Chemistry of Heterocyclic Compounds, Vol. 34, No. 11, 1998

ASYMMETRIC SYNTHESIS OF 3-AMINO-β-LACTAMS *via* STAUDINGER KETENE-IMINE CYCLOADDITION REACTION (REVIEW)

Claudio Palomo and Jesus Maria Aizpurua

Recent advances in asymmetric synthesis of 3-amino-β-lactams *via* Staudinger ketene-imine cycloaddition reaction are summarized.

1. INTRODUCTION

The β-lactam skeleton is currently the key structural element of the most widely employed class of antimicrobial agents, the β-lactam antibiotics (for reviews see [1]). Some of the well known representatives are penicillins **1**, cephalosporins **2**, cephamycins **3**, 1-oxacephalosporins **4**, and monolactams like aztreonam **5** and carumonam **6**, among many others [1, 2]. In fact, since the discovery and structural elucidation of penicillin G and the closely related cephalosporin C, much work has been made on this important field of research for two main reasons: first, because of the permanent need for new drugs displaying broader antibacterial activity and/or different biological properties, and, second, because of the necessity of new β-lactam antibiotics to combat bacteria which have built up a resistance against the most traditional compounds [3].

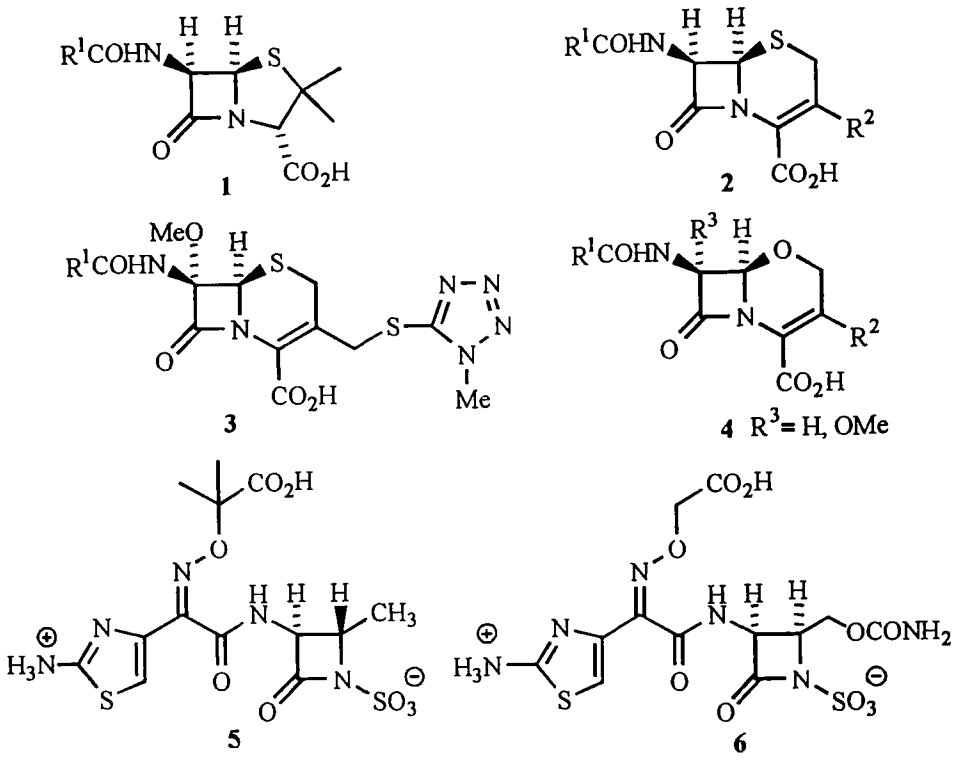
As a consequence of this interest, a large number of methods for the production of β-lactams have been developed and the topic has been amply documented and reviewed several times (for comprehensive reviews see [4]). Among the existing methods, however, the hydroxamate methodology [5], the metalloester enolate-imine condensation [6], the chromium carbene-imine reaction [7a] (for a review on organometallic reagents in β-lactam synthesis, see [7b]), and the [2+2] cycloaddition of ketenes with imines, also known as the Staudinger reaction [8], have been the most often employed for the construction of the azetidin-2-one ring. In particular, the latter has provided useful and economical pathways to 3-amino β-lactams (see review [9]) mainly due to the ready availability of ketenes generated by dehydrohalogenation of their corresponding acid chlorides and a tertiary organic base (for recent reviews on asymmetric synthesis of β-lactams, see [10]). Consequently, it is not surprising that over these last years, this reaction has acquired central importance, from both academic and industrial standpoints, for the asymmetric synthesis of β-lactams (see reviews [11a-c]). In this context, the diastereoselective synthesis of nonracemic β-lactams can be generally accomplished by using a combination of either achiral ketenes and chiral imines or chiral ketenes and achiral imines.

The present account summarizes some of the recent advances in this field along with our own contribution to the Staudinger reaction.

2. ASYMMETRIC INDUCTION FROM THE IMINE COMPONENT

The asymmetric induction in the reaction of achiral ketenes with imines has been achieved from both positions of the imine partner. In this regard, imines derived from chiral aldehydes and achiral amines or imines derived from

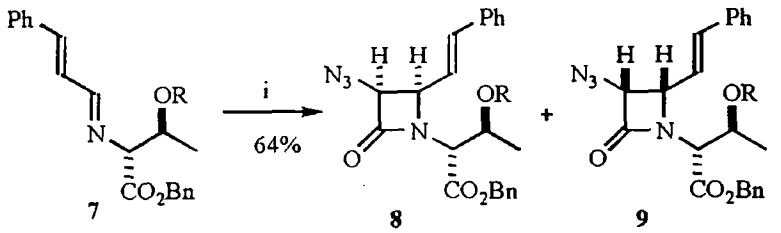
Departamento de Quimica Organica, Universidad del Pais Vasco. Facultad de Quimica, Apdo. 1072, 20080 San Sebastian, Spain. Published in Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1448-1462, November, 1998. Original article submitted July 24, 1998.



Representative families of β-lactam antibiotics characterized by the presence of the amino function at the Cα position of the β-lactam carbonyl

achiral aldehydes and chiral amines have been employed. In the latter case, however, β-lactams are often produced, if at all, with low levels of diastereoselectivity. The most promising examples have been reported independently by Bose [12] and Gunda [13]. For instance (Scheme 1) it has been found that the imine **7**, derived from the amino acid threonine, upon treatment with azidoacetyl chloride and triethylamine affords β-lactams **8** and **9** with stereoselectivity ratio of 95:5 [12]. Replacing the TBS group by TPS leads to a slight increase in diastereoselectivity. On the other hand, there is little influence on diastereoselectivity by using the corresponding methyl, ethyl, and *p*-nitrobenzyl esters of TPS-protected threonine. Dane salt of glycine also affords the same level of reaction diastereoselectivity to give the corresponding *cis*-3-amino-β-lactam.

Scheme 1

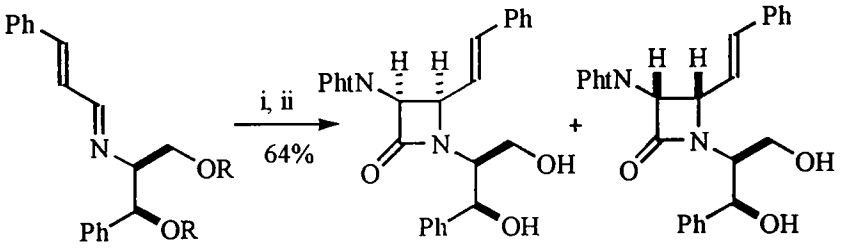


R = TPS (triphenylsilyl) 95:5
R = TBS (*tert*-butyldimethylsilyl) 90:10

i, N_3CH_2COCl, Et_3N, CH_2Cl_2, -40 °C

As reported by Gunda [13] (Scheme 2), the imine **10a** gave β-lactams **11** and **12** with very low diastereoselectivity (2:1) but using the imine 10b with a more bulky O-protective group, the β-lactams **11** and **12** were produced with acceptable diastereoselectivity (8:1).

Scheme 2



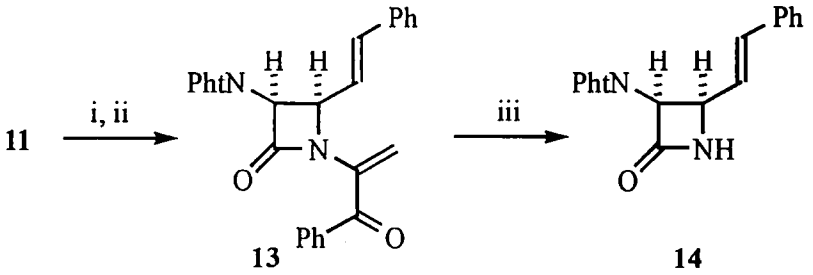
10 **a** R = $SiMe_3$ **11** **12**

b R = $SiMe_2{}^tBu$

i, $PhtNCH_2COCl$, Et_3N, CH_2Cl_2, -40 °C; ii, 5% HF (aq.), CH_3CN

Removal of the substituent at N(1) in **11** was accomplished in three steps through **13** to give deprotected lactam **14** in 52% yield from **13** (Scheme 3).

Scheme 3

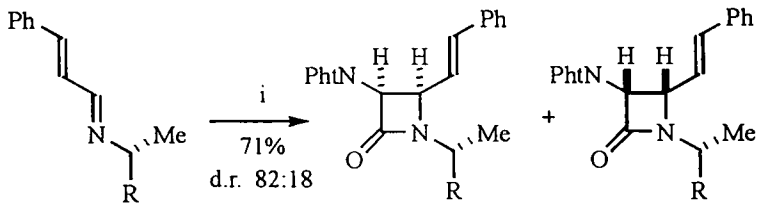


13 **14**

i, AcCl, collidine; ii, CrO_3; iii, $KMnO_4$

Imines **15**, derived from both (*R*)-1-(phenyl)ethylamine and (*R*)-1-(1-naphthyl)ethylamine, have also been employed in the Staudinger reaction [14]. The latter often produces the best results in terms of stereoselectivity. For instance, the reaction of **15** with phthalimidoacetyl chloride and triethylamine provided β-lactams **16** and **17** in a ratio of 82:18 (Scheme 4).

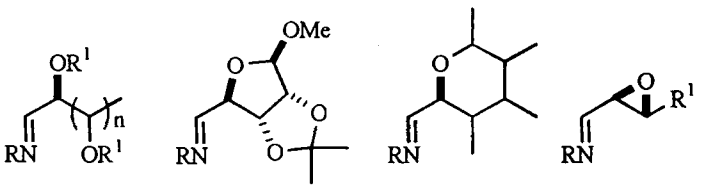
Scheme 4



15 R = 1-Naphthyl **16** **17**

i, $PhtNCH_2COCl$, Et_3N, toluene, -78 °C — r. t.

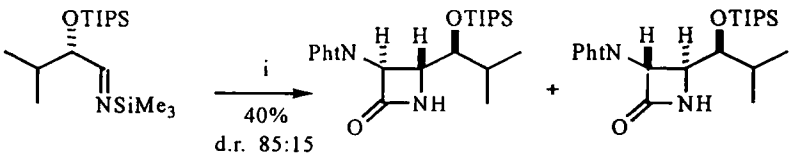
The most common approach to achieve good diastereoselectivity involves the use of α-oxyaldehyde-derived imines **18**, sugaraldehyde-derived imines **19**, **20**, and α,β-epoxyimines **21** [15]. In these cases, the β-lactams often presents a relative cis configuration (*vide infra*).



18 **19** **20** **21**

Recently, Panuncio and co-workers [16] have reported a case of *trans*-diastereoselectivity. The method (Scheme 5), involves the reaction of phthalimidoacetyl chloride with N-trimethylsilyl imines such as **22** and triethylamine under refluxing of toluene.

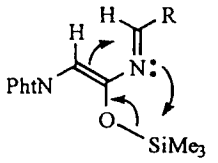
Scheme 5



22 **23** **24**

i, $PhtNCH_2COCl$, Et_3N, toluene, reflux

Apparently, β-lactams **23** and **24** are formed through the intermediate **25**.

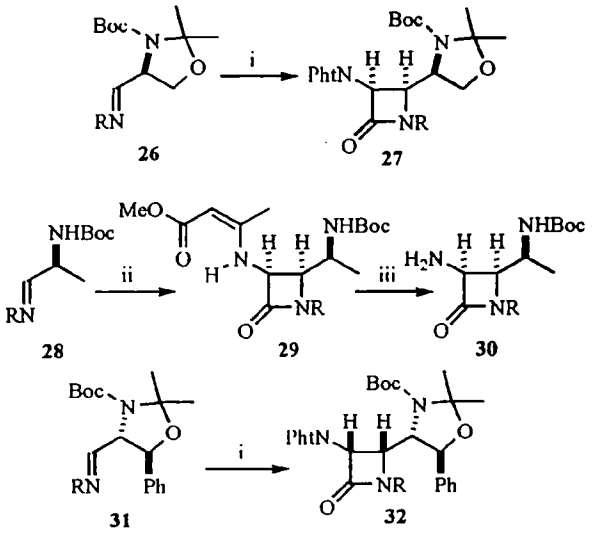


25

Alternatively, the use of N-Boc-α-amino imines **26** (Scheme 6), readily obtainable from α-amino aldehydes and, hence, from α-amino acid esters, also leads to enantiomerically pure β-lactams [17]. For example, the reaction of **26** with phthalimido ketene, generated in its turn, from phthalimidoacetyl chloride and triethylamine, affords the respective β-lactams **27a,b** as single diastereomers in yields of 41% and 85%, respectively. Likewise, the reaction of the Dane salt of glycine with imines **28a,b** in the presence of phenyl phosphorodichloridate and triethylamine gives the corresponding vinylamino β-lactams **29a,b** in yields of 48% and 46% respectively. The latter compounds, on treatment with 2 equivalents of *p*-toluenesulfonic acid at room temperature for 5 min, furnishes the 3-amino-β-lactams **30a,b** in yields of 85% and 98%, respectively. In a similar manner, it has recently been found that imines **31a,b** upon treatment with phthalimidoketene provide **32a,b** in yields of 73% and 91%, respectively [18]. In general, a wide variety of N-Boc-α-amino imines can be employed in such a cycloaddition reaction to provide β-lactams either as potential monobactam precursors or as synthetic intermediates for the construction of other heterocycles of interest [19].

The origin of the extremely high asymmetric induction observed in these reactions can be rationalized (Fig. 1) on the basis of the stereoelectronic effect exerted by the σ* (C—X) orbital (X being an electronegative atom and

Scheme 6



a R = 4-MeOC$_6$H$_4$ b R = PhCH$_2$

i, PhtNCH$_2$COCl, Et$_3$N, CH$_2$Cl$_2$, -78 °C → r. t., 20 h; ii, MeO$_2$CCH=C(Me)NHCH$_2$CO$_2$K, PhOPOCl$_2$, Et$_3$N, CH$_2$Cl$_2$, -40 °C → r. t.; iii, *p*-TsOH, Me$_2$CO, r. t., 5 min

C a stereogenic carbon atom) over the HOMO of the transition states leading to the formation of the C(3)—C(4) bond [17].

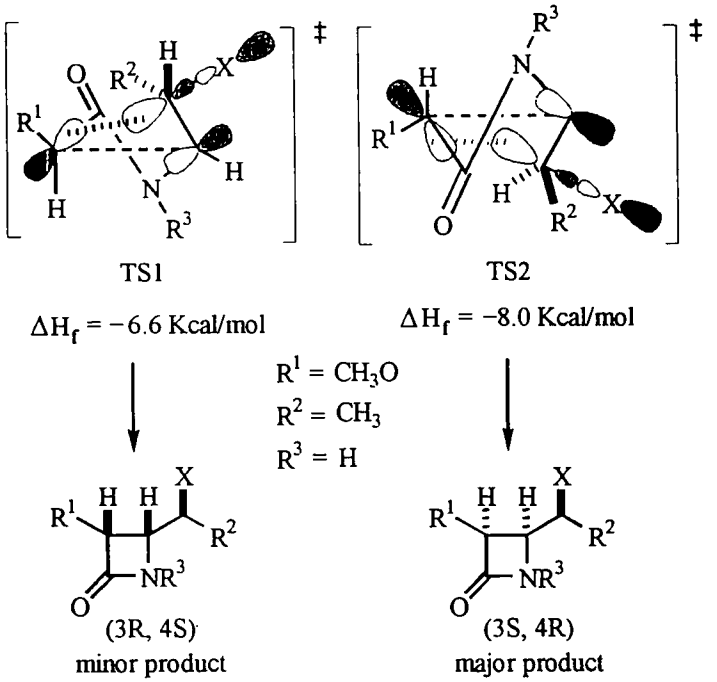
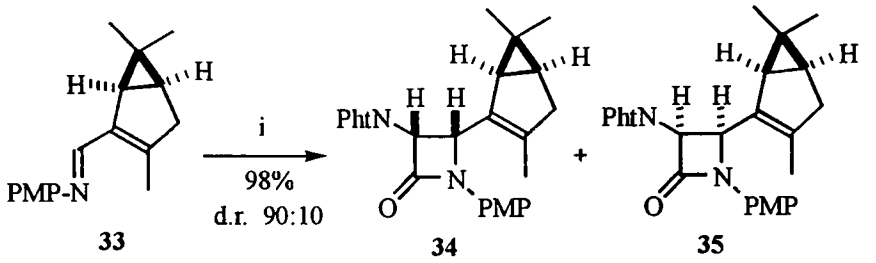


Fig. 1. Calculated transition states corresponding to the formation of *cis*-(3*R*,4*S*)- and *cis*-(3*S*,4*R*)-4-[(*S*)-1-aminoethyl-3-methoxyazetidin-2-ones. TS1 exhibits an angular arrangement between C_3 and the exocyclic C-X bond, whereas TS2 corresponding to the major product has a linear disposition for the same atoms. The reason for the angular arrangement in Ts1 is the steric interaction between the methyl group (R^2) and the forming β-lactam ring. In Ts2 this steric interaction does not occur and as a consequence the HOMO-σ* stabilization takes place more efficiently.

α-Alkylaldehyde-derived imines, on the other hand, have not been successful for the Staudinger reaction in terms of both chemical reactivity and diastereoselectivity. Nonetheless, Bhawal [20] has shown that the imine **33** (Scheme 7) upon treatment with phthalimido ketene leads to a mixture of β-lactams **34** and **35** in good yield and diastereoselectivity. Azidoacetyl chloride also gives the corresponding β-lactam, albeit in somewhat less stereoselectivity (d. r. 86:14).

Scheme 7



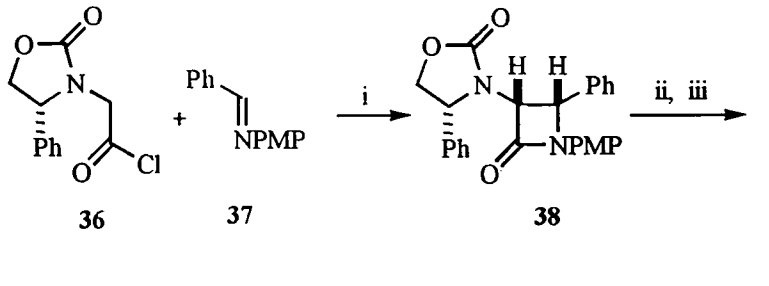
33 **34** **35**

i, $PhtNCH_2COCl$, Et_3N, CH_2Cl_2, -78 °C → r. t., 20 h

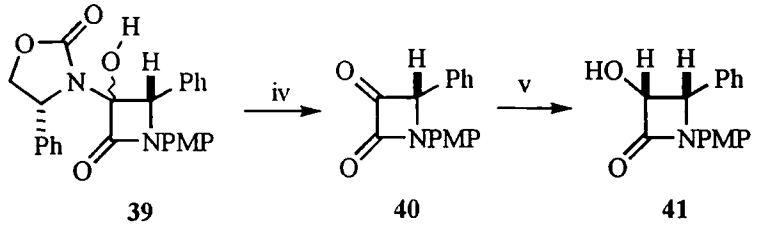
3. ASYMMETRIC INDUCTION FROM THE KETENE COMPONENT

Another important strategy for the synthesis of nonracemic 3-amino-β-lactams involves the reaction of the Evans-Sjogren ketenes [21, 22], generated from their corresponding oxazolidinylacetyl chlorides and triethylamine, with aldimines. One example (Scheme 8) is the reaction of the acid chloride **36** and triethylamine, with benzaldimine **37**, to provide **38** in 83% yield. Most notably this compound, upon deprotonation and subsequent α-hydroxylation, leads to the intermediate α-amidocarbinol **39** that undergoes loss of the oxazolidinone moiety to give the α-keto-β-lactam **40**. The reduction of **40** by means of $NaBH_4$ proceeds with complete stereoselectivity to give **41**, the cyclized form of the Taxol side chain [23]. Contemporary to this work, Holton [24] has reported a conceptually similar route to **41**.

Scheme 8



36 **37** **38**

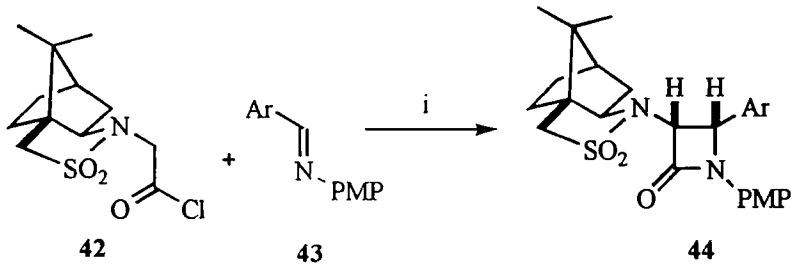


39 **40** **41**

i, Et_3N, CH_2Cl_2, -78 °C → r. t., 4 h, 83%; ii, LiHMDS, THF, -78 °C → r. t., 1,5 h; iii, MoOPH (3 equiv.), -78 °C, 6 h; iv, SiO_2 or Δ, 40%; v $NaBH_4$, MeOH

The acid chloride **42** on treatment with aldimines **43** has also been found (Scheme 9) to produce β-lactams **44** as single diastereomeric products. Nonetheless, removal of the camphorsultam moiety by acid or base hydrolysis, as well as by reductive techniques, has been unsuccessful [25]. In this instance, the method outlined in Scheme 8 might be beneficial for removing the chiral auxiliary.

Scheme 9

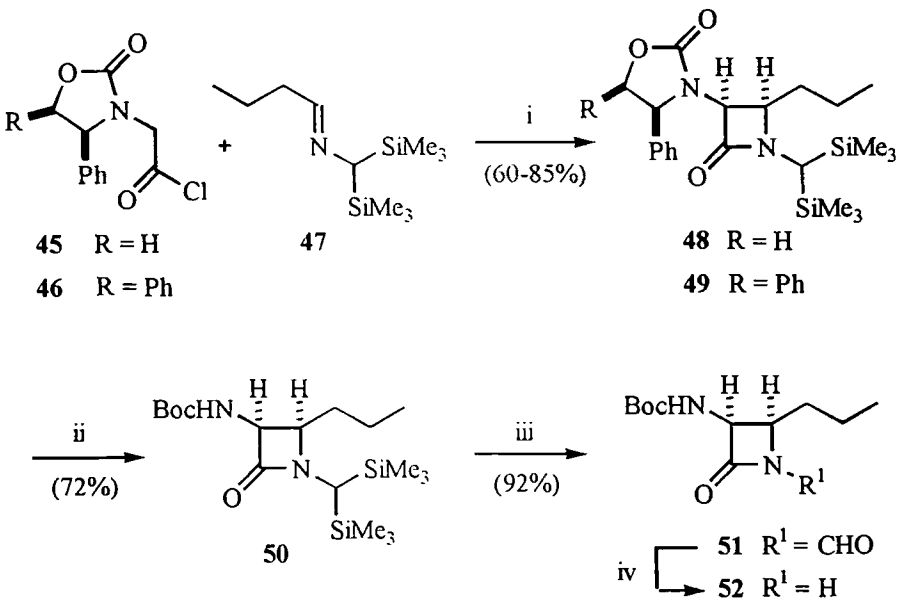


42 **43** **44**

i, Et_3N, CH_2Cl_2, -23 °C — r. t., 15 h

The majority of the investigations on this topic have dealt, however, with the use of nonenolizable aldehyde derived imines. Enolizable imines cannot be employed in such a reaction because of their facile isomerization to enamines. Recently, it has been found that N-bis(trimethylsilyl)methyl imines circumvent this problem [26]. For example (Scheme 10) the reaction of **45** with **47** and triethylamine in refluxing chloroform gives **48** in 75% yield along with its trans-diastereomer, epimeric at C(4) position, in a ratio of 90:10. The major isomer **48** can be transformed into the N-Boc derivative **50** through removal of the oxazolidinone moiety according to the Evans procedure and subsequent introduction of the Boc group. However, better yields can be achieved from the β-lactam **49**, obtained by reaction of the new aminoketene precursor **46** with **47**. In this instance, simple exposure of **49** to hydrogen over Perlman's catalyst in the presence of di-*tert*-butyldicarbonate affords the same β-lactam **50** in 96% yield. As Scheme 10 shows, the bis(trimethylsilyl)methyl group can be removed from the cycloadduct **50** by treatment with cerium(IV) ammonium nitrate (CAN) and subsequent N-deformylation of the resulting intermediate **51**. In this way, the product **52** was formed in 88% yield [27].

Scheme 10

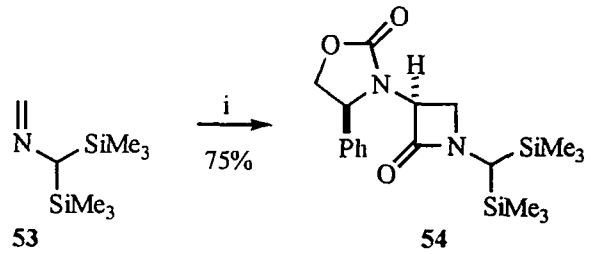


45 R = H
46 R = Ph
47
48 R = H
49 R = Ph
50
51 R^1 = CHO
52 R^1 = H

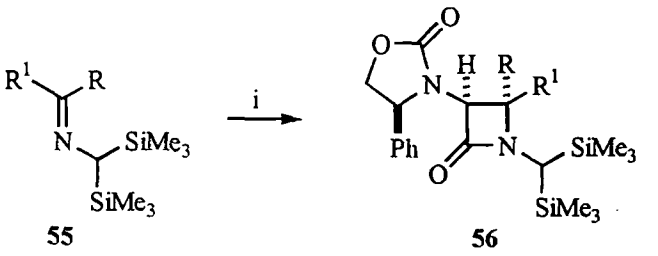
i, Et_3N, $CHCl_3$, reflux, 20 h; ii, Li (6 equiv.), NH_3, THF then $(Boc)_2O$, CH_2Cl_2, r. t. or H_2, $Pd(OH)_2$, EtOH, $(Boc)_2O$, 60—80 psi, r. t.; iii, $(NH_4)_2Ce(NO_3)_6$, MeCN, H_2O), 0 °C, 6 h; iv, $NaHCO_3$, $NaHSO_3$, Na_2CO_3, H_2O, Me_2CO, r. t., 5 h

In general, a wide variety of N-alkylidene C,C-bis(trimethylsilyl)methyl amines can be employed in such a reaction. The resulting β-lactams are usually obtained with diastereomeric *cis:trans* ratios ranging from 70:30 to 98:2, with the only exception of glyoxylate imines that do not give any diastereoselectivity independently of the substituent at the imine nitrogen atom. The remarkable thermal stability of these imines also becomes apparent in the reaction of ketenes with the imine **53** (Scheme 11), the first isolable and stable methanimine, that allows direct formation of 4-unsubstituted β-lactams. For example, the reaction of **45** with **53** leads to **54** in 75% isolated yield and with perfect symmetric induction at C(3) position [28].

Scheme 11



53 **54**



55 **56**

a R = Me, R^1 = Me 70%, d.e. > 98%

b R = Me, R^1 = Me 69%, d.e. > 98%

c R = Me, R^1 = Me 70%, d.e. > 98%

d R = Me, R^1 = Et 80%, d.e. > 70%

e R = Me, R^1 = $PhCH_2CH_2$ 60%, d.e. > 49%

i, 45, Et_3N, $CHCl_3$, reflux., 16 h

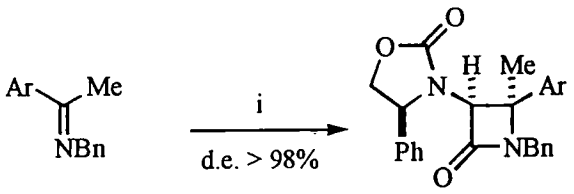
This strategy can also be employed for the construction of β-lactams with quaternary stereogenic centers at C(4) position by simply using ketimines [29]. However, as Scheme 11 illustrates, while symmetrical ketimines **55a-c** give β-lactams **56** with virtually complete diastereoselectivity, unsymmetrical ketimines **55d,e** derived from aliphatic ketones lead to low levels of reaction diastereoselection. In contrast, aralkyl ketone-derived imines also give single diastereomers (Scheme 12). For instance, the reaction of **45** with ketimines **57a** and **57b** gives **58a,b** in good yields and complete diastereoselectivity. Under the same conditions, however, **57c** provides **58c** in 80% d. e. On the other hand, it should also be mentioned that α-alkoxyketone-derived imines upon treatment with achiral ketenes also afford β-lactams with almost complete diastereoselectivity [29].

Another approach to 3-amino β-lactams involves the use of diimines **59** [30]. As Scheme 13 illustrates, both bis-β-lactams **60** and **61** can be made accessible by the Staudinger reaction [31]. The latter can be converted easily into the 4-formylazetidin-2-one **62**.

4. DOUBLE STEREODIFFERENTIATING CYCLOADDITIONS

Recently it has been found that the concept of double asymmetric induction can also be applied to [2+2] cycloadditions of ketenes with imines [32] (Scheme 14). However, the reaction still needs to be improved. For ex-

Scheme 12



57 58

a Ar = Ph 70%

b Ar = 4-MeOC$_6$H$_4$ 65%

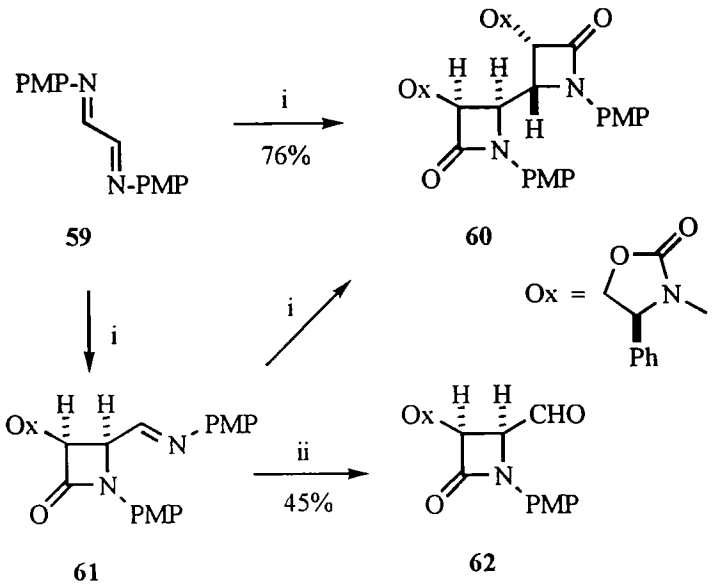
c Ar = PhCH=CH 67%

i, **45**, Et$_3$N, CHCl$_3$, -78 °C — r. t., 20 h

ample, in the reaction of the imine **63** with the Evans-Sjogren ketene **45** in which both reactants are mismatched, the result is the formation of a mixture of β-lactams **64** and **65** in 40:60 ratio respectively. Hitherto, the most interesting stereochemical outcome has been found in the reaction of the imine **66** with **45** to afford β-lactams **67** and **68** in a ratio of 85:15. Thus, the matched relationship between the amine component of the imine **66** and the ketene partner affords an Evans-selective reaction, albeit in moderate diastereoselectivity [33]. An interesting variant of this reaction has been reported by Panunzio [34] (Scheme 15) in which the imine **69** upon treatment with **45** gave **70** and **71** in a ratio of 90:10. In this instance, the reaction is believed to occur through **72**. In any case, it should be noted that the configuration at C(4) of the β-lactam ring in **70** is the opposite to that predicted by the imine partner as it was indicated in Fig. 1 (also see Scheme 5).

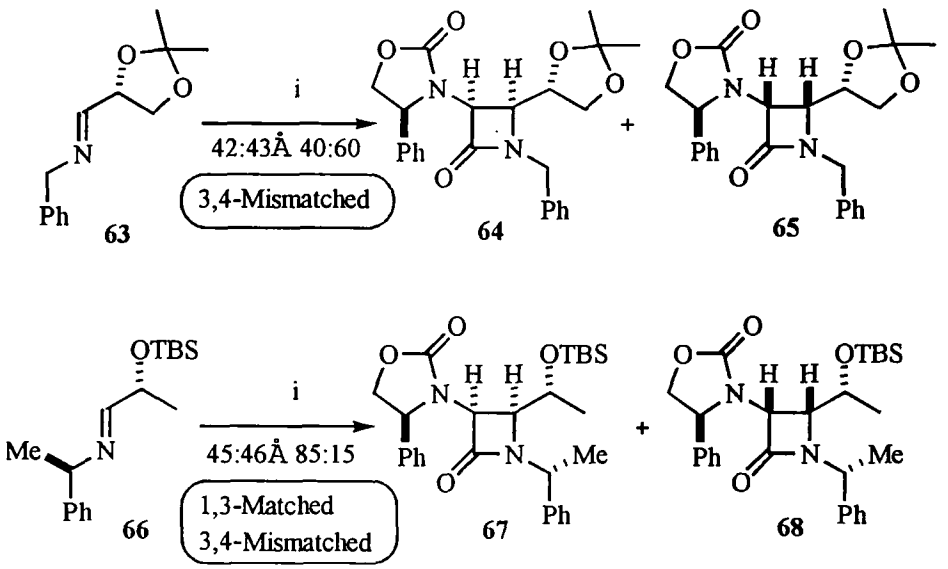
As Scheme 16 illustrates, the stereoselective reduction of 4-acyl β-lactams **75**, readily obtainable from the acid chloride of **74** and Grignard reagents, constitutes a good alternative pathway to get β-lactams **76** essentially as single isomers. Thus, starting from β-lactams with configuration predicted by the imine partner such as **73** and/or its enantiomer, it is possible to obtain the remaining *cis*-diastereomers that are not directly accessible *via* simple and double stereodifferentiating cycloadditions [33].

Scheme 13



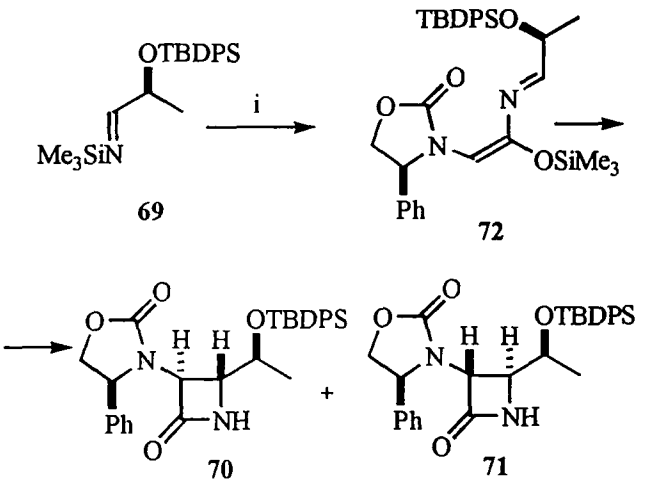
i, **45**, Et$_3$N, CH$_2$Cl$_2$, -78 °C — r. t., ii, HCl 5%

Scheme 14



i, 45, Et_3N, CH_2Cl_2, -78 °C — r. t., 20 h

Scheme 15

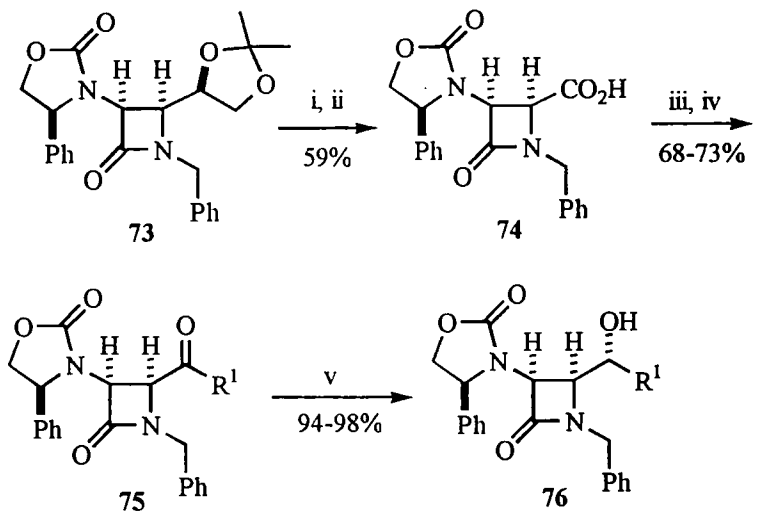


i, 45, Et_3N, toluene, 0 °C — reflux, 6 h

5. APPLICATION TO THE SYNTHESIS OF CARBACEPHEM INTERMEDIATES

An important application of the ketene-imine cycloaddition over recent years has been made in the synthesis of carbacephem intermediates [35]. An illustrative example is Lorabide or Loracarbef which possesses a spectrum of biological activity similar to Ceclor, but is substantially superior in chemical stability. At present, this family of compounds is not directly accessible via fermentation processes or by the structural modification of naturally occurring β-lactam antibiotics [36].

Scheme 16

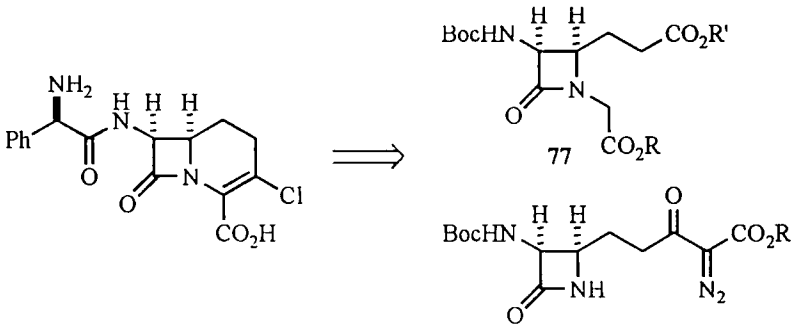


i, TosOH, THF, H_2O; ii, $NaIO_4$, $KMnO_4$; iii, $SOCl_2$; iv, R^1MgX; v, L-Selectride

The most convenient approaches to carbacephems have focused on the chemical synthesis of suitable monocyclic intermediates for subsequent intramolecular cyclization leading to the bicyclic carbacephem framework [35, 37]. Two representative examples of the latter are the Dieckmann cyclization of **77** [38] and the rhodium acetate mediated carbene insertion into the N—H bond of the β-lactam **78** [39, 40]. Various syntheses of both **77** and **78** have employed the ketene-imine cycloaddition as the key step (Scheme 17). For instance (Scheme 18) Fujisawa and Shimizu [41] have utilized the imine **79**, which upon treatment with azidoacetyl chloride gave **80** in 42% yield. Deoxygenation of **80** and reduction of the azido group in **81** generated **82** as a suitable intermediate of Loracarbef. The same authors reported the synthesis of protected β-lactam **83** and its conversion to 4-hydroxymethyl-β-lactam **84** as an intermediate of the antibiotic Carumonam 6 [42] (Scheme 19).

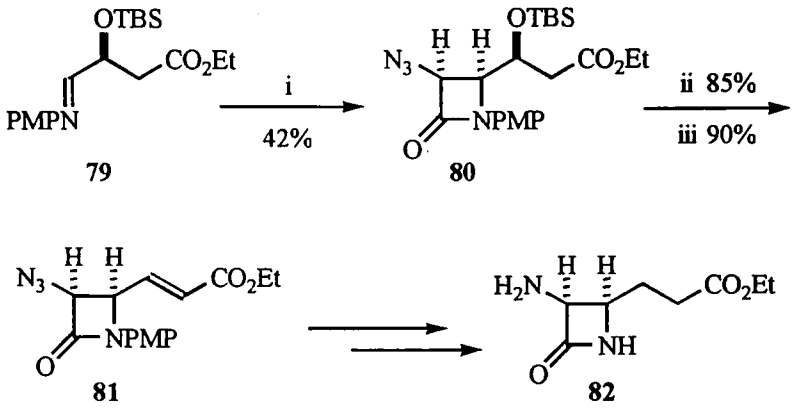
Other syntheses have involved the use of the aminoketene of Evans-Sjogren and imines bearing a carboxyl group surrogate. In these cases, two methods to remove the oxazolidinyl moiety from the resulting cycloadducts have been reported, namely, a dissolving metal reduction [39] and treatment with trimethylsilyl iodide [43]. Alternatively, the use of **46** allows a more convenient access to Loracarbef intermediates [44]. For example, the reaction of **46** with the imine **85** gives the β-lactam adduct **86** in 71% yield. Exposure of **86** to hydrogen over Perlman's catalyst in THF as solvent containing di-*tert*-butyldicarbonate leads to the removal of the oxazolidinone moiety to-

Scheme 17



Synthetic approaches to Loracarbef antibiotic

Scheme 18



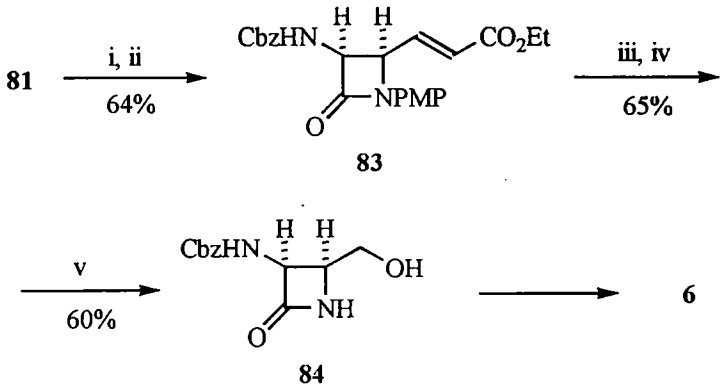
i, N_3CH_2COCl, Et_3N, CH_2Cl_2, -78 °C → r. t., 18 h;
ii, 36% aq. HF, EtOH; iii, MsCl, DBU, toluene, 80 °C, 1 h

gether with the reduction of the double bond giving the N-Boc derivative **87** in 84% yield. This compound has been transformed easily into the Loracarbef intermediate **88**.

6. CONCLUSIONS

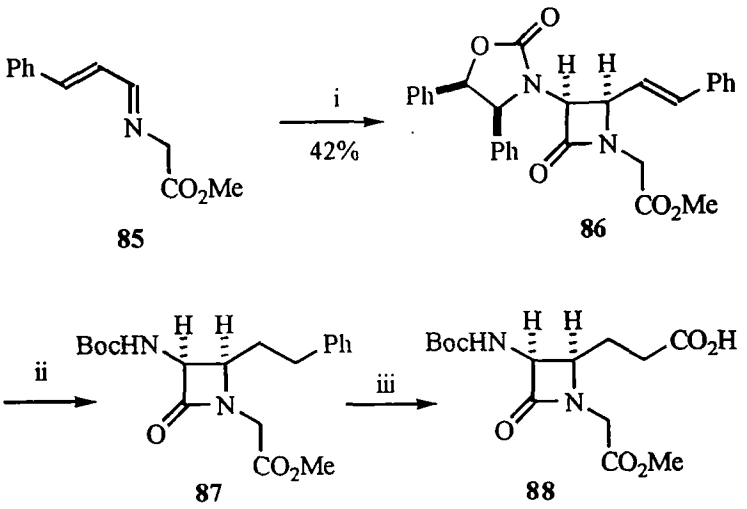
The examples gathered in this short survey illustrate the most recent developments of the ketene-imine cycloaddition reaction for the asymmetric synthesis of β-lactams. These small heterocycles are not only crucial for the advancement of synthetic antibiotics, but are also new promising building blocks of β-amino acid derivatives [45]. Therefore, it is to be expected that improvements in their stereocontrolled preparation will contribute to render them the synthetic intermediates of choice for chemists working in the fields of peptide synthesis or heterocyclic chemistry.

Scheme 19



i, $(NH_4)_2S$, MeOH; ii, Cbz-Cl, Et_3N, CH_2Cl_2;
iii, 5% mol OsO_4, $NaIO_4$, dioxane; iv, $NaBH_4$; v, CAN, CH_3CN

Scheme 20



i, 46 Et_3N, CH_2Cl_2, -78 °C — r. t., 18 h;
ii, H_2, $Pd(OH)_2$, EtOH, $(Boc)_2O$, 60—80 psi, r. t.;
iii, $RuCl_3$ (cat.), MeCN, H_2O, r. t., 2 h

ACKNOWLEDGEMENTS

We thank the following institutions for financial support of our research in β-lactam chemistry: Ministerio de Educacion y Cultura (Spanish Government), Eusko Jaurlaritza (Basque Government), Euskal Herriko Unibertsitatea-Universidad del Pais Vasco (University of the Basque Country). All collaborators cited within the references are also acknowledged.

REFERENCES

1. (a) W. Durkheimer, J. Blumbach, R. Lattrell, K. H. Scheunemann, Angew. Chem. Int. Ed. Engl., **24**, 80 (1985).
   (b) Chemistry and Biology of β-Lactam Antibiotics, R. B. Morin and M. Gorman (eds.), Academic Press, New York, Vol. 1-3 (1982).
   (c) R. Southgate, C. Branch, S. Coulton, and E. Hunt, in: Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products, G. Lukacs (ed.), Springer-Verlag, Berlin, **2**, 621 (1993).
   (d) R. Southgate, Contemp. Org. Synth., **1**, 417 (1994).
2. R. Southgate, S. Elson, in: The Chemistry of Organic Natural Products, W. Herz, H. Grisebach, G. W. Kirby, and Ch. Tamm (eds.), Springer-Verlag, Wien, **47**, 1 (1985).
3. The Chemistry of β-Lactams, M. I. Page (ed.), Chapman and Hall, London (1992).
4. (a) G. A. Koppel in: Small Ring Heterocycles, A. Hassner (ed.), Wiley, New York, **42**, 219 (1983).
   (b) J. Backes in: Houben-Weyl, Methoden der Organischen Chemie, Band E16B. E. Muller and O. Bayer (eds.), Thieme, Stuttgart (1991), p. 31.
   (c) N. DeKimpe in: Comprehensive Heterocyclic Chemistry II, A. Padwa (ed.), **1B**, 507 (1996).
5. M. J. Miller, Acc. Chem. Res., **28**, 299 (1995).
6. (a) D. J. Hart and D. C. Ha, Chem. Rev., **89**, 1447 (1989).
   (b) M. J. Brown, Heterocycles, **29**, 2225 (1989).
   (c) G. I. Georg in: Natural Product Chemistry, A.-ur. Rahman (ed.), Elsevier, Amsterdam, **4**, 431 (1989).
   (d) T. Fujisawa and M. Shimizu, Rev. Heteroatom. Chem., **15**, 203 (1996).
   (e) G. Cainelli, M. Panunzio, P. Andreoli, G. Martelli, G. Spunta, D. Giacomini, and E. Bandini, Pure Appl. Chem., **62**, 605 (1990).
   (f) G. Cainelli, M. Panunzio, D. Giacomini, G. Martelli, G. Spunta, and E. Bandini, in: Chemical Synthesis, Gnosis to Prognosis, C. Chatgilialoglu and V. Snieckus (eds.), Kluwer Academic, Amsterdam (1996), p. 25.

7. (a) L. S. Hegedus, Acc. Chem. Res., **28**, 299 (1995).
(b) M. A. Barrett and M. A. Stutgess, Tetrahedron, **44**, 5615 (1988).
8. H. Staudinger, Liebigs Ann. Chem., Bd 356, S. 51 (1907).
9. F. H. Van der Steen and G. Van Koten, Tetrahedron, **47**, 7503 (1991).
10. (a) R. C. Thomas, in: Recent Progress in The Chemical Synthesis of Antibiotics, G. Lukacs and M. Ohno (eds.), Springer-Verlag, Berlin (1990), p. 533.
(b) R. J. Ternansky and J. M. Morin, Jr., in: The Organic Chemistry of β-Lactams, G. I. Georg (ed.). WCH, New York (1993), p. 257.
(c) L. Ghosez and J. Marchand-Brynaert, in: Comprehensive Organic Synthesis, B. Trost and I. Fleming (eds.), Pergamon, Oxford, **5**, 85 (1991).
11. (a) R. D. G. Cooper, B. W. Daugherty, and D. B. Boyd, Pure Appl. Chem., **59**, 485 (1987).
(b) F. H. Van der Steen and G. Van Koten, Tetrahedron, **47**, 5703 (1991).
(c) G. I. Georg and V. T. Ravikumar, in: The Organic Chemistry of β-Lactams, G. I. Georg (ed.), WCH, New York (1993), p. 295.
12. A. K. Bose, M. S. Manhas, J. M. van der Veen, S. S. Bari, and D. R. Wagle, Tetrahedron, **48**, 4831 (1992).
13. T. E. Gunda and F. Sztaricskai, Tetrahedron, **53**, 7985 (1997).
14. G. I. Georg and Z. Wu, Tetrahedron Lett., **35**, 381 (1991).
15. (a) C. Hubschwerlen and G. Schmid, Helv. Chim. Acta, **66**, 2206 (1983).
(b) D. R. Wagle, G. Garai, J. Chiang, M. G. Monteleone, B. E. Kurys, T. W. Strohmeyer, V. R. Hedge, M. S. Manhas, and A. K. Bose, J. Org. Chem., **53**, 4227 (1988).
(c) B. K. Banik, M. S. Manhas, Z. Kaluza, J. K. Barakat, and A. K. Bose, Tetrahedron Lett., **33**, 3603 (1992).
(d) C. Palomo, M. Oiarbide, A. Esnal, A. Landa, J. Y. Miranda, and A. Linden, J. Org. Chem., and references therein (1998).
16. E. Bandini, G. Martelli, G. Spunta, A. Bongini, and M. Panunzio, Tetrahedron Lett., **37**, 4409 (1996).
17. C. Palomo, F. P. Cossio, C. Cuevas, B. Lecea, A. Mielgo, P. Roman, A. Luque, and M. Martinez-Ripoll, J. Am. Chem. Soc., **114**, 9360 (1992).
18. (a) M. Jayaraman, A. R. A. S. Deshmukh, and B. M. Bhawal, Tetrahedron, **52**, 8989 (1996).
(b) M. Jayaraman, V. G. Puranik, and B. M. Bhawal, Tetrahedron, **52**, 9005 (1996).
19. C. Palomo, F. P. Cossio, C. Cuevas, J. M. Ontoria, J. M. Odriozola, and S. Munt, Bull. Soc. Chim. Belg., **101**, 541 (1992).
20. M. Jayaraman, A. R. A. S. Deshmukh, and B. M. Bhawal, Tetrahedron, **52**, 3741 (1996).
21. (a) D. A. Evans and E. B. Sjogren, Tetrahedron Lett., **27**, 3783 (1985).
(b) D. L. Boger, J. B. Myers, Jr., J. Org. Chem., **56**, 5385 (1991).
(c) M. Muller, D. Bur, T. Tschamber, and J. Streith, Helv. Chim. Acta, **74**, 767 (1991).
22. I. Ojima, Chem. Res., **28**, 383 (1995).
23. C. Palomo, J. M. Aizpurua, J. I. Miranda, A. Mielgo, and J. M. Odriozola, Tetrahedron Lett., **34**, 6325 (1993).
24. R. A. Holton and J. H. Liu, Bioorg, Med. Chem. Lett., **3**, 2475 (1993).
25. V. Srirajan, V. G. Puranik, A. R. A. S. Deshmukh, and B. M. Bhawal, Tetrahedron, **52**, 5579 (1996).
26. C. Palomo, J. M. Aizpurua, M. Legido, R. Galarza, P. M. Deya, J. Dunogues, J. P. Picard, A. Ricci, and G. Seconi, Angew. Chem. Int. Ed. Engl., **35**, 1239 (1996).
27. C. Palomo, J. M. Aizpurua, A. Mielgo, and R. Galarza, Chem. Eur. J., **3**, 1432 (1997).
28. C. Palomo, J. M. Aizpurua, M. Legido, and R. Galarza, Chem. Commun., 233 (1997).
29. C. Palomo, J. M. Aizpurua, J. M. Garcia, R. Galarza, M. Legido, R. Urchegui, P. Roman, A. Luque, J. Server-Carrio, and A. Linden, J. Org. Chem., **62**, 2070 (1997).
30. B. Alcaide, Y. Martin-Cantalejo, J. Perez-Castells, J. Rodriguez-Lopez, M. A. Sierra, A. Monge, and V. Perez-Garcia, J. Org. Chem., **57**, 5921 (1992).
31. B. Alcaide, Y. Martin-Cantalejo, J. Perez-Castells, M. A. Sierra, and A. Monge, J. Org. Chem., **61**, 9156 (1996).
32. C. Niu, T. Petterson and M. J. Miller, J. Org. Chem., **61**, 1014 (1996).
33. C. Palomo, J. M. Aizpurua, A. Mielgo, and A. Linden, J. Org. Chem., **61**, 9186 (1996).
34. E. Bindini, G. Martelli, G. Spunta, and M. Panunzio, Synlett., 1017 (1997).
35. R. D. G. Cooper, in ref. 3, 7985.
36. J. B. Deeter, D. A. Hall, C. L. Jordan, R. M. Justice, M. D. Kinnick, J. M. Morin, Jr., J. W. Paschal, and R. J. Ternansky, Tetrahedron Lett., **34**, 3051 (1993).

37. J. Kant and D. G. Walker, in: The Organic Chemistry of β-Lactams, G. I. Georg (ed.), VCH, New York (1993), p. 121.
38. (a) M. Hatanaka and T. Ishimaru, Tetrahedron Lett., **24**, 4837 (1983).
(b) B. G. Jackson, J. P. Gardner, and P. C. Heath, Tetrahedron Lett., **31**, 6317 (1990).
(c) M. J. Zmijewski, B. S. Briggs, A. R. Thompson, and I. G. Wright, Tetrahedron Lett., **32**, 1621 (1991).
(d) C. W. Doecke, M. A. Staszak, and W. D. Luke, Synlett., 985 (1991).
(e) J. W. Frazier, M. A. Staszak, and L. O. Weigel, Tetrahedron Lett., **33**, 857 (1992).
(f) P. R. Guzzo and M. J. Miller, J. Org. Chem., **59**, 4862 (1994).
39. (a) D. A. Evans, E. B. Sjogren, Tetrahedron Lett., **26**, 3787 (1985).
(b) C. C. Bodurow, B. D. Boyer, J. Brennan, C. A. Bunnell, J. E. Burks, M. A. Carr, C. W. Doecke, T. M. Eckrich, J. W. Fischer, J. P. Gardner, B. J. Graves, R. C. Hines, P. Hoying, B. G. Jackson, M. D. Kinnick, C. D. Kochert, J. S. Lewis, W. D. Luke, L. L. Moore, J. M. Morin, Jr., R. L. Nist, D. E. Prather, D. L. Sparks, and W. C. Vladuchick, Tetrahedron, **30**, 2321 (1989).
(c) C. Bodurow and M. A. Carr, Tetrahedron Lett., **30**, 4081 (1989).
(d) R. K. Vaid and T. E. Hopkins, Tetrahedron Lett., **38**, 6981 (1997).
40. (a) S. Oumoch and G. Rousseau, Heterocycles, **43**, 2615 (1997).
(b) S. Oumoch and G. Rousseau, Bull. Soc. Chim. Fr., **133**, 997 (1996).
(c) M. G. Stocksdale, S. Ramurthy, and M. J. Miller, J. Org. Chem., **63**, 1221 (1998).
41. T. Fujisawa and M. Shimizu, Jpn. Kokai Tokkyo Koho JP 07,300,490 [95,300,490] (1995); Chem. Abstr., **124**, 260700d (1996).
42. T. Fujisawa, A. Shibuya, D. Sato, and M. Shimizu, Synlett., 1067 (1995).
43. J. W. Fischer, J. M. Dunigan, L. D. Hatfield, R. C. Hoying, J. E. Ray, and K. L. Thomas, Tetrahedron Lett., **34**, 4755 (1993).
44. C. Palomo, I. Ganboa, A. Kot, and L. Dembkowski, J. Org. Chem., 199 (in press).
45. C. Palomo, J. M. Aizpurua, and I. Ganboa, in: Enantioselective Synthesis of α-Amino Acids., E. Juaristi (ed.), Wiley-VCH, New York (1997), p. 279.