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A new synthesis of (±) and (+)-2,6,7,7a-tetrahydro-1β-hydroxy-4-formyl-7aβ-methylindenes

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Abstract. A new method for the preparation of the synthon (±)-2,6,7,7a-tetrahydro-1β-hydroxy-4-formyl-7aβ-methylindene (1,a) for the total synthesis of steroids in both (±) and (+) forms, starting from the known β-ketoester, (±)-methyl 1β-*t*-butoxy-5,6,7,7a-tetrahydro-7aβ-methyl-5-keto-4-indancarboxylate (2,a) has been described. An alternative route to (1,a) has been investigated. Although the compound, (±)-1β-hydroxy-5,6,7,7a-tetrahydro-7aβ-methyl-5-keto-4-methoxymethylindan (2,b) could not be prepared, interesting pathways leading to two unexpected products, (±)-5,6,7,7a-tetrahydro-4,7a-dimethyl-5H-indene-1,5-dione and (±)-2,6-diketo-3-methyltricyclo-(5,2,1,0)decan-8-ol (3 and 4), were encountered during an attempted annelation reaction of the ketone, N-diethylamino-5-methoxypentan-3-one (6), with 2-methylcyclopentan-1,3-dione (5). Trapping of the intermediate, (±)-3a,4,5,6,7,7a-hexahydro-3a-hydroxy-4-methylene-7a-methylindene-1,5-dione (7), through the formation of the adduct, (±)-3a,4,5,6,7,7a-hexahydro- 3a-hydroxy-4- (1′, 3′-diketo-2′-methylcyclopentano-2′-methylene) -7a-methylindene-1,5-dione (8), established the mechanism of the formation of the products (3 and 4).

Keywords. New synthesis; racemic and asymmetric synthesis; steroid synthone.

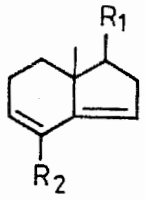
1. Introduction

The syntheses of (±) and (+)-2,6,7,7a-tetrahydro-1β-hydroxy-4-formyl-7aβ-methylindenes (1,a) were reported earlier by us (Banerjee *et al* 1976, 1983), the yield in the last oxidation step being moderate and inconsistent, depending upon the brand of the reagent used. This prompted us to look for alternative routes.

2. New synthesis of (±) and (+)-2,6,7,7a-tetrahydro-1β-hydroxy-4-formyl-7aβ-methylindenes

2.1 *Synthesis of (±)-2,6,7,7a-tetrahydro-1β-hydroxy-4-formyl-7aβ-methylindene*

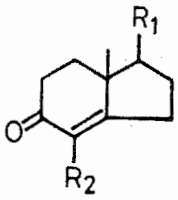
Our starting material of choice for this synthesis was the diketoester (9, b or c), which has been earlier prepared by Collins and Tomkins (1977) and Ellis *et al* (1974). With the view to improving upon the yields obtained by the above workers, we utilized the β-ketoacid (2, c), prepared by Micheli *et al* (1975) from the enedione (10) which was prepared earlier by Boyce and Whitehurst (1959) in 70%



1

a, R_1 = OH ; R_2 = CHO

b, R_1 = O+ ; R_2 = CHO



2

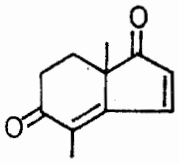
a, R_1 = O+ ; R_2 = CO_2CH_3

b, R_1 = OH ; R_2 = CH_2OCH_3

c, R_1 = O+ ; R_2 = CO_2H

d, R_1 = OH ; R_2 = H

e, R_1 = O+ ; R_2 = H



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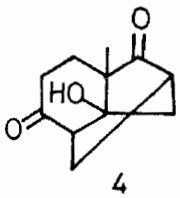

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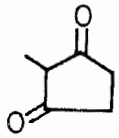

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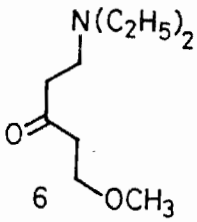

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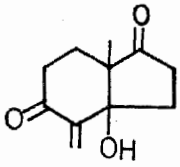

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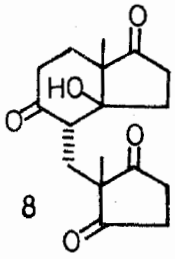

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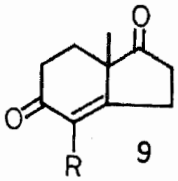
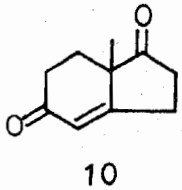


9

a, R = CO_2H ; b, R = CO_2CH_3

c, R = $CO_2C_2H_5$; d, R = CH_3



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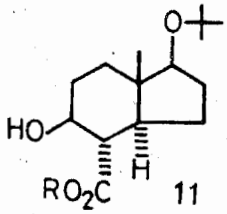

11

a, R = H

b, R = CH_3

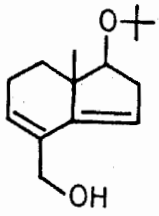

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Chart 1.

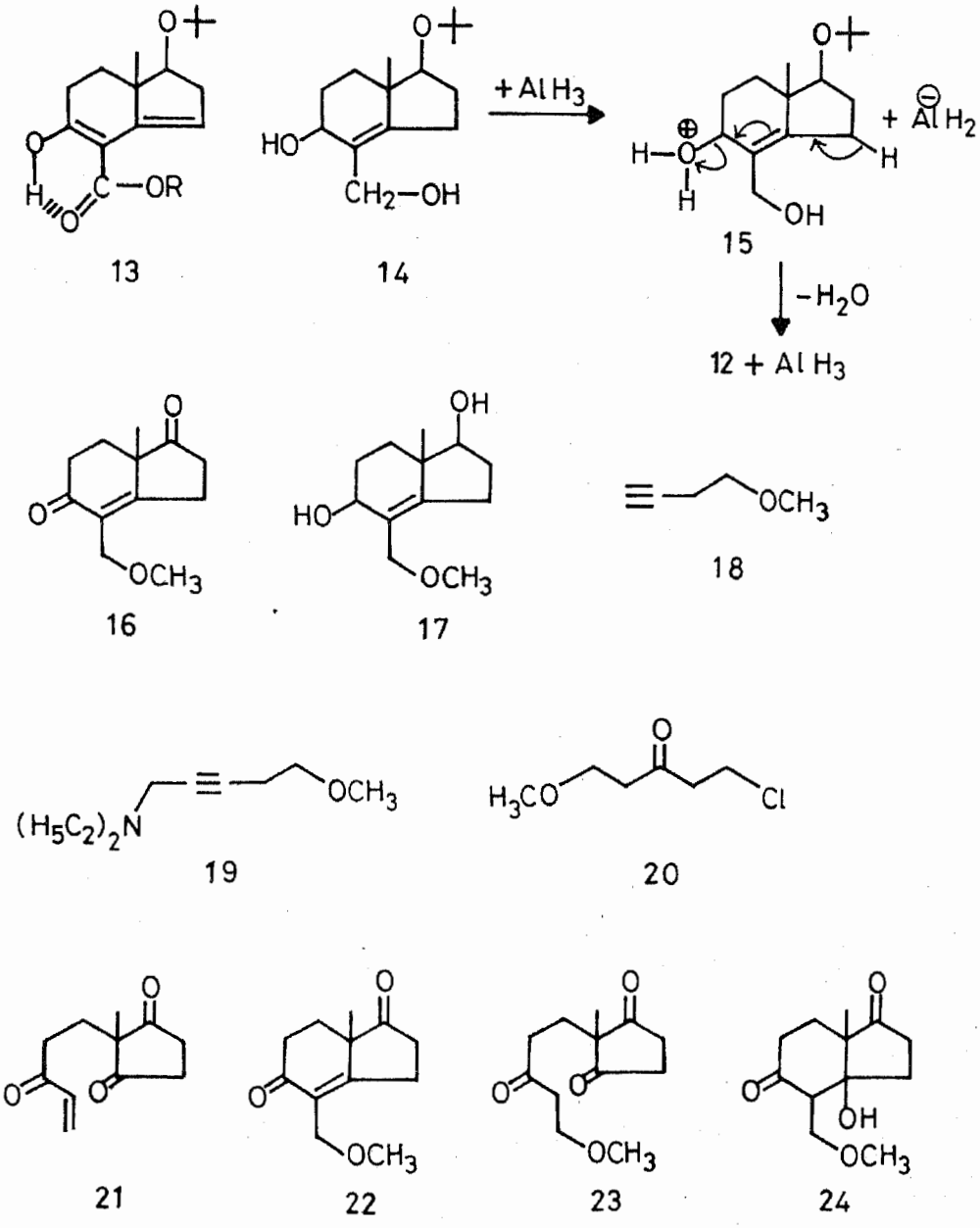

Chart 2.

yield. By adopting a modified one-step procedure of Zoretic *et al* (1976), we could obtain the enedione (10) in 90% yield. Following Micheli's method of selective reduction of the enedione (10) to the ketol (2, d), and subsequent treatment of the latter with isobutylenephosphoric acid-borontrifluoride etherate, afforded the *t*-butyl ether (2, e) in almost quantitative yield. The compound (2, e) was converted to the β-ketoacid (2, c) by treatment with methylmagnesiumcarbonate (MMC) (Balasubrahmanyam and Balasubramanian 1973) in 63% yield. Sodium borohydride reduction of the unsaturated ketoacid (2, c) and its ester (2, a) furnished the saturated hydroxyacid (11, a) and its ester (11, b) by the conjugate hydride addition followed by the reduction of the keto group in accordance with earlier observations (Nystron and Brown 1947; Hochstein and Brown 1948; Hochstein 1949; Dorrow

et al 1950; Bates *et al* 1954). The configuration assigned to 11, a and b, was proved by direct comparison with authentic samples prepared by the method of Baggiolini *et al* (1982).

Lithium aluminium hydride reduction of the acid (2, c) or its ester (2, a) afforded the diene alcohol (12). This obviously happened by the preferential reduction of the ester function, presumably due to the predominant existence of 2, c and a, as their enolates (13), followed by the reduction of the keto group to give the unsaturated diol (14) which underwent acid-catalysed allylic dehydration giving the dienol (12).

Aluminium hydride, derived from lithium aluminium hydride and aluminium chloride and known to reduce an unsaturated carbonyl without attacking the ethylenic linkage under mild conditions, reduced the unsaturated ketoester (2, a) to the dienol (12) in 95% yield; the probable mechanism, as schematically represented, appears to be an initial attack of the Lewis acid, aluminium hydride, on the secondary hydroxyl of 14 to form the oxycarbonium cation (15) and $\ominus AlH_2$, followed by the splitting of a water molecule and proton to yield the dienol (12) with the regeneration of aluminium hydride. The same mechanism is supposed to be operative in the case of lithium aluminium hydride reduction.

The best yield (> 80%) of the *t*-butoxyaldehyde (1, b) was obtained when the dienol (12) was oxidized with active manganese dioxide (Attenburrow *et al* 1952) or with dimethyl sulphoxide-oxalyl chloride (Swern oxidation) (Mancuso *et al* 1978). Acidic removal of the *t*-butoxy group furnished the (±) hydroxy aldehyde (1, a).

2.2 *Synthesis of (+)-2,6,7,7a-tetrahydro-1β-hydroxy-4-formyl-7aβ-methylindene*

For our present synthesis of the (+)-hydroxy aldehyde (1, a), we started with the (+)-enedione (10), prepared by the recently reported procedure of Hajos and Parrish (1985), which was converted to the (+)-β-ketoacid (2, c) by our method for the preparation of (±)-2, c. The (+)-methyl ester (2, a) was then converted to the (+)-hydroxy aldehyde (1, a) by the reduction of the former with aluminium hydride, followed by the allylic oxidation of the resulting (+)-dienol (12).

3. Investigation of another route for the synthesis of (±)-2,6,7,7a-tetrahydro-1β-hydroxy-4-formyl-7aβ-methylindene

3.1 *Attempted preparation of (+)-5,6,7,7a-tetrahydro-4-methoxymethyl-7aβ-methylindan-1,5-dione*

In our alternative new synthesis of the (±)-hydroxy aldehyde (1, a) we envisaged its preparation from the enedione ether (16) by its reduction to the enediol ether (17), followed by facile allylic dehydration, ether cleavage and oxidation. We intended to prepare 16 by the annelation of the dione (5) with the amino keto ether (6). The Mannich base (19), prepared from 2-methoxyethylacetylene (18), on hydration with mercuric sulphate and sulphuric acid gave a maximum yield of 25% of 6. Later, the compound (6) could be prepared in an overall yield of 56%, when the chloro methoxy ketone (20), prepared in 68% yield from 3-methoxypropionyl chloride, aluminium chloride and ethylene, was interacted with diethylamine. The annelation reaction between the amino ketone (6) and the dione (5), carried out

following Banerjee's procedure (Banerjee *et al* 1976), or by refluxing in xylene with PTS, gave a product which on purification by chromatography furnished a less polar compound, proved to be the dienedione (3) from its spectral data, and a more polar compound which was found to be 2,6-diketo-3-methyl-tricyclo[5,2,1,0] decan-8-ol (4), earlier reported by Danishefsky and Migdalof (1969) during the base catalysed cyclization of the vinyl triketone (21). The structure of the dienedione (3) was confirmed by hydrogenating it to the known enedione (9d). The compound (4), obtained in our annelation reaction, might have been formed from the vinyl triketone of Danishefsky and Migdalof during the base catalysed cyclization of the vinyl triketone (21). The structure of the dienedione (3) was confirmed by hydrogenating it to the known enedione (9d). The compound (4), obtained in our annelation reaction, might have been formed from the vinyl triketone of Danishefsky (1969), resulting by the elimination of methanol from the initially formed methoxy triketone (23). The compound (23), prepared independently, furnished the keto alcohol (4) by treatment with pyridine-benzene.

The cyclization of the methoxy triketone (23), as well as attempted annelations of the dione (5) with different annelating agents under various conditions failed to form 22. This led to the conclusion that the base-induced methanol elimination in the intermediate aldol (24), derived from 23, was more facile than dehydration to 22. The aforementioned methanol elimination formed the unsaturated hydroxy-enone (7) which by dehydration and isomerization finally gave the dienone (3). We could prove that this was indeed the pathway followed by trapping the postulated intermediate (7) by carrying out the well-known (Kuo *et al* 1965) self-catalysed annelation reaction of the acidic dione (5), used in excess, with the methoxy triketone (23) and isolating the expected adduct (8) formed by the addition of 5 to 7.

4. Experimental

All melting points (hot stage) and boiling points are uncorrected. All recorded temperatures are on the Celsius scale. Only one enantiomer of a racemic pair has been displayed in the charts. UV spectra were recorded in 95% ethanol on a Schimadzu UV-190 double beam spectrophotometer. IR spectra were taken on a Perkin-Elmer model 781 spectrophotometer. NMR spectra were recorded on a Varian T60, Varian HA-100, Jeol Fx 900 or Bruker WH-270 NMR spectrophotometer. Chemical shifts were quoted relative to TMS ($\delta = 0$ ppm) as internal standard. Mass spectra were recorded on a Jeol MS-DX 303 with a built-in direct inlet system. All organic extracts were dried over anhydrous sodium sulphate. Analytical and preparative layer chromatography were carried out using silica gel supplied by BDH (Bombay) or Acme Synthetic Chemicals (Bombay). For column chromatography Acme Silica gel or BDH neutral alumina was used.

4.1 (±)-*7,7a-Dihydro-7aβ-methyl-1,5(6H)-indandione* (10)

A mixture of 2-chloroethyl methyl ketone (106 g, 1 mol) and the dione (5) (75 g, 0·67 mol) in water (600 ml) was stirred for 4 h and then heated under reflux with stirring for 16 h. The mixture was extracted with chloroform and the organic layer washed successively with water, aq. $NaHCO_3$, water and brine. Removal of the

solvent and distillation of the residue afforded the dione (10) (148 g, 90%); IR (neat): ν_{max} 1670, 1740 cm^{-1}; ^1H NMR (CCl_4) δ1·28 (*s*, 3H, $C\underline{H}_3$), 1·7–3·1 (*m*, 8H, methylene), 5·78 (*bs*, 1H, vinylic).

4.2 (±)-*7aβ-Methyl-7,7a-dihydro-1β-hydroxy-5(6H)-indanone,* (2, d)

To a chilled solution (−10°) of the indandione (10) (80 g, 0·24 mol) in ethanol (400 ml) was added $NaBH_4$ (5 g, 0·13 mol) in ethanol at a rate to maintain the internal temperature between −5 and −10°. The reaction mixture was then allowed to warm up to +5° and then cooled again to −10° and the pH adjusted between 5 and 7 by the addition of 2N HCl, the dark brown solution turning orange. The solvent was removed under vacuum (45°) and the residue was extracted with ethyl acetate. The residue, after removal of the ethyl acetate and purification by column chromatography (silica gel, $CHCl_3$), afforded the indanone (2, d) (78 g, 96%); IR (neat): ν_{max} 3400, 1660 cm^{-1}.

4.3 (±)-*1β-t-Butoxy-7aβ-methyl-7,7a-dihydro-5(6H)-indanone,* (2, e)

This compound was prepared following the method of Micheli *et al* (1975). Thus from the indanone (2, d) (40 g), BF_3 $(C_2H_5)_2O$ (10 ml), H_3PO_4 (4·2 ml, 47% solution), dichloromethane (400 ml) and liquid isobutylene (200 ml), there was obtained the *t*-butyl ether (2, e) (50 g, 95%). The product, on purification by column chromatography (silica gel, ethyl acetate-hexane, 1 : 4), melted at 60–61° (reported 62–65°); IR (neat): ν_{max} 1665 cm^{-1}; ^1H NMR (CCl_4) δ1·02 (*s*, 3H, $C\underline{H}_3$), 1·04 [*s*, 9H, $C(C\underline{H}_3)_3$], 1·8–2·9 (*m*, 8H, methylene), 3·58 (*dd*, J = 8 Hz, 1H, $C\underline{H}$ = O), 5·56 (*t*, J = 2 Hz, 1H, vinylic).

4.4 (±)-*5,6,7,7a-Tetrahydro-1β-t-butoxy-7aβ-methyl-5-keto-4-indancarboxylic acid,* (2,c)

A mixture of *t*-butyl ether (2,c) (50 g, 0·23 mol) and MMC in dimethylformamide (335 ml) was heated in a preheated (125°) oil bath with stirring under N_2 for 2 h, the internal temperature being maintained at 115°. The solution was cooled and poured into ice and conc. HCl. The aqueous phase was extracted with benzene and the organic phase with 15% aq. Na_2CO_3. Acidification of the basic solution, followed by extraction with benzene and removal of the solvent in the vacuum (45°), gave a yellowish brown oily compound (35 g) which solidified on standing; crystallization from chloroform-hexane furnished the carboxylic acid (2,c) (26·5 g, 44%) as yellow crystals, m.p. 105° (reported 103–109°), IR ($CHCl_3$) ν_{max} 1600, 1620, 1735 cm^{-1}; ^1H NMR ($CDCl_3$), δ1·2 [(*s*, 12H, $C\underline{H}_3$,$C(C\underline{H}_3)_3$], 1·4–2·8 (*m*, methylene), 3·62 (*dd*, J = 8 Hz, 1H, $C\underline{H}$–O), 11·9 (*bs*, 1H, $CO_2\underline{H}$).

Removal of the solvent from the neutral fraction gave the starting compound (15 g), the yield based on the recovery being 63%.

4.5 (±)-*1β-t-Butoxy-7aβ-methyl-3aα,4β,5,6,7,7a-hexahydro-5β-hydroxy-4α-indancarboxylic acid,* (11, a)

To a cooled and stirred solution of the carboxylic acid (2,c) (1·2 g, 4·5 mmol) in ethanol (20 ml) $NaBH_4$ (0·5 g, 12 mmol) was added in small portions and the stirring continued for 12 h. The excess $NaBH_4$ was decomposed with water and

most of the ethanol was removed. The residue was taken up in chloroform, washed with water and brine, and dried. The solvent was removed and the residual solid crystallized from ethanol-hexane to yield the hydroxy acid (11, a) (0·05 g, 78%) m.p. 115°; IR (nujol) ν_{max} 3280, 1720 cm^{-1}; $^{-1}$H NMR ($CDCl_3 + CF_3CO_2H$) δ 0·87 (*s*, 3H, $C\underline{H}_3$), 1·25 [*s*, 9H, $C(C\underline{H}_3)_3$], 1·4–2·2 (*m*, 9H, methylene and angular), 2·57 (*bt*, J = 8 Hz, 1H, $C\underline{H}\cdot CO_2H$) 3·59 [*bt*, J = 10 Hz, 1H, $C\underline{H}\cdot OC(CH_3)_3$], 4·03 (*dt*, J = 10 and 8 Hz, 1H, C<u>H</u>OH), MS, *m/e* (relative intensity) 214 (36, *M*-56) 196 (43), 178 (40%); Found: C 66·28, H 9·66; $C_{15}H_{26}O_4$ requires C 66·63, H 9·69%.

4.6 (±)-*Methyl 1*β-t-*butoxy-5,6,7,7a-tetrahydro-7a*β-*methyl-5-keto-4-indancarboxylate,* (2, a)

A solution of diazomethane in ether (76 ml, 0·076 mmol/ml) was added dropwise with stirring to a suspension of the unsaturated β-ketoacid (2, c) (1, 34 g, 5 mmol) in ether (50 ml). After stirring for 10 min, the solvent was removed and the residue crystallized from hexane to obtain the ester (2, a) (1·4 g > 99%); m.p. 76–77° (reported 76·5–77°); IR (nujol) ν_{max} 1670, 1730 cm^{-1}; ^{1}H NMR (CCl_4), δ 1·1 [*s*, 12H, $C\underline{H}_3$ and $(CC\underline{H}_3)_3$], 1·6–2·72 (*m*, 8H, methylene), 3·6 (*bt*, J = 7 Hz, 1H, C<u>H</u>-O), 3·7 (*s*, 3H, $CO_2C\underline{H}_3$).

4.7 (±)-*Methyl 1*β-t-*butoxy-7a*β-*methyl-3a*α,*4*β,*5,6,7,7a-hexahydro-5*β-*hydroxy-4*α-*indancarboxylate,* (11b)

To a cooled and stirred solution of the ketoester (2, a) (0·7 g, 2·5 mmol) in ethanol (10 ml) $NaBH_4$ (0·23 g, 6 mmol) was added in small portions and the stirring continued for 12 h. After the usual work-up, the *trans* hydroxy ester (11, b) (0·65 g, 91%) was isolated; IR($CHCl_3$) ν_{max} 3600, 1735 cm^{-1}; ^{1}H NMR (CCl_4) δ 0·8 (*s*, 3H, $C\underline{H}_3$), 1·16 [*s*, 9H, $C(C\underline{H}_3)_3$], 1·22–2·52 (*m*, 10H, methylene, angular and $C\underline{H}\cdot CO_2CH_3$), 3·04 (*bs*, 1H, D_2O exchangeable, CHO<u>H</u>), 3·34 [*t*, J = 8 Hz, 1H, C<u>H</u>–$OC(CH_3)_3$], 3·6 (*s*, 3H, $CO_2C\underline{H}_3$), 3·62 (*m*, 1H, C<u>H</u>OH). Found: C 67·31, H 9·86; $C_{16}H_{28}O_4$ requires C 67·57, H 9·93%.

4.8 (±)-*1*β-t-*Butoxy-2,6,7,7a-tetrahydro-4-hydroxymethyl-7a*β-*methylindene,* (12)

(a) A solution of the ketoacid (2, c) (2 g, 7·5 mmol) in dry THF (15 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (0·5 g, 13 mmol) in dry ether (10 ml) at 0°, and the stirring continued for 1 h. The mixture was stirred for 4 h more at the room temperature. The excess $LiAlH_4$ was decomposed by the addition of water at 0°, followed by the addition of ice-cold 6N HCl (10 ml) and stirring for 1 h. The ethereal layer was separated, washed with water, aq. $NaHCO_3$ and brine, and dried. Removal of the solvent and purification of the residue by column chromatography (silica gel, $CHCl_3$) yielded the diene alcohol (12) (1·32 g, 75%); IR (neat) ν_{max} 3450, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0·9 (*s*, 3H, $C\underline{H}_3$), 1·18 [*s*, 9H, $C(C\underline{H}_3)_3$], 1·4–2·56 (*m*, 6H, methylene), 3·78 [*t*, J = 7 Hz, 1H, C<u>H</u>–O–C$(CH_3)_3$], 4·24, (*s*, 2H, $C\underline{H}_2OH$); 5·49 (*bt*, 1H, vinylic), 5·8 (*bt*, 1H, vinylic); ^{13}C NMR ($CDCl_3$) δ 15·36 (*q*, $\underline{C}H_3$), 23·17 (*t*, $\underline{C}H_2CCH_3$), 28·57 [*q*, C($\underline{C}H_3)_3$], 33·64 (*t*, $\underline{C}H_2$, CH_2CCH_3), 38·13 (*t*, $\underline{C}H_2CH$–O), 44·96 (*s*, $\underline{C}CH_3$), 62·98 (*t*, $\underline{C}H_2OH$), 72·45 [*s*, $\underline{C}(CH_3)_3$], 81·13 (*d*, $\underline{C}H$–O), 117·24 (*d*, vinylic $\underline{C}H$), 125·7

(*d*, vinylic C̲H), 132·99 (*s*, H_3 C C–C̲ = CH), 143·98 (*s*, $HOCH_2$-C̲=CH); Found: C 76·35, H 10·18; $C_{15}H_{24}O_2$ requires C 76·22, H 10·24%.

(b) To a stirred and cooled (0°) suspension of $LiAlH_4$ (0·5 g, 13 mmol) in dry ether (10 ml) was added a solution of the ketoester (2, a) (2·1 g, 7·5 mmol) in dry ether (15 ml) and the stirring continued at 0° for 1 h and at the room temperature for 4 h. After the usual work-up, the diene alcohol (12) (1·5 g, 85%) was obtained.

(c) To a stirred and cooled (0°) suspension of $LiAlH_4$ (0·09 g, 23·6 mmol) in dry ether (100 ml) under N_2 was added a suspension of powdered, freshly sublimed $AlCl_3$ (1·17 g, 8·8 mmol) in ether (10 ml) and the mixture stirred for 1 h. A solution of the ketoester (2, a), (2·2 g, 7·9 mmol) in dry ether (100 ml) was added over a period of 20 min, the mixture stirred at 0° for 1 h and then at the room temperature for 30 min. The cooled (0°) mixture was treated with cold 6N HCl and stirred for 1 h. The product was extracted with ether, washed with brine and dried. Removal of the solvent afforded the diene alcohol (12) (1·76 g, 95%).

4.9 (±)-*1*β-t-*Butoxy-2,6,7,7a-tetrahydro-4-formyl-7a*β-*methylindene,* (1, b)

(a) To a solution of the alcohol (12) (3·5 g, 14·8 mmol) in *n*-hexane (250 ml) was added active MnO_2 (35 g) and the mixture stirred. The progress of the oxidation was monitored by TLC. When all the alcohol had been consumed (6 h), the mixture was stirred for 5 min after dilution with ether. The crude material, after concentrating the solution, was chromatographed over neutral alumina (C_6H_{14}–$CHCl_3$) to afford the aldehyde (1, b) (2·8 g, 81%); IR($CHCl_3$) ν_{max} 2750, 1690, 1650, 1610 cm^{-1}; UV(C_2H_5OH) λ_{max} 222 nm (ϵ 16, 200); ^1H NMR ($CDCl_3$) δ 0·88 (*s*, 3H, C̲H_3), 1·17 [*s*, 9H, C(C̲H_3)$_3$], 1·52–2·47 (*m*, 6H, methylene), 3·79 [*t*, *J* = 7 Hz, 1H, C̲HOC(CH_3)$_3$], 6·4 (*bt*, 1H, vinylic), 6·69 (*bt*, 1H, vinylic), 9·52 (*s*, C̲HO); Found: C 77·07, H 9·48; $C_{15}H_{22}O_2$ requires C 76·88, H 9·46%.

(b) To a stirred and cooled (−78°) solution of oxalyl chloride (3·75 ml, 41 mmol) in dry CH_2Cl_2 (95 ml) was added DMSO (6·38 ml, 82 mmol) and after stirring for 20 min the alcohol (12) (3·5 g, 14·8 mmol) in CH_2Cl_2 (40 ml) was added dropwise. After another 20 min, triethylamine (26 ml, 185 mmol) was added and the mixture warmed to the room temperature, and 10 min later, poured into water. The aqueous layer was extracted thrice with CH_2Cl_2 and the combined CH_2Cl_2 layer was washed once with 1% HCl and then with 5% Na_2CO_3, dried, concentrated and chromatographed [neutral alumina, C_6H_{14}–$CHCl_3$ (2:1)] to give the aldehyde (1, b) (3 g, 85%).

4.10 (±)-*2,6,7,7a-Tetrahydro-1*β-*hydroxy-4-formyl-7a*β-*methylindene,* (1, a)

The diene aldehyde (1, b) (0·34 g, 1·5 mmol) was suspended in conc. HCl (6 ml) and stirred for 24 h under N_2 at 20°, followed by extraction with ether. The extract was washed with water and brine and then dried. Removal of the ether and purification of the residue by PTLC (C_6H_{14}-$CHCl_3$, 3:1) gave the hydroxy aldehyde (1, a) (0·22 g, 85%), identical with the one prepared by us earlier.

4.11 (+)-*Methyl (1S,7aS)-1*-t-*butoxy-5,6,7,7a-tetrahydro-7a-methyl-5-keto-4-indancarboxylate,* (2, a)

Esterification of the carboxylic acid [(+)-2, c], prepared by the method of Micheli

et al (1975) and the starting material [(+)-10] for which was prepared by a recent method of Hajos and Parrish (1985), with diazomethane gave [(+)-2, a] in 99% yield; $[\alpha]_D^{25}$ +30° ($CHCl_3$, C 1·0).

4.12 (+)-*(1S,7aS)-1*-t-*Butoxy-2,6,7,7a-tetrahydro-4-hydroxymethyl-7a-methylindene,* (12)

Reduction of the ketoester [(+)-2, a] with aluminium hydride followed by the usual work-up gave the diene alcohol [(+)-12] in 96% yield; $[\alpha]_D^{25}$ +59·2° ($CHCl_3$, C 1·0).

4.13 (+)-*(1S,7aS)-1*-t-*Butoxy-2,6,7,7a-tetrahydro-4-formyl-7a-methylindene,* (1, b)

The chiral hydroxy compound [(+)-12] was oxidized by active MnO_2 or DMSO-$(COCl)_2$ (Swern oxidation) to furnish the diene aldehyde [(+)-1, b] in > 80% yield; $[\alpha]_D^{25}$ +40·6° ($CHCl_3$, C 1·0).

4.14 (+)-*(S,7aS)-2,6,7,7a-tetrahydro-1-hydroxy-4-formyl-7a-methylindene,* (1, a)

Removal of the *t*-butoxy group from the ether [(+)-1, b] by treatment with conc. HCl afforded the hydroxy aldehyde [(+)-1, a] in 85% yield, $[\alpha]_D^{25}$ +36° ($CHCl_3$, C 1·0).

4.15 *4-Methoxybut-1-yne,* (18)

The title compound (18) was prepared by a modification of the method reported earlier (McCusker and Kraeger 1937). Acetylene was bubbled through a stirred suspension of sodamide, prepared from Na(9 g, 0·39 gatom) and dry ammonia (550 ml). To the resulting slurry of sodium acetylide was added dropwise 2-methoxyethyl bromide (48 g, 0·35 mmol) in 2 h, the bubbling of acetylene and stirring being continued throughout. The ammonia was allowed to evaporate and a saturated solution of NH_4Cl was carefully added. The mixture was cooled in a bath of ice-salt mixture and neutralized with 6N HCl. The product was distilled by heating the reaction mixture on a water-bath, then dried and redistilled to afford 4-methoxybut-1-yne (18) (20 g, 66%); b.p. 74–76°; IR (neat) ν_{max} 3300, 2850, 2150 cm^{-1}; ^1H NMR (CCl_4) δ 1·9 (*t*, *J* = 2 Hz, 1H, C ≡ $\underline{H}$). 2·4 (*dt*, *J* = 2 and 7 Hz, 2H, $C\underline{H}_2C \equiv C$), 3·35 (*s*, 3H, $OC\underline{H}_3$), 3·45 (*t*, *J* = 7 Hz, 2H, $OC\underline{H}_2$).

4.16 *N-Diethylamino-5-methoxypent-2-yne,* (19)

A mixture of 4-methoxybut-1-yne (18) (40 g, 0·48 mol), diethylamine (37 g, 0·5 mol), acetic acid (30 g, 0·5 mol), formalin (60 ml, 35%, 0·7 mol), CuCl (0·8 g, 0·008 mol) and water (40 ml) was stirred under N_2 for 60 h and then basified (pH 13) with aq. NaOH, saturated with $(NH_4)_2SO_4$ and extracted thrice with ethyl acetate. The extract was washed with brine and dried, and the solvent removed. The Mannich base (19) (50 g, 63%) was isolated by distillation; b.p. 135–140°/60 mm; ^1H NMR (CCl_4) δ1·02 [*t*, *J* = 7 Hz, 6H, $N(CH_2C\underline{H}_3)_2$], 2·4 [*m*, 6H, $N(C\underline{H}_2CH_3)_2$ and $C\underline{H}_2(CH_2OCH_3)_2$], 3·3 (*s*, 5H, $OC\underline{H}_3$ and $C \equiv C\underline{H}_2N$), 3·35 (*m*, 2H, $C\underline{H}_2O$); Found: C 71·23, H 11·4, N 8·31; $C_{10}H_{19}NO$ requires C 70·96, H 11·32, N 8·28%.

4.17a *N-Diethylamino-5-methoxypentan-3-one*, (6)

(i) A mixture of the Mannich base (19) (3·3 g, 19·5 mmol), conc. H_2SO_4 (1·4 ml) and $HgSO_4$ (0·25 g, 0·8 mmol) in water (15 ml) was stirred under N_2 for 12 h at 0°, then basified (pH 13) with aq. NaOH, saturated with $(NH_4)_2SO_4$ and extracted with ethyl acetate. The extract was washed with brine and the solvent removed. The residue was chromatographed over neutral alumina. Elution with C_6H_{14}–$CH_3{\cdot}CO_2C_2H_5$ (10:1) gave the starting compound (19) (1·02 g, 30%) and subsequent elution with C_6H_{14}–$CH_3CO_2C_2H_5$ (1:1) afforded the amino ketone (6) (0·44 g, 12%) as a liquid; IR (neat) ν_{max} 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ1·02 [*t*, J = 7 Hz, 6H, $N(CH_2\underline{CH_3})_2$], 2·52 [*m*, 10H, $\underline{CH_2}N(\underline{CH_2}CH_3)_2$ and $\underline{CH_2}OCH_2$], 3·28 (*s*, 3H, OCH_3), 3·64 (*t*, J = 7 Hz, 2H, OCH_2); MS, *m/e* (relative intensity) 187 (27, M^+), 86 [100%, $CH_2N(CH_2CH_3)_2$]. Further elution with ethyl acetate gave polymeric material.

(ii) The aforementioned mixture of the Mannich base (19), conc. H_2SO_4, $HgSO_4$ and water was stirred under N_2 at room temperature for 15 h. After the usual work-up and purification, (0·93 g, 25%) of the amino ketone (6) was obtained.

4.17b *1-Chloro-5-methoxypentan-3-one* (20): This compound, required for the preparation of the amino ketone (6) in an improved yield by the second method, was prepared by the following two procedures.

(i) To the powdered freshly sublimed $AlCl_3$ (67 g, 0·56 mol) in CH_2Cl_2 (250 ml) at 0° was added dropwise 3-methoxypropionyl chloride (56 g, 0·46 mol) and ethylene was bubbled through the mixture for 4–5 h, the temperature being maintained between 0–5°. The reaction mixture was poured into crushed ice containing conc. HCl (100 ml) and extracted with CH_2Cl_2. The organic layer was washed successively with water, aq. $NaHCO_3$, water and brine, and dried. After removal of the solvent under diminished pressure, the residue was chromatographed over neutral alumina. The first fraction (C_6H_{14}–C_6H_6, 1:1) gave di-2-chloroethyl ketone (5·66 g, 8%), identified by its spectral analysis and comparison with an authentic sample (Baddeley *et al* 1953); IR (neat) ν_{max} 1715 cm^{-1}; ^1H NMR (CCl_4) δ2·92 (*t*, J = 7 Hz, 2H, $\underline{CH_2}CO$), 3·74 (*t*, J = 7 Hz, 2H, $\underline{CH_2}Cl$). The second fraction (C_6H_{14}–$CHCl_3$, 1:3) yielded, after removal of the solvent, the unstable 1-chloro-5-methoxypentan-3-one (20) (34·8 g, 68%); b.p. 131–135°/5 mm; IR (neat) ν_{max} 1720 cm^{-1}; ^1H NMR (CCl_4) δ2·66 (*t*, J = 7 Hz, 2H, $CO\underline{CH_2}CH_2O$), 2·93 (*t*, J = 6 Hz, 2H, $COCH_2\underline{CH_2}Cl$), 3·33 (*s*, 3H, OCH_3), 3·58–3·8 (*m*, 4H, $\underline{CH_2}O$ and $\underline{CH_2}Cl$).

(ii) To a cooled and vigorously stirred solution of 3-chloropropionic acid (1·08 g, 10 mmol) in dry ether (40 ml) was added dropwise in 30 min an ethereal solution, prepared from 2-methoxyethyl bromide (2·78 g, 20 mmol) and Li (0·3 g, 0·04 g atom), under N_2 and the faintly turbid solution was stirred at room temperature for 4 h. To this was added dropwise under stirring ice-cold dil. HCl. The ethereal layer was separated and the aqueous phase was extracted thrice with ether. The combined extract was washed with aq. Na_2CO_3 and water, and dried. Removal of the solvent gave the chloromethoxy ketone (20) (0·35 g, 23%).

To a stirred ice-cold solution of diethylamine (1·46 g, 20 mmol) in benzene (15 ml) was added dropwise the chloromethoxy ketone (20) (1·5 g, 10 mmol) and

the mixture left for 4 h at 0°. It was basified (pH > 13) with dil. NaOH and extracted with ethyl acetate. After removal of the solvent and purification of the residue by chromatography the amino ketone (6) (1·5 g, 81%) was obtained.

4.18 *(±)-5,6,7,7a-Tetrahydro-4,7a-dimethyl-5H-indene-1,5-dione (3) and (±)-2,6-diketo-3-methyltricyclo(5,2,1,0)decan-8-ol,* (4).

(a) A mixture of the aminoketone (6) (1·25 g, 6·5 mmol), the dione (5) (0·85 g, 7·6 mmol), pyridine (1·75 g, 22 mmol) and xylene (10 ml) was heated under reflux for 20 h. The mixture was diluted with $CHCl_3$ and washed successively with dil. HCl, water, aq. $NaHCO_3$, water and brine. After removal of the $CHCl_3$, PTS (1·25 g, 7 mmol) was added and the mixture was heated under reflux with a Decan-Stark attachment for 4 h, cooled, thoroughly washed with water, concentrated under vacuum and chromatographed over silica gel. Elution with $CHCl_3$ initially gave 5,6,7,7a-tetrahydro-4,7a-dimethyl-5H-indene-1,5-dione(3) (0·71 g, 59%) which was further purified by short-path distillation, bath temp. 136–140° (2 mm); UV (C_2H_5–OH) λ_{max} 290 (ϵ 9,300), 300 nm (ϵ 11,000); IR (neat) ν_{max} 1710, 1670 cm^{-1}; ^1H NMR (CCl_4) 1·28 (*s*, 3H, C$\underline{H}_3$), 1·88 (*s*, 3H, olefinic C$\underline{H}_3$) 1·6–2·82 (*m*, 4H, methylene), 6·32 (*d*, J = 3 Hz, 1H, olefinic α-H), 7·06 (*d*, J = 3 Hz, 1H, olefinic β-$\underline{H}$); MS *m/e* (relative intensity) 176 (10, M^+), 161 (8), 133 (100%); Found: C 74·91, H 6·9; $C_{11}H_{12}O_2$ requires C 74·97, H 6·86%.

Subsequent elution with $CHCl_3$ furnished the white crystalline compound (4) (0·12 g, 12%), which was recrystallized from C_6H_{14}–C_6H_6; m.p. 170–171° (reported 172–174°), IR (nujol) ν_{max} 3360, 1735, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ1·13 (*s*, 3H, C$\underline{H}_3$), 1·62–2·66 (*m*, 10H, methylene and methine protons), 4·9 (*s*, 1H, O$\underline{H}$ exchangeable with D_2O); MS *m/e* (relative intensity) 194 (30, M^+). 69 (100%).

(b) A mixture of the amino ketone (6) (0·6 g, 3·1 mmol), the dione (5) (0·42 g, 3·8 mmol), PTS (0·85 g, 11 mmol) and xylene (50 ml) was heated under reflux for 20 h. After the usual work-up and purification the dienedione (3) (0·3 g, 49%) and the tricyclic keto alcohol (4) (0·017 g, 14%) were obtained.

4.19 *Catalytic hydrogenation of (±)-5,6,7,7a-tetrahydro-4,7a-dimethyl-5H-indene-1,5-dione* (3)

An ethanolic solution of dienedione (3) (0·26 g, 1·5 mmol) was hydrogenated over 5% Pd-C catalyst (0·03 g) for 4 h, when a little more than 1 equivalent of H_2 was absorbed. The catalyst was filtered off and the ethanol removed under vacuum and the residue chromatographed over silica gel. (C_6H_{14}–CH_3CO_2, C_2H_5, 1:1) to give the known monoenone (9,d) (0·25 g, > 99%). The structure was confirmed by a direct comparison of the spectral data and TLC with those of an authentic specimen.

4.20a *(±)-2-(5'-Methoxy-3'-ketopentyl)-2-methylcyclopentan-1,3-dione* (23): A solution of the amino ketone (6) (1·9 g, 10 mmol) and the dione (5) (1·1 g, 10 mmol) in dry C_6H_6 and pyridine (2·3 g, 30 mmol) was stirred at room temperature for 24 h and then cooled, diluted with C_6H_6, washed successively with dil. HCl, water, aq. $HaHCO_3$ and water, and dried. The solvent was removed under vacuum and the residue on short-path distillation gave the cyclopentandione (23) (1·54 g, 66%); bath temp. 176–183° (1 mm); IR (neat) ν_{max} 1750, 1710, 1705,

1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ1·11 (*s*, 3H, CH_3), 1·92 (*t*, *J* = 7 Hz, 2H, $CH_2 \cdot CH_3$), 2·5 (*t*, *J* = 7 Hz, 2H, $CH_2CH_2CCH_3$), 2·63 (*t*, *J* = 6 Hz, 2H, OCH_2CH_2), 2·81 (*s*, 2H, ring methylene), 2·83 (*s*, 2H, ring methylene), 3·32 (*s*, 3H, OCH_3), 3·62 (*t*, *J* = 6 Hz, 2H, OCH_2); ^{13}C NMR ($CDCl_3$) δ 18·66 (*q*, CH_3), 27·77 (*t*, CH_2CCH_3), 34·73 (*t*, ring methylene), 37·07 (*t*, $CH_2CH_2CCH_3$), 42·72 (*t*, OCH_2CH_2), 55·08 (*s*, CCH_2), 58·66 (*q*, OCH_3), 67·3 (*t*, OCH_2), 208·16 (*s*, acyclic CO), 215·77 *s*, ring CO); MS, *m/e* (relative intensity) 226 (10, M^+), 211 (20), 125 (100%); Found: C 63·58, H 8·04; $C_{12}H_{18}O_3$ requires C 63·7, H 8·02%.

4·20b (±)-*2-(3'-ketopent-4'-enyl)-2-methylcyclopentan-1,3-dione* (21): (i) A solution of di-2-chloroethyl ketone (5 g, 33 mmol) in monoglyme (20 ml) was added with stirring at room temperature under N_2 to a suspension of the sodium salt of the dione (5), prepared from Na dust (0·9 g, 0·4 g atom) and the dione (5) (4·45 g, 40 mmol) in monoglyme (10 ml) at 0–5°. The mixture was stirred for 12 h at room temperature and then cooled, acidified with dil. HCl, saturated with NaCl and extracted with ether. The extract was washed with aq. $NaHCO_3$ and water, and dried. Removal of the solvent gave the vinyl triketone (21) (5·5 g, 70%); IR (neat) ν_{max} 1760, 1725, 1685, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ1·14 (*s*, 3H, CH_3), 1·95 (*t*, *J* = 7 Hz, 2H, CH_2CCH_3), 2·62 (*t*, *J* = 7 Hz, 2H, $COCH_2$, $C \cdot CH_3$), 2·7–2·94 (*m*, 4H, ring methylene), 5·86 (*dd*, *J* = 9 and 2 Hz, 1H, vinylic), 6·16–6·29 (*m*, 2H, vinylic).

(ii) *Base-catalysed addition to the vinyl triketone* (21) — To a solution of sodium methoxide (0·5 g, 10 mmol) in methanol (10 ml) was added at 0° in 10 min a solution of the vinyl triketone (21) in methanol (10 ml). The solution was then allowed to attain the room temperature and stirred for 8 h. The methanol was removed under vacuum and the residue, after acidification with 2% HCl, was extracted with ether. The extract was dried, the solvent removed and the residue chromatographed over silica gel (C_6H_{14}–$CH_3CO_2C_2H_5$, 2:1) to obtain the methoxy triketone (23) (3·1 g, 66%).

4.21 (±)-*3a,4,5,6,7,7a-Hexahydro-3a-hydroxy-4-(1',3'-diketo-2'-methylcyclopentano-2'-methylene)-7a-methylindene-1,5-dione* (8)

A mixture of the triketone (23) (0·57 g, 2 mmol), the dione (5) (0·28 g, 2·5 mmol), pyridine (0·6 g, 7·8 mmol) and dry benzene (10 ml) was stirred at room temperature for 12 h and then diluted with benzene and washed successively with dil. HCl, aq. $NaHCO_3$ and water, and dried. After removal of the solvent, the solid residue was crystallized to yield the hydroxy tetraketone (8) (0·61 g, 74%); m.p. 192–194°; IR (nujol) ν_{max} 3405, 1740, 1730, 1710 cm^{-1} ^1H NMR (DMSO-d_6) δ 0·94 [*s*, 3H, $COC(CH_3)CHOH$], 1·06 [*s*, 3H, $CO(CH_3)CO$], 1·32–2·78 (*m*, 15H, methylene and methine), 6·8, (*s*, 1H, OH, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6) 11·84 [*q*, $C(CH_2)COH$], 20·68 [*q*, $CO(CH_3)CO$], 23·07 (*t*, $CH_2CH_2CCH_3$), 25·72 (*t*, CCH_2), 29·92 (*t*, HOC), 32·64 (*t*, $CH_2CH_2CCH_3$), 34·54 (*t*, $HOCCH_2CH_2$), 36·15 (*t*, $COCH_2CH_2CO$), 36·69 (*t*, $COCH_2CH_2CO$), 48·26 (*d*, COCH), 52·12 (*s*, $HOCH_2CO$), 53·54 (*s*, $CO(CH_3)CO$), 86·02 (*s*, COH), 207 [*s*, $COC(CH_3)CO$], 217·78 (*s*, CH_2COCH), 218·1 [*s*, $COC(CH_3)OCH$]; MS *m/e* (relative intensity) 306 (27, M^+) 288 (12), 260 (8), 195 (25), 177 (20), 125 (85), 113 (100%); Found: C 66·7, H 7·21; $C_{17}H_{22}O_5$ requires C 66·65, H 7·24%.

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