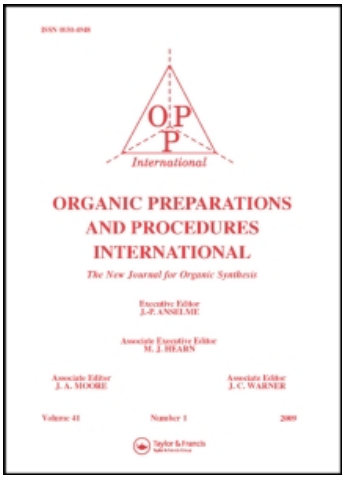

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STEREOSELECTIVE SYNTHESES OF THE METHYL ESTERS OF (E)- AND (Z)-2-METHYL-6-OXOHEFT-2-EOIC ACID

Martin G. Banwell[a]; Jasmine C. Jury[a]
[a] Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT, AUSTRALIA

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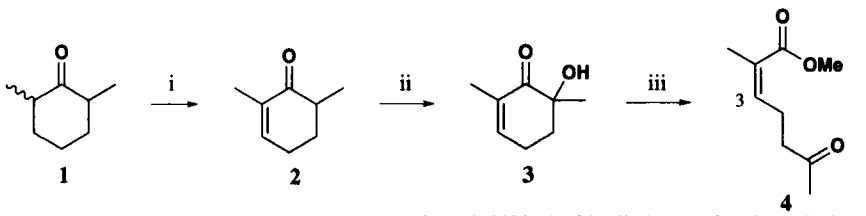
STEREOSELECTIVE SYNTHESES OF THE METHYL ESTERS OF (*E*)- AND (*Z*)-2-METHYL-6-OXOHEPT-2-ENOIC ACID

Submitted by Martin G. Banwell* and Jasmine C. Jury
(10/22/03)

Research School of Chemistry, Institute of Advanced Studies
The Australian National University, Canberra, ACT 0200, AUSTRALIA
E-mail: mgb@rsc.anu.edu.au

In connection with another study, we required access to preparatively useful quantities of each of the title keto-esters **4** and **8**. Both compounds have been described previously[1-3] and the latter has been exploited[1] in a total synthesis of an ionone component found in fragrant oils extracted from a Himalayan plant. However, these previous approaches have suffered from a need to separate *E*- and *Z*-isomeric forms of appropriate precursors[1] or other purification problems.[2,3] Herein we detail new, efficient and completely stereoselective approaches to each of these useful synthons that avoids the need for any chromatographic or other separation of isomers and which can be conducted on scales comparable to those reported earlier.

The route leading to the *Z*-isomer **4** is shown in *Scheme 1* and starts with the conversion of commercially available 2,6-dimethylcyclohexanone (**1**) into the corresponding unsaturated

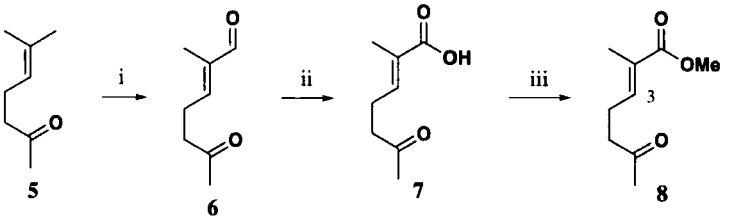


Reagents and conditions: i) NBS, AIBN (cat.), $ClCH_2CH_2Cl$, 83°C, 4.75 h; ii) KHMDS, toluene/THF, -78°C, 0.75 h then 3-phenyl-2-phenylsulfonyl oxaziridine, -78°C, 1 h; iii) $Pb(OAc)_4$, C_6H_6/MeOH, 40°C, 3 h.

Scheme 1

equivalent **2** using a simple and effective (60%) bromination/dehydrobromination sequence developed by Kende *et al.*[4] α-Hydroxylation of compound **2** was achieved using the Davis oxaziridine[5] and the resulting previously unreported acyloin **3** (66%) was then subject to oxidative cleavage with lead tetraacetate in methanol.[6] In this manner the target keto-ester **4** was obtained in 84% yield.

The synthesis of compound **8** (*Scheme 2*) started with the γ,δ-unsaturated ketone **5**, available commercially for *ca.* $0.12/g, which was oxidized in a regio- and stereo-selective manner with selenium dioxide to give the previously reported[7] keto-aldehyde **6** in 49% yield. Pinnick oxidation[8] of compound **6** afforded the corresponding acid **7** (87%), which was converted into ester **8** (95%) using diazomethane.



Reagents and conditions: i) SeO_2/silica gel, *t*-BuOOH, CH_2Cl_2, 18°C, 48 h; ii) $NaClO_2$, $NaH_2PO_4 \cdot H_2O$, 2-methyl-2-butene, *t*-BuOH/THF/water, 0-18°C, 20 h; iii) CH_2N_2, CH_2Cl_2/diethyl ether, 18°C, 2 h

Scheme 2

The ^1H NMR spectral data derived from each of compounds **4** and **8** matched those reported in the literature. Furthermore, the previously unreported ^{13}C NMR data were also in full accord with the assigned structures. The illustrated double-bond geometries in each of these products follows from the chemical shift of the C-3 proton which resonates at δ 5.82 for compound **4** and δ 6.63 for isomer **8**. The latter shift reflects the deshielding effect exerted by the carbomethoxy group on the *cis*-related proton at C-3 in compound **8**. NOESY experiments provided further support for these assignments.

EXPERIMENTAL SECTION

General experimental procedures have been described elsewhere.[9] Lead tetraacetate (Aldrich) was dried under vacuum over a mixture of phosphorus pentoxide and potassium hydroxide pellets before being used.

2,6-Dimethyl-2-cyclohexen-1-one (2).- The conversion of 2,6-dimethylcyclohexanone (**1**, Aldrich) into the title compound was carried out according to the method of Kende *et al.*[4] Thus, a magnetically stirred solution of ketone **1** (4.44 g, 35 mmol) in 1,2-dichloroethane (30 mL) was heated at reflux then treated with *N*-bromosuccinimide (6.94 g, 39 mmol) and AIBN (71 mg, 0.43 mmol). After a further 4.75 h, the reaction mixture was cooled to 18°C then diluted with diethyl ether (30 mL), washed with sodium metabisulfite (1 × 50 mL of a 5 w/v% aqueous solution), sodium bicarbonate (1 × 50 mL of a saturated aqueous solution) and brine (1 × 50 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil. Flash chromatography of this material (silica gel, 2:98 → 1:9 v/v ethyl acetate/hexane gradient elution) afforded 2,6-dimethyl-2-cyclohexen-1-one (**2**)[4] (2.60 g, 60%) as a clear, colorless oil. ^1H NMR ($CDCl_3$): δ 6.58 (m, 1 H), 2.34–2.20 (complex m, 3 H), 1.94 (m, 1 H), 1.66 (dd, *J* = 3.2 and 1.7 Hz, 3 H), 1.60 (m, 1 H), 1.03 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$): δ 202.2, 144.4, 134.7, 41.4, 31.1, 25.1, 15.9, 15.0; IR (NaCl): ν_{max} 2963, 2928, 1672, 1455, 1375, 1115, 995, 883 cm^{-1}; MS: *m/z* 124 ($M^{+\cdot}$, 39%), 82 (100), 54 (30).

2,6-Dimethyl-6-hydroxy-2-cyclohexen-1-one (3).- A solution of ketone **2** (2.49 g, 21 mmol) in THF (55 mL) was added to a magnetically stirred solution of potassium hexamethyldisilazide (44.3 mL of an 0.5 M solution in toluene, 22 mmol) in THF (90 mL) maintained at –78°C under

a nitrogen atmosphere. After 0.75 h the now bright-orange mixture was treated with a solution of 3-phenyl-2-phenylsulfonyl oxaziridine (9.06 g, 34 mmol) in THF (30 mL) and the resulting mixture stirred at –78°C for 1 h then quenched with NH_4Cl (25 mL of a saturated aqueous solution) and warmed to 18°C. The separated aqueous phase was extracted with diethyl ether (3 × 100 mL) and the combined organic phases washed with brine (1 × 300 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica gel, 5:1 v/v hexane/ethyl acetate elution). Concentration of the appropriate fractions (R_f 0.3) afforded the title acyloin **3** (1.86 g, 66%) as a clear, colorless oil. ^1H NMR ($CDCl_3$): δ 6.57 (m, 1 H), 3.75 (broad s, 1 H, OH), 2.29 (m, 2 H), 2.03–1.85 (complex m, 2 H), 1.68 (dd, J = 3.4 and 1.9 Hz, 3 H), 1.18 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ 202.9, 145.3, 132.3, 72.8, 35.5, 24.1, 23.8, 15.5; IR (NaCl): ν_{max} 3489, 2974, 2929, 1671, 1357, 1341, 1197, 1151, 1099, 1028, 983, 883 cm^{-1}; MS: *m/z* 140 ($M^{+\cdot}$, <1%), 112 (61), 82 (100), 54 (32); HRMS: $C_8H_{12}O_2$ requires $M^{+\cdot}$, 140.0837. Found $M^{+\cdot}$, 140.0839.

(*Z*)-2-Methyl-6-oxohept-2-enoic Acid Methyl Ester (4).- A magnetically stirred solution of compound **3** (965 mg, 6.9 mmol) in methanol (13 mL) was treated, portionwise, with a solution of lead tetraacetate (6.06 g, 13.7 mmol) in benzene (55 mL) and the resulting mixture heated at 40°C for 3 h. The cooled reaction mixture was then treated with water (70 mL) and diethyl ether (70 mL). The separated aqueous phase was extracted with dichloromethane (1 × 100 mL) then diethyl ether (1 × 100 mL) and the combined organic phases washed with $NaHCO_3$ (1 × 50 mL of a saturated aqueous solution) and brine (1 × 50 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil. Flash chromatography of this material (silica gel, 5:1 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_f 0.4) afforded the title keto-ester **4**[1] (980 mg, 84%) as a clear, colorless oil. ^1H NMR ($CDCl_3$): δ 5.82 (m, 1 H), 3.61 (s, 3 H), 2.56 (m, 2 H), 2.45 (m, 2 H), 2.02 (s, 3 H), 1.75 (d, J = 1.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$): δ 207.6, 167.8, 141.0, 127.6, 51.0, 42.7, 29.4, 23.6, 20.2; IR (NaCl): ν_{max} 2954, 1712, 1646, 1456, 1436, 1365, 1241, 1129, 1052, 770 cm^{-1}; MS: *m/z* 170 ($M^{+\cdot}$, 1%), 138 (71), 127 (28), 95 (100), 67 (45); HRMS: $C_9H_{14}O_3$ requires $M^{+\cdot}$, 170.0943. Found $M^{+\cdot}$, 170.0941.

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.65; H, 8.62

(*E*)-2-Methyl-6-oxohept-2-enal (6).- Selenium dioxide adsorbed on silica was prepared by adding the oxide (557 mg, 5.0 mmol, 0.5 mole equiv.) to a magnetically stirred suspension of silica gel 60 (9.2 g) in ethanol/water (60 mL of a 5:1 v/v mixture) then concentrating the resulting mixture on a rotary evaporator until a free flowing powder was obtained. Dichloromethane (30 mL) and *t*-butylhydroperoxide (2.5 mL of a 5–6 M solution in nonane, 12.5-15 mmol, Aldrich) were added to this powder and the resulting slurry treated with alkene **5** (1.28 g, 10.2 mmol), stirred at 18°C for 48 h then filtered through a sintered glass funnel. The solids thus retained were washed with dichloromethane (200 mL) and the combined filtrates were cooled to 0°C (ice-bath) then treated, over 0.5 h, with sodium metabisulfite (100 mL of a

20% w/v aqueous solution). The separated aqueous phase was extracted with dichloromethane (3 × 100 mL) and the combined organic phases washed with sodium bicarbonate (1 × 100 mL of a saturated aqueous solution) and brine (1 × 100 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting clear colorless oil was subjected to flash chromatography (silica gel, 5:1 → 2:1 v/v hexane/ethyl acetate gradient elution). Concentration of the appropriate fractions (R_f 0.2 in 2:1 v/v ethyl acetate/hexane) afforded the title keto-aldehyde **6**[7] (695 mg, 49%) as a clear, colorless oil. ^{1}H NMR ($CDCl_3$): δ 9.34 (s, 1 H), 6.41 (m, 1 H), 2.68–2.52 (complex m, 4 H), 2.15 (s, 3 H), 1.72 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ 208.7, 135.9, 123.8, 68.4, 43.2, 29.9, 21.8, 13.6; IR (NaCl): ν_{max} 2978, 2931, 1717, 1685, 1645, 1363, 1161, 1048, 873 cm^{-1}; MS: *m/z* 140 ($M^{+\cdot}$, <1%), 122 (17), 112 (28), 97 (100); HRMS: $C_8H_{12}O_2$ requires $M^{+\cdot}$, 140.0837. Found $M^{+\cdot}$, 140.0838.

(*E*)-2-Methyl-6-oxohept-2-enoic Acid (7).- A magnetically stirred solution of aldehyde **6** (205 mg, 1.46 mmol) in *t*-butanol (8 mL) and water (2 mL) was treated with 2-methyl-2-butene (1.5 mL of a 2 M solution in THF, 3 mmol) followed by sodium dihydrogen phosphate monohydrate (244 mg, 1.56 mmol). After standing for 0.2 h at 18°C, the resulting solution was cooled to 0°C and treated, in one portion, with sodium chlorite (384 mg, 4.25 mmol). Stirring was continued at 0-18°C for 20 h then the reaction mixture was quenched with HCl (6 mL of a 0.5 M aqueous solution) and extracted with dichloromethane (4 × 25 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a colorless oil which was subjected to flash chromatography (silica gel, 2:1 → 1:1 v/v hexane/ethyl acetate gradient elution). Concentration of the appropriate fractions (R_f 0.2 in 2:1 v/v hexane/ethyl acetate) afforded the title ketoacid **7** (198 mg, 87%) as a clear, colorless oil. ^{1}H NMR ($CDCl_3$): δ 6.81 (m, 1 H), 2.60 (t, *J* = 6.9 Hz, 2 H), 2.46 (t, *J* = 6.9 Hz, 2 H), 2.16 (s, 3 H), 1.85 (broad s, 3 H); ^{13}C NMR ($CDCl_3$): δ 207.3, 173.2, 142.9, 128.0, 41.8, 29.9, 22.9, 12.0; IR (NaCl): ν_{max} 3414, 2930, 1711, 1689, 1644, 1417, 1363, 1282, 1166 cm^{-1}; MS: *m/z* 156 ($M^{+\cdot}$, 1%), 155 (3), 154 (5), 138 (41), 95 (77), 43 (100); HRMS: $C_8H_{12}O_3$ requires $M^{+\cdot}$, 156.0786. Found $M^{+\cdot}$, 156.0783.

(*E*)-2-Methyl-6-oxohept-2-enoic Acid Methyl Ester (8).- A solution of the carboxylic acid **7** (84 mg, 0.5 mmol) in dichloromethane (3 mL) was cooled to *ca.* −10°C (ice-salt bath) then treated with an excess of ethereal diazomethane. The resulting mixture was allowed to warm to 18°C and after standing for 2 h was concentrated under reduced pressure to give a light-yellow oil. Flash chromatography of this material (silica gel, 5:1 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_f 0.15) afforded the title keto-ester **8**[1–3] (87 mg, 95%) as a clear, colorless oil. ^{1}H NMR ($CDCl_3$): δ 6.63 (tq, *J* = 7.3 and 1.5 Hz, 1 H), 3.68 (s, 3 H), 2.55 (t, *J* = 7.1 Hz, 2 H), 2.40 (m, 2 H), 2.12 (s, 3 H), 1.81 (broad s, 3 H); ^{13}C NMR ($CDCl_3$): δ 207.6, 167.8, 141.0, 127.6, 51.0, 42.7, 29.4, 23.6, 20.2; IR (NaCl): ν_{max} 2953, 1714, 1650, 1436, 1268, 1123, 746 cm^{-1}; MS: *m/z* 170 ($M^{+\cdot}$, 1%), 138 (67), 95 (100); HRMS: $C_9H_{14}O_3$ requires $M^{+\cdot}$, 170.0943. Found $M^{+\cdot}$, 170.0940.

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.32; H, 7.98.

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