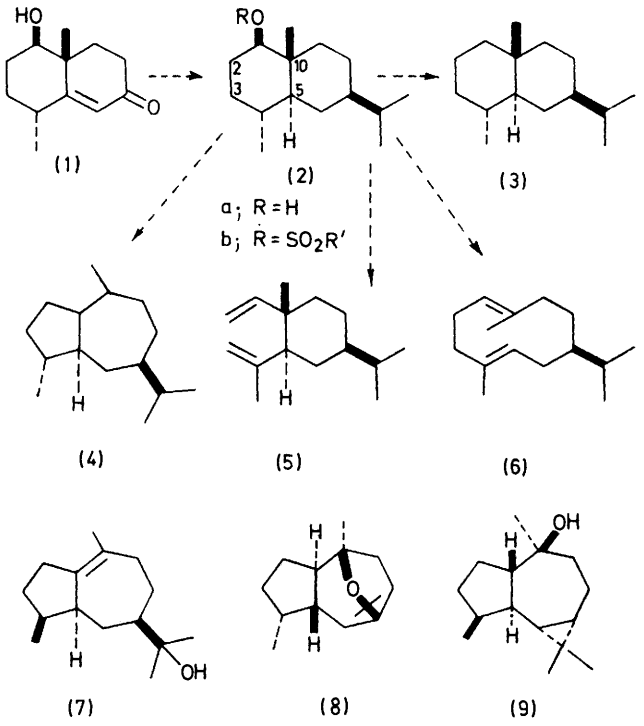
# Synthesis of 4,4a-5,6,7,8-Hexahydro-5β-hydroxy-4aβ,8α-dimethylnaphthalen-2(3*H*)-one, a Versatile Intermediate for Sesquiterpene Synthesis

By **Michiharu Kato, Hiroshi Kurihara, Hiroshi Kosugi, Masataka Watanabe, Shigeru Asuka, and Akira Yoshikoshi,*** Chemical Research Institute of Non-aqueous Solutions, Tohoku University, Sendai 980, Japan

Two routes have been examined from 5β-acetoxy-4,4a,5,6,7,8-hexahydro-4aβ-methylnaphthalen-2(3*H*)-one (10) to 4,4a,5,6,7,8-hexahydro-5β-hydroxy-4aβ,8α-dimethylnaphthalen-2(3*H*)-one (1), a key intermediate for the synthesis of some types of sesquiterpenoid. The route shown in Scheme 2 is preferable to that in Scheme 1 (although the former is slightly the more lengthy), giving compound (1) in *ca.* 48% overall yield from (10).

THE title compound (1) is potentially a versatile key intermediate for the synthesis of some representative types of sesquiterpene. Compound (2a) would be obtainable on



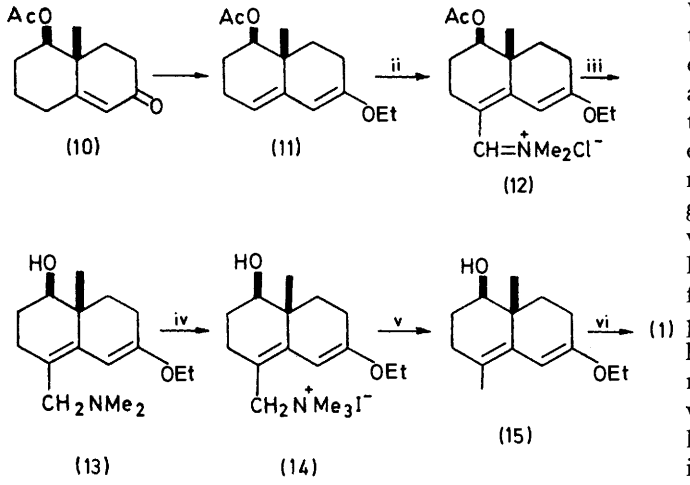

saturation of the olefinic double bond followed by introduction of an isopropyl carbon unit at the ketone function. Selinane (3) or guaiane (4) sesquiterpenes could be derived from (2a) on removal of the hydroxy-group or by solvolytic rearrangement after conversion of the hydroxy-group into an appropriate leaving group such as sulphonates [as in (2b)], respectively. In fact, some guaiane sesquiterpenoids [bulnesol [1] (7), kessane [2] (8), and globulol [3] (9)] have been synthesised from compound (1). On the other hand, fission of the peripheral (2,3-) or central (5,10-) bond would lead to elemane (5) or germacrane (6) sesquiterpenes.

Previously we reported [1] the synthesis of the hydroxy-octalone (1) by the route shown in Scheme 1 from the acetoxy-octalone (10), readily available from the Wieland-Miescher ketone *via* a known procedure.[4] We describe here the details of this synthesis of (1) and an improved route (Scheme 2).

The unstable enol ether (11) was prepared from (10) according to Burn's procedure,[5] *i.e.* by reaction with triethyl orthoformate and a catalytic amount of toluene-*p*-sulphonic acid in dioxan (Scheme 1). The crude enol ether was successively treated with the Vilsmeier reagent ($Me_2N{\cdot}CHO$–$POCl_3$ or $Me_2N{\cdot}CHO$–$COCl_2$), lithium aluminium hydride, and then methyl iodide to obtain the ammonium salt (14) *via* the iminium salt (12) and the amine (13). None of compounds (12)—(14) was sufficiently stable for analytically pure material to be obtained, although they were characterised spectroscopically. Reductive cleavage of the carbon–nitrogen bond in (14) was performed with Raney nickel. This reaction, however, was capricious; it gave the hydroxy-octalone (1) in good yield in some cases after acidic hydrolysis of the resultant enol ether (15) (which was also unstable), but complex mixtures were produced in other cases, and optimum conditions for this reaction were not established. The poor reproducibility might be ascribed to high sensitivity of the reaction to the activity of the Raney nickel used, or to impurities in the substrate which deactivated the Raney nickel, or to both. An equatorial orientation of the newly formed methyl group in (1) was ascertained from the coupling constant (1.8 Hz [6]) of the olefinic

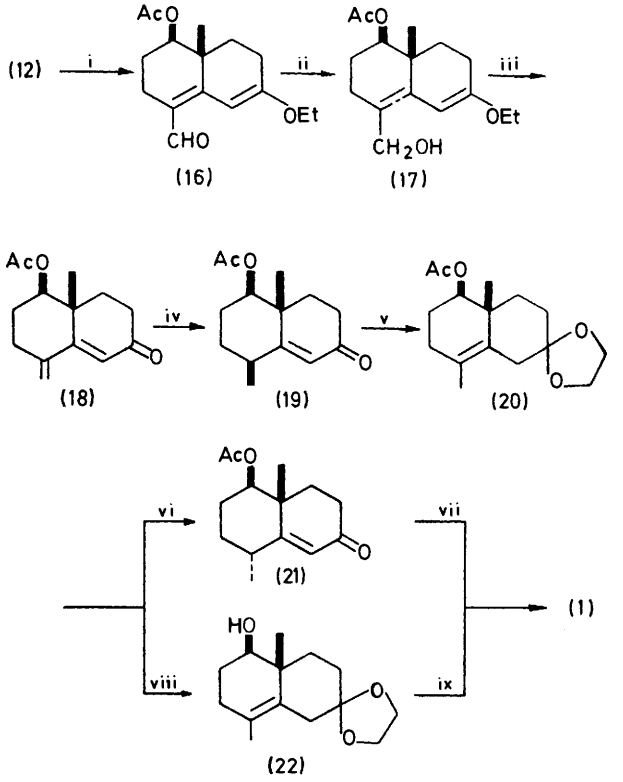
[1] M. Kato, H. Kosugi, and A. Yoshikoshi, *Chem. Comm.*, 1970, 185.
[2] M. Kato, H. Kosugi, and A. Yoshikoshi, *Chem. Comm.*, 1970, 934.
[3] J. A. Marshall and J. A. Ruth, *J. Org. Chem.*, 1974, **39**, 1971.
[4] C. B. Boyce and J. S. Whitehurst, *J. Chem. Soc.*, 1960, 2680.
[5] D. Burn, *Tetrahedron*, 1964, **20**, 597.
[6] H. J. Ringold, *J. Amer. Chem. Soc.*, 1963, **85**, 1699.

$^1$H n.m.r. doublet. The best result obtained from reductive cleavage of the ammonium salt (14) was an overall yield of the hydroxy-octalone (1) from (10) of *ca.* 60%.




SCHEME 1 i, $(EtO)_3CH$–TsOH; ii, Vilsmeier reagent; iii, $LiAlH_4$; iv, MeI; v, Raney Ni; vi, $H_2SO_4$–$H_2O$

Although the foregoing route to (1) was relatively expeditious, the obstacle in the reductive cleavage of (14) could not be circumvented. We then turned to another




SCHEME 2 i, NaOAc–$H_2O$; ii, $NaBH_4$; iii, HOAc–$H_2O$; iv, $H_2$–Pd($BaSO_4$); v, $(CH_2OH)_2$–TsOH; vi, $Me_2CO$–TsOH; vii, $K_2CO_3$–MeOH; viii, $LiAlH_4$; ix, HCl–$H_2O$

route (Scheme 2). The formyl enol ether (16) was obtained as a stable crystalline compound in high yield on hydrolysis of the crude iminium salt (12) with aqueous sodium acetate, and reduction of the product with borohydride afforded the corresponding alcohol (17). This acid- and heat-sensitive alcohol was immediately treated with acetic acid at room temperature to achieve dehydration, affording the dienone (18) in high yield. The oily octalone (19) was then obtained by partial hydrogenation over palladium–barium sulphate. As expected, the secondary methyl group in (19) was axial, as was evidenced by the singlet [6] nature of the olefinic proton n.m.r. signal. To epimerise the axial secondary methyl group to an equatorial one, the acetoxy-octalone (19) was treated with toluene-*p*-sulphonic acid in benzene; however the product was contaminated with an unidentified by-product which was difficult to remove on a preparative scale. In an improved procedure, the crystalline acetal (20) was prepared, and deacetalised after recrystallisation. The resultant acetoxy-octalone (21) was hydrolysed with potassium carbonate giving the hydroxy-octalone (1). The final product was also derived in a similar overall yield from (20) by reduction with lithium aluminium hydride of the acetal (20), and hydrolysis of the resultant hydroxy-octalin (22).

By Scheme 2, the hydroxy-octalone (1) was prepared from (10) in *ca.* 48% over-all yield.

## EXPERIMENTAL

I.r. spectra were taken with a Hitachi EPI-32 spectrophotometer, and n.m.r. spectra with a JEOL C-60-HL spectrometer (60 MHz) for solutions in $CDCl_3$ unless otherwise stated. Tetramethylsilane was used as an internal standard and coupling constants are given in Hz.

*5β-Acetoxy-2-ethoxy-3,4,4a,5,6,7-hexahydro-4aβ-methylnaphthalene* (11).—Ethyl orthoformate (33 ml, *ca.* 0.2 mol) and toluene-*p*-sulphonic acid (600 mg) were added to a solution of the acetoxy-octalone [4] (10) (48 g, 0.216 mol) in dry dioxan (200 ml), and the mixture was stirred at room temperature for 3 h. Pyridine (15 ml) was added, and the mixture was poured into ice–water and extracted with ether. The extract was washed with water and brine, and dried. Removal of the solvent left the enol ether (11), a glassy mass (52.2 g), $\nu_{max.}$ (film) 1 735, 1 653, 1 620, 1 245, and 1 030 cm$^{-1}$, $\delta$ ($CCl_4$) 1.01 (3 H, s), 1.14 (3 H, t, *J* 7), 1.99 (3 H, s), 3.70 (2 H, q, *J* 7), 4.5—4.8 (1 H, m, AcOC*H*), and 4.97 (2 H, m, =CH).

Although analytically pure material could not be obtained, the crude product was sufficiently pure to be used in the next step (as shown by g.l.c.).

*8-Dimethylaminomethyl-2-ethoxy-5β-hydroxy-3,4,4a,5,6,7-hexahydro-4aβ-methylnaphthalene* (13).—A solution of dimethylformamide (22 g, 0.3 mol) in dry dichloromethane (100 ml) was added to a stirred solution of phosgene * (22 g, 0.22 mol) in the same solvent (100 ml) in an ice-bath. The Vilsmeier reagent was precipitated as a solid with evolution of carbon dioxide. A solution of the enol ether (11) (40 g, 0.16 mol) in the same solvent (100 ml) was added dropwise, giving a red solution immediately. After stirring for 3 h, the solvent was removed *in vacuo* at room temperature to leave a viscous deep red oil. A solution of the oil in dry tetrahydrofuran (500 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (8.0 g) in dry ether (400 ml) under nitrogen, and the mixture was stirred

* More reproducible results were obtained with phosphoryl chloride, see later.

at room temperature for 12 h. The excess of reagent was decomposed with wet ether and then with a small quantity of water. Work-up gave the crude tertiary amine (13) (32.9 g) as a pale yellow oil, $\nu_{max.}$ (film) 3 400, 1 643, and 1 615 $cm^{-1}$, δ 1.00 (3 H, s), 1.30 (3 H, t, *J* 7), 2.20 (6 H, s, $NMe_2$), 3.85 (2 H, q, *J* 7), and 5.62 (1 H, s, =CH).

Attempts to obtain a pure sample were unsuccessful.

*8-Dimethylaminomethyl-2-ethoxy-5β-hydroxy-3,4,4a,5,6,7-hexahydro-4aβ-methylnaphthalene Methiodide* (14).—Methyl iodide (14 ml, *ca.* 0.22 mol) was added to a stirred solution of the crude amine (13) (25.0 g) in dry ethanol (100 ml) in an ice-bath, and stirring was continued at room temperature for several h. A small quantity of dry ether was added, and the mixture was stirred for an additional few min. The precipitate was collected by filtration, washed with dry ether several times, and then dried *in vacuo* to yield the ammonium salt (14) as a hygroscopic powder (39 g), m.p. 200 °C (decomp.), $\nu_{max.}$ (KBr) 3 400, 1 630, and 1 600w $cm^{-1}$. Attempts to obtain an analytically pure sample were unsuccessful.

*4,4a,5,6,7,8-Hexahydro-5β-hydroxy-4aβ,8α-dimethylnaphthalen-2(3H)-one* (1).—The best result for the reductive cleavage of the ammonium salt (14) was obtained as follows. A suspension of (14) (12 g) and Raney nickel (W-2; 100 g) in dry ethanol (250 ml) was saturated with hydrogen at room temperature, and the mixture was refluxed for 3 h with stirring. After filtration, the solution was concentrated *in vacuo* leaving an oil, which was extracted with ether several times. The combined extracts were evaporated to give the crude hydroxy-enol ether (15) (5.2 g) as an oil, $\nu_{max.}$ (film) 3 400, 1 645, and 1 620 $cm^{-1}$, δ 0.93 (3 H, s,) 1.58 (3 H, s), 3.40 (1 H, t, *J* 9, C*H*OH), and 5.23 (1 H, s, =CH).

The crude (15) was dissolved in 2N-sulphuric acid (15 ml) and ethanol (30 ml), and stirred at room temperature for 12 h. The mixture was concentrated *in vacuo*, and the residue was added to water and extracted with dichloromethane. Work-up gave an oil, which was filtered through a short silica gel column in ether. Removal of the solvent from the filtrate left the *hydroxy-octalone* (1) (4.0 g) as an oil, b.p. 135 °C (bath temp.) at 0.2 mmHg, $\nu_{max.}$ (film) 3 400, 1 660, and 1 610 $cm^{-1}$, δ 1.07 (3 H, d, *J* 6), 1.20 (3 H, s), 3.07 (1 H, s, OH), 3.45 (1 H, q, *J* 6, C*H*OH), and 5.81 (1 H, d, *J* 1.8). A sample for analysis was obtained by evaporative distillation *in vacuo* (Found: C, 74.0; H, 9.7. $C_{12}H_{18}O_2$ requires C, 74.2; H, 9.3%).

*5β-Acetoxy-2-ethoxy-8-formyl-3,4,4a,5,6,7-hexahydro-4aβ-methylnaphthalene* (16).—To prepare the Vilsmeier reagent, phosphoryl chloride (2.58 ml, *ca.* 33.9 mmol) was added dropwise to purified dimethylformamide (7.56 ml, *ca.* 109 mmol) with stirring under nitrogen in an ice-bath. After the exothermic reaction had subsided, a solution of the freshly prepared enol ether (11) (6.32 g, 30 mmol) in dimethylformamide (20 ml) was added dropwise. The mixture was then stirred at room temperature for 4 h and poured into a large excess of saturated aqueous sodium acetate in an ice-bath. The precipitate was collected by filtration, washed with cold water, and dried *in vacuo* at room temperature, giving the crude formyl enol ether (16) (6.50 g). Recrystallisation from dichloromethane gave pale yellow *needles*, m.p. 126—127 °C, $\nu_{max.}$ (KBr) 1 728, 1 645, 1 605, and 1 572 $cm^{-1}$, δ 1.20 (3 H, s), 1.37 (3 H, t, *J* 7), 1.5—2.8 (8 H, m), 2.10 (3 H, s, Ac), 3.96 (2 H, q, *J* 7), 4.80 (1 H, m, AcOC*H*), 6.37 (1 H, s, =CH), and 10.25 (1 H, s, CHO) (Found: C, 69.0; H, 7.7. $C_{16}H_{22}O_4$ requires C, 69.0; H, 8.0%).

*5β-Acetoxy-4,4a,5,6,7,8-hexahydro-4aβ-methyl-8-methylenenaphthalen-2(3H)-one* (18).—Sodium borohydride (137 mg, 3.62 mmol) was added to a stirred solution of the formyl enol ether (16) (3.3 g, 12 mmol) in ethanol (25 ml) in an ice-bath, and stirring was continued for a further 30 min. The mixture was allowed to warm to room temperature over 1 h, poured into ice–water, and extracted with dichloromethane. The combined extracts were washed with brine and dried. Removal of the solvent gave the alcohol (17) (3.22 g) as an oil, $\nu_{max.}$ (film) 3 400, 1 730, 1 645, and 1 618 $cm^{-1}$, δ 1.03 (3 H, s), 1.33 (3 H, s, *J* 7), 1.5—2.6 (9 H, m), 2.05 (3 H, s), 3.85 (2 H, q, *J* 7), 4.15 (2 H, q, C$H_2$OH), 4.77br (1 H, t, AcOC*H*), and 5.54 (1 H, s, =CH).

This alcohol was sensitive to heat and acid, and decomposed even on a silica gel t.l.c. plate. Since the n.m.r. spectrum, however, indicated it to be almost homogeneous, the crude product was used without purification in the next step.

The alcohol (4.81 g, *ca.* 17.2 mmol) was dissolved in aqueous acetic acid (80%; 20 ml), and, after stirring at room temperature for 3 h, the mixture was poured into ice–water. The product was extracted with ether, and the extract was washed successively with water, aqueous sodium hydrogen carbonate, and brine, and dried. Evaporation left an oil, which crystallised. Recrystallisation from ether–light petroleum (10 : 1) gave the pure *dienone* (18) (3.45 g, 87%) as pale yellow needles, m.p. 58.5—59.5 °C, $\nu_{max.}$ (KBr) 1 750, 1 680, 1 630w, and 1 608w $cm^{-1}$, δ 1.20 (3 H, s), 1.5—2.7 (8 H, m), 2.07 (3 H, s), 4.85 (1 H, dd, *J* 10.5 and 5.3, AcOC*H*), 5.05 and 5.18 (each 1 H, s, C=C$H_2$), and 6.02 (1 H, s, =CH) (Found: C, 71.4; H, 7.9. $C_{14}H_{18}O_3$ requires C, 71.8; H, 7.7%).

*5β-Acetoxy-3,4,4a,5,6,7-hexahydro-4aα,8-dimethylnaphthalen-2(1H)-one Ethylene Acetal* (20).—The dienone (18) (2.73 g, 11.7 mmol) was hydrogenated over 5% palladium–barium sulphate (560 mg) in ethyl acetate (35 ml) under atmospheric pressure. After absorption of 0.95 equiv. of hydrogen, the catalyst was filtered off, and the filtrate evaporated *in vacuo* to give a viscous oil. Although the product was contaminated by a by-product, the main product was the 8β-methyloctalone (19), as shown by spectral data: $\nu_{max.}$ (film) 1 735, 1 673, and 1 615 $cm^{-1}$, δ 2.08 (3 H, s), 4.70 (1 H, m, AcOC*H*), and 5.86 (*ca.* 1 H, s, =CH).

A mixture of the above octalone, ethylene glycol (5 ml), toluene-*p*-sulphonic acid (15 mg), and benzene was azeotropically refluxed for 12 h (Dean–Stark water separator). The mixture was then diluted with water and extracted with ether. The extract was successively washed with aqueous sodium hydrogen carbonate, water, and brine, and then dried. Removal of the solvent left a crystalline residue, which was recrystallised from ether–light petroleum (10 : 1) to give *needles* of (20) (2.49 g, 76%), m.p. 116—117 °C, $\nu_{max.}$ (KBr) 1 730 $cm^{-1}$, δ 1.13 (3 H, s), 1.63 (3 H, s), 1.3—2.8 (10 H, m), 2.05 (3 H, s), 3.96 (4 H, s, $OCH_2CH_2O$), and 4.85 (1 H, t, AcOC*H*) (Found: C, 68.8; H, 8.9. $C_{16}H_{24}O_4$ requires C, 68.5; H, 8.6%).

*Attempted Direct Epimerisation of the Octalone* (19).—A solution of the 8β-methyloctalone (19) (198 mg), obtained on hydrogenation of the dienone (18) as described above, and a catalytic amount of toluene-*p*-sulphonic acid in benzene was refluxed under nitrogen overnight. Water was added, and the product was extracted with ether. The extract was washed, dried, and evaporated to leave an oil, which was passed through a short silica gel column in ether. The eluate gave an oil (185 mg) on concentration. Spectral data and g.l.c. showed that this was the acetoxy-octalone (21) contaminated by an unidentified product (<10%). Attempted separation on a preparative scale was unsuccessful.

*The Hydroxy-octalone* (1) *from the Acetoxy-acetal* (20) via *the Acetoxy-octalone* (21).—A solution of the acetoxy-acetal (20) (280 mg, 1 mmol) and a catalytic amount of toluene-*p*-sulphonic acid in acetone (30 ml) was refluxed overnight and then poured into water. The product was extracted with ether, and the extract was washed and dried. The residual oil obtained on evaporation was passed through a short silica gel column in ether, affording the acetoxy-octalone (21) (200 mg) as an oil, $\nu_{max.}$ (film) 1 730, 1 670, 1 610, 1 235, and 1 030 $cm^{-1}$, δ 1.10 (3 H, d, *J* 6), 1.30 (3 H, s), 2.05 (3 H, s), 4.70 (1 H, m, AcOC*H*), and 5.85 (1 H, d, *J* 1.8, =CH).

Potassium carbonate (120 mg) was added to a solution of the above acetoxy-octalone (146 mg, 0.62 mmol) in methanol (2 ml), and the mixture was stirred at room temperature for 2 h under nitrogen. It was then diluted with water and extracted with ether. The extract was washed with water and brine, and dried. Removal of the solvent left the hydroxy-octalone (1) (86 mg, 61%). The product was homogeneous in t.l.c. and identified by i.r.

*The Hydroxy-octalone* (1) *from the Acetoxy-acetal* (20) via *the Hydroxy-acetal* (22).—The acetoxy-acetal (20) (177 mg, 0.63 mmol) dissolved in dry ether (2 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (15 mg, 0.40 mmol) in the same solvent (1 ml) in an ice-bath under nitrogen. After stirring for an additional 30 min at room temperature, water was added and the mixture was filtered. The filtrate was washed and dried. Evaporation left the hydroxy-acetal (22) (130 mg) as an oil, $\nu_{max.}$ (film) 3 400 $cm^{-1}$, δ 1.07 (3 H, s), 1.62 (3 H, s), 3.50 (1 H, m, C*H*OH), and 3.97 (4 H, s, $OCH_2CH_2O$).

A solution of the above hydroxy-acetal (81 mg) in methanol (6 ml) containing N-hydrochloric acid (1 ml) was refluxed for 2 h and then diluted with water. The product was extracted with ether, washed, and then dried. Removal of the solvent gave the hydroxy-octalone (1) (54 mg, 71%) as an oil, homogeneous on t.l.c. and identified by i.r. and n.m.r. spectra.

[7/671 *Received*, 22*nd April*, 1977]