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The Structure and Function of Oestrogens. IX* Synthesis of the *trans* Isomer of 5,5,10b-Trimethyl-4b,5,6,10b,11,12-hexahydrochrysene-2,8-diol

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Abstract

Alkylation of ketene methyl trimethylsilyl acetal (10) with 1ξ-acetoxy-6-methoxy-2-(*p*-methoxyphenyl)-2-methyl-1,2,3,4-tetrahydronaphthalene (9) in the presence of zinc iodide gave 84% of methyl (1′*RS*,2′*RS*)-2-[6′-methoxy-2′-(*p*-methoxyphenyl)-2′-methyl-1′,2′,3′,4′-tetrahydronaphthalen-1′-yl]ethanoate (11a). Cyclization of the derived acid (11b) with methanesulfonic acid gave 89% of 2,8-dimethoxy-10b-methyl-*cis*-4b,10b,11,12-tetrahydrochrysen-6(5*H*)-one (12a), Clemmensen reduction of which afforded 52% of 2,8-dimethoxy-4b-methyl-*cis*-4b,5,6,10b,11,12-hexahydrochrysene (12b). Oxidation of (12b) with dichlorodicyanobenzoquinone gave 70% of the conjugated enone (4), which upon hydrogenation over 10% palladium/charcoal gave a 5:1 ratio of 2,8-dimethoxy-10b-methyl-*trans*-4b,10b,11,12-tetrahydrochrysen-6(5*H*)-one (14) and the *cis* isomer (12a). Exhaustive methylation of the *trans* ketone (14) yielded 49% of 2,8-dimethoxy-5,5,10b-trimethyl-*trans*-4b,10b,11,12-tetrahydrochrysen-6(5*H*)-one (16), which upon Clemmensen reduction followed by *O*-demethylation afforded 5,5,10b-trimethyl-*trans*-4b,5,6,10b,11,12-hexahydrochrysene-2,8-diol (2).

Introduction

The quinone methide hypothesis for oestrogen action, and the rationale for the synthesis and bioassay of strategically *C*-methylated hexahydrochrysenediols has been outlined previously.[1–5] Synthesis of the *cis*-fused 5,5,10b-trimethylhexahydrochrysenediol (1) was achieved by cyclization of an intermediate (3) having the three methyl groups already in place[5] (Scheme 1). The corresponding *trans*-hydrochrysene derivative (2) was not accessible by this route,[5] and we now report its synthesis via the angularly methylated conjugated enone (4).

Results and Discussion

Synthesis of the enone (4) was first attempted by allylic oxygenation of the angularly methylated tetrahydrochrysene derivative (8) (Scheme 2). The latter was

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[1] Collins, D. J., and Matthews, W. A., *Aust. J. Chem.*, 1979, **32**, 1093.
[2] Collins, D. J., Matthews, W. A., and Stone, G. M., *Aust. J. Chem.*, 1979, **32**, 1107.
[3] Collins, D. J., and Stone, G. M., *Aust. J. Biol. Sci.*, 1983, **36**, 305.
[4] Collins, D. J., Stone, G. M., and Axelson, M., *Aust. J. Biol. Sci.*, 1983, **36**, 315.
[5] Collins, D. J., Cullen, J. D., Fallon, G. D., and Gatehouse, B. M., *Aust. J. Chem.*, 1984, **37**, 2279.

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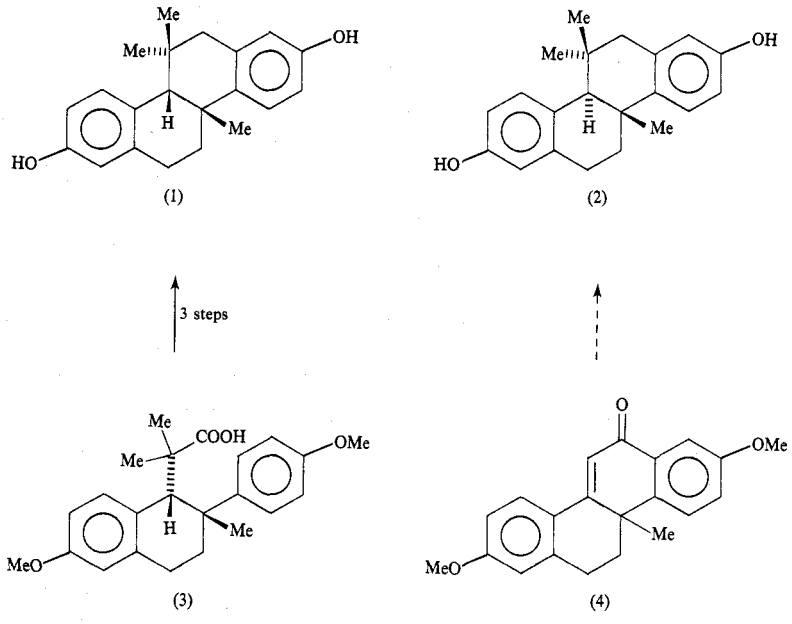
prepared from methyl *m*-methoxyphenylpropanoate by essentially the same sequence as that reported previously,[1,2,6] but the intermediate acyloin was prepared in better yield and higher purity via the corresponding bis-trimethylsilyl derivative (5) (cf.[7]). Conversion of the tetrahydrochrysene (6) into the angularly methylated derivative (8) was accompanied by formation of 30% of the dihydrochrysene (7) which could not readily be removed, hence the 7:3 mixture of (8) and (7) was used directly. Attempts to oxygenate compound (8) with pyridinium chlorochromate (cf.[8]), t-butyl chromate (cf.[9,10]), t-butyl perbenzoate (cf.[11]) or mercuric acetate afforded complex mixtures; there was no reaction with selenium dioxide in refluxing glacial acetic acid or refluxing dioxan. Attention was then turned to the alternative approach to the enone (4) illustrated in Scheme 3.

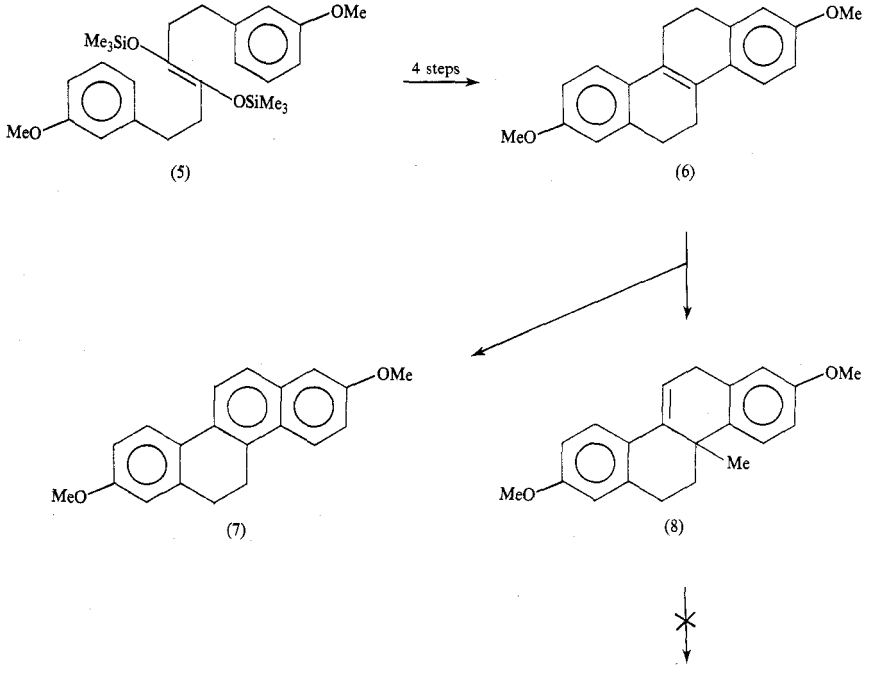


Scheme 1

Reaction of the 1-acetoxytetralin derivative (9)[5] with ketene methyl trimethylsilyl acetal (10)[12] in dichloromethane in the presence of zinc iodide afforded 85% of the ester (11a), together with a small amount of the byproduct (13) formed by eliminative rearrangement of (9) (cf.[5]). The ^{1}H n.m.r. spectrum of the crude product showed only one signal each for the angular methyl (δ 1·23) and the ester methyl group (δ 3·47) indicating that only one epimer was formed, and the mass and ^{13}C n.m.r. spectra were in full accord with structure (11a). Direct cyclization of the ester (11a) to give the ketone (12a) by treatment with methanesulfonic acid proceeded very slowly.

[6] Birch, A. J., and Smith, H., *J. Chem. Soc.*, 1951, 1882.
[7] Bloomfield, J. J., Owsley, D. C., and Nelke, J. M., *Org. React.*, 1967, **23**, 259.
[8] Bonadies, F., and Di Fabio, R., *J. Org. Chem.*, 1984, **49**, 1647.
[9] Yamakawa, K., Nishitani, K., and Yamamoto, A., *Chem. Lett.*, 1976, 177.
[10] Boyle, P. H., Cocker, W., Grayson, D. H., and Shannon, P. V. R., *J. Chem. Soc. C*, 1971, 1073.
[11] Rawlinson, D. J., and Sosnovsky, G., *Synthesis*, 1972, 1.
[12] Ainsworth, C., Chen, F., and Yu-Neng Kuo, *J. Organomet. Chem.*, 1972, **46**, 59.

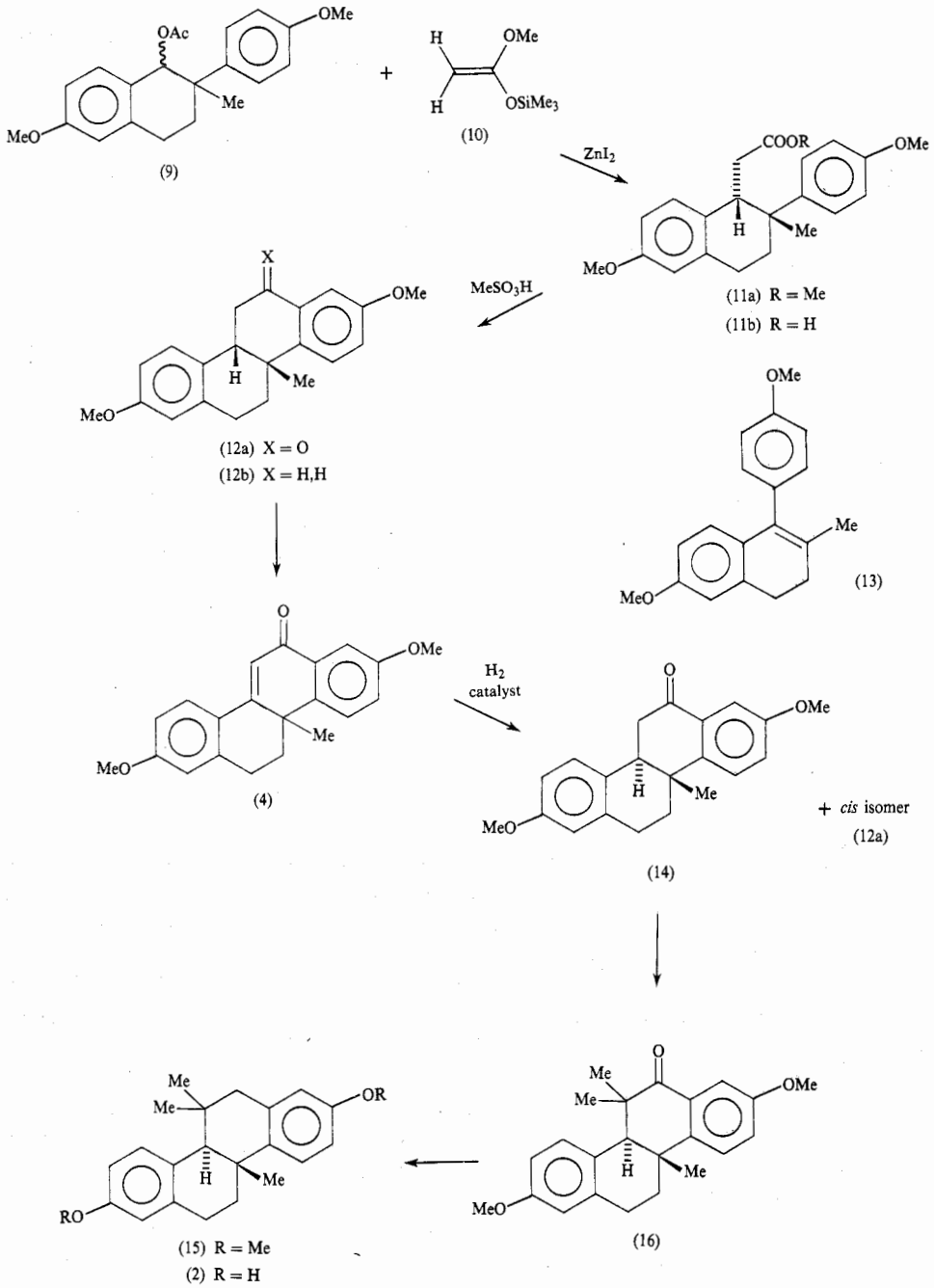
The ester (11a) was therefore hydrolysed to the acid (11b) which upon treatment with methanesulfonic acid for 12 h at room temperature yielded 89% of the ketone (12a). This showed the expected carbonyl absorption at 1680 cm^{-1} and n.m.r. and mass spectral data were consistent with structure (12a). Clemmensen reduction of this gave compound (12b) which was identical with an authentic specimen of this *cis*-hexahydrochrysene derivative which had been prepared previously.[2] This enables unambiguous assignment of the stereochemistry depicted in the precursor ester (11a).



Scheme 2

Attempts to effect phenylselenation of the ketone (12a) by treatment of the lithium enolate with phenylselenyl bromide or chloride were unsuccessful. Attempted α-bromination of the ketone (12a) by treatment with *N*-bromosuccinimide was also unsuccessful, so the α-substitution/elimination approach to the enone (4) was not pursued. Treatment of the ketone (12a) with dichlorodicyanobenzoquinone in methanol at reflux for 24 h effected incomplete oxidation, but the use of benzene as solvent at room temperature provided 70% of the required α,β-unsaturated ketone (4), which showed λ_{max} 228 mm (18200) and 339 mm (16900), and infrared carbonyl absorption at 1640 cm^{-1}. The ^1H n.m.r. spectrum showed the olefinic proton as a singlet at δ 6·80. Catalytic hydrogenation of the enone (4) over 10% palladium/charcoal gave a 5 : 1 ratio of the expected *trans* ketone (14) and the *cis* isomer (12a). This mixture was inseparable and was used directly in the next step. Two successive methylations of the mixture by the use of sodium methylsulfinyl methide and methyl iodide afforded the pure *trans* trimethyl ketone (16) in 49% yield after recrystallization from isopropyl alcohol. The ^1H and ^{13}C n.m.r. spectra of the ketone (16) were fully consistent with the assigned structure and showed that it

was free of the corresponding *cis* isomer. Clemmensen reduction of the ketone (16) afforded 70% of the deoxo compound (15) which upon treatment with hydrobromic acid/glacial acetic acid at reflux for 3 h under nitrogen gave the required trimethylated *trans*-hexahydrochrysenediol (2).



Scheme 3

The oestrogenic activity of compound (2) and of related hydrochrysenediols will be reported in a later paper.

Experimental

Melting points and boiling points are uncorrected. Ultraviolet spectra were measured with a Hitachi 150-20 spectrophotometer. Infrared spectra were obtained with a Jasco IRA-1 diffraction grating infrared spectrophotometer. ^{1}H n.m.r. spectra were measured at 60 MHz with a Varian EM 360 A spectrometer, at 90 MHz with a Bruker WD-90 spectrometer or at 300 MHz with a Bruker AM 300 spectrometer. ^{13}C n.m.r. spectra were measured at 75·45 MHz with a Bruker AM 300 spectrometer. N.m.r. chemical shifts (δ) are in ppm from internal $SiMe_4$; b means broad and exch means that the proton exchanges upon shaking with D_2O. Mass spectra were measured at 70 eV with a VG Micromass 7070F spectrometer. Unless indicated otherwise, only the principal ion peaks (intensities > 10%) are reported. Preparative thin-layer chromatography (t.l.c.) was carried out on plates (20 cm by 20 cm) coated with either Merck PF254 alumina or Merck PF254 silica gel, activated at 100°C for 1 h. Column chromatography was carried out by using Ajax basic alumina (activity 2, Cat. No. 1661), Merck silica gel for chromatography, or Florisil (60–100 mesh). For flash column chromatography, Merck silica gel 60 (No. 9385, 230-400 mesh) was used. Light petroleum refers to the fraction of b.p. 60–80°. Microanalyses were carried out by AMDEL, Melbourne.

(a) 2,8-Dimethoxy-5,6,11,12-tetrahydrochrysene (6)

Sodium metal (5·6 g, 0·24 mmol) was dispersed in boiling toluene (280 ml) under a nitrogen atmosphere. To this suspension was added a mixture of methyl 3-(*m*-methoxyphenyl)propanoate[1] (20·0 g, 0·10 mol) and chlorotrimethylsilane (22·6 g, 0·21 mol) in toluene (120 ml) during 30 min. More chlorotrimethylsilane (22·6 g, 0·21 mol) was added, and the mixture was stirred for 4 h. The cooled solution was filtered through sintered glass under nitrogen, the solvent removed, and the bistrimethylsilyl enol ether (5) was distilled (16·6 g, 67%), b.p. 185–187°/0·3 mm. The distillate was dissolved in methanol and stirred for 24 h. Removal of the solvent gave 4-hydroxy-1,6-bis(*m*-methoxyphenyl)hexan-3-one (11·5 g) as a viscous yellow liquid.

Polyphosphoric acid, freshly prepared from orthophosphoric acid (90 ml) and phosphorus pentoxide (60 g), was cooled to 40° and added to the above acyloin (8·0 g, 27 mmol) with vigorous stirring. After 20 min the mixture was poured into ice/water (200 ml) and stirred for 10 min. The product was collected, dried under vacuum (40°/150 mm), and crystallized from ethyl acetate (with a trace of hydroquinone) to give pale yellow needles of 2,8-dimethoxy-5,6,11,12-tetrahydrochrysene (6) (6·1 g, 86%), m.p. 164–165° (lit.[1] 164–165°). The i.r. and n.m.r. spectra were identical with those reported previously for compound (6).[1]

(b) 2,8-Dimethoxy-4b-methyl-4b,5,6,12-tetrahydrochrysene (8)

Epoxidation of 2,8-dimethoxy-5,6,11,12-tetrahydrochrysene (6) with *m*-chloroperbenzoic acid in a two-phase mixture containing aqueous sodium bicarbonate[1] gave 58% of the corresponding epoxide, m.p. 147–150° (lit.[1] 151–152°), and reaction of this with methylmagnesium bromide in diethyl ether as described previously[1] gave a 7 : 3 mixture (200 mg) of 2,8-dimethoxy-4b-methyl-4b,5,6,12-tetrahydrochrysene (8) and 2,8-dimethoxy-5,6-dihydrochrysene (7) which was used directly for the next step.

(c) Attempted Allylic Oxidation of 2,8-Dimethoxy-4b-methyl-4b,5,6,12-tetrahydrochrysene (8)

(i) *With pyridinium chlorochromate.*—A mixture of the hydrochrysene (8) (100 mg, 0·33 mmol) and pyridinium chlorochromate (292 mg, 1·3 mmol) in dry dichloromethane (25 ml) was stirred at room temperature for 2·5 h. Diethyl ether (25 ml) was added and the mixture was filtered. The filtrate was washed with water (3×25 ml), dried ($MgSO_4$) and evaporated. The residual gum was dissolved in toluene/ethyl acetate (1 : 1) and filtered through a short Florisil column. Evaporation of the solvent gave an orange gum (90 mg) which showed no starting material by analytical t.l.c. (silica, 10% ethyl acetate in light petroleum). Preparative t.l.c. (silica, 10% ethyl acetate in light petroleum) gave three bands (R_F 0·5, 0·3 and 0·2). Of these, only

the most polar component showed carbonyl absorption, and the frequency (ν_{max} 1755 cm^{-1}) suggests that this is an ester or lactone, formed by ring cleavage.

Another reaction carried out at −75° to −10° for several hours gave a similar mixture of products.

(ii) *With t-butyl chromate.*—To a stirred solution of the 4b-methyltetrahydrochrysene (8) (100 mg 0·33 mmol) in carbon tetrachloride (10 ml) containing acetic anhydride (0·5 ml) and glacial acetic acid (1 ml) was added a solution of t-butyl chromate (2 M, 0·5 ml), and the mixture was stirred overnight at room temperature. The excess of t-butyl chromate was destroyed by the addition of a solution of oxalic acid (1 g) in water (10 ml) and by warming the mixture for 1 h. The organic phase was separated, washed with saturated sodium bicarbonate solution (3×20 ml), water (3×20 ml), dried ($MgSO_4$) and evaporated to give an orange gum (120 mg). Preparative t.l.c. (silica, 10% ethyl acetate in light petroleum) gave products similar to those obtained in (i). A similar reaction carried out at −72° for 2·5 h, then at −10° for 2·5 h gave essentially the same result.

(iii) *With selenium dioxide.*—A mixture of compound (8) (100 mg, 0·33 mmol), selenium dioxide (40·3 mg, 0·36 mmol) and water (1 ml) in glacial acetic acid (20 ml) was refluxed overnight. The mixture was allowed to cool to room temperature, filtered through a Celite pad, and the filtrate was poured into water (100 ml). The precipitate, which was collected, washed with water, and dried, was shown (i.r. and ^1H n.m.r.) to be starting material.

(d) Attempted Reaction of t-Butyl Peroxybenzoate with 2,8-Dimethoxy-4b-methyl-4b,5,6,12-tetrahydrochrysene (8)

A solution of t-butyl peroxybenzoate (64 mg, 0·33 mmol) in dry benzene (5 ml) was added to a mixture of the hydrochrysene (8) (100 mg, 0·33 mmol) and freshly prepared cuprous bromide (0·6 mg, 4·0 μmol) in refluxing dry benzene (15 ml). After 48 h at reflux the reaction mixture was cooled, diethyl ether was added, and the extract was washed with saturated sodium bicarbonate solution (2×50 ml), water (3×50 ml), then dried ($MgSO_4$) and evaporated. Analytical t.l.c. (silica; 10% ethyl acetate in light petroleum) showed mainly starting material together with a number of minor products. The ^1H n.m.r. and infrared spectra showed no evidence of a benzoylation product.

(e) Treatment of 2,8-Dimethoxy-4b-methyl-4b,5,6,12-tetrahydrochrysene (8) with Mercuric Acetate

A mixture of the hydrochrysene (8) (200 mg, 0·66 mmol) and mercuric acetate (200 mg, 0·63 mmol) in glacial acetic acid (10 ml) was refluxed for 2 h during which time some metallic mercury separated. The mixture was poured into water (100 ml), extracted with diethyl ether (3×20 ml), washed with saturated sodium bicarbonate solution (2×50 ml), water (3×50 ml), dried ($MgSO_4$) and evaporated to give a brown solid. This was shown by t.l.c. (silica, 10% ethyl acetate in light petroleum) to be a mixture of starting material and several other products. The ^1H n.m.r. and infrared spectra of the crude product gave no evidence of the required acetoxy compound.

(f) Ketene Methyl Trimethylsilyl Acetal (10)

The method was essentially that described by Ainsworth *et al.*[12] A solution of butyllithium (1·5 M, 66·7 ml) in hexane was added to a stirred solution of diisopropylamine (10·6 g, 0·1 mol) in dry tetrahydrofuran (75 ml), under nitrogen at 0°, during 5 min and allowed to stir for a further 15 min. The solution was cooled to −78° and methyl acetate (7·47 g, 0·1 mol) was added during 5 min; the solution was stirred for a further 30 min, then trimethylchlorosilane (25 ml) was added during 5 min. The solution was allowed to warm up to room temperature and stirred for a further 30 min. The white precipitate was filtered off under nitrogen, the volatiles were evaporated (at up to 100°), and fractional distillation of the residue gave a 3:2 (^1H n.m.r.) mixture (10·1 g) of ketene methyl trimethylsilyl acetal (10) and its *C*-silylated isomer, b.p. 110–116° (lit.[13] 45–50°/30 mm). The ^1H n.m.r. spectrum of (10) showed δ (60 MHz, $CDCl_3$*) 0·05, s, $SiMe_3$; 2·95, d, *J* 3 Hz, $=CH_2$; 3·08, d, *J* 3 Hz, $=CH_2$; 3·38, s, OMe.

* $CHCl_3$ used as internal standard.

[13] Burlachenko, G. S., Baukov, Yu. I., and Lutsenko, I. F., *J. Gen. Chem. USSR*, 1972, **42**, 379.

(g) Methyl (1'RS,2'RS)-2-[6'-Methoxy-2'-(p-methoxyphenyl)-2'-methyl-1',2',3',4'-tetrahydronaphthalen-1'-yl]ethanoate (11a)

To a solution of 1ξ-acetoxy-6-methoxy-2-(*p*-methoxyphenyl)-2-methyl-1,2,3,4-tetrahydronaphthalene (9)[5] (4·52 g, 13·3 mmol) and the ketene acetal (10) [3·23 g, of the isomeric mixture ≡ 13·3 mmol of (10)] in dry dichloromethane (75 ml) was added anhydrous zinc iodide (4·25 g, 13·3 mmol). The suspension was stirred under nitrogen at 0° for 2 h, then allowed to warm to room temperature and stirred for 3 h. After treatment with saturated sodium bicarbonate (150 ml), the mixture was filtered through Celite and the aqueous phase was extracted with dichloromethane (2×50 ml). The extract was dried ($MgSO_4$) and evaporated to yield a colourless oil which after flash chromatography (silica; 10% ethyl acetate in light petroleum) to remove the byproduct 6-methoxy-1-(*p*-methoxyphenyl)-2-methyl-3,4-dihydronaphthalene (13),[5] gave a white solid, recrystallization of which from ethanol afforded pure *methyl (1'RS,2'RS)-2-[6'-methoxy-2'-(p-methoxyphenyl)-2'-methyl-1',2',3',4'-tetrahydronaphthalen-1'-yl]ethanoate* (11a) (3·97 g, 84%) as colourless needles, m.p. 106–108° (Found: C, 74·7; H, 7·3. $C_{22}H_{26}O_4$ requires C, 74·6; H, 7·4%). ν_{max} (Nujol) 1720s, 1605s, 1570m, 1530s, 1485m, 1460m, 1420m, 1375m, 1360m, 1330m, 1285m, 1260s, 1240s, 1140s, 1110s, 1060m, 1005m, 990w, 890w, 850s, 820s, 795s, 780m, 775w, 690m cm^{-1}. ^1H n.m.r. δ (300 MHz, $CDCl_3$) 1·23, s, 2'-Me; 1·98–2·18, m, H3',3',4',4'; 2·92–3·00, m, H2,2; 3·40–3·60, m, H1'; 3·47, s, CO_2Me; 3·78, s, OMe; 3·80, s, OMe; 6·60–6·70, m, H5',7'; 6·89, d, *J* 9 Hz, H3'',5''; 7·07, d, *J* 9 Hz, H8'; 7·35, d, *J* 9 Hz, H2'',6''. ^{13}C n.m.r. δ (75 MHz, $CDCl_3$) 26·2, t, C3' or C4'; 26·8, q, 2'-Me; 27·4, t, C4' or C3'; 39·2, s, C2'; 40·5, t, C2; 45·3, d, C1'; 51·3, q, ester Me; 55·1, q, OMe; 55·2, q, OMe; 111·9, d, C7'; 113·5, d, C5'; 113·7, d, C5'', C3; 127·0, d, C2'', C6''; 130·3, d, C8'; 131·8, s, C1''; 135·5, s, C4a' or C8a'; 140·5, s, C8a' or C4a'; 157·7, s, C6' or C4''; 158·0, s, C4'' or C6'; 173·6, s, C1. Mass spectrum: *m/z* 354 (18%), 323 (4), 281 (6), 267 (17), 246 (25), 206 (100), 175 (53), 146 (16), 133 (17), 125·5 (2), 121 (12).

*(h) 2,8-Dimethoxy-10b-methyl-*cis*-4b,10b,11,12-tetrahydrochrysen-6(5H)-one (12a)*

A solution of the methyl ester (11a) (1·0 g, 2·82 mmol) and sodium hydroxide (10 g) in methanol (100 ml) was refluxed under nitrogen for 2 h, then poured into a 1:1 mixture of ice and concentrated hydrochloric acid. The mixture was extracted with ether (3×100 ml), and the extract was washed with water (3×100 ml), then extracted with 10% sodium hydroxide solution (3×50 ml). The aqueous phase was poured into a 1:1 mixture of ice and concentrated hydrochloric acid and the product was collected. Recrystallization from aqueous ethanol gave *(1'RS,2'RS)-2-[6'-methoxy-2'-(p-methoxyphenyl)-2'-methyl-1',2',3',4'-tetrahydronaphthalen-1'-yl]ethanoic acid* (11b) as colourless needles (920 mg, 96%), m.p. 141–146°. A satisfactory microanalysis of this compound was not obtained. ν_{max} (Nujol) 3600–2000bm, 1700s, 1610m, 1580w, 1500m, 1460m, 1380w, 1340w, 1290m, 1255s, 1185m, 1160w, 1125w, 1040w, 970w, 865w, 830m cm^{-1}. ^1H n.m.r. δ (300 MHz, $CDCl_3$) 1·23, s, 2'-Me; 1·90–2·20, m, H2,2,3',3'; 2·90–3·00, m, H4',4'; 3·45–3·50, m, H1'; 3·77, s, 2×OMe; 6·65–6·80, m, H5',7'; 6·88, d, *J* 9 Hz, H2'',6''; 7·12, d, *J* 9 Hz, H8'; 7·33, d, *J* 9 Hz, H3'',5''. Mass spectrum: *m/z* 340 (16%), 267 (13), 193 (12), 192 (100), 175 (10), 174 (10), 147 (17), 146 (18), 133 (15), 121 (12), 44 (10).

A solution of the acid (11b) (130 mg, 0·38 mmol) in methanesulfonic acid (15 ml) was stirred overnight at room temperature under nitrogen. The yellow solution was poured onto ice (200 g) and the reaction flask was rinsed with water (2×50 ml); the combined aqueous suspension was extracted with diethyl ether (3×20 ml) and the extract was washed with saturated sodium bicarbonate (3×50 ml), then dried ($MgSO_4$) and evaporated. Recrystallization of the residue from methanol gave *2,8-dimethoxy-10b-methyl-*cis*-4b,10b,11,12-tetrahydrochrysen-6(5H)-one* (12a) as colourless needles (110 mg, 89%), m.p. 137·5–139° (Found: C, 77·9; H, 6·5. $C_{21}H_{22}O_3$ requires C, 78·2; H, 6·9%). λ_{max} (EtOH) 223 nm (ε 31000), 253 nm (ε 8730). ν_{max} (Nujol) 1680s, 1610m, 1570m, 1500s, 1470s, 1430m, 1390m, 1310m, 1270s, 1250m, 1160w, 1130w, 1040w, 1030w, 870w, 850w, 820w, 730w cm^{-1}. ^1H n.m.r. δ (300 MHz, $CDCl_3$) 1·41, s, 10b-Me; 1·72–1·86, m, H11; 2·15–2·30, m, H11; 2·70–2·96, m, H5,5,12,12; 3·20, dd, *J* 6 Hz, 10 Hz, H4b; 3·76, s, OMe; 3·82, s, OMe; 6·60, d, *J* 3 Hz, H1; 6·74, dd, *J* 3 Hz, 9 Hz, H3; 7·12, d, *J* 9 Hz, H4; 7·15, dd, *J* 3 Hz, 9 Hz, H9; 7·42, d, *J* 9 Hz, H10; 7·44, d, *J* 3 Hz, H7. ^{13}C

n.m.r. δ (63 MHz,* $CDCl_3$) 26·5, q, 10b-Me; 26·7, t, C11 or C12; 32·7, t, C12 or C11; 36·2, s, C10b; 44·0, d, C4b; 44·1, t, C5; 55·2, q, OMe; 55·5, q, OMe; 108·5, d, C3; 112·6, d, C7; 113·6, d, C1; 122·6, d, C9; 128·2, d, C4 or C10; 129·9, d, C10 or C4; 130·2, s, C4a; 132·4, s, C6a or C12a; 136·1, s, C12a or C6a; 143·8, s, C10a; 157·9, s, C2,8; 197·5, s, C6. Mass spectrum: *m/z* 322 (100%), 308 (18), 307 (86), 279 (15), 188 (21), 175 (17), 162 (11), 161 (20), 148 (10), 135 (12), 134 (17), 121 (11), 115 (11), 91 (10).

*(i) 2,8-Dimethoxy-4b-methyl-*cis*-4b,5,6,10b,11,12-hexahydrochrysene (12b)*

The ketone (12a) (200 mg, 0·62 mmol) was added to a vigorously stirred mixture of zinc amalgam, prepared from zinc powder (10 g) and mercuric chloride (1 g), toluene (10 ml), glacial acetic acid (1 ml), water (25 ml) and concentrated hydrochloric acid (20 ml). The stirred mixture was heated under reflux, and more concentrated hydrochloric acid (100 ml) was added during the next 12 h. The mixture was worked up in the usual way to yield an off-white solid which was recrystallized twice from light petroleum and once from ethanol to give 2,8-dimethoxy-4b-methyl-*cis*-4b,5,6,10b,11,12-hexahydrochrysene (12b) as colourless prisms (100 mg, 52%), m.p. 127–128° (lit.[2] 128–129°). The i.r. and ^1H n.m.r. spectra were identical with those previously reported.[2]

*(j) Attempted Phenylselenation of 2,8-Dimethoxy-10b-methyl-*cis*-4b,10b,11,12-tetrahydrochrysen-6(5H)-one (12a)*

To a solution of lithium diisopropylamide prepared from diisopropylamine (0·18 ml, 1·2 mmol) and butyllithium (0·75 ml, 1·6 M), in dry tetrahydrofuran (20 ml) at −78°, under a nitrogen atmosphere, was added a solution of the hydrochrysenone (12a) (322 mg, 1·0 mmol) in dry tetrahydrofuran (2 ml). The solution was stirred for 15 min, then a solution of phenylselenyl bromide (283 mg, 1·2 mmol) in dry tetrahydrofuran (5 ml) was added rapidly. The cold solution was poured into hydrochloric acid (0·5 M, 50 ml) and extracted with diethyl ether (3×50 ml). The extract was washed with water (3×100 ml), dried ($MgSO_4$) and evaporated to give a yellow solid, the ^1H n.m.r. of which showed it to be a mixture of starting material and phenylselenol. Recovery of the starting ketone (12a) was effected by filtration through basic alumina (activity II, 20% ethyl acetate in light petroleum).

(k) 2,8-Dimethoxy-10b-methyl-11,12-dihydrochrysen-6(10bH)-one (4)

To a solution of ketone (12a) (1·52 g, 4·71 mmol) in dry benzene (50 ml) at room temperature was added a solution of 2,3-dichloro-5,6-dicyanobenzoquinone (1·22 g, 5·32 mmol) in dry benzene (20 ml) during 15 min. The dark green solution was stirred at room temperature under nitrogen for 48 h, during which time the insoluble hydroquinone precipitated. Flash chromatography (silica, 20% ethyl acetate in light petroleum) of the crude product gave a yellow solid which was treated with charcoal and recrystallized from ethanol to give *2,8-dimethoxy-10b-methyl-11,12-dihydrochrysen-6(10bH)-one* (4) (1·06 g, 70%) as pale yellow plates, m.p. 155–156° (Found: C, 79·0; H, 6·6. $C_{21}H_{20}O_3$ requires C, 78·7; H, 6·3%). λ_{max} (EtOH) 228 nm (ε 18200), 330 nm (ε 16900). ν_{max} (CCl_4) 3000w, 2940s, 1640bs, 1600bs, 1490m, 1465m, 1430s, 1380w, 1330s, 1290m, 1160w, 1140m, 1080m, 1040m, 920w, 880m cm^{-1}. ^1H n.m.r. δ (300 MHz, $CDCl_3$) 1·37, s, 10b-Me; 1·85, 1·87, 1·89, 1·91, 1·93, 1·96, m, H11; 2·52, dd, *J* 5 Hz, 14 Hz, H11; 3·01, dd, *J* 6 Hz, 18 Hz, H12; 3·17, 3·19, 3·21, 3·23, 3·25, 3·27, 3·29, m, H12; 3·85, s, OMe; 3·90, s, OMe; 6·74, d, *J* 3 Hz, H1; 6·80, s, H5; 6·86, dd, *J* 3 Hz, 9 Hz, H9; 7·19, dd, *J* 3 Hz, 9 Hz, H3; 7·53, d, *J* 9 Hz, H4; 7·71, d, *J* 3 Hz, H7; 7·71, d, *J* 9 Hz, H10. ^{13}C n.m.r. δ (63 MHz, $CDCl_3$) 26·3, t, C11 or C12; 26·7, q, 10b-Me; 34·6, t, C12 or C11; 38·3, s, C10b; 55·5, s, OMe; 55·6, s, OMe; 107·7, d, C3; 113·3, d, C1 or C7; 113·4, d, C7 or C1; 120·1, d, C5 or C9; 121·3, d, C9 or C5; 125·7, s, C4b; 127·2, d, C4 or C10; 127·9, d, C10 or C4; 131·6, s, C12a; 131·8, s, C4a; 138·8, s, C6a; 143·2, s, C10a; 161·2, s, C2 or C8; 161·4, s, C8 or C2; 184·8, s, C6. Mass spectrum: *m/z* 320 (85%), 306 (21), 305 (100), 277 (9).

* 63-MHz ^{13}C n.m.r. spectra were provided by Dr S. R. Johns and Mr I. Willing, Division of Chemicals and Polymers, CSIRO, Melbourne.

*(l) 2,8-Dimethoxy-10b-methyl-*trans*-4b,10b,11,12-tetrahydrochrysen-6(5H)-one (14)*

A mixture of the α,β-unsaturated ketone (4) (200 mg, 0·63 mmol) and 10% palladium on charcoal (10 mg) in ethanol (50 ml) was stirred under one atmosphere of hydrogen for 12 h. The reaction mixture was filtered through Celite, the solvent was evaporated and the residue was crystallized from ethanol to give 156 mg of a 5 : 1 *trans/cis* mixture of *2,8-dimethoxy-10b-methyl-4b,10b,11,12-tetrahydrochrysen-6(5H)-one* (14) and (12a), m.p. 125–127° (Found: C, 78·1; H, 6·6. $C_{21}H_{22}O_3$ requires C, 78·2; H, 6·9%). ν_{max} (Nujol) 1680s, 1600s, 1505s, 1460bs, 1380m, 1330s, 1310m, 1290s, 1270s, 1240s, 1040s, 890m, 850m, 825m, 710m cm^{-1}. ^1H n.m.r.* δ (300 MHz, $CDCl_3$) 1·09, s, 10b-Me; 1·88–2·00, m, H 11; 2·54, ddd, *J* 2·6 Hz, 6·3 Hz, 13·0 Hz, H 11; 2·74, dd, *J* 14·7 Hz, 18·7 Hz, H 4b; 3·00–3·10, m, H 12,12; 3·31–3·42, m, H 5,5; 3·81, s, OMe; 3·87, s, OMe; 6·72, d, *J* 2·7 Hz, H 1; 6·78, dd, *J* 2·7 Hz, 8·5 Hz, H 3; 7·13–7·19, m, H 4,9; 7·46, d, *J* 8·8 Hz, H 10; 7·58, d, *J* 2·9 Hz, H 7. ^{13}C n.m.r.* δ (63 MHz, $CDCl_3$) 21·2, q, 10b-Me; 26·3, t, C 11 or C 12; 33·4, t, C 12 or C 11; 35·9, s, C 10b; 38·6, t, C 5; 41·9, d, C 4b; 55·2, q, OMe; 55·5, q, OMe; 110·0, d, C 3; 111·9, d, C 7; 113·9, d, C 1; 121·9, d, C 9; 125·8, d, C 4 or C 10; 126·4, d, C 10 or C 4; 129·1, s, C 4a; 132·3, s, C 6a or C 12a; 136·7, s, C 12a or C 6a; 146·1, s, C 10a; 158·0, s, C 2 or C 8; 158·2, s, C 8 or C 2; 197·7, s, C 6. Mass spectrum: *m/z* 322 (100%), 308 (20), 307 (83), 279 (14), 188 (22), 175 (16), 162 (12), 161 (12), 148 (12), 135 (12), 134 (16), 121 (11). This mixture of isomers was not separable by chromatography and was used in the next step.

*(m) 2,8-Dimethoxy-5,5,10b-trimethyl-*trans*-4b,5,6,10b,11,12-hexahydrochrysene (15)*

To a stirred solution of sodium methylsulfinylmethide, prepared from sodium hydride (30 mg, 1·3 mmol) in dry dimethyl sulfoxide (5 ml) under nitrogen, was added the 1 : 5 *cis/trans* mixture of 10b-methylchrysenone (14) (200 mg, equivalent to 0·62 mmol). The deep green reaction mixture was stirred at room temperature for 30 min, then an excess of methyl iodide (1 ml) was added dropwise and the yellow solution was stirred for a further 30 min. Workup in the usual manner gave a pale yellow oil which was shown by ^1H n.m.r. to be incompletely methylated. Resubjection to the same methylation procedure gave, after crystallization from isopropyl alcohol, 2,8-dimethoxy-5,5,10b-trimethyl-*trans*-4b,10b,11,12-tetrahydrochrysen-6(5*H*)-one (16) (106 mg, 49%), m.p. 121–123°, as pale yellow prisms. ν_{max} (Nujol) 1670s, 1605s, 1490s, 1410w, 1385m, 1315s, 1290m, 1260m, 1220s, 1040s, 840s, 720m cm^{-1}. ^1H n.m.r. δ (300 MHz, $CDCl_3$) 1·05, s, 10b-Me; 1·48, s, Me (*gem*); 1·62, s, Me (*gem*); 1·91–2·01, m, H 11; 2·25–2·32, m, H 11; 2·82–3·05, m, H 12,12; 3·21, s, H 4b; 3·81, s, OMe; 3·87, s, OMe; 6·73, d, *J* 2·8 Hz, H 1; 6·77, dd, *J* 2·8 Hz, 8·6 Hz, H 3; 7·11, dd, *J* 2·9 Hz, 8·8 Hz, H 9; 7·36, d, *J* 8·7 Hz, H 4; 7·40, d, *J* 2·9 Hz, H 7; 7·56, d, *J* 8·7 Hz, H 10. ^{13}C n.m.r. δ (75 MHz, $CDCl_3$) 21·8, q, 10b-Me; 25·8, q, Me (*gem*); 27·6, t, C 11 or C 12; 29·8, q, Me (*gem*); 35·7, t, C 12 or C 11; 36·7, s, C 10b; 46·2, s, C 5; 50·6, d, C 4b; 55·1, q, OMe; 55·5, q, OMe; 110·6, d, C 3; 111·1, d, C 7; 113·9, d, C 1; 125·4, d, C 10; 128·8, s, C 4a; 129·5, d, C 4; 129·9, d, C 9; 131·6, s, C 12a; 139·1, s, C 6a; 145·0, s, C 10a; 158·2, s, C 2 or C 8; 158·3, s, C 8 or C 2; 205·0, s, C 6. Mass spectrum: *m/z* 350 (100%), 336 (14), 335 (56), 307 (46), 293 (12), 289 (14), 203 (11), 189 (22), 175 (97), 161 (17), 148 (21), 121 (12), 115 (12), 91 (12).

A mixture of amalgamated zinc, prepared from powdered zinc (10 g, 0·15 mol) and mercuric chloride (1 g, 3·7 mmol), the *trans*-trimethylchrysenone (16) (150 mg, 0·43 mmol), toluene (20 ml), glacial acetic acid (2 ml) and water (50 ml) was stirred under reflux for 24 h with the slow addition of concentrated hydrochloric acid (240 ml). Workup in the usual manner and crystallization from ethanol gave colourless prisms of *2,8-dimethoxy-5,5,10b-trimethyl-*trans*-4b,5,6,10b,11,12-hexahydrochrysene* (15) (101 mg, 70%), m.p. 107–108° (Found: M^+, 336·210±0·003. $C_{23}H_{28}O_2$ requires 336·209). ν_{max} (CCl_4) 2920s, 2830m, 1600bs, 1485m, 1460s, 1390m, 1375m, 1280s, 1185m, 1150s, 1100m, 1040s, 910m, 860bm cm^{-1}. ^1H n.m.r. δ (300 MHz, $CDCl_3$) 0·82, s, 10b-Me; 1·26, s, Me (*gem*); 1·41, s, Me (*gem*); 1·57, s, H 4b; 2·00, t, *J* 7·5 Hz, H 11,11; 2·59, d, *J* 16 Hz, H 6; 2·76, d, *J* 16 Hz, H 6; 2·79–2·88, m, H 12,12; 3·79, s, OMe; 3·81, s, OMe; 6·58, d, *J* 2·6 Hz, H 1 or H 7; 6·70–6·79, m, H 7 or H 1, H 3, H 9; 7·19, d, *J* 8·7 Hz, H 4 or H 10; 7·50, d, *J* 8·2 Hz, H 10 or H 4. ^{13}C n.m.r. δ (75 MHz,

* ^1H and ^{13}C n.m.r. spectra were obtained by subtraction of the signals corresponding to the *cis*-hydrochrysenone (1b).

$CDCl_3$) 22·4, q, 10b-Me; 26·7, q, Me (*gem*); 27·6, t, C11; 31·7, q, Me (*gem*); 32·2, s, C5; 38·8, s, C10b; 40·3, t, C12; 50·1, t, C6; 52·1, d, C4b; 55·1, q, 2×OMe; 109·7, d, C3 or C9; 112·4, d, C9 or C3; 113·1, d, C1 or C7; 113·8, d, C7 or C1; 127·5, d, C4 or C10; 128·2, d, C10 or C4; 132·1, s, C4a or C10a; 135·3, s, C10a or C4a; 139·2, s, C6a or C12a; 141·0, s, C12a or C6a; 157·1, s, C2,8. Mass spectrum: *m/z* 336 (62%), 322 (24), 321 (100), 293 (12), 215 (10), 201 (11), 161 (11), 147 (19), 135 (11), 134 (21).

(n) 5,5,10b-Trimethyl-trans-*4b,5,6,10b,11,12-hexahydrochrysene-2,8-diol (2)*

Concentrated hydrobromic acid (48%, 4 ml) was added during 3 h to a refluxing solution of the dimethyl ether (15) (100 mg, 0·3 mmol) in glacial acetic acid (6 ml) under nitrogen. The mixture was poured into ice/water (100 ml), extracted with ethyl acetate/toluene (1 : 1, 3×20 ml), and the organic phase was extracted with 1 M sodium hydroxide solution. Acidification of the alkaline extract gave a pale pink precipitate which was collected, chromatographed (silica; 5% diethyl ether in benzene) and crystallized from aqueous methanol to give off-white microcrystals of *5,5,10b-trimethyl*-trans-*4b,5,6,10b,11,12-hexahydrochrysene-2,8-diol* (2), m.p. 207–212° (37 mg, 40%) (Found: M^+, 308·177±0·003. $C_{21}H_{24}O_2$ requires 308·177). ^1H n.m.r. δ (300 MHz, $CDCl_3$) 0·81, s, 10b-Me; 1·25, s, Me (*gem*); 1·40, s, Me (*gem*); 1·98, dd, *J* 7 Hz, 8 Hz, H11,11; 2·42–2·96, m, H4b,6,6,12,12; 4·58, s, OH (exch); 4·59, s, OH (exch); 6·52, d, *J* 3 Hz, H1 or H7; 6·63–6·71, m, H7 or H1 and H3,9; 7·14, d, *J* 9 Hz, H4 or H10; 7·34, d, *J* 8 Hz, H10 or H4. Mass spectrum: *m/z* 308 (55%), 294 (22), 293 (100), 265 (20), 251 (10), 250 (10), 201 (10), 187 (16), 173 (10), 159 (10), 147 (25), 145 (13), 137 (10), 135 (10), 133 (33), 129 (10), 121 (24), 120 (29), 107 (21), 57 (13), 55 (13).

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