Synthesis of Chiral Aspyrone, A Multi-functional Dihydropyranone Antibiotic

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Aspyrone (1) was elaborated in an optically pure form by a key reaction involving the highly diastereoselective addition of tetrahydropyranone enolate to 2-tosloxy-aldehyde and the subsequent in situ formation of an epoxide.

Synthetic work on biologically active 5-oxygenated dihydropyranones osmundalactone (2),1) phoma lactone (3),2)3 acetylpoma lactone (4),4) asperlin (5),5)6 and their isomers directed our interest toward the chiral synthesis of more complex congeners aspyrone (1). This substance was isolated as one of the antibiotics from a culture broth of the Aspergillus species,7–10) and had a characteristic structural feature arising from the skeletal rearrangement on its biosynthetic pathway of polyketide11–13) (Fig. 1). Its absolute stereochemistry was determined as being of (SS,6R,1'S,2'S)-form by X-ray crystallographic and degradative works.14)15) In a previous paper,16) we have briefly reported the first total synthesis of optically active aspyrone (1) from readily available carbohydrate precursors. In this paper, we described details of the total synthesis of aspyrone (1).

As 1 has an α,β-unsaturated-δ-lactone structure with a 1',2'-epoxypropyl moiety at the α-position of the lactone, it was difficult to introduce the leaving group for the double bond after forming the epoxide ring. The leaving group should have been present before constructing the epoxide function. Since the epoxypropyl moiety had the stereochemistry of 1'S,2'S as already described, it was preferable to construct the epoxide ring by the cyclization method, rather than to epoxidize an olefinic intermediate. As illustrated in Scheme 1, we anticipated the tandem nucleophilic addition of an enolate to 2-tosloxy-propanal and subsequent ring closure to an epoxide as the key step for building up the target skeleton. The most desirable intermediates would thus be (R)-1-formylethyl p-toluenesulfo nate (10) and (SS,6R)-5-t-butyldimethylsiloxy-6-methyl-3-pheny selenotetrahydro-2H-pyran-2-one (16). If the enolate of 16 attacks the Si face of aldehyde 10, the epoxide would have the (1'S,2'S)-configuration (trans-epoxide), and the product would be, on the contrary, (1'R,2'S)-epoxide (cis-epoxide) in the case of attack on the Re face of the carbonyl group. It was uncertain, at the initial stage, to predict whether the reaction product would be a mixture of diastereomers or not.

As shown in Scheme 2, 10 was derived from 3,4-O-isopropylidene-δ-mannitol (6).14) Tosylation of the terminal hydroxy groups and subsequent reduction with lithium aluminum hydride gave 7, which was re-esterified to 8 with tosyl chloride and triethylamine. Deprotection of 8 with aqueous trifluoroacetic acid and oxidation of the resultant diol 9 with sodium metaperiodate gave unstable 10, which changed easily to a hydrate form while standing in the air. For the other chiral segment 16, δ-hamnial diacetate (11)15) was chosen as a readily available precursor. A Fieser reaction16) on 11 gave an anomic mixture of 2,3-unsaturated glycose (12; α/β = 8/1), which was saponified and re-protected as t-butyldimethylsilyl (TBS) ether (13). Successive hydrogenation and debenzylation of 13, and subsequent oxidation of 14 with pyridinium dichromate17) afforded tetrahydropyranone (15). Phenylselenylation of 15 gave diastereomeric mixture 16. At the convergent step, 16 was successively treated with lithium hexamethyldisilazide and then with 10 at −78°C, with subsequent cyclization of

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the epoxide ring. The crude reaction product was oxidized with hydrogen peroxide and shaken with sodium hydrogen carbonate to yield 5-protected aspyrone (17) having the desired trans-epoxide in a 61% yield in 3 steps. Deprotection of 17 with the fluoride anion provided pure aspyrone (1). Its spectroscopic and physicochemical properties were identical with those of the natural compound. The mother liquor of 17 was carefully examined to check for the presence of the stereoisomer of 17. Thus, the foregoing sample was concentrated to give less than 0.4% of a mixture of 17 and its isomer, which was converted to a mixture of acetates 18 and 19 to avoid any overlapping of the NMR signals. Its 1H-NMR spectrum revealed the presence of less than 0.2% of an isomeric cis-epoxide. The stereochemistry of the epoxide moiety was determined by comparing the coupling constants of protons on the epoxide ring, i.e., 2.0 Hz for the trans-epoxide and 4.2 Hz for the cis-epoxide. In both compounds, the dihedral angle between 4-H and 5-H was estimated to be nearly 90° as indicated by their coupling constants (3.3 Hz for 18 and 3.8 Hz for 19) and Dredging model. On the other hand, the dihedral angle between 1'-H and 4-H was presumed to be 50–70°, or 290–310° from the allyllic coupling constants. Moreover, the signal for 2'-H of 18 was shifted to a higher field than that of 19, with 3'-H of 19 also being shifted to a higher field. These results indicated that 2'-H of 18 and 3'-H of 19 were presumably located in the shielding sphere caused by magnetic anisotropy of the pyranone carbonyl group as depicted in Fig. 2. The observation of homohylic spin coupling (20) with respect to 1'-H of both isomers is consistent with the foregoing conformational assessment. The stereochemical orientation of 18 may be applicable to aspyrone (1), because the chemical shifts and coupling patterns of the epoxide and olefinic protons were similar between them. In the epoxide-forming step, the ratio of 62:0.15 would reflect the result of face-selection in the nucleophilic attack by the enolate anion, as the cyclization reaction was rapid and the configurational difference in possible reaction intermediates would spuriously affect the cyclization rate. Therefore, it is suggested that the enolate might attack the aldehyde carbonyl exclusively at the Si face. Rationalization of such face-selectivity against 2-tosyloxyaldehyde is now under investigation, and the results will be published in due course.

Experimental
Boiling point (bp) and melting point (mp) data are uncorrected.
1H-NMR spectra were recorded on a JEOL JNM FX-100, GSX-270, and GSX-400 spectrometers, and IR spectra on a JASCO IR-810 infrared spectrometer. Optical rotation was measured with a JASCO DIP-4 polarimeter, and mass spectra were recorded on a JEOL JMS D-303HF spectrometer. Unless otherwise stated, 3-nitrobenzyl alcohol was used as the matrix for FAB-MS analyses. The 1H-NMR data for compounds 12 to 14 refer to those of the major z-isomers.

1,6-Dideoxy-3,4-O-isopropylidene-a-mannitol (7). To a solution of 6 (6.0 g, 27 mmol) in 75 ml of dry pyridine was added portionwise 11.4 g of p-nitro-phenylsulfonyl chloride (59.8 mmol), and the resultant reaction mixture was stirred for 2 h in an ice-cooling bath and then kept standing overnight in a refrigerator. The reaction mixture was diluted with water and extracted with ether. The extract was successively washed with water, cold dil. H2SO4, and aq. NaHCO3, and dried over anhyd. MgSO4. Evaporation of the solvent gave a crystalline dithioate (quant.), melting at 114–115°C (fine needles from benzene). Anal. Found: C, 51.83; H, 5.65; S, 12.38%. Calcul. for C22H22O11S2: C, 52.06; H, 5.70; S, 12.09%. [β]D + 58.0° (c = 2.5, CHCl3). FAB-MS m/z: 553 (M + Na)+, 575 (M + H + Na)+, 535 (M + H + H2O). 1H-NMR (CDCl3): δ: 1.27 (6H, s, CH3C), 2.45 (6H, s, Ar-Me x 2), 3.21 (2H, -OH x 2), 3.7–3.9 (4H, m, 2-H - 5-H), 4.08 (2H, dd, J = 10.5, 5.5 Hz, 1-H + 6-H), 4.32 (2H, dd, J = 10.5, 2.0 Hz, 1-H + 6-H), 7.36 (4H, d, J = 6.2 Hz, Ar-H x 2), 7.81 (4H, d, J = 8.2 Hz, Ar-H x 2). IR νmax cm⁻¹: 3080 (C=C), 3020 (CH), 1740 (C=O), 1470 (CH2). 13C-NMR (CDCl3): δ: 130.8 (CH), 124, 117.6, 1108, 1072, 961. 1H-NMR (CDCl3): δ: 1.32 (6H, d, J = 6.0 Hz, 1-H + 6-H), 1.38 (6H, s, CH3C), 3.5-3.9 (6H, 2-H - 5-H).

1,6-Dideoxy-3,4-O-isopropylidene-a-mannitol 2,5-di-p-toluenesulphonate (8). A mixture of foregoing diol 7 (1.6 g, 8.4 mmol), p-toluenesulfonyl chloride (5.0 g, 21 mmol) and triethylamine (2.0 g, 19.8 mmol) in 12 ml of dry pyridine was kept standing overnight at 0°C. The reaction mixture was then diluted with water and extracted with ether. The extract was successively washed with water, cold dil. H2SO4, and aq. NaHCO3, and dried over anhyd. MgSO4. Evaporation of the solvent gave a crude dithioate which was purified by column chromatography on alumina and recrystallized from MeOH to yield 3.8 g (92.7%) of pure 8 mp 91.5 – 92.5°C (fine needles). Anal. Found: C, 55.38; H, 6.18%. Calcul. for C22H22O11S2: C, 55.41; H, 6.06%. [β]D + 20.0° (c = 1.3, CHCl3). IR νmax cm⁻¹: 3000, 1600, 1360, 1236, 1190, 1180, 928, 910, 820, 784. 1H-NMR (CDCl3): δ: 1.25 (6H, d, J = 6.3 Hz, 1-H + 6-H), 1.28 (6H, s, CH3C), 2.45 (6H, s, Ar-Me x 2), 3.83 (2H, sep, (high-order splittings), 3-H and 4-H), 4.62 (2H, m, 2-H and 5-H), 7.34 (4H, d, J = 8.2 Hz, Ar-H x 2), 7.80 (4H, d, J = 8.2 Hz, Ar-H x 2).

1,6-Dideoxy-2,5-di-p-toluenesulphonate (9). A mixture of dithioate 8 (1.0 g, 2.2 mmol) and 47% of trifluoroacetic acid was stirred for 1.5 h at 50°C. After removing the solvent under reduced pressure, the residue was chromatographed on silica gel, eluting with benzene–AcOEt (4:1), to yield 0.75 g (81.6%) of 9 mp 94.5–95.5°C (needles from ether). FAB-MS m/z: 459 (M + H)+, 481 (M + Na)+, 497 (M + K)+. Anal. Found: C, 51.78; H, 5.66; S, 14.22%. Calcul. for C22H22O11S2: 2H2O: C, 51.38; H, 5.82. S, 13.99%. [β]D + 10.5° (c = 7.2, CHCl3). IR νmax cm⁻¹: 3540, 1595, 1490, 1352, 1188, 1172, 1128, 1095, 932, 879, 818, 658. 1H-NMR (CDCl3): δ: 1.23 (6H, d, J = 6.4 Hz, 1-H + 6-H), 2.46 (6H, s, Ar-Me x 2), 2.50 (2H, br, s, -OH x 2), 2.69 (2H, d, J = 7.8 Hz, 3-H + 4-H), 4.61 (2H, dq, J = 7.8, 6.4 Hz, 2-H + 5-H), 7.36 (4H, d, J = 8.3 Hz, Ar-H x 2), 7.79 (4H, d, J = 8.3 Hz, Ar-H x 2).

(R)-1-Formylphenyl p-toluenesulphonate (10). To a solution of foregoing 9 (0.7 g, 1.5 mmol) in 15 ml of aq. MeOH was added NaOH (0.4 g, 19 mmol), and the reaction mixture was stirred for 40 min at room temperature. The mixture was then diluted with water and extracted with ether. The extract was successively washed with water and dried over sodium sulfate, and dried over anhyd. MgSO4. Evaporation of the solvent gave a colorless oil (hydrate form, νmax cm⁻¹: 3500, 1600, 1360), which was chromatographed on silica gel (dried in an oven at 135°C for 2 h). Elution with benzene–AcOEt (10:1) gave 0.6 g (86.2%) of 10. 1H-NMR (CDCl3): δ: 1.37 (3H, d, J = 7.1 Hz, -Me), 2.55 (6H, s, -CH3), 3.20 (2H, d, J = 10.5 Hz, 3-H + 4-H), 4.61 (2H, dq, J = 7.8, 6.4 Hz, 2-H + 5-H), 7.36 (4H, d, J = 8.3 Hz, Ar-H x 2), 7.79 (4H, d, J = 8.3 Hz, Ar-H x 2).
4-O-Butiltetrahydro-2,3,5-trideoxy-3-R-tetrahydro-hexopyranose (14). To a solution of acetate 12 (1.8 g, 6.9 mmol) in 10 ml of MeOH was added a solution of K₂CO₃ (1.6 g, 11.6 mmol) in a small amount of water, and the resulting mixture was stirred for 5 h at room temperature. The reaction mixture was diluted with water and extracted with CH₂Cl₂. The extract was dried with anhyd. Na₂SO₄ and concentrated to give a quantitative yield of an alcohol. FAB-MS (glycerol) m/z: 221 (M + H), 243 (M + Na⁺, added with NaCl). HR-FAB-MS: calcd. for C₃₅H₅₁O₁₂; C₂₂H₂₂O₇ (M⁺ + H); found. 221.1129. 'H-NMR (CDCl₃) δ: 1.0 (3H, d, J = 6.1 Hz, 6-H₂), 1.54 (1H, δ), 3.75 (1H, d, J = 0.9, 6.1 Hz, 5-H), 3.85 (1H, dm, J = 0.9, 4.4 Hz), 4.59 (1H, d, J = 12.0 Hz, Ar-CH), 4.80 (1H, d, J = 12.0 Hz, Ar-CH), 5.04 (1H, m, H-1, 5.77 (1H, dd, J = 10.0, 2.7, 2.0 Hz, 2-H), 5.93 (1H, dm, J = 10.0, 3.7 Hz), 7.26-7.36 (7H, Ar-CH). IR νmax (cm⁻¹): 3420, 3040, 2975, 2940, 2895, 1500, 1455, 1405, 1378, 1190, 1175, 1148, 1130, 1010, 946, 960. 1508.

A mixture of the foregoing alcohol (4.6 g, 20.9 mmol), triethylamine (5.5 g, 54.4 mmol), dimethylaminopyridine (0.3 g), and t-butylchloroformide (0.3 g) in 15 ml of THF was stirred for 30 h at 45 ± 50°C. The reaction mixture was then diluted with water and extracted with hexane. The extract was washed with water and dried over anhyd. Na₂SO₄. Evaporation of the solvent and purification of the residue by column chromatography on Florisil gave 6.9 g (98.9%) of 13. HR-FAB-MS m/z: M⁺ + H) calcd. for C₃₅H₅₁O₁₂Si; C₃₅H₅₁O₁₂Si; M⁺ + H; found. 233.5943. 3.0015. 'H-NMR (CDCl₃) δ: 0.88 (3H, s, Me), 0.98 (3H, s, Me), 0.89 (3H, s, 6-Bu), 1.22 (3H, t, J = 1.0 Hz, 6-Bu), 3.80 (1H, d, J = 10.7, 6.1 Hz, 5-H), 3.88 (1H, ddd, J = 8.7, 2.7, 1.5 Hz, 4-H), 4.58 (1H, d, J = 11.7, Ar-CH), 4.78 (1H, d, J = 11.7 Hz, Ar-CH), 5.02 (1H, m, H-1), 5.69 (1H, ddd, J = 10.2, 2.7, 1.9 Hz, 2-H), 5.84 (1H, dm, J = 10.3 Hz, 3-H), 7.25-7.38 (7H, Ar-CH). IR νmax (cm⁻¹): 3090, 2960, 2930, 2900, 2860, 1490, 1460, 1306, 1252, 1152, 1100, 1072, 1045, 1010, 882, 839, 775. 1512.

Compound 13 (5.0 g, 15.0 mmol) was dissolved in abs. EtOH and shaken with a catalytic amount of 10% Pd-C in an atmosphere of hydrogen until the calculated volume of the gas had been absorbed. After removing the catalyst by filtration, the filtrate was concentrated, and the residue was chromatographed on silica gel to give an amorphous mixture (ca. 4 ± 6) of 14 (amorphous solid). Yield. 3.1 g (84.1%). Anal. Found: C, 58.01; H, 10.38%. Calcd. for C₃₄H₄₃O₁₄Si: C, 58.50; H, 10.64%. IR νmax (KBr) cm⁻¹: 2930, 2960, 2940, 1476, 1365, 1254, 1090, 1022, 972, 765.

(5S,6R)-5-(Butyltetrahydro-2,3,5-trIDEOXY-3-R-TETRAHYDRO-Hexopyranose (15). To a solution of hemiacetal 14 (2.0 g, 8.1 mmol) in 15 ml of dry DMF was added 0.6 g of PDC (6.0 g, 16.0 mmol), and the reaction mixture was stirred overnight at room temperature. The mixture was extracted with hexane-ether, and the extract was concentrated to give a colorless oil which was chromatographed on silica gel, eluting with hexane-ether (10:1). The product was recrystallized from hexane to give 1.7 g of prisms, mp 68–69°C. Anal. Found: C, 58.90; H, 10.01%. Calcd. for C₃₄H₄₃O₁₄Si: C, 58.97; H, 9.90%. [α]D = 74.0° (c = 10.7, CHCl₃). IR νmax (KBr) cm⁻¹: 2960, 2930, 2900, 2860, 1748, 1465, 1345, 1318, 1258, 1238, 1090, 894, 842, 780. 'H-NMR (CDCl₃) δ: 0.99 (6H, s, Si-Me₂), 0.90 (9H, s, t-Bu), 1.30 (3H, t, J = 10.5 Hz, 6-Bu), 1.59 (2H, m), 2.35 (10H, m), 2.68 (3H, ddd, J = 4.7, 6.6, 6.1 Hz, 5-H), 4.28 (1H, d, J = 6.3, 6.1 Hz).
with water and extracted with ethyl acetate. The extract was washed with aq. NaHCO₃ and dried over anhyd. Na₂SO₄. Evaporation of the solvent gave a pale yellow oil which was purified by preparative TLC (benzene-ethyl acetate = 1:1) and recrystallized from benzene. Yield, 40 mg (57.1%), m.p 112–112.5°C (prisms, lit.10) 110–112°C). HREI-MS m/z (M+H⁺): calcd. for C₉H₁₁O₅, 185.0813; found, 185.0805. (M + H⁺ – H₂O) calcd.

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References