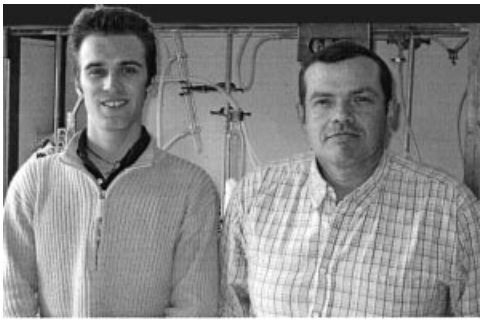


François-Xavier Felpin (left) was born in Villefranche-sur-Saône (France) in 1977. During his undergraduate education he worked in the laboratory of Dr. Charles Mioskowski (CEA Saclay, France) under the direction of Dr. Eric Doris on the synthesis of labeled amino acids by rearrangement of cyclopropanone hydrate. Since 2000, he has been pursuing a Ph.D. in synthetic organic chemistry under the guidance of Professor Jacques Lebreton at the University of Nantes. His research efforts have been focused on the total synthesis of alkaloids (anabasine, anatabine, sedamine, lobeline, deoxoprosopinine, etc.). After his Ph.D. he will be undertaking postdoctoral studies in the laboratory of Professor Robert S. Coleman at Ohio State University.

Jacques Lebreton (right) was born in Guérande (France) in 1960. He received his Ph.D. degree (1986) from the University of Paris XI-Orsay under the supervision of Professor Eric Brown (Le Mans). His thesis work included the total synthesis of C-nor-D-homosteroids. In 1986, he started his first post-doctoral fellowship with Professor James A. Marshall at the University of South Carolina, working on the [2,3]-Wittig rearrangement and its application in total synthesis. Following a second post-doctoral fellowship with Professor Robert E. Ireland at the University of Virginia, working on the total synthesis of monensine, in 1990 he joined the laboratories of CIBA-GEIGY (Novartis) in Basle, where he worked in Dr. Alain De Mesmaeker's group in the area of antisense oligonucleotides. In 1994, he joined the CNRS and spent a few years in the group of Dr. Jean Villéras (UMR-CNRS 6513, Nantes) involved in organometallic chemistry. In 1998, he was promoted to Professor at the University of Nantes. His major research interests are organometallic chemistry, synthesis of bioactive molecules (HIV and central nervous system diseases), and synthesis of labeled molecules to study biological processes.

MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.

This success is largely due to the introduction and the development of stable, reactive, and functional group tolerant metal alkylidenes as olefin metathesis catalysts. Of the several catalysts described in the literature, two of the most popular are the molybdenum-based (**1**) and ruthenium-derived (**2**) catalysts developed by Schrock[3] and Grubbs,[4] respectively (see Figure 1).

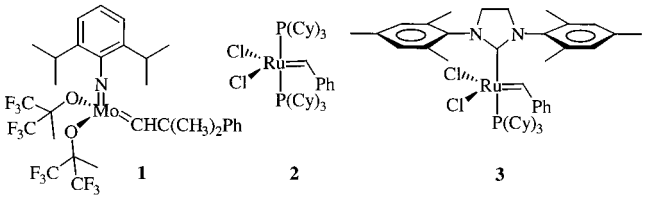


Figure 1. Commercially available metathesis catalysts

These two commercially available catalysts **1** and **2** are complementary in their reactivity. Ruthenium catalyst **2** is air- and moisture-stable and is active in the presence of a variety of functional groups (alcohols, carbonyls, amides, carboxylic acids), thus widening the scope of RCM. The more reactive molybdenum catalyst **1** is sensitive to air and moisture and less tolerant of functionality. Nevertheless, it is more efficient in RCM reactions on highly substituted olefins.

A few years ago, a more active second-generation ruthenium catalyst **3** was introduced by Grubbs.[5] This new catalyst **3**, now commercially available, combines the qualities of both catalysts **1** and **2**: higher thermal stability, wider functional group tolerance, and lower sensitivity to double bond substitution.

In contrast, it was well established that free amines are generally incompatible with metathesis reactions,[6] causing catalyst inhibition by chelation of the basic nitrogen atom with the (alkylidene)metal compound. However, it is possible to overcome this problem: the basic nitrogen atom is deactivated by conversion into suitable functions such as an amide or carbamate. In addition, it has been demonstrated that protonation of the amine to afford the corresponding ammonium salts is tolerated by first- and second-generation Grubbs' catalysts **2** and **3**, avoiding the use of protecting groups. Typically, RCM reactions of secondary amines are carried out on the hydrochloride salts,[7] with *p*-toluenesulfonic acid[8] being used in only a few cases. Catalysts **1** and **2** are compatible with less basic amines, particularly with anilines,[9] enamines,[10] and substituted pyridine[11] with electronegative substituents or with hindered tertiary amines.[12]

RCM reactions have been largely used in the construction of small, medium, and large nitrogen-containing rings.[13−16] To emphasize the potential of RCM reactions in this field, this microreview presents syntheses of natural alkaloids containing a piperidine or pyrrolidine heterocycle formed by this strategy. Substituted five- or six-membered N-heterocycles are found in innumerable natural products and pharmaceutical compounds and they continue to attract considerable attention, due to their broad and important biological activities. It should be pointed out that over 12,000 piperidine derivatives have been mentioned in clinical or preclinical studies during the last 10 years.[17] The development of new methods for the synthesis of pyrrolidine-[18] or piperidine-based compounds[19] is therefore of considerable importance, particularly approaches leading to chiral derivatives of these ring skeletons.[20]

This microreview covers the literature published from 2000 to January 2003 relating to the total synthesis of natural alkaloids containing a five- or six-membered N-heterocyclic construct by an RCM reaction. We also include a few pertinent examples of closely related natural products.

2. 2-Substituted Piperidines and 4,5-Dehydropiperidines

The family of chiral 2-substituted piperidines and 4,5-dehydropiperidines has been a target of particular interest. Enantioselective syntheses of members of this family − coniine (**4**), pipecoline (**5**), anabasine (**6**), anatabine (**7**), β-conhydrine (**8**), pipecolic acid (**9**), baikiain (**10**) and sedamine (**11**; Figure 2) − have continually been the focus of many studies. Among them, the efficient synthesis of these natural products by use of an RCM reaction as the key step has recently been reported in the literature.[12,21] In the particular case of the 2-substituted 4,5-dehydropiperidines, an RCM reaction is one of the most efficient strategies, construction of the heterocycle and formation of the double bond in the right position occurring simultaneously in a single step.

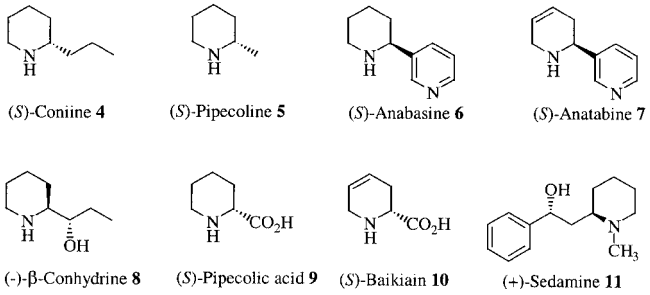
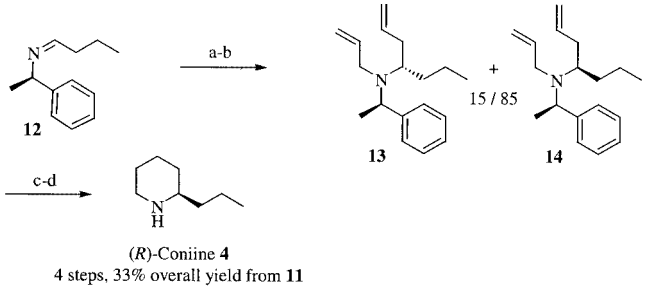


Figure 2. Structures of natural 2-substituted piperidines and 4,5-dehydropiperidines

Coniine (**4**), one of the simplest alkaloids and one of the poisonous alkaloids of the hemlock (*Conium maculatum L.*) (and one of the most toxic, thinking of Socrates), still remains a popular target for the demonstration of new synthetic methodology in the piperidine field. Thus, it is not so surprising that four enantiomeric syntheses of coniine (**4**) in both enantiomeric forms through the use of an RCM reaction have been published in the last three years.[12,21a−21d]

A synthesis of (*R*)-coniine (**4**), as presented in Scheme 1, was described by Vankar et al.[21a] Treatment of chiral imine **12**, derived from butanal and (*R*)-α-methylbenzylamine,

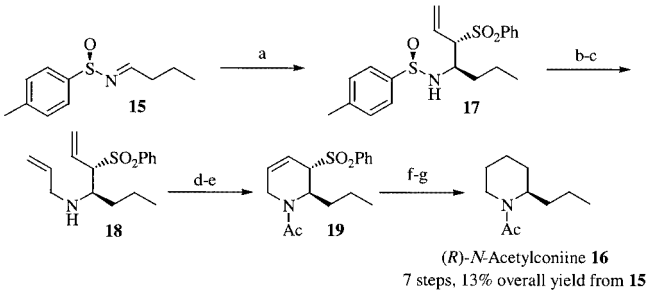
with allylzinc bromide provided the secondary amine, which was then *N*-alkylated to give an inseparable diastereoisomeric mixture of dienes **13** and **14** in a ratio of 15:85. This diene mixture was subjected to an RCM reaction in the presence of Grubbs' catalyst **2** to furnish, after separation by chromatography on silica gel, the desired cyclized diastereoisomer. This was then hydrogenated to afford (*R*)-coniine (**4**) in 58% overall yield. In a similar manner, starting from acetaldehyde, (*R*)-pipecoline (**5**) has been synthesized in five steps with 33% overall yield.



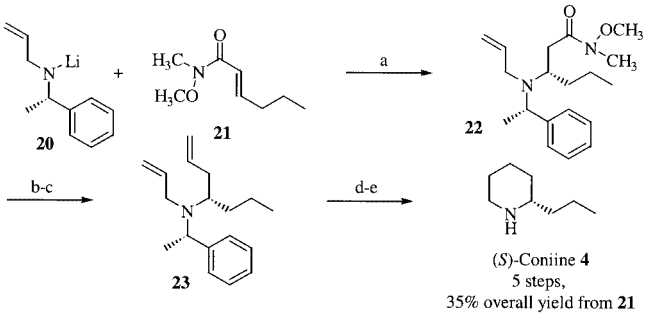
Scheme 1. Reagents and conditions: (a) allyl bromide, Zn, $CeCl_3 \cdot 7H_2O$, room temp., 1 h, 82%; (b) allyl bromide, NaH, THF, nBu$_4$NI, reflux, 8 h, 70%; (c) **2** (10 mol %), CH_2Cl_2, room temp., 24 h, 64%; (d) H_2, Pd/C, room temp., 8 h, 90%

Another synthesis of (*R*)-coniine (**4**) as its *N*-acetyl derivative **16**, based on the addition of lithiated allyl phenyl sulfone carbanion to chiral *N*-sulfinylimine **15**, was achieved by Hassner et al.[21b] (Scheme 2). Addition of the lithiated allyl phenyl sulfone (formed by treatment of the allyl phenyl sulfone with LDA) to chiral alkyl-*N*-sulfinylimine **15** [prepared from (*S*)-*p*-toluenesulfonamide and butanal in 70% yield] gave a 1:1:3 mixture of three diastereoisomers, from which the major isomer **17** was obtained in 52% yield after separation by flash column chromatography. The secondary amine **18** was obtained in 63% overall yield by sequential desulfinylation of **17** with TFA and *N*-monoallylation. At this stage, all attempts to perform an RCM reaction on free amine **18** or its hydrochloride salt by use of Grubbs' catalyst **2** were unsuccessful. In contrast, after acetylation of amine **18**, treatment of the corresponding amide with Grubbs' catalyst **2** in CH_2Cl_2 at room temp. gave the 4,5-dehydropiperidine **19** in high yield (92%). Catalytic hydrogenation of **19** followed by reductive desulfonation with sodium amalgam afforded *N*-acetyl-(*R*)-coniine **16** in 54% yield for the two-step process.

A diastereoselective Michael addition of chiral lithium amide **20** to α,β-unsaturated amide **21** was used by Davies et al.[12] to perform an efficient synthesis of (*S*)-coniine (**4**), as shown in Scheme 3. Conjugated addition of chiral lithium amide **20** to the α,β-unsaturated Weinreb amide **21** yielded the desired amino amide **22** in 65% yield with an excellent diastereoselectivity (> 95% *de*). Reduction of the Weinreb amide **22** to the corresponding aldehyde with DIBAL-H and subsequent Wittig methylenation produced the diene **23** in 62% yield from **22**. Subjection of the latter compound **23** to the RCM reaction with (benzylidene)ruthenium catalyst **2** proceeded in very good yield to provide the cyclized intermediate, which, after removal of the chiral auxiliary by hydrogenolysis with simultaneous hydrogenation of the double bond and treatment with HCl, afforded (*S*)-coniine (**4**) hydrochloride in 86% yield for the two steps.



Scheme 2. Reagents and conditions: (a) allyl phenyl sulfone, LDA, THF, −100 °C, 45 min, 52%; (b) TFA, MeOH, 0 °C, 3 h, 87%; (c) allyl bromide, K_2CO_3, DMF, 0 °C to room temp., 12 h, 73%; (d) AcCl, Et_3N, CH_2Cl_2, 0 °C to room temp., 3 h, 80%; (e) **2** (5 mol %), CH_2Cl_2, room temp., 2.5 h, 92%; (f) H_2, Pd/C, MeOH, room temp., 2 h, 87%; (g) Na(Hg), Na_2HPO_4, MeOH, −10 °C to 0 °C, 2 h, 62%

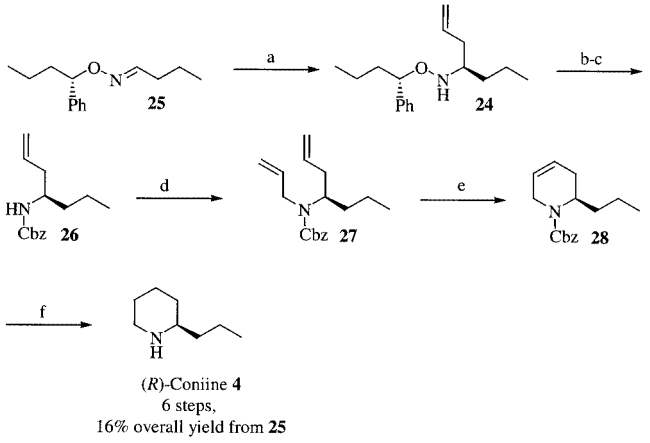


Scheme 3. Reagents and conditions: (a) THF, −78 °C, 65%, > 95% *de*; (b) DIBAL-H, THF, −78 °C; (c) PPh_3CH_3Br, $NaNH_2$, CH_2Cl_2, −40 °C to room temp., 62% (2 steps), > 95% *de*; (d) **2** (4 mol %), CH_2Cl_2, reflux, 12 h, 91%, > 95% *de*; (e) H_2 (5 atm), Pd/C, MeOH, room temp., then HCl, 95%

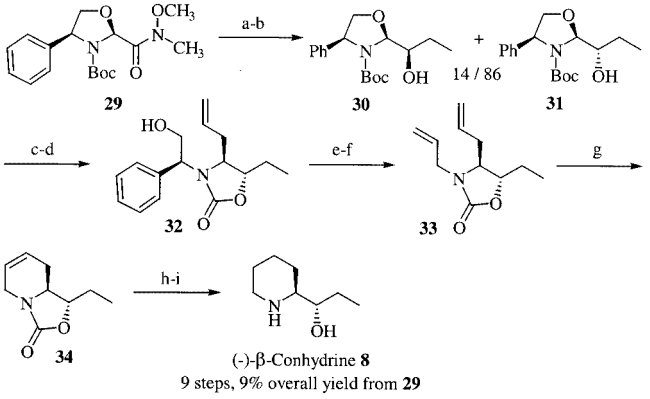
The syntheses of (*S*)-homopipecolic acid and (*S*)-homoproline acid, from methyl (*E*,*E*)-hepta-2,5-dienoate and *tert*-butyl (*E*,*E*)-hexa-2,4-dienoate, respectively, have also been achieved by this approach.

Moody et al.[21c−21d] have described an asymmetric synthesis of (*R*)-coniine (**4**) in which the chiral synthon **24** is prepared by diastereoselective addition of the allylmagnesium bromide to the (*S*)-*O*-(1-phenylbutyl)aldoxime **25** [prepared from commercial (*R*)-1-phenylbutanol in two steps with 54% overall yield; Scheme 4]. The carbamate **26** was converted into the corresponding *N*-allyl derivative **27** in 90% yield by treatment with allyl bromide in the presence of sodium hydride. Then, RCM on **27** in the presence of Grubbs' catalyst **2** yielded the tetrahydropyridine intermediate **28** in 88% yield. This was then subjected to Pd-catalyzed hydrogenation to give the (*R*)-coniine (**4**) as its hydrochloride salt in 76% overall yield.

(−)-β-Conhydrine (**8**), another piperidine hemlock alkaloid, was synthesized by Couty et al.,[21e−21f] starting with



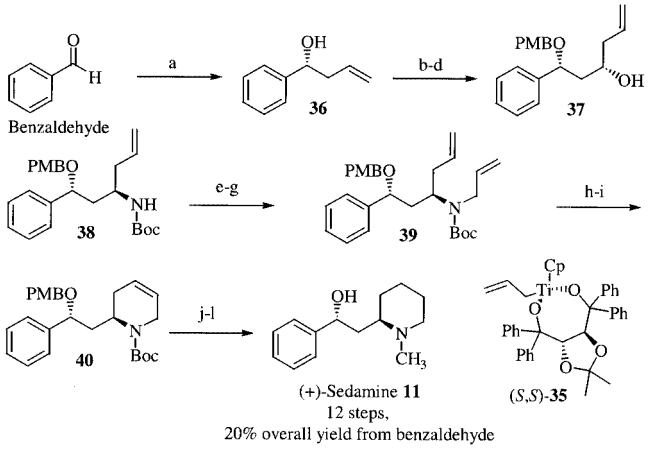
Scheme 4. Reagents and conditions: (a) allylmagnesium bromide, $BF_3{\cdot}Et_2O$, toluene, −78 °C, 51%, > 95% *de*; (b) Zn, AcOH, H_2O, THF, ultrasound, 50 °C; (c) Cbz-Cl, K_2CO_3, THF, H_2O, 0 °C to room temp., 52% (2 steps), 90% *ee*; (d) allyl bromide, NaH, DMF, 0 °C to room temp., 90%; (e) **2** (10 mol %), CH_2Cl_2, reflux, 88%; (f) H_2, Pd/C, MeOH, room temp., 1.5 h, then HCl, 76%



Scheme 5. Reagents and conditions: (a) EtMgBr, Et_2O, 5 °C, 30 min; (b) $NaBH_4$, EtOH, −78 °C, 30 min, 71% (2 steps); (c) NaH, THF, reflux, 2 h, 82%; (d) allyltrimethylsilane, CH_2Cl_2, $TiCl_4$, −78 °C to room temp., 71%; (e) Na, THF, EtOH, NH_3, −40 °C, 20 min, 93%; (f) allyl bromide, NaH, DMF, room temp., 30 min, 74%; (g) 2 (2.5 mol %), CH_2Cl_2, reflux, 2 h, 79%; (h) H_2, Pd/C, EtOH, room temp., 2 h, 92%; (i) LiOH, EtOH, H_2O, reflux, 5 h, 45%

N-Boc-2-acyloxazolidine **29**, as shown in Scheme 5. Weinreb amide **29** [prepared in three steps in 78% overall yield from (*S*)-phenylglycinol] was treated with ethylmagnesium bromide to deliver the corresponding ethyl ketone, which was then reduced with $NaBH_4$ at low temperature to yield a diastereoisomeric mixture in an 86:14 ratio in favor of the desired isomer **31**. The stereoselectivity observed for this reduction can be explained in terms of Felkin−Anh control. The major isomer **31** was isolated, after separation by chromatography, in 71% yield from **29** (on a 36 mmol scale). Transcarbamation of **31**, induced by treatment with NaH, gave the bicyclic oxazolidinone, which was subjected to $TiCl_4$-mediated allylation with allyltrimethylsilane to provide the *trans*-oxazolidinone **32** with a high stereoselectivity (98% *de*) in 71% yield. Reductive debenzylation of **32** with sodium furnished the corresponding oxazolidinone, and subsequent *N*-allylation was achieved in 74% yield by use of NaH and allyl bromide to give the diene **33**. Treatment of **33** with Grubbs' catalyst **2** in refluxing CH_2Cl_2 provided a 79% yield of the bicyclic intermediate **34**. To complete the synthesis, catalytic hydrogenation of **34** followed by alkaline hydrolysis provided (−)-β-conhydrine (**8**).

A short and efficient synthesis of (+)-sedamine (**11**) in 12 steps from benzaldehyde and in an overall yield of 20%, as outlined in Scheme 6, was described by Cossy et al.[21g−21h] Two successive enantioselective allylations with TADDOL-based allyltitanium reagent **35** and its enantiomer installed the two asymmetric centers. Allylation of benzaldehyde with (*S*,*S*)-**35** afforded the homoallylic alcohol **36** in 90% yield and 93% *ee*. In the next steps, protection of the alcohol function of **36**, followed by oxidative cleavage of the olefin moiety, produced the corresponding aldehyde. This was immediately treated with (*R*,*R*)-**35** to furnish the chiral alcohol **37** as a 94:6 diastereoisomeric mixture in 72% overall yield. Under Mitsunobu conditions, homoallylic alcohol **37** was transformed with DPPA into the corresponding azide. LAH reduction and subsequent protection of the amine yielded its *N*-Boc carbamate **38**. Conversion of this carbamate **38** into the allyl derivative **39** by a standard procedure gave a 91% yield. Treatment of a solution of the *N*-allylcarbamate **39** in benzene with Grubbs' catalyst **2** afforded the desired 3,4-dehydropiperidine **40** in 94% yield. Subsequent catalytic hydrogenation and removal of the protecting groups, followed by LAH reduction of the *N*-Boc group into the *N*-methyl group, provided (+)-sedamine (**11**) in 98% *de* after recrystallization.



Scheme 6. Reagents and conditions: (a) (*S*,*S*)-**35**, Et_2O, −78 °C, 3 h, 90%, 93% *ee*; (b) PMB-Br, *t*BuOK, THF, room temp., 4 h, 96%; (c) OsO_4, THF, H_2O, room temp., 5 min, then $NaIO_4$, room temp., 4 h; (d) (*R*,*R*)-**35**, Et_2O, −78 °C, 3 h, 75% (2 steps); (e) DPPA, PPh_3, DEAD, THF, 0 °C to room temp., 12 h, 82%; (f) $LiAlH_4$, Et_2O, 0 °C to room temp., 2 h, 94%; (g) $(Boc)_2O$, dioxane, 0 °C to room temp., 19 h, 85%; (h) KHMDS, THF, DMF, 30 min 0 °C, then allyl bromide, room temp., 2 h, 91%; (i) **2** (5 mol %), benzene, room temp., 16 h, 94%; (j) H_2, PtO_2, EtOAc, room temp., 1 h, 94%; (k) DDQ, CH_2Cl_2, H_2O, room temp., 15 min, 75%; (l) $LiAlH_4$, THF, reflux, 6 h, 78%

As a part of our program directed towards the preparation of nicotine (**41**) analogues for the assessment of

their structure-activity relationships, we have synthesized, from a common chiral homoallyl azide **42**, the principal piperidine and pyrrolidine alkaloids isolated from *Nicotiana tabacum*[21i−21j,22] (see Figure 3).

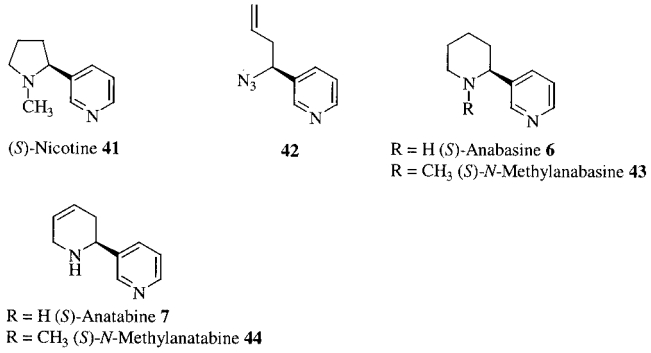


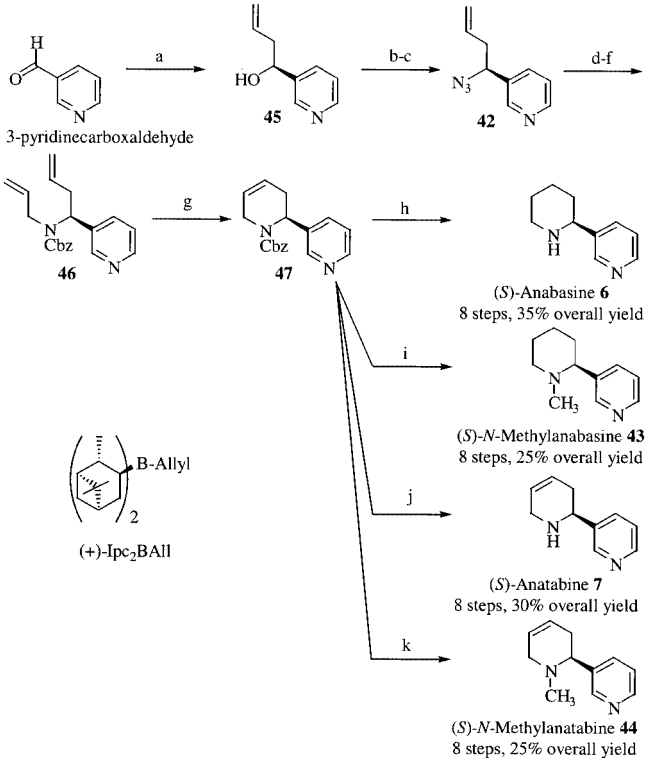
Figure 3. Principal piperidine and pyrrolidine alkaloids from *Nicotiana tabacum*

The synthesis of (*S*)-nicotine (**41**) was achieved in only four steps, with an overall yield of 51%, from 3-pyridinecarboxaldehyde, the key step being an intramolecular hydroboration/cycloalkylation of the azido-olefin intermediate **42** to construct the pyrrolidine ring.

At this point, it was obvious that RCM on the *N*-allylamine derived from the homoallylic azide **42** would offer the opportunity to construct the ring and concomitantly introduce the olefin in the right position to afford (*S*)-anatabine (**7**) in a straightforward manner.

The synthesis of the four chiral piperidine alkaloids **6**, **7**, **43**, and **44** is presented in Scheme 7. Allylation of nicotine aldehyde with *B*-allyldiisopinocampheylborane [(+)-Ipc$_2$-Ball] gave the corresponding (*R*)-homoallylic alcohol **45** in 94% yield and with an *ee* of 94%. Chiral azide **42** was synthesized in high yield in a two-step sequence by mesylation of alcohol **45**, followed immediately by stereoselective nucleophilic displacement with azide anion. Next, reduction of the azide **42** with tin chloride gave rise to the corresponding amine, which was subsequently protected as its benzyl carbamate and then *N*-allylated to provide RCM precursor **46** in good overall yield. *N*-Allylation of the carbamate provided a reliable solution to the problem of clean monoallylation of the free amine. When RCM was performed on the hydrochloride pyridinium salt of **46** with Grubbs' catalyst **2**, the desired 4,5-dehydropiperidine **47** was isolated in 82% yield. Optimal yields were obtained when 5 mol % of the catalyst was used, followed by the addition of 2.5 mol % after 4 h.

Completion of the synthesis of the four chiral piperidine alkaloids **6**, **7**, **43**, and **44** from the key intermediate **47** proved to be straightforward and could be achieved by a single-, two-step, or three-step, one-pot procedure, depending on the target alkaloid. Treatment of (*S*)-**47** with hydrogen in the presence of Pd catalyst caused simultaneous hydrogenation of the double bond and hydrogenolysis of the Cbz group to give (*S*)-anabasine (**6**). The (*S*)-*N*-methylanatabine **44** was obtained by treatment of **47** with LAH, resulting in the reduction of the Cbz group to *N*-Me. For the synthesis



Scheme 7. Reagents and conditions: (a) (+)-Ipc$_2$BAll, Et_2O, −100 °C, 1 h, 94%, 94% *ee*; (b) MsCl, CH_2Cl_2, Et_3N, 0 °C, 10 min, 100%; (c) NaN_3, DMF, 60 °C, 4 h, 97%, 94% *ee*; (d) $SnCl_2{\cdot}2H_2O$, MeOH, 0 °C to room temp., 3 h, 98%; (e) BnCOCl, K_2CO_3, CH_2Cl_2, 0 °C to room temp., 30 min, 76%; (f) NaH, DMF, 0 °C to room temp., 30 min, 76%; (g) HCl gas, then **2** (7.5 mol %), CH_2Cl_2, reflux, 8 h, 79%; (h) H_2, Pd/C, EtOH, room temp., 14 h, 82%; (i) H_2, Pd/C, HCHO, MeOH, room temp., 24 h, 88%; (j) $BF_3{\cdot}Et_2O$, $(CH_3)_2S$, CH_2Cl_2, room temp., 6 h, 67%; (k) $LiAlH_4$, THF, 0 °C to room temp., 6 h, 71%

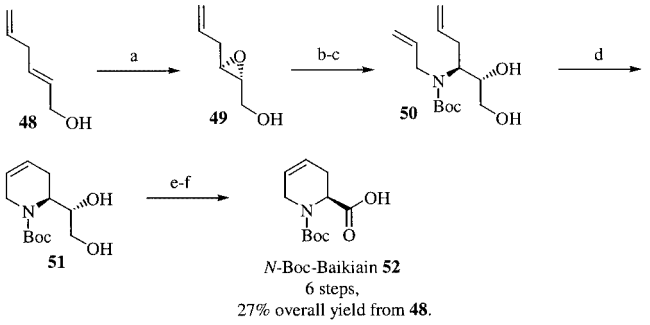
of (*S*)-anatabine (**7**), the cleavage of Cbz in intermediate **47** was achieved by treatment with dimethyl sulfide in the presence of boron trifluoride−diethyl ether. Finally, **47** was stirred in MeOH with aqueous formaldehyde under hydrogen in the presence of Pd catalyst, resulting in hydrogenation of the double bond and cleavage of the Cbz, to afford (*S*)-anabasine (**6**) in situ. This was *N*-methylated through the reduction of the iminium moiety to give (*S*)-*N*-methylanabasine **43.**

Pipecolic acid (**9**), a non-proteinogenic α-amino acid, and related structures have attracted considerable attention because of their use as proline analogues in modified peptides and their interesting biological properties.[23,24] Some of these compounds have also been employed as building blocks in the synthesis of potential pharmaceutical drugs[25] and are regarded as advanced key intermediates for the preparation of piperidine natural products.[26]

4,5-Dehydropipecolic acid (baikiain, **10**), isolated from *Baikiaea plurijuga*, has been the focus of only a few syntheses.[21k−21l,27]

An efficient formal asymmetric synthesis of (*S*)-baikiain (**10**) as outlined in Scheme 8 has been published by Pericàs and Riera.[21k]

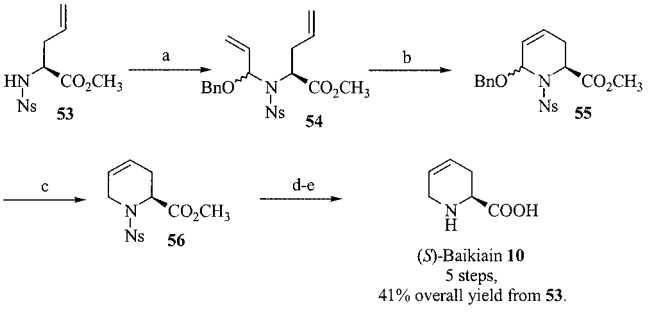
The readily available allyl alcohol **48** was converted under catalytic Sharpless epoxidation conditions to the epoxy al-



Scheme 8. Reagents and conditions: (a) *t*BuOOH, D-(−)-DET, $Ti(iPrO)_4$, CH_2Cl_2, MS (4 Å), −20 °C, 84%, 93% *ee*; (b) allylamine, $LiClO_4$, CH_3CN; (c) $(Boc)_2O$, $NaHCO_3$, MeOH, ultrasound, 60% (2 steps); (d) **2** (8 mol %), CH_2Cl_2, room temp., 72%; (e) $NaIO_4$, THF, H_2O, 92%; (f) $NaClO_2$, *t*BuOH, H_2O, NaH_2PO_4, 81%, 99% *ee*

cohol **49** in 82% yield and in 93% *ee*. Regioselective titanium(IV)-mediated ring-opening of the 2,3-epoxy alcohol **49** with allylamine, followed by Boc protection, gave the doubly unsaturated amino diol **50** in 60% overall yield. RCM in the presence of Grubbs' catalyst **2** and CH_2Cl_2 as solvent at room temp. afforded the tetrahydropyridine **51** in 72% yield. Subsequent oxidative diol cleavage with $NaIO_4$ provided the aldehyde, which was oxidized by the Dalcanale chlorite procedure to provide the expected *N*-Boc-baikiain **52** in 75% yield for these two steps. Starting from recrystallized amino diol intermediate **51**, *N*-Boc-baikiain **52** was obtained in 99% *ee*. In completion of this work, several 2-substituted piperidines as well as pipecolic acid (**9**) were prepared from the key intermediate **52**.

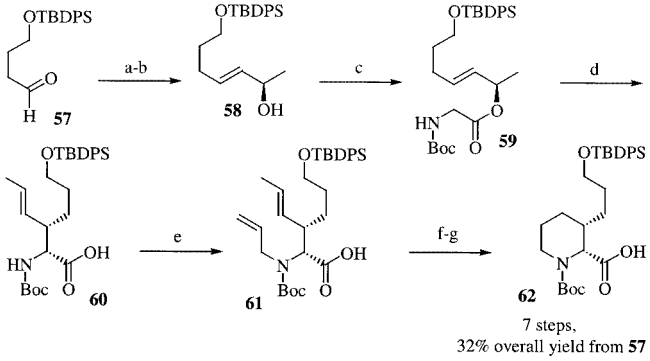
Another synthesis of (*S*)-baikiain (**10**), from (4-nitrobenzenesulfonyl)-protected allylglycine **53** (Scheme 9), was published by Rutjes et al.[21] Treatment of **53** with benzyl propadienyl ether in the presence of $Pd(OAc)_2$ at room temp. gave the desired N,O-acetal **54** in 84% yield as 1:1 mixture of diastereoisomers. RCM was performed on this mixture with use of Grubbs' catalyst **2** to give cyclic N,O-acetals **55** in 90% yield. The mixture of cyclic N,O-acetals **55** was treated with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$ to afford the 1,2 adduct **56** in 88% yield and in enantiomerically pure form as judged by chiral HPLC analysis. Finally, the sulfonamide and ester functions on **56** were removed, giving (*S*)-baikiain (**10**) in 61% overall yield.



Scheme 9. Reagents and conditions: (a) benzyl propadienyl ether, $Pd(OAc)_2$, dppp, Et_3N, CH_3CN, 1 h, room temp., 84%; (b) **2**, room temp., 90%; (c) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C to room temp., 88%; (d) PhSH, K_2CO_3, DMF, room temp; (e) LiOH, MeOH, H_2O, 61% (2 steps)

3. 2,3-Disubstituted Piperidines

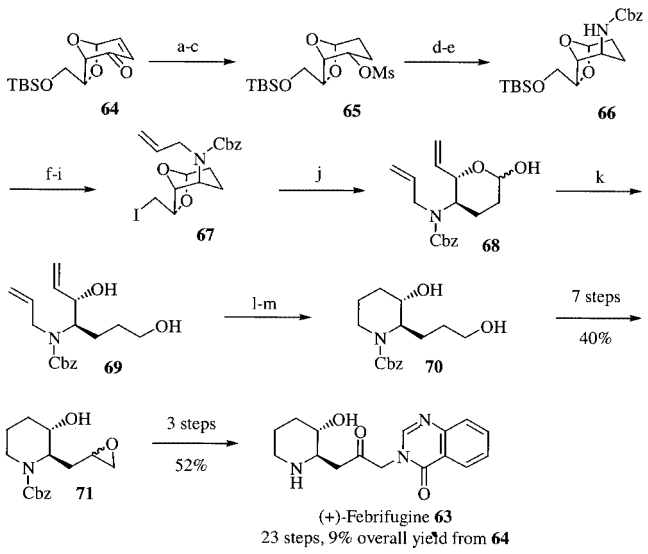
Another example of the synthesis of a related pipecolic acid with substitution at the C-3 position, with an Ireland−Claisen rearrangement and an RCM as key steps, has been reported by Ellman et al.,[28] as illustrated in Scheme 10.



Scheme 10. Reagents and conditions: (a) acetonyltriphenylphosphonium chloride, Na_2CO_3, dioxane, H_2O, reflux, 24 h, 73%; (b) catecholborane, (*S*)-2-methyl-CBS-oxazaborolidene, toluene, −78 °C, 6 h, 94%, 88% *ee*; (c) *N*-Boc-Gly, DMAP, DIC, CH_2Cl_2, 0 °C to room temp., 12 h, 99%; (d) LDA, THF, −20 °C to −78 °C, then $ZnCl_2$, THF, −78 °C to room temp., 10 h, 87%; (e) allyl iodide, NaH, THF, 0 °C to room temp., 72 h, 63%; (f) **2** (5 mol %), room temp., 12 h; (g) H_2 (50 psi), 10% Pt/C, EtOAc, room temp., 16 h, 86% (2 steps)

The known aldehyde **57** was subjected to a Wittig condensation with acetonyltriphenylphosphonium chloride in the presence of Na_2CO_3 as base to give the (*E*)-α,β-unsaturated methyl ketone stereoselectively. This ketone was treated with catecholborane in the presence of catalytic amounts of (*S*)-2-methyl-CBS-oxazaborolidene to produce the (*R*)-allylic alcohol **58** in 88% *ee* and 69% yield for the two steps. This alcohol was coupled with *N*-Boc-glycine to provide, in high yield, the *trans*-allylic amino ester **59**. Subjection of the ester **59** to a chelate−enolate Claisen rearrangement, with LDA as the base in the presence of zinc chloride to stabilize the (*Z*)-enolate ester through internal chelation, gave the unsaturated amino acid **60** as a single diastereoisomer in 87% yield. At best, *N*-allylation of **60** was effected in 63% yield with allyl iodide and NaH, without affecting the carboxylic acid function, to afford the RCM precursor **61**. This intermediate was stirred with Grubbs' catalyst **2** in CH_2Cl_2 at room temp. to deliver the corresponding 4,5-dehydropiperidine, which was then hydrogenated to afford the C-3 substituted pipecolic acid **62** in 86% overall yield and in 94% *ee*.

A synthesis of (+)-febrifugine (**63**), an antimalarial agent isolated from *Dichroa febrifuga* and *Hydrangea umbellata*, using RCM to construct the piperidine moiety, was described by Ogasawara et al.[29] (Scheme 11).



Scheme 11. Reagents and conditions: (a) $NaBH_4$·$CeCl_3$, MeOH, 0 °C, 90%; (b) H_2, PtO_2; (c) MsCl, Et_3N; (d) NaN_3, DMF, reflux, 76% (3 steps); (e) $LiAlH_4$, THF, then CbzCl, K_2CO_3, 93%; (f) allyl bromide, NaH, DMF, 90%; (g) TBAF, THF; (h) MsCl, Et_3N; (i) LiI, THF; (j) Zn, AcOH, EtOH, 87% (4 steps); (k) $NaBH_4$, EtOH, 94%; (l) **2** (5 mol %); (m) H_2, PtO_2, 89% (2 steps)

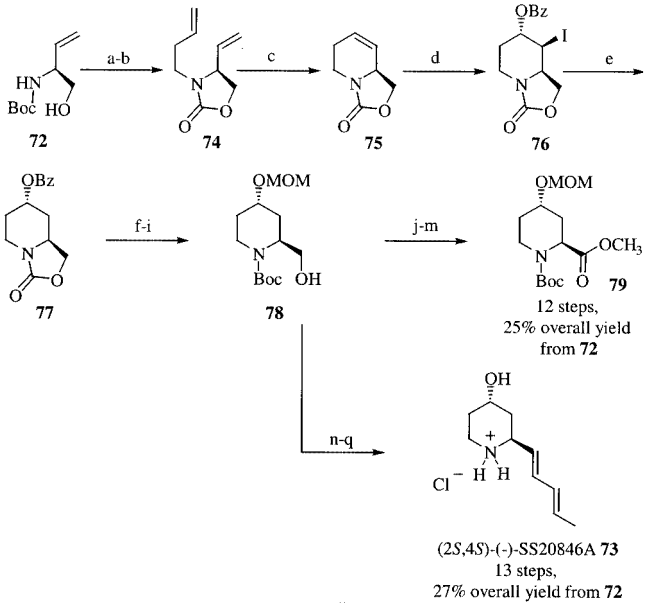
Starting with enone **64**, prepared from furfural in enantiomerically pure forms either catalytically or enzymatically, diastereoselective reduction of the ketone to the *endo*-allyl alcohol, followed by hydrogenation of the double bond and mesylation, afforded the compound **65**. Treatment of mesylate **65** with sodium azide gave the corresponding azide, which was transformed into the carbamate **66** by one-pot reduction carbamoylation, in 63% overall yield from **64**. Successive *N*-allylation of **66** with allyl bromide, removal of the silyl protecting group, and mesylation of the hydroxy functionality, followed by iodine displacement, furnished the iodo derivative **67**. Upon treatment with zinc, compound **67** was converted into a lactol intermediate **68**, which was further reduced with $NaBH_4$ to afford the dihydroxydiene **69**. RCM of **69** in the presence of Grubbs' catalyst **2** provided the desired dedihydropiperidine. This was then hydrogenated, without affecting the benzylcarbamate protecting group, to give the piperidinediol **70** in 89% overall yield.

To complete the total synthesis of (+)-febrifugine (**63**), connection of the 4-quinozoline to the piperidine moiety **70** was achieved in 10 steps via the epoxide **71**. The overall yield of (+)-febrifugine (**63**) from the chiral building block was 9% in 23 steps.

4. 2,4-Disubstituted Piperidines

4-Hydroxypipecolic acids have been isolated from plants and have also been identified as constituent cyclopeptide antibiotics.

Johnson et al.[30] has described an expedient methodology to access these structures in both enantiomeric forms from (*S*)- and (*R*)-vinylglycinol *N*-Boc derivative **72**, as depicted in Scheme 12. In completion of this work, a synthesis of (−)-SS20846A (**73**), which shows interesting biological properties, was also presented.



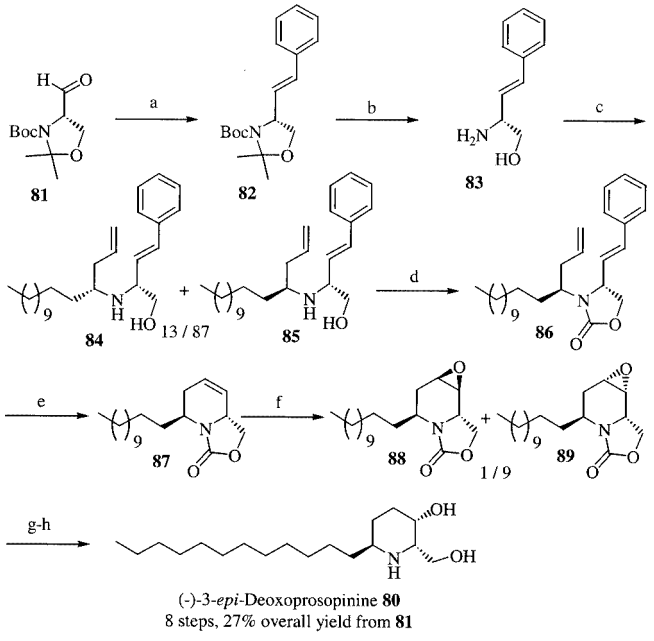
Scheme 12. Reagents and conditions: (a) NaH, THF; (b) NaH, 4-bromo-1-butene, LiI, DMF, 81% (2 steps); (c) **2**, CH_2Cl_2, 24 h, 88%; (d) I_2, BzOAg, benzene, 75%; (e) Raney Ni, THF, MeOH; (f) KCN, MeOH, H_2O; (g) MOMCl, Hünig's base, CH_2Cl_2, 94% (3 steps); (h) 3 N NaOH, MeOH, H_2O, reflux, 24 h; (i) $(Boc)_2O$, EtOAc, 73% (2 steps); (j) Dess−Martin, THF; (k) $NaClO_2$, NaH_2PO_4; (m) CH_2N_2, 68% (3 steps); (n) Dess−Martin, CH_2Cl_2, 73%; (o) $CH_3-CH=CH-CH=PPh_3$, THF; (p) I_2, benzene, hv, 30 min; (q) AcCl, MeOH, 100%

Chiral starting materials were prepared from 2-butene-1,4-diol in a three-step sequence, with a *Pseudomonas cepacia* lipase-catalyzed kinetic resolution being used to introduce the chirality. Diethylenic oxazolidinone **74** was obtained in 81% yield from *N*-Boc (or *N*-Cbz) vinylglycinol **72** by treatment with NaH to afford the oxazolidinone intermediate, which was *N*-alkylated with 4-bromo-1-butene in the presence of NaH and LiI. Metathesis precursor **74** was then cyclized in the presence of ruthenium catalyst **2** in CH_2Cl_2 to provide bicyclic oxazolidinone **75** in 88% yield. Upon Prevost oxidation of compound **75** with silver benzoate and iodine, iodobenzoate **76** was formed as a single diastereoisomer (the structure was confirmed by X-ray crystallographic analysis) in 75% yield. Next, efficient dehalogenation of **76** was carried out with Raney nickel to give the benzoate **77**. After a protecting group exchange, in a one-pot procedure with KCN and MOMCl, followed by subsequent basic hydrolysis of the oxazolidinone and Boc protection of the piperidine, the key intermediate **78** was isolated from **77** in 69% overall yield. Dess−Martin oxidation of the primary alcohol **78** to the corresponding aldehyde, with subsequent Dalcanale chlorite oxidation to the acid and treatment with diazomethane, gave the MOM-protected *trans*-4-hydroxypipecolic methyl ester **79** in 68% overall yield. Wittig olefination of this aldehyde intermediate

with $CH_3-CH=CH-CH=PPh_3$ gave the diene as an (*E*)/(*Z*) = 20:80 mixture, which was converted into an inseparable mixture of a 85:15 ratio in favor of the desired (*E*) isomer by photoisomerization. The final step was the complete deprotection of this diene, performed on the (*E*)/(*Z*) mixture with acetyl chloride in methanol to furnish (−)-SS20846A (**73**) as its hydrochloride salt.

5. 2,3,6-Trisubstituted Piperidines

In continuation of our program directed towards the total synthesis of products of biological interest, we turned our attention to the synthesis of the *Prosopis* alkaloid family, which exhibits a wide range of physiological properties including analgesic, anaesthetic, and antibiotic activity.[31] While the natural products have been widely targeted in total synthesis, only a few analogues have been reported in the literature.[32] We therefore envisaged a total synthesis of the 3-*epi*-deoxoprosopinine (**80**), which to the best of our knowledge has not yet been synthesized (Scheme 13). We focused our efforts on the development of a novel route for the synthesis of chiral tetrahydropyridines.[33] Indeed, we anticipated the extraordinary versatility of these units as key tools in multistep synthesis. We first investigated a novel strategy to produce enantioenriched tetrahydropyridines starting from the commercially available Garner aldehyde **81**. The study began with the stereoselective olefination of Garner aldehyde **81** by Emmons-Wadsworth reaction in good yield (75%) to give **82**. Deprotection of oxazolidine and Boc groups in acidic media afforded the amino alcohol **83** in quantitative yield. We next developed a two-step, one-pot strategy based on the diastereoselective allylation of imine formed in situ from amino alcohol **83** and dodecyl aldehyde. The observed stereoselectivity in favor of the *trans* isomer **85** (*trans*/*cis* = 87:13, separated by flash chromatography) was anticipated on the basis of the generally accepted transition state under chelation control (Figure 4).



Scheme 13. Reagents and conditions: (a) $PhCH_2P(O)(OEt)_2$, BuLi, THF, −78 °C, 1 h, room temp., 12 h, 75%; (b) 12 N HCl, MeOH, 60 °C, 4 h; (c) $C_{12}H_{25}CHO$, THF, $MgSO_4$, room temp., 12 h, then allylmagnesium bromide, −78 °C to −10 °C, 5 h, 56% of **85** (2 steps); (d) carbonyldiimidazole, Et_3N, CH_2Cl_2, room temp., 18 h, 91%; (e) **3** (5 mol %), CH_2Cl_2, reflux, 1 h, 99%; (f) *m*CPBA, CH_2Cl_2, room temp., 72 h, 80% of **89**; (g) $LiBHEt_3$, THF, 0 °C to room temp., 2 h, 98%; (h) 8 N KOH, MeOH, 100 °C, 18 h, 90%

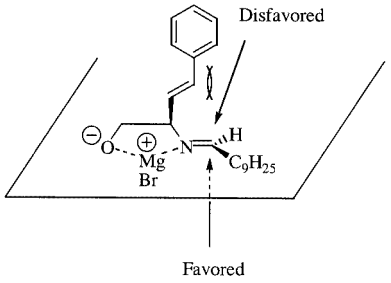


Figure 4. Chelation-controlled transition state model

With a stereoselective method for the installation of the desired 2,6-substituents now to hand, efforts were directed towards the intramolecular cyclization by RCM. However, it was found that RCM was incompatible with a free amine such as **85**, so we decided to mask the amino alcohol function as its corresponding oxazolidinone **86**. RCM on **86** with the second-generation Grubbs' catalyst **3** thus provided the desired tetrahydropyridine **87** in excellent yield. Epoxidation of the double bond with *m*CPBA afforded a separable mixture of *exo*- and *endo*-epoxides **88** and **89** with good selectivity (1:9, respectively; the structure was confirmed by X-ray crystallographic analysis). Finally, the regioselective reduction of **89** with Super-Hydride® and the subsequent hydrolysis of the oxazolidinone in basic medium afforded the desired (−)-3-*epi*-deoxoprosopinine (**80**).[34]

6. Polyhydroxylated Piperidines

Natural polyhydroxylated piperidines (so-called azasugars, due to the N atom replacing the ring oxygen atom in the sugar) and their analogues have attracted a great deal of attention in recent years. Many representatives, such as 1-deoxynojirimycin (**90**), 1-deoxymannojirimycin (**91**), deoxygalactostatin (**92**), 3-*epi*-fagomine (**93**), and fagomine **94** (Figure 5), exhibit significant biological properties as potent

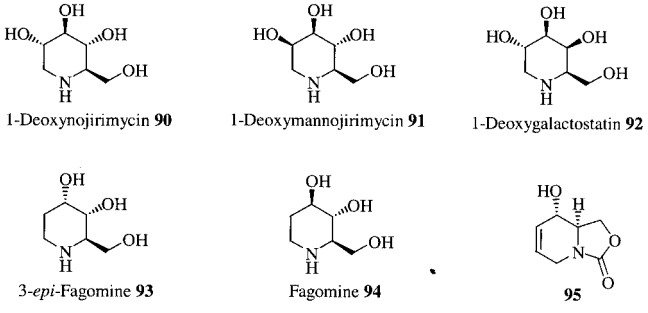
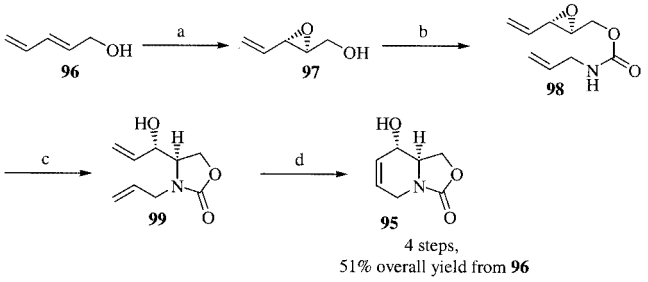


Figure 5. Natural polyhydroxylated piperidines

inhibitors of glycosidases and glycosyltransferases. The therapeutic importance of polyhydroxylated piperidines as new agents for treatment of diseases related to metabolic disorders involving carbohydrates, such as diabetes, cancer and viral infections, is clear and has stimulated much effort towards their preparation.[35]

In this context, oxazolopyridinone **95** (Figure 5) has been used as a common synthetic intermediate for the synthesis of 1-deoxynojirimycin (**90**),[36] 1-deoxymannojirimycin (**91**),[37] and deoxygalactostatin (**92**). Different syntheses of **95**, requiring more than 10 steps, have also been reported in the literature.[38]

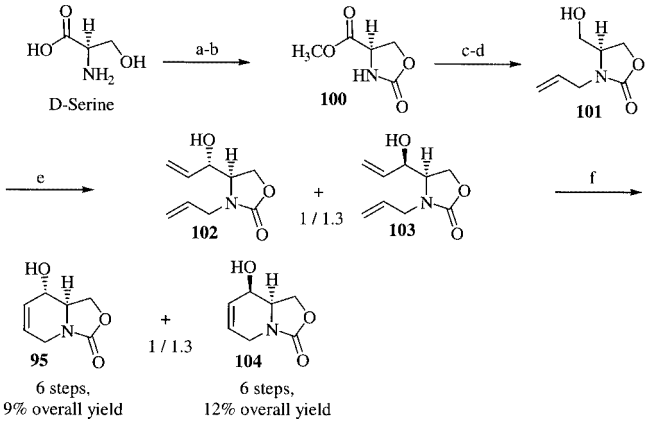
An elegant four-step enantioselective synthesis of this key intermediate **95** in 51% overall yield has been published by Pericàs and Riera[39] (Scheme 14). Sharpless asymmetric epoxidation of the readily available (*E*)-2,4-pentadien-1-ol (**96**) furnished the crude epoxy alcohol **97** (> 91% *ee*). This was then treated, without purification, with a mixture of allyl isocyanate and triethylamine in diethyl ether at 60 °C in a sealed tube to afford allyl carbamate **98** in 59% yield for the two steps. Intramolecular regioselective ring-opening of epoxide **98** was efficiently carried out by treatment with sodium bis(trimethylsilyl)amide in THF to give the desired oxazolidinone **99** in 88% yield. The olefin metathesis reaction with Grubbs' (benzylidene)ruthenium catalyst **2** in CH_2Cl_2 at room temp. provided the oxazolopyridinone **95** in 99% yield.



Scheme 14. Reagents and conditions: (a) *t*BuOOH, L-(+)-DIPT, Ti(*i*PrO)$_4$, CH_2Cl_2, MS (3 Å); (b) allyl isocyanate, Et_3N, Et_2O, 60 °C, 59% (2 steps); (c) NaHMDS, THF, room temp., 88%; (d) **2**, CH_2Cl_2, room temp., 99%

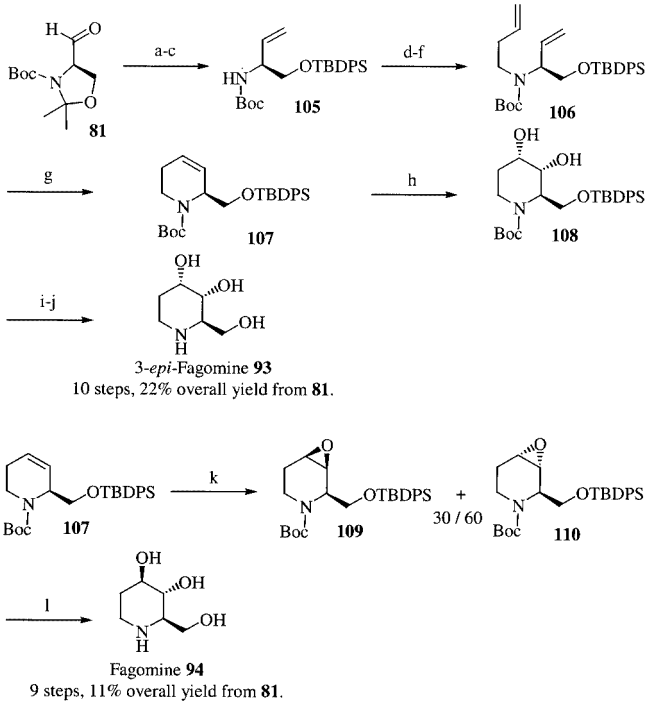
Another synthesis of the key intermediate **95** from serine with modest stereocontrol was described by Lin et al.[40] as outlined in Scheme 15.

D-Serine was converted into oxazolidinone **100** by a two-step sequence in 86% overall yield. *N*-Allylation of **100** with allyl bromide and NaH, followed by reduction of methyl ester with $NaBH_4$, provided primary alcohol **101**. Swern oxidation of the alcohol **101** gave the aldehyde, which was then trapped with vinylmagnesium bromide to furnish an inseparable 1:1.3 mixture of the allylic alcohols **102** and **103** in 53% yield for this transformation. Treatment of this mixture with Grubbs' catalyst **2** in CH_2Cl_2 provided a high yield of oxazolopyridinone **95** and its diastereoisomer **104**, which were separated on a silica gel column. A separable 1:1.3 mixture of the key oxazolopyridinone **95** and its diastereoisomer **104** was obtained in 21% yield from a seven-step sequence.



Scheme 15. Reagents and conditions: (a) $SOCl_2$, MeOH, reflux, 12 h; (b) triphosgene, K_2CO_3, toluene, H_2O, room temp., 86% (2 steps); (c) allyl bromide, NaH, DMF, 65%; (d) $NaBH_4$, MeOH, 74%; (e) DMSO, $(COCl)_2$, CH_2Cl_2, $EtN(iPr)_2$, vinylMgBr, CH_2Cl_2, 53%; (f) **2** (10 mol %), CH_2Cl_2, room temp., 96%

Takahata et al.[41] completed a synthesis of 3-*epi*-fagomine (**93**) and (+)-fagomine (**94**) from Garner aldehyde **81** derived from D-serine as presented in Scheme 16.



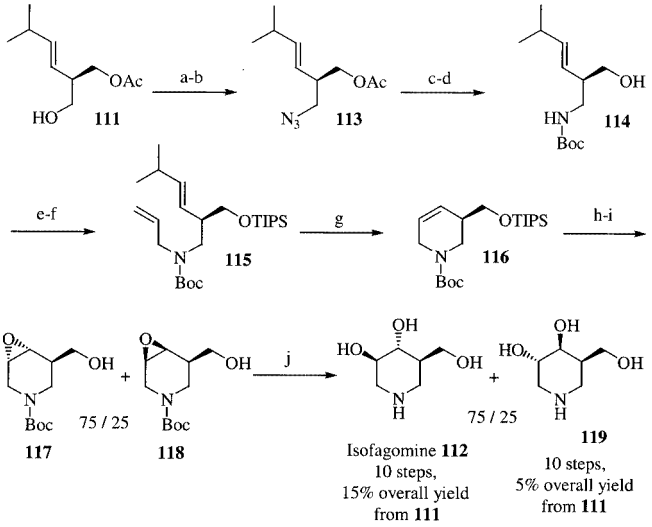
Scheme 16. Reagents and conditions: (a) Ph_3PCH_3Br, NaHMDS, THF, 63%; (b) APTS·H_2O, MeOH; (c) TBDPSCl, DMAP, imidazole, CH_2Cl_2, 72% (2 steps); (d) TFA, CH_2Cl_2; (e) 4-bromo-1-butene, K_2CO_3, CH_3CN; (f) $(Boc)_2O$, Et_3N, CH_2Cl_2, 60% (3 steps); (g) **2**, CH_2Cl_2, 97%; (h) K_2OsO_4·$2H_2O$, NMO, H_2O, acetone, 92%; (i) 10% HCl, dioxane; (j) Dowex 1X2 (OH^-) form, 91% (2 steps); (k) oxone®, CF_3COCH_3, $NaHCO_3$, aq. Na_2EDTA, CH_3CN, 90%; (l) H_2SO_4, dioxane, H_2O, 75%

Wittig methylenation of **81** was followed by selective hydrolysis of the acetonide group and protection of the liberated alcohol function as a silyl ether to give **105** in 45% overall yield. All attempts to perform *N*-alkylation directly on the *N*-Boc carbamate **105** with 4-bromo-1-butene failed. After cleavage of the *N*-Boc protecting group, however, the resulting amine was subsequently mono-*N*-alkylated and reprotected as a Boc derivative to afford the desired RCM substrate **106** in 60% overall yield. RCM of **106** in the presence of Grubbs' catalyst **2** proceeded smoothly, to give the key intermediate **107** in excellent yield. Under modified Upjohn conditions, dihydroxylation of **107** occurred at the less hindered face *anti* to the siloxymethyl substituent and furnished diol **108** as a single diastereoisomer in 92% yield. Cleavage of the protecting groups under acidic conditions, followed by treatment with ion-exchange resin, gave 3-*epi*-fagomine (**93**) in 91% yield.

Epoxidation of **107** with dioxirane generated in situ from oxone® and 1,1,1-trifluoroacetone was found to be much less stereoselective than dihydroxylation, and delivered both *syn*-**109** and *anti*-**110** epoxides in 60% and 30% yields, respectively, after separation by chromatography.

Concomitant acidic hydrolysis of the epoxide *anti*-**110** and protecting groups provided fagomine (**94**) in 75% yield. The completely selective hydrolysis of the epoxide *anti*-**110** was consistent with nucleophilic attack of water on the C-4 at the more remote position *syn* with respect to the 2-substituent.

A chemoselective asymmetrization of tris(hydroxymethyl)-methane was used by Guanti and Riva[42] to prepare the chiral starting material **111** for the synthesis of isofagomine (**112**; Scheme 17).

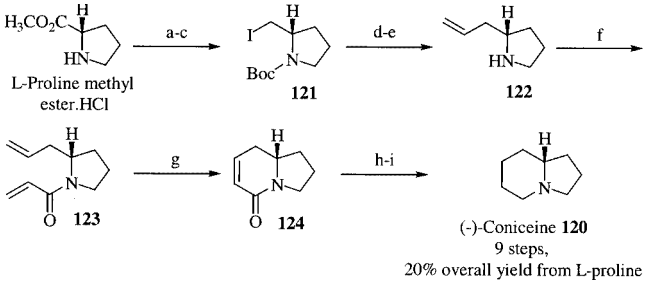


Scheme 17. Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2, −30 °C; (b) NaN_3, DMF, 50 °C, 89% (2 steps); (c) PCL, THF, H_2O, pH = 7, room temp., 97%; (d) PPh_3, THF, H_2O, room temp., then Boc-ON, Et_3N, room temp., 93%; (e) TIPSCl, imidazole, room temp., 88%; (f) allyl bromide, NaH, DMF, room temp., 92%; (g) **2**, CH_2Cl_2 (0.036 M), reflux, 95%; (h) TBAF, THF, room temp., 96%; (i) *m*CPBA, CH_2Cl_2, reflux, 72%; (j) EtOAc, 3 M HCl, room temp., 47%

Subsequent activation of alcohol **111** as a mesylate and displacement with azide yielded **113**. Enzymatic hydrolysis of the acetate **113** with *Pseudomonas cepacia* (PCL), followed by conversion of the azide into the corresponding *N*-Boc-protected amine **114**, was carried out with triphenylphosphane and 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (Boc-ON). Reduction of the azide **113** with triphenylphosphane prior to acetate removal afforded the undesired acetamide through an intramolecular acyl transfer. After protection of the hydroxy group in **114** with TIPSCl, the carbamate was then allylated under basic conditions to furnish the diethylenic derivative **115**. The use of a bulkier silylated group was necessary to suppress competitive intramolecular silyl migration from the oxygen to the nitrogen atom. It was found that the RCM reaction could be performed on **115** under conventional ring-closing conditions with Grubbs' catalyst **2** to give **116** in high yield; the steric hindrance of the branched substrate and the liberation of isopropylethylene instead of ethylene did not perturb the process. Subsequent desilylation of **116**, followed by treatment with *m*CPBA under unusually harsh conditions, afforded an inseparable mixture of the two epoxides **117** and **118** in a 75:25 ratio and 72% yield. Finally, acidic hydrolysis of the epoxide mixture resulted, in moderate yield, in separable isofagomine (**112**) and its stereoisomer **119** in a 75:25 ratio.

7. Indolizidines

A synthesis of (−)-coniceine (**120**), the simplest indolizidine framework, from L-proline methyl ester hydrochloride in nine steps and in 20% overall yield, was developed by Chang et al.[43] (Scheme 18).

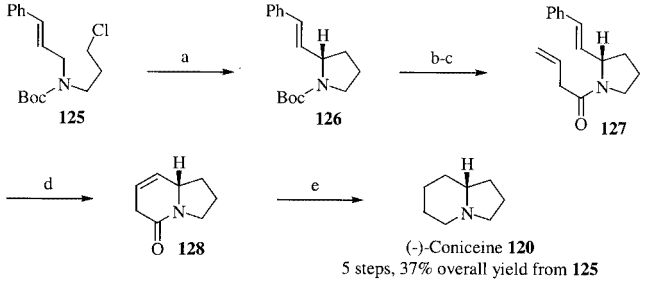


Scheme 18. Reagents and conditions: (a) $LiAlH_4$, THF, reflux, 2 h; (b) $(Boc)_2O$, CH_2Cl_2, 60 °C, 12 h, 90% (2 steps); (c) I_2, PPh_3, imidazole, Et_2O, 0 °C to room temp., 40 min, 89%; (d) vinylMgBr, CuI, THF, −40 °C to room temp., 3 h, 87%; (e) TFA, CH_2Cl_2, 0 °C, 1 h, 99%; (f) acryloyl chloride, CH_2Cl_2, Et_3N, 0 °C to room temp., 3 h, 65%; (g) **3** (5 mol %), CH_2Cl_2, room temp., 3 h, 74%; (h) H_2, PtO_2, EtOAc, room temp., 3 h, 95%; (i) see ref.[44], 63%

Reduction of L-proline methyl ester hydrochloride with LAH, followed by *N*-Boc protection, afforded *N*-protected prolinol, which was converted into the iodine derivative **121** in 80% overall yield. Subsequent treatment of **121** with lithium divinylcuprate, followed by cleavage of the protecting group, gave the secondary amine **122** in 85% overall yield.

N-Allylation of **122** was unsuccessful under various reaction conditions: diallylated quaternary ammonium salt was formed as a major product. To overcome this, and in order to introduce the requisite double bond into the RCM substrate, secondary amine **122** was treated with acryloyl chloride to furnish the desired unsaturated amide **123** in 65% yield. RCM of **123** was then effected with second-generation Grubbs' catalyst in CH_2Cl_2 at room temp. to give the unsaturated bicyclic lactam **124** in 74% yield. Finally, hydrogenation of **124**, followed by LAH reduction of the lactam as described in the literature,[44] furnished (−)-coniceine (**120**).

A short route to indolizidine alkaloids, as illustrated by the synthesis of (−)-coniceine (**120**), was published by Beak et al.[45] (see Scheme 19).



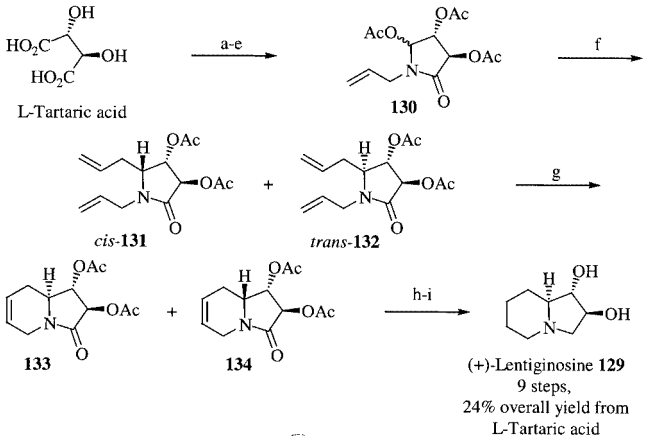
Scheme 19. Reagents and conditions: (a) *n*BuLi, (−)-sparteine, −78 to −25 °C, 3 h, 60%, 94% *ee*; (b) TFA, CH_2Cl_2, room temp., 2 h; (c) diethyl cyanophosphonate, vinylacetic acid, Et_3N, DMF, 0 °C to room temp., 12 h, 85% (2 steps); (d) **3** (5 mol %), CH_2Cl_2, reflux, 28 h, 86%; (e) see ref.[46], 85% (2 steps)

Lithiation/cyclization of the readily available *N*-Boc-*N*-(3-chloropropyl)cinnamylamine **125** with *n*BuLi/(−)-sparteine afforded the *N*-Boc-2-styrylpyrrolidine **126** in 65% yield after recrystallization, with an *ee* of 94%. The Boc group was then removed from **126** after treatment with TFA, and the resulting pyrrolidine salt was converted into the amide **127** in 85% yield. RCM was applied on the diene **127** with the second-generation Grubbs' catalyst **3** in refluxing CH_2Cl_2 to give the bicyclic lactam **128** in good yield. First-generation Grubbs' catalyst **2** was less efficient. (−)-Coniceine (**120**) can be synthesized from this last intermediate by stepwise reduction.[46]

Numerous alkaloids possessing polyhydroxylated indolizidine structures have been isolated from natural sources and have been the subject of many synthetic studies.[47] Some of them display a wide range of biological activities as glycosidase enzyme inhibitors.

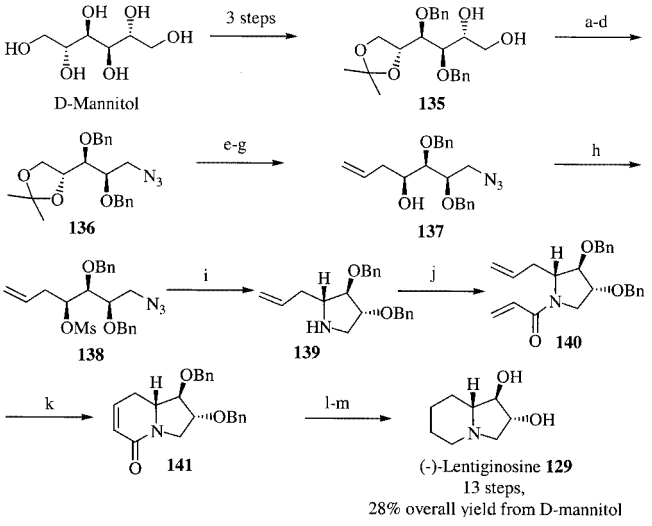
A synthesis of (+)-lentiginosine (**129**) from L-tartaric acid, as presented in Scheme 20, was published by Pilli et al.[48].

N-Allylimide **130** was prepared in 82% yield from tartaric acid in five steps. Addition of allyltrimethylsilane to *N*-allyl lactam **130,** in the presence of either $TiCl_4$ or $BF_3{\cdot}OEt_2$, proceeded in 89% yield via an *N*-acyliminium intermediate without diastereoselectivity to afford *cis*-**131** and *trans*-**132**. In continuation of the synthesis, ring-closing metathesis was performed on the 1:1 mixture of *trans*-**131** and *cis*-**132** with Grubbs' catalyst in CH_2Cl_2 to afford a separable mixture of



Scheme 20. Reagents and conditions: (a) AcCl, reflux; (b) allylamine, CH_2Cl_2, room temp; (c) AcCl, reflux, 99% (3 steps); (d) $NaBH_4$, EtOH, −23 °C; (e) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 76% (2 steps); (f) allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, 0 °C, 89%; (g) **2** (4 mol %), CH_2Cl_2, 88%; (h) H_2, PtO_2, EtOAc; (i) $LiAlH_4$, THF, 82% (2 steps)

bicyclic lactams **133** and **134** in good yield. After separation, hydrogenation of the lactam *trans*-**133**, followed by LAH reduction, gave the (+)-lentiginosine (**129**).



Scheme 21. Reagents and conditions: (a) $Pb(OAc)_4$, CH_2Cl_2, 0 °C to room temp., 4 h; (b) $NaBH_4$, EtOH, 0 °C, 1 h; (c) TsCl, Et_3N, CH_2Cl_2, room temp., 12 h; (d) NaN_3, DMF, 80 °C, 12 h, 80% (4 steps); (e) TFA, THF, H_2O, reflux, 8 h, 97%; (f) $Pb(OAc)_4$, CH_2Cl_2, 0 °C to room temp., 3 h; (g) $SnCl_4$, allyltributyl tin, CH_2Cl_2, −78 °C, 1 h, 82% (2 steps), 98% *de*; (h) MsCl, Et_3N, CH_2Cl_2, 0 °C to room temp., 6 h, 92%; (i) $LiAlH_4$, THF, reflux, 12 h, 68%; (j) acryloyl chloride, Et_3N, CH_2Cl_2, 0 °C to room temp., 12 h, 85%; (k) **2** (10 mol %), toluene, reflux, 24 h, 86%; (l) H_2, Pd/C, EtOH, room temp., 24 h; (m) $LiAlH_4$, THF, reflux, 12 h, 97%

Scheme 21 illustrates a synthesis of (−)-lentiginosine (**129**) from a chiral synthon **135** prepared from D-mannitol in three steps, published by Singh et al.[49] Oxidative cleavage of the diol **135** with lead tetraacetate gave the corresponding aldehyde, which was further transformed into azide **136** by classical reduction and tosylate activation, followed by sodium azide treatment. After acidic hydrolysis of the acetonide moiety in **136**, cleavage oxidation of the vicinal diol gave the corresponding aldehyde, which, without

purification, reacted with allyltributylstannate in the presence of $SnCl_4$ to provide the all-*syn* diastereoisomer **137** with excellent diastereoselectivity. The highly selective addition of the allyl group to the *Si*-face of the aldehyde can be explained in terms of a more rigid five-membered chelation-controlled transition state **A** rather than a flexible six-membered half-chair analogue **B**, as indicated in Figure 6. To form a pyrrolidine ring system, alcohol **137** was subsequently activated as the mesylate **138**, followed by treatment with LAH in refluxing THF to liberate the amine, which in turn displaced the mesylate group by an intramolecular S_N2 mechanism to afford the cyclized product **139** in 68% yield. After conversion of the secondary amine **139** into acrylamide **140**, RCM was accomplished in 86% yield in refluxing toluene in the presence of Grubbs' catalyst **2** to afford **141**. Finally, debenzylation of **141** by catalytic hydrogenation, followed by LAH reduction of the lactam, provided (−)-lentiginosine (**129**).

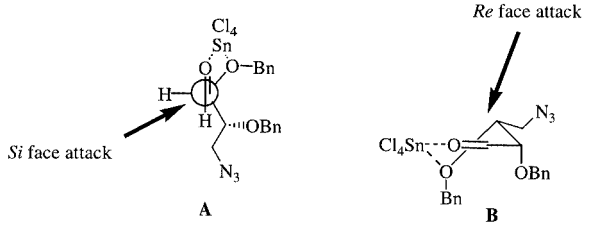
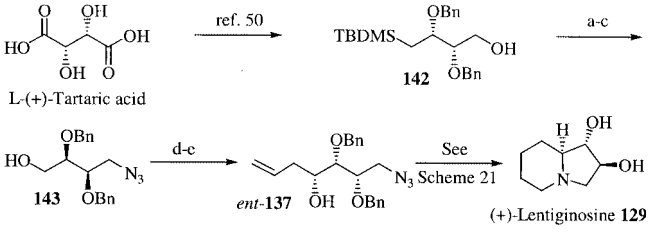


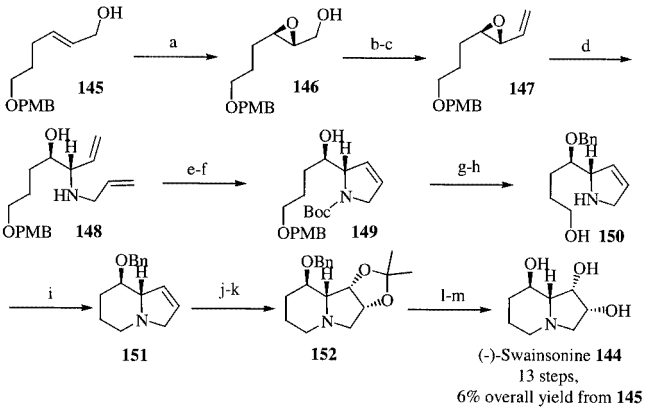
Figure 6. Chelation-controlled transition states models

A formal synthesis of (+)-lentiginosine (**129**) from the *ent*-homoallylic alcohol **137**, as depicted in Scheme 22, was also described. This latter alcohol was prepared from L-(+)-tartaric acid via the known intermediate **142**,[50] which was subjected to a mesylation, followed by azide treatment, and then desilylated to afford the alcohol **143**. The oxidation of **143** to the corresponding aldehyde was attempted by various standard methods without success: lower yields and/or partial isomerization were noted. However, conversion of **143** into aldehyde by the Kim−Corey method (NCS and dimethyl sulfide), followed by allylation as described previously on the crude mixture, afforded the *ent*-homoallylic alcohol **137** in 70% yield and in a diastereoisomeric ratio of 96:4.



Scheme 22. Reagents and conditions: (a) TsCl, Et_3N, CH_2Cl_2, 0 °C, 12 h; (b) NaN_3, DMF, 80 °C, 12 h, 60% (2 steps); (c) TBAF, THF, 0 °C, 8 h, 95%; (d) NCS, Me_2S, toluene, −25 °C, 4 h, then Et_3N, room temp., 5 min; (e) $SnCl_4$, allyltributyl tin, CH_2Cl_2, −78 °C, 1 h, 70% (2 steps), 92% *de*

A particularly elegant and straightforward synthesis of (−)-swainsonine (**144**) by a route involving the Sharpless



Scheme 23. Reagents and conditions: (a) D-(−)-DIPT, $Ti(OiPr)_4$, *t*BuOOH, MS (4 A), CH_2Cl_2, −15 °C, 2.5 h, 52%, 92% *ee*; (b) $(COCl)_2$, DMSO, CH_2Cl_2, −50 °C, 1 h, then Et_3N, −50 °C, 5 min, 94%; (c) methyltriphenylphosphonium bromide, KHMDS, toluene, 0 °C to room temp., 3 h, 67%; (d) allylamine, APTS·H_2O, sealed tube, 105 °C, 3 d, 88%; (e) $(Boc)_2O$, Et_3N, THF, room temp., 24 h, 98%; (f) **2** (6.5 mol %), CH_2Cl_2, reflux, 20 h, 95%; (g) NaH, THF, BnBr, nBu_4NI, room temp., 2 days, 74%; (h) TFA, anisole, CH_2Cl_2, room temp., 90 min, 88%; (i) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 10 min, then Et_3N, 0−4 °C, 5 d, 74%; (j) AD-mix-α, $(DHQ)_2PHAL$, *t*BuOH, $CH_3SO_2NH_2$, 4 °C, 7 d; (k) 2,2-dimethoxypropane, APTS, CH_2Cl_2, room temp., 3 h, 50% (2 steps); (l) H_2, $PdCl_2$, MeOH, room temp., 30 min, 100%; (m) 2 N HCl, THF, room temp., 20 h, 94%

epoxidation to induce chirality, as outlined in Scheme 23, was reported by Pyne et al.[51] The (*E*)-allylic alcohol **145**, prepared in a three-step sequence from commercially available 4-pentyn-1-ol under Sharpless catalytic asymmetric epoxidation conditions, gave the corresponding (2*R*,3*R*)-epoxy alcohol **146** in 52% yield and in 92% *ee*. Swern oxidation and Wittig methylation of the aldehyde intermediate provided the chiral vinyl epoxide **147**. Regioselective ring-opening was performed by heating vinyl epoxide **147** in a sealed tube at 105 °C with an excess of allylamine in the presence of TsOH for 3 d, to afford the *anti*-amino alcohol cleanly as the sole diastereoisomer **148** in 88% yield. Prior to RCM, the amine function was protected as a Boc derivative, which was then heated at reflux with Grubbs' catalyst **2** at high dilution to provide the 2,5-dihydropyrrole **149** in 94% yield for the two steps. From **149**, standard protective group manipulations liberated the amino alcohol **150**. Primary alcohol **150** was then activated by treatment with CBr_4 and Ph_3P to promote indolizidine formation through an intramolecular *N*-alkylation to give **151** in 74% yield. The dihydroxylation of **151** with AD-mix-α or -β proceeded with excellent diastereoselectivities (92:2 and 95:5 respectively). The degree of facial selectivity in this dihydroxylation can be explained in terms of the addition of the bulky osmium reagent to the α-face of the molecule, since attack from the β-face would be hindered by the pseudoaxial protons $H_{8\alpha}$ and $H_{3\beta}$, as shown in Figure 7. In contrast, a poor diastereoselectivity (2:1) was obtained on use of OsO_4/NMO. For practical reasons, the crude diol obtained with AD-mix-α was converted into the known acetonide **152**, which was isolated as a single diastereoisomer in an overall purified yield of 50%. To complete the total synthesis, removal of the protecting groups gave (−)-swainsonine (**144**).

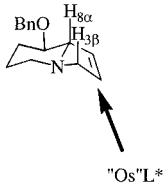
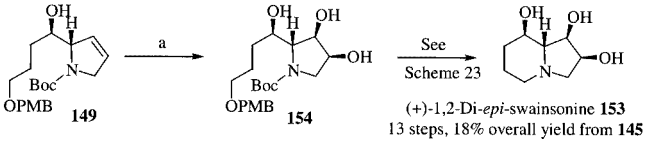


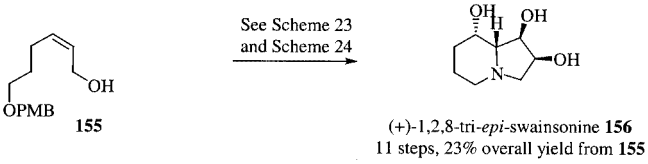
Figure 7. Dihydroxylation of **142**

In the light of this work, (+)-1,2-di-*epi*-swainsonine (**153**) was synthesized from the 2,5-dihydropyrrole **149** in a similar way, just by reversing the order of the dihydroxylation and cyclization reactions, as presented in Scheme 24. The key feature of this approach is the excellent diastereoselectivity of the dihydroxylation of **149** with OsO_4/NMO, affording triol **154** as a single diastereoisomer in 90% yield. The stereochemical outcome of this dihydroxylation can be explained on the basis of the steric effects of the C-2 substituent on 2,5-dihydropyrrole **149**.



Scheme 24. Reagents and conditions: (a) $K_2OsO_4{\cdot}2H_2O$, NMO, acetone, H_2O, room temp., 24 h, 90%

A synthesis of (+)-1,2,8-tri-*epi*-swainsonine (**156**, see Scheme 25) from (*Z*)-allylic alcohol **155** by similar chemistry is also described.

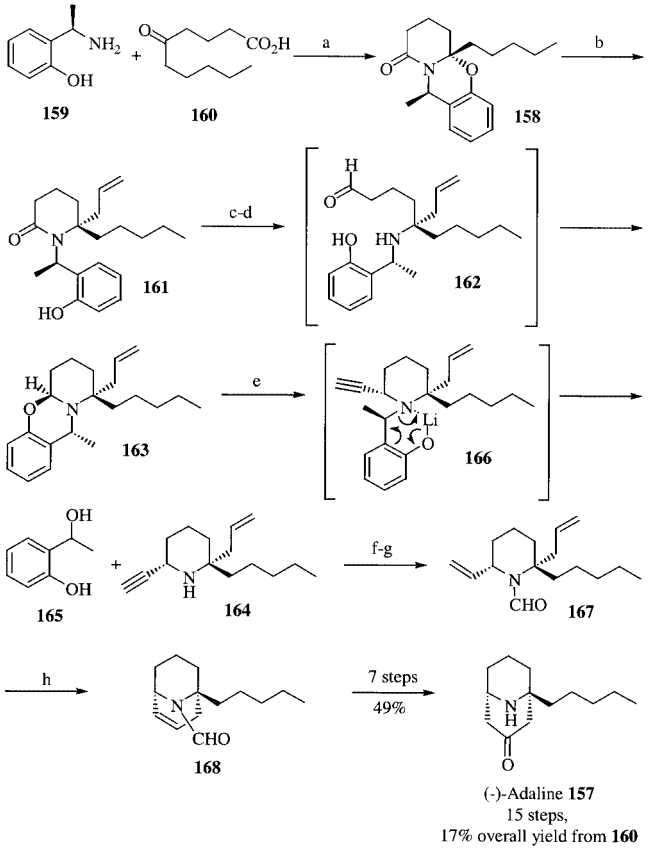


Scheme 25

Another synthesis of swainsonine (**144**) by ring-rearrangement metathesis (RRM) has been published by Blechert et al.[52] Blechert's work is discussed in Section 14.

8. Bridged Bicyclic Alkaloids

RCM is an efficient tool with which to construct bridged bicyclic alkaloids containing a nitrogen atom in the one-atom bridge, as illustrated by the synthesis of (−)-adaline (**157**), a major alkaloid from the chemical defense secretion of the European two-spotted ladybird *Adalia bipunctata*, published by Kibayashi et al.[53] (Scheme 26). It should be noted that a methodology concerning a general approach to the synthesis by RCM of racemic bridged azabicyclic systems containing a nitrogen atom in the one-atom bridge of an [*n*.3.1] core (*n* = 2, 3, 4) has also been published by Martin et al.[54]. Both approaches take advantage of the equilibrium in favor of a diaxial disposition of the two alkenyl substituents in *N*-acyl *cis*-2,6-piperidine derivatives, in order to avoid a 1,3 strain with the *N*-acyl group, providing a suitable orientation of the olefins for the RCM reaction (see Figure 8).



Scheme 26. Reagents and conditions: (a) benzene, reflux, 88%, > 96% *de*; (b) allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, 50 °C, 76%, > 88% *de*; (c) LiH_2NBH_3, THF, 40 °C, 45 min, 88%; (d) TPAP, NMO, CH_3CN, MS (4 Å), room temp., 30 min, 80%; (e) lithium acetylide ethylenediamine complex, THF, 40 °C, 1.5 h, 88%; (f) HCl, MeOH, then TsOH, trimethyl orthoformate, 90 °C, 12 h, 93%; (g) H_2, Lindlar catalyst, MeOH, room temp., 80 min, 92%; (h) **3** (15 mol %), benzene, 50 °C, 40 min, 99%

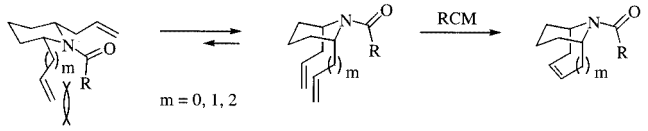
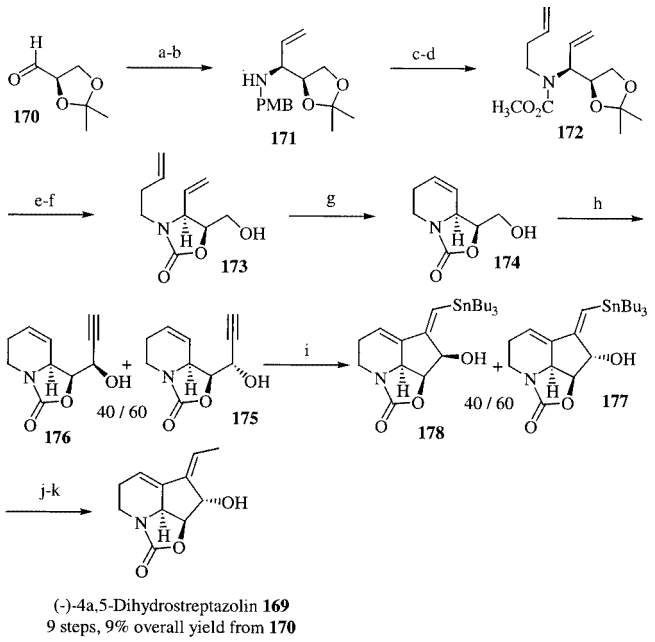


Figure 8. Conformational equilibrium of *cis*-2,6-dialkenyl-substituted *N*-acylpiperidines

To start the synthesis, a $TiCl_4$-promoted allylation reaction with allyltrimethylsilane was performed on the chiral N,O-acetal **158** [prepared with high diastereoselectivity (46:1) from (*S*)-2-(1-aminoethyl)phenol (**159**) and an appropriate oxo acid **160**], via the *N*-acyliminium ion, to generate the chiral quaternary center in **161** with high diastereoselectivity (16:1) and in 76% yield.[55] Reductive lactam ring-opening of **161** with lithium amidotrihydroborate ($LiNH_2BH_3$, LAB) and oxidation of the resulting amino alcohol by the catalytic TPAP/NMO procedure afforded al-

dehyde **162**, which underwent dehydrocondensation to give the tricyclic N,O-acetal **163** as a single diastereoisomer in 70% overall yield. Compound **163** was converted in a one-pot, two-step process into the (6*S*)-ethylnylpiperidine **164** in high yield and with total stereoselectivity: nucleophilic alkynylation with lithium acetylide ethylenediamine complex in THF at 40 °C occurred with complete inversion of configuration, followed by unexpected concomitant removal of the racemic 1-(2-hydroxyphenyl)ethanol (**165**) by C−N bond cleavage. This stereocontrol is attributed to lithium−oxygen coordination activating the C2−O bond and favoring the attack of the organometallic species by an S_N2-type mechanism to open the N,O-acetal. At this stage, the formation of a six-membered chelated lithium phenoxide complex **166** permitted the elimination of the remaining chiral auxiliary as racemic material **165**. Treatment of the hydrochloride salt of **164** with methyl orthoformate yielded the corresponding formamide, and exposure of this material to hydrogen in the presence of Lindlar catalyst afforded the diene **167**. An RCM reaction carried out on *cis*-2,6-dialkenylformamide **167** with Grubbs' first-generation catalyst **2** in benzene under reflux conditions provided cyclized compound **168** in 90% yield. On switching to an imidazoylruthenium-based catalyst, the reaction was completed in a shorter time in almost quantitative yield. Although hydrochloride salts rather than the corresponding amines have traditionally been employed as substrates in RCM reactions, this reaction failed on the amine derived from *N*-formyl compound **167**, most probably due to the diequatorial position of the alkenyl groups (as indicated by NMR studies). From the chiral homotropane **168**, the completion of the total synthesis of (−)-adaline (**157**) was effected in seven steps, including dihydroxylation, regioselective protection, Barton−McCombie deoxygenation, and oxidation, in 49% overall yield.



Scheme 27. Reagents and conditions: (a) PMB-NH_2, Et_2O, $MgSO_4$, 0 °C, 3 h, 100%; (b) vinylMgCl, Et_2O, THF, 0 °C to room temp., 12 h, 84%, 96% *de*; (c) 4-bromo-1-butene, K_2CO_3, NaI, nBu_4NI, DMF, 70 °C, 15 h, 74%; (d) CH_3OCOCl, Na_2CO_3, benzene, 75 °C, 17 h, 91%; (e) 80% aqueous AcOH, 80 °C, 4 h; (f) 10% aqueous KOH, MeOH, room temp., 2 h, 80% (2 steps); (g) **2** (3 mol %), benzene, 60 °C to room temp., 13 h, 90%; (h) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 20 min, then Et_3N, −78 °C to −40 °C, 1 h, then ethynylMgBr, −78 °C to 0 °C, 63% (2 steps); (i) Bu_3SnH, AIBN, benzene, reflux, 5 h, 82%; (j) I_2, CH_2Cl_2, 0 °C, 1 h, 93%; (k) CH_3Li, $ZnBr_2$, $[Pd(PPh_3)_4]$ (3 mol %), THF, Et_2O, DMF, 60 °C, 2 h, 73%

9. Tricylic Alkaloids

A short and efficient synthesis of (−)-4a,5-dihydrostreptazolin (**169**) in only nine steps from D-glyceraldehyde acetonide **170** (Scheme 27) was published by Cossy, Meyer, et al.[56]

The chiral starting material **170** was treated with *p*-methoxybenzylamine to afford the corresponding aldimine, which was treated directly with vinylmagnesium chloride to furnish the allylic amine **171** with high diastereoselectivity (up to 98:2) and in 84% overall yield. Performing the *N*-alkylation of secondary amine **171** with 4-bromo-1-butene and K_2CO_3 at high concentration in the presence of NaI and nBu_4NI yielded the tertiary allylic amine. This was then debenzylated by treatment with methyl chloroformate to furnish the corresponding carbamate **172** in 68% yield for the two steps. Transformation of the carbamate **172** into the oxazolidinone **173** was accomplished by acidic hydrolysis of the acetonide and subsequent methanolic KOH treatment with 80% overall yield. Access to tetrahydropyridine **174** in 90% yield was achieved by treatment of precursor **173** with Grubbs' catalyst **2** in benzene at 60 °C. Swern oxidation was effected on alcohol **174** and the resulting aldehyde was directly trapped at −40 °C with an excess of ethynylmagnesium bromide to give the diastereoisomeric propargyl alcohols **175** and **176** in a 60:40 ratio in 63% yield. This procedure avoids the isolation of the aldehyde intermediate, which is unstable due to hydration and isomerization problems. The mixture was treated with tributyltin hydride in the presence of a catalytic amount of AIBN in refluxing benzene to promote radical-mediated enyne cyclization, affording (*Z*)-vinyl stannanes **177** and **178**, which were easily separated by flash chromatography, in a 60:40 ratio. The synthesis of (−)-4a,5-dihydrostreptazolin (**169**) was then completed from (*Z*)-vinyl stannane **177** in 70% overall yield by iododestannylation followed by Pd-catalyzed cross-coupling of the resulting vinyl iodide with methylzinc bromide.

Kibayashi et al.[57] reported an efficient route to the racemic 5-azatricyclo[6.3.1.$0^{1,5}$]dodecane core skeleton **179** of FR901483 (**180**), an immunosuppressive agent isolated from the fermentation broth of *Cladobotryum* sp. No 11231 (Figure 9).

Ketalization of the ketone **181**, followed by oxidative cleavage of the double bond, afforded the aldehyde **182**, which was treated with ethanolamine in the presence of $NaBH_4$ to give the secondary amine **183** (Scheme 28). Acid treatment of **183** provided the corresponding amino oxo alcohol, which in turn gave the tricyclic oxazolidine **184** on

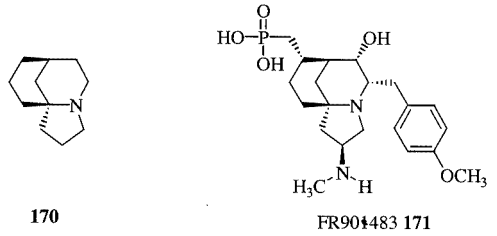
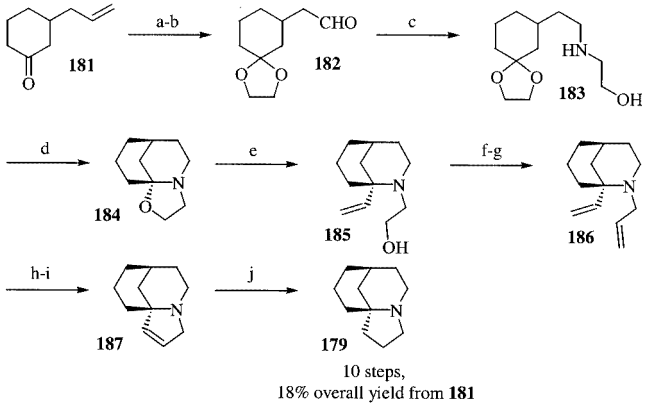


Figure 9. 5-Azatricyclo[6.3.1.0^{1,5}]dodecane core skeleton and FR901483 (**171**)



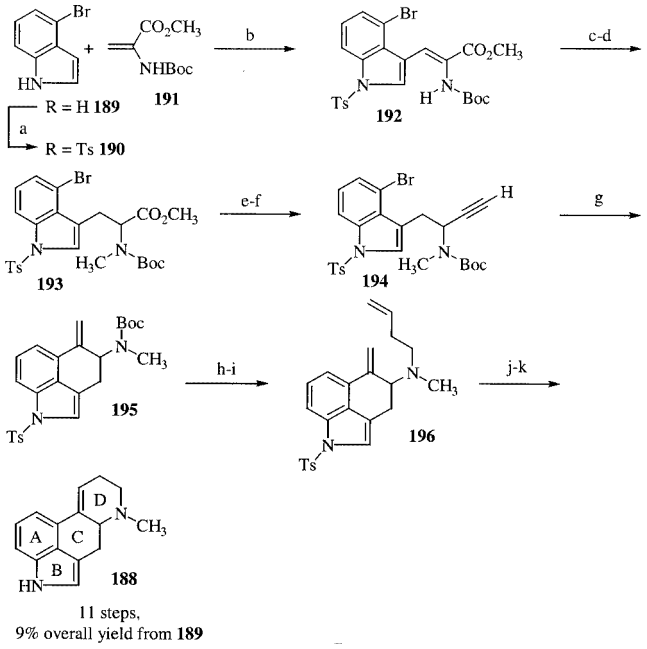
Scheme 28. Reagents and conditions: (a) $(CH_2OH)_2$, TsOH; (b) $NaIO_4$, OsO_4, 90% (2 steps); (c) ethanolamine, $NaBH_4$, MeOH, 83%; (d) HCl, MeOH, reflux, then $CHCl_3$, reflux, 14 h, 80%; (e) $(CH_2{=}CH)_3Al$, Et_2O, room temp., 4 h, 93%; (f) Swern oxidation; (g) Ph_3PCH_3Br, BuLi; (h) HCl, MeOH, 62% (3 steps); (i) **2** (20 mol %), CH_2Cl_2, room temp., 48 h, 68%; (j) H_2, Pd/C, MeOH, 75%

heating at reflux in chloroform. The 1-vinylated azabicyclononane **185** was obtained in 93% yield by treatment of tricyclic oxazolidine **184** with an excess of trivinylalane in diethyl ether, through a nucleophilic bridgehead alkylation on the "anti-Bredt iminium ion" **B** (see Figure 10). Swern oxidation of **185** and Wittig olefination gave the diene **186**, which, after treatment with HCl, was subjected to ring-closing metathesis with Grubbs' catalyst **2** in CH_2Cl_2 at room temp. to afford the azatricyclododecene compound **187** in 68% yield. Under these conditions, olefin metathesis using free tertiary amine **186** was inefficient. Hydrogenation of **187** provided the azatricylic core skeleton **179** of FR901483 (**180**) in 75% yield.

Figure 10. Complexation of AlR_3 and C−C bond formation

10. Tetracyclic Alkaloids

A novel route to ergot alkaloids by RCM was developed by Martin et al.[58] through the synthesis of a C8-unsubstituted tetracyclic ring system **188** from 4-bromoindole (**189**), as depicted in Scheme 29.

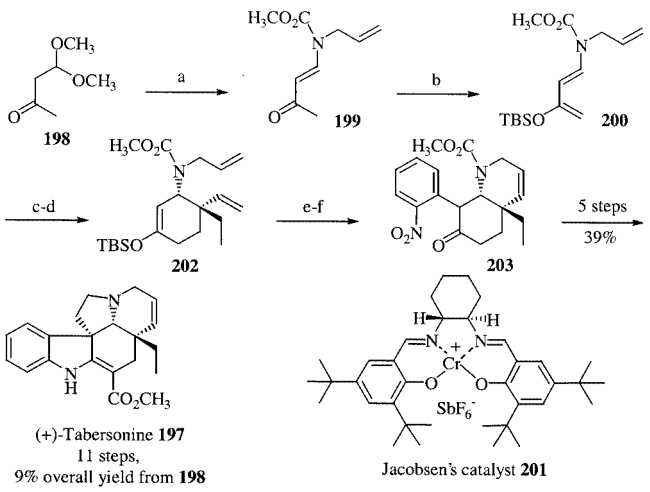


Scheme 29. Reagents and conditions: (a) NaH, TsCl, 74%; (b) $Pd(OAc)_2$, $NaHCO_3$, *p*-chloranil, 76%; (c) MeI, Ag_2O, DMF, 89%; (d) H_2 (100 psi), $[(PPh_3)_3RhCl]$, MeOH, 99%; (e) DIBAL-H, CH_2Cl_2; (f) (1-diazo-2-oxopropyl)phosphonate, K_2CO_3, MeOH, 73% (2 steps); (g) $[Pd(PPh_3)_4]$, Bu_4NCl, piperidine, HCOOH, CH_3CN, 85 °C, 42%; (h) TsOH, MeOH, 80%; (i) 4-bromo-1-butene, Cs_2CO_3, THF, 89%; (j) **1**, benzene, reflux, 86%; (k) Mg, MeOH, 98%

4-Bromoindole (**189**) was converted into its *N*-tosyl derivative **190** and then subjected to a Pd-mediated coupling with a protected dehydroalanine **191** to afford the dehydrotryptophan **192** in 56% overall yield. After *N*-methylation of **192**, hydrogenation of the dehydroamino ester with Wilkinson's catalyst provided the desired racemic bromotryptophan **193**[59] without hydrogenolysis of the aryl bromide. Reduction of the ester **193** with DIBAL-H gave the corresponding aldehyde, which was directly treated with Bestmann reagent to afford the acetylene intermediate **194**. After considerable efforts to construct the C-ring, it was found that the desired tricyclic ring system **195** was obtained from the acetylene **194** in 42% yield by use of a Heck reaction followed by hydride capture.[60] Acid-catalyzed hydrolysis of the *N*-Boc moiety of **195** and *N*-alkylation of the resulting secondary amine with 4-bromo-1-butene gave the D-ring precursor **196** in 71% overall yield. There are only a few examples of RCM reactions involving exocyclic olefins and phenyl-substituted alkenes.[61] Nevertheless, this reaction was performed on **196** in the presence of Schrock catalyst **1** in refluxing benzene to afford the desired tetracyclic compound **188** in high yield after cleavage of the *N*-tosyl group. RCM with the less reactive Grubbs' catalyst **2** resulted in only small quantities of cyclized product.

11. Pentacyclic Alkaloids

A beautiful, concise, and highly stereocontrolled asymmetric synthesis of (+)-tabersonine (**197**), as well as four other alkaloids of the *Aspidosperma* family, was effected by Rawal et al.[62] in 11 steps by a gram-scale route using RCM as one of the key steps, as depicted in Scheme 30.



Scheme 30. Reagents and conditions: (a) methyl *N*-allylcarbamate, $CHCl_3$, TsOH, reflux, 44 h, 45%; (b) TBSCl, NaHMDS, THF, −78 °C, 2 h, 100%; (c) ethylacrolein, Jacobsen's catalyst **201**, CH_2Cl_2, MS (4 Å), −40 °C, 2 d, 84%, 96% *ee*; (d) Ph_3PCH_3Br, BuLi, THF, −78 °C to room temp; (e) **2** (7.2 mol %), CH_2Cl_2, reflux, 44 h; (f) (*o*-nitrophenyl)phenyliodonium fluoride, THF, DMSO, room temp., 3.5 h, 59%, (3 steps)

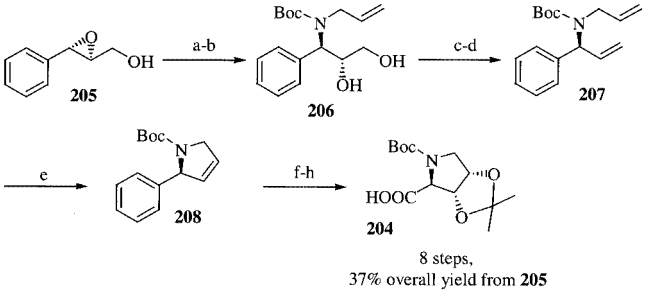
Acid-catalyzed treatment of the commercially available monoacetal **198** with methyl *N*-allylcarbamate afforded the diene precursor **199** in 45% yield on a large scale. The vinylogous imide **199** was then treated with a slight excess of NaHMDS, followed by trapping of the resulting enolate with TBSCl at low temperature to furnish a quantitative crude yield of diene **200**. An asymmetric hetero-Diels−Alder reaction between the diene **200** and ethylacrolein, catalyzed by Jacobsen's chiral (salen)Cr^{III} complex **201**, gave the desired cycloadduct **202** in 91% yield and with 96% *ee* (on a multigram scale 85% yield and 95% *ee*). After Wittig methylenation of the aldehyde **202**, the resulting diethylenic compound was subjected to RCM in the presence of Grubbs' catalyst **2**. The reaction mixture was then concentrated and treated directly with (*o*-nitrophenyl)phenyliodonium fluoride (NPIF) to afford, in multigram quantities, the precursor of the indole unit **203** in 57−62% overall yield from **202**. It is worth noting that the RCM reaction was also carried out on racemic material **202** both with ruthenium Grubbs' catalyst **2** in CH_2Cl_2 (40 °C) and with Schrock's molybdenum catalyst **1** in benzene (60 °C) to give the hexahydroquinone ring system in 75% and 88% yields, respectively, after purification.

From the precursor of the indole unit **203**, (+)-tabersonine (**197**) was obtained in five steps and in 39% overall yield.

12. Pyrrolidines

Much less work regarding the synthesis of natural pyrrolidine products by application of RCM technology has been published.

Riera et al.[63] reported a formal synthesis of L-3,4-dihydroxyproline, a natural α-amino acid isolated in 1994, as



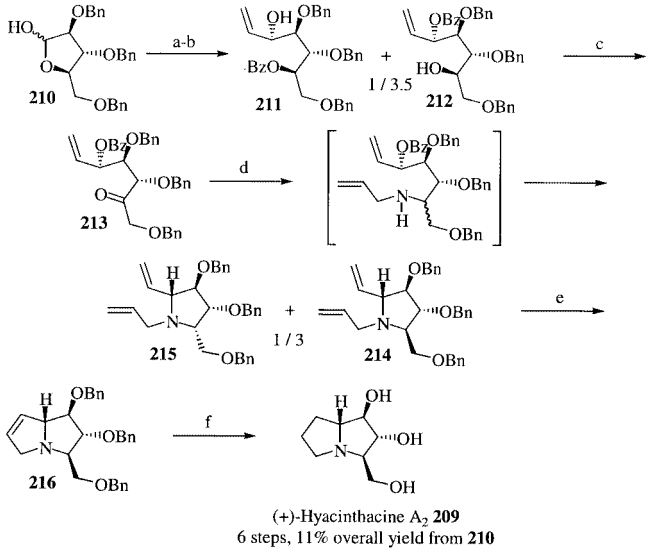
Scheme 31. Reagents and conditions: (a) allylamine, $Ti(OiPr)_4$, CH_2Cl_2, 65 °C, 8 h, 97%; (b) $(Boc)_2O$, $NaHCO_3$, MeOH, room temp., 12 h, 95%; (c) Cl_2CS, DMAP, CH_2Cl_2, room temp., 2 h; (d) 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine, 65 °C, 24 h, 72% (2 steps); (e) **2** (5 mol %), CH_2Cl_2, room temp., 1 h, 99%; (f) OsO_4, $K_2Fe(CN)_6$, K_2CO_3, *t*BuOH, H_2O, room temp., 24 h, 99%; (g) 2,2-dimethoxypropane, acetone, APTS, room temp., 3 h, 96%; (h) $RuCl_3$, $NaIO_4$, $NaHCO_3$, CCl_4, CH_3CN, H_2O, room temp., 55 h, 59%

its protected derivative **204**, as shown in Scheme 31. Subsequent regioselective ring-opening of the chiral epoxy alcohol **205** (prepared in 99% *ee* from cinnamyl alcohol by asymmetric Sharpless epoxidation) with allylamine in the presence of titanium tetraisopropoxide, followed by protection of the resulting amine as its Boc derivative, gave the diol **206** in high overall yield. *N*-Boc-aminodiol **206** was then efficiently deoxygenated to the corresponding bis(olefin)-protected amine **207** in 72% yield by the standard Corey−Hopkins procedure: formation of the cyclic thiocarbonate with thiophosgene and heating with 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine. Next, a solution of the RCM precursor **207** in CH_2Cl_2 at room temp. was treated with Grubbs' catalyst **2** to give the desired pyrrolidine **208** in excellent yield. Finally, dihydroxylation of **208** occurred with total facial selectivity, *anti* to the phenyl ring, to afford the diol, which was protected as an acetonide. To complete the synthesis from this last intermediate, catalytic ruthenium tetraoxide oxidation of the phenyl delivered the carboxylic acid, providing the protected L-3,4-dihydroxyproline **204** in 50% overall yield.

13. Pyrrolizidines

A short synthesis of (+)-hyacinthacine A_2 (**209**) in six steps from 2,3,5-tri-*O*-benzyl-D-arabinofuranose (**210**) and in an overall yield of 11% was described by Martin et al.[64] (Scheme 32). Highly stereoselective addition of divinylzinc to the commercially available lactol **210** gave the corresponding allylic alcohol, which was converted with poor regioselectivity into a mixture of benzoates in a 3.5:1 ratio in favor of the required allylic benzoate **212**. This mixture was oxidized by the Swern method with trifluoroacetic anhy-

dride and DMSO to provide, after separation by chromatography, the desired ketone **213**. To construct the *N*-allylated pyrrolidine RCM substrate, reductive amination of **213** with allylamine in the presence of $NaBH_3CN$ afforded the corresponding allylamines. In situ intramolecular nucleophilic displacement of the benzoate, occurring with complete inversion of configuration, then gave a diastereoisomeric mixture of D-*manno* and L-*gulo* derivatives **214** and **215** in a 3:1 ratio and in 78% overall yield. The RCM was performed on this epimeric mixture of the corresponding hydrochloride salts in the presence of 16 mol % Grubbs' catalyst **2** in toluene at 60 °C to give, after purification, the tetrahydropyrrolizine **216** in 30% yield (75% based on the recovered starting material). Hydrogenation of the double bond and cleavage of the benzyl protecting groups was carried out by treatment with H_2 in the presence of Pd/C to afford the (+)-hyacinthacine A_2 (**209**) in 82% yield.

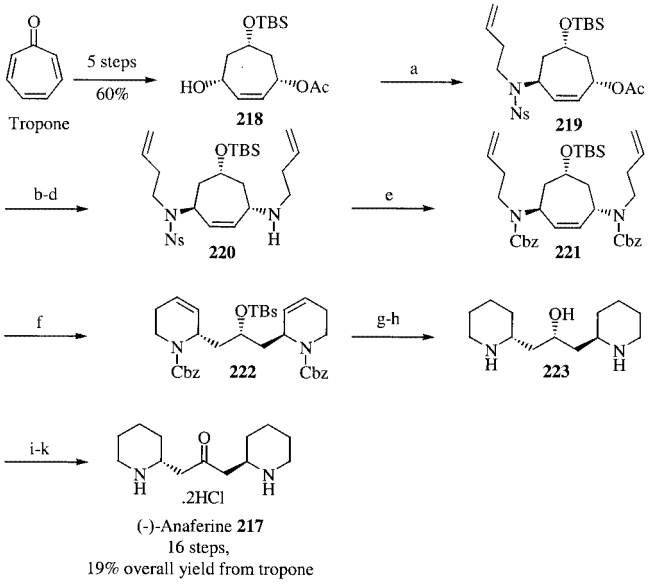


Scheme 32. Reagents and conditions: (a) $(CH_2{=}CH)_2Zn$, 95%; (b) BzCl, nBu_4NI, CH_2Cl_2, 1 N NaOH, 0 °C, 3 h; (c) TFAA, DMSO, Et_3N, CH_2Cl_2, −78 °C to room temp., 63% (2 steps); (d) allylamine, AcOH, $NaBH_3CN$, MS (3 Å), MeOH, 0 °C to 40 °C, 6 d, 78%; (e) **2** (16 mol %), toluene, 60 °C, 72 h, 30%; (f) H_2, Pd/C, MeOH, THF, 6 N HCl, room temp., 20 h, 82%

14. Blechert's Approach

The Blechert group has made an important contribution to the field of alkaloid synthesis by combining RCM with ring-opening metathesis (ROM) and cross metathesis (CM). Intramolecular RCM−ROM or the RCM−ROM−CM domino process [so-called ring-rearrangement metathesis (RRM)] have been successfully applied to chiral cyclopentene and cycloheptene derivatives for efficient syntheses of various natural alkaloids[52,65] and related compounds.[66] By starting from an easily accessible chiral cyclic olefin precursor bearing one (or two) olefin substituent(s), the combination of ROM with simple (or double) RCM proceeds with complete transfer of chirality from carbo- to newly formed N-heterocycles. A similar strategy has been employed to provide a variety of carbo-[67] and O-heterocyclic[68] products.

The power of RCM-ROM as a synthetic tool is illustrated in the first synthesis of (−)-anaferine (**217**),[69] isolated in 1962 from *Withania somnifara* Dunal, by a tandem ring rearrangement metathesis using a combination of ROM and two RCMs, as outlined in Scheme 33.

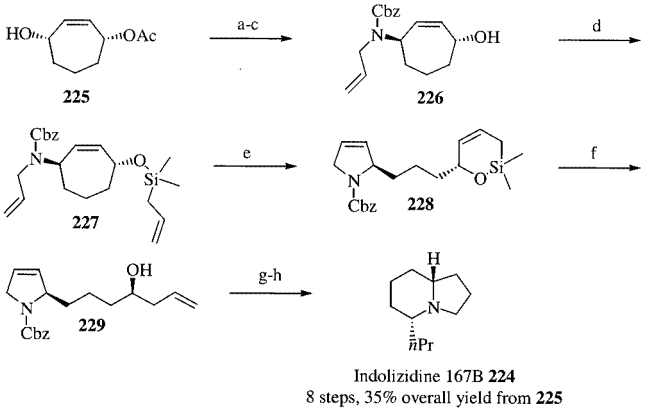


Scheme 33. Reagents and conditions: (a) *N*-(but-3-enyl)-*N*-(nosyl)-amine, PPh_3, DEAD, THF, 0 °C to room temp., 18 h, 89%; (b) KCN, MeOH, room temp., 15 h, 86%; (c) MsCl, pyridine, 0 °C to room temp., 18 h, 82%; (d) but-3-enylamine, K_2CO_3, CH_3CN, 70 °C, 18 h, 86%; (e) K_2CO_3, PhSH, DMF, 70 °C, 30 min, then CbzCl, 0 °C to room temp., 3 h, 86%; (f) **2** (10 mol %), CH_2Cl_2, reflux, 48 h, 87%; (g) H_2, Pd/C, MeOH, room temp., 12 h, 87%; (h) concd. HCl, EtOH, room temp., 12 h, 90%; (i) $(Boc)_2O$, Et_3N, MeOH, 70 °C, 5 h, 98%; (j) PCC, MS (4 Å), CH_2Cl_2, room temp., 15 h, 100%; (k) 3 N HCl, MeOH, room temp., 15 h, 100%

The starting chiral material **218** was prepared from commercially available tropone in five steps, including an enzymatic asymmetrization. A classical Mitsunobu reaction on **218** using *N*-(but-3-enyl)-*N*-(nosyl)amine as precursor of the amine side chain was introduced with complete inversion of configuration at the reaction center to afford **219** in 89% yield. Introduction of the same side chain with retention of configuration was more problematic: (allyl)Pd-catalyzed substitution failed. After cleavage of the acetate of **219**, however, the resulting allylic alcohol was subsequently treated with mesyl chloride to give the chloride intermediate, which was heated with but-3-enylamine to furnish the bis(amine) **220** in 61% overall yield. This transformation proceeded through two successive reactions with complete inversion of configuration, furnishing a chiral material **220** with excellent diastereoselectivity (96:4). In a one-pot, two-step process, the *N*-nosyl protecting group on **220** was cleaved and the liberated bis(amine) was reprotected as the Cbz-carbamate **221** in 86% yield. Tandem ring rearrangement metathesis was then carried out on **221** with Grubbs'

catalyst **2** in refluxing CH_2Cl_2 to result in the clean formation of bis(tetrahydropyridine) **222** in 87% yield. At this stage of the synthesis, the cleavage of the silyl ether with fluoride failed, as it also did in acidic media, giving side-products with isomerization of the double bond probably induced by traces of ruthenium. To overcome these problems, the bis(tetrahydropyridine) **222** was first hydrogenated to the corresponding bis(piperidine), which was treated in acidic medium to afford the amino alcohol **223** in 78% overall yield. This intermediate was successively protected as its di-*tert*-butylcarbamate, oxidized with PCC, and finally treated with dilute aqueous HCl to give (−)-anaferine hydrochloride (**217**) in 98% overall yield.

An elegant feature of this strategy is that the synthesis is highly modular: ring size and also olefin-containing side chains can all easily be varied. To highlight this methodology, an enantioselective synthesis of indolizidine 167B (**224**) was achieved by Blechert et al. in eight steps and with 35% overall yield from chiral cycloheptene derivative **225**, as presented in Scheme 34.



Scheme 34. Reagents and conditions: (a) *N*-allyl-*N*-(nosyl)amine, PPh_3, DIAD, THF, room temp., 88%; (b) K_2CO_3, PhSH, DMF, 70 °C, then CbzCl, 0 °C, 84%; (c) NaCN, MeOH, room temp., 100%; (d) allyl(chloro)dimethylsilane, Et_3N, DMAP, CH_2Cl_2, 0 °C, 90%; (e) **2** (5 mol %), CH_2Cl_2, reflux, 4 h; (f) TBAF, THF, 0 °C to room temp., 92% (2 steps); (g) Dess−Martin periodinane, CH_2Cl_2, 2 h, 73%; (h) H_2, Pd/C, MeOH, room temp., 15 h, 79%

By use of the chemistry previously described in Scheme 33, the intermediate **226** was obtained in three steps and in 78% overall yield from chiral cycloheptenediol monoacetate **225**. Alcohol **226** was treated with allyl(chloro)-dimethylsilane to furnish the RRM precursor **218** in high yield. Treatment of **227** with Grubbs' catalyst **2** in refluxing CH_2Cl_2 resulted, through ROM-two-RCM reactions, in the formation of intermediate **228** which, upon addition of TBAF to the resulting mixture, afforded the pyrrolidine derivative **229** in 92% yield. To complete the synthesis, alcohol **229** was subsequently oxidized with Dess−Martin periodinane and hydrogenated on Pd/C to provide indolizidine 167B **224**.

15. Conclusion

In summary, the recent examples of total synthesis of alkaloids described in this report illustrate the broad spectrum of the potential offered by RCM reactions to produce functionalized heterocycles. Crucial to the efficiency of the RCM-based synthesis of complex alkaloids is the ability to use the formed double bond to go further to the target. In the future, the development of more active catalysts with improved functional group tolerance, particularly towards basic functional groups, may be expected. Another important challenge will be the development of the catalyzed asymmetric ring-closing metathesis reaction (ARCM)[70] to afford enantiomerically pure substituted N-heterocycles.

Acknowledgments

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