Preparation of Optically Pure 3'-Methylspiro[imidazolidine-4,4'(1'H)-quinazoline]-2,2',5(3'H)-trione by Combination of Optical Resolution and Racemization

Masafumi Yamagishi,† Yoshihisa Yamada,† Ken-ichi Ozaki,† Tadamasa Da-te,‡ Kimio Okamura,‡ Mamoru Suzuki,† and Kazuo Matsumoto*,†

Research Laboratory of Applied Biochemistry, Tanabe Seiyaku Co., Ltd., 16-89, Kashima-3-chome, Yodogawa-ku, Osaka 532, Japan, and Organic Chemistry Research Laboratory, Tanabe Seiyaku Co., Ltd., Kawagishi, Toda, Saitama 335, Japan

Received October 2, 1991

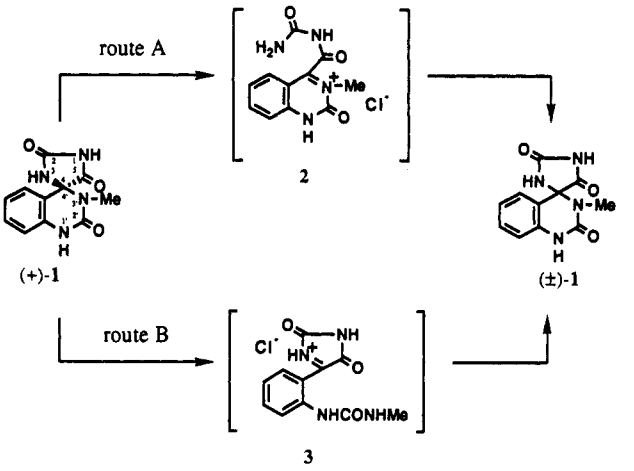
Optically pure 3'-methylspiro[imidazolidine-4,4'(1'H)-quinazoline]-2,2',5(3'H)-trione was prepared by optical resolution using brucine as a resolving agent. The resulting optically pure spirohydantoin was racemized by refluxing in 1,2-dichlorobenzene for 17 h, or more effectively upon heating in 10% HCl at 90 °C for 2 h. In the acid-catalyzed racemization, the introduction of difluoromethyl group at the 3-nitrogen of hydantoin ring increased the racemization rate, while the introduction of methyl group at the 3-nitrogen reduced it. These results suggest that the acid-catalyzed racemization proceeds via the *N*-acyliminium ion generated by the cleavage of the N_3–C_4 bond of the spirohydantoin ring.

Several spirohydantoin derivatives which exhibit potent aldose reductase (AR) inhibitory activity are of potential value in the therapy of diabetic complications.[1] We have previously reported the synthesis of a variety of spiro[imidazolidine-4,4'(1'H)-quinazoline]-2,2',5(3'H)-triones by the reactions of isatin derivatives with either urea or isothiourea, followed by acid treatment.[2,3] Of these, 3'-methylspiro[imidazolidine-4,4'(1'H)-quinazoline]-2,2',5-(3'H)-trione (1) showed strong AR inhibitory activity. It is known that AR has a highly stereospecific binding site for spirohydantoins;[4] recent investigations showed that the AR inhibitory activity resides essentially in one enantiomer.[5] We therefore focused our attention on a preparation of optically pure 1.

Optical resolution has been used as one of the convenient methods to obtain an optically active compound. If an undesired enantiomer could be racemized, a combination of optical resolution and racemization could become a more efficient synthetic method. In this paper, we report on the optical resolution of racemic compound 1 as well as the thermal or the acid-catalyzed racemization of the optically pure enantiomers (+)-1 and (−)-1. The mechanism of the acid-catalyzed racemization is also discussed.

Racemic compound 1 was synthesized by the reaction of 1-methylcarbamoylisatin with 2-ethyl-2-isothiourea hydrobromide, followed by heating with hydrochloric acid (HCl) as previously reported.[3c] The optical resolution of 1 was achieved using brucine, which was found to be the best resolving agent among several bases [e.g., quinine, (−)-cinchonidine, (+)-cinchonine, and (*R*)-(+)-α-methylbenzylamine] we examined. Thus, a crystalline complex of (+)-1 with brucine was obtained by treatment of 1 with brucine dihydrate in MeOH–H_2O (3:2). Subsequently, the complex was treated with 2% HCl to give optically pure enantiomer (+)-1 in 41% yield. Optically pure enantiomer (−)-1 was obtained from the filtrate containing a complex of (−)-rich 1 with brucine by a similar treatment in 40% yield. The absolute configuration of (+)-1 was determined as *R* based on the X-ray crystallographic analysis of the crystalline complex of (+)-1 with brucine (Figure 1). Testing of the enantiomers (+)-1 and (−)-1 for the AR inhibitory activity showed that the activity resides predominantly in (*R*)-(+)-1.[6]

Scheme I



We observed that (+)-1 melted at 174–176 °C and solidified at near 200 °C; this solid no longer melted at 280 °C. Since the melting point of racemic 1 is over 280 °C,[3] the elevation of the melting point suggested thermal racemization of (+)-1. In order to confirm racemization, (+)-1 was heated in 1,2-dichlorobenzene under reflux for 17 h. Indeed, (+)-1 was partially (~84%) racemized. Furthermore, we examined the racemization under several conditions. As a result, it was found that the rate of the racemization was dramatically accelerated by an addition of acid. The compound (+)-1 was completely racemized in 10% HCl under heating at 90 °C for 2 h, or in the

† Research Laboratory of Applied Biochemistry.
‡ Organic Chemistry Research Laboratory.

(1) (a) Kador, P. F.; Kinoshita, J. H.; Sharpless, N. E. *J. Med. Chem.* **1985**, *28*, 841. (b) Kador, P. F.; Robison, W. G.; Kinoshita, J. H. *Ann. Rev. Pharmacol. Toxicol.* **1985**, *25*, 691. (c) Masson, E. A.; Boulton, A. J. M. *Drugs* **1990**, *39*, 190.

(2) (a) Tani, J.; Yamada, Y.; Ochiai, T.; Ishida, R.; Inoue, I.; Oine, T. *Chem. Pharm. Bull.* **1979**, *27*, 2675. (b) Tani, J.; Yamada, Y.; Oine, T.; Ochiai, T.; Ishida, R.; Inoue, I. *J. Med. Chem.* **1979**, *22*, 95.

(3) (a) Yamagishi, M.; Ozaki, K.; Ohmizu, H.; Yamada, Y.; Suzuki, M. *Chem. Pharm. Bull.* **1990**, *38*, 2926. (b) Yamagishi, M.; Yamada, Y.; Ozaki, K.; Tani, J.; Suzuki, M. *Ibid.* **1991**, *39*, 626. (c) Yamagishi, M.; Ozaki, K.; Yamada, Y.; Da-te, T.; Okamura, K.; Suzuki, M. *Ibid.* **1991**, *39*, 1694.

(4) Sarges, R.; Bordner, J.; Dominy, B. W.; Peterson, M. J.; Whipple, E. B. *J. Med. Chem.* **1985**, *28*, 1716.

(5) (a) Sarges, R.; Schnur, R. C.; Belletire, J. L.; Peterson, M. J. *J. Med. Chem.*, **1988**, *31*, 230. (b) Sarges, R.; Goldstein, S. W.; Welch, W. M.; Swindell, A. C.; Siegel, T. W.; Beyer, T. A. *Ibid.* **1990**, *33*, 1859.

(6) The IC_{50}-values of (+)-1 and (−)-1 against rabbit lens aldose reductase were 3.1×10^{-7} and 3.4×10^{-6} M, respectively.

0022-3263/92/1957-1568$03.00/0

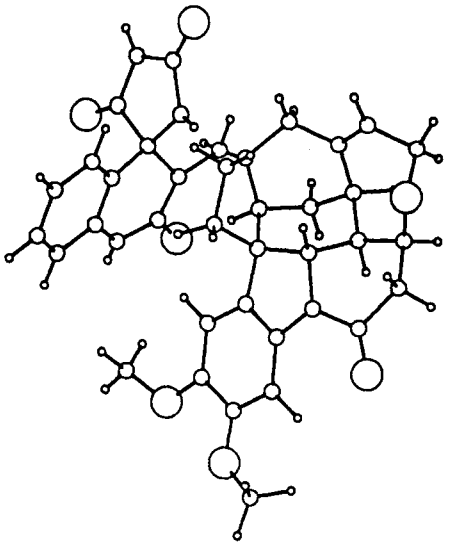


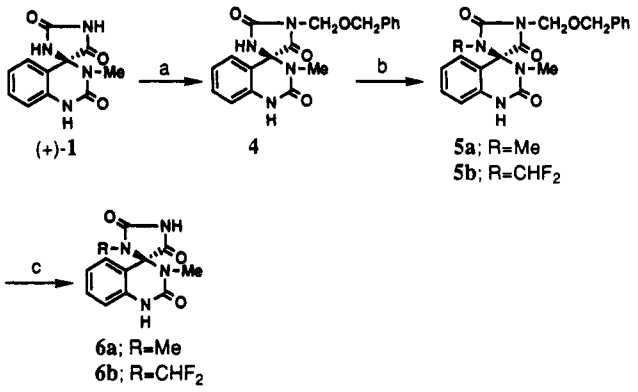
Figure 1. Perspective view of the complex of (+)-1 with brucine.

presence of boron trifluoride–etherate in acetonitrile under reflux for 3 h. Similarly, the enantiomer (−)-1 was also racemized under the same conditions. In contrast, the racemization did not occur under basic conditions. To our knowledge, this is the first example of the racemization of spirohydantoin derivatives under neutral or acidic conditions, although base-catalyzed racemization of some 5-monosubstituted hydantoins has been well-known.[7] For comparison, we examined racemization of an optically active spirohydantoin derivative (sorbinil), (4*S*)-6-fluoro-2,3-dihydrospiro[4*H*-1-benzopyran-4,4′-imidazolidine]-2′,5′-dione,[5b] in concentrated HCl under heating at 90 °C for 18 h and found that racemization of sorbinil did not occur at all. This result implies that the quinazoline skeleton plays an important role in the racemization of (+)-1. This unusual racemization let us to investigate the mechanism of the acid-catalyzed racemization of (+)-1 in further detail.

As possible mechanisms of the racemization of (+)-1 under acidic conditions, we considered two pathways involving the *N*-acyliminium ion **2** through route A and the *N*-acyliminium ion **3** through route B (Scheme I). In order to clarify the mechanism, we investigated the relationship between the rate of the racemization and the electron density of nitrogen atom at the 3-position. In the case of the route A, the decrease of the electron density of the 3-nitrogen should accelerate the rate of racemization whereas the increase of the electron density should retard this rate. In the case of the route B, the reverse effects may be expected. Therefore, the rate of the racemization for (+)-1 was compared with those of the optically pure compounds (**6a** and **6b**) substituted with a methyl group as an electron-donating group[8] and a difluoromethyl group as an electron-withdrawing group[9] on the 3-nitrogen.

Optically pure compounds **6a** and **6b** were prepared from (+)-1 as shown in Scheme II. After introduction of a (benzyloxy)methyl group to protect the nitrogen at the 1-position,[10] the nitrogen atom at the 3-position was alkylated with methyl iodide or chlorodifluoromethane,[11] followed by hydrogenolytic elimination of the protecting group to give **6a** and **6b**. The time courses of the racemization for (+)-1, **6a**, and **6b** were evaluated by treatment in 20% HCl–*N*,*N*-dimethylformamide (DMF) at 90 °C. As shown in Figure 2A, the racemization of (+)-1 (K_R = 3.19 h^{-1}) proceeded at a rate of about 10 times that of **6a** (K_R = 0.37 h^{-1}), whereas **6b** was racemized too fast to calculate the rate constant under this condition. At 50 °C (Figure 2B), the racemization of (+)-1 was very slow, whereas **6b** was readily racemized (K_R = 1.44 h^{-1}).

Scheme II[a]



[a] Key: (a) $ClCH_2OCH_2Ph$, NaH, DMF; (b) MeI (or CHF_2Cl), NaH, DMF; (c) H_2, Pd-black, MeOH.

The results show that the increase of the electron density of the 3-nitrogen (i.e., **6a**) reduced the racemization rate, while the decrease of the electron density of the 3-nitrogen (i.e., **6b**) increased it. These results suggest that the acid-catalyzed racemization of (+)- or (−)-1 proceeds via the *N*-acyliminium ion **2** (Scheme I, route A).[12]

This effective acid-catalyzed racemization suggests a potentially useful synthesis of (4*R*)-3′-methylspiro[imidazolidine-4,4′(1′*H*)-quinazoline]-2,2′,5(3′*H*)-trione ((+)-1), which is a potent AR inhibitor.

Experimental Section

Melting points (mp) were measured by the use of a Yamato MP-21 melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu IR-420 spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were determined on a Bruker AC-200 instrument (200 MHz) using tetramethylsilane as an internal standard. Mass spectra (MS) were taken on a Hitachi M-2000A double-focusing mass spectrometer at an ionizing potential of 70 eV. Specific rotations were measured with a Perkin-Elmer 243 automatic polarimeter using a 10-cm cell. All the data for X-ray structural analysis were collected with a Rigaku AFC/5 FOS four-circle diffractometer. Column chromatography was carried out with Kieselgel 60 (230–400 mesh, E. Merck), and analytical TLC was performed with precoated Kieselgel 60F_{254} plates (0.25-mm thickness, E. Merck).

Materials. (Benzyloxy)methyl chloride was prepared from benzyl alcohol and paraformaldehyde according to the reported method.[13]

(7) (a) Bovarnick, M.; Clarke, H. T. *J. Am. Chem. Soc.* **1938**, *60*, 2426. (b) Dudley, K. H.; Bius, D. L. *J. Heterocycl. Chem.* **1973**, *10*, 173. (c) Lazarus, R. A. *J. Org. Chem.* **1990**, *55*, 4755.

(8) (a) Ceppi, E.; Eckhardt, W.; Grob, C. A. *Tetrahedron Lett.* **1973**, 3627. (b) Brown, H. C. *J. Am. Chem. Soc.* **1945**, *67*, 378.

(9) (a) Bolton, P. D.; Hepler, L. G. *Q. Rev., Chem. Soc.* **1971**, *25*, 521. (b) Kurz, J. L.; Farrar, J. M. *J. Am. Chem. Soc.* **1969**, *91*, 6057.

(10) (a) Ware, E. *Chem. Rev.* **1950**, *46*, 403. (b) Orazi, O. O.; Corral, R. A. *Tetrahedron* **1961**, *15*, 93. (c) Orazi, O. O.; Corral, R. A.; Schuttenberg, H. *J. Chem. Soc., Perkin Trans. 1* **1974**, 219.

(11) The compound prepared from 1 with 2.0 equiv of methyl iodide in the presence of 2.0 equiv of NaH in DMF was identical with an authentic sample: 1,3,3′-trimethylspiro[imidazolidine-4,4′(1′*H*)-quinazoline]-2,2′,5(3′*H*)-trione (Capuano, L.; Benz, K. *Chem. Ber.* **1977**, *110*, 3849).[10c] Therefore, the second N-alkylation of 1 occurred at the 3-position.

(12) We previously reported that 3,4-dihydro-4-hydroxy-3-methyl-4-ureidocarbonyl-2(1*H*)-quinazolinone was converted into the spirohydantoin 1 upon heating with acid. We assumed that this acid-catalyzed cyclization also takes place via the *N*-acyliminium ion **2**.[3a]

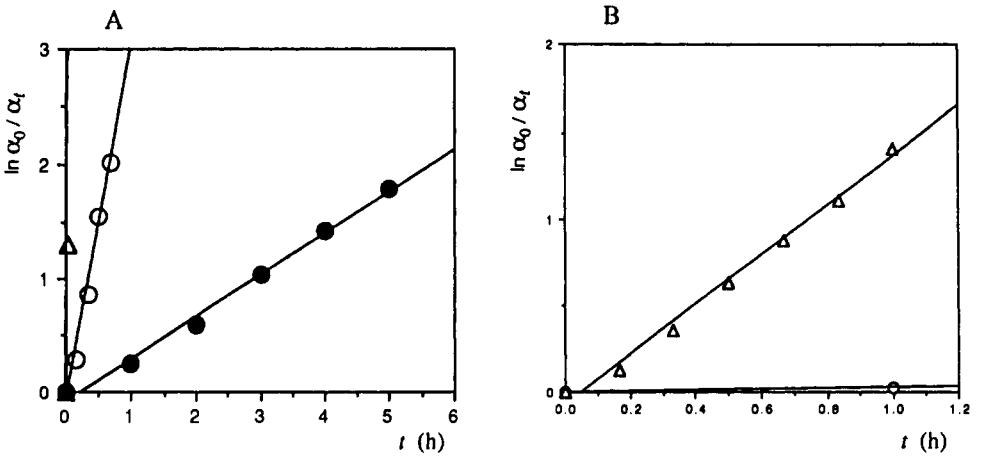


Figure 2. Time course of racemization of (+)-1, **6a**, and **6b**. A: treated in 20% HCl–DMF at 90 °C. B: treated in 20% HCl-DMF at 50 °C. Key: ○, (+)-1; ●, **6a**; △, **6b**; α_0, initial optical rotation; α_t, optical rotation at t (h).

Optical Resolution of 1 with Brucine. A mixture of 1 (12.3 g, 0.05 mmol) and brucine dihydrate (21.5 g, 0.05 mmol) was heated in MeOH–H_2O (3:2) solution (625 mL) until it became a clear solution and then allowed to cool slowly. The precipitates were collected, and the filtrate (A) was saved. The precipitates were recrystallized twice from MeOH–H_2O (3:2) to give the brucine adduct of 1 (14.7 g, 46%): mp 264–265 °C dec; $[\alpha]^{25}_D$ –67.0° (*c* 1, DMF). Anal. Calcd for $C_{34}H_{36}N_6O_7$: C, 63.74; H, 5.66; N, 13.12. Found: C, 63.73; H, 5.70; N, 13.09.

This complex was treated with 2% HCl (80 mL) for 1 h at room temperature. The resulting precipitates were collected and recrystallized from MeOH–H_2O (3:2) to give (+)-1 (5.0 g, 41% from racemic 1): mp 174–176 °C; $[\alpha]^{25}_D$ +34.7° (*c* 1, EtOH), $[\alpha]^{22}_D$ +42.2° (*c* 1, DMF); IR (Nujol) 1780, 1720, 1700, 1670 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.87 (3 H, s), 6.80–7.40 (4 H, m), 9.02 (1 H, s), 9.90 (1 H, s), 11.20 (1 H, br); MS *m/e* 246 (M^+). Anal. Calcd for $C_{11}H_{10}N_4O_3 \cdot {}^1/_2H_2O$: C, 51.76; H, 4.34; N, 21.95. Found: C, 51.54; H, 4.25; N, 21.49.

The original filtrate A was evaporated in vacuo, and the residue was treated with 2% HCl (80 mL) for 1 h at room temperature. The resulting solid (racemic 1, 1.7 g) was filtered off and the filtrate was evaporated in vacuo to 30–40 mL. The resulting crystals were collected and recrystallized from MeOH–H_2O (3:2) to give (–)-1 (4.9 g, 40% from racemic 3): mp 174–176 °C; $[\alpha]^{25}_D$ –34.7° (*c* 1, EtOH), $[\alpha]^{22}_D$ –42.0° (*c* 1, DMF); IR (Nujol) 1780, 1720, 1700, 1670 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.87 (3 H, s), 6.80–7.40 (4 H, m), 9.03 (1 H, s), 9.90 (1 H, s), 11.25 (1 H, br); MS *m/e* 246 (M^+). Anal. Calcd for $C_{11}H_{10}N_4O_3 \cdot {}^1/_2H_2O$: C, 51.76; H, 4.34; N, 21.95. Found: C, 51.68; H, 4.25; N, 21.59.

(4*R*)-1-[(Benzyloxy)methyl]-3′-methylspiro[imidazolidine-4,4′(1′*H*)-quinazoline]-2,2′,5(3′*H*)-trione (4). To a solution of (+)-1 (9.85 g, 39 mmol) in DMF (100 mL) was added in portions sodium hydride (NaH) (60% mineral oil dispersion) (1.56 g, 39 mmol). The mixture was stirred at room temperature for 30 min, (benzyloxy)methyl chloride (6.11 g, 39 mmol) was added, and stirring was continued for 1 h. After being poured into ice–water, the mixture was extracted with AcOEt. The organic layer was washed with H_2O, dried ($MgSO_4$), and evaporated in vacuo. The crude product was recrystallized from MeOH–H_2O to give 4 (11.46 g, 81%): mp 170–171 °C; $[\alpha]^{20}_D$ +13.8° (*c* 1, MeOH); IR (Nujol) 1795, 1730, 1675 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.73 (3 H, s), 4.60 (2 H, s), 5.01 (2 H, s), 6.88–7.00 (3 H, m), 7.27–7.41 (6 H, m), 9.56 (1 H, s), 10.05 (1 H, s); MS *m/e* 366 (M^+). Anal. Calcd for $C_{19}H_{18}N_4O_4$: C, 62.29; H, 4.95; N, 15.29. Found: C, 62.10; H, 4.92; N, 15.19.

(4*R*)-3,3′-Dimethylspiro[imidazolidine-4,4′(1′*H*)-quinazoline]-2,2′,5(3′*H*)-trione (6a). To a solution of 4 (1.1 g, 3 mmol) in DMF (20 mL) was added in portions NaH (60% mineral oil dispersion) (0.12 g, 3 mmol). The mixture was stirred at room temperature for 30 min, methyl iodide (0.19 ml, 3 mmol) was added, and stirring was continued for 1 h. After being poured into ice–water, the mixture was extracted with $CHCl_3$. The organic layer was washed with H_2O, dried ($MgSO_4$), and evaporated in vacuo to give crude (4*R*)-1-[(benzyloxy)methyl]-3,3′-dimethylspiro[imidazolidine-4,4′(1′*H*)-quinazoline]-2,2′,5(3′*H*)-trione (**5a**) (1.14 g, quant) as a colorless syrup: IR (neat) 1788, 1733, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.74 (3 H, s), 2.87 (3 H, s), 4.71 (2 H, s), 5.16 (2 H, s), 6.80–7.01 (3 H, m), 7.28–7.39 (6 H, m), 9.10 (1 H, s); MS *m/e* 380 (M^+). Pd black (0.1 g) was added to a solution of **5a** (1.14 g, 3 mmol) in EtOH (20 mL), and the mixture was subjected to hydrogenolysis on a Parr apparatus for 15 h at a H_2 pressure of 45 psi. The catalyst was filtered off, and the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH (98:2)) to give **6a** (0.70 g, 90%): mp 243–244 °C (isopropyl alcohol); $[\alpha]^{25}_D$ +48.0° (*c* 1, DMF); IR (Nujol) 1782, 1736, 1673 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.54 (3 H, s), 2.72 (3 H, s), 6.90–7.05 (3 H, m), 7.30–7.38 (1 H, m), 10.05 (1 H, s), 11.58 (1 H, br); MS *m/e* 260 (M^+). Anal. Calcd for $C_{12}H_{12}N_4O_3$: C; 55.38; H, 4.65; N, 21.53. Found: C, 55.31; H, 4.60; N, 21.33.

(4*R*)-3-(Difluoromethyl)-3′-methylspiro[imidazolidine-4,4′(1′*H*)-quinazoline]-2,2′,5(3′*H*)-trione (6b). To a solution of 4 (2.0 g, 5.5 mmol) in DMF (20 mL) was added in portions NaH (60% mineral oil dispersion) (0.22 g, 5.5 mmol). The mixture was stirred at room temperature for 30 min, DMF (20 mL) solution containing a large excess of chlorodifluoromethane was added, and stirring was continued for 15 h at 50 °C in a sealed tube. After being cooled, the resulting mixture was poured into water, and then the mixture was extracted with AcOEt. The organic layer was washed with water, dried ($MgSO_4$), and evaporated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$–AcOEt (9:1)) to give (4*R*)-1-[(benzyloxy)methyl]-3-(difluoromethyl)-3′-methylspiro[imidazolidine-4,4′(1′*H*)-quinazoline]-2,2′,5(3′*H*)-trione (**5b**) (1.93 g, 85%) as a colorless syrup: IR (neat) 1805, 1743, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.91 (3 H, s), 4.75 (2 H, s), 5.22 (2 H, s), 6.86–6.98 (3 H, m), 7.02 (1 H, t, J = 58.8 Hz), 7.30–7.40 (1 H, m), 9.03 (1 H, br); MS *m/e* 416 (M^+). Pd black (0.18 g) was added to a solution of **5b** (1.80 g, 4.3 mmol) in EtOH (20 mL), and the mixture was subjected to hydrogenolysis on a Parr apparatus for 15 h at a H_2 pressure of 45 psi. Workup as described for **6a** gave **6b** (1.2 g, 94%): mp 217–218 °C dec (MeOH–H_2O); $[\alpha]^{26}_D$ +14.3° (*c* 1, DMF); IR (KBr) 1807, 1742, 1671 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.78 (3 H, s), 6.89–7.14 (3 H, m), 7.28 (1 H, t, J = 58.4 Hz), 7.34 (1 H, m), 10.22 (1 H, s), 12.48 (1 H, br); MS *m/e* 296 (M^+). Anal. Calcd for $C_{12}H_{10}N_4O_3F_2$: C, 48.65; H, 3.40; N, 18.91; F, 12.83. Found: C, 48.57; H, 3.34; N, 18.87; F, 12.75.

Racemization of (+)-1. (a) By heating. A suspension of (+)-1 (0.50 g, 2 mmol) in 1,2-dichlorobenzene (5 mL) was refluxed for 17 h. After the suspension was cooled, the resulting precipitates were collected, washed with diethyl ether, and dried to give partially racemized 1 (0.49 g, 98%): mp > 280 °C; $[\alpha]^{22}_D$ +6.6° (*c* 1, DMF).

(13) Connor, D. S.; Klein, G. W.; Taylar, G. N.; Boeckman, R. K.; Medwid, J. B. *Organic Syntheses*; Noland, W. E., Ed.; Wiley: New York, 1988; Collect. Vol. VI, p 101.

(b) With 10% HCl. A suspension of (+)-1 (1.00 g, 4 mmol) in 10% HCl (10 mL) was heated at 90 °C for 2 h. After the suspension was cooled, the resulting precipitates were collected, washed with H_2O, and dried to give racemic 1 (0.97 g, 97%): mp > 280 °C; $[\alpha]^{22}_D$ +0.0° (c 1, DMF).

Racemization of (-)-1. Racemization of (-)-1 (1.00 g, 4 mmol) was carried out according to method b described for the racemization of (+)-1 to give racemic 1 (0.95 g, 95%): mp > 280 °C; $[\alpha]^{22}_D$ -0.1° (c 1, DMF).

Racemization of 6a. Racemization of **6a** (1.00 g, 3.8 mmol) was carried out according to method b described for the racemization of (+)-1 to give racemic **6a** (0.91 g, 91%): mp > 280 °C; $[\alpha]^{22}_D$ +0.1° (c 1, DMF).

Racemization of 6b. Racemization of **6b** (1.00 g, 3.4 mmol) was carried out in 10% HCl (10 mL) at 90 °C for 15 min to give racemic **6b** (0.90 g, 90%): mp 249-250 °C dec; $[\alpha]^{26}_D$ 0.0° (c 1, DMF).

Rate Constants for Racemization of (+)-1, 6a, and 6b. A solution of (+)-1, **6a**, or **6b** (20 mg) in 20% HCl (1.5 mL)-DMF (0.5 mL) was stirred at 90 °C (or 50 °C) in a sealed tube. After the solution was cooled, the optical rotation (α_t) of the resulting compound was measured. These racemizations can be regarded as first-order reactions because linear relationships are found between ln α_0/α_t and time t, as shown in Figure 2. The rate constant of racemization (k_R/h) was calculated by the least-squares method based on eq 1, where α_0 is the initial value of the optical rotation and α_t is a value of the optical rotation at time t h.

$$\ln \alpha_0/\alpha_t = k_R t \quad (1)$$

Crystallography. The diffraction experiment for the complex of (+)-1 with brucine was carried out using a colorless transparent prism with dimensions of 0.70 × 0.30 × 0.10 mm^3 obtained from ethanol-water. The four-circle diffractometer (AFC/5, RIGAKU) was used with graphite-monochromated CuKα radiation (λ = 1.5418 Å). The unit cell dimensions were determined from angular setting of 20 reflections (2θ values in the range of 40-60°). The structure was solved by the direct methods using SIR85[14] and difference Fourier method. The refinement of atomic parameters was carried out using full-matrix least-squares methods with anisotropic temperature factors for the non-hydrogen atoms. Of 36 hydrogen atoms, 23 atoms were located on the difference Fourier maps and refined with isotropic temperature factors. The positions of other hydrogen atoms were assumed geometrically and fixed throughout the refinement. The anomalous scattering factors of N and O atoms were included in the refinement. Throughout the refinement, the function $\sum w(|Fo| - |Fc|)^2$ was minimized. During the final refinement stage, the weighting scheme of $\sqrt{w} = 1/\sigma|Fo|$ was used. The final R value was 0.052 (Rw = 0.061). The atomic scattering factors were taken from *International Tables for X-ray Crystallography*.[15]

Acknowledgment. We are grateful to Dr. I. Chibata, President, and Dr. S. Saito, Research and Development Executive, for their encouragement and interest. Thanks are due to Drs. T. Tosa, M. Takeda, S. Oshiro, I. Inoue, T. Oine, and R. Yoshioka for their valuable comments during this study.

Supplementary Material Available: Crystal data parameters, final atomic coordinates, anisotropic thermal parameters, bond lengths, and bond angles for the complex of (+)-**3** with brucine (21 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(14) SIR85: A computer program for automatic analysis of phase problems: Giaccovazzo, C.; Cascarano, G. L.; Polidori, G.; Spagna, R.; Viterbo, D. *Acta Crystallogr., Sect. A* **1982**, *38*, 663; *Ibid.* **1987**, *43*, 22.

(15) Ibers, J. A., Hamilton, W. C., Eds. *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, England, 1974; Vol. IV.

Formation of 3-[1'-(Dimethylphenylsilyl)ethyl]azetidin-2-ones: Stereocontrolled Formal Approach to (±)-Thienamycin and (±)-β-(Hydroxyalkyl)aspartic Acid Derivatives

Claudio Palomo,* Jesus M. Aizpurua, Raquel Urchegui, and Miren Iturburu

Departamento de Química Orgánica, Facultad de Química, Universidad del País Vasco, Apartado 1072, 20080-San Sebastián, Spain

Received August 7, 1991

Reaction between (±)-β-(dimethylphenylsilyl)alkanoyl chlorides and imines of glyoxylic esters provided a route to (±)-*cis*-3-[1'-(dimethylphenylsilyl)ethyl]-4-alkoxycarbonyl β-lactams, while addition of the Fleming's silylcuprate reagent to methyl crotonate and further enolate trapping by the above imines furnished the corresponding (±)-*trans*-3-[1'-(dimethylphenylsilyl)ethyl]-4-alkoxycarbonyl β-lactams. These β-lactams, upon appropriate chemical manipulations, provided a stereocontrolled route to (±)-thienamycin precursors and (±)-β-(hydroxyalkyl)aspartic acid derivatives.

Appropriately substituted monocyclic azetidin-2-ones have wide applicability in the synthesis of β-lactam antibiotics[1] and also in the preparation of many natural products including both α- and β-amino acids.[2] One example is the β-lactam 1 derived from aspartic acid,[3] which upon chemical manipulations affords suitable intermediates for natural product synthesis,[4] including a variety of

(1) For some reviews on β-lactams antibiotics, see: (a) *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic: New York, 1982; Vol. 1-3. (b) *Recent Advances in The Chemistry of β-Lactam Antibiotics*; Brown, A. G., Roberts, S. M., Eds.; The Royal Society of Chemistry: Bourlington House, London, 1984.

(2) For a recent review, see: Manhas, M. S.; Wagle, D. R.; Chiang, J.; Bose, A. K. *Heterocycles* **1988**, *27*, 1755.

(3) Zervas, L.; Winitz, M.; Greenstein, J. P. *J. Org. Chem.* **1957**, *22*, 1515.

(4) (a) Coppola, G. M.; Schuster, H. F. in *Asymmetric Synthesis*; John Wiley: New York, 1987; p 204. For some recent examples, see: (b) Baldwin, J. E.; Adlington, R. M.; Collins, D. W.; Schofield, C. J. *J. Chem. Soc., Chem. Commun.* **1990**, 720; *Tetrahedron* **1990**, *46*, 4733. (c) Thomas, E. J.; Williams, A. C. *J. Chem. Soc., Chem. Commun.* **1987**, 992. (d) Roe, J. M.; Thomas, E. J. *Synlett* **1990**, 727.

0022-3263/92/1957-1571$03.00/0