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From β-lactams to α- and β-amino acid derived peptides

Review Article

C. Palomo, J. M. Aizpurua, I. Ganboa, and **M. Oiarbide**

Departamento de Química Orgánica, Facultad de Química,
Universidad del País Vasco, San Sebastián, Spain

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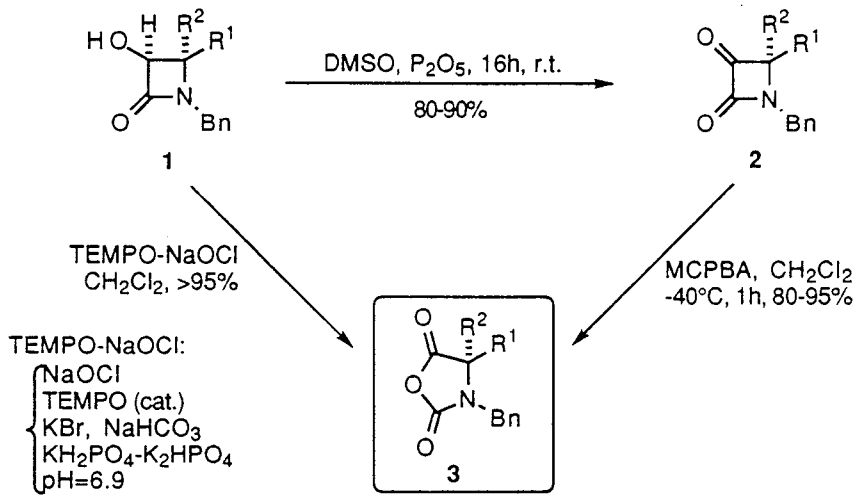
Summary. The potential of β-lactams as intermediates for the access to α- and β-amino acid-derived peptides is shortly reviewed, with major focus on the technologies developed in our group. The two general strategies lie, on one side, in the oxidative ring expansion of 3-hydroxy β-lactams to *N*-carboxy α-amino acid anhydrides or Leuch's anhydrides and subsequent coupling with α-amino acid esters and, on the other side, in the nucleophilic ring opening of *N*-Boc-β-lactams. Both approaches have been successfully applied to the synthesis of α,β-diamino acid, α-amino-β-hydroxy acid, polyhydroxylated α-amino acid, α,α-disubstituted α-amino acid, β-amino acid, β-amino-α-hydroxy acid and β,β-disubstituted β-amino acid derived peptides. Because of the mild reaction conditions needed for the above transformations and the highly stereoselective procedures employed for the construction of the starting β-lactam ring, the whole process allows the production of optically pure final products.

Keywords: Amino acids – Amino alcohols – β-Lactams – NCA – Peptides – Synthesis

Introduction

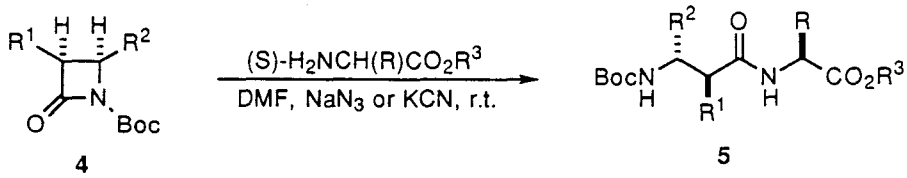
There are a number of reasons for the current interest in the synthesis of unusual amino acids, particularly by the need to prepare peptidomimetics, synthetic enzymes and new drugs (Degrado, 1988; Toniolo, 1990; Giannis et al., 1993; Liskamp, 1994; Gante, 1994). As a result, a number of suitable methods for the synthesis of both α- and β-amino acids have been developed over the last years, and the topic has been comprehensively reviewed several times (Williams, 1989; O'Donell, 1988; Duthaler, 1994; Bailey et al., 1995; Smith, 1995; Juaristi et al., 1994; Cole, 1994; Cardillo et al., 1996; Barret, 1997). However, the majority of the investigations on this subject deal with the



Scheme 1

synthesis of the non-proteinogenic amino acids, rather than with the generation of simultaneously amino-protected and carboxy-activated species ready for subsequent peptide couplings (Humphrey and Chamberlin, 1997; Elmore, 1997). During the course of our investigations on β-lactams we have discovered that Baeyer-Villiger oxidation of racemic α-keto β-lactams **2** (Scheme 1), readily obtained from α-hydroxy β-lactams **1**, takes place regioselectively to give α-amino acid *N*-carboxy anhydrides **3** (NCAs) (Cossío and Palomo, 1988). The well recognized importance of this particular class of mixed anhydrides in α-amino acid chemistry (Kricheldorf, 1987) led us to develop this approach into a general method for the synthesis of non-racemic NCAs that would proceed in an one-pot operation without the need to isolate the intermediate α-keto β-lactams. We found that stable nitroxide free radicals, such as 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO) in combination with a solution of commercial bleach fulfills this criterion and provides NCAs from α-hydroxy β-lactams in yields higher than 95% (Palomo et al., 1996a). Accordingly, much of our work has been centered on [2 + 2] cycloaddition reactions of α-hydroxyketene equivalents with imines as the means for obtaining the required α-hydroxy β-lactams in a convergent fashion (Backes, 1991; Georg et al., 1992) although the ester enolate-imine condensation could also be employed for the same purpose (Ojima et al., 1992, 1996).

Besides their usefulness as valuable precursors of NCAs, α-hydroxy β-lactams have also been found to be excellent building blocks of α-hydroxy β-amino acid derivatives by exploiting the reaction with nucleophiles at the β-lactam carbonyl group (Mukerjee et al., 1978; Manhas et al., 1988; Ojima, 1995). At the beginning of our work on this subject, little was known on β-lactam ring opening by carbon nucleophiles (Spero et al., 1995; Ojima et al., 1995; Baldwin et al., 1995) and even less on coupling reactions with α-amino acid esters. The only reported investigation on this topic was due to Drey and his co-workers who attempted the coupling reaction of a β-lactam framework



Scheme 2

with α-amino acid esters, albeit with very little success (Drey et al., 1973). On the other hand, it is well known that some simple monocyclic β-lactams, carrying suitable electron-withdrawing groups at *N*-position, possess antimicrobial activity and/or act as inhibitors of transpeptidases, β-lactamases and elastases (Page et al., 1992, 1998; Neu, 1992; Frére et al., 1992; Waley, 1992; Pratt, 1992). Therefore, on this basis, we reasoned that if the final result of the β-lactam ring opening by an enzyme results in its O-acylation, a coupling reaction between monocyclic β-lactams and α-amino acid esters should be possible. If so, the neat effect would be a conceptually new approach to peptide synthesis incorporating β-amino acid segments. Our initial trials to probe this hypothesis were performed with *N*-Boc-β-lactams **4** (Scheme 2), and the finding was that the β-lactam ring could efficiently be opened by both oxygen and nitrogen nucleophiles in the presence of sodium azide or potassium cyanide as promoters of the reaction. Presumably, an acyl azide or an acyl cyanide intermediate should be formed in such a reaction. Although no evidence has yet been found for such an assumption, as a matter of fact, no β-lactam ring opening usually takes place in the absence of these additives. Our method has recently found some new applications in the synthesis of fluoroalkylisoserinates (Abouabdellah and Bégué, 1997), and some cyclic peptides as the ADDA conjugates (Cundy and McCarthy, 1998) and (−)-panteamine A (Rzasa and Romo, 1998). On the other hand, since the overall process would imitate the alcoholysis of β-lactams promoted by class C β-lactamases (Page et al., 1998; Waley, 1992), the term "enzymemimetic" was adopted for these coupling reactions leading to the β-amino acid-derived peptides **5**.

This account summarizes our studies on the preparation of α- and β-amino acid derived peptides and related systems from readily available β-lactam synthetic building blocks (Palomo et al., 1997a; Ojima and Delaloge, 1997).

α-Amino acids: synthesis of α-amino acid *N*-carboxy anhydrides

α-Amino acid *N*-carboxy anhydrides, NCAs, or Leuchs anhydrides offer both amino group protection and carboxylate activation simultaneously. As a consequence, they have found wide application in peptide synthesis and numerous procedures have been reported for their preparation, all of them involving reaction between α-amino acids and dehydrating agents (Kricheldorf, 1987; Daly et al., 1988; Fuller et al., 1990; Savrda and Wakselman, 1992; Wilder and Mobashery, 1992; Schierlinger and Burger, 1992; Hsiao et al., 1992; Frerort

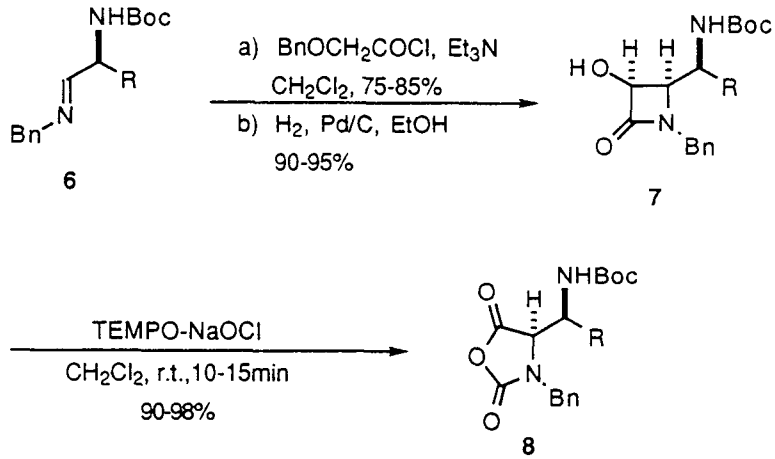
and Coste, 1992; Itoh et al., 1992; Xue and Naider, 1993; Collet et al., 1996). It was our consideration that if NCAs could be generally accessible from non α-amino acid precursors, a new approach to peptide segments would be facilitated.

Synthesis of α,β-diamino acid *N*-carboxy anhydrides

α,β-Diamino carboxylic acids are uncommon naturally occurring amino acids which attracted considerable interest (Palomo et al., 1997a). The approach to their *N*-α-carboxy anhydrides (Scheme 3), takes advantage of the highly diastereoselective cycloaddition of ketenes to imines **6**, derived from *N*-Boc α-amino aldehydes, developed in our laboratory (Palomo et al., 1992).

The method involves an one-pot double oxidation sequence of α-hydroxy β-lactams **7** using TEMPO and KBr in combination with fresh commercial bleach (from now on refered to as TEMPO-NaOCl), whose pH ~ 12.7 was adjusted to neutrality in order to avoid possible epimerization of the resulting NCA **8**. Reactions can be performed at 0°C and are almost complete in a few minutes using a twofold excess of 1M NaOCl and a catalytic amount of TEMPO. Without catalyst, the starting α-hydroxy β-lactams are recovered unchanged after 24h at room temperature. As shown in the scheme, the method allows the formation of (*R*)-α-amino acid-derived NCAs **8** from *(S)*-α-amino aldehydes (imines) and *vice versa* with completely predictable stereochemical control and essentially total optical purity (Palomo et al., 1992, 1994a). Furthermore, both amino moieties are differently protected and thus, incorporation of these amino acids into peptide chains either at the α- or β-position is possible *via* this procedure.

More recently, we applied this procedure to the synthesis of piperazine-2-carboxylic acids and derived peptides (Palomo et al., 1997b), Scheme 4. Our



R: Me, $CHMe_2$, CH_2Ph

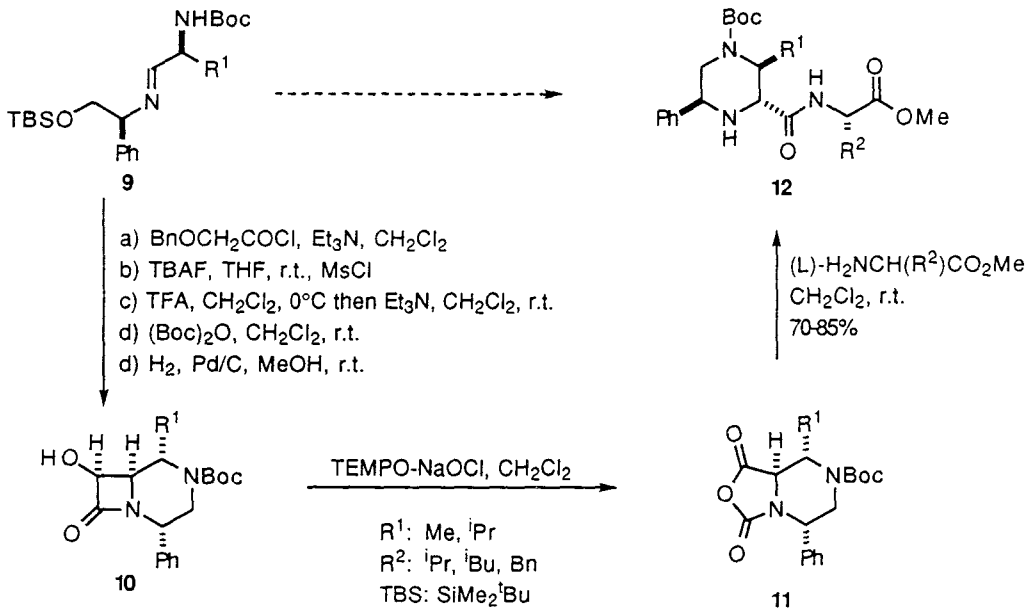
Scheme 3

approach to these compounds, which have attracted some interest due to their biological activity, begins with the formation of the corresponding bicyclic α-hydroxy β-lactam **10** from **9** via [2 + 2] cycloaddition of benzyloxyketene and subsequent formation of the piperazine ring. Further TEMPO assisted oxidative ring expansion of **10** to the NCA **11** took place smoothly, and the final treatment with α-amino acid esters gave the 2,3,5-trisubstituted piperazine-derived peptides **12** in optically pure form.

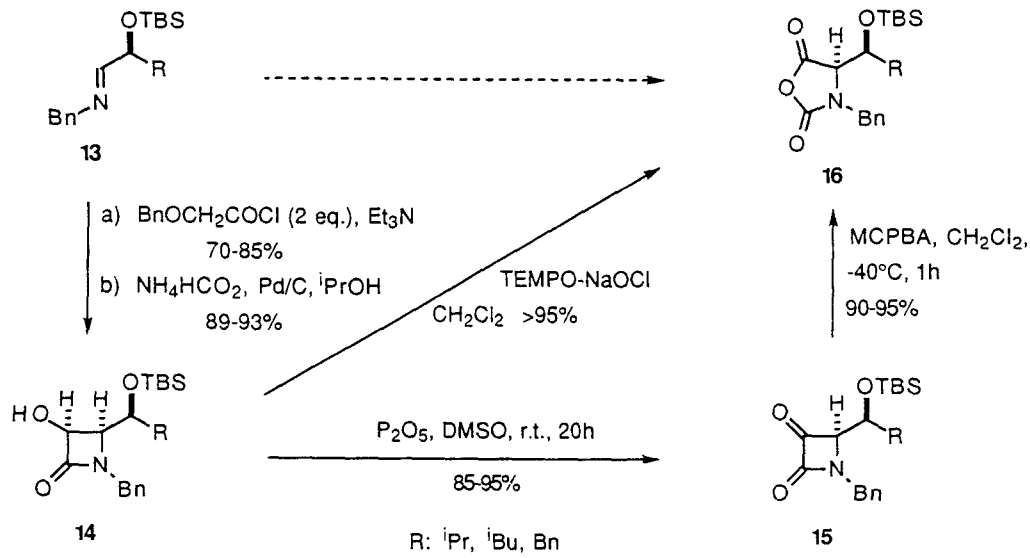
Parallel to these studies we also examined an alternative β-lactam approach to these α,β-diamino acid peptides which will be illustrated later.

Synthesis of α-amino-β-hydroxy acid *N*-carboxy anhydrides

The above methodology has also been extended, upon either the one-pot or the two step version, to α-hydroxyaldehyde-derived imines, particularly for the preparation of threonine-derived NCAs **16**, Scheme 5 (Palomo et al., 1994b, 1996a). For example, the reaction of imines **13** with benzyloxyketene and further debenzylation of the resulting cycloadducts led to the α-hydroxy β-lactams **14** in good yields. Subsequent oxidation of each compound **14** with P_2O_5 in DMSO gave the corresponding α-keto β-lactams **15**. We have also observed that reduction of these α-keto β-lactams with sodium borohydride proceeds with complete stereoselectivity to give the starting α-hydroxy β-lactams **14**, thus proving the lack of epimerization during the oxidation procedure. Finally, Baeyer-Villiger oxidation of each α-keto β-lactam **15** furnished the expected NCAs **16** in excellent yields, albeit in some instances they were contaminated with *m*-chloroperbenzoic acid. Nevertheless, the direct one-pot



Scheme 4



Scheme 5

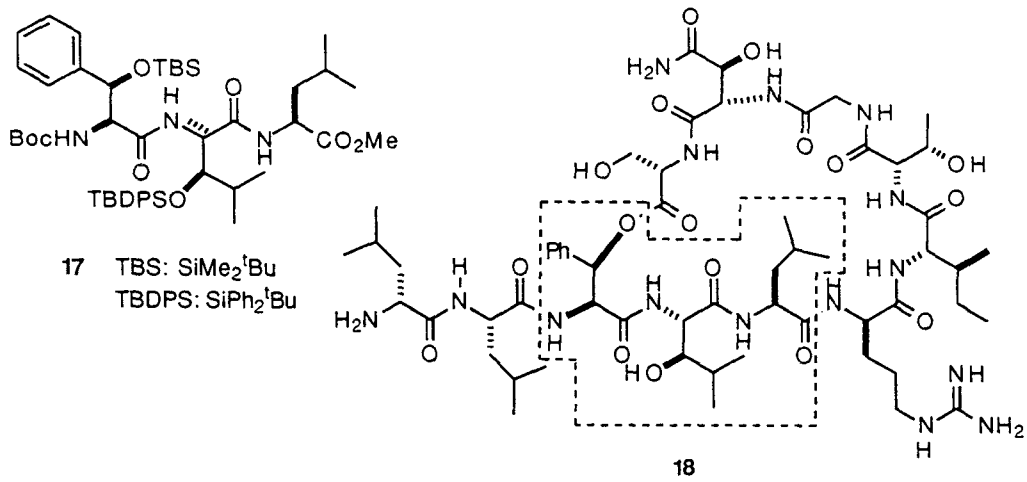
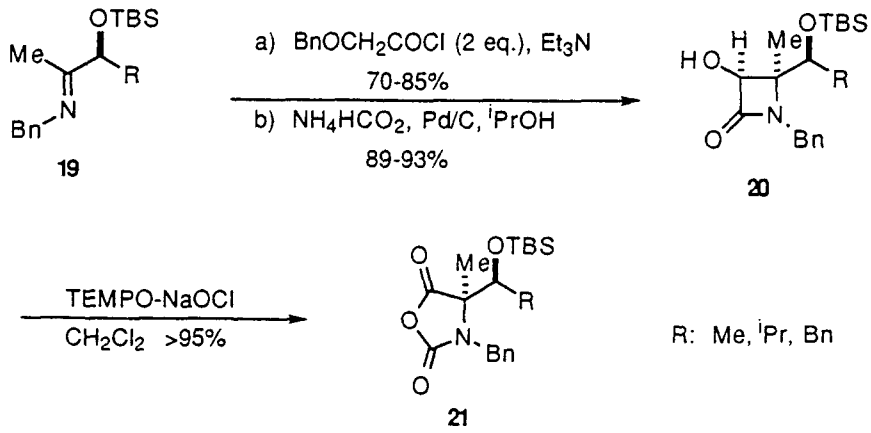


Fig. 1

transformation of α-hydroxy β-lactams into the desired NCAs has been found to be the method of choice.

This approach has been successfully applied, in a sequencial manner, to the synthesis of key fragments of macrocyclic peptides. For instance (Fig. 1), the tripeptide **17**, present in the macrocyclic antibiotic lysobactin **18**, was synthesized from the O-TBDPS analog of NCA **16** (R = ^{i}Pr) (Palomo et al., 1996b).

Due to the importance of α-methyl β-alkylserines for the study and design of new bioactive targets (Altmann and Mutter, 1988; Seebach and Venanci, 1994; Wohr and Mutter, 1995), we have also developed the above approach



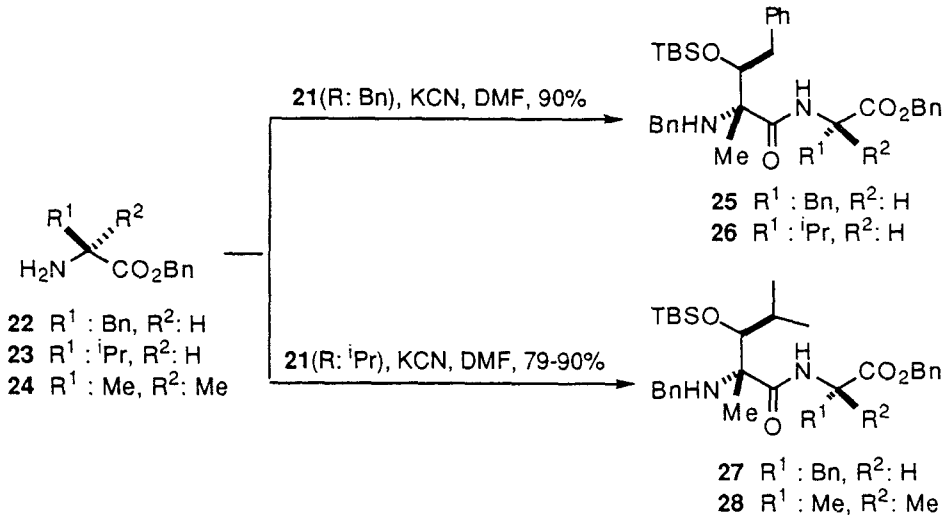
Scheme 6

into a general method for the synthesis of α-branched α-amino β-hydroxy acid *N*-carboxy anhydrides (Palomo et al., 1995a). The key step of this approach is the cycloaddition reaction of benzyloxyketene with α-alkoxyketone-derived imines **19** as readily available starting materials which possess the required structural subunit of the desired amino acid and, at the same time, provide chirality to the corresponding NCA precursors, Scheme 6. Using standard cycloaddition conditions we got the corresponding β-lactams in good yields and, most notably, as single diastereomers (Palomo et al., 1997c). Subsequent removal of the benzyl protective group from the resulting cycloadducts, led to the α-hydroxy β-lactams **20**. The ring expansion of these cycloadducts carried out with NaOCl and TEMPO provided NCAs **21** in yields higher than 95%.

After the preparation of α,α-disubstituted NCAs, we explored their reaction with several α-amino acid esters, but problems arose leading to yields below 10%. However, as Scheme 7 illustrates, the desired coupling reactions of α-amino acid esters with the above NCAs were achieved efficiently using potassium cyanide as additive. Under these conditions amino acid esters **22** and **23** coupled with **21** to provide **25**, **26** and **27** in good yields. Likewise, even the bulky Aib-methyl ester **24** coupled with **21** to give **28** in 79% yield.

Synthesis of polyhydroxylated α-amino acid *N*-carboxy anhydrides

Among the functionalized α-amino acids, those bearing a polyhydroxylated chain are of major importance in nature. Besides all types of glycopeptides, some other polyhydroxylated α-amino acids are encountered in important classes of biologically active compounds. A representative example is the polyhydroxylated α-amino acid **30**, present in polyoxins **29** (Fig. 2). The synthesis of these types of non-proteinogenic amino acids and their further coupling with either other amino acid residues or sugar moieties is of current interest. We found our three step [2 + 2] cycloaddition/β-lactam ring expan-



Scheme 7

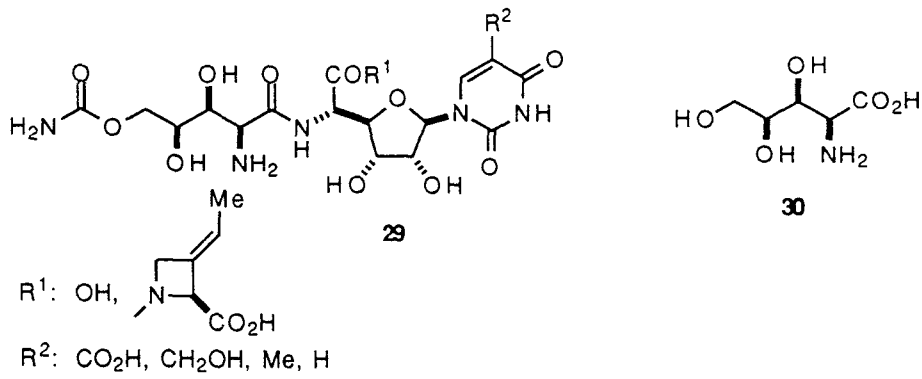
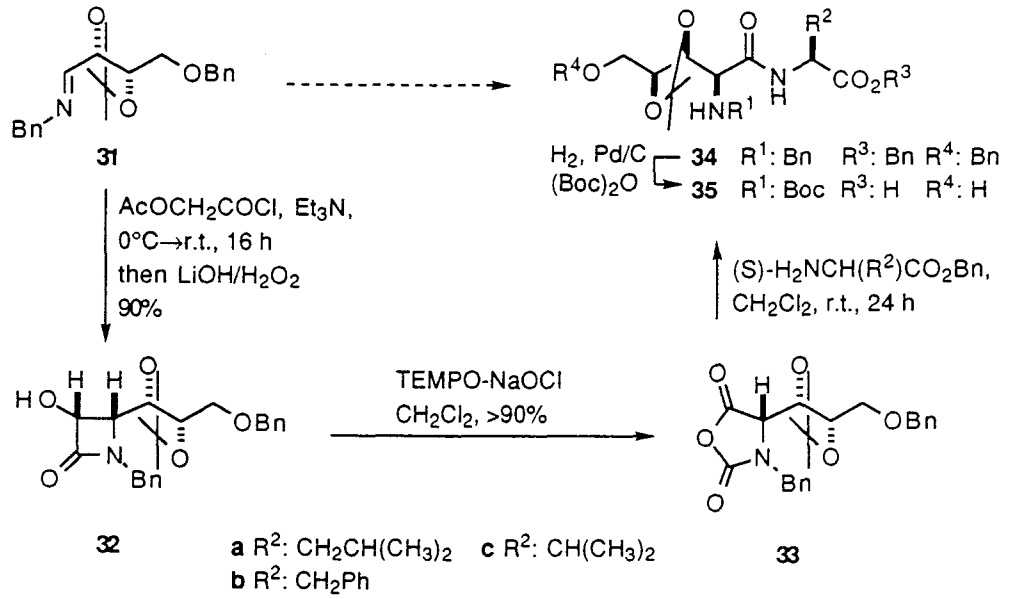


Fig. 2

sion/peptide coupling strategy very suitable for this purpose (Palomo et al., 1997d, 1998a).

Thus, we have recently established a practical route towards polyoxamic acid-derived peptides **35** via the NCA intermediate **33** (Scheme 8). Like in previous examples, cycloaddition of imine **31** with acetoxyketene and subsequent treatment with $LiOH/H_2O_2$ afforded β-lactam **32** as the only stereoisomeric product. The transformation of **32** into the NCA **33** took place under usual conditions in 1–2 minutes and further coupling reaction with α-amino acid esters afforded the peptides **34a–c** in high yields, which were then transformed into **35**. Remarkably, during the peptide coupling step, a variable degree of epimerization at C-α was observed when some solvents different from dichloromethane or diethyl ether were used. In addition, a good agreement was found between the isomerization ratio in MeCN, $MeNO_2$, DMF, Me_2SO and HMPA and the dipole moment of the solvent.



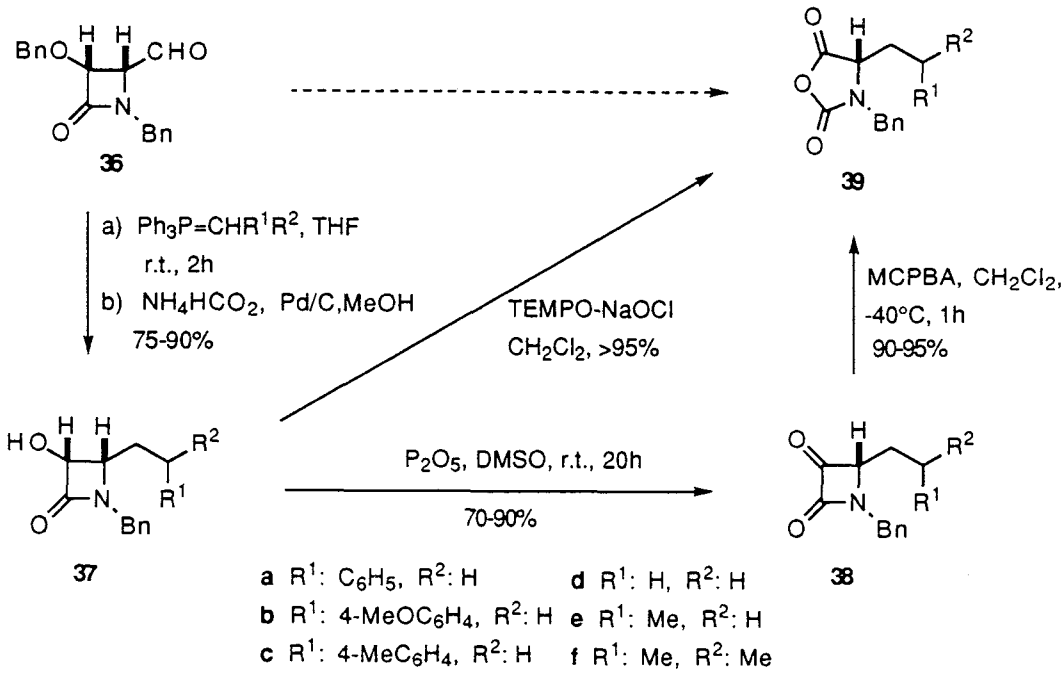
Scheme 8

Synthesis of aryl alanine, homoaryl alanine and tert-leucine derived *N*-carboxy anhydrides

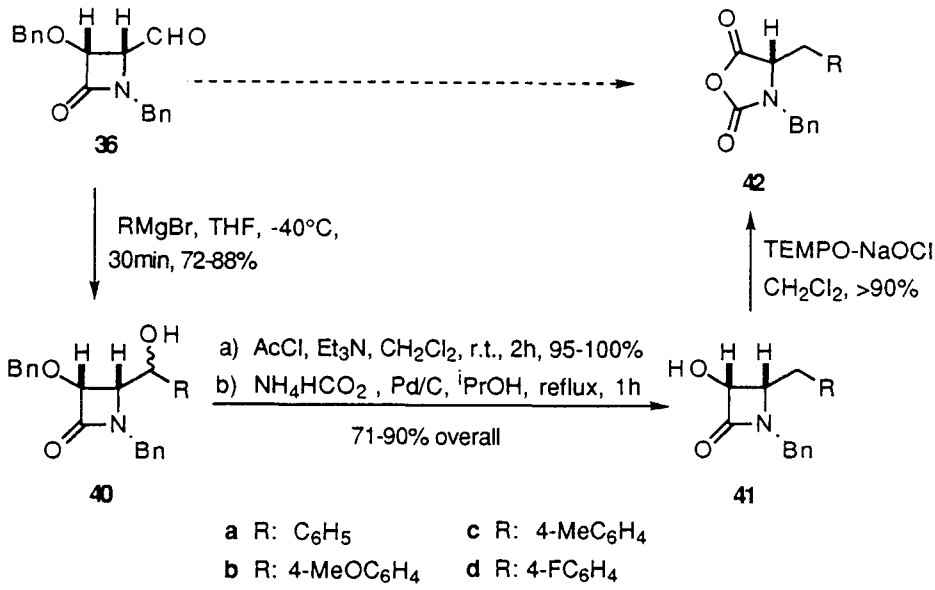
The scope of the β-lactam/NCA method has also been demonstrated by the synthesis of aryl alanines and homoaryl alanines (Palomo et al., 1994c). The key step of the approach to these compounds is the use of the 3-benzyloxy-4-formyl β-lactam **36** as a synthetic equivalent of a nonracemic α-amino hemimalonaldehyde.

As Scheme 9 illustrates, the synthesis of homoaryl alanine NCAs starts from **36** by using the Wittig reaction followed by hydrogenation of the resulting olefinic intermediates. Subsequent oxidation of carbinols **37** and Baeyer-Villiger rearrangement of the α-keto β-lactam intermediates **38** afforded the desired NCAs **39** in good yields. Once again, considerable yield improvement (typical yield > 95%) was observed by performing the direct transformation of **37** into **39** promoted by TEMPO. On the other hand (Scheme 10), simple Grignard addition to the formyl β-lactam **36** followed by deoxygenation of the resulting mixture of epimeric β-lactams **40** furnished **41** in good yields. One-pot sequential oxidation of these compounds gave NCAs **42** formally derived from aryl alanines.

The starting 4-formyl β-lactam **36** was prepared as shown in Scheme 11, although other procedures are also available (Wagle and Bose, 1988; Annunziata, Cinquini and Cozzi 1993; Jayaraman and Bhawal, 1994). In a similar way, the formyl β-lactam **47** was prepared by cycloaddition of benzyloxyketene to the ketimine **44** leading to **46** in perfect asymmetric induction at the newly created stereogenic centers. Subsequent deprotection of the acetonide group and further oxidative cleavage of the resulting diol gave **47** in good overall yield. With this material in hand, the synthesis of dipeptide segments



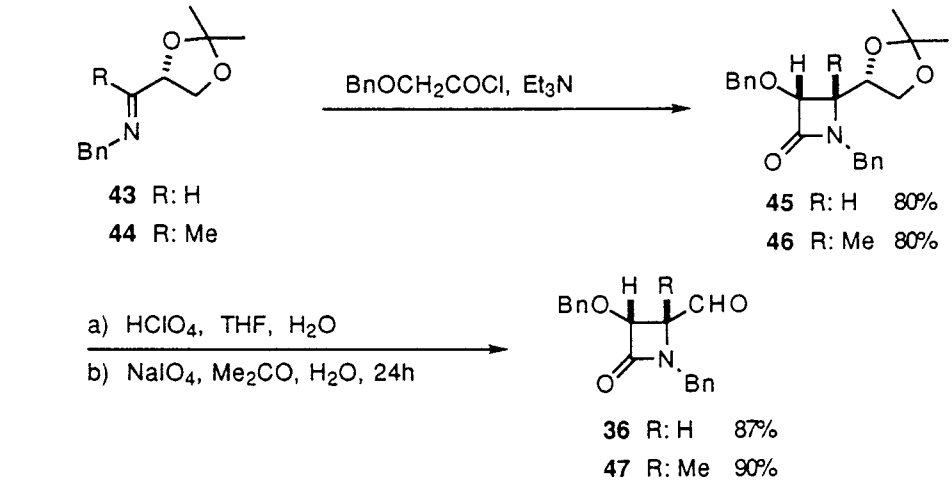
Scheme 9



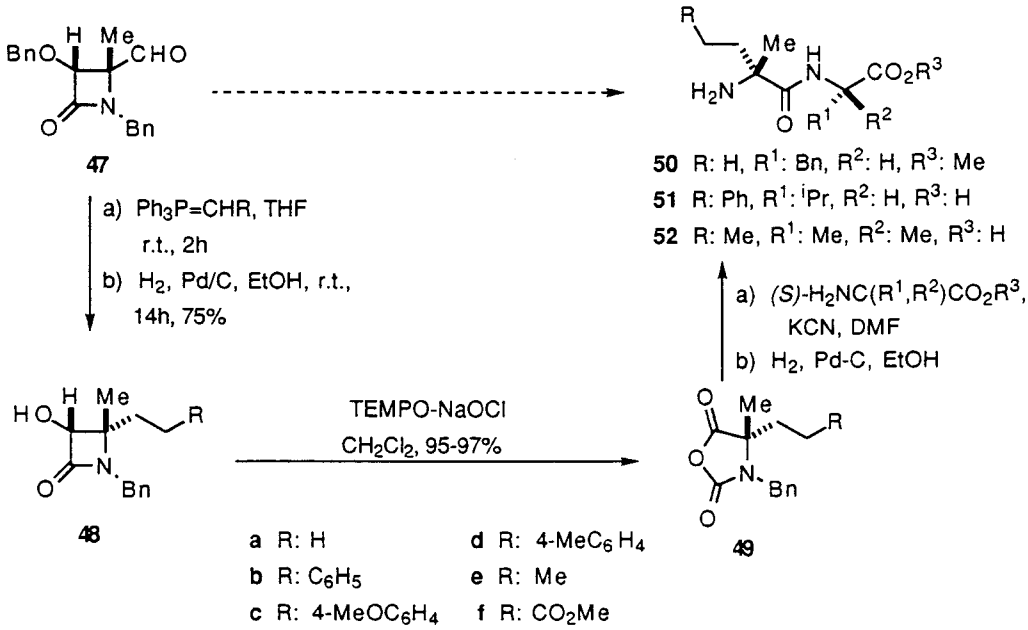
Scheme 10

containing α,α-disubstituted α-amino acids was feasible by our procedure (Palomo et al., 1996c).

As Scheme 12 shows, when **48**, prepared from **47**, was treated with NaOCl and a catalytic amount of TEMPO, the corresponding NCAs **49** were formed

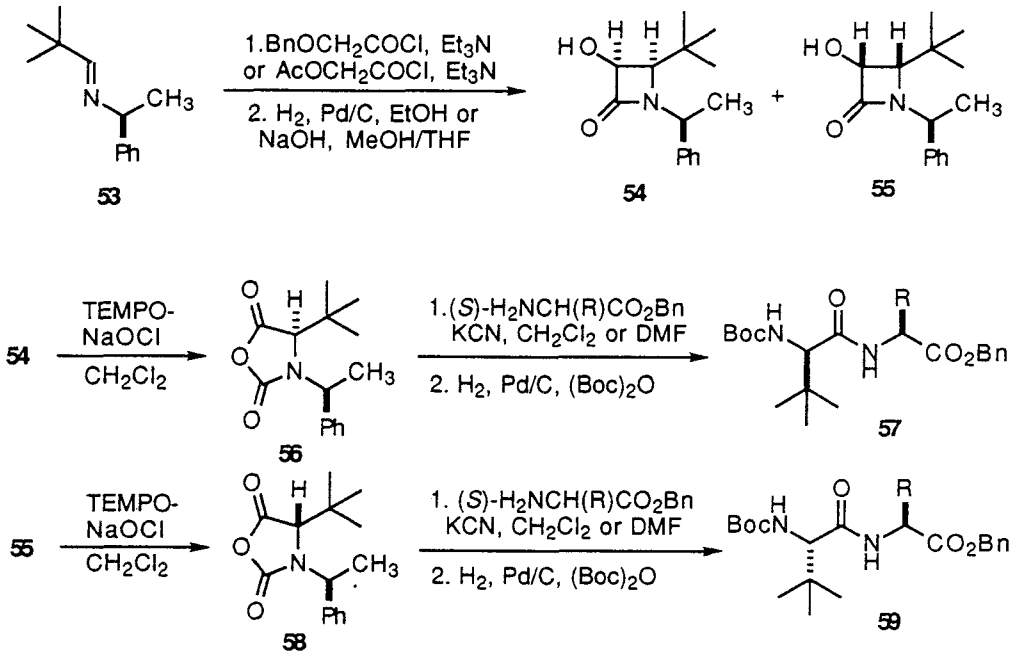


Scheme 11



Scheme 12

in yields up to 97%. In accordance with the results outlined previously, NCAs **49a** and **49b** showed to be resistant to ring opening by α-amino acid esters such as (S)-phenylalanine methyl ester and (S)-valine benzyl ester, but with the addition of potassium cyanide the coupling reaction proceeded cleanly to give, after hydrogenation over Pd/C, dipeptides **50** and **51** in 73% and 71% yield, respectively. Under these conditions, even the bulky Aib-benzyl ester could be efficiently coupled with the NCA **49e** to give the corresponding dipeptide product which upon *N,O*-didebenzylation afforded **52** in 70% yield.



Scheme 13

In the same way, amino acids bearing a bulky substituent at the α-position, which are interesting models for bioactive studies of conformationally restricted peptides, could also be prepared by our approach. The non-proteinogenic *tert*-leucine can be cited as a good example having found some practical therapeutic applications. To validate our strategy for the synthesis of peptides comprised of this amino acid, we have designed and carried out the reactions depicted in Scheme 13. Since we had to start with the achiral aldehyde pivalaldehyde, we selected to use a chiral amine as the chiral inductor of the cycloaddition process. Although the reaction of ketenes with **53** occurred without any diastereoselectivity, the mixture of isomers could be easily separated by crystallization giving rise to both diastereomerically pure compounds **54** and **55**. Ring expansion of both **54** and **55** led to **56** and **58**. The coupling steps that follow took place smoothly in the presence of KCN. Final removing of the chiral protecting group on the nitrogen thus allowed a convenient access to both configurational forms of *tert*-leucine derived peptides **57** and **59** in good overall yields (Palomo et al., 1997e).

β-Amino acids

In connection with the above studies on NCAs we have also developed the application of β-lactams as synthetic equivalents of β-amino acids. It is well known that β-lactams undergo hydrolytic cleavage of the carbon-nitrogen amidic bond leading to β-amino acids under both acidic and basic conditions. However, the harsh reaction conditions often required to carry out this trans-

Fig. 3

formation can cause partial or complete epimerization, not only at the α-position of the β-lactam ring, but also in other positions of the β-lactam product. This is particularly true for compounds of general structure **60** or **61** (Fig. 3). In this regard, we have developed a mild method for ring opening of β-lactams consisting in the previous activation of the β-lactam carbonyl group and subsequent treatment with *O*- and *N*-nucleophiles in the presence of sodium azide or potassium cyanide as the promoters of the acylation reaction (Palomo et al., 1995b). These aspects will be illustrated in the following sections.

β-Amino α-hydroxy acids

The synthesis of β-amino α-hydroxy acids for their incorporation into peptides has been well documented and still continues to be of current interest within the domain of new enzyme inhibitors. Important members of this class of compounds (Fig. 4), are bestatin **62** and amastatin **63**, two low molecular weight amino peptidase inhibitors, with antitumor and antimicrobial activity.

The synthesis of these compounds requires the coupling of two structural units, the corresponding *N*-terminal β-amino-α-hydroxy acid and the *C*-terminal amino acid leucine or the *C*-terminal tripeptide Val-Val-Asp, respectively.

Our approach (Palomo et al., 1994d) to (−)-bestatin **62** (Scheme 14), involves *N*-dearylation of **64** and subsequent installation of the Boc group at the *N*-position to activate the β-lactam carbonyl group. At first, the coupling reaction of the *N*-Boc β-lactam **65** with (*S*)-leucine benzyl ester was examined in methylene chloride at room temperature, but under these conditions a

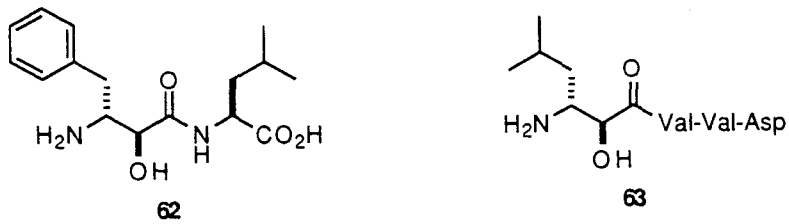
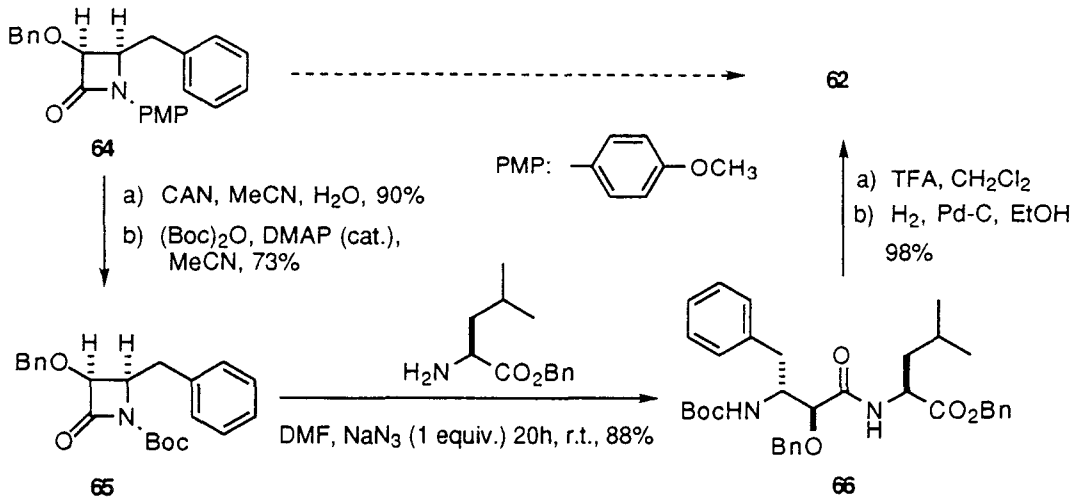
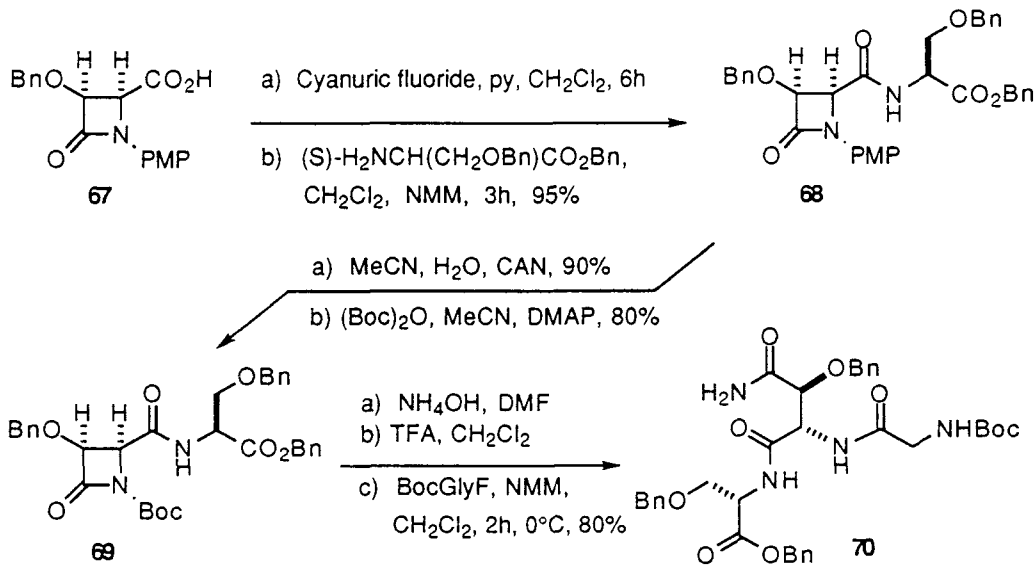


Fig. 4



Scheme 14



Scheme 15

fourfold excess of the α-amino acid ester was required to get the desired dipeptide product **66**. However, when the reaction was performed in DMF and in the presence of NaN_3 it took place smoothly by using equimolar amounts of both coupling components.

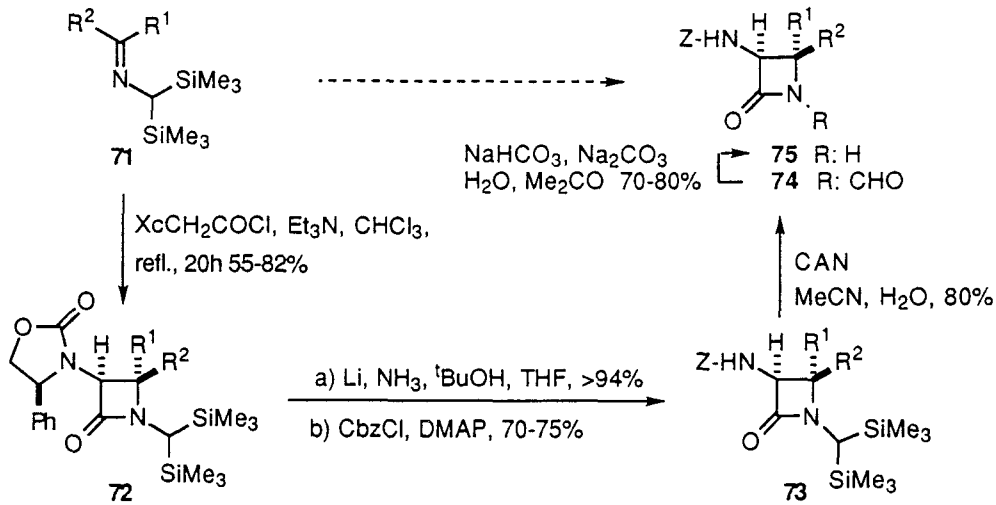
As Scheme 15 illustrates, this approach was also employed for the synthesis of the β-hydroxy aspartic acid derived tripeptide **70** found in the antibiotic lysobactin (Palomo et al., 1996b). The synthesis started from the 4-carboxy β-lactam **67**, as a β-hydroxy aspartic acid form possessing the β-carboxyl group and the α-amino moiety simultaneously protected. The dipeptide unit **68** was

obtained in 95% overall yield after activation of the carboxy group with cyanuric fluoride and subsequent coupling with *O*-benzyl-*L*-(*S*)-serine benzyl ester according to Carpino's procedure. Next, the β-lactam **68** was *N*-dearylated and converted into **69** in good overall yield. The ring opening of **69** with 25% NH_4OH aq. in DMF as solvent proceeded to give the expected open product in 90% yield which on *N*-Boc deprotection followed by acylation with Boc-GlyF and NMM gave tripeptide **70** in 70% overall yield.

α,β-Diamino acids

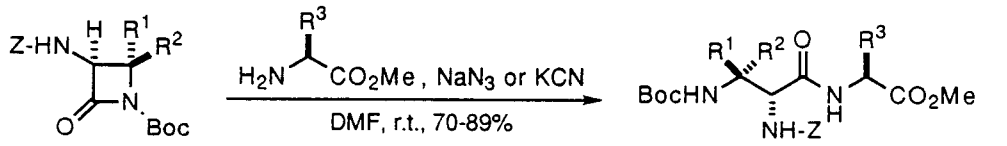
As pointed out, α,β-diamino acids are of particular interest in the development of new peptidomimetics and, therefore, syntheses that allow their incorporation into peptide chains, either by the α- or the β-amino function, are of considerable importance. These facts led us to prepare several 3-amino-4-alkyl β-lactams differently protected at the amino moieties and, on the light of the above results, to study their coupling with α-amino acid esters.

The synthesis of the 3-amino β-lactams involves the reaction of the Evans-Sjögren ketene, generated from the corresponding acid chloride and triethylamine, with imines **71** (Palomo et al., 1996d, 1997f). Conversion of the resulting β-lactams **72** into the Cbz-derivative **75** can be carried out as shown in Scheme 16 by prior remotion of the chiral inducer followed by protection of the amino group with Cbz-Cl to give **73**. Subsequent treatment of **73** with



a	R^1: H	R^2: Me	**g**	R^1: H	R^2: $CH_2CH_2CO_2{}^tBu$
b	R^1: H	R^2: Et	**h**	R^1: Me	R^2: Me
c	R^1: H	R^2: ^nPr	**i**	R^1: Et	R^2: Et
d	R^1: H	R^2: ^iPr	**j**	R^1: ^nPr	R^2: ^nPr
e	R^1: H	R^2: CH_2CH_2Ph	**k**	R^1: Me	R^2: Et
f	R^1: H	R^2: Bn	**l**	R^1: Me	R^2: CH_2CH_2Ph

Scheme 16



76 R^1: H R^2: CH_2CH_2Ph
77 R^1: Me R^2: Me

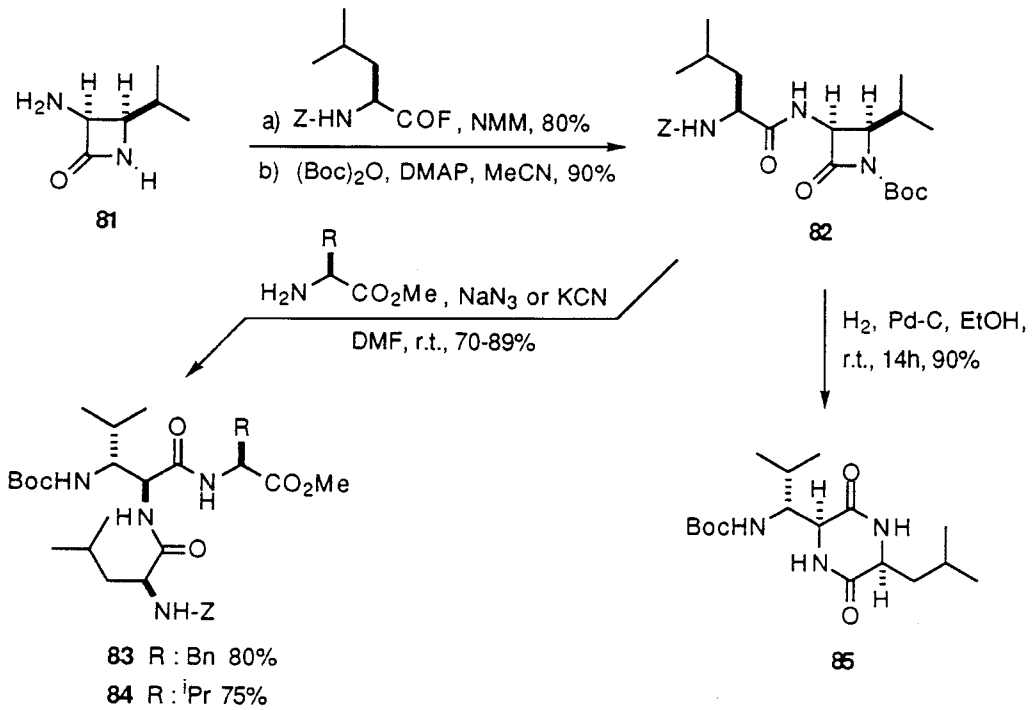
78 R^1: H R^2: CH_2CH_2Ph R^3: Bn
79 R^1: H R^2: CH_2CH_2Ph R^3: ^{i}Pr
80 R^1: Me R^2: Me R^3: Bn

Scheme 17

CAN in acetonitrile-water gave **74** which, upon *N*-deformylation, provided the *N*-H β-lactams **75**.

As shown in Scheme 17, the approach to dipeptide products **78–80** was guided by the observation that the introduction of the Boc group at N_1 position in β-lactams **75a** and **75b** proceeded chemoselectively to give the differently protected β-lactams **76** and **77**, respectively.

Then the β-lactam **76** coupled efficiently with both (*S*)-phenylalanine methyl ester and (*S*)-valine methyl ester in *N,N*-dimethylformamide in the presence of NaN_3, to give **78** and **79** in good yields. However, the β-lactam **77**, bearing a C_4 quaternary carbon atom, did not react with these α-amino acid esters even when a twofold excess of NaN_3 was added. Nevertheless, the



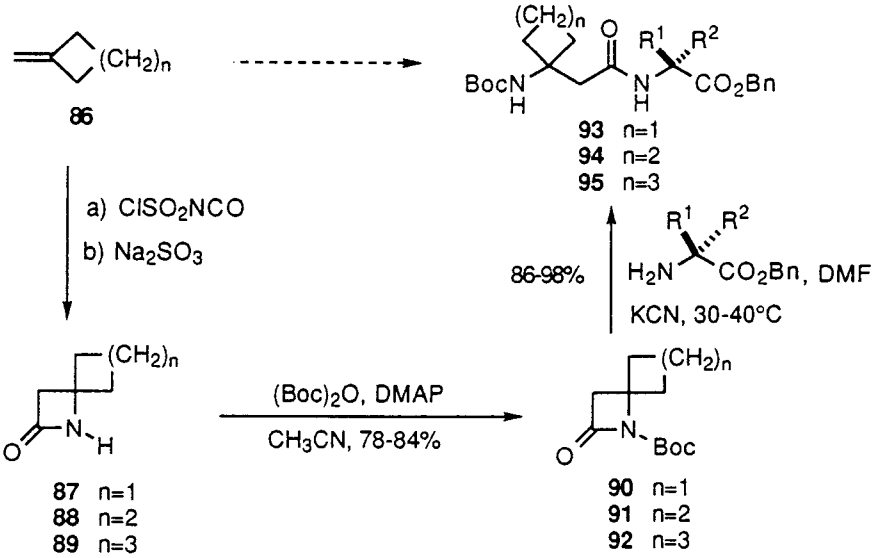
Scheme 18

coupling reaction can efficiently be effected by changing the additive NaN_3 by KCN. Under these conditions the dipeptide **80** was produced within about 10h in 89% isolated yield. Further examples are shown in Scheme 18. For instance, **82**, prepared from **81** could be transformed into the tripeptides **83** and **84** as well as into the piperazinedione **85** (Palomo et al., 1996e).

β,β-Disubstituted β-amino acids

β-Amino acids with no additional functionality at α-position are also of current interest. In particular, their incorporation into a peptide structure confers conformational properties well distinguished from their α-amino acid counterparts. Within this context, the design and study of conformationally restricted β-amino acids is an attractive area of research (Krauthäuser and Gellman, 1997; Koert, 1997; Seebach et al., 1997). In this regard, we have recently disclosed the synthesis of new β,β-dialkyl β-amino acids and their coupling with α-amino acid esters (Palomo et al., 1998b). These peptides (e. g. **93**, **94** and **95**) (Scheme 19), due to the cyclic nature of the β-substitution pattern are believed to display an extra level of conformational rigidity.

The synthetic pathway, as shown in Scheme 19 starts with the known chlorosulfonyl isocyanate-alkene cycloaddition reaction. Further transformation of the resulting adducts **87–89** into the key *N*-Boc intermediates **90–92** was carried out in the usual way. The final coupling step between such activated β-lactams and α-amino acid esters worked too slowly at room temperature. However, keeping the reaction mixture at 40°C was enough for



Scheme 19

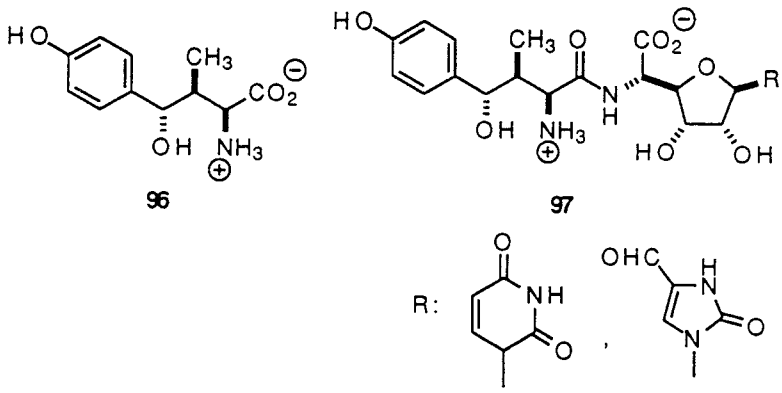


Fig. 5

completion of the reaction within 16 hours. An even a greater shortening of the reaction time was achieved by using water as cosolvent at room temperature, albeit an appreciable lowering on the chemical yields was observed. We also prepared the corresponding α-chlorinated β-lactams and compared their reactivity under different conditions. From these results it could be confirmed that electron withdrawing groups at the α-position of the *N*-Boc β-lactams increase their acylating power.

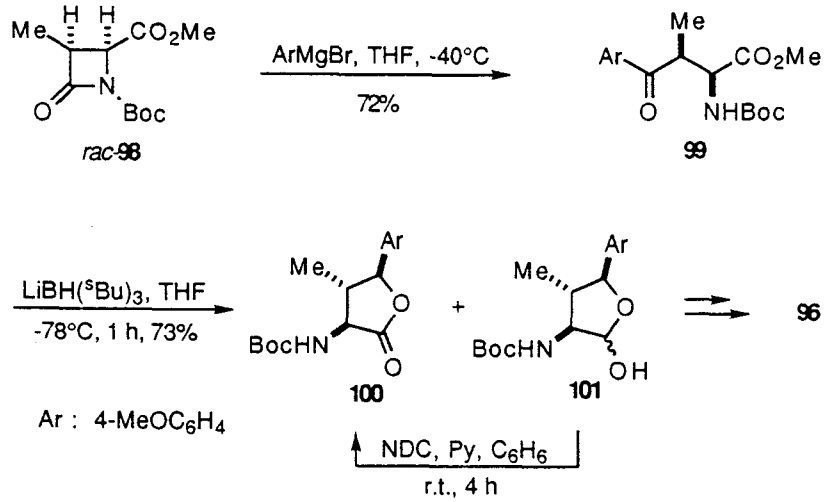
β-Amino ketones and derived α-amino acids and amino diols

In the course of our investigations on β-lactams as acylating agents, we have also demonstrated the utility of the reaction between *N*-Boc-β-lactams and carbon nucleophiles providing β-amino ketones and functionalized α-amino acids (Palomo et al., 1994e). One example is the synthesis of the γ-hydroxy α-amino acid **96** present in the antibiotic nikkomycin **97** (Fig. 5).

We found that aryl Grignard reagents (Scheme 20), on treatment with *rac*-**98**, react selectively with the imide function to afford exclusively the product **99** without overaddition to the resulting keto group. L-Selectride reduction of **99** gave the amino lactone **100** and the hemiacetal **101** in a ratio of 62:38. The latter could be smoothly oxidized with nicotinic-chromic anhydride (NDC) to **101** and thus the overall yield of the reduction step and cyclization was 73%.

Conclusions

The results presented in this review demonstrate that appropriately substituted monocyclic β-lactam frameworks can efficiently be employed for the construction of both α- and β-amino acid-derived peptides. In particular, the ring expansion of α-hydroxy β-lactams promoted by NaOCl in combination with TEMPO has opened a concise way to α-amino acid *N*-carboxy anhydrides. As a consequence, short peptide segments involving non-



Scheme 20

proteinogenic α-amino acids can be made accessible without the necessity to previously prepare each individual non-proteinogenic α-amino acid.

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Authors' address: Dr. Claudio Palomo, Departamento de Química Orgánica, Facultad de Química, Universidad del País Vasco, Apdo. 1072, E-20080 San Sebastián, Spain, E-mail: qoppanic@sc.ehu.es

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