SUPPORTING INFORMATION

STUDIES IN IN IRIDOID SYNTHESIS PART 1. CHEMOSELECTIVE TRANSFORMATIONS OF CIS-1,2,4,6-TETRAHYDROPHTHALIC ANHYDRIDE

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1. General Procedure

2. Synthetic Procedure and Characterization of 3, 5, 6-10.

1. GENERAL PROCEDURES

Preparative Reactions were monitored by thin layer chromatography using Merck F254 aluminium-backed precoated silica gel plates. Developed plates were visualised with a combination of ultraviolet, iodine vapour and either anisaldehyde or ceric ammonium sulfate solutions. Work-up typically involved threefold extraction with an organic solvent. The extracts were combined to give the organic phase. Column chromatography was performed using Merck Kieselgel 60: 70—230 mesh for gravity columns and 230—400 mesh for flash chromatography. Cycloadditions were performed in purpose made thick walled glass tubes fitted with a pressure valve and surrounded by a steel sheath during reactions. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium–benzophenone ketyl, dichloromethane from phosphorous pentoxide and toluene from sodium. Other reagents and solvents were purified according to standard procedures.

Analytical Melting points were determined using a Reichert-Jung Thermovar hot-stage microscope and are uncorrected. Optical rotations were measured on a Perkin-Elmer 141 Polarimeter using chloroform solutions. Infrared spectra were recorded as solutions in chloroform on a Paragon 1000 FT-IR Spectrometer. ^{1}H NMR spectra were recorded on a Varian VXR-200 at 200 MHz, Varian Mercury 300 MHz or Varian Unity spectrometer at 400 MHz. ^{13}C spectra were recorded on the same instruments operating at 50, 75 and 100 MHz respectively. All spectra were recorded in deuteriochloroform, using $CHCl_3$, δ 7.26 as an internal standard. All chemical shifts are reported in ppm. H_A and H_B have been used arbitrarily in the NMR assignments to distinguish diastereotopic protons. Elemental analyses were recorded using a Fison's Instruments Elemental Analyser EA1108. Mass spectra were recorded on a VG micromass 16F spectrometer. In the absence of elemental analyses on oils and gums, accurate mass determinations were performed on a Kratos Limited MS9/50 spectrometer. All mass spectral data were obtained using Electron Impact techniques unless otherwise stated.

2. Synthetic Procedure and Characterization of 3, 5, 6-10.

2.1 (3a*R, 7a*S**)-3a,4,7,7a-Tetrahydro-3*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^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^3) at 0 °C. Water (5 cm^3) was added and the solvent was removed under reduced pressure. The residue was treated with 2 M H_2SO_4 (200 cm^3) and, after standing for 16 h, was extracted with ethyl acetate. The extract was dried ($MgSO_4$), 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 0.1 mm Hg (lit., 128—130 °C at 2.8 mm Hg); $\nu_{max}(CHCl_3)/cm^{-1}$ 1771 (CO); δ_H (200 MHz, $CDCl_3$) 1.70—1.95 (1H, m, 3a-H), 2.15—2.70 (4H, m, 4-H_2 and 7-H_2), 2.70—2.83 (1H, m, 7a-H), 4.00 (1H, dd, *J* 8.9 and 2.2 Hz, 3-H_A) 4.30 (1H, dd, *J* 8.9 and 5.1 Hz, 3-H_B) and 5.63—5.83 (2H, m, 5-H and 6-H); δ_C (50 MHz, $CDCl_3$) 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 **3**.

2.2 Methyl diisopropylammonium (1*S, 2*R**)-cyclohex-4-ene-1,2-dicarboxylate (5)**

Diisopropylamine (6.0 cm^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^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 *ammonium salt* **5** (9.70 g, 85%), mp 81—83 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3025 (NH_2^+), 1726 (CO ester), 1556 (CO carboxylate); δ_H (200 MHz, $CDCl_3$) 1.22 [12H, d, *J* 6.5 Hz, 2 x CH(CH_3)$_2$], 2.15—2.70 (4H, m, 3-H_2 and 6-H_2), 2.72—3.00 (2H, m, 1-H and 2-H), 3.13 [2H, sept, *J* 6 x 6.5 Hz, 2 x C*H*(CH$_3$)$_2$], 3.60 (3H, s, CO_2CH_3), 5.50—5.72 (2H, m, 4-H and 5-H) and 8.17 (2H, br. s, NH_2^+); δ_C (50 MHz, $CDCl_3$) 19.2 (CH(*C*H$_3$)$_2$), 25.8 and 27.7 (C-3 and C-6), 40.2 and 41.7 (C-1 and C-2), 45.9 (CO_2CH_3), 51.1 (*C*H(CH$_3$)$_2$), 125.1 and 126.4 (C-4 and C-5), 175.3 and 178.1 (CO_2^- and *C*O$_2$CH$_3$) (Found: C, 63.0; H, 9.8; N, 4.8. Calc. for $C_{15}H_{27}N_2O_4$: C, 63.0; H, 9.5; N, 4.9%).

2.3 (4*R, 5*S**)-4,5-di(hydroxymethyl)cyclohexene (6):**

Diisobutylaluminium hydride (1.5 M solution in toluene, 80 cm^3, 120 mmol) was slowly added to a stirred solution of the lactone **3** (11.10 g, 80 mmol) in dry toluene (300 cm^3) at –78^0 C and the resulting solution was stirred for 1 h at –78 C. The reaction was quenched with 3 M HCl (20 cm^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 ($MgSO_4$) 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 lactol **8** (8.10 g, 72%). Further elution with ethyl acetate yielded diol **6** (2.61 g, 23%), δ_H (200 MHz, $CDCl_3$) 1.80—2.20 (6H, m, 3-H_2, 4-H, 5-H and 6-H_2), 3.45—3.68 (4H, m, 2 x CH_2OH), 3.95—4.35 (2H, br.s, 2 x CH$_2$O*H*), 5.47—5.60 (2H, m, 1-H and 2-H).

2.4 Methyl hydrogen (1*S, 2*R**)-cyclohex-4-ene-1,2-dicarboxylate (7)**

a) The salt **5** (6.30 g, 22.1 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 ($MgSO_4$) 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.,[34] 81.2—83.1 °C); $\nu_{max}(CHCl_3)/cm^{-1}$ 1736 (COester), 1714 (CO acid); δ_H (200 MHz, $CDCl_3$) 2.20—2.68 (4H, m, 3-H_2 and 6-H_2), 2.98—3.07 (2H, m, 1-H and 2-H), 3.69 (3H, s, CO_2CH_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 (1.52 g, 10.0 mmol) in methanol (60 cm^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^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 brine, dried

($MgSO_4$) 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 (3a*R, 7a*S**)-3a,4,7,7a-Tetrahydro-3*H*-isobenzofuran-1-ol (8)**

a) Diisobutylaluminium hydride (1.5 M solution in toluene, 5.3 cm^3, 8.0 mmol) was added in one portion to a stirred solution of the lactone **3** (1.00 g, 7.2 mmol) in dry toluene (30 cm^3) at –78 °C and the resulting solution was stirred for 1 h at –78 °C. Then HCl (3 M, 2 cm^3) 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 ($MgSO_4$) 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 lactol **8** (0.93 g, 92%), as an inseparable mixture (~8:1 by NMR) of diastereomers, $\nu_{max}(CHCl_3)/cm^{-1}$ 3601 (OH); δ_H (200 MHz, $CDCl_3$) *major* 1.64—2.09 (1H, m, 3a-H), 2.10—2.70 (4H, m, 4-H_2 and 7-H_2), 2.55—75 (1H, m, 7a-H), 4.00 (1H, dd, *J* 8.9 and 2.2 Hz, 3-H_A) 4.30 (1H, dd, *J* 8.9 and 5.1 Hz, 3-H_B) and 5.72 (2H, m, 5-H, 6-H); δ_C (50 MHz, $CDCl_3$) 22.9 (C-4), 23.2 (C-7), 32.8 (C-3a), 41.3 (C-7a), 72.2 (C-3), 103.4 (C-1), 124.6 and 124.7 (C-5 and C-6).

b) Diisobutylaluminium hydride (1.5 M solution in toluene, 80 cm^3, 120 mmol) was slowly added to a stirred solution of the lactone **3** (11.10 g, 80 mmol) in dry toluene (300 cm^3) at -78^0 C and the resulting solution was stirred for 1 h at -78^0 C. The reaction was quenched with 3 M HCl (20 cm^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 ($MgSO_4$) 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 lactol **8** (8.10 g, 72%). Further elution with ethyl acetate yielded diol (4*R**, 5*S**)-4,5-di(hydroxymethyl)cyclohexene **6** (2.61 g, 23%), δ_H (200 MHz, $CDCl_3$) 1.80—2.20 (6H, m, 3-H_2, 4-H, 5-H and 6-H_2), 3.45—3.68 (4H, m, 2 x CH_2OH), 3.95—4.35 (2H, br.s, 2 x CH_2O*H*), 5.47—5.60 (2H, m, 1-H and 2-H).

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

n-Butyllithium (2.5 M solution in hexane, 8.6 cm^3) was added to a stirred slurry of methyltriphenylphosphonium iodide (8.65 g, 21.4 mmol) in tetrahydrofuran (40 cm^3) 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 cm^3) was slowly added and the mixture was stirred for 30 min at 25 °C. 1 M HCl (100 cm^3) was added and the mixture was extracted with ethyl acetate. The organic extract was dried ($MgSO_4$) 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 yielded the vinyl alcohol **9** (0.81 g, 89%), $\nu_{max}(CHCl_3)/cm^{-1}$ 3620 (OH); δ_H (300 MHz, $CDCl_3$) 1.66 (1H, br.s, OH), 1.79—2.12 (4H, m, 3-H_2 , 4-H and 6-H_A), 2.23—2.33 (1H, m, 6-H_B), 2.54—2.63 (1H, m, 5-H) 3.48 (1H, dd, *J* 10.6 and 6.5 Hz, 1'-H_A), 3.56 (1H, dd, *J* 10.6 and 6.8 Hz, 1'-H_B), 5.04 (1H, ddd, *J* 10.3, 2.1 and 0.9 Hz, 2"-H_A), 5.08 (1H, ddd, *J* 17.2, 2.1 and 1.2 Hz, 2"-H_B), 5.60—75.71 (2H, m, 1-H and 2-H) and 5.87 (1H, ddd, *J* 17.2, 10.3 and 8.5 Hz, 1"-H); δ_C (75 MHz, $CDCl_3$) 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 (1*R, 6*R**)-6-Vinyl-3-cyclohexene-1-carbaldehyde (10)**

Dimethyl sulfoxide (0.33 cm^3, 0.36 g, 4.64 mmol) was added to a stirred solution of oxalyl chloride (0.20 cm^3, 0.29 g, 2.32 mmol) in dichloromethane (3 cm^3) at –78 °C. After 10 min a solution of **9** (320 mg, 2.32 mmol) in dichloromethane (2 cm^3) was added and the solution was stirred for 30 min. Triethylamine (38 cm^3, 1.48 g, 14.6 mmol) was added and the mixture was stirred for 45min 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 ($MgSO_4$) 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%),δ_H (400 MHz, $CDCl_3$)), 2.02—2.70 (4H, m, 1-H, 2-H_2 , and 5-H_A), 2.55—2.70 (1H, m, 5-H_B), 2.84—2.99 (1H, m, 6-H) 5.08 (2H, m, 2"-H_2), 5.60—75.71 (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).