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Stereodivergent routes in organic synthesis: Carbohydrates, amino acids, alkaloids and terpenes

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Table of contents

Stereodivergent routes in organic synthesis: Carbohydrates, amino acids, alkaloids and terpenes

Carmen Nájera,[a]* Francisco Foubelo,[a,b,c] José M. Sansano[a,b,c] and Miguel Yus[a]

The natural occurrence of enantio- and diastereomers is often encountered. In addition, the synthesis of these stereoisomers is important for structure determination and for the study of structure-activity-relationships. Stereodivergent routes simplify the access to these molecules starting from a common material. This review is focused on the synthesis of carbohydrates, amino acids, alkaloids and terpenes using this efficient strategy. In the case of carbohydrates, such as monosaccharides, carbasugars, aminosugars and azasugars, carbohydrates are usually employed as common starting materials. As a very common strategy, configurations of hydroxy groups are inverted by S_N2 methods playing with protection and deprotection processes. For the synthesis of acyclic α-AAs diastereoselective methods using mainly Garner's aldehyde have been described. Diastereodivergent routes allowed the synthesis of β-hydroxy- and β-amino-α-amino acids, as well as of β- and γ-amino acids. Heterocyclic and cyclic amino phosphonic acids were synthesized using diastereodivergent routes. Alkaloids containing five- and six-membered saturated azaheterocycles needed multistep stereodivergent routes as well as other alkaloids, such as enantiomers of balanol, vincamine, anatoxin and codeine and diastereomeric isochaetominines C and galanthamines. In the terpene field, sesquiterpenes β-santalene, α-curcumene and α-cuparenone and the diterpene scopadulcic acid A were synthesized using enantiodivergent routes.

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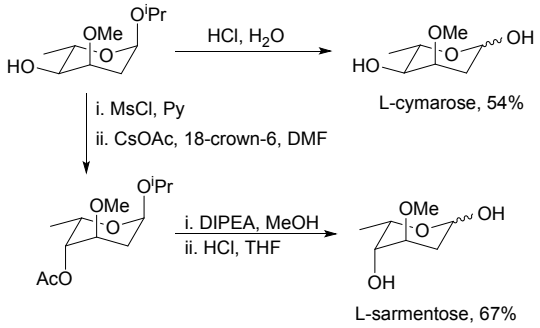
1. Introduction

The control of the regio- and stereochemistry in synthetic processes is a fundamental issue for the preparation of organic molecules. In order to access to different regio- and stereoisomers starting from the same substrate, efficient regiodivergent[1] and stereodivergent[2] catalytic methodologies have been developed. An alternative strategy is the development of stereodivergent multistep routes focused on the asymmetric synthesis of enantiomeric or/and diastereomeric natural products and other bioactive compounds also from the same starting material. In this review article, selective stereodivergent pathways (without stereoisomers separation) to give stereoisomeric products such as carbohydrates, amino acids, alkaloids and terpenes will be covered. Since both enantiomers of different diastereomers are often found in several groups of natural products and in bioactive molecules, minor but also major changes must be done in the synthetic routes. Processes involving separation of enantiomers or diastereomers will be not considered as stereodivergent routes.

2. Carbohydrates

2.1 Monosaccharides

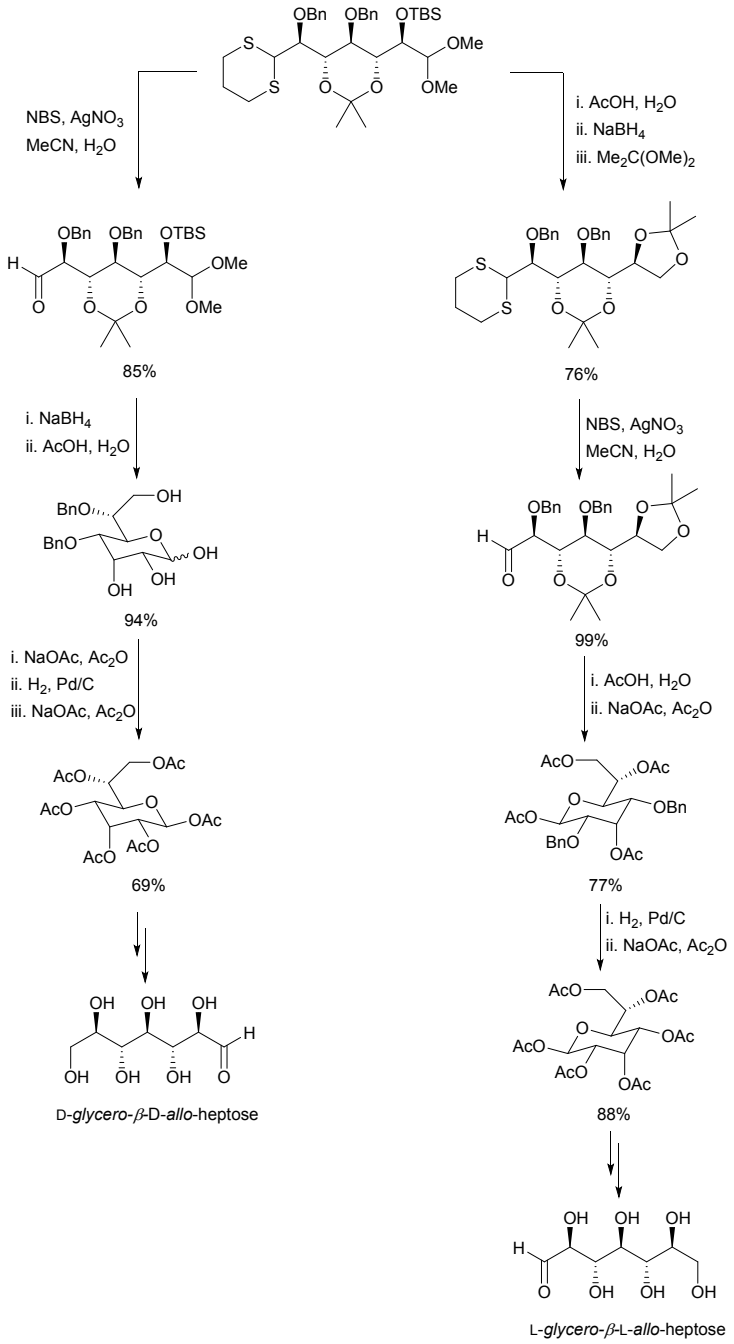
Diastereomeric divergent routes to the 2,6-dideoxyhexoses L-cymarose and L-sarmentose have been described by Brasholz and Reiβig.[3] Starting from a *ribo*-configured pyranoside, which was initially prepared from *O*-trityl-(*S*)-α-hydroxypropanal and 1-lithio-1-methoxyallene, by hydrolysis with aqueous HCl gave L-cymarose in 54% yield (Scheme 1). Alternatively, this pyranoside was epimerized to the corresponding acetate by mesylation and S_N2 reaction with CsOAc in the presence of 10-crown-6 and by subsequent acetate deprotection and hydrolysis free L-sarmentose was obtained. In this case, just an inversion of the configuration of the carbon atom bearing the hydroxy group at the 4-position of the pyranoside gave the other diastereomer.



Scheme 1 Diastereodivergent synthesis of L-cymarose and L-sarmentose.

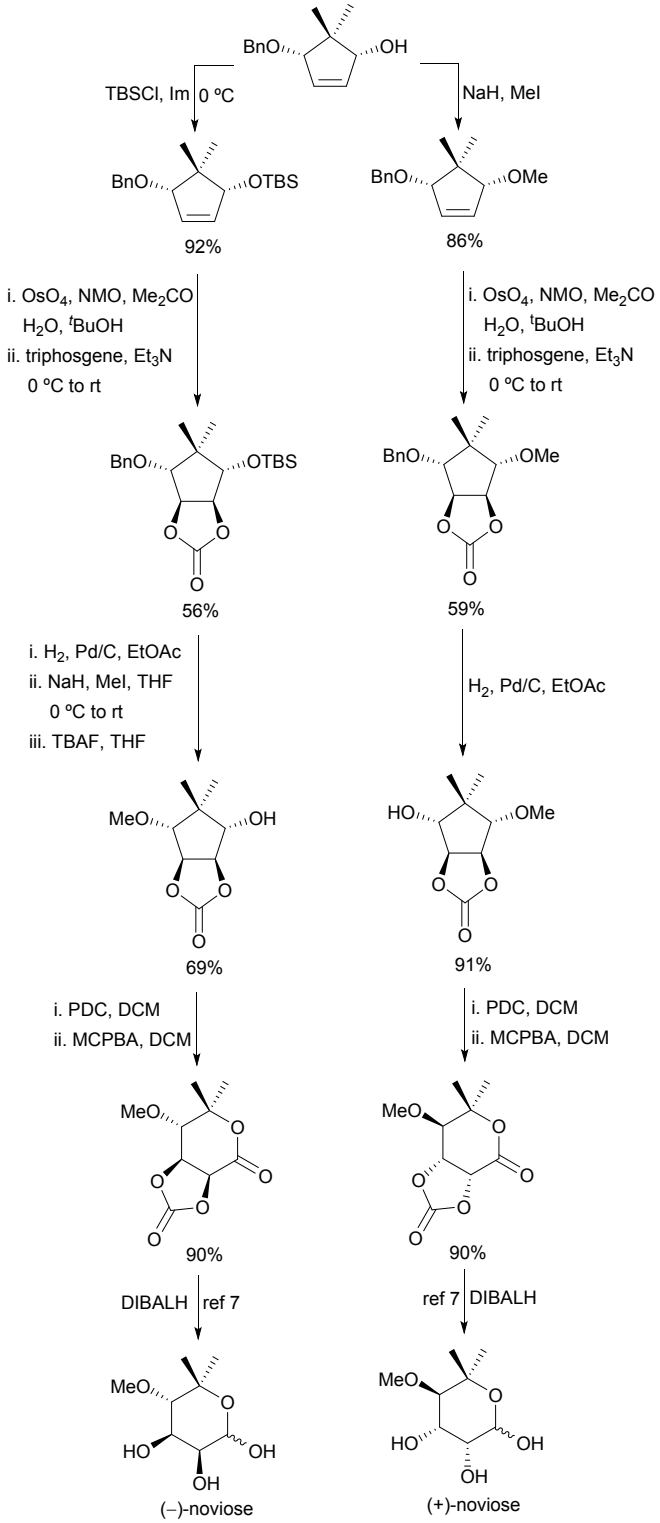
Enantiodivergent routes to D,D- and L,L-*glycero*-β-*allo*-heptopyranoses from 2,2-dioxan-5-one have been reported by Majewski and co-workers.[4] This dioxanone was transformed by aldol condensation into a deprotected dialdehyde, which is the common precursor of both enantiomers of *glycero*-*allo*-heptose (Scheme 2). Dithiane hydrolysis

of this compound using Corey's protocol ($NBS/AgNO_3$)[5] gave the corresponding aldehyde, which was reduced to the expected alcohol. Subsequent deprotection of the acetal and the TBS group afforded a pyranoside, which was further acetylated, debenzylated and acetylated again to provide the hexaacetate of D-*glycero*-β-D-*allo*-heptopyranose in 22% overall yield. For the L-enantiomer, a similar approach was performed, the main difference being the intramolecular acetalyzation of the aldehyde from the dithiane protection with the OH group at the 5-position giving a 14/86 mixture of separable α/β epimers. Final debenzylation and acetylation gave the hexaacetate L-*glycero*-β-L-*allo*-heptopyranose in 20% overall yield.



Scheme 2 Enantiodivergent synthesis of *glycero-allo*-heptoses

Noviose, a rare sugar present in many biologically active molecules such as novobiocin and tiacumicin, has been prepared by an enantiodivergent strategy to access both antipodes from (–)-pantolactone by Reddy and co-workers.[6] (–)-Pantolactone was transformed into the common intermediate, in which one allylic alcohol was protected as benzyl ether. Dihydroxylation of the benzyl silyl ether and treatment with triphosgene gave the corresponding carbonate (Scheme 3). Debenzylation followed by methylation and desilylation provided the alcohol, which was oxidized by PDC and subjected to Baeyer-Williger oxidation to give the corresponding lactone, which was reduced using DIBALH[7] to afford (–)-noviose. For the preparation of its (+)-enantiomer, the benzyl methyl ether was submitted to a similar route.

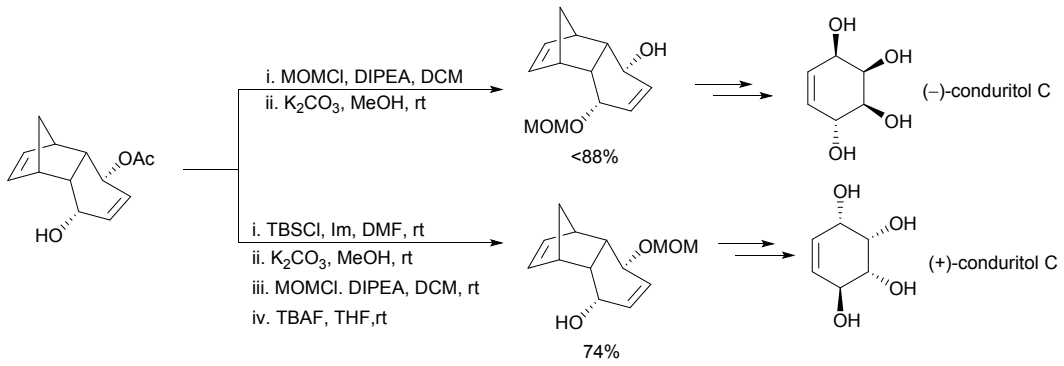


Scheme 3 Enantiodivergent routes for the synthesis of (−)- and (+)-noviose.

2.2 Carbasugars

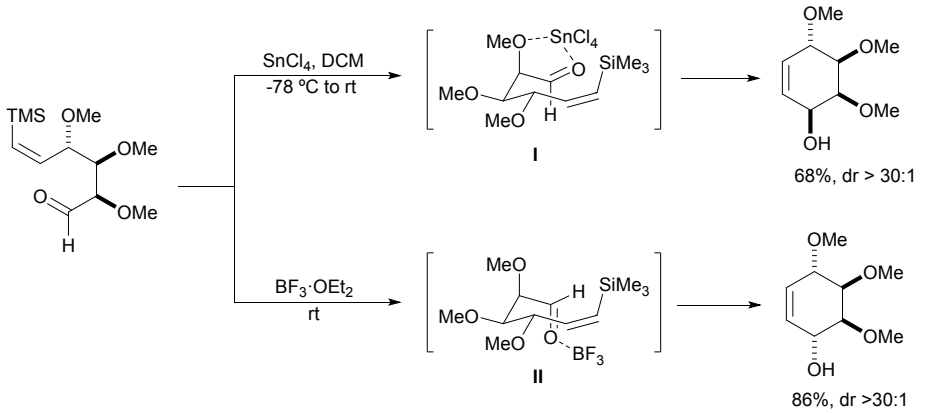
Monosacharides, in which a methylene group replaces the endocyclic oxygen are named carbasugars, are the most important class of glycomimetics. Natural and synthetic carbasugars have shown interesting biological activities mainly as antibiotics and

glycosidase inhibitors.[8] Enantio- and diastereodivergent syntheses of conduritols were described by Takano[9] and Weinreb[10] groups, respectively. Based on different protecting groups, the synthesis of both (–)- and (+)-conduritol C has been carried out from the Diels-Alder adduct allylic alcohol resulting from a lipase PS mediated resolution of the precursor *meso*-diol. This alcohol was protected by MOMCl, and then the acetate was hydrolyzed to a hydroxy group of the precursor of (–)-conduritol C (Scheme 4).[9] Enantiodivergently, silyl protection and hydrolysis of the acetate group, followed by MOM protection and desilylation, afforded the precursor of (+)-conduritol C.



Scheme 4 Enantiodivergent routes to conduritol C precursors.

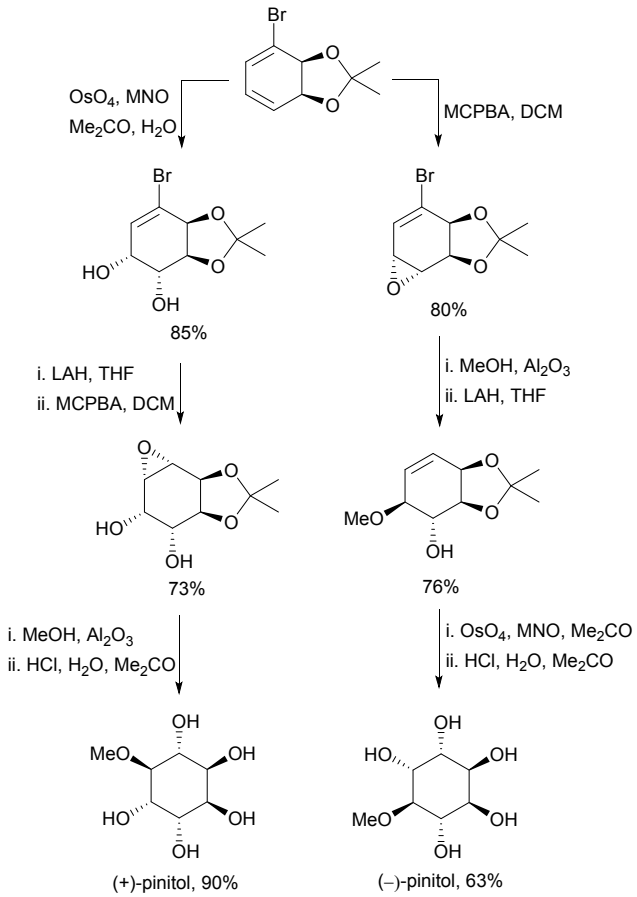
An unexpected cyclization of a racemic vinylsilane-aldehyde took place in a diastereodivergent manner depending on the Lewis acid used.[10] In the case of $SnCl_4$ or $BF_3{\cdot}OEt_2$ two diastereomeric trimethylated cyclitols were obtained (Scheme 5). The formation of the 1,2-*syn* isomer has been explained *via* a chelated chair-like transition state **I** induced by $SnCl_4$. However, using a nonchelating Lewis acid such as $BF_3{\cdot}OEt_2$ a complexation with the carbonyl group in transition state **II** can take place.



Scheme 5 Diastereodivergent routes to trimethylated conduritols.

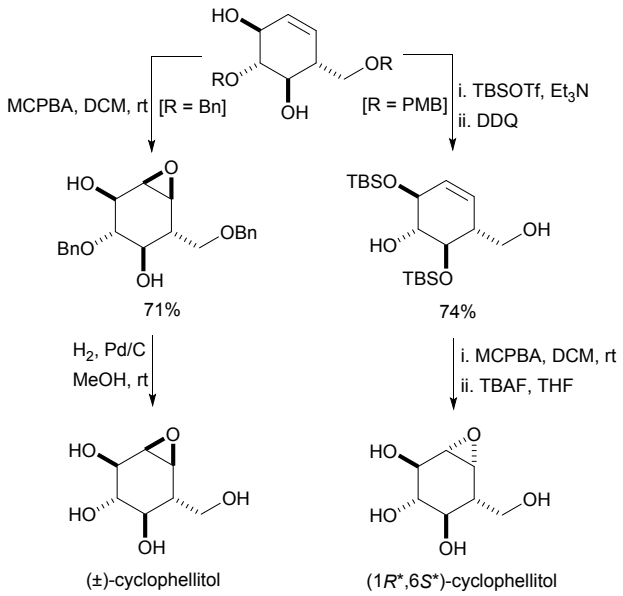
Pinitol, the monomethylated inositol, occurred in various plant sources with both enantiomers. Hudlicky and co-workers[11] reported an efficient enantiodivergent synthesis

of (+)-and (–)-pinitol from a common chiral diene prepared by microbial oxidation of bromobenzene by *Pseudomonas putida* 39-D.[12] Initial osmylation of the more electron-rich double bond, followed by dehalogenation, epoxidation and ring opening, gave (+)-pinitol (Scheme 6). On the other hand, epoxidation of the same double bond followed by methanolysis afforded a cyclohexene intermediate, which was osmylated to a diol providing (–)-pinitol after the final acetal deprotection.



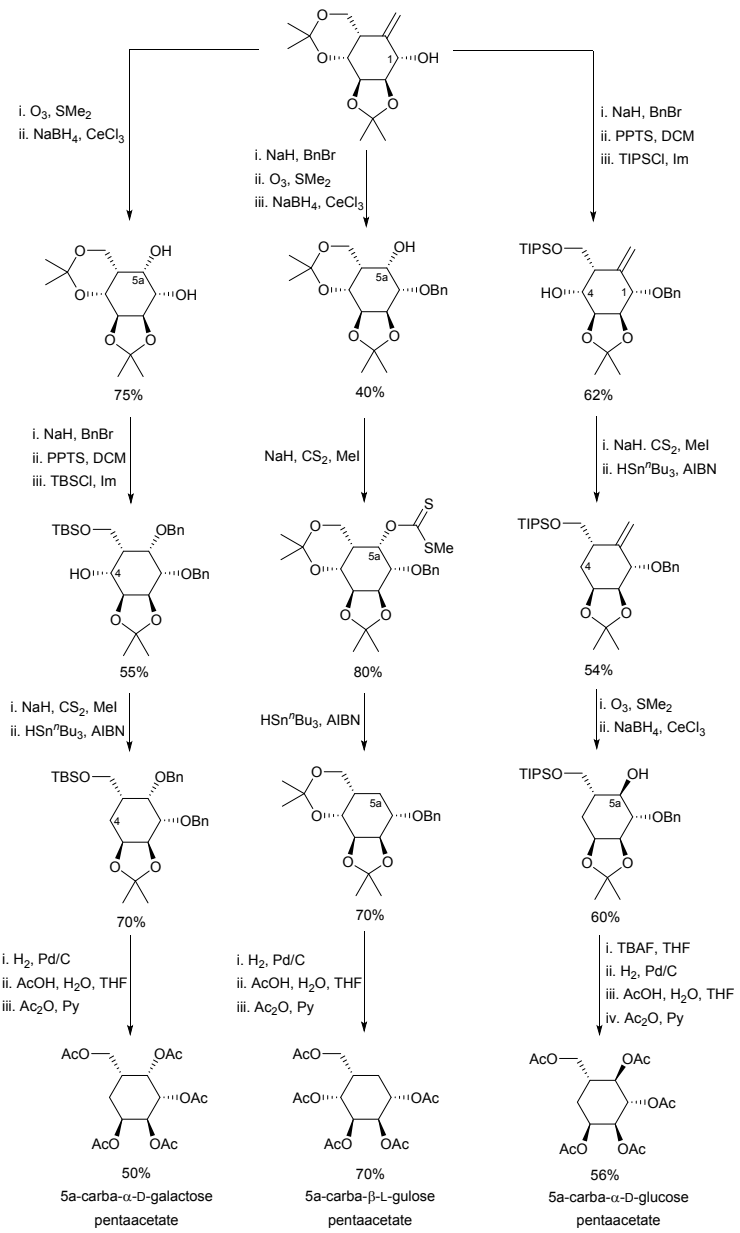
Scheme 6 Enantiodivergent routes to (+)- and (–)-pinitol.

Natural (+)-cyclophellitol has higher potency than castanospermine or norjirimycin as glycosidase inhibitor. Racemic cyclophellitol and (1*R**,6*S**)-cyclophellitol have been synthesized by the Arjona and Plumet group.[13] The diastereodivergent synthesis has been performed starting from a differently protected cyclohexenediol to control the key epoxidation step. The dibenzylated cyclohexenediol was treated with MCPBA and then deprotected to (±)-cyclophellitol, which was isolated and characterized as its tetraacetyl derivative in 80% yield after these two steps (Scheme 7). Whereas, the *p*-methoxybenzyl protected cyclohexenediol was disilylated and after PMB-deprotection with DDQ it was submitted to epoxidation and final desilylation giving diastereomeric (1*R**,6*S**)-cyclophellitol, which was also isolated as tetraacetate in 75% yield after the last two steps.



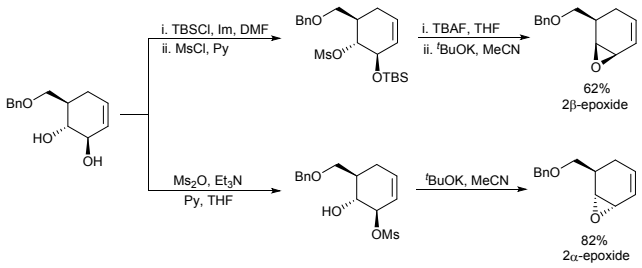
Scheme 7 Diastereodivergent routes to (±)-cyclophellitol and its (1*R**,6*S**)-diastereomer.

Three different carbasugars have been prepared by the Gómez and López group[14] starting from D-mannose based on a radical cyclization. The common intermediate is a polyhydroxylated *exo*-methylenecyclohexanone derivative. In the case of 5a-carba-α-D-galactose pentaacetate, the alkene was submitted to ozonolysis and reduction at C-5 affording the corresponding diol, which was further benzylated and the acetal group hydrolyzed. Silylation of the primary hydroxy group was followed by transforming it into the corresponding xanthate, which led to a 5a-carbagalactose derivative by treatment with tri-*n*-butyltin hydride. Conventional deprotection steps, followed by acetylation, yielded the corresponding tetraacetate (Scheme 8). For the preparation of 5a-carba-β-L-gulose pentaacetate the starting alkene was benzylated at 1-OH and submitted to ozonolysis and reduction with moderate diastereoselectivity (3:1 mixture). Deoxygenation provided a gulose derivative, which was submitted to common deprotection steps and acetylation to give the final tetraacetate. The synthetic route for 5a-carba-D-glucose implied inversion in the 5a-OH group and deoxygenation at C-4. Initial benzylation of the 1-OH, followed by selective deprotection of the acid labile primary isopropylidene acetal and by silyl protection of 6-OH, allowed selective deoxygenation at C-4. Further ozonolysis-reduction gave the desired isomer with moderate diastereoselectivity (2.5:1). Conventional deprotection steps and acylation provided the glucose derivative (Scheme 8).



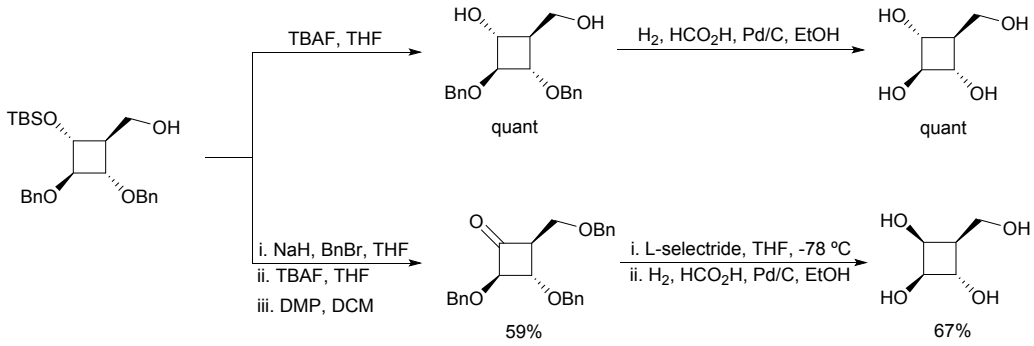
Scheme 8 Diastereodivergent routes to 5a-carba-α-D-galactose, 5a-carba-β-L-gulose and 5a-carba-α-D-glucose pentaacetates.

Diastereomeric carba-analogues of glycal-derived vinyl epoxides have been prepared from tri-*O*-acetyl-D-glucal by Di Bussolo and co-workers.[15] The common intermediate *trans* diol, obtained from the glucal derivative, was selectively monosilylated and mesylated (Scheme 9). Further desilylation and cyclization provided the (−)-2β-epoxide in 62% overall yield. Whereas, mesylation of the allylic hydroxyl group followed by base treatment afforded the (−)-2α-epoxide in 82% yield.



Scheme 9 Diastereodivergent routes to carba-analogues of D-galactal and D-allal-derived vinyl epoxides.

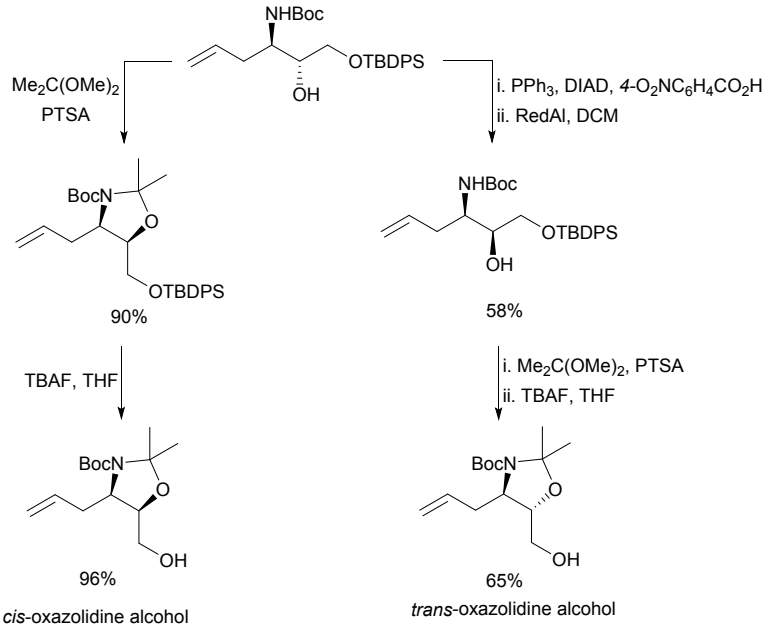
A stereodivergent synthesis of 4-membered carbasugars has been carried out from vitamin C by Compain and co-workers.[16] Diastereomeric carbasugars were prepared from a common intermediate 2,3-dibenzylated 4-silylated cyclobutylmethanol. This substrate was stepwise deprotected to the carbaoxetanose (1*R*, 2*r*, 3*S*, 4*s*)-4-(hydroxymethyl)cyclobutane-1,2,3-triol in quantitative yield (Scheme 10). On the other hand, benzylation of the primary alcohol followed by desilylation and oxidation with Dess-Martin periodinane (DMP) provided the corresponding ketone, which was reduced with L-Selectride giving the epimeric alcohol. Final deprotection by hydrogenolysis afforded cyclobutanic pseudogalactose (1*S*,2*R*,3*s*,4*s*)-4-(hydroxymethyl)cyclobutane-1,2,3-triol.



Scheme 10 Diastereodivergent routes to 4-membered carbasugars.

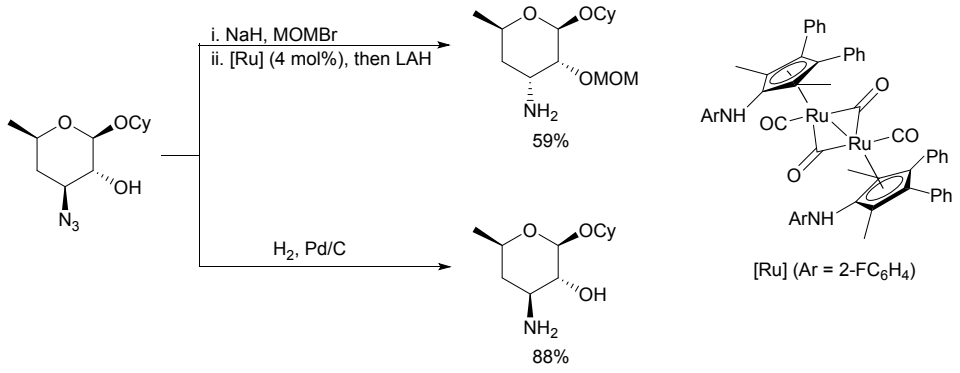
2.3 Aminosugars

Conduramines are aminocyclohexenetriols that also have significant glycosidase inhibitory activity being synthetic precursors of amino- and diaminocyclitols. Riera and co-workers[17] have described a diastereodivergent synthesis of *cis*- and *trans*-isomers of an oxazolidine alcohol, as building blocks for the synthesis of all isomers of deoxyconduramines, and after dihydroxylation of the double bond to aminocyclitols. Starting from a β-amino alcohol with the *anti*-configuration *cis*-oxazolidine was synthesized by reaction with 2,2-dimethoxypropane and desilylation (Scheme 11). For the *trans*-isomer the amino alcohol was submitted to Mitsunobu conditions and reduction to give the *syn*-amino alcohol, which was treated under the same reaction conditions to afford the *trans*-oxazolidine alcohol.



Scheme 11 Diastereodivergent routes to oxazolidine alcohols precursors of deoxyconduramines and aminocyclitols.

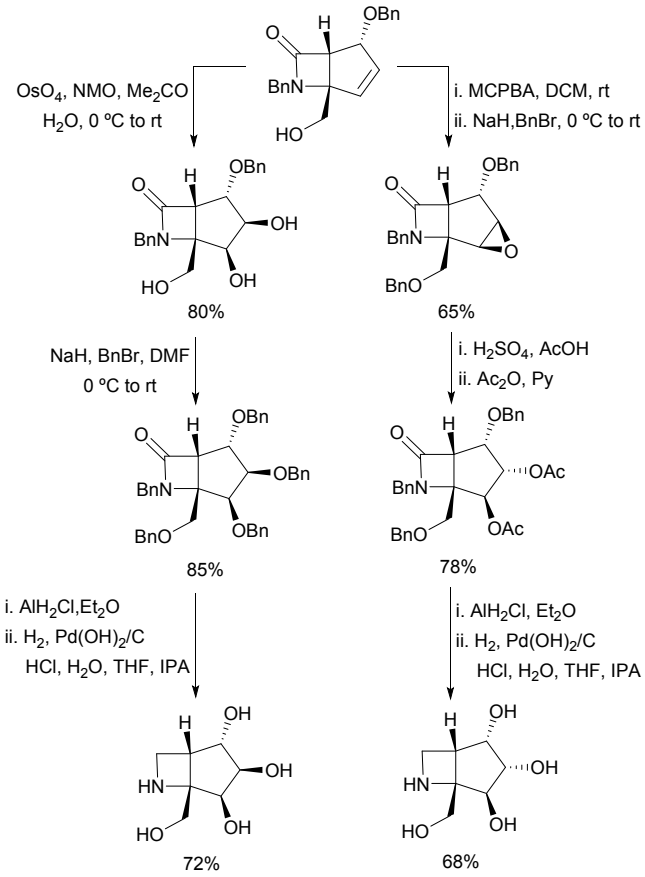
Based on diastereodivergent reduction of β-azido alcohols the Park and Rhee group reported the synthesis of 3,4,6-trideoxy-3-amino sugars.[18] The common 3-azido carbohydrate was treated with MOMCl to protect the 2-OH and then the azido group was reduced by Ru catalysis under photolytic conditions to the corresponding imine and then $LiAlH_4$ was added to produce the 2-MOM-protected (2*R*,3*R*)-isomer (Scheme 12). Whereas, by Pd-catalyzed hydrogenation the (2*R*,3*S*)-amino sugar was prepared. A new class of iminosugars has been recently reported by Compain and co-workers.[19]



Scheme 12 Diastereodivergent route to 3,4,6-trideoxy-3-amino sugars.

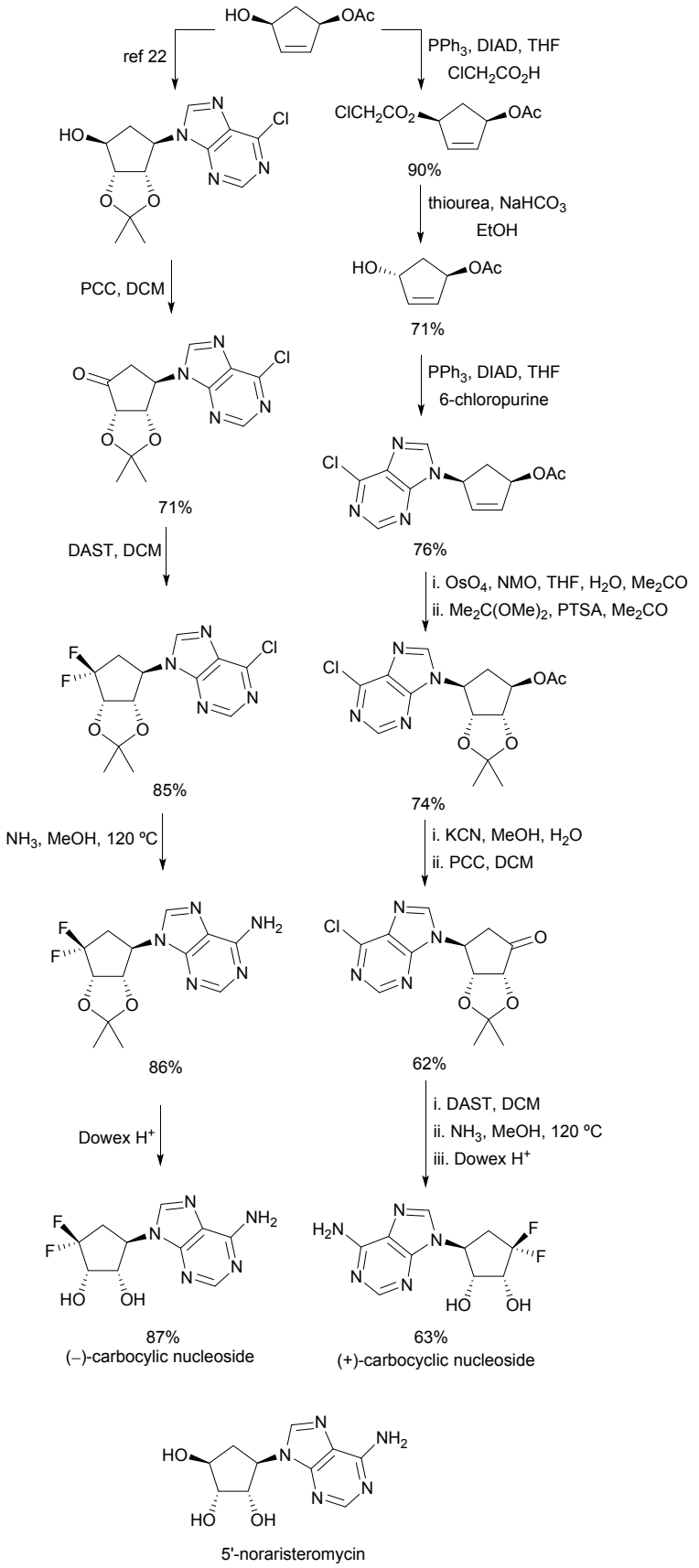
Polyhydroxylated bicyclic azetidines have been diastereodivergently prepared from the same 6-aza-bicyclo[3.2.0]heptane derivative. Initial dihydroxylation, followed by perbenzylation of the four hydroxy groups and subsequent reduction with AlH_2Cl and

reductive debenzylation the corresponding bicyclic iminosugar was obtained (Scheme 13). On the other hand, epoxidation and further benzylation gave the epoxide, which was opened with AcOH and acetylated. Final carbonyl reduction and Pd-catalyzed hydrogenation afforded the bicyclic analogue of 1-deoxygulonojirimycin.



Scheme 13 Diastereodivergent route to polyhydroxylated bicyclic azetidines.

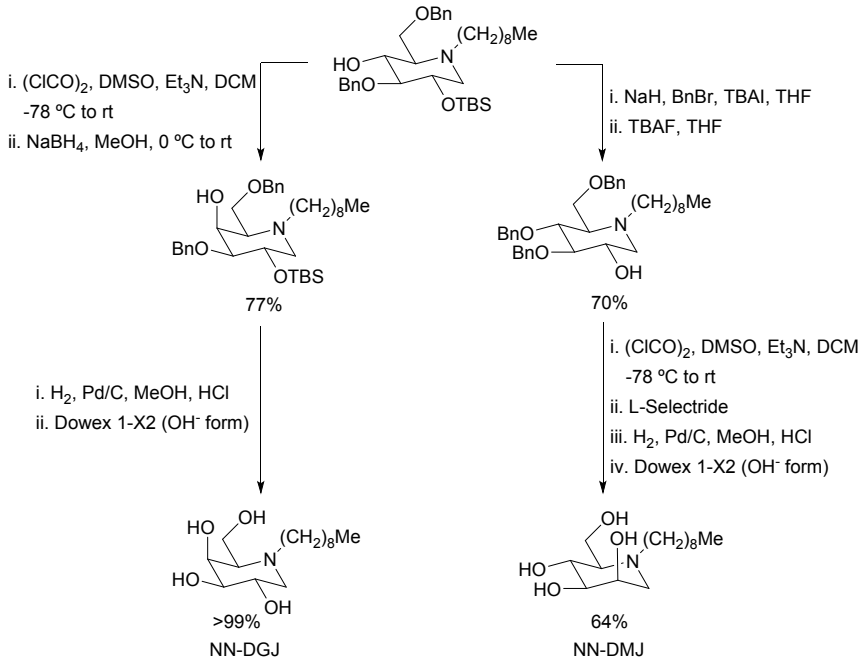
Enantiodivergent routes to 4,4'-difluoro analogue of 5'-noraristeromycin, a potential antiviral drug, have been carried out by Schneller and co-workers.[20] From (+)-(1*R*,4*S*)-4-hydroxy-2-cyclopenten-1-yl acetate[21] the carbocyclic nuceloside[22] was prepared, which was oxidized to a ketone (Scheme 14). The incorporation of the geminal difluoro moiety was performed with diethylaminosulfur trifluoride (DAST), which by ammonolysis and final deprotection with Dowex, provided (–)-5-(6-amino-9*H*-purin-9-yl)-3,3-difluorocyclopentane-1,2-diol. For the preparation of its enantiomer the starting material was submitted to Mitsunobu conditions using dichloroacetic acid in order to invert the configuration of the hydroxyl group. A second Mitsunobu reaction with 6-chloropurine, followed by dihydroxylation, isopropylidenation and deacetylation, produced the enantiomeric alcohol, which was oxidized and fluorinated to provide the corresponding (+)-enantiomer. Only the (–)-enantiomer displayed promising antiviral potential against vaccinia and cowpox and human cytomegalovirus.



Scheme 14 Enantiodivergent routes to 4,4'-difluoro analogue of 5'-noraristeromycin.

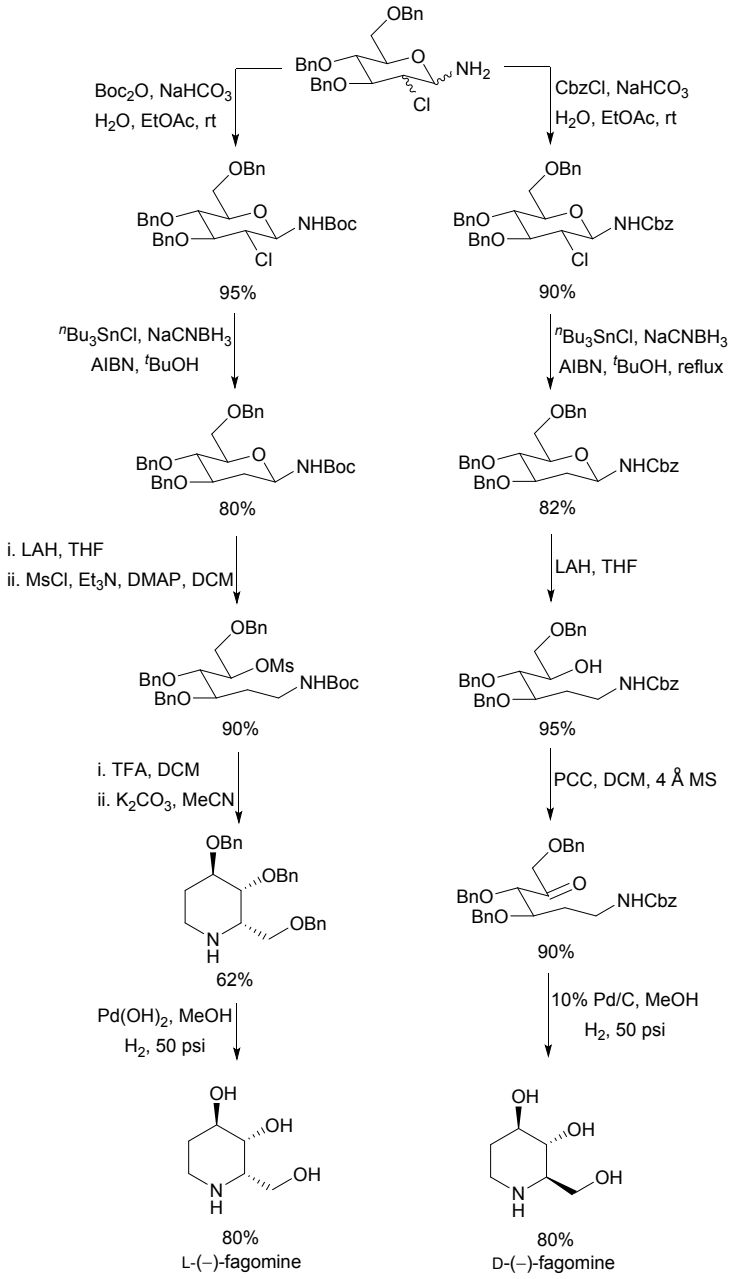
2.4 Azasugars

Polyhydroxylated piperidines (azasugars) containing a nitrogen atom in the place of the oxygen atomof the carbohydrate also posses biological activity as glycosidase inhibitors.[23] Diastereodivergent routes to *N*-alkylated 1-deoxygalactonojirimycin and 1-deoxymannojirimycin derivatives have been performed from a protected 1-deoxynijirimycin intermediate by the Campain and Martin group.[24] The stereodivergent strategy is based on the Swern oxidation of the free OH groups at C-2 and C-4, followed by hydride reduction. Starting from an azasugar the inversion was carried out at C-4 and also at C-2 to yield *N*-nonyl 1-deoxygalactonojirimycin (NN-DGJ) and *N*-nonyl 1-deoxymannojirimycin (NN-DMJ), respectively (Scheme 15).



Scheme 15 Diastereodivergent routes to *N*-nonyl 1-deoxygalactonojirimycin and 1-deoxymannojirimycin.

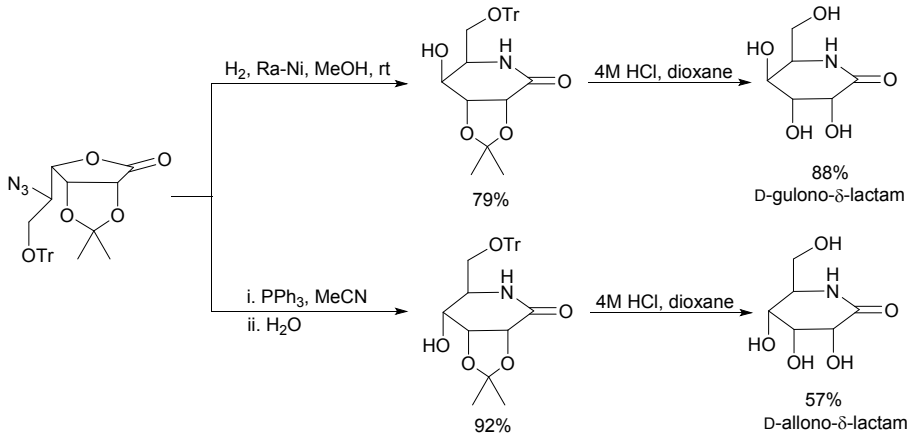
For diastereodivergent routes to D- and L-fagomines, with potent antihyperglycemic effect and having potentiation of glucose-induced insulin secretion,[25] a 2-chloroamine obtained from 3,4,6-tri-*O*-benzyl-D-glucal has been used as common substrate by Vankar and co-workers.[26] The main key features of the synthesis is the cyclization step *via* a S_N2 reaction in the case of L-(−)-fagomine, whereas in the other case an intramolecular reductive amination gave the other D-diastereomer (Scheme 16). Using the same divergent routes starting from 3,4,6-tri-*O*-benzyl-D-galactal, which was transformed into the 2-chloro azasugar, the corresponding L-(+)- and D-(+)-1,2-dideoxy-galactostatins were synthesized as well.



Scheme 16 Diastereodivergent routes to (–)- and (+)-fagomines.

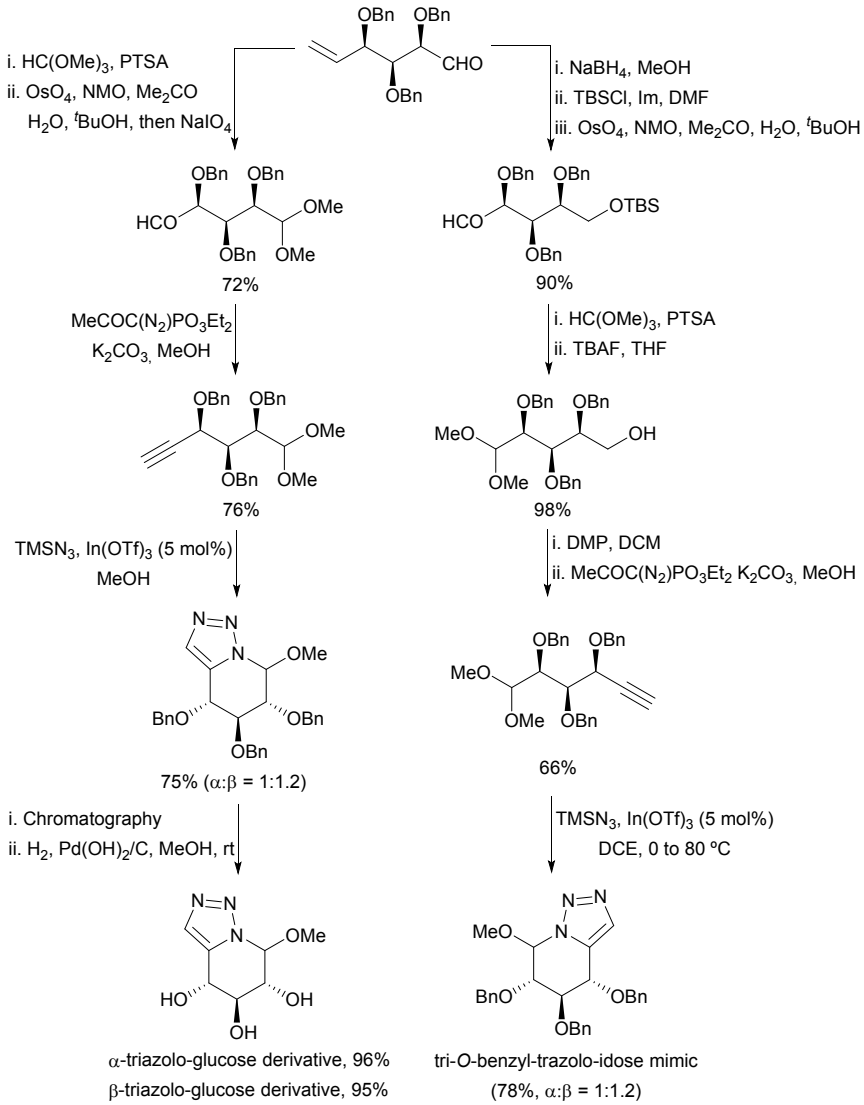
Nishimura and co-workers[27] reported a general route to all eight stereoisomeric δ-glyconic-δ-lactams (glucono-, mannono-, galactono-, talono-, altrono-, idono-, gulono- and allono-δ-lactam) from the corresponding γ-lactones for biological evaluation as glycosidase inhibitors. The strategy involved diastereodivergent δ-lactam formation with configurational retention or inversion at C-4 of a starting δ-lactone. For instance, D-gulono- and allono-δ-lactams were prepared from L-mannonic acid δ-lactone as shows Scheme 17. The starting compound is 2,3:5,6-di-*O*-isopropylidene-L-mannonic acid γ-lactone, which was transformed into an azide and used as common intermediate. By catalytic reduction with Raney-Ni the lactone was transformed into the protected D-glucono-δ-lactam, which was deprotected with hydrochloric acid in dioxane to provide the expected lactam in good yields. On the other hand, the azide was treated with PPh_3

and after hydrolysis the protected D-allono-δ-lactam was obtained. Final hydrolysis with aqueous HCl gave rise to the expected lactams.



Scheme 17 Diastereodivergent route to D-gulono- and D-allono-δ-lactams.

A chemical library of 1,2,3-triazolo-carbohydrate mimetics has been prepared by Taguchi and co-workers[28] starting from D-glucose, D-mannose and D-galactose. The diastereodivergent route consisted in a $In(OTf)_3$ catalyzed azidation-1,3-dipolar cycloaddition of 1,1-dimethoxyhex-5-yne derivatives with $TMSN_3$ as the key step to form 4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyridines. For example, the stereodivergent synthesis of triazolo-glucose/idose mimetics is illustrated in Scheme 18. Starting from the chiral 2,3,4-tri-*O*-benzylhex-5-enal, easily prepared from D-glucose, it was transformed into the dimethyl acetal and then after catalytic dihydroxylation into a 5,5-dimethoxypentanal derivative. The homologation under Ohira-Bestmann conditions using $MeCOC(N_2)PO_3Me_3$-K_2CO_3 gave the key alkyne to perform the azidation-intermolecular Huisgen reaction providing the corresponding cycloadduct as a mixture of α:β = 1:1.2 epimers. After chromatographic separation and hydrogenolysis the triazole-glucose mimetics were isolated. For the enantiodivergent synthesis of the triazolo-idose mimetic, the starting aldehyde was transformed into the enantiomeric 5,5-dimethoxypentanal derivative by reduction-silylation-dihydroxylation-acetalyzation-desilylation. This aldehyde was treated as before to afford the enantiomeric triazolo-idose mimetic.



Scheme 18 Enantiodivergent route to triazolo-glucose and idose mimetics.

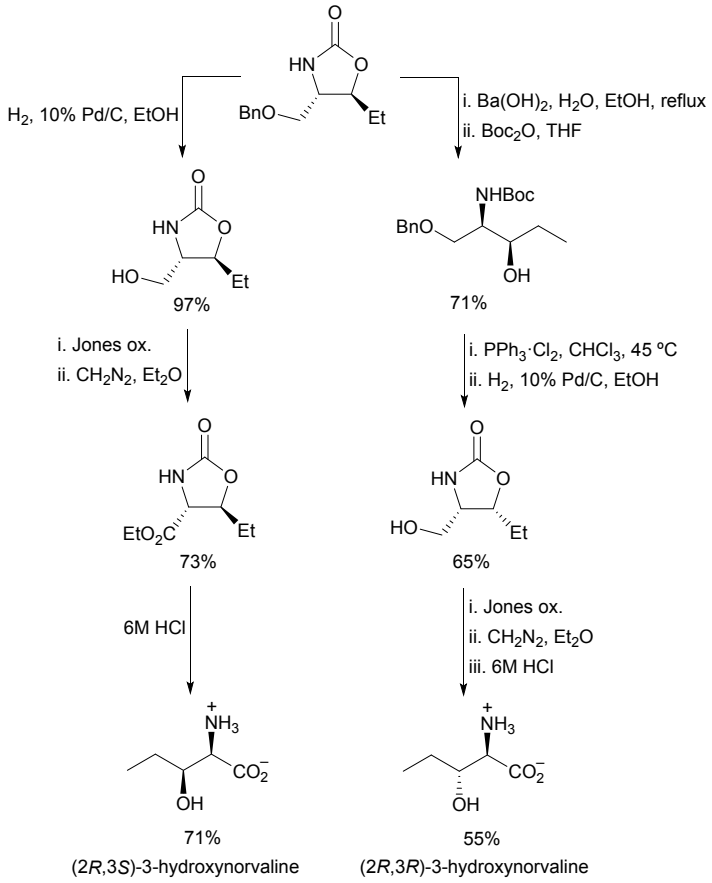
It can be concluded that stereodivergent routes to carbohydrates are mainly based on retention or inversion of the configuration of hydroxyl groups and using carbohydrates as starting chiral materials.

3. Amino acids and peptides

3.1 α-Amino acids

Natural and non-natural α-amino acids are an important class of compounds of chemical and biological significance and specially to be incorporated into a peptide. Therefore, a number of synthetic building blocks and templates, as well as asymmetric catalytic methods, have emerged in the last decades.[29] Diastereodivergent routes to β-hydroxy-α-amino acids such as threonine analogues have been described by Misiti and co-workers[30] starting from a 4,5-disubstituted oxazolidine-2-one. A *trans*-oxazolidin-2-one was the common intermediate for the preparation of (2*R*,3*S*)- and (2*R*,3*R*)-hydroxynorvalines

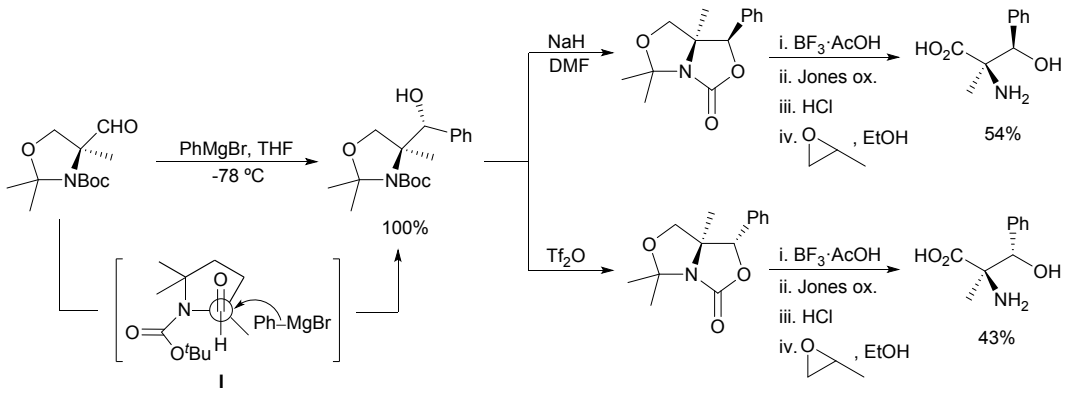
(Scheme 19). For the first amino acid, the oxazolidine-2-one was debenzylated and the primary hydroxyl group was oxidized and the acid esterified with diazomethane. Final hydrolysis with 6M HCl provided the mentioned α-amino acid. The synthesis of the (2*R*,3*R*)-diastereomer required an inversion of configuration at C-3. For this purpose the starting *trans*-oxazolidin-2-one was opened with $Ba(OH)_2$ followed by protection of the amino group. This Boc-protected β-amino alcohol was treated with the solid complex $Ph_3P{\cdot}Cl_2$ to give the *cis*-oxazolidin-2-one, which was submitted to the same transformations than the *trans*-derivative to provide the *anti*-β-hydroxynorvaline.



Scheme 19 Diastereodivergent routes to (2*R*,3*S*)- and (2*R*,3*R*)-3-hydroxynorvalines.

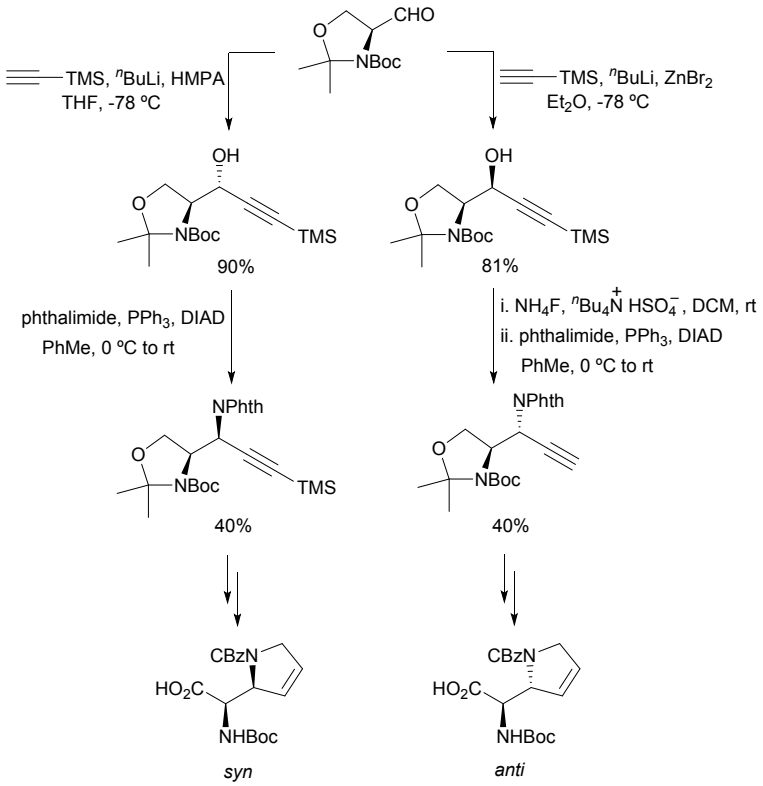
Garner's aldehyde[31] and its enantiomer are valuable building blocks for the asymmetric synthesis of α-amino acids.[32] The Avenoza and Cativiela group[33] has used the α-methyl derivatives as common starting materials for the diastereodivergent synthesis of all isomers of α-methyl-β-phenylserine. To (*S*)-*N*-Boc-*N,O*-isopropylidene-α-methyl-β-methylserinal was added phenylmagnesium bromide giving the *anti*-alcohol according to a non-chelating controlled Felkin-Ahn attack (**I**) on the less hindered face. Then cyclization promoted by NaH gave the bicyclic oxazolidine-2-one and, after deprotection of the acetonide moiety with the $BF_3{\cdot}AcOH$ complex followed by oxidation and acid hydrolysis, afforded (2*R*,3*R*)-α-methyl-β-methylserine (Scheme 20). For the synthesis of the (2*R*,3*S*)-diastereomer the *anti*-alcohol was treated with triflic anhydride to give the bicyclic oxazolidine-2-one with inversion of configuration at the benzylic

carbon atom. The same diastereodivergent routes have been carried out with the (*R*)-*N*-Boc-*N,O*-isopropylidene-α-methylserinal to provide (2*S*,3*S*)- and (2*S*,3*R*)-α-methyl-β-phenylserines. The same group has prepared α-methylthreonines by addition of MeMgBr Instead of PhMgBr) to the α-methyl Garner's aldehyde following similar diastereodivergent routes.[34]



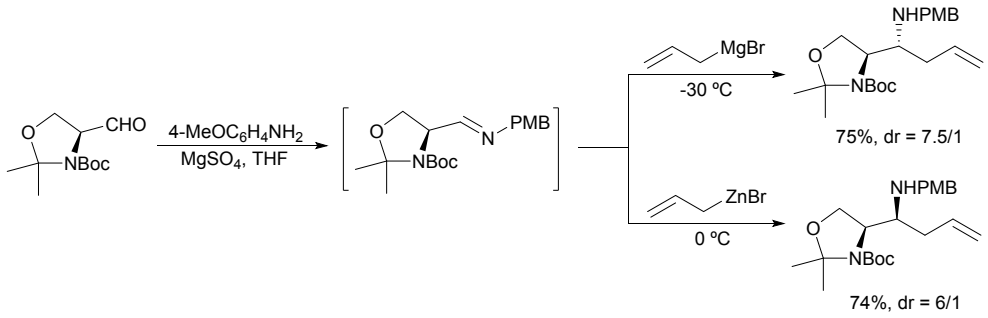
Scheme 20 Diastereodivergent routes to (2*R*,3*R*)- and (2*R*,3*S*)-α-methyl-β-phenylserines.

From Garner's aldehyde, Chattopadhyay and co-workers[35] designed a diastereodivergent route to epimeric 2-pirrolidinylglycine derivatives, precursors of α,β-diamino acids. The second stereocenter was stablished by addition of trimethylsilylethinyllithium in the absence or presence of $ZnBr_2$ followed by Mitsunobu-type amination with phthalimide (Scheme 21). Further transformations afforded *syn*- and *anti*-pyrrolidinylglycine derivatives.



Scheme 21 Diastereodivergent routes to *syn*- and *anti*-2-pyrrolidinylglycine derivatives.

Diastereodivergent synthesis of α,β-diamino acid building blocks has been carried out also from Gardner's aldehyde by the same group.[36] By formation of its imine derived from the condensation of the aldehyde with 4-methoxybenzylamine, the *in situ* allylation with allylmagnesium bromide at -30 ºC or with allylzinc bromide at 0 ºC provided the corresponding *anti*- and *syn*-homoallylic amines, respectively (Scheme 22). These amines were converted into different α,β-diamino acids.

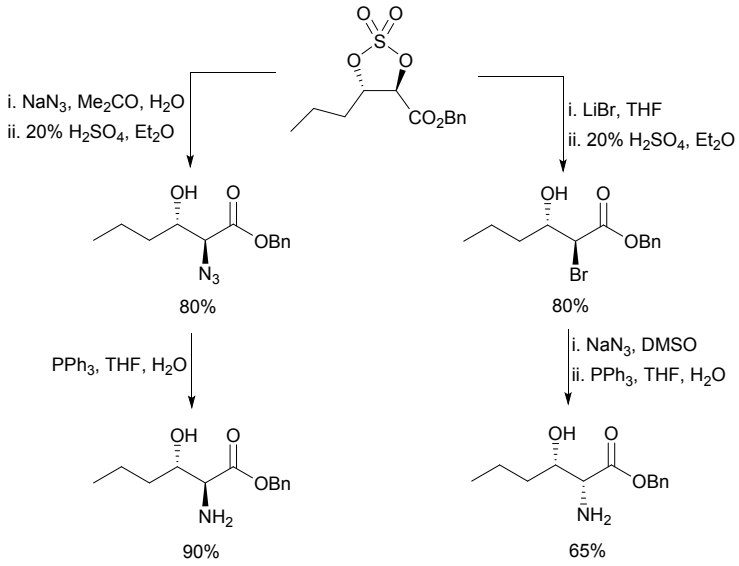


Scheme 22 Diastereodivergent route to *anti*- and *syn*-homoallylamines.

A diastereodivergent route to optically pure *syn*- and *anti*-β-substituted serine derivatives has been reported by Hruby and co-workers.[37] As an example, the common intermediate cyclic sulfate -prepared from the corresponding diol resulting by Sharpless asymmetric dihydroxylation in the presence of AD-mix-α of the α,β-unsaturated benzyl

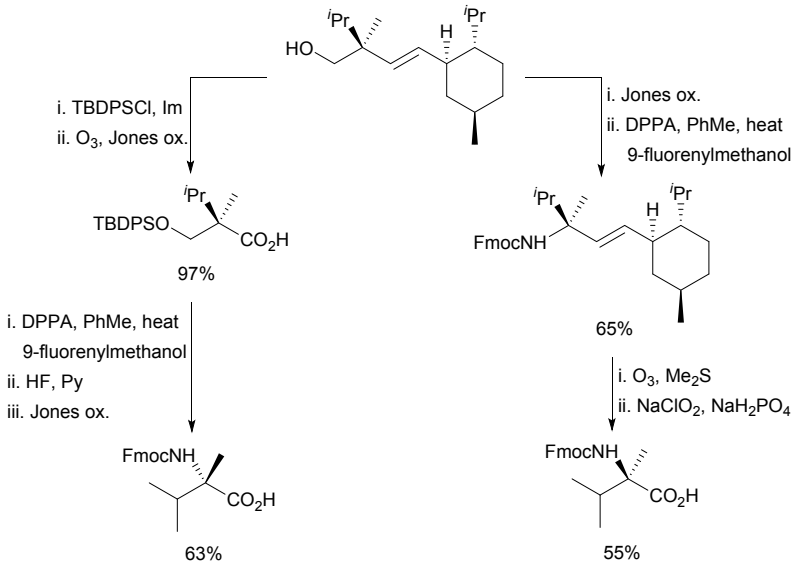
ester- was transformed into a β-hydroxy α-amino acid. Ring-opening of this sulfate with NaN_3 with inversion of the configuration at the α-position, and reduction of azido esters with PPh_3 gave (2*S*,3*S*)-β-propyl substituted serine (Scheme 23). On the other hand, the sulfate was treated with LiBr and then with NaN_3 to give the *syn*-azido ester, according to two inversions of the configuration, which was reacted with PPh_3 to the corresponding (2*R*,3*S*)-β-propyl serine derivative.

The enantiomeric sulfate from AD-mix-β dihydroxylation can be also used for the diastereodivergent synthesis of (2*R*,3*R*)- and (2*S*,3*R*)-β propyl serine derivatives. Starting from azido esters, the synthesis of cysteine derivatives was also accomplished.



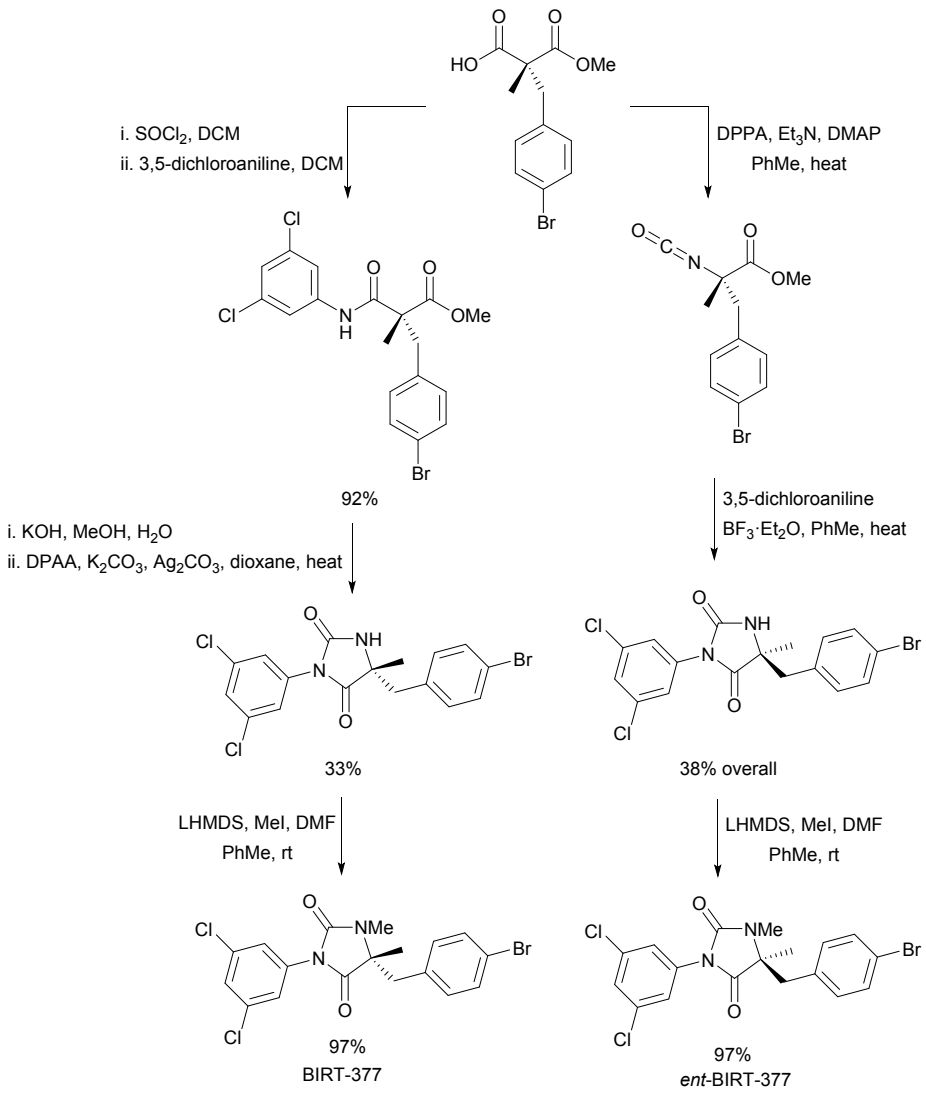
Scheme 23 Diastereodivergent routes to (2*S*,3*S*)- and (2*R*,3*S*)-β-propyl serine derivatives.

An enantiodivergent approach to α,α-dialkylated α-amino acids using Curtius rearrangement as the key step was reported by Spino and Gobdout.[38] The common alcohol intermediate was transformed into (*S*)-α-methylvaline by silylation followed by ozonolysis to a chiral acid, which was treated with diphenylphosphoryl azide (DPPA) and then submitted to desilylation and oxidation (Scheme 24). In the other route to (*R*)-α-methylvaline, oxidation followed by DPPA treatment and quenching with 9-fluorenylmethanol provided the protected allylic amine. Subsequent ozonolysis to an aldehyde and oxidation with $NaClO_2$ afforded *N*-Fmoc-protected (*R*)-α-methylvaline.



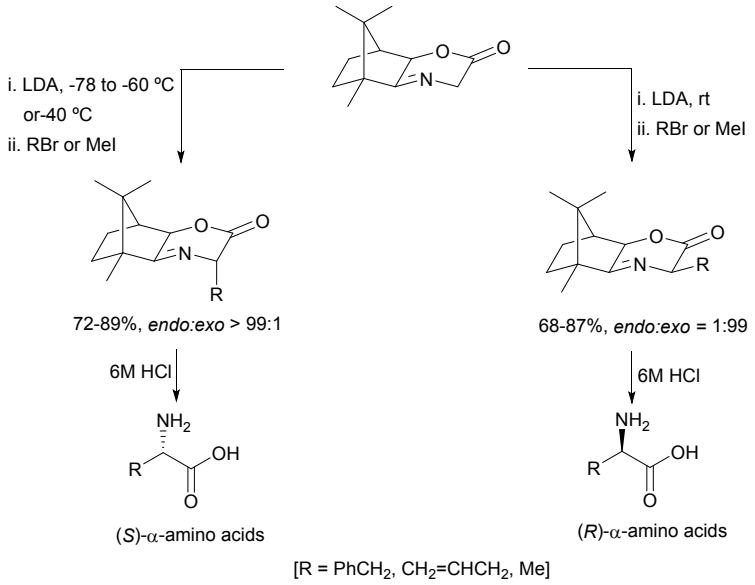
Scheme 24 Enantiodivergent routes to (*S*)- and (*R*)-α-methylvaline derivatives.

The LFA-1 antagonist BIRT-377 mediates leukocyte adhesion that is implicated in a number of immunological processes. Both enantiomers have been prepared using Curtius rearrangement as the key step by Back and co-workers.[39] Starting from dimethyl 2-(4-bromobenzyl)-2-methylmalonate the desymmetrization with porcine liver esterase (PLE) gave the common intermediate. The amide was prepared by condensation of its acyl chloride with 3,5-dichloroaniline and after ester hydrolysis followed by Curtius rearrangement using DPPA gave the hydantoin, which by final *N*-methylation, provided the corresponding BIRT-377 was obtained (Scheme 25). Enantiodivergently, its enantiomer was prepared by treatment of the starting half ester first with DPPA, giving the isocyanate, followed by addition of 3,5-dichloroaniline in the presence of $BF_3 \cdot Et_2O$ the hydantoin was formed, which was submitted to final *N*-methylation in an overall yield of 37%.



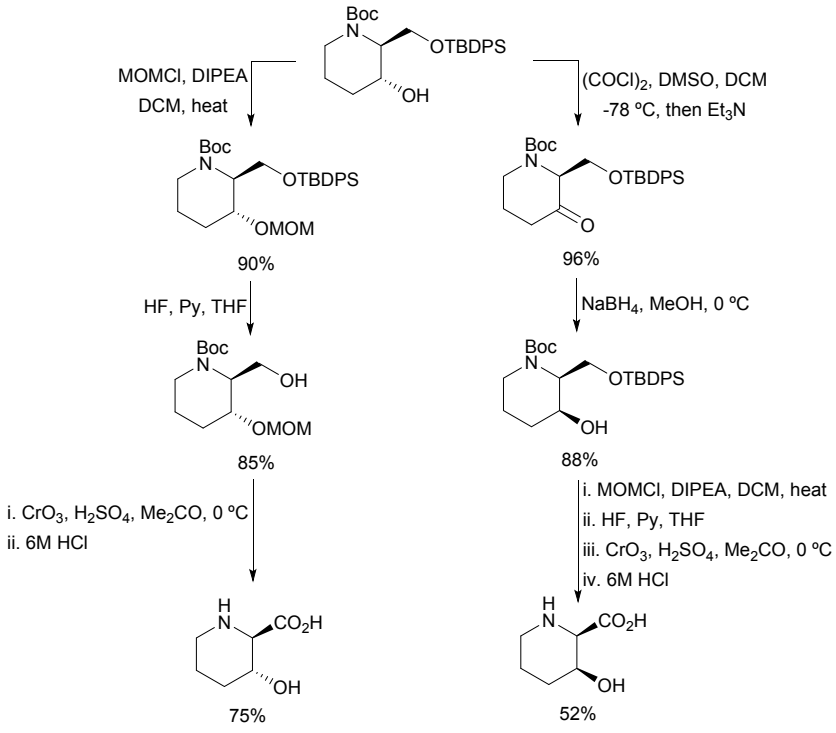
Scheme 25 Enantiodivergent routes to BIRT-377 and *ent*-BIRT-377.

Recently, Liu and co-workers[40] have described a temperature-dependent enantiodivergent route to (*R*)- and (*S*)-α-amino acids by alkylation of a camphor-based tricyclic iminolactone. Using LDA as base at low temperature *endo*-alkylation took place giving (*S*)-AAs after HCl hydrolysis, whereas deprotonation at room temperature, either with LDA or KO^{t}Bu, afforded *exo*-products, precursors of (*R*)-AAs (Scheme 26).



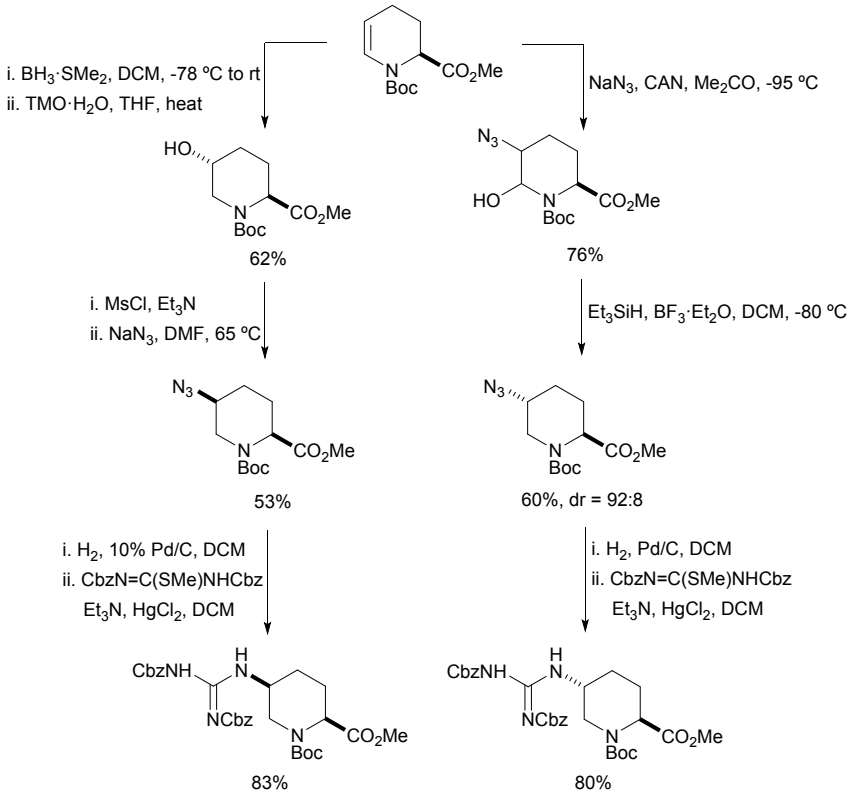
Scheme 26 Enantiodivergent routes to (*S*)- and (*R*)-AAs.

Heterocyclic 3-hydroxypipecolic acids have been synthesized in a diastereodivergent manner using a L-serinol derivative as starting material by Jourdant and Zhu.[41] The common intermediate is a *N*-Boc disubstituted piperidine, which after protection of the secondary alcohol and desilylation, the resulting primary alcohol was oxidized and hydrolyzed to afford (2*R*,3*S*)-3-hydroxypipecolic acid (Scheme 27). On the other hand, the *cis*-derivative was obtained by Swern oxidation of the secondary alcohol and reduction with $NaBH_4$ giving the expected (2*R*,3*S*)-3-hydroxypipecolic acid using the previously described steps.



Scheme 27 Diastereodivergent routes to (2*R*,3*R*)- and (2*R*,3*S*)-3-hydroxypipecolic acid.

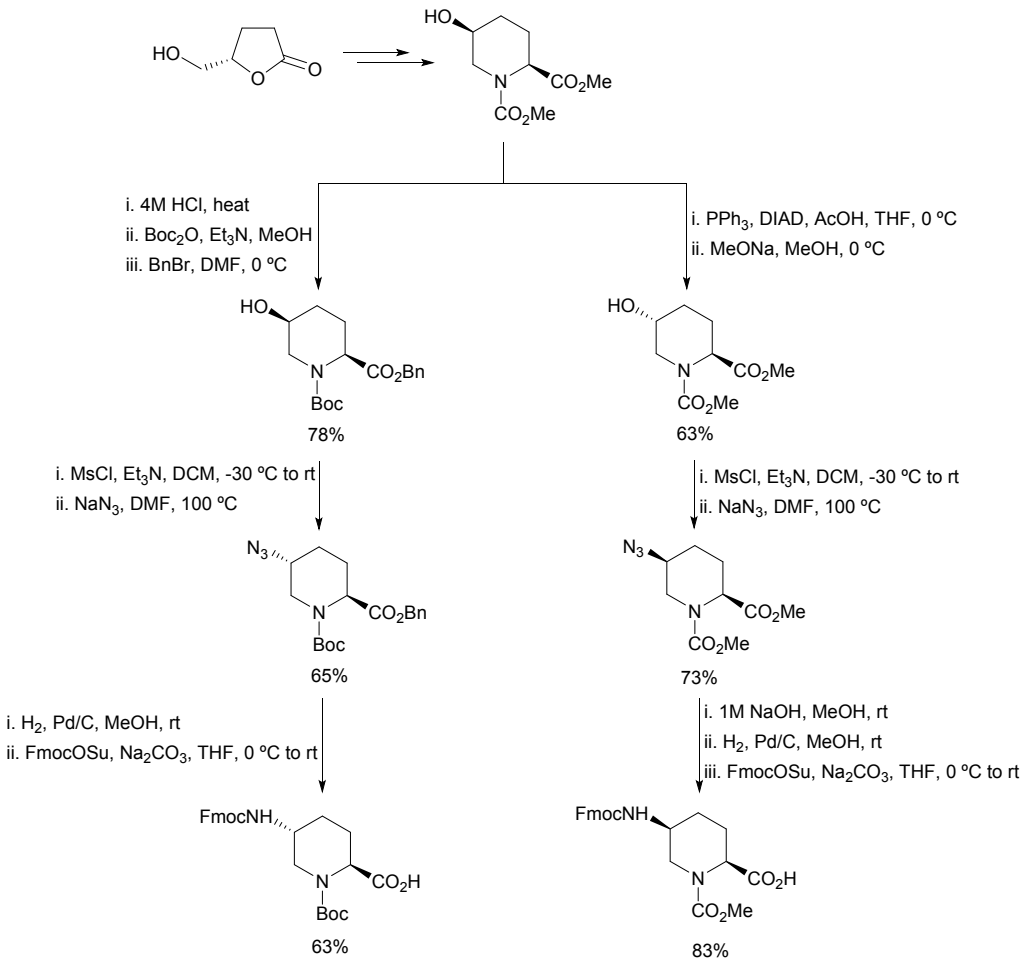
La Corre and Dhimane[42] have reported diastereodivergent routes to *cis*- and *trans*-5-guanidinopipecolic acids from methyl *N*-Boc-5,6-dehydropipecolate prepared from racemic methyl *N*-Boc-pipecolate. For the *cis*-derivative the common intermediate was submitted to hydroboration-oxidation with trimethylamine *N*-oxide (TMO) to provide *trans*-5-hydroxypipecolate, which was mesylated and allowed to react with NaN_3 and then submitted to hydrogenolysis, to give *cis*-5-aminopipecolate. By reaction of the amino group with *N,N*-di(benzyloxycarbonyl)-*S*-methylthiourea the *cis*-isomer of arginine analogue was obtained (Scheme 28). In the other route to the *trans*-isomer, the dehydropipecolate was treated with NaN_3 and cerium(IV) ammonium nitrate (CAN) to provide, after reduction of the α-amino ether moiety, methyl *trans*-5-azidopipecolate. Hydrogenolysis of the azido group and guanidine formation led to the *trans*-arginine-protected *cis*-5-guanidinopipecolate.



Scheme 28 Diastereodivergent routes to methyl *cis*- and *trans*-5-guanidinopipecolates.

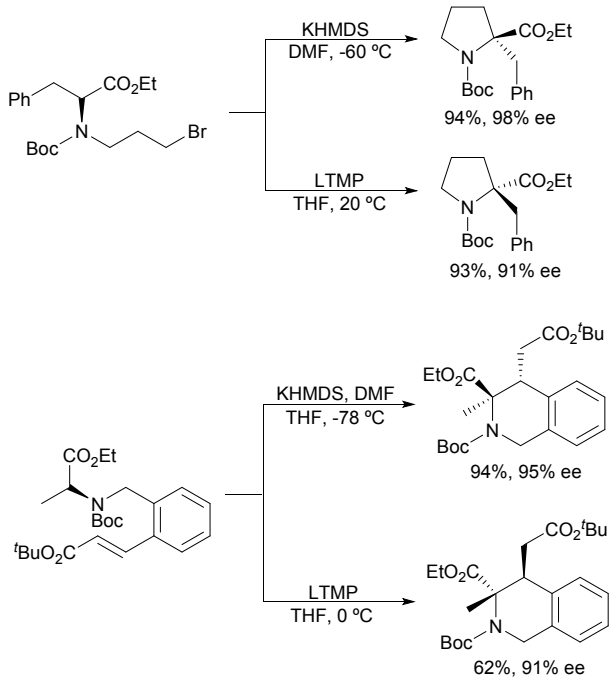
Enantioenriched 5-aminopipecolic acids have been diastereodivergently prepared from commercially available (*S*)-γ-(hydroxymethyl)butyrolactone by the Contini and Occhiato group.[43] This lactone was transformed into methyl *cis*-5-hydroxypipecolate which, by functional and protecting group manipulation, provided protected *trans*-4-aminopipecolic acid (Scheme 29). For the preparation of the *cis*-derivative the configuration of the hydroxyl group at the 5-position was inverted under Mitsunobu

conditions. The *cis*-isomer was used to construct a cyclic arginine-glycine-aspartic acid-containing peptidomimetic, which compete with biotinylated vitronectin for binding with the isolated $\alpha_V\beta_3$-integrin (IC_{50} = 4.2 ± 0.9 nM).



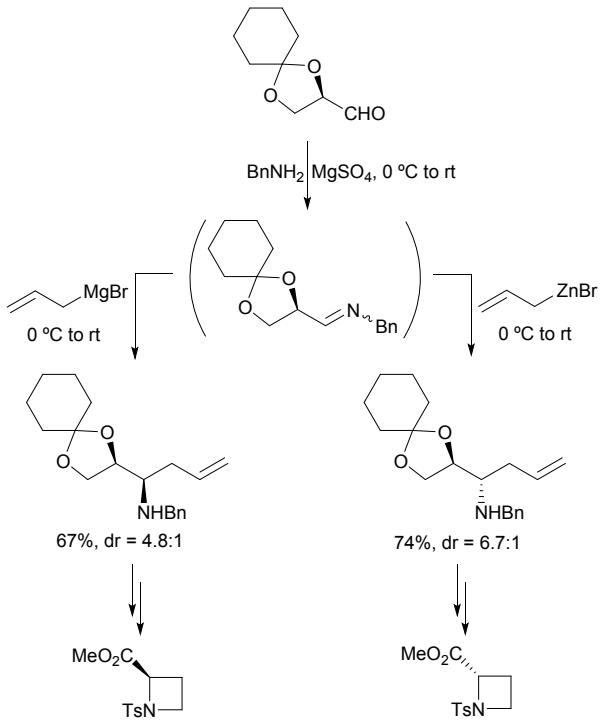
Scheme 29 Diastereodivergent routes to (1*S*,5*R*)- and (1*S*,5*S*)-5-aminopipecolic acid derivatives.

Kawabata and co-workers[44] have reported enantiodivergent routes for the intramolecular cyclization of chiral enolates *via* memory of chirality. In the case of ethyl *N*-3-bromopropyl *N*-Boc-phenylalaninate the cyclization using KHMDS as base in DMF at -60 ºC gave the (*S*)-prolinate derivative in 94% yield and 98% ee, whereas using lithium 2,2,6,6-tetramethylpiperidine (LTMP) in THF at 20 ºC the corresponding enantiomer was formed in 93% yield and 91% ee (Scheme 30). Other examples with different amino esters provided different 4- and 5-membered amino acid derivatives. Alternatively, conjugate addition in the cinnamate containing alaninate gave the tetrahydroisoquinoline amino acid in enantiodivergent manner.



Scheme 30 Enantiodivergent routes to heterocyclic amino acids *via* memory of chirality.

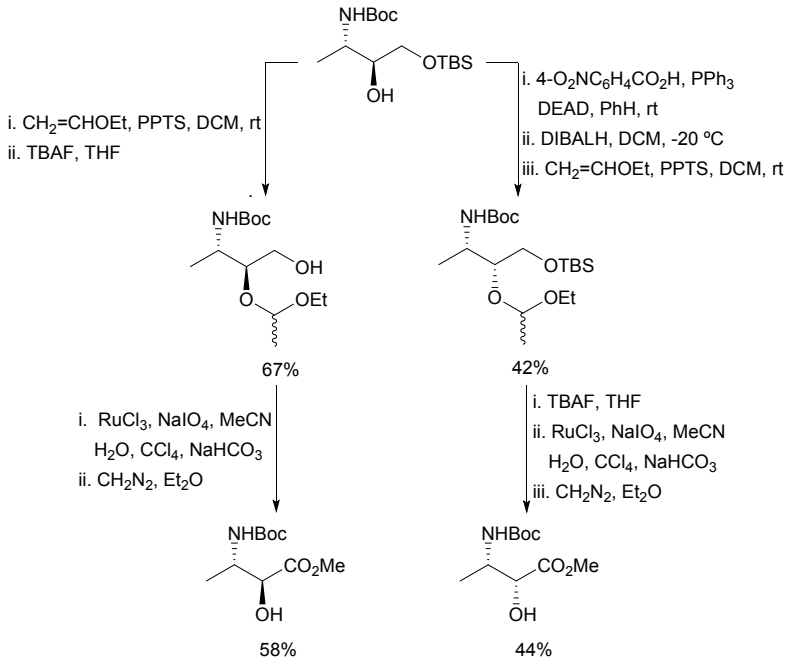
As it was previously described in Scheme 22, the diastereodivergent addition of allylmagnesium bromide or allylzinc bromide to an imine gave the corresponding *syn*- and *anti*-homoallylamines. This strategy has been used by the same authors[45] using (*R*)-2-cyclohexylideneglyceraldehyde and *N*-benzylamine derived imine (Scheme 31). The corresponding homoallylic amines have been further transformed into methyl (*R*)- and (*S*)-azetidine-2-carboxylates.



Scheme 31 Diastereodivergent routes to homoallylamines precursors of methyl (*R*)- and (*S*)-azetidine α-carboxylates.

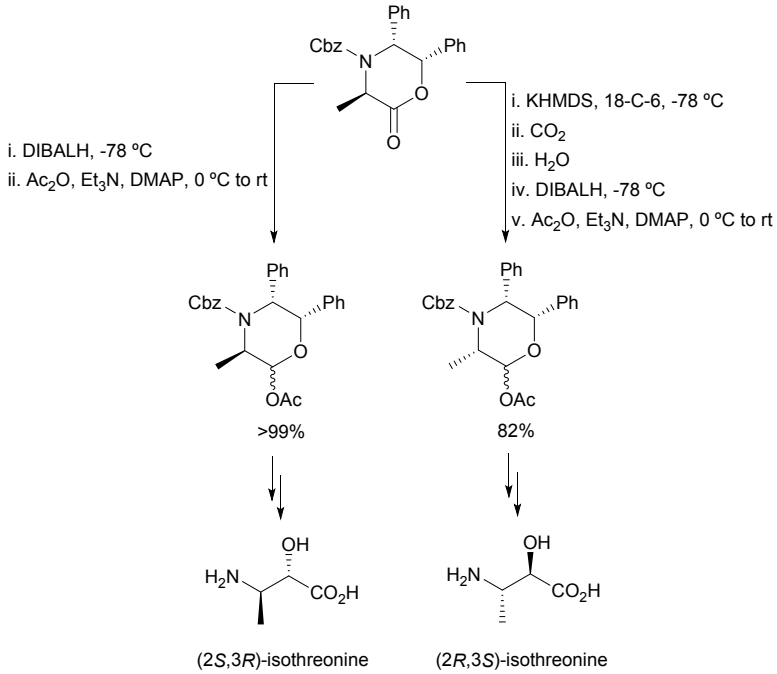
3.2 β-Amino acids

In the field of β-amino acids, α-hydroxy-β-amino acids have received especial attention due to their utility as substrates for the synthesis of a wide variety of peptide isosteres[46] and as constituents of several natural products such as paclitaxel,[47] bestatin (aminopeptidases inhibitor),[48] KRI 1314 (a renin inhibitor),[49] microginin (an ACE inhibitor)[50] and dideoxykanamycin A (an antibacterial agent).[51] The Pericás and Riera group[52] reported diastereodivergent routes to *anti*- and *syn*-α-hydroxy-β-amino acids from *anti*-3-amino-1,3-diols. Starting from the monosilylated derivative, by functional group transformations, the corresponding methyl *N*-Boc protected *anti*-α-hydroxy-β-amino ester was prepared. On the other hand, by Mitsunobu inversion of the secondary hydroxy group the *syn*-α-hydroxy-β-amino ester was synthesized (Scheme 32).



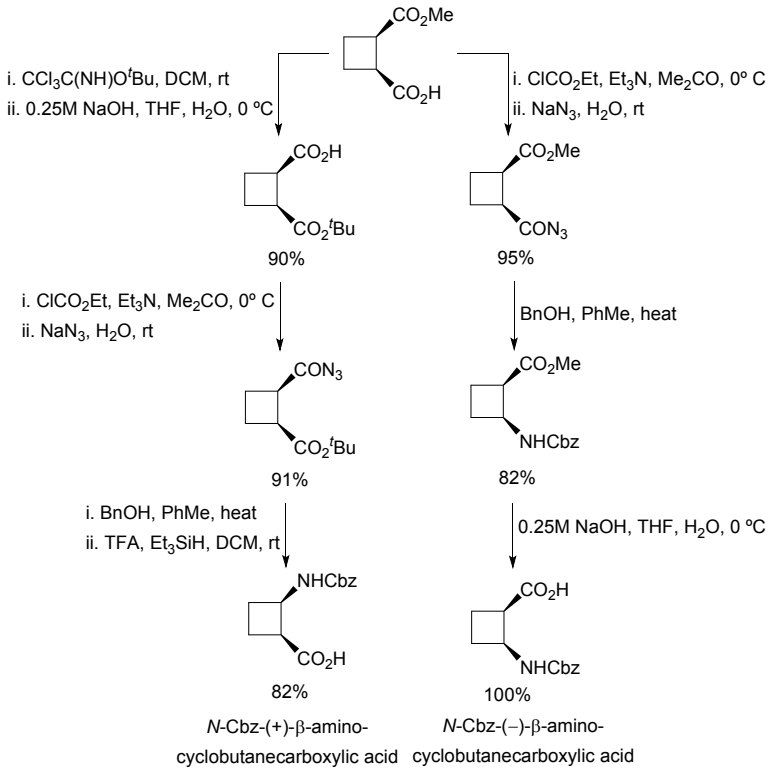
Scheme 32 Diastereodivergent routes to α-hydroxy-β-amino acid methyl esters.

Williams and co-workers[53] have described the diastereodivergent synthesis of tetrahydro-1,4-oxazinones precursors of enantiomeric isothreonines and nor-*C*-statines. In Scheme 33 the routes for α-hydroxy-β-amino acids, starting from *anti*-3-methyloxazinone have been depicted. This compound was transformed into the corresponding oxazinone precursor of (2*S*,3*R*)-isothreonine by treatment with DIBALH and acetylation of the intermediate lactol. The other epimeric oxazinone was prepared by enolization followed by reduction and acetylation.



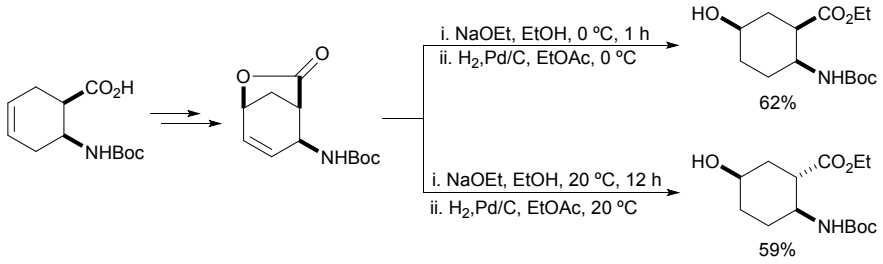
Scheme 33 Diastereodivergent routes to oxazinones precursors of enantiomeric isothreonines.

Conformationally constrained β-amino acids[54] and β-oligomers[55] have interesting biological properties allowing the production of novel antibiotics and nonhaemolytic agents among other pharmaceuticals. Enantiodivergent synthesis of (+)- and (–)-2-aminocyclobutane-1-carboxylic acids has been reported by Ortuño and co-workers.[56] Starting from a chiral half-ester, which results from the enzymatic desymmetrization of *meso*-cyclobutane-1,2-dicarboxylic acid methyl ester, methyl (+)-β-aminocyclobutane-1-carboxylate was prepared using Curtius rearrangement and protecting group transformations (Scheme 34). On the other hand, the (–)-enantiomer was synthesized by Curtius rearrangement on the carboxylic acid. These β-amino acids have been self-condensed and coupled with one another to provide bis(cyclobutene)-β-dipeptides.



Scheme 34 Enantiodivergent routes to Cbz-protected (+)- and (–)-β-aminocyclobutanecarboxylic acids.

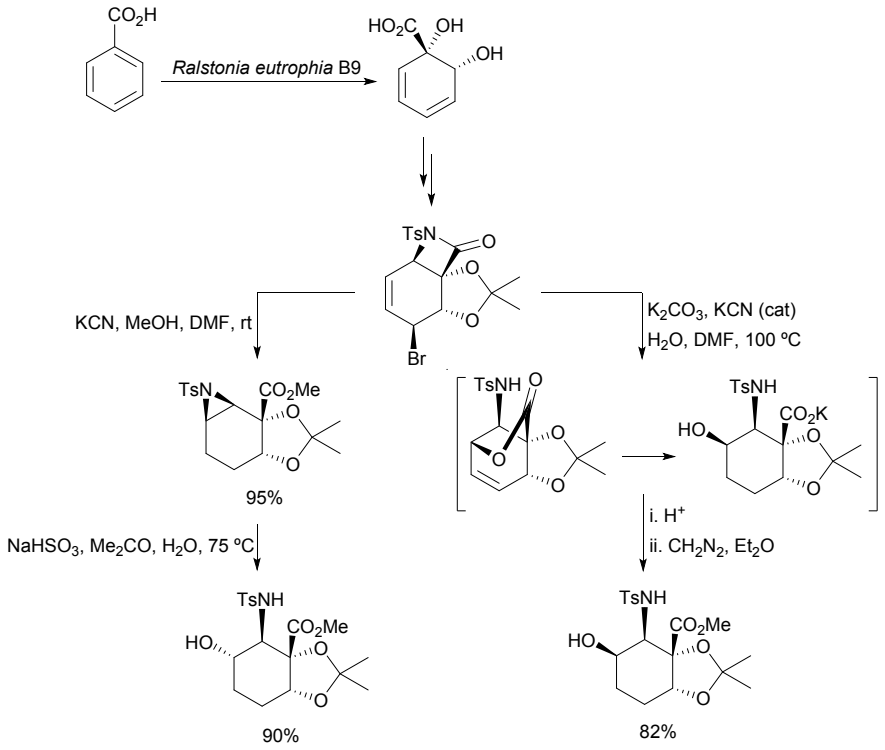
Temperature-dependent diastereodivergent routes to cyclohexane-5-hydroxy-β-amino esters have been carried out by Fülöp and co-workers.[57] As starting compound a cyclohexene *cis*-β-amino acid was used, which was transformed into the common intermediate by iodolactonization-deiodination. This lactone was opened with NaOEt at 0 ºC giving after hydrogenation the (1*R**, 2*S**,5*R**)-5-hydroxy-β-amino ester. However, performing the lactone opening at room temperature epimerization of C-1 occurred giving the *trans*-diastereomer (Scheme 35). These 5-hydroxylated-β-amino esters were used for the synthesis of *exo*-methylenic cyclohexane β-amino acid derivatives.



Scheme 35 Diastereodivergent routes to cyclohexane 5-hydroxy-β-amino ester derivatives.

Diastereodivergent synthesis of protected β-amino-γ-hydroxy esters from a common bicyclic β-lactam has been achieved by Carrera and co-workers.[58] Starting from benzoic acid and using enzymatic dihydroxylation with the mutant strain *Ralstonia eutropha* B9, an enantiopure *cis*-cyclohexadiendiol was obtained. This compound was

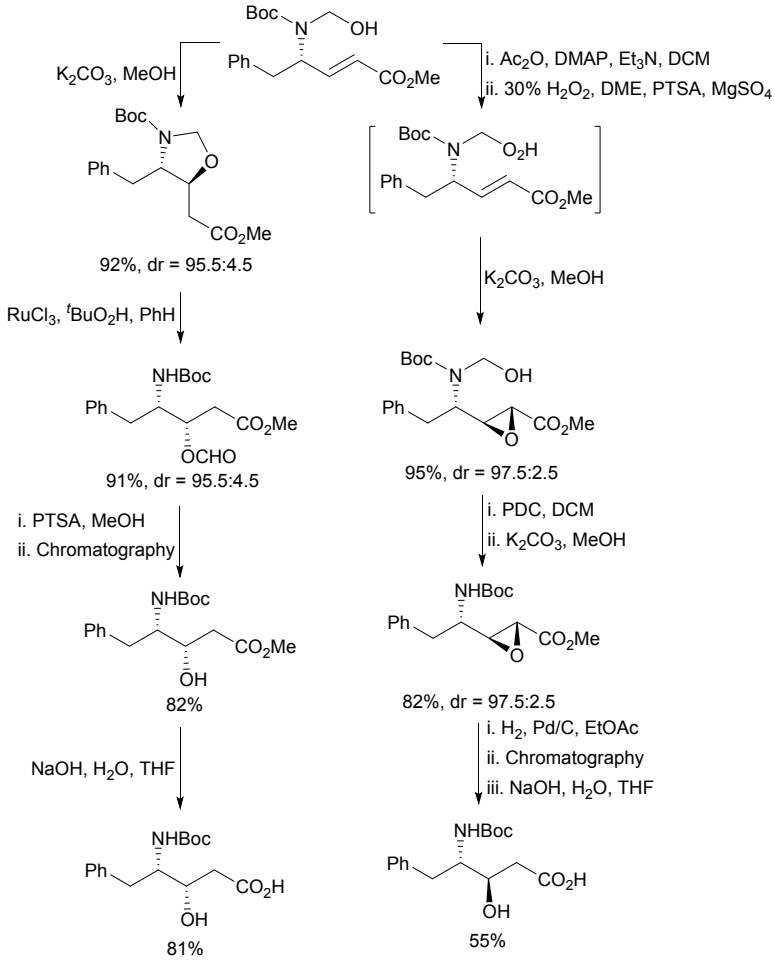
further transformed into the β-lactam, which by treatment with KCN in methanol gave an aziridine. Further treatment with $NaHSO_3$ in aqueous acetone gave the protected β-amino-γ-hydroxy ester (Scheme 36). Treatment with K_2CO_3 in water at 100 ºC, the starting lactam gave a γ-lactone by intramolecular S_N2' attack of the carboxylate on the allyl bromide, which was hydrolyzed *in situ* to the corresponding β-amino acid and after esterification with diazomethane to the diastereomeric β-amino -γ-hydroxy methyl ester.



Scheme 36 Diastereodivergent routes to β-amino-γ-hydroxy esters.

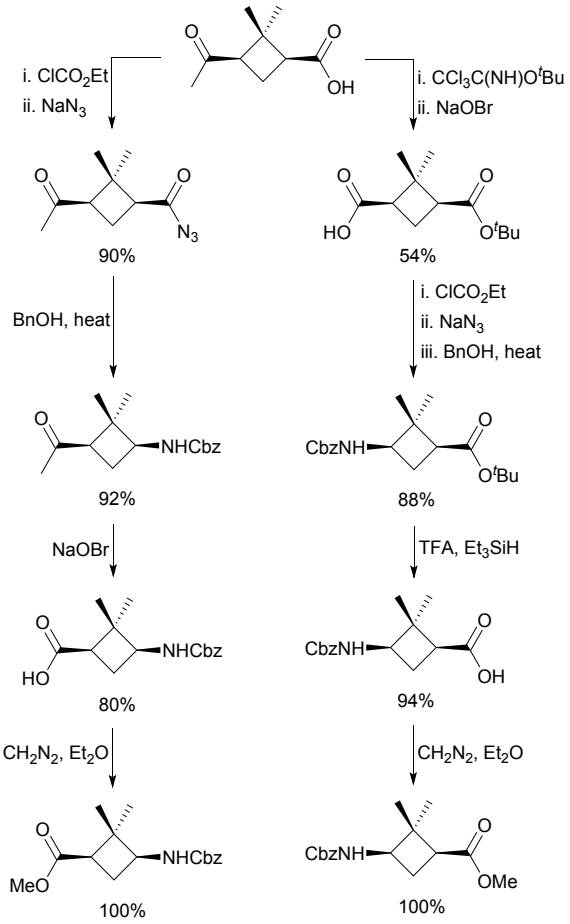
3.3 γ-Amino acids

Aliphatic γ-amino-β-hydroxy acids are found in a number of natural and synthetic compounds with protease inhibitory activity.[59] Kim and co-workers[60] have studied diastereodivergent routes to (3*S*,4*S*)- and (3*R*,4*S*)-4-amino-3-hydroxy-5-phenylpentanoic acid (AHPPA) from a *N*-Boc-L-phenylalanine derivative as common precursor. By intramolecular conjugate addition of this product a *trans*-oxazolidine was formed, which after oxidative cleavage and hydrolysis, gave a mixture of *syn*- and *anti*-diastereomers separable by column chromatography. Final ester hydrolysis provided the *N*-Boc derivative of (3*S*,4*S*)-AHPPA (Scheme 37). On the other hand, direct intramolecular epoxidation of the starting compound gave opposite configuration of the hydroxy group at the 3-position. Therefore, the *N*-hydroxymethyl group was acetylated and oxidized with H_2O_2 to a *N*-hydroperoxymethyl group. Without isolation, this hydroperoxide was transformed into the corresponding epoxide under basic conditions. Removal of the *N*-hydroxymethyl group by PDC oxidation and methanolysis, followed by hydrogenolysis of the epoxide, afforded a mixture of *anti*- and *syn*-isomers. Subsequent separation by column chromatography and ester hydrolysis provided *N*-Boc protected (3*R*,4*S*)-AHPPA.



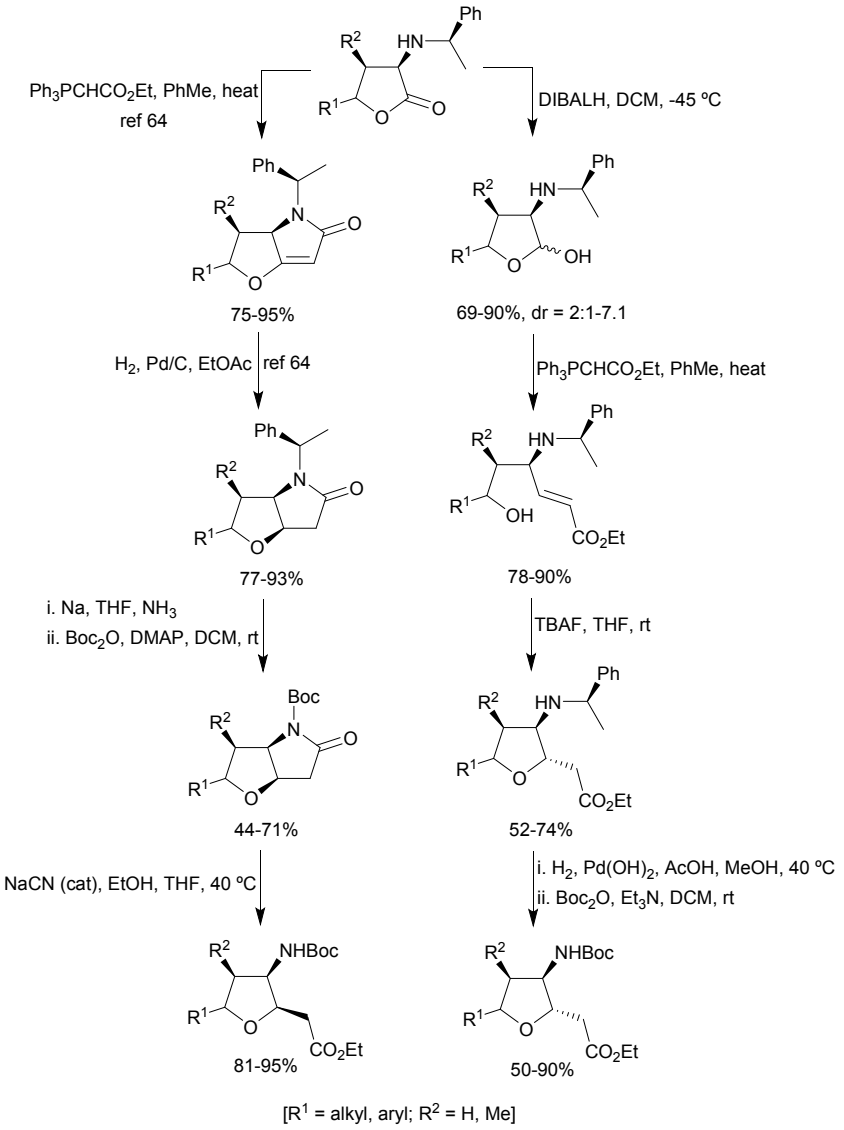
Scheme 37 Diastereodivergent routes to (3*S*,4*S*)- and (3*S*,4*R*)-*N*-Boc-AHPPAs.

γ-Aminobutiric acid (GABA) and derivatives are inhibitory neurotransmitters of the central nervous system (CNS).[59a] Ortuño and co-workers[61] have synthesized (–)- and (+)-3-amino-2,2-dimethyl-1-carboxylic acids in an enantiodivergent manner starting from (–)-*cis*-pinononic acid easily accessible by oxidative cleavage of (–)-verbenone. This acid was converted into the acyl azide, which was submitted to a Curtius rearrangement in the presence of benzyl alcohol to produce the corresponding carbamate. Lieben degradation of the methyl ketone with NaOBr followed by methylation with diazomethane provided methyl (–)-3-amino-2,2-dimethylcyclobutane-1-carboxylate (Scheme 38). Alternatively, half ester, prepared from (–)-*cis*-pinononic acid,[62] was submitted to Curtius rearrangement to provide the carbamate precursor of methyl (+)-3-amino-2,2-dimethylcyclobutane-1-carboxylate. These compounds were incorporated into diastereomeric bis(cyclobutane)-γ-dipeptides.



Scheme 38 Enantiodivergent routes to (–)- and (+)-3-amino-2,2-dimethylcyclobutane-1-carboxylic acid derivatives.

Recently, Jakubec and co-workers[63] have reported diastereodivergent routes to cyclic analogues of 2,3-*cis*- and 2,3-*trans*-γ-aminobutyric acid (GABA). For the 2,3-*cis*-substituted GABA analogues, a carbon chain extension of the starting γ-substituted 2-aminobutanolides[64] by a modified Wittig reaction was used, whereas for the *trans*-isomer a Horner-Wadsworth-Emmons (HWE) reaction and an intramolecular oxa-Michael addition were the key steps. By reaction of several lactones with Ph_3PCHCO_2Et followed by hydrogenation bicyclic lactams were obtained.[64] These lactams were submitted to sodium-mediated debenzylation followed by Boc protection providing 2,3-*cis*-GABA analogues (Scheme 39). On the other hand, by DIBALH reduction to lactols followed by HWE reaction gave unsaturated esters, which underwent intramolecular 5-*exo*-*trig* cyclization using TBAF as base. After final debenzylation 2,3-*trans*-GABA analogues were isolated.

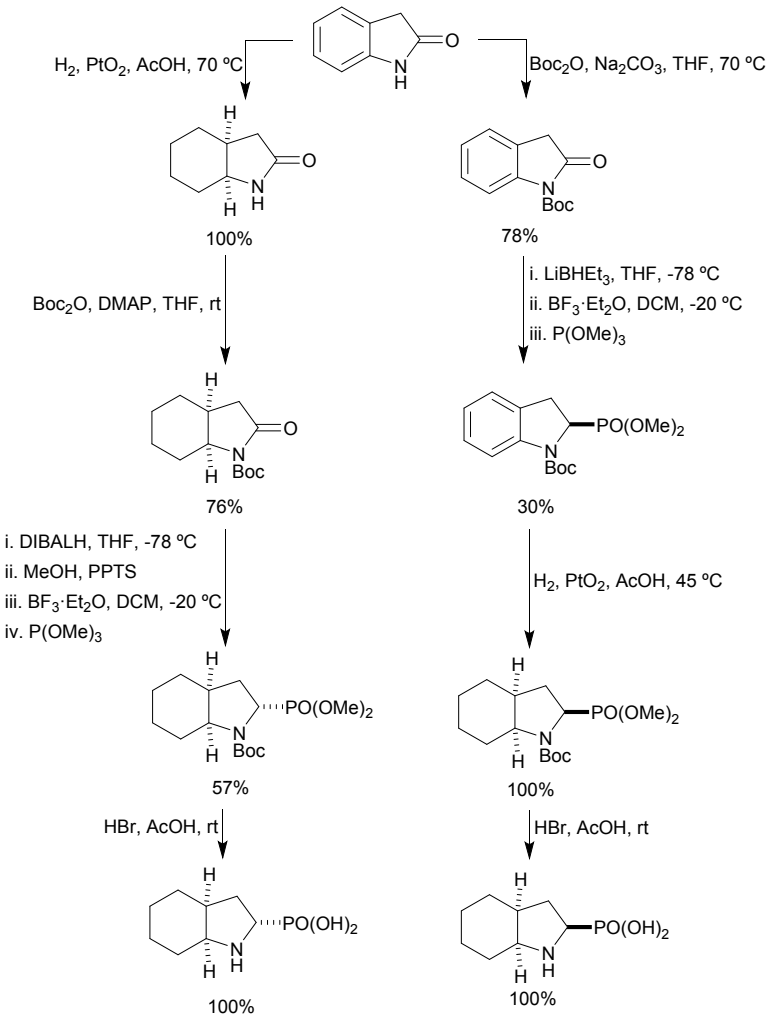


Scheme 39 Diastereodivergent routes to 2,3-*cis*- and 2,3-*trans*-substituted GABA analogues.

3.4 Aminophosphonic acids

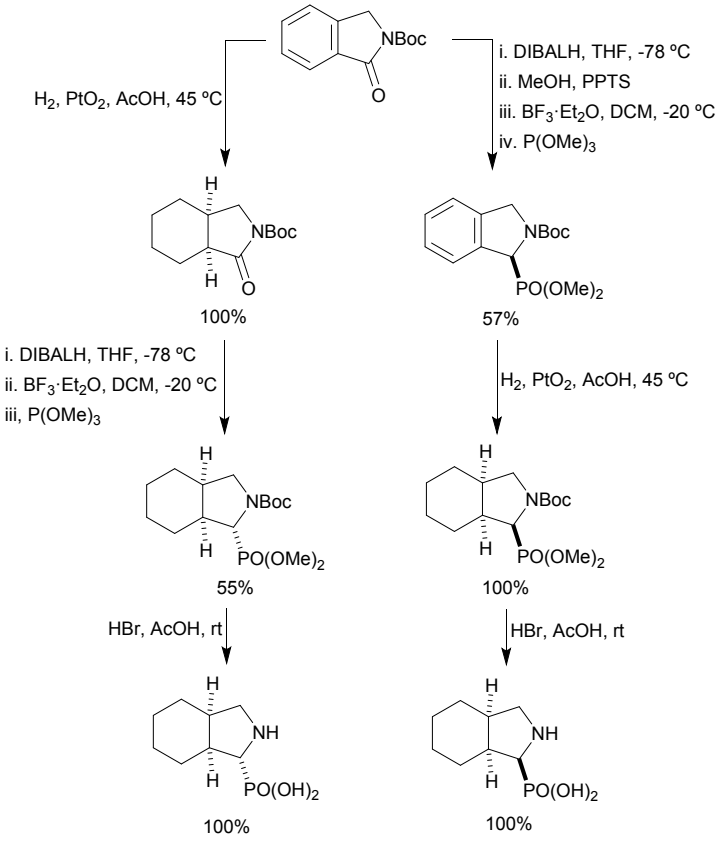
α-Aminophosphonic acids are surrogates of α-amino acids where the planar carboxylic acid is replaced by a sterically more demanding tetrahedral phosphonic acid. They have received especial interest in agrochemistry and in medicinal chemistry.[65] Diastereodivergent routes to racemic octahydroindole-2-phosphonic acids analogues of phosphoproline have been prepared by the Ordóñez and Cativiela group[66] from 2-indolinone. This *cis*-derivative was prepared by hydrogenation of the aromatic ring followed by *N*-Boc protection. Then, DIBALH reduction gave an unstable hemiaminal, which was treated *in situ* with MeOH and catalytic PPTS, to yield a methoxyaminal. After treatment with $P(OMe)_3$ in the presence of $BF_3 \cdot Et_2O$ gave, through a *N*-acyliminium intermediate, dimethyl *N*-Boc-octahydroindole-2-phosphonate with (2*S**,3a*S**,7a*S**) stereochemistry. Final treatment with HBr provided the *cis*-phosphonic acids (Scheme 40). The synthesis of the epimeric (2*R**,3a*S**,7a*S**)-derivative was carried out by *N*-Boc protection of 2-indolinone and reduction with lithium triethylborohydride (Super-

Hydride®) to the hemiaminal that, after treatment with $BF_3 \cdot Et_2O$ and $P(OMe)_3$, afforded the *N*-Boc-indoline-2-phosphonate. After hydrogenation of the benzene ring and deprotection the corresponding *trans*-phosphonic acid was obtained.



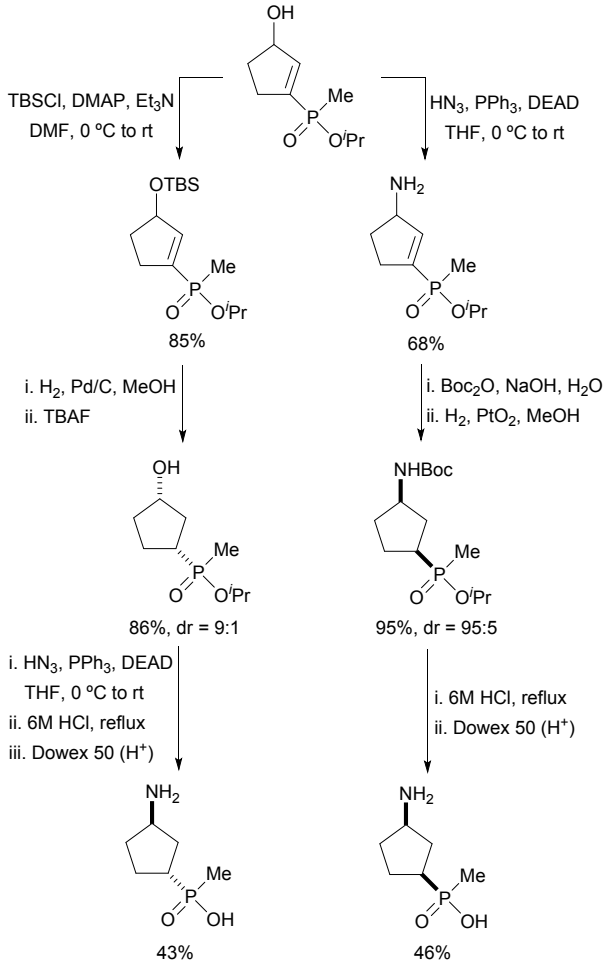
Scheme 40 Diastereodivergent routes to *cis*- and *trans*-octahydroindole-2-phosphonic acids.

The same group reported diastereodivergent routes to other phosphoproline derivatives having an octahydroisoindole instead of an octahydroindole bicyclic system.[67] In this case, *N*-Boc-isoindolin-1-one was used as common starting compound. By hydrogenation of the benzene ring, followed by DIBALH reduction of the carbonyl group, the iminium intermediate was treated with $P(OMe)_3$ giving the *cis*-phosphonate, which was deprotected to the *cis*-aminophosphonic acid (Scheme 41). For the *trans*-derivative, *N*-Boc-isoindolin-1-one, was first prepared and after reduction with DIBALH and treatment with $BF_3 \cdot Et_2O$ and $P(OMe)_3$ the corresponding *trans*-phosphonate was obtained. Final hydrogenation and treatment with HBr provided the *trans*-aminophosphonic acid.



Scheme 41 Diastereodivergent routes to (1*R**,3a*R**,7a*S**)- and (1*S**,3a*R**,7a*S**)-octahydroisoindole-1-phosphonic acids.

Diastereodivergent synthesis of racemic (3-aminocyclopentane)alkylphosphinic acids, considered as conformationally restricted analogues of GABA, has been performed by Hanrahan and co-workers.[68] For instance, starting from (β-hydroxycyclopent-1-en)isopropylmethylphosphinate, its silylation followed by hydrogenation gave a 9:1 mixture of *cis/trans*-cyclopentane derivatives. After desilylation, the mixture of alcohols was aminated under Mitsunobu conditions to give, after HCl hydrolysis and purification by ion exchange chromatography, the corresponding *trans*-(3-aminocyclopentane)methylphosphinic acid (Scheme 42). In the other case, the starting material was first aminated under Mitsunobu conditions and then *N*-Boc protected and hydrogenated to provide the saturated cyclopentane derivatives in 95/5 *cis/trans* diastereomeric ratio. After final hydrolysis and purification the *cis*-(3-aminocyclopentane)methylphosphinic acid was isolated. The same methodology has been carried out starting from (3-hydroxycyclopent-1-ene)-*n*-butylethylphosphinate.

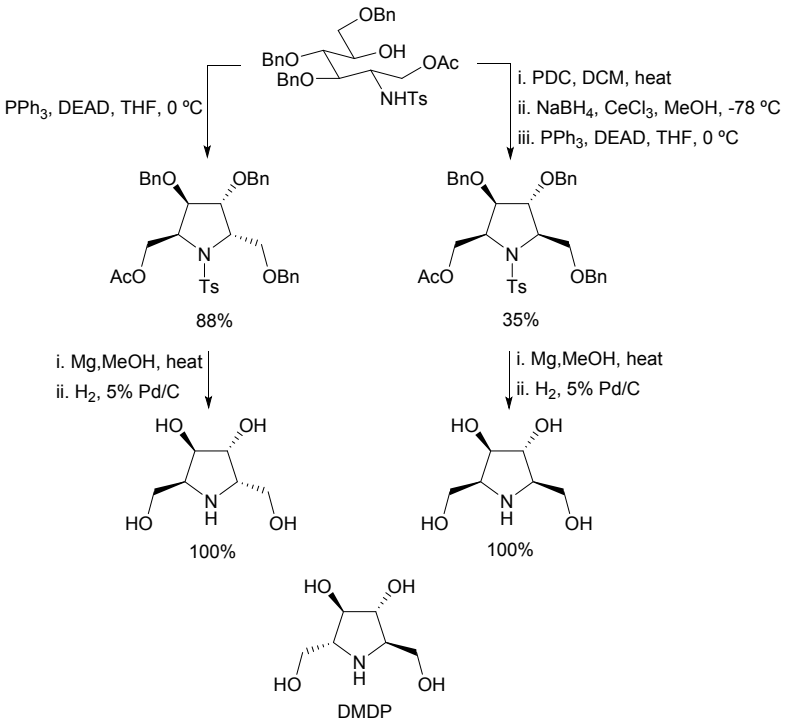


Scheme 42 Diastereodivergent routes to *trans*- and *cis*-(3-aminocyclopentane)methylphosphonic acids.

4. Alkaloids

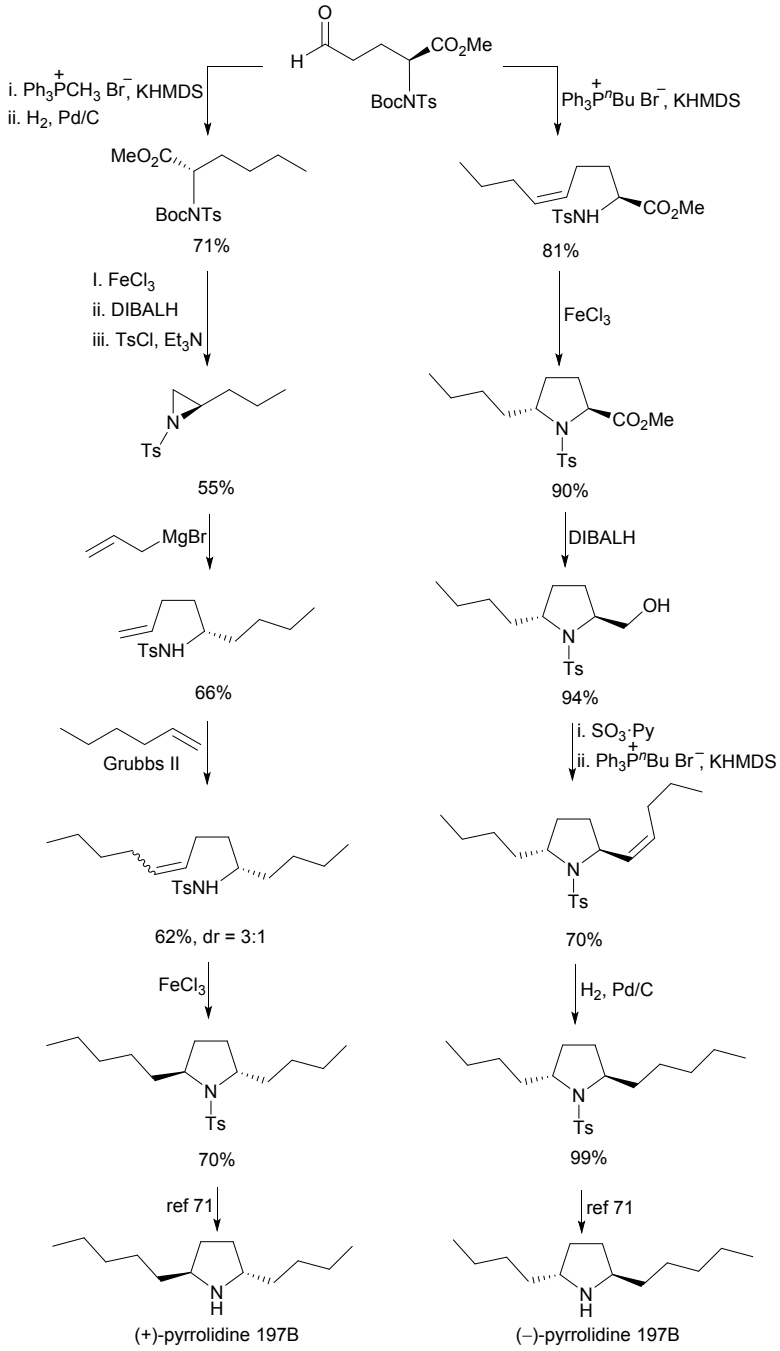
4.1 Pyrrolidine derivatives

Naturally occurring 3,4-dihydroxy-2,5-bis(hydroxymethyl)pyrrolidine (DMDP) and its analogues are selective inhibitors of glycosidases as polyhydroxylated piperidines.[23] Kumar and Ramesh[69] have reported diastereodivergent routes to two diastereomers of DMDP from tri-*O*-benzyl-D-glucal as starting chiral material, which was transformed into a common intermediate *via* cleavage of the O-C-1 bond. This protected β-amido pentaol was submitted to cyclization under Mitsunobu conditions and after *N*-detosylation and deacetylation with magnesium, followed by catalytic hydrogenation, provided (2*S*,3*R*,4*R*,5*S*)-DMDP (Scheme 43). Alternatively, the common intermediate was oxidized and reduced to its epimer at C-5, which after cyclization under Mitsunobu conditions, gave the hydroxylated *N*-tosylpyrrolidine. Final reductive deprotection as above mentioned afforded (2*R*,3*R*,4*R*,5*S*)-DMDP.



Scheme 43 Diastereodivergent routes to (2*S*,3*R*,4*R*,5*S*)- and (2*R*,3*R*,4*R*,5*S*)-DMDP.

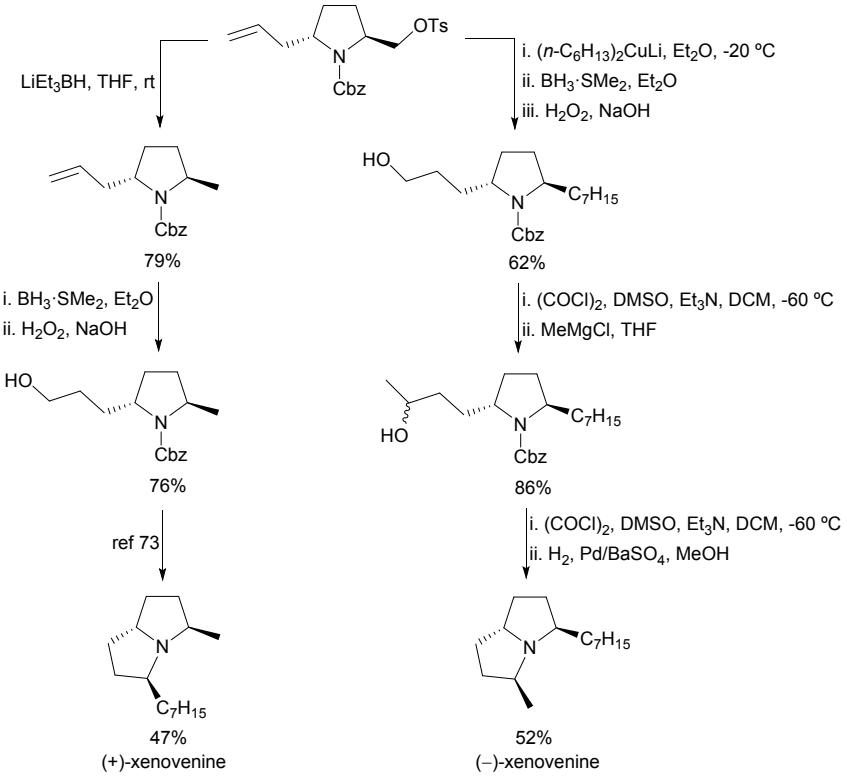
The Martín and Padrón group[70] has reported enantiodivergent routes to (+)- and (−)-pyrrolidine 197B alkaloids, which have homolytic and antibiotic activities, from L-glutamic acid. For the first enantiomer, the common starting aldehyde was submitted to Wittig olefination followed by hydrogenation. *N*-Boc deprotection, DIBALH reduction and tosylation provided the corresponding aziridine, which was opened by allylmagnesium bromide, and the resulting *N*-tosylamine was first submitted to an alkene-metathesis reaction and then to $FeCl_3$-catalyzed intramolecular hydroamination. Final desulfonylation[71] gave (+)-pyrrolidine 197B (Scheme 44). In the other route, the aldehyde was olefinated and then cyclized under $FeCl_3$ catalysis to yield a *trans*-pyrrolidine derivative. This intermediate was reduced with DIBALH to a primary alcohol and oxidized to an aldehyde, which was homologated by Wittig olefination and, after further hydrogenation, provided after deprotection[71] the (−)-pyrrolidine 197B.



Scheme 44 Enantiodivergent routes to (+)- and (–)-pyrrolidine 197B alkaloids.

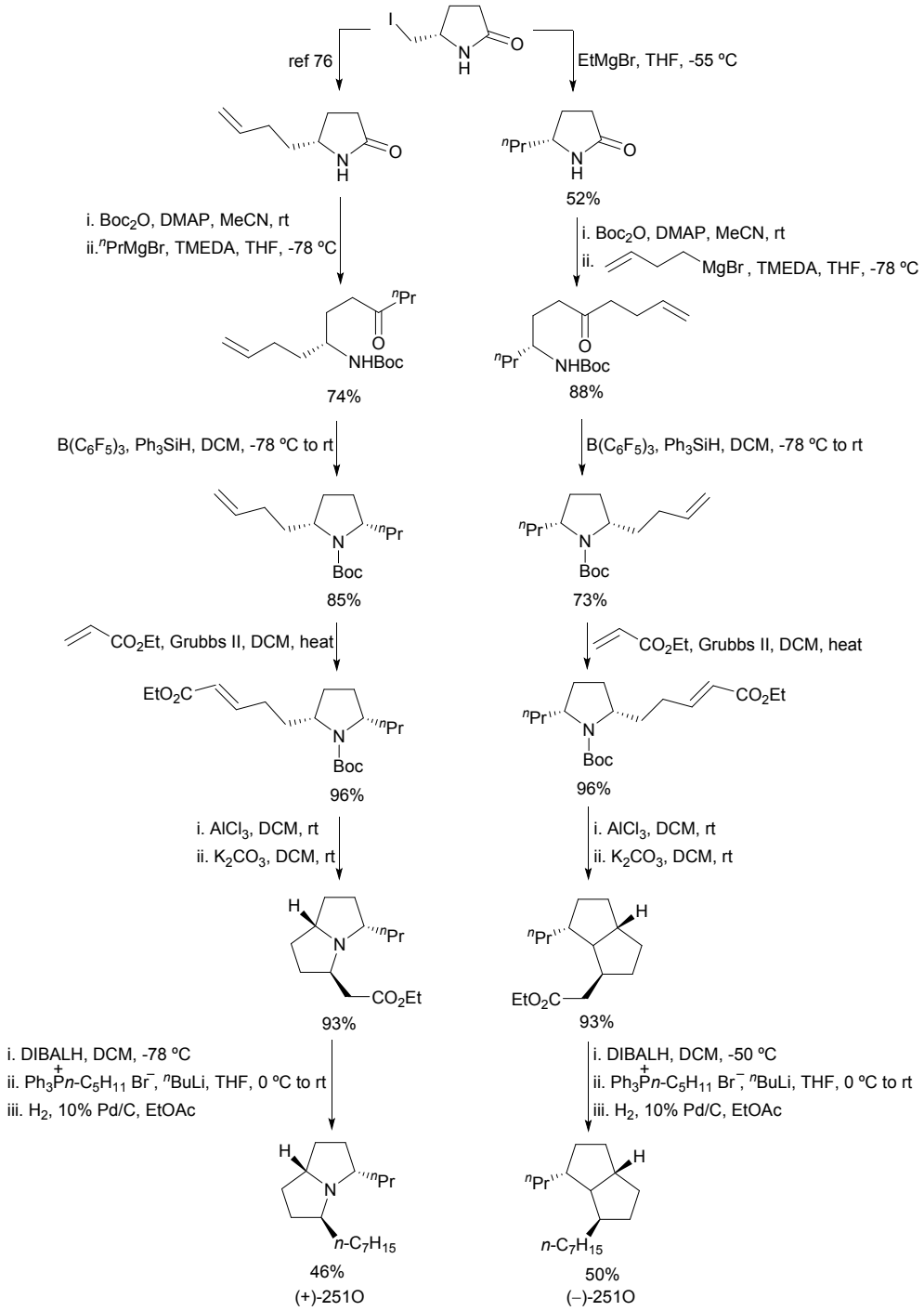
Enantiopure *trans*-2,5-disubstituted pyrrolidines are constituent units of natural pyrrolizidine and indolizidine alkaloids constituents of ant venom and frog poison. Lhommet and co-workers[72] have synthesized the pyrrolizidine alkaloids (+)- and (–)-xenovenine, found in ant venom (*Solenopsis xenovenum*), by enantiodivergent routes from the same chiral intermediate. The synthesis of (+)-xenovenine began by reduction of the tosylate with the superhydride to the *trans*-pyrrolidine, followed by oxidative hydroboration of the allyl substituent and final oxidation and hydrogenation[73] (Scheme 45). In the case of (–)-xenovenine, the tosylated alcohol underwent nucleophilic displaced with *n*-hexyl$_2$CuLi and the resulting *trans*-pyrrolidine was oxidatively hydroborated. The

resulting alcohol was oxidized to an aldehyde and by addition of MeMgBr a mixture of diastereomeric alcohols was obtained. After oxidation and hydrogenation, the (–)-alkaloid was obtained.



Scheme 45 Enantiodivergent routes to (+)- and (–)-xenovenine.

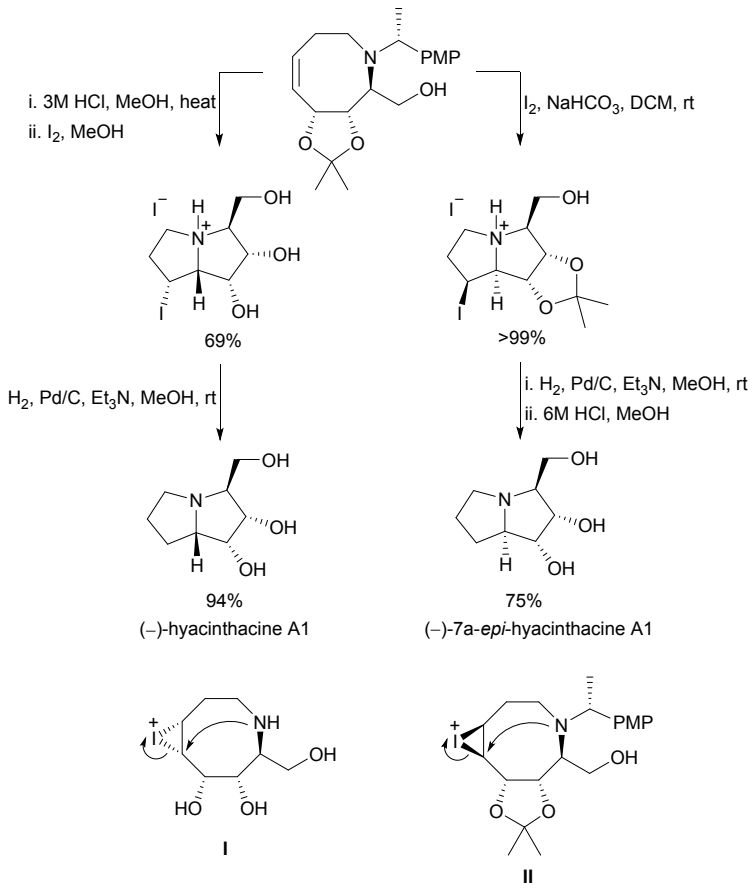
Enantiodivergent routes to poison-frog pyrrolizidine alkaloids 251O and *trans*-223B have been reported by Toyooka and co-workers[74] determining their absolute stereochemistry. The pyrrolizidine 251O has been detected in poison-frogs of Madagascar and in Malagasy ants. Enantiodivergent routes started from the common intermediate lactam,[75] which was transformed into the corresponding homoallyl lactam,[76] *N*-Boc protected and opened with *n*-propylmagnesium bromide to give a ketone. After cyclization and subsequent reduction of the iminium ion with Ph_3SiH, the *cis*-pyrrolidine was obtained. Cross-metathesis with ethyl acrylate to yield the ester and subsequent cyclization promoted by $AlCl_3$, followed by treatment with K_2CO_3, afforded the pyrrolizidine. Finally, half-reduction of the ester with DIBALH, followed by Wittig olefination of the resulting aldehyde and hydrogenation, furnished (+)-251O (Scheme 46). For the synthesis of its (–)-enantiomer, the iodomethyl lactam was alkylated with *n*-hexylmagnesium bromide, then Boc-protection and ring opening with 4-butenylmagnesium bromide afforded a ketone, which was cyclized to the enantiomeric lactam. Further transformations as above mentioned provided *ent*-251O.



Scheme 46 Enantiodivergent routes to (+)- and (-)-2510 pyrrolizidine alkaloids.

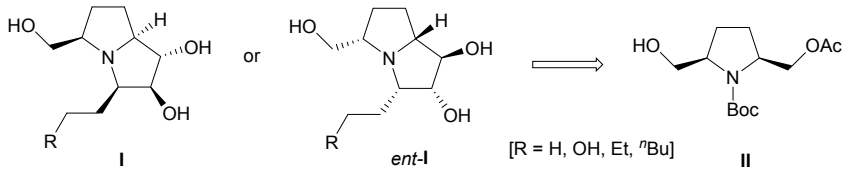
Polyhydroxylated pyrrolizidine alkaloids have emerged as potential therapeutic agents due to their bioactivity as inhibitors of glycosyl hydrolases.[23,77] Based on a transannular iodoamination of substituted 1,2,3,4,7,8-hexahydroazocine scaffolds, Davies and co-workers[78] developed diastereodivergent routes to the synthesis of (–)-hyacinthacine A1 and (–)-7a-*epi*-hyacinthacine A1. The common eight membered starting compound was transformed into (–)-hyacinthacine A1 by deprotection with HCl, followed by diastereoselective iodoamination and hydrogenolysis (Scheme 47). On the

other hand, performing firstly the diastereoselective hydroamination and then hydrogenolysis provided (–)-7a-*epi*-hyacinthacine A1. The different stereochemical outcome during the intramolecular iodoamination can be explained by the reversible iodonium conformation in intermediates **I** and **II**.



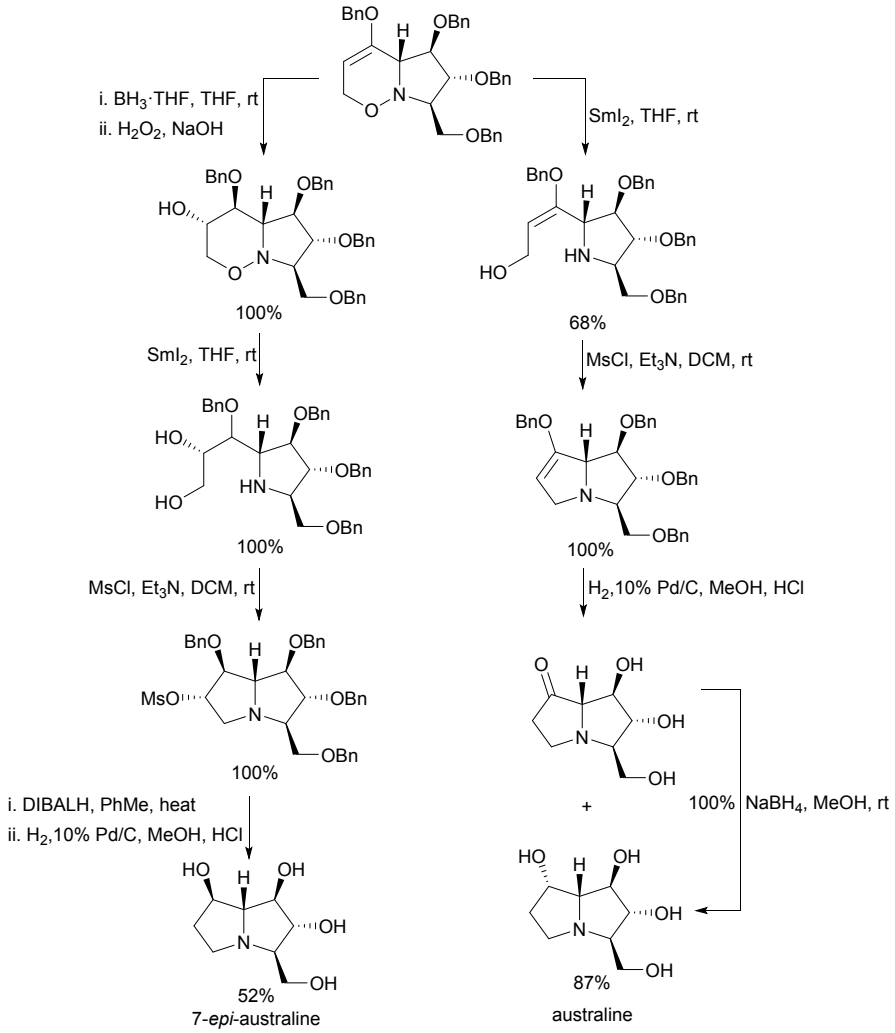
Scheme 47 Diastereodivergent routes to (–)-hyacintacine A1 and (–)-7a-*epi*-hyacintacine A1 and proposed intermediates **I** and **II**.

The Minehira, Kato and Toyooka group[79] described enantiodivergent routes to related hyacinthacine alcaloids with structures **I** and *ent*-**I** from the chiral *N*-Boc-*cis*-2,5-dihydroxymethyl monoacetate **II**[80] (Scheme 48).



Scheme 48 Enantiomeric trihydroxylated pyrrolizidines.

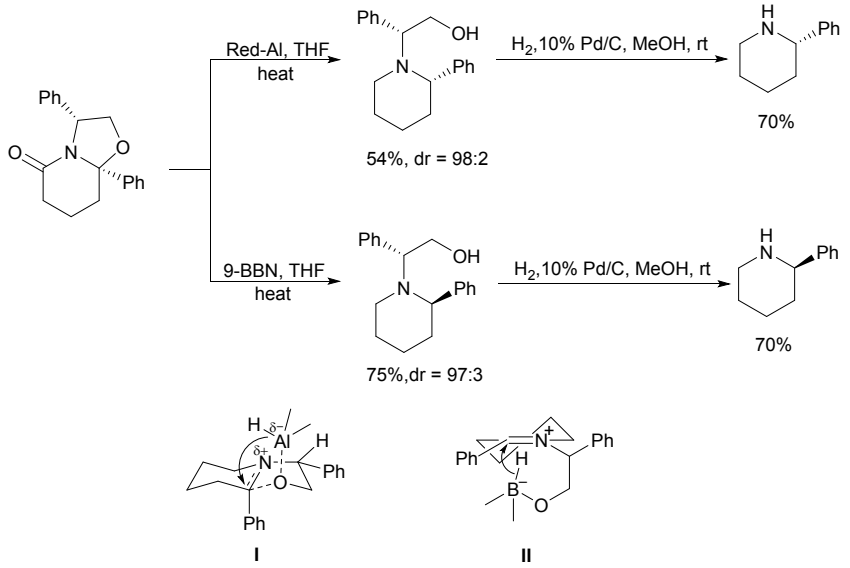
Diastereodivergent routes to 7-hydroxypyrrolizidine alkaloids such as casuarina and 7-*epi*-australina have been reported by Reiβig and Goti groups[81] from a bicyclic 1,2-oxazine derivative, prepared by reaction of lithiated 1-benzyloxyallene with a carbohydrate-derived nitrone.[82] Quantitative hydroboration-oxidation of this oxazinone by the *Si*-face, followed by reductive ring opening with Zn or SmI_2 and dimesylation of the diol unit, gave the intramolecular S_N2 yielding the corresponding pyrrolizidine. Reductive deoxygenation of the mesylate with DIBALH and final debenzylation with hydrogen gave 7-*epi*-australine (Scheme 49). When the same oxazinone was first subjected to a chemoselective reduction of the N-O bond with the $[Mo(CO)_6]/NaBH_4$ combination or SmI_2 the pyrrolidine derivative was obtained. After mesylation, a ring closing took place providing a pyrrolizidine, which after hydrogenation gave a mixture of australine and its 7-oxo derivative. This mixture was treated with $NaBH_4$ to provide australine in 59% overall yield.



Scheme 49 Diastereodivergent routes to 7-*epi*-australine and australine.

4.2. Piperidine derivatives

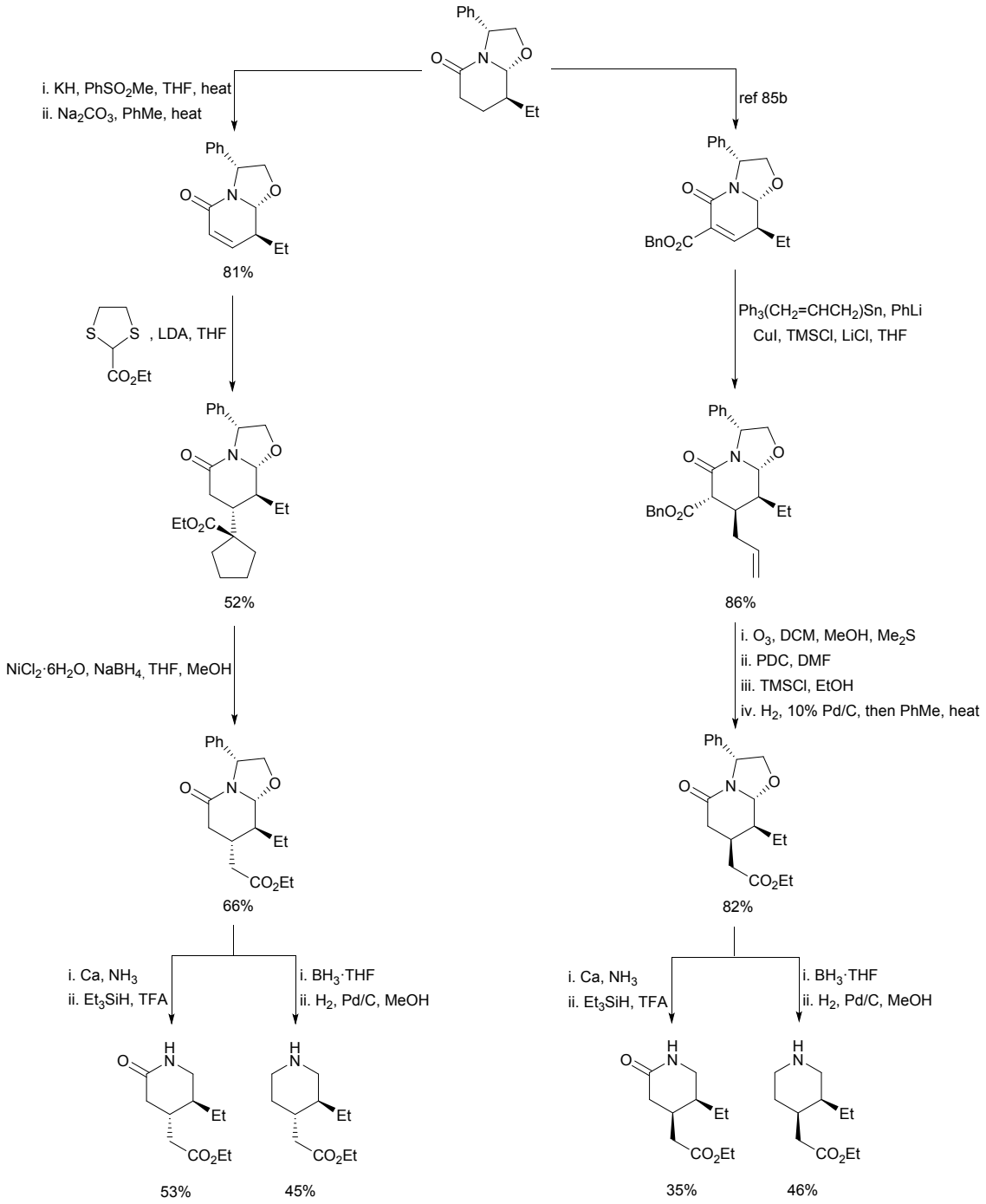
The piperidine moiety is present in many natural alkaloids and other biologically active compounds, and also in compounds such as hydrogenated quinolines, iosquinolines, indolizidines and quinolizidines derivatives.[23,83] Amat and co-workers[84] described enantiodivergent routes to 2-arylpiperidines from a bicyclic lactam derived from (*R*)-phenylglycinol. The key step is the reductive deoxygenation with Red-Al or with 9-BBN, which took place with retention or inversion of the configuration, respectively (Scheme 50). Final hydrogenolysis afforded (*S*)- or (*R*)-2-phenylpiperidine, respectively. To explain the observed stereochemistry, intermediates **I** and **II** were proposed. In intermediate **I**, after complexation with Red-Al, hydride delivering took place by the same face than the C-O bond. However, using 9-BBN an ion paired intermediate **II** was formed followed by intramolecular hydride delivery from the preferred conformation. The same methodology allowed diastereodivergent routes to *cis*- and *trans*-3-ethyl-2-phenylpiperidine. In addition, a concise route to the tobacco alkaloid (*S*)-2-(3-pyridyl)piperidine (−)-anabasine was also reported.



Scheme 50 Enantiodivergent route to (*S*)- and (*R*)-2-phenylpiperidine.

The same group reported diastereodivergent routes to enantiopure ethyl *cis*- and *trans*-3-ethylpiperidineacetates.[85] The key step is the conjugate addition of an enolate or a cuprate to unsaturated bicyclic lactams. Starting from the saturated bicyclic lactam, after treatment with KH and methyl phenylsulfinate, followed by heating of the resulting sulfoxides, the corresponding unsaturated lactam was obtained (Scheme 51). The conjugate addition of the enolate of ethyl 1,3-dithiolane-2-carboxylate took place with high diastereoselectivity under thermodynamic control and, after desulfuration, the corresponding ester was obtained. Subsequent reduction of the carbonyl group with borane and reductive cleavage of the oxaziridine ring gave, after debenzylation, *trans*-3-ethyl-4-piperidineacetate derivative. Alternatively, hydrogenolysis of the C-N bond with calcium in liquid NH_3 and treatment with Et_3SiH in TFA afforded the *trans*-lactam. For the *cis*-series, the starting bicyclic lactam was transformed into the unsaturated lactam[85b] which, after conjugated addition of lithium allylcuprate under kinetic control, gave a

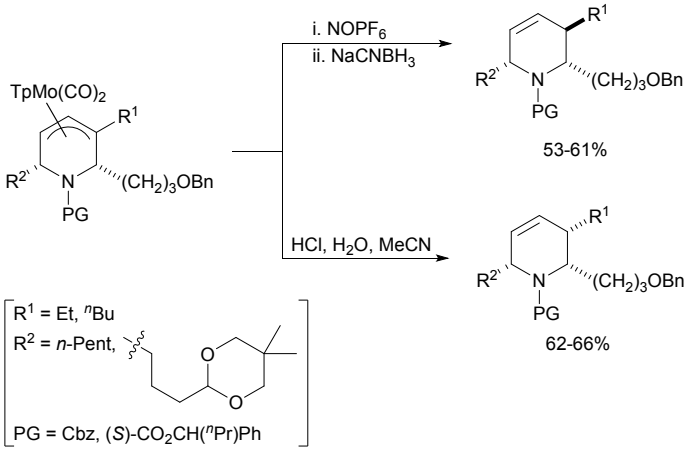
83:17 mixture of diastereomers. The allyl substituent was transformed into the acetate by ozonolysis followed by oxidation of the resulting aldehyde and esterification. Following the above-mentioned functional group transformations, the *cis*-series were obtained.



Scheme 51 Diastereodivergent routes to substituted *cis*- and *trans*-lactams and piperidines.

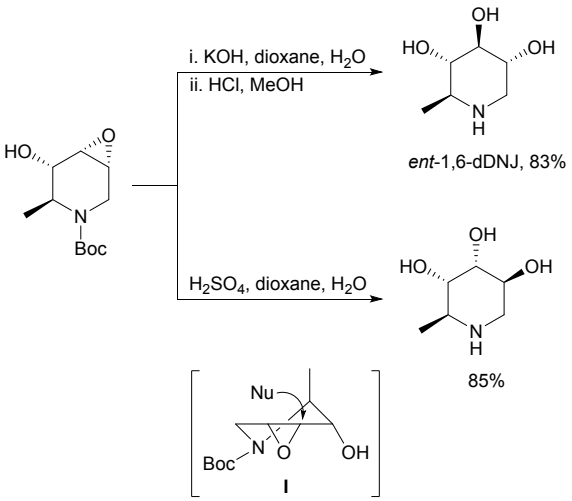
Diastereodivergent routes to 2,3,6-trisubstituted piperidines have been reported by Liebeskind and co-workers[86] from (±)-Tp(CO)$_2$(η^3)-pyridinylmolybdenum complexes. Depending on the demetalation protocol 2,6-*cis*-3-*trans*- or 2,3,6-*cis*-systems were

obtained. The preparation of pyridinyl molybdenum scaffolds with hydridotrispyrazolylborate (Tp) as ligand were previously described by the same group.[87] Demetalation using $NOPF_4$ and then addition of the hydride from $NaCNBH_3$ on the resulting cationic intermediate delivered the 2,6-*cis*-3-*trans*-dehydropiperidines. On the other hand, protodemetalation under acidic conditions placed hydrogen at the more substituted end of the η^3-allylmolibdenum and *syn* to the TpMo unit giving *cis*-2,3,6-trisubstituted dehydropiperidines (Scheme 52). This methodology has been applied to the synthesis of indolizidines (±)-209I and (±)-8-*epi*-209F, as well as (−)-indolizidine 251AA and (−)-dehydroindolizidine 233E.



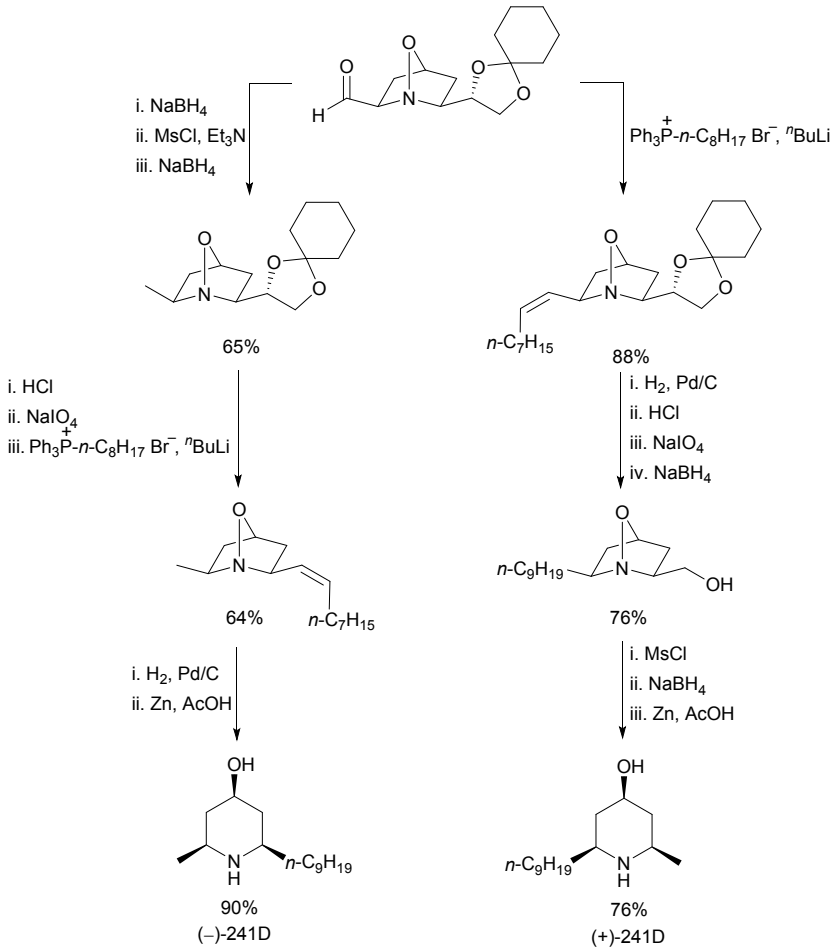
Scheme 52 Diastereodivergent routes to 2,6-*cis*-3-*trans*- and *cis*-2,3,6-trisubstituted dehydropiperidines.

A bicyclic piperidine epoxide intermediate has been used by Park and co-workers[88] for the diastereodivergent synthesis of hydroxylated piperidines. By treatment of this intermediate with KOH a *trans*-diaxial ring opening (**I**; Furst-Partner control[89]) took place giving after *N*-Boc deprotection with HCl, *ent*-1,6-dideoxynojirimycin (dDNJ) (Scheme 53). Alternatively, treatment with H_2SO_4 provided 5-amino-1,5,6-trideoxyaltrose.



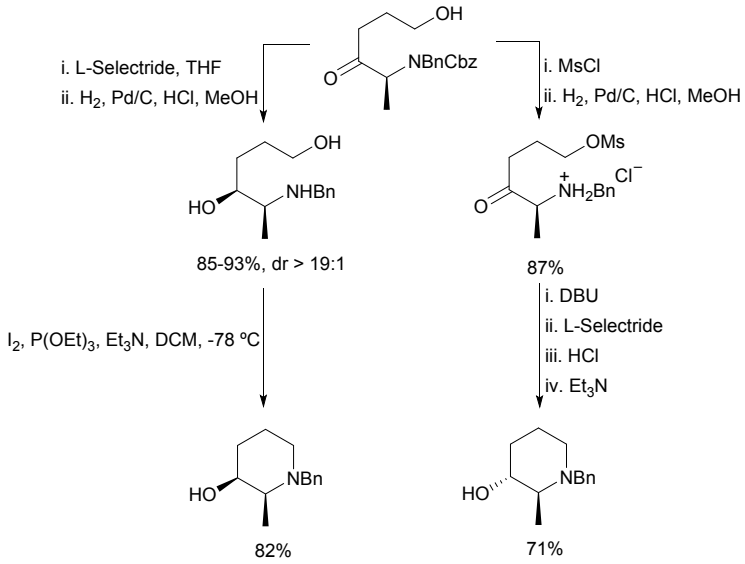
Scheme 53 Diastereodivergent routes to *ent*-1,6-didehydrodeoxynojirimycin and its diastereomer.

The dendrobate alkaloid 241D and its 4-oxo derivative are potent inhibitors of histrionicotoxin binding to the nicotine receptor as well as the noncompetitive blocker of acetylcholine to nicotinic receptor channel complex. Saha and Chattopadhyay[90] have performed enantiodivergent routes to (+)- and (–)-241D. These compounds are a subclass of *cis*-2,6-disubstituted piperidines, which are ubiquitous in the plant and animal kingdom. The common oxazabicycle starting compound has been prepared from (*R*)-2,3-*O*-cyclohexylideneglyceraldehyde. For the synthesis of (–)-241D, the aldehyde functionality was reduced to an alcohol, which after mesylation and reductive removal, provided the corresponding methyl-substituted oxazacycle in 65% overall yield. Then, the dioxolane moiety was transformed into a nonyl chain through acid-mediated deprotection to the diol, oxidative cleavage to the corresponding aldehyde and Wittig olefination to the (*Z*)-alkene. Hydrogenation of the C=C bond and final reductive cleavage of the N-O bond provided (–)–241D (Scheme 54). By reversal synthetic manipulation through the conversion of the aldehyde to a nonyl chain and the dioxolane moiety to a methyl group the (+)-enantiomer was prepared.



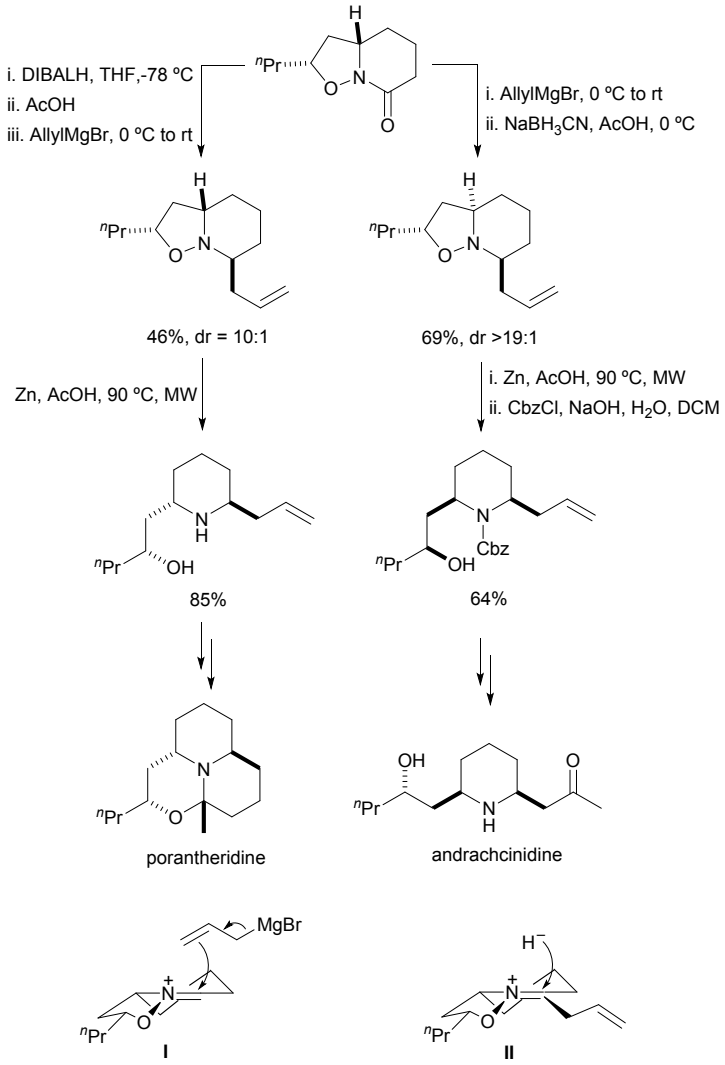
Scheme 54 Enantiodivergent routes to (–)- and (+)-241D alkaloids.

Koskinen and co-workers[91] have reported diastereodivergent routes to *cis*- and *trans*-2-substituted 3-piperidinols. The core motif of numerous bioactive compounds such as the selective nonpeptic human neurokinin-1 substance P receptor antagonists L-733,060 and CP-99,994, the natural products febrifugine (antimalarial) and halofuginone (antiprotozoal), was designed. The common starting materials, hydroxyketones, were prepared from α-amino acids. In Scheme 55, the synthesis of *cis*-and *trans*-2-methyl-3-hydroxypiperidinols has been depicted. Reduction of the keto group with L-Selectride and subsequent Cbz-deprotection by catalytic hydrogenation, gave a diol, which was submitted to a modified Apel cyclization[92] (PPh_3/I_2) using $P(OEt)_3$ delivering the *cis*-*N*-benzylpiperidinol. On the other hand, for the *trans*-piperidinol the hydroxy ketone was mesylated and, after Cbz-deprotection and liberation of the free amine with DBU, the ketone was reduced with L-Selectride and final Et_3N-induced cyclization providing the desired diastereomer. Following the methodology described for the *cis*-isomer, L-33,060·HCl was also prepared.



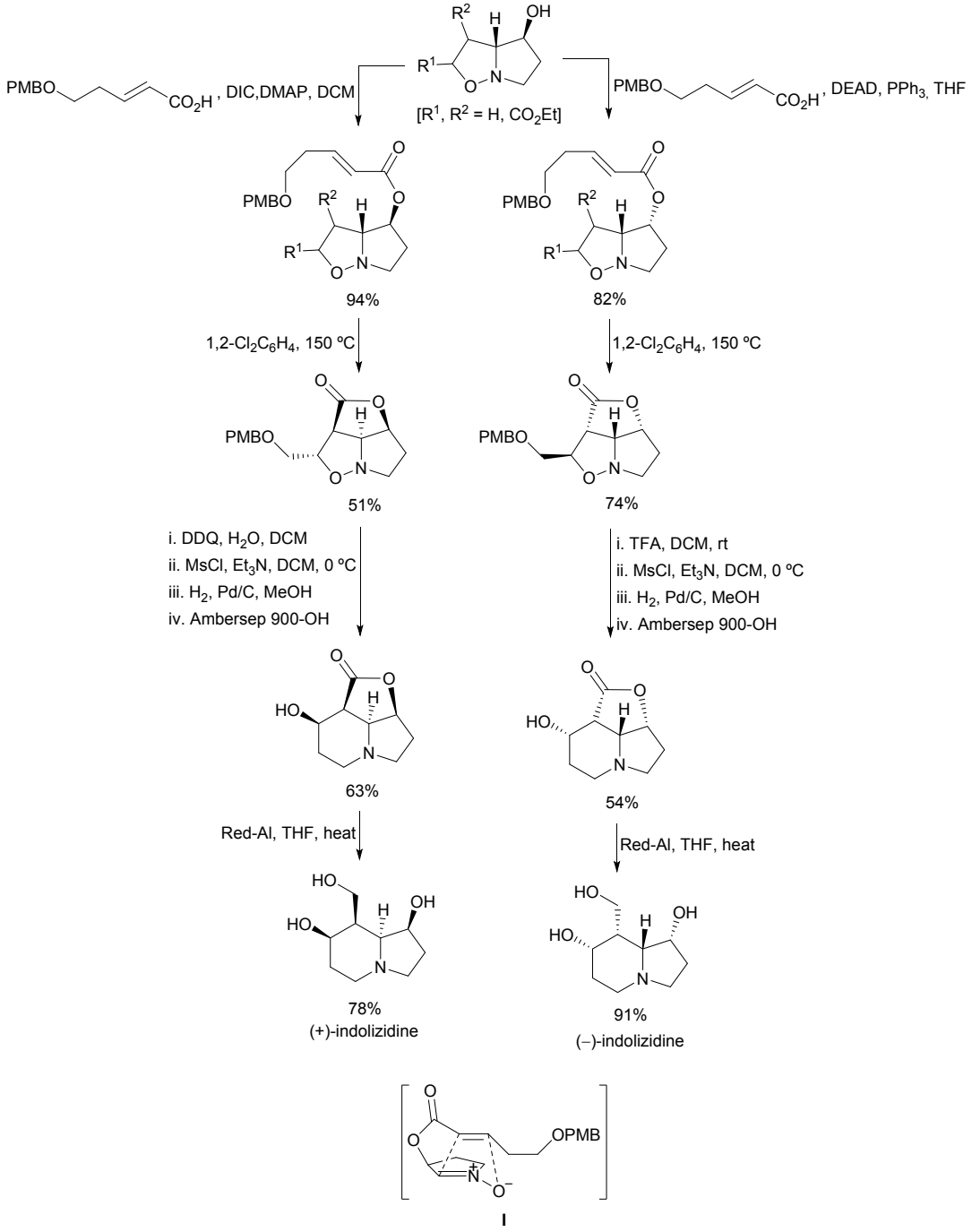
Scheme 55 Diastereodivergent routes to *cis*- and *trans*-3-hydroxy-2-methylpiperidinols.

A particular subclass within the family of piperidines contains a 2-oxygenated side chain, such as sedamine, halosaline, 8-*epi*-halosaline, pelletierine, lobeline, andrachcinidine and porantheridine. The Vincent and Kouklovsky group[93] has reported diastereodivergent routes to access racemic bicyclic isoxazolidine precursors of 2,6-disubstituted piperidines from a *N*-alkoxy benzylic lactam. This lactam was reduced with DIBALH and then allylmagnesium bromide was added to the resulting iminium cation **I** to furnish the 2,6-*trans*-disubstituted piperidine after N-O cleavage (Scheme 56). The addition of allylmagnesium bromide and then reduction with $NaBH_3CN$ (through intermediate **II**) provided the 2,6-*cis*-disubstituted piperidine after Zn-reduction and N-Cbz protection. The *trans*-piperidine has been used for the formal synthesis of porantheridine.[94] The *cis*-2,6-disubstituted piperidine is a precursor of andrachcinidine.



Scheme 56 Diastereodivergent routes to *trans*- and *cis*-2,6-disubstituted piperidines.

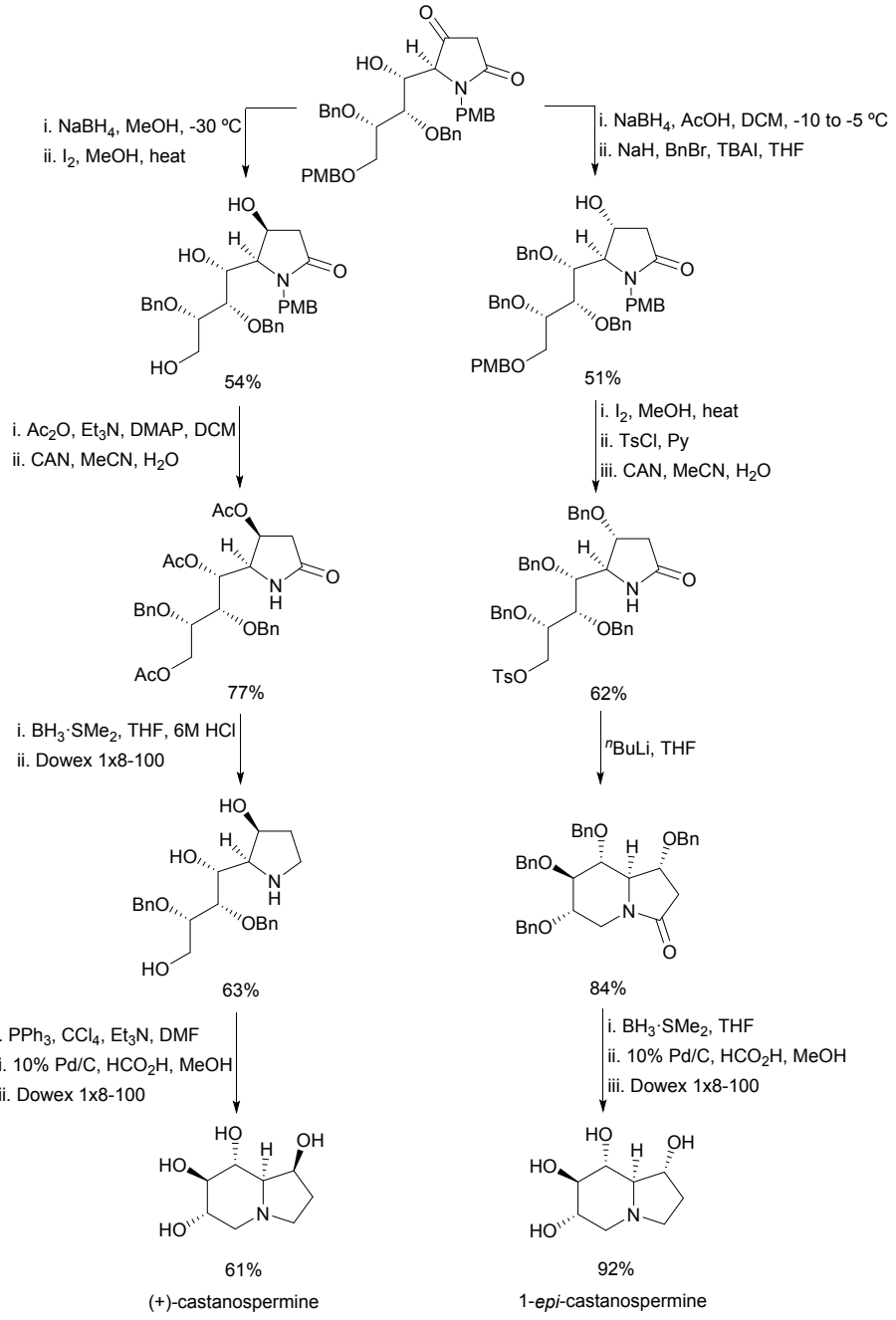
Natural polyhydroxylated indolizidine alkaloids are not only α- and β-glucosidase inhibitors, but also, they showed antiviral activity.[23,83] The Cordero and Brandi group[95] has performed the enantiodivergent synthesis of enantiopure trihydroxyindolizidines from the cycloadduct of a cyclic nitrone with styrene, ethyl acrylate and fumaronitrile. For the synthesis of (+)-trihydroxyindolizidine, the bicyclic isoxazolidines were acylated with PMB-protected (*E*)-5-hydroxy-2-pentenoic acid. The resulting ester underwent the domino retro-cycloaddition/intramolecular cycloaddition in refluxing *o*-dichlorobenzene through transition state **I**. Deprotection with DDQ afforded an alcohol, which after mesylation was hydrogenated to give a tricyclic indolizidine through a domino isoxazolidine ring opening/intramolecular nucleophilic substitution. Final reduction of the lactone moiety afforded the (+)-trihydroxyindolizidine (Scheme 57). In the case of using Mitsunobu conditions for the esterification step of bicyclic oxazolidine alcohol with (*E*)-*O*-PMB-5-hydroxy-2-pentenoic acid, inversion of the configuration at C-4 took place. After performing the retro-cycloaddition/intramolecular cycloaddition and deprotection of the PMB ether with TFA, the same steps mentioned above furnished the (−)-trihydroxyindolizidine.



Scheme 57 Enantiodivergent routes to (+)- and (–)-trihydroxyindolizidines.

Diastereodivergent routes to castanospermine and 1-*epi*-castanospermine have been achieved by Huang and co-workers[96] from a common chiral building block, that means, a tetramic acid derivative. This compound was regioselectively reduced with $NaBH_4$ giving a 7:1 mixture of diastereomeric alcohols. The primary alcohol was obtained by debenzylation with iodine in refluxing methanol and the resulting triol was triacetylated. Deprotection of the lactam with CAN and reduction with borane afforded a pyrrolidine, which was cyclized and then debenzylated to castanospermine (Scheme 58).

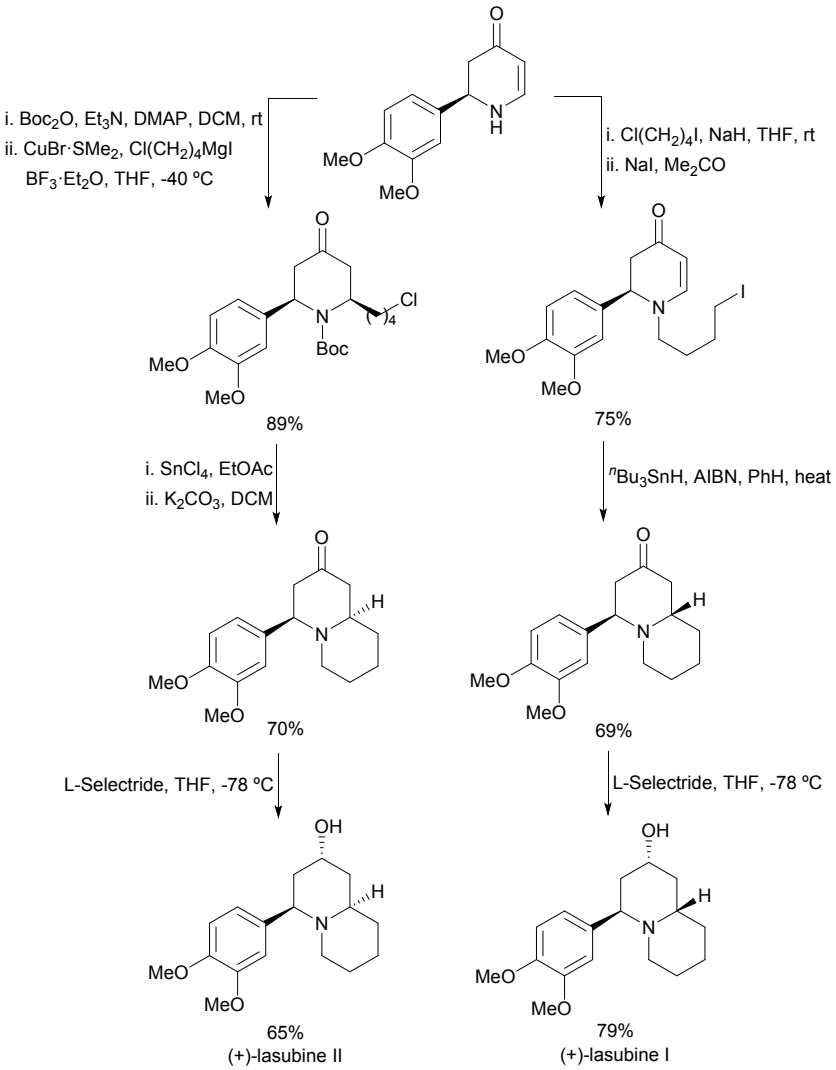
The inversion of the configuration during the reduction of the ketone in the starting tetramic acid derivative was achieved in the presence of AcOH at -10 to 5 ºC. After benzylation of the diol and debenzylation of the primary alcohol it was tosylated, and the lactam deprotected. Cyclization took place after NH deprotection of the lactam with *n*-BuLi followed by reduction of the carbonyl group and debenzylation with a 10% Pd/C-catalyzed transfer hydrogenation to provide 1-*epi*-castanospermine.



Scheme 58 Diastereodivergent routes to (+)-castanospermine and 1-*epi*-castanospermine.

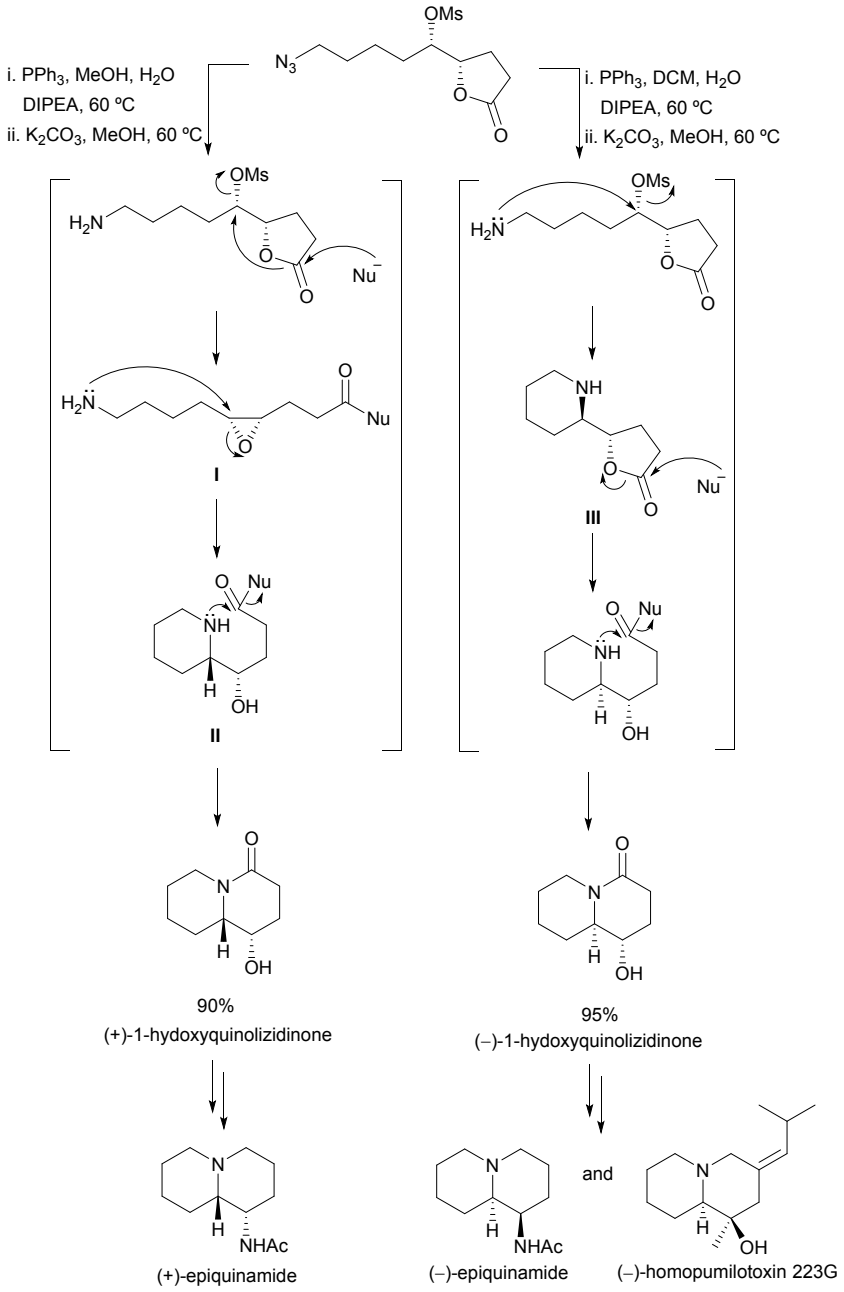
Quinolizidine alkaloids are present mainly in plants and in amphibians, and display a broad range of biological activities.[23,83] Lasubines I and II are two quinolizidine

alkaloids isolated from plants of the Lythraceae family, which have been prepared by Carretero and co-workers[97] using diastereodivergent routes. The key common intermediate is a chiral dihydropyridone obtained by a Cu-catalyzed asymmetric aza-Diels-Alder reaction of Danishefsky's diene with a *N*-tosyl aldimine. Conjugate addition of the cuprate derived from 4-chloro-*n*-butylmagnesium under Comins conditions[98] ($CuBr{\cdot}SMe_2/BF_3{\cdot}Et_2O$) to *N*-Boc dihydropyridone provided mainly the *cis*-2,6-disubstituted piperidone with 9:1 dr. Boc deprotection using $SnCl_4$ and cyclization under basic conditions gave the quinolizidine ketone, which was reduced with L-Selectride to yield (+)-lasubine II (Scheme 59). For the synthesis of (+)-lasubine I, the starting dihydropyridone was *N*-alkylated with 4-chloro-1-iodo-*n*-butane and then treated with NaI to prepare the corresponding iodo derivative able to be subjected to radical cyclization giving mainly the *trans*-quinolizidinone, which was reduced to the expected (+)-lausabine I.



Scheme 59 Diastereodivergent routes to (+)-lasubine II and I.

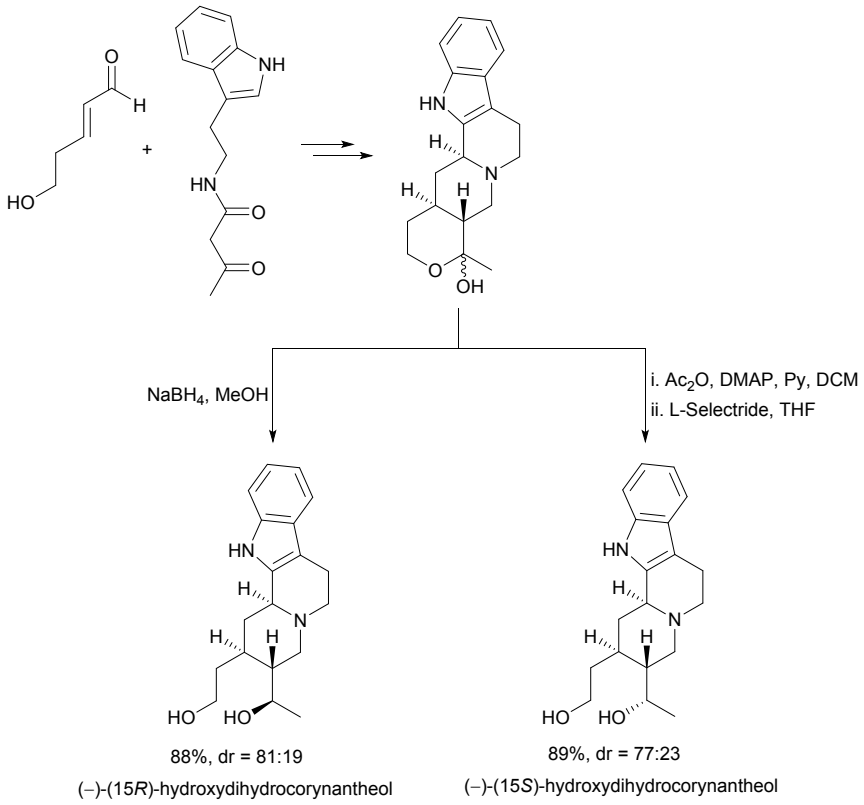
Kim and co-workers[99] have reported diastereodivergent routes to 1-hydroxyquinolizidinone isomers precursors of natural quinolizidines (–)-homopumiliotoxin 223G and epiquinamides.[100,101] The key step is the sequential cyclization of the common precursor, a chiral hydroxy lactone prepared through Sharpless asymmetric dihydroxylation and subsequent lactonization of ethyl (*E*)-9-bromonon-4-enoate. Cyclization of this lactone by means of a Staudinger reaction using DIPEA as base in MeOH provided (+)-1-hydroxyquinolizidinone, precursor (+)-epiquinamide[101] isolated from poison frog *Epipedobates tricolor* (Scheme 60). For the other (–)-isomer the cyclization was performed in acetonitrile instead of methanol. This (–)-1-hydroxyquinolizidinone has been used for the synthesis of (–)-epiquinamide[101] and (–)-homopumiliotoxin 223,[100] which was isolated from the poison of *Dendrobates pumilio*. The authors explain that in the first case the presence of enough water in the solvent favors that the nucleophilic MeOH would induce the formation of the epoxide, which gave the piperidine and then the lactam through intermediates **I** and **II**. However, with the less nucleophilic solvent the amino group would lead to the intramolecular S_N2 process to form the piperidine ring (intermediate **III**) and then the addition of the solvent would force the lactone opening and subsequent cyclization through **III**.



Scheme 60 Diastereodivergent routes to (+)- and (–)-1-hydroxyquinolizidiones.

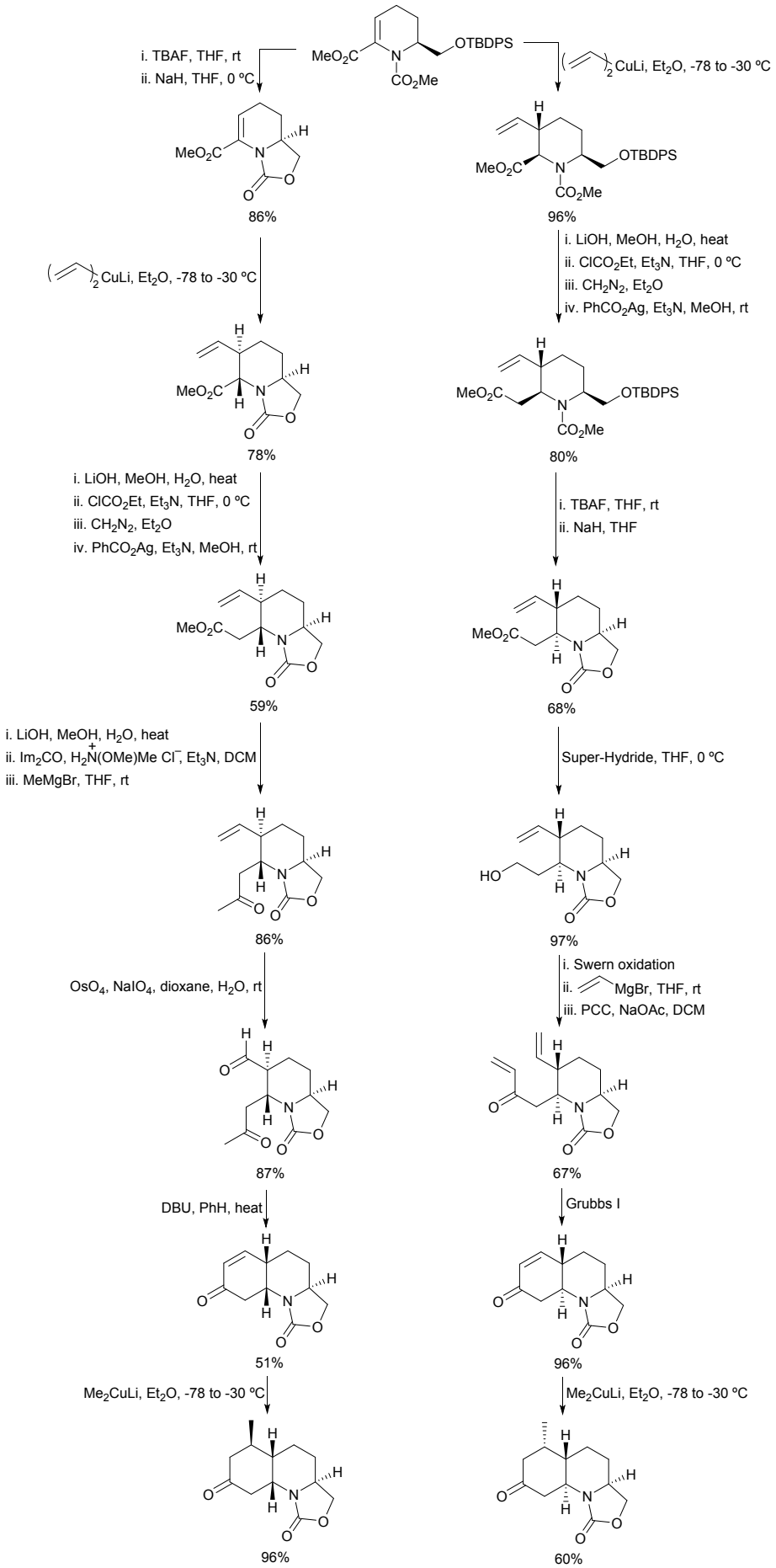
The coryantheine and ipecac alkaloid families contain a wide number of naturally occurring compounds with a quinolizidine structural motif. They are mainly isolated from the leaves of *Uncaria tormentosa* (cat claw) and the roots of *Cephaelis ipecacuanha* (Rubiaceae) with a long history of usage as herbal drugs. Diastereodivergent routes to (–)-(15*S*)-hydroxydihydrocorynantheol, alkaloid isolated from an endemic tree of Puerto Rico (*Antirhea portoricensis*, Rubiaceae), and its (15*R*)-epimer have been reported by Franzén and co-workers.[102] The common lactol intermediate was prepared by an one-pot process using (*E*)-5-hydroxypent-2-enal and a β-keto amide using (*R*)-*O*-(trimethylsilyl)diphenylprolinol as organocatalyst as key step for the construction of the quinolizidine carbon skeleton. This lactol was used as crude product and was reduced with $NaBH_4$ giving a 81:19 mixture of diols, which was characterized as the nonnatural

(–)-(15*R*)-hydroxydihydrocorynantheol in 57% overall yield (Scheme 61). However, the opening of the lactol by acetylation gave a ketone, which was reduced with L-Selectride giving the natural (–)-(15*S*)-hydroxydihydrocorynantheol with 77:23 diastereomer ratio and in 50% combined overall yield, from the β-keto amide.



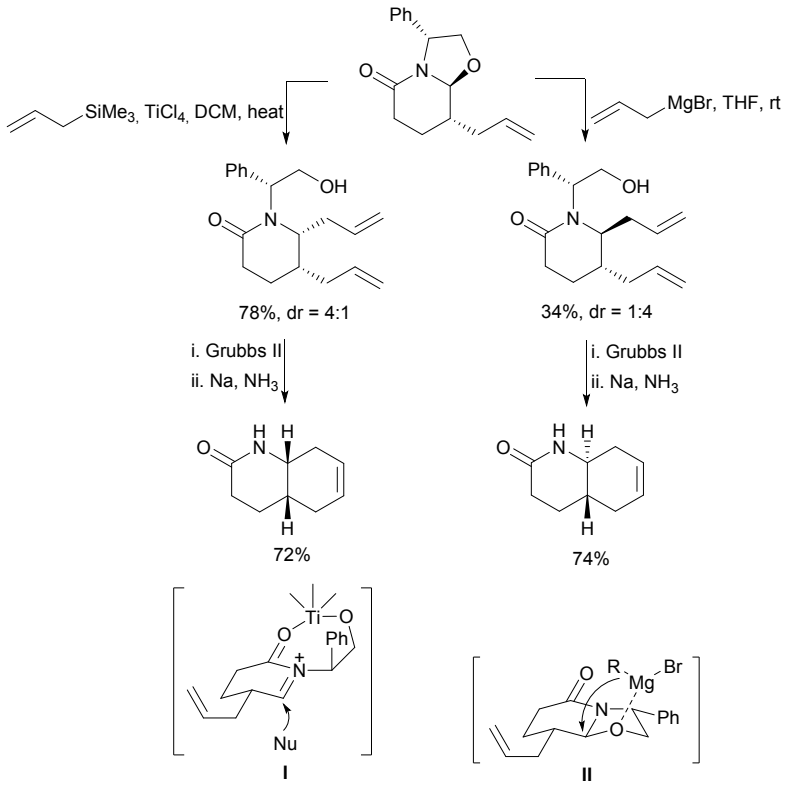
Scheme 61 Diastereodivergent routes to (–)-(15*R*)- and (–)-(15*S*)-hydroxydihydrocorynantheol.

Decahydroxyquinolines and mainly 2,5-disubstituted derivatives are constituents of poison frog alkaloids.[23,83] The Toyooka and Nemoto group[103] has performed diastereodivergent routes to *cis*- and *trans*-fused 2,5-disubstituted octahydroquinoline ring systems. As common starting material an enamino ester[104] was used. For the *cis*-fused decahydroquinoline, the primary alcohol was disilylated and cyclized to afford the fused oxazolidinone. After conjugate addition of vinyllithium cuprate, the ester functionality was homologated by an Arndt-Eistert reaction. By transformation of the ester into the Weinreb amide the corresponding methyl ketone was obtained. The vinyl substituent was transformed into a formyl group and then an intramolecular aldol reaction provided the cyclic enone, which by conjugate addition of methyllithium cuprate furnished the *cis*-fused decahydroquinoline (Scheme 62). For the *trans*-isomer conjugate addition of vinyllithium cuprate was followed by ester homologation and then formation of the oxazolidinone. The ester group was reduced and submitted to Swern oxidation, addition of vinylmagnesium bromide to the resulting aldehyde and PCC oxidation to afford a vinyl ketone. After a ring-closing metathesis reaction using Grubbs I catalyst and conjugate addition of methylmagnesium cuprate the corresponding *trans*-fused decahydroquinoline was obtained.


i. TBAF, THF, rt
ii. NaH, THF, 0 ºC
MeO2C
OTBDPS
CO2Me
(2) CuLi, Et2O, -78 to -30 ºC
86%
96%
(2) CuLi, Et2O, -78 to -30 ºC
i. LiOH, MeOH, H2O, heat
ii. ClCO2Et, Et3N, THF, 0 ºC
iii. CH2N2, Et2O
iv. PhCO2Ag, Et3N, MeOH, rt
78%
80%
i. LiOH, MeOH, H2O, heat
ii. ClCO2Et, Et3N, THF, 0 ºC
iii. CH2N2, Et2O
iv. PhCO2Ag, Et3N, MeOH, rt
i. TBAF, THF, rt
ii. NaH, THF
59%
68%
i. LiOH, MeOH, H2O, heat
ii. Im2CO, H2N(OMe)Me Cl−, Et3N, DCM
iii. MeMgBr, THF, rt
Super-Hydride, THF, 0 ºC
86%
97%
OsO4, NaIO4, dioxane, H2O, rt
i. Swern oxidation
ii. MgBr, THF, rt
iii. PCC, NaOAc, DCM
87%
67%
DBU, PhH, heat
Grubbs I
51%
96%
Me2CuLi, Et2O, -78 to -30 ºC
Me2CuLi, Et2O, -78 to -30 ºC
96%
60%

Scheme 62 Diastereodivergent routes to *cis*- and *trans*-fused decahydroquinolines.

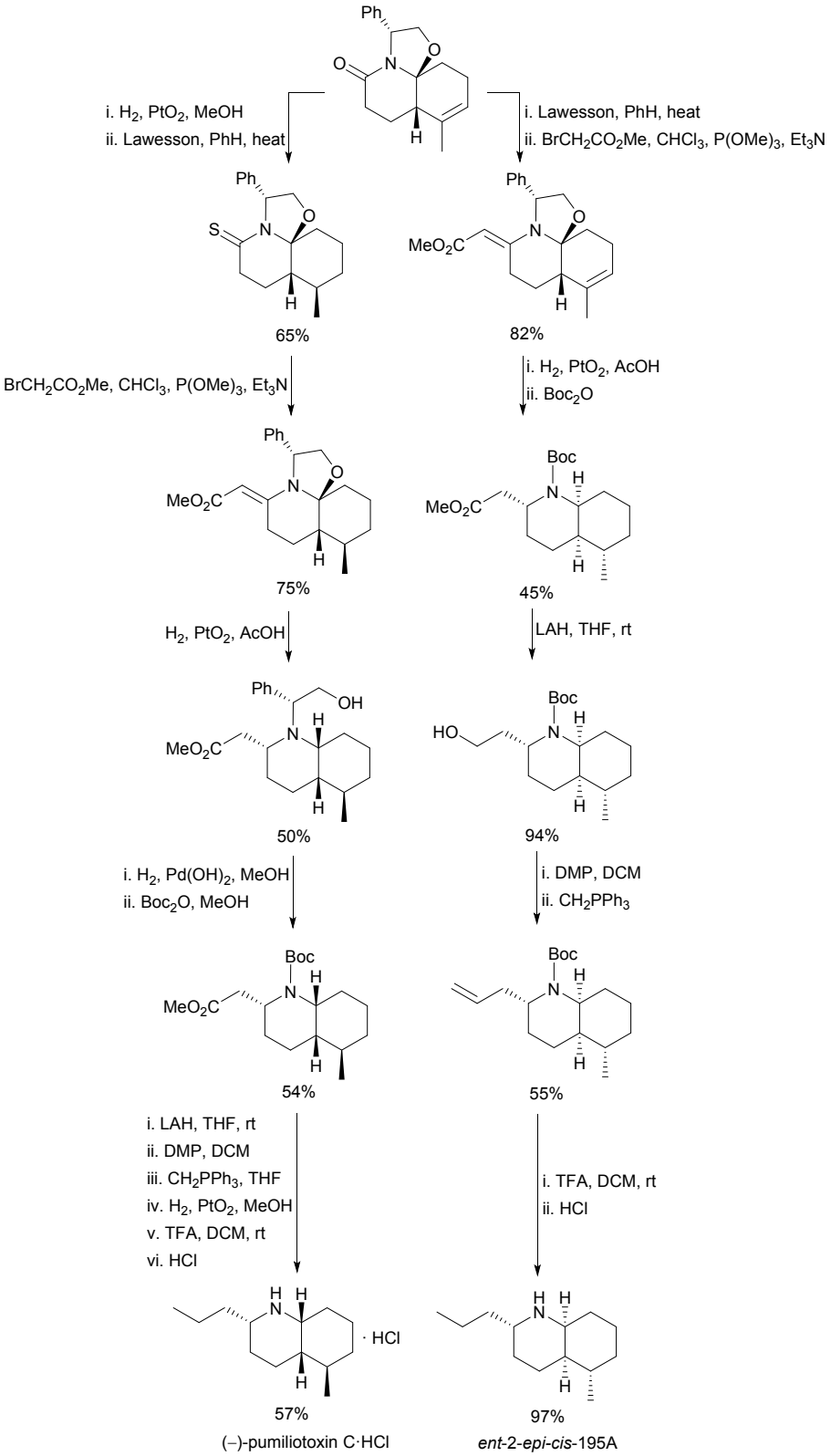
The Amat and Bosch group[105] has used 8-allyl substituted oxazolopiperidone lactam,[106] prepared from (*R*)-phenylglycinol and δ-oxo esters, as common starting material for the synthesis of *cis*- and *trans*-hexahydroquinolones. By means of allyltrimethylsilane in the presence of $TiCl_4$ the *cis*-derivative was the major isolated product according to intermediate **I**, which after ring closing metathesis and final removal of the phenylethanol moiety with sodium in liquid ammonia provided enantiopure *cis*-hexahydroquinolone (Scheme 63). The stereoselectivity of the α-amidoalkylation was reversed using allylmagnesium bromide by participation of intermediate **II**, to give the *trans*-diallylated product, which was further transformed as above into the *trans*-hexahydroquinolone.



Scheme 63 Diastereodivergent routes to *cis*- and *trans*-hexahydroquinolines.

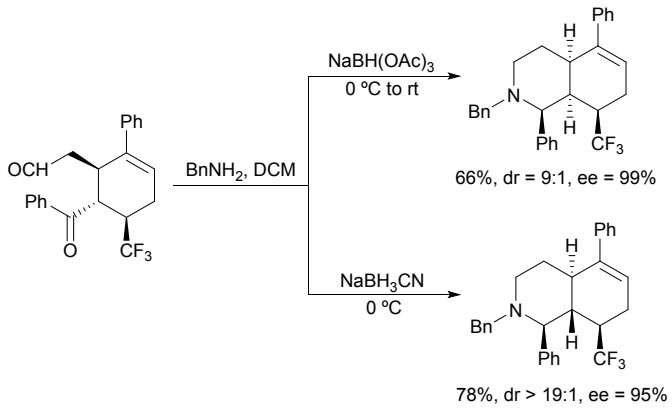
The same group[107] has prepared 2,5-disubstituted *cis*-decahydroquinolines including (–)-pumiliotoxin C (*cis*-195A) and (–)-*ent*-2-*epi*-*cis*-195A from a tricyclic hydroquinoline lactam as common starting material. This lactam was prepared from a diketo diester and (*R*)-phenylglycinol. For the preparation of (–)-pumiliotoxin C the starting lactam was hydrogenated and then converted into the thioamide with Lawesson's reagent. By means of Eschenmoser sulfide contraction conditions, the β-enamino ester was obtained. Subsequent hydrogenation gave the desired *cis*-junction in the decahydroquinoline unit by cleavage of the C-O bond, and the saturation of the

unsaturated ester. Further functional group transformations provided (–)-pumiliotoxin C hydrochloride (Scheme 64). Unexpectedly, reversing the order of the two first steps gave the corresponding epimer, which was further transformed as above into *ent*-2-*epi*-*cis*-195A.



Scheme 64 Diastereodivergent routes to (–)-pumiliotoxin C and *ent*-2-*epi*-*cis*-195A.

Diastereodivergent routes to enantiopure *cis*- and *trans*-fused trifluoromethylated octahydroisoquinolines have been reported by Chen and co-workers.[108] The starting cyclohexene was obtained by a Diels-Alder reaction of (*E*)-1,1,1-trifluoro-4-phenylbut-3-en-2-one with 4-phenylhexa-2,4-dienal organocatalyzed by a chiral protected (4*R*)-aminodiarylprolinol. Unexpectedly, the reductive amination step took place in a diastereodivergent manner giving *cis*-fused octahydroisoquinoline using $NaBH(OAc)_3$ (Scheme 65). However, when $NaBH_3CN$ was employed in this reductive amination step the epimerization at the α-carbon was not observed and the *trans*-isomer was obtained in 78% yield and 95% ee.

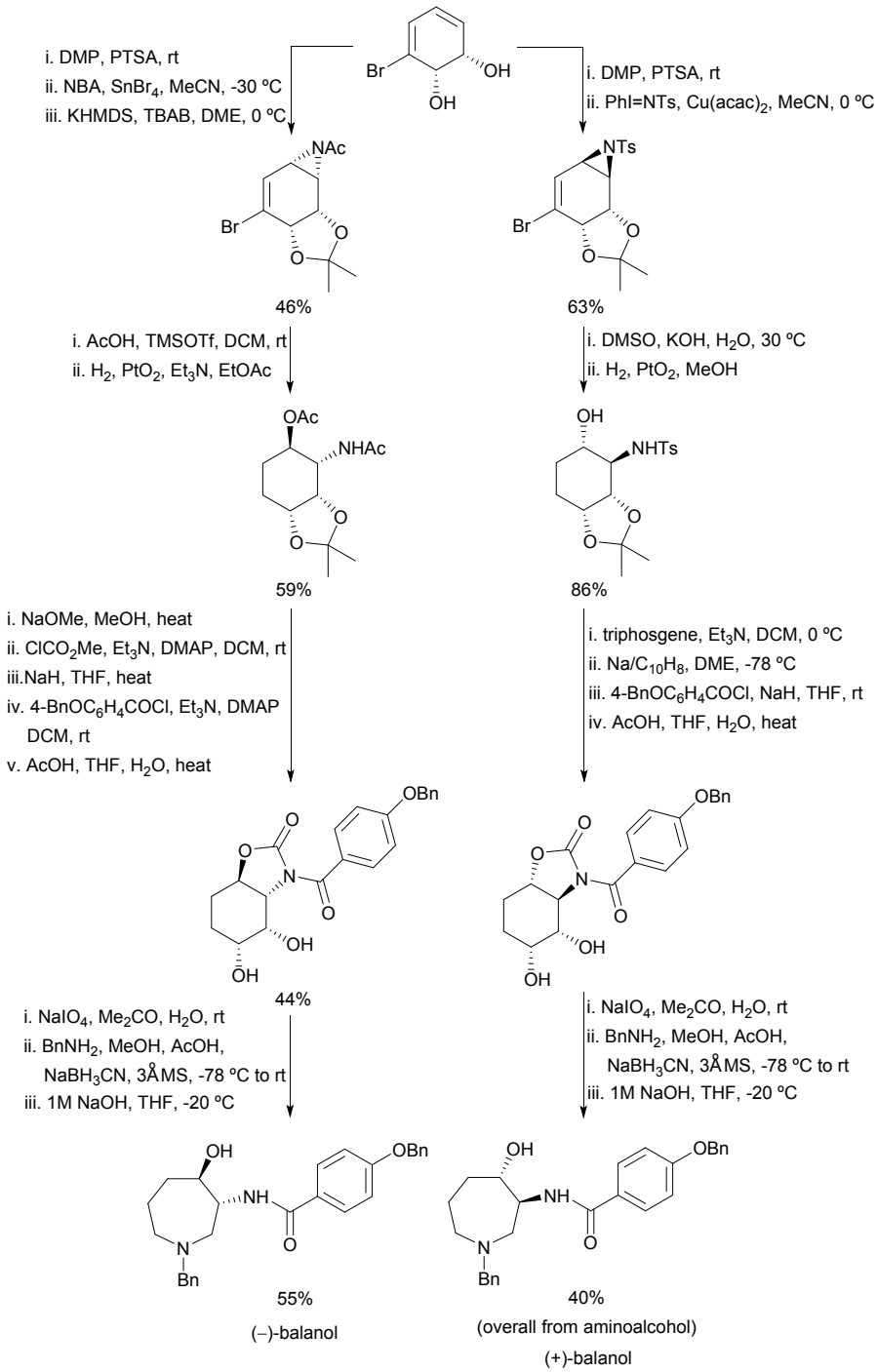


Scheme 65 Diastereodivergent routes to *cis*- and *trans*-fused trifluoromethylated octahydroisoquinolines.

4.3. Other alkaloids

Formal total synthesis of both enantiomers of balanol, a fungal metabolite inhibitor of protein kinase C, has been carried out by Hudlicky and co-workers[109] from 1-bromo-2,3-dihydroxycyclohexa-4,6-diene obtained by the whole cell fermentation of bromobenzene with the recombinant strain *Escherichia coli* JM109 (pDTG 01).[110] The key diastereodivergent step is the preparation of the corresponding vinylaziridines. The all-*cis*-isomer was obtained by reaction of the common intermediate, the acetonide of the diol, with *N*-bromoacetamide (NBA) in the presence of $SnBr_4$ followed by a KHMDS-mediated elimination (Scheme 66). This aziridine was transformed into a 4:1 mixture of *trans*- and *cis*-acetates, which were separated by column chromatography to give, after hydrogenation, the fully saturated compound. After transformation into the oxazolidinone, it was benzoylated and the acetonide hydrolyzed and then submitted to oxidative cleavage to provide a dialdehyde. Final reductive amination with benzylamine and hydrogenolysis of the oxazolidinone furnished (–)-balanol, a hexahydroazepine derivative. For the synthesis of the enantiomeric form, the *anti*-disposed aziridine was obtained by aziridination of the dienediol with PhI=NTs. After ring opening with KOH in DMSO and hydrogenation the corresponding protected *trans*-amino alcohol was obtained. Then, the oxazolidinone was prepared using triphosgene and the tosyl group was removed with sodium naphthalenide to provide after acylation and hydrogenolysis

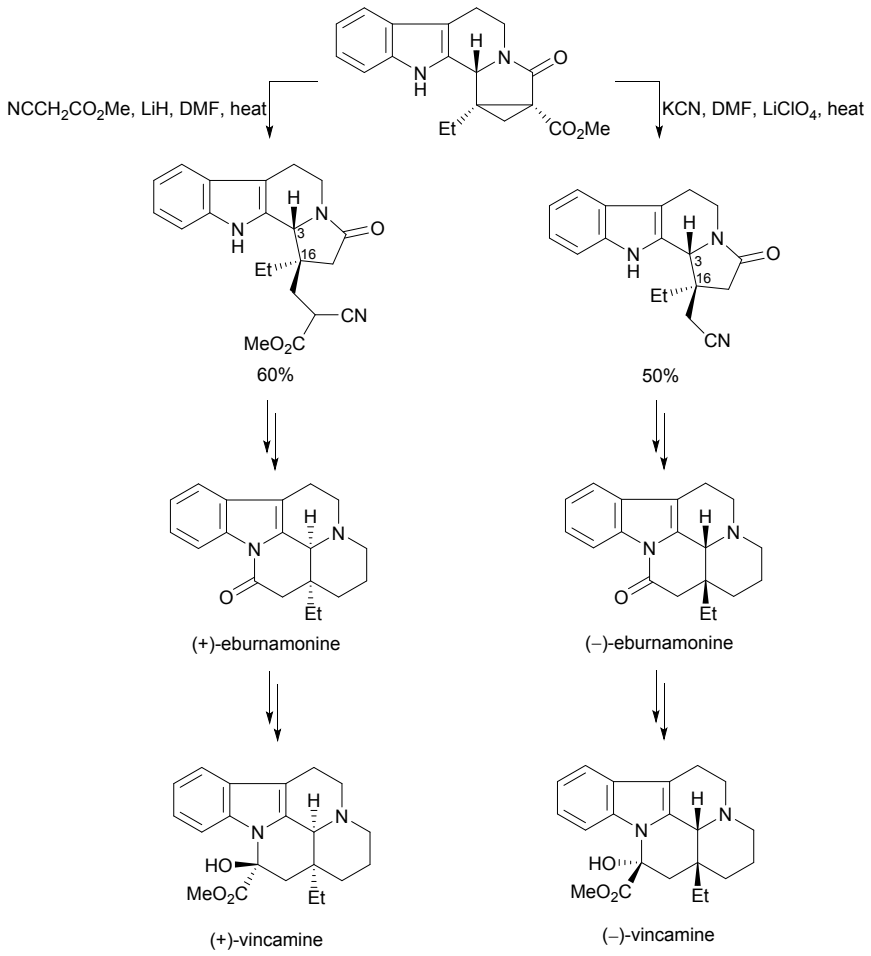
of the acetonide diol. Following the same transformations than before (+)-balanol was obtained in 40% overall yield from 2-(*N*-tosylamino)cyclohexanol.



Scheme 66 Enantiodivergent routes to (–)- and (+)-balanol.

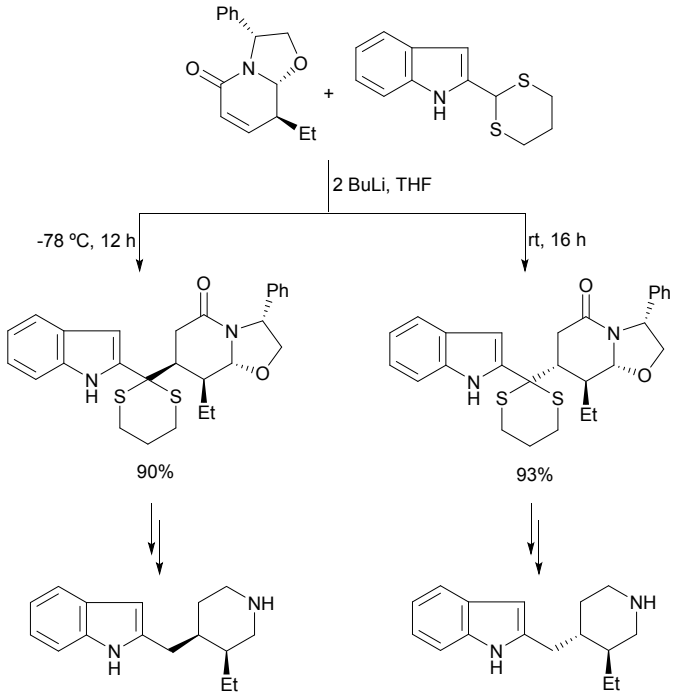
The natural occurrence of both enantiomers appears in the group of *vinca* alcaloids, which contain an indole unit. Winterfield and co-workers[111] described enantiodivergent routes to both vincamine enantiomers from a tetracyclic lactam, prepared by reaction of tryptamine with a cyclopropanecarboxaldehyde. Treatment with methyl cyanoacetate

followed by opening of this γ-lactam, subsequent rotation with formal inversion at C-16 and final cyclization provided a new lactam, which was further transformed into (+)-eburnamonine,[112] precursor of (+)-vincamine (Scheme 67). By nucleophilic ring opining with KCN isomerization at C-3 took place on the acid-catalyzed cyclization to form an acyl indole, which was further transformed into (–)-eburnamonine,[113] used in the synthesis of (–)-vincamine.



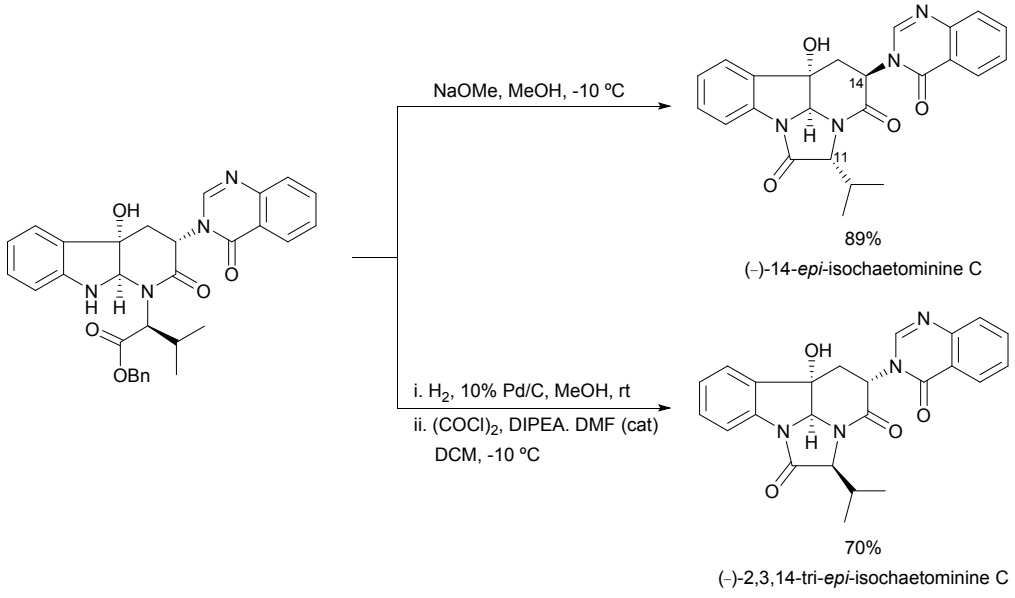
Scheme 67 Enantiodivergent routes to (+)- and (–)-vincamine.

A phenylglycinol-derived lactam has been used for the diastereodivergent synthesis of *cis*- and *trans*-2-[(3-ethyl-4-piperidyl)methyl]indole, a key intermediate in the synthesis of tetracyclic alkaloids,[83] by the Amat and Bosch group.[114] The crucial step was the conjugate addition of lithiated 2-(2-indolyl)-1,3-dithiane to an unsaturated lactam. Under kinetic control the *cis*-isomer was obtained in 4:1 diastereomeric ratio, while under thermodynamic control the enantiopure *trans*-isomer was only formed (Scheme 68).



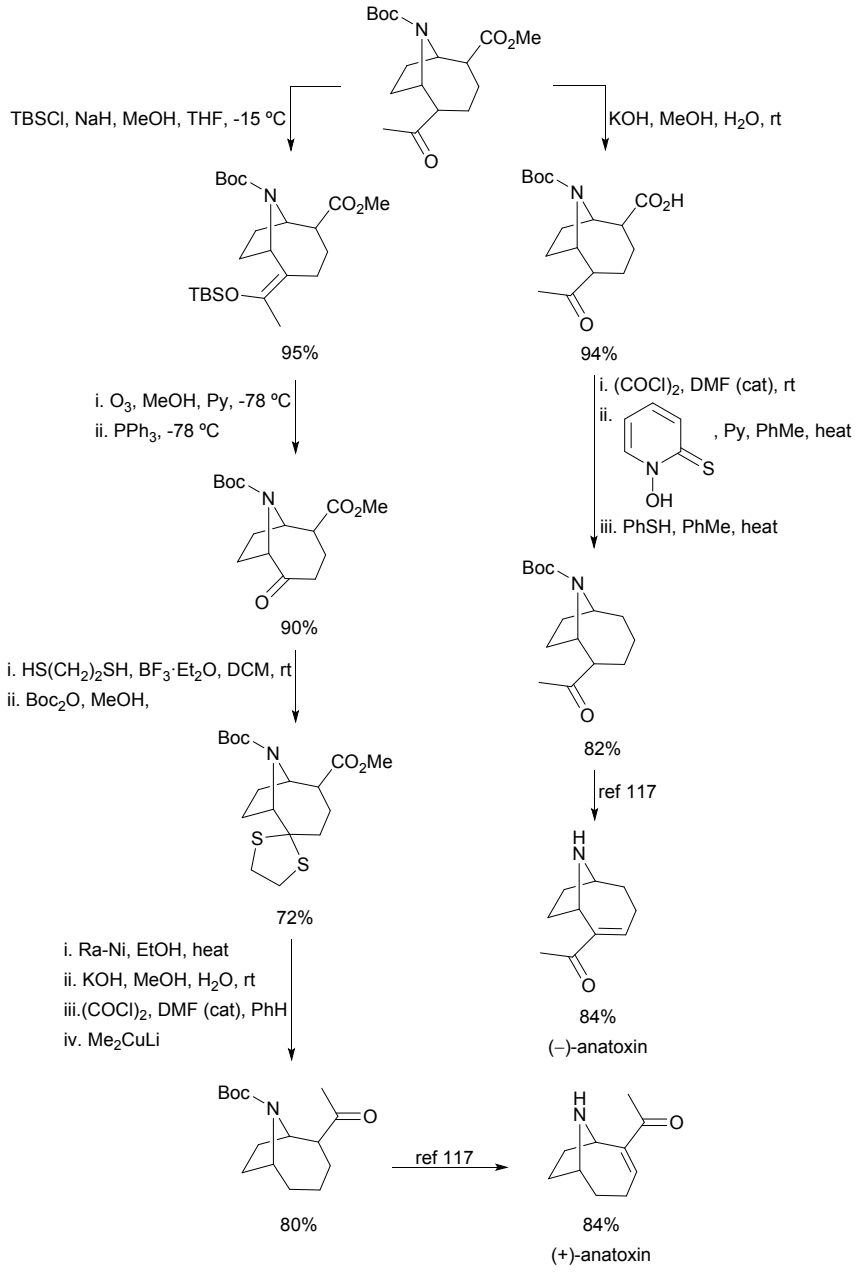
Scheme 68 Diastereodivergent route to *cis*- and *trans*-(piperidylmethyl)indoles.

Chaetominine-type alkaloids are mainly isolated from endophitic fungi. Huang and co-workers[115] have reported diastereodivergent routes to (–)-14-*epi*-isochaetominine C, the enantiomer of the (+)-natural product, and (–)-2,3,14-tri-*epi*-isochaetominine C, starting from L–tryptophan. As common starting material, a dihydroindole was used. By treatment with NaOMe a bis-epimerization at C-11 and C-14 occurred giving after lactamization (–)-14-*epi*-isochaetomicine C (Scheme 69). On the other hand, debenzylation of the starting compound followed by cyclization led to 2,3-tri-*epi*-isochaetominine C.



Scheme 69 Diastereodivergent routes to (–)-isochaetominine isomers.

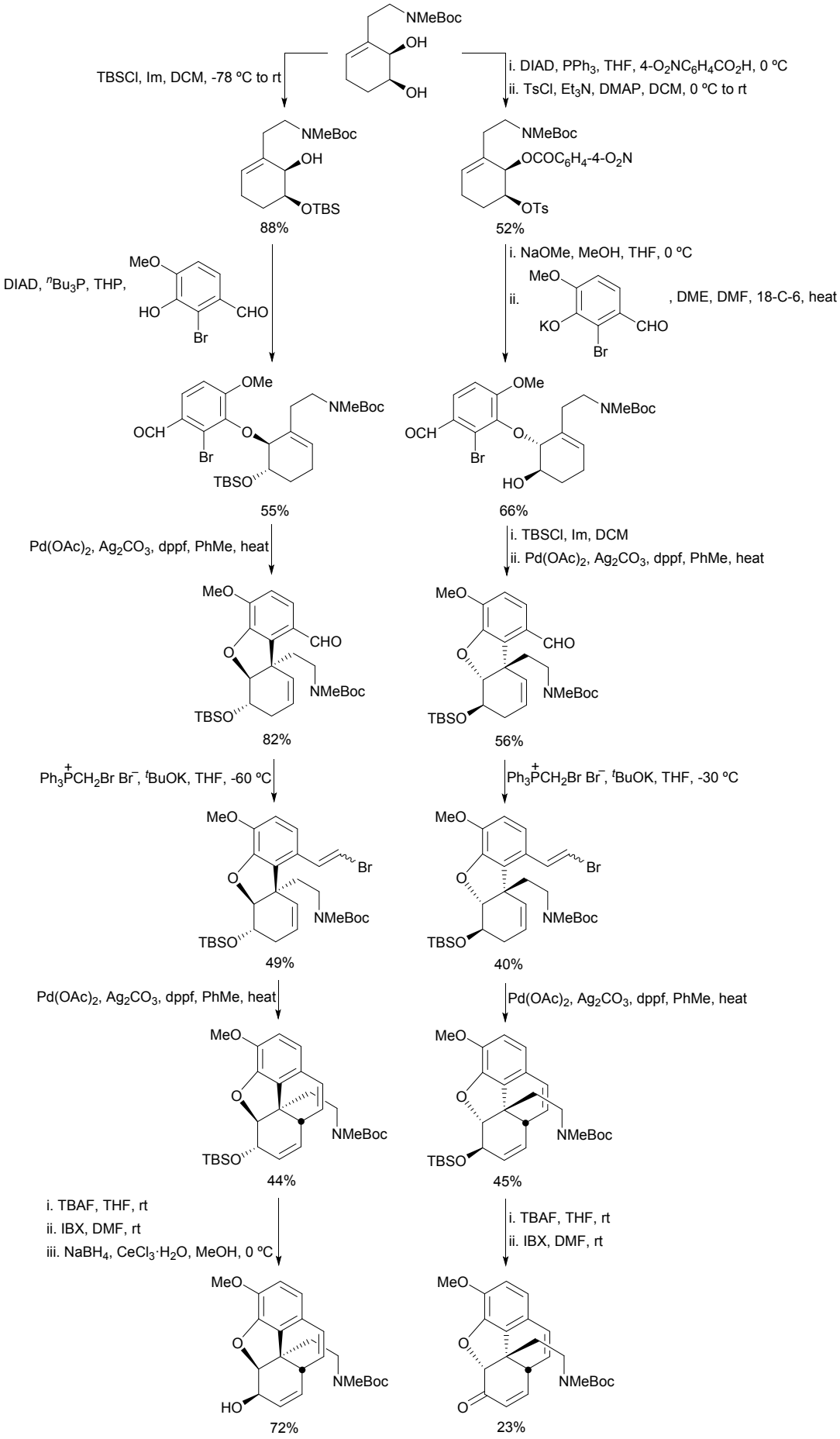
Rapoport and co-workers[116] performed the enantiodivergent synthesis of natural (+)-anatoxine and its enantiomer from L-glutamic acid. The natural alkaloid is a strong nerve-dipolarizing agent isolated from strains of the freshwater blue-green alga *Anabaena flos-aquae* de Breb. A homotropane was used as common starting material, which was transformed into a mixture of ketones by ozonolysis of its silyl enol ether. The keto group was protected as thioacetal and a Boc-deprotection was performed. Reprotection with Boc_2O followed by hydrogenolysis of the thioacetal gave the 2-deoxo compound. Conversion of the ester group into a methyl ketone and final selenenylation/oxidation[117] and *N*-protection provided (+)-anatoxin in 18% overall yield (Scheme 70). The unnatural enantiomer was prepared from the same intermediate, which was hydrolyzed to the corresponding acid and then transformed into its acyl chloride. Treatment with 1-hydroxy-2 (1*H*)-piperidinethione gave the *O*-acyl thiohydroximate, which was treated with thiophenol to afford the decarboxylated homotropane. After the same selenenynation/oxidation[117] and *N*-Boc deprotection (–)-anatoxin was obtained in 30% overall yield.

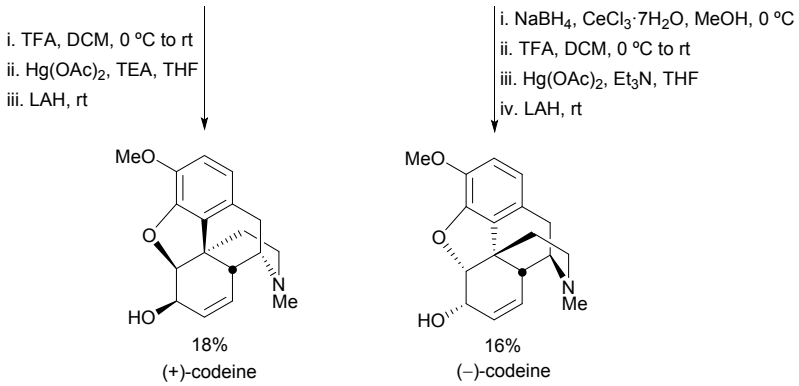


Scheme 70 Enantiodivergent routes to (+)- and (–)-anatoxin.

Hudlicky and co-workers[118] have performed the enantiodivergent synthesis of (+)- and (–)-codeine using a dienediol, obtained *via* enzymatic dihydroxylation of β-bromoethylbenzene with the recombinant strain *Escherichia coli* JM109 (pDTG 601) that over-expresses toluene dioxygenase. The key intermediate is an amino diol, which was monosilylated and the free hydroxy group was submitted to Mitsunobu conditions using bromoisovanillin as nucleophile. Further Heck reaction followed by a Wittig reaction and a second Heck cyclization gave the tetracyclic intermediate. The stereochemistry of C-6 was adjusted by desilylation, IBX oxidation and reduction to the allyl alcohol, which was deprotected with TFA. Final aminomercuration, followed by reduction with LAH, gave *ent*-codeine in a total number of 14 steps from β-bromoethylbenzene (Scheme 71). For

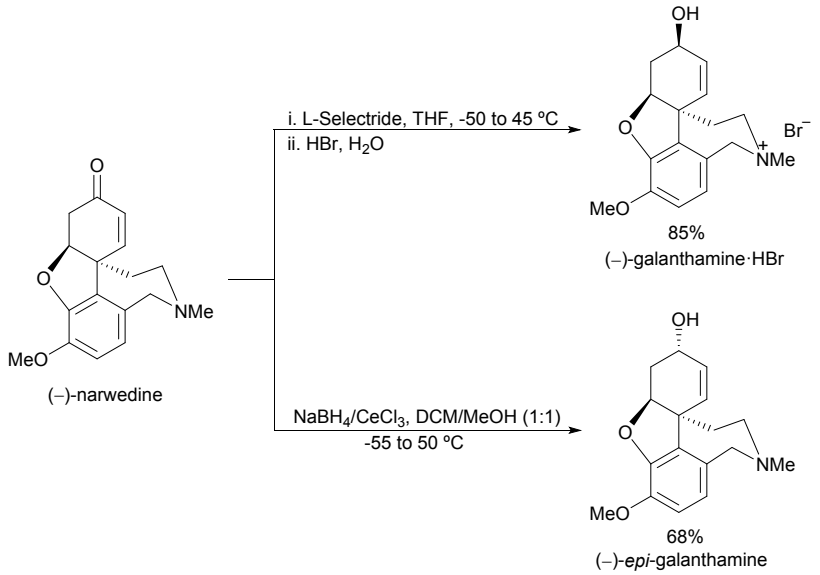
the natural enantiomer, Mitsunobu reaction with 4-nitrobenzoic acid and tosylation of the other hydroxy group, and then the sequence mentioned above, provided (–)-codeine.


NMeBoc
OH
OH
TBSCl, Im, DCM, -78 ºC to rt
i. DIAD, PPh3, THF, 4-O2NC6H4CO2H, 0 ºC
ii. TsCl, Et3N, DMAP, DCM, 0 ºC to rt
NMeBoc
OH
OTBS
88%
NMeBoc
OCOC6H4-4-O2N
OTs
52%
DIAD, nBu3P, THP,
MeO
HO
CHO
Br
i. NaOMe, MeOH, THF, 0 ºC
ii.
MeO
KO
CHO
Br
, DME, DMF, 18-C-6, heat
OMe
NMeBoc
OCH
O
Br
TBSO
55%
OMe
NMeBoc
OCH
O
Br
HO
66%
Pd(OAc)2, Ag2CO3, dppf, PhMe, heat
i. TBSCl, Im, DCM
ii. Pd(OAc)2, Ag2CO3, dppf, PhMe, heat
MeO
CHO
O
NMeBoc
TBSO
82%
MeO
CHO
O
NMeBoc
TBSO
56%
Ph3PCH2Br Br−, tBuOK, THF, -60 ºC
Ph3PCH2Br Br−, tBuOK, THF, -30 ºC
MeO
Br
O
NMeBoc
TBSO
49%
MeO
Br
O
NMeBoc
TBSO
40%
Pd(OAc)2, Ag2CO3, dppf, PhMe, heat
Pd(OAc)2, Ag2CO3, dppf, PhMe, heat
MeO
O
NMeBoc
TBSO
44%
MeO
O
NMeBoc
TBSO
45%
i. TBAF, THF, rt
ii. IBX, DMF, rt
iii. NaBH4, CeCl3·H2O, MeOH, 0 ºC
i. TBAF, THF, rt
ii. IBX, DMF, rt
MeO
O
NMeBoc
HO
72%
MeO
O
NMeBoc
O
23%



Scheme 71 Enantiodivergent routes to (+)- and (–)-codeine.

Diastereodivergent routes to all four stereoisomers of galanthamine have been described by Prabahar and co-workers.[119] The naturally occurring (–)-galanthamine has been approved for the treatment of mild to moderate Alzheimer's disease. Starting from (–)-narwedine, obtained by kinetic dynamic resolution of the corresponding racemate, the reduction with L-Selectride occurred through equatorial hydride attack. Then, after treatment with HBr, (–)-galanthamine hydrobromide was finally isolated (Scheme 72). However, using $NaBH_4/CeCl_3$ (Luche conditions) an axial hydride attack was predominantly observed to afford (–)-epigalanthamine. By using the same methodology with (+)-narwedine, (+)-galanthamine was obtained.

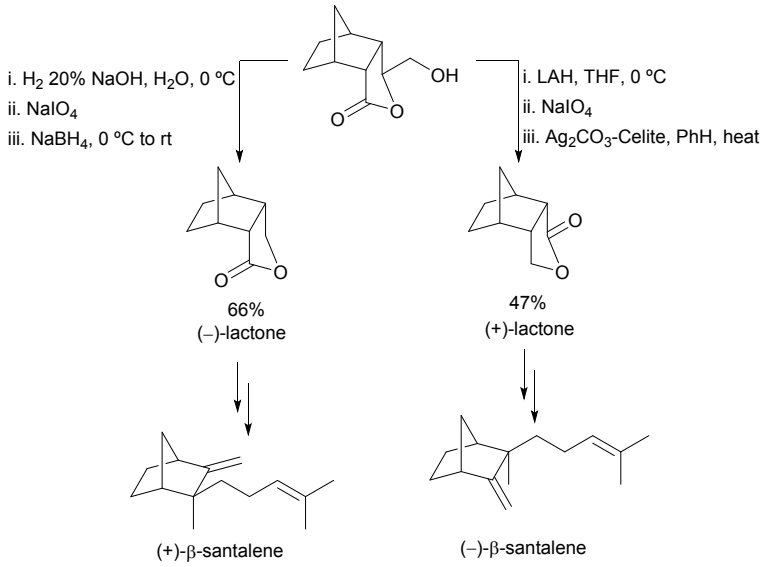


Scheme 72 Diastereodivergent routes to (–)-galanthamine and (–)-epigalanthamine.

5. Terpenes

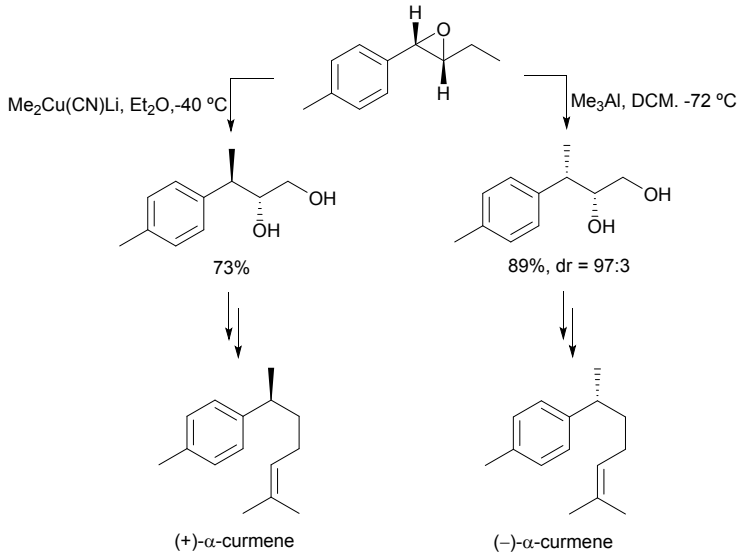
Nowadays terpenes play only a minor role as potential drugs because of their structural complexity, limited tractability and availability.[120] Enantiodivergent route to both enantiomers of β-santalene and also of *epi*-β-santalene were described by Takano and co-workers[121] starting from (*S*)-5-hydroxymethylbuten-2-olide,[122] accessible from D-

mannitol. This butanolide was heated in the presence of cyclopentadiene giving the *endo*-cycloadduct, which was further transformed into the common precursor of (–)- and (+)-bicyclic lactones. Hydrolysis of the saturated lactone, followed by treatment of the resulting carboxylate with sodium periodate and then with $NaBH_4$ in the same flask furnished the (–)-lactone, precursor of (+)-β-santalene, in 66% overall yield (Scheme 73). On the other hand, the reduction of the starting lactone with $LiAlH_4$ and subsequent oxidation of the alcohol to and aldehyde with $NaIO_4$ and final oxidation to acid with Ag_2CO_3-Celite in refluxing benzene provided the (+)-lactone in 47% overall yield, direct precursor of (–)-β-santalene. The common intermediate has been transformed into (+)- and (–)-bicyclic dimethylenones precursors of (+)- and (–)-*epi*-β-santalenes. All these sesquiterpenes are constituents of East Indian sandalwood oil.



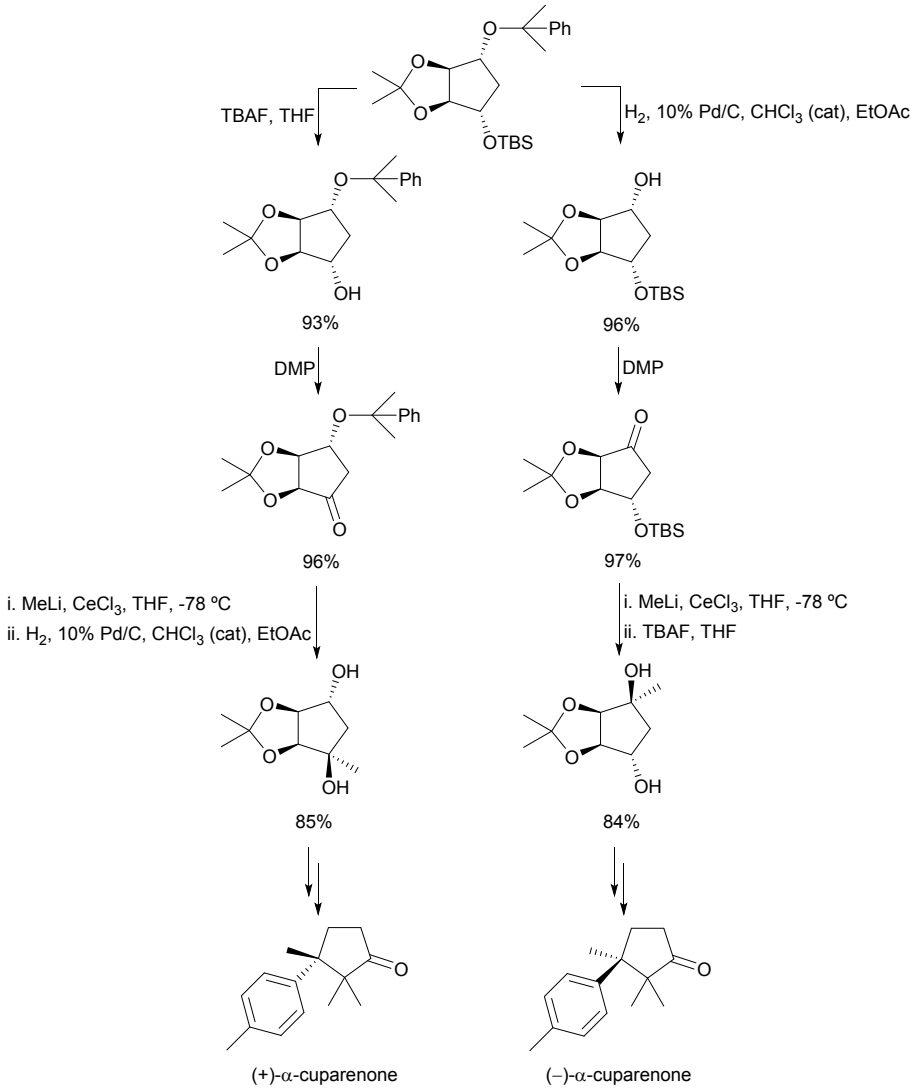
Scheme 73 Enantiodivergent routes to (+)- and (–)-β-santalenes.

The same group described enantioselective routes to aromatic biasabolane sesquiterpenes (+)- and (–)-α-curcumene from the epoxide obtained by Sharpless epoxidation of *trans*-4-methylcinnamate alcohol.[123] This (–)-3-(4-tolyl)glycidol was treated with lithium dimethylcyano cuprate to afford the corresponding diol in 73% yield (Scheme 74). This diol was further transformed into (–)-α-curcumene. Alternatively, the glycidol was treated with trimethylaluminum providing the other diastereomeric diol precursor of (+)-α-curcumene.



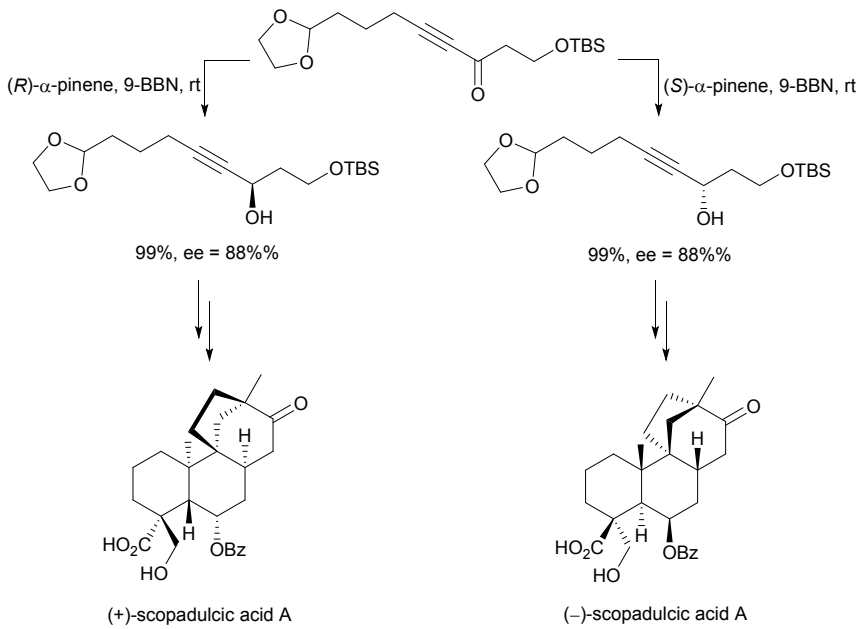
Scheme 74 Enantiodivergent routes to (+)- and (–)-α-curmenes.

α-Cuparenone is a sesquiterpene occurring in both enantiomeric forms in nature. Ogasawa and co-workers[124] have reported enantiodivergent routes to (–)- and (+)-α-cuparenone from an acetonide obtained from (–)-(*cis*-1,4)-4-cumyloxy-2-cyclopenten-1-ol.[125] Desilylation of the acetonide, followed by Dess-Martin oxidation, produced the corresponding ketone which, by reaction with MeLi in the presence of $CeCl_3$, gave diastereoselectively the tertiary alcohol. Final deprotection of the cumyl group by hydrogenation provided the (+)-diol precursor of (+)-α-cuparenone (Scheme 75). On the other hand, hydrogenolysis of the starting acetonide, followed by oxidation, provided the corresponding ketone, which reacted with MeLi giving, after desilylation, the enantiomeric (–)-diol precursor of (–)-α-cuparenone.



Scheme 75 Enantiodivergent routes to (+)- and (–)-α-cuparenone.

Overman and co-workers[126] reported enantiodivergent routes to (+)- and (–)-scopadulcic acid A, a diterpene isolated from *Scoparia dulcis* L., a perennial herb found in many tropical countries used as herbal remedy against a variety of disorders. Hayashi and co-workers have studied their pharmacological profile as antiviral[127] and antitumor[128] activities. As common starting intermediate an ynone was employed, which was reduced to the (*R*)-alcohol with (*R*)-*B*-isopinocamphenyl-9-borabicyclo[3.3.1]nonane [(*R*)-Alpine-Borane].[129] This is a precursor of (+)-scopadulcic acid A (Scheme 76). Besides, the (*S*)-enantiomer was prepared using (*S*)-Alpine-Borane.



Scheme 76 Enantiodivergent routes to (+)- and (–)-scopadulcic acid A.

6. Conclusions

Enantio- and diastereodivergent routes to carbohydrates such as monosaccharides, carbasugars, aminosugars and azasugars are mainly based on protecting group strategies. Generally, other carbohydrates are used as starting materials. Inversion of the configuration of hydroxy groups is carried out in two steps by sulfonation and S_N2 reaction or by direct Mitsunobu procedure. Alternatively, it was performed by two steps involving oxidation to a carbonyl group followed by diastereoselective reduction. In the case of unsaturated compounds epoxidation and hydroxylation methods are common stereodivergent routes. Diastereodivergent routes to acyclic α-amino acids can be mainly performed using Garner's aldehyde. For heterocyclic α-AAs functional group transformations using pipecolic acid derivatives are involved in diastereodivergent routes. Structurally different β- and γ-AAs have been prepared diastereodivergently. Diastereomeric octahydroindole and isoindole phosphonic acids are accessible by diastereodivergent routes. The group of alkaloids, such as pyrrolidines, pyrrolizidines, piperidines, indolizidines, quinolizidines, decahydroquinolines and octahydroisoquinolines are mainly prepared through diastereodivergent multistep routes. Other alkaloids, such as balanol, vincamine, anatoxin and codeine have been prepared using enantiodivergent routes, whereas (–)-*epi*- and tri-*epi*-isochaetominine C, (–)-galanthamine and *epi*-galanthamine were synthesized by means of diastereodivergent routes. Some enantiomeric sesquiterpenes such as β-santalene, α-curcumene and α-cuparenone have been prepared through enantiodivergent routes as well as the diterpene scopadulcic acid A.

Abbreviations

AA: amino acid

Ac: acetyl

ACE: angiotensin-converting enzyme

AHPPA: 4-amino-3-hydroxy-5-phenylpentanoic acid

AIBN: azobisisobutyronitrile

Alpine-Borane: *B*-isopinocanphenyl-9-borabicyclo[3.3.1]nonane

Ambersep 900 OH: strong basic anion exchange resin

9-BBN: 9-borabicyclononane

BIRT-377: (5*R*)-5-[(4-bromophenyl)methyl]-3-(3,5-dichlorophenyl)-1,5-dimethyl-2,4-imidazolidinedione

Bn: benzyl

Boc: *tert*-butoxycarbonyl

Bu: butyl

Bz: benzoyl

18-C-6: 18-crown-6

CAN: cerium ammonium nitrate

cat: catalyst, catalytic amount

Cbz: benzyloxycarbonyl

CNS: central nervous system

Cy: cyclohexyl

DAST: diethylaminosulfur trifluoride

DBU: 1,8-diazabicycloundec-7-ene

DCE: 1,2-dichloroethane

DCM: dichloromethane

dDNJ: 1,6-dihydroxynojirimycin

DDQ: dichloro dicyano quinone

DEAD: diethyl azodicarboxylate

DIAD: diisopropyl azodicarboxylate

DIBALH: diisopropylaluminum hydride

DIC: diisopropylcarbodiimide

DIPA: diisopropylamine

DIPEA: diisopropylethylamine

DMAP: 4-dimethylaminopyridine

DMDP: 3,4-dihydroxy-2,5-bis(hydroxymethyl)pyrrolidine

DME: 1,2-dimethoxyethane

DMF: dimethylformamide

DMP: Dess-Martin periodinane

DMSO: dimethyl sulfoxide

Dowex: ion exchange resine

DPPA: diphenylphosphoryl azide

dppf: 1,1'-bis(diphenylphosphino)ferrocene

Et: ethyl

Fmoc: 9-fluorenylmethyl

GABA: γ-aminobutyric acid

h: hour(s)

HMPA: hexamethylphosphoramide

HWE: Horner-Wadsworth-Emmons

IBX: 2-iodoxybenzoic acid

Im: imidazol

IPA: isopropyl alcohol

KHMDS: potassium hexamethyldisilazide

KRI: key risk indicator

LAH: lithium aluminum hydride

LDA: lithium diisopropylamide

LFA-1: lynphocite function-associate antigen

LHMDS: lithium hexamethyldisilazide

L-Selectride: lithium tri-*sec*-butylborohydride

LTDM: lithium 2,2,6,6-tetramethylpiperidine

MCPBA: *meta*-chloroperbenzoic acid

Me: methyl

MOM: methoxymethyl

Ms: mesyl, methanesulfonyl

MW: microwaves

NBA: *N*-bromoacetamide

NBS: *N*-bromosuccinimide

NMO: morpholine *N*-oxide

NN-DGJ: *N*-nonyl-1-deoxygalactonojirimycin

NN-DMJ: *N*-nonyl-1-deoxymannojirimycin

ox.: oxidation

PCC: pyridinium chlorochromate

PG: protecting group

Pd/C: palladium on carbon

PDC: pyridinium dichromate

Phth: phthalimidyl

PLE: porcine liver estearase

PMB: *para*-methoxybenzyl

PMP: *para*-methoxyphenyl

PPPA: diphenylphosphonyl azide

PPTS: pyridinium *para*-toluenesulfonate

Pr: propyl

PTSA: *para*-toluenesulfonic acid

Py: pyridine

quant: quantitative

Ra-Ni: Raney nickel

RedAl: sodium bis(2-methoxyethoxy)aluminum hydride

ref: reference

rt: room temperature

[Ru]: ruthenium complex

Su: succinimide

TBAB: tetrabutylammonium bromide

TBAF: tetrabutylammonium fluoride

TBAI: tetrabutylammonium iodide

TBDPS: *tert*-butyldiphenylsilyl

TBS: *tert*-butyldimethylsilyl

^{t}Bu: *tert*-butyl

Tf: triflic, trifluoromethylsulfonyl

TFA: trifluoroacetic acid

THF: tetrahydrofuran

TIPS: triisopropylsilyl

TMEDA: tetramethylethylene diamine

TMO: trimethylamine *N*-oxide

Tp: hydrido-tris-pyrazolylborate

Trityl, Tr: triphenylmethyl

Conflict of interest

There are no conflicts to declare.

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Biographies

Professor Carmen Nájera was born in Nájera (La Rioja) in 1951 and was graduated from the University of Zaragoza in 1973, obtaining her doctorate in chemistry from the University of Oviedo in 1979. She spent postdoctoral stays at the ETH (Zurich), the Dyson Perrins Laboratory (Oxford), Harvard University, and Uppsala University. She became Associate Professor in 1985 at the University of Oviedo and Full Professor in 1993 at the University of Alicante. She is coauthor of more than 400 papers (h 68), 6 patents and 30 book chapters and has supervised more than 45 PhD students, belonging also to the Editorial Board of several international journals. She has been awarded with the 2006

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Francisco Foubelo was born in 1961. He studied chemistry at the University of Oviedo from which he received B.S. (1984), M.S. (1986), and Ph.D. (1989) degrees. After a postdoctoral stay (1989–1991) as a Fulbright fellow at Princeton University, he moved to the University of Alicante where he became Associate Professor in 1995 and Full Professor in 2002. Dr. Foubelo has co-authored more than 150 papers, and his current research interests are focused on the development of new synthetic methodologies involving chiral sulfinimines and on metal-promoted functionalization of alkenes and alkynes.

José Miguel Sansano was born in Rojales (Alicante), studied chemistry at the University of Alicante, where he obtained his B.Sc. and Ph.D. degrees in 1988 and 1994, respectively. His Thesis was supervised by Prof. C. Nájera and dealt about sulfone chemistry. After spending a two-year postdoctoral stay at the University of Leeds (U.K.) with Prof. R. Grigg, he joined the University of Alicante in 1996, where he was appointed Associate Professor in 2001. In 2010 he was promoted to Full Professor in the same University. He was invited visiting Professor at Chuo University in 2014 and in the UFRJ (Brazil). He is coauthor of more than 140 articles and he has supervised 13 PhD students.

Professor Miguel Yus was born in Zaragoza (Spain) in 1947, and received his BSc (1969), MSc (1971) and PhD (1973) degrees from the University of Zaragoza. After spending two years as a postdoctoral fellow at the Max Planck Institut für Kohlenforschung in Mülheim a.d. Ruhr he returned to Spain to the University of Oviedo where he became associate professor in 1977, being promoted to full professor in 1987 at the same university. In 1988 he moved to a chair in Organic Chemistry at the University of Alicante. Professor Yus has been visiting professor at different institutions and universities among them ETH-Zentrum, Oxford, Harvard, Uppsala, Marseille, Tucson, Okayama, Paris, Strasbourg, Bolonia, Sassari, Tokyo and Kyoto. He is co-author of more than 600 papers (and six patents) and has supervised 62 Doctoral Theses (already presented), and delivered about 250 lectures, most of them abroad. His bibliometric data are more than 25.000 citations and h-index 74. He has received several international awards being also named Active Academician from the European Academy of Sciences and Arts, and Academic Member of the Athens Institute for Education and Research. Professor Yus has been in the Advisory Board of more than 30 international journals being also Editor-in-Chief of Letters in Organic Chemistry and Open Chemistry. Professor Yus founded the new chemical company MEDALCHEMY S.L. to commercialize fine chemicals.

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