Synthesis of (±)-*cis*-6-Methyltetrahydropyran-2-ylacetic Acid, a Natural Product from *Viverra civetta*, using Organoselenium-mediated Cyclisation Reactions

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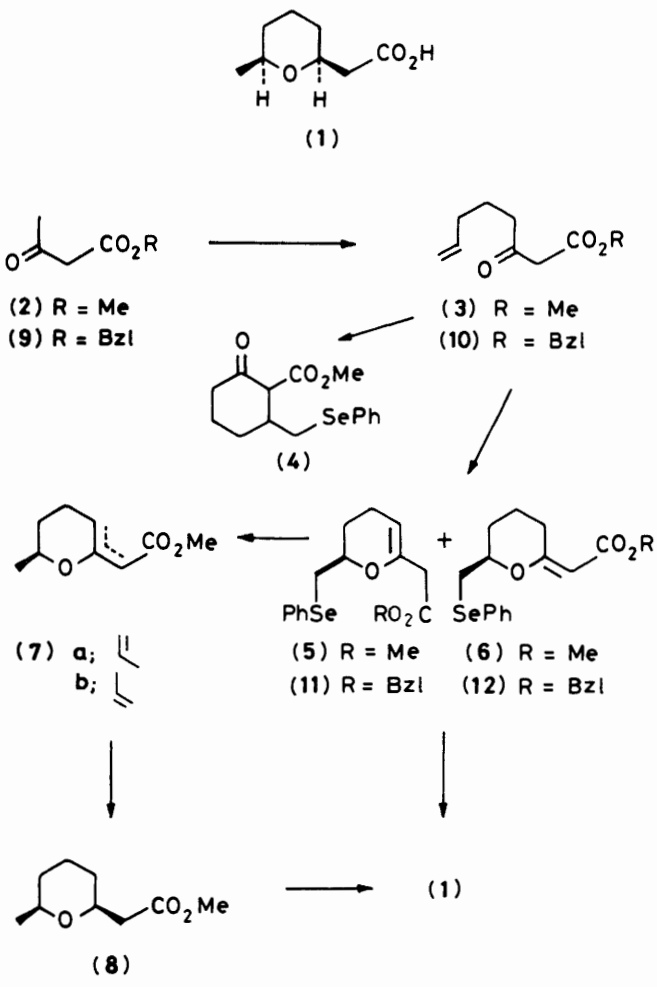
Two highly stereoselective syntheses of the natural product (±)-*cis*-6-methyltetrahydropyran-2-ylacetic acid (**1**) are described. The shorter of these is a three-step synthesis involving kinetic alkylation of the dianion derived from benzyl acetoacetate with 4-bromobut-1-ene, followed by organoselenium-mediated cyclisation with *N*-phenylselenophthalimide, to give benzyl 6-phenylselenomethyl-5,6-dihydro-4*H*-pyran-2-ylacetate (**11**) and benzyl 6-phenylselenomethyltetrahydropyran-2-ylideneacetate (**12**), which upon reaction with Raney nickel under 100 atm of hydrogen directly affords compound (**1**).

Natural products isolated from the glandular secretion of the civet cat (*Viverra civetta*) have long been sought as they are important perfumery constituents. Recently, a minor acidic component has been isolated and its structure determined as (2*S*,6*S*)-*cis*-6-methyltetrahydropyran-2-ylacetic acid (**1**).[1,2] Syntheses of this material have already been reported.[1,3] Here we describe in full[4] our routes to (±)-(**1**) using an organoselenium-mediated cyclisation reaction as the key synthetic step.[5]

Kinetic alkylation of the dianion derived from methyl acetoacetate (**2**) with 4-bromobut-1-ene gives compound (**3**) in 81% yield. Treatment of the alkenyl-β-keto ester (**3**) with *N*-phenylselenophthalimide[7] and one equivalent of tin tetrachloride in methylene dichloride cleanly gave a product (**4**) in 83% yield† which was shown, by ^{1}H n.m.r. spectroscopy, to be that derived by cyclisation from the central carbon atom of the β-keto ester to the alkene unit. However, similar treatment of compound (**3**) with *N*-phenylselenophthalimide and a trace amount (0.01 equiv.) of the Lewis acid $SnCl_4$, resulted in cyclisation *via* the enolic oxygen atom of the β-keto ester, to give a 9:1 mixture of compounds (**5**) and (**6**) in 84% yield.§

While a pure sample of compound (**5**) could be obtained by column chromatography on silica gel, separation was not necessary during the synthesis of compound (**1**). Thus, the mixture of (**5**) and (**6**) was treated with tri-n-butyltin hydride[8] and azobisisobutyronitrile to effect the removal of the phenylseleno group giving compound (**7**), again as a mixture of double bond isomers. Stereospecific reduction of compound (**7**) proved difficult, but was achieved using Raney nickel at 60 °C under 100 atm of hydrogen, to give the *cis*-hydropyranyl ester (**8**). This ester was identical with previously synthesised material.[1,3] Hydrolysis of compound (**8**) with 10% sodium hydroxide gave (±)-*cis*-6-methyltetrahydropyran-2-ylacetic acid (**1**) in 92% yield, identical in all respects with authentic material (Scheme). The overall yield of compound (**1**) by this sequence was a respectable 35% from commercially available starting materials.

In the second, shorter synthesis we chose to combine the reduction steps with the final deprotection reaction. Reaction of the dianion from benzyl acetoacetate[10] (**9**) with 4-bromobut-1-ene gave the alkylated product (**10**) (72%). This, upon cyclisation as before with *N*-phenylselenophthalimide and $SnCl_4$ (0.01 equiv.), gave a 57% yield of compounds (**11**) and (**12**) in the ratio 4:1. Reduction of this mixture with Raney nickel–H_2 gave compound (**1**) directly in 47% isolated yield. Thus, in this one reaction the phenylseleno group is removed, the carbon–carbon double bond is reduced stereospecifically, and the benzyl protecting group is cleaved (Scheme). The overall yield by this route was 19%; however none of the steps were optimised.



Scheme. Bzl = $C_6H_4CH_2$

† We thank Dr. Judith A. Morton for this experiment.

§ A full discussion of the mechanism involved in these reactions together with many other examples will be presented in detail at a later date.

Experimental

M.p.s were determined using a Kofler hot-stage apparatus and are uncorrected. I.r. spectra were recorded with a Perkin-Elmer 298 spectrometer and ^{1}H n.m.r. spectra with a Varian EM 360A, Jeol FX90Q, or Bruker WH250 spectrometer, for solutions in deuteriochloroform with tetramethylsilane as internal standard. Mass spectra were obtained using a V.G. Micromass 7070 spectrometer. Light petroleum refers to the fraction with b.p. 40—60 °C, and ether to diethyl ether. Solutions were dried over anhydrous sodium sulphate, and solvents by standard methods. Chromatography was performed on MN-Silica gel 60 230—400 mesh, under pressure.

Preparation of Methyl 3-*Oxo-oct*-7-*enoate* (**3**).—To a suspension of sodium hydride (3.84 g, 80.0 mmol, 50% dispersion in oil, washed twice with light petroleum and once with tetrahydrofuran) in dry tetrahydrofuran (200 ml) under argon, at 0 °C, was added dropwise methyl acetoacetate (**2**) (8.87 g, 76.5 mmol). The resulting clear solution was stirred at 0 °C for 5 min, cooled to −10 °C, and n-butyl-lithium (56.7 ml; 1.35M-solution in hexane; 76.5 mmol) added, to produce a pale yellow solution. After being stirred at −10 °C for 10 min, 4-bromobut-1-ene (10.33 g, 76.5 mmol) was added, and the mixture allowed to warm slowly to room temperature. After being stirred overnight at room temperature, the reaction mixture was poured into saturated ammonium chloride (50 ml) and ether (120 ml). The layers were separated and the aqueous layer extracted with ether (3 × 80 ml). The combined organic layers were washed with saturated sodium chloride solution (40 ml), dried (Na_2SO_4), and the solvent removed under reduced pressure, to afford an oil, which was purified by distillation, to give methyl 3-oxo-oct-7-enoate (**3**) (10.50 g, 81%); b.p. 79—80 °C/0.3 mmHg; $\nu_{max.}$(film) 3 420, 2 946, 1 740, 1 712, 1 639, 921, and 727 cm^{-1}; δ (60 MHz) 6.04—4.72 (3 H, m), 3.68 (3 H, s), 3.40 (2 H, s), 2.51 (2 H, *ca.* t), and 2.22—1.30 (4 H, m); *m/z* 170 (M^+), 116, 74, 43, and 41.

Cyclisation of Methyl 3-*Oxo-oct*-7-*enoate* (**3**) *using* N-*Phenylselenophthalimide and* $SnCl_4$ (1 equiv.).—To a mixture of compound (**3**) (0.34 g, 2.0 mmol), and *N*-phenylselenophthalimide (0.64 g, 2.1 mmol), in dry dichloromethane (10 ml) under argon, at room temperature, was added tin tetrachloride (2.0 ml of a 1M-solution in dichloromethane; 1.0 equiv.). The solution was stirred for 5 min and light petroleum (20 ml) added to precipitate phthalimide, which was removed by filtration. The filtrate was poured into saturated aqueous sodium hydrogen carbonate (7 ml) and ether (10 ml), and the layers separated. The aqueous layer was extracted by further portions of ether (3 × 10 ml), and the combined organic extracts were washed with brine (7 ml), dried (Na_2SO_4), and the solvent removed under reduced pressure to give an oil. Chromatography on silica gel (ether—light petroleum, 1:9) gave *methyl* 2-*oxo*-6-(*phenyl selenomethyl*)*cyclohexanecarboxylate* (**4**) (0.54 g, 83%) as a colourless oil; $\nu_{max.}$(film) 2 949, 1 746, 1 714, 1 650, 1 610, 1 580, 1 480, 1 440, 1 284, and 1 208 cm^{-1}; δ (250 MHz) 12.39 (0.65 H, s, enol OH), 7.60—7.47 (2 H, m), 7.22—7.01 (3 H, m), 3.66 (2.1 H, s, OMe enol form), 3.64 (0.9 H, s, OMe keto form), 3.42 (0.35 H, d, COC*H*CO_2Me keto form, *J* 13.0 Hz), 3.21 (0.65 H, dd, C*H*$_A$H$_B$SePh enol form, *J* 1.7 and 11.8 Hz), 3.11 (0.35 H, dd, C*H*$_A$H$_B$SePh keto form, *J* 3.5 and 15.0 Hz), 2.87—2.70 (2 H, m), 2.32—2.23 (2 H, m), 2.18—1.97 (1 H, m), and 1.76—1.44 (3 H, m) (Found: C, 55.7; H, 5.9. $C_{15}H_{18}O_3Se$ requires C, 55.39; H, 5.58%).

Cyclisation of Methyl 3-*Oxo-oct*-7-*enoate* (**3**) *using* N-*Phenylselenophthalimide and* $SnCl_4$ (0.01 equiv.).—To a mixture of compound (**3**) (2.00 g, 11.8 mmol) and *N*-phenylselenophthalimide (3.92 g, 13.0 mmol), in dry dichloromethane (40 ml) under argon, at room temperature, was added tin tetrachloride (120 μl of a 1M-solution in dichloromethane, 0.01 equiv.). The solution was stirred for 2 h, and light petroleum (80 ml) added to precipitate phthalimide, which was removed by filtration. The filtrate was poured into saturated aqueous sodium hydrogen carbonate (30 ml) and ether (50 ml), and the layers separated. The aqueous layer was extracted by further portions of ether (3 × 50 ml), and the combined organic extracts were washed with brine (30 ml), dried (Na_2SO_4), and the solvent removed under reduced pressure to give an oil. Chromatography on silica gel (ether–light petroleum, 1:4) gave a 9:1 mixture of *methyl* 6-*phenylselenomethyl*-5,6-*dihydro*-4H-*pyran*-2-*ylacetate* (**5**) and methyl 6-phenylselenomethyltetrahydropyran-2-ylideneacetate (**6**), as a colourless oil (3.22 g, 84%). Compound (**6**) was detected in the ^{1}H n.m.r. spectrum by the chemical shift of the C*H*=C proton [δ 5.3; for (**5**) δ 4.6]. Further column chromatography with slower elution afforded pure compound (**5**) as a colourless oil; $\nu_{max.}$(film) 3 065, 3 050, 2 940, 2 920, 2 840, 1 740, 1 678, 1 630, 1 575, 1 475, and 1 432 cm^{-1}; δ (250 MHz) 7.57—7.48 (2 H, m), 7.30—7.20 (3 H, m), 4.65 (1 H, t, C=C*H J* 3.3 Hz), 4.06 (1 H, m), 3.69 (3 H, s), 3.18 (1 H, dd, C*H*$_A$H$_B$SePh, *J* 5.8 and 12.5 Hz), 3.01 (2 H, s), 3.00 (1 H, dd, CH$_A$*H*$_B$SePh, *J* 6.7 and 12.5 Hz), and 2.10—1.60 (4 H, m); *m/z* 326 (M^+, ^{80}Se), 169, and 95 (Found: C, 55.2; H, 5.65. $C_{15}H_{18}O_3Se$ requires C, 55.39; H, 5.58%).

Reduction of Compounds (**5**) *and* (**6**) *using Tri-n-butyltin Hydride.*—To a solution of compounds (**5**) and (**6**) (1.02 g, 3.14 mmol) in dry refluxing toluene (30 ml), was added a mixture of tri-n-butyltin hydride (1.37 g, 1.5 equiv.) and azobisisobutyronitrile (100 mg), dropwise during 15 min. The resulting mixture was refluxed for a further 30 min. Evaporation of the toluene gave a residue which was purified by chromatography on silica gel (light petroleum→light petroleum–ethyl acetate, 95:5) to give *methyl* 6-*methyl*-5,6-*dihydro*-4H-*pyran*-2-*ylacetate* (**7a**) and methyl 6-methyltetrahydropyran-2-ylideneacetate (**7b**) (0.42 g, 79%). As before compound (**7b**) was detected in the ^{1}H n.m.r. spectrum by the chemical shift of the C*H*=C proton [δ 5.27; for (**7a**) δ 4.63]. Reduction as above for pure (**5**), gave on chromatography compound (**7a**) only, as a colourless oil; $\nu_{max.}$(film) 2 970, 2 950, 2 930, 2 850, 1 745, 1 705, 1 677, 1 630, 1 433, 1 405, 1 370, and 1 340 cm^{-1}; δ (250 MHz) 4.63 (1 H, t, *J* 3.4 Hz), 3.97 (1 H, symmetrical m, 12 lines, C*H*O, *J* 2.5, 8.3, and 6.3 Hz), 3.68 (3 H, s), 3.02 (2 H, s), 2.20—1.42 (4 H, m), and 1.26 (3 H, d, *J* 6.3 Hz); *m/z* 170 (M^+), 155, 139, 111, 101, and 96 (Found: C, 63.9; H, 8.5. $C_9H_{14}O_3$ requires C, 63.51; H, 8.29%).

Hydrogenation of Compound (**7**).—A solution of compound (**7**) (0.05 g, 0.29 mmol) in ethanol (7 ml) over Raney nickel (W4; 5 wt. equiv.) was subjected to 100 atm of hydrogen at 60 °C for 20 h. Filtration, and evaporation of the solvent, gave pure methyl *cis*-6-methyltetrahydropyran-2-ylacetate (**8**)[1] (0.036 g, 71%); $\nu_{max.}$(film) 2 970, 2 930, 2 860, 1 745, 1 440, 1 370, 1 340, 1 285, 1 200, and 1 170 cm^{-1}; δ (250 MHz) 3.83—3.60 (4 H, m, incorporating s at δ 3.68), 3.47 (1 H, symmetrical m, 12 lines, C*H*O, *J* 6.6, 1.9, and 9.8 Hz), 2.57 (1 H, dd, C*H*$_A$H$_B$CO$_2$Me, *J* 15.0 and 7.1 Hz), 2.39 (1 H, dd, CH$_A$*H*$_B$CO$_2$Me, *J* 15.0 and 5.7 MHz), 1.85—1.45 (5 H, m), and 1.20—1.10 (4 H, m, incorporating d at 1.15, *J* 6.6 Hz); identical with the previously reported compound.[1]

Preparation of cis-6-*Methyltetrahydropyran*-2-*ylacetic Acid* (**1**) *by Hydrolysis of Compound* (**8**).—Compound (**8**) was saponified as previously described,[1] to give pure *cis*-6-methyltetrahydropyran-2-ylacetic acid (**1**) as a white solid (0.03 g, 92%); m.p. 51—52 °C (lit.,[1] for racemic compound 52—53 °C); $\nu_{max.}$(film) 3 500—2 500br, 2 965, 2 925, 2 855, 1 710, 1 440, 1 368, 1 295, and 1 200 cm^{-1}; δ (250 MHz) 3.84—3.72 (1 H, m,

C*H*O), 3.53 (1 H, m, MeC*H*O), 2.59 (1 H, dd, $CH_AH_BCO_2H$, *J* 15.0 and 7.5 Hz), 2.48 (1 H, dd, $CH_AH_BCO_2H$, *J* 15.0 and 5.0 Hz), and 1.90—1.15 (9 H, m, incorporating d at δ 1.19, *J* 6.3 Hz); and was identical with the natural product.[1,2]

Preparation of Benzyl 3-Oxo-oct-7-enoate (**10**).—To a suspension of sodium hydride (0.9 g, 18.8 mmol, 50% dispersion in oil, washed twice with light petroleum and once with tetrahydrofuran) in dry tetrahydrofuran (50 ml) under argon, at 0 °C, was added dropwise benzyl acetoacetate (**9**) (3.2 g, 16.7 mmol). The resulting pale yellow anion was stirred at 0 °C for 5 min, cooled to −10 °C, and n-butyl-lithium (12.1 ml; 1.4M-solution in hexane, 17.0 mmol) was added to produce a deep red solution. After it had been stirred for 10 min, 4-bromobut-1-ene (2.30 g, 17.0 mmol) was added and the mixture allowed to warm to room temperature. Overnight the red colour was quenched and the reaction mixture was poured into saturated ammonium chloride (20 ml) and ether (30 ml). The layers were separated and the aqueous layer extracted with further portions of ether (3 × 20 ml). The combined organic layers were washed with saturated sodium chloride solution (10 ml), dried (Na_2SO_4), and the solvent removed under reduced pressure, to afford an oil which was purified by chromatography on silica gel (light petroleum–ether 9:1) to give *benzyl 3-oxo-oct-7-enoate* (**10**) (2.92 g, 72%); $\nu_{max.}$(film) 3 072, 2 929, 1 736, 1 719, 1 634, 1 146, 731, and 684 cm^{-1}; δ (60 MHz) 7.33 (5 H, s), 6.00—4.74 (5 H, m, incorporating s at δ 5.12), 3.43 (2 H, s), 2.46 (2 H, *ca.* t), and 2.26—1.46 (6 H, m); *m/z* 246 (M^+), 105, 91, 58, and 43 (Found: C, 73.4; H, 7.6. $C_{15}H_{18}O_3$ requires C, 73.15; H, 7.37%).

Cyclisation of Benzyl 3-Oxo-oct-7-enoate (**10**).—To a mixture of compound (**10**) (1.0 g, 4.1 mmol) and *N*-phenylselenophthalimide (1.37 g, 4.5 mmol) in dry dichloromethane (20 ml) under argon, at room temperature, was added tin tetrachloride (41 μl of a 1M-solution in CH_2Cl_2; 0.01 equiv.). The solution was stirred for 2 h and light petroleum (40 ml) added to precipitate phthalimide, which was removed by filtration. The filtrate was poured into saturated aqueous sodium hydrogen carbonate (15 ml) and ether (20 ml), and the layers separated. The aqueous layer was extracted by further portions of ether (3 × 20 ml) and the combined organic layers were washed with brine (15 ml), dried (Na_2SO_4), and the solvent removed under reduced pressure to give an oil. Chromatography on silica gel (ether–light petroleum 1:4) gave a 4:1 mixture of *benzyl 6-phenylselenomethyl-5,6-dihydro-4H-pyran-2-ylacetate* (**11**) and *benzyl 6-phenylselenomethyltetrahydropyran-2-ylideneacetate* (**12**) (0.94 g, 57%); $\nu_{max.}$(film) 2 931, 1 742, 1 670, 1 640, 1 240, 1 145, 1 113, 1 042, and 905 cm^{-1}; δ (60 MHz) 7.60—7.00 (10 H, m), 5.27 (0.2 H, s, C=C*H*CO_2Bzl), 5.06 (2 H, s, CH_2Ph), 4.53 (0.8 H, s, C=C*H*CH_2), 3.89 (1 H, m), 2.98 (2 H, m), and 2.20—1.31 (6 H, m); *m/z* 402 (M^+, ^{80}Se), 92, 91, 65, and 41 (Found: C, 62.6; H, 5.6. $C_{21}H_{22}O_3Se$ requires C, 62.84; H, 5.52%).

Reaction of Compounds (**11**) *and* (**12**) *with Raney Nickel.*—A solution of compounds (**11**) and (**12**) (0.4 g, 1.0 mmol) in ethanol (10 ml) over Raney nickel (W4, 5 wt. equiv.) was subjected to 100 atm of hydrogen at 60 °C for 20 h. Filtration followed by extensive extraction of the catalyst with hot ethanol (5 × 30 ml) and evaporation gave a crude residue which was dissolved in aqueous sodium hydrogen carbonate (10 ml). The aqueous solution was washed with ether (2 × 20 ml) then acidified with 3M-hydrochloric acid and extracted with ether (3 × 20 ml). The ether extracts were dried (Na_2SO_4) and the solvent removed under reduced pressure to give *cis*-6-methyltetrahydropyran-2-ylacetic acid (**1**) (74 mg, 47%), identical with previously synthesised material.

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