Amino Acids (2005) 29: 101–130
DOI 10.1007/s00726-005-0193-x

Amino Acids
Printed in Austria

Recent advances in asymmetric synthesis of pipecolic acid and derivatives

Review Article

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Received November 23, 2004
Accepted February 16, 2005
Published online May 10, 2005;

Summary. This review covers the literature relating to asymmetric syntheses of pipecolic acid derivatives from 1997 to present. This review is organized according to the position and the degree of substitution of the piperidinic cycle. In a first section, syntheses of pipecolic acid itself are described. Then, successively, syntheses of C-3, C-4, C-5, C-6 substituted pipecolic acid derivatives are reported. Finally, syntheses of unsaturated pipecolic acid derivatives are presented before the last part devoted to the polysubstituted pipecolic acid derivatives.

Keywords: Pipecolic acid – Pipecolic acid derivatives – Amino acids – Asymmetric syntheses – Asymmetric catalysis

Pipecolic acid (so named pipecolinic acid, homoproline, or 2-piperidinecarboxylic acid) is a non proteinogenic amino acid (Fig. 1). This compound is a component of several secondary metabolites in plants and fungi (Zacharius et al., 1952). Pipecolic acid, that is a metabolite of lysine, is also found in human physiological fluids and is thought to play an important role in the central inhibitory γ-aminobutyric acid system (Gutierrez and Delgado-Coello, 1989; Bernasconi et al., 1986).

Pipecolic acid serves as a substrate of some peptides and polyketide synthetases, resulting in the formation of secondary metabolites with interesting pharmacological activities such as the immunosuppressors rapamycin (Smith III et al., 1997), FK506 (Ireland et al., 1996) and immunomycin, or the antitumor antibiotic sandramycin (Boger et al., 1996). It is also a precursor to numerous compounds such as synthetic peptides (Copeland et al., 1990), local anaesthetics or potential enzyme inhibitors (Flynn et al., 1987).

Many chemists have been inspired by the important bioactivities of pipecolic acid and derivatives and have therefore developed new enantioselective methods to synthesize these compounds.

Recent reviews, devoted to the asymmetric synthesis of piperidines, included some syntheses of pipecolic acid derivatives (Weintraub et al., 2003; Felpin and Lebreton, 2004; Buffat, 2004). This review outlines the recent developments in asymmetric synthesis of pipecolic acid and derivatives from 1997 to now; a preceding report in this journal having compiled works prior to 1997 (Couty, 1999). The different syntheses described here are listed according to the position and degree of substitution of the piperidinic cycle; but chemical and enzymatic resolutions are excluded.

Pipecolic acid

Although an increasing number of works are devoted to the synthesis of mono or polysubstituted pipecolic acid derivatives, the synthesis of enantiopure pipecolic acid itself remains a centre of interest for chemists. In less than five years, near the asymmetric syntheses by stoechiometric chiral induction, catalytic asymmetric syntheses of pipecolic acid have increased and, as a matter of fact, constitute the major part of this section.

Photocatalytic process

One of important chiral source for the preparation of pipecolic acid derivatives was α-amino acids. L-lysine **2** was recently used in a photocatalytic redox-combined process to afford pipecolic acid with various enantiomeric

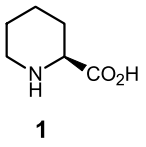


Fig. 1

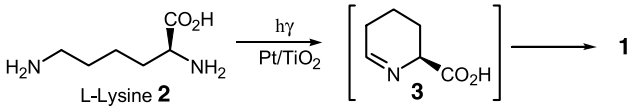


Fig. 2

excess by using as semiconductor photocatalysts titanium (IV) oxide or cadmium (II) sulphide (Pal et al., 2003). This catalytic one-step synthesis of L-pipecolic acid was an example of green chemistry process because only ammonia was liberated as a by-product (Fig. 2).

Chemoenzymatic synthesis

Chemoenzymatic synthesis of (*S*)-2-cyanopiperidine **6** provided an access to (*S*)-pipecolic acid (Nazabadioko et al., 1998). This synthesis is based on a (*R*)-oxynitrilase-catalysed reaction for the enantioselective preparation of the bromo cyanhydrine derivative **5**. This compound was transformed in two steps in the piperidine **6** (Fig. 3): first, the transformation of hydroxyl group in trifluoromethanesulfonyloxy and its substitution by benzylamine, and second, the subsequent cyclization by a slower substitution of the bromine yielded compound **6**. A careful hydrolysis to prevent racemization followed by hydrogenolysis gave enantiopure compound **1**.

Asymmetric induction from β-amino alcohol

(*S*)-Phenylglycinol was used as chiral inductor in our group for an enantioselective synthesis of compound **1** (Agami et al., 2000). Morpholine **9** was obtained from the condensation between phenylglycinol derived amino alcohol **8** and glyoxal in the presence of thiophenol. The key-step was a highly diastereoselective ene-iminium cyclisation between iminium ion (generated by action of Lewis acid) and the vinylsilane moieties. The stereoselectivity was explained by an attack of the vinylsilane group in an *anti* position with respect to the phenyl substituent. The intermediate **10** was converted in three steps into (*S*)-pipecolic acid **1** (Fig. 4).

Phenylglycinol **11** was also used as starting material in the following approach (Roos et al., 2000). Lactone **12**, prepared in three steps from (*S*)-phenylglycinol **11**, was alkylated with a bromotriflate to afford diastereoisomerically pure compound **13**. Treatment of **13** with hydrogen induced cleavage of the benzyloxycarbonyl group with concomitant cyclization and debenzylation of the cyclic lactone to give enantiopure **1** with 45% yield (Fig. 5).

Enantioselective protonation and decarboxylation

Enantioselective protonation was applied on amide enolate **15** derived from piperidine-2-carboxylic derivative **14** (Fig. 6). High enantiomeric excess (up to 95%) for the protected pipecolic acid derivative **16** was obtained with diamine **17** as chiral proton source and in the presence of LiBr (Martin et al., 1997).

Enantioselective decarboxylation-reprotonation, in the presence of a chiral base, of the *N*-acyl malonate **18**

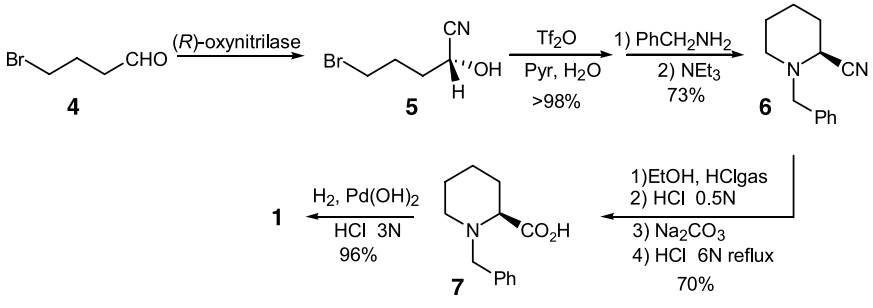


Fig. 3

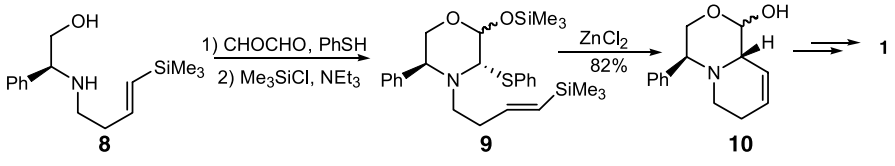


Fig. 4

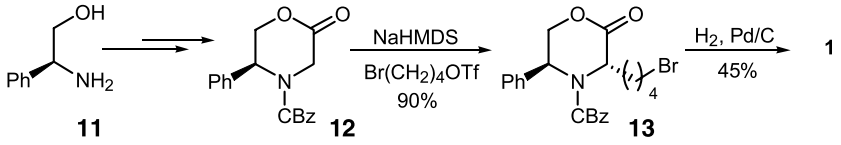


Fig. 5

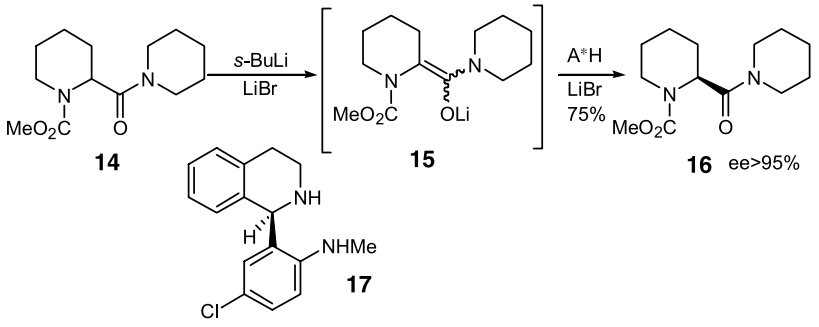


Fig. 6

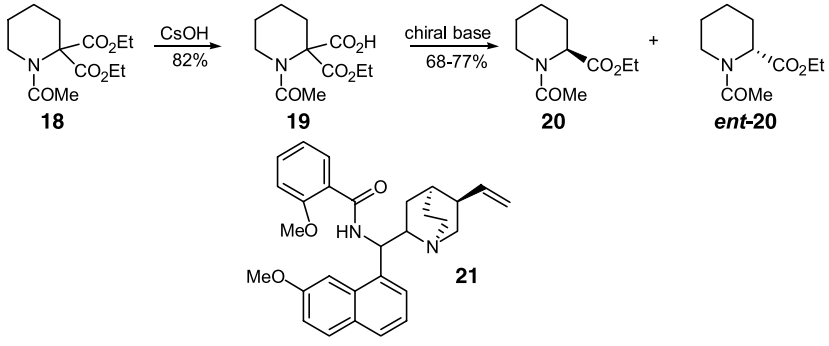


Fig. 7

has been examined as a route to optically enriched *N*-acetyl pipecolic acid ethyl ester **20** (Rogers et al., 2003). The best result was obtained with the quinine alkaloid-derived base **21** *i.e.* 52% enantiomeric excess in favour of the *S*-enantiomer of pipecolate ester **20** (Fig. 7).

Asymmetric catalysis

Ring-closing metathesis (RCM) has been exploited in a recent synthesis of pipecolic acid (Ginesta et al., 2002) from the known enantiomerically enriched epoxyalcohol **23**, synthesized from the allylic alcohol **22** via a Sharpless epoxidation (Fig. 8). Nucleophilic epoxide ring-opening

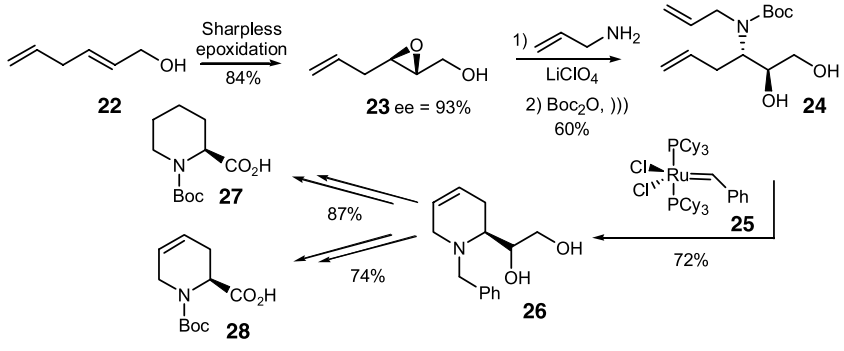


Fig. 8

using allylamine was followed by protection of the amino group by Boc_2O. The key intermediate **26** was obtained by a RCM, catalyzed by the Grubbs' reagent **25**, of the doubly unsaturated amine **24** with 72% yield. Hydrogenation and oxidation led to *N*-Boc-pipecolic acid **27** in 99% ee after recrystallisation; whereas oxidation of the diol fragment in **26** gave an unsaturated pipecolic acid derivative: the *N*-Boc-baikiain **28**.

Compound **30** was prepared from the precursor 3-hydroxypiperidine hydrochloride **29** in three steps with 59% yield (Fig. 9). This unsaturated piperidine **31** was hydrogenated with the Noyori catalyst (*S*)-BINAP-$RuCl_2$ to yield (*S*)-*N*-Boc-pipecolic acid **27** in 87% yield in high enantioenrichment after one recrystallization (Wilkinson et al., 2000).

Catalytic phase transfer alkylation of *tert*-butyl ester **32** with 1-chloro-4-iodobutane using the chiral quaternary ammonium cinchonidine salt **35a** and solid $CsOH \cdot H_2O$ as base afforded the (*S*)-chlorobutylated ester **33** in 99% ee (Corey et al., 1998). The conversion of **33** into the *tert*-butyl ester of pipecolic acid **34** was accomplished in three steps in high yield (Fig. 10).

Catalytic asymmetric Strecker synthesis was used in an elegant way to produce amino acids particularly the pipecolic acid methyl ester **40**. The amino nitrile **38** was

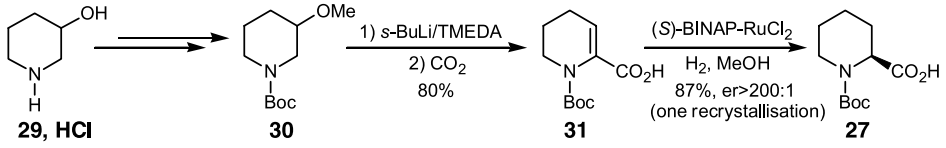


Fig. 9

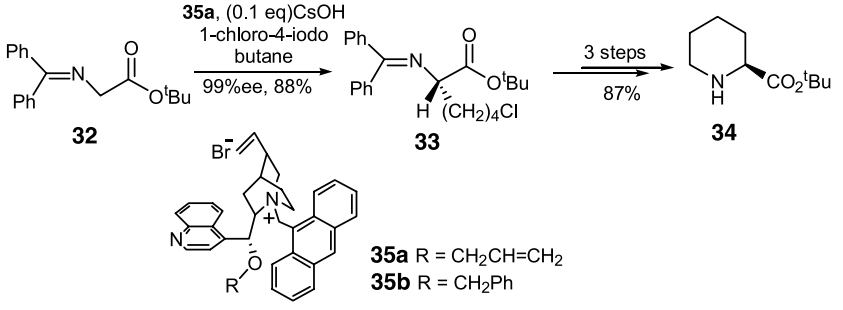


Fig. 10

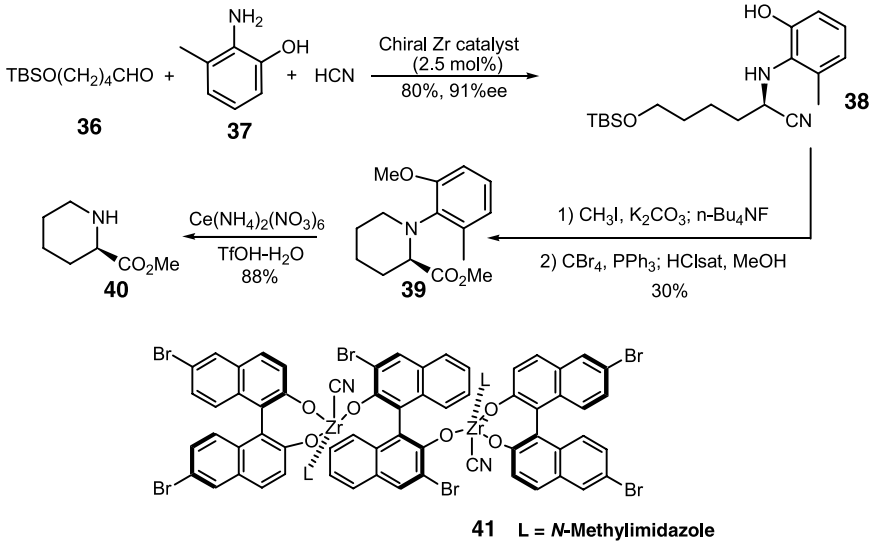


Fig. 11

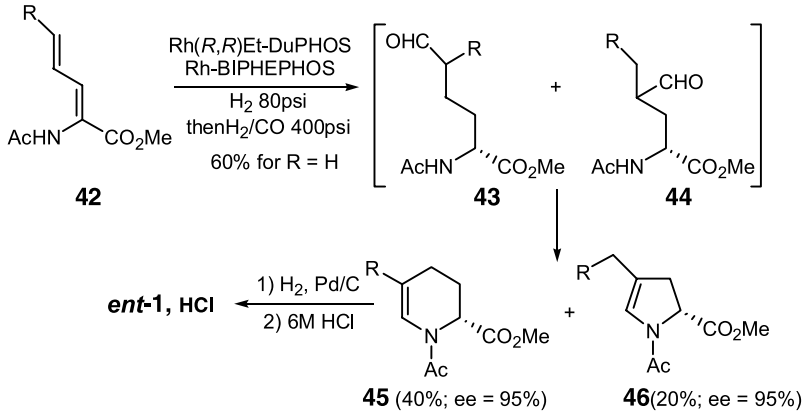


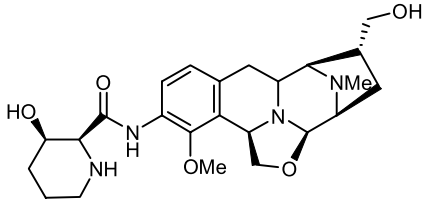
Fig. 12

synthesized with high yield and enantioselectivity, via a three component asymmetric process, from aldehyde **36**, amine **37**, and hydrogen cyanide using a chiral zirconium catalyst **41** (Ishitani et al., 2000). Standard transformations from the amino nitrile **38** led to the ester **40** (Fig. 11).

Recently, works were reported (Teoh et al., 2002, 2003), describing the synthesis of five and six-membered cyclic amino acids *via* tandem rhodium-catalyzed asymmetric hydrogenation, hydroformylation-cyclization sequence in a one-pot procedure (Fig. 12). Dienamido ester **42** was treated by two catalysts system: H_2/Rh-Et-DuPHOS then H_2/CO/Rh-BIPHEPHOS, producing asymmetric hydrogenation of the enamine and hydroformylation of the double bond in **42**. When the R group was an hydrogen, the selective cyclisation was in favour of compound **45**, which was easily purified by chromatography and was subsequently transformed into the chlorhydrate of (*R*)-pipecolic acid ***ent*-1**.

C-3 substituted pipecolic acid derivatives

C-3-substituted pipecolic acid derivatives constitute the common structural sub-units of a wide variety of naturally occurring alkaloids and drugs. For example, tetrazomine is an antitumor antibiotic that contains the unusual amino acid *cis*-3-hydroxypipecolic acid (Scott et al., 1998, 2002).



(-)-Tetrazomine

3-Hydroxypipecolic acid

Asymmetric induction

a) From imine

The key coupling reaction between 2-silyloxyfuran **47** and 2,3-*O*-isopropylidene-D-glyceraldehyde *N*-benzyl imine **48** in the presence of TBSOTf gave rise to 4,5-*anti*-5,6-*anti*-configured butenolide **49** as the predominant isomer (Battistini et al., 1997). Catalytic hydrogenation provided the saturation of the double bond with concomitant removal of the benzyl group. Ring opening of the lactone moiety by the amino group was achieved by treating compound **50** with neat 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at 80°C. Four steps furnished aldehyde **52** which was oxidized and the resulting protected amino acid was finally converted to *trans*-(2*S*,3*S*)-3-hydroxypipecolic acid **53** in two-steps deprotective protocol (Fig. 13).

b) From β-amino alcohol

An efficient and stereodivergent approach to *cis* and *trans*-3-hydroxy pipecolic acid has been described from protected *L*-serinol **54** (Jourdant and Zhu, 2000). Swern oxidation of compound **54** gave the aldehyde **55** which was reacted with Büchi's Grignard reagent to afford the amino diol **56** in excellent yield and diastereoselectivity (*anti*:*syn* = 15/1) (Fig. 14). A Felkin-Anh model renders account of this *anti* selectivity. Catalytic hydrogenation followed by *N*-protection as *tert*-butoxycarbamate gave piperidine **57** in 80% overall yield. A straightforward three steps sequence was applied to transform the diol into the alcohol **59**. Then, Jones oxidation and hydrolysis of MOM and Boc functions gave *trans*-(2*R*,3*R*)-3-hydroxypipecolic acid ***ent*-53**.

In view to develop a synthesis of *cis*-(2*R*,3*S*)-3-hydroxypipecolic acid **62**, the same authors described

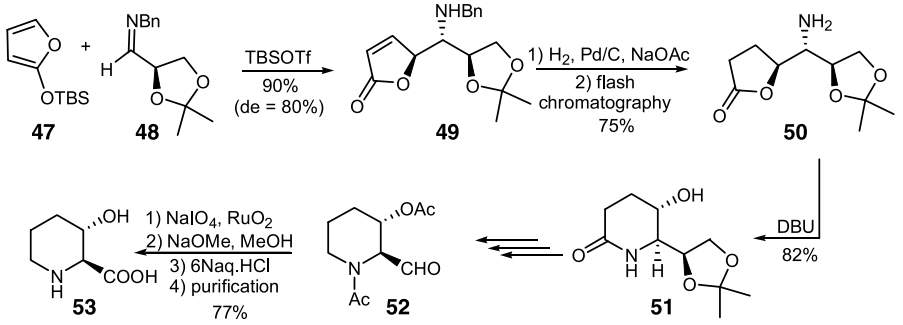


Fig. 13

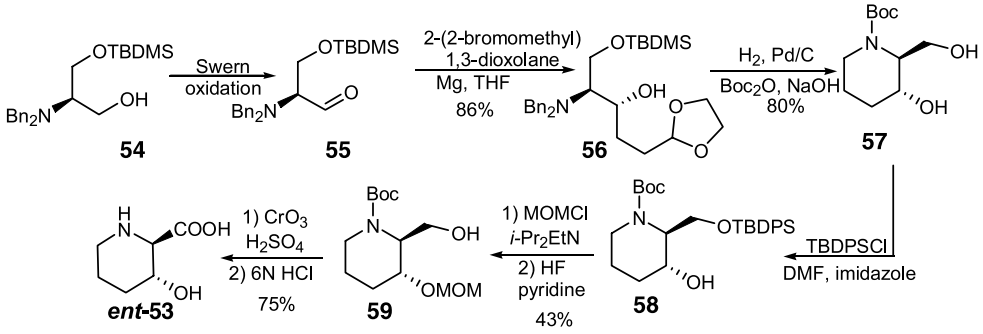


Fig. 14

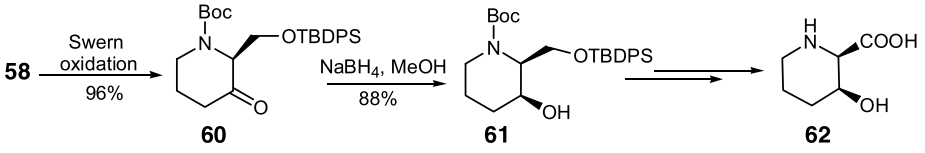


Fig. 15

the highly stereoselective (single stereoisomer) reduction of ketone **60** into **61** with $NaBH_4$ (Fig. 15) which was converted into the *cis*-pipecolic acid derivative **62** in 52% overall yield by the same route described for the synthesis of ***ent*-53**.

c) From the Williams lactone

As Fig. 16 illustrates, the synthesis of ***ent*-53** started from commercially available lactone **63** which was converted into the corresponding boron enolate with di-*n*-butyl triflate (Scott et al., 1998). Diastereoselective aldol condensation with 4-pentenal provided the *anti*-β-hydroxy aldol product **64** in 69% yield. Ozonolysis was followed by a mild catalytic hydrogenation to afford, via sequential CBz deprotection and reductive amination, the compound **65** which was hydrogenolyzed to give enantiopure amino acid ***ent*-53** (Fig. 16).

Asymmetric catalysis

The aldol coupling reaction between the chloro aldehyde **67** and the trimethylsilyl enol ether derivative of *tert*-

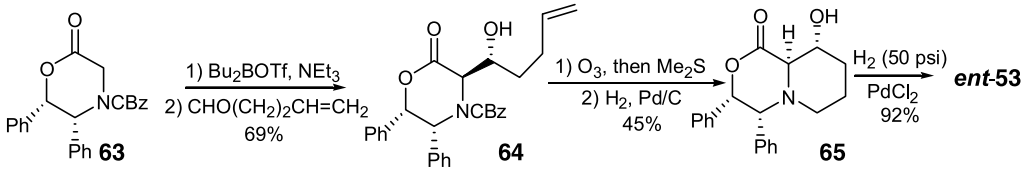


Fig. 16

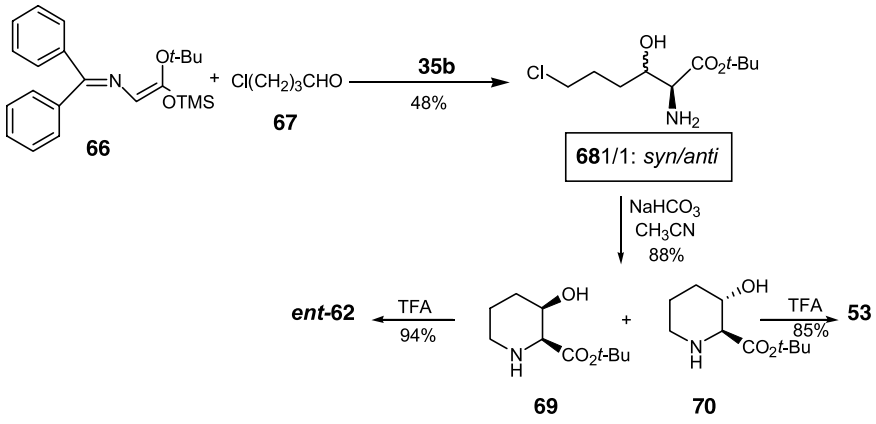


Fig. 17

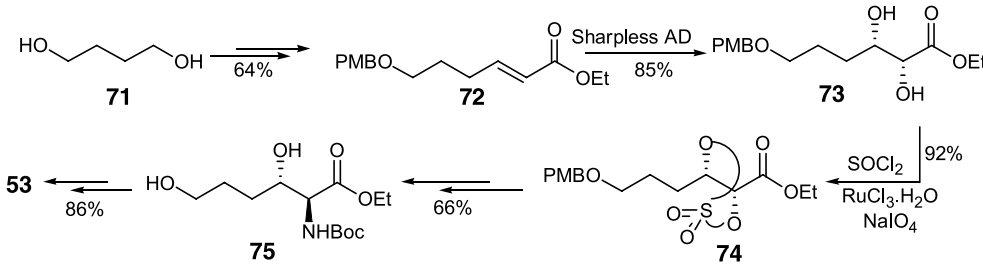


Fig. 18

butylglycinate-benzophenone Schiff base **66** using the cinchonidine-derived bifluoride salt **35b** (see p. 5) gave a mixture 1/1 of two *syn*/*anti* amino alcohols diastereomers **68** (Horikawa et al., 1999). After cyclisation and chromatographic separation, each isomer **69** and **70** were converted respectively into the diastereoisomeric amino acids **53** and ***ent*-62** (Fig. 17).

Very recently, an asymmetric route to 3-hydroxypipecolic acid used Sharpless asymmetric dihydroxylation of the unsaturated ester **72**, easily obtained from the commercially available diol **71** (Bodas and Kumar, 2004). Asymmetric dihydroxylation of olefin **72** using $(DHQ)_2PHAL$ ligand gave the diol **73** in 85% yield and 97% ee (Fig. 18). The regioselective opening of the cyclic sulphate **74** at C-2, the α-position, was achieved with NaN_3, and the subsequent reduction of the azido group in the presence of Boc_2O gave the amino diol **75**. This compound was subjected to cyclisation using methanesulfonyl chloride and triethylamine. The subsequent ester hydrolysis group and deprotection of the Boc group furnished enantiopure amino acid **53**.

3-Alkylpipecolic acid

Asymmetric induction

a) From allylic alcohol

The amino acid **79**, substituted by an alkyl chain, was obtained via two key-steps: a 3,3-Claisen rearrangement

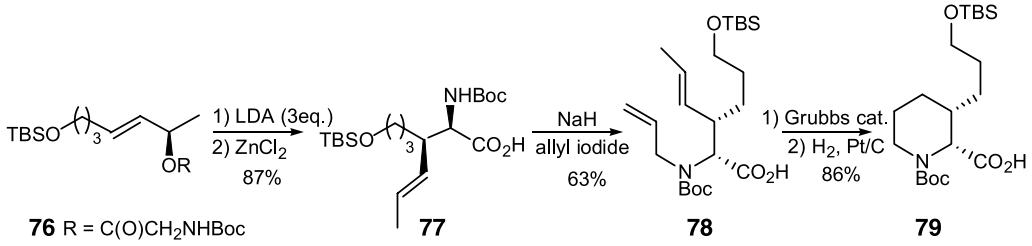


Fig. 19

and a ring closing metathesis (Souers and Ellman, 2000). Chiral ester **76** was submitted to a modified Kazmaier 3,3 Claisen rearrangement procedure to set the two contiguous stereocenters of amino acid **77**. This rearrangement proceeded from the zinc-chelated *Z*-ester enolate to afford **77** as a single isomer, which was assigned as the *syn* diastereoisomer with *E*-alkene stereochemistry according to a chair transition state. Allylation of the *N*-Boc compound **77** was followed by a ring closing metathesis and an hydrogenation of the resulting double bond to afford the pipecolic acid derivative **79** in 94% enantiomeric excess (Fig. 19).

b) From the Husson synthon

Compound **81**, easily prepared from the 2-cyano-6-phenyloxazolopiperidine synthon **80** (Zaparucha et al., 1999) was a common intermediate in the synthesis of various 3-alkylpipecolic acid derivatives. Michaël addition of various dialkyl cuprate reagents to compound **81**, in a mixture of diethyl ether/THF afforded compounds **82** as a single diastereoisomer in each case. The stereochemical outcome corresponded to an axial addition of the organometallic reagent onto a *quasi*-trans conformer of **81**. Hydrogenolysis gave the unnatural pipecolic acids **83** in nearly quantitative yield (Fig. 20).

c) From β-amino alcohols

The synthesis of 3-vinyl and 3-allenyl pipecolic acid derivatives was developed in our group, by using a methodology similar to those previously described *i.e.* a stereoselective ene-iminium cyclization induced from an amino alcohol possessing either an allylsilane or a propargylsilane function. In the first example, amino alcohol **84** was engaged in the same sequence that amino alcohol **8** in Fig. 4 (Agami et al., 1998a). The key cyclization step is entirely distereoselective, stereoselechemical course of this reaction was rationalized by AM1 calculations. Straightforward transformations led to enantiopure 3-vinyl pipecolic acid methyl ester **86**. Contrary to the precedent, amino alcohol **87** with a propargylsilane function cyclized spontaneously in THF/water medium to give bicyclic hemiketal **88** which after oxidation gave diastereoisomerically pure lactone **89** (Agami et al., 1998b). A mild deprotection sequence afforded the allenic amino ester **90**, with only 55% enantiomeric excess, due to a partial racemization during the deprotection steps (Fig. 21).

3-Arylpipecolic acid

Asymmetric induction from Evans auxiliary

The synthesis of *N*-Fmoc-(2*S*,3*R*)-3-phenylpipecolic acid **95a** and *N*-Fmoc-3-(di-(*tert*-butyl)phosphonomethyl)-phenyl)-pipecolic acid **95b** respectively as conformationally constrained phenylalanine analogue and phosphotyrosyl mimetic were recently described (Liu et al., 2002a, b). The introduction of chirality at both the 2-

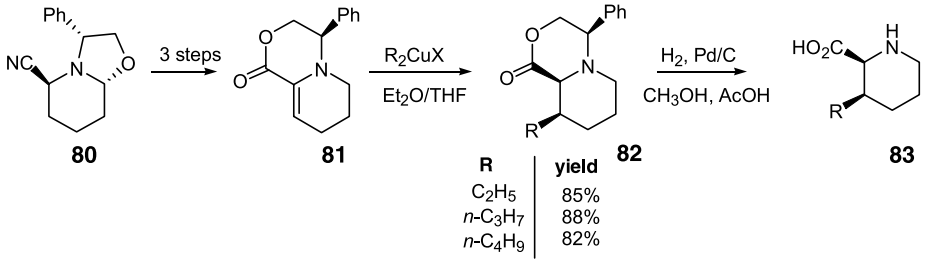


Fig. 20

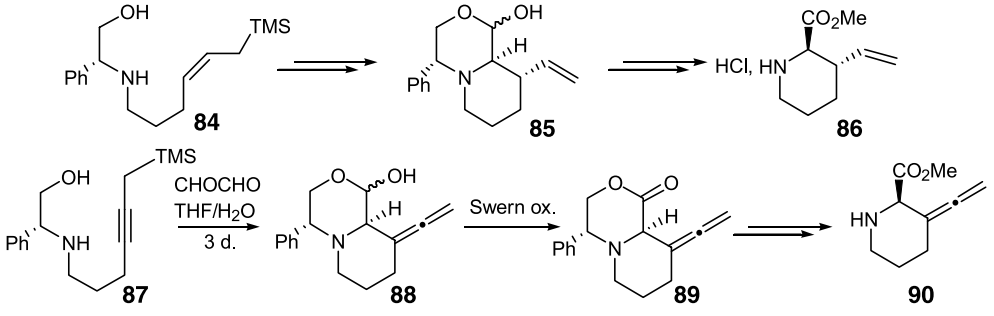


Fig. 21

and 3-positions was achieved from the Evans auxiliary's derivatives **91**. 1,4-Addition allowed the creation of the first stereocenter; and the introduction of a 2-amino functionality was initiated by asymmetric azidation at the C-α position. The resulting azido alcohols **92** were transformed into aldehydes **93** which were submitted to a ring closing by reductive amination using 10% Pd/C. Finally, esters **94** were readily converted to the *N*-Fmoc-pipecolic acid derivatives **95a** and **95b** (Fig. 22).

Asymmetric catalysis

3-Phenylpipecolic acids **101** and **104** were obtained with use of iridium-catalyzed allylic substitution followed by an intramolecular olefin metathesis (Kanayama et al., 2003). Imines **98** and ***ent*-99** which are precursors of pipecolic acids have been obtained diastereoselectively and with high enantioselectivity by using two different base systems in the presence of iridium catalyst with various reaction conditions (Fig. 23).

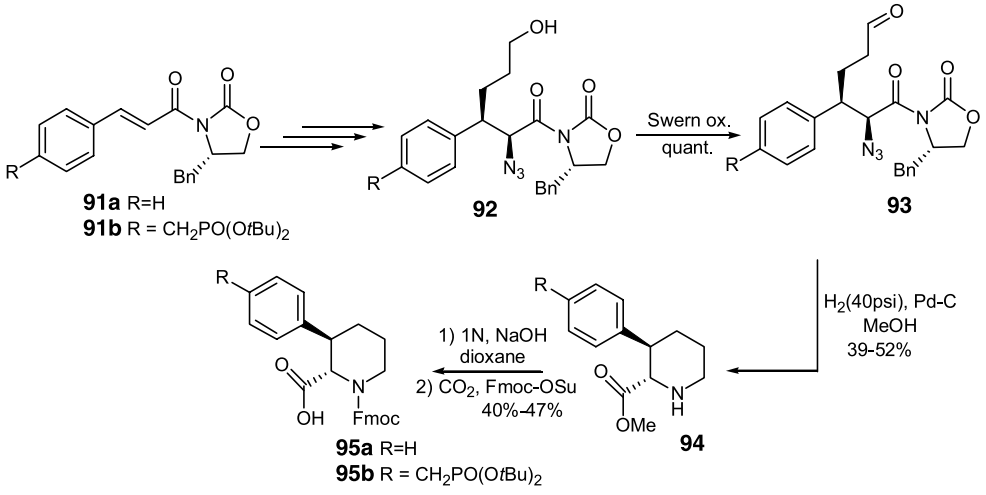


Fig. 22

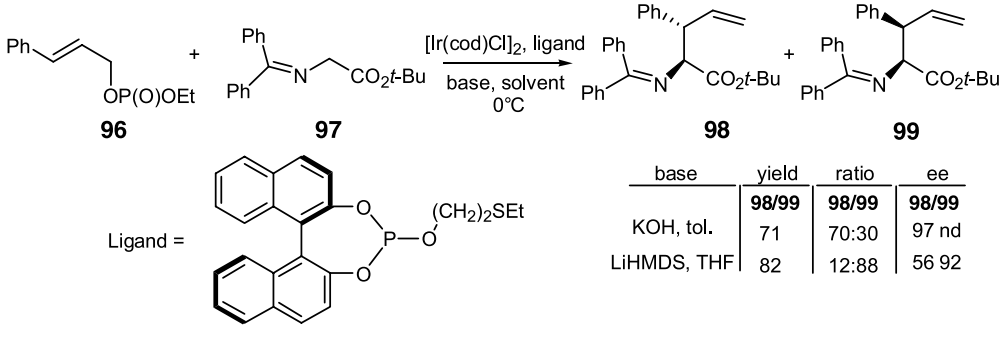


Fig. 23

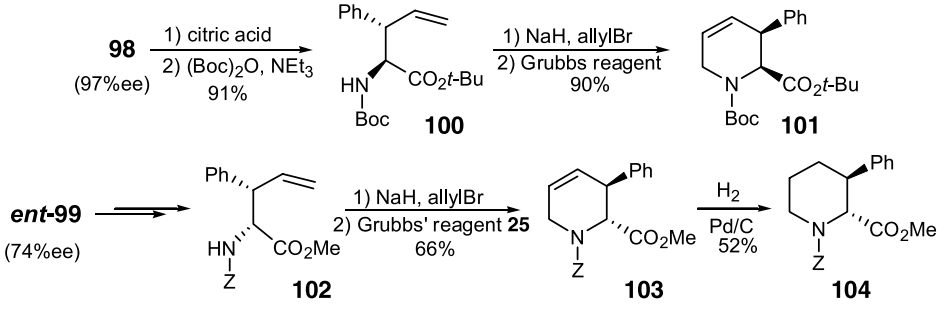


Fig. 24

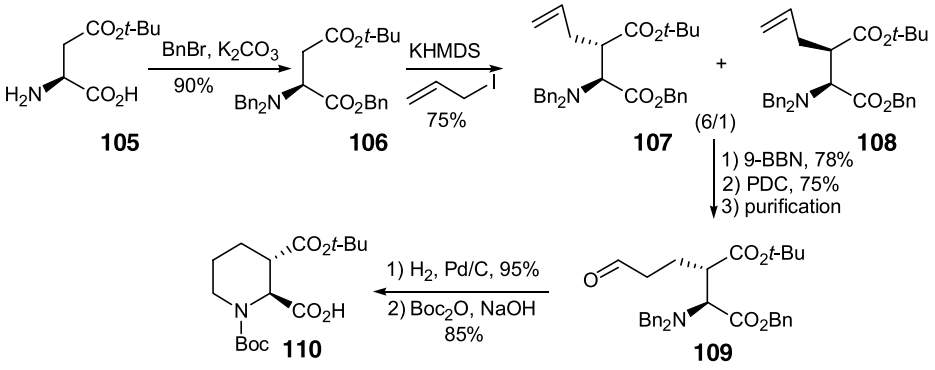


Fig. 25

After protection steps, compounds **100** and **102** were alkylated by allyl bromide and the cyclisations were performed with the Grubbs'catalyst **25** to afford respectively the 3-phenyl pipecolic acid derivatives **101**, possessing an insaturation, and **104** (Fig. 24).

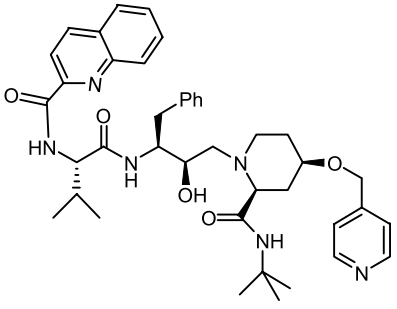
3-Carboxypipecolic acid

Asymmetric induction from amino acid

2,3-Piperidine dicarboxylic acid are structurally constrained aspartic acid derivative. In the following sequence (Xue et al., 2002), enantiomerically pure **110** has been synthesized in five steps starting from L-aspartic acid *tert*-butyl ester (Fig. 25). The enolate formation of the tribenzyl derivative **106** was conducted using KHMDS as the base and allyl iodide as the electrophile. Under these conditions, compounds **107** and **108** were obtained as an inseparable 6:1 mixture, in favour of the compound **107**. This selectivity was explained by the formation of a seven-membered K-chelated cyclic enolate, which resulted in the preferential attack of the electrophile opposite to the bulky *N*,*N*-dibenzylamino residue. Finally, the cyclisation step involved a reductive- amination reaction of the diastereoisomerically pure aldehyde **109**.

C-4 substituted pipecolic acid derivatives

4-Substituted pipecolic acids constitute one of the largest studied class of pipecolic acid derivatives. It is likely due to the important biological property of one of these elements: the (2*S*,4*R*)-4-hydroxypipecolic acid which is a component of Palinavir, a highly potent inhibitor of the human immunodeficiency virus (HIV) (Lamarre et al., 1997; Beaulieu et al., 1997).



Palinavir

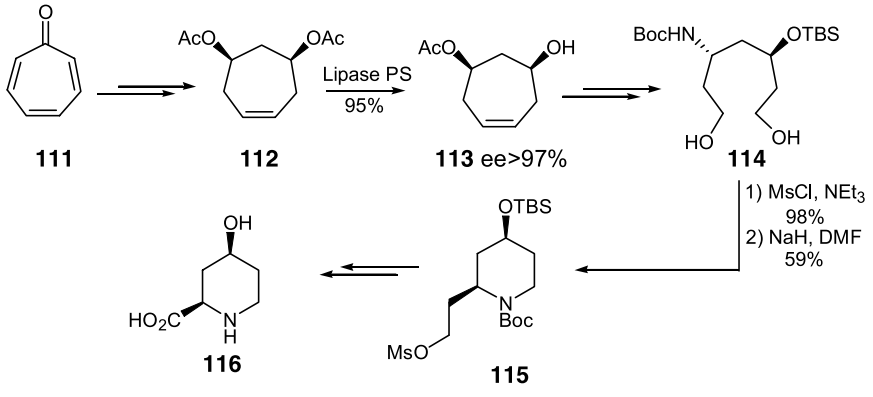


Fig. 26

4-Oxopipecolic acid has also attracted much attention since it was found to be a structural element in the cyclic peptidolactone antibiotic virginiamycin S[1] (Vanderhaeghe et al., 1971). This section is mainly ascribed to the syntheses of these two compounds; some synthetic sequences providing an access to both products.

4-Hydroxy and 4-oxopipecolic acid derivatives

Desymmetrization reaction

An interesting reaction of desymmetrization was used in the synthesis of *cis*-(2*R*,4*S*)-4-hydroxypipecolic acid **116** (Celestini et al., 2002). The meso-diacetate **112**, obtained from commercially available tropolone **111**, was desymmetrized in clearcut manner under hydrolysis conditions in the presence of Lipase PS to give enantioenriched monoacetate **113**, which was transformed into the diol **114**. The critical piperidine ring formation was produced, via a favored 6-*exo*-tet intramolecular cyclization, by treating compound **114** with mesylchloride and the unstable dimesylate was directly subjected to cyclization by reaction with NaH in DMF (Fig. 26). Two steps allowed an access to enantiopure amino acid **116**.

Asymmetric induction

a) From glycidol

Both enantiomers of *cis*-4-hydroxypipecolic acid have been prepared by an asymmetric synthesis by using (*S*) or (*R*)-glycidol as the chiral source (Haddad and Larchevêque, 1999). The key-step involved a stereoselective hydrogenation of a six-membered cyclic imine which was obtained by reduction and cyclization of the cyano β-hydroxy ketone **118** (Fig. 27).

b) From D-glucoheptono-1,4-lactone

Another synthesis of enantiomerically pure 4-hydroxypipecolic acid started from commercially available and inexpensive *D*-glucoheptono-1,4-lactone **120** (Di Nardo et al., 1999). When treated with 10% triethylamine in chloroform, this lactone underwent a double β-elimination process to give a mixture of 2-furanone **121** and **122** in 90% yield (Fig. 28). After some transformations, a separable mixture of compounds **123** and **124** was obtained. Product **123** was transformed in eight steps into amino compound **125**. The opening of this lactone and the cyclization by nucleophilic displacement of the mesylate by the amino group in basic medium gave the (2*R*,4*S*)-4-hydroxypipecolic acid **116**. The same synthetic route was

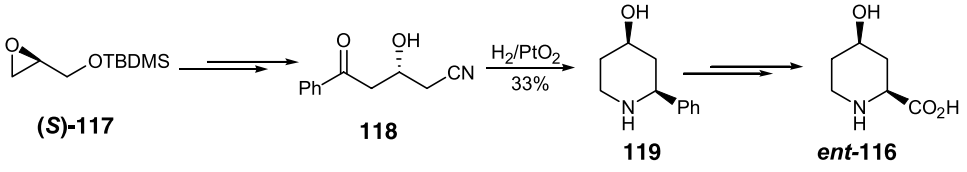


Fig. 27

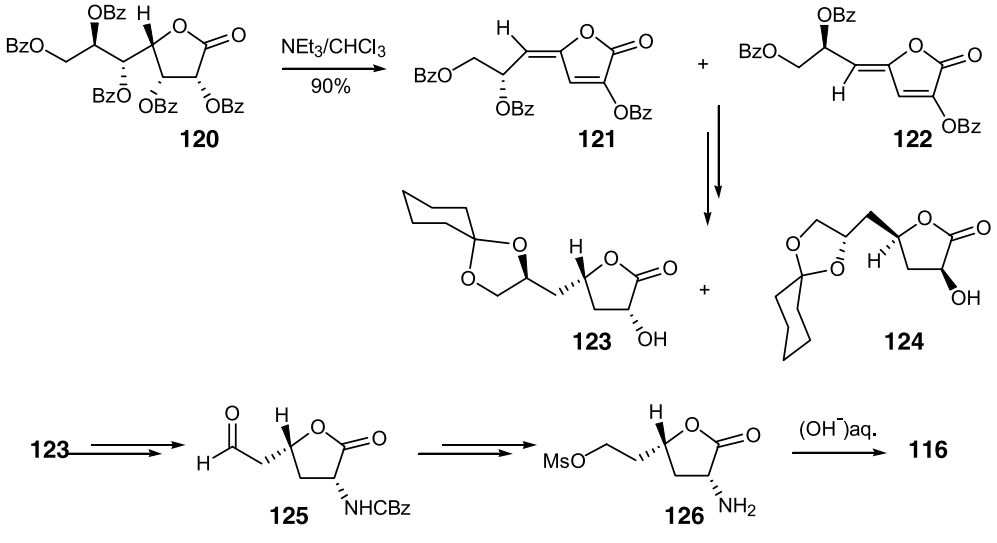


Fig. 28

employed for the preparation of ***ent*-116**, starting from **124**.

c) From the Williams lactone

A recent work reported the synthesis of 6-bromomethyl-4H-1,3 dioxin **128** as an equivalent of bromomethyl vinyl ketone (Greshock and Funk, 2002). The authors exploited the reactivity of this product in a very efficient asymmetric synthesis of amino acid ***ent*-116**. The totally diastereoselective alkylation of the Williams lactone **127** was followed by heating. Then, the enone functionality was unveiled by a facile retrocycloaddition reaction of the 1,3-dioxin ring and the nucleophilic site *i.e.* the amino group could react to afford the bicyclic compound **130**. Stereoselective reduction and removal of the Williams auxiliary concluded this concise synthesis of ***ent*-116** (Fig. 29).

d) From acylpiridinium salt

Another approach used as starting material the chiral acylpyridinium salt **131**, formed *in situ* from (4-methoxy-3-isopropylsilyl)pyridine and the chloroformate of (−)-*trans*-2-(α-cumyl)cyclohexanol. Addition of vinylmagnesium bromide and reaction with sodium methoxide afforded diastereoisomerically pure dihydropyridone **133** in good yield (Brooks and Comins, 2000). Stereoselective reduction of the keto group with K-selectride afforded the piperidinol **135**, which was hydrogenated to give enantiopure amino acid ***ent*-116** (Fig. 30).

e) From chiral imines

Chiral imines appeared as good substrate for the synthesis of these amino acids. In this field, diatereoselective allylation followed by hetero Diels-Alder reactions have been examined.

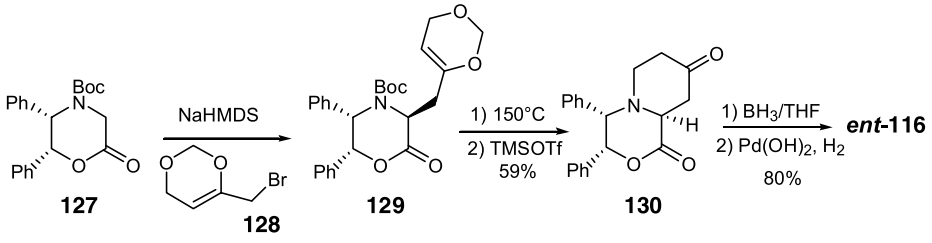


Fig. 29

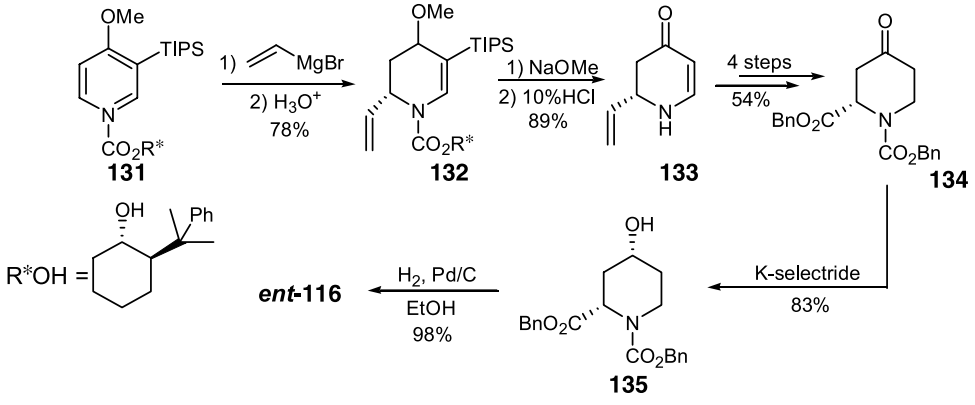


Fig. 30

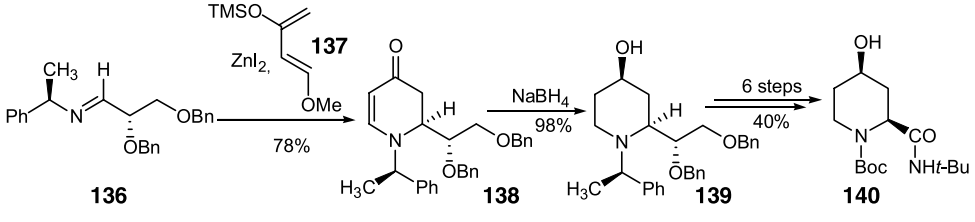


Fig. 31

N-benzylimines derived from glyceraldehyde **136** underwent diastereoselective tandem Mannich-Michaël reaction with Danishefsky's diene **137** in the presence of Lewis acids (Badorrey et al., 2002). The best conditions to perform this conversion was the following: ZnI_2 as Lewis acid and the use of the matched pair (*R*)-methylbenzylamine and (*S*)-2,3-di-*O*-benzylglyceraldehyde (Fig. 31).

The same authors described earlier, *via* an identical route a synthesis of 4-oxopipecolic acid (Badorrey et al., 1999).

4-Oxo-pipecolic acid derivative was also obtained by another hetero-Diels-Alder reaction (Lau et al., 2002). Sequential addition of TFA, $BF_3 \cdot Et_2O$ and 2-trimethylsilyloxy-butadiene **143** onto the resulting imine, obtained beforehand by reaction between ethylglyoxalate **142** and α-methylbenzylamine **141**, afforded a mixture of two diastereoisomers **144** and **145** respectively in a $7/5$ ratio. The interest of this method was its efficiency on a large scale since, starting from *S*-$(-)$-α-methylbenzylamine a batch of 69 g of the pure diastereoisomer **144** was prepared with 45% overall yield (Fig. 32).

$TiCl_4$-mediated addition of allyltrimethylsilane to *N*-tosyliminoglyoxylate of (*R*)-8-phenylmenthol **146** afforded allyl amine **147** with good yield and high selectivity (Kulesza et al., 2002). The excellent diastereoselection was attributed to face to face π–π interaction between the aryl moiety and the unsaturated reacting site. Therefore, the approach was favoured from the pro-*R* side of the imine (Fig. 33). Cyclization ene-acyliminium with formaldehyde gave the two diastereoisomers **148** and **149** (d.e. $= 1.7/1$).

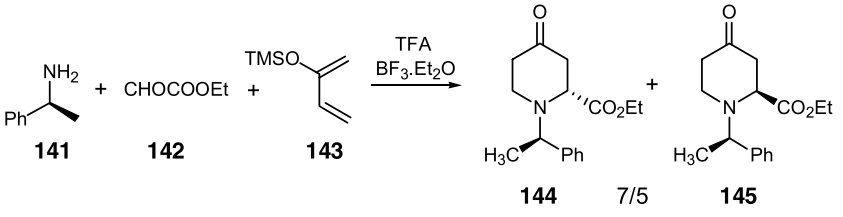


Fig. 32

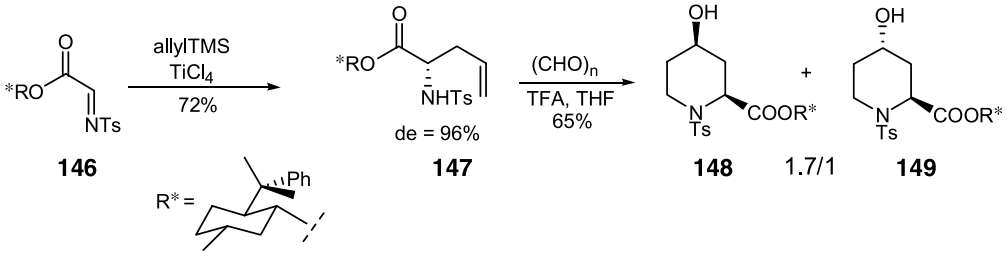


Fig. 33

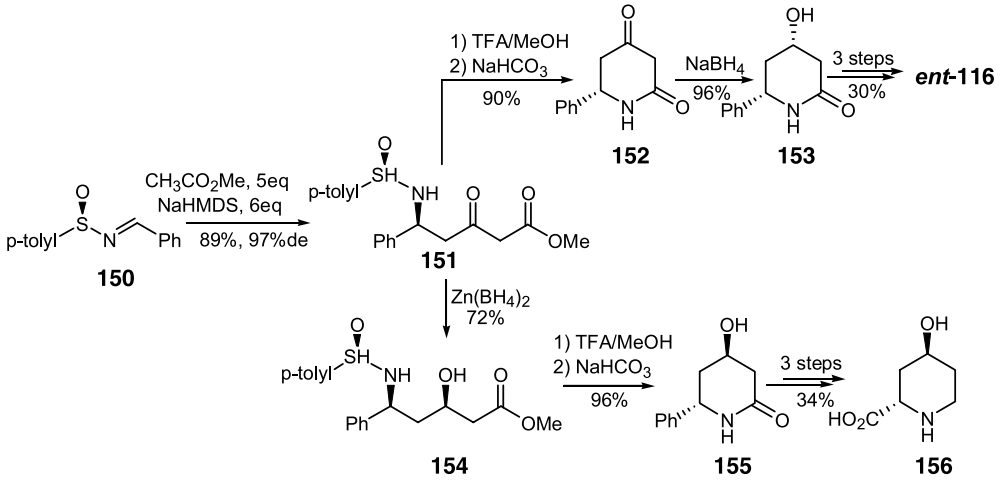


Fig. 34

Sulfoximine **150** reacted with an excess of methyl acetate to afford keto ester **151** with a very high diastereoselectivity (Davis et al., 2000). Key-steps in these syntheses were the stereoselective reductions of the dione **152** and of the β-ceto ester **151**, allowing respectively the synthesis of *cis* and *trans* 4-hydroxy pipecolic acids ***ent*-116** and **156** (Fig. 34).

f) From β-amino alcohols

In the course of our research on the synthesis of pipecolic acid derivatives, we have developed a common strategy which provides a very efficient access to 4-hydroxypipecolic acid ***ent*-116** and to 4-methylpipecolic acid **163**, by using as a key-step the stereoselective attack of an allylsilane onto an iminium ion (Agami et al., 2001). This reaction gave lactol **158** from (*R*)-phenylglycinol derived amino alcohol **157** and glyoxal with a quasi-quantitative yield (Fig. 35). A diastereoselective reduction of the keto group in compound **159** afforded the alcohol **160** which was hydrogenolyzed to give enantiopure amino acid ***ent*-116**.

The unsaturated lactone **161** was obtained in two steps from ***ent*-157**. Reaction with hydrogen in the presence of platinum oxide afforded a separable mixture of two diastereoisomers in a 75/25 ratio (Fig. 36). Hydrogenolysis of the major compound **162** afforded (2*R*,4*R*)-4-methyl pipecolic acid **163**, a key component for the preparation of a very selective thrombin inhibitor (2*R*,4*R*)-MQPA or Argatroban® (Kikumoto et al., 1984).

Phenylglycinol-derived oxazolidine **164** was used in a $3+3$ unit assembly strategy (Partogyan-Halim et al., 2003). The synthesis of 4-oxopipecolic acid started by the alkylation of *N*-(cyanomethyl)-4-phenyloxazolidine **164** with allyl chloride **165** (Fig. 37). The diastereoselection was not very good (de = 42%) but the major isomer **166** was transformed into the bicyclic compound **167**, *via* an ene-iminium cyclisation. Enantiopure amino acid **168** was obtained in two steps from **167**.

The following synthesis (Sabat and Jonhson, 2001) used as starting material protected vinylglycinol **169** to synthesize the *trans* isomer of 4-hydroxypipecolic acid **173** (Fig. 38). Two keys transformation were involved: a ring-closing metathesis with Grubbs' catalyst to obtain bicyclic compound **171** and a Prevost reaction for the installation of the 4-hydroxy substituent in product **172**.

g) From amino acids

A cyclization similar to that described above (Fig. 39 and see Fig. 33) was used from new enantioenriched amino acids possessing an unsaturation. (Rutjes et al., 1999).

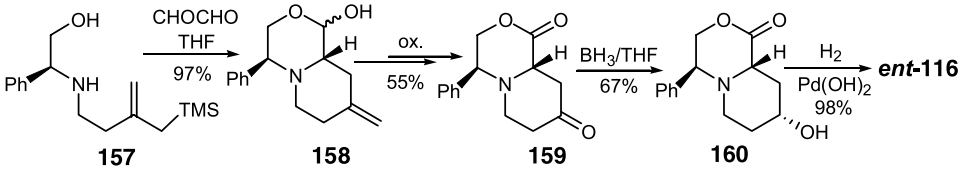


Fig. 35

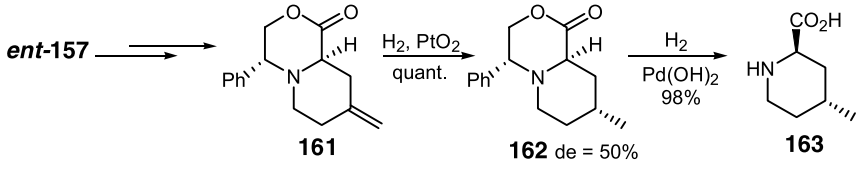


Fig. 36

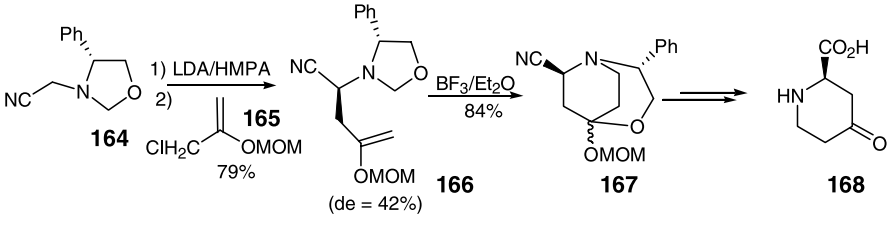


Fig. 37

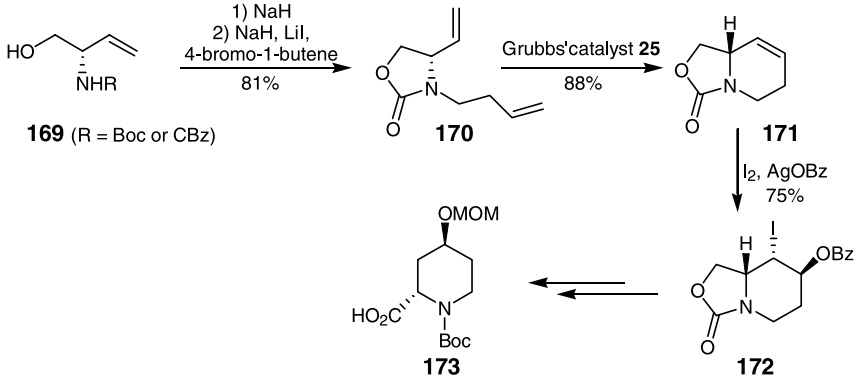


Fig. 38

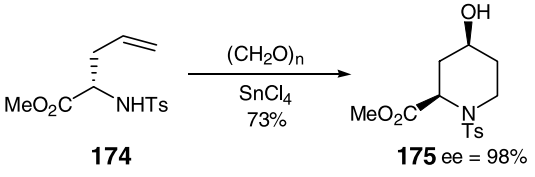


Fig. 39

Thus, for example, compound **174** reacted with formaldehyde in presence of $SnCl_4$, via an ene-iminium cyclization to give amino ester **175** without loss of enantioselectivity.

The synthesis of enantiopure 4-oxo and 4-hydroxypipecolic acid derivatives **179** and **140** combined both a Michaël addition of an aspartic acid derivative **176** and an intramolecular Dieckmann condensation to build the piperidine ring, as illustrated on Fig. 40 (Bousquet et al.,

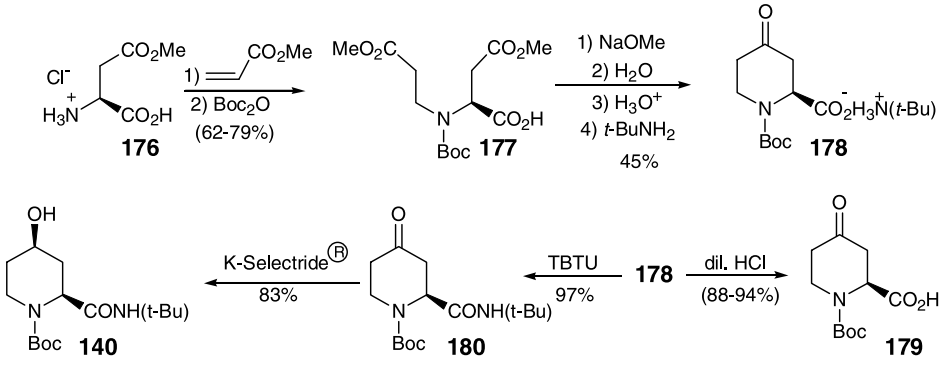


Fig. 40

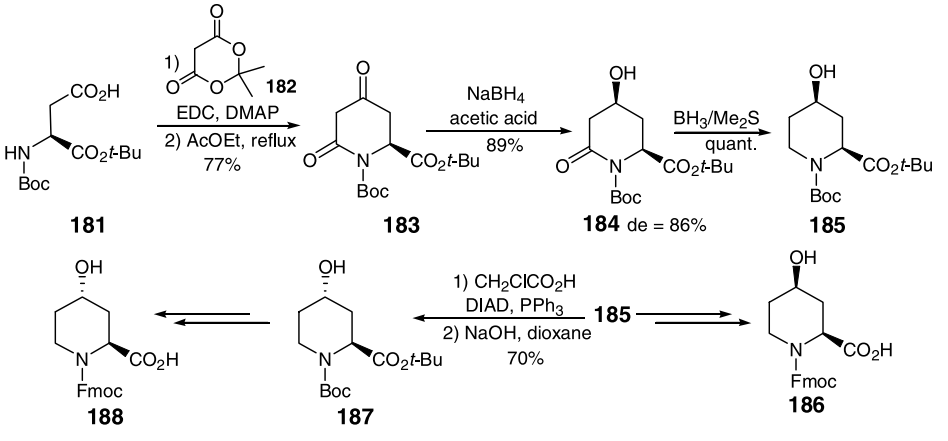


Fig. 41

1997). Amino acid **179** was obtained from the salt **178** following a simple wash with dilute acid, whereas compound **140** was got after treatment of salt **178** with TBTU (2-[1H-benzotriazol-1-yl]-1,1,3,3-tetramethyluronium tetrafluoroborate) followed by stereoselective reduction of ketone **180**.

Aspartic acid was also the starting material in a recent synthesis of enantiopure *cis* and *trans*-4-hydroxypipecolic acid derivatives **186** and **188**, which are conveniently protected for solid-phase peptide synthesis (Marin et al., 2004). The protected amino acid **181** was condensed with Meldrum's acid **182** in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) and DMAP and cyclized to afford *N*-acylated 4,6-dioxopiperidine **183**. Diastereoselective reduction of the keto group, followed by the reduction of the amide function gave 4-hydroxypipecolate **185**. This compound was transformed in three steps into the Fmoc derivative **186**; in another way, a Mitsunobu inversion, deprotection of *N*-Boc and *tert*-butyl ester functional groups and a subsequent reprotection, gave compound **188** (Fig. 41).

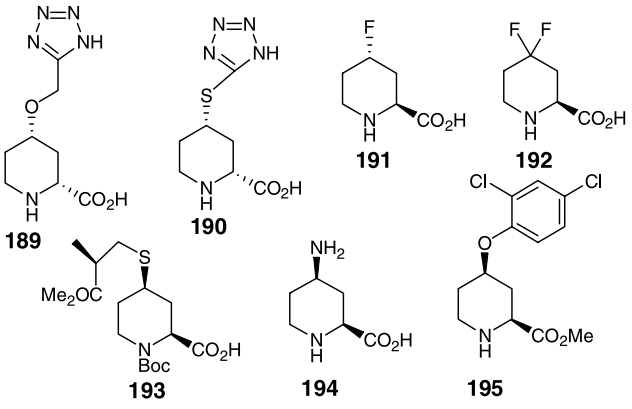


Fig. 42

Others C-4 substituted pipecolic acid derivatives

From 4-hydroxypipecolic acid

At last, others derivatives have been synthesized by using mainly as starting material 4-hydroxypipecolic acid. Few examples are cited below *i.e.*, the synthesis of hydroxyl derivatives **189** and **195** (Orstein et al., 1998; Bellier et al., 1998), thio derivatives **190**, **193** (Sata et al., 2002); amino **194** (Machetti et al., 2004) and fluoro **191** and **192** (Golubev et al., 2001) products (Fig. 42).

C-5 substituted pipecolic acid derivatives

In this short section are presented the syntheses of C-5-substituted pipecolic acid derivatives.

Asymmetric induction

a) From β-amino alcohol

A stereoselective allylsilane-iminium ion cyclization reaction was used for the synthesis of 5-ethyl pipecolic acid derivatives **201** and **203** (Cellier et al., 2000). The alkylation of the anion of **196** with **197** afforded a 3:1 mixture of the diastereomeric oxazolidines **198** and **199**. Treatment of these oxazolidines **198** and **199** with TMSOTf furnished piperidines **202** and **200** in respectively 96 and 62% yield with good diastereoselectivity (Fig. 43). Standard transformations from **202** and **200** led respectively to the pipecolic acids **201** and **203**.

b) From amino acid

The 5-hydroxypipecolic acid, previously synthesized by the group of Bailey (Adams et al., 1996), was the starting material in the synthesis of novel chiral six-membered PNA analogue (Shirude et al., 2004). Displacement of

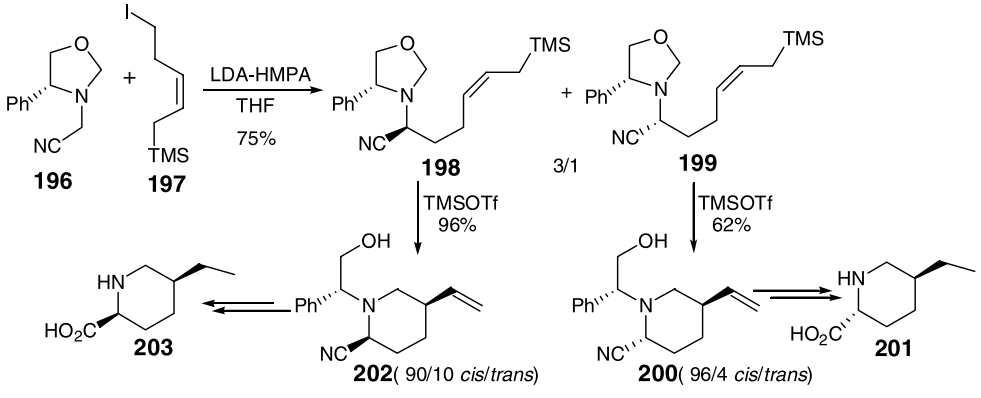


Fig. 43

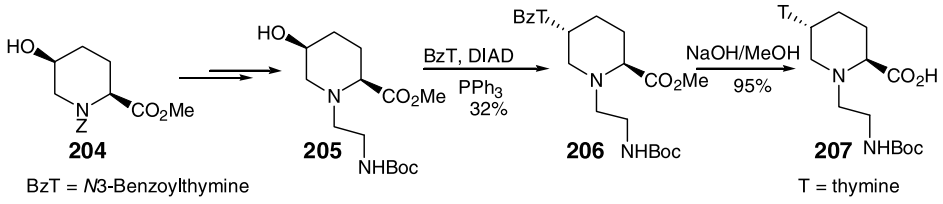


Fig. 44

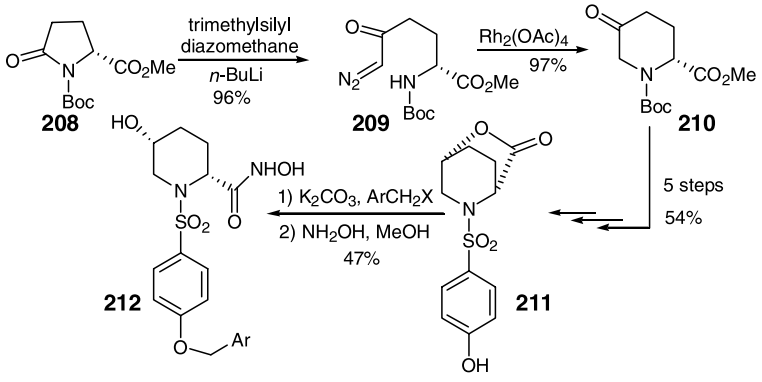


Fig. 45

the C5-(*S*)-hydroxyl function in protected compound **205** with *N*3-benzoylthymine under Mitsunobu reaction conditions yielded the pipecolic ester derivative **206**. The hydrolysis of the ester function and the *N*3-benzoyl deprotection of thymine gave the desired PNA monomer **207** used for PNA synthesis (Fig. 44).

5-oxopipecolic ester **210** was efficiently prepared from *N*-Boc-pyroglutamate ester **208** in two steps (Fig. 45): reaction of the anion of TMS-diazomethane onto compound **208** and rhodium catalyzed cyclisation of the resulting diazo-ketone **209**. This derivative was next transformed into the pipecolic hydroxamic acid **212** whose biological activity was studied onto TNF-α converting enzyme (Letavic et al., 2002).

C-6 substituted pipecolic acid derivatives

6-Substituted pipecolic acid derivatives are interesting not only for their potential bioactivity but also as starting material for synthesizing biologically active piperidine alkaloids.

6-Oxopipecolic acid

Asymmetric induction from amino acid

The 6-oxopipecolate **214** is an attractive synthon for the preparation of substituted piperidines and pipecolic acid derivatives. A convenient synthesis of the enantiopure methyl 6-oxopipecolate was performed starting from inexpensive chlorohydrate of (*S*)-lysine **2** (Davies et al., 1996). The product **213** was obtained in three steps with a good overall yield. Cyclisation of this adipamide **213** to methyl 6-oxopipecolate **214** was achieved in refluxing trifluroacetic acid (Fig. 46).

6-Alkylpipecolic acid

Asymmetric induction

a) From amino acid

6-Alkylpipecolic acids **220** were efficiently synthesized in five steps starting from α-*tert*-butyl β-methyl

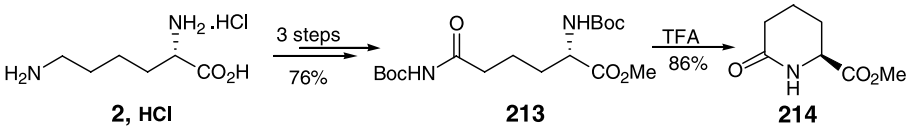


Fig. 46

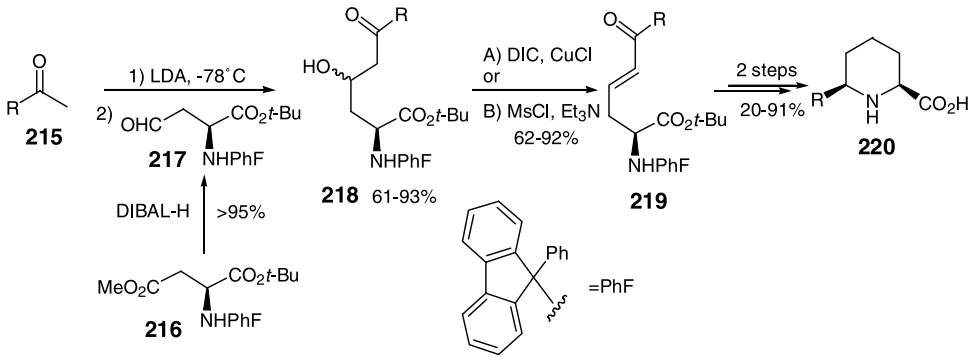


Fig. 47

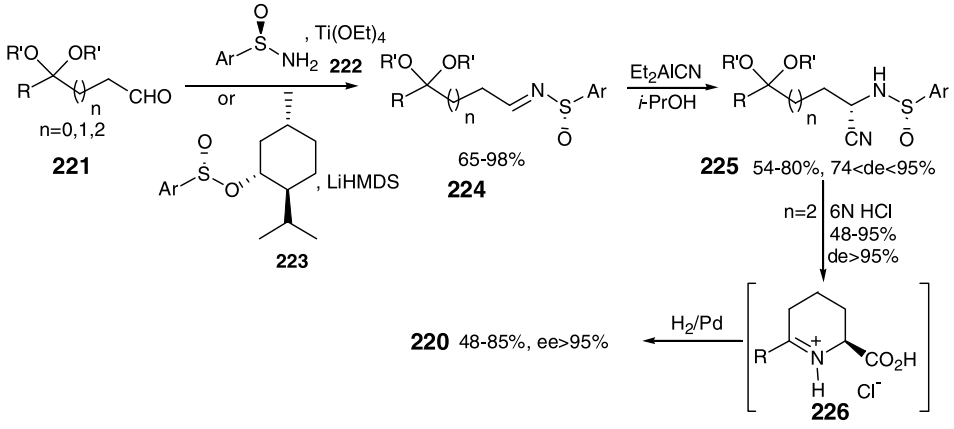


Fig. 48

N(PhF)aspartate **217** (Swarbrick et al., 1999) (Fig. 47). The methyl ester of **216** was chimioselectively reduced to give the aldehyde **217**. Aldol condensation with the methyl alkyl ketones **215**, followed by dehydratation of the resulting alcohol led to the enones **219**. Reductive amination and hydrolysis of the *tert*-butyl ester group furnished the *cis*-alkyl pipecolic acid **220**.

b) From imine

Masked oxo sulfinimines were very attractive starting material for the asymmetric synthesis of prolines and *cis*-6-alkylpipecolic acids **220** (Davis et al., 2001). Sulfinimines **224** were generated in one-pot by treating the aldehyde **221** with either commercially available (*S*)-(+)-*p*-toluenesulfinamide **222** with 5 equiv of $Ti(OEt)_4$ or by menthyl sulfinate **223** in presence of LiHMDS (Fig. 48). The sulfinimine-mediated Strecker synthesis involved addition of [EtAl(O-*i*-Pr)CN], generated *in situ*, to the sulfinimines **224**. Hydrolysis of the diastereomerically pure amino nitriles **225** gave directly the iminium ion salt **226**. After hydrogenation, the *cis*-6-alkylpipecolic acids **220** were isolated with various yields and in high enantiomeric excesses.

Two different strategies were used to isolate 6-alkylated pipecolic acid derivatives (Carbonnel et al., 2000, 2002). As illustrated on Fig. 49, the first one involved the

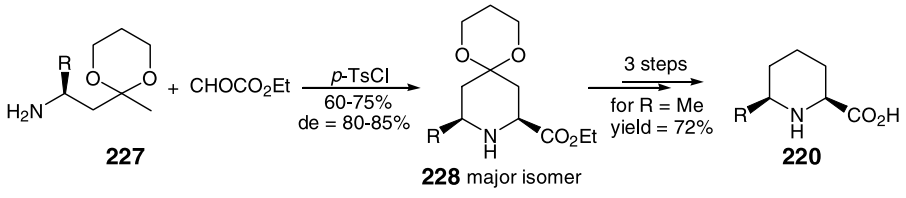


Fig. 49

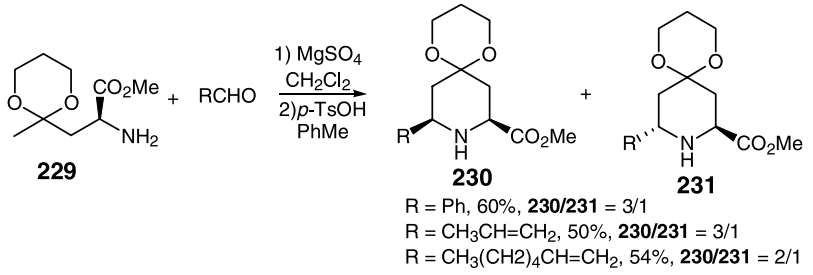


Fig. 50

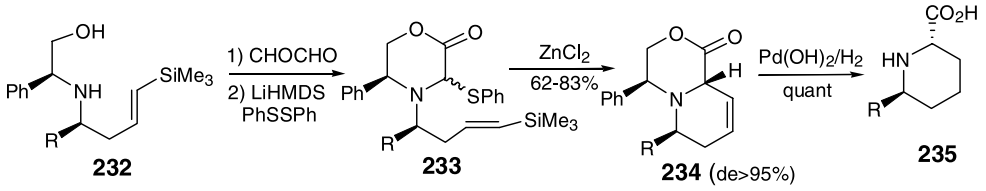


Fig. 51

condensation of an α-chiral alkylamine **227** with alkyl glyoxylate which gave the *cis*-piperidines **228** as major isomer. Three steps led to 6-alkyl pipecolic acids **220**.

The second pathway involved the reaction between an α-chiral carboxylamine, derived from a chiral amino acid and an achiral aldehyde. 2,6-*Cis* and *trans*-pipecolic acid derivatives **230** and **231** were obtained with various yield and diastereoisomeric ratios (Fig. 50). According to the authors, this last approach, although it could be an alternative route for the preparation of *trans*-6-pipecolic acid derivatives, was unsatisfactory in terms of yield and stereoselectivity.

c) From β-amino alcohol

As we have seen above, an attractive strategy for the synthesis of *cis* 6-alkylpipecolic acids **220** is cyclisation/reduction of oxo α-amino acids. The limitation is that it does not allow access to the *trans* 6-alkylpipecolic acids. We previously developed in our group a new method to produce the β-amino alcohols **232**, derived from phenylglycinol, bearing an *E* vinylsilane moiety (Fig. 51). Morpholinones **233** were obtained in two steps from these β-amino alcohols (Agami et al., 2002). The bicyclic lactones **234** were generated with an excellent diastereoselectivity, via a vinylsilane-iminium ion cyclization reaction. The treatment of the resulting compounds **234** with palladium hydroxide in the presence of hydrogen furnished the *trans*-6-alkylpipecolic acids **235**.

Asymmetric catalysis

A recent work reported, in this journal, the asymmetric synthesis of all stereoisomers of 6-methylpipecolic acids (Takahata and Shimizu, 2003). The strategy involved the judicious choice of the ligand in a first asymmetric dihydroxylation (AD) of the diene **236**. In the following example, the (*S*)-diol **237** was obtained with $(DHQ)_2$-Pyr ligand. The second AD onto the secondary alcohol **238**,

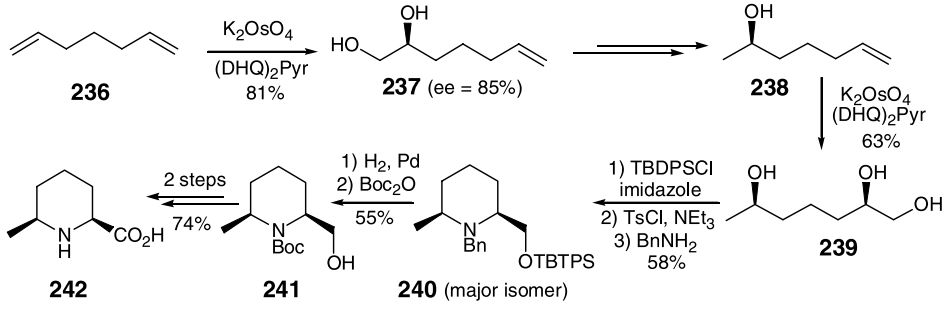


Fig. 52

which was obtained via a Sharpless epoxydation followed by a reduction, gave the triol **239** precursor of the 6-methylpipecolic acid **242** (Fig. 52).

Unsaturated pipecolic acid derivatives

Asymmetric induction

a) From imidazolidine

The baikiain is a natural amino acid present in rhodesian teak. An access to this compound was already described in the section ''pipecolic acid'' (see compound **28**, p. 4). Another recent asymmetric synthesis of this amino acid was reported (Guillena and Nájera, 2000). This synthesis illustrated the utility of a new reagent in asymmetric synthesis of α-amino acids: the 1,5-dimethyl-4-phenylimidazolidin-2-one-derived iminic glycinimide **246**. This compound was prepared in four steps from the commercially available imidazolidinone **243**. For example, the dialkylation of compound **246** with *Z*-1,4-dichloro-2-butene in presence of DBU and lithium chloride gave directly *C*- and *N*-dialkylated product **247** with an excellent diastereoselectivity. The participation of a chelated Z-enolate in which lithium chloride acts as Lewis acid was invoked to render account of the observed stereoselectivity. The hydrolysis of **247** afforded (−)-baikiain **248** (Fig. 53).

b) From amino acid

Ring closing metathesis (RCM) was used with success to give unsaturated pipecolic acid derivatives. In this way, the group of Rutjes started with various enantiopure amino acid-derived diolefins (**249**, **250** and **251**) (Rutjes and Schoemaker, 1997). The cyclizations were carried out by using the Grubbs' reagent **25**. For these *N*-protected allyl amines, the reaction had been shown to be an efficient transformation for providing enantiopure substituted pipecolic acid derivatives **252**, **253**, **254** and **255** (Fig. 54).

More recently, the same group has developed an efficient route for the synthesis of enantiopure *cis*-2,6-disubstituted unsaturated pipecolic acid derivatives (Tjen et al., 2000). Protected allylglycine **256** reacted with benzylpropadienylether **257** in the presence of $Pd(OAc)_2$ to afford the N,O-acetals **258** as a mixture 1/1 of two diastereoisomers. RCM reaction with the use of Grubbs' reagent **25** furnished the cyclic N,O-cyclic acetals **259**. Compound

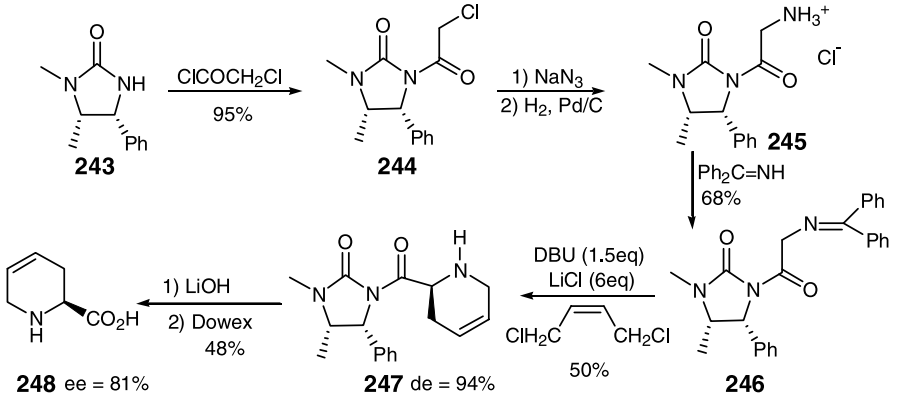


Fig. 53

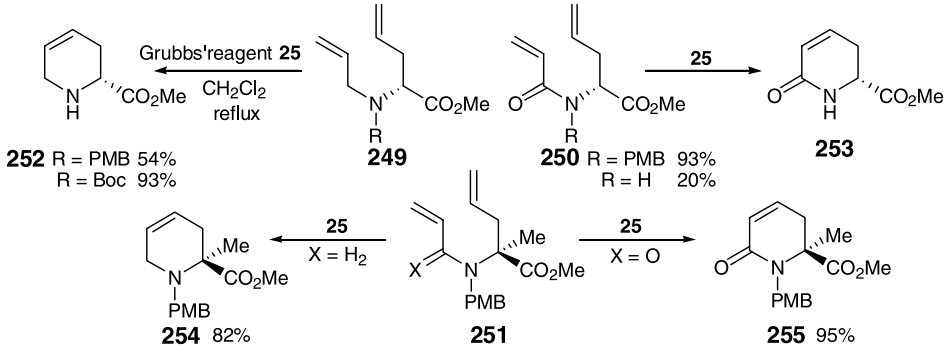


Fig. 54

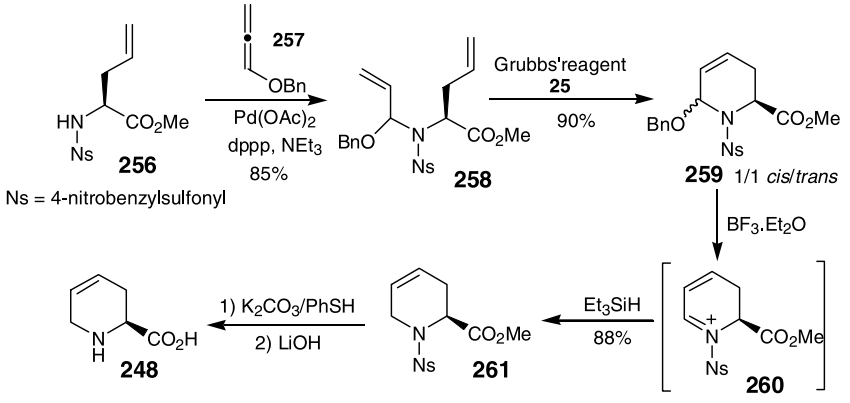


Fig. 55

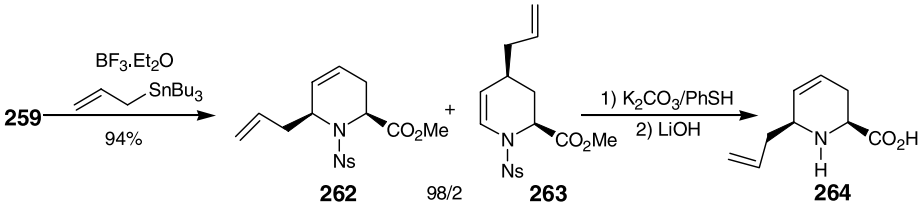


Fig. 56

259 was treated with a variety of nucleophiles in the presence of $BF_3 \cdot E_2O$. Thus, the nucleophile Et_3SiH reacted on the transient N-sulfonyliminium intermediate **260** and provided pipecolic ester **261** with 88% yield (Fig. 55). Removal of the protecting groups resulted in the formation of enantiopure baikiain **248**.

When the cyclic N,O-acetal **259** was treated by allyltributyltin, a mixture (98/2) of 1,2-adduct **262** and 1,4-adduct **263** was obtained, both as single isomers (Fig. 56). The formation of the *cis*-isomer was explained by an attack of the nucleophile in an *anti* position to the *N*-benzylsulfonylgroup which adopted a quasi axial position in a boat-like transition state. Deprotection of compound **262** yielded amino acid **264**.

The preparation of a poly(ethylene glycol)-supported protecting group of the silylethylethylsulfonyl (SES) **265** and its use in the synthesis of the cyclic amino acids by RCM was reported (Varray et al., 2002). The compound **265** reacted first with enantiomerically pure L-allylglycine methyl ester and was next alkylated with allyl bromide to give **266**. RCM reaction offered PEG-supported amino ester **267**, which was treated in refluxing 6N HCl to provide the deprotected amino acid. In the case presented on Fig. 57, the chlorhydrate of baikiain was obtained enantiopure, confirming that no racemization had occurred during the cleavage process.

Vinyloguous amide **272** has been synthesized in view to study its activity against enzymes involved in bacterial lysine biosynthesis (Caplan et al., 2000). Protected L-propargyl glycine **268** was treated by chlorooximido acetate to afford the 1,3-dipolar cycloaddition product, isoxazole **269** as a single regioisomer. Formation of the vinylogous amide **270** moiety was achieved by treatment of **269** with a catalytic amount of molybdenum hexacarbonyl and 1 equiv. of water in refluxing acetonitrile. Exposure of **270** to excess trifluoroacetic acid gave compound **271**, which

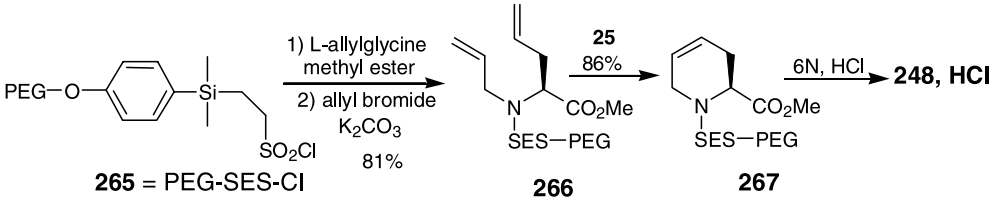


Fig. 57

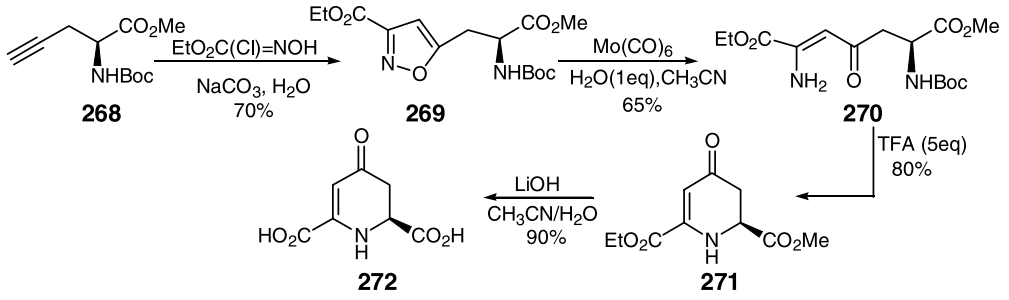


Fig. 58

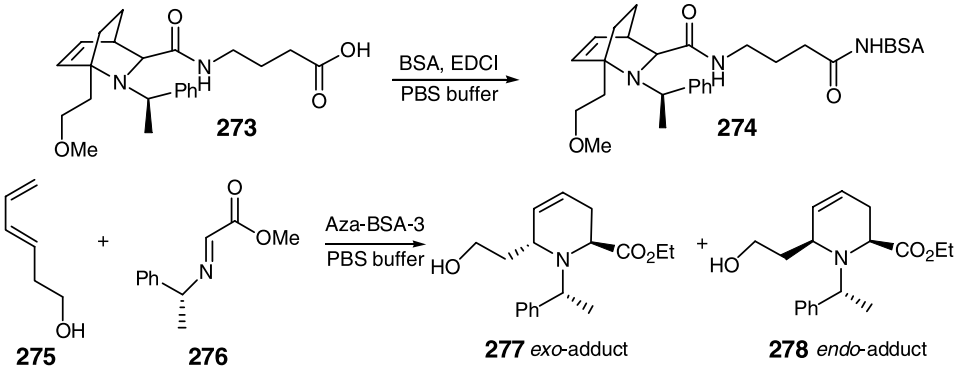


Fig. 59

was hydrolyzed to yield functionalized amino acid **272**. This compound proved to be an excellent competitive inhibitor of DHDP reductase (Fig. 58).

c) From imine

Recently, the first example of an antibody-catalyzed aza Diels-Alder reaction was described (Shi et al., 2002). The authors described the synthesis of the hapten **273** and the coupling with carrier protein Bovine Serum Albumine (BSA) which afforded immunogen **274**. Immunization of rabbits with **274** provided polyclonal antibodies, Aza-BSA-3, which catalyzed the Diels-Alder reaction between the diene **275** and the dienophile **276**. The *exo*-adduct **277** was isolated as major isomer with high diastereoselectivity ($exo/endo = 13/1$). The ratio was reversed ($exo/endo = 1/4$) if the Diels-Alder reaction was led under the catalysis of mixed protic acid (CF_3CO_2H/CH_3SO_3H) without polyclonal antibodies (Fig. 59).

Polysubstituted pipecolic acid derivatives

4 and 4,6-Substituted pipecolic acid derivatives

Asymmetric induction from β-amino alcohol

Always interested in the synthesis of pipecolic acid derivatives, using functionalized β-amino alcohols, we developed in our group an access to the polysubstituted pipecolic acids **282** (Agami et al., 2000). We started with the amino alcohols **279**. They reacted with glyoxal to afford the bicyclic compounds **280** with a total diastereocontrol of the stereocenter at the ring junction (Fig. 60). A

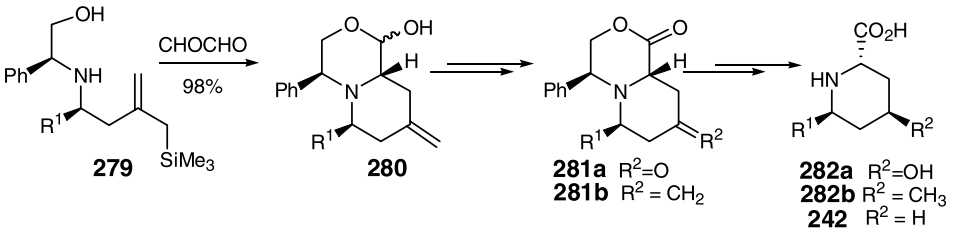


Fig. 60

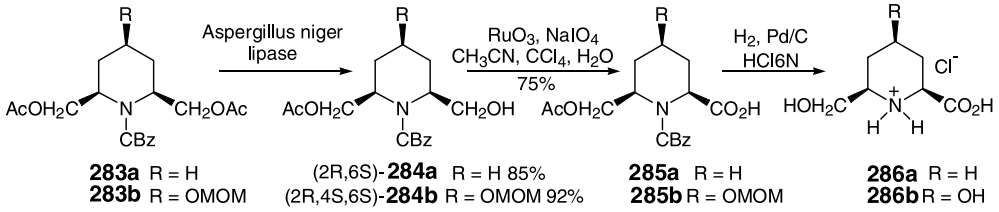


Fig. 61

straightforward sequence was applied to transform the hemiacetals into the lactones **281**. In a few steps, these lactones were converted into the polysubstituted pipecolic acids **282** and **242** (when R^2 substituent was an hydrogen).

Desymmetrization reaction

Both enantiomers of *cis*-6-(hydroxymethyl)-**286a** and *cis*, *cis*-4-hydroxy-6-(hydroxymethyl)-**286b** pipecolic acids have been synthesized from diesters **283a**,**b**. Alcohols **284a**,**b** were obtained by enzymatic desymmetrization of these diesters **283** in the presence of *Aspergillus niger* lipase (Chênevert and Morin, 1999). These alcohols **284a**,**b** (ee > 98%) were oxidized to give carboxylic acids, which were hydrogenated in acidic medium to afford the corresponding amino acids **286**. The enantiomers of **286** were obtained from the same starting materials **283a**,**b** by protection of the primary alcohol, hydrolysis of the acetates and the same steps previously described (Fig. 61).

4,5-Disubstituted pipecolic acid derivatives

Asymmetric induction from amino acids

The 4,5-epoxypipecolic acid **289** was easily prepared from baikiain **248** (Ho and Zabriski, 1998). Epoxidation of **287** was achieved using *m*-chloroperoxybenzoic acid and afforded *cis*-epoxide **288** as a single isomer (Fig. 62). The formation of the epoxide on the same face as the free carboxyl occurred because of a directing effect in the nonpolar solvent (CH_2Cl_2). Deprotection gave epoxyacid **289**, which was a substrate for L-pipecolate oxidase and caused an irreversible inactivation of this enzyme.

The starting material of the following synthesis was the azido derivative **290**, available in nine steps from *S*-glutamic acid. The ring expansion proceeded via an hydrogenation reaction to furnish piperidine **291**. The key-step was the chemoselective methylenation of the amide carbonyl group in **292** with dimethyltitanocene (Herdeis and Heller, 1997). Diastereoselective hydroboration, oxidation and deprotection sequence gave all-*cis* amino acid **294** (Fig. 63).

Addition of the serine-derived zinc/copper reagents **295a**,**b** with enantiomerically pure (η^3-allyl)iron tetracarbonyl salt **296a**,**b**, followed by oxidative removal of the iron tetracarbonyl unit with ceric ammonium nitrate gave respectively the diastereoisomerically pure adducts **297a**,**b** (Jackson et al., 1997). Epoxidation of each vinylphenylsulfones **297a** and **297b** in the presence of lithium *tert*-butylperoxide afforded the corresponding epoxiranes **298a** and **298b** as inseparable 1/1 mixture of diastereoisomers. The cyclizations occurred in the presence of the

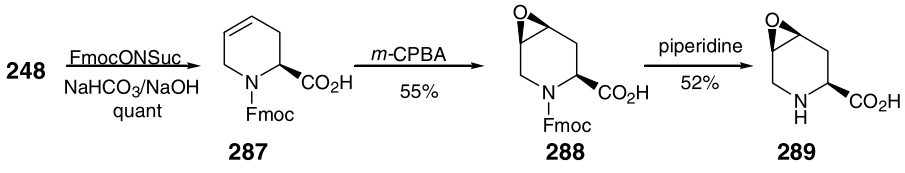


Fig. 62

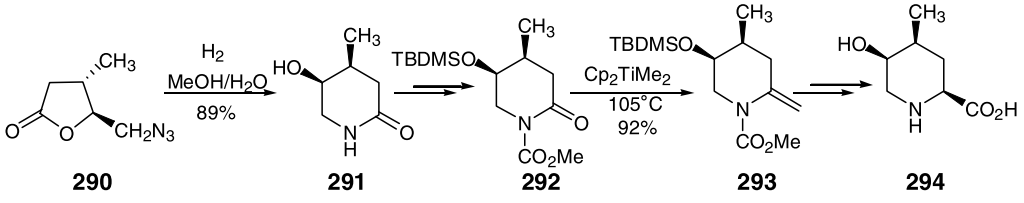


Fig. 63

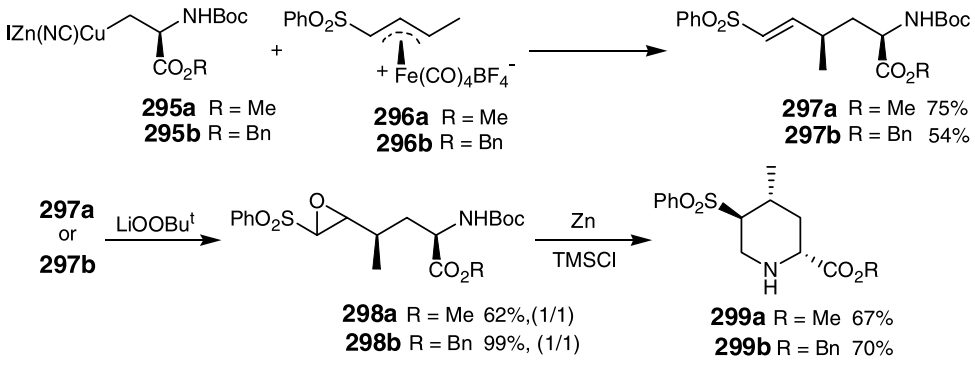


Fig. 64

couple Zn/TMSCl which furnished respectively compounds **299a** and **299b** as single stereoisomers (Fig. 64). Lewis acid presumably catalyzed an isomerization of the phenylsulfonyloxirane to the corresponding α-phenylsulfonyl aldehyde and zinc produced the intramolecular reductive-amination. Products **299** were likely the result of epimerisation at the carbon bearing the phenylsulfonyl group to the all-equatorial isomer in the presumed intermediate imine.

3,6-Disubstituted pipecolic acid derivative

Asymmetric induction from imine

The key-step of the synthesis outlined on Fig. 65 was an aza-Diels Alder reaction between 1,3-cyclohexadiene **300** and a chiral imine **301**, which was derived from (*R*)-phenylethylamine and ethylglyoxylate (Maison and Adiwidjaja, 2002). A mixture of *exo* and *endo* azabicyclooctenes **302** and **303** was obtained, favouring the *exo* product. Ozonolysis and reduction of the resulting instable intermediate dialdehyde afforded the pipecolate derivative **304** which, after reduction gave highly functionalized amino ester **305** (Fig. 65).

Polysubstituted pipecolic acid derivatives

Desymmetrization reaction

One interesting approach of α-quaternary pipecolic acid derivative involved a symmetry-breaking enolisation reaction of the *meso*-piperidine diester **306** (Goldspink et al., 1999). Treatment of **306** with the *bis*-lithium amide base **307**, followed by alkylation with electrophiles furnished products **308** in good yield as a single diastereoisomer, and in high enantioselectivity (ee $\geq$ 98%). This high degree of diastereoselectivity was explained considering the geometry of intermediate exocyclic enolate. Further regioselective modifications of these compounds were possible as shown on Fig. 66 to obtain pipecolic acid derivatives **309** and **310**.

Asymmetric induction

a) From chiral aldehydes

An asymmetric aldol reaction was used for the short syntheses of polyhydroxylated α-methylated pipecolic acids (Grandel et al., 1998). *N*-protected alanine esters **311** were deprotonated with LDA and subsequent addition of metal salts presumably resulted in the formation of

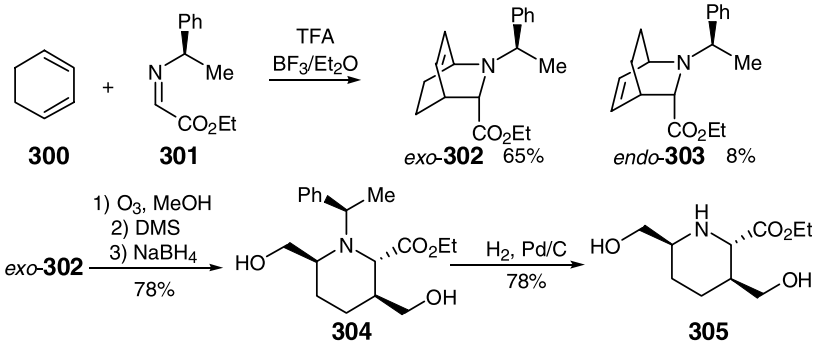


Fig. 65

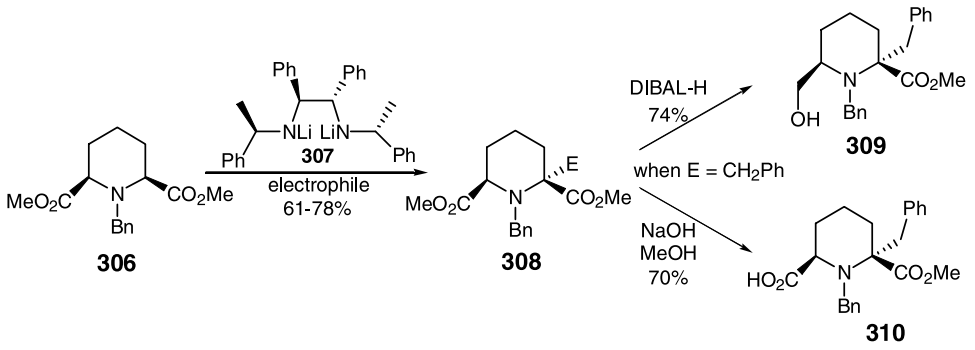


Fig. 66

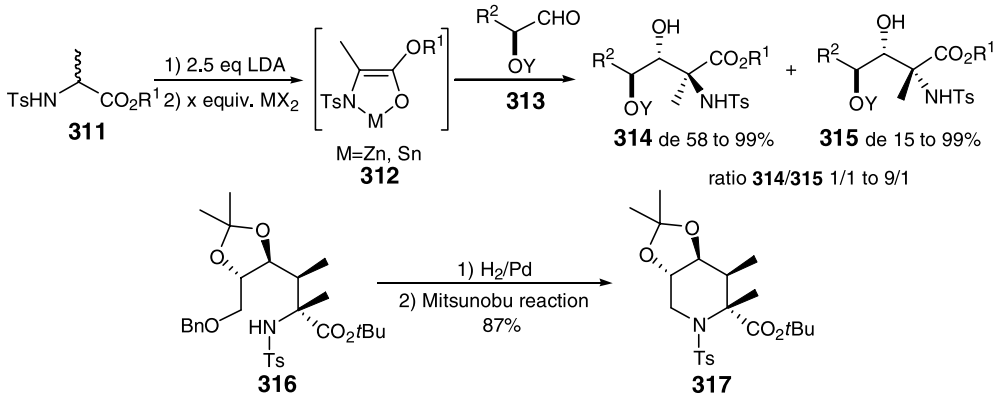


Fig. 67

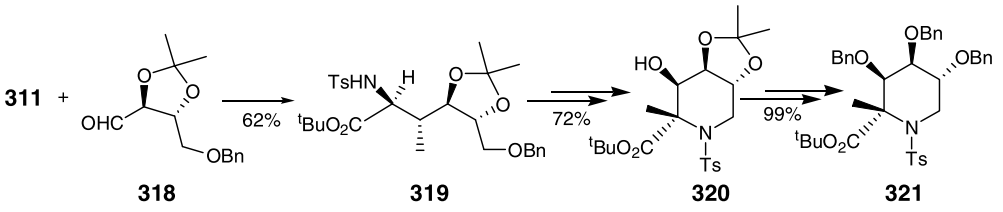


Fig. 68

intermediates **312**. Reacting with chiral aldehydes **313**, they led preferentially to the two aldol products **314** and **315** (Fig. 67). Due to the importance of the polyhydroxylated amino acids and also in order to determine the configuration of the two new stereogenic centers formed, two of the aldol products were converted into the pipecolic derivatives. For example, the benzyl ether in **316** was removed and then subjected to the Mitsunobu reaction, which gave the tosylated pipecolic derivative **317**.

This approach was applied to more functionalized aldehydes (Kummeter and Kazmaier, 2003). The aldol reaction between **311** and the protected threose derivative **318** provided a mixture of three diastereoisomers. The major compound **319**, the 2,3-*anti* 3,4-*anti* isomer, isolated in 62% yield was debenzylated and subjected to Mitsunobu conditions to afford after perbenzylation polyhydroxylated amino acid **321** (Fig. 68).

b) From the Schöllkopf synthon

Recently, α-quaternary pipecolic acid derivatives were synthesized (Andrei et al., 2004). The alkylation of **322** with 4-bromo-1-butene afforded the 2-*gem*-dialkyl derivatives in about 80% yield and diastereoisomeric excess higher than 95%. In this reaction, the alkylating agent approaches the carbanionic site in a *trans* manner with respect to the isopropyl site (Fig. 69). The transformation into the diazoketones **324** was followed by intramolecular rhodium(II)-carbenoid cyclization reaction which produced two diastereoisomers **325** (major isomer) and **326** (minor isomer). In three steps, major isomers **325**

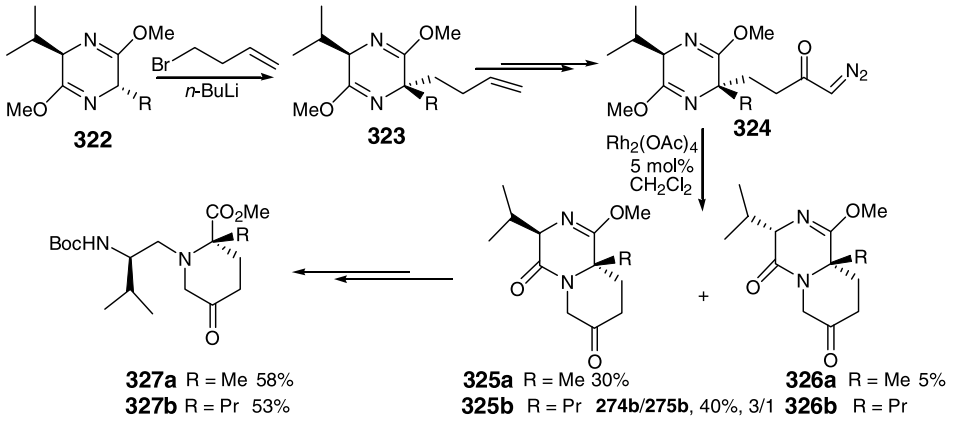


Fig. 69

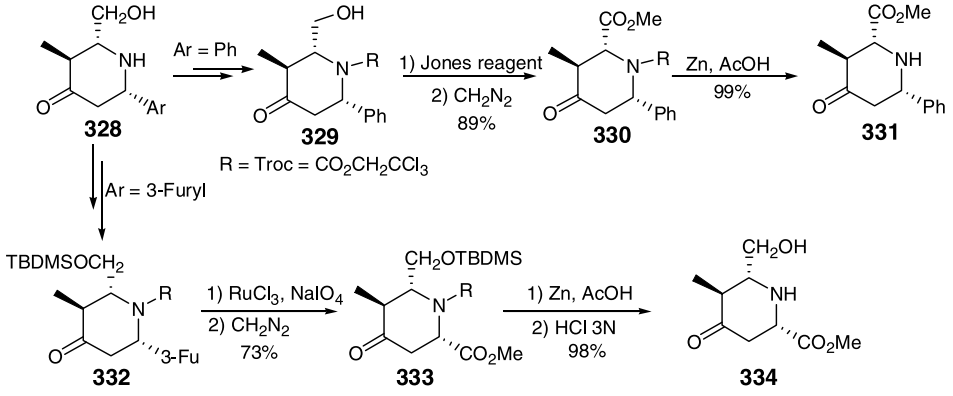


Fig. 70

were transformed into cyclic α-quaternary-α-amino acids **327**. The stereochemistry at the α-position could be inverted by changing the order of the alkylations of the Schöllkopf chiron.

c) From piperidone

Enantiomerically pure 4-piperidones **328** have been used as starting material in the synthesis of several pipecolic acid derivatives which are conformationaly constrained dipeptide isosteres (Barluenga et al., 1998). Two examples were shown on Fig. 70. Protected compound **328** (Ar=Ph) was rapidly oxidized, esterified and deprotected to afford with good overall yield amino ester **331**. In another way, when Ar = 3-furyl, oxidation followed by cleavage of the OTBDMS and the Troc protecting groups in **332** yielded the hydroxymethyl pipecolic acid **334**.

d) From D-glucal

The incorporation of an amide functionality was realized onto 3-hydroxypipecolic acid derivative in view to produce novel hydroxylated δ-lactam derivatives (Koulocheri et al., 2002). This class of compounds received attention due to their significant properties as anti-inflammatory and antimetastatic activities. Furanyl azide **335** was efficiently prepared in high enantiomeric excess from the readily available D-glucal according to a reported method. Subsequent transformations produced the dihydropyridinone **336**, the key-intermediate for these two syntheses. The reduction resulted in the formation of alcohol **337** as a single diastereoisomer. The reduction or the oxidation of the double bond gave either the target (2*R*,3*S*)-3-hydroxy pipecolic acid δ-lactam **338** or the (2*R*,3*R*,4*S*,5*S*)-trihydroxypipecolic acid δ-lactam derivative **339** respectively with 24 and 20% overall yield from furanyl azide **335** (Fig. 71).

e) From lactone

Lactone **340**, obtained according an already described procedure was a suitable intermediate for the synthesis of highly hydroxylated pipecolic acids (Shilvock et al., 1998 and 1999). Chemo- and stereoselective reduction of imine **341** with sodium cyanoborohydride gave amino

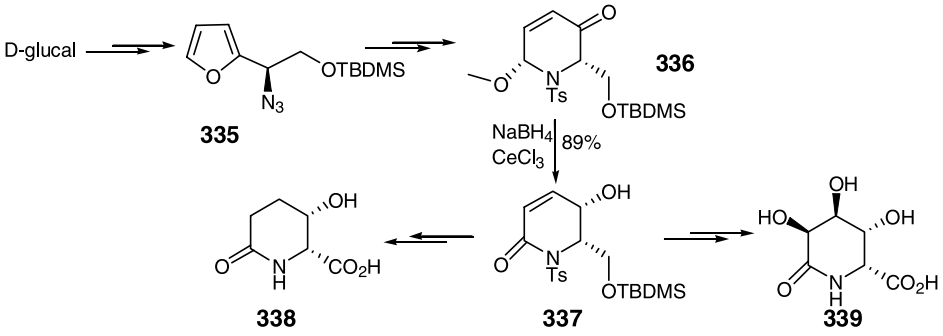


Fig. 71

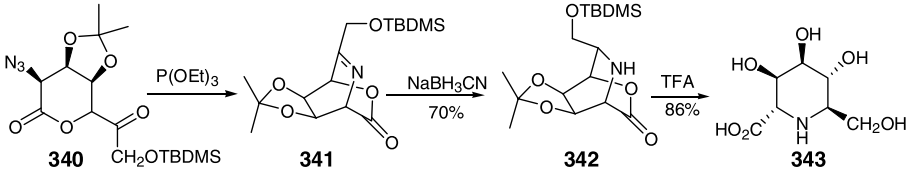


Fig. 72

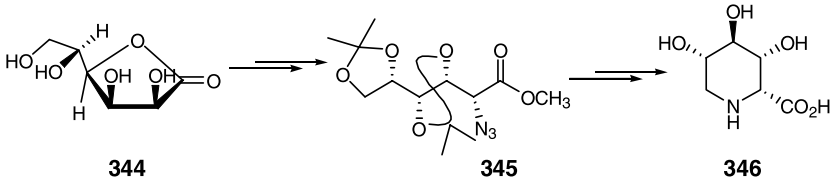


Fig. 73

lactone **342**. The free manno-pipecolic acid **343** was obtained directly by treatment with aqueous trifluoroacetic acid (Fig. 72).

The synthesis described on Fig. 73 commenced with the L-gulonic acid-γ-lactone **344**, which was efficiently transformed into the azido idonate **345** (Lee et al., 2000). Compound **346** was obtained in four steps from **345**. The cyclization occurred in the presence of hydrogen and palladium on carbon and the deprotection step led to the polyhydroxypipecolic acid derivative **346**.

With the aim to investigate structure-activity relationships of azasugar series toward metalloproteinase, an analogue route to this described above, was followed with gulono and glucono lactone as starting materials (Fig. 74). Then, the following four isomers **347**–**350** were synthesized and tested (Moriyama et al., 2003). The compound **348** (R=Ph) exhibited a potent inhibitory activity against TNF-α converting enzyme, an important target for medicinal chemists.

In summary, this review showed the large armamentarium available to organic chemists for the construction of pipecolic acid derivatives. Most of these approaches are based on stereoselective syntheses using chiral inductors. But, during these last years, have emerged new strategies

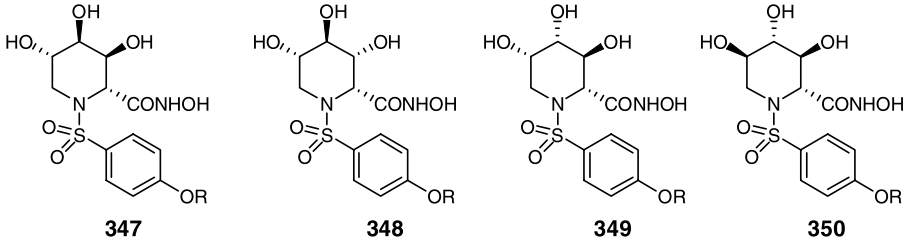


Fig. 74

using asymmetric catalysis; advances in this field are credibly the most exciting and useful way to synthesize these cyclic amino acids. The significant and various biological properties of these compounds constitute the main theme of all works reported here.

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