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Enantiospecific Synthesis of Heterocycles from α-Amino Acids

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I. Introduction

The development of methods for the asymmetric synthesis of chiral compounds has been an area of intense research over the last decade.[1] The interest in the preparation of chiral compounds in enantiomerically pure form has greatly increased lately due to several factors: the enantioespecificity shown by most biological systems in their responses to drugs, the regulatory pressure on the pharmaceutical industry to market chiral drugs as single enantiomers, and the strong drive for synthetic efficiency. Special attention has been devoted to the asymmetric synthesis of heterocyclic compounds, due to the fundamental biological roles they play. Researchers in this field have relied heavily on enantiospecific processes proceeding from the chiral pool to gain access to this broad class of compounds.[2] Of all the members of the chiral pool, amino acids, due to their versatility,[2a] have been the most extensively used for the synthesis of chiral, enantiomerically pure heterocycles. The proteinogenic amino acids possess a limited but

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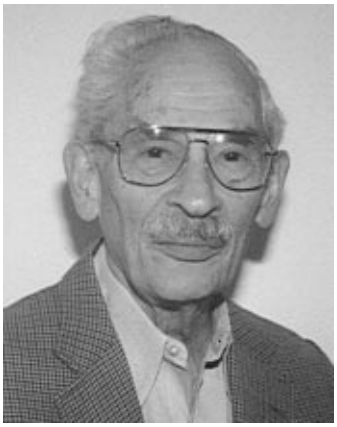


Henry Rapoport was born in Brooklyn, NY, in 1918. He received in B.S. (1940) and Ph.D. (1943) degrees from the Massachusetts Institute of Technology. After two years in industry on the penicillin project, he received a National Research Fellowship and worked with Dr. Lyndon Small on the opiates at the National Institutes of Health. In 1946 he joined the Chemistry Department at the University of California, Berkeley, where he is currently Professor Emeritus. His research interests have been, and continue to be, in the areas of natural products and synthesis.

significant number of functional groups, which facilitates synthetic operations; their protection−deprotection−activation chemistry is thoroughly documented[3] and they are readily available commercially, usually in both enantiomeric forms. This article reviews the use of amino acids as enantiomerically pure starting materials for the synthesis of heterocyclic compounds for the period from 1986 to March 1994; the prior efforts in this area have been adequately covered.[2a,c] An account of the use of optically active *N*-protected α-amino aldehydes in enantiospecific synthesis (including applications to the synthesis of several heterocyclic compounds) has also appeared.[4]

We have focused our attention on methodologies in which the amino acid is incorporated, totally or partially, in the final product. The use of amino acids as removable chiral auxiliaries for asymmetric induction is not covered. The synthesis of cyclic peptides is not covered unless they contain another heterocyclic system besides the cyclopeptide itself. The material presented is organized according to the amino acid employed as starting material; a special chapter is devoted to present synthetic methods of general applicability to different amino acids.

II. Determination of Enantiomeric Purity

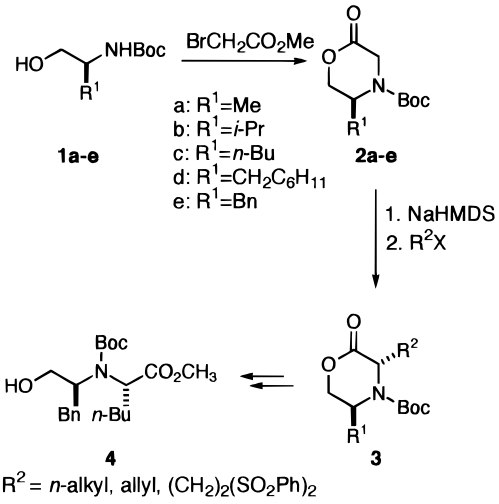
Over the past decade the efficiency of asymmetric synthesis has been developed to the point where enantiomer ratios of >95/5 are routinely achieved. This level of selectivity has in turn led to a demand for increased accuracy and reliability of the analytical methods for determination of enantiomer ratios. Methods of analysis based on GC[5] or HPLC[6] using chiral stationary phases are the most sensitive and accurate, while NMR-based methods employing chiral shift or solvating reagents, although less sensitive, are more rapid and convenient.[7] These methods allow the determination of enantiomer ratios when both enantiomers of the compound to be analyzed are available. When this is not the case, derivatization of the potential enantiomer mixture with an excess of a chiral agent whose enantiomer ratio (preferably ≥99.5/0.5) is known followed by NMR, GC, or HPLC analysis of the resulting diastereoisomers is the method of choice, provided that the detection sensitivity has been established. In the latter method it is necessary to demonstrate that kinetic resolution has not occurred, and this is best done by showing that equal amounts of diastereomers are formed with a racemic reagent. The output of all of the above determinations is a ratio of enantiomers which can be straightforwardly converted to the traditional % enantiomeric excess (ee) or more directly reported as enantiomer ratio (er).[8]

Surprisingly, perusal of the literature on asymmetric synthesis reflects a state of confusion about the standards that should be used not only for the determination of enantiomer ratios, but also for the presentation of the data. In a large percentage of cases the question of the enantiomeric purity of the compounds prepared was not addressed at all, while in a majority of articles the determination was carried out by chiroptical methods, which, it must be stressed, are unreliable.[9]

III. General Methodology

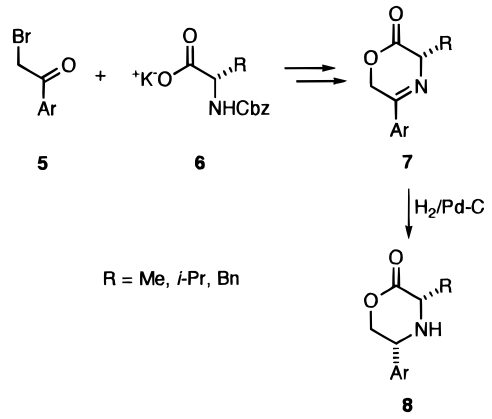
Several general syntheses of heterocyclic systems from α-amino acids or derivatives have been reported. Tetrahydro-5-alkyl-1,4-oxazin-2-ones (**2a**−**e**) were prepared in one reactor from the corresponding amino alcohols **1a**−**e**, ethyl bromoacetate, and Boc_2O (in 30−67% yields), and stereoselectively alkylated at position-3 to give *trans*-tetrahydro-3,5-dialkyloxazinones (**3**, *trans*/*cis* ratio, 14/1 to 100/0),[10] which are useful synthetic intermediates (Scheme 1). Thus the product of the alkylation of **2e** with *N*-butyl iodide was hydrolyzed and esterified to give **4** (60% overall), an intermediate in the synthesis of the nonpeptide renin inhibitor A-68064.[11] The enantiomer ratio of the starting material is most probably maintained throughout the synthesis, since the original stereogenic center should not be affected by the conditions used.

Scheme 1



A route to the *cis* isomers **8** was developed by stereoselective hydrogenation of 2,3-dihydro-6*H*-3-alkyl-1,4-oxazin-2-ones (**7**), prepared by condensation of the potassium salt of the corresponding *N*-Cbz amino acid **6** with aromatic α-bromo ketones **5**, followed by Cbz deprotection and cyclization (50−90% overall)[12] (Scheme 2). Catalytic hydrogenation of **7** using 10% Pd−C afforded **8** with >98% diastereo-

Scheme 2

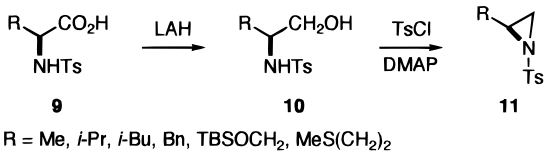


meric stereoselectivity (eight examples, 35−80% yields). The enantiomer ratio of the tetrahydrooxazinones **8** was not determined, despite the fact that the hydrogen attached to the stereogenic center in the dihydrooxazinones **7** is fairly acidic, and this may result in racemization. The dihydrooxazinones **7** could, in principle, also be used to gain access to a greater variety of compounds if addition of carbon nucleophiles to the imine could be carried out successfully (if R = Ph, the system would lend itself very nicely for the preparation of C-alkylated α-aryl amino acids).

A preparatively useful, improved synthesis of chiral *N*-tosylaziridines **11** was recently developed by reduction of *N*-tosylamino acids, followed by *O*-tosylation and base-catalyzed ring closure of the alcohols **10** (67−89% overall)[13] (Scheme 3). Alcohols **10** were shown to be enantiomerically pure by analysis of their MTPA esters (500 MHz ^{1}H NMR analysis).

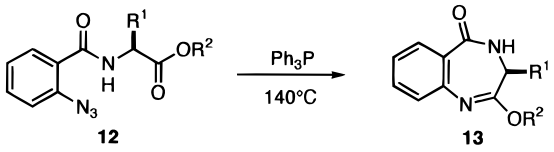
An intramolecular aza-Wittig reaction was used for the synthesis of a series of 1,4-benzodiazepin-5-ones

Scheme 3



13 from *N*-(*o*-azidobenzoyl)amino acid esters **12** (39−86%) via the Staudinger reaction[14] (Scheme 4). The

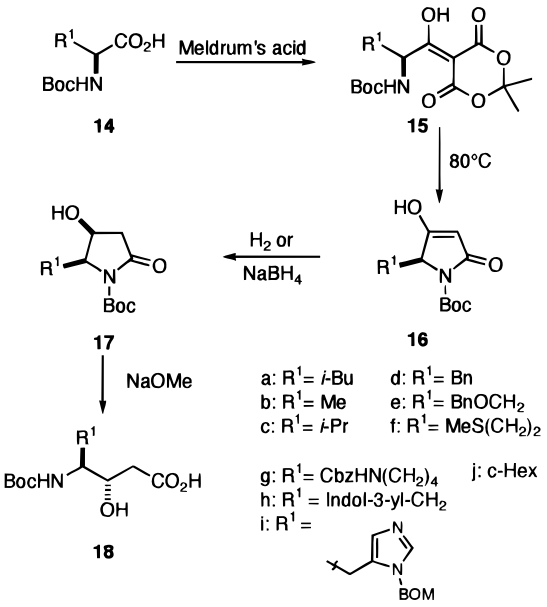
Scheme 4



value of this approach for the preparation of these potentially psychoactive agents as pure enantiomers remains to be seen, since the enantiomer ratios of the products were not determined.

Chiral tetramic acids **16**, prepared by condensation of the corresponding *N*-Boc-amino acid with Meldrum's acid followed by thermolysis of the intermediate enols **15**, proved to be convenient precursors of the statine analogues **18**[15,16] (Scheme 5). Overall yields were good except for the case of the histidine derivative, where problems were encountered in the

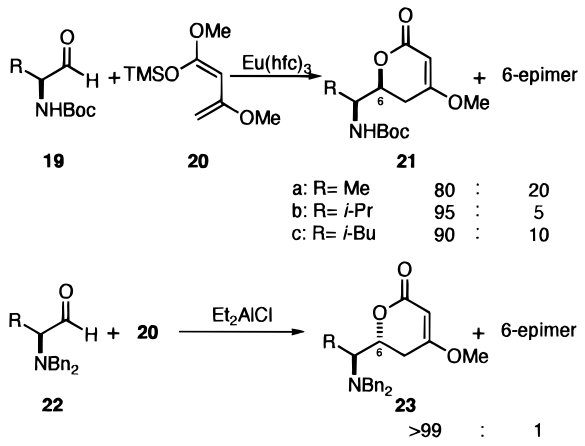
Scheme 5



cyclization step (**15i** to **16i**, 26% yield).[16] Some racemization during the sequence took place since **18i** (the only compound whose enantiomer ratio was determined) had an er of only 94/6.[16a] Lactam **16j** underwent a stereoselective aldol condensation with isovaleraldehyde in a synthesis of a cyclic dipeptide renin inhibitor.[15b] The serine-derived tetramic acid was used in a synthesis of a (2*S*,3*R*)-3-hydroxyproline derivative.[16b]

The application of *N*-protected α-amino aldehydes as dienophiles in hetero-Diels−Alder reactions has already been reviewed.[4] Recent progress in this area has allowed the stereocontrolled synthesis of unsaturated *δ*-lactones **21** and **23**, which are precursors

Scheme 6



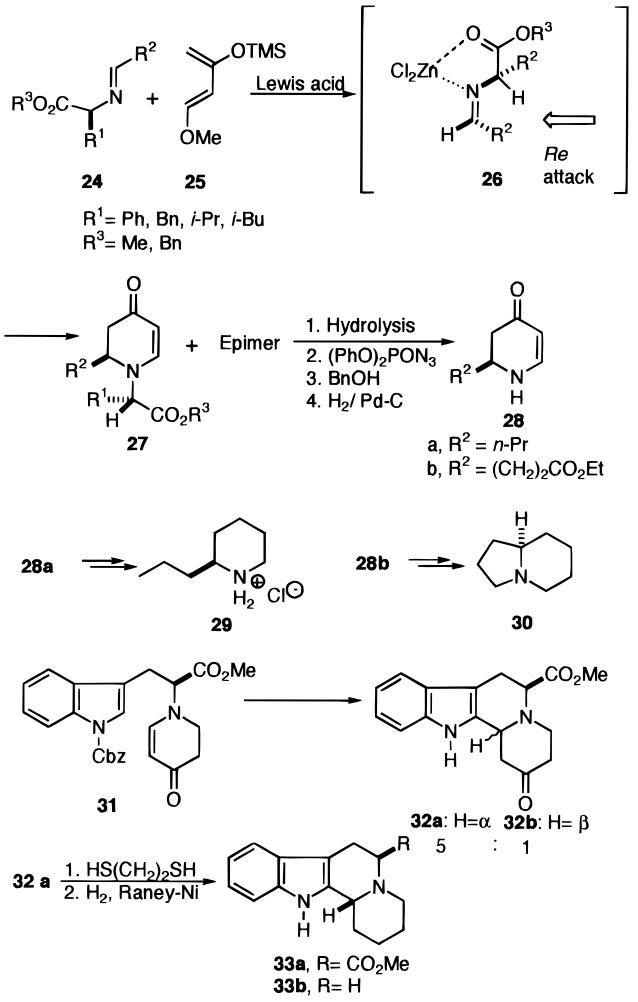
of β-amino alcohols and statine analogues.[17] The sense of stereoselection was governed by the size of the nitrogen protecting group; thus the Lewis acid-catalyzed cycloaddition of *N*-Boc-amino aldehydes **19** with diene **20** afforded the *threo* lactones **21** selectively, resulting from a chelation-controlled addition, while the Et_2AlCl-catalyzed reaction of *N*,*N*-dibenzylamino aldehydes **22** with **20** gave the *erythro* (nonchelation controlled) isomers **23** with complete diastereoselectivity. The cycloadditions proceeded with complete retention of configurational integrity (Scheme 6).

An entry into the piperidine, indolizidine, and indoloquinolizidine systems was developed on the basis of a tandem Mannich−Michael reaction (formally a hetero-Diels−Alder reaction) of α-imino esters **24** with diene **25**.[18] The cyclizations preferentially gave the (6*S*)-piperidones **27** by attack of the diene to the *Re* face of the chelated intermediate **26** (Scheme 7). The highest diastereomer ratios were obtained with isoleucine imines (>94/6). Nitrogen deprotection of **27** required an elaborate sequence of ester hydrolysis, Curtius rearrangement to a benzyl carbamate, and hydrogenolysis to yield dihydropyridines **28a**,**b** (50−80% overall).[18d] Ultimately, **28a** was converted into (*S*)-coniine hydrochloride (**29**) in a straightforward way (five steps, 48% overall), and **28b** into (*R*)-δ-coniceine (**30**, five steps, 15% overall). The tryptophyldihydropyridine **31**, prepared from Cbz-tryptophan formaldimine and Danishefsky's diene in 63% yield, was transformed into the indoloquinolizidine **33a**, an intermediate in Rapoport's synthesis of **33b**, in four steps (42% overall).[18d]

This method for the preparation of dihydropyridines **28** could, conceivably, be used for the preparation of 2,6-disubstituted piperidine alkaloids (*vide infra*) if 2-substituted dienes were used in the cycloaddition reaction (followed by reduction of the intermediate 2,6-disubstituted dihydropyridines). An alternative way for the preparation of these alkaloids would be the 1,4-addition of cuprates to **28** (most probably protected as a carbamate to activate the enaminone system toward nucleophilic addition).[18i]

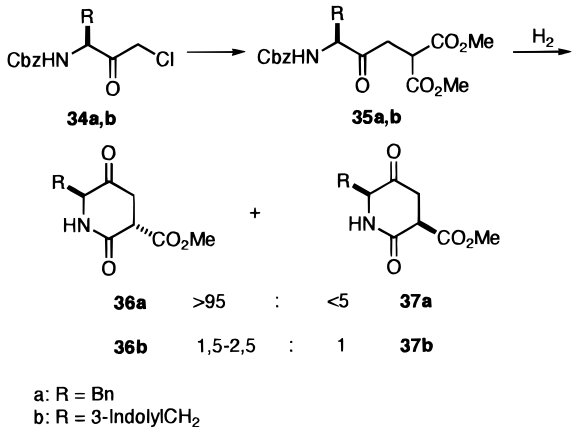
Increasingly, lactams are being used as conformational constraints for probing the bioactive conformations of peptides. 2,5-Diketopiperidines **36** and **37**, used as conformationally constrained analogues of ketomethylene dipeptides, were prepared from the

Scheme 7



corresponding *N*-Cbz-α′-amino-α-chloro ketones **34** (obtained from the corresponding *N*-Cbz-amino acid-mixed anhydride and diazomethane followed by reaction with HCl) and dimethyl malonate (Scheme 8).

Scheme 8

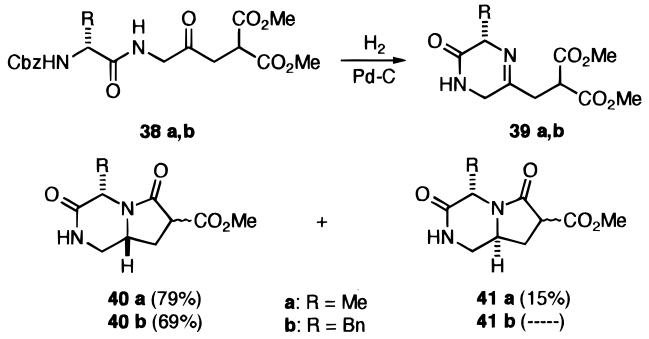


The resulting ketones **35** underwent hydrogenolytic cleavage of the *N*-protecting group and cyclization to give **36** and **37** (40−60% overall).[19] The diastereoselectivity of the cyclization was strongly dependent on the nature of R. The enantiomer ratios of **35**−**37** were not determined, and this is of some concern due to the tendency of *N*-carbamoyl-α-amino ketones to

enolize toward the *N*-bearing carbon under alkaline conditions, leading to racemization.[20]

In a closely related approach to the perhydropyrrolo[1,2-*a*]pyrazines **40a**,**b**, which are conformationally restricted X-Gly-Gly tripeptides, the malonates **38a**,**b**, prepared from the corresponding dipeptide α-chloro ketone as above, afforded **40a**,**b** selectively on hydrogenation[21] (Scheme 9). The enantiomer

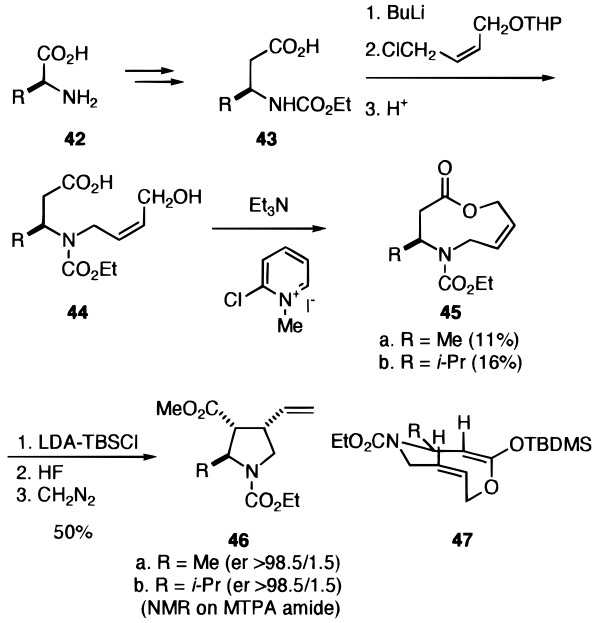
Scheme 9



ratios of **40a**,**b** were not determined, despite the intermediacy of **39**, which possesses a fairly acidic hydrogen attached to its stereogenic center, in their formation.

2,3,4-Trisubstituted pyrrolidines (**46**) were stereoselectively prepared by an enolate Claisen rearrangement of azalactones **45**, which were in turn obtained from the corresponding amino acid **42a**,**b** by an Arndt−Eistert procedure, followed by *N*-alkylation, and lactonization. Carefully controlled enolization of **45** (excess LDA-TBDMSCl, −100 °C to room temperature) gave the rearranged pyrrolidines **46a**,**b** with complete diastereoselection via a boatlike transition state **47**[22] (Scheme 10). This methodology

Scheme 10



might be of use for the synthesis of kainic acid analogues (*vide infra*) by using D-serine as starting material and an appropriately substituted chloroalkenol for the akylation of **43**.

IV. The Aliphatic Amino Acids

The aliphatic amino acids are inexpensive and readily available in both enantiomeric forms (except D-isoleucine). Due to the lack of functionality of their side chains they have been used almost exclusively for the construction of molecules which incorporate a chiral center with the amino acid side chain (methyl, isopropyl, isobutyl, or *sec*-butyl group) attached.

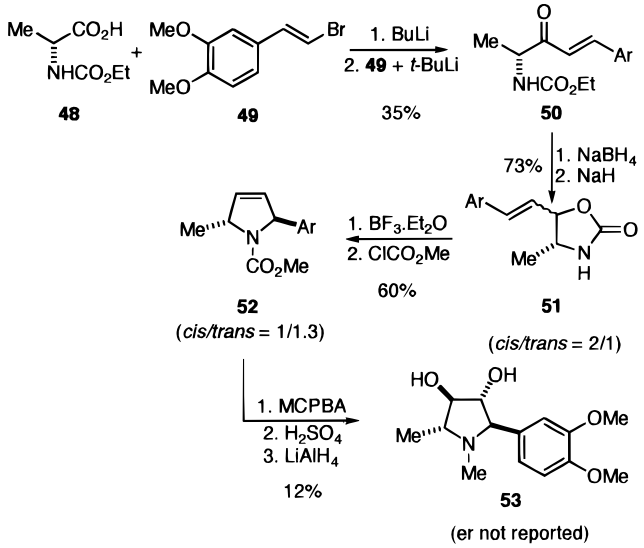
A. Alanine

Alanine has been used extensively as starting material to gain access to 2-methyl-substituted pyrrolidines or piperidines, which are fairly common structural features among several alkaloid families. (−)-Codonopsine (**53**), a hypotensive, substituted pyrrolidine, was synthesized in eight steps from *N*-ethoxycarbonyl-D-alanine (**48**). The key step was the $BF_3{\cdot}Et_2O$ promoted decarboxylative rearrangement of the allylic oxazolidinone **51** to the Δ^3-pyrrolidine **52**, presumably occurring through a carbenium ion intermediate (Scheme 11). Epoxidation of **52**, followed by solvolysis and carbamate reduction completed the synthesis of **53** (0.7% overall yield), whose optical rotation was close to the published value for the natural material, but whose enantiomer ratio was not further measured.[23a]

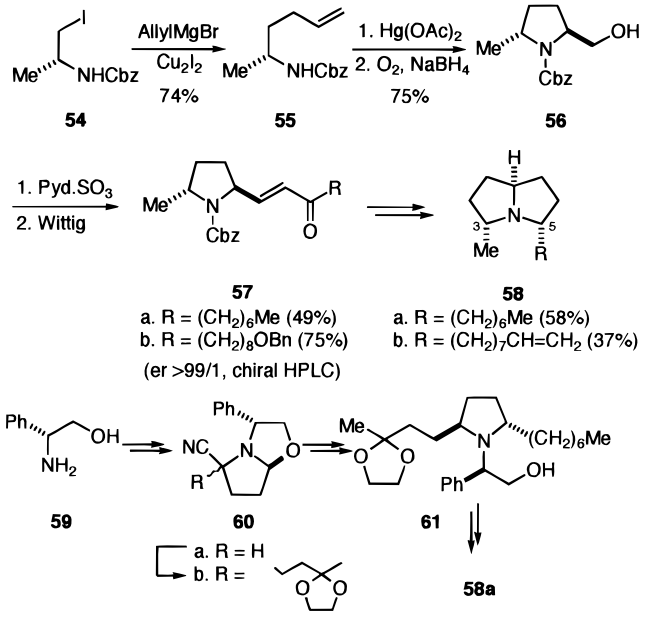
An alternative approach to the codonopsin alkaloids from tartaric acid has been reported, although the sequence is rather long and nonstereoselective.[23b]

Takahata *et al.* have developed a practical, highly diastereoselective synthesis of *trans*-2,5-disubstituted pyrrolidines from alanine. The key step was the kinetically controlled ($Hg(OAc)_2$, THF, room temperature), Hg(II)-promoted cyclization of butenylcarbamate **55** to give a pyrrolidino mercury compound which afforded exclusively *trans* alcohol **56** on oxidation[24a−c] (Scheme 12). Alcohol oxidation of **56** followed by Wittig−Horner reaction and hydrogenation allowed for a clean entry to the 3-methyl-5-substituted pyrrolizidine skeleton. In this way (+)-xenovenine (**58a**), an ant venom alkaloid, was prepared in 8% overall yield from D-alanine; **58b**,

Scheme 11



Scheme 12



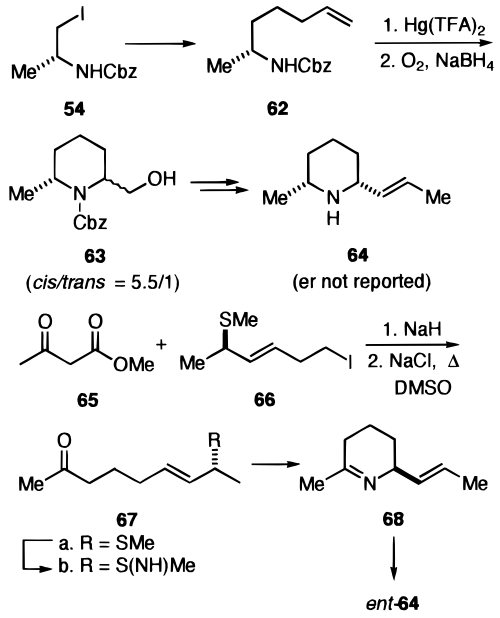
another ant venom component, was obtained in a straightforward fashion from pyrrolidino ether **57b**.[24a] This approach compares favorably with an alternative synthesis of **58a** reported by Husson and coworkers,[24d] who prepared **58a** from (*R*)-(+)-phenylglycinol (**59**) in seven steps (10% overall yield). The only drawback in Husson's efficient approach is that the control of the ring juncture relative configuration is not high (a 3/1 mixture of epimers was formed); this is a very common problem in the synthesis of *trans* disubstituted pyrrolidines.

The extension of the Hg(II)-promoted cyclization approach to the synthesis of piperidines was not straightforward, since the kinetically controlled cyclization of pentenyl carbamates, such as **62**, gave an almost 1/1 mixture of *cis* and *trans* 2,5-disubstituted piperidines. Under thermodynamically controlled conditions ($Hg(TFA)_2$, $MeNO_2$, room temperature), however, a *cis* selective cyclization ensued. In this manner, **62** yielded *cis*-**63** as the major product (5.5/1 *cis*/*trans* ratio); *cis*-**63** (isolated in 53% yield) was ultimately converted into (−)-pinidine **64** (5 steps from **63**, 44%)[25a] (Scheme 13).

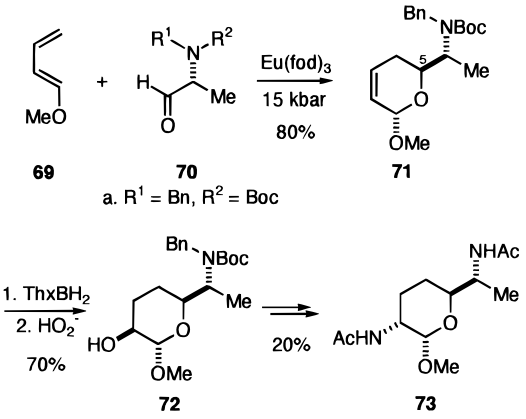
For the preparation of the unnatural (+)-pinidine, a superior, short, stereoselective synthesis from (*S*)-(−)-ethyl lactate has been reported.[25b] Alkylation of the enolate of methyl acetoacetate with iodide **66** (prepared in eight steps from (−)-ethyl lactate) gave ketone **67** after decarboxylation. A totally diastereoselective [2,3] sigmatropic rearrangement of a sulfonimine prepared from **67** gave (+)-pinidine after *in situ* reduction of the intermediate tetrahydropyridine **68**.

The high-pressure, Eu-mediated cycloaddition of diene **69** with protected alaninals **70** has been used for the synthesis of purpurosamine B, a sugar component of the aminoglycosidic antibiotic gentamycin C_2[26] (Scheme 14). The stereochemical outcome of the cyclization was shown to depend on the nature of the nitrogen protecting group,[26a,27] thus **70a** afforded a 16/1 mixture of **71** and its C-5 epimer on cyclization (80%). Regioselective hydroboration−oxidation of **71**

Scheme 13



Scheme 14



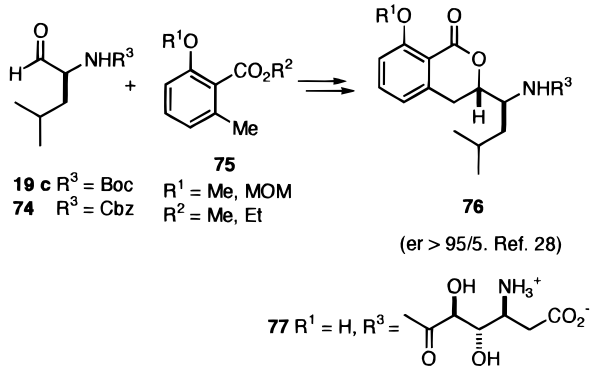
gave alcohol **72** which was transformed into the protected purpurosamine B (**73**) by a sequence involving debenzylation, alcohol oxidation, oxime formation, reduction, and acetylation.[26] The optical rotation of **73** was close to the published value for the natural material; its enantiomer ratio was not further measured.

B. Leucine

Several groups have reported the use of *N*-protected leucinals **19c** and **74** to gain access to the *δ*-lactam system of AI-77-B (**77**), a gastroprotective compound isolated from *Bacillus pumillus* AI-77.[28−30] Addition of the stabilized, benzylic carbanion derived from **75** to aldehydes **19c** and **74** proceeded with moderate, chelation-controlled diastereoselectivity (ratio: 2.2/1−5/1) to give lactone **76** in low to moderate yield (30−45%). Further straightforward elaboration afforded the natural product, benzopyran **77** (Scheme 15).

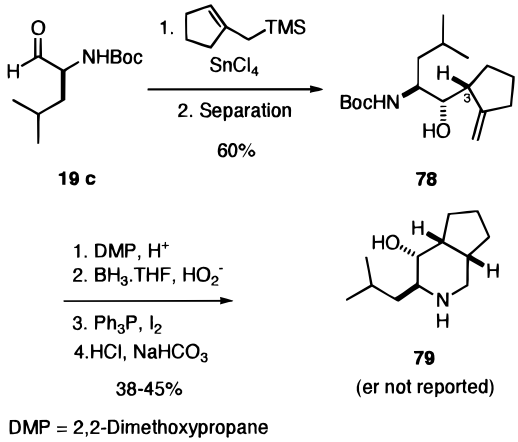
The interesting cyclopentane-fused piperidine **79** has been obtained from Boc-leucinal **19c** by a sequence starting with aldehyde allylation by an allyl silane, to give alcohol **78** with complete diastereoselection at the hydroxyl bearing carbon (1.3/1 mixture at C-3).[31] Acetonide formation and hydrobora-

Scheme 15



tion-oxidation afforded an alcohol which was iodinated and cyclized to give piperidine **79** (25% overall yield) (Scheme 16). Determination of the enantiomer

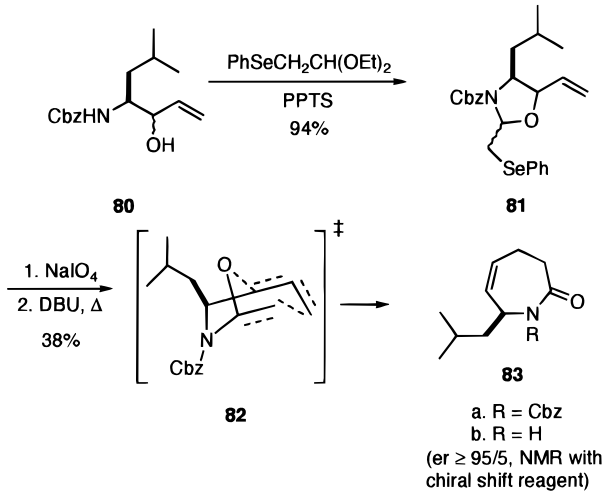
Scheme 16



ratio was not reported.

Asymmetric, unsaturated seven-membered lactams (azepinones) are a class of heterocycles to which only scant attention has been devoted. A clever approach to one member of this class has been developed, starting from allyl alcohol **80**, prepared from (*S*)-leucine in six steps (40% overall yield)[32] (Scheme 17).

Scheme 17

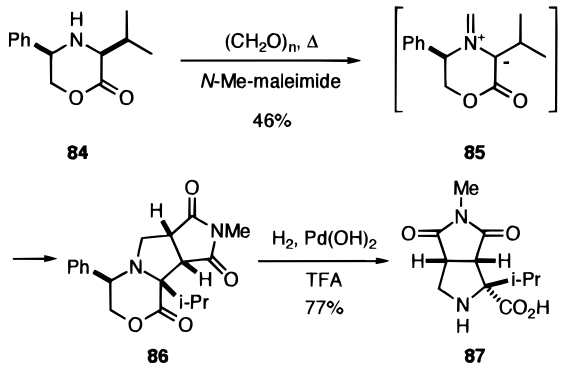


Phenylselenoacetal **81**, obtained by treatment of **80** with phenylselenoacetaldehyde dimethylacetal, was used as the key intermediate. Thus oxidation of **81** followed by thermolysis of the intermediate selenoxides gave a 1,6-diene which underwent a Claisen rearrangement to afford the desired 2-azepinone **83a** (38%). Treatment of **83a** with HBr gave **83b** in quantitative yield. The key Claisen rearrangement presumably proceeds through the chairlike transition state **78**. ^{1}H NMR measurements showed that **83** had an er ≥95/5.

C. Valine

2-Morpholinone **84**, obtained by hydrogenation of the cyclocondensation product of valine and α-bromoacetophenone, afforded the chiral ylide **85** on treatment with paraformaldehyde. This ylide gives endo selective [3 + 2] cycloadditions with maleimides, and this fact has been used to develop a diastereoselective synthesis of (*R*)-α-isopropylprolines.[33] Thus the reaction of **84** with paraformaldehyde in the presence of *N*-methylmaleimide gave the tricycle **86** as the only identifiable product (46%); use of other dipolarophiles did not afford the desired cycloadducts. Finally, hydrogenolysis of **86** gave the (*R*)-α-substituted proline **87** (Scheme 18).

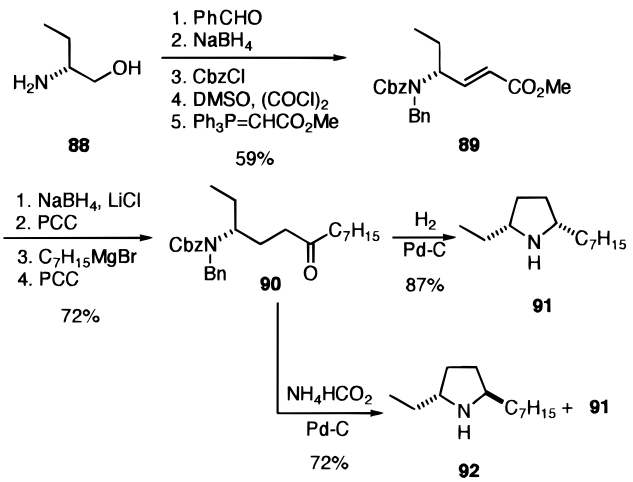
Scheme 18



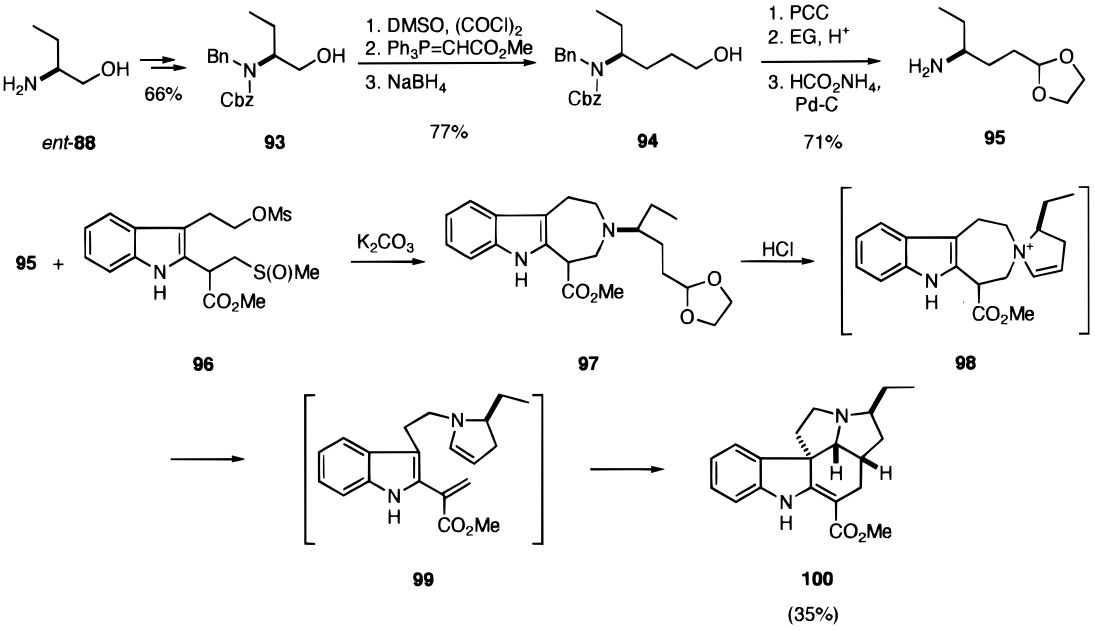
D. Miscellaneous

cis- and *trans*-5-ethyl-2-heptylpyrrolidines were prepared in a straightforward fashion from (*R*)-2-amino-1-butanol (**88**). Thus **88** was transformed into γ-amino ketone **90** in nine steps (42% overall yield); the latter was converted into the 2,5-disubstituted pyrrolidines **91** and **92** by two different hydrogenation procedures: catalytic hydrogenation gave *cis*-**91**

Scheme 19



Scheme 20



exclusively (87%), while transfer hydrogenation using NH_4HCO_2 as the hydrogen source gave a mixture of *cis*-**91** and *trans*-**92** in a 3/2 ratio[34a] (Scheme 19). Both **91** and **92** were enantiomerically pure as judged by ^{1}H NMR and HPLC analysis of their MTPA amides.

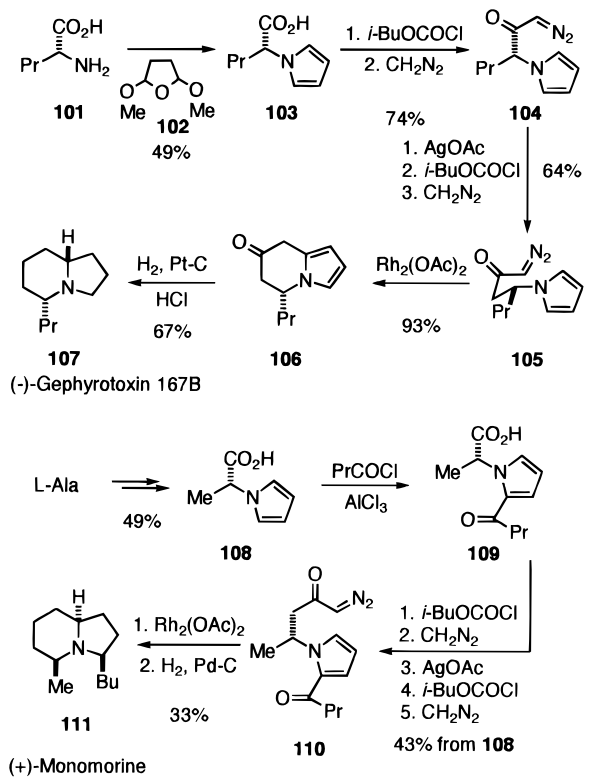
A more flexible method for preparing *trans*-2,5-dialkylpyrrolidines (from (*R*)-(+)-phenylglycinol) has been developed (*cf.* Scheme 12), although the diastereoselectivity displayed by this last method is only marginally better than the one depicted in Scheme 19.[34b]

An elaborate enammonium ion formation, Hoffmann elimination, and intramolecular Diels−Alder reaction sequence has been developed for the synthesis of the pentacyclic pseudoaspidosperma alkaloid (+)-20-epiibophyllidine (**100**) from (*S*)-2-amino-1-butanol (*ent*-**88**).[35] The required intermediate amino acetal (**97**) was prepared by condensation of indole **96** with amine **95**, obtained from *ent*-**88** in a straightforward fashion (9 steps, 36% overall yield). The key stereoselective tandem cyclization−elimination−cycloaddition (*endo* selective) took place on deprotection of the acetal group of **97** with HCl, to give **100** (35%) as the sole isomer (Scheme 20).

A stereoselective approach to the synthesis of indolizidine alkaloids, based on the reduction of bicyclic pyrroles, has been reported.[36a] The key pyrroles were prepared from D-norvaline and L-alanine, respectively, by a double Arndt−Eistert homologation, to give α-diazo-*β*′-amino ketones **105** and **110** (in this case, after the prior Friedel−Crafts introduction of a propyl ketone onto the aromatic ring, which ultimately became the butyl side chain in (+)-monomorine). Ketocarbene insertion into an aromatic C−H bond and stereoselective reduction completed the concise syntheses of (−)-gephyrotoxin 167B (**107**) and (+)-monomorine (**111**) (Scheme 21).

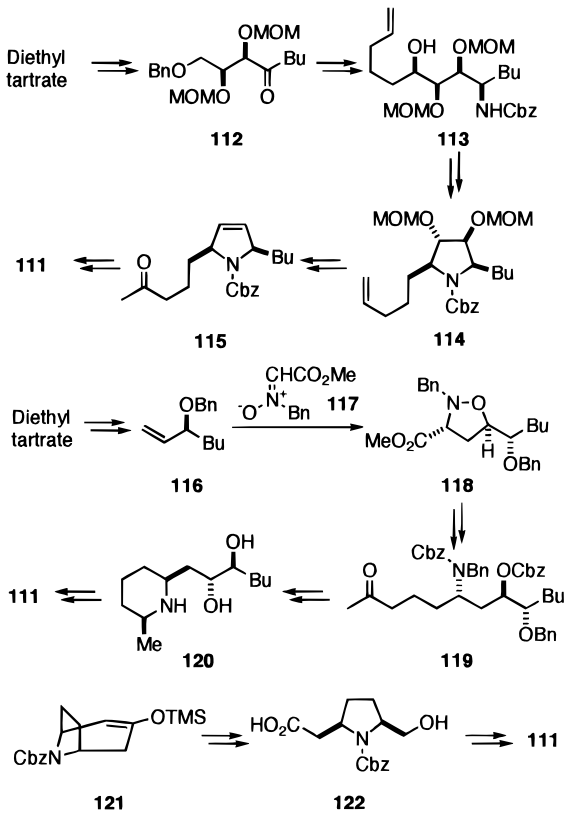
Alternative approaches to (+)-monomorine (**111**) from non-amino acidic starting materials have been developed.[36b−e] Kibayashi has developed two different syntheses of **111** from diethyl L-tartrate.[36b−d] Both approaches are rather lengthy, especially due to the

Scheme 21



excess of functionality (the two OH groups, which must be protected, deprotected, and then removed) present in the starting material. The enantioselective deprotonation of 8-azabicyclo[3.2.1]octan-3-one to give the optically active silyl enol ether **121** was the key step in Momose's synthesis of (+)-monomorine[36e] (Scheme 22). Ozonolysis followed by reduction of **121** afforded **122**, which after extension of both side chains and reductive cyclization gave **111**. This synthesis is somewhat longer (13 steps) than the one depicted in Scheme 21, but it is much more efficient (24% overall yield).

Scheme 22



V. The Aromatic Amino Acids

The aromatic amino acids are readily available in both enantiomeric forms. The reactivity of the aromatic side chains makes them ideally suited for the construction of bicyclic systems such as tetrahydroisoquinolines, tetrahydrocarbolines, and pyrroloindoles.

A. Phenylalanine

Phenylalanine has been used for the synthesis of heterocycles bearing a benzyl or a cyclohexylmethyl group attached to a stereogenic center, as well as for the preparation of tetrahydroisoquinoline alkaloids.

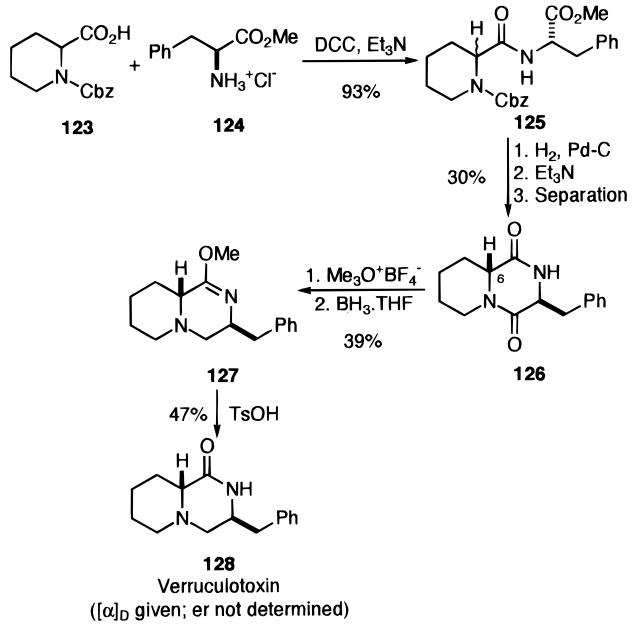
Two related routes to the mycotoxic oxopiperazine alkaloid verruculotoxin (**128**) from phenylalanine and pipecolic acid have been reported.[37,38] The bicyclic skeleton of **128** was readily assembled by condensation of racemic *N*-Cbz-pipecolic acid (**123**) and (*S*)-Phe-OMe·HCl (**124**), followed by carbamate deprotection and lactam closure, to give **126** (30%, plus its C-6 epimer, 26%) (Scheme 23). Completion of the synthesis required the differentiation of the carbonyl groups in order to achieve a selective reduction of the tertiary lactam; this was achieved by secondary amide protection as a lactim ether followed by tertiary amide reduction with BH_3·THF; deprotection of the lactim ether completed the synthesis of (−)-verruculotoxin (**128**).[37]

The condensation of sodium (*S*)-pipecolate (**129**) with aziridine **130**[13] avoided the selective reduction sequence of the previous synthesis and offered a more efficient way of synthesizing **128**[38] (Scheme 24).

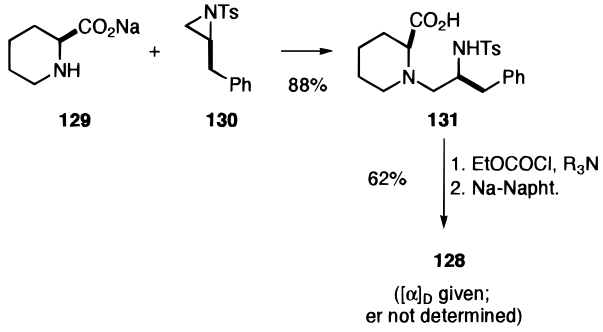
Lactone **136** has been a widely used intermediate for the synthesis of renin inhibitors which act as transition-state mimics.[39] A highly stereoselective synthesis of **136** starting from phenylalanine and passing through some interesting oxopiperidine intermediates has been described.[39] Phosphonate **133**, prepared from phenylalanine in four steps, gave acid **134** on reaction with methyl 3-methyl-2-oxobutanoate followed by hydrolysis (with concomitant double bond migration). The *N*-trityl group prevented the racemization of **133** and **134** under the basic conditions used in this sequence.[20] Lactam closure of **134** followed by ketone reduction gave an all *cis*-2-oxopiperidine which isomerized to lactone **136** on acid treatment (Scheme 25).

The tetracyclic skeleton of the antitumor antibiotic quinocarcin (**141**) has been prepared, although with some difficulty, from phenylalanine.[40] The tetrahydroisoquinoline moiety, **137**, was obtained from (*S*)-phenylalanine by a Pictet−Spengler cyclization followed by esterification and reduction (44%). Coupling of the 2,3,5-trichlorophenyl ester **138** with **137** and subsequent alcohol oxidation gave aminal **139** (78%) as a mixture of diastereoisomers. Iminium ion cyclization (promoted by $TiCl_4$) established the desired iminoazepinoisoquinoline system as a 1/1 mixture of diastereoisomers which were separated after Cbz deprotection and *N*-methylation, to give **140**. Thedesired aminonitrile **141** was obtained from **140** following standard transformations (Scheme 26).

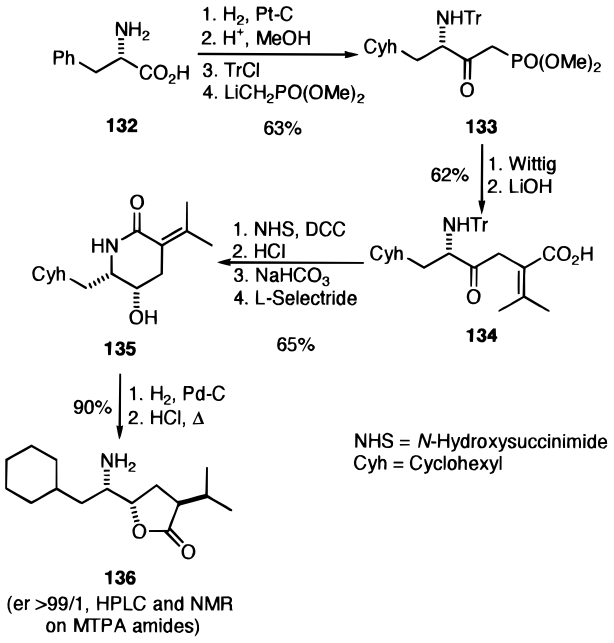
Scheme 23



Scheme 24



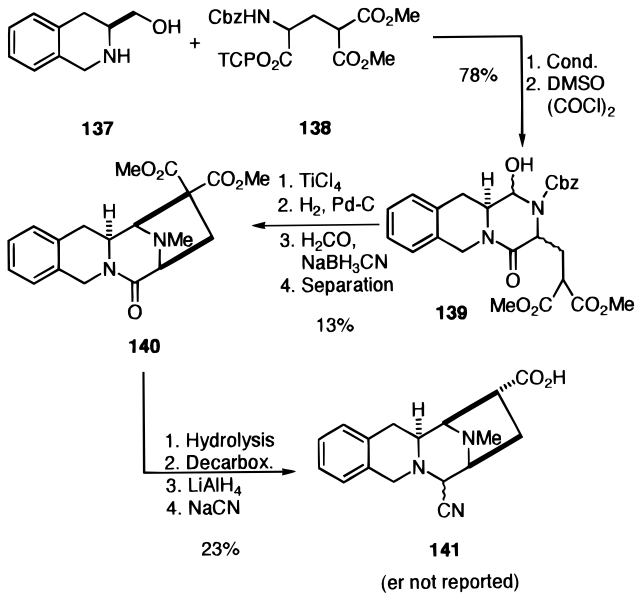
Scheme 25



132 **133** **134** **135** **136**

(er >99/1, HPLC and NMR on MTPA amides)

Scheme 26



137 **138** **139** **140** **141**

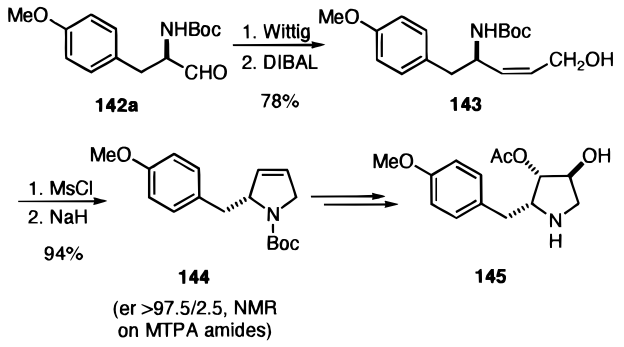
(er not reported)

B. Tyrosine

(*R*)-Methoxytyrosine aldehydes **142** have been employed as starting materials for two different syntheses of the antifungal antibiotic (−)-anisomycin (**145**).[41,42] *Z*-Selective Wittig−Horner reaction of **142a** with bis(2,2,2-trifluoroethyl)[(methoxycarbonyl)methyl]phosphonate followed by DIBAL reduction of the resulting *cis* unsaturated ester afforded amino alcohol **143**, which was mesylated and cyclized to give the 2,5-dihydropyrrole **144**, an intermediate in Meyer's synthesis of **145**[41a,b] (Scheme 27).

Reaction of the anion **146**, generated by the electrolysis of the corresponding trichloroacetate, with **142b** gave the aldol product **147** as a mixture of epimers (Scheme 28). Acid hydrolysis followed by treatment with $NaHCO_3$ gave lactam **148**; monodechlorination and cyclization of the resulting chloro alcohol gave epoxide **149** as a 1/1 mixture of diastereoisomers at C-3 and C-4. Epoxide opening under

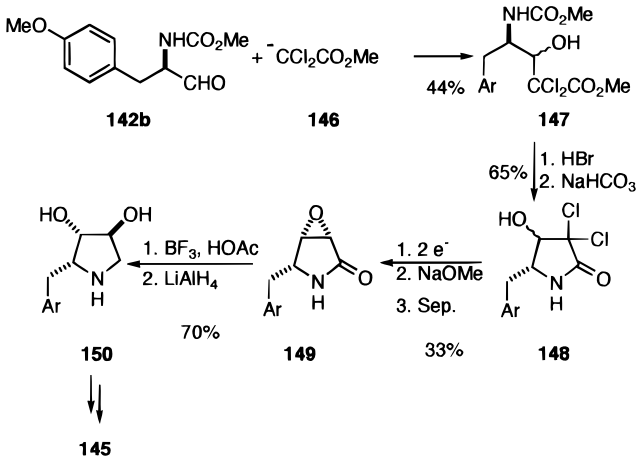
Scheme 27



142a **143** **144** **145**

(er >97.5/2.5, NMR on MTPA amides)

Scheme 28

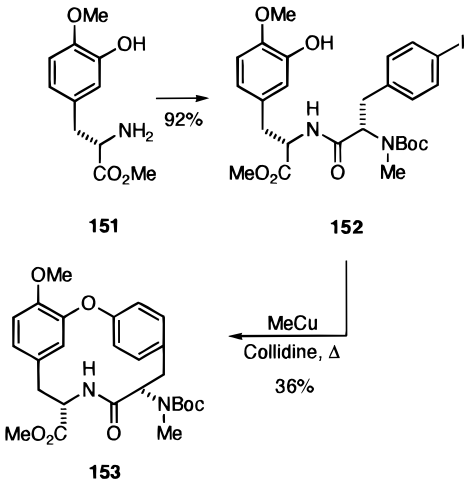


142b **146** **147** **148** **149** **150** **145**

acidic conditions was followed by lactam reduction to give (−)-deacetylanisomycin (**150**).[42]

Tyrosine appeared ideally suited for the synthesis of the unusual 14-membered dipeptide lactam **153**, a part of the bouvardin family of antitumor antibiotics. Thus, tyrosine was converted into 3-hydroxy-*O*-methyltyrosine methyl ester (**151**) and *N*-Boc-*N*-methyl-4-iodophenylalanine by a series of standard transformations (Scheme 29). Coupling of these two

Scheme 29



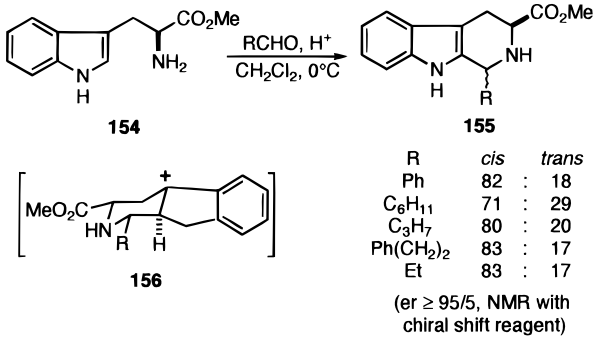
151 **152** **153**

compounds afforded dipeptide **152**, which was submitted to Ullmann macrocyclization conditions to yield **153**.[43a,b] A related approach involving an oxidative diphenol coupling to give **153** also has been described.[43c,d]

C. Tryptophan

An ample variety of indole alkaloids incorporate in their structures the tetrahydro-β-carboline system, which is readily accessible from a Pictect−Spengler cyclization of an appropriately substituted tryptophan and an aldehyde or aldehyde precursor. Due to this fact, a good deal of attention has been paid to the stereochemical control of this reaction. It has been shown that the low-temperature (below room temperature) Pictet−Spengler reaction of N_b-unsubstituted tryptophan methyl ester (**154**) with aldehydes gives *cis*-carbolines **155** with moderate diastereoselection (≈4/1 ratio) and complete retention of the absolute configuration (Scheme 30). The ob-

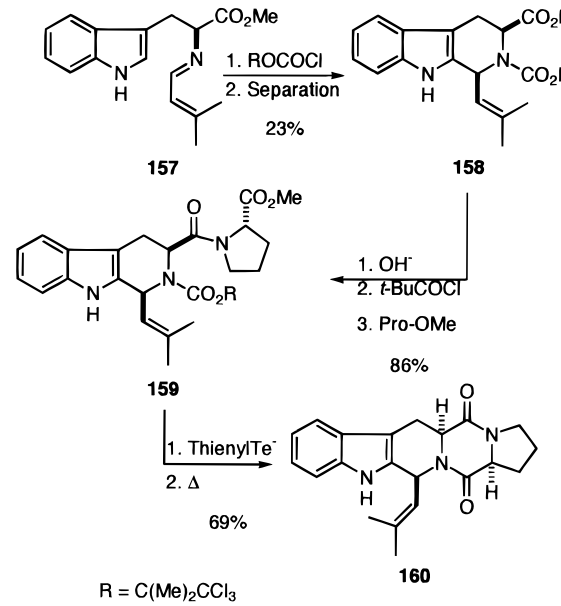
Scheme 30



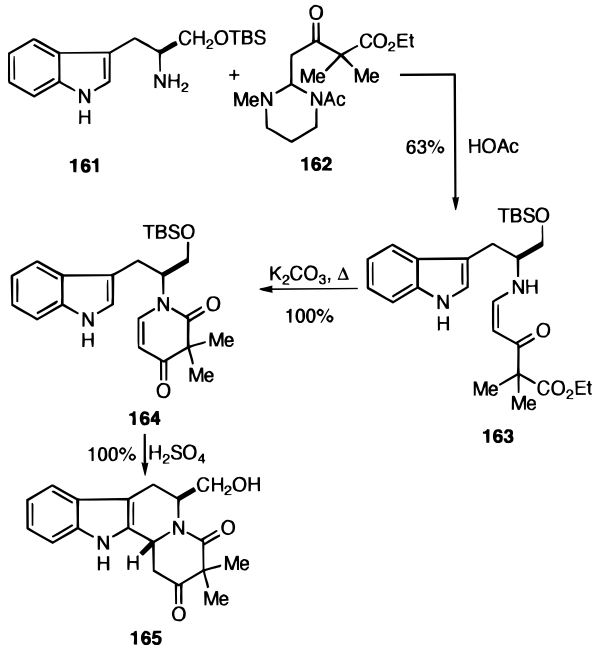
served diastereoselectivity could be explained by the intermediacy of the carbenium ion **156**, possessing two equatorial substituents.[44] On the other hand, N_b-substituted tryptophans afforded mainly the *trans* products, possibly to avoid steric interactions among three contiguous equatorial substituents in the intermediate N_b-substituted carbenium ion.[45]

The 2,2,2-trichloro-1,1-dimethylethyl chloroformate-promoted Pictet−Spengler cyclization of imine **157** was the key step in Cava's synthesis of 6-demethoxyfumitremorgin C (**160**), an analogue of the tremorgenic mycotoxin fumitremorgin C[46] (Scheme 31). The desired carboline (*cis*-**158**) was obtained as the minor

Scheme 31



Scheme 32



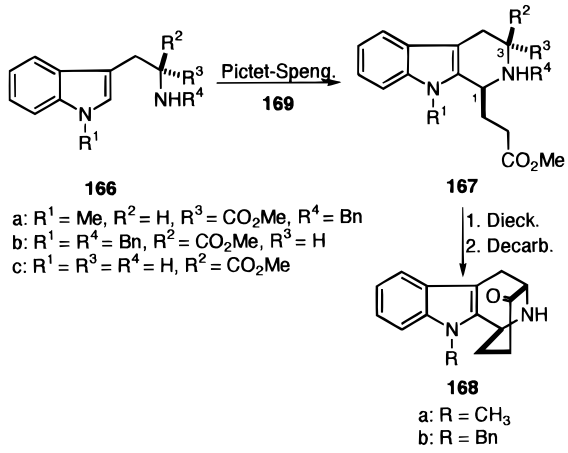
product from the cyclization (as expected from the stereochemical considerations presented above; *cis*/*trans* ratio 1/2). Coupling of the tricycle **158** to proline methyl ester was carried out using standard methodology, and afforded **159**, which was decarbamoylated by reaction with the thienyl telluroate anion, and cyclized in refluxing toluene to give the desired compound **160**.

A Pictet−Spengler reaction was also used for an efficient and stereoselective synthesis of the *N*(5),-*N*(10)-methylenetetrahydrofolate model **165**.[47] Thus the silyl ether **161** (prepared from tryptophan in two steps, 37% yield) was condensed with aminal **162** to give the vinylogous amide **163**; lactamization of **163** afforded **164** which was subjected to the Pictet−Spengler reaction to yield the tricycle **165** with complete *trans* selectivity, as expected for an N_b-substituted tryptophan[45,47] (Scheme 32).

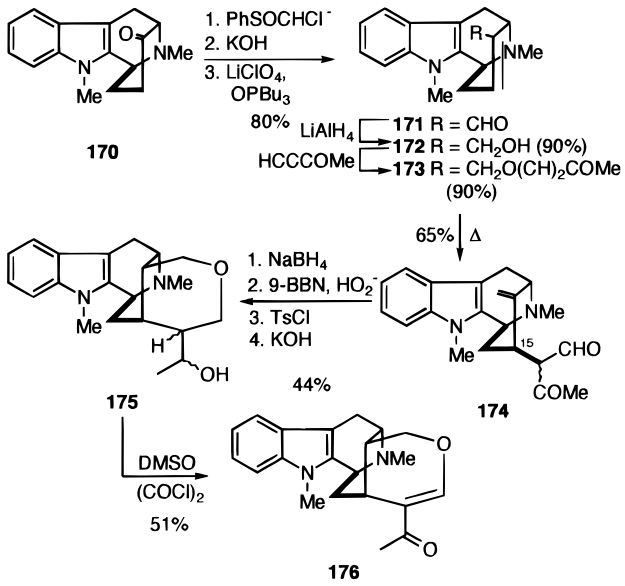
The degree of stereocontrol that can be exerted over the Pictet−Spengler cyclization has been vividly exemplified in the preparation of the tetracyclic ketones **168a**,**b**, which have been used in the syntheses of a variety of indole alkaloids.[48−50] The Dieckmann condensation of the 1,3-disubstituted tetrahydro-β-carbolines **167** should lead to the tetracycles **168** regardless of the configuration of the readily epimerized C-3 center, the final absolute configuration of **168** being controlled by the configuration at C-1.

The Pictet−Spengler cyclization of tryptophan methyl esters **166** with methyl 3-formylpropionate (**169a**) or 2-ketoglutaric acid (**169b**) have allowed the use of either enantiomer of tryptophan as starting material. Thus Cook and co-workers[48a] carried out the *trans* selective, thermodynamically controlled reaction of (*R*)-tryptophan ester **166a** with **169a** to give **167a** with total diastereoselectivity. Dieckmann condensation (NaH) and decarboxylation completed the synthesis of **168a**, which had an er >98/2 as judged by ^{1}H NMR analysis in the presence of a chiral shift reagent (Scheme 33).

Scheme 33



Scheme 34



Magnus *et al.*[49] condensed (*S*)-tryptophan ester **166b** with **169b** under kinetic conditions (PhH−dioxane, 80 °C) to give, after esterification, a 1/2 mixture of **167b** and its C-1 epimer (80% combined yield); **167b** was transformed into **168b** by the aforementioned Dieckmann cyclization−decarboxylation sequence. By ^{1}H NMR analysis in the presence of a chiral solvating agent, **168b** was shown to be enantiomerically pure.

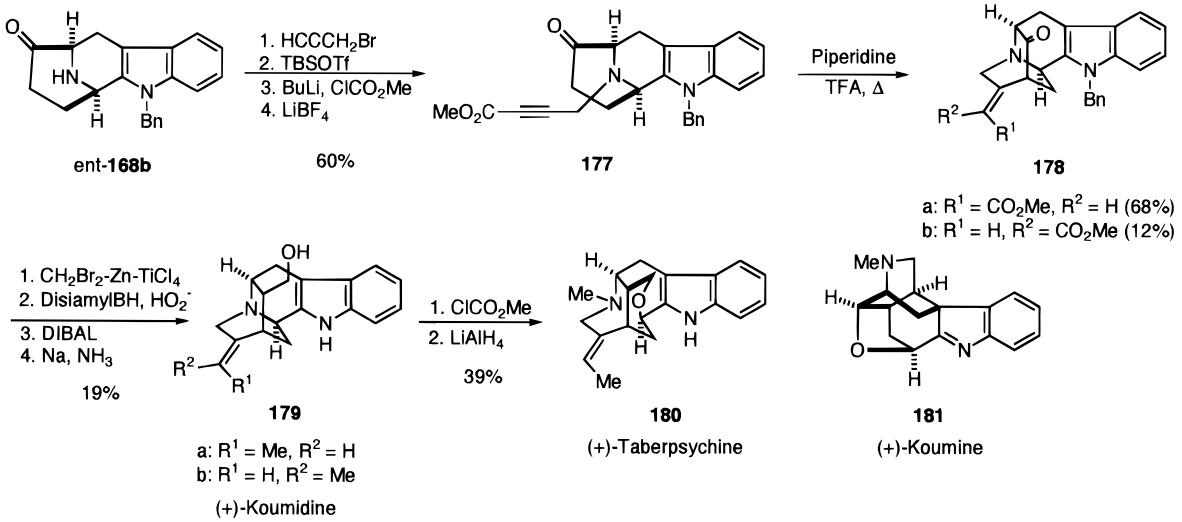
As discussed above, the Pictet−Spengler cyclization of N_b-unsubstituted tryptophan esters gives mainly *cis* 1,3-disubstituted tetrahydro-*β*-carbolines if performed under kinetic conditions (TFA, 0 °C).[44] Bailey *et al.*[50] made use of this fact to obtain a 4/1 mixture of **167c** and its C-1 epimer (61% combined yield) from (*S*)-ester **166c**, then **167c** was converted into **168c** in five steps (23%, er >97.5/2.5 as determined by HPLC).

A synthesis of the macroline-related alkaloid (−)-alstonerine (**176**) from ketone **170**, prepared by Cook's method, has been reported.[48a] The key steps were the stereoselective introduction of the C-15 side chain in **174** by Claisen rearrangement of allyl ether **173** (prepared by addition of a masked formyl anion to the ketone in **170**, followed by elimination and standard manipulations of the aldehyde function to give the desired allyl ether) and the hydroboration−oxidation of the exo methylene group in **174**, which allowed the closure of the dihydropyran ring of **175** with the required relative configuration; oxidation of **175** gave the desired (−)-alstonerine (**176**) (Scheme 34).

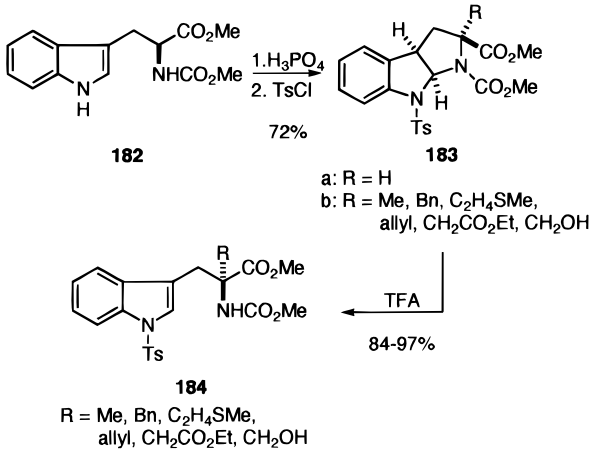
Magnus *et al.* have used the enantiomer of **168b** to synthesize the antipodes of the alkaloids koumine, taberpsychine, and koumidine.[49] The assembly of the quinuclidine core of these alkaloids was achieved by intramolecular Michael reaction of keto ester **177**. The minor product of this cyclization, **178b**, was converted into (+)-koumidine (**179b**) in four steps, while the major isomer was transformed into (+)-taberpsychine (**180**) via a retro-Mannich reaction−cyclization of **179a** (Scheme 35). This also constitutes a formal synthesis of (+)-koumine, since (−)-taberpsychine has been transformed into (−)-koumine by oxidative rearrangement with $SeO_2-H_2O_2-H^+$.

The versatile reactivity of the indolic C2−C3 double bond has been used to develop a procedure for the stereospecific α-alkylation of tryptophan which gives the *S* enantiomer selectively. Thus, cyclization of carbamate **182** with H_3PO_4 followed by *N*-tosylation afforded the hexahydropyrrolo[2,3-*b*]indole **183a** as a single diastereoisomer (enantiomerically pure, as judged by ^{19}F NMR of the MTPA amides of detosy-

Scheme 35



Scheme 36



lated **183a**). The alkylation of the enolate of **183a** with a variety of electrophiles proceeded with total stereoselection (44−83%). Ring opening of the alkylated pyrroloindoles **183b** gave the alkylated tryptophans **184** in excellent yields[51] (Scheme 36).

VI. The Hydroxy- and Sulfur-Containing Amino Acids

A. Serine and Threonine

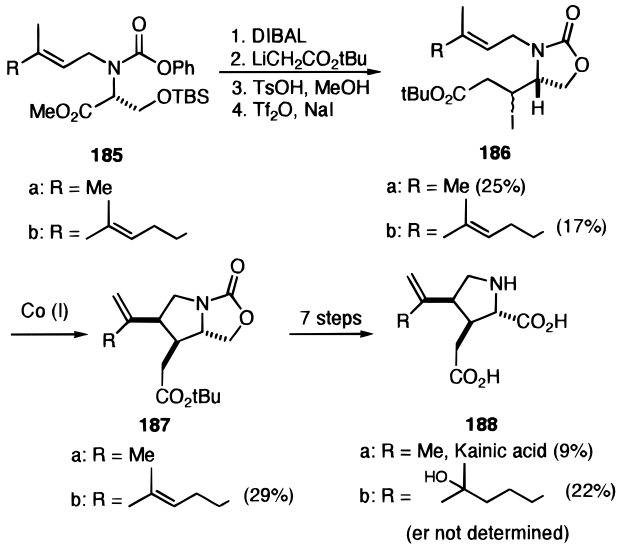
The presence of a hydroxyl group in the side chain of serine and threonine makes them especially attractive starting materials for the synthesis of amino hydroxylic (such as amino sugars) and amino acidic compounds (such as kainic acid and its analogues).

In a series of articles, Baldwin and co-workers have explored the use of serine as starting material for the synthesis of the neuroexcitatory kainic acid and related kainoids.[52] A novel, cobalt-mediated cyclization of iodoalkenes **186** was used for the construction of the trisubstituted pyrrolidine skeleton of the kainoids **188**. Reaction of **186a**,**b** with cobaloxime-(I) resulted in the formation of an organo-Co(III) intermediate which after homolysis, cyclization, and *β*-elimination, afforded the pyrrolidines **187a**,**b** along with other cyclized and noncyclized byproducts. The bicyclic carbamates **187a**,**b** were transformed by a lengthy sequence (involving several deprotections and alcohol oxidation to the C-2 carboxyl group) into kainic acid (**188a**) and the kainoid **188b** (Scheme 37).

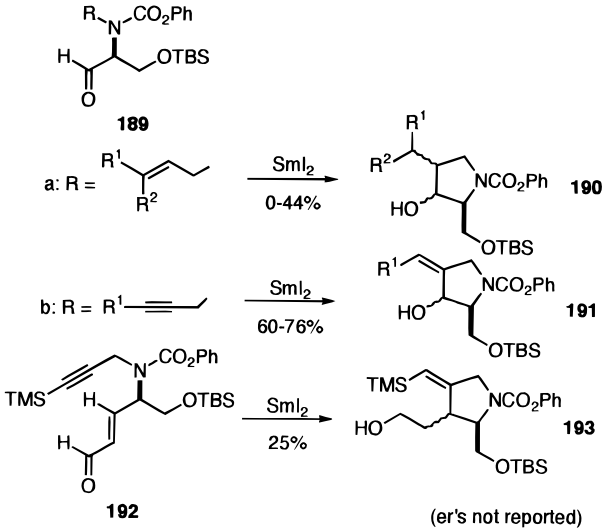
A related radical cyclization−elimination approach to 2,3,4-trisubstituted pyrrolidines (the substitution pattern found in kainic acid) involved the reaction of the unsaturated aldehydes **189** with the oxophilic reducing agent samarium(II) iodide.[53] The highest yielding cyclization was obtained when a propargyl system was used to trap the intermediate ketyl radical (**189b**); nevertheless, the cyclization proceeded stereorandomly in all the cases studied. Enantiomer ratios for the reaction products were not determined despite the fact that α-amino aldehydes, such as **189** and **192**, readily undergo racemization under basic or acidic conditions (Scheme 38).

A more convergent approach to kainic and *allo*-kainic acids has been developed by Barco *et al.*, by using a remarkably efficient and stereoselective double Michael addition of α-amino esters **195** and

Scheme 37



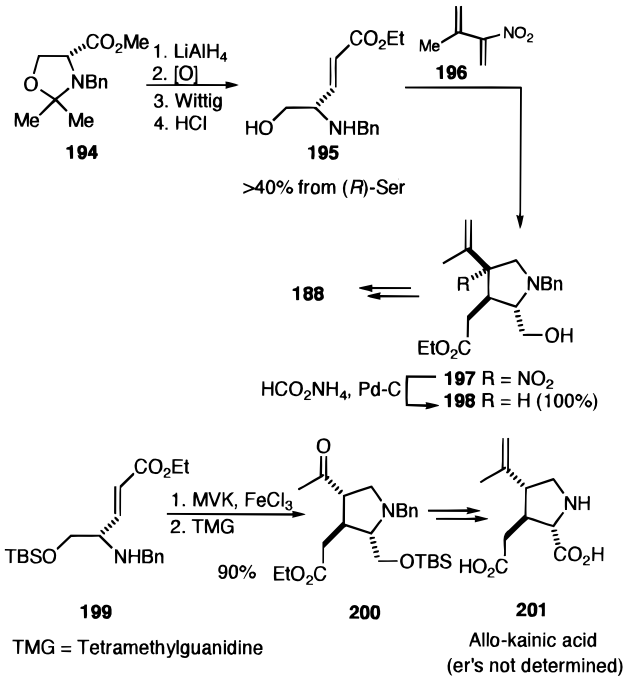
Scheme 38



199 with Michael acceptors, resulting in the formation of a five-membered ring.[54] The stereochemical outcome of the cycloaddition is dependent on the steric requirements of the initial Michael acceptor. Thus, when **195** was reacted with nitrobutadiene **196**, the cycloadduct **197**, bearing the relative configuration of kainic acid, was obtained,[54a] while the adduct with the relative *allo*-kainic acid configuration was obtained from the reaction of **199** with methyl vinyl ketone[54b] (Scheme 39). Conversion of **197** into the desired 2,3,4-trisubstituted pyrrolidine (**198**) proceeded by a remarkable, stereoselective hydrogenolysis of the nitro group. The stereochemical outcome of these cycloadditions has been rationalized by invoking a transition state with an antiperiplanar orientation between the acceptor chain and the enolate or nitronate anion (resulting in a *trans* relationship between the substituents and, thus, in a transition state of lower energy) in the intramolecular Michael reaction.[54b]

The application of *N*-protected α-amino aldehydes as dienophiles in hetero-Diels−Alder reactions has already been discussed. The use of serine-derived aldehydes in these reactions leads to heavily oxygenated dihydropyrans, ideally substituted for the syn-

Scheme 39



thesis of destomic acid (**206**), a component of the aminocyclitol antibiotics destomicins A−C, and galantinic acid (**211**), a component of the antibiotic galantin I.[55] Initial cycloaddition of diene **203** and serinal **202**, followed by elimination and reduction gave alcohol **204** stereoselectively (ratio, 87/8/4/1 favoring the depicted stereoisomer). Alkene dihydroxylation followed by adjustment of the protecting groups gave **205**, an intermediate in the synthesis of destomic acid (**206**)[55a,c] (Scheme 40). Pyran **210**, a key intermediate in the synthesis of galantinic acid (**211**) was prepared following a closely related sequence.[55a,b]

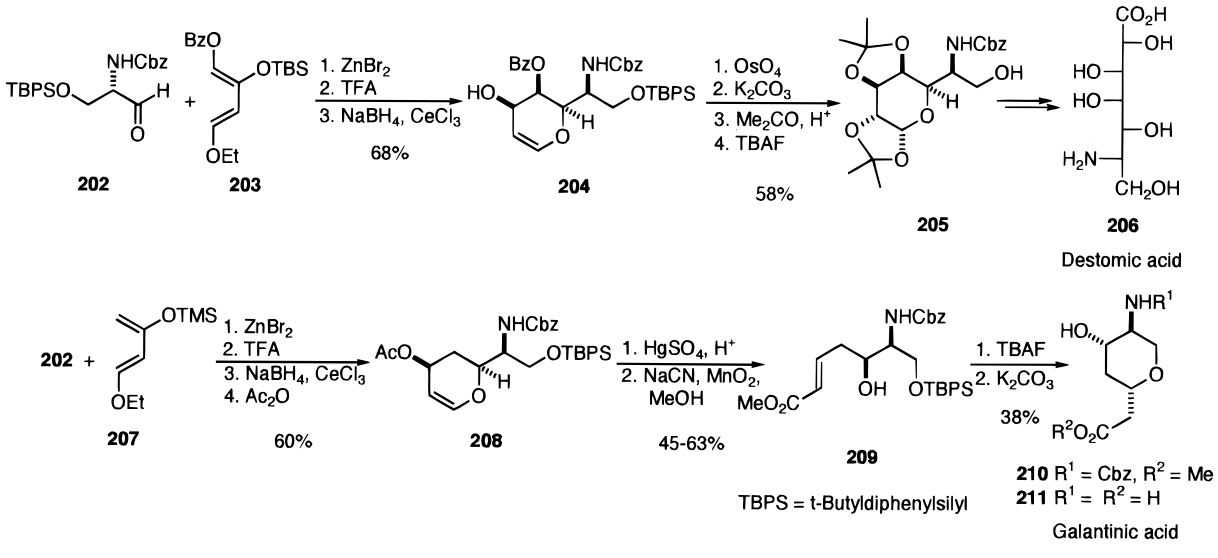
The scope of the cycloadditions that the α-amino aldehydes undergo has been broadened by the use of their derived imines for the Staudinger ketene imine addition reaction. Highly substituted azetidinones obtained by this process were shown to be valuable synthetic intermediates.[56] Azetidinones **214** were obtained by the Staudinger reaction of serine- and threonine-derived imines **213** with alkoxy- and acyloxyacetyl chlorides **212**. The deprotected derivatives **215** were deoxygenated and rearranged to afford *cis*-4,5-disubstituted 2-oxopyrrolidines **216** stereoselectively. Alternatively, oxidation of **217** followed by Grignard addition and deoxygenation provided a highly stereoselective route to 3,4,5-trisubstituted 2-oxopyrrolidines **219**[56] (Scheme 41).

The vicinal diamine **220**, prepared from serine, provided the chirality in a concise synthesis of tetrahydrofolic acid (**226**)[57] (Scheme 42). Nucleophilic addition of the primary amino group of **220** to **221**, followed by *N*-protection, alcohol oxidation and reductive amination gave the key intermediate **225**. Cyclization of diamine **225** to the desired **226** was achieved via a reductive amination of an intermediate quinone. Remarkably, the enantiomer ratio of the final product was >99/1 despite the intermediacy of the α-amino aldehyde **223**, which should be prone to racemization.

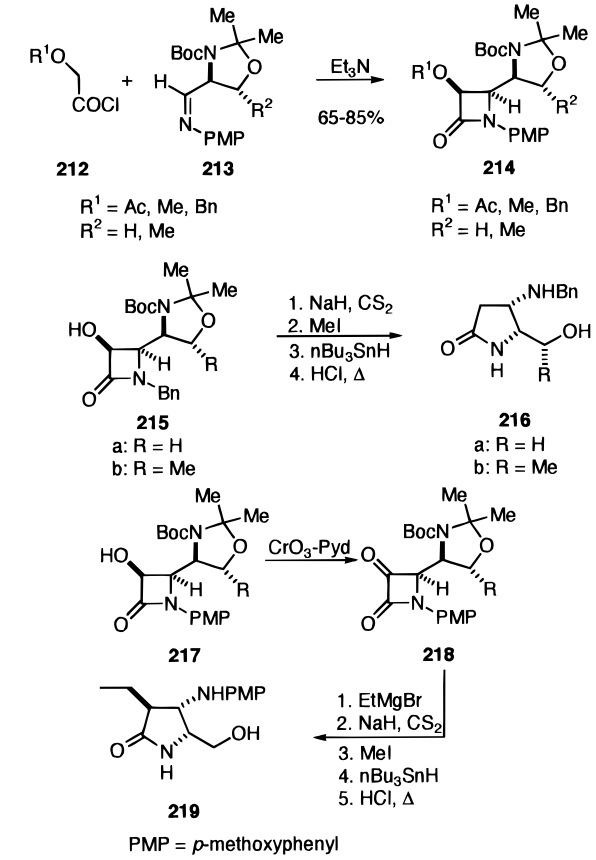
Oxazolines and thiazolines are common structural features of peptides isolated from bacteria and marine invertebrates. Two short and efficient preparations of this class of compounds starting from hydroxy α-amino acid-containing peptides have been reported.[58,59] Peptides and thiopeptides **227** were first prepared, and afforded oxazolidines and thiazolidines **228**, respectively, under Mitsunobu reaction conditions.[58] Alternatively, serine- and threonine-containing dipeptides **229** gave oxazolidines **230** when treated with the Burgess reagent[59] (Scheme 43). No epimerization of the involved stereogenic centers was detected under both protocols.

From a more general viewpoint, serine has been used for the preparation of a series of enantiomerically pure, useful reagents. The iodide **231** was treated with Zn/Cu under ultrasound irradiation to generate a zinc homoenolate which was acylated with α-alkoxy and α-aminoacetyl chlorides; the resulting ketones were reduced with metal hydrides to give lactones **232** with modest stereoselectivity (low to modest yields)[60] (Scheme 44). Lactones **232** are

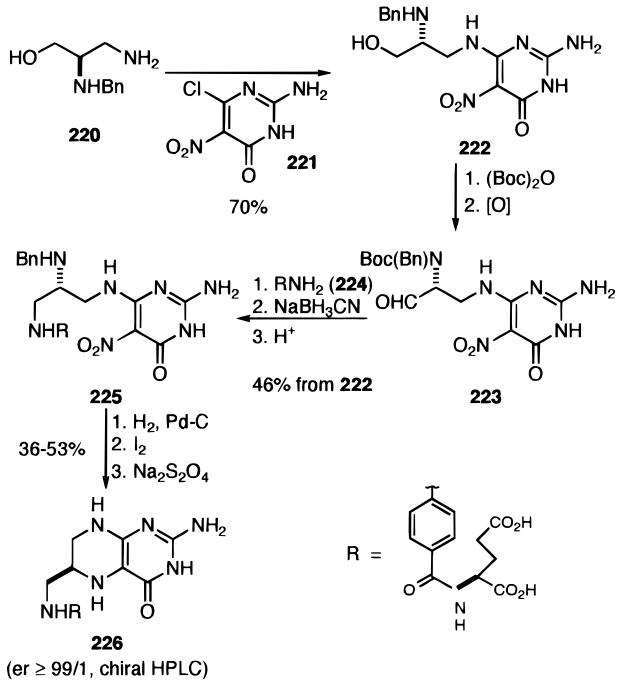
Scheme 40



Scheme 41



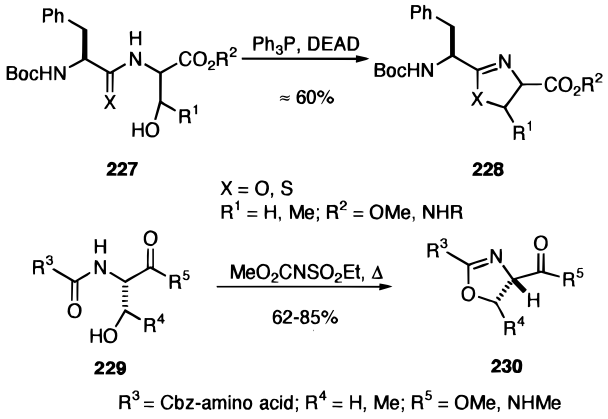
Scheme 42



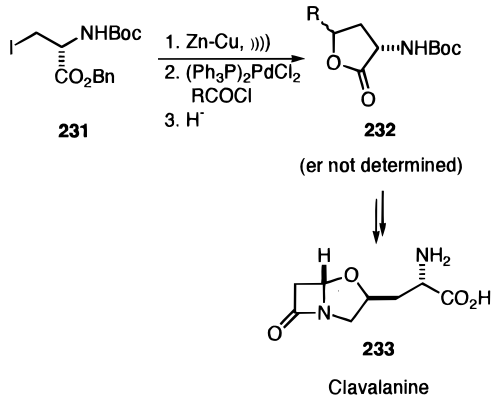
intermediates in the synthesis of the antibiotic clavalanine (**233**).

Acetals **236** are useful, enantiomerically pure dienophiles designed for the synthesis of α-hydroxycyclohexenecarboxylic acids.[61] Serine has been efficiently converted into acetals **236** via potassium (*R*)-glycidate (**234**, two steps, 55%). Epoxide opening with PhSH followed by acetalyzation with pivalaldehyde or cyclohexylcarboxaldehyde gave (*R*)-**235** in

Scheme 43

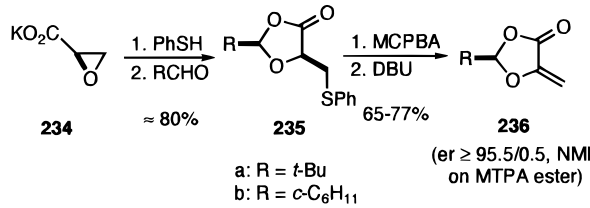


Scheme 44



≥94/6 diastereoselectivity. Sulfide oxidation and elimination completed the synthesis of **236**. Reaction of **236b** with cyclopentadiene gave 20/1 *exo* selectivity (77%), while **236a** reacted even more selectively (50/1, 85%)[61] (Scheme 45).

Scheme 45

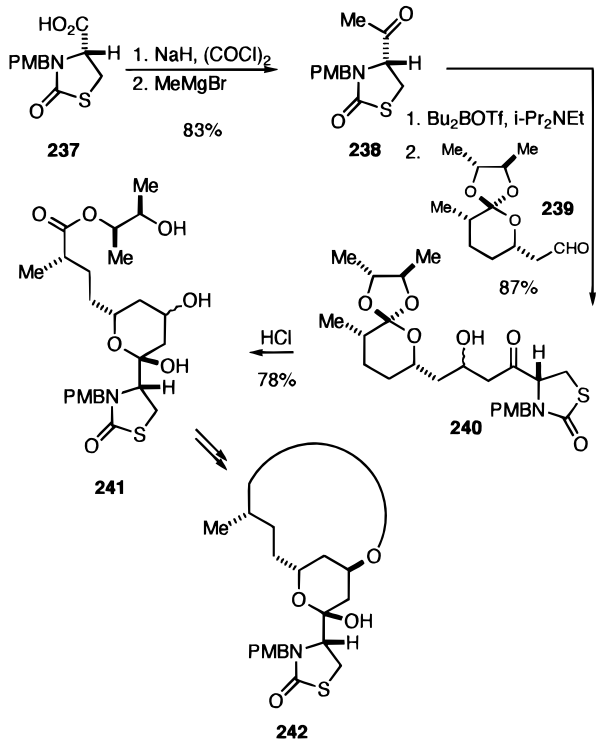


B. Cysteine

The major synthetic applications of cysteine have been in the construction of the thiazolidine rings present in certain natural products, more conspicuously in the latrunculins A−D and M (general structure **242**), a series of ichthyotoxins isolated from the sponge *Latrunculia magnifica* (Keller).[62]

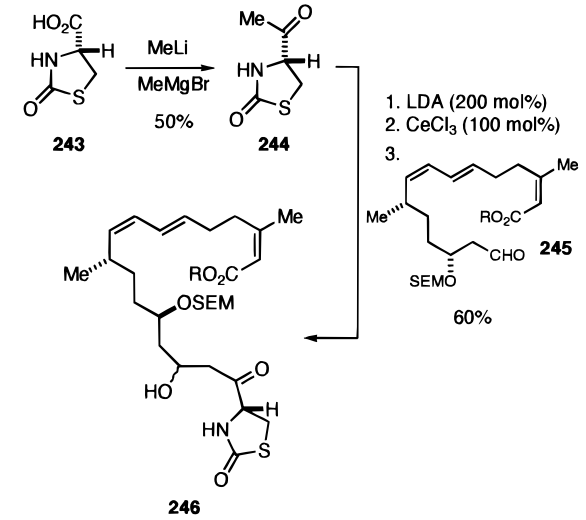
Smith and co-workers[62] have developed a convergent approach to the latrunculins A and B, in which the key step was the moderately stereoselective aldol condensation of the boron enolate generated from ketone **238** (prepared by alkylation of the acid chloride derived from **237** with MeMgBr) with aldehyde **239**, to give ketol **240** (diastereomer α/β ratio 4/1). Orthoester deprotection occurred with concomitant acetal formation to give **241**, which was converted into latrunculins A and B by standard operations[62] (Scheme 46).

Scheme 46



In a closely related approach, White *et al.*[63] employed the aldol condensation of the lithio cerio dianion of **244** with aldehyde **245** to give a 1/1 mixture of epimers **246**, which were converted into latrunculin A by standard operations[63] (Scheme 47).

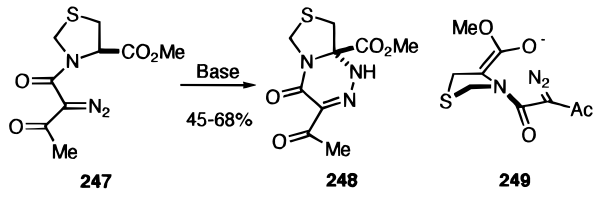
Scheme 47



In both approaches the $[\alpha]_D$ of the final product was close to that of the natural material, but the enantiomer ratios of the intermediates were not determined, leaving open the question of the degree of retention of enantiomer excess during the alkylation of acid chloride **237** and of acid **243** and, especially, during the aldol condensations.

A curious, enantiospecific intramolecular enolate amination took place when diazo ketone **247** was treated with a variety of bases; this yielded the enantiomerically pure (by ^1H and ^{19}F NMR analysis of the MTPA amides) triazabicyclo[4.3.0]non-3-ene **248** in fair to good yields (Scheme 48). The amination

Scheme 48



(enantiopure, NMR of MTPA amides)

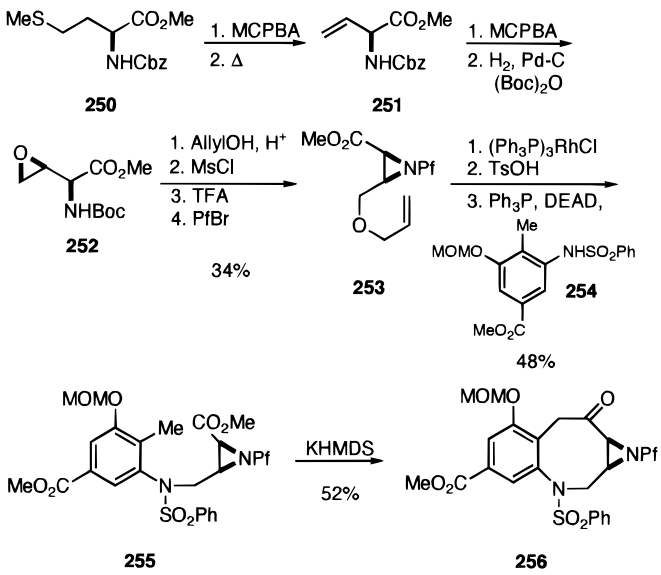
of the ester enolate occurred with retention of configuration, presumably via an intermediate (such as **249**) possessing axial chirality due to restricted amide rotation.[64]

C. Methionine

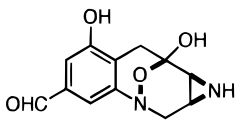
(*S*)-Methionine is a convenient source of (*S*)-vinylglycine,[2a] and this densely functionalized α-amino acid has been used for the synthesis of a variety of interesting compounds.

Rapoport and co-workers have reported the synthesis of hexahydroazocine **256**, an intermediate in a projected synthesis of the antitumor antibiotic FR900482 (**257**) from epoxide **252**, easily obtained from *N*-Cbz-methionine methyl ester (**250**) in four steps[65] (Scheme 49). Regioselective, acid-catalyzed

Scheme 49



Pf = 9-Phenylfluorenyl



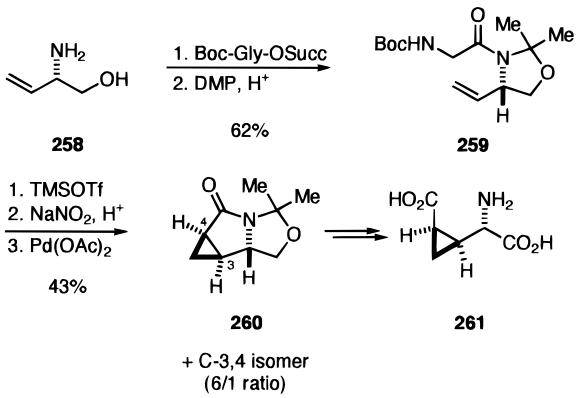
257
FR900482

epoxide opening with allyl alcohol followed by aziridine closure gave the allyl ether **253**. After deallylation, coupling to sulfonamide **254** under Mitsunobu

reaction conditions afforded diester **255**, which was closed to the desired hexahydroazocine ring by a Claisen reaction. The ease of closure of the eight-membered ring is noteworthy; this is probably due to the severe conformational constraints imposed by the fused aryl and aziridine rings.

A strained azabicyclo[3.1.0]hexanone, **260**, has been used as the key intermediate for the synthesis of *cis*-α-(carboxycyclopropyl)glycine **261**, an interesting, neurologically active, conformationally restricted glutamate analogue.[66] Intramolecular cyclopropanation of a diazo ketone obtained from aminal **259** provided **260** with modest stereoselectivity. In turn, **259** was straightforwardly prepared from amino alcohol **258** (Scheme 50).

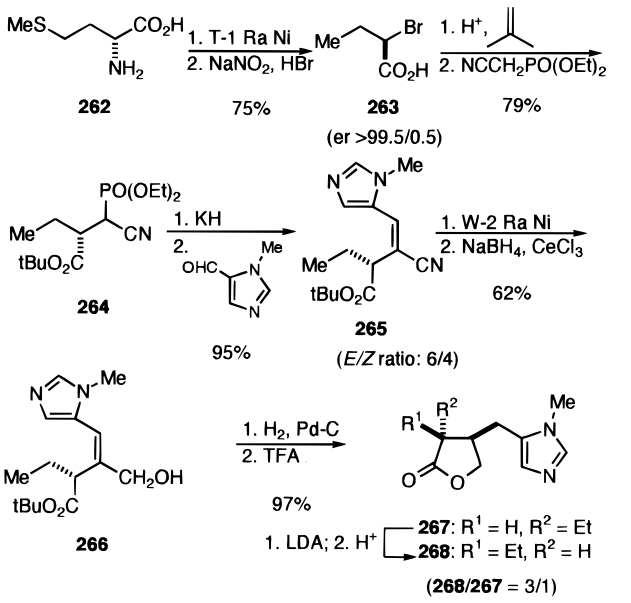
Scheme 50



258 **259** **260** **261**

(+)-Pilocarpine (**268**), a drug used for the treatment of glaucoma, has been synthesized starting from (*R*)-2-bromobutyric acid (**263**), prepared from (*R*)-methionine in two steps (alternatively, **263** was also prepared from (*R*)-2-amino-1-butanol).[67] The introduction of the imidazole-containing side chain was achieved by Wittig reaction of the cyanophosphonate **264** (prepared by alkylation of the anion of unsubstituted cyanophosphonate with **263**) with the corresponding imidazole aldehyde. Selective reduction of the cyano function was achieved in two stages, to provide **266**. The key step in the synthesis was the hydrogenation of allyl alcohol **266** which set the required configuration at C-4 with complete stereoselectivity. Lactonization of the hydroxy ester thus obtained gave (+)-isopilocarpine (**267**) which was epimerized to (+)-pilocarpine by kinetically controlled protonation of the lactone enolate (Scheme 51).

Scheme 51



262 **263** **264** **265** **266**

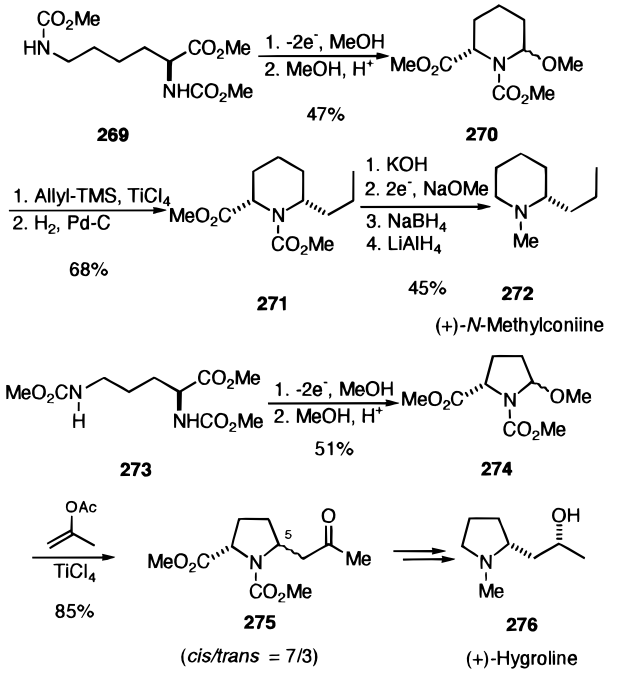
VII. The Basic Amino Acids

A. Lysine and Ornithine

Lysine and ornithine have not been extensively used for the preparation of heterocycles, probably due to the limited synthetic versatility of the amino group of their side chains. Nevertheless, the electrochemical oxidation of the side chain amino group of lysine and ornithine has been used to some extent for the preparation of piperidines and pyrrolidines.

The anodic oxidation of protected lysine and ornithine provides a convenient route to the cyclic α-methoxylated carbamates **270** and **274**, which have been used as key intermediates in the syntheses of piperidine and pyrrolidine alkaloids.[68] Thus methoxypiperidine **270** was stereoselectively allylated (allyl TMS, $TiCl_4$) to give *trans*-2,6-disubstituted piperidine **271** (after alkene reduction), which was electrochemically decarboxylated to a methoxypiperidine and then reduced to complete a concise synthesis of (+)-*N*-methylconiine (**272**) (Scheme 52).

Scheme 52



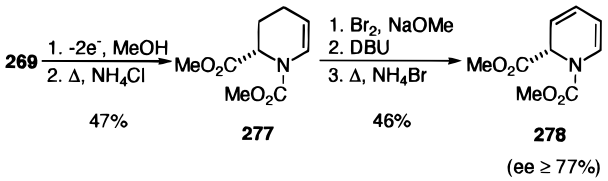
269 **270** **271** **272** **273** **274** **275** **276**

This approach should also be applicable for the synthesis of other 2-substituted piperidine alkaloids, such as (+)-conhydrine and (+)-sedamine, which incorporate hydroxyl groups in their side chains, by reaction with the appropriate nucleophile (a silyl enol ether or a cyanohydrin). The reaction of the lower homologue **274** with isopropenyl acetate proceeded

with lower selectivity to give **275** as a mixture of *cis*−*trans* isomers. This mixture was used for the preparation of (+)-hygroline of modest enantiomeric purity (ee ≈ 42%).[68]

A slight variation of the oxidation−methoxylation procedure was used to prepare the first optically active 1,2-dihydropyridine, **278**.[69a] Thermolysis of the initial oxidation product (an α-methoxyamine) in the presence of NH_4Br gave tetrahydropyridine **277** (100% ee, based on the rotation of a reduction product). Bromomethoxylation, bromide elimination, and thermolysis completed the synthesis of **278** (≥77% ee, based on the rotation of a reduction product) (Scheme 53). Diene **278** could be used to

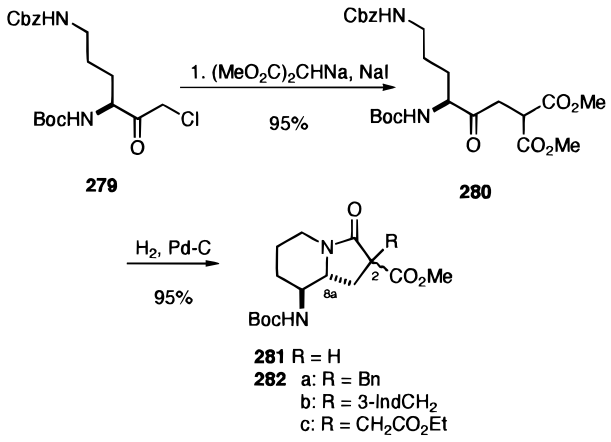
Scheme 53



synthesize the macrocyclic dilactone alkaloids carpaine and azimine (*cis*,*cis* 2,3,6-trisubstituted piperidines) by slight modification of a previous racemic synthesis.[69b−d]

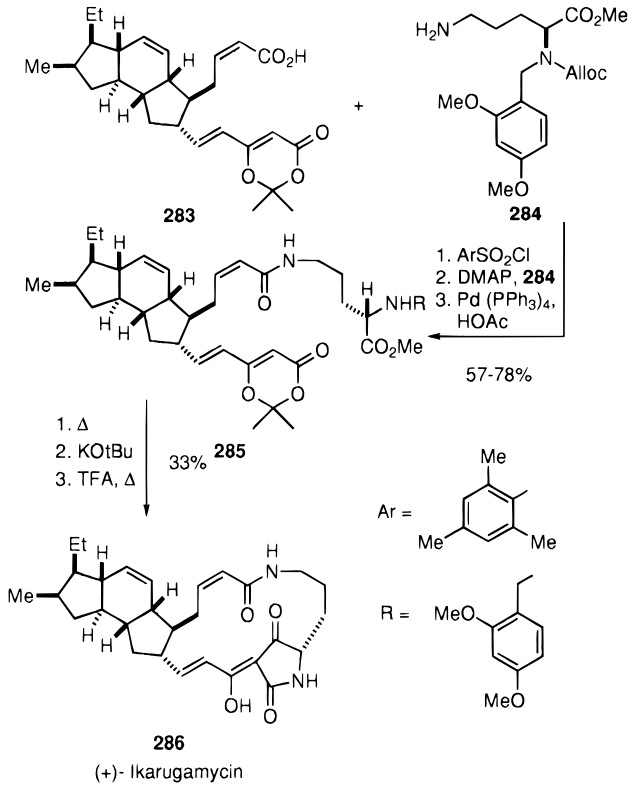
Bicyclic lactams **282a**−**c** are conformationally constrained ornithyl dipeptide analogues and have been designed as mimics of the central part of a β-turn in proteins. Their syntheses were accomplished via the stereoselective reductive amination followed by lactamization of ketone **280** (to give **281**), itself easily obtained from the ornithine-derived chloro ketone **279**. Alkylation of the ketoamide **281** with the appropriate electrophile afforded the desired lactams **282a**−**c** with moderate stereoselectivity (2*R*/2*S* ratio, 5/1)[70] (Scheme 54).

Scheme 54



(+)-Ikarugamycin (**286**) is a macrocyclic lactam antibiotic which incorporates a chiral tetramic acid in its structure. Boeckman and co-workers[71a] and Paquette and co-workers[71b] have independently achieved the total synthesis of **286** using two closely related strategies. In both approaches the key step was the coupling of a tricyclic synthon, such as **283**, with a suitably protected ornithine derivative (**284**) to give **285** (after the removal of the Alloc group). Transformation of **285** into the desired (+)-ikarugamycin was effected by macrolactamization, followed by intramolecular Dieckman condensation and deprotection (Scheme 55).

Scheme 55



B. Histidine

Histidine has been used for the synthesis of carbamate and urea analogues of the alkaloid pilocarpine.[72] Regioselective benzylation involving crystallization of the N^{τ}-benzyl derivative allowed for a straightforward preparation of carbamate **289**.[72a] The urea analogue was prepared by an intramolecular Mitsunobu cyclization of the intermediate aroyl urea, prepared from **288**,[72b] to yield cyclic urea **290**. Methylation, debenzylation by transfer hydrogenolysis, and mild hydrolysis then gave the urea analogue **291** (Scheme 56).

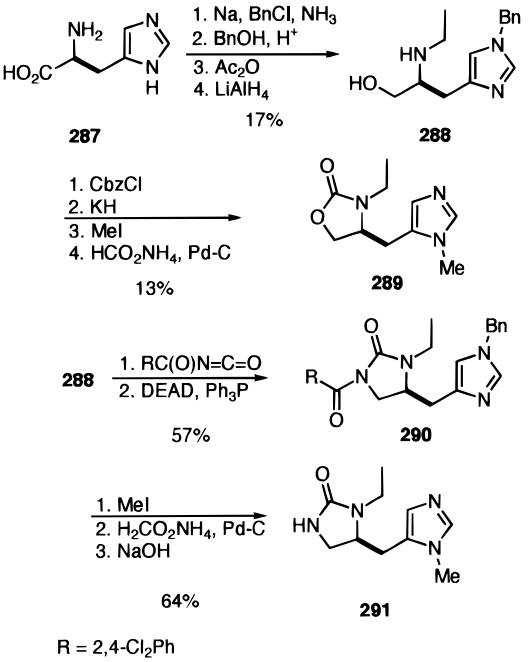
VIII. The Acidic Amino Acids and Their Derivatives

Aspartic and glutamic acids have been the most extensively used α-amino acids in the synthesis of chiral heterocycles, especially by invoking pyroglutamates for the preparation of pyrrolidine derivatives such as pyrrolizidines and indolizidines.

A. Aspartic Acid

Aspartic acid has been widely used for the synthesis of enantiomerically pure chiral heterocycles, especially for the preparation of β-lactams (and derivatives thereof), pyrrolidines, and piperidines. The multiple synthetic operations undergone by aspartic acid can been grouped into a few types of transformations (referring to the carbon atom of the

Scheme 56

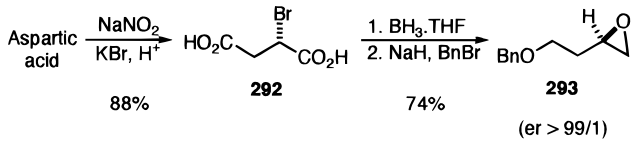


chain undergoing the key reaction in the synthetic sequence).

1. C-1,C-2 Functionalization

An efficient synthesis of [2-(benzyloxy)ethyl]-oxirane (**293**), an intermediate for the synthesis of a variety of biologically important compounds, was developed via reduction−cyclization−protection of (*S*)-bromosuccinic acid (**292**), with complete retention (with inversion of the absolute configuration) of the integrity of the initial stereogenic center of aspartic acid, the precursor of **292**[73] (Scheme 57).

Scheme 57

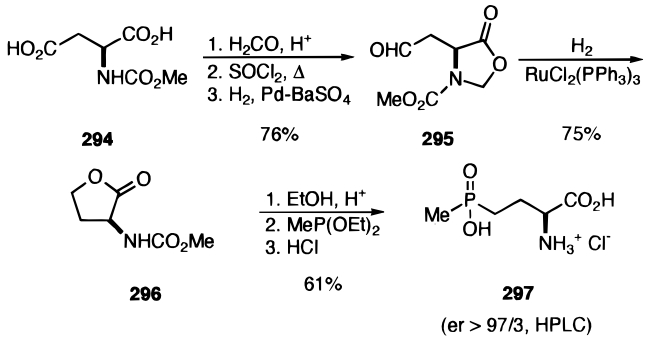


2. C-4 Functionalization

γ-Butyrolactones and lactams are another useful class of synthetic intermediates readily available in enantiomerically pure form from aspartic acid. Thus the *N*-protected homoserine lactone **296**, an intermediate in the synthesis of the herbicide L-phosphinotricin (**297**), was prepared from *N*-(methoxycarbonyl)aspartic acid (**294**) in four steps (**296** is also available from methionine).[74] The differentiation of the α- and β-carboxylic groups was achieved via ozaxolidinone formation followed by a Rosenmund reduction of the free acid to give aldehyde **295**[75] (Scheme 58).

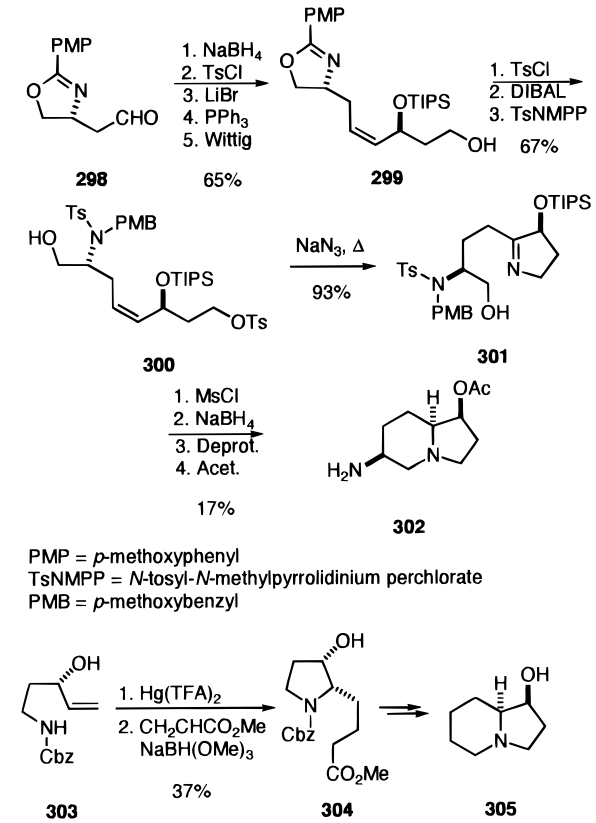
A linear synthesis of the toxic indolizidine alkaloid (−)-slaframine (**302**) starting from the oxazoline aldehyde **298** has been reported.[76a] The protected aldehyde **298** (prepared by reduction of the corresponding thioester, *vide infra*) was transformed into a phosphonium salt which underwent *cis*-selective Wittig reaction with the appropriate aldehyde to give

Scheme 58



299. The key step was an intramolecular [2 + 3] dipolar cycloaddition of an intermediate unsaturated azide (prepared from tosylate **300**) to give imine **301**. The rest of the synthesis proceeded uneventfully, but the whole sequence was somewhat lengthy (23 steps from aspartic acid)[76a] (Scheme 59).

Scheme 59



A much shorter alternative synthesis of the 1-hydroxyindolizidine skeleton of slaframine has been reported.[76b] Alcohol **303** (prepared by kinetic resolution of the racemic alcohol using a Sharpless epoxidation) underwent a stereoselective intramolecular aminomercuration to give a mercurated pyrrolidine. Michael addition of a radical, generated from the intermediate organomercury compound, to methyl acrylate gave pyrrolidine **304**; straightforward elaboration of **304** afforded the desired indolizidine **305**.

3. C-3 Functionalization

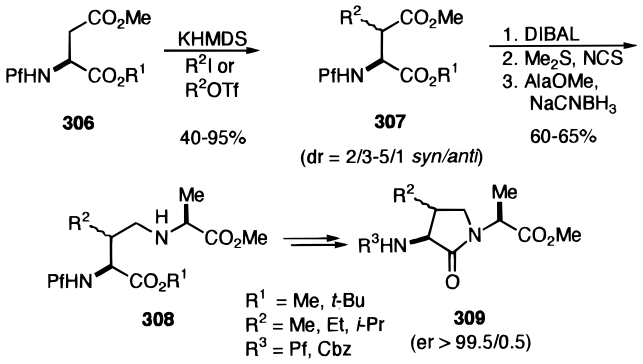
Alkylation of the enolate of the ω-carboxyl group has been widely used to introduce substituents at the 3-position of aspartate esters. The resulting products

are valuable intermediates for the synthesis of heterocyclic compounds. The main difficulty posed by this approach is the possible competitive formation of the enolate of the α-carboxyl group; this problem usually has been solved by reduction of the α-carboxylate prior to alkylation or by using carefully controlled conditions and/or *N*-protecting groups that hinder the deprotonation at C-2.

Substituted γ-lactams, which are mimics of conformationally constrained peptides, can be efficiently prepared by selective functionalization at C-3 in aspartic acid.

Rapoport and co-workers have shown that *N*-phenylfluorenyl aspartate diesters **306** can be regioselectively enolized and alkylated at C-3 without affecting the absolute configuration at C-2.[77] The alkylated aspartates **307** were regioselectively reduced and coupled to alanine methyl ester to give amino esters **308** which were cyclized to lactams **309** (Scheme 60). In this manner, conformationally constrained analogues of the dipeptides Val-Ala, Ile-Ala, and β-MeLeu-Ala were prepared.

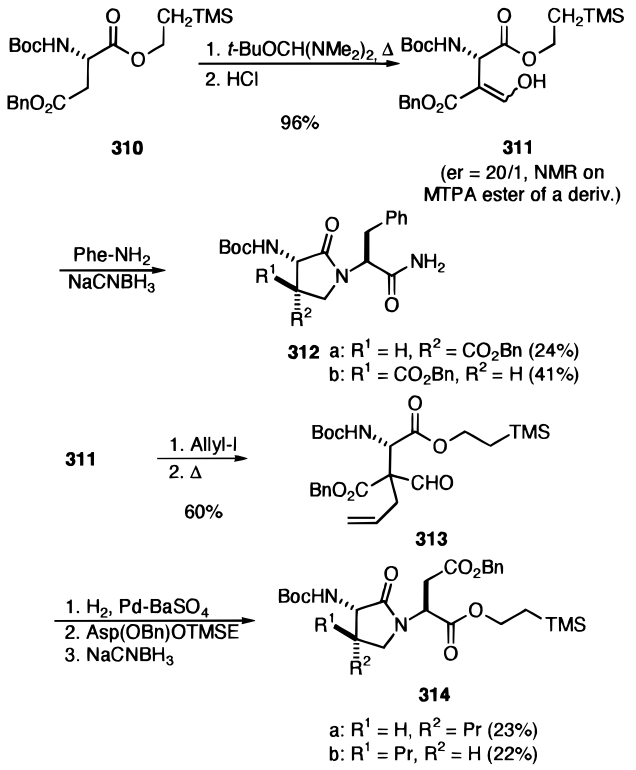
Scheme 60



In a related approach Garvey *et al.* prepared lactams **312** and **314** via regioselective formylation of aspartate **310** (which occurred with ~5% racemization) to give **311**.[78] The key intermediate **311** was reductively aminated to give **312a**,**b** or alkylated and then reductively aminated (with concomitant decarboxylation) to give **314a**,**b**. Both sequences showed low stereoselection for the introduction of the substituent at C-3 (Scheme 61).

A double alkylation (on the nitrogen atom and on C-3) of aspartate diesters was used to develop an efficient synthesis of pipecolates **318** and **326**, key intermediates in Rapoport's synthesis of (−)-vindoline and (+)-vincamine.[79,80] The unsaturated pipecolate **318** was prepared by *N*-alkylation of aspartate **315** followed by *N*-phenylfluorenylation (to prevent racemization under the subsequent reactions) and cyclization. Double-bond introduction and alkylation occurred uneventfully and with total diastereoselectivity, to give tetrahydropyridine **318**. *N*-Alkylation with methoxytryptophyl bromide **319** followed by an iminium ion cyclization gave a tetracyclic system very prone to racemization via a retro-Mannich reaction−recyclization; however, *N*-acetylation avoided this problem and gave amide **321**. Dieckmann cyclization followed by methanolic opening of an intermediate seven-membered lactam gave **322**, which rearranged to **323** on oxidation with *t*-BuOCl. **323** was transformed into (−)-vindoline by standard procedures[79] (Scheme 62).

Scheme 61



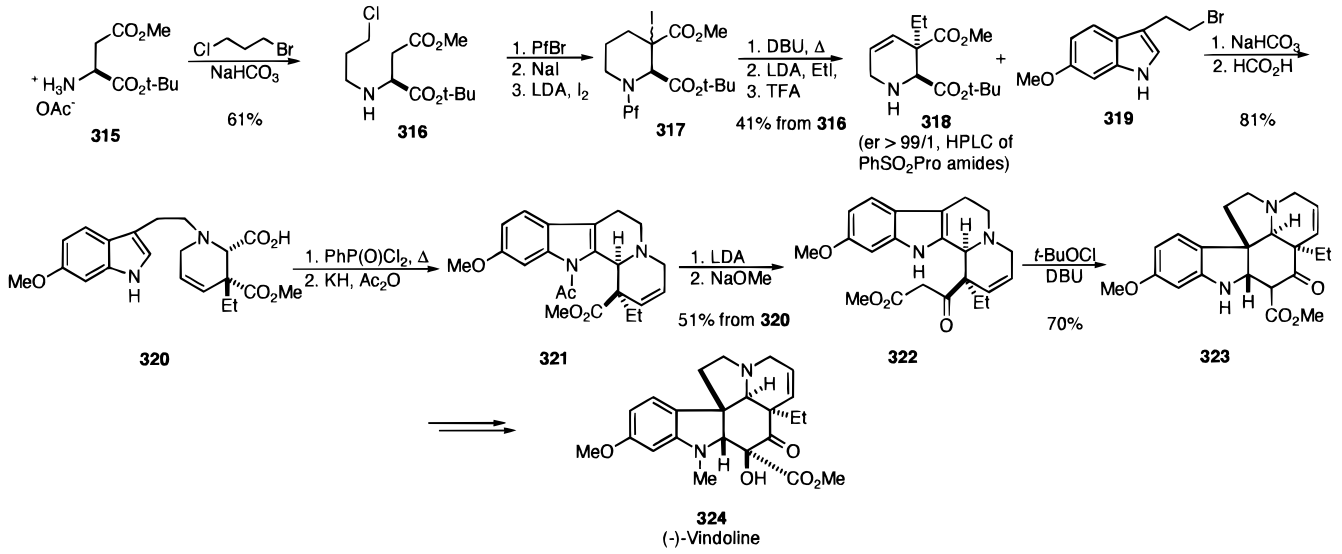
The sequence of *N*- followed by *C*-alkylations was reversed for the preparation of pipecolate **326**, which was transformed into the tetracycle **328** by a sequence analogous to that described above; tetracycle **328** was then elaborated to the desired (+)-vincamine[80] (Scheme 63).

On a different note, the usually bothersome need for protecting group use in amino acid chemistry has been exploited as an opportunity to develop very stereoselective C−C bond-forming reactions by McGarvey and co-workers.[81,82] They used the oxazoline moiety in thioester **331a** to control the diastereoselection of the ester enolate alkylation reactions via either a chelated (to give **332b** mainly) or nonchelated transition state (to give **332a** mainly).[81a] The chelated enolate of **331a** also underwent stereoselective aldol condensations (to give **333**, er 79/21 to 50/1).[81b] Thioester **331a** was easily alkylated to give ketone **331c**, or reduced to the aldehyde **331b**, which in turn underwent a stereodivergent allylation depending on the reaction conditions (chelating or nonchelating)[81c] (Scheme 64).

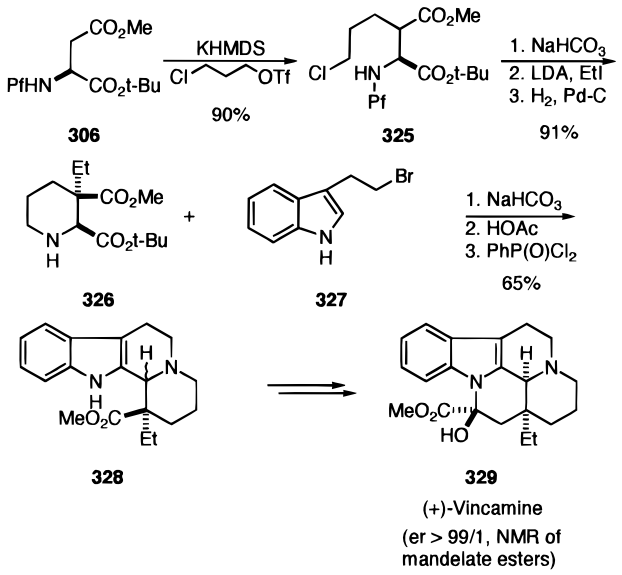
The aldol products **333** also provided access to enantiomerically pure branched chain structures like **336**, present in the ansamicins and other polyene macrolide antibiotics. The sequence proceeded via stereoselective alkylation or allylation of an aldehyde derived from **333**, followed by oxazoline oxidation with DDQ and oxidative ring opening of the resulting oxazole with singlet oxygen (to give a triamide) followed by hydrolysis[82] (Scheme 65).

Aspartic acid is ideally suited for the synthesis of β-lactams, which are very versatile synthetic intermediates.[83] This propensity was used to develop a stereoselective synthesis of the dipeptide antibiotic

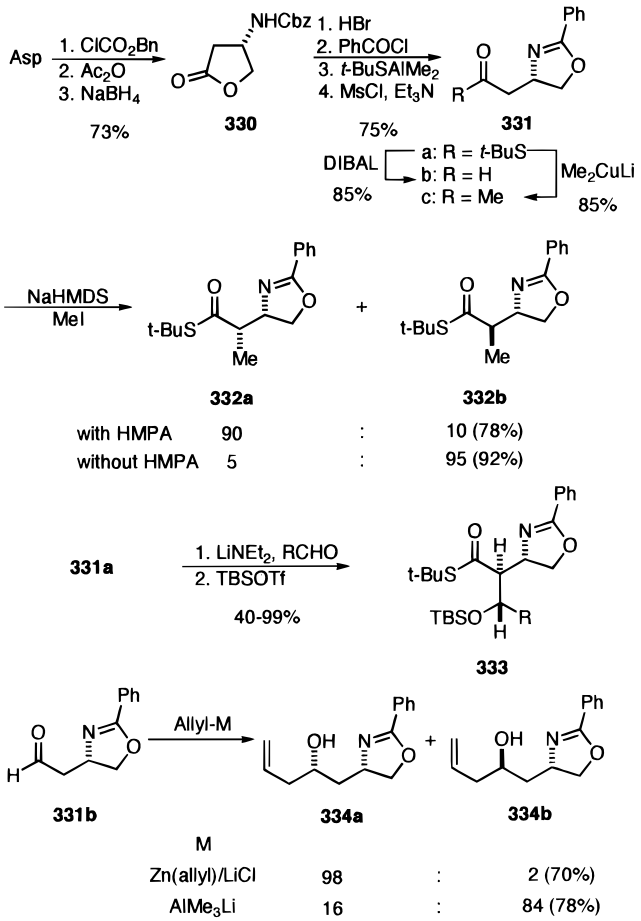
Scheme 62



Scheme 63



Scheme 64



alahopcin (**341b**).[84] Setting the key stereocenter at C-3 in **341** was achieved by allylation of a β-lactam enolate derived from **338** (prepared from **337** by *N*-silylation and lactam formation by treatment with *t*-BuMgCl), the alkylation occurring with complete *trans* diastereoselection.[85] Introduction of the hydroxyamide moiety present in alahopcin required an elaborate sequence of protection and deprotection steps prior to β-lactam opening. Dealanylalahopcin (**341a**) was prepared by oxidative cleavage of **340** followed by a series of deprotections[84b,c] (Scheme 66).

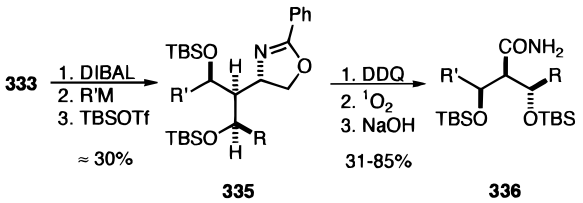
The stereoselective alkylation of aspartic acid-derived β-lactams has been extended to allow the construction of a quaternary chiral center in a key intermediate for the synthesis of the lankacidin antitumor antibiotics **346**[86] (Scheme 67). Thus the aldol condensation of β-lactam **343** with aldehyde **344** followed by oxidation gave ketone **345** with fair selectivity. A subsequent series of protections and deprotections afforded the target lactone **346**.

B. Asparagine

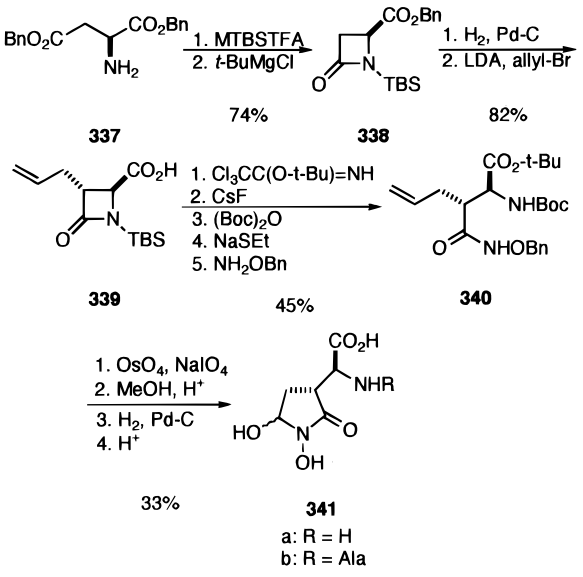
The major application of asparagine for heterocyclic synthesis has been for the construction of chiral hydropyrimidines.

Konopelski and co-workers have introduced the enantiomerically pure dihydropyrimidinone **349** (prepared from asparagine in four steps) as a useful synthon for the preparation of β-aryl-β-amino acids and of α-disubstituted carboxylic acids.[87] Palladium-catalyzed Michael addition of iodoanisole (and other

Scheme 65

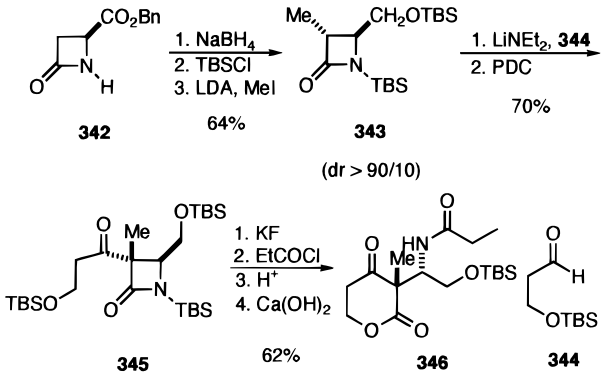


Scheme 66



MTBSTFA = *N*-Me-*N*-(*t*-butyldimethylsilyl)trifluoroacetamide

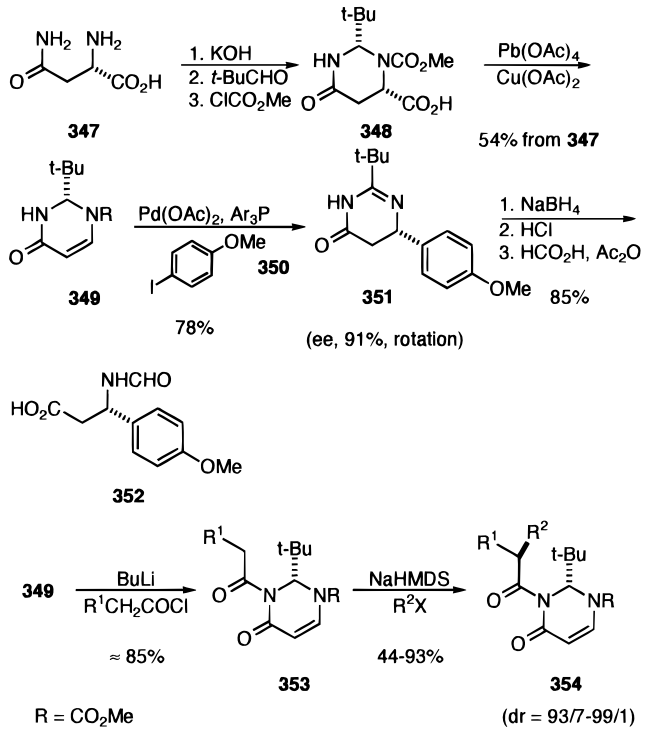
Scheme 67



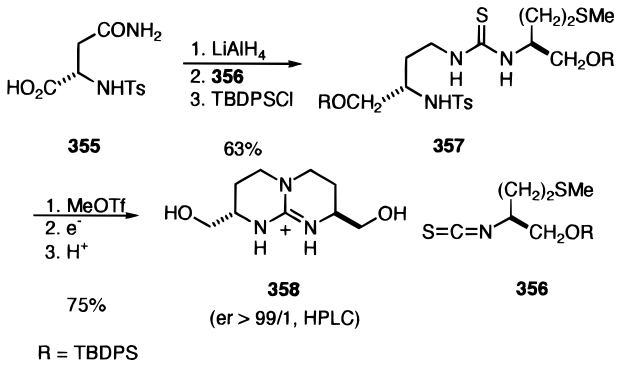
iodobenzenes) to **349** occurred with accompanying hydride transfer to give **351**, which could be deprotected in high yield.[87] The arylation reaction took place with some loss of configurational integrity; however, dihydropyrimidinone **349** also proved to be a valuable chiral auxiliary for enolate alkylations, through the common chelation mechanism[87c] (Scheme 68).

Bicyclic guanidine **358** is a chiral, enantioselective anion receptor used in molecular recognition studies. Two closely related approaches to this molecule have been published.[88,89] Schmidtchen and co-workers have derived the left part of **358** from *N*-tosylasparagine (**355**) by reduction to an amino alcohol and coupling to the synthon for the right portion, **356** (derived from methionine), to give thiourea **357**. Isothiuronium ion formation with methyl triflate triggered a double cyclization to yield **358** after deprotection[88] (Scheme 69).

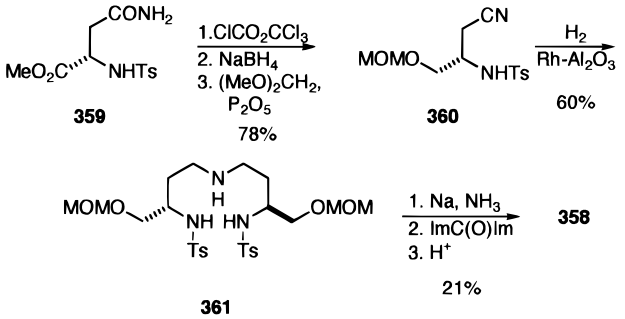
Scheme 68



Scheme 69



Scheme 70



Asparagine has also been used by Mendoza and coworkers as starting material for both rings of **358**, taking advantage of the formation of a secondary amine on the hydrogenation of nitrile **360** (usually a troublesome side reaction). Tosylate deprotection, cyclization with thiocarbonyl bisimidazole, and acetal hydrolysis afforded the desired **358**[89] (Scheme 70).

C. Glutamic Acid

Glutamic acid is, by far, the most widely used amino acid for the synthesis of chiral heterocycles.

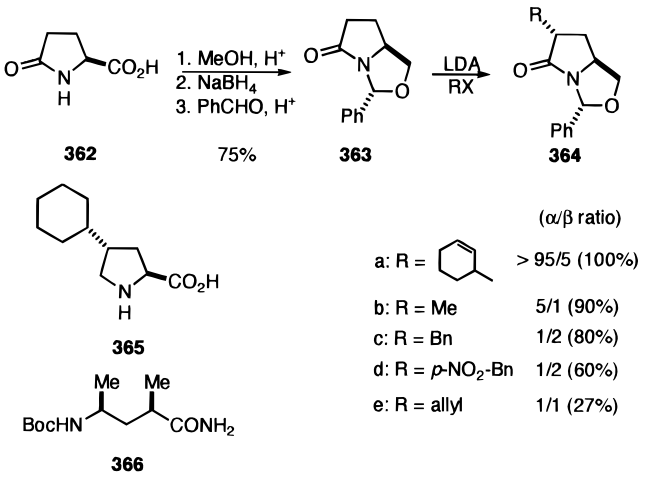
This preeminence is due to the existence of an α-amino-δ-carboxy group in a five-carbon chain, which makes it ideally suited for the synthesis of pyrrolidine rings. This fact has been exploited in a large number of syntheses of pyrrolidine, pyrrolizidine, and indolizidine alkaloids, frequently proceeding through *NH*- or *N*-substituted pyroglutamates.

The wide variety of applications of glutamic acid can be grouped in just a few different types of synthetic transformations.

1. C-4 Alkylation

The readiness of the cyclization of glutamic acid to pyroglutamic acid (**362**) together with the steric bias introduced by the carboxy substituent attached to the chiral center in the γ-lactam ring have been used for the stereoselective preparation of 4-substituted pyroglutamates **364** by enolate alkylation. The stereoselectivity of the alkylation of the enolate of bicycle **363** was highly dependent on the electrophile used; unfortunately, a clear pattern of stereoselection cannot be drawn from the results shown in Scheme 71.[90,91] Thus **364a** was converted into proline **365**,

Scheme 71

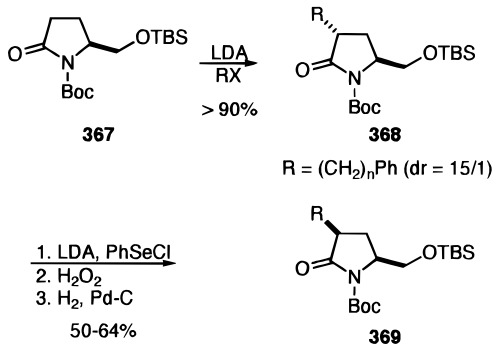


an intermediate on the synthesis of the hypotensive agent Fosenopril,[90] while **364b** was used for the preparation of **366**, to be used in a projected synthesis of the calyculin antibiotics.[91]

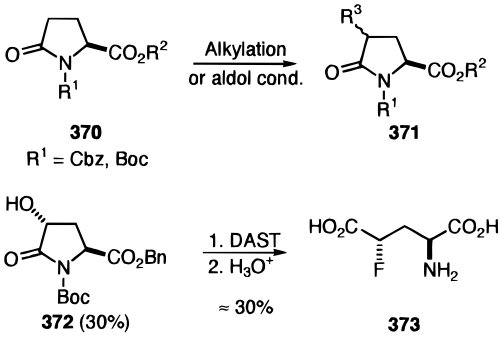
Better results were obtained for the monocyclic system **367**, from which both epimers of the 4-substituted pyroglutamate, **368** and **369**, were selectively prepared.[92] The initial alkylation of **367** gave the *trans*-pyrrolidone with complete stereoselection; the β-epimer resulted from the reduction of a Δ^3-pyrrolidone (prepared by selenylation and oxidation of **368**) (Scheme 72).

The hydroxylation, alkylation, or aldol condensation reactions of the enolates derived from pyroglutamates **370** with the intact C-2 carboxy group have been reported, but are plagued with problems: sluggish reactions, low diastereoselectivity, and, last but not least, the lack of reliable data about the extent of retention of configuration at C-2 of the reaction products **371**.[93−95] The hydroxylated lactam **372** was ultimately converted to 4-fluoroglutamic acid (**373**) (Scheme 73).

Scheme 72

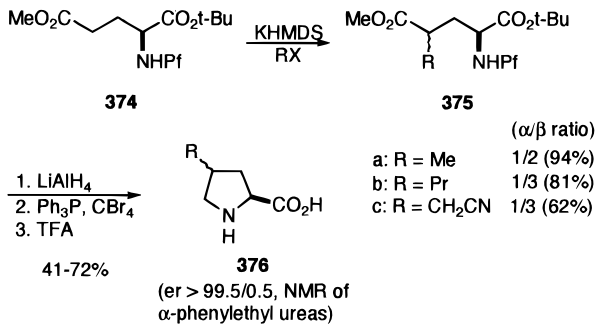


Scheme 73



An enantiospecific (at C-2), but poorly diastereoselective, route to 4-alkylprolines (**376**), based on the regioselective enolate formation−alkylation of *N*-(phenylfluorenyl)glutamate **374**, that partly solves the aforementioned problems, has been reported (the *N*-Pf group prevents the enolization of the C-1 carboxylate, thus preserving the configurational integrity of the stereogenic center during the alkylation).[96] The 4-alkylglutamates **375** were converted into the prolines **376** by ester reduction followed by a Mitsunobu-type cyclization (Scheme 74).

Scheme 74

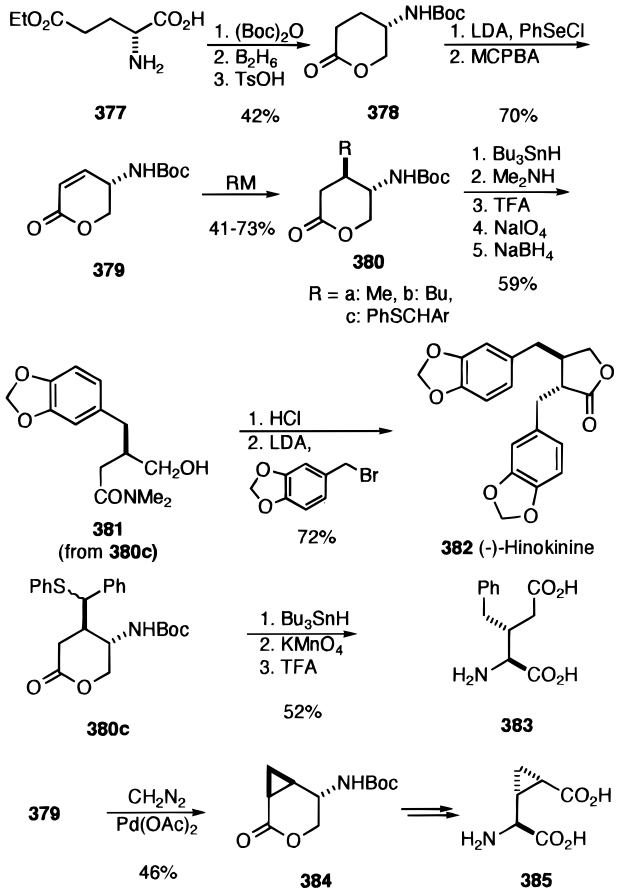


2. Reactions of 3,4-Dehydroglutamate Surrogates

The introduction of a 3,4-double bond into the glutamate gives access to the functionalization of C-3, and this has been used in a number of natural products syntheses. Every case reported, however, proceeded by prior reduction of the carboxyl group at C-1 to an alcohol to prevent the loss of the configurational integrity of the stereogenic center.

The δ-lactone **379**, prepared from monoester **377** by *N*-protection, chemoselective reduction, and cyclization, underwent stereoselective 1,4-addition with cuprates and sulfide-stabilized carbanions, to give the *trans* δ-lactones **380**;[97a,98] **380c** was elaborated to the

Scheme 75

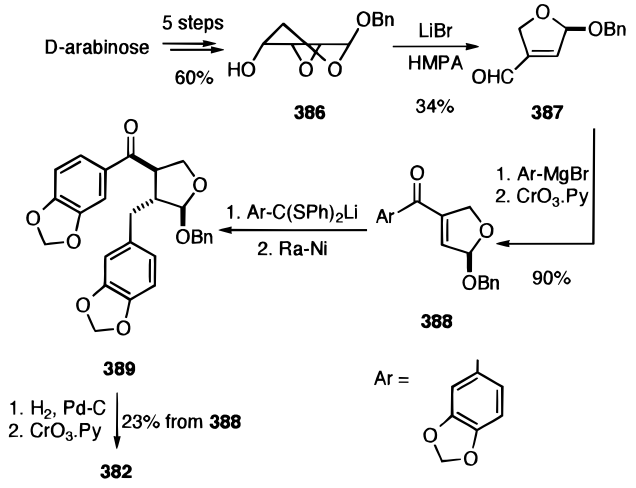


antileukemic lignan lactone (−)-hinokinin (**382**)[97a] by desulfurization, lactone opening, and oxidative degradation of the resulting amino alcohol, to give **381** (Scheme 75). Lactone closure and stereoselective enolate alkylation completed the synthesis of **382**. The kainoid analogue **383** was also prepared from **380c**, by a sequence involving desulfurization and amino alcohol oxidative degradation.[98] Stereoselective carbenoid addition to **379** gave cyclopropane **384**, an intermediate on the synthesis of the conformationally restricted glutamic acid analogue **385**, which has been used as a tool in neurochemical research.[99]

An alternative approach to (−)-hinokinine (**382**) starting from D-arabinose has been described.[97b] The tetrahydrofuran core of **382** was constructed by ring contraction of epoxide **386**; Grignard addition to aldehyde **387**, followed by alcohol oxidation and 1,4 addition of a sulfide-stabilized carbanion to the resulting enone gave **389**, which was deprotected and oxidized to yield **382** (Scheme 76). This synthesis is slightly shorter (12 vs 13 steps) than the one depicted in Scheme 75 and gives the same overall yield (~4%). A good deal of the synthetic effort put into both approaches goes into eliminating the surplus functionality of the starting materials (one extra carbon in glutamic acid and the extra hydroxyl groups in arabinose), which greatly reduces the overall efficiency of the sequences.

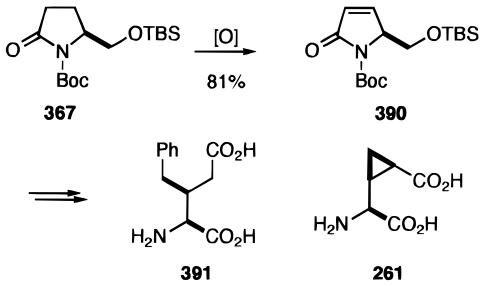
The 1,4-addition of nucleophiles to lactone **379** afforded products with *3R* configuration. In contrast, additions to the unsaturated lactam **390** (prepared from **367** via a selenoxide elimination) gave the *3S* stereoisomers.[98,99] In this way the stereoisomers of

Scheme 76



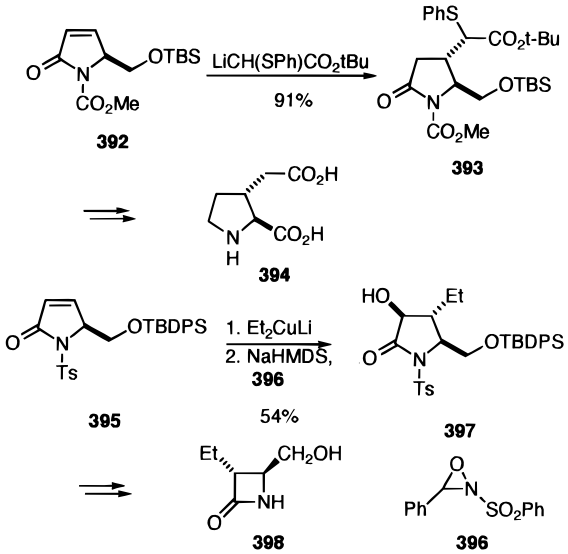
the compounds described in Scheme 75, **391** and **261**, could also be stereoselectively prepared from glutamic acid (Scheme 77).

Scheme 77



This stereoselective protocol for glutamate alkylation at C-3 was utilized again for the synthesis of the kainic acid analogue **394**[100] and the potential intermediate for carbapenem preparation **398**[101] (Scheme 78).

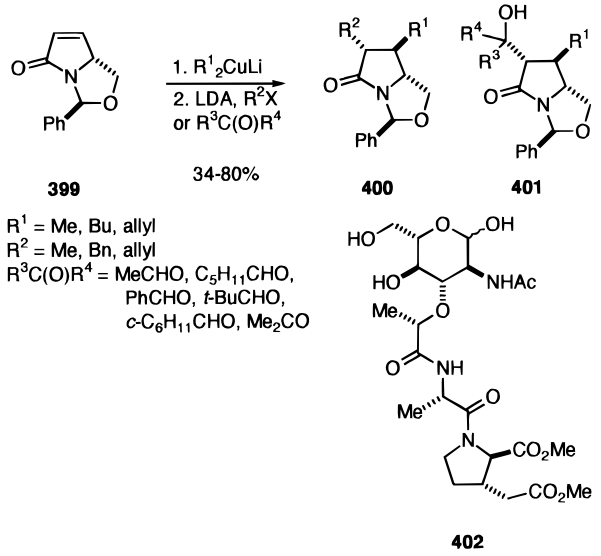
Scheme 78



α,β-Unsaturated lactams usually need to be substituted at nitrogen by an electron-withdrawing group, as in the cases shown above, in order to undergo clean 1,4-addition with cuprates. An exception to this generalization is the behavior of bicyclic

lactam **399** (prepared from (*R*)-glutamic acid) which gave high yields of the corresponding C-4 addition products, whose enolates underwent stereoselective alkylation and aldol reactions.[102a] The aldol products **401** were isolated as single stereoisomers of unassigned configuration at the hydroxyl-bearing carbon. The high efficiency of the cuprate additions is most probably a consequence of the pyramidalization of the nitrogen atom due to the strain of the bicyclic structure. The product from the addition of diallyl cuprate to **399** (**400**, R^1 = allyl, R^2 = H) was ultimately converted into the conformationally constrained *N*-acetylmuramyl dipeptide analogue **402**[102b] (Scheme 79).

Scheme 79



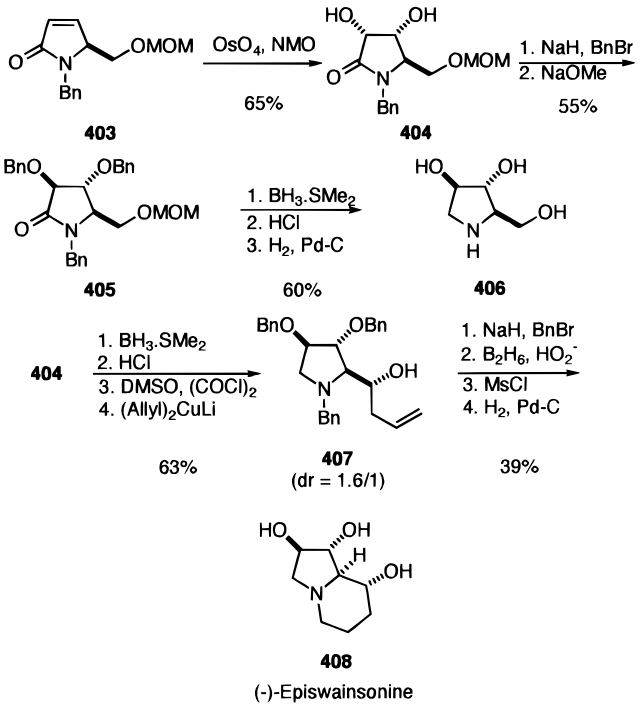
The biological activities of a large number of polyhydroxylated pyrrolidines, pyrrolizidines and indolizidines have spurred the interest in the synthesis of these classes of compounds. The stereoselective bishydroxylation of dehydropyroglutamate **403** and its derivatives (to give **404**) has been widely used to gain access to these systems. Thus the α-glucosidase inhibitor **406** and the indolizidine (−)-episwainsonine (**408**) were prepared from the *trans*-dihydroxy pyrrolidone **405** (produced by epimerization at C-4 of the initial hydroxylation product **404**)[103a,b] (Scheme 80).

The epimers of the aforementioned compounds, **412** and swainsonine (**414**), were prepared from unsaturated lactone **410**, derived from (*R*)-glutamic acid by nitrosation and cyclization.[2a]

The *R* configuration of the stereogenic center in **410** directed the bishydroxylation to give the correct absolute configuration at the hydroxyl-bearing carbons. Protection of the hydroxyl groups followed by lactone reduction and standard manipulation of the resulting diol gave an amino mesylate which cyclized *in situ* to give the pyrrolidine ring with the required 2*S* configuration.[103a,b]

The α-mannosidase inhibitory and immunoregulatory properties displayed by swainsonine and its analogues have made them very attractive targets for synthesis. Due to the polyhydroxylic nature of this kind of compounds, it is not surprising that carbohydrates and tartaric acid have been favored as starting materials,[104a−d] although a route based

Scheme 80

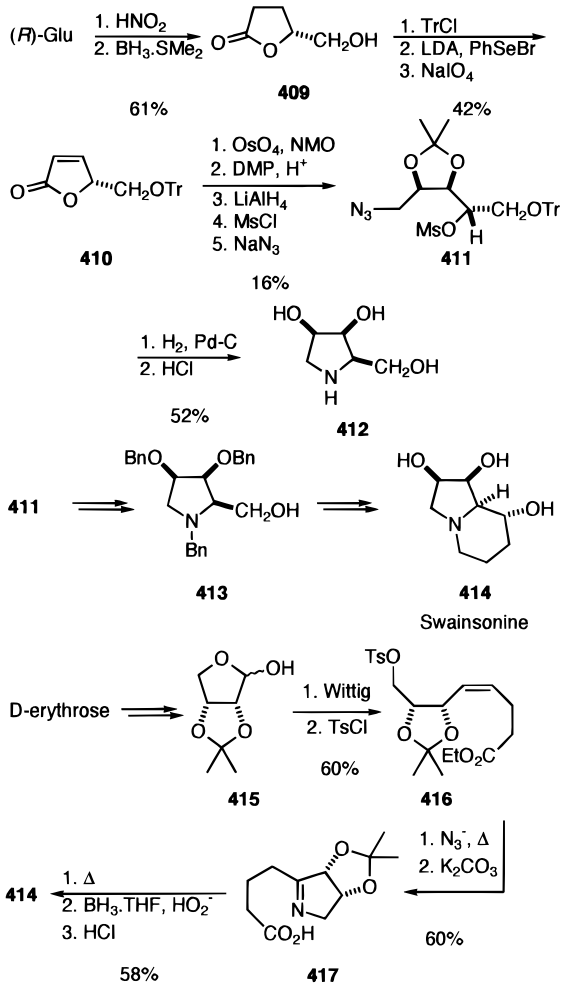


on an asymmetric Sharpless epoxidation also has been reported.[104e] By far, the most concise and efficient synthesis of **414** is the one reported by Cha and co-workers.[104b] D-Erythrose was used as starting material, and the key step was the intramolecular 1,3-dipolar cycloaddition of an olefinic azide (prepared from **415** by Wittig reaction, tosylation, and displacement with azide anion). The resulting pyrroline was ultimately transformed into swainsonine by standard operations (Scheme 81).

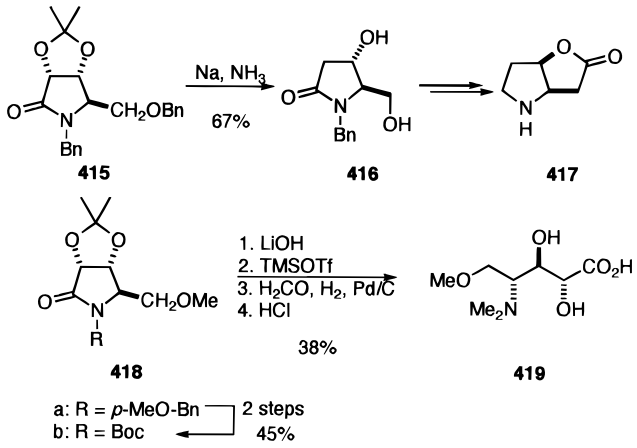
Monohydroxylic products, such as the Geissman−Waiss lactone (**417**, an intermediate in the synthesis of several pyrrolizidine alkaloids), were obtained by dissolving metal reduction of acetonide **415**,[103c] although this route is not very efficient, since a large number of steps must be employed to introduce the desired hydroxyl group at C-3, to eliminate the extra hydroxyl group introduced at C-4, to extend the chain at C-1, and, finally, to invert the configuration of the C-3 hydroxyl group. Far more practical and efficient syntheses of **417**, starting from 4-hydroxy-L-proline[105a] and (*R*)-malic acid,[105b] have been reported. The use of *p*-methoxybenzyl as the nitrogen protecting group in **418** allowed the preparation of open-chain compounds without epimerization after exchange for a Boc group[105c] (Scheme 82).

Further extension of the scope of this dihydroxylation methodology was achieved by chain extension at C-5 of the glutamate moiety. Thus introduction of a one-carbon unit (by vinylation−ozonolysis) resulted in the synthesis of 1,7a-diepialexine (**424**) from **420** after extensive manipulation.[106] Vinylation and reduction of **420** gave a mixture of epimeric alcohols (**421**); the minor isomer was transformed into pyrrolidine **422** by a one carbon degradation and a sequence of protection, activation, cyclization, and deprotection reactions (Scheme 83). Completion of the synthesis of **424** required a two-carbon extension of the C-5 side chain (achieved by allylation of an

Scheme 81



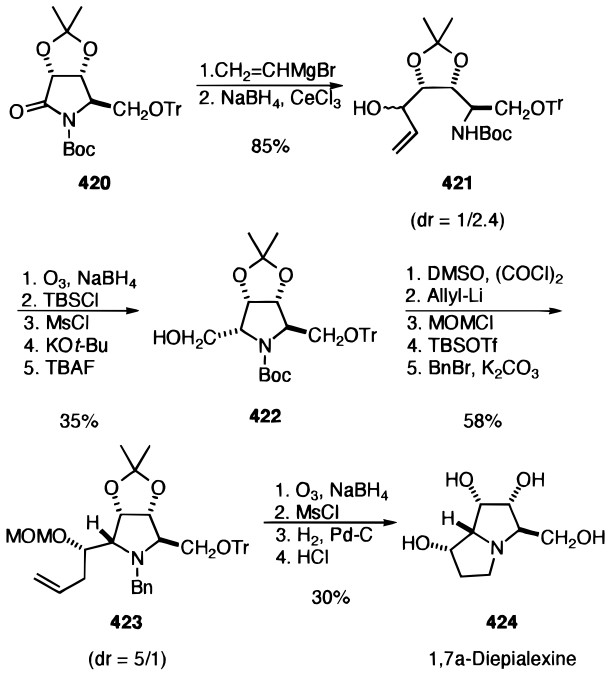
Scheme 82



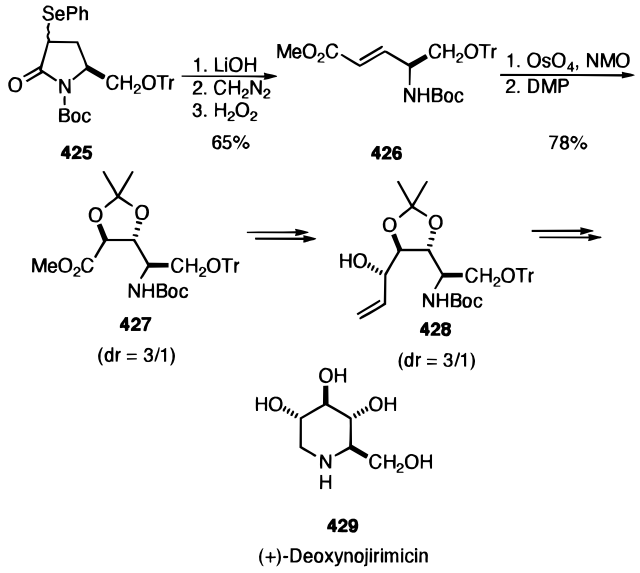
aldehyde prepared from **422**, followed by ozonolysis and the required protection and deprotection steps) prior to the final cyclization. The main drawbacks of this sequence are its length and the low diastereoselectivity of the C−C bond-forming reactions.

A closely related protocol was applied to the open-chain dehydroglutamate **426** to provide the piperidine alkaloid (+)-deoxynojirimycin (**429**)[107a] (Scheme 84). Predictably, the stereoselectivity of the dihydroxylation of the acyclic **426** is much lower than in the cyclic cases. As an alternative to this approach, several short and efficient, carbohydrate-based syntheses of (+)-deoxynojirimycin have been published

Scheme 83



Scheme 84



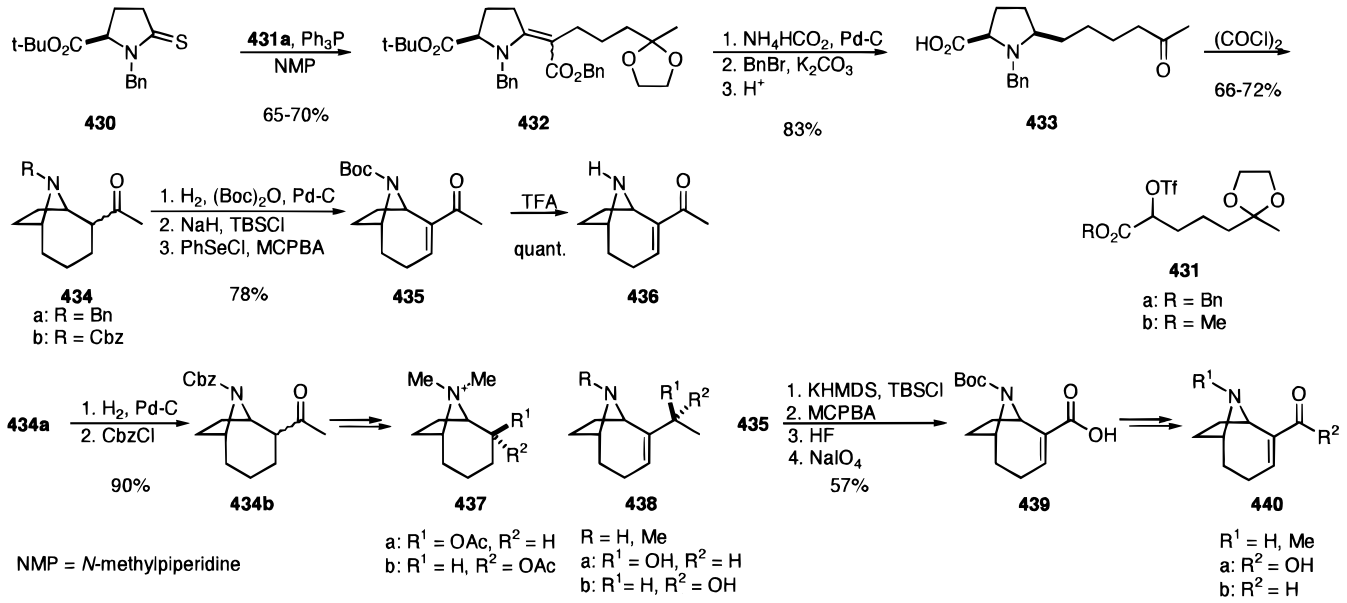
(usually, a carbohydrate will be the starting material of choice for the synthesis of the polyhydroxylated members of the piperidine, pyrrolidine, pyrrolizidine, indolizidine, and quinolizidine families of alkaloids).[107b]

3. C-5 Alkylation

The last two examples of the preceding section showed how the electrophilic nature of C-5 in pyroglutamates could be exploited to increase the complexity of the synthetic targets. Now we turn to C−C bond formation at C-5 in glutamates, a process that has been used primarily to prepare bicyclic systems.

A widely used manner of achieving C−C bond formation at C-5 in pyroglutamates has involved the preparation of vinylogous carbamates. This popularity stems from the mild reaction conditions used in their preparation, which ensured the maintenance of the configuration at the stereogenic centers.

Scheme 85



Anatoxin-a (**436**), the most potent agonist known for the nicotinic acetylcholine receptor, and several of its analogues were prepared from (*R*)-glutamic acid via a vinylogous carbamate. Thus *S*-alkylation−sulfur extrusion of thiolactam **430** with triflate **431a** gave vinylogous carbamate **432**. Hydrogenolysis of **432** followed by hydrolysis of the protecting groups yielded keto acid **433**. Decarbonylation of **433** with $(COCl)_2$ afforded an iminium ion which underwent an intramolecular Mannich reaction to give bicyclic ketone **434**, which in turn was efficiently converted into anatoxin-a in four steps.[108] A large set of anatoxin-a analogues (**437**, **438**, **440**) was prepared starting from Cbz-dihydroanatoxin **434b**, or Boc-anatoxin-a **435**[108] (Scheme 85).

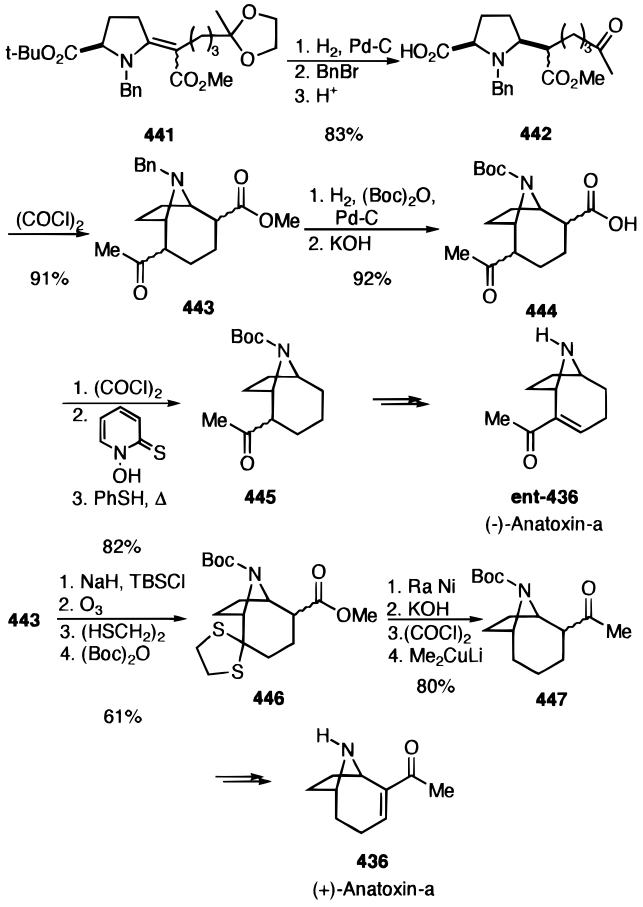
An ingenious twist to the preceding sequence allowed the enantiodivergent synthesis of both (+)- and (−)-anatoxin-a from (*S*)-glutamic acid. Thus iminium ion cyclization of **442**, stereoselectively prepared from vinylogous carbamate **441** by hydrogenation, afforded the quasi-symmetric bicycle **443**, which, by selective removal of one of the side chains, gave either **445** and **447**, which were converted into (−)- and (+)-anatoxin-a, respectively[109] (Scheme 86).

Again, the stereoselective hydrogenation of a tetrasubstituted vinylogous carbamate (**448**), derived from pyroglutamate, was used for the preparation of an intermediate for the synthesis of the β-lactam antibiotic 6-epi-PS-5 (**450**)[110] (Scheme 87).

The nucleophilicity of vinylogous carbamate **453** was used to build the indolizidine skeleton of the angiotensin-converting enzyme inhibitor A58365A (**457**).[111a] Thus **453** underwent bisacylation (on C and on N) when treated with anhydride **452**. Oxidation of **454** gave pyridone **455**, which after a carboxyl inversion reaction afforded the desired **457** (Scheme 88).

The core of the isomeric iso-A58365A (**462**) was assembled by a Michael addition of thiolactam **459** to diazoenone **458** followed by diazothioamide coupling, to yield bicycle **460**. α-Hydroxylation of the enone in **460** followed by α′-alkylation and removal of the protecting groups afforded **462**[111b] (Scheme 89).

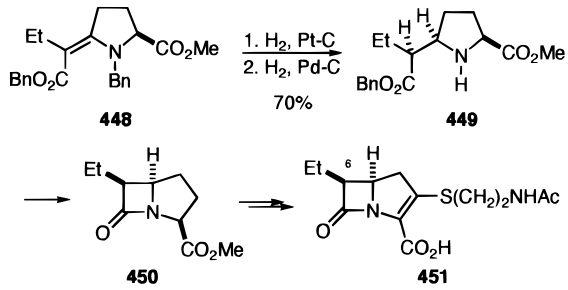
Scheme 86



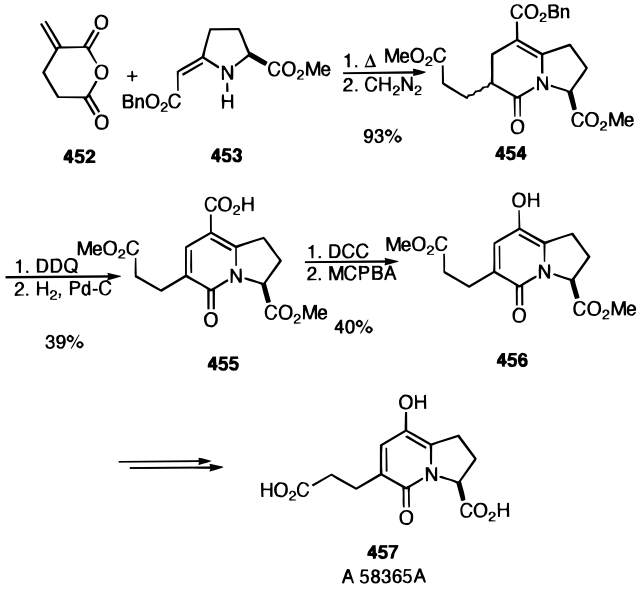
Reaction of nitromethane with thioimidate salts derived from pyroglutamate thiolactams provided the nitroenamines **464**, which were reduced and cyclized to the conformationally restricted piperazines **465**[112] (Scheme 90).

C-5 alkylation through reaction of β-dicarbonyl compounds with imidates derived from tosylate **466** provided vinylogous carbamates **467** and **470**, which were reduced and then subjected to side-chain elongation to give pyrrolidines **468** and **471**, the precur-

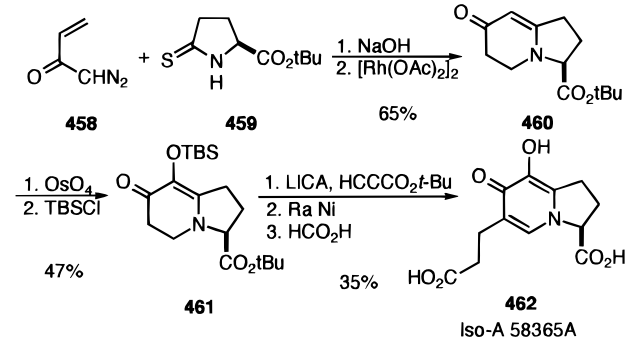
Scheme 87



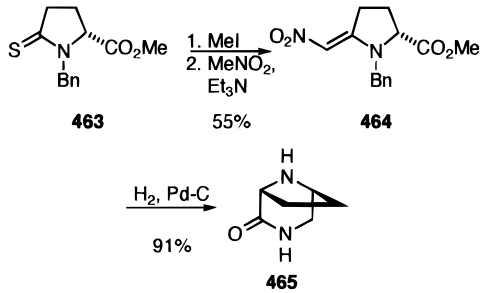
Scheme 88



Scheme 89

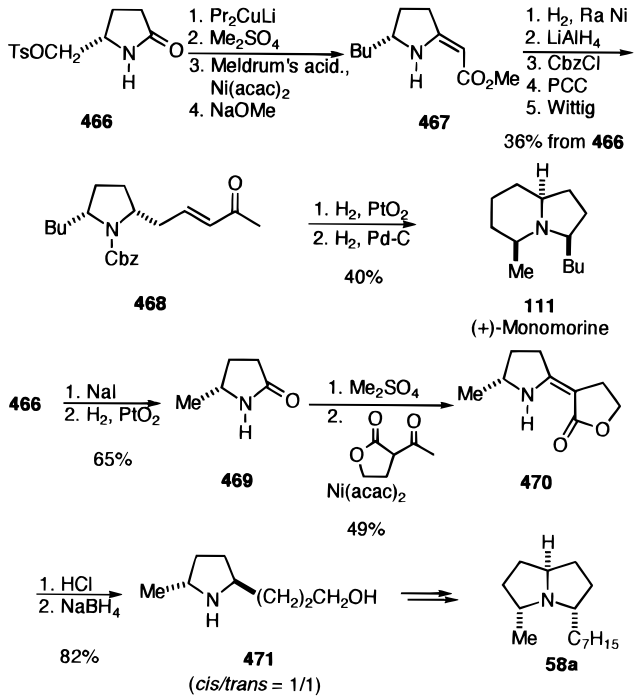


Scheme 90



sors of the bicyclic ant venoms (+)-monomorine (**111**) and **58a**[113] (Scheme 91). A general feature of the preparation of 2,5-disubstituted pyrrolidines by this approach is that the *cis* isomers are usually obtained with complete stereoselectivity, while the stereo-

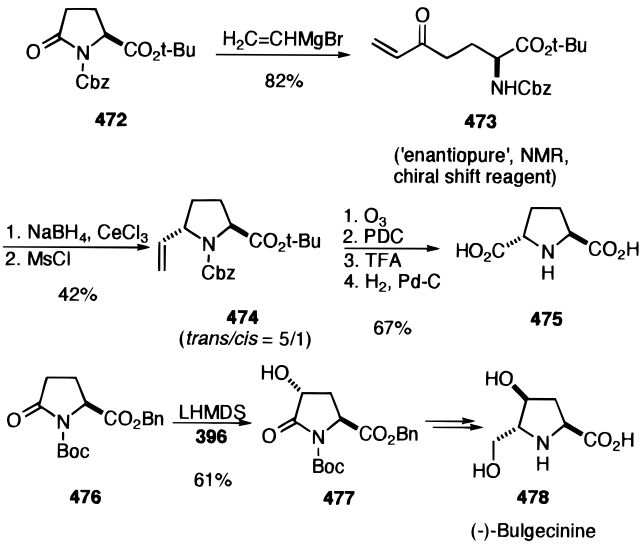
Scheme 91



selectivity of the formation of the *trans* isomers is moderate at best.[114]

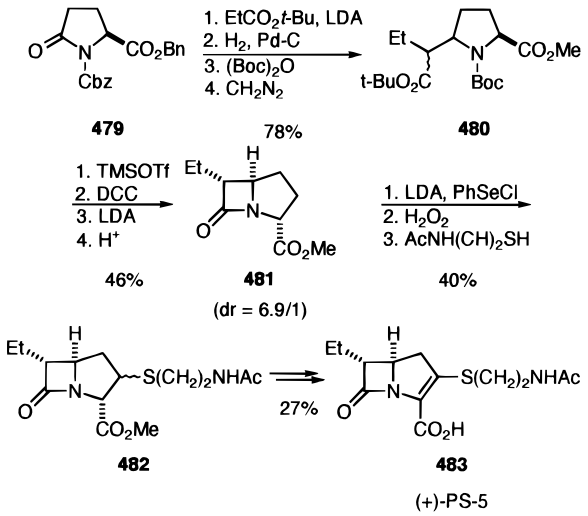
Pyroglutamates bearing an *N*-alkoxycarbonyl protecting group were alkylated at C-5 by Grignard reagents to give enantiomerically pure ketones (i.e. **473**). This transformation is remarkable, since the fairly acidic hydrogen attached to the stereogenic center was not abstracted under the basic reaction conditions employed. Enone **473** was ultimately converted into the naturally occurring amino diacid **475** by reduction of the keto group, mesylation of the resulting alcohol, and cyclization to pyrrolidine **474**. One-carbon degradation of the vinyl side chain of **474** then gave the desired **475**.[115a] In a similar fashion the alkaloid (−)-bulgecinine (**478**) was obtained from the hydroxypyroglutamate **477** by a sequence involving inversion of configuration of the secondary hydroxyl-bearing carbon[115b] (Scheme 92).

Scheme 92



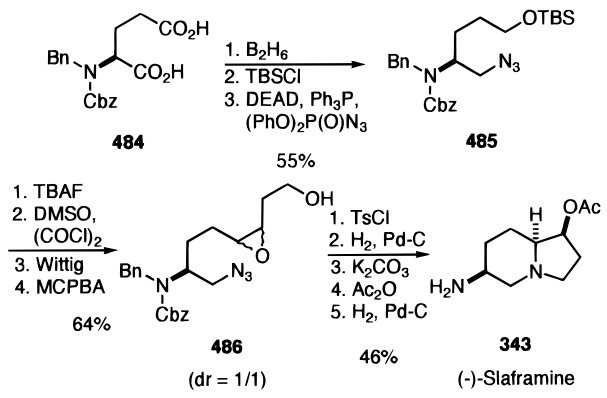
It also proved possible to add ester enolates to *N*-alkoxycarbonyl protected pyroglutamates, and this transformation provided a stereoselective synthesis of the antibiotic (+)-PS-5 (**483**).[116] Thus the keto ester obtained from the alkylation of **479** was reductively cyclized to give **480**, after protection of the amine and carboxyl groups. Standard *tert*-butyl ester deprotection and lactam closure afforded a mixture of epimeric bicycles which was converted into pure **481** by kinetically controlled protonation of the β-lactam enolate. Conjugate addition of the appropriate thiol to an α,β-unsaturated ester, prepared from **481**, gave **482**, which was ultimately converted into (+)-PS-5 (**483**) by an elaborate oxidation sequence (Scheme 93).

Scheme 93



Chain extension of a C-5 aldehyde by a Wittig reaction followed by an azide displacement at C-1 was the approach used by Pearson and co-workers to prepare the key intermediate (azido epoxide **486**) in their synthesis of the indolizidine alkaloid (−)-slaframine (**343**)[117] (Scheme 94). Thus reduction of

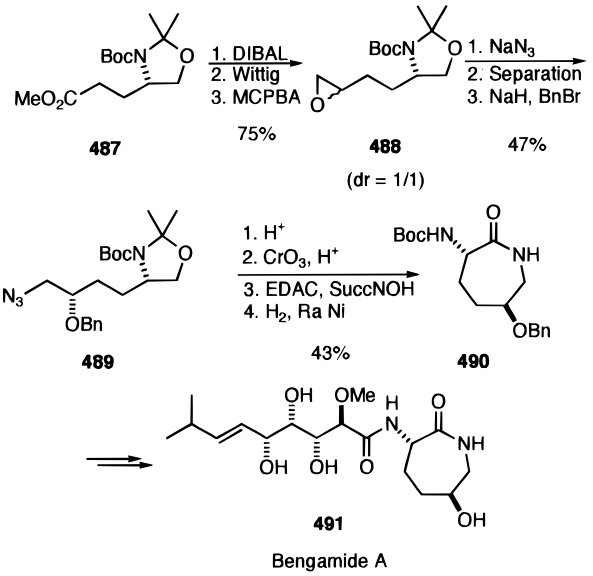
Scheme 94



diacid **484**, followed by selective protection of the C-5 hydroxyl group and Mitsunobu reaction on the C-1 hydroxyl group afforded **485**, which was transformed into epoxide **486** (as a mixture of stereoisomers) in four steps. The 3*S*,4*R* isomer of epoxide **486** was efficiently elaborated into (−)-slaframine by a sequence involving an intramolecular epoxide opening by an amine (prepared by azide reduction) and a subsequent alkylation of the nitrogen by a tosylate (at C-1).

A related Wittig reaction−epoxidation sequence on a glutamate C-5 aldehyde was used to prepare **488**, a key intermediate in the synthesis of bengamide A.[118] Epoxide opening, acetal hydrolysis, primary alcohol oxidation, and lactam closure completed the synthesis of the heterocyclic core of bengamide A (**490**) (Scheme 95).

Scheme 95



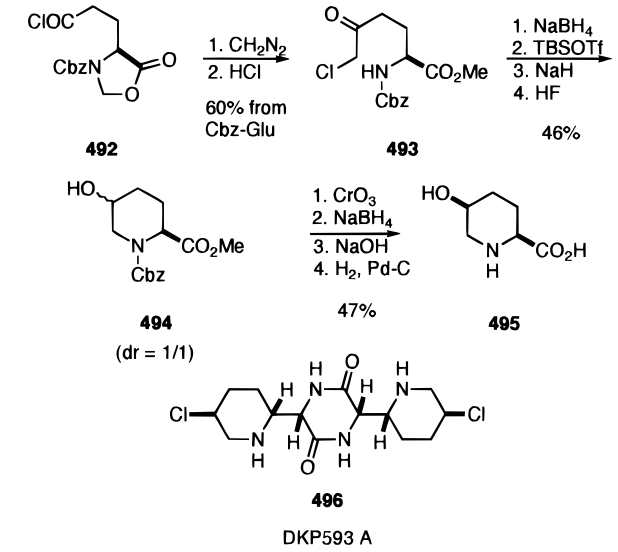
C−C bond formation at C-5 on an acyclic glutamate derivative (bearing an ω-substituent in a carboxylic acid oxidation state) was achieved by reaction of the acid chloride **492** with diazomethane and HCl.[119] The resulting product, chloro ketone **493**, was reduced and cyclized to give **494** as a mixture of epimers at the hydroxyl-bearing carbon. This mixture was funnelled to acid **495** by oxidation of the alcohol to a ketone and stereoselective reduction of the ketone to the β-alcohol, followed by ester hydrolysis. It is not clear if the sequence occurred with complete retention of configuration at C-2, since **495** was only of 86% ee (from rotation data, which are very unreliable, especially in aqueous solutions).[119] Acid **495** is an intermediate in a projected synthesis of the antitumor antibiotic DKP593A (**496**) (Scheme 96).

Acid chloride **492** was also used for Grignard reagent addition to give ketone **497** (in high yield), which in turn was used to prepare pyrrolodiazepine **499**, a conformationally restricted analogue of the ACE inhibitors[120] (Scheme 97).

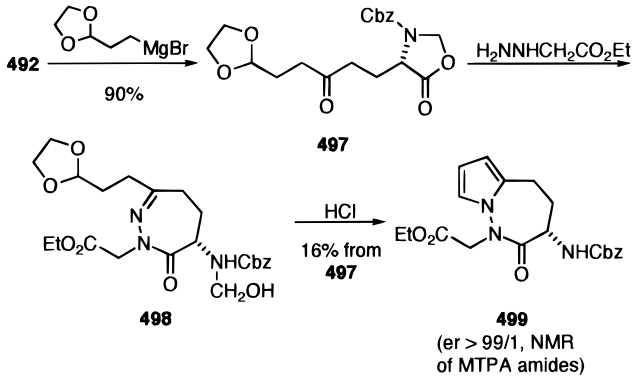
Alkylation of iodide **500**, derived from glutamic acid (in which the C-5 substituent is at the alcohol oxidation state) with a sulfur-stabilized carbanion led to ketone **501**, which cyclized to **502** on acid treatment. Aminal reduction (to give a 2,6-disubstituted pyrrolidine), followed by adjustment of the oxidation state of the side chain and deprotection completed the synthesis of solenopsin B (**503**).[121a]

Five steps are necessary to prepare iodide **500** from glutamic acid, and this results in a rather lengthy synthesis of **503**. A shorter and more efficient route to solenopsin B, based on the stereoselective reduc-

Scheme 96



Scheme 97



tion of keto ester **504** (prepared from myristoyl chloride) has been reported.[121b] Construction of the piperidine ring with the correct absolute and relative configuration was achieved by an intramolecular 1,3-dipolar cycloaddition of the olefinic azide **506** (prepared in five steps from **504**) (Scheme 98).

4. C-1 Alkylation

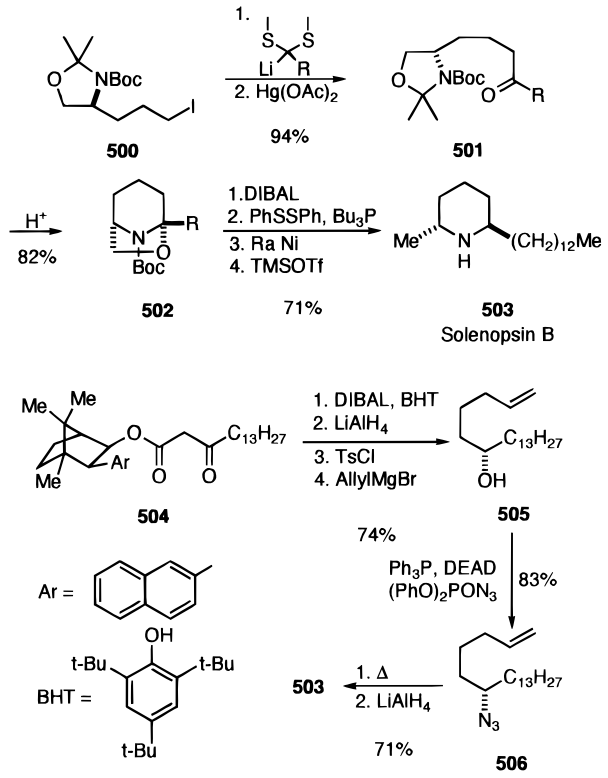
Chain extension of glutamic acid at the C-1 position has been carried out on cyclic and acyclic substrates bearing the C-1 functional group at the alcohol, aldehyde or acid oxidation state.

A simple, stereoselective synthesis of the indolizidine alkaloid (−)-gephyrotoxin 167B (**107**) from alcohol **507** via C-1 chain extension has been reported.[122] The pyrrolidine ring of **107** was constructed by stereoselective intramolecular reductive amination of ketone **509**, available by a double chain extension from pyroglutamyl alcohol **507** (Scheme 99).

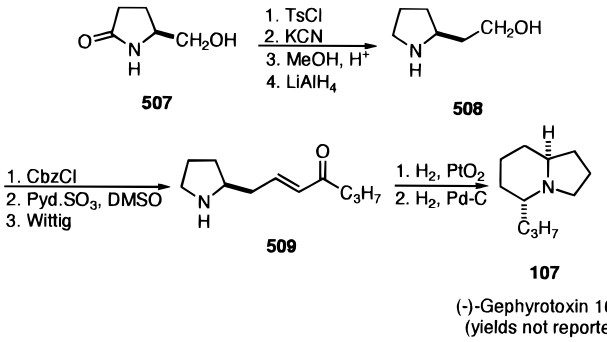
Wittig reaction of a *N*-Boc-glutamate aldehyde derived from **510** gave diene pyrrolidone **511** which was used in model studies for the synthesis of *Aristotelia* alkaloids (i.e. **512**)[123] (Scheme 100).

The assignment of the relative and absolute configuration of the γ-butyrolactone acetogenin (+)-muricatacin (**514**) was based on a synthesis starting from lactonic acid **513**, prepared by nitrosation of glutamic acid. The synthesis involved the alkylation of the acid chloride derived from **513** with the

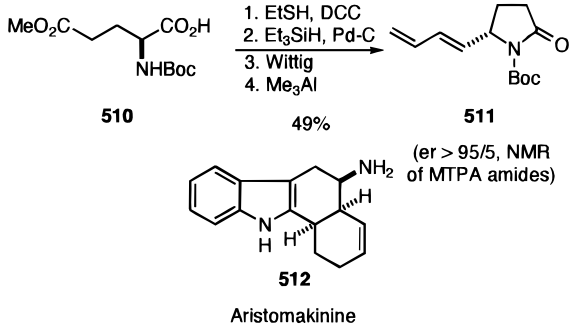
Scheme 98



Scheme 99



Scheme 100

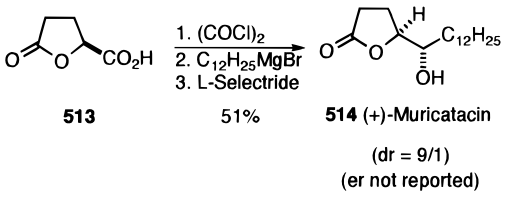


corresponding Grignard reagent, followed by stereoselective ketone reduction[124] (Scheme 101). Unfortunately, the enantiomeric purity of **514** was not determined despite the fact that the intermediate α-alkoxy ketone should be easily racemized.

5. Miscellaneous

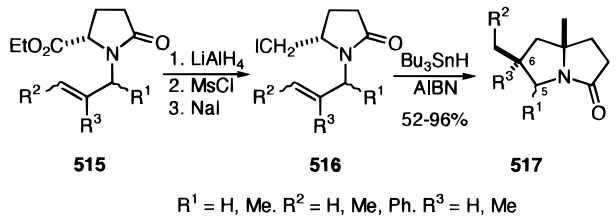
Smith and co-workers studied the radical cyclization of *N*-allylpyroglutamates **516** and found that the reaction proceeded in fair to excellent yield and with

Scheme 101



exo selectivity to give pyrrolizidines **517**.[125] Excellent stereocontrol in the formation of the C-6 center was achieved; however, no stereocontrol could be exerted on the introduction of the C-5 substituent (Scheme 102).

Scheme 102



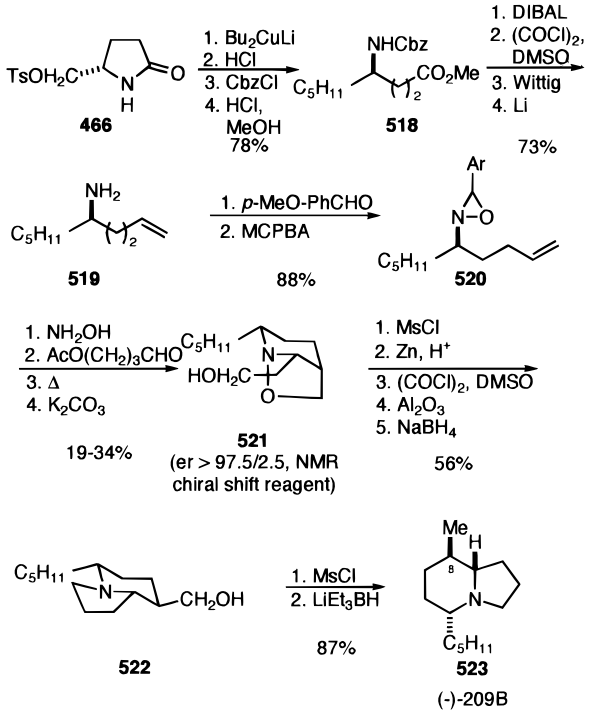
A highly stereoselective approach to enantiomerically pure 5,8-disubstituted indolizine alkaloids, based on an intramolecular nitrone cycloaddition, has been reported.[126] The required nitrone was prepared by side-chain extension of pyroglutamate **466** to give ester **518**, after adjustment of the protecting groups and lactam hydrolysis. Reduction of the ester function of **518** to the aldehyde followed by Wittig reaction and amine deprotection gave eneamine **519**. An imine derived from this eneamine was selectively oxidized to the oxaziridine **520**, which after reaction with hydroxylamine and then with the appropriate aldehyde, gave the desired nitrone, which cyclized on heating to give **521**. Closure of the pyrrolidine ring and inversion of configuration at C-8 completed the synthesis of the poison-dart frog alkaloid (−)-209B (**523**) (Scheme 103).

Evans *et al.* have reported the synthesis of the amino acid target of the diphtheria toxin (diphthamide, **530b**).[127] The approach taken was to prepare the imidazole nucleus by cyclocondensation of a benzylimine derived from amide **527**, followed by stereoselective azidation of the enolate of **528** (Scheme 104).

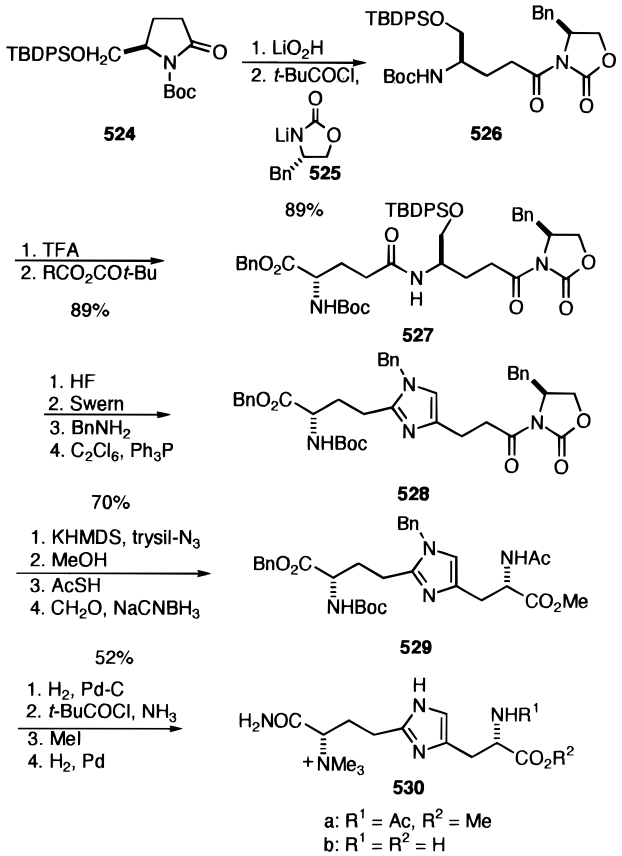
Bicyclic lactam **538**, an intermediate on the synthesis of the antitumor antibiotic quinocarcin (**539**), was prepared from pyroglutamate **531** by a sequence in which the acyliminium ion cyclization of enol ether **535** to give bicycle **536** was the key step.[128] Preparation of the precursor for the cyclization was carried out by coupling acid chloride **531** and amine **532**. Reaction of the resulting amide **533** with Bredereck's reagent followed by stereoselective reduction and alcohol protection gave **534**. Adjustment of the oxidation states of the amide and silyl ether groups of **534** afforded the desired aminal **535**, which was cyclized and deprotected to yield **537**, as a mixture of epimers. The mixture was converted into the desired **538** in four steps (Scheme 105).

Fukuyama and co-workers have recently used the reduction of thiol esters to aldehydes with Et_3SiH and catalytic Pd/C[129] to allow the conversion of α-amino

Scheme 103

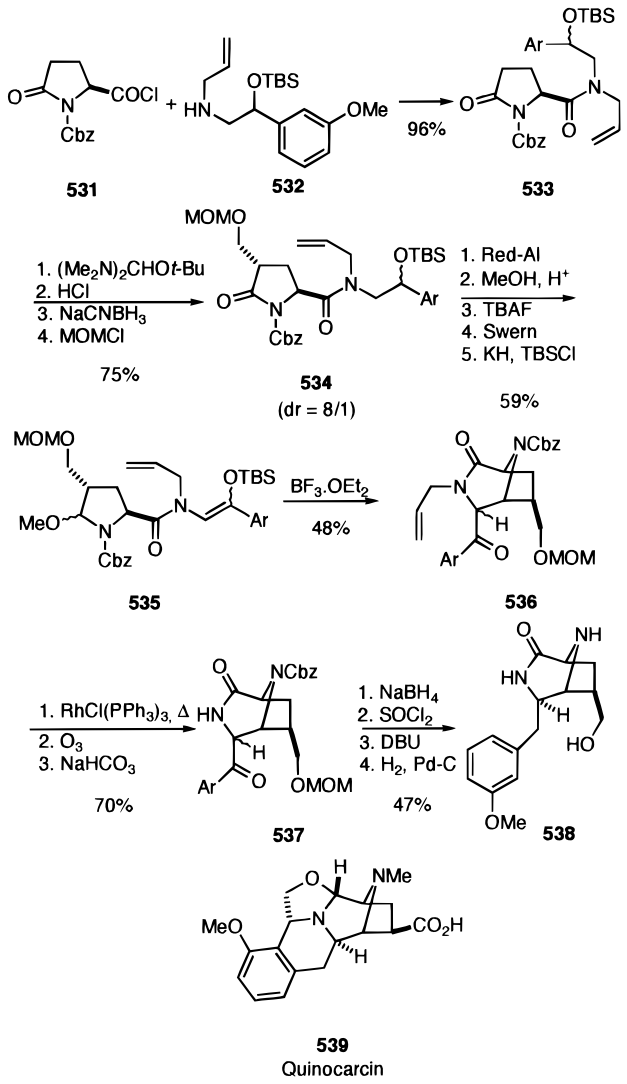


Scheme 104

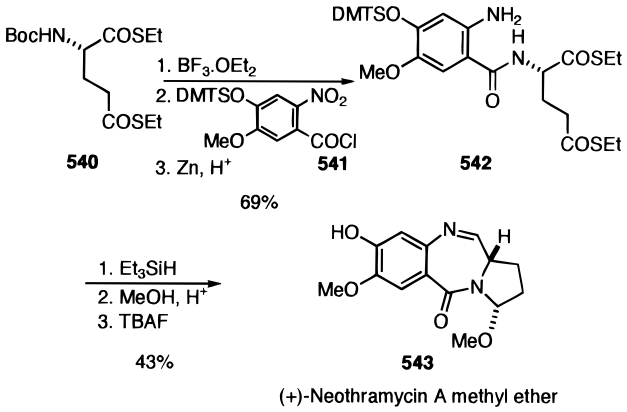


acids to α-amino aldehydes without racemization. This method was employed as the key step in the synthesis of the antitumor antibiotic (+)-neothramycin (**543**). It proceeded via reduction of the amino dithiol ester **542** to a dialdehyde which cyclized *in situ* to provide the neothramycin skeleton[129] (Scheme 106). The synthetic **543** showed an optical rotation lower than that of the natural material, although it

Scheme 105



Scheme 106



was claimed that the optical rotation of **543** depended on the amount of water present in the solvent. No further determination of the enantiomer ratio was carried out.

The same workers also applied the thiol ester reduction to the preparation of acetal **545**, in that way setting the correct absolute configuration in their synthesis of the antitumor antibiotic cyanocycline A (**554**).[130] The synthesis proceeded from **545** by construction of the pyrrolidine ring of cyanocycline, via acylation of the enolate of **545**. Reaction of the dienolate of vinylogous urethane **546** with aldehyde **547** gave lactone **548**, which afforded oxime **550** after extensive manipulation. Oxime reduction followed by Pictet−Spengler condensation of the resulting amine with the appropriate α-alkoxyacetaldehyde gave **551**, from which the pentacyclic core of cyanocycline (**552**) was obtained after ketal deprotection and cyanation. Adjustment of the oxidation state of the aromatic ring and the lactam present in **552**, and a series of protection and deprotection steps completed the synthesis of cyanocycline A (**554**) (Scheme 107).

IX. The Proline Family

Quite naturally, proline and the hydroxyprolines have been used widely, mainly for the synthesis of pyrrolidine ring containing compounds, especially pyrrolidine, pyrrolizidine, and indolizidine alkaloids.

A. Proline

Two closely related syntheses of the pyrrolo[2,1-*c*]-[1,4]benzodiazepine alkaloid tilivalline (**557**) starting from proline have been reported.[131,132] Both approaches relied on the stereoselective Mannich addition of indole to a pyrrolobenzodiazepine electrophile (imine[131] or acyliminium ion[132]), easily assembled by coupling of proline derivative **559** or proline itself with the appropriate aromatic carboxylate (**558** or **561**) (Scheme 108).

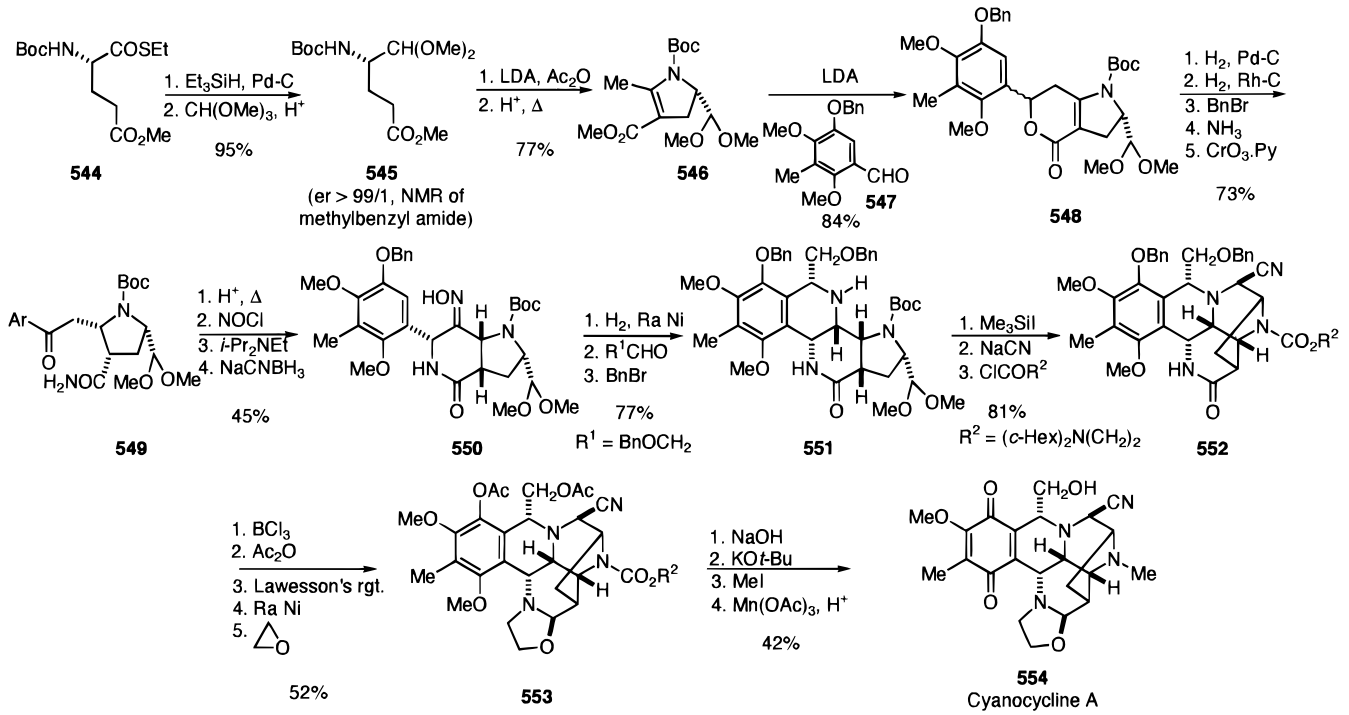
As an alternative to partial reduction of pyrrolidones (pyroglutamic acid derivatives), anodic methoxylation of *N*-protected proline esters affords 5-methoxyprolines (i.e. **564**) which have been used for the synthesis of a variety of mono and bicyclic systems. Reaction of **564** with alkylcopper reagents in the presence of BF_3 (but not with other types of organocopper reagents) led to stereoselective *trans* addition; the products, **565**, were elaborated into the ant pheromone **567** and related *trans*-2,5-disubstituted pyrrolidines by extension of the C-2 side chain[133] (Scheme 109).

The related Boc-methoxyproline **568** reacted with silylketene acetals **569** under Lewis acid catalysis to give *cis* addition, although with low diastereoselectivity. The 5*R*,6*S* isomer of the product (**480**) was ultimately transformed in an advanced intermediate in the synthesis of the carbapenem (+)-PS-5 (**483**)[134] (Scheme 110).

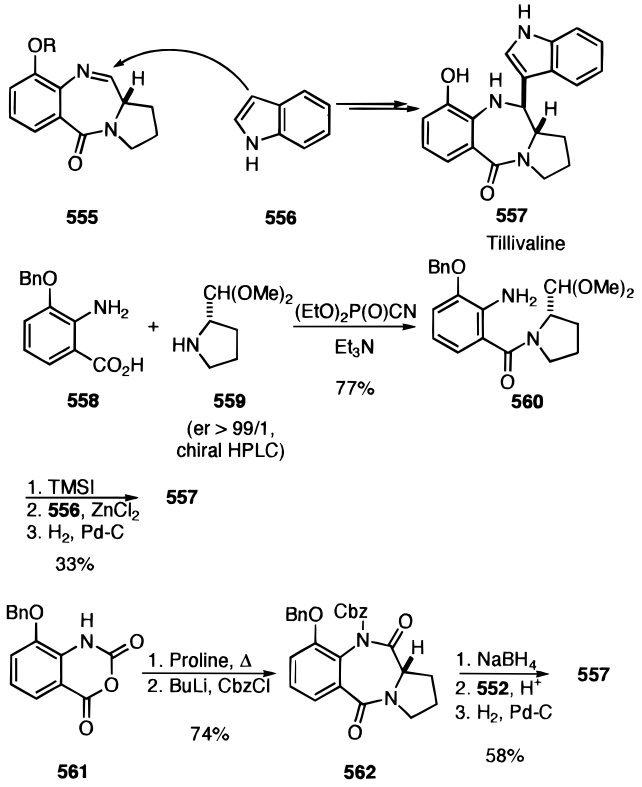
In a similar fashion, *N*-substituted 5-methoxyprolines, prepared by the anodic methoxylation of **572**, gave a mixture of bicyclic lactams **573** on $TiCl_4$-promoted-acyliminium ion cyclization. Lactams **573** were converted into enamines **574** which are key intermediates in a projected synthesis of **575**, conformationally constrained peptide analogues designed to map the receptor bound conformation of thyroliberin (TRH)[135] (Scheme 111).

An elegant approach to the pyrrolizidine ring system based on an atom-transfer annulation of proline-derived allyl haloamides has been described.[136,137] Iodoacetamide **577**, prepared from Boc-prolinal (**576**), underwent a highly stereoselective cyclization on irradiation in the presence of $(Bu_3Sn)_2$ and EtI, to give iodide **578**, which was transformed

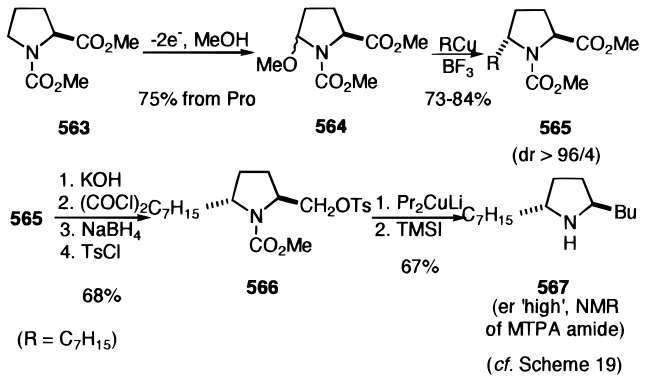
Scheme 107



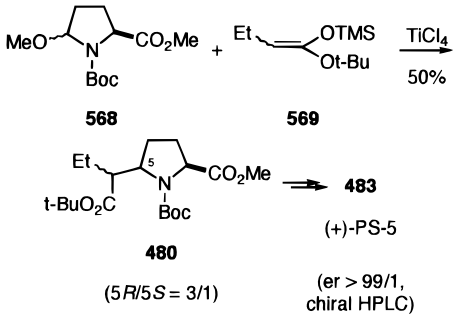
Scheme 108



Scheme 109



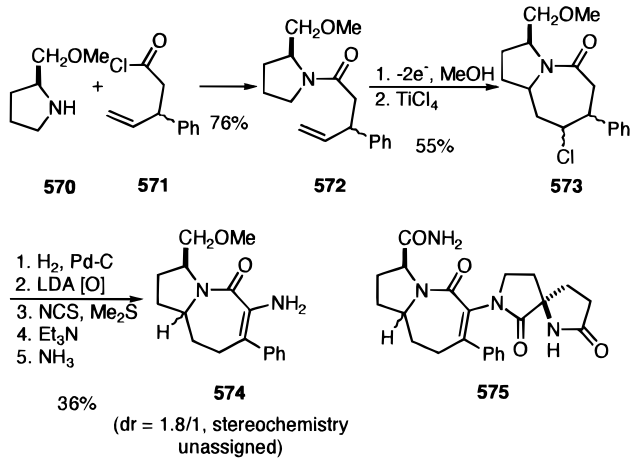
Scheme 110



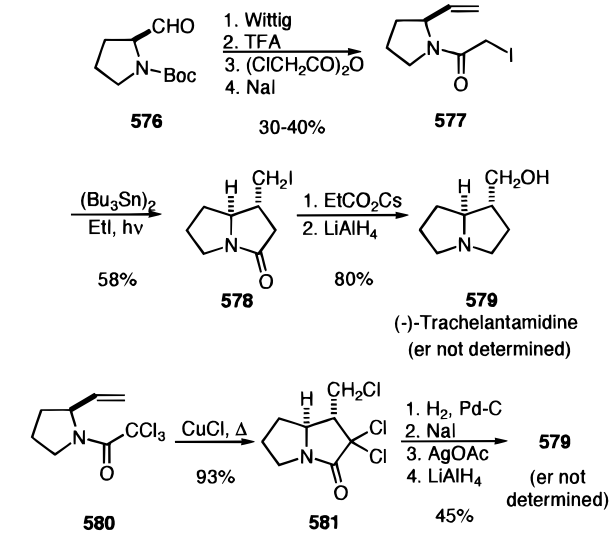
into (−)-trachelantamidine in a straightforward way[136] (Scheme 112). Much in the same vein, the trichloroacetamide **580** underwent a Cu(I)-promoted cyclization to give **581** with complete stereoselection; **581** was finally transformed into **579** in four steps.[137] In both syntheses the authors provide only chiroptical data to prove the enantioespecificity of their approaches, but the intermediacy of the configurationally labile prolinals in the reaction sequence is of some concern with regard to the enantiomeric purity of the final products. Nevertheless, both approaches are short and efficient.

A short, highly stereoselective synthesis of the pyrrolizidine skeleton, based on the stereoselective aldol condensation of an acyliron enolate and a prolinaldehyde, has been developed by Davies and co-workers. The stereochemical outcome of the aldol condensation between Boc-prolinal (**576**) and the aluminum enolate of **582** was dictated by the absolute configuration of the iron acetyl complex. Thus the *S* enantiomer of **582** gave *R*-alcohol **583** selec-

Scheme 111

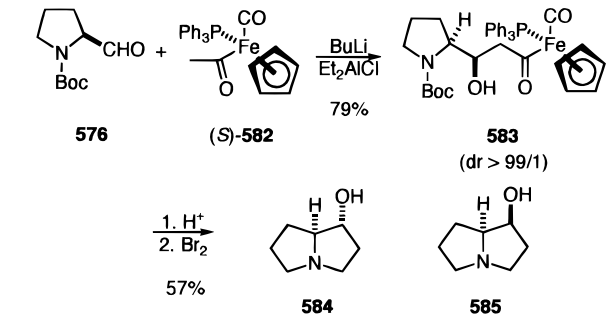


Scheme 112



tively; cyclization of **583** to **584** was achieved by Boc deprotection and iron decomplexation. The *R* isomer of **582** gave the epimer of **583** at the hydroxyl bearing carbon (er, 97/3), which was subsequently transformed into **585**[138] (Scheme 113). It should be noted

Scheme 113

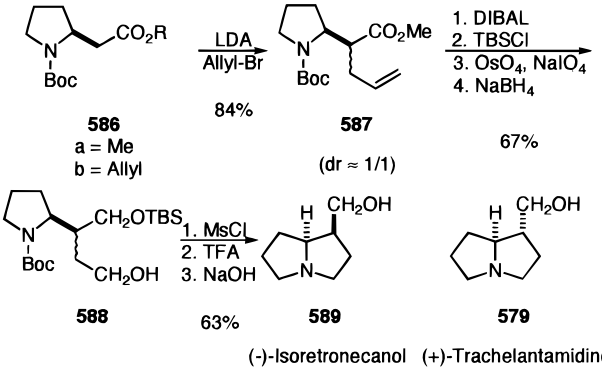


that Boc-prolinal usually undergoes aldol additions with low stereoselectivity.

A conceptually different, less stereoselective approach to the necine bases **579** and **589** involved the homoprolines **587**, obtained by allylation of the enolate of **586a** (or via a Claisen rearrangement of the allyl ester **586b**).[139a] One-carbon degradation of the allyl side chain of either isomer of **587**, to alcohol **588**, followed by alcohol mesylation and cyclization completed the syntheses of (−)-isoretronecanol (**589**) and (+)-trachelantamidine (**579**).

Numerous studies on the synthesis of **579** and **589** have been carried out. An outstanding alternative approach to the necine bases, based on the enantioselective alkylation of an acyclic thioimide, followed by biscyclization, has been developed by Nagao and co-workers[139b] (Scheme 114).

Scheme 114



Far more difficult targets, the pumiliotoxin alkaloids, have also been synthesized from proline.

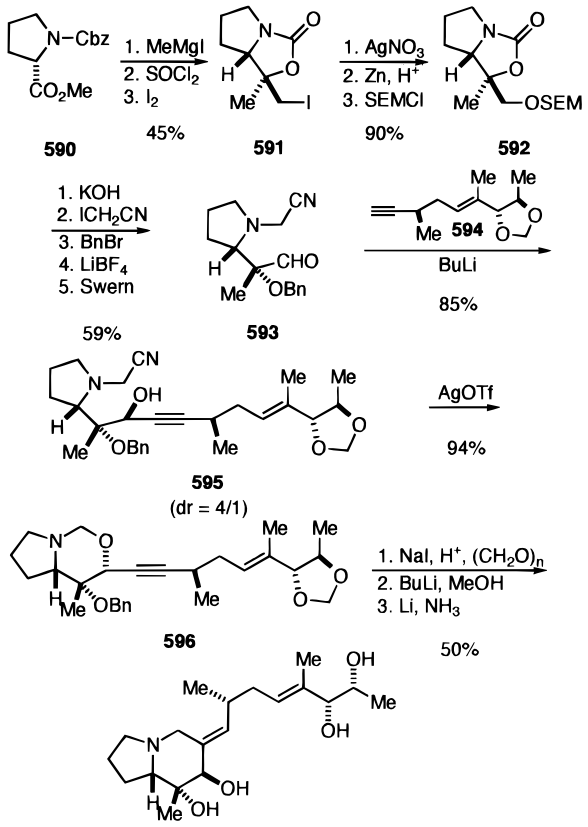
Overman and co-workers have expanded their elegant iminium ion cyclization approach to the cardiotonic pumiliotoxin alkaloids to achieve the first total synthesis of one of the most complex members of the family: (+)-allopumiliotoxin 339A (**597**).[140] The key intermediate, cyclization precursor **596**, was obtained by addition of **594** to aldehyde **593**, which in turn was prepared from iodide **591**, easily obtainable from proline (Scheme 115).

The iodide-promoted cyclization of **596** (by trapping of an intermediate iminium ion with the C−C triple bond, to give a vinyl cation, which in turn was trapped by iodide) gave rise to the desired indolizidine system with complete stereoselectivity. Removal of the vinyl iodide and debenzylation completed the synthesis of **597**.

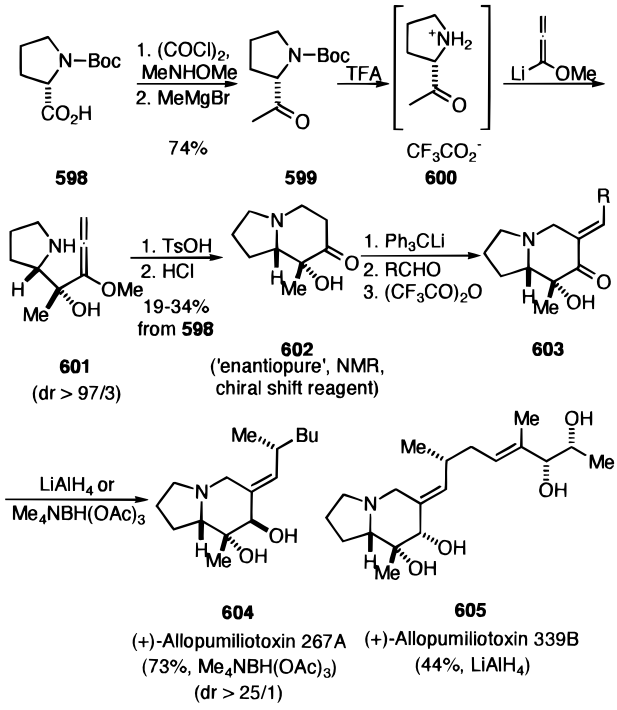
A slight variation was introduced to prepare allopumiliotoxins 267A and 339B (**604** and **605**, respectively). Thus the six-carbon side chains of **604** and **605** were introduced by an aldol condensation of the bicyclic ketone **602** with the appropriate aldehyde followed by dehydration of the resulting aldol. Stereoselective reduction of the resulting enone produced the desired configuration at C-7. The key ketone **602** was assembled by a remarkable addition of an allenyllithium reagent to the salt **600** (to avoid racemization) followed by acid-catalyzed addition of the amine to the allene group[141] (Scheme 116).

A Pd-catalyzed intramolecular addition of a pyrrolidine to an allylic epoxide was used by Trost and co-workers to set up the indolizidine skeleton in their synthesis of allopumiliotoxin 339B.[142] Thus addition of titanate **606** to ketone **600** followed by intramolecular sulfide displacement gave the cyclization precursor **608** (as a mixture of epimers). Intramolecular attack of the amine on the allylic epoxide took place upon treatment of **608** with $(dba)_3Pd_2 \cdot CHCl_3$ to give indolizidine **609** (Scheme 117). Hydroxyl-directed epoxidation of the more substituted

Scheme 115



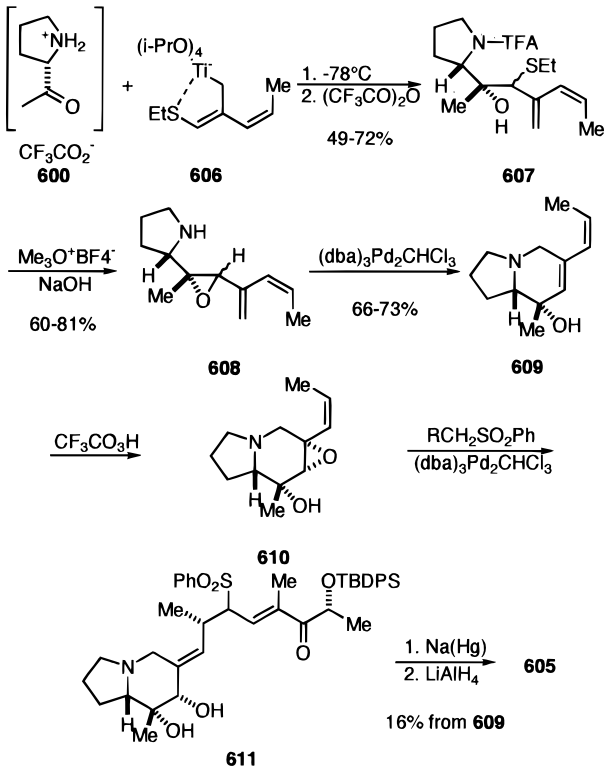
Scheme 116



double bond afforded the substrate (a vinyl epoxide) for the Pd-mediated introduction of the appropriate side chain.

A more conventional (and rather nonstereoselective) construction of the indolizidine system (present in the antiretroviral agent castanospermine) starting

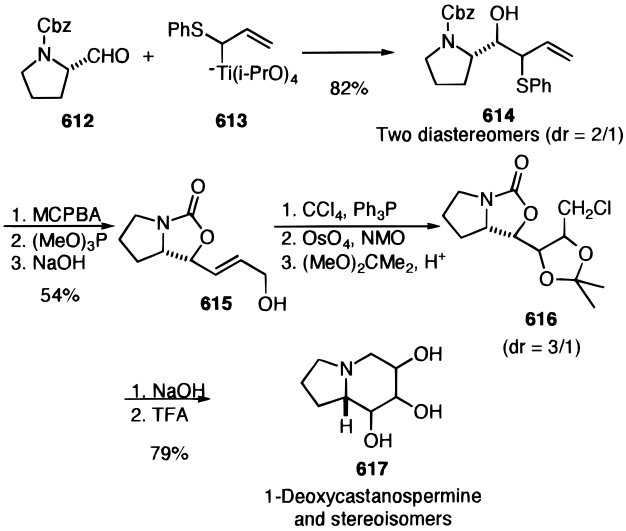
Scheme 117



from prolinaldehyde **612** has been presented.[143a] The major drawback of this approach is the low diastereoselectivity of the hydroxyl introduction steps (the isomer with the castanospermine relative configuration is the very minor product of the sequence).

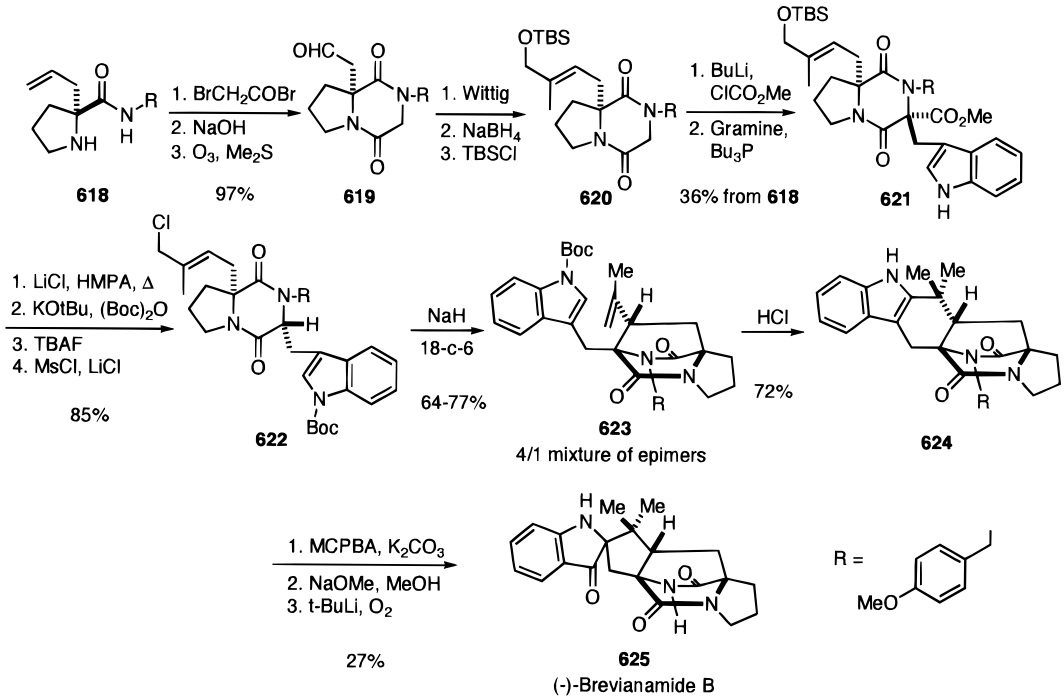
Quite naturally, sugars comprise far better starting materials for the synthesis of castanospermine and its stereoisomers. Several recent syntheses, starting from D-glucono-δ-lactone,[143b] L-gulonolactone,[143c] or D-glucose,[143d] provide much more controlled and efficient ways of synthesizing this family of polyhydroxylated indolizidines (Scheme 118).

Scheme 118



A remarkable synthesis of the hexacyclic alkaloid (+)-brevianamide B (**625**) from proline has been reported by Williams and co-workers.[144a] The α-allylated proline **618** (prepared by a method developed

Scheme 119



by Seebach)[144b] was condensed with bromoacetyl bromide and subsequently ozonized to give aldehyde **619**, which was elongated to **620** via a Wittig reaction. Carbomethoxylation of **620**, followed by Kametani condensation (gramine, Bu_3P) gave indole **621**; decarboxylation, *N*-protection, and chloride introduction gave the cyclization precursor **622**. The key intramolecular S_N2' cyclization (of **622** to give **623**) occurred with moderate stereoselection. The synthesis of (−)-brevianamide was completed by Boc hydrolysis and olefin−cation cyclization (to give **624**), followed by oxidation, rearrangement to the desired indoxyl and *N*-deprotection (Scheme 119).

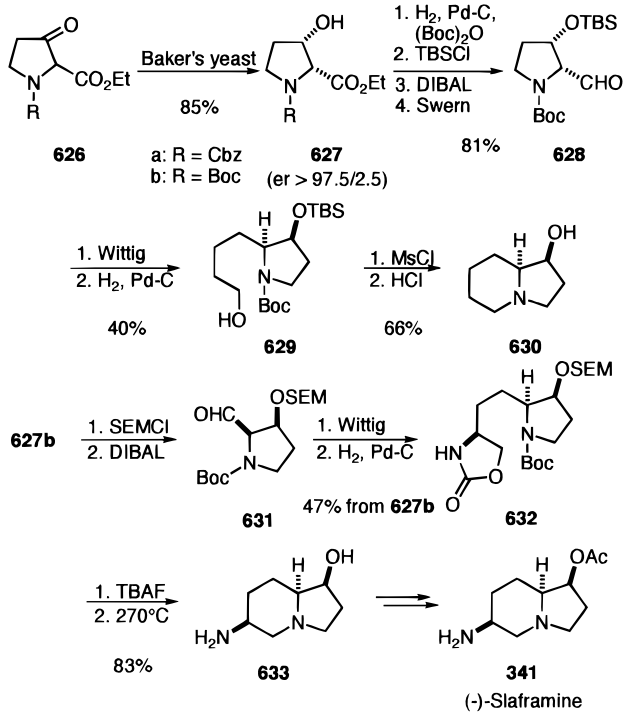
B. Hydroxyprolines

The presence of a hydroxyl group in the proline ring of the hydroxyprolines offers a useful handle for the introduction of substituents in the pyrrolidine ring. In this way 4-arylprolines[145a,b] and 4-fluoroprolines[145c] have been prepared from 4-(tosyloxy)-proline and 4-hydroxyproline, respectively. 4-Alkylideneprolines have been prepared by Wittig reaction on a 4-oxoproline, obtained by oxidation of 4-hydroxyproline.[145d]

An improvement in the procedure for the enantioselective preparation of (2*R*,3*S*)-3-hydroxyproline (**627**) of high er (enantiomer ratio) by bakers' yeast reduction of keto ester **626** has been reported.[146a] The *β*-hydroxy ester **627b** formed in this way was used for the synthesis of (1*S*)-1-hydroxyindolizidines **630**[146a] and (−)-slaframine[146b] by Wittig reaction of the prolinals **628** and **631** with the appropriate C_3 phosphonium salt, followed by cyclization (Scheme 120).

An alternative synthesis of (−)-slaframine was achieved by Julia coupling of prolinal **638** with the dianion of sulfone **640**, followed by double-bond reduction and cyclization of the resulting mixture of alkenes **641**[146c] (Scheme 121).

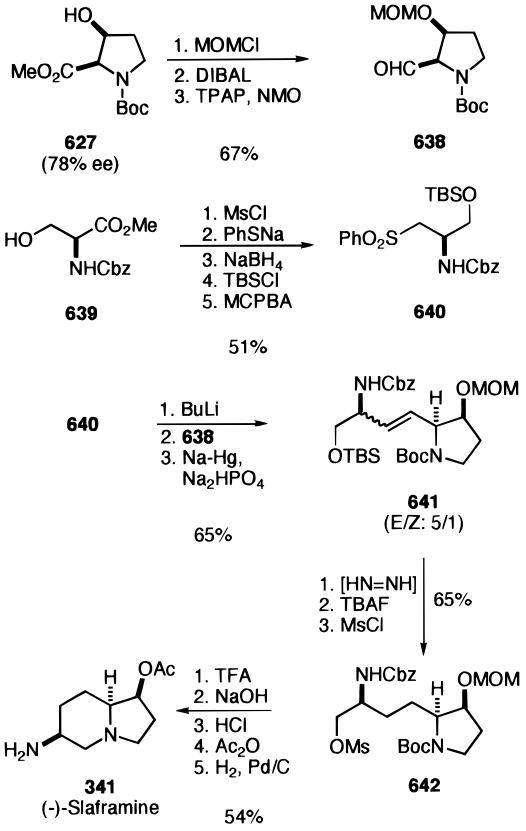
Scheme 120



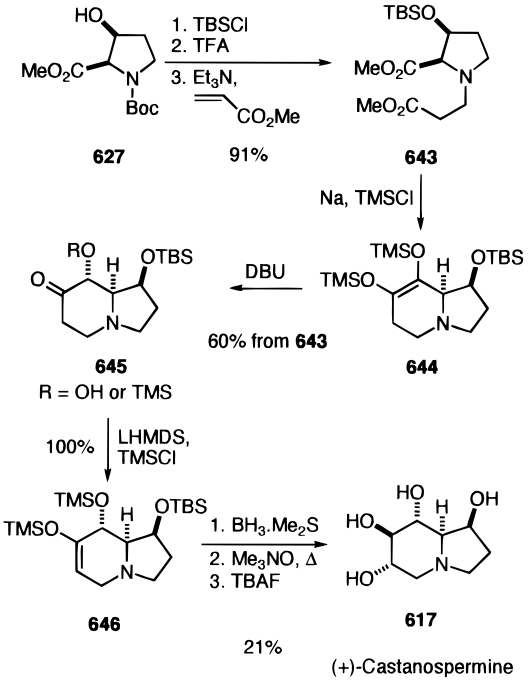
The 3-hydroxyproline methyl ester **627** was used for the synthesis of (+)-castanospermine (**617**). The piperidine ring was annulated onto the pyrrolidine ring by an acyloin condensation of diester **643**, prepared by Michael addition of an *O*-protected derivative of **627** to methyl acrylate. Treatment of the resulting **644** with DBU surprisingly afforded ketone **645** as the sole product. Introduction of the remaining hydroxyl group was achieved by hydroboration of silyl enol ether **646**, which occurred with poor stereoselectivity[147] (Scheme 122).

trans-4-Hydroxy-L-proline was employed as starting material for the stereoselective preparation of

Scheme 121



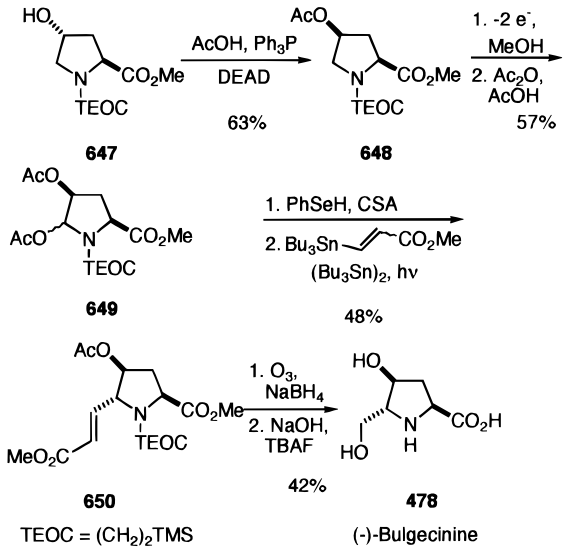
Scheme 122



bulgecinine (**478**). Mitsunobu reaction of ester **647** gave acetate **648**, which has the correct configuration at C-4. Introduction of the hydroxymethyl side chain at C-5 was carried out by anodic methoxylation of **648**, followed by a stereoselective radical homologation of an intermediate selenide derived from acetate **649**[148] (Scheme 123).

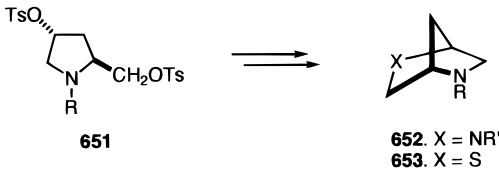
The *trans*-4-hydroxyprolines have also been used to prepare derivatives of 2,5-diazabicyclo[2.2.1]-heptane **652** which are precursors of antibacterial

Scheme 123



quinolones, and of 2-thia-5-azabicyclo[2.2.1]heptane (**653**) via a double nucleophilic displacement of ditosylate **651**[149] (Scheme 124).

Scheme 124



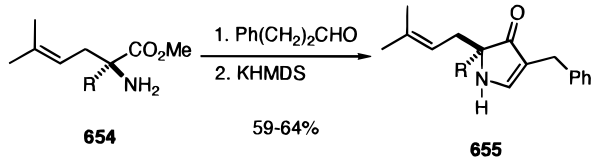
X. Addendum

The material covered in this Addendum was published during the period July 1993 to March 1994.

A. General Methodology

Imines of α-alkylamino acid esters have been used for the synthesis of 3,5,5-trisubstituted 4-pyrrolidinones **655** by conversion to the corresponding potassio enamines which underwent intramolecular acylation to give the desired products[150] (Scheme 125).

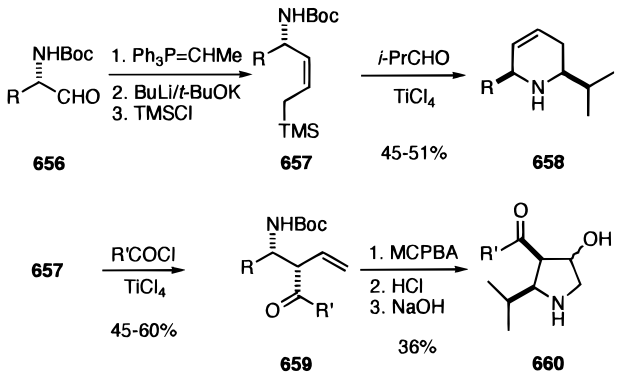
Scheme 125



Allylsilanes, prepared from α-amino aldehydes by Wittig reaction, afforded *cis*-2,6-disubstituted piperidines **658** on treatment with aldehydes in the presence of a Lewis acid (via imminium ion cyclization). α-Vinyl-*β*-aminocarbonyl compounds (**659**) were obtained when acid chlorides were used instead of aldehydes, allowing for an entry into the 2,3,4-trisubstituted pyrrolidine system (**660**)[151] (Scheme 126).

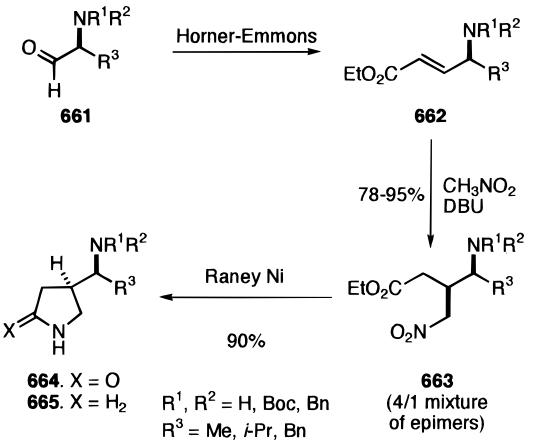
When 3-[1-(methylamino)alkyl]pyrrolidines (**665**) are attached to the 7-position of fluoroquinolones, the resulting compounds show broad-spectrum antibac-

Scheme 126



terial activity. A general synthesis of pyrrolidines **665** has been developed via the moderately stereoselective conjugate addition of nitromethane to the unsaturated esters **662**, followed by reductive cyclization[152] (Scheme 127).

Scheme 127



B. The Aliphatic Amino Acids

Claisen rearrangement of ketene acetals derived from tetrahydro-6-vinyl-5-methyl-1,4-oxazin-2-ones (**668**, prepared from Boc-alaninal) gave $\Delta^{4,5}$-pipecolic esters **669** stereoselectively. Further elaboration of these units afforded the indolizidine alkaloid (+)-monomorine (**111**)[153] (Scheme 128).

Several bicyclic γ-lactam dipeptide analogues (**671**) were synthesized from (*S*)-3-butenylglycine and a series of amino acids by peptide coupling followed by double-bond cleavage (to an aldehyde) and cyclization to give a bicyclic aminal[154] (Scheme 129).

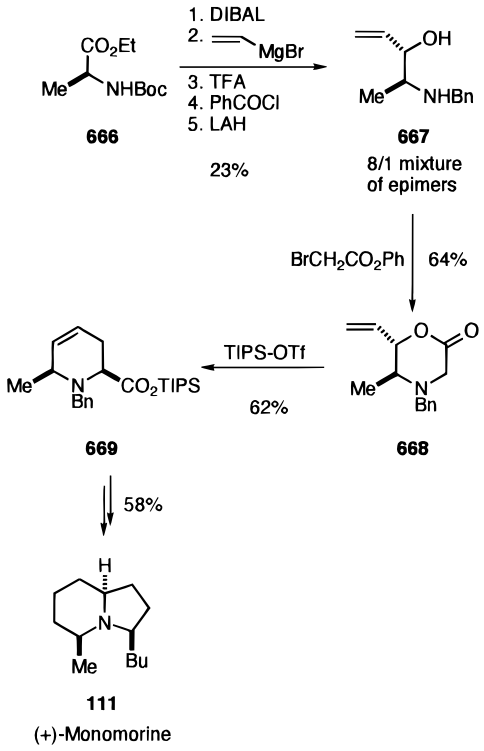
A short synthesis of (+)-pseudoconhydrine (**674**) from L-norvaline has been reported.[155] The key step was the asymmetric dihydroxylation of the *N*-alkenylurethane **672**, which proceeded with moderate stereoselection (Scheme 130).

C. The Aromatic Amino Acids

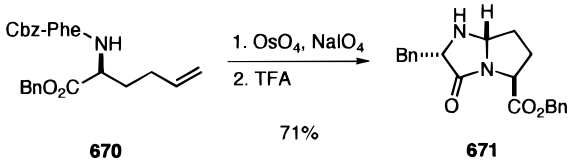
1. Phenylalanine, Substituted Phenylalanines, and Tyrosine

Full details of the synthesis of the 10-membered dipeptide lactam **153** from tyrosine and its use for the synthesis of deoxyboubardin have been published.[156]

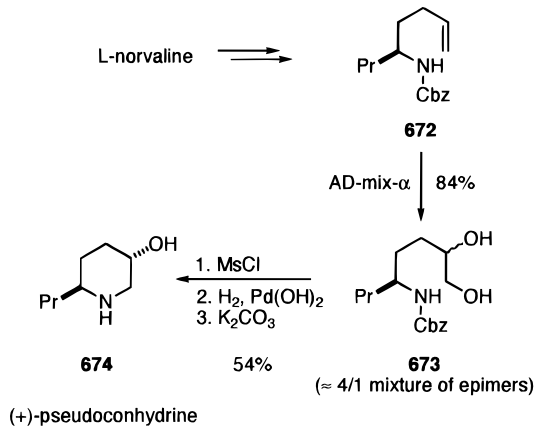
Scheme 128



Scheme 129



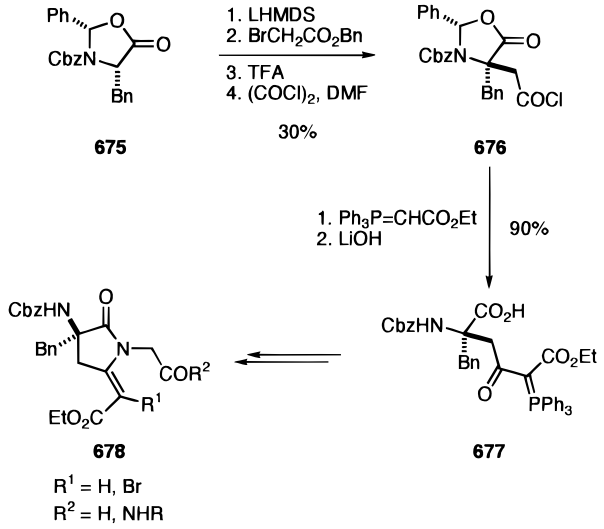
Scheme 130



Cyclic acylated enamino ester dipeptide analogues (**678**, purported serine protease inhibitors) have been prepared via lactonization of keto acid phosphorane **677**, which was obtained from phenylalanine[157] (Scheme 131).

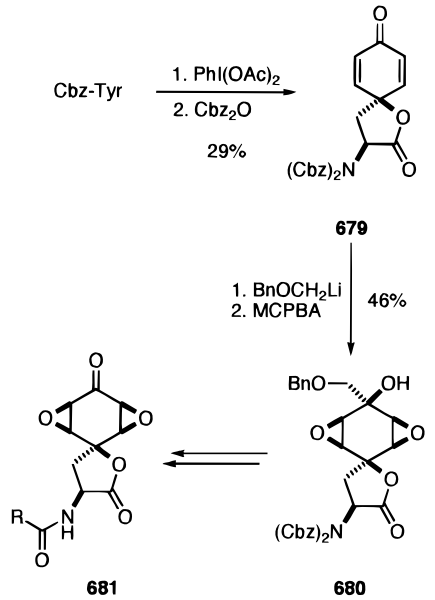
Oxidative cyclization of Cbz-tyrosine afforded spirocyclic dienone **679**, an ideal precursor to the core portion of the antibiotic aranorosin. The introduction of the diepoxide moiety present in the target **681** required the previous stereoselective addition of an α-alkoxyorganolithium reagent to the carbonyl group in order to activate the C=C bond toward oxidation. Hydroxyl-directed diepoxidation of the intermediate

Scheme 131



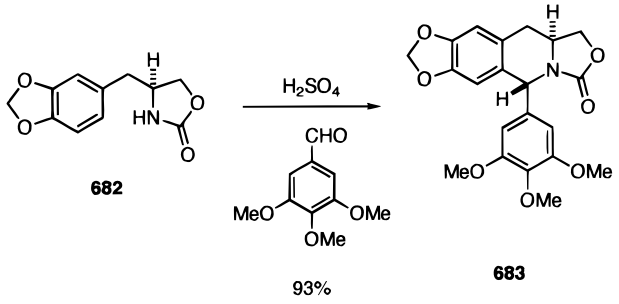
dienol gave the desired aranorosin precursor **680**[158] (Scheme 132).

Scheme 132



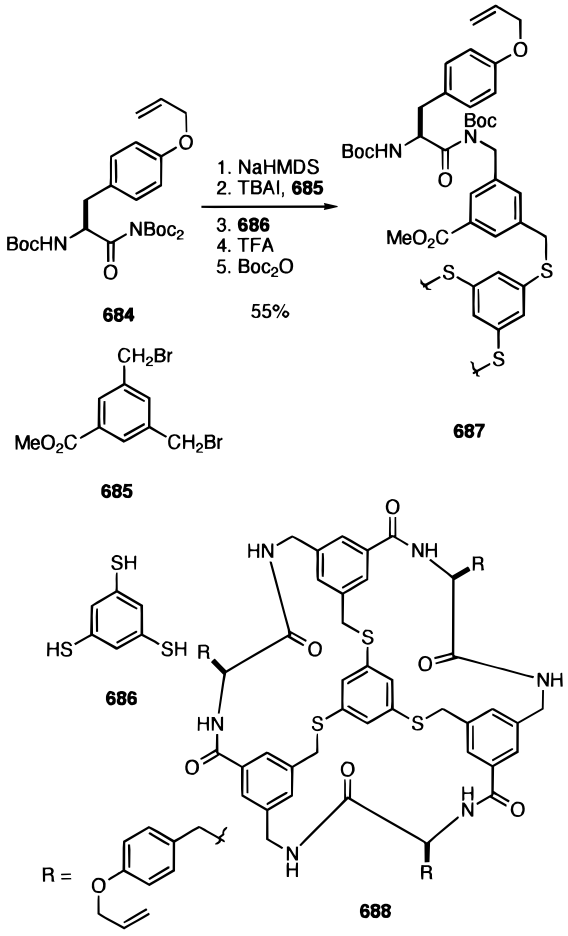
Bischler−Napieralski reaction of oxygenated phenylalaninol derived carbamates (**682**) with 3,4,5-trimethoxybenzaldehyde provided aza analogues of podophyllotoxin (**683**)[159] (Scheme 133).

Scheme 133



A practical synthesis of an enantioselective receptor for peptides using phenylalanine as starting material has been published.[160] The strategy used involved addition of a Boc-tyrosine amide anion derivative (prepared from **684** by deprotonation and Boc migration) to methyl 3,5-bis(bromomethyl)benzoate; the resulting bromide was used to triply alkylate *sym*-trimercaptobenzene to give **687**; macrolactamization of the resulting product afforded the desired receptor molecule **688** (Scheme 134).

Scheme 134



Livinghouse and co-workers have developed a stereoselective imidotitanium−alkyne [2 + 2] cycloaddition which has been applied to the total synthesis of (+)-preussin (**692**).[161] The alkynyl amine required for the cyclization was obtained by reacting imine **689** with a mixture of DIBAL, $(i\text{-Bu})_3$Al, and allenylmagnesium bromide, followed by *O*-benzylation and hydrolysis of the imine (Scheme 135).

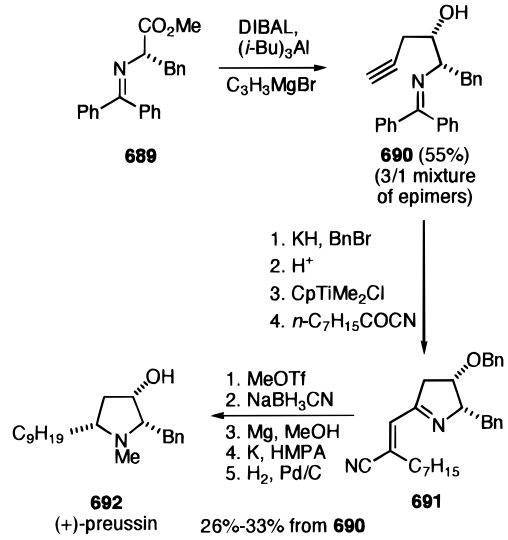
2. Tryptophan

Extensions of the studies on the diastereo- and enantioselectivity of the Pictet−Spengler reaction of the tryptophan esters have been published,[162] some of which were directed toward the synthesis of fumitremorgin analogues (**692**).[163]

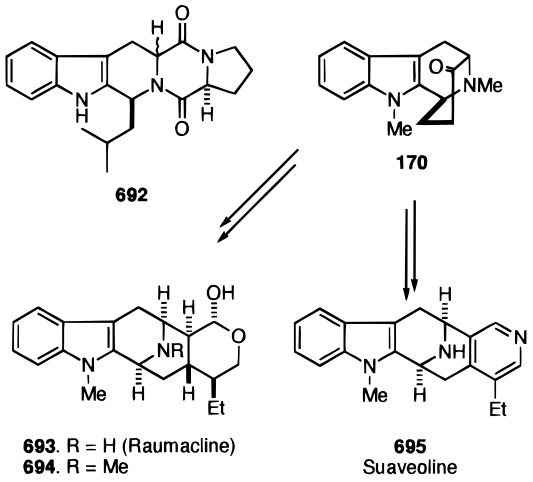
Further studies on the synthesis of tetracyclic ketone **170** and its analogues and their use for the chirospecific synthesis of the indole alkaloids (−)-raumacline (**693**), (−)-N_b-methylraumacline (**694**), and (−)-suaveoline (**695**) have been disclosed[164] (Scheme 136).

Tryptophan-derived imines gave Diels−Alder adducts with Danishefsky's diene, which were subse-

Scheme 135



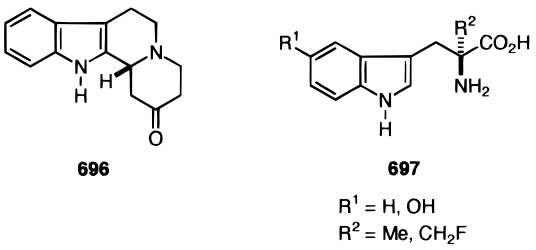
Scheme 136



quently cyclized to indolo[2,3-*a*]quinolizidin-2-ones (**696**), viable intermediates for the synthesis of reserpine (*cf.* Scheme 7).[165]

The acid-promoted cyclization of tryptophan esters to pyrroloindoles (*cf.* Scheme 36) has been used to prepare α-substituted 5-hydroxytryptophan derivatives[166] and α-(fluoromethyl)tryptophan analogues (**697**)[167] (Scheme 137).

Scheme 137



D. The Hydroxy- and Sulfur-Containing Amino Acids

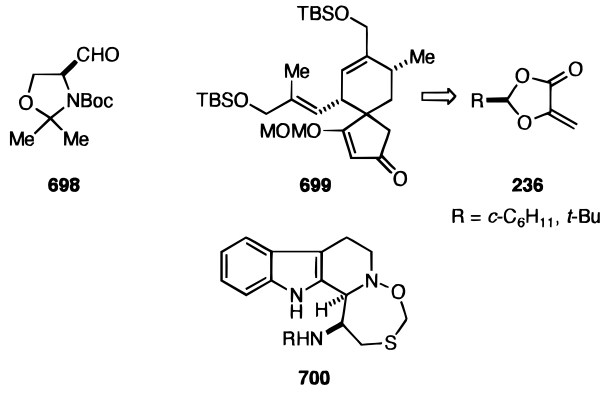
A review of the use of *β*-hydroxy-α-amino aldehydes in the total synthesis of amino sugars has appeared.[168]

An improved procedure for the preparation of Garner aldehyde (**698**) from serine has been described.[169]

The application of dioxolane **236** (prepared from serine) to the synthesis of the top half of the aglycon of the antibiotic kijanimicin (kijanolide, **699**) has been published.[170]

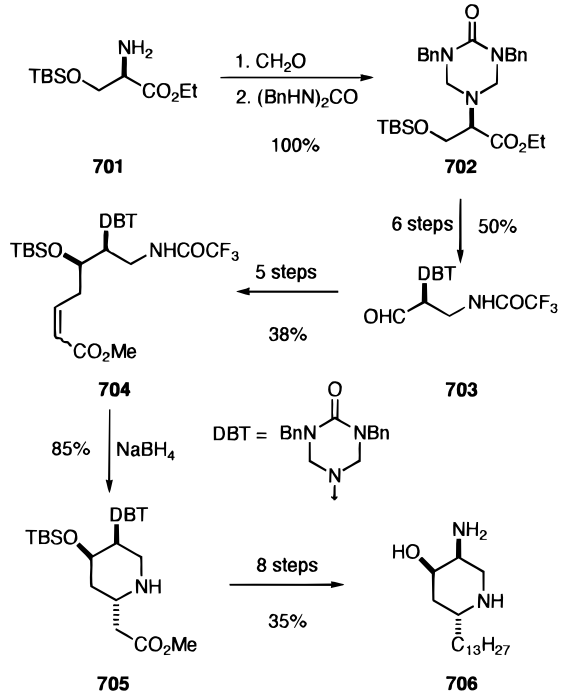
The Pictet−Spengler cyclization of N_b-alkoxytryptamines with serine-derived aldehydes has been studied in order to provide a model system for the synthesis of the eudistomins (**700**)[171] (Scheme 138).

Scheme 138



The use of the dibenzyltriazone group for amino protection is the most salient feature of a lengthy synthesis of (+)-tetrahydropseudodistomin (**706**) from D-serine, which also established the absolute configuration of the calmodulin agonists pseudodistomins A and B. The key step on the synthesis was the stereoselective construction of the piperidine ring by intramolecular Michael addition of unsaturated ester **704**[172] (Scheme 139).

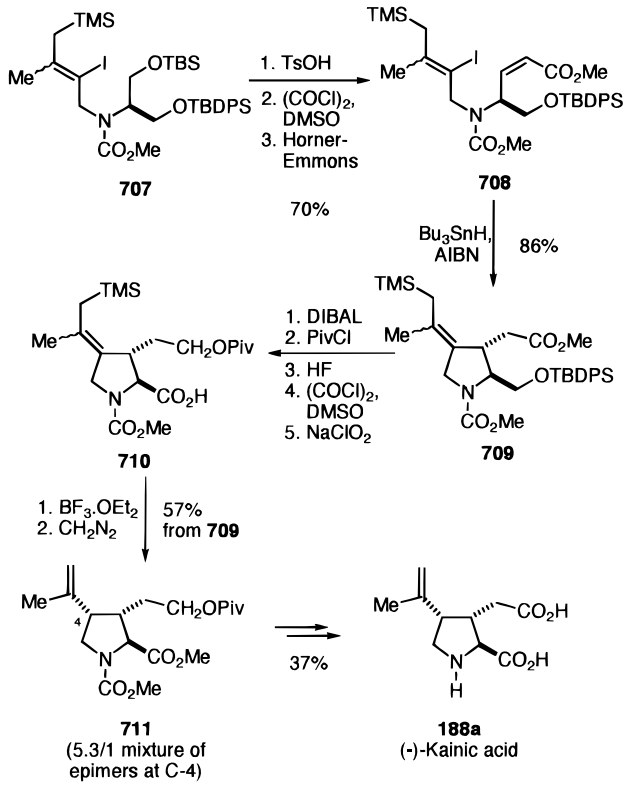
Scheme 139



A recently published stereoselective syntheses of (−)-kainic acid and (+)-allokainic acid from serine involved the stereoselective cyclization of a vinyl radical generated from vinyl iodide **708**. The configuration at C-4 could be controlled by careful

selection of the conditions for the protodesilylation of the allyl-TMS group[173] (Scheme 140).

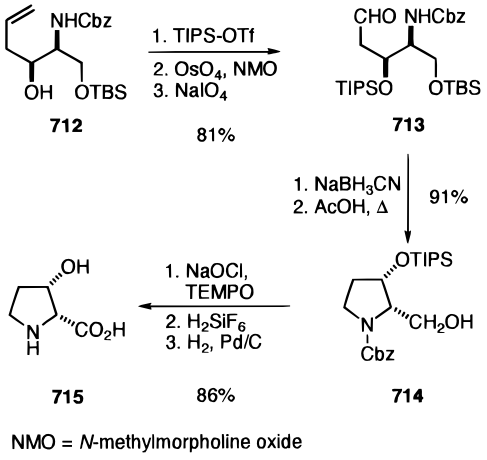
Scheme 140



Oxidation of threonine-containing dipeptides with the Dess−Martin periodinane afforded the corresponding ketones which were cyclodehydrated to provide highly functionalized oxazoles.[174]

A nonenzymatic preparation of (2*R*,3*S*)-3-hydroxyproline has been reported.[175] Stereoselective allylation of *N*-Cbz-*O*-TBS-serinal gave homoallylic alcohol **712** (diastereomer ratio > 95/5), which was converted into the desired hydroxyproline **715** in a straightforward fashion (Scheme 141). Despite the high yields

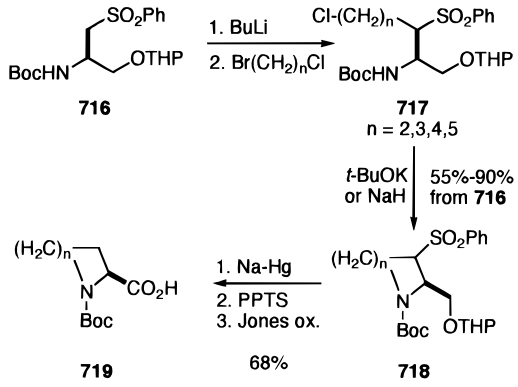
Scheme 141



of the individual steps, this sequence is not as efficient as the preparation of derivatives of **715** by enzymatic reduction of keto ester **626** (Scheme 120).

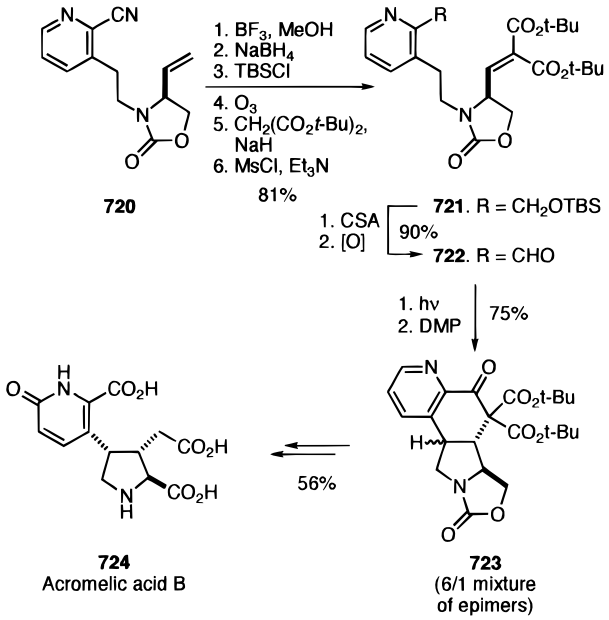
Double alkylation (first on carbon and then on nitrogen) of anions derived from sulfone **716** led to the efficient formation of heterocyclic amino acids **719**[176] (Scheme 142).

Scheme 142



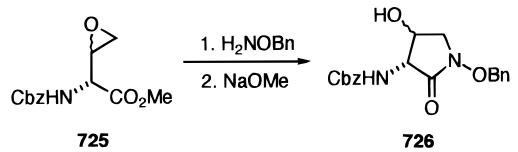
An intramolecular Diels−Alder reaction of a photochemically generated *o*-quinodimethane with a tethered enoate (prepared from oxazolidinone **722**) was the key step in an efficient synthesis of acromelic acids B (**724**) and E.[177] The required piridooxazolidinone was obtained by coupling of 2-cyano-3-(2-hydroxyethyl)pyridine with a vinyl glycinol derivative (prepared from methionine) (Scheme 143).

Scheme 143



A vinyl glycine epoxide was used for the preparation of several stereoisomers of 1,3-dihydroxy-3-amino-pyrrolidin-2-one (**726**), which are partial agonists at the glycine regulatory site of the NMDA receptor[178] (Scheme 144).

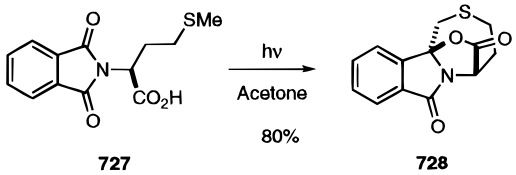
Scheme 144



An exotic ring system has been prepared from methionine: photolysis of *N*-phthaloyl methionine in

acetone yielded the highly unusual tetracycle **728** in good yield[179] (Scheme 145).

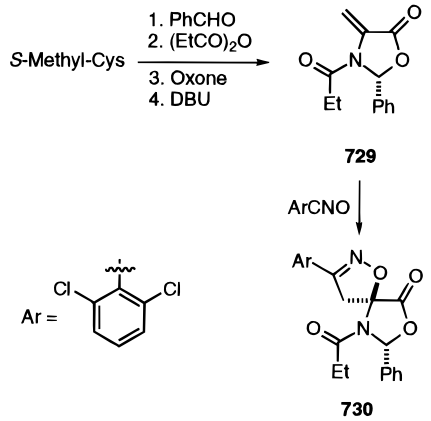
Scheme 145



727 **728**

Another exotic ring system, that of dioxaspiro nonene **730**, was prepared from cysteine. 4-Methyleneoxazolidinone **729**, prepared in four steps from *S*-methylcysteine, underwent a regio- and stereoselective 1,3-dipolar cycloaddition with 2,6-dichlorobenzonitrile oxide to give the bicyclic oxime **730**[180] (Scheme 146).

Scheme 146



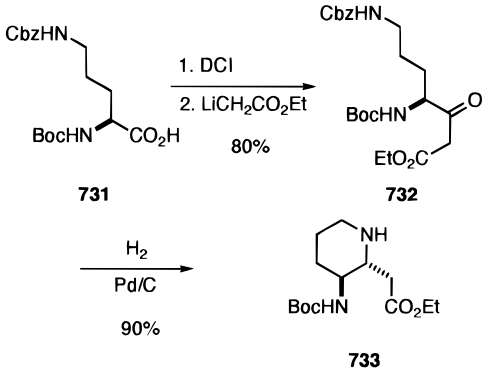
729

730

E. The Basic Amino Acids

Claisen condensation of an activated ornithine derivative with ethyl lithioacetate, followed by catalytic hydrogenation gave a *trans* 3-amino-2-piperidineacetic acid derivative (**733**), used as a peptide conformational constraint[181] (Scheme 147).

Scheme 147



731 **732**

733

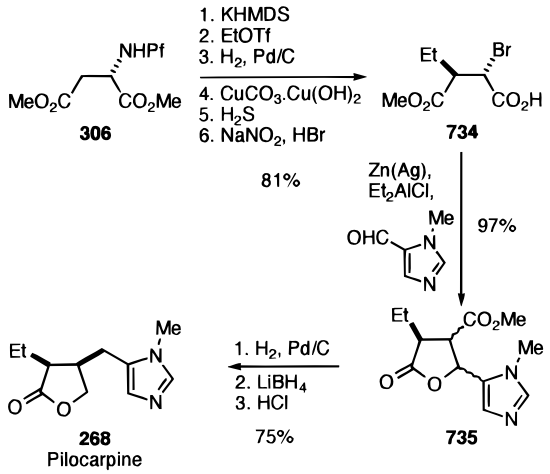
DCI = 1,1-dicarbonyldiimidazole

F. The Acidic Amino Acids

1. Aspartic Acid

An efficient synthesis of (+)-pilocarpine (**268**) from aspartic acid has been reported. This approach featured a highly diastereoselective alkylation of an *N*-phenylfluorenyl aspartate diester (**306**), followed by the replacement of the amino group by a bromine atom and a modified Reformatsky reaction of the resulting α-bromo acid **734** with 1-methylimidazole-5-carboxaldehyde to give lactone **735** (10/1 mixture of epimers at the carboxymethyl-bearing carbon). Hydrogenolysis of lactone **735**, followed by reduction of the carboxymethyl group and treatment with HCl gave (+)-pilocarpine **268**[182] (Scheme 148).

Scheme 148



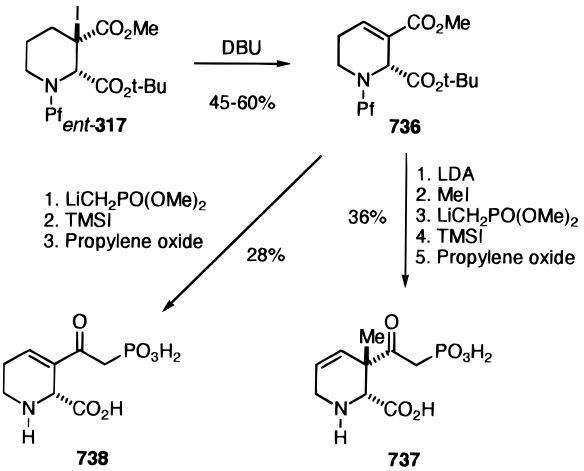
306 **734**

268 Pilocarpine **735**

A synthesis of 4-oxoproline from aspartic acid was achieved by the C-1 carboxy and amino groups protection by oxazolidinone formation with hexafluoroacetone, followed by diazo ketone formation and carbenoid insertion into the N−H bond.[183]

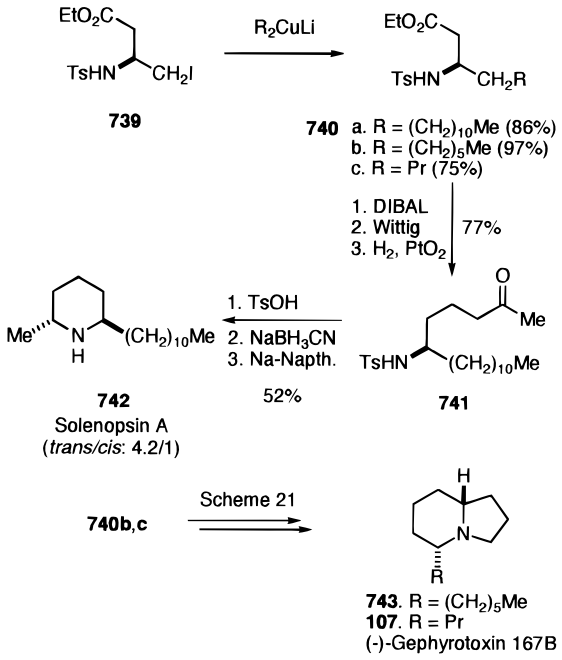
A synthesis of the NMDA receptor antagonist β-ketophosphonate-substituted piperidine carboxylic acids (**737**, **738**, and analogues), based on methodology developed by Rapoport and co-workers (*cf.* Scheme 62),[184] has been reported[185] (Scheme 149).

Scheme 149



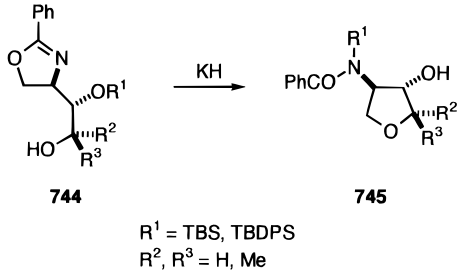
Jefford and co-workers have reported the preparation of solenopsin A via chain extension at C-1 of iodide **739** (prepared from aspartic acid in four steps)-by a cuprate displacement; cyclization of tosylaminododecanone **741**, prepared by chain extension of **740a** (Wittig reaction) at C-4, completed the synthesis of solenopsin A (**742**)[186] (Scheme 150). Indolizidines 167B (**107**) and 209D (**743**) were prepared from iodide **739** by a extension of the procedure described in Scheme 21.[187]

Scheme 150



McGarvey and co-workers have extended the usefulness of the aspartate-derived oxazolines **331** by showing that the alcohols **744** derived from them undergo a base-induced rearrangement to the amido tetrahydrofurans **745** (Scheme 151), which may

Scheme 151



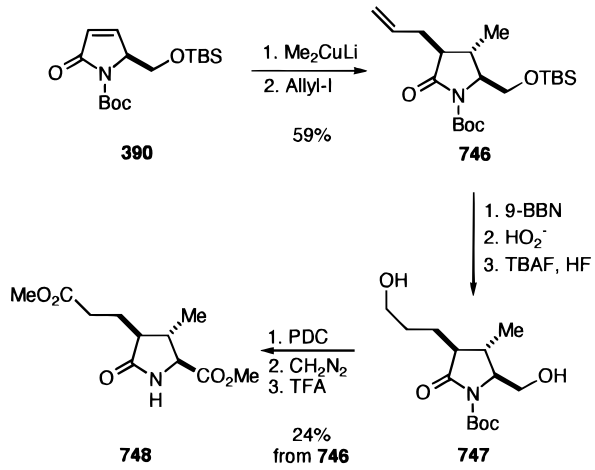
provide some application for the synthesis of hydrolytically stable nucleoside analogues.[188]

2. Glutamic Acid

Dehydropyroglutamate **390** was used as a chiral starting material to establish the absolute configuration of the ozonolysis product of the Krill fluorescent compound F (**748**, a trisubstituted 2-pyrrolidinone).[189] The key step in the synthesis was the one-pot bisalkylation of **390** with Me_2CuLi and allyl iodide (to trap the intermediate enolate), giving lactam **746**. Standard manipulation of **746** led to the desired pyrrolidin-2-one **748** (Scheme 152).

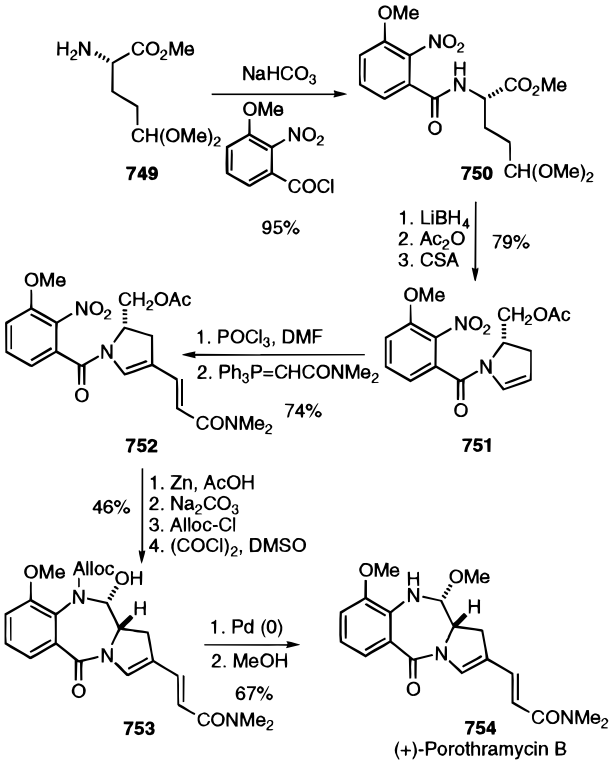
Fukuyama and co-workers have applied the reduction of thioesters to the preparation of dimethyl acetal **749** from glutamic acid; **749** was used as the starting material for the synthesis of the potent antitumor compound (+)-porothramycin B (**754**). Acylation of **749** with the appropriate acid chloride, followed by cyclization of the resulting amide, gave enamide **751**; formylation of **751** followed by Wittig reaction of the resulting aldehyde furnished the unsaturated amide **752**, which cyclized to the desired pyrrolo[1,4]-benzodiazepine **754** upon reduction of the nitro

Scheme 152



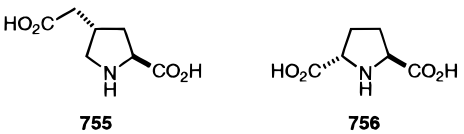
group, Swern oxidation of the hydroxymethyl side chain, and removal of the Alloc group[190] (Scheme 153).

Scheme 153



A straightforward synthesis of (2*S*,4*S*)-2-carboxy-4-pyrrolidineacetic acid (**755**, a conformationally constrained 2-aminoadipic acid analogue) by alkylation of a pyroglutamate has been reported[191] (Scheme 154). In a related work an *N*-carboxymethyl pyro-

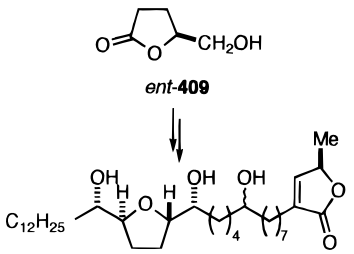
Scheme 154



glutamate has been reduced with DIBAL to the corresponding hydroxyaminal, which after trapping with cyanide and hydrolysis afforded diacid **756**.[192]

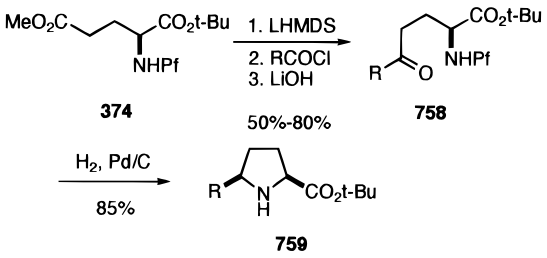
A synthesis of a structural representative of the cytotoxic monotetrahydrofuranyl annonaceous acetogenins (**757**) that uses glutamic acid as starting material has been reported.[193] The core tetrahydrofuran moiety of **757** was prepared from alcohol *ent*-**409**, readily available from glutamic acid by nitrosation and lactonization (Scheme 155).

Scheme 155



Acylation of enolates of *N*-Pf-glutamate esters followed by decarboxylation of the resulting keto esters affords enantiomerically pure δ-oxo α-amino esters possesing a variety of substituents at the δ-position (**758** R = primary, secondary, or tertiary alkyl, Ph). The resulting amino ketones are readily transformed into *cis*-2,5-disubstituted pyrrolidines, which are useful intermediates for the synthesis of certain ant venoms[194] (Scheme 156).

Scheme 156



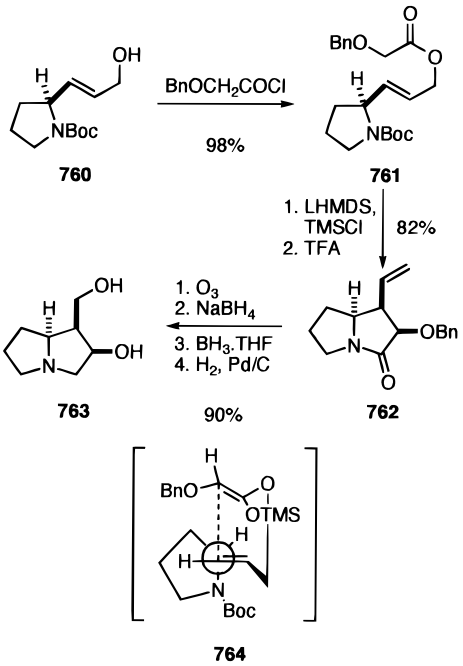
G. Proline

Proline continues to be a favorite starting material for the construction of the pyrrolizidine alkaloids. Thus, a synthesis of the necine base (−)-petasinecine (**763**) which makes use of a highly stereoselective Ireland−Claisen rearrangement to set the configuration of two of the three chiral centers of the molecule has been reported. The required allyl ester **761** was straightforwardly prepared from allyl alcohol **760**, in turn obtained via Horner−Emmons homologation of Boc-prolinal. The diastereoselection observed in the rearrangement of **761** can be explained by the intermediacy of transition state **764**[195] (Scheme 157).

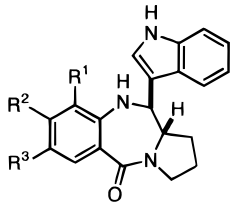
Shioiri and co-workers have extended their synthesis of tilivalline (**557**, Scheme 108) to the preparation of hibrid tilivalline analogues that present the substitution patterns of the powerful antitumor compounds antramycin and tomaymycin (**765**)[196] (Scheme 158).

In a further example that extends the usefulness of the anodic methoxylation of prolines, alkynyl-substituted proline ester **768** (prepared by acylation of prolinol **766**, followed by oxidation and esterification) was submitted to an anodic oxidation−iminium

Scheme 157

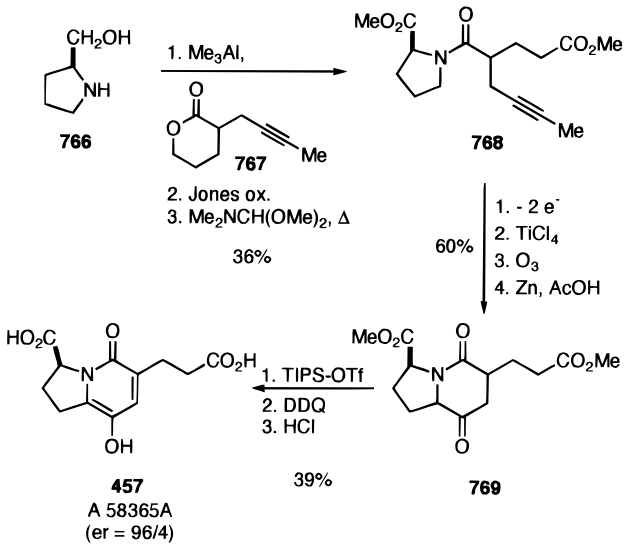


Scheme 158



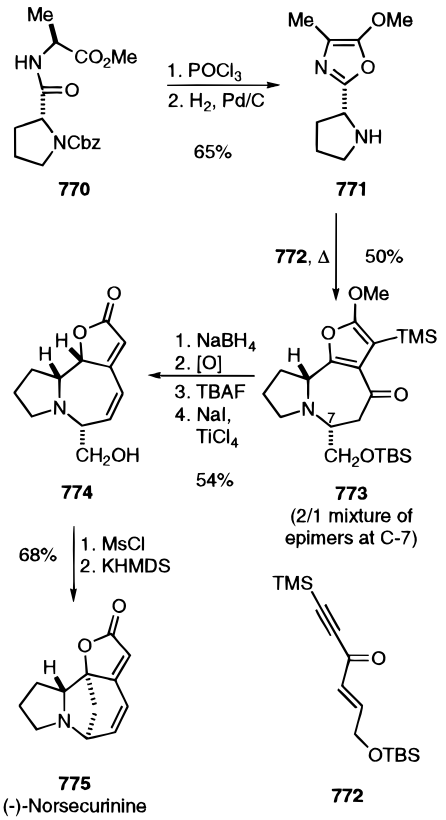
ion cyclization sequence to afford indolizinedione **769**, which was ultimately transformed into the angiotensin-converting enzyme inhibitor A58365A (**457**)[197] (Scheme 159).

Scheme 159



An intramolecular Diels−Alder cycloaddition of an acetylenic oxazole derived from proline dipeptide **770** has been used as the key step in a synthesis of the complex tetracyclic alkaloid (−)-norsecurinine **775**

Scheme 160



(Scheme 160). The cycloaddition afforded a mixture of tricyclic oxazoles **773**. Ketone reduction and elimination of the resulting alcohol with Martin's reagent ($[PhC(CF_3)_2O]_2SPh_2$) led to the introduction of the double bond in the seven-membered ring. Unraveling of the unsaturated γ-butyrolactone, mesylation of the primary hydroxyl group, and transannular alkylation completed the synthesis of **775**.[198]

XI. Conclusion

The exponential growth in the past 10 years of enantiospecific syntheses has been fueled by the biological imperative of single compound active factors and has been strongly influenced by regulatory support. It will continue to grow at an explosive rate.

A contributing factor has been, and continues to be, the development of effective methods for securing such syntheses. While more activity has concentrated on chiral auxiliaries, the use of readily available, enantiomerically pure starting materials has demonstrated its utility as a basis for enantioespecific synthesis.

In particular, as we have attempted to demonstrate in this review, specific enantiomers of α-amino acids are excellent versatile starting materials for many heterocycles. This application can only be expected to accelerate as increasingly effective methods are developed for retaining α-center configuration intact as another stereogenic center is generated.

This emphasis on configurational purity carries the corollary of more quantitative data for its determination. The classical specific rotation and the various NMR methods, although convenient, will no longer suffice. Chromatographic methods are being used more and more and may become a requirement for any claim of the extent of enantiomeric purity.

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