Synthetic Approaches to Enantiomerically Pure 8-Azabicyclo[3.2.1]octane Derivatives

Gian P. Pollini,*,† Simonetta Benetti,‡ Carmela De Risi,† and Vinicio Zanirato*,†

Dipartimento di Scienze Farmaceutiche, Università di Ferrara, Via Fossato di Mortara 17-19, I-44100 Ferrara, Italy, and Dipartimento di Chimica, Università di Ferrara, Via Luigi Borsari 46, I-44100 Ferrara, Italy

Received November 18, 2005 (Revised Manuscript Received March 13, 2006)

Contents

1. Introduction

The 8-azabicyclo[3.2.1]octane framework (tropane), occurring both in natural and in synthetic compounds, is of considerable interest because of the wide range of biological activities that these substances display. Many tropane derivatives play a key role in a myriad of neurological and psychiatric diseases such as Parkinson, depression, schizophrenia, and panic disorder. Cocaine antagonists, which are employed in the treatment of cocaine addiction, and tropane-related compounds recently used as radiopharmaceuticals also deserve considerable attention.[1]

Over 200 tropane alkaloids are known to occur in natural sources, and they have been isolated from many different plant families including *Solanaceae*, *Erythroxylaceae*, *Convolvulaceae*, *Proteaceae*, *Rhizophoraceae*, *Brassicaceae*, and *Euphorbiaceae*.

* To whom correspondence should be addressed. Telephone: +39-0532-291286. Fax: +39-0532-291296. E-mail: pol@unife.it.
† Dipartimento di Scienze Farmaceutiche, Università di Ferrara.
‡ Dipartimento di Chimica, Università di Ferrara.

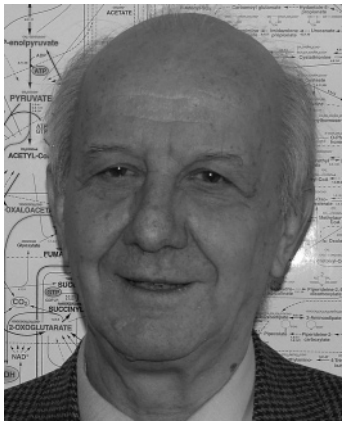
While (−)-cocaine is the flagship compound, the tropane alkaloid pathway is known to produce many medicinally important natural substances, with all of them featuring the aza-bridged bicyclic framework as the key structural element. Representative examples include hyoscyamine (racemic mixture: atropine) and hyoscine (also known as scopolamine). Moreover, special attention has been given to the interesting tropane-type alkaloid (+)-ferruginine, isolated from the arboreal species *Darlingia ferruginea* and *Darlingia darlingiana*, as well as calystegines, a family of polyhydroxylated nortropane alkaloids, derived from the tropane alkaloid pathway. Their name comes from *Calystegia sepium*, where they were first identified in 1988 and since then found in a variety of fruits and vegetables. Calystegines are subdivided in three groups (A, B, and C) on the basis of the number of hydroxy groups present (three, four, or five, respectively). In all cases, a tertiary hydroxy group is part of an original aminoketal moiety at the bridgehead position (Figure 1). Calystegines show a striking resemblance to monosaccharides and have a high therapeutic potential as specific glycosidase inhibitors.[2]

The broad range of neurochemical activity associated to bridged azabicycles coupled with their unusual architecture makes short, versatile, stereocontrolled synthetic routes to these compounds of tremendous potential value.

1.1. Tropane Derivatives: Graphic Representation and Configurational Analysis

Embarking on the present review, our main concern was to draw synthetic schemes that were readily understandable and comparable with each other. To this end, the structural diagrams depicting stereochemistry needed a uniformity of style. Concerning the tropane derivatives, throughout the paper, we depicted a cycloheptane ring with C3 as the apex carbon and with the 1,5-nitrogen bridge above it as the basic structure. With this assumption, we used bold wedges to show the stereo-orientation of hydrogens and/or substituents at the bridgehead carbons. In the corresponding three-dimensional molecular model, such valence bonds are cis diequatorial and β-oriented. Because of the presence of a symmetry plane, the unsubstituted 8-azabicyclo[3.2.1]octane nucleus as well as 3-tropinone are *meso* compounds. The same symmetry element is also present in tropine and pseudotropine or in nuclei in which a symmetric pattern of substituents, α or β oriented, are located on the carbon framework: an example is teloidine (Figure 2). In these achiral nuclei, the tetrahedrally coordinated C3 is a pseudoasymmetric carbon atom, and according to Cahn−Ingold−Prelog (CIP) rules,[3] the reflection-invariant (*R*/*S*)

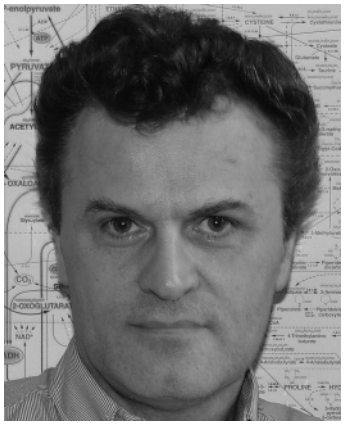
10.1021/cr050995+ CCC: $59.00
Published on Web 04/08/2006



Gian Piero Pollini was born in Genoa, Italy, in 1938. He graduated in chemistry from Pavia University in 1962 under the guidance of Prof. Giorgio Traverso. He began his research and teaching careeer at the University of Perugia as Assistant Professor (1964–1967), and then (in 1968), he moved to the University of Ferrara, where he has been Full Professor of Organic Chemistry in the Faculty of Pharmacy since 1981. He was Chairman of the "Dipartimento di Scienze Farmaceutiche" (1983–1990) and Dean of the Faculty of Pharmacy (1994–2000). His research interests include the design and development of new methods and reagents and their application to the synthesis of natural and non-natural targets with interesting biological and chemical properties.

Born in1947 in Ferrara, Italy, Simonetta Benetti received her degree in chemistry in 1971 from the University of Ferrara. Since 1982, she has occupied the position of Associated Professor of Organic Chemistry at the "Dipartimento di Chimica" of the same university. Since 1971, she has carried out research on the synthesis of natural organic substances and their structural analogues of particular pharmaceutical interest and had studied new synthetic methods of general applicability.

Born in Ferrara, Italy, in 1967, Carmela De Risi received her degree in chemistry from the University of Ferrara in 1992 and her Ph.D. in organic chemistry in 1996. In 1999, she was appointed as Researcher at the "Dipartimento di Scienze Farmaceutiche", University of Ferrara. Her main research interests include synthesis of biologically active natural compounds, general synthetic methodologies, amino acids, and heterocycles.



Vinicio Zanirato was born in Fenil del Turco (RO), Italy, in 1957. He graduated in Chimica e Tecnologie Farmaceutiche from the University of Ferrara in 1982. He received his Ph.D. in pharmaceutical sciences in 1987, working in the field of prostaglandin synthesis under the supervision of Professor M. Guarneri. After a further 3 years as a postdoctoral researcher at the "Dipartimento di Scienze Farmaceutiche" of the University of Ferrara, he became Researcher. In 1998, he was promoted to the position of Associate Professor at the University of Siena, and in January 2003, he came back to the University of Ferrara, where he was appointed as an Associate Professor of Organic Chemistry of the Faculty of Pharmacy. His research interests include natural product synthesis and new reaction methodologies.

descriptors must be used. Any different C substitution makes the nuclei chirals: this is actually the common case in naturally occurring tropane derivatives.

Most of the nonracemic tropane derivatives has been obtained by derivatization of natural cocaine or by resolution of the corresponding racemic compounds, in turn easily assembled through the original and still widely used biomimetic Mannich-type construct for the tropane skeleton, developed over a half a century ago by Willstätter, Robinson, and Schöpf.[4]

This review concentrates on methodologies that provide enantioselective routes to chiral substituted 8-azabicyclo-[3.2.1]octane nuclei considering that chiral structures belonging to this family have often acted as vehicles for the invention of new strategies for their construction. Moreover, synthetic approaches to several specific targets, which serve to illustrate the value of a new developed strategy, have also been included.

The asymmetric routes to substituted tropane derivatives have been classified in subsections (2−4) according to the way the asymmetry has been introduced.

Thus, papers dealing with syntheses of the target molecules involving starting materials belonging to the "chiral pool" are discussed in section 2, papers describing examples of prochiral substrates successfully used as starting building blocks are covered in section 3, while papers concerning synthetic routes to enantiopure tropanes starting from a racemic mixture are collected in section 4. In the last section, only papers dealing with enzymatic kinetic resolution have been considered. Although still very important, we have not included any other classical resolution method.

2. Starting from the Chiral Pool

Naturally occurring enantiopure compounds have been used to import stereogenic centers and functionalities suitable

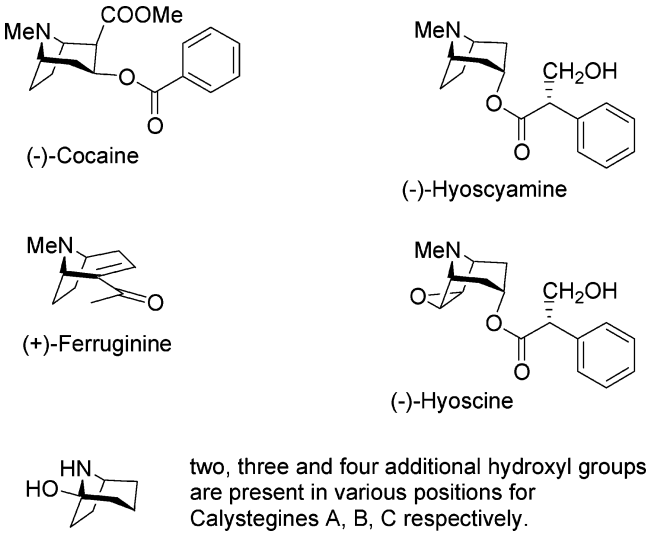


Figure 1.

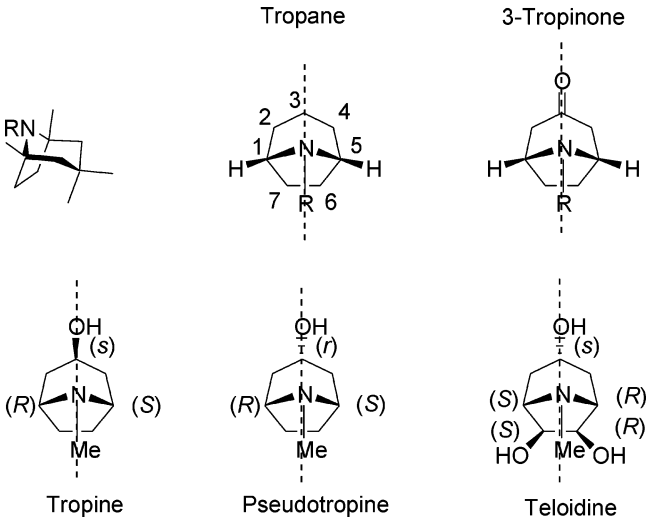


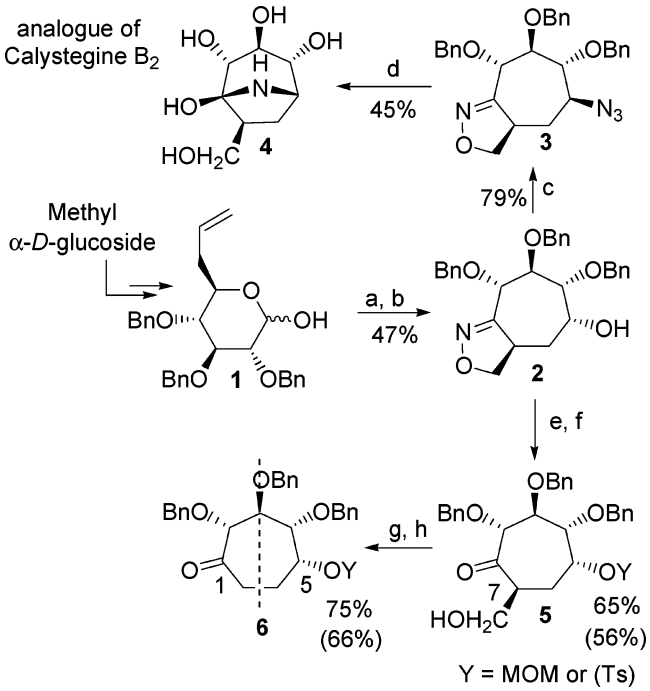
Figure 2.

for the construction of selected alkaloids. Usually, the major limitation of these approaches is the fact that only one of the enantiomers of the target compounds can be prepared. Therefore, strategies that allow for the preparation of both enantiomers of the alkaloids from a common intermediate are particularly attractive. Because we focused our attention on methods for the de novo synthesis of chiral tropane nuclei, synthetic approaches starting from the natural cocaine are not included in this review. It is not surprising that synthetic chemists selected carbohydrate synthons to prepare highly functionalized tropanes such as calystegines, while, on the other hand, natural glutamic acid is well-suited to obtain ferruginine, with its azabicyclic core being functionalized to a lesser extent.

2.1. Sugars

Because of the structural resemblance of calystegines to monosaccharides and the availability of a wide range of carbohydrates as sources of enantiopure building blocks that might provide much of the required functionalization and stereochemistry, a number of elegant approaches to the synthesis of different calystegines have been developed. The sugar selected depends upon the specific target; D-glucose, D-galactose, and D-mannose have been commonly used.

Scheme 1[a]



[a] Reagents: (a) $NH_2OH{\cdot}HCl$, CH_3ONa, CH_3OH reflux; (b) NaOCl, CH_2Cl_2; (c) $ZnN_6{\cdot}2py$, PPh_3, DIAD; (d) H_2-Pd, $AcOH/H_2O$; (e) CH_3OCH_2Cl, iPr_2NEt, CH_2Cl_2 or TsCl, pyridine; (f) H_2, Ra/Ni, CH_3OH/H_2O, $B(OH)_3$; (g) $DMSO/(COCl)_2$, Et_3N, −60 °C; and (h) Zn, TMEDA, AcOH/EtOH.

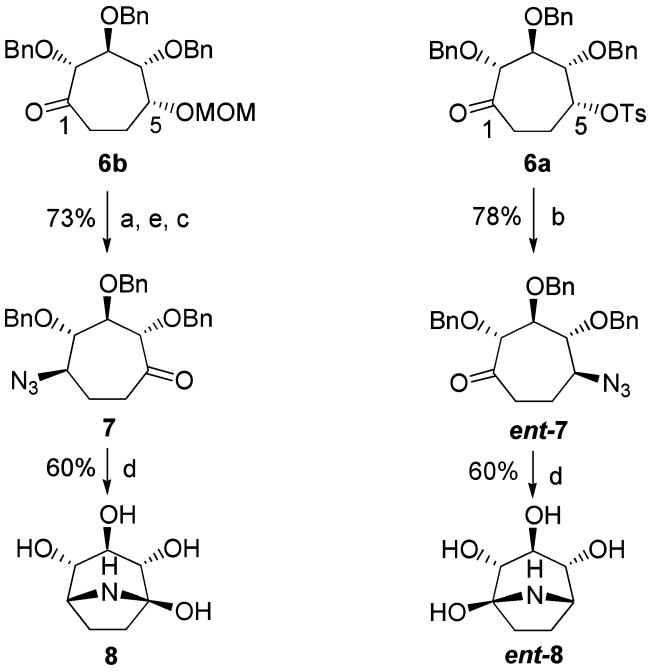
The intramolecular cycloaddition of an olefinic nitrile oxide (INOC) derived from D-glucose was the key step of a new access to polyhydroxylated cycloheptane derivatives, suitable intermediates for further elaboration to a C7-substituted calystegine B_2 analogue (Scheme 1).[5]

Thus, the D-glucose derivative **1** was converted to the cycloheptane−isoxazoline intermediate **3**. Its reductive opening released the masked carbonyl group leading to a highly functionalized seven-membered carbocycle, which served to prepare the C7 hydroxymethyl-substituted calystegine B_2 analogue **4**. Extension of this scheme to the synthesis of the natural alkaloid[6] required the removal of the hydroxymethyl group at C7 of compound **5**. This operation has been effected in 65−70% yield via oxidation to the corresponding formyl group followed by the retro-Claisen reaction. The pattern of substituents on the formed carbocycle allowed for the synthesis of both calystegine B_2 enantiomers (Scheme 2). In particular, nitrogen introduction at C5 led to the protected azidocycloheptanone ***ent*-7**, whereas nitrogen introduction at C1, followed by oxidation at C5, yielded the corresponding enantiomer. Total catalytic hydrogenolysis on Pd black in aqueous acetic acid gave the two calystegine B_2 enantiomers.

A different approach to these polyhydroxylated nortropanes is based on a regiospecific ring enlargement of the polysubstituted cyclohexanone **9**, in turn prepared from D-glucose by standard carbohydrate chemistry. The pivotal ring expansion demanded the kinetically controlled silylenol-etherification of compound **9** (Scheme 3).[7] After that, the methylene ring insertion reaction was readily achieved in a two-step sequence involving cyclopropanation with diethylzinc−methylene iodide reagent followed by the opening of the resulting cyclopropane derivative **10** by the treatment with $FeCl_3$.

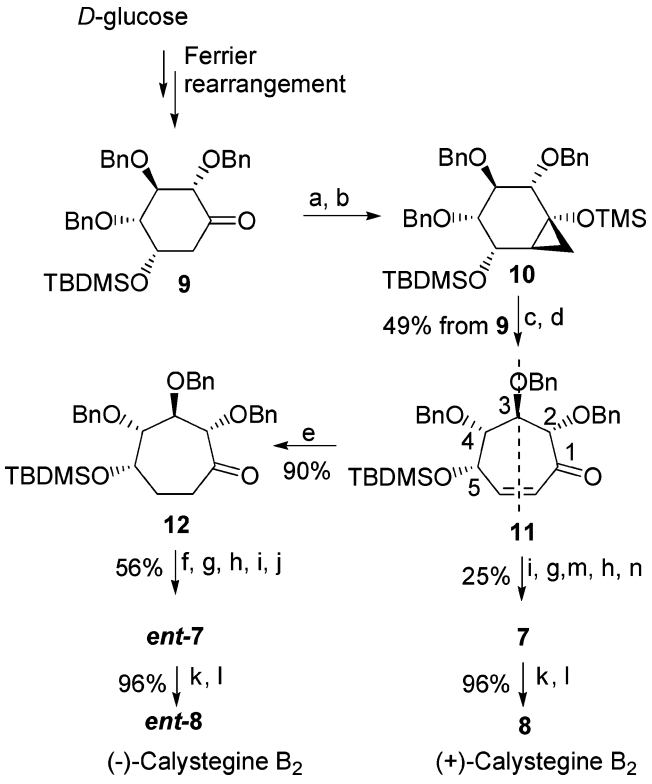
It is noteworthy that, taking advantage of the pseudosymmetry of the intermediate cycloheptenone derivative **11**, the

Scheme 2[a]



[a] Reagents: (a) DIBAH, Et_2O, −50 °C; (b) NaN_3, DMF, 80 °C; (c) DMSO/$(COCl)_2$, Et_3N; (d) H_2-Pd, AcOH/H_2O; and (e) ZnN_6·2py, PPh_3, DIAD and then CH_3OH, H^+.

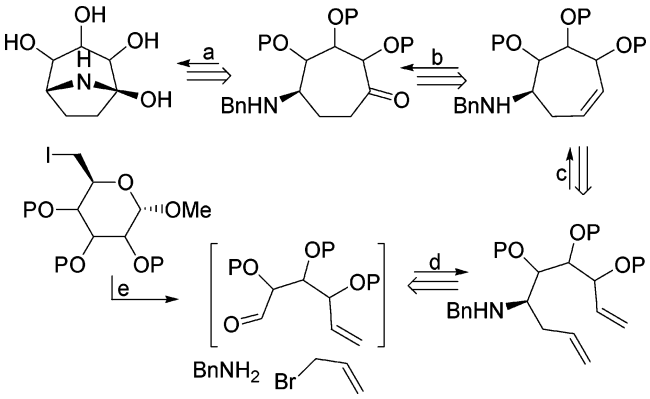
Scheme 3[a]



[a] Reagents: (a) LDA, TMSCl, THF, −70 °C; (b) Et_2Zn, CH_2I_2, toluene, 0 °C; (c) $FeCl_3$, DMF, 70 °C; (d) AcONa, CH_3OH, reflux; (e) H_2, Pd/C, EtOH; (f) $NaBH_4$; (g) MsCl, DMAP; (h) NaN_3, DMF; (i) *n*-Bu_4NF, THF; (j) PCC, CH_2Cl_2; (k) H_2, Pd/C, AcOH/H_2O; (l) NaOH, pH 11; (m) DIBAH, Et_2O, −60 °C; and (n) Dess−Martin, CH_2Cl_2.

methodology allowed for the preparation of both enantiomers of calystegine B_2. In fact, thanks to a judicious manipulation of functional groups, the nitrogen atom could be introduced as an azide either at position C5 or at C1, thus obtaining the natural stereoisomer or its enantiomer, respectively.

Scheme 4[a]



[a] Synthetic steps: (a) catalytic hydrogenation; (b) hydroboration−oxidation; (c) ring-closing olefin metathesis; (d) Barbier-type allylation; and (e) zinc-mediated domino reaction.

Ring-closing metathesis (RCM) has become one of the most useful reactions in organic chemistry for its efficiency and selectivity and has been widely applied for the preparation of highly functionalized medium-sized carbocycles. The high potential of this methodology did not escape to research groups involved in this area as demonstrated by the publication, during a 1 year period, of three approaches to calystegine alkaloids making use of this straightforward synthetic strategy.

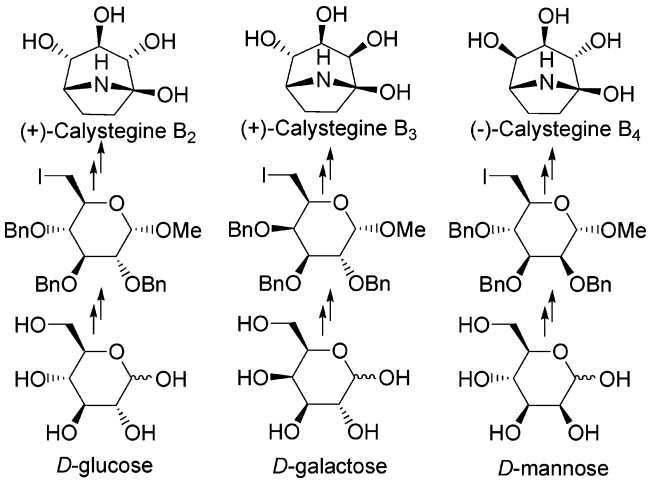
Skaanderup and Madsen[8] envisioned the preparation of the nortropane skeleton of different calystegines B by hydroboration−oxidation of cycloheptene derivatives possessing the correct absolute configuration at the different stereocenters (Scheme 4). These intermediates could in turn be obtained from a metathesis reaction of appropriately functionalyzed 1,8-nonadienes. The next logical disconnection led to allyl bromide, benzylamine, and enal derivatives, with the latter being derived from the fragmentation of known methyl 6-iodo-glycosides.

This strategy employs as the starting move a zinc-mediated tandem reaction, where zinc serves a dual purpose by mediating both the fragmentation of the iodoglycosides and the three carbon-chain elongation at C1 of the imine intermediates. A common key point was the control of the configuration at the carbon incorporating the nitrogen substituent.

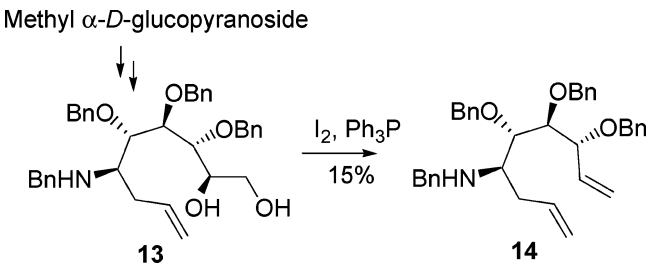
Fortunately, the Barbier-type allylation led predominantly to benzylamine derivatives having *R* configuration at the new stereocenter as it is in natural calystegines. The functionalized 1,8-nonadienes are converted into cycloheptene derivatives by RCM. Regioselective hydroboration and oxidation gave the corresponding cycloheptanones, which have eventually been fully deprotected to produce (+)-calystegine B_2 and, for the first time, (+)-calystegine B_3 and (−)-calystegine B_4, starting from D-glucose, D-galactose, and D-mannose, respectively (Scheme 5). Shortly before, a similar strategy had been successfully applied by Hanna et al.[9] to prepare (+)-calystegine B_2.

Almost contemporaneously, Marco-Contelles and de Opazo[10] described a quite similar approach to calystegine B_2 (Scheme 6). The formal synthesis of the natural target was achieved starting from methyl α-D-glucopyranoside, with the main drawback being the very low yield (15%) in the transformation of the 1,2-diol derivative **13** into the desired

Scheme 5



Scheme 6



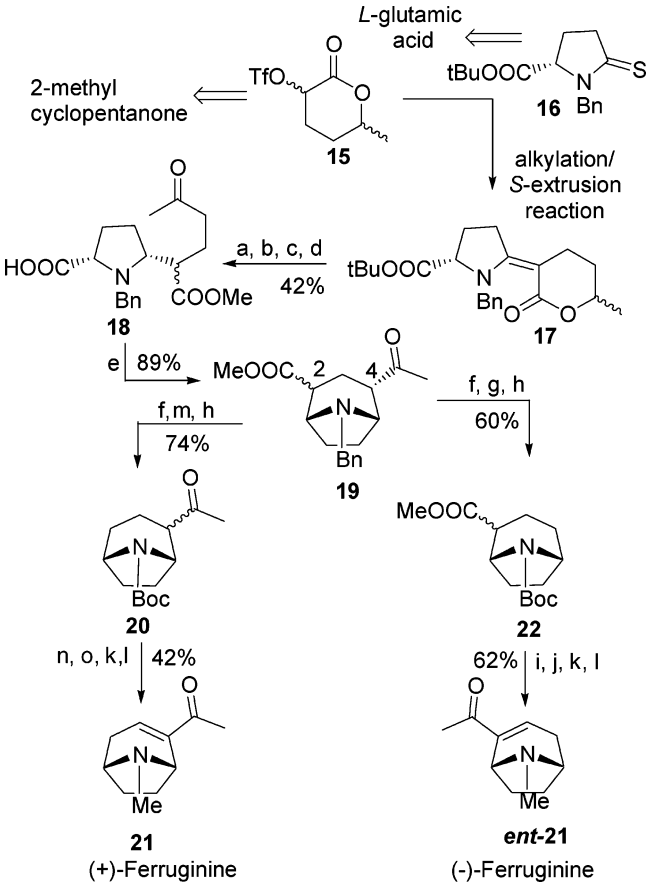
olefin **14**. This finding highlights the usefulness of the zinc-mediated tandem reaction combined with RCM in the conversion of iodo sugars into carbocycles.

2.2. Amino Acids

Amino acids are particularly useful precursors for the asymmetric synthesis of alkaloids and have been widely employed to this end. Most of them are cheap, and all of them contain the nitrogen of the target alkaloid. In particular, L-pyroglutamic acid and D- and L-glutamic acid have been successfully utilized as chiral building blocks for the construction of tropane ring systems.

Rapoport et al.[11] described the syntheses of (+)- and (−)-ferruginine alkaloids by selective manipulation of the C2 and C4 side chains of a versatile chiro 2,4-disubstituted tropane derivative **19** (Scheme 7), with the asymmetry being introduced using L-glutamic acid for the preparation of the starting thiolactam **16**. Its alkylation with the 2-triflate δ-lactone **15**, in turn derived from 2-methylcyclopentanone, generated an α-thioiminium ion, which underwent the *S*-extrusion reaction producing the vinylogous carbamate **17**, further transformed to the *cis*-pyrrolidine keto acid **18** through a sequence of steps including hydrogenation, N-rebenzylation, basic methanolysis, and final acid hydrolysis. The key 6-*endo*-*trig* iminium ion cyclization occurred with high stereoselectivity, with the acetyl group occupying an equatorial position on the six-membered ring. The divergent synthesis exploited the selective removal of the side chains at C2 or C4 through their transformation to carboxyl groups and subsequent reductive decarboxylation by photolysis of the corresponding thioxamate esters. In both cases, the introduction of the double bond was effected by α-selenation of the carbonyl function followed by oxidative elimination. Nitrogen-atom deprotection and subsequent methylation completed the syntheses.

Scheme 7[a]

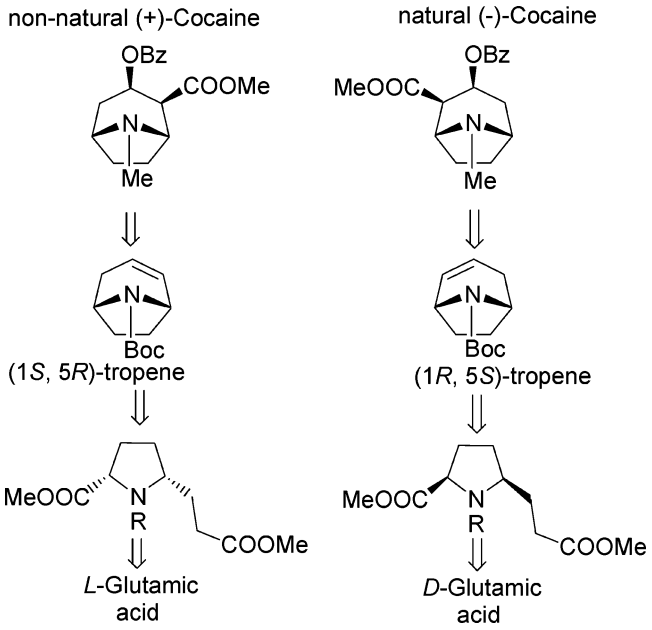


[a] Reagents: (a) H_2, Pt/C; (b) $NaHCO_3$, CH_3OH; (c) $(COCl)_2$, DMSO; (d) H^+, H_2O; (e) i, $(COCl)_2$; ii, 60 °C; (f) H_2, Pd/C, $(Boc)_2O$; (g) i, KHMDS; ii, TMSCl; iii, O_3, $(CH_3)_2S$; (h) i, *i*BuO_2CCl; ii, 2-mercaptopyridine *N*-oxide; iii, h*ν*, *ter*BuSH; (i) i, LDA; ii, PhSeCl; iii, $NaIO_4$; (j) i, KOH; ii, *i*BuO_2CCl, isoxazolidine; iii, CH_3Li; (k) TFA; (l) CH_2O, $NaBH_3CN$; (m) KOH; (n) i, NaH; ii, TBSCl; and (o) i, PhSeCl; ii, *m*-CPBA; iii, Na_2CO_3.

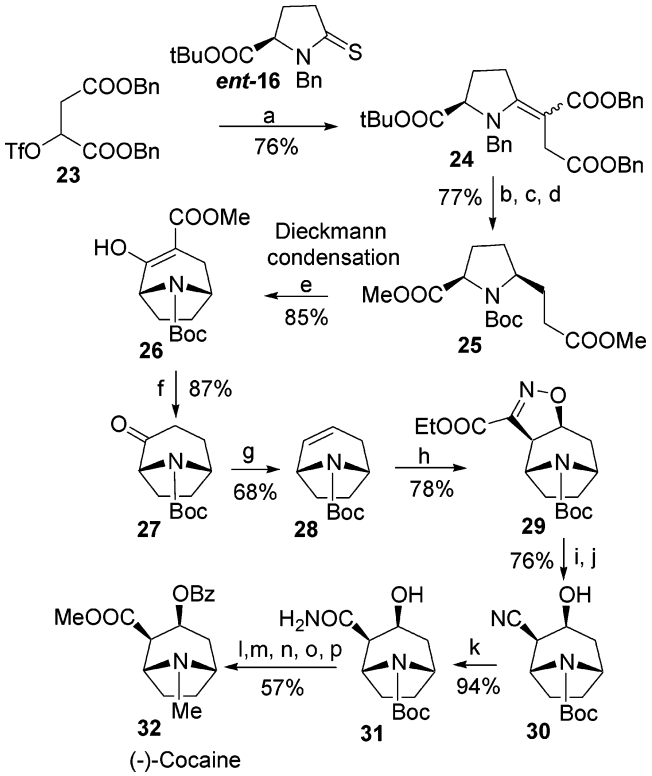
The same research group[12] utilized D- and L-glutamic acid as chiral building blocks for the enantiospecific synthesis of natural (−)-cocaine and its enantiomer, respectively (Scheme 8). Because cocaine is a *cis*-2,3-disubstituted tropane, they planned to introduce its axial−equatorial substituents by regio- and stereospecific functionalization of the carbon−carbon double bond of chiral 2-tropenes, in turn derived by a transannular cyclization (Dieckmann condensation) of appropriately *cis*-5-substituted D- or L-proline ester.

Thus, (−)-cocaine was prepared from the pyrrolidine derivative **25** (Scheme 9). This compound has been obtained from thiolactam (*R*)-1-benzyl-5-thionoproline *tert*-butyl ester ***ent*-16**, in turn prepared from D-glutamic acid, by sulfide contraction and subsequent catalytic hydrogenation to secure totally stereoselectively the stereochemistry at C5. In details, alkylation of the triflate **23** of dibenzyl D,L-malate with the (*R*)-thiolactam ***ent*-16**, followed by sulfur extrusion, gave the vinylogous carbamate **24** as a mixture of isomers, which was directly reduced. A sequence of high yielding steps led to the N-protected diester **25**, which underwent Dieckmann cyclization in 85% yield producing the bicyclic derivative **26**, which was demethoxycarbonylated to the ketone **27** and converted to (1*R*,5*S*)-tropene **28** by the base-induced reaction of the corresponding tosylhydrazone derivative. The 1,3-dipolar cycloaddition between the *N*-Boc-nortropene **28** and ethoxycarbonylformonitrile *N*-oxide proceeded with complete regioselectivity and *exo*-stereoselectivity to afford the ex-

Scheme 8



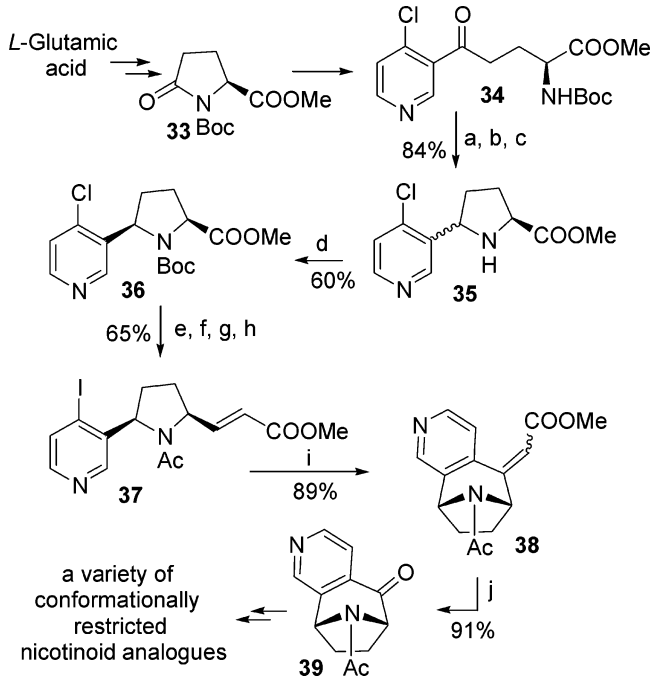
Scheme 9[a]



[a] Reagents: (a) i, Ph_3P, CH_2Cl_2; ii, *N*-methylpiperidine; (b) NH_4HCO_2, Pd/C, CH_3OH; (c) CH_3OH, HCl; (d) $(Boc)_2O$; (e) KHMDS, THF, −78 °C; (f) NaI, pyridine, reflux; (g) i, *p*-$TsNHNH_2$; ii, NaH; (h) $Cl(C{=}NOH)CO_2Et$, Et_3N; (i) i, NaOH; ii, H_3O^+; (j) heating at 110 °C; (k) Na_2CO_3, H_2O_2; (l) $(PhCO)_2O$, DMAP; (m) TFA; (n) CH_2O, $NaBH_3CN$; (o) $NaNO_2$, AcOH/Ac_2O; and (p) CH_2N_2.

pected cycloadduct **29** in good yield. Mild hydrolysis gave the corresponding carboxylic acid, which underwent thermal decarboxylation and fragmentation of the isoxazoline ring to give the β-hydroxy nitrile **30**. At this stage, the conversion of the nitrile to the corresponding acid without affecting the C2 stereocenter was accomplished by a two-step sequence involving hydrolysis with aqueous H_2O_2 in the presence of Na_2CO_3, followed by nitrosation of the generated primary

Scheme 10[a]



[a] Reagents: (a) HCl, EtOAc; (b) $NaHCO_3$; (c) $NaBH_4$, AcOH; (d) $(Boc)_2O$, Et_3N; (e) $CaCl_2$, $NaBH_4$; (f) NaI, AcCl; (g) K_2CO_3, CH_3OH; (h) i, $(COCl)_2$, DMSO, Et_3N; ii, trimethyl phosphonoacetate, KHMDS; (i) $Pd(OAc)_2$, PPh_3, Et_3N; and (j) O_3, AcOH, $(CH_3)_2S$.

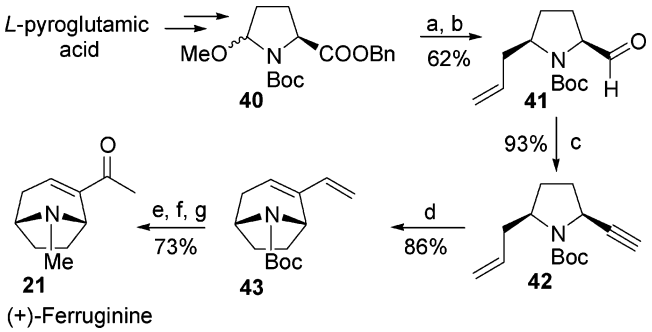
amide **31**. Eventually, the esterification with diazomethane gave enantiopure (−)-cocaine **32** in 8.5% yield over 16 steps.

Following the same protocols, non-natural (+)-cocaine was synthesized from (1*S*,5*R*)-*N*-Boc-nortropene, in turn prepared from L-glutamic acid.

Conformationally restricted annulated nicotine analogues have also been prepared enantioselectively starting from both D- and L-glutamic acid (Scheme 10).[13] The rather unstable 4-chloropyridinyl ketone **34** was easily prepared by regioselective addition of *ortho*-lithiated 4-chloropyridine to the pyroglutamate derivative **33** and used with minimal delay in the next acidic N-deprotective step. Subsequent treatment with aqueous $NaHCO_3$ caused intramolecular cyclization to an imine intermediate, which was reductively converted to a cis/trans mixture of 2,5-disubstituted pyrrolidines **35**, with the major cis diastereomer being easily separated by a fortuitous exclusive N-protection occurring by treatment with $(Boc)_2O$ and Et_3N. Subsequent chloro−iodo exchange and side-chain extension gave the intermediate **37**, an immediate precursor for the [3.2.1] bicyclic skeleton. The construction of the pyrido[3,4-*b*]tropane framework was achieved by an intramolecular Heck cyclization giving **38** in 89% yield, and the corresponding ketone **39**, derived by ozonolysis, could be tranformed into a wide variety of nicotine analogues.

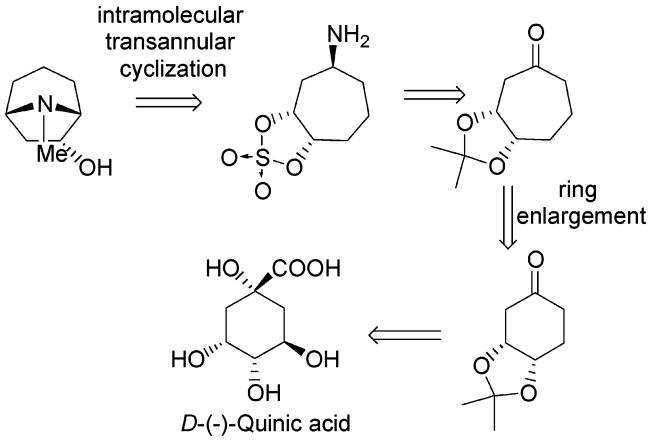
The salient feature of an interesting approach to (+)-ferruginine was an enyne metathesis reaction furnishing the enantiomerically pure tropane nucleus (Scheme 11).[14] The inexpensive L-pyroglutamic acid has been used as the starting chiral material to obtain the key pyrrolidine derivative **42** bearing at C2 and C5 the required unsaturated arms in a cis relationship. The known[15] aminal **40** was treated with BF_3 and allyltrimethylsilane to give the cis product as the major diastereomer (cis/trans = 4:1). The aldehyde **41** obtained by reduction of the benzyl ester was homologated using a modified version of the Gilbert reagent, allowing us to obtain the required enyne moiety successfully.

Scheme 11[a]



[a] Reagents: (a) $BF_3{\cdot}Et_2O$, allyltrimethylsilane; (b) i, $LiAlH_4$, THF; ii, Dess−Martin periodinane, CH_2Cl_2; (c) $CH_3COCN_2PO(OEt)_2$, K_2CO_3, CH_3OH; (d) Grubbs catalyst, CH_2Cl_2, reflux; (e) $PdCl_2$, $CuCl_2$, H_2O/DMF; (f) TFA, CH_2Cl_2 and then K_2CO_3; and (g) CH_2O, $NaCNBH_3$, CH_3CN.

Scheme 12



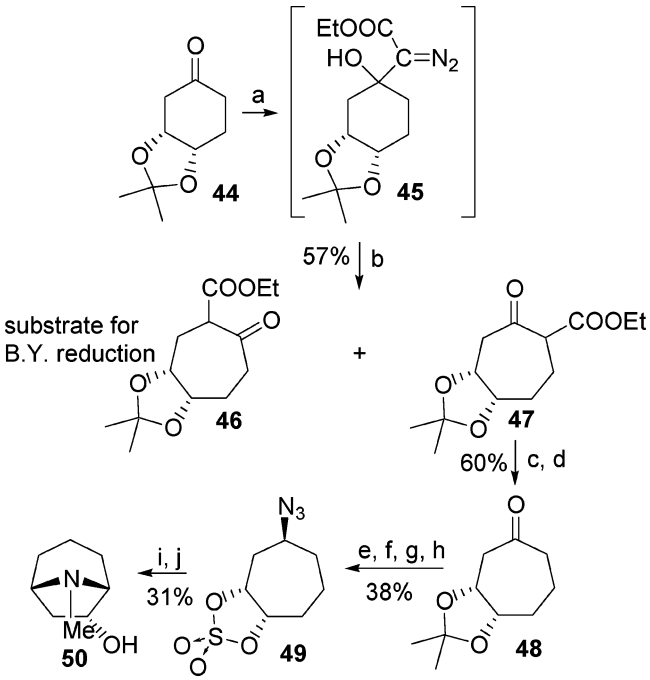
Interestingly, a first generation Grubbs catalyst proved to be superior to the second generation ones in the enyne metathesis reaction, which resulted in a clean construction of the tropane skeleton in high isolated yield (86%). Wacker oxidation of the exocyclic double bond of **43** produced the required methyl ketone moiety, with the remaining steps to complete the synthesis of the alkaloid (+)-ferruginine **21** being N-Boc-deprotection and N-methylation.

2.3. Other Chiral Building Blocks

Besides carbohydrates and amino acids, α-hydroxy acids represent another widely used class of chiral starting materials. Thus, hydroxy acids such as malic and tartaric acid and, to a lesser extent, quinic acid, have been often used as chiral sources. Our own interest in the field goes back several years ago when we developed a synthetic strategy for the construction of the 8-azabicyclo[3.2.1]octane framework using (−)-quinic acid as the chiral educt and featuring a transannular nucleophilic substitution on a chiral cyclic sulfate as the key step (Scheme 12).[16]

A major challenge appeared to be the ring enlargement step, because a good level of regioselectivity was required to complete successfully the enantioselective approach to the chiral 8-azabicyclo[3.2.1]octane framework. Thus, the reaction of the optically active cyclohexanone derivative **44**, prepared in a five-step sequence from D-quinic acid, with ethyl diazoacetate furnished the α-diazo intermediate **45**, which was then subjected to pyrolysis to yield a 3:7 regioisomeric mixture of the cycloheptanone derivatives **46** and **47** (Scheme 13).

Scheme 13[a]



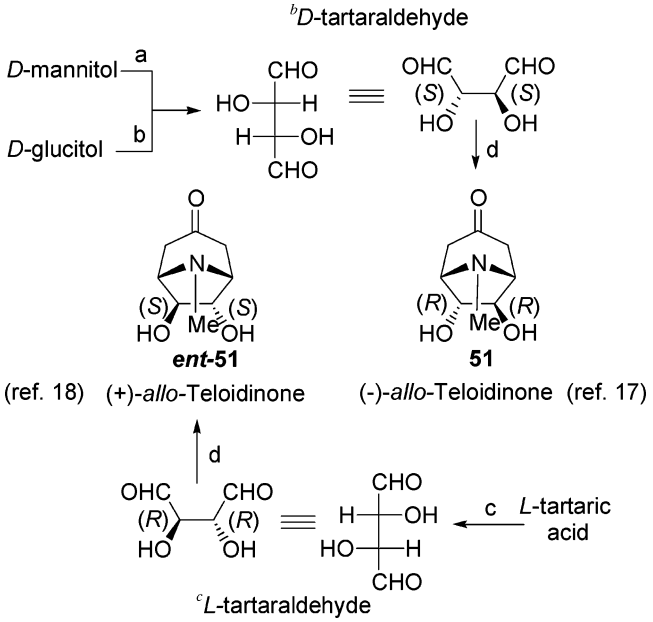
[a] Reagents: (a) N_2CHCO_2Et, LDA, THF; (b) benzene reflux; (c) BnOH, DMAP, toluene reflux; (d) i, H_2, Pd/C; ii, DME reflux; (e) $NaBH_4$; (f) i, MsCl, Et_3N; ii, NaN_3, DMF; (g) CH_3OH, HCl; (h) $SOCl_2$, Et_3N and then $RuCl_3$, $NaIO_4$; (i) H_2, Pd/C and then heating in dioxane/H_2O/H_2SO_4; and (j) i, ClCOOEt, K_2CO_3; ii, $LiAlH_4$, THF, reflux.

Fortunately, the barely regioselective methylene ring insertion reaction was partially mitigated by the ability of bakers' yeast (BY) to reduce only the minor undesired β-ketoester **46**, allowing us to recover the required regioisomer **47**. Hydrogenolytic decarbalkoxylation of the corresponding benzyl ester and a series of stereocontrolled functional group manipulations yielded the chiral azido cyclic sulfate **49**, which, after a reductive step, underwent the expected intramolecular displacement reaction, giving rise to the optically active 6-*endo*-hydroxy tropane **50**.

Interestingly, in the late 1950's, three different groups[17,18] described the synthesis of both antipodes of 6-*exo*,7-*endo*-dihydroxy-3-tropanone (*allo*-teloidinone **51** and ***ent*-51**) through the same Mannich-type reaction involving an enolizable optically active aldehyde. Their findings clearly showed that the Robinson synthesis and related Mannich-type condensation could take place without any racemization at the stereogenic center adjacent to the aldehyde function. In particular, the levorotatory *allo*-teloidinone was produced starting from D-tartaraldehyde, while the corresponding dextrorotatory enantiomer was formed using L-tartaraldehyde as the chiral educt (Scheme 14). Unfortunately, the use of D- and L-descriptors could have created some confusion, with the L-tartaraldehyde being derived from 3,4-isopropyliden-D-glucitol[19] or 3,4-isopropyliden-D-mannitol,[20] while the corresponding D-chiral template was obtained from L-tartaric acid.[18] However, the paper[21] entitled "Some Difficulties and Common Errors Related to the Designation of Sugar Configurations", which textually reports: "for a long time, dextrorotatory tartaric acid was assigned the D prefix because it could be obtained by a direct oxidation of D-glucose", has served to clarify unambiguously the results summarized in Scheme 14.

Besides clarifying this point, we believe that much more attention should be deserved to the pioneering work of these

Scheme 14[a]



[a] Reagents: (a) ref 20; (b) ref 19; (c) ref 18; and (d) acetonedicarboxylic acid, CH_3NH_2·HCl, pH 5.2, 7 days at 25 °C, 19% yield. [b] Designated L-tartaraldehyde in refs 17a and 17b. [c] Designated D-tartaraldehyde in ref 18.

authors in the tropane area, considering that 30 years later 2,3-isopropylidene tartaraldehyde is still considered as an unknown compound[22] and 6- and 7-hydroxylated tropane derivatives have been recently synthesized in racemic form and subsequently resolved by the chemical method to evaluate their dopamine transporter (DAT) and serotonin transporter (SERT) activity.[23,53]

3. Starting from Prochiral Substrates

According to IUPAC recommendations,[24] a molecule is defined prochiral if it can be made chiral in a single desymmetrization step, as, for instance, the replacement of an existing atom by a different one as well as the addition to a trigonal system of a new atom or group. When an optically active agent is involved, different cases may occur, e.g., the use of chiral auxiliaries, the use of chiral reagents, or the use of chiral catalysts, which will be discussed in that order.

3.1. Use of Chiral Auxiliaries

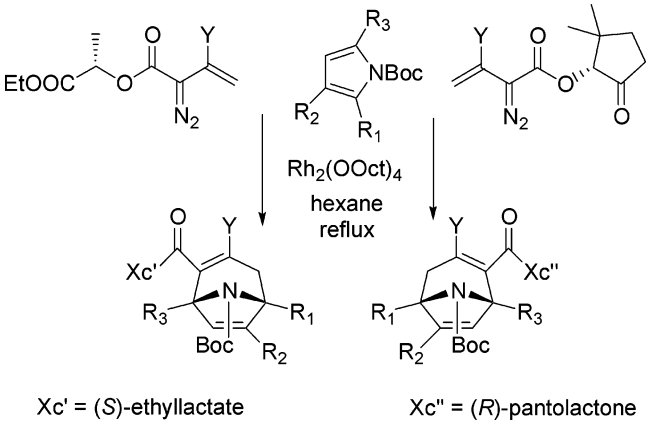
Ideally, a stoichiometric chiral auxiliary is an enantiomerically pure molecule satisfying the following requirements: (1) it can be easily attached to a prochiral substrate; (2) it must control the stereoselectivity in the subsequent reactions; and (3) it can be readily removed from the diastereomeric products.

Chiral auxiliaries have been successfully used in the synthesis of tropane ring systems. After we have explicated their roles, they can be, in principle, removed, recovered, and recycled, as in the examples discussed in sections 3.1.1 and 3.1.2, as well as destroyed in the cleavage step as in the examples collected in the sections 3.1.3 and 3.1.4.

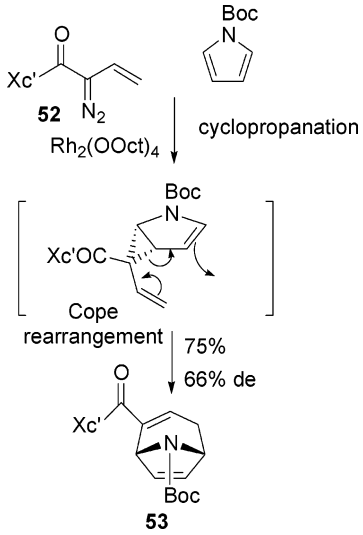
3.1.1. Esters of Enantiomerically Pure Alcohols

A series of enantiomerically enriched tropanes has been obtained by the reaction of various N-Boc-protected pyrroles

Scheme 15



Scheme 16

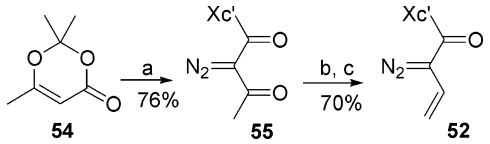


with rhodium-stabilized vinylcarbenoids containing either (*R*)-pantolactone or (*S*)-lactate as inexpensive chiral auxiliaries (Scheme 15).[25] The carbenoids formed during rhodium-(II)-catalyzed decomposition of vinyldiazomethane esters react with pyrrole derivatives to produce enantiomerically enriched tropanes, with the diastereoselectivity ranging from 40 to 80%. Interestingly, the use of (*R*)-pantolactone as the auxiliary reagent resulted in the tropane formation with opposite asymmetric induction compared to the one obtained with the (*S*)-lactate auxiliary. The syntheses of (−)-ferruginine ***ent*-21** and (−)-anhydroecgonine methyl ester **58** (see Scheme 18) were performed by taking advantage of the stereochemical outcome induced by the chiral auxiliary.

The vinyl diazomethane derivative **52** and *N*-Boc-pyrrole have been used as the counterparts in the key 3 + 4 annulation step, yielding the tropane derivative **53** (Scheme 16). The overall 3 + 4 annulation occurs by a tandem cyclopropanation/Cope rearrangement. The stereochemistry induced in the first step was subsequently transferred to the final product by means of a Cope rearrangement of the divinyl cyclopropane intermediate. The high asymmetric induction has been ascribed to an interaction between the carbonyl ester of the auxiliary and the carbenoid, resulting in a rigid orientation during the cyclopropanation step.

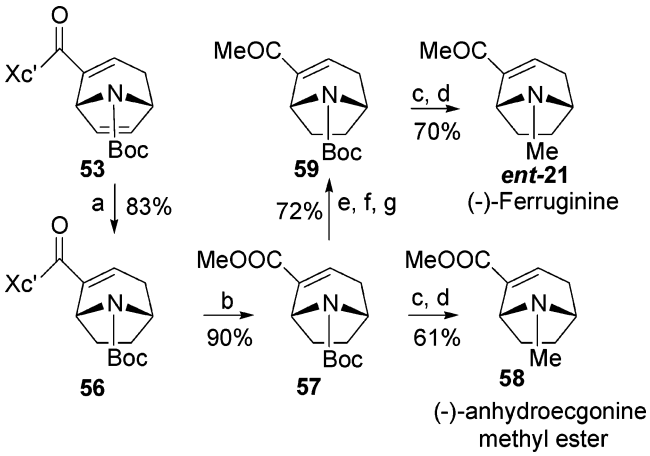
The required vinyldiazomethane derivative **52** has been prepared by the reaction of the diketene−acetone adduct **54** and ethyl (*S*)-lactate to give the corresponding β-ketoester, which, upon subsequent treatment with *p*-acetamidobenzene-

Scheme 17[a]



[a] Reagents: (a) i, (*S*)-ethyl lactate, toluene reflux; ii, *p*-ABSA, CH_3CN, Et_3N; (b) $NaBH_4$, EtOH; and (c) $POCl_3$, Et_3N, CH_2Cl_2.

Scheme 18[a]



[a] Reagents: (a) H_2, $(PPh_3)RhCl$; (b) NaOMe; (c) TFA; (d) CH_2O, $NaCNBH_3$; (e) $LiOH·H_2O$; (f) $SOCl_2$; and (g) MeMgBr, $CuBr·SMe_2$.

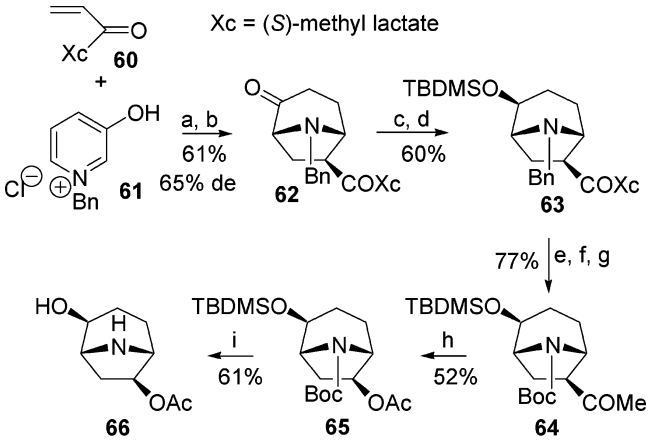
sulfonyl azide (*p*-ABSA) as a diazo-transfer agent, furnished the diazoacetate **55**. Its conversion to the derivative **52** has been accomplished by successive treatments with sodium borohydride (reduction) and phosphorus oxychloride (dehydration) (Scheme 17).

Conversion of **53** to (−)-anhydroecgonine methyl ester **58** was achieved by catalytic hydrogenation, removal of both the chiral auxiliary and Boc group, followed by reductive N-methylation (Scheme 18). On the other hand, conversion at the proper stage of the ester of **57** into an acetyl group opened the way to (−)-ferruginine ***ent*-21**.

Methyl (*S*)-lactate has also been successfully employed as an inexpensive chiral auxiliary from the "chiral pool" in the asymmetric synthesis of (−)-Bao Gong Teng A **66**, an alkaloid isolated from the Chinese herb *Erycible obtusifolia* (Convolvulaceae), which has been used to treat glaucoma (Scheme 19).[26]

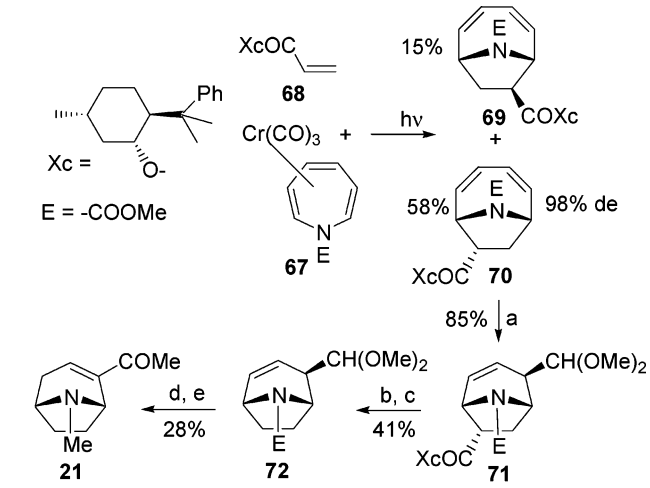
The enantiospecific synthesis took advantage of the regio- and diastereoselective 1,3-dipolar cycloaddition between the acrylate **60** and the betaine of *N*-benzyl-3-hydroxypyridinium chloride **61**. A good conversion of educts to cycloadducts could be obtained under particular experimental conditions, resulting after a careful investigation. The best results in term of selectivity (65% for the major isomer) and yield (90%) were obtained when a solution of dipolarophile and betaine (1.5:1 ratio) in EtOAc was left at room temperature for 10 days. As expected, the cycloaddition occurred preferentially at the *re* face of the chiral dipolarophile, producing predominantly the 6-*exo* cycloadduct with the appropriate absolute configuration of the natural alkaloid together with a small amount of the corresponding 6-*endo* isomer. Because of the thermal instability of the cycloadducts, they were hydrogenated and the major ketone **62** was isolated in 61% overall yield by chromatography on silica gel. Its reduction, using the bulky lithium tri-*tert*-butoxyaluminum hydride, gave predominantly the desired 2-*exo*-hydroxy compound

Scheme 19[a]



[a] Reagents: (a) Et_3N, EtOAc, room temperature for 10 days; (b) H_2, Pd/C; (c) $LiAlH(Ot\text{-}Bu)_3$, THF; (d) TBDMSOTf, CH_2Cl_2; (e) H_2, Pd/C, $(Boc)_2O$; (f) KOH; (g) i, $(COCl)_2$; ii, Me_2CuLi; (h) MCPBA; and (i) HCl/EtOH.

Scheme 20[a]

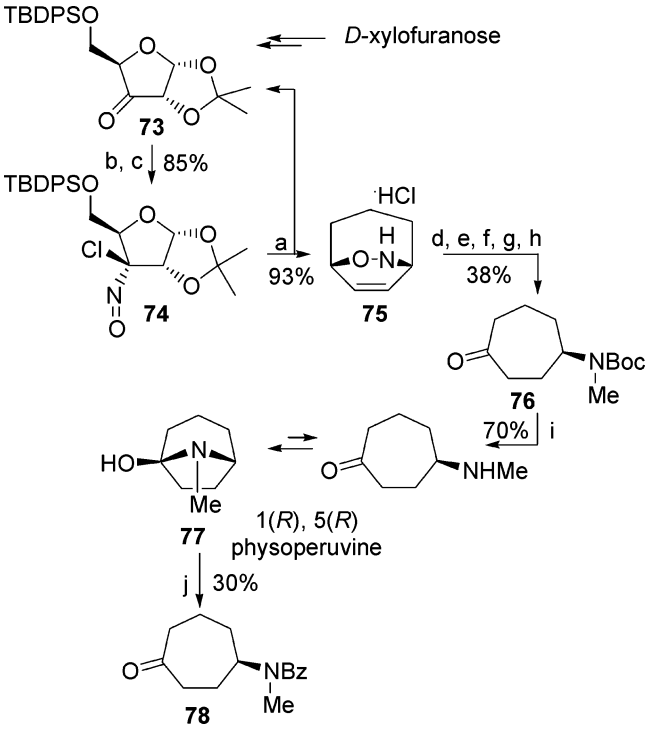


[a] Reagents: (a) $Tl(ONO_2)_3·3H_2O$, CH_3OH; (b) LiOH, CH_3OH:H_2O; (c) i, *i*BuO_2CCl, *N*-methylmorpholine; ii, 2-mercaptopyridine *N*-oxide; iii, hν, *ter*BuSH; (d) TFA, H_2O/acetone; and (e) i, MeMgBr; ii, $LiAlH_4$, Et_2O; iii, Dess−Martin periodinane, CH_2Cl_2.

easily protected as TBDMS derivative **63**. Debenzylation with simultaneous N-Boc protection was required prior to transform the carboxy group into a methyl ketone. In the next step of the synthesis, the Bayer−Villiger oxidation of **64** gave the 6-*exo*-acetoxy derivative **65**, which, by acid-promoted removal of both protective groups, produced compound **66**, which exhibits the same optical rotation as the natural alkaloid (9% overall yield).

Auxiliary-based induction during Cr(0)-mediated [$6\pi + 2\pi$] cycloaddition of azepine derivatives provided a direct entry to chiral nonracemic homotropane products, which could be converted to tropane derivatives through an appropriate ring-contraction technology (Scheme 20).[27] In details, photocycloaddition of the N-substituted azepine−Cr(0) complex **67** with the acrylate **68** incorporating (−)-8-phenylmenthol as the chiral auxiliary gave the expected *endo*-adduct **70** in 58% yield along with a minor quantity (15%) of the unexpected *exo*-adduct **69**, with each of them produced in diastereomerically pure form.

Scheme 21[a]



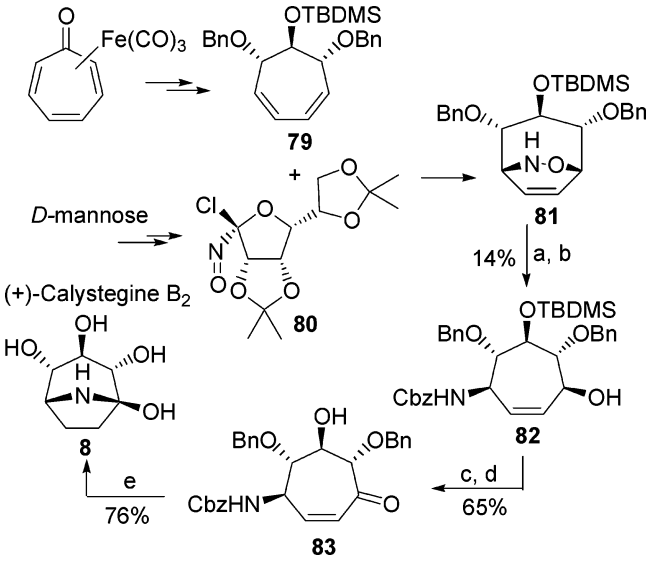
[a] Reagents: (a) cyclohepta-1,3-diene, $CHCl_3$/*i*PrOH/H_2O, 4 °C; (b) NH_2OH·HCl, $NaHCO_3$; (c) *t*BuOCl, CH_2Cl_2; (d) H_2, $Pd(OH)_2$/C, CH_3OH; (e) $ClCO_2Bn$, Na_2CO_3; (f) $LiAlH_4$, THF reflux; (g) $(Boc)_2O$, DIPEA; (h) PCC, CH_2Cl_2; (i) TFA and then Na_2CO_3; and (j) BzCl, pyridine, CH_2Cl_2.

Exposure of the major epimer **70** to thallium trinitrate (TTN) in MeOH produced in excellent yield (85%) the single optically pure tropane **71** via bond reorganization of an intermediate derived by regioselective oxythallation of the 1,3-diene function. In this way, the enantiomeric purity established in the initial [6π + 2π] cycloaddition step has retained during the intriguing ring-contraction step. The synthetic value of the formed tropane derivative was demonstrated by its conversion to (+)-ferruginine **21**. Thus, saponification followed by decarboxylation via Barton thiohydroxamate ester protocol gave compound **72**, which was converted to the targeted alkaloid through a routine series of functional-group interchanges. The approach appears to be the first total synthesis of the natural product in optically pure form.[27]

3.1.2. C-Nitroso Carbohydrates

The asymmetric variant of the hetero-Diels−Alder cycloaddition of *C*-nitroso compounds, carrying a chiral auxiliary, with dienes, has been widely studied. In this context, asymmetric cycloadditions of dienes to α-chloronitroso compounds derived from carbohydrate ketones have been successfully used for the syntheses of 1(*R*),5(*R*)-physoperuvine **77** and (+)-epibatidine (Scheme 21).[28] Thus, the reaction of the chiral α-chloronitroso compound **74**, prepared from D-xylose, with 1,3-cycloheptadiene gave in high yield (93%) the bicyclic adduct **75** together with the chiral auxiliary in an easily recyclable form (by oximation and oxidation with *t*-BuOCl). The chiral dihydrooxazine **75**, whose enantiomeric excess (ee) was shown to be 96% through derivatization with (+)-camphor-10-sulfonyl chloride, has been employed to produce 1(*R*),5(*R*)-physoperuvine **77**, with the corresponding enantiomer being the major alkaloid of *Physalis peruviana* Linne. The salient steps along the synthesis are the N−O bond reductive cleavage and the required Boc protection of the basic nitrogen prior to pyridinium chlorochromate (PCC) oxidation of the alcoholic function. In the final step, Boc removal permitted the formation of the bicyclic skeleton of the non-natural 1(*R*),5(*R*)-physoperuvine **77**.

Scheme 22[a]

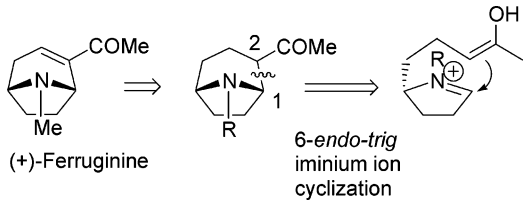


[a] Reagents: (a) BnOCOCl, CH_2Cl_2, Na_2CO_3; (b) $Mo(CO)_6$, CH_3CN/H_2O; (c) PCC, CH_2Cl_2; (d) HF, H_2O/CH_3CN; and (e) H_2, Pd/C.

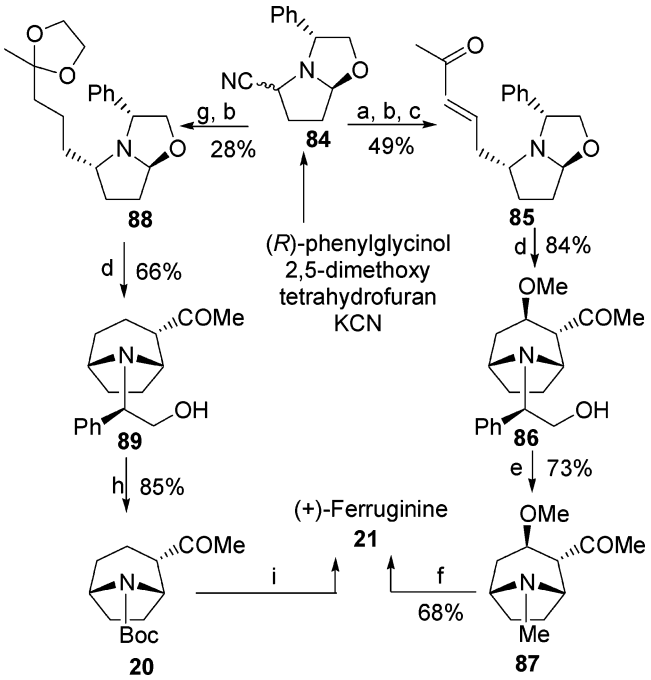
Because of the contradictory values of the rotatory power reported in the literature and some cloudy stereodrawings, we have chosen to refer to the absolute configurations 1(*S*),5(*S*) of the bridgehead carbons as for the natural alkaloid.

A synthetic approach to (+)-calystegine B_2 also took advantage of a hetero-Diels−Alder cycloaddition reaction (Scheme 22). Soulié et al.[32] employed the chiral nitroso dienophile **80** derived from D-mannose as the counterpart of the known[33] trisubstituted cycloheptadiene **79**, in turn previously taken to racemic calystegine B_2 by the same authors. The [4 + 2] cycloaddition readily gave the dihydrooxazine derivative **81** in 67% yield as a single enantiomer. Its derivatization with (*S*)-mandelic acid furnished only one diastereoisomer. Enantiopure **81** was converted into the optically active tropane derivative through a very sound protocol. Thus, after benzyloxycarbonyl N-protection, the $Mo(CO)_6$ reductive cleavage of the N−O bond gave compound **82** allowing for the creation of both amino and alcohol groups simultaneously and with the correct stereochemistry

Scheme 23



Scheme 24[a]



[a] Reagents: (a) LDA, $BrCH_2CH(OEt)_2$; (b) Li/NH_3, (c) i, HCl diluted; ii, $(MeO)_2POCH_2COCH_3$, DIPEA; (d) H_2SO_4, CH_3OH, 60 °C; (e) H_2, $Pd(OH)_2$, CH_2O; (f) TsOH, benzene at reflux; (g) LDA, $Br(CH_2)_3C(OCH_2CH_2O)\text{-}CH_3$; (h) H_2, Pd/C, $(Boc)_2O$; and (i) ref 11.

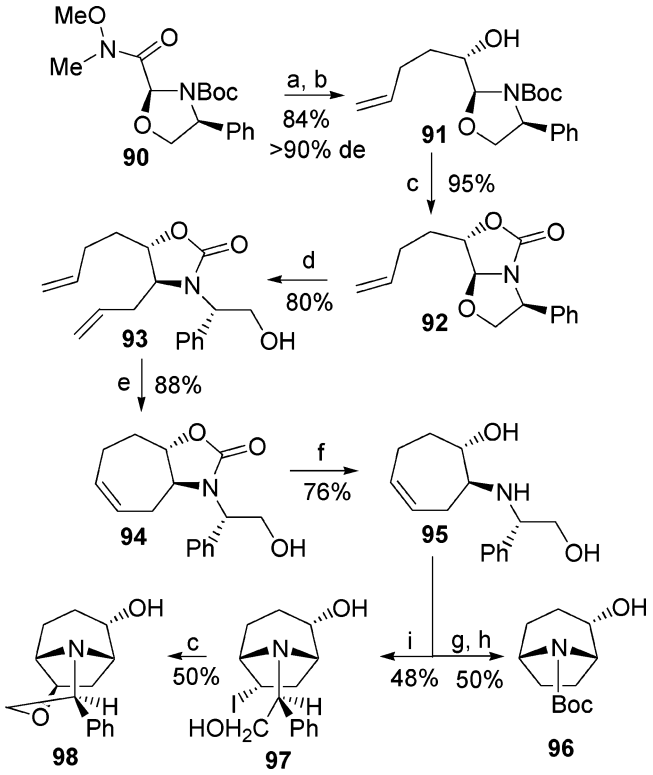
on the cyclic seven-carbon framework. Oxidation of the allylic alcohol and O-desilylation produced the key cycloheptenone **83**, which was eventually subjected to hydrogenation to give the natural alkaloid **8** in 13% overall yield.

3.1.3. Phenylglycinol Derivatives

The CN(*R*,*S*) method developed by Husson et al.[34] has been applied to a nice synthesis of (+)-ferruginine **21** using (*R*)-phenylglycinol as a chiral auxiliary for the construction of the 8-azabicyclo[3.2.1]octane nucleus (Scheme 24). The C_1-C_2 bond disconnection led us to select an iminium ion cyclization as the pivotal reaction on the route to the natural tropane alkaloid, with a retrosynthetic approach identical to that followed by Rapoport et al.[11] starting from L-pyroglutamic acid (Schemes 7 and 23).

The starting chiral material, 2-cyano-5-oxazolopyrrolidine **84**, was easily prepared in one step from (*R*)-phenylglycinol, dimethoxytetrahydrofuran, and potassium cyanide (Scheme 24). Compound **84** could be taken to derivatives **85** and **88**, which can be considered equivalents of the pyrrolinium salt involved in the biosynthesis of tropane alkaloids. The CN(*R*,*S*) method consists of the stereocontrolled introduction, α to the nitrile function, of an alkyl chain bearing a C-nucleophile center able to add to a transient pyrrolinium ion. Thus, the tropane derivatives **86** and **89** were stereoselectively obtained in 84% yield via Mannich-type cyclization. The introduction of the 2-pentanone chain led to the known

Scheme 25[a]

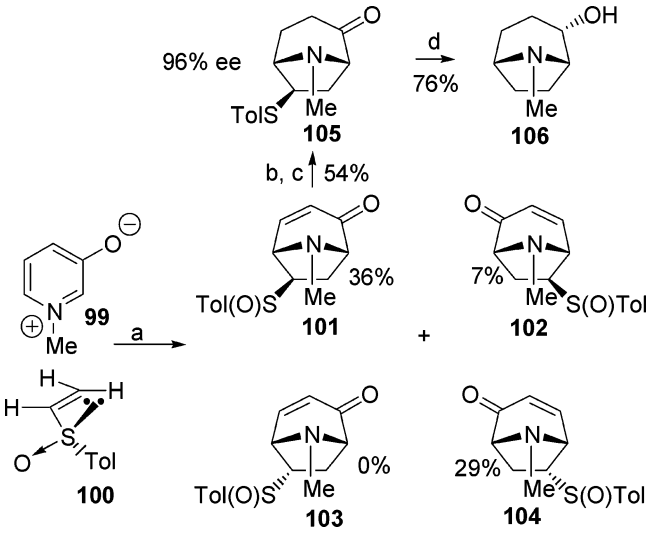


[a] Reagents: (a) but-4-enylmagnesium bromide; (b) $NaBH_4$, EtOH, −78 °C; (c) NaH, THF, reflux; (d) $TiCl_4$, allyltrimethylsilane, CH_2Cl_2; (e) Grubbs catalyst, CH_2Cl_2; (f) KOH, $EtOH/H_2O$, reflux; (g) i, $Hg(OAc)_2$, THF/H_2O; ii, $NaBH_4$, NaOH; (h) H_2, Pd/C, $(Boc)_2O$; and (i) NIS, CH_2Cl_2, −78 °C.

enantiopure **20** already converted to (+)-ferruginine by Rapoport et al.,[11] while insertion of the 3-penten-2-one chain opened a new straightforward route to the alkaloid. The second alkyl chain had the merit of simplifying the creation of the double bond in the targeted tropene alkaloid. In fact, hydrogenolytic removal of the chiral auxiliary and the direct N-methylation of the free amine furnished the 3-methoxy derivative **87**, which, by heating in the presence of *p*-toluenesulfonic acid, gave optically pure (+)-ferruginine in 68% yield.

A new access to tropanes based on RCM of diolefinic oxazolidinones has been recently described (Scheme 25),[35] using as a key starting material the Weinreb amide **90** carrying the prochiral glyoxylic acid moiety bound to (*S*)-phenylglycinol. The chiral auxiliary was especially suited to control the diasteroselectivity of processes occurring at both carbons of the prochiral substrate. Thus, the reaction of **90** with but-4-enylmagnesium bromide gave the corresponding 2-acyl oxazolidine, which underwent diastereoselective reduction with sodium borohydride at −78 °C to produce the α-hydroxy oxazolidine **91** [>90% diastereomeric excess (de)]. Transcarbamation to **92** followed by treatment with $TiCl_4$ in the presence of allyltrimethylsilane provided the stereodefined *trans*-diolefinic oxazolidinone **93**. Subsequent RCM in the presence of Grubbs catalyst furnished the expected five,seven-membered bicyclic oxazolidinone derivative **94** in good yield (88%). Its base-catalyzed hydrolysis generated the amino alcohol **95**, bearing the chiral appendage at the nitrogen atom. The pivotal aminocyclization was accomplished by treatment with *N*-iodosuccinimmide (NIS) to give compound **97**, eventually etherified to the tricyclic compound **98**, still incorporating the original chiral auxiliary. Alternatively, compound **95** was converted to the

Scheme 26[a]



[a] Reagents: (a) THF, 90 °C, 4 days; (b) PBr_3, DMF, 0 °C; (c) H_2, Pd/C; and (d) Raney−Ni (W4), EtOH, reflux.

hydroxy tropane derivative **96** through aminomercuration−reduction followed by N-debenzylation and N-Boc protection.

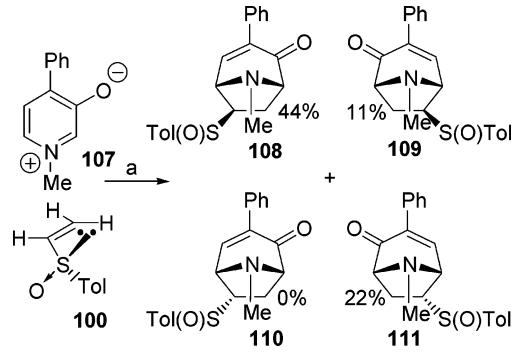
3.1.4. Chiral Sulfinylethene

A Japanese group[36] described an enantioselective synthesis of (1*S*)-(−)-2α-tropanol **106** through the first asymmetric 1,3-dipolar cycloaddition reaction of (*R*)-*p*-tolyl vinyl sulfoxide **100** and 1-methyl-3-oxidopyridinium **99** (Scheme 26). The reaction gave a mixture of three of the four possible diastereomers, with their separation being accomplished by silica-gel-column chromatography. The absolute configuration of the major *exo* cycloadduct **101** was determined by its conversion to the optically active tropane derivative **106**. The remaining problem was the removal of the chiral auxiliary, namely, the sulfoxide appendage. To this end, the sulfoxide **101** was first reduced with phosphorus tribromide to the corresponding sulfide and then submitted to catalytic hydrogenation to saturate the double bond. Subsequent desulfurization of **105** with Raney−nickel (W-4) afforded the tropanol **106**, whose spectral data were consistent with those of the corresponding known enantiomer that has been previously prepared starting from natural cocaine and employed for pharmacological studies.

Similarly, the 1,3-dipolar cycloaddition reaction of the chiral (*R*)-*p*-tolyl vinyl sulfoxide **100** with 4-phenyl-oxidopyridinium betaine **107** afforded a mixture of both *exo* and *endo* tropenone derivatives with good diastereoselectivity and complete regioselectivity (Scheme 27).[37] The stereochemical outcome and the stereoisomeric ratio are substantially identical with those obtained by Koizumi et al.[36] (Scheme 26). Chromatography of the crude mixture led to the separation of the *endo* product **111** from the *exo* products **108** and **109**, which were eventually separated by crystallization. The isolated compounds were converted enantiospecifically to the optically active 2-alkyl-3-phenyl tropanes **114** and ***ent*-114** (Scheme 28). These targets, often referred to as WIN series compounds, represent important tools for pharmacological studies, with the main structural feature being the lack of the 3α-benzoyl ester functionality present in cocaine.

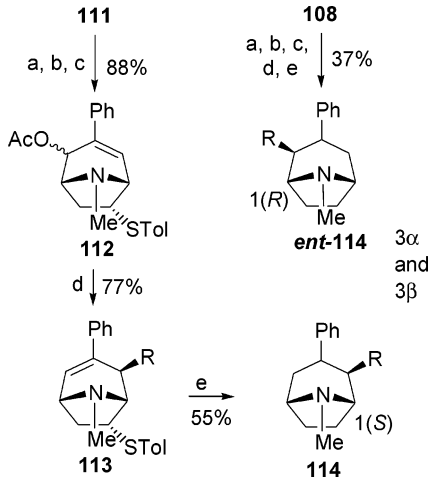
Thus, the reduction of both the carbonyl and the sulfoxide groups in **111** opened the way to *O*-acetyl sulfide **112**, which

Scheme 27[a]



[a] Reagents: (a) 1,4-dioxane, reflux, 24 h.

Scheme 28[a]



[a] Reagents: (a) $NaBH_4$, $CeCl_3$, CH_3OH; (b) Ac_2O, pyridine; (c) PCl_3, DMF; (d) RMgBr, CuCN, Et_2O; and (e) Raney−Ni (W2), EtOH, reflux.

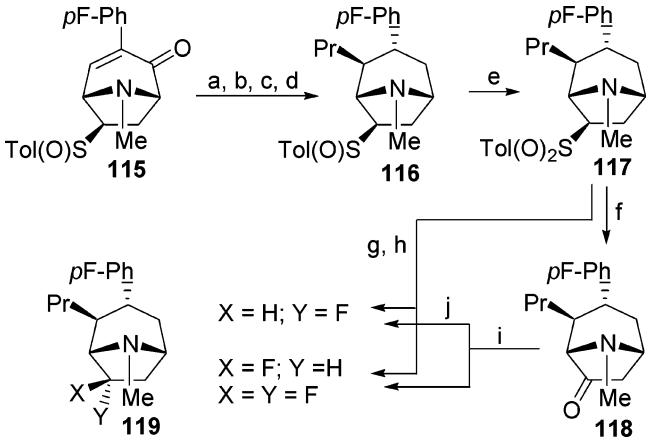
underwent a regio- and diastereoselective CuCN-catalyzed cross-coupling reaction with Grignard reagents to afford alkene intermediates **113** bearing the 2-alkyl substituents exclusively with β orientation (Scheme 28). A subsequent one-step desulfurization and double-bond hydrogenation reaction using Raney−nickel (W2) afforded the desired 2-alkyl-3-phenyl-tropane derivatives **114** as a mixture of 3β and 3α stereoisomers. When compound **108** was submitted to the same sequence of reactions as for **111**, the diastereomeric mixture ***ent*-114** was obtained.

The likewise prepared and isolated *exo* diastereomer **115** was transformed into 2-propyl-3-*p*-*F*-phenyl-7-*p*-tolyl sulfoxide tropane derivative **116** (Scheme 29).[38] In this case, chemical modification of the *p*-tolyl sulfoxide moiety other than reduction was effected. Thus, oxone oxidation of the sulfoxide **116** to the corresponding sulfone **117** followed by a further oxidation with oxodiperoxymolybdenum(pyridine)−(hexamethylphosphoric triamide) (MoOPH) served for introducing a carbonyl group at C7 of the intermediate **118**. Interestingly, either **117** or **118** was employed for the preparation of optically pure 7-fluorotropanes of general formula **119** to be used as structural probes of the DAT.

3.2. Use of Chiral Reagents

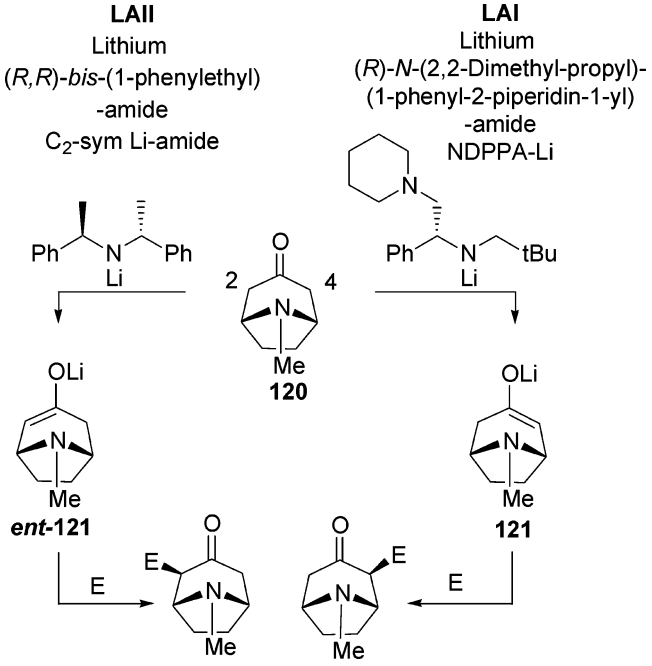
Enantiomerically enriched products can, in principle, be obtained by treatment of prochiral substrates with a stoichiometric amount of chiral reagents. In this context, approaches to the tropane skeleton entailing on the use of

Scheme 29[a]



[a] Reagents: (a) *n*-PrMgBr, CuBr·$(CH_3)_2S$, TMSCl, THF, −78 °C; (b) $LiBH_4$, THF; (c) *n*-BuLi, THF and then PhOC(S)Cl, −78 °C; (d) *n*-Bu_3SnH, AIBN, toluene, 60 °C; (e) oxone, CH_3OH :H_2O; (f) *n*-BuLi, MoOPH, THF, −78 °C; (g) *n*-BuLi, *N*-fluorobenzensulfonimide, THF, −78 °C; (h) Na(Hg), Na_2HPO_4, CH_3OH; (i) DAST, CH_2Cl_2; and (j) DIBAH, CH_2Cl_2.

Scheme 30



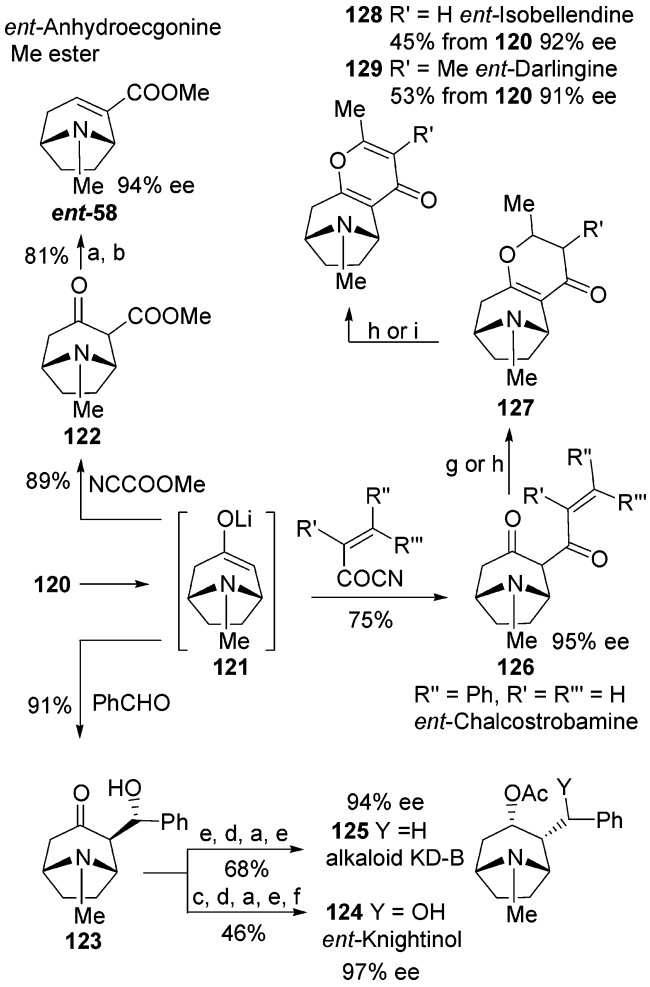
chiral bases, chiral organometallic complexes, and chiral borane hydride are discussed in the following subsections.

3.2.1. Chiral Bases

The commercially available tropinone constitutes an ideal prochiral substrate for effecting desymmetrizations such as enantioselective proton abstraction by means of optically pure lithium amide bases. This operation can be considered as the cornerstone of several asymmetric approaches to natural and non-natural alkaloids as well as to tropane-based inhibitors of the DAT.

Thus, Majewski and Lazny showed that the lithium amide derived from the bidentate amine (*R*)-NDPPA (LAI in the Scheme 30) attacks preferably a hydrogen at C4 of tropinone **120**, whereas the (*R*,*R*)-C_2 symmetrical lithium amide (LAII in the Scheme 30) prefers to abstract the proton from C2 (Scheme 30).[39] They also found that the presence of LiCl is essential to obtain high selectivity (>90% ee) in the

Scheme 31[a]

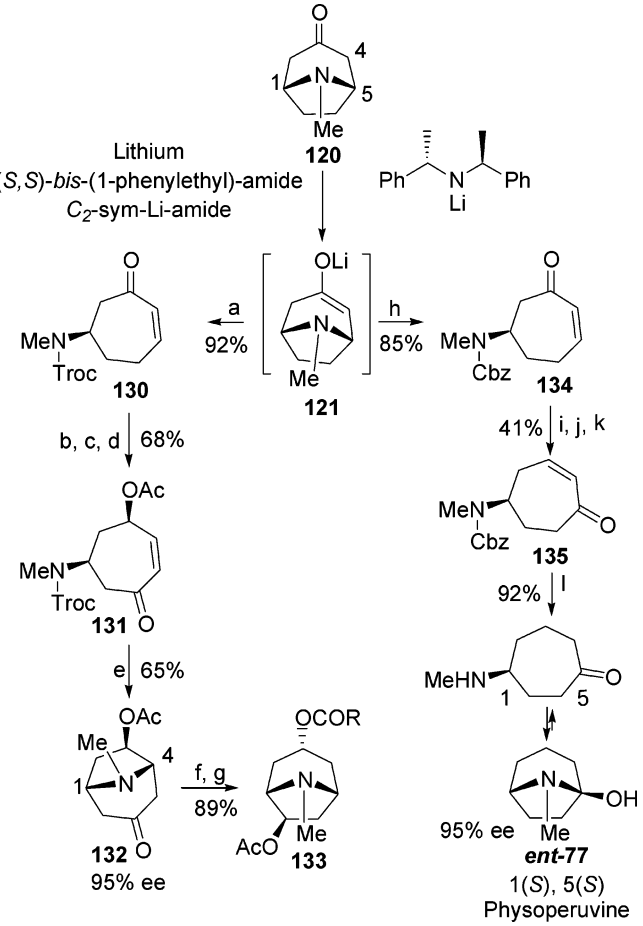


[a] Reagents: (a) H_2, PtO_2; (b) $(CF_3CO)_2O$; (c) TBDMS-Cl, Et_3N; (d) SiO_2; (e) Ac_2O; (f) Bu_4NF; (g) Na_2CO_3, EtOH; (h) Et_3N; and (i) i, $CuBr_2$; ii, NH_3.

deprotonation step. The chiral nonracemic tropinone lithium enolates have three nucleophilic centers (oxygen, carbon, and nitrogen) and can react at each of these, depending upon the electrophile used. Under the kinetic control conditions required for the enantioselective deprotonation of **120**, most acyl cyanides as well as aldehydes reacted at the carbon nucleophilic center. The resulting products were successfully transformed into several tropane alkaloids (Scheme 31).

The stereoselective formation of **121** has been further established through its successful utilization in the synthesis of the alkaloid anhydroecgonine. To this end, the β-keto ester **122**, obtained via methoxycarbonylation of **121**, was reduced using H_2 over Adam's catalyst and the resulting alcohol was dehydrated to afford compound ***ent*-58** with 94% ee and 72% yield along the synthetic sequence starting from tropinone **120**. Several benzyltropane and pyranotropane alkaloids were prepared using the appropriate electrophile and the absolute configuration of the natural substances assigned by correlation with anhydroecgonine. Interestingly, on the route to benzyltropanes *ent*-knightinol **124** and alkaloid KD-B **125**, a mild epimerization step with SiO_2 was required to establish the *endo*-benzyl or the *endo*-α-hydroxybenzyl group at C2, prior to C3 carbonyl reduction of **123**. In fact, the aldol-like reaction between the chiral nonracemic tropinone lithium enolate and benzaldehyde led to an axial (*exo*) orientation of the C2 side chain because of hydrogen-bonding stabiliza-

Scheme 32[a]

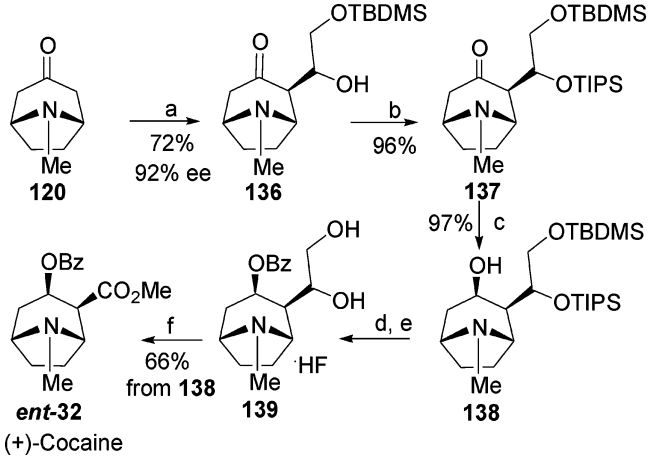


[a] Reagents: (a) $ClCO_2CH_2CCl_3$; (b) $NaBH_4$, $CeCl_3$; (c) Ac_2O, Et_3N; (d) i, H_2SeO_3; ii, PDC; (e) Zn, EtOH; (f) H_2, PtO_2; (g) Ac_2O or Tg_2O; (h) CbzCl; (i) H_2O_2, KOH; (j) NH_2NH_2; (k) PDC; and (l) H_2, Pd/C.

tion. Cinnamoylcyanide was the acylating agent employed to yield *ent*-chalcostrobamine **126**, whereas acylations with 2-bromocrotonyl and tigloyl cyanides, followed by ring-closure reactions, were the steps on the route to pyranotropanes *ent*-isobellendine **128** and *ent*-darlingine **129**, respectively. The enantiopurity of the synthesized alkaloids was in the range of 92−97% ee as determined by ^{1}H NMR with (*S*)-(+)-trifluoro-1-(9-anthranyl)-ethanol (TFAE).

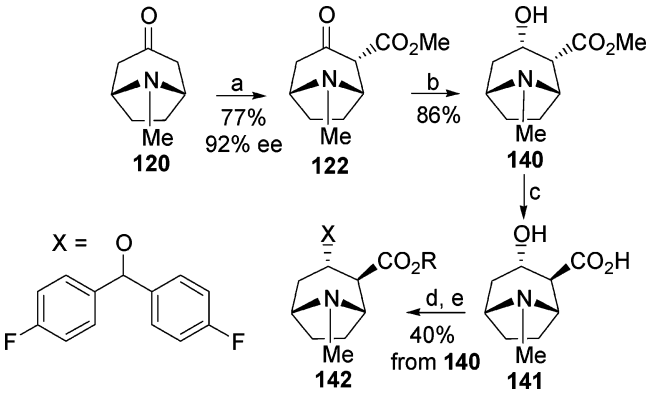
A total of 2 years later, the same authors found that the lithium enolate **121**, in turn prepared by using lithium (*S*,*S*)-bis(1-phenylethyl)-amide in place of NDPPA-Li in the asymmetric deprotonation step, underwent a retro-Michael ring-opening reaction upon treatment with chloroformates (Scheme 32).[40] The derived cycloheptenone derivatives **134** and **130** have been successfully utilized in syntheses of 1(*S*),5(*S*)-physoperuvine ***ent*-77** and 3α,6*β*-dihydroxylated tropanes **133**, respectively. A 1,3-enone transposition, via Wharton rearrangement, transformed **134** into the regioisomeric aminocycloheptenone **135**, which was subjected to catalytic hydrogenation to yield ***ent*-77** in 95% ee. The synthetic sequence leading to the dihydroxy tropane derivatives **133** presented two salient steps, namely, the Luche reduction of the enone **130** and the one-pot H_2SeO_3-PDC sequential oxidation, which resulted in the 1,4-transposition of the carbonyl group. The final amino deprotection of **131** permitted the in situ cyclization assessing the tropane nucleus. In the Scheme 32, we stress the fact that, referring to the numbering of starting tropinone, the nitrogen atom continues

Scheme 33[a]



[a] Reagents: (a) i, (*S*,*S*)-bis(1-phenylethyl)amide, LiCl, −78 °C, THF; ii, $TBSOCH_2CHO$; (b) TIPSOTf, 2,6-lutidine; (c) Li/NH_3; (d) PhCOCl, Et_3N; (e) HF; and (f) i, $RuCl_3$-$NaIO_4$; ii, $TMSCHN_2$.

Scheme 34[a]



[a] Reagents: (a) i, *n*-BuLi, (*R*)-NDPPA; ii, $NCCO_2Me$, THF; (b) H_2, PtO_2; (c) H_2O, reflux; (d) HCl gas, ROH; and (e) 4,4′-difluorobenzhydrol, *p*-TsOH, benzene, reflux.

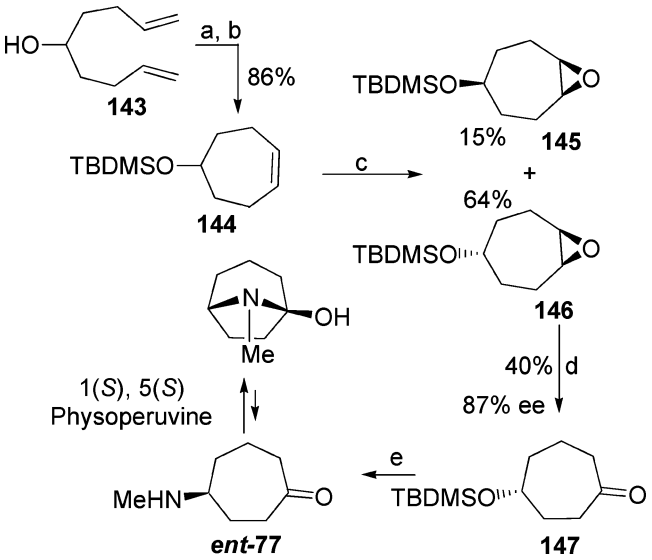
to bind C1 and C5 in ***ent*-77**, whereas it binds C1 and C4 in the tropane derivative **132**.

More recently, the strategy based on the enantioselective deprotonation of tropinone has been used to prepare the nonnatural (*S*)-(+)-cocaine as well as a series of highly potent and selective DAT ligands (Scheme 33).[41] Thus, the chiral nonracemic tropinone lithium enolate has been trapped in situ by O-protected glycolaldehyde affording the aldol product **136** as a single diastereomer in 72% yield and 92% ee.

To avoid the formation of the mixture of keto and enol tautomers, hydroxyalkylation was preferred over direct carbomethoxylation. As expected, the introduction of the two-carbon unit proceeded with *β* orientation and its transformation into the thermodynamically unstable axial carboxylate group was accomplished by RuO_4 oxidation of the diol moiety of **139**. Methyl ester formation by treatment with $TMSCHN_2$ eventually furnished (+)-cocaine, whose enantiomeric purity was 90%.

A paper describing a further application of this methodology has recently appeared.[42] Thus, 3-tropinone was asymmetrically deprotonated by the lithium salt of chiral amine (*R*)-NDPPA and then treated with methyl cyanoformate to give (−)-2-carbomethoxytropinone **122** with 92% ee (Scheme 34). The subsequent stereocontrolled operations, namely, catalytic carbonyl reduction followed by C2 epimerization,

Scheme 35[a]



[a] Reagents: (a) Grubbs catalyst, CH_2Cl_2; (b) TBDMSCl, imidazole; (c) saccharin-based oxaziridine, Na_2CO_3, $CHCl_3$, 6 days; (d) *i*-PrLi, (−)-α-isosparteine; and (e) ref 47.

led to the *β*-hydroxy acid **141** that was easily transformed into a series of (*S*)-2*β*-carboalkoxy-3α-[bis(4-fluorophenyl)-methoxy]tropane analogues **142** to be used as novel probes for the DAT.

3.2.2. Chiral Organometallic Complexes

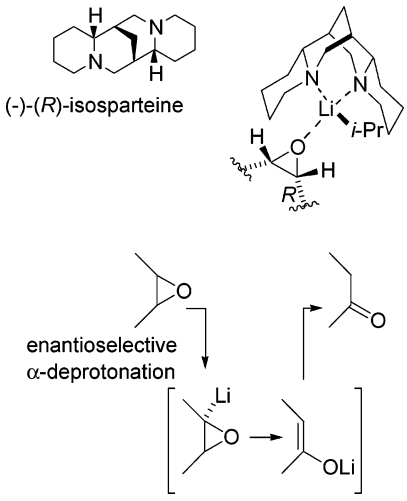
The reaction of chiral organo-Li and organo-Mo complexes with substrates having a prochiral tetrahedral carbon and a prochiral trigonal system, respectively, led to the formation of chiral nonracemic products, useful intermediates for the synthesis of optically active tropane derivatives.

A synthetic approach entailing on an asymmetric rearrangement of the achiral *trans*-5-silyloxy cycloheptene oxide **146** to the chiral 4-silyloxycycloheptanone **147** paved the way to a formal synthesis of 1(*S*),5(*S*)-physoperuvine ***ent*-77** (Scheme 35).[43] Thus, the trans prochiral substrate **146**, prepared from 1,8-nonadien-5-ol **143** through the sequence: catalytic RCM, O-silylation, and trans diastereoselective (trans/cis = 4.1:1) epoxidation using a saccharin-based oxaziridine, was desymmetrized using *i*-PrLi and (−)-α-isosparteine as a chiral ligand affording, with >87% ee, the (*R*)-4-silyloxy cycloheptanone **147**, a known intermediate[47] in the synthesis of physoperuvine ***ent*-77** (see Scheme 40).

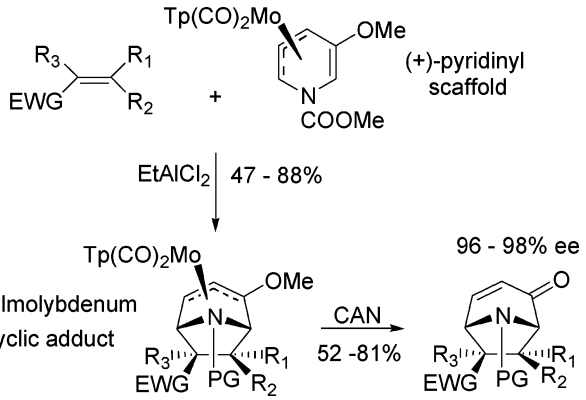
Interestingly, the featuring enantiotopic α deprotonation of the epoxide succeeded a ring rearrangement producing a ketone (Scheme 36). The desymmetrization, as a result of the selective removal of the hydrogen at the (*R*)-configured carbon of the epoxide ring, may be explained considering a isosparteine-RLi-epoxide complex, where the C−H bond on the epoxide *R* stereocenter is held closer to the organolithium than the *S* stereocenter.[44]

Stoichiometric enantiopure *π* complexes of molybdenum bound to hydridotris(1-pyrazolyl)borate ligand (Tp) have been used in an elegant access to optically active tropane structures bearing various substituents around the tropane skeleton (Scheme 37).[45a] Previous observations had showed that the $TpMo(CO)_2$ auxiliary of a reactant pyridinyl scaffold constitutes an ideal metal−ligand set capable of mediating *multiple* and *sequential* regio- and stereoselective functionalizations of various *π* substrates. Herein, a general, convergent, and enantiocontrolled route to highly functionalized

Scheme 36



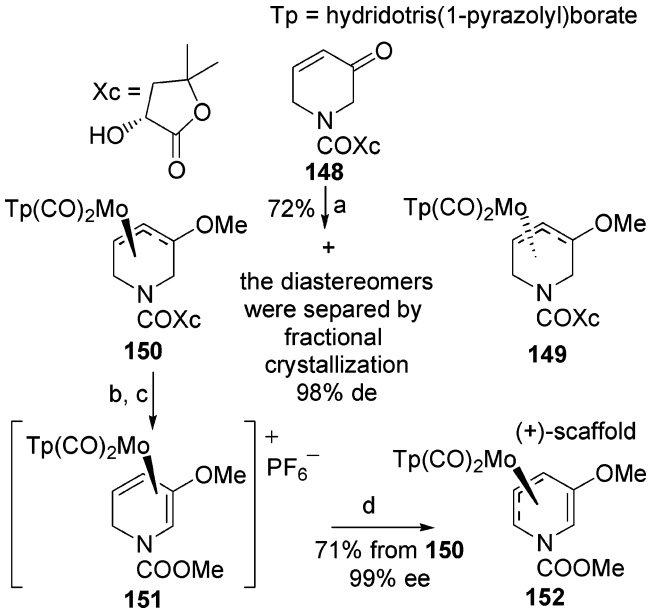
Scheme 37



tropanes has been opened using an enantiopure η^3-pyridinyl scaffold. The enantiospecificity of the method arises from the [5 + 2] attachment of various electron-deficient alkenes to a single face of the chiral scaffold, with the formation of new C−C bonds occurring exclusively from the face opposite the metal−ligand moiety. Thus, the cycloaddition reactions initiated by the Lewis acid $EtAlCl_2$ afforded η^3-allylmolybdenum bicyclic adducts in good to excellent yield and with good *exo*/*endo* selectivities. The synthetic sequence is concluded by ceric ammonium nitrate (CAN)-mediated oxidative demetalation furnishing enone derivatives with high enantiomeric purity (96−98% ee) and well-suited for further synthetic manipulations.

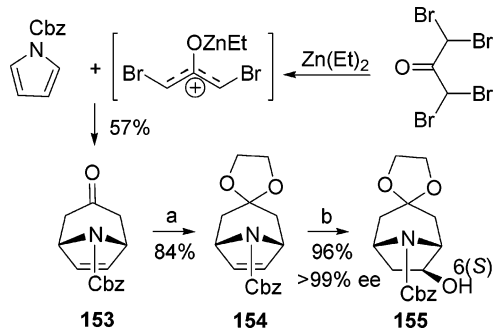
The preparation of the enantiomeric organometallic complexes starts with the oxidative addition of $Mo(DMF)_3(CO)_3$ to the dihydropyridone **148**, armed with (*R*)-pantolactone as the chiral auxiliary, followed by O-methylation (Scheme 38). The robust *O*-methyl molibdenum complexes **149** and **150**, generated as a diastereomeric mixture, were conveniently separed by crystallization. Removal of the chiral auxiliary required SmI_2-induced deoxygenation of the α-carbamyloxy lactone, as shown in the Scheme 38 for the diastereomer **150**. The enantiomeric free base, after treatment with methylchloroformate, was subjected to hydride abstraction using Ph_3CPF_6. The resulting cationic diene complex **151** was eventually deprotonated to the corresponding neutral enantiopure (+)-scaffold **152**, which has been used in the cycloaddition reactions according to the strategy outlined above. Very recently, Zhang and Liebeskind[45b] described a successful approach to the total sythesis of (−)-Bao Gong

Scheme 38[a]



[a] Reagents: (a) i, $Mo(CO)_3(DMF)_3$, TBDMSCl; ii, KTp; iii, TBAF; iv, CH_3I; (b) i, SmI_2, HMPA, CH_3OH; ii, $ClCO_2Me$, 3 N aqueous NaOH; (c) Ph_3CPF_6; and (d) Et_3N.

Scheme 39[a]



[a] Reagents: (a) $(CH_2OH)_2$, PPTS, benzene reflux; and (b) i, (−)-$(Ipc)_2BH$, THF; ii, CH_3OH, NaOH, H_2O_2.

Teng A in 35% yield and >99% ee by using their organometallic chiron, and this protocol could be considered as the shorter method for a rapid assemblage of the tropane core.

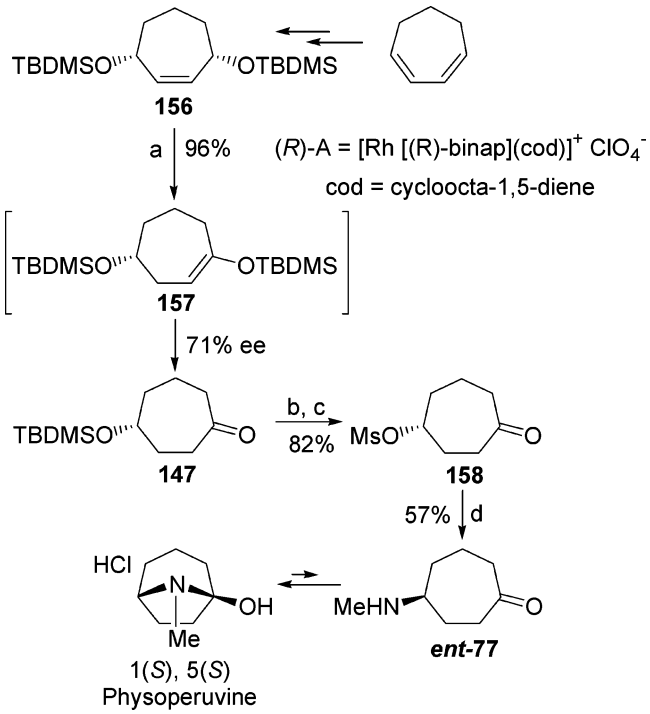
3.2.3. Chiral Borane Hydride

A sole example of desymmetrization via enantioselective hydroboration using a pinene-derived chiral borane reagent has been described in the literature (Scheme 39).[46] The starting symmetrical tropenone derivative 153 was obtained by [4 + 3] cycloaddition of a N-protected pyrrole and the oxyallyl cation generated in situ from tetrabromoacetone and diethylzinc. Acetalization of the carbonyl group to prevent the formation of byproducts was followed by hydroboration with (−)-diisopinocampheylborane in THF at −28 °C. After oxidative hydrolysis, the chiral alcohol **155** was obtained in good yields and excellent ee (>99%). The absolute configuration was determined to be 6(*S*), applying Mosher's method.

3.3. Use of Chiral Catalysts

Examples of prochiral substrates desymmetrized through the intervention of chiral reactants acting as catalysts (i.e., in substoichiometric amount) are collected in this section.

Scheme 40[a]



[a] Reagents: (a) (*R*)-A, $ClCH_2CH_2Cl$, reflux and then Bu_4NF, THF, 0 °C; (b) HF-CH_3CN; (c) CH_3SO_2Cl, pyridine; and (d) 40% aqueous CH_3NH_2/CH_3OH, room temperature.

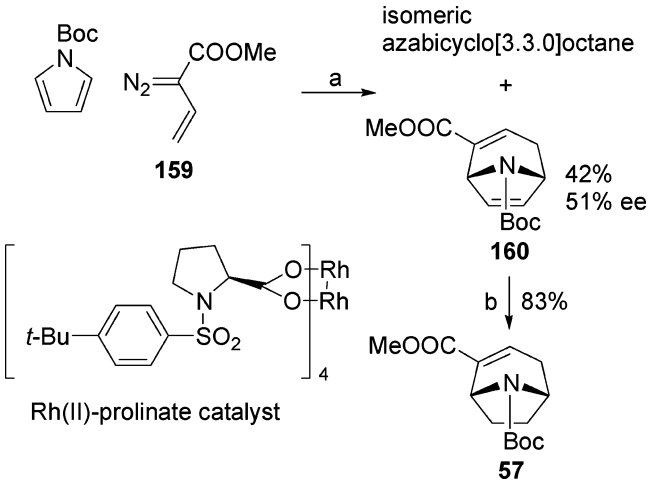
Synthetic chiral catalysts such as the [Rh{(*R*)-binap}-(cod)]$^+ClO_4^-$ and tetrakis-[*N*-(4-*tert*-butylbenzenesulfonyl)-L-prolinato]dirhodium as well as natural catalysts such as the amino acid proline and enzymes have been successfully used.

Thus, an enantiocontrolled asymmetric synthesis of 1(*S*),-5(*S*)-physoperuvine ***ent*-77** has been accomplished through desymmetrization of *meso*-3,7-bis-*tert*-butyldimethylsiloxycycloheptene **156** in the presence of a chiral rhodium(I)-binap catalyst (Scheme 40).[47] The optically active 4-*tert*-butyldimethylsiloxycycloheptanone **147** was produced in 71% ee by hydrolytic workup of the silylenolether intermediate **157**. The corresponding mesylate **158** was treated with aqueous methanolic methylamine furnishing the natural alkaloid physoperuvine, isolated as the hydrochloride.

Besides the use of a stoichiometric amount of a chiral auxiliary on the vinylcarbenoid reagent, Davies et al.,[25] in their approach to chiral nonracemic functionalized tropanes, explored the possibility of developing chiral rhodium(II) carboxylates as effective catalysts for the tandem asymmetric cyclopropanation/Cope rearrangement, already discussed in section 3.1.1 (Scheme 17). Indeed, rhodium(II) prolinate-catalyzed decomposition of the vinyldiazomethane **159** in the presence of *N*-Boc-pyrrole furnished the desired azabicyclo[3.2.1]octane **160** along with the isomeric azabicyclo-[3.3.0]octane (Scheme 41). However, in a series of experiments, the ee values did not exceed 51%, a rather disappointing result if compared with the reasonable level of asymmetric induction (65−70% de) obtained by using α-hydroxy esters as chiral auxiliaries on the carbenoid (Scheme 15). In any case, the authors converted the 3 + 4 annulated product to scalemic mixtures of known compounds, eventually resolved by recrystallization of their diastereomeric di-*p*-toluoyl tartrate salts.

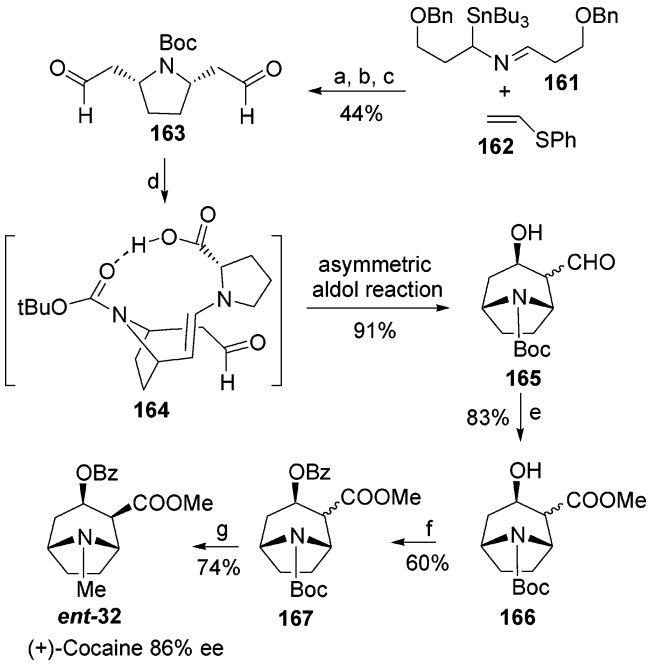
A total synthesis of (+)-cocaine via desymmetrization of a *meso*-dialdehyde has been recently reported,[48] with the

Scheme 41[a]



[a] Reagents: (a) Rh^{II}-prolinate catalyst, pentane reflux; and (b) H_2, $(PPh_3)RhCl$.

Scheme 42[a]

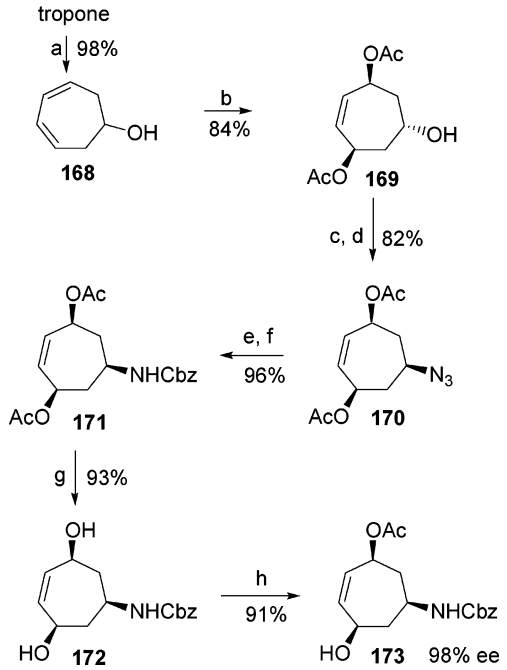


[a] Reagents: (a) *n*-BuLi; (b) $(Boc)_2O$; (c) i, Li, NH_3/THF; ii, TPAP, NMO; (d) L-proline, toluene; (e) i, $NaClO_2$; ii, CH_2N_2; (f) $(PhCO)_2O$, DMAP; and (g) i, TFA; ii, CH_2O, $NaBH_3CN$.

tropane skeleton being constructed with good enantioselectivity and moderate diastereoselectivity through a proline-catalyzed intramolecular enol-*exo*-aldol reaction (Scheme 42). The *meso*-dialdehyde **163** was obtained as the sole product using a highly stereoselective 2-azaallyllithium [3 + 2]-cycloaddition strategy.

The L-proline-catalyzed aldol reaction provided in 91% yield a 1:1 mixture of inseparable C(2) epimers **165** that were immediately converted to the methyl esters **166**. Gratifyingly, benzoylation of the secondary hydroxyl allowed the separation of diastereomers **167** by HPLC. Removal of the Boc carbamate from the desired C(2) axial epimer and reductive amination afforded cocaine with 86% ee but with opposite optical rotation with respect to the targeted natural alkaloid. The puzzling stereochemical outcome of the proline-catalyzed intramolecular aldol reaction could be due to

Scheme 43[a]



[a] Reagents: (a) $NaBH_4$, CH_3OH, −15 °C; (b) $Pd(OAc)_2$, MnO_2, benzoquinone, AcOH, $LiOAc(H_2O)_2$; (c) MsCl, Et_3N; (d) NaN_3, DMF; (e) Lindlar catalyst, H_2, EtOH; (f) $ClCO_2Bn$, EtOAc, aqueous Na_2CO_3; (g) K_2CO_3, CH_3OH; and (h) Amano P-30 lipase, isopropenyl acetate, 50 °C.

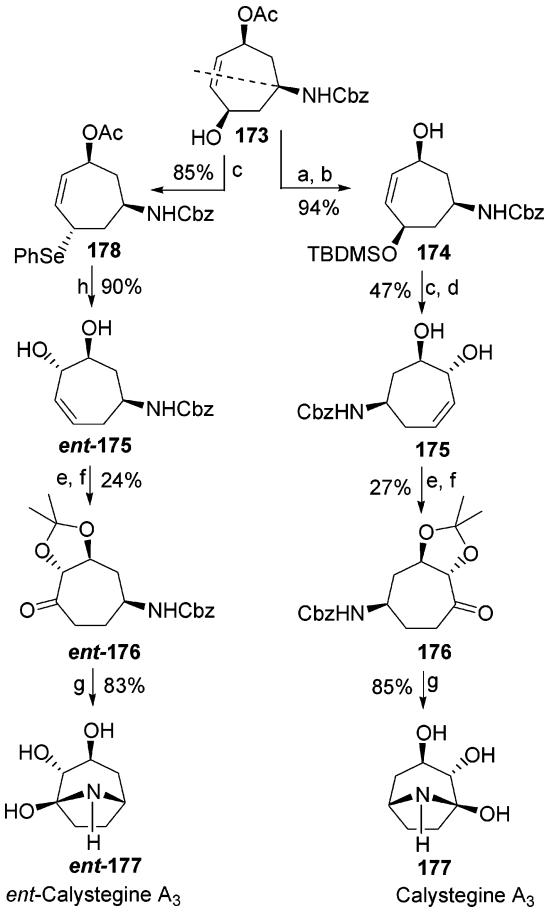
hydrogen bonding occurring between carboxy and carbamate groups in the transition state.

A new approach to the synthesis of (+)- and (−)-calystegine A_3 starting from 6-amino-2-cycloheptene-1,4-diol derivatives illustrates an interesting application of the enzymatic desymmetrization process in the tropane area (Schemes 43 and 44).[49]

Reduction of tropone with sodium borohydride gave the cycloheptadienol **168** that was subjected to the diacetoxylation conditions developed by Bäckvall et al.,[50] producing the symmetric diacetoxy alcohol **169** (Scheme 43). The nitrogen functionality was introduced by displacement of the corresponding mesylate with sodium azide. At this stage, it has been supposed that a functionality larger than the azide group would allow the enzyme to efficiently distinguish the two flanks of the stereocenter. Thus, the azide was hydrogenated to give the primary amine, in turn protected as benzyl carbamate **171**. The corresponding diol **172** was subsequently treated with Amano P-30 lipase in isopropenyl acetate and *tert*-butyl methyl ether, leading to the optically active monoacetate **173** in 98% ee through a high-yielding sequence of reactions. When the pseudosymmetry of this intermediate is taken advantage of, both enantiomers of calystegine A_3 were accessible (Scheme 44).

The stereodivergent syntheses started with different protecting-group manipulations, leading to the formation of compounds **174** and **178**, which underwent efficient stereoselective sigmatropic rearrangement to yield the enantiomeric cycloheptene derivatives **175** and ***ent*-175**, respectively. Unfortunately, the synthetic process suffered a barely regioselective hydroboration step, with the desired enantiomeric cycloheptanone derivatives **176** and ***ent*-176** being obtained in 27 and 25% yield, respectively. The subsequent order of deprotection of the diol and amine functionalities was important because of the acidic instability of the α,β-dihydroxy ketones. To this end, hydrogenolytic N-deprotec-

Scheme 44[a]



[a] Reagents: (a) TBDMSCl, DMF, imidazole; (b) NaCN, CH_3OH; (c) i, MsCl, Et_3N; ii, $NaBH_4$, Ph_2Se_2; (d) i, H_2O_2, THF, CH_2Cl_2; ii, HF, CH_3CN; (e) acetone, Amberlyst 15; (f) i, BH_3·DMS, Et_2O, −20 °C; ii, H_2O_2, NaOH; iii, PCC, 4 Å molecular sieves, CH_2Cl_2; (g) i, H_2, $Pd(OH)_2$, CH_3OH; ii, THF, H_2O, HCl; iii, NaOH, D_2O, pH > 11.0; and (h) i, H_2O_2, THF, CH_2Cl_2; ii, K_2CO_3, CH_3OH.

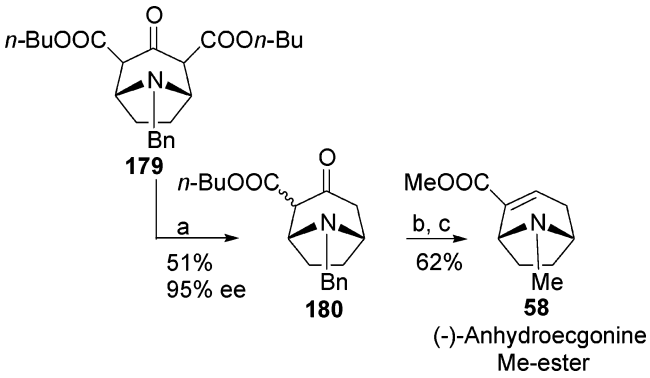
tion was anticipated to the acetonide hydrolysis. The enantiomeric calystegines A_3 were isolated as the hydrochlorides, owing to the tendency of the free bases to decomposition.

The PLE-mediated asymmetric dealkoxycarbonylation of *meso*-tropinone diesters, readily prepared by Robinson's tropinone synthesis, was utilized to open a new route to (−)-anhydroecgonine methyl ester (Scheme 45).[51]

Looking at suitable substrates and biocatalysts for desymmetrization, Node et al.[51] discovered the dibutyl ester **179** and PLE as the best choice (51% yield and 95% ee). Moreover, the appropriate nitrogen basicity was also found to be an important factor to reach high yield and ee. Both the ee and the absolute configuration of β-keto ester **180** could be indirectly known by its conversion to anhydroecgonine methyl ester **58**. Transesterification, N-alkyl substitution, carbonyl reduction, and dehydration were the reactions on the route to **58**. The specific rotation of the obtained alkaloid, matching that of the anhydroecgonine methyl ester derived from natural (−)-cocaine, led us to assess the stereochemical outcome of the enzymic desymmetrization.

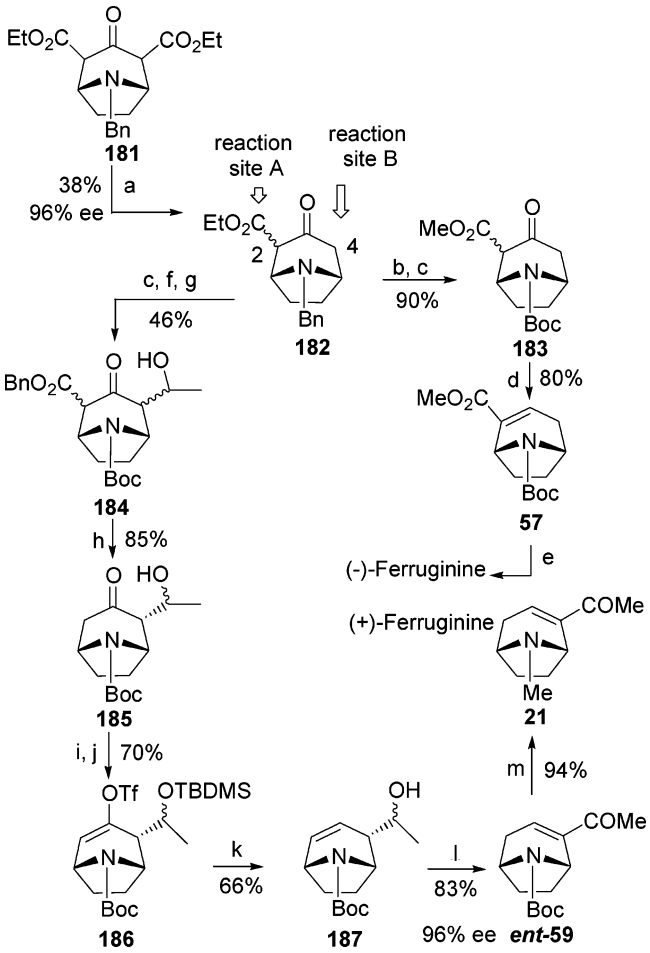
The Japanese group,[52] further utilizing the PLE-catalyzed asymmetric dealkoxycarbonylation strategy, developed a new enantiodivergent synthesis of ferruginine (Scheme 46). The optically active β-keto ester **182**, prepared from the prochiral

Scheme 45[a]



[a] Reagents: (a) PLE, phosphate buffer (pH 8.0); (b) i, Na, CH_3OH; ii, H_2, Pd/C; iii, CH_2O, HCOOH, $(CH_2O)_n$, CH_3OH; and (c) i, $NaBH_4$; ii, $POCl_3$.

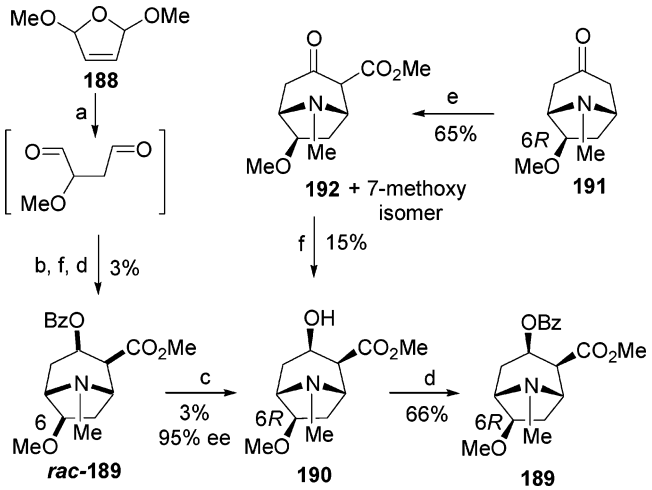
Scheme 46[a]



[a] Reagents: (a) PLE, phosphate buffer (pH 8.0); (b) Na, CH_3OH; (c) i, H_2, Pd/C; ii, $(Boc)_2O$, Et_3N; (d) i, Bu_4NBH_4; ii, $(CF_3CO)_2O$, Et_3N; (e) refs 11 and 25; (f) BnOH, DMAP, toluene reflux; (g) NaH, LDA, CH_3CHO, THF; (h) i, H_2, Pd/C; ii, HCl catalyzed, Δ; (i) TBDMSCl, imidazole, DMF; (j) KO-*t*-Bu, $PhNTf_2$, THF; (k) i, $Pd(OAc)_2$, Ph_3P, Et_3N, HCOOH; ii, TBAF; (l) i, PCC; ii, DBU; and (m) i, TFA; ii, CH_2O, $NaBH_3CN$.

tropinone-type diester **181**, was a suitable intermediate for a divergent approach to both (+)- and (−)-ferruginine by the introduction of a C_2 unit at C4 (path B) or by conversion of the ester moiety at C2 into an acetyl group (path A), respectively. In the last case, transesterification and N-protective-group exchange furnished the β-keto ester **183**, which, upon reduction and subsequent β elimination, afforded the known[11,25] α,β-unsaturated methyl ester **57**. Thus, by

Scheme 47[a]



[a] Reagents: (a) i, CH_3OH, H^+; ii, 0.2 M H_2SO_4; (b) monomethyl ester of acetonedicarboxylic acid, CH_3NH_2·HCl, citrate buffer solution; (c) PLE, H_2O, 37 °C, pH 7.0; (d) PhCOCl, Et_3N, DMAP; (e) LDA, NC-CO_2Me, −78 °C; and (f) Na/Hg, pH 4.

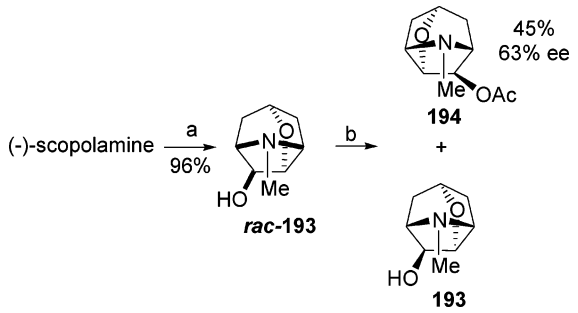
intercepting previous syntheses, the present approach represents a formal asymmetric synthesis of (−)-ferruginine. Instead, a completely new approach was developed to obtain its enantiomer. The 1-hydroxyethyl group insertion at C4 of the tropane framework gave compound **184**, which was easily transformed into **185** by one-pot hydrogenolysis−decarboxylation. The other salient chemical transformations were the palladium(0)-catalyzed reduction of the triflate **186**, the oxidation of the homoallylic alcohol **187**, and subsequent double-bond isomerization giving the conjugated enone ***ent*-59** in good yield and 96% ee. Eventually, (+)-ferruginine **21** was obtained following the classical protocol.

4. Starting from Racemates: Enzymatic Kinetic Resolutions

To obtain one of the two enantiomers, a racemic mixture has to be resolved; as stated in the Introduction, only papers taking advantage of enzymatic kinetic resolution processes are collected and discussed in this section. Thanks to the existence of two diastereomeric transition states, which must be different in energy, in an enzymatically controlled reaction, one of the enantiomers reacts faster than the other one. In this way, if the reaction is stopped before completion, the starting material will be enriched in the slower reacting enantiomer.

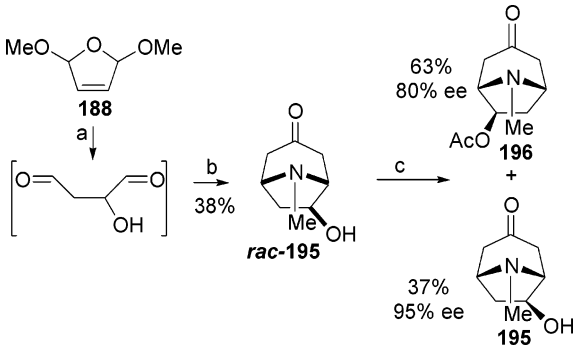
The PLE-catalyzed benzoyl ester hydrolysis of the racemic mixture of two-carbon bridge methoxylated cocaine analogue ***rac*-189** was employed for achieving its optical resolution (Scheme 47).[53] The chiral nonracemic **189** and hydroxyester **190** were recovered with 82 and 95% ee, respectively. However, the practicability of the method was diminished because of the inadequate chemical yield (35 and 3%, respectively). To elucidate the enantiopreference of the enzyme in the kinetic resolution step, the authors prepared the optically active **189** by an independent synthetic route featuring a problematic regioselective methoxycarbonylation of the known enantiopure 6(*R*)-*exo*-methoxytropinone **191**. The successful enantiospecific synthesis of the cocaine analogue **189** led us indirectly to assign the absolute configuration of the chiral compounds formed in the PLE-catalyzed hydrolysis.

Scheme 48[a]



[a] Reagents: (a) saponification; and (b) Chirazyme L-6, CH_3CN, vinyl acetate.

Scheme 49[a]



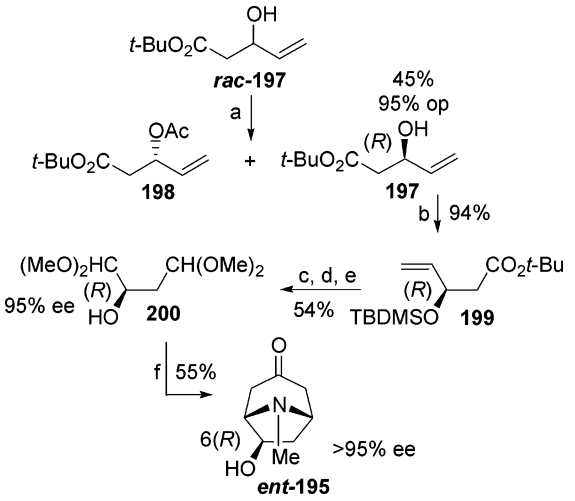
[a] Reagents: (a) 3 N HCl; (b) CH_3NH_2, NaOAc, acetonedicarboxylic acid; and (c) Chirazyme L-6, acetone, vinyl acetate.

A second example of the feasibility of enzymatic reactions for the synthesis of enantiomerically enriched tropane alkaloids is offered by the lipase-mediated resolution of the known tropane derivatives scopoline ***rac*-193** and 6-hydroxytropinone ***rac*-195** (Schemes 48 and 49).[54] The racemic starting materials were prepared following reported protocols. In particular, saponification of the natural scopolamine afforded scopoline, whereas a modified Robinson procedure using 2,5-dihydro-2,5-dimethoxyfuran **188** as the 2-hydroxysuccinaldehyde precursor, served to prepare 6-hydroxytropinone. After an extensive study by screening a variety of lipases at different temperatures in different solvents and in the presence of vinyl acetate as an acyl donor, the authors found the Chirazyme L-6 from *Pseudomonas* sp. as the best enzyme for this purpose.

As anticipated, because of the steric hindrance of the alcohol moiety, racemic scopoline turned out to be a difficult substrate for resolution (63% ee with 45% conversion). On the contrary, racemic 6-hydroxytropinone in acetone gave the corresponding (+)-enantiomer **195** with 95% ee in 35% yield. The protocol opened a convenient access to enantiomerically enriched tropane derivatives, although the enantiopreference of the enzyme could not be determined. Consequently, the absolute configurations of the chiral nonracemic compounds were only tentatively assigned.

The original and classical Mannich-type construction for the tropane skeleton[4] has been widely employed to accede to functionalized tropane derivatives of relevant value for pharmacological studies. Using acetonedicarboxylic acid, methylamine hydrochloride, and succindialdehyde as the three component compounds, the achiral tropinone is formed. However, when succindialdehyde was simply replaced with 2-hydroxy succindialdehyde, chiral racemic tropanes could be formed (Scheme 49).

Scheme 50[a]



[a] Reagents: (a) PS-C lipase, vinyl acetate, pentane; (b) TBDMSCl, imidazole, DMF; (c) i, O_3, CH_3OH, −78 °C and then $(CH_3)_2S$; ii, $CH(OCH_3)_3$, CH_3OH, *p*-TsOH, 0 °C; (d) i, DIBAH, toluene −78 °C; ii, $CH(OCH_3)_3$, CH_3OH, *p*-TsOH, 0 °C; (e) TBAF, THF; (f) i, HCl; ii, CH_3NH_2·HCl, acetonedicarboxylic acid, citrate buffer.

Although malic acid has been extensively used as the chiral educt in many asymmetric syntheses,[55] no enantioselective variant of the Robinson-type reaction featuring malic aldehyde as the chiral component has been described in the literature. It was anticipated that the use of 2(*R*)- or 2(*S*)-hydroxy succindialdehyde (malic aldehyde) as a chiral control element in the classical biomimetic construct for the tropane skeleton would lead enantioselectively to 6(*R*)- or 6(*S*)-hydroxy tropinone.[56] The synthetic plan to the required C4-starting chiral material benefited from published reports related to the synthesis of *tert*-butyl (*R*)-3-hydroxy-4-pentenoate **197** (Scheme 50). The latter compound constituted a formidable precursor, having one stereogenic center and two different functional groups at both ends, which could be taken into aldehyde groups by oxidation or reduction, respectively.

The kinetic resolution of the racemic β-hydroxy ester performed via lipase-catalyzed esterification with vinyl acetate afforded a sufficient amount of enantiopure material **197** to go on with the synthetic project. Thus, after the secondary hydroxyl group was protected as its *tert*-butyldimethylsilyl ether **199** under standard conditions, ozonolysis served to establish the required four-carbon chain. In details, quenching with Me_2S and treatment at 0 °C with methanol and trimethyl orthoformate in the presence of *p*-toluenesulfonic acid gave the α-hydroxyaldehyde protected as the corresponding dimethyl acetal. Reduction of the *tert*-butyl ester to a formyl group by the action of diisobutylaluminum hydride at −78 °C and then its protection furnished the tetraacetal **200**, a chiron of the pivotal malic dialdehyde. Indeed, compound **200** worked perfectly as a component in the classical Robinson−Schöpf protocol; the levorotatory enantiopure 6-*exo*-hydroxy tropinone ***ent*-195** formed with complete diastereo- and enantioselectivity. In such a way, an alternative route to this interesting chiral tropane derivative was opened. Importantly, the approach served to confirm the absolute configuration for the enantiopure materials reported in the previously discussed enzymic resolution (Scheme 49).

In addition, the stereochemical outcome proved the D-malicaldehyde to be configurationally stable under the reaction conditions, a fact not completely predictable. However, a careful inspection of the chemical literature showed that a parallel behavior has been already described for D- and L-tartaraldehydes[17,18] (see section 2.3).

5. Conclusions

The tropane alkaloid family contains a large array of natural products sharing a common 8-azabicyclo[3.2.1]octane skeleton, endowed with numerous and remarkable biological activities. Substances in this family have been traditionally known and used for centuries in folk medicine.

Since the middle of the 19th century, the elucidation of their structure and their synthesis have contributed to no small degree to the development of organic chemistry. Given the diverse range of activities displayed by molecules based on the tropane framework, it is reasonable to expect the discovery of new and interesting properties displayed by analogues based on this framework. Therefore, it is not surprising that tropane-based compounds continue to attract the attention of researchers calling for the development of new synthetic methodologies to reproduce these natural products and synthesize their analogues stereoselectively, improving the existing methods.

6. Acknowledgment

The authors thank Mr. L. A. Costache for his help with the English version. Financial support has been granted by MIUR (COFIN 2004) and the University of Ferrara.

7. References

(1) (a) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435. (b) O'Hagan, D. *Nat. Prod. Rep.* **1997**, *14*, 637. (c) Fodor, G.; Dharanipragada, R., *Nat. Prod. Rep.* **1994**, *11*, 443. (d) Lounasmaa, M.; Tamminen, T. *The Tropane Alkaloids in Alkaloids*; Academic Press: New York, 1993; pp 1−114.
(2) Dräger, B. *Nat. Prod. Rep.* **2004**, *21*, 211.
(3) Prelog, V.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 567.
(4) (a) Willstätter, R. *Ber.* **1896**, *29*, 936. (b) Willstätter, R. *Liebigs Ann. Chem.* **1903**, *326*, 23. (c) Robinson, R. *J. Chem. Soc.* **1917**, *111*, 762. (d) Schöpf, C.; Lehman, G. *Liebigs Ann. Chem.* **1935**, *518*, 1.
(5) Duclos, O.; Duréault, A.; Depezay, J. C. *Tetrahedron Lett.* **1992**, *33*, 1059.
(6) Duclos, O.; Mondange, M.; Duréault, A.; Depezay, J. C. *Tetrahedron Lett.* **1992**, *33*, 8061.
(7) (a) Boyer, F. D.; Lallemand, J. Y. *Synlett* **1992**, 969. (b) Boyer, F. D.; Lallemand, J. Y. *Tetrahedron* **1994**, *50*, 10443.
(8) (a) Skaanderup, P. R.; Madsen, R. *Chem. Commun.* **2001**, 1106. (b) Skaanderup, P. R.; Madsen, R. *J. Org. Chem.* **2003**, *68*, 2115.
(9) Boyer, F. D.; Hanna, I. *Tetrahedron Lett.* **2001**, *42*, 1275.
(10) Marco-Contelles, J.; de Opazo, E. *J. Org. Chem.* **2002**, *67*, 3705.
(11) Hernàndez, A. S.; Thaler, A.; Castells, J.; Rapoport, H. *J. Org. Chem.* **1996**, *61*, 314.
(12) Lin, R.; Castells, J.; Rapoport, H. *J. Org. Chem.* **1998**, *63*, 4069.
(13) Turner, S. C.; Zhai, H.; Rapoport, H. *J. Org. Chem.* **2000**, *65*, 861.
(14) Aggarwal, V. K.; Astle, C. J.; Rogers-Evans, M. *Org. Lett.* **2004**, *6*, 1469.
(15) Kim, S.; Hayashi, K.; Kitano, Y.; Tada, M.; Chiba, K. *Org. Lett.* **2002**, *4*, 3735.
(16) Barco, A.; Benetti, S.; De Risi, C.; Marchetti, P.; Pollini, G. P.; Zanirato, V. *Tetrahedron* **1999**, *55*, 5923.
(17) (a) Zeile, K.; Heusner, A. *Chem. Ber.* **1957**, 1869. (b) Stern, R.; Wasserman, H. H. *J. Org. Chem.* **1959**, *24*, 1689.
(18) Hardegger, E.; Furter, H. *Helv. Chim. Acta* **1957**, 872.
(19) Bourne, E. J.; McSweeney, G. P.; Stacey, M.; Wiggins, L. F. *J. Chem. Soc.* **1952**, 1408.
(20) Fischer, H. O. L.; Appel, H. *Helv. Chim. Acta* **1934**, *17*, 1574.
(21) Abernethy, J. L. *J. Chem. Ed.* **1956**, *33*, 88.
(22) (a) Dhavale, D. D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1989**, *54*, 4100. (b) Krief, A.; Dumont, W.; Pasau, P.; Lecomte, Ph. *Tetrahedron* **1989**, *45*, 3039.

(23) (a) Simoni, D.; Roberti, M.; Rondanin, R.; Baruchello, R.; Rossi, M.; Invidiata, F. P.; Merighi, S.; Varani, K.; Gessi, S.; Borea, P. A.; Marino, S.; Cavallini, S.; Bianchi, C.; Siniscalchi, A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 823. (b) Simoni, D.; Rossi, M.; Bertolasi, V.; Roberti, M.; Pizzirani, D.; Rondanin, R.; Baruchello, R.; Invidiata, F. P.; Tolomeo, M.; Grimaudo, S.; Merighi, S.; Varani, K.; Gessi, S.; Borea, P. A.; Marino, S.; Cavallini, S.; Bianchi, C.; Siniscalchi, A. *J. Med. Chem.* **2005**, *48*, 3337.
(24) Moss, G. P. *Pure Appl. Chem.* **1996**, *68*, 2193.
(25) (a) Davies, H. M. L.; Huby, N. J. S. *Tetrahedron Lett.* **1992**, *33*, 6935. (b) Davies, H. M. L.; Matasi, J. J.; Hodges, L. M.; Huby, N. J. S.; Thornley, C.; Kong, N.; Houser, J. H. *J. Org. Chem.* **1997**, *62*, 1095.
(26) Pham, V. C.; Charlton, J. L. *J. Org. Chem.* **1995**, *60*, 8051.
(27) Rigby, J. H.; Pigge, F. C. *J. Org. Chem.* **1995**, *60*, 7392.
(28) (a) Hall, A.; Bailey, P. D.; Rees, D. C.; Wightman, R. H. *Chem. Commun.* **1998**, 2251. (b) Hall, A.; Bailey, P. D.; Rees, D. C.; Rosair, G. M.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 329.
(29) Ray, A. B.; Kabuto, C. *Heterocycles* **1982**, *19*, 1233.
(30) McPhail, A. T.; Pinder, A. R. *Tetrahedron* **1984**, *40*, 1661.
(31) Sahai, M.; Ray, A. B. *J. Org. Chem.* **1980**, *45*, 3265.
(32) Faitg, T.; Soulié, J.; Lallemand, J. Y.; Ricard, L. *Tetrahedron: Asymmetry* **1999**, *10*, 2165.
(33) Soulié, J.; Faitg, T.; Betzer, J. F.; Lallemand, J. Y. *Tetrahedron* **1996**, *52*, 15137.
(34) (a) Gauthier, I. G.; Royer, J.; Husson, H. P. *J. Org. Chem.* **1997**, *62*, 6704. (b) Gauthier, I. G.; Royer, J.; Husson, H. P. *Eur. J. Org. Chem.* **2002**, 1484.
(35) Agami, C.; Couty, F.; Rabasso, N. *Tetrahedron Lett.* **2001**,*42*, 4633.
(36) (a) Takahashi, T.; Kitano, K.; Hagi, T.; Nihonmatsu, H.; Koizumi, T. *Chem. Lett.* **1989**, 597. (b) Takahashi, T.; Fujii, A.; Sugita, J.; Hagi, T.; Kitano, K.; Arai, Y.; Koizumi, T. *Tetrahedron: Asymmetry* **1991**, *2*, 1379.
(37) Araldi, G. L.; Prakash, K. R. C.; George, C.; Kozikowski, A. P. *Chem. Commun.* **1997**, 1875.
(38) Prakash, K. R. C.; Trzcinska, M.; Johnson, K. M.; Kozikowski, A. P. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1443.
(39) Majewski, M.; Lazny, R. *J. Org. Chem.* **1995**, *60*, 5825.
(40) (a) Majewski, M.; Lazny, R. *Synlett* **1996**, 785. (b) Majewski, M.; Lazny, R.; Ulaczyk, A. *Can. J. Chem.* **1997**, *75*, 754.
(41) Lee, J. C.; Lee, K.; Cha, J. K. *J. Org. Chem.* **2000**, *65*, 4773.
(42) Zou, M. F.; Agoston, G. E.; Belov, Y.; Kopajtic, T.; Katz, J. L.; Newman, A. H. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1249.
(43) Hodgson, D. M.; Robinson, L. A.; Jones, M. L. *Tetrahedron Lett.* **1999**, *40*, 8637.
(44) Hodgson, D. M.; Lee, G. P.; Marriott, R. E.; Thomson, A. J.; Wisedale, R.; Witherington, J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2151.
(45) (a) Malinakova, H. C.; Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 3909. (b) Zhang, Y.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2006**, *128*, 465.
(46) Cramer, N.; Laschat, S.; Baro, A.; Frey, W. *Synlett* **2003**, 2175.
(47) Hiroya, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1995**, 2205.
(48) Mans, D. M.; Pearson, W. H. *Org. Lett.* **2004**, *6*, 3305.
(49) Johnson, C. R.; Bis, S. J. *J. Org. Chem.* **1995**, *60*, 615.
(50) Bäckvall, J. E.; Bystrom, S. E.; Nordberg, R. E. *J. Org. Chem.* **1984**, *49*, 4619.
(51) Node, M.; Nakamura, S.; Nakamura, D.; Katoh, T.; Nishide, K. *Tetrahedron Lett.* **1999**, *40*, 5357.
(52) Katoh, T.; Kakiya, K.; Nakai T.; Nakamura, S.; Nishide, K.; Node, M. *Tetrahedron: Asymmetry* **2002**, *13*, 2351.
(53) (a) Kozikowski, A. P.; Simoni, D.; Baraldi, P. G.; Lampronti, I.; Manfredini S. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 441. (b) Simoni, D.; Roberti, M.; Andrisano, V.; Manferdini, M.; Rondanin, R.; Kozikowski, A. P. *J. Org. Chem.* **1998**, *63*, 4834. (c) Simoni, D.; Roberti, M.; Andrisano, V.; Manferdini, M.; Rondanin, R.; Invidiata, F. P. *Farmaco* **1999**, *54*, 275.
(54) Cramer, N.; Laschat, S.; Baro, A. *Synlett* **2003**, 2178.
(55) (a) Coppola, G. M.; Schuster, H. F. *Chiral α-Hydroxy Acids in Enantioselective Synthesis*; Wiley-VCH: Weinheim, Germany, 2002, pp 167−313. (b) Gawronski, J.; Gawronska, K. *Tartaric and Malic Acids in Synthesis: A Source Book of Building Blocks, Ligands, Auxiliaries and Resolving Agents*; Wiley-VCH: Weinheim, Germany, 1999.
(56) Pollini, G. P.; De Risi, C.; Lumento, F.; Marchetti, P.; Zanirato, V. *Synlett* **2005**, 164.

CR050995+