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Asymmetric Synthesis of *anti*-α,β-Disubstituted β-Amino Acid Derivatives by Reaction of *N*-Alkoxycarbonyl-1-methoxyamines with Optically Active 2-Oxazolidinones

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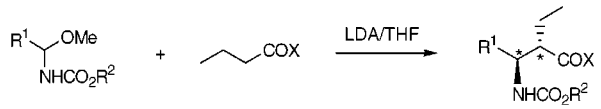
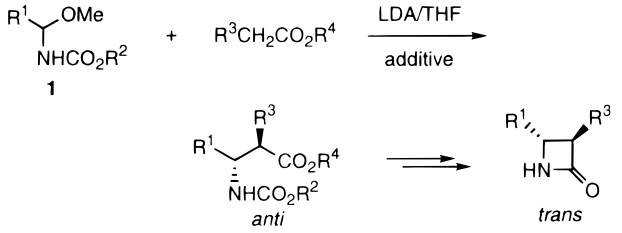
ABSTRACT



The reaction of *N*-alkoxycarbonyl-1-methoxyamines and (4*S*)-3-butyryl-4-isopropyl-2-oxazolidinone afforded the corresponding adducts with *anti* selectively (60% de). Both *anti*- and *syn*-α,β-disubstituted β-amino acid methyl esters were obtained in 98% ee from the adducts. The enantiomerically pure precursor for the synthesis of carbapenem antibiotic PS-5 was prepared by this method.

Enantioselective synthesis of β-amino acids serves as one of the potential routes for asymmetric synthesis of β-lactams. For this purpose, a number of reactions of imines with ester enolates or ketenes have been reported by employing chiral imines, ester enolates, or ketenes as chiral substrates.[1,2] On the other hand, we have already reported that the reaction of *N*-alkoxycarbonyl-1-methoxyamines **1**[3] and esters with LDA in the presence or absence of $TiCl_n(OPr\text{-}i)_{4-n}$ (n = 1−4) as an additive is a useful method for the stereoselective synthesis of *anti*-α,β-disubstituted β-amino acid derivatives and *trans*-α,β-disubstituted β-lactams (Scheme 1).[4] Furthermore, we have also explored the asymmetric synthesis of β-substituted β-amino acid derivatives by the reaction of **1**

Scheme 1



(1) For reviews, see: (a) Hart, D. J.; Ha, D.-C. *Chem. Rev.* **1989**, *89*, 1447. (b) Brown, M. *J. Heterocycles* **1989**, *29*, 2225. (c) van der Steen, F. H.; van Koten, G. *Tetrahedron* **1991**, *47*, 7503.

(2) For recent reports, see: (a) Annunziata, R.; Cinquini, M.; Cozzi, F.; Molteni, V.; Schupp, O. *J. Org. Chem.* **1996**, *61*, 8293. (b) Shankar, B. B.; Kirkup, M. P.; McCombie, S. W.; Clader, J. W.; Ganguly, A. K. *Tetrahedron Lett.* **1996**, *37*, 4095. (c) Baldoli, C.; Buttero, P. D.; Lincandro, E.; Papagni, A. *Tetrahedron* **1996**, *52*, 4849. (d) Palomo, C.; Aizpurua, J. M.; García, J. M.; Galarza, R.; Lengido, M.; Urchegui, R.; Román, P.; Luque, A.; Server-Carrió, J.; Linden, A. *J. Org. Chem.* **1997**, *62*, 2070. (e) Cainelli, G.; Giacomini, D.; Galletti, *Synthesis* **1997**, 886. (f) Ruhland, B.; Bombrun, A.; Gallop, M. A. *J. Org. Chem.* **1997**, *62*, 7820. (g) Molteni, V.; Annunziata, R.; Cinquini, M.; Cozzi, F.; Benaglia, M. *Tetrahedron Lett.* **1998**, *39*, 1257. (h) Karupaiyan, K.; Srirajan, V.; Deshmukh, A. R. A. S.; Bhawal, B. M. *Tetrahedron Lett.* **1998**, *39*, 4375. (i) Matsui, S.; Hashimoto, Y.; Saigo, K. *Synthesis* **1998**, 1161. (j) Cainelli, G.; Galletti, P, Giacomini, D. *Tetrahedron Lett.* **1998**, *39*, 7779. (k) Ohtake, H.; Imada, Y.; Murahashi, S. *J. Org. Chem.* **1999**, *64*, 3790. (l) Podlech, J.; Steurer, S. *Synthesis* **1999**, 650 and references therein.

(3) *N*-Alkoxycarbonyl-1-methoxyamines **1** were prepared from the corresponding *N*-alkoxycarbonyamines by anodic oxidation in methanol: Shono, T.; Hamaguchi, H.; Matsumura, Y. *J. Am. Chem. Soc.* **1975**, *97*, 4264.

(4) Shono, T.; Kise, N.; Sanda, F.; Ohi, S.; Yoshioka, K. *Tetrahedron Lett.* **1989**, *30*, 1253.

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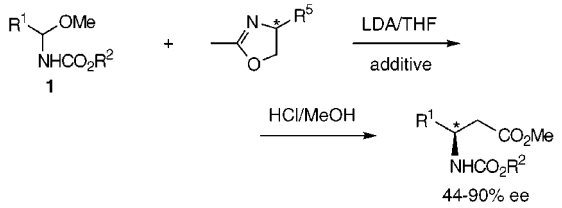
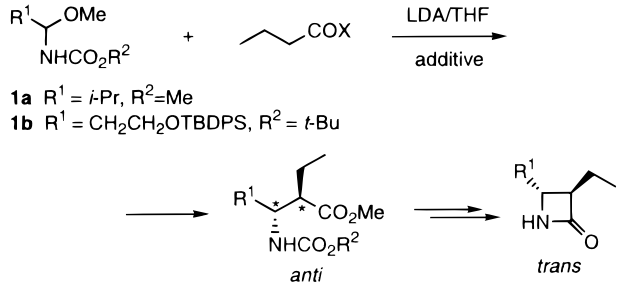
Scheme 2



and chiral 2-methyl-2-oxazolines with LDA (Scheme 2).[5] Herein we report the asymmetric synthesis of *anti*-α,*β*-disubstituted *β*-amino acid derivatives by the reaction of **1** and chiral butyric acid derivatives with LDA (Scheme 3),

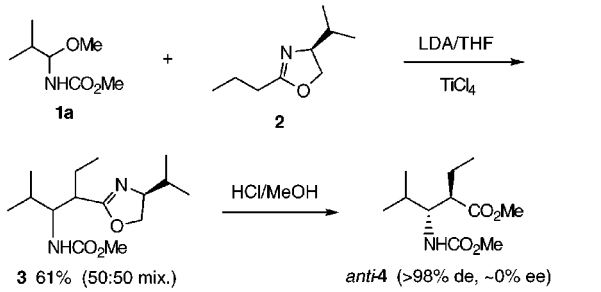
Scheme 3



since chiral *trans*-α-ethyl-*β*-(*β*-hydroxyethyl)-*β*-lactam derivatives are useful precursors[6] for the asymmetric synthesis of *β*-lactam antibiotic PS-5.[7,8] The present method is characterized by the fact that amines can be used instead of imines as in the methods described.[1,2] The advantage of this method is that *γ*-alkoxylated **1** can now be used as a substrate. This is not the case in the former methods since the amine corresponds to an unstable imine because of its susceptibility to *β*-elimination.[9]

As we have already reported,[4] the reaction of **1b** and (−)-menthyl butyrate with LDA gave the *anti* adduct in a 50% de, but the ee value of the *anti* adduct was low (35% ee). Our first attempt to improve the ee value of the adduct using (4*S*)-4-isopropyl-2-propyl-2-oxazoline (**2**), prepared from L-valine, in place of (−)-menthyl butyrate (Scheme 4). The reaction of **1a** and **2** with LDA in the presence (61% yield) or absence of $TiCl_4$ (42% yield) afforded adduct **3** as a 50:50 mixture of two diastereomers (by ^{1}H NMR analysis).

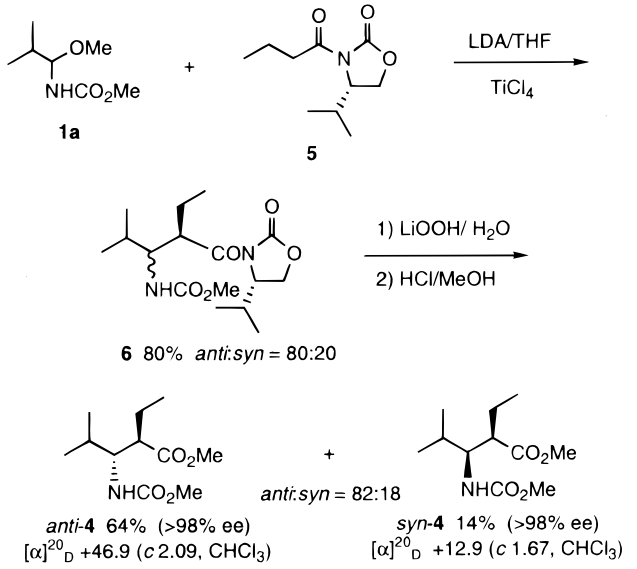
Scheme 4



The conversion of **3** to *β*-amino acid methyl ester **4** gave only the *anti* isomer, though it was almost racemic.

Next, (4*S*)-3-butyroyl-4-isopropyl-2-oxazolidinone (**5**) was used as a chiral substrate (Scheme 5). The reaction of **1a**

Scheme 5



and **5** with LDA in the presence of $TiCl_4$ afforded adduct **6** as an 80:20 mixture of two diastereomers (by ^{1}H NMR analysis) in an 80% yield. When the reaction was carried out without $TiCl_4$, the yield of **6** was very low (<20%). The hydrolysis and subsequent esterification of **6** gave **4** as an 82:18 mixture of two diastereomers (by isolation), in which the major and minor diastereomers of **4** were assigned to be *anti* and the *syn*, respectively, by comparison of their spectroscopic data with those of authentic samples.[4] Their ee values were greater than 98%, according to ^{1}H NMR analysis with Eu(hfc)$_3$. Although their absolute stereochemistries could not be confirmed, it seems that the *anti* isomer is 2*R*,3*R* and the *syn* isomer is 2*R*,3*S* from the results described below.

This reaction offers an effective method for the asymmetric synthesis of the precursor of carbapenem antibiotic PS-5.[6] The reaction of **1b** and **5** with LDA in the presence of $TiCl_4$ gave adduct **7** as an 80:20 diastereomeric mixture in 86% yield (Scheme 6). The diastereochemistry of each isomer of

(5) Shono, T.; Kise, N.; Sanda, F.; Ohi, S.; Tsubata, K. *Tetrahedron Lett.* **1988**, *29*, 231.

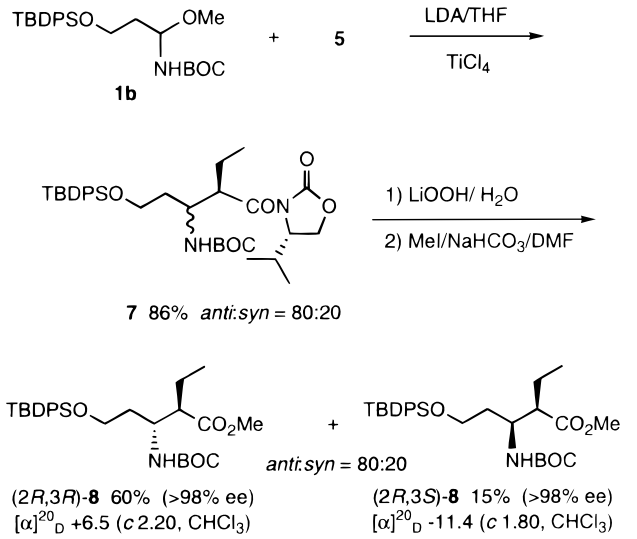
(6) (a) Favara, D.; Omodei-Sali, A.; Consonni, P.; Depaoli, A. *Tetrahedron Lett.* **1982**, *23*, 3105. (b) Okano, K.; Izawa, T.; Ohno, M. *Tetrahedron Lett.* **1983**, *24*, 217.

(7) Yamamoto, K.; Yoshioka, T.; Kato, Y.; Shibamoto, K.; Shimauchi, Y.; Ishikura, T. *J. Antibiotics* **1980**, *33*, 796 and references therein.

(8) For recent reports of asymmetric synthesis of (+)-PS-5, see: (a) Ishibashi, H.; Kameoka, C.; Kodama, K.; Ikeda, M. *Tetrahedron* **1996**, *52*, 489. (b) Jacobi, P. A.; Murphree, S.; Rupprecht, F.; Zheng, W. *J. Org. Chem.* **1996**, *61*, 2413. (c) Miyata, O.; Fujiwara, Y.; Ninomiya, I.; Naito, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2167.

(9) Only one example of the reaction of imines derived from 3-benzyloxypropanal has been reported with boron enolates: Iimori, T.; Ishida, Y.; Shibasaki, M. *Tetrahedron Lett.* **1986**, *27*, 2153.

Scheme 6



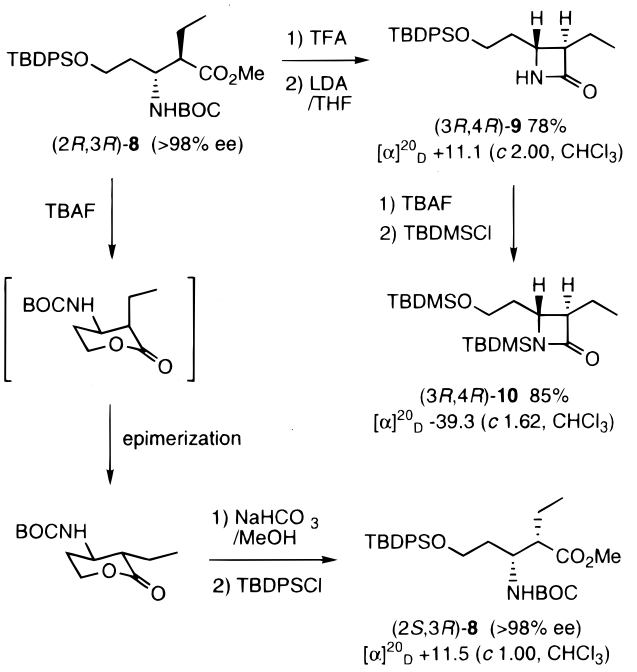
7 was assigned by its transformation to known β-amino acid methyl ester **8**.[4] The major isomer proved to be the *anti* and the minor the *syn* isomer (*anti*:*syn* = 80:20 by isolation). The ee values of both diastereomers of **8** were measured to be greater than 98% by ^{1}H NMR analysis with Eu(hfc)$_3$. The *anti* isomer of **8** was transformed to the *trans* β-lactam **9**, which is the precursor of PS-5 (Scheme 7). The absolute stereochemistry of the optically active β-lactam **9** was confirmed to be 3*R*,4*R* by its conversion to known *N*,*O*-disilylated β-lactam **10**: $[\alpha]^{20}_D$ −39.3 (*c* 1.62, $CHCl_3$) (lit.[6b] −39.59). Therefore, optically active *anti*-**8** was assigned to be (2*R*,3*R*)-**8.** Epimerization of the (2*R*,3*R*)-*anti*-**8** to (2*S*,3*R*)-*syn*-**8** disclosed that the absolute configuration of *syn*-**8** obtained from *syn*-**7** was 2*R*,3*S*, since these optically active *syn* isomers of **8** showed opposite specific rotations as exhibited in Scheme 7.

The present reaction proceed through (1) simultaneous in situ generation of an enolate from **5** and an *N*-alkoxycarbonylimine from **1** and (2) subsequent nucleophilic addition of the former to the latter.[4] It is well-known that Li-chelated Z-enolates are formed from 3-acyl-2-oxazolidinones by treatment with LDA.[10] It is likely that the initially formed Li enolate is transformed to the Ti enolate by the addition of $TiCl_4$.[11] The *anti* stereoselectivity can be explained by

(10) (a) Evans, D. A. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. III, pp 87−90. (b) Heathcock, C. H. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. III, pp 184−188.

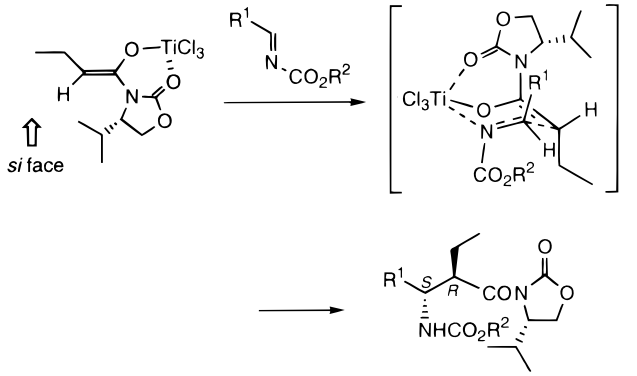
(11) (a) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986. (b) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047.

Scheme 7



considering the six-membered transition state (chair form) as shown in Scheme 8. The Ti-chelated Z-enolate derived from **5** reacts with an *N*-alkoxycarbonylimine completely at the less hindered side (*si* face) and gave adducts which have 2*R* configuration.

Scheme 8



Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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