Reviews

Diastereoselective construction of small building blocks *via* [2+2] cycloadditions involving ketenes: A direct incorporation of α-, β-, and γ-amino acids into peptides*

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Data concerning diastereoselective construction of peptides *via* β-lactams obtained from [2+2] cycloaddition reactions with participation of ketenes are summarized.

Key words: α-amino acid *N*-carboxy anhydrides, β-amino-α-hydroxy acids, α,β-diamino acids, macrocyclic peptides, 1,3-polyols and amino polyols, pyrrolizidine alkaloids, β,γ-dihydroxy acids, γ-amino-β-hydroxy acids.

1. Introduction

There are a number of reasons for the current interest in the synthesis of unusual amino acids, particularly the need to prepare peptidomimetics, synthetic enzymes, and new drugs (see reviews[2–7]). As a result, a number of suitable methods for the synthesis of both α- and β-amino acids have been developed over the last few years. Several comprehensive reviews concerning syntheses of both α-amino acids[8–12] and β-amino acids have been published.[13,14] However, most of the investigations on this subject deal with the synthesis of the non-proteinogenic amino acids in their free forms, rather than with the generation of simultaneously *N*-protected and COOH-activated species ready for subsequent peptide coupling. Towards this goal Heimgartner has developed the azirine-oxazolone method (Scheme 1), putting into practice the idea of amino group activation and providing a way for the incorporation of α,α-disubstituted α-amino acids into peptides.[15]

Carboxyl group activation has been accomplished, on one hand, through the formation of α,α-dialkyl oxazolones and their coupling with α-amino acid esters (Scheme 2)[16] and, on the other hand, by the *in situ* generation of amino ketenes as reactive species. In this context, the photolysis of chromium α-aminocarbene complexes and their subsequent coupling with α-amino acid esters[17] (Scheme 3) as well as the chain extension of α-amino acids *via* the Arndt-Eistert reaction and trapping of the resulting β-amino diazoketenes with α-amino acid esters and dipeptides[18,19] (Scheme 4) were developed. A single-step synthesis of racemic di- and tripeptides from unnatural β-hydroxy- and β-mercapto α-amino acids by the Ugi reaction has also been recently described.[20]

During the course of our investigations on β-lactams we discovered that Baeyer—Villiger rearrangement (Scheme 5) of racemic α-keto-β-lactams (**2**) readily

* Presented in part at the IXth European Symposium on Organic Chemistry, Warsaw, Poland, June 18—23, 1995.[1]

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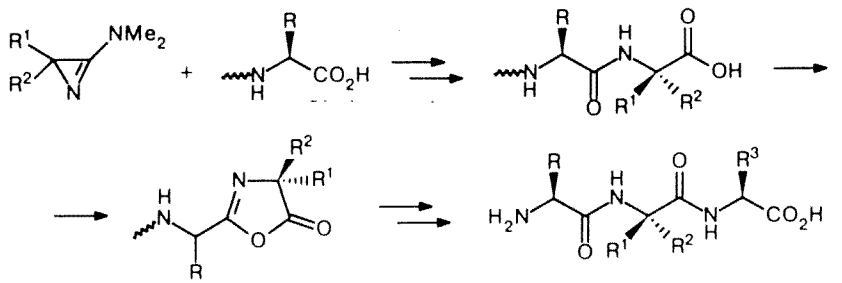
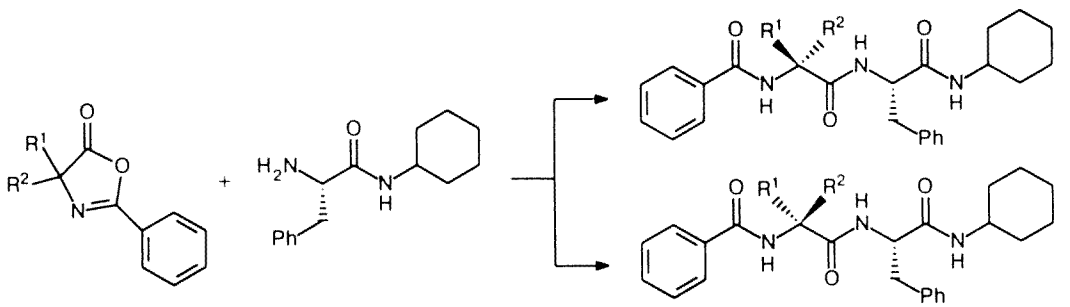
Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 11, pp. 2604—2623, November, 1996.

1066-5285/96/4511-2463 $15.00

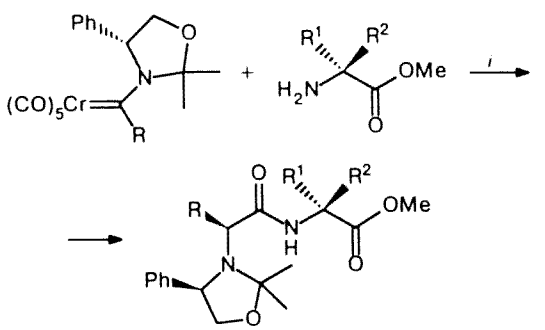
Scheme 1



Scheme 2

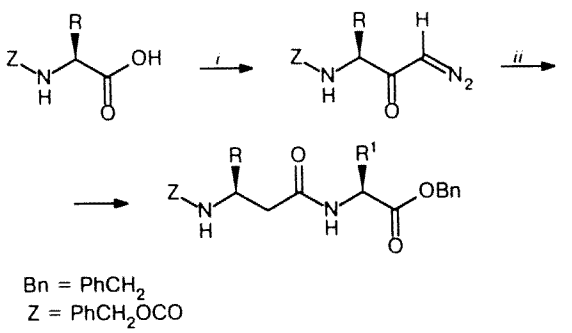


Scheme 3

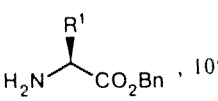


Reagents and conditions: *i*, hν, 0 °C, THF, CO (4—5 atm).

Scheme 4



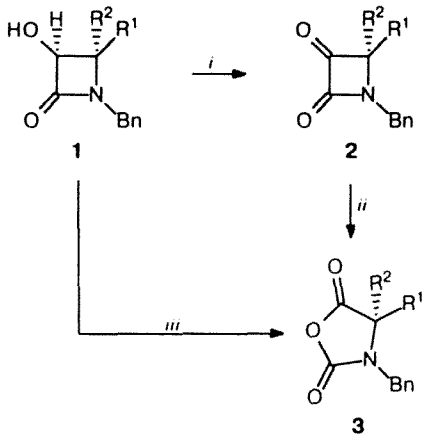
Reagents and conditions: *i*. 1) NEt_3, $ClCO_2Et$; 2) H_2CN_2;

ii.  , 10% AgO_2CPh, NEt_3.

obtainable from α-hydroxy-β-lactams (**1**) takes place regioselectively to give α-amino acid *N*-carboxy anhydrides (NCAs) (**3**).[21] The well recognized importance of this particular class of mixed anhydrides in α-amino acid chemistry[22,23] led us to develop this approach into a general method for the synthesis of homochiral NCAs that would proceed in a single one-pot operation without the need to isolate the intermediate α-keto-β-lactams. We found that the stable nitroxide free radical, 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%.[24] In this context, much of our work has been centered on [2+2] cycloaddition reactions of α-hydroxyketene equivalents with imines to obtain the required α-hydroxy-β-lactams in a convergent fashion (a general review on β-lactams (Ref. 25) and a comprehensive review concerning cycloaddition of ketenes to imines (Ref. 26) should be mentioned), although ester enolate-imine condensation could also be employed for the same purpose.[27,28]

Besides being useful as valuable precursors of NCAs, α-hydroxy-β-lactams have also been found to be excel-

Scheme 5



Reagents, conditions, and yields: *i.* DMSO, P_2O_5, 16 h, ~20 °C, 89—90%; *ii.* *m*-$ClC_6H_4CO_3H$ (MCPBA), CH_2Cl_2, −40 °C, 1 h, 80—90%; *iii.* NaOCl, TEMPO, > 95%.

lent building blocks of α-hydroxy-β-amino acid derivatives by exploiting nucleophilic reactions at the β-lactam carbonyl group (see comprehensive reviews 29—32). When we initiated our investigations on this subject, little was known about β-lactam ring opening by carbon nucleophiles[33—39] and even less about coupling reactions with α-amino acid esters.[40,41] Therefore, we studied both aspects with the aim of establishing new reaction methodology for the incorporation of β-amino acid derivatives into peptides.

This account summarizes our studies on α-, β-, and γ-amino acid peptides and related systems derived from β-lactams as readily available synthetic building blocks.

2. *Synthesis of* α-*amino acid N-carboxy anhydrides*

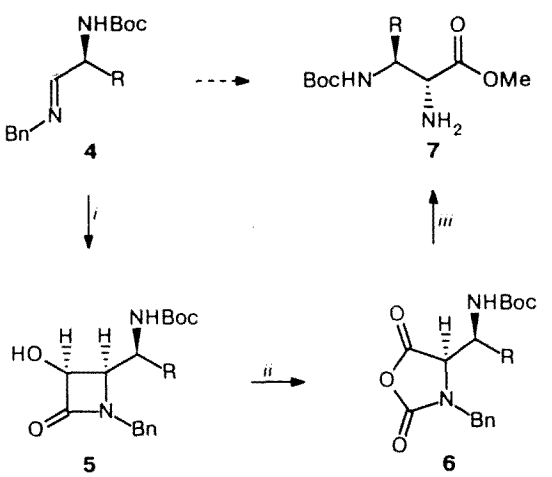
α-Amino acid *N*-carboxy anhydrides, NCAs, or Leuchs anhydrides, offer both amino group protection and carboxylate activation simultaneously. As a consequence, they have found wide application in peptide synthesis and numerous procedures have been reported for their preparation, all of them involving reactions between an α-amino acid and dehydrating agents.[42—51] Therefore, we considered that a conceptually new approach to peptide segments would be facilitated if NCAs could be obtained from non-α-amino acid precursors. To this end, we have developed the first tactically new approach to NCAs, proceeding by an unprecedented ring expansion of α-hydroxy-β-lactams (this topic is treated in a review,[52] another method for ring expansion of α-hydroxy-β-lactams is described in Ref. 53).

2.1. α,β-Diamino acid *N*-carboxy anhydrides

2,3-Diamino carboxylic acids are uncommon naturally occurring amino acids that have aroused considerable interest (see Refs. 54—62). This particular class of amino acids, when incorporated into peptides with either the β- or the α-amino group as part of the backbone, might provoke changes in polarity, additional hydrogen-bonding interactions, and may make the peptide basic. α,β-Diamino acids can also serve as substitutes for α-hydroxy-β-amino acid-derived peptides to probe their structural specificity and topology.[63] Interest in α,β-diamino acids also stems from their occurrence in cyclic peptides and biologically active substances, *e.g.* capreomycin,[64] pyrimidoblamic acid,[65,66] auisqualic acid,[67,68] willardiine,[69] mimosine.[70] β-Substituted 2,3-diamino acids are also useful intermediates for the synthesis of imidazolines, which have been employed as amide bond replacements in the design of peptidomimetics.[71—74]

The approach to α,β-diamino acid *N*-α-carboxy anhydrides (Scheme 6) takes advantage of the highly diastereoselective cycloaddition of ketenes to imines derived from *N*-Boc-α-amino aldehydes (Boc = Bu^{t}OCO) developed in our laboratory.[75] The method[24] involves a one-pot double oxidation sequence of α-hydroxy-β-lactams (**5**) using TEMPO in combination with fresh commercial bleach whose pH = 12.7 was adjusted to neutrality in order to avoid possible epimerization of the resulting NCA (**6**). Reactions can be conducted at 0 °C and are almost complete in a few minutes using a twofold excess of 1 *M* NaOCl and a catalytic amount of TEMPO. Without the catalyst, the starting α-hydroxy-β-lactams are recovered unchanged after 24 h of reaction at room temperature. As shown in the scheme, the method allows the formation of (*R*)-α-amino acids (**7**) from (*S*)-α-amino aldehydes (imi-

Scheme 6



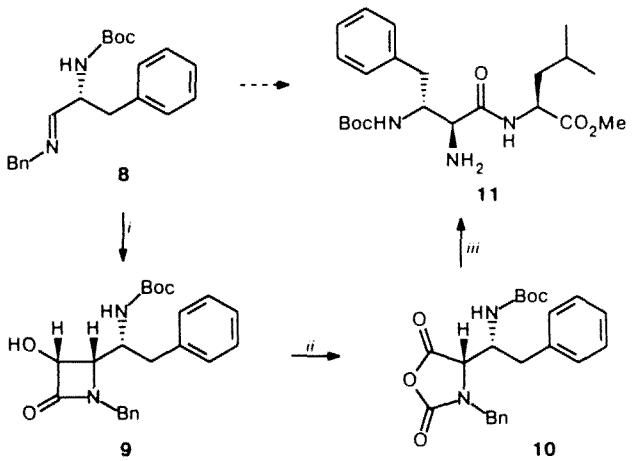
R = Me, $CHMe_2$, CH_2Ph

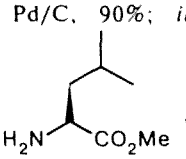
Reagents and conditions: *i.* 1) $BnOCH_2COCl$, NEt_3, CH_2Cl_2, 75—85%; 2) H_2, Pd/C, EtOH, 90—95%; *ii.* 1 *N* NaOCl, TEMPO, $NaHCO_3$, KH_2PO_4—K_2HPO_4, KBr (pH 6.9), CH_2Cl_2, ~20 °C, 10—15 min, 90—98%; *iii.* 1) MeOH, boiling, 72—90%, 2) H_2, 10% Pd/C, EtOH.

nes **4**) and *vice versa* with completely predictable stereochemical control and optical purity. Furthermore, both amino moieties are differentially protected and thus incorporation of these amino acids into peptide chains either at the α- or β-positions becomes possible *via* this procedure.

The use of the enantiomers of imines **4** makes it possible to obtain the corresponding enantiomeric azathreonines and peptides thereof. This latter aspect is illustrated (Scheme 7) by the synthesis of aminodeoxybestatin **11**, an inhibitor of aminopeptidase-M equipotent to the known bestatin.[63] For example, imine **8**, on treatment with benzyloxyacetyl chloride and triethylamine followed by hydrogenolysis of the resulting 3-benzyloxy-β-lactam, led to hydroxylactam (**9**) in good yield. Treatment of **9** with TEMPO and NaOCl as above gave the NCA **10** in 97% yield, which on coupling with (*S*)-leucine methyl ester furnished the corresponding dipeptide product. Subsequent *N*-debenzylation of the latter led to **11** in good overall yield. For the synthesis of azathreonine-NCAs in a two-step procedure see Ref. 76.

Scheme 7



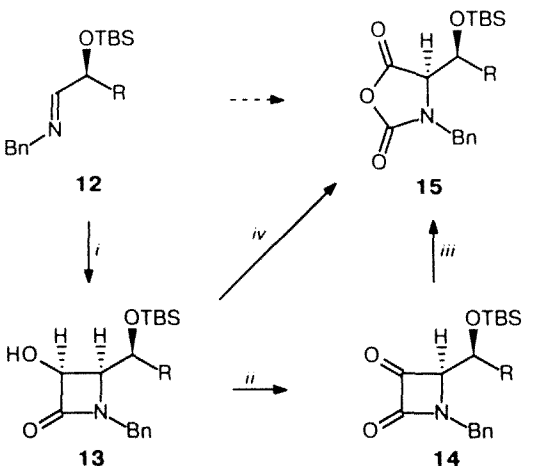
Reagents, conditions, and yields: *i.* 1) $BnOCH_2COCl$, NEt_3, 2) H_2, Pd/C, 90%; *ii.* 1 *N* NaOCl, TEMPO, 97%; *iii.* 1)  , CH_2Cl_2, −20 °C, 85%; 2) H_2, 10% Pd/C, EtOH, 97%.

Along with these studies we also examined an alternative β-lactam approach to these α,β-diamino acid peptides, which will be discussed in section 3.2.

2.2. α-Amino-β-hydroxy acid *N*-carboxy anhydrides

The above reaction methodology has also been extended to threonine NCAs[77] as a potential novel route to peptide segments of macrocyclic antibiotics. For example (Scheme 8), treatment of imines (**12a—c**) with benzyloxyketene and further debenzylation of the resulting cycloadducts led to the α-hydroxy-β-lactams (**13a—c**) in good yields. Subsequent oxidation of each compound **13** with P_2O_5 in DMSO gave the corresponding α-keto-β-lactams (**14**). 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 **13**, thus proving the lack of epimerization during their oxidation. Finally, Baeyer—Villiger rearrangement of each α-keto-β-lactam **14** furnished the expected NCAs (**15**) in excellent yields although, in some instances, they were contaminated with *m*-chloroperbenzoic acid. Nonetheless, the direct one-pot transformation of α-hydroxy-β-lactams into the desired NCAs has been found to be the method of choice.

Scheme 8

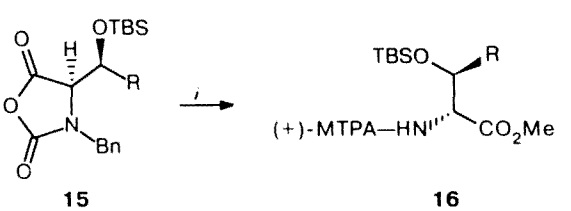


a: R = Pr^i, **b:** R = Bu, **c:** R = Bn
TBS = Bu^{t}SiMe$_2$

Reagents, conditions, and yields: *i.* 1) $BnOCH_2COCl$ (2 equviv.), NEt_3, 70—85%; 2) NH_4CO_2H, Pd/C, Pr^{i}OH, 89—93%; *ii.* P_2O_5, DMSO, ~20 °C, 20 h, 85—95%; *iii.* MCPBA, CH_2Cl_2, −40 °C, 1 h, 90—95%; *iv.* NaOCl, TEMPO (cat.), $NaHCO_3$, KH_2PO_4, K_2HPO_4 (pH = 6.9), CH_2Cl_2, > 95%.

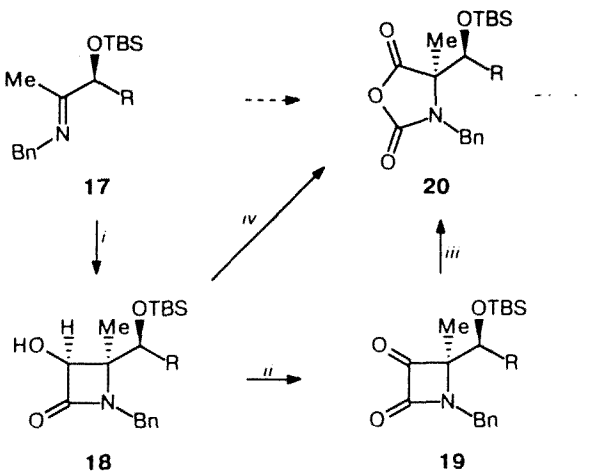
The optical purity of these NCAs was determined (Scheme 9) by their prior conversion into the respective

Scheme 9



Reagents and conditions: *i.* 1) MeOH, boiling, 1 h; 2) NH_4CO_2H, Pd/C; 3) (+)-MTPA—Cl, NEt_3.

Scheme 10



a: R = Me; **b:** R = Bn; **c:** R = Pr^i

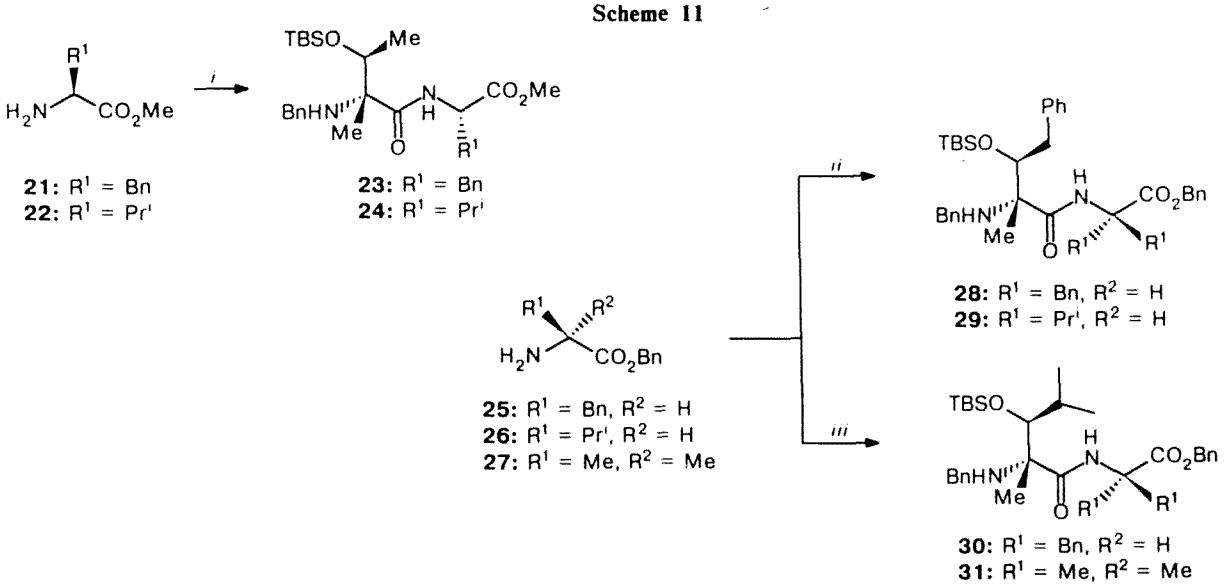
Reagents, conditions, and yields: *i.* 1) $BnOCH_2COCl$ (2 equiv.), NEt_3, 70—85%; 2) NH_4CO_2H, Pd/C, Pr^{i}OH, 89—93%; *ii.* P_2O_5, DMSO, ~20 °C, 20 h, 80—92%; *iii.* MCPBA, CH_2Cl_2, 80—90%; *iv.* NaOCl, TEMPO (cat.), $NaHCO_3$, KH_2PO_4, K_2HPO_4 (pH = 6.9), CH_2Cl_2, > 95%.

O-protected threonines and subsequent acylation with Mosher acid chloride ((+)-MTPA-Cl) to form compounds **16**.

Owing to the importance of α-methyl-β-alkylserines for the study and design af new bioactive targets,[78—80] the above approach has also been developed into a general method for the synthesis of α-branched α-amino-β-hydroxy acid *N*-carboxy anhydrides.[81] The key to the approach was the use of α-alkoxyketone-derived imines (**17**). These are readily available starting materials that incorporate the required structural subunit of the desired amino acid and, at the same time, provide chirality to the corresponding NCA precursors (Scheme 10). When we started this work, no general method for the synthesis of homochiral β-lactams with quaternary stereogenic centers at C(4) was available. For this reason we explored the cycloaddition of benzyloxyketene with the aforementioned imines in the hope of obtaining the expected cycloadducts with high diastereoselectivity. Indeed, using standard cycloaddition conditions we got the corresponding β-lactams in good yields and, most notably, as single diastereomers. Subsequent removal of the benzyloxy protective group from the resulting cycloadducts led to the α-hydroxy-β-lactams (**18**). The absolute configuration assigned to the adducts was based initially on the assumption of a uniform reaction mechanism and then was confirmed by a single crystal X-ray analysis of **18c**. Conversion of these adducts into the corresponding NCAs **20** was first carried out in a two-step procedure involving oxidation of each β-lactam **18** to the respective α-keto-β-lactam **19** and further Baeyer—Villiger rearrangement, but better yields were obtained by performing this oxidation sequence in a one-pot operation using TEMPO in combination with NaOCl. In these instances, the insertion of the oxygen atom also takes place regioselectively between both carbonyl groups.

After the preparation of α-branched α-amino-β-hydroxy acid NCAs, we explored their coupling reactions with several α-amino esters, but problems arose leading to yields below 10%. However, as Scheme 11 illustrates, the desired coupling reactions of α-amino esters with the above NCAs were achieved efficiently using potassium cyanide as additive. Under these conditions amino esters **21** and **22** coupled with **20a** to give dipeptides **23** and **24** in 87 and 90% isolated yields. In a similar way α-amino acid esters **25** and **26** gave **28**, **29**

Scheme 11



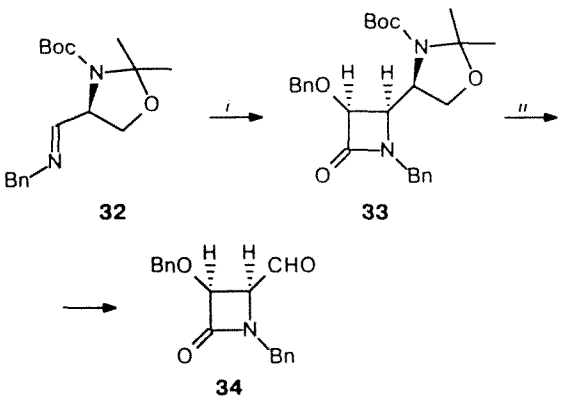
Reagents, conditions, and yields: *i.* **20a**, KCN, DMF, 90%; *ii.* **20b**, KCN, DMF, 90%; *iii.* **20c**, KCN, DMF, 79—90%.

and **30** in good yields too. Under these conditions even the bulky Aib-methyl ester **27** coupled with **20c** to give **31** in 79% yield.

2.3. Arylalanine and homoarylalanine derived *N*-carboxy anhydrides

The potential of the β-lactam-NCA method is also demonstrated by the synthesis of aryl- and homoarylalanines.[82] The key to the approach (Scheme 12) is the use of the *N,O*-protected β-formyl-β-lactam **34** as a common homochiral synthetic building block readily obtained from the β-lactam **33**.

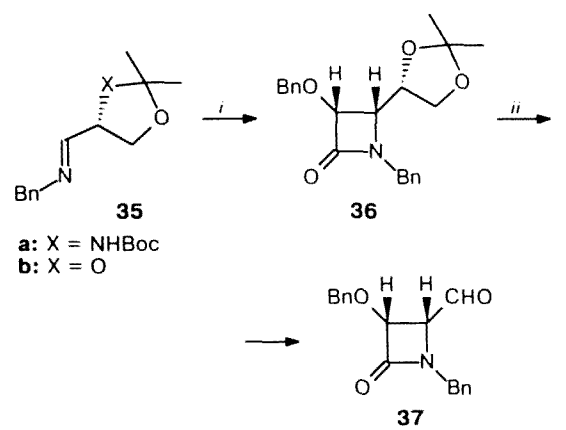
Scheme 12



Reagents, conditions, and yields: *i.* $BnOCH_2COCl$, NEt_3, 76%; *ii.* 1) 3 *N* HCl, MeOH, boiling, 75%; 2) $NaIO_4$, Me_2CO-H_2O, 24 h, ~20 °C, 95%.

Similarly, the enantiomer (**35**) of the imine **32** (Scheme 13), after *N,O*-dideprotection and subsequent oxidative cleavage, furnished the β-lactam **37**. The latter

Scheme 13



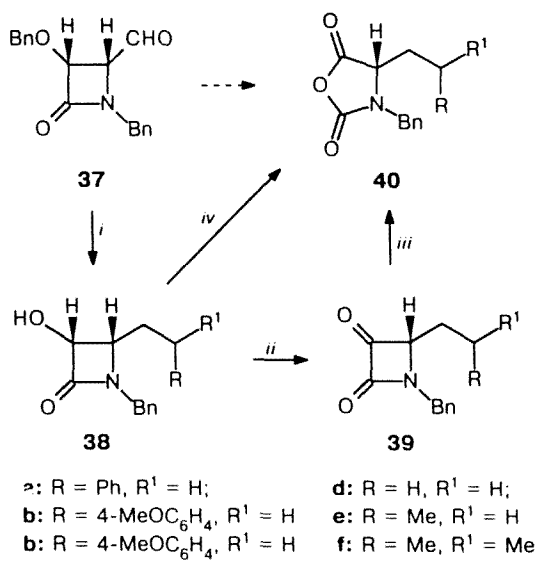
a: X = NHBoc
b: X = O

Reagents, conditions, and yields: *i.* $BnOCH_2COCl$, NEt_3, 65—80%; *ii.* 1) TsOH, THF, H_2O, 90%; 2) $NaIO_4$, Me_2CO, H_2O, 95%.

can also be produced in a similar way from Bose's cycloadduct **36** derived from the glyceraldehyde imine **35b**.[83] In both cases yields were generally high and the reactions were performed in gram quantities.

As Scheme 14 illustrates, the synthesis of homoarylalanine NCAs starts from aldehyde **37** by using the Wittig reaction followed by hydrogenolysis of the resulting olefinic intermediates under Pd/C. Subsequent oxidation and Baeyer—Villiger rearrangement of the α-keto-β-lactam intermediates **39** afforded the desired NCAs **40** in good yields. Once again, considerable yield improvement (typically >95%) was observed by performing the direct transformation of **38** into **40** promoted by TEMPO. It is interesting to note that this approach involving β-formyl-β-lactam elongation also allows the synthesis of other structurally different NCAs depending on the preselected Wittig reagent. At the same time (Scheme 15), simple Grignard addition to the formyl-β-lactam **37** followed by deoxygenation of the resulting mixture of epimeric β-lactams **41** furnished **42** in good yields. One-pot double oxidation of these products gave NCAs **43** formally derived from arylalanines.

Scheme 14

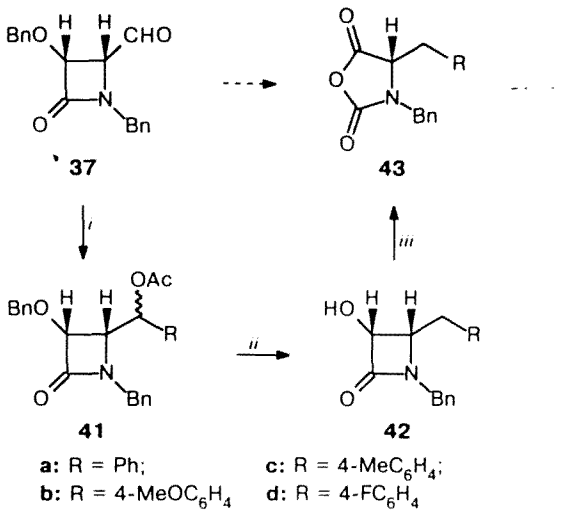


a: R = Ph, R^1 = H;
b: R = 4-$MeOC_6H_4$, R^1 = H
b: R = 4-$MeOC_6H_4$, R^1 = H
d: R = H, R^1 = H;
e: R = Me, R^1 = H
f: R = Me, R^1 = Me

Reagents, conditions, and yields: *i.* 1) $Ph_3P{=}CHRR^1$, THF, ~20 °C, 2 h; 2) NH_4CO_2H, Pd/C, MeOH, 75—90%; *ii.* P_2O_5, DMSO, ~20 °C, 20 ч, 70—90%; *iii.* MCPBA, CH_2Cl_2, −40 °C, 1 h, 90—95%; *iv.* NaOCl, TEMPO (cat.), $NaHCO_3$, KH_2PO_4, K_2HPO_4 (pH = 6.9).

In view of the increasing importance of α,α-disubstituted α-amino acids for the study and design of structurally defined peptides, peptidomimetics, and, in general, potent bioactive targets,[2—7] the above β-formyl-β-lactam elongation has also been extended to the synthesis of dipeptide segments containing this class of amino acids.[86] The cycloaddition of benzyloxyketene to the

Scheme 15

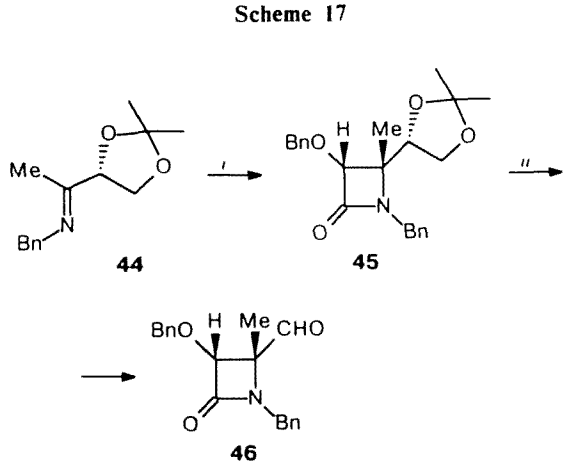


a: R = Ph; **c:** R = 4-MeC_6H_4;
b: R = 4-$MeOC_6H_4$ **d:** R = 4-FC_6H_4

Reagents, conditions, and yields: *i.* 1) RMgBr, THF, −40 °C, 30 min, 72—88%; 2) AcCl, NEt_3, CH_2Cl_2, −20 °C, 2 h, 95—100%; *ii.* NH_4CO_2H, Pd/C, Pr^iOH, boiling, 1 h, total yield 71—90%; *iii.* NaOCl, TEMPO, pH = 6.9, >90%.

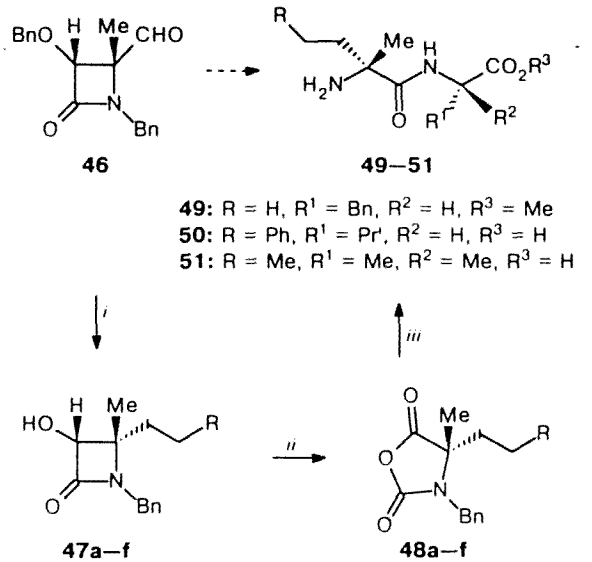
ketimine **44** leads to lactam **45** with perfect asymmetric induction at the newly created stereogenic centers. Subsequent deprotection of the acetonide group and further oxidative cleavage of the resulting diol gave formyl-β-lactam **46** in good overall yield (Scheme 16). With this material in hand, the synthesis of β,β-disubstituted α-hydroxy-β-lactams **47** was performed as above using the Wittig reaction, followed by hydrogenolysis of the benzyloxy protective group and simultaneous double bond reduction. As Scheme 17 shows, when these compounds were treated with NaOCl and a catalytic amount of TEMPO the corresponding NCAs **48** were formed in yields up to 97%. In accordance with the results outlined previously, NCAs **48a** and **48b** were 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 on charcoal, dipeptides **49** and **50** in yields of 73 and 71%, respectively. Under these conditions, even the bulky benzyl α-aminobutyrate could be efficiently coupled with the NCA **48e** to give the corresponding dipeptide derivative, which upon *N,O*-didebenzylation afforded dipeptide **51** in 70% yield.

Scheme 17



Reagents, conditions, and yields: *i.* $BnOCH_2COCl$, NEt_3, 80%; *ii.* 1) $HClO_4$, THF, H_2O; 2) $NaIO_4$, Me_2CO, H_2O, 24 h, 90%.

Scheme 17



49: R = H, R^1 = Bn, R^2 = H, R^3 = Me
50: R = Ph, R^1 = Pr^i, R^2 = H, R^3 = H
51: R = Me, R^1 = Me, R^2 = Me, R^3 = H

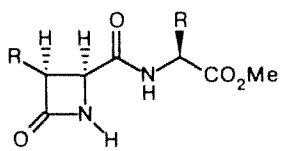
a: R = H; **d:** R = 4-MeC_6H_4;
b: R = Ph; **e:** R = Me;
c: R = 4-$MeOC_6H_4$ **f:** R = CO_2Me

Reagents, conditions, and yields: *i.* 1) $Ph_3P{=}CHRR^1$, THF, −20 °C, 2 h; 2) H_2, Pd/C, EtOH, −20 °C, 14 h, 75%; *ii.* NaOCl, TEMPO (cat.), 95—97%; *iii.* 1) (*S*)-$H_2NCR^1R^2CO_2R^3$, KCN, DMF; 2) H_2, Pd/C, EtOH, 70—73%.

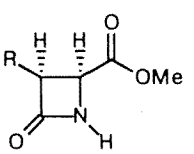
3. β-Amino acids

In connection with the above studies on NCAs we also developed the use of β-lactams as synthetic equivalents of β-amino acids. It is well known that β-lactams undergo hydrolytic cleavage of the C—N amidic linkage to form β-amino acids under both acidic and basic conditions.[29—32] However, the harsh reaction conditions often required to carry out this transformation can

cause partial or complete epimerization, not only at the α-position of the β-lactam ring, but also at other positions of the β-lactam product. This is particularly true for compounds of general structure **52** or **53**, in which the exocyclic methyl ester group can, in its turn, be easily cleaved. In concert with these problems, little was known about the behaviour of β-lactams as acylating agents for peptide synthesis before we started our work on this subject. The only investigation on this topic was reported by Drey and his co-workers, who attempted the coupling reaction of a β-lactam framework with α-amino acid esters but with very little success.[40] At the same time, it is also well known that some simple monocyclic β-lactams, when carrying suitable electron-withdrawing groups at the N atom, possess antimicrobial activity and/or act as inhibitors of transpeptidases, β-lactamases, and elastases.[87] Therefore, on this basis we reasoned that if the final result of the opening of the β-lactam ring by an enzyme results in its *O*-acylation, a parallel coupling reaction between monocyclic β-lactams and α-amino acid esters should be possible. If so, the net effect would be a conceptually new approach to peptide synthesis incorporating β-amino acid segments.



52

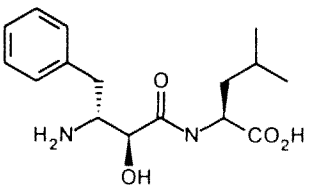


53

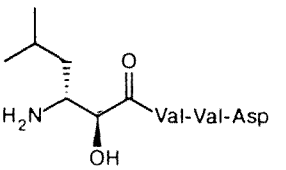
Our initial trials to probe this hypothesis were made on *N*-Boc-β-lactams and the finding was that the β-lactam ring could efficiently be opened by both oxygen and nitrogen nucleophiles in the presence of sodium azide or potassium cyanide as promoters of the reaction[88] (see also Refs. 89, 90). Presumably an acyl azide or an acyl cyanide intermediate should be formed in such a reaction. Although no evidence has yet been found for this assumption, it remains a fact that β-lactam ring opening generally does not take place in the absence of these additives. On the other hand, since the overall process would imitate the alcoholysis of β-lactams promoted by class C β-lactamases,[91] the term *enzyme-mimetic* was adopted for these coupling reactions. This aspect will be illustrated in the following sections through some representative examples that add new perspectives to β-amino acid chemistry.

3.1. β-Amino α-hydroxy acids

The synthesis of β-amino-α-hydroxy acids to be incorporated into peptides has been well documented and still continues to be of current interest within the domain of new enzyme inhibitors.[92] Important members of this class of compounds are bestatin **54** and amastatin **55**, two low molecular weight peptidic immunomodifiers[93,94] with antitumor and antimicrobial activity.[95] 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.



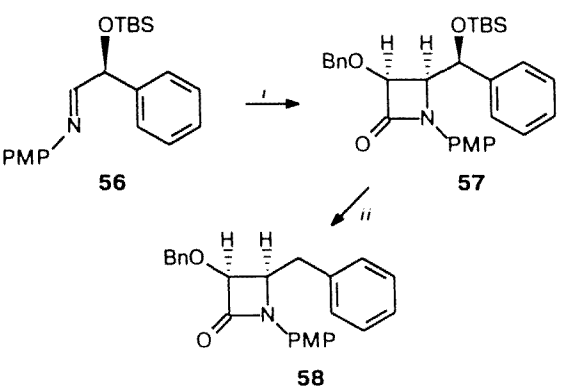
54



55

Our approach to (−)-bestatin **54** involves the cycloaddition of benzyloxyketene to the imine **56** (Scheme 18) according to the procedure of Terashima[96] and subsequent desilylation and deoxygenation of the resulting adduct **57** (PMP is *p*-methoxyphenyl) under

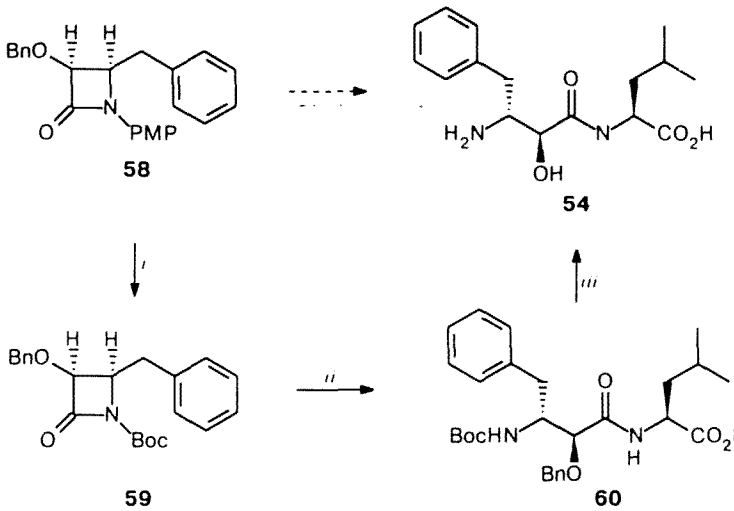
Scheme 18

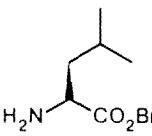


Reagents, conditions, and yields: *i.* $BnOCH_2COCl$, NEt_3; *ii.* 1) Bu_4^nNF, CH_2Cl_2, 95%; 2) NaH, CS_2, THF, 0 °C, MeI, −20 °C, 30 min, 100%; 3) Bu_3^nSnH, Et_3B, C_6H_6, −20 °C, 60%.

modified Barton's conditions. The β-lactam **58**, which is the cyclized form of the bestatin β-amino acid, is then *N*-dearylated under the action of cerium ammonium nitrate (CAN) and activated with the introduction of the Boc group to this position. At first (Scheme 19) the coupling reaction of the resulting *N*-Boc-β-lactam **59** with (*S*)-leucine benzyl ester was examined in methylene chloride at room temperature, but under these conditions a fourfold excess of the α-amino acid ester was required to give complete conversion into the de-

Scheme 19

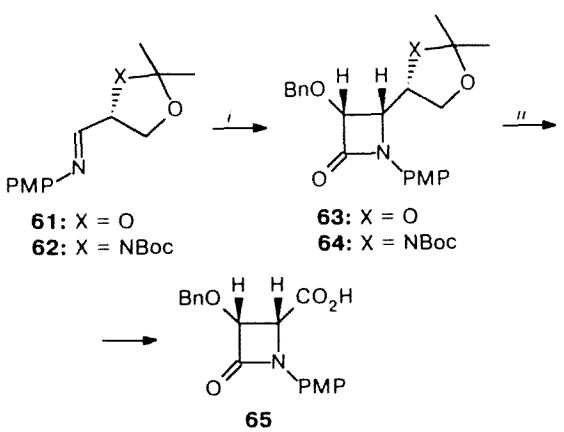


Reagents, conditions, and yields: *i.* 1) CAN, MeCN, H_2O, 90%; 2) $(Boc)_2O$, DMAP, MeCN, 73%; *ii.*  , DMF, NaN_3 (1 equiv.), 20 h, ~20 °C, 88%; *iii.* 1) TFA, CH_2Cl_2; 2) H_2, Pd/C, EtOH, 98%.

sired dipeptide product **60**. However, when the reaction was performed in DMF and in the presence of NaN_3 the coupling proceeded by using equimolar amounts of both components[97] (see also Ref. 98).

This strategy was also employed for the synthesis of β-hydroxyaspartic acid derivatives. β-Hydroxyaspartic acid itself appears to play an important role in blood clotting proteins[99] and its derivatives have been found in macrocyclic antibiotics like lysobactin,[100–103] *vide infra*. The synthesis of the starting β-lactam (Scheme 20) was carried out from imines **61** and **62** *via* cycloaddition; in both cases one diastereomer was formed. The resulting

Scheme 20

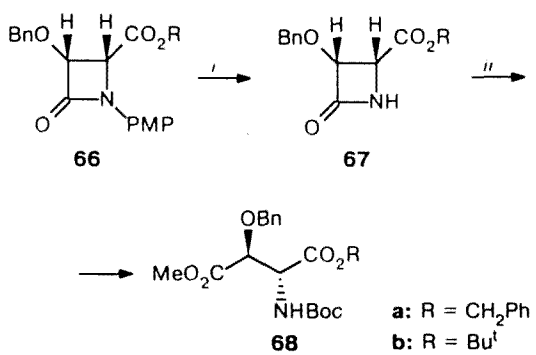


Reagents, conditions, and yields: *i.* $BnOCH_2COCl$, NEt_3, 80–85%; *ii.* 1) HCl, MeOH, 100%; 2) $NaIO_4$, Me_2CO–H_2O, $KMnO_4$, ~20 °C, 75%.

β-lactams **63** and **64** were then converted into the 4-carboxy derivative **65** in good overall yield. It should be mentioned that the use of chiral glyoxylates in this cycloaddition reaction afforded the corresponding 4-alkoxycarbonyl β-lactams, albeit with poor diastereoselectivity.[104]

The β-lactams **67a** and **67b** can be obtained by esterification of the acid **65**, followed by *N*-dearylation of the esters **66a** and **66b** obtained, respectively (Scheme 21). Ring opening of the NH β-lactams **67** by means of chlorotrimethylsilane in methanol led to the corresponding β-benzyloxy aspartate **68b**.

Scheme 21

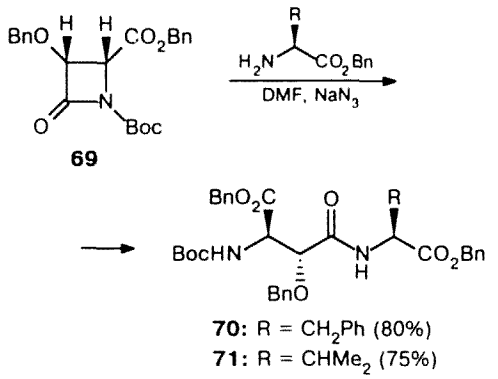


Reagents, conditions, and yields: *i.* CAN, MeCN, H_2O, 70–80%; *ii.* 1) MeOH, $ClSiMe_3$; 2) $(Boc)_2O$, 70–75%.

At the same time, the introduction of the Boc group at the *N*-position of the β-lactam **67a** led to the lactam **69**, which then (Scheme 22) was coupled with (*S*)-phenylalanine and (*S*)-valine benzyl esters to give dipep-

tides **70** and **69**, respectively. Both couplings proceeded efficiently in the presence of NaN_3 but, in its absence, only 50% conversion was observed in the reaction of lactam **69** with (*S*)-valine benzyl ester.[97]

Scheme 22



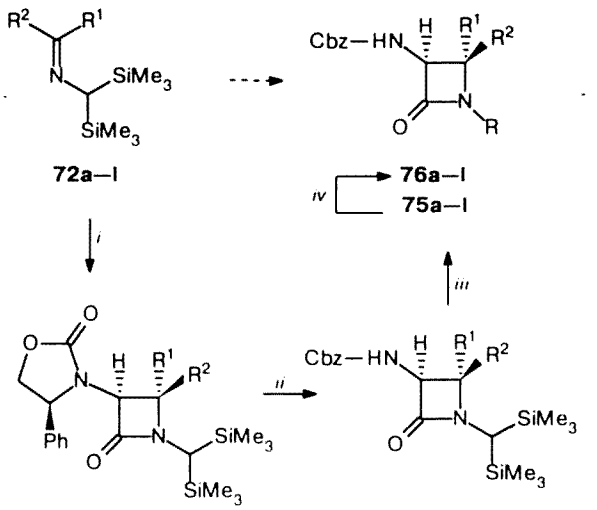
3.2. α,β-Diamino acids

As pointed out in section 2.1, α,β-diamino acids are of particular interest in the development of new peptidomimetics and syntheses that allow their incorporation into peptide chains by either the α- or the β-amino function. These facts led us to prepare β-alkyl-α-amino-β-lactams with differently protected amino moieties and, in the light of the above results, to study their coupling with α-amino acid esters.

Although the cycloaddition reaction of imines with ketenes generated from acid chlorides and tertiary amines has provided a useful approach to diverse β-lactam compounds, it has not hitherto been viable with enolizable imines, in part because of their instability, and in part because of competitive deprotonations.[105] Efforts from this laboratory to solve this problem resulted in the development of imines **72**, which, in spite of their remarkable stability, react with the Evans—Sjogren ketene XcCH=C=O (Xc = 2-oxo-4-phenyl-oxazolidin-3-yl), generated from the corresponding acid chloride and triethylamine, to form β-lactams **73** with excellent diastereomeric ratios and, most notably, with perfect asymmetric induction at the C(3) atom.[106] This method (Scheme 23) is applicable for the construction of homochiral β-lactams with linear as well as branched chains at the β-C atom. Removal of the chiral auxilliary followed by protection of the amino group led to the Cbz-derivatives **74**, which by treatment with CAN in acetonitrile—water gave *N*-formyl-β-lactams **75**. The latter were deformylated to the desired N—H β-lactams **76** under slightly basic conditions.

It was also found that an alternative removal of the *N*-bis(trimethylsilyl)methyl substituent with CAN in methanol directly afforded the corresponding NH β-lactams. However, the subsequent cleavage of the

Scheme 23

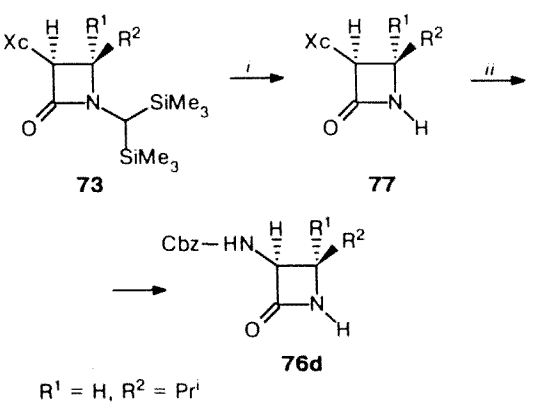


a: R^1 = H, R^2 = Me
b: R^1 = H, R^2 = Et
c: R^1 = H, R^2 = Pr^n
d: R^1 = H, R^2 = Pr^i
e: R^1 = H, R^2 = CH_2CH_2Ph
f: R^1 = H, R^2 = Bn
g: R^1 = H, R^2 = $CH_2CH_2CO_2Bu^t$
h: R^1 = Me, R^2 = Me
i: R^1 = Et, R^2 = Et
j: R^1 = Pr^n, R^2 = Pr^n
k: R^1 = Me, R^2 = Et
l: R^1 = Me, R^2 = CH_2CH_2Ph

Reagents, conditions, and yields: *i.* $XcCH_2COCl$, NEt_3, $CHCl_3$, boiling, 20 h, 55—82%; *ii.* 1) Li, NH_3, Bu^tOH, THF, >94%; 2) CbzCl, DMAP, 70—75%; *iii.* $(NH_4)_2Ce(NO_3)_6$, MeCN, H_2O, 80%; *iv.* $NaHCO_3$, Na_2CO_3, H_2O, Me_2CO, 70—80%.

oxazolidinone moiety followed by Cbz-protection of the free amino group was only viable for 4-isopropyl β-lactam **77** (Scheme 24).

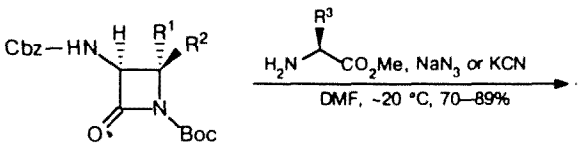
Scheme 24



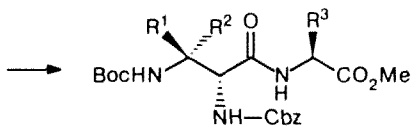
R^1 = H, R^2 = Pr^i

Reagents, conditions, and yields: *i.* $(NH_4)_2Ce(NO_3)_6$, MeOH, ~20 °C, 6 h, 80%; *ii.* 1) Li, NH_3, Bu^tOH, THF, 80%; 2) CbzCl, DMAP, 70%.

Scheme 25



78: R^1 = H, R^2 = CH_2CH_2Ph
79: R^1 = Me, R^2 = Me



80: R^1 = H, R^2 = CH_2CH_2Ph, R^3 = Bn
81: R^1 = H, R^2 = CH_2CH_2Ph, R^3 = $CHMe_2$
82: R^1 = Me, R^2 = Me, R^3 = Bn
83: R^1 = Me, R^2 = Me, R^3 = $CHMe_2$

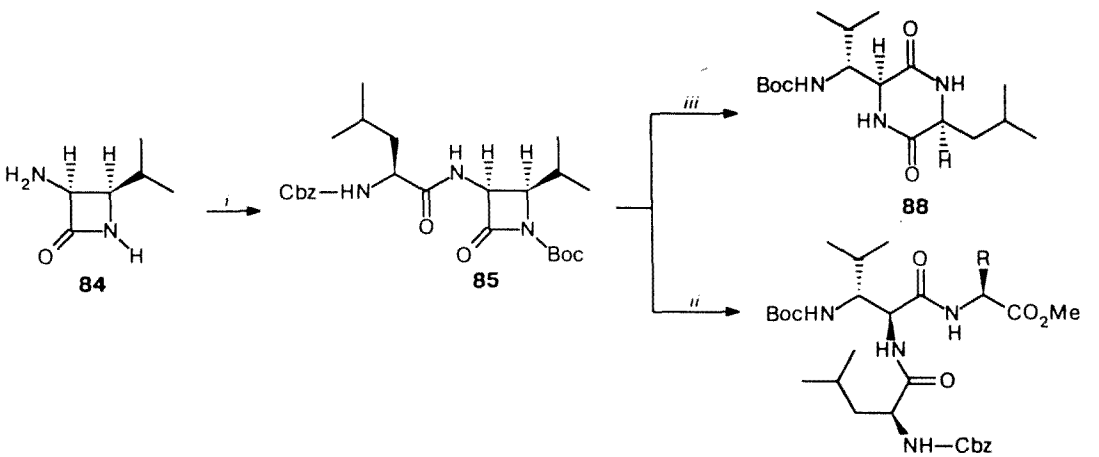
The approach to dipeptide products was guided by the observation that the introduction of the Boc group at the endocyclic N atom in β-lactams **76e** and **76h** proceeded chemoselectively to give the differently protected β-lactams **78** and **79**, respectively (Scheme 25). Further, the presence of an electron-withdrawing group at this N atom also anticipated the expected enzymemimetic ring opening with α-amino acid esters. However, while the β-lactam **78** coupled efficiently with both (*S*)-phenylalanine methyl ester and (*S*)-valine methyl ester in DMF in the presence of NaN_3 promoter to give dipeptides **80** and **81** in good yields, the β-lactam **79** with a quaternary C(4) atom did not react with these α-amino acid esters, even when a twofold excess of NaN_3 was added. Nonetheless, the coupling reaction can be effected efficiently by replacing the additive NaN_3 with KCN. Under these conditions the dipeptide product **82** was produced within about 10 h in 89% isolated yield and dipeptide **83** in 85% yield after about 20 h of reaction.

Further examples are shown in Scheme 26. For example, acylation of β-lactam **84** with (*S*)-Cbz-leucine fluoride ((*S*)-Cbz-LeuF) in the presence of *N*-methylmorpoline (NMM) according to Carpino's procedure and subsequent introduction of *N*-Boc led to the β-lactam **85**. This β-lactam dipeptide also coupled efficiently under the influence of either NaN_3 or KCN with both (*S*)-phenylalanine methyl ester and (*S*)-valine methyl ester to give tripeptides **86** and **87** in 80 and 75% yields, respectively. When the β-lactam **85** was subjected to hydrogenolysis, the piperazinedione **88** was produced smoothly in 90% isolated yield. Clearly, these examples demonstrate that the approach developed can be readily extended to the synthesis of cyclic peptides, peptidomimetics, and biologically active substances incorporating α,β-diamino acids as key segments.[107]

4. Macrocyclic peptides

There are several macrocyclic peptides containing non-natural α-amino acids, particularly α-amino-β-hydroxy acids.[108] Most of these complex compounds have useful biological properties and often act as potent antibiotics. Two representative examples are vancomycin[109] and lysobactin (**89**).[99] The latter is a macrocyclic peptide lactone isolated from the fermentation of *Lysobacter* Sp.AICC53042 and shows a similar mode of antibacte-

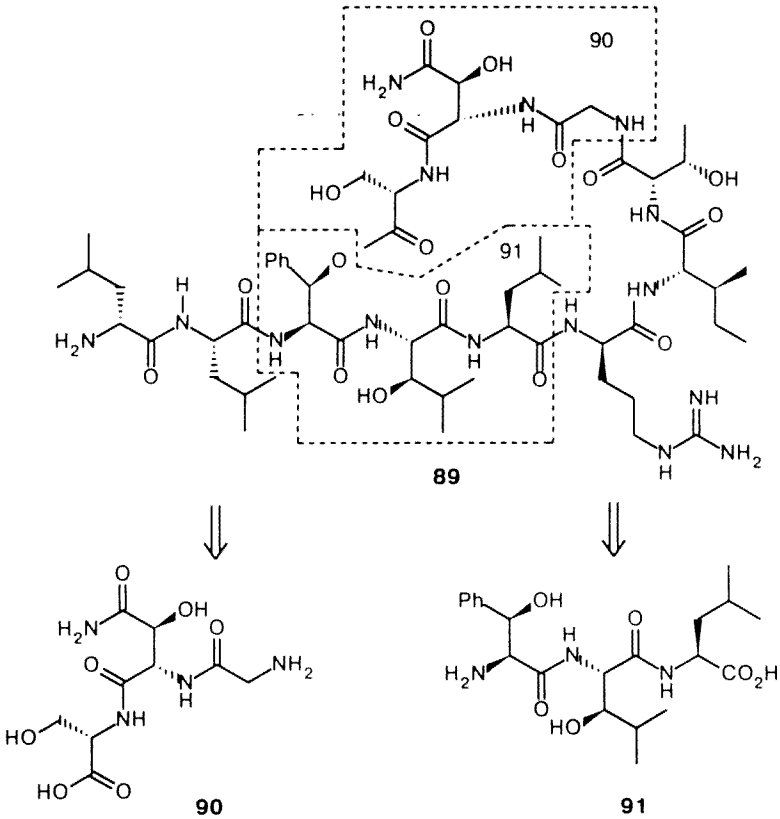
Scheme 26



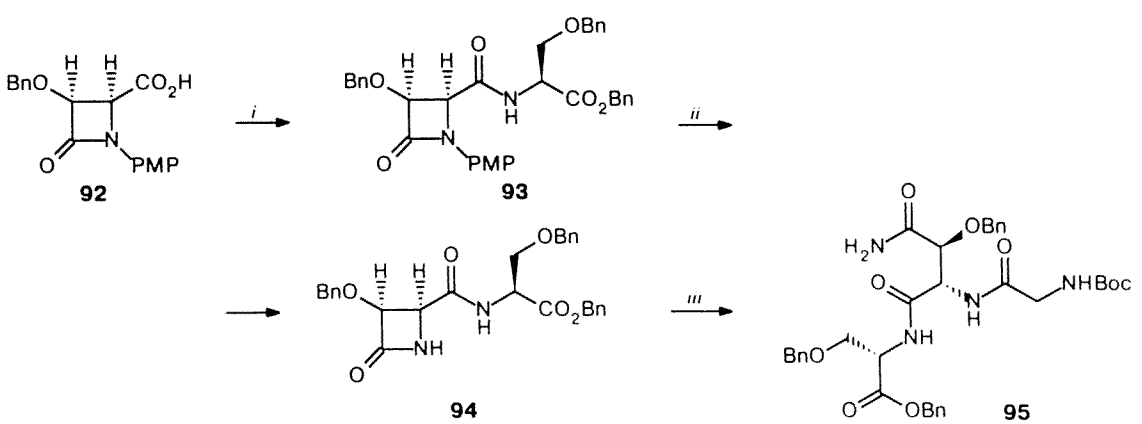
86: R = Bn (80%)
87: R = $CHMe_2$ (75%)

Reagents, conditions, and yields: *i.* 1) Cbz—HN(H)(CHMe$_2$)COF, NMM, 80%; 2) $(Boc)_2O$, DMAP, MeCN, 90%; *ii.* H_2NCH(R)CO_2Me, NaN_3 or KCN, DMF, –20 °C, 70–89%; *iii.* H_2, Pd/C, EtOH, –20 °C, 14 h, 90%.

Scheme 27



Scheme 28



Reagents, conditions, and yields: *i.* 1) Cianuric fluoride, Py, CH_2Cl_2, 6 h; 2) (S)-$H_2NC(CH_2OBn)CO_2Bn$, CH_2Cl_2, NMM, 3 h, 95%; *ii.* 1) MeCN, H_2O, CH_2Cl_2, 90%; 2) $(Boc)_2O$, MeCN, DMAP, 80%; *iii.* 1) NH_4OH, DMF, 90%; 2) BocGlyF, NMM, CH_2Cl_2, 2 h, 0 °C, 80%.

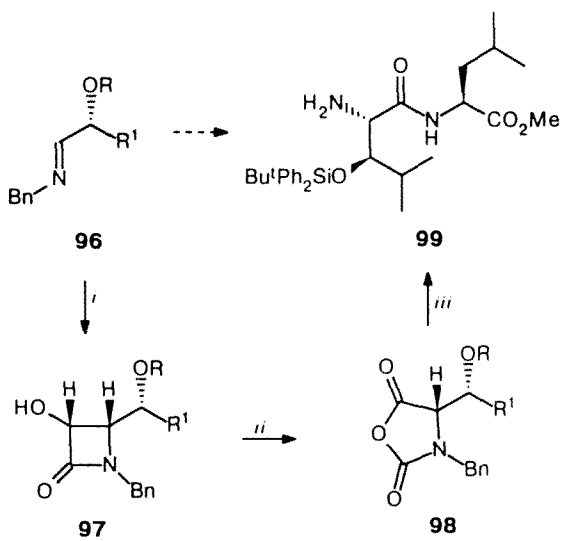
rial action to that of vancomycin. Using the β-lactam approach to both α- and β-amino acids described in the earlier sections, the synthesis of the non-proteinogenic α-amino-β-hydroxyacid derived peptides **90** and **91** occurring in this antibiotic can be achieved with high diastereoselectivity and efficiency.[110]

Synthesis of tripeptide **90** (Scheme 28) started from β-carboxy-β-lactam **92**, which is a form of β-hydroxyaspartic acid possessing a β-carboxyl group and a α-amino moiety simultaneously protected. The dipeptide unit **93** was obtained in 95% overall yield after activation of the carboxy group with cyanuric fluoride and subsequent cou-

pling with *O*-benzyl-*L*-serine benzyl ester according to Carpino's procedure. Next, the β-lactam **93** was *N*-dearylated and converted into lactam **94** in good overall yield. The ring opening of **94** with 25% NH_4OH aq in DMF as solvent proceeded to give the expected product in 90% yield, which on *N*-Boc deprotection and further acylation with Boc-glycyl fluoride (Boc—GlyF) and NMM gave tripeptide **95** in 80% yield[110] (for a conventional synthesis of β-hydroxyaspartyl dipeptides, see Ref. 111).

The strategy for the synthesis of tripetide **91** is shown in Schemes 29 and 30. The key step in this strategy was the anticipated stereocontrolled synthesis of β-lactams **97a** and **97b** incorporating the required structural subunits of the desired non-proteinogenic α-amino-β-hydroxy acids. These were prepared by cycloaddition of benzyloxyketene to imines **96a** and **96b**, respectively, followed by hydrogenolysis of the benzyloxy protective group. Subsequent exposure of both compounds to a solution of commercial bleach and a catalytic amount of TEMPO afforded NCAs **98a** and **98b** in 95 and 96% yields, respectively. The coupling reaction of **98a** with (*S*)-leucine benzyl ester in methylene chloride as solvent proceeded cleanly to give dipeptide **99** in 90% yield after *N*-debenzylation of the resulting intermediate dipeptide product. Finally, as shown in Scheme 30, acylation of **99** with the NCA **98b** carried out in DMF as solvent in the presence of NaN_3 gave the tripeptide **100** in 70% yield.[110]

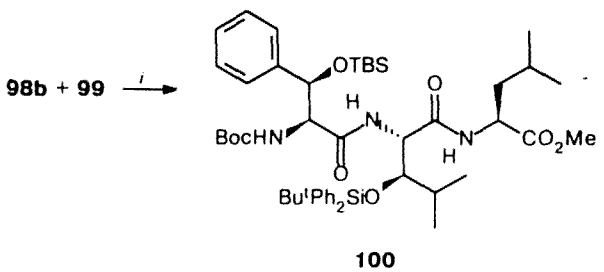
Scheme 29



a: R = Bu^tPh_2Si, R^1 = Pr^i
b: R = Bu^tMe_2Si, R^1 = Ph

Reagents, conditions, and yields: *i.* 1) $BnOCH_2COCl$ (2 equiv.), NEt_3, CH_2Cl_2, −78 °C→−20 °C, 20 h; 2) NH_4HCO_2, Pd/C, Pr^iOH, boiling, 1 h, 70—78%; *ii.* 1 *M* NaOCl, TEMPO (cat.), −20 °C, 95—96%; *iii.* 1) *S*-LeuOMe, CH_2Cl_2, −20 °C, 15 h, 95%; 2) H_2, Pd/C, EtOH, −20 °C, 15 h, 85%.

Scheme 30



100

Reagents, conditions, and yield: *i.* DMF, NaN_3 (1 equiv.), −20 °C, 15 h, 70%.

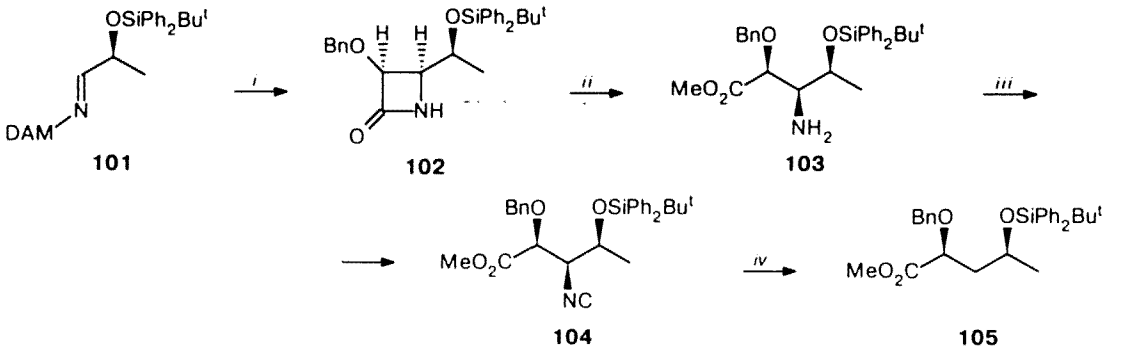
The preceding synthesis of the non-proteinogenic β-hydroxy-α-amino acid peptides of lysobactin is just one example that demonstrates the potential utility of this approach to peptide segments found in other macrocyclic compounds.[8,108]

5. 1,3-Polyols and amino polyols

In conjunction with the above studies we have also developed a β-lactam route to 2-amino-1,3-polyol chains using an iterative cycloaddition of alkoxyketenes to α-silyloxyaldehyde-derived imines as the key reaction.[112] As Scheme 31 illustrates, the synthesis starts with the transformation of the imine **101** to β-lactam **102**. Subsequent ring opening under mild acid conditions provided the α,γ-dialkoxy-β-amino ester **103** in almost quantitative yield, which was next converted into the isocyanide **104**. Reduction of the latter proved to be difficult under Barton's conditions, but using Chatgilialoglu's reagent, tris(trimethylsilyl)silane, the reduction proceeded efficiently to give the 1,3-diol **105** in 80% yield.[112]

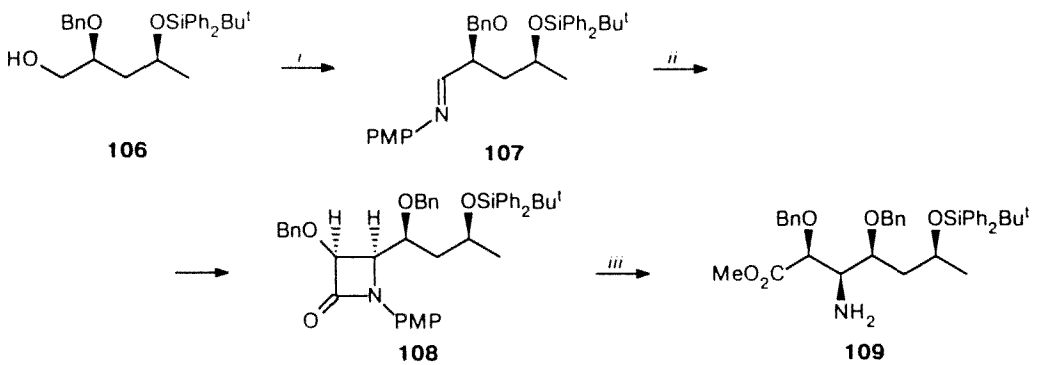
The second cycle of the iterative process is shown in Scheme 32. The hydroxy derivative **106**, obtained by reduction of ester **105** with lithium diisobutylaluminum hydride, was oxidized to the corresponding aldehyde and converted into the imine **107**. Treatment of this imine with benzyloxyketene led to the β-lactam **108** in 75% yield as a single diastereomer. Subsequent *N*-dearylation and further ring opening provided the β-amino-α,γ,ε-polyol chain **109** in 50% overall yield. Deamination of **109** followed by repetition of the above sequence of reactions should generate more extended amino polyols. This synthesis nicely illustrates how a number of 1,3-diol subunits can be incorporated in a carbon chain by relying on the predictable stereochemistry provided by the cycloaddition reaction of alkoxyketenes with α-oxyaldehyde-derived imines.

Scheme 31



Reagents, conditions, and yields: *i.* 1) $BnOCH_2COCl$, NEt_3, 80%; 2) CAN, MeCN, H_2O, 75%; *ii.* MeOH, $ClSiMe_3$, 0 °C→–20 °C, 2 h, 98%; *iii.* 1) Ac_2O—HCO_2H, 85%; 2) $(Cl_3CO)_2CO$, NEt_3, CH_2Cl_2, 0 °C, 15 h, *iv.* $(SiMe_3)_3SiH$, AIBN, toluene, 80 °C, 30 min, 80%.

Scheme 32



Reagents, conditions, and yields: *i.* 1) $(Cl_3CO)_2CO$, DMSO, NEt_3, CH_2Cl_2, 80%; 2) $4\text{-}MeOC_6H_4NH_2$, CH_2Cl_2, $MgSO_4$, 100%; *ii.* $BnOCH_2COCl$, NEt_3, 75%; *iii.* 1) CAN, MeCN, H_2O, 50%; 2) MeOH, $ClSiMe_3$, 0 °C → –20 °C, 2 h, 100%.

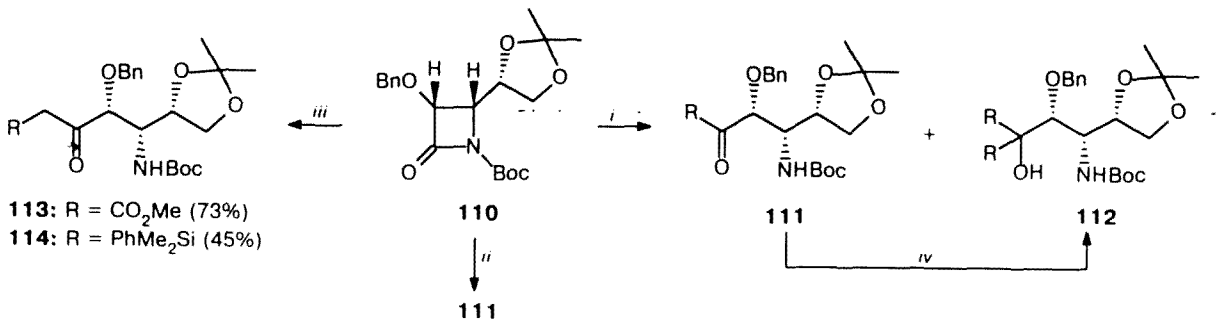
6. β-*Amino ketones and derived hydroxy compounds*

Because of the general interest in aminopolyols and biologically active peptides, another approach to these attractive targets has also been delineated in our laboratory.[113] The approach was based on the successful implementation of the N(1)—C(2) β-lactam cleavage by means of heteronucleophiles discussed in the earlier sections. On the one hand, we expected that ring opening of β-(1-alkoxyalkyl)-substituted β-lactams by carbon nucleophiles would provide β-aminoketones, which after diastereoselective reduction would provide a route to more complex aminopolyols and, on the other hand, the same reaction carried out on *N*-Boc-β-lactams with alkyl substituents at the β-C atom would generate precursors of peptide isosteres and/or renin inhibitors.

Our approach to aminopolyols is illustrated in Scheme 33. The most significant feature is that the reaction of aryl Grignard reagents at low temperature (–40 °C) with the *N*-Boc-β-lactam **110**, obtained from **63**, affords exclusively β-amino ketones **111** in 90—96% yields. Overaddition could not be observed under these conditions even when an excess of the reagent was present in the reaction medium. At the same time, when the reaction was performed at room temperature instead of –40 °C, only tertiary alcohols were obtained. In contrast to these observations, reaction of lactam **110** with primary alkylmagnesium halides as well as with alkyllithiums at –40 °C invariably led to a mixture of the corresponding β-amino ketones **111** and β-amino carbinols **112**, along with the starting β-lactam. Alternatively, the use of Gilman cuprates afforded good results in terms of chemoselectivity, although the yields were only moderate (R = Me, 50%; R = Bu^n, 67%). As shown in Scheme 33, β-amino ketones carrying additional functionality, such as **113** and **114**, could also be prepared by this method in good yields.

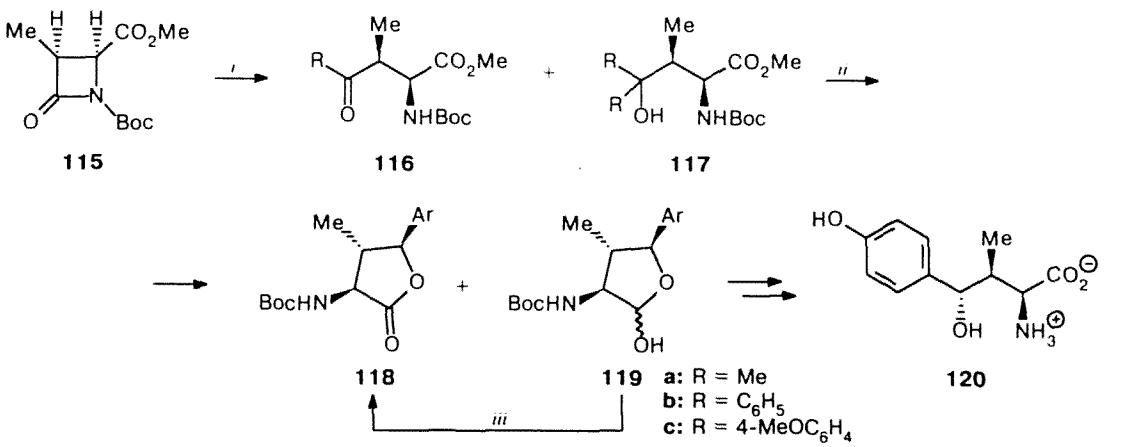
Another example that illustrates the utility of this procedure is shown in the synthesis of the α-amino-γ-hydroxy acid **120** present in the nucleoside antibiotic nikkomycin (**121**) as a structural segment[114] (for a recent review of nucleoside antibiotics, see Ref. 115). The

Scheme 33



Reagents, conditions, and yields: *i.* RMgX or RLi, THF, −40 °C, 1 h; *ii.* ArMgX (1.3 equiv.), THF, −40 °C, 1 h, 90%, or R_2CuLi, Et_2O, 0 °C→−20 °C; *iii.* CH_2=C(OLi)OMe (2 equiv.), THF, −40 °C, or $PhMe_2SiCH_2MgCl$, THF, −20 °C; *iv.* RMgX, −78 °C→−20 °C.

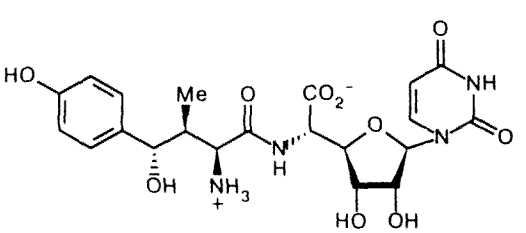
Scheme 34



Reagents, conditions, and yields: *i.* RMgBr, THF, −40 °C, 60—80%; *ii.* $LiBH(Bu^s)_3$, THF, −78 °C, 1 h, 73%; *iii.* NDC, Py, C_6H_6, −20 °C, 4 h.

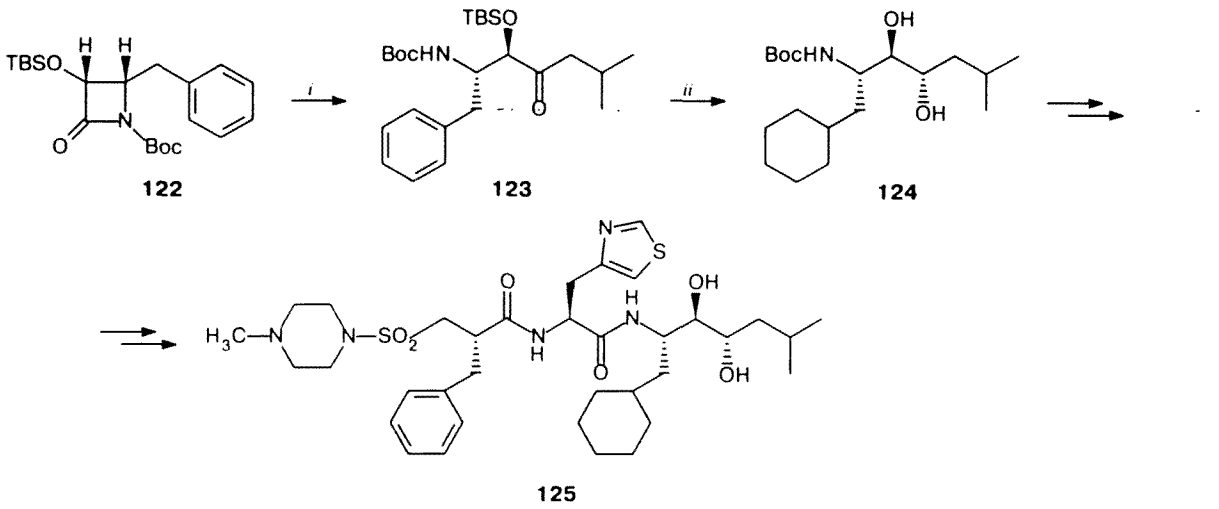
method takes advantage of the fact that Grignard reagents react with *rac*-**115** selectively at the lactam carbonyl group to afford exclusively products **116** and **117**. At the same time, while methylmagnesium bromide gave a mixture of **116a** and **117a** along with the starting compound **115** in a ratio 70:10:20, respectively, aryl Grignard reagents only gave β-amino ketones **116b** and **116c** in 80 and 72% yields, respectively. *L*-Selectride reduction of **116b** gave the amino lactone **118** and the hemiacetal **119** in a ratio of 62 : 3, respectively. This hemiacetal was oxidized to the amino lactone by using the mixed nicotinic-chromic anhydride (NDC) reagent developed in our laboratory.[116] By that means, the overall yield of **118** was 73%. This result illustrates the viability of the approach for the synthesis of β-alkyl-α-amino-γ-hydroxy acids in optically pure forms starting from homochiral *cis*-β-alkyl-γ-alkoxycarbonyl β-lactams.

This approach to β-amino ketones has also been extended to the synthesis of alkyl-substituted 1,2,3-amino diols.[1,117] As shown in Scheme 35, when lactam **122** is treated with isobutylmagnesium chloride, β-amino ketone **123** forms along with the corresponding overaddition product (10%). The reduction of **123** under chelation-controlled conditions led to the corresponding carbinol together with its epimer in a ratio 90 : 10, respectively. Hydrogenolysis of the major isomer and further saturation of the phenyl ring afforded the 1,2,3-aminodiol **124**, a constituent of the potent inhibitor of human renin A-725-17 (**125**), which is undergoing clinical evaluation as a therapeutic agent for the treatment of hypertension and congestive heart failure.[119,120]

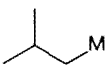


121

Scheme 35

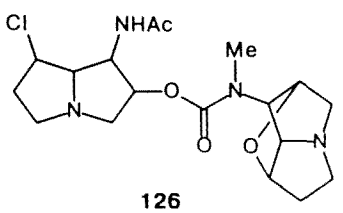


122 **123** **124** **125**

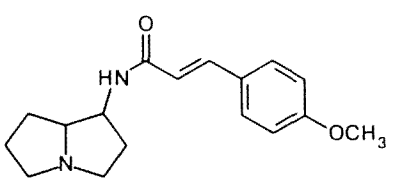
Reagents, conditions, and yields: *i.*  MgCl , THF, −40 °C, 70%; *ii.* 1) n-Bu_4NF; 2) $NaBH_4$; 3) H_2 (3.5 atm), Rh—Al.

7. Pyrrolizidine alkaloids

In the course of our studies on the cycloaddition of ketenes with *N*-Boc-α-aminoaldehyde-derived imines we observed that the resulting cycloadducts easily underwent intramolecular rearrangement by attack of the exocyclic amino group on the β-lactam carbonyl to form γ-lactams.[121] This approach to five-membered rings has been exploited to obtain necine bases bearing the 1,2-aminoalcohol functionality,[122] which occurs, for instance, in some pyrrolizidine alkaloids such as lolidine (**126**), absouline (**127**), and related systems.[123]



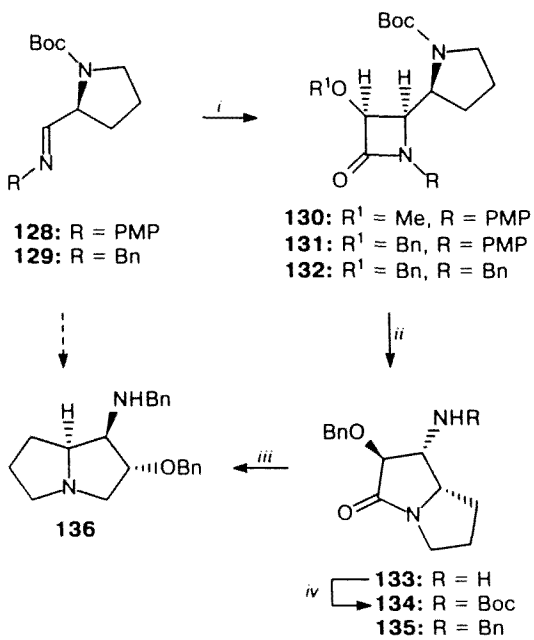
126



127

For example (Scheme 36), treatment of methoxyketene, generated from methoxyacetyl chloride and triethylamine, with the prolinal imine **128** afforded the β-methoxy-β-lactam **130** in 85% yield and as a single diastereomer. Likewise, reaction of benzyloxyketene with both imines **128** and **129** proceeded with virtually complete diastereoselectivity to give lactams **131** and **132** in 75% and 70% yields, respectively. The absolute configuration given for the adducts is based on a single crystal X-ray analysis of lactam **130** and the assumption of a

Scheme 36



128: R = PMP
129: R = Bn

130: R^1 = Me, R = PMP
131: R^1 = Bn, R = PMP
132: R^1 = Bn, R = Bn

136

133: R = H
134: R = Boc
135: R = Bn

Reagents, conditions, and yields: *i.* R^1OCH_2COCl, NEt_3, CH_2Cl_2, −78 °C→−20 °C, 70—85 %; *ii.* 1) $(NH_4)_2Ce(NO_3)_6$, MeCN, H_2O; 2) $ClSiMe_3$, MeOH, boiling or F_3CCO_2H, CH_2Cl_2, then 12 *N* HCl, EtOH, boiling, 70%; *iii.* BH_3, SMe_2, THF, boiling, 2 h, NaOAc, MeOH, 5 min, then I_2, $CHCl_3$; *iiii.* $(Boc)_2O$, NEt_3, CH_2Cl_2, boiling.

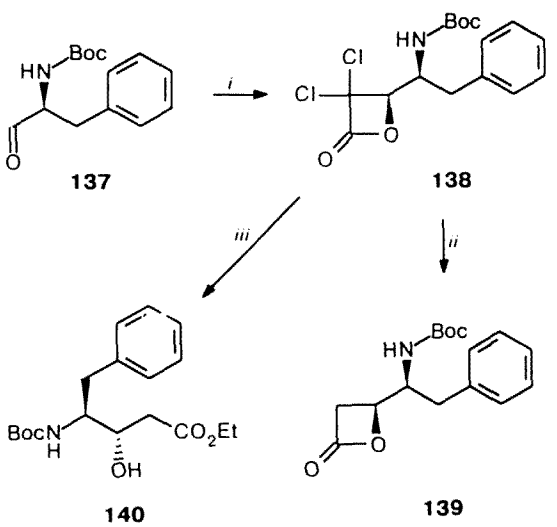
uniform reaction mechanism. The β-lactam **131**, when subjected to *N*-dearylation and further treatment with chlorotrimethylsilane in methanol, gave the γ-lactam **133**, which was isolated as the *N*-Boc derivative **134**. The acylation of **133** with (+)-MTPA acid chloride and triethylamine to form a single diastereomer proved its optical purity. Treatment of compound **134** with trifluoroacetic acid followed by 12*N* HCl in refluxing ethanol gave the bicyclic compound **135**, which then was converted into the pyrrolizidine framework **136**.

8. β,γ-Dihydroxy and γ-amino-β-hydroxy acids

On the basis of the results achieved on opening of the nucleophilic β-lactam ring, particularly by means of α-amino acid esters, the analogous reaction on β-lactones derived from both α-oxyaldehydes and α-amino aldehydes was also explored in our laboratory. In fact, two modes of β-lactone ring opening have been described arising from either acyl—oxygen or alkyl—oxygen bond fission but results achieved to date concerning the first mode of cleavage have not been uniformly good.[124–127] We reasoned that β-lactones bearing electron-withdrawing groups at the α-position would be able to undergo nucleophilic attack by α-amino acid esters to form peptides that include segments of β-hydroxycarboxylic acids. In particular, starting from β-lactones derived from α-amino aldehydes it would be possible to obtain biologically active peptide mimics.[128]

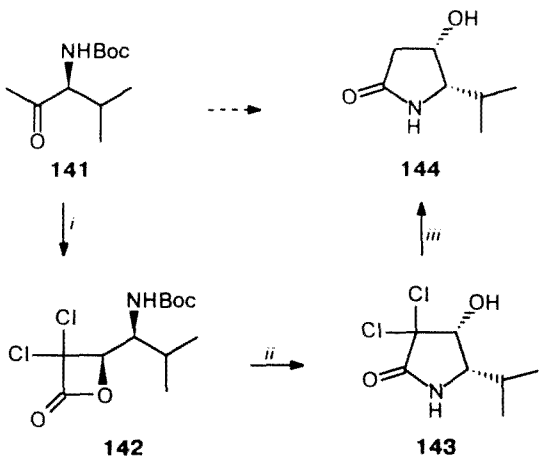
As Scheme 37 illustrates, the reaction of dichloroketene, generated from dichloroacetyl chloride and triethylamine, with the *N*-Boc-α-amino aldehyde **137** afforded the β-lactone **138** in 30% yield. Exposure of this β-lactone product to hydrogenolysis in EtOH for 20 h gave the known ester **140**,[129] which is the key component of some HIV protease inhibitors, *vide infra*. At the same time, when the dehalogenation of lactone **138** was conducted under non-solvolytic conditions, the β-lactone ring was preserved and product **139** was obtained in almost quantitative yield. In a similar way (Scheme 38) reaction of dichloroketene, generated from trichloroacetyl chloride and Zn/Cu, with aminoketene **141** followed by intramolecular cyclization afforded the γ-lactam **143** in 35% yield over the two steps. On dehalogenation, this compound gave the known hydroxy derivative **144**,[131] thus proving both the stereochemical course of the cycloaddition and its synthetic utility.

Scheme 37



Reagents, conditions, and yields: *i*. $Cl_2CHCOCl$, NEt_3, −78 °C→−20 °C, 30—35%; *ii*. H_2, Pd/C, NEt_3, EtOAc, 98%; *iii*. H_2, Pd/C, NEt_3, EtOH, 98%.

Scheme 38

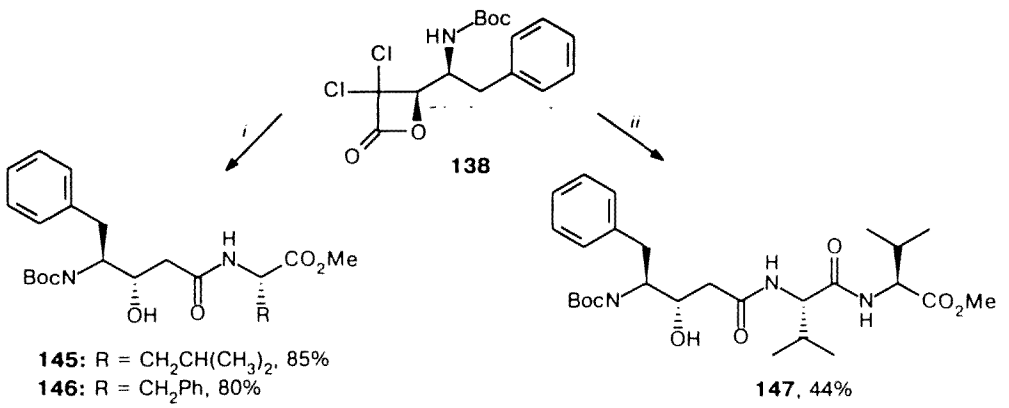


Reagents, conditions, and yields: *i*. Cl_3CCOCl, Zn/Cu, 35%; *ii*. $ClSiMe_3$, MeOH, 6 h, ≥ 90%; *iii*. H_2, Pd/C, EtOAc, NEt_3, 90%.

We also have found (Scheme 39) that lactone **138** efficiently coupled with amino acid esters to form, after dehalogenation, the corresponding acyl derivatives such as **145** and **146** in good yields. Though a somewhat lower yield was observed in the coupling reaction of **138** with the dipeptide (*S*)-Val-ValOMe to give **147**, these results show the potential of the approach to synthesize HIV protease inhibitors.[131] In contrast, and in agreement with our initial hypothesis, the β-lactone **139** was inert to ring opening by α-amino acid esters under the same conditions, in which the ring of **138** clearly did open.

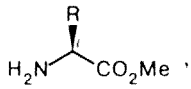
In addition to these results we also have found (Scheme 40) that slow addition of trichloroacetyl chloride to a mixture of α-silyloxy aldehydes **148** and Zn/Cu in diethyl ether furnished the corresponding β-lactones in 60—85% yields and in each case as single diastereomers. The coupling reaction of both **149a** and **149b** with (*S*)-ValOMe also proceeded efficiently to give, after hydrogenolysis and desilylation, the corresponding

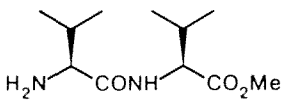
Scheme 39



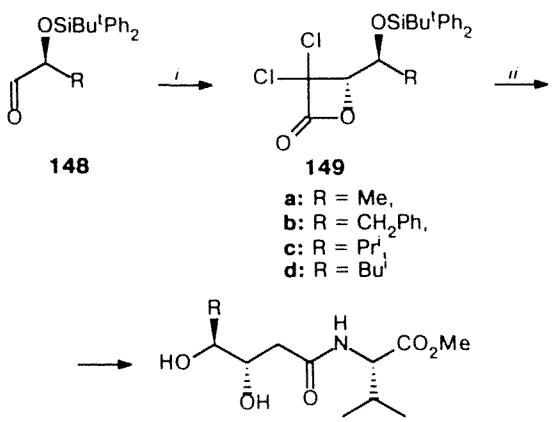
145: R = $CH_2CH(CH_3)_2$, 85%
146: R = CH_2Ph, 80%

147, 44%

Reagents, conditions, and yields: *i.* 1)  , CH_2Cl_2, ~20 °C, 24 h; 2) H_2, Pd/C, NEt_3, EtOAc, ~20 °C, 24 h;

ii. 1)  , ~20 °C, 24 h; 2) H_2, Pd/C, NEt_3, EtOAC, ~20 °C.

Scheme 40



150: R = CH_3, 75%
151: R = CH_2Ph, 60%

Reagents, conditions, and yields: *i.* Cl_3CCOCl, Zn/Cu, Et_2O, 4 h, ~20 °C, 60—85%; *ii.* 1) (*S*)-ValOMe, CH_2Cl_2, 24 h; 2) H_2(1 atm), Pd/C, NEt_3, EtOAc, 15 h, ~20 °C; 3) *n*-Bu_4NF, THF.

acyl derivatives **150** and **151**. Although this work is still in its preliminary stages the approach developed seems promising for the incorporation of β-hydroxycarboxylic acids into short peptide fragments.[132*]

* C. Palomo, J. I. Miranda, and A. Linden, Unpublished results.

9. Conclusion

It is evident from the results presented in the above sections that appropriately substituted β-lactam frameworks constitute effective tools for the incorporation of a wide variety of both β- and α-amino acids into short peptide segments. Owing to the reliable enzymemimetic coupling reaction of β-lactams with α-amino acid esters under racemization-free conditions, the synthesis of many peptide segments and derived products may be now considered as a routine task, whenever the adequate β-lactams can be prepared. Therefore, the forthcoming development of novel procedures to procure homochiral azetidin-2-ones bearing any substitution pattern by single-step and convergent approaches, would be highly desirable. In addition to these aspects, the discovery that α-hydroxy-β-lactams can be directly transformed into simultaneously amino-protected and carboxyl-activated forms of α-amino acids from non-α-amino acid precursors renders the β-lactam-NCA method a very promising tool for the synthesis of complex peptide targets.

We thank the following organizations for financial support for our research in β-lactam chemistry: Ministry of Education and Science of Spain (Ministerio de Educacion y Ciencia); Basque Government (Eusko Jaurlaritza), and Basque Country University (Euskal Herriko Unibertsitatea—Universidad del Pais Vasco). All collaborators cited within the references are also acknowledged.

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Received June 3, 1996