Asymmetric Synthesis of ß-Amino Acids and α-Substituted β-Amino Acids

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1 Introduction

In the recent years, there has been increasing interest in the synthesis of proteinogenic and non-proteinogenic amino acids.[1] This is due to the wide utility of such compounds as components of proteins, peptides and as starting materials for the synthesis of naturally occurring biologically active compounds.

α-Amino acids[2] are the most abundant in this class of compounds, as they are the main components of peptides, enzymes and proteins,[3] and they have been utilised as chiral reagents for a variety of synthetic applications. β- and γ-amino acids, although less abundant than their α-analogues, are also present in peptides,[4] and in the free form they show interesting pharmacological effects. Enantiomerically pure β-amino-α-hydroxy acids are of considerable importance because they are the crucial components of medicinally useful molecules such as taxol,[5] an anti-tumour agent, bestatin,[6] an immunological response modifier, and certain small peptides possessing antihypertensive activity. β,γ-Diamino acids are also present in nature; for example the emericedins are inhibitors of long chain fatty acid oxidation and were isolated from the culture broth of *Emericella quadrilineata* IFO 5859.[7] Furthermore β-amino acids are synthetic precursors of β-lactams, which are potentially biologically active and of current interest.[8]

In addition many physiologically active compounds are present among the class of γ-amino acids. γ-Aminobutyric acid (GABA) is a very simple compound and a major inhibitory neurotransmitter; indeed when the concentration of GABA in the brain decreases, seizures and other neurological disorders occur.[9] β-Hydroxy γ-amino acids also display important biological activities: (*R*)-carnitine for example plays an important role in converting stored body fat into energy, because its primary role is to transport large fat molecules into cellular compartments where the fats can be metabolised. (2*S*,3*S*,4*R*)-4-Amino-3-hydroxy-2-methylpentanoic acid is a constituent fragment of the antitumour antibiotic bleomycin and the tripeptide mollusc toxin janolusimide. Dolaisoleuine (DIL) is a component of the polypeptide dolastatin 10,[10] one of the most active antineoplastic substances presently known.

The design of receptor-selective peptide and peptidomimetic ligands with highly potent and specific biological properties[11] has become one of the most important areas in bioorganic chemistry, medicinal chemistry, molecular biology and other related research areas. At the present time there is rapid growth in the number of endogenous and exogenous biologically active peptides under investigation. Most of these peptides are short lived molecules, easily degraded by enzymes, with little or no therapeutic use. To convert them into useful drugs it is often necessary to transform these compounds into more resistant molecules.[12] Small cyclic peptides show increased resistance to enzymatic degradation and constrained flexibility as compared to their linear analogues. Consequently, they frequently exhibit higher biological selectivity and activity. Furthermore incorporation of α-alkyl α-amino acids into peptides results in conformational restrictions and increased rigidity, leading to enhanced resistance towards protease enzymes and to the favouring of particular secondary structures. Indeed, owing to severe restrictions of the rotational freedom around their N−C(α) and C(α)−C=O bond, α-alkylated α-amino acids may be generally expected to display helix-inducing properties.[13]

There is considerable interest in the synthesis of unnatural amino acids in order to introduce them into a peptide sequence.[14] They can be divided into α-substituted α-amino acids,[15] β-amino acids and γ-amino acids.

This review is intended to give a brief summary of some of the more recent developments in the synthesis of β-amino acids and α-substituted β-amino acids. The first part is concerned with an overview of the naturally occurring compounds containing β-amino acids. The second part summarises results on the synthesis of natural and unnatural β-amino acids, by routes involving the enzymatic resolution of racemic mixtures, the intermediary preparation of perhydropyrimidin-4-ones and the conjugate addition of ammonia equivalents to α, β-unsaturated esters and imides which are all topics near to the scientific interest of the authors. For a more complete overview of the methods developed to obtain enantiomerically pure β-amino acids, including hydrogenation of 3-aminoacrylates and nucleophilic addition of enolates to imines, see two recent excellent reviews.[16]

2 Natural Occurrence of Molecules containing β-Amino Acids

Cyclic and non-cyclic peptides with important pharmacological properties have been isolated from marine organisms or from plants. These compounds contain, in addition to unusual acid

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Claudia Tomasini was born in Bologna and studied at the University of Bologna, where she graduated in 1982 and gained her Ph.D. in 1987. Thereafter she obtained a grant from Italian C.N.R. (National Research Council) spending a year at Dyson Perrins Laboratory in Oxford, working with Professor Jack E. Baldwin. Currently she works as Research Associate at the University of Bologna. Her current research interests are centred on the stereoselective functionalisation of double bonds for the synthesis of polysubstituted α- and β-amino acids in optically pure form.

moieties such as D-amino acids and hydroxy acids, non-proteinogenic α- and β-amino acids, α-substituted β-amino acids and γ-amino acids. Here we briefly describe the natural occurrence and the properties of some molecules containing β-amino acid derivatives.

2.1 Molecules containing β-Amino Acids and α-Alkyl β-Amino Acids

The dolastatins[10] form an heterogeneous group of potent antineoplastic and cytostatic peptides isolated from the Indian Ocean sea hare *Dolabella auricularia*. They are simply numbered from 1 to 12 and do not have a coherent set of structures. Indeed some are linear and some are cyclic and all contain unusual components such as modified amino acids residues, lactone units, polyketide fragments and thiazole rings. Dolastatins 11 and 12 (Fig. 1) are cyclic depsipeptides, which have recently been isolated and structurally elucidated. These molecules exhibit cell growth inhibitory activity against the murine P388 lymphocytic leukaemia and contain a 2-methyl-3-aminopentanoic acid.

This α-substituted β-amino acid is also contained in the structure of majusculamide C[17] (Fig. 2), a cyclic depsipeptide from *Lyngbya majuscula*, which is a toxic blue–green alga and grows abundantly on the pinnacles in the lagoon of Enewetak Atoll in the Marshall Islands. Majusculamide C controls the growth of a number of fungal plant pathogens such as *Phytophthora infestans*, the causative

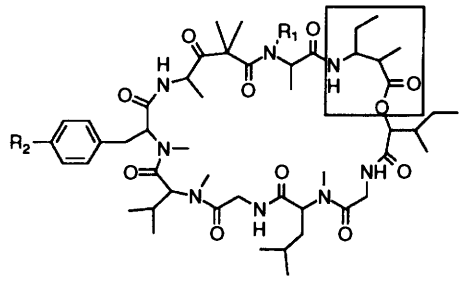


Figure 1 Dolastin 11, R_1=H; R_2=CH_3O
Dolastin 12, R_1=CH_3; R_2=H

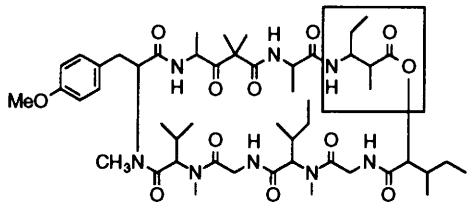


Figure 2 Majusculamide C

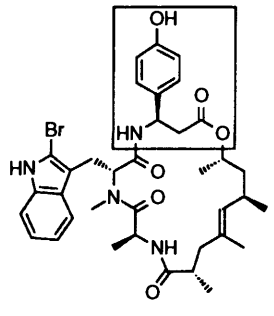


Figure 3 Jasplakinolide

organism of tomato late blight, and *Plasmopora viticola*, the causative organism of grape downy mildew.

β-Tyrosine, an unsubstituted β-amino acid, is contained in jasplakinolide[18] (Fig. 3), which was the first mixed macrocyclic polyketide–depsipeptide to be isolated from a marine organism. This sponge metabolite is of considerable interest because of its anthelminthic, insecticidal, ichthyotoxic and antifungal properties.

β-Phenylglycine [(+)-(*R*)-3-amino-3-phenylpropanoic acid] is a

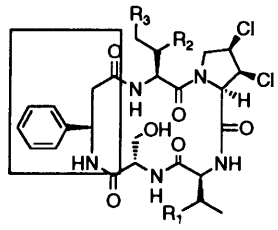


Figure 4 Astin A: R_1=H, R_2=OH, R_3=H
Astin B: R_1=OH, R_2=H, R_3=H
Astin C: R_1=H, R_2=H, R_3=H
Cyclochlorotine: R_1=H, R_2=H, R_3=OH
Asterin: R_1=H, R_2=H, R_3=CH_3

β-amino acid structurally related to β-tyrosine and is contained in a group of cyclic pentapeptides, astins A, B and C and asterin[19] (Fig. 4), from the medicinal plants *Aster tataricus* L.f. (Compositae), known in Chinese medicine as containing several terpenoids and saponins. Also astins A, B and C are antitumour agents. A very similar molecule is cyclochlorotine,[20] which is one of the toxic metabolites of *Penicillium islandium* Sopp, the mould of islandia yellow rice.

Furthermore, longer chain and more complicated α-substituted β-amino acids are contained in onchidin[21] (Fig. 5) and motuporin[22] (Fig. 6), which are both cytotoxic cyclic peptides. Indeed, onchidin

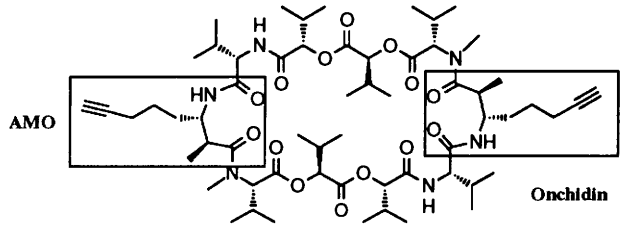


Figure 5

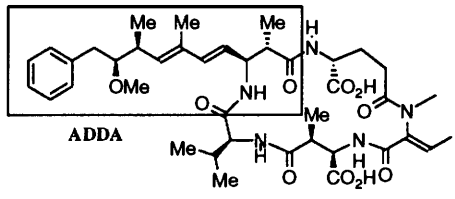


Figure 6 Motuporin

is a cytotoxic depsipeptide isolated from the pulmonate mollusc *Onchidium* sp. Its cyclic structure is made of two identical halves and contains two moieties of a new β-amino acid: 3-amino-2-methyl oct-7-ynoic acid (AMO).

Motuporin is a cyclic pentapeptide from *Theonella swinhoei* Gray collected in Papua New Guinea and is a potent protein phosphatase-1 inhibitor. It contains a very complicated α-methyl β-amino acid bearing several chiral centres, simply called ADDA.

2.2 Molecules containing β-Amino α-Hydroxy Acids

β-Amino-α-hydroxy acids are important components in a variety of biologically interesting compounds. A number of protease inhibitors, for example, derive their activity from the ability of the β-amino α-hydroxy acid motif to act as a transition state mimic of peptide hydrolysis. Here we show some β-amino α-hydroxy acids contained in biologically active molecules. Most of them are naturally occurring, but some have been obtained by synthesis as promising anti-AIDS or antihypertensive agents.

One of the best known molecules containing an β-amino α-hydroxy acid is taxol[5] (Fig. 7), which is composed of a polyoxygenated diterpene and (2*R*,3*S*)-phenylisoserine. Although the role of the phenylisoserine side chain of taxol has not yet been fully

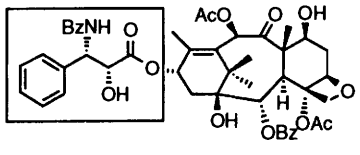


Figure 7 Taxol

determined, it plays an import role in the biological function of this antitumour agent For instance one of the C-2′ or C-3′ polar functionalities can be removed without significant effect, but the removal of both or the interchange of their position causes dramatic loss of activity

Another example of a biologically active β-amino α-hydroxy acid is isothreonine, which is the side chain of the glycopeptide 1-*N*-(D-*threo*-3-amino-2-hydroxybutanoyl)-2′,3′-dideoxykanamicin A[23] (Fig 8), a good antibacterial agent

Bestatin[6] (Fig 9) is a simple dipeptide containing (2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanoic acid [abbreviated as (2*S*,3*R*)-

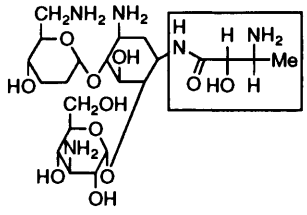


Figure 8 Dideoxykanamicin A

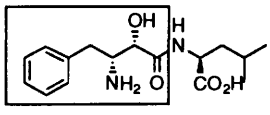


Figure 9 Bestatin

AHPA] and L-leucine and is an immunological response modifier It has been isolated from culture filtrates of *Streptomyces olivoreticuli* and inhibits aminopeptidase B and leucine aminopeptidase but not aminopeptidase A, carboxypeptidases, or endopeptidases Studies on derivatives in which the amino group is protected show that the free amino group is essential for the activity and the carboxyl group is also important

The (2*S*,3*S*) epimer of AHPA is contained in two synthetic tripeptides, kynostatins (KNI)-227 and (KNI)-272[24] (Fig 10), which are highly potent HIV-1 protease inhibitors and are promis-

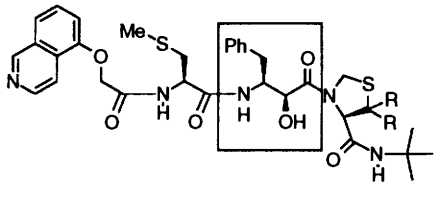


Figure 10 (KNI) 227, R=Me
(KNI) 272, R=H

ing candidates as selective anti-AIDS agents The configuration of the hydroxy group has a profound effect, indeed, replacement of (2*S*,3*S*)-AHPA with its (2*S*,3*R*) epimer leads to a significant loss of activity This stereochemical preference is surprising since it is opposite to that observed for bestatin

Many others small peptides have been isolated from sponges or algae and contain β-amino α-hydroxy acids For instance, keramamide F (KF)[25] (Fig 11) is a cytotoxic natural product found in small quantities in a *Theonella* sponge This cyclic peptide contains a remarkable array of unusual amino acids including an isoserine residue as a side chain

Scytonemyn A[26] (Fig 12) is a cyclic peptide from the blue–green alga *Scytonema* sp (strain U-3-3) (Scytonemataceae) and possess

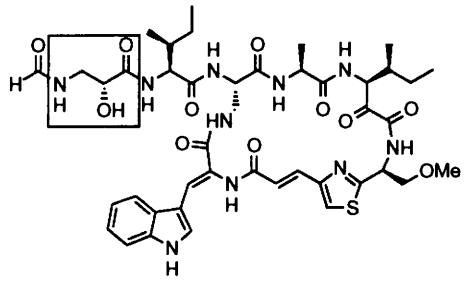


Figure 11 Keramamide F

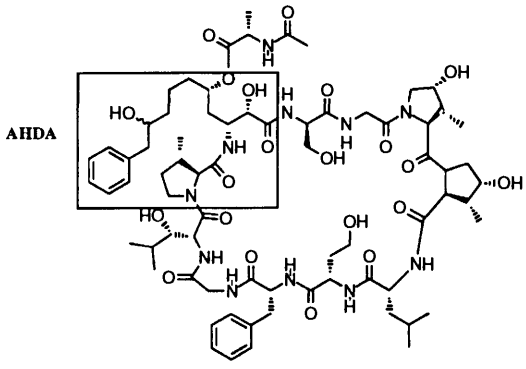


Figure 12 Scytonemin A

potent calcium antagonistic properties As well as some proteinogenic α-amino acids, such as alanine, glycine and leucine, scytonemin A contains (2*S*,3*R*,5*S*)-3-amino-2,5,9-trihydroxy-10-phenyldecanoic acid (AHDA) which is a novel β-amino acid including several chiral centres

Microsclerodermins[27] (Fig 13) are cyclic hexapeptides from a deep water sponge of the genus *Microscleroderma* The structures of microsclerodermins A and B are very similar and were determined by interpretation of spectral data They both contain a novel and complex β-amino acid (2*S*,3*R*,4*S*,5*S*,6*S*,11*E*)-3-amino-6-methyl-12-(*p*-methoxyphenyl)-2,4,5-trihydroxydodec-11-enoic acid (AMMTD) and a known γ-amino acid such as GABOB (3*R*)-4-amino-3-hydroxybutyric acid

Finally microginin[28] (Fig 14) is a linear tetrapeptide and contains a novel 3-amino-2-hydroxydecanoic acid (called AHDA like the previous one) in the (2*S*,3*R*) configuration The molecule has recently been isolated from the freshwater blue–green alga

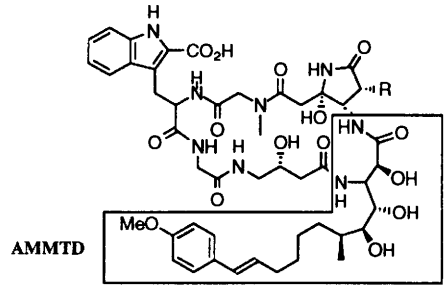


Figure 13 Microsclerodermin A, R=OH
Microsclerodermin B, R=H

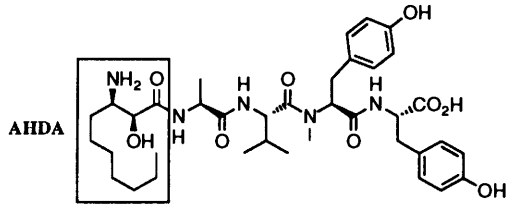


Figure 14 Microginin

Microcystis aeruginosa and was found to possess angiotensin-converting enzyme (ACE) inhibitory properties, which is of considerable medical interest since ACE inhibitors have been developed as antihypertensive agents

Naturally occurring ACE inhibitors often suffer from problems such as poor oral absorption, short duration of action, proteolytic instability and rapid biliary excretion For this reason some new synthetic compounds are currently being developed as promising antihypertensive agent Figs 15[29] and 16[30] show the structures of synthetic renin[31] inhibitors, containing the novel β-amino-α-hydroxy acid cyclohexylnorstatine, (2*R*,3*S*)-3-amino-4 cyclohexyl-2-hydroxybutyric acid

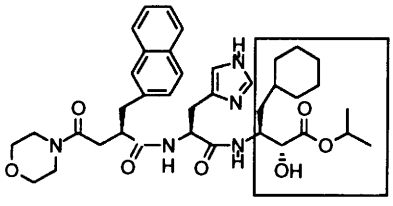


Figure 15

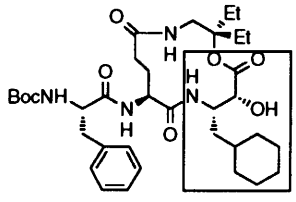


Figure 16

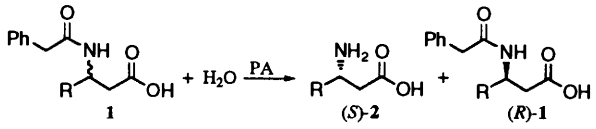
3 Synthetic Methods

3.1 Enzymatic Resolution of Racemates

Several methods for the synthesis of racemic β-amino acids have been developed These methods are often cheap and easy to perform, but an extra step is essential to resolve the racemate, as the fundamental requirement in the design of these compounds is to obtain amino derivatives with high optical purity In addition to the classical resolution of racemates utilising the formation of diastereoisomeric salts by reaction with enantiomerically pure amines, enantiomerically pure β-amino acids have recently been prepared by routes involving the enzymatic resolution of racemates

Hydrolytic enzymes are especially well suited for the kinetic resolution of racemic α-amino acid derivatives [32] This method has therefore found numerous industrial applications Derivatives such as esters, amides or hydantoins are selectively hydrolysed The different approaches are classified according to the bond cleaved by enzymatic assistance The major processes are amide or nitrile hydrolysis by *aminopeptidases* or *nitrilases*, cleavage of *N*-acyl groups by *acylases*, ester hydrolysis by *lipases* or *proteases*, and cleavage of hydantoins by *hydantoinases* If, after separation, only one enantiomer is required, the undesired one can be racemised and the reaction mixture can be separated again

Despite the prominent role of the enzymatic resolution of racemates in the production of α-amino acids, far fewer results on its application for the preparation of enantiopure β-amino acids are available Indeed a disadvantage of the enzymatic methods is often the narrow tolerance of the substrate, thus the different position of the chiral centre, usually α to the carbonyl group, can be a reason why the more popular methods for the enzymatic separation of α-amino acid derivatives fail when applied to β-amino acid derivatives Until now the most promising method appears to be the selective hydrolysis of *N*-phenylacetyl derivatives of β-amino acids with penicillin acylase (PA) Indeed several *N* phenylacetyl β-amino acids have been selectively hydrolysed with good results by two research groups [33] Both enantiomers can be obtained in good yield with a high degree of optical purity These advantage are rarely experienced when resolution based upon the crystallisation of diastereoisomeric derivatives is used Examination of the data shows that, for all substrates examined by both groups, penicillin acylase preferentially hydrolyses the (*S*)-enantiomer (Scheme 1, Table 1)



Scheme 1

Table 1 Substrates examined and results for the hydrolysis experiments

R	$[\alpha]_D$ of (*S*) **2**	Yield of (*S*) **2** (%)[a]	$[\alpha]_D$ of **2** (lit)[b]
CH_3[20a]	+34 8	78	+35
C_2H_5[20a]	+38 0	75	+38 5
Ph[20a]	+7 5	88	−6 9[c]
CH_3[20b]	+38 3	77	+34 3
Ph[20b]	+6 5	—	−6 3
CF_3[20b]	+27 6	86	—
C_2F_5[20b]	+37 0	78	—
C_3F_7[20b]	+26 9	84	—
2 FC_6H_4[20b]	+3 0	67	—
4 FC_6H_4[20b]	+3 9	73	—

[a] Yield referred to theoretical 50% of the (*R*) isomer is reported [b] See refs 33(*a*) and 33(*b*) [c] The $[\alpha]_D$ value

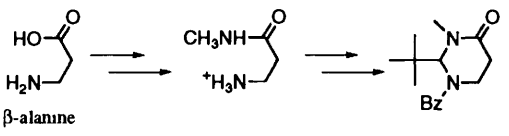
Penicillin acylase is used on an industrial scale for the production of 6 aminopenicillanic acid, the starting material for the synthesis of semi-synthetic penicillins Furthermore it is well established that it shows a high degree of stereoselectivity in hydrolysing phenylacetyl esters and amides, together with a low degree of substrate specificity The protein has a single-amino-acid catalytic centre [34] Its *in vivo* role remains unclear, however, and the observation that expression of the *Escherichia coli* enzyme *in vivo* is regulated by both temperature and phenylacetic acid has prompted speculation that the enzyme could be involved in the assimilation of aromatic compounds as carbon sources in the organism's free living mode The crystal structure of penicillin acylase has recently been reported and shows that the protein is kidney shaped in cross-section with a deep cup-shaped depression in the centre The structures of the enzyme complexed with phenylacetic acid (a competitive inhibitor) locate the binding site for the side chain of the substrate The phenyl moiety of the inhibitor points towards the interior of the protein into a mainly hydrophobic pocket which is lined with many aromatic residues and hydrophobic side chain The complementary fit explains the specificity of the enzyme towards the phenyl moiety of a broad range of substrates The proposed catalytic mechanism shows the role of the bridging water (as a virtual base) and the α amino group to enhance the nucleophilicity of serine B1

3.2 Synthesis of β-Amino Acids and α-Substituted β-Amino Acids through the Intermediary Preparation of Perhydropyrimidin-4-ones

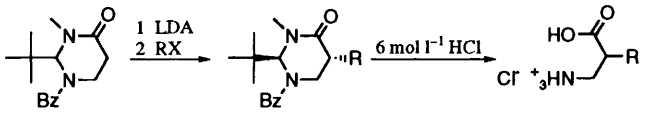
Perhydropyrimidin 4-ones and dihydropyrimidin-4-ones are an interesting class of heterocyclic compounds which represent protected forms of β-amino acids, so that the α- and the β-position can be functionalised as desired

Following a route previously described for the preparation of 2-*tert*-butylimidazolidin-4 one,[35] a useful starting material in the synthesis of α-branched α-amino acids, Juaristi and Seebach envisaged the preparation of 2-*tert*-butylperhydropyrimidin-4-one derivatives starting from β-alanine, *N*-methylamide and pivalaldehyde[36] (Scheme 2)

The perhydropyrimidin-4-one was alkylated with high *trans*-diastereoselectivity *via* the corresponding enolate (Scheme 3) The high diastereoselectivity observed is attributed to the steric



Scheme 2 Bz=PhC(O)



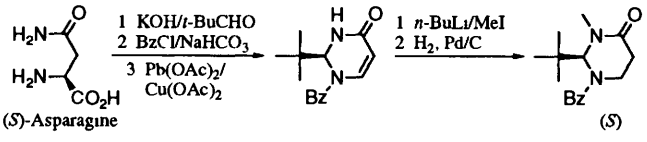
Scheme 3

Table 2 Diastereoselectivity of lithium-enolate alkylations

RX	Diastereoselectivity (%)	Isolated yield (%)
CH_3I	96 7	77
$PhCH_2Br$	95 5	75
Bu^nI	>96 0	76
$n\ C_6H_{13}I$	>96 0	76
$CH_2{=}CHCH_2Cl$	86 0	78

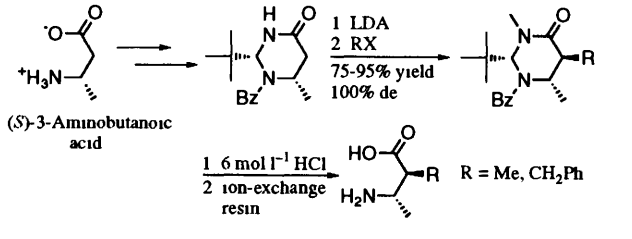
hindrance generated by an axial disposition of the *tert*-butyl group at C-2, which directs addition to the enolate face opposite to this group The acidic hydrolysis of the heterocycle affords in quantitative yield the corresponding racemic α-alkylated β-amino acids (Table 2)

Furthermore the enantiomerically pure (*S*)-2-*tert*-butylperhydropyrimidin-4-one was obtained by replacing β-alanine with (*S*) asparagine,[37] following a procedure described by Konopelsky [38] Indeed the condensation of (*S*)-asparagine with pivalaldehyde, followed by protection of the amino group, afforded the (2*S*,6*S*)-1-benzoyl-2-*tert*-butyl-6-carboxyperhydropyrimidin-4-one The carboxy side chain was eliminated under oxidative decarboxylation conditions and afforded the corresponding enone, which was subsequently reduced *via* catalytic hydrogenation (Scheme 4)



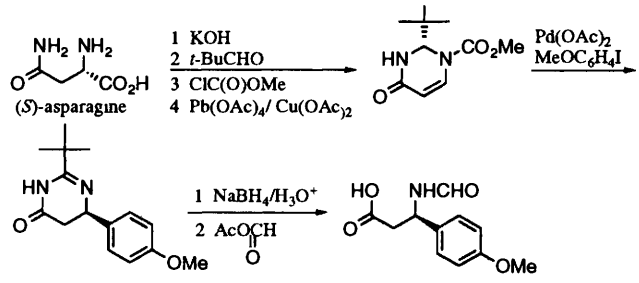
Scheme 4

In order to synthesise enantiomerically pure 2-substituted 3-aminobutanoic acids, 6-methylperhydropyrimidin-4-ones were prepared starting from enantiomerically pure 3-aminobutanoic acid [39] (*R*)- and (*S*)-3-Aminobutanoic acids were obtained pure through separation of the diastereoisomers of the corresponding (1′*S*)-*N*-phenylethyl derivatives In the formation of the corresponding 2-*tert*-butylperhydropyrimidin-4-ones, from each stereoisomer the corresponding *cis*-products predominate (*cis trans* ratio 95 5) The subsequent alkylation [lithium diisopropylamide (LDA), RX] furnishes the 5-substituted derivatives as a single stereoisomer Hydrolysis of these 5,6-dialkylperhydropyrimidin-4-ones leads to the corresponding α-substituted β-amino acids in the free form and high optical purity (Scheme 5)



Scheme 5

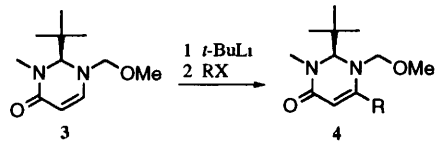
Konopelski, following the theme of 'self-reproduction of chirality' pioneered by Seebach, prepared enantiomerically pure dihydropyrimidinones *via* pivalaldehyde acetalisation of the potassium salt of asparagine to form the corresponding pyrimidinone carboxylate as a single stereoisomer[38] (Scheme 6) Methoxycarbonyl



Scheme 6

functionalisation at the secondary amine followed by oxidative decarboxylation with lead(IV) acetate delivered the corresponding dihydropyrimidin-4-one as a single enantiomer Then, the heterocycle was submitted to palladium-catalysed conjugate addition of aryl iodide, which afforded the desired product as a single stereoisomer Treatment of the adduct with $NaBH_4/H_3O^+$, followed by acidic hydrolysis, afforded (*S*)-β-tyrosine-*O*-methyl ether hydrochloride in high yield

In order to obtain various enantiomerically pure β-amino acids, the chiral dihydropyrimidin-4-one, synthesized from aspartic acid, was deprotonated at C-6 with *tert*-butyllithium at −78°C [40] The corresponding carbanion reacts with alkyl halides and aldehydes to give the corresponding alkylated products in high yield (Scheme 7, Table 3)

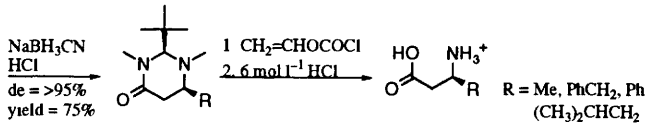


Scheme 7

Table 3 Chemical yield of the alkylation of (*S*)-2-dihydropyrimidin-4-one **3** at C-6

Electrophile	Yield of **4** (%)
CH_3I	95
$PhCH_2Br$	55
CH_3CH_2I	55
PhI	27

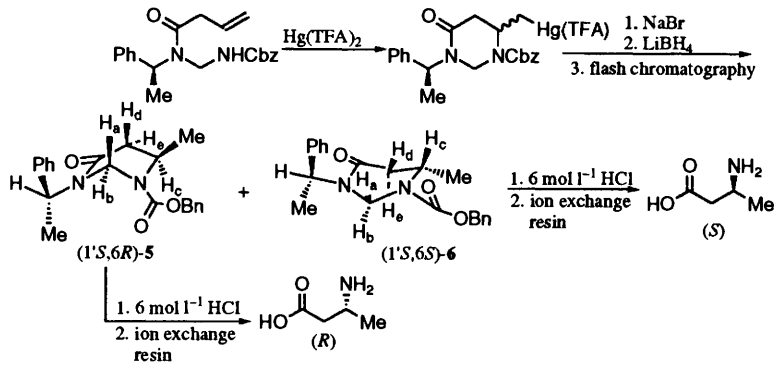
Reduction of the carbon–carbon double bond with $NaBH_3CN$ in the presence of hydrochloric acid afforded the corresponding 2,6-*cis*-perhydropyrimidin-4-one with good yield and high diastereoisomeric selectivity (Scheme 8) Demethylation of the



Scheme 8 R=Me, $PhCH_2$, Ph, $(CH_3)_2CHCH_2$

amine nitrogen and hydrolysis were combined in the last step to give the desired β-amino acids The heterocycle was first treated with vinyl chloroformate in refluxing 1,2-dichloromethane [41] The resulting carbamate was then refluxed with ethanolic HCl to achieved dealkylation and furnished enantiomerically pure β-alkyl β-amino acids

In recent years we have been interested in the electrophile-



Scheme 9

Table 4 Diastereoselectivity and chemical yield for the alkylation of 6-methylperhydropyrimidin-4-ones **5** and **6**

Substrate	*T*/°C	Equiv. of LiHMDS[a]	Alkylating agent	Yield (%)	Dialkylated (%)	*trans: cis* ratio
5	0	0.9	EtI	84.2	—	87:13
5	0	1.1	EtI	78.3	11.4	96:4
5	−20	1	EtI	89.3	3.1	91:9
5	−78 to room temp.	1	EtI	85.8	9.7	94:6
6	0	0.8	EtI	76.8	—	85:15
6	0	1.1	EtI	92.1	7.9	94:6
6	−78 to room temp.	1	EtI	88.5	10.0	97:3
6	0	1	Bu^{t}I	56.1	—	87:13
6	0	1	BnBr	89.8	—	93:7

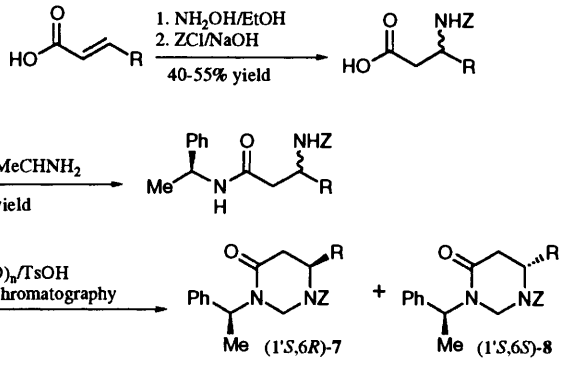
[a] LiHMDS = lithium hexamethyldisilazide

promoted cyclofunctionalisation of unsaturated substrates containing an internal nucleophile, associated with the use of (*S*)-1-phenylethylamine as a chiral source.[42] This strategy affords diastereoisomeric mixtures of heterocycles, which can easily be separated by flash chromatography. Following this approach, our first synthesis of the 6-methylperhydropyrimidin-4-ones started from the amide obtained from the reaction of hexahydrotriazine and but-3-enoyl chloride (Scheme 9). The adduct was recovered in quantitative yield and converted *in situ* into the corresponding amide under an atmosphere of ammonia; mercury(II) trifluoroacetate [$Hg(TFA)_2$] promoted the cyclisation of the benzyloxycarbonyl protected derivative. The reduction of the carbon–mercury bond with $LiBH_4$ delivered the perhydropyrimidin-4-ones in 70% overall yield as a 63:37 diastereoisomeric mixture. The isomers were separated by flash chromatography and separately submitted to acidic hydrolysis, affording respectively (*S*)- and (*R*)-3-aminobutanoic acid after purification on cationic exchange resin. The particular conformation which each heterocycle assumes was established by detailed ^1H NMR studies. Indeed the chiral group on C-1 shows a strong tendency to assume a rigid conformation with the hydrogen eclipsing the carbonyl group; the results of NOE experiments performed on both isomers confirm the stereochemical assignment.

The 6-methyl-perhydropyrimidin-4-ones (1′*S*,6*R*)-**5** and (1′*S*,6*S*)-**6** were submitted to alkylation by treatment of the corresponding lithium enolate with various alkyl iodides.[43] The alkylation always proceeded with high *trans* selectivity delivering useful intermediates to α-substituted β-amino acids, as shown in Table 4.

The diastereoisomeric ratio increases with the use of a bulkier electrophile. Furthermore, both the *trans*: *cis* ratio and the amount of dialkyl derivative increase if the reaction temperature decreases. Moreover the diastereoisomeric ratio and the amount of dialkyl derivative increase with increase in the proportion of the base. The results suggest that the dialkylation occurs faster on the *cis* than on the *trans*-5,6-disubstituted diastereoisomer.

In order to analyse how the bulkiness of the substituent at C-6 affects the diastereoselectivity of the alklyation reaction, we prepared several perhydropyrimidinones[44] (Scheme 10), following a well-known procedure described by Steiger on cinnamic acid. Racemic β-amino acids were obtained by addition of 2 equivalents of free hydroxylamine to alk-2-enoic acids in ethanol at reflux. The hydroxylamine behaves both as a nucleophile and a reducing agent for the 3-hydroxylamino intermediate. Following this method, β-amino acids were obtained and protected at the nitrogen with benzyl chloroformate. The products were converted into the corresponding (*S*)-phenylethylamido derivatives. The corresponding perhydropyrimidin-4-ones (1′*S*,6*R*)-**7** and (1′*S*,6*S*)-**8** were easily obtained by treatment with paraformaldehyde and toluene-*p*-sulfonic acid in benzene at reflux and fully separated by flash chromatography.



Scheme 10 **a**; R = Et
b; R = Pr^n
c; R = Ph

At first we considered the methylation reaction, because α-methyl β-amino acids are becoming of great interest, as they are components of a number of molecules which display interesting biological properties. For instance (2*S*,3*R*)-2-methyl-3-aminopentanoic acid has been isolated as a hydrolysis fragment of several

biologically interesting natural products such as the marine peptide antifungal agents majuscolamide C[17] and the antitumour agents dolastatins 11 and 12.[10] The methylation at C-5 of perhydropyrimidin-4-ones afforded increasing diastereoselectivity on going from ethyl to propyl to phenyl groups (Table 5).

Table 5 Diastereoselectivity and chemical yield for the methylation of perhydropyrimidin-4-ones **7** and **8**

Starting material	*T*/°C	Alkylating agent	Yield (%)	*trans*:*cis* ratio	Dialkylated (%)
7a	−78 to room temp.	MeI	60	84:16	—
7a	−20	Me_2SO_4	80	78:22	—
7b	−20	Me_2SO_4	81	78:22	—
7c	−20	Me_2SO_4	50	92:8	—
8a	−20	Me_2SO_4	80	82:18	7
8b	−20	Me_2SO_4	86	77:23	—
8c	−20	Me_2SO_4	50	92:8	—

We then studied in detail the dialkylation at C-5 of the *cis* and *trans*-5-methyl-6-ethyl perhydropyrimidin-4-ones: while the alkylation of the lithium enolate of the 5,6-*trans*-product **9** with ethyl iodide affords the dialkyl derivatives in 5% overall yield, the alkylation of the 5,6-*cis*-derivative **10** produces a mixture of 5-dialkylated pyrimidin-4-ones in quantitative yield and in 91:9 diastereoisomeric ratio (Scheme 11, Table 6). This outcome establishes that the relative configuration of C-5 and C-6 of the heterocycle strongly influences the rate of dialkylation, and thus the diastereoisomeric ratio of the monoalkylation. Moreover, the same alkylated compound was obtained as the major product, starting from either the *trans*-**9** or the *cis*-**10** compound. The absolute configuration of the major isomer was established by means of NOE difference experiments and shows that the preferred isomer is obtained from the attack of the ethyl group from the same side of the ethyl at C-6. This new approach allows chiral α, α-disubstituted β-amino acids to be obtained.

Table 6 Diastereomeric product ratios and chemical yields for the dialkylation reaction of perhydropyrimidin-4-ones **9** and **10**

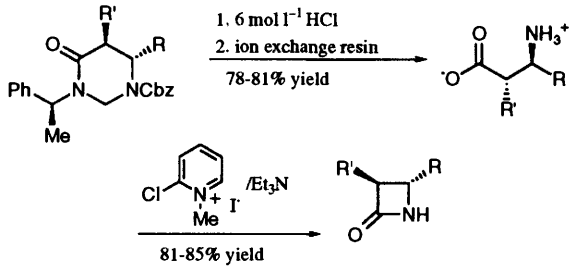
Starting material	*T*/°C	*t*/h	Diastereoisomeric ratio **11a**:**11b**	Yield (%)
9	0	1	96:4	5
9	room temp.	72	90:10	47
10	0	1	91:9	99

In order to test how the bulkiness of the alkylating agent affects the diastereoisomeric ratio, the (1′*S*,6*R*)-and (1′*S*, 6*S*)-6-ethyl, 6-propyl and 6-phenyl perhydropyrimidin-4-ones **7a**, **7b**, **7c**, **8a**, **8b**, and **8c** were submitted to alkylation with ethyl iodide and/or benzyl bromide. The results are reported in Table 7 and show that the reaction occurs in high yield and high diastereoselection in all the analysed cases.

The hydrolysis of the heterocycles was performed with 6 mol l^{-1} HCl at reflux for 24 hours and delivered the corresponding β-amino acid hydrochlorides with no racemisation (Scheme 12). The (*S*)-1-phenylethylamine was separated during the work-up and the purification of the amino acid from sodium chloride was performed on a

Table 7 Diastereoisomeric product ratios and chemical yields for the alkylation reaction of perhydropyrimidin-4-ones **7** and **8**

Starting material	Alkylating agent	Yield (%)	*trans*:*cis* ratio
7a	EtI	78	96:4
7b	EtI	90	>99:1
7b	$PhCH_2Br$	85	>99:1
7c	EtI	96	>99:1
8a	$PhCH_2Br$	95	>99:1
8b	EtI	92	>99:1
8b	$PhCH_2Br$	88	>99:1
8c	EtI	80	>99:1



Scheme 12

column of cation exchange resin using NH_4OH (1.5 mol l^{-1}) as eluent. Finally, in order to show another possible use of α-substituted β-amino acids, some selected β-amino acids were submitted to cyclisation with 2-chloro-1-methylpyridinium iodide in the presence of triethylamine and afforded the corresponding 3,4-*trans*-disubstituted β-lactams in high yield.

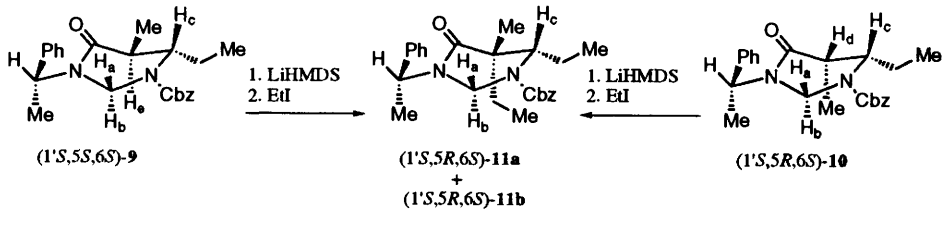
3.3 Synthesis of Enantiomerically Pure β-Amino Acids by Conjugate Addition to α, β-Unsaturated Esters and Imides

Among the strategies for the synthesis of enantiomerically pure β-amino acids, diastereoselective 1,4-additions of chiral amines to α, β-unsaturated esters and additions of amines to chiral α, β-unsaturated acyl derivatives have attracted much interest.[45]

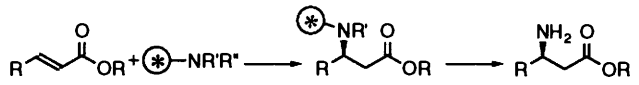
The first approach has been studied by several research groups. The general method is to add a 'chiral ammonia,' usually an asymmetric secondary amine, to a Michael acceptor, generally an unsaturated *tert*-butyl ester. The reaction produces a new chiral centre β to the ester group and the diastereoselectivity depends on the ester, on the 'chiral ammonia' utilised and on the reaction conditions.

All the proposed methods are quite recent. One of the first good results was achieved in 1986 by Hawkins and coworkers,[46a] who obtained a 55% diastereoisomeric excess upon addition of a C_2 symmetric chiral secondary amine such as a dihydroazepine. On the other hand a much better diastereoisomeric excess (97% de) was obtained utilising the lithium salt **12** of the same C_2 symmetric chiral secondary amine as nucleophile (Scheme 14). Removal of the dimethyl binaphthyl moiety under reductive conditions gave the deprotected (*R*)-β-amino acids.

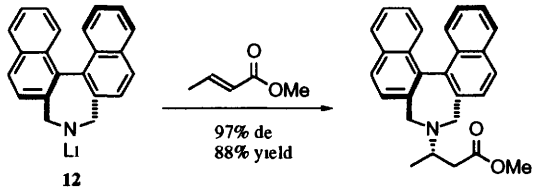
In a recent development of this work,[46b] the addition of the



Scheme 11

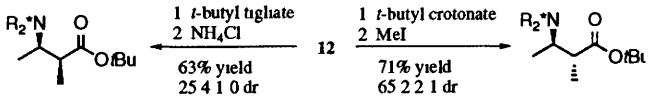


Scheme 13



Scheme 14

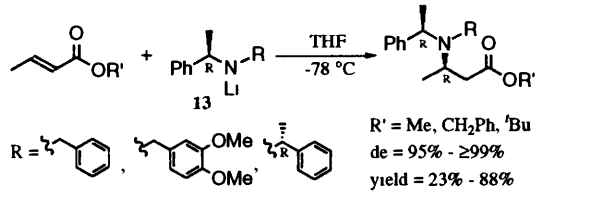
lithium salt of the dihydroxyazepine to *tert*-butyl crotonate in dimethoxyethane at −63 °C, followed by quenching with methyl iodide, afforded the derivative of *tert*-butyl 3-amino-2-methylbutanoate as a 65 2 2 1 mixture of diastereoisomers (Scheme 15) The lithium amide and the electrophile add *anti* across the



Scheme 15

carbon–carbon double bond of the ester This result was confirmed by transforming the 3-amino-2-methyl ester into the corresponding *trans*-β-lactam, by reduction with $Pd(OH)_2/C$ of the dihydroazepine, esterification of the amino group and cyclisation with 2-chloro-1-methylpyridinium iodide In order to obtain the *syn* isomer, the lithium amide was added to *tert*-butyl tiglate in DME at −46 °C The addition product was obtained in 63% yield and a 25 4 1 0 ratio of diastereoisomers, with the *syn*-isomer in excess

Recently, the lithium amide derived from (*R*)-*N*-(α-methylbenzyl)benzylamine (*R*)-**13** has been used by Davies and coworkers as a synthetic equivalent of ammonia in a Michael addition to benzyl crotonate,[47] the addition occurs with 95% de and gives, after debenzylation, the (−)-(*R*)-3-aminobutanoic acid (Scheme 16) Treatment of methyl *p*-benzyloxycinnamate with the same lithium amide generated the corresponding adduct as a single diastereoiso-



Scheme 16

mer The hydrogenolysis in EtOH with $Pd(OH)_2$ on charcoal afforded the corresponding (*S*)-β-amino acids in quantitative yield The method has been further developed and the change from the benzyl ester to the *tert*-butyl ester increased the selectivity

Furthermore the enolate formed by the 1,4-addition was trapped with various electrophiles under diastereoisomeric control of both chiral centres Indeed the conjugate addition of lithium (*R*)-(α-methylbenzyl)benzylamide (*R*)-**13** to *tert*-butyl esters followed by *in situ* hydroxylation with (+)-(camphorsulfonyl)oxaziridine (+)-**14** provides the corresponding *anti*-β-amino α-hydroxy amino acid derivative with excellent diastereoselectivity (Scheme 17) The synthesis of enantiomerically pure 3-phenylisoserine derivatives[48a] has been of great interest in recent years, particularly with respect to the synthesis of taxol,[15] a complex diterpene which exhibits strong antitumour/antileukaemic activity and is currently considered a major lead in cancer chemotherapy Thus the hydroxylation of the intermediate enolate of the *tert*-butyl cinnamate proceeds in 86% yield and 92% de (Scheme 17) Debenzylation of the adduct occurs in quantitative yield affording the *anti*-compound In order to obtain the *syn*-relative stereochemistry required by the natural product, an inversion of the C 2 centre was realised through treatment of the *anti* amino alcohol under Mitsunobu conditions in 80% yield

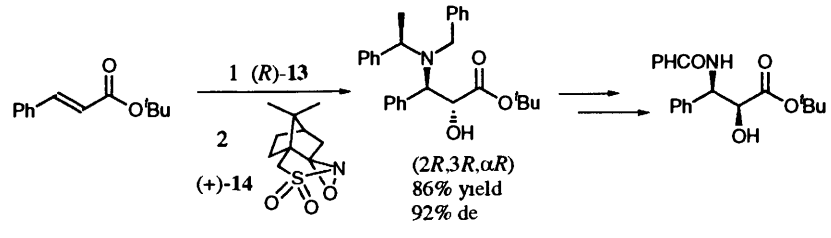
Following the same protocol, the 3-amino-2-hydroxydecanoic acid (AHDA), an unusual amino acid present in the angiotensin-converting enzyme inhibitor microginin,[28] was obtained as both the (2*R*,3*R*)-*anti* and (2*S*,3*R*)-*syn* diastereoisomer[48b] (Scheme 18)

In contrast, the synthesis of the unusual amino acid allophenylnorstatine, the crucial fragment responsible for the activity of kynostatins 227 and 272,[24] required some modifications[48c] (Scheme 19) In fact the tandem addition–hydroxylation reaction performed on the homologous ester of the *tert*-butyl cinnamate proceeded with little selectivity at the α-centre, if the reaction was performed with the (*R*)-enantiomer of the lithium amide (*R*)-**13** as nucleophile and (+)-(camphorsulphonyl)oxaziridine (+)-**14** as electrophile This reaction, repeated with the (*S*)-enantiomer of the lithium amide (*S*)-**13**, gave a 22 1 selectivity in favour of the *anti*-compound, thus showing that the poor selectivity observed with the (*R*)-amine was a consequence of using the 'mismatched' pairing

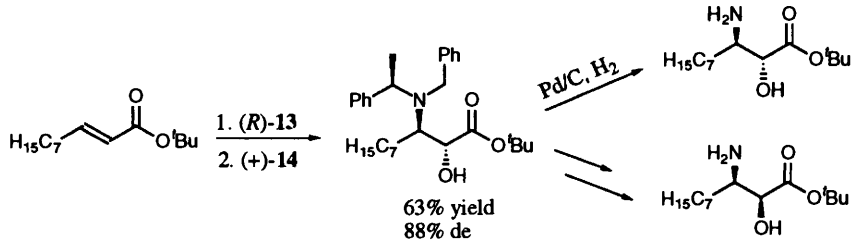
For the synthesis of *anti*-α-alkyl β-amino acids, alkyl halides were utilised to trap the enolate obtained by the Michael addition[34a,b] (Scheme 20) In this case the diastereoisomeric excesses are less satisfactory and indicate that a variety of factors are responsible for determining the extent of diastereofacial discrimination shown by an incoming electrophile For this reason a detailed study on better conditions to obtain the *anti*- or the *syn*-α-substituted β-amino acids was undertaken To obtain the *anti*-derivative, the Michael adduct was quenched, worked-up and subsequently deprotonated and treated with the required alkyl halide On the other hand, the addition of (*R*)-(α-methylbenzyl)benzylamide (*R*)-**13** to α-alkyl α,β-unsaturated *tert*-butyl esters, followed by quenching with a proton source, afforded the *syn*-α-alkyl β-amino acid

Following the second method, the conjugate addition of (*R*)-**13** to *tert*-butyl (*E*)-2-methylpent-2-enoate was performed in toluene and the reaction mixture was diluted with THF prior to quenching the reaction with the hindered acid 2,6-di-*tert*-butylphenol With this procedure the (2*S*,3*R*)-2 methyl-3-aminopentanoic acid,[49c] a component of majusculamide C,[17] was generated in good yield and >91 1 *syn anti* selectivity, after reduction of the amine moiety and acid hydrolysis of the ester (Scheme 21)

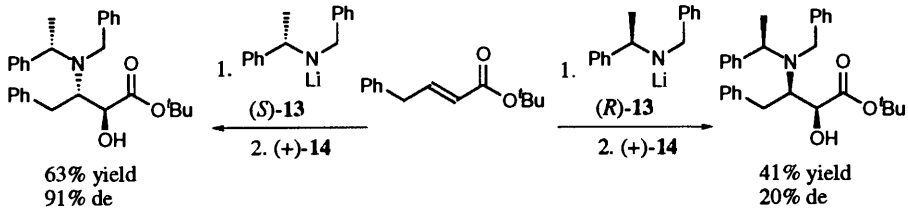
Concerning the stereoselective conjugate addition of lithium (α-methylbenzyl)benzylamide to *tert*-butyl cinnamate, a theoretical model has been proposed, using molecular modelling techniques [50] The authors carried out calculations on α,β-unsaturated systems in the s *cis* conformation, in accord with recent experimental findings Initial calculations were associated with modelling the approach of the achiral nucleophile dibenzylamide to the 3-*Si* face of *tert*-butyl cinnamate, assuming that the approach trajectory of the amide would be oriented in the plane perpendicular to the α,β-saturated system and that lithium chelation is operative When the amide is



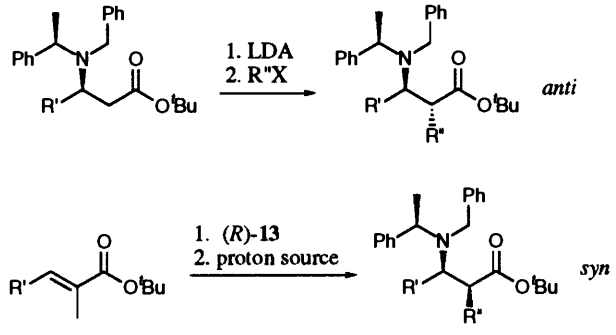
Scheme 17



Scheme 18



Scheme 19



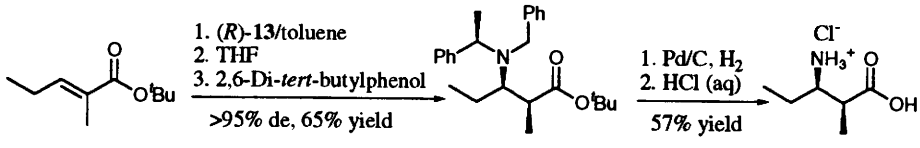
Scheme 20

near the system, the conformation is similar to a *butterfly*, placing the phenyl rings approximately parallel to each other (Scheme 22). Then the conformation of lithium (α-methylbenzyl)benzylamide was considered in the proximity of the electrophile. Although it is unreasonable to assume that the butterfly conformation is necessarily the global minimum for the transition states, the authors compared the four possible butterfly conformations A, B, C and D. Conformation A has the lowest energy and alone maintains the butterfly conformation; thus sterically demanding methyl group at position A can be tolerated, without disrupting the butterfly arrangement.

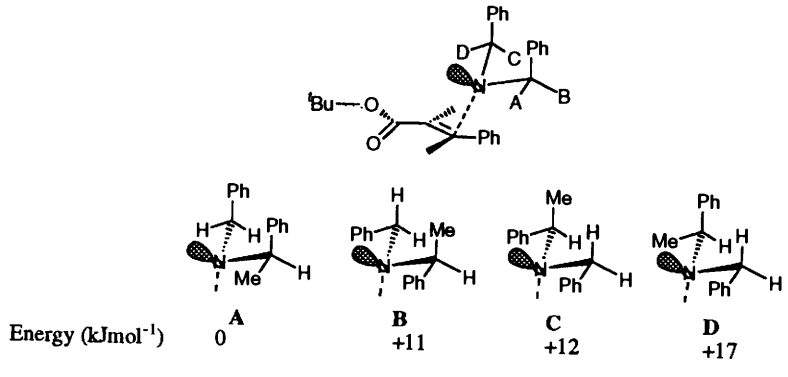
The structure associated with A suggests that in the tandem addition–enolate quench methodology, large electrophiles will be attacked by the enolate generated from α,β-unsaturated esters and amides *anti* to the amide moiety, if the chelated structure remains intact. This hypothesis was experimentally verified by the authors.[49a]

In a conceptually related system to the Davies work, Yamamoto and coworkers achieved the synthesis of a β-lactam framework *via* a three-component coupling reaction.[51a] The key step of this synthetic method is the conjugate addition of lithium (*R*)-(α-methylbenzyl)benzylamide to an α,β γ,δ-diunsaturated *tert*-butyl ester followed by quenching of the resulting enolate and deprotonation of the β-amino ester followed by aldol condensation with acetaldehyde. So three new chiral centre are obtained with good stereocontrol (Scheme 23).

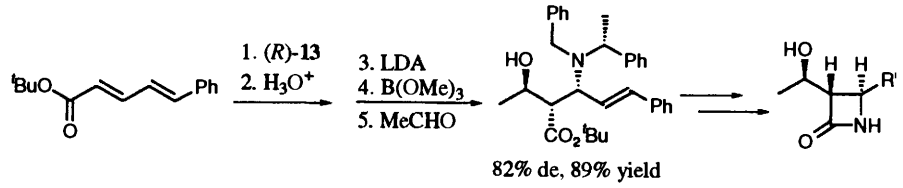
This three-component coupling approach has been applied to the synthesis of a 1β-methylcarbapenem key intermediate.[51b] Indeed the conjugate addition of *N*-benzyl-*N*-[(*R*)-1-phenylethyl]amine to (*R*)-(*E*)-*tert*-butyl 5-[(*tert*-butyldimethylsilyl)oxy]-4-methylpent-2-enoate produces the (3*S*,4*R*)-*syn*-adduct with essentially 100% de in 84% yield, where the addition of the (*S*)-amine to the same substrate afforded the (3*S*,4*R*)-*syn*-adduct with essentially 100% de in 95% yield.



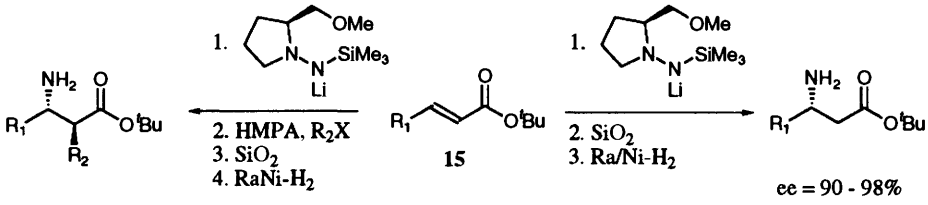
Scheme 21



Scheme 22



Scheme 23



Scheme 24

In a similar way Enders and coworkers have recently developed a diastereo- and enantio-selective synthesis of α-alkyl/aryl β-amino acids by tandem 1,4-addition/α-alkylation.[52] The 'chiral ammonia' utilised by these authors is (*S*)-(-)-2-methoxymethyl-1-trimethylsilylaminopyrrolidine (TMS-SAMP), readily prepared from the well established auxiliary (*S*)-(−)-1-amino-2-methoxymethylpyrrolidone (SAMP) by metallation with *n*-butyllithium and *N*-silylation with chloromethylsilane in 95% yield. By adding the lithium salt of TMS-SAMP to various methyl and *tert*-butyl α,β-unsaturated esters the corresponding (*S*,*S*)-3-amino ester derivatives were obtained with 93–98% de and 32–67% yield and readily transformed into the corresponding (*S*)-β-amino acids by reduction of the SAMP moiety with Raney Ni/H_2 (Scheme 24, Table 8). If the addition of the lithium salt of TMS-SAMP was followed by treatment of the reaction mixture with HMPA (3 equiv.) and the appropriate alkyl halide, both the α- and the β-position were functionalised with diastereoisomeric excesses ranging from 63 to ≥96% in the favour of the *anti*-stereoisomer (Scheme 25).

The second approach to enantiomerically pure β-amino acids is a result of the addition of an achiral amine to chiral acyl derivatives, such as chiral imides or esters.

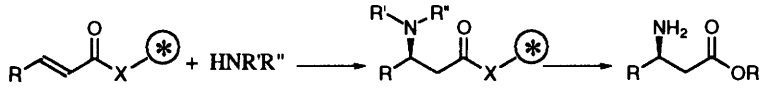
Following this strategy, d'Angelo and Maddaluno achieved very high stereocontrol in the conjugate addition of amines to chiral αβ-ethylenic esters using high pressure as an activating condition to produce β-amino esters with good chemical yield and variable de ranging from 5 to ≥99%, depending on the reaction conditions[53] (Scheme 26). The authors attributed this stereochemical outcome to the 'π-stacking' model, in which the aryl group of the inductor shields a face of the crotonate unit, thereby directing the amine addition to the other face.

Our interest in this field is represented by the addition of *O*-benzylhydroxylamine to an α,β-unsaturated system, obtained by reaction of various α,β-unsaturated acyl chlorides with (4*S*,5*R*)-1,5-dimethyl-4-phenylimidazolidin-2-one in the presence of a Lewis acid[54] (Scheme 27). The role of the Lewis acid is both to chelate the two carbonyls in order to produce a rigid chiral unsaturated system which reacts with the nucleophile on a preferred face and to enhance the reactivity of the electrophile imide. Indeed when the reaction was performed in the absence of a Lewis acid, no addition product was observed. Various Lewis acids were utilised as chelating agents and the best results were obtained with $TiCl_4$ and $AlMe_2Cl$ (Table 9). In particular the addition of *O*-benzylhydroxylamine catalysed by 2 equivalents of $AlMe_2Cl$ furnished the β-amino derivative in 89:11 diastereoisomeric ratio and 83% yield.

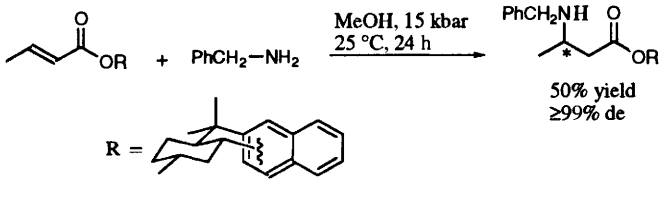
The nucleophilic attack on the aluminium-chelated crotonyl imide

Table 8 Chemical yield and diastereoisomeric ratio of the tandem-addition of TMS-SAMP-Li and alkyl halides to *tert*-butyl ester **15**

R_1	R_2	Yield (%)	De (%)	R_1	R_2	Yield (%)	De (%)
C_2H_5	CH_3	56	77	Ph	C_2H_5	34	>96
C_2H_5	C_2H_5	48	66	Ph	*n*-C_3H_7	68	>96
C_2H_5	*n*-C_3H_7	53	68	Ph	*n*-C_4H_9	64	>96
C_2H_5	*n*-C_4H_9	33	65	Ph	allyl	52	>96
C_2H_5	$PhCH_2$	26	76	Ph	$PhCH_2$	67	>96
C_2H_5	$(CH_2)_3COH$	51	>96	Ph	$PhCH_2$	48	>96
n-$C_{11}H_{23}$	C_2H_5	41	63	*p*-$MeOC_6H_4$	CH_3	53	>96

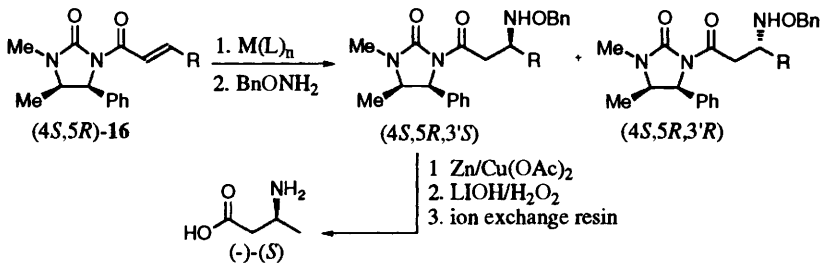


Scheme 25

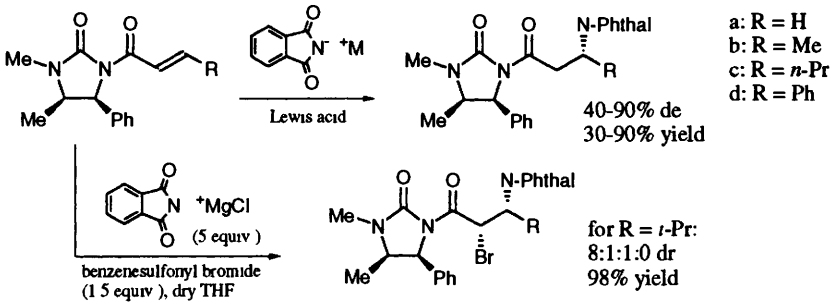


Scheme 26

derivative would preferably occur from the C_β-R*e* face of the s-*cis* conformation, resulting in the formation of the (4*S*,5*R*,3′*R*) isomer as the major product, while a complete inversion of selectivity was observed when $TiCl_4$ was utilised as Lewis acid. In order to demonstrate the formation of a chelate system and to rationalise the experimental results, we compared the ^1H NMR spectrum of the starting material with the spectra of its complexes with $AlMe_2Cl$ (2 equiv.) and $TiCl_4$ (1 equiv.). The ^1H NMR spectra of the complexes, identical at −60°C and at room temperature, suggest that both metals strongly chelate the two carbonyls of the imide. The inversion of selectivity



Scheme 27



Scheme 28

Table 9 Ratios of the diastereomeric products of the 1,4-addition of benzylhydroxylamine to imide **16**

R	$M(L)_n$ (equiv)	Yield (%)	Diastereoisomeric (%) (4S,5R,3'S)	(4S,5R,3'R)
CH_3	$ZnCl_2$ (1)	92	55	45
CH_3	$TiCl_4$ (1)	80	80	20
n-C_3H_7	$TiCl_4$ (1)	90	77	23
n-C_3H_7	$TiCl_2(OPr^i)_2$ (1)	38	50	50
CH_3	$AlCl(Me)_2$ (1)	65	26	74
CH_3	$AlCl(Me)_2$ (1 4)	65	19	81
CH_3	$AlCl(Me)_2$ (2)	70	20	80
n C_3H_7	$AlCl(Me)_2$ (1 4)	81	13	87
n C_3H_7	$AlCl(Me)_2$ (2)	83	11	89

could be ascribed to the difference in the metal–oxygen bond length and bond angles between the titanium and aluminium complexes

Furthermore the (+)-(3*S*)-butanoic acid was obtained from the *O*-benzylhydroxylamino adduct by reduction of the N—O bond with Zn/Cu in acetic acid and subsequent hydrolysis of imidazolidin-2-one with $LiOH/H_2O_2$ in THF/water

In a development of this work, the diastereoselective functionalisation of both the α- and the β-position was analysed with the addition of chloromagnesium phthalimide[55] (Scheme 28) The reaction, performed with 5 equivalents of nucleophile, afforded the β-phthalimido derivative with a 95 5 diastereoisomeric ratio and 90% yield Furthermore the resulting enolate was trapped by performing the reaction in the presence of benzenesulfonyl bromide and the *syn*-2-bromo-3-phthalimido derivative was obtained in good yield and high diastereoselectivity and then transformed into the corresponding *anti*-2-azido-3-phthalimido derivative by displacement of the bromide with sodium azide

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