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Asymmetric syntheses of pipecolic acid and derivatives

Review Article

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Summary. Results in the field of asymmetric synthesis of pipecolic acid derivatives are reviewed. Three sections describe the asymmetric syntheses of the title compounds (i) from the chiral pool (α-amino acids or carbohydrates) (ii) using a chiral auxiliary either derived from terpenes, α-amino acids, tartaric acid, an amine or β-amino alcohols (iii) by means of asymmetric catalysis.

Keywords: Amino acids – Pipecolic acid – Pipecolic acid derivatives – Asymmetric synthesis – Hemisyntheses – Chiral auxiliaries

Introduction

L-Pipecolic acid **1** (Fig. 1) is a natural non proteinogenic α-amino acid commonly found in plants. This *L*-proline homologue is biosynthesized from *D*-lysine (Leistner and Spenser, 1973), but its biological role still remains obscure. Although being sometimes incorporated in complex biologically active molecules such as Rapamycin (Nicolaou et al., 1993), or FK 506 (Ireland et al., 1996), the syntheses of which represent a breakthrough in modern chemistry, pipecolic acid and related compounds, most often occur free in biological systems.

Numerous natural or man-made derivatives of this amino acid display interesting biological properties, such as anesthetic (Tuller and Bollen, 1969), NMDA antagonist (Ornstein et al., 1989), anticoagulant (Okamoto et al., 1981), or glycosidase inhibition (Bruce et al., 1992).

In addition, *L*-pipecolic acid, as well as other amino acids showing a 6-membered ring, have been used in peptide chemistry as analogues of *L*-proline (Copeland et al., 1990; Williams et al., 1992). Introduction of these compounds into peptides induce a β-turn, and this modification of the secondary structure can result in an advantageous change of the biological activity. Many pipecolic acid derivatives (Kemp and Sun, 1982), especially those bear-

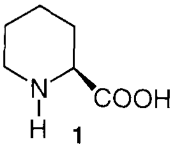

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Fig. 1

ing the tetrahydroisoquinoline skeleton (Chen and Goel, 1995; Kazmiersky and Hruby, 1988) have been developed for this purpose and some of these compounds will be presented thereafter.

The widespread use of pipecolic acid derivatives in therapeutic chemistry and the fact that these compounds can be viewed as intermediates for the synthesis of alkaloids has boosted research towards new preparations of these target molecules in optically pure form. The aim of this review is to present some of the methodologies, with the exception of resolutions, that have been used so far to reach enantiopure pipecolic acid derivatives.

The first part of this report deals with the hemisyntheses of the title compounds starting from the chiral pool. In these approaches, the chirality present in the substrate is incorporated into the target molecule and sometimes allows for the diastereoselective creation of extra chiral centers. The second part is devoted to the syntheses based on a chiral induction, the inductor being either recovered or immolated in the process. The end of this review will present some syntheses in which the «state of the art», namely asymmetric catalysis, was employed to introduce chirality.

1 Hemisyntheses of pipecolic acid derivatives from the chiral pool

1.1 Hemisyntheses from α-amino acids

The first important chiral source for the preparation of optically pure pipecolic acid derivatives are obviously α-amino acids. *L*-Lysine **2** was first employed in an asymmetric synthesis of pipecolic acid **1** (Aketa et al., 1976). An interesting feature of this work relies on the fact that the two enantiomers **1** and *ent*-**1** can be produced from **2** depending on the acidic medium used in the key diazotation step (Fig. 2).

A more lengthy procedure also based on diazotation of a protected form of **2** has been devised (Fujii and Miyoshi, 1975). Although the overall yield is low (15%), the enantiomeric excess of the produced **1** is good, based on optical rotation. In a more recent work (Kisfaludy and Korenczki, 1982), the one-step production of **1** using disodium nitrosyl-pentacyanoferrate (II) as the oxidant of the amine moiety is reported (Fig. 3).

Electrochemical oxidation (Irie et al., 1985) of the protected *L*-lysine derivative **5** gives piperidine **6**, suitable for acyliminium chemistry in the 6-position of the heterocyclic ring (Fig. 4).

In a similar field, methyl-6-oxo-pipecolate **7** was prepared in four steps from *L*-lysine by Moloney (Hermitage and Moloney, 1994) and this

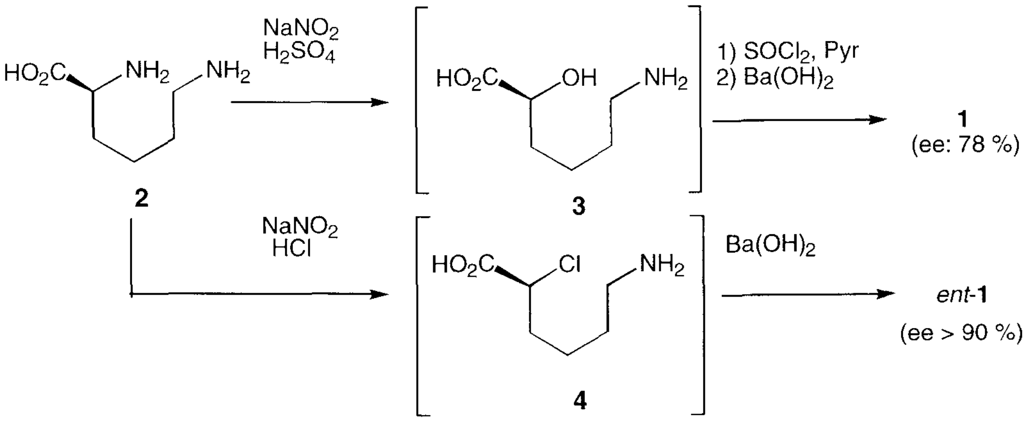


Fig. 2

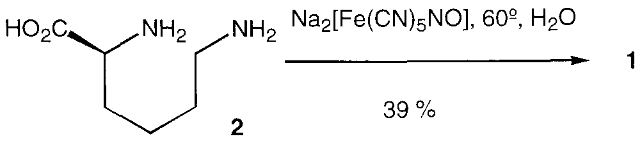


Fig. 3

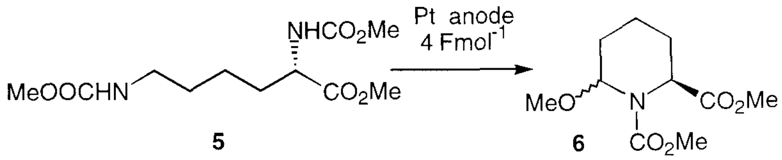


Fig. 4

piperidone was recently used by Murray (Murray and Starkey, 1996) for the synthesis of pipecolic acid derivatives **8** and **9** which can be considered as constrained analogues of *L*-lysine (Fig. 5).

In the same paper, Murray describes the straightforward preparation of α-β unsaturated lactam **11** from aspartic acid derivative **10** in four steps and with a 27% overall yield (Fig. 6).

This densely functionalised heterocycle will undoubtedly allow the preparation of interesting pipecolic acid derivatives. Aspartic acid was also employed by Golubev (Golubev et al., 1995) for the synthesis of 4-oxo-pipecolic acid **15**. The intermediate **14**, resulting from the conjugated addition of the amine moiety onto the enone, could in turn be transformed into *cis*-4-hydroxy and *trans*-4-hydroxy pipecolic acids **16** and **17**. This work is based on the use of an original protecting group, hexafluoroacetone, whose condensation with aspartic acid gave protected compound **12** (Fig. 7).

Pipecolic acids substituted in the 5-position can be obtained from 4-oxo-piperidine **19**, prepared itself in ten steps from *L*-glutamic acid **18** (Bailey and Bryans, 1988, Fig. 8).

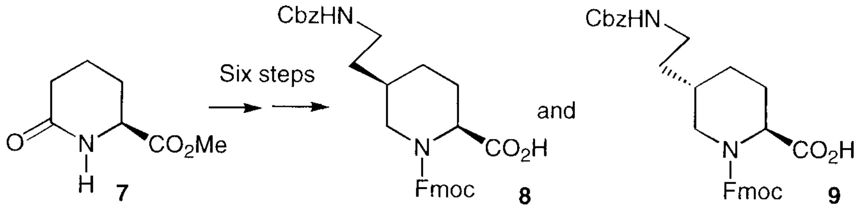


Fig. 5

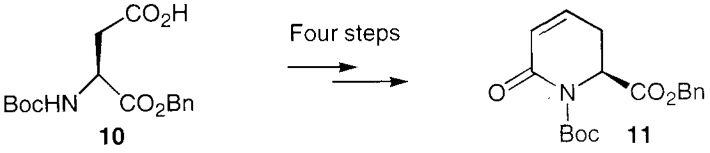


Fig. 6

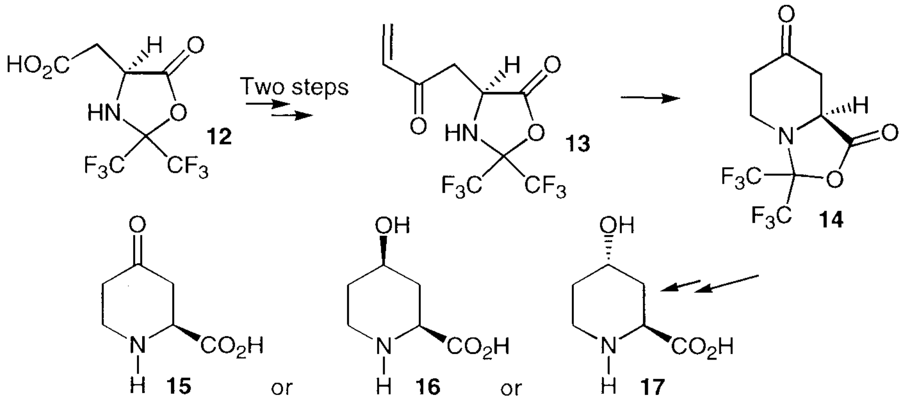


Fig. 7

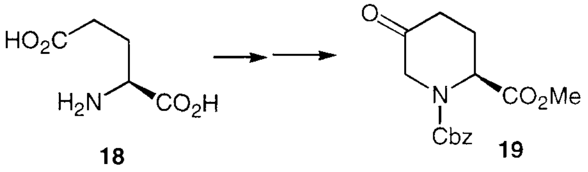


Fig. 8

More recently, Herdeis (Herdeis and Hengel, 1991) synthetised 5-hydroxy-2-piperidone **20**, easily accessible from *L*-glutamic acid. This interesting synthon was then transformed in several steps into 5-hydroxy (Herdeis and Heller, 1993) or 5-chloro (Herdeis et al., 1994) pipecolic acids **21**, **22** and **23** (Fig. 9).

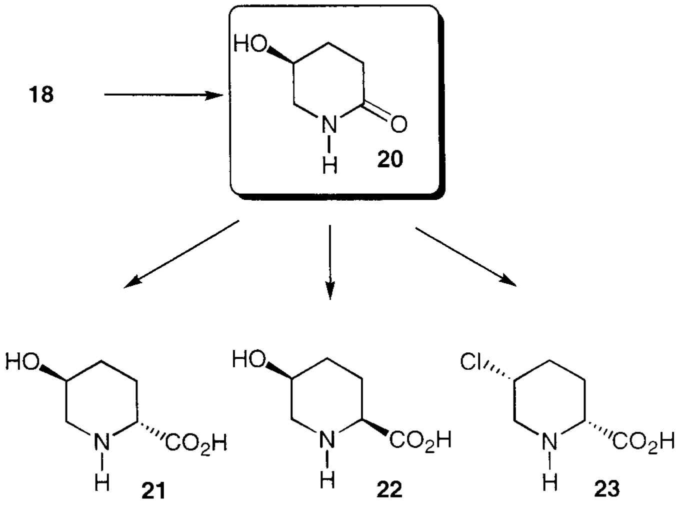


Fig. 9

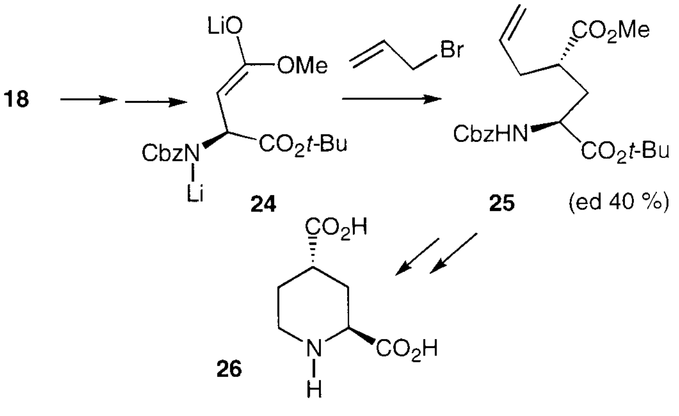


Fig. 10

L-Glutamic acid also served for the synthesis of pipecolic acid derivatives: *trans* 2,4-dicarboxypiperidine **26** was prepared through a diastereoselective allylation of γ-enolate **24** (Del Bosco et al., 1995, Fig. 10).

A very straightforward and high yielding access to 6-alkoxypipecolate **28** was recently reported by Ojima (Ojima et al. 1995), through an hydroformylation of (*S*)-allylglycine derivative **27**. The thus obtained heterocycle **28** was then used as starting compound for the diastereoselective introduction of a butyl side chain in the 6-position (Fig. 11).

Another rapid preparation of the piperidine ring started from the *L*-serine derived organozine reagent **29**, whose palladium-mediated coupling with acryloyl chloride followed by N-Boc deprotection, induced an intramolecular conjugate addition, similarly as in compound **13** (*vide supra*), and allowed a synthesis of 4-oxo-pipecolate **30** (Jackson et al., 1994, Fig. 12).

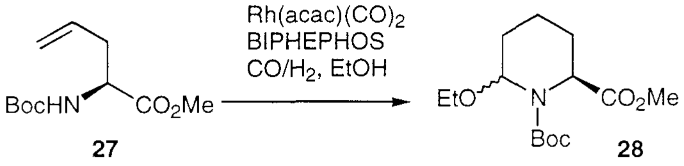


Fig. 11

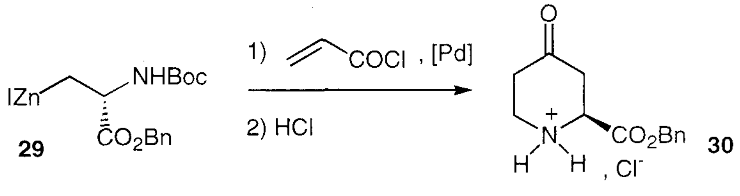


Fig. 12

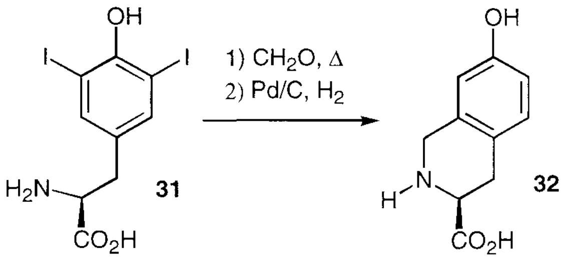


Fig. 13

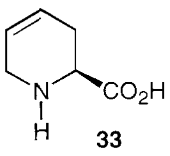


Fig. 14

Phenylalanine-derived amino acids were used for the construction of an impressive amount of aromatic pipecolic acid derivatives using most often a Pictet-Spengler reaction. As already mentioned, these bicyclic aromatic amino acids are used to induce conformational changes into peptides. For example (Fig. 13) the constrained tyrosyne analogue **32** was prepared in two steps from 3′,5′-diiodo-*L*-tyrosine **31** (Verschueren et al., 1991).

In this section ought also to be mentioned the hemisyntheses starting from *L*-baikiain **33** (Fig. 14) a natural unsaturated pipecolic acid derivative (Callens et al., 1982; Fujita et al., 1963; Hanson and Russell, 1989).

1.2 *Hemisyntheses from carbohydrates*

Polyhydroxylated piperidines have attracted considerable attention in the last 15 years since these analogues of pyranoses, in which the ring oxygen is replaced by nitrogen and the anomeric hydroxyl group is lacking, were found to be almost always inhibitors of the corresponding glycosidases. In this respect, 2*S*,3*R*,4*R*,5*S*-trihydroxypipecolic acid **35**, a natural polyhydroxylated pipecolic acid derivative, was shown to be a glucosidase and iduronidase inhibitor. This biological activity may provide interesting therapeutic solutions to various deregulations of metabolic processes, and a huge amount of synthetic work has been done in this area in order to transform carbohydrates into polyhydroxylated piperidines, including pipecolic acid derivatives. Some examples are listed in the Table 1. Particularly impressive are the works of Fleet et al. and Vasella et al. who developed this delicate chemistry, always bearing in mind preoccupations with SAR (structure-activity relationships).

Notwithstanding all the impressive successes of the syntheses presented in this section, a major drawback appears: targets prepared through hemisyntheses are obviously of limited choice, since the availability of a suitable precursor is not always possible, particularly in terms of absolute configuration. However, the search for new bioactive compounds, for example by molecular modeling, cannot suffer such a limitation and that is one of the reasons why organic chemists have devised a plethora of asymmetric syntheses in which an *external* chiral center acts as a «chiral inductor» without being incorporated into the target. Compared to hemisyntheses, the main advantage relies on the fact that this chiral auxiliary is most often available in both enantiomeric forms, so that the absolute configuration of the target may be chosen. The following section will present some of the methodologies that were applied, or specially devised, for the construction of enantiopure pipecolic acid derivatives.

2 Asymmetric syntheses of pipecolic acid derivatives by stoechiometric chiral induction

2.1 *Terpene derived chiral auxiliaries*

Terpenes are not the main chiral source used for the enantioselective elaboration of the piperidine nucleus of pipecolic acid derivatives by chiral induction. Two interesting papers, however, report on this strategy. Wanner (Wanner and Stamenitis, 1993) found that high de could be reached in the diastereoselective alkylation of dioxazinone **54**, prepared by condensation of racemic pipecolic acid and the terpenic hydroxy acid **53**, thus allowing a preparation of α-substituted pipecolic acid **55** with ee's up to 99% after a final hydrolysis step in which the inductor could be recovered (Fig. 15).

Recently, Hoarau (Hoarau et al., 1996) prepared (*R*)-homoallyl glycine derivative **58**. The key step involves a diastereoselective alkylation of the Schiff base **57** derived from (*S*,*S*,*S*)-2-hydroxypinan-3-one. Transformation of this compound into 5-hydroxy pipecolic esters **59** and **60** was effected in four steps, including a non stereoselective epoxydation of the alkene,

Table 1. Hemisyntheses of hydroxylated pipecolic acid derivatives using carbohydrates

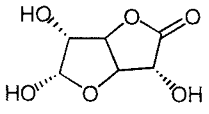
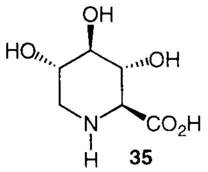
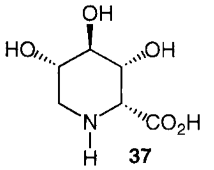
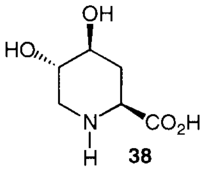
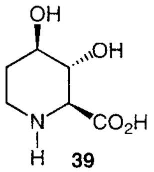
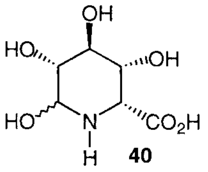
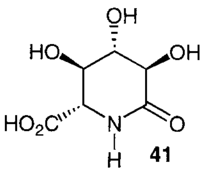
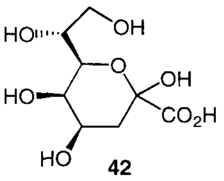
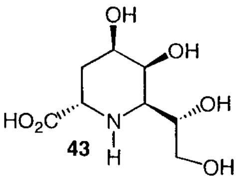
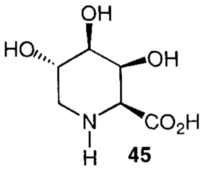
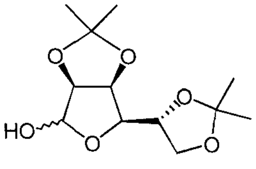
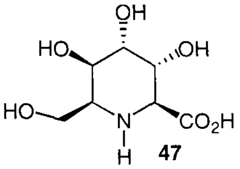
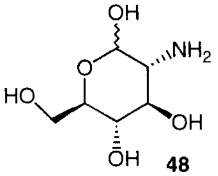
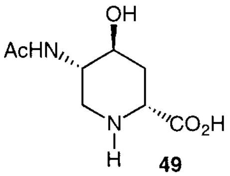
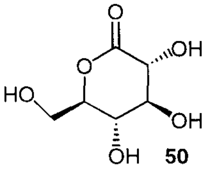
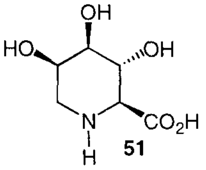
Starting carbohydrate	Pipecolic acid derivative	Reference
 **34** *D*-glucuronolactone	 **35**	Bashyal et al., 1986
D-Glucose **36**	**35**	Bernotas and Ganem, 1985
D-Glucose **34**	 **37**	Bashyal et al., 1986
D-Glucose **36**	 **38**	Bashyal et al., 1987a,b
D-Glucose **36**	 **39**	Fleet and Witty, 1990
D-Glucose **36**	 **40**	Paulsen and Mäckel, 1973
D-Glucose **36**	 **41**	Guntha and Mereyala, 1994
 **42** KDO	 **43** + C-2 Diastero isomer	Norbeck and Kramer, 1987

Table 1. *Continuted*

Starting carbohydrate	Pipecolic acid derivative	Reference
D-galactose **44**	 **45**	Tong et al., 1990
 **46** Diacetone mannose	 **47**	Bruce et al., 1992
 **48** Glycosamine	 **49**	Clinch and Vasella, 1987 Glänzer et al., 1991
 **50**	 **51**	Ki et al., 1994

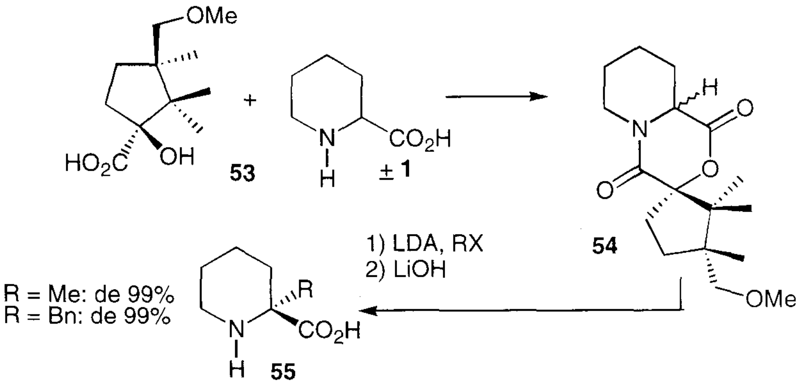


Fig. 15

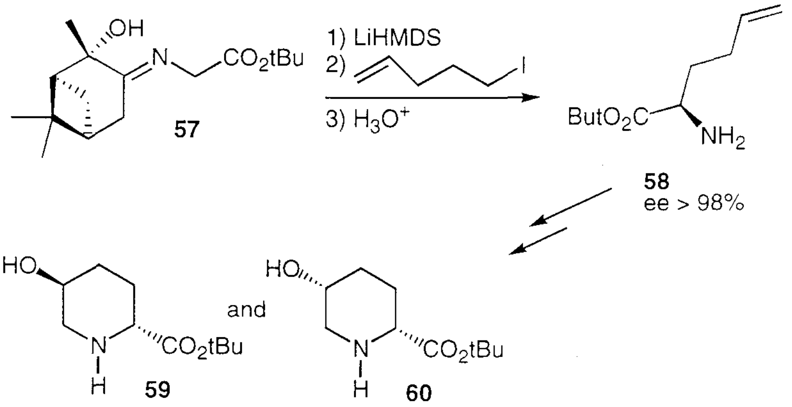


Fig. 16

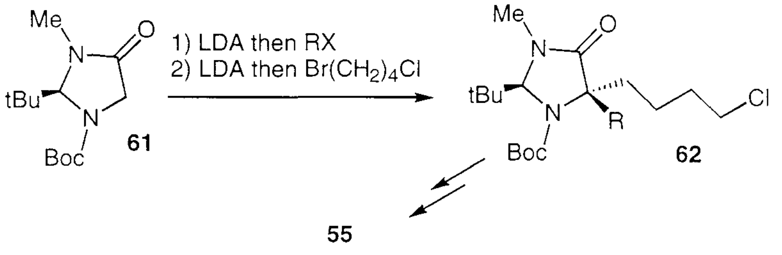


Fig. 17

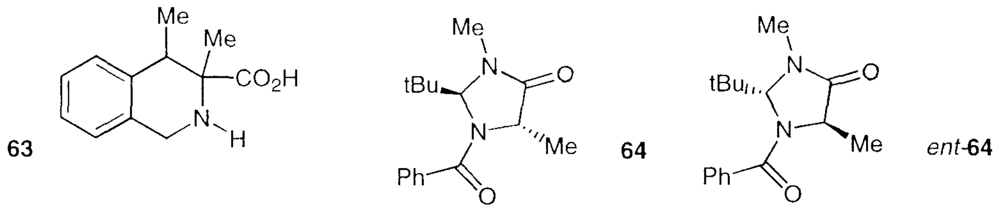
transformation of the resulting epoxides into the corresponding bromhydrins, N-deprotection and final ring closure (Fig. 16).

2.2 Boc-BMI as chiral auxiliary

Boc-BMI **61** is a chiral glycine anion equivalent developed by Seebach. Both enantiomers are available, being prepared by resolution. Besides many other applications, these heterocycles have been used for the asymmetric synthesis of α-susbtituted pipecolic acid derivatives **55** (Seebach and Fitzi, 1986). Two successive alkylations allow for the diastereoselective creation of the quaternary chiral center, and (S)-pipecolic acid derivatives are eventually obtained in three steps from **62** with high optical purity and an overall yield ranging from 35 to 62% (Fig. 17).

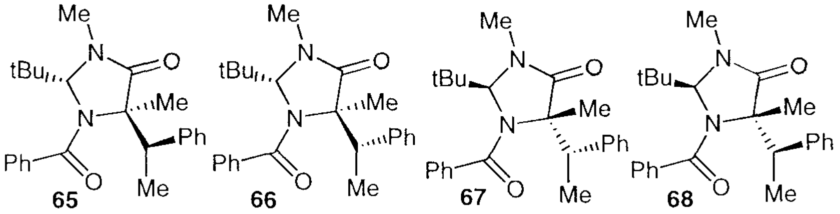
2.3 Amino acid derived chiral auxiliaries

The aforementioned Seebach's methodology has been used by Kazmiersky (Kazmiersky et al., 1994) for the construction of all four stereoisomers of α,β-dimethyl-1,2,3,4 tetrahydroisoquinoline-3-carboxylic acid **63**, designed for the topographical control of peptide conformation. This asymmetric synthesis now starts with imidazolidinones **64** and *ent*-**64**, derived respectively from (*S*) and (*R*) -alanine (Fig. 18).



63 **64** *ent*-**64**

Fig. 18



65 **66** **67** **68**

Fig. 19

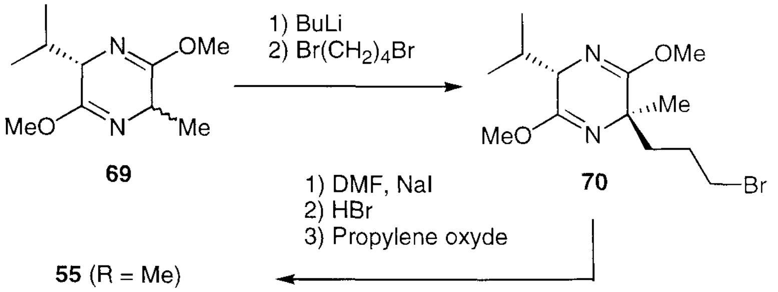


Fig. 20

Alkylation of enolates generated from each of these heterocycles with racemic α-bromo ethylbenzene occurred with high diastereoselectivity (ie: *anti* attack of the electrophile with respect to the *tert*-butyl substituent). After chromatographic separation, isolated compounds **65**–**68** (Fig. 19) could be separately transformed in three steps into all of the stereoisomers of **63**, *via* a Pictet-Spengler reaction.

L-valine, through the famous Schöllkopf's (Schöllkopf et al., 1987) methodology, allowed a synthesis of (R)-α-methyl pipecolic acid **55** (R = Me). This work is based on the diastereoselective alkylation of bis-lactim ether **69**. Cyclisation of the produced bromide **70** was followed by hydrolysis to give **55** with 95% ee and with an overall yield of 57% (Fig. 20).

In a recent paper, Andrews (Andrews et al., 1996) did also make use of an amino acid: *L*-serine, for asymmetric synthesis of pipecolic acid derivatives based on chiral induction. The authors make use of the Seebach's «self generation of chirality» principle already mentioned (*vide supra*). Thus, N-acylation of oxazolidines **71** resulting from condensation of *L*-serine and pivalaldehyde with ω-bromo acid chloride, gave pure *cis*

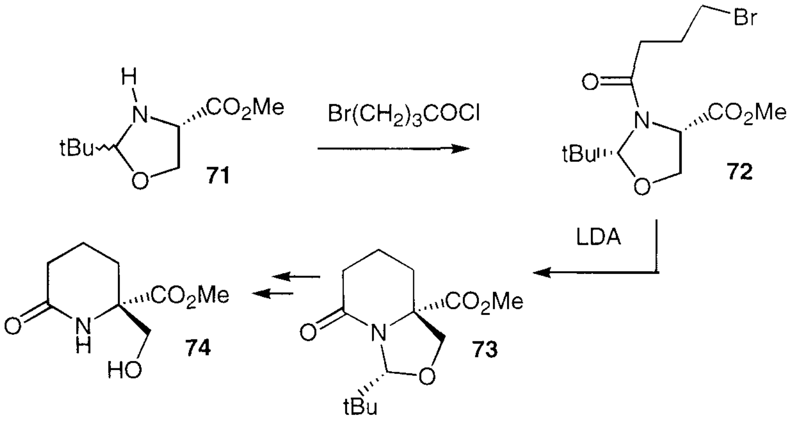


Fig. 21

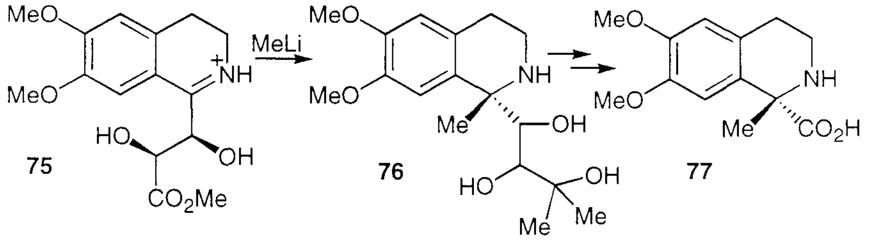


Fig. 22

diastereoisomer **72**. Totally diastereoselective intramolecular alkylation of the enolate generated from **72** was followed by hydrolysis in order to give lactam **74** (Fig. 21).

2.4 *Hydroxy acid derived chiral auxiliaries*

L-tartaric acid was used as chiral inductor for the synthesis of 1-methyl tetrahydroisoquinoline-1-carboxylic acid **77** (Czarnocki et al., 1992) The induction occurs when an excess of methyl lithium is reacted with the *L*-tartaric acid derived iminium ion **75**: addition of the organometallic occured with complete stereocontrol, and the aminotriol **76** produced was then transformed in 5 steps into **77**, with an overall yield of 35% (Fig. 22).

2.5 *Amine derived chiral auxiliaries*

Because of their low cost, (*R*)-phenylethylamine **78** and its enantiomer have been widely used as chiral inductors for the asymmetric syntheses of nitrogen containing heterocycles. As regards pipecolic acid derivatives, aza Diels-Alder reaction was often the key step of the strategies based on the use of this amine. To reach this goal, Bailey (Bailey et al., 1991) reacted imine **79**, resulting from the condensation of ethyl glyoxylate and **78** (or *ent*-**78**) with various dienes. The cycloadducts were obtained with yields and de ranging

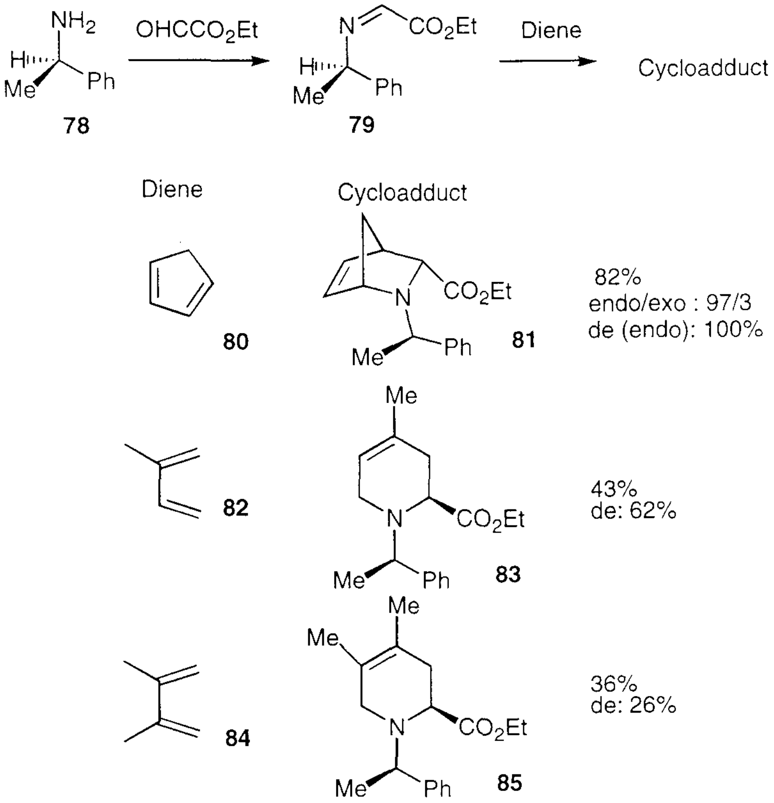


Fig. 23

respectively from 21 to 89% and 26 to 100%. Some examples are summarized in Fig. 23.

Compound **83** was then used for the enantioselective synthesis of (2*S*,4*R*)-4-methyl pipecolate, a substructure of an important thrombin inhibitor.

A similar reaction was recently used by Mellor (Mellor et al., 1995) for the synthesis of optically pure bicyclic amino acid **88** and *ent*-**88**, and these compounds were incorporated in bioactive peptides, as analogues of proline. Benzyl ester was now used in place of ethyl ester as presented above, and though the target **88** could be obtained in a single hydrogenation step from **87**, the observed stereoselectivity (de:33%) of the key step aza Diels-Alder reaction was much lower (Fig. 24).

Another recent paper reports on the use of this strategy for the preparation of bicyclic pipecolic acid derivative **90**, which is a component of a HIV-1 protease inhibitor (Trova and McGee, 1995, Fig. 25).

Yield and diastereoselectivity were however quite modest in this approach.

Recently, an elegant work of Beaulieu et al. (Gillard et al., 1996) was reported, describing the scaleable preparation of (2*S*,4*R*)-4-hydroxypipecolic acid **97**, a constituent of Palinavir, this latter being a highly potent inhibitor of HIV-1 protease. The synthesis is based on the nucleophile-mediated ene-iminium cyclisation of intermediate **92**, prepared from (*S*)-*ent*-**78**:

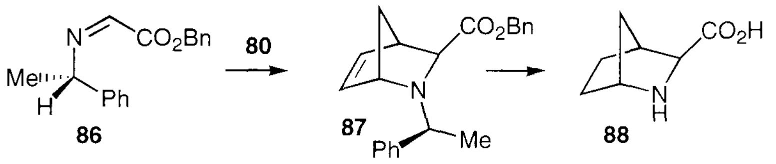


Fig. 24

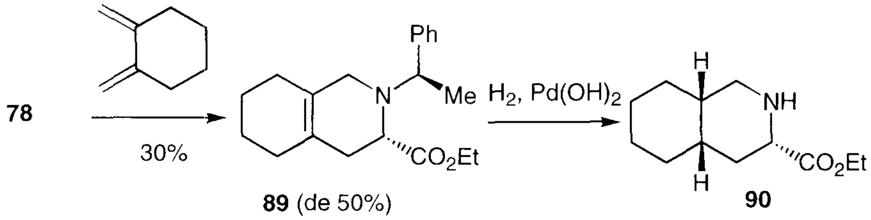


Fig. 25

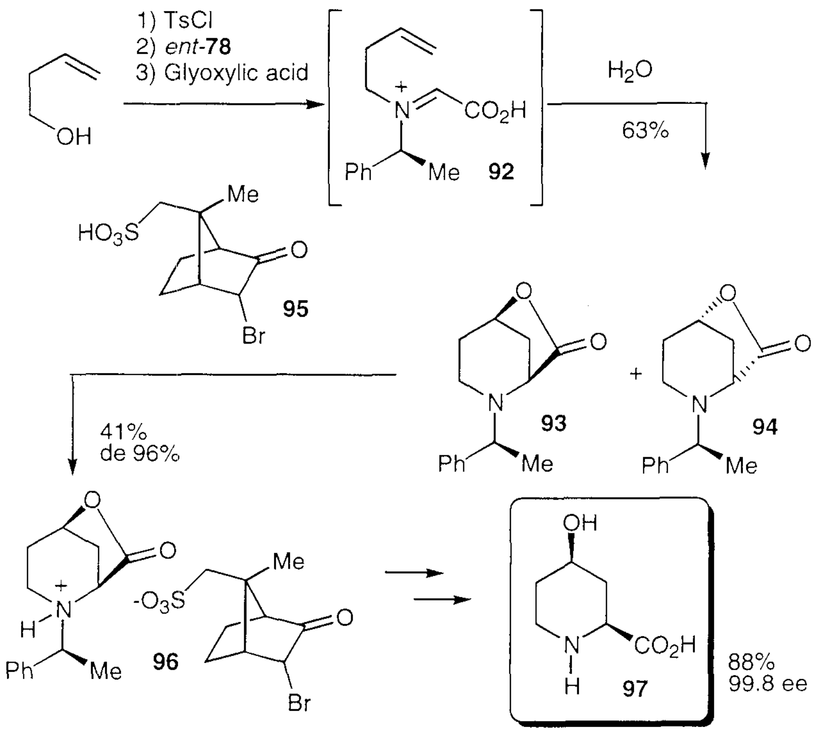


Fig. 26

The stereospecificity of this reaction accounts for the production of *cis*-stereoisomers **93** and **94** (6/4 ratio) and although the diastereoselectivity is low, pure compound **96** could be separated on a large scale from the mixture through selective crystallization and was then transformed in three steps into **97** (Fig. 26).

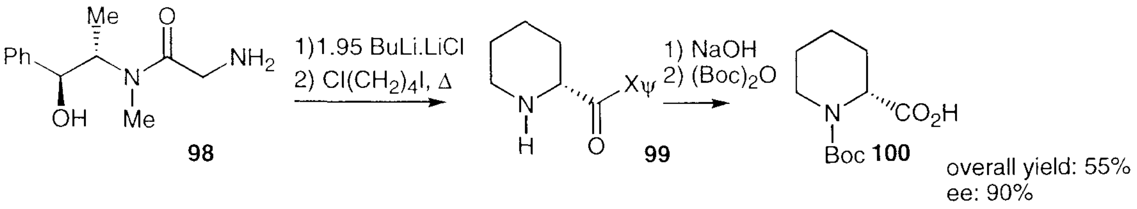


Fig. 27

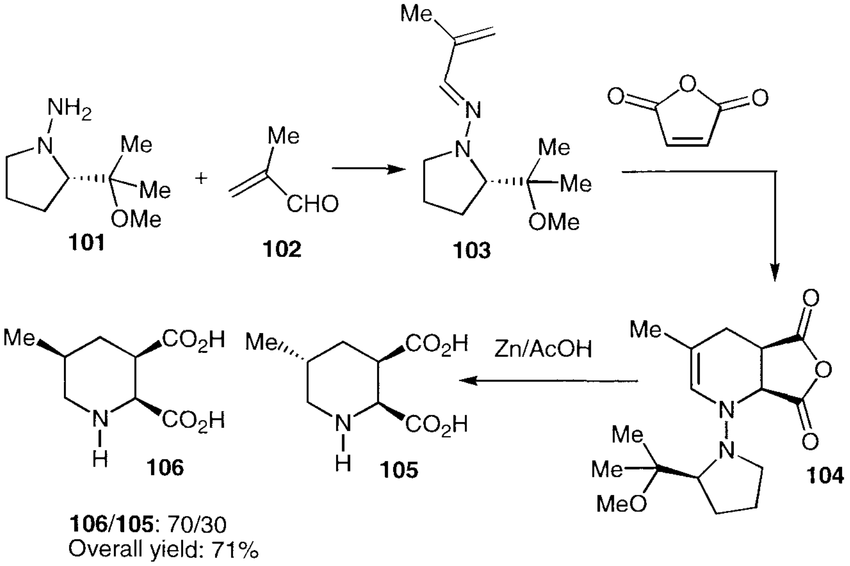


Fig. 28

2.6 *Amino alcohol derived chiral auxiliaries*

β-Amino alcohols (amino acid-derived or ephedrine family-derived), probably the most popular chiral auxiliaries employed in asymmetric synthesis, were indeed used for the preparation of pipecolic acid derivatives. In this field, Myers (Myers et al., 1995) reported the highly diastereoselective alkylation of enolates derived from pseudoephedrine glycinamides. This effective reaction in terms both of yield and selectivity allowed the preparation of a wide range of enantiopure *α*-amino acids, including (*R*)-N-Boc pipecolic acid **100** (Fig. 27).

L-Prolinol-derived hydrazine **101** was used by Beaudegnies (Beaudegnies and Ghosez, 1994) in an asymmetric aza Diels-Alder reaction. Condensation of this hydrazine with enals gave azadienes **103**, whose cycloaddition with reactive dienophiles occurred smoothly at room temperature to give **104** with high diastereoselectivity, as exemplified in Fig. 28.

Reductive cleavage of **104** concomitantly reduced the double bond and produced pipecolic acids **105** and **106**, the inductor being recovered in high yield.

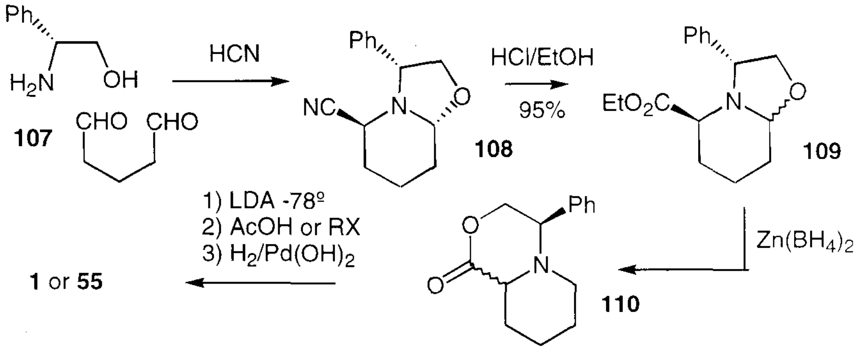


Fig. 29

Phenyl glycinol **107** was also used frequently in this field since this amino alcohol is available in both enantiomerically pure forms and its amine moiety can be «incorporated» into the target piperidine through cleavage of the benzylic carbon-nitrogen bond.

Berrien (Berrien et al., 1994) reported the preparation of lactone **110** starting with (*R*)-**107** (Fig. 29).

Although being produced as a mixture of stereoisomers, enolates derived from these lactones could be alkylated with high de (93–97%) and provided, after hydrogenolysis, **1** or α-substituted pipecolic acids **55**. This methodology also permitted the synthesis of 6-substituted pipecolic acid derivatives albeit with low stereoselectivity.

(*R*) or (*S*)-Phenyl glycinol **107** was also used in our laboratory (Agami et al., 1997; Agami and Couty, 1990) as a chiral auxiliary for the preparation of optically pure pipecolic acid derivatives through three different approaches.

The first one is based on a totally stereoselective nucleophile mediated ene-iminium cyclisation of intermediate **109**. We found that this iminium ion was produced when N-substituted phenyl glycinol derived amino alcohols as **108** (Fig. 30) were condensed with aqueous glyoxal. The addition of the ene moiety onto the iminium ion occurs in this intermediate with a total stereoselectivity (i.e. *anti* attack with respect to the phenyl substituent of the morpholine ring). The stereospecificity of the concerted addition of the external nucleophile on the double bond accounts for the production of the diastereoisomer **110**.

The latter was then transformed in three steps into optically pure 4-substituted pipecolic acid derivatives. One important parameter of this reaction was the nucleophilicity of the ene conterpart: the cyclisation occured spontaneously upon reaction with glyoxal if the double bond was reactive enough, that is to say when the ene moiety was substituted at the carbon that must support a positive charge in the transition state of the cyclisation(*eg* amino alcohols **112**, **113**, **114**, Fig. 31). On the other hand, in case of amino alcohols **108** and **115**, cyclisation had to be performed in non aqueous medium, the iminium ion being now generated through the reaction of an aminothioether and a Lewis acid.

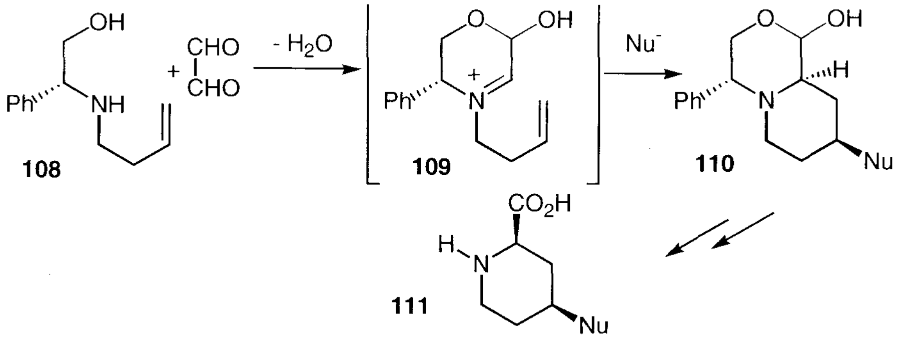


Fig. 30

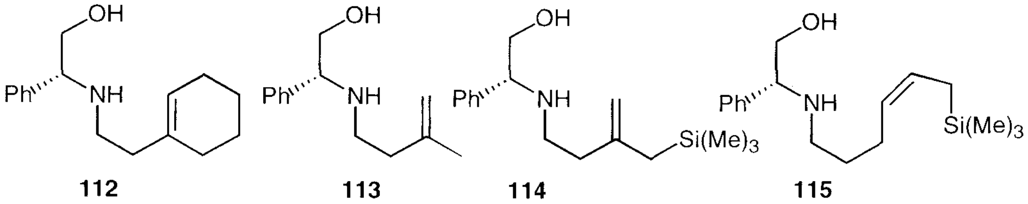


Fig. 31

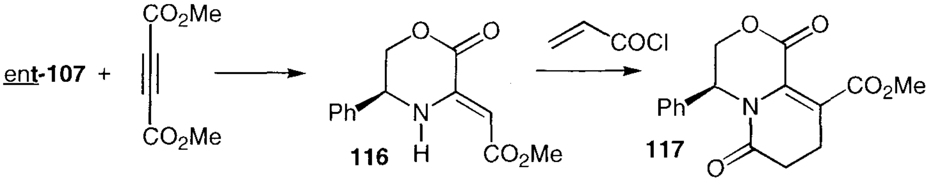


Fig. 32

This work allowed the preparation of various 4-substituted or unsaturated pipecolic acid derivatives, these latter being eventually produced when allyl silanes **114** and **115** were used.

Another approach was recently developed (Agami et al., 1996a) starting with morpholinone **116**, resulting from the condensation of (*S*)-phenyl glycinol and acetylene dimethyl dicarboxylate. Cyclocondensation of this compound with acryloyl chloride gave bicyclic enaminoester **117** (Fig. 32).

The ethylenic double bond of this molecule was hydrogenated and this reaction led stereoselectively to either the *cis*-hydrogenated or the *trans*-hydrogenated **118** or **119** , depending on the experimental conditions (Fig. 33). Each of these compounds was then transformed in three steps into 3-carboxy pipecolic acid derivatives **120** and **121**. These α-amino acids can be viewed as conformationally restricted analogues of NMDA.

The last approach we recently disclosed (Agami et al., 1996b) was based on the stereoselective reduction of 2-acyl oxazolidine **122**, prepared in four steps from (*R*)-phenyl glycinol. The obtained alcohol **123** (de 90%) was transformed in five steps into bicyclic oxazolidine **124**, the opening of which by

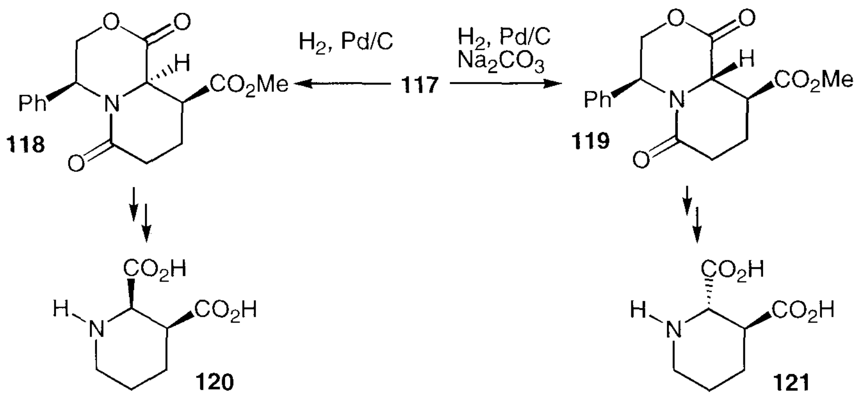


Fig. 33

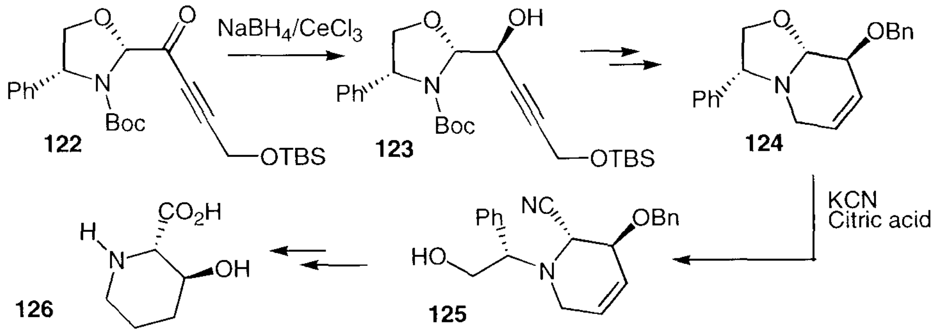


Fig. 34

HCN led stereoselectively to **125** and the latter was readily transformed into *trans* 3-hydroxy pipecolic acid derivative **126** (Fig. 34).

3 Asymmetric syntheses of pipecolic acid derivatives by catalytic chiral induction

Asymmetric catalysis was less frequently used for the preparation of pipecolic acid derivatives. Enzymes were employed with success in this field by Chênevert (Chênevert and Morin, 1996) who recently reported the enzymatic desymmetrization of *meso* diester **127** under the action of *Aspergillus niger lipase.* The alcohol **128** thus produced (ee > 98%) was then converted in two steps and 48% overall yield into (2*S*,6*R*)-6-hydroxymethyl pipecolic acid **129** (Fig. 35).

The preparation of *ent*-**129** in four steps (46% yield) from **128** was also reported.

Kazlauskas (Ng-Youn-Chen et al., 1994) screened various lipases for the kinetic resolution of pipecolate esters and found that partially purified ANL (lipase from *Aspergillus niger*, AP-6 from Amano-Enzyme-Co) was the best biocatalyst for this operation, as illustrated in Fig. 36.

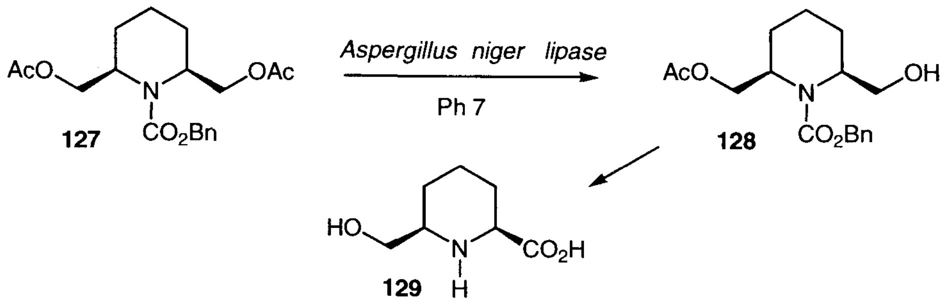


Fig. 35

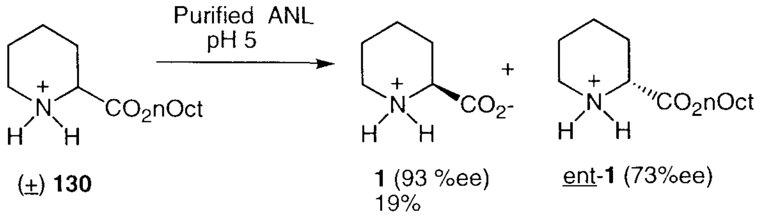


Fig. 36

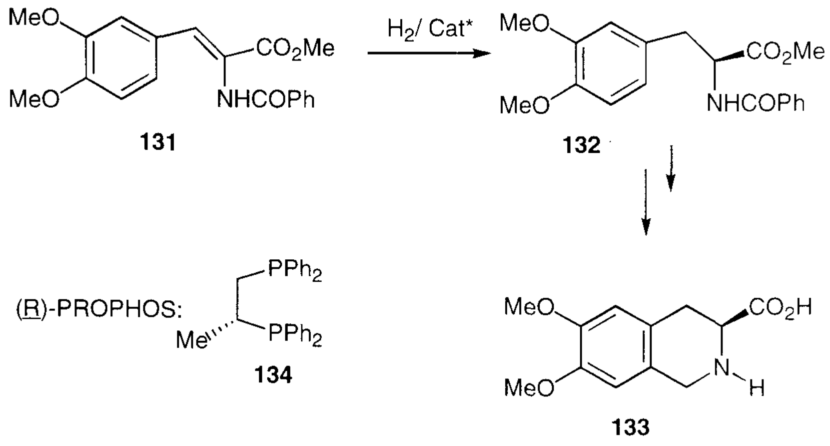


Fig. 37

Asymmetric catalytic hydrogenation was also used by some authors. O'Reilly (O'Reilly et al., 1990) reported the asymmetric hydrogenation of **131** using (*R*)-PROPHOS **134** as a chiral ligand for the ruthenium catalyst (Fig. 37). The protected amino acid **132** was then converted into pure (*S*)-**133**, a useful pipecolic acid derivative for drug synthesis.

In this field, Foti (Foti and Comins, 1995) described (Fig. 38) the catalytic asymmetric hydrogenation of enamido ester **135** with Noyori's ruthenium catalyst: (*R*)-BINAP $RuCl_2$.

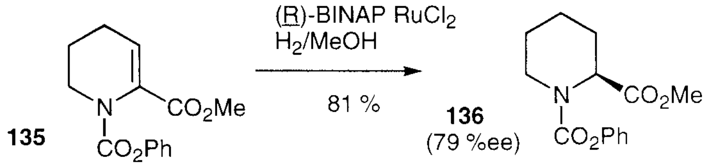


Fig. 38

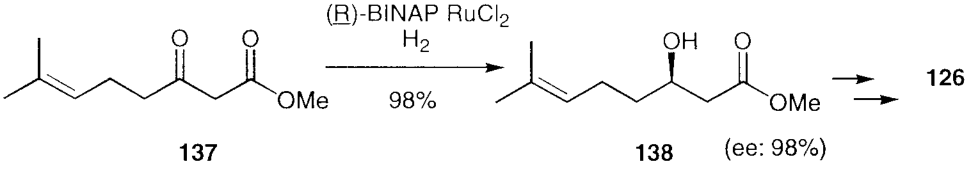


Fig. 39

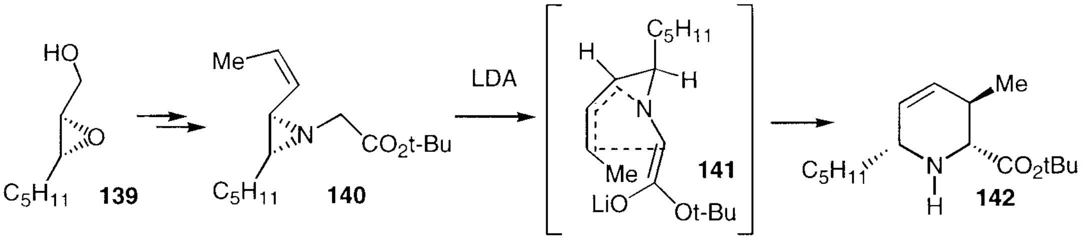


Fig. 40

Catalytic asymmetric hydrogenation of β-ketoester **137** could be performed very effectively (Greck et al., 1996), using a similar catalyst and the optically pure alcohol **138** thus obtained was used as chiral starting compound for the ten step preparation, including a stereoselective amination of ester enolate derived from **138**, of enantiopure 3-hydroxypipecolic acid **126** (Fig. 39).

To close this section, the elegant work of Somfai (Ahman and Somfai, 1995) ought not to be omitted. These researchers used the most popular asymmetric catalytic reaction: Sharpless's epoxydation, to prepare epoxy alcohol **139** (>95% ee). This compound was in turn transformed into vinyl aziridine **140**. The key-step of this synthesis (Fig. 40) consisted in a stereoselective aza-[2,3]-Wittig rearrangement *via* the transition state **141** and gave pipecolic acid derivative **142**.

This compound was then employed as the starting material for the synthesis of an indolizidine alcaloïd.

Concluding remarks

The diversity of approaches used to reach pipecolic acid derivatives as presented in this review highlights the importance of these molecules. As a matter of fact, the piperidine core present in these compounds places them at the junction of three important families of natural products. First, they belong indeed to the family of α-amino acids. On the other hand, when polyhydroxylated, they can be considered as aza-sugars, an intensively studied subfamily of carbohydrates. Finally, some of these molecules can be considered as intermediates for the synthesis of alcaloïds (Greck et al., 1996; Ahman and Somfai, 1995). This probably explains why reports devoted to their preparation have increased so much in the last decade.

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