SHORT PAPER

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Stereoselective synthesis of (2R, 3R)- and (2S, 3S)-2-(4-hydroxyphenyl)-3-hydroxymethyl-1,4-benzodioxan-6-carbaldehyde

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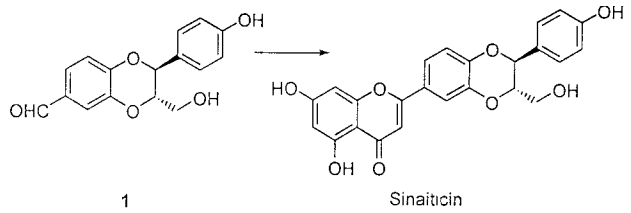
A novel stereoselective synthetic approach to 1,4-benzodioxane lignans was reported in which (2R, 3R)- and (2D, 3S)-2-(4-hydroxyphenyl)-3-hydroxymethyl-1,4-benzodioxan-6-carbaldehyde were first synthesised.

A number of lignans containing the 1,4-benzodioxan nucleus possess cytotoxic and hepatoprotective activities.[1,2] Recently we have reported the total synthesis of racemic sinaiticin (Scheme 1), a flavonolignans of the 1,4-benzodioxan type which was isolated from Sinaiticum leaves found in Sinai region of Egypt. 2-(4-Hydroxyphenyl)-3-hydroxymethyl-1,4-benzodioxan-6-carbaldehyde was the key intermediate.[3,4] This species exhibits significant inhibitory activity against the murine lymphocytic leukaemia P-388 cell line.[3] An unsolved problem in this area has been the asymmetric synthesis of chiral 1,4-benzodioxan moiety.[5] In continuation of our studies on the total synthesis of 1,4-benzodioxan lignans, we now report a first enantioselective synthetic approach to the key intermediate (2R, 3R)- and (2S, 3S)-2-(4-hydroxyphenyl)-3-hydroxymethyl-1,4-benxodioxan-6-carbaldehyde which is outlined in Scheme 2. This type of 1,4-benzodioxancarbaldehydes has been used as a synthetic building block for the synthesis of natural 1,4-benzodioxan lignans.[6]



Scheme 1

As shown in Scheme 1, 1-4-hydroixycinnamic acid (**2**) was converted to a benzyl ether (**3**) in 90% yield by esterification with acidic methanol followed by treatment with benzyl chloride. Reduction of **3** gave the corresponding unsaturated alcohol (**4**) in 90% yield. The asymmetric dihydroxylation of **4** by AD-mix afforded (1S, 2S)-**5** in 91% ee. and 86% yield.[7] (1S, 2D)-**5** was treated with *N*-tosylimidazole in dry THF to give the oxirane (1S, 2S)-**6** in 72% yield.[8] Mitsunobu reaction between (1S, 2S)-**6** and 3-benzyloxy-4-hydroxybenzaldehyde gave the characterised ether (1R, 2S)-**7** in 81% yield.[9,10] In this reaction the absolute configuration of C_1-position was inverted completely by a S_{N_2} nucleophilic displacement with 3-benzyloxy-4-hydroxybenzaldehyde. The two benzyl groups of (1R, 2S)-**7** were removed by hydrogenolysis under atmospheric pressure with hydrogen in the presence of 5% palladised charcoal in ethyl acetate to afford (1R, 2S)-**8** in 88% yield in which the epoxide moiety remained intact.[5] (1R, 2S)-**8** underwent cyclisation with potassium carbonate to afford (2R, 3R)-**1** in 93% yield. In this reaction an intramolecular nucleophilic attack at the C_2- position of the oxirane by the phenolic hydroxy as its potassium salt led to a complete inversion of the absolute configuration of the C_2-position and the formation of 1,4-benzodioxane.[11] The ^{1}H-NMR spectrum of (2R, 3R)-**1** H-3 contained a doublet signal at δ 5.06 with a coupling constant of (*j* = 8.1 Hz) indicating a typical of *trans* isomer and *threo* configuration. Similarly, asymmetric dihydroxy reaction of **4** by AD-mix-β afforded (1R, 2R)-**5** in 90% ee. and 83% yield.[7] (1R, 2R)-**5** was treated in the same four steps to afford (2S, 3S)-**1** in good yield.

The advantages of this synthetic approach are: (i) 2-aryl- and 3-aryl-1,4-benzodioxane lignans can be synthesized regioselectively when 3-benzyloxy-4-hydroxybenxaldehyde and 4-benzyloxy-3-hydroxybenzaldehyde was used respectively; (ii) S_N2 nucleophilic displacement at two chiral carbons led to the complete inversion of the absolute configuration of them, so that the absolute configuration of the 1,4-benzodioxan can be established and *trans* isomers is a single produce.

Experimental

The ^{1}H NMR and ^{13}C NMR data were recorded with Bruker AM-80 or AM-400 MHz spectrometers. The chemical shifts are reported in p.p.m. relative to TMS. Optical rotations were determined on a JASCO J-20C polarimeter with 0.2 dm tube. Mass spectra were recorded on a ZAB-HS mass spectrometer. Microanalyses were performed on a MOD-1106 elemental analyser. Chira analysis was performed on Varian Dynamax SD-300 using chiralcel column CDMPC (150 × 4.6 mm D) with hexane/isopropyl alcohol as eluant. Flash column chromatographs were generally performed on silica gel (200–300 mesh) eluting with petroleum ether : EtOAc and TLC inspections on silica gel GE_{254} plates with petroleum ether " EtOAc if not noted especially below.

4-benzyloxycinnamyl alcohol (**4**): At –10 °C, to the suspension of $LiAH_4$ (1.7 g, 45 mmol) in dry diethyl ether (100 ml), compound **3** (8.0 g, 30 mmol) in dry THF (100 ml) was added dropwise. The mixture was stirred at this temperature for 1 h. Then, the reaction was quenched with ice-water, extracted with ether and the combined organic layer was washed with brine, then dried with Na_2SO_4. The solvent was distilled off under reduced pressure, the residue was subject to flash chromatography using petroleum ether and ethyl acetate (5:1, v/v) as eluent. A white solid **4** (6.5 g) was obtained in 90% yield. M.P. 105–106°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.23 (d, 2H = *J* 5.8Hz), 5.13 (s, 2H), 6.15 (dt, 1H, *J* = 6.0 Hz 15.8 Hz), 6.47 (d, 1H = *J* 15.8 Hz), 6.83~7.42 (m, 9H). MS(EI): 240, 149, 118, 91. (Found: C, 78.01; H, 6.72. $C_{16}H_{16}O_2$ requires C, 79.97; H, 6.71%).

(1S, 2S)-1-(4-benzolxyphenyl)-2,3-dihydroxypropanol (1S, 2S)-(**5**): To a stirred solution of *t*-BuOH (50 ml) and H_2O (50 ml) was added AD-mix-α (14 g), $MeSO_2NH_2$ (950 mg g), the mixture was stirred at room temperature until both phases were clear, and then cooled to 0 °C, compound **4** (2.4 g, 0.1 mol) was added at once, the mixture was stirred vigorously at 0 °C until TLC revealed the absence of **4**. The reaction was quenched at 0 °C by addition of Na_2SO_3 (15 g) then warmed to room temperature and stirred for 0.5 h The reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL) and dried (Na_2SO_4), the CH_2Cl_2 was distilled off. The residue was subject to flash

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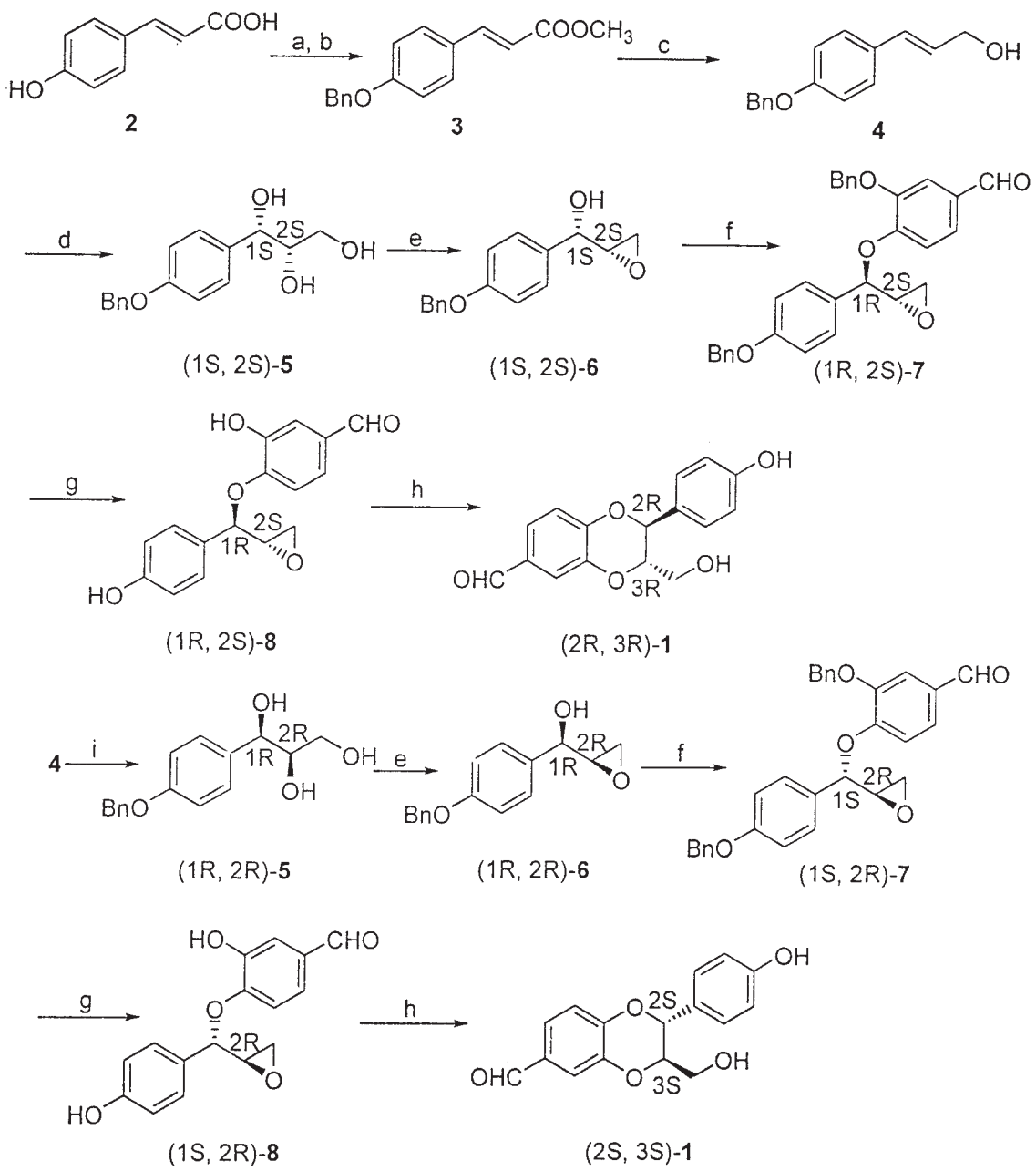
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*



Scheme 2 Reagents and conditions: (a) MeOH, H_2SO_4, 90°C, 16 h. (b) BnCl, DMF, K_2CO_3, 160°C, 3 h (a and b 90%). (c) LAH, THF, –10 C, 1 h, (90%). (d) Ad-mix-α, *t*-BuOH, H_2O, 0 °C, 20 h, (86%). (e) *N*-tosylimidazole, NaH, THF, r.t., 2 h, (72%). (f) DEAD, Ph_3P, 4-benzyloxy-3-hydroxybenxaldehyde, THF, rt, 24 h, (81%). (g) Pd/C (5%), H_2, EtOAc, rt, 6 h, (80%). (h) K_2CO_3,m MeOH, r.t., 1 h (93%). (i) AD-mix-β, *t*-BuOH, H_2O, 0 °C, 20 h (83%).

chromatography using petroleum ether and ethyl acetate (1:1, v/v) as eluent. A white powder (1S, 2S)-**5** (2.4 g) was obtained in 86% yield. M.p. 152–153 °C. Optical purity: 91% e.e. $[\alpha]_D^{25}$ –59 (*c* = 1.00, MeOH). ^{1}H NMR (200MHz, D_6 acetone): δ 3.34 and 3.41 (2dd, 2H, *J* = 2.7Hz, 9.8Hz), 3.59 (m, 1H), 4.56 (d, 1H, *J* = 6.0Hz), 5.10 (s, 2H), 6.91~7.49 (m, 9H). MS (EI): 274, 256, 165, 91. (Found: C, 70.01; H, 6.60. $C_{16}H^{18}O_4$ requires C, 70.05; H, 6.61%).

(1R, 2R)-1-(4-benzyloxphenyl)-2,3-dihydroxypropanol (1R, 2R)-(**5**): By a procedure similar to the preparation of (1S, 2S)-**5**, the reaction of **4** (2.4 g, 0.1 mmol), AD-mix-β (14 g), $MeSO_2NH_2$ (950 mg), t-BuOH 50 ml) and H_2O (50 ml), gave (1R, 2R)-**5** (2.3g) in 83% yield. Optical purity: 90% e.e. (1R, 2R)-**5**: A white powder. M.p. 170–172°C. $[\alpha]_D^{25}$ + 56 (*c* = 1.50, MeOH). (Found: C, 70.02; H, 6.63. $C_{16}H_{18}O_4$ requires C, 70.05; H, 6.61%). Other spectra data were the same as those of (1S, 2S)-**5**.

(1S, 2S)-2,3-epoxy-1-(4-benzyloxyphenyl)-propanol (1S, 2S)-(**6**): Sodium hydride (50% oil dispersion) (270 mg, 5.6 mmol) was placed in a dry flask equipped with magnetic stirrer and drying tube, and washed free of oil with pentane. Dry THF (10 ml) was added followed by (1S, 2S)-**5** (770 mg, 2.8 mmol), and the mixture was stirred for 1 h at room temperature. *N*-tosylimidazole (650 mg, 2.9 mmol) was then added and the suspension stirred for a further 3 h. The reaction mixture was then poured with stirring into ice-water, extracted with diethyl ether and the combined organic layer was washed with brine, then dried with Na_2SO_4. The solvent was distilled off under reduced pressure, the residue was subjected to flash chromatography using petroleum ether and ethyl acetate (4:1, v/v) as eluent to afford (1S, 2S)-**6** (520 mg, 72%) as a colourless oil $[\alpha]_D^{20}$ -40 (*c*=1.00, $CHCl_3$). ^{1}H NMR (400MHz, $CDCl_3$): δ 2.76 and 2.83 (2dd, 2H, *J*=3.0Hz, 8.8Hz). 3/17 (m, 1H), 4.36 (d, 1H, *J*=6.3Hz), 5.14 (s, 2H), 6.84~7.41 (m, 9H). MS (EI): 256, 243, 139, 91. (Found: C, 74.95; H, 6.30; $C_{16}H_{16}O_3$ requires C, 74.98; H 6.29%).

(1R, 2R)-2,3-epoxy-1-(4-benzyloxyphenyl)-propanol (1R, 2R)-(**6**): By a procedure similar to the preparation of (1S, 2S)-**6**, the reaction

of (1R, 2R)-**5** (770 mg, 2.8 mmol) with N-tosylimidazole (650 mg, 2.9 mmol) gave (1R, 2R)-**6** (500 mg) as a colourless oil in 70% yield., (1R, 2R)-**6**: $[\alpha]^{20}_D$ + 42 (*c*=1.00, $CHCl_3$). (Found: C, 74.93; H, 6.27. $C_{16}H_{16}O_3$ requires C, 74.98; H, 6.29%). Other spectra data were the same as those of (1S, 2S)-**6**.

(1R, 2S)-4-benzyloxy-3-[2,3-epoxy-1-(4-benzyloxyphenyl)-propoxyl]-benzaldehyde (1R, 2S)-(**7**): A solution of PPh_3 (520 mg, 2.0 mmol) and (1S, 2S)-**6** (460 mg, 1.8 mmol) in dry THF (10 ml) was added dropwise to a solution of 3-benzyloxy-4-hydroxybenzaldehyde[11] (450 mg, 2.0 mmol) and DEAD (350 mg, 2.0 mmol) at room temperature under nitrogen. After stirring the mixture overnight at room temperature, the mixture was evaporated in vacuum. The residue was subjected to flash chromatography using petroleum ether and ethyl acetate (2:1, v/v) as eluent. A white solid (1R, 2S)-**7** (680 mg) was obtained in 81% yield. M.P. 88–89°C $[\alpha]^{20}_D$ + 7 (*c*=1.00, $CHCl_3$). ^{1}=H NMR (400MHz, D_6 acetone): δ 2.76 and 2.79 (2dd, 2H, *J*=2.7 Hz, 5.5 Hz), 3.38 (m, 1H), 5.08 (s, 2H), 5.31 (s, 2H), 5.42 (d, 1H, *J*=4.0 Hz), 7.00–7.72 (m, 17H), 9.77 (s, 1H). MS (EI): 466, 375, 269, 227, 91. (Found: C, 77.26, H, 5.63. $C_{30}H_{26}O_5$ requires C, 77.23; H, 5.62%).

(1S, 2R)-4-benzyloxy-3-[2,3-epoxy-1-(4-benzyloxyphenyl)-propoxyl]-benzaldehyde (1S, 2R)-(**7**): By a procedure similar to the preparation of (1R, 2S)-**7**, Mitsunobu reaction of (1R, 2R)-**6** gave (1S, 2R)-**7** (670 mg) in 80% yield. (1S, 2R)-**7**: A white powder. M.p. 94–95 °C. $[\alpha]^{20}_D$ –8 (*c*=1.00, $CHCl_3$). (Found: C, 77.20; H, 5.64. $C_{30}H_{26}O_5$ requires C, 77.23; H, 5.62%). Other spectra data were same as those of (1R, 2F)-**7**.

(1R, 2S)-4-benzyloxy-3-[2,3-epoxy-1-(4-benzyloxyphenyl)-propoxyl]-benzaldehyde (1R, 2S)-(**8**): A solution of (1R, 2S0-**7** (470 mg, 1.0 mmol) in ethyl acetate (10 ml) was hydrogenated over 5% Pd–C (950 mg) under an H_2 atmosphere. The reaction mixture was filtered and the filtrate was concentrated. The residue was subjected to flash chromatography using petroleum ether and ethyl acetate (1:2, v/v) as eluent. A white solid (1R, 2S)-**8** (250 mg, 88%) was obtained. M.p. 110–112 °C; $[\alpha]_d$ + 12 (*c* 1.0. $CHCl_3$); ^{1}H-NMR (D_6 acetone, 400 Hz): δ 2.82 and 2.87 (2dd, 12.2 Hz, 2.5 Hz, 2 H), 3.41 (m, 1 H), 5.35 (d, 4 Hz, 1H), 6.80–7.43 (m, 6H), 9.70 (s, 1H). MS (*m/z*): 286, 149, 137, 119; IR (KBr/cm^{-1}): 3506, 3286, 3010, 2844, 1707, 1596, 1514, 1271, 1237; Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.12.; H, 4.93. Found: C, 67.18; H, 4.95.

(1S. 2R)-4-hydroxy-3-[2,3-epoxy-1-(4-benzyloxyphenyl)-propoxyl]-benzaldehyde (1S, 2R)-(**8**): By a procedure similar to the preparation of (1R, 2S)-**8** debenzylation of (1S, 2R)-**7** (470 g, 1.0 mmol), gave (1S, 2R)-**8** (240 mg) in 83% yield. (1S, 2R)-**8**: A white powder. M.p. 129–131 °C; $[\alpha]_D$ –13 (*c* 1.0, $CHCl_3$); Anal. Calcd for $C_{16}H_{14}O_5$; C, 67.12; H, 4.93; Found: C, 67.20; H, 4.92: Other spectra data were same as those of $(1R, 2F)_b$.

(2R, 3R)-3-(4-hydroxyphenyl)-2-hydroxymethyl-1,4-benzodioxan-6-carbaldehyde (2R, 3R)-(**1**): A mixture of (1R, 2S)-**8** (90 mg, 0.3 mmol) and anhydrous K_2CO_3 (140 mg, 1.0 mmol) in MeOH (5 ml)was stirred at room temperature for 20 min. The solvent was evaporated and 2 N HCl (2 ml) was added, then the mixture was extracted with EtOAc. The combined organic was washed with brine and dried with Na_2SO_4. The solvent was removed under reduced pressure. The residue was subjected to flash chromatography using petroleum ether and ethyl acetate (1:2. v/v) as eluent to afford (2R, 3R)-**1** (80 mg, 93%) as a white solid. M.P. 147–148°C: $[\alpha]^{25}_D$ +28 (*c* 0.9, $CHCl_3$); ^{1}H-NMR (D_6-acetone, 400 Hz): δ 3.47 and 3.72 (2dd, 12.5 Hz, 2.6 Hz, 2H), 4.13 min (m, 1H), 5.06 (d, 8.1 Hz, 1H), 6.68–7.47 (m, 6H), 9.83 (s, 1H); ^{13}C-NMR (D_6-acetone, 100 Hz): 55.8, 61.5, 77.5, 79.5, 112.9–133.0, 191.2; MS (*m/z*): 286, 268, 232, 149, 137, 107; IR (KBr/cm^{-1}): 3480, 3207, 2911, 2857, 1743, 1603, 1499, 1274, 1214; Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.12; H, 4.93. Found: C, 67.10; H, 4.91.

(2S, 3S)-3-(4-hydroxyphenyl)-2-hydroxymethyl-1,4-benzodioxan-6-carbaldehyde (2S, 3S)-(**1**): By a procedure similar to the preparation of (2R, 3R)-**1**, cyclization of (1S, 2R)-**8** (90 mg, 0.3 mmol) gave (2S, 3S)-**1** (90 mg) in 94% yield. (2S, 3S)-**1**: A white powder. M.p. 117–119 °C' $[\alpha]^{25}_D$ –25 (*c* 0.9, $CHCl_3$); Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.12; H, 4.93. Found: C, 67.14; H, 4.92. Other spectra data were same as those of (2R, 3R)-**1**.

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