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STEREOSPECIFIC SYNTHESIS OF OPTICALLY ACTIVE 2-PHENYLSULFONYL-3-(1-HYDROXYETHYL)-4-AZETIDINONE: A PRECURSOR OF THIENAMYCIN-TYPE CARBAPENEMS

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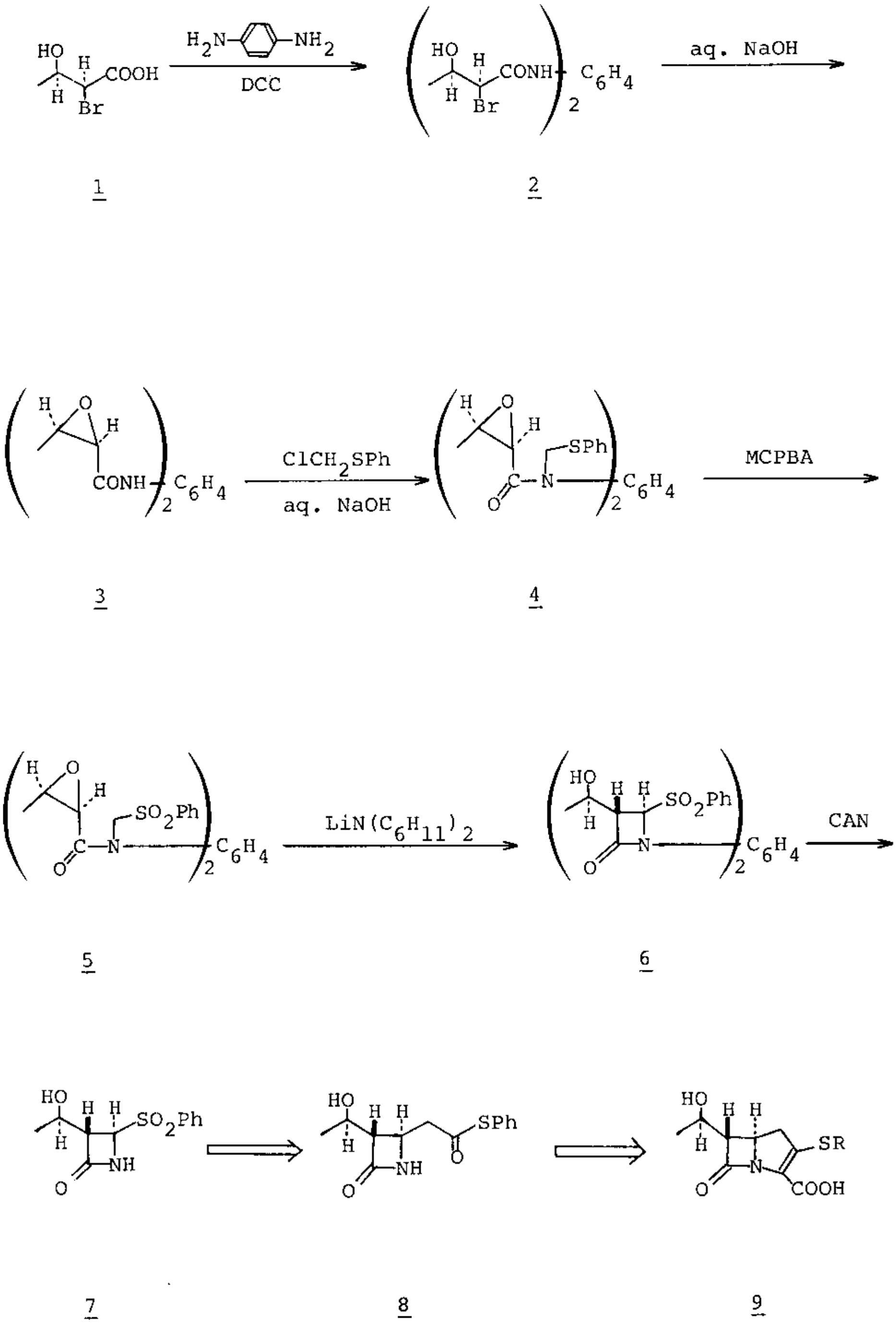
Abstract - Stereospecific synthesis of optically active (2R,3S)-2-phenylsulfonyl-3-(1R-hydroxyethyl)-4-azetidinone from L-threonine is described. This compound is one of the key compounds for the synthesis of the thienamycin-type carbapenems.

The emerging importance of carbapenems has resulted in recent syntheses using a variety of different strategies, usually involving a method through an intermediate such as the optically active 3-(1-hydroxyethyl)-2-phenylsulfonyl-4-azetidinone. This compound is a key intermediate for the synthesis of the thienamycin-type carbapenem,[1] and has already been synthesized from L-threonine[2] and from various naturally occurring sources via the 4-acetoxy derivatives.[3] Recently, we have been working toward devising a more suitable and economical method for the industrial production of this compound which would overcome such problems as price of reagents and starting material, number of steps involved, overall yield, period of production, effluent treatment and so on. In this paper, we wish to report an economical synthesis of 2-phenyl-3-(1-hydroxyethyl)-4-azetidinone (7).

Treatment of p-phenylenediamine with 2 equivalents of (2S,3R)-2-bromo-3-hydroxybutyric acid (1),[3a] obtained from L-threonine, by use of dicyclohexylcarbodiimide (DCC) as a condensing reagent in tetrahydrofuran (THF) gave

Scheme 1.



(2S,3R)-1,4-bis[(2-bromo-3-hydroxybutyryl)amino]benzene (2) in 72% yield as a crystalline solid, mp 183-185°C. Epoxidation of compound (2) in CH_2Cl_2 with 50% aqueous NaOH solution by use of triethylbenzylammonium iodide as a phase-transfer catalyst gave an epoxide (3) as a crystalline solid, mp 201-205°C, in 83% yield. Reaction of 3 with 3 equivalents each of chloromethylphenylsulfide and 50% aqueous NaOH in the presence of catalytic amount of triethylbenzylammonium iodide at 20°C with vigorous stirring gave a bisphenythiomethylated compound (4) as a viscous oil in 88% yield. Oxidation of this sulfide (4) with *m*-chloroperbenzoic acid in CH_2Cl_2 gave a sulfone (5) as a powder in 94% yield. Cyclization of 5 with 4 equivalents of lithium dicyclohexylamide in THF-hexamethylphosphortriamide (HMPTA) (4:1) at -78°C gave a bis(β-lactam) compound (6, *trans-trans*) as a crystalline solid in 83% yield. In this reaction, there was no isolation of either *trans-cis* nor *cis-cis* isomers. The only isolated β-lactam compound was the *trans-trans* isomer (6), as to the substituents of 2-phenylsulfonyl and 3-(1-hydroxyethyl) groups at the C-2 and C-3 positions. Deprotection of nitrogen was carried out as follows. Treatment of a suspension of 5 in acetonitrile-water (2:1) with 13 equivalents of ammonium cerium(IV) nitrite (CAN) at room temperature for 2 days gave a sulfone (7) as a powder in 77% yield. This sulfone (7) had already been converted to phenythioester (8)[1] which was a key intermediate for the syntheses of thienamycin-type carbapenems (9). Thus, we achieved the synthesis of an important precursor to thienamycin-type carbapenems from L-threonine in good overall yield.

EXPERIMENTAL

All melting points are uncorrected. Optical rotation was obtained using a Perkin-Elmer 241 Polarimeter. ^{1}H NMR spectra were determined at 60 MHz with a Varian T-60 spectrometer using tetramethylsilane as an internal standard. The infrared absorption spectra were determined on a Jasco IR A-2 spectrophotometer, and mass spectra were obtained on a JMS-01SG mass spectrometer. Elemental analyses were performed by the Analytical Centre of Analytical and Metabolic Research Laboratories, Sankyo Co., Ltd.

(2S,3R)-1,4-Bis[(2-bromo-3-hydroxybutyryl)amino]benzene (2)

To a solution of *p*-phenylenediamine (14.7 g, 136 mmol) in THF (220 ml) was added a solution of (2S,3R)-2-bromo-3-hydroxybutyric acid (1, 50 g, 273 mmol) in THF (150 ml) at ice-cooling temperature with stirring. To this resulted mixture was added crystalline dicyclohexylcarbodiimide (56.3 g, 273 mmol). After stirring at 5°C for 1 h, the mixture was stirred overnight at room temperature. The precipitated DCC-H_2O urea was filtered by suction. The filter cake was washed with a small amount of THF. The combined organic layer was diluted with EtOAc (1500 ml). The organic layer was washed two times with 10% HCl (300 ml), and sat. $NaHCO_3$ aq, and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give 43 g of 2 (72% yield) as a crystalline solid which was employed for the next reaction without purification. An analytical sample was recrystallized from EtOAc-acetone. mp 183-185°C. ^1H NMR (acetone-d_6) δ 1.25 (6H, d, J=6 Hz), 4.12 (2H, quintuplet, J=6 Hz), 4.39 (2H, d, J=6 Hz), 4.57 (2H, broad, O*H*), 7.55 (4H, s), 9.53 (2H, bs, N*H*). IR ν_{max}(Nujol) 3260, 1668, 1612 cm^{-1}. Anal. Calcd. for $C_{14}H_{18}O_4N_2$: C, 38.37; H, 4.11; N, 6.40; Br, 36.48%. Found: C, 38.41; H, 4.18; N, 6.37; Br, 36.41%.

(2R,3R)-1,4-Bis[(2,3-epoxybutyryl)amino]benzene (3)

To a suspension of 2 (34 g, 77.6 mmol) and triethylbenzylammonium iodide (4 g) in CH_2Cl_2 (160 ml) was added gradually 50% NaOH (12.2 ml, 233 mmol, 3 equivalents) at room temperature with vigorous stirring. After stirring for 1.5 h, the reaction mixture was diluted with CH_2Cl_2 (1000 ml), washed with water, dried over $MgSO_4$, and concentrated *in vacuo* to give a crystalline solid. The solid was suspended in CH_2Cl_2 (100 ml), and then to this suspension was added *n*-hexane (1000 ml) with vigorous stirring to precipitate 17.7 g of 3 (82.4 % yield) as a crystalline solid; mp 201-205°C (from $CHCl_3$-EtOAc), which was employed for the next reaction without further purification. ^1H NMR ($CDCl_3$) δ 1.37 (6H, d, J=5 Hz), 3.35 (2H, quintuplet, J=5 Hz), 3.60 (2H, d, J=5 Hz), 7.55 (4H, s), 7.98 (2H, bs, N*H*). IR ν_{max}(KBr) 3330, 1690, 1552, 1512 cm^{-1}. Anal. Calcd. for $C_{14}H_{16}O_4N_2$: C, 60.86; H, 5.84; N, 10.14%. Found: C, 61.04; H, 5.76; N, 9.95%.

(2R,3R)-1,4-Bis[(N-phenylthiomethy-N-2,3-epoxybutyryl)amino]benzene (4)

To a suspension of 3 (5.52 g, 20 mmol), chloromethylphenylsulfide (9.5 g, 60 mmol), and triethylbenzylammonium iodide (1 g) in CH_2Cl_2 (20 ml) was added 50% NaOH (3.14 ml, 60 mmol) at 20°C with vigorous stirring. After stirring for 1 h, the reaction mixture was diluted with CH_2Cl_2 (700 ml), washed with water, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily mixture. This mixture was diluted with $CHCl_3$ (40 ml), deposited with *n*-hexane (600 ml) and decanted to obtain an oily material. This treatment was repeated once more to give 9.2 g of 4

(88% yield) as a viscous oil which was employed for the next reaction without further purification. ^{1}H NMR ($CDCl_3$) δ 1.20 (6H, d, J=5 Hz), 2.7-3.1 (4H, m), 4.88, 5.52 (4H, AB-q, J=14 Hz), 7.0-7.4 (14H, m). IR ν_{max}($CHCl_3$) 1675, 1508 cm^{-1}. MS m/z 520 (M^+), 411, 327. Anal. Calcd. for $C_{28}H_{28}O_4N_2S_2$: C, 64.55; H, 5.38; N, 5.38; S, 12.32%. Found: C, 64.22; H, 5.58; N, 5.10; S, 12.01%.

(2R,3R)-1,4-Bis[(N-phenylsulfonylmethyl-N-2,3-epoxybutyryl)amino]benzene (5)

To a solution of 4 (9.3 g, 8.26 mmol) in CH_2Cl_2 (140 ml) was added m-chloroperbenzoic acid (16.4 g) at ice cooling temperature with stirring. After stirring at room temperature for 30 min, the reaction mixture was diluted with EtOAc (800 ml), the resulting solution was washed several times with aq. 20% Na_2SO_3 to remove m-chloroperbenzoic acid and m-chlorobenzoic acid and brine, dried over $MgSO_4$, and concentrated in vacuo to give an oily residue. This residue was re-dissolved in EtOAc (50 ml) and large excess n-hexane was added gradually with vigorous stirring to deposit a viscous oil. Separation with decantation, and drying in vacuo to give 5 (9.73 g, 93.6%) as a powder which was employed for the next reaction without purification. ^{1}H NMR ($CDCl_3$) δ 1.23 (6H, d, J=5 Hz), 2.85-3.25 (4H, m), 4.97 (a little broad) and 5.48 (4H, AB-q, J=14 Hz), 7.5-8.1 (14H, m). IR ν_{max}($CHCl_3$) 1692, 1510 cm^{-1}. MS m/z 443(M^+-$PhSO_2$), 218, 162.

(2R,3S)-1,4-Bis[2-phenylsulfonyl-3-(1R-hydroxyethyl)-4-azetidinon-1-yl]benzene (6)

To a stirred and cooled (-78°C) solution of 5 (9.53 g, 16.3 mmol) in THF-HMPT (4:1, 150 ml) was added under nitrogen a solution of dicyclohexylamine Li salt which was prepared from addition of n-butyl lithium (1.6 M n-hexane solution, 41 ml) to a solution of dicyclohexylamine (11.8 g, 65.1 mmol, 4 equivalents) in THF (60 ml). After stirring at -78°C for 30 min, the reaction mixture was quenched with AcOH-THF (1:9, 30 ml), and diluted with EtOAc (800 ml), and the solution was washed with aq. 10% HCl, water, sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo to give 6 (7.91 g, 83% yield) as a pale yellow crystalline solid which was employed for the next reaction without purification. An analytical sample was recrystallized from acetone. mp 270-272°C (decomp). ^{1}H NMR (DMF-d_7) δ 1.00 (6H, d, J=6 Hz), 3.58 (2H, dd, J=2, 3 Hz, C_3-H), 4.10 (2H, m), 5.25 (2H, d, J=5 Hz, OH), 5.89 (2H, d, J=2 Hz, C_4-H), 7.45 (4H, s), 7.5-8.2 (10H, m). IR ν_{max}(KBr) 3525, 1770, 1520 cm^{-1}. Anal. Calcd. for $C_{28}H_{28}N_2O_8S_2$: C, 57.49; H, 4.79; N, 4.79; S, 10.97%. Found: C, 57.31; H, 4.97; N, 4.91; S, 10.46%.

(2R,3S)-2-Phenylsulfonyl-3-(1R-hydroxyethyl)-4-azetidinone (7)

To a suspension of 6 (585 mg, 1 mmol) in CH_3CN (40 ml) was added a solution of ammonium cerium(IV) nitrate (7.4 g) in water (20 ml) at room temperature. The suspension turned gradually to a clean solution. After stirring at room temperature for 44 h, the reaction mixture was diluted with EtOAc, washed with water, sat $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated *in vacuo* to give a crystalline solid. The solid was suspended in EtOAc (50 ml) and deposited with excess *n*-hexane to give 7 (392 mg, 77% yield) as a powder. An analytical sample was recrystallized from EtOAc. mp 146-148°C. $[\alpha]_D^{24}$ +7.8° (c=5.0, MeOH). ^1H NMR ($DMF-d_7$) δ 1.10 (3H, d, J=6 Hz), 3.44 (1H, dd, J=2, 4 Hz), 4.10 (1H, m), 4.96 (1H, d, J=2 Hz), 7.5-8.1 (5H, m), 8.95 (1H, bs, NH). IR ν_{max}(Nujol) 3360, 1773 cm^{-1}. Anal. Calcd. for $C_{11}H_{13}NO_4S$: C, 51.76; H, 5.13; N, 5.49; S, 12.62%. Found: C, 51.62; H, 5.20; N, 5.41; S, 12.47%.

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