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The 3-Hydroxypiperidine Skeleton: Key Element in Natural Product Synthesis

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The 3-hydroxypiperidine moiety is a privileged scaffold that is encountered in many bioactive compounds and natural products. This review summarizes the investigations of various research groups concerning the synthesis of natural products containing this scaffold.

Introduction

Natural products often form an inspiration for synthetic organic chemists, because of their biological properties and structural design. In the majority of natural products, so-called privileged skeletal fragments can be identified such as the benzodiazepinone and quinazoline structures. Another privileged scaffold in nature is the 3-hydroxypiperidine (or 5-hydroxypiperidine) motif, which is present in a variety of natural products. An important subclass consists of polyhydroxypiperidines (azasugars), of which since the isolation of the first member nojirimycin (**1**, Figure 1)[1] in 1966 more than one hundred derivatives have been isolated. These azasugars have formed attractive synthetic targets for many research groups.[2] A more diverse class is composed of natural products containing a mono-3-hydroxypiperidine scaffold.[3] Two amino acids displaying this structure are 3-hydroxypipecolic acid (**2**) and its regioisomer 5-hydroxypipecolic acid (**3**),[4] which for example have been used in the synthesis of conformationally restricted peptides.[5] (–)-Swainsonine (**4**) was isolated from *Rhizoctonia leguminicola*

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and attracted the attention of medicinal chemists due to its pharmacological properties and reached phase I clinical trials as an anticancer drug. Another subclass, the 2,6-disubstituted piperidin-3-ols, is commonly encountered in nature and most of its members show interesting pharmacological activities. A representative is (–)-prosopinine (**5**), which has been isolated from the *Prosopis africana* and displays antibiotic and anaesthetic activities.[6] The C-2 isomer (prosophylline, not shown) was isolated from the same plant, showing similar properties. Another interesting alkaloid is (–)-morusimic acid D (**6**), which was isolated from riped fruit of the Turkish white mulberry plant.[7] (–)-Cassine (**7**) was isolated from the leaves and twigs of the *Cassia excelsa* in 1964[8] and its absolute structure was elucidated in 1966.[9] In 1977, the isolation of (+)-spectaline (**8**) from the *Cassia spectabilis* was reported.[10] This alkaloid highly resembled the structure of (–)-cassine (**7**) and is a potent antifungal agent. Saturated nitrogen heterocycles are well-known components of ant venoms, and recently analysis of the venom of the ant *Myrmicaria melanogaster* showed the presence of the alkaloid **9**.[11] Other natural compounds possessing the 3-hydroxy skeleton include lepadins A, B and C,[12] (+)-febrifugine and (+)-isofebrifugine (vide infra).[13]

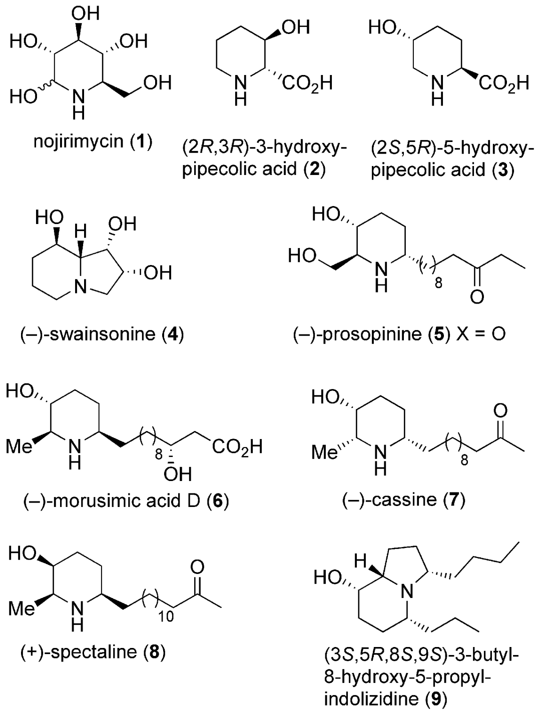


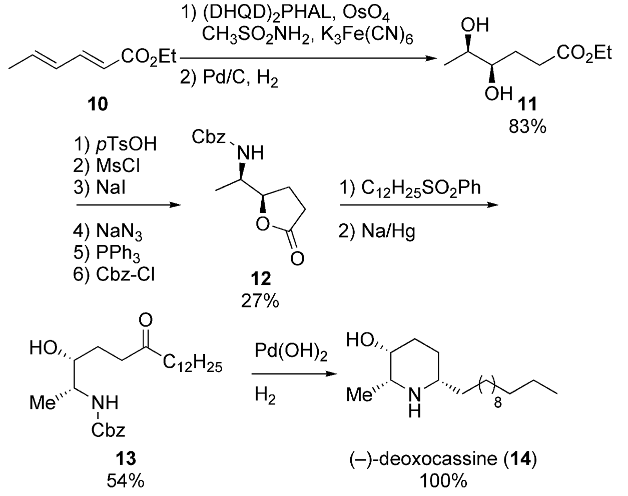
Figure 1. 3-Hydroxypiperidine-containing natural products.

In this review, we aim to provide an overview of enantioselective approaches to natural products containing the latter scaffold (mono-3-hydroxypiperidine, not *O*-substituted),[14] which have been published from the year 2000 onwards. In developing syntheses of the enantiopure 3-hydroxypiperidine motif, two key elements can be distinguished, namely the introduction of chirality, which may occur by resolution or an enantioselective step, and the actual formation of the piperidine ring with the desired substitution pattern. This overview of synthetic approaches is grouped around the different cyclization strategies that can be used to form the piperidine ring system.

2. Piperidine Formation via Intramolecular Nucleophilic Attack

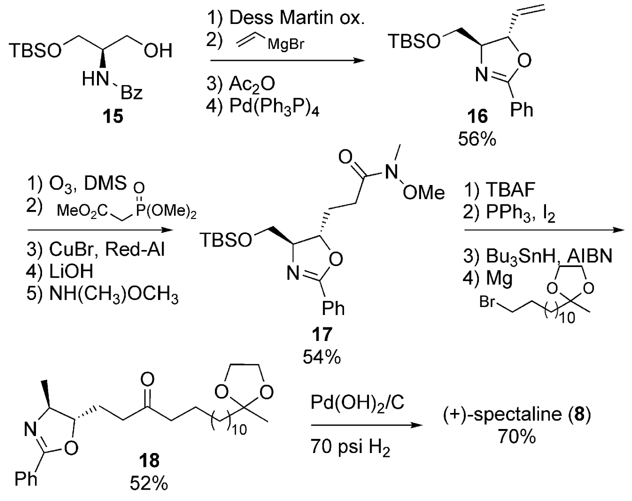
2.1 Cyclization via Reductive Amination

Due to the nucleophilic nature of the nitrogen atom, there are many examples in which the piperidine ring is formed by nucleophilic attack of the nitrogen onto an aldehyde function under reductive conditions. Using this methodology several natural products or derivatives thereof have been synthesized such as (+)-carpamic acid,[15] *cis*- and *trans*-3-hydroxypipecolic acid (*cis*- and *trans*-**2**, respectively),[16] (–)-cassine (**7**),[17] (3*S*,5*R*,8*S*,9*S*)-3-butyl-8-hydroxy-5-propylindolizidine (**9**),[18] and deoxoprosophylline (**59**).[19] A particular example is the synthesis of (–)-deoxocassine (**14**) as published by Kumar and co-workers (Scheme 1).[20] The readily accessible sorbate **10** was selectively dihydroxylated using osmium tetroxide and $(DHQD)_2$-PHAL as a chiral ligand and after hydrogenation of the double bond diol **11** was obtained in good yield and enantioselectivity. Subsequently, diol **11** was converted into lactone **12** in six steps. Coupling of lactone **12** with a sulfone fragment under basic conditions, followed by treatment with sodium amalgam gave the cyclization precursor **13** in 54% yield. Finally, hydrogenolysis of the Cbz group and diastereoselective reductive amination afforded the desired product **14** in quantitative yield.



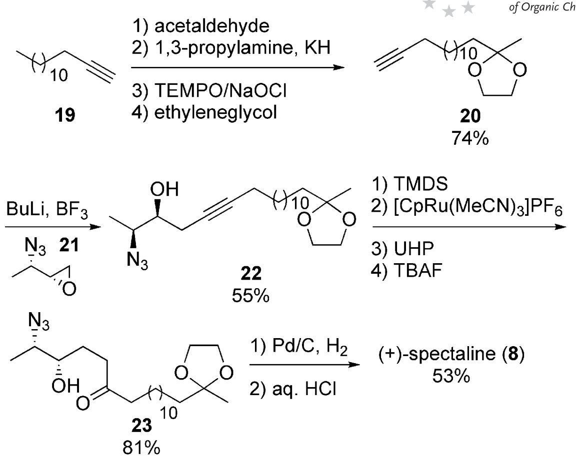
Scheme 1.

A one-pot deprotection/cyclization procedure was applied by Ham and co-workers[21] (Scheme 2) in the synthesis of (+)-spectaline (**8**). The unprotected alcohol of serinol derivative **15** was oxidized, followed by reaction with vinylmagnesium bromide to afford the corresponding allylic alcohol. After formation of the acetate, oxazoline **16** was formed as a single isomer via the corresponding π-allyl Pd complex {[Pd(PPh$_3$)$_4$], K$_2$CO$_3$ in acetonitrile} in good yield. Subsequently, substrate **16** was converted into Weinreb amide **17** in five straightforward steps in an overall yield of 54%. The last steps toward the cyclization precursor **18** were deprotection and deoxygenation of the secondary hydroxyl followed by a Grignard reaction onto the Weinreb amide. The cyclization to afford (+)-spectaline (**9**) involved an elegant one-pot multistep procedure. Thus, unmasking of the oxazoline, followed by intramolecular reductive amination and deprotection of the terminal ketone occurred consecutively by simple treatment with a catalytic amount of Pd(OH)$_2$ in acetic acid/methanol (1:9) under hydrogen atmosphere (70 psi). In this fashion (+)-spectaline (**8**) was obtained in 70% yield. A few years later, this strategy was also applied in a total synthesis of (–)-swainsonine (**4**).[22]



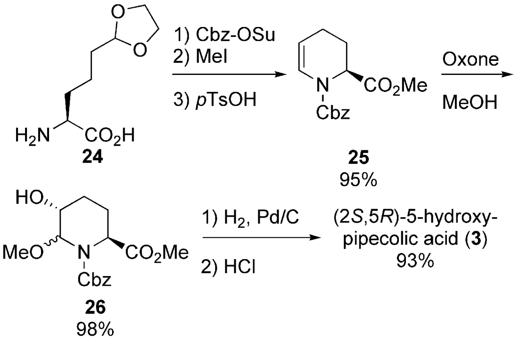
Scheme 2.

The same natural product **8** was synthesized by Trost and co-workers (Scheme 3).[23] In this strategy, the formation of the six-membered ring also proceeded by a reductive amination, this time by in situ azide reduction. Alkyne **19** was functionalized with a masked ketone to afford compound **20** in four steps in 74% yield. Generation of the alkynyllithium salt from the terminal alkyne **20**, followed by addition onto the enantiomerically pure azido epoxide **21**, furnished product **22**. The stage was now set for a regioselective introduction of the ketone at the distal position of the alkyne. Ruthenium-catalyzed hydrosilylation, followed by oxidation of the silane afforded the desired ketone **23**. The stereoselective reductive amination of this ketone was performed under influence of Pd/C and hydrogen pressure. Thus, subsequent reduction of the azide, formation of the imine and stereoselective hydrogenation delivered the desired piperidine skeleton. Treatment of the crude mixture with aqueous HCl to remove the acetal functionality allowed isolation of the (+)-spectaline target (**8**).



Scheme 3.

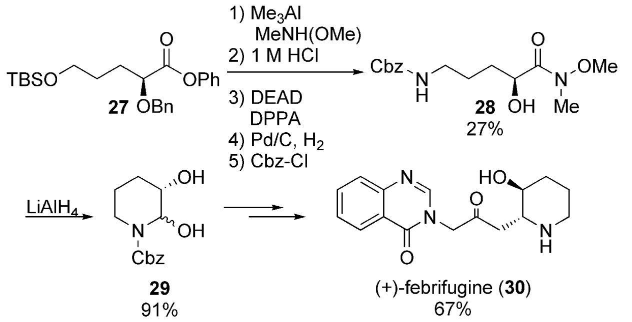
A slightly different reductive strategy was developed by Blaauw and co-workers. The non-natural amino acid allysine ethylene acetal (**24**) was after protection treated with *p*TsOH to afford the cyclic enamide **25** (Scheme 4). Epoxidation of the double bond with concomitant ring opening by methanol afforded *N*,*O*-acetal **26** in a highly diastereoselective manner. Hydrogenation and subsequent acidic hydrolysis led to the synthesis of (2*S*,5*R*)-5-hydroxypipecolic acid (**3**),[24,25] *N*,*O*-acetal **26** served also as a building block for the synthesis of (–)-febrifugine (*ent*-**30**).[26]



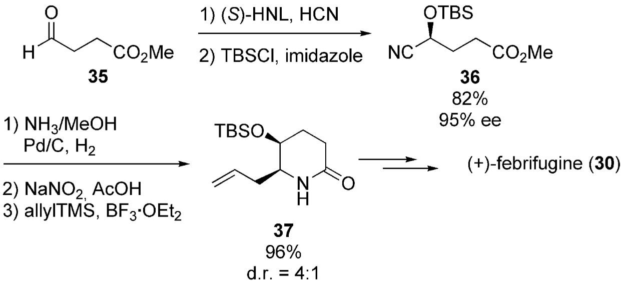
Scheme 4.

Kobayashi and co-workers published a strategy for the synthesis of (+)-febrifugine (**30**), which was also based on unmasking of an aldehyde and subsequent cyclization (Scheme 5). The sequence commenced with the trimethylaluminum-mediated transformation of ester **27**[27] into the corresponding Weinreb amide. In the following four steps, the Cbz-protected nitrogen was installed and the hydroxyl was deprotected to deliver the cyclization precursor **28**. The Weinreb amide was reduced with LiAlH$_4$ to the aldehyde and the piperidine ring **29** was formed in 91% yield.[28] Key intermediate **29** was then converted in a few steps into (+)-febrifugine (**30**).

(+)-Isofebrifugine (**34**) was also synthesized by Kobayashi and co-workers based on a different approach (Scheme 6).[29] The optically pure 3-benzyloxy acetal **31** was prepared from D-arabinose in seven steps. Next, the double bond was hydrogenated and the Cbz-protected amine was inserted by oxycarbenium ion chemistry. The aromatic side chain was then introduced as a whole by *N*-acyliminium ion chemistry with simultaneous opening of the ring. Oxidation of the alcohol to the aldehyde provided the cyclization pre-

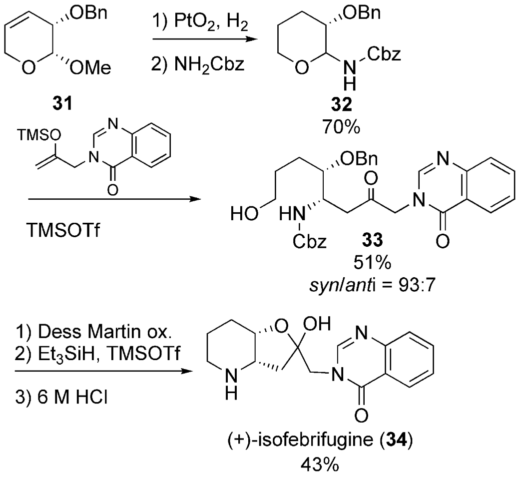


Scheme 5.



Scheme 7.

cursor. Subsequently, the piperidine ring was formed under reductive conditions, after which deprotection furnished (+)-isofebrifugine (**34**).

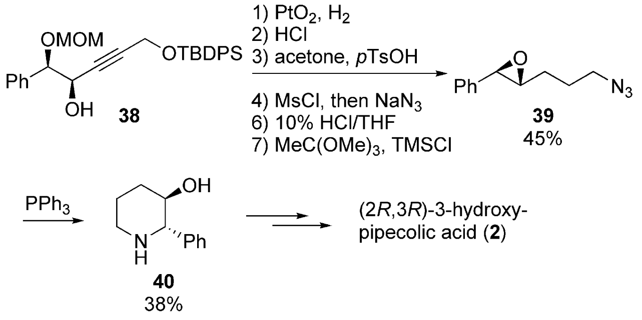


Scheme 6.

In our group, a chemoenzymatic approach[30] was designed for the synthesis of (+)-febrifugine (**30**).[26] The sequence commenced with a chemoenzymatic step, the conversion of aldehyde **35** into the corresponding cyanohydrin under influence of the enzyme (*S*)-hydroxynitrile lyase (HNL, Scheme 7). After subsequent protection of the hydroxyl, cyanohydrin **36** was obtained in 82% yield and 95% *ee*. Next, reductive cyclization under influence of ammonia in methanol afforded the cyclic *N*,*N*-acetal which by diazotization was smoothly converted into the corresponding *N*,*O*-acetal. Treatment with allyltrimethylsilane and a Lewis acid ($BF_3 \cdot OEt_2$) delivered **37** in a 4:1 diastereomeric ratio, of which the *cis*-isomer served as a key intermediate in the total synthesis of (+)-febrifugine (**30**).

2.2 Piperidine Formation by Nucleophilic Displacement

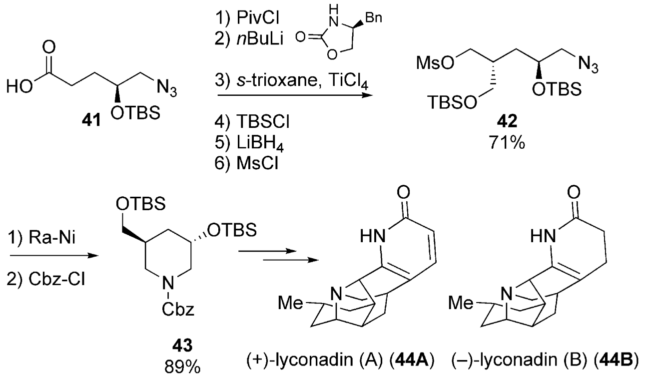
Another commonly used method to synthesize the piperidine motif proceeds via nucleophilic substitution of a good leaving group by the nitrogen atom. In this way, there is no need for reductive conditions and therefore there is a broader compatibility with functional groups. In 2001, Haddad and co-workers presented a strategy to perform the cyclization by opening of an epoxide (Scheme 8) and applied this in the total synthesis of (2*R*,3*R*)-3-hydroxypipecolic acid (**2**).[31] The starting material **38** was prepared from *O*-protected methyl mandelate in two steps by a known protocol.[32]



Scheme 8.

Next, the cyclization precursor **39** was obtained via a six-step sequence including the key step, epoxidation under Sharpless conditions. The cyclization was then performed using PPh_3 in the presence of water, by intramolecular nucleophilic displacement at the benzylic position after Staudinger reduction of the azide function. In this fashion, the desired piperidine ring **40** was isolated in a moderate yield of 38%. In a few steps, intermediate **40** was further converted into the natural product **2**. Several years later, Kumar and co-workers published a total synthesis of both *trans*-3-hydroxypipecolic acids by a similar strategy.[33]

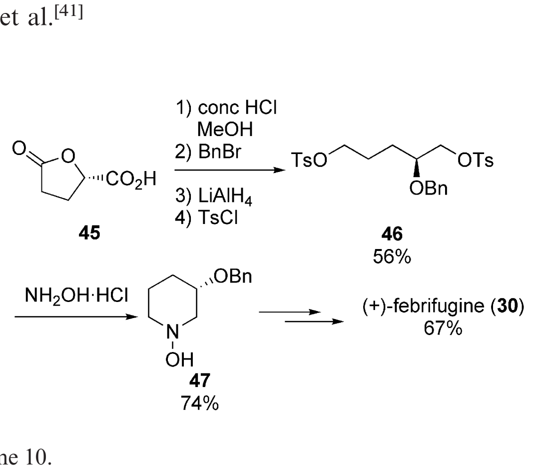
A similar cyclization strategy involves the nucleophilic substitution of an activated hydroxyl function. Smith and co-workers recognized this strategy as an opportunity to develop a synthesis of (+)-lyconadin A (**44A**) and (–)-lyconadin B (**44B**, Scheme 9).[34] The key intermediate **42** was prepared beginning with the conversion of the known acid **41**[35] into the mixed anhydride, followed by reaction with the chiral auxiliary benzyl oxazolidinone to afford the precursor for the aldol reaction. After aldol reaction of the titanium enolate with trioxane and immediate hydroxyl protection, the stage was set to introduce the mesylate. Thus, the chiral auxiliary was removed under reductive conditions and the formed hydroxyl was treated with mesyl chloride to afford cyclization precursor **42**. Subjection to Raney nickel afforded the piperidine ring by azide reduction, followed by in situ displacement of the mesylate. Cbz-protection of the secondary amine afforded **43** in quantitative yield, which was a precursor for the total synthesis of both lyconadins A and B.



Scheme 9.

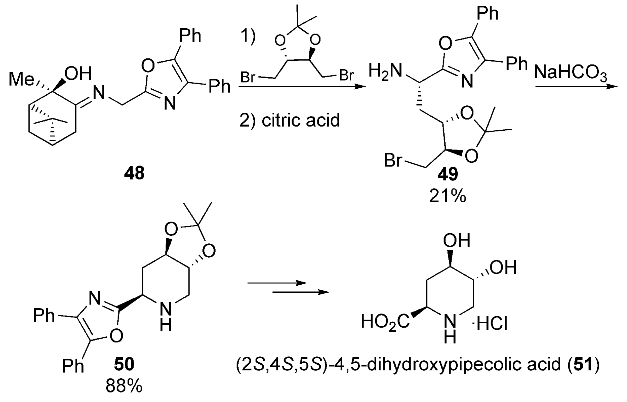
(–)-Prosopinine (**5**) was synthesized by Cossy and co-workers by a similar approach, only a two-step process was applied, in which the azide was reduced first and the cyclization was performed in a subsequent step.[36] A related approach was developed by Sasaki and co-workers for a total synthesis of (+)-deoxoprosopinine (**71**).[37] An example of the cyclization of a tosyl-protected nitrogen was given by Bäckvall and co-workers in the synthesis of (+)-pseudoconhydrine (*ent*-**82**).[38] Recently, the group of Arévalo-García published an example of a cyclization involving a Boc-protected nitrogen onto a mesylate, which was applied in the total synthesis of (+)-deoxoprosopinine (**71**) and (–)-deoxoprosophylline (**59**).[39]

A somewhat unusual approach was pursued by Caprio and co-workers in 2005 and applied in a total synthesis of (+)-febrifugine (**30**, Scheme 10).[40] The sequence started with acid catalyzed ring opening of chiral lactone **45** and subsequent benzyl protection. Reduction with $LiAlH_4$, followed by ditosylation of the resulting diol gave 1,5-ditosylate **46**. Cyclization proceeded in the presence of hydroxylamine hydrochloride to afford *N*-hydroxypiperidine **47** in 74%, which was after a number of steps converted into (+)-febrifugine (**30**). A similar but more stepwise approach to the same natural product was described earlier by Hatakeyama et al.[41]



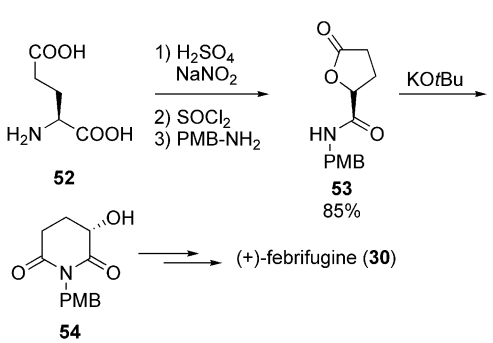
Scheme 10.

A total synthesis of 4,5-dihydroxypipecolic acid (**51**) was developed by Thieme and co-workers based on cyclization by nucleophilic bromide displacement (Scheme 11).[42] The starting azomethine **48** could be readily obtained from 2-aminomethyl-4,5-diphenyl-1,3-oxazole and (1*R*,2*R*,5*R*)-2-hydroxypinanone. Treatment with two equivalents of LDA and the dibromide afforded the alkylation product in low yield and high stereoselectivity (*dr* 95:5). The chiral auxiliary was smoothly split off by hydrolysis in the presence of citric acid to afford cyclization precursor **49**. Treatment with $NaHCO_3$ afforded the piperidine moiety **50** in 88% yield, which could be converted into the enantiopure natural product **51**.



Scheme 11.

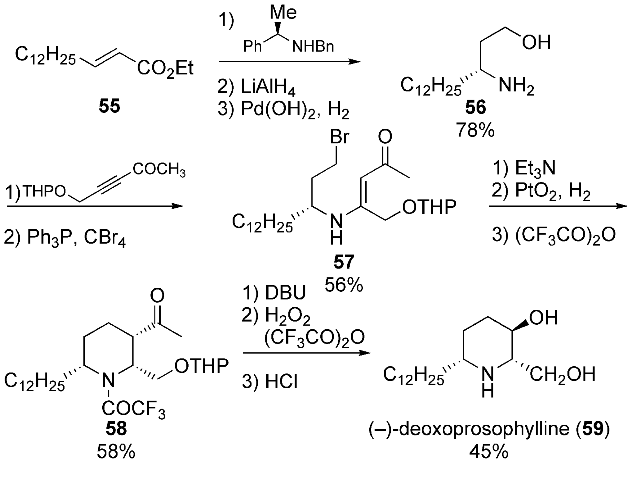
An elegant concerted procedure was developed by Huang and co-workers for the total synthesis of (+)-febrifugine (**30**, Scheme 12).[43] Lactone **53** was prepared from (*S*)-glutamic acid (**52**) by one-pot diazotization/acid chloride formation and amidation in an overall yield of 85%. Treatment of lactone **53** with KO*t*Bu in THF resulted in the expected ring opening-ring formation sequence to afford 2,5-dioxopiperidine **54** in 90% yield. This key intermediate was then converted into the desired alkaloid **30**.



Scheme 12.

Application of this strategy to syntheses of *epi*-pseudoconhydrine (*epi*-**82**), (2*S*,3*S*)-3-hydroxypipecolic acid (*ent*-**2**), (–)-morusimic acid D (**6**) and (–)-awajanomycin were published a few years later.[44] Analogous strategies for the total synthesis of (+)-febrifugine (**30**),[45,46]and (2*S*,3*R*)-3-hydroxypipecolic acid (*epi*-**2**)[47] were developed by other research groups.

A slightly different approach, attack of the enamine instead of the nitrogen, was provided by Ma and co-workers in a total synthesis of (–)-deoxocassine (**14**), (+)-azimic acid and (–)-deoxoprosophylline (**59**).[48] The strategies for building up these three molecules were similar and are exemplified by the synthesis of the latter alkaloid **59** in Scheme 13. First, fragment **55** was coupled to the chiral amine by asymmetric conjugate addition, followed by $LiAlH_4$ reduction and hydrogenolysis to provide the desired γ-amino alcohol **56** in a yield of 78% over three steps. The conjugate addition of **56** to the alkynone proceeded well in DMF at room temperature and subsequent treatment with PPh_3 and CBr_4 produced bromide **57** as precursor for the nucleophilic displacement. Indeed, refluxing in acetonitrile afforded the corresponding cyclic enamine in moderate yield. Hydrogenation afforded selectively the *cis*-product, and subsequent protection of the N atom with trifluoroacetic anhydride gave piperidine **58**.

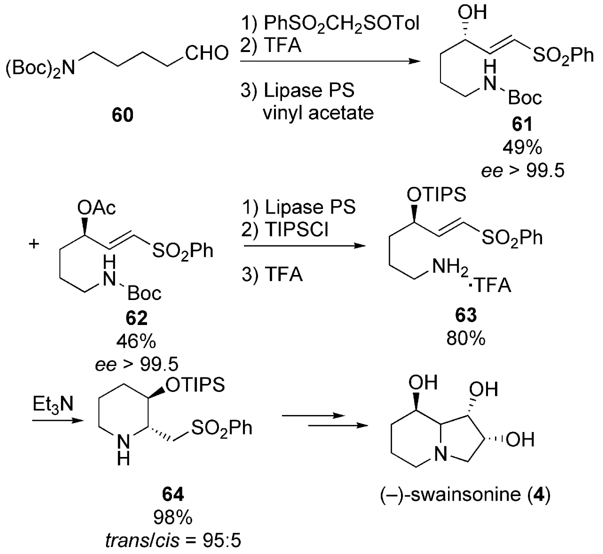


Scheme 13.

Epimerization of the 3-acetyl group under the action of DBU produced a 1:10 mixture of starting material vs. product, which could be separated by column chromatography. Next, the acetyl group was successfully converted into the corresponding acetate by Baeyer–Villiger oxidation with in situ generated trifluoroperacetic acid. This oxidation product was fully hydrolyzed with 6 M HCl to afford alkaloid **59**. This methodology was also applied in a total synthesis of (–)-julifloridine (**75**) by Back and co-workers.[49]

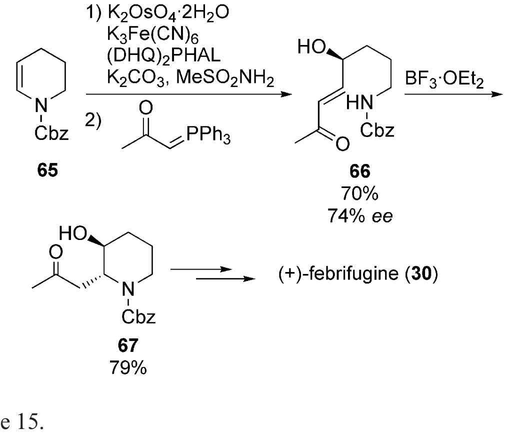
2.3 Conjugate Addition to Obtain the Piperidine Skeleton

A somewhat less applied synthetic path to the desired piperidine skeleton involves conjugate addition, which was applied by De Carretero et al. in a synthesis of (–)-swainsonine (**4**, Scheme 14).[50] The α,β-unsaturated sulfone **61** was prepared by reaction of *p*-tolylsulfinyl phenylsulfonyl methane with the di-Boc protected derivative **60** of 5-aminopentanal, followed by mono-deprotection of the amine in a yield of 86%. Substrate **61** was resolved by lipase-catalyzed conversion of one enantiomer into acetate **62** in almost 50% yield. The acetate was converted back into the hydroxy function by treatment with lipase, followed by OH-protection with TIPSCl. TFA-Mediated Boc-deprotection afforded the free amine **63** in 80% over three steps. Under influence of triethylamine, the cyclized product **64** was formed by conjugate addition in almost quantitative yield and high diastereoselectivity. The sequence was completed in five more steps to afford (–)-swainsonine (**4**).



Scheme 14.

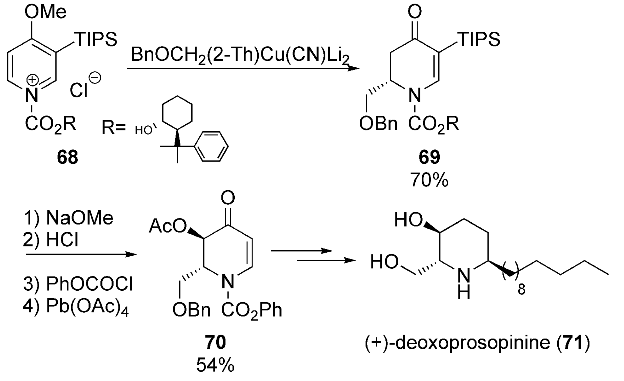
Another example of this strategy was provided by Takeuchi and co-workers and applied in a total synthesis of (+)-febrifugine (**30**, Scheme 15).[51] The chirality was introduced by asymmetric dihydroxylation of tetrahydropiperidine **65**. Despite extensive optimization the enantioselectivity remained moderate, but could be improved by crystallization in a later stage. A Wittig reaction onto this *N*,*O*-acetal afforded the ring opened product **66** in 70% yield over two steps. Subjection to $BF_3{\cdot}OEt_2$ resulted in a *trans*-selective conjugate addition to deliver piperidine ring **67** as a single isomer. This structure functioned as a building block in the total synthesis of (+)-febrifugine (**30**).



Scheme 15.

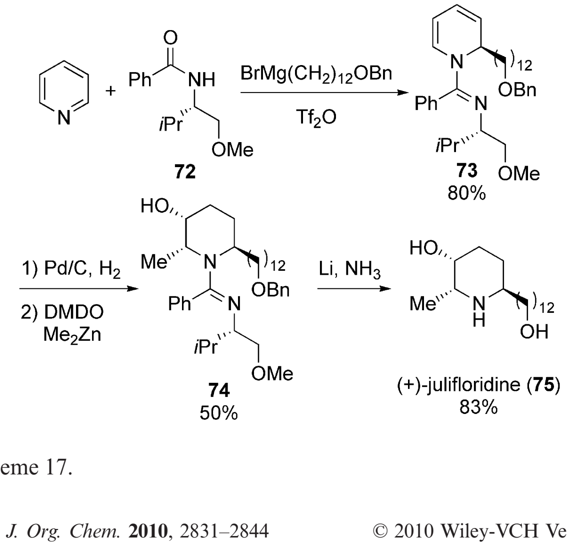
3. Reduction of Pyridine Derivatives to Piperidine Rings

A more rarely used, but direct access to the piperidine system is provided by diastereoselective addition of nucleophiles onto chiral pyridinium salts. The group of Comins is one of the pioneers in this field and synthesized a range of natural products by using this strategy. Recently, a total synthesis of (+)-deoxoprosopinine (**71**) was published as depicted in Scheme 16.[52] The pyridine salt **68**[53] was treated with a higher order cyanocuprate to afford dihydropyridone **69** in 70% yield in a fully diastereoselective manner. Reaction with sodium methoxide, followed by addition of aqueous acid resulted in removal of the TIPS group and the auxiliary group on the nitrogen. Subsequently, the nitrogen was reprotected by reaction with phenyl chloroformate. Treatment with lead(IV) acetate afforded **70** in 57% yield with a *de* value higher than 98%. This intermediate was successfully converted into product **71**.



Scheme 16.

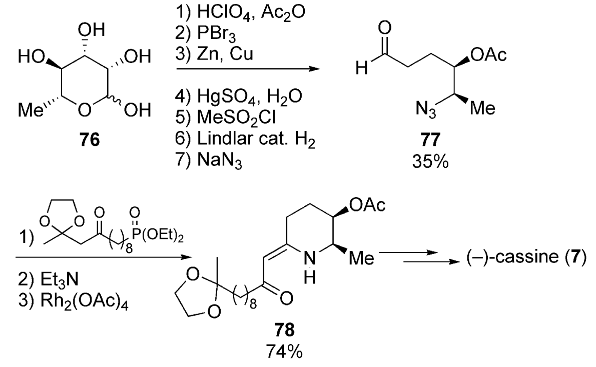
Charette and co-workers showed a different approach for the synthesis of (+)-julifloridine (**75**), in which the chirality was induced through the formation of a chiral salt by the condensation of pyridine with an enantiopure amide (Scheme 17).[54] After this condensation a Grignard reagent was added in the same pot to form product **73** in a regio- and diastereoselective fashion. After monohydrogenation, the resulting enamine was subjected to an epoxidation-methylation procedure to afford the protected natural product **74** in excellent yield. Removal of the benzyl protecting group and the chiral auxiliary was achieved upon treatment with lithium in ammonia to obtain (+)-julifloridine (**75**).



Scheme 17.

4. Cycloaddition Reactions in the Synthesis of the Piperidine Motif

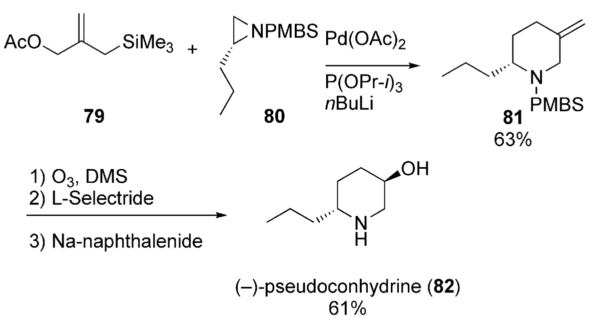
Cycloaddition reactions are amongst the most effective methods for the rapid synthesis of functionalized cyclic systems in a stereocontrolled manner. This strategy is diverse, the piperidine ring can be obtained by for example a 1,3-dipolar cycloaddition or a hetero Diels–Alder reaction. Herdeis and co-workers developed a method for the synthesis of (–)-cassine (**7**) by using a 1,3-dipolar cycloaddition of an azide with an α,β-unsaturated ester (Scheme 18).[55]



Scheme 18.

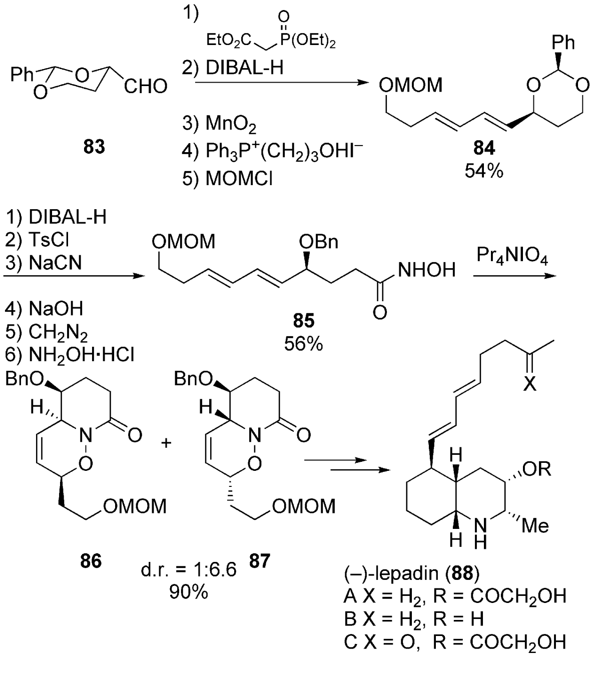
To this end, (+)-rhamnose (**76**), a cheap starting material, was transformed to diacetylrhamnal in a three-step one-pot process. Subsequently, a four-step sequence including a modified Perlin oxidation and a chemoselective reduction of the double bond provided the aldehyde **77**. The next sequence [Horner–Wadsworth–Emmons (HWE) reaction, 1,3-dipolar cycloaddition, isomerization/triazoline opening] took some optimization, but the best option turned out to be an one-pot sequence. After the HWE reaction and 1,3-dipolar cycloaddition, triethylamine was added and the isomerization/triazoline opening took place. Upon addition of a small amount of rhodium acetate, nitrogen was extruded and the product **78** was isolated in 74% yield. This key intermediate was converted into (–)-cassine (**7**) in a number of steps.

Harrity et al. investigated a [3+3] cycloaddition as a basis for the total synthesis of (–)-pseudoconhydrine (**82**).[56] It was anticipated that the reaction of Pd-trimethylenemethane (Pd-TMM) complexes with aziridines would provide a potentially efficient technique for the synthesis of nitrogen heterocycles. Thus, the enantiomerically pure aziridine **80** was prepared in three steps from the appropriate amino acid by the method of Craig (Scheme 19).[57] The commercially available reagent 2-[(trimethylsilyl)methyl]-2-propen-1-yl (**79**) was chosen as a convenient source for the in situ generation of the Pd-TMM complex. Indeed, the Pd-TMM complex was formed upon addition of $Pd(OAc)_2$ to give a regioselective addition onto the aziridine at the less hindered site and furnish product **81** in enantiopure form. This intermediate was readily converted into the natural product in a three step process. Ozonolysis, followed by L-selectride reduction provided the 3-hydroxypiperidine moiety as a single diastereoisomer. Finally, removal of the PMBS group afforded (–)-pseudoconhydrine (**82**) in 61% yield over the last three steps.



Scheme 19.

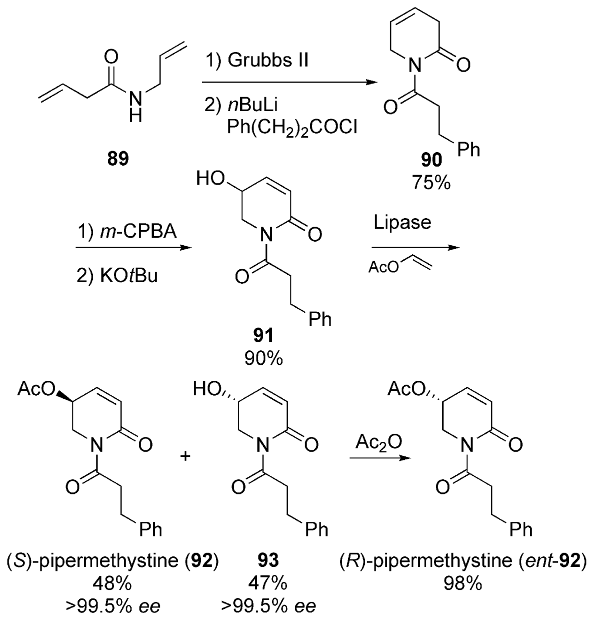
An elegant method involving an intramolecular acylnitroso Diels–Alder reaction was discovered by Kibayashi and co-workers (Scheme 20).[58] The sequence started with a HWE reaction of aldehyde **83**[59] to give the corresponding α,β-unsaturated ester in an *E*/*Z* ratio of 20:1. The major isomer was transformed into the aldehyde by a reduction and oxidation sequence and subsequent Wittig olefination yielded the desired (3*E*,5*E*)-isomer in 69% yield along with a small amount (9%) of the (3*Z*,5*E*) isomer. The free alcohol was protected as a MOM-ether so that product **84** was obtained in almost quantitative yield. Reductive ring opening of the benzylidene acetal with DIBAL-H was followed by conversion of the primary hydroxyl into the hydroxamic acid **85** in five steps. Upon periodate-mediated oxidation, the in situ generated acylnitroso compound underwent intramolecular [4+2] cycloaddition to yield the *trans*-oxazinolactam **87** as the major isomer in a moderate diastereoselectivity of 6.6:1. This lactam served as a key intermediate in a synthesis of (–)-lepadins A, B and C. Two years later, the same procedure was applied in a total synthesis of (+)-azimine and (+)-carpaine.[60]



Scheme 20.

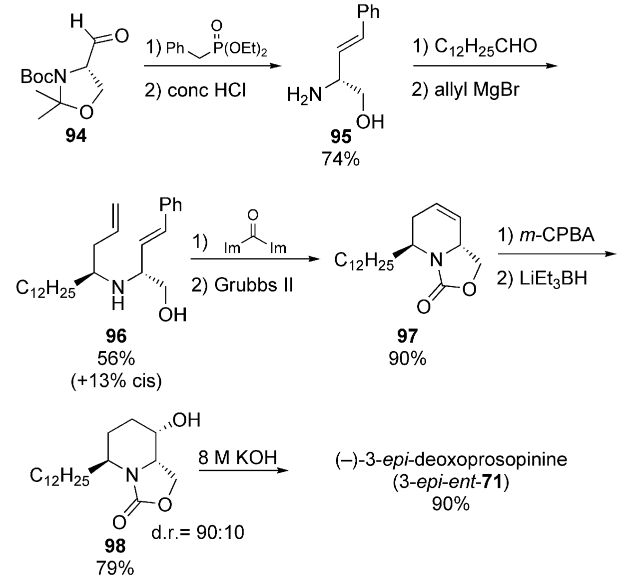
5. RCM-Mediated Piperidine Formation

An efficient approach is formation of the piperidine ring by a ring-closing metathesis (RCM) strategy. In this way, a tetrahydropyridine is obtained with the double bond in a specified position, providing obvious opportunities to functionalize the ring. A straightforward method was developed by Liebeskind and co-workers (Scheme 21).[61] RCM precursor **89** was obtained by coupling of 3-butenoic acid with allylamine. Subjection to the second-generation Grubbs catalyst ("Grubbs II") afforded the corresponding piperidone ring in 80% yield. Subsequent protection of the lactam nitrogen with hydrocinnamoyl chloride provided imide **90**. Next, the allylic alcohol **91** was prepared by epoxidation with *m*-CPBA followed by treatment of the resulting epoxide with a catalytic amount of KO*t*Bu. Four commercially available lipases were then screened for activity and stereoselectivity in order to resolve the enantiomers. PPL lipase turned out to be the best, providing the products in high yield and excellent enantioselectivity. By use of this procedure, naturally occurring (*S*)-pipermethylsystine (**92**) was obtained, while acylation of the other enantiomer afforded (*R*)-pipermethylsystine (*ent*-**92**). The synthesis of all stereoisomers of 3-hydroxypipecolic acid (**2**) was also reported by Takahata and co-workers by a similar strategy.[62]



Scheme 21.

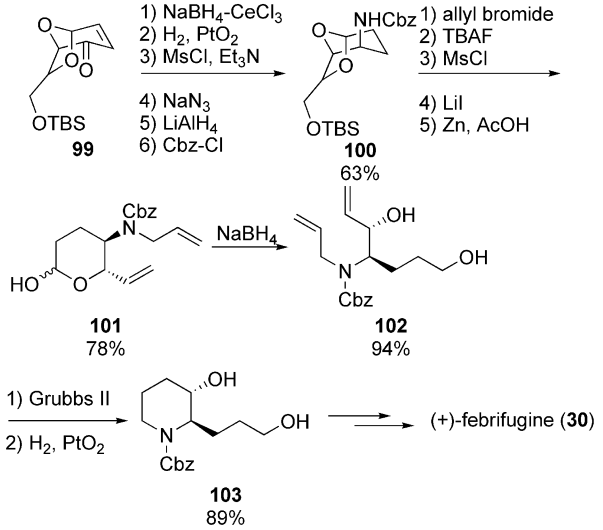
Lebreton and co-workers developed a strategy based on two key steps, involving diastereoselective allylation of a chiral imine and a RCM step (Scheme 22).[63] The efficacy of this methodology was demonstrated with a total synthesis of (–)-3-*epi*-deoxoprosopinine (3-*epi*-*ent*-**71**). The first aim concerned the synthesis of chiral amino alcohol **95** starting from Garner's aldehyde **94**. HWE olefination afforded the corresponding *E*-product as the sole isomer, after which acidic removal of the protecting groups gave the desired amino alcohol **95**.



Scheme 22.

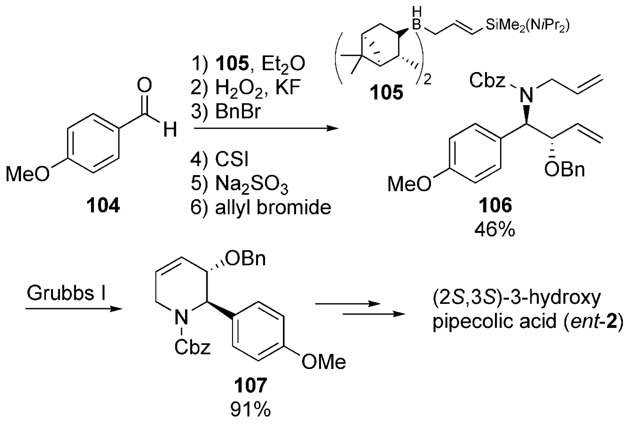
Next, imine formation using dodecanal, followed by in situ alkylation with allylmagnesium bromide in a diastereoselective fashion (*trans*/*cis* = 87:13) provided compound **96**. Both the nitrogen and the hydroxyl were protected by the corresponding oxazolidinone, and by RCM under Grubbs II conditions the bicyclic structure **97** was obtained. Epoxidation of the olefin gave a separable mixture of *endo*- and *exo*-epoxides in a 9:1 ratio. By opening of the epoxide of the major isomer with $LiEt_3BH$ the hydroxyl group in the C-3 position was installed. The final step comprised the deprotection of amine and hydroxyl functions by hydrolysis of the oxazolidinone, which was achieved under harsh basic conditions to provide the desired product 3-*epi*-*ent*-**71** in 90% yield.

The Ogasawara group also envisaged to construct a piperidine ring by RCM and applied this strategy in the synthesis of (+)-febrifugine (**30**, Scheme 23).[64] Chiral building block **99**, prepared from furfural,[65] was diastereoselectively converted into the *endo*-allylic alcohol by convex-face selective 1,2-reduction, followed by hydrogenation to the saturated alcohol. Next, the resulting hydroxyl was converted into the Cbz-protected nitrogen compound **100** in a four-step sequence. *N*-Allylation of the carbamate delivered the first olefin necessary for the RCM reaction. The second one was introduced via a four-step sequence involving (i) TBS group removal, (ii) mesylation, (iii) iodination, and (iv) elimination. The resulting hemiacetal **101** was then further reduced with $NaBH_4$ to afford diolefin **102**. RCM in the presence of Grubbs II catalyst furnished the unsaturated piperidine in 89% yield, and subsequent hydrogenation gave piperidinediol **103**, which was a key intermediate in the synthesis of (+)-febrifugine (**30**).



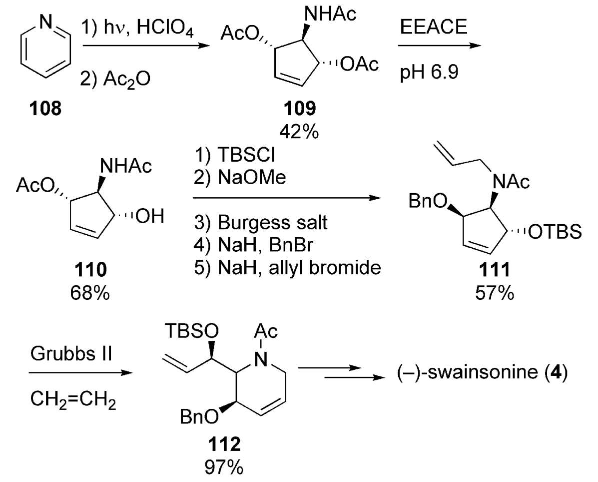
Scheme 23.

The aim for Jung and co-workers was to synthesize (2*S*,3*S*)-3-hydroxypipecolic acid (*ent*-**2**) by RCM (Scheme 24).[66] First, *p*-anisaldehyde (**104**) was subjected to Brown's asymmetric aldol reaction to afford the desired protected diol enantioselectively.[67] In the next step, the Cbz-protected nitrogen was introduced in a regio- and diastereoselective fashion (*dr* 49:1) by amination with chlorosulfonyl isocyanate (CSI). Allylation with allyl bromide afforded compound **106** quantitatively, which was then readily cyclized under Grubbs I conditions to give the unsaturated piperidine **107** in 91% yield. This building block was converted into the desired natural product (*ent*-**2**) in a few steps.



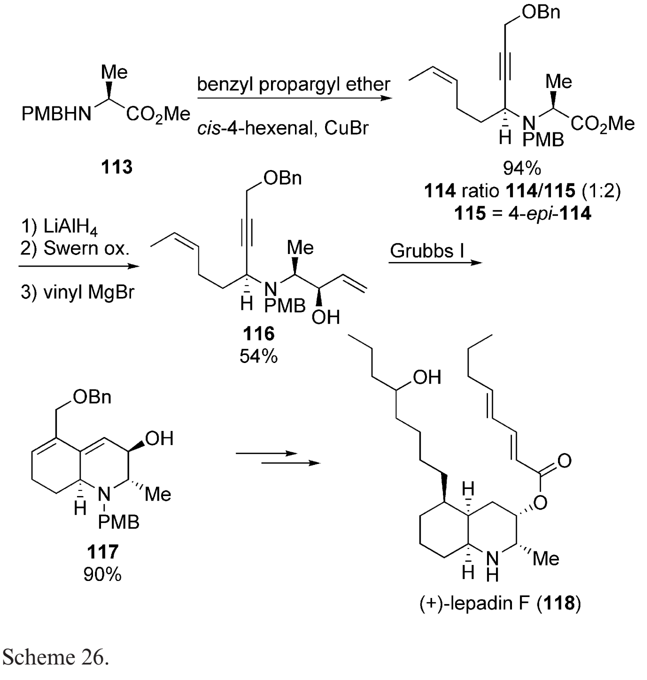
Scheme 24.

In the Mariano group a well-designed strategy was developed based on ruthenium-catalyzed ring rearrangement metathesis of a cyclopentene derivative (Scheme 25). In situ generated pyridinium perchlorate was–upon irradiation–transformed into *trans,trans*-3,5-dihydroxy-4-aminocyclopentene, which was isolated as its triacetyl derivative **109**.[68] This *meso*-compound was enzymatically desymmetrized with EEACE (electric eel acetyl cholinesterase) producing the monoalcohol **110**. Subsequent functional group modifications afforded the cyclization precursor **111** in 57% yield over five steps. Tandem ring-closing/ring-opening metathesis of the *N*-allylacetamidocyclopentene was conducted by using an ethylene-saturated solution containing Grubbs II catalyst to yield the desired skeleton **112** in 97% yield. This key intermediate **112** was then converted into (–)-swainsonine (**4**).



Scheme 25.

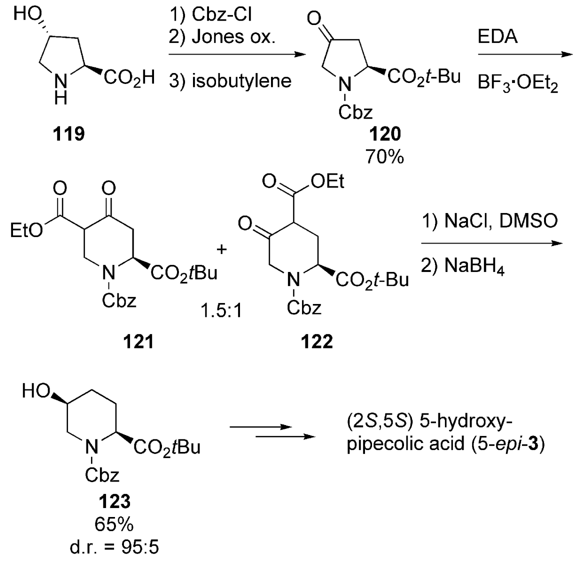
An efficient strategy for the synthesis of (+)-lepadin F (**118**) was designed by Blechert and co-workers using tandem ene-yne-ene RCM (Scheme 26).[69] As starting material was chosen for L-alanine which was esterified with methanol and PMB-protected at the N atom. Condensation with *cis*-4-hexenal, followed by copper-catalyzed addition of benzyl propargyl ether led to a mixture of propargylamines **114** and **115** (*dr* 1:2), which could be separated after reduction with $LiAlH_4$. The minor isomer was converted into the desired allylic alcohol **116** by Swern oxidation and a Grignard reaction with vinylmagnesium bromide. Grubbs I turned out to be the best catalyst to carry out the tandem ene-yne-ene RCM reaction providing product **117** in 90% yield. The latter product was converted by some side chain modifications into the natural product **118**.



Scheme 26.

6. Ring-Expansion to the Piperidine Skeleton

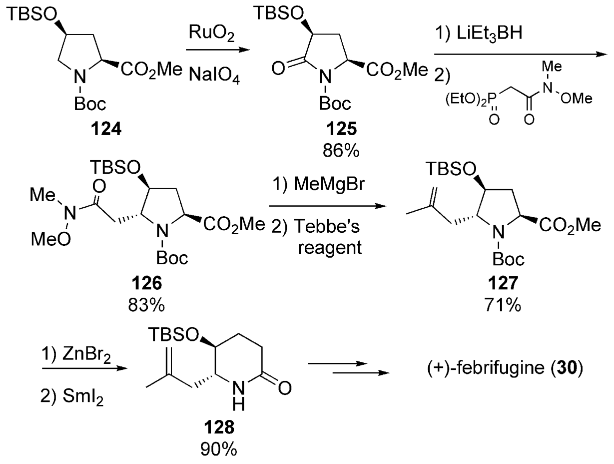
Regioselective ring-expansion of pyrrolidine derivatives provides an alternative way to access the piperidine ring system. An advantage of this strategy is that several enantiomerically pure proline derivatives are commercially available. Avery and co-workers used this approach for the synthesis of (2*S*,5*S*)-5-hydroxypipecolic acid (5-*epi*-**3**), based on the ring expansion of *trans*-4-hydroxy-L-proline (**119**, Scheme 27).[70]



Scheme 27.

After protection of the amine and acid functions, the hydroxyl was oxidized in a Jones oxidation and protected in 70% overall yield. Keto ester **120** was then treated with $BF_3{\cdot}OEt_2$ and ethyl diazoacetate (EDA) to yield the two regioisomeric ring-expansion products **121** and **122**. The latter one was decarboxylated, followed by diastereoselective ketone reduction to alcohol **123**, from which in a number of steps the natural product (5-*epi*-**3**) was obtained. In addition, the other regioisomer **122** could be efficiently converted into the related 4-hydroxypipecolic acid.

Starting from the same building block, Honda and coworkers developed a total synthesis of (+)-febrifugine (**30**, Scheme 28).[71] Proline derivative **124** was protected according to a literature procedure to afford compound **125**.[72] Oxidation of the pyrrolidine ring was performed with ruthenium(IV) oxide to give the desired lactam **125** in 86% yield. Partial lactam reduction with $LiEt_3BH$, followed by HWE reaction of the resulting *N*,*O*-acetal in the presence of NaH and subsequent conjugate addition gave Weinreb amide **126** stereoselectively as a single product. Grignard addition of methylmagnesium bromide onto the Weinreb amide afforded the methyl ketone, which was transformed into olefin **127** on methylenation with Tebbe's reagent. The Boc group was removed by using zinc bromide providing the corresponding amine, which was then subjected to samarium diiodide-promoted reductive deamination. The methanol in the reaction mixture functioned as the proton source to furnish lactam **128** in 90% yield, which could be converted into (+)-febrifugine (**30**).

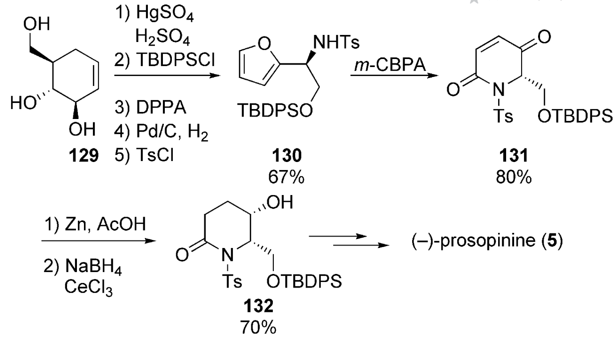


Scheme 28.

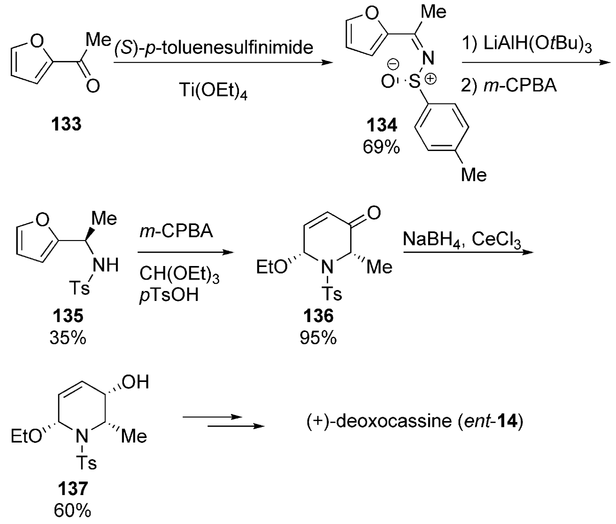
7. Furan Derivatives as Precursor for the Piperidine Moiety

The aza-Achmatowicz oxidative rearrangement affords facile access to substituted piperidines starting from furan derivatives. Two examples of this strategy were recently published by different research groups. Haroutounian and co-workers applied this methodology in a formal synthesis of (–)-prosopinine (**5**, Scheme 29).[73] The sequence commenced with the formation of a furan derivative through reaction of D-glucal (**129**) with $HgSO_4$, followed by protection of the resulting primary hydroxyl with TBDPSCl.[74] From there, the desired *N*-furfurylsulfonamide (*S*)-**130** could be readily obtained in 73% yield over three steps. The aza-Achmatowicz rearrangement was performed by exposure of **130** to an excess of *m*-CPBA and furnished the piperidine ring **131**. Modified Luche reduction of the ketolactam afforded the corresponding allylic alcohol in a fully diastereselective manner. Subsequent hydrogenation of the double bond afforded piperidine **132**, which served as a key intermediate in the total synthesis of (–)-prosopinine (**5**).

Padwa and co-workers developed a method for the total synthesis of (+)-deoxocassine (*ent*-**14**) starting from 2-acetylfuran (Scheme 30).[75] To construct an enantiopure tosylaminofuran, they made use of the elegant sulfinimine chemistry that was developed previously.[76]



Scheme 29.

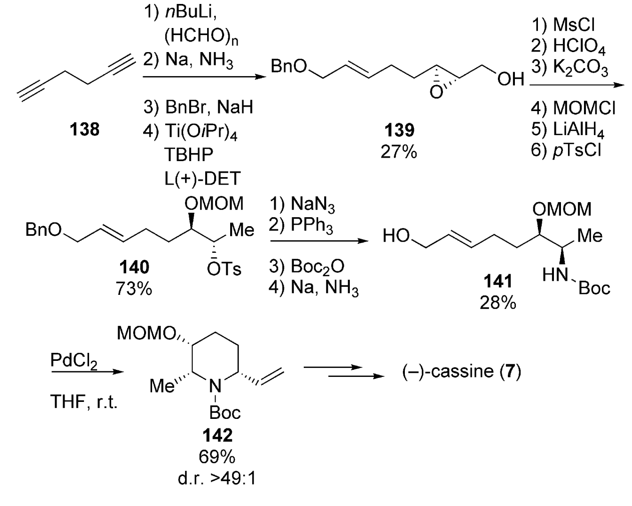


Scheme 30.

Condensation of (*S*)-(+)-*p*-toluenesulfinimine with furan derivative **133** in the presence of $Ti(OEt)_4$ afforded the chiral sulfinimine **134**. Stereoselective reduction of the sulfinimine was carried out at low temperature with LiAlH(O*t*Bu)$_3$ and was followed by immediate oxidation with *m*-CPBA to give the desired *N*-tosylaminofuran **135**. This sulfonamide was subjected to the aza-Achmatowicz oxidation ring-expansion with *m*-CPBA. The initially formed hemiaminal was immediately treated with trimethyl orthoformate and catalytic $BF_3{\cdot}OEt_2$ which furnished *N*,*O*-acetal **136** in 95% yield. The ketone was stereospecifically reduced under Luche conditions with $NaBH_4$ and $CeCl_3$ to afford the 3-hydroxypiperidine moiety **137**, which was a crucial scaffold in the total synthesis of (+)-deoxocassine (*ent*-**14**).

8. Palladium Catalyzed Formation of the Piperidine Skeleton

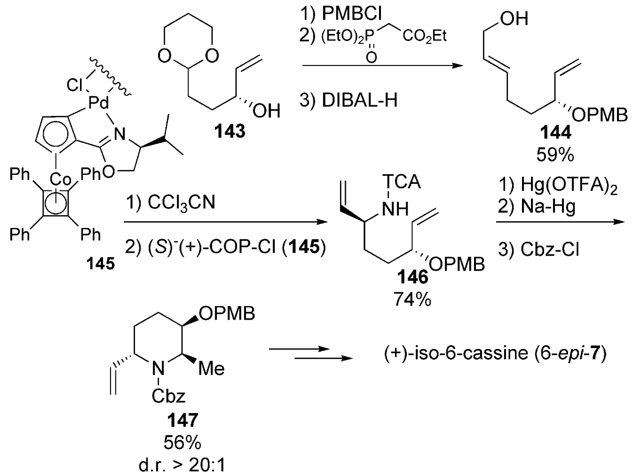
An interesting approach was chosen by Makabe and coworkers, who described a total synthesis of (–)-cassine (**7**) based on a Pd^{II}-catalyzed cyclization.[77] The precursor for this reaction was obtained by a lengthy procedure starting from 1,5-hexadiyne (**138**, Scheme 31). Initially, a dienediol was prepared using Rosenblum's procedure in 51 % yield.[78] Next, monobenzylation with benzyl bromide, followed by Sharpless asymmetric epoxidation gave epoxide **139** in an *ee* of 98 %. Then, a four step sequence was applied to switch the epoxide to the terminal position and protect the secondary hydroxy function. Regioselective epoxide opening with $LiAlH_4$ and subsequent tosylation of the resulting secondary hydroxyl gave tosylate **140** in 96 % yield. The Boc-protected amine was introduced by a three-step sequence including azide substitution of the tosylate, Staudinger reduction of the azide and Boc protection. Deprotection of the primary hydroxyl with sodium in liquid ammonia afforded precursor **141**, which upon treatment with 5 mol-% $PdCl_2$ in THF at room temperature afforded cyclization product **142** (*dr* > 49:1) in 69 % yield. The major isomer was used in a total synthesis of (–)-cassine (**7**).



Scheme 31.

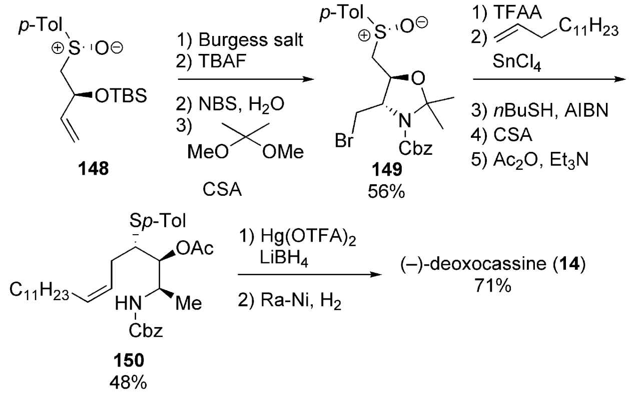
9. Cyclization via Amidomercuration

An unique method was recently reported by Han and coworkers, who published a synthesis of (+)-iso-6-cassine (6-*epi*-**9**) based on a stereoselective intramolecular amidomercuration (Scheme 32).[79] The enantiopure starting material was formed via lipase-catalyzed kinetic resolution of the corresponding racemic allyl alcohol **143** in 12 % yield and 99 % *ee* after two catalytic cycles.[80] Subsequently, the allylic alcohol **144** was formed in 90 % yield over three steps including a HWE olefination. The alcohol was then converted into a trichloroacetimidate to give an enantioselective Overman rearrangement induced by a chiral cobalt oxazoline palladacycle resulting in the *N*-trichoroacetyl derivative **146**. Subjecting this intermediate to $Hg(OTFA)_2$ in the presence of K_2CO_3 gave the desired product in a high diastereoselectivity of 20:1, including removal of the trichloroacetyl group under these conditions. Reductive cleavage of the mercury under reductive conditions, followed by Cbz protection of the resulting amine afforded piperidine **147**, which served as an intermediate in a total synthesis of (+)-iso-6-cassine (6-*epi*-**7**).



Scheme 32.

Recently a synthesis of (–)-deoxocassine (**14**) was published by Raghavan and co-workers by invoking a similar cyclization strategy (Scheme 33).[81] Their synthesis commenced with the reaction between silyl ether **148**[82] and Burgess' salt to form the corresponding sulfoxide, followed by TBS deprotection under influence of TBAF. Reaction with NBS and subsequent protection with 2,2-dimethoxypropane yielded acetonide **149**. Subjection to a one-pot Pummerer rearrangement, followed by an ene-reaction furnished the homo-allylic sulfide. The last steps to the cyclization precursor involved debromination, removal of the acetonide and acetylation of the alcohol to give compound **150**. The piperidine ring was then formed in two steps by cyclization under influence of $Hg(OTFA)_2$ followed by the reductive mercury removal. In this way, the *cis*-piperidine ring was obtained after which removal of the sulfide and Cbz group gave (–)-deoxocassine (**14**) in 71 % over the last three steps.



Scheme 33.

10. Conclusions

Over the years, 3-hydroxypiperidine-containing natural products have attracted considerable attention of organic and medicinal chemists. This attention has resulted in various new approaches to synthesize the 3-hydroxypiperidine motif in enantiopure form, of which the most recent examples have been reviewed in this contribution focusing on applications in total synthesis.

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