thiazolidine-2-thiones. This chiral induction proved to be strikingly effective for asymmetric syntheses of various C1-β-substituted carbapenems.

Supplementary Material Available: Tables of crystal data of compound **10b**, atomic parameters for non-hydrogen atoms, fractional coordinates for hydrogen atoms, anisotropic thermal parameters for non-hydrogen atoms, bond length and valance angles, torsion angles, and observed and calculated structure factors in compounds **10b**, the perspective view for the crystallographic structure of **10b**, and experimental details and results in the reaction of **2** with **3** (or *dl*-**13**) (10 pages). Ordering information is given on any current masthead page.

Lewis Acid Mediated Condensation of Chiral Imide Enolates. A General Approach to the Synthesis of Chiral Carbapenem Precursors

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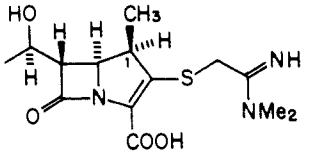
The search for carbapenem antibiotics possessing enhanced chemical and metabolic stability has generated considerable synthetic activity directed toward the synthesis of 1-β-methylcarbapenem carboxylic acids, such as (−)-(1*R*,5*S*,6*S*)-1-methyl-2-[[2-(dimethylamino)-2-iminoethyl]thio]-6-[(1*R*)-1-hydroxyethyl]-1-carbapenem (**1**).[1] The control of the stereo-

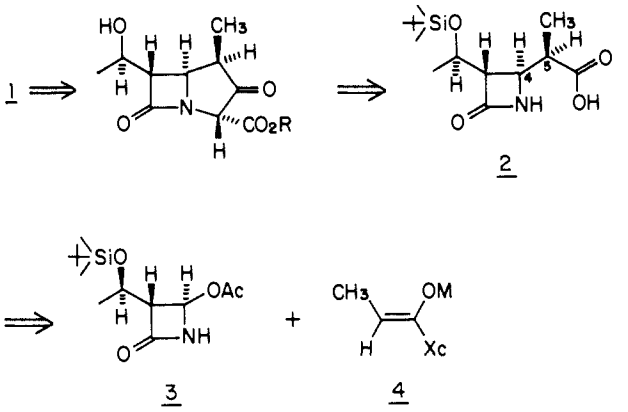


1

chemistry at the 1-position is a critical problem in the synthesis of this new generation of β-lactam antibiotics.[1a]

In this paper we wish to report the results of a highly successful double-asymmetric synthesis leading to the 1-β-methyl carbapenem antibiotic precursor **2** in ≥98% enantiomeric excess from readily available optically active azetidinone **3**.[2] The key feature in the strategy is the utilization of chiral oxazolidone enolates[3] in Lewis acid mediated carbon–carbon bond-forming reactions for the introduction of chirality at C-5 (**2**).

The structural analysis of the C-4 → C-5 bond connection of **2** reveals that the coupling of two optically pure fragments **3** and **4** could be incorporated as a logical step in their synthesis.[4] Recent investigations[3] have demonstrated the utility of propionyloxazolidone carboximides in achieving high levels of diastereofacial selection. In direct analogy with prior report,[3b] the illustrated

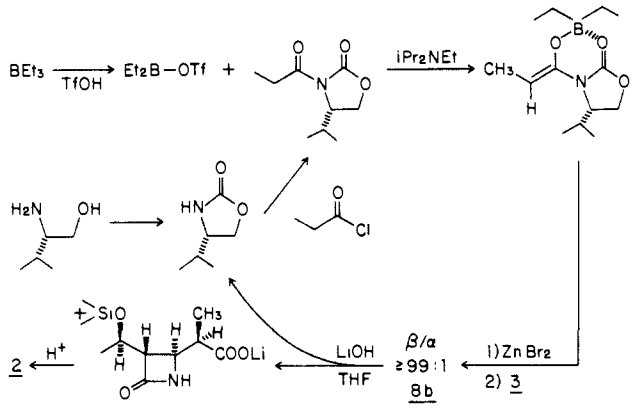


2

3 **4**

carboximides **6** and **7** were transformed into their respective *Z* silyl enol ethers[5] **8** and **9** (1.05 equiv of LDA, 1.10 equiv of Me_3SiCl, THF, −78 °C → room temperature). Reaction of 1.5 equiv of the enol ether **8** and **9** with the azetidinone **3** in CH_2Cl_2 (0.3 M in CH_2Cl_2 at room temperature) in the presence of a catalytic amount of ZnI_2 afforded the β-lactam carboximides **10**α and **10**β as illustrated in Scheme I. Although the chemical yields were generally quite high (78–93%), the diastereoselectivity of the process was only moderate (40–60%).[6]

Evans has extensively demonstrated the high level of efficiency of dialkylboryl enolates of carboximides in aldol condensations.[3] We have found that the dialkylboryl enolates of carboximides react smoothly with the azetidinone **3** with a high degree of diastereoselectivity under Lewis acid conditions. The Lewis acid used determined the optimum stoichiometry of enol to azetidinone and the degree of diastereoselection. The diethylboryl enolates were selectively generated by treatment of the propionamide with Et_2BOTf[7] and *i*-Pr_2NEt (0.3 M in CH_2Cl_2, −78 °C or room temperature)[8] and to this solution was added the Lewis acid followed by the azetidinone **3** at room temperature. A ≥95% mass recovery of products was obtained and the diastereomer analysis was determined by HPLC on the unpurified reaction products.[9] Treatment of the crude product **10** with 1.0 M LiOH in THF at room temperature affords **2** in 73% isolated yield (β/α ≥ 99) based on **3**.[10,11]



(1) (a) Shih, D. H.; Baker, F.; Cama, L.; Christensen, B. G. *Heterocycles* **1984**, *1*, 29. (b) Leanza, W. J.; Ratcliffe, R. W.; DiNinno, F.; Patel, G.; Wildonger, D.; Muthard, D.; Wilkening, R. R.; Christensen, B. G. Abstract 332, *23rd Interscience Conference Antimicrobial Agent and Chemotherapy* Las Vegas, 1983. (c) Shih, D. H.; Fayter, J. A.; Baker, F.; Cama, L.; Christensen, B. G. *Ibid.* Abstr. 333. (d) Kropp, H.; Sundelof, J. G.; Kahan, J. S.; Huber, J.; Bohn, D.; Gerckens, L.; Kahan, F. M.; Birnbaum, J. *Ibid.* Abstr. 334.

(2) (a) Leanza, W. J.; DiNinno, F.; Muthard, D. A.; Wilkening, R. R.; Wildonger, K. J.; Ratcliffe, R. W.; Christensen, B. G. *Tetrahedron* **1983**, *39*, 2505 and references cited therein. (b) Reider, P. J.; Grabowski, E. J. J. *Tetrahedron Lett.* **1982**, *23*, 2293 and references cited therein. (c) Hanessian, S.; Bedeschi, A.; Battistini, C.; Mongelli, N.; *J. Am. Chem. Soc.* **1985**, *107*, 1438 and references cited therein.

(3) (a) For a recent review, see: Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23. (b) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

(4) R. Ratcliffe found in preliminary studies that (*Z*)-1-methoxy-1-[(trimethylsilyl)oxy]-1-propene (**4**) gave a 80:20 α/β mixture **8** (Xc = OCH_3) in the presence of different Lewis acids (unpublished work).

(5) Silyl enol ether *Z*/*E* mixtures have been prepared by using TMSOTf/Et_3N/CCl_4/room temperature. The stereochemistry of the silyl enol ether was confirmed by NMR. This is the subject of a separate report to be published.

(6) Independent generation of the zinc enolate via exchange of the lithium enolate with $ZnBr_2$ affords the β-lactam carboximides in a **10**β:**10**α ratio of 80:20.

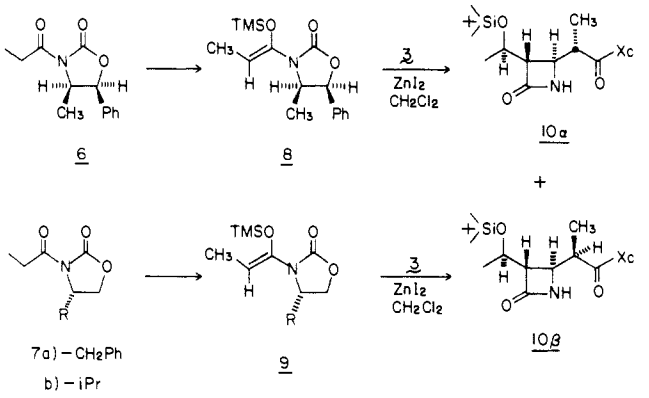
(7) (a) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099. (b) The reagent of choice is the Et_2BOTf due to the high purity of commercially available Et_3B (Texas Alkyls, Inc.) and its convenient in situ generation. Nonreproducible results were obtained with *n*-Bu_2BOTf in CH_2Cl_2 or Et_2O which is commercially available from Aldrich.

(8) The generation and the stereochemistry of the Si, Sn, and B enolates of the chiral carboximides is the subject of a separate report to be published.

(9) **HPLC assay**: Altex Ultrasphere-Octyl, 5 μm, 25 cm × 416 mm i.d.; acetonitrile/water/H_3PO_4, 70:30:0.1, v/v; 1.1 mL/min; retention times (min) **8**β 12.0, **8**α 16.4.

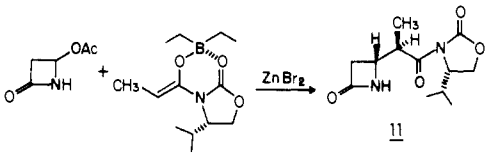
(10) The oxazolidinone is recovered ≥90% yield.

Scheme I



Chiral recognition of tin enolates has been extensively explored by Fujita.[12] The tin enolate was selectively generated by treatment of the propionamide **7b** with $Sn(OTf)_2$[13] and *i*-Pr_2NEt (0.3 M in CH_2Cl_2, −78 °C → room temperature) and to this solution was added the $ZnBr_2$ followed by the azetidinone **3**. Product 80.3%, was obtained in a **10**β:**10**α ratio of 92:8.

The asymmetric induction of the tin enolate with **3** can be rationalized according to a reaction process via a Felkin-type transition state.[14] It is, however, novel that the boron enolate



shows the same stereochemical outcome as tin. This boron-mediated reaction parallels the Li and Na enolate alkylations in the chiral carboximides described by Evans[3b] rather than the boron aldol condensation in the same system.[15]

The methodology described herein constitutes a new approach to the construction of chiral carbapenem precursors. Further synthetic and mechanistic studies on this interesting process are under way.

Acknowledgment. We thank Dr. J. P. Springer for X-ray analysis and R. Reamer and L. DiMichele for recording and interpreting ^1H and ^{13}C NMR spectra. We are also grateful to Drs. R. Conn and D. Melillo for helpful discussions during this work and Marian Spears for her help in preparing this manuscript.

Supplementary Material Available: Complete physical data for compounds **10**β/**10**α and **2**, Table I, diastereoselective condensation of silyl enol ethers of chiral carboximide (Scheme I), and diastereoselective condensation of diethylboryl enolate of **7b** in the presence of Lewis acids (5 pages). Ordering information is given on any current masthead page.

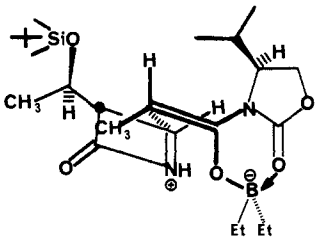
(11) Satisfactory spectral and elemental analyses were obtained. Absolute configuration was confirmed by comparison of the physical data of **2**β and **2**α authentic samples[1a] whose stereochemistry had been confirmed by X-ray analysis.

(12) Nagao, Y.; Yamada, S.; Kumagai, T; Ochiai, M.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1985**, 1418.

(13) Procedure reported by Batchelor et al. (Batchelor, R. J.; Ruddick, J. N. R.; Sams, J. R.; Aubke, F. *Inorg. Chem.* **1977**, *16*, 1414) was modified. Tin(II) (trifluoromethyl)sulfonate was formed when an excess of CF_3SO_3H (60 mL Aldrich) was reacted with 10.0 g (52.74 mmol, Aldrich 99.99+%) of anhydrous stannous chloride. The reaction mixture was heated at 80–85 °C for 24 h. After cooling to room temperature, the $Sn(OTf)_2$ was precipitated with 300 mL of anhydrous Et_2O, filtered in Schlenk ware, and rinsed with of Et_2O (3 × 50 mL). The $Sn(OTf)_2$ was dried in vacuo.

(14) Houk, K. N. *Pure Appl. Chem.* **1983**, *55*, 277 and references cited therein.

(15) This highly efficient enantioselective alkylation was further extended to provide 3-unsubstituted-4-substituted β-lactams **11** as a major diastereoi-



somer (≥99:1) in 95% yield. The stereochemistry was confirmed by X-ray analysis (4*R*,5*R*). In contrast, the tin enolate affords at 59:41 ratio of [(4*R*,5*R*)/(4*S*,5*R*)] under the same reaction conditions.

Novel Intramolecular Stereoselective Addition of Electrogenerated Radical Species to the Aromatic Ring[1]

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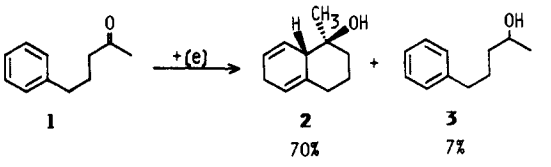
We have previously reported a novel electroreductive cyclization of nonconjugated olefinic and acetylenic ketones yielding cyclic tertiary alcohols.[2] This cyclization was remarkable in its regio- and stereoselectivities. Recently, we have also found a novel electroreductively induced intramolecular addition of a carbonyl group to an aromatic ring.

A typical reaction is shown in eq 1.[3] This intramolecular



(1)

addition was highly controlled by the material of the cathode, the type of solvents, and the electrolyte. Tin was the best cathode, whereas Cu, Zn, Pb, Al, graphite, Pt, Ni, and Ti did not give satisfactory yield and selectivity. Although *i*-PrOH was a satisfactory solvent, ethanol, DMF, dioxane, and THF gave rather poor results. The effect of the cation of the electrolyte was interesting. Tetraalkylammonium salts such as Et_4NOTs and Bu_4NBr gave good results, while no cyclized product was obtained when $LiClO_4$ was used as the electrolyte.

The product **2** seemed to be practically a single stereoisomer on the basis of ^1H NMR[4] and GLC analyses and could be further purified by recrystallization from carbon tetrachloride.[6] This

(1) Electroorganic Chemistry. 98.

(2) (a) Shono, T.; Mitani, M. *J. Am. Chem. Soc.* **1971**, *93*, 5284. (b) Shono, T.; Nishiguchi, I.; Ohmizu, H. *Ibid.* **1978**, *100*, 545. (c) Shono, T.; Nishiguchi, I.; Ohmizu, H. *Chem. Lett.* **1976**, 1233.

(3) The electroreduction of 5-phenyl-2-pentanone (**1**) (1.0 g, 6.16 mmol) was carried out by using a Sn cathode (5 × 10 cm^2) and a carbon rod anode at room temeprature in isopropyl alcohol (40 mL) containing Et_4NOTs (10 g) as a supporting electrolyte. The cathodic and anodic chambers were separated by a ceramic diaphragm and 5*F*/mol of electricity was passed (0.2 A). After usual working up, 1-hydroxy-1-methyl-1,2,3,4,6,9-hexahydronaphthalene (**2**) (70%) and 5-phenyl-2-pentanol (**3**) (7%) were isolated by column chromatography on silica gel.

(4) A trace amount (<1%) of stereoisomer, though not confirmed, seemed to exist. Radical cyclization has been known to proceed with a moderate cis selectivity.[5] The stereoselectivity observed in this cyclization is, however, much higher (cis/trans = ~100) than that (~3.8) reported for the typical radical cyclization. This high stereoselectivity may be well explained by the repulsion between two negatively charged groups as shown in Scheme I.

(5) (a) Beckwith, A. L. J.; Blair, I.; Phillipou, G. *J. Am. Chem. Soc.* **1974**, *96*, 1613. (b) Garst, J. F.; Hines, J. B. *Ibid.* **1984**, *106*, 6443.

(6) **2**: mp 102–103 °C; UV (hexane) λ_{max} 210 nm (ϵ 2043); IR (KBr) 3350, 1660, 1650, 1270, 1180, 1165, 1118, 1112, 1099, 958, 920, 908, 865, 785, 680 cm^{-1}; ^1H NMR (CCl_4) δ 0.99 (s, 3 H), 1.12–2.30 (m, 7 H), 2.52–2.68 (br s, 3 H), 5.32–5.45 (br s, 1 H), 5.61–5.95 (m, 2 H); ^{13}C NMR ($CDCl_3$) 21.78 (q), 24.15 (t), 26.76 (t), 34.89 (t), 41.98 (d), 48.88 (t), 74.43 (s), 118.27 (d), 124.07 (d), 125.71 (d), 135.96 (s) ppm; mass spectrum, *m/e* 164 (M^+).

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