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Syntheses of the sedum and related alkaloids

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Contents

1. Introduction

The syntheses of the sedum alkaloids can be divided into two groups. The larger group append the side chain onto a preformed nitrogen heterocycle. This group can be further divided into those that use a pyridine and those that use a piperidine. In the case of piperidine starting materials, this is most often done by nucleophilic attack onto a piperidinyl electrophile, such as an *N*-acyliminium ion, or by 1,3-dipolar cycloaddition of a cyclic nitrone with an alkene. The other more diverse group of syntheses includes those that employ a variety of techniques to construct the piperidine ring.

The sedum alkaloids featured in this review are sedamine (**1**), sedridine (**2**), andrachamine (**3**), halosaline (**4**), sedinone (**5**), sedinine (**6**), sedacrine (**7**) and sedacryptine (**8**) (Fig. 1). The structure shown for andrachamine is the revised structure (compare Schemes 23 and 37). A number of ring hydroxylated sedamines are also included, as well as its diastereomer, allosedamine (**9**). Related alkaloids are hygroline (**10**), and its diastereomer, pseudohygroline (**11**), which are pyrrolidines. The family of eight tetraponerine alkaloids (**T1-8**) possess a second amino group in place of the alcohol and have been isolated in both piperidine and pyrrolidine forms (Table 1). Pinidinol (**12**) and dumetorine (**13**) are also featured.

All of these compounds possess either a 1,3-aminoalcohol or a 1,3-diamine with a nitrogen in a heterocyclic ring. While they may not be biochemically related, they are synthetically very close and, in a great many cases the same synthetic strategies have been applied. Related alkaloids that lack one of the stereo centres (e.g. the ketone analogues) are excluded from this review.

This review is organised around the synthetic methodology used, rather than the natural product molecule prepared. Table 2 lists the syntheses discussed in this review according to the target.

Interest in the synthesis of these alkaloids has been ongoing for nearly half a century and they have become a testing ground for methodology, especially in terms of the control of the relative and, latterly, absolute stereochemistry of the 1,3-aminoalcohol system that they all possess. Their biological activity has been less of a reason for these investigations, with the exception of the tetraponerines which are potent insecticides. This is likely to change because, recently, the use of substituted pyridines and piperidines as anti-Alzheimer's agents has been the subject of a patent.[1]

2. Pyridine strategies

The pyridine strategy was employed in the first three syntheses of sedamine in the 1950s. Marion employed the (unregioselective) hydration of pyridyl phenyl acetylene.

Keywords: sedum; alkaloids; pyridine pyrrolidine; piperidine.

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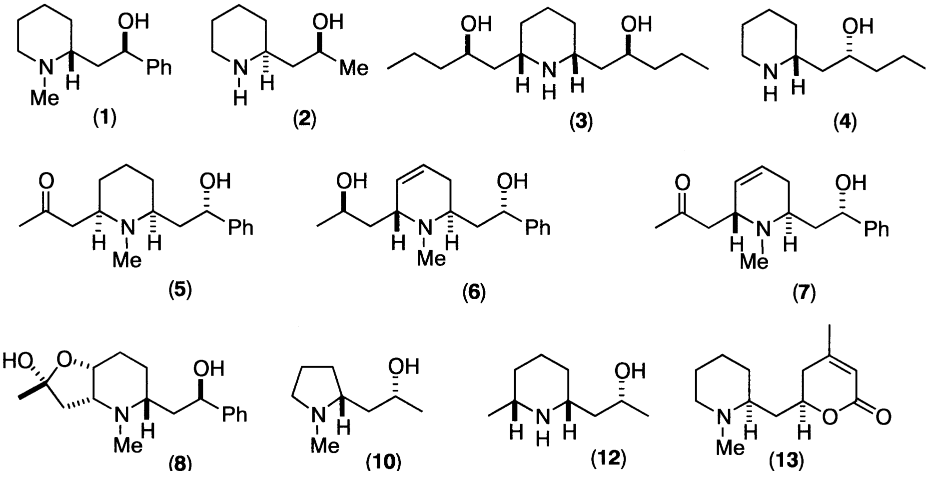
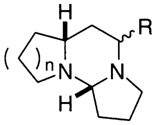


Figure 1. Sedum and related alkaloids.

Table 1. The tetraponerine alkaloids

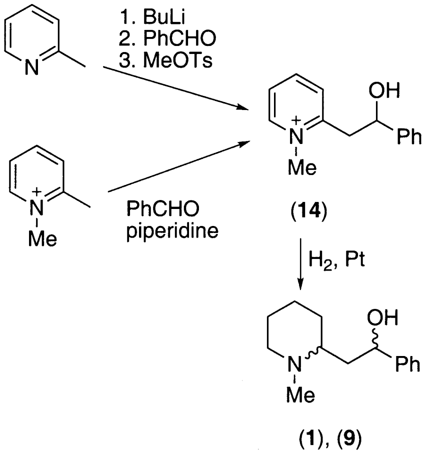


Tetraponerine no.	*n*	R	Orientation of R
T1	1	*n*-propyl	β
T2	1	*n*-propyl	α
T3	2	*n*-propyl	β
T4	2	*n*-propyl	α
T5	1	*n*-pentyl	β
T6	1	*n*-pentyl	α
T7	2	*n*-pentyl	β
T8	2	*n*-pentyl	α

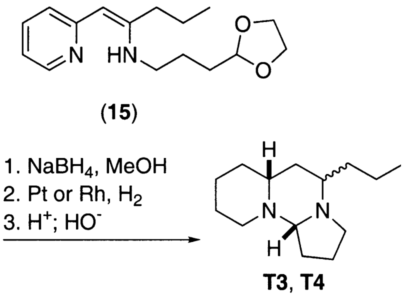
Table 2. Molecule/scheme correlation

Target	Schemes
Sedamine (**1**) or allosedamine (**9**)	1, 6, 7, 8, 13, 15, 16, 17, 19, 26, 28, 35, 46, 47, 53, 65, 77
Sedridine (**2**)	29, 30, 31, 36, 45, 70, 75
Andrachamine (**3**)	37[a], 23
Halosaline (**4**)	29, 57, 74
Sedinone (**5**)	21
Sedinine (**6**)	10
Sedacrine (**7**)	22
Sedacryptine (**8**)	10, 24, 51, 52
Hygroline (**10**) or pseudohygroline (**11**)	3, 18, 32, 36, 78, 79
Pinidinol (**12**)	14, 71, 73
Dumetorine (**13**)	40
Tetraponerines (**T1**–**T8**)	2, 4, 27, 33, 38, 39, 63, 66, 67, 68, 69, 76

[a] Incorrectly assigned structure.



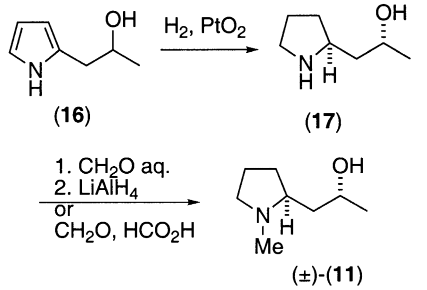
Scheme 1.



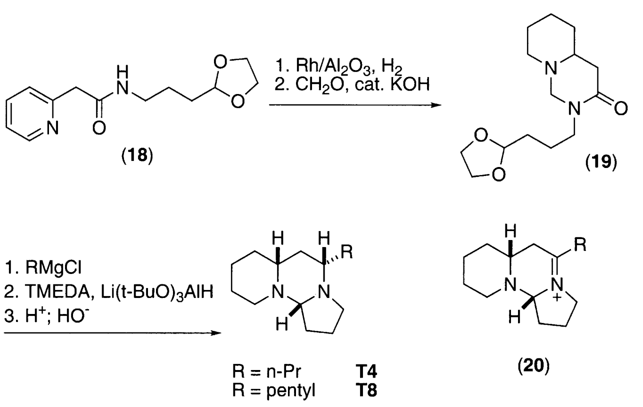
Scheme 2.

Beyerman employed the addition of picolinyl anion or an *N*-methylpicolinium nucleophile to benzaldehyde (Scheme 1).[2] The pyridinium ion (**14**) was then reduced by catalytic hydrogenation over platinum. Schöpf also used this reduction in 1959.[3] Catalytic hydrogenation of the phenacylpyridinium salt (**14**) over platinum yielded a mixture of racemic sedamine (**1**) and allosedamine (**9**). Both of these could be resolved using dibenzoyltartaric acid. Sedridine (**2**)[4], pinidinol (**12**)[5] and tetraponerines-3 and -4 (**T3**, **T4**) (Scheme 2)[6] have been prepared similarly. In the case of the pyrrolidines, the appropriate starting material would be pyrrole (**16**), and this approach, yielding pseudohygroline (**11**), has been reported (Scheme 3).[7]

The pyridine strategy is typically short, but these simple pathways yield mixtures of (racemic) diastereomers. The

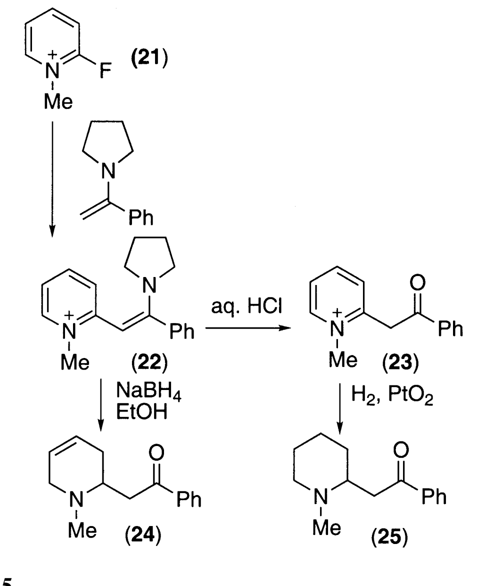


Scheme 3.

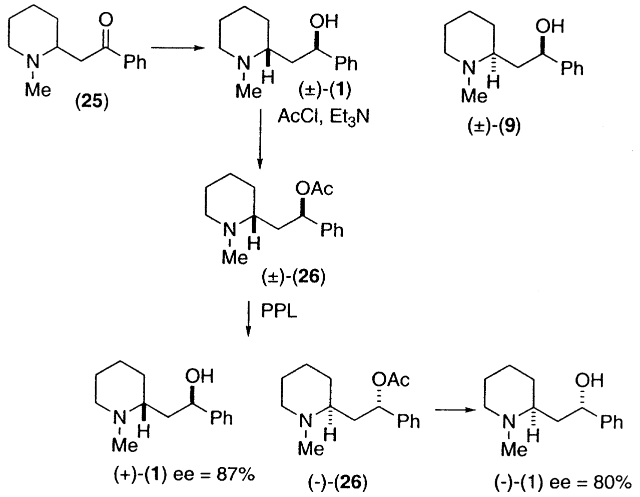


Scheme 4.

Jones tetraponerine synthesis was, however, modified to be diastereoselective (Scheme 4).[8] The piperidine aminal (**19**) was formed by reduction of the pyridine (**18**) and then ring closure was achieved with formaldehyde. Addition of a Grignard reagent, followed by reduction, presumably of the iminium ion intermediate (**20**) and, hence, under stereoelectronic control, gave the natural all *cis* form.



Scheme 5.

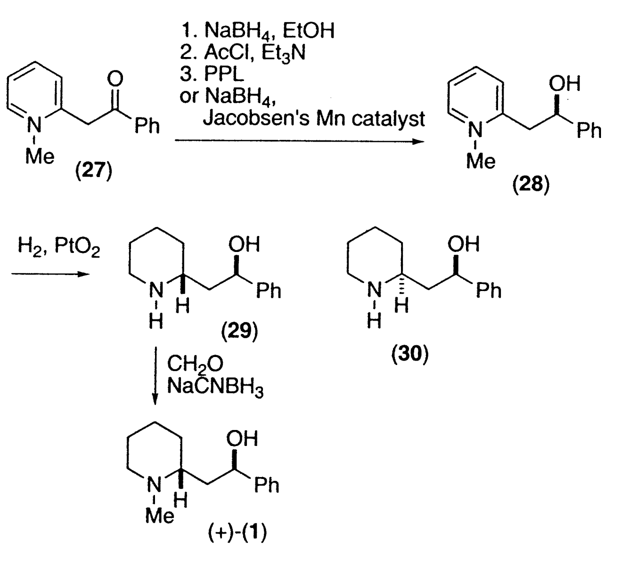


Scheme 6.

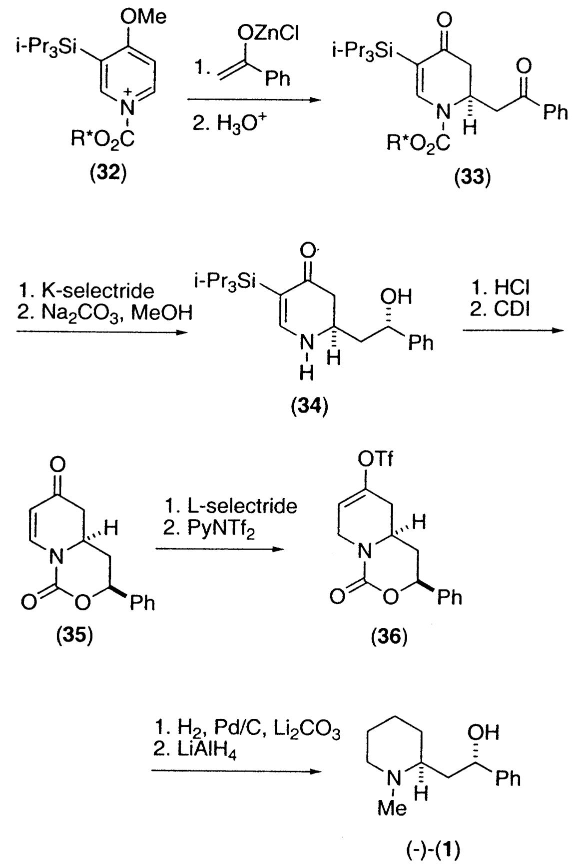
Meth-Cohn and co-workers noted the similarity between an α-halopyridinium salt and a Vilsmeier reagent.[9,10] This prompted them to attempt the displacement of the halide with modest nucleophiles. The best combination turned out to be a fluoropyridinium salt, such as (**21**), and a pyrrolidino-enamine (Scheme 5). The use of α,α'-difluoropyridines allowed the introduction of two different side chains, a technique that should prove useful for the synthesis of some of the more complex sedum alkaloids. The enamine products (**22**) could be hydrolysed to the corresponding ketones (**23**). An alternative transformation was regioselective reduction to the tetrahydropyridine (**24**). They were also able to reduce the pyridinium ring selectively to the ketopiperidine (**24**) by catalytic hydrogenation over Pt.

They also tackled the problem of generating enantioenriched materials (Scheme 6).[11] Sodium borohydride reduction of the ketopiperidine (**25**) gave a mixture of sedamine (**1**) and allosedamine (**9**). (+) and (−)-Sedamine (**1**) could then be obtained by kinetic resolution of the acetate (**26**) using porcine pancreatic lipase (PPL).

In order to improve on these routes, a number of asymmetric reducing agents were applied to 2-phenacylpyridine (**27**). Several were ineffective, namely baker's

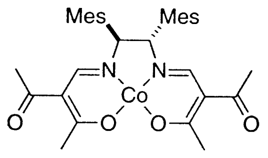


Scheme 7.



Scheme 8.

yeast, a BINAP–Pd complex and the CBS reagent. Some others were effective in reducing the ketone, but the product (**28**) had a low ee (DIPCl, a BINAP–Ru complex). Finally, a modified version of Jacobson's catalyst was found to be highly effective (Scheme 7). Subsequently, a survey of various cobalt and manganese β-ketoiminato complexes showed that (**31**) was the most effective catalyst giving the alcohol in 92% ee.[12] Alternatively, the pyridylketone (**27**) could be reduced with sodium borohydride and acetylated. PPL kinetic resolution could then be used to obtain the optically active alcohol in excellent ee. The pyridine could then be reduced to give a mixture of norsedamine (**29**) and norallosedamine (**30**) (70:30). Norsedamine (**29**) can be easily converted to sedamine by reductive amination.



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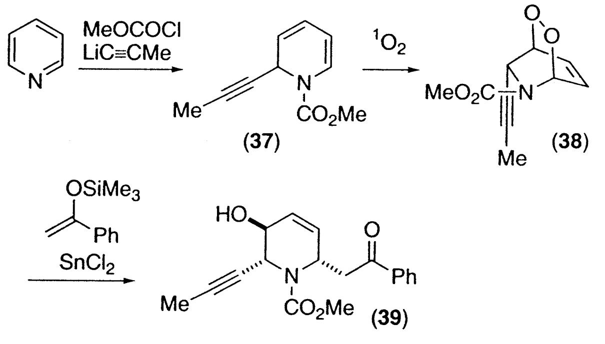
Comins has applied his asymmetric pyridinium methodology to the synthesis of sedamine (Scheme 8).[13] The source of the chirality is the 8-phenylmenthyl or the 2-cumylcyclohexanol groups. The acylpyridinium salts react with a variety of enolates, but the de depends on the counterion, with zinc and magnesium giving the best yields and diastereoselectivities.

The second chiral centre could then be introduced by reduction of the ketone with K-selectride with excellent stereocontrol. This is in contrast with the reduction of other ketocarbamates (Table 3). Removal and recovery of the chiral auxiliary then allowed the removal of the ring functional groups.

A highly inventive method has been reported by Natsume and Ogawa involving the use of pyridine as the starting material for (±)-sedacryptine (**8**), a relatively complex *sedum* alkaloid (Scheme 9).[14] Treatment of pyridine with a chloroformate and an acetylide ion yielded the expected dihydropyridine (**37**) which underwent a subsequent Diels–Alder reaction with singlet oxygen. In the presence of a Lewis acid, the peroxide oxygen of (**38**) α to nitrogen could be displaced with quite clean inversion. This sequence put in place the key features of sedacryptine: the two side chains, *cis* to each other, and the ring hydroxy group.

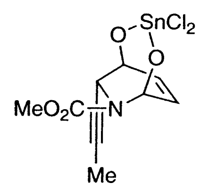
Table 3. Diastereoselectivity in the reduction of α-piperidinylketones

Substituent on nitrogen	Reagent	Ratio sedamine/allosedamine structure	Comment	Ref.
Me	$NaBH_4$	1:1		9
	H_2, Pt/C	1:1		17
	$NaBH_4$	1:1		17
	DIBAL	0:100		17
	$LiAlH_4$	70:30		17
	$LiAlH_4$	1:1	Piperidinone	19
	$LiAl(Ot\text{-}Bu)_3H$	4:1	(**7**)→(**6**)	67
α-Me-benzyl	$LiAlH_4$	1:1	Lactam	24
H	$Zn(BH_4)_2$	6:1		21
	$LiEt_3BH$	6:1	H_2O_2 work-up	21
	$LiAl(Ot\text{-}Bu)_3H$	35:65		25
CO_2Et	$LiAlH_4$	Modest		21
	$Zn(BH_4)_2$	Modest		21
	$LiEt_3BH$	3:1		21,50
	KEt_3BH	Modest		21
CO_2Me	$LiAlH_4$	1:1		20,22
	$NaBH_4$	70:30		25
	$LiAl(Ot\text{-}Bu)_3H$	98:2		25,26
	$LiBH_4$	3:1	Sedacryptine (**8**)	14
CO_2R^*	K-selectride	>99:1	Scheme 8	13



Scheme 9.

The Lewis acid chosen was tin(II) chloride and it is proposed that this compound also undergoes oxidative addition to the peroxide bond. The nucleophilic attack therefore actually involves the tin(IV) complex (**40**).



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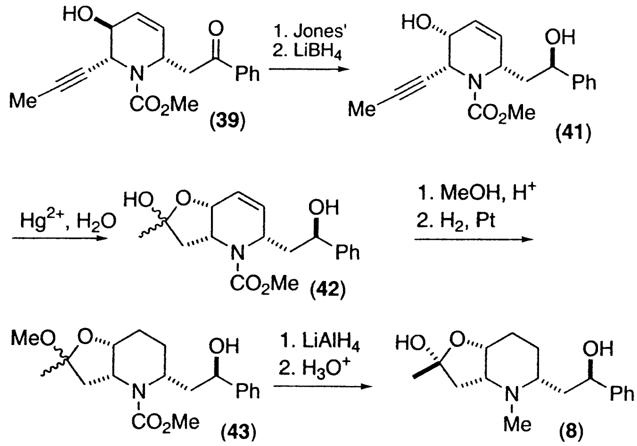
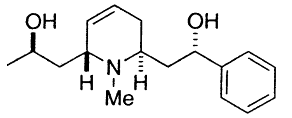
The stereochemistry of the alcohol group of (**39**) was then inverted by oxidation and reduction (Scheme 10). The side chain ketone was reduced at the same time. This resulted in a mixture of distereoisomeric alcohols (≈3:1). The major product of the reduction, (**41**), was carried through to (±)-sedacryptine. Hydration of the alkyne gave a mixture of diastereoisomeric hemiacetals (**42**). After protection as a full acetal, the alkene was removed by hydrogenation over Pt and the carbamate (**43**) was reduced with $LiAlH_4$ to give a 4:1 mixture at the inconsequential acetal centre. Hydrolysis of the acetal then yielded crystalline sedacryptine as a single isomer.



Scheme 10.

A similar but somewhat longer sequence was used by the same group to synthesise sedinine (**6**).[15]



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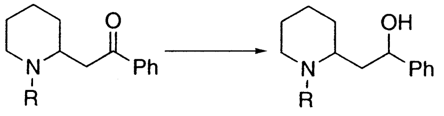
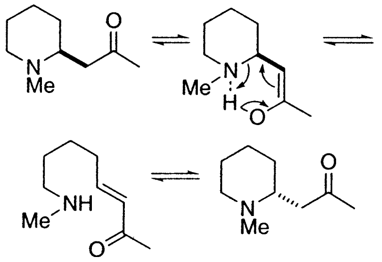
3. Piperidine strategies

Amongst the piperidine routes, a common strategy is the reaction of an aminal with a silyl enol ether under Lewis acidic conditions. This strategy in particular necessitates a subsequent stereoselective reduction of the resulting ketopiperidine (Scheme 11). Numerous reagents have been employed and these are summarised in Table 3.



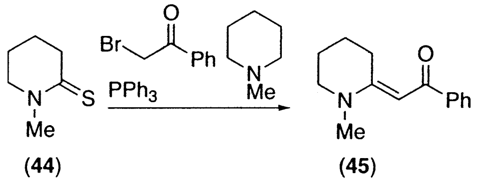
Scheme 11.

A potential problem with this strategy is apparent when R is an alkyl group. The starting ketopiperidines are configurationally unstable, racemising via a retro-Michael/Michael pathway (Scheme 12), catalysed by the molecule's own basic nitrogen.[16] They are configurationally stable when the nitrogen lone pair is not available, i.e. as their salts, if R is an electron withdrawing group or if the nitrogen heterocycle is a lactam. The same effect is observed in the pyrrolidine series.[7]



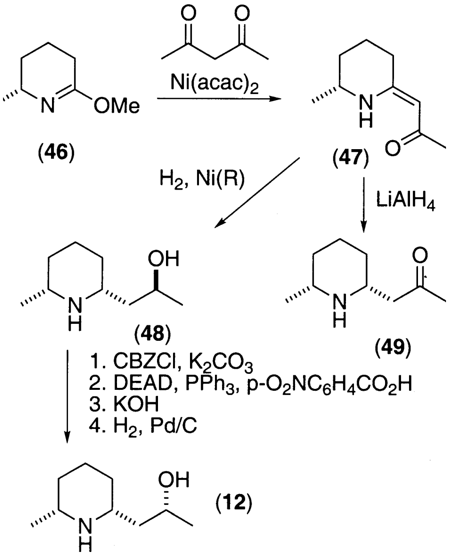
Scheme 12.

A number of methods have been employed to generate the required ketopiperidine. Ghiaci employed an Eschenmoser contraction of the thioamide (**44**) (Scheme 13).[17] This yielded an enamine (**45**) which could be reduced in two steps to (±)-sedamine (**1**) or allosedamine (**9**). A variety of reagents were examined (Table 3).



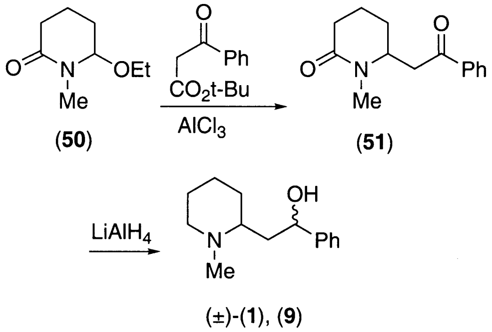
Scheme 13.

A similar enamide (**47**) was prepared as part of a synthesis of pinidinol (**12**), by the nickel-catalysed reaction of acetylacetone with the imidate (**46**) (Scheme 14).[18] Reduction with Raney nickel gave a single stereoisomer (**48**). The stereochemistry resulting from the reduction of the alkene can be ascribed to the steric effect of the methyl substituent. Quite why the reduction of the ketone is so stereoselective is unclear and it is not apparent which functional group is reduced first. Protection of the nitrogen was followed by inversion of the alcohol. Deprotection then yielded natural pinidinol (**12**). Alternatively, $LiAlH_4$ reduction of the enamine (**47**) yielded pinidinone (**49**).



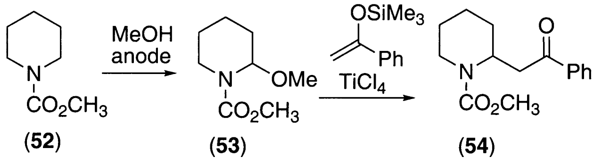
Scheme 14.

Ozawa employed a piperidinone (**50**) derived from glutaric acid (Scheme 15).[19] The carbon side chain was introduced by the addition of *t*-butylbenzoyl acetate in the presence of excess aluminium trichloride. Under these reaction conditions, loss of the *t*-butyl group and decarboxylation followed.



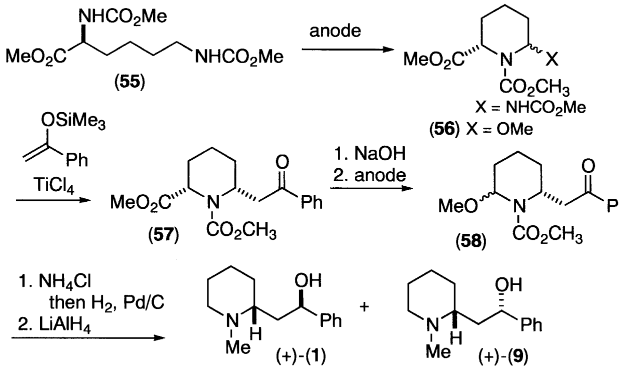
Scheme 15.

Anodic methoxylation is a more widespread procedure. The required starting material is then an *N*-protected piperidine. An electron withdrawing protecting group is generally used, and the choice falls on the methyl carbamate group as it can easily be converted to a methyl group at the end of the synthesis. Shono was able to prepare the 2-methoxypiperidine (**53**), and then displace the methoxy group with the silyl enol ether of acetophenone (Scheme 16).[20] Both titanium tetrachloride and boron trifluoride could be employed as Lewis acids. Pilli was able to improve on this method by employing catalytic amounts of TMS triflate as the Lewis acid.[21] The ketone (**54**) could then be converted to sedamine (**1**).

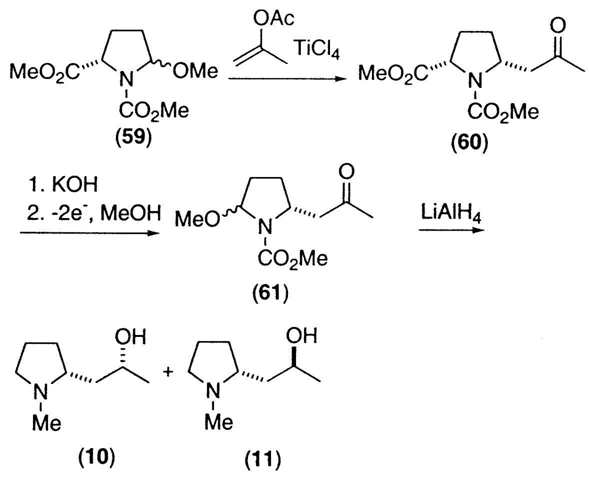


Scheme 16.

The method by definition gives racemic products. It was modified by Tanaka who prepared a substituted piperidine (**56**) by the electro-oxidation of protected lysine (**55**) (Scheme 17).[22] Subsequent displacement of the methoxy group by the enol ether in the presence of $TiCl_4$ gave a 10:1 mixture of diastereoisomers. The major product (**57**) was the *cis*-isomer which was converted to a mixture of sedamine (**1**) and allosedamine (**9**). This sequence includes the removal of the stereocontrolling ester group which was achieved by a second electro-oxidation.



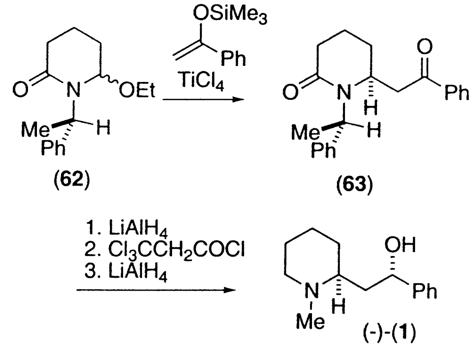
Scheme 17.



Scheme 18.

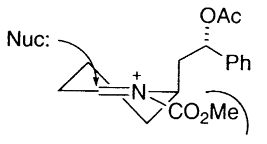
Starting from L-proline or L-ornithine, Shono was able to generate the related pyrrolidine aminal (**59**).[23] Displacement of the methoxy group by 2-acetoxypropene gave a 7:3 mixture of the two ketones, a distinctly poorer ratio than that obtained in the piperidine series (Scheme 18). Electrochemical conversion of the carboxyl group to an aminal, and hydride reduction, yielded a separable mixture of hygroline and pseudohygroline, each of about 40% ee, reflecting the greater difficulty in the control of stereochemistry of the five-membered rings.

Naito employed a chiral controller on the nitrogen atom, but the addition of an enol ether of acetophenone to the lactam in the presence of titanium tetrachloride showed only modest selectivity and returned some of an elimination product (Scheme 19).[24] After reduction of the carbonyl groups to give a 1:1 mixture of isomeric alcohols, the piperidine was dealkylated in a von Braun reaction.



Scheme 19.

Hootelé was able to use the anodic oxidation method to convert sedamine into the more highly substituted alkaloids, sedinone (**5**) and sedacrine (**7**) (Scheme 20).[25] Anodic oxidation of the protected sedamine (**64**) gave the expected aminal (**65**). Treatment with a silyl enol ether under Shono's conditions yielded the disubstituted piperidine. A single isomer, assigned the *cis* structure (**66**), was obtained. The structure is in accordance with a stereoelectronically controlled addition of the enol ether to an intermediate iminium ion (**67**), with the side chain axial, to avoid the steric interaction with the methoxycarbonyl group.



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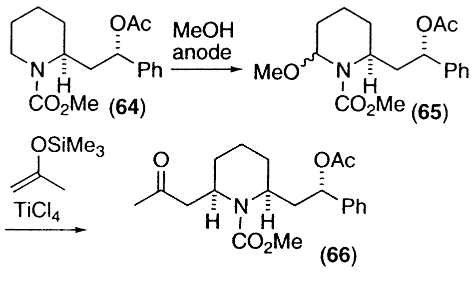
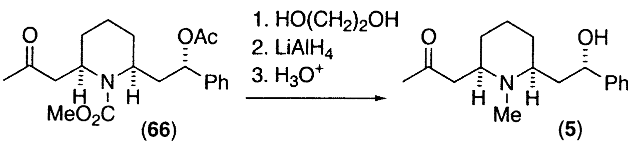


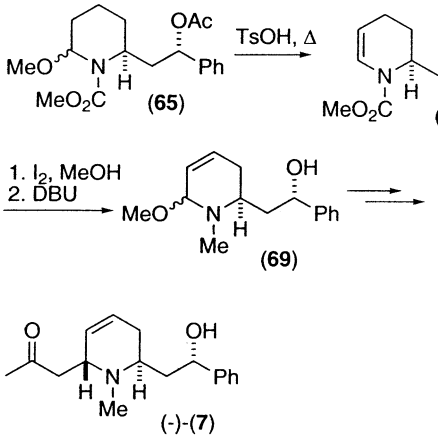
Scheme 20.

Protection of ketone (**66**) then allowed selective reduction of the carbamate (Scheme 21). On deprotection, however, partial epimerization occured. The stereochemical lability of β-aminoketones has already been noted. The pure natural product (**5**) could be obtained as its hydrochloride salt by fractional crystallisation.



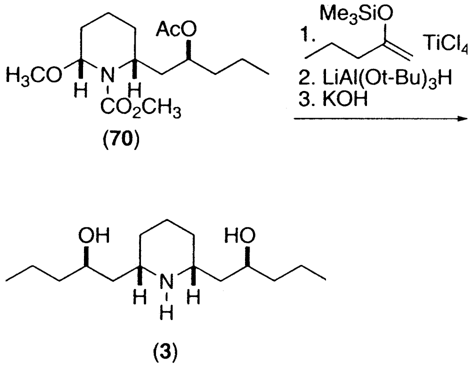
Scheme 21.

The same oxidised sedamine derivative (**65**) could also be converted to sedacrine (**7**) (Scheme 22), which has a double bond in the piperidine ring. Elimination of methanol gave the ene-carbamate (**68**). Halomethoxylation using either bromine or iodine was followed by DBU treatment. Only the iodine could be eliminated. Following the previous procedure yielded a mixture of sedacrine and its isomer, separable by fractional crystallisation.



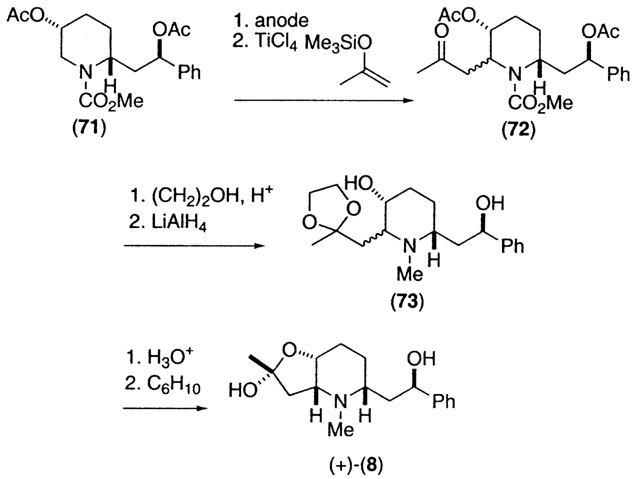
Scheme 22.

Andrachamine (**3**) was also prepared using this addition to an iminium ion (Scheme 23).[26]



Scheme 23.

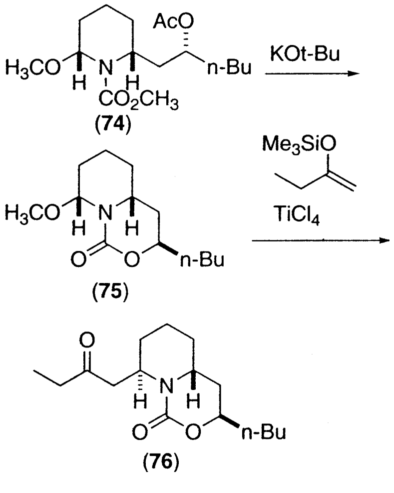
The presence of an oxygen substituent on the ring, introduced by enamide hydroboration–oxidation, resulted in a poor conversion during the electro-oxidation step which may be due to inductive destabilisation of the intermediate cation.[27] Sedacryptine (**8**) could, however, be prepared in this way, by electro-oxidation of the protected hydroxysedamine derivative (**71**) (Scheme 24). The problem of modest selectivity in the addition of the silyl enol ether was overcome in the last step. After neutralisation, the two diastereoisomers could equilibrate (as in Scheme 12), and the *cis* isomer could cyclise to the hemiacetal (**8**). It was observed that this form was particularly favoured in nonpolar solvents, such as cyclohexane.



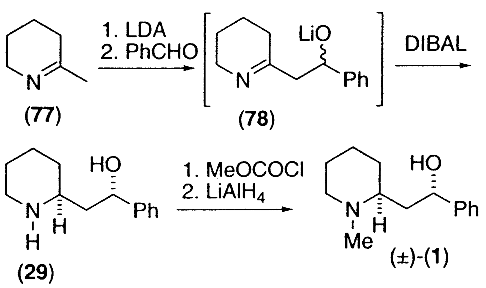
Scheme 24.

The stereochemical outcome of the addition to the iminium ion can be reversed if a cyclic carbamate, such as (**75**), is employed so that the side chain is forced to be equatorial, rather than axial (Scheme 25). This was employed in Hootelé's synthesis of possible andrachamine structures to generate *trans*, rather than *cis*, disubstituted piperidines.[26]

Vaultier has turned the disconnection around.[28] Rather than add a side chain nucleophile to a piperidine electrophile, he was able to deprotonate the imine (**77**) and react it with benzaldehyde in an aza-aldol process (Scheme 26). Reduction of the adduct (**78**) in situ with DIBAL was entirely diastereoselective. Methylation was then achieved via reduction of a carbamate.

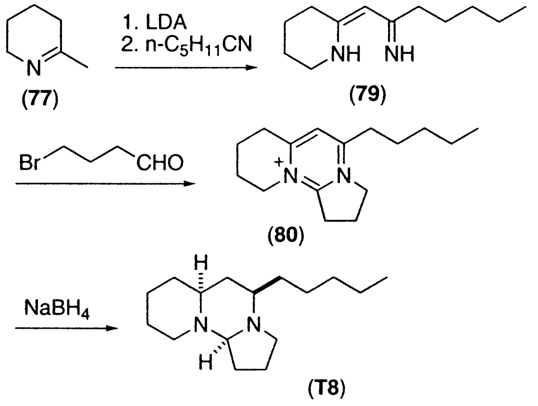


Scheme 25.



Scheme 26.

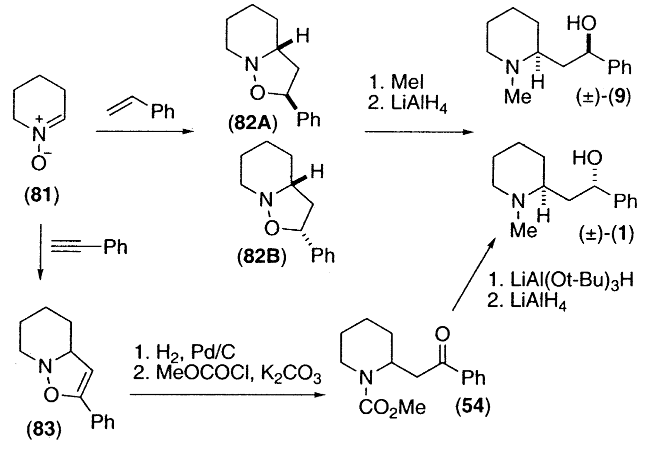
Condensation of the same carbanion with hexanenitrile was employed by Barluenga to prepare (±)-tetraponerine-8 (**T8**) (Scheme 27).[29] The azadiene (**79**) which was produced efficiently only under carefully controlled conditions, underwent alkylation and condensation with 4-bromobutanal to give a pyrimidinium salt. Mild reduction yielded the racemic natural product.



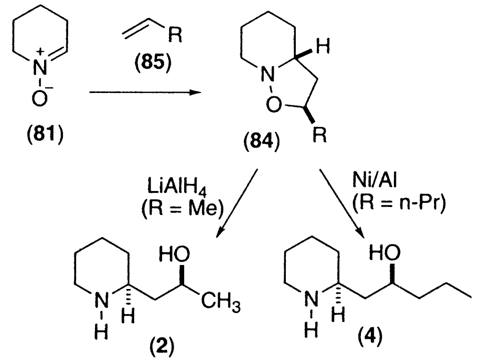
Scheme 27.

4. Syntheses using nitrones and other cycloadditions

An elegant solution to the problem of adding the side-chain and controlling the relative stereochemistry was reported in pioneering work by Tufariello.[30] Cycloaddition of the nitrone (**81**) to styrene gave a mixture of isoxazolidines (**82A,B**) (Scheme 28). Regioselectivity was complete, but the minor product was due to some secondary orbital interactions. Quaternisation of the nitrogen and cleavage of the O–N bond yielded allosedamine (**9**) as the major product (3.5:1). The sedamine system can be accessed using phenylacetylene as the dipolarophile.[25] The isoxazoline (**83**) can be converted to intermediate ketopiperidine (**54**). The best reducing agent for the ketone was found to be lithium tri(*t*-butoxy)aluminium hydride. The use of either propylene[30] or 1-pentene[26] in place of styrene gave exclusively sedridine (**2**) and halosaline (**4**) after N–O bond cleavage,



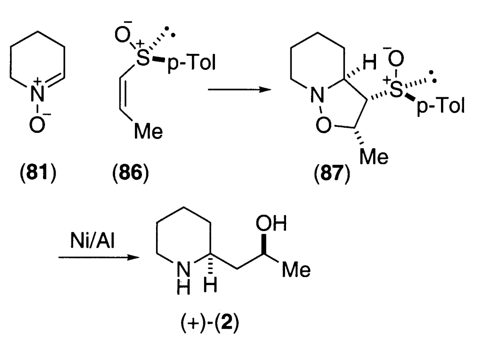
Scheme 28.



Scheme 29.

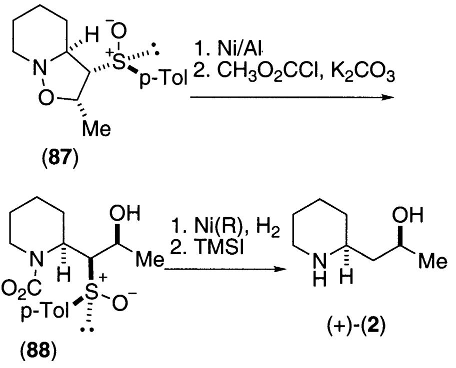
a reflection of the absence of secondary orbital interactions (Scheme 29).

Hootelé modified the reaction by employing a chiral sulfoxide (**86**) as the dipolarophile (Scheme 30).[31] The piperidine-based nitrone (**81**) reacted with the *Z*-propenylsulfoxide (**86**) to give a mixture of two stereoisomers. Both arise from *exo*-cycloaddition, but differ in the facial selectivity of the sulfoxides. However, the de was very high. In contrast, the corresponding alkynyl- and *E*-alkenylsulfoxides gave products of quite low de. The major cycloadduct from the *Z*-alkenylsulfoxide was converted to sedridine (**2**) by desulfurisation and O–N bond cleavage in a single step using Ni/Al alloy.

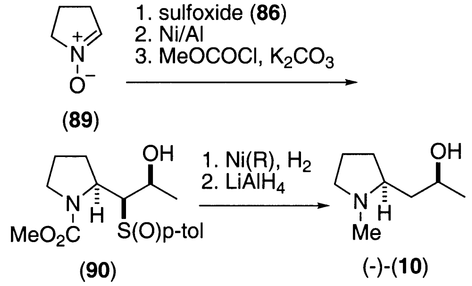


Scheme 30.

This reduction proceeded with partial epimerisation at both chiral centres. This was suppressed by selective O–N bond cleavage, followed by *N*-protection (Scheme 31). Desulfurisation was then achieved with only a small amount of alcohol epimerisation. Deprotection gave sedridine (**2**). Hygroline (**10**) was prepared analogously from the nitrone (**89**) (Scheme 32).

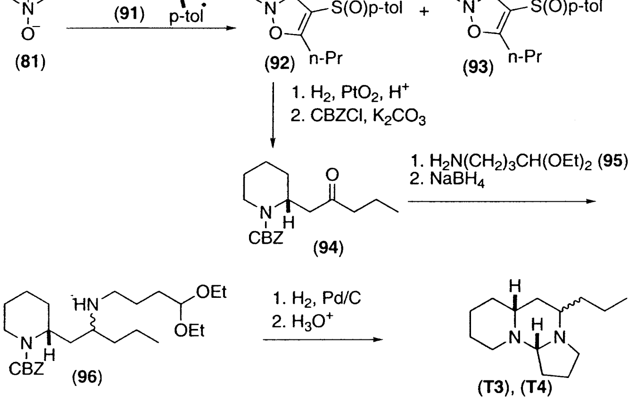


Scheme 31.



Scheme 32.

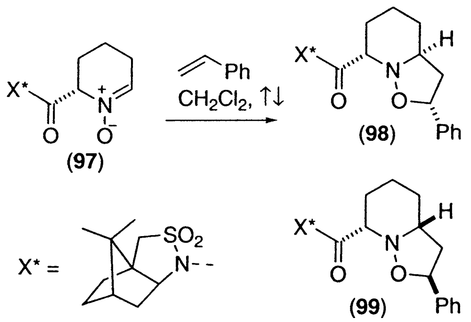
The alkynylsulfoxide (**91**) has been employed in a tetraponerine synthesis (Scheme 33).[32] As the de of the cycloadducts is zero and they must be chromatographically separated, this amounts to a resolution. Cleavage of the N–O bond by hydrogenation yielded the ketones directly. These were condensed with the amine (**95**) and the resulting imines were reduced with $NaBH_4$ with modest



Scheme 33.

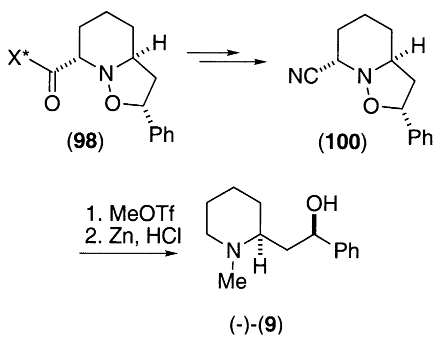
stereoselectivity. Acid-catalysed cyclisation then yielded a mixture of stereoisomeric tetraponerines. This paper includes very useful tables of NMR and chiroptical data, the collection of which has clarified ambiguities in the structures of the tetraponerines.

Oppolzer has also used a chiral nitrone (**97**), this time with a sultam auxiliary (Scheme 34).[33] The cycloaddition was highly facially selective. In addition, the auxiliary provided the added benefit of shutting down secondary orbital interactions, as both isomeric products were from steric control.



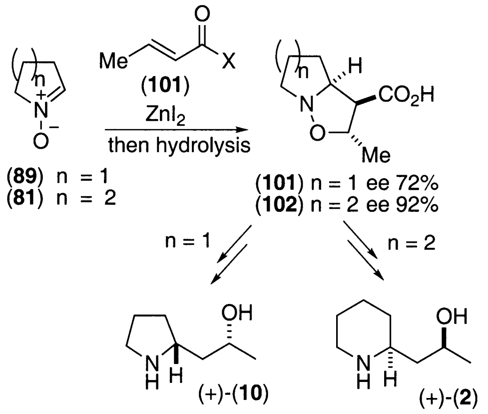
Scheme 34.

The chiral controller group of the major cycloadduct was then removed by conversion to a cyanide (Scheme 35). *N*-methylation of isoxazolidine (**100**) generated a quaternary hydroxylammonium salt which was reduced to effect removal of the cyano group and cleavage of the O–N bond, giving allosedamine (**9**) directly.

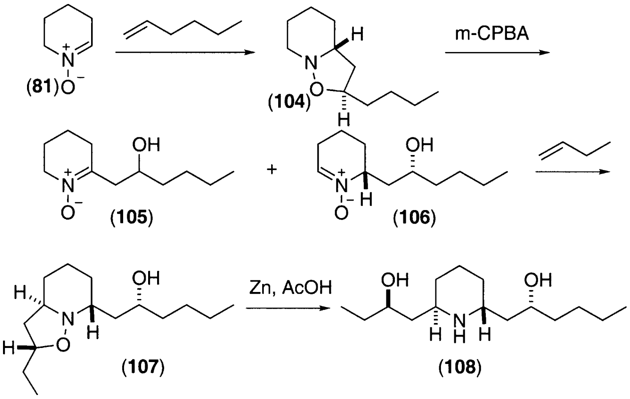


Scheme 35.

Evans' oxazolidines, as their crotyl derivatives (**101**), have also been used as chiral auxiliaries in the syntheses of sedridine and hygroline (Scheme 36).[34] The highest diastereoselectivites were obtained in the presence of ZnI_2 which coordinates to both the nitrone and the oxazolidinone. The latter compound chelates zinc ions and its conformation becomes locked. Under these conditions, the piperidinyl nitrone (**81**) gave better results than the pyrrolidinyl nitrone (**89**).



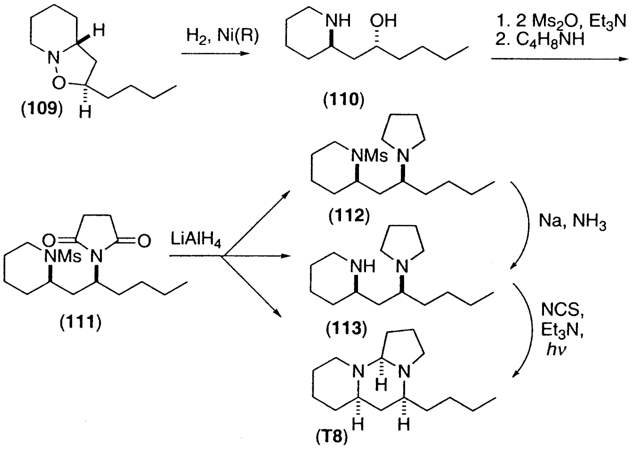
Scheme 36.



Scheme 37.

The nitrone strategy has also been used for the synthesis of a disubstituted sedum alkaloid, andrachamine (Scheme 37).[35] The nitrone (**81**) underwent cycloaddition with 1-hexene in refluxing dichloromethane to give the isoxazolidine as a single (racemic) isomer (**104**). Oxidation of this heterocycle with *m*-CPBA yielded a mixture of the new nitrones (**105**) and (**106**), unfortunately in favour of the undesired ketonitrone (**105**). From the reaction of this mixture with 1-butene the desired isoxazolidine (**107**) could be isolated in modest yield. O–N Bond cleavage then yielded (**108**) which was believed to be the natural product. The structure of andrachamine was subsequently corrected.

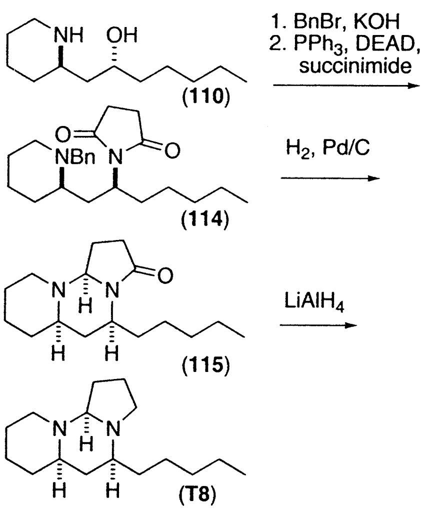
The homologous isoxazolidine intermediate (**109**) has been



Scheme 38.

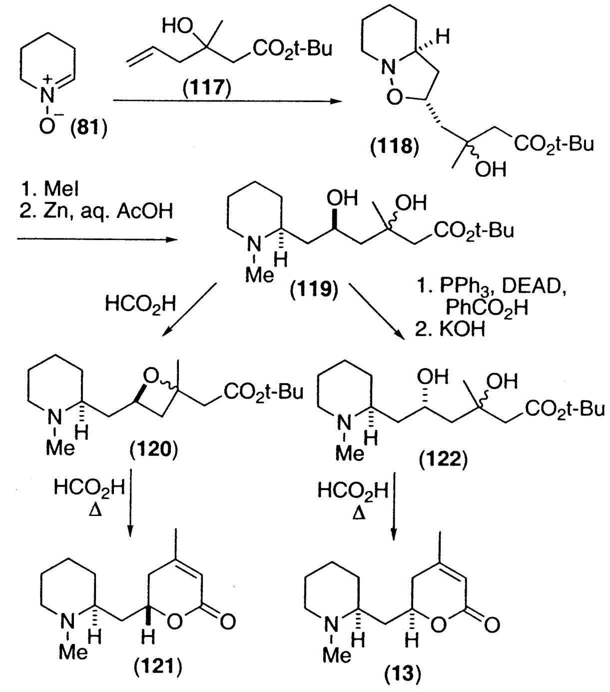
employed in a synthesis of tetraponerine-8 (**T8**) (Scheme 38).[36] Cleavage of the O–N bond gave the expected *anti*-1,3-aminoalcohol (**110**) which was doubly mesylated. Substitution with succinimide introduced the second nitrogen. Reduction of imide (**111**) with $LiAlH_4$ then yielded a mixture of three compounds: the sulfonamide (**112**), the diamine (**113**) and tetraponerine-8 (**T8**), presumably formed by the interception of a partially reduced succinimide by a deprotected piperidine. The sulfonamide (**112**) could be brought to the diamine (**113**) by reductive cleavage of the N–S bond, and the diamine could, in turn, be converted to tetraponerine-8 (**T8**) using a variation of the Hofmann-Loeffler-Freytag reaction.[37]

The synthesis was subsequently improved by the use of a benzyl group for selective protection of the amino group (Scheme 39).[38] A Mitsunobu reaction with succinimide yielded the desired product stereospecifically, but this was accompanied by a number of by-products. This was converted to tetraponerine-8 (**T8**) by a two-step reduction sequence.



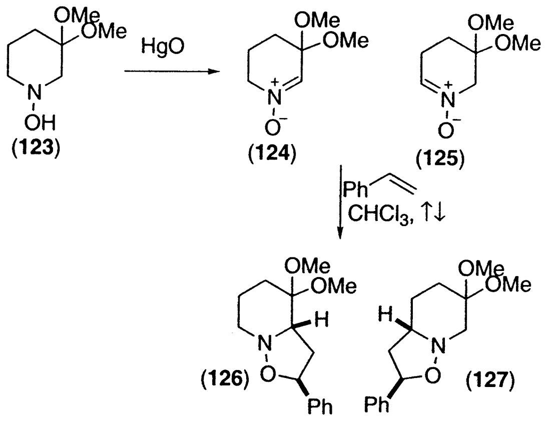
Scheme 39.

Hassner has used the cycloaddition in a synthesis of the West African yam natural product, dumetorine (**12**) (Scheme 40).[39] The alkene (**117**), a Barbier adduct, underwent cycloaddition to give the oxazolidine (**118**) as a mixture of isomers due to the chirality of the tertiary alcohol. After *N*-alkylation of the cycloadduct and O–N bond cleavage, attempted deprotection of the ester (**119**) yielded an oxetane (**120**), which underwent further reaction on heating to give *epi*-dumetorine (**121**). Dumetorine was prepared by inversion of the secondary alcohol of (**119**) under Mitsunobu conditions. Saponification of the benzoate ester was followed by acid treatment to yield (±)-dumetorine (**13**).

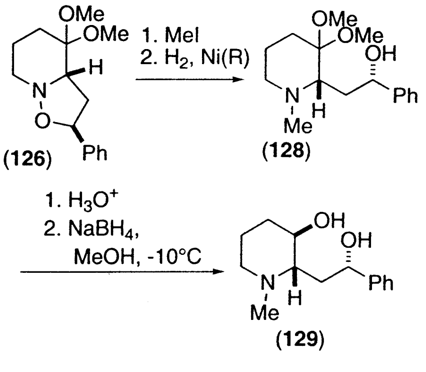


Scheme 40.

Nitrone chemistry has additionally been used for the synthesis of ring-hydroxylated alkaloids (Scheme 41).[40] Once again, modest selectivity in nitrone formation is the major handicap of this process. Oxidation of the hydroxylamine (**123**) with mercuric oxide yielded a mixture of regioisomeric nitrones, (**124**) and (**125**), the product ratio being highly sensitive to the reaction temperature. After the 1,3-dipolar cycloaddition with styrene, the regioisomeric isoxazolidines, (**126**) and (**127**), could be separated.



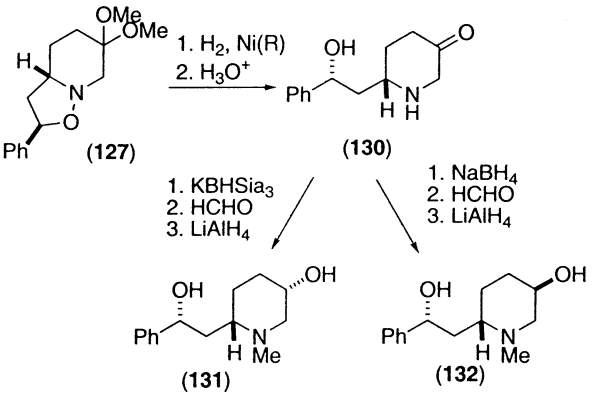
Scheme 41.



Scheme 42.

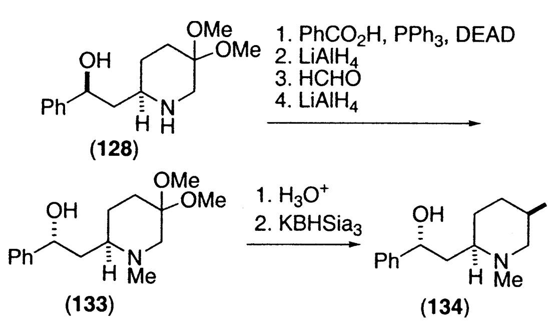
After chromatographic separation, these isoxazolidines could be converted to the natural products, 3-hydroxynorallosedamine, 3-hydroxyallosedamine (**129**), 5-hydroxyallosedamine and 5-hydroxysedamine (Scheme 42). *N*-Methylation and O–N bond cleavage of the isomer (**126**) gave the acetal (**128**). Hydrolysis of the acetal, followed by reduction of the ketone with sodium borohydride yielded 3-hydroxyallosedamine (**129**).

Raney nickel reduction of the other cycloadduct (**127**) yielded the aminoalcohol (**130**) which could be converted to either diastereomer of 5-hydroxyallosedamine, (**131**) or (**132**), by the appropriate choice of reducing agent, with installation of the *N*-methyl group by oxazine reduction (Scheme 43).

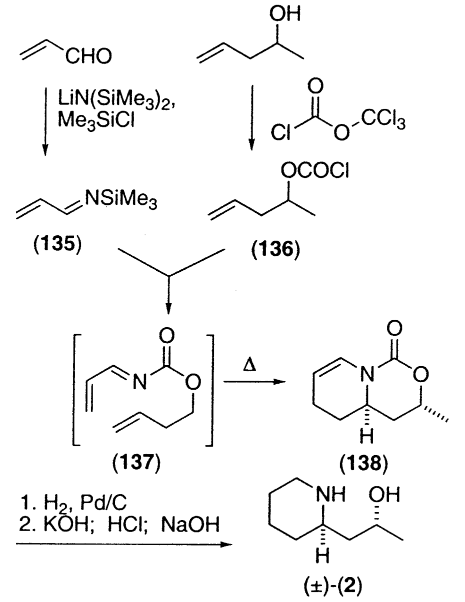


Scheme 43.

Alternatively, the use of the Mitsunobu reaction allowed access from the aminoalcohol (**130**) (which was resolved in this instance, by the formation of the dibenzoyl tartrate salt) to the sedamine series, although not with perfect fidelity, perhaps due to some neighbouring group participation (Scheme 44). Similar chemistry to Scheme 43 then led to 5-hydroxysedamine (**134**).



Scheme 44.



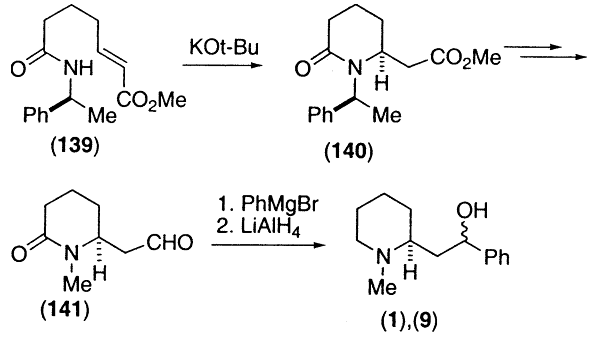
Scheme 45.

Very little work has been reported using other cycloadditons. Yamamoto's group have synthesised (±)-sedridine (**2**) by an intramolecular aza-Diels–Alder reaction (Scheme 45).[41] The heterodiene (**137**) was prepared by the reaction between an imine (**135**) derived from acrolein and a choroformate (**136**). This underwent Diels–Alder cyclization on heating in a one-pot process to give, apparently, a single stereoisomer (**138**). Reduction of the enamine (**138**) and hydrolysis of the carbamate group yielded sedridine (**2**).

5. Heterocycle construction

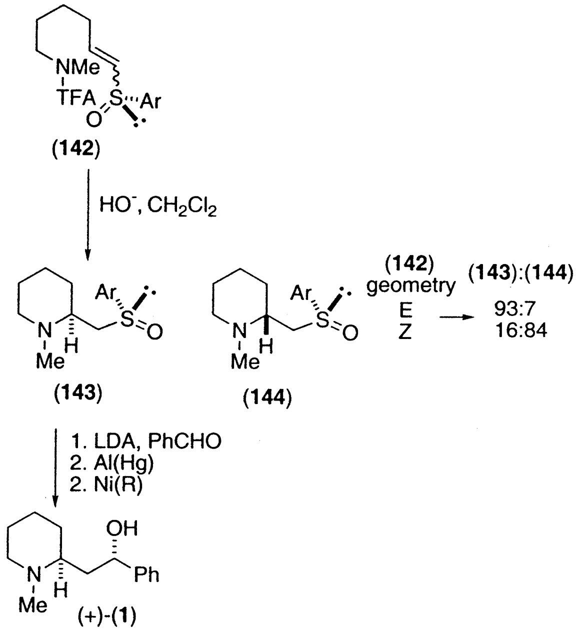
5.1. Michael addition

Wakabayashi has achieved the intramolecular Michael addition of an amide to an enone (Scheme 46).[42] The use of an α-methylbenzyl substituent on the nitrogen resulted in modest diastereoselectivity. He was able to convert the major isomer to sedamine (**1**) and allosedamine (**9**). This involved the addition of phenylmagnesium bromide to the aldehyde (**141**) to give a 1:1 mixture of stereoisomers.



Scheme 46.

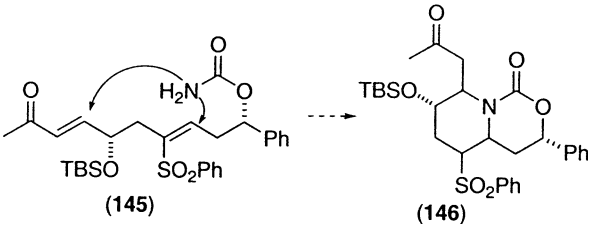
Pyne has also used an intramolecular Michael addition, this time employing a chiral sulfoxide to control the stereochemistry (Scheme 47).[43] The solvent polarity had a distinct effect on the selectivity, while the nature of the S-aryl group was less important. The *E* and *Z* isomers gave opposite diastereoisomers. To complete the synthesis the carbanion α to sulfur was generated and quenched with benzaldehyde



Scheme 47.

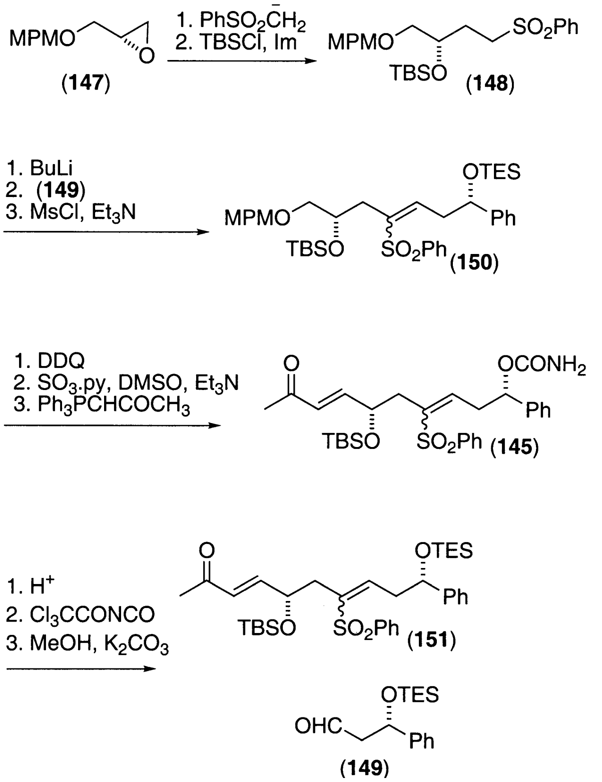
to give a mixture of adducts in a ratio of 6:1:1. The major isomer was desulfurised to give sedamine (**1**). A direct one-step reduction resulted in some erosion of stereochemistry, a problem which was solved by the use of a two step reduction, sulfoxide to sulfide, and then desulfurization.

Perhaps the most ambitious and elegant Michael strategy is in Hirama's synthesis of sedacryptine (**8**).[44] Based on earlier Michael studies, it was suggested that the diene (**145**) would undergo two Michael additions to generate a sedacryptine-like structure (**146**) in one pot (Scheme 48).

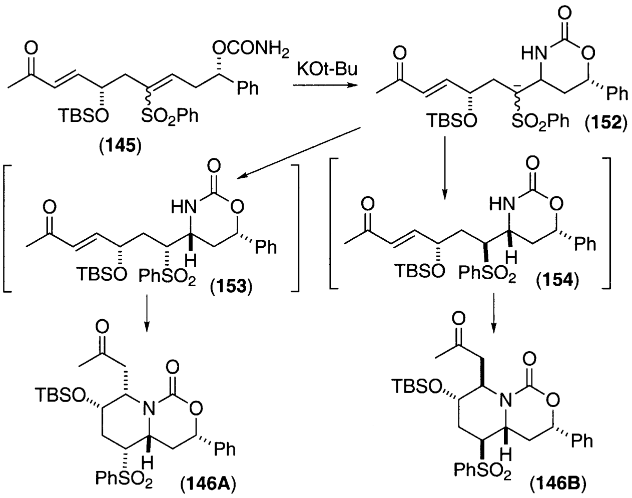


Scheme 48.

The diene (**145**) was constructed by taking advantage of the properties of the desired electron withdrawing groups (Scheme 49). This was achieved by employing sulfonyl carbanions to open a glycidol derivative (**147**) and to condense with a chiral aldehyde (**149**) (prepared by a baker's yeast reduction). Subsequent introduction of an aldehyde group allowed a Wittig reaction with a stabilised ylide bearing the ketone group.



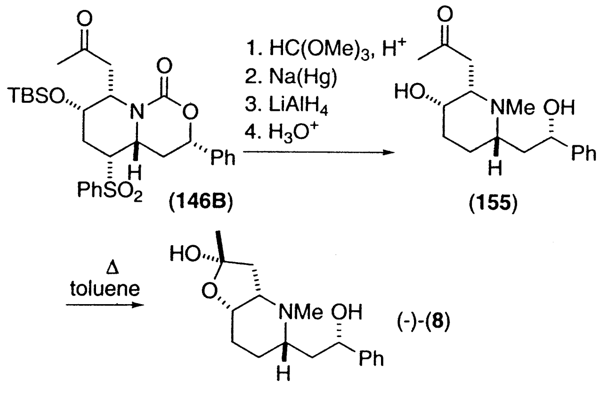
Scheme 49.



Scheme 50.

Base treatment of the carbamate (**145**) yielded a mixture of two diastereoisomeric products, (**146A**) and (**146B**) (Scheme 50). The minor product (**146B**) possessed the sedacryptine stereochemistry. In the major product (**146A**), the incorrect stereochemistry came from the second Michael addition of the sequence. These two products arose from Michael addition of the carbamate to the unsaturated sulfone followed by protonation of the sulfone anion (**152**). The stereochemical sense of this protonation then caused the divergent pathways. The second Michael addition then proceeded with the sulfonyl group pseudo-equatorial in both cases, resulting in the different stereochemistries of the second ring.

The minor product (**146B**), with sedacryptine stereochemistry, could then be converted to the natural product (**8**) by a routine series of transformations, including removal of the sulfone group with sodium amalgam and a final heating in a non-polar solvent to form the hemiacetal (Scheme 51).

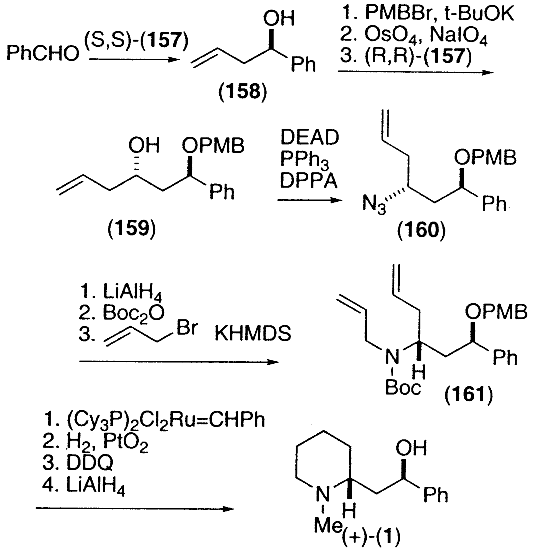


Scheme 51.

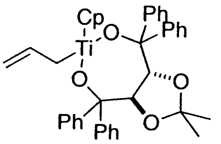
An identical sequence also converted the major isomer (**146A**) to the natural product (**8**) (Scheme 52). This is because, in the last step, heating causes equilibration of the diastereoisomeric ketones, (**156**) and (**155**), via the retro-Michael–Michael mechanism (Scheme 12). Only (**155**) can undergo hemi-acetalisation to give sedacryptine (**8**).

5.2. Metathesis reactions

Cossy employed two enantioselective allylations to generate both chiral centres using the TADDOL-based allyltitanium reagent (**157**), or its enantiomer (Scheme 53).[45] The homoallylic alcohol (**158**) was prepared using this reagent.[46] Displacement of the free alcohol with a nitrogen nucleophile under Mitsunobu conditions lead to a substrate (**161**) suitable for ring-closing metathesis. This was achieved with Grubbs' catalyst. Reduction of the double bond and two deprotections then gave sedamine (**1**).



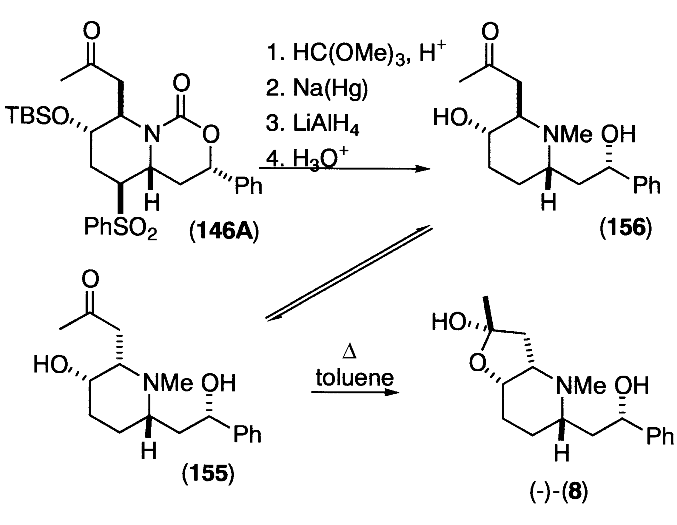
Scheme 53.



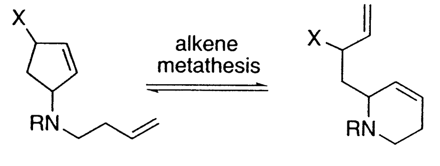
(157)

Blechert and Stratgies have employed metathesis methods elegantly to both halosaline (**4**)[47] and to four of the tetraponerines.[48] Their essential concept was that a cyclopentene ring bearing an unsaturated side chain would be in equilibrium with the corresponding heterocycle in the presence of a metathesis catalyst (Scheme 54). The concept relies on the lesser ring strain of the six-membered ring system, and the relief of crowding around the groups and X and R.

Additionally, in the presence of another suitably reactive alkene such as allyltrimethylsilane, it should be possible to effect an intermolecular cross metathesis to extend the

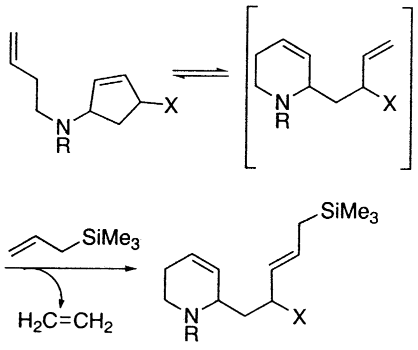


Scheme 52.



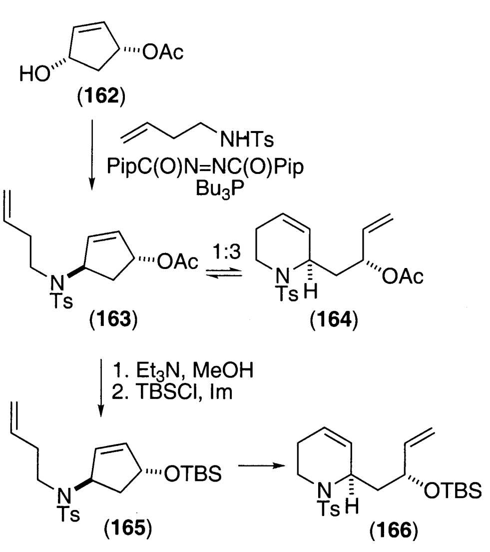
Scheme 54.

side chain (Scheme 55). Most importantly, none of the metathesis reactions should affect the stereocentres, which would be faithfully relayed from the cyclopentenyl starting material.



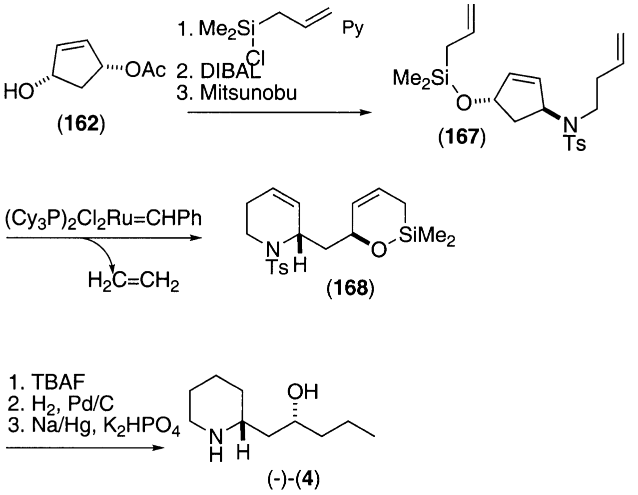
Scheme 55.

For the synthesis of halosaline (**4**), the monoacetate (**162**), which can be prepared in high ee from the corresponding diacetate,[49] was converted to the sulfonamide (**163**) with inversion of stereochemistry with a Mitsunobu reaction (Scheme 56). The equilibrium was established in the presence of Grubbs' catalyst and proved to be only 3:1 in favour of the nitrogen heterocycle (**164**). In contrast, changing to the TBS ether (**165**) resulted in the exclusive formation of the desired heterocycle (**166**). Additional steric hindrance around the oxygen had proved sufficient to tip the balance. Performing the metathesis in the presence of ethylene, to suppress dimerisation, resulted in the optimum yields. The enantiomeric material was also available by simple modification of the starting cyclopentene.

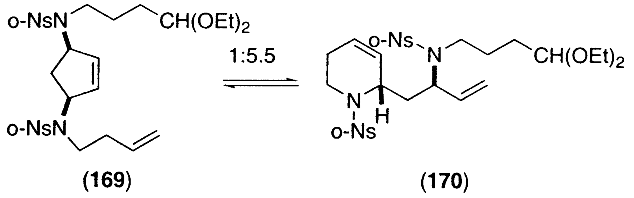


Scheme 56.

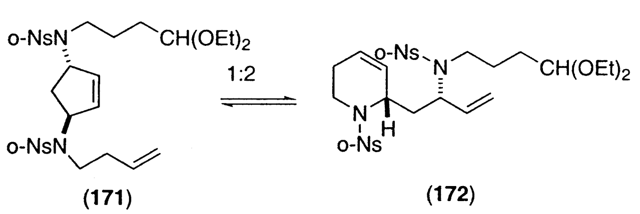
The subsequent intramolecular cross metathesis proved to be disappointing, especially as a one-pot procedure. The authors therefore attempted to make this reaction also intramolecular (Scheme 57). Treatment of the triene (**167**) with Grubbs' catalyst resulted in the expected domino metathesis process. Desilylation of (**168**) and reduction of the double bonds yielded halosaline (**4**).



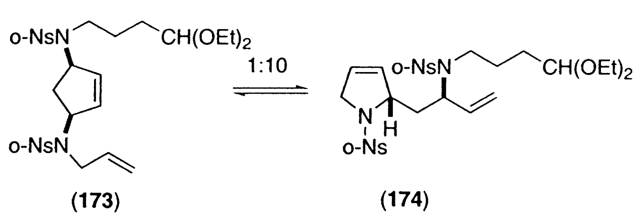
Scheme 57.



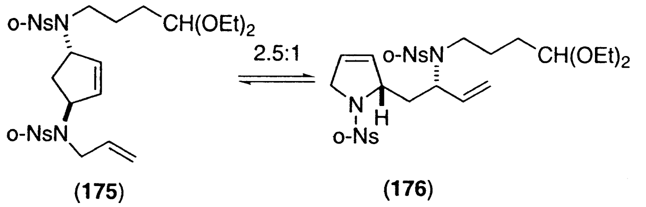
Scheme 58.



Scheme 59.



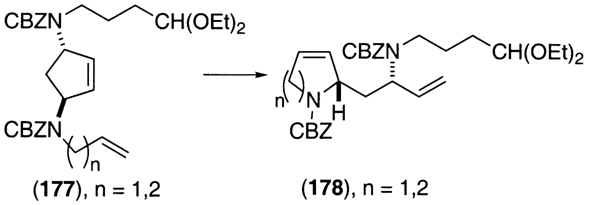
Scheme 60.



Scheme 61.

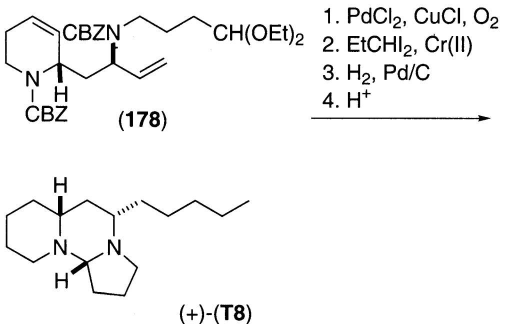
Related methodology was applied to the synthesis of four tetraponerines. The position of the metathesis equilibria was found to depend not only on the nitrogen protecting group, but also on the relative geometry of the starting material substituents (Schemes 58–61). The equilibria involving the *cis* isomers, (**169**) and (**173**), both favoured the products to a greater extent than those with the *trans* isomers, (**171**) and (**175**). In one case, (**175**)/(**176**), (Scheme 61), the starting material was actually favoured.

Surprisingly, a simple change of protecting group to CBZ ensured that both of the less tractable *trans* isomers proceeded completely to their metathesis products (**178**) (Scheme 62).



Scheme 62.

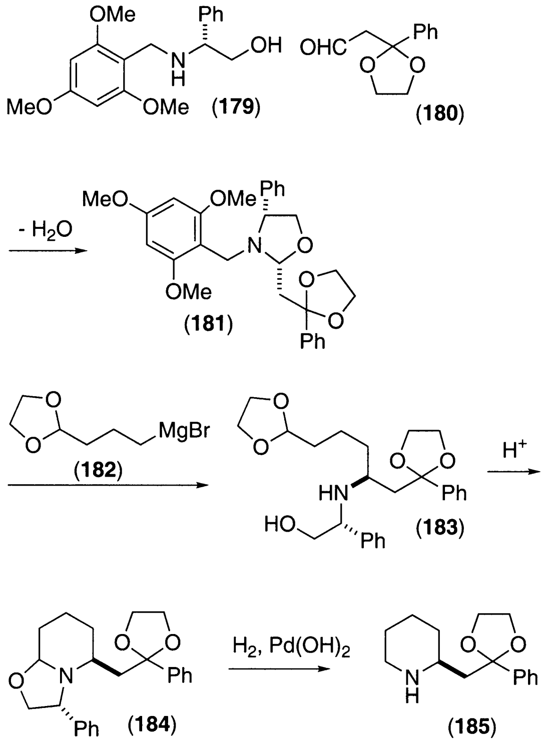
The metathesis products could be converted to the natural products by side chain elaboration, involving a clever use of the Takai reaction, and aminal formation, illustrated for tetraponerine-8 (**T8**) (Scheme 63).



Scheme 63.

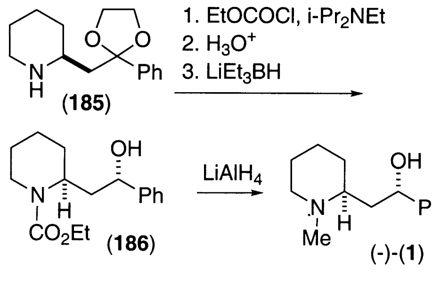
5.3. Condensation and alkylation

Higashiyama constructed the piperidine ring using a phenylglycine-derived chiral controller (Scheme 64).[50] Condensation of a phenylglycinol derivative (**179**) with an appropriately substituted aldehyde (**180**) gave a single *cis* oxazolidine (**181**) as the thermodynamic product. Addition of the Grignard reagent (**182**) to (**181**) was then stereoselective, with oxazolidine opening and cleavage of the C–O bond with inversion. In this step, rather surprisingly, the trimethoxybenzyl group was also cleaved. Treatment of the product (**183**) with acid resulted in a reorganisation involving only the aldehyde-derived dioxolane and yielding a product (**184**) that is essentially a protected sedaminone. The chiral controller could then be cleaved by catalytic hydrogenation.



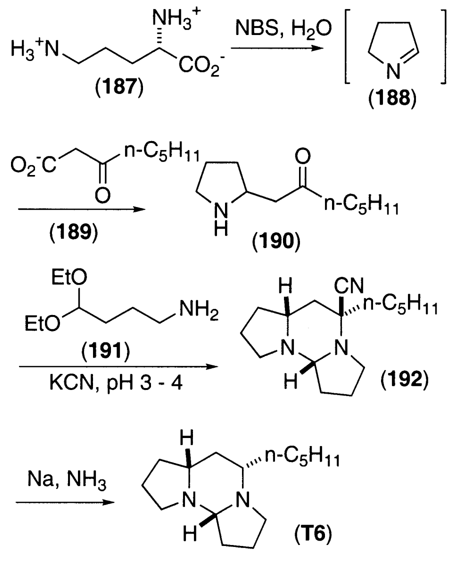
Scheme 64.

To avoid subsequent racemisation, the amine (**185**) was protected as a carbamate (Scheme 65). The ketone could then be deprotected and reduced. Finally, reduction of the carbamate (**186**) gave sedamine (**1**).



Scheme 65.

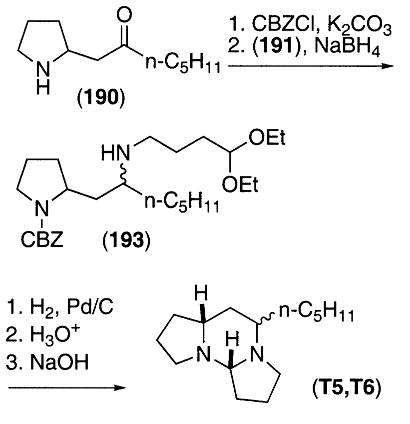
A number of methods have been employed to construct the heterocyclic rings of tetraponerines. Tetraponerines-5 and -6, (**T5**, **T6**) are based on two pyrrolidine rings. Ornithine (**187**) was treated with NBS under low pressure (rotavap) to give the cyclic imine (**188**) as an aqueous solution (Scheme 66).[51] Under very slightly basic conditions, this imine condensed with a β-ketocarboxylate (**189**) to give a β-aminoketone (**190**). Condensation with a protected form



Scheme 66.

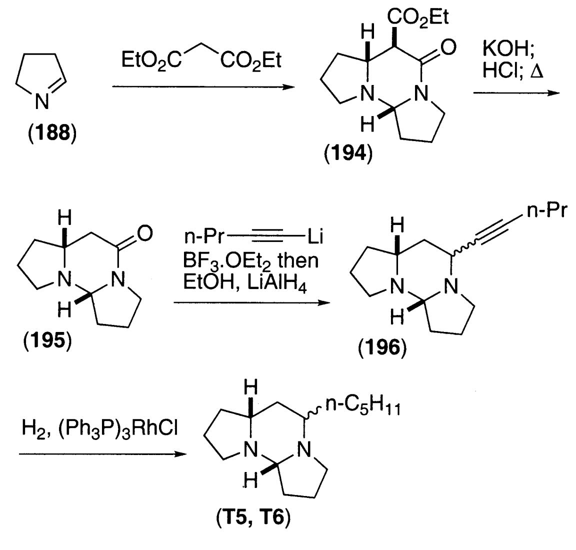
of 4-aminobutanal (**191**) in the presence of excess cyanide, now under somewhat acidic conditions, directly delivered the tetraponerine skeleton (**192**). Reductive removal of the cyanide yielded tetraponerine-6 (**T6**). This final procedure places the pentyl side chain in an equatorial position.

Alternatively, the β-aminoketone (**190**) could be *N*-protected and used in the reductive alkylation of the same protected 4-aminobutanal (**191**) (Scheme 67). This yielded a mixture of diamines (**193**) in an approximately 1:1 ratio. Routine protecting group chemistry then yielded a separable mixture of tetraponerines-5 and -6 (**T5**, **T6**). Although this may not be an elegant route to these compounds, it served its purpose, i.e. the provision of material to compare with the scarce natural products.



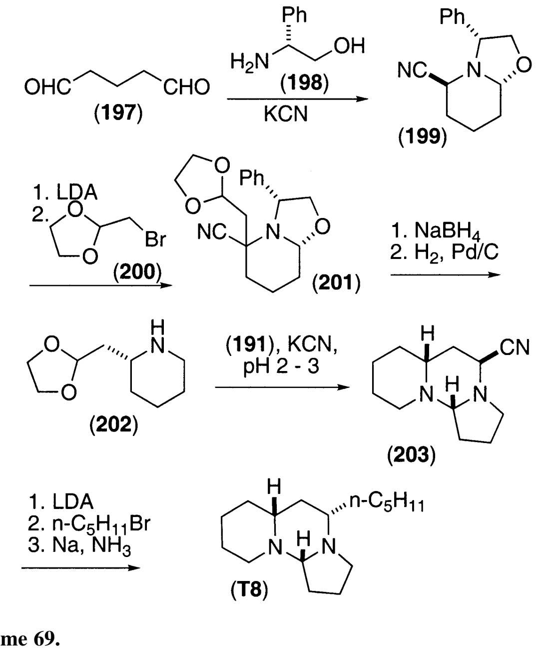
Scheme 67.

A very concise route to one group of tetraponerines using the same imine (**188**) has been reported.[52] Condensation between 2 equiv. of the imine (**188**) and one equivalent of diethyl malonate yielded the tricycle (**194**) (Scheme 68). After removal of the superfluous ester group, the lactam (**195**) was treated with various carbon nucleophiles, followed by reducing agents. In contrast to the results of Jones (Scheme 4), only less basic carbanions such as acetylides were effective. The products, (**196**), were converted routinely to tetraponerines-5 and -6, (**T5**, **T6**).

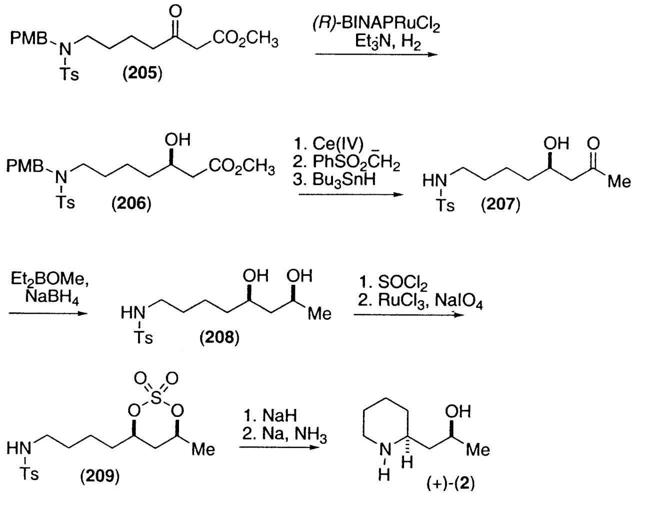


Scheme 68.

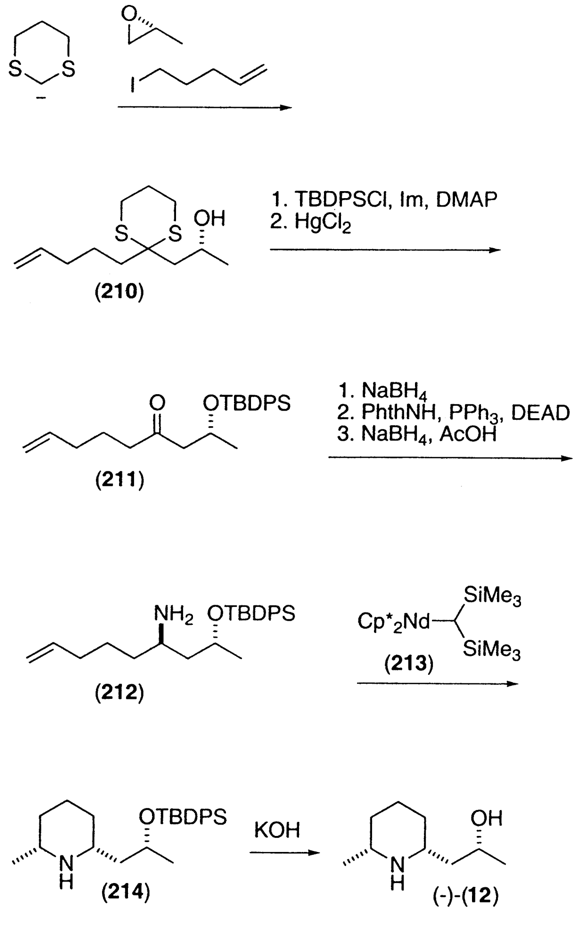
The chemistry of imines and cyanide has also been applied to the synthesis of tetraponerine-8 (**T8**), which contains a piperidine ring, by application of the CN (*R*,*S*) method (Scheme 69).[53] Condensation of the chiral aminoalcohol (**198**) and glutardialdehyde (**197**) in the presence of cyanide yielded the aminal (**199**), containing the required piperidine ring. Alkylation α to the cyano group, followed by removal of the cyanide, yielded a single piperidine stereoisomer (**201**) (the use of BuLi, rather than LDA, resulted in nucleophilic attack on the nitrile).[54] Removal of the chiral auxiliary and a second condensation yielded the tricyclic core (**203**). The remaining side chain was introduced by alkylation and reductive removal of the cyanide.



Scheme 69.

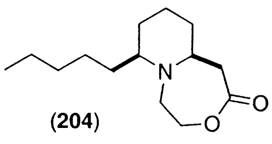


Scheme 70.



Scheme 71.

The same strategy has been applied to the synthesis of all eight of the tetraponerines,[55] and also to the ladybird beetle alkaloid, calvine (**204**).[56]

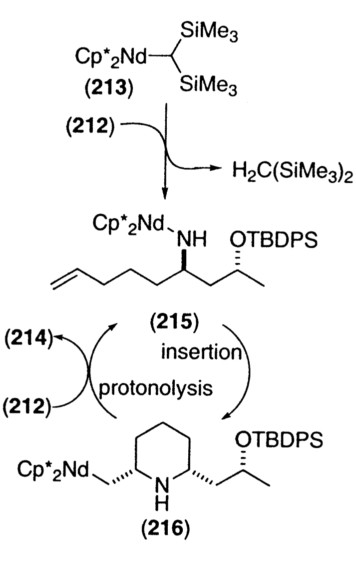


(**204**)

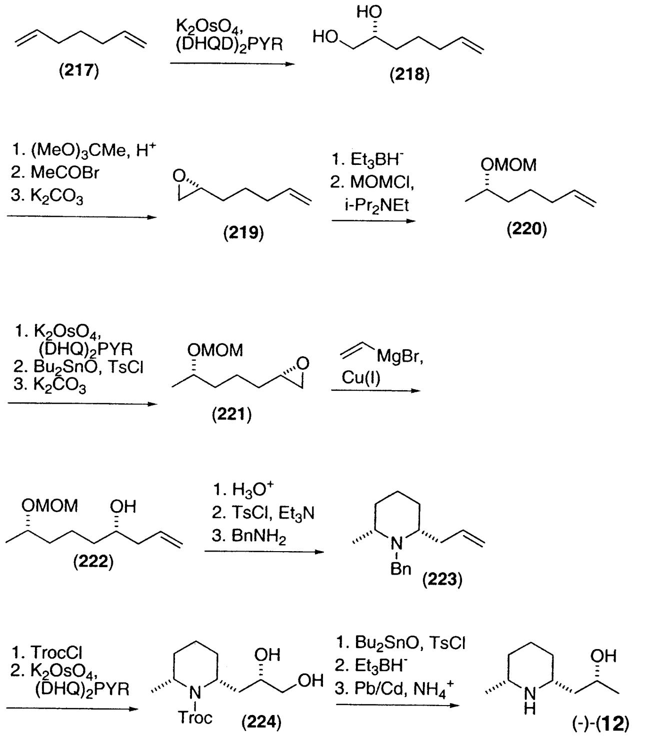
Gallagher synthesised sedridine (**2**) from an acyclic presursor (Scheme 70).[57] The β-ketoester (**205**) was reduced under Noyori conditions and then converted to the methyl ketone (**207**). *syn*-Selective reduction yielded the diol (**208**) that was converted to a 1,3-cyclic sulfate (**209**). Base treatment, followed by acidic work-up, resulted in cyclisation. Finally deprotection gave sedridine (**2**). The synthesis is particularly notable for its use of a 1,3-cyclic sulfate, rather than the more common 1,2-cyclic sulfate.[58]

Molander has reported a synthesis of pinidinol (**11**) based on the formation of the piperidine ring by insertion of an alkene into a nitrogen–lanthanide bond (Scheme 71).[59] The substrate was prepared by a one-pot alkylation of dithiane with an epoxide and an alkenyl iodide. After protection of the alcohol and unmasking of the ketone, the reduction was moderately stereoselective. The new alcohol group was converted routinely into a primary amine. Model systems had indicated that a large lanthanide with bulky ligands would result in the best stereoselectivity, and therefore $Cp^*NdCH(SiMe_3)_2$ (**213**) was chosen. The catalytic cycle involves conversion of an aminolanthanide (**215**) to an alkyl lanthanide (**216**) (Scheme 72). This species is protonated by another molecule of the amine (**212**) to liberate the product (**214**) and maintain the cycle. Under modified conditions, it is possible to use more highly substituted alkenes in these cyclisations.[60]

A multistep synthesis of pinidinol (**11**) relies on three separate asymmetric dihydroxylations (ADs) to install the three chiral centres (Scheme 73).[61] Mono-dihydroxylation of 1,6-heptadiene gave a diol which could be partially deoxygenated by closure to an epoxide and nucleophilic reduction. The remaining alkene underwent the second dihydroxylation. This time, closure to the epoxide permitted the introduction of a third alkene unit as a cuprate. Conversion of the two oxygen groups to tosylates was then followed by closure of the heterocycle. After a change of protecting groups, the third AD was followed by removal of the superfluous hydroxyl moiety and deprotection. While the sequence illustrated in Scheme 73 gives the natural



Scheme 72.



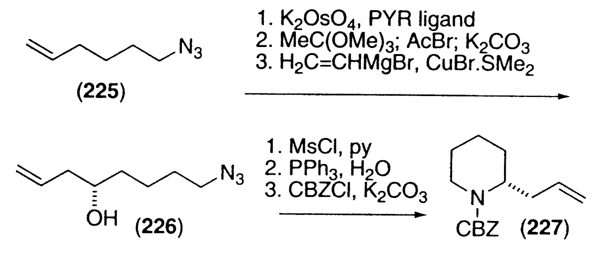
Scheme 73.

product, the appropriate choice of AD mixes can lead to any of the possible stereoisomers.

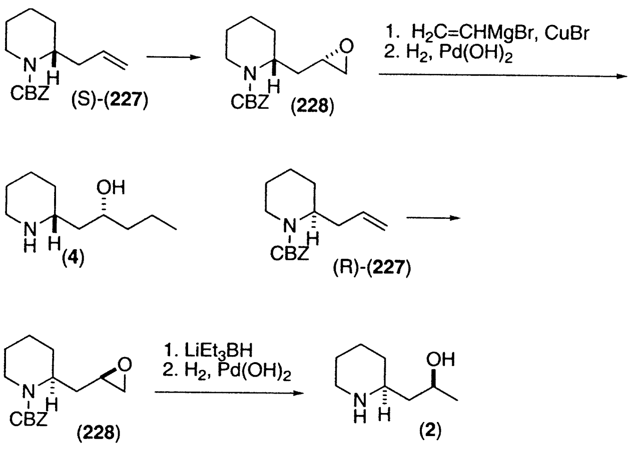
The same group has also used a mutiple-AD strategy to prepare a number of sedum alkaloids, including sedridine (**2**) (Scheme 74).[62] The strategy allows the synthesis of any stereoisomer by judicious choice of chiral ligand in the AD reaction. The piperidine was formed by AD of unsaturated azide (**225**) and routine conversion of the resulting diol to a homoallylic alcohol (**226**). The corresponding mesylate underwent cyclization when the azide group was reduced.[63]

An unexceptional sequence converted the new terminal alkene (**227**) to the epoxide (**228**) which could be opened with an in situ vinyl cuprate, followed by hydrogenation, to give halosaline (**4**) (Scheme 75). Reduction of the enantiomeric epoxide, prepared analogously, yielded sedridine (**2**).

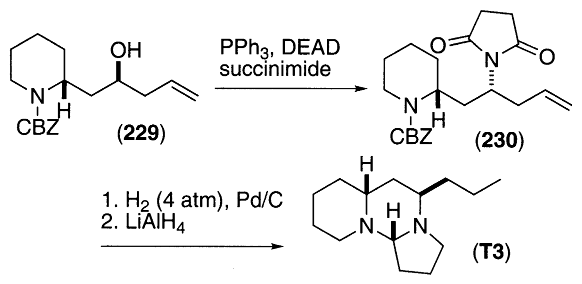
By taking advantage of the ability of succinimide to participate in Mitsunobu reactions, intermediates in these pathways could be converted to tetraponerine alkaloids (Scheme 76) according to the procedure of Merlin et al. (Scheme 39).



Scheme 74.

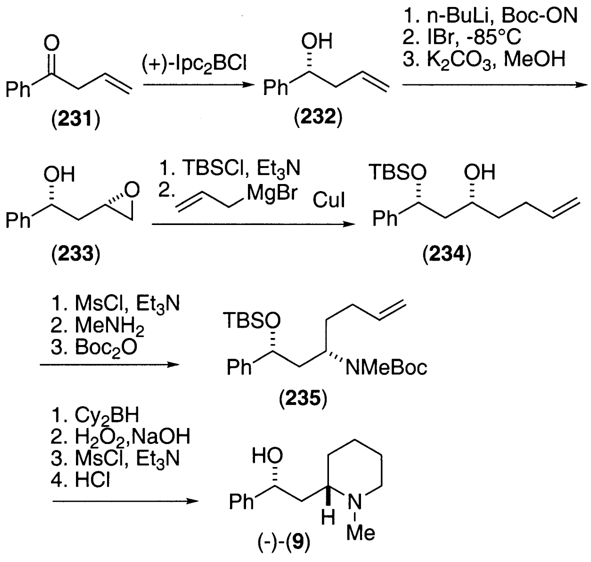


Scheme 75.



Scheme 76.

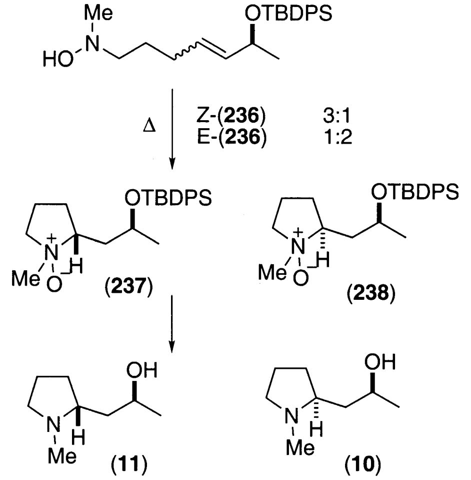
A straightforward synthesis of (−)-allosedamine (**9**) has been reported very recently by Felpin and Lebreton (Scheme 77).[64] Asymmetry was introduced by reduction of the surprisingly stable non-conjugated ketone (**231**). The alcohol (**232**) was converted to the epoxide (**233**) using the cyclo-iodination method of Cardillo. After protection, ring opening with an allyl cuprate species, generated in situ, gave the second alcohol (**234**). This was converted to



Scheme 77.

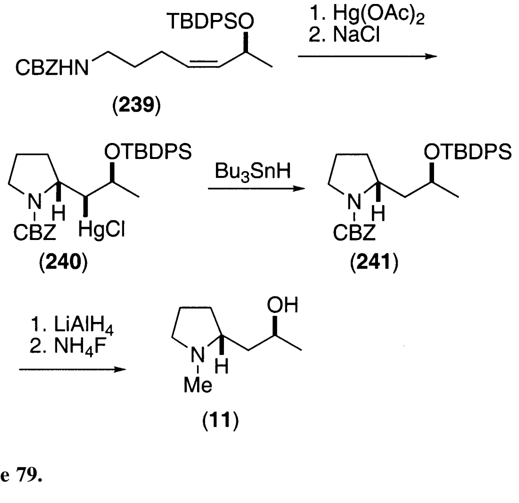
the amine derivative (**235**) by substitution of the corresponding mesylate and a subsequent protection step. Methylamine was the nucleophile of choice as the use of azide resulted in decomposition via intramolecular cycloaddition. Hydroboration–oxidation of the alkene moiety of (**235**) allowed subsequent ring closure on deprotection to complete the synthesis.

The reverse-Cope elimination has been applied by Knight to the synthesis of hygroline (**10**) (Scheme 78).[65] This rarely-used reaction is very sensitive to the structure of the hydroxylamine starting material. Few six-membered rings can be formed, a serious obstacle to its application to the sedum alkaloids. In addition, the reaction is inhibited by alkene substitution, although a nearby ether substituent has an activating effect.



Scheme 78.

Knight found that an ether substituent could also influence the stereochemistry of the reaction. The *cis* and *trans* isomers of the hydroxylamine (**236**) were prepared using ethyl lactate as the source of the chiral centre. All underwent the reverse-Cope cyclisation, the *N*-methyl substrates being distinctly faster. Modest diastereoselectivity was observed. The products, (**237**) and (**238**), were converted to hygroline (**10**) and pseudohygroline (**11**) by reduction of the *N*-oxide and desilylation.



Scheme 79.

An alternative method of addition of nitrogen to an alkene has been put forward by Perlmutter (Scheme 79).[66] Treatment of the *Z*-alkene (**239**) with mercuric acetate, followed by radical demercuration, yielded, after manipulation of the protecting groups, pseudohygroline (**11**). The cyclisation shows excellent diastereoselectivity, giving (**240**) with only a small amount of the isomeric mercurial being formed which could be easily removed by crystallization.

Acknowledgements

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Biographical sketch

Roderick Bates was born in Hampshire, England in 1965. He received a BSc from Imperial College, London in 1986 and a PhD in 1989 under the guidance of Professor Steven V. Ley. After a postdoctoral stay at Colorado State University with Professor L. S. Hegedus, he moved to the University of North Texas as an Assistant Professor, then to Chulalongkorn University in Bangkok, Thailand. He is currently a researcher at the Chulabhorn Research Institute, working on methodology for natural product synthesis and applications of transition metals, amongst which cobalt is his current favourite.

Kanicha Sa-Ei, from Fang in Northern Thailand, graduated from Chiang Mai University in 2000 with a BS in Chemistry and moved to Chulalongkorn University in Bangkok to pursue organic chemistry research. He plans to graduate with an MS degree in 2002 under the guidance of Professor Roderick Bates. His current research focuses cyclofunctionalisation reactions catalysed by palladium (II). He will continue his studies at Wayne State University, Detroit, Michigan.