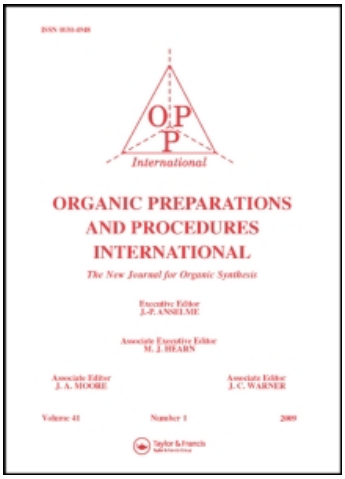

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RECENT ADVANCES IN THE STEREOSELECTIVE SYNTHESIS OF HYDROXYLATED PYRROLIZIDINES. A REVIEW

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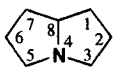
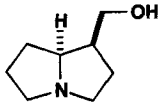
INTRODUCTION

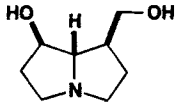
The 1-azabicyclo[3.3.0]octane skeleton (**1**) (pyrrolizidine, hexahydropyrrolizine) represents the nucleus of a diverse group of alkaloids isolated from both plants and animal sources throughout the world.[1] Among the most interesting are those alkaloids that have been isolated from species in the Boraginaceae family, in the Asteraceae (Compositae), and in the Fabaceae (Leguminosae). Naturally occurring pyrrolizidines can be subdivided into two main domains based on the structural features present in the heterocycle core: the *necine* bases, such as isoretronecanol (**2**), hastanecine (**3**), and rosmarinecine (**4**), with a one carbon branch at C-1, and the *alexines*, such as alexine (**5**) and australine (**6**), with a one carbon branch at C-3 (Figure 1).



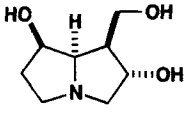
1-azabicyclo[3.3.0]octane (**1**)



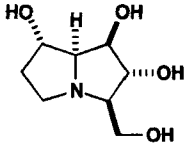
isoretronecanol (**2**)



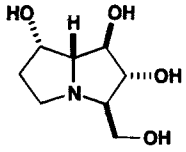
hastanecine (**3**)



rosmarinecine (**4**)



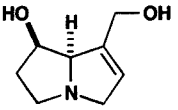
alexine (**5**)



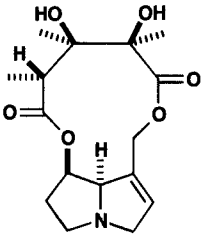
australine (**6**)

FIG. 1

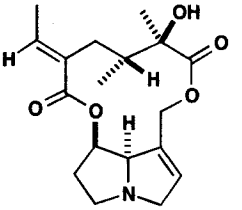
The necine series is further subdivided based on the presence of a 1,2-unsaturation (*e.g.* **7**) or a single bond. The nitrogen bases vary in substitution and chirality, often containing a number of isolated or contiguous hydroxyl functions. As a common feature, the majority of natural necine alkaloids, *e.g.* **8** and **9**, are composed of a hydroxylated pyrrolizidine core (the necine base) spanned by a macrocyclic moiety through one or more ester linkages (the necic acid). Typically, the acidic unit harbours a variety of substituents with multiple chiral centers (Figure 2). On the contrary, the alexines are found in nature as unconjugated bases.



retronecine (**7**)



monocrotaline (**8**)



integerrimine (**9**)

FIG. 2

The pyrrolizidines, both natural and synthetic, have been shown to exhibit diverse biological activities even in their unconjugated forms, ranging from hepatotoxicity and carcinogenicity to antispasmodic, anaesthetic, and antiinflammatory activities.[2] In addition, some of these derivatives have potential as glycosidase inhibitors and antiviral agents, both as free bases and as alkaloidal glycosides.[3]

The combination of the potent biological activities and intriguing multichiral architecture has made hydroxylated pyrrolizidines the subject of stereocontrolled assembly of both natural compounds and synthetic congeners.[4,5] The present article mainly highlights recent approaches to saturated hydroxylated pyrrolizidines, including our own results, which utilize enantiomerically pure precursors and exploit diastereoselective synthetic procedures. Also included in the present discussion are a few syntheses of racemic compounds where the control of the relative stereochemistry of the various chiral centers in the molecules represents a key issue. Synthetic procedures to unsaturated pyrrolizidine derivatives are excluded, as are those processes directed toward preparation of complex conjugated alkaloids and alkylated derivatives lacking hydroxyl functions. These topics have been the subjects of a number of recent accounts.[4,5]

The review is subdivided into three main sections: (I) synthesis of necines; (II) synthesis of alexines; (III) synthesis of miscellaneous hydroxylated congeners. The necine section is further divided into: (1) syntheses drawing from chiral non-racemic precursors; (2) procedures exploiting chiral auxiliaries; (3) diastereoselective entries to racemic compounds.

The literature cited covers the period 1989 to Fall 1995. Work prior to 1989 was covered by excellent articles and book chapters.[6] A series of annual reports reviewing the chemistry of pyrrolizidine alkaloids is available.[5]

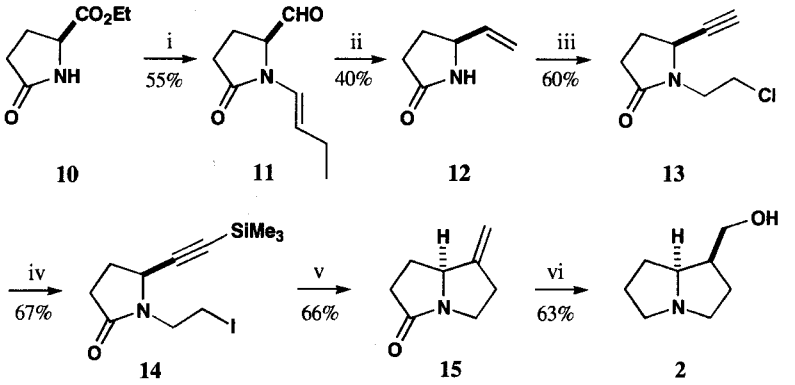
I. SYNTHESIS OF NECINES

The most common synthetic procedures to chiral non-racemic and chiral racemic necine bases involve condensation of heteroatom-containing substrates by means of various elongation reagents. In the homochiral domain, the majority of the approaches to simple necines utilizes proline derivatives or suitable amino acids as substrates of choice, being the chirality of the precursors trans-

ferred to the newly created stereocenters of the target. There are also few asymmetric syntheses exploiting carbohydrates as chiral sources mainly targeted to the preparation of diol and triol derivatives. Some examples use asymmetric catalysis or enzyme-based procedures to introduce chirality into a given precursor which is then elaborated into a pyrrolizidine by way of enantioconservative chemical transformations. Often, a chiral auxiliary derived from the natural chiral pool is the template with which the homochiral pyrrolizidine frame is constructed. Racemic diastereoselective syntheses utilize diverse chemistry to install the substituents in the pyrrolizidine nucleous with proper control of the relative stereochemistry.

1. Using Chiral Non-racemic Precursors

Numerous chemists have responded to the challenge of creating de novo the multichiral necine cores, and substantial advance has been reported. In a remarkable asymmetric synthesis of naturally occurring (–)-isoretronecanol (**2**),[7] ethyl pyroglutamate (**10**), quickly obtainable from L-glutamic acid, was used as the chiral non-racemic building block.

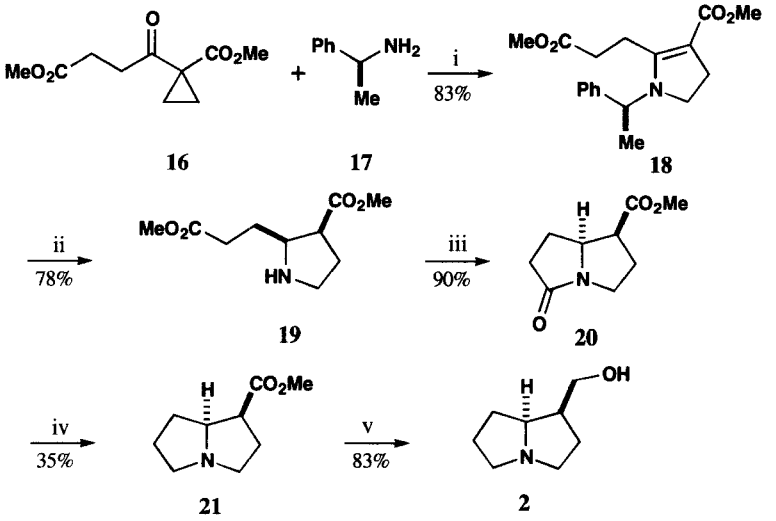


Scheme 1. *Reagents and conditions*: i, butanal, P_2O_5, toluene; then $NaBH_4$; then DCC, DMSO, H_3O^+, heat; ii, $Ph_3PCH_3{}^+Br^-$/Bu^{t}OK, THF; then HCl; then aq. NaOH, 95°; iii, Br_2; then Bu^{t}OK, Bu^{t}OH; then $BrCH_2CH_2Cl$, THF; iv, Bu^{n}Li, Me_3SiI; then NaI, acetone; v, AIBN, Bu_3SnH, benzene; then *p*-TsOH; then AcOH, CH_2Cl_2, DMAP; vi, $BH_3{\cdot}SMe_2$; then H_2O_2, NaOH.

In the event, the original stereocenter was retained as the bridgehead carbon C-8 in **2**, while imparting diastereoselectivity during the last stage of the sequence. The key intermediate of the synthesis was (*S*)-5-vinylpyrrolidin-2-one (**12**), obtained, in turn, from pyroglutamic acid derivative **10**. As shown in Scheme 1, reaction of **10** with butanal and subsequent reduction of the ester moiety with $NaBH_4$ gave a protected 5-hydroxymethylpyrrolidin-2-one intermediate, which was directly transformed to aldehyde **11** by Moffatt oxidation.

A series of three consecutive reactions including Wittig one-carbon elongation, acidic deprotection, and re-annulation of the formed open-chain amino acid by basic treatment afforded vinyl lactam **12** in 22% overall yield from **10**. The next reaction of the synthesis was the conversion of

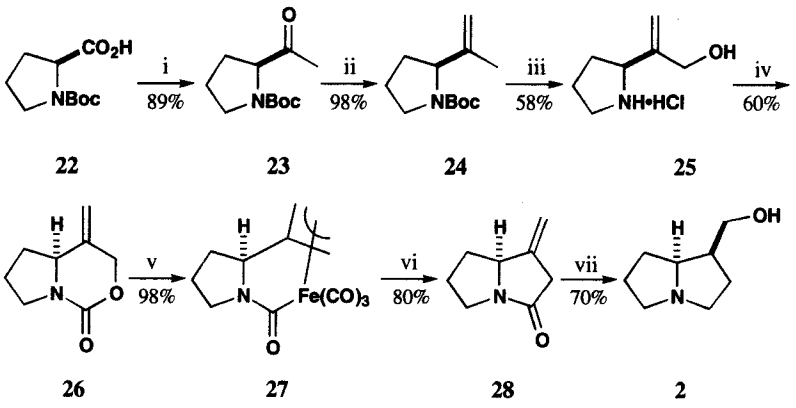
the vinyl moiety embodied in **12** into an ethynyl group. Bromination of **12** followed by exposure to *tert*-butoxide in *tert*-butyl alcohol gave an ethynyl intermediate which was transformed to protected pyrrolidinone **13** by treatment with 1-bromo-2-chloroethane. Reaction of **13** with butyllithium, quenching with iodotrimethylsilane, and Finkelstein exchange gave iodide **14** in a good 67% yield. The construction of the pyrrolizidine ring was effected by radical cyclization of **14** promoted by AIBN/Bu_3SnH; subsequent desilylation with toluene-*p*-sulfonic acid followed by reaction with acetic acid and DMAP, furnished bicyclic lactam **15**. Hydroboration-oxidation of **15**, while converting the alkene moiety to hydroxymethyl function with exclusive facial selectivity, simultaneously reduced the lactam carbonyl to give (–)-isoretronecanol (**2**).



Scheme 2. *Reagents and conditions*: i, toluene, reflux; ii, H_2, PtO_2, MeOH; then H_2, Pd/C, MeOH; iii, toluene, 90°; iv, Lawesson's reagent, toluene, reflux; then MeI; then $NaBH_4$, MeOH; v, $LiAlH_4$, THF, -80°.

(*S*)-α-Methylbenzylamine (**17**) was the inexpensive chiral source in a short asymmetric synthesis of the same necine derivative **2**.[8] The opening move was the reaction of cyclopropane **16** with homochiral amine **17** to furnish dihydropyrrole **18** (Scheme 2). Catalytic hydrogenation of the dihydropyrrole gave a major *cis*-diastereoisomer with a high margin of selectivity (90% de) which was converted to pyrrolidine **19** by hydrogenolytic removal of the *N*-methylbenzyl moiety. Ring closure to bicyclic lactam **20** was obtained by simply heating **19** in toluene. All that remained was the reduction of the lactam moiety accompanied by conversion of the carbomethoxy group to hydroxymethyl; and this was obtained by treating **20** with Lawesson's reagent followed by reduction of the formed thiolactam to give **21** and subsequent exposure to $LiAlH_4$ to afford the target compound **2**.

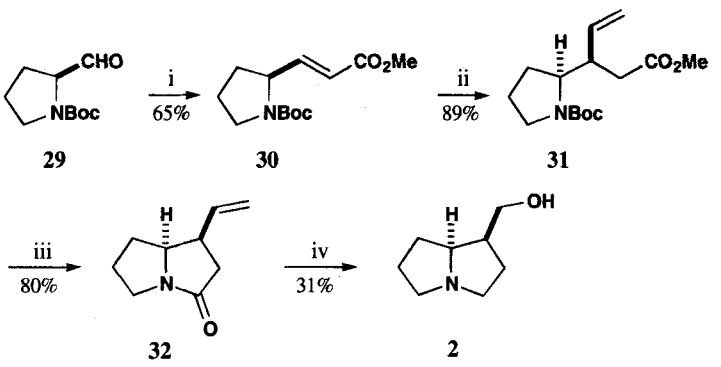
To develop a short entry to **2**, Ley and Knight[9] utilized commercially available *N*-Boc-L-proline (**22**) as a chiral pyrrolidine template (Scheme 3).



Scheme 3. *Reagents and conditions*: i, CDI, THF; then MeONHMe·HCl; then MeMgCl, THF, 0°; ii, $Ph_3P{=}CH_2$, Et_2O, 0°; iii, SeO_2, Bu^tOOH, CH_2Cl_2, 35°; then HCl; iv, MeOCOCl, Et_3N, CH_2Cl_2; then NaH, toluene; v, $Fe_2(CO)_9$, benzene, ultrasonication; vi, CO, 305 atm., benzene, 105°; vii, BH_3,THF, reflux; then NaOH, H_2O_2; then HCl, MeOH, reflux.

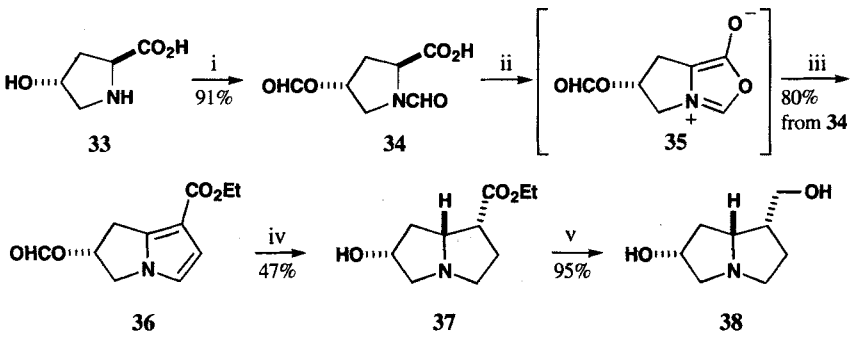
Conversion of the proline derivative **22** into the corresponding *N*-methyl-*N*-methoxy amide via an acyl imidazolide and subsequent treatment of the formed amide with methyl magnesium chloride gave ketone **23**, which was transformed to alkene **24** by Wittig reaction. Methyl-to-hydroxymethyl oxidation within **24** using selenium dioxide and *tert*-butyl hydroperoxide followed by acidic *N*-deprotection furnished allylic alcohol hydrochloride salt **25**. Treatment of **25** with methyl chloroformate, followed by base, gave cyclic carbamate **26**, which was transformed into the π-allyltricarbonyliron lactam complex **27** using diiron nonacarbonyl under ultrasonic irradiation. Exhaustive carbonylation under forcing conditions was the way in which the complex **27** was converted into the corresponding lactam **28**. Finally, hydroboration-oxidation reaction furnished (–)-isoretronecanol (**2**) stereospecifically, which was isolated as its stable picrate salt.

Again, L-proline was the chiral precursor of an expeditious synthesis of (–)-isoretronecanol (**2**).[10] According to Scheme 4, two-carbon homologation of *N*-Boc-L-prolinal (**29**) using methoxycarbonylmethylene triphenylphosphorane produced the *E*-configured seven carbon enoate **30**, which underwent stereoselective addition of divinylcuprate reagent to produce **31** in excellent yield and remarkable diastereofacial preference favoring the *syn* isomer (6:1 *syn*/*anti* ratio). After hydrolytic cleavage of the Boc group, the cyclization to **32** was achieved using DMAP as catalyst in refluxing pyridine. The final reactions simply involved oxidative cleavage of the vinyl moiety embodied in **32** with $NaIO_4$-$RuCl_3$ reagents, diazomethane esterification of the formed carboxylic acid to a bicyclic lactam, and exhaustive $LiAlH_4$ reduction to (–)-isoretronecanol (**2**) (15% overall yield from **29**). The minor *anti* isomer resulted from the organocuprate addition to **30** was also exploited to produce (–)-trachelanthamidine (compound **44**, *vide infra*) by the same set of reactions.



Scheme 4. *Reagents and conditions*: i, $Ph_3P{=}CHCO_2Me$, THF; ii, $(CH_2{=}CH)_2CuLi$, TMSCl, -30°; iii, HCl, AcOH; then pyridine, DMAP, reflux; iv, $NaIO_4$, $RuCl_3$; then CH_2N_2; then $LiAlH_4$.

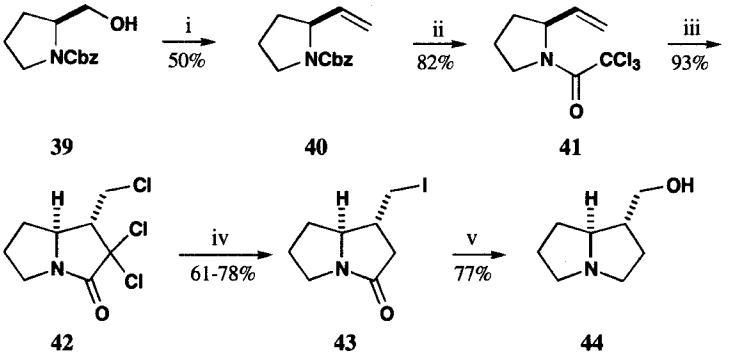
In a study directed towards the synthesis of potentially bioactive macrocyclic dilactones incorporating a saturated pyrrolizidine diol, Robins *et al.*[11] envisioned hydroxylated necine **38** as a suitable pyrrolizidine component. Thus, according to a chironic approach (Scheme 5), (–)-4-hydroxy-L-proline (**33**) was employed as the starting material to access pyrrolizidine **38**.



Scheme 5. *Reagents and conditions*: i, Ac_2O, HCO_2H; ii, Ac_2O; iii, $HC{\equiv}CCO_2Et$; iv, NH_3; then H_2, Rh/C; v, $LiAlH_4$.

N,O-Diformyl derivative **34**, obtained from proline **33** in 91% yield, was subjected to regiospecific 1,3-dipolar cycloaddition with ethyl propiolate, affording dihydropyrrolizine **36** through the intermediacy of mesoionic oxazolone **35**. Base-promoted removal of the formyl protecting group within **36** followed by stereoselective *cis*-hydrogenation of the aromatic portion of the heterocycle from the less hindered β-face (Rh/C as a catalyst) produced saturated ester **37** as the sole detectable isomer. The final reduction of **37** with $LiAlH_4$ provided hydroxylated necine **38** in a good 33% overall yield from proline **33**.

The cyclization of a radical derived from homolysis of the C-Cl bond in a *N*-allyl-α-trichloroacetamide by a copper(I)-catalysis was the key step with which Seijas and colleagues[12] projected and executed the synthesis of the naturally occurring alkaloid (–)-trachelanthamidine (**44**). Protected L-prolinol **39**, readily available from L-proline, was devised as the chiral starting material. Thus, as shown in Scheme 6, Swern oxidation of the hydroxymethyl function of **39** and subsequent Wittig elongation gave vinylpyrrolidine **40**. Cbz-Protected pyrrolidine **40** was then transformed into the key trichloroacetamide intermediate **41** by acidic deprotection followed by treatment with trichloroacetyl chloride and DMAP.

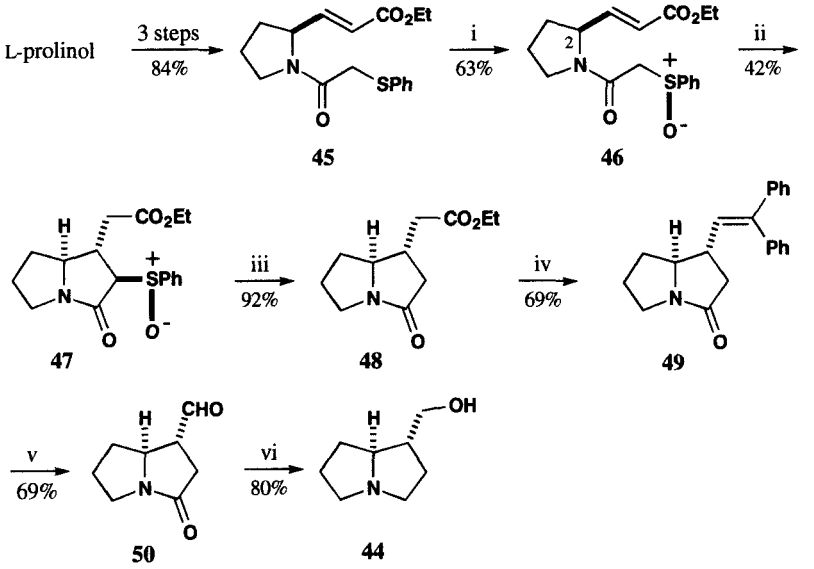


Scheme 6. *Reagents and conditions*: i, Swern oxidation; then $Ph_3P{=}CH_2$; ii, HBr, AcOH; then CCl_3COCl, DMAP; iii, CuCl, MeCN, 150°; iv, H_2, Pd/C or Bu_3SnH; then NaI, acetone; v, AgOAc; then $LiAlH_4$.

The radical cyclization to **42** was achieved by heating **41** in acetonitrile in the presence of CuCl in a sealed tube and proved to be completely diastereoselective. Hydrogenolytic or Bu_3SnH-promoted removal of the two geminal chlorine atoms in lactam **42** and subsequent chlorine-to-iodine Finkelstein exchange gave iodide **43**, which was converted, in the final stages of the sequence, to the expected compound **44** by two consecutive reactions, namely the replacement of the iodine atom by an acetoxy function and simultaneous reduction of the lactam and acetoxy groups.

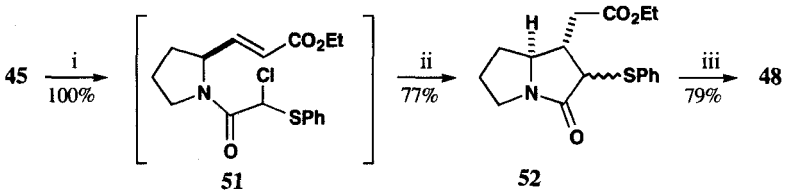
With L-prolinol as chiral precursor, Ikeda and coworkers[13] examined an intramolecular Michael reaction of suitably functionalized α-phenylsulfinylacetamide of type **46** to access the same alkaloid **44**. As shown in Scheme 7, treatment of the major diastereomeric sulfoxide **46**, obtained from L-prolinol via the homologated intermediate **45**, with a catalytic amount of sodium ethoxide in ethanol gave the bicyclic lactam **47**, via intramolecular conjugate addition of the enolate to the α,β-unsaturated ester moiety. Unfortunately however, prior to cyclization, substantial epimerization at C-2 carbon occurred, likely arising from base-promoted abstraction of the acidic proton in 2-position, and this led to concomitant formation of a substantial amount (39%) of an unwanted diastereoisomer (not shown). After chromatographic separation of the mixture, isomer **47** was desulfurized with Raney nickel in ethanol to give optically pure pyrrolizidinone **48**, which was finally transformed into (–)-trachelanthamidine (**44**) in four steps. Thus, reaction of **48** with excess phenylmagnesium bromide

followed by treatment of the resulting alcohol with methanesulfonyl chloride in triethylamine gave the diphenylethene **49** in 69% yield. Ozonolysis of **49** followed by treatment with dimethylsulfide afforded the aldehyde **50** which was directly reduced to the target **44** by hydride treatment.



Scheme 7. *Reagents and conditions*: i, $NaIO_4$, aq. acetone or MCPBA, CH_2Cl_2; ii, NaOEt, EtOH, 0°; iii, Raney nickel, EtOH; iv, PhMgBr; then MsCl, Et_3N; v, O_3, Me_2S; vi, $LiAlH_4$, THF, reflux.

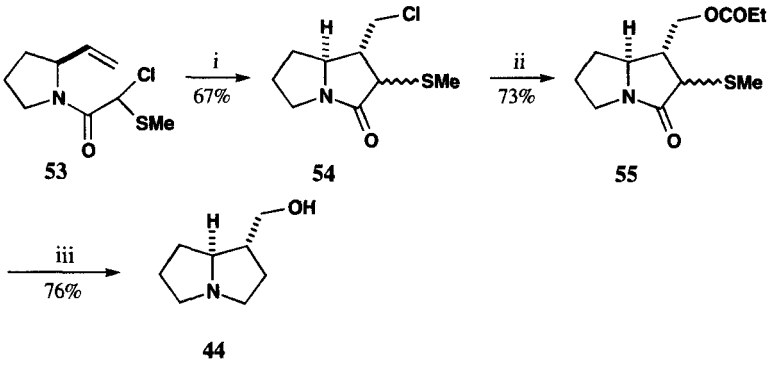
In order to overcome the difficulties related to the base-catalyzed intramolecular annulation of **46**, the same authors[14] developed an alternative procedure to convert **45** into bicyclic lactam **48** in a diastereocontrolled fashion. This goal was reached by adopting a tributyltin hydride-mediated radical cyclization protocol (Scheme 8). Chlorination of **45** with *N*-chlorosuccinimide gave the sulfide **51**, in quantitative yield, which was cleanly cyclized to **52** upon exposure to tributyltin hydride-AIBN in refluxing toluene. Although **52** was obtained as a 6:4 diastereomeric mixture, the subsequent nickel Raney-promoted desulfurization gave rise to a single enantiomer **48**, the key intermediate of the previously disclosed synthesis.



Scheme 8. *Reagents and conditions*: i, NCS; ii, Bu_3SnH, AIBN, toluene, reflux; iii, Raney nickel.

A highly improved protocol to **44** was devised by the same Japanese group[15] based on ruthenium-catalyzed chlorine atom transfer cyclization of a *N*-allylic thioacetamide of type **53**. As shown

in Scheme 9, the sequence started from chloride **53** which was obtained in six steps from L-prolinol. Heating a benzene solution of **53** in the presence of $RuCl_2(PPh_3)_3$ at 140 ° gave bicyclic lactam **54** as a 7:3 C-2 epimeric mixture. According to an optimal protocol, treatment of **54** with cesium propanoate in boiling chlorobenzene in the presence of 18-crown-6 ether resulted in preferential formation of bicyclic lactam **55** contaminated with a trace amount of an unwanted cyclopropane derivative.



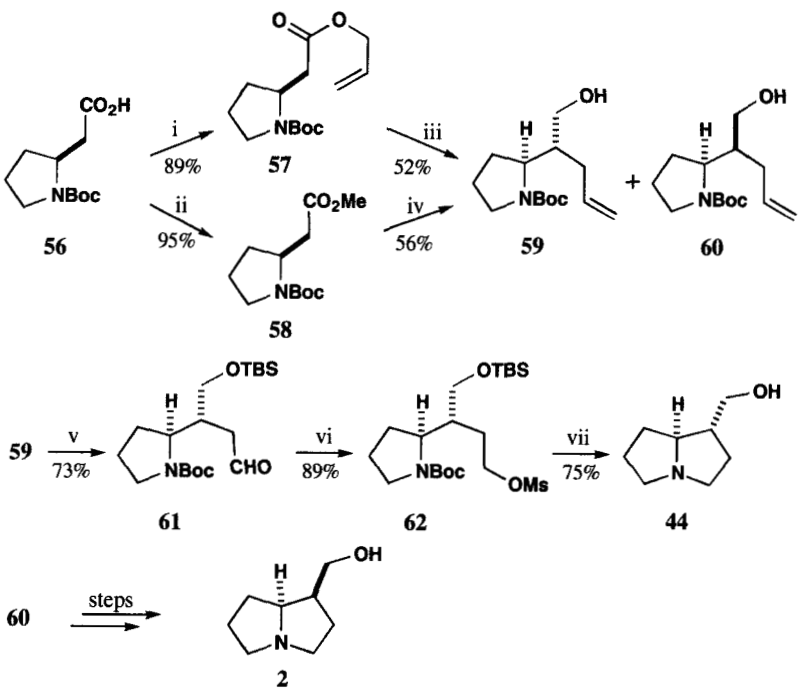
Scheme 9. *Reagents and conditions*: i, $RuCl_2(PPh_3)_3$, benzene, 140°; ii, $EtCO_2Cs$, chlorobenzene, reflux, 18-crown-6 ether; iii, Raney nickel; then LiAlH4, THF, reflux.

Compound **55** was then desulfurized with Raney nickel to afford a lactam intermediate as a single stereoisomer, which was finally transformed to (–)-trachelanthamidine (**44**) by reduction with $LiAlH_4$ in refluxing THF. Overall, the reaction sequence from **53** comprised four steps (10 steps from L-prolinol) with a good 37% overall yield.

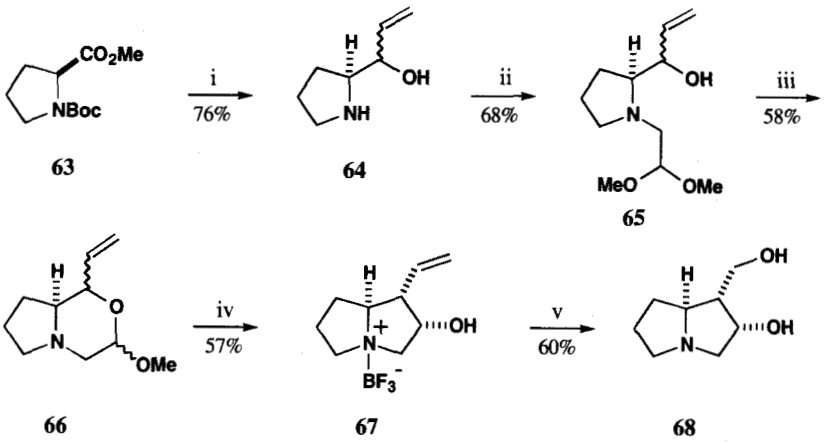
A brief asymmetric approach to both necines **2** and **44** was introduced by Knight [16,17] utilizing (*S*)-homoproline **56**. The key epimeric intermediates **59** and **60** were obtained as a mixture (at best 1.5:1, typically 1-1.2:1) by two alternative non-selective transformations as depicted in Scheme 10 via intermediates **57** and **58**, respectively. After chromatographic separation, *erythro* isomer **59** was protected as the TBS ether and the alkene function then cleaved by oxidative excision of the terminal methylene carbon to give aldehyde **61**.

Sequential $NaBH_4$ treatment and mesylation allowed the synthesis of the advanced intermediate **62**, which was easily transformed to **44** by removal of the Boc and silyl ether protections and base-catalyzed ring closure. Analogously, *threo* diastereoisomer **60** was converted to (–)-isoretronecanol (**2**).

Zirconium-mediated diastereoselective ring contraction of vinylmorpholine derivatives like **66** was the pivotal reaction with which Taguchi and coworkers[18] synthesized (–)-macronecine (**68**), the enantiomer of naturally occurring (+)-macronecine (Scheme 11). DIBALH reduction of **63** to an aldehyde derivative and subsequent addition of vinylmagnesium bromide gave, after deprotection, amino alcohol **64** as a 5:1 diastereomeric mixture. *N*-Alkylation of the free amine with α-bromoacetaldehyde dimethyl acetal in the presence of the Hünig base, afforded alcohols **65** which were



Scheme 10. *Reagents and conditions*: i, allylic alcohol, DCC, DMAP; ii, $SOCl_2$, MeOH; iii, LHMDS, THF, -78°; then TMSCl, reflux; then MeOH, H_2O; then CH_2N_2, Et_2O; then DIBALH, $BF_3{\cdot}OEt_2$; iv, LHMDS, THF, HMPA, allyl bromide; then DIBALH, $BF_3{\cdot}OEt_2$; v, TBSCl, imidazole, DMF, 35°; then OsO_4, $NaIO_4$; vi, $NaBH_4$; then MsCl, Et_3N, CH_2Cl_2, 0°; vii, TFA, CH_2Cl_2, 0°; then aq. NaOH.



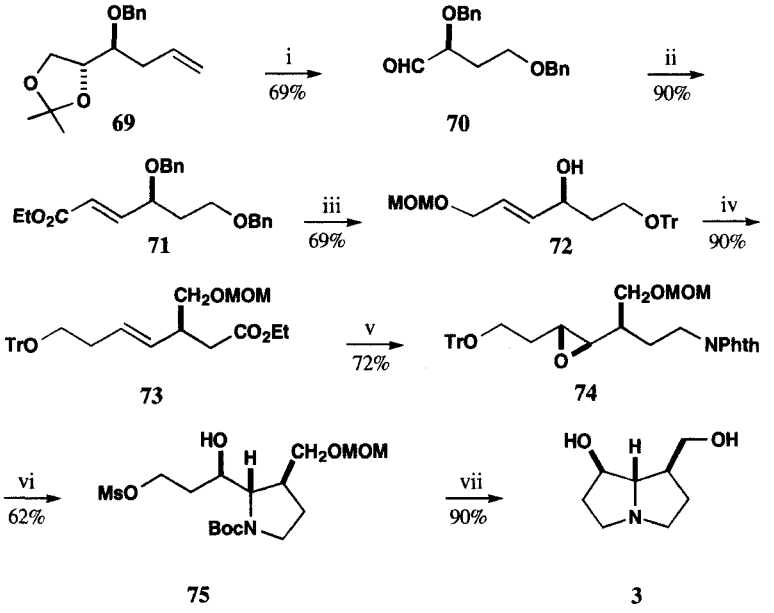
Scheme 11. *Reagents and conditions*: i, DIBALH, THF, -78°; then vinylmagnesium bromide; then TFA; ii, α-bromoacetaldehyde dimethyl acetal, Pr^i_2EtN, MeCN, reflux; iii, TsOH, benzene, reflux; iv, "Cp_2Zr", THF; then $BF_3{\cdot}OEt_2$; v, O_3, -78°; then NaBH4; then aq. NaOH.

converted to bicyclic morpholines **66**, a mixture of four diastereoisomers, via TsOH-promoted ring closure. Reaction of the mixture **66** in THF with zirconocene equivalent "Cp_2Zr", prepared *in situ*

from Cp_2ZrCl_2 with 2 equiv of *n*-butyllithium followed by BF_3 etherate, readily gave pyrrolizidine complex **67** as a single isomer.

Noticeably, the stereochemistry of **67** was not affected by the different stereoisomers present in the mixture **66**. Ozonolysis of **67** to an aldehyde and reduction with $NaBH_4$ followed by decomplexation in aqueous sodium hydroxide gave (–)-macronecine (**68**) in 60% yield, which corresponds to a 10% overall yield from **63**.

A practical multi-step synthesis of hastanecine (**3**) has been devised by Mulzer,[19] focused on a regioselective ortho ester Claisen rearrangement (Scheme 12). Starting with enantiomerically pure triol **69**, obtainable in multigram quantity from 2,3-*O*-isopropylidene-D-glyceraldehyde, intermediate



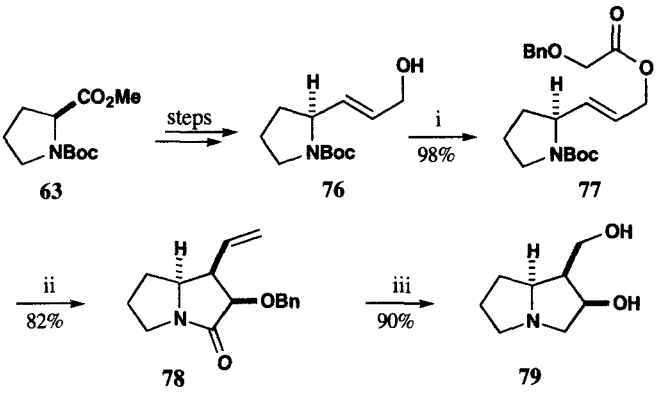
Scheme 12. *Reagents and conditions*: i, O_3, MeOH, -78°; then $NaBH_4$, MeOH, -78° to rt; then BnBr, NaH, DMF; then AcOH, H_2O; then $Pb(OAc)_4$, CH_2Cl_2; ii, $(EtO)_2PCH_2CO_2Et$, NaH, THF; iii, DIBALH, THF, -20°; then MOMCl, Pr^i_2EtN, CH_2Cl_2, 0°; then Na, NH_3, -40°; then TrCl, DMAP, pyridine; iv, $MeC(OEt)_3$, $EtCO_2H$, 100°; v, DIBALH, THF, -20°; then PPh_3, PhthNH, DEAD, THF; then MCPBA, CH_2Cl_2, $NaHCO_3$, 0°; vi, N_2H_4, EtOH; then Boc_2O, Pr^i_2NH, THF; then H_2, Pd/C, cat. HCl; then MsCl, pyridine, CH_2Cl_2; vii, TFA, MeOH.

70 was first prepared, which was homologated to unsaturated ester **71** by a Horner-Wittig protocol and then transformed to the key alcohol **72**. Interestingly, the same intermediate **72** was also prepared, with similar efficiency, adopting a chirospecific Sharpless resolution procedure starting from a suitable racemic six-carbon allylic alcohol derivative. Heating this compound with triethyl orthoacetate resulted in clean formation of the C-3 branched ester **73** via stereoselective ortho ester Claisen rearrangement. A sequence of three reactions, *i.e.* reduction of the ester moiety to a primary alcohol, Mitsunobu amination, and double bond epoxidation ensured conversion of **73** into the major epoxide **74** (3-4:1 diastereomeric ratio), which was elaborated into the pyrrolidine precursor **75** by regio- and

stereoselective ring closure and functional groups manipulation. Acidic cleavage of the carbamoyl protection easily allowed the second annulation to take place producing hastanecine (**3**), the necine base embodied into biologically promising alkaloid hastacine.

The first synthesis of petasinecine (**79**), the necine base of the natural alkaloid petasinine, was reported by the same author[20] using L-proline derivative **63** as the chiral progenitor. As shown in Scheme 13, the sequence features an Ireland-Claisen rearrangement. Methyl ester **63** was first homologated by two carbon atoms to compound **76**, which was then transformed to **77** by simple chemistry.

Treatment of **77** with lithium hexamethyldisilazide and trimethylsilyl chloride resulted in formation of pyrrolizidinone **78** in a single operation with complete diastereoselectivity. Preparation of petasinecine (**79**) was finally completed by conversion of the vinyl group to hydroxymethyl, reduction of the lactam carbonyl, and hydrogenolytic removal of the *O*-benzyl protection.



Scheme 13. *Reagents and conditions*: i, $BnOCH_2COCl$, pyridine; ii, LHMDS, TMSCl, THF, -110 to 0°; then TFA, BuOH; iii, O_3, MeOH, -78°; then $NaBH_4$, MeOH, -78°; then BH_3•THF, THF, 60°; then H_2, Pd/C, MeOH.

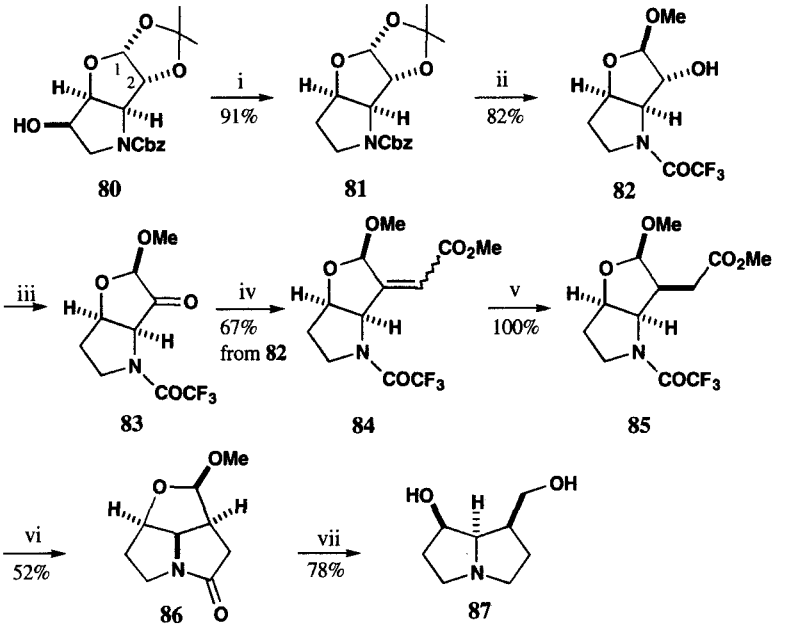
For densely oxygenated homochiral heterocycles, including the necine bases of this report, carbohydrates are attractive starting materials since they are available equipped with a wide variety of hydroxyl substituents and chiralities. At a first glance, the carbohydrate-based approach seems to be less versatile than a strategy exploiting small templates endowed with a single stereocenter; however, the ample availability of carbohydrates strongly facilitates the choice of the precursor suitable to implement a given target compound.

In the strategy adopted by Fleet[21] in his synthesis of platynecine (**87**) from D-glucose, the exocyclic carbon of **87** was derived from C-1 of the starting sugar (*i.e.* **80**), while a two-carbon unit was introduced at C-2 of the sugar via a Wittig elongation (Scheme 14).

Thus, the protected amine **80**, easily available from D-glucose, was transformed to a triflate which, with $NaBH_4$ in acetonitrile, gave the deoxygenated intermediate **81**. After replacement of the Cbz-protecting group with hydrogenolytically stable CF_3CO, methanolysis of the isopropylidene protection gave the methyl furanoside **82** as the dominant anomer (13:1 β/α ratio), in which only

the hydroxyl in 2-position is unprotected. Selective oxidation of **82** to ketone **83** was performed by exposure to pyridinium chlorochromate. The ketone was then elongated by two carbons with the stabilized Wittig reagent carboxymethylene triphenylphosphorane to afford a mixture of the unsaturated esters **84**.

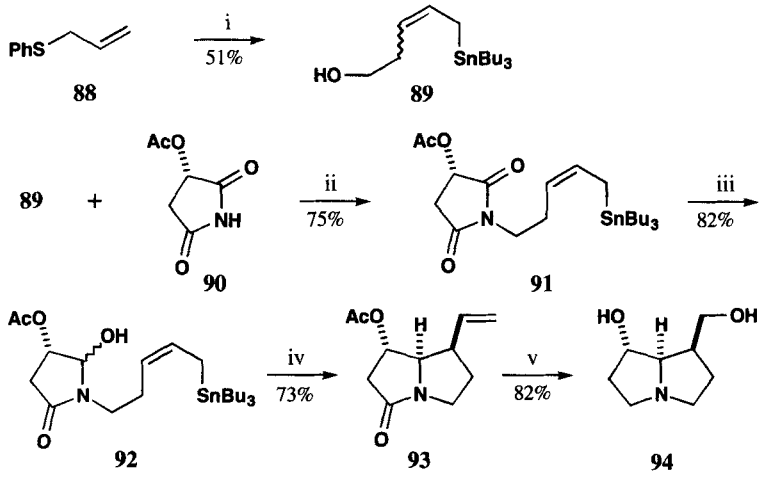
Catalytic hydrogenation over palladium on carbon gave a single isomer **85** which was directly transformed to **86** by removal of the trifluoroacetate protecting group and spontaneous cyclization. Hydrolysis of the methyl furanoside **86**, followed by concomitant reduction of the resulting lactol moiety and the lactam carbonyl, gave platynecine (**87**) in a remarkable 20% overall yield from glucosamine **80**.



Scheme 14. *Reagents and conditions*: i, $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, -30°; then $NaBH_4$, MeCN; ii, H_2, Pd/C; then $(CF_3CO)_2O$; then HCl, MeOH; iii, PCC; iv, $Ph_3P{=}CHCO_2Me$; v, H_2, Pd/C, EtOAc; vi, MeONa, MeOH; vii, aq. TFA; then $LiAlH_4$, THF.

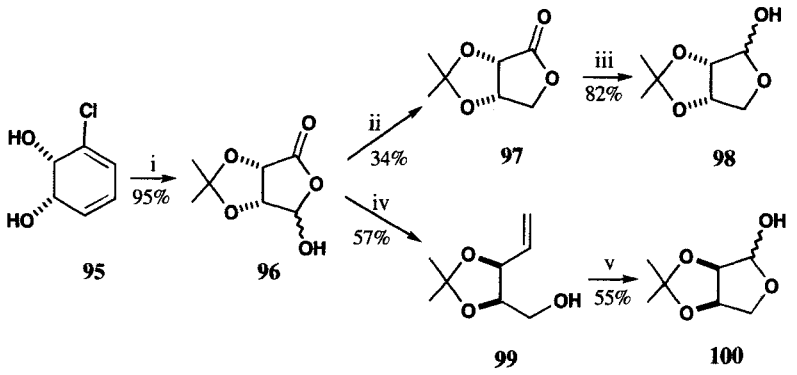
In a skilful work devoted to access various enantiopure or racemic pyrrolizidine bases, Keck and colleagues[22] adopted an intramolecular acyliminium ion cyclization on suitable allylstannanes as the pivotal operation. For (–)-dihydroxyheliotridane (**94**) to be formed, a proper key allylstannane intermediate, **92**, had to be generated first, exploiting L-malic acid as the chiral source (Scheme 15). The opening maneuver was the coupling of L-malic-derived imide **90** with alcohol **89**, which was obtained as a *E*/*Z* isomeric mixture by a three-step sequence from allyl sulfide **88**. The event furnished, under Mitsunobu conditions, allylstannane **91** in a good 75% isolated yield. Subsequent regioselective half-reduction of **91** with $NaBH_4$ at -45° gave rise to the allylstannane **92** as a mixture of C-2 stereoisomers, ready for the key annulation step. The acyliminium ion ring closure was carried

out simply by exposing **92** to triethylamine and methanesulfonyl chloride, to produce pyrrolizidinone **93** in 73% yield. This reaction successfully occurred with high levels of stereoselectivity and afforded the less thermodynamically favored *endo* product **93** as a single isomer. Ozonolysis of **93** followed by hydride reduction of the formed aldehyde allowed (–)-dihydroxyheliotridane (**94**) to be prepared in a good 37% overall yield from chiral imide **90**.



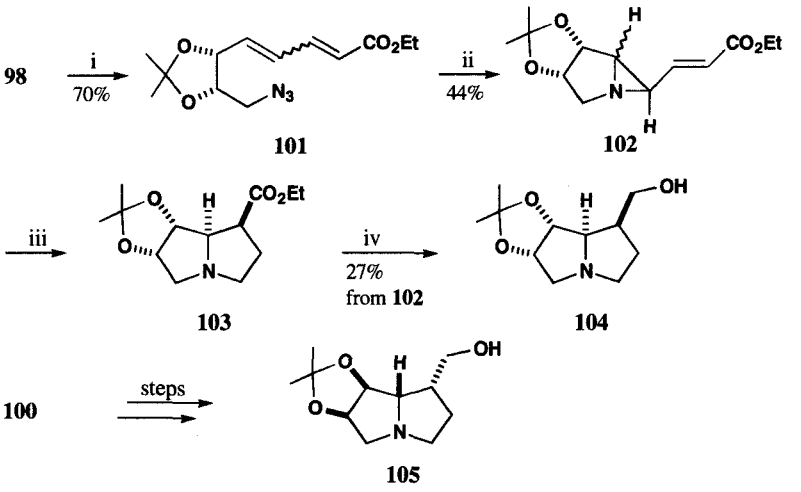
Scheme 15. *Reagents and conditions*: i, Bu^{n}Li, THF, -78 to 0°; then ethylene oxide, -78°; then Bu$_3$SnH, AIBN, toluene, 80°; ii, PPh_3, DEAD, THF; iii, $NaBH_4$, MeOH, -45°; iv, Et_3N, $MeSO_2Cl$, CH_2Cl_2; v, O_3, MeOH, -78°; then $LiAlH_4$, THF, reflux.

In his continuing effort to develop asymmetric strategies of truly general synthetic value, Hudlicky[23] exploited pseudo-symmetric lactone **96**, a chiral equivalent of *meso*-tartaric acid, as a divergent precursor of both enantiomers of the protected trihydroxyheliotridane alkaloids **104** and **105**.



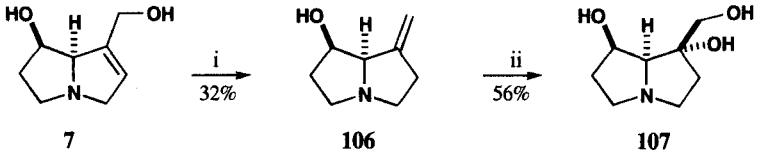
Scheme 16. *Reagents and conditions*: i, DMP, acetone, *p*-TsOH; then O_3, EtOAc; then DMS; ii, $NaBH_4$, MeOH; iii, DIBALH, CH_2Cl_2; iv, $Ph_3P{=}CH_2$, CH_2Cl_2; then $LiAlH_4$, Et_2O; v, O_3, CH_2Cl_2; then DMS.

Efficiently, enantiomerically pure lactone **96** was prepared via chloro dienediol **95** by microbial oxidation of chlorobenzene by employing genetically manipulated strains of *Pseudomonas putida*. As lactone **96** contains a latent plane of symmetry, it can be manipulated, in a divergent manner, to either L-erythrose derivative **98** or D-erythrose compound **100** by controlling the order of the chemical operations at the two lactol or carbonyl localities, as detailed in Scheme 16. The opening reaction to (+)-trihydroxyheliotridane derivative **104** was the Wittig reaction of **98** with 4-ethoxy-4-oxobut-2-enylidene triphenylphosphorane to produce a 5:1 mixture of (*Z*,*E*)- and (*E*,*E*)-dienol derivatives which were converted to azides **101** by simple chemistry (Scheme 17). Subjecting **101** to reflux in benzene resulted in conversion to vinylaziridines **102** via [4+1]azide-diene annulation. These compounds were then stereoselectively transformed to a single pyrrolizidine **103** by pyrolysis followed by hydrogenation of the formed unstable enamine intermediate. Subsequent reduction with $LiAlH_4$ afforded (+)-trihydroxyheliotridane **104** as the protected acetonide. In an analogous fashion, protected (–)-trihydroxyheliotridane **105** was synthesized from the key intermediate **100**.



Scheme 17. *Reagents and conditions*: i, Ph_3P=CHCH=$CHCO_2Et$, CH_2Cl_2; then Tf_2O, pyridine, CH_2Cl_2; then NaN_3, 18-crown-6 ether, CH_2Cl_2; ii, benzene, reflux; iii, FVP, 520°, vacuum; then H_2, Pd/C, MeOH; iv, $LiAlH_4$, THF.

A short enantioselective partial synthesis of hadinecine (**107**), an unusual trihydroxylated pyrrolizidine alkaloid bearing a hydroxy group at the quaternary C-1 carbon, was described by Benn and Hanselmann[24] by starting with (+)-retronecine (**7**) (Scheme 18).

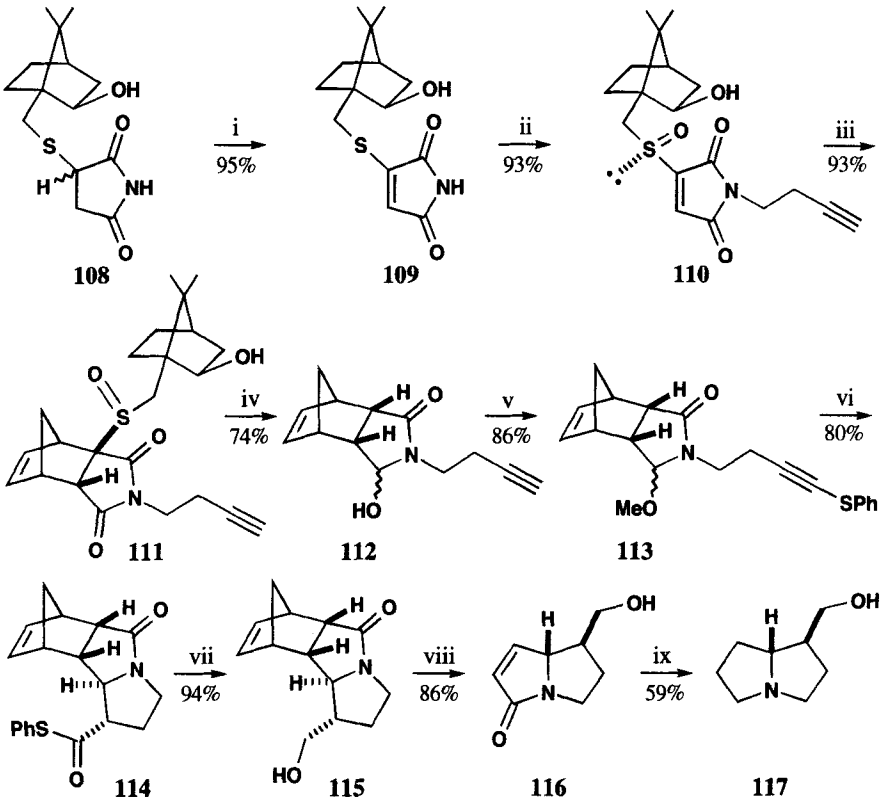


Scheme 18. *Reagents and conditions*: i, $SOCl_2$; then Zn, aq. H_2SO_4; ii, OsO_4, NMO, acetone, H_2O.

Thus, **7** was first converted by a two-step reductive elimination to exocyclic alkene **106**, which was then treated with catalytic OsO_4 in the presence of *N*-methylmorpholine *N*-oxide. As a result, hadinecine (**107**) was obtained in a reasonable 56% yield, via stereoselective dihydroxylation from the α-face of the molecule.

2. Using Chiral Auxiliaries

The exploitation of enantiomerically pure compounds as auxiliaries to induce chirality into a given synthetic target or into a key intermediate represents a widely pursued technique in organic synthesis. In the event, the chiral information resident in the auxiliary is transferred, during the various phases of the synthesis, to the growing molecule. The chiral inductor is then removed at an appropriate stage of the process. Where the stereochemical and constitutional integrity of the auxiliary is conserved, the recovered inductor can be usefully recycled thus amplifying the synthetic scope of the entire procedure.



Scheme 19. *Reagents and conditions*: i, NCS, CCl_4, reflux; ii, 3-butyn-1-ol, Ph_3P, THF, 0°; then DEAD, THF, 0° to rt; then MCPBA, CH_2Cl_2, 0° to rt; iii, cyclopentadiene, $ZnCl_2$, CH_2Cl_2, -75°; iv, $NaBH_4$, HCl, MeOH, 0°; then SmI_2, Bu^{t}OH, HMPA; v, pyridinium *p*-toluenesulfonate, MeOH; then $(PhS)_2$, LHMDA, THF, -70° to rt; vi, HCO_2H; vii, $NaBH_4$, MeOH, 0°; viii, FVP, 500°, vacuum; ix, H_2, PtO_2, EtOH; then $LiAlH_4$, THF, reflux.

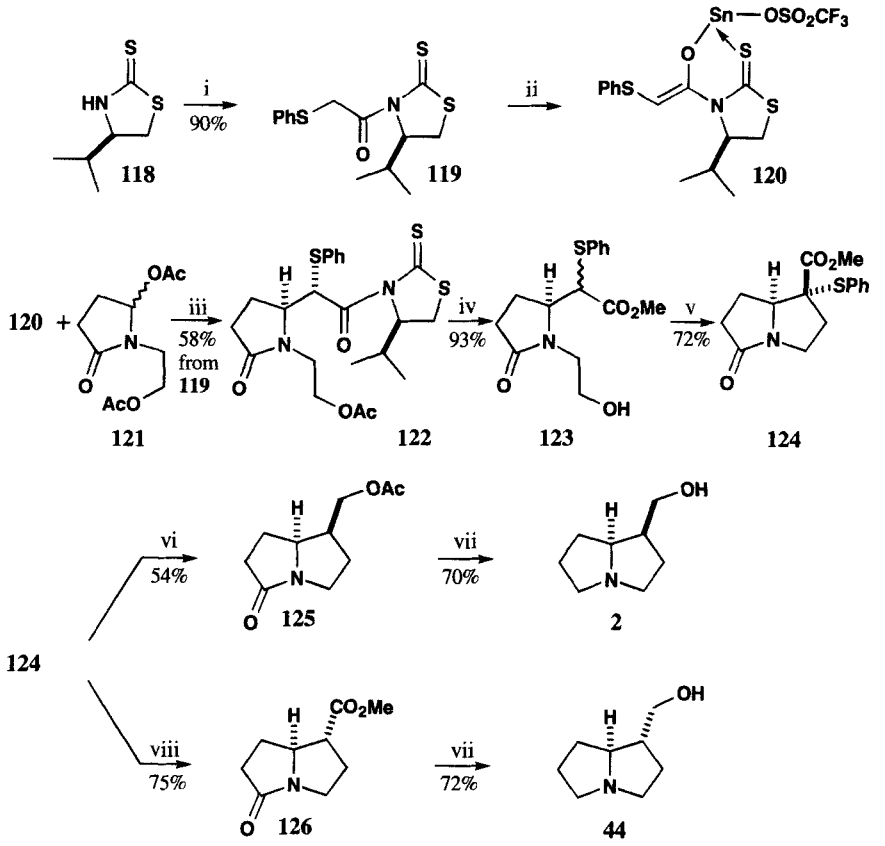
According to this approach, Koizumi[25] utilized enantiopure 10-mercaptoisoborneol as a temporary chirality inductor during a clever synthesis of (+)-laburnine [(+)-trachelanthamidine] (**117**). As illustrated in Scheme 19, in order to access the key tricyclic lactam **112**, a chiral precursor of the target alkaloid **117**, a series of seven reactions had to be performed. Thus, the chiralized succinimide **108**, easily obtained from the base catalyzed coupling of maleimide with 10-mercaptoisoborneol, was heated with *N*-chlorosuccinimide to obtain, after chlorination and spontaneous dechlorination, maleimide **109**. Exposure of imide **109** to 3-butyn-1-ol under Mitsunobu conditions gave rise to a *N*-3-butynyl intermediate which was then oxidized with 3-chloroperoxybenzoic acid to the sulfoxide **110**.

Diels-Alder cycloaddition of dienophile **110** with cyclopentadiene resulted in formation of tricyclic compound **111** with a high diastereomeric control (96% de). Regioselective reduction of **111** followed by removal of the chiral auxiliary by samarium-induced desulfinylation afforded the lactam **112** as a variable epimeric mixture. After protection of the free hydroxyl function, intermediate **112** was converted to sulfide **113** which, upon exposure to formic acid, produced the thioester **114**, exclusively. Reduction of **114** with $NaBH_4$ afforded the alcohol **115** which was subjected to flash vacuum pyrolysis at 500° to give the bicyclic amide **116** by a Diels-Alder cycloreversion process. Catalytic hydrogenation of the unsaturated moiety within **116** and subsequent reduction of the lactam carbonyl with $LiAlH_4$ furnished (+)-laburnine (**117**).

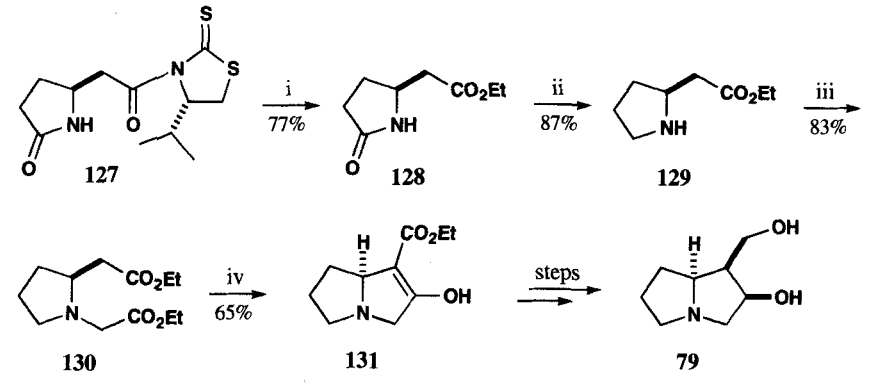
A diastereoselective divergent synthesis of natural (–)-isoretronecanol (**2**) and (–)-trachelanthamidine (**44**) was developed by the Nagao's group[26] exploiting (4*R*)-isopropyl-1,3-thiazolidine-2-thione (**118**) as the chiral auxiliary (Scheme 20). Reaction of chiral tin(II) enolate **120**, derived from **118** via intermediate **119**, with protected lactam **121**, obtained from succinic anhydride by a four-step sequence, gave a mixture of four diastereoisomeric products, from which the predominating amide **122** (82% de) was separated in a pure form. The auxiliary moiety within **122**, having accomplished its task, was removed by base-promoted saponification resulting in formation of a carboxylic acid which was protected as a methyl ester mixture **123** (60:40 diastereomeric ratio). To forge the pyrrolizidine skeleton, the alcohol **123** was first transformed into a terminal iodide and then annulated via enolate formation to the desired pyrrolizidinone **124**, stereospecifically.

Compound **124** represents a divergent precursor, which was exploited to create either isoretronecanol (**2**) or trachelanthamidine (**44**). For **2**, methyl ester **124** was reduced to an alcohol and then desulfurized and protected to pyrrolizidinone **125** with moderately high stereoselectivity (71:29 diastereomeric ratio). Reduction of the lactam carbonyl and deacetylation of **125** gave isoretronecanol (**2**). On the contrary, direct desulfurization of **124** with excess Raney nickel followed by treatment with sodium methoxide gave thermodynamically stable ester **126** as a single isomer. Hydride treatment of lactam **126** afforded trachelanthamidine (**44**).

The same research group[27] utilized slightly modified chemistry to access various homochiral pyrrolizidines bearing one or two hydroxyl substituents. As an example, the asymmetric synthesis of (–)-petasinecine (**79**) is outlined in Scheme 21.



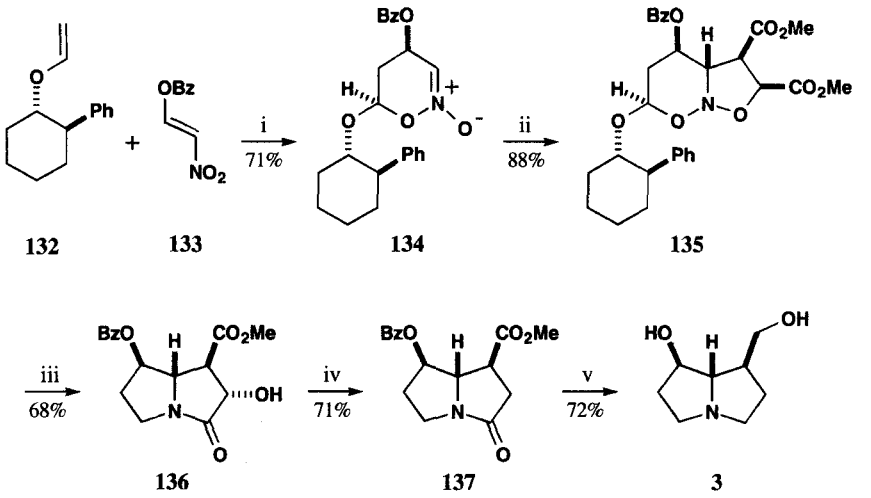
Scheme 20. *Reagents and conditions*: i, $PhSCH_2CO_2H$, DCC-DMAP, CH_2Cl_2; ii, $Sn(OSO_2CF_3)_2$, *N*-ethylpiperidine, THF, -78°; iii, THF, -5° to 0°; iv, KOH, MeOH; then CH_2N_2; v, MsCl, Et_3N, THF; then NaI, THF; then LDA, -78° to -30° ; vi, $LiAlH_4$, THF, 0°; then Raney nickel, EtOH, 70°; then AcCl, Et_3N, THF; vii, LiAlH4, THF, 0°; viii, Raney nickel, EtOH, 70°; then NaOMe, MeOH.



Scheme 21. *Reagents and conditions*: i, K_2CO_3, EtOH; ii, Lawesson's reagent, toluene, 105°; then Et_3OBF_4, CH_2Cl_2; then $NaBH_3CN$, MeOH, AcOH; iii, $BrCH_2CO_2Et$, EtOH, Na_2CO_3; iv, Dieckmann annulation.

According to the usual protocol (*vide supra*), chiralized amide **127** was thus prepared and straightforwardly elaborated into pyrrolidinone **128** by treatment with ethanolic K_2CO_3 with concomitant recovery of the thiazolidinthione auxiliary. Elaboration of **128** to pyrrolidine **129** was performed by treatment with Lawesson's reagent followed by removal of the thiocarbonyl group. *N*-Protection with ethyl bromoacetate easily afforded diester **130** which was annulated to pyrrolizine **131** by a clean Dieckmann reaction. Stereoselective reduction of both the double bond and the carboxyethyl functions in **131** according to a known protocol[28] afforded (–)-petasinecine (**79**).

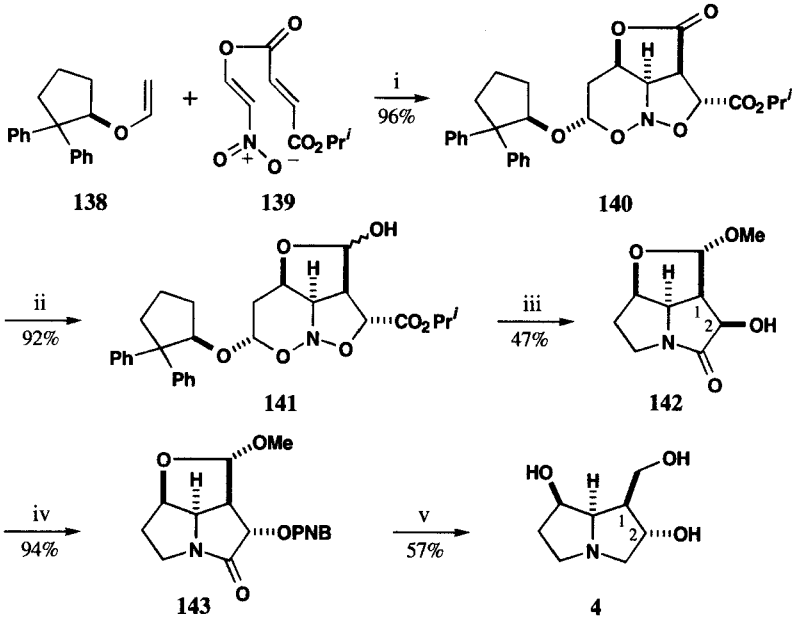
A short and efficient asymmetric synthesis of (–)-hastanecine (**3**), the necine base of hastacine, isolated from *Cacalia hastata*, was recently described by Denmark and Thorarensen[29] employing (1*S*,2*R*)-2-phenylcyclohexanol as a chiral auxiliary. The key reaction of the synthesis features a sequential [4+2]/[3+2] cycloaddition, as illustrated in Scheme 22.



Scheme 22. *Reagents and conditions*: i, $Ti(OPr^i)_2Cl_2$, CH_2Cl_2, -90° to -78°; ii, dimethyl maleate, benzene; iii, 260 psi H_2, Raney nickel, MeOH; iv, PhOCSCl, DMAP, pyridine; then Bu_3SnH, AIBN; v, $LiAlH_4$, THF, reflux.

The opening move was a titanium diisopropoxide dichloride-promoted cycloaddition between homochiral vinyl ether **132** and nitroalkene **133** to afford nitronate **134** with high selectivity (13:1 diastereomeric ratio). The nitronate **134** was found to be a reactive dipole which combined with dimethyl maleate to afford nitroso acetal **135** as a single diastereoisomer. The removal of the auxiliary and the formation of the hastanecine skeleton required the hydrogenolysis of the nitroso-acetal portion. After extensive trial, optimal conditions were found using Raney nickel at high pressure of hydrogen in methanol which afforded the hydroxylactam **136** in excellent enantiomeric purity (97.7% ee). In addition to **136**, the auxiliary, (1*S*, 2*R*)-2-phenylcyclohexanol, was recovered almost quantitatively. Lactam **136** is overfunctionalized as compared to the target hastanecine (**3**); thus the remainder stages of the synthesis involved deoxygenation at C-2 and reduction of the amide and the ester

moieties in **136**. The deoxygenation to pyrrolizidinone **137** was easily attained by first transforming **136** into a thiocarbonate which was then reacted with tributyltin hydride and AIBN. Final hydride reductions of the ester function as well as the amide carbonyl and the benzoate protection gave rise to (–)-hastanecine (**3**) in an appreciable 22% yield for the six-stage sequence from **133**. The versatility of this tandem cycloaddition protocol to richly equipped nitrogen containing polycyclics was further exploited by the same group to assemble (–)-rosmarinecine (**4**), the necine base portion of the alkaloid rosmarinine.[30]



Scheme 23. *Reagents and conditions*: i, MAPh, CH_2Cl_2, -78°; ii, $LiBu^s_3BH$, THF, -78°; iii, H_2 160 psi, Raney nickel; then MeOH, TsOH, $CH(OMe)_3$, reflux; iv, 4-$NO_2C_6H_4CO_2H$, Ph_3P, DEAD, THF; v, TFA; then RedAl, THF, reflux.

As shown in Scheme 23, the synthesis started with nitroalkene **139**, which was easily prepared by combining potassium nitroacetaldehyde with isopropyl fumaroyl chloride. The reaction of **139** with the chiral vinyl ether **138**, derived from (*R*)-2,2-diphenylcyclopentanol, in the presence of an excess of methyl aluminium bis(2,6-diphenylphenoxide) (MAPh) afforded the nitroso acetal **140** in 96% yield and overall 25:1 *exo/endo* ratio.

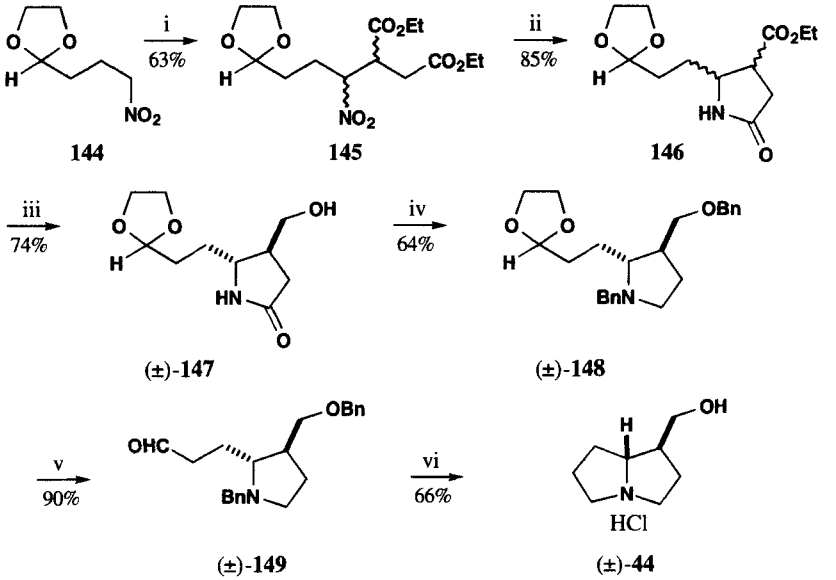
Thus, this cycloaddition installed all the stereocenters of **4** with the correct configuration (except at C-2) in a sole operation. Next, compound **140** was selectively reduced with lithium tri(*sec*-butyl)borohydride to afford the lactol **141** in excellent yield. The lactol was then subjected to forced hydrogenolysis conditions, to afford, after acid-promoted methylation of the lactol moiety, the tricyclic lactam-lactol **142** in a very satisfying yield, while recovering the cyclopentanol auxiliary. At this point, inversion at C-2 was required for the correct absolute configuration in **4**; and this was achieved by a Mitsunobu reaction with 4-nitrobenzoic acid as the nucleophile. The enantiomeric

excess of the 4-nitrobenzoate **143** so obtained was judged to be up to 97%.

To complete the synthesis, deprotection of the methyl acetal within **143** and reduction of the resulting lactol was requested. Thus, aqueous trifluoroacetic acid treatment followed by RedAl reductive workup furnished (–)-rosmarinecine (**4**) in a 57% isolated yield for the two steps. Overall, the synthesis of **4** was accomplished in seven steps and 22% yield from **139**.

3. Diastereoselective Procedures to Racemic Compounds

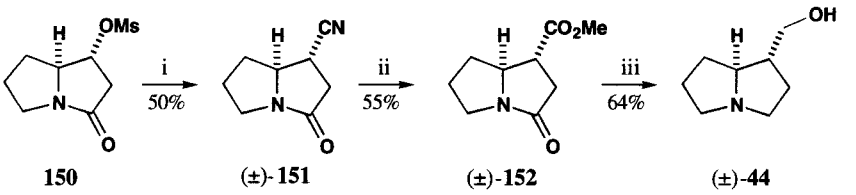
Controlling diastereoselectivity during carbon-carbon bond formation is a major concern for effective entry to a multichiral substance; and this concept has been widely utilized in both the homochiral (*vide supra*) and racemic domains. A remarkable example is the synthesis of racemic trachelanthamidine [(±)-**44**] recently reported by Hesse and coworkers,[31] utilizing inexpensive nitromethane, acrylaldehyde, and diethyl fumarate as synthetic precursors (Scheme 24). Conjugate addition of protected nitroaldehyde **144**, easily obtained from nitromethane and acrylaldehyde, to diethyl fumarate produced homologated diester **145** as a mixture of stereoisomers. Subsequent reduction of the nitro group to an amine resulted in cyclization to pyrrolidinones **146** as a 1:1 diastereomeric mixture. Remarkably, when the ester moiety in **146** was subjected to $NaBH_4$ reduction, a single racemic alcohol was obtained to which structure (±)-**147** was assigned. After benzylation of both the terminal hydroxyl and the lactam nitrogen, the carbonyl group was reduced with $LiAlH_4$ in THF to give pyrrolidine (±)-**148** whose aldehyde function was liberated by acidic hydrolysis to compound (±)-**149**. The final annulation to racemic trachelanthamidine [(±)-**44**] was effected, after hydrogenolytic debenzylation, via intramolecular reductive amination.



Scheme 24. *Reagents and conditions*: i, CsF, Al_2O_3, MeCN, diethyl fumarate, 80°; ii, H_2, Pd/C, EtOH, AcOH; iii, $NaBH_4$, MeOH, Bu^{t}OH, 82°; iv, NaH, BnBr, Bu_4NI, THF, 67°; then $LiAlH_4$, THF, 67°; v, THF, aq. HCl, 40°; vi, H_2, Pd/C, AcOH; then MeOH, HCl.

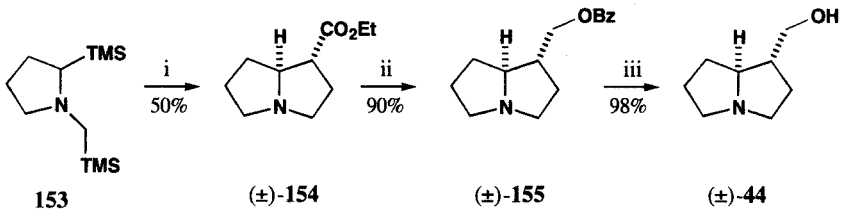
The same racemic alkaloid (±)-**44** was unexpectedly obtained by Proctor and colleagues[32] during a quite recent study directed to the asymmetric synthesis of pyrrolizidine ring systems.

As shown in Scheme 25, treatment of homochiral pyrrolizidinone **150**, an advanced intermediate in the asymmetric synthesis of the natural (–)-(1*R*,8*S*)-1-hydroxypyrrolizidine (**226**, *vide infra*), with sodium cyanide in dimethyl sulfoxide at 90° gave *exo* nitrile (±)-**151** in which complete loss of stereochemical integrity had occurred. Methanolysis of (±)-**151** to the ester (±)-**152** followed by reduction of the lactam carbonyl afforded racemic trachelanthamidine [(±)-**44**] as a single diastereoisomer.



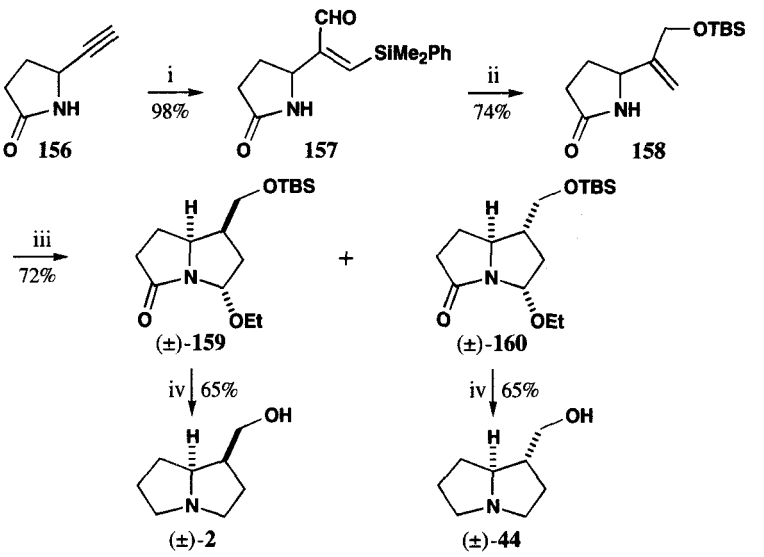
Scheme 25. *Reagents and conditions*: i, NaCN, DMSO, 90°; ii, HCl gas, MeOH, 0°; iii, $LiAlH_4$, THF, reflux.

Diastereospecific 1,3-dipolar cycloaddition of non-stabilized azomethine ylide precursors was applied by Pandey and Lakshmaiah[33] in an elegant approach to racemic trachelanthamidine [(±)-**44**] and isoretronecanol [(±)-**2**]. To access (±)-**44**, azomethine ylide equivalent **153** was reacted with ethyl acrylate in acetonitrile in the presence of silver(I) fluoride, a one electron oxidant promoting ylide generation through sequential electron-TMS^+-electron transfer process (Scheme 26). There was obtained racemic pyrrolizidine (±)-**154**, stereoselectively (7:3 *cis/trans* ratio), accompained by minor amounts of regioisomeric materials (15%). Reduction of the ester moiety within (±)-**154** with $LiAlH_4$ and subsequent benzoylation of the formed carbinol resulted in isolation of pure benzyloxy derivative (±)-**155** which was transformed into racemic trachelanthamidine [(±)-**44**] by base-promoted deprotection.



Scheme 26. *Reagents and conditions*: i, AgF, ethyl acrylate, MeCN; ii, $LiAlH_4$, THF; then Et_3N, THF, BzCl; iii, NaOH, MeOH.

Construction of the basic skeleton of pyrrolizidine alkaloids can be achieved by using rhodium-catalyzed silylformylation of alkynyl substituted pyrrolidines followed by amidocarbonylation. With this strategy, the Ojima group[34,35] succeeded in preparing both racemic alkaloids (±)-**2** and (±)-**44**.

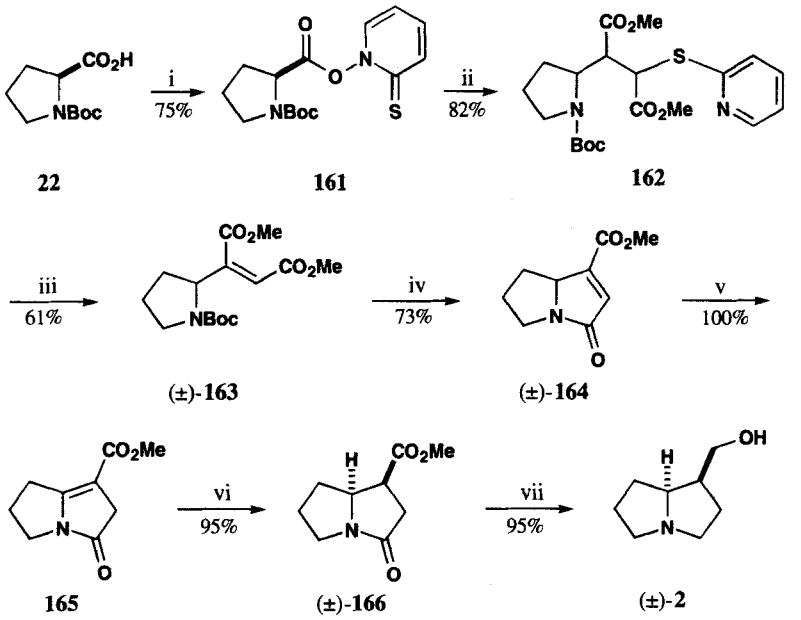


Scheme 27. *Reagents and conditions*: i, $HSiMe_2Ph$, CO 300 psi, $Rh(acac)(CO)_2$, toluene; ii, $NaBH_4$, EtOH, H_2O, 0° to rt; then TsH, MeCN, reflux; then TBSCl, imidazole, DMF, 40°; iii, CO, H_2 1,600 psi, $HRh(CO)(PPh_3)_3$, $HC(OEt)_3$, 100°; then chromatography; iv, TBAF, THF; then $LiAlH_4$, THF, reflux.

As shown in Scheme 27, the authors started with silylformylation of 5-ethynyl-2-pyrrolidinone (**156**) using phenyldimethylsilane and a catalytic amount of $Rh(acac)(CO)_2$ under 300 psi of carbon monoxide to afford pyrrolidinone aldehyde **157** as the only product. The reduction of the formyl group in **157** with $NaBH_4$ followed by desilylation and subsequent protection gave alkenyl pyrrolidinone **158**, which was subjected to the amidocarbonylation catalyzed by $HRh(CO)(PPh_3)_3$. The reaction produced a 2:1 diastereomeric mixture of (±)-**159** and (±)-**160** through an intramolecular process. Once separated, the individual compounds were successfully converted to pyrrolizidine alkaloids (±)-**2** and (±)-**44**, respectively, through removal of the silyl protecting group (TBAF) followed by $LiAlH_4$ reduction of the amidal and amido groups in good yields (65%).

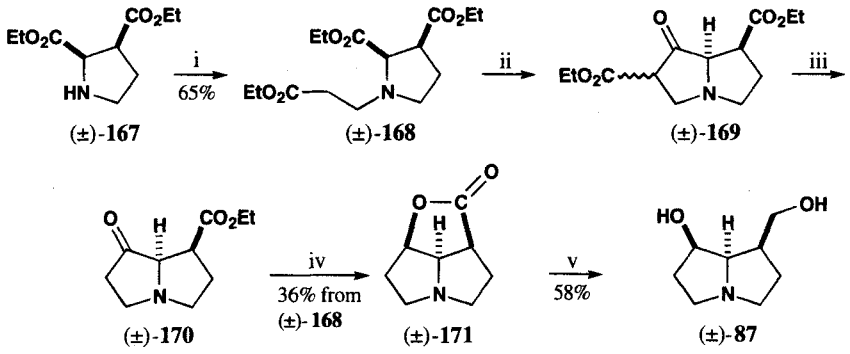
An interesting radical approach to racemic isoretronecanol [(±)-**2**] was introduced by Thierry[36] inspired upon the Barton's radical decarboxylation of amino acids. First, *N*-Boc-protected L-proline **22** was transformed to the thiohydroxamic derivative **161** and then irradiated by a sunlump in the presence of an excess of dimethyl fumarate, to give the adduct **162** as a mixture of diastereoisomers with loss of the chirality of the proline stereocenter (Scheme 28).

Sulfoxide-mediated elimination then gave rise to olefin (±)-**163**. Cleavage of the *N*-Boc group (TFA) followed by neutralization with aqueous ammonia produced the racemic pyrrolizidinone (±)-**164** which, during silica-gel column purification, underwent double bond migration to **165**. Catalytic hydrogenation of **165** provided saturated *cis*-pyrrolizidinone (±)-**166**, which was finally converted into isoretronecanol [(±)-**2**] by conventional hydride reduction.



Scheme 28. *Reagents and conditions*: i, Bu^{i}OCOCl, *N*-methylmorpholine, 2-mercaptopyridine 1-oxide, -15°; ii, dimethyl fumarate, 2 x 100W tungsten lamps; iii, MCPBA, $CHCl_3$; then reflux, toluene; iv, TFA; then NH_4OH; v, silica gel purification; vi, H_2, Pd/C; vii, $LiAlH_4$.

A simple approach to dihydroxylated necine alkaloid *rac*-platynecine [(±)-**87**] was devised by Röder[37] using racemic pyrrolidine dicarboxylate (±)-**167** as a synthon (Scheme 29).

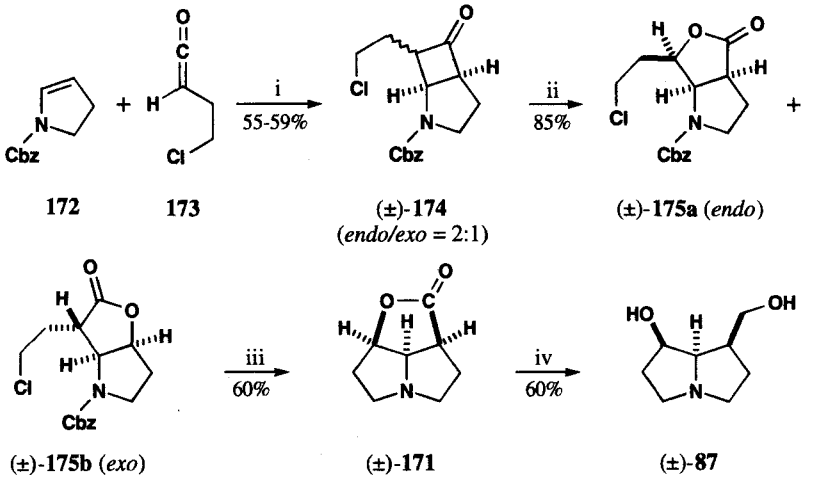


Scheme 29. *Reagents and conditions*: i, ethyl acrylate; ii, NaH; iii, aq. HCl, reflux; iv, KBH_4, KOH; v, $LiAlH_4$.

The starting move was the introduction of a suitable three-carbon chain to nitrogen of (±)-**167** to form (±)-**168** followed by Dieckmann reaction to give the annulated compound (±)-**169** as a mixture of diastereoisomers. Selective saponification and decarboxylation resulted in removal of the C-6 ester group to produce pyrrolizidinone (±)-**170** which was diastereospecifically reduced to 1,7-*cis*-lactone (±)-**171** upon exposure to potassium borohydride. Further reduction of the lactone moiety

within (±)-**171** using $LiAlH_4$ afforded (±)-**87** in moderate isolated yield.

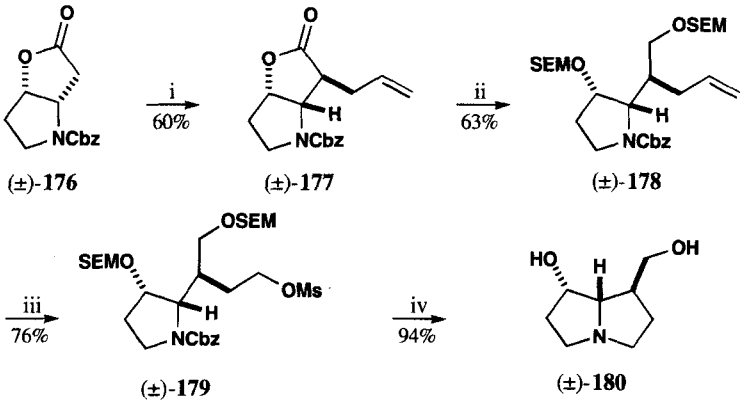
To gain access to racemic platynecine [(±)-**87**], the Correia's group[38] exploited the [2+2] cycloaddition of endocyclic enecarbamate **172** with the alkylketene chloride **173**, generated *in situ* from 4-chlorobutyryl chloride (Scheme 30). The reaction proved highly stereoselective, and gave rise to a mixture of *endo/exo* isomers (±)-**174** in 55-59% yield, whose ratio depended upon the reaction conditions and was estimated to be 2:1 when the reaction was run to completion. Baeyer-Villiger ring expansion of bicyclic butanones (±)-**174** (MCPBA) afforded a 2:1 mixture of the *endo* γ-lactone (±)-**175a** and *exo* γ-lactone (±)-**175b**, possibly arising from *endo* (±)-**174** and *exo* (±)-**174**, respectively. Hydrogenolytic cleavage of the *N*-Cbz protecting group within **175a,b** promoted an intramolecular ring closure to yield the hydrochloride salt of the azatricyclic lactone (±)-**171** as the sole isomer. In the event, *endo* (±)-**175a** seems to be responsible for the observed cyclization, whereas its *exo* counterpart decomposes since the intramolecular ring closure is hardly hampered by geometrical constraint. The final reduction of (±)-**171** with lithium aluminium hydride provided (±)-platynecine [(±)-**87**] in 60% yield.



Scheme 30. *Reagents and conditions*: i, hexane, reflux; ii, MCPBA, $NaHCO_3$, CH_2Cl_2; iii, $Pd(OH)_2$, MeOH, H_2 20 psi; iv, $LiAlH_4$, THF, reflux.

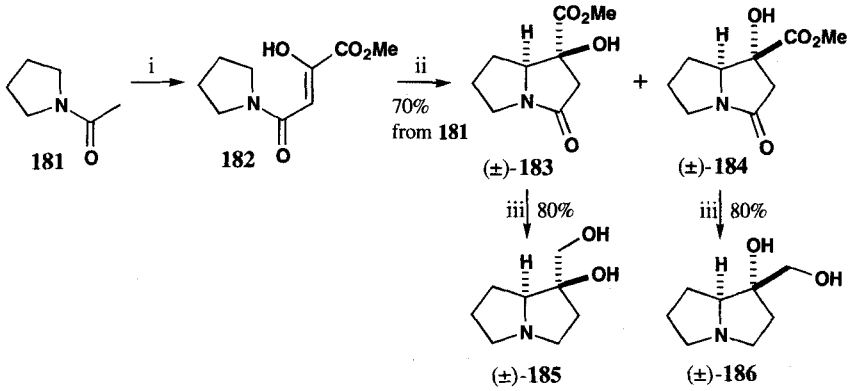
An interesting achievement in this area is Gallager's diastereoselective synthesis of *rac*-turneforcidine [(±)-**180**] (Scheme 31).[16] The synthesis began with racemic Geissman Weiss lactone (±)-**176** which was allylated, via the enolate, to produce (±)-**177** as a single diastereoisomer. Subsequent reduction of (±)-**177** ($NaBH_4$) gave a diol which was protected as its bis-SEM ether (±)-**178**.

Reductive cleavage of the alkene function in (±)-**178** by sequential treatment with OsO_4-$NaIO_4$ and $NaBH_4$ provided a carbinol which was converted to mesylate (±)-**179** in the usual manner. The final transformations to the target alkaloid (±)-**180** involved hydrogenolytic removal of the Cbz protection, spontaneous ring closure to a pyrrolizidine, and cleavage of the two SEM groups.



Scheme 31. *Reagents and conditions*: i, LHMDS, THF, -78°, allyl bromide; ii, $NaBH_4$, EtOH; then SEMCl, Pr^iNEt_2, CH_2Cl_2; iii, OsO_4, $NaIO_4$; then $NaBH_4$; then MsCl, Et_3N; iv, H_2, Pd/C, EtOAc, Li_2CO_3; then TBAF, THF.

The first total synthesis of racemic curassanecine [(±)-**185**], a bicyclic alkaloid isolated from *Heliotropium curassavicum*, bearing an unusual C-1 geminal substitution as found in the hadinecine (**107**, *vide supra*), was realized by Gramain and coworkers[39] from *N*-acetylpyrrolidine (**181**). The synthesis also permitted preparation of the C-1 epimer of the natural alkaloid, (±)-**186**, in the racemic form (Scheme 32). The photocyclization of the α-keto ester **182** (enolic form shown), obtained by condensation of methyl oxalate on the anion of **181**, led to a separable racemic 1:1 mixture of hydroxy esters (±)-**183** and (±)-**184**, whose relative stereochemistry was confidently assigned, as indicated, on the basis of extensive NMR investigations and correlation with a couple of aryl-substituted congeners of proven stereochemistry.

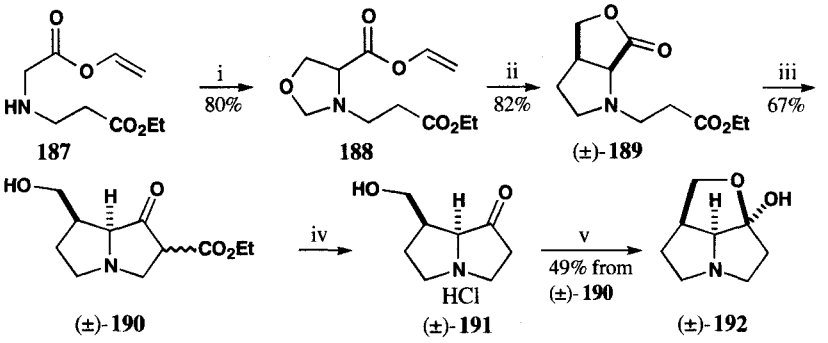


Scheme 32. *Reagents and conditions*: i, LDA, THF; then $(CO_2Me)_2$; ii, hv; iii, $LiAlH_4$, THF.

A single transformation employing $LiAlH_4$ finally ensured concomitant reduction of the lactam carbonyls and the ester moieties of the precursors (±)-**183** and (±)-**184**, giving diastereoisomerically pure alkaloids (±)-**185** and (±)-**186**, respectively. Overall, the reported procedure encompassed

only three steps and afforded each alkaloid in a quite good 28% yield from the common pyrrolidine precursor **181**.

The rather unusual 1,7-anhydronecine hemiacetal [(±)-**192**] was obtained by Joucla[40] during a study aimed at developing a diastereoselective procedure towards pyrrolizidines, based on azomethine ylide cycloaddition reactions. Thus, as shown in Scheme 33, aminoester **187**, easily prepared by Michael-type addition of glycine allyl ester to ethyl acrylate, was allowed to react with an excess of formaldehyde at 110° to furnish racemic oxazolidine **188** as a single product.



Scheme 33. *Reagents and conditions*: i, CH_2O, 110°; ii, FVT, 550°; iii, LDA, THF; iv, HCl; then heating; v, NH_3.

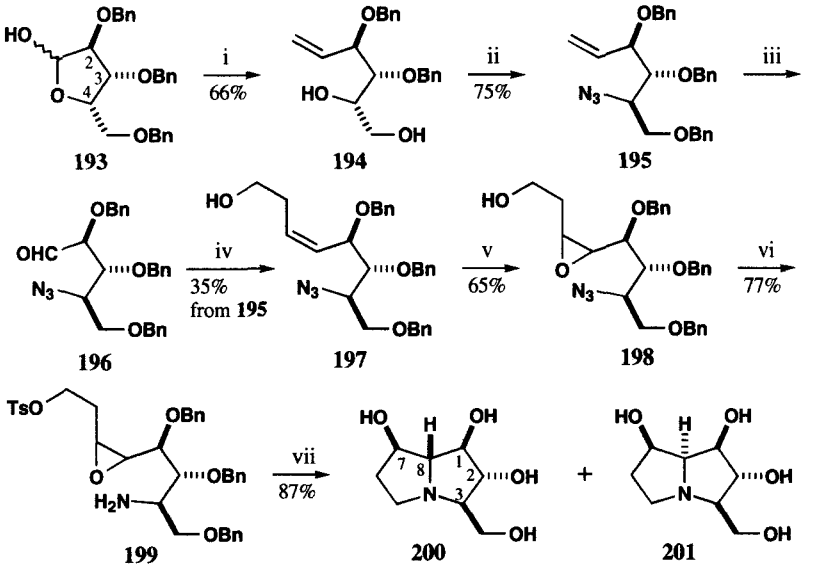
Flash vacuum thermolysis of **188** led to a single pyrrolidine (±)-**189**, with good stereo- and regioselectivity which was then subjected to Dieckmann condensation (LDA in THF) to produce pyrrolizidinone (±)-**190**. Hydrolysis of ester (±)-**190** with HCl and decarboxylation occurred on heating, leading to (±)-**191** as a hydrochloride salt which, upon neutralization with ammonia, gave stable necine hemiacetal (±)-**192** as a racemate.

II. SYNTHESIS OF ALEXINES

In contrast to the extensive research effort directed toward synthesis of necine bases described in the previous section, only a limited number of research reports dealing with the synthesis of closely related alexines have appeared during the period covered by this review.

Remarkable approaches to enantiopure alexins have been reported, being the studies focused on mapping the overall stereochemistry of the target pyrrolizidines onto the chirality resident in a carbohydrate precursor. For example, Pearson and Hines[41] reported a short route to the naturally occurring anti-HIV active (+)-7-epiaustraline (**200**) and the non-natural (–)-7-epialexine (**201**) by exploiting L-xylose as a common chiral template. The elegant synthesis (Scheme 34) began with protected L-xylofuranose **193**, which was prepared from commercial L-xylose. The C-2, C-3, and C-4 stereocenters in **193** correspond to C-1, C-2, and C-3 of the targets and, while the stereocenters at C-2 and C-3 were conserved, C-4 had to be reverted. This was done during the stereoselective introduction

of the nitrogen at C-4. The stereochemistry at C-7 and C-8 had to be generated *de novo*. Wittig one-carbon elongation of lactol **193** provided six-carbon homologated alcohol **194** which was transformed to azide **195** via SN_2 triflate displacement, with inversion of configuration. Ozonolysis of **195** cleanly provided azidoaldehyde **196** which was elongated by three carbons to create the eight-carbon skeleton of the final pyrrolizidines. The unsaturated alcohol **197** so formed, was then subjected to epoxidation to create the two required novel stereocenters.

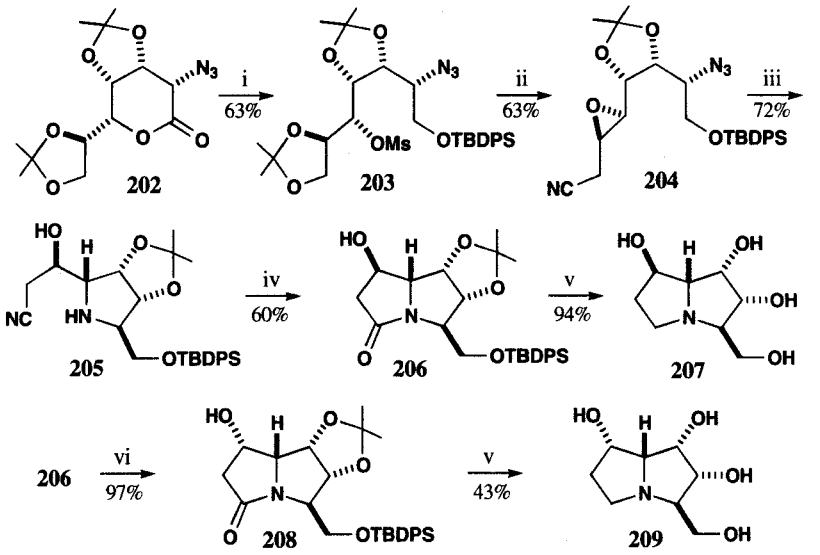


Scheme 34. *Reagents and conditions*: i, $Ph_3P^+CH_3Br^-$, BuLi, THF, -78° to rt; ii, Tf_2O, pyridine, CH_2Cl_2, -40 to 0°; then Bu_4NN_3, benzene; iii, O_3; then Me_2S, -78° to rt; iv, $Ph_3P^+(CH_2)_3OHBr^-$, KHMDS, THF, Me_3SiCl; then HCl; v, MCPBA, CH_2Cl_2, 0° to rt; vi, TsCl, pyridine, DMAP, CH_2Cl_2, -15°; then H_2, Pd/C, Et_2O, EtOH; vii, K_2CO_3, EtOH, reflux; then separation; then H_2, Pd/C, EtOH.

Disappointingly, however, a 1:1 mixture of *cis*-configured epoxides **198** was generated owing to the nonselective character of this reaction, and this required the diastereoisomers to be separated at an appropriate stage of the sequence. The key operation was a tandem epoxide opening-intramolecular displacement involving amine **199** (2:1 α,β-mixture), which was obtained from azide **198** via tosylation of the terminal CH_2OH followed by azide-to-amine reduction. The reaction produced, after full deprotection, 7-epialexine (**201**) as expected (minor compound, 29%) and, quite surprisingly, 7-epiaustraline (**200**) (major compound, 58%), arising from inversion of configuration at C-7.

In designing a divergent approach to 1,7-diepiaustraline (**207**) and 1-epiaustraline (**209**) (Scheme 35), Fleet and coworkers[42] used the readily available seven-carbon azide **202** as a common starting substrate. It contains five stereocenters and an almost complete carbon skeleton; only one carbon atom has to be added and no other stereocenters need to be created to achieve the goals. A set of routine transformations, including reductive opening of the lactone frame, protection of the primary

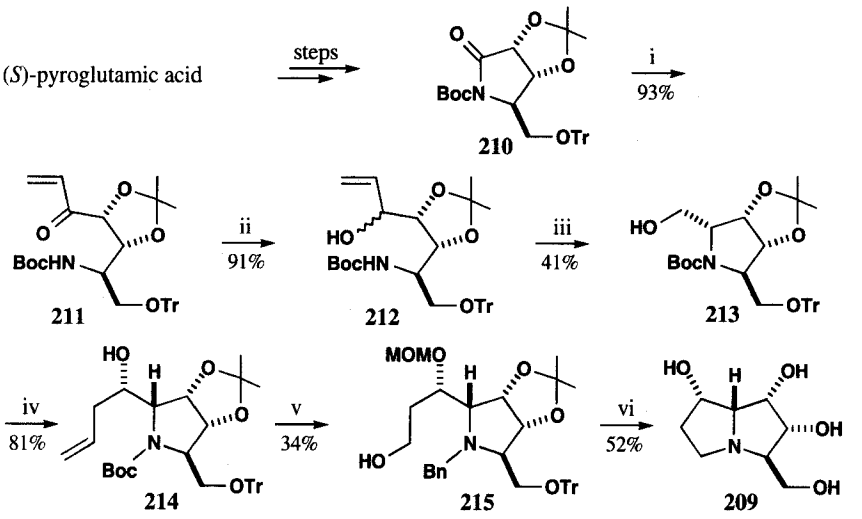
hydroxyl, and mesylation of the secondary OH, gave rise to open-chain seven-carbon azide **203** which was elaborated into epoxide **204** by selective deprotection of the terminal acetonide, base-assisted epoxide formation, activation of the primary OH as a triflate, and one-carbon elongation with LiCN. Upon hydrogenation, compound **204** spontaneously annulated to pyrrolidine **205** via stereospecific intramolecular epoxide cleavage, strongly favoring, in this instance, a 5-*exo*-tetra cyclization mode.



Scheme 35. *Reagents and conditions*: i, DIBALH, THF; then $NaBH_4$, MeOH; then TBDPSCl, imidazole, DMF; then MsCl, DMAP, pyridine; ii, AcOH, aq. dioxane; then $Ba(OMe)_2$, MeOH; then Tf_2O, CH_2Cl_2; then LiCN, CH_2Cl_2, THF; iii, H_2, Pd/C, EtOAc; iv, aq. NH_3, EtOH, 100°; v, BH_3,THF; then aq. CF_3CO_2H; vi, PCC, CH_2Cl_2; then $NaBH_4$, EtOH, 0°.

Next, bicyclic lactam **206**, a divergent intermediate, was generated by hydrolysis. Since the complete chirality of alexine **207** is present in **206**, it was directly transformed into **207** by reduction of the lactam carbonyl followed by acidic deprotection. For stereoisomer **209**, stereochemical inversion at C-7 was, instead, required; and this involved a suitable oxidation-reduction selective protocol using the conventional PCC-$NaBH_4$ reagent pair to give protected pyrrolizidinone **208**. All that remained was carbonyl reduction followed by full deprotection, and this was attained by sequential BH_3 reduction and acidic treatment to produce 1-epiaustraline (**209**).

A further example exploiting the chiron approach is the multistep total synthesis of 1-epiaustraline (**209**) developed by Ikota,[43] starting with (*S*)-pyroglutamic acid (Scheme 36). Thus, advanced intermediate **210** was first homologated to ketone **211** which was then reduced to allylic alcohols **212** (1:2.4 diastereomeric ratio). Ozonolysis of the double bond and subsequent reductive work-up allowed transformation of **212** into a mixture of polyols, the major isomer being then converted to pyrrolidine **213** by silylation of the terminal hydroxyl group, mesylation of the remainder OH, and ring-closure followed by desilylation.

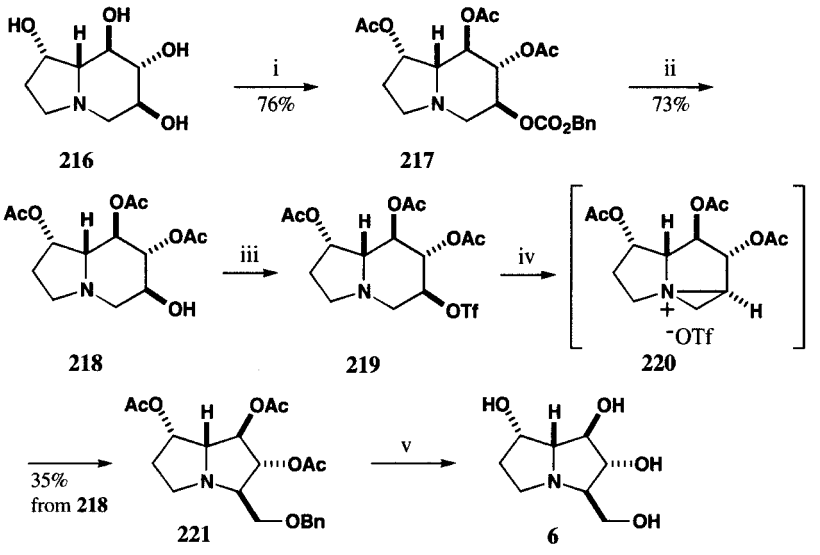


Scheme 36. *Reagents and conditions*: i, CH_2=CHMgBr, THF, -40 to -50°; ii, $NaBH_4$, $CeCl_3$, MeOH; iii, O_3, CH_2Cl_2, -78°; then $NaBH_4$, EtOH; then TBSCl, imidazole, DMF, 0°; then MsCl, Et_3N, CH_2Cl_2; then Bu^{t}OK, THF; then TBAF, THF; iv, Swern oxidn.; then allyllithium, -78°; v, MOMCl, *N,N*-diethylaniline, CH_2Cl_2; then TBSOTf, 2,6-lutidine, CH_2Cl_2; then TBAF, THF; then BnBr, K_2CO_3, acetone; then O_3, CH_2Cl_2, -78°; then $NaBH_4$, EtOH; vi, MsCl, Et_3N, CH_2Cl_2; then Pd/C, H_2, EtOH; then aq. HCl, MeOH, 60°.

Swern oxidation of the hydroxymethyl function to formyl group and subsequent homologation by two carbon atoms, via allylation, gave rise to unsaturated pyrrolidine **214** preferentially (5.4:1 diastereomeric ratio), that was finally converted to bicyclic target **209**, via intermediate **215**, by conventional chemistry.

Exploiting natural castanospermine (**216**), which was isolated as a pure crystalline material in a 1 Kg quantity from the seeds of the australian legume *Castanospernum australe*, the New Zeeland team guided by Tyler[44] prepared a wide series of variously substituted hydroxylated congeners including australine (**6**) and some australine analogues (Scheme 37). Thus, for example, tri-*O*-acetylcastanospermine **218**, obtained from **216** via the 6-carbonate **217**, was treated with trifluoromethanesulfonic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine, and the resulting unstable triflate **219** was reacted *in situ* with excess benzyl alcohol to give the australine isomer **221** as the major product, via the intermediacy of an aziridinium ion intermediate **220**. Catalytic debenzylation of **221** and full deacetylation gave rise to natural australine (**6**).

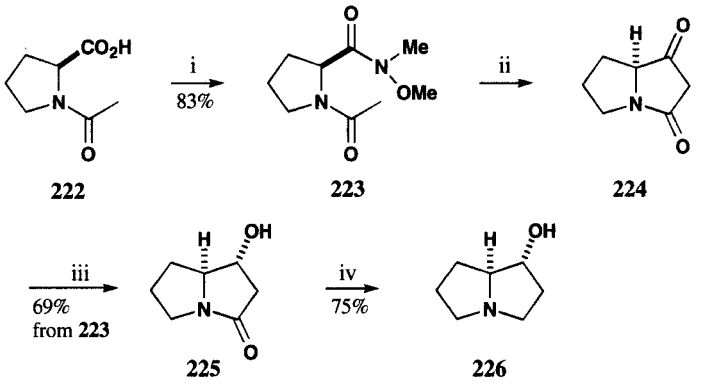
This unusual ring contraction was also exploited by the same group[44] to obtain a number of alexine-related alkaloids including fluorinated, chlorinated, and aminated derivatives, the structure of which were ascertained by extensive X-ray crystallographic analyses.



Scheme 37. *Reagents and conditions*: i, $(Bu_3Sn)_2O$, toluene, reflux; then BnOCOCl, -20°; then Ac_2O, pyridine; ii, Pd/C, H_2, EtOAc, EtOH; iii, Tf_2O, 2,6-di-*t*-butyl-4-methylpyridine; iv, benzyl alcohol; v, H_2, Pd/C; then aq. NH_3.

III. SYNTHESIS OF UNNATURAL CONGENERS

Another active area in the realm of hydroxylated pyrrolizidines was the preparation of deshydroxymethyl necine or alexine analogues, exploiting carbohydrate-based chirons or amino acid precursors. The first example focuses on straight elaboration of *N*-acetyl-L-proline (**222**) into (–)-(1*R*, 8*S*)-1-hydroxypyrrolizidine (**226**) as outlined in Scheme 38.[32]

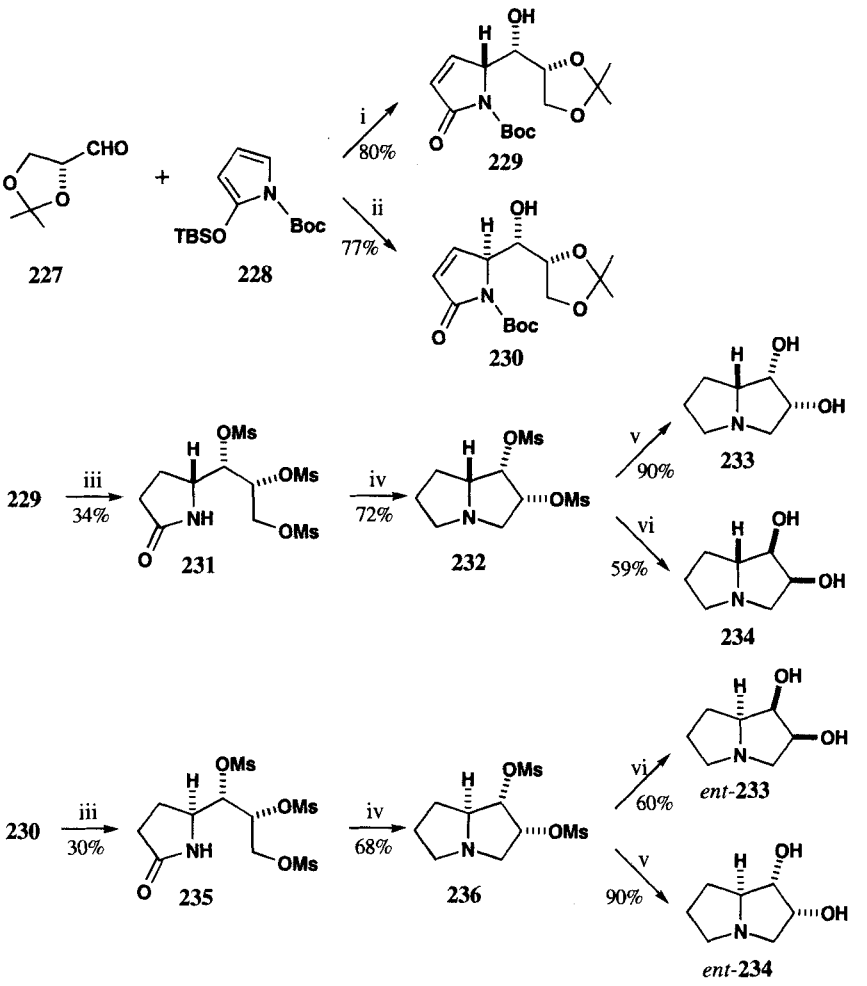


Scheme 38. *Reagents and conditions*: i, $(CH_2)_5NMe$, $ClCO_2Bu^i$, CH_2Cl_2, -15°; then HCl•HNMe(OMe); ii, LHMDS, THF, -78°; iii, $NaBH_4$, EtOH; iv, $LiAlH_4$, THF, reflux.

Thus, amino acid **222** was conveniently transformed into the corresponding *N*-methyl-*N*-methoxy amide **223** by the mixed anhydride method, and the product successfully cyclized to enan-

tiomerically pure pyrrolizidin-1,3-dione **224** by LHMDS-promoted intramolecular condensation. Selective reduction of **224** with sodium borohydride resulted in regio- and stereoselective formation of alcohol **225** (95:5 diastereomeric ratio), which was finally reduced to the target pyrrolizidine **226** by conventional $LiAlH_4$ treatment.

Utilizing D-glyceraldehyde acetonide (**227**) (or its L-enantiomer) all four isomers of *cis*-1,2-dihydroxypyrrolizidine, **233**, **234**, and their enantiomers *ent*-**233** and *ent*-**234**, were recently prepared in our laboratory according to a highly divergent protocol (Scheme 39).[45]

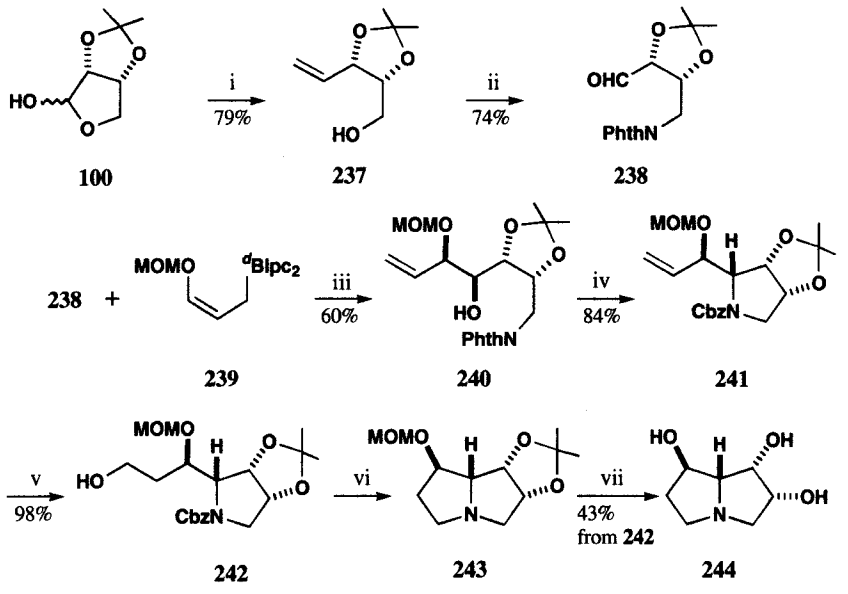


Scheme 39. *Reagents and conditions*: i, $SnCl_4$, Et_2O, -80°; ii, BF_3•Et_2O, Et_2O, -85°; iii, H_2, Pd/C, THF; then HCl; then $MeSO_2Cl$, pyridine; iv, BH_3·DMS, THF; then DBU, benzene, reflux; v, Na-Hg, Et_2O, Pr^iOH; vi, $Bu_4N^+BzO^-$, toluene, reflux; then NaOMe, MeOH.

Unsaturated γ-lactams of type **229** and **230** were envisioned to be ideal building blocks for the preparation of **233** and **234**, as they incorporate the complete seven carbon skeleton of the final pyrrolizidines and are equipped with suitable substitution and chirality. Enantiomerically pure crys-

talline unsaturated lactams **229** and **230** were first prepared by Lewis acid-promoted condensation of **227** with the pyrrole-based siloxydiene **228**. In the event, the nature of the Lewis acid catalyst played a decisive role in controlling the stereochemical course of the condensation, allowing the selective preparation of either **229** ($SnCl_4$ as catalyst) or its C-4 epimer **230** (BF_3 etherate as catalyst). Then, lactam **229** was converted to **231** via hydrogenation followed by acidic treatment and permesylation. This compound was transformed into pyrrolizidine **232** by a two-step protocol consisting of carbonyl reduction with borane-dimethyl sulfide complex followed by DBU-assisted annulation. For the intermediate **232** to be converted to either **233** or **234**, a divergent protocol had to be employed. Enantioconservative deprotection to the free base **233** was performed by exposing **232** to Na-Hg in 2-propanol. On the contrary, recourse to tetrabutylammonium benzoate in toluene resulted in efficient displacement of the two adjacent OMs groups by the benzoate anion with configurational inversion to produce a benzoyl derivative, which was transformed to the free base **234** upon treatment with NaOMe in methanol. Paralleling the scheme and utilizing the same chemistry, but reversing the mode of the final transformations, *ent*-**233** and *ent*-**234** were synthesized from **230**, via intermediates **235** and **236**.

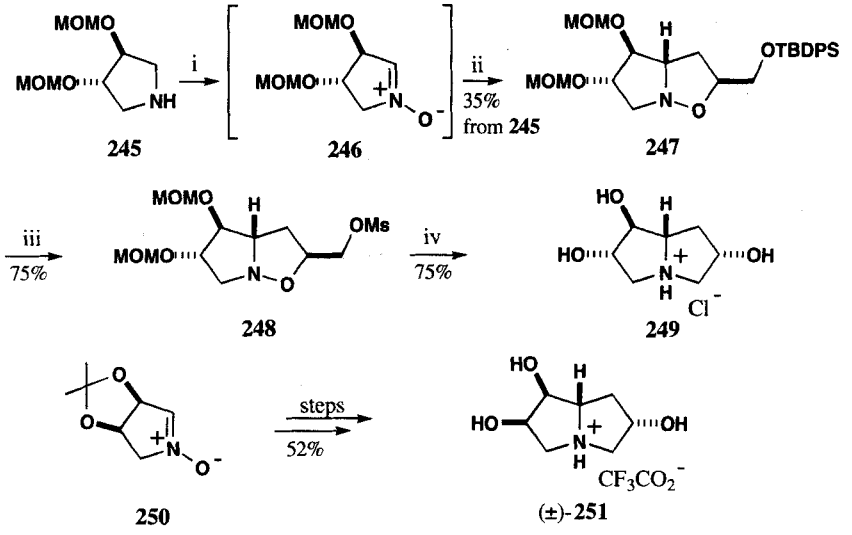
In their elegant approach directed toward the synthesis of the trihydroxylated pyrrolizidine **244**, Burgess and Henderson[46] exploited the asymmetric allylation between the chiral four-carbon aldehyde **238** and homochiral borane **239** as the pivotal homologation reaction. As illustrated in Scheme 40, the multistep synthesis started with 2,3-*O*-isopropylidene-D-erythrose (**100**), readily available from D-isoascorbic acid. One-carbon Wittig homologation afforded alkene **237** which was



Scheme 40. *Reagents and conditions*: i, $Ph_3P{=}CH_2$, THF, -25°; ii, PhthNH, DEAD, PPh_3, THF, 0°; then O_3, MeOH, CH_2Cl_2, -78°; then Me_2S; iii, $BF_3{\cdot}Et_2O$, -78°, THF; then H_2O_2, $NaHCO_3$, 40°; iv, MsCl, Et_3N, CH_2Cl_2, -78°; then $MeNH_2$, EtOH, 25°; then CbzCl, $NaHCO_3$, THF, H_2O; v, 9-BBN, THF; then H_2O_2, $NaHCO_3$; vi, MsCl, Et_3N, CH_2Cl_2, -78°; then H_2, 1,000 psi, EtOH; vii, HCl, THF, H_2O, 65°; then ion exchange chromatography.

transformed into the key aldehyde intermediate **238** by Mitsunobu amination followed by ozonolysis of the terminal double bond. According to a double asymmetric protocol, aldehyde **238** was reacted with homochiral borane derivative **239**, obtained from (+)-pinene, in the presence of BF_3 etherate to produce, after H_2O_2 treatment, homologated seven-carbon alkene **240** with exceptionally high stereocontrol. The subsequent steps in the synthesis centered around ring-closures and manipulation of the protecting groups. Thus, the first annulation to pyrrolidine **241** was carried out by mesylation of the free hydroxyl, followed by deprotection of the amine function, which resulted in spontaneous cyclization, and final *N*-Cbz protection. Hydroboration-oxidation of **241** produced **242** which underwent the second cyclization to pyrrolizidine **243** by conventional chemistry involving mesylation of the terminal hydroxyl followed by hydrogenolytic removal of the Cbz protecting group. Removal of the isopropylidene and MOM protections, and routine ion exchange chromatography afforded the desired product **244** with a quite satisfactory 13% overall yield for the entire sequence from **100**.

To gain access to homochiral trihydroxylated pyrrolizidine **249**, Wightman and McCaig[47] utilized L-tartrate derived dihydroxypyrrolidine **245** as the chiral starting unit. As shown in Scheme 41, exposure of **245** to Davis' reagent resulted in formation of unstable nitrone **246** which was coupled to allyl-*tert*-butyldiphenylsilyl ether to afford the cycloadduct **247** as the only isolable compound. The *O*-TBDPS protection was replaced by mesyl to produce **248**; hydrogenolytic cleavage of the N-O bond in **248** then resulted in spontaneous ring closure to produce a protected pyrrolizidine, which was liberated by acidic treatment to afford (1*S*,2*S*,6*S*,8*S*)-1,2,6-trihydroxypyrrolizidine (**249**), characterized as its hydrochloride. Similar chemistry was also exploited by the same authors[47] to forge a racemic isomer of **249**, namely trihydroxypyrrolizidine (±)-**251**, by starting with *meso*-nitrone **250**.

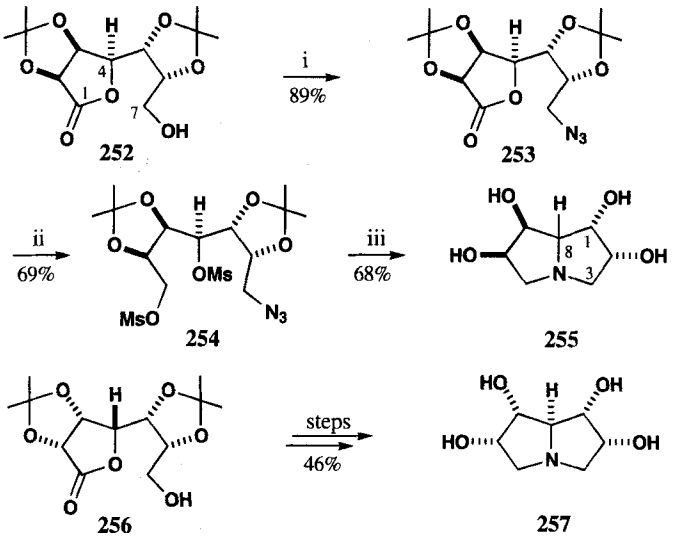


Scheme 41. *Reagents and conditions*: i, Davis' reagent, $CHCl_3$; ii, CH_2=$CHCH_2OTBDPS$, $CHCl_3$, reflux; iii, TBAF, THF; then MsCl, Et_3N, CH_2Cl_2; iv, H_2, Pd/C, EtOH; then aq. HCl.

As part of a continuing study focused on the exploitation of enantiomerically pure sugar derivatives en route to, among other targets, polyhydroxylated nitrogen heterocycles, Fleet and coworkers[48,49] described efficient syntheses of the densely oxygenated pyrrolizidines **255** and **257** by starting with heptonolactones of suitable substitution and chirality. The synthesis of homochiral pyrrolizidine **255** requires the joining by nitrogen of C-1, C-4, and C-7 of the diacetonide **252** (Scheme 42). A key feature of **255** is that it possesses a non-stereogenic center at C-8, and, since C-8 in **255** derives from C-4 of the starting lactone **252**, the introduction of nitrogen with inversion or retention of configuration will still result in the synthesis of pseudo C_2-symmetric **255**.

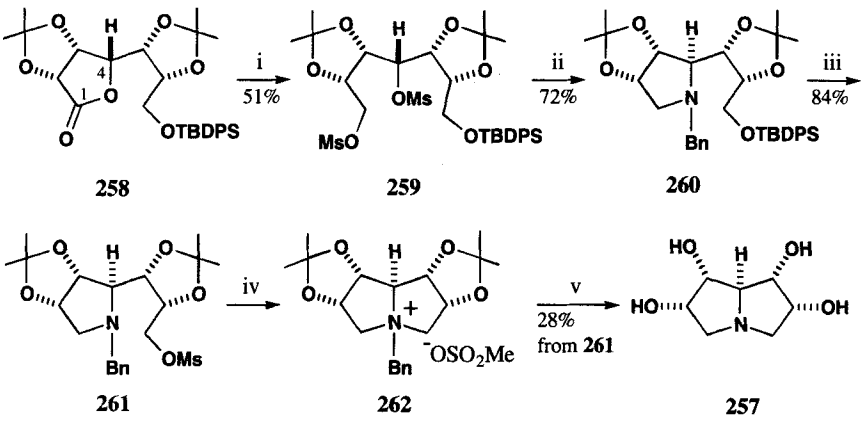
Esterification of the primary alcohol in **252** with triflic anhydride, followed by displacement of the triflate with NaN_3 gave the fully protected azide **253**. Reduction of the lactone **253** with $NaBH_4$ afforded a diol intermediate, which was easily converted to dimesylate **254**. Hydrogenation of the azide group within **254** to an amine followed by treatment with sodium acetate resulted in simultaneous double cyclization to a protected pyrrolizidine which was liberated by acidic treatment to form the target pyrrolizidine **255** with a remarkable 42% overall yield from **252**.

By exactly the same chemistry, tetrahydroxylated *meso*-pyrrolizidine **257** derived from isopropylidene-protected D-*glycero*-D-*gulo*-heptono-1,4-lactone **256**.



Scheme 42. *Reagents and conditions*: i, Tf_2O, pyridine; then NaN_3, DMF; ii, $NaBH_4$, EtOH; then MsCl, pyridine; iii, H_2, Pd/C, EtOH; then NaOAc; then aq. TFA.

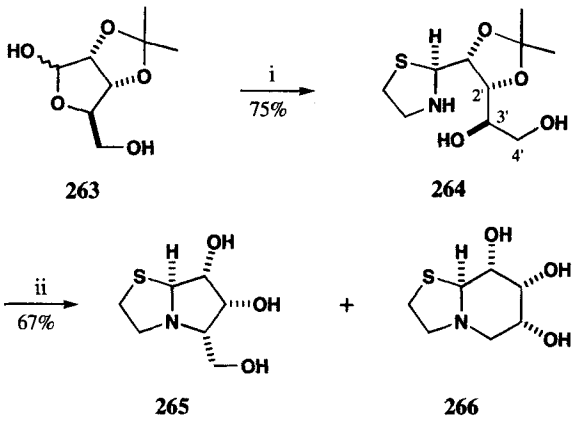
An alternative synthesis of **257** from protected lactone **258** emphasized preliminary formation of a pyrrolidine ring between C-1 and C-4 (Scheme 43).[49] Reduction of the lactone **258** with $LiAlH_4$ gave rise to an open-chain diol which was directly transformed into dimesylate **259** by trivial chemistry. Nitrogen was introduced by treatment of **259** with benzylamine to afford silylated *N*-benzylpyrrolidine **260**.



Scheme 43. *Reagents and conditions*: i, $LiAlH_4$, THF; then MsCl, pyridine, DMAP; ii, $BnNH_2$; iii, TBAF, THF; then MsCl, pyridine, DMAP; iv, spontaneous cyclization; v, H_2, Pd/C, EtOH; then aq. TFA.

The silyl protecting group in **260** was replaced with a mesyl moiety to produce **261**, which underwent spontaneous annulation to **262**. Cleavage of the *N*-benzyl group by catalytic hydrogenation followed by acidic treatment finally afforded the same *meso*-pyrrolizidine **257** as that prepared by the above described procedure.

Isosteric variants of certain bioactive compounds often result in novel structures displaying even more potency as compared to the activity of the native counterparts. According to this line of thought, the synthesis of the quite unusual thiazolo-pyrrole derivative **265**, an analogous representative of the australine family, was planned and executed, moving from protected D-ribose **263** and cysteamine (Scheme 44).[50]



Scheme 44. *Reagents and conditions*: i, $HSCH_2CH_2NH_2$•HCl, MeONa, MeOH; ii, Bu_3^nP, DIAD, THF, reflux; then 1N HCl, THF.

Treatment of **263** with cysteamine in methanol at room temperature afforded a thioaminal diastereomeric mixture with a strong preference for the (*S*)-configured derivative **264** (*S*:*R* = 92:8). The subsequent cyclization of **264** to bicyclic derivatives **265** and **266** was attempted under a variety of conditions ranging from conventional Mitsunobu protocol (Bu_3^nP-DIAD) to the activating PPh_3-CCl_4-Et_3N system in acetonitrile, to Bu^nLi-TsCl. In particular, when **264** was treated with Bu_3^nP-DIAD in refluxing THF, a 1:1 mixture of australine-type compound **265** and castanospermine-type derivative **266** were formed after complete deprotection in a 67% combined yield.

Mechanistically, the concomitant formation of both an indolizidine and a pyrrolizidine nucleus can be attributed to competitive annulation paths involving either the C-3' hydroxyl or the C-4' hydroxyl at the end of the chain of **264**. As intermediary species, a terminal epoxide or an activated phosphinium entity can be postulated, responsible for the observed unselective annulation behavior.

IV. CONCLUSION

This review has covered a number of recent synthetic methodologies to access hydroxylated pyrrolizidines, including approaches that exploit homochiral precursors and auxiliaries, as well as procedures adopting, as a key stage, enzyme-promoted generation of the chirality. Few examples of significant diastereoselective syntheses have been discussed, wherein the target pyrrolizidines are formed as racemates. Alkaloids related to the necine skeleton are well represented with a variety of remarkable syntheses in both the homochiral and racemic domains. On the contrary, scant attention has been paid to the development of viable approaches to the alexins and unnatural hydroxylated pyrrolizidines, despite the great potential displayed by these substances in biology and in medicinal chemistry.

In the majority of the procedures discussed herein, the pyrrolizidine skeleton was forged onto a preexisting pyrrolidine nucleus containing a resident carbon chain annulated during an advanced stage of the synthesis. In some instances, quite versatile totally synthetic procedures were devised, suitable to implementation of a number of stereoisomers and congeners for a given class of compounds, both natural and unnatural. No doubt, this synthetic issue represents a remarkable premium when targets of biological interest are involved. In this respect, the design and development of flexible routes adopting uniform chemistry associated with modular synthetic tactics should be encouraged as a tool to gain molecular diversity. A fascinating advance could be the application of combinatorial synthesis towards the construction of small pyrrolizidine libraries to be used for rapid identification of new biological leads. In this review we attempted to discuss all pertinent research articles which appeared during the chosen period, though a few important contributions might have been omitted.

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