Improved Total Synthesis of (±)-Drimenin

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A highly efficient three-step synthesis of the sesquiterpene (±)-drimenin (**4**) from the β-keto ester (**1**) is described. Compound (**1**) was prepared in five steps from linalool.

Several drimane sesquiterpenes show interesting biological activities[1] and a number of total syntheses of this important class of natural products have recently been published.[2-4] Drimenin (**4**) and isodrimenin (**5**), two naturally occurring isomeric lactones,[3] can provide a convenient entry to more functionalised and more biologically active members of the drimane class, for example warburganal[2a,2b] and polygodial.[2a,2b] The reported total syntheses[2a,4] of compounds (**4**) and (**5**) are not very satisfactory, especially as large quantities of material are required.

We report in this paper, a high-yielding total synthesis of (±)-drimenin (**4**) in three steps from the known β-keto ester (**1**)[5] (Scheme 1).

A Wittig reaction of compound (**1**) with $Ph_3P{=}CH_2$, carried out by refluxing $Ph_3P^+MeBr^-$ and $NaNH_2$ in toluene followed by decantation at ambient temperature in a salt-free solution,[6] gave the oily unsaturated ester (**2**) in 85% yield and high epimeric purity [δ (60 MHz) 3.5 (fine s)]. The reaction was carried out under very mild conditions and no epimerisation of the 1β-CO_2Me group occurred. The use of more vigorous conditions, *e.g.* refluxing the reaction mixture, or of other bases for the formation of the ylide $Ph_3P{=}CH_2$[7] such as Bu^nLi in ether or tetrahydrofuran, NaH in dimethyl sulphoxide, or even $NaNH_2$ in toluene without decantation, gave an epimeric mixture of the 1α- and 1β-methoxycarbonyl methylene esters (**2**) [δ (60 MHz) 3.42 and 3.5 (two fine s)] in various proportions. The epimers could not be separated by conventional chromatographic techniques.

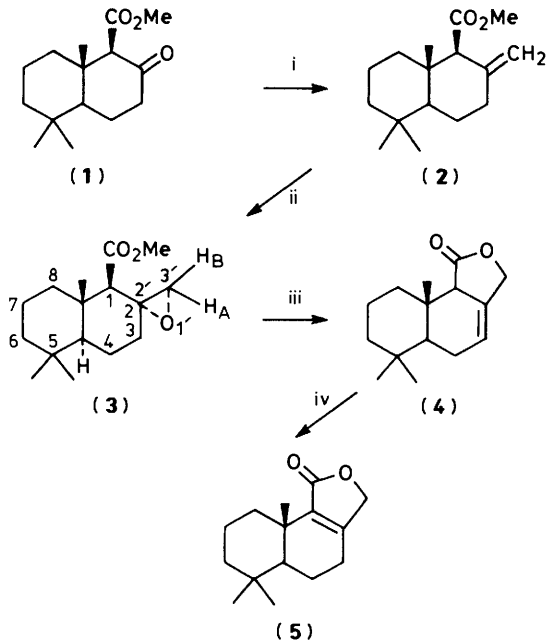
Attempts to obtain the corresponding acid, known as albicanic acid,[8] by refluxing the ester in alcoholic KOH or in quinoline–acetic acid,[9] or with Bu^tOK in dimethyl sulphoxide[10] were not successful.

Epoxidation of compound (**2**) by *m*-chloroperbenzoic acid in methylene dichloride produced the crystalline epoxy ester (**3**) in 90% yield. The t.l.c. properties and the ^1H n.m.r. spectra of this compound (**3**) (see Experimental section) suggested it to be a single epimer. As the formation of the epoxide on the β face of the molecule is unlikely because of the steric hindrance of the 1β-CO_2Me and 8aβ-Me groups, it was assigned the α-epoxide structure (**3**).

Acid-catalysed treatment of compound (**3**) with toluene-*p*-sulphonic acid in refluxing chloroform gave crystalline (±)-drimenin (**4**) quantitatively. One recrystallisation from hexane gave m.p. 96—97 °C (lit.,[2a,4c-f] 97—98 °C). All the spectroscopic data are in accord with the literature.[2a,4c-f] The overall yield for the three-step sequence was 75%.

Alkali-catalysed isomerisation of (±)-drimenin (**4**) by MeONa in methanol[3] gave pure crystalline (±)-isodrimenin (**5**) quantitatively. Compound (**5**) is a useful intermediate for the synthesis of further drimane-type sesquiterpenes.[2a,b]

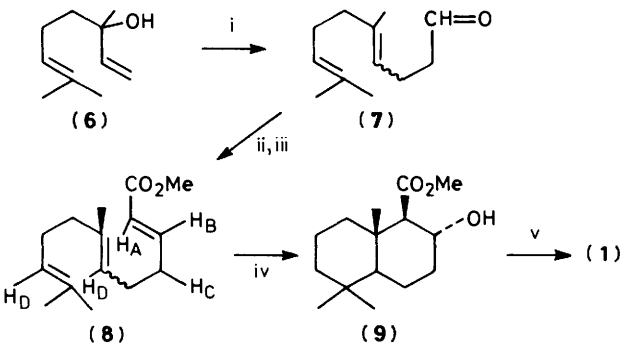
The quantities of drimenin or isodrimenin that can be obtained by the above method are limited by the availability of the β-keto ester (**1**). This key compound was obtained by Eschenmoser[5a] during a study of the biomimetic cyclisations of



Scheme 1. *Reagents:* i, $Ph_3P^+MeBr^-$, $NaNH_2$, toluene; ii, m-CPBA, CH_2Cl_2; iii, p-$MeC_6H_4SO_3H$, $CHCl_3$; iv, MeONa, MeOH

methyl 7,11-dimethyldodeca-2,6,10-trienoate (**8**) (Scheme 2). By separate and laborious synthesis of each of the four stereoisomers of the ester (**8**), and subsequent acid-catalysed cyclisation, Eschenmoser proved that the only requirement for the production of compound (**1**) with the desired stereochemistry was the *trans*-configuration of the Δ^2 double bond. We have developed a very simple synthesis starting from the (±)-linalool that is easily adapted to large-scale preparations and which gives the methyl ester (**8**) as a mixture of two geometrical Δ^6 *cis*- and *trans*-isomers; each of these has the necessary Δ^2 *trans* configuration, and the latter configuration readily gives the β-keto ester (**1**) (Scheme 2).

Thus, heating linalool (**6**) and ethyl vinyl ether in an autoclave at 180 °C for 8 h in the presence of H_3PO_4[11] gave the aldehyde (**7**) as a mixture of Δ^4 *cis*- and *trans*-isomers. Condensation of the aldehyde (**7**) with malonic acid in pyridine–piperidine solution[12] stereoselectively gave the Δ^2 *trans*-dodecatrienoic acid. The crude acid was converted into its methyl ester (**8**) and purified by distillation (b.p. 110—120 °C, 1 mmHg). Cyclisation of compound (**8**) in formic acid–sulphuric acid[5a] gave a crystalline formate which, without purification, was saponified to the hydroxy ester (**9**). Jones oxidation[13] of compound (**9**) gave the pure (±)-β-keto ester (**1**), the physical properties of which are consistent with the literature.[5] The overall yield from linalool was 36%.



Scheme 2. *Reagents:* i, ethyl vinyl ether; ii, $CH_2(CO_2H)_2$; iii, MeOH, H^+; iv, Eschenmoser's cyclisation; v, Jones reagent

Experimental

M.p.s were determined with a Büchi 510 apparatus and are uncorrected. I.r. spectra were obtained for solutions in CCl_4 and recorded on a Perkin-Elmer 247 spectrometer. ^1H N.m.r. spectra were obtained for solutions in CCl_4, with tetramethylsilane as internal reference, at 60 MHz on a Varian E.M. 360 instrument at room temperature. Mass spectra were recorded on a Hewlett Packard 5980 A instrument. Analytical t.l.c. was carried out on Merck Kieselgel (G and HF_{254} or G and $AgNO_3$ 3.5%), using mixtures of ether–light petroleum as eluant, and were developed with aqueous H_2SO_4 or with iodine. Preparative column chromatography was effected on Kieselgel, Merck (0.063—0.200 mm) or on Florisil, Fluka (100—200 mesh). Ether refers to diethyl ether.

Methyl (1β,4aα,8aβ)-*Decahydro*-5,5,8a-*trimethyl*-2-*methylenenapthalene*-1-*carboxylate* (**2**).—A solution of $Ph_3P^+MeBr^-$ (28.6 g, 0.08 mol) and $NaNH_2$ (4 g, 0.102 mol) in toluene (250 ml) was heated under reflux for 3 h under nitrogen. After the suspension had settled (*ca.* 15 min), the decanted warm clear yellow solution was poured on to a solution of methyl (1β,4aα,8aβ)-decahydro-5,5,8a-trimethyl-2-oxonaphthalene-1-carboxylate (**1**) (10 g, 0.04 mol), in toluene (50 ml). The reaction mixture was stirred at room temperature for 1 h. Further ylide was extracted with anhydrous toluene (100 ml) by refluxing the residue of the settled suspension for 1 h, and poured into the solution of (**1**). Stirring was continued until the starting material disappeared (t.l.c.). The reaction mixture was washed twice with water, dried (Na_2SO_4) and the toluene was evaporated under reduced pressure. Most of the Ph_3PO was removed as a precipitate, by treatment of the semisolid residue twice with warm light petroleum (200 ml). After evaporation of the solvent the oily product was purified by column chromatography (eluant: light petroleum–ether 10:1). Pure *methylene ester* (**2**) (8.5 g, 85%) was obtained as an oil, $\nu_{max.}$ 3 080, 1 730, 1 640, and 890 cm^{-1}; δ_H 0.8 (6 H, s), 0.95 (3 H, s), 2.6 (1 H, s), 3.5 (3 H, s), and 4.6 (2 H, d, *J* 8 Hz); *m/z* 250 (M^+, 14%), 235 (8), 218 (5), 137 (100), 123 (99), and 114 (70) (Found: C, 76.9; H, 10.5. $C_{16}H_{26}O_2$ requires C, 76.80; H, 10.40%).

Methyl [1β,4aα,8aβ,2(1′)α]-*Octahydro*-5,5,8a-*trimethylnapthalene*-2(1H)-*spiro*-2′-*oxirane*-1-*carboxylate* (**3**).—A solution of *m*-chloroperbenzoic acid (7 g, 0.04 mol) in CH_2Cl_2 (80 ml) was added dropwise to a stirred solution of the methylene ester (**2**) (8.5 g, 0.034 mol) in CH_2Cl_2 (100 ml). Stirring was continued at room temperature for 3 h. The reaction was followed by t.l.c. The above mixture was washed with a dilute solution of Na_2SO_3, then twice with $NaHCO_3$ (5%) and with water until neutral. Removal of the solvent, after drying (Na_2SO_4), afforded the crude epoxy ester (**3**). Recrystallisation twice from light petroleum gave the pure *product* (**3**) (8.1 g, 90%), m.p. 94—96 °C; $\nu_{max.}$ 1 740 cm^{-1}; δ_H 0.68 (3 H, s), 0.72 (3 H, s), 2.35 (1 H, s), 2.3 (1 H_A, d, J_{AB} 6 Hz), 3.0 (1 H_B, d, J_{BA} 6 Hz), and 3.35 (3 H, s); *m/z* 266 (M^+, 0.5%), 251 (5.2), 235 (8), 219 (7), 141 (100), 137 (30), 130 (46), and 95 (34) (Found: C, 72.1; H, 9.7. $C_{16}H_{26}O_3$ requires C, 72.18; H, 9.77%).

(5aα,9aβ,9bβ)-5,5a,6,7,8,9,9a,9b-*Octahydro*-6,6,9a-*trimethylnaphtho*[1,2-c]*furan*-1(3H)-*one* (*Drimenin*) (**4**).—A solution of the epoxy ester (**3**) (6 g, 0.023 mol) and toluene-*p*-sulphonic acid (0.5 g) in $CHCl_3$ (100 ml) was refluxed for 3 h. The reaction was monitored by t.l.c. After cooling, the mixture was washed twice with water, dried (Na_2SO_4), and the solvent removed to leave a crystalline residue. This was recrystallised from methanol and gave pure drimenin (**4**) (5.1 g, 95%), m.p. 96—97 °C (lit.,[2a,4c–f] 97—98 °C). Sublimation of this product did not change the m.p.; $\nu_{max.}$ 1 780 cm^{-1}; δ_H 0.85 (3 H, s), 0.92 (6 H, s), 2.63 (1 H, br s), 4.52 (2 H, br s), and 5.65 (1 H, br s); *m/z* 234 (M^+, 1.8%), 219 (4.0), 124 (72), 111 (75), 109 (100), 107 (7.0), 91 (9.0), and 69 (12.0) (Found: C, 76.6; H, 9.7. Calc. for $C_{15}H_{22}O_2$: C, 76.92; H, 9.40%).

(5aα,9aβ)-4,5,5a,6,7,8,9,9a-*Octahydro*-6,6,9a-*trimethylnaphtho*[1,2-c]*furan*-1(3H)-*one* (*Isodrimenin*) (**5**).—This compound was prepared by isomerisation of drimenin (**4**) (0.5 g, 0.02 mol) in MeONa–MeOH (20 ml) as described in the literature.[3] Pure crystalline isodrimenin (**5**) was obtained quantitatively. Recrystallisation from hexane gave a sample (0.45 g), m.p. 89—91 °C; $\nu_{max.}$ 1 765, 1 670 cm^{-1}; δ_H 0.9 (6 H, s), 1.1 (3 H, s), and 4.35 (2 H, s); *m/z* 234 (M^+, 36.5%), 219 (100), 201 (5.0), 189 (7), 163 (12), 151 (54), and 91 (27).

5,9-*Dimethyldeca*-4,8-*dienal* (**7**).—Synthetic linalool (**6**) (770 g, 5 mol), ethyl vinyl ether (720 g, 10 mol), and H_3PO_4 (3 ml) were heated in an autoclave at 140 °C for 8 h. The solution was treated with triethylamine (5 ml) and the volatile by-products were removed under water pump vacuum. Distillation of the residue under reduced pressure gave the aldehyde (**7**) as a mixture of two geometrical isomers (680 g, 75%), b.p. 92—96 °C (1.5 mmHg) (lit.,[11] 120 °C, 17 mmHg).

Methyl 7,11-*Dimethyldodeca*-2,6,10-*trienoate* (**8**).—To a stirred solution of malonic acid (104 g, 1 mol) in pyridine (300 ml) and piperidine (30 ml), compound (**7**) (90 g, 0.5 mol) was added dropwise during 1 h, at room temperature. This mixture was set aside at this temperature for 5 h and was then heated on a water-bath for about 2 h, until no more CO_2 was evolved. After the mixture had been cooled, it was made neutral with 10% aqueous HCl (2 l) and extracted with ether. The usual work-up gave the crude acid (**8**) (108 g). Esterification of this acid was carried out in methanol (500 ml) and H_2SO_4 (3 ml). The mixture was refluxed for 8 h, cooled to room temperature, diluted with cold water (2 l), and extracted with ether to give the crude methyl ester (**8**) (115 g). Purification by distillation under reduced pressure gave a colourless oil, b.p. 110—120 °C (1 mmHg) (96 g overall yield 82%); $\nu_{max.}$ 1 725, 1 660 cm^{-1}; δ_H 1.55 (9 H, 2 s), 2.0 (8 H, m), 3.55 (3 H, s), 4.98 (2 H_D, br s), 5.65 (1 H_A, d, J_{AB} 14 Hz), and 6.82 (1 H_B, 2 t, J_{AB} 14 Hz J_{BC} 6 Hz).

Methyl (1β,4aα,8aβ)-*Decahydro*-5,5,8a-*trimethyl*-2-*oxonaphthalene*-1-*carboxylate* (**1**).—Following the method developed by Eschenmoser,[5a] the triene methyl ester (**8**) (30 g, 0.127 mol) was added slowly during 1 h to a cold solution of 99% HCO_2H (600 ml) and H_2SO_4 (60 ml). The mixture was stirred for 3 h at room temperature. It was then poured into ice-cold water and extracted with ether. After the usual work-up a crude residue (28.6 g, 80%) was obtained. Recrystallisation from hexane gave white crystals of the formate, m.p. 106—108 °C (lit.,[5a] 109 °C).

The crude formate (25 g, 0.088 mol) was hydrolysed in a solution of KOH (10 g), methanol (500 ml), and water (50 ml) overnight at room temperature. After acidification with acetic acid (10 ml), the solution was extracted with ether and treated as usual. The crude product (19.2 g), recrystallised from hexane, gave white crystals of the 2α-hydroxy-1β-methyl ester (**9**) (16.2 g 72%), m.p. 90—92 °C (lit.,[5a] 91—92 °C).

A solution of the hydroxymethyl ester (**9**) (15.2 g, 0.06 mol), in acetone (300 ml), was oxidised at 20 °C with Jones reagent[13] until the orange colour persisted (50 ml). After 15 min, the mixture was poured in cold water (2 l) and extracted with ether. The ethereal layer was washed with saturated NaCl, $NaHCO_3$, and water, dried (Na_2SO_4), and evaporated. The white solid (15 g) was recrystallised from hexane to give pure crystalline β-keto ester (**1**) (13.6 g, 90%), m.p. 85—86 °C (lit.,[5a] 83.5—84 °C; lit.,[5b] 85.5—87 °C); $\nu_{max.}$ 1 720, 1 760 cm^{-1}; δ_H 0.87 (3 H, s) 0.93 (3 H, s), 1.1 (3 H, s), 2.97 (1 H, s), and 3.55 (3 H, s) (Found: C, 71.1; H, 9.4. Calc. for $C_{15}H_{24}O_3$: C, 71.42; H, 9.52%).

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