Recent Advances in the β-Lactam Synthon Method

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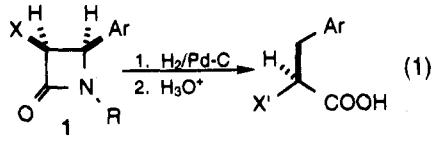
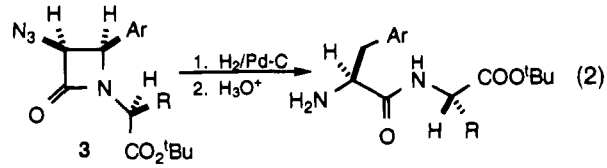
The synthesis of β-lactams has been extensively studied for a long time in connection with the naturally occurring β-lactam antibiotics. However, only limited attention had been drawn to the use of β-lactams as synthetic intermediates when we started the development of the "β-lactam synthon method".[1] It is well-known that the cleavage of the β-lactam ring takes place usually at the N–C(O) bond by nucleophilic reagents including water. For example, Wasserman has developed a useful methodology using the cleavage of the N–C(O) bond for the synthesis of macrocyclic alkaloids.[2] Conceptually, however, other types of cleavage are also possible. Among these possibilities, we have discovered that the cleavage of the N–C^4 bond proceeds exclusively in a palladium-catalyzed hydrogenolysis (e.g., ambient pressure of hydrogen at 50 °C in methanol) when an aryl substituent is attached to the C-4 position.[3] The observed facile reductive N–C^4 bond cleavage is ascribed to the strain energy of the β-lactam skeleton.[4] This discovery led us to develop efficient and versatile methods for the synthesis of aromatic α-hydroxy acids and α-amino acids and their derivatives[3] (eq 1) since a variety of 4-aryl β-lactams can easily be obtained through [2 + 2] cycloaddition of ketenes to arylaldimines.[1,5]



(1)

X = N_3 or BnO; X' = H_2N or HO

When an arylaldimine of an enantiopure amine, e.g., (*S*)-1-arylethylamine and (*S*)-amino acid ester, is used for ketene–imine cycloaddition, a mixture of diastereomeric β-lactams is formed, which can readily be separated to each enantiopure diastereomer by flash chromatography.[1] Once these enantiopure β-lactams are obtained, the reductive cleavage of their N–C^4 bonds leads to the formation of enantiopure aromatic α-hydroxy acids,[1,9] α-amino acids,[1,3] dipeptides[6–8] (eq 2), and azetidines which are further converted to polyamines, polyamino alcohols, and polyamino ethers.[9]



(2)

Oligopeptide synthons can also be easily synthesized through combinations of the dipeptide synthons **3**.[5–8,10] Since it is confirmed that no racemization takes place at any chiral center in the β-lactam intermediate during reductive cleavage, this method provides a unique route to peptide building blocks with excellent enantiomeric purity. For example, this method was successfully applied to the synthesis of a potent analog of enkephalin, which is an opioid peptide in the brain.[10,11] We have also found that the reductive cleavage on Pd–C proceeds with complete inversion of configuration at C–4 (!).[4] This finding enabled us to synthesize C-3 ^2H (or ^3H) labeled dipeptides stereospecifically, which are useful for metabolic and enzymic studies.[4]

The first-generation β-lactam synthon method described above is based on enantiopure diastereomeric β-lactams which are obtained through chromatographic separations of two diastereomers. We have found that the asymmetric cycloaddition of chiral ketenes[12] to chiral imines can achieve excellent stereoselectivity regardless of the chirality (*R* or *S*) of imines, and thus the process provides an extremely effective route to the direct precursors of enantiopure

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(1) As a comprehensive review: Ojima, I. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH Publishers: New York, 1992; pp 197–255.

(2) (a) Wasserman, H. H.; Leadbetter, M. R.; Kopka, I. E. *Tetrahedron Lett.* **1984**, *25*, 2391. (b) Wasserman, H. H.; Robinson, R. P. *Ibid.* **1983**, *24*, 3669. (c) Wasserman, H. H.; Berger, G. D.; Cho, K. R. *Ibid.* **1982**, *23*, 465. (d) Wasserman, H. H.; Matsuyama, H. *J. Am. Chem. Soc.* **1981**, *103*, 461. (e) Bormann, D. *Chem. Ber.* **1970**, *103*, 1797. (f) Combie, L.; Jones, R. C.; Osborne, S.; Mat-Zin, Ab. R. *J. Chem. Soc., Chem. Commun.* **1983**, 959, 960.

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(5) Review: Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH Publishers: New York, 1992; pp 295–368 and references cited therein.

(6) (a) Hatanaka, N.; Ojima, I. *Chem. Lett.* **1981**, 231. (b) Hatanaka, N.; Abe, R.; Ojima, I. *Ibid.* **1981**, 1297.

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(8) Ojima, I.; Nakahashi, K.; Brandstadter, S. M.; Hatanaka, N. *J. Am. Chem. Soc.* **1987**, *109*, 1798.

(9) (a) Yamashita, M.; Ojima, I. *J. Am. Chem. Soc.* **1983**, *105*, 6339. (b) Ojima, I.; Yamato, T.; Nakahashi, K. *Tetrahedron Lett.* **1985**, *26*, 2035. (c) Ojima, I.; Zhao, M.; Yamato, T.; Nakahashi, K.; Yamashita, M.; Abe, R. *J. Org. Chem.* **1991**, *56*, 5263.

(10) (a) Ojima, I.; Yoda, N.; Abe, R.; Yatabe, M.; Hatanaka, N.; Yamashita, M. In *Peptide Chemistry 1982*; Sakakibara, S., Ed.; Protein Research Foundation: Osaka, Japan, 1983; pp 29–34. (b) Yamashita, M.; Abe, R.; Hatanaka, N.; Ojima, I. *Ibid.* pp 85–90.

(11) Hatanaka, N.; Abe, R.; Ojima, I. *Chem. Lett.* **1982**, 445.

(12) Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3783.

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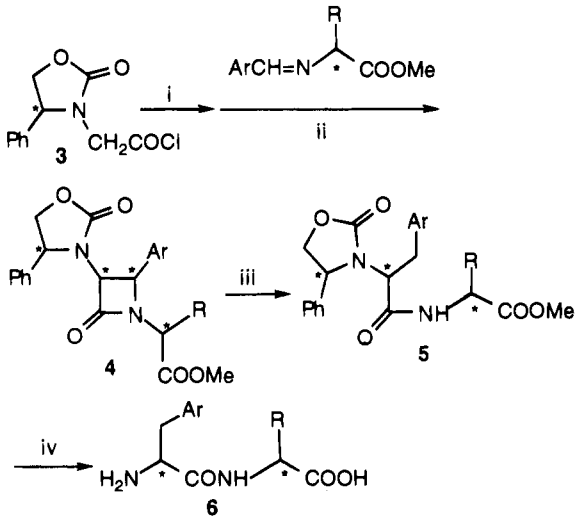
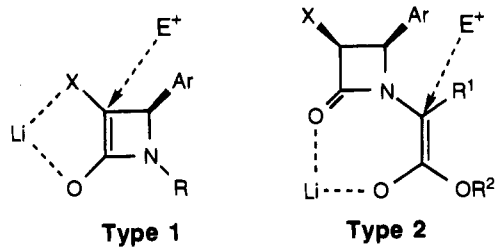
Scheme 1[a]



[a] (i) NEt_3, CH_2Cl_2, −78 °C; (ii) CH_2Cl_2, −78 to 0 °C, 2 h; (iii) (a) H_2, Pd−C, MeOH, 50 °C, 5 h, (b) 1 N NaOH/THF, room temperature, 1 h, (c) H_3O^+; (iv) Li/NH_3/*t*-BuOH, −78 °C, 15 min.

Chart 1



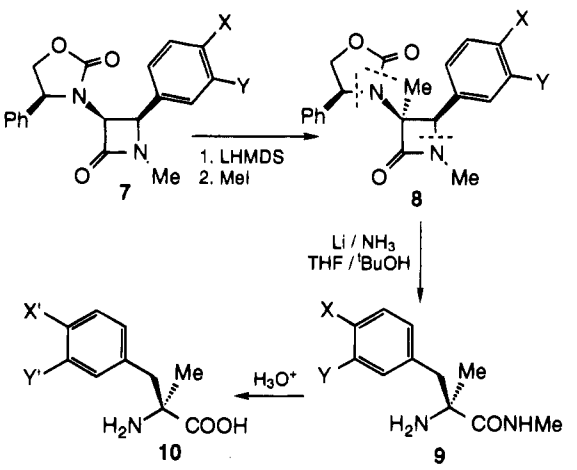
dipeptides with desired configurations.[13,14] The β-lactams **4** were converted to the corresponding N-protected dipeptides **5** quantitatively through hydrogenolysis over Pd−C. The modified Birch reduction of **5** gave the corresponding enantiopure dipeptides **6** in excellent yields (Scheme 1).[13,14] This newer method is particularly useful for the introduction of unnatural amino acid residues with desired absolute configurations into physiologically active peptides and enzyme inhibitors.

Simple asymmetric synthesis of enantiopure α-amino acids is also achieved by the asymmetric [2 + 2] cycloaddition of the chiral ketene generated from **3** to arylaldimines followed by reductive cleavage as well; e.g., (*S*)-phenylalanine and *O*,*O*-dimethyl-DOPA with >99.5% ee (ee = enantiomeric excess) were synthesized in high yields.[14]

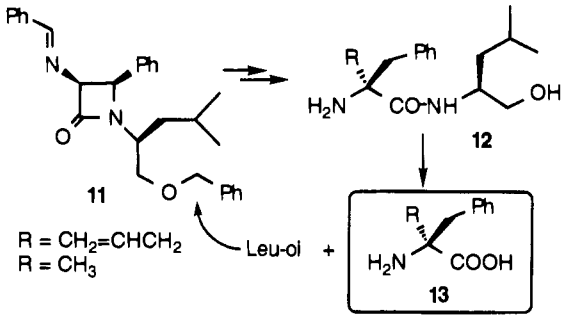
Asymmetric Synthesis of α-Alkyl-α-amino Acids and Their Derivatives

The significance of non-protein amino acids has recently been recognized in connection with the design and synthesis of enzyme inhibitors as potential pharmaceutical drugs and also for the study of enzymatic reaction mechanisms. Among these non-protein amino acids, α-alkyl-α-amino acids have been attracting medicinal and biochemical interest.[15,16] α-Alkyl-α-amino acids provide a challenging synthetic problem

Scheme 2



Scheme 3



for chemists since they have chiral quaternary carbons. Among possible ways to obtain these amino acids, asymmetric synthesis is obviously the method of choice. In fact, we have successfully developed new and efficient synthetic methods to solve this important problem through extremely stereoselective alkylations of chiral β-lactams.[14,17-20]

We have successfully achieved two types of asymmetric alkylation, (i) the alkylation of the C-3 carbon of a β-lactam (type 1) and (ii) the alkylation of a side chain carbon bonding to the β-lactam nitrogen (type 2) as illustrated in Chart 1.[14,17-20]

We have applied the type 1 alkylation for the asymmetric synthesis of (*S*)-α-methylphenylalanine and (*S*)-α-methyl-DOPA via the corresponding (3*S*)-3-methyl-3-oxazolidinyl β-lactams **8** with >99.5% de (de = diastereomeric excess) (Scheme 2).[14]

The type 1 alkylation was also applied to β-lactam **11**. Using allyl bromide or methyl iodide, the alkylation proceeded with >99.5% de in both cases; deprotection followed by hydrogenolysis over 10% Pd−C (R = Me) or dissolving metal reduction (R = allyl) gave the corresponding dipeptide derivatives **12**, which were hydrolyzed to give α-alkylphenylalanines **13**, regenerating (*S*)-leucinol for the preparation of **11** (Scheme 3).[19]

The type 2 alkylation was first applied to the asymmetric synthesis of (*S*)-α-alkylalanines (Scheme

(13) Ojima, I.; Chen, H.-J. C. *J. Chem. Soc., Chem. Commun.* **1987**, 625.
(14) Ojima, I.; Chen, H.-J. C.; Qiu, X. *Tetrahedron* **1988**, *44*, 5307.
(15) Jung, M. J. In *Chemistry and Biochemistry of Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: New York, 1985; p 227.
(16) E.g.: (a) Ramalingam, K.; Woodard, R. W. *Tetrahedron Lett.* **1985**, *26*, 1135. (b) Paul, P. K. C.; Sukumar, M.; Bardi, R.; Piazzesi, A. M.; Valle, G.; Toniolo, C.; Balaram, P. *J. Am. Chem. Soc.* **1986**, *108*, 6363 and references cited therein.
(17) Ojima, I.; Qiu, X. *J. Am. Chem. Soc.* **1987**, *109*, 6537.
(18) Ojima, I.; Shimizu, N.; Qiu, X.; Chen, H.-J. C.; Nakahashi, K. *Bull. Soc. Chim. F.* **1987**, 649.
(19) Ojima, I.; Chen, H.-J. C.; Nakahashi, K. *J. Am. Chem. Soc.* **1988**, *110*, 278.
(20) Ojima, I.; Komata, T.; Qiu, X. *J. Am. Chem. Soc.* **1990**, *112*, 770.

Scheme 4

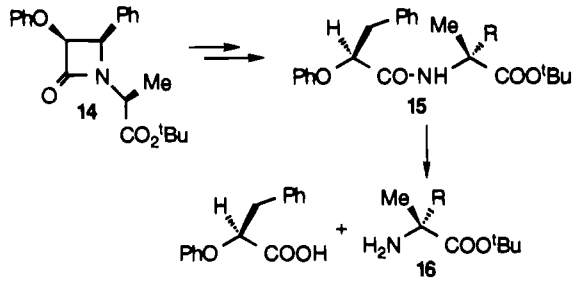
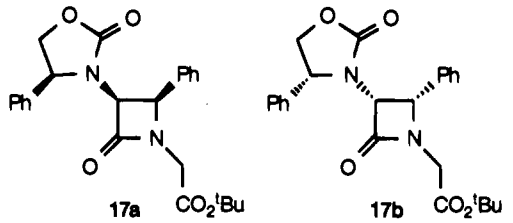
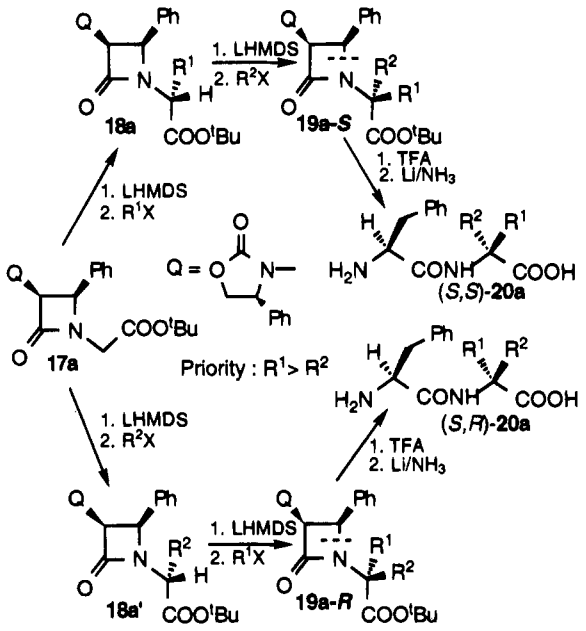


Chart 2



Scheme 5

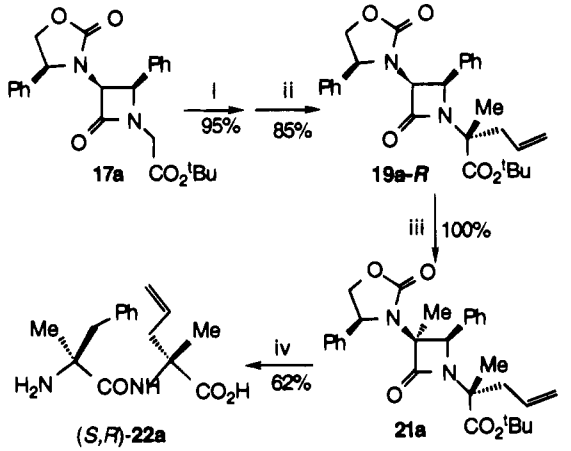


4).[14,17] The β-lactam enolate generated by treating β-lactam **14** with LDA was reacted with an alkyl bromide to give 3-alkyl β-lactam ester **15** (>98% de) in excellent yield. The hydrogenolysis of **15** on Pd–C giving **16**, followed by hydrolysis, yielded enantiopure (*R*)-α-alkylalanine (**16**) in high yield.

We have extended the type 2 alkylation to the asymmetric single and double alkylations of chiral β-lactam acetate **17**, which is a chiral glycinate as well as a phenylalanylglycinate equivalent (Chart 2).[20]

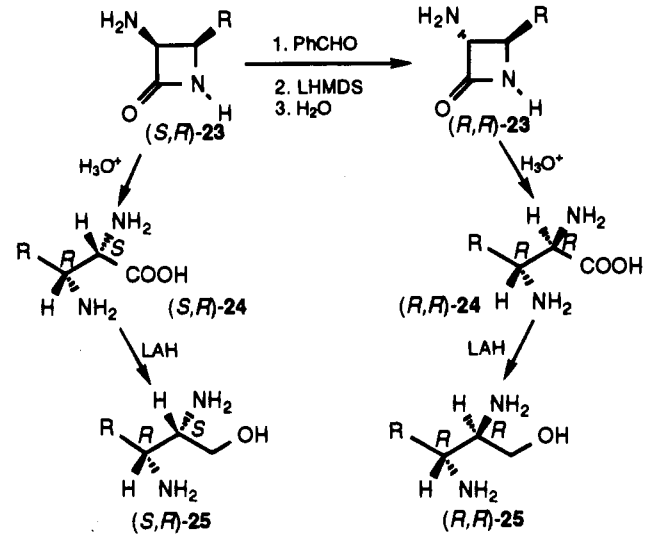
Sequential asymmetric double alkylation of the β-lactam ester **17a** (3*S*,4*R*) using methyl iodide, allyl bromide, and benzyl bromide gave doubly alkylated β-lactam esters **19a** (>99% de) in high yields (Scheme 5).[20] The doubly alkylated β-lactams **19a** thus obtained were readily converted to the corresponding dipeptides **20a** in high yield via dissolving metal reduction (Scheme 5).[20] The salient advantage of this method is that a quaternary chiral center of desired configuration can be created just by changing the order of the addition of the two alkyl halides used ($R^1 \neq R^2$). The same procedure using **17b** gives the corresponding (*R*,*S*)- and (*R*,*R*)-dipeptides **20b**.[20]

Scheme 6[a]



[a] (i) (a) LiHMDS, −78 °C, THF, (b) MeI; (ii) (a) LiHMDS, −78 °C, THF, (b) CH_2=$CHCH_2Br$; (iii) (a) LiHMDS, −20 °C, THF, (b) MeI; (iv) (a) TFA, −20 °C, (b) $LiNH_2$/THF/*t*-BuOH, −78 °C, (c) Dowex 50X-2.

Scheme 7



Sequential asymmetric triple alkylation of **17a** by the combination of the type 1 and type 2 alkylations was also successfully achieved as exemplified in Scheme 6, which gave optically pure (*S*)-α-methylphenylalanyl-(*R*)-α-allylalanine, (*S*,*R*)-**22a**.[20]

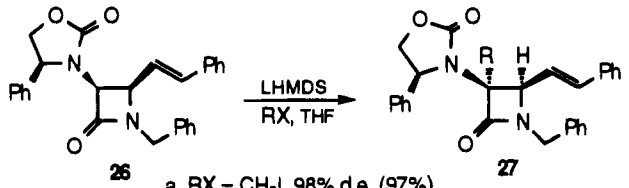
Asymmetric Synthesis of α,β-Diamino Acids and Their Derivatives

We developed a powerful method for the synthesis of enantiopure nonaromatic amino acids and their derivatives using the cleavage of the N–C(O) bond of β-lactam intermediates.

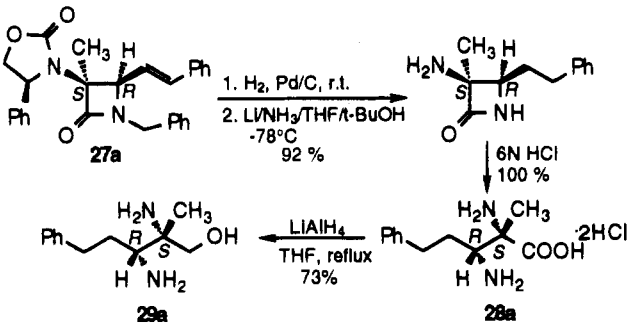
As Scheme 7 illustrates, 3-amino β-lactams (*S*,*R*)- and (*R*,*R*)-**23** are readily converted to the corresponding α,β-diamino acids, (*S*,*R*)- and (*R*,*R*)-**24**, respectively, in quantitative yield by acidic hydrolysis, and are further transformed to their diamino alcohols, (*S*,*R*)- and (*R*,*R*)-**25**, in high yield through $LiAlH_4$ (LAH) reduction.[1,21] The *cis*-β-lactam (*S*,*R*)-**23** can be epimerized to its trans isomer (*R*,*R*)-**23**. Accordingly,

(21) Pei, Y. Dissertation, State University of New York at Stony Brook, 1990.

Scheme 8



Scheme 9



from (*S*,*R*)-**23** obtained via asymmetric [2 + 2] cycloaddition have been synthesized the *S*,*R*- and *R*,*R* isomers of **24** and **25**.[1,21] Since the enantiomeric *cis*-β-lactam (*R*,*S*)-**23** can readily be obtained by using (*R*)-**9**, all four stereoisomers of **24** and **25** can be synthesized by this protocol. It should be noted that *trans*-β-lactams (*R*,*R*)- and (*S*,*S*)-**23** can be obtained directly by chiral ester enolate–imine cyclocondensation.[22]

The protocol illustrated in Scheme 7 can be combined with the type 1 alkylation. For example, we carried out the asymmetric alkylation of (3*S*,4*R*)-4-styryl β-lactam **26** at the C-3 position with methyl iodide and allyl bromide.[23] The reaction gave the corresponding alkylated β-lactams, **27a** and **27b**, respectively, with extremely high stereoselectivity in high yields (Scheme 8).

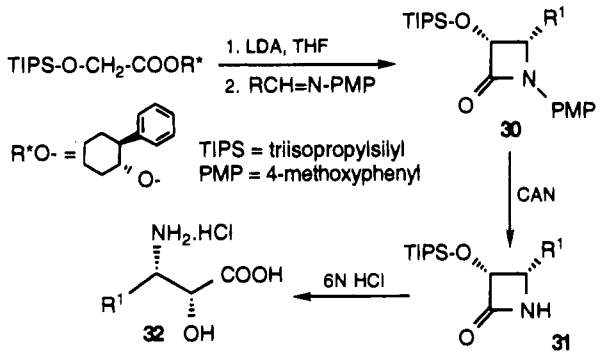
The 3-methyl β-lactam **27a** was further converted to enantiopure (2*S*,3*R*)-diamino acid (*S*,*R*)-**28a** and (2*S*,3*R*)-diamino alcohol (*S*,*R*)-**29a**, bearing a chiral quaternary center at the C-2 position in high yields (Scheme 9).[22]

This newer version of the β-lactam synthon method provides efficient and convenient routes to various enantiopure diamino acids and diamino alcohols, which are useful intermediates for the synthesis of enzyme inhibitors, modified peptides, chiral macrocycles, and chiral ligands or reagents for asymmetric synthesis.

Asymmetric Synthesis of Norstatine and Its Analogs

Norstatine, statine, and their analogs have been used extensively as crucial amino acid residues in peptide-based inhibitors of such enzymes as renin and HIV-I protease. These amino acid residues provide effective transition state mimics of the substrates for the peptidases.[24] Although a number of methods have been developed for statine and its analogs,[25] only a few methods are available for norstatine and its analogs to date.[26] We have developed new and efficient routes to the latter with high enantiomeric purity (Scheme 10).[27]

Scheme 10[a]



[a] R_1 = ^{i}Bu, cyclohexylmethyl, 2-phenylethenyl, phenyl, 4-fluoromethyl, 4-(trifluoromethyl)phenyl, 2-furyl, 2-(2-furyl)ethenyl, crotyl, isobutenyl, etc.

The key β-lactam intermediates, (3*R*,4*S*)- and (3*S*,4*R*)-**30** with 90–99% ee, were obtained in 70–90% yields through chiral enolate–imine cyclocondensations. Reactions were carried out by treating (−)- or (+)-*trans*-2-phenylcyclohexyl TIPSO-acetate (TIPSO = triisopropylsiloxy) with LDA to generate a chiral ester enolate, followed by the addition of an *N*-PMP-aldimine (PMP = *p*-methoxyphenyl) in THF at −78 to −95 °C. Removal of PMP with ceric ammonium nitrate (CAN) followed by acidic hydrolysis gave (2*R*,3*S*)- or (2*S*,3*R*)-3-amino-2-hydroxypropanoic acid (**32**), i.e., isoserines, with >90% ee in excellent yields.[27] (Scheme 10 shows only the 2*R*,3*S* series for simplicity.)

The 2-phenylethenyl, 2-furyl, and 2-(2-furyl)ethenyl groups in these β-lactams can easily be manipulated for further functional group transformations. For example, β-lactam **30c** bearing 2-phenylethenyl at C-4 was converted to a 4-(2-phenylethyl) β-lactam and then to a 4-(2-cyclohexylethyl) β-lactam in high yield. These β-lactams were hydrolyzed with 6 N HCl at 25 °C to afford the corresponding (2*R*,3*S*)-3-amino-2-hydroxyalkanoic acids in high yields (Scheme 11).[27]

Since norstatine and its analogs are important amino acid residues for inhibitors of enzymes such as renin and HIV protease,[24,28,29] facile incorporation of various α-hydroxy-β-amino acid residues into peptides is particularly significant. We have developed a ring-opening coupling method for the synthesis of dipep-

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(24) Rich, D. H. *J. Med. Chem.* **1985**, *28*, 263 and references cited therein.
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(26) E.g.: (a) Ito, Y.; Kamijo, T.; Harada, H.; Terashima, S. *Heterocycles* **1990**, *30*, 299. (b) Kobayashi, Y.; Takemoto, Y.; Ito, Y.; Terashima, S. *Tetrahedron Lett.* **1990**, *31*, 3031. (c) Matsumoto, T.; Kobayashi, Y.; Takemoto, Y.; Ito, Y.; Kamijo, T.; Harada, H.; Terashima, S. *Ibid.* **1990**, *31*, 4175. (d) Iizuka, K.; Kamijo, T.; Harada, H.; Akahane, K.; Kubota, T.; Umeyama, H.; Ishida, T.; Kiso, Y. *J. Med. Chem.* **1990**, *33*, 2707.
(27) Ojima, I.; Park, Y. H.; Sun, C. M.; Brigaud, T.; Zhao, M. *Tetrahedron Lett.* **1992**, *33*, 5737.
(28) Greenlee, W. J. *J. Med. Res. Rev.* **1990**, *10*, 173 and references cited therein.
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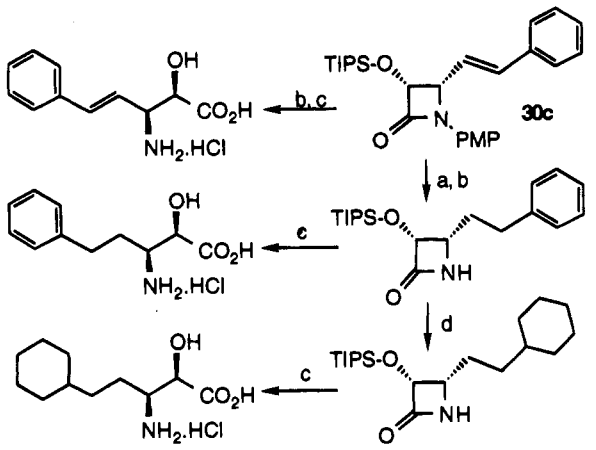
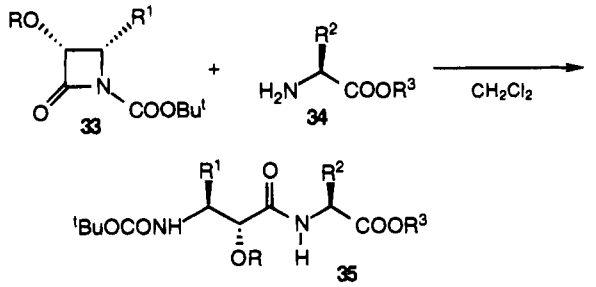
Scheme 11[a]



[a] (a) H_2/Pd–C, MeOH–AcOEt, 25 °C; (b) CAN, CH_3CN–H_2O; (c) 6 N HCl, 25 °C; (d) H_2/Rh–C (800 psi), MeOH, 50 °C.

Scheme 12[a]



[a] (a) R^1 = *i*-Bu; (b) R^1 = Ph; (c) R^1 = c-$C_6H_{11}CH_2$; (d) R^1 = PhCH=CH; R^2 = $PhCH_2$, *i*-Bu, *i*-Pr, indolylmethyl; R^3 = Me, *t*-Bu.

tides bearing α-hydroxy-β-amino acid residues.[30] Salient features of this new coupling method include the reaction conditions being mild and neutral, no racemization detected, and no coupling agent required.

The ring-opening coupling of 3-hydroxy β-lactams **33a–d** proceeds smoothly at 25 °C under neutral conditions in CH_2Cl_2 to give the corresponding *N*-*t*-BOC-dipeptides **35** (*t*-BOC = *tert*-butoxycarbonyl) in excellent yields (Scheme 12).[30]

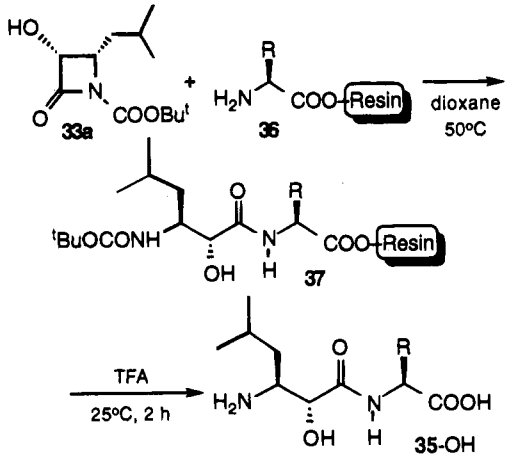
However, steric hindrance at the 3-position of the 1-*t*-BOC-β-lactam **33** exerts a marked influence on the rate of the coupling, e.g., the reactions of 1-*t*-BOC-3-(ethoxyethoxy) β-lactam **33a**-EE (EE = ethoxyethyl) proceed sluggishly in refluxing CH_2Cl_2, but without decomposition, to give **35a**-OMe in high yields. The reactions of **33a**-TIPS and **33a**-EE virtually did not proceed at 25 °C for 18 h. In contrast, 1-*t*-BOC-3-(*t*-BOC-O) β-lactam **33a**-BOC reacts with (*S*)-Phe-OMe smoothly at 25 °C to give *O*-*t*-BOC-**35aa**-OMe in excellent yield. The bulky C-4 substituent of **33** as well as R^2 of **34** also affects the coupling rate to some extent.[30] It is worth mentioning that (*S*)-Pro-OMe (a secondary amine) reacted with **33a** and **33c** smoothly at 25 °C to give the corresponding dipeptides in 91–92% yields.[30]

This novel peptide coupling is applicable to a solid phase peptide synthesis system. Encouraging preliminary results were obtained using the "Wang resin"[31] (Scheme 13); e.g., the coupling of **33a** with

(30) (a) Ojima, I.; Sun, C. M.; Park, Y. H. *J. Org. Chem.* **1994**, *59*, 1249. See also a related work by Palomo et al.: (b) Palomo, C.; Aizpurua, J. M.; Cuevas, C. *J. Chem. Soc., Chem. Commun.* **1994**, 1957.

(31) The "Wang resin" is a commercially available polystyrene-based polymer resin bearing a (hydroxymethyl)-phenoxymethyl tether.

Scheme 13



the resin-bound Gly (**36a**) and Phe (**5b**) at 50 °C gave the corresponding resin-bound dipeptides **37a** (2 h) and **37b** (30 h) in high yields, which were treated with trifluoroacetic acid (TFA) at 25 °C for 2 h to give the TFA salt of dipeptides **35ae**-OH and **35aa**-OH in 72% and 78% isolated yields, respectively.[30] Although reactions are sluggish at 25 °C and thus some activation protocol should be developed, the coupling process is very clean and warrants extensive further investigation.

Syntheses of Paclitaxel, Docetaxel, and New Taxoid Antitumor Agents

Taxol (paclitaxel), a complex diterpene, isolated from the bark of *Taxus brevifolia* (Pacific yew), is currently considered the most exciting lead in cancer chemotherapy.[32,34] Taxotere (docetaxel), a semisynthetic analog, also has shown great promise.[33,34] Paclitaxel has been approved by the FDA for the treatment of advanced ovarian cancer (1992) and for breast cancer (1994). For other cancers, paclitaxel is currently in phase II clinical trials in the United States.[34] Docetaxel is currently in phase II and phase III clinical trials in the United States, Europe, and Japan.[34] Although the total synthesis of paclitaxel provided synthetic chemists with a great academic challenge,[35,36] it has been shown that a readily available precursor can be isolated from the leaves of *Taxus baccata* (European yew) or *Taxus Wallichiana* (Hima-

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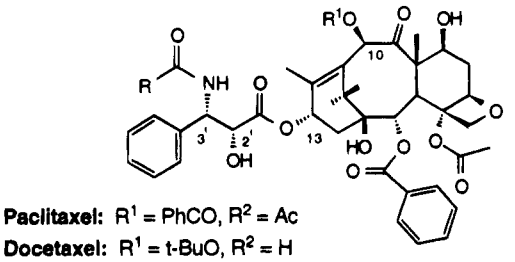
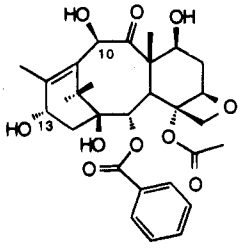
(36) (a) Holton, R. A.; Somoza, C.; Kim, H. B.; Liang, F.; Biedieder, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597. (b) Holton, R. A.; Kim, H.-B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1599.

layan yew).[37,38] Extraction of the fresh leaves yields 10-deacetylbaccatin III (**38**), (1 g/1 kg).[37] With the availability of **38**, a sufficient supply of paclitaxel can be secured in a semisynthetic fashion. It should be noted that the C-13 amino acid moiety, i.e., the *N*-acyl-(2*R*,3*S*)-3-phenylisoserine moiety, is crucial for the strong antitumor activity of paclitaxel and docetaxel.[32,33] Moreover, modifications of the C-13 side chain can provide a new series of paclitaxel analogs which may have higher potency, better bioavailability, different tumor specificity, and less unwanted toxicity.

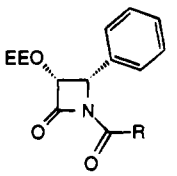
We have successfully developed a highly efficient and practical method for the semisynthesis of paclitaxel, docetaxel, and their analogs via 1-acyl-3-hydroxy β-lactams as the key intermediates.[39-47]



Paclitaxel: R^1 = PhCO, R^2 = Ac
Docetaxel: R^1 = t-BuO, R^2 = H



10-Deacetylbaccatin III (38)

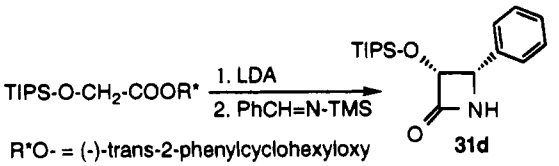


39a: R = Ph
39b: R = t-BuO

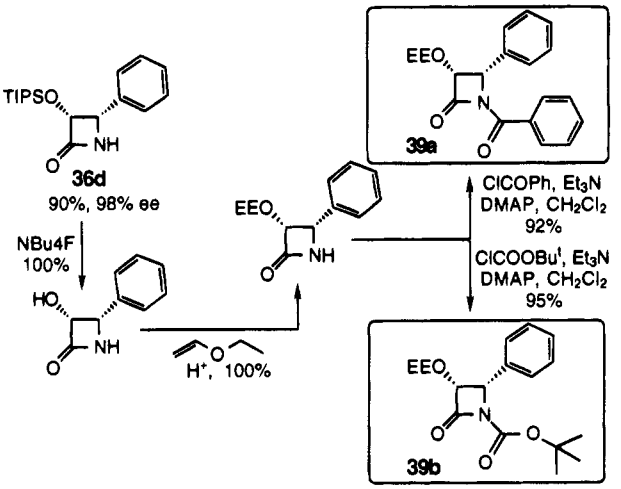
We applied the lithium chiral ester enolate–imine cyclocondensation strategy (vide supra) for the asymmetric synthesis of (3*R*,4*S*)-3-(silyloxy)-4-phenylazetidin-2-one (**31d**, 96–98% ee) using a TMS-aldimine instead of a PMP-aldimine which gave **31d** directly (Scheme 14).[39,40]

We and others have found that 1-benzoyl-(3*R*,4*S*)-3-EEO-4-phenyl-2-azetidinone (**39a**) (EEO = ethoxyethoxy) serves as the key intermediate for the synthesis of paclitaxel.[40,48] We have also found that 1-*t*-BOC-(3*R*,4*S*)-3-EEO-4-phenyl-2-azetidinone (**39b**) is an excellent intermediate for the synthesis of docetaxel.[41] Both 1-acyl-3-EEO-4-phenyl β-lactams **39a** and **39b** are readily derived from **36d** (Scheme 15), which are coupled to baccatin IIIs with proper protecting groups in excellent yields (Scheme 16). Thus, this synthetic method opened highly efficient and practical routes to paclitaxel, docetaxel and their analogs. In fact, this protocol has been adapted in the Nicolaou

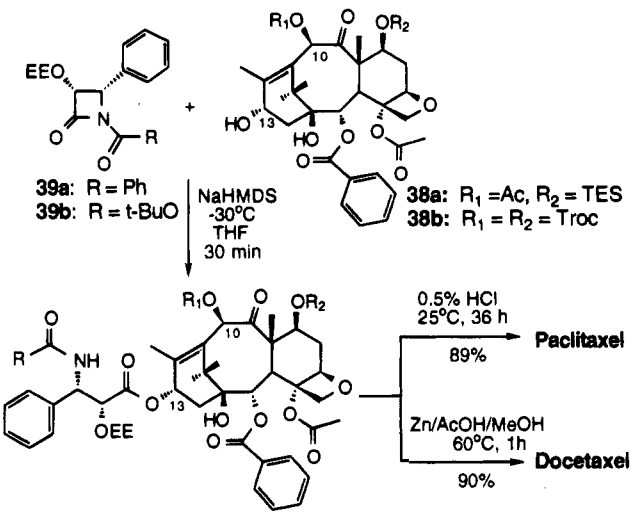
Scheme 14



Scheme 15



Scheme 16



40a: R = Ph, R_1 = Ac, R_2 = TES, 93%
40b: R = ^{t}BuO, R_1 = R_2 = Troc, 95%

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total synthesis of paclitaxel,[35] and also in structure-activity relationship (SAR) studies of taxoids by different research groups.[49] Our own SAR studies have led to the development of several highly promising "Second Generation Paclitaxels", which possess much better cytotoxicity and antitumor activity than the parent paclitaxel, especially against multi-drug-resistant (MDR) cancer phenotypes.[46,47]

Conclusion

This paper has described a unique synthetic method, the β-lactam synthon method, developed in our laboratory, which is based on the use of enantiopure β-lactams as useful synthetic intermediates. The method has been successfully applied to (i) biologically active oligopeptide syntheses; (ii) extremely stereoselective labeling of dipeptides; (iii) asymmetric syntheses of non-protein amino acids, their dipeptides and derivatives that are very important as key structures in enzyme inhibitors as well as modifiers of biologically active peptides; and (iv) highly efficient and practical synthesis of paclitaxel, docetaxel, their analogs, and new taxoids that are highly potent anticancer agents. Although the β-lactam skeleton is just a four-membered cyclic amide, it has been giving us unexpectedly rich organic chemistry, with still more to come in the future.

The author would like to thank his dedicated and talented co-workers and collaborators whose names appear in the references cited. This work has been supported by grants from the National Institutes of Health (NIGMS). Generous support from Rhone-Poulenc Rorer, Indena, SpA, Ajinomoto Co., Inc., and the Center for Biotechnology at Stony Brook in conjunction with the New York State Science & Technology Foundation is also gratefully acknowledged.

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