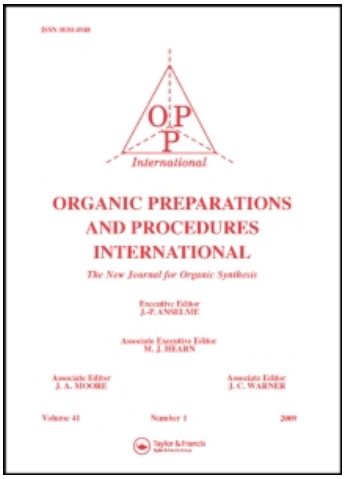


## Organic Preparations and Procedures International

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

# HETEROSUBSTITUTED CARBOCYCLIC α-AMINO ACIDS. A REVIEW

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**To cite this Article** Gelmi, M. L. and Pocar, D.(2003) 'HETEROSUBSTITUTED CARBOCYCLIC α-AMINO ACIDS. A REVIEW', Organic Preparations and Procedures International, 35: 2, 141 — 205

**To link to this Article: DOI:** 10.1080/00304940309355832

**URL:** http://dx.doi.org/10.1080/00304940309355832

ORGANIC PREPARATIONS AND PROCEDURES INT., 35 (2), 141-205 (2003)

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## INTRODUCTION

In recents years,[1] increased attention has been focused on the preparation of carbocyclic α-amino acids (Acc) characterized by α,α-substitution which improves stability towards hydrolytic metabolic degradation. Furthermore, the conformational rigidity and the presence of a further substituent on the ring allow for the formation of stereoisomeric derivatives whose interest is related to the attempts to clarify the conformational role of the substituent in bioreceptorial interactions.[1c,2] These structural features make carbocyclic amino acids important biological targets both as single molecules and as components of bioactive peptides in place of natural amino acids. In these cases, important changes in peptide conformation were observed and consequent change of interaction with enzymatic active site produces a change of bioactivity.[3]

As evinced by the increasing number of papers in the literature, a great deal of effort has been expended in the preparation of carbocyclic amino acids unsubstituted on the ring or substituted with alkyl or aryl groups.[1] Recently, increased attention as been focused on the preparation of the above compounds having one or more heterosubstituents linked to the ring. Heteroatoms such as oxygen, sulfur and nitrogen at the β- or γ-position allow the acquisition of constrained amino acids in which the skeleton of a natural amino acid is included. The presence of more than one heteroatom allows to change the polarity of the amino acid with consequent change of bioavailability. For example, a new and very promising research field is related to the preparation of hydroxy- and polyhydroxycarbocyclic amino acids, which are considered mimetic of carbohydrates but are characterized by a greater metabolic stability. The presence of a phosphonate group is very important in amino acids having agonist or antagonist activity against amino acid receptors in the CNS system. Furthermore, heterosubstituted carbocyclic amino acids have been used as the key starting materials for the preparation of other classes of non-heterosubstituted amino acids, which are usually bioactive molecules, exploiting the reactivity of the heterosubstituent.

## I. GENERAL CONSIDERATIONS

The aim of this review is to present an as complete description as possible and classification of synthetic methodologies of the known carbocyclic amino acids (generally defined as $Ac_nc$) bearing one or more substituents linked to the carbocyclic ring through a heteroatom. To facilitate the location of an item of interest, the carbocyclic amino acids are classified according to ring size. Accordingly, the main sections consider 1-aminocyclopropane- ($Ac_3c$), 1-aminocyclobutane- ($Ac_4c$), 1-aminocyclopentane- ($Ac_5c$), 1-aminocyclohexane-($Ac_6c$), 1-aminocycloheptane-1-carboxylic acids ($Ac_7c$), respectively. Mention is made also of the more representative classes of the corresponding bicyclic compounds, *i.e.* 2-aminobicyclo[3.1.0]hexane- ($Ac_{[3.1.0]}c$), 2-aminobicyclo[2.2.1]heptane- ($Ac_{[2.2.1]}c$) and 2-aminobicyclo[2.2.2]octane-2-carboxylic acids ($Ac_{[2.2.2]}c$).

A further classification is by the different heteroatom substituents. Thus in each chapter, sections are to be found dedicated to amino acids substituted with halo, nitrogen, oxygen, sulphur and phosphorus groups. For each compound or group of compounds, methods of synthesis are detailed.



Clearly, the above classification does not allow the grouping of the synthetic methodologies. However, this is of little importance because only a few general strategies were used to obtain the basic ring of 1-aminocycloalkane-1-carboxylic acids. Many methodologies are specific and, though important by themselves, they have been used only in isolated cases. Accordingly they cannot be incorporated in general schemes. The more general and wide used synthetic processes are four and are indicated as methods A, B, C, D listed below. In the text, for each described procedure, the specific method has been indicated whenever possible.

*1. Transformations and derivatization reactions of pre-existing cyclic compounds (Meth. A).* This method was used mainly for the preparation of $Ac_4c$, $Ac_5c$, $Ac_6c$, $Ac_{[2.2.1]}c$ and $Ac_{[2.2.2]}c$ compounds. The good availability of suitably functionalised starting compounds is essential.

*2. Cyclocondensations reactions of open-chain compounds (Meth. B).* Not surprisingly, this methodology is the most general one and offers a large number of possibilities to easily produce all the rings from the three-membered to the six-membered and also [3.1.0]-membered ones. The necessary functional groups are easily created during the cyclization reaction.

*3. Cycloaddition reactions (Meth. C).* They appear to be used as the method of choice for the direct or indirect obtention, in stereocontrolled way, of three-membered rings (diazo compounds and alkenes), six-, [2.2.1]- and [2.2.2]-membered rings, (Diels-Alder reaction of substituted dienes with functionalised dienophyles).

*4. Ring closing metathesis (RCM) (Meth. D).* This procedure has been used for

preparing rings from five-membered to seven-membered.

In general, the functionalization with the amino acid moiety of the ring was done: a) both for methodology A and B using *i)* the Strecker or Bucherer-Berg reactions, when starting from a ketone or *ii*) by the classical Hofmann or Curtius rearrangements when starting from dicarboxylic acid derivatives;

b) for methodology C using *i)* conditions a) indicated above or *ii*) using a dienophile containing the amino acid moiety;

c) for methodology D using chiral bislactim compounds and hydrolysis after RCM reaction.

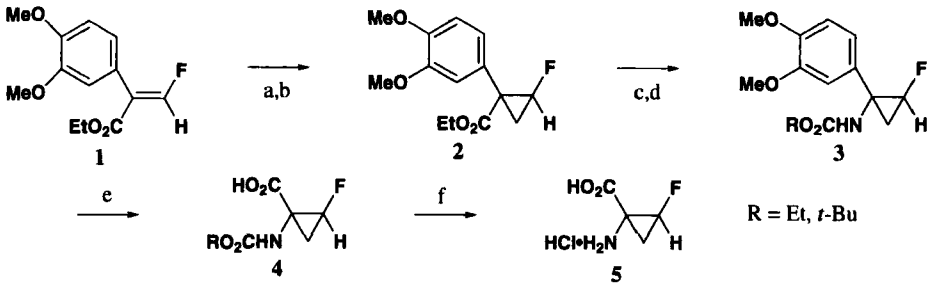
## II. 1-AMINOCYCLOPROPANE-1-CARBOXYLIC ACIDS

Two general and useful synthetic approaches have been used for the preparation of 1-aminocyclopropanecarboxylic acids, namely the reaction of olefin derivatives with diazo compounds (Meth. C) and the intramolecular cyclocondensation reaction (Meth. B). As substituents, both halogen, oxygen and sulfur atoms have been linked to the ring. Cycloaddition reactions of diazomethane to readily available heterosubstituted alkylideneoxazolones (*Scheme 3*) is probably the method of choice for producing cyclopropane amino acids. Procedures are straightforward and yields are generally satisfactory. In general, a medium *cis/trans* diastereoselection is observed in favor of the *cis* isomer. Using Meth. C a single example of chiral synthesis of $Ac_3c$ compounds was reported starting from chiral acrylates (*Scheme 3*). Two examples on the use of Meth. B were reported. In this case starting from a chiral chain good results in term of enantioselection were achieved (*Scheme 7*). It is to be underlined that with the exception of halogen-substituted compounds, no examples of non protected amino acids were reported probably due to the unstability of heterosubstituted rings.



### *1. Halo $Ac_3c$ Compounds*

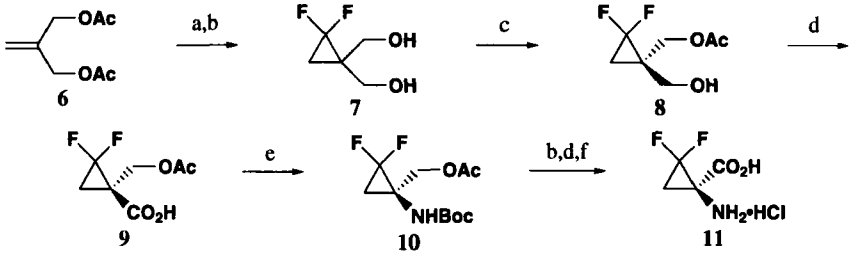
The main synthetic approach to 2-halo compounds follows methodology C and reaction of a halocarbene with an olefin or reaction of a haloolefin and diazomethane were used. Monofluoro- and 2,2-difluorocyclopropane carboxylic acids have been prepared by relatively simple procedures (*Schemes 1* and *2*). However, only in the second case an optically active compound was obtained. Recently[4] the synthesis (Meth. C) of diasteromeric 2-fluoro-1-amino-cyclopropane-1-carboxylic acids **5** ($FAc_3c$) was reported starting from the 2-aryl-3-fluoroacrylate **1** which was reacted with diazomethane giving a mixture of *trans*- and *cis*-cyclopropane carboxylic esters **2** (*trans/cis* = 3:1) (*Scheme 1*). After transformation of the ester group into the protected amino group (compounds **3**), the aryl group was oxidized giving compounds **4** which were hydrolyzed to amino acids **5**.



a) $CH_2N_2/Et_2O$, 0°C; b) hv, acetone (90%); c) $NH_2NH_2$, $H_2O$, EtOH; d) HCl, $NaNO_2$, then ROH, reflux (54%); e) $NaIO_4/RuCl_3$, $CCl_4$/MeCN/$H_2O$ or $O_3/H_2O_2$, $CH_2Cl_2$, reflux (95%); f) R = *t*-Bu: aq. HCl/AcOEt; R = Et: HBr/AcOH, reflux (30%)

**Scheme 1**

The enantioselective synthesis of *R*-1-amino-2,2-difluorocyclopropane-1-carboxylic acid **11**[5] was achieved according to Meth. C starting from diacetate **6** which was reacted with difluorocarbene giving **7** (*Scheme 2*).

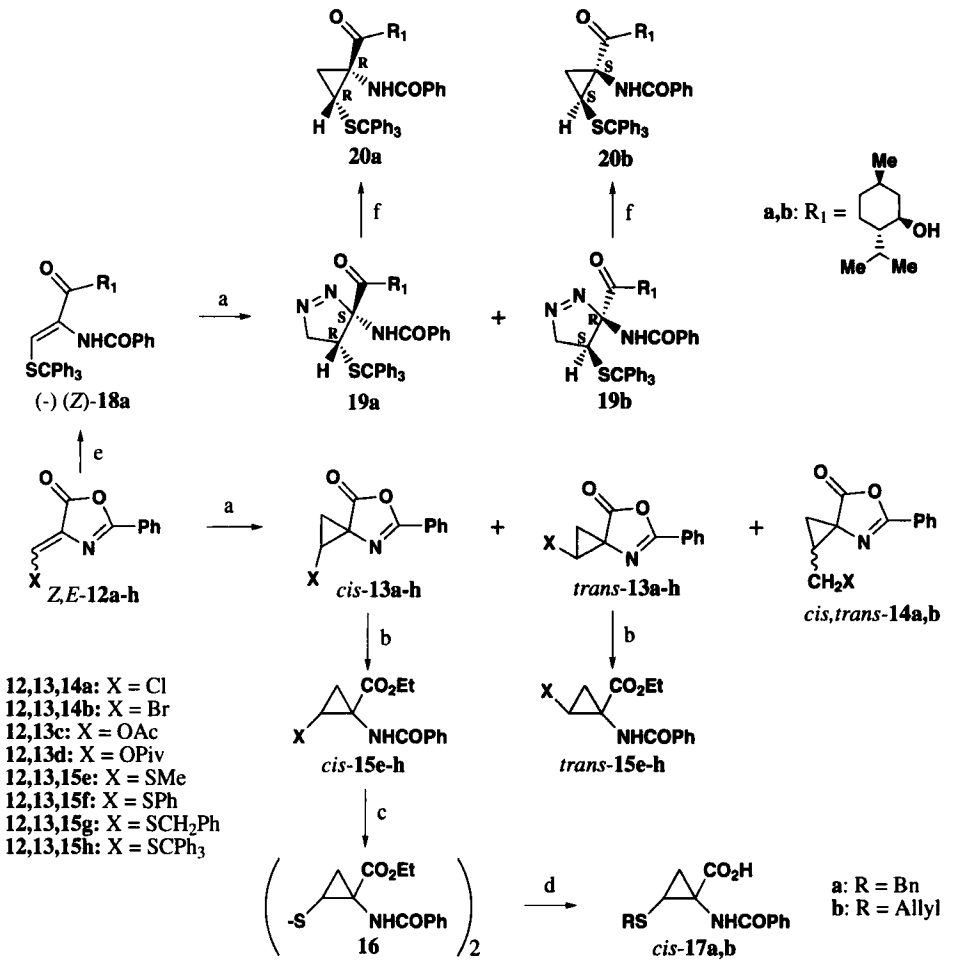


a) $ClF_2CCO_2Na$, diglyme, 180°C; b) $K_2CO_3$, MeOH/$H_2O$ (45%); c) Vinyl acetate, PS (96%); d) Jones oxid.; e) DPPA/*t*-BuOH/TEA, benzene, reflux; f) aq. HCl/AcOEt (46%)

**Scheme 2**

The lipase-catalyzed asymmetric acetylation with Amano PS from *Pseudomonas cepacia* of the pro-chiral alcohol **7** gave the chiral monoacetate **8** in excellent yield and enantioselectivity (88% *ee*). Compound **8** was transformed into **11** according to the synthetic procedure depicted in *Scheme 2*.

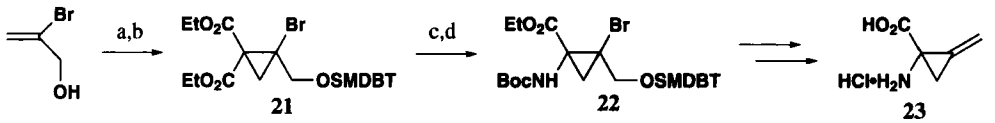
The synthesis of chloro and bromo spiro compounds **13a,b** (*Scheme 3*), the precursors of 2-chloro- or 2-bromo $Ac_3c$ compounds, was reported[6] using the 4-halomethylene-2-phenyl-5(4*H*)oxazolones **12a,b**. The reaction resulted in the formation of a mixture of *cis*- and *trans*-spiro compounds **13a,b**. In both cases the diazomethane insertion by-products **14a,b** were obtained. The formation of compounds **13a** was favored starting from the chloro derivative **12a** (73%; *cis/trans* = 20:53). This ratio has been revised (*cis/trans* = 53:20).[6d] By way of contrast, starting from **12b**, compounds **13b** were obtained as the minor products (17%; *cis/trans* = 15:2.5). Two other synthetic approaches to bromo derivatives were reported. The 2-bromo $Ac_3c$ derivative **22**[7] is the synthetic intermediate for the preparation of 1-amino-2-methylenecyclopropane-1-carboxylic acid **23**, an $Ac_3c$ deaminase inhibitor. As depicted in *Scheme 4* compound




a) $CH_2N_2$, $CH_2Cl_2$; b) EtOH, DMAP (60-77%); c) $I_2$, EtOH (97%); d) RBr, CTACl, NaOH, THF/$H_2O$, amino-iminomethanesulfinic acid (67-74%); e) (-)-menthol, $(Et_2SnCl)_2O$, benzene, reflux (78%); f) 150°C (65%)

**Scheme 3**

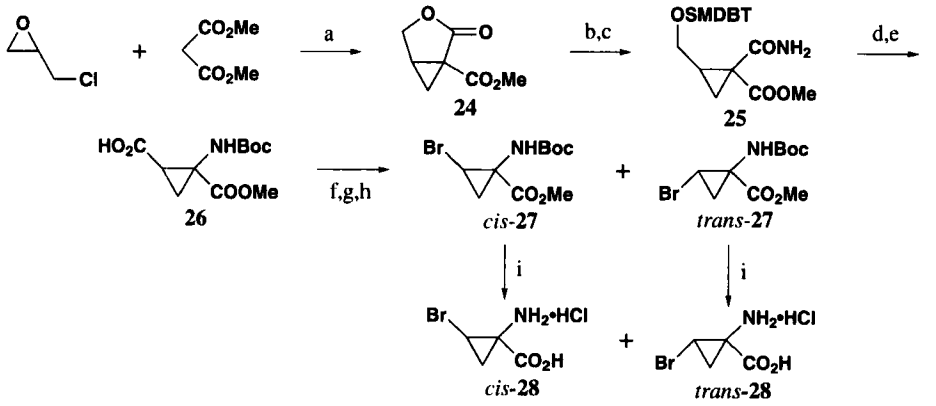
**21** was obtained (Meth. C) from 2-bromoprop-2-en-1-ol which was reacted with diazomalonate. The amino acid derivative **22** was obtained from compound **21** by the Curtius reaction.




a) TBDMSCl; b) $N_2C(CO_2Et)_2$, $Rh(OAc)_2$ (75%); c) NaOH, EtOH; d) $ClCO_2Et$, $NaN_3$, then toluene, reflux, then *t*-BuOH, reflux (57%)

**Scheme 4**

A different approach (Meth. B) to introduce the bromine atom on the cyclopropyl ring was followed by Wick *et al.* (*Scheme 5*).[8] By reaction of epichlorohydrin and dimethyl malonate the lactone **24** was obtained which was selectively transformed into the monoamide **25** after

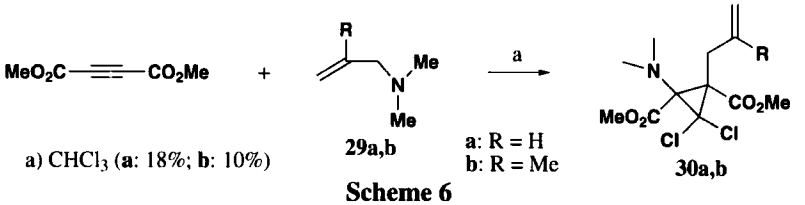



a) MeONa, MeOH; b) $NH_3$/MeOH; c) TBDMSCl; d) $Pb(OAc)_4$, *t*-BuOH, then $Bu_4NF$; e) $RuCl_3/NaIO_4$ (38%); f) NMM/$ClCO_2i$-Bu, -15°C; g) NHPT, -15°C; h) ALBN/$BrCCl_3$, reflux (52%); i) 6N HCl, 80°C (*cis*: 68%; *trans*: 75%)

**Scheme 5**

reaction with ammonia and protection of the hydroxy group. The amido group was transformed into the protected amino group and, after deprotection of the hydroxy group and its oxidation under mild conditions, compound **26** was obtained. By the radical decarboxylative bromination, according to Hunsdiecker reaction, the bromo compounds *cis*- and *trans*-**27** (3:1) were obtained and separated. Complete hydrolysis allowed the isolation of the amino acids *cis*- and *trans*-**28**. Comparing this synthetic procedure to those reported in *Scheme 3* it has to be observed that the overall yields of protected amino acid derivatives **13b** and **27** are comparable (less than 20%), but the diastereoselection is better when starting from oxazolone.

The formation of dichloro amino acids **30a,b**, as by products, was reported by Schwas *et al.*[9] from methyl acetylenedicarboxylate and dimethylallylamines **29** in $CHCl_3$ as the solvent and a dichlorocarbene donor (Meth. C) (*Scheme 6*).

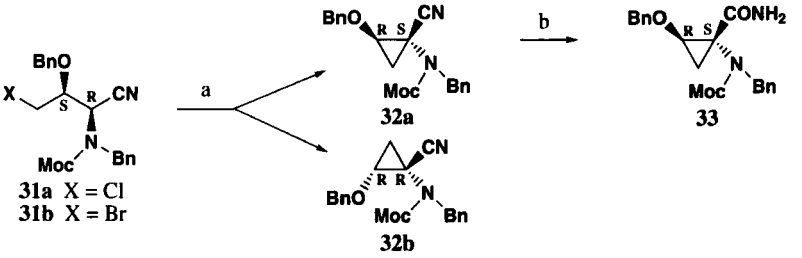



a) $CHCl_3$ (**a**: 18%; **b**: 10%)

**Scheme 6**

### *2. Oxygen $Ac_3c$ Compounds*

No free OH-substituted amino acids have been reported. Following Meth. B, Cativiela *et al.*[10] reported the diastereoselective synthesis of chiral (1*S*,2*R*)-2-benzyloxy derivative **33** (*Scheme 7*) from the corresponding nitrile **32a**. The latter was obtained with compound **32b** in good diastereomeric excess by an intramolecular cyclization of chiral compounds **31a** or **31b** (**32a/32b**, 98:2) under basic conditions. However, nor nitriles **32** nor the amide **33** have been hydrolyzed to the corresponding acids.




a) KOH, DMF (82%); b) $H_2O_2$, NaOH, EtOH (87%)

**Scheme 7**

A similar situation is depicted in *Scheme 3*. According to Meth. C, the 4-acyloxymethylene-2-phenyl-5(4*H*)oxazolones **12c,d**[6c] can be used for the preparation of 2-acyloxy-1-aminocyclopropanecarboxylic acid derivatives **13c** and **13d** which were obtained in 76% and 73% yield, respectively which low diastereoselection (*cis/trans* = 34:42 and 43:30, respectively).

### *3. Sulfur $Ac_3c$ Compounds*

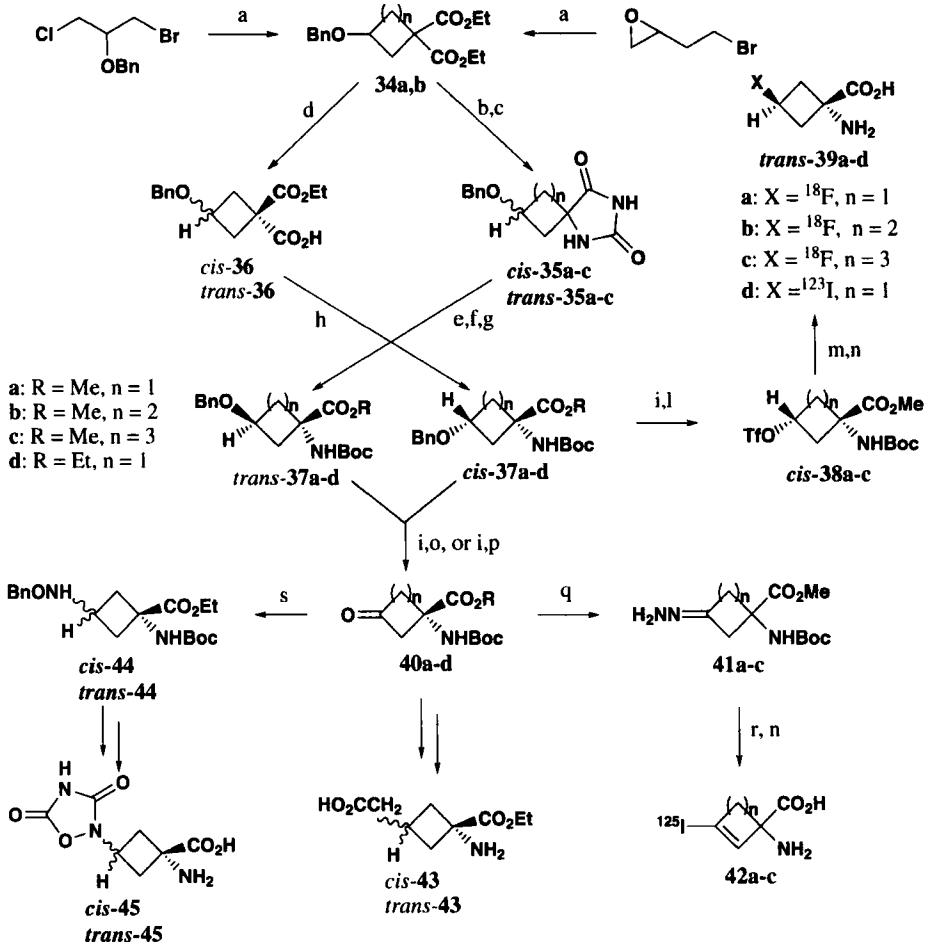
Cyclopropane amino acids bearing a RS substituent have been prepared in fair number by relatively short procedures and with appreciable diastereo- and enantioselectivity. Examples are reported in *Scheme 3*.[11] In fact, compounds **13,15,17** were obtained according to Meth. C from 4-alkyl- or 4-phenylsulfanylmethylene-2-phenyl-5(4*H*)-oxazolones *Z/E*-**12e-h** which, on reacting with diazomethane (affording spirooxazolones **13e-h**: *cis/trans* = 3:1 to 5:1 ratio) and ethanolysis, were transformed into compounds **15e-h**. The trityl derivative **15h** is useful for the preparation of a large number of 2-alkylsulfanyl derivatives **17**. In fact, on treating *cis*-**15h** with iodine, the disulfide derivatives **16** were obtained and alkylated under PTC conditions in the presence of amino-iminomethanesulfinic acid, as the reductant, giving the acids **17a,b**. The same authors[12] have achieved the asymmetric synthesis of the 1-amino-2-*S*-trityl $Ac_3c$ derivatives from chiral (-)-menthyl aminoacrylate (*Z*)-**18a** obtained as depicted in *Scheme 3*. The reaction of compound **18a** with diazomethane gave two stable diastereomeric pyrazolines **19a** and **19b** (1:1.4) with *cis* relationship between nitrogen and sulfur atoms. On melting at 150° for ten minutes, the pyrazolines **19a** and **19b** gave cyclopropyl compounds 1*R*,2*R*-**20a** and 1*S*,2*S*-**20b**. This transformation occurs with retention of configuration at C-α of the amino acid. The synthesis of enantiomeric compounds of **20a** and **20b** was effected.

## III. 1-AMINOCYCLOBUTANE-1-CARBOXYLIC ACIDS

The 3-heterosubstituted $Ac_4c$ compounds are highly representative and the most common method for their preparation consists in the use of functionalized heterosubstituted cyclobutanes (*i.e.* heterosubstituted cyclobutanones or cyclobutanecarboxylic acids from a cyclocondensation reaction of heterofunctionalized chains; Meth. B). A different approach takes advantage of the use of heterofunctionalized bicyclo[1.1.0]butanes (Meth. A).

### *1. Halo $Ac_4c$ Compounds*

The method for preparing 3-fluoro derivatives was applied only to labeled halogen derivatives and this approach (triflate exchange) (*Scheme 8*) can be used also for larger-ring compounds, thus appearing of general scope. Diastereomeric separation is possible. Similarly, a




a) NaH, $CH_2(CO_2Et)_2$, dioxane; b) $NH_4OH$; c) NaOCl, $H_2O$, 0°C (60%); d) KOH/EtOH, $H_2O$, then 6M HCl (72%); e) $Ba(OH)_2$, then $H_3O^+$; f) $(t\text{-BuCO})_2O$, MeOH, TEA, 60°C; g) R = Me: $CH_2N_2$, $Et_2O$ (n = 1: 30%); h) R = Et: DPPA, TEA, toluene 80°C, then *t*-BuOH, 110°C (58%); i) $H_2$, Pd/C, MeOH (89%); l) $(Tf)_2O$, $CH_2Cl_2$, Py (64%); m) X = $^{18}F$: $K^+/^{18}F^-$; X = $^{123}I$: [$^{123}I$]-NaI; K222, $H_2O$/MeCN; n) 6M HCl, X = F: 30%; o) R = Me: PCC, DMF; p) R = Et: $RuO_4$, $NaIO_4$, $H_2O/CCl_4$ (80%); q) $NH_2NH_2$, DBN, EtOH, reflux; r) 3% $H_2O_2$, [$^{123}I$]-NaI, then 0.1N HCl; s) $BnONH_2$, $NaBH_3CN$, MeOH (50%) **Scheme 8**

3-iodo compound was prepared. Another way to the same iodo compound was indicated, probably of low preparative value (no indication of yield and absolute configuration). The new tumor-avid labeled 1-amino-3-fluorocyclobutane-1-carboxylic acid ($FAc_4c$) *trans*-**39a** has been synthesized[13] from **34a**, obtained by reaction of diethyl malonate and 1-chloro-2-benzyloxy-3-

bromopropane (Meth. B). Compound **34a** gave a mixture of diastereomeric hydantoins **35a** (70%, *cis/trans* = 75:25) which were separated. The main compound *cis*-**35a** was transformend into the aminoester *cis*-**37a** (*Scheme 8*). Deprotection of the oxygen atom and its functionalization with a triflate group gave *cis*-**38a**. Reaction with fluoride ion and hydrolysis gave the labelled compound *trans*-**39a**. In line with the above synthetic procedure the labelled *trans* 1-amino-3-iodocyclobutane-1-carboxylic acid **39d** was prepared.[14]

The same authors[14] report the synthesis of the labelled unsaturated iodo derivative **42a** from ketone **40a**, through the corresponding hydrazone **41a**. Treatment of this compound with iodine and hydrogen peroxide, deprotection of amino and carboxylic groups gave **42a**.

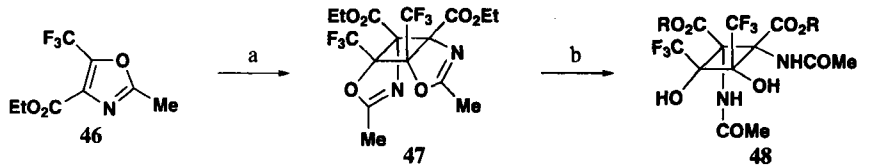
### *2. Nitrogen $Ac_4c$ Compounds*

A mixture of *cis* and *trans* protected 1,3-diaminocyclobutane-1-carboxylic acid derivatives **44** (1:1) were prepared from ketone **40d** by reacting with *O*-benzylhydroxylamine in the presence of cyanoborohydride. They are precursors of the new selective methatropic glutamic acid (mGluR5a) receptor agonists **45**. (*Scheme 8*)[15] Compound **40a** was used for the preparation of hydrazone **41a** (*Scheme 8*).[14]

### *3. Oxygen $Ac_4c$ Compounds*

An alternative way to 3-oxygen substituted protected amino acid **37** (**37d** R = Et) was reported from **34a** (*Scheme 8*)[16] which consists in selective hydrolysis to the monocarboxylic acids *cis*- and *trans*-**36**. The Curtius reaction on this mixture followed by reaction with *t*-BuOH produced the corresponding *N*-protected diastereomeric amino acids **37d**. The preparation of compound **37d** *via* Curtius transposition is more efficient (43% overall yield) to respect of the preparation of **37a** (13%) *via* hydantoin **35**. The mixture of compounds **37d**, after deprotection of the oxygen atom and oxidation afforded the 3-keto derivative **40d** as precursor for the preparation of bioactive amino acids *cis*- and *trans*-**43**.

A synthesis of uncommon dihydroxy-$Ac_4c$ compounds was reported[17] from oxazole **46** dimerized to **47** (*Scheme 9*). The treatment of the latter with hydrogen bromide gave the protected amino acids **48** (quantitative yield, *cis* relationship between the nitrogen and oxygen atoms). Though interesting in itself, the synthetic procedure to **48** is not of general scope.

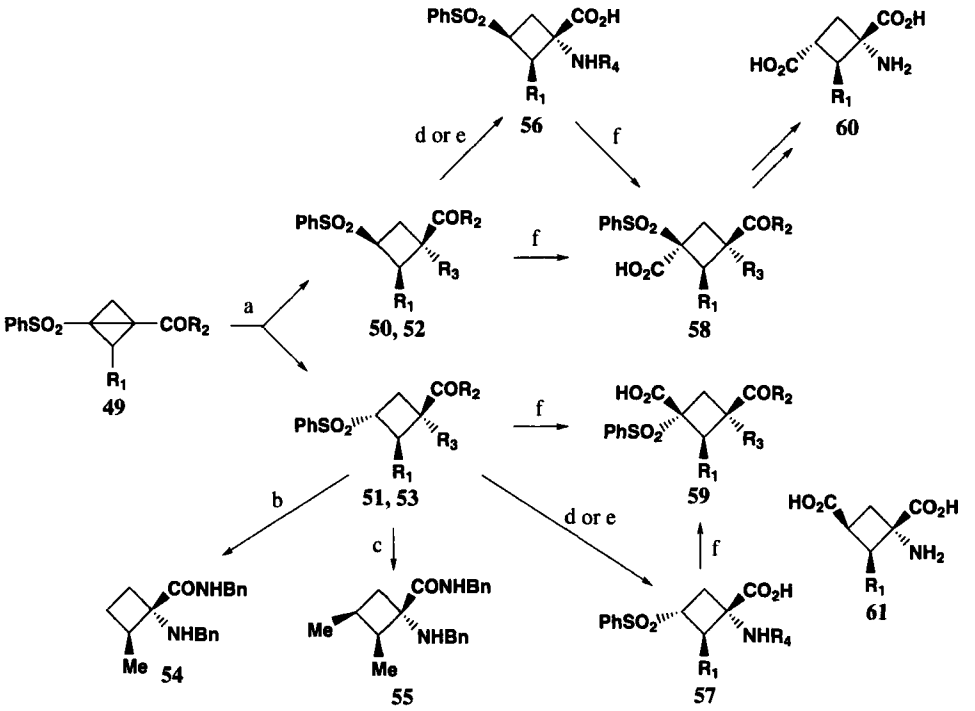



a) MeCN, hv; b) 48% HBr

**Scheme 9**

### *4. Sulfur $Ac_4c$ Compounds*

Several derivatives of 3-phenylsulfonyl-1-aminocyclobutane-1-carboxylic acid, which are the precursors for the preparation of the bioactive 1,3-dicarboxylic amino acids **60** and **61**, were prepared by rearrangement of 3-(phenylsulfonyl)bicyclo[1.1.0]butane-1-carboxylic acid derivatives **49** (Meth. A)[18] (*Scheme 10*).




$R_1$ = H, Me, *i*-Pr, $R_2$ = OH, OMe, OEt, NHBn, $N(CH_2)_5$. **50,51** $R_3$ = NHBn; **52,53** $R_3$ = $N_3$

a) $BnNH_2$, 140°C (56-90%) or $NaN_3$, DMF or NMP, 85°C, TMGA (80-95%); b) Na/Hg, MeOH/THF; c) BuLi, -78°C, MeI, then method b; d) $R_4$ = H: Pd/C, $HCO_2NH_4$, MeOH, 50°C (60-70%); e) $R_4$ = COPh: method d, then PhCOCl (60-70%); f) BuLi, -78°C, $CO_2$, THF

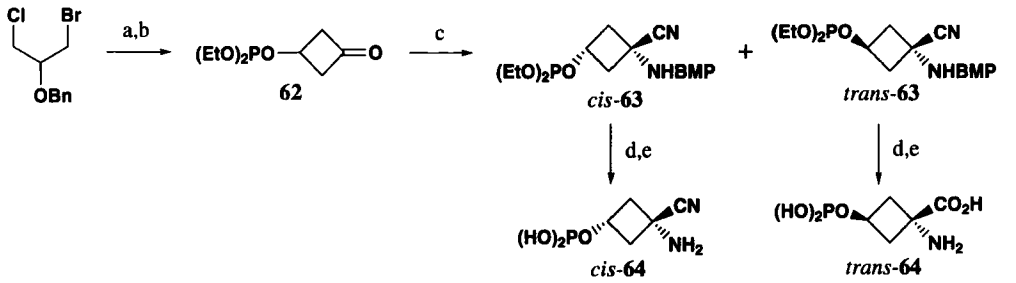
**Scheme 10**

The addition of a nitrogen nucleophile (*i.e.* benzylamine or sodium azide) to **49** gave the diastereomeric amino compounds **50** and **51** or the corresponding 1-azido derivatives **52** and **53**. In many cases the addition reaction of amine was diastereoselective, the *trans-S,N* products **50** being preferred according to *cis* addition of the amino group and the proton delivered by the amino group itself. Instead, the addition of the azido group gave a mixture of *trans-S,N* and *cis-S,N* stereomers. However, when the azidation reaction was applied to the free acids (**49**: $R_2$ = OH) in DMF in the presence of tetramethylguanidine, only the *cis-S,N* compound **53** ($R_2$ = OH, $R_3$ = $N_3$) was detected. As an example, the benzylamine derivative **51** ($R_1$ = Me, $R_2$ = NHBn, $R_3$

= NHBn) was desulfurated producing **54** or alkylated at C-3 and then desulfurated producing **55**. The best method to reduce the azido group in compounds **52** and **53** consisted of the use of ammonium formate in methanol in the presence of palladium giving the amino acid derivatives **56** and **57** ($R_4$ = H). Finally, C-3 carbon on the cyclobutyl ring was carboxylated by treating both the azido acids **52** or **53** and the *N*-protected compounds **56** or **57** ($R_4$ = COPh) with *n*-BuLi at -78° and carbon dioxide. A mixture of *cis*- and *trans*-acids **58,59** ($R_3$ = $N_3$, NHCOPh) was obtained. They were transformed into the dicarboxylic acids **60** and/or **61**.

### *5. Phosphorus $Ac_4c$ Compounds*

The reported procedure, useful for obtaining phosphono amino acids **64** (*Scheme 11*),[19] which are known to act as antagonists at excitatory amino acid receptors, is relatively simple, but




a) $MePO(OEt)_2$, BuLi, THF, -78°C; b) $H_2Pd/C$, then $RuCl_3/NaIO_4$, $CH_2Cl_2$ (45%); c) $PMBNH_2$, NaCN, MeOH/AcOH (53%); d) CAN, MeCN, $H_2O$ or $H_2$, Pd/C; e) 6M HCl (74-76%)

**Scheme 11**

diastereoselection is moderate. In any case, separation of *cis* and *trans* isomers could be accomplished easily. They were synthesized (Meth. A) starting from diethyl 3-oxocyclobutylphosphonate **62**, obtained from 1-chloro-2-benzyloxy-3-bromopropane. The reaction of **62** with *p*-methoxybenzylamine and sodium cyanide producing a mixture of the diastereomers *cis*- and *trans*-**63** (*cis/trans*, 3:2). The isomers were separated and the *p*-methoxybenzyl group was removed under mild oxidative conditions using ceric ammonium nitrate or catalytic hydrogenation giving *N*-unprotected compounds which were hydrolyzed to amino acids *cis*- and *trans*-**64**.

## IV. 1-AMINOCYCLOPENTANE-1-CARBOXYLIC ACIDS

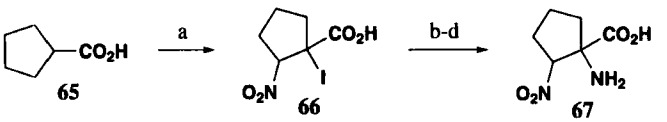
A large number of heterosubstituted $Ac_5c$ compounds were synthesized with functionalization both at C-2 and C-3. Furthermore poly-heterosubstituted compounds were reported. The most common starting materials for 2- or 3-heterosubstituted $Ac_5c$ compounds are cyclopentanones or cyclopentanecarboxylic acids (Meth. A) which were functionalized with a heteroatom. Both RCM reaction (Meth. D) and intramolecular cyclocondensation starting from heterofunctionalized chains (Meth. B) were reported. In this case, as a key precursor, a chiral sugar was used for the preparation of polyhydroxylated compounds.

### *1. Halo $Ac_5c$ Compounds*

2-Halo-1-aminocyclopentanecarboxylic acids are scarcely considered: a single synthesis (besides the 1-chloro isomer) of 2-chlorocyclopentane derivative **89**[20] (*Scheme 15*, see p. 156) was reported (low yields, 16%) from aziridine **88**, obtained from ethyl α,β-cyclopentenecarboxylate **87** and 3-acetoxyaminoquinazolinone. The method for cyclobutane analogs (*Scheme 8*) was applied to 5-membered labelled 3-fluoro derivative *trans*-**39b** and iodo derivative **42b** (n = 2).[14] In this case too, yields and configuration are unknown.

### *2. Nitrogen $Ac_5c$ Compounds*

A relatively straightforward synthesis (no yield) for 1-amino-2-nitrocyclopentanecarboxylic acid **67**, a metabolite of *Aspergillus wentii*, a plant growth inhibitor, was reported by a fermentation process using the above microorganism.[21] The synthesis was also done starting from cyclopentanecarboxylic acid **65**[22] which was transformed (Meth. A) with iodine and $N_2O_4$ into intermediate **66** and then into amino acid **67** (*Scheme 12*). As shown in *Scheme 8* the hydrazone derivative **41b** (n = 2) was obtained. The yield was not given.




65 66 67

a) $N_2O_4$, $I_2$, $Et_2O$, 0°C; b) Pyridine, then $H_2O$/HCl; c) $H_2O$, reflux; d) 31% $NH_4OH$

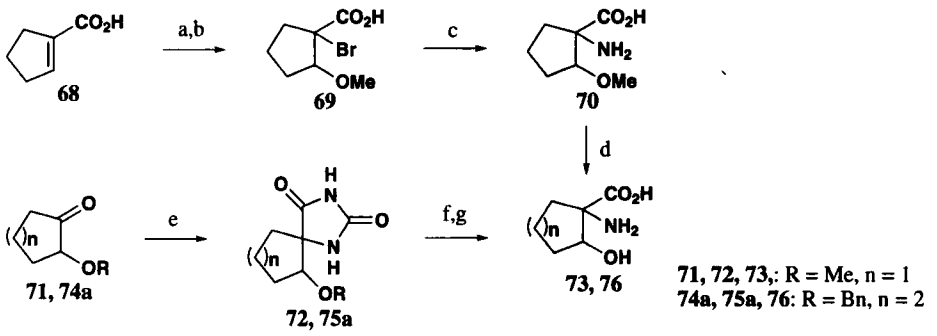
**Scheme 12**

### *3. Oxygen $Ac_5c$ Compounds*

Hydroxy substituted 1-aminocyclopentane-1-carboxylic acids are the most studied family. Syntheses of both 2-, 3- and polyhydroxy derivatives are reported.

#### *i. Substitution at C-2*

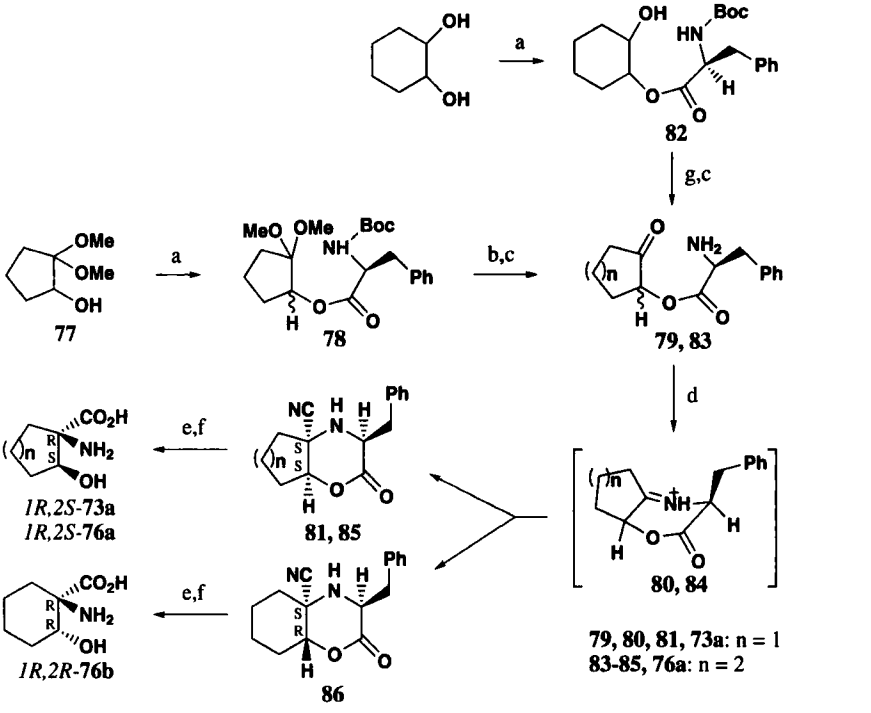
Different synthetic approaches to 2-hydroxy $Ac_5c$ compounds were described. The achiral stereomeric 2-OH compounds **73** were prepared according to *Scheme 13* both starting from 1-cyclopentene-1-carboxylic acid **68** and ketone **71**. Better results were observed starting from **71** both in term of yield and diasteroselection. When **68** (Meth. A) was reacted with $Hg(OAc)_2$ in methanol and then with bromine, compound **69** was obtained. The reaction with ammonia (compound **70**) and hydrolysis gave the amino acids *cis*- and *trans*-**73** in 45% overall yield and in about 1:1 ratio.[23] Instead, the use of the Bucherer synthesis (*Scheme 13*) led to a mixture of diastereomeric amino acids *cis*- and *trans*-**73** with improved yields (60%) and diastereoselection (84:16, the major product having the carboxy and hydroxy groups *cis*).[24] Ketone **71** (Meth. A) on reaction with KCN and $(NH_4)_2CO_3$ afforded the hydantoin **72** which was hydrolyzed under basic conditions and demethylated to **73**.




a) $Hg(OAc)_2$, MeOH; b) KBr, $Br_2$, hν, $H_2O$ (47%); c) $NH_4OH$; d) 49% HI, reflux; e) KCN, $(NH_4)_2CO_3$, EtOH (69%); f) $Ba(OH)_2$, $H_2O$; g) 48% HBr

**Scheme 13**

Two chiral approaches to 2-hydroxy amino acids, having *N,O-cis* relationship, characterized by good diastereo- and enantioselection (*Schemes 14 and 38*) have been reported. Chiral compound 1*R*,2*S*-**73a** (41% overall yield from **78**) (*Scheme 14*) was reported by Ohfune *et al.*[25] starting from 1,1-dimethoxy-2-cyclopentanol (**77**) (Meth. A). Reaction of **77** with *N*-*t*-butoxycarbonyl-L-phenylalanine gave **78** and deprotection of both ketone and amino functional groups

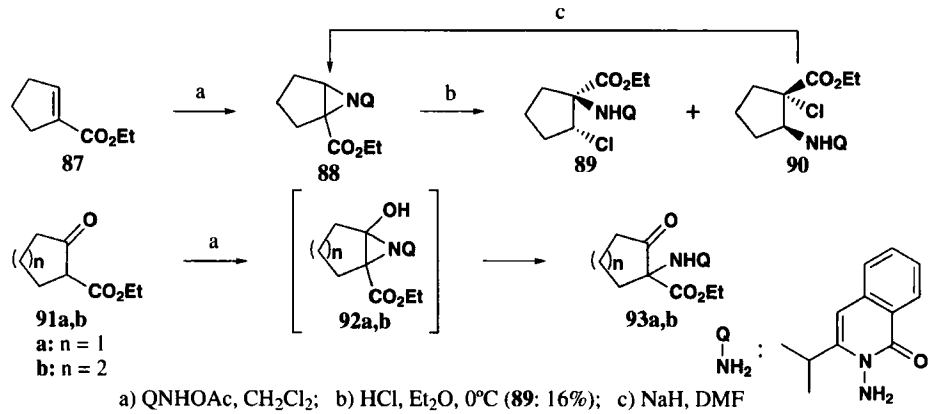



a) Boc-L-Phe, WSCD, DMAP (90%); b) *p*-TSA, acetone; c) TFA (89%); d) n = 1: $MgSO_4$, AcONa, MeCN, then TMSCN, $ZnCl_2$, *i*-$Pr_2O$ (78%); n = 2: NaCN, 2-propanol; e) *t*-buthyl hypochlorite, THF, 0°C, then TEA; f) 12M HCl (60%); g) Jones reagent, acetone

**Scheme 14**

produced compound **79** which was condensed to intermediates **80**. The addition reaction of cyanide ion resulted in good diastereoselection (5*S*,6*S*/5*S*,6*R* = 92:2) and the major isomer **81** was isolated. Removal of the chiral phenylalanyl moiety from the major diastereomer and hydrolysis gave enantiopure amino acid **73a**. The synthesis of the 1*S*,2*R*-enantiomer of **73a** was also reported using D-phenylalanine as chiral auxiliary. The synthesis of chiral β-hydroxy unsaturated $Ac_5c$ compound **232** (*Scheme 38*, see p. 175) was reported starting from chiral bislactim **220a** (Meth. D).[26] Hydrolysis gave amide **231a** which was protected at nitrogen atom giving **231b**. Using the ring-closing methatesis reaction, protected compound **232** was obtained (40% overall yield from **220a**).

The 2-oxo-$Ac_5c$ compound **93a**[20] was obtained using 3-acetoxyaminoquinazolinone (QNHOAc) as nitrogen donor. By reacting with ethyl 2-oxo-cyclopentanecarboxylate **91a** (*Scheme 15*) compound **93a** (77%) was formed through the 2-hydroxyaziridine intermediate **92a**. The synthesis of benzocondensed compounds was also reported.

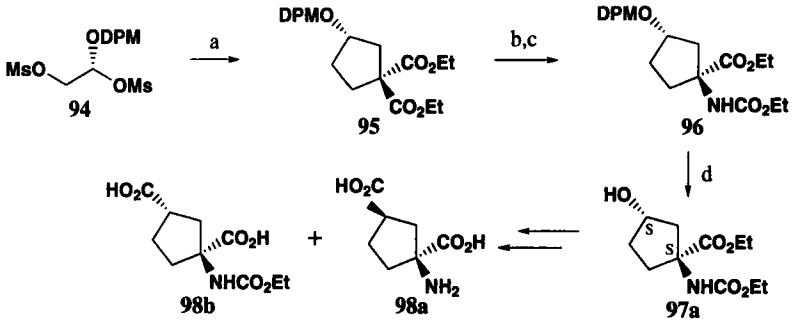



a) QNHOAc, $CH_2Cl_2$; b) HCl, $Et_2O$, 0°C (**89**: 16%); c) NaH, DMF

**Scheme 15**

*ii. Substitution at C-3*

All stereomeric 3-hydroxy compounds and their derivatives have been prepared, with some attention to stereoselective approaches. A simple and highly diastereo- and enantioselective method exists for the preparation of the *S,S* isomer (*Scheme 16*) and a satisfactory procedure has been devised to produce both the *S,S* (the latter less efficiently) and the *S,R* isomer (*Scheme 17*) from relatively common intermediates. According to *Scheme 8* (Meth. B) a mixture of achiral *cis*- and *trans*-3-hydroxy compounds (*O*-benzylated) **37b** were obtained. The *cis*-**37b** derivative was transformed into the triflate derivative *cis*-**38b** and from the *cis/trans* mixture the corresponding ketone **40b** was isolated. Yields were not reported.[14] The 1*S*,3*S*-1-amino-3-hydroxycyclopentanecarboxylic acid derivative **97a** (62% from **94**) was reported by Ma *et al.*[27] (*Scheme 16*) starting from chiral compound **94**, which was cyclized (Meth. B) to the cyclopentyl derivative **95** by reaction with diethyl malonate. The ethoxycarbonyl group *trans* to the DPM group was selectively hydrolyzed.

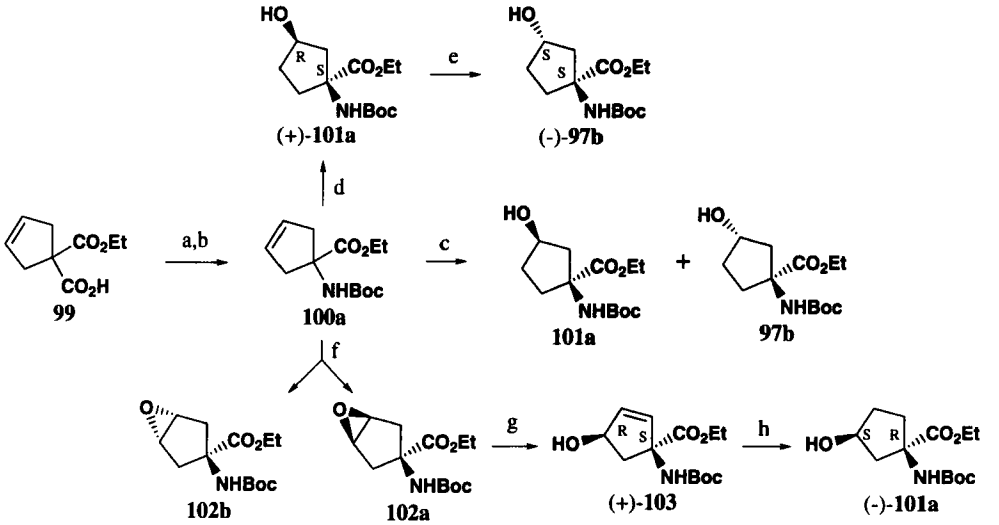



a) $CH_2(CO_2Et)_2$, EtONa/EtOH (70%); b) NaOH, EtOH; c) DPPA, TEA, benzene, reflux, then EtOH (88%); d) $H_2$/Pd, EtOH (100%)

**Scheme 16**

The corresponding acid was converted into the enantiopure carbamate 1*S*,3*S*-**96** by means of a Curtius rearrangement (only 3% of the *cis* isomer was formed). The DPM group is essential for enantioselectivity during the ester hydrolysis. In fact, when benzyl was used as protecting group only a 1:3 *cis/trans* stereomeric ratio was obtained. The hydroxy protecting group was removed giving *N,O-trans*-**97a** which is the precursor of the bioactive 1-amino-1,3-cyclopentanedicarboxylic acids **98a,b**. A different synthetic approach to chiral 3-hydroxy-$Ac_5c$ derivatives was followed by Hodgson[28] (*Scheme 17*) starting from the 1-amino-3-cyclopentenecarboxylic acid derivative **99** (Meth. A) taking advantage of the selectivity in the hydroboration reaction of the double bond assisted by the amide moiety.






a) $(COCl)_2$, $CH_2Cl_2$; b) $NaN_3$, acetone/$H_2O$, then *t*-BuOH, $SnCl_4$, toluene (71%), c) $BH_3$, THF, then $H_2O_2$, NaOH; d) $BF_3$•$Et_2O$, [(+)-IpcBH$_2$]$_2$TMEDA, THF, -40°C, then $H_2O_2$, NaOH (74%); e) AcOH, $Ph_3P$, THF, DEAD, then $K_2CO_3$ (58%); f) MCPBA, TEA, $CH_2Cl_2$ (59%); g) *s*-BuLi, (-)sparteine, $Et_2O$, -78°C (18%); h) $H_2$/Pd, EtOH (78%)

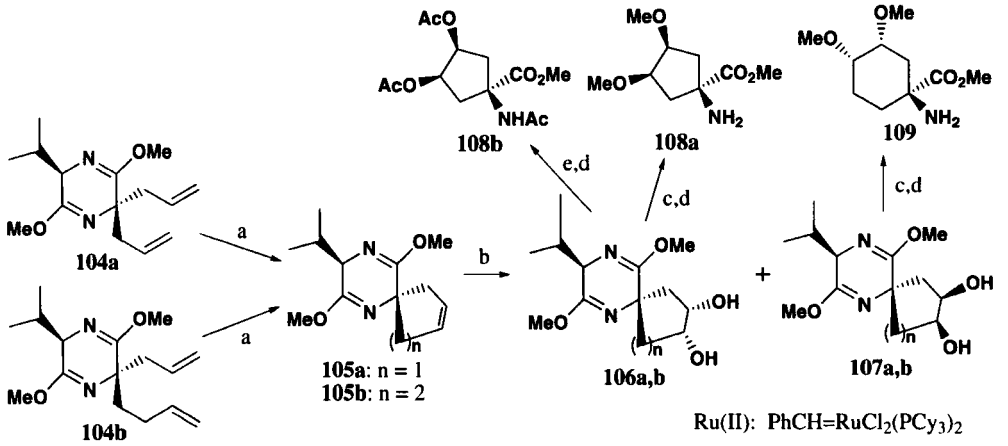
**Scheme 17**

This route appears to be less diastereoselective, but allowed to obtain the *R,S* isomer. Compound **100a** was prepared from **99**, *via* the acid chloride and subsequent Curtius rearrangement. When reacted with $BH_3$ and then oxidized, compound **100a** gave, after a few minutes, a mixture of diastereomeric hydroxy derivatives **101a** and **97b** in 77:23 ratio. Prolonging the reaction time favored the formation of compound **101a** (**101a/97b**: 30 min: 84:16; 17 h: 95:5) with lowering of yield (10 min: 84%; 30 min: 73%). Different reagents and reaction conditions were tested for the asymmetric hydroboration reaction of **100a**. The best reagent was (+)-$IpcBH_2$ which gave compound *1S,3R*-**101a** (48% ee; 94%) having the *cis* relationship between nitrogen and oxygen atoms. The enantiomer *1R,3S*-**101a** could be obtained using (-)-$IpcBH_2$. Alcohol *1S,3R*-**101a** was converted into chiral compound *1S,3S*-**97b** (56% from **100a**) by Mitzunobu isomerization at C-3 carbon. An alternative, but less efficient diastereo- and enantioselective synthesis of compound (-)-**101a** (Meth. A) was followed by the same authors starting from **100a** which was epoxidized giving a mixture of two diastereomeric epoxides **102a** and **102b** (85:15). The major isomer **102a** was rearranged to the allylic alcohol *1S,3R*-**103** in very low yield (18%) and enantiomeric excess (33%) using s-BuLi/(-)-sparteine. After hydrogenation, the alcohol **103** was transformed into chiral compound *1R,3S*-**101a**, the precursor of dicarboxylic amino acid **98a**. The synthesis of 3-keto amino acid **123** was reported by oxidation of compounds **97** or **101b** (*Scheme 22*, see p. 161).[35]



*iii. Substitution at C-3,4*

Methods to 3,4-dihydroxy compounds are reported, but only the compounds having *cis* relationship between the OH substituents are known. Moreover, in two cases (*Scheme 18*) only protected OAc and OMe derivatives have been described. A single example of free OH substituents has been reported (*Scheme 19*), but without indication of yields and diastereomeric ratio. An original diastereoselective synthesis of 1-amino-3,4-dihydroxycyclopentane-carboxylic acids **108** (*Scheme 18*), in which the two hydroxy groups are *cis* with respect to the amino one,

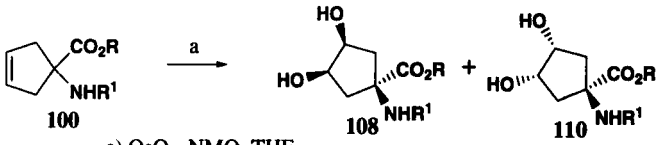



a) 2% Ru(II), DEC; b) $OsO_4$, NMO, $Me_2CO$, $H_2O$, 0°C (71%); c) NaH, MeI, DMF/THF; d) 0.1 M TFA, $MeCN/H_2O$; e) $Ac_2O$, DMAP, $CH_2Cl_2$

**Scheme 18**

was reported by Hammer[29] starting from the chiral spiro compound **105a** obtained from alkylated bislactim **104a** through Ru(II)-catalyzed ring-closing metathesis reaction (RCM) (Meth. D). The addition of catalytic osmium tetroxide in the presence of *N*-methylmorpholine *N*-oxide afforded the diasteromeric dihydroxylated compouds **106a** and **107a** in 3:1 ratio. Compound **106a** was transformed into the corresponding dimethoxyamino acid **108a** (35%) through methylation and hydrolysis. The diacetoxyamino acid **108b** (60%) was also obtained by hydrolysis of **106a** followed by acetylation.

A different synthetic approach[30] to 3,4-dihydroxy $Ac_5c$ compounds **108** and **110** (*Scheme 19*), the inhibitors of zinc metalloendopeptidases, was reported from cyclopentene derivatives **100** (Meth. A) by reaction with osmium tetroxide. The reaction formed a mixture of diastereomeric compounds **108** and **110**. Yield and diastereomeric ratio were not reported.

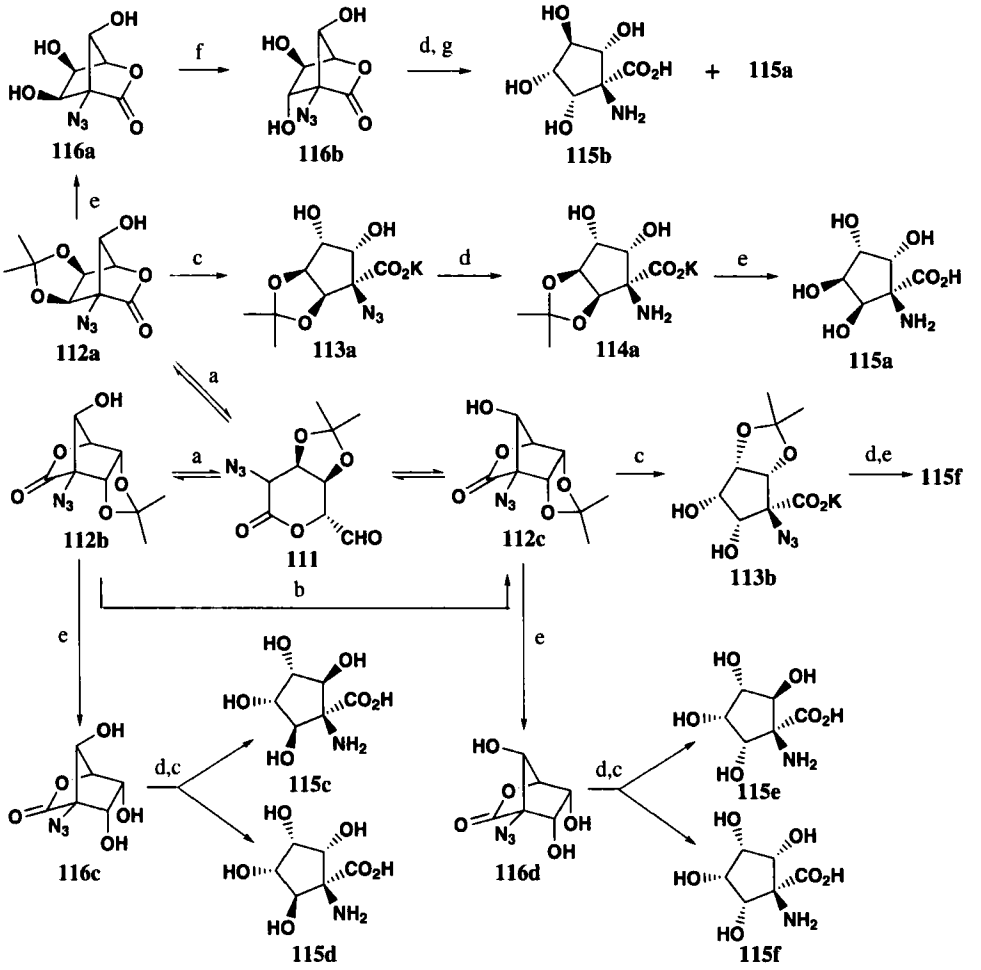



a) $OsO_4$, NMO, THF

**Scheme 19**

*iv. Polysubstitution*

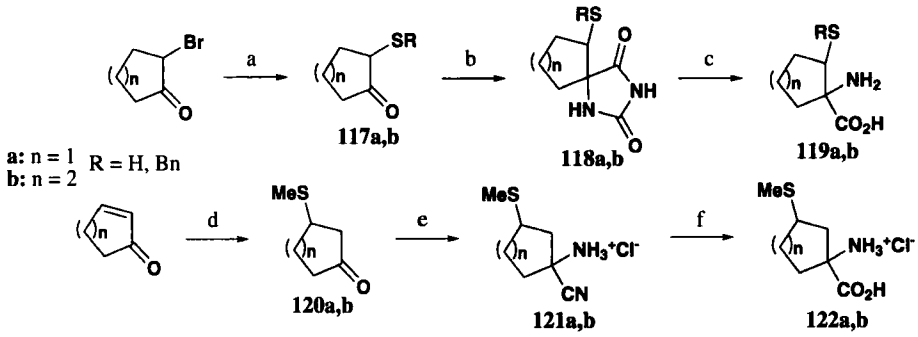
Several polyhydroxy compounds (diastereomeric 1-amino-2,3,4,5-tetrahydroxycyclopentanecarboxylic acids (*Scheme 20*) have been prepared, starting from sugar-like precursors. Procedures are relatively straightforward in view of the complexity of the products. Compounds **115**[31] were obtained from chiral azidolactones **112a-c**. Lactones **112a** and **112b** were obtained from epimeric aldehydes **111** by an intramolecular closure of the azido anion (Meth. B) (*Scheme 20*) in a different ratio depending on the base used to generate the anion ($F^-$: **112a/112b** = 58:15;. $N_3^-$: **112a/112b** = 22:66). The epimerization of lactone **112b** to lactone **112c** occurred in ammonia through an aldol equilibration. Lactone **112a** was reacted with aqueous potassium carbonate giving the hydrolysis product **113a** which was transformed into the amino acidic compound **115a** (98% overall yield) after azido group reduction (intermediate **114**) and removal of the protecting group. The same lactone **112a** was transformed into diastereomeric amino acid **115b** using the same reactions, but with a different sequence: deprotection of hydroxy groups (compound **116a**), isomerization of the hydroxy group (compound **116b**), reduction of the azido group and hydrolysis. Amino acid **115b** was obtained as the major isomer together with a minor amount of **115a**. Starting from either **112b** or **112c** *via* the same reaction sequence (deprotection of hydroxy groups, reduction of azido function, hydrolysis of lactone group), a mixture of amino acids **115c/115d** (70%, 1:8) and **115e/115f** (54%, 6:1) was obtained, respectively. In contrast, starting from **112c** by hydrolysis of the lactone group as the first step, followed by reduction and deprotection reactions, the amino acid **115f** was the only diastereomeric compound (79% overall yield). The same authors reported on the synthesis of amide or hydantoin derivatives of amino acids **115a,d,f**.[32]




**Scheme 20**

### 4. *Sulfur $Ac_5c$ Compounds*

The 2- and 3-alkylthiocyclopentanones **117a** and **120a**, prepared as described in *Scheme 21*, were used for the preparation (Meth. A) of diastereomeric cysteino- or methionino-like amino acids **119a**[33] and **122a**.[34] The Bucherer-Berg and Strecker reactions were respectively used for the preparation of intermediates **118a** and **121a** which were hydrolyzed to the corresponding amino acids **119a** and **122a**. The diastereomeric amino acids **122a** were obtained in 1:1.3 ratio and were separated. The stereochemistry was not assigned.

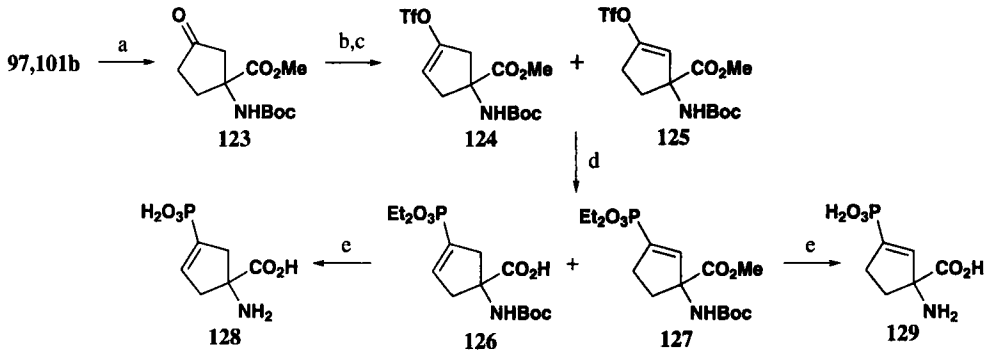



a) BnSH; b) KCN, $(NH_4)_2CO_3/H_2O$; c) $Ba(OH)_2$; d) MeSH, CuOAc, hydroquinone (38%); e) $KCN/NH_4Cl/ H_2O$, $NH_3$, 0°C; f) 6N HCl

**Scheme 21**

### *5. Phosphorus Acyc Compounds*

Both unsaturated (*Scheme 22*) and saturated (*Scheme 23*) 1-amino-3-phosphono-cyclopentene- and cyclopentane-1-carboxylic acid were reported. Yields are satisfactory, but diastereoselection, when applicable, is absent. No enantioselective methods have been reported till now. Unsaturated compounds[35] **128** and **129** (*Scheme 22*) were obtained from the mixture of

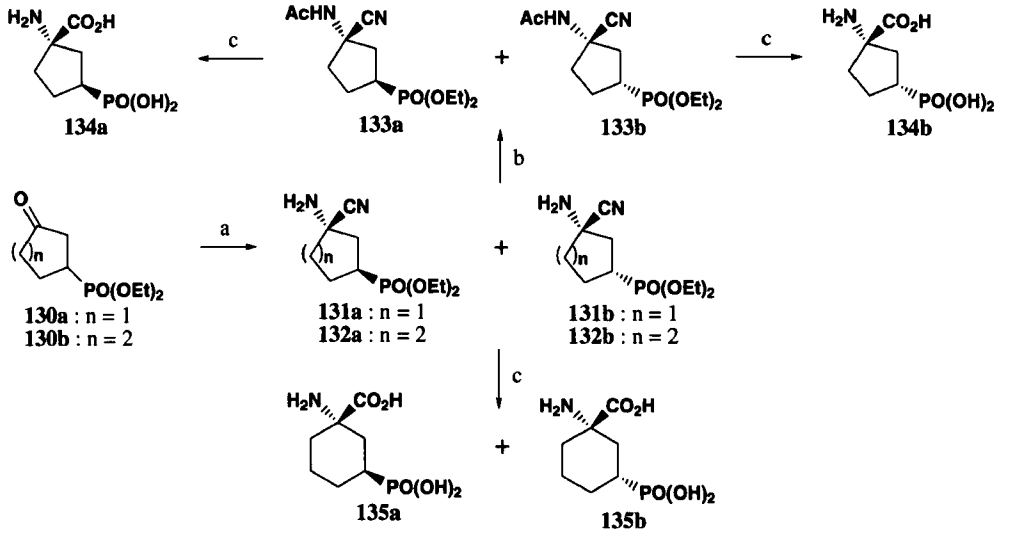



a) $Cr_3O$-Py, $CH_2Cl_2$ (70%); b) LDA-DME, -78°C; c) $Tf_2NPh$, 0°C (28%); d) $HPO(OEt)_2$, TEA, DMF, $(Ph_3P)_4Pd$, 70°C, then flash chromatography (**126**: 80%; **127**: 12%); e) 6N HCl (**128**: 97%; **129**: 57%)

**Scheme 22**

stereomeric methyl esters **97,101b** (Meth. A). The corresponding ketone **123** was obtained by oxidation and converted into a regioisomeric mixture of enol triflates **124** and **125**. The Pd-catalyzed addition of diethylphosphate afforded in very good yield the corresponding compounds **126** and **127** (6.5:1) which were separated and hydrolyzed to amino acids **128** and **129**. A different approach was followed for the synthesis of the corresponding saturated diasteromeric compounds **134a** and **134b** (*Scheme 23*).[36] Diastereomeric compounds **131a** and **131b** (80%, 1:1) were obtained using the Strecker reaction from ketone **130a** (Meth. A) obtained from cyclopentenone through a hydrophosphinylation reaction (73%). Their separation was achieved by acetylation and chromatography (**133a**: 46% and **133b**: 24%). The hydrolysis gave the corre-

sponding amino acids **134a** (95%) and **134b** (80%). The 3-phosphino $Ac_5c$ compound **278** was prepared by Johnson *et al.* according to *Scheme 46* but the reactions and yields were not detailed.[37]




a) $NH_4Cl$, $NH_4OH$, NaCN; b) $Ac_2O$, Py, then flash chromatography; c) 6N HCl

**Scheme 23**

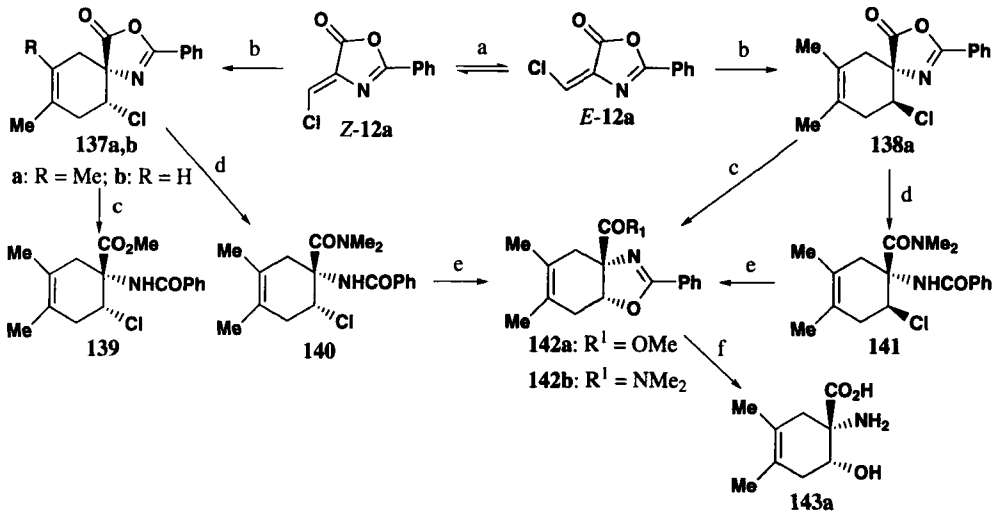
## V. 1-AMINOCYCLOHEXANE-1-CARBOXYLIC ACIDS

Several syntheses of $Ac_6c$ compounds functionalized at C-2, C-3 and C-4 or polyfunctionalized with heteroatoms are known, the derivatives substituted with an oxygen atom being the more representative. The two main synthetic procedures adopted for their preparation made use of *i)* cyclohexanones bearing an heteroatom on the ring and using Strecker or Bucherer-Berg reactions for the introduction of the amino acidic moiety (Meth. A) and *ii*) of the Diels-Alder reaction (Meth. C). As for $Ac_3c$ compounds both oxazolones and aminoacrylates are the most common starting materials in the Diels-Alder cycloaddition reaction and the heteroatom can be linked to the diene or the dienophile.

### *1. Halo $Ac_6c$ Compounds*

Few examples of halo substituted $Ac_6c$ compounds are reported in the literature *i.e.* the protected 2-chlorocyclohexane derivatives, which were transformed into the more interesting hydroxy derivative **143a**, and the 4-iodo compound as intermediate of a synthetic pathway.

The two diastereomeric 1-amino-6-chlorocyclohex-3-ene-1-carboxylic acid derivatives **137a** and **138a** were prepared[38] according to methodology C (*Scheme 24*). $EtAlCl_2$ catalyzed the Diels-Alder reaction between chloromethyleneoxazolone *Z*-**12a** and 2,3-dimethylbutadiene (**136a**) giving a single diastereomeric adduct **137a** with *cis* relationship between the nitrogen and

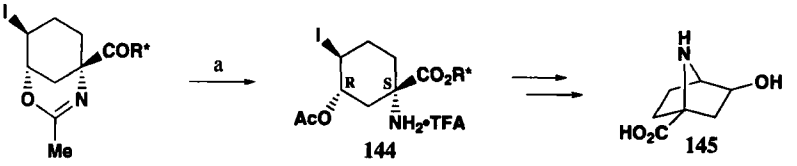


a) $CH_2Cl_2$, hv; b) 2,3-dimethylbutadiene **136a** or isoprene **136b**, $EtAlCl_2$, $CH_2Cl_2$ (70%); c) MeOH/*p*-TSA (87%); d) $Me_2NH$, EtOH (95%); e) $Na_2CO_3$, MeCN; f) EtOH, HCl, then propylene oxide (50%)

**Scheme 24**

chloro atoms. It was transformed into ester **139**. Similarly, cycloadduct **137b** was obtained with good regioselectivity from isoprene (**136b**). It was possible to obtain the diasteromeric adduct **138a** from oxazolone *Z*-**12a** which was partially isomerized to *E*-**12a** (1:1) by UV light. The reaction mixture was directly used for the cycloaddition reaction with **136a** and a mixture of cycloadducts **137a** and **138a** (67%, 54:46) was isolated. Treatment of adducts **137a** and **138a** with dimethylamine produced the corresponding amides **140** and **141** which were separated. As for $Ac_4c$ and $Ac_5c$ ring system, the labelled fluoro-$Ac_6c$ compound *trans*-**39c** and the iodo compound **42c** (n = 3) were reported. For their synthesis see *Scheme 8*.[14] Yields and stereochemistry were not reported.

The chiral 3-acetoxy-4-iodo derivative[39] **144** (*Scheme 25*), an important intermediate for the preparation of constrained 4-hydroxyproline **145**, was obtained (Meth. A) from the corresponding oxazine **250b** (see *Scheme 40*, p. 177).



a) TFA, $THF/H_2O$ (99%)

**Scheme 25**

### 2. *Nitrogen $Ac_6c$ Compounds*

Poor information exists about 2- and 3-amino compounds which are reported but without synthetically useful data. Instead, both diastereomers of 1,4-diamino acids (constrained

ornitine analogs) have been successfully prepared by traditional procedures (*Schemes 26-28*). The 2-amino $Ac_6c$ compound **146** (*Figure 1*) was cited[40] and for its synthesis the Fondaker's procedure is indicated. However, no data were given for starting materials, intermediates and yields. The 3-amino $Ac_6c$ compound **147** was also reported[41] for its anticonvulsant activity, but the synthetic scheme was not reported (*Figure 1*).

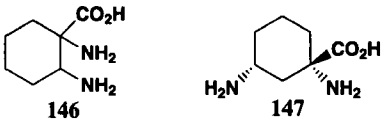
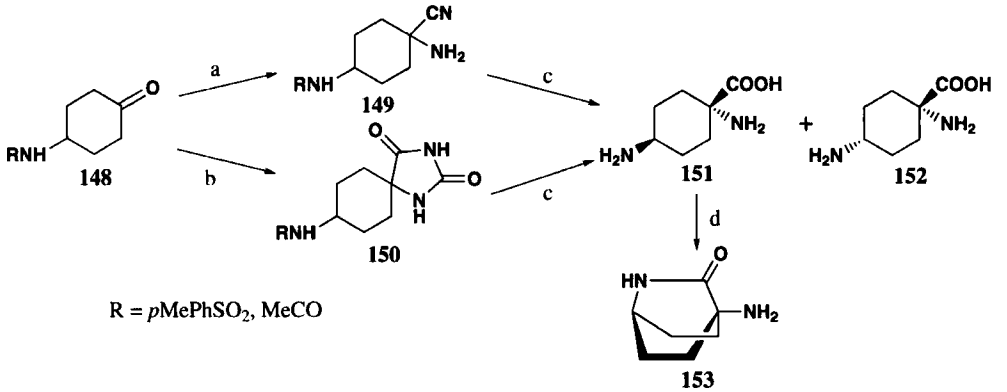



**Fig. 1**

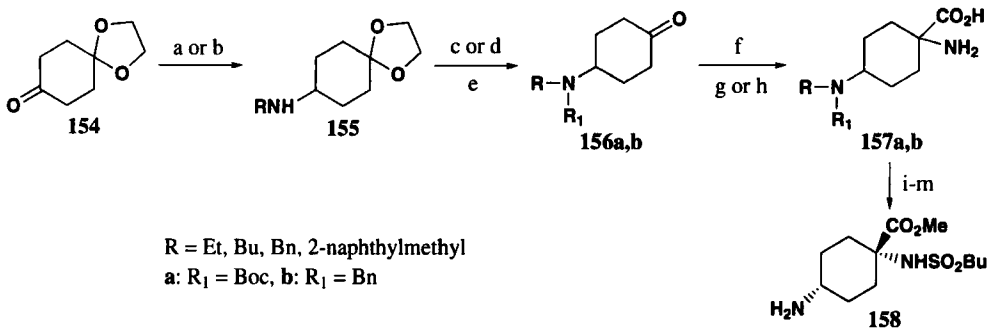
Different synthetic approaches were used for the preparation of the isomeric 1,4-diamino acids **151** and **152**, which are ornitine analogues (Meth. A). The first synthesis was reported in 1973[42] starting from 4-toluenesulfonylaminocyclohexanone **148** (*Scheme 26*). Nitrile **149** was prepared in quantitative yield by Strecker reaction and hydrolyzed to the diasteromeric




a) KCN, $NH_4Cl$, MeOH/$H_2O$ (100%); b) KCN, $(NH_4)_2CO_3$ (90%); c) AcOH, 12N HCl, 120°C; d) MeOH, HCl

**Scheme 26**

compounds **151** and **152** (60:40) in very low yields. The use of Bucherer-Libe reaction followed by hydrolysis of hydantoin **150** gave compounds **151** and **152** in 60% yield with inverted ratio (20:80). The *N,N-trans* configuration of isomer **151** was confirmed by spontaneous cyclization of its methyl ester hydrochloride to the bicyclic compound **153**. The above amino acids were also prepared from 4-acetamidocyclohexanone *via* similar routes but yields were not given. A different approach to 4-amino $Ac_6c$ derivatives (*Scheme27*) was reported[43] from 1,4-cyclohexanedione monoketal **154** (Meth. A) which was transformed by a reductive amination reaction into a series of amines **155**. After deprotection of the ketone group and protection of the amino function (intermediate **156a**, $R_1$ = Boc), the amino acidic compounds **157a** were obtained by the classical Bucherer-Berg procedure followed by hydrolysis. However, yield and configurations of the products were not reported. A diastereoselective route to compound **158** was used by Himmelsbach *et al.* (Meth. A) (*Scheme 27*).[44] From **154** and benzylamine, compound **155** (R = Bn, 72%)

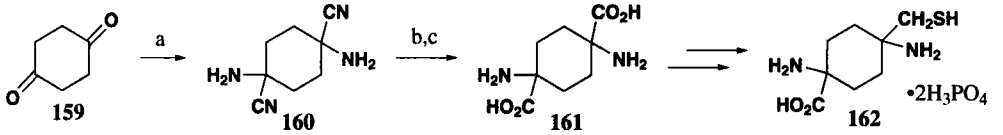



a) $RNH_2$, AcOH, $NaBH(OAc)_3$, 1,2-dichloroethane; b) R = Bn: $BnNH_2$, MeOH, Ni-Raney (72%); c) $R_1$ = Boc: TFA, $H_2O$, then $(Boc)_2O$, TEA, DMAP, THF; d) $R_1$ = Bn: BnBr, DIPEA, MeOH (75%); e) 1N HCl (100%); f) KCN, $(NH_4)_2CO_3$; g) $R_1$ = Boc: LiOH; h) R = $R_1$ = Bn: AcOH, HCl 37%, 50°C (77%); i) MeOH (61%); l) $CH_2Cl_2$, $BuSO_2Cl$, pyridine (48%); m) $H_2$, MeOH, Pd/C, 5 bar, 50°C (38%)

**Scheme 27**

was obtained, alkylated and hydrolyzed to **156b** ($R_1$ = Bn, 75%). The Bucherer reaction and hydrolysis gave the *N,N-cis*-**157b** compound. Protection of the carboxy and amino groups as methyl ester and sulfonylamide, and reduction of the benzyl group formed compound **158**, an important precursor for antithrombotic compounds. Other amides were reported.

1,4-Diamino-1,4-cyclohexanedicarboxylic acid **161** was used for the preparation of the 4-aminoethanthiol derivative **162** as antiradiation agent (*Scheme 28*).[45] Compound **161** was obtained from 1,4-cyclohexanedione **159** (Meth. A) which was converted (Strecker reaction) into 1,4-diamino-1,4-cyclohexanedicarbonitrile **160** and hydrolyzed. Yield was not given.




a) KCN, $NH_4Cl$, $H_2O$; b) $H_2SO_4$ conc.

**Scheme 28**

### *3. Oxygen $Ac_6c$ Compounds*

As far as oxygen-containing substituents are concerned it is obvious that cyclohexene and cyclohexane-1-amino-1-carboxylic acids bearing one or more *free* OH groups are the most interesting compounds of this family and numerous other derivatives have been prepared in view of their transformation into them. However, it should be considered that the final step (mainly a deprotection step) is not always described, notwithstanding it should be considered possible in principle. Compounds having from one to four OH groups are known. In the following text monohydroxylated compound are treated separately from polyhydroxylated ones. Table 1 offers an overview for easier location of items. The three main methodologies for their preparation are Meth. C, A, D. It appears that one most useful way to construct the cyclohexane skeleton is by

the Diels-Alder cycloaddition reaction. Good possibilities for the introduction of precursor groups of the OH function and carbon containing ring or chain are given and steric control is satisfactory in many cases. Functionalized or not functionalized dienes have been used and as dienophyles alkylidene-imidazolones, methylene-oxazolidinones and, far more interestingly, alkylidene–oxazolones or substituted 2-aminoacrylates have been extensively employed for generating monocyclic or bicyclic precursors. Of importance, both in the case of oxazolones and in the case of acrylates is the presence of a chiral substituent, which can induce chirality in the cycloaddition product and ultimately in the final hydroxy amino acid. A case of chiral center on the oxazolidinones is also known.

**Table 1**

| Basic structure | Configuration | N° | Scheme |
|---|---|---|---|
| 2-HO-cyclohexane | 1*R**,2*S** | **76a** | 31 |
| | 1*R**,2*R** | **76b** | 31 |
| | 1*S*,2*R* and 1*R*,2*S* | **76a** | 36/14 |
| | 1*S*,2*S* and 1*R*,2*R* | **76b** | 36/14 |
| | 1*R**,2*S** | **185** | 31 |
| 3-HO-cyclohexane | 1*S*,3*R* | **247** | 39 |
| | 1*S*,3*R* | **252b** | 40 |
| | 1*R*,3*R* and 1*S*,3*S* | **252a** | 40 |
| 4-HO-cyclohexane | ---- | **210** | 35/41 |
| | ---- | **211** | 35/41 |
| 2-HO-3-cyclohexene | 1*S*,3*S* | **223** | 38 |
| | 1*S*,3*R* | **224** | 38 |
| 2-HO-4-cyclohexene | 1*S**,2*R** | **143** | 24/30 |
| 3-HO-4-cyclohexene | 1*S*,3*S* (protected) | **238** | 39 |
| | 1*R*,3*R* (protected) | **239** | 39 |
| 2,4-di-HO-cyclohexane | 1*S**,2*R**,4*S** | **176** | 30 |
| | 1*R**,2*S**,4*S** | **190** | 31 |
| 2,5-di-HO-cyclohexane | 1*S**,2*R**,5*R** | **172** | 30 |
| | 1*S**,2*R**,5*S** | **175** | 30 |
| 2,6-di-HO-cyclohexane | 1*r**,2*R**,6*S** | **267** | 43 |
| 3,4-di-HO-cyclohexane | 1*S*,3*R*,4*S* (protected) | **109** | 18 |
| 3,4,5-tri-HO-cyclohexane | 1*S*,3*R*,4*R*,5*R* | **270** | 44 |
| 2,3,4,5-tetra-HO-cyclohexane | 1*R*,2*S*,3*R*,4*S*,5*R* | **274** | 45 |

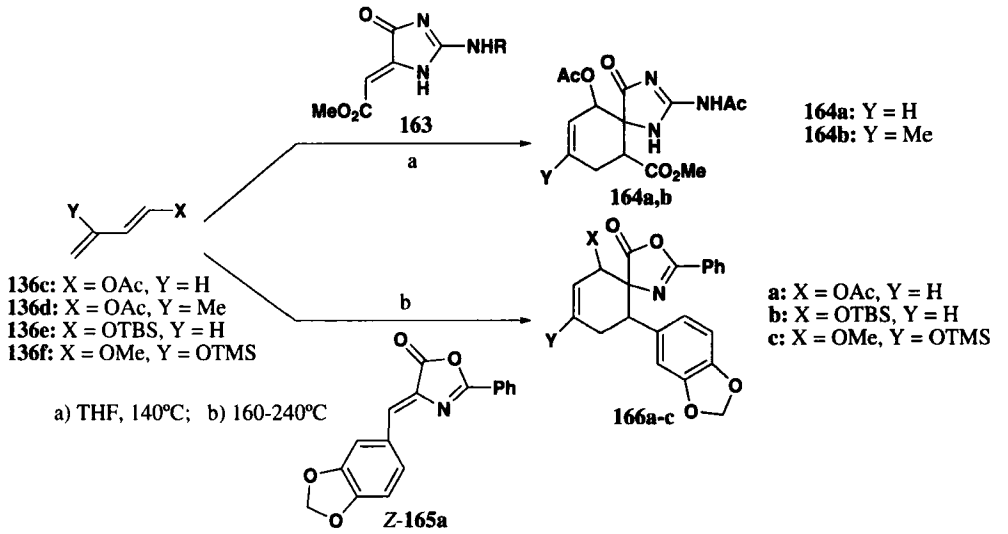
An interesting and widely used possibility is offered by the versatility of the double bond in the cyclohexene derivatives directly obtained from Diels-Alder cycloadditions. Besides traditional reactivity, cases of intramolecular interaction with reactive groups have been described which allow the introduction of further hydroxy groups with high regio- and stereo-control (iodo-oxazination and lactonization reactions). Methodology A was applied when an

oxygen functionalized cyclohexanone was used but in this case the availability of other substituents on the ring is limited. Moreover, this synthetic approach is very good when chiral syntheses were requested. The ring closing metathesis reaction (Meth. D) offers the possibility to obtain both β- or γ-hydroxy unsaturated $Ac_6c$ compounds in the chiral form but in general with low diastereoselection. Furthermore, the overall yields of amino acid are generally low.

*i. Monosubstituted compounds*

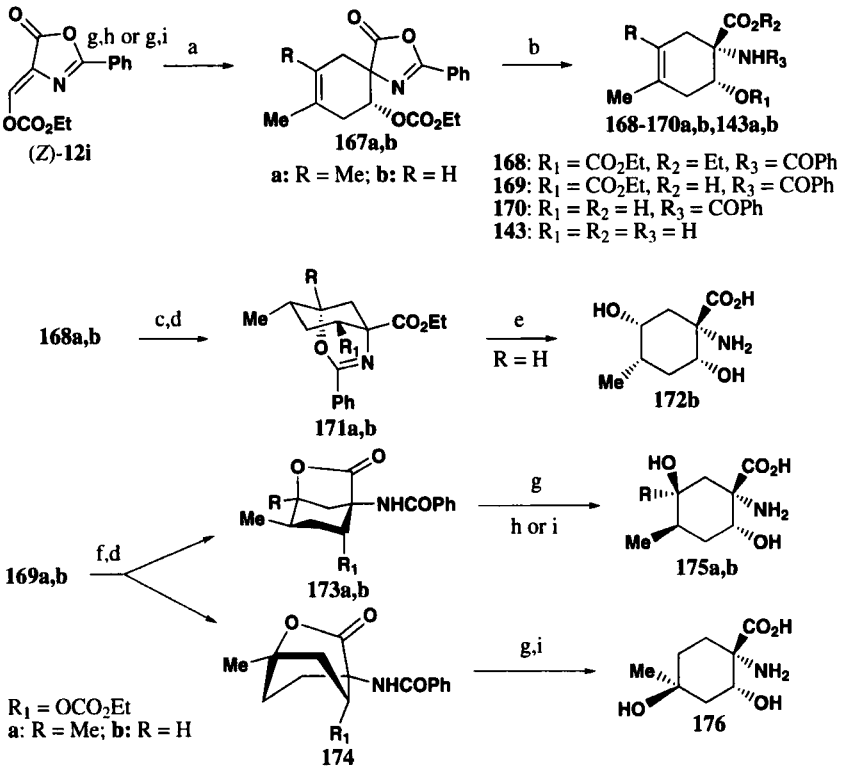
In the following chapters the preparation of different monohydroxy amino acids was reported according to the three different methodologies reported before. The use of Diels-Alder reaction allowed to introduce the oxygen atom both in β and δ position. The use of heterofunctionalized dienes like 1-acetoxybutadiene (**136c**), 1-acetoxy-3-methylbutadiene (**136d**), 1-tributylsilyloxybutadiene (**136e**), 1-methoxybutadiene (**136g**) or 1-trimethylsilyloxybutadiene (**136h**) ensures the functionalization of the β-position of the cyclohexyl ring. Instead, Danishefsky's diene (**136f**) or 2-methoxybutadiene (**136i**) ensure the δ-functionalization. The first examples of Meth. C, albeit scarcely detailed, consisted in the use of imidazolones and oxazolones as dienophiles.

The use of imidazolone **163** and 1-acetoxybutadiene (**136c**) or 1-acetoxy-3-methylbutadiene (**136d**) (Meth. C) at high temperature formed a mixture of isomeric and regioisomeric compounds in poor yield (15-50%). *Scheme 29* describes the major regioisomeric compounds **164** characterized by a β-acetoxy substitution.[46] The cycloaddition reaction of 4-ylideneoxazolone *Z*-**165a** with dienes was first reported in 1989.[47] The reaction was done with dienes **136c,e,f** at high temperature (Meth. C) giving the corresponding cycloadducts **166a-c** in 50-100% yield (*Scheme 29*). Both for compounds **164** and **166** the configuration was not assigned.




**Scheme 29**

According to Meth. C, three different synthetic approaches were adopted for the preparation of the *N,O-cis* hydroxy compounds. The first one,[38] reported in *Scheme 24*, takes advantage of the use of both β-chlorocycloadducts **137a** and **138a**. In fact, a single diastereomer **143a** was obtained using oxazolines **142** as key intermediates (Meth. A). As expected, the *N,Cl-trans* cycloadduct **138a** or the corresponding amide derivative **141** on reaction with methanol in the presence of an acid or basic catalyst, respectively, were transformed into the oxazoline derivatives **142a** (80%) or **142b** (91%). The use of the diastereomeric amide *N,Cl-cis*-**140** under basic conditions gave the same oxazoline **142b** (95%). For its formation it was assumed the anchimeric assistance of the amido group. The hydrolysis of oxazolines **142** gave the amino acid **143a**. An improvement of yields in compound **143a** was observed starting directly from oxazolone *Z*-**12i** [48] (*Scheme30*). Oxazolone **12i** having an ethoxycarbonyloxy group at the double bond, is the sole



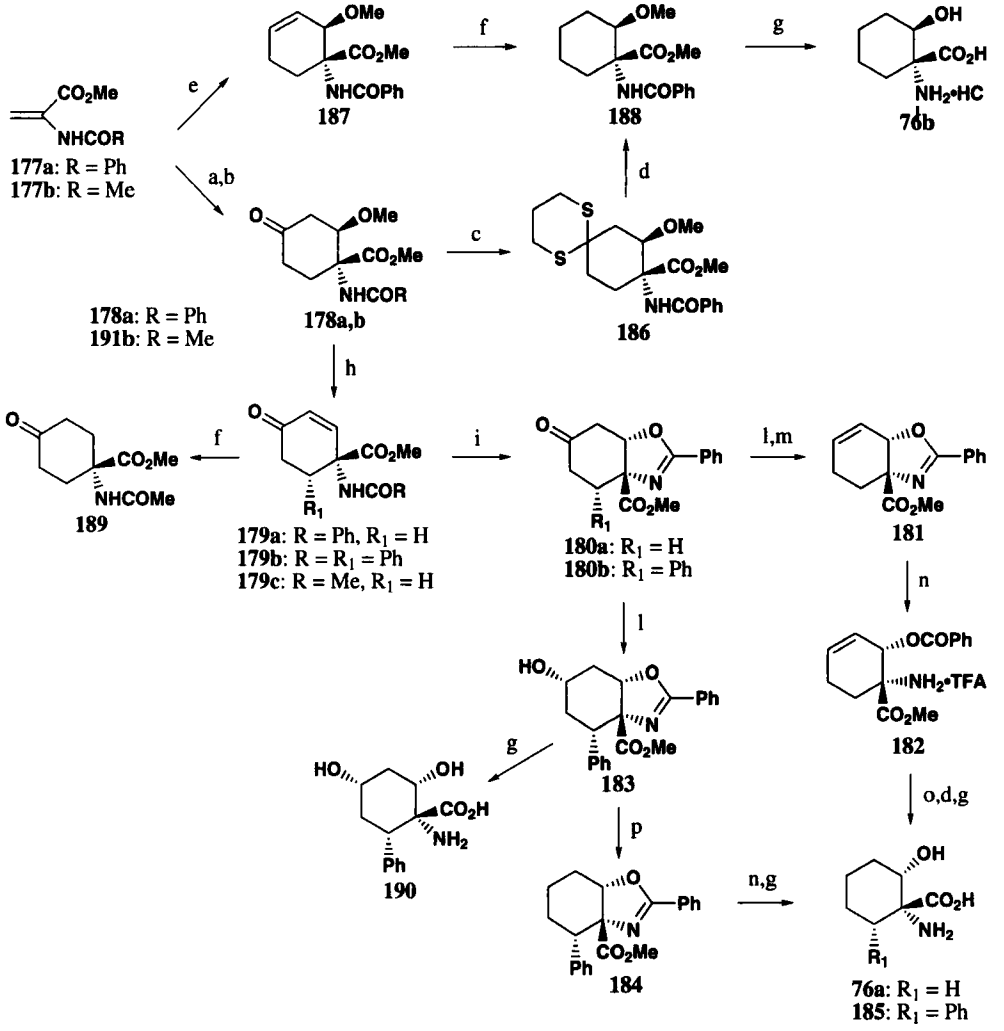

a) **136a** or **136b**, $EtAlCl_2$, $CH_2Cl_2$ (70%); b) **168:** EtOH, $H^+$ (65-70%); **169**: THF, HCl (68-60%); **170**: NaOH, EtOH, then $H^+$ (68%); **143**: $Na_2O_2$, $H_2O$, 50°C (74-78%); c) NIS, $CH_2Cl_2$; d) $Bu_3SnH$, $CH_2Cl_2$; e) HCl, reflux (92%); f) $NaHCO_3$, $I_2/I^-$, EtOH; g) NaOH, $THF/H_2O$, then $H^+$; h) R = Me: $Na_2O_2$, $H_2O$, 50°C; i) R = H: 20% HCl, reflux

**Scheme 30**

heterosubstituted dienophile which was used in a Diels-Alder reaction for the introduction of the hydroxy group in the β-position (Meth. C). The diastereoselective synthesis of *N,O-cis*-β-hydroxy unsaturated $Ac_6c$ compounds **143a,b** was reported by reaction of *Z*-**12i** with 2,3-

dimethylbutadiene (**136a**) and 2-methylbutadiene (**136b**). The reaction was catalyzed by ethylaluminum dichloride and gave a single cycloadduct **167** which was selectively deprotected to compounds **168-170** or to the free amino acids **143** (74-78%).

The third approach takes advantage of the use of the acrylate **177a** and diene **136f** but suffers from many stages and low overall yield.[49] (*Scheme 31*) The *N,O-cis* saturated isomer **76a** (25% from **177a**) was obtained from cycloadduct **178a** transformed into unsatutated ketone **179a**

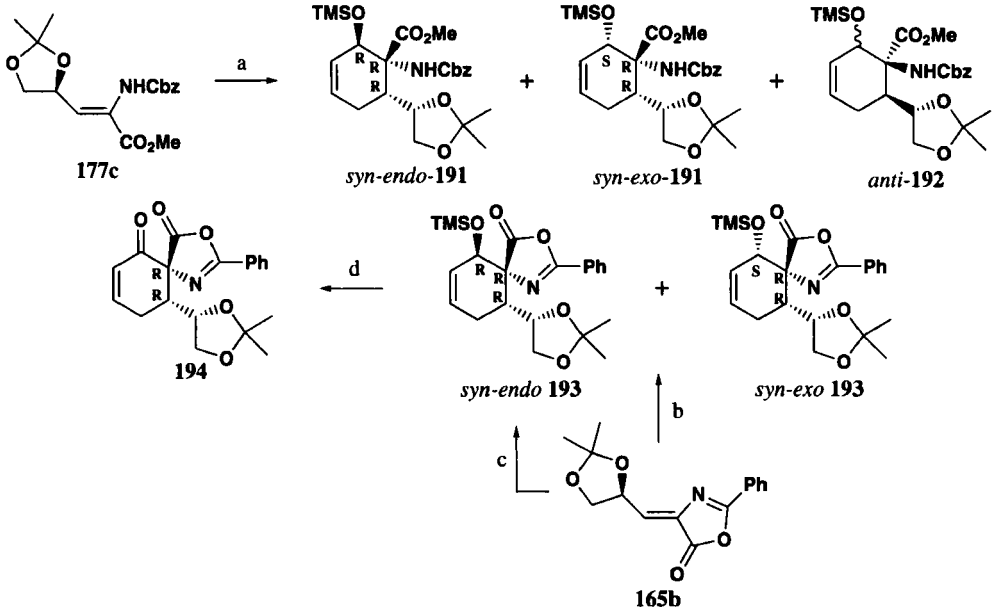



a) **136f**, dioxane, reflux; b) NaF, THF, then column chromatography (48%); c) 1,3-propanedithiol, $BF_3$•$Et_2O$, $CH_2Cl_2$ (77%); d) Ni-Raney, EtOH (62%); e) **136g**, toluene, 85°C (72%); f) $H_2$/Pd-C, MeOH or $CH_2Cl_2$ (78-99%); g) HCl, 100°C: **76b**:12N (84%), **76a**: 6N, (76%), **185**: 10N (63%); h) DBU, $CH_2Cl_2$, 25°C (96%); i) TMSOTf, $CH_2Cl_2$ (90-100%); l) $NaBH_4$, THF, $R_1$ = H: -10°C (62%), $R_1$ = Ph: -78°C (98%); m) MsCl, TEA, $CH_2Cl_2$ (95%); n) TFA, THF, 80°C (95%); o) AcCl, TEA, $CH_2Cl_2$ (80%); p) PhCSCl, DMAP, MeCN, then $Bu_3SnH$, AIBN, toluene (70%)

**Scheme 31**

after methoxy group elimination. The key intermediate oxazoline **180a** allowed to introduce a β-oxygen atom on the ring. The reduction of the keto group in **180a** to hydroxy followed by water elimination produced **181**. Attempts to reduce the double bond failed; instead, the hydrolysis of the oxazoline ring gave the amino acid derivative **182** which was first protected at the nitrogen atom and then hydrogenated and hydrolyzed to racemic amino acids **76a**. The synthesis of the 6-phenyl-substituted *N,O-cis* derivative **185**,[50] (50% overall yield) (*Scheme 31*) was reported by the same authors from oxazoline **180b** obtained from **179b** (see *Scheme 34* for its preparation). In this case the elimination of the hydroxy group was done by reduction of the ketone to alcohol **183** from which oxazoline **184** was obtained by activation of the hydroxy group and reduction. Compound **184** was hydrolyzed to **185**. The 1-aminoacrylate **177a** was also used for the preparation of the *N,O-trans* 2-hydroxy $Ac_6c$ compounds **76b**[49] by reaction with dienes **136f** or **136g** (Meth. C) (*Scheme 31*). Cycloadducts **178a** and **187** were obtained, respectively (only small amounts of the *cis* isomer were detected (10%)). The keto group in **178a** (R = Ph) was reduced, *via* thioacetal **186**, to compound **188** (22% overall yield). Better yields (59% from **177a**) in the preparation of **76b** were achieved when the same compound **188** was obtained from **187** by reduction of the double bond. The hydrolysis of **188** formed the racemic amino acid **76b**. Resolution of both racemic *trans*-**188** and *cis*-**182** was done with L-phenylalanine and *S*-2-acetoxypropionyl chloride, respectively.

Three chiral dienophiles were used in the Diels-Alder reaction: the acrylate **177c** and the oxazolone **165b** having a chiral dioxolane residue on the methylenic carbon and the oxazolidinone **195** having a chiral center on the ring. The chiral synthesis of the β-hydroxy $Ac_6c$ compounds **191** and **193** (*Scheme 32*) was reported from **177c** and oxazolone **165b**, respectively,

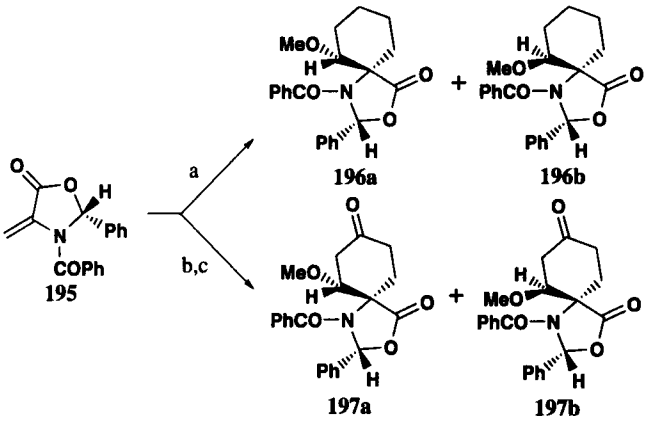



a) **136h** ,$CH_2Cl_2$, 14 Kbar, 60°C (70%); b) **136h**, $CH_2Cl_2$, 25°C (70%); c) **136h**, $CH_2Cl_2$, 12.5 kbar, 25°C (90%); d) citric acid, MeOH, then $MnO_2$, $CHCl_3$ (60%)

**Scheme 32**

using 1-TMSO-butadiene (**136h**) (Meth. C).[51] The acrylate worked at 60° and 14kbar giving a mixture of two diastereomeric *syn* compounds *endo*-**191**, *exo*-**191** and the *anti* derivative **192** in 6:3:1 ratio (70%). Better results were observed with the more reactive oxazolone **165b** which reacted at room temperature giving two *syn* cycloadducts *endo*-**193** and *exo*-**193** (1:2; 70%). After deprotection at the oxygen atom and oxidation, they were transformed into the chiral 2-keto derivative **194**. Starting from **165b** and under pressure, only the pure diastereomer *N,O-trans endo*-**193** (90%) was obtained. In all cases stereochemical control both at C-1 and C-6 (*R,R* configuration) was observed and the 2*R* isomer was favored with respect to the 2*S* one. In conclusion the use of oxazolone **165b** and diene **136h** is a good way for the chiral synthesis of *N,O-trans* β-hydroxy or β-oxo unsaturated $Ac_6c$ compounds.

The chiral methyleneoxazolidinone **195** was used as dienophile in Diels-Alder reactions (Meth. C) and was less reactive than ylideneoxazolones (*Scheme 33*).[52] When reacted with 1-methoxybutadiene (**136g**) the corresponding chiral cycloadducts **196a,b** (51%, 82:18) were

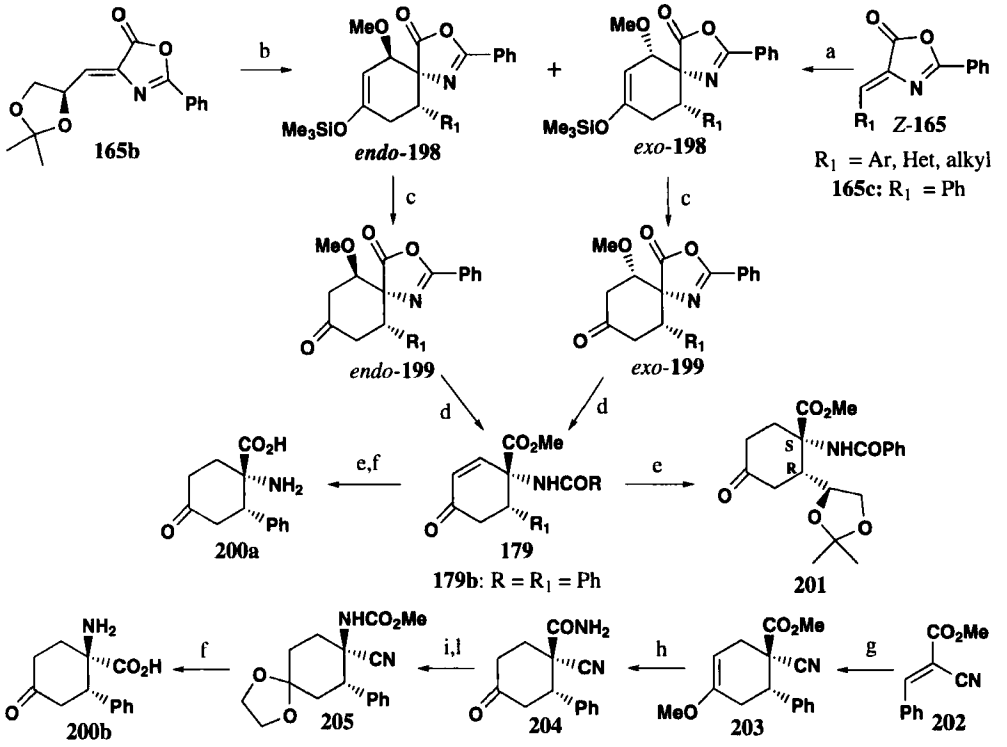



a) **136g**, $CH_2Cl_2$, 60°C (51%); b) **136f**, $CH_2Cl_2$, 60°C; c) HCl 5%, $Et_2O$ (40%)

**Scheme 33**

obtained at 60° in 10 days. The cycloaddition reaction was regioselective both diastereomers having the *S* configuration at the spiro carbon. This synthetic approach is more general considering the possibility to eliminate the chiral residue by simple hydrolysis of the heterocyclic ring. The same compound **195** was reacted with diene **136f**, which allowed to obtain a β,δ-oxygen substituted cycloadducts **197a,b** (40%, 1:1) operating at 60° for 2 days. Also in this case a good regioselectivity and *S* control on spiro center was observed.

The stereochemistry of the cycloaddition of Danishefsky's diene (Meth. C) was detailed both starting from *Z*-phenylydeneoxazolone **165c**[53] and chiral oxazolone **165b**[51,54] operating at 120° and room temperature, respectively (*Scheme 34*).

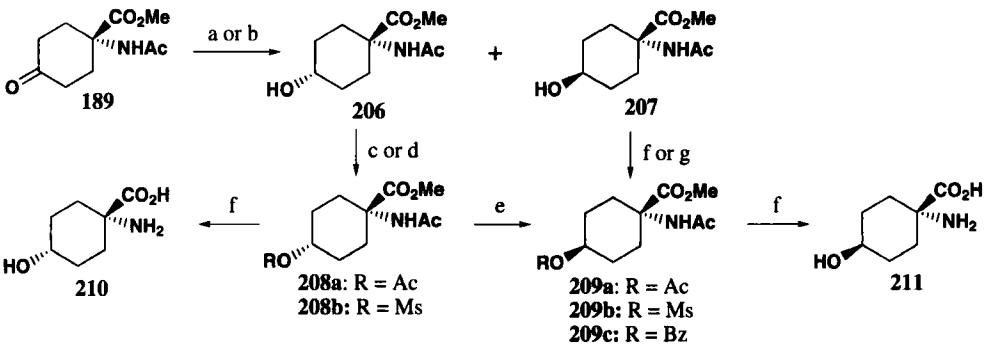



a) **136f**, toluene, 120°C; b) **136f**, $CH_2Cl_2$, 25°C; c) 0.005 N HCl/THF (1:4); d) MeOH/DBU; e) $H_2$, Pd/C, $CH_2Cl_2$ (100%); f) 6N HCl, then EtOH, propylene oxide; g) **136i**, $Me_2CO/H_2O$, reflux (65%); h) $NH_3$, MeOH, then c (95%); i) $OH(CH_2)_2OH$, TsOH, reflux; l) NBS, $Hg(OAc)_2$, MeOH (58%)

**Scheme 34**

Two diastereomeric cycloadducts *exo*-**198** and *endo*-**198** ($R_1$ = Ph) were obtained from **165c**, and were hydrolyzed directly to the corresponding ketones *exo*-**199** and *endo*-**199** ($R_1$ = Ph; 93%, 45:55). Methoxy group elimination (**179b**), reduction of the double bond and hydrolysis gave ketone **200a** (55% overall yield; *cis*-relationship between the amino and phenyl groups). The cycloaddition reaction of Danishefsky's diene (Meth. C) was applied also to a series of arylidene- and heteroarylideneoxazolones[55] and to alkylideneoxazolones **165**.[56] Chiral oxazolone **165b** afforded the diastereomeric compounds *exo/endo*-**199** (1:1). They were transformed into the chiral unsaturated ketone **179** ($R_1$ = dioxolane) (48%,[51] 76%[54]). This was reduced to 1*S*,2*R*-**201** as depicted in *Scheme 34*. The methoxy group elimination is easier in the case of *endo* compound. Keto-amino acid **200b** (*trans*-relationship between amino and phenyl) was obtained from methyl *E*-2-cyanocinnamate **202** and **136i** (Meth. C) (*Scheme 34*). The cycloadduct **203** was obtained which, after ammonolysis of the ester group and hydrolysis of the enol (compound **204**), protection of ketone and Hofmann transposition, gave **205** which was hydrolyzed to **200b** (66%).[53]

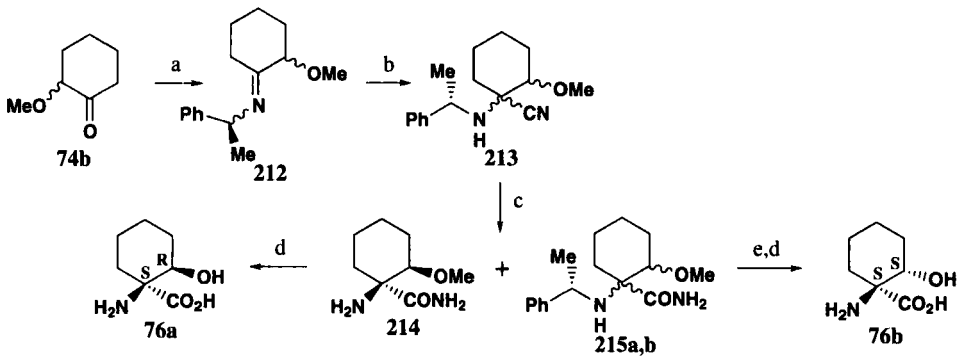
Compound **189** (*Scheme 31*, from acrylate **177b** and **136f**; Meth. C), was used to prepare diastereomeric 4-hydroxy-1-amino acids **210** and **211** by reduction of the ketone group (Meth. A) (*Scheme 35*).[57] $NaBH_4$ favored the formation of the *N,O-cis* compound **206** (**206/207**,




a) $NaBH_4$, EtOH, 0°C (91%); b) L-Selectride, THF, -78°C (91%); c) R = Ac: $Ac_2O$, $Sc(TfO)_3$, MeCN (75%); d) R = Ms: MsCl, TEA, $CH_2Cl_2$, 40°C (68%); e) CsF, BzOH, DMF 80°C (68%); f) HCl 6N, reflux(70-78%).

**Scheme 35**

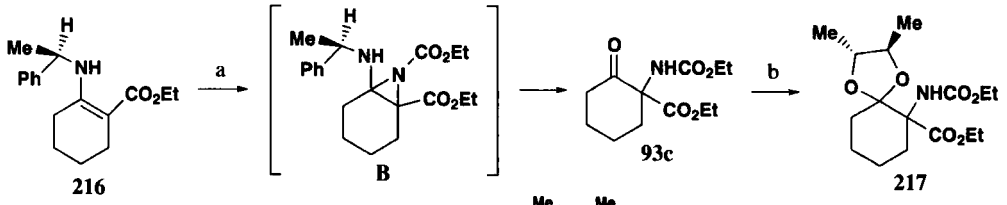
80:20). In contrast, L-selectride produced isomer **207** as the major one (**206/207**, 10:90). The mixture of compounds **206,207** was *O*-acetylated (**208a,209a**) or *O*-mesylated (**208b,209b**) and separated. The hydrolysis of **208b** and **209b** gave the corresponding amino acids **210** and **211**. Compound **208b** was converted into the diastereomer **209c** with CsF and benzoic acid. According to methodology A and using oxygen substituted cyclohexanones as starting materials different synthetic approaches to 1-amino-2-hydroxycyclohexanecarboxylic acids (**76**) were reported and all four stereomers were synthesized and isolated. The first example was the synthesis of an achiral diastereomeric mixture of the 2-hydroxy derivatives **76** according to the synthetic pathway depicted in *Scheme 13* from ketone **74a** through hydantoin **75a**.[58] The enantioselective synthesis of the diastereomeric *1R,2S-* and *1R,2R*-1-amino-2-hydroxycyclohexanecarboxylic acids **76a** and **76b** (*Scheme14*) was reported by Ohfune[25] (Meth. A) by transforming 1,2-cyclohexanediol into a mixture of the diastereomeric ketones **83** (1:1, 70%), through intermediates **82**. Following the synthetic scheme adopted for the analogous cyclopentyl derivatives, ketones **83** were transformed into a mixture of diastereomeric enantiopure amino acids **76a** and **76b** (4:1) in 64% overall yield. The four isomeric 1-amino-2-hydroxycyclohexanecarboxylic acids **76** were obtained by Fondaker[59] (*Scheme 36*) starting from the racemic ketone **74b** (Meth. A) which was reacted with (*S*)-1-phenylethylamine (PEA) giving a mixture of *E* and *Z* isomers **212** (10:1). The reaction with trimethylsilyl cyanide produced four stereomers **213**. Depending on the solvent, the *N,O-trans/cis* ratio was changed. Thus, in MeOH *trans* isomers **213** were favoured (*trans/cis* = 74:26), whereas the *cis* compounds **213** (*trans/cis*= 25:75) was predominant in hexane. The hydrolysis of diastereomeric nitriles **213** gave a complex mixture which was separated giving a mixture of *N,O-trans* aminoamides **215a,b** and the hydrogenolyzed *N,O-cis* compound **214**. The latter was hydrolyzed to amino acid *1S,2R*-**76a** (86%, 88% *ee*). Separation of diastereomers *trans*-**215a,b** followed by hydrogenolysis and hydrolysis of the major stereomer afforded the amino acid (1*S*,2*S*)-**76b** (89%, 98% *ee*). The authors also described the preparation and isolation of the corresponding enantiomeric acids *1R,2S*-**76a** and *1R,2R*-**76b** when the (*R*)-1-PEA was used as the chiral auxiliary.

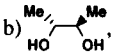



a) (*S*)-1-PEA toluene, 120°C (93%); b) TMSCN, $ZnCl_2$, MeOH or hexane (98-99%); c) $H_2SO_4$ from -10 to 0°C, then silica gel; d) HCl 12N; e) LPLC: Lobar, then $H_2$ Pd/C, EtOH, 45°C, 5 bar

**Scheme 36**

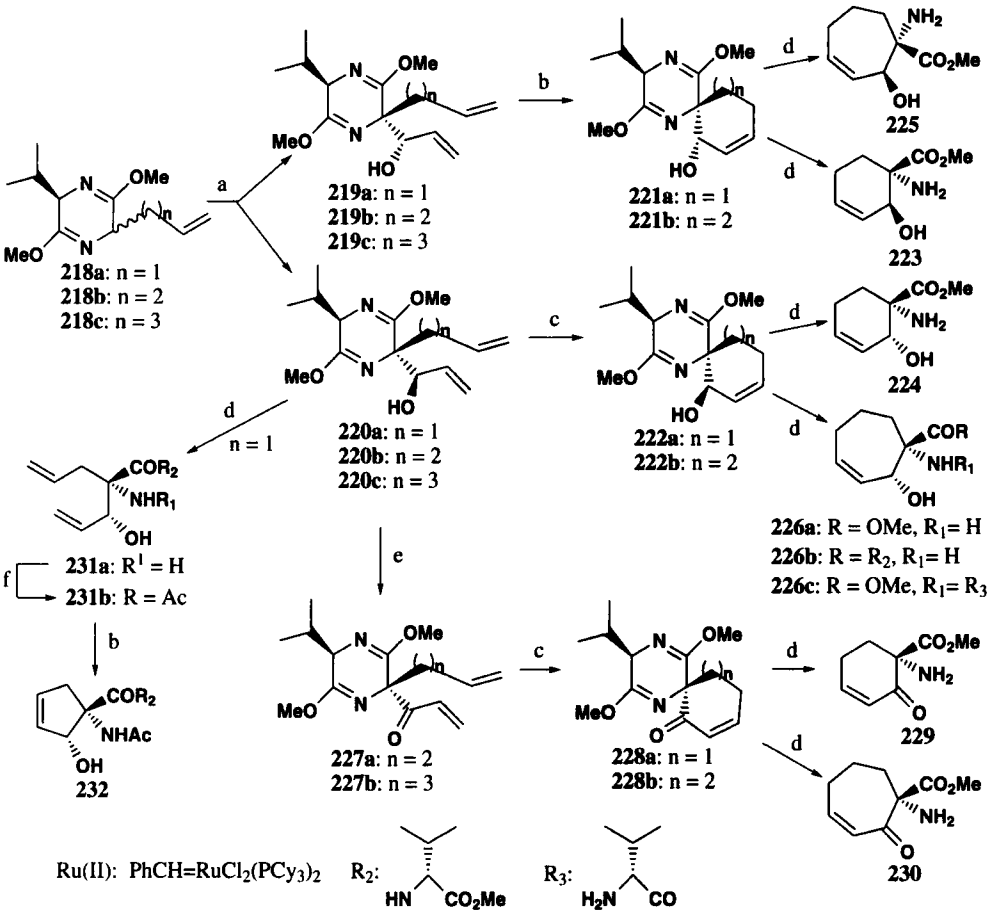
Two synthetic procedures to β-oxo $Ac_6c$ compounds were reported the first one being more convenient (Meth. A) in term of starting material, yield and stereocontrol (*Scheme 37*).[60] In fact, starting from the chiral β-enamino ester **216** and ethyl *N*-[(4-nitrobenzenesulphonyl)oxy]-carbonate (through aziridine **B**) compound **93c** was obtained which was transformed into the




a) $NsONHCO_2Et$, $CH_2Cl_2$; b)  , TsOH, $CH_2Cl_2$

**Scheme 37**

corresponding ketal **217** (95%, 60% *d.e.*). Alternatively, using the same synthetic procedure applied to the $Ac_5c$ ring (Meth. A) (*Scheme 15*), β-ketoester **91b** or its silyl enolate were trasformed into 2-oxo derivative **93b** (60-70%) through intermediate **92b**.[20] The synthesis of benzocondensed derivatives was also reported. Methodology D was used for the preparation both of C-β and C-γ amino acids starting from chiral bislactims having a hydroxy functionalized chain (*Scheme 38*).[26] The reaction is general for the preparation of β-hydroxy $Ac_5c$, $Ac_6c$ and $Ac_7c$, but in the first case a different patway was followed. By reacting **218a-c**, with acrolein, two diastereomeric hydroxy derivatives **219a-c** and **220a-c** were obtained in about 1:2 ratio. From compounds **219b,c** and **220b,c** spiro compounds **221a,b** (**a**: 89%, **b**: 88%) and **222a,b** (**a**: 59%, **b**: 63%) were obtained, respectively. Formation of the five-membered spiro-ring failed. Hydrolytic cleavage of **221a** and **222a** gave **223** and **224**, respectively, in 81 and 60% yield. Amino ester **225** was obtained in 66% yield from **221b**. By contrast, in the case of **222b**, a mixture of hydrolysis compounds **226a-c** was found (65%). Bislactims **220b,c** were also used for

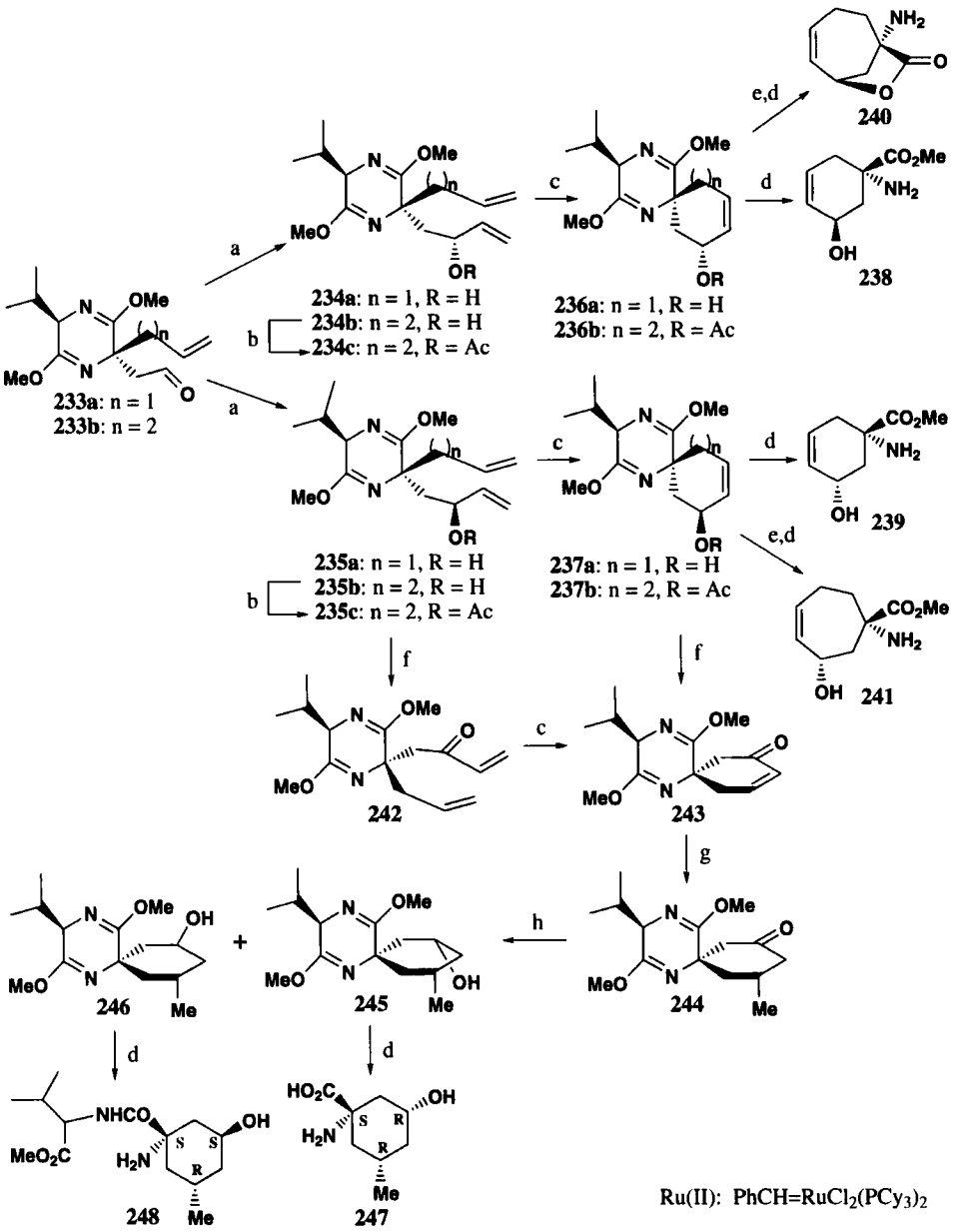



a) BuLi, THF, $CH_2CHCHO$, -78°C (63-70%); b) 2% Ru(II), benzene 20°C; c) 2% Ru(II), DEC, **222**: reflux, **228a**: 40°C, **228b**: 80°C; d) 0.2M TFA, MeCN; e) $(COCl)_2$, DMSO, $CH_2Cl_2$, -60 to -10°C (71-73%); f) $Ac_2O$, DMAP, $CH_2Cl_2$ (90-93%)

**Scheme 38**

the preparation of β-ketoamino esters **229,230**.[61] The oxidation of the hydroxy group produced **227a,b** transformed into the corresponding spiro-compounds **228a** (69%) and **228b** (28%). The hydrolysis of these latter resulted in low yield giving ketones **229** (37%) and **230** (47%), respectively. For the preparation of γ-hydroxy $Ac_6c$ compounds the pathway depicted in *Scheme 39* was followed (Meth. D).[62] Starting from the bislactims **234a** and **235a** (38% yield from reaction of compound **233a** with vinylmagnesium bromide) the corresponding enenantiopure derivatives **236a** (73%) and **237a** (75%) were isolated which were transformed into the unsaturated amino esters **238** and **239** in very low yields (38, 19%, respectively) having the *N,O-trans* and *N,O-cis* relationships, respectively. The saturated 3-hydroxy $Ac_6c$ compounds functionalized with a methyl group at C-5[63] (*Scheme 39*), were obtained from bislactims **234a** and **235a** (mixture of compounds) by oxidation to the keto derivative **242** which was transformed, using ring closing

methatesis reaction, into spiro cyclohexenone **243** (37% overall yield). It was possible to increase the ketone yield (52%) starting from the cyclic compounds **236a,237a** by the Swern oxidation.

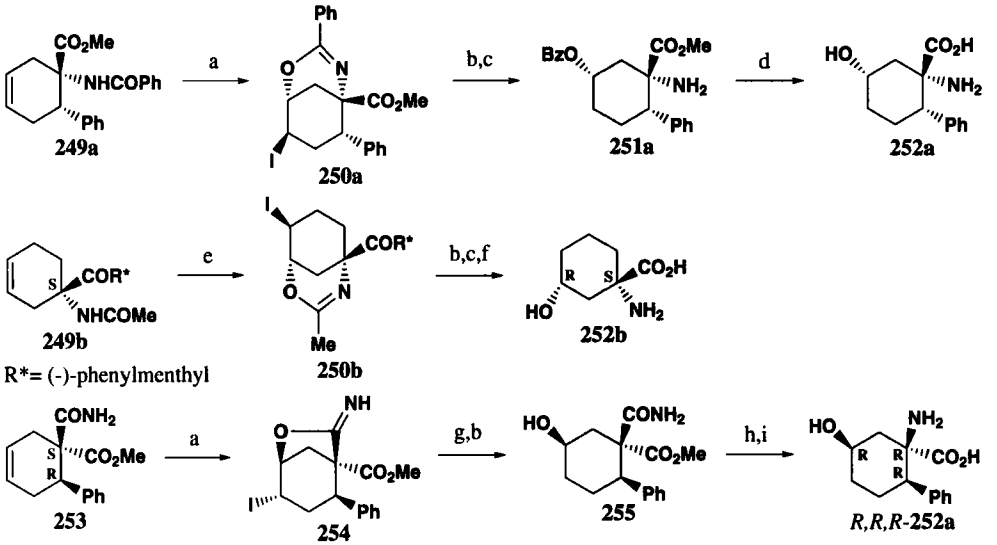



a) vinylmagnesium bromide, $Et_2O$, 0°C; b) $Ac_2O$, DMAP, $CH_2Cl_2$ (90-93%); c) 2% Ru(II), DEC; d) TFA, 0.1 M, $H_2O$/MeCN; e) NaOH/ $H_2O$; f) $(COCl)_2$, DMSO (74-79%); g) $LiCuMe_2$, $Et_2O$ (91%); h) $NaBH_4$, MeOH, -10°C (94%)

**Scheme 39**

The unsaturated ketone **243** was reacted with lithium dimethylcuprate giving a single diastereomer **244** which was reduced to a mixture of alcohols **245** and **246** (37 and 57%, respectively). Mild hydrolysis gave the amino acid **247** (38%) and the protected one **248** (77%), respectively.

An alternative and more efficient way (better yield and diastereocontrol) to γ-hydroxy compounds is shown in *Scheme 40*. The 1-amino-3,4-cyclohexenecarboxylic acid derivatives **249a,b**, obtained through Diels-Alder reaction and having an amidated nitrogen atom, were the starting materials for the regio- and stereocontrolled functionalization of C-3 on the cyclohexyl ring with an hydroxy group (Meth. A). The diastereoselective synthesis of compound **252a** (*Scheme 40*) was reported[64] using the iodo-oxazination reaction which allowed to control the *cis* relationship between the oxygen and nitrogen atoms. Oxazine **250a** was obtained from

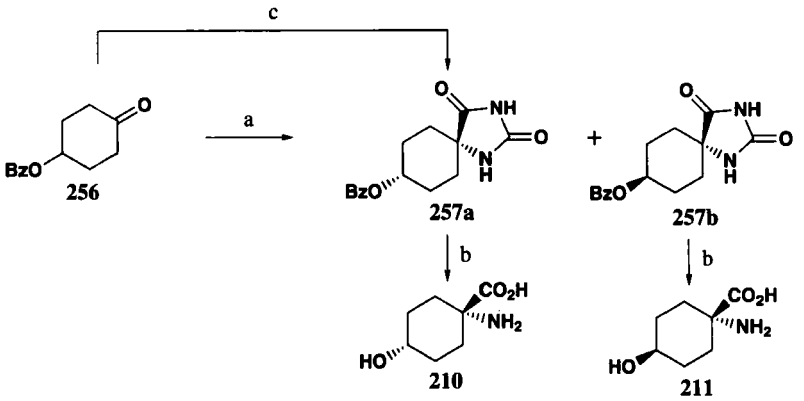



a) $I_2$/dioxane; b) $Bu_3SnH$, $CH_2Cl_2$, 60°C; c) TFA, THF/$H_2O$, 80°C; d) KOH, EtOH, then $H^+$; e) NIS, $CH_2Cl_2$; f) 6N HCl; g) $H_2O$; h) NBS, $Hg(OAc)_2$, DMF; i) 3N HCl

**Scheme 40**

cycloadduct **249a** and was transformed into **251a** by iodine reduction and hydrolytic cleavage. Hydrolysis of **251a** gave amino acid **252a**. The chiral *1S,3R*-hydroxyamino acid **252b** (53% overall yield) was obatined by the same authors[65] from the chiral cycloadduct **249b** using, in the iodo-oxazination reaction, NIS instead of iodine (intermediate **250b**) (*Scheme 40*). A way to chiral compounds *N,O-cis*-**252a**[66] is from the chiral cycloadduct *1S,2R*-**253**, taking advantage of the presence of a carboxamido group (*Scheme 40*). Compound **253** was reacted with iodine giving the intermediate **254**. After removal of the iodine atom and hydrolysis (intermediate **255**), Hoffman transposition and hydrolysis, the chiral amino acid *1R,3R,5R*-**252a** was isolated in 70% overall yield. Enantiomer *1S,3S,5S*-**252a** was also reported.

4-Hydroxy $Ac_6c$ compounds were prepared from 4-benzoyloxycyclohexanone **256** using Bucherer-Berg reaction (Meth. A) (*Scheme 41*).[67] A mixture of two diastereomeric hydantoins **257a** and **257b** was obtained in favor of the *N,O-trans* derivative (*cis/trans*, 1:3). They

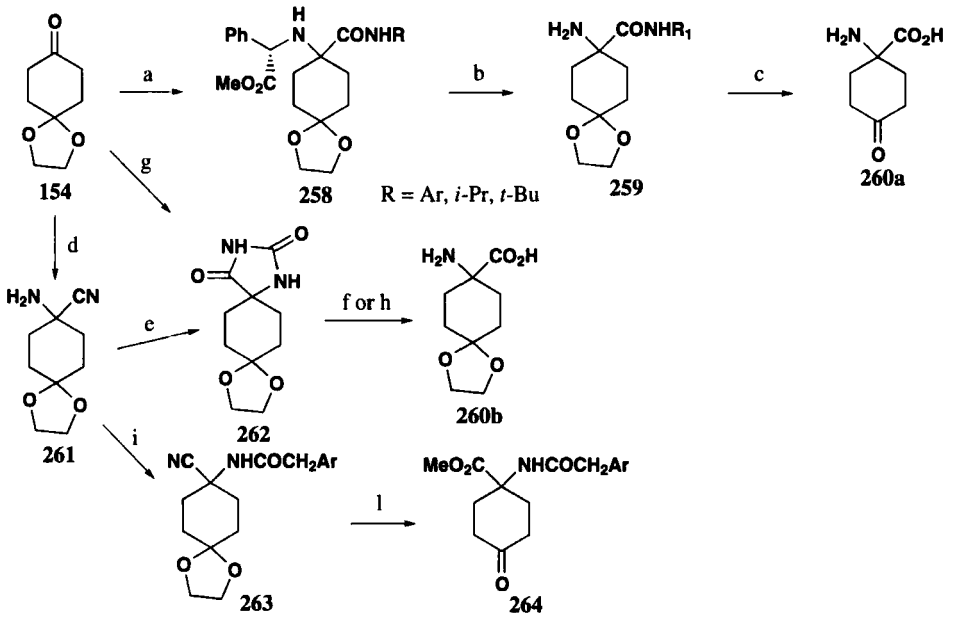



a) KCN, $(NH_4)_2CO_3$, EtOH/$H_2O$, 100°C; b) $Ba(OH)_2$, 150°C; c) KCN, $NH_4Cl$, EtOH/$H_2O$, then KOCN

**Scheme 41**

were separated and transformed into the corresponding amino acids **210** and **211**. Alternatively, the *cis*-isomer **257a** was selectively prepared by treating **256** with KCN/$NH_4Cl$ and cyclizing the amino nitrile with KOCN. This method compared to those reported in *Scheme 35* appears less diasteroselective and versatile in term of revertion of diasteroselection.

The synthesis of 4-oxo $Ac_6c$ compounds (*Scheme 42*) was made *via* three-component reaction of 1,4-cyclohexanone monoacetal **154**, phenylalanine as nitrogen donor and an




a) L-Phe, RNC, MeOH, -78 to 25°C (80-88%); b) MeOH, $Pd(OH)_2$, $H_2$ (58-70%); c) 6N HCl, reflux (60%); d) KCN, $NH_3$; e) $(NH_4)_2CO_3$; f) $Ba(OH)_2$; g) NaCN, $(NH_4)_2CO_3$, $H_2O$, 60°C; h) 0.5 N NaOH, reflux; i) $ArCH_2COCl$, TEA, THF, 0°C; l) $CH_2Cl_2$, $H_2SO_4$, MeOH, 40°C

**Scheme 42**

isocyanide (Meth. A).[68] The reaction formed compound **258** which was deprotected to **259** and hydrolyzed giving **260a**. A way to amino acid **260b** (*Scheme 42*), protected at the keto moiety, was reported from **154** (Meth. A). The Strecker reaction afforded nitrile **261**, then transformed into hydantoin **262**. The hydrolysis of the heterocyclic ring under basic conditions gave amino acid **260b**.[69] Alternatively,[70] compound **260b** was obtained by hydrolysis with sodium hydroxide of the hydantoin **262** directly obtained from acetal **154** with sodium cyanide and ammonium carbonate. Yields were not reported. The 4-keto amino acid derivatives **264**[71] (*Scheme 42*) (used as insecticide) were prepared from aminonitrile **261** which was acylated to compounds **263**. The nitrile group was transformed into ester **264** by reacting with $CH_2Cl_2$, $H_2SO_4$ and methanol. By an analogous procedure, the synthesis of 4-methoxy derivatives was reported.

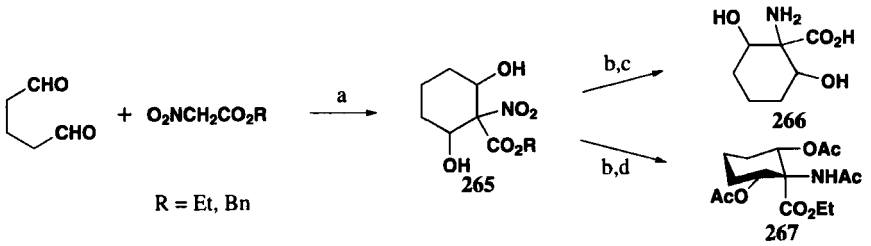
*ii. Polysubstituted compounds*

Several dihydroxy-$Ac_6c$ derivatives were reported, *i.e.* the 2,4-, 2,5-, 2,6- and 3,4-derivatives. In most cases the above described amino acidic compounds were used for further transformations. The synthesis of the 2,4-dihydroxy derivative **190**[50] (Meth. A) (*Scheme 31*) was reported from oxazoline **180b**. The keto group was selectively reduced giving the *O,O-cis* dihydroxy compound **183**, transformed into amino acid **190** (51% overall yield).

Regio- and diastereoselective syntheses of 2,5-dihydroxy derivatives were reported from the 2-hydroxy derivatives **168** and **169** (Meth. A) (*Scheme 30*).[48] The *cis* relationship between the hydroxy groups was ensured starting from esters **168a,b** which, through the iodo-oxazination reaction followed by reduction of iodine with tributyltin hydride, were transformed into **171a,b** in 70-75% overall yields. On reaction with HCl, compound **171b** was converted into the expected dihydroxy derivative **172b** (92%), but **171a** gave amino acid **143a**. To ensure the *trans* relationship between the hydroxy groups, the iodo-lactonization reaction was applied to acids **169a,b**. According to *Scheme 30*, these compounds were transformed into lactones **173a** (41%) and **173b**. From **169b** a second regioisomer **174** was obtained (**173b/174**, T= 25°, 1:2; T= 45°, 1:3.5). The hydrolysis of both the lactone and benzamido groups in compounds **173** and **174**, afforded 2,5- and 2,4-dihydroxyamino acids **175a** (67%), **175b** (89%) and **176** (56%), respectively. As for the corresponding $Ac_5c$ derivatives, the methodology D was used for the preparation of the chiral (*1S,3R,4S*)-1-amino-3,4-dihydroxycyclohexanecarboxylic acid derivative **109** (62% overall yield) from functionalized lactim **105b** through the dihydroxy derivative **107b**, which was the major isomer (**106b/107b**, 6:82) (*Scheme 18*).[29] In contrast to the $Ac_5c$ analogue, the *N,O-trans* relationship was preferred in this case.

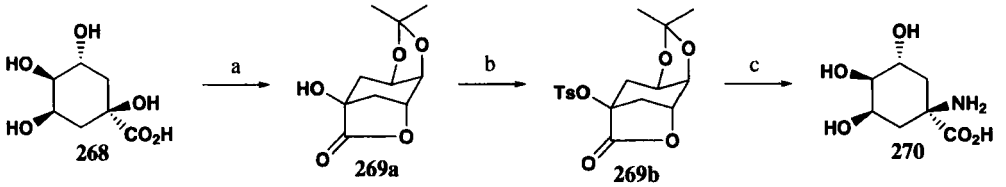
2,6-Dihydroxy $Ac_6c$ compounds **266**[72] (*Scheme 43*) were prepared by a condensation reaction of glutaraldehyde and nitroacetate (intermediate **265**) (Meth. B) and reduction and hydrolysis. The *trans* relationship between acetate and acetamido groups was proposed for compound **267**. From (-)-quinic acid **268**[73] the chiral 1-amino-3,4,5-trihydroxycyclohexanecarboxylic acid **270** was obtained according to *Scheme 44* (Meth. A). Compound **268** was trans-

formed into the lactone **269a** which was tosylated to compound **269b**. This was transformed into **270** by reaction with ammonia and hydrolysis.




a) AcONa, EtOH (R = Et, 40%); b) $H_2$, Raney Ni (30%); c) $Ba(OH)_2$ (89%); d) $Ac_2O$

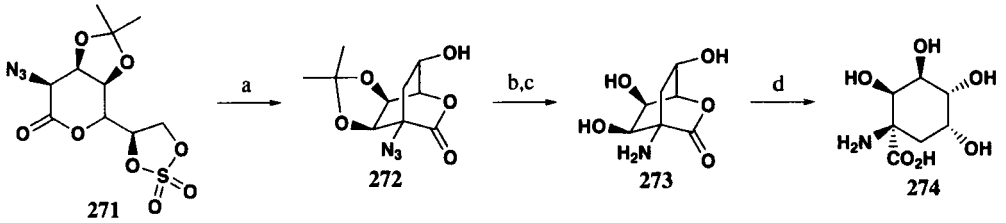
**Scheme 43**




a) acetone, $H^+$ (77%); b) TsCl, Py (97%); c) $NH_3$, EtOH, then $Ba(OH)_2$ (53%)

**Scheme 44**

The enantioselective synthesis (Meth. B) (*Scheme 45*) of 1-amino-2,3,4,5-tetrahydroxy-cyclohexanecarboxylic acid **274** was reported from the azidolactone **272**, obtained from **271**, which was deprotected and reduced to amino compound **273**. The hydrolysis of the lactone function gave the corresponding amino acid **274** in 56% yield.[31b]




a) NaH, DMF, then $H^+/H_2O$ (59%); b) $CF_3CO_2H$, $H_2O$ (70%); c) $H_2$/Pd, $H_2O$; d) TEA, $H_2O$ (56%)

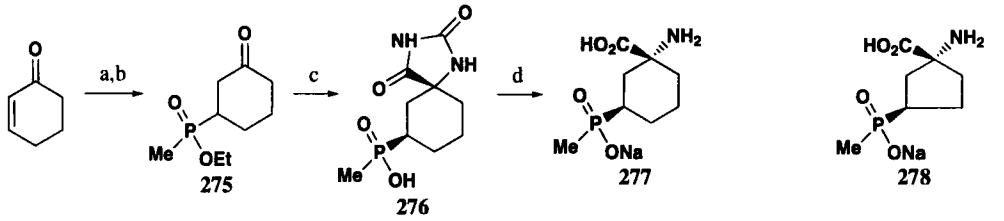
**Scheme 45**

### *4. Sulfur $Ac_6c$ Compounds*

According to synthetic *Scheme 21*, the 2-thiobenzyl derivative **119b** was synthesized as described for the 2-thio $Ac_5c$ analogue.[33] The 3-methylthio derivatives **122b** (stereomeric mixture) were obtained (*Scheme 21*) from 2-cyclohexenone (Meth. A) through the nitrile intermediate **121b** (36% overall yield).[34]

### *5. Phosphorus $Ac_6c$ Compounds*

The diastereoselective synthesis of the 3-phosphino $Ac_6c$ compound **277**,[74] an inhibitor of glutamine synthetase, was reported. Reaction of 2-cyclohexenone with methyl phosphonite afforded **275**. It was transformed into spiro hydantoin derivatives **276** (92:8). The major isomer is indicated in *Scheme 46*. The hydrolysis of **276** gave the amino acid derivative **277**, having *N,P-trans* relationship, in 96% *d.e.*




a) $MeP(OEt)_2$, EtOH; b) 6N HCl, reflux; c) KCN, $(NH_4)_2CO_3$, $EtOH/H_2O$, 55°C (73%); d) $Ba(OH)_2$, $H_2O$, reflux, then Dowex 50 ($NH_4OH$), then NaOH (60%)

**Scheme 46**

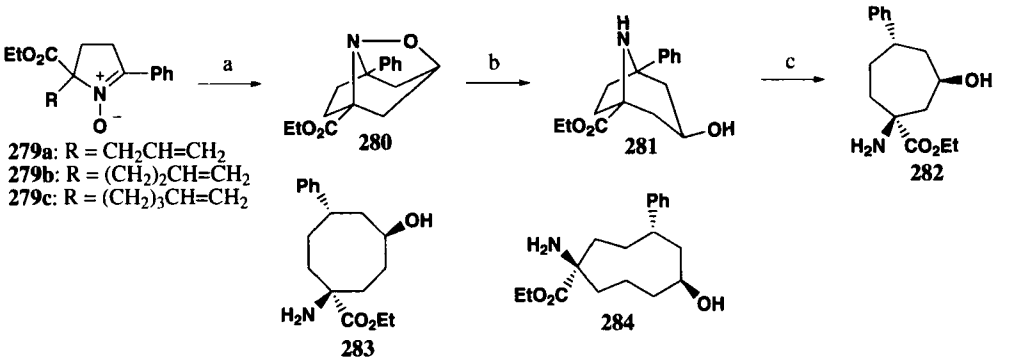
Two diastereomeric bioactive 3-phosphono derivatives **135a** and **135b** (1:4) were synthesized according to *Scheme 23*, already discussed for the $Ac_5c$ analogues. The amino nitrile derivatives **132a** and **132b** were obtained in 81% yield and hydrolyzed to compounds **135**.[36]

## VI. 1-AMINOCYCLOHEPTANE-1-CARBOXYLIC ACIDS

Few examples of heterosubstituted $Ac_7c$ compounds were reported, all of them having an hydroxy group as substituent. For their preparation *i*) the RCM reaction (Meth. D) and *ii*) the 1,3-dipolar cycloaddition reaction (Meth. C) were used.

### *1. Oxygen $Ac_7c$ Compounds*

The preparation of unsaturated β-hydroxy- and γ-hydroxy $Ac_7c$ compounds was reported using the RCM reaction (Meth. D). Both diastereomeric β-hydroxy amino esters **225** and **226**[26] and the corresponding ketone **230**[61] were prepared in satisfactory yield according to the pathways depicted in *Scheme 38* (see analogous $Ac_6c$ syntheses for details). According to the synthetic pathway depicted in *Scheme 39*, both diastereomeric unsaturated γ-hydroxy $Ac_7c$ compounds were obtained from[63] bislactims **234b** and **235b** deriving from **233b** (36 and 43% yield, respectively). The RCM reaction did not work when applied directly to hydroxy compounds which were transformed into the acetoxy derivatives **234c** and **235c**. Good yields were obtained when these latter were cyclized giving **236b** and **237b**. After hydrolysis the unsaturated amino esters **240** and **241** were obtained in 48 and 30% yield, respectively, having the *N,O-trans* and *N,O-cis* relationships, respectively, as demonstrated by the lactone structure of compound **240**. The preparation of 4-hydroxy $Ac_7c$ compound **282** was done by an intramolecular cycloaddition reaction of nitrone **279a** functionalized with an allyl chain (Meth. C) (*Scheme 47*).[75]




a) toluene, reflux (79%); b) $H_2$, Pd/C (82%); c) $H_2$, Pd/C, 40 psi (86%)

**Scheme 47**

The reaction afforded cycloadduct **280** transformed, by hydrogenolysis, into **281**.The catalytic hydrogenation of **281** under high pressure led to the cycloheptane amino ester **282** with *N,O-cis* relationship. Using the same synthetic strategy, 4-hydroxycyclooctyl- **283** and 5-hydroxycyclononyl-1-amino esters **284** were obtained from **279b,c**, respectively.

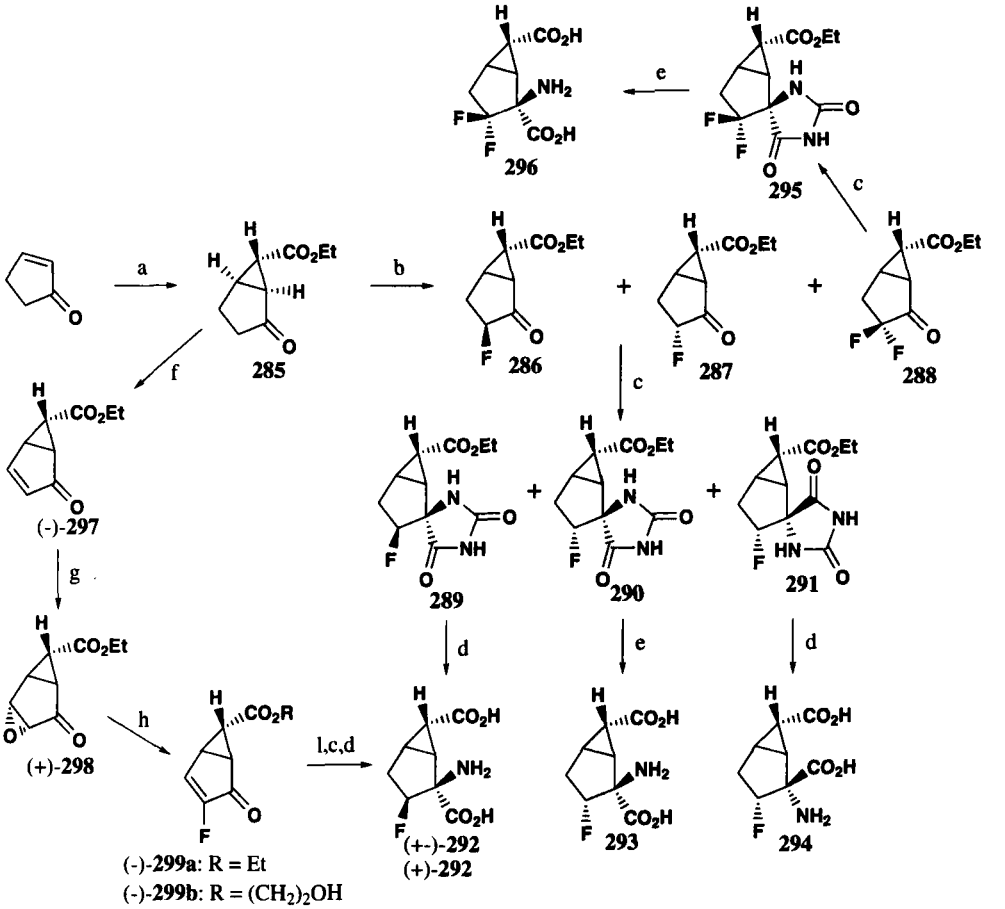
## VII. 2-AMINOBICYCLO[3.1.0]HEXANE-2,6-DICARBOXYLIC ACIDS

A large number of heterosubstituted 2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives were reported because of their interest as potent agonists on the aminoacidic receptors in the CNS system. As heteroatoms, F, N, O, S and P were linked at the C-5 ring both at C-3 and/or C-4. The preparation of a series of fluoro-substituted compounds at C-3 ring was also reported. The main synthetic approaches to these compounds were *i*) the cyclocondensation reaction giving a heterofunctionalized bicyclo[3.1.0]hexane ring (Meth. B) and *ii*) the cyclopropanation reaction of cyclopentenone (Meth. C) followed by functionalization of the cyclopentyl ring. In this case the ethyl 2-oxo carboxylate **285**, obtained from cyclopropanation reaction of 2-cyclopentenone, was the common starting material for the preparation of a large number of heterosubstituted $Ac_{[3.1.0]}c$ compounds.

### *1. Halo $Ac_{[3.1.0]}c$ Compounds*

Several fluoro-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acids (*i.e.* 3-fluoro-, 4-fluoro-, 3,3-difluoro-, 6-fluoro-, 6-fluoro-4-hydroxy- and 6-fluoro-4-oxo) were prepared and in some cases both diastereoselective and enantioselective syntheses were reported. Compound **285** was used to prepare 3-fluoroamino acids **292-294**[76] (*Scheme 48*). α-Fluorination of ketone **285** produced a mixture of the bis-fluorinated compound **288** (27%) and of two diastereomeric compounds **286** and **287** (50%, 1:3). These latter were reacted under Bucherer-Berg conditions to yield three hydantoins **289, 290** and **291** which were hydrolyzed to the corresponding amino acids **292,293** and **294**. The racemic hydantoin **289** was resolved and each enantiomer gave (+)-

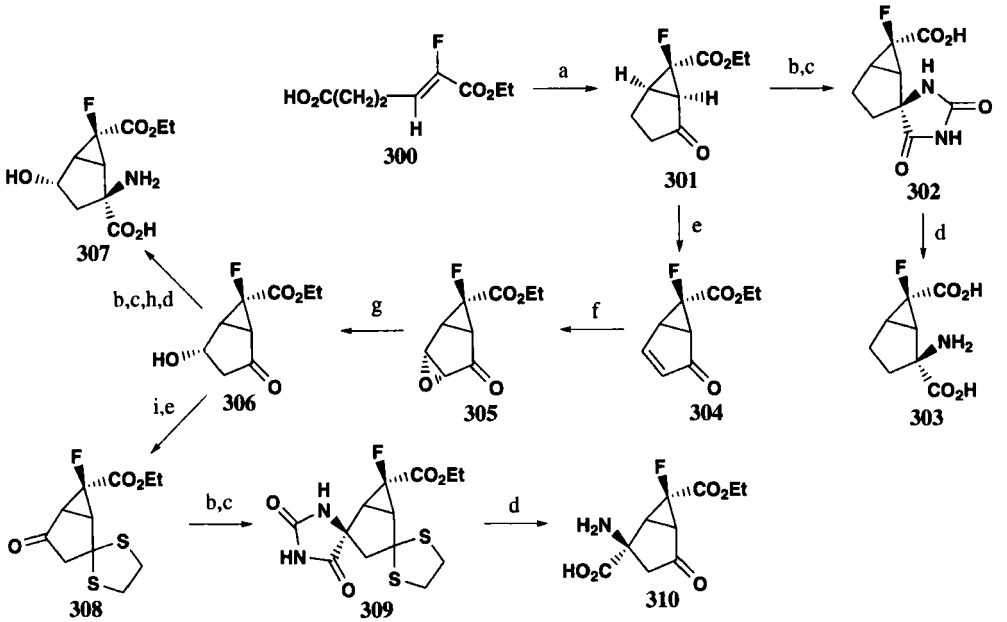
or (-)-**292**. Starting from difluoro intermediate **288**, the 3,3-difluoro amino acid **296** (26%) was obtained through hydantoin **295**. A different and more efficient approach for the chiral synthesis of compound *N,F-cis* (+)-**292** was followed from chiral ketone **285**, which was transformed into the unsaturated ketone (-)-**297**.




a) $EtO_2CCH_2SMe_2$•Br, DBU, PhMe; b) LHMDS, TMSCl, THF, then $(PhSO_2)_2NF$, $CH_2Cl_2$ (50%); c) $(NH_4)_2CO_3$, KCN, EtOH/$H_2O$; d) 60% $H_2SO_4$; e) 2.5 or 3M NaOH, $H_2O$; f) LHMDS, TMSCl, THF, then $Pd(OAc)_2$, MeCN (86%); g) TBHP, Triton B, PhMe (73%); h) KF•HF, ethylene glycol (46%); l) $H_2$, Pd/C, EtOH (75%)

**Scheme 48**

The epoxidation reaction gave a single diastereomer (+)-**298** which, on reaction with potassium fluoride in ethylene glycol, gave two unsaturated fluorinated esters (-)-**299a,b** (18:28). Reduction of the double bond followed by Bucherer-Berg reaction and hydrolysis afforded *1S,2R,3S,5R,6S*-(+)-**292** (48%). For the preparation of 6-*N,F-cis* fluoroamino acids **303,307** and **310**[76] a different approach was followed (Meth. B) (*Scheme 49*). In fact, starting from ethyl *Z*-2-fluoro-5-carboxy-2-pentenoate **300**, an intramolecular reaction using $Cu(TBS)_2$ afforded compound **301** which was transformed into the amino acid *1R*,2S*,5R*,6R**-**303** (34%) *via*




a) $(COCl)_2$, hexane, reflux, then $CH_2N_2$, $Et_2O$, then $Cu(TBS)_2$, benzene, reflux (27%); b) 1N NaOH; c) $(NH_4)_2CO_3$, KCN, EtOH/$H_2O$ (99%); d) 60% $H_2SO_4$, 150°C; e) LHMDS, TMSCl, THF, then $Pd(OAc)_2$, MeCN (89%); f) TBHP, Triton B, PhMe (98%); g) $(PhSe)_2$, $NaBH_4$, AcOH, EtOH (76%); h) EDC•HCl, EtOH, DMAP, DMF; i) TBDSMCl, imidazole, DMF, then $HS(CH_2)_2SH$, $BF_3$•$Et_2O$, $CHCl_3$; l) DMSO, DCC, Py-TFA (73%)

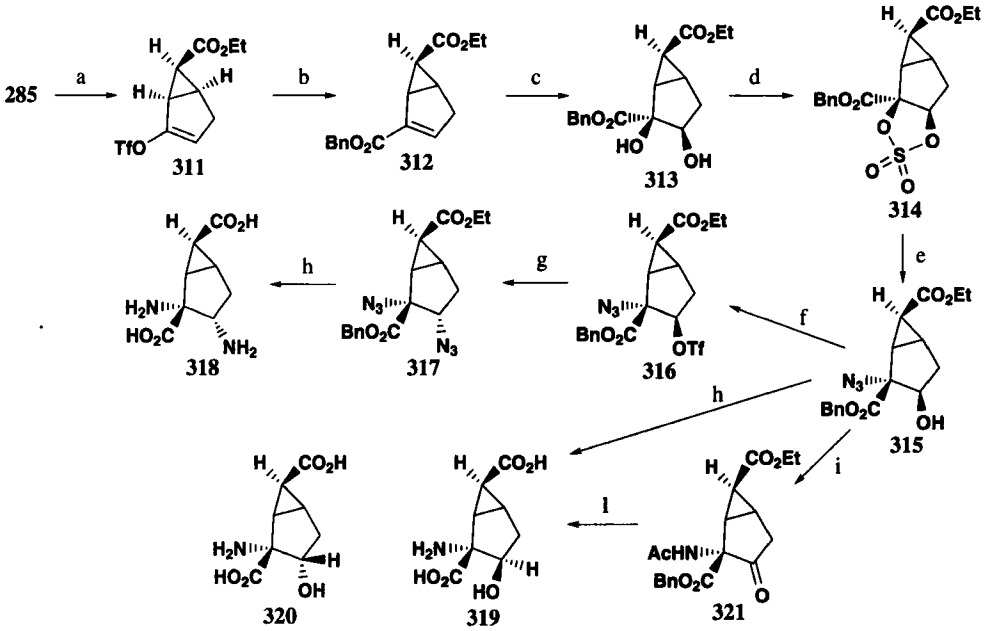
**Scheme 49**

hydantoin **302**. The 4-hydroxy and 4-oxo-amino acids *1R*,2S*,4S*,5S*,6S**-**307** and *1R*,2S*,5S*,6S**-**310** were prepared from **301** by way of epoxide **305** and unsaturated ketone **304**. The epoxide was regioselectively reduced to 4-hydroxy ketone **306** in which the fluorine and oxygen atoms are *trans*. According to the usual synthetic procedure reported before, compound **306** was transformed into amino acid **307** in very low yield (3%). The protection of the keto group and the oxidation of the hydroxy group in compound **306** gave intermediate **308** (48%), the precursor of the 4-keto-amino acid **310**. The synthesis of (+)- and (-)-**310** was achieved from chiral hydantoins **309**. From resolved pure enantiomers of 6-fluoroketone **301** both the syntheses of chiral (+)- and (-)-**303** and (+)-**310** were reported following the above described procedures. According to *Scheme 51* (see p. 186), the *1S*,2R*,4S*,5S*,6S**-4-fluoro-2-amino acid **331** was obtained by reacting the 4-hydroxy compound **324a** with diethylaminosulfur trifluoride.[77]

### *2. Nitrogen $Ac_{[3.1.0]}c$ Compounds*

Amino-(2,3- and 2,4-derivatives), azido- and nitro-substituted amino acids were reported. The preparation of chiral (*1S,2R,3S,5R,6S*)-2,3-diaminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid **318**[78] (*Scheme 50*) was made from hydroxy compound **315** (see below for its prepa-

ration) which was transformed into triflate **316**. The reaction with sodium azide formed the diazido derivative **317** as single diastereomer which was reduced and hydrolyzed to the diamino



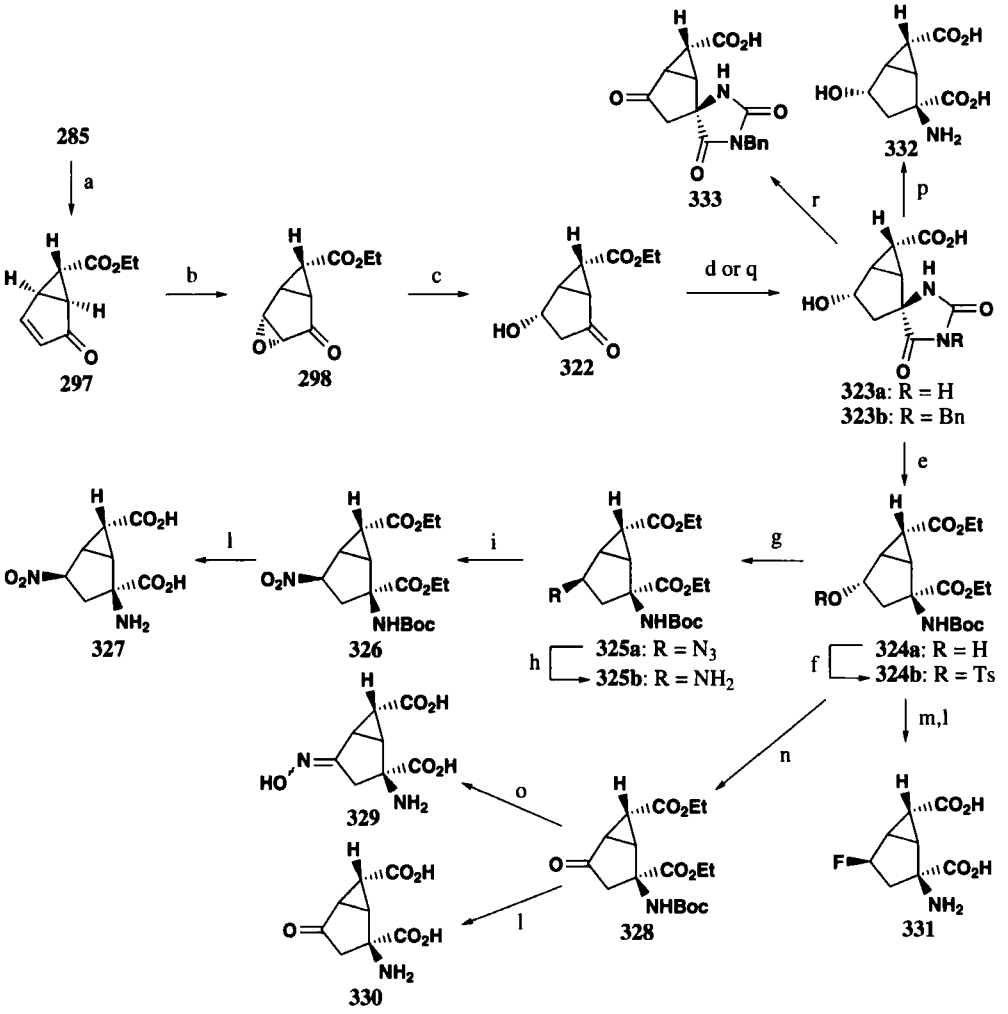

a) DIPEA, THF, BuLi, *N*-phenyl-*bis*(trifluoromethylsulfonyl)imine, -78 to 25°C (87%); b) $Pd(OAc)_2$, $Ph_3P$, BnOH, DMF, CO (75%); c) $K_2[OsO_2(OH)_4]$, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, $K_2CO_3$, $MeSO_2NH_2$, *t*BuOH, $H_2O$ (46%, *ee* 63%; 26%, *ee* 99%); d) $SOCl_2$, $CH_2Cl_2$, 40°C, then $NaIO_4$, $RuCl_3 \cdot H_2O$ (98%); e) $NaN_3$, $H_2O$, acetone, 50°C (62%); f) $(TfO)_2O$, Py, $CH_2Cl_2$, -78°C (86%); g) $NaN_3$, DMF, 80°C (49%); h) AcOH, $H_2O$, $H_2$, Pd/C, then 10% HCl (87%); i) $CH_2Cl_2$, PCC, 0°C (78%); l) thioacetic acid, 70°C, then $LiBH_4$, EtOH, $H_2O$, -50°C (88%), then 10% HCl (70%)

**Scheme 50**

acid **318** in which the two nitrogen atoms are *cis*. Diastereoselective synthesis of (*1R*,2R*,4S*,5S*,6R**)-4-azido-, -4-amino- and -4-nitro-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acids was reported (*Scheme 51*) from tosylated **324b**. The azido derivative **325a** was obtained by reacting the tosylate with azide ion. The reduction of the azido group gave the amino compound **325b**. Several 4-amino derivatives were also reported by reacting amine **325b** with the appropriate reagent.[77] The oxidation reaction of the amino group to nitro group with peracid gave **326** in poor yield. Finally, the deprotection of amino and carboxy groups gave the 4-nitro-amino acid **327** (*Scheme 51*).[79] The 4-hydroxyimino compounds **329** (*E/Z*, 2:1) were obtained from ketone **328** on reaction with hydroxylamine and hydrolysis.[77]

### *3. Oxygen $Ac_{[3.1.0]}c$ Compounds*

Two diastereomeric 3-hydroxy, the *N,O-trans* 4-hydroxy and the corresponding 3- and 4-cheto derivatives were synthesized. Furthermore, the chiral 3,4-dihydroxy compounds were reported. The synthesis of diastereomeric chiral (*1S,2R,3R,5R,6S*)- and (*1S,2R,3S,5R,6S*)-3-hydroxyamino



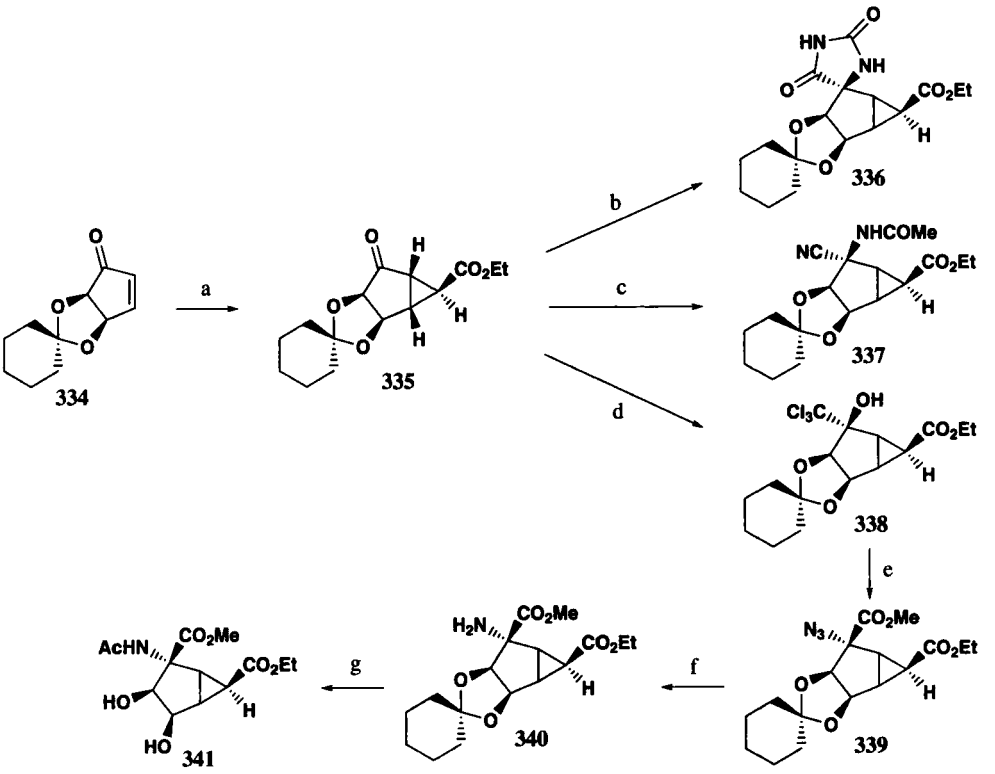

a) TMSCl, TEA, $CH_2Cl_2$, 0°C then $Pd(OAc)_2$, MeCN (80%); b) TBHP, DBU, THF, 0°C (89%); c) *N*-acethyl-L-cysteine, $Na_2B_4O_7$, $(PhSe)_2$, $H_2O$, EtOH, THF (82%); d) $(NH_4)_2CO_3$, KCN, EtOH/$H_2O$; e) 2M NaOH, then EtOH, $SOCl_2$, 0°C, then $NaHCO_3$, THF, $Boc_2O$ (26% from **323a**); (f) TsCl, Py (91%); g) $NaN_3$, DMSO, 35°C (98%); h) $Ph_3P$, THF/$H_2O$ (62%); i) *m*ClPBA, $CHCl_3$ (9%); l) EtOAc, HCl, 0°C, then 1N NaOH (**327**: 71%; **330**: 31%); m) DAST, $CH_2Cl_2$; n) PDC, $CH_2Cl_2$ (98%); o) AcOEt, HCl, 0°C, then $NH_2OH$•HCl, AcONa, EtOH/$H_2O$, 80°C (84%), then 1N NaOH/THF (60-68%) p) 1N NaOH (90%); q) method d then DMF, $NaHCO_3$, BnBr, 100°C (19%); r) Jones' reagent, acetone, 0°C (88%)

**Scheme 51**

acids was done using an original synthetic stategy starting from **285** (*Scheme 50*)[78] whose enol triflate **311** was transformed into unsaturated carboxylate **312**. Asymmetric dihydroxylation gave the chiral *cis*-diol **313** which was protected at oxygen atoms. By reacting sulphate **314** with sodium azide compound **315** was obtained which was reduced and hydrolyzed to chiral amino acid **319** having *N,O-trans* atoms. By contrast, when **315** was oxidized to ketone **321** and then reduced and hydrolyzed. A mixture of the two diastereomeric alcohols **319** and **320** (1:1) was obtained. The diastereoselective synthesis of (*1R*,2R*,4R*,5S*,6S**)-4-hydroxy-2-

amino[3.1.0]cyclohexane-2,6-dicarboxylic acid **332**[77] was reported from hydroxy ketone **322** obtained by regioselective reduction of epoxide **298** (*Scheme 51*). The hydroxyketone **322** was trasformed into a mixture of hydantoins (1:1). The desired diastereomer **323a** was isolated by HPLC (26%) or by crystallization (8%) and hydrolyzed to **332** (90%). Hydantoin **323a** was transformed into protected 4-hydroxyamino acid **324a**. The synthesis of the methoxy derivative was also reported. Two different synthetic approaches to 4-oxoamino acids were reported (*Scheme 51*).[77] The first gave poor yield (19%) and was done by transformation of hydroxyketone **322** into benzylated hydantoin **323b** oxidized to ketone **333**. Deprotection was not attempted. The second route resulted in the 4-oxo-amino acid **330** starting from protected amino acid **324a** which was oxidized to ketone **328** and then hydrolyzed.

The enantioselective synthesis of *1S,2R,3S,4R,5R,6R*-3,4-dihydroxy-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid **341** was performed from the chiral unsaturated ketone **334** (*Scheme 52*).[80]




a) $EtO_2CCH_2SMe_2$•Br, DBU, $CHCl_3$ (96%); b) $(NH_4)_2CO_3$, KCN, EtOH/$H_2O$, 70°C (50%); c) KCN, $NH_4Cl$, $Al_2O_3$/ultrasound, then MeCOCl, DIPEA (60%); d) LHMDS, $CHCl_3$, (94%); e) DBU, 18-Crown-6, $NaN_3$, MeOH (84%); f) $H_2$, Pd/C, AcOEt, 30 psi (71%); g) MeCOCl, TEA, $CH_2Cl_2$, then TFA, $H_2O$ (67%)

**Scheme 52**

The cyclopropanation reaction of **334** (Meth. C) occurred in quantitative yield and gave a single diastereomer **335**. The Bucherer-Berg and Strecker reactions resulted in the hydantoin

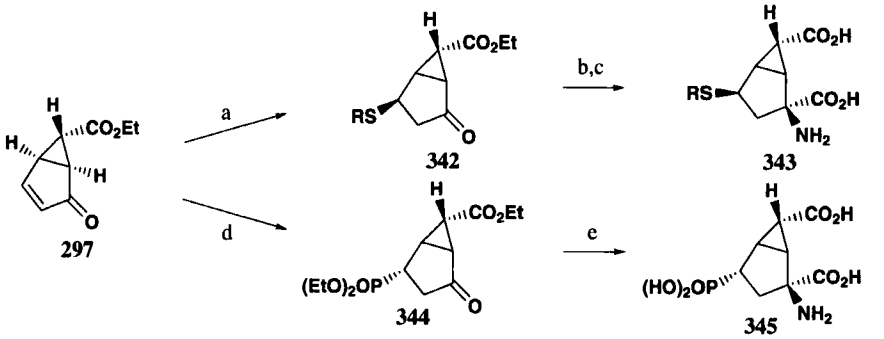
**336** and nitrile **337**, as pure isomers, having the amino group *cis* to the hydroxy ones. By contrast, using a modified Corey-Link reaction, it was possible to prepare the amino acid derivative **341** having the opposite configuration at C-2. On reacting **335** with $CHCl_3$ in the presence of the base, compound **338** was obtained and was rearranged to **339** by sodium azide in basic conditions. Reduction of azido group to **340**, protection of amino group and deprotection of hydroxy groups afforded the chiral amino acid derivative **341**.

### *4. Sulfur $Ac_{[3.1.0]}c$ Compounds*

A series of *(1S*,2R*,4S*,5S*,6S*)*-4-thioaryl- or -4-thioalkyl-2-aminobicyclo[3.1.0] hexane-2,6-dicarboxylic acids **343** were prepared as depicted in *Scheme 53* from intermediate **297** which was reacted with mercaptans giving **342** in good yield. **342** was transformed into amino acids **343** *via* the Bucherer-Berg reaction. Oxidation to sulfoxide and sulfone was also described.[81]

### *5. Phosphorus $Ac_{[3.1.0]}c$ Compounds*

Using the Strecker reaction in the presence of alumina and ultrasound, the *1S*,2R*,4R*,5S*,6S**-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxy-4-phosphonic acid **345** was prepared from intermediate **344** obtained by reacting **297** with triethyl phosphite (*Scheme 53*).[77]




a) RSH, THF, TEA; b) $(NH_4)_2CO_3$, KCN, EtOH/$H_2O$; c) 2N NaOH; d) $(EtO)_3P$, PhOH, 100°C (92%); e) KCN, $NH_4Cl$, $Al_2O_3$/ultrasound, then MeCOCl, DIPEA (55%), then 6N HCl, reflux (99%)

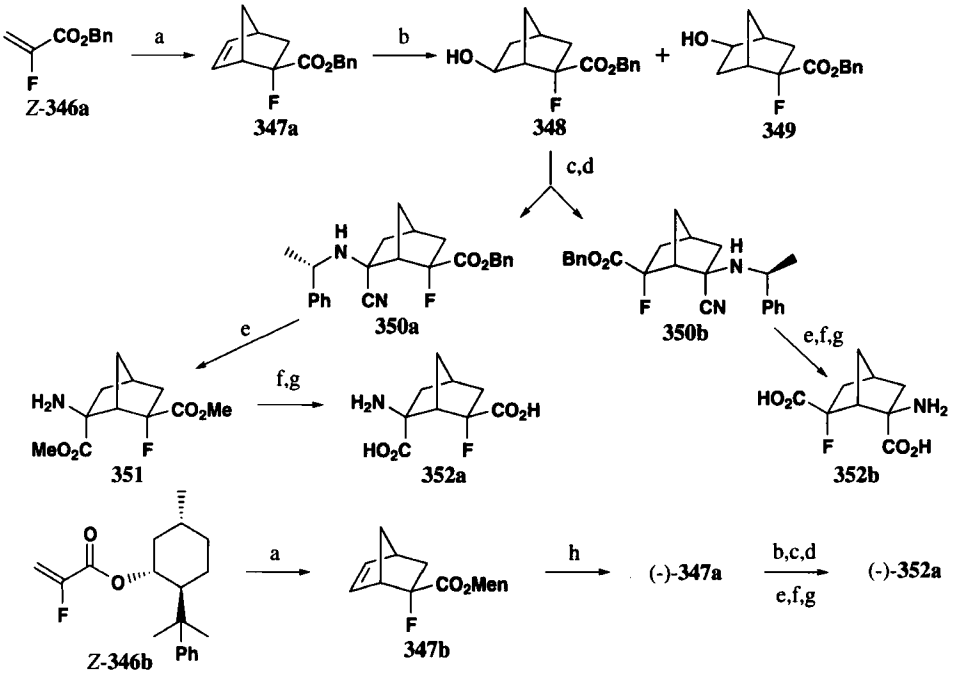
**Scheme 53**

## VIII. 2-AMINOBICYCLO[2.2.1]HEPTANE-2-CARBOXYLIC ACIDS

Two general methodologies were used for the preparation of heterosubstituted 2-aminonorbornane-2-carboxylic acid derivatives: *i*) the Diels-Alder reaction applied to heterosubstituted dienes or dienophyles (Meth. C) and *ii*) the hetero-functionalization of norbornane/norbornene ring (Meth. A) obtained through a Diels-Alder reaction. The first offers the advantages depicted for cyclohexyl derivative syntheses and is the more representative. The formation of both *exo*- and *endo*- diastereomeric compounds is achieved. As heteroatoms, only the fluoro, oxygen and sulfur atoms are linked to the norbornane ring.

### *1. Halo $Ac_{[2.2.1]}c$ Compounds*

The diastereoselective synthesis of 2-fluoro-6-aminonorbornane-2,6-dicarboxylic acid[82] was reported from the 2-fluoronorbornene derivative *exo*-**347a**, obtained as single diastereomer from Z-**346a** by cycloaddition reaction with cyclopentadiene **136l** (Meth. C) (*Scheme 54*).




a) cyclopentadiene **136l**, $Et_2AlCl$, $CH_2Cl_2$ (**347a**: 72%, **347b**: 90%); b) $BH_3{\cdot}SMe_2$, $C_{12}H_{26}$/THF, then $H_2O_2$, NaOH (68%); c) Dess-Martin reagent, $CH_2Cl_2$ (99%); d) (*S*)-1-phenylethylamine, $TiCl_4$, then TMSCN, $AlCl_3$ (70%); e) HCl, AcOH, then $CH_2N_2$ (49%); f) $Ti(O\text{-}iPr)_4$, BnOH (69%); g) $H_2$/Pd(OH) (68%); h) NaOH, then BnOH, EDC (70%)

**Scheme 54**

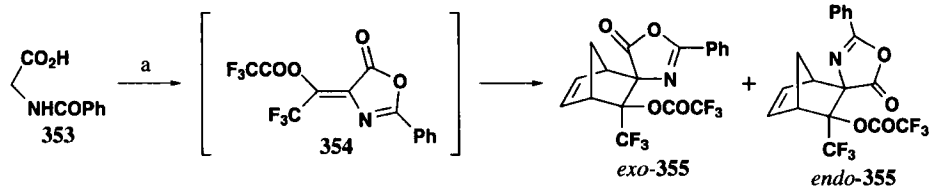
Compound **347a** was hydroxylated giving two regioisomeric compounds **348** and **349** (1.7:1) with *exo* selectivity. The major isomer **348** was oxidized to the corresponding ketone which reacted poorly in both the Strecker and Bucherer reactions. However, using (*S*)-phenylethylamine in the presence of $TiCl_4$ followed by trimethylsilyl cyanide, two diastereomers **350a,b** (31:39) were formed. After separation, **350a** and **350b** were transformed into the corresponding chiral amino acids **352a,b** according to *Scheme 54*. The same authors report on the chiral synthesis of *1S,2S,4S,6S*-**352a**. Starting from chiral acrylate *Z*-**346b** and cyclopentadiene **136l** the chiral *exo*- **347b** (92% *d.e.*) was obtained and transformed into (-)-**347a**. According to the synthetic pathway depicted before, (-)-**347a** was transformed into the chiral compound (-)-**352a**.

### *2. Oxygen $Ac_{[2.2.1]}c$ Compounds*

Both 3-, 5- and 6-hydroxy $Ac_{[2.2.1]}c$ compounds were prepared and, depending on the synthetic approach, the *exo* and/or *endo* selectivity was achieved. Regio- and diastereoselective syntheses of polyhydroxylated compounds are described. The Diels-Alder reaction of heterosub-

stituted dienophiles and cyclopentadiene is the classical method to obtain 2-amino-3-hydroxynorbornene-2-carboxylic acids (Meth. C).

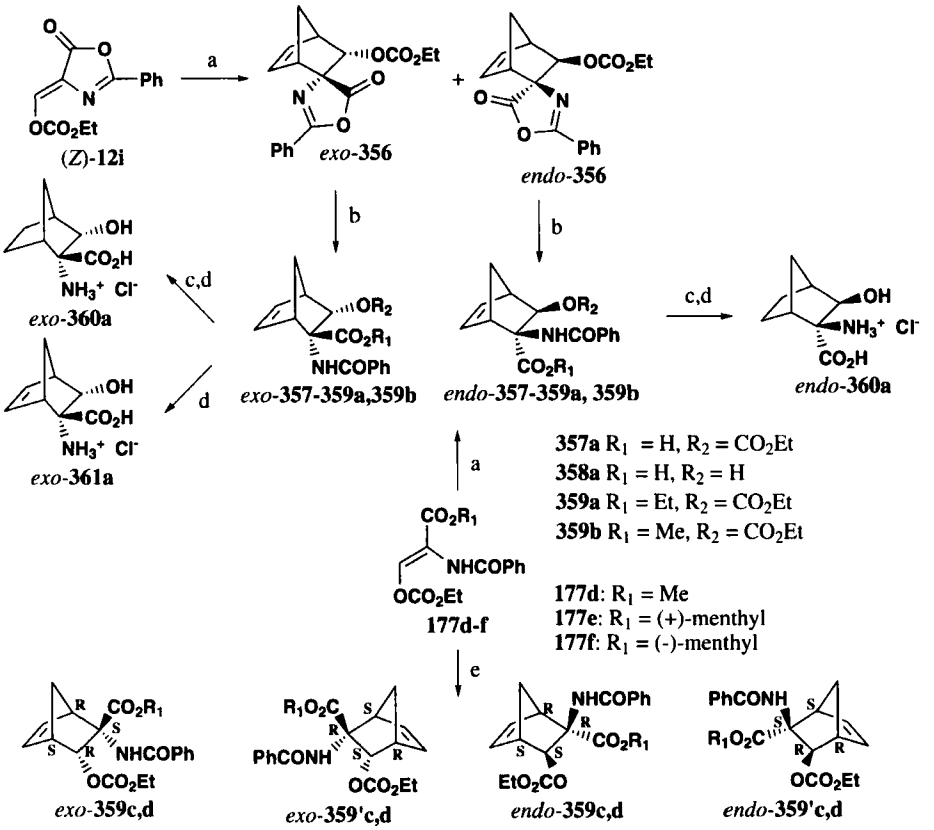
Cufos *at al.*[83] reported the synthesis of a mixture of *exo*-**355** and *endo*-**355** adducts (4:1) by a "one pot" reaction starting from hippuric acid **353**, trifluoroacetic anhydride and cyclopentadiene, *via* oxazolone intermediate **354** (*Scheme 55*). The hydrolysis of the oxazolone ring was




a) cyclopentadiene, $(CF_3CO)_2O$, DMF, 0°C (80%)

**Scheme 55**

not reported. The 2-amino-3-hydroxynorbornane-2-carboxylic acids *exo*-**360** and *endo*-**360**[84a] (*Scheme 56*) were obtained from oxazolone *Z*-**12i** and cyclopentadiene **136j** (Meth. C). The



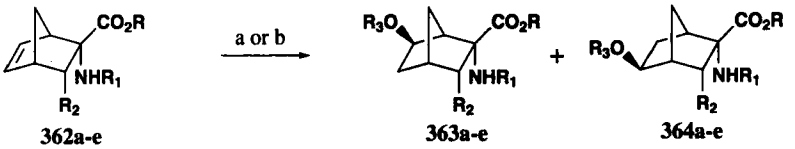

**359c,359'c**: $R_1$ = (+)-menthyl; **359d,359'd**: $R_1$ = (-)-menthyl

a) cyclopentadiene **136j**, Lewis acid, $CH_2Cl_2$ (from **12i**: 70-90%; from **177**: 45-50%); b) **357a**: THF, HCl (100%); **358a**: EtOH, $Me_2NH$ (60%), **359a**: EtOH, $H^+$ (90%); c) $H_2$/ Pd, EtOH (100%); d) 20% HCl, 100°C (80-95%); e) **136**, $Mg(ClO_4)_2$, ultrasound, $CH_2Cl_2$ (90%)

**Scheme 56**

cycloaddition reaction was catalyzed by Lewis acids and formed two cycloadducts *exo*-**356** and *endo*-**356** (70:30). Different Lewis acids ($EtAlCl_2$, $Mg(ClO_4)_2$, $Ce(OTf)_4$, and $Yb(OTf)_3$) were tested and the best results were obtained with $EtAlCl_2$ (74%), $Li(ClO_4)_2$ (88%) and $Mg(ClO_4)_2$ (90%). The hydrolysis of the oxazolone ring to compounds **357a** followed by deprotection to compounds **358a**, reduction and hydrolysis gave the corresponding amino acids *exo*- and *endo*-**360**. The synthesis of 1-amino-2-ethoxycarbonyloxyacrylate **177d** and of the chiral analogues **177e,f** was reported (*Scheme 56*).[84b] They were used for a cycloaddition reaction with cyclopentadiene. The acrylate **177d** was less reactive than oxazolone **12i** and the reaction worked both with $EtAlCl_2$ (45%) and $Mg(ClO_4)_2$ (50%), giving cycloadducts *exo*- and *endo*-**359b**. Interestingly, the *exo/endo* ratio was reverted (25:75) when starting from the same acrylate (**177d**) and $EtAlCl_2$. Reaction of chiral acrylates **177e,f** using $Mg(ClO_4)_2$ and ultrasound resulted in an improvement of yields (90%) and a 70:30 *exo/endo* ratio was obtained. The cycloaddition reaction gave four diastereomeric cycloadducts *exo*-**359cd,**, *exo*-**359'c,d**, *endo*-**359c,d** and *endo*-**359'c,d** with satisfactory diastereoselectivity (*exo*: 79% *d.e.; endo*: 87% *d.e.*).

The regioselective hydroboration of a series of norbornene amino acid derivatives **362** was studied by Brands[85] *at al.* using both $BH_3$.THF and catecholborane in the presence of a rhodium catalyst followed by oxidative workup (Meth. A) (*Scheme 57*). *Exo* selectivity was




**362a-e** **363a-e** **364a-e**

**a**: R = Et; $R_1 = CO_2Bn$; $R_2$ = H
**b**: R = Et; $R_1$ = COPh; $R_2$ = H
**c**: R = Me; $R_1$ = CHO; $R_2$ = CH(Me)$NBn_2$
**d**: R = Me; $R_1$ = H; $R_2$ = CH(Me)$NBn_2$
**e**: R = Me; $R_1 = CO_2Me$ $R_2$ = CH(Me)$NBn_2$

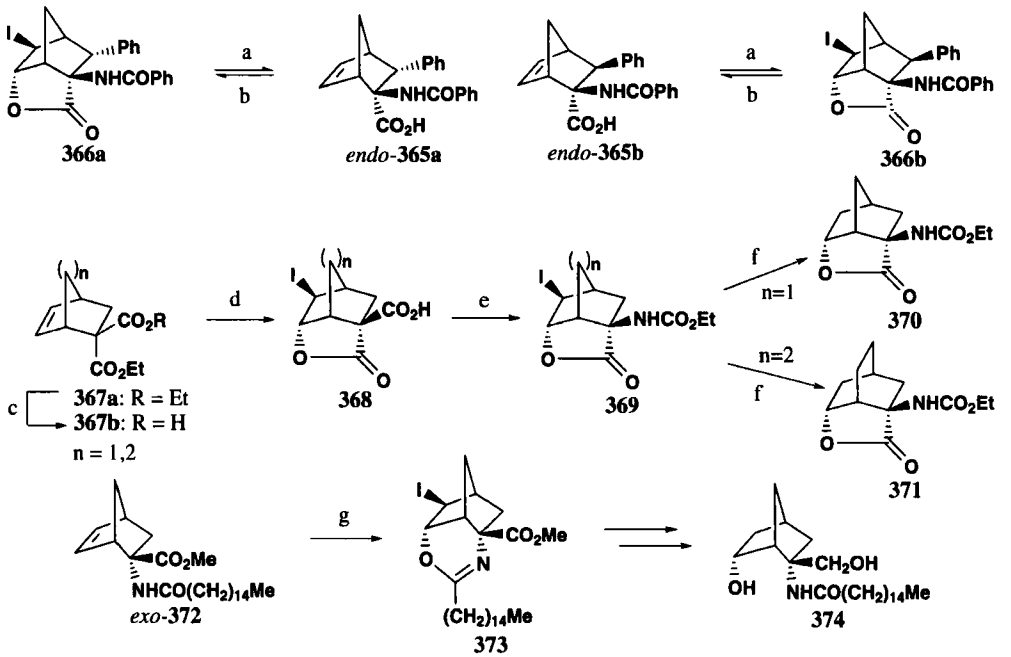
$R_3$ = OH, Ac

a) $BH_3$•THF, then $H_2O_2$, then $Ac_2O$, TEA, DMAP, $CH_2Cl_2$; b) catecholborane, $(Cl(COD)_2Rh)_2$•$4Ph_3P$, THF, then $H_2O_2$, then $Ac_2O$, TEA, DMAP, $CH_2Cl_2$

**Scheme 57**

observed in all cases, but the regioselectivity at C-5 (compound **364**) and C-6 (compound **363**) was dependent on the substituents and kind of the transition metal catalyst. Starting from **362a** and operating with $BH_3$ the **363/364** ratio is 62:38, but in presence of the catalyst a inverted ratio was observed (22:78). Moreover, when the compounds **362c-d** functionalized at C-3 were used, the C-6 regioisomer **363** was preferred in all cases and its amount was increased by use of the catalyzed reaction.

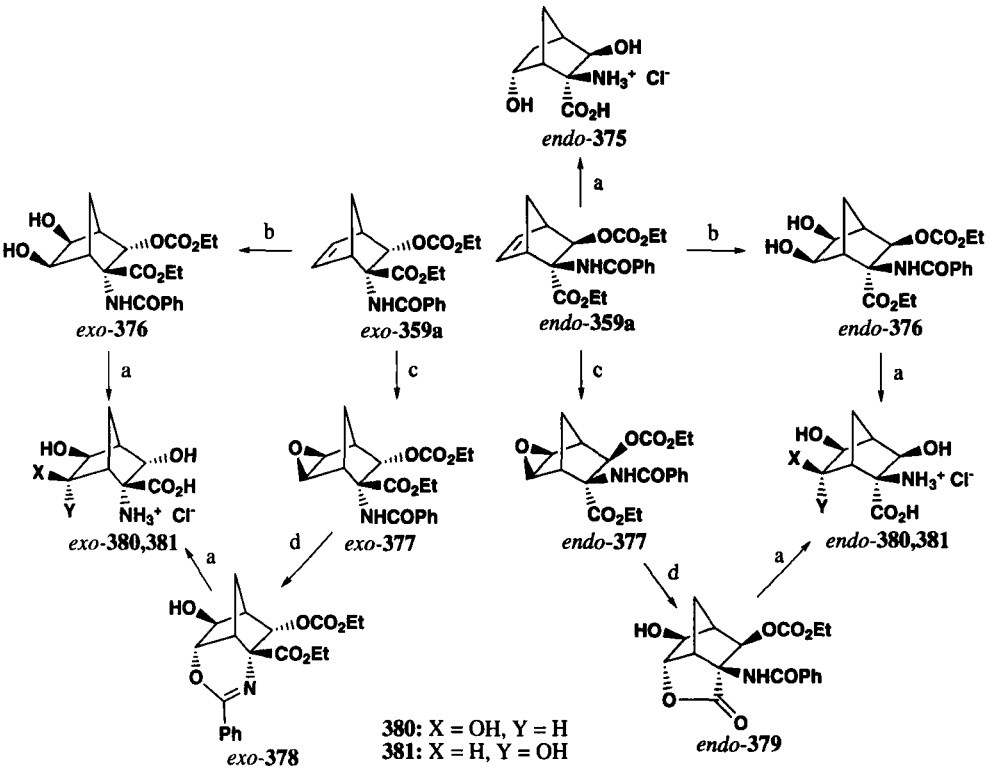
Taking advantage on the use of the iodolactonization reaction starting from *endo*-carboxylates (Meth. A), the regio and stereoselective functionalization of C-6 with an hydroxy group can be done giving the *N,O-trans* compounds (*Scheme 58*).




a) $I_2$, $NaHCO_3$ (46-50%); b) Zn, AcOH (40-92%); c) MeOH, THF, NaOH; d) $NaHCO_3$, $I_2$, KI, $H_2O$; e) $SOCl_2$, reflux, then $NaN_3$, acetone, then EtOH reflux; f) $(n\text{Bu})_3SnH$, azobisisobutyronitrile, THF, $Et_2O$; g) $I_2$, $CH_2Cl_2$ (93%)

**Scheme 58**

When compounds *endo*-**365a** and **365b** were treated with iodine in basic conditions the iodo lactone derivatives **366a,b** were isolated, respectively. Attempts to eliminate the iodine atom with zinc in acetic acid produced the starting olefins **365** (*Scheme 58*).[86] Protected lactone **370** was prepared from diethyl 2,2-norbornenedicarboxylate **367a** (n = 1) which was selectively hydrolyzed to *exo* carboxylate **367b** (Meth. A) (*Scheme 58*). The iodolactonization reaction gave the iodo lactone **368** which was transformed, by Curtius reaction, into **369**. Iodine elimination with tributyltin hydride afforded lactone **370**.[87] Instead, when iodo-oxazination reaction on *exo* compounds was used, the functionalization of C-6 with the oxygen atom (Meth. A) (*Scheme 58*) occurred giving the *N,O-cis* compound. From *exo* ester **372** and using iodine, the oxazine derivative **373** was obtained which was the precursor of compound **374** an inhibitor of protein kinase.[88] The direct formation of amino acid *endo*-**375**, having two *trans* hydroxy groups at C-3 and C-6, was observed when the *endo* ester **359a** was hydrolyzed in acidic conditions (Meth. A) (*Scheme 59*).[89] Four diastereomeric 2-amino-3,5,6-trihydroxynorbornanecarboxylic acids[89] were prepared with *trans-cis* (compound *exo*-**380**), *cis-cis* (compound *endo*-**380**), *trans-trans* (compound *exo*-**381**) and *cis-trans* (compound *endo*-**381**) relationships between OH-3 and OH-5 and between the latter and OH-6. They were obtained from esters *exo*- and *endo*-**359a** taking advantage of the presence of the double bond and the benzoylamino group in the *exo* series, and of the carboxy group in the *endo* series (Meth. A). When esters *exo*- and *endo*-**359** were reacted with osmium tetroxide the



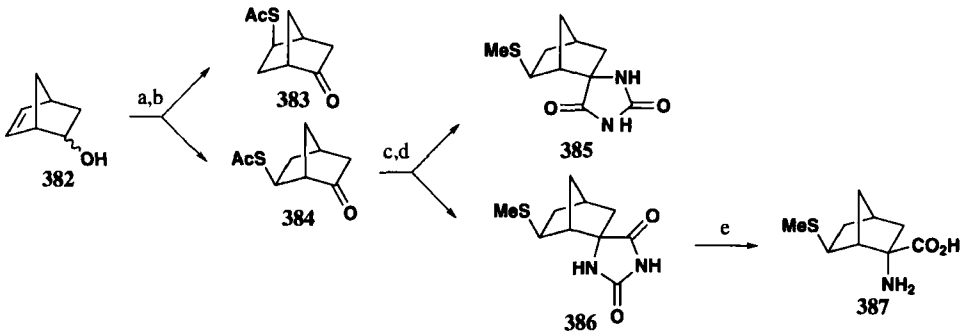

a) 20% HCl, 100°C (80-90%); b) $OsO_4$, NMO, acetone/$H_2O$ (74-80%); c) MCPB, $CHCl_3$ (67-99%); d) $TiCl_4$, $CH_2Cl_2$ (66-75%)

**Scheme 59**

diols *exo*-**376** and *endo*-**376** were obtained, respectively, which were hydrolyzed to aminoacids *exo*- and *endo*-**380**. The epoxidation reaction of ester *exo*-**359** produced compound *exo*-**377** which was transformed into oxazine *exo*-**378** and hydrolyzed to amino acid *exo*-**381**. From ester *endo*-**359**, the epoxide *endo*-**377** was obtained together with the lactone *endo*-**380**. The epoxide *endo*-**377** was transformed into *endo*-**379** and hydrolyzed to amino acid *endo*-**381**.

### *3. Sulfur $Ac_{[2.2.1]}c$ Compounds*

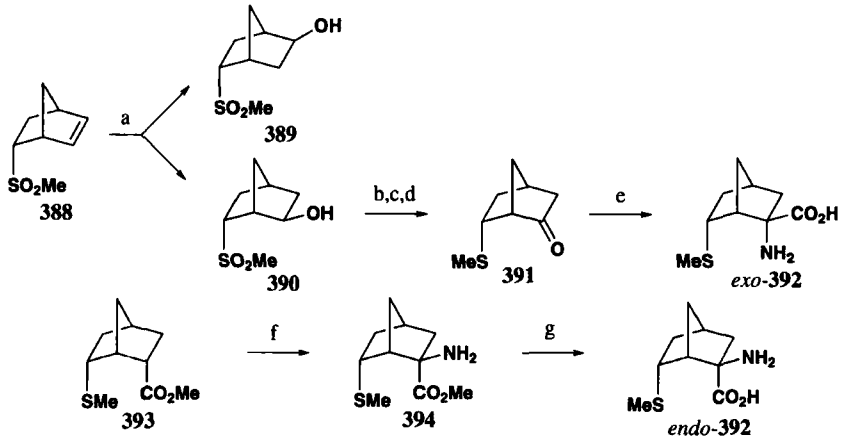
Three diastereomeric 2-amino-6-methylthio-norbornane-2-carboxylic acids were reported in the literature (Meth. A). The first one[90] (*Scheme 60*), with an *exo* methylthio group, was prepared from acetylthio-ketone **384** obtained from alcohol **382** through addition of thio-lacetic acid followed by oxidation of the hydroxy group (regioisomeric mixture: **383/384**, 1:1). Compound **384** was converted into the methylthio derivative and, by the Bucherer reaction, transformed into a mixture of diastereomeric spirohydantoins **385** and **386** (1:4). The hydrolysis of the major isomer **386** gave amino acid **387**.




a) AcSH, $C_6H_6$, AIBN; b) Jones' reagent, 0°C (88%); c) MeI, MeONa (85%); d) $(NH_4)_2CO_3$, KCN (95%); e) $Ba(OH)_2$ 120°C, then $H^+$(90%)

**Scheme 60**

Both *exo*-[91] and *endo*-amino acids[92] **392** (Meth. A) (*Scheme 61*) having an *endo*-thiomethyl group were reported by Glass *at al.* starting in the first case from alcohol **390** obtained from olefin **388** as a regioisomeric mixture with **389** (5:3, 83%). Compound **390** was




a) $BH_3$, THF, then $H_2O_2$, NaOH (83%); b) TBDMSCl, imidazole DMF; c) DIBALH, toluene; d) DMSO, oxalyl chloride, $CH_2Cl_2$ (28%); e) $(NH_4)_2CO_3$, KCN, 80°C, then $Ba(OH)_2$, then $H^+$ (51%); f) *N,N*-diisopropylamine, THF, -78°C, BuLi, HMPA, *O*-(mesitylenesulfonyl)hydroxylamine (38%); g) MeOH, $H_2O$, NaOH

**Scheme 61**

transformed into ketone **391** in low yield (28%) which gave **392** (51%) after Bucherer reaction and hydrolysis. *Endo*-**392** was obtained by a basic amination reaction of ester **393**. The reaction gave a single diastereomer **394** which was hydrolyzed to the corresponding amino acid *endo*-**392**.

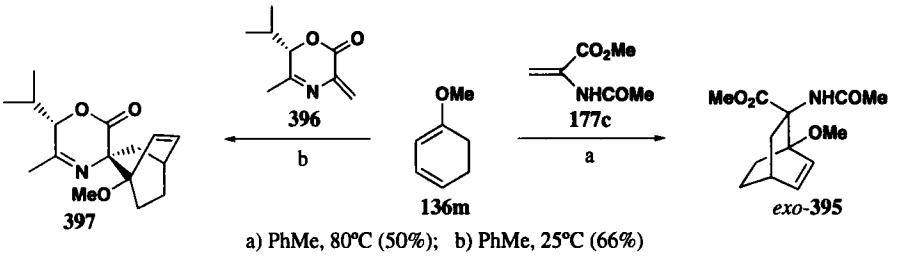
## IX. 2-AMINOBICYCLO[2.2.2]OCTANE-2-CARBOXYLIC ACIDS

Only oxygen substituted $Ac_{[2.2.1]}c$ compounds were described in the literature. The 1-methoxy- or 1-silyloxy-1,3-cyclohexadienes **136m,n** were used in the cycloaddition reaction with several dienophiles for the preparation of 2-aminobicyclo[2.2.2]oct-5-ene-2-carboxylic acid

derivatives in which an oxygen atom is linked at C-1 (Meth. C).

### *1. Oxygen $Ac_{[2.2.1]}c$ Compounds*

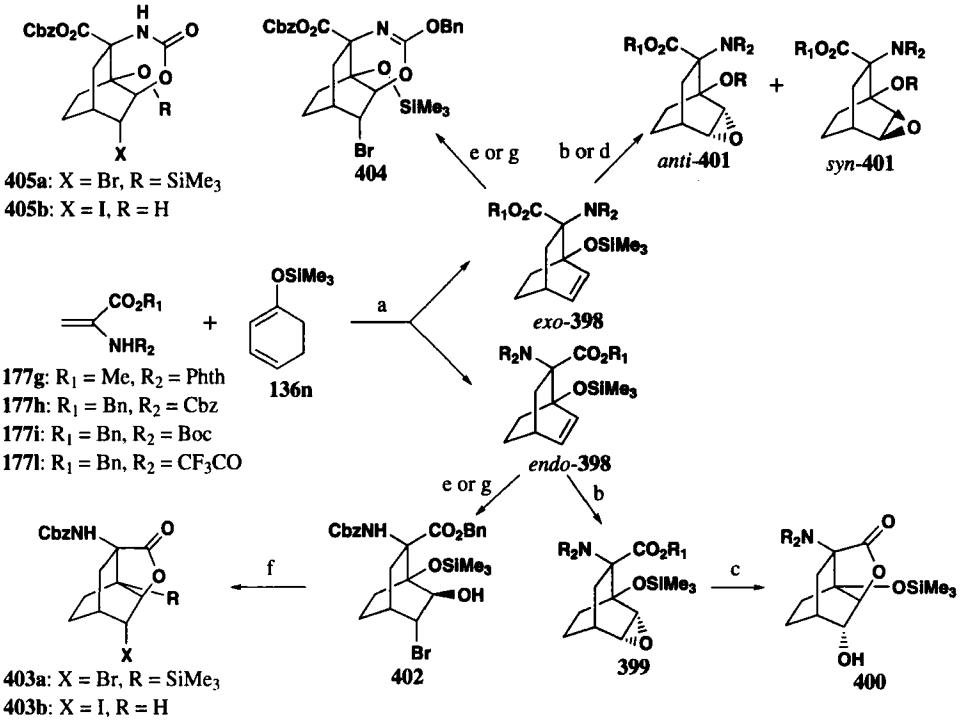
Reacting diene **136m** with acrylate **177c** gave a single regioisomeric adduct *exo*-**395** (*Scheme 62*).[93] Using chiral *S*-methyleneoxazinone **396** and diene **136m** the chiral spiro compound **397** was obtained as the major isomer ($^1$H NMR: **397**: 94%; other diastereomers: 6%) (*Scheme 62*).[94]




a) PhMe, 80°C (50%); b) PhMe, 25°C (66%)

**Scheme 62**

The reaction of aminoacrylates **177g-l** with diene **136n** gave two diastereomeric compounds *exo*-**398** and *endo*-**398** (*Scheme 63*) with the same regiochemistry but with a




a) PhMe, 120°C (51-72%); b) R = $SiMe_3$: MCPBA, $NaHCO_3$, toluene, 25°C (75-97%); c) $CH_2Cl_2$, $TiCl_4$, -78°C (36-66%); d) R = H: $CH_2Cl_2$, $BF_3$•$Et_2O$ (100%), then MCPBA, toluene, 0°C (67%); e) NBS, dioxane, $H_2O$, 25°C (*endo:* 60%, *exo:* 88%); f) THF, *t*BuOK, -78°C (60%); g) $I_2$, $CHCl_3$, $H_2O$ (lactone 74%, urethan 22%)

**Scheme 63**

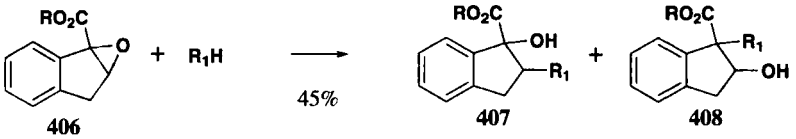
different *exo/endo* ratio depending on the substituent on nitrogen atom.[95] In fact, from **177g** an 1.6:1 *exo/endo* ratio was found. In other cases the ratio was in favor of the *endo* isomer and the best result was obtained when $R_2 = CF_3CO$ (*exo/endo*, 1:3.3). The adducts were epoxidized, the stereochemical results depending both on the *exo* or *endo* configuration of the starting material and, in the case of the *exo* adduct, on the kind of $R_1$ and $R_2$ groups.[96]

Starting from the *endo* adducts **398**, the epoxidation reaction took place from the less hindered face of the olefin giving single diastereomers *anti*-**399** which were transformed into lactones **400** by reacting with $TiCl_4$. Instead, starting from the *exo* adducts **398** a mixture of isomeric epoxides *anti*-**401** (major) and *syn*-**401** was obtained. Interestingly, when *exo*-**398** having $R_2$= Phth was desilylated and then epoxidized, only the *syn* epoxide **401** was otained. By contrast, starting from *exo*-**398** with $R_2 = CF_3CO$ the same reaction sequences produced only the *anti* epoxide **401**. In order to obtain the *syn* epoxides the same authors tested a different synthetic approach *via* halohydrin.[97] Treating the *endo* adduct **398** with NBS in aqueous dioxane, a mixture of the corresponding halohydrin **402** and lactone **403a** was obtained (**402/403a**, 5:1). The halohydrin **402** was quantitatively transformed into **403a** by a basic treatment. Under the same reaction conditions the *exo* adduct **398** afforded a mixture of bromo oxazine **404** and bromo urethan **405a** (**404/405a**, 1:1.4). By reaction with iodine in water and starting from a mixture of *exo* and *endo* adducts the corresponding iodo lactone **403b** and iodo urethan **405b** were obtained. The 6-hydroxy lactone **371** was obtained from **367a** (n = 2) according to the synthetic pathway depicted for the norbornane analogue **370** (Meth. A) (*Scheme 58*).[87]



## X. MISCELLANEOUS

The addition of amines to 1,2-epoxyindane-1-carboxylate derivatives **406** gave a mixture of regioisomeric β-amino-α-hydroxy- and α-amino-β-hydroxy acid derivatives **407** and **408** (*Scheme 64*). A different ratio of the two compounds was obtained depending on the bulkyness of the ester function in **406** and of the attacking nucleophile.[98]

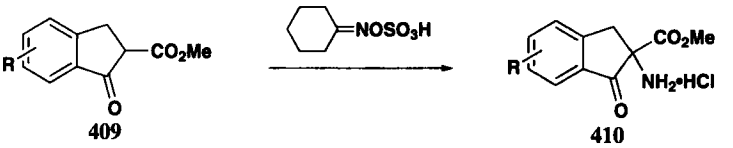



406 407 408

R = Et, $R_1$ = MeN$(CH_2)_2$CN or MeNH: **407/408**, 22:1
R = *t*Bu, $R_1$ = MeNH: **407/408**, 1:10
R = *t*Bu, $R_1$ = MeN$(CH_2)_2$CN: **407/408**, 3:1

**Scheme 64**

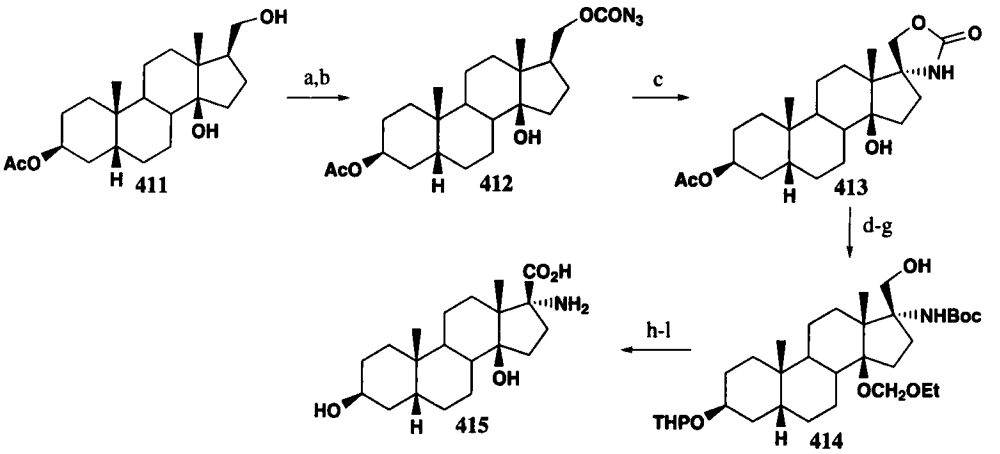
A series of ethyl 2-aminoindane-2-carboxylates **410** was prepared as precursors for the preparation of compounds having anthropodicide activity (*Scheme 65*). Keto esters **409** were aminated in basic conditions using the imine derived from cyclohexanone and hydroxylamine-*O*-sulfonic acid giving **410**.[100] Steroidal amino acid **415** (having digitalis steroidal skeleton), with




a) toluene, DABCO, 50°C, then 1N HCl (50%)

**Scheme 65**

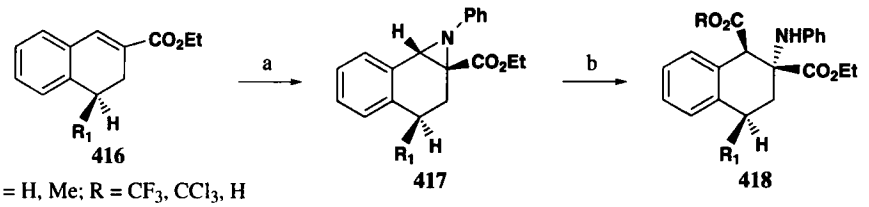
the amino acid functions on C-5 ring, was produced from steroidal compound **411** which was transformed into acyl azide **412** and pyrolyzed to the cyclic urethan **413**. Hydrolysis of this ring and protection both of nitrogen atom and tertiary hydroxy produced intermediate **414** which was transformed into amino acid **415** (*Scheme 66*).[99]




a) triphosgene, pyridine, $CH_2Cl_2$; b) $NaN_3$, $Me_2CO$ (72%); c) tetrachloroethane, 140°C (70%); d)KOH, EtOH; e) DHP, TsOH, dioxane; f) chloromethyl ethyl ether, DIPEA, $CH_2Cl_2$, 0°C; g) $Boc_2O$, NaOH, *t*BuOH (52%); h) PDC, $CH_2Cl_2$; i) $KMnO_4$, $NaH_2PO_4$ *t*BuOH; l) TsOH, $MeCN/H_2O$ (48%)

**Scheme 66**

Carbomethoxyaziridines **417**, obtained from **416** and phenyl azide, were the starting material for the diastereoselective preparation of tetrahydronaphthalene derivatives **418** (85-90%) after their treatment with organic acids (*Scheme 67*).[101]




$R_1$ = H, Me; R = $CF_3$, $CCl_3$, H

a) $PhN_3$, $CH_2Cl_2$; b) $RCO_2H$, benzene (85-90%)

**Scheme 67**

## ABBREVIATIONS

AIBN = azobisisobutyronitrile

Boc-L-Phe = *N*-*t*-butoxycarbonyl-L-phenylalanine

Bn = benzyl

Bz = benzoyl

CAN = ceric ammonium nitrate

Cbz = carbobenzyloxy

ClPBA = chloroperbenzoic acid

CTACl = cetyltrimethylammonium chloride

$Cu(TBS)_2$ = *bis*(*N*-*t*-butylsalicylaldimine) copper (II)

DABCO = 1,4-diazabicyclo[2.2.2]octane

DAST = diethylaminosulfur trifluoride

DBN = 1,5-diazabicyclo[4.3.0]non-5-ene

DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

DEC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

DEAD = diethyl azodicarboxylate

DHP = 3,4-dihydro-2*H*-pyran

$(DHQD)_2PHAL$ = bis(dihydroquinidine)phthalazine

DIBAL = diisobutylaluminum hydride

DIPEA = diisopropylethylamine

DMAP = 4-dimethylaminopyridine

DME = ethylene glycol dimethyl ether

DMF = dimethylformamide

DPM = diphenylmethyl

DPPA = diphenylphosphoryl azide

EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

HMPA = hexamethylphosphorotriamide

Ipc = *iso*pinocamphenyl

LDA = lithium diisopropylamide

LHMDS = lithium hexamethyldisilylamide

MCPBA = *m*-chloroperbenzoic acid

Men = menthyl

MsCl = mesyl chloride

NHPT = 1,2-dihydro-1-hydroxypyridine-2-thione

NBS = *N*-bromosuccinimide

NIS = *N*-iodosuccinimide

NMM = *N*-methylmorpholine

NMO = *N*-methylmorpholine *N*-oxide

NMP = 1-methyl-2-pyrrolidinone
Ns = 4-nitrobenzenesulfonyl
PCC = pyridinium chlorochromate
PDC = pyridinium dichromate
PEA = phenylethylamine
Piv = pivaloyl
PMB = *p*-methoxybenzyl
$PMBNH_2$ = *p*-methoxybenzylamine
PS = *Pseudomonas cepacia* (Amano)
PTC = phase-transfer catalysis
Py = pyridine
RCM = ring closing metathesis
TBDMSCl = *t*-butyldimethylsilyl chloride
TBHP = *t*-butylhydroperoxide
TEA = triethylamine
TFA = trifluoroacetic acid
Tf = trifluoromethylsulfonyl
TMEDA = *N,N,N',N'*-tetramethylethylenediamine
TMGA = tetramethylguanidine
TMSOTf = trimethylsilyl triflate
TMSCl = chlorotrimethylsilane
TMSCN = trimethylsylil cyanide
TMS = trimethylsilyl
WSCD = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide·HCl

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***(Received January 8, 2002; in final form September 23, 2002)***