



Tetrahedron: Asymmetry report number 104

## Recent progress on the stereoselective synthesis of cyclic quaternary $\alpha$ -amino acids

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## ABSTRACT

The most recent papers describing the stereoselective synthesis of cyclic quaternary  $\alpha$ -amino acids are collected in this review. The diverse synthetic approaches are classified according to the size of the ring and taking into account the bond that is formed to complete the quaternary skeleton.

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**Abbreviations:** Ac, acetyl; AcOH, acetic acid; ACCA, 1-aminocyclopropanecarboxylic acid; acac, acetylacetonate; ACPD, 1-amino-1,3-cyclopentane dicarboxylic acid; Acd, 4-amino-1,2-dithiolane-4-carboxylic acid; Afc, *O,O*-isopropylidene- $\alpha$ -hydroxymethylserine; AIBN, 2,2'-azobisisobutyronitrile; AIDA, 1-aminoindane-1,5-dicarboxylic acid; APCPr, 1-amino-2-phosphonomethylcyclopropanecarboxylic acid; APICA, 1-amino-5-phosphoindane-1-carboxylic acid; AP4, *l*-2-amino-4-phosphonobutanoic acid; BINAP, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl; BINOL, 1,1'-bi-2-naphthol; Bn, benzyl; Boc, *tert*-butoxycarbonyl; BOP, benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate; BtH, benzotriazole; BuLi, butyl lithium; Bz, benzoyl; CALB, *Candida antarctica* lipase B; CAN, ceric ammonium nitrate; Cbz, benzyloxycarbonyl; CLEC, chiral ligand-exchange chromatography; Daf, 9-amino-9-fluorene-carboxylic acid; DABCO, 1,4-diazabicyclo[2.2.2]octane; DAM, di-*p*-anisylmethyl; DBDA, dibenzyl azodicarboxylate; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCC, *N,N*-dicyclohexylcarbodiimide; DCE, 1,2-dichloroethane; DDQ, 2,3-dichloro-5,6-dicyano-*p*-benzoquinone; DEAD, diethyl acetylenedicarboxylate; DEAD, diethyl azodicarboxylate; DIAD, diisopropyl azodicarboxylate; DMA, *N,N'*-dimethylacetamide; DMB, 3,4-dimethoxybenzyl; DMAP, 4-dimethylaminopyridine; DMEA, dimethylethanolamine; DME, 1,2-dimethoxyethane; DMF, *N,N'*-dimethylformamide; DMPDAP, 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine; DMSO, dimethylsulfoxide; DPPA, diphenylphosphorazide; dppp, 1,3-bis(diphenylphosphino)propane; dr, diastereoisomeric ratio; EDA, ethylenediamine; EDC, *N*-ethyl-*N'*-dimethylaminopropylcarbodiimide hydrochloride; ee, enantiomeric excess; er, enantiomeric ratio; HMPA, hexamethylphosphoramide; HOBT, *N*-hydroxybenzotriazole; HPLC, high performance liquid chromatography; HYDIA, 2-amino-3-hydroxybicyclo[3.1.0]hexane-2,6-dicarboxylic acid; IBCF, isobutylchloroformate; LDA, lithium diisopropylamide; LiHMDS, lithium bis(trimethylsilyl)amide; LPLC, low pressure liquid chromatography; LTMP, lithium 2,2,6,6-tetramethylpiperidide; KHMDS, potassium bis(trimethylsilyl)amide; MABR, methylaluminum bis(4-bromo-2,6-di-*tert*-butyl phenoxide); MAO, methylaluminoxane; MBA, methylbenzylamine; *m*-CPBA, *m*-chloroperbenzoic acid; MOM, methoxymethyl; MOMBA, methoxymethylbenzylamine; MS, molecular sieves; Ms, methanesulfonyl (mesyl); MTPA, methoxytrifluorophenylacetic acid; NaHMDS, sodium bis(trimethylsilyl)amide; NBS, *N*-bromosuccinimide; NMM, *N*-methylmorpholine; NMO, morpholine *N*-oxide; NMP, *N*-methylpyrrolidin-2-one; Ns, nitrobenzenesulfonyl; PCC, pyridinium chlorochromate; PLE, pig liver esterase; PMB, *p*-methoxybenzyl; mGlu, metabotropic glutamate; PPTS, pyridinium *p*-toluenesulfonic acid; RCM, ring closing metathesis; rt, room temperature; SAMI, (*S*)-1-amino-2-methoxymethylindoline; SAMP, (*S*)-1-amino-2-methoxymethylpyrrolidine; TBAB, tetra-*n*-butylammonium bromide; TBAF, tetra-*n*-butylammonium fluoride; TBS, *tert*-butyldimethylsilyl; TDCl, *N,N*-thiocarbonyldiimidazole; TEA, triethylamine; Tf, trifluoromethanesulfonyl; TFA, trifluoroacetic acid; TFAA, trifluoroacetic anhydride; TFOH, trifluoromethanesulfonic acid; THF, tetrahydrofuran; TMAH, tetramethylammonium hydroxide; TMSCl, trimethylsilyl chloride; TMSI, trimethylsilyl iodide; TMSCN, trimethylsilyl cyanide; TMSE, trimethylsilylethyl; Tol, tolyl; TsOH, *p*-toluenesulfonic acid; Ts, *p*-toluenesulfonyl (tosyl).

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## 1. Introduction

Linear peptides are highly flexible molecules that can adopt many conformations in solution and, of these, only a few are responsible for their biological activity. The construction of novel peptide sequences with tailor-made enhanced properties is one of the most challenging areas in biomimetic research. The incorporation of rigid amino acid surrogates provides very useful information on the bioactive conformation and results in beneficial physiological effects. Between these rigid amino acids the use of quaternary compounds is one of the most interesting approaches, and for this reason during the last few years many procedures toward the stereoselective synthesis of these compounds have been described. In this context, we have previously reviewed (1998 and 2000) the stereoselective synthesis of these interesting compounds,<sup>1,2</sup> and, taking into account the great quantity of procedures reported, more recently we have published an update on the stereoselective synthesis of the acyclic  $\alpha$ -amino acids<sup>3</sup> that we complete now with a corresponding update of the cyclic systems.

Before beginning the summary of the new procedures concerning the stereoselective synthesis of these cyclic derivatives, it is worth mentioning that apart from our own contributions, during the last years some reviews that have focused on particular aspects have been published in relation to the synthesis of some cyclic amino acid and derivatives,<sup>4,5</sup> the synthesis of heterosubstituted carbocyclic  $\alpha$ -amino acids,<sup>6</sup> the synthesis of some fluorinated acyclic and cyclic amino acids,<sup>7</sup> the synthesis of unnatural  $\alpha$ -amino acids,<sup>8</sup> and the modelling and synthesis of some conformationally constrained amino acids.<sup>9</sup> Much more recently, the synthesis of the family of enantiomerically pure 1-amino-2-phenylcycloalkancarboxylic acids,<sup>10</sup> an excellent review of 1-aminocyclopropane-carboxylic acids,<sup>11,12</sup> the catalytic asymmetric synthesis of  $\alpha$ -amino acids including some quaternary derivatives,<sup>13</sup> the synthesis of cyclic  $\alpha$ -amino acids and their use in the preparation of stable conformational short peptides,<sup>14</sup> and also some recent approaches toward the asymmetric synthesis of quaternary amino acids<sup>15</sup> have been reported.

Nevertheless, and in spite of all these reviews, some of which are from a general point of view and others focused on some particular aspects or families of compounds, we review all methodologies in a manner that should be useful to organic experimentalists.

Some data concerning the structural analysis of cyclic amino acids in small and medium size  $Ac_nC$  (1-aminocycloalkancarboxylic acids) have been completed during these years and the synthesis and structural studies of model peptides containing these cyclic amino acids have been reported.<sup>16–24</sup> Apart from these classical rings, the conformational tendencies of other cyclic amino acids such as Hms(Ipr) or *O,O*-isopropylidene- $\alpha$ -hydroxymethylserine,<sup>25</sup> Afc or 9-amino-9-fluorene-carboxylic acid,<sup>26,27</sup> Daf or 9-amino-4,5-diazafluorene-9-carboxylic acid,<sup>28,29</sup> Adt 4-amino-1,2-dithiolane-4-carboxylic acid,<sup>30</sup> the axially chiral  $\alpha$ -amino acids Bip and Bin<sup>31–37</sup> or the Bip system incorporating a crown ether receptor<sup>38</sup> have been reported. More recently, the synthesis and properties of antAib, a novel tetrasubstituted  $\alpha$ -amino acid of the  $Ac_5C$  type possessing a fused anthracene fluorophore have also been reported.<sup>39,40</sup>

Theoretical calculations focused on the study of the conformational tendencies of 1-aminocycloalkancarboxylic acids ( $Ac_nC$ ) have been reported.<sup>41–43</sup> Of these compounds the cyclopropane derivatives have attracted the attention of many researchers, probably due to the particular characteristics that the cyclopropane ring confers to the amino acid. When additional substituents are incorporated into the ring, two stereogenic centers are formed and, as a consequence, new stereoisomers are possible. In the particular case of the incorporation of one phenyl ring as a substituent (named,  $c_3Phe$ ), the compound can be considered as a constrained phenylalanine and in this case several theoretical studies have been reported<sup>44</sup> to explain the behavior previously described by our group.<sup>45,46</sup> The presence of an additional phenyl group in a different carbon atom ( $c_3diPhe$ ) confers peculiar characteristics to the molecule, which have been reported both from an experimental<sup>47</sup> and theoretical points of view.<sup>48</sup> The case of the cyclopropane derivative in which both phenyl substituents are on the same carbon atom ( $c_3Dip$ ) seems particularly interesting since it has been reported that it confers important tendencies to give a  $\gamma$ -turn in some model peptides.<sup>49,50</sup> The structural tendencies of other cyclopropane derivatives such as  $c_3Val$ <sup>51,52</sup> or other 2-phenyl-1-aminocycloalkancarboxylic acids such as  $c_3Phe$ <sup>53</sup> and  $c_6Phe$ <sup>54–56</sup> have also been reported. Additionally, the theoretical study of 8-aminopentacycloundecane-8-carboxylic acid has been reported.<sup>57</sup> Very recently, the helical screw sense exclusively governed by stereogenic centers in the side chain of some cyclic amino acids has been reported.<sup>58–60</sup>

Finally, some systematic structure–activity relationships between biological properties of peptides incorporating quaternary cyclic amino acids have also been reported.<sup>61–63</sup>

## 2. Synthesis of 1-aminocycloalkancarboxylic acids

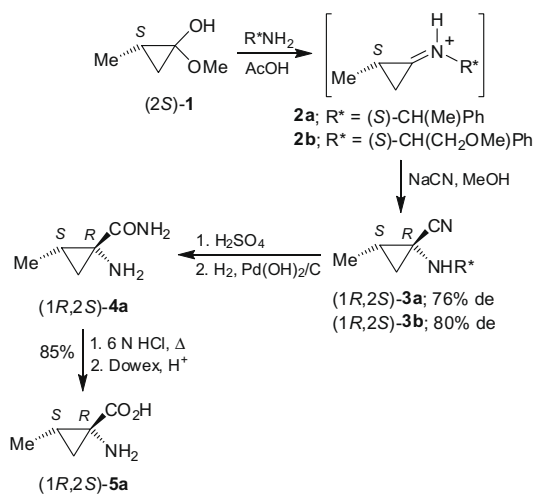
### 2.1. Using cyclic compounds as starting materials

One of the most useful methodologies to prepare 1-aminocycloalkancarboxylic acids in a stereoselective manner involves the use of cyclic compounds (typically aldehydes but ketones for the synthesis of quaternary  $\alpha$ -amino acids) as starting materials, although in this case the introduction of both functional groups (amino and carboxylic group) is necessary. Of all reported methodologies, the Strecker reaction<sup>64,65</sup> and related synthesis have been repeatedly used. The diastereoselective Strecker reaction involves the addition of cyanide or its equivalents to the previously formed C=N bond from the corresponding ketone and a chiral amine, and subsequent hydrolysis of the nitrile group. For the Strecker reaction, several chiral auxiliaries such as (*S*)- $\alpha$ -methylbenzylamine ( $\alpha$ -MBA),<sup>66</sup> (*R*)-phenylglycinol,<sup>67</sup> (*R*)-phenylglycine amide,<sup>68</sup> (*S*)-*p*-toluene- and (*S*)-butanesulfinimides,<sup>69</sup> (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP),<sup>70</sup> (*S*)-1-amino-2-methoxymethylindoline (SAMI),<sup>71</sup> and 2,3,4,6-tetra-*O*-pivaloyl- $\beta$ -D-galactopyranosyl amine<sup>72</sup> have been used.

The stereoselective syntheses of 1-aminocycloalkancarboxylic acids using this methodology have been grouped depending on the size and type of the starting carbonyl compound.

The 1-aminocyclopropanecarboxylic acids probably are the most interesting carbocyclic  $\alpha$ -amino acids, and several methodologies have been described for their stereoselective synthesis. However, to the best of our knowledge the work of Fadel et al.<sup>66</sup> is the only example reported in the literature, in which the Strecker reaction has been used for their stereoselective synthesis. In this context, reaction of cyclopropanone hemiacetal (2*S*)-**1** with the chiral amine (*S*)- $\alpha$ -MBA or (*S*)- $\alpha$ -methoxymethylbenzylamine ((*S*)-MOMBA) afforded the imines **2a,b**, which by addition of NaCN, gave the  $\alpha$ -aminonitriles (1*R*,2*S*)-**3a,b** with moderate diastereoselective excess. Hydrolysis of diastereoisomerically pure (1*R*,2*S*)-**3a,b** with concentrated sulfuric acid at 0 °C followed by hydrogenolysis over Pd(OH)<sub>2</sub>/C provided the amine amide (1*R*,2*S*)-**4a**, which by treatment with 6 N HCl at reflux gave (1*R*,2*S*)-1-amino-2-methylcyclopropanecarboxylic acid **5a** (allonorcoronamic acid) in 85% yield (Scheme 1).

On the other hand, condensation of the cyclobutanones ( $\pm$ )-**6a–c**<sup>73</sup> with (*S*)- $\alpha$ -MBA in the presence of a catalytic amount of acetic acid or *p*-toluenesulfonic acid (TsOH) followed by addition of sodium cyanide<sup>74</sup> or trimethylsilyl cyanide (TMSCN)<sup>75</sup> in the presence of ZnCl<sub>2</sub> afforded the  $\alpha$ -aminonitriles *cis*-**7a–c**, *trans*-**8a–c**, *cis*-**9a–c**, and *trans*-**10a–c** in moderate yield and diastereoisomeric ratio. The results are summarized in Table 1.

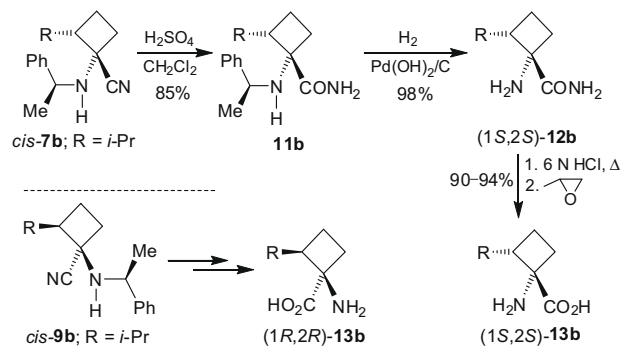


Scheme 1.

Hydrolysis of diastereoisomerically pure *cis*-**7b** (R = *i*-Pr) with concentrated sulfuric acid at 0 °C gave the amide **11b** in 85% yield, which by hydrogenolysis over Pd(OH)<sub>2</sub>/C furnished the amine amide (1*S*,2*S*)-**12b** in 98% yield. Finally, hydrolysis of (1*S*,2*S*)-**12b** with 6 N HCl under reflux followed by treatment with propylene oxide in ethanol gave the  $\alpha$ -amino acid (1*S*,2*S*)-**13b** in 90–94% yield. Under identical conditions, *cis*-**9b** was transformed into (1*R*,2*R*)-**13b** (Scheme 2).<sup>74</sup>

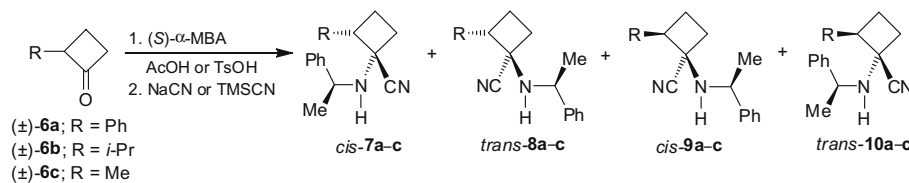
In a similar way, treatment of the mixture of  $\alpha$ -amino nitriles **8–10c** with concentrated sulfuric acid at 0 °C followed by separation and subsequent hydrogenolysis with HCO<sub>2</sub>NH<sub>4</sub>, Pd/C conditions, and hydrolysis with concentrated HCl led to (1*R*,2*R*)-**13c**, (1*S*,2*S*)-**13c**, and (1*R*,2*S*)-**14c** as hydrochloride salts (Scheme 3).<sup>75</sup>

Recently, Fadel et al.<sup>76</sup> have reported the stereoselective synthesis of (1*R*,2*R*)-1-amino-2-hydroxycyclobutanecarboxylic acid **13d**, a serine derivative from racemic or enantiomerically pure 2-benzoyloxycyclobutanone **6d** (R = OBn), and (1*R*,2*R*)- and (1*S*,2*S*)-1,2-diaminocyclobutanecarboxylic acid **13e** an ornithine derivative, from racemic 2-aminocyclobutanone **6e**. For this purpose, the condensation of either ( $\pm$ )- or enantiopure **6d** with (*S*)- $\alpha$ -MBA followed by addition of sodium cyanide gave the corresponding  $\alpha$ -amino nitrile mixture **7–10d**. The formation of the four diastereoisomers **7–10d** using (*R*)- or (*S*)-**6d** was probably due to the partial racemization of enantiomerically pure starting ketone under Strecker conditions.<sup>76a</sup> On the other hand, one-pot reaction of **6e** with (*S*)- $\alpha$ -MBA in the presence of AcOH and NaCN afforded, under thermodynamic control, only two major stereoisomers **8e** and **10e**



Scheme 2.

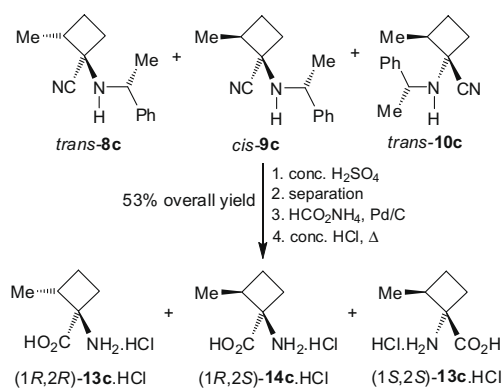
**Table 1**  
Preparation of  $\alpha$ -amino nitriles from the ketones ( $\pm$ )-**6a–c**



Entry	Conditions	R	Yield (%)	Diastereoisomeric ratio			
				7	8	9	10
1	NaCN, DMSO, 55–60 °C	<b>a</b> = Ph <sup>a</sup>	54	51	<2.5	45	<1.5
2	NaCN, MeOH, 55–60 °C	<b>a</b> = Ph	43	52	2.5	44	<1.5
3	NaCN, DMSO, 55–60 °C	<b>b</b> = <i>i</i> -Pr	46	56	1.0	42	<1
4	NaCN, MeOH, 55–60 °C	<b>b</b> = <i>i</i> -Pr	42	54	<1.0	44	<1
5	TMSCN, MeOH, ZnCl <sub>2</sub> , 0 °C	<b>c</b> = Me <sup>b</sup>	—	6	46	11	37
6	TMSCN, hexane, ZnCl <sub>2</sub> , –10 °C	<b>c</b> = Me <sup>b</sup>	—	11	15	33	41

<sup>a</sup> Similar results were obtained using (*R*)-phenylglycinol and (*R*)-MOMBA.

<sup>b</sup> The chiral amine was (*R*).

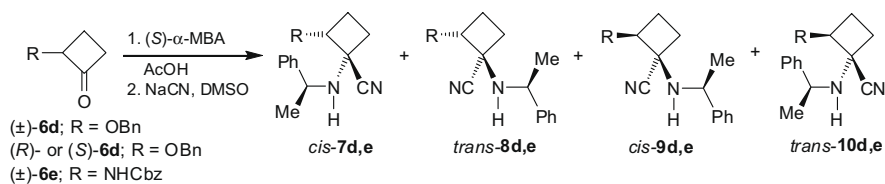


Scheme 3.

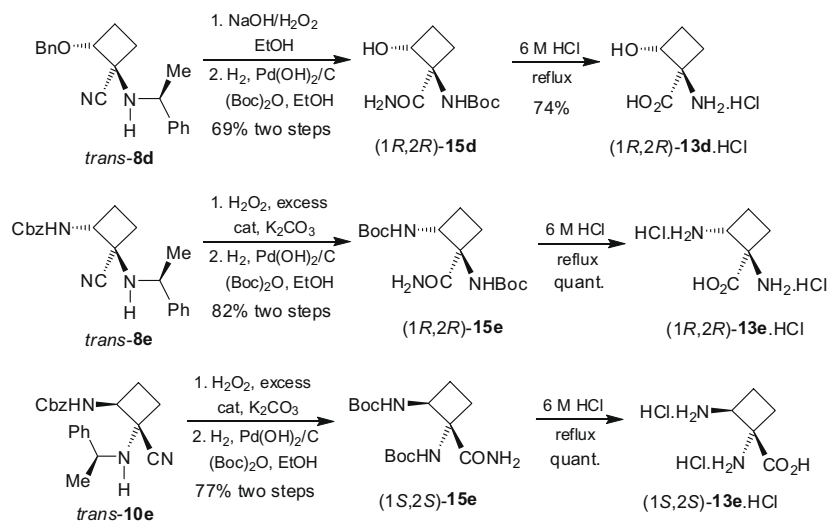
in 55:45 ratio in excellent yield.<sup>76b</sup> The results are summarized in Table 2.

Hydrolysis of diastereoisomerically pure *trans*-**8d** (R = OBn) with hydrogen peroxide and ethanolic potassium hydroxide solution followed by hydrogenolysis over Pd(OH)<sub>2</sub>/C in the presence of di-*tert*-butylcarbonate [(Boc)<sub>2</sub>O] afforded the amide

**Table 2**  
Asymmetric Strecker reaction of ketones **6d,e**



Entry	Ketone	Conditions		Yield (%)	Diastereoisomeric ratio			
		Time	Temperature (°C)		<b>7d,e</b>	<b>8d,e</b>	<b>9d,e</b>	<b>10d,e</b>
1	( $\pm$ )- <b>6d</b>	4 h	20	52	35	15	35	15
2	( $\pm$ )- <b>6d</b>	4 days	50	54	10	40	10	40
3	( <i>R</i> )- <b>6d</b>	4 h	20	55	75	13	6	6
4	( <i>R</i> )- <b>6d</b>	4 days	50	54	28	60	2	10
5	( <i>S</i> )- <b>6d</b>	5 h	20	55	5.8	2.5	72.5	19.2
6	( $\pm$ )- <b>6e</b>	3 days	50	90	—	45	—	55



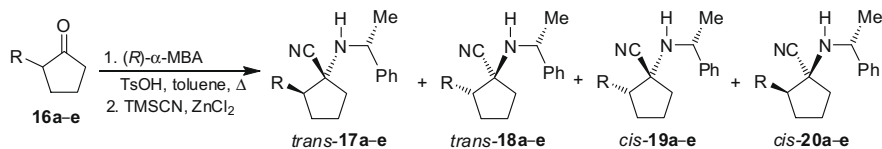
Scheme 4.

(1*R*,2*R*)-**15d** in 69% yield. Finally, hydrolysis of (1*R*,2*R*)-**15d** with 6 M HCl under reflux gave the quaternary  $\alpha$ -amino acid (1*R*,2*R*)-**13d** in 74% yield as hydrochloride salt. Under identical conditions *trans*-**8e** and *trans*-**10e** were transformed into quaternary 1,2-diamino acids (1*R*,2*R*)- and (1*S*,2*S*)-**13e** in good chemical yield (Scheme 4).<sup>76</sup>

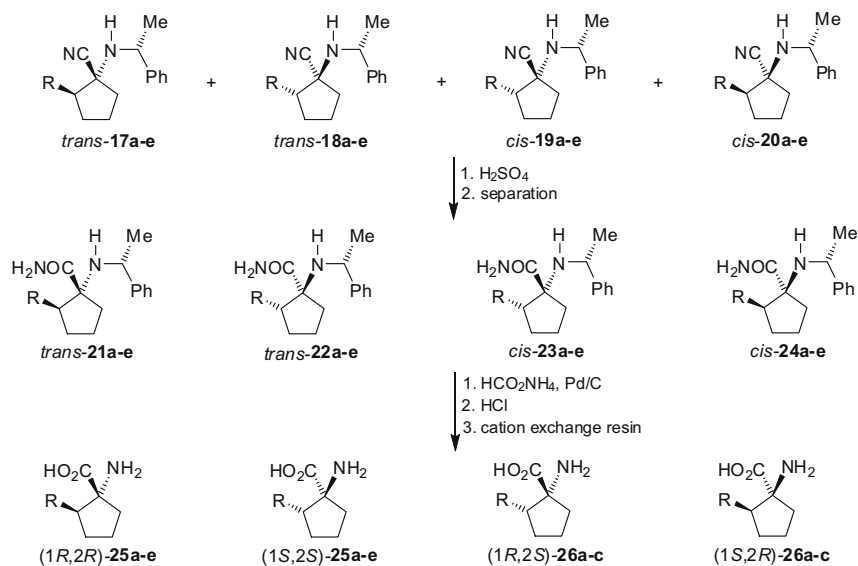
On the other hand, condensation of the 2-alkylcyclopentanones **16a–e**<sup>77</sup> with (*R*)- $\alpha$ -MBA in the presence of a catalytic amount of TsOH followed by addition of TMSCN and ZnCl<sub>2</sub> in methanol or hexane under thermodynamically or kinetically controlled conditions produced the four diastereoisomeric  $\alpha$ -amino nitriles **17a–e** to **20a–e**. The results are summarized in Table 3.<sup>78</sup>

Hydrolysis of the mixture of  $\alpha$ -amino nitriles **17a–e** to **20a–e** obtained using methanol as solvent with concentrated sulfuric acid produced the diastereoisomerically pure  $\alpha$ -amino carboxamides **21a–e** to **24a–e**, after separation by flash chromatography and preparative HPLC. Hydrogenolysis of diastereoisomerically pure  $\alpha$ -amino carboxamides **21a–e**, **22a–e**, **23a–c**, and **24a–c** with HCO<sub>2</sub>NH<sub>4</sub> and Pd/C followed by hydrolysis with concentrated HCl and subsequent treatment with cation exchange resin gave the 2-alkylated 1-aminocyclopentanecarboxylic acids (1*R*,2*R*)- and (1*S*,2*S*)-**25a–e**, and (1*R*,2*S*)- and (1*S*,2*R*)-**26a–c** (Scheme 5).<sup>78</sup>

Condensation of the 5-bromo-1-indanone **27**, which is easily obtained from 3-bromobenzaldehyde, with (*R*)-phenylglycinol followed by addition of TMSCN and subsequent treatment with HCl,

**Table 3**Asymmetric Strecker reaction of the ketones ( $\pm$ )-**16a–e**

Entry	R	Conditions	Yield (%)	Diastereoisomeric ratio			
				17	18	19	20
1	a = OMe	MeOH, 20 °C, 12 h	98	41	22	29	8
2	a = OMe	Hexane, –10 °C, 18 h	98	10	0	61	29
3	b = Me	MeOH, 25 °C, 24 h	100	55	24	16	5
4	b = Me	MeOH, –10 °C, 3 h	100	45	30	21	4
5	b = Me	Hexane, –10 °C, 3 h	100	43	5	47	5
6	c = Et	MeOH, 25 °C, 24 h	98	57	23	14	6
7	c = Et	MeOH, –10 °C, 3 h	98	45	21	28	6
8	c = Et	Hexane, –10 °C, 3 h	82	39	5	45	11
9	d = <i>i</i> -Pr	MeOH, 25 °C, 24 h	86	44	23	28	5
10	d = <i>i</i> -Pr	MeOH, –10 °C, 3 h	92	37	4	47	12
11	d = <i>i</i> -Pr	Hexane, –10 °C, 3 h	84	12	4	57	27
12	e = <i>t</i> -Bu	MeOH, 25 °C, 24 h	74	61	23	14	2
13	e = <i>t</i> -Bu	MeOH, –10 °C, 3 h	36	26	0	59	15
14	e = <i>t</i> -Bu	Hexane, –10 °C, 3 h	37	5	1	66	28

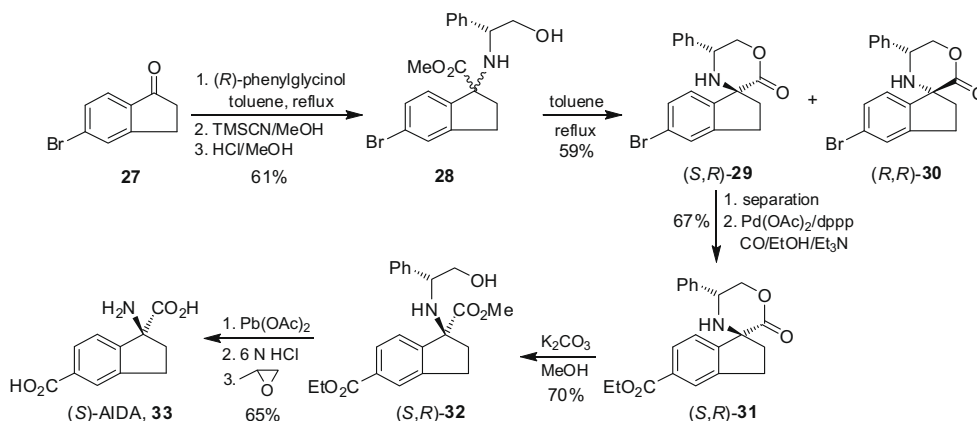
a; R = OMe, b; R = Me, c; R = Et, d; R = *i*-Pr, e; R = *t*-Bu**Scheme 5.**

afforded the mixture of  $\alpha$ -amino esters **28** in 61% yield and 7:1 diastereoisomeric ratio, which, under reflux in toluene gave the spiro derivatives (*S,R*)-**29** and (*R,R*)-**30** in 59% yield. Palladium-catalyzed carbonylation of diastereoisomerically pure (*S,R*)-**29** with  $\text{Pb}(\text{OAc})_2$  and 1,3-bis(diphenylphosphino)propane (dppp) in ethanol produced the derivative (*S,R*)-**31** in 67% yield, which, by cleavage of spiro ring with  $\text{K}_2\text{CO}_3$  in methanol produced the diester (*S,R*)-**32** in 70% yield. Finally, oxidative cleavage of benzyl fragment in (*S,R*)-**32** with  $\text{Pb}(\text{OAc})_2$  followed by acidic hydrolysis and subsequent treatment with propylene oxide furnished the 1-aminoindane-1,5-dicarboxylic acid **33** [(*S*)-AIDA] in 65% yield and this is an antagonist of metabotropic glutamate receptors (Scheme 6).<sup>79</sup>

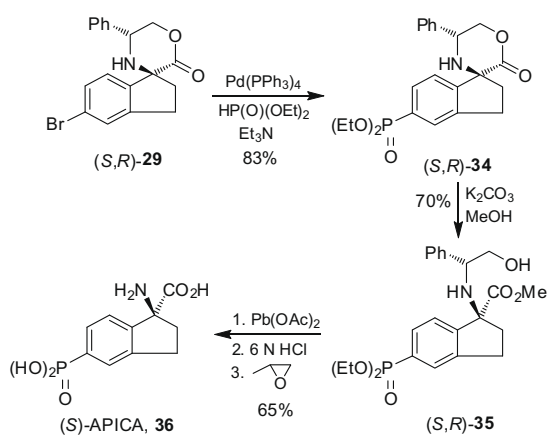
On the other hand, palladium-catalyzed phosphonylation of diastereoisomerically pure (*S,R*)-**29** with diethyl phosphite produced the ethyl phosphonate (*S,R*)-**34** in 83% yield, which by

cleavage of spiro ring with  $\text{K}_2\text{CO}_3$  in methanol led to diester (*S,R*)-**35** in 70% yield. Finally, oxidative cleavage of benzyl fragment in (*S,R*)-**35** with  $\text{Pb}(\text{OAc})_2$  followed by acidic hydrolysis and subsequent treatment with propylene oxide furnished the 1-amino-5-phosphoindane-1-carboxylic acid **36** [(*S*)-APICA] in 65% yield (Scheme 7).<sup>79</sup>

Schann et al.<sup>80</sup> reported the first stereoselective synthesis of aminopyrrolidinedicarboxylic acids **41** and **42**, which have been used in the preparation of glutamate receptor compounds.<sup>81</sup> Thus, the Bucherer–Bergs reaction<sup>82</sup> of (*S*)-**37**, readily obtained from (*2S,4R*)-4-hydroxyproline, with  $(\text{NH}_4)_2\text{CO}_3$  and KCN in ethanol gave the spirohydantoin mixture **38** in 68–78% yield, which by basic hydrolysis followed by treatment with  $\text{SOCl}_2$  and methanol under reflux afforded, after chromatographic separation, the amino esters (*2S,4S*)-**39** and (*2S,4R*)-**40**. *N*-Boc protection of (*2S,4S*)-**39** and (*2S,4R*)-**40** followed by cleavage of benzyl protecting group by



Scheme 6.



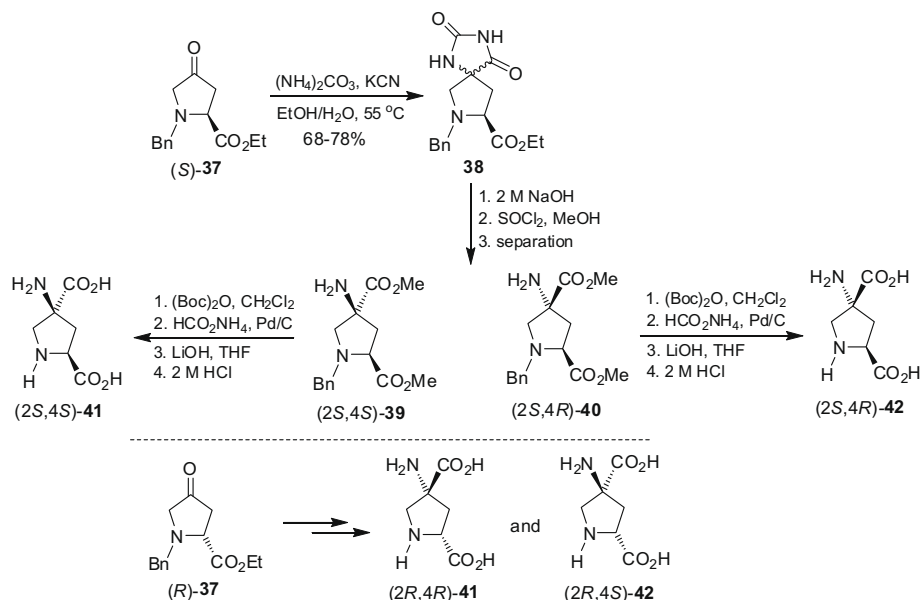
Scheme 7.

hydrogenolysis under HCO<sub>2</sub>NH<sub>4</sub> and Pd/C conditions, and subsequent saponification and cleavage of Boc protecting group with HCl gave the amino acids (2S,4S)-**41** and (2S,4R)-**42**, respectively.

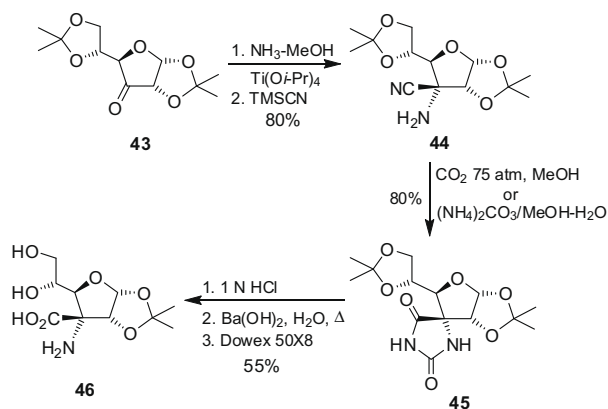
Under identical conditions, (R)-**37** was transformed into (2R,4R)-**41** and (2R,4S)-**42** (Scheme 8).

On the other hand, reaction of the ulose **43**, readily obtained by oxidation of diacetone-D-glucose, with ammonia in the presence of Ti(Oi-Pr)<sub>4</sub> followed by addition of TMSCN provided the glycol- $\alpha$ -amino nitrile **44** in 80% yield as the only detectable stereoisomer, which by treatment with carbon dioxide in MeOH at 75 atm/85 °C or (NH<sub>4</sub>)<sub>2</sub>CO<sub>3</sub> in MeOH–H<sub>2</sub>O at 70 °C gave the spirohydantoin **45** in 80% yield. Selective hydrolysis of one of the acetonides of **45** with 1 N HCl followed by hydantoin ring opening with barium hydroxide and subsequent ion-exchange chromatography, furnished the quaternary glycoamino acid **46** in 55% yield in three steps (Scheme 9).<sup>83</sup>

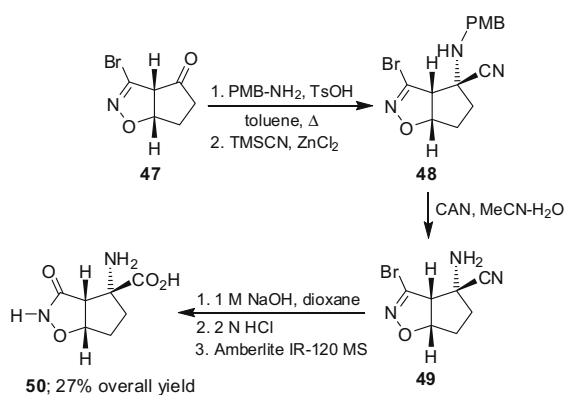
Recently De Micheli et al.<sup>84</sup> reported the stereoselective synthesis of conformationally constrained  $\alpha$ -amino acid **50**, an analogue of aspartic acid, based on the Strecker methodology. Thus, TsOH-catalyzed condensation of the ketone **47** with 4-methoxybenzylamine (PMB–NH<sub>2</sub>) followed by addition of TMSCN in the presence of ZnCl<sub>2</sub> afforded the cyano derivative **48** as a single detectable stereoisomer. Cleavage of PMB protecting group in **48** with cerium(IV) ammonium nitrate (CAN) provided the  $\alpha$ -amino nitrile **49**, which by hydrolysis and subsequent ion-exchange chromatography gave



Scheme 8.



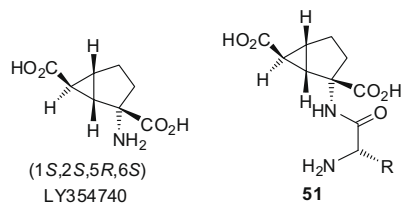
Scheme 9.



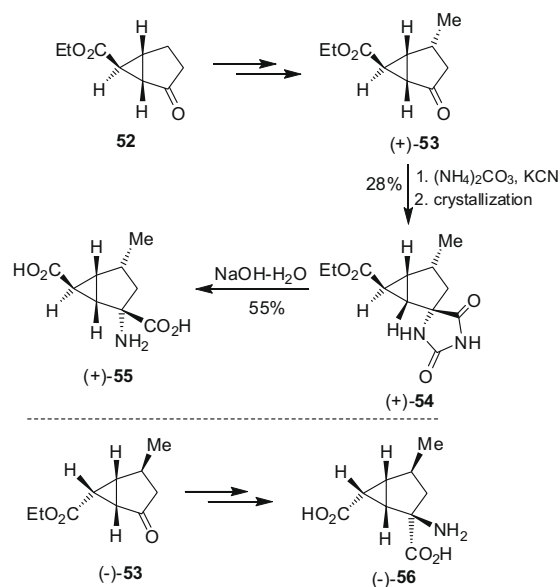
Scheme 10.

the conformationally constrained  $\alpha$ -amino acid **50** in 27% overall yield (Scheme 10).

Conformationally constrained (1*S*,2*S*,5*R*,6*S*)-2-aminobicyclo[3.1.0]hexane 2,6-dicarboxylic acid, also known as (LY354740),<sup>85</sup> is a highly potent and selective agonist for group II metabotropic glutamate (mGlu) receptors, specifically mGlu2 and mGlu3, that has been found to possess anxiolytic, antipsychotic, anticonvulsant, anti-Parkinsonian, analgesic, and neuroprotective properties *in vivo*.<sup>86</sup> Additionally the peptides of type **51** are effective prodrugs of LY354740.<sup>87</sup> For this reason several analogues of LY354740 have been prepared.



Monn et al.<sup>88</sup> reported the synthesis of conformationally constrained  $\alpha$ -amino acids (+)-**55** and (–)-**56**, which were evaluated as mGlu receptors. In this context, reaction of the enantiomerically pure bicyclic ketone (+)-**53**, obtained from **52**,<sup>89</sup> with  $(\text{NH}_4)_2\text{CO}_3$  and KCN in ethanol gave the spirohydantoin (+)-**54** in 28% yield after crystallization, which by basic hydrolysis gave the conformationally constrained  $\alpha$ -amino acid (+)-**55** in 55% yield. In a similar way, (–)-**53** was transformed into (–)-**56** (Scheme 11).

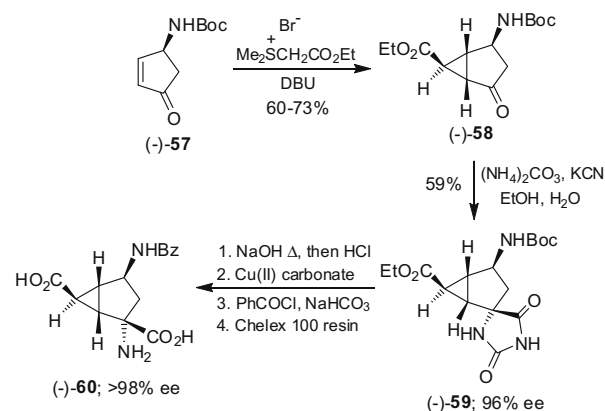


Scheme 11.

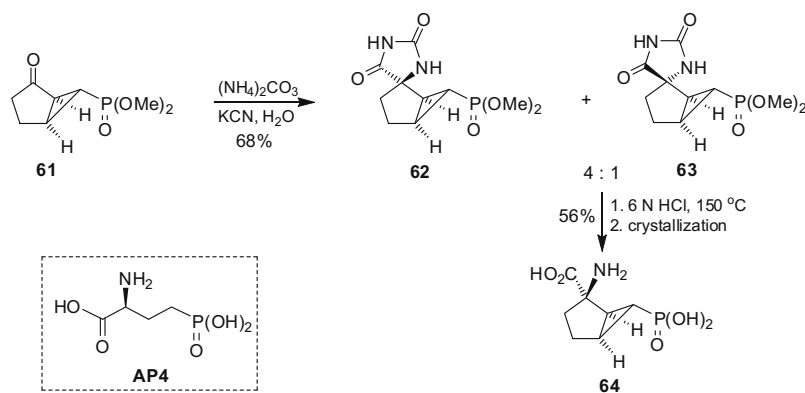
On the other hand, Lee and Miller<sup>90</sup> reported the stereoselective synthesis of conformationally constrained  $\alpha$ -diamino acid (–)-**60** starting from the cyclic ketone (–)-**57**. In this context, the intermolecular cyclopropanation of the  $\alpha,\beta$ -unsaturated ketone (–)-**57** with the sulfonium ylide obtained from (ethoxycarbonylmethyl)dimethylsulfonium bromide and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded the bicyclic ketone (–)-**58** in 60–73% yield,<sup>91</sup> which, by a Bucherer–Bergs reaction with  $(\text{NH}_4)_2\text{CO}_3$  and KCN in ethanol provided the spirohydantoin (–)-**59** in 59% yield and 96% ee. Basic hydrolysis of (–)-**59** and sequential treatment with copper(II) carbonate, benzoyl chloride, and ion-exchange chromatography furnished the  $\alpha$ -diamino acid (–)-**60** with >98% ee (Scheme 12).

Mann et al.<sup>92</sup> reported the synthesis of constrained cycloalkyl analogue of glutamic acid **64** with a  $\omega$ -phosphonic acid function, an analogue of AP4.<sup>93</sup> Thus, reaction of the bicyclic ketone **61** with  $(\text{NH}_4)_2\text{CO}_3$  and KCN in  $\text{H}_2\text{O}$  produced the spirohydantoin **62** and **63** in 68% yield and 4:1 ratio as an inseparable mixture of diastereoisomers, from which by acidic hydrolysis and crystallization the  $\alpha$ -amino acid **64** could be obtained in 56% yield (Scheme 13).

On the other hand, reaction of the enantiomerically pure bicyclic ketone (–)-**66**, obtained in nine steps from chiral methyl ester (1*R*,5*R*)-**65**, with ammonia in the presence of  $\text{Ti}(\text{O}i\text{-Pr})_4$  in



Scheme 12.



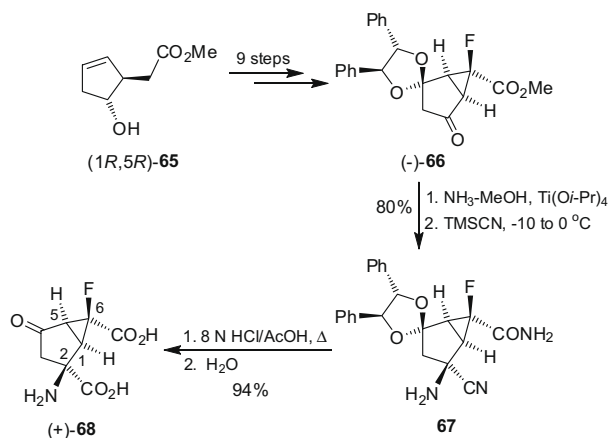
Scheme 13.

methanol followed by addition of TMSCN afforded the  $\alpha$ -amino nitrile **67** in 80% yield and 13.1:1 diastereoisomeric ratio, which by crystallization and subsequent hydrolysis with 8 N HCl and AcOH furnished the enantiomerically pure conformationally constrained fluoro  $\alpha$ -amino acid (+)-**68** in 94% yield (Scheme 14).<sup>94</sup>

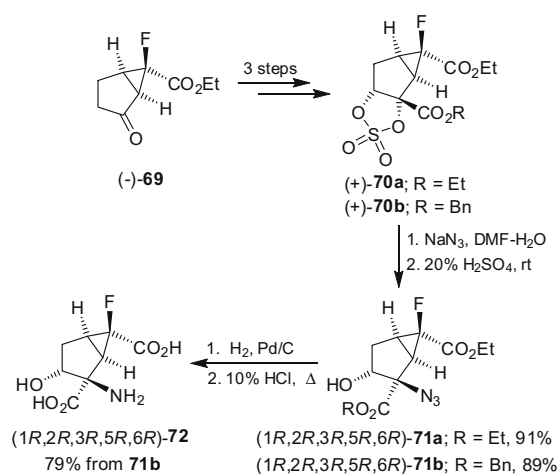
Nakazato et al.<sup>95,96</sup> reported the synthesis of several conformationally constrained fluoro  $\alpha$ -amino acids, which were evaluated as potent and selective group II metabotropic glutamate receptor antagonists. For example, reaction of the enantiomerically pure cyclic sulfates (+)-**70a,b**, obtained in three steps from the bicyclic ketone (–)-**69**, with sodium azide followed by treatment with sulfuric acid gave the azide derivatives (1*R*,2*R*,3*R*,5*R*,6*R*)-**71a,b** in good yield. Catalytic hydrogenation of benzyl ester and azide functions in **71b** followed by acidic hydrolysis provided the conformationally constrained  $\alpha$ -amino acid (1*R*,2*R*,3*R*,5*R*,6*R*)-**72** in 79% yield (Scheme 15).

On the other hand, reaction of (1*R*,2*R*,3*R*,5*R*,6*R*)-**71a** with trifluoromethanesulfonyl anhydride (Tf<sub>2</sub>O) in pyridine afforded the derivative (–)-**73**, which by treatment with KNO<sub>2</sub> in the presence of 18-crown-6 and subsequent addition of water gave the compound (1*R*,2*R*,3*S*,5*R*,6*R*)-**74** in 80% yield. Reduction of azide group in **74** under Staudinger conditions<sup>97</sup> using PMe<sub>3</sub> followed by basic hydrolysis produced the  $\alpha$ -amino acid (1*R*,2*R*,3*S*,5*R*,6*R*)-**75** in 48% yield (Scheme 16).<sup>95</sup>

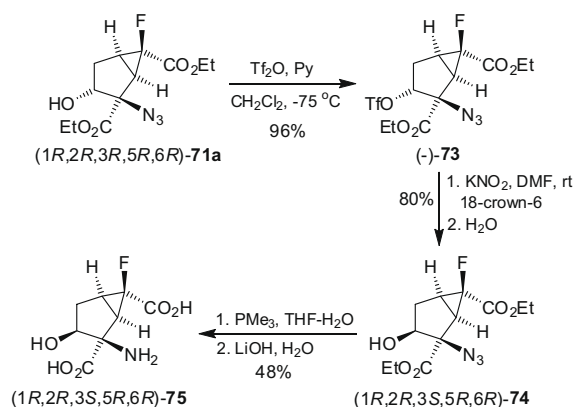
Additionally, enantiomerically pure (1*R*,2*R*,3*R*,5*R*,6*R*)-**71a** and (1*R*,2*R*,3*S*,5*R*,6*R*)-**74** have been transformed into conformationally constrained  $\alpha$ -amino acids (1*R*,2*R*,3*R*,5*R*,6*R*)-**76** and (1*R*,2*R*,3*S*,5*R*,6*R*)-**77a,b**, respectively, which have been evaluated as potent and selective group II metabotropic glutamate receptor antagonists (Scheme 17).<sup>95,96</sup>



Scheme 14.



Scheme 15.

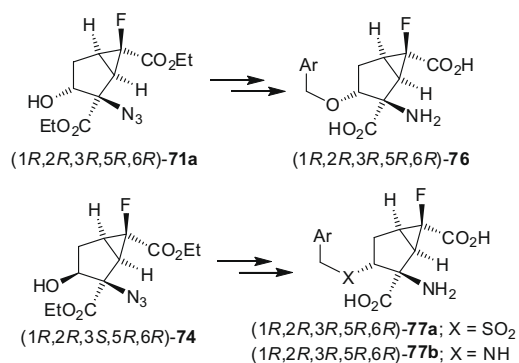


Scheme 16.

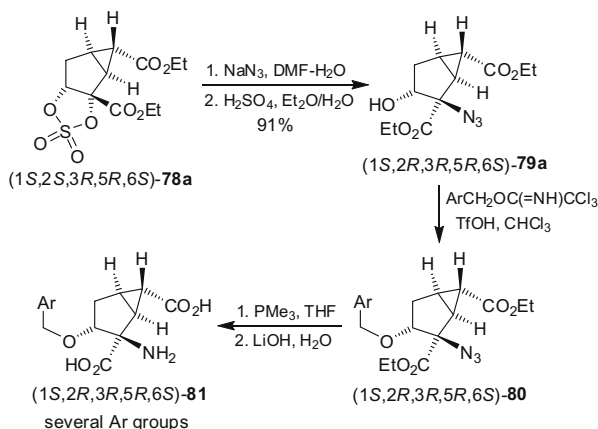
On the other hand, reaction of cyclic sulfate (1*S*,2*S*,3*R*,5*R*,6*S*)-**78a** with sodium azide followed by treatment with sulfuric acid gave the azide derivative (1*S*,2*R*,3*R*,5*R*,6*S*)-**79a** in 91% yield. Reaction of **79a** with benzyl trichloroacetimidates (ArCH<sub>2</sub>-OC(=NH)CCl<sub>3</sub>) in the presence of a catalytic amount of trifluoromethanesulfonic acid (TfOH) afforded the corresponding ether derivatives (1*S*,2*R*,3*R*,5*R*,6*S*)-**80**. Reduction of the azide function in **80** with PMe<sub>3</sub> and subsequent basic hydrolysis produced the  $\alpha$ -amino acids (1*S*,2*R*,3*R*,5*R*,6*S*)-**81** (several aryl groups were used) (Scheme 18).<sup>96a</sup>

Very recently, Woltering et al.<sup>98</sup> reported the stereoselective synthesis of (1*S*,2*R*,3*R*,5*R*,6*S*)-2-amino-3-hydroxybicyclo[3.1.0]-





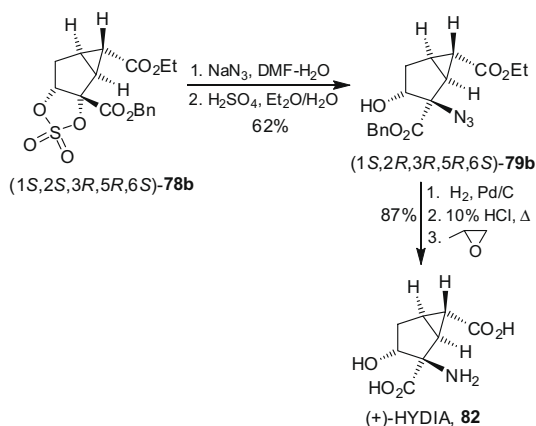
Scheme 17.



Scheme 18.

hexane-2,6-dicarboxylic acid (+)-HYDIA **82**, a group II mGlu receptor. Thus, the selective ring opening of cyclic sulfate (1S,2S,3R,5R,6S)-**78b** with sodium azide afforded the azide derivative (1S,2R,3R,5R,6S)-**79b** in 62% yield. Catalytic hydrogenation of the benzyl ester and azide functions of **79b** followed by acidic hydrolysis and subsequent treatment with propylene oxide produced the (+)-HYDIA **82** in 87% yield (Scheme 19).

Oxidation of the alcohol group in (1S,2R,3R,5R,6S)-**79b** with PCC gave the corresponding ketone (1S,2R,5R,6S)-**83** in 67% yield, and subsequent reduction with NaBH<sub>4</sub> afforded the alcohol (1S,2R,3S,5R,6S)-**84** in 51% as a single diastereoisomer. Catalytic hydrogenation of the benzyl ester and azide functions in **84**



Scheme 19.

followed by acidic hydrolysis and subsequent treatment with propylene oxide produced the  $\beta$ -hydroxy- $\alpha$ -amino acid (1S,2R,3S,5R,6S)-**85** in 86% yield. On the other hand, treatment of **79b** with Tf<sub>2</sub>O in pyridine provided the triflate (1S,2R,3R,5R,6S)-**86** in 86% yield and a subsequent S<sub>N</sub>2 reaction using sodium azide furnished (1S,2R,3S,5R,6S)-**87** in 49% yield as a single diastereoisomer. Catalytic hydrogenation of the benzyl ester and azide functions of **87** followed by acidic hydrolysis and subsequent treatment with propylene oxide produced the  $\alpha,\beta$ -diamino acid (1S,2R,3S,5R,6S)-**88** in 79% yield (Scheme 20).<sup>98</sup>

Reaction of the (+)-pentacyclo[5.4.0.0.2.6.0.3.10.0.5.9]undecane-8-one **89** with (NH<sub>4</sub>)<sub>2</sub>CO<sub>3</sub> and KCN in H<sub>2</sub>O produced the spirohydantoin **90** in 83% yield as the main product, and hydrolysis of **90** with barium hydroxide gave the quaternary  $\alpha$ -amino acid (–)-**91** in 67% yield. Under identical conditions, the enone (–)-**92** was transformed into the quaternary  $\alpha$ -amino acid (+)-**94** through the spirohydantoin (+)-**93** (Scheme 21).<sup>99</sup>

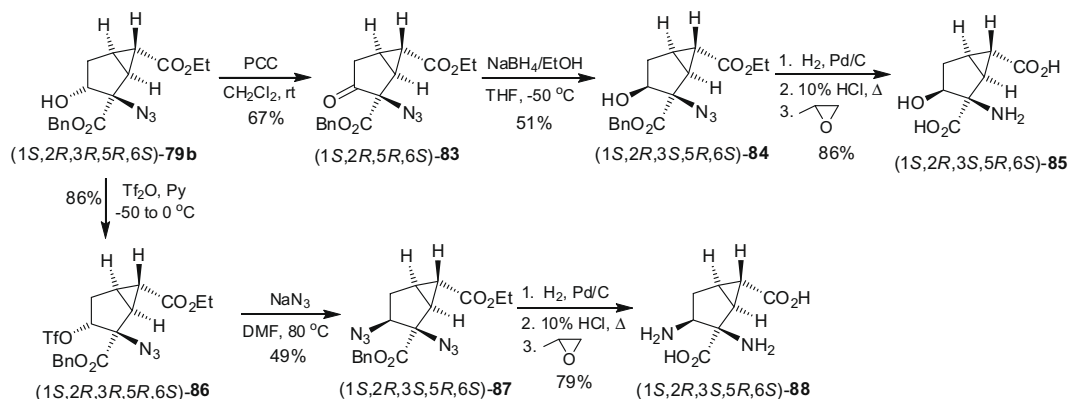
Condensation of the 2-methoxycyclohexanone ( $\pm$ )-**95a** with (*S*)- $\alpha$ -MBA followed by addition of TMSCN in the presence of ZnCl<sub>2</sub> in methanol gave the  $\alpha$ -amino nitriles mixture **96a** (*cis/trans* = 26:74 ratio) under thermodynamic control, and (*cis/trans* = 75:25) under kinetic control conditions. Hydrolysis of the mixture of  $\alpha$ -amino nitriles *cis/trans*-**96a** with concentrated sulfuric acid produced, after chromatographic separation, the mixture of the  $\alpha$ -amino carboxyamides *cis/trans*-**97a**, and the hydrogenolyzed product (1S,2R)-**98a**. Low pressure liquid chromatography (LPLC) separation of the carboxyamides *cis/trans*-**97a** afforded the diastereoisomerically pure  $\alpha$ -amino carboxyamide *trans*-**97a** [(1S,2S,1'S)-**97a**], which by hydrogenolysis over Pd/C followed by hydrolysis with 12 M HCl and subsequent ion-exchange chromatography on a Dowex 50W column led to (1S,2S)-1-amino-2-hydroxycyclohexanecarboxylic acid **99a**. On the other hand, acidic hydrolysis of **98a** and subsequent treatment with Dowex resin gave the quaternary  $\alpha$ -amino acid (1S,2R)-**100a** (Scheme 22).<sup>100</sup>

Frahm et al.<sup>101</sup> reported the stereoselective synthesis of 1,2-diaminocyclohexanecarboxylic acids (1R,2R)- and (1S,2S)-**99b** starting from the 2-benzoylamino-cyclohexanone ( $\pm$ )-**95b** by applying the Strecker methodology. Thus, the condensation reaction of ( $\pm$ )-**95b** with (*R*)- $\alpha$ -MBA followed by addition of TMSCN in the presence of ZnCl<sub>2</sub> in methanol or hexane, under thermodynamic conditions, afforded the corresponding  $\alpha$ -amino nitriles mixture *cis/trans*-**96b** in 99% yield, which by hydrolysis with concentrated sulfuric acid at –20 °C produced, after LPLC separation, the  $\alpha$ -amino carboxyamides (1R,2R,1'R)-**97b** and (1S,2S,1'R)-**101b** in 19% and 8% yields, respectively. Hydrogenolysis of diastereoisomerically pure **97b** and **101b** over Pd/C followed by hydrolysis with 12 M HCl and subsequent ion-exchange chromatography gave the corresponding  $\alpha,\beta$ -diamino acids (1R,2R)- and (1S,2S)-**99b** in 97% yield (Scheme 23).

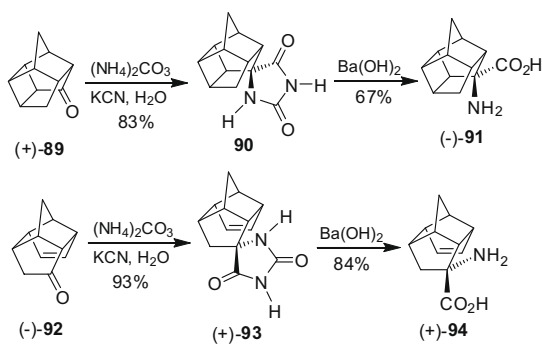
On the other hand, condensation of ethyl 2-cyclohexanoneacetate ( $\pm$ )-**95c** with (*R*)- $\alpha$ -MBA followed by addition of TMSCN in the presence of ZnCl<sub>2</sub> in methanol under kinetic or thermodynamic control gave the  $\alpha$ -amino nitriles mixture *cis/trans*-**96c** in 96% yield. Hydrolysis of the mixture of  $\alpha$ -amino nitriles **96c** with concentrated sulfuric acid at –20 °C followed by chromatographic separation and subsequent hydrogenolysis over HCO<sub>2</sub>NH<sub>4</sub>, Pd/C conditions produced the azabicyclo compounds (1R,2S)- and (1S,2R)-**102** (Scheme 24).<sup>102</sup>

Reaction of the enantiopure ketone **103**<sup>103</sup> with (NH<sub>4</sub>)<sub>2</sub>CO<sub>3</sub> and KCN followed by treatment with (Boc)<sub>2</sub>O produced the spirohydantoin **104** and **105** in 49% yield and 5:2 dr. Basic hydrolysis of diastereoisomerically pure **104**, obtained after chromatographic separation, afforded the quaternary  $\alpha$ -amino acid (*S,S*)-**106** in 91% yield (Scheme 25).<sup>104</sup>

Condensation of the ketones **107a,b** with (*S*)- $\alpha$ -MBA followed by addition of HCN in the presence of a catalytic amount of ZnI<sub>2</sub>



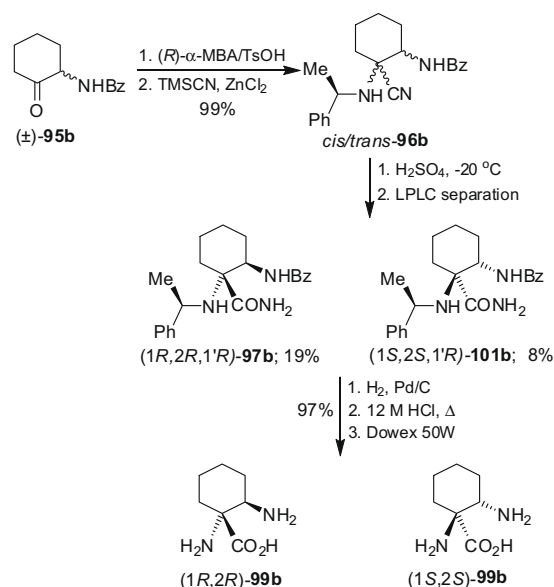
Scheme 20.



Scheme 21.

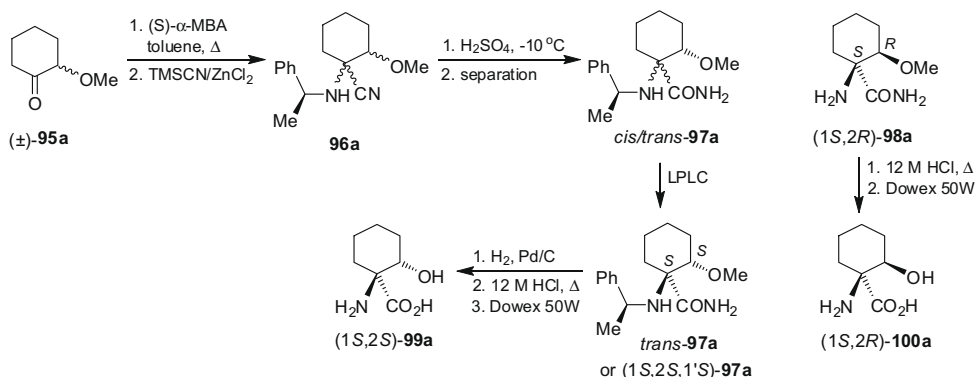
afforded the  $\alpha$ -amino nitriles mixture **108a,b**. Hydrolysis of **108a** with concentrated sulfuric acid furnished the  $\alpha$ -amino carboxyamides (1S,1'S)-**109a** and (1R,1'S)-**110a** in 86% yield and 10:1 diastereoisomeric ratio. Hydrolysis of **108b** under identical conditions gave the  $\alpha$ -amino carboxyamides (1S,1'S)-**109b** and (1R,1'S)-**110b** in 50% yield and 45:55 dr. Hydrogenolysis of diastereoisomerically pure (1S,1'S)-**109a** over Pd/C followed by acidic hydrolysis provided the quaternary  $\alpha$ -amino acid (S)-**111a** in quantitative yield. In a similar way (1R,1'S)-**110b** was transformed into (R)-**111b** in quantitative yield (Scheme 26).<sup>105</sup>

In a similar way, condensation of the ketones **107a–c** with (R)-phenylglycinol followed by addition of TMSCN afforded the  $\alpha$ -amino nitriles mixture **112a–c**. Hydrolysis of **112a,b** with concentrated sulfuric acid produced the corresponding  $\alpha$ -amino carboxyamides (1S,1'R)-**113a,b** and (1R,1'R)-**114a,b** with a predominance of

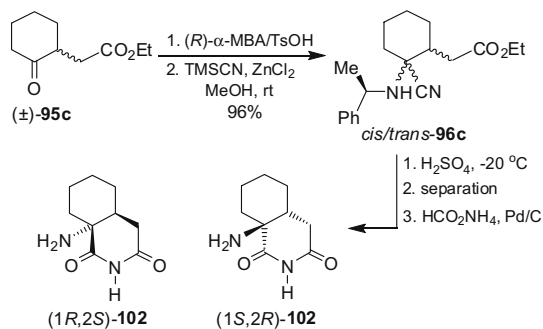


Scheme 23.

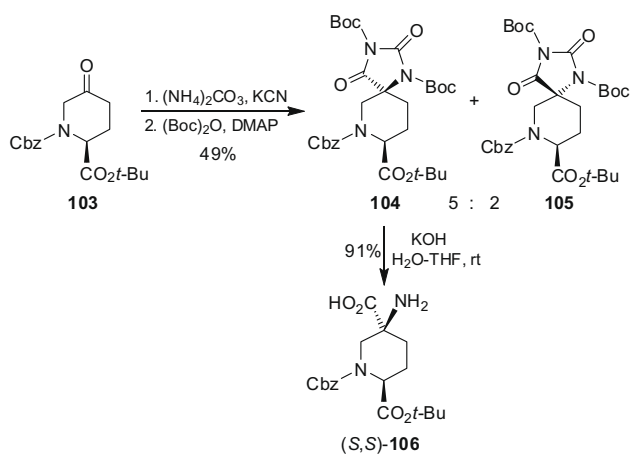
(1S,1'R)-**113a,b**, and small quantities of the lactones (1S,1'R)-**115a,b**. On the other hand, hydrolysis of **112c** under identical conditions gave the lactone (1S,1'R)-**115c** as the principal product, which by treatment with dry ammonia led to the  $\alpha$ -amino carboxyamide (1S,1'R)-**113c**. Oxidative cleavage of the chiral auxiliary fragment in diastereoisomerically pure (1S,1'R)-**113a–c** with



Scheme 22.



Scheme 24.



Scheme 25.

$\text{Pb}(\text{OAc})_2$  followed by acidic hydrolysis and subsequent treatment with propylene oxide provided the quaternary  $\alpha$ -amino acids (*S*)-**111a–c** in 60–72% yield (Scheme 27).<sup>105</sup>

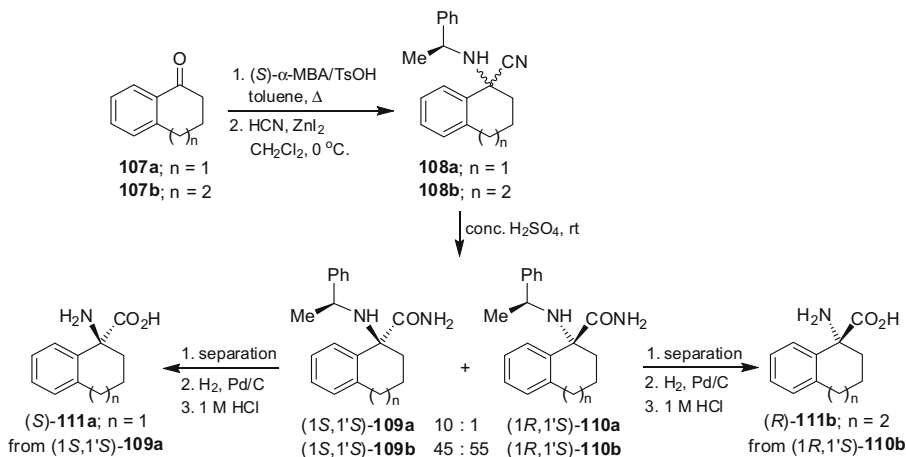
Warmuth et al.<sup>106</sup> reported the stereoselective synthesis of conformationally constrained lysine derivatives (*S,S*)-**122** and (*R,S*)-**123**. In this context, selective monoprotection of one of the carbonyl groups of the diketone **116** using 1,2-ethanedithiol in the presence of a catalytic amount of  $\text{BF}_3 \cdot \text{OEt}_2$  followed by reaction with  $(\text{NH}_4)_2\text{CO}_3$  and KCN gave the corresponding spirohydantoin mixture **117** in almost quantitative yield, which by cleavage of the thioacetal group with  $\text{AgNO}_3$  and subsequent treatment with  $(\text{Boc})_2\text{O}$  in the presence of a catalytic amount of 4-dimethylamino-

pyridine (DMAP) produced the *N,N'*-bis-Boc-protected spirohydantoin mixture **118** in 79% yield. Condensation of **118** with (*R*)-phenylglycinol followed by reduction of the imine formed with  $\text{NaBH}(\text{OAc})_3$  in THF and subsequent chromatographic separation afforded the diastereoisomerically pure (*S,S,1'R*)-**119** and (*R,S,1'R*)-**120** in 38% and 45% yield, respectively. Oxidative cleavage of chiral auxiliary fragment in (*S,S,1'R*)-**119** with  $\text{Pb}(\text{OAc})_2$  followed by hydrolysis with HCl and subsequent *N*-Boc-protection led to (*S,S*)-**121** in 62% yield, which by hydrolysis and esterification gave the lysine analogue (*S,S*)-**122** in 41% yield. In a similar way, (*R,S,1'R*)-**120** was transformed into (*R,S*)-**123** (Scheme 28).

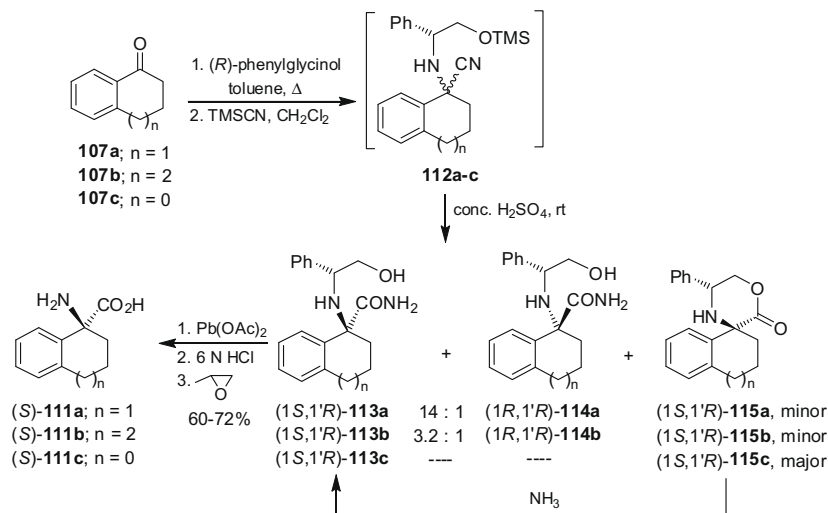
Condensation of the ketone ( $\pm$ )-**124** with (*S*)- $\alpha$ -MBA in the presence of  $\text{TiCl}_4$  followed by addition of TMSCN in the presence of  $\text{AlCl}_3$  afforded, after separation, the corresponding  $\alpha$ -amino nitriles **125a** and **125b** in 31 and 39% yield, respectively. Reaction of the enantiomerically pure ketone (+)-**124** under identical conditions gave the  $\alpha$ -amino nitrile **125a** in 68% yield as a single stereoisomer. Hydrolysis of the benzyl ester, nitrile, and *N*-debenzylation in the diastereoisomerically pure **125a** with HCl and acetic acid at 160 °C followed by addition of diazomethane gave the dimethyl ester (–)-**126** in 49% yield, and this was transformed into dibenzyl ester (–)-**127** by ester exchange reaction with benzyl alcohol in the presence of  $\text{Ti}(\text{O}i\text{-Pr})_4$ . Finally, cleavage of the benzyl groups in (–)-**127** under hydrogenolysis over  $\text{Pd}(\text{OH})_2/\text{C}$  produced the conformationally constrained glutamic acid derivative (–)-**128** in 68% yield. Under identical conditions, **125b** was transformed into (+)-**128** (Scheme 29).<sup>107</sup>

In some cases the intramolecular Strecker reaction has been used as an interesting methodology focused on the synthesis of quaternary  $\alpha$ -amino acids. For example, intramolecular condensation of the ketones **95d–g** in the presence of TFA afforded the ketimine mixture **129d–g** and **131d–g**, presumably under rapid equilibrium through the enamines **130d–g**. Addition of  $\text{NaCN}/\text{TFA}$  (condition A) or  $\text{TMSCN}/\text{ZnCl}_2$  (condition B) to the imine mixture **129d–g** and **131d–g** gave the  $\alpha$ -amino nitriles (*1S,6S*)-**132d–g** and (*1S,6R*)-**133d–g** in moderate to excellent yield and with low to good diastereoselective ratio. The cyanide addition to the ketimines having an alkyl side chain gave a small amount of the (*1R*)-stereoisomers. The results are summarized in Table 4.<sup>108</sup>

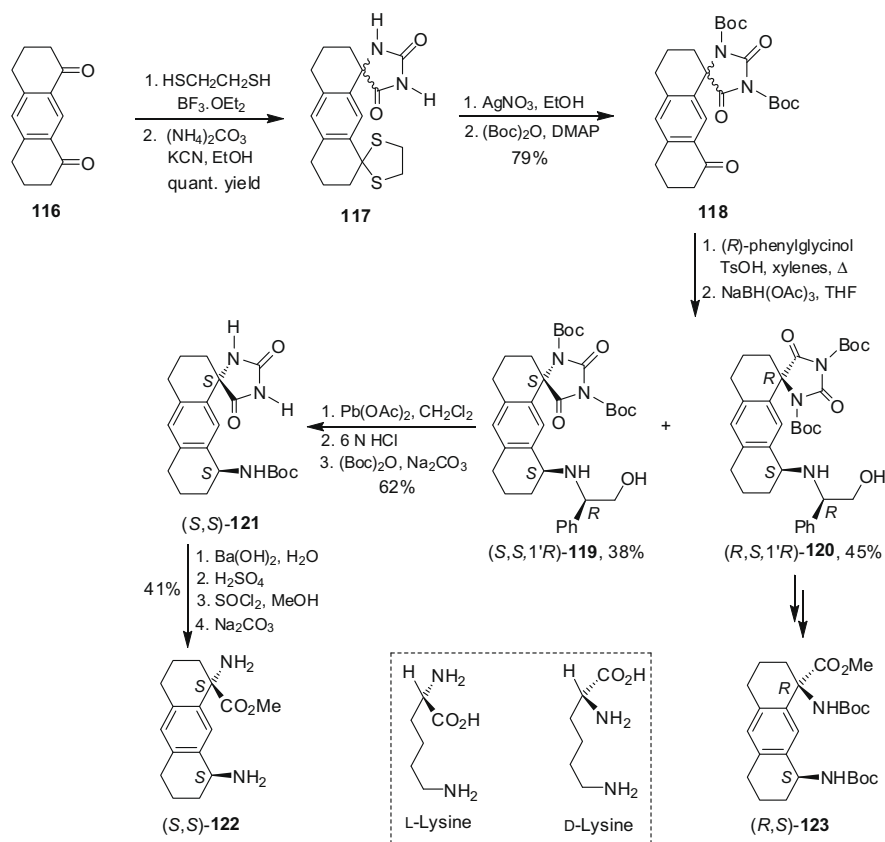
Oxidation of (*1S,6S*)-**132d** (*R* = Bn) with 1,4-diazabicyclo[2.2.2]octane (DABCO) and *tert*-butyl hypochlorite (*t*-BuOCl) followed by hydrolysis with concentrated HCl gave the (*1R,2S*)-1-amino-2-hydroxycyclohexanecarboxylic acid **100a** in 92% yield. On the other hand, oxidation of (*1S,6R*)-**133g** (*R* = *t*-Bu) with ozone and subsequent hydrolysis with concentrated HCl afforded the (*1R,2R*)-**99a** in 90% yield (Scheme 30).<sup>108</sup>



Scheme 26.



Scheme 27.



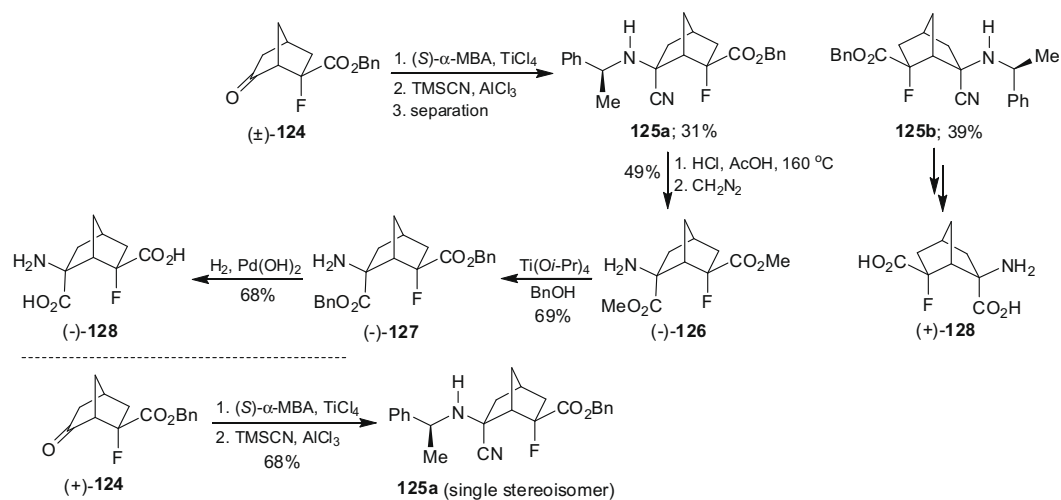
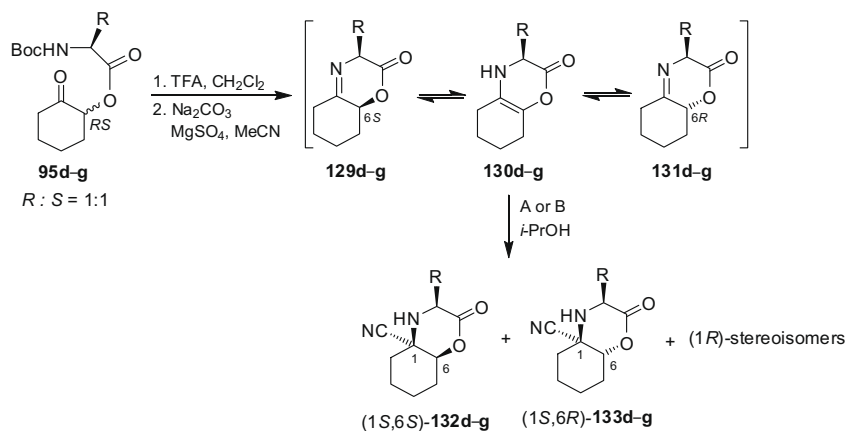
Scheme 28.

This methodology has also been used in the stereoselective synthesis of several quaternary  $\alpha$ -amino acids.<sup>109</sup>

The electrophilic  $\alpha$ -amination of carbonyl compounds is a conceptually attractive method for the synthesis of nitrogenated compounds by C–N bond formation.<sup>110</sup> In this context, apart from Strecker and related reactions, it has been reported that cyclic quaternary  $\alpha$ -amino acids can be alternatively obtained through electrophilic amination reactions starting from molecules containing a carbonyl functionality. For example, Pellacani et al.<sup>111</sup> reported that the  $\alpha$ -amination of enamine **134** bearing (*R*)- $\alpha$ -MBA, with ethyl *N*-[(4-nitrobenzenesulfonyl)oxy]carbamate (NsONHCO<sub>2</sub>Et)

as electrophilic aminating reagent, gave the quaternary  $\alpha$ -amino derivative **136** in 95% yield and 60% ee, through the aziridine intermediate **135**. The stereochemistry of **136** was not reported (Scheme 31).

On the other hand, the  $\alpha$ -amination of  $\alpha$ -keto esters **137** using azodicarboxylates as the electrophilic aminating reagent, in the presence of 5–20 mol % of chiral catalyst such as  $\beta$ -isocupreidine **138**<sup>112</sup> (a constrained quinidine-derivative), the urea **139**,<sup>113</sup> cinchonine **140**,<sup>114</sup> chiral guanidine **141** with a seven-membered-ring structure,<sup>115</sup> palladium complex **142**,<sup>116</sup> and (*S,S*)-ip-pybox **143**<sup>117</sup> afforded the corresponding  $\alpha$ -aminated derivatives **144** in good

**Table 4**Formation of  $\alpha$ -amino nitriles (1*S*,6*S*)-**132d–g** and (1*S*,6*R*)-**133d–g** from **95d–g**

Entry	R	Ratio of <b>129:131</b>	Ratio of <b>132:133:(1R)</b> -stereoisomers (Yield %)	
			A: NaCN/TFA	B: TMSCN/ZnCl <sub>2</sub>
1	<b>d</b> = Bn	50:50	66:34:ND (96)	41:59:ND (89)
2	<b>e</b> = Indm <sup>a</sup>	50:50	77:23:ND (56)	33:67:ND (48)
3	<b>f</b> = <i>i</i> -Bu	50:50	39:42:19 (86)	18:71:11 (73)
4	<b>g</b> = <i>t</i> -Bu	20:80	16:82:02 (88)	05:90:05 (80)

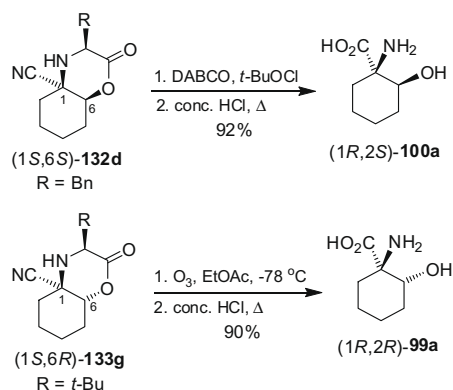
ND = (1*R*)-stereoisomers were not detected by <sup>1</sup>H NMR.<sup>a</sup> Indm = 2-indolylmethyl fragment.

yield and excellent levels of enantioselectivity, which are important precursors of quaternary cyclic  $\alpha$ -amino acids. The results are summarized in Table 5.

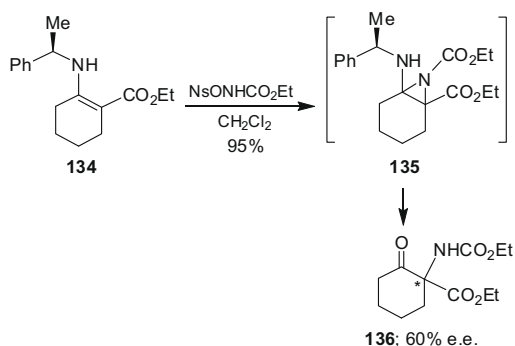
Asymmetric organocatalysis utilizes organic molecules to induce chirality in various C–C, C–N, and C–O bond-forming reactions.<sup>118</sup> For example, the enantioselective catalytic  $\alpha$ -amination of the carboxaldehydes **145a–c** with dibenzyl azodicarboxylate in the presence of (*R*)-proline (20 mol %) produced the corresponding  $\alpha$ -aminated products **146a–c** in good yield and >99% ee. Oxidation of the aldehyde group in **146a,b** with NaClO<sub>2</sub> followed by esterification with (trimethylsilyl)diazomethane (TMSCHN<sub>2</sub>) gave the esters **147a,b** in 82% yield (Scheme 32).<sup>119</sup>

Hydrolysis of **147b** with pyridine and trifluoroacetic anhydride (TFAA), followed by N–N bond cleavage with SmI<sub>2</sub> and subsequent treatment with propylene oxide gave the (*S*)-AIDA **33** in 70% yield. On the other hand, palladium-catalyzed phosphonylation of **147a** furnished the ethyl phosphonate **148** in 77% yield, which by hydrolysis followed by N–N bond cleavage and subsequent treatment with propylene oxide led to (*S*)-APICA **36** in 80% yield (Scheme 33).<sup>119</sup>

Very recently, Shibasaki et al.<sup>120</sup> reported the catalytic asymmetric  $\alpha$ -amination of the succinimide **149**. Thus, reaction of **149** with di-*tert*-butyl azodicarboxylate in the presence of a catalytic amount of (*R*)-**150** derived from *D*-valine, La(Oi-Pr)<sub>3</sub>, and



Scheme 30.



Scheme 31.

*N,N*-dimethylacetamide (DMA) in chloroform at 0 °C afforded the corresponding  $\alpha$ -aminated product (*R*)-**151** in quantitative yield and 92% ee (condition A). Identical results were obtained using a catalytic amount of (*R*)-**150**, and readily available and much less expensive  $\text{La}(\text{NO}_3)_3$  and *H-D-Val-Ot-Bu* in ethyl acetate at 0 °C.<sup>121</sup> Treatment of **151** with  $\text{HCl}(\text{g})$  in toluene followed by cleavage of the N–N bond by hydrogenation over Raney-Ni and recrystallization led to the enantiomerically pure (*R*)-3-amino-3-ethoxycarbonylpyrrolidin-2,5-dione **152** in 66% yield (Scheme 34). The quaternary  $\alpha$ -amino derivative **152** is a key intermediate in the synthesis of AS-3201 (Ranirestat), a highly potent aldose reductase inhibitor.<sup>122</sup>

Other methodology focused on the stereoselective synthesis of cyclic  $\alpha$ -amino acids starting from cyclic carbonyl compounds is the amidation reaction, which is carried out using nitrogen as the nucleophilic reagent. For example, Satoh et al.<sup>123</sup> reported the synthesis of the cyclic quaternary  $\alpha$ -amino acids (*R*)- and (*S*)-**157** through the selective ring-opening of diastereoisomerically pure sulfinyloxiranes (2*S*,3*R*,*R*<sub>S</sub>)-**154** and (2*R*,3*R*,*R*<sub>S</sub>)-**155**. In this context, reaction of the  $\beta$ -tetralone with the lithium  $\alpha$ -sulfinyl carbanion generated from enantiomerically pure (*R*)-chloromethyl *p*-tolyl sulfoxide and lithium diisopropylamide (LDA) afforded the adduct **153** as a mixture of two diastereoisomers in 82% yield, which by treatment with *t*-BuOK gave the sulfinyloxiranes (2*S*,3*R*,*R*<sub>S</sub>)-**154** and (2*R*,3*R*,*R*<sub>S</sub>)-**155** in 93% yield and 3:1 dr. These compounds were separated by column chromatography. Treatment of diastereoisomerically pure (2*S*,3*R*,*R*<sub>S</sub>)-**154** with sodium azide followed by oxidation of the resulting aldehyde intermediate with a methanolic solution of iodine and KOH produced the azido methyl ester (*R*)-**156** in 82% yield, which by catalytic hydrogenation led to enantiomerically pure (*R*)-**157** in 98% yield. In a similar way, (2*R*,3*R*,*R*<sub>S</sub>)-**155** was transformed into (*S*)-**157** (Scheme 35).

Recently, Honda et al.,<sup>124</sup> in order to obtain the (*R*)-deoxydysibetaine and 4-*epi*-dysibetaine, carried out the addition of the lithium salt of chloroform to the ketone **158**, which is readily obtained from (*R*)-4-hydroxyproline, to give the alcohol **159** in 74% yield and high diastereoselectivity, which by treatment with DBU and sodium azide in the presence of 18-crown-6 under modified Corey–Link reaction<sup>125</sup> gave the dimethyl ester **161** in 56% yield through the intermediate epoxide **160**. Reduction of azide group in **161** with  $\text{H}_2$  over Raney-Ni followed by protection of resulting primary amine with  $(\text{Boc})_2\text{O}$  furnished the protected quaternary  $\alpha$ -amino acid **162** in 75% yield, and subsequent treatment with  $\text{Sml}_2$  in THF–HMPA or THF–DMEA afforded the  $\delta$ -lactam<sup>126</sup> (*R*)-**163** in >90% yield (Scheme 36).

## 2.2. Construction of the ring by cyclization reactions

Due to the wide range of methodologies reported on the construction of the cyclic by C–C bond formation, we have decided to organize this section according to the size of the ring to be prepared. Since the Grubbs reaction is common to different cycles it can be considered independently.

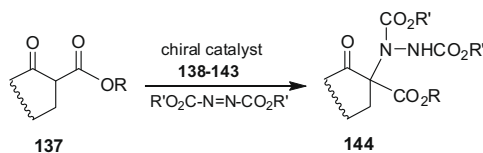
Enantiomerically pure epichlorohydrins have been used as bifunctional electrophiles for the asymmetric synthesis of aminocyclopropanecarboxylic acids. For example, treatment of chiral glycine equivalent **165** obtained from enantiopure **164**, with 2.1 equiv of sodium bis(trimethylsilyl)amide (NaHMDS) followed by addition of (*R*)-epichlorohydrin gave the cyclopropane derivative **166** in 69% yield. Hydrolysis of **166** afforded the (1*R*,2*R*)-1-amino-2-(hydroxymethyl)cyclopropanecarboxylic acid **167** in 59% yield. On the other hand, Swern-oxidation of **166** followed by reductive amination—performed with aniline and  $\text{NaBH}_3\text{CN}$ —produced the compound **168** in good yield. Subsequent hydrolysis furnished the diamino acid (1*R*,2*S*)-**169** in 62% yield. Under identical conditions, the alkylation of **165** with (*S*)-epichlorohydrin and subsequent reactions produced the quaternary  $\alpha$ -amino acids (1*R*,2*S*)-**170** and (1*R*,2*R*)-**171** (Scheme 37).<sup>127</sup>

In a similar way, alkylation of chiral glycine equivalent (*S*)-**173**, obtained in four steps from carboxylic acid (*S*)-**172**, with (*R*)-epichlorohydrin gave the cyclopropane derivative **174**, which under identical conditions to those described in Scheme 37 was transformed into quaternary  $\alpha$ -amino acids (1*S*,2*R*)-**170** (*X* = OH) and (1*S*,2*S*)-**171** (*X* = NHPh). Alkylation of (*S*)-**173** with (*S*)-epichlorohydrin afforded the cyclopropane derivative **175**, which was transformed into quaternary  $\alpha$ -amino acids (1*R*,2*S*)-**170** and (1*R*,2*R*)-**171** (Scheme 38).<sup>128</sup>

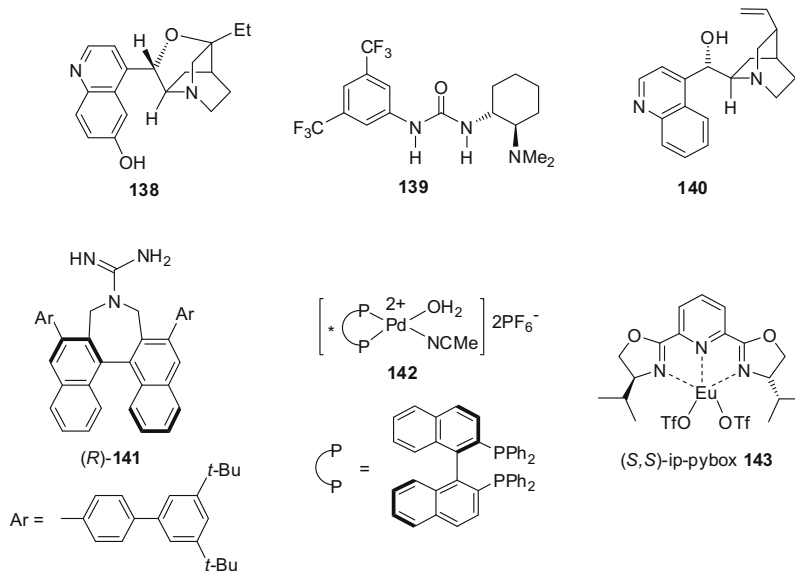
On the other hand, treatment of **174** with 1-phenyl-3-(trifluoroacetyl)urea **176** and diisopropyl azodicarboxylate (DIAD) under Mitsunobu<sup>129</sup> conditions afforded the urea **177** in 65% yield, which by cleavage of the trifluoroacetyl group with aqueous  $\text{K}_2\text{CO}_3$  led to compound **178** in 76% yield. Finally, hydrolysis of **178** produced the quaternary diamino acid (1*S*,2*S*)-**179** in 24% yield (Scheme 39).<sup>128</sup>

Recently, Acher et al.<sup>130</sup> reported the utility of (1*S*,2*R*)- and (1*R*,2*R*)-1-amino-2-(hydroxymethyl)cyclopropanecarboxylic acid derivatives **180** and **185**<sup>131</sup> in the synthesis of (1*S*,2*R*)- and (1*R*,2*R*)-1-amino-2-phosphonomethylcyclopropanecarboxylic acids **184** and **186** (APCPr),<sup>132</sup> which were evaluated at the recombinant group III metabotropic glutamate receptor. Thus, the bromination of (1*S*,2*R*)-**180** with  $\text{CBr}_4$  and polymer bond  $\text{PPh}_3$  in the presence of triethylamine led to bromo derivative (1*S*,2*R*)-**181** in 56% yield. In order to prevent the cyclopropane cleavage in the next Arbuzov reaction,<sup>133</sup> the Boc protecting group was replaced by a more electron-withdrawing trifluoroacetyl group, obtaining (1*S*,2*R*)-**182** in 95% yield. Arbuzov reaction of **182** with trimethyl phosphite gave the corresponding phosphonate (1*S*,2*R*)-**183** in 51% yield, which by hydrolysis, followed by ion exchange chroma-

**Table 5**  
Enantioselective hydrazination of **137** in the presence of chiral catalysts **138–143**



Substrate	R	R'	Catalyst	Yield (%)	ee (%) (Config)	Ref.
	<i>t</i> -Bu	<i>t</i> -Bu	<b>138</b>	99	89 ( <i>S</i> )	112
	<i>i</i> -Pr	<i>t</i> -Bu	<b>139</b>	98	91 ( <i>S</i> )	113
	Et	Bn	<b>140</b>	95	90 ( <i>R</i> )	114
	Et	<i>t</i> -Bu	<b>141</b>	99	97 ( <i>R</i> )	115
	Et	Bn	<b>142</b>	73	93 ( <i>R</i> )	116
	<i>t</i> -Bu	<i>t</i> -Bu	<b>143</b>	81	95 ( <i>R</i> )	117
	Et	<i>t</i> -Bu	<b>138</b>	86	83 ( <i>S</i> )	112
	Me	<i>t</i> -Bu	<b>139</b>	52	87 ( <i>S</i> )	113
	Et	Bn	<b>140</b>	92	84 ( <i>R</i> )	114
	Et	<i>t</i> -Bu	<b>141</b>	99	98 ( <i>R</i> )	115
	<i>t</i> -Bu	<i>t</i> -Bu	<b>139</b>	90	90 ( <i>S</i> )	113
	<i>t</i> -Bu	<i>t</i> -Bu	<b>139</b>	93	90 ( <i>S</i> )	113
	Et	Bn	<b>142</b>	94	99 ( <i>S</i> )	116
	Me	<i>t</i> -Bu	<b>139</b>	99	87 ( <i>S</i> )	113
	Et	<i>t</i> -Bu	<b>141</b>	99	97 ( <i>R</i> )	115
	Me	<i>t</i> -Bu	<b>142</b>	56	95 ( <i>S</i> )	116

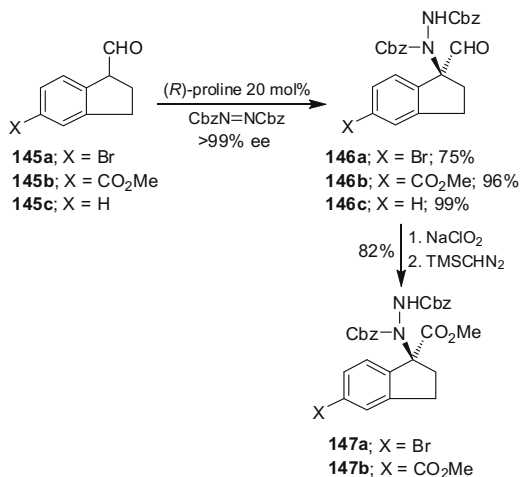


tography produced the enantiomerically pure (1*S*,2*R*)-**184**, APCPr in 96% yield. Under identical conditions, (1*R*,2*R*)-**185** was transformed into (1*R*,2*R*)-**186**, APCPr (Scheme 40).

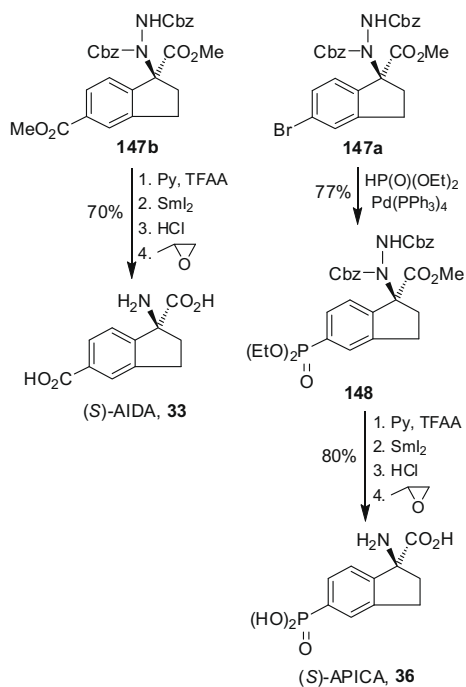
Carboni et al.<sup>134</sup> reported the application of Belokon's Ni(II) complex (*S*)-**187** (a glycine equivalent) in the diastereoselective synthesis of (1*S*,2*R*)- and (1*R*,2*S*)-allonorcoronamic acid **5a** through a double alkylation. In this context, treatment of Ni(II) complex (*S*)-**187** with potassium *tert*-butoxide followed by addition of sulfate (*S*)-**188** gave the corresponding enolate **189**, which

by intramolecular alkylation afforded the cyclopropane derivative (*S*,1*S*,2*R*)-**190** in 70% yield. Acidic hydrolysis of **190** followed by ion exchange chromatography produced the (1*S*,2*R*)-allonorcoronamic acid **5a** in 96% yield. Alkylation of Ni(II) complex (*S*)-**187** with the sulfate (*R*)-**188** followed by hydrolysis gave the (1*R*,2*S*)-allonorcoronamic acid **5a** (Scheme 41).

Recently, Fox et al.<sup>135</sup> reported the catalytic stereoselective synthesis of (1*R*,2*S*)-dehydrocoronamic acid methyl ester **196**, through a double alkylation of glycine anion equivalents **191a,b**. Thus,



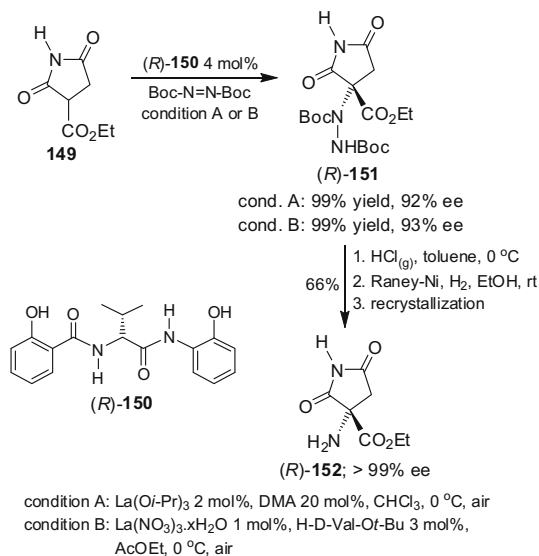
Scheme 32.



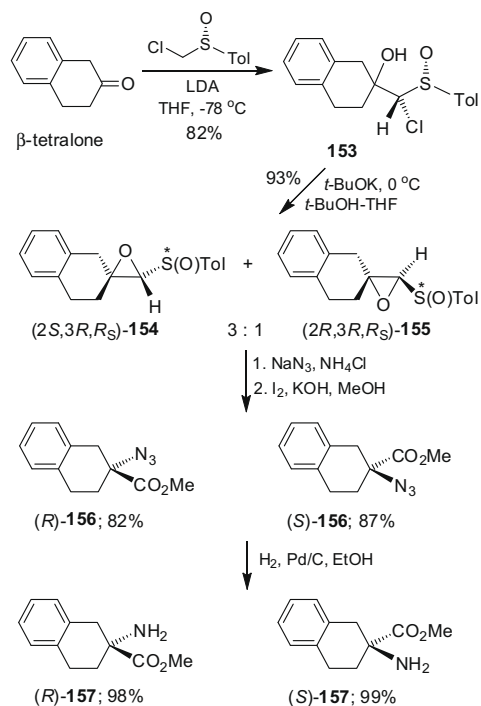
Scheme 33.

asymmetric allylic alkylation of **191a,b** with 3,4-epoxy-1-butene in the presence of a catalytic amount of (*S,S*)-**192**-(allylPdCl)<sub>2</sub> complex afforded the allyl derivatives mixture **193a,b** in quantitative yield and 3:2 dr, which by mesylation followed by treatment with NaH or potassium *tert*-butoxide in THF, gave the cyclopropanes **194a,b** and dihydroazepines **195a,b**. Hydrolysis of the mixture of **194a** and **195a** followed by separation led to (1*R*,2*S*)-**196** in 14% yield and 88% ee (Scheme 42).<sup>136</sup>

Reaction of 2,3-epoxy-1,1,1-trifluoropropane **197** with the sodium salt of **198** gave the  $\gamma$ -hydroxy nitrile derivative **199** in 73% yield and 30% de, which by reaction with tosyl chloride (TsCl) followed by treatment with NaH and subsequent recrystallization afforded the diastereoisomerically pure cyclopropyl cyanide (1*S*,2*S*)-**200** in 70% yield. Oxidative degradation of the pyrrole ring of **200** with NaIO<sub>4</sub> in the presence of a catalytic amount of RuCl<sub>3</sub> produced the  $\alpha$ -amino nitrile (1*S*,2*S*)-**201** in 71% yield. Subsequent hydrolysis with HCl furnished the enantiomerically pure trifluoronorcoronamic acid (1*S*,2*S*)-**202** in 67% yield (Scheme 43).<sup>137</sup>



Scheme 34.

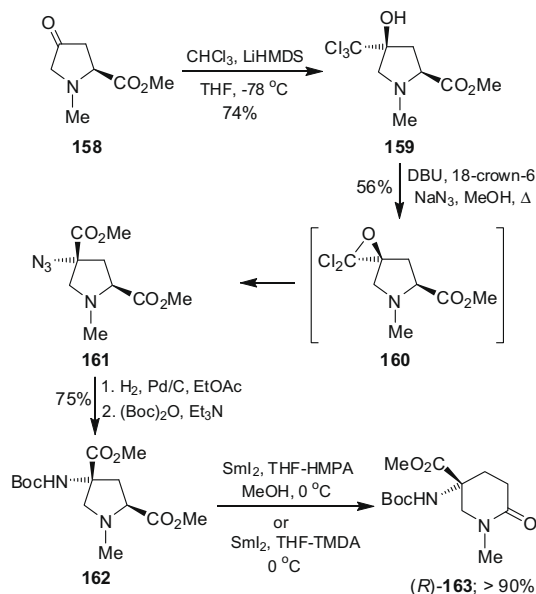


Scheme 35.

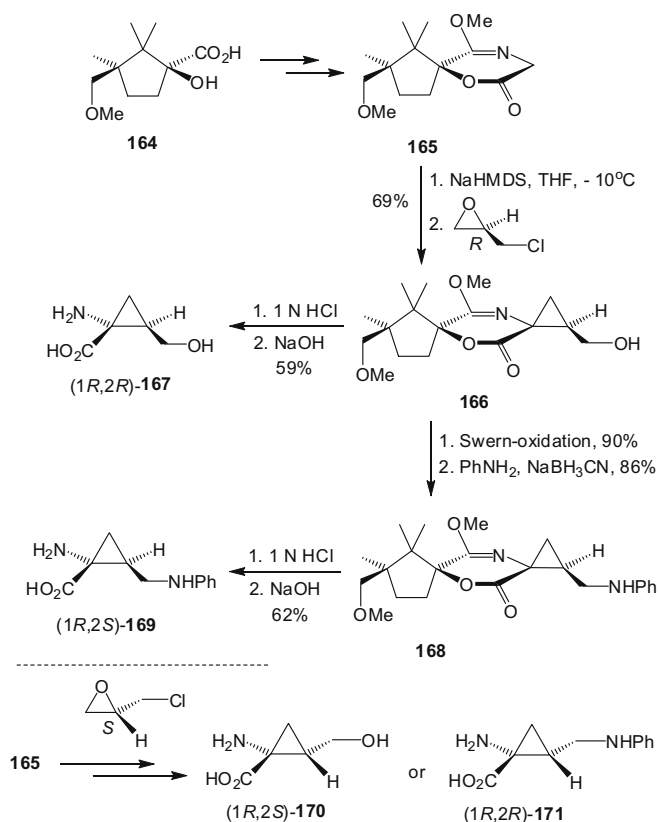
In a similar way, reaction of **197** with the sodium salt of **203** gave the  $\gamma$ -hydroxy nitrile **204**, which by reaction with TsCl followed by treatment with sodium hydride and subsequent recrystallization furnished the diastereoisomerically pure cyclopropyl cyanide (1*R*,2*S*)-**205** in 70% yield. Hydrolysis of nitrile function of **205** with hydrogen peroxide under basic conditions produced the amide (1*R*,2*S*)-**206** in 79% yield, which by Hoffman rearrangement<sup>138</sup> followed by oxidative degradation of aromatic ring of **207** with NaIO<sub>4</sub> in the presence of a catalytic amount of RuCl<sub>3</sub> produced the enantiomerically pure *N*-Boc-trifluoronorcoronamic acid (1*R*,2*S*)-**208** in 30% yield (Scheme 44).<sup>137</sup>

Synthesis of enantiomerically pure 1-aminocycloalkancarboxylic acids starting from  $\alpha$ -amino acids is another methodology that has been used. For example, Donkor et al.<sup>139</sup> reported the synthesis of all four diastereoisomers of *N*-Cbz-2,3-methanoleucine





Scheme 36.



Scheme 37.

from L- and D-valine. Deamination of L-valine with  $\text{NaNO}_2/\text{H}_2\text{SO}_4$  followed by reduction of the carboxylic acid with  $\text{LiAlH}_4$  produced the corresponding diol (*S*)-**209** in 42% yield. This compound was transformed into cyclic sulfate (*S*)-**210** in 91% yield. Reaction of (*S*)-**210** with the sodium dimethyl malonate afforded the cyclopropane derivative (*R*)-**211** in 84% yield and selective hydrolysis with KOH and subsequent Curtius rearrangement<sup>140</sup> with diphenylphosphorazide (DPPA) in the presence of triethylamine (TEA)

followed by addition of benzyl alcohol gave the diprotected  $\alpha$ -amino acid (*1S,2R*)-**212** in good yield. Finally, hydrolysis of (*1S,2R*)-**212** with KOH gave (*1S,2R*)-**213** in 91% yield (Scheme 45).

On the other hand, selective hydrolysis of (*R*)-**211** with KOH followed by treatment with hydrazine gave the compound **214**, which by reaction with  $\text{NaNO}_2/\text{H}_2\text{SO}_4$  and subsequent esterification with diazomethane provided the azide derivative **215**. Curtius rearrangement of **215** followed by hydrolysis with KOH furnished (*1R,2R*)-**216** (Scheme 46). Under identical conditions the diastereoisomers (*1R,2S*)-**213** and (*1S,2S*)-**216** were obtained from D-valine.<sup>139</sup>

Frick et al.<sup>141</sup> reported the stereoselective synthesis of protected 2,3-methano amino acids (*1S,2S*)-**224** and (*1R,2R*)-**225**, which are analogues of ornithine and glutamic acid, respectively. Initially, treatment of **218**, obtained from epoxide **217**,<sup>142</sup> with 3,5-dinitrobenzoic acid under Mitsunobu conditions gave the corresponding 3,5-dinitrobenzoate **219** in 91% yield. This compound was reacted with NaH to give the cyclopropane derivative **220** in 81% yield. Cleavage of the benzyl protecting group with  $\text{H}_2$  over Pd/C followed by treatment with TFA furnished the lactone (*1R,6R*)-**221** in 97% yield. The synthesis of the lactone (*1S,6S*)-**221** was reported by Frick et al.<sup>142</sup> (Scheme 47).

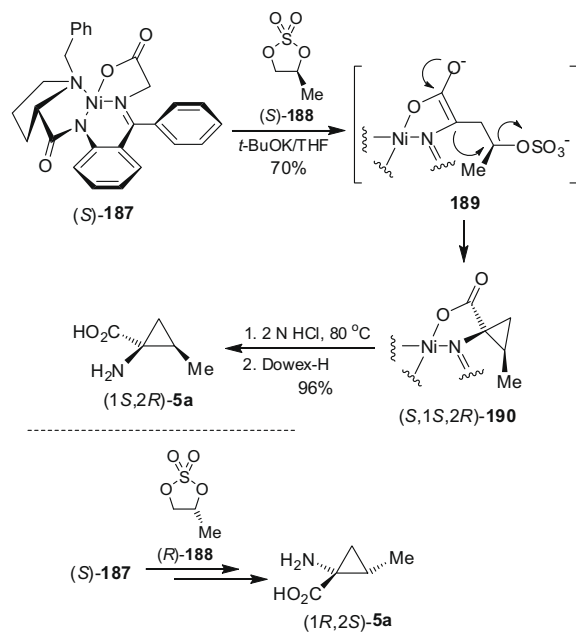
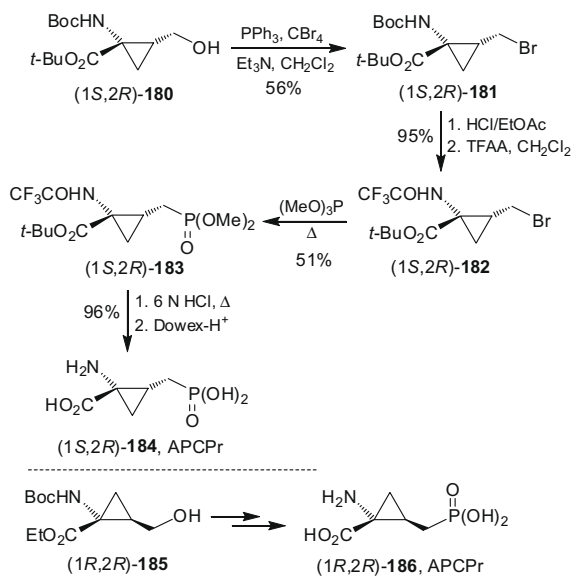
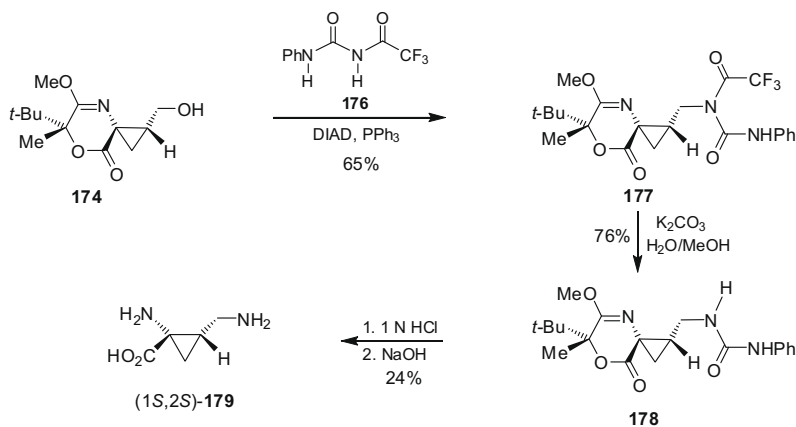
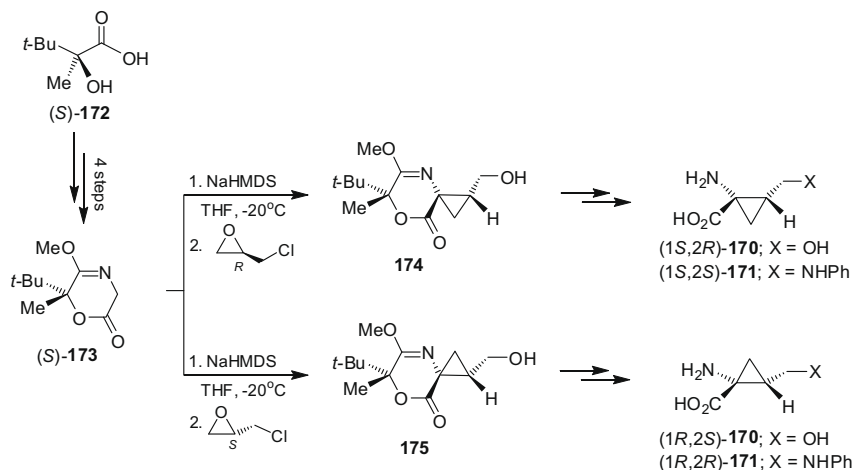
Reaction of (*1S,6S*)-**221**<sup>142</sup> with ethyl chloroformate followed by treatment with sodium azide and subsequent Curtius rearrangement of the corresponding azide under heating and the addition of benzyl alcohol produced the *N*-Cbz-amino derivative (*1S,6S*)-**222** in 90% yield, which by hydrolysis with LiOH and subsequent esterification with MeI afforded the protected amino acid (*1S,2S*)-**223** in 93% yield. Reaction of (*1S,2S*)-**223** with methanesulfonyl chloride (MsCl) followed by reaction with sodium azide and subsequent reduction of the azido group with  $\text{H}_2$  over Pd-BaSO<sub>4</sub> in the presence of (Boc)<sub>2</sub>O gave the protected 2,3-methanoornithine analogue (*1S,2S*)-**224** in 79% yield (Scheme 48).<sup>141</sup>

Under identical conditions to those described in the Scheme 48, (*1R,6R*)-**221** was transformed into (*1R,2R*)-**223** in good yield and subsequent oxidation with pyridine-SO<sub>3</sub> followed by treatment with sodium chlorite gave the methyl 2,3-methanoglutamate derivative (*1R,2R*)-**225** in 80% (Scheme 49).<sup>141</sup>

Chiral didehydroamino acid derivatives from a cyclic glycine template have been used in the stereoselective synthesis of cyclopropane amino acid derivatives through diastereoselective cyclopropanation reactions by using Corey's ylide. For example, reaction of (*S*)-oxazinone **227**, obtained in four steps from (*S*)-2-hydroxyisovaleric acid **226**, with acetaldehyde and propanaldehyde in the presence of K<sub>2</sub>CO<sub>3</sub> and tetrabutylammonium bromide (TBAB) produced the didehydroamino acid derivatives (*S*)-**228a,b** with high selectivity in 50–55% yield. Treatment of these compounds with Corey's dimethylsulfoxonium methylide gave the cyclopropanation products **229a,b** in moderate yield and 9:1 diastereoisomeric ratio. Hydrolysis of diastereoisomerically pure **229a,b** with HCl afforded the (*1S,2R*)-allonorcoronamic acid **5a** in 60% yield and (*1S,2R*)-allocoronamic acid **5b** in 67% yield (Scheme 50).<sup>143</sup>

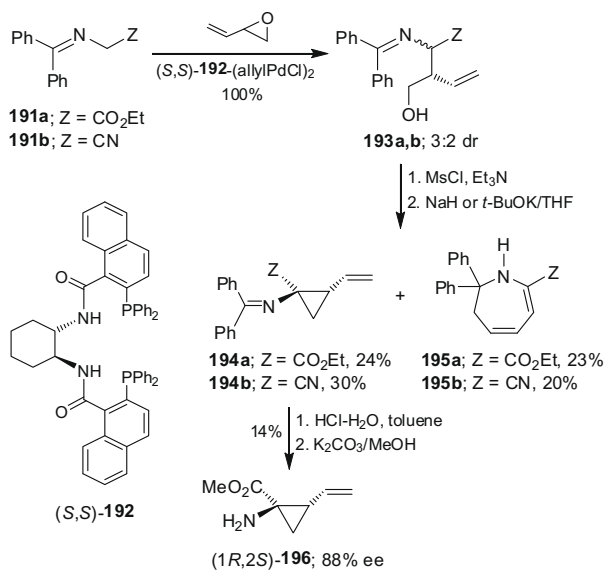
On the other hand, condensation of the protected (*S*)-pyrazine-2-one **231**, obtained in three steps from (*S*)- $\alpha$ -aminoketone **230**, with acetaldehyde and propanaldehyde furnished the (*Z*)- $\alpha,\beta$ -unsaturated compounds (*S*)-**232a,b** in 88 and 86% yield, respectively. Treatment of these compounds with Corey's dimethylsulfoxonium methylide gave the cyclopropanation products **233a,b** in moderate yield and 23:1 dr. Hydrolysis of diastereoisomerically pure **233a** with HCl afforded the enantiomerically pure (*1S,2R*)-allonorcoronamic acid **5a** in 24% yield (Scheme 51).<sup>144</sup>

Didehydroamino acid derivatives from cyclic glycine templates have also been used in the stereoselective synthesis of cyclopropane amino acid derivatives, through diastereoselective cyclopropanation reactions with phosphorus or sulfur ylides. For example,

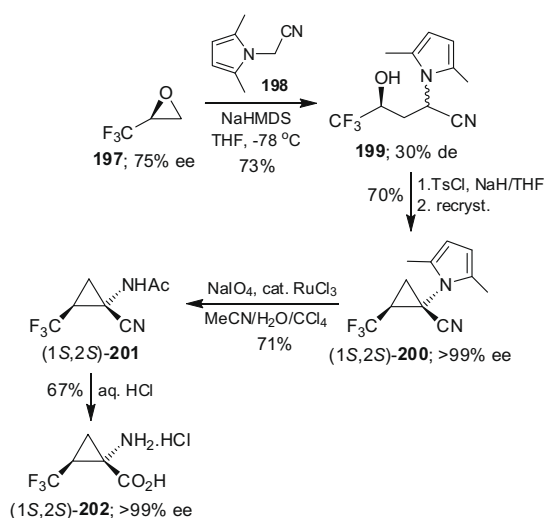


addition of  $\text{Me}_2\text{C}(\text{Li})\text{PPh}_3$  or  $(\text{CD}_3)_2\text{CD}_2(\text{Li})\text{SO}$  to the dehydroalanine (*S*)-**234** afforded the spiro derivatives (3*S*,6*S*)-**235a,b** in excellent yield and diastereoselectivity (>98:2), which by treatment with TFA gave the diketopiperazines (3*S*,6*S*)-**236a,b** in good yield. Final-

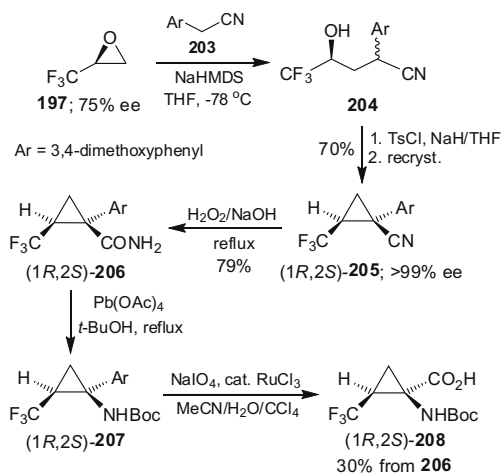
ly, hydrolysis of **236a,b** with 6 M HCl followed by esterification with  $\text{SOCl}_2/\text{MeOH}$  produced the corresponding methyl ester hydrochloride salts (*S*)-**237a,b** in excellent yield (Scheme 52).<sup>145</sup>



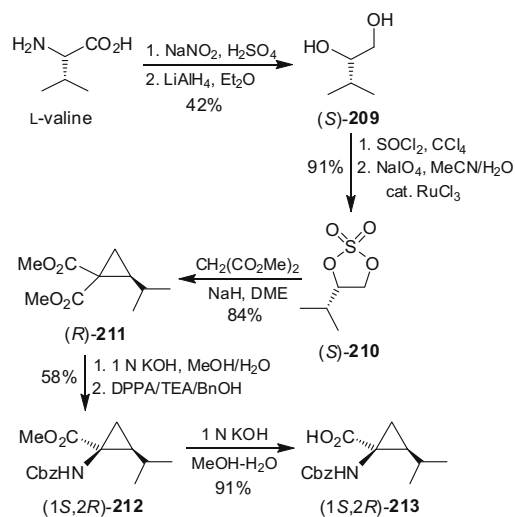
Scheme 42.



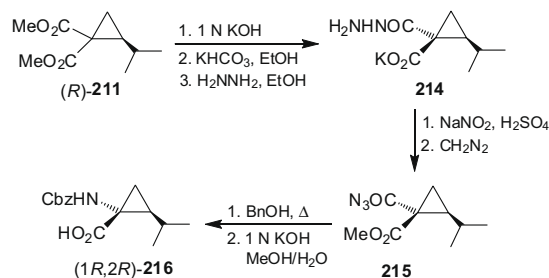
Scheme 43.



Scheme 44.



Scheme 45.

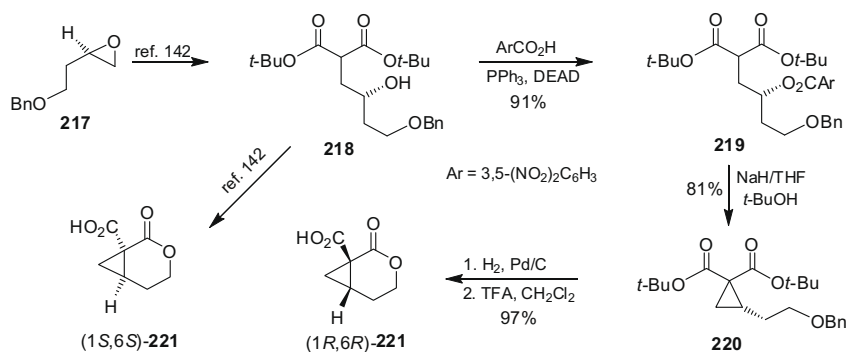


Scheme 46.

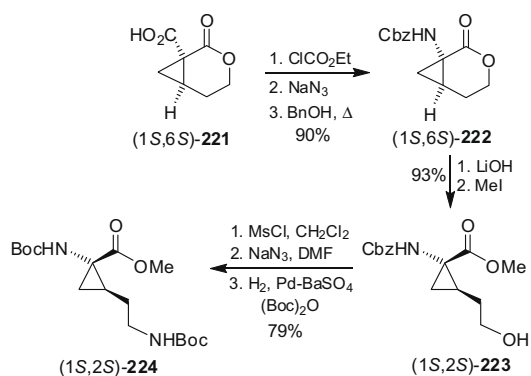
Enantioselective organocatalytic intermolecular cyclopropanation of protected dehydroalanine **238** with the ammonium ylide generated from reaction of *tert*-butyl bromoacetate with catalytic amounts of quinine derivatives **239** or **240** and Cs<sub>2</sub>CO<sub>3</sub> as a base afforded the cyclopropane compound (+)-**241** in 97% ee using **239** as a catalyst, and (–)-**241** in 90% ee using **240** as a catalyst (Scheme 53).<sup>146</sup>

On the other hand, condensation of (*R*)-**242** with benzylamine followed by addition of TMSCN afforded a mixture of  $\alpha$ -amino nitriles (1*R*,2*S*)-**243** and (1*S*,2*S*)-**244** in 75% yield and 85:15 diastereoisomeric ratio. Protection of the amino function of diastereoisomerically pure (1*R*,2*S*)-**243** with methyl chloroformate (MocCl) gave (1*R*,2*S*)-**245** in 98% yield, which by selective cleavage of the *tert*-butyldimethylsilyl (TBS) protecting group with acetic acid and subsequent reaction with PPh<sub>3</sub> and chloroform or bromoform led to the derivatives (1*R*,2*S*)-**246a,b** in excellent yield. Intramolecular alkylation of (1*R*,2*S*)-**246a** with KOH-DMF or potassium *tert*-butoxide in THF gave the cyclopropylaminonitrile (1*S*,2*R*)-**247** in 82% yield and >98:2 dr, which by treatment with hydrogen peroxide under basic conditions furnished the amide (1*S*,2*R*)-**248** in 87% yield (Scheme 54).<sup>147</sup>

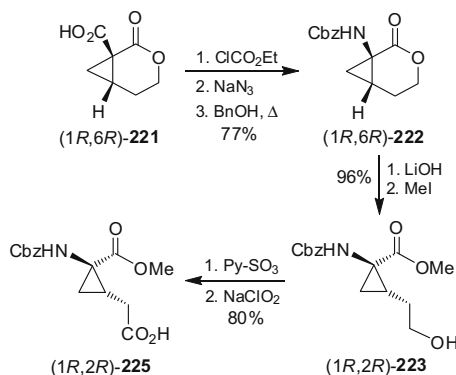
Wanner et al.<sup>148</sup> reported the synthesis of all four stereoisomers of 1-amino-2-(hydroxymethyl)cyclobutanecarboxylic acid (1*S*,2*S*)-, and (1*R*,2*R*)-**13f**, (1*S*,2*R*)- and (1*R*,2*S*)-**14f** through a double alkylation of the chiral glycine equivalent (*R*)-**173**. In this context, reaction of (*R*)-**173** with *s*-BuLi in THF at –78 °C followed by addition of but-3-enyl triflate afforded the alkylated products **249a** and **249b** in 69% yield and 95.5:4.5 dr. The use of other bases and 4-bromobut-1-ene as the alkylating reagent gave both low yield and diastereoselectivity. Oxidation of the terminal double bond



Scheme 47.



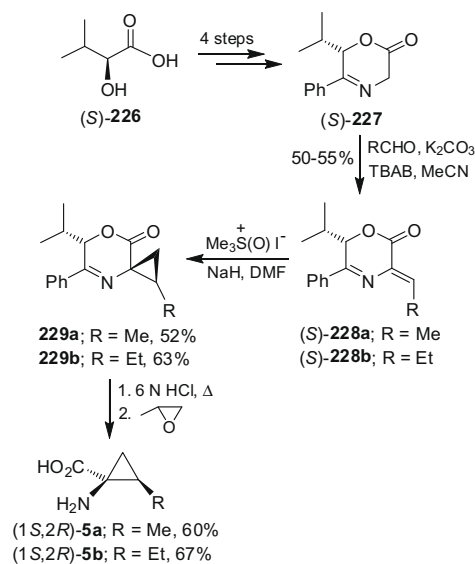
Scheme 48.



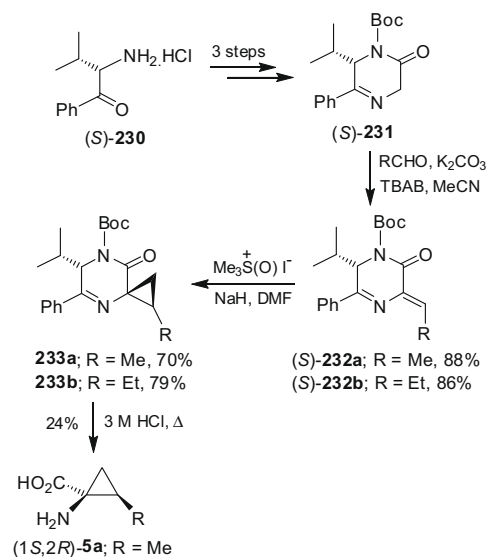
Scheme 49.

of the butenyl side chain in **249a,b** with a catalytic amount of  $\text{OsO}_4$  in combination with  $\text{Me}_3\text{NO}$  as a co-oxidant followed by selective protection of primary hydroxy group with *tert*-butyldimethylsilyl chloride (TBSCl) and subsequent selective replacement of secondary hydroxy group with  $\text{PPh}_3$  and  $\text{I}_2$  produced the iodohydrins **250a–d** in good overall yield and 4:4:1:1 dr. Reaction of **250a–d** with phosphazenic base ( $t\text{-BuP}_4$ ) gave the corresponding cyclobutane derivatives, which by treatment with tetrabutylammonium fluoride (TBAF) and subsequent separation by preparative HPLC furnished the hydroxyl derivatives **251a–d** in good yield and 48:31:18:3 dr. Finally, hydrolysis of diastereoisomerically pure **251a** led to  $(1S,2S)$ -**13f** in 71% yield. In a similar way, **251b** afforded  $(1S,2R)$ -**14f** in 76% yield. The diastereoisomers  $(1R,2R)$ -**13f** and  $(1R,2S)$ -**14f** were obtained from  $(S)$ -**173** (Scheme 55).

Dialkylation of *N*-(diphenylmethylene)glycine ethyl ester **191a** with 1,4-diiodo derivative  $(S)$ -**253**, obtained in 4 steps from

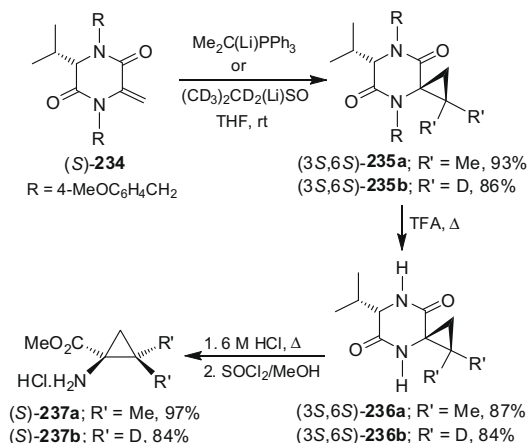


Scheme 50.

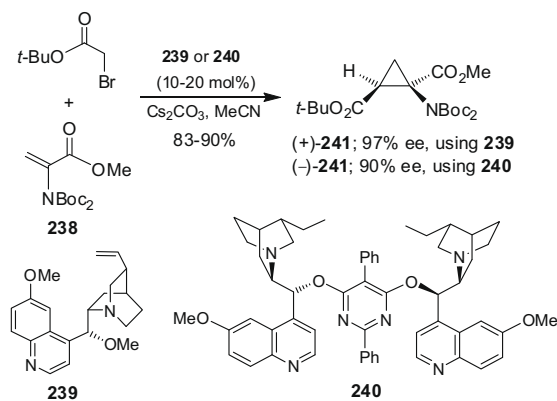


Scheme 51.

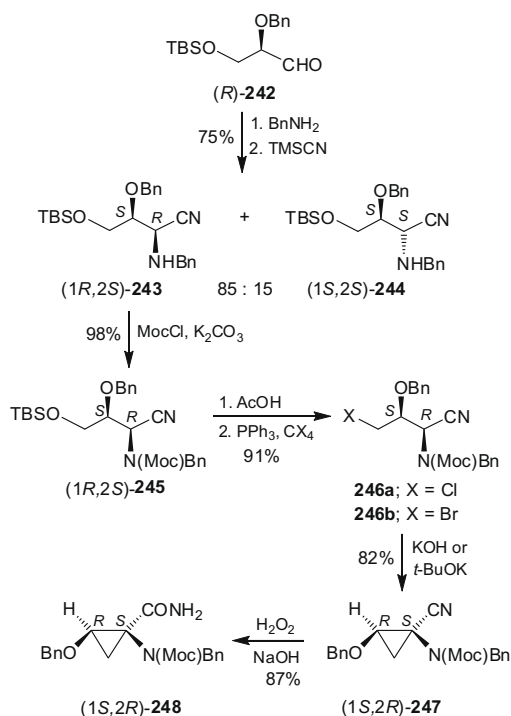
$(S)$ -malic acid dimethyl ester **252**, afforded the cyclopentane derivative mixture **254** in 2:1 dr. Hydrolysis of **254** with 2 M  $\text{HCl}$  followed by treatment with  $(\text{Boc})_2\text{O}$  and subsequent



Scheme 52.



Scheme 53.



Scheme 54.

chromatographic separation gave the diprotected quaternary  $\alpha$ -amino acids (1S,3S)-255 and (1R,3S)-256 in 36 and 19% yield, respectively, and these were used in the preparation of the thymine derivatives 257 and 258 (Scheme 56).<sup>149</sup>

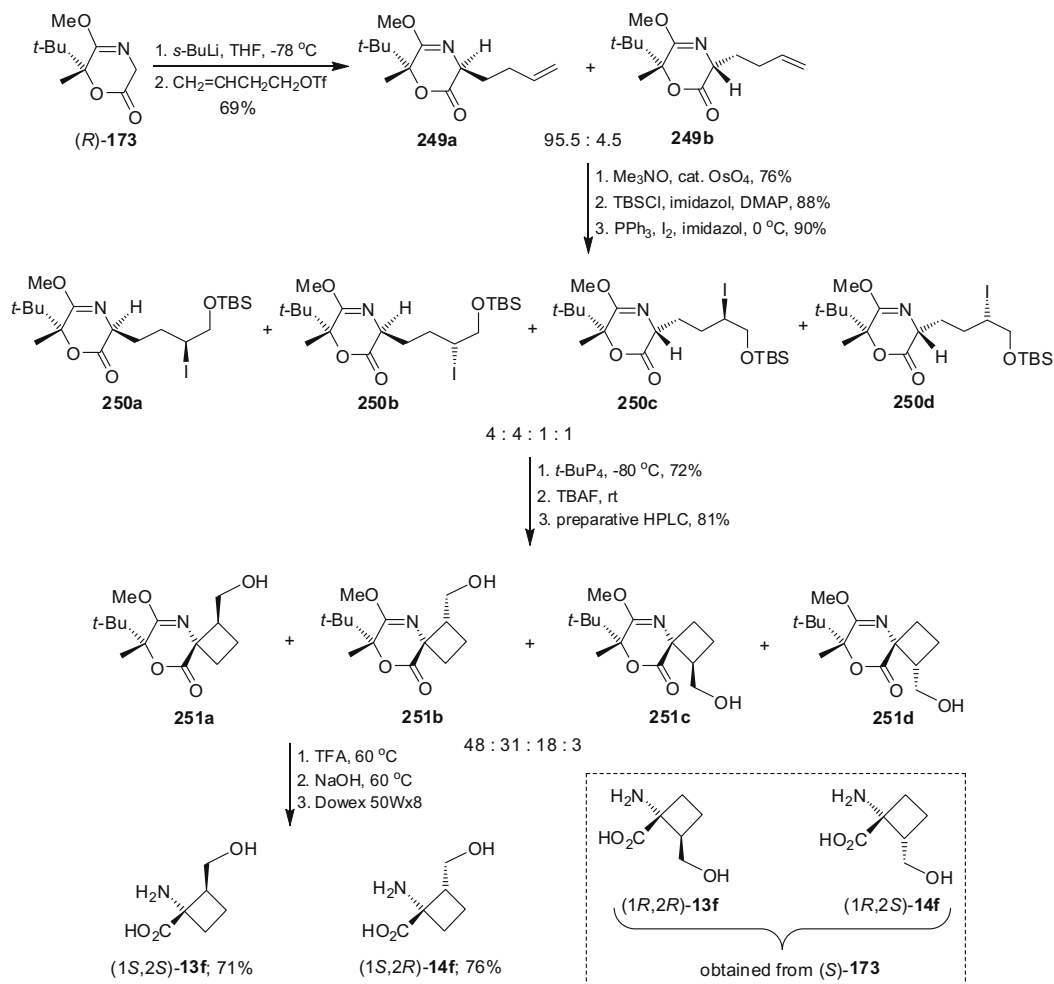
On the other hand, reduction of dicarboxylic acid (S,S)-259 with LiAlH<sub>4</sub> followed by treatment with I<sub>2</sub> and PPh<sub>3</sub> afforded the diiodide 260 in 83% yield. Dialkylation of ethyl isocyanoacetate with 260 followed by hydrolysis and subsequent treatment with (Boc)<sub>2</sub>O gave the ethyl 1-N-Boc-aminocyclopentanecarboxylate 261 in 59% yield. Ozonolysis of 261 followed by treatment with NaBH<sub>4</sub> and subsequent oxidation of the resulting diol with oxone gave the dicarboxylic acid 262 in 25% overall yield. On the other hand, hydrogenation of 261 over Pd/C produced the diprotected quaternary  $\alpha$ -amino acid 263 in 99% yield. Finally, ozonolysis of 261 followed by treatment with benzylamine and subsequent reduction with NaBH<sub>3</sub>CN produced the compound 264 in 53% yield (Scheme 57).<sup>150</sup>

Ma et al.<sup>151</sup> reported the stereoselective synthesis of (S)-1-aminoindane-1,6-dicarboxylic acid 269 and related analogues, through the intramolecular acylation of enantiopure  $\alpha,\alpha$ -disubstituted amino acid (S)-266. In this context, the protection of (R)-phenylglycine with methyl chloroformate followed by condensation with benzaldehyde dimethyl acetal afforded the *cis*-oxazolidinone (2R,4S)-265, which by alkylation with *tert*-butyl bromoacetate followed by hydrolysis produced the carboxylic acid (S)-266. Reaction of (S)-266 with PCl<sub>5</sub> followed by treatment with AlCl<sub>3</sub> gave the acylated product (S)-267 in 92% yield, and this was hydrogenated over Pd/C to provide the cyclic  $\alpha$ -amino acid (S)-268 in 94% yield. Sequential iodination with I<sub>2</sub>/Hg(OTf)<sub>2</sub>, palladium-catalyzed carbonylation under Pd(OAc)<sub>2</sub>/CO/MeOH conditions, and hydrolysis led to (S)-269 in 40% overall yield (Scheme 58).

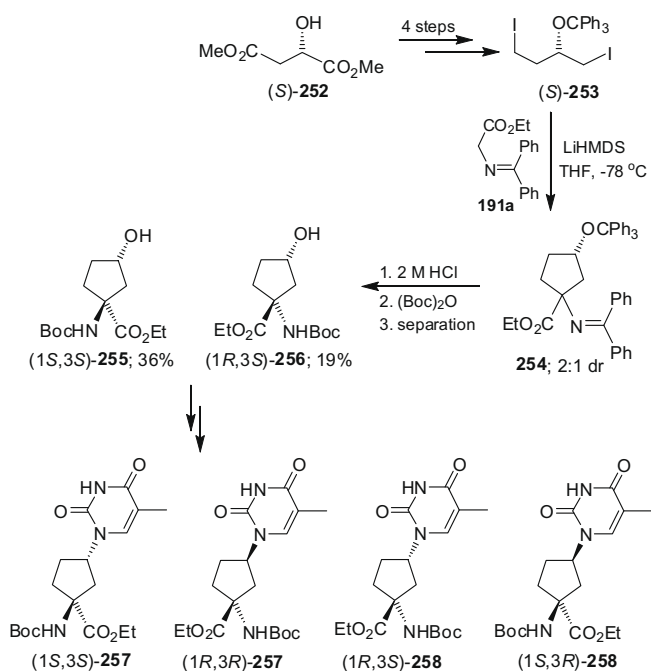
On the other hand, treatment of (S)-268 with acetyl chloride catalyzed with AlCl<sub>3</sub> followed by Baeyer-oxidation using *m*-chloroperbenzoic acid (*m*-CPBA) and subsequent hydrolysis produced the phenol derivative (S)-270 in good yield. Iodination of (S)-270 with I<sub>2</sub>/pyridine followed by palladium-catalyzed carbonylation using Pd(OAc)<sub>2</sub>/CO/EtOH afforded the diester (S)-271 in 55% overall yield, and this compound was hydrolyzed with TMSI to give the conformationally constrained (S)-272 in 75% yield. Additionally, iodination of (S)-270 followed by palladium-catalyzed phosphorylation with Pd(PPh<sub>3</sub>)<sub>4</sub>/HP(O)(OEt)<sub>2</sub> afforded the phosphonate (S)-273 in 58% yield, which by hydrolysis with TMSI gave the phosphonic acid (S)-274 in 82% yield (Scheme 59).<sup>151</sup>

Asymmetric Strecker reaction of 4-methylbenzaldehyde with (R)-phenylglycinol and NaCN followed by hydrolysis and subsequent intramolecular esterification with TsOH afforded the corresponding lactone mixture 275 in 57% yield. Alkylation of 275 with *tert*-butyl bromoacetate and subsequent opening of the lactone ring with Et<sub>3</sub>N/MeOH produced the alkylated products (S,R)-276 and (R,R)-277 in 65% yield and 4:1 dr. Cleavage of the chiral auxiliary of diastereoisomerically pure (S,R)-276 with Pd(OAc)<sub>4</sub>/NaOAc followed by acidic hydrolysis and subsequent protection of the resulting amino group with methyl chloroformate led to (S)-278 in 75% yield. Subsequent intramolecular acylation with oxalyl chloride and AlCl<sub>3</sub> gave (S)-279 in 93% yield. Benzylic bromination of (S)-279 with *N*-bromosuccinimide (NBS) catalyzed with 2,2'-azobisisobutyronitrile (AIBN) produced the bromo derivative (S)-280 in 87% yield. This compound was oxidised with Ag<sub>2</sub>O and AgNO<sub>3</sub> and subsequent esterification with MeI/K<sub>2</sub>CO<sub>3</sub> furnished the diester (S)-281 in 64% yield. Reduction of the ketone function of (S)-281 by Pd/C-catalyzed hydrogenation gave (S)-282 in 97% yield, which by hydrolysis with 6 N HCl and subsequent treatment with propylene oxide afforded the (S)-AIDA 33 in 78% yield (Scheme 60).<sup>151</sup>

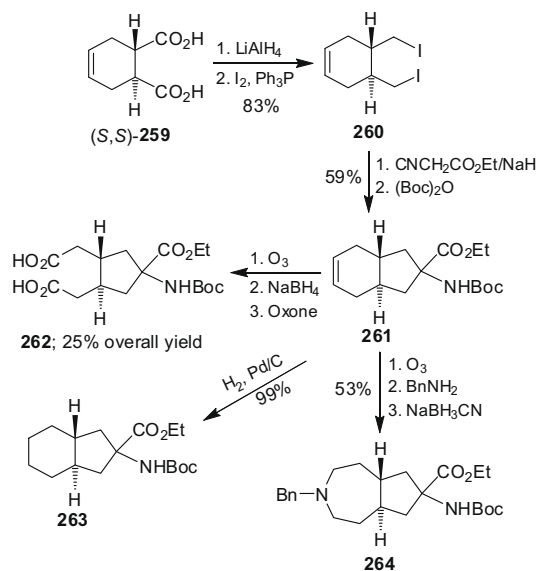
The alkylidene carbene C-H insertion is another strategy for the enantioselective synthesis of conformationally constrained  $\alpha$ -amino acids. For example, reaction of (R)-283, obtained in six



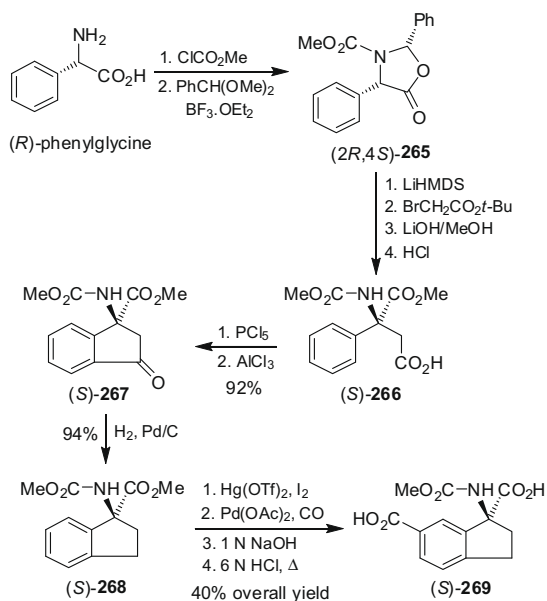
Scheme 55.



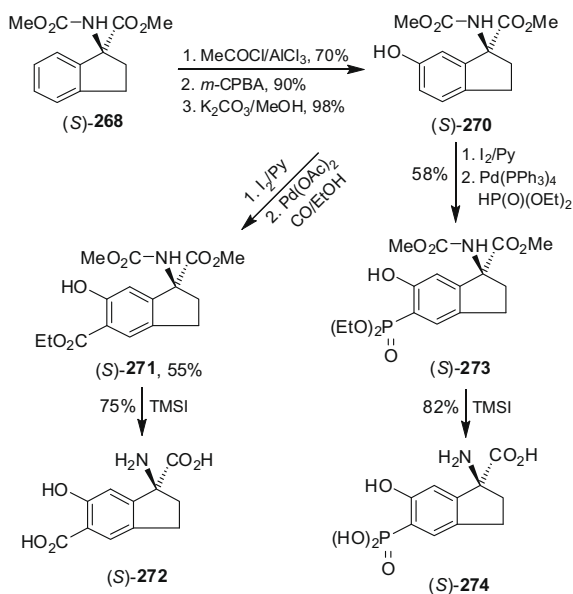
Scheme 56.



Scheme 57.



Scheme 58.



Scheme 59.

steps from L-serine, with lithium (trimethylsilyl)diazomethane generated in situ by treatment of (trimethylsilyl)diazomethane with *n*-BuLi gave the alkylidene carbene **284**, which through a 1,5-C–H insertion reaction produced the spiro compound (S)-**285** in 62% yield. Catalytic hydrogenation of (S)-**285** over Pd/C afforded the hydrogenated product (1S,3R)-**286** in 79% yield as a single diastereoisomer, which by cleavage of the acetonide function with BF<sub>3</sub>·2AcOH furnished the alcohol (1S,3R)-**287** in 60–70% yield. Finally, Dess–Martin periodinane oxidation of (1S,3R)-**287** followed by treatment with sodium chlorite afforded the (1S,3R)-*N*-Boc-2,5-methanoleucine **288** in 70% yield and >95% ee (Scheme 61).<sup>152</sup>

In a similar way, treatment of (R)-**289**, obtained from L-serine, with lithium (trimethylsilyl)diazomethane led to a 1,5-C–H insertion reaction that gave the spiro compound (S)-**290** in 69% yield. Catalytic hydrogenation of this compound over Pd/C produced (1S,3R)-**291** in 79% yield and >10:1 dr. Selective cleavage of TBS protecting group in (1S,3R)-**291** with HF/MeCN led to diol

(1S,3R)-**292** in 81% yield, which by oxidation of hydroxy groups with RuCl<sub>3</sub>/NaIO<sub>4</sub> followed by treatment with HCl and subsequent ion exchange chromatography afforded the quaternary α-amino acid (1S,3R)-ACPD, **293**, in 49% yield (Scheme 62).<sup>153</sup>

Treatment of **295a,b**, obtained from (R)-glyceraldehyde dimethyl acetal **294**, with NBS in MeCN afforded the bicyclic lactone **297** in 42% yield. This product is probably obtained through the oxidation of **295** to the imine intermediate **296** followed by an intramolecular attack of the free OH group on the carbon–nitrogen double bond. Hydrolysis of bicyclic lactone **297** with HCl and subsequent cleavage of the TBS protecting group gave the quaternary α-amino acid methyl ester **298** (Scheme 63).<sup>154,155</sup>

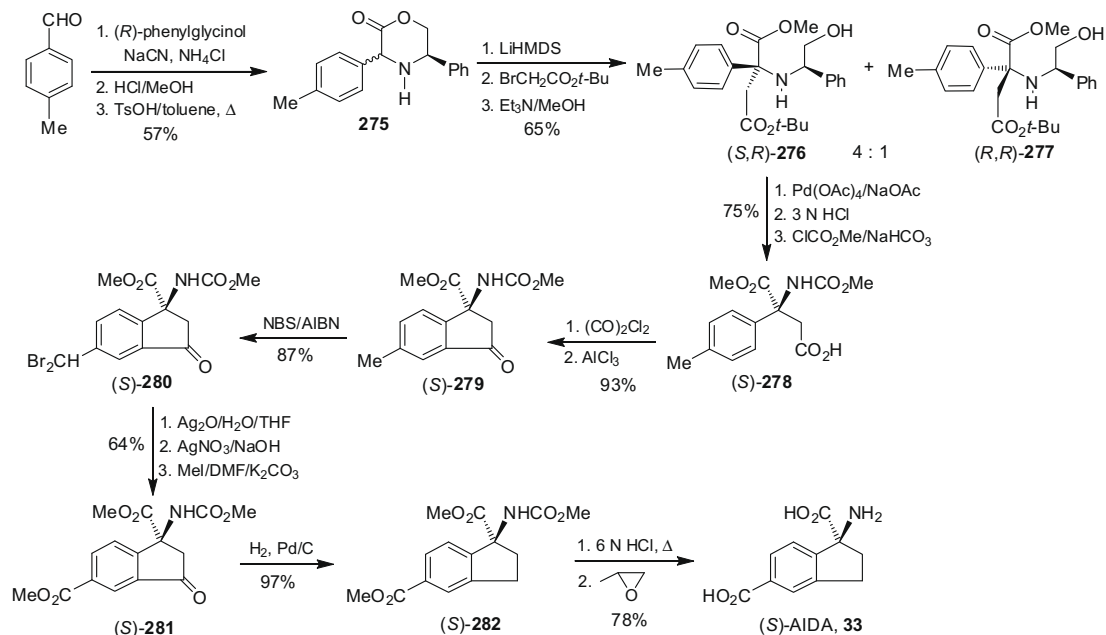
Alkylation of commercially available (R)-bislactim ether **299** with the dibromide **300** and *n*-BuLi in THF at –78 °C afforded the alkylated product (2R,5S)-**301** in 95% yield and 93:7 dr, which by treatment with diluted *n*-BuLi furnished the corresponding spiro derivative (2R,5R)-**302** in 99% yield as a single diastereoisomer. Hydrolysis of (2R,5R)-**302** gave the methyl ester of 2-aminotetraline-2-carboxylic acid (R)-**157** in 98% yield (Scheme 64).<sup>156</sup>

Jørgensen et al.<sup>157</sup> reported the first highly enantioselective catalytic alkylation of ketimines, a methodology used for the synthesis of quaternary α-amino acids. In this context, addition of ketene acetal **304** to the ketimine **303** in the presence of a catalytic amount of (R,R)-Ph-pybox-Zn(OTf)<sub>2</sub> **305** afforded the Mannich base **306** in 98% yield and 93% ee. Selective N-protection of **306** with (Boc)<sub>2</sub>O gave the compound **307** in 78% yield, which by treatment with Cs<sub>2</sub>CO<sub>3</sub> produced the δ-lactone **308** in 79% yield by spontaneous cyclization of the resulting phenol function (Scheme 65).

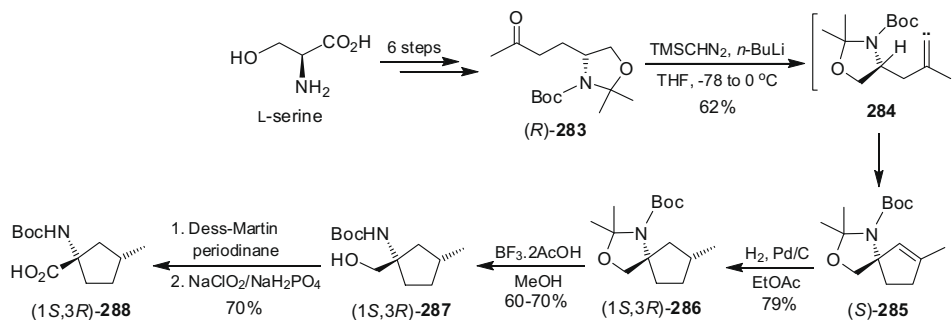
On the other hand, the first direct organocatalytic enantioselective Mannich reaction of the ketimine **309** with several aldehydes in the presence of a catalytic amount of the chiral amine **310** afforded the corresponding Mannich products **311a–h** and **312a–h** in good yield and with moderate to excellent diastereoisomeric ratio (4:1 to >20:1), with a predominance of **311a–h**. These compounds can be used as intermediates in the synthesis of quaternary α-amino acids (Scheme 66).<sup>158</sup>

Olefin metathesis is a fundamental chemical reaction involving the rearrangement of carbon–carbon double bonds and can be used to couple, cleave, ring-close, ring-open, or polymerize olefinic molecules. The widely accepted view that olefin metathesis revolutionized the different fields of synthetic chemistry led to the award of the 2005 Nobel Prize in Chemistry to Yves Chauvin, Robert H. Grubbs, and Richard R. Schrock ‘for the development of the metathesis method in organic synthesis’.<sup>159</sup> The ring closing metathesis (RCM) synthetic methodology has also been used in the stereoselective synthesis of different sizes of cyclic α-amino acids,<sup>160</sup> and in this review we present this methodology as an independent section. For example, Ru(II)-catalyzed ring-closing metathesis reaction of dialkylated compounds **313a,b**, obtained from bislactim ether (R)-**299**, in 1,2-dichloroethane (DCE), gave the spiro derivatives **314a,b**, which by dihydroxylation of the five- and six-membered-rings with a catalytic amount of OsO<sub>4</sub> in combination of morpholine N-oxide (NMO) afforded the diols **315a,b** and **316a,b**. Treatment of the diols **315a,b** with methyl iodide and sodium hydride followed by hydrolysis with TFA produced the conformationally constrained cyclic α-amino acids methyl esters **317a,b**. Hydrolysis of diol **315a** with TFA followed by acetylation gave the acetylated α-amino acid methyl ester **318a** (Scheme 67).<sup>161</sup>

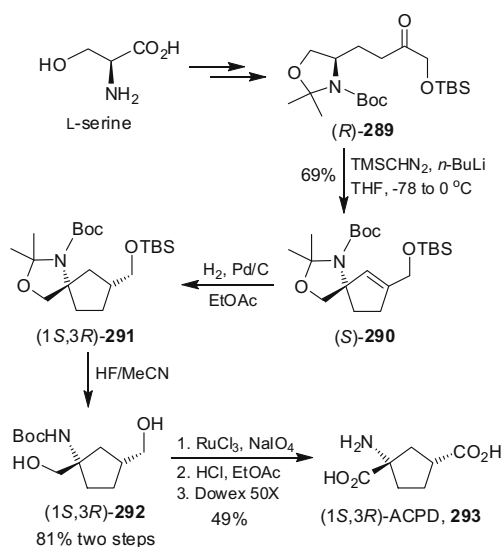
Ring closing metathesis of dialkylated derivatives **313a–d** in the presence of a catalytic amount of Grubbs second generation catalyst PhCH=RuCl<sub>2</sub>(IMes)(PCy<sub>3</sub>) under microwave-assisted heating gave the corresponding spiro compounds with five-, six-, and seven-membered rings containing a double bond **314a–d** in 63–99% yield. Hydrolysis of the bis-lactim ether of **314a–d** with TFA at room temperature or under microwave conditions followed by treatment with (Boc)<sub>2</sub>O afforded the *N*-Boc protected quaternary



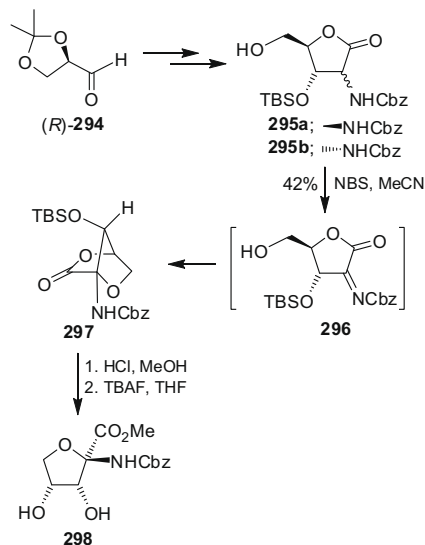
Scheme 60.



Scheme 61.



Scheme 62.

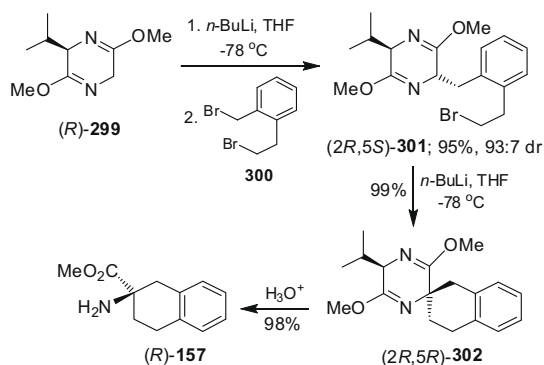


Scheme 63.

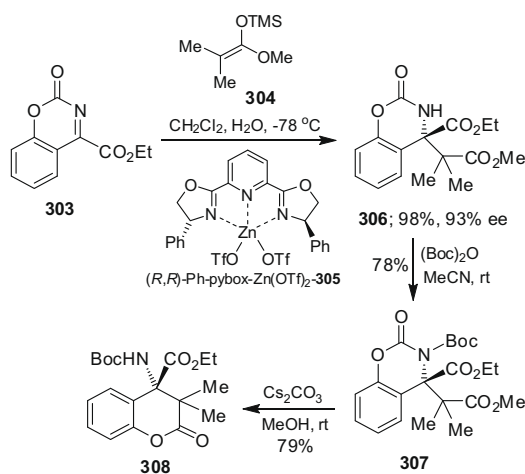
amino acid ethyl esters **319a–d** in good yield, which by basic hydrolysis under microwave-assisted heating produced the amino acids **320a–d** in 76–93% yield (Scheme 68).<sup>162</sup>

Cascade Ru(II)-catalyzed ring closing metathesis reaction of **321a,b** produced the RCM products **322a,b** in excellent yield. In a similar way, reaction of **323a–c** obtained from **321a,b**, under





Scheme 64.



Scheme 65.

identical conditions furnished the conformationally constrained amino acids **324a–c** in good yield (Scheme 69).<sup>163,164</sup>

Diels–Alder reaction of **324a,b,d** with diethyl acetylenedicarboxylate (DEAD) followed by aromatization with MnO<sub>2</sub> gave the conformationally constrained  $\alpha$ -amino acids **325a,b,d** in good yield (Scheme 70).<sup>164</sup>

On the other hand, ring closing metathesis reaction of triene **327**, readily obtained from **326**, in the presence of a catalytic amount of PhCH=RuCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> in toluene at 85 °C gave the product (2*R*,7*R*)-**328** in 58% yield.<sup>165</sup> Ring closing metathesis reaction of

triene **326** in the presence of a catalytic amount of PhCH=RuCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> in toluene at 85 °C gave **329** in 90% yield,<sup>165,166</sup> and a quantitative yield was obtained when the reaction of **326** was carried out under microwave-assisted heating. Identical results were obtained when PhCH=RuCl<sub>2</sub>(IMes)(PCy<sub>3</sub>)<sub>2</sub> was used as a catalyst.<sup>166</sup> Hydrolysis of **329** with 0.1 M TFA gave the constrained  $\alpha$ -amino acid methyl ester (2*R*,7*R*)-**330** in 35% yield (Scheme 71).<sup>167</sup>

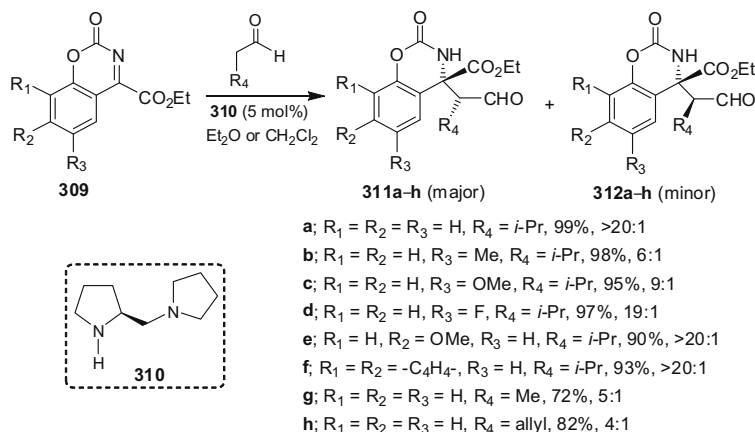
Ring closing metathesis reaction of tetraene **331** in the presence of 10 mol % of PhCH=RuCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> in toluene at 85 °C in order to obtain the spirane **332** was unsatisfactory, probably due to a sterically congested substrate. The more reactive PhCH=RuCl<sub>2</sub>(IMes)(PCy<sub>3</sub>) catalyst also failed to effect the spiroannulation of **331**. However, ring closing metathesis reaction of less bulky tetraene **333**, obtained by hydrolysis of **331**, under identical conditions gave the spiranes **334** and **335** in 73% yield and 3:2 isomeric ratio (Scheme 72).<sup>168</sup>

On the other hand, Ru(II)-catalyzed ring closing metathesis reaction of diastereoisomerically pure **336** gave the cyclic  $\alpha$ -amino acid methyl ester **337** in 96% yield (Scheme 73).<sup>169</sup>

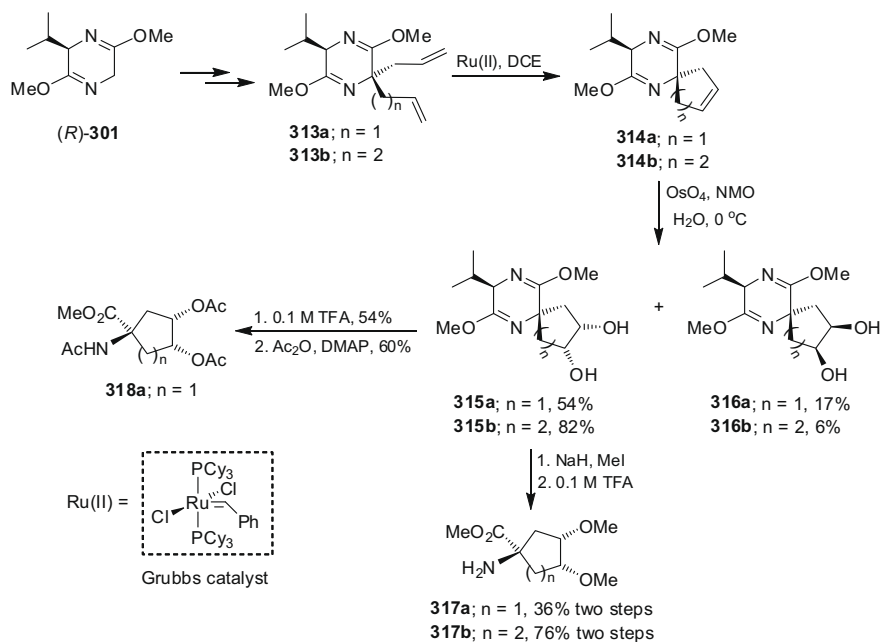
Chemoselective allylation of imino ester **338** with allylzinc bromide afforded the diene **339** in 95% yield as a single diastereoisomer, which by ring closing metathesis reaction in the presence of Grubbs first generation catalyst PhCH=RuCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> gave the cyclic amino ester **340** in 92% yield and >98% de. Cleavage of the benzyl group in **340** under H<sub>2</sub>/Pd(OH)<sub>2</sub> conditions provided the amino ester **341** in almost quantitative yield, which by treatment with TBAF and subsequent ion-exchange chromatography furnished the quaternary  $\alpha$ -amino acid **342** in 70% yield (Scheme 74).<sup>170</sup>

Undheim et al.<sup>171</sup> reported the stereoselective synthesis of rigidified homoserine analogues **350** and **351** through the ring closing metathesis reaction. In this context, reaction of hydroxy derivative **343** in the presence of a catalytic amount of PhCH=RuCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> in DCE at 65 °C gave the spiro compound **344** in 72% yield. Swern oxidation of **344** produced the  $\alpha,\beta$ -unsaturated ketone **346** in 74% yield. On the other hand, oxidation of **343** under Swern conditions furnished the ketone **345** in 79% yield, which by ring closing metathesis reaction in the presence of a catalytic amount of PhCH=RuCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> in benzene at 70 °C afforded the spiro derivative **346** in 37% yield. Conjugate addition of lithium dimethylcuprate to **346** furnished **347** in 91% yield and high diastereoselectivity (Scheme 75).

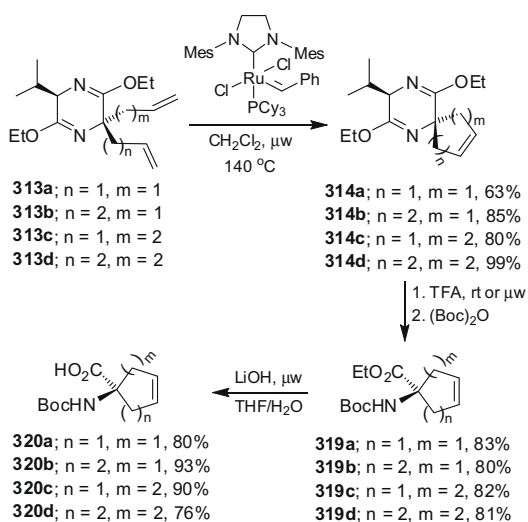
Reduction of the carbonyl group of **347** with NaBH<sub>4</sub> in methanol afforded the alcohols **348** and **349** in 37% and 57% yield, respectively. Hydrolysis of diastereoisomerically pure **348** with 0.1 M TFA gave the amino ester **350** in 38% yield, whereas the hydrolysis



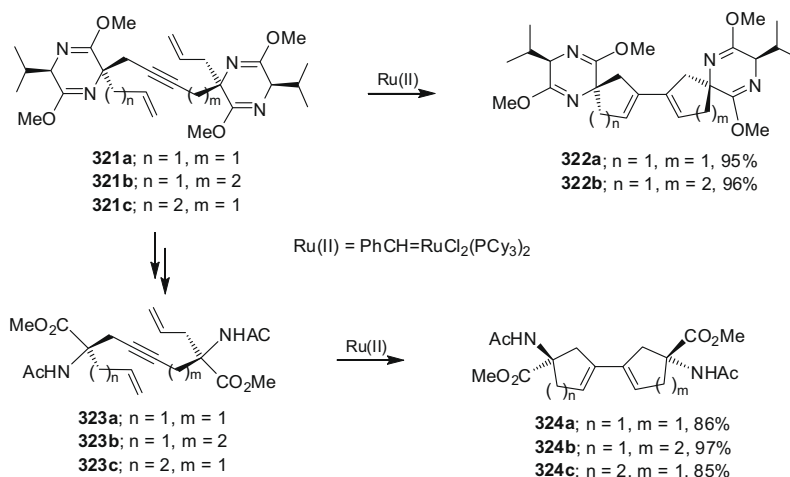
Scheme 66.



Scheme 67.



Scheme 68.

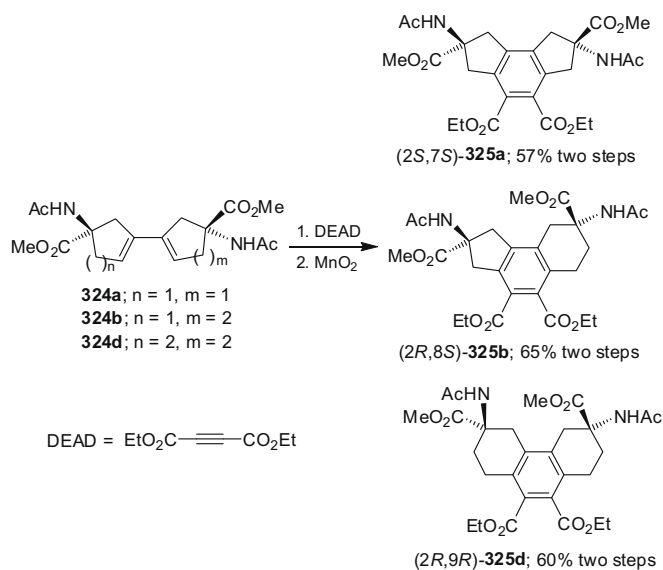


Scheme 69.

of **349** under identical conditions afforded the dipeptide **351** in 77% yield (Scheme 76).<sup>171</sup>

Møller and Undheim<sup>172</sup> reported the synthesis of spiro derivatives **354** and **357** by palladium-mediated 5-*exo-trig*-spiroannulation, and these compounds are precursors of functionalized cyclic quaternary  $\alpha$ -amino acids. Thus, the lithiation of **352** followed by addition of 2,3-dibromopropene gave the diene **353** in 60% yield and >98% de, and treatment of **353** with a catalytic amount of Pb(OAc)<sub>2</sub> in the presence of PPh<sub>3</sub>/Ag<sub>2</sub>CO<sub>3</sub> afforded the spiro compound **354** in 60% yield. In a similar way, reaction of **355**, obtained from **352**,<sup>172b</sup> produced the spiro derivative **356** in 60% yield, and treatment with a catalytic amount of NiCl<sub>2</sub>(dppp) and MeMgBr led to compound **357** in 64% yield (Scheme 77).

On the other hand, aldol reaction of **358a,b** using Cs<sub>2</sub>CO<sub>3</sub> as a base in acetonitrile afforded the spiroannulated compounds **359a,b** in 49% and 63% yield, respectively, and subsequent hydrolysis with 0.1 M TFA gave the amino esters **360a,b** in 56% and 59% yield, respectively (Scheme 78). Using this methodology the  $\alpha$ -amino acid methyl esters **360c-f** were obtained from the appropriate substrates.<sup>173</sup>



Scheme 70.

### 2.3. Cycloadditions and related reactions

Direct incorporation of an 'amino acid synthetic equivalent' into an alkene by transition metal catalyzed diazo decomposition has also been used for the synthesis of quaternary 1-aminocyclopropanecarboxylic acids.<sup>174,175</sup> For example, the asymmetric catalytic cyclopropanation of styrene with  $\alpha$ -nitro- $\alpha$ -diazocarbonyl compounds **361a–d** in the presence of a catalytic amount of **362–366** as a chiral catalyst afforded the cyclopropane derivatives *trans*- and *cis*-**367a–d** in good selectivity *trans:cis*, but with low enantioselectivity.<sup>176</sup> The results are summarized in Table 6.

Moreau and Charette<sup>177</sup> reported the catalytic asymmetric cyclopropanation of styrene with iodonium ylides derived from nitroacetates. For example, reaction of phenyliodonium with methyl nitroacetate gave the corresponding phenyliodonium ylide **368**, which by cyclopropanation reaction with styrene in the presence of a catalytic amount of isopropilidene bis(4-phenyl-2-oxazo-

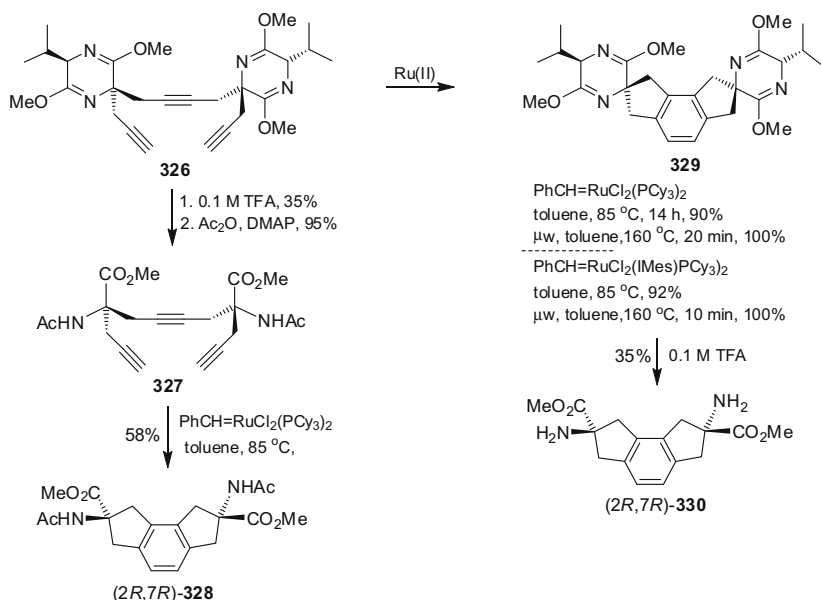
line) **366a** and  $\text{AgSbF}_6$ , afforded the methyl 1-nitrocyclopropyl carboxylate **367a** in 79% yield and excellent diastereo and enantioselectivity (similar results were obtained using others alkyl and aryl alkenes). Reduction of the nitro group of **367a** with  $\text{Zn}/\text{HCl}$  in 2-propanol furnished the aminoester **369** in 89% yield (Scheme 79).

On the other hand, reaction of chiral carbenes **370a,b** with terminal olefins in toluene under reflux produced the corresponding cyclopropanes **371a,b** and **372a,b** as a mixture of both *cis* diastereoisomers in low yield and 2:1 and 1.5:1 diastereoisomeric ratio, respectively, with a predominance of **371a,b** (Scheme 80).<sup>178</sup>

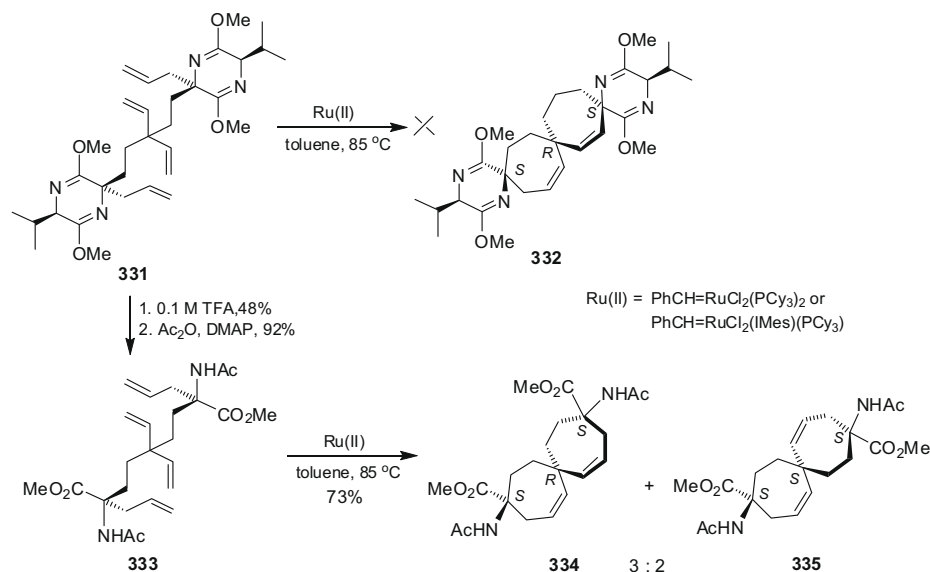
Reaction of (*Z*)-**373** with (–)-menthol in the presence of bis-(dibutylchlorotin)oxide gave the aminoacrylate (*Z*)-**374** in 78% yield, and subsequent treatment with diazomethane in dichloromethane produced the  $\Delta^1$ -pyrazolines **375a** and **375b** in 93% yield and 1.8:1 dr, (reversal of diastereoselectivity was observed when (+)-menthol was used as chiral auxiliary). Heating of diastereoisomerically pure **375a** and **375b** at 150 °C afforded the constrained cysteines derivatives (1*S*,2*S*)- and (1*R*,2*R*)-**376**, respectively, in good yield and diastereoselectivity. Saponification of (1*S*,2*S*)-**376** with  $\text{NaOH}$  in methanol gave the carboxylic acid (1*S*,2*S*)-**377** in 44% yield (Scheme 81).<sup>179</sup>

1,3-Dipolar cycloaddition of  $\alpha,\beta$ -unsaturated compound **379**, obtained from Horner–Wadsworth–Emmons reaction of (*S*)-**294** and the phosphonate **378**, with diazomethane followed by photolysis of the resultant pyrazoline gave the cyclopropane derivative **380** in 87% yield.<sup>180</sup> Hydrolysis of the acetonide in **380** with  $\text{HCl}$  afforded the corresponding diol, which when oxidized with  $\text{NaIO}_4$  produced the aldehyde (1*R*,2*S*)-**381** in good yield. Reduction of **381** with  $\text{NaBH}_4$  and subsequent saponification of methyl ester gave (1*R*,2*S*)-**382** in good yield. Finally, cleavage of the *N*-Boc protecting group in (1*R*,2*S*)-**382** followed by treatment with propylene oxide provided the  $\alpha$ -aminocyclopropanecarboxylic acid (1*R*,2*S*)-**170** in excellent yield (Scheme 82).<sup>181</sup>

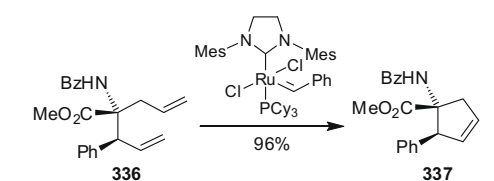
Reaction of aldehyde (1*S*,2*R*)-**381** with *N*-methylglycine and [60]fullerene afforded the fulleropyrrolidine **384** in 25% yield, through the 1,3-dipolar cycloaddition of the in situ produced azomethine ylide **383**. Cleavage of the *N*-Boc protecting group of **384** with TMSI in chloroform led to compound **385** in 89% yield (Scheme 83).<sup>182</sup>



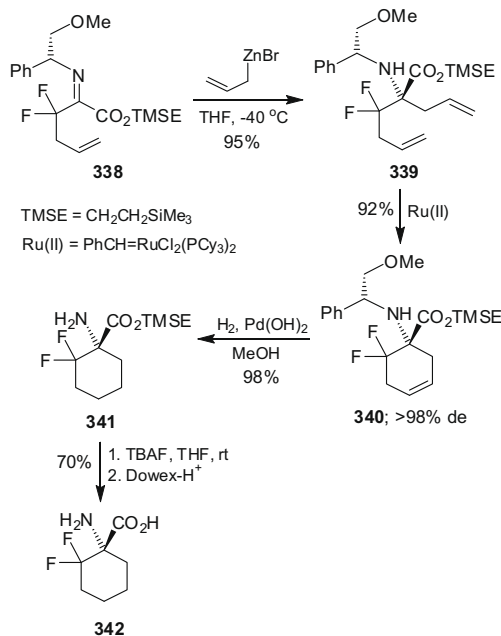
Scheme 71.



Scheme 72.

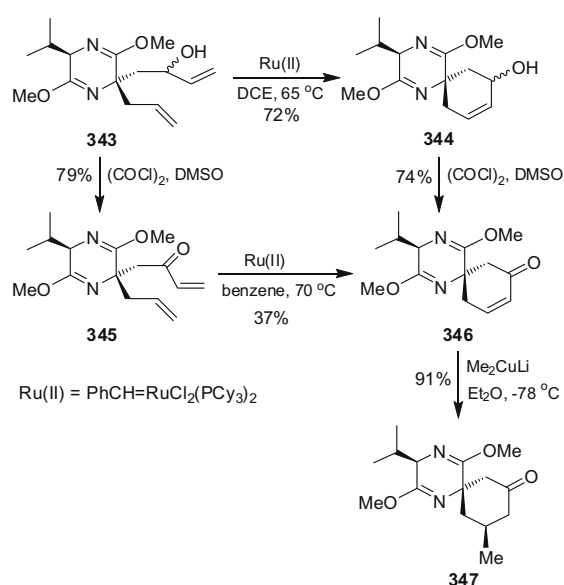


Scheme 73.



Scheme 74.

On the other hand, 1,3-dipolar cycloaddition of diazomethane to  $\alpha,\beta$ -unsaturated compound **386** followed by photolysis of the resultant pyrazoline gave the cyclopropane derivative **387** in 48% yield, which by saponification of the methyl ester and cleavage of the acetonide using pyridinium *p*-toluenesulfonic acid (PPTS), gave the keto amino acid (1*R*,2*R*,1'*R*,3'*R*)-**388** in 35% yield. In a sim-

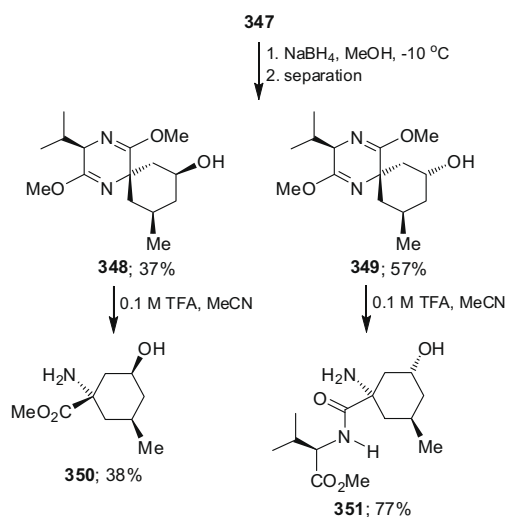


Scheme 75.

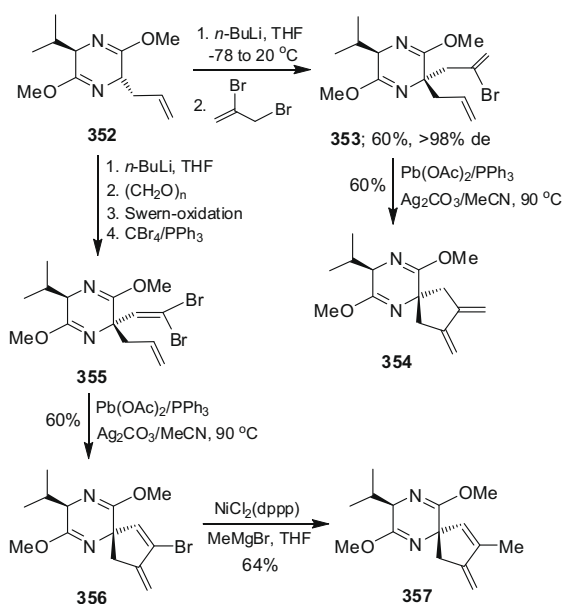
ilar way, reaction of **389** with diazomethane followed by photolysis produced the diprotected quaternary  $\alpha$ -amino acid (1*S*,2*S*,1'*S*,3'*R*)-**390** in 45% yield (Scheme 84).<sup>183</sup>

Recently, Avenoza et al.<sup>184</sup> reported the asymmetric [2+2] cycloaddition of 2-acylaminoacrylates **391** with donor olefins **392** in the presence of a catalytic amount of sterically hindered aluminum aryloxides, such as methylaluminum bis(4-bromo-2,6-di-*tert*-butyl phenoxide) (MABR) and methylaluminumoxane (MAO) as a Lewis acid. These reactions gave the constrained protected serine analogues *c*<sub>4</sub>Ser(OBn) **393a–h** and **394**.<sup>185</sup> The results are summarized in Table 7. The best diastereoselectivity was obtained in the reaction of vinyl ether bearing (1*R*,2*S*)-2-phenylcyclohexyl fragment as a chiral auxiliary (entries 3, 6 and 9).

Recently, Tanaka et al.<sup>186</sup> reported the synthesis of  $\alpha,\alpha$ -disubstituted  $\alpha$ -amino esters **396a–g** by Rh-catalyzed [2+2+2] cycloaddition of 1,6-diyne **395a–g** with protected dehydroamino ester **391c**. In all cases the compounds **396a–g** were obtained in good yield and with good enantioselectivity and, in the case of



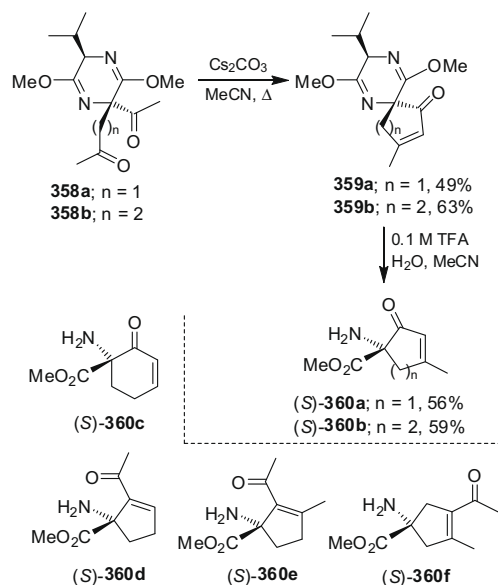
Scheme 76.



Scheme 77.

unsymmetrical 1,6-diyne, moderate regioselectivity was observed. The results are summarized in Table 8.

Pyne et al.<sup>187</sup> reported the synthesis of conformationally constrained cyclopentenylglutamate analogues in a regioselective and diastereoselective manner using a formal [3+2] cycloaddition reaction of chiral dehydroamino esters. For example, [3+2] cycloaddition of ylide **398a** generated in situ from ethyl 2,3-dienoate **397a** with the chiral dehydroamino ester (*R*)-**399** gave the mixture of the two regioisomers **400a** and **401a** in 17% and 49% yield, respectively, after column chromatographic separation. In a similar way, cycloaddition of **398b,c**, obtained from **397b,c** with (*R*)-**399** afforded the spiro compounds **400b,c** in 38% and 78% yield, respectively, as single diastereoisomers. Hydrolysis of enantiomerically pure **400a–c** with HCl followed by ion-exchange chromatography and subsequent treatment with HCl produced the conformationally constrained amino acids **402a–c** in good yield as chlorohydrate salt. In a similar way, **401a** was transformed into the quaternary  $\alpha$ -amino acid (*S*)-**403** (Scheme 85).



Scheme 78.

Reaction of dehydroamino ester **404** with ethyl butynoate **405** in the presence of PPh<sub>3</sub> gave the cycloadducts **406** and **407** in 87% yield and 60:40 dr, which by successive selective hydrolysis of the N=CPh<sub>2</sub> group, *N*-Cbz protection, preparative HPLC separation, and hydrolysis of the esters afforded the cyclic glutamic acid analogues (*R*)- and (*S*)-**402a** in good yield (Scheme 86).<sup>187</sup>

Diels–Alder reaction of (*S*)-**228c** with cyclopentadiene at room temperature gave, after flash chromatography, the cycloadduct *endo*-**408** in 85% yield and 15% of other diastereoisomers, and with cyclohexa-1,3-diene at 90 °C afforded the cycloadduct *endo*-**409** in 88% yield and 12% of other diastereoisomers. Hydrolysis of the imine moiety of the cycloadducts *endo*-**408** and *endo*-**409** followed by catalytic hydrogenation of double bond C=C and subsequent hydrolysis of the ester function with 6 N HCl produced the constrained  $\alpha$ -amino acids (*S*)-**410** and (*S*)-**411**, respectively, in good yield (Scheme 87).<sup>144,188</sup>

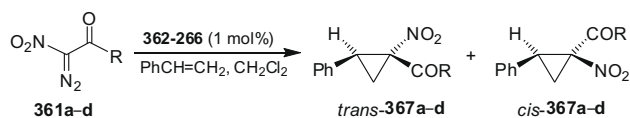
In a similar way, Diels–Alder reaction of (*S*)-**232c** with cyclopentadiene and cyclohexa-1,3-diene gave, after flash chromatography, the cycloadducts *endo*-**412** and *endo*-**413** as the main diastereoisomers, respectively. Catalytic hydrogenation of these compounds over Pd/C followed by hydrolysis with 6 N HCl and subsequent ion-exchange chromatography furnished the  $\alpha$ -amino acids (*S*)-**410** and (*S*)-**411** in moderate yield (Scheme 88).<sup>144</sup>

Diels–Alder cycloaddition of chiral methylene piperazine-2,5-diones **414a–g** with cyclopentadiene gave the four diastereoisomers *exo*-**415a–g**, *exo*-**416a–g**, *endo*-**417a–g**, and *endo*-**418a–g** in low to moderate yield and with good *exo/endo* selectivity. The results are summarized in Table 9.<sup>189</sup>

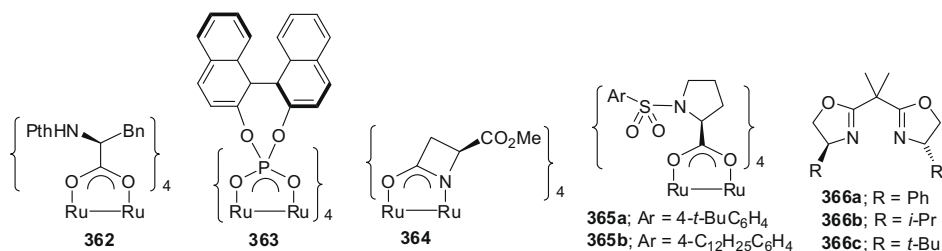
Diels–Alder cycloaddition of chiral acrylates **419a,b**, bearing (+)- or (–)-menthyl as a chiral auxiliary with cyclopentadiene in the presence of EtAlCl<sub>2</sub> or Mg(ClO<sub>4</sub>)<sub>2</sub> under thermal or ultrasound conditions gave the four diastereoisomers *exo*-**420a,b**, *exo*-**421a,b**, *endo*-**422a,b**, and *endo*-**423a,b** in moderate to good yield, good *exo/endo* selectivity, and good enantioselectivity. The results are summarized in Table 10.<sup>190</sup>

On the other hand, enantioselective Diels–Alder cycloaddition of achiral acrylate **424** with cyclopentadiene in the presence of a catalytic amount of chiral ligands **366a**, **425**, **426**, and **427**, and Mg(ClO<sub>4</sub>)<sub>2</sub> or Ce(OTf)<sub>4</sub>·H<sub>2</sub>O gave the spiro compounds mixture of two *endo*-**428a,b** and two *exo*-**429a,b**, both with poor enantioselectivity.<sup>190,191</sup> The results are summarized in Table 11.

**Table 6**  
Asymmetric cyclopropanation of styrene with  $\alpha$ -nitro- $\alpha$ -diazocarbonyl compounds **361a–d**

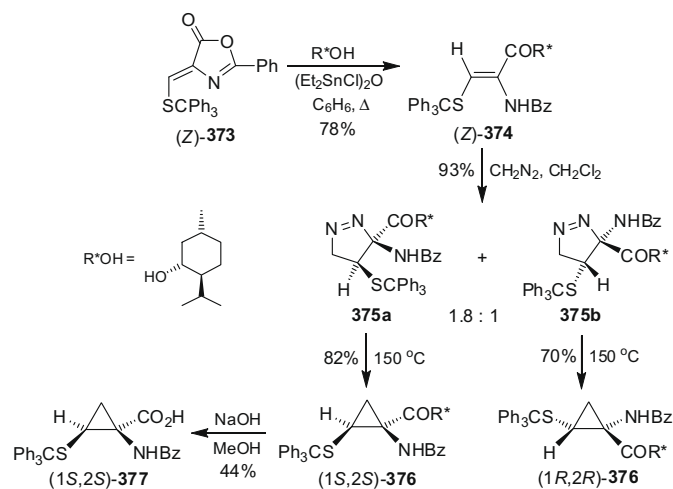
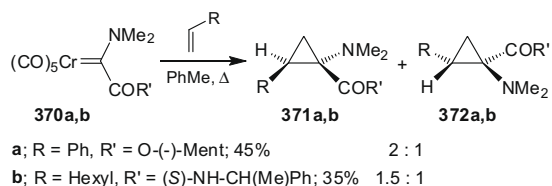
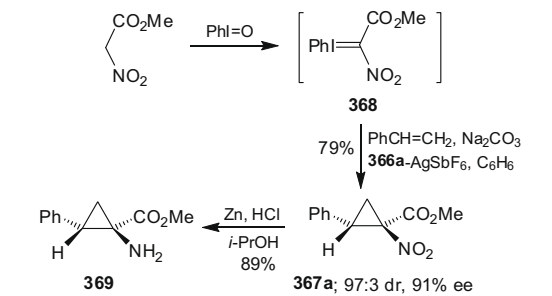


Substrate	Catalyst	Additive	Yield (%)	Ratio (trans:cis)	% ee (trans)	% ee (cis)
<b>361a</b> ; R = OMe	<b>362</b>	—	75	86:14	28	13
<b>361b</b> ; R = OEt	<b>362</b>	—	72	83:17	30	0
<b>361c</b> ; R = <i>Or</i> -Bu	<b>362</b>	—	68	68:32	41	6
<b>361d</b> ; R = Ph	<b>362</b>	—	64	39:61	31	13
<b>361b</b> ; R = OEt	<b>363</b>	—	71	75:25	13	16
<b>361b</b> ; R = OEt	<b>364</b>	—	76	86:14	33	0
<b>361b</b> ; R = OEt	<b>365a</b>	—	89	89:11	2	17
<b>361b</b> ; R = OEt	<b>365b</b>	—	74	79:21	8	10
<b>361a</b> ; R = OMe <sup>a</sup>	<b>366a</b>	(BzO) <sub>2</sub>	27	90:10	nd	nd
<b>361a</b> ; R = OMe <sup>a</sup>	<b>366a</b>	EDA (20%)	55	90:10	72	51
<b>361a</b> ; R = OMe <sup>a</sup>	<b>366a</b>	EDA (10%)	52	90:10	66	49
<b>361a</b> ; R = OMe <sup>b</sup>	<b>366a</b>	PhNHNH <sub>2</sub>	39	90:10	70	49
<b>361a</b> ; R = OMe <sup>a</sup>	<b>366b</b>	EDA (10%)	16	95:05	68	nd
<b>361a</b> ; R = OMe <sup>a</sup>	<b>366c</b>	EDA (10%)	7	95:05	63	nd



<sup>a</sup> In the presence of 5 mol % of Cu(MeCN)<sub>4</sub>PF<sub>6</sub>.

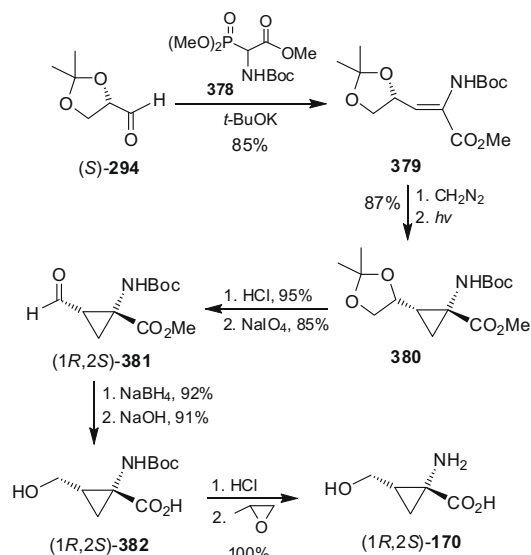
<sup>b</sup> Cu(II)OTf<sub>2</sub> was used as the copper source.



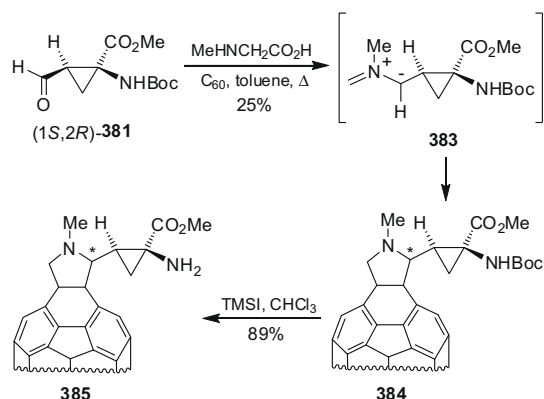
amount of the second *exo*-**431b** (0.3%) and *endo*-**432b** (0.9%) isomers were detected). Hydrogenation of the C=C double bond of diastereoisomerically pure *exo*-**431** followed by selective hydrolysis with Na<sub>2</sub>CO<sub>3</sub> and subsequent oxidation of alcohol group led to the  $\beta$ -keto ester *exo*-**433** in excellent yield. This compound was used in the synthesis of *cis*-3-carboxycyclopentylglycine (1*S*,3*R*,1'*S*)-**434a** and its epimer (1*S*,3*R*,1'*R*)-**434b** (Scheme 89).

Gelmi et al.<sup>194</sup> reported that Diels–Alder cycloaddition of chiral aminoacrylate **391a**, bearing the (*-*)-8-phenylmenthyl group as a

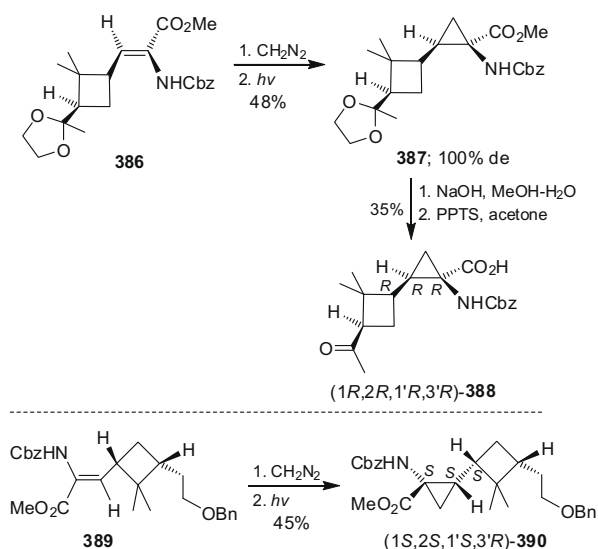
Recently, Pellegrino et al.<sup>192</sup> reported that the Diels–Alder cycloaddition of acylaminoacrylate **430**, bearing the (*-*)-8-phenylmenthyl group as a chiral auxiliary, with cyclopentadiene in the presence of a catalytic amounts of Mg(ClO<sub>4</sub>)<sub>2</sub> under ultrasound conditions gave the adducts *exo*-**431a,b** and *endo*-**432a,b** in 87% yield and 7:1 dr, with a predominance of *exo*-**431a** (only trace



Scheme 82.



Scheme 83.



Scheme 84.

chiral auxiliary, with cyclopentadiene in the presence of a catalytic amount of  $\text{Mg}(\text{ClO}_4)_2$  under ultrasound conditions gave the norbornenes *exo*-**435** and *endo*-**436** in 84% yield, a ratio of 83:17 and

with high diastereoselectivity (*exo* 97% and *endo* 96%). Selective hydrolysis of major *exo*-**435** produced the enantiopure constrained  $\alpha$ -amino acid *exo*-**437** in 79% yield (Scheme 90).

On the other hand, oxidative cleavage of the C=C double bond of norbornene *exo*-**435** with potassium permanganate furnished (1*S*,2*R*,4*S*)-**438** in 81% yield, and selective hydrolysis of the ester function under basic conditions provided the tricarboxylic acid (1*S*,2*R*,4*S*)-**439** in 80% yield. Finally, hydrolysis of amide function of (1*S*,2*R*,4*S*)-**439** with 6 M HCl gave the quaternary  $\alpha$ -amino acid (1*S*,2*R*,4*S*)-**440** in 83% yield. In a similar way, (1*R*,2*S*,4*R*)-*endo*-**436** was transformed into quaternary  $\alpha$ -amino acid (1*S*,2*S*,4*R*)-**441** (Scheme 91).<sup>193,194</sup>

Dihydroxylation of C=C double bond in the norbornene *exo*-**435** with NMO in the presence of a catalytic amount of osmium tetroxide afforded the diol *exo*-**442**,<sup>195</sup> which by cleavage of C<sub>5</sub>–C<sub>6</sub> bond with sodium periodate gave the bisaldehyde (1*S*,2*R*,4*S*)-**443**. Reductive amination of bisaldehyde **443** with *p*-methoxybenzylamine (PMBNH<sub>2</sub>) and sodium triacetoxyborohydride as a reducing agent provided the derivative (1*S*,5*S*,6*S*)-*exo*-**444**, which by treatment with sodium in methanol produced the constrained  $\alpha$ -amino acid (1*S*,5*S*,6*S*)-*exo*-**445** in 57% overall yield. In a similar way, (1*R*,2*S*,4*R*)-*endo*-**436** was transformed into quaternary  $\alpha$ -amino acid (1*R*,5*R*,6*S*)-*endo*-**446** (Scheme 92).<sup>196</sup>

On the other hand, reductive amination of bisaldehydes ( $\pm$ )-**447a,b** using (*R*)- $\alpha$ -MBA and sodium triacetoxyborohydride afforded, after chromatographic separation, the azabicyclo derivatives (1*R*,5*R*,6*R*,1'*R*)-*exo*-**448a**, (1*S*,5*S*,6*S*,1'*R*)-*exo*-**448b**, (1*R*,5*R*,6*S*,1'*R*)-*endo*-**449a**, and (1*S*,5*S*,6*R*,1'*R*)-*endo*-**449b** in 25%, 28%, 12%, and 10% yield, respectively. Cleavage of the benzyl group by hydrogenolysis over Pd/C on diastereoisomerically pure *exo*-**488a,b** and *endo*-**489a,b** followed by hydrolysis with 6 N HCl gave the constrained  $\alpha$ -amino acids (1*R*,5*R*,6*R*)-*exo*-**450**, (1*S*,5*S*,6*S*)-*exo*-**450**, (1*R*,5*R*,6*S*)-*exo*-**451**, and (1*S*,5*S*,6*R*)-*exo*-**451** in good yield (Scheme 93).<sup>197</sup>

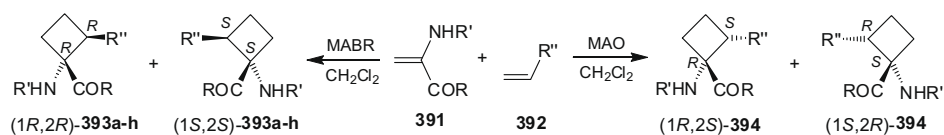
## 2.4. Resolution procedures

### 2.4.1. Chemical resolution

Mash et al.<sup>198</sup> reported the synthesis of 2-amino-4-bromo-7-methoxyindane-2-carboxylic acid (*S*)-**461** by chemical resolution. In this context, a double alkylation of ethyl glycinate **452a** with 2,3-bis(bromomethyl)-4-bromoanisole **453** afforded the racemic compound ( $\pm$ )-**454**, which by hydrolysis of imine function furnished the corresponding  $\alpha$ -amino ester ( $\pm$ )-**455** in 33% yield. Coupling of ( $\pm$ )-**455** with the *N*-Boc-phenylalanine (*S*)-**456** in the presence of benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) gave a 50:50 mixture of the dipeptides (*R,S*)-**457** and (*S,S*)-**458** in 93% yield, and these were separated by column chromatography. Cleavage of the *N*-Boc protecting group of diastereoisomerically pure (*S,S*)-**458** with TFA produced the dipeptide (*S,S*)-**459**, which was treated with phenylisothiocyanate and triethylamine to furnish the corresponding thiourea (*S,S*)-**460** in 71% yield. Finally, hydrolysis of (*S,S*)-**460** with HCl provided the quaternary  $\alpha$ -amino acid (*S*)-**461** in 83% yield (Scheme 94). The  $\alpha$ -amino acid (*S*)-**461** has been used in the synthesis of piperazine-2,5-diones.

Monn et al.<sup>199</sup> reported the synthesis of heterobicyclic  $\alpha$ -amino acids (–)– and (+)–**465a,b** by resolution, and these compounds were evaluated as agonist for group II mGlu receptors. In this context, reaction of furan or thiophene with ethyl diazoacetate in the presence of  $\text{Rh}_2(\text{OAc})_4$  produced the bicyclic adducts ( $\pm$ )-**462a,b** in (20–40%) yield. Reaction of ( $\pm$ )-**462a,b** with  $(\text{NH}_4)_2\text{CO}_3$  and KCN followed by saponification gave the ( $\pm$ )-carboxylic acids **463a,b** in 72% yield. These compounds were resolved by selective crystallization of either the (*R*)- or (*S*)-phenylglycinol salts (–)–**464** or (+)–**464**, respectively. Hydrolysis of diastereoisomerically pure salts

**Table 7**  
[2+2] Cycloaddition of dehydroamino esters **391** with vinyl ethers **392**



Entry	Product	R	R'	R''	Yield (%)	(1R,2R):(1S,2S)
1	<b>393a</b>		COMe	OEt	13	15:85
2	<b>393b</b>		COMe	OEt	30	40:60
3	<b>393c</b>	OMe	COMe		45	>98:02
4	<b>393d</b>	OMe	COMe		70	76:24
5	<b>393e</b>	OMe	COMe		55	60:40
6	<b>393f</b>	OMe	COCF <sub>3</sub>		18	>98:02
7	<b>393g</b>	OMe	COCF <sub>3</sub>		56	80:20
8	<b>393h</b>	OMe	COCF <sub>3</sub>		30	60:40
9	<b>394</b>	OMe	COMe		62	02:98 <sup>a</sup>

<sup>a</sup> The configuration of the products was (1R, 2S) and (1S, 2R) with the predominance of (1S, 2R).

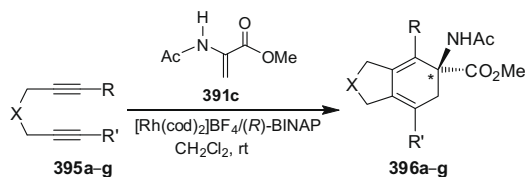
(–)-**464a,b** and (+)-**464a,b** followed by ion-exchange chromatography furnished the enantiomerically pure (–)- and (+)-**465a,b** in good yield (Scheme 95).

The diastereoisomer (–)-**465b** has been transformed into sulfoxides **469** and **470** as well as sulfone **472**, and these compounds were evaluated as potent, selective, and orally bioavailable agonist for mGlu2/3 receptors. Thus, esterification of (–)-**465b** with thionyl chloride in methanol followed by treatment with (Boc)<sub>2</sub>O gave the methyl ester **466** in 79% yield, which by oxidation with *m*-CPBA afforded the sulfoxides mixture **467** and **468** in 5% and 89% yield, respectively. Hydrolysis of diastereoisomerically pure **467** and **468** produced the quaternary  $\alpha$ -amino acids **469** and **470** in 56% and 69% yield, respectively. On the other hand, oxidation of sulfoxide function in **467** with *m*-CPBA provided the corresponding sulfone **471** in 84% yield, which by hydrolysis afforded the quaternary  $\alpha$ -amino acid **472** in 71% yield (Scheme 96).<sup>200</sup>

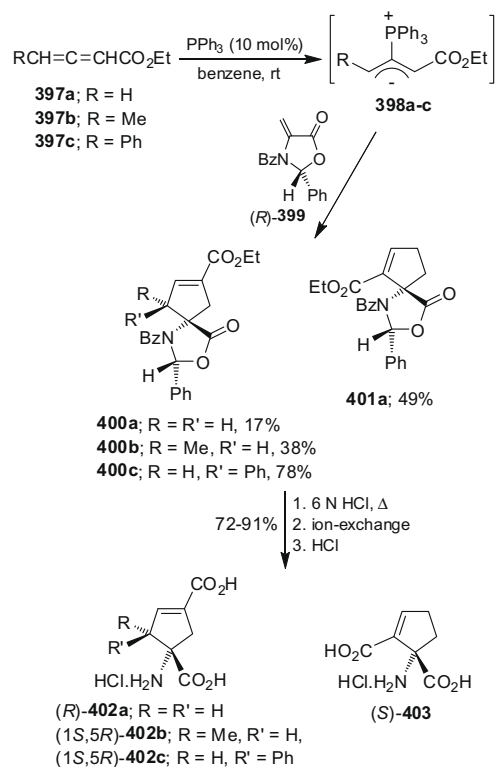
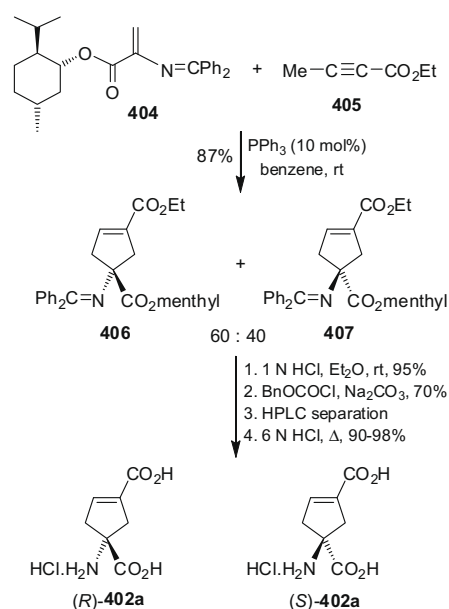
On the other hand, Bucher–Bergs reaction of 6-bromo-2-tetralone **473** with (NH<sub>4</sub>)<sub>2</sub>CO<sub>3</sub> and KCN gave the spirohydantoin **474** in 81% yield, which by cleavage of the hydantoin ring and esterification afforded the methyl ( $\pm$ )-2-amino-6-bromotetraline-2-carboxylate **475** in 54% yield. Resolution of ( $\pm$ )-**475** as the *L*-mandelic acid salt produced the ammonium salt (*S,S*)-**476** in 25% yield, and treatment with (Boc)<sub>2</sub>O/Et<sub>3</sub>N followed by basic hydrolysis produced the constrained *N*-Boc  $\alpha$ -amino acid (*S*)-**477** in 77% yield. This compound was converted in four steps into (2*S*)-*N*-Boc-amino-6-(diethylphosphono)tetraline-2-carboxylic acid **478** (Scheme 97).<sup>201</sup>

Treatment of ( $\pm$ )-**480**, which is readily obtained from ( $\pm$ )-**479**, with (*S*)-phenylalanine cyclohexylamide **481** in *N*-methylpyrrolidin-2-one (NMP) at 90 °C followed by column chromatography separation produced the diastereoisomerically pure (1*S*,2*S*,1'*S*)-**482a** and (1*R*,2*R*,1'*S*)-**482b** in 36% and 35% yield, respectively.



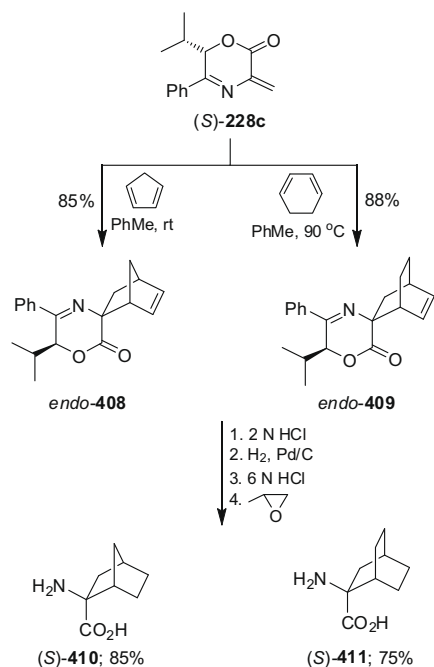
**Table 8**Rh(I)/(*R*)-BINAP-catalyzed enantioselective [2+2] cycloaddition of **395a–g** with **391c**

Substrate	Product (%) yield (% ee)
	 <b>396a</b> ; 95% (96% ee)
	 <b>396b</b> ; 90% (93% ee)
	 <b>396c</b> ; 91% (98% ee)
	 <b>396d</b> ; 68% (99% ee)
	 <b>396e</b> ; 84% (99% ee)
	 <b>396f</b> ; 53% (99% ee) <b>396f'</b> ; 20% (99% ee)
	 <b>396g</b> ; 67% (99% ee)

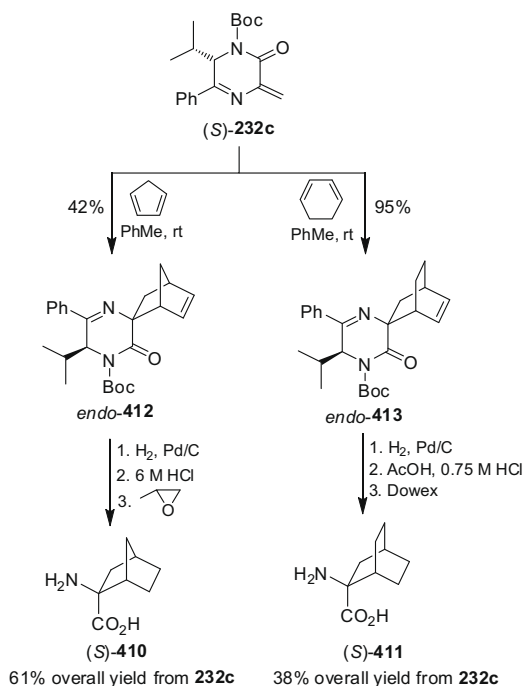
**Scheme 85.****Scheme 86.**

Subsequent hydrolysis and treatment with propylene oxide furnished the 1-amino-2-hydroxycyclohexanecarboxylic acid (1*S*,2*S*)- and (1*R*,2*R*)-**99a** in good yield (Scheme 98).<sup>202</sup>

In a similar way, treatment of ( $\pm$ )-**483** with (*S*)-2-acetoxypropionyl chloride (**S**)-**484** in the presence of triethylamine followed by column chromatography separation gave the diastereoisomerically pure (1*S*,2*R*,1'*S*)-**485** and (1*R*,2*S*,1'*S*)-**486** in 40% and 50% yield, respectively. Hydrogenation of (1*S*,2*R*,1'*S*)-**485** and (1*R*,2*S*,1'*S*)-**486** over Pt/C followed by hydrolysis and subsequent treatment



Scheme 87.



Scheme 88.

with propylene oxide led to (1*S*,2*R*)- and (1*R*,2*S*)-**100a** in good yield (Scheme 99).<sup>202</sup>

Recently, Gelmi et al.<sup>194</sup> reported the synthesis of the four diastereoisomers of constrained  $\alpha$ -amino acids *exo*-**437** and *endo*-**487** by resolution. In this context, treatment of ( $\pm$ )-*exo*-**437** with (*R*)- $\alpha$ -MBA gave the corresponding diastereoisomeric salts, hydrolysis of which afforded after crystallization the enantiomerically pure (1*R*,2*R*,4*R*)-**437** and (1*S*,2*S*,4*S*)-**437** in 31% and 37% yield, respectively. In a similar way, the resolution of ( $\pm$ )-*endo*-**487** gave the enantiomerically pure (1*R*,2*S*,4*R*)-**487** and (1*S*,2*R*,4*S*)-**487** in 42 and 40% yield, respectively (Scheme 100).

Reaction of *N*-protected amino acids RCO-Bin-OH ( $\pm$ )-**488a,b** with (*S*)-**481** in the presence of *N*-hydroxybenzotriazole (BtOH) and *N*-ethyl-*N'*-dimethylaminopropylcarbodiimide hydrochloride (EDC) in  $\text{CH}_2\text{Cl}_2$  followed by column chromatography separation afforded the diastereoisomerically pure (*R,S*)-**489a,b** and (*S,S*)-**490a,b** in good yield. Hydrolysis of diastereoisomerically pure (*R,S*)-**489a,b** and (*S,S*)-**490a,b** followed by esterification with MeOH/HCl furnished the H-Bin-OMe (*R*)- and (*S*)-**491** in good yield (Scheme 101).<sup>203</sup>

On the other hand, reaction of racemic diesters ( $\pm$ )-*cis*-**492** with commercially available (1*S*,2*S*,5*S*)-2-hydroxy-3-pinanone **493** in the presence of  $\text{BF}_3 \cdot \text{OEt}_2$  afforded the corresponding Schiff bases (*S*)-*cis* and (*R*)-*cis*-**494**. Crystallization of the diastereoisomeric mixture gave (*S*)-*cis*-**494** as a single diastereoisomer. The remaining diastereoisomer (*R*)-*cis*-**494** could not be isolated from mother liquor either by crystallization or by chromatography on silica gel. However, (*R*)-*cis*-**494** could be converted into the (*S*)-*cis*-**494** diastereoisomer by thermal equilibration. Hydrolysis of diastereoisomerically pure (*S*)-*cis*-**494** followed by treatment with  $(\text{Boc})_2\text{O}$  furnished the enantiomerically pure *N*-Boc-protected methyl ester (*S*)-*cis*-**495**. Under identical conditions, *N*-Boc-protected methyl ester (*S*)-*trans*-**497** was obtained from ( $\pm$ )-*trans*-**496** (Scheme 102).<sup>204</sup>

Treatment of racemic Boc-[OH]<sub>2</sub>-Bip-OMe ( $\pm$ )-**498** with the ditosylate (*R*)-**499** in the presence of  $\text{Cs}_2\text{CO}_3$  in DMF at 60 °C gave the methyl esters *N*-Boc-[2*O*-C-6]-(*R*)-Bip-OMe (*R,R*)-**500** and *N*-Boc-[2*O*-C-6]-(*S*)-Bip-OMe (*R,S*)-**501** in 25% and 26% yield, respectively. Cleavage of ether function of (*R,R*)-**500** with large excess of  $\text{BBr}_3$  followed by esterification with thionyl chloride and methanol produced the (*R*)-binaphthol and H-[OH]<sub>2</sub>-Bip-OMe (*R*)-**502** (Scheme 103).<sup>205,206</sup>

On the other hand, epoxidation of **319a** with *m*-CPBA afforded the epoxides **503** and **504** in 59% yield and 85:15 dr. Desymmetrization of the major epoxide isomer **503** with *s*-BuLi in the presence of (–)-sparteine gave the allyl alcohol (1*S*,4*R*)-**505** in 14% yield and 33% ee, which by hydrogenation over Pd/C provided the alcohol (1*S*,3*R*)-**256** in 71% yield. Treatment of (1*S*,3*R*)-**256** with acetic acid under Mitsunobu conditions produced the alcohol (1*S*,3*S*)-**255** in 58% yield, and subsequent mesylation followed by reaction with NaCN and hydrolysis with 6 M HCl led to (1*S*,3*R*)-ACPD **293** in 45% yield. In a similar way, (1*S*,3*R*)-**256** was transformed into (1*S*,3*S*)-ACPD **506** in 34% overall yield (Scheme 104).<sup>207</sup>

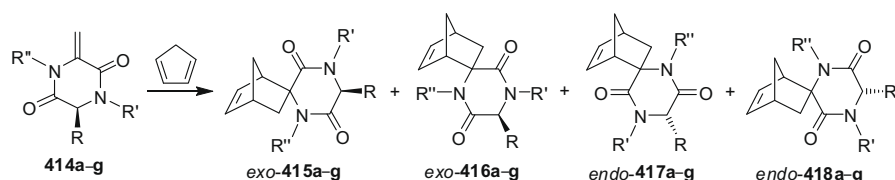
Recently, Varie et al.<sup>208</sup> reported a pilot-plant desymmetrization of the cyclic *meso*-epoxide **507a** using a chiral lithium amide prepared from (*R,R*)-diamine **508** and *n*-BuLi to give the allyl alcohol (1*S*,4*R*)-**509** in 72% yield and 99.3% ee. However, treatment of *meso*-epoxide **507b** under identical conditions gave the allyl alcohol (1*S*,4*S*)-**510** in only 3% yield and 48% ee (Scheme 105).

#### 2.4.2. Enzymatic resolution

Enzymatic hydrolysis of prochiral bis(2,2,2-trifluoroethyl)-2,2-dimethylcyclopropane-1,1-dicarboxylate **511** with pig liver esterase (PLE) gave the (*R*)-2,2-dimethyl-1-(2,2,2-trifluoroethoxycarbonyl)cyclopropane-1-carboxylic acid (*R*)-**512** in 62% yield and >95% ee, which by Curtius rearrangement with diphenylphosphoryl azide (DPPA) followed by work-up with ethanol gave the diprotected  $\alpha$ -amino acid (*S*)-**513** in 34% yield. Finally, basic hydrolysis of (*S*)-**513** produced the (*S*)-1-amino-2,2-dimethylcyclopropane-1-carboxylic acid (*S*)-**514** in 75% yield and >84% ee (Scheme 106).<sup>209</sup>

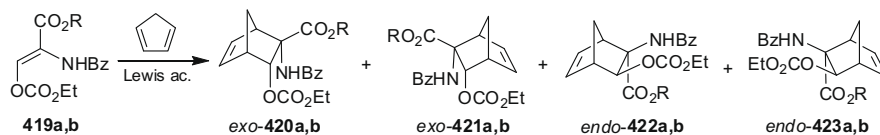
Recently, Beaulieu et al.<sup>210</sup> reported the pilot plant large-scale synthesis of (1*R*,2*S*)-1-amino-2-vinylcyclopropanecarboxylic acid methyl ester (1*R*,2*S*)-**196** from ( $\pm$ )-*trans*-**515** using inexpensive esterase enzyme (Alcalase) as a resolution agent. In this context, treatment of ( $\pm$ )-*trans*-**515**, obtained in three steps from **452b**, with a large excess of Alcalase under  $\text{Na}_2\text{HPO}_4$  buffer conditions at pH 8.1–8.2 produced (1*R*,2*S*)-**515** in 49% yield and 97% ee, and (1*S*,2*R*)-**516** with 99% ee, after separation.<sup>211</sup> Hydrolysis of

**Table 9**  
Diels–Alder cycloaddition of **414a–g** with cyclopentadiene



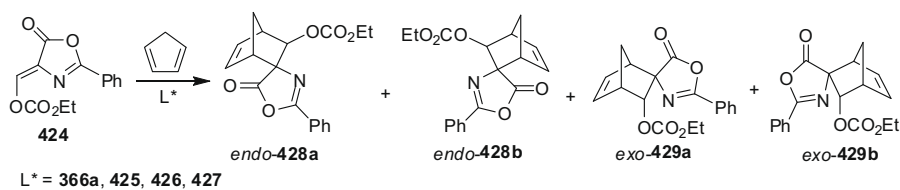
Dienophile	R	R'	R''	Yield (%)	<b>415:416:417:418</b>
<b>414a</b>	Me	Ac	H	60	10:17:1:1
<b>414b</b>	Me	Ac	Ac	50	Trace:1.2:trace:1
<b>414c</b>	Me	Me	H	<10	Not determined
<b>414d</b>	<i>i</i> -Pr	Ac	H	60	12:1.4:1:0
<b>414e</b>	<i>i</i> -Pr	Ac	Ac	Trace	Not determined
<b>414f</b>	4-AcOC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	Ac	H	60	7:1:1:0
<b>414g</b>	4-AcOC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	Ac	Ac	Trace	Not determined

**Table 10**  
Asymmetric Diels–Alder cycloaddition of **419a,b** with cyclopentadiene

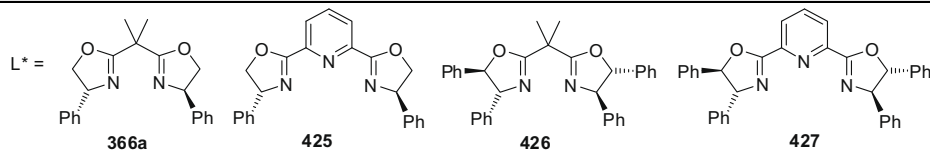


R	Conditions	Yield (%)	<i>exo:endo</i>	<b>420:421</b> (de)	<b>422:423</b> (de)
<b>419a</b>	(–)-Menthyl (EtAlCl <sub>2</sub> ,))	36	70:30	23:77 (54)	87:13 (74)
<b>419b</b>	(+)-Menthyl Mg(ClO <sub>4</sub> ) <sub>2</sub> , Δ	50	77:23	90:10 (80)	07:93 (86)
<b>419a</b>	(–)-Menthyl Mg(ClO <sub>4</sub> ) <sub>2</sub> , Δ	50	77:23	10:90 (80)	93:07 (86)
<b>419b</b>	(+)-Menthyl Mg(ClO <sub>4</sub> ) <sub>2</sub> ,))	90	78:22	89:11 (78)	07:93 (86)
<b>419a</b>	(–)-Menthyl Mg(ClO <sub>4</sub> ) <sub>2</sub> ,))	90	77:23	10:90 (80)	92:08 (84)

**Table 11**  
Enantioselective Diels–Alder cycloaddition of **424** with cyclopentadiene



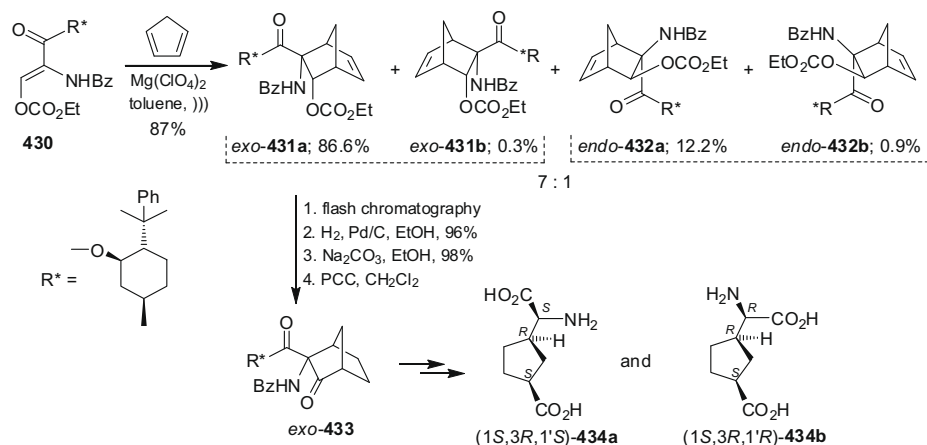
Conditions	<i>t</i> (h)	<i>exo:endo</i>	<i>endo</i> ratio	<i>exo</i> ratio
<b>366a</b> -Mg(ClO <sub>4</sub> ) <sub>2</sub>	48	75:25	43:57	50:50
<b>366a</b> -Ce(OTf) <sub>4</sub> ·H <sub>2</sub> O <sup>a</sup>	75	70:30	50:50	50:50
<b>425</b> -Mg(ClO <sub>4</sub> ) <sub>2</sub>	100	70:30	50:50	50:50
<b>425</b> -Ce(OTf) <sub>4</sub> ·H <sub>2</sub> O <sup>a</sup>	150	75:25	50:50	50:50
<b>426</b> -Mg(ClO <sub>4</sub> ) <sub>2</sub>	24	80:20	47:53	43:57
<b>427</b> -Mg(ClO <sub>4</sub> ) <sub>2</sub>	24	75:25	56:44	66:34
<b>427</b> -Ce(OTf) <sub>4</sub> ·H <sub>2</sub> O <sup>a</sup>	200	75:25	50:50	50:50



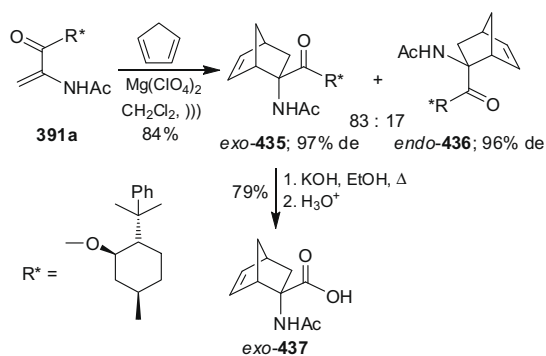
<sup>a</sup> In the presence of molecular sieves.

(1*R*,2*S*)-**196** with HCl gave the (1*R*,2*S*)-**196** in 64% yield as hydrochloride salt with >97% ee (Scheme 107). The vinyl-ACCA deriva-

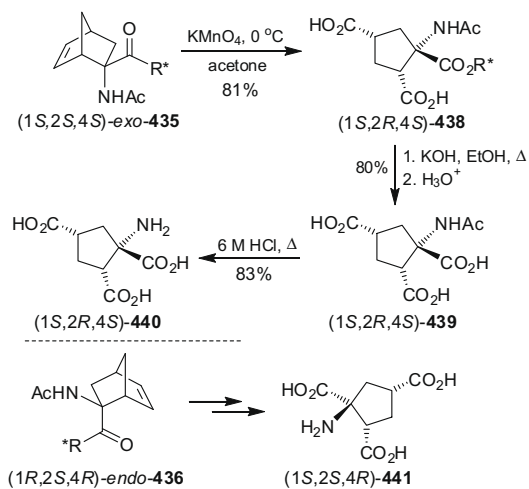
tive (1*R*,2*S*)-**196** is an important building block for the preparation of HCV protease inhibitors.<sup>212</sup>



Scheme 89.

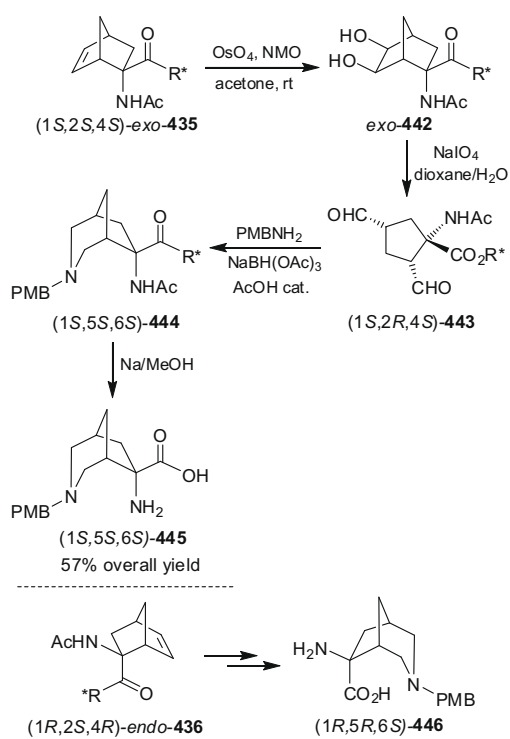


Scheme 90.



Scheme 91.

Kirihara et al.<sup>213</sup> reported an efficient synthesis of (*R*)- and (*S*)-1-amino-2,2-difluorocyclopropanecarboxylic acid **521** by lipase-catalyzed desymmetrization of diol **517** or diacetate **522**. Thus, lipase-catalyzed transesterification of prochiral diol **517** with vinyl acetate as the acyl donor in the presence of lipase PS from *Pseudomonas cepacia* in benzene and diisopropyl ether afforded the corresponding mono-acetylated product (*R*)-**518** in 97% yield and 91.3% ee. Oxidation of (*R*)-**518** followed by treatment with DPPA and subsequent work-up with *tert*-butyl alcohol and  $\text{Et}_3\text{N}$  under reflux

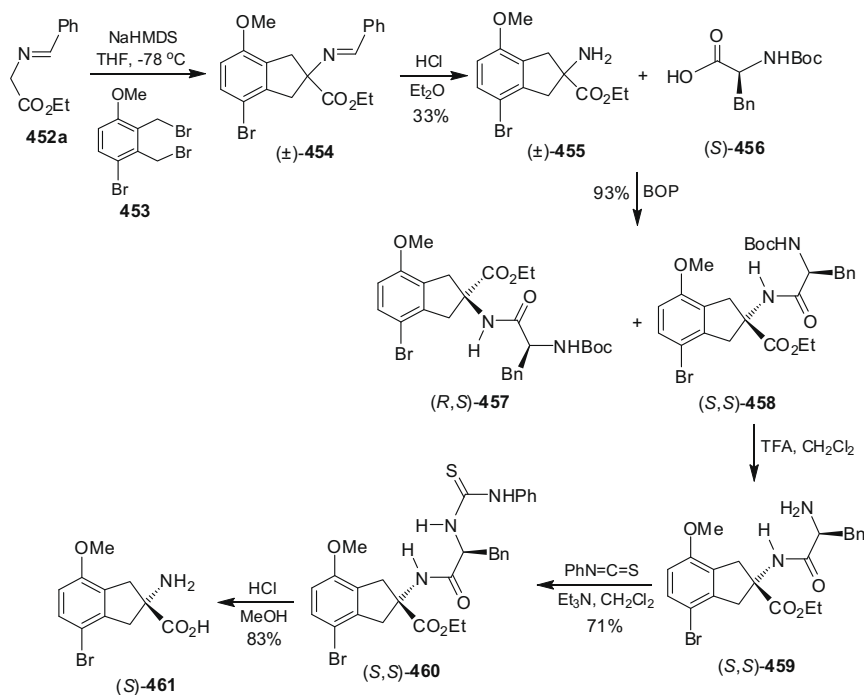
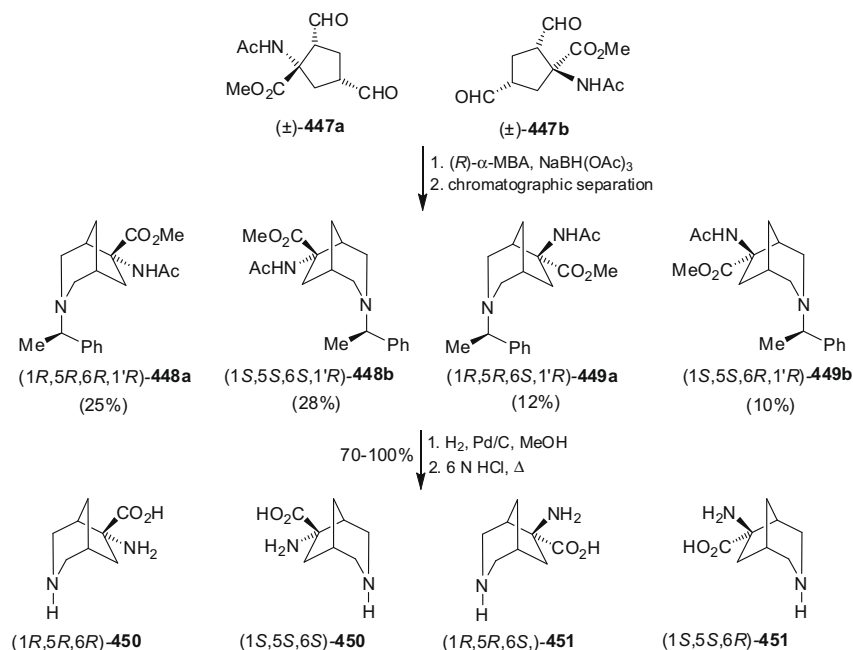


Scheme 92.

gave the carbamate (*R*)-**519** in 51% yield. Cleavage of the acetyl group of (*R*)-**519** produced the *N*-protected aminoalcohol (*R*)-**520** in 66% yield and >99% ee, which by oxidation followed by hydrolysis led to (*R*)-**521** in 99% yield as hydrochloride salt (Scheme 108).

On the other hand, lipase-catalyzed deacetylation of the prochiral diacetate **522** with lipase PS in a mixed solvent of acetone and phosphate buffer gave the corresponding mono-acetylated product (*S*)-**518** in 86% yield and 91.7% ee, which under identical conditions to those described in the Scheme 108, was transformed into (*S*)-1-amino-2,2-difluorocyclopropanecarboxylic acid **521** as hydrochloride salt (Scheme 109).<sup>213</sup>

Catalytic hydrolysis of ( $\pm$ )-**523** with lipase CALB from *Pseudomonas cepacia* in a mixed solvent of acetone and phosphate buffer gave the corresponding monoacid (3*S*,5*S*,6*S*)-**524** and the residual diester (3*R*,5*R*,6*R*)-**523**, both with >99% ee. Hydrolysis of (3*S*,5*S*,6*S*)-**524** and (3*R*,5*R*,6*R*)-**523** furnished the constrained

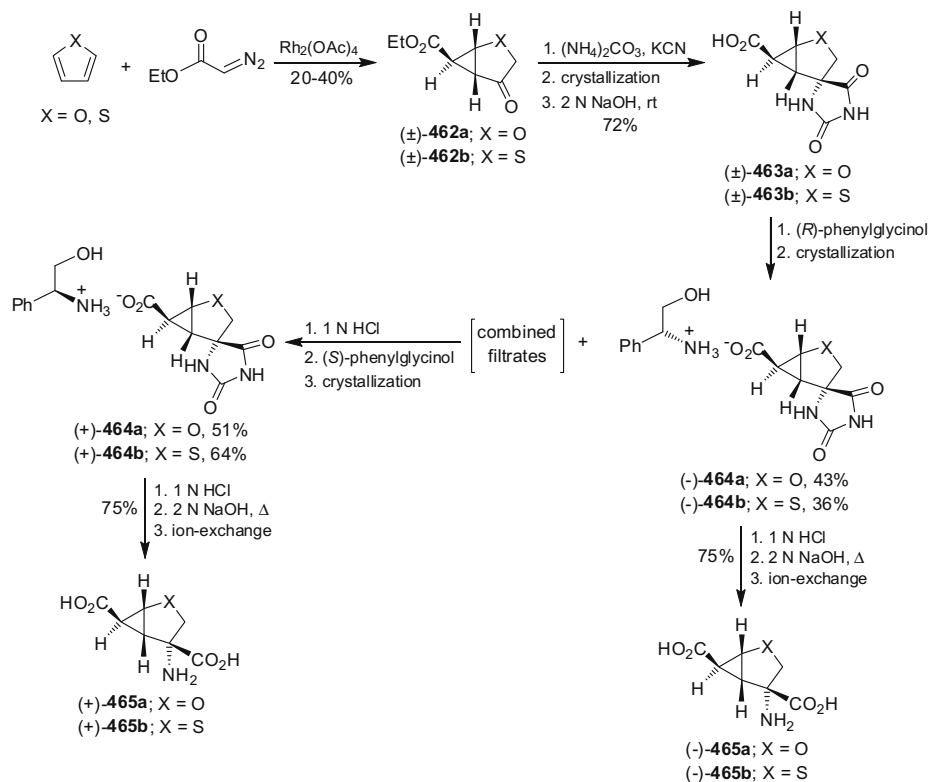


$\alpha$ -amino acids (3aS,5S,6aS)-**525** and (3aR,5R,6aR)-**525** in 60% and 74% yield, respectively (Scheme 110).<sup>214</sup>

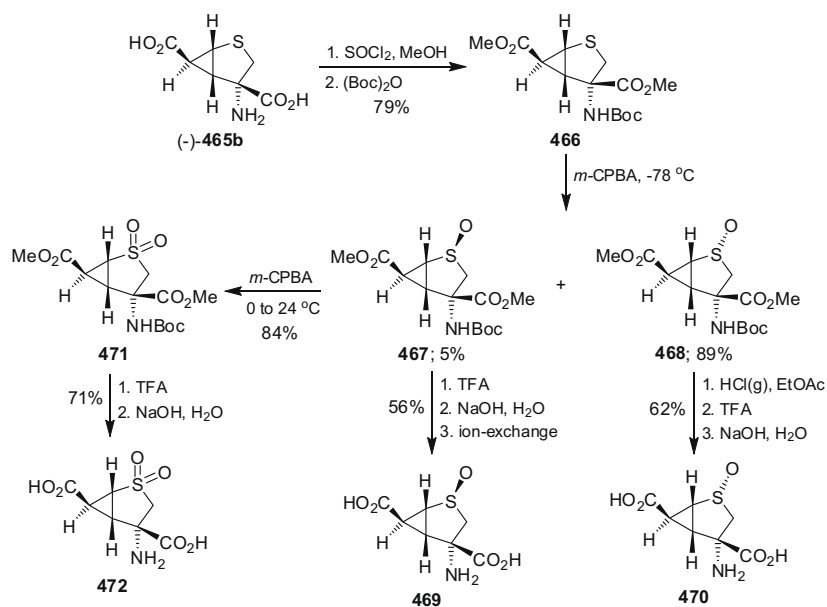
In a similar way, hydrolysis of (±)-**526** using lipase proleather (Subtilysin Carlsberg) in acetone and phosphate buffer gave the monoacid (3aR,5S,6aR)-**527**, the product derived from the hydrolysis of methyl ester linked to position 5, and the residual diester (3aS,5R,6aS)-**526**, both with >99% ee. Similar results were obtained with papain-catalyzed hydrolysis of (±)-**526**, but with reversal of the stereochemistry. Hydrolysis of (3aR,5S,6aR)-**527** and (3aS,5R,6aS)-**526** led to the constrained  $\alpha$ -amino acids (3aR,5S,6aR)-**528**

and (3aS,5R,6aS)-**528** in 78% and 64% yield, respectively (Scheme 111).<sup>214,215</sup>

On the other hand, the pig liver esterase (PLE) enzymatic desymmetrization of diacetate **529** afforded the monoacetate (S)-**530** with 80% ee along with diol **531**. The monoacetate (S)-**530** was transformed in three steps into diprotected alkyne (S)- and (R)-**532**. Addition of the carbanion derived from (S)-**532** to the lactone **533** gave the compound **534** in 68% yield as a 1:1 mixture of anomers. Partial reduction of the alkyne followed by the spiroketalization and subsequent cleavage of the silyl protecting groups



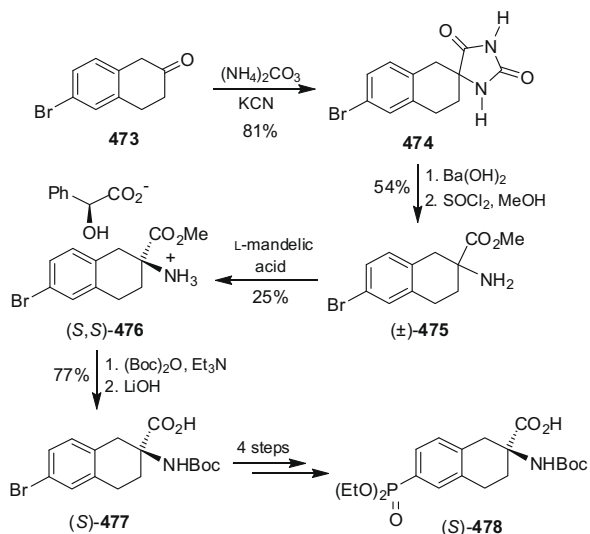
Scheme 95.



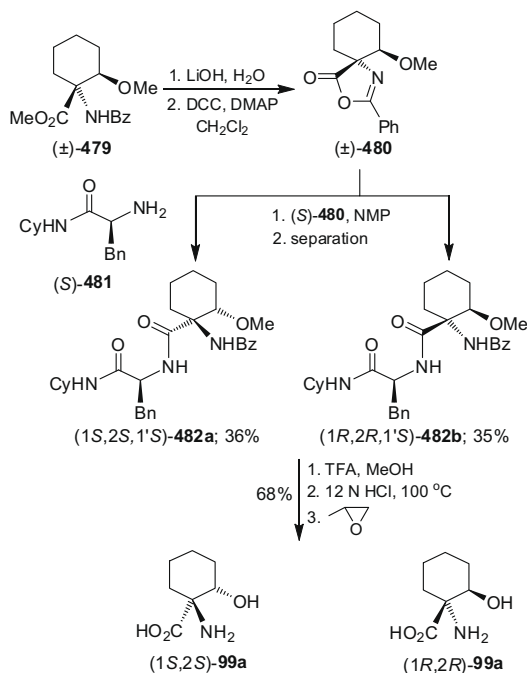
Scheme 96.

with TBAF, acetylation, and HPLC separation produced the spiro derivative **535** in 53% overall yield. Reduction of the azide and olefin functional groups and simultaneous removal of (DMB) protecting group in **535** in the presence of acetic anhydride furnished the acetamide **536** in 59% yield. Oxidation of **536** with Dess–Martin periodinane and NaClO<sub>2</sub> gave the  $\alpha$ -*N*-acetylgalactosaminylserine derivative **537** in 89% yield. In a similar way, (*R*)-**532** was transformed into derivative **538** (Scheme 112).<sup>216</sup>

Metathesis reaction of **539**, which is readily obtained by dialkylation of dimethyl malonate with 4-bromo-1-butene, in the presence of Grubbs catalyst gave the cycloheptene **540** in 98% yield. Epoxidation of this compound with *m*-CPBA followed by hydrolysis with sulfuric acid afforded the cycloheptane-*trans*-1,2-diol ( $\pm$ )-**541** in 80% yield. Kinetic resolution of ( $\pm$ )-**541** with Amano AK in vinyl acetate produced the diol (*4R,5R*)-**541** and the monoacetate (*4S,5S*)-**542** in 43% and 33% yield, respectively, both with >99%



Scheme 97.

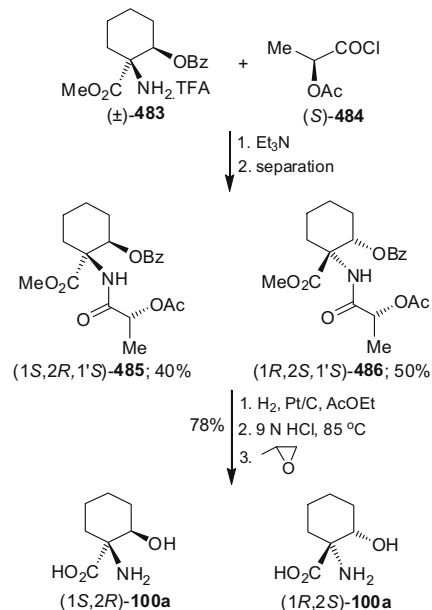


Scheme 98.

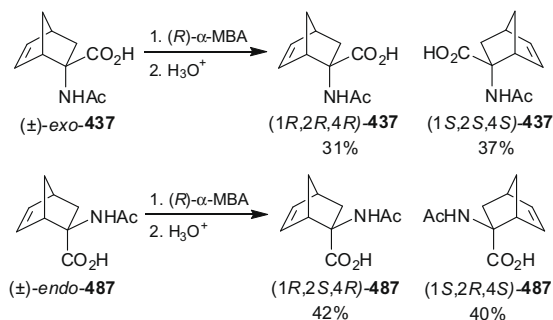
ee. Methylation of (4*R*,5*R*)-**541** with MeI and Ag<sub>2</sub>O produced the dimethoxy compound (4*R*,5*R*)-**543** in quantitative yield, and selective hydrolysis with NaOH followed by Curtius rearrangement and subsequent work-up with benzyl alcohol furnished the cyclic amino acid (4*R*,5*R*)-**544** in 92% yield (Scheme 113).<sup>217</sup>

#### 2.4.3. HPLC resolution

Semipreparative chiral HPLC resolution of (±)-**546**, obtained in four steps from α,β-dehydroamino acid derivative **545**, using a mixture of 10-undecenoate/3,5-dimethylphenylcarbamate of amylose covalently attached to allylsilica gel (CSP-2) as a chiral stationary phase afforded the enantiomerically pure (2*R*,3*R*)- and (2*S*,3*S*)-**546**. Hydrolysis of each enantiomer gave the constrained cyclopropane analogues of phenylalanine c<sub>3</sub>diPhe (2*R*,3*R*)- and (2*S*,3*S*)-**547** in excellent yield as hydrochloride salt (Scheme 114).<sup>218</sup>



Scheme 99.

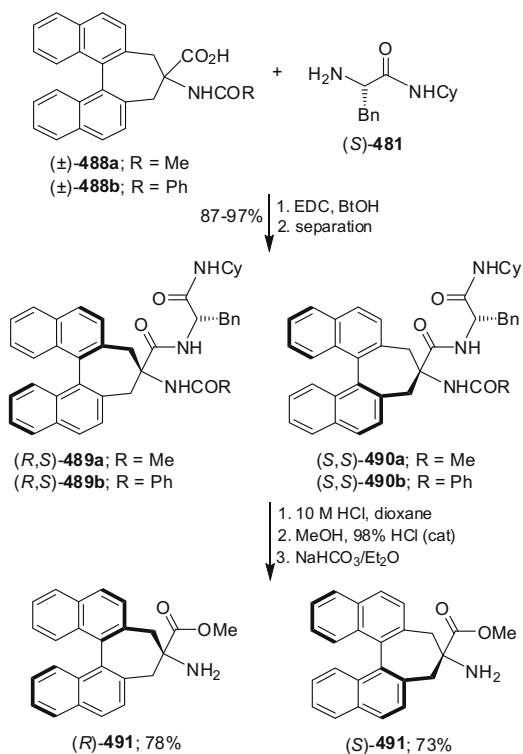


Scheme 100.

In a similar way, chiral HPLC resolution of (±)-**549**, obtained in three steps from α,β-dehydroamino acid derivative **548**, using a mixture of 10-undecenoate/3,5-dimethylphenylcarbamate of cellulose linked to allylsilica gel (CSP-1) as a chiral stationary phase afforded the enantiomerically pure (*R*)- and (*S*)-**549**, which by cleavage of the benzoyl group with hydrazine followed by hydrolysis gave the constrained cyclopropane analogues of valine c<sub>3</sub>Val (*R*)- and (*S*)-**514** in excellent yield as hydrochloride salt (Scheme 115).<sup>219</sup>

Chiral HPLC resolution of *trans*-c<sub>4</sub>Phe (±)-**550**, using CSP-1 as a chiral stationary phase and a mixture of hexane/2-propanol/chloroform (95/3/2) as eluent afforded the enantiomerically pure (1*S*,2*R*)- and (1*R*,2*S*)-**550**. Hydrolysis of each enantiomer gave the constrained cyclobutane analogues of phenylalanine (1*S*,2*R*)-*N*-Boc-c<sub>4</sub>Phe-OH (1*S*,2*R*)-**551** and (1*R*,2*S*)-*N*-Boc-c<sub>4</sub>Phe-OH (1*R*,2*S*)-**551** in excellent yield. Under identical conditions, (±)-**552** gave (1*R*,2*R*)-*N*-Cbz-c<sub>4</sub>Phe-OH (1*R*,2*R*)-**553** and (1*S*,2*S*)-*N*-Cbz-c<sub>4</sub>Phe-OH (1*S*,2*S*)-**553** in excellent yield (Scheme 116).<sup>220</sup>

Chiral HPLC resolution of *cis*-*N*-(1-cyano-2-phenylcyclopentyl)benzamide (±)-**554** using CSP-1 as a chiral stationary phase and a mixture of hexane/2-propanol/acetone (95/3/2) as eluent afforded the enantiomerically pure (1*R*,2*R*)- and (1*S*,2*S*)-**554**, hydrolysis of which produced the constrained cyclopentane analogues of phenylalanine (1*R*,2*R*)-c<sub>5</sub>Phe and (1*S*,2*S*)-c<sub>5</sub>Phe **555** in excellent yield as hydrochloride salt. Finally, reaction of (1*R*,2*R*)-



Scheme 101.

and (1*S*,2*S*)-**555** with TMSCl followed by addition of benzyl chloroformate (CbzCl) furnished the (1*R*,2*R*)-*N*-Cbz-*c*<sub>5</sub>Phe-OH and (1*S*,2*S*)-*N*-Cbz-*c*<sub>5</sub>Phe-OH **556** in 60% and 65% yield, respectively. In a similar way, (±)-**557** afforded the (1*R*,2*S*)-*c*<sub>5</sub>Phe and (1*S*,2*R*)-*c*<sub>5</sub>Phe **558** in 95% and 92% yield, respectively, and these compounds were transformed into (1*R*,2*S*)-*N*-Boc-*c*<sub>5</sub>Phe-OH and (1*S*,2*R*)-*N*-Boc-*c*<sub>5</sub>Phe-OH **559** (Scheme 117).<sup>221</sup>

Natalini et al.<sup>222</sup> reported the preparative resolution of 1-aminoinidane-1,5-dicarboxylic acid (±)-AIDA **33** by chiral ligand-exchange chromatography (CLEC), using (*S*)-*N,N*-dimethylphenyl-

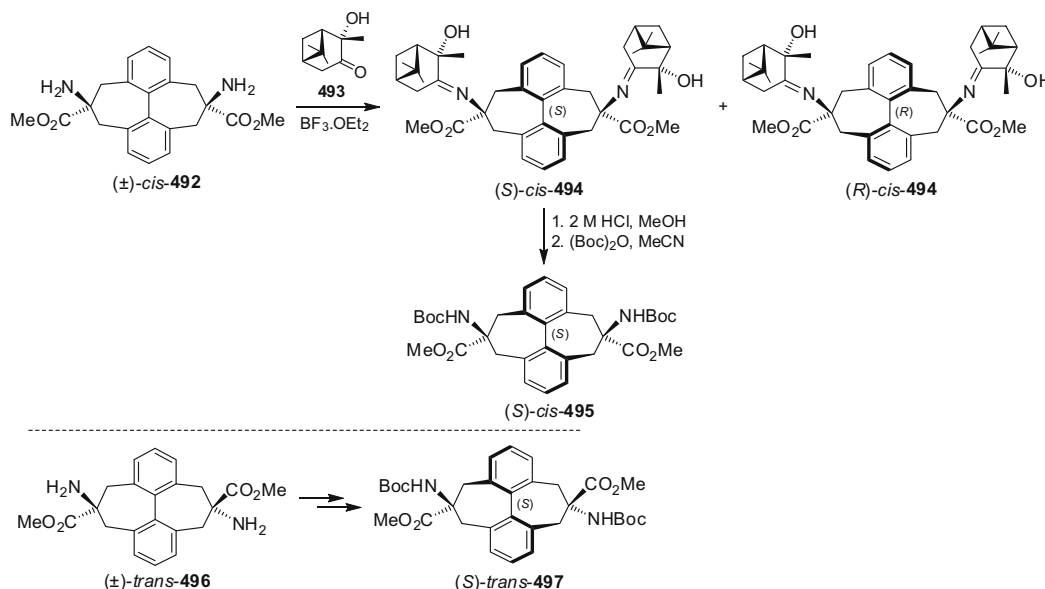
alanine as the chiral selector in the mobile phase, obtaining the enantiomerically pure (*S*)- and (*R*)-AIDA **33** with high ee (Scheme 118).

On the other hand, chiral HPLC resolution of methyl *cis*-1-benzamido-2-phenylcyclohexanecarboxylate (±)-**560** using CSP-2 as a chiral stationary phase and a mixture of hexane/2-propanol/chloroform (96/1/3) as eluent to afford enantiomerically pure (1*R*,2*R*)- and (1*S*,2*S*)-**560**, which by hydrolysis with HCl under reflux produced the constrained cyclohexane analogues of phenylalanine (1*R*,2*R*)-*c*<sub>6</sub>Phe and (1*S*,2*S*)-*c*<sub>6</sub>Phe **561** in quantitative yield as hydrochloride salt. Finally, reaction of (1*R*,2*R*)- and (1*S*,2*S*)-**561** with TMSCl followed by addition of CbzCl provided the (1*R*,2*R*)-*N*-Cbz-*c*<sub>6</sub>Phe-OH and (1*S*,2*S*)-*N*-Cbz-*c*<sub>6</sub>Phe-OH **562** in 70% and 80% yield, respectively. (Scheme 119).<sup>223</sup>

Esterification of (1*R*,2*R*)- and (1*S*,2*S*)-**561** with thionyl chloride and methanol followed by coupling with protected aspartic acid (*S*)-*N*-Cbz-Asp(O*t*-Bu)-OH using *i*-BuOCOCl in the presence of NMM produced the protected dipeptides (*S*,1*R*,2*R*)-**563** and (*S*,1*S*,2*S*)-**564** in 90% yield. Subsequent deprotection with TFA followed by hydrogenolysis over Pd/C led to the enantiomerically pure aspartame analogues H-(*S*)-Asp-(1*R*,2*R*)-*c*<sub>6</sub>Phe-OMe, (*S*,1*R*,2*R*)-**565** (sweet) and H-(*S*)-Asp-(1*S*,2*S*)-*c*<sub>6</sub>Phe-OMe, (*S*,1*S*,2*S*)-**566** (bitter), in 96% and 98% yield, respectively (Scheme 120).<sup>224</sup>

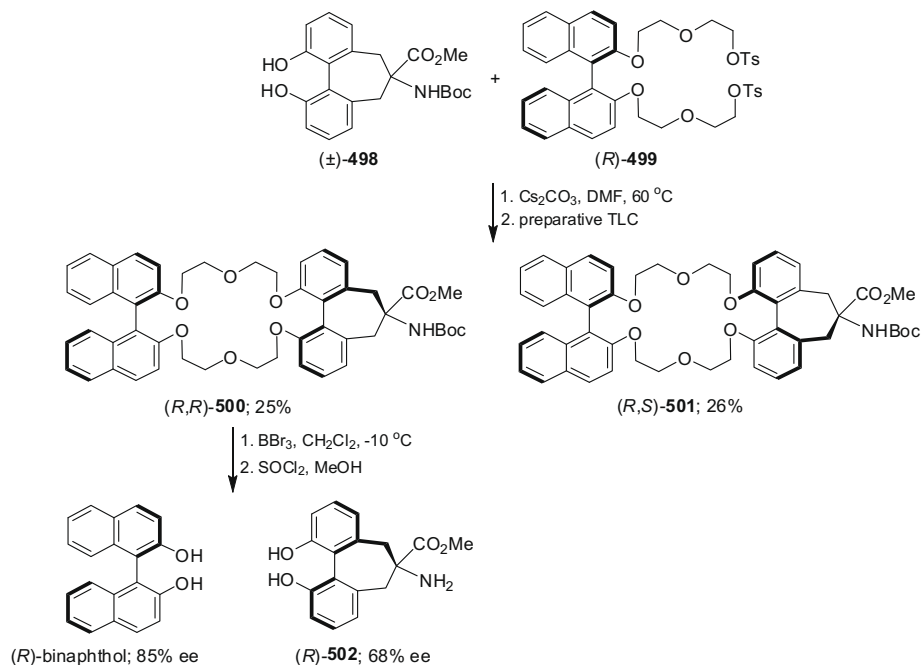
On the other hand, chiral HPLC resolution of *trans*-*N*-(1-cyano-2-phenylcyclohexyl)acetamide *trans*-(±)-**567** using CSP-1 as a chiral stationary phase and a mixture of hexane and 2-propanol (93:7) as eluent gave the enantiomerically pure (1*R*,2*S*)- and (1*S*,2*R*)-**567**, which by hydrolysis with HCl under reflux produced the constrained cyclohexane analogues of phenylalanine (1*R*,2*S*)-*c*<sub>6</sub>Phe and (1*S*,2*R*)-*c*<sub>6</sub>Phe **568** as hydrochloride salts in 92% and 98% yield, respectively. Finally, reaction of (1*R*,2*S*)- and (1*S*,2*R*)-**568** with (Boc)<sub>2</sub>O in tetramethylammonium hydroxide (TMAH) furnished the (1*R*,2*S*)-*N*-Boc-*c*<sub>6</sub>Phe-OH and (1*S*,2*R*)-*N*-Boc-*c*<sub>6</sub>Phe-OH **569** in 50% and 46% yield, respectively (Scheme 121).<sup>225</sup>

Enantiomerically pure (1*R*,2*S*)- and (1*S*,2*R*)-**568** were transformed into enantiomerically pure aspartame analogues H-(*S*)-Asp-(1*R*,2*S*)-*c*<sub>6</sub>Phe-OMe (*S*,1*R*,2*S*)-**570** (sweet) and H-(*S*)-Asp-(1*S*,2*R*)-*c*<sub>6</sub>Phe-OMe (*S*,1*S*,2*R*)-**571** (bitter) under identical conditions to those described above (Scheme 122).<sup>226</sup>

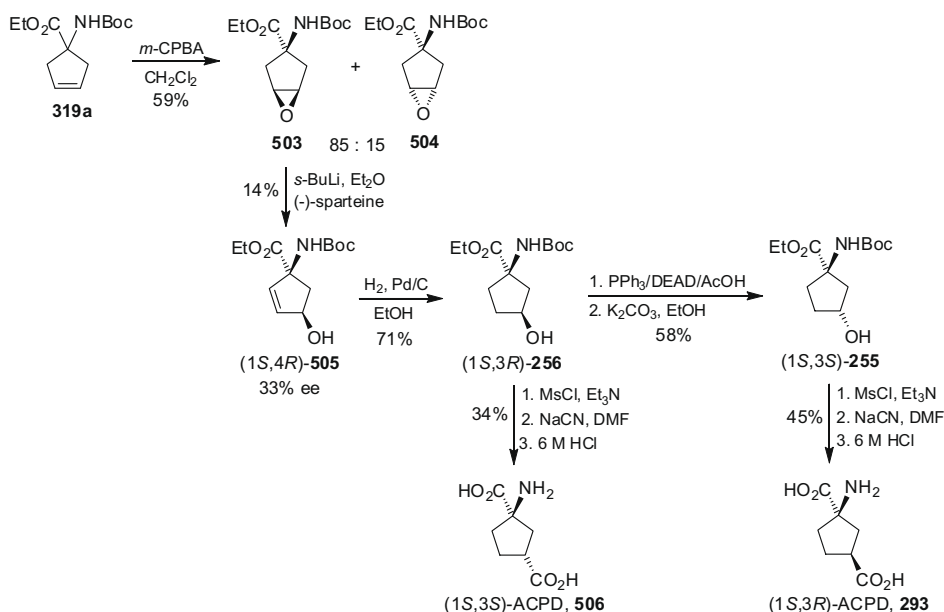


Scheme 102.





Scheme 103.



Scheme 104.

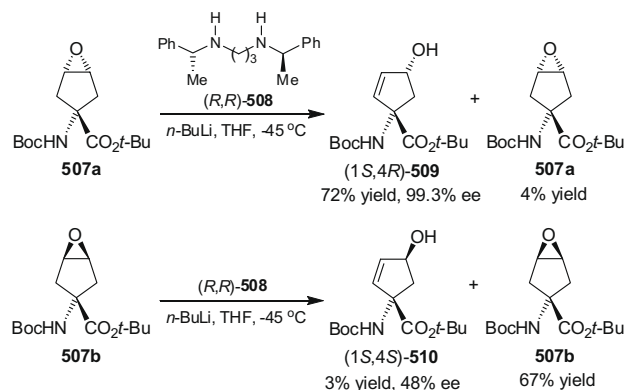
### 3. Synthesis of azacycloalkane-2-carboxylic acids

#### 3.1. Using cyclic compounds as starting materials

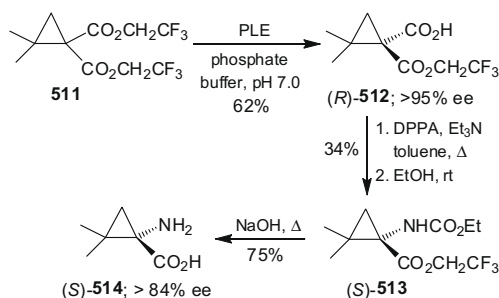
One of the most useful procedures to the stereoselective synthesis of these compounds involves alkylation reactions using the non-quaternary cyclic amino acids as starting materials whenever stereochemical control can be achieved. For example, Wulff et al.<sup>227</sup> reported the highly diastereoselective alkylation of enantiopure aziridine-2-carboxylic acid ethyl esters **572** and **573**<sup>228</sup> with complete retention of the stereochemistry. In this context, treatment of **572** with LDA at -78 °C in 1,2-dimethoxyethane (DME) and diethyl ether followed by addition of several alkylating

agents afforded the alkylated compounds **574a–j** as single stereoisomers and in good yields with complete retention of the stereochemistry. Similar results were obtained in the methylation of **573** (R = Ph), with the methylated product **575** obtained with high diastereoselectivity and in 91% yield.<sup>229</sup> Treatment of **575** with triflic acid and anisole produced the trisubstituted aziridine **576** in 84% yield (Scheme 123).

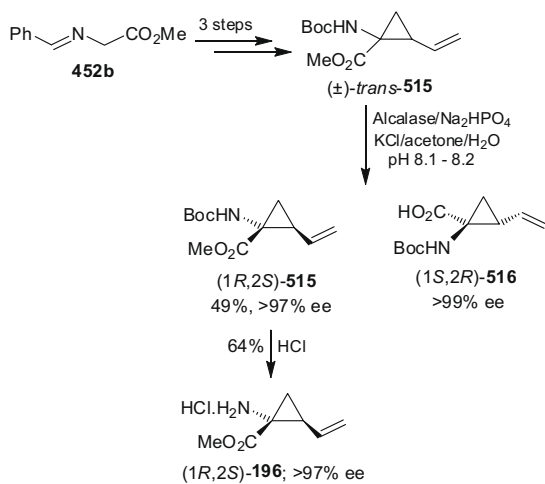
This methodology has been extensively used for the stereoselective synthesis of  $\alpha$ -alkylprolines. Since most of the examples have been collected in a recent review,<sup>230</sup> we only report here the most recent papers. Sommer and Williams<sup>231</sup> reported the stereoselective synthesis of <sup>13</sup>C-labeled  $\alpha$ -alkyl- $\beta$ -methylproline ethyl ester (2R,3S)-**579**, a key intermediate in the elaboration of



Scheme 105.



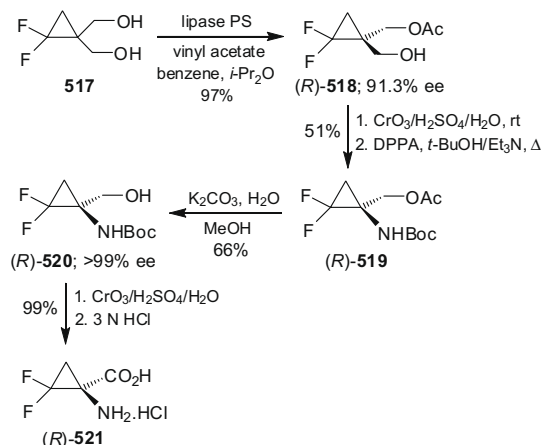
Scheme 106.



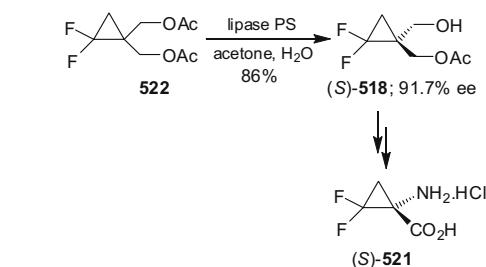
Scheme 107.

paraherquamides E, F and related derivatives, through the stereocontrolled allylation of β-methylproline ethyl ester (2S,3S)-577. In this context, treatment of β-methylproline ethyl ester (2S,3S)-577, obtained from expensive 1-<sup>13</sup>C-(S)-isoleucine, with KHMDS at -78 °C followed by addition of allyl iodide 578 afforded the α-allylated product (2R,3S)-579 in 88% yield as a single diastereoisomer. Identical results were obtained in the allylation of (2R,3S)-580, obtained in several steps from (R)-α-MBA and the inexpensive 1-<sup>13</sup>C-ethyl bromoacetate. The stereochemistry obtained in the allylation of (2S,3S)-577 and (2R,3S)-580 is influenced strongly by the methyl group in the β-position on the proline ring (Scheme 124).

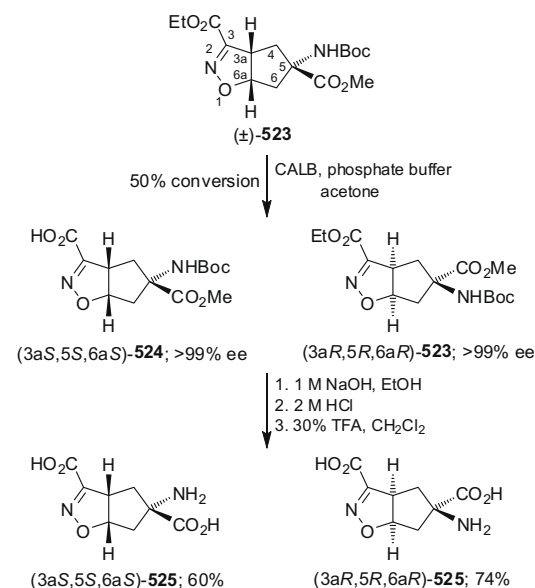
Very recently, Chandan and Moloney<sup>232</sup> reported the synthesis of 2,2,5-trisubstituted pyrrolidines 585a–c from allylic pyrroluta-



Scheme 108.

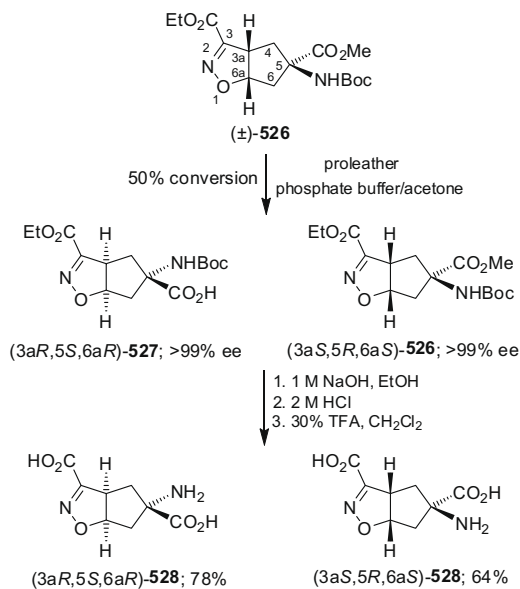


Scheme 109.



Scheme 110.

mates 581a–c by Ireland–Claisen ester rearrangement. Thus, treatment of 581a–c with LiHMDS and Al(*i*-OPr)<sub>3</sub> in the presence of quinine under Kazmaier's conditions<sup>233</sup> gave the rearrangement products 582a–c in good yield as single diastereoisomers through the transition state A. Interestingly, the Claisen rearrangement only occurred in the presence of quinine. Esterification of 582a–c with MeOH and TsOH followed by treatment with Lawesson's reagent afforded the thiolactams 583a–c, which by an Eschenmoser sulfide contraction<sup>234</sup> with diethyl bromomalonate and sodium



Scheme 111.

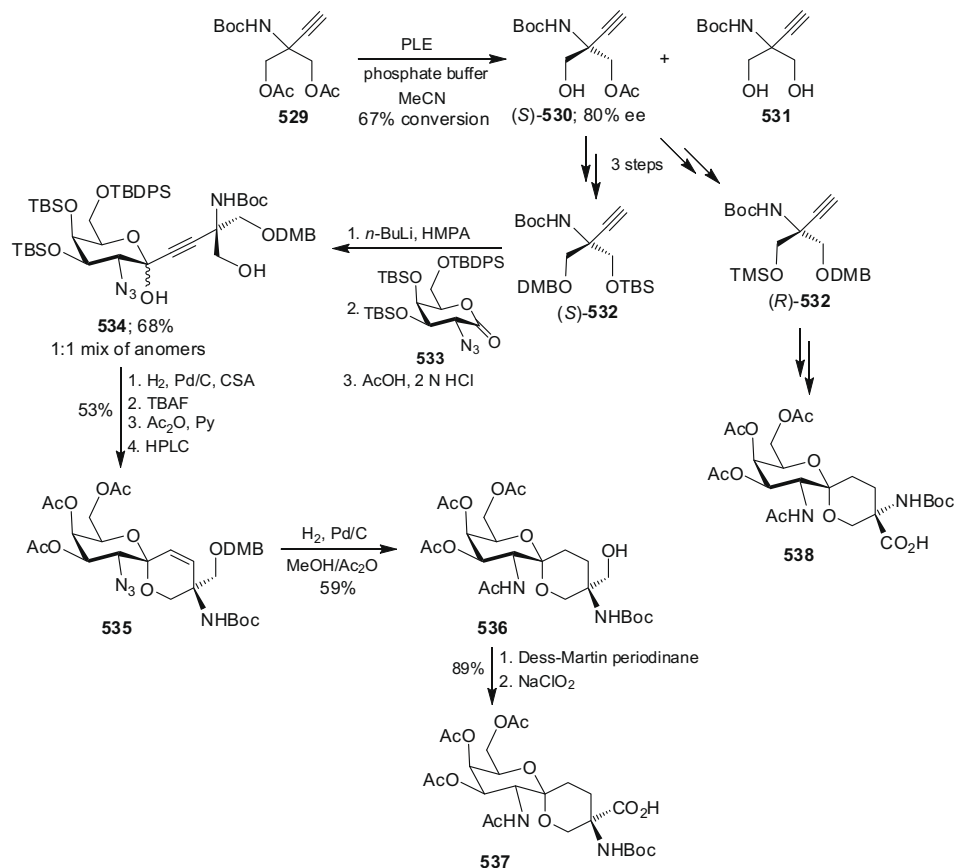
bicarbonate produced the enamines **584a–c** in good yield. Finally, reduction of enamine function in **584a–c** with sodium cyanoborohydride provided the corresponding 2,2,5-trisubstituted pyrrolidines **585a–c** in good yield as single diastereoisomers (Scheme 125).

In 1981, Seebach et al.<sup>235</sup> reported a methodology that formally allows the direct  $\alpha$ -alkylation of L-proline without loss of the enan-

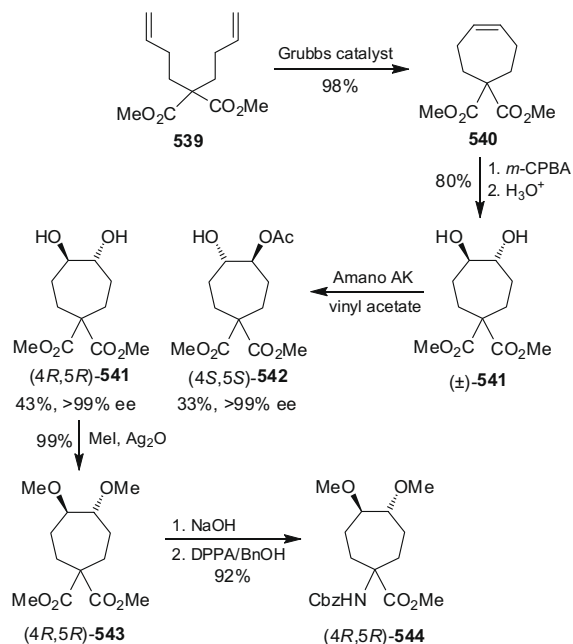
tiomeric purity and with retention of the configuration, thus constituting a showcase of their concept of *self-reproduction of chirality*.<sup>236</sup> In recent years, this methodology has been used for the stereoselective synthesis of quaternary proline analogues. For example, treatment of the oxazolidinone (3S,7aR)-**586**, readily obtained from L-proline<sup>237</sup> with LDA in THF at  $-78^\circ\text{C}$  followed by addition of 3-bromoprop-1-yne gave the  $\alpha$ -alkylated product (3S,7aR)-**587** in 24% yield as a single diastereoisomer. Subsequent cleavage of the oxazolidinone moiety with TMSCl in methanol under microwave conditions followed by treatment with CbzCl furnished the N-Cbz protected  $\alpha$ -propargyl proline (R)-**588** in 73% yield. Cycloaddition of (R)-**588** with the appropriate azide derivative followed by treatment with CuSO<sub>4</sub> and Cu(0) under microwave conditions afforded the corresponding triazoles (R)-**589a–d** in 62–79% yield (Scheme 126).<sup>238</sup>

On the other hand, aldol reaction of the oxazolidinone (3S,7aR)-**590**, readily obtained from L-proline,<sup>235b,235c</sup> with the Garner's aldehyde<sup>239</sup> (R)-**591** afforded the aldol products **592** and **593** in 58% yield and 4:1 dr. Dess–Martin oxidation of **592** followed by reduction with NaBH<sub>4</sub> gave **593** in 43% yield, and this was used in the synthesis of (2S,3S,4R,7R,9S)-kaitocephalin.<sup>240</sup> Under identical conditions, aldol reaction of (3S,7aR)-**590** with the aldehyde (S)-**591** gave **594** and **595** in 51% yield and 2:3 dr. Oxidation of **594** followed by reduction with NaBH<sub>4</sub> gave **595** in 31% yield, and this was used in the synthesis of (2R,3S,4R,7R,9S)-kaitocephalin<sup>241</sup> (Scheme 127).

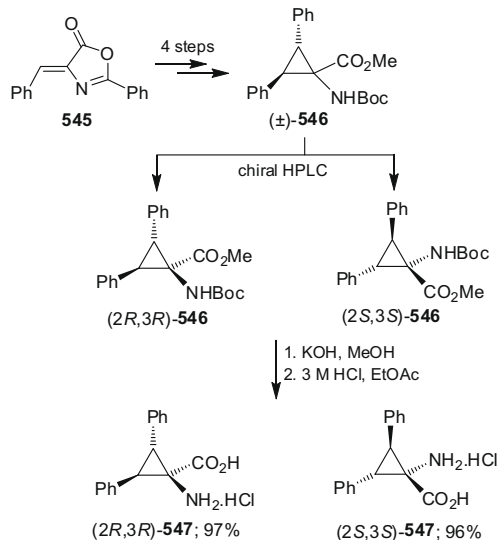
Aldol reaction of enantiopure *trans*-**596** with Garner's aldehyde (S)-**597**<sup>242</sup> afforded the aldol products in 60% yield as a complex mixture, indicating a mismatched double stereodifferentiation, whereas the same reaction using the aldehyde (R)-**597** gave the aldol product **598** in 40–50% yield as a single diastereoisomer, which



Scheme 112.



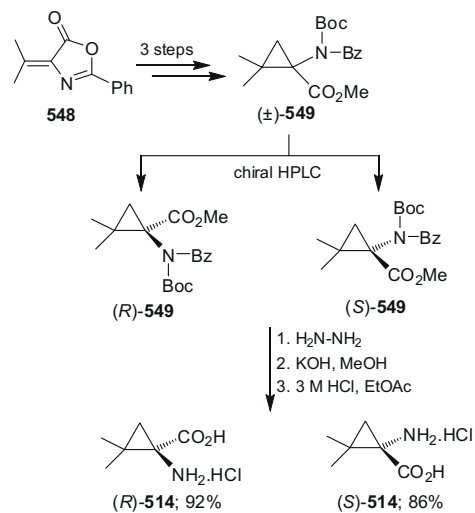
Scheme 113.



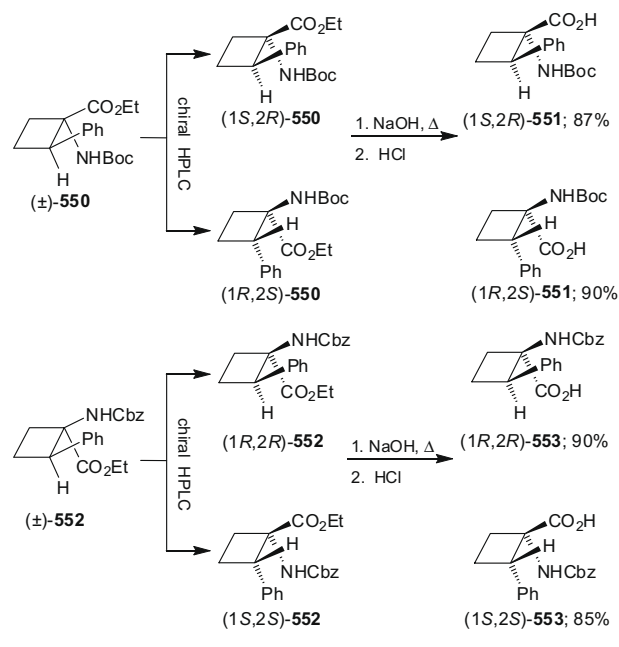
Scheme 114.

confirms a matched double stereodifferentiation. On the other hand, treatment of *trans*-**596** with LDA in THF at  $-78\text{ }^{\circ}\text{C}$  followed by addition of *N*-acylimidazole (*S*)-**599** gave the corresponding  $\beta$ -keto ester **600** in 40–50% yield as a single diastereoisomer, which by reduction of the keto function with DIBAL at  $-78$  to  $25\text{ }^{\circ}\text{C}$  gave the  $\beta$ -hydroxy ester **601** in 86–93% yield and >30:1 dr. The latter compound is an epimer of **598** and is a key compound for the synthesis of (2*R*,3*S*,4*R*,7*R*,9*S*)-kaiotocephalin (Scheme 128).<sup>243</sup>

Recently, we reported<sup>244</sup> a versatile methodology for the synthesis of (2*R*,3*aS*,7*aS*)-2-methyloctahydroindole-2-carboxylic acid **605**. Treatment of (*S,S,S,R*)-**603**, obtained in three steps from (*S*)-indoline-2-carboxylic acid **602**, with LDA in THF at  $-78\text{ }^{\circ}\text{C}$  followed by addition of several alkyl electrophiles produced the alkylated products **604a–c** in good yield. In these compounds both the trichloromethyl group and the newly introduced substituent are *cis* to each other on the *exo* side of the bicyclic constituted by the



Scheme 115.



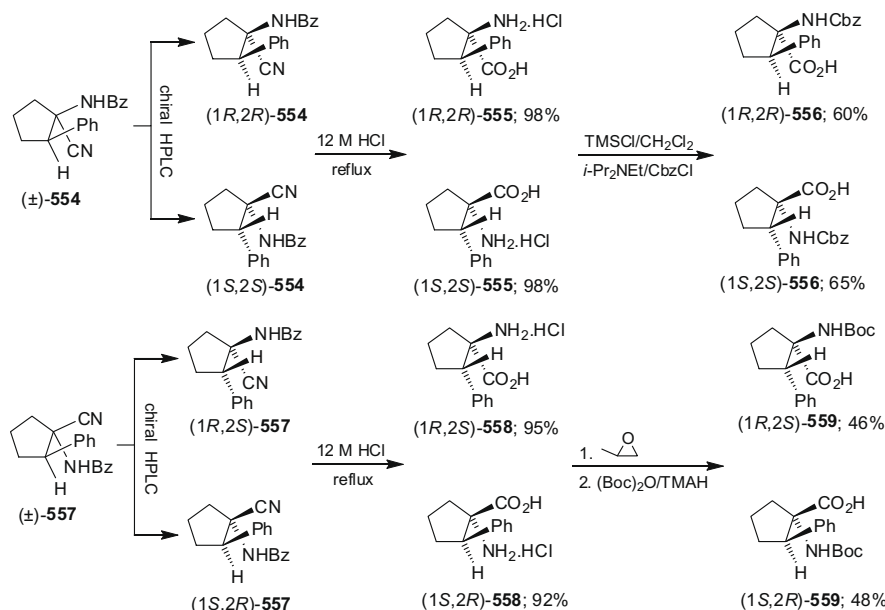
Scheme 116.

two five-membered rings, as in the pioneering investigations by Seebach.<sup>235b</sup> Hydrolysis of (*S,S,S,R*)-**604a** with 6 N HCl in acetic acid gave the  $\alpha$ -methylated indoline (2*R*,3*aS*,7*aS*)-**605** in 92% yield as the hydrochloride salt (Scheme 129).

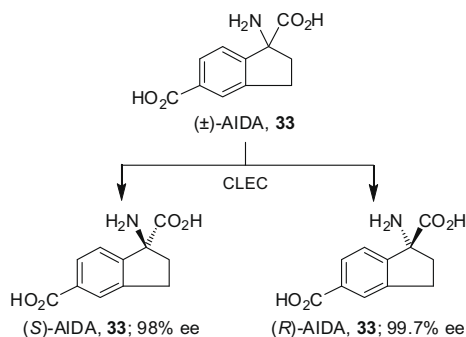
Treatment of enantiopure **606** with LDA followed by addition of several alkyl halides produced the 3,3-disubstituted bicyclic derivatives **608a–f** in good yield and with >95% diastereoselectivity, through the exocyclic lithium enolate **607** (Scheme 130).<sup>245</sup>

Symmetry-breaking enolization reaction of *meso*-diester **610**, obtained in three steps from dipicolinic acid **609**, with the chiral bis-lithium amide base **611** followed by addition of several alkylating reagents afforded the alkylated compounds **612a–f** in good yield and with >98% ee (Scheme 131).<sup>246</sup>

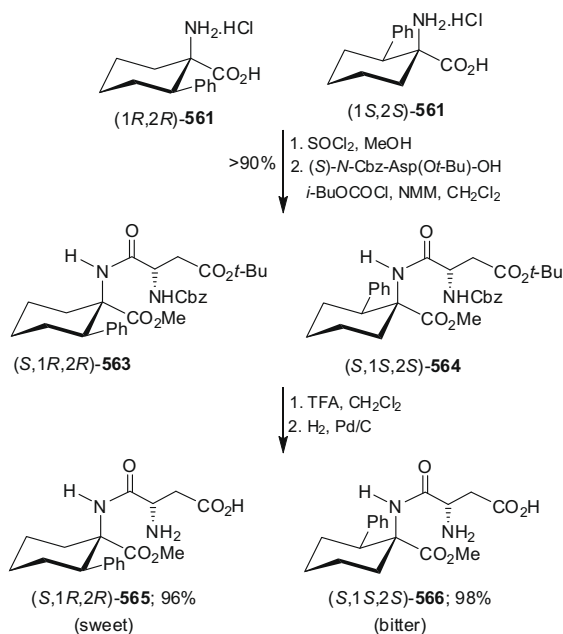
Hou et al.<sup>247</sup> have reported the synthesis of (*R*)- and (*S*)-2-alkyl pipercolic acids **617a–e** by diastereoselective alkylation of (*R*)-5-phenylmorpholin-2-one **613**. In this context, commercially available (*R*)-phenylglycinol was transformed in three steps into



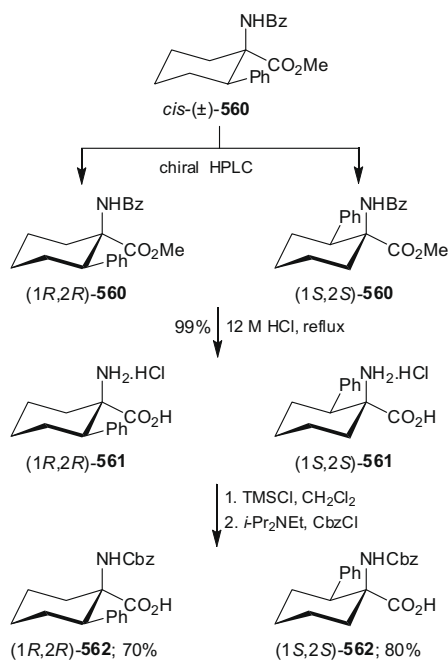
Scheme 117.



Scheme 118.



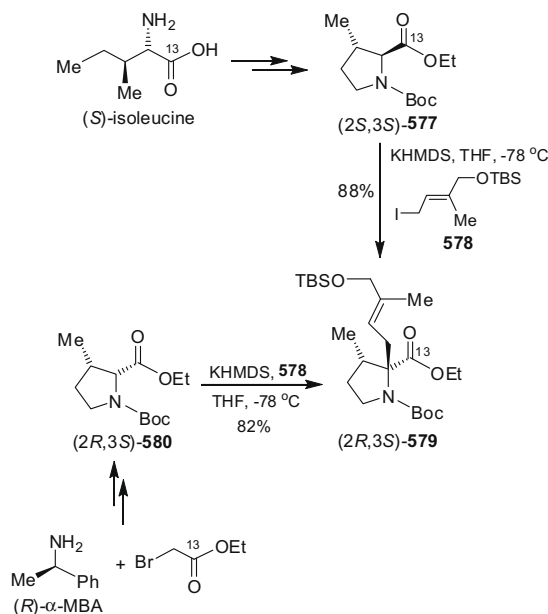
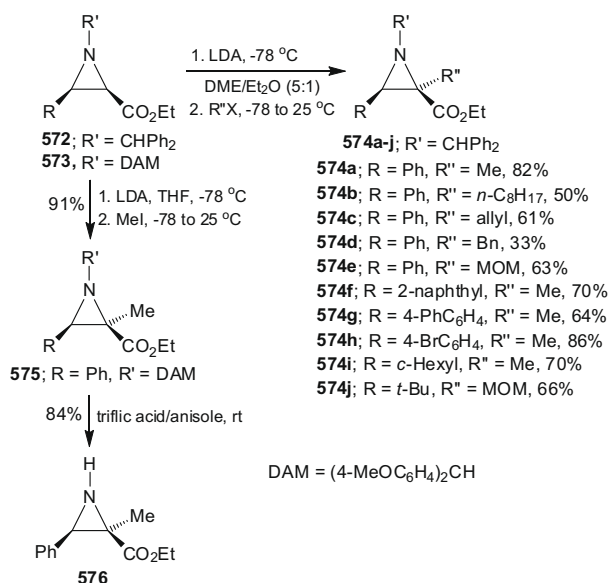
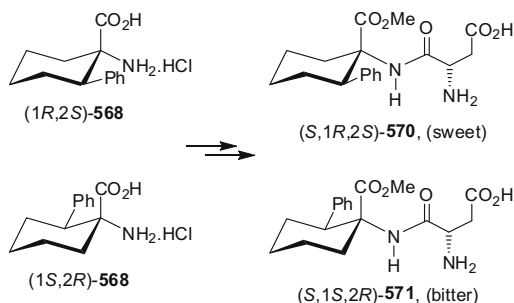
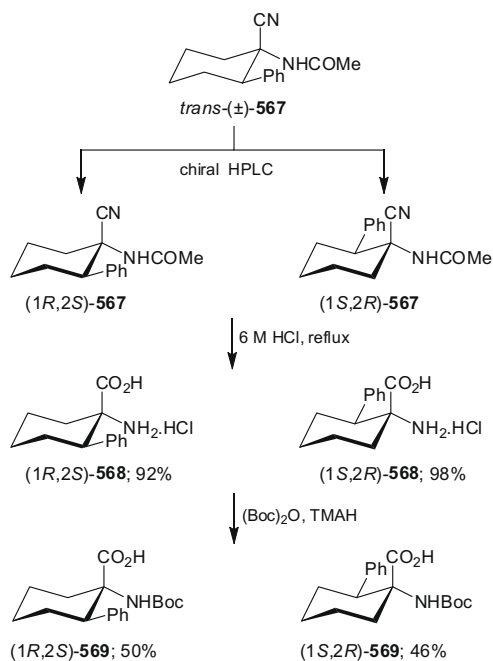
Scheme 119.



Scheme 120.

(R)-613 in 34% overall yield, and treatment of this compound with NaHMDS followed by the addition of 1,4-diiodobutane gave the iodide derivative (R,R)-614 in 65% yield as a single diastereoisomer. Cleavage of Boc protecting group of (R,R)-614 with TFA and subsequent cyclization under basic conditions produced the (4R,9aR)-oxazin-2-one 615 in 65% yield. Treatment of 615 with KHMDS followed by addition of several alkyl halides afforded the corresponding alkylated compounds (4R,9aS)-616a–d and (4R,9aR)-616e in good yield and diastereoselectivity. Hydrogenation of (4R,9aS)-616a–d and (4R,9aR)-616e in the presence of Pearlman's catalyst gave the 2-substituted pipercolic acids (S)-617a–c and (R)-617e in quantitative yield (Scheme 132).

On the other hand, Porzi et al.<sup>248</sup> reported the synthesis of unnatural dipeptides (2S,2'S)-622 and (3S,2'S)-623 through an alkylation–cyclization reaction using the monolactim ether



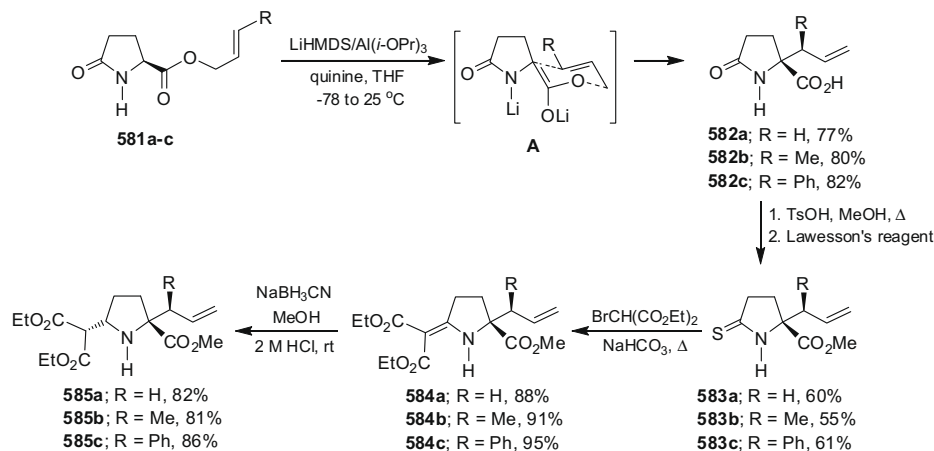
(*S*)-**618** as starting material. In this context, treatment of (*S*)-**618** with LiHMDS followed by addition of 1-chloro-4-iodobutane and  $\alpha,\alpha'$ -dibromo-*o*-xylene afforded the monoalkylated products **619a,b** in moderate yield and 98:2 dr, which by heating in DMF gave the bicyclic derivatives **620a,b** in good yield. Reaction of **620a,b** with LiHMDS and subsequent addition of methyl iodide provided the methylated compounds **621a,b** in 80–85% yield and with 1,4-*trans* induction. Successive cleavage of the benzyl group with Li/NH<sub>3</sub>, treatment with Et<sub>3</sub>OBf<sub>4</sub>, and acidic hydrolysis furnished the dipeptides (2*S*,2'*S*)-**622** and (3*S*,2'*S*)-**623a** in 65% yield (Scheme 133).

### 3.2. Construction of the ring by cyclization reactions

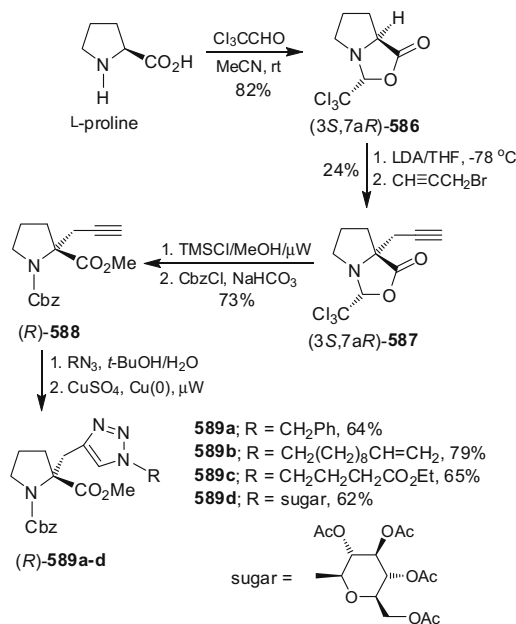
The following paragraphs cover all current methodologies for cyclization reactions and these are arranged according to the strategy involved. The first one involves the N–C bond formation starting from quaternary acyclic compounds in which the stereocenter has been previously formed. For example, nosylation reaction of methyl  $\alpha$ -alkylserinates **624a–c** with *o*-NsCl and excess of KHCO<sub>3</sub> in acetonitrile under reflux provided the *N*-nosyl aziridines **625a–c** in good yield (Scheme 134).<sup>249</sup>

On the other hand, treatment of (*R*)-5-phenylmorpholin-2-one **613** with NaHMDS followed by addition of several alkylating reagents gave the corresponding alkylated compounds (*R,R*)-**626a–f** in 49–79% yield as single diastereoisomers. Treatment of these compounds with KHMDS and subsequent addition of 1,4-diiodobutane (the alkylation of **626e,f** did not proceed) followed by cleavage of Boc protecting group with TFA and subsequent cyclization under basic conditions produced the (4*R*,9*aR*)-oxazin-2-one **627a–d** in 56–67% yield. Hydrogenation of **627a–d** in the presence of Pearlman's catalyst gave the 2-substituted pipercolic acids (*R*)-**617a–c** in quantitative yield (Scheme 135).<sup>247</sup>

In a similar way, treatment of (*S*)-**618** with LiHMDS followed by the addition of allyl bromide provided **628** in 85% yield and 85:15 dr,<sup>250</sup> which by alkylation using LiHMDS as a base and  $\alpha,\alpha'$ -dibromo-*o*-xylene as an alkylating reagent afforded the dialkylated derivative (3*R*,6*S*)-**629** in 80% yield. Heating of (3*R*,6*S*)-**629** in DMF produced the bicyclic derivative **630** in 85% yield, and treatment of this compound under identical conditions to those described for **621a,b** gave (3*R*,2'*S*)-**631** in 67% yield (Scheme 136).<sup>248</sup>



Scheme 125.



Scheme 126.

Maruoka et al.<sup>251</sup> reported the catalytic enantioselective synthesis of tetrahydroisoquinoline- and dihydroisoquinoline-3-carboxylic acid derivatives **634a-c** and **636a,c** by a phase-transfer alkylation-cyclization process. Thus, treatment of Schiff bases **632a-c**, obtained from *p*-chlorobenzaldehyde and the appropriate  $\alpha$ -amino acid *tert*-butyl esters, with  $\alpha,\alpha'$ -dibromo-*o*-xylene and 50% KOH in the presence of  $C_2$ -symmetric chiral quaternary ammonium salt (*S,S*)-3,4,5- $F_3$ -Ph-NAS-Br **633** followed by hydrolysis with citric acid and subsequent treatment with excess of  $\text{NaHCO}_3$  produced the (3*R*)-3-alkyl-1,2,3,4-tetrahydroisoquinolines derivatives **634a-c** in moderate yield and good enantioselectivity. In a similar way, alkylation of **632a,c** with **635** in the presence of **633** followed by hydrolysis with HCl and subsequent treatment with excess of  $\text{NaHCO}_3$  produced the (3*R*)-3-alkyl-3,4-dihydroisoquinoline derivatives **636a,c** in good yield and enantioselectivity (Scheme 137).

Formation of the C–N bond can be achieved by cyclization of carbenoid intermediates. For example, intramolecular cyclization of enantiopure carbenoids **637a,b**, obtained from (R)-**299**, in the presence of a catalytic amount of  $\text{Rh}_2(\text{OAc})_4$  in  $\text{CH}_2\text{Cl}_2$  gave the bicyclic compounds **638a,b** with complete chemoselectivity at the adjacent annular nitrogen and a preference for carbon–carbon

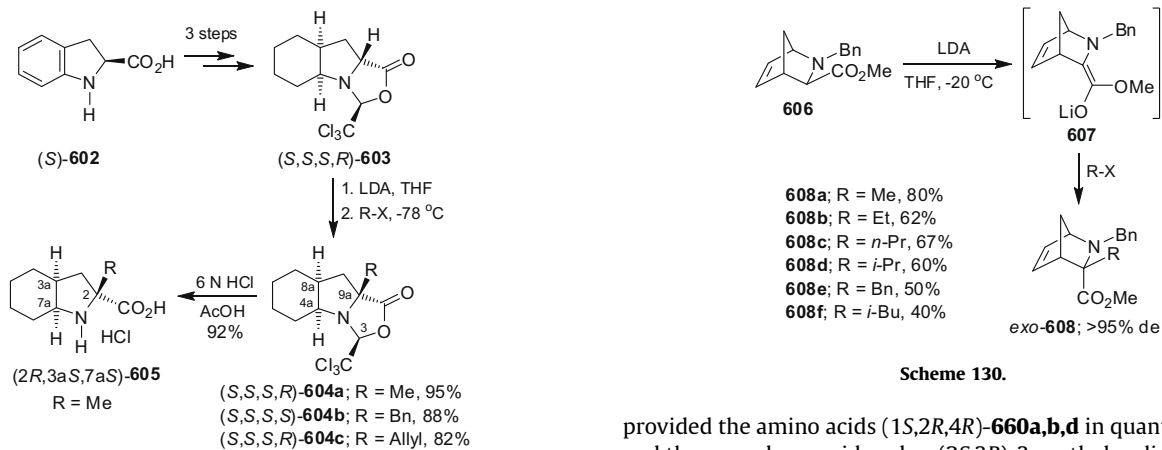
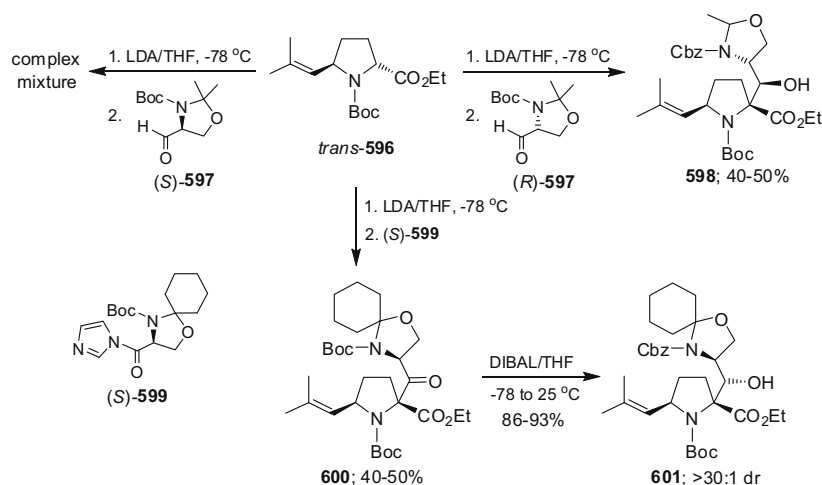
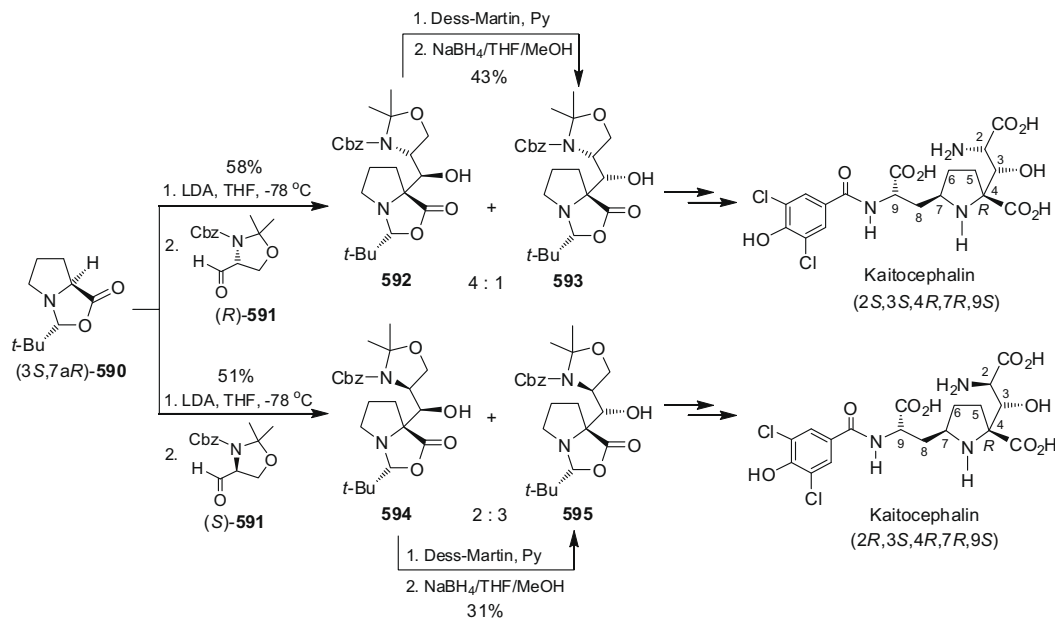
double bond additions or C–H insertions. Hydrolysis of **638a,b** with 3 M HCl followed by treatment with  $(\text{Boc})_2\text{O}$  and triethylamine produced the protected dipeptides **639a,b** (Scheme 138).<sup>252</sup>

In a similar way, intramolecular cyclization of enantiopure carbenoids (2*S*,5*R*)-**640a,b** in the presence of a catalytic amount of  $\text{Rh}_2(\text{OAc})_4$  afforded the bicyclic compounds **643a,b** as the main products, and **644a,b**, probably due to isomerization at C-5 through the intermediates **641** and **642**. Chemoselective opening ring of the iminoether function in the diastereoisomerically pure **643a,b** with 3 M HCl followed by treatment with  $(\text{Boc})_2\text{O}$  and triethylamine produced the corresponding dipeptides (2*S*,2'*R*)-**645a,b** in moderated yield. Under identical conditions the enantiopure carbenoids (2*R*,5*R*)-**646a,b** were transformed into the dipeptides (2*R*,2'*R*)-**645a,b** (Scheme 139).<sup>253</sup>

Another protocol reported by our group involved the large scale reduction of enantiopure ketone **548**,<sup>254</sup> obtained in several steps from **647** by a Diels–Alder reaction. In this context, reduction of **648** with K-selectride in THF at  $-78^\circ\text{C}$  afforded the mixture of alcohols (axial **649** and equatorial **650**) in 98% yield and an 85:15 ratio. Treatment of these compounds with MsCl and triethylamine followed by base-promoted internal nucleophilic displacement with sodium hydride and DMF gave the 7-azabicyclo[2.2.1]heptane derivative **651** in 75% yield (Scheme 140).<sup>255</sup>

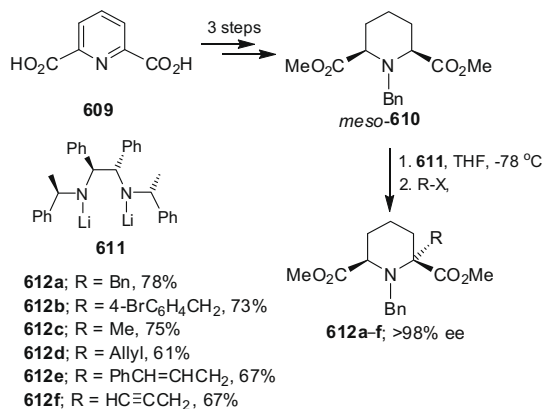
Cleavage of the acetonide function of **651** with PPTS in acetone–water provided the corresponding diol **652** in 67% yield, which by oxidation with  $\text{NaIO}_4$  and  $\text{RuCl}_3$  followed by hydrolysis with 6 N HCl gave the (1*S*,2*R*,4*R*)-7-azabicyclo[2.2.1]heptane-1,2-dicarboxylic acid as hydrochloride salt **653** in 75% yield. On the other hand, oxidation of **652** with  $\text{NaIO}_4$  furnished the aldehyde (1*S*,2*R*,4*R*)-**654** in 90% yield, which by Wittig reaction with  $\text{RCH}=\text{PPh}_3$  provided the vinyl derivatives (1*S*,2*R*,4*R*)-**655a-e** in 75–99% yield. The vinyl derivative **655a** was also obtained through the two-step Corey–Winter<sup>256</sup> procedure. In this context, reaction of diol **652** with *N,N'*-thiocarbonyldiimidazole (TDCI) provided the thiocarbonate **656** in 83% yield. Treatment of **656** with 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine (DMPDAP) led to **655a** in 86% yield. Finally, hydrogenation of C=C double bond of **655a-e** over  $\text{Pd}(\text{OH})_2$  followed by hydrolysis with 6 N HCl afforded the (1*S*,2*R*,4*R*)-proline derivatives **657a-d** in good yield (Scheme 141).<sup>257</sup>

Additionally, the aldehyde (1*S*,2*R*,4*R*)-**654** has been used in the synthesis of 7-azanorbornane  $\beta$ -substituted prolines.<sup>258</sup> For example, reduction of aldehyde function in (1*S*,2*R*,4*R*)-**654** with  $\text{NaBH}_4$  followed by treatment with MsCl and triethylamine produced the corresponding mesylate (1*S*,2*R*,4*R*)-**658**, which by nucleophilic substitution afforded the compounds (1*S*,2*R*,4*R*)-**659a-e** in 60–100% yield. Hydrolysis of (1*S*,2*R*,4*R*)-**659a,b,d** with 6 M HCl

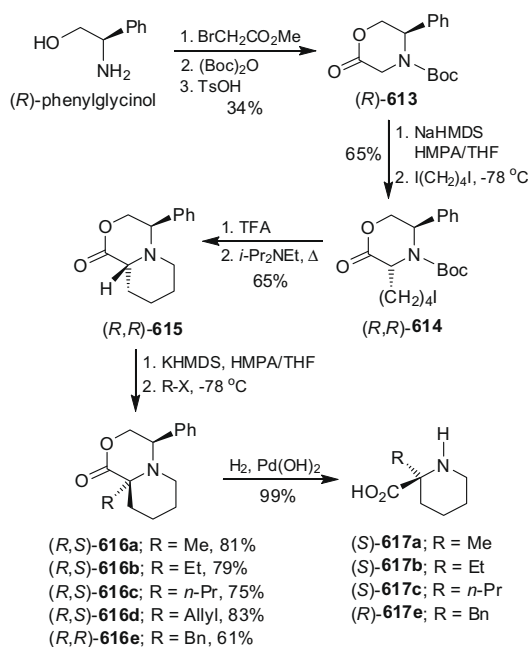


provided the amino acids (1S,2R,4R)-660a,b,d in quantitative yield, and these can be considered as (2S,3R)-3-methylproline, (2S,3R)-3-methylthiomethylproline and (2S,3R)-3-carboxymethylproline





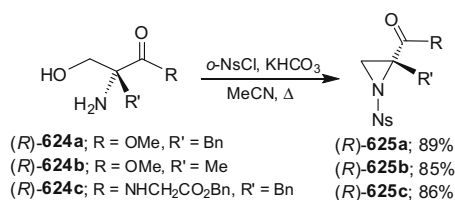
Scheme 131.



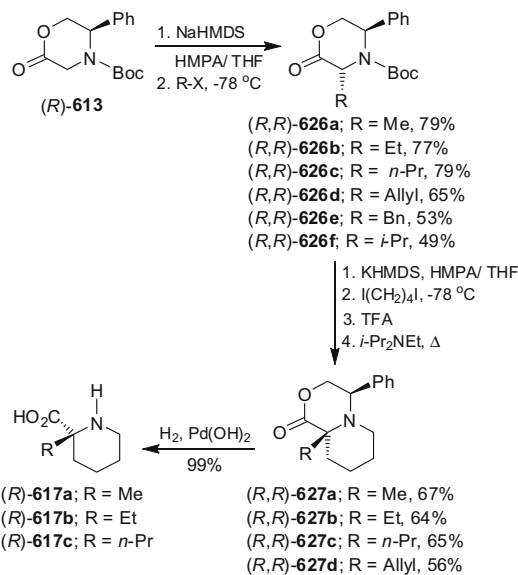
Scheme 132.

analogues. Additionally, (1*S*,2*R*,4*R*)-**659e** was transformed into amino compounds (1*S*,2*R*,4*R*)-**661a–d** (Scheme 142).

The second reported methodology involves the formation of a  $\alpha$ -C– $\beta$  bond. In this case the stereoselectivity of the cyclization

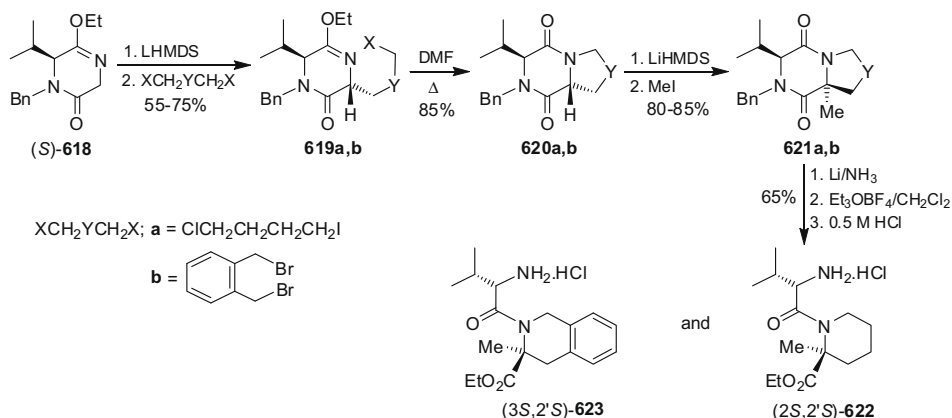


Scheme 134.

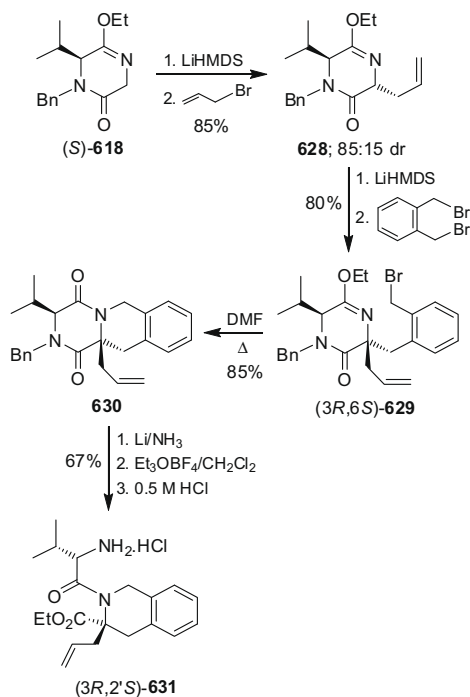


Scheme 135.

reaction depends on the chirality of the non-quaternary  $\alpha$ -amino acid used as starting material, wherever the chirality of the stereocenter can be remembered to some extent (memory of chirality). This methodology has been repeatedly used for the stereoselective synthesis of four-, five-, six- and seven-membered rings. These results have been collected in recent reviews,<sup>259</sup> and we therefore only describe here the most recent papers. For example, Kawabata et al.<sup>260,261</sup> reported the four-membered cyclization for the straightforward synthesis of cyclic amino acids with tetrasubstituted stereocenters from chiral  $\alpha$ -amino acids through memory of chirality. In this context, treatment of **662a,b** with KHMDS in DMF at  $-60^\circ\text{C}$  furnished the four-membered compounds **663a,b** with good enantioselectivity and retention of configuration, while the use of lithium 2,2,6,6-tetramethylpiperidine (LTMP) as a base



Scheme 133.

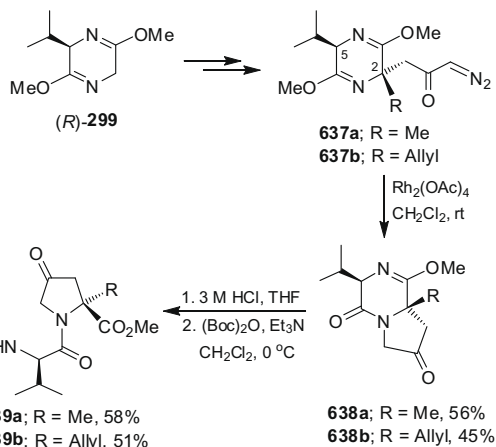


Scheme 136.

in THF at  $-20^{\circ}\text{C}$  led to **663a,b** with good enantioselectivity but with inversion of the configuration. Treatment of (*R*)-**663a** with methanolic NaOMe followed by cleavage of the *N*-Boc protecting group with 4 N HCl gave the azetidine derivative (*R*)-**664** in 56% yield (Scheme 143).

In a similar way, treatment of **665** and **666** with KHMDS in DMF at  $-60^{\circ}\text{C}$  provided the piperidine derivative **667** in 84% yield and 97% ee, and the azepane **668** in 31% yield and 83% ee (**666** was recovered). The stereochemical course of the cyclization was with retention of the configuration (Scheme 144).<sup>260</sup>

Recently, Kawabata et al.<sup>262</sup> reported that the asymmetric cyclization of **662a–c** ( $n = 2$ ), **669a–c** ( $n = 3$ ), and **665a–c** ( $n = 4$ ) using powdered KOH as an efficient base in DMSO at  $20^{\circ}\text{C}$  afforded the



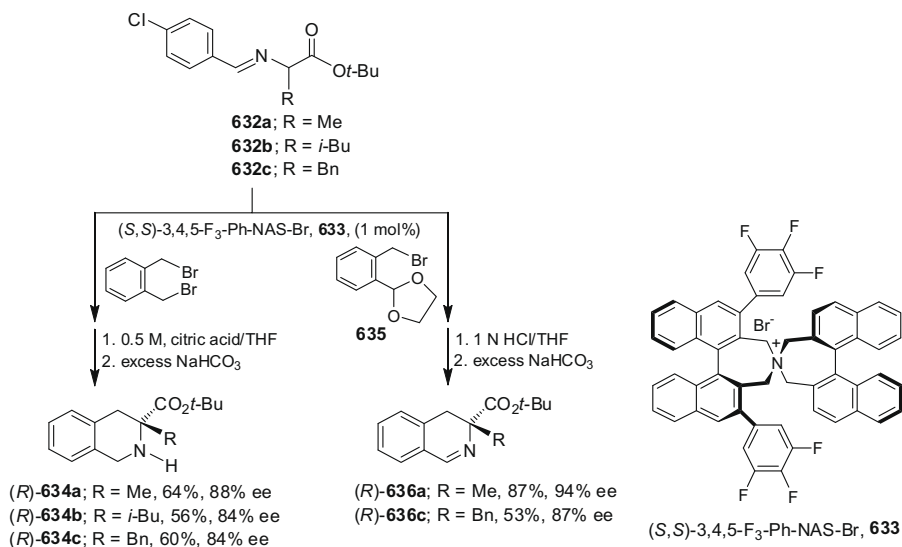
Scheme 138.

four-, five-, and six-membered compounds **663a–c**, **670a–c** and **667a–c**, respectively, in good yield and excellent enantioselectivity. The results are summarized in Table 12.

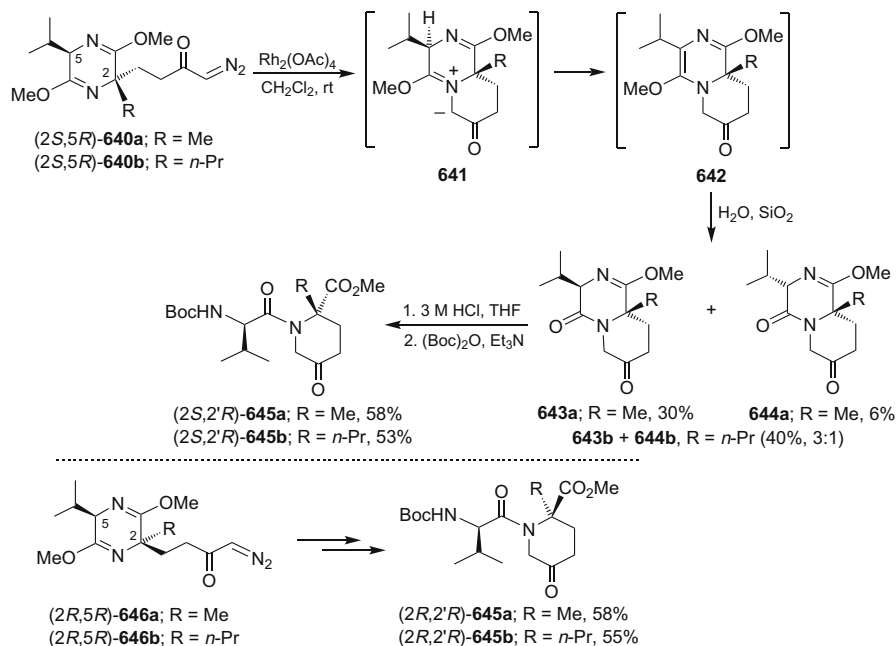
This protocol has been used in the synthesis of Fmoc-cyclic amino acid **671**, which is expected to be a useful building block for conformationally constrained peptides of biological interest. In this context, treatment of isoleucine derivative **669d** with powdered KOH in DMSO at  $20^{\circ}\text{C}$  afforded the cyclic product **670d** in 94% yield as a single diastereoisomer, which by hydrolysis with HCl and subsequent *N*-Fmoc protection led to the proline derivative **671** in 53% yield (Scheme 145).<sup>262</sup>

Very recently, Kawabata et al.<sup>263</sup> reported the asymmetric intramolecular alkylation of  $\beta$ -alcoxy- $\alpha$ -amino esters through memory of chirality methodology. In this context, treatment of serine derivatives **672a**, **673a–f**, and **674a** with CsOH as an efficient base in DMSO at  $20^{\circ}\text{C}$  afforded the cyclization products **675a**, **676a–f**, and **677a** in 13–89% yield and enantioselectivities in the range 82–94%. The results are summarized in Table 13.

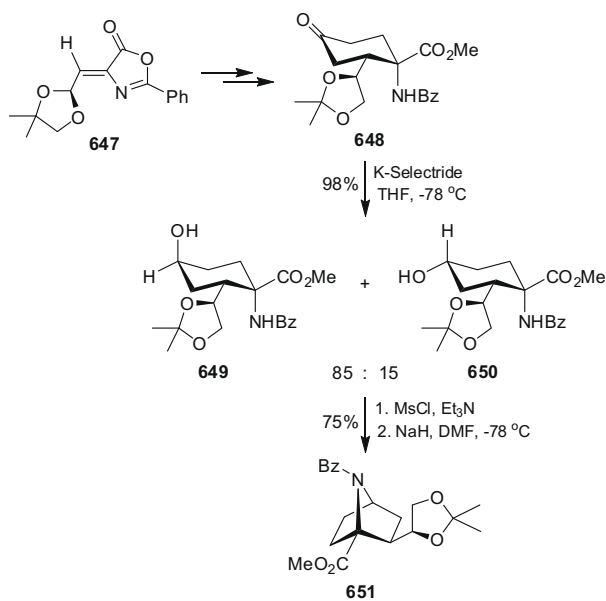
Memory of chirality in intramolecular conjugate addition of enolates is another methodology used for the asymmetric synthesis of nitrogen heterocycles with contiguous quaternary stereocenters. For example, treatment of  $\alpha,\beta$ -unsaturated derivatives **678a,b** with KHMDS in DMF-THF at  $-78^{\circ}\text{C}$  gave the piperidine deriva-



Scheme 137.



Scheme 139.



Scheme 140.

tives **679a,b** as a single detectable diastereoisomers in moderate yield. Seven-membered ring cyclization of  $\alpha,\beta$ -unsaturated compound **678c** proceeded to give **679c** in 91% ee, albeit in only 19% yield (Scheme 146).<sup>264</sup> Compounds **679a–c** are precursors of conformationally constrained L-glutamate analogues.

On the other hand, treatment of  $\alpha,\beta$ -unsaturated compound **680** with KHMDS in DMF–THF at  $-78^\circ\text{C}$  gave the tetrahydroisoquinoline derivative **681** as a single diastereoisomer in 95% ee and 94% yield.<sup>261,264</sup> Treatment of **680** with LTMP in THF at  $0^\circ\text{C}$  led to *ent*-**681** as a single diastereoisomer in 91% ee and 62% yield (Scheme 147).<sup>261</sup>

The third methodology reported involves the cyclization by C–C bond formation, starting from the corresponding quaternary  $\alpha$ -amino acids previously obtained with both chains appropriately functionalized. For example, ring closing metathesis of dialkylated

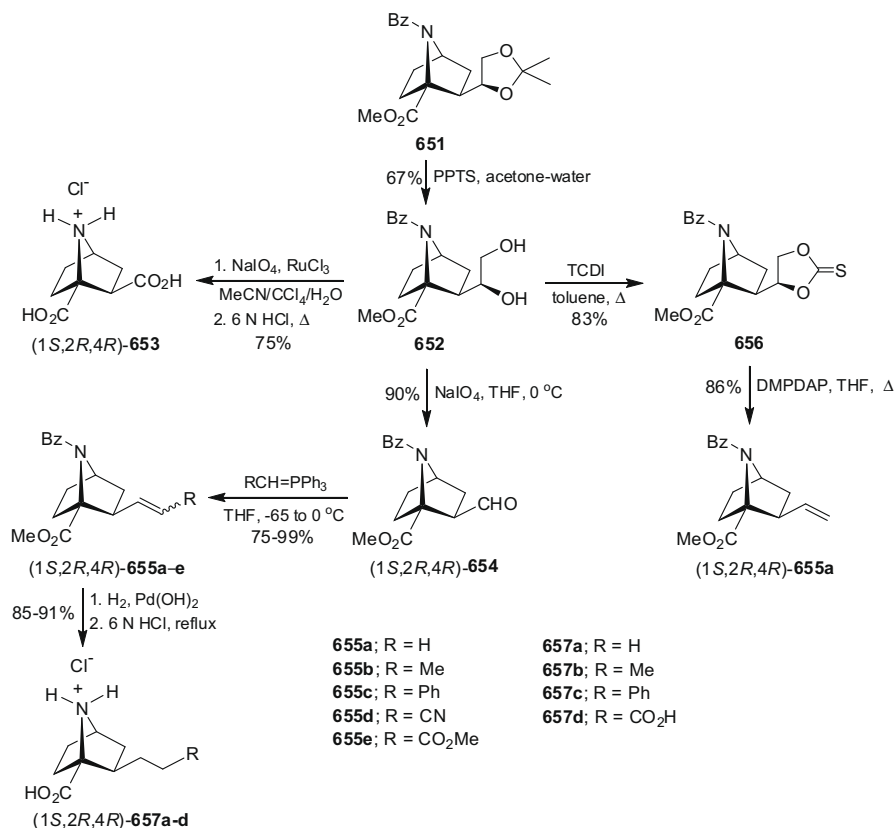
derivative (*R*)-**683**, obtained in three steps from **682**,<sup>265</sup> in the presence of a catalytic amount of  $\text{PhCH}=\text{RuCl}_2(\text{PCy}_3)_2$  in benzene under reflux gave the corresponding six-membered derivative (*R*)-**684** in 94% yield. Subsequent hydrogenation of the C=C double bond over Pd/C afforded the  $\alpha$ -quaternary pipercolic acid derivative (*R*)-**685** in 95% yield (Scheme 148).<sup>266</sup>

Finally, the one-pot aza-Darzens reaction has been reported as a competitive alternative for the synthesis of aziridine carboxylic acids. For example, aza-Darzens reaction<sup>267</sup> of (*S*)-sulfimine **686a** with the lithium  $\alpha$ -bromo enolate generated from methyl  $\alpha$ -bromopropionate **687** and LiHMDS in THF at  $-78^\circ\text{C}$ , afforded the corresponding aziridines (*S*<sub>5</sub>,2*R*,3*S*)-**688** and (*S*<sub>5</sub>,2*S*,3*S*)-**689** in 55% and 21% yield, respectively. Oxidation of diastereoisomerically pure (*S*<sub>5</sub>,2*R*,3*S*)-**688** with *m*-CPBA gave the *N*-tosyl aziridine (2*R*,3*S*)-**690** in excellent yield. On the other hand, reaction of diastereoisomerically pure (*S*<sub>5</sub>,2*R*,3*S*)-**688** with MeMgBr provided the aziridine (2*R*,3*S*)-**691** in 92% yield (Scheme 149).<sup>268</sup>

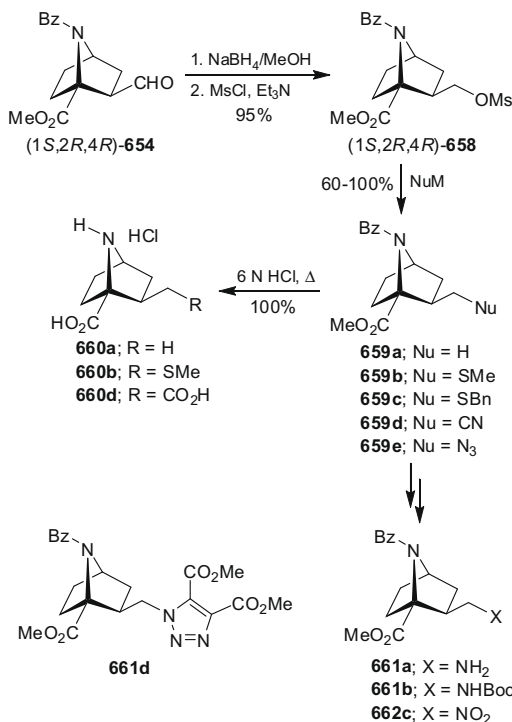
In a similar way, the one-pot reaction of (*S*)-sulfimines **686b,c** with the lithium  $\alpha$ -bromo enolate generated from methyl 3-benzyl-oxy-2-bromopropionate **692**<sup>269</sup> and LiHMDS in THF at  $-78^\circ\text{C}$  produced the aziridines (*S*<sub>5</sub>,2*S*,3*S*)-**693b** and (*S*<sub>5</sub>,2*R*,3*S*)-**694b** (R = Ph) in 70% yield and 95:5 dr, and the aziridines (*S*<sub>5</sub>,2*S*,3*S*)-**693c** and (*S*<sub>5</sub>,2*R*,3*S*)-**694c** (R = *E*-MeCH=CH) in 79% yield and 15:85 dr. Selective cleavage of *N*-sulfinyl bond in (*S*<sub>5</sub>,2*S*,3*S*)-**693b** with TFA gave the aziridine (2*S*,3*S*)-**695b** in 76% yield, whereas the treatment of (*S*<sub>5</sub>,2*R*,3*S*)-**694c** with excess of MeMgBr provided the aziridine (2*R*,3*S*)-**696c** in 86% yield (Scheme 150).<sup>270</sup>

### 3.3. Cycloadditions and related reactions

This strategy has been elegantly used to the synthesis of different types of prolines and derivatives, and it is especially useful in the synthesis of polysubstituted (polyfunctional) prolines. Nevertheless, most of the published papers have been gathered in our recent review.<sup>230</sup> As a result we only include here the reports that have appeared very recently. For example, Xie et al.<sup>271</sup> reported a practical asymmetric synthesis of highly substituted proline derivatives **698** and **700** on a multi-kilogram scale. In this context, [3+2] cycloaddition reaction of methyl acrylate with the enantiopure

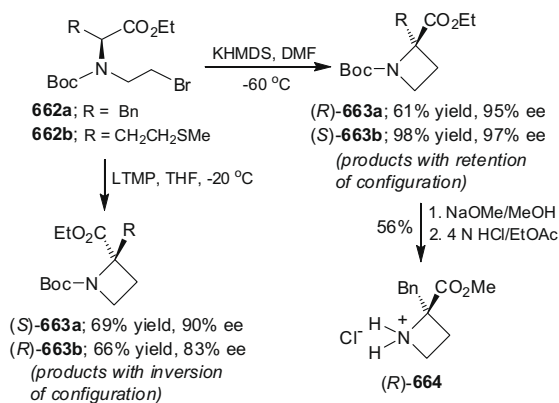


Scheme 141.

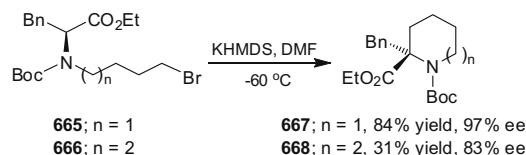


Scheme 142.

imine (*S*)-**697a**, readily obtained by condensation of *L*-leucine *tert*-butyl ester with 2-thiazolecarboxaldehyde, in the presence of a catalytic amount of hydroquinine, AgOAc, and molecular sieves, produced the proline derivative **698** in 85:15 epimeric ratio. Treat-



Scheme 143.



Scheme 144.

ment of the resulting compound with (*R*)-1,1'-binaphthyl-2,2'-dehydrogenophosphate in 2-propanol and subsequent crystallization gave **698** in 99.9:0.1 er and 57% overall yield. In a similar way, [3+2] cycloaddition reaction of (*S*)-**697a** with methyl vinyl ketone in the presence of a catalytic amount of cinchonidine and AgOAc gave the proline derivative **699** as a mixture of  $\alpha/\beta$  epimers

in 98:2 ratio, which by treatment with 10 mol % of DBU gave the  $\beta$  epimer **700** as the main product with 73:27 er (Scheme 151).

Very recently, Kobayashi et al.<sup>272</sup> reported the [3+2] cycloaddition reaction of different imines ( $\pm$ )-**701** with several acrylates **702** in the presence of a catalytic amount of the bisoxazolines **703a–e** and Ca(Oi-Pr)<sub>2</sub> in THF and molecular sieves. The substituted pyrrolidine derivatives **704** were obtained in high yields and with high diastereoselectivities and enantioselectivities (Scheme 152).

The [3+2] cycloaddition reaction was used by Kobayashi et al.<sup>272</sup> in the synthesis of enantiomerically pure pyrrolidine cores of hepatitis C virus RNA-dependent polymerase inhibitors and potentially effective antiviral agents. In this context, [3+2] cycloaddition reaction of *tert*-butyl acrylate with the enantiopure imines (*R*)-**697a,b** in the presence of a catalytic amount of the bisoxazolines **703a,b** and Ca(Oi-Pr)<sub>2</sub> in THF and molecular sieves produced the pyrrolidine derivatives **705a,b** in high yield with perfect diastereoselectivities and high enantioselectivities (Scheme 153).

Another approach to generate enantiomerically enriched poly-substituted prolines or pyrrolidine derivatives is the 1,3-dipolar cycloaddition between electrophilic alkenes and stabilized or non-stabilized dipolarophiles, respectively. This strategy allows the creation of up to four stereogenic centers in only one step and gives high regioselectivity and *endo/exo*-diastereoselectivities. For example, Nájera et al.<sup>273</sup> reported the stereoselective synthesis of poly-substituted prolines (2*R*,4*R*,5*S*)- and (2*S*,4*S*,5*R*)-**707** by a 1,3-dipolar cycloaddition. In this context, the cycloaddition reaction between the racemic imino ester ( $\pm$ )-**697b** with acrylate bonded to methyl (*S*)-lactate **706** in the presence of a catalytic amount of AgOAc and KOH in toluene afforded the polysubstituted proline (2*R*,4*R*,5*S*)-**707** in 77% yield and 96% de. In similar way, reaction of ( $\pm$ )-**697b** with acrylate bonded to methyl (*R*)-lactate **706** gave the polysubstituted proline (2*S*,4*S*,5*R*)-**707** in 77% yield and 96% de. (2*R*,4*R*,5*S*)-**707** and (2*S*,4*S*,5*R*)-**707** were transformed into (2*R*,4*R*,5*S*)- and (2*S*,4*S*,5*R*)-**708**, two promising potential drugs, particularly for the hepatitis C virus RNA-dependent polymerase inhibitors and potentially effective antiviral agents (Scheme 154).

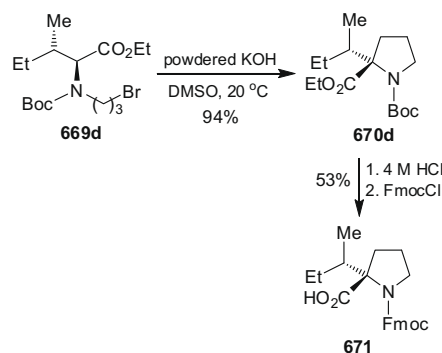
Recently, Nájera et al.<sup>274</sup> reported that the catalytic enantioselective 1,3-dipolar cycloaddition reaction of racemic benzylideneiminoglycinates **709a–d** with *tert*-butyl acrylate in the presence of a catalytic amount of (*S*,*a*,*R*,*R*)-**710**, AgClO<sub>4</sub> and triethylamine or 1,4-diazabicyclo[2.2.2]octane (DABCO) as a base afforded the

corresponding prolines **711a,b** and **712c,d** with high enantiomeric ratio (Scheme 155).<sup>275</sup>

1,3-Dipolar cycloaddition reaction of racemic methyl *N*-benzylidenealaninate **713** with the vinyl sulfone in the presence of copper(I)/click ferrophos complex **714** and CuOAc produced the quaternary methyl proline derivative **715** in 83% yield and 93% ee (Scheme 156).<sup>276</sup>

Very recently, Carretero et al.<sup>277</sup> reported the stereoselective synthesis of 3-pyrrolines **719a,b** by asymmetric 1,3-dipolar cycloaddition reaction. Thus, the reaction of racemic methyl *N*-benzylidenealaninates **713a,b** with *trans*-1,2-bisphenylsulfonyl ethylene **716** in the presence of a catalytic amount of Cu(MeCN)<sub>4</sub>PF<sub>6</sub>, Fesulfos (*R*)-**717** and Et<sub>3</sub>N afforded the quaternary methyl proline derivatives **718a,b** in good yield and with good enantioselectivity. Subsequent treatment of these compounds with Na(Hg) gave the quaternary derivatives **719a,b** in 85% and 77% yield, respectively. (Scheme 157).

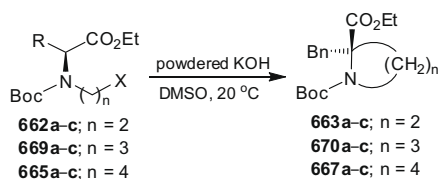
Cyclopropanation reaction of a cyclic dehydroaminoacid derivative allowed the synthesis of newly constrained quaternary pipercolic derivatives. Thus, the reaction of (*S*)-2,3-didehydropipercolate **721**, obtained in five steps from *N,N*-diprotected  $\alpha$ -lysine methyl ester **720**, with dimethylsulfoxonium methylide afforded the 2,3-methano-6-methoxypipercolate (2*S*,3*R*)-**722** in 73% yield, which by treatment with NaBH<sub>4</sub> in formic acid gave the 2,3-methanopipercolate (2*S*,3*R*)-**723** in 75% yield and 85% ee. Finally, hydrolysis of (2*S*,3*R*)-**723** with TMSI produced the (2*S*,3*R*)-methanopipercolic acid **724** in 50% yield (Scheme 158).<sup>278</sup>



Scheme 145.

Table 12

Asymmetric cyclization of  $\alpha$ -amino acids derivatives with KOH/DMSO at 20 °C

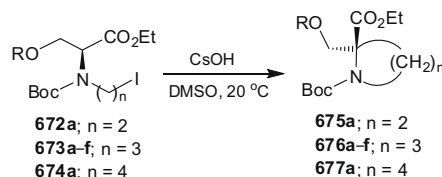


Entry	R	X	Product	Yield (%)	ee (%)
1	<b>a</b> = Bn	Br	<b>663a</b> ; <i>n</i> = 2	82	99 (R)
2	<b>b</b> = MeSCH <sub>2</sub> CH <sub>2</sub>	Br	<b>663b</b> ; <i>n</i> = 2	85	99 (S)
3	<b>c</b> = <i>i</i> -Pr	Br	<b>663c</b> ; <i>n</i> = 2	79	99 <sup>a</sup>
4	<b>a</b> = Bn	Br	<b>670a</b> ; <i>n</i> = 3	91	99 (S)
5	<b>b</b> = MeSCH <sub>2</sub> CH <sub>2</sub>	Br	<b>670b</b> ; <i>n</i> = 3	91	98 (S)
6	<b>c</b> = <i>i</i> -Pr	Br	<b>670c</b> ; <i>n</i> = 3	94	98 <sup>a</sup>
7	<b>a</b> = Bn	Br	<b>667a</b> ; <i>n</i> = 4	73	90 <sup>a</sup>
8	<b>b</b> = MeSCH <sub>2</sub> CH <sub>2</sub>	Br	<b>667b</b> ; <i>n</i> = 4	86	88 <sup>a</sup>
9	<b>c</b> = <i>i</i> -Pr	Br	<b>667c</b> ; <i>n</i> = 4	74	94 <sup>a</sup>
10	<b>a</b> = Bn	I	<b>667a</b> ; <i>n</i> = 4	97	97 <sup>a</sup>
11	<b>b</b> = MeSCH <sub>2</sub> CH <sub>2</sub>	I	<b>667b</b> ; <i>n</i> = 4	89	97 <sup>a</sup>
12	<b>c</b> = <i>i</i> -Pr	I	<b>667c</b> ; <i>n</i> = 4	90	98 <sup>a</sup>

<sup>a</sup> The configuration was not reported.

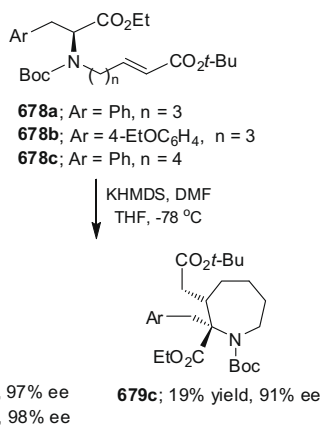
Table 13

Asymmetric cyclization of serine derivatives

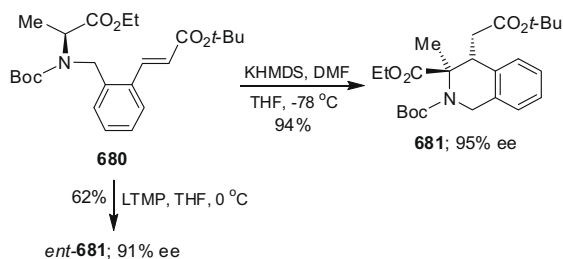


Entry	Substrate	Product	Yield (%)	ee (%)
1	<b>672a</b> ; R = <i>t</i> -Bu	<b>675a</b> ; <i>n</i> = 2	74	92 <sup>a</sup>
2	<b>673a</b> ; R = Bn	<b>676a</b> ; <i>n</i> = 3	84	86 (S)
3	<b>673b</b> ; R = Me	<b>676b</b> ; <i>n</i> = 3	75	82 (S)
4	<b>673c</b> ; R = MOM	<b>676c</b> ; <i>n</i> = 3	72	82 (S)
5	<b>673d</b> ; R = TBDPS	<b>676d</b> ; <i>n</i> = 3	13	88 (S)
6	<b>673e</b> ; R = PMB	<b>676e</b> ; <i>n</i> = 3	88	92 (S)
7	<b>673f</b> ; R = <i>t</i> -Bu	<b>676f</b> ; <i>n</i> = 3	89	93 (S)
8	<b>674a</b> ; R = <i>t</i> -Bu	<b>677a</b> ; <i>n</i> = 4	77	94 <sup>a</sup>

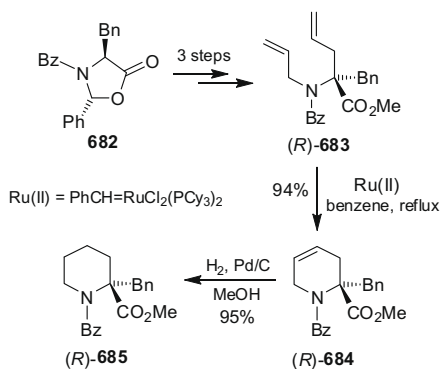
<sup>a</sup> The configuration was not reported.



Scheme 146.



Scheme 147.



Scheme 148.

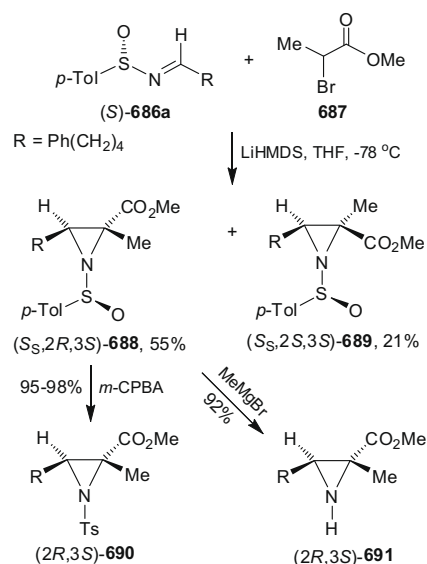
### 3.4. Resolution procedures

#### 3.4.1. Chemical resolution

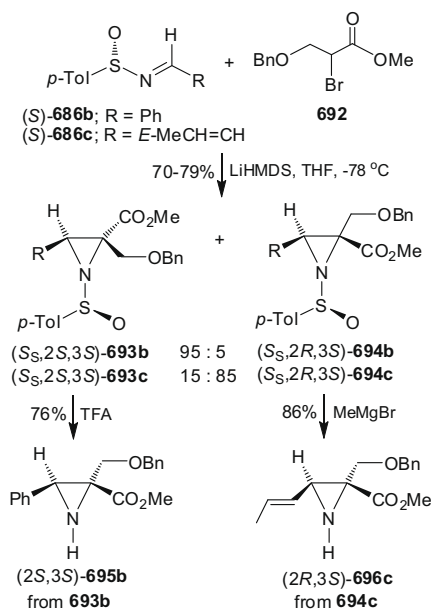
Reaction of alcohol ( $\pm$ )-**726**, obtained from ( $\pm$ )-**725**,<sup>279</sup> with (*R*)-methoxytrifluorophenylacetic acid [(*R*)-MTPA] in the presence of *N,N'*-dicyclohexylcarbodiimide (DCC) and DMAP followed by crystallization gave the diastereoisomeric esters (1*S*,2*S*,4*R*,2'*R*)-**727** and (1*R*,2*R*,4*S*,2'*R*)-**728** in 95% yield and >95% enantiomeric purity. Hydrolysis of **727** and **728** with methanolic NaOMe followed by hydrolysis with 6 N HCl at 60 °C furnished the enantiomerically pure (1*S*,2*S*,4*R*)-**729** and (1*R*,2*R*,4*S*)-**729**, respectively, and these are analogues of 3-hydroxyproline (Scheme 159).<sup>280</sup>

#### 3.4.2. HPLC resolution

Preparative HPLC resolution of  $\beta$ -lactam ( $\pm$ )-**730** on CSP-1 as a chiral stationary phase gave the  $\beta$ -lactams (*S*)- and (*R*)-**730** with 85% and 92% enantiomeric purity. Subsequent saponification of these compounds provided the conformationally constrained amino acids (*S*)- and (*R*)-**731**. On the other hand, reduction of the



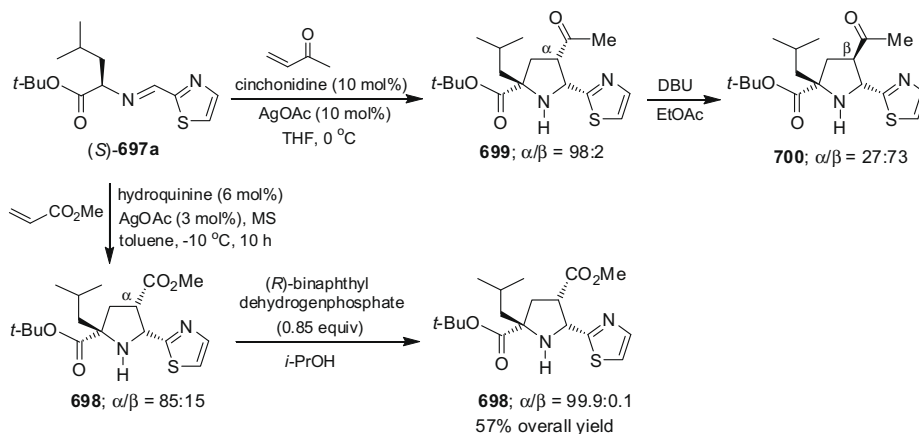
Scheme 149.



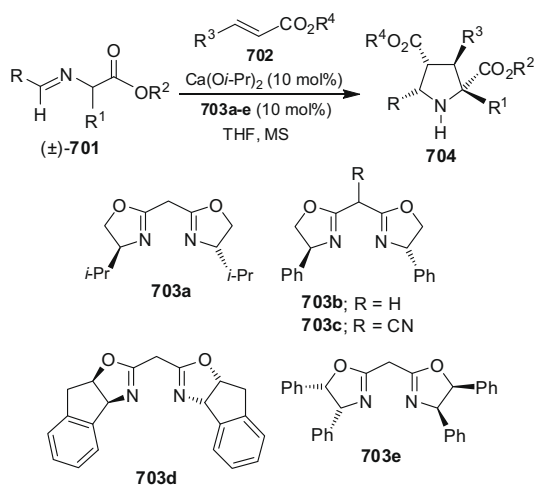
Scheme 150.

amide function of (*S*)- and (*R*)-**730** with Ph<sub>2</sub>SiH<sub>2</sub> and RhH(CO)(PPh<sub>3</sub>)<sub>3</sub> followed by cleavage of PMB protecting group under H<sub>2</sub> and Pd(OH)<sub>2</sub> provided the enantiomerically pure Phe-derived conformationally constrained amino esters (*S*)- and (*R*)-**732** (Scheme 160).<sup>281</sup>

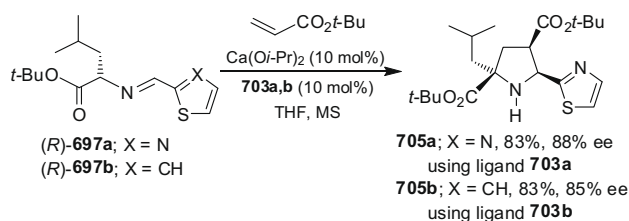
Preparative HPLC resolution of ( $\pm$ )-**733**, obtained from **545a**, on CSP-1 as a chiral stationary phase gave the enantiomerically pure (1*S*,2*S*,4*R*)-**733** and (1*R*,2*R*,4*S*)-**733**, which were separately treated with 6 N HCl to give the enantiomerically pure proline-phenylalanine chimeras (1*S*,2*S*,4*R*)- and (1*R*,2*R*,4*S*)-**734** in 95% yield as the hydrochloride salt. Oxidative cleavage of the phenyl substituent on the azabicyclic ring of (1*S*,2*S*,4*R*)- and (1*R*,2*R*,4*S*)-**733** produced the corresponding carboxylic acids (1*S*,2*R*,4*R*)- and (1*R*,2*S*,4*S*)-**735** in 45% yield. Hydrolysis of these compounds provided the enantiomerically pure (1*S*,2*R*,4*R*)- and (1*R*,2*S*,4*S*)-3-carboxyproline analogues **736** in 95% yield. On the other hand, the conversion of the carboxylic acid function of (1*S*,2*R*,4*R*)- and (1*R*,2*S*,4*S*)-**735** into



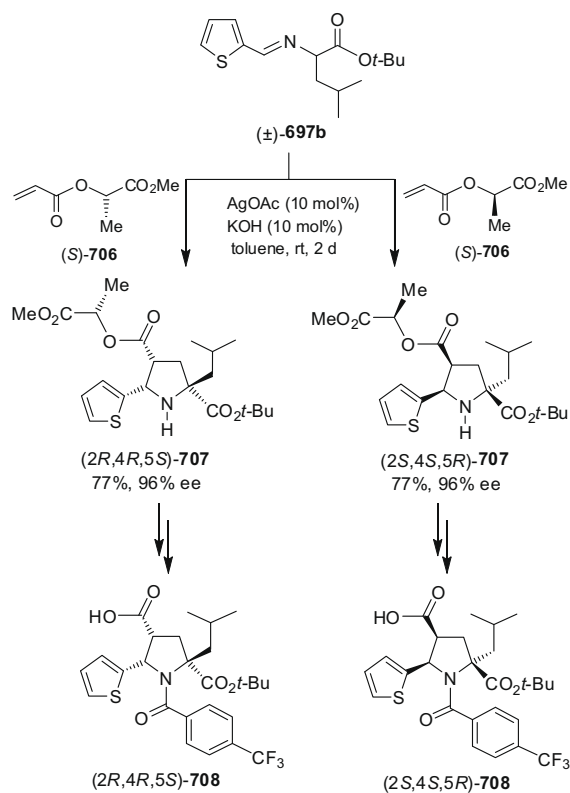
Scheme 151.



Scheme 152.



Scheme 153.



Scheme 154.

methyl alcohols (1S,2R,4R)- and (1R,2S,4S)-737 was carried out by treatment with isobutylchloroformate (IBCF) and triethylamine followed by reduction with  $\text{NaBH}_4$ . Finally, Dess–Martin oxidation of the alcohol function of (1S,2R,4R)- and (1R,2S,4S)-737 gave the corresponding aldehyde derivatives (1S,2R,4R)- and (1R,2S,4S)-738 in 80% yield, and these proved to be a versatile synthetic intermediate in the preparation of a wide variety of  $\beta$ -substituted azabicyclic prolines (Scheme 161).<sup>282</sup>

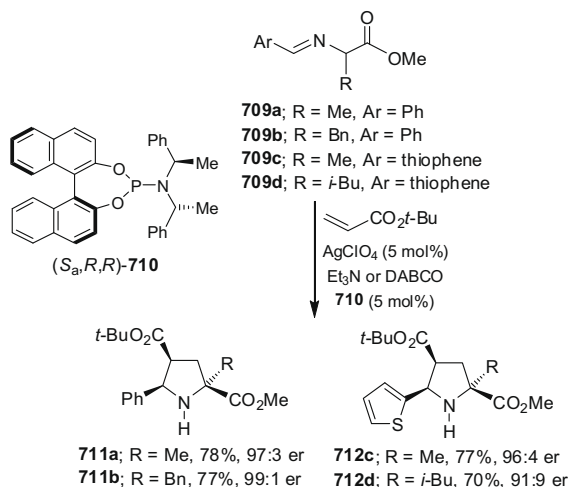
### 3.5. Miscellaneous and notes added in proofs

Several other special cyclization procedures useful for very particular cases have been reported. For example, the Pictet–Spengler cyclization of *N*-sulfonyl- $\beta$ -phenylethylamines 739a,b with menthyl  $\alpha$ -chloro- $\alpha$ -phenylseleno propionate 740 in the presence of

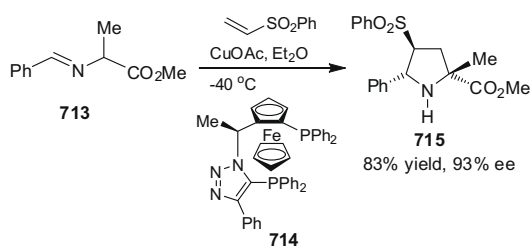
$\text{SnCl}_4$  gave the corresponding 1,2,3,4-tetrahydroisoquinoline-1-carboxylates derivatives 741a,b in moderate yield and good diastereoselectivity after crystallization (Scheme 162).<sup>283</sup>

Pictet–Spengler cyclization of quaternary oxazolidines 742a–d in the presence of  $\text{TiCl}_4$  and  $\text{Et}_3\text{N}$  provided the corresponding tetrahydroisoquinolines 743a–d with good regioselectivity, which by cleavage of the benzyl functionality under  $\text{H}_2$  and  $\text{Pd}(\text{OH})_2$  gave the quaternary amino acids 744a–d in 30–96% yield (Scheme 163).<sup>284</sup>

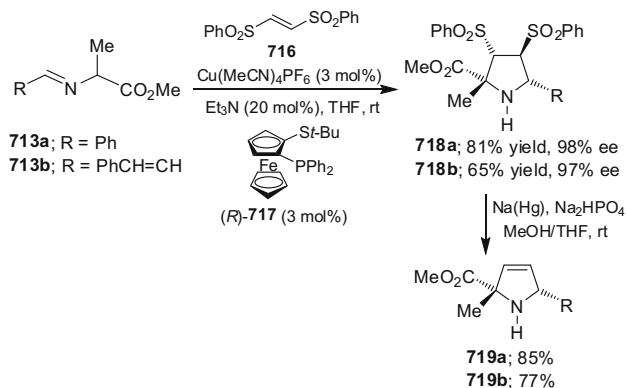
On the other hand, Pictet–Spengler cyclization of quaternary *N*-Boc-*N*-MOM- $\alpha$ -methyl- and  $\alpha$ -allyltryptophan derivatives 746a,b, obtained from alkylation of 745, with HCl in ethyl acetate afforded the corresponding tryptoline derivatives 747a,b in good yield, where the MOM protecting group serves as a formaldehyde equivalent (Scheme 164).<sup>285</sup>



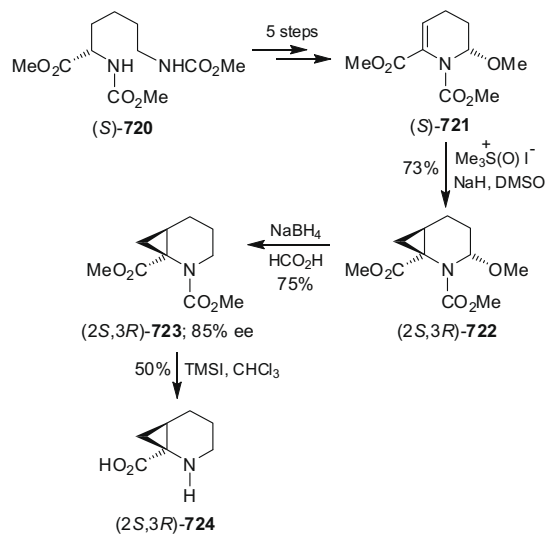
Scheme 155.



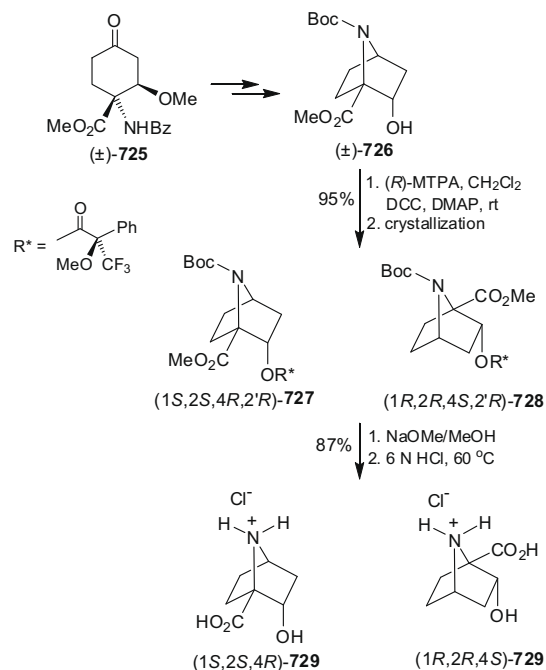
Scheme 156.



Scheme 157.



Scheme 158.



Scheme 159.

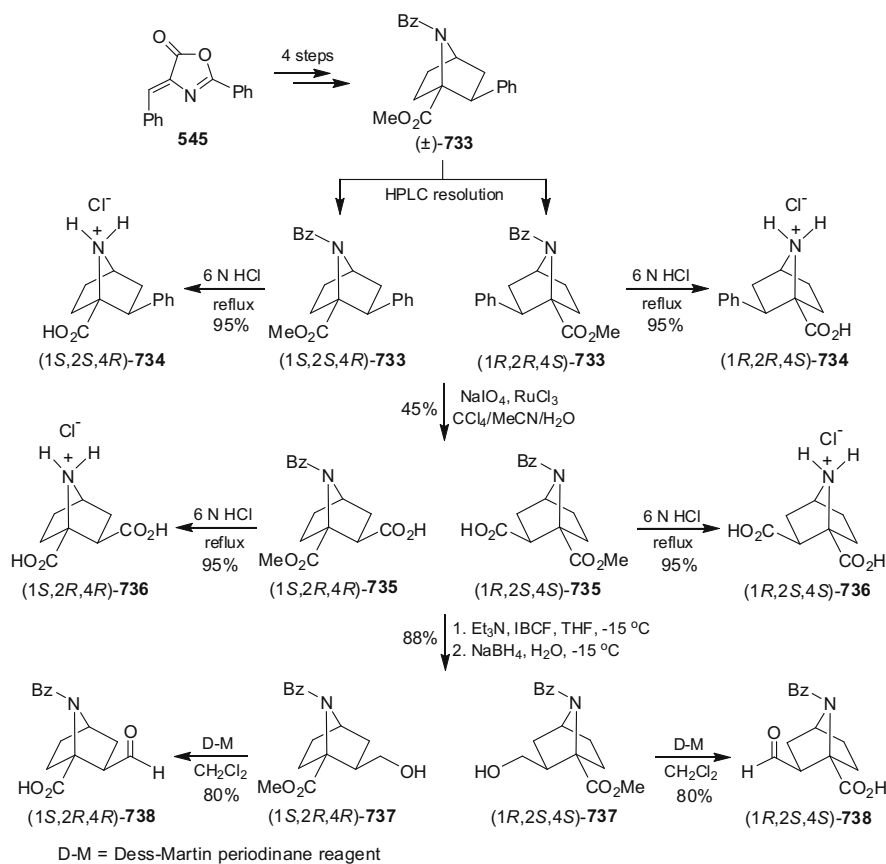
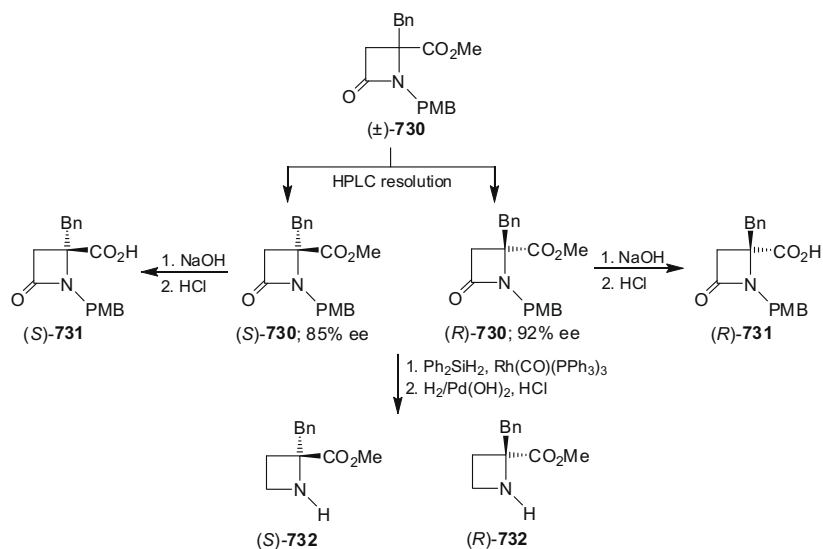
Reaction of enantiopure quaternary  $\alpha$ -amino acid derivative **748** with paraformaldehyde in formic acid followed by treatment with H<sub>2</sub>O and TsOH provided the lactone *cis*-**752** and the hydroxy ester *trans*-**753** in 50% and 32% yield, respectively. The transformation from **748** to *cis*-**752** and *trans*-**753** should occur through the chair-like *N*-tosyliminium intermediate **749** followed by cyclization to give the secondary cation **750**, which is stabilized by the ester carbonyl group to produce the dioxycarbenium ion **751**. Finally, the hydrolysis of **751** followed by treatment with TsOH gave the lactone *cis*-**752** and the hydroxy ester *trans*-**753** (Scheme 165).<sup>286</sup>

Clayden et al.<sup>287</sup> reported the synthesis of  $\alpha$ -methyl kainic acid (an  $\alpha$ -methylproline 3,4-disubstituted system) by the stereospecific lithiation–dearomatizing cyclization of the chiral benzamide (*R,R*)-**754**. Thus, reaction of the benzamide (*R,R*)-**754** with *tert*-BuLi at  $-78$  °C followed by treatment with 0.5 M HCl produced the

corresponding bicyclic compound **755** as a single stereo- and regioisomer in 70% yield. Conjugated addition of Me<sub>2</sub>CuLi to **755** followed by cleavage of the benzyl fragment with CAN and subsequent treatment with (Boc)<sub>2</sub>O gave **756** in 66% yield, which in turn was transformed into  $\alpha$ -methyl kainic acid after 12 steps (Scheme 166).

Finally, during the corrections of this review, Makosza et al.<sup>288</sup> reported the stereoselective synthesis of (*2R*)-4-nitroarylprolines **759a–c** through oxidative nucleophilic substitution of hydrogen in nitroarenes using the chiral carbanion of *L*-proline derivative (*3S,7aR*)-**590**, applying the self-reproduction of chirality methodology. Thus, treatment of (*3S,7aR*)-**590** with KHMDS in THF–DMF at  $-78$  °C followed by the addition of corresponding nitroarene afforded the  $\sigma^H$  adduct **757**, which by oxidation with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) gave the 4-nitroaryl derivatives

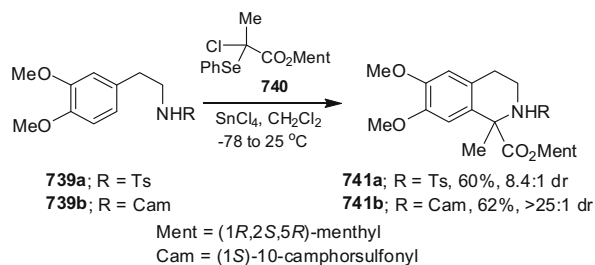




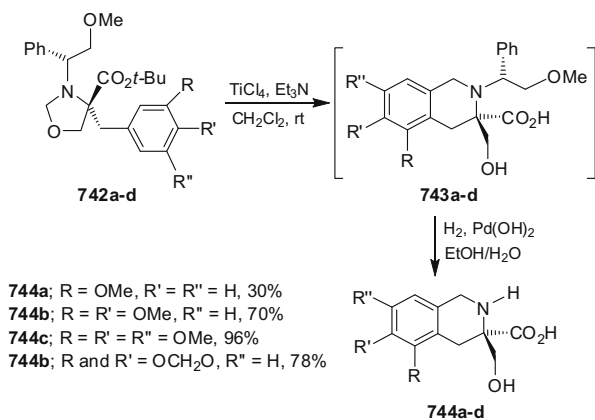
**758a–c** as a single detectable diastereoisomers with 29–72% yield (reaction with 2-fluoro, 2-chloro and 2-methylnitrobenzene failed). Hydrolysis of (3*S*,7*aR*)-**758a–c** with HBr and subsequent treatment with propylene oxide led to the (2*R*)-4-nitroarylprolines **759a–c** with 55–85% yield (Scheme 167).

#### 4. Concluding remarks

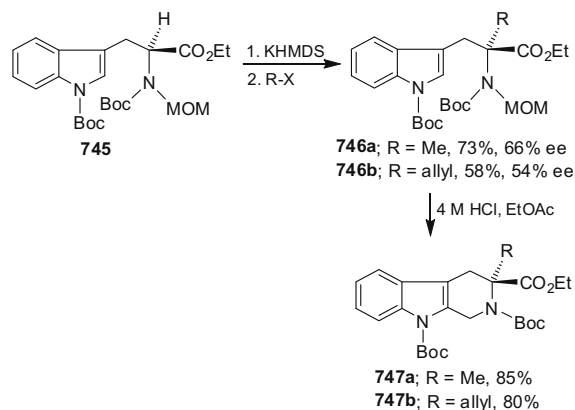
In this review, we have covered recent progress in the development of new synthetic methodologies for the preparation of cyclic  $\alpha,\alpha$ -dialkylamino acids, and we have also discussed extensions to



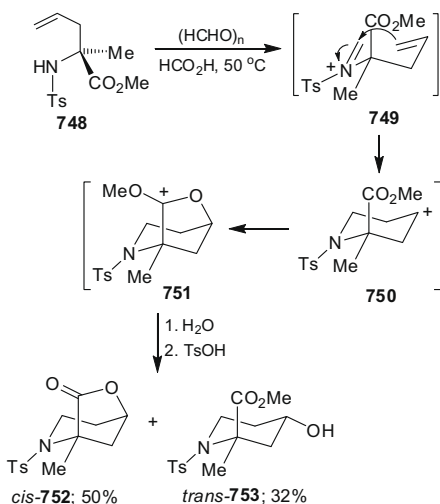
Scheme 162.



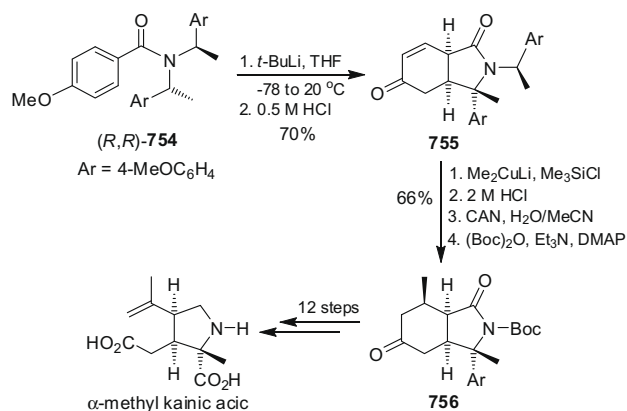
Scheme 163.



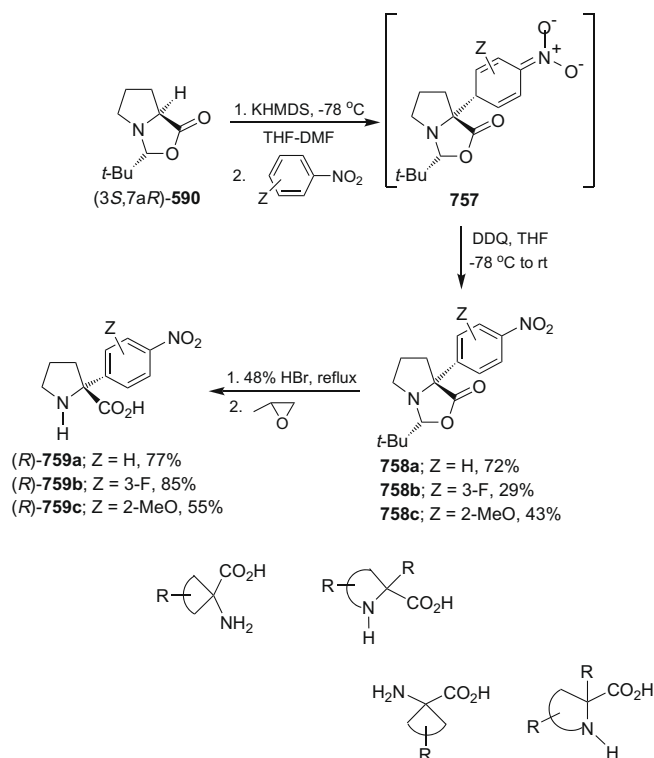
Scheme 164.



Scheme 165.



Scheme 166.



Scheme 167.

well-established synthetic routes. The use of cyclic compounds as starting materials is one of the most convenient procedures reported.

The construction of the cycle using cyclization or cycloaddition reactions both in a diastereoselective or in an enantioselective manner is one excellent alternative. All of these strategies can be completed with the use of resolution procedures (chemical, enzymatic or chromatographic) that have emerged as another good alternative.

All of these methodologies give the synthetic organic chemist the opportunity to select the most appropriate way to obtain the desired cyclic  $\alpha,\alpha$ -dialkylamino acid in enantiomerically pure form on both a laboratory scale and a multigram scale.

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n (Group E40 and Project MI041/2007). This project has been funded in whole or in part with Federal funds from the National Cancer Institute, National Institutes of Health, under Contract Number N01-CO-12400. The content of this publication does not necessarily reflect the view or the policies of the Department of Health and Human Services, nor does the mention of trade names, commercial products, or organizations imply endorsement by the US Government. This research was supported (in part) by the Intramural Research Program of the NIH, National Cancer Institute, Center for Cancer Research.

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