Upon further heating at 80 °C, this rearranges to the previously observed **6b**.

A proposed mechanism to explain the formation of these products is outlined in Scheme I. Upon thermolysis, the aziridine opens to the ylide **2**. The ylide does not undergo a [2 + 3] cycloaddition to form pyrrolidine **4** but instead closes to the 4-oxazoline **3**. As we had observed in a recent study of oxazolium salt reduction,[4] the 4-oxazoline **3** can react with DMAD in a [2 + 2] manner to yield **5**. Under the harsh conditions employed in the thermolysis of **1a**, the intermediate **5a** rapidly rearranges via ring opening and reclosure to the pyrroline **6a**. However, in the case of aziridine **1b**, oxazoline formation occurs at a much lower temperature, and adduct **5b** can be intercepted. Further heating brings about the same isomerization to the pyrroline **6b**.

The absence of [2 + 3] cycloaddition products in this reaction is striking. An unfavorable steric interaction between the *tert*-butyl group and adjacent groups probably destabilizes planar ylide structures such as **2**. This could make electrocyclic ring closure to the relatively more flexible oxazoline rapid in comparison to the dipolar cycloaddition which is not observed. A few other examples of the aziridine/oxazoline interconversion exist[10] although this is the first case involving an *N*-alkyl group and no substitutent at the C-4 oxazoline position. The **5** → **6** conversion has not been observed previously. This process allows access to pyrrolines of a rather unusual substitution pattern, but its principal ramification is a cautionary one: there is no guarantee that 1:1 adducts obtained from reactive dipolarophiles and 2-acylaziridines will be derived from the [2 + 3] cycloaddition. The 4-oxazoline tautomer is thermally accessible as initially pointed out by Baldwin et al.,[10a] and this isomer reacts with DMAD to give **6** via a labile intermediate **5**. A preliminary reevaluation of the classical work on trapping of dipoles from *N-arylaziridines* with acetylenic dipolarophiles has revealed no anomalies in adduct structure; these experiments do indeed give [2 + 3] cycloadducts as initially reported.[1] However, the *N-alkyl* systems are not so simple. Preliminary results suggest that only those aziridines having bulky *N*-alkyl groups are likely to follow the alternative pathway described here, but the system is in delicate balance. This topic will be discussed further in a full paper.

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(9) The structure of **5b** is clear from the ^1H and ^{13}C NMR evidence. In particular, the absence of long-range coupling between the methine protons rules out structure **4** where extensive precedent requires $J_{2,5}$ = ca. 5 ± 2 Hz *regardless* of stereochemistry (see, for example, ref 3a-c). The strongest evidence for **5b** is the excellent match of ^{13}C spectra with analogous structures obtained by 2 + 2 addition of DMAD + independently generated 4-oxazolines (ref 4). Adduct **5b** lacks a bridgehead substituent compared to the earlier precedents, and the corresponding ^{13}C signal (71.9 ppm) becomes a doublet.

(10) (a) Baldwin, J.; Pudussery, R. G.; Quereshi, A. K.; Sklarz, B. *J. Am. Chem. Soc.* **1968**, *90*, 5325. (b) see ref 3g. (c) Hiyama, T.; Taguchi, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1974**, 2909. (d) Carrie, R. *Tetrahedron* **1976**, *32*, 1995. (e) Kobayashi, Y.; Kumadaki, I.; Yoshida, T. *Heterocycles* **1977**, 387. (f) El-Din, M. N.; Mourad, A. E.; Mekamer, R. *Heterocycles* **1985**, *23*, 1155.

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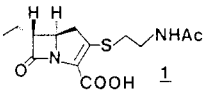
Asymmetric Synthesis of the Carbapenem Antibiotic (+)-PS-5

Summary: An asymmetric synthesis of (+)-PS-5 (**1**) has been accomplished by a route utilizing the anti-selective boron enolate–imine condensation reaction with extremely high asymmetric induction.

Sir: Recently we have found that 9-BBN enolates derived from *S*-phenyl alkanethioates react with imines smoothly, giving anti β-amino acid derivatives in a stereoselective manner.[1] One characteristic feature of this condensation reaction is that amines such as benzylamine and *p*-methoxybenzylamine can be utilized as an imine component,[2] suggesting that the use of optically active imines derived from α-methylbenzylamine and 1-(1-naphthyl)ethylamine[3] could provide optically active β-amino acid derivatives convertible to *trans*-carbapenem antibiotics. In this paper we wish to report a highly efficient asymmetric synthesis of (+)-PS-5 (**1**),[4] which is a *trans*-carbapenem antibiotic



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active against gram-positive and gram-negative bacteria including β-lactamase producing organisms. Although the elegant asymmetric syntheses of (+)-PS-5 (**1**) have been reported very recently,[5] the present synthesis is completely different from those already reported.

The imine **4** (1.2 equiv) derived from 3-(trimethylsilyl)-2-propynal and (*S*)-α-methylbenzylamine[6] was added at −40 °C to the boron enolate **3** prepared from *S*-phenyl butanethioate (**2**), 9-BBNOTf, and diisopropylethylamine (0 °C, 1 h) (Scheme I). The reaction mixture was gradually warmed to 25 °C and stirred for 20 h. After the reaction was quenched with pH 7.0 phosphate buffer and workup and short-path, silica gel chromatography, the B–N bond of the condensation products was cleaved with concentrated HCl in ether–methanol (2:1, 25 °C, 5 h) to give the β-amino acid derivative in 69% yield. These products consisted of the anti adduct **5** and the syn adducts **6** and **6′** in a ratio of 5.2:1. Exposure of the mixture **5**, **6**, and **6′** to *tert*-butylmagnesium chloride (2 equiv) in ether at 0 °C for 3 h[7] furnished the trans-β-lactam **7** in 68% yield, together with the cis-β-lactams **8** and **8′** in 3% yield.[8,9] The

(1) (a) Iimori, T.; Shibasaki, M. *Tetrahedron Lett.* **1985**, *26*, 1523; (b) **1986**, *27*, 2149. (c) Iimori, T.; Ishida, Y.; Shibasaki, M. *Ibid.* **1986**, *27*, 2153.

(2) In the case of lithium enolates such imines cannot be used. See: Ha, D.-C.; Hart, D. J.; Yang, T.-K. *J. Am. chem. Soc.* **1984**, *106*, 4819.

(3) For asymmetric synthesis of β-lactams using such amines, see: (a) Ojima, I.; Inaba, S. *Tetrahedron Lett.* **1980**, *21*, 2077, (b) 2081. (c) Melillo, D. G.; Cvetovich, R. J.; Ryan, K. M.; Sletzinger, M. *J. Org. Chem.* **1986**, *51*, 1498. (d) Gennari, C.; Venturini, I.; Gislon, G.; Schimperna, G. *Tetrahedron Lett.* **1987**, *28*, 227.

(4) Yamamoto, K.; Yoshioka, T.; Kato, Y.; Shibamoto, N.; Okamura, K.; Shimauchi, Y.; Ishikura, T. *J. Antibiot.* **1980**, *33*, 796.

(5) For total synthesis of (±)-PS-5, see: (a) Bateson, J. H.; Hickling, R. I.; Roberts, P. M.; Smale, T. C.; Southgate, R. *J. Chem. Soc., Chem. Commun.* **1980**, 1084. (b) Kametani, T.; Honda, T.; Nakayama, A.; Sasaki, Y.; Mochizuki, T.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2228. (c) Hatanaka, M.; Nitta, H.; Ishimaru, T. *Tetrahedron Lett.* **1984**, *25*, 2387. For total synthesis of (+)-PS-5, see: (d) Favara, D.; Omodei-Sale, A.; Consonni, P.; Depaoli, A. *Ibid.* **1982**, *23*, 3105. (e) Okano, K.; Izawa, T.; Ohno, M. *Ibid.* **1983**, *24*, 217. (f) Hsiao, C.-N.; Ashburn, S. P.; Miller, M. J. *Ibid.* **1985**, *26*, 4855. (g) Evans, D. A.; Sjogren, E. B. *Ibid.* **1986**, *27*, 3119. (h) Hart, D. J.; Lee, C.-S.; Pirkle, W. H.; Hyon, M. H.; Tsipouras, A. *J. Am. Chem. Soc.* **1986**, *108*, 6054.

(6) The boron enolate condensed with the imine derived from 1-(1-naphthyl)ethylamine only in a low yield.

(7) Birkofer, L.; Schramm, J. *Liebigs Ann. Chem.* **1975**, 2195.

(8) The anti β-amino acid derivative was converted to the trans β-lactam in 83% yield, while the syn derivative was transformed into the cis β-lactams only in 23% yield.

(9) R_f values of the β-lactams are 0.7 for **7** and 0.5 and 0.4 for the cis β-lactams (silica gel; ether–hexane, 1:1).

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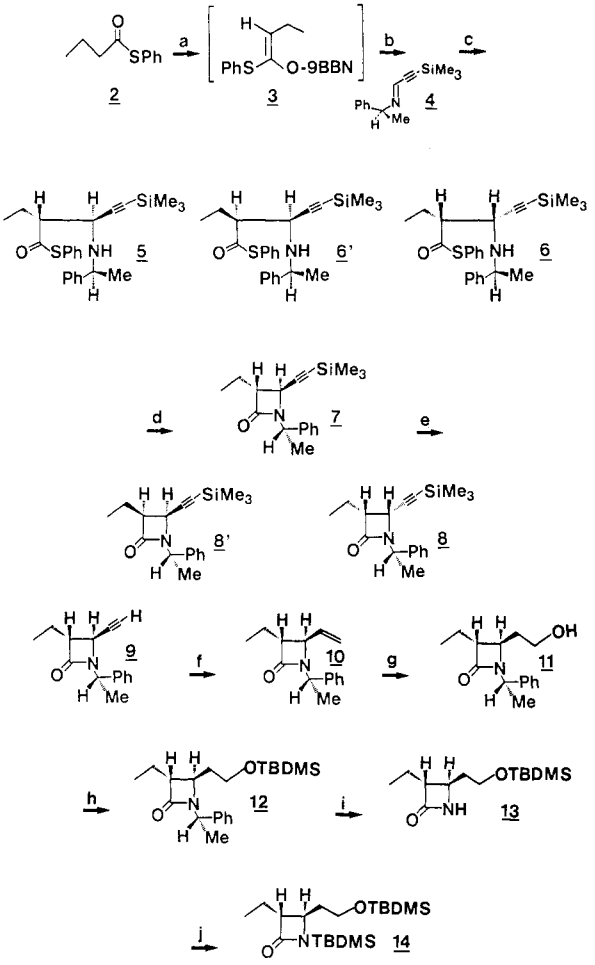
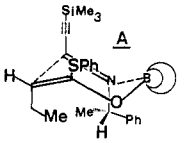
Scheme I[a]



[a] Reagents: (a) 9-BBNOTf (1.2 equiv), *i*-Pr_2EtN (1.2 equiv), CH_2Cl_2, −78 → 0 °C (1 h); (b) −40 → 25 °C (20 h), quench at −78 °C with pH 7.0 phosphate buffer; (c) concentrated HCl, ether–MeOH (2:1), 0 → 25 °C (5 h); (d) *t*-BuMgCl (2 equiv), ether, −78 → 0 °C (3 h); (e) Bu_4NF (1.5 equiv), THF, 0 °C, 0.5 h; (f) Lindlar catalyst, petroleum ether-toluene (2:1), 1 atm of H_2 pressure, 25 °C, 5 h; (g) Sia_2BH (2.5 equiv), THF, 0 °C, 2 h, and then 30% H_2O_2, 6 N NaOH, 0 → 25 °C; (h) TBDMSCl (3 equiv), Et_3N (3 equiv), DMF, 0 °C, 0.5 h; (i) Na, liquid NH_3, −78 °C, 1 h, quench with aqueous NH_4Cl; (j) TBDMSCl (3 equiv), NEt_3 (3 equiv), DMF, 0 °C, 0.5 h.

400-MHz NMR spectrum of the trans-β-lactam **7** revealed that **7** is at least 95% diastereomerically pure,[10] while the diastereomeric ratio of the cis-β-lactams is ca. 1.3:1. The trans-β-lactam **7** was then converted to **9** by treatment with tetrabutylammonium fluoride in THF (100%), followed by semihydrogenation with Lindlar catalyst (1 atm of H_2 pressure) in petroleum ether–toluene (2:1) to give **10** in quantitative yield. Exposure of **10** to disiamylborane in THF (2.5 equiv, 0 °C, 2 h) followed by oxidative workup (6 N NaOH, 30% H_2O_2) provided the hydroxy-β-lactam **11** in 91% yield. After protection of **11** as *tert*-butyldimethylsilyl ether (92%),[11] the β-lactam **12** was then treated with sodium in liquid ammonia (−78 °C, 1 h), to give **13** in 83% yield. Finally, the β-lactam **13** was converted to the disilyl β-lactam **14** in 93% yield, $[\alpha]^{25}_D$ −37.73° (*c* 2.25, $CHCl_3$) [lit.[5e] $[\alpha]^{25}_D$ −39.59° (*c* 2.92, $CHCl_3$)]. Since **14** has previously been transformed into (+)-PS-5 (**1**),[5b,d,e] this constitutes a highly efficient asymmetric synthesis of (+)-PS-5 (**1**) starting with *S*-phenyl butanethioate.

Extremely high asymmetric induction in the present condensation reaction appears to be caused by the two factors mentioned below. One is that as already pointed out by Yamamoto,[12] the asymmetric α-methylbenzyl moiety goes to the axial position in the cylic transition state, and the other is that the ethyl moiety also occupies the axial position in the cyclic transition state.[1] Owing to these factors, the transition state A appears to be the most preferable, providing the β-amino acid derivative **5** in a highly stereoselective manner.

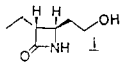


In conclusion, we wish to emphasize that the present synthesis involves the anti-selective boron enolate–imine condensation reaction with extremely high asymmetric induction as a key step.[13]

Supplementary Material Available: Experimental procedures for compounds **5**–**14** (5 pages). Ordering information is given on any current masthead page.

(10) Recently we have found that the diethylaluminum enolate of *S*-*tert*-butyl butanethioate condenses with imines in an anti-selective manner. Application of this condensation reaction to the asymmetric synthesis of (+)-PS-5 gave the unsatisfactory result in terms of asymmetric induction.

(11) The hydroxyl group was protected temporally, because the β-lactam **i** is higher water soluble.



(12) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Am. Chem. Soc.* **1984**, *106*, 5031.

(13) After completion of this manuscript, a highly efficient asymmetric synthesis of *cis*-carbapenem antibiotics has appeared. See: Yamada, T.; Suzuki, H.; Mukaiyama, T. *Chem. Lett.* **1987**, 293.

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The Pyranoside Ring as a Nucleophile in Aldol Condensations[1]

Summary: The enolate derived from a 2-deoxy-3-keto-hexopyranoside undergoes aldol condensations in high yields. With respect to the newly formed bond, the orientation at C2 is always axial, indicating that the pyranoside moiety exerts excellent stereoselectivity at that center. Although the enolate appears to induce little facial selectivity in the aldehyde partner, α-substituents in the latter have a profound effect, the product being formed according to the Felkin–Anh model. Thus, the acetonides of *R* (D) and *S* (L) glyceraldehydes react to give syn and anti products, respectively, with complete stereoselectivity in each case.

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