1. General Procedure


2.1 (3\textsuperscript{a}R\textsuperscript{a}, 7a\textsuperscript{a}R\textsuperscript{a})-3a,4,7a-Tetrahydro-3\textsuperscript{H}-isobenzofuran-1-one (3)

A solution of cis-1,2,4,6-tetrahydrophthalic anhydride 4 (15.2 g, 100 mmol) in dry N,N-dimethylformamide (50 cm\textsuperscript{3}) was added dropwise over a period of 2 h to a stirred solution of sodium borohydride (3.0 g, 80 mmol) in dry N,N-dimethylformamide (50 cm\textsuperscript{3}) at 0 °C. Water (5 cm\textsuperscript{3}) was added and the solvent was removed under reduced pressure. The residue was treated with 2 M H\textsubscript{2}SO\textsubscript{4} (200 cm\textsuperscript{3}) and, after standing for 16 h, was extracted with ethyl acetate. The extract was dried (MgSO\textsubscript{4}) and the solvent was removed under reduced pressure. The residue was purified by vacuum distillation to give the lactone 3 (7.7 g, 56%), bp 76—78 °C at 2.8 mm Hg; [\alpha]\textsubscript{D}\textsuperscript{20} (c 1, CHCl\textsubscript{3}) 5.47—5.60 (2H, m, 1-H and 2-H). δ\textsubscript{1}H (50 MHz, CDCl\textsubscript{3}) 22.0 (C-4), 24.7 (C-7), 31.9 (C-3a), 37.2 (C-7a), 72.7 (C-3), 124.8, 125.1 (C-5 and C-6) and 179.0 (C=O).

Flash chromatography of the distillation residue on silica gel (150 g) using ethyl acetate–hexane (2:3) afforded a further 3.0 g (22%) of lactone 3 (7.7 g, 56%), bp 76—78 °C at 2.8 mm Hg; [\alpha]\textsubscript{D}\textsuperscript{20} (c 1, CHCl\textsubscript{3}) 22.0 (C-4), 24.7 (C-7), 31.9 (C-3a), 37.2 (C-7a), 72.7 (C-3), 124.8, 125.1 (C-5 and C-6) and 179.0 (C=O).

2.2 Methyl diisopropylammonium (1\textsuperscript{a}R\textsuperscript{a}, 2\textsuperscript{a}R)-4-cyclohex-4-ene-1,2-dicarboxylate (5)

Diisopropylamine (6.0 cm\textsuperscript{3}, 42.8 mmol) was added to a stirred solution of cis-1,2,4,6-tetrahydrophthalic anhydride 4 (6.08 g, 40.0 mmol) in methanol (200 cm\textsuperscript{3}). The resulting solution was stirred at 25 °C for 90 min. The solvent was removed in vacuo to give a solid residue (11.5 g). Recrystallisation from ethyl acetate–hexane yielded the \textit{ammonium salt} 5 (9.70 g, 85%), mp 81—83 °C; ν\textsubscript{max}(CHCl\textsubscript{3})/cm\textsuperscript{-1} 3025 (NH\textsubscript{2}), 1726 (CO carboxylate), δ\textsuperscript{13}C (CDCl\textsubscript{3}) 122 [12H, d, J 6.5 Hz, 2 x CH(CH\textsubscript{3})\textsubscript{2}], 215—2.70 (4H, m, 4-H and 7-H), 2.70—2.83 (1H, m, 7a-H), 4.00 (1H, dd, J 8.9 and 2.2 Hz, 3-H\textsubscript{a}), 4.30 (1H, dd, J 8.9 and 5.1 Hz, 1-H and 2-H), 5.63—5.83 (2H, m, 5-H and 6-H); δ\textsuperscript{13}C (50 MHz, CDCl\textsubscript{3}) 22.0 (C-4), 24.7 (C-7), 31.9 (C-3a), 37.2 (C-7a), 72.7 (C-3), 124.8, 125.1 (C-5 and C-6) and 179.0 (C=O).

2.3 (4\textsuperscript{R}-, 5\textsuperscript{S}-)-4,5-di(hydroxymethyl)cyclohexene (6):

Diisobutylaluminium hydride (1.5 solution in toluene, 80 cm\textsuperscript{3}, 120 mmol) was slowly added to a stirred solution of the lactone 3 (11.10 g, 80 mmol) in dry toluene (300 cm\textsuperscript{3}) at −78 °C and the resulting solution was stirred for 1 h at −78 °C. The reaction was quenched with 3 M HCl (20 cm\textsuperscript{3}) and the aqueous phase was adjusted to pH 2 by the addition of 1 M HCl. The aqueous phase was extracted with ethyl acetate, the combined organic extract was dried (MgSO\textsubscript{4}) and the solvent was removed under reduced pressure. Chromatography of the residue (13.50 g) on silica gel (400 g) using ethyl acetate–hexane (1:3) as eluent afforded the \textit{ol} 6 (8.10 g, 72%). Further elution with ethyl acetate yielded diol 6 (2.61 g, 23%), δ\textsubscript{1}H (200 MHz, CDCl\textsubscript{3}) 1.80—2.20 (6H, m, 3-H, 4-H, 5-H and 6-H), 3.45—3.68 (4H, m 2 CH\textsubscript{2}OH), 3.95—4.35 (2H, br.s, 2 x CH\textsubscript{2}OH), 5.47—5.60 (2H, m, 1-H and 2-H).

2.4 Methyl hydrogen (1\textsuperscript{S}-, 2\textsuperscript{R})-4-cyclohex-4-ene-1,2-dicarboxylate (7)

a) The salt 5 (6.30 g, 22.7 mmol) was added to a stirred mixture of ethyl acetate–water (50:50). 1 M HCl was added dropwise until pH 3 was reached. The aqueous phase was extracted with ethyl acetate, dried (MgSO\textsubscript{4}) and the solvent was removed under reduced pressure to give a residue (3.91 g). Recrystallisation from acetone–hexane furnished the half ester 7 (3.66 g, 90%), mp 81—83 °C (lit. 81—83 °C); ν\textsubscript{max}(CHCl\textsubscript{3})/cm\textsuperscript{-1} 1736 (COester), 1714 (CO acid); δ\textsubscript{13}C (200 MHz, CDCl\textsubscript{3}) 2.20—2.68 (4H, m, 3-H, 4-H, and 6-H), 2.98—3.07 (2H, m, 1-H and 2-H), 3.69 (3H, s, CO\textsubscript{2}CH\textsubscript{3}) and 5.54—5.78 (2H, s, 4-H and 5-H).

b) Potassium carbonate (0.70 g, 5.1 mmol) was added to a stirred solution of cis-1,2,4,6-tetrahydrophthalic anhydride (1.5 g, 10.0 mmol) in methanol (60 cm\textsuperscript{3}). The resulting mixture was stirred at 25 °C for 16 h. The solvent was removed under reduced pressure and the resulting oil was dissolved in ethyl acetate (100 cm\textsuperscript{3}). This solution was acidified to pH 4 with 1 M HCl and the aqueous phase was extracted with ethyl acetate. The organic extract was washed with water, dried...
(MgSO₄) and the solvent was removed under reduced pressure to give a residue (0.98 g). Recrystallisation from acetone–hexane gave 7 (0.90 g, 49%), mp 82—83 °C.

2.5 (3aR*, 7aS*)-3a,4,7,7a-Tetrahydro-3H-isobenzofuran-1-ol (8)

a) Disobutylaluminium hydride (1.5 M solution in toluene, 5.3 cm³, 80 mmol) was added in one portion to a stirred solution of the lactone 3 (1.00 g, 7.2 mmol) in dry toluene (30 cm³) at –78 °C and the resulting solution was stirred for 1 h at –78 °C. Then HCl (3 M, 2 cm³) was added to the reaction mixture which was subsequently acidified to pH 2 by further addition of 1 M HCl. The aqueous phase was extracted with ethyl acetate, the organic extract was dried (MgSO₄) and the solvent was removed under reduced pressure. The resulting oil (1.12 g) was chromatographed on silica gel (400 g) using ethyl acetate–hexane (1:3) as eluent afforded the aldehyde (116 mg, 37%), δ₁H (200 MHz, CDCl₃) 1.20—1.39 (6H, m, 3-H₂, 4-H, 5-H and 6-H₂), 3.45—3.68 (4H, m, 2 x CH₂O).

b) Disobutylaluminium hydride (1.5 M solution in toluene, 80 cm³, 120 mmol) was slowly added to a stirred solution of the lactone 3 (11.10 g, 80 mmol) in dry toluene (300 cm³) at –78 °C and the resulting solution was stirred for 1 h at –78 °C. The reaction was quenched with 3 M HCl (20 cm³) and the aqueous phase was adjusted to pH 2 by the addition of 1 M HCl. The aqueous phase was extracted with ethyl acetate, the combined organic extract was dried (MgSO₄) and the solvent was removed under reduced pressure. Chromatography of the residue (13.50 g) on silica gel (400 g) using ethyl acetate–hexane (1:3) as eluent afforded diol (4.93 g, 6.6 mmol) with a 8:1 mixture (~8:1 by NMR) of diastereomers, δ₁H (300 MHz, CDCl₃) 1.66 (1H, br.s, OH), 1.79—2.12 (4H, m, 3-H₂, 4-H and 6-H₂), 2.23—2.33 (1H, m, 5-H), 2.54—2.63 (1H, m, 1'-H), 2.84—2.99 (1H, m, 6-H). 5.08 (2H, m, 2''-H₂), 5.60—7.57 (2H, m, 3-H and 5-H, 6-H). 8.9 and 5.1 Hz, 3-H₂); δ₁C (75 MHz, CDCl₃) 25.6 (C-3), 30.1 (C-6), 38.2 (C-5), 39.2 (C-4), 64.8 (C-1'), 115.2 (C-2''), 125.6 (C-1 and C-2) and 139.3 (C-1'').

2.6 (4R*, 5R*)-4-Hydroxymethyl-5-vinylcyclohexene (9)

n-Butyllithium (2.5 M solution in hexane, 8.6 cm³) was added to a stirred slurry of methyltriphenylphosphonium iodide (8.65 g, 21.4 mmol) in tetrahydrofuran (40 cm³) at 0 °C. The resulting solution was warmed to 25 °C and stirred for 2 h. A solution of lactol 8 (0.93 g, 6.6 mmol) in tetrahydrofuran (20 cm³) was slowly added and the mixture was stirred for 30 min at 25 °C. 1 M HCl (100 cm³) was added and the mixture was extracted with ethyl acetate. The organic extract was dried (MgSO₄) and the solvent was removed under reduced pressure to give a yellow residue (1.02 g). Chromatography on silica gel (100 g) using ethyl acetate–hexane (1:4) as eluent afforded the vinyl alcohol 9 (0.81 g, 89%), δ₁H (300 MHz, CDCl₃) 3.56 (1H, dd, J 10.6 and 6.5 Hz, 1''-Ha), 3.60 (1H, dd, J 10.6 and 6.8 Hz, 1''-Ha), 5.04 (1H, ddd, J 10.3, 2.1 and 0.9 Hz, 2''-Ha), 5.08 (1H, ddd, J 17.2, 2.1 and 1.2 Hz, 2''-Ha), 5.60—7.57 (2H, m, 1-H and 2-H) and 5.87 (1H, ddd, J 17.2, 10.3 and 8.5 Hz, 1''-Ha) δ₁C (75 MHz, CDCl₃) 25.6 (C-3), 30.1 (C-6), 38.2 (C-5), 39.2 (C-4), 64.8 (C-1'), 115.2 (C-2''), 125.4 and 125.6 (C-1 and C-2) and 139.3 (C-1'').

2.7 (1R*, 6R*)-6-Vinyl-3-cyclohexene-1-carbaldehyde (10)

Dimethyl sulfoxide (0.33 cm³, 0.36 g, 21.4 mmol) was added to a stirred solution of oxalyl chloride (0.20 cm³, 0.29 g, 2.32 mmol) in dichloromethane (3 cm³) at –20 °C. After 10 min a solution of 9 (320 mg, 2.32 mmol) in dichloromethane (2 cm³) was added and the solution was stirred for 30 min. Triethylamine (38 cm³, 1.48 g, 14.6 mmol) was added and the mixture was stirred for 45 min then warmed to 25 °C. Saturated aqueous ammonium chloride was added and the mixture was extracted with dichloromethane. The organic extract was washed with brine, dried (MgSO₄) and the solvent was removed under reduced pressure to give a liquid (351 mg). Flash chromatography on silica gel (30 g) using ethyl acetate–hexane (1:9) as eluent afforded the aldehyde 10 (116 mg, 37%), δ₁H (400 MHz, CDCl₃) 2.02—2.70 (4H, m, 1-H, 2-H₂, and 3-H₂), 2.55—2.70 (1H, m, 3-H₂), 2.84—2.99 (1H, m, 6-H), 5.08 (2H, m, 2''-H₂), 5.60—7.57 (2H, m, 3-H and 4-H), 5.90 (1H, ddd, J 17.1, 10.5 and 7.6 Hz, 1''-H) and 9.69 (1H, d, J 1.2 Hz, 1''-H).