An alternative explanation, at least for our systems, is that the rate-determining step changes with Meisenheimer complex stability.[13] In the DNB–MCP reaction, the rate-determining transformation may be elimination from the relatively stable DNB Meisenheimer complex. In this case the observed primary isotope effect would be anticipated. However, in the nitrobenzene–MCP reaction, formation of the unstable Meisenheimer complex may be rate determining, a situation that is consistent with the absence of a primary isotope effect. Similar multistep reaction pathways have been examined in detail and are believed to involve rate-determining Meisenheimer complex formations.[14]

It is evident that these reactions are complex, particularly when the diversity of possible nucleophiles, substrates, and reaction conditions is considered. A definitive clarification of the actual pathways involved awaits further experimentation.

Experimental Section

NMR spectra were recorded on a Varian EM-390 or a GE/NIC NT-360 spectrometer. Chemical shifts are reported in parts per million relative to tetramethylsilane. Infrared spectra were recorded on a Perkin-Elmer 983 spectrophotometer. UV–visible spectra were obtained on a Varian Cary 219 spectrophotometer. Mass spectra were obtained on a Finnigan 4023 gas chromatograph/mass spectrometer equipped with a 50-M SE-52 fused silica capillary column. Preparative thin-layer chromatography (PTLC) was carried out on commercially prepared silica gel plates (Analtech), and visualization was by ultraviolet light. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

Meisenheimer Complex 1. A mixture of 100 mg (1.04 mmol) of sodium *tert*-butoxide, 107 mg (0.502 mmol) of 1,3,5-trinitrobenzene (TNB), 57 μL (0.50 mmol) of methyl 2-chloropropionate (MCP), and 1 mL of *N,N*-dimethylformamide (DMF) was heated at 60 °C for 1 h and poured into 10 mL of water. The resulting red, aqueous mixture was extracted with three 5-mL portions of dichloromethane, treated with 3 g of sodium chloride, and extracted with eight 10-mL portions of diethyl ether. Combination, drying ($MgSO_4$), and concentration of the ether layers afforded a residue, which was purified by PTLC (20% methanol in dichloromethane eluent), giving 15 mg of **1** as a dark red oil: ^1H NMR (DMSO-d_6) δ 1.40 (s, 3 H), 3.58 (s, 3 H), 5.68 (m, 1 H), 8.44 (m, 2 H); ^{13}C NMR (DMSO-d_6) 24.9 (q), 44.6 (d), 53.4 (q), 75.0 (s), 122.9 (s), 126.7 (s), 128.2 (d), 128.2 (s), 128.8 (d), 169.8 (s); UV-vis (DMF) λ_{max} 448, 502 nm.

Methyl 2-(2,4-Dinitrophenyl)propionate (3). An ice-cold mixture of 100 mg (1.04 mmol) of sodium *tert*-butoxide and 0.5 mL of DMF was treated dropwise with a solution of 84 mg (0.50 mmol) of 1,3-dinitrobenzene (DNB) and 57 μL (0.50 mmol) of methyl 2-chloropropionate (MCP) in 0.5 mL of DMF. The purple mixture was allowed to warm to room temperature and poured into 10 mL of 1 N HCl. Extraction with three 10-mL portions of diethyl ether followed by combination, drying ($MgSO_4$), and concentration of the ether layers afforded a residue, which was purified by PTLC (50% petroleum ether in dichloromethane eluent), giving 47 mg (37% yield) of **3** as an oil: IR (neat) 3099, 2952, 1738, 1605, 1534, 1349 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.68 (d, 3 H, J = 7 Hz), 3.72 (s, 3 H), 4.45 (q, 1 H, J = 7 Hz), 7.78 (d, 1 H, J = 8 Hz), 8.47 (dd, 1 H, J = 8, 2 Hz), 8.81 (d, 1 H, J = 2 Hz); mass spectrum (70 eV), m/e (relative intensity) 208 (22), 102 (27), 77 (45), 76 (22), 65 (25), 59 (100), 51 (30), 43 (98). Anal. Calcd for $C_{10}H_{10}N_2O_6$: C, 47.25; H, 3.97; N, 11.02. Found: C, 47.62; H, 3.90; N, 11.29.

Acknowledgment. Acquisitions of mass spectral data by Dr. V. O. Brandt and ^{13}C NMR data by Dr. L. S. Simeral are gratefully acknowledged. We thank the Callery Chemical Co. for a gift of sodium *tert*-butoxide.

Registry No. 1, 111870-36-1; 2, 111902-85-3; 3, 93742-87-1; DCNB, 33224-18-9; TNB, 99-35-4; MCP, 17639-93-9; DNB, 99-65-0; deuterium, 7782-39-0.

(13) We are indebted to a referee for his suggestions regarding this possible mechanism.

(14) Buncel, E.; Crampton, M. R.; Strauss, M. J.; Terrier, F. *Electron Deficient Aromatic- and Heteroaromatic-Base Interactions*; Elsevier: New York, 1984; pp 313–321.

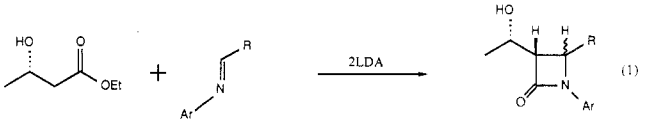
An Asymmetric Synthesis of Carbapenem Antibiotic (+)-PS-5 from Ethyl 3-Hydroxybutanoate

Gunda I. Georg* and Joydeep Kant

Department of Medicinal Chemistry, University of Kansas, Lawrence, Kansas 66045-2500

Received May 13, 1987

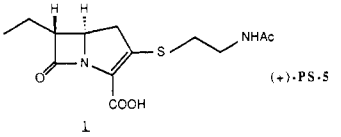
Recently, we[1] and others[2] have demonstrated that readily available esters of optically active 3-hydroxybutyric acid are of great utility in the convergent synthesis of thienamycin and related β-lactam antibiotics.[3] As detailed in eq 1, dianion arylaldimine condensation produces 3-



(1)

Ar = p-methoxyphenyl

(hydroxyethyl)-2-azetidinones with the correct absolute stereochemistry at position 3 of the β-lactam ring system as needed for the elaboration of the total synthesis of thienamycin, antibiotic PS-5 (**1**), and related penems. We now report the full details of an extension of this methodology toward the asymmetric synthesis of carbapenem antibiotic (+)-PS-5 (**1**).[4,5] Our strategy relies on the



(+)-PS-5

1

(1) (a) Georg, G. I.; Kant, J.; Gill, H. S. *J. Am. Chem. Soc.* **1987**, *109*, 1129. (b) Georg, G. I.; Gill, H. S. *J. Chem. Soc., Chem. Commun.* **1985**, 1433. (c) Georg, G. I.; Gill, H. S.; Gerhardt, C. *Tetrahedron Lett.* **1985**, *26*, 3903. (d) Georg, G. I. *Tetrahedron Lett.* **1984**, *25*, 3779.

(2) Ha, D.-C.; Hart, D. J.; Yang, T.-K. *J. Am. Chem. Soc.* **1984**, *106*, 4819. Chiba, T.; Nagatsuma, M.; Nakai, T. *Chem. Lett.* **1984**, 1927. Cainelli, G.; Contento, M.; Giacomini, D.; Panunzio, M. *Tetrahedron Lett.* **1985**, *26*, 937. Iimori, T.; Shibasaki, M. *Tetrahedron Lett.* **1985**, *26*, 1523. Chiba, T.; Nakai, T. *Chem. Lett.* **1985**, 651. Chiba, T.; Nakai, T. *Tetrahedron Lett.* **1985**, *26*, 4647. Hart, D. J.; Ha, D.-C. *Tetrahedron Lett.* **1985**, *26*, 5493. Chiba, T.; Nagatsuma, M.; Nakai, T. *Chem. Lett.* **1985**, 1343. Iimori, T.; Shibasaki, M. *Tetrahedron Lett.* **1986**, *27*, 2149. Iimori, T.; Ishida, Y.; Shibasaki, M. *Tetrahedron Lett.* **1986**, *27*, 2153. Hatanaka, M. *Tetrahedron Lett.* **1987**, *28*, 83.

(3) For reviews on the synthesis of carbapenem β-lactam antibiotics, see: (a) Nagahara, T.; Kametani, T. *Heterocycles* **1987**, *25*, 729. (b) Labia, R.; Morin, C. *J. Antibiot.* **1984**, *37*, 1103. (c) Ratcliffe, R. W.; Albers-Schonberg, G. In *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic: New York, 1982; Vol. 2, p 227. (d) Hoppe, D. *Nachr. Chem., Tech. Lab.* **1982**, *30*, 24. (e) Kametani, T.; Fukumoto, K.; Ihara, M. *Heterocycles* **1982**, *17*, 463. (f) Brown, A. G.; Roberts, S. M. In *Recent Advances in the Chemistry of β-Lactam Antibiotics*; The Royal Society of Chemistry: Burlington House, London, 1984. (g) Southgate, R.; Elson, S. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Tamm, C., Eds.; Springer: New York, 1985; p 1.

(4) Isolation of (+)-PS-5: Okamura, K.; Hirata, S.; Koki, A.; Hori, K.; Shibamoto, N.; Okumura, Y.; Okabe, M.; Okamoto, R.; Kouno, K.; Fukagawa, Y.; Shimauchi, Y.; Ishikura, T.; Lein, J. *J. Antibiot.* **1979**, *32*, 262. Okamura, K.; Koki, A.; Sakamoto, M.; Kubo, Y.; Mutoh, Y.; Fukagawa, Y.; Kuono, K.; Shimauchi, Y.; Ishikura, T.; Lein, J. *J. Ferment. Technol.* **1979**, *57*, 265. For related carpapenems with a 6-ethyl side chain such as PS-7, NS-5, and OA-6129A, see ref 3g.

0022-3263/88/1953-0692$01.50/0

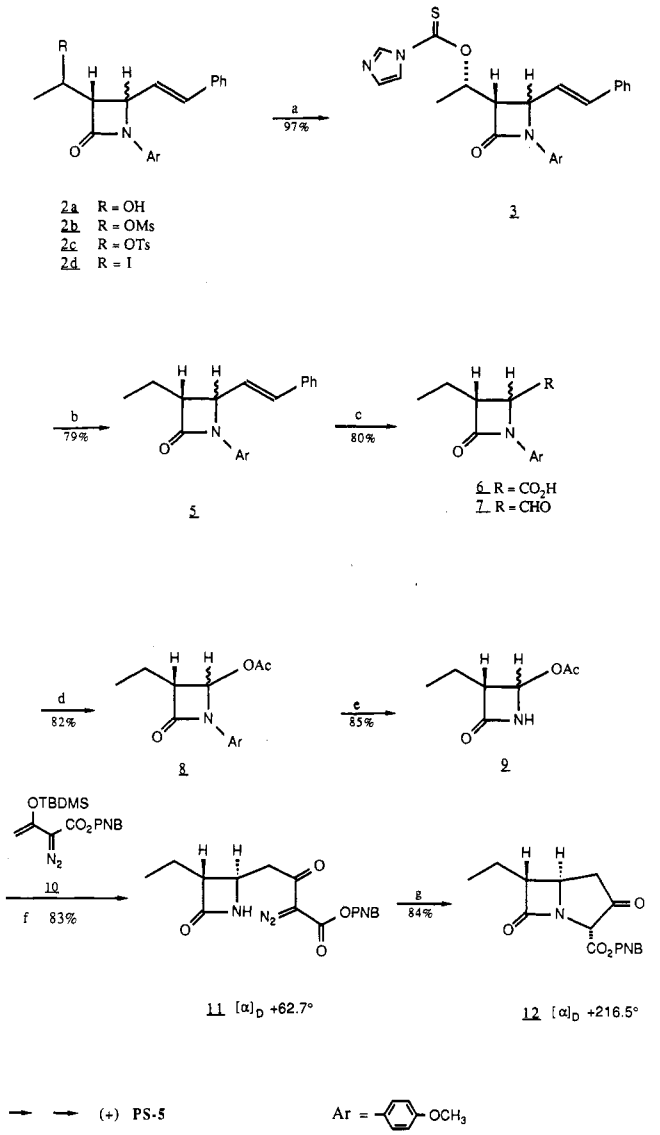
recognition that (*S*)-(+)-ethyl 3-hydroxybutanoate can be utilized as a synthon for optically active esters of butyric acid. The asymmetric center in ethyl 3-hydroxybutanoate directs the introduction of the correct absolute stereochemistry at the α-position (carbon 3 of the β-lactam ring) in the enolate imine condensation. In a second step, the asymmetric center originally necessary for the diastereoselective addition to the α-position will be destroyed by a deoxygenation step. Introduction of the correct stereochemistry at position 4 of the β-lactam ring system follows previously reported methodology[1] via a trans substitution reaction.

As reported in our previous publications,[1] β-lactam **2a** (Scheme I) can be obtainted in high chemical and optical yield through reaction of the dianion of (*S*)-(+)-ethyl 3-hydroxybutanoate[6] and *N*-anisylcinnamylideneamine as a 1:1 cis–trans mixture. Deoxygenation of β-lactam **2a** to produce the 3-ethyl-2-azetidinone **5** was affected with optimal yield (76% overall) in a two-step sequence. Thioimidazolide **3** was prepared from **2a** and thiocarbonyldiimidazole in 97% yield. Reduction of thioimidazolide **3** (crude **3** can be utilized in this reaction) with sodium borohydride in dry dimethyl sulfoxide at 90 °C for 2 h gave a clean conversion to the desired 3-ethyl-2-azetidinone **5** in 79% yield. It is noteworthy that reduction of thioimidazolide **3** with tributyltin hydride, the usual conditions for a Barton[7] deoxygenation, leads to complex reaction mixtures containing less than 10% of the 3-ethyl β-lactam **5** under a variety of reaction conditions. In order to obtain some information whether this deoxygenation might occur through a radical pathway or a nucleophilic displacement, we conducted some control experiments. It is well-known that the thioimidazolides of cholesterol and diacetone-D-glucose can be deoxygenated with tributyltin hydride by a radical pathway.[7] Treatment of these two thioimidazolides with sodium borohydride in DMSO, however, produced the corresponding alcohols only. We are, therefore, of the opinion that the deoxygenation of **3** with sodium borohydride is most noteably a S_N2 nucleophilic displacement and does not occur via a radical pathway.

Our results, therefore, suggest that the *N*-thiocarbonylimidazole group can serve as an equivalent for the tosylate group in the deoxygenation of alcohols. This alternative deoxygenation methodology could be of synthetic value, especially when the formation of the tosylate (see below) is slow or in other systems where the hydroxyl group is prone to elimination.

Deoxygenation in comparable overall yield of 71% could also be achieved in a three-step sequence. β-Lactam **2a** was first mesylated to give mesylate **2b** (96% yield) and then underwent Finkelstein exchange to produce the iodo derivative **2d** in 93% yield, accompanied by 3% of the elimination product **4a**.[8] Reduction of **2d** with sodium borohydride in dimethyl sulfoxide (80% yield) at 90 °C for 2 h or reduction with tributyltin hydride[9] (80% yield)

Scheme I[a]



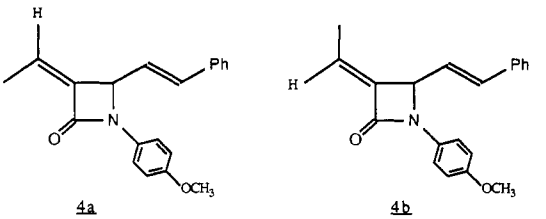
[a] (a) Thiocarbonyldiimidazole, THF, N_2, reflux, 5 h; (b) sodium borohydride, DMSO, 90 °C, 2 h; (c) potassium permanganate, sodium periodate, THF/H_2O, 25 °C, 20 h; (d) lead tetraacetate, DMF/HOAc (8:2), N_2, 80 °C, 1 h; (e) ammonium cerium(IV) nitrate, CH_3CN/H_2O, −5 °C, 45 min; (f) zinc chloride, dichloromethane, N_2, 25 °C, 3 h; (g) rhodium acetate, benzene, N_2, reflux, 45 min.

(5) Synthesis of antibiotic PS-5: (a) Corbett, D. F.; Eglington, A. J. *J. Chem. Soc., Chem. Commun.* **1980**, 1083. (b) Wasserman, H. H.; Han, W. T. *Tetrahedron Lett.* **1984**, *25*, 3747. (c) Okano, K.; Izawa, T.; Ohno, M. *Tetrahedron Lett.* **1983**, *24*, 217. (d) Hatanaka, M.; Nitta, H.; Ishimaru, T. *Tetrahedron Lett.* **1984**, *25*, 2387. (e) Kametani, T.; Honda, T.; Nakayama, A.; Sasaki, Y.; Mochizuki, T.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2228. (f) Favara, D.; Omodei-Salé, A.; Consonni, P.; Depaoli, A. *Tetrahedron Lett.* **1982**, *23*, 3105. (g) Bateson, J. H.; Hickling, R. I.; Roberts, P. M.; Smale, T. C.; Southgate, R. *J. Chem. Soc., Chem. Commun.* **1980**, 1084. (h) Hsiao, C.-N.; Ashburn, S. P.; Miller, M. J. *Tetrahedron Lett.* **1985**, *26*, 4855. (i) Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1986**, *27*, 3119. (j) Hart, D. J.; Lee, C.-S. *J. Am. Chem. Soc.* **1986**, *108*, 6054; (k) Hart, D. J.; Ha, D.-C. *J. Antibiot.* **1987**, *40*, 309.

(6) *S* Enantiomer: Seebach, D.; Sutter, M. A.; Weber, R. H.; Zueger, M. F. *Org. Synth.* **1984**, *63*, 1. Wipf, B.; Kupfer, E.; Bertazzi, R.; Leuenberger, H. G. W. *Helv. Chim. Acta* **1982**, *65*, 495. Kramer, A.; Pfander, H. *Helv. Chim. Acta* **1982**, *65*, 293. Ethyl (*S*)-3-hydroxybutanoate, methyl (*R*)-3-hydroxybutanoate, and (*R*)-3-hydroxybutyric acid are commercially available from Fluka. (*S*)-3-Hydroxybutyric acid sodium salt, and (*R*)-3-hydroxybutyric acid sodium salt are available from Aldrich. In these studies we utilized (*S*)-(+)-ethyl 3-hydroxybutanoate as purchased from Fluka.

(7) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

(8) The presence of (*E*)-enelactam **4b**, indicates that elimination occurs after the substitution reaction. For more details, see ref 1a and literature cited there.



in refluxing benzene for 2 h produced the desired 3-ethyl-2-azetidinone **5** in 71% overall yield.

Alternate, but lower yielding, pathways involved tosylation of **2a**, resulting in the formation of tosylate **2c** in 52% yield accompanied by 45% recovered starting material after 2 days at 25 °C. Reduction of the tosylate **2c** with sodium borohydride[10] yielded 70% azetidinone **5**. Direct conversion of 3-(hydroxyethyl)-2-azetidinone **2a** to the 3-iodomethyl derivative **2d** through Mitsunobu type reactions produced mixtures of the iodo derivative **2d** and enelactams **4a** and **4b**.[8] Reaction of **2a** with triphenylphosphine, diethyl azodicarboxylate, and methyl iodide[11] in tetrahydrofuran gave a 2:1:1 mixture of the desired iodo β-lactam **2d** (30% yield) and elimination products **4a** (20%) and **4b** (20%).[8] The system triphenylphosphine, diethl azodicarboxylate, and zinc iodide[12] lead after 2 days to the formation of 15% iodo lactam **2d**, 30% enelactams **4a** and **4b** (1:1 mixture), and 30% recovered starting materials.

Oxidative cleavage of the double bond in **5** was then accomplished[1a] with potassium permanganate and sodium periodate to yield the carboxylic acid **6** in 80% yield. A two-step sequence via cleavage of the double bond with osmium tetroxide and sodium periodate followed by oxidation of the resulting aldehyde **7** with potassium permanganate produced the carboxylic acid **6** in a comparable yield (71%). Subjecting the carboxylic acid **6** to oxidative decarboxylation[13] with lead tetraacetate gave the acetoxy derivative **8** in 82% yield in a 5:8 cis-*trans* ratio.[14]

After oxidative dearylation[1a,15] with ammonium cerium(IV) nitrate (85% yield), the acetoxyazetidinone **9**[16] was treated with enol ether **10** and zinc chloride in methylene chloride[13] to produce trans β-lactam **11** in 83% yield. Conversion of the diazo keto ester **11** to the bicyclic ketone **12** was effected according to the Merck protocol[17] in 84% yield. The overall yield for the formation of the bicyclic keto ester **12** from β-lactam **2a** was 28% in seven steps. Comparison of the optical rotations[18] of intermediates **11** and **12** with values reported[5f] indicate an ee of 96.9% and 96.6%, respectively. This underscores again the high diastereoselectivity achieved in the dianion imine condensation.

Since the bicyclic keto ester **12** has previously been converted[5f] to (+)-PS-5 (**1**), we have accomplished a further example of an asymmetric synthesis of this β-lactam antibiotic.

Experimental Section

NMR data were obtained as $CDCl_3$ solutions on a Varian FT-80 A or XL 300 spectrometer, and chemical shifts are reported in parts per million (ppm) relative to internal tetramethylsilane (0.00 ppm). Infrared spectra were obtained on a Beckman IR-32 spectrophotometer as chloroform solutions. Optical rotations were taken in chloroform at room temperature on a Perkin-Elmer Model 241 polarimeter. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Electron-impact mass spectra (EIMS), chemical-ionization mass spectra (CIMS), and high-resolution mass spectra (HRMS) were recorded on a Varian CH-5 or Ribermag R-10-10 spectrometer by Dr. Charles Judson and Robert Drake. Microanalyses were obtained on a Hewlett-Packard Model 185 CHN analyser by Tho I. Nguyen at the University of Kansas. All reactions requiring anhydrous conditions were performed under a positive atmosphere of nitrogen in oven-dried glassware. Tetrahydrofuran (THF) was distilled from benzophenone ketyl prior to use. Chromatographic separations were performed by flash chromatography on Baker silica gel (60–200 mesh).

(1′*S*,3*S*,4*R*)- and (1′*S*,3*S*,4*S*)-1-(4-Methoxyphenyl)-3-[1′-[(methylsulfonyl)oxy]ethyl]-4-(2′-phenylethenyl)-2-azetidinone (2b). To a solution of **2a** (500 mg, 1.54 mmol) in dry dichloromethane (15 mL) at 0 °C was added triethylamine (0.43 mL, 3.08 mmol) followed by adding dropwise methanesulfonyl chloride (0.24 mL, 3.08 mmol). After the solution was stirred for 4 h at 0 °C, the solution was poured into water, and the aqueous layer was extracted with ether (3 × 15 mL). The ether layer was washed with 10% sodium bicarbonate solution (2 × 10 mL) and brine (2 × 10 mL), dried (magnesium sulfate), and evaporated to give a dark yellow oil, which was chromatographed on silica gel with ethyl acetate–hexanes (1:4) as eluents to give 592.8 mg (96%) of **2b** as a colorless oil (1:1 mixture of cis and trans isomers that can be separated by column chromatography): IR ($CHCl_3$) 1750 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) cis isomer δ 1.57 (d, J = 6.5 Hz, 3 H, CH_3), 3.05 (s, 3 H, SO_2CH_3), 3.55 (m, 1 H, C-H_3), 3.75 (s, 3 H, OCH_3), 4.72 (dd, J = 5.0 and 8.7 Hz, 1 H, C-H_4), 5.05 (m, 1 H, CH), 6.35 (dd, J = 8.0 and 16.0 Hz, 1 H, CH), 6.85 (d, J = 16.0 Hz, 1 H, CH), 7.35 (m, 9 H, aromatic); ^1H NMR ($CDCl_3$) trans isomer δ 1.62 (d, J = 6.5 Hz, 3 H, CH_3), 3.05 (s, 3 H, SO_2CH_3), 3.27 (m, 1 H, C-H_3), 3.70 (s, 3 H, OCH_3), 4.55 (dd, J = 2.5 and 8.7 Hz, 1 H, C-H_4), 5.15 (m, 1 H, CH), 6.16 (dd, J = 8.0 and 16.0 Hz, 1 H, CH), 6.75 (d, J = 16.0 Hz, 1 H, CH), 7.30 (m, 9 H, aromatic); $[\alpha]_D$ +43.86 ($CHCl_3$, c 1.4; 1:1 mixture of cis and trans isomers; oil); EIMS (cis–trans, 1:1), m/e 401 (M^+), 43 (base); HRMS for $C_{21}H_{23}NSO_5$ requires m/e 401.1296, found 401.1307. Anal. Calcd for $C_{21}H_{23}NSO_5$: C, 62.82; H, 5.77; N, 3.49. Found: C, 62.78; H, 5.88; N, 3.48.

***rel*-(1′*S*,3*S*,4*R*)- and (1′*S*,3*S*,4*S*)-1-(4-Methoxyphenyl)-3-[1′-[(*p*-tolylsulfonyl)oxy]ethyl]-4-(2′-phenylethenyl)-2-azetidinone (2c) from (2a).** To a solution of **2a** (325 mg, 1.0 mmol) in 10.0 mL of dry pyridine was added *p*-toluenesulfonyl chloride (670 mg, 3.52 mmol) at 0 °C. After the solution was stirred for 2 days at room temperature, the solution was poured into water, and the aqueous layer was extracted with ether. The ether layer was washed with 10% sodium bicarbonate solution (2 × 10 mL) and brine (1 × 10 mL), dried (magnesium sulfate), and evaporated to give a yellow oil, which was chromatographed on silica gel with ethyl acetate–hexane (1:1) to give 248 mg (52%) of the pure **2c** as a mixture of cis–trans (1:1) isomers as a yellow oil along with 215 mg (45%) of starting material **2a**: IR ($CHCl_3$) 1740 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.47 (t, J = 6.5 Hz, 3 H, CH_3), 1.56 (t, J = 6.5 Hz, 3 H, CH_3), 2.42 (s, 6 H, CH_3Ar), 3.25 (m, 2H, C-H_3), 3.76 (s, 6 H, OCH_3), 4.52–4.70 (m, 2 H, C-H_4), 5.25 nm, 2 H, CH), 6.15–6.35 (m, 2 H, CH), 6.72–6.95 (m, 2 H, CH), 7.25–7.90 (m, 26 H, aromatic); EIMS, m/e 477 (M^+), 43 (base); HRMS for $C_{27}H_{27}NO_5S$ requires 477.1608, found 477.1604.

β-Lactam 2d. A solution of **2b** (500 mg, 1.25 mmol) in dry acetone (15 mL) was refluxed for 12 h in the presence of anhydrous sodium iodide (375 mg, 2.5 mmol). The hot solution was poured into 25 mL of water, and the aqueous layer was extracted with dichloromethane (10 × 3 mL); the dichloromethane was washed with a 10% solution of sodium bicarbonate (1 × 5 mL), a 10% solution of sodium thiosulfate (2 × 5 mL), and water (1 × 5 mL). The organic layer was dried over magnesium sulfate and evaporated in vacuo to give the crude product, which was chromatographed on silica gel with ethyl acetate–hexanes (1:1) as eluents to yield 503 mg (93%) of **2d** as a light yellow oil, which solidified

(9) This reaction was carried out under dilute conditions and on a small scale. Otherwise, a decrease in yield was observed.
(10) Georg, G.; Durst, T. *J. Org. Chem.* **1983**, *48*, 2092.
(11) Loibner, H.; Zbiral, E. *Helv. Chim. Acta* **1976**, *59*, 2100.
(12) Ho, P.-T.; Davis, N. *J. Org. Chem.* **1984**, *49*, 3027.
(13) Reider, P. J.; Grabowski, E. J. *J. Tetrahedron Lett.* **1982**, *23*, 2293. Barrett, A. G. M.; Quayle, P. *J. Chem. Soc., Chem. Commun.* **1981**, 1076.
(14) The analogous oxidative decarboxylation of a 1:1 cis–trans mixture of 3-[1′-[(*tert*-butyldimethylsilyl)oxy]ethyl]-1-(4′-methoxyphenyl)-2-azetidinone-4-carboxylic acid proceeded with complete cis–trans isomerization.[1a] The sterically less demanding 3-ethyl substituent apparently causes the observed 5:8 cis–trans ratio in this case.
(15) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.
(16) 4-Acetoxy-3-ethyl-2-azetidinone (**9**) has also been utilized for the formation of penems. Longo, A.; Lombardi, P.; Gandolfi, C.; Franceschi, G. *Tetrahedron Lett.* **1981**, *22*, 355.
(17) Ratcliffe, R. W.; Salzmann, T. N.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 31.
(18) The reported optical rotations for intermediates **11** and **12** are $[\alpha]_D$ +62.7 and $[\alpha]_D$ +216.5 respectively. Please see ref 5f.
(19) For the acids **6** and the acetoxy derivatives **9**, optical rotations were not taken because of the presence of some impurities.

on standing. Also obtained was (Z)-enelactam **4a** (11.4 mg, 3%) from the column as a side product.

2d (cis and trans, 1:1): mp 136–137 °C (ethyl acetate and hexanes); IR ($CHCl_3$) 1735 cm^{-1} (C=O); $[\alpha]_D$ −117.8 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.05 (d, *J* = 6.5 Hz, 3 H, CH_3), 2.15 (d, *J* = 6.5 Hz, 3 H, CH_3), 3.25 (dd, *J* = 2.5 and 8.6 Hz, 1 H, C-H_4), 3.66 (s, 6 H, OCH_3), 3.95 (dd, *J* = 5.12 and 8.6 Hz, 1 H, C-H_4), 4.40 (ddd, *J* = 2.5, 5.20, and 7.5 Hz, 2 H, C-H_3), 4.75 (m, 2 H, CH), 6.05–6.55 (m, 2 H, CH), 7.40–7.61 (m, 20 H, aromatic); EIMS, *m/e* 433 (M^+), 157 (base); HRMS for $C_{20}H_{20}NO_2I$ requires 433.0537, found 433.0545. Anal. Calcd for $C_{20}H_{20}NO_2I$: C, 55.44; H, 4.65; N, 3.23. Found: C, 55.61; H, 4.98; N, 3.16.

***rel*-(1′*S*,3*S*,4*R*)- and (1′*S*,3*S*,4*S*)-1-(4-Methoxyphenyl)-3-[1′-[(*N*-thiocarbonylimidazolyl)oxy]ethyl]-4-(2′-phenylethenyl)-2-azetidinone (3).** A solution of **2a** (350 mg, 1.08 mmol) in tetrahydrofuran (4 mL) was refluxed in the presence of 1,1-thiocarbonyldiimidazole (420 mg, 2.32 mmol) for 5 h under an atmosphere of nitrogen. The solution was poured into 15 mL of water, and the aqueous layer was extracted with ether (2 × 10 mL), dried (magnesium sulfate), and evaporated to give almost pure **3** as a oil containing 1:1 mixture of cis and trans isomers. For analytical purposes, the compound was purified by chromatography (silica gel; ethyl acetate–hexanes, 1:1) to yield 387 mg (98%) of compound **3**: IR ($CHCl_3$) 1745 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ (cis–trans, 1:1), 1.65 (t, *J* = 6.2 Hz, 3 H, CH_3), 1.70 (t, *J* = 6.2 Hz, 3 H, CH_3), 3.45 (m, 1 H, C-H_3), 3.55 (m, 1 H, C-H_3), 3.75 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.15 (m, 2 H, CH), 4.52 (dd, *J* = 2.5 and 8.0 Hz, 1 H, C-H_4), 4.85 (t, *J* = 5.0 Hz, 1 H, C-H_4), 6.25 (dd, *J* = 8.0 and 15.0 Hz, 2 H, CH), 6.70–7.90 (m, 24 H, aromatic), 8.25 (s, 2 H, aromatic); EIMS, *m/e* 433 (M^+), 157 (base); HRMS for $C_{24}H_{23}N_3O_3S$ requires 433.1459, found 433.1463.

(*Z*)-Enelactam 4a: mp 97–98 °C; IR ($CHCl_3$) 1740, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.11 (d, *J* = 8 Hz, 3 H, CH_3), 3.79 (s, 3 H, OCH_3), 4.91 (d, *J* = 8 Hz, C-H_4), 5.75 (m, 1 H, CH), 6.21 (q, *J* = 8 Hz, 1 H), 6.79–7.61 (m, 11 H, CH, ArH); EIMS, *m/e* 305 (M^+, base); HRMS for $C_{20}H_{19}NO_2$ requires *m/e* 305.1415, found 305.1404.

(*E*)-Enelactam 4b: oil; IR ($CHCl_3$) 1740, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72 (d, *J* = 7.5 Hz, 3 H, CH_3), 3.75 (s, 3 H, OCH_3), 4.98 (d, *J* = 8.0 Hz, 1 H, C-H_4), 6.0–6.42 (m, 2 H, CH), 6.70–7.45 (m, 10 H, aromatic); EIMS, *m/e* 305 (M^+, base); HRMS for $C_{20}H_{19}NO_2$ requires *m/e* 305.1415, found 305.1404.

***rel*-(3*R*,4*R*)- and (3*R*,4*S*)-3-Ethyl-1-(4-methoxyphenyl)-4-(2′-phenylethenyl)-2-azetidinone (5).** To a solution of **3** (75 mg, 0.18 mmol) in 5 mL of dry dimethyl sulfoxide was added, in portions, sodium borohydride (20 mg, 0.5 mmol) under an inert atmosphere of nitrogen. The solution was stirred for 2 h at 90 °C and then poured into a cold solution of saturated ammonium chloride (5 mL). The aqueous layer was extracted with ether, dried (magnesium sulfate), and evaporated to give a yellow oil, which was purified by chromatography over silica gel with ethyl acetate and hexanes (1:1) as eluents to give **5** (43 mg, 79%) as a mixture of cis–trans (1:1) isomers: IR ($CHCl_3$) 1740 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.09 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.26 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.81–1.94 (m, 4 H, CH_2), 2.90–3.45 (m, 2 H, CH_3), 3.75 (s, 6 H, OCH_3), 4.25 (dd, *J* = 2.5 and 8.0 Hz, 1 H, C-H_4), 4.65 (dd, *J* = 5.5 and 8.0 Hz, 1 H, C-H_4), 6.25 (ddd, *J* = 2.5, 8.0, and 16.0 Hz, 2 H, CH), 7.45–7.70 (m, 20 H, aromatic); EIMS, *m/e* 307 (M^+), 134 (base); HRMS for $C_{20}H_{21}NO_2$ requires 307.1571, found 307.1566.

β-Lactam 5 from 2c. The same procedure as employed for the conversion of **3** to **5** was used. Yield 70%.

(3*R*,4*R*)- and (3*R*,4*S*)-3-Ethyl-1-(4-methoxyphenyl)-4-(2-phenylethenyl)-2-azetidinone (5) from 2d. The same procedure was utilized as employed for the conversion of **3** to **5** with sodium borohydride. Yield 80% as a mixture of cis–trans (1:1) isomers, $[\alpha]_D$ +67.98 (*c* 1.44, $CHCl_3$).

β-Lactam 5 from 2d. A solution of **2d** (75 mg, 0.17 mmol) in dry benzene (10 mL) was refluxed in the presence of tributyltin hydride (0.1 mL, 0.34 mmol) and a catalytic amount of AIBN (8 mg) for a period of 2 h under an atmosphere of nitrogen. The solution was cooled, and the benzene layer was washed with water (2 × 3 mL) and brine (2 × 3 mL), dried (magnesium sulfate), and evaporated to give a yellow oil, which was purified further by chromatography (silica gel; ethyl acetate–hexanes, 1:1) to give 41 mg (80%) of the pure compound **5**.

β-Lactam 2d from 2a. To a solution of **2a** (323 mg, 1.0 mmol) in 5 mL of dry tetrahydrofuran at room temperature was added triphenylphosphine (576 mg, 2.2 mmol), diethyl azodicarboxylate (576 mg, 2.2 mmol), and methyl iodide (310 mg, 2.2 mmol) under an atmosphere of nitrogen. After the mixture was stirred for 16 h, the mixture was poured into the flask containing 15 mL of brine, and then the aqueous layer was extracted with ether (3 × 10 mL), dried (magnesium sulfate), and evaporated to give a dark brown oil. On chromatography (silica gel; ethyl acetate–hexanes, 1:4, three different products were isolated: β-lactam **2d** in 30% yield, enelactam **4a** in 20% yield, and enelactam **4b** in 20% yield.

Acknowledgment. Financial assistance from the National Institutes of Health (Grant 21612), The American Heart Association of Kansas (Grant KS-87-G-17), and the Biomedical Research Grant RR 5606 at the University of Kansas is acknowledged. We thank V. Huseby and L. Lampe for their help in preparing the manuscript.

Registry No. **1**, 67007-79-8; **2a** (isomer 1), 101977-76-8; **2a** (isomer 2), 101977-77-9; **2b** (isomer 1), 112245-38-2; **2b** (isomer 2), 112245-39-3; **2c** (isomer 1), 112113-94-7; **2c** (isomer 2), 112245-40-6; **2d** (isomer 1), 112113-95-8; **2d** (isomer 2), 112245-41-7; **3** (isomer 1), 112113-96-9; **3** (isomer 2), 112245-42-8; **4a**, 112113-97-0; **4b**, 112113-98-1; **5** (isomer 1), 103733-13-7; **5** (isomer 2), 112245-43-9; **6** (isomer 1), 112113-99-2; **6** (isomer 2), 112245-44-0; **7** (isomer 1), 112114-00-8; **7** (isomer 2), 112245-45-1; **8** (isomer 1), 112114-01-9; **8** (isomer 2), 112245-46-2; **9** (isomer 1), 103775-03-7; **9** (isomer 2), 103775-02-6; **10**, 93788-48-8; **11**, 83997-55-1; **12**, 79252-31-6.

Supplementary Material Available: Physical data for compounds **6–9**, **11**, and **12** (4 pages). Ordering information is given on any current masthead page.

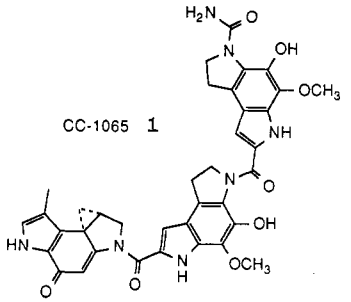
Total Synthesis of (+)- and (−)-CPI-CDPI$_2$: (+)-(3b*R*,4a*S*)- and (−)-(3b*S*,4a*R*)-Deoxy-CC-1065

Dale L. Boger*[1a] and Robert S. Coleman[1b]

Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

Received September 22, 1987

CC-1065 (**1**, NSC-298223), an antitumor antibiotic isolated from *Streptomyces zelensis*[2a] initially identified by spectroscopic techniques[2b] and confirmed in a single-crystal X-ray structure determination,[2c] possesses exceptional, potent in vitro cytotoxic activity, antimicrobial activity, and confirmed, potent in vivo antitumor activity.[3] The



(1) (a) National Institutes of Health research career development award recipient, 1983–1988 (CA 01134). Alfred P. Sloan research fellow, 1985–1989. (b) National Institutes of Health predoctoral trainee, 1984–1985 (GM 07775). David Ross Fellow, Purdue University, 1986–1987.

(2) (a) Hanka, L. J.; Dietz, A.; Gerpheide, S. A.; Kuentzel, S. L.; Martin, D. G. *J. Antibiot.* **1978**, *31*, 1211. Martin, D. G.; Biles, C.; Gerpheide, S. A.; Hanka, L. J.; Krueger, W. C.; McGovren, J. P.; Mizsak, S. A.; Neil, G. L.; Stewart, J. C.; Visser, J. *Ibid.* **1981**, *34*, 1119. (b) Martin, D. G.; Chidester, C. G.; Duchamp, D. J.; Mizsak, S. A. *J. Antibiot.* **1980**, *33*, 902. (b) Chidester, C. G.; Krueger, W. C.; Mizsak, S. A.; Duchamp, D. J.; Martin, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 7629.

0022-3263/88/1953-0695$01.50/0