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Stereoselective synthesis of quaternary α-amino acids. Part 2: Cyclic compounds

Carlos Cativiela * and María Dolores Díaz-de-Villegas *

Department of Organic Chemistry, ICMA, Universidad de Zaragoza-CSIC, 50009 Zaragoza, Spain

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1. Introduction

In the first part of this review[1] we discussed the important role that α,α-disubstituted amino acids have played in the design of peptides with enhanced properties, owing to the conformational restrictions induced by the incorporation of these residues into peptides. These conformational restrictions are increased when the amino acid moiety is incorporated within a ring structure, so in the second part of this review we would like to focus our attention on the stereoselective synthesis of cyclic quaternary α-amino acids.

Several papers have been published that describe, from an experimental[2–9] and theoretical[10,11] point of view, the influence of a symmetric carbocycle containing the quaternary α-carbon of an amino acid,

* Corresponding authors. E-mail: cativiela@posta.unizar.es, loladiaz@posta.unizar.es

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i.e. a 1-aminocycloalkanecarboxylic acid (Ac_nc). A number of interesting papers have dealt with the particular cases of 1-aminocyclopropanecarboxylic acid (Ac_3c),[12–20] 1-aminocyclobutanecarboxylic acid (Ac_4c),[21,22] 1-aminocyclopentanecarboxylic acid (Ac_5c),[23] 1-aminocyclohexanecarboxylic acid (Ac_6c),[23–27] 1-aminocycloheptanecarboxylic acid (Ac_7c),[28,29] 1-aminocyclooctanecarboxylic acid (Ac_8c),[30] 1-aminocyclononanecarboxylic acid (Ac_9c)[31] and 2-amino-2-carboxyadamantane.[32] Other carbocycles, such as 2-aminoindane-2-carboxylic acid (Aic) or 2-aminotetraline-2-carboxylic acid (Atc), have also been studied.[33,34]

Among the 1-aminocycloalkanecarboxylic acids the cyclopropane derivatives have attracted the particular attention of many researchers, probably due to the special characteristics that the cyclopropane ring confers on the peptide in which it is incorporated (significant conformational restrictions). When new substituents are incorporated into the cyclopropane unit new stereogenic centres are formed and new stereoisomers are possible. 'Cyclopropylogues' of many proteinogenic amino acids have been described and some of them have been incorporated into peptides in order to study the relationship between absolute stereochemistry and macroscopic properties. In particular, the four stereoisomers of 1-amino-2-phenylcyclopropanecarboxylic acid, 2,3-methanophenylalanine or c_3Phe, according to different nomenclature systems, have been studied.[7,35–39] Other compounds involving 1-amino-2-methylthiomethylcyclopropanecarboxylic acid (c_3Met),[37,40–46] 1-amino-2-isopropylcyclopropanecarboxylic acid (c_3Leu),[47] 1-amino-2-(2-guanidinoethyl)cyclopropanecarboxylic acid (c_3Arg)[48,49] and 1-aminocyclopropane-1,2-dicarboxylic acid (c_3Asp)[50] have also been studied. Recently, the β-turn modulation by the cyclohexane analogues of phenylalanine (c_6Phe) has been described.[51]

A very interesting way to decrease the conformational freedom of peptides is to incorporate residues in which the amino group forms part of the ring. This kind of amino acid constitutes a new family of compounds that can be considered as being related to prolines such as 2-aziridinecarboxylic acid, 2-pyrrolidinecarboxylic acid, proline itself, 2-piperidinecarboxylic acid, 2-indolinecarboxylic acid or tetrahydroisoquinoline-3-carboxylic acid (Tic). Although these compounds have been studied, there are very few references concerning the quaternary amino acids and only some α-alkylprolines have been studied in detail.[52–54]

For these reasons we have divided this review into two parts: the first part concerns the asymmetric synthesis of 1-aminocycloalkanecarboxylic acids and the second part covers 1-azacycloalkane-2-carboxylic acids (Fig. 1).

Fig. 1.

2. 1-Aminocycloalkanecarboxylic acids

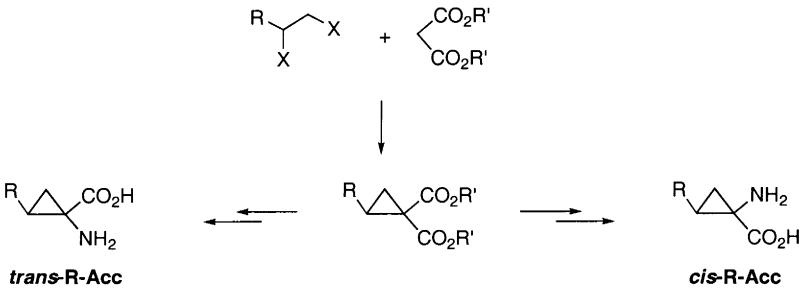
In this review we considered it appropriate to classify the different methodologies described in the literature for the asymmetric synthesis of 1-aminocycloalkanecarboxylic acids using a disconnection approach for each ring size.

2.1. 1-Aminocyclopropanecarboxylic acids

As described previously, the cyclopropane derivatives are probably the most interesting 1-aminocycloalkanecarboxylic acids and, as such, reviews covering their synthesis in racemic form[55,56] as well as a more recent review dealing with their stereoselective synthesis[57] have already been published. Nevertheless, these reviews do not cover the different approaches to the asymmetric synthesis of these compounds that have appeared in the literature in recent years.

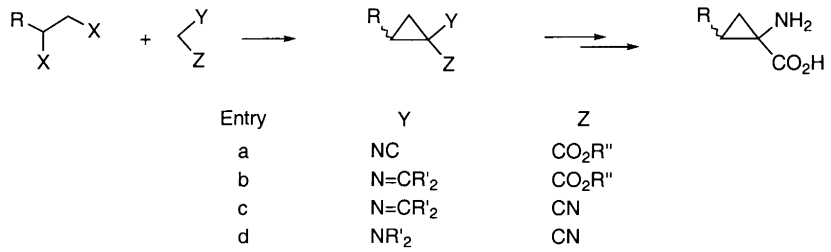
2.1.1. Alkylation of a glycine equivalent with a 1,2-electrophile

Since Ingold[58] described the first synthesis of 1-aminocyclopropanecarboxylic acid (Acc, according to an old nomenclature system) from diethyl malonate and ethylene dibromide in 1922, this methodology has been widely used for the synthesis of numerous racemic alkyl derivatives. The presence of the third substituent in the cyclopropane ring allows the two ester functions to be differentiated in such a way that a Curtius or a Hofmann rearrangement leads to the synthesis of the corresponding *cis* or *trans* derivatives (Scheme 1).



Scheme 1.

The use of other *N*-substituted glycine derivatives (Scheme 2) allows the synthesis of the precursors of the cyclopropane derivatives of the amino acids without using a rearrangement reaction.

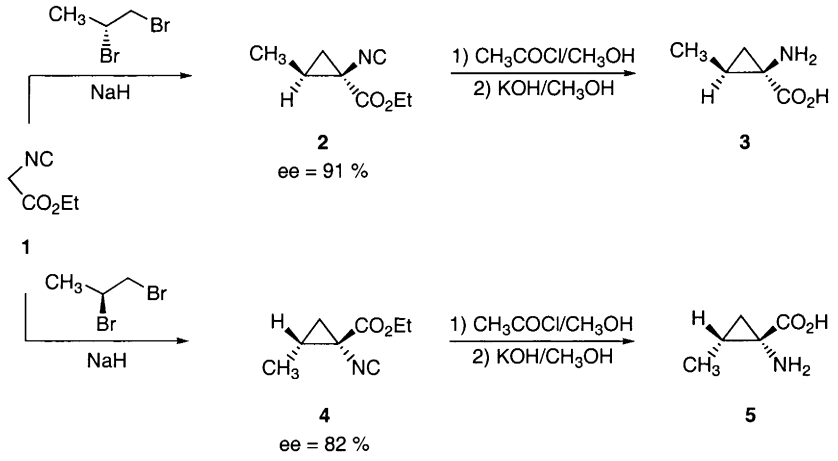


Entry	Y	Z
a	NC	CO_2R''
b	$N{=}CR'_2$	CO_2R''
c	$N{=}CR'_2$	CN
d	NR'_2	CN

Scheme 2.

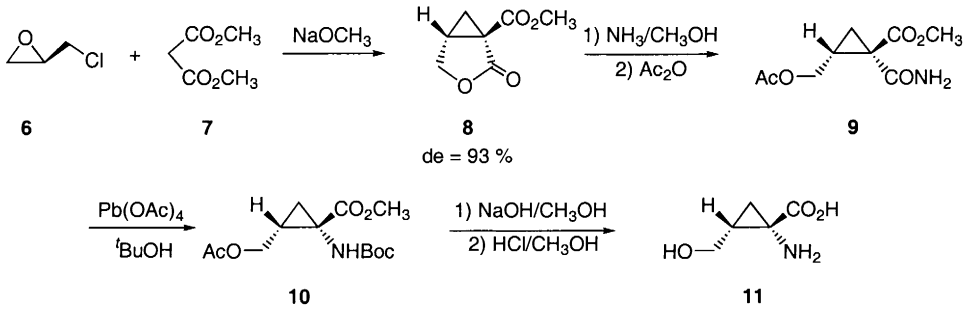
The first application of this methodology to the asymmetric synthesis of 2-substituted 1-aminocyclopropanecarboxylic acids was described by Pirrung[59] who, in 1986, described the synthesis of both enantiomers of *allo*-norcoronamic acid (*cis*-methyl-Acc). The reaction of 1,2-dibromopropane with ethyl isocyanoacetate preferentially leads to *cis* compounds and, on using enantioenriched (*R*)- or (*S*)-1,2-dibromopropane, (1*R*,2*S*)- or (1*S*,2*R*)-1-amino-2-methylcyclopropanecarboxylic acids are obtained with 91 and 82% enantiomeric excess, respectively (Scheme 3).

The same author later described[60] the diastereoselective synthesis of (1*S*,2*R*)-1-amino-2-hydroxymethylcyclopropanecarboxylic acid (2-hydroxymethyl-Acc), a homoserine analogue, by cycloalkylation of dimethyl malonate using enantiomerically pure (*R*)-epichlorohydrin. Aminolysis of the lactone obtained in this way, acetylation of the hydroxymethyl group and Hofmann rearrangement



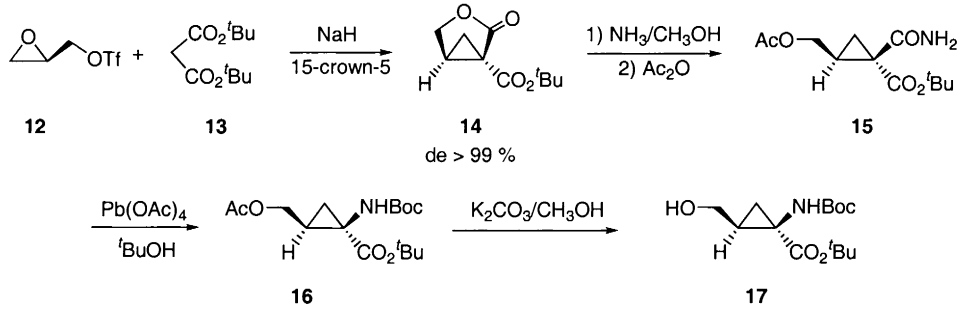
Scheme 3.

gave a precursor of the desired amino acid from which the free amino acid can be obtained (Scheme 4). Starting from (*S*)-epichlorohydrin the opposite enantiomer is obtained.



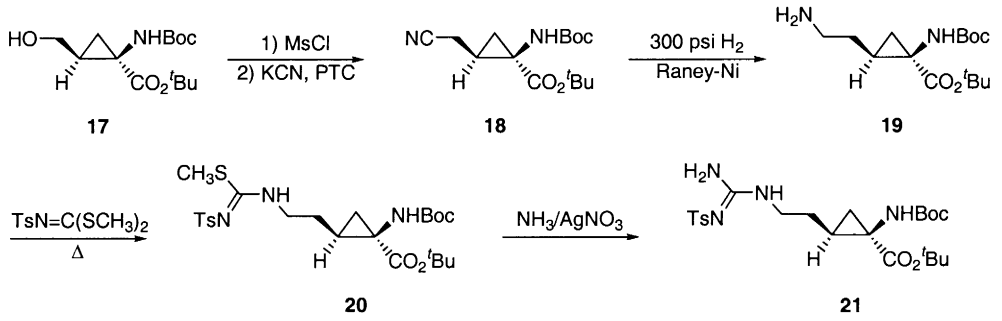
Scheme 4.

Based on this strategy several modifications have been published recently that have allowed the synthesis, in enantiomerically pure form, of various 2-substituted cyclopropaneamino acids of biological interest. In this context Burgess has developed the most complete methodology. The use of di-*tert*-butyl malonate as a glycine equivalent and (*R*)-glycidyl triflate as the 1,2-dielectrophile allows the synthesis of enantiomerically pure lactone **14**,[61] which was transformed into different cyclopropaneamino acids. The (1*R*,2*S*)-1-amino-2-hydroxymethylcyclopropanecarboxylic acid derivative is obtained by treatment of the lactone with methanolic ammonia to obtain an amide, which is submitted to Hofmann rearrangement after acetylation of the hydroxymethyl side chain (Scheme 5).



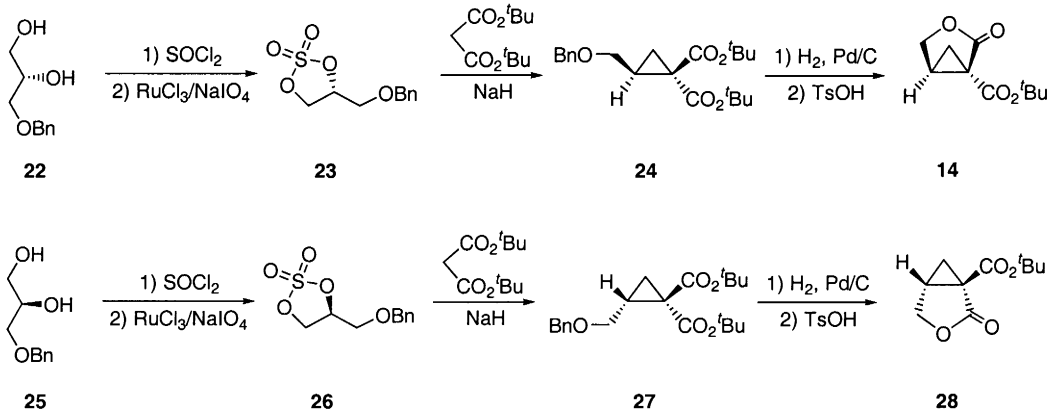
Scheme 5.

The side chain of amino acid derivative **17** is further elaborated to give the amine and guanidine functionalities of (1*R*,2*S*)-ornithine and (1*R*,2*S*)-arginine surrogates. Homologation of the side chain by transformation of the alcohol moiety into a nitrile by mesylation and reaction with potassium cyanide under phase transfer conditions, followed by reduction of the nitrile, cleanly affords the cyclopropylornithine derivative **19**. This compound is transformed into the cyclopropylarginine derivative **21** by introduction of the guanidine functionality in a two-step procedure according to Scheme 6.



Scheme 6.

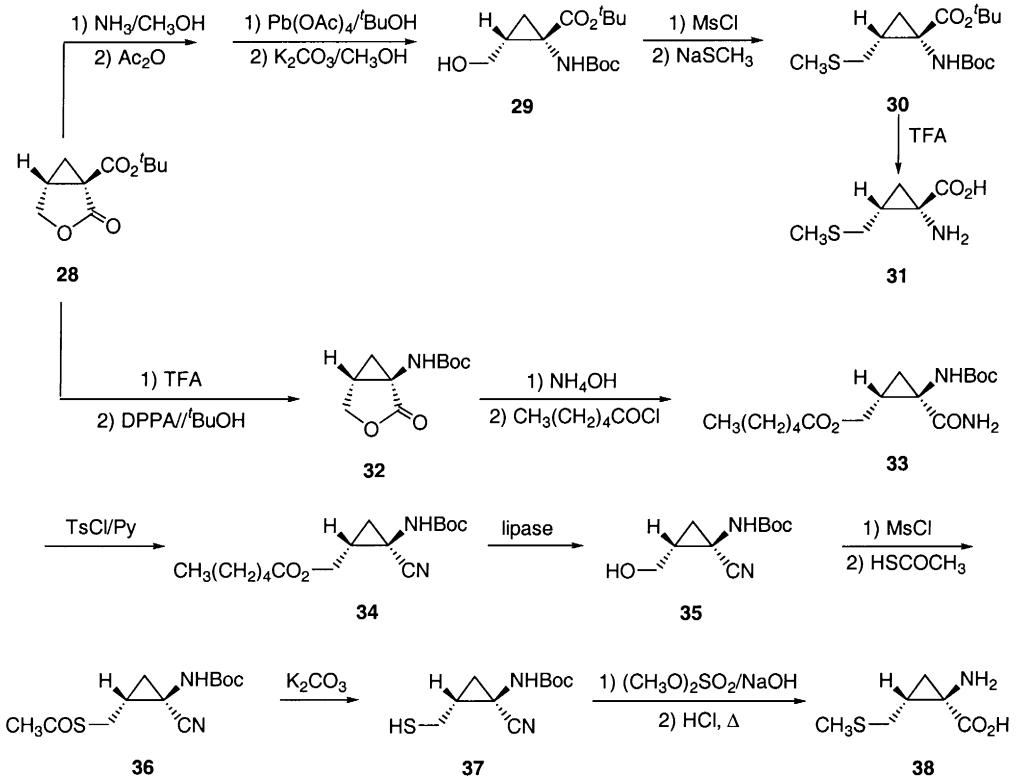
The synthesis of lactone **14** and its enantiomer **28** were subsequently scaled-up and optimised starting from monoprotected triol **22** (or **25**), which was obtained from L-glucono-1,4-lactone[62] or D-mannitol[63] as the source of chirality according to Scheme 7.



Scheme 7.

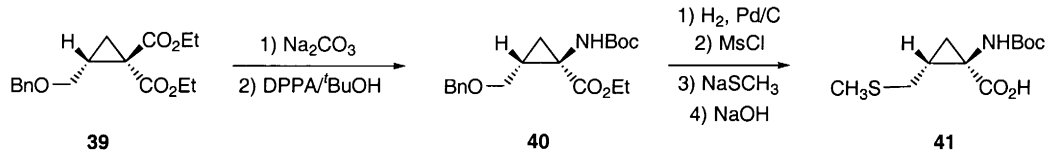
Lactone **14** and its enantiomer **28** have been used as starting materials in the synthesis of all four stereoisomers of 2,3-methanomethionine.[64] Conversion of the lactone **28** into (1*S*,2*R*)-1-amino-2-methylthiomethylcyclopropanecarboxylic acid can be achieved using (1*S*,2*R*)-1-amino-2-hydroxymethylcyclopropanecarboxylic acid derivative **29**, obtained following a synthetic methodology similar to that described above for its enantiomer, by mesylation, displacement with sodium thiomethoxide and hydrolysis. In the route to (1*R*,2*R*)-1-amino-2-methylthiomethylcyclopropanecarboxylic acid the initial step is the transformation of the *tert*-butoxycarbonyl group into the amino functionality by a Curtius rearrangement. Opening of the resulting lactone with aqueous ammonium hydroxide, followed by esterification of the alcohol moiety with hexanoyl chloride and dehydration of the amide to a nitrile, affords intermediate **34**, which has to be deprotected under neutral conditions using the lipase from *Candida cylindracea*. The introduction of the sulfur functionality is then achieved by displacement of the corresponding mesylate with thioacetic acid followed by base-mediated cleavage of the acetate to

give the thiol and subsequent methylation of the thiol moiety. Finally, exhaustive acid hydrolysis gives the free amino acid (Scheme 8).



Scheme 8.

A more convenient synthesis of the (1*R*,2*R*)-enantiomer starts from diester **39**,[62] obtained by condensation of compound **26** with diethyl malonate. Selective hydrolysis of the less hindered ester group of the diester and Curtius rearrangement affords a suitable precursor for the desired compound, as debenzylation of the hydroxy moiety followed by mesylation and nucleophilic displacement cleanly affords (1*R*,2*R*)-*N*-Boc-1-amino-2-methylthiomethylcyclopropanecarboxylic acid (Scheme 9).

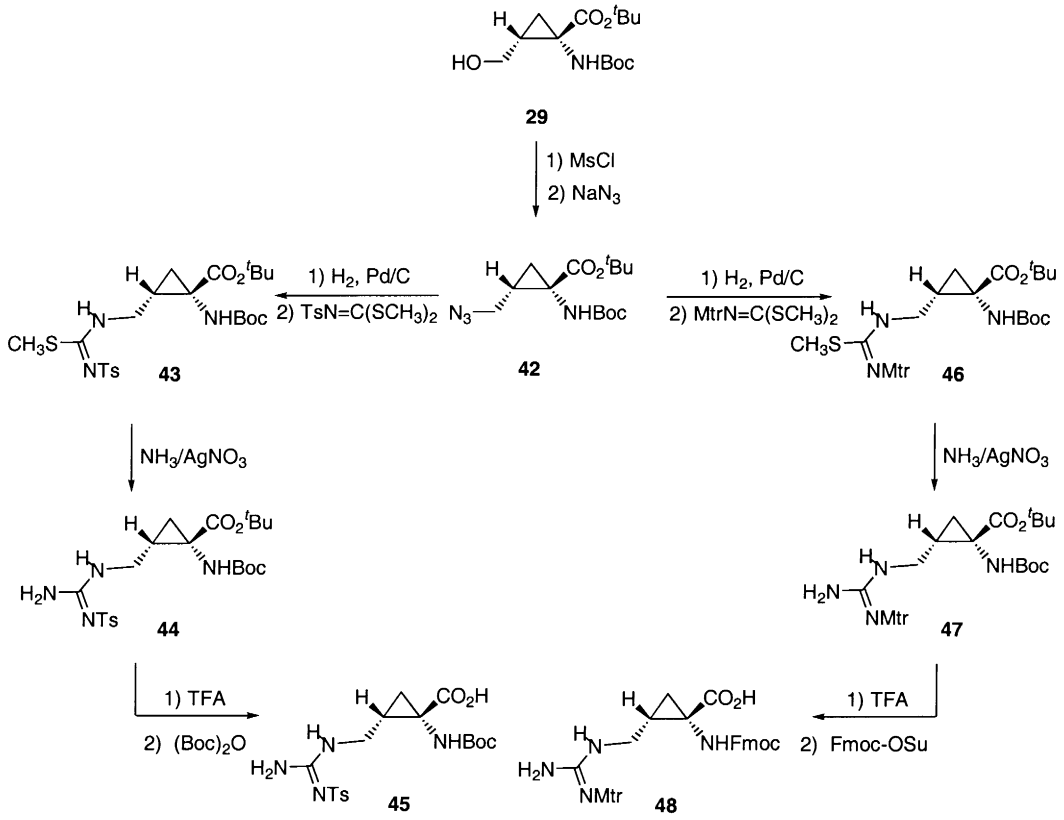


Scheme 9.

By using enantiomers of opposite configuration as starting compounds the corresponding enantiomers of (1*R*,2*S*) and (1*S*,2*S*) configuration can be obtained.

All four stereoisomers of carnosadine have been shown to be accessible following a similar methodology[65] from the hydroxy derivative **29** (obtained from lactone **28**), from compound **40** (obtained from the diester **39**) or from their corresponding enantiomers. Mesylation of compound **29** followed by azide displacement and introduction of the guanidine group affords compounds of the *cis* series (Scheme 10). Compounds of the *trans* series are easily prepared from compound **40** by mesylation, azide displacement and introduction of the guanidine functionality (Scheme 11). Products from both

series were manipulated to give protected forms that are suitable for peptide synthesis using the Boc or the Fmoc approach.

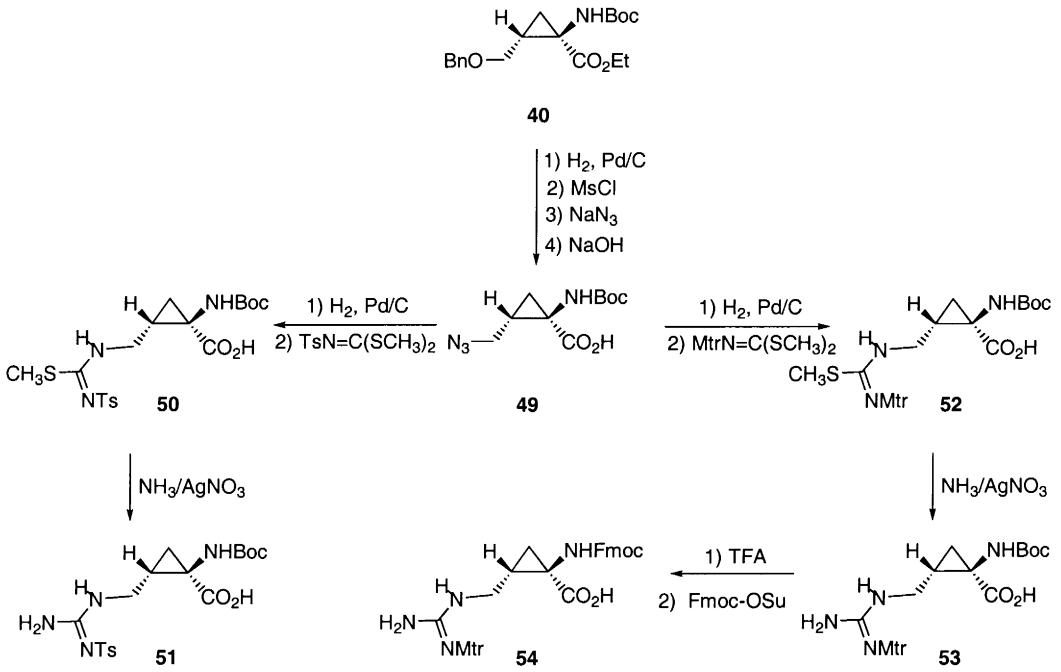


Scheme 10.

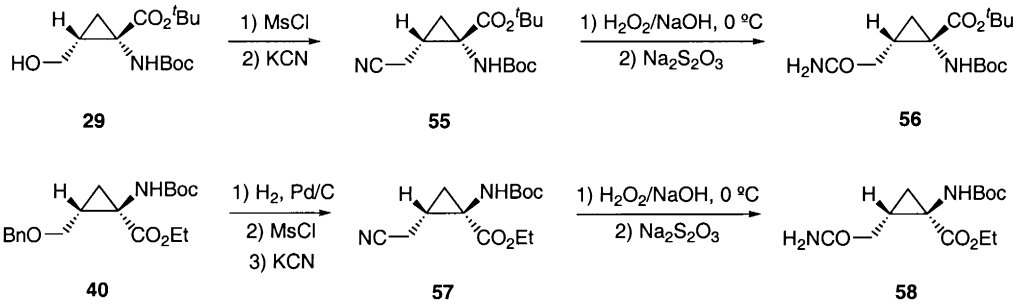
Compounds **29** and **40** have also been used as starting materials[66] in the preparation of enantiomerically pure *cis* and *trans* stereoisomers of 1-amino-2-aminocarbonylmethylcyclopropanecarboxylic acid in a protected form suitable for peptide synthesis (Scheme 12). In this case nucleophilic substitution of mesylate with sodium cyanide, followed by carefully controlled hydrolysis of the nitrile with 30% hydrogen peroxide and sodium hydroxide in ethanol at 0°C, allows the synthesis of the side chain of glutamine.

Enantiomerically pure D- and L-valine have been described[67] as very useful and available starting materials for the synthesis of all four stereoisomers of 1-amino-2-isopropylcylopropanecarboxylic acid that are suitably protected for peptide synthesis as *N*-Boc derivatives. Cyclic sulfate **59**, prepared from L-valine in a four-step procedure, reacts with dimethyl malonate or diethyl gluconate, respectively, to afford key intermediates for the synthesis of (*R*,*S*)- and (*S*,*S*)-leucine surrogates following standard transformations (Scheme 13). Enantiomers of opposite configuration can be obtained starting from D-valine.

More recently[68] a new enantiomerically pure cyclopropane derivative **69**, obtained from diol **66**, has been described as a suitable intermediate for the synthesis of 2,3-methanoamino acids with extended side chains. From this compound (1*R*,2*R*)-2-(2-benzyloxycarbonylamino)ethyl-1-*N*-*tert*-butoxycarbonylaminocyclopropanecarboxylic acid, a cyclopropyllysine derivative, (1*R*,2*S*)-ethyl 1-*N*-*tert*-butoxycarbonylamino-2-carboxymethylcyclopropanecarboxylate, a methanalogue of glutamic



Scheme 11.



Scheme 12.

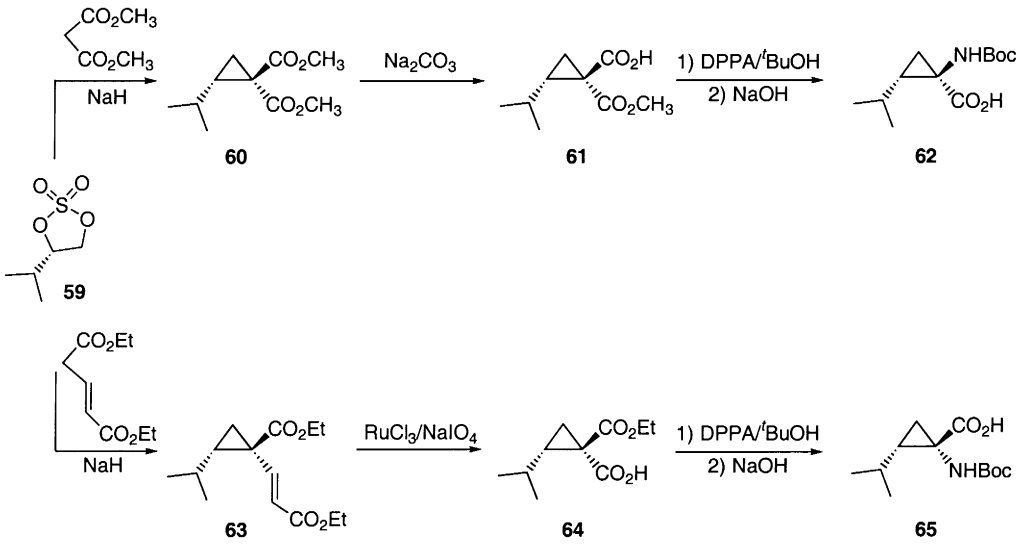
acid, and (1*R*,2*R*)-2-(2-benzyloxycarbonylguanidinyl)ethyl-1-*N*-*tert*-butoxycarbonylaminocyclopropane carboxylic acid, an arginine surrogate, have been obtained (Scheme 14).

Methyl benzylideneglycinate has recently been described as an excellent precursor of 2-substituted-1-aminocyclopropanecarboxylic acids. By using a cyclic sulfate obtained from (*S*)-1,2-propanediol as a chiral 1,2-electrophile, (1*S*,2*R*)-*allo*-norcoronamic acid has been obtained[69] (Scheme 15).

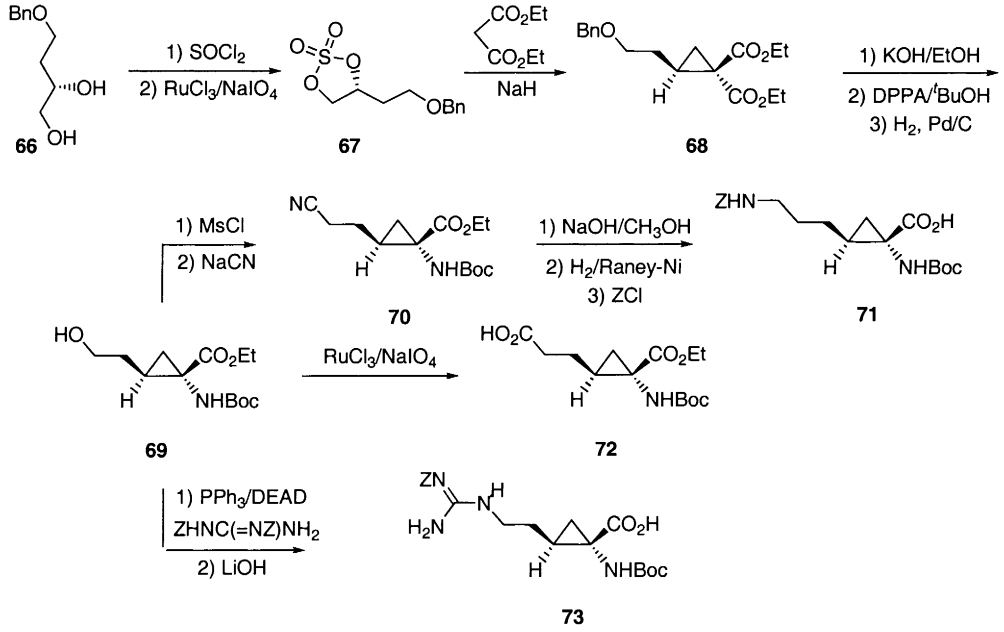
The use of chlorosulfates **78** and **84**, obtained, respectively, from (*S*)-1,2,4-butanetriol and (*S*)-1,2,5-pentanetriol, as 1,2-dielectrophiles leads to 2-(*n*-chloroalkyl)cyclopropane derivatives. These compounds can be cyclised to (2*S*,3*R*)-2,3-methanoproline[70] and (2*S*,3*R*)-2,3-methanopipecolic acid,[71] respectively, according to Schemes 16 and 17.

The cyclic sulfate obtained from (*S*)-1,2-propanediol has also been used to prepare (1*R*,2*R*)-norcoronamic acid using methyl malonate as a nucleophile.[72] In this case regioselective saponification of the cyclopropane derivative obtained, followed by Curtius rearrangement and subsequent hydrolysis, gives the desired amino acid in enantiomerically pure form (Scheme 18).

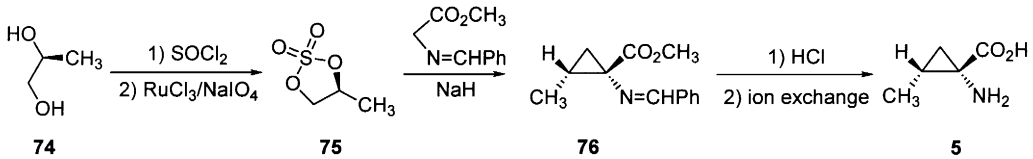
Finally, the cyclic sulfate obtained from (1*R*,2*R*)-1,2-diphenyl-1,2-ethanediol reacts with diethylgluta-



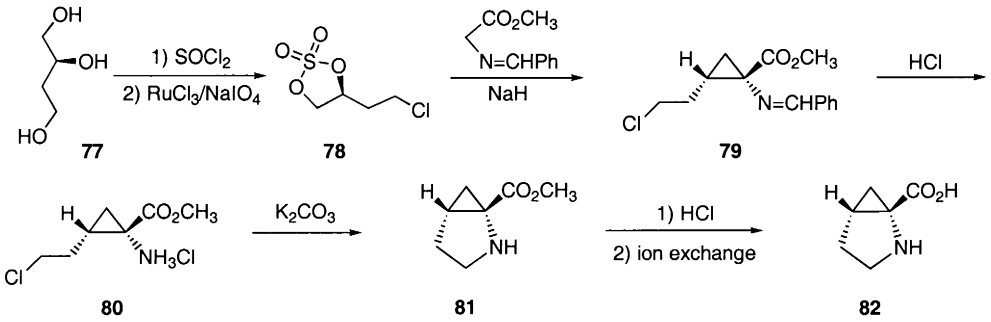
Scheme 13.



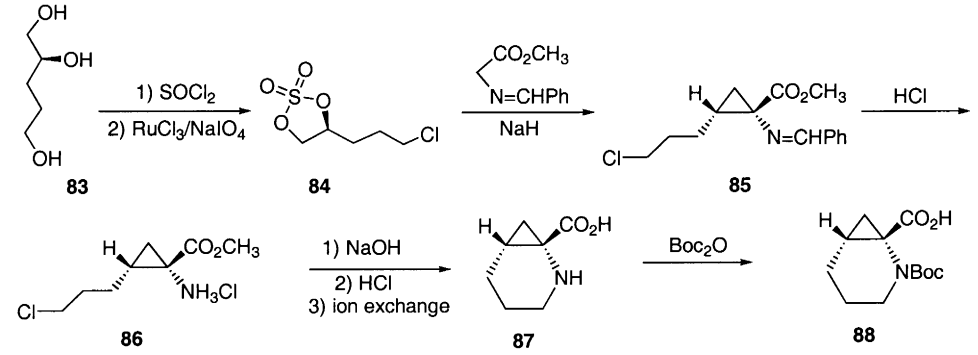
Scheme 14.



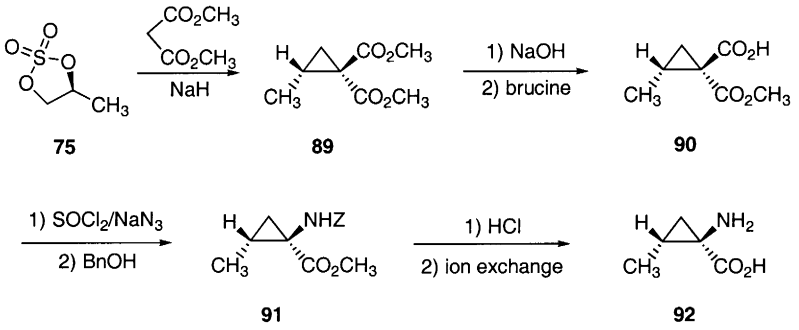
Scheme 15.



Scheme 16.



Scheme 17.



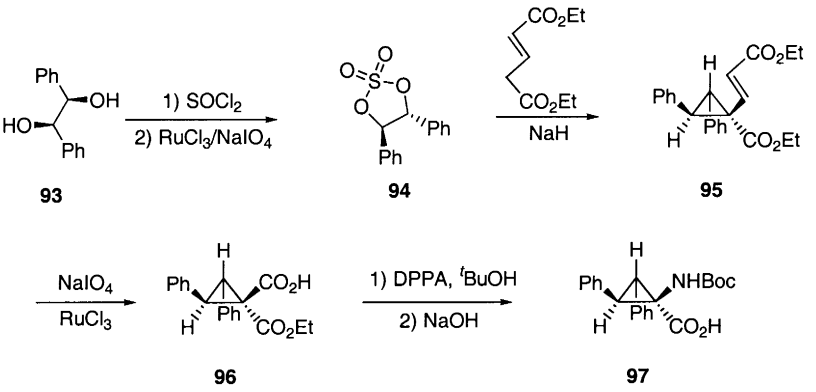
Scheme 18.

conate to give cyclopropane **95**, which can be conveniently elaborated to afford the (1*S*,2*S*)-1-amino-2,3-diphenylcyclopropanecarboxylic acid, as shown in Scheme 19.[73]

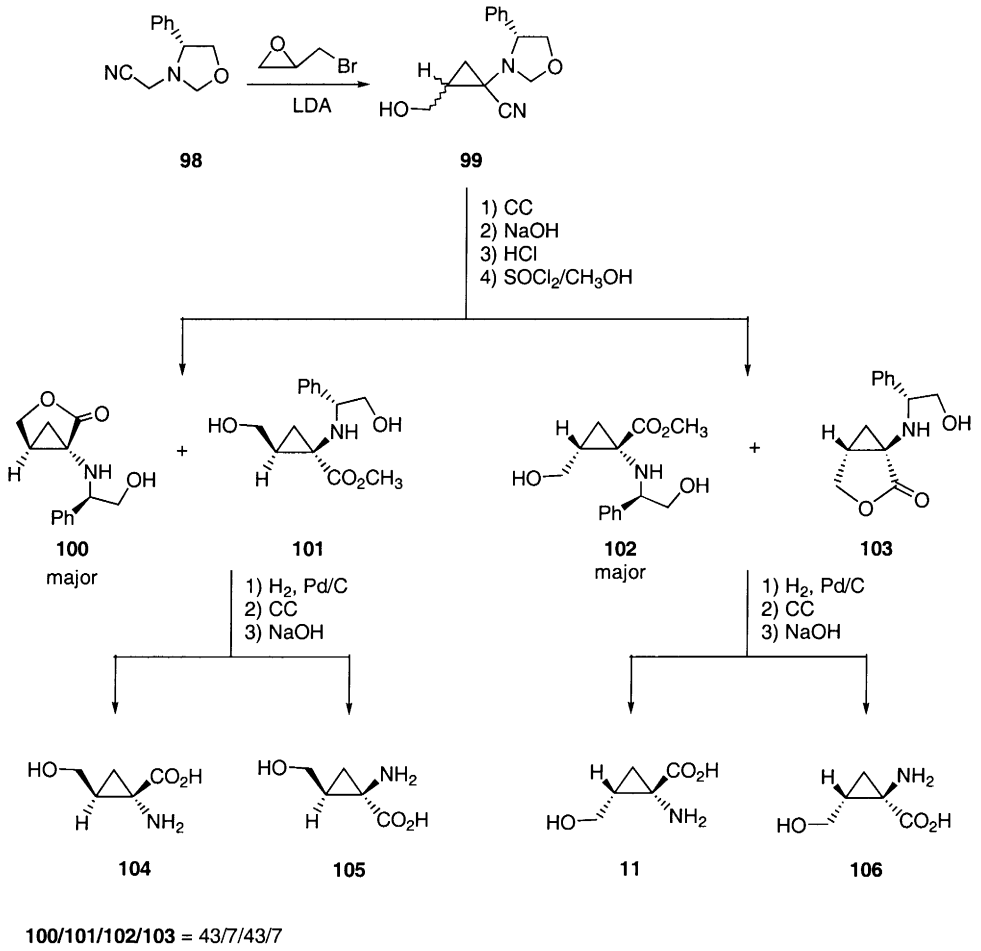
A different possibility for the diastereoselective synthesis of these cyclopropane derivatives is the double alkylation of a chiral glycine equivalent. Following this approach Husson et al. used chiral oxazolidine **98** to perform the asymmetric synthesis of several cyclopropylamino acids. Reaction of this compound with racemic epibromohydrin gives all four possible diastereoisomers and these have to be separated. Chromatographic separation allows the isolation of two pairs of compounds, each pair consisting of a *cis* and a *trans* compound. After lactonisation of the *trans* compound the two components of the mixture can be separated by a second column chromatography process and their hydrolysis leads to cyclopropyl homoserine in enantiomerically pure form, albeit in low chemical yield[74,75] (Scheme 20).

Methyl ester **107**, an intermediate in the previous synthetic route, has been subsequently converted into *allo*-coronamic acid[76] and carnosadine[77] according to Scheme 21.

Chiral cyclic glycine equivalents usually give rise to better selectivities in asymmetric synthesis

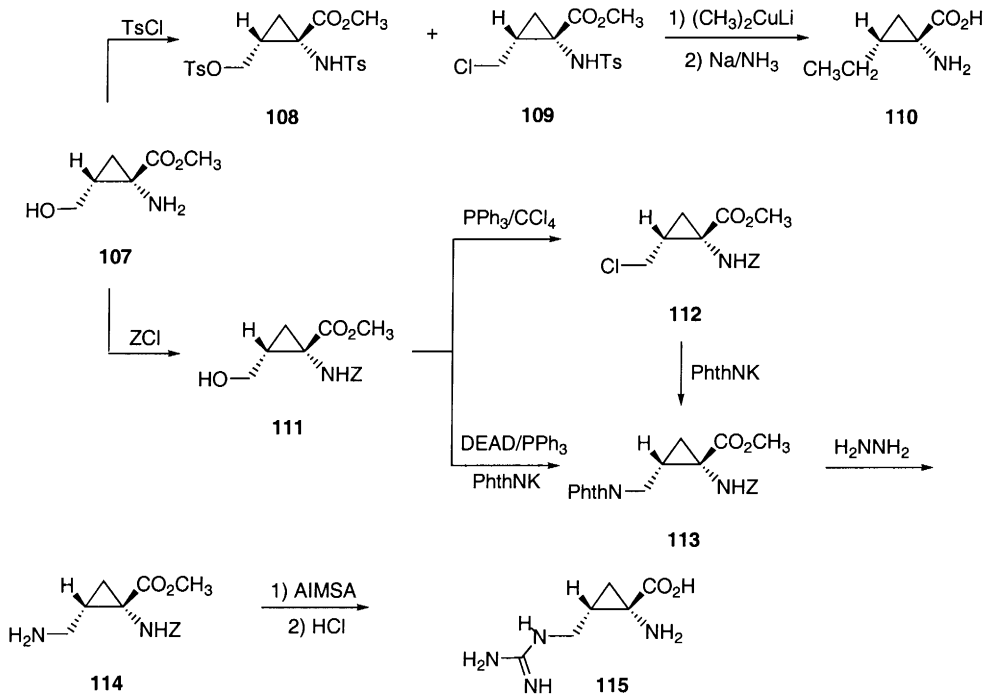


Scheme 19.



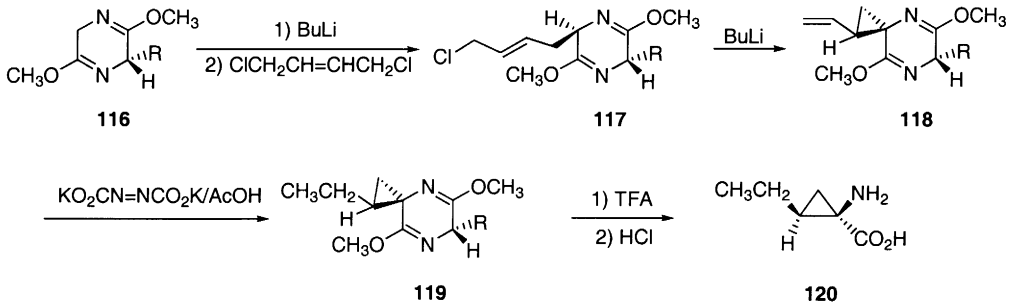
Scheme 20.

processes and in this context bis-lactim ethers described by Schöllkopf have been one of the best chiral intermediates for the asymmetric synthesis of amino acids. Bis-lactim ethers derived from L-valine and glycine or L-*tert*-leucine and glycine have been used as starting materials in the synthesis of (1*R*,2*S*)-



Scheme 21.

allo-coronamic acid, the key step being the intramolecular alkylation of the lithium azaenolate derived from allylic chloride **117**[78] (Scheme 22).



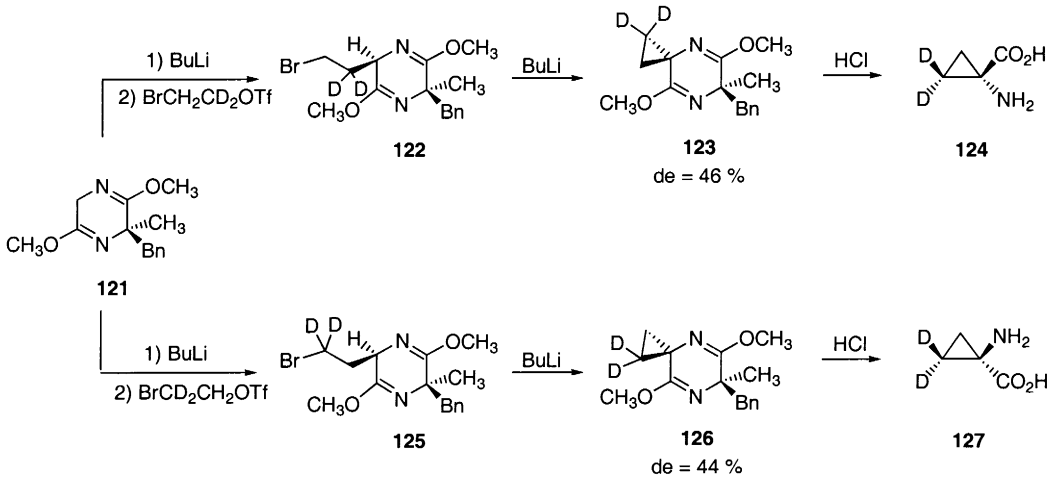
Entry	R	*cis/trans* **118**	de % *cis* **118**
a	^{i}Pr	71/29	94
b	^{t}Bu	86/14	96

Scheme 22.

Starting from the bis-lactim derived from (*R*)-α-methylphenylalanine and glycine, a similar strategy has been applied by Woodard et al.[79] for the synthesis of some deuterated 1-amino-cyclopropanecarboxylic acids (Scheme 23).

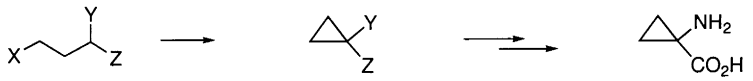
2.1.2. Intramolecular cyclisation of γ-functionalised α-amino acid derivatives

The intramolecular base-induced cyclisation of an amino acid precursor containing an appropriate leaving group in the γ position is a well known route to 1-aminocyclopropanecarboxylic acids, and several leaving groups have been used in the synthesis of Acc (Scheme 24). Nevertheless, the diastereo-



Scheme 23.

selective base-induced cyclisation of chiral compounds has hardly been used and there are only a few examples of the application of this methodology to the asymmetric synthesis of some 2-substituted 1-aminocyclopropanecarboxylic acids, and even these gave only moderate results.[80,81] To this end, commercially available (*S*)-methyl 3-hydroxy-2-methylpropionate is used as the starting material and the source of chirality in the synthesis of (1*S*,2*S*)-norcoronamic acid. After silylation of the hydroxy group, aldehyde **129** is obtained by partial reduction of the methyl ester. Strecker reaction of **129** affords an almost equimolecular mixture of aminonitriles, which is subsequently transformed into the corresponding mixture of chloroimines. These compounds undergo base-promoted cyclisation to yield a diastereomeric mixture of cyclopropane derivatives in which *trans* compound **133** predominates. Hydrolysis of the benzylideneamino and nitrile moieties leads to the amino acid (Scheme 25).



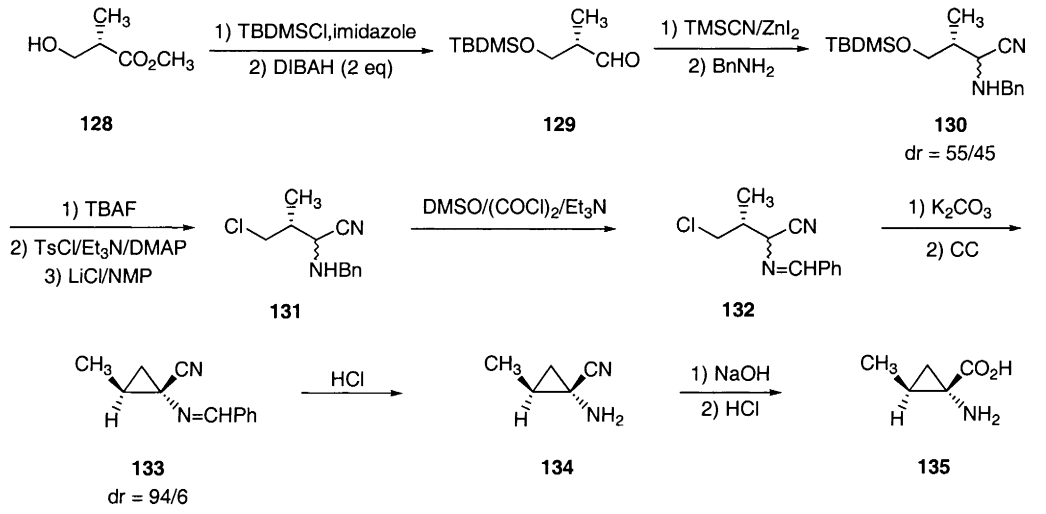
Entry	Y	Z
a	NHCOR	CO_2R'
b	NHR	CO_2R'
c	N_3	CO_2R'
d	$N{=}CR'_2$	CN

Scheme 24.

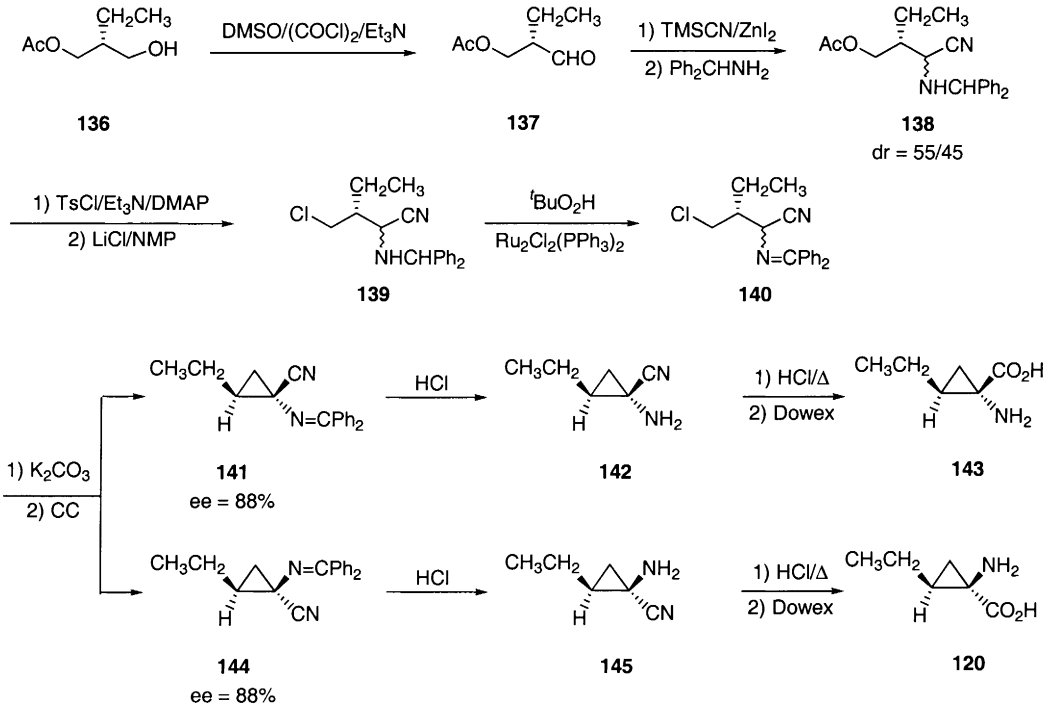
In a similar way (1*S*,2*S*)-coronamic acid and (1*R*,2*S*)-coronamic acid are obtained from readily available (*R*)-2-(hydroxymethyl)butyl acetate, as shown in Scheme 26.

Salaün has also described[82,83] the palladium(0)-catalysed alkylation of (4*S*)-1-chloropent-2-en-4-ol by the anion of *N*-(diphenylmethyleneamino)acetonitrile, followed by $S_{N'}$ cyclisation under Mitsunobu conditions. The cyclisation reaction gives a mixture of products from which cyclopropanecarbonitriles can be isolated, with the ratio of *cis* and *trans* compounds depending on the reaction conditions. From the mixture of cyclopropanecarbonitriles (1*S*,2*S*)-homocoronamic acid with 84% enantiomeric excess is obtained by reduction of the imine with diimide, followed by acid hydrolysis of the nitrile (Scheme 27).

The same principle can be applied to the reaction of chiral imines, prepared from aminoacetonitrile and enantiomerically pure 2-hydroxypinan-3-one, with a mixture of *E*- and *Z*-1,4-dichlorobut-2-enes in the presence of base and palladium(0) complexes.[83,84] By careful choice of the order of addition of the reagent, the amount of base and the nature of the co-solvent, the 1-imino-2-vinylcyclopropanecarbonitrile

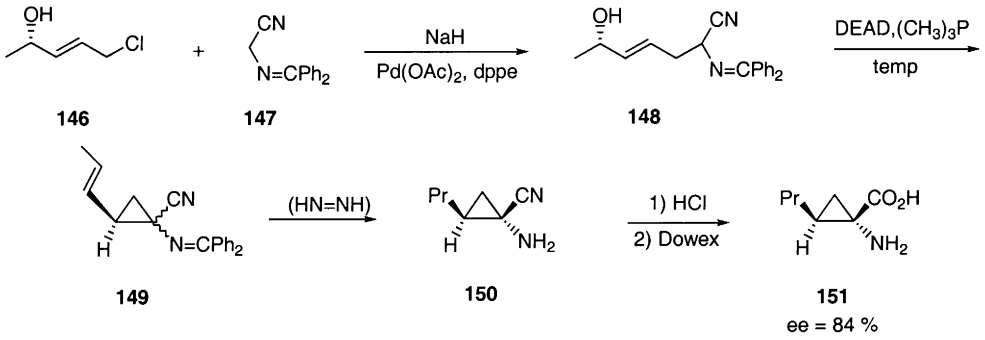


Scheme 25.



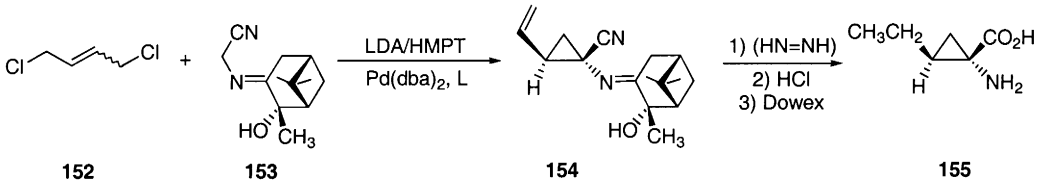
Scheme 26.

of *trans* configuration is obtained with total stereoselectivity but low diastereomeric excess, probably due to palladium(0)-induced reversible ring opening of the vinylcyclopropane moiety. The use of (*S*)- or (*R*)-BINAP palladium(0) complexes has been tested in order to improve the enantioselectivity, and with these chiral palladium(0) complexes *trans*-cyclopropanecarbonitrile **154** is also obtained with low diastereoselectivity. The absolute stereochemistry of the compounds obtained is not discussed in this paper. Finally, reduction of the compound obtained under the optimal conditions with diimide, followed by acid hydrolysis, led to coronamic acid with 32% enantiomeric excess (Scheme 28).



Entry	temp	*cis/trans* **149**
a	r.t.	91/9
b	- 10 ºC	90/10
c	- 25 ºC	93/7

Scheme 27.



Entry	L	de % *trans* **154**
a	PPh_3	2.4
b	*(S)*-BINAP	3
c	*(R)*-BINAP	32
d*	*(S)*-BINAP	19
e*	*(R)*-BINAP	15

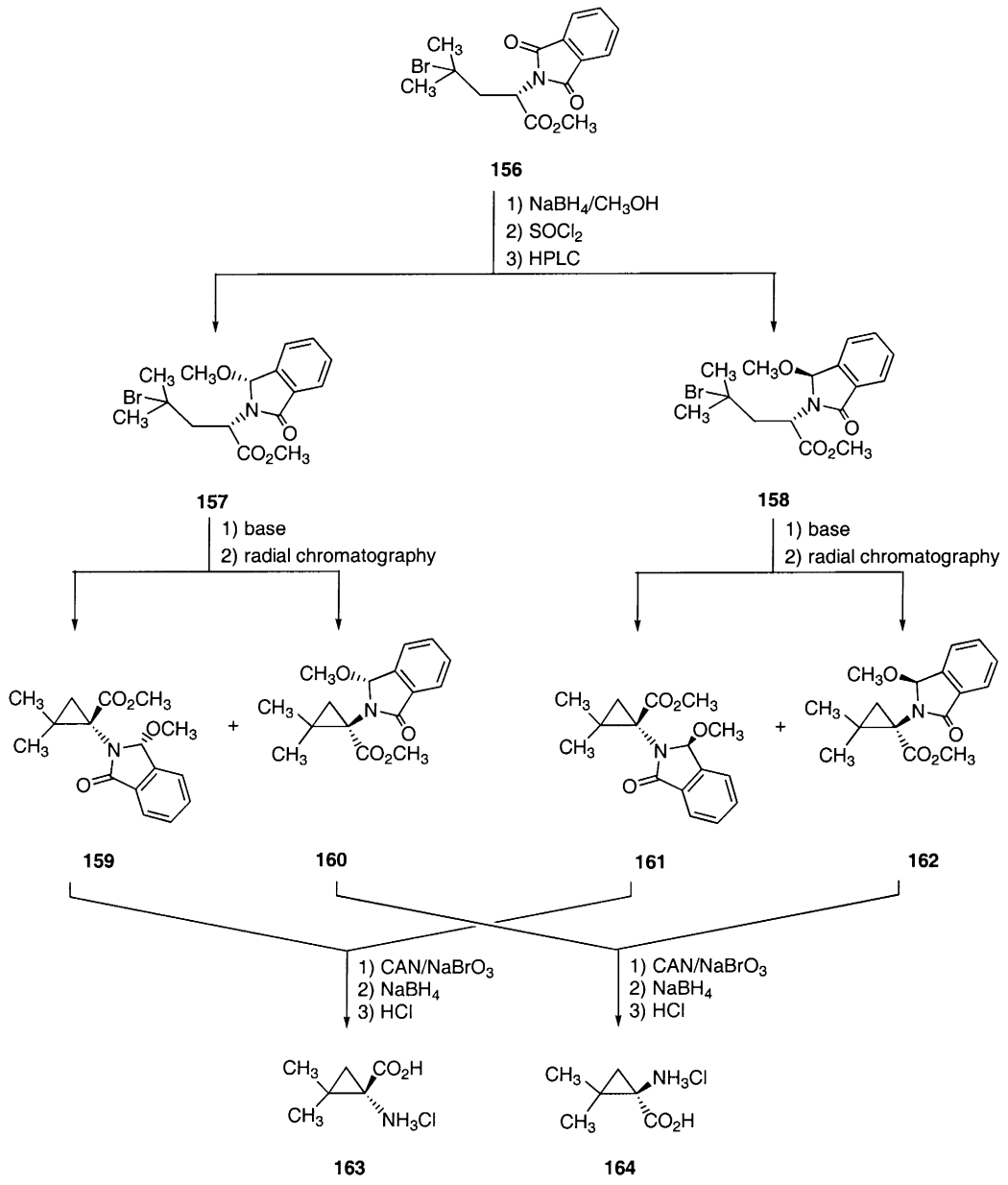
* ent-**151**

Scheme 28.

Easton et al. [85] have recently reported the conversion of (*S*)-leucine into compound **156** and subsequent manipulation of the *N*-phthaloyl group of (*S*)-*N*-phthaloyl-4-bromoleucine. Treatment of the phthalimide with sodium borohydride in methanol gave a pair of diastereomeric α-methoxyamides that could be separated and cyclised diastereoselectively to give 2,3-methanovaline derivatives. The isolated product ratio of both possible diastereoisomers arising from cyclisation depends on the nature of the base used to induce the reaction. Finally, regeneration and removal of the phthaloyl substituent by successive treatment with ceric ammonium nitrate/sodium bromate and sodium borohydride, followed by acid hydrolysis, released the corresponding amino acid as the hydrochloride (Scheme 29).

2.1.3. Asymmetric ylide reactions on α,β-didehydroamino acids

Since ylides were recognised as synthetically useful reagents with the birth of the Wittig reaction in 1953, the chemistry of ylides has grown rapidly and they are now considered powerful and versatile synthetic tools in organic synthesis. The use of ylides in asymmetric synthesis has been reviewed recently,[86]

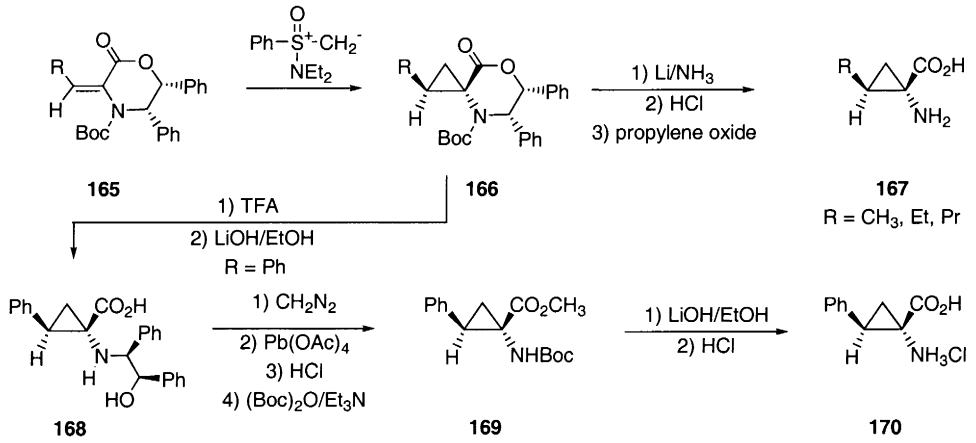


Entry	base	159/160	161/162
a	NaH	34/58	-
b	NaH	-	10/84
c	$NaOCH_3$	87/4	-
d	$NaOCH_3$	-	63/30

Scheme 29.

revealing that the use of these ylides in the asymmetric synthesis of 1-aminocyclopropanecarboxylic acids remains relatively undeveloped as only a few references have been published in the literature.

In 1991 Williams et al.[87,88] described the first asymmetric synthesis of 2-substituted 1-aminocyclopropanecarboxylic acids in which ylides were used to cyclopropanate the double bond of a chiral didehydroamino acid derivative. The latter derivatives were in turn obtained by an Emmons–Horner–Wadsworth condensation of various aldehydes with *erythro*-4-(*tert*-butoxycarbonyl)-3-(dimethoxyphosphoryl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one. α,β-Dehydrolactone adducts were smoothly cyclopropanated with ylides to furnish the desired cyclopropanes in high chemical and optical yields when the ylide of racemic {[(diethylamino)methyl]phenyl}oxosulfonium tetrafluoroborate was used. Subsequent treatment of cyclopropyl lactones with lithium in liquid ammonia provided the *N*-Boc-protected amino acids from which free amino acids were obtained by acid hydrolysis. When the substituent at C_2 was a phenyl group a multi-step sequence to the final amino acid hydrochloride, avoiding reductive or oxidative conditions, had to be developed (Scheme 30).



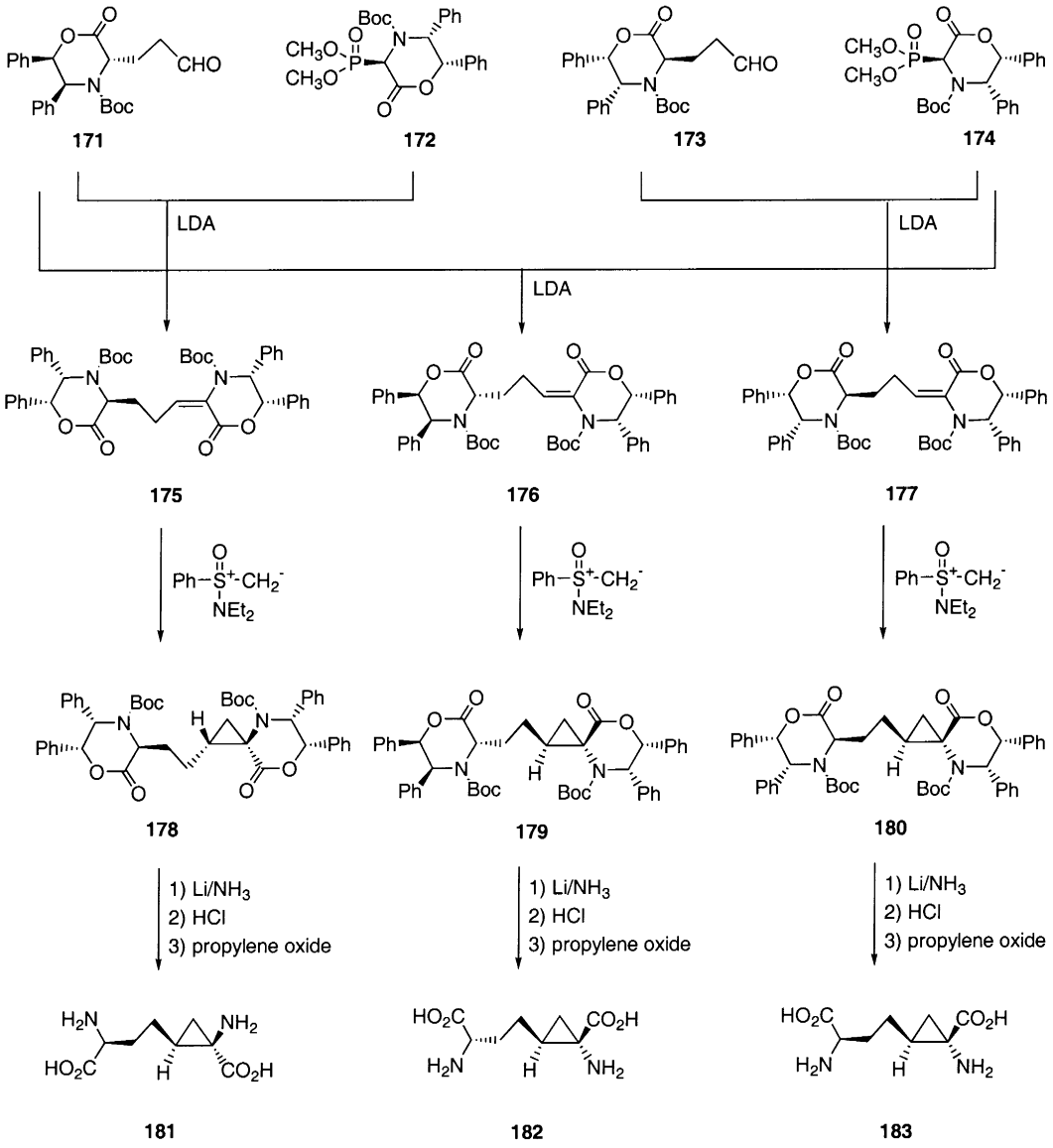
Entry	R	de%
a	CH_3	100
b	CH_3CH_2	100
c	$CH_3CH_2CH_2$	100
d	C_6H_5	100

Scheme 30.

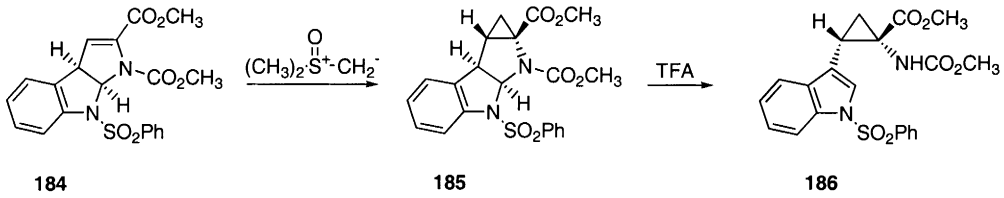
This approach has recently been applied to the synthesis of (2*R*,3*R*,6*S*)-, (2*S*,3*S*,6*S*)- and (2*S*,3*S*,6*R*)-2,2-methano-2,6-diaminopimelic acids[89] from chiral 5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-ones unsaturated at C_2, obtained by condensation of 3-(dimethoxyphosphoryl)- and 3-(formylethyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-ones. When alkenes **175**, **176** and **177** were treated with [(diethylamino)phenyl]oxosulfonium methylide the corresponding cyclopropanes were isolated as single diastereoisomers. Removal of the chiral auxiliary and subsequent hydrolysis afforded the corresponding amino acids. Depending on the absolute configuration of the starting material, amino acids of different absolute configuration can be obtained according to Scheme 31.

Crich et al. have described[90] the addition of the dimethylsulfoxonium methylide (Corey's ylide) to a chiral tricyclic compound. This procedure led to a tryptophane cyclopropane analogue from which the free amino acid was not obtained (Scheme 32).

Meyers et al.[91] have described the cyclopropanation of unsaturated chiral bicyclic lactams **187**, derived from (*R*)-phenylglycinol, with the dimethylsulfoxonium methylide followed by removal of the

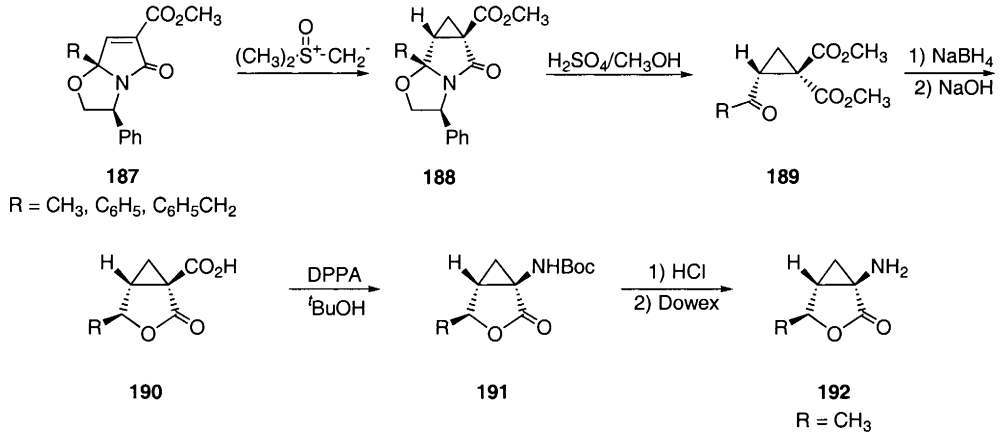


Scheme 31.



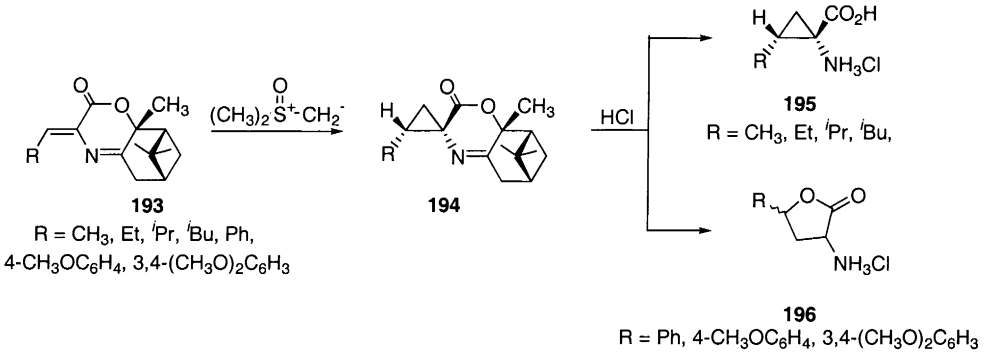
Scheme 32.

chiral auxiliary and Curtius rearrangement to afford 2-substituted 1-aminocyclopropanecarboxylic acid derivatives in enantiomerically pure form (Scheme 33).



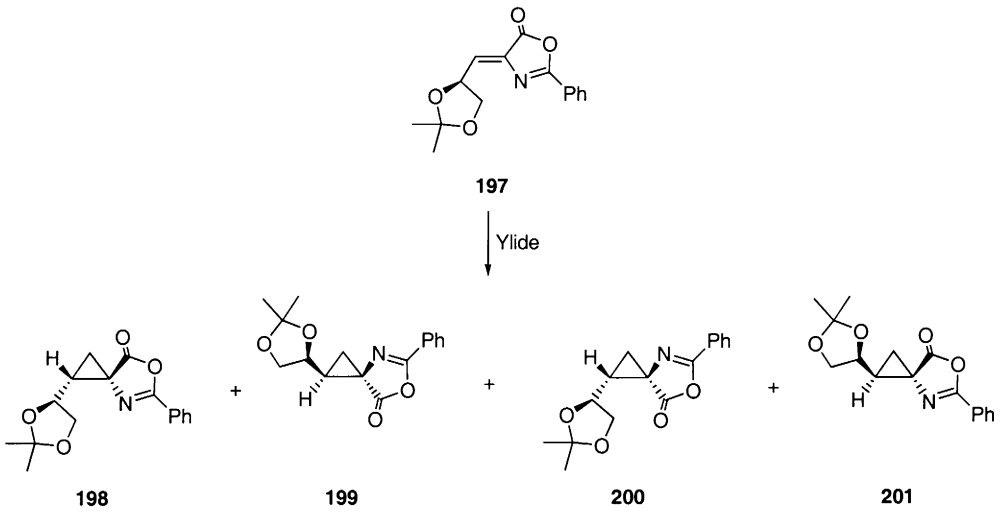
Scheme 33.

The (1*R*,2*R*,5*R*)-2-hydroxypinan-3-one-based didehydroamino acid derivatives could be smoothly cyclopropanated by the action of dimethylsulfoxonium methylide to give spirocyclopropane as single diastereoisomers in good yields.[92] The spiro compounds were easily converted by acid hydrolysis into enantiomerically pure 2-alkyl-1-aminocyclopropanecarboxylic acids, although hydrolysis to 2-aryl-1-aminocyclopropanecarboxylic acids was not possible under acidic conditions and racemic lactones **196** were isolated (Scheme 34).



Scheme 34.

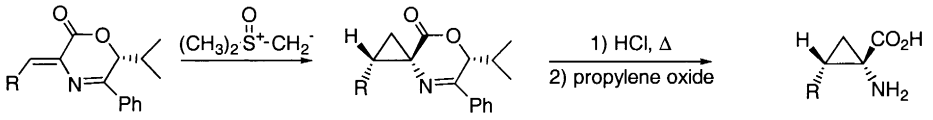
Our group has reported[93] the use of chiral oxazolone **197**, derived from mannitol, as a synthetic precursor in the asymmetric synthesis of cyclopropylamino acids with different side chains. The basis of this strategy is the fact that the dioxolane ring can be transformed into the appropriate substituent after the cyclopropanation reaction. When this specially designed oxazolone, which is unsaturated at C_4, was treated with dimethylsulfoxonium methylide or [(diethylamino)phenyl]oxosulfonium methylide under various conditions, mixtures of *cis* and *trans* cyclopropanes were obtained. The *cis*/*trans* selectivity was found to depend on the solvent and reaction temperature and, in all cases, both *cis* and *trans* diastereofacial selectivities were quite good, especially in apolar solvents at low temperature (Scheme 35). The four diastereoisomers obtained in the methylide insertion can be separated easily and elaborated further to afford enantiomerically pure 2-substituted 1-aminocyclopropanecarboxylic acids, and this process will be described later in this review.



Entry	Ylide	Solvent	temp.	198+199 / 200+201	198/199	200/201
a	$(CH_3)_2SOCH_2$	DMF	r.t.	40/60	61/39	78/22
b	$(CH_3)_2SOCH_2$	DMF	0 ºC	35/65	61/39	81/19
c	$(CH_3)_2SOCH_2$	DMF	- 20 ºC	28/32	63/37	85/15
d	$(CH_3)_2SOCH_2$	DMSO	r.t.	25/75	56/44	60/40
e	$(CH_3)_2SOCH_2$	CH_2Cl_2	r.t.	37/63	88/12	97/3
f	$(CH_3)_2SOCH_2$	CH_2Cl_2	0 ºC	47/53	91/9	98/2
g	$(CH_3)_2SOCH_2$	CH_2Cl_2	- 20 ºC	52/48	94/6	98/2
h	$(CH_3)_2SOCH_2$	toluene	r.t.	49/51	82/18	96/4
i	$(CH_3)_2SOCH_2$	toluene	0 ºC	54/46	81/19	97/3
j	$(CH_3)_2SOCH_2$	toluene	- 20 ºC	70/30	85/15	97/3
h	$PhNEt_2SOCH_2$	DMF	r.t.	56/44	47/53	63/37
l	$PhNEt_2SOCH_2$	DMF	0 ºC	67/33	75/25	80/20
m	$PhNEt_2SOCH_2$	DMF	- 20 ºC	73/27	80/20	86/14
n	$PhNEt_2SOCH_2$	DMSO	r.t.	53/47	62/38	70/30
o	$PhNEt_2SOCH_2$	CH_2Cl_2	r.t.	34/66	73/27	90/10
p	$PhNEt_2SOCH_2$	CH_2Cl_2	0 ºC	38/62	74/26	90/10
q	$PhNEt_2SOCH_2$	CH_2Cl_2	- 20 ºC	53/47	74/26	91/9
r	$PhNEt_2SOCH_2$	toluene	r.t.	61/39	79/21	97/3
s	$PhNEt_2SOCH_2$	toluene	0 ºC	63/37	85/15	98/2
t	$PhNEt_2SOCH_2$	toluene	- 20 ºC	62/38	87/13	98/2
u	$PhNEt_2SOCH_2$	ether	r.t.	57/43	82/18	97/3
v	$PhNEt_2SOCH_2$	ether	0 ºC	55/45	81/19	97/3
w	$PhNEt_2SOCH_2$	ether	- 20 ºC	55/45	83/17	98/2
x	$PhNEt_2SOCH_2$	THF	r.t.	51/49	77/23	92/8
y	$PhNEt_2SOCH_2$	THF	0 ºC	50/50	78/22	93/7
z	$PhNEt_2SOCH_2$	THF	- 20 ºC	51/49	80/20	96/4
a'	$PhNEt_2SOCH_2$	hexane	r.t.	72/28	86/14	96/4
b'	$PhNEt_2SOCH_2$	hexane	0 ºC	82/18	87/13	96/4
c'	$PhNEt_2SOCH_2$	hexane	- 20 ºC	83/17	87/13	96/4

Scheme 35.

Unsaturated 3,6-dihydro-2*H*-1,4-oxazin-2-ones **202** reacted with Corey's dimethylsulfoxonium methylide to give 1-aminocyclopropanecarboxylic acid derivatives with quite good diastereoselectively.[94] From these compounds enantiomerically pure (1*S*,2*R*)-*allo*-norcoronamic and (1*S*,2*R*)-*allo*-coronamic acids were obtained by acid hydrolysis (Scheme 36).

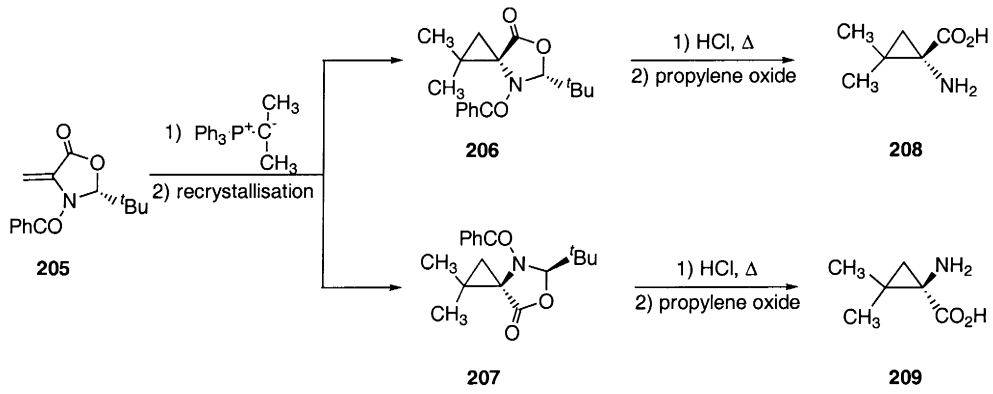


202 **203** **204**

Entry	R	dr
a	CH_3	90/10
b	CH_3CH_2	90/10

Scheme 36.

Finally, the reaction between (*S*)-*N*-benzoyl-2-*tert*-butyl-4-methylene-1,3-oxazolidin-5-one and isopropylidenetriphenylphosphorane at room temperature has been described,[95] and gives the corresponding spirocyclopropane derivatives with no diastereoselectivity. However, separation of the equimolecular mixture of the two diastereoisomers by recrystallisation and flash chromatography, followed by further acid hydrolysis, gave the enantiomerically pure (*R*)- and (*S*)-2,3-methanovaline. As such, this methodology can be considered as a resolution rather than an asymmetric synthesis (Scheme 37).



205 **206** **207** **208** **209**

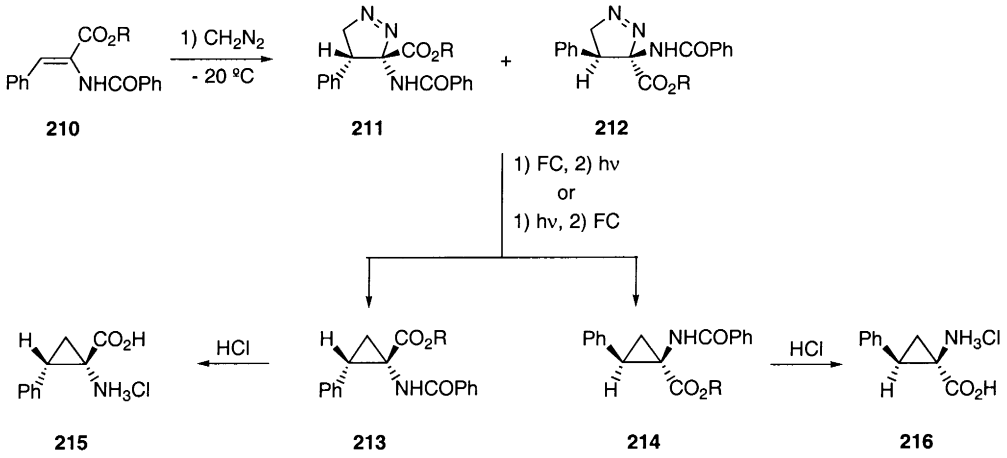
Scheme 37.

2.1.4. The use of diazo compounds on double bonds

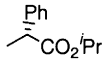
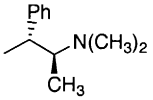
The use of diazo compounds is one of the most interesting strategies for the synthesis of organic compounds containing a cyclopropane ring. In particular, the addition of diazo compounds to α,β-didehydroamino acids constitutes one of the most interesting alternatives for the synthesis of 1-aminocyclopropanecarboxylic acids. The reaction occurs by a 1,3-dipolar cycloaddition to give a pyrazoline that rapidly evolves by extruding nitrogen either thermally or photochemically to give the corresponding cyclopropane derivatives.

This synthetic methodology, which is widely used in the synthesis of racemic compounds, has been applied to the asymmetric synthesis of cyclopropylamino acids starting from chiral α,β-didehydroamino acid derivatives. Chiral α-benzoylamino cinnamic esters **210**, obtained by stereoselective ring opening of *Z*-2-phenyl-4-benzylidene-5(4*H*)-oxazolone with chiral alcohols, undergo diastereoselective

cyclopropanation.[96,97] Reaction of these compounds with diazomethane leads to diastereomeric mixtures of the corresponding pyrazolines with low diastereoselectivity. Wherever possible, stereoisomeric pyrazolines are isolated and photolytically decomposed to the respective cyclopropyl compounds. Alternatively, photolytic decomposition of the diastereomeric mixture of pyrazolines leads to the stereoisomeric mixture of cyclopropane derivatives, which can be separated and isolated by flash chromatography. Hydrolysis of the isolated compounds affords the corresponding amino acids in enantiomerically pure form (Scheme 38).



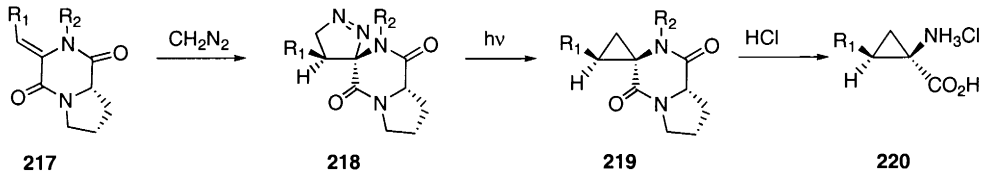
210 **211** **212** **215** **213** **214** **216**

Entry	R	211/212
a		60/40
b		65/35

Scheme 38.

In order to obtain a better diastereoselectivity, homochiral alkylidene or benzylidene diketopiperazines **217** have been used as starting compounds.[96–98] These compounds react with diazomethane to give the corresponding pyrazoline almost as a single diastereoisomer. Photolysis of the intermediate pyrazoline produces the corresponding spirocyclopropane, also almost as a single diastereoisomer, along with, in some cases, other by-products. Among the various derivatives tested, *N*-Boc diketopiperazines seem to be the most appropriate as they are stable compounds and photolysis of the pyrazolines obtained upon their reaction with diazomethane leads to the corresponding cyclopropyl derivatives in good yields and without the generation of any other by-products. Finally, after acidic hydrolysis the amino acid is obtained as its hydrochloride salt (Scheme 39).

Viallefont has also used chiral α,β-didehydroamino acid derivatives as starting materials. In these cases the amino and acid functions form part of a chiral oxazinone derived from pinanone.[99] The insertion of the diazomethane at the exocyclic double bond occurs at the less hindered face, giving rise to the corresponding pyrazoline as a single diastereoisomer, which could not be isolated. Nevertheless, thermal decomposition of this pyrazoline gives two diastereomeric cyclopropanes, which are not separable in any case, together with ethylenic compounds. Acid hydrolysis of both isolated 2-methylcyclopropyl derivatives leads to enantiomerically pure (1*S*,2*R*)- and (1*R*,2*R*)-1-amino-2-methylcyclopropanecarboxylic acids in 34.5 and 8.5% yield, respectively. Acid hydrolysis of the mixture of 2-ethylcyclopropyl deriv-

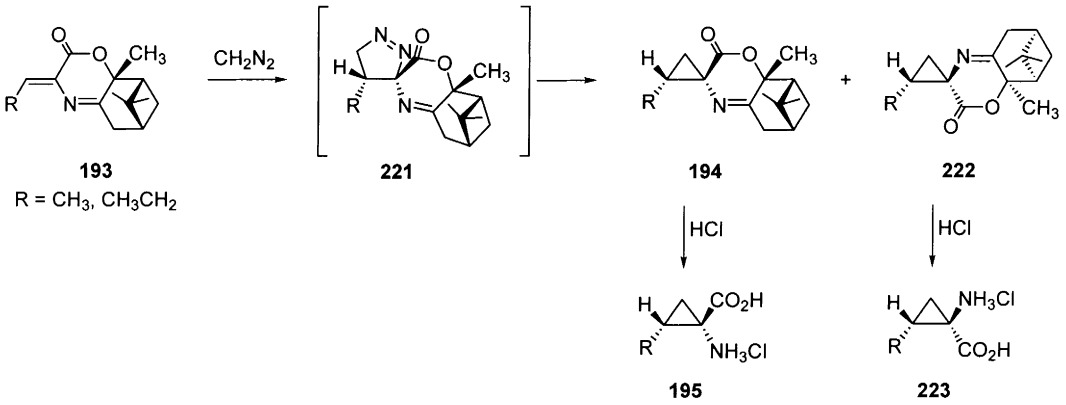


217 218 219 220

Entry	R_1	R_2	dr
a	Ph	CH_3CO	> 95/5
b	Ph	PhCO	> 95/5
c	Ph	Boc	> 95/5
d	CH_3	Boc	> 95/5
e	CH_3CH_2	Boc	> 95/5
f	^{i}Pr	Boc	> 95/5

Scheme 39.

atives affords a 70:30 mixture of (1*S*,2*R*)- and (1*R*,2*R*)-1-amino-2-ethylcyclopropanecarboxylic acids in only 25% yield (Scheme 40).



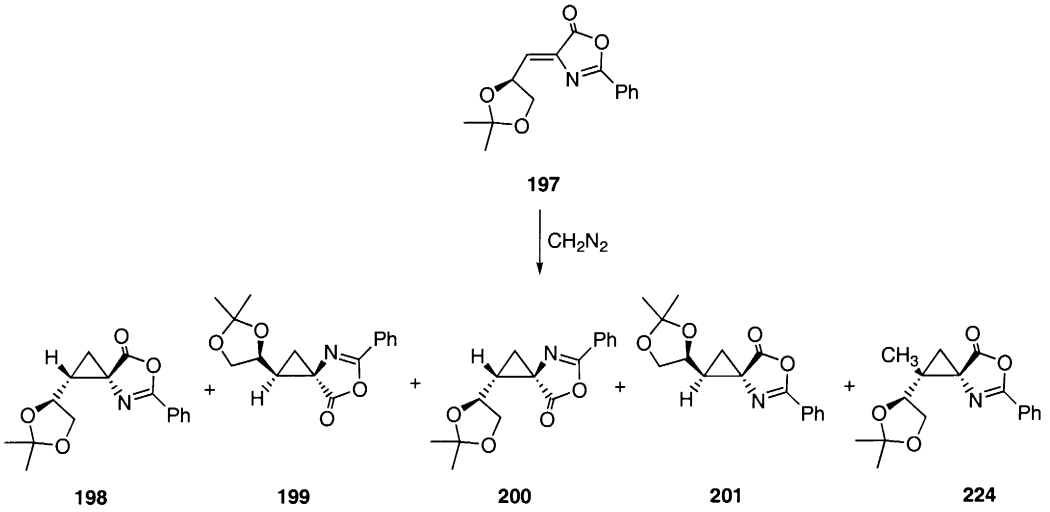
193 (R = CH_3, CH_3CH_2) 221 194 222 195 223

Scheme 40.

Two different strategies have been developed that use chiral α,β-didehydroamino acid derivatives containing the mannitol unit. The first strategy involves the reaction of chiral oxazolone **197** with diazomethane to afford a mixture of five spiro-compounds that can be isolated by flash chromatography.[100,101] The addition reaction occurs with a high *cis*/*trans* selectivity, as well as excellent diastereoselectivity for both *cis* and *trans* compounds. The formation of compound **224**, derived from further reaction of a *C*-methylation compound with diazomethane to yield the corresponding spiro-oxazolone, can be avoided by the use of non-polar solvents. In these solvents good *cis*/*trans* selectivity, as well as a very good *cis* and *trans* stereoselectivity, is observed in all cases. A decrease in the reaction temperature led to only a slight improvement in both *cis*/*trans* selectivity and stereoselectivity and, in all cases, the stereoselectivity observed for *trans* spiro-azlactones was better than for *cis* spiro-azlactones (Scheme 41).

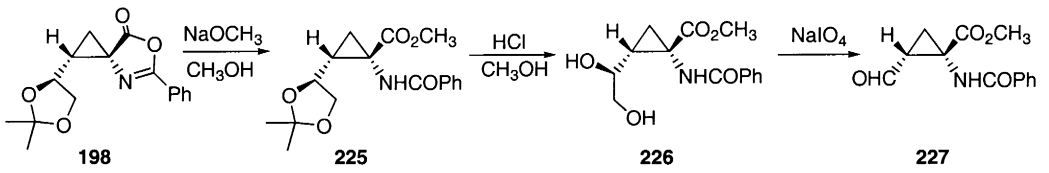
In order to develop a simple and versatile methodology for the synthesis of cyclopropylamino acids, the major compound **198** was converted into the corresponding 2-formyl derivative **227**. This conversion was achieved by methanolysis of the oxazolone upon treatment with 1% sodium methoxide in methanol, followed by acid hydrolysis of the acetonide and oxidative cleavage of the resulting diol[102] (Scheme 42).

Starting from compound **227** as a common intermediate, several cyclopropylamino acids have been



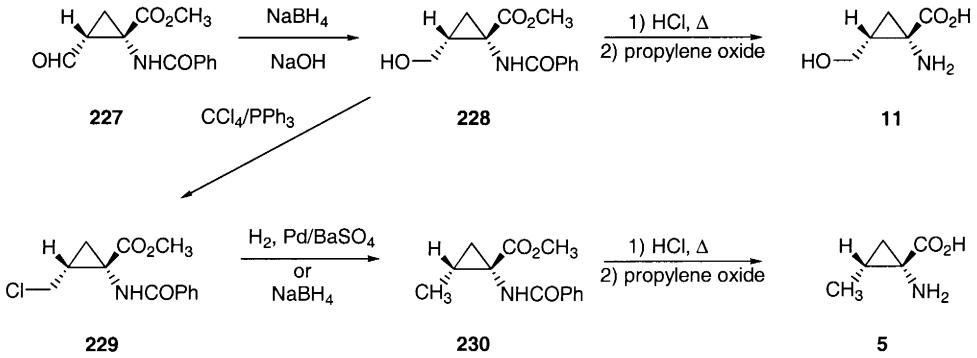
Entry	Solvent	temp.	224	198+199 / 200+201	198/199	200/201
a	ether	0 ºC	23 %	73/27	84/16	92/8
b	hexane	0 ºC	traces	77/23	84/16	87/13
c	CCl_4	0 ºC	traces	84/16	88/12	91/9
d	benzene	0 ºC	traces	81/19	90/10	93/7
e	CCl_4	- 20 ºC	traces	83/17	85/15	91/9
f	hexane	- 20 ºC	traces	78/22	84/16	87/13
g	hexane	- 50 ºC	traces	83/17	88/12	90/10
h	hexane	- 75 ºC	traces	83/17	90/10	90/10

Scheme 41.



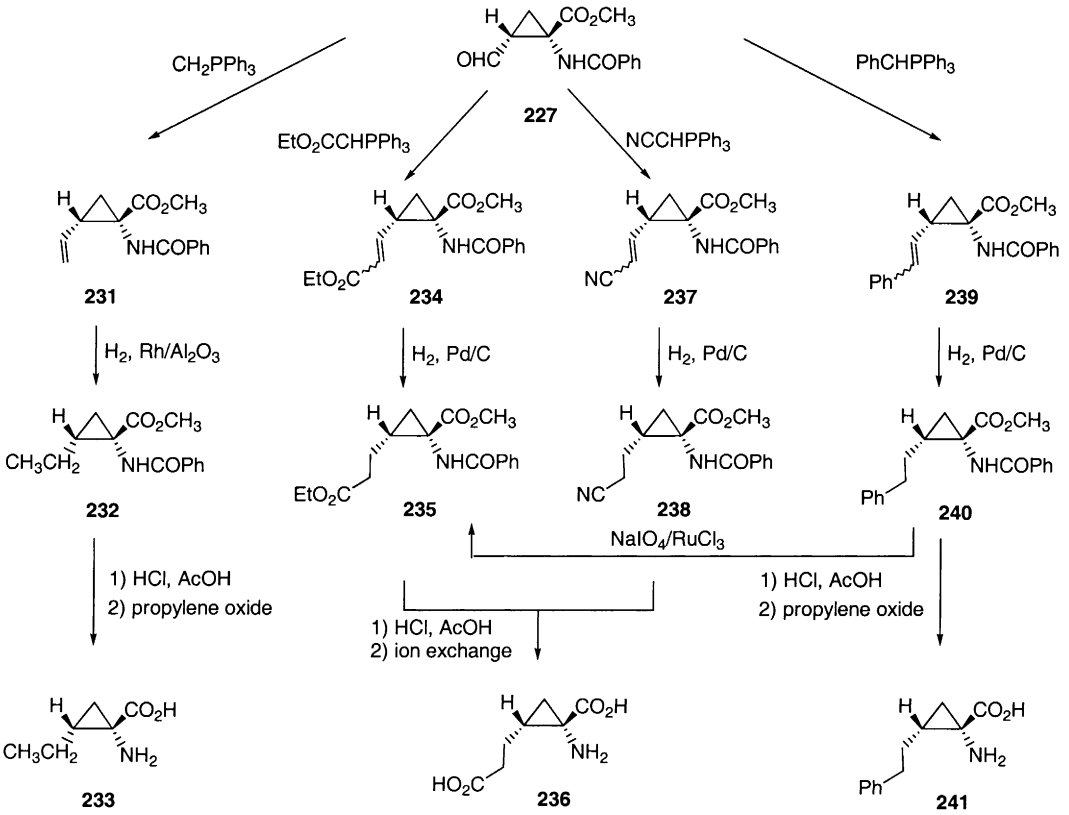
Scheme 42.

obtained by different synthetic routes. Reduction of the aldehyde allows the synthesis of (1*S*,2*R*)-1-amino-2-hydroxymethylcyclopropanecarboxylic and (1*S*,2*R*)-*allo*-norcoronamic acid[103] (Scheme 43).



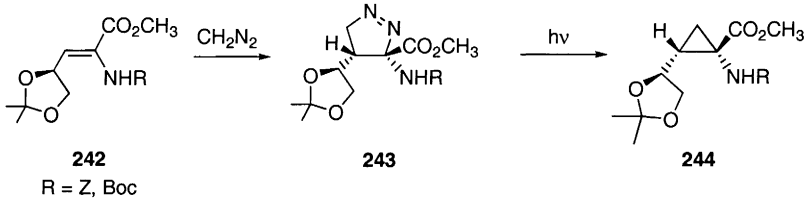
Scheme 43.

Wittig olefination of compound **227** with non-stabilised, stabilised and semi-stabilised ylides allows the synthesis of (1*S*,2*R*)-*allo*-coronamic acid[102] and some new cyclopropyl amino acids[104] according to Scheme 44.



Scheme 44.

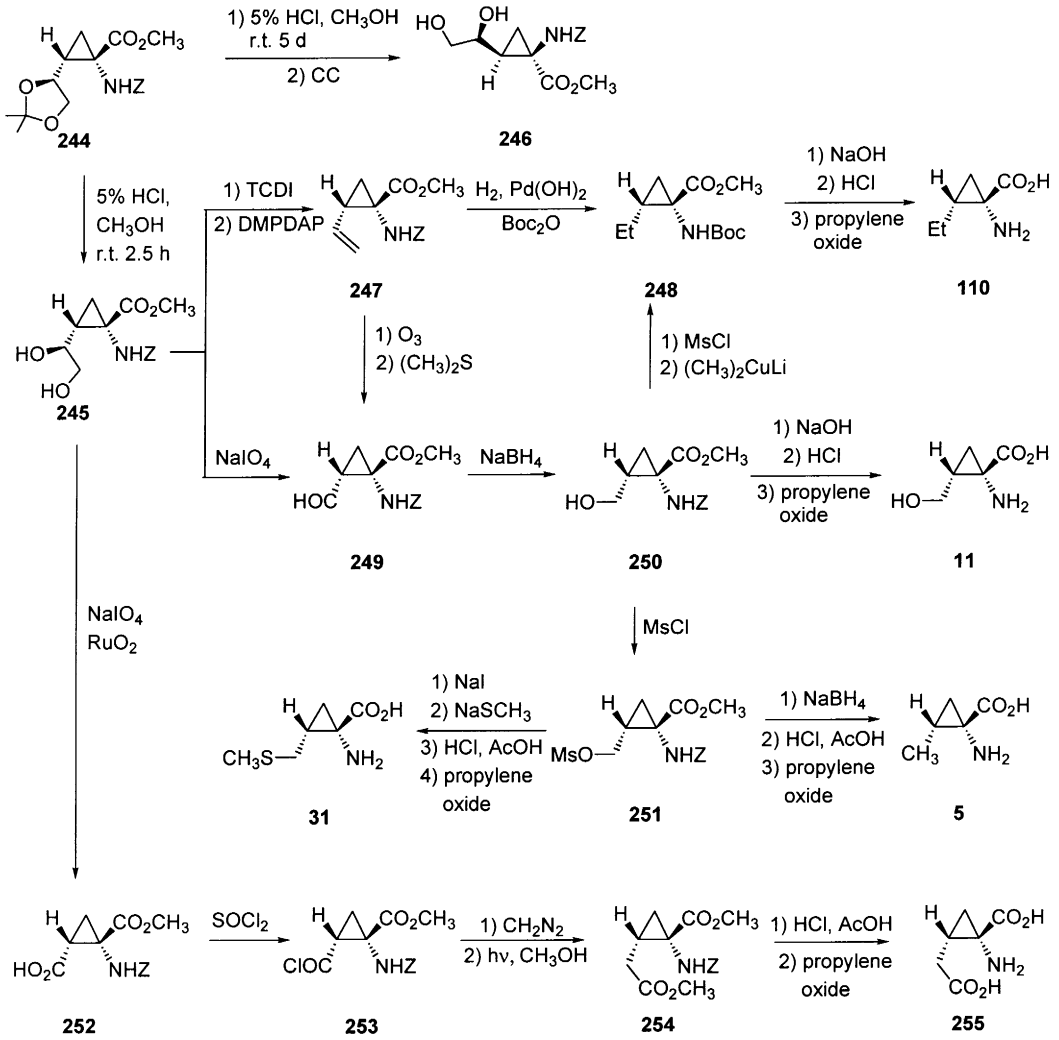
On the other hand, highly diastereoselective cyclopropanation of chiral α,β-didehydroamino acid derivatives **242**, obtained from D-glyceraldehyde acetonide, furnishes the corresponding pyrazoline as a single diastereoisomer.[105,106] Decomposition of the pyrazoline by irradiation allowed the synthesis of cyclopropanes **244**, which are useful intermediates in the synthesis of enantiopure Acc derivatives (Scheme 45). In this step the authors observed the formation of a small amount of insertion olefin and some by-products, which were removed by recrystallisation. The production of a number of the by-products can be avoided by performing the irradiation on a dilute dichloromethane solution at low temperature and in the presence of benzophenone as a photosensitiser.[107]



Scheme 45.

The subsequent synthetic step involved hydrolysis of the acetonide. Treatment of compound **244** with 5% HCl in methanol for 2.5 hours gave diol **245** without epimerisation and this compound can be

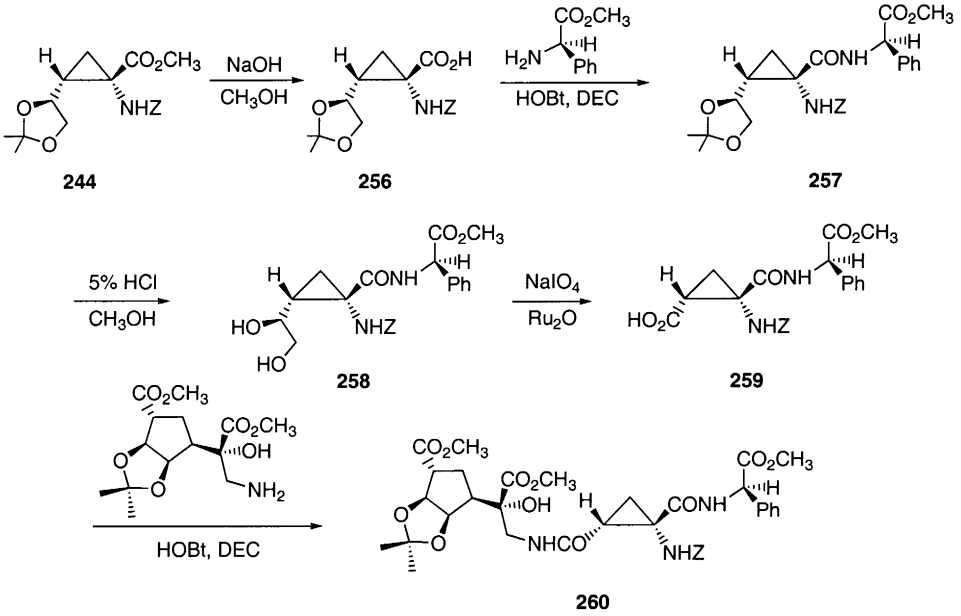
used as a versatile intermediate in the synthesis of enantiopure Acc derivatives, as shown in Scheme 46.[105,106,108,109] On the other hand, hydrolysis for longer time periods led to epimerisation and an equimolecular mixture of epimers, which were separable by column chromatography, was obtained after 5 days.[110]



Scheme 46.

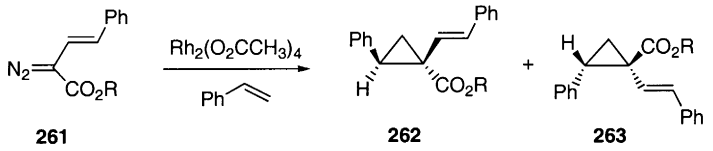
Small peptides containing enantiomerically pure (1*S*,2*R*)-1-benzyloxycarbonylaminocyclopropanedicarboxylic acid or its enantiomer were obtained by the same authors (Scheme 47).[110]

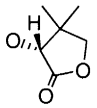
The metal-catalysed decomposition of diazoesters in the presence of an alkene to generate a carbenoid capable of adding to a double bond is one the most used and interesting strategies for the synthesis of cyclopropane acid derivatives. Although cyclopropanation reactions with α-diazoacetate derivatives occur with moderate diastereoselectivity to afford *cis*/*trans* mixtures of cyclopropanes, vinyldiazomethanes undergo remarkably stereoselective cyclopropanations. Taking this behaviour into account, Davies et al. have developed a new asymmetric synthesis of 1-aminocyclopropanecarboxylic acid derivatives. The diastereoselective approach to the synthesis consists of the use of chiral vinyldiazo compounds, derived from a chiral alcohol, that are decomposed by rhodium(II) complexes in the presence of styrene to afford



Scheme 47.

the corresponding cyclopropanes of *cis* stereochemistry. Very high levels of induction are observed when α-hydroxy acids are used as chiral auxiliaries and diastereoselectivity is improved on increasing the size of the side chain of the α-hydroxy acid. A further enhancement of the diastereoselectivity is observed on using a lactone instead of an open chain ester, and optimal levels of induction are observed when pantolactone is used as a chiral auxiliary. Moreover, the use of complementary chiral auxiliaries allowed a new entry into both series of enantiomeric vinylcyclopropanes with predictable absolute stereochemistry. On the other hand, steric and electronic modifications of the catalyst structure were shown to have major effects on the asymmetric induction[111,112] (Scheme 48).

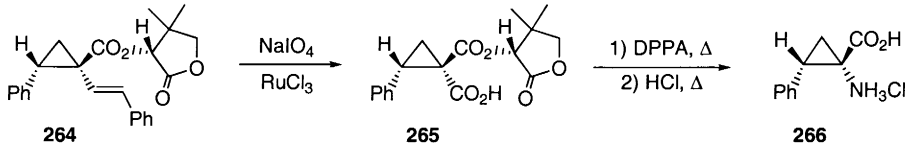


Entry	R	262/263
a	*(S)*-OCH(CH$_3$)CO$_2$CH$_3$	84/16
b	*(S)*-OCH(^{i}Pr)CO$_2$CH$_3$	89/11
c	*(S)*-OCH(^{t}Bu)CO$_2$CH$_3$	90/10
d		5/95

Scheme 48.

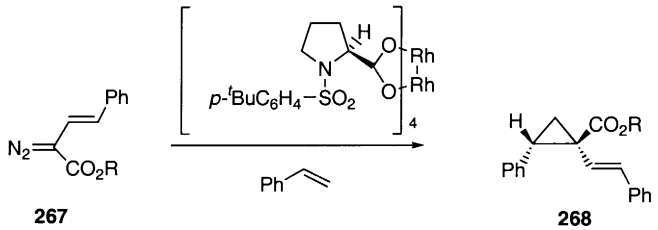
Oxidative cleavage of the major compound isolated, Curtius rearrangement of the resulting carboxylic acid and subsequent hydrolysis affords enantiomerically pure 1-amino-2-phenylcyclopropanecarboxylic acid in enantiomerically pure form (Scheme 49).

The enantioselective version of this reaction has been performed using rhodium(II) *N*-(arenesulfonyl)prolinate to catalyse the decomposition of vinyldiazo compounds in the presence



Scheme 49.

of alkenes to give *cis* cyclopropanes with good enantioselectivity.[113,114] A detailed study using rhodium(II) *N*-(*p*-*tert*-butylbenzenesulfonyl)prolinate as a catalyst was undertaken to determine the key factors that control the enantioselectivity. The study concluded that the level of asymmetric induction is strongly enhanced by the use of non-polar solvents, while increasing the size of the ester on the carbenoid results in a significant drop in enantioselectivity (Scheme 50).



Entry	R	Solvent	ee%
a	CH_3	CH_2Cl_2	74
b	CH_3	benzene	84
c	CH_3	pentane	90
d	CH_3CH_2	CH_2Cl_2	68
e	CH_3CH_2	pentane	84
f	^{i}Pr	CH_2Cl_2	43
g	^{i}Pr	pentane	76
h	^{t}Bu	CH_2Cl_2	9
i	^{t}Bu	pentane	50

Scheme 50.

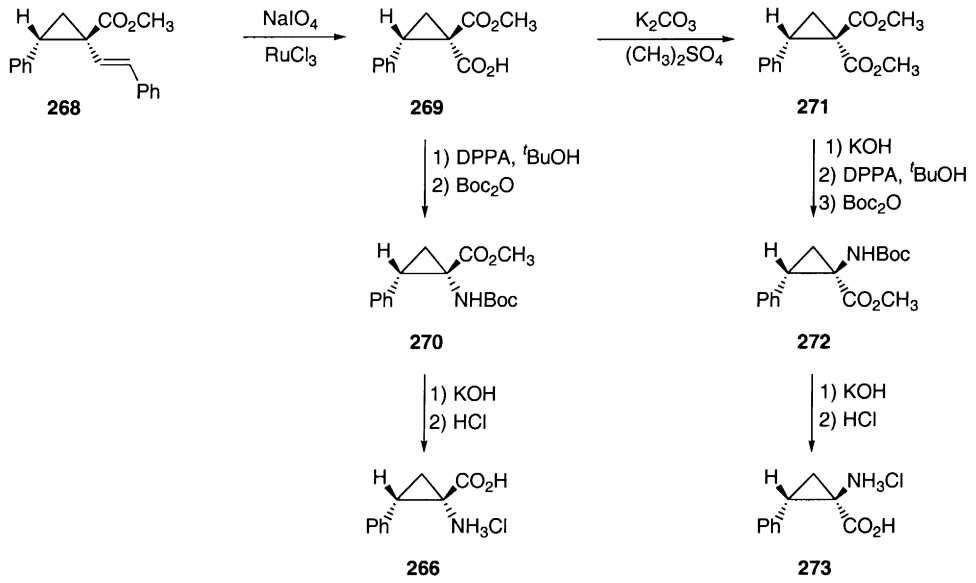
Even better results have been obtained with rhodium(II) *N*-(*p*-dodecylbenzenesulfonyl)prolinate as a catalyst at −78°C. Under these conditions enantiomerically pure **268** is obtained and, from this compound, a stereodivergent synthesis to (1*S*,2*S*)- and (1*R*,2*S*)-1-amino-2-phenylcyclopropanecarboxylic acids has been developed (Scheme 51). Following this approach, and by using the appropriate enantiomer of the catalyst, the four enantiomers of 1-amino-2-phenylcyclopropanecarboxylic acid can be obtained.

The synthesis and evaluation of novel dirhodium tetraprolinate catalysts containing bridging prolinate ligands has recently been described. It was found that such compounds catalyse the same cyclopropanation reaction, in some cases with excellent enantioselectivity.[115,116]

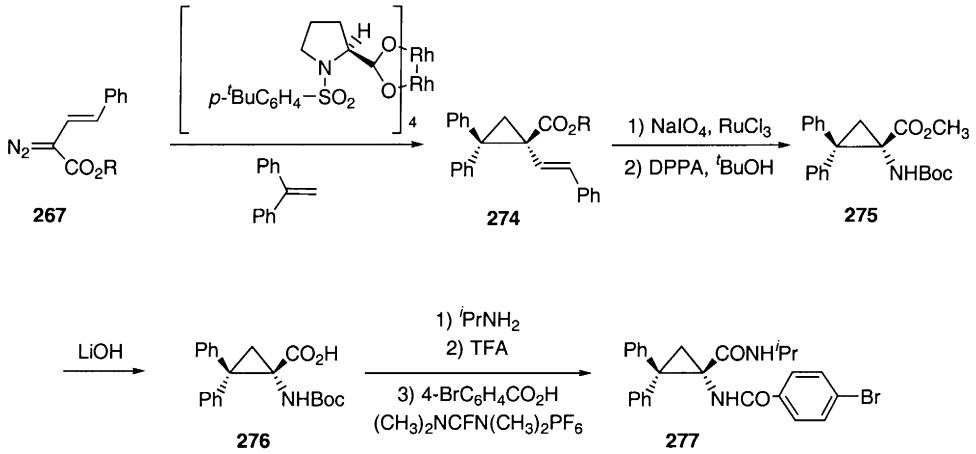
More recently, Burgess et al. screened some libraries of metal complex–ligand combinations to perform the asymmetric cyclopropanation of 1,1-diphenylethylene and found that rhodium(II) *N*-(*p*-*tert*-butylbenzenesulfonyl)prolinate and *N*-(*p*-dodecylbenzenesulfonyl)prolinate are the most effective catalysts.

Using a similar strategy to that developed by Davies and co-workers, a fully protected derivative of 1-amino-2,2-diphenylcyclopropanecarboxylic acid has been obtained[117] (Scheme 52).

The intramolecular cyclopropanation of diazomalonate derivatives, catalysed by chiral copper catalysts, leads to the corresponding cyclopropanolactones with good yields and moderate



Scheme 51.



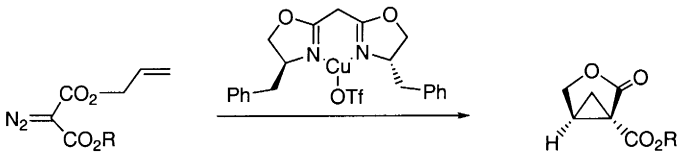
Scheme 52.

enantioselectivity[118] (Scheme 53). These compounds have proved to be very useful intermediates in the synthesis of Acc derivatives, as described above.

2.1.5. Other cyclopropanation reactions

Highly stereoselective cyclopropanation of allylic alcohols bearing a β-D-glucopyranose-derived moiety, under Simmons–Smith conditions using halomethylzinc reagents, affords the corresponding cyclopropyl derivative with excellent yields and diastereoselectivities. The level of induction depends on the stereochemistry of the alkene moiety. Whereas cyclopropanation of the *E*-isomer afforded the diastereomerically pure cyclopropane when iodomethylzinc was used as the reagent, it was necessary to generate the more reactive chloromethylzinc reagent and decrease the temperature to reach a 97% diastereomeric excess when a *Z*-olefin was used as the starting material[119] (Scheme 54).

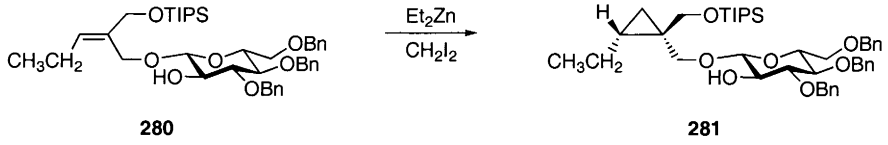
After cleavage of the chiral auxiliary and appropriate treatment of the residue, all four stereoisomers of 1-amino-2-ethylcyclopropanecarboxylic acid were obtained in enantiomerically pure form. The synthetic



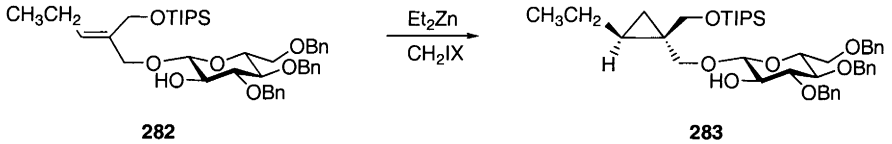
278 279

Entry	R	ee%
a	CH_3	11
b	^tBu	32

Scheme 53.



280 281



282 283

Entry	X	temp	de %
a	I	- 20 ºC	90
b	I	0 ºC	50
c	Cl	-20 ºC	93
d	Cl	-60 ºC	97

Scheme 54.

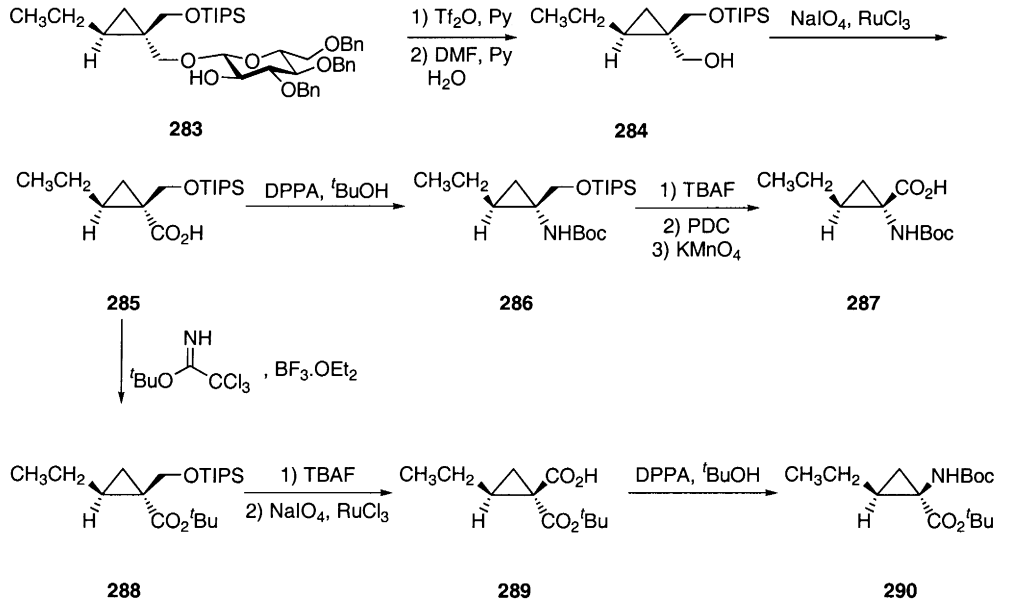
route to (1*S*,2*S*) and (1*R*,2*S*) diastereoisomers from compound **283** is represented in Scheme 55. Diastereoisomers of (1*R*,2*R*) and (1*S*,2*R*) configuration are obtained from compound **281** in a similar way.

2.1.6. Strecker synthesis

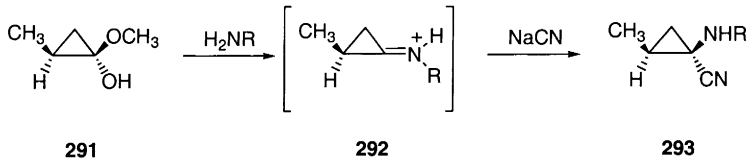
To the best of our knowledge the work of Fadel et al. is the only example in the literature in which the Strecker synthesis has been used in the asymmetric synthesis of 1-aminocyclopropanecarboxylic acid derivatives.[120,121] The reaction involves addition of cyanide to chiral alkylcyclopropane hemiacetals in the presence of a chiral amine to provide the corresponding amino nitriles (Scheme 56).

Hydrolysis of amino nitriles leads to the corresponding amides, which upon hydrogenolysis give amino amide **295**. From this compound the free amino acid is obtained after acid hydrolysis followed by ion exchange chromatography (Scheme 57).

When racemic alkylcyclopropane hemiacetals are used as starting compounds, a mixture of *cis* and *trans* amino nitriles is obtained and, in this case, *cis* and *trans* diastereoselectivities are roughly the same. This methodology has been applied to the asymmetric synthesis of (*R*)- and (*S*)-1-amino-2,3-dimethylcyclopropanecarboxylic acid[120] as well as (1*R*,2*S*)- and (1*S*,2*R*)-1-amino-2-methylcyclopropanecarboxylic acid and (1*R*,2*S*)- and (1*S*,2*R*)-1-amino-2-ethylcyclopropanecarboxylic acid.[121]

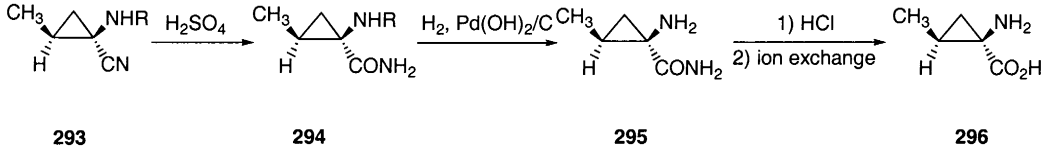


Scheme 55.



Entry	R	de %
a	*(S)*-CH(CH$_3$)Ph	76
b	*(R)*-CH(CH$_3$)Ph	74
c	*(R)*-CH(CH$_2$OCH$_3$)Ph	80

Scheme 56.



Scheme 57.

2.1.7. Resolution procedures

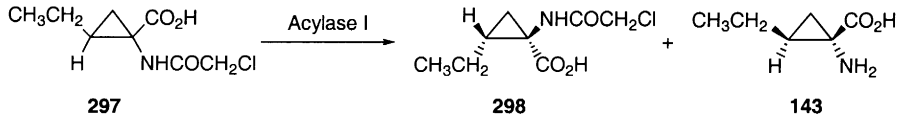
Classical resolution procedures based on recrystallisation of diastereomeric compounds have been applied in some cases to the isolation of these interesting compounds in enantiomerically pure form. For example, both enantiomers of *E*-1-amino-2-phenylcyclopropanecarboxylic acid have been resolved after several recrystallisations with brucine,[122] and resolution of both enantiomers of the corresponding methyl esters of *Z* configuration was accomplished using optically active dibenzoyl tartaric acids as the resolving agents.[123]

Racemic 1-amino-2-methyl- and 1-amino-2-ethylcyclopropanecarboxylic acids of *Z* configuration have been resolved by successive recrystallisations after coupling of their methyl ester hydrochlorides with (*R*)- or (*S*)-2-hydroxy-2-phenylacetic acid,[124] and *N*-formyl-1-amino-2,2-

dimethylcyclopropanecarboxylic acid has been resolved using (−)-quinine by fractional recrystallisation from chloroform and ether.[125]

Preparative high performance liquid chromatography using bonded polysaccharide-derived stationary phases has been found to be a useful tool for the preparation of the four stereoisomers of 1-amino-2-phenylcyclopropanecarboxylic acid. Both *cis* and *trans* methyl 1-*tert*-butoxycarbonylamino-2-phenylcyclopropanecarboxylates can be resolved into enantiomers using these chiral stationary phases.[126]

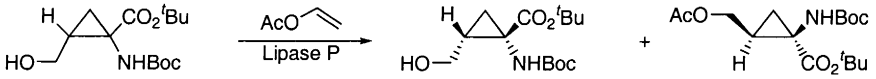
Enzyme-catalysed reactions have also been applied to the resolution of some cyclopropanecarboxylic acids. Good results were obtained in the resolution of (1*R*,2*S*)- and (1*S*,2*R*)-1-amino-2-ethylcyclopropanecarboxylic acids when the *N*-chloroacetyl derivative was hydrolysed by Porcine Kidney Acylase I[124] (Scheme 58).



297 **298** **143**

Scheme 58.

Acetylation of *tert*-butyl 2-hydroxymethyl-1-*tert*-butoxycarbonylaminocarboxylate, mediated by Amano Lipase P, leaves the enantiomer of 1*S*,2*R* configuration unacetylated, but the enantiomeric excess of this unreacted material after 53% conversion was only 54%[64] (Scheme 59).



299 **300** **301**

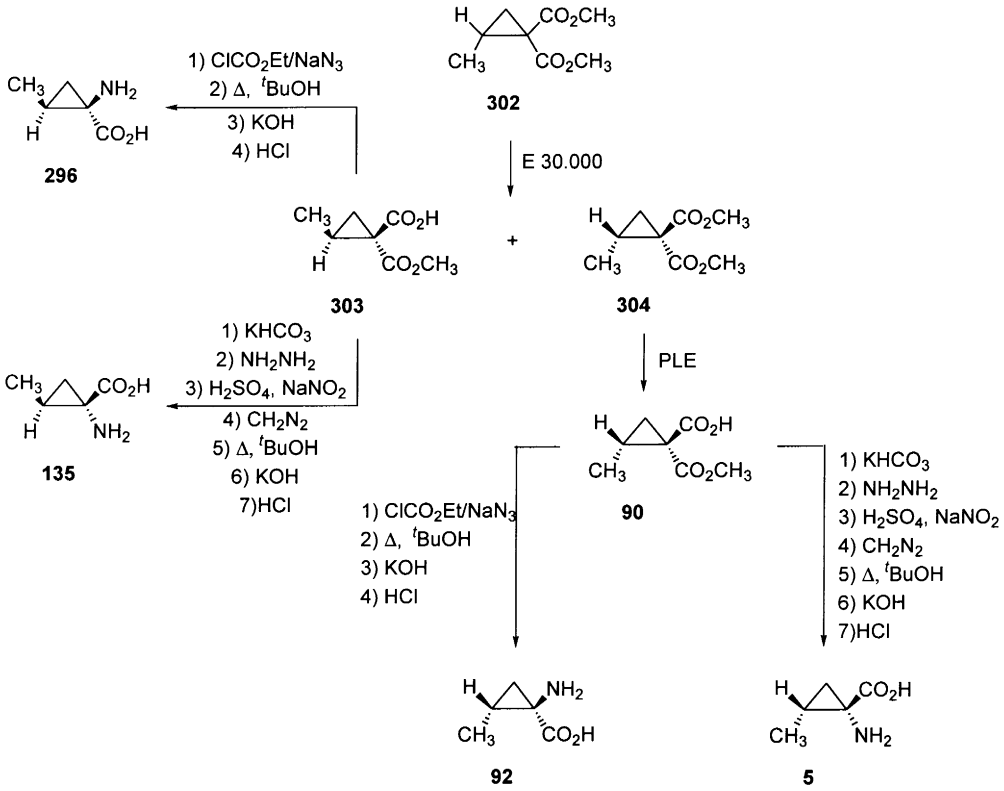
Scheme 59.

1-Amino-2-methylcyclopropanecarboxylic acid has been obtained from racemic 2-methylcyclopropanedicarboxylic acid dimethyl ester after selective enzymatic reactions with pig liver esterase and an esterase (E 30 000) from Gist Brocades to give enantiomerically pure monocarboxylic acids.[127] The fact that both enzymes possess complementary selectivities and the application of a stereodivergent route to 1-aminocyclopropanecarboxylic acids allows the synthesis of all four stereoisomers of 1-amino-2-methylcyclopropanecarboxylic acid (Scheme 60). A similar approach has been applied to the synthesis of (1*R*,2*S*)- and (1*S*,2*S*)-1-amino-2-vinylcyclopropanecarboxylic acid.[128]

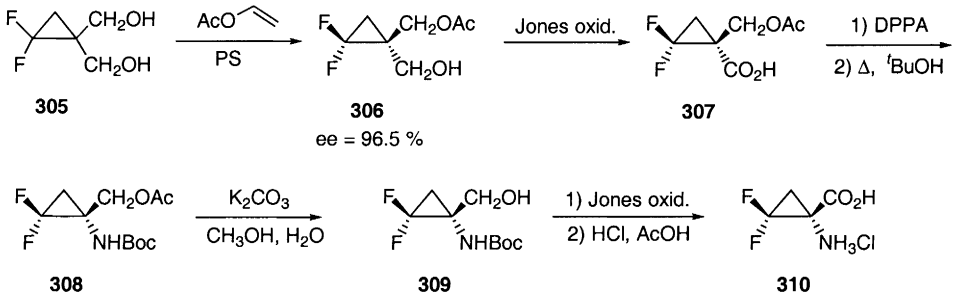
Finally, the enantioselective synthesis of (*R*)-1-amino-2,2-difluorocyclopropanecarboxylic acid has been achieved by lipase-catalysed asymmetric acetylation of a pro-chiral diol as the key step, as shown in Scheme 61.[129] The use of *Pseudomonas cepacia* (PS) gives excellent enantioselectivity and high chemical yields of monoacetate. Oxidation of the hydroxymethyl group followed by Curtius rearrangement and conversion of the *O*-acetylhydroxymethyl moiety into the carboxylic acid provides the desired amino acid.

2.1.8. Miscellaneous

Palladium(0)-catalysed azidation of 1-(1-alkenyl)cyclopropyl esters proceeds with complete retention of configuration to provide precursors of cyclopropylamino acids. In this way, (1*R*,2*S*)-1-amino-2-methylcyclopropanecarboxylic acid can be obtained by palladium(0)-catalysed azidation of (1*R*,2*S*)-1-(1-alkenyl)-2-methylcyclopropyl mesylate followed by reduction of the azide and oxidative cleavage of the allylic double bond[130] (Scheme 62).



Scheme 60.

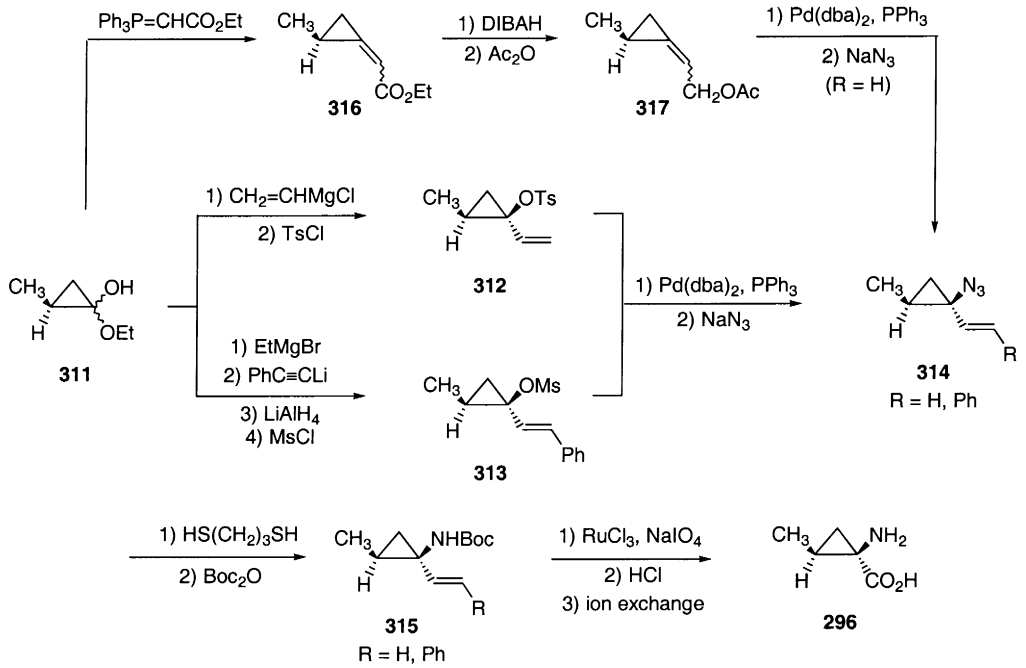


Scheme 61.

Alternatively, compound **314** (R=H) was obtained by Wittig olefination of hemiacetal **311**, followed by reduction of the ester to give the corresponding allylic alcohol, esterification with acetic anhydride and palladium(0)-catalysed azidation.

2.2. 1-Aminocyclobutanecarboxylic acids

Despite the interest in the study of this new type of conformational restriction there are, to the best of our knowledge, no references concerning the synthesis or the use of these compounds in their enantiomerically pure form. The only references existing in the literature are related to racemic compounds, which is beyond the scope of this review.



Scheme 62.

2.3. 1-Aminocyclopentanecarboxylic acids

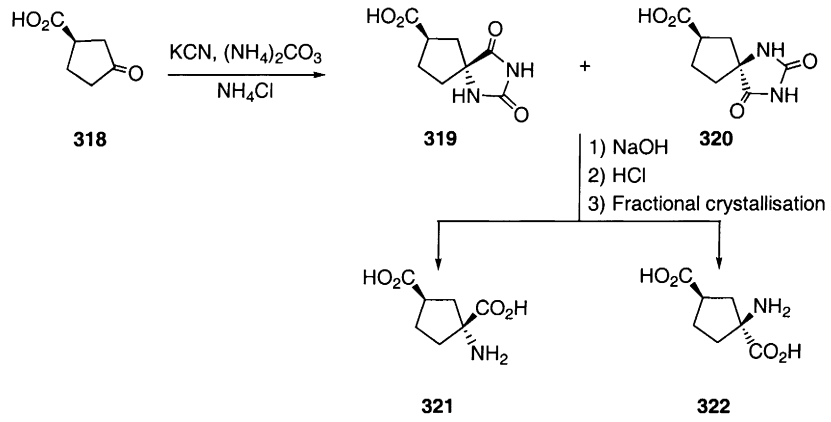
2.3.1. Bucherer–Bergs synthesis

Starting from a cyclopentane ring the Strecker or Bucherer–Bergs reactions are probably the most frequently used methods to prepare this family of compounds. In this context, the four stereoisomers of 1-aminocyclopentane-1,3-dicarboxylic acid (ACPD), which are conformationally constrained analogues of glutamate that have been found to act as excitatory amino acids, were obtained from 3-oxocyclopentanecarboxylic acid.[131] A mixture of the (1*S*,2*R*) and (1*R*,2*R*) stereoisomers of ACPD was obtained from the (*R*)-enantiomer after Strecker-type formation of hydantoin followed by hydrolysis. Fractional crystallisation of the mixture allows the isolation of both compounds in diastereomerically pure form. The (1*R*,2*S*) and (1*S*,2*S*) stereoisomers are obtained in the same way from (*S*)-3-oxocyclopentanecarboxylic acid (Scheme 63).

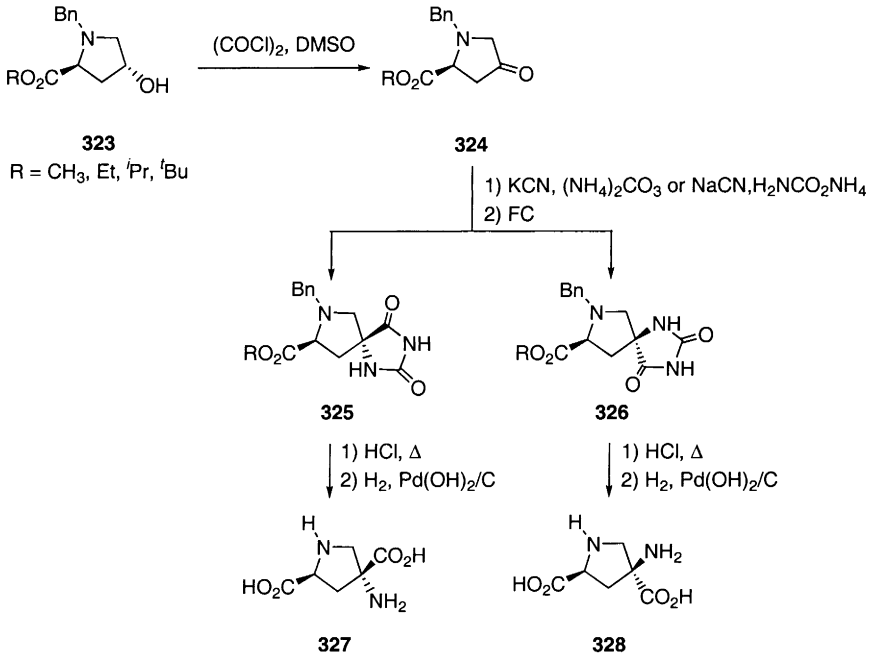
A diastereoselective Bucherer–Bergs reaction has been applied to the synthesis of the four stereoisomers of 4-aminopyrrolidin-2,4-dicarboxylic acid (APDC), which are aza analogues of ACPD, using enantiomerically pure proline derivatives as starting materials.[132,133] (2*S*,4*S*)-APDC and (2*S*,4*R*)-APDC are prepared in a stereochemically-controlled fashion from *N*-benzyl-L-*trans*-4-hydroxyproline according to Scheme 64. Increasing the steric bulkiness of the ester group led to an increase in the diastereoselectivity of the reaction. *N*-Benzyl-D-*cis*-4-hydroxyproline is the starting material in the synthesis of (2*R*,4*R*)-APDC and (2*R*,4*S*)-APDC.

The same methodology has been used in the synthesis of (2*S*,4*S*)- and (2*S*,4*R*)-4-amino-4-carboxy-2-(phosphonomethyl)pyrrolidine, which can be viewed as novel conformationally constrained analogues of 2-amino-5-phosphonopentanoic acid (AP5) incorporated into the pyrrolidine ring[134] (Scheme 65).

The four stereoisomers of 1-aminocyclopentane-1,3,4-tricarboxylic acid (ACPT) can be obtained by Bucherer–Bergs or Strecker reactions starting from (1*R*,2*S*)-, (1*R*,2*R*)- or (1*S*,2*S*)-dimethyl cyclopentan-4-one-1,2-dicarboxylate. *meso*-(1*R*,2*S*)-Dimethyl cyclopentan-4-one-1,2-dicarboxylate afforded a pair of



Scheme 63.

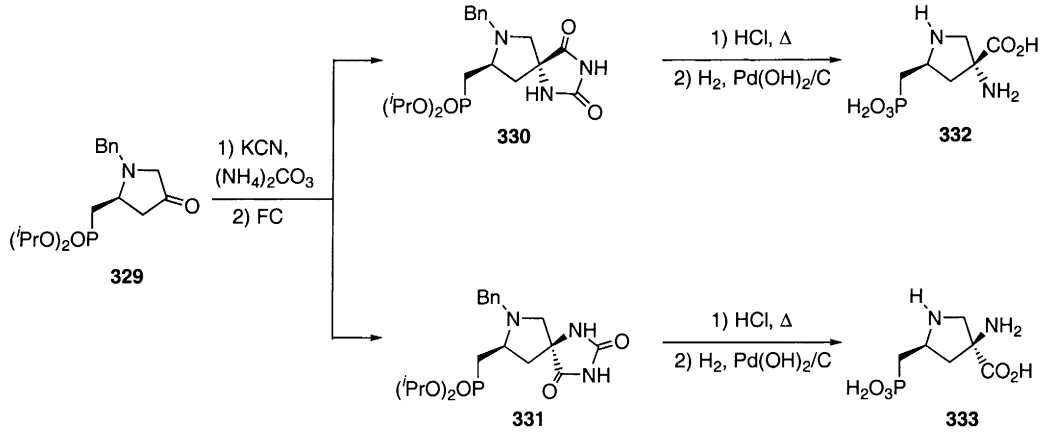


Entry	R	325/326
a	CH_3	75/25
b	Et	78/22
c	^{i}Pr	84/16
d	^{t}Bu	96/4

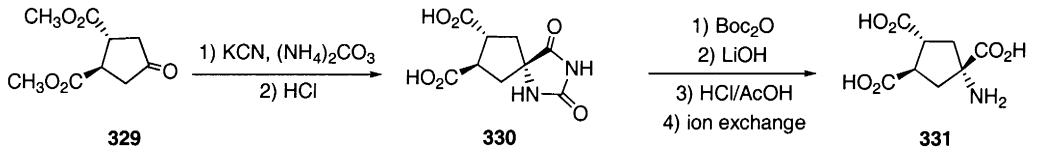
Scheme 64.

meso spirohydantoins whereas the (1*R*,2*R*) and (1*S*,2*S*) diastereoisomers led to a single compound that, in each case, possesses C_2 symmetry. Careful hydrolysis of the resulting spirohydantoins, to minimise epimerisation, and separation of isomeric amino acids by ion exchange chromatography led to the corresponding amino acids.[135] Scheme 66 represents the synthetic route to the (3*R*,4*R*) diastereoisomer of ACTP.

(1*S*,2*S*,5*R*,6*S*)-2-Aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740), a potent, selective

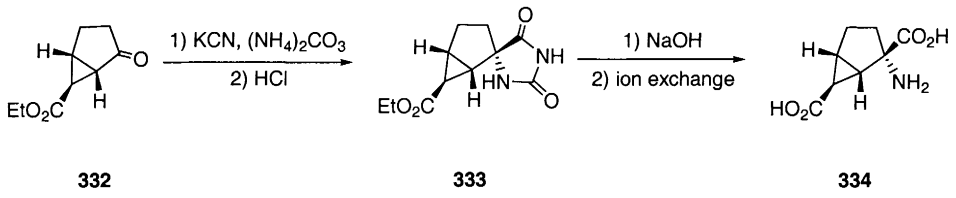


Scheme 65.



Scheme 66.

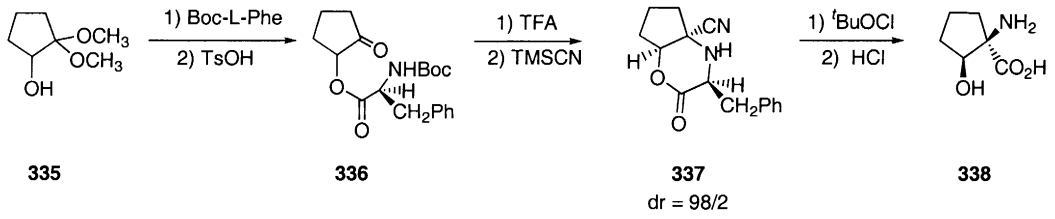
and orally active group 2 metabotropic glutamate receptor agonist possessing anticonvulsant and anxiolytic properties, has recently been obtained by using a similar methodology.[136] The desired compound was obtained from a cyclopentenone derivative following the reaction sequence shown in Scheme 67.



Scheme 67.

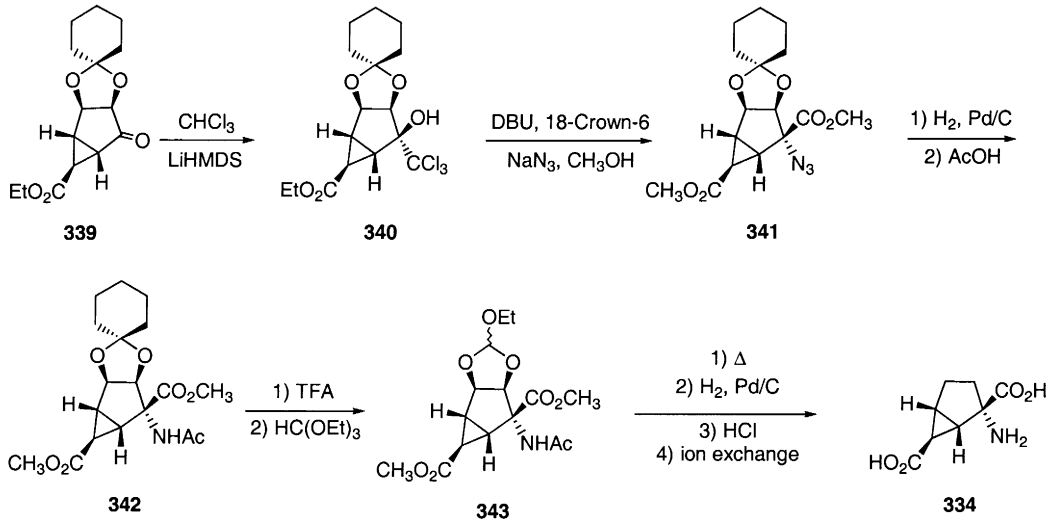
1-Aminocyclopentanecarboxylic acids have also been obtained by intramolecular Strecker synthesis according to the methodology developed by Ohfune et al.[137,138] Esterification of (*S*)-*N*-*tert*-butoxycarbonylphenylalanine with 1,1-dimethoxy-2-cyclopentanol and subsequent acid-catalysed cyclisation leads to an intermediate that, after removal of the *N*-Boc protecting group with trifluoroacetic acid and treatment of the resulting trifluoroacetate salt with sodium cyanide, gives an 80:20 mixture of diastereomeric amino nitriles. The use of trimethylsilyl cyanide as a cyano transferring reagent leads to significant improvements in both yield and selectivity and a 98:2 mixture of diastereomeric amino nitriles, from which the major diastereoisomer has been isolated, is obtained. Treatment of the amino nitrile with *tert*-butyl hypochlorite and triethylamine, followed by hydrolysis with concentrated hydrochloric acid, leads to (1*S*,2*R*)-1-amino-2-hydroxycyclopentanecarboxylic acid (Scheme 68).

Chloroform anion addition followed by azide displacement of the alcohol also allows the construction of the amino acid moiety on a carbonyl group with a stereochemical outcome opposite to the traditional Bucherer–Bergs and Strecker reactions. This approach has been applied to the synthesis of (1*S*,2*S*,5*R*,6*S*)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740) from dihydroxycyclopentanone derivative **339**.[139] Chloroform addition occurs with total diastereoselectivity to afford a trichloromethylcar-



Scheme 68.

binol that, by treatment with sodium azide, led to the corresponding azido ester. From this compound LY354740 has been obtained according to Scheme 69.



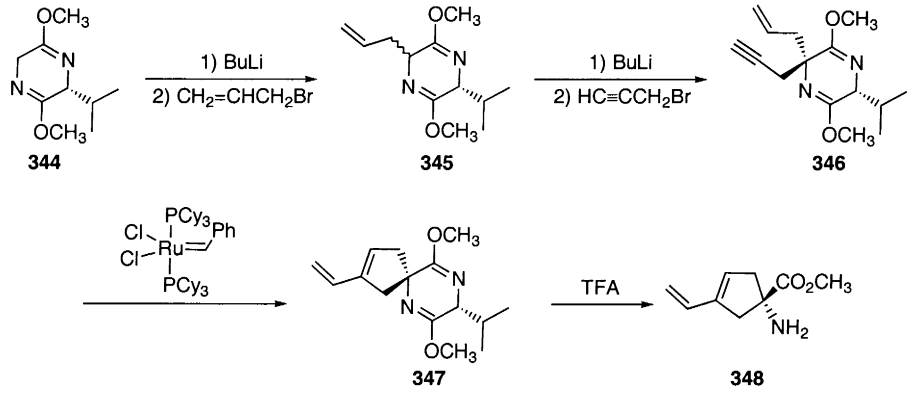
Scheme 69.

2.3.2. Ring closing metathesis and cycloisomerisation

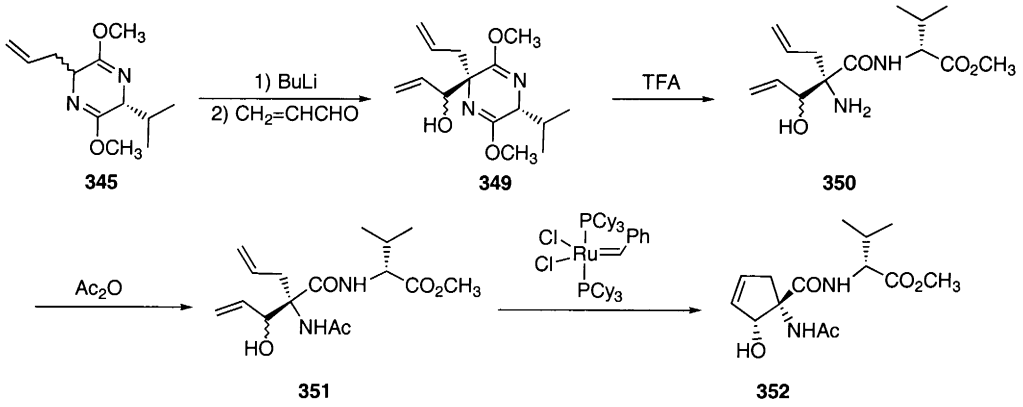
In recent years, the use of the ring closing metathesis reaction (RCM) for the creation of cyclic systems from acyclic diolefins has increased tremendously in significance as a result of the development of effective carbenoid ruthenium(II) complexes as catalysts. Undheim et al. developed a synthetic methodology to obtain 1-aminocyclopentanecarboxylic acids asymmetrically.[140–142] In this methodology stereoselective alkylation reactions, using the Schöllkopf procedure,[143–145] were employed to obtain the appropriate chiral bisalkenylated amino acid derivatives and these were combined with Grubbs' methodology[146] for ruthenium(II)-catalysed ring closing metathesis.

Starting from diastereomerically pure 5-allyl-5-propagyl bis-lactim **346**, a metathesis reaction cleanly affords the corresponding five-membered derivative from which the enantiomerically pure amino acid can be obtained by mild hydrolysis[141] (Scheme 70).

Aldol reaction of compound **345** with acrolein yields the corresponding 1,2-addition compound of *trans* stereochemistry, but with low stereoselectivity at the α-hydroxy carbon (de=33%). Once the major compound is isolated, formation of the five-membered spiro-ring cannot be achieved unless hydrolytic cleavage of the bis-lactim is effected prior to the cyclisation reaction. Under these conditions ring closing metathesis proceeds smoothly at ambient temperature to yield the five-membered serine analogue[142] (Scheme 71).



Scheme 70.



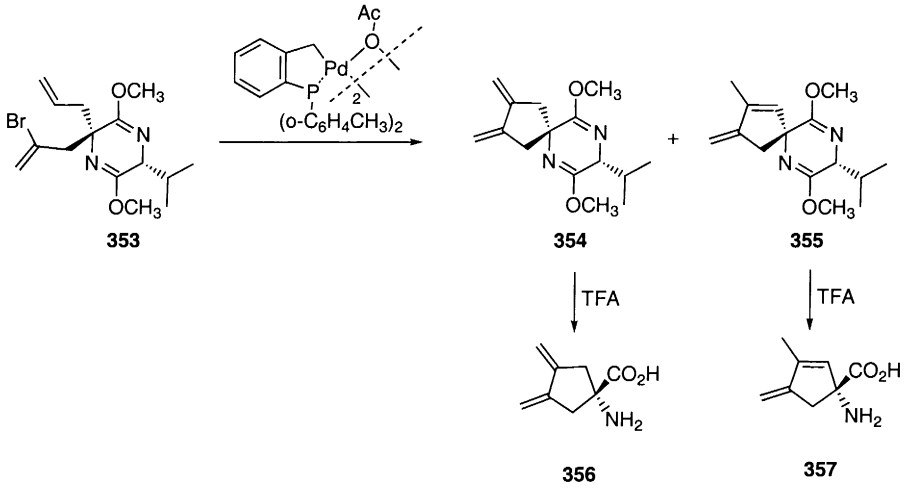
Scheme 71.

Palladium-mediated cycloisomerisation of a diastereomerically pure bis-lactim, containing the appropriate unsaturated substituents, has been used to obtain 1-aminocyclopentanecarboxylic acids that incorporate a diene in their structure. In this way, an almost equimolecular mixture of cyclisation compounds was obtained from compound **353** and, after isolation and acid hydrolysis, achiral **356** and enantiomerically pure **357** were obtained[147] (Scheme 72).

2.3.3. Cycloaddition reactions

The synthesis of four stereoisomers of the new conformationally restricted ACPD analogue 2-aminobicyclo[2.1.1]hexane-2,5-dicarboxylic acid has been achieved by an intramolecular photochemical [2+2] cycloaddition reaction of an appropriately functionalised dehydroglutamate, which is easily obtained in enantiomerically pure form from L-serine following the Seebach methodology.[148] Irradiation of the diene affords a mixture of four bicyclic compounds from which the major (1*R*,2*S*,4*R*,5*R*) stereoisomer can be isolated by column chromatography. Subsequent hydrogenolysis enables the rest of the stereoisomers to be isolated as single compounds. Scheme 73 shows the synthesis of the corresponding stereoisomers.[149]

The triphenylphosphine-catalysed cycloaddition reaction between allenes and activated alkenes has been used to obtain novel conformationally restricted L-glutamate analogues. Whereas the cycloaddition reaction between chiral oxazolidinone **371** and ethyl buta-2,3-dienoate in the presence of triphenylphosphine affords a mixture of regioisomeric compounds as well as a dimer, when ethyl penta-2,3-dienoate is



Scheme 72.

used as the allene a single cycloadduct is obtained. Acid hydrolysis of the spirooxazolidinones obtained in this way gives the corresponding amino acids in enantiomerically pure form[150] (Scheme 74).

Williams and Fegley have developed an asymmetric synthesis of cucurbitine, a naturally occurring amino acid found in the seeds of several cucurbita species, using a 1,3-dipolar cycloaddition.[151] In their approach, 1,3-dipolar cycloaddition of an azomethine ylide, generated from *N*-benzyl-*N*-(methoxymethyl)trimethylsilylmethylamine, to α,β-dehydrolactone **377** gives the corresponding pyrrolidine as a single diastereoisomer, which can be easily hydrolysed to the desired compound (Scheme 75).

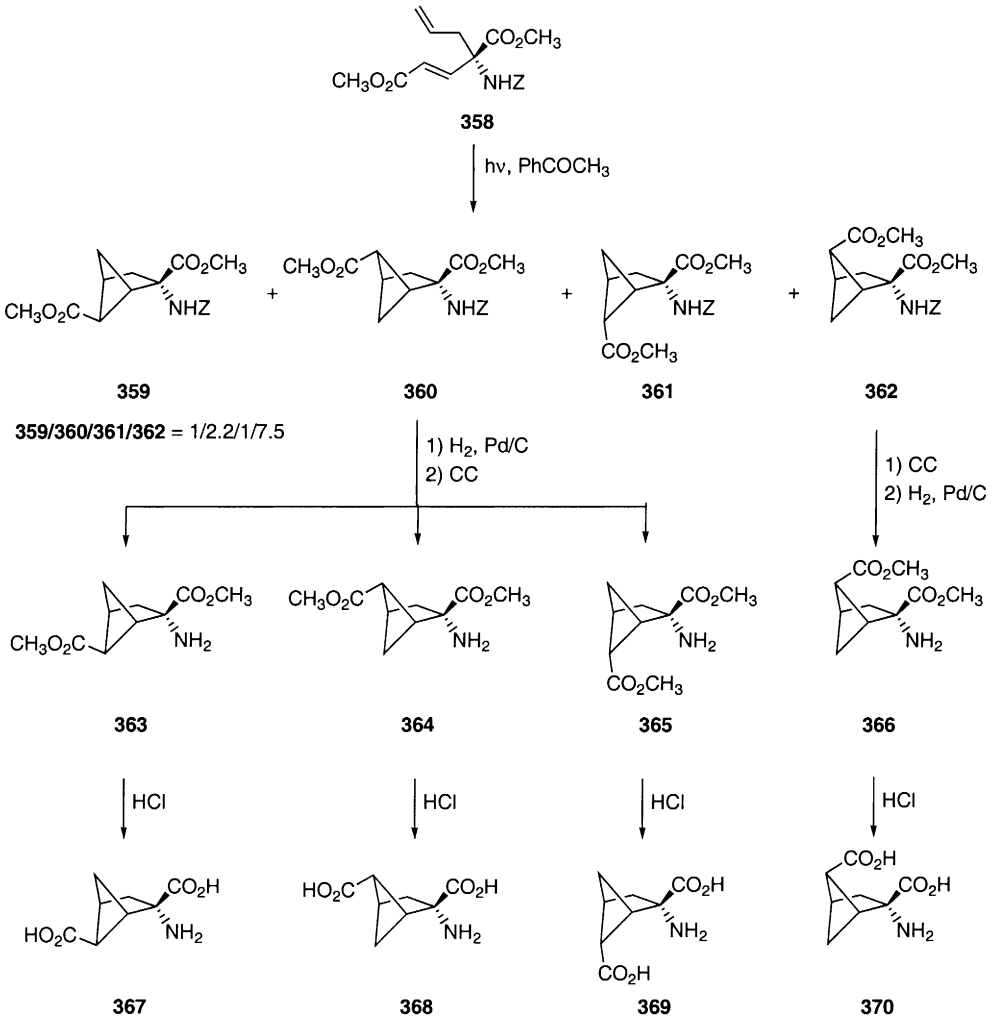
2.3.4. Resolution procedures

Several resolution procedures have been applied to the isolation of 1-aminocyclopentanecarboxylic acids in enantiomerically pure form and this is probably due to the fact that there are only a few procedures that allow the asymmetric synthesis of the corresponding cyclopentane derivatives.

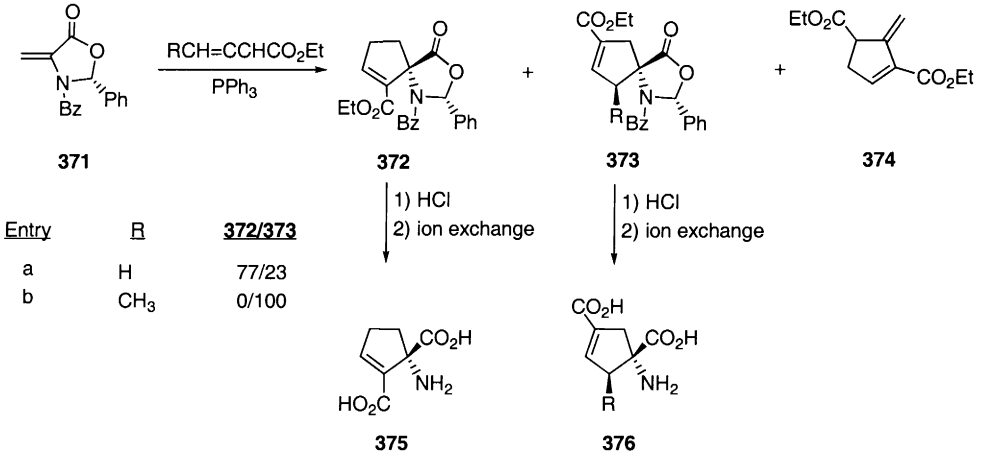
Conformationally constrained ACPD analogues, 3-aminobicyclo[3.3.0]octane-1,3-dicarboxylic acids, have been resolved by fractional crystallisation of the (*S*)-brucine-spirohydantoine diastereomeric salts. Racemic spirohydantoines have been obtained by Bucherer–Bergs reaction on ketone **380**[152] (Scheme 76).

Monn et al. have achieved the synthesis of 2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid, a conformationally constrained analogue of glutamic acid, by resolving racemic hydantoines with (*R*)- or (*S*)-1-phenylethylamine or a chiral resolution agent.[153] To gain access to the heterocyclic analogues, 2-oxa-4-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid and 2-thia-4-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid, (*R*)- or (*S*)-1-phenylethylglycinol have been used as chiral resolving agents.[154] The synthesis of the racemic hydantoines was accomplished through a Bucherer–Bergs reaction on the appropriate cyclopentanone, as shown in Scheme 77.

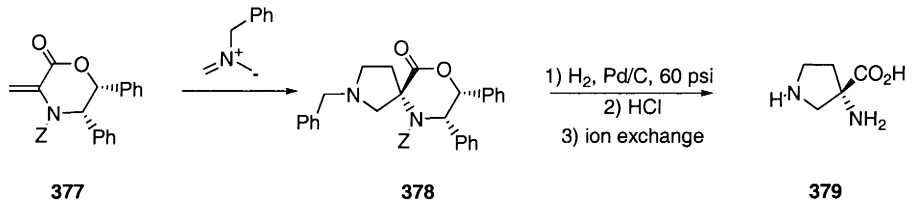
Diastereomeric compounds obtained in the reaction of the racemic amino acid with a chiral compound have been separated in certain cases using chromatographic techniques. For example, *cis* and *trans* 1-aminocyclopentane-1,3-dicarboxylic acids were resolved by simple column chromatography of their diastereomeric α-boroxazolidinone-ɣ-phenylethylamides or ɣ-phenylethanolamides. The amino acid reacts with triethylborane to quantitatively afford the corresponding boroxazolidinone derivative, which is coupled efficiently with (*R*)-phenylglycinol using the reagent Brop. This compound is chromatographed on a silica gel column to afford both isolated diastereoisomers in quantitative yield. The same procedure



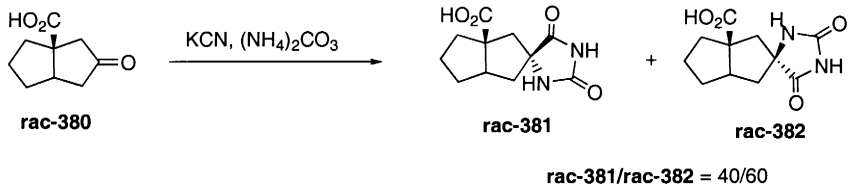
Scheme 73.



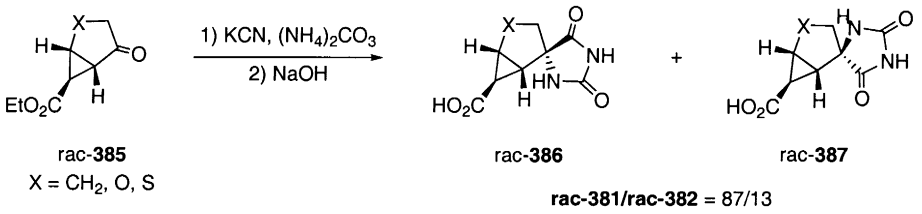
Scheme 74.



Scheme 75.

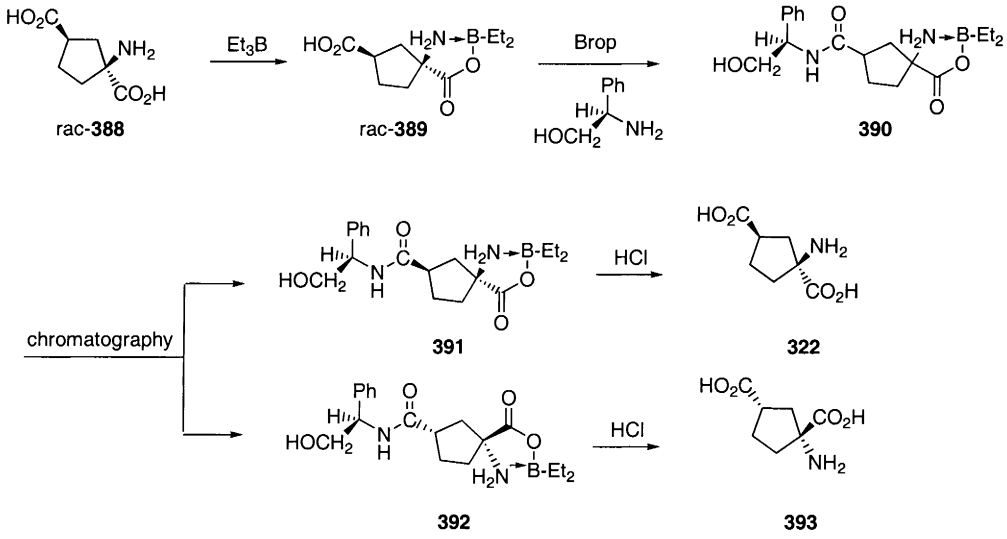


Scheme 76.



Scheme 77.

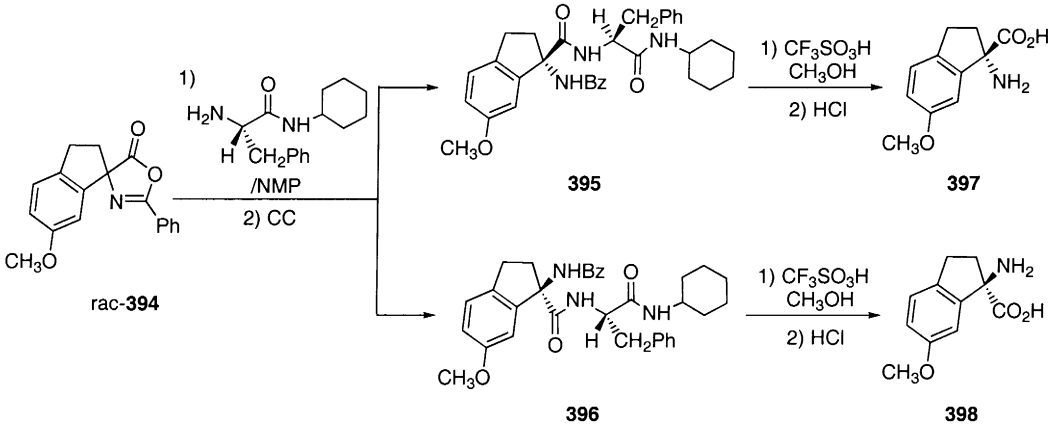
can be applied to the corresponding amides derived from (*R*)-phenylethylamide, but in this case only the *trans* compound can be efficiently resolved. Final hydrolysis to the free amino acids is achieved after treatment with 6N hydrochloric acid[155] (Scheme 78).



Scheme 78.

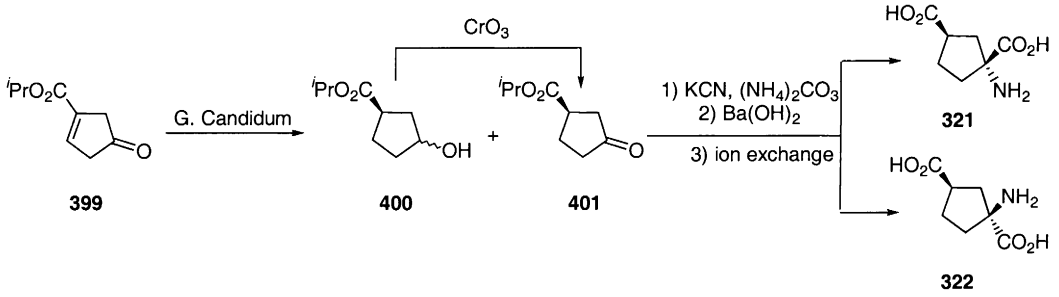
Perhaps the best general procedure for the resolution of quaternary amino acids is the methodology developed by Obrecht et al. This approach involves the coupling reaction between the *N*-acylated α,α-disubstituted amino acids with amides derived from phenylalanine and the separation of the resulting diastereoisomers. This procedure has been successfully applied to the resolution of an α-indane-derived

amino acid.[156] Cyclisation of the *N*-benzoylamino acid by the action of an activating agent, such as *N*,*N*-dicyclohexylcarbodiimide or 1,1′-carbonyldiimidazole, affords the corresponding 2-phenyloxazolone. Treatment of this compound with a chiral cyclohexylamide derived from phenylalanine provides diastereomeric dipeptides that can be easily separated by column chromatography and hydrolysed to the enantiomerically pure amino acids (Scheme 79).



Scheme 79.

Finally, a chemoenzymatic synthesis of *cis* and *trans* 1-aminocyclopentane-1,3-dicarboxylic acids has been described by Azerad et al.[157] In their approach, 3-carboxycyclopentenone isopropyl ester is converted into highly enriched (*S*)-3-carboxycyclopentanone isopropyl ester. Subsequent Bucherer–Bergs reaction using the enantiomerically pure chiral ketone allows the synthesis of (1*S*,3*S*)- and (1*R*,3*S*)-1-aminocyclopentane-1,3-dicarboxylic acid as shown in Scheme 80. Acidic treatment of the amino acids leads to C-3 epimerisation and, in this way, (1*S*,3*R*)- and (1*R*,3*R*)-stereoisomers are also obtained.

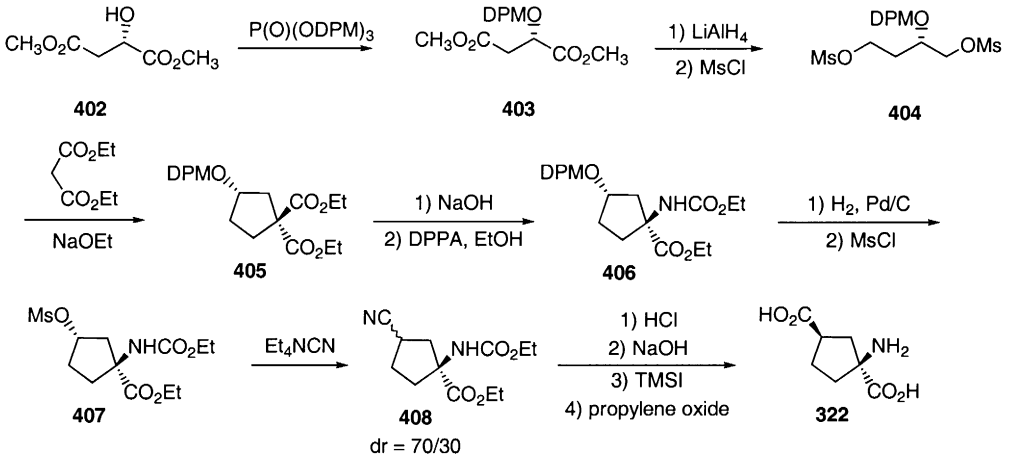


Scheme 80.

2.3.5. Miscellaneous

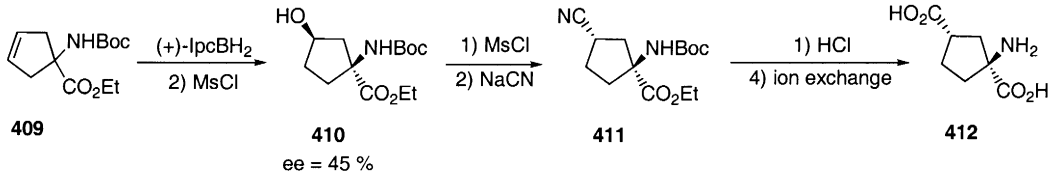
Ma et al.[158] achieved the synthesis of enantiomerically pure (1*S*,3*R*)-1-aminocyclopentane-1,3-dicarboxylic acid using dimethyl (*S*)-malate as the enantiomerically pure starting material by following classical procedures that occur with controlled stereochemistry. Reduction of the diester and subsequent mesylation provides a dielectrophile that reacts with diethyl malonate to give the corresponding cyclisation product. Selective hydrolysis followed by Curtius rearrangement generates the amino acid moiety and then the substituent on C-3 was conveniently elaborated to the desired carboxylic acid group (Scheme 81).

Finally, enantioenriched 1-aminocyclopentane-1,3-dicarboxylic acids have been obtained from ethyl 1-*tert*-butoxycarbonylamino-3-cyclopentencarboxylate by enantioselective hydroboration of the double



Scheme 81.

bond of the ring using (+)-IpcBH$_2$. This reaction occurs with a high stereoselectivity in favour of the *cis* compound **410** and with moderate enantiomeric excess (45%). Subsequent mesylation of the alcohol, reaction with sodium cyanide and hydrolysis provides enantioenriched amino acid of (1*S*,3*S*)-configuration according to Scheme 82.[159] The same sequence of transformations on the minor compound, with inverted configuration at C_3, leads to enantioenriched (1*S*,3*R*)-1-aminocyclopentane-1,3-dicarboxylic acid and by using (−)-IpcBH$_2$ the corresponding enantiomers can be obtained.



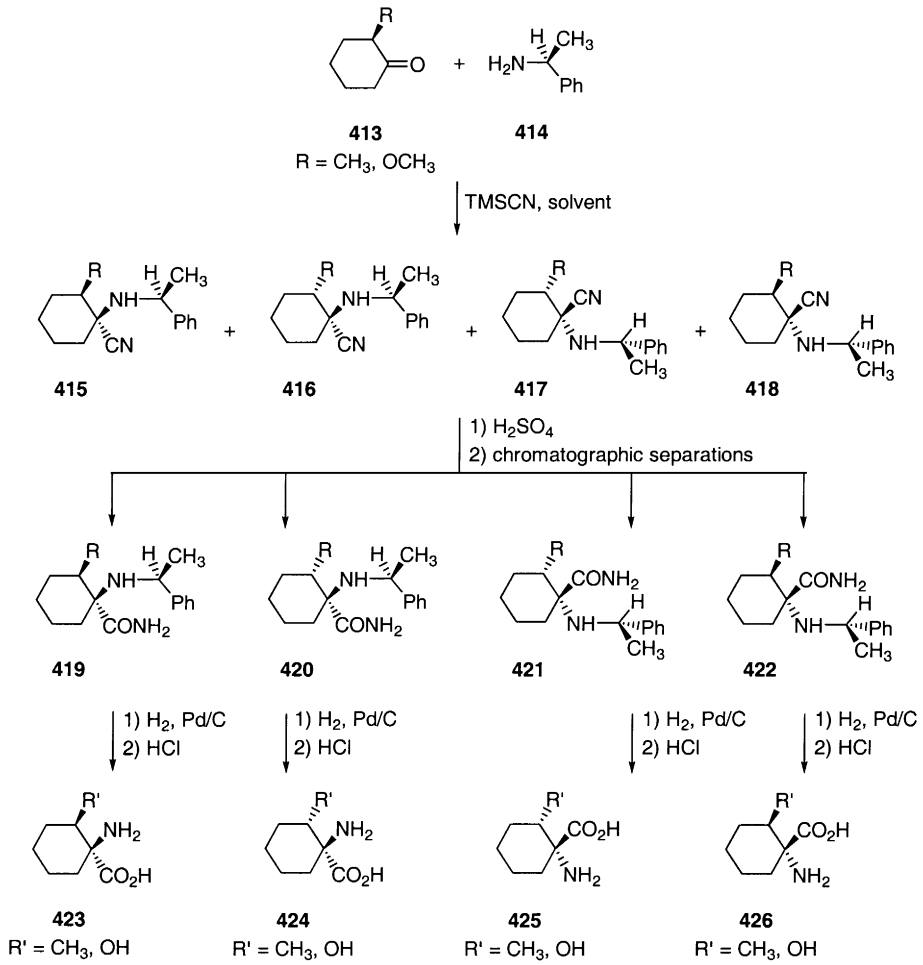
Scheme 82.

2.4. 1-Aminocyclohexanecarboxylic acids

2.4.1. Strecker synthesis

Frahm et al. have recently described the synthesis of some 2-substituted 1-aminocyclohexane carboxylic acids by asymmetric Strecker synthesis using racemic 2-substituted cyclohexanones and (*S*)-α-methylbenzylamine as starting materials.[160,161] Cyanide addition leads to the four possible amino nitriles and it was found that both *trans*/*cis* selectivity and *trans* and *cis* diastereoselectivity were dependent on the solvent. In methanol the amino nitrile formation was under thermodynamic control, leading predominantly to the *trans*-configured products. In hexane, however, nitrile formation was kinetically controlled, with the *cis*-configured compounds being the major products. After careful separation of the α-amino amides obtained by partial hydrolysis of the α-amino nitriles, hydrogenolysis and acidic hydrolysis afforded the corresponding amino acids in enantiomerically pure form (Scheme 83).

An intramolecular Strecker synthesis developed by Ohfune et al. has also been applied to the asymmetric synthesis of 1-aminocyclohexanecarboxylic acids.[137,138] Condensation of (*S*)-*N*-*tert*-butoxycarbonylphenylalanine with racemic *trans*-1,2-cyclohexanediol, followed by Jones oxidation and removal of the Boc group, gives a mixture of imines that, after cyclisation, was submitted to Strecker reaction. Isolation of the diastereomeric compounds obtained and subsequent oxidation and hydrolysis afford the corresponding 1-amino-2-hydroxycyclohexanecarboxylic acids (Scheme 84).



Entry	R	Solvent	416 + 418/415 +417	416/418	415/417
a	CH_3	CH_3OH	76/24	71/29	79/21
b	CH_3	hexane	37/63	84/16	76/24
c	OCH_3	CH_3OH	74/26	73/27	88/12
d	OCH_3	hexane	25/75	85/15	61/39

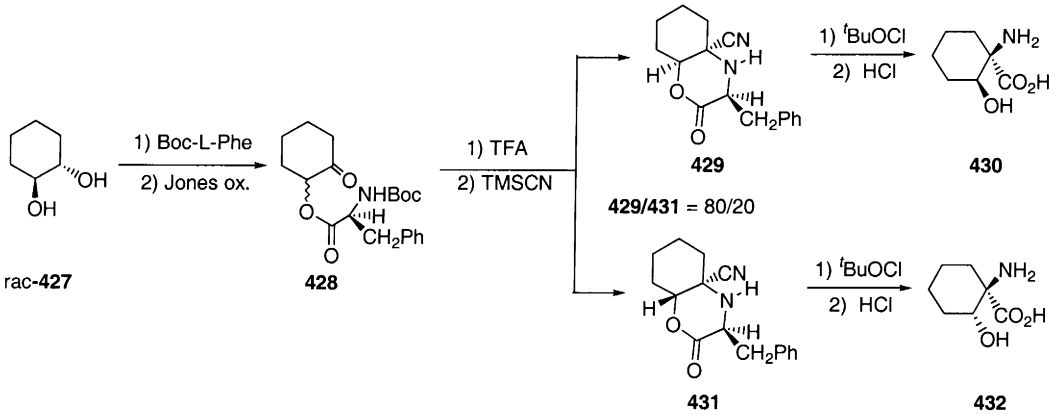
Scheme 83.

2.4.2. Ring closing metathesis and cycloisomerisation

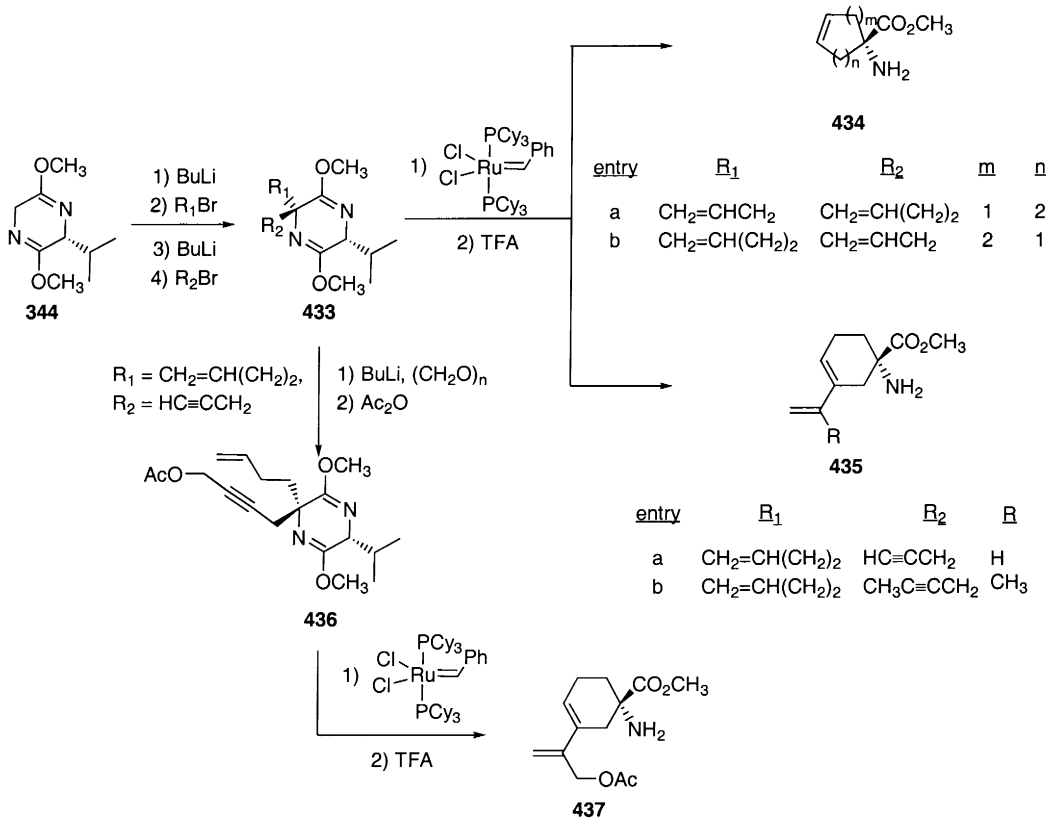
The ring closing metathesis (RCM) synthetic methodology developed by Undheim et al. has been used in the asymmetric synthesis of 1-aminocyclohexanecarboxylic acids. The starting substrates are diastereomerically pure geminal diolefins obtained by bisalkylation of Schöllkopf bis-lactim and the ring closing metathesis reactions are ruthenium-catalysed.

Starting from diastereomerically pure 5-allyl-5-butenyl bis-lactim or 5-propargyl-5-butenyl bis-lactim **433**, a metathesis reaction affords the corresponding six-membered derivative whose absolute configuration depends on the order of introduction of the two different alkenes. Mild hydrolysis releases enantiomerically pure amino acids[140,141] (Scheme 85).

Aldol reaction of 5-butenyl bis-lactim **438** with acrolein yields the corresponding 1,2-addition com-



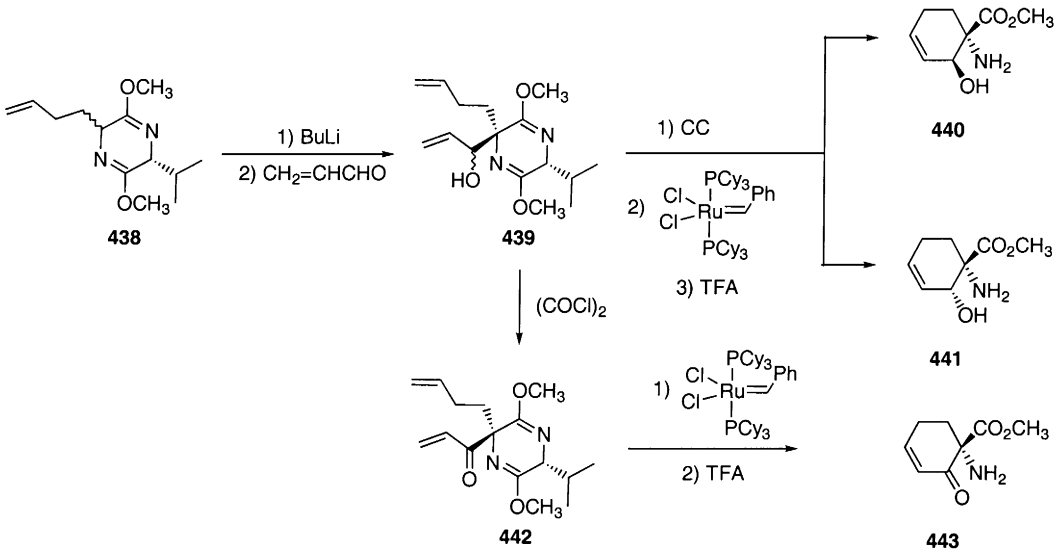
Scheme 84.



Scheme 85.

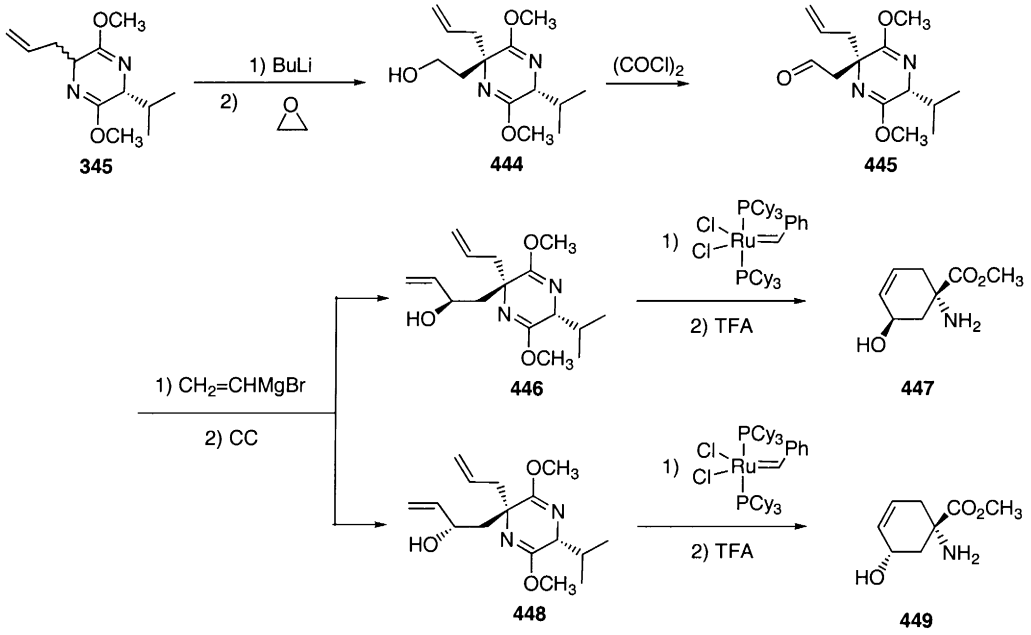
pound of *trans* stereochemistry with low stereoselectivity at the α-hydroxy carbon (de=33%). Once isolated, both compounds are submitted to ring closing metathesis conditions and hydrolytic cleavage of the bis-lactim ether. This procedure yields the corresponding 1-aminocyclohexanecarboxylic acids[142] and Swern oxidation of the allylic alcohol mixture **439**, followed by ruthenium-mediated metathesis and hydrolysis, allows the synthesis of α,β-unsaturated oxo derivatives of cyclic amino acids[162] (Scheme 86).

If ring closing metathesis is performed on hydroxy dienes **446** and **448**, obtained by reaction of



Scheme 86.

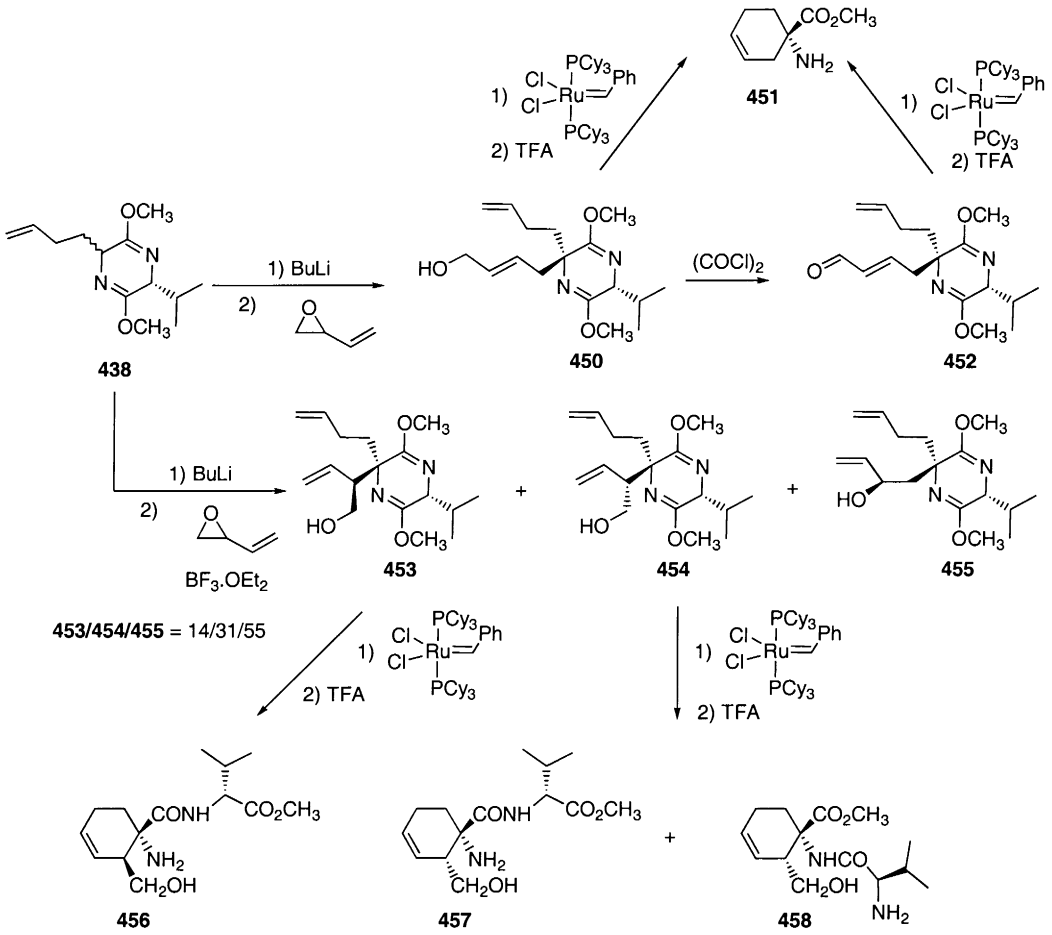
ethylene oxide with bis-lactim **345** followed by oxidation and vinylmagnesium bromide addition, constrained homoserine analogue precursors are obtained[163] (Scheme 87).



Scheme 87.

The use of vinyloxirane as an electrophile in the alkylation of bis-lactim **438** leads to hydroxymethylated dienes. The formation of a 1,4-addition compound or epoxide ring opening products depends on the reaction conditions. Hydroxymethylated dienes have been used as starting materials in the synthesis of 1-amino-3-cyclohexenecarboxylic acid and 1-amino-2-hydroxymethyl-3-cyclohexenecarboxylic acid according to Scheme 88.[164]

Palladium-mediated cycloisomerisation of diastereomerically pure bis-lactims that contain two unsaturated substituents has also been used to obtain 1-aminocyclohexanecarboxylic acids containing a diene



Scheme 88.

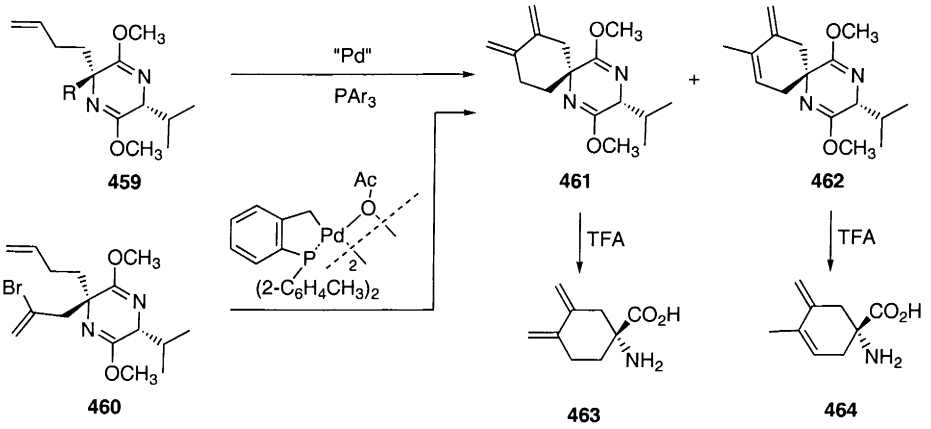
in their structure. The relative amount of *exo* and *endo* Heck products depends on the nature of the two unsaturated substituents on the starting bis-lactim and also on the palladium catalyst used[147] (Scheme 89).

2.4.3. Diels–Alder reactions

The Diels–Alder reaction is one of the most effective methods for obtaining six-membered rings with a high degree of stereochemical control. This reaction can be used in the synthesis of cycloaliphatic amino acids provided that the appropriate reactive dienophile is accessible. For example, α,β-didehydroalaninate derivatives have proved to be good dienophiles in Lewis acid-catalysed Diels–Alder reactions.[165,166]

Chiral *N*-acetyl α,β-didehydroalaninate derivatives react with cyclopentadiene in the presence of different Lewis acid catalysts.[167–169] The rate of the Diels–Alder reaction, the *exo*/*endo* selectivity and both *exo* and *endo* diastereoselectivities depend on the nature of the Lewis acid used as the catalyst, with titanium tetrachloride being the most appropriate homogeneous catalyst. The use of this Lewis acid leads to high chemical yields of adducts even at low temperatures and on using a subestequiometric amount of the catalyst.

exo/*endo* Selectivity depends on the nature of the chiral auxiliary used in the reaction. So, whereas



Entry	R	"Pd"	PAr_3	354/355
a	$HC{\equiv}CCH_2$	$Pd(OAc)_2$	PPh_3	99/1
b	$HC{\equiv}CCH_2$	$Pd_2(dba)_3.CHCl_3$	P(*o*-tolyl)$_3$	99/1
c	$CH_2{=}C(Br)CH_2$	$Pd(OAc)_2$	PPh_3	87/13

Scheme 89.

the (−)-menthyl α,β-didehydroalaninate preferentially gives the stereoisomer with the ester group in the *exo* position, the *N*-acetyl α,β-didehydroalaninate of (−)-*cis*-3-isobornyl neopentyl ether favours the stereoisomer with the ester group situated in the *endo* position. In this way the two auxiliaries behave in a complementary way with respect to the observed stereoselectivity. In both cases the diastereofacial selectivity was excellent, although higher diastereofacial selectivity is observed in the *exo* case (Scheme 90).

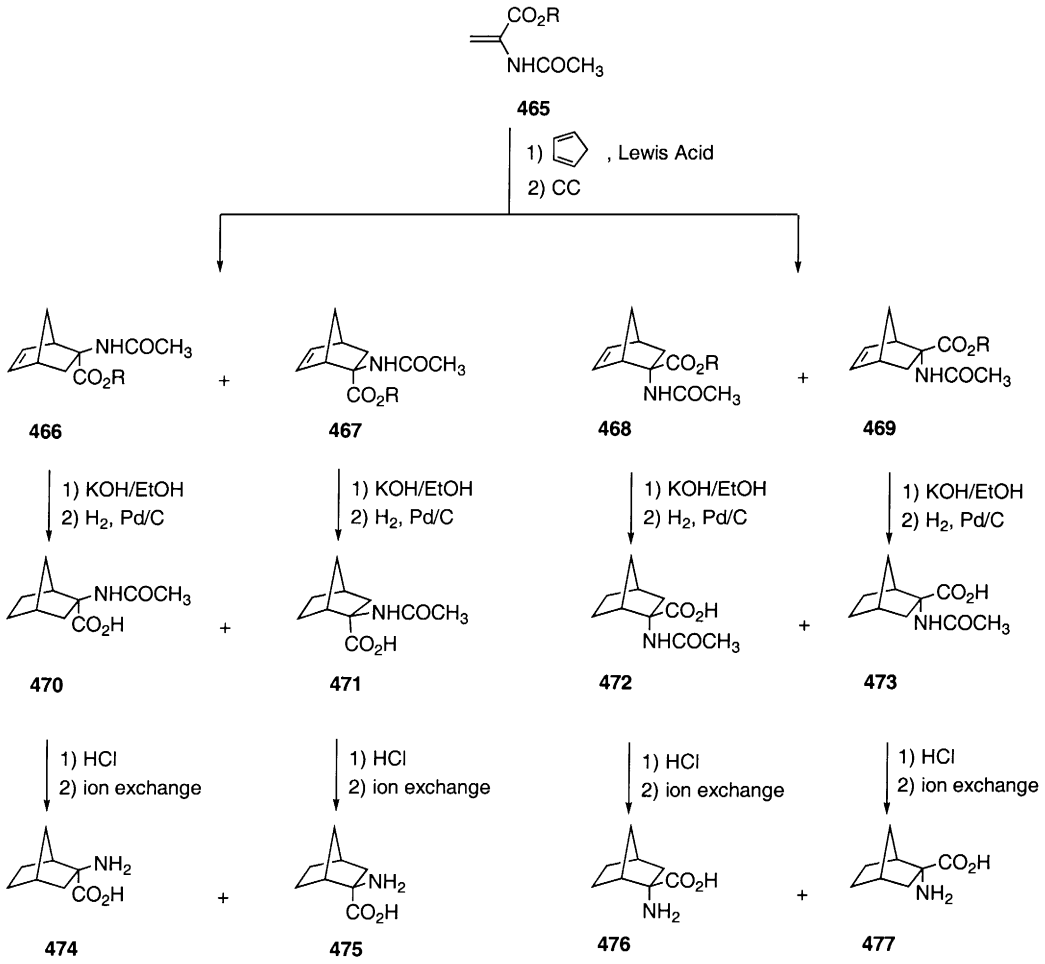
The Diels–Alder reaction between (−)-menthyl α,β-didehydroalaninate and cyclopentadiene has also been carried out using several solids as heterogeneous catalysts, thus demonstrating that such compounds can be used as effective catalysts in this reaction. In the absence of solvent, very high percentages of conversion are observed. The best catalyst is silica gel, and both *exo*/*endo* and diastereofacial selectivities are very similar to those obtained when homogeneous catalysts are used.[170]

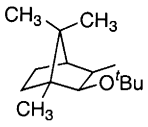
The use of chiral Lewis acids as catalysts has led to excellent results in some enantioselective Diels–Alder reactions. In this context, methyl α,β-didehydroalaninate was reacted with cyclopentadiene in the presence of a number of chiral catalysts in order to obtain 2-aminonorbornane-2-carboxylic acids enantioselectively.[171]

The use of different aluminium chiral catalysts gives good yields, although neither *exo*/*endo* selectivity nor diastereofacial selectivity are observed. When the titanium catalyst derived from chiral diol *trans*-α,α′-(2,2′-dimethyl-1,3-dioxolane-4,5-diyl)bis(diphenylmethanol) was used, moderate *exo*/*endo* ratios and diastereofacial selectivities were obtained (Scheme 91).

Less reactive dienes also react with α,β-didehydroalanine derivatives.[172] Good yields and excellent diastereofacial selectivities were obtained when (−)-8-phenylmenthol was used as a chiral auxiliary in the Diels–Alder reaction between the corresponding α,β-didehydroalaninate and 1,3-butadiene and, indeed, only one stereoisomer was obtained in its enantiomerically pure form. Reaction of the Diels–Alder adduct with *N*-iodosuccinimide leads to the direct hydroxylation of the alkene moiety through a dihydro-1,3-oxazine intermediate, a process that allows entry to the synthesis of a new type of constrained homoserine (Scheme 92).

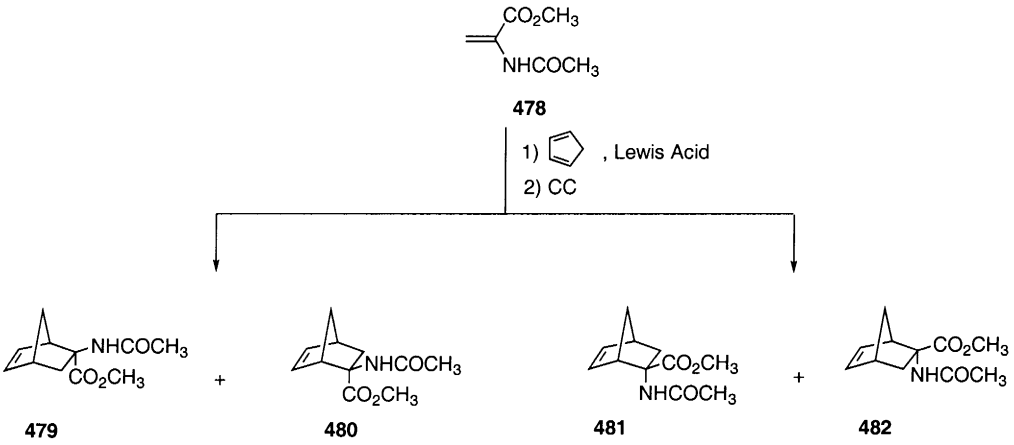
Chiral (*R*)- and (*S*)-4-methyleneoxazolidin-5-ones, which are cyclic α,β-didehydroalanine derivatives,

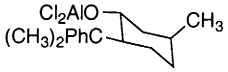
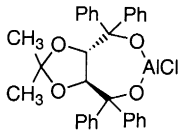
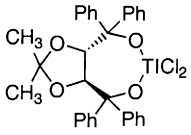


Entry	R	Lewis Acid/eq	T	466 + 467 /468 + 469	466/467	468/469
a		$TiCl_4$/1.1	25 º	31/69	77/23	95/5
b		$TiCl_4$/0.75	25 º	19/81	86/14	97/3
c		$TiCl_4$/1.1	0 º	21/79	86/14	92/8
d		$TiCl_4$/0.75	0 º	19/81	89/11	90/10
e		$TiCl_4$/1.1	- 20 º	22/78	86/14	92/8
f		$TiCl_4$/0.75	- 20 º	19/81	87/13	91/9
g		$TiCl_4$/0.75	25 º	55/45	>99/1	>99/1
h		$TiCl_4$/1.1	0 º	62/38	>99/1	>99/1
i		$TiCl_4$/0.5	0 º	62/38	>99/1	>99/1

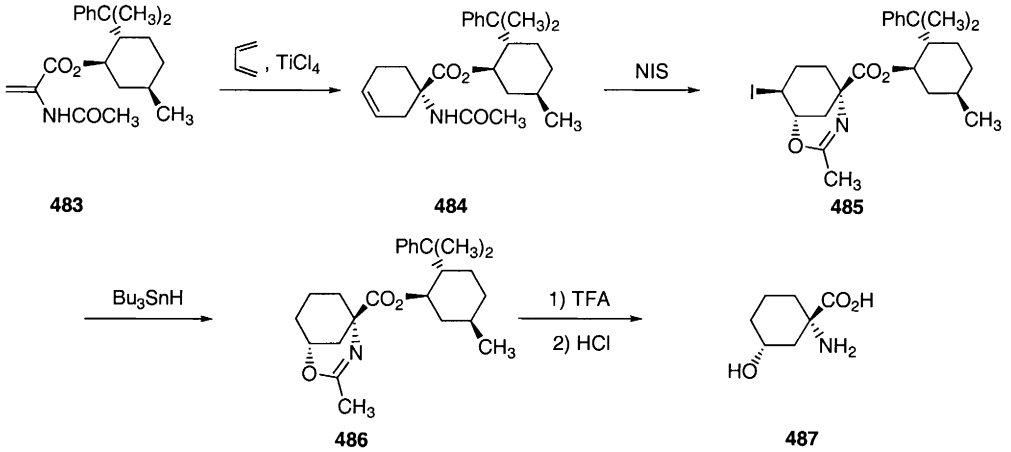
Scheme 90.

behave as excellent dienophiles in the Diels–Alder reaction with numerous dienes and allow the synthesis of 1-aminocyclohexanecarboxylic acids in good yields. The thermally induced reaction of these substrates with cyclopentadiene and cyclohexadiene occurs with high *exo* diastereoselectivity and very good diastereofacial selectivity, giving rise to the corresponding Diels–Alder cycloadducts from which bicyclic amino acids are obtained.[173–175] In some cases the initially formed adducts undergo



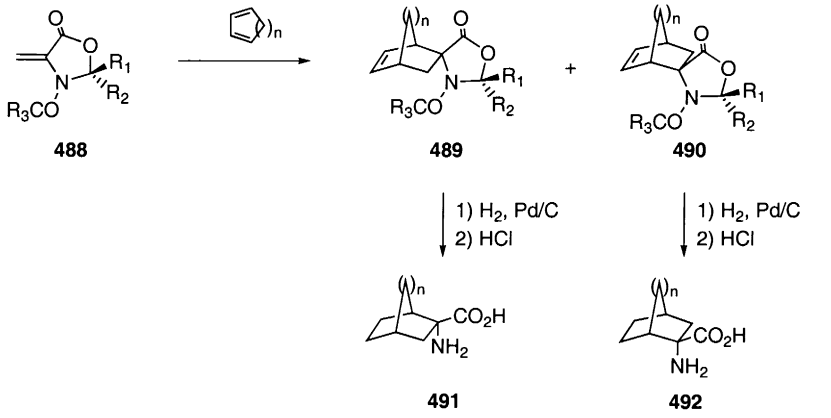
Entry	Lewis acid	479 + 480 /481 + 482	479/480	481/482
a		46/54	50/50	50/50
b		47/53	50/50	45/55
c		52/48	50/50	47/53
d		23/77	15/85	15/85

Scheme 91.



Scheme 92.

epimerisation at the amino-acetal carbon, although the stereochemical integrity of the quaternary amino acid stereogenic centre is maintained (Scheme 93).



Entry	R_1	R_2	R_3	n	490/491
a	^{t}Bu	H	Ph	1	97/3
b	^{t}Bu	H	Ph	2	97/3
c	H	Ph	Ph	1	3/97
d	H	Ph	Ph	2	3/97*
e	H	Ph	CH_3	1	7/93

* epimers at C_2

Scheme 93.

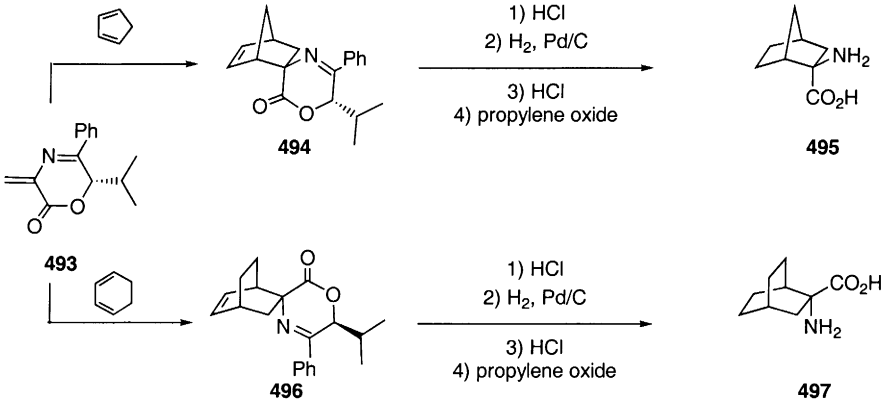
Thermally induced Diels–Alder reactions of 4-methyleneoxazolidin-5-ones with substituted 1,3-cyclohexadienes and substituted 1,3-butadienes give *exo* diastereomeric adducts. Epimerisation at the amino-acetal carbon is also observed in some cases. As far as we know, these Diels–Alder adducts have not been converted into the corresponding bicyclic or cyclic amino acids.[176]

The chiral α,β-didehydroalanine derivative (6*S*)-6-isopropyl-3-methylene-5-phenyl-3,6-dihydro-2*H*-4-oxazin-2-one acts as a reactive dienophile in thermally induced Diels–Alder reactions with cyclopentadiene and cyclohexadiene.[177] In the reaction with cyclopentadiene the *endo*-cycloadduct **494** is obtained preferentially, whereas upon reaction with cyclohexadiene the *exo*-adduct **496** is the major compound. The corresponding bicyclic amino acids are obtained from diastereomerically pure Diels–Alder adducts according to Scheme 94.

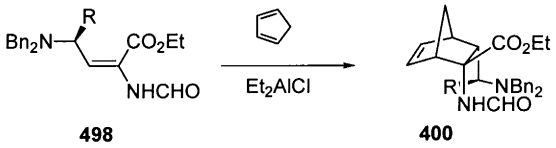
The extension of this methodology to more hindered didehydroamino acid derivatives, in order to obtain a general procedure for the synthesis of constrained amino acids derived from natural or non-natural amino acids in a six-membered ring, has been extremely difficult due to the low reactivity of substituted didehydroamino acid derivatives.

The first example of this approach to appear in the literature involves the Diels–Alder reaction between chiral ethyl esters derived from γ-*N*,*N*-dibenzylamino α,β-didehydroamino acid and cyclopentadiene in the presence of diethylaluminium chloride as a catalyst.[178] Cycloaddition occurs with complete *endo*-selectivity, with respect to the formylamino group, and very high diastereofacial selectivity (Scheme 95). Further elaboration of the resulting Diels–Alder adducts to give free amino acids was not described.

Chiral α,β-didehydroamino acid derivative **500**, which is easily obtained from D-mannitol, does not react with dienes under thermal activation even in the presence of Lewis acid catalysts. Nevertheless, under a pressure of 14 kbar this compound reacts with 1-trimethylsilyloxy-1,3-butadiene to give a mixture



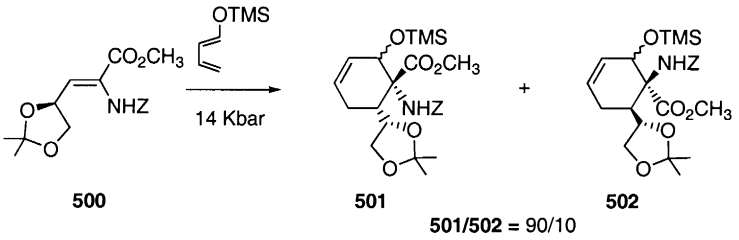
Scheme 94.



Entry	R	de %
a	CH_3	96
b	$PhCH_2$	82
c	^{i}Bu	86
d	$TBDMSOCH_2$	78

Scheme 95.

of products that can be isolated by chromatography. The resulting cycloadducts are precursors of amino acids, although such transformations to the corresponding amino acids are not described[179] (Scheme 96).



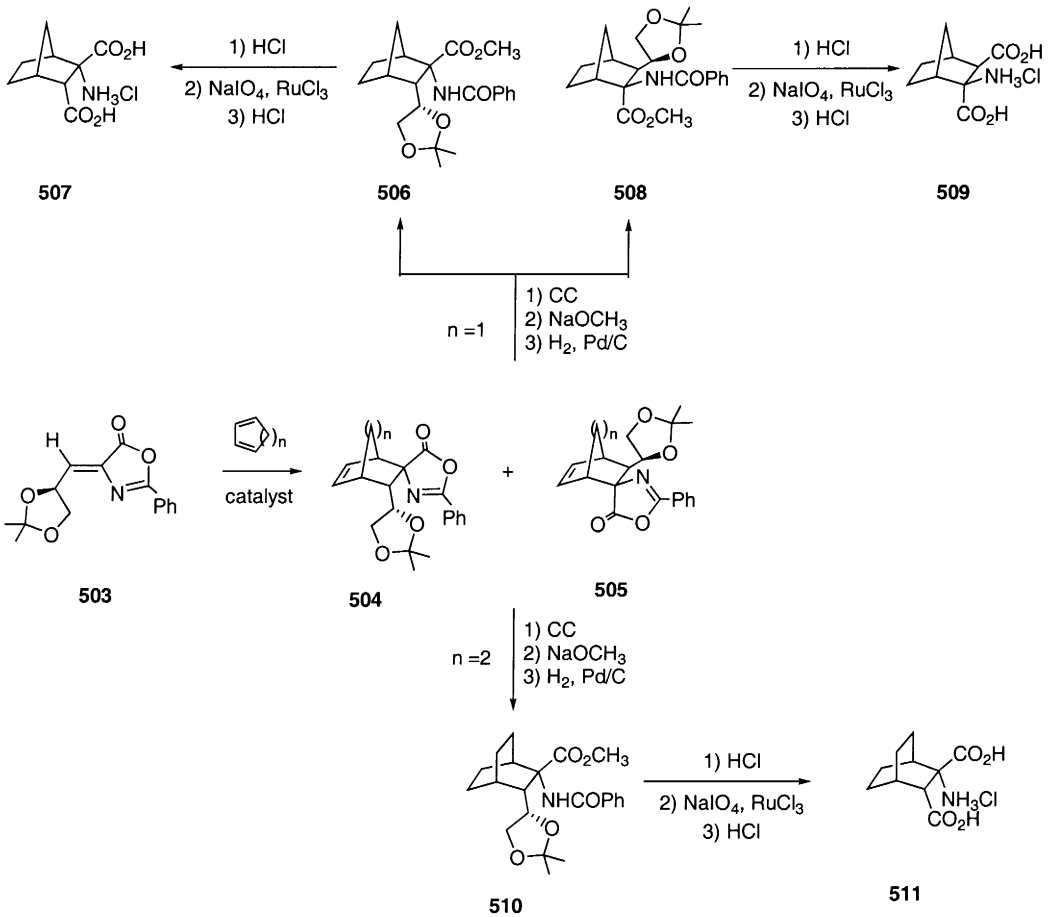
Scheme 96.

2-Oxazolin-5-ones are among the most important precursors of α-amino acids and have proved to be very useful in the synthesis of cyclic compounds. In this field our group has reported the excellent behaviour of achiral (*Z*)-2-phenyl-4-benzylidene-5(4*H*)-oxazolone as a dienophile in a reaction that has allowed the synthesis of several 1-aminocyclohexanecarboxylic acids as racemic compounds.[180–184]

Recently, our group has developed a very interesting asymmetric version of this approach using (*Z*)-2-phenyl-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-ylmethylen]-5(4*H*)-oxazolone as a chiral dienophile.

Thermal reaction of chiral oxazolone **503** with the cyclic dienes cyclopentadiene and cyclohexadiene affords a mixture of the four possible Diels–Alder adducts.[185–187] The reaction with cyclopentadiene shows *exo*-selectivity, whereas upon reaction with cyclohexadiene the *endo*-adduct **505** is obtained preferentially. In both cases the *endo* and *exo* diastereofacial selectivities are very high. At room

temperature the *exo*/*endo* selectivity and diastereofacial selectivities are not influenced by the solvent polarity. When the reaction is performed at low temperature better selectivities are observed. The use of Lewis acids as catalysts increases the reaction rate of slow reactions, although the formation of cycloadducts from *E*-oxazolone is observed in some cases. In order to minimise the formation of these compounds lithium perchlorate has to be used as a catalyst. Isolated major cycloadducts have been transformed into a new class of conformationally constrained (*S*)-aspartic acid analogues[188,189] (Scheme 97).



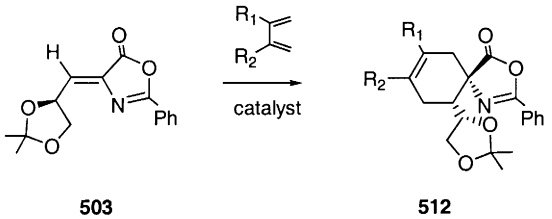
Entry	n	catalyst	**504/505**	rd *exo*	rd *endo*
a	1	none	64/36	90/10	96/4
b	1	none	71/29	98/2	>98/2
c*	1	$LiClO_4$	56/44	80/20	78/22
d	2	none	32/68	98/2	98/2
e	2	$LiClO_4$	30/70	75/25	69/31

* - 40 ºC

Scheme 97.

Open chain dienes such as 2,3-dimethylbutadiene, 2-methyl-1,3-butadiene and butadiene also react with chiral oxazolone **503** to afford the corresponding Diels–Alder adducts. Good conversions and diastereofacial selectivities are obtained with the use of lithium perchlorate.[187] On reaction with 2-

methyl-1,3-butadiene a high *para* regioselectivity is observed in addition to a good diastereofacial selectivity (Scheme 98).



503 **512**

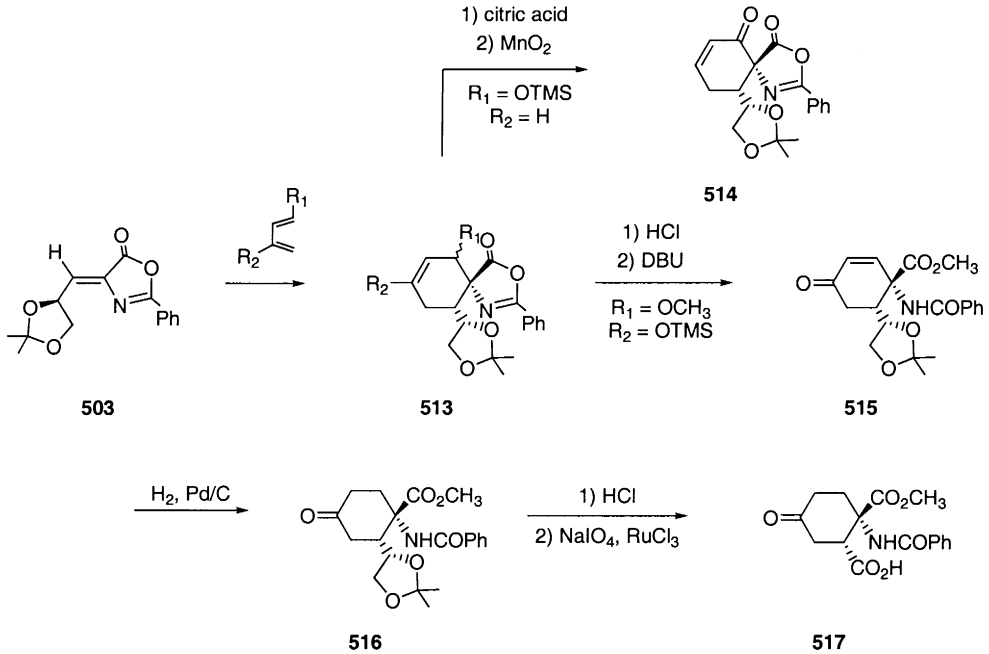
Entry	R_1	R_2	catalyst	rd
a	CH_3	CH_3	none	92/8
b	CH_3	CH_3	$LiClO_4$	85/15
c	H	H	$LiClO_4$	81/19
d*	H	CH_3	$LiClO_4$	82/18

* *para* regioselectivity = 91/9

Scheme 98.

E-Oxazolone has also been used as the dienophile in Diels–Alder reactions and, in this case, the use of heterogeneous catalysts is advisable in order to avoid *E–Z* isomerisation of the reactant.[190]

1-Trimethylsilyloxy-1,3-butadiene and Danishesfky's diene undergo a highly diastereoselective Diels–Alder reaction with chiral oxazolone **503**.[179,191,192] Danishesfky's diene cycloadduct has been converted into a 1-amino-4-oxo-1,3-cyclohexanedicarboxylic acid derivative (Scheme 99).

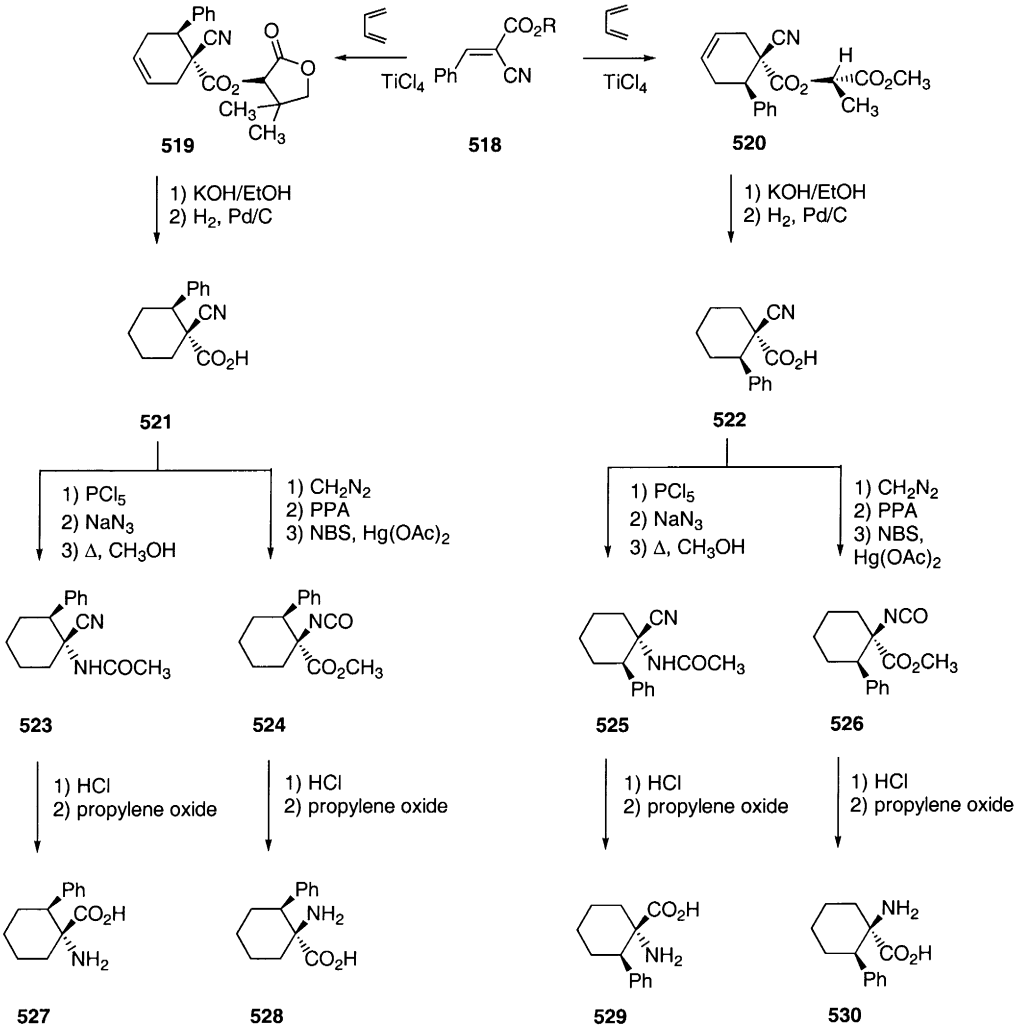


503 **513** **514** **515** **516** **517**

Scheme 99.

The use of (*E*)-2-cyanocinnamates as dienophiles constitutes a very interesting alternative for the synthesis of conformationally constrained phenylalanine analogues. This substrate behaves as an ex-

cellent dienophile in the presence of $TiCl_4$ and both the cyano and the ester groups can be conveniently elaborated to provide the amino acid moiety. When butadiene was used as the diene, the use of two complementary auxiliaries, (*S*)-ethyl lactate or (*R*)-pantolactone, and the possibility of using alternative and complementary degradation sequences allows the synthesis of the four 1-amino-2-phenylcyclohexanecarboxylic acids. These acids are obtained in enantiomerically pure form following a protocol with stereocontrolled and stereodivergent transformations[193] (Scheme 100).

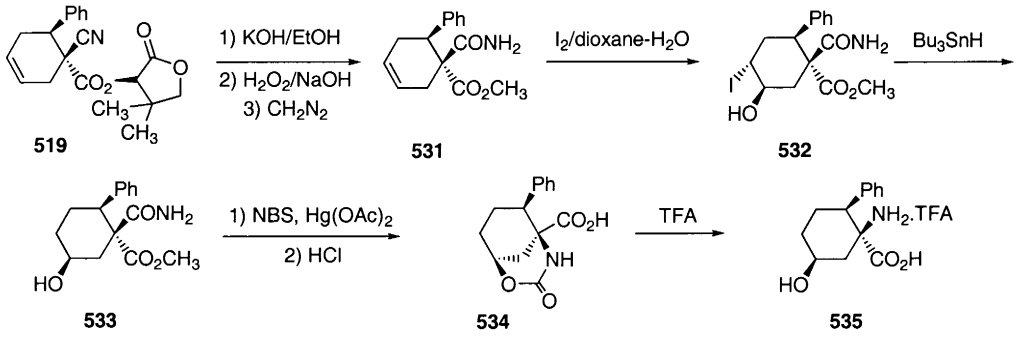


Scheme 100.

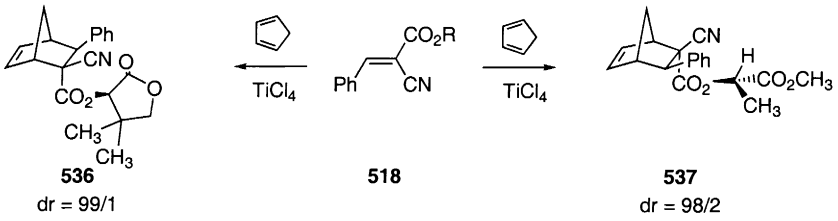
Butadiene Diels–Alder adducts have been conveniently elaborated to new enantiomerically pure constrained α-amino-γ-hydroxy acids. The key step of the synthesis is the regioselective hydroxylation of the alkene moiety by treatment of an amido ester intermediate with iodine, followed by deiodination of the resulting iodohydrins, as shown in Scheme 101 for compound **519**.[194]

The same dienophile has also been reacted with cyclopentadiene using homogeneous[195] and heterogeneous catalysts,[196] although in this case the cycloadducts were not transformed into the corresponding cycloaliphatic amino acids (Scheme 102).

Finally, Diels–Alder reaction of dehydro compounds **538** has recently been described.[197] Among the



Scheme 101.



Scheme 102.

Lewis acids tested boron trifluoride produced the best results. On using this catalyst *Z–E* isomerisation of the starting compounds was not observed and the corresponding Diels–Alder cycloadducts derived from cycloaddition with 2,3-dimethylbutadiene, isoprene and cyclopentadiene were obtained with total stereoselectivity. Cleavage of the ester function, followed by hydrolysis of the imine moiety, leads to the corresponding unsaturated amino acids. Catalytic hydrogenation of Diels–Alder cyloadducts yielded saturated cycloadducts. When starting from compound **539** an equimolecular mixture of isomers, which were easily separated by column chromatography, was obtained. Final hydrolysis of saturated compounds led to amino acids **541**, **542** and **546** (Scheme 103).

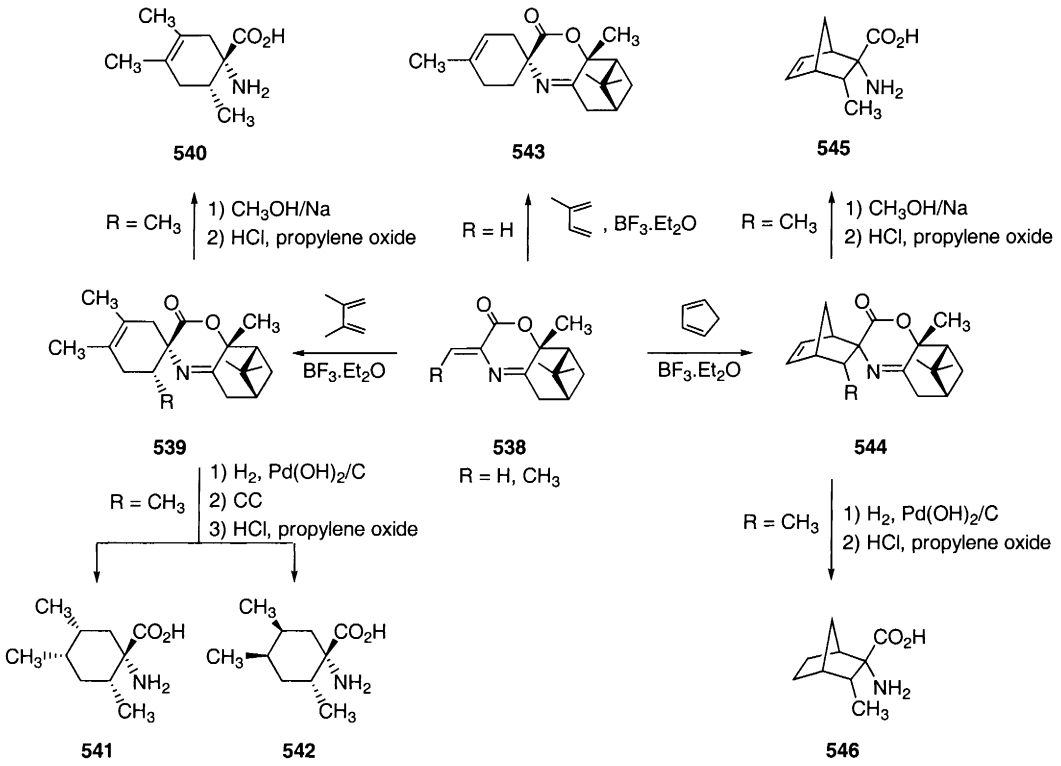
2.4.4. Resolution procedures

Certain 1-aminocyclohexanecarboxylic acids have been resolved using chromatographic techniques after their transformation into diastereomeric mixtures by coupling the racemic amino acid with a chiral compound.

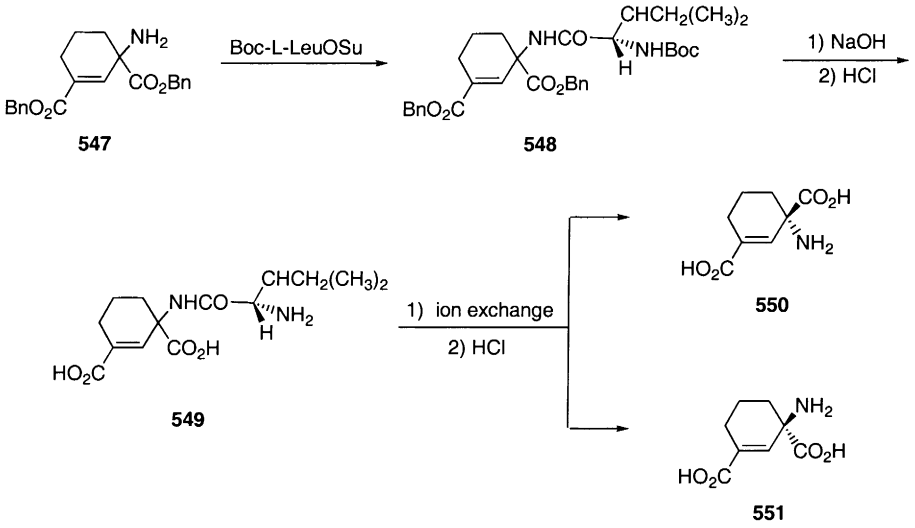
To this end 1-amino-2-cyclohexene-1,3-dicarboxylic acid (DHCGA), an unsaturated cyclic analogue of glutamic acid, was coupled with L-leucine and the diastereomeric mixture of dipeptides resolved by anion exchange chromatography. The racemic material was prepared from 3-carboxy-4-cyclohexenone by a Bucherer–Bergs reaction[198] (Scheme 104).

The diastereomeric α-boroxazolidinone-γ-phenylethylamides derived from *cis*- and *trans*-1-aminocyclohexane-1,3-dicarboxylic acid and the γ-phenylethanolamide derived from the *trans* amino acid were not sufficiently separated to obtain a quantitative resolution. However, *cis*-1-aminocyclohexane-1,3-dicarboxylic acid was successfully separated after its reaction with triethylborane followed by coupling with (*R*)-phenylglycinol according to the Azerad methodology described above[155] (Scheme 105).

Diastereomeric dipeptides obtained by coupling of α- and β-tetralin-derived *N*-benzoylamino acids and the cyclohexylamide derived from phenylalanine, through a 2-phenyl-5-oxazolone intermediate, have been successfully resolved by application of the methodology developed by Obrecht et al.[156,199] according to Scheme 106.

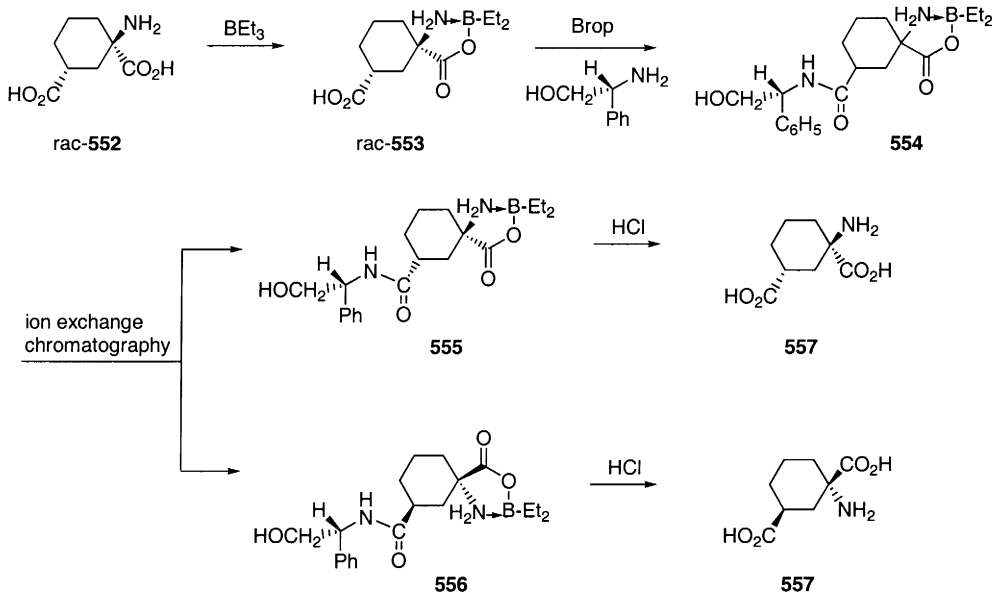


Scheme 103.

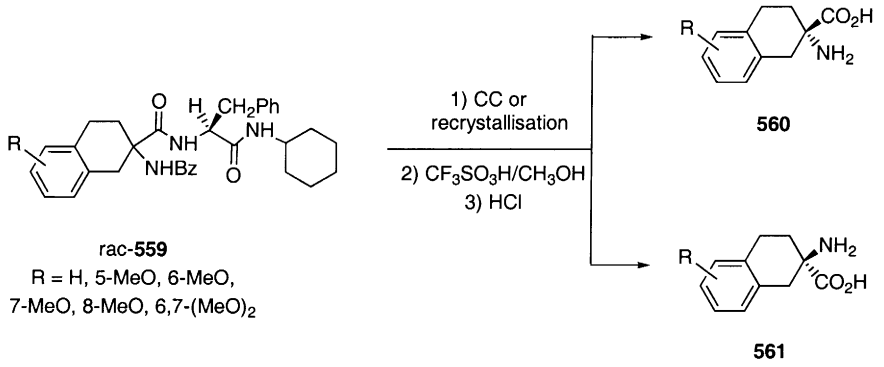


Scheme 104.

Azerad et al.[157] have described a chemoenzymatic synthesis of *cis*- and *trans*-1-aminocyclohexane-1,3-dicarboxylic acids based on the stereospecific microbial reduction of racemic ketoesters. Oxidation of the isolated hydroxy acids, followed by Bucherer–Bergs reaction using the enantiomerically pure chiral ketones, allows the synthesis of the amino acids in enantiomerically pure form. Starting from 3-carboxycyclohexanone the (1*R*,3*R*) diastereoisomer can be obtained in high yields. 3-Carboxy-2-



Scheme 105.



Scheme 106.

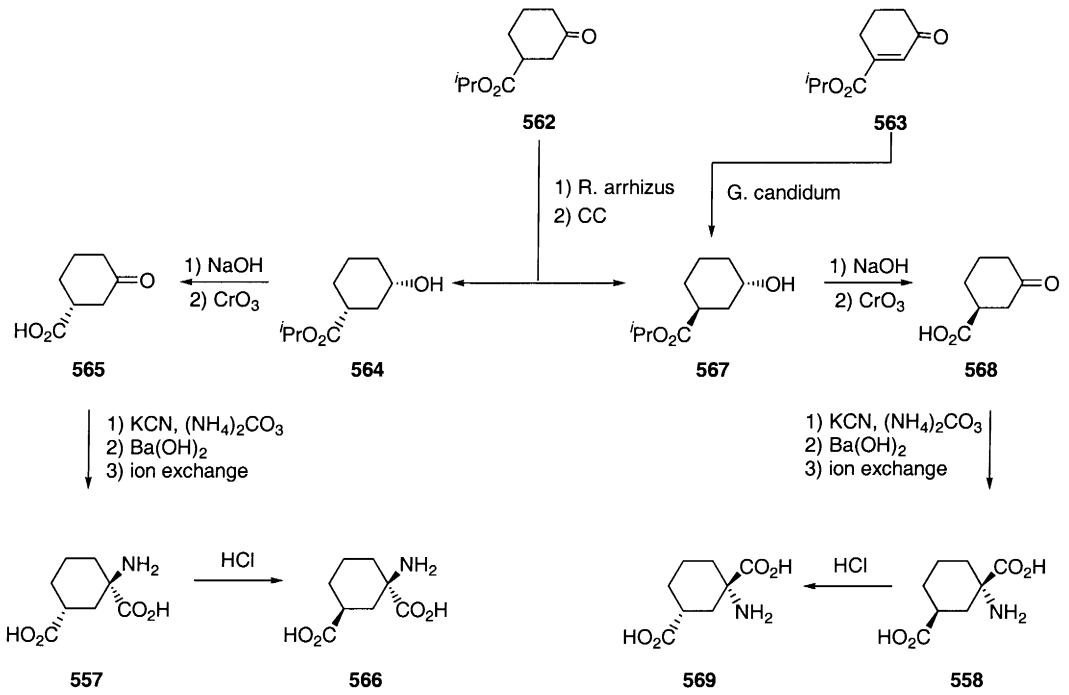
cyclohexenone is a more suitable precursor for the synthesis of the (1*S*,3*S*) diastereoisomer. Epimerisation at C_3 by heating in an acidic medium for several days allows the synthesis of the (1*R*,3*S*) and (1*R*,3*S*) diastereoisomers (Scheme 107).

2.5. 1-Aminocycloheptanecarboxylic acids

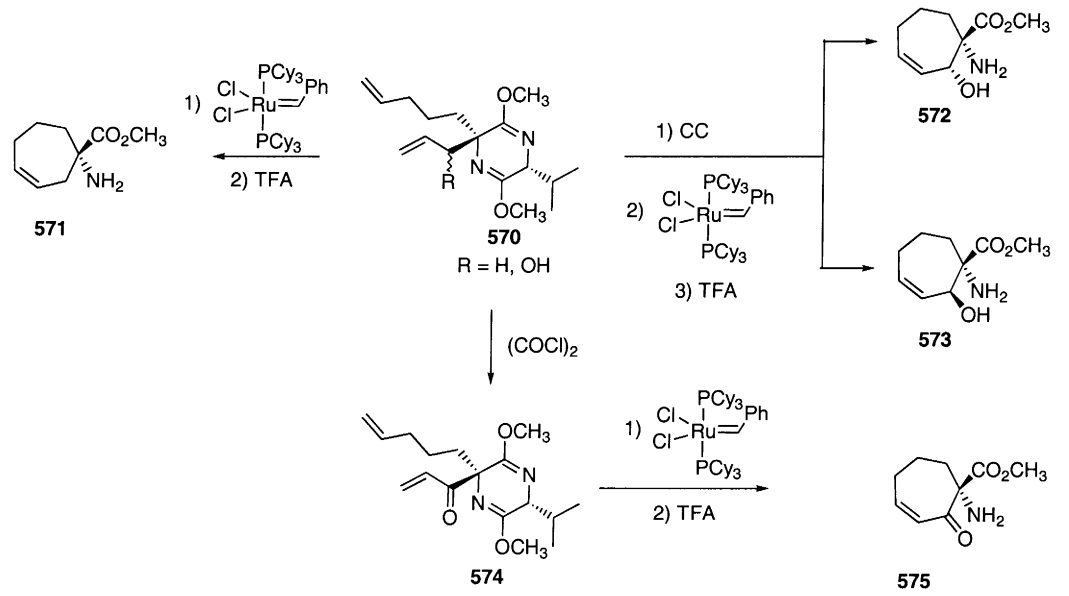
2.5.1. Ring closing metathesis

Cyclic α-amino acids and 1-amino-2-hydroxy acids in which the α-carbon of the amino acid is incorporated into a seven-membered ring have been synthesised by ring closing metathesis according to the Undheim methodology starting from the bis-lactim with the appropriate alkenyl substituents at C_5[140,142,162] (Scheme 108).

The alkylation of bis-lactim **576** with ethylene oxide affords an ethanol derivative, which upon oxidation and vinylmagnesium bromide addition leads to a pair of epimeric alcohols that are readily separable by chromatography. In this case no reaction took place under ring closing metathesis conditions unless the hydroxyl groups in these substrates were protected as the acetates. In the subsequent ring



Scheme 107.

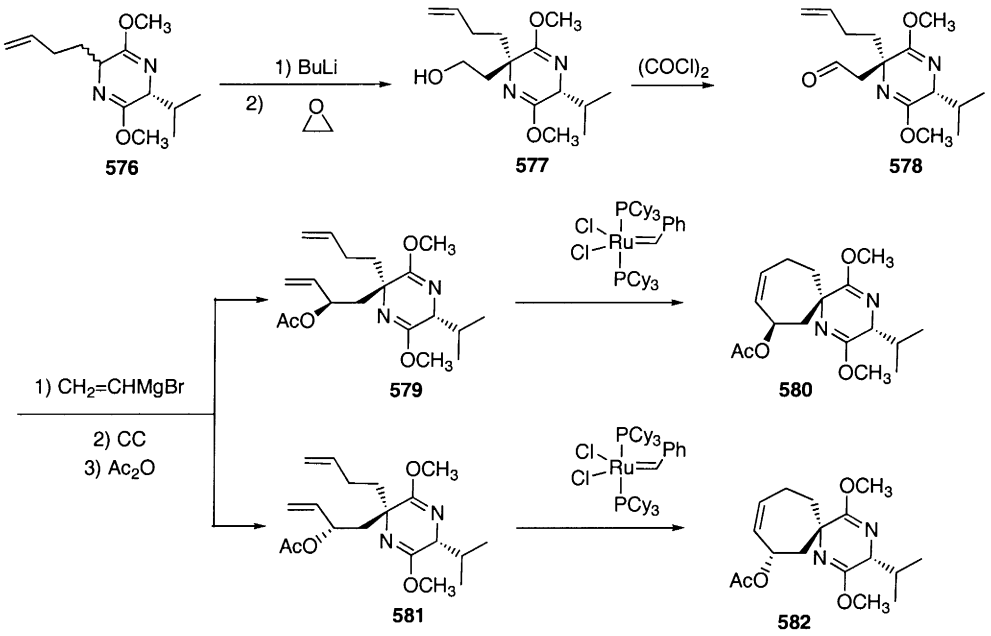


Scheme 108.

closing metathesis, exceptionally high yields of seven-membered compounds were obtained[163] (Scheme 109).

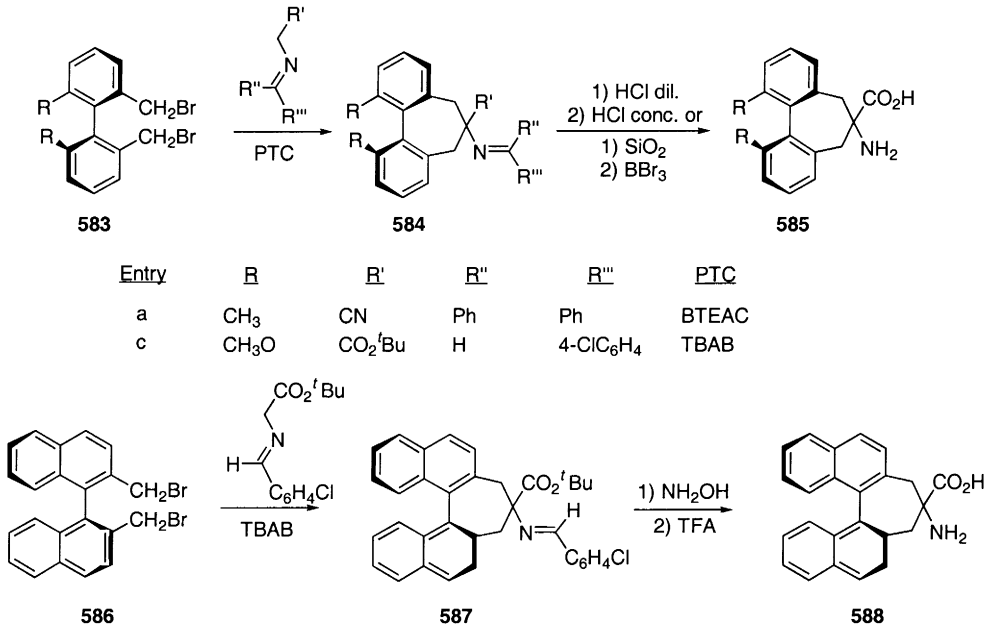
2.5.2. *Miscellaneous*

There are a number of examples in the literature dealing with the synthesis of seven-membered cyclic amino acids with axial dissymmetry. In this context Závada et al.[200] have described the synthesis of



Scheme 109.

6-amino-1,11-dimethyl-6,7-dihydro-5*H*-dibenzo[a,c]cycloheptene-6-carboxylic acid, the first chiral α-amino acid without an asymmetric carbon atom. This compound was synthesised in enantiomerically pure form by using the corresponding dibromide as the chiral starting material under phase transfer catalysis and with ethyl acetoacetate or diphenylmethyleneglycinate as the nucleophile. The same methodology has been used to prepare new derivatives[201,202] following the general reaction pathway outlined in Scheme 110.



Scheme 110.

3. 1-Azacycloalkane-2-carboxylic acids

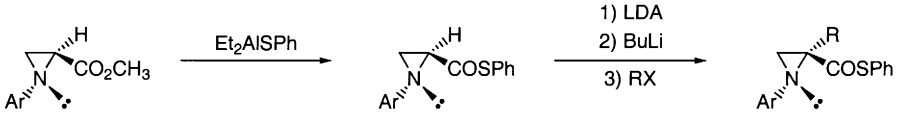
In this part of the review we would like to include all cyclic systems related to proline that involve a variation in the size of the ring. This discussion clearly includes systems that contain an additional substituent at the α-carbon of the amino acid moiety.

3.1. Aziridine-2-carboxylic acids

N-Activated aziridine-2-carboxylic acids are playing increasingly important roles in strategies for the asymmetric synthesis of proteinogenic and non-proteinogenic α-amino acids because they undergo highly regio- and stereocontrolled ring opening with nucleophiles. Indeed the asymmetric synthesis of aziridines has recently been reviewed.[203] However, in spite of the interest in these systems, only a few methods exist for the asymmetric synthesis of 2-substituted aziridine-2-carboxylic acids, which would be excellent intermediates for the synthesis of quaternary α-amino acids.

3.1.1. Self-reproduction of chirality

N-Benzyl- and *N*-(phenylethyl)aziridine-2-carboxylic acids are alkylated by direct enolisation of the 1-benzylphenylthio ester and reaction with electrophiles. In this case the nitrogen in the three-membered ring acts as a stereogenic centre and this is configurationally stable at low temperature[204] (Scheme 111). Whereas the reaction of (1*S*,2*S*)-aziridines takes place with total retention to afford a single diastereoisomer of the alkylated compound, alkylation of (1*R*,2*R*)-aziridines is much less selective and mixtures of diastereoisomers are obtained.



589 **590** **591**

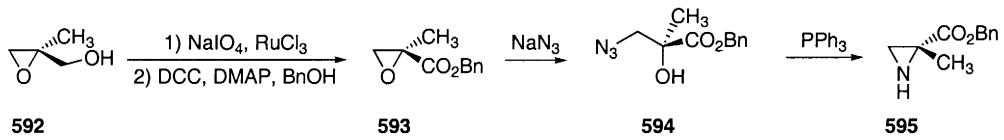
Entry	Ar	RX
a	CH_2Ph	CH_3I
b	*(S)*-$CH(CH_3)Ph$	CH_3I
c	*(S)*-$CH(CH_3)Ph$	CH_3CH_2I
d	*(S)*-$CH(CH_3)Ph$	$CH_2{=}CHCH_2Br$
e	*(S)*-$CH(CH_3)Ph$	$PhCH_2Br$

Scheme 111.

3.1.2. Synthesis from epoxides

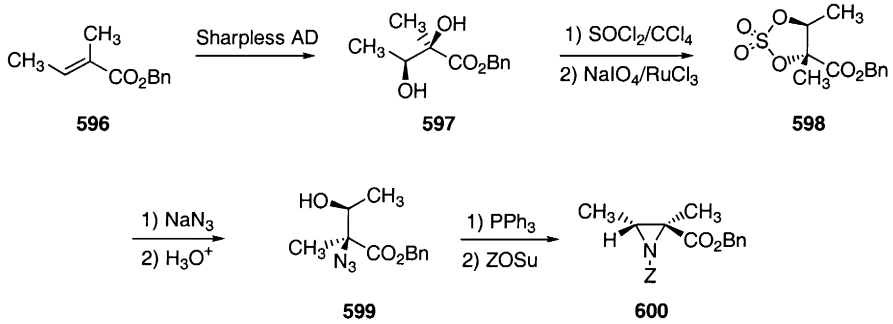
Starting from (*R*)-2-methylglycidol, Goodman et al.[205,206] have obtained benzyl (*R*)-2-methylaziridine-2-carboxylate in enantiomerically pure form. Oxidation of the alcohol with ruthenium oxide followed by esterification and regioselective ring opening provides the corresponding azido alcohol, which generates the aziridinecarboxylate upon cyclisation with triphenylphosphine (Scheme 112).

The same authors[206] have described the synthesis of (2*S*,3*S*)-benzyl *N*-benzyloxycarbonyl-2,3-dimethylaziridine-2-carboxylate from benzyl tiglate. In this case Sharpless asymmetric epoxidation of the benzyl tiglate provides a chiral diol from which the enantiomerically pure aziridinecarboxylate is obtained (Scheme 113).



592 593 594 595

Scheme 112.

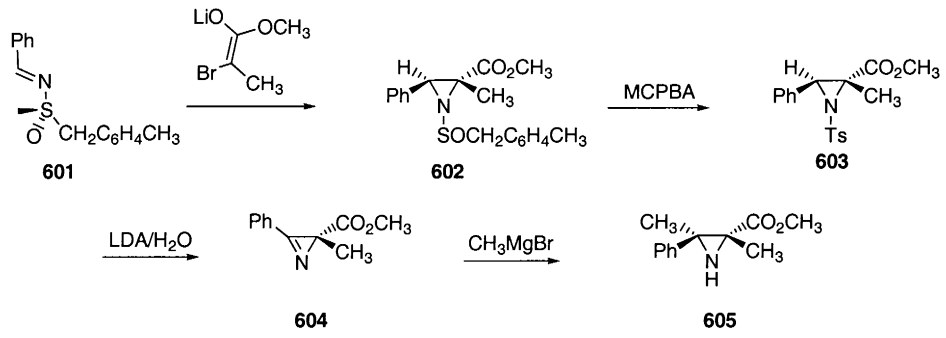


596 597 598 599 600

Scheme 113.

3.1.3. Miscellaneous

Davis et al.[207] have obtained chiral *trans*-(2*R*,3*S*)-*N*-(*p*-toluenesulfinyl)-2-methyl-2-carbomethoxy-3-phenylaziridine by Darzens-type condensation between (*S*)-benzylidene-*p*-toluenesulfinamide and the lithium enolate generated from methyl α-bromopropionate. The *trans* (major) compound was obtained with good yield and selectivities and was transformed into the corresponding *N*-tosyl aziridine. This compound was in turn transformed into chiral methyl (*R*)-2*H*-azirin-2-carboxylate on treatment with LDA and it adds Grignard reagents to afford more substituted aziridine-2-carboxylates[208] (Scheme 114).

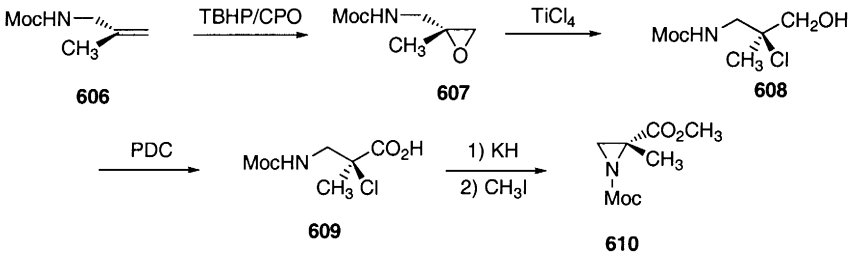


601 602 603 604 605

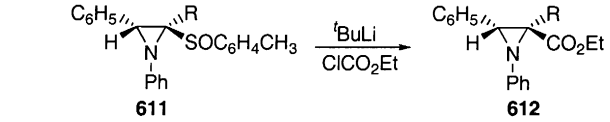
Scheme 114.

N-Methoxycarbonyl methallylamine has been epoxidised in high yield and excellent enantioselectivity using chloroperoxidase (CPO), isolated from *Caldariomyces fumago*, as a catalyst. The resultant epoxide was converted to (*R*)-dimethyl 2-methylaziridine-1,2-dicarboxylate in three additional steps according to Scheme 115.[209]

It has also been reported[210] that treatment of chiral 2-sulfinylaziridines with *tert*-butyllithium generates aziridinyllithiums that react with electrophiles to afford 2-substituted aziridines. When ethyl chloroformate is used as the electrophile the aziridine-2-carboxylic acid derivatives are obtained (Scheme 116).



Scheme 115.

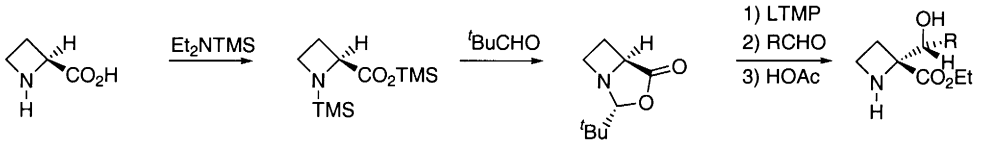


Scheme 116.

3.2. *Azetidine-2-carboxylic acids*

3.2.1. *Self-reproduction of chirality*

The stereoselective hydroxyalkylation of azetidine-2-carboxylic acid reported by Seebach[211] is one of the few references in the literature dealing with the asymmetric synthesis of α-substituted azetidine-2-carboxylic acids. In this paper (*S*)-azetidine-2-carboxylic acid is converted into trimethylsilyl (*S*)-*N*-(trimethylsilyl)azetidine-2-carboxylate, which reacts with pivalaldehyde to afford an intermediate oxazolidinone. To avoid racemisation in the synthesis of oxazolidinone **615** the reaction time and temperature must be carefully controlled. Enolisation with base, followed by quenching with an aldehyde, leads to the corresponding hydroxyalkylation compounds with low yields and moderate to good diastereoselectivities (Scheme 117).



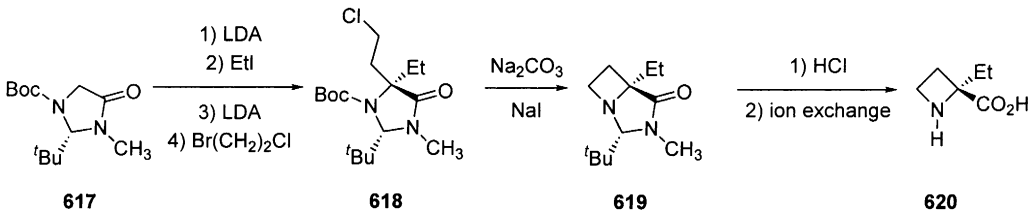
Entry	R	de %
a	CH_3	60
b	Ph	> 96
c	4-C_6H_5-C_6H_4	> 96
d	4-$(CH_3)_2N$-C_6H_4	> 96
e	3,4,5-$(CH_3O)_3$-C_6H_2	> 96
f	2-pyridyl	> 96
g	3-pyridyl	> 96
h	4-pyridyl	> 96

Scheme 117.

3.2.2. *Cyclisation of chiral amino acid derivatives*

Alkylation of the enantiomerically pure glycine derivative *tert*-butyl (*S*)-2-*tert*-butyl-3-methyl-4-oxo-imidazolidinecarboxylate **617** with a simple alkyl halide, followed by reaction with 1-bromo-2-

chloroethane, gives a geminally 5,5-disubstituted imidazolidinone. After removal of the Boc protecting group, intramolecular cyclisation leads to bicyclic derivative **619**, from which (*S*)-2-ethylazetidine-2-carboxylic acid is obtained by acid hydrolysis[212] (Scheme 118).

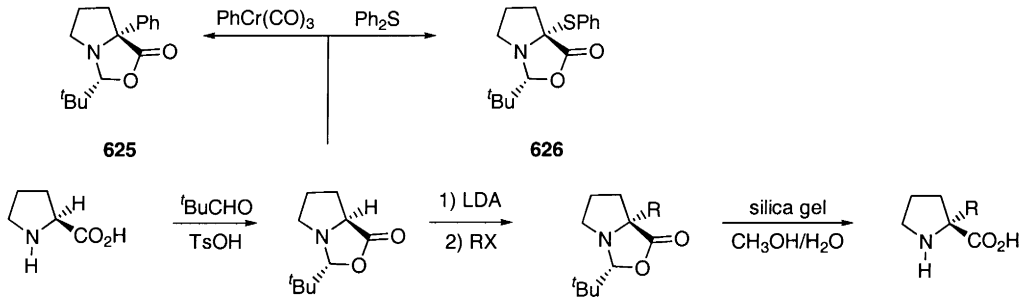


Scheme 118.

3.3. α-Alkylprolines

3.3.1. Self-reproduction of chirality

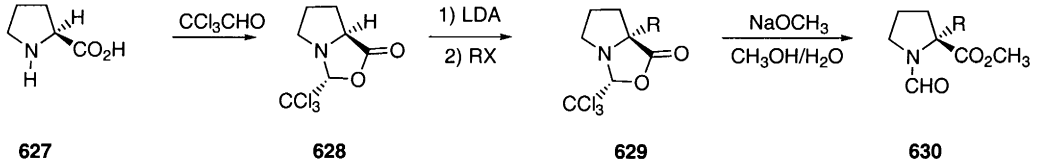
There are several references related to different strategies for the asymmetric synthesis of α-substituted proline derivatives. Among them, one the most important is the application of the self-reproduction of chirality, a concept developed by Seebach.[213] This strategy uses L-proline as the starting material and this is alkylated at the α-carbon without loss of optical purity and with retention of configuration.[214–216] To this end L-proline is condensed with pivalaldehyde to give a single stereoisomer of 2-*tert*-butyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one. Deprotonation with LDA gives a chiral, non-racemic enolate, which combines with alkyl halides to afford the corresponding alkylated compound as a single diastereoisomer in generally high yields. This intermediate can also be phenylated with (benzene)(tricarbonyl)chromium and thiolated with diphenyldisulfide. Hydrolytic cleavage of the products, which can be troublesome under acidic conditions, can be performed under mild conditions using a suspension of silica gel in methanol/water according to Johnson's procedure.[217] Following hydrolysis, the pure α-alkylproline can be obtained by filtration, thereby avoiding the tedious ion exchange purification (Scheme 119).



Entry	RX	de %
a	CH_3I	> 98
b	$CH_2{=}CHCH_2Br$	> 98
c	$PhCH_2Br$	> 98
d	$CH_2{=}N(CH_3)_2Cl$	> 98
e	$CH_3O_2CCH_2Cl$	> 98
f	$(CH_3)_2NOCCH_2Cl$	> 98

Scheme 119.

Condensation of L-proline with trichloroacetaldehyde provides the corresponding 2-trichloromethyloxazolidinone. This compound has proven to be a valuable synthetic precursor to enantiomerically pure α-alkylproline derivatives as it can be alkylated at the α-position to afford the corresponding alkylated compound as a single diastereoisomer with retention of configuration[218] (Scheme 120).

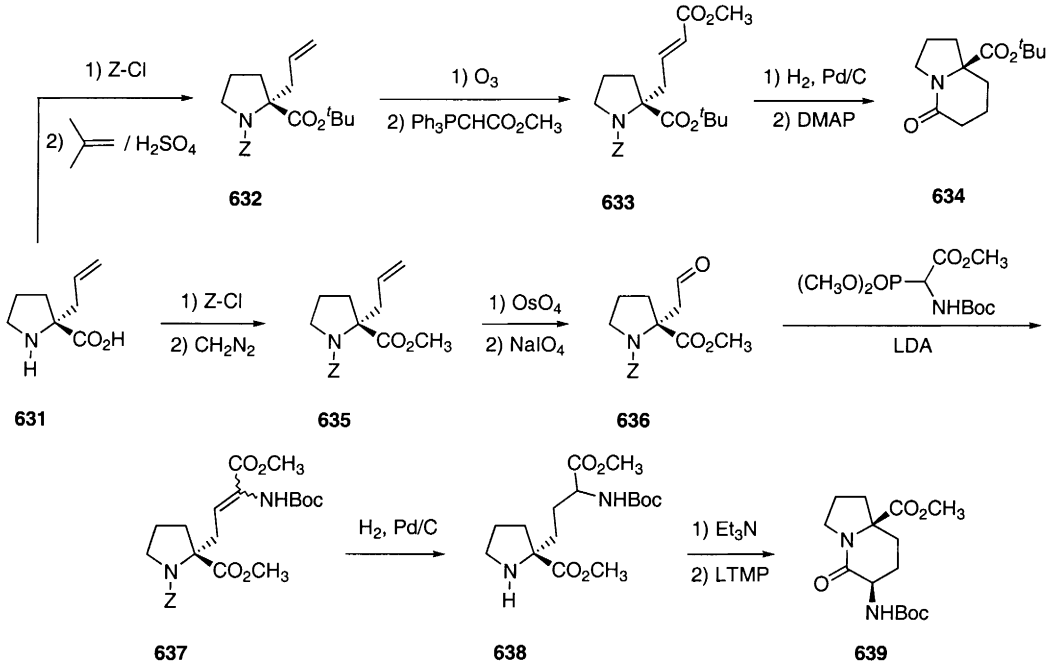


627 628 629 630

Entry	RX	de %
a	CH_3I	> 95
b	$CH_2{=}CHCH_2Br$	> 95
c	$PhCH_2Br$	> 95
d	$CH_3O_2CCH_2I$	> 95

Scheme 120.

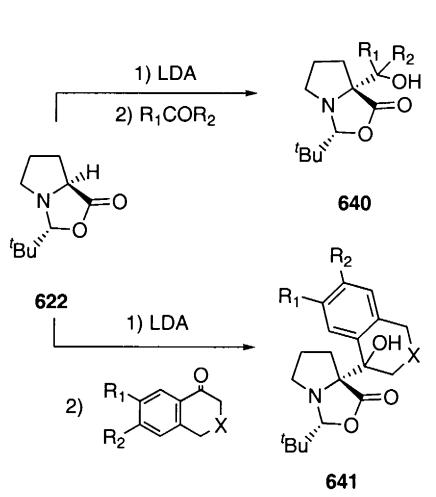
Following this methodology, enantiomerically pure α-allylproline has been synthesised and used as an intermediate in the synthesis of more complex α-alkylproline derivatives that are used to form new type-βVI-turn peptide mimics.[219–221] Some examples of such reactions are gathered in Scheme 121.



631 632 633 634 635 636 637 638 639

Scheme 121.

Addition of compound **622** to carbonyl groups of aldehydes and ketones gives two isomers that are epimeric at the carbinol centre but with one epimer predominating to the extent of more than 70%[215] (Scheme 122).



Entry	R_1COR_2	ds %*
a	CH_3CHO	94
b	PhCHO	94
c	^{t}BuCHO	83
d	CH_3COCH_3	-
e	$CH_3COCH_2CO_2CH_3$	51
f	$3,4\text{-}(CH_3O)_2C_6H_3COCH_2NO_2$	83

* at the carbinol centre

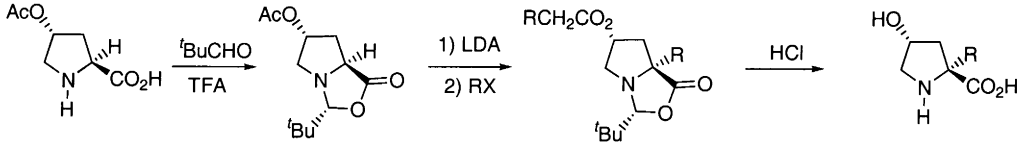
Entry	R_1	R_2	X	ds %*
a	H	H	CH_2	73
b	H	CH_3	CH_2	72
c	CH_3	CH_3	NCO^tBu	> 95

* at the carbinol centre

Scheme 122.

Michael additions and acylation reactions have also been described. In Michael additions the formation of constitutional isomers is observed and in acylation reactions the compounds obtained are rather unstable.

The same principle has been applied to the synthesis of 2-alkyl-4-hydroxyprolines starting from (2*S*,4*R*)-4-hydroxyproline (Scheme 123). The alkylation reaction with different alkyl halides on the dienolate generated by treatment of compound **643** with LDA occurs with retention of configuration and 2-methyl-, 2-allyl- and 2-benzyl-4-hydroxyprolines have been obtained.[222] When carbonyl compounds are used as electrophiles a mixture of diastereoisomers at the carbinol centre is obtained.



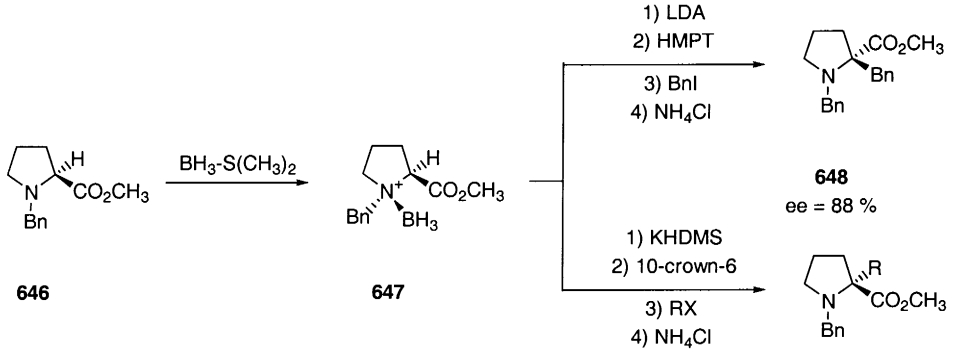
642 **643** **644** **645**

Entry	RX	de %
a	CH_3I	> 95
b	$CH_2{=}CHCH_2Br$	> 95
c	$PhCH_2Br$	> 95

Scheme 123.

The asymmetric synthesis of α-alkylproline derivatives from a chiral borane–amine adduct, which can be obtained as a single diastereoisomer from proline, has recently been described.[223] Optimal results were obtained by generation of the enolate by treatment with LDA followed by quenching in the presence of HMPT or by treatment with KHMDS in the presence of 18-crown-6. The two protocols are complementary and both enantiomers of α-benzylproline have been obtained. It should be noted that the inversion of enantioselectivity is observed due to the presence of the crown ether (Scheme 124).

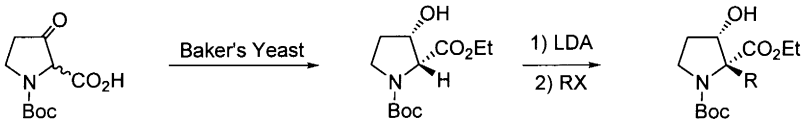
N-Boc-(2*R*,3*S*)-3-hydroxyproline ethyl ester, which is readily available from racemic 3-ketoproline by Baker's yeast reduction, has been alkylated with different electrophiles with retention of configuration and with moderate to good yields and excellent diastereoselectivity.[224] The procedure is a general one



Entry	RX	ee %
a	$PhCH_2I$	80
b	CH_3OTf	88
c	$CH_3(CH_2)_4OTf$	92
d	$(CH_3)_2CH(CH_2)_2OTf$	86
e	$2,5\text{-}(CH_3)_2C_6H_3CH_2I$	91

Scheme 124.

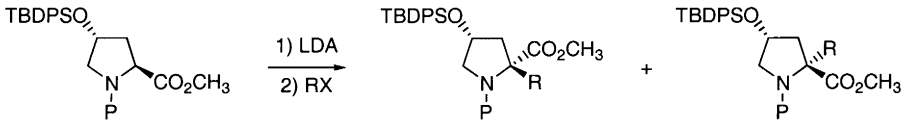
for the synthesis of α-alkyl-β-hydroxyproline derivatives and one such compound has been used as an intermediate in the synthesis of paraherquamide A (Scheme 125).



Entry	RX	de %
a	CH_3I	> 98
b	$Br(CH_2)_4Br$	> 98
c	$PhCH_2Br$	> 98
d	$(CH_3)_2C{=}CHCH_2I$	> 98
e	$CH_3(TBSOCH_2)C{=}CHCH_2I$	> 98

Scheme 125.

The alkylation of *N*-Boc- and *N*-benzoyl-(2*S*,4*R*)-4-*tert*-butyldiphenylsilyloxyproline methyl ester with a range of alkyl halides in the presence of HMPT occurs with moderate to good yields. The diastereoselectivity of the alkylation reaction is dependent on the alkylating reagent and the *N*-protecting group. Whereas retention of configuration is observed upon alkylation of the *N*-Boc derivative with allylic or homoallylic halides, the use of benzylic halides leads preferentially to products with inversion of configuration at Cα. Alkylation of the *N*-benzoyl derivative occurs with inversion when benzylic and allylic halides are used and, in the case of benzylic halides, high selectivities are observed[225] (Scheme 126).



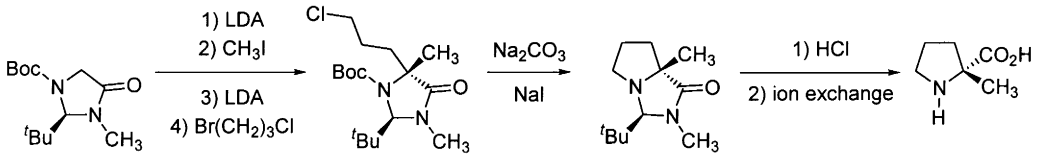
653 654 655

Entry	P	RX	654/655
a	Boc	CH_3I	23/77
b	Boc	$CH_2{=}CHCH_2Br$	40/60
c	Boc	$(CH_3)_2C{=}CCH_2Br$	36/64
d	Boc	$CH_2{=}C(CH_3)CH_2Br$	37/63
e	Boc	$CH_2{=}CHCH_2CH_2Br$	23/77
f	Boc	$CH_2{=}CHCH_2CH_2I$	27/73
g	Boc	$PhCH_2Cl$	71/29
h	Boc	$PhCH_2Br$	70/30
i	Boc	$4\text{-}CH_3OC_6H_4CH_2Cl$	66/34
j	Bz	$CH_2{=}CHCH_2Br$	77/23
k	Bz	$CH_2{=}CHCH_2CH_2I$	37/63
l	Bz	$PhCH_2Br$	> 95/5
m	Bz	$4\text{-}CH_3C_6H_4CH_2Cl$	91/9
n	Bz	$4\text{-}CH_3OC_6H_4CH_2Cl$	> 95/5

Scheme 126.

3.3.2. *Cyclisation of chiral amino acid derivatives*

In a different general approach the pyrrolidine ring of proline is constructed from the side chain of an amino acid equivalent carrying the appropriate leaving group. In this way, when the enantiomerically pure glycine derivative *tert*-butyl (*R*)-2-*tert*-butyl-3-methyl-4-oxo-imidazolidinecarboxylate is alkylated, first with methyl iodide and then with 1-bromo-3-chloropropane, (*R*)-2-methylproline is obtained by hydrolysis after cyclisation[212] (Scheme 127).



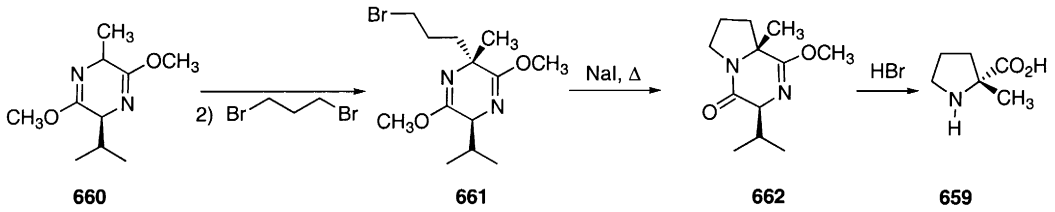
656 657 658 659

Scheme 127.

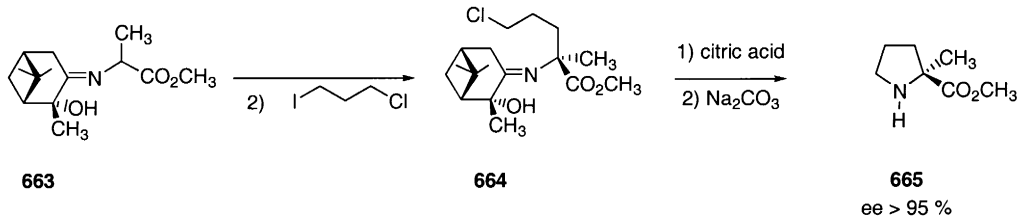
In a similar approach, the elegant Schöllkopf methodology, developed for the synthesis of acyclic quaternary amino acids, has been used in the synthesis of 2-alkylproline derivatives using the appropriate dielectrophiles. Starting from the commercially available bis-lactim ether of *cyclo*-(L-Val-Ala), alkylation with 1,3-dibromopropane provides the corresponding dialkylated bis-lactim ether, which upon cyclisation by heating in the presence of sodium iodide affords the (*R*)-2-methylproline precursor **662**[226] (Scheme 128).

Viallefont has described the synthesis of cyclic amino acids using a similar strategy: highly diastereoselective alkylation of Schiff bases, derived from alanine and enantiomerically pure (2*R*,3*R*,5*R*)-2-hydroxypinan-3-one, with 1-chloro-3-iodopropane followed by hydrolytic cleavage and cyclisation affords (*S*)-α-methylproline methyl ester[227,228] (Scheme 129).

Chiral 3,6-dihydro-2*H*-1,4-oxazin-2-one **666**, derived from alanine, has been diastereoselectively dialkylated with 1,3-diiodopropanes using 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,2,3-

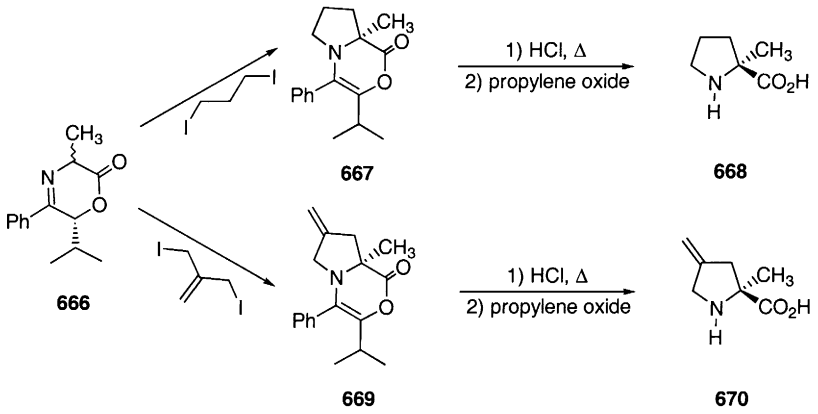


Scheme 128.



Scheme 129.

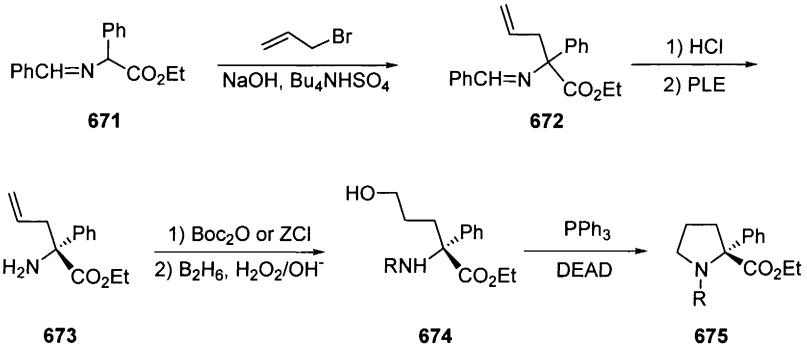
diazaphosphorine (BEMP) as a base in the presence of lithium iodide.[229,230] Subsequent acid hydrolysis at 150°C in a sealed tube and treatment with propylene oxide to release the free amino acid afforded (*S*)-α-methylproline derivatives in 99% enantiomeric excess (Scheme 130).



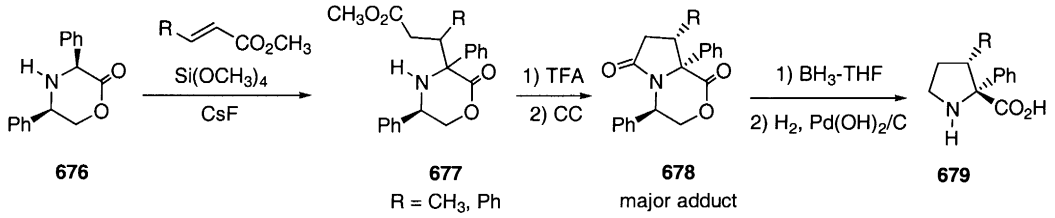
Scheme 130.

Van Betsbrugge et al.[231] have developed a new strategy based on the Mitsunobu ring closure reaction of an alcohol to construct the pyrrolidine ring. The *N*-benzylidene phenylglycine ethyl ester was allylated under phase-transfer catalysis conditions and the resulting product was enzymatically resolved using pig liver esterase. Hydroboration and oxidation of the double bond of the resolved (*R*) enantiomer and subsequent ring closure using the Mitsunobu protocol give rise to the corresponding (*R*)-α-phenylproline derivative (Scheme 131).

Enantiomerically pure phenylglycine has been used as a starting material to prepare (3*S*,5*R*)-diphenylmorpholin-2-one, an interesting chiral heterocyclic compound that is a precursor of different amino acids. This compound reacts with acrylates by a 1,4-addition reaction to give a mixture of products from which the major compound can be isolated, after lactamisation, and used to obtain enantiomerically pure 3-substituted 2-phenylprolines through chemoselective reduction of the lactam ring followed by hydrogenolysis. The substituent at C_3 depends on the acrylate used in the reaction[232] (Scheme 132).



Scheme 131.



Scheme 132.

3.3.3. 1,3-Dipolar cycloadditions

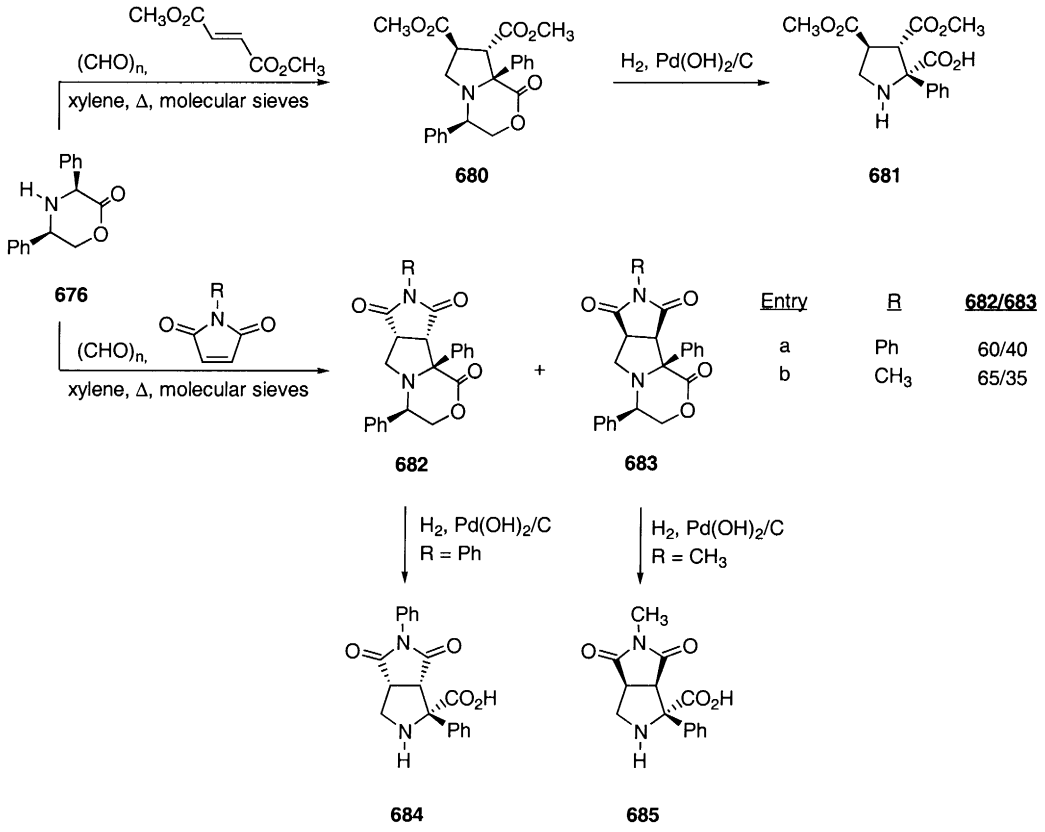
1,3-Dipolar cycloadditions of chiral stabilised azomethine ylides represent another methodology that has been scarcely used in the synthesis of α-alkylproline derivatives. In this way, however, (3*S*,5*R*)-3,5-diphenylmorpholinone reacts with formaldehyde to generate an azomethine ylide that is capable of undergoing diastereoselective 1,3-dipolar cycloadditions with different dipolarophiles. These reactions give the corresponding bicyclic cycloadducts. The diastereoselectivity of the reaction depends on the reaction conditions and is better under thermal activation than in a Lewis acid-catalysed cycloaddition. The resulting cycloadducts can be conveniently elaborated to afford α-phenylproline derivatives[233] (Scheme 133).

1,3-Dipolar cycloadditions of azomethine ylides, generated by deprotonation of Schiff bases of amino acid esters, with *N*-acryloyl-(*S*)-proline benzyl ester give pyrrolidines in satisfactory yields and with very high stereoselectivities. In each case only four of the eight possible diastereoisomers are detected and a single stereoisomer is formed in a large excess. After isolation of the major compound, a simple acid hydrolysis releases the corresponding α-alkylproline derivative in enantiomerically pure form[234] (Scheme 134).

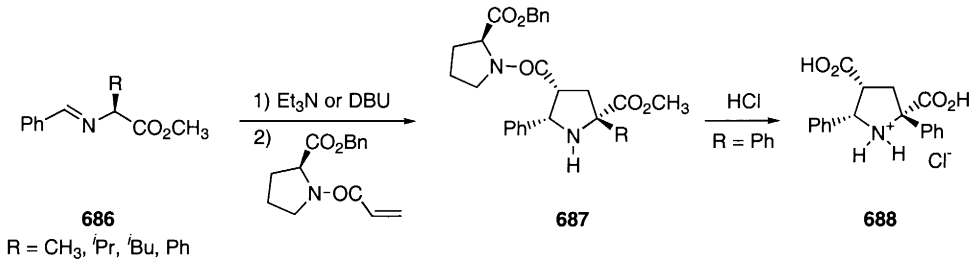
Reaction of chiral arene tricarbonyl chromium imine complexes with methyl acrylates, in the presence of lithium bromide and triethylamine, gives cycloaddition compounds in good yields and with excellent diastereoselectivities. Oxidative decomplexation of the single diastereoisomer detected allows the synthesis of the corresponding α-alkylproline derivative in excellent yield[235] (Scheme 135).

A diastereoselective 1,3-dipolar cycloaddition reaction between azomethine ylides, derived from amino acids, and chiral sulfinimines produces *N*-sulfinyl imidazolidines, which can be considered as azaproline derivatives, in enantiomerically pure form according to Scheme 136.[236]

Azaproline derivatives have also been obtained through a highly diastereoselective 1,3-dipolar cycloaddition between commercially available trimethylsilyldiazomethane and chiral acrylates incorporating the camphor sultam auxiliary. The reaction uses α-methacryloyl sultam as a dipolarophile and gives an optically active Δ^1-pyrazoline, which upon acidification furnishes the corresponding Δ^2-pyrazoline.



Scheme 133.

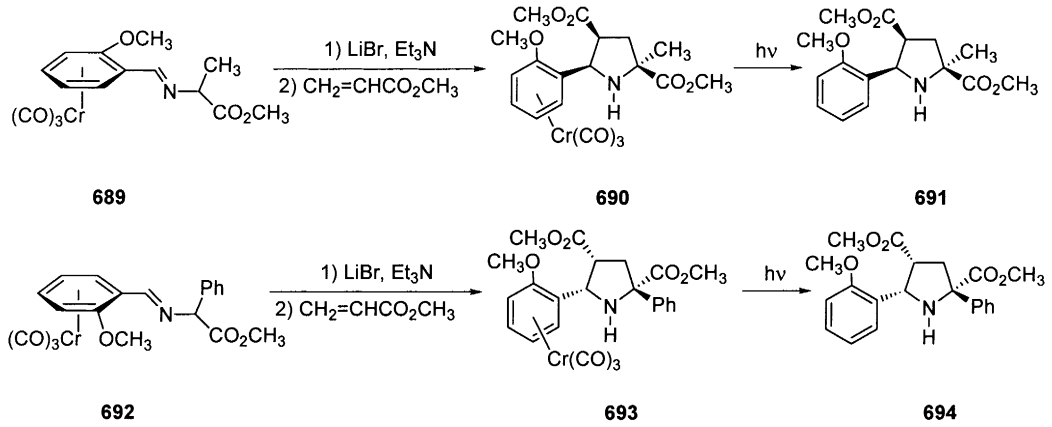


Scheme 134.

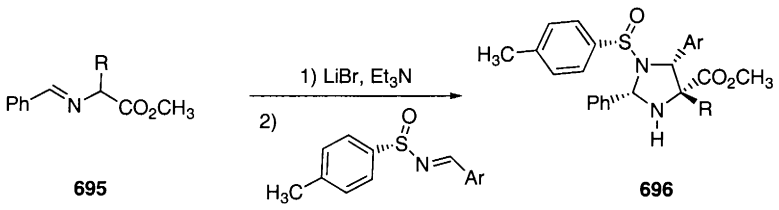
Subsequent C=N reduction, chemoselective protection and auxiliary removal affords a useful azaproline analogue[237] (Scheme 137).

3.3.4. *Miscellaneous*

A new method for the stereoselective α-methylation of *N*-methoxycarbonyl L-proline methyl ester has been reported by Matsumura et al.[238] The synthetic strategy consists of the diastereoselective introduction of a substituent at the 5-position of proline under the influence of the carbomethoxy group. Subsequent diastereoselective introduction of a substituent in the α-position, under the influence of the substituent at C_5, and removal of the C_5 substituent would lead to the desired α-substituted proline. To this end electrochemical methoxylation of *N*-methoxycarbonyl L-proline methyl ester, followed by the replacement of the methoxy group with a phenylthio group, has been performed to afford an almost

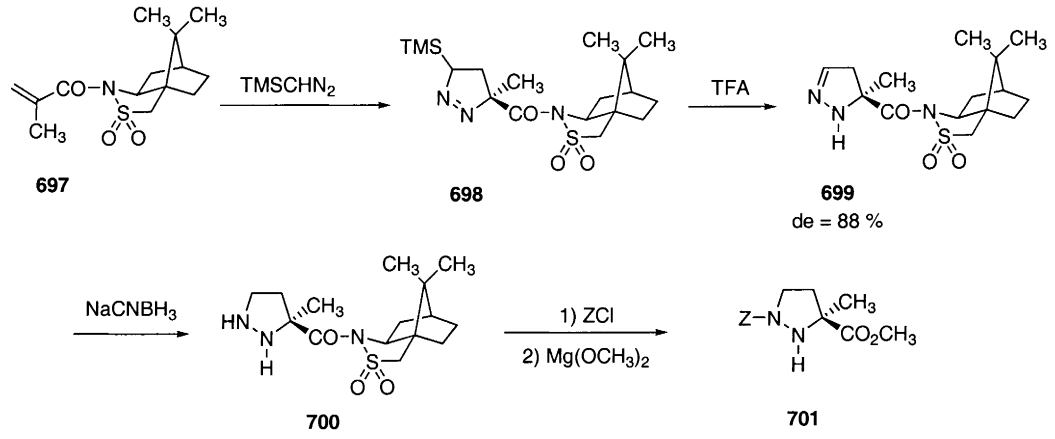


Scheme 135.



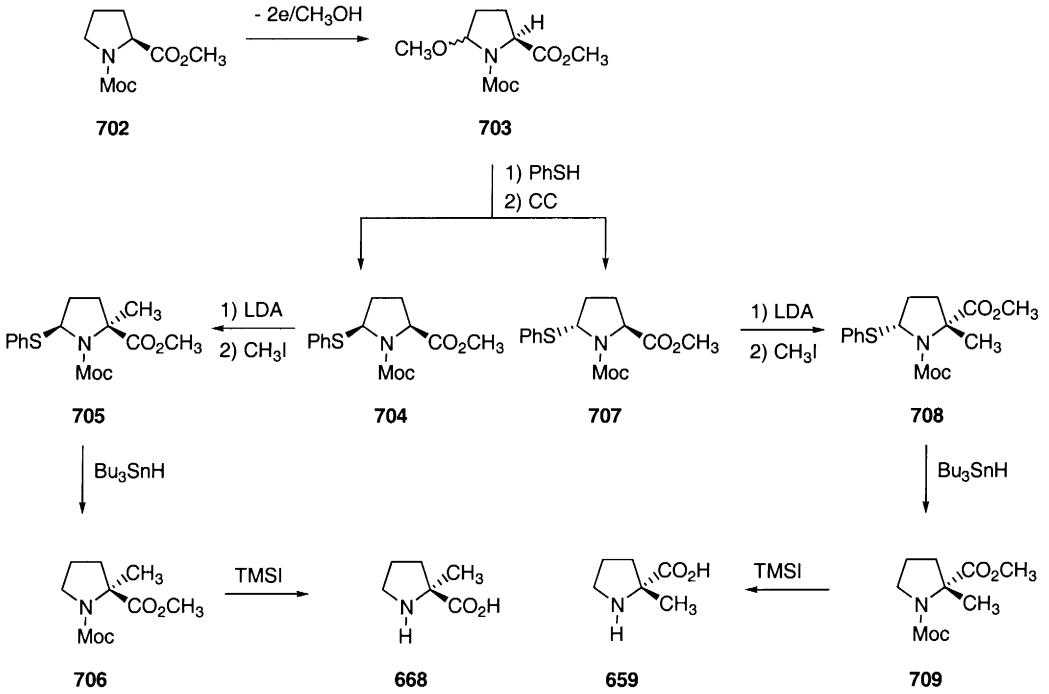
Entry	R	Ar	dr
a	$PhCH_2$	Ph	95/5
b	CH_3	Ph	95/5
c	$PhCH_2$	4-$NO_2C_6H_4$	97/3
d	$(CH_3)_2CHCH_2$	4-$NO_2C_6H_4$	98/2

Scheme 136.



Scheme 137.

equimolecular mixture of stereoisomers, which can be easily separated. Subsequent α-methylation and reductive removal of the phenylthio group leads to both enantiomers of α-methylproline (Scheme 138).



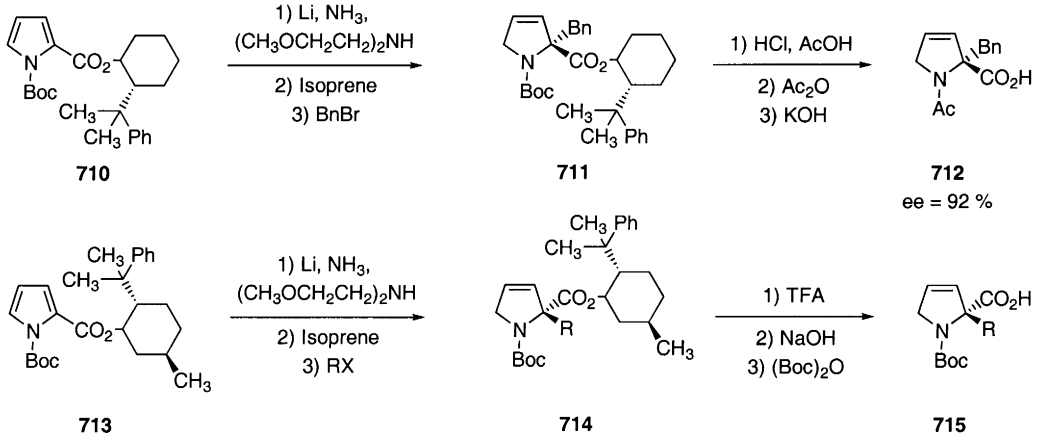
Scheme 138.

Stereoselective Birch reduction of chiral pyrrole derivatives has been applied to the asymmetric synthesis of β-dehydroproline derivatives.[239] Reduction of chiral esters **710** or **711** with lithium metal in liquid ammonia in the presence of bis(2-dimethoxyethyl)amine, followed by quenching with an alkylhalide, gives the corresponding α-alkyl-β-dehydroproline in very high yields. Subsequent removal of the chiral auxiliary followed by protection under standard conditions yields the amino acid derivatives with good enantiomeric excesses (Scheme 139).

The synthesis of some interesting conformationally-constrained prolines that possess a 7-azabicyclo[2.2.1]heptane skeleton has been described.[240] The key chiral precursor **716** can be obtained in enantiomerically pure form from L-glutamic acid. From this compound several 1-carboxy-7-azabicycloheptane amino acids have been obtained in enantiomerically pure form. 3-Hydroxy, 3-fluoro and 3,3-difluoro derivatives can be obtained according to Scheme 140. Mixtures of compounds that are epimeric at C_3 are obtained and, in most cases, the two epimers can be separated.

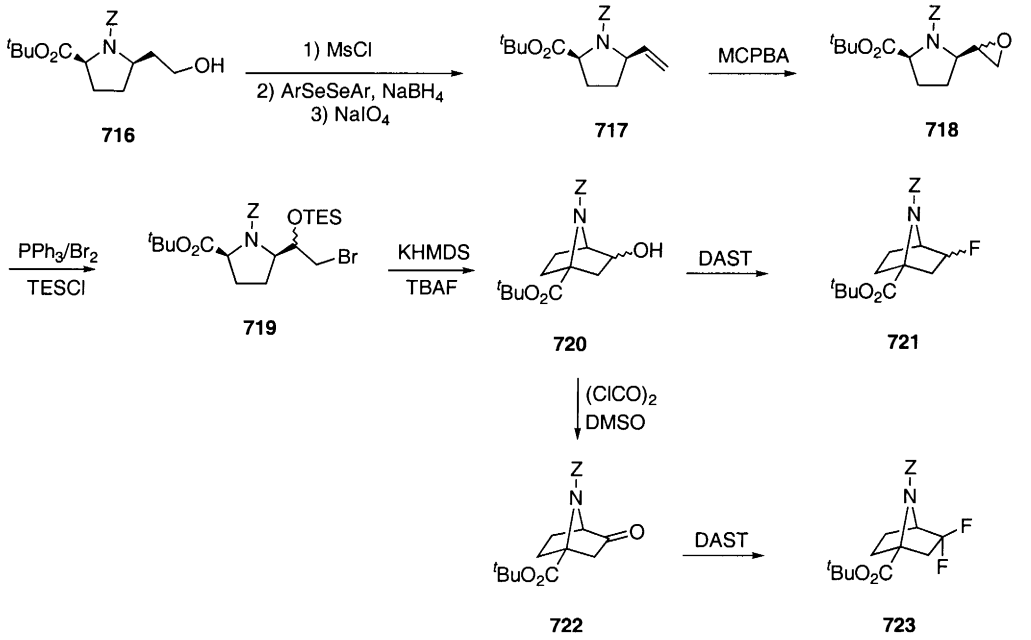
Ketone **722**, obtained from the epimeric mixture of alcohols **720**, has served as a synthetic intermediate in the synthesis of 3-phenyl, 3-aminomethyl, 3-(2-hydroxyethyl) and 3-(2-aminoethyl) derivatives, as shown in Scheme 141.[240]

In order to obtain the 7-azabicyclo[2.2.1]heptane amino acid with the side chain of glutamic acid at C_2, compound **730** was obtained from L-serine and this is the key step in the transannular alkylation to form the [2.2.1]-ring. Dihydroxylation of compound **730**, followed by selective protection, oxidation and reductive removal of the silyl ether, gives ketone **733**. The side chain of glutamic acid was then introduced through a Wittig olefination[241] (Scheme 142).



Entry	RX	ee %
a	CH_3I	78
b	EtI	86
c	^{i}BuI	90
d	BnBr	90

Scheme 139.

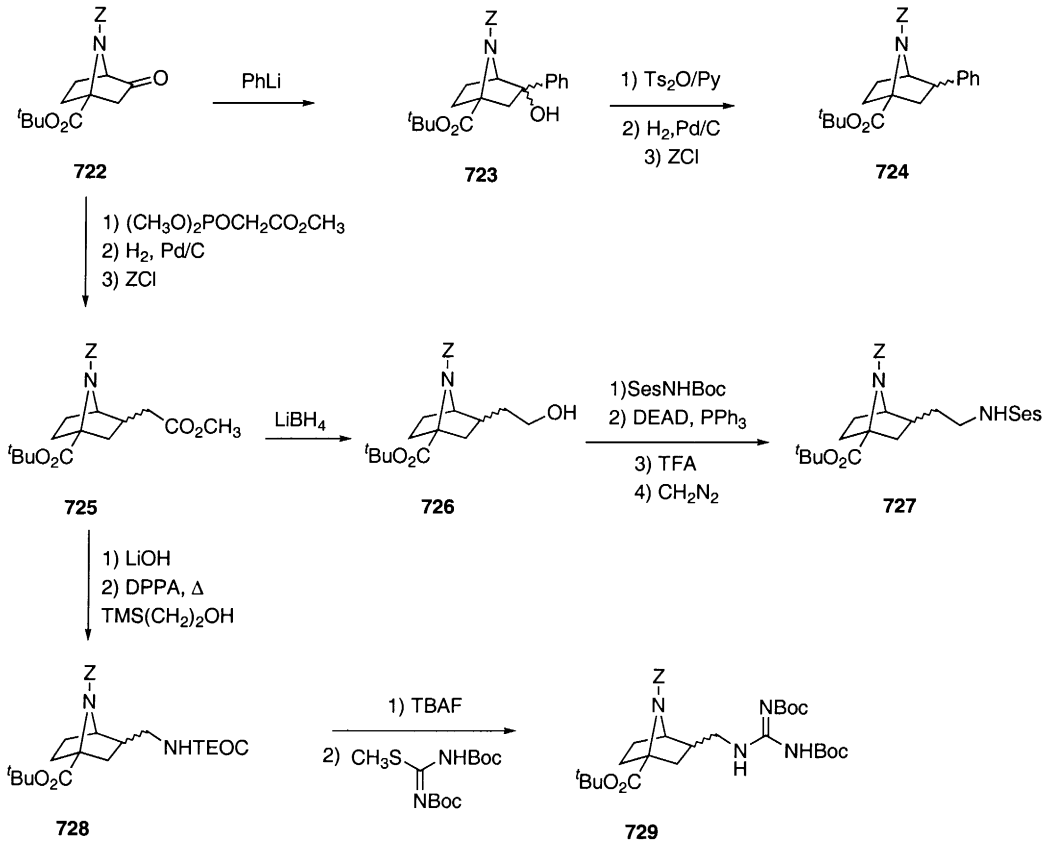


Scheme 140.

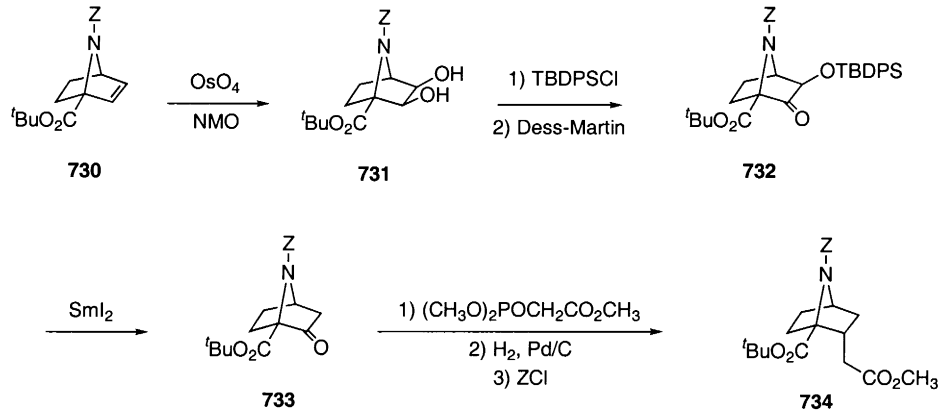
3.4. α-Alkylpipecolic acids

3.4.1. Cyclisation of chiral amino acid derivatives

Some of the synthetic methodologies developed for the asymmetric synthesis of α-alkylprolines are based on the construction of the heterocyclic ring by intramolecular cyclisation of a geminally



Scheme 141.

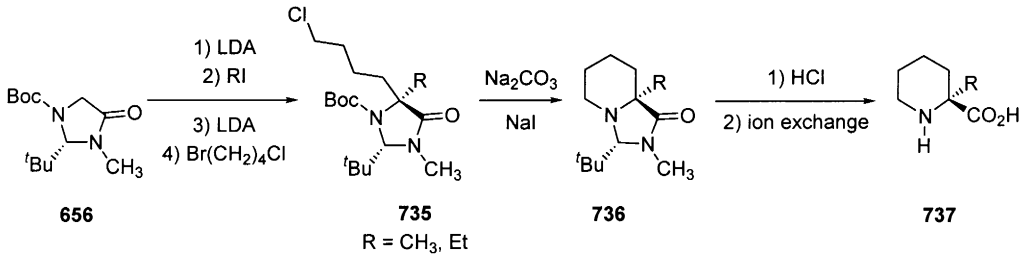


Scheme 142.

disubstituted glycine equivalent carrying an appropriate leaving group on the side chain. A number of these systems have been extended to the asymmetric synthesis of α-alkylpipecolic acids.

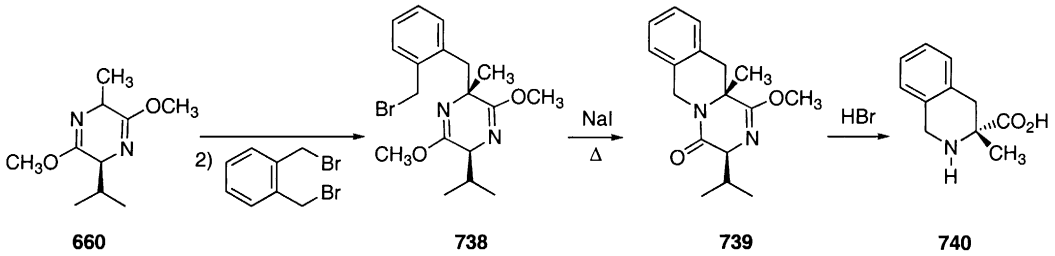
For example, when *tert*-butyl (*S*)-2-*tert*-butyl-3-methyl-4-oxo-imidazolidinecarboxylate is alkylated first with an alkyl halide and then with 1-bromo-4-chlorobutane, (*S*)-2-alkylpipecolic acids are obtained after cyclisation and acid hydrolysis according to the Seebach procedure described before[212] (Scheme 143).

The Schöllkopf methodology has been applied to the synthesis of (*R*)-3-methyltetrahydroiso-



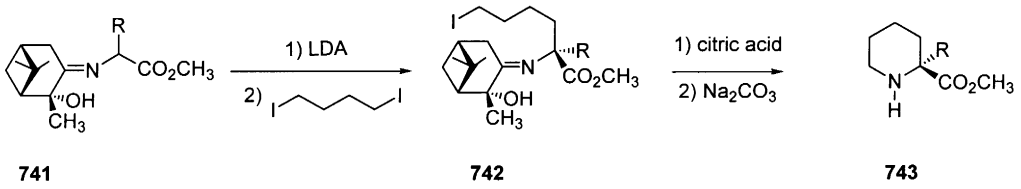
Scheme 143.

quinoline-3-carboxylic acid using the bis-lactim ether of *cyclo*-(L-Val-Ala) as the starting material and 1,2-dibromomethylbenzene as the dielectrophile[226] (Scheme 144).



Scheme 144.

According to the Viallefont methodology, diastereoselective alkylation of Schiff bases derived from alanine, phenylalanine or norvaline and enantiomerically pure (2*R*,3*R*,5*R*)-2-hydroxypinan-3-one with 1,4-diiodobutane, followed by hydrolytic cleavage and cyclisation, affords methyl esters of (*S*)-α-alkylpipecolic acid[227,228] (Scheme 145).

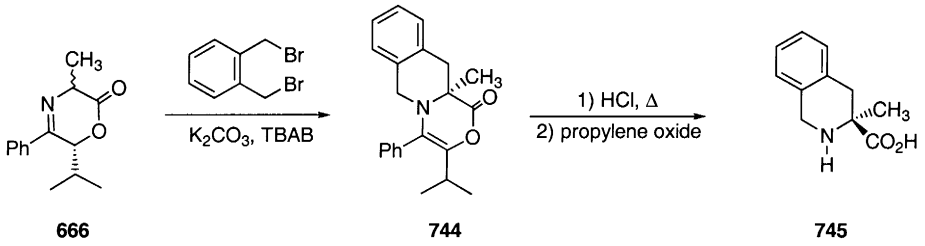


Entry	R	ee %
a	CH_3	> 95
b	$PhCH_2$	71
c	Pr	5

Scheme 145.

Diastereoselective alkylation of chiral 3,6-dihydro-2*H*-1,4-oxazin-2-one **666**, derived from alanine with 1,2-dibromomethylbenzene under phase transfer catalysis conditions, furnishes a tricyclic system that, upon acid hydrolysis at 150°C in a sealed tube and treatment with propylene oxide, releases enantiomerically pure (*S*)-3-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid[230] (Scheme 146).

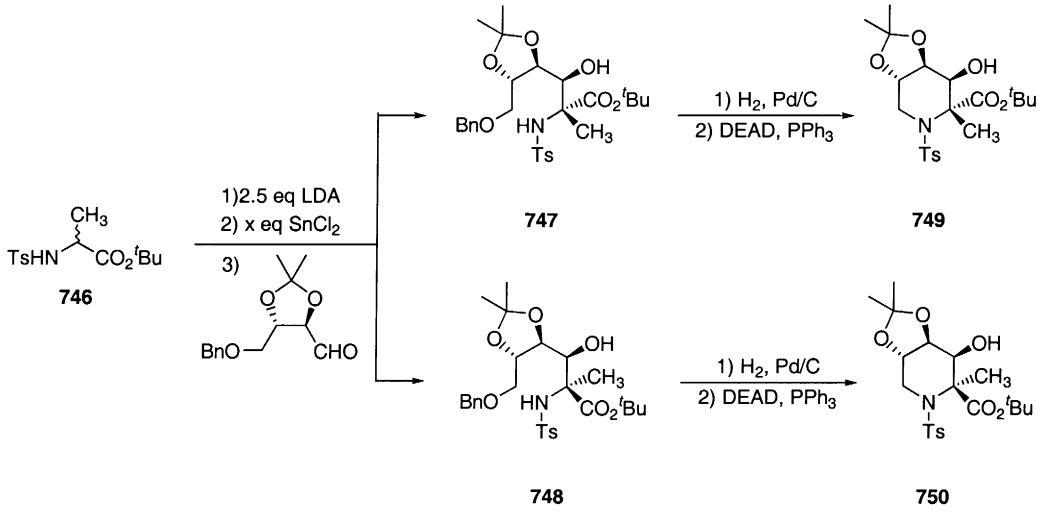
Kazmaier et al.[242,243] have developed a new synthetic route to α-alkylpipecolic acids based on a highly diastereoselective aldol reaction of chelated enolates derived from *N*-protected amino acid esters. According to this method chelated enolate-derived *N*-tosyl alanine *tert*-butyl ester adds chiral aldehyde 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose to give the corresponding *syn* and *anti* aldol products. Both selectivity and diastereoselectivity in the aldol addition depends on the amount of metal salt used and



666 **744** **745**

Scheme 146.

the best results are obtained with more than two equivalents of tin chloride. After cleavage of the benzyl ether and subsequent cyclisation under Mitsunobu conditions, α-methylpipecolic acid derivatives can be obtained (Scheme 147).



Entry	x	747/748	747 de %	748 de %
a	1.2	67/33	76	> 99
b	2.5	78/22	95	> 99

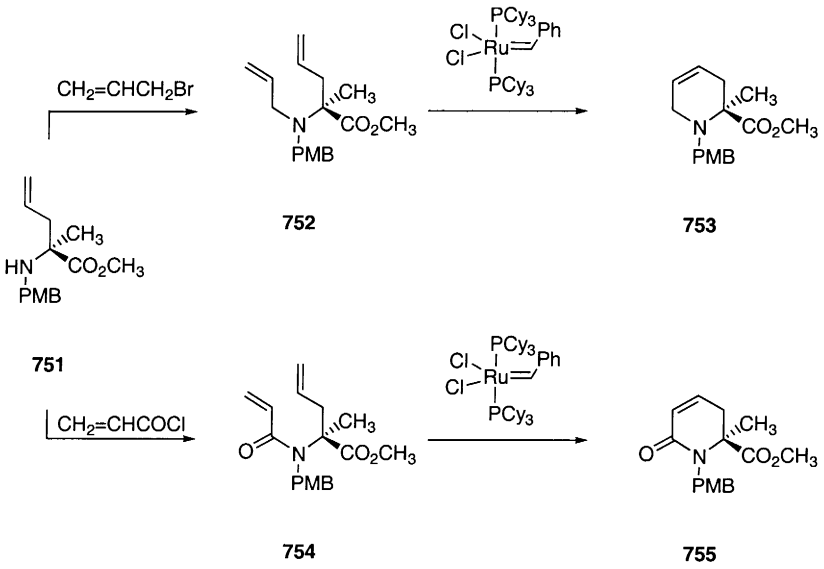
Scheme 147.

L-α-Methyl-α-allylglycine has served as a synthetic precursor in the synthesis of α-methylpipecolic acid derivatives by ruthenium-catalysed ring closing olefin metathesis.[244] The amino acid is first converted into its *N*-4-methoxybenzyl derivative and then *N*-acylated with acryloyl choride or *N*-allylated. Treatment of these compounds with a carbenoid ruthenium(II) catalyst provides the enantiomerically pure cyclic amino acid precursors in good yields (Scheme 148).

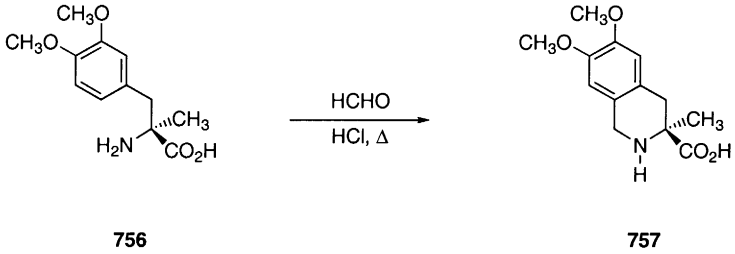
3.4.2. Miscellaneous

6,7-Dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid has been obtained through a Pictet–Spengler cyclisation by reaction of (*S*)-α-methyl-DOPA with 35% formaldehyde, as shown in Scheme 149.[245]

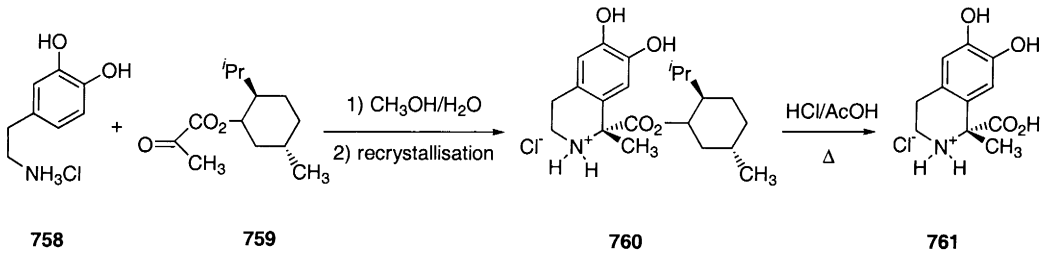
Condensation of dopamine with (1*S*,2*R*,5*S*)-menthylpyruvate affords a mixture of diastereoisomers from which the pure (1*R*)-diastereoisomer was isolated by repeated recrystallisations. Acid hydrolysis of the menthyl ester furnishes (*R*)-6,7-dihydroxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid[246] (Scheme 150).



Scheme 148.



Scheme 149.

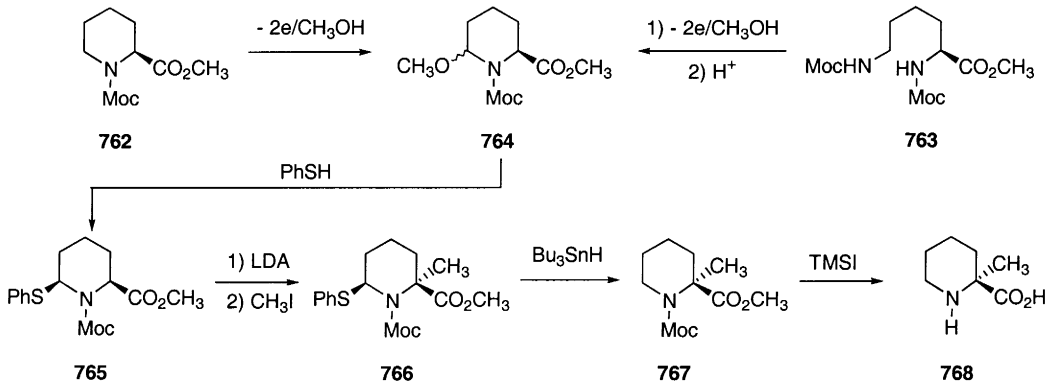


Scheme 150.

Electrochemical methoxylation at C_5 of *N*-methoxycarbonyl L-pipecolic acid methyl ester or *N*,*N*′-dimethoxycarbonyl L-lysine methyl ester, according to Matsumura's procedure,[238] gives a mixture of 5-methoxy compounds. Replacement of the methoxy group with a phenylthio group affords only one diastereoisomer of the corresponding 5-phenylthiopipecolic acid derivative, which is subsequently methylated at the α-position. Final reductive removal of the phenylthio group leads to (*S*)-α-methylpipecolic acid in 84% enantiomeric excess (Scheme 151).

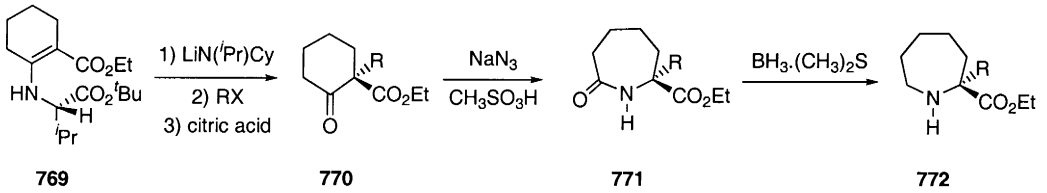
3.5. α-Alkylazepane- and azocane-2-carboxylic acids

Georg et al. have developed a versatile methodology for the synthesis of optically active α-alkylated azepane and 2-carboxylic acid and ester derivatives involving Schmidt rearrangement of optically active



Scheme 151.

cyclic β-keto esters.[247] The starting materials are obtained through diastereoselective alkylation of the lithium enamine of ethyl 2-oxocyclohexanecarboxylate utilising the readily available *tert*-butyl ester of L-valine as a chiral auxiliary. Schmidt rearrangement occurs with retention of configuration and in excellent yield and selective reduction of the amide carbonyl group completes the synthesis of enantiomerically pure α-alkyl azepane 2-carboxylic acid derivatives (Scheme 152).

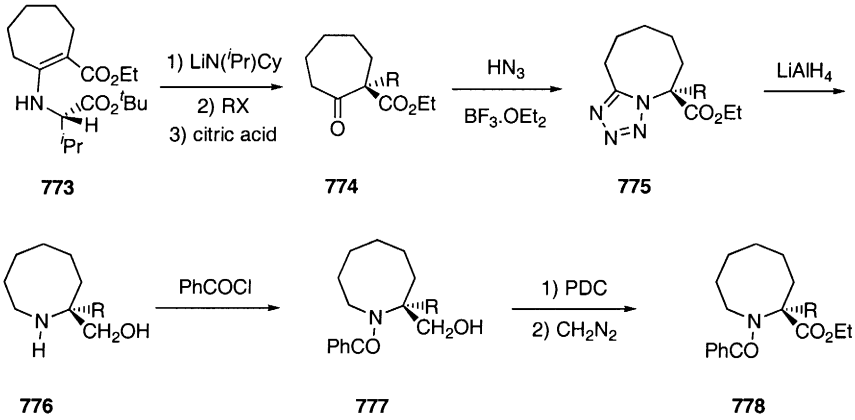


Entry	RX	ee %
a	$PhCH_2Br$	> 95
b	(2-naphthyl)CH_2Br	> 95
c	4-$BrC_6H_4CH_2Br$	> 95
d	3-$ClC_6H_4CH_2Br$	> 95
e	$CH_3O_2CCH_2Br$	59

Scheme 152.

Optically active α-alkylated azepane and 2-carboxylic acids can be obtained using chiral 1-alkyl 2-oxocycloheptanecarboxylates, obtained by diastereoselective alkylation of the lithium enamine derived from ethyl 2-oxocycloheptanecarboxylate and the available *tert*-butyl ester of L-valine. These intermediates are submitted to the Schmidt rearrangement to afford tetrazoles. Subsequent reduction of the tetrazole ring, protection of the nitrogen of the resulting aminoalcohols and oxidation of the hydroxymethyl group give enantiomerically pure α-alkyl azocane 2-carboxylic acid derivatives[248] (Scheme 153).

Finally, diastereoselective alkylation of the imine derived from alanine and (2*S*,3*S*,5*S*)-2-hydroxypinan-3-one with 1,5-diiodopentane, followed by hydrolytic cleavage and cyclisation affords the methyl ester of (*R*)-2-methylazepane-2-carboxylic acid in enantiomerically pure form[227,228] (Scheme 154).

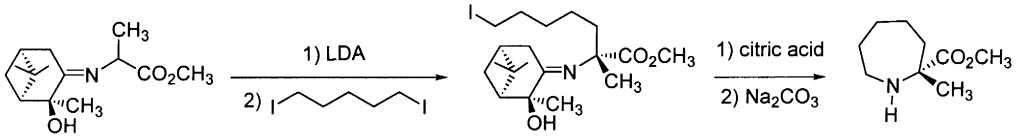


773 774 775

776 777 778

Entry	RX	ee %
a	$PhCH_2Br$	97
b	(2-naphthyl)CH_2Br	> 99
c	3-$ClC_6H_4CH_2Br$	98
d	CH_2=$CHCH_2Br$	96

Scheme 153.



779 780 781

Scheme 154.

4. Concluding remarks

The three-dimensional structure of the side chain moieties of an amino acid is characterised by the torsional angles χ^1, χ^2, etc. Torsional angles, in conjunction with the backbone angles, define the position of the side-chain functional groups and are of key importance in understanding the mode of action of peptides. Thus the synthesis of non-proteinogenic amino acids with well-defined complementary χ characteristics has been the focus of several research groups in recent years.[249]

Conformationally constrained amino acids play an important role in controlling the orientation of the side chain of the amino acid by restricting torsional angles χ^1 and χ^2 and, in this context, cyclic amino acids have proven to be useful tools in restricting torsional angle χ^1 by tethering Cα to Cβ.

As we have shown in this review, different synthetic approaches can be used to build up a wide variety of cyclic structures. Most of these approaches are based on stereoselective syntheses using chiral auxiliaries and the selection of the most appropriate synthetic methodology depends on the type and size of the ring in question.

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Appendix A. Abbreviations

Ac=CH_3CO
Acc=1-aminocyclopropanecarboxylic acid
Ac_nc=1-aminocycloalkanecarboxylic acid
Ac_3c=1-aminocyclopropanecarboxylic acid
Ac_4c=1-aminocyclobutanecarboxylic acid
Ac_5c=1-aminocyclopentanecarboxylic acid
Ac_6c=1-aminocyclohexanecarboxylic acid
Ac_7c=1-aminocycloheptanecarboxylic acid
Ac_8c=1-aminocyclooctanecarboxylic acid
Ac_9c=1-aminocyclononanecarboxylic acid
ACPD=1-aminocyclopentane-1,3-dicarboxylic acid
ACPT=1-aminocyclopentane-1,3,4-tricarboxylic acid
Aic=1-aminoindane-2-carboxylic acid
AIMSA=aminoiminomethanesulfonic acid
APCD=4-aminopyrrolidine-2,4-dicarboxylic acid
Atc=1-aminotetraline-2-carboxylic acid
BTEAC=benzyltriethylammonium chloride
BEMP=2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,2,3-diazaphosphorine
BINAP=2,2′-bis(diphenylphosphino-1,1′-binaphthyl)
Bn=$C_6H_5CH_2$
Boc=$(CH_3)_3COCO$
Brop=bromotris(dimethylamino)phosphonium hexafluorophosphate
Bu=$CH_3CH_2CH_2CH_2$
^{t}Bu=$(CH_3)_3C$
Bz=C_6H_5CO
CC=column chromatography
c_3Arg=1-amino-2-(2-guanidinoethyl)cyclopropane-1,2-dicarboxylic acid
c_3Asp=1-aminocyclopropane-1,2-dicarboxylic acid
c_3Leu=1-amino-2-isopropylcyclopropanecarboxylic acid
c_3Met=1-amino-2-methylthiomethylcyclopropanecarboxylic acid
c_3Phe=1-amino-2-phenylcyclopropanecarboxylic acid
c_6Phe=1-amino-2-phenylcyclohexanecarboxylic acid
CPO=chloroperoxidase
Cy=cyclohexyl
DAST=diethylaminosulfur trifluoride
dba=dibenzylideneacetone
DBU=1,8-diazabicyclo[5.4.0]undec-7-ene
DCC=dicyclohexylcarbodiimide
de=diastereomeric excess
DEAD=diethyl azadicarboxylate
DEC=1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
DIBAH=diisobutylaluminium hydride
DMAP=4-dimethylaminopyridine
DMF=dimethylformamide

DMPDAP=1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine
DMSO=dimethylsulfoxide
DPPA=diphenylphosphorylazide
dppe=1,2-bis(diphenylphosphino)ethane
DPM=diphenylmethyl
dr=diastereomeric ratio
ds=diastereoselectivity
ee=enantiomeric excess
Et=CH_3CH_2
FC=flash chromatography
Fmoc=9-fluorenylmethoxycarbonyl
KHMDS=potassium hexamethyldisilylamide
HOBt=*N*-hydroxybenzotriazole
HMPT=hexamethylphosphorus triamide
HPLC=High Performance Liquid Chromatography
Ipc=isopinocampheyl
LDA=lithium diisopropylamide
Leu=leucine
LiHMDS=lithium hexamethyldisilylamide
LTMP=lithium 2,2,6,6-tetramethylpiperidine
MCPBA=*m*-chloroperoxybenzoic acid
Moc=CH_3OCO
Ms=CH_3SO_2
Mtr=4-methoxy-2,3,5-trimethylbenzenesulfonyl
NBS=*N*-bromosuccinimide
NIS=*N*-iodosuccinimide
NMP=1-methyl-2-pyrrolidinone
NMO=4-methylmorpholine *N*-oxide
PDC=pyridinium dichromate
PPA=polyphosphoric acid
Ph=C_6H_5
Phe=phenylalanine
PhthN=phthalimidoyl
Pr=$CH_3CH_2CH_2$
^{i}Pr=$(CH_3)_2CH$
PS=*Pseudomonas cepacia*
PLE=pig liver esterase
PMB=*p*-methoxybenzyl
PTC=phase transfer catalyst
Py=pyridine
rd=diastereomeric ratio
Ses=β-trimethylsilylethanesulfonyl
Su=succinimide
TBAB=tetrabutylammonium bromide
TBAF=tetrabutylammonium fluoride
TBDMS=*tert*-butyldimethylsilyl

TBDPS=*tert*-butyldiphenylsilyl
TBHP=*tert*-butylhydroperoxide
TCDI=thiocarbonyldiimidazole
TES=triethylsilyl
TEOC=trimethylsilylethoxycarbonyl
TIPS=triisopropylsilyl
Tf=CF_3SO_2
Tic=1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
TFA=trifluoroacetic acid
THF=tetrahydrofuran
TMS=trimethylsilyl
Ts=*p*-toluensulfonyl
Z=$C_6H_5CH_2OCO$

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