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The Structure and Function of Oestrogens. VIII* Synthesis of 5,5,10b-Trimethyl-*cis*-4b,5,6,10b,11,12-hexahydrochrysene-2,8-diol from 6-Methoxy-3,4-dihydronaphthalen-1(2*H*)-one

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Abstract

Treatment of 2-hydroxymethylene-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (13a) with *p*-methoxyphenyllead triacetate afforded 93% of 2-formyl-6-methoxy-2-(*p*-methoxyphenyl)-3,4-dihydronaphthalen-1(2*H*)-one (14a) which upon deformylation and methylation gave 60% of 6-methoxy-2-(*p*-methoxyphenyl)-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one (17). An alternative route to the α,α'-disubstituted ketone (17) by way of 6-methoxy-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one (15) and 2-chloro-6-methoxy-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one (16) was less efficient. Lithium aluminium hydride reduction of the ketone (17) followed by acetylation yielded 80% of 1ξ-acetoxy-6-methoxy-2-(*p*-methoxyphenyl)-2-methyl-1,2,3,4-tetrahydronaphthalene (23), treatment of which with the trimethylsilyl enol ether of ethyl 2-methylpropanoate in the presence of zinc iodide afforded 71% of ethyl (1*SR*,2*RS*)-2-methyl-2-[6′-methoxy-2′-(*p*-methoxyphenyl)-2′-methyl-1′,2′,3′,4′-tetrahydronaphthalen-1′ξ-yl]propanoate (26a). Treatment of the ester (26a) or the corresponding acid (26b) with methanesulfonic acid yielded 68 or 82% respectively, of 2,8-dimethoxy-5,5,10b-trimethyl-*cis*-4b,10b,11,12-tetrahydrochrysen-6(5*H*)-one (27a); Clemmensen reduction of this followed by demethylation with hydrobromic acid in acetic acid gave 49% of *cis*-5,5,10b-trimethyl-4b,5,6,10b,11,12-hexahydrochrysene-2,8-diol (7a).

The sterochemistry of the ring junction in compound (7a) was established by X-ray crystallography of the corresponding dimethyl ether (27b).

Introduction

In connection with the quinone methide hypothesis for oestrogen action,[1–4] we previously described the synthesis of the *cis* and *trans* isomers of the angularly methylated hydrochrysenediol (1b).[1,2] We reasoned[1] that the unexpectedly low oestrogenic activity of the hydrochrysenediols (1a) might be due to their active-site-promoted dehydrogenation to chrysene-2,8-diol (3) through a cascade of tautomerized quinone methides (Scheme 1). If so, the introduction of an angular methyl group, as in (1b), should prevent this and thereby enhance oestrogenic activity. In fact, *cis*- and *trans*-(1b) were not significantly more oestrogenic than the parent compounds

* Part VII, *Aust. J. Biol. Sci.*, 1983, **36**, 315.

[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.

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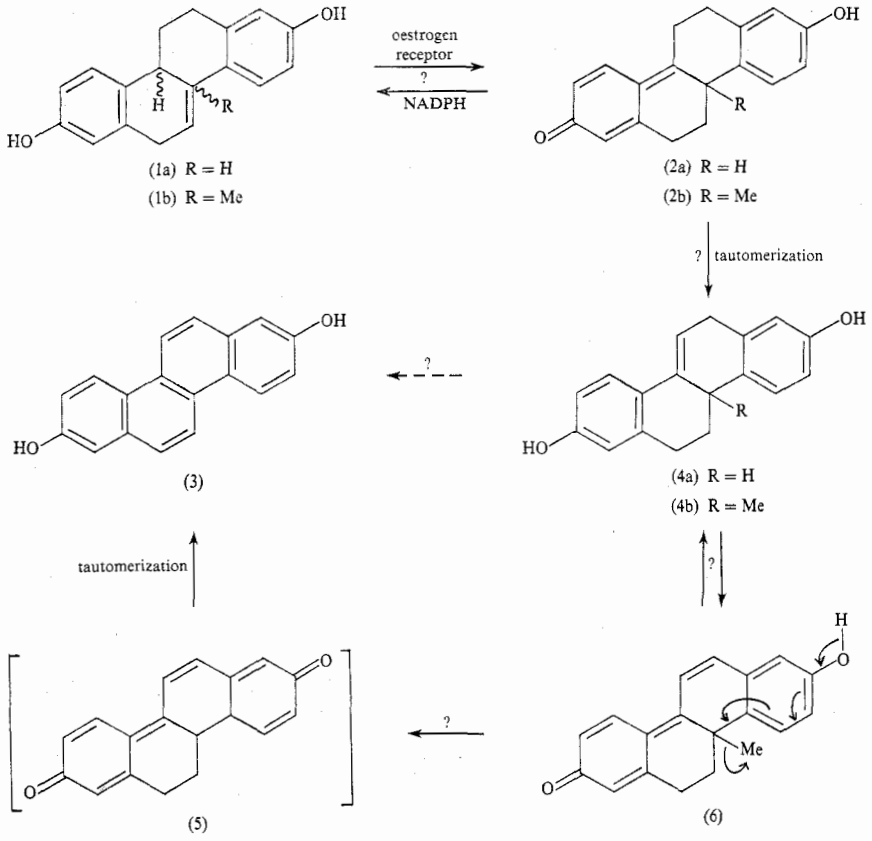


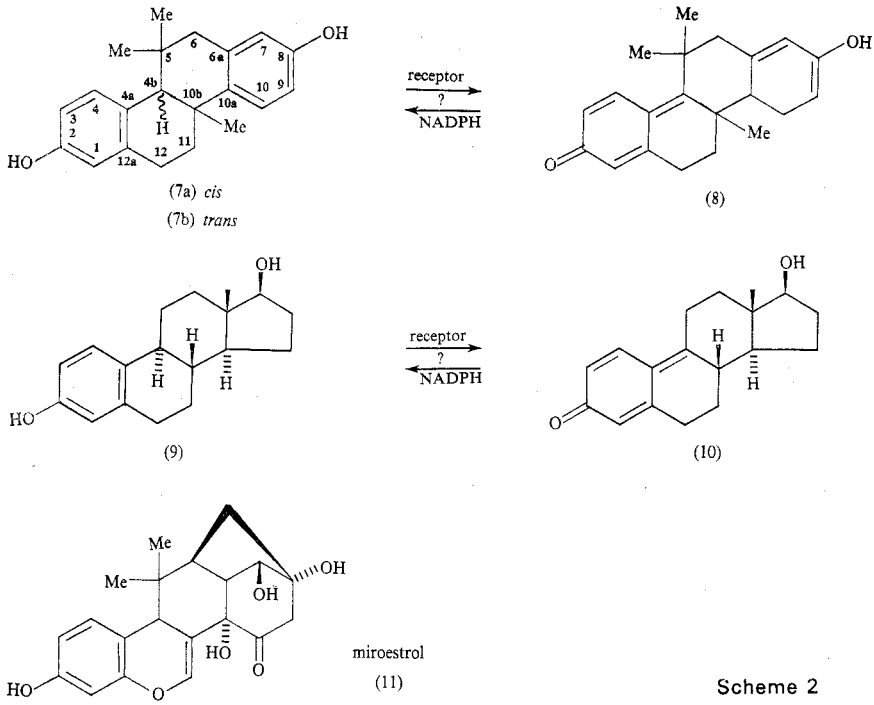
Scheme 1

(1a).[2] This negative result has doubtful significance, but one possible explanation is that the quinone methide (6), derivable from (1b) through (2b) and (4b), might suffer *in vivo* demethylation to give (3) through tautomerization of the quinonoid compound (5) (Scheme 1). The objective of the present study was therefore to synthesize the *cis*- and *trans*-hexahydrochrysene derivatives (7a) and (7b) in which the combination of an angular methyl group and an appropriately placed *gem*-dimethyl group should effectively block tautomerization of the potentially derivable quinone methide (8) (Scheme 2). Our recent proof,[3,4] by the use of specifically trideuterated oestradiol,[5] that the 9α-hydrogen (deuterium) atom of oestradiol (9) suffers no net exchange during oestrogenic stimulation of the mouse makes involvement of the quinone methide (10) very unlikely in normal circumstances, unless the same hydrogen which is removed to give (10) is replaced.[4] Nevertheless, it is still possible that quinone methide formation from oestradiol (9), or from oestrogens in general, might be involved in oestrogen-promoted carcinogenesis.[4] Interest therefore remains in potential oestrogens such as (7a) and (7b) for which tautomerization of the corresponding quinone methide [in this case (8)] is blocked by substituents. Additional

[5] Collins, D. J., *Aust. J. Chem.*, 1983, **36**, 403.

interest in the synthesis of (7a) and (7b) stems from empirical structure–activity relationships: the plant extractive miroestrol (11) (Scheme 2), which has a *gem*-dimethyl group in the same relative position as that in (7a) and (7b), showed even higher oestrogenic activity than that of the natural hormone oestradiol (9).[6] A *gem*-dimethyl group located at a position equivalent to C 11 in a steroid cannot, therefore, have a serious negative effect on the interaction of the oestrogen with the receptor macromolecules, and might even have a potentiating influence.

This paper describes the synthesis of 5,5,10b-trimethyl-*cis*-4b,5,6,10b,11,12-hexahydrochrysene-2,8-diol (7a), and the proof of its stereochemistry by X-ray crystallography of the corresponding dimethyl ether (27b).



(7a) *cis*
(7b) *trans*

(8)

(9)

(10)

miroestrol
(11)

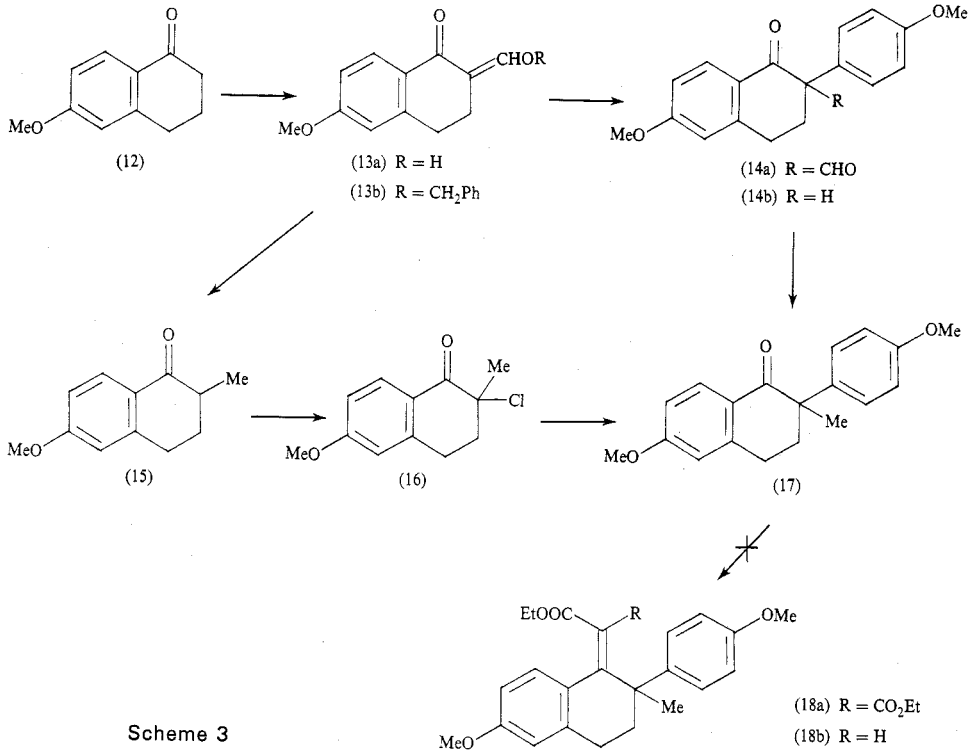
Scheme 2

Results and Discussion

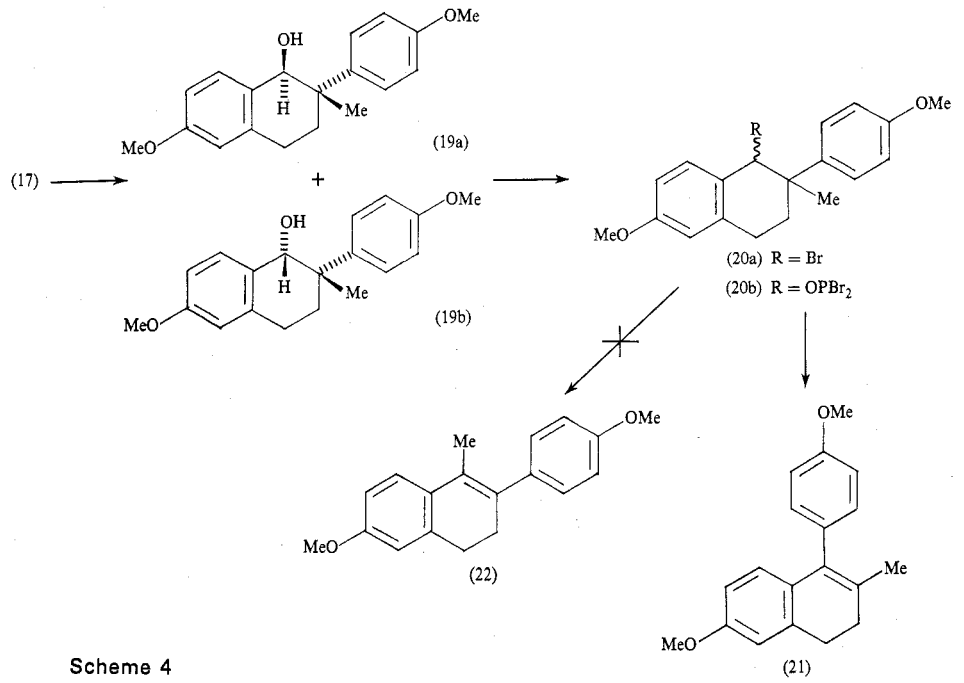
The overall synthetic plan was, first, to effect the successive *p*-anisylation and methylation of 6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (12) (not necessarily in that order) to give compound (17) (Scheme 3), then to construct the *gem*-dimethylated ketone (27a) (Scheme 4), which upon deoxygenation and demethylation should give (7a).

The new procedure recently developed by Pinhey and Rowe for the α-arylation of β-dicarbonyl compounds with aryllead triacetates[7,8] seemed appropriate for the conversion of (12) into (14b), especially since the known hydroxymethylene ketone

[6] Pope, G. S., Grundy, H. M., Jones, H. E. H., and Tait, S. A. S., *J. Endocrinol.*, 1958, **17**, XV.
[7] Pinhey, J. T., and Rowe, B. A., *Aust. J. Chem.*, 1979, **32**, 1561.
[8] Pinhey, J. T., and Rowe, B. A., *Aust. J. Chem.*, 1980, **33**, 113.



Scheme 3



Scheme 4

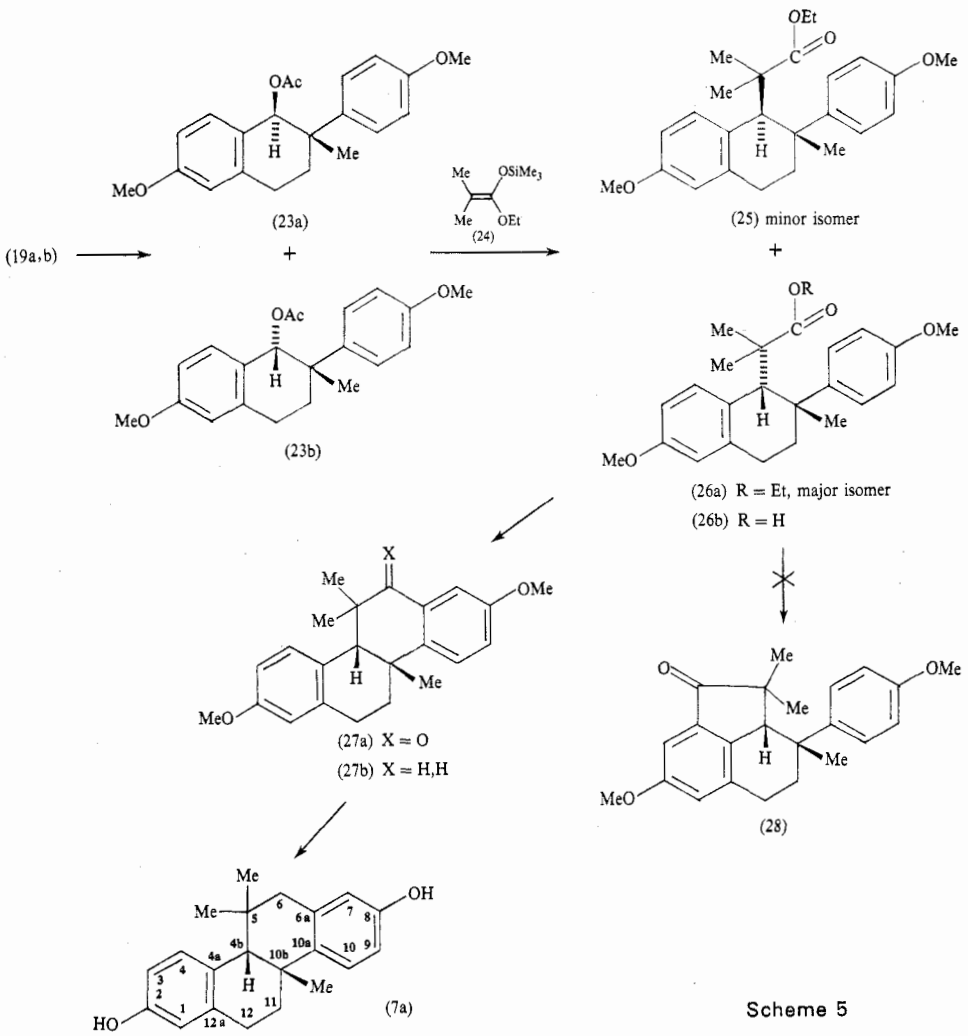
(13a) is derivable from (12) in very high yield.[9] Treatment of (13a) with *p*-methoxyphenyllead(IV) triacetate afforded 93% of the crude 2-formyl-2-(*p*-methoxyphenyl) ketone (14a). Pinhey and Rowe recently reported on the arylation of a number of other α-hydroxymethylene ketones by the use of aryllead triacetates.[10] The 2-formyl-2-*p*-methoxyphenyl ketone (14a) showed all of the expected spectroscopic characteristics, but owing to its high susceptibility to deformylation it was not obtained analytically pure. Base-catalysed deformylation of the keto aldehyde (14a) with 10% potassium hydroxide in methanol or 10% potassium carbonate in methanol gave only 30 or 36% of (14b), respectively, but adsorption of (14a) onto grade II basic alumina and elution with light petroleum containing dichloromethane (10%) afforded 81% of the recrystallized 2-*p*-methoxyphenyl-3,4-dihydronaphthalen-1(2*H*)-one (14b). Methylation of the ketone (14b) by the use of methyl iodide and sodium hydride in dimethyl sulfoxide afforded 74% of the pure α-methylated ketone (17), corresponding to 56% overall yield from 6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one; in tetrahydrofuran or dimethylformamide as solvent the yields in the methylation step were only 34 and 60%, respectively. The α,α-disubstituted ketone (17) was also obtained by the following less efficient route. Hydrogenolysis of the benzoyloxymethylene ketone (13b) gave an almost quantitative yield of the 2-methyl ketone (15),[11] and chlorination of this with sulfuryl chloride in carbon tetrachloride produced the crystalline 2-chloro-2-methyl ketone (16) in excellent yield. Treatment of the chloro ketone (16) with *p*-methoxyphenylmagnesium bromide in tetrahydrofuran gave, upon rearrangement of the intermediate *cis*-chlorohydrin (cf.[12]), only 25% of the required arylated ketone (17); this corresponds to an overall yield of about 19% from 6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one. Thus the sequence (12) → (13a) → (14a) → (14b) → (17), involving use of the aryllead reagent, is clearly superior for the preparation of (17) from (12).

An attempt to condense the ketone (17) with the anion prepared from diethyl malonate gave none of the compound (18a). Not surprisingly, the relatively unreactive ketone (17) also failed to give (18b) either by a Reformatsky reaction with ethyl 2-bromoacetate, or by treatment with the sodium salt of triethyl phosphonoacetate[13,14] in 1,2-dimethoxyethane.

Reduction of the ketone (17) with lithium aluminium hydride gave almost exclusively one epimer of the alcohol (19), but its stereochemistry has not been determined (see below). Treatment of the alcohol (19a) or (19b) with phosphorus tribromide in ether or benzene, and chromatography of the product over alumina gave none of the bromide (20a); the only isolable product was the styrenoid compound (21). When the alcohol (19a) or (19b) was treated with phosphorus tribromide in pyridine at room temperature for 5 h the ^{1}H n.m.r. spectrum of the product indicated that it was a 3 : 5 mixture of the bromide (20a) and the alcohol (19a) or (19b), but reaction for a further 5 h gave only the eliminative rearrangement product (21). The ^{1}H n.m.r. spectrum of compound (21) (m.p. 99·5–100·5°) showed a signal at δ 1·72 for a vinylic methyl group, and the other physical data were in accord with structure

[9] Banerjee, D. K., Chatterjee, S., Pallai, C. N., and Bhatt, M. V., *J. Am. Chem. Soc.*, 1956, **78**, 3769.
[10] Pinhey, J. T., and Rowe, B. A., *Aust. J. Chem.*, 1983, **36**, 789.
[11] Kieboom, A. P. G., and Van Bekkum, H., *Synthesis*, 1970, 476.
[12] Hussey, A. S., and Herr, R. R., *J. Org. Chem.*, 1959, **24**, 843.
[13] Wadsworth, W. S., and Emmons, W. D., *J. Am. Chem. Soc.*, 1961, **83**, 1733.
[14] Wolinsky, J., and Erickson, K. L., *J. Org. Chem.*, 1965, **30**, 2208.

(21). The other possible product, compound (22), was reported to have a melting point of 136°.[15] Compound (21) has been mentioned previously in a patent,[16] but no physical data were given. An authentic specimen of compound (21) was prepared by treatment of the 2-methyl ketone (15) with *p*-methoxyphenylmagnesium bromide; workup (spontaneous dehydration occurred) gave (21) which was identical with the material described above. The formation of compound (21) upon treatment of the alcohol (19a) or (19b) with phosphorus tribromide is not really surprising owing to the expected stability of potential carbonium ions at both C 1 and C 2. Elimination of either bromide or of dibromophosphite ion from (20a) or (20b) respectively to give the carbonium ion at C 1, followed by aryl migration to form the tertiary C 2 carbonium ion, then proton loss from C 1 would yield compound (21).



Scheme 5

[15] Silverman, M., and Bogert, M. T., *J. Org. Chem.*, 1946, **11**, 34.
[16] Phillips, D. K., (Sterling Drug Inc.), U.S. Pat. 3,813,430, 28 May 1974 (*Chem. Abstr.*, 1974, **81**, 37425r).

Reetz and coworkers[17–19] have recently reported on the alkylation of silyl enol ethers of ketones and esters with S_N1-reactive halides and acetates. For example, they showed that ethyl 2-methylpropanoate trimethylsilyl enol ether (24) could be α-t-butylated by reaction with t-butyl chloride in the presence of zinc chloride.[17] They also showed that benzylic acetates could be used to alkylate the trimethylsilyl enol ethers of ketones.[18] This work led us to attempt the Lewis acid-catalysed reaction of compound (23a) or (23b) with the trimethylsilyl enol ether (24) derived from ethyl 2-methylpropanoate. When such a reaction (Scheme 5) was carried out with one pure isomer of (23) in dichloromethane in the presence of zinc iodide at 5° for 2 h, then at room temperature for 3 h, it gave 23% of compound (21) together with 66% of the ester (26a) and 4% of its diastereoisomer (25), separated by flash chromatography. The use of a 3 : 4 mixture of the epimeric acetates (23a,b) (stereochemistry unassigned) gave the same ratio of (26a) and (25), confirming the S_N1 nature of the alkylation. The stereochemistry of the ester (26a) follows unambiguously from that of the derived hydrochrysene derivative (27b); the X-ray crystallographic analysis of this is described below.

Hydrolysis of the ester (26a) with 5% potassium hydroxide in ethylene glycol at reflux for 12 h gave 83% of the corresponding carboxylic acid (26b). An attempt to effect ring closure of (26b) by treatment with polyphosphoric acid at 100° for 2 h gave a red tar, but treatment of (26b) with methanesulfonic acid containing phosphorus pentoxide afforded 82% of the crystalline ketone (27a). The ^{1}H n.m.r. and ^{13}C n.m.r. spectra of the ketone clearly support structure (27a) rather than the possible alternative structure (28) which has a 1,4-disubstituted benzene ring; in addition, the i.r. absorption of the carbonyl group 1690, 1680 cm^{-1} (Nujol), 1678 cm^{-1} (CCl_4) fits the 3,4-dihydronaphthalen-1(2*H*)-one substructure of (27a) rather than the indan-1-one entity of (28). It was not necessary to use the acid (26b) for ring closure; treatment of the ester (26a) with methanesulfonic acid at 10–15° for 4 h under nitrogen gave 68% of the pure ketone (27a). An attempt to effect ring closure of the minor isomer of the ester (25) in a similar way gave a complex mixture of products which was not examined further.

Attempted Wolff–Kishner reduction of the ketone (27a) resulted in partial demethylation and the recovery of some starting material but Clemmensen reduction proceeded smoothly to give 62% of the pure hexahydrochrysene derivative (27b). Demethylation of (27b) by means of hydrobromic/acetic acid afforded 79% of 5,5,10b-trimethyl-*cis*-4b,5,6,10b,11,12-hexahydrochrysene-2,8-diol (7a). The *trans* isomer (7b) is being synthesized by a different route; this, and the biological activity of (7a) and (7b), will be described in due course.

Stereochemistry

The stereochemistry of the ring junction in the trimethylated hexahydrochrysene derivative (27b) was shown to be *cis* by X-ray crystallography (see Fig. 1). The details are given in the Experimental section. The *cis* ring junction established that its precursor (26a) must have the stereochemistry shown in which the bulky isobutyrate group is *cis* to the anisyl group.

[17] Reetz, M. T., and Schwellnus, K., *Tetrahedron Lett.*, 1978, 1455.
[18] Reetz, M. T., Hüttenhain, S. H., and Hübner, F., *Synth. Commun.*, 1981, **11**, 217.
[19] Reetz, M. T., *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 96.

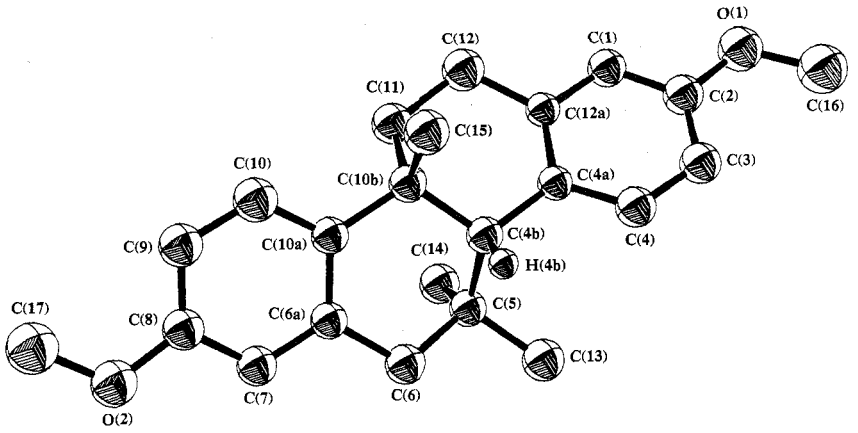


Fig. 1. Molecular structure of compound (27b) with numbering scheme. Hydrogen atoms have been omitted except for H(4b) which has been included so that the stereochemistry of the ring junction can be clearly seen. Thermal ellipsoids are scaled to 50% probability except for H(4b) which is a sphere of arbitrary size.

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 A56/60 spectrometer, or at 90 MHz with a Bruker WD-90 spectrometer. ^{13}C n.m.r. spectra were measured at 22·63 MHz with a Bruker WH-90 spectrometer. The n.m.r. data are given in the following manner: chemical shifts (δ) are in ppm from internal $SiMe_4$. Multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad; exch., proton exchanges upon shaking with D_2O. Mass spectra were measured at 70 eV with a VG Micromass 7070 F 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 the Australian Microanalytical Service, Melbourne.

(a) 6-Methoxy-3,4-dihydronaphthalen-1(2H)-one (12)

6-Methoxy-3,4-dihydronaphthalen-1(2*H*)-one, m.p. 77·5–78° (lit.[9] 77–78·5°), from Aldrich, showed the following n.m.r. data: ^{1}H n.m.r. δ (90 MHz, $CDCl_3$) 2·15, q, *J* 6·3 Hz, H3,3; 2·60, t, *J* 6·3 Hz, $COCH_2$; 2·95, t, *J* 6·3 Hz, H4,4; 3·85, s, OMe; 6·70, d, *J* 2 Hz, H5; 6·80, dd, *J* 2 Hz, *J* 8 Hz, H7; 8·00, d, *J* 8 Hz, H8. ^{13}C n.m.r. δ ($CDCl_3$) 23·0, t, C3; 30·2, t, C4; 38·9, t, C2; 55·4, q, OMe; 112·6, d, C5 or C7; 113·1, d, C7 or C5; 126·4, s, C4a; 129·6, d, C8; 147·0, s, C8a; 164·6, s, C6; 197·2, s, C1.

(b) 2-Hydroxymethylene-6-methoxy-3,4-dihydronaphthalen-1(2H)-one (13a)

A solution of 6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (34·8 g, 0·15 mol) in dry benzene (250 ml) was added to a vigorously stirred mixture of sodium methoxide (11·6 g, 0·5 mol) and ethyl formate (36·5 g, 0·5 mol) in dry benzene (250 ml) cooled to 5° under nitrogen. After the addition was complete the reaction mixture was kept at room temperature for 7 h with vigorous stirring. The mixture was washed with water (2 × 100 ml), and extracted with 1 M sodium hydroxide (2 × 100 ml). Acidification of the combined aqueous washings with concentrated hydrochloric acid containing ice (1 : 1) gave a precipitate which was collected and dried. Recrystallization from light petroleum afforded 2-hydroxymethylene-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (13a) as greenish-yellow plates (36·9 g, 92%), m.p. 68–69° (lit.[9] 67–68°). ^{1}H n.m.r. δ (90 MHz, $CDCl_3$) 2·52, t, H3,3; 2·85,

t, H4,4; 3·85, s, OMe; 6·70, d, *J* 2 Hz, H5; 6·82, dd, *J* 2 Hz, *J* 8 Hz, H7; 7·90, d, *J* 8 Hz, H8; 7·90, s, =CHOH, 14·65, bs, =CHO**H** (exch.). ^{13}C n.m.r. δ ($CDCl_3$) 22·3, t, C3; 29·4, t, C4; 55·5, q, OMe; 108·2, s, C2; 112·9, d, C5 or C7; 113·1, d, C7 or C5; 126·1, s, C4a; 128·8, d, C8; 144·5, s, C8a; 163·5, s, C6; 172·6, d, =CHOH; 184·5, s, C1.

The enol benzoate (13b), prepared in the usual way, had m.p. 128–129° (lit.[11] 130–130·5°). ^{1}H n.m.r. δ (90 MHz, $CDCl_3$) 2·97, apparent s, H3,3,4,4; 3·84, s, OMe; 6·7–8·2, m, 8 aromatic H; 8·56, s, =CH–O–. ^{13}C n.m.r. δ ($CDCl_3$) 23·6, t, C3; 28·8, t, C4; 55·5, q, OMe; 112·7, d, C5 or C7; 113·3, d, C7 or C5; 121·1, s, C2; 127·2, s, C1′ or C4a; 128·5, s, C4a or C1′; 128·8, d, C3′,5′; 130·3, d, C8, 2′6′; 134·2, d, C4′; 141·9, d, =CH–O–; 145·9, s, C8a; 162·8, s, ester CO or C6; 163·7, s, C6 or ester CO; 186·1, s, C1.

(*c*) p-*Methoxyphenyllead*(IV) *Triacetate*

A mixture of lead tetraacetate (50 g, 0·11 mol) (vacuum-dried over KOH), dichloroacetic acid (140 g, 1·09 mol) and anisole (16 g, 0·15 mol), in dry chloroform (200 ml), was stirred at room temperature for 1 h. The mixture was then washed with water (2 × 250 ml) and treated with light petroleum (1·5 l.). The yellow precipitate thus formed was filtered, then stirred with glacial acetic acid (250 ml) and chloroform (200 ml) for 1 h, then the chloroform solution was washed with water (2 × 250 ml). The chloroform solution was stirred with a further portion of glacial acetic acid (250 ml) for 1 h. The chloroform solution was washed with water (2 × 250 ml), then light petroleum (1·5 l.) was added. The resulting suspension was stored at 2° for 48 h, filtered, then dried in vacuum over acetic anhydride (storage in this fashion for more than 5 h caused decomposition). *p*-Methoxyphenyllead(IV) triacetate was produced as colourless crystals (25·5 g, 47%), m.p. 190–200° (dec.)* (lit[10] 139–141°). ν_{max} (Nujol) 3700–3150bm, 1720bw, 1640–1520bs, 1490s, 1480–1380bs, 1300m, 1260s, 1180 cm^{-1}. ^{1}H n.m.r. δ (90 MHz, $CDCl_3$) 2·05, s, $OCOCH_3$; 3·85, s, OMe; 7·05, d, *J* 9 Hz, H2,6; 7·62, d, *J* 9 Hz, H3,5.

(*d*) *2-Formyl-6-methoxy-2-*(p-*methoxyphenyl*)*-3,4-dihydronaphthalen-1*(2H)*-one* (*14a*)

A mixture of the 2-hydroxymethylene ketone (13a) (8·0 g, 0·04 mol), *p*-methoxyphenyllead(IV) triacetate (26·5 g, 0·05 mol) and dry pyridine (10·3 g, 0·13 mol), in dry chloroform (70 ml), was stirred for 3 h at room temperature. The mixture was washed with 1 M sulfuric acid (200 ml), filtered to remove lead sulfate, and the filtrate was washed with water (2 × 200 ml). Evaporation of the dried extract followed by chromatography on silica gel (20% diethyl ether in light petroleum) gave *2-formyl-6-methoxy-2-*(p-*methoxyphenyl*)*-3,4-dihydronaphthalen-1*(2H)*-one* (14a) as a dark yellow oil (11·3 g, 93%), b.p. 200°/0·1 mm (dec.). ν_{max} (film): 2950w, 2840w, 1720m, 1660m, 1600s, 1505s, 1340m, 1250s, 1220m, 1180m, 1120m, 1020m, 820m cm^{-1}. ^{1}H n.m.r. δ (90 MHz, $CDCl_3$) 2·60–2·95, m, H3,3,4,4; 3·77, s, OMe; 3·84, s, OMe; 6·57–7·30, m, H5,7; 6·85, d, *J* 9 Hz, H2′,6′; 7·14, d, *J* 9 Hz, H3′,5′; 8·12, d, *J* 9 Hz, H8; 10·07, s, CHO. ^{13}C n.m.r. δ ($CDCl_3$) 25·6, t, C3; 28·5, t, C4; 55·1, q, OMe; 55·4, q, OMe; 63·9, d,† C2; 112·4, d, C5 or C7; 113·5, d, C7 or C5; 114·7, d, C3′,5′; 125·4, s, C4a or C1′; 125·7, s, C1′ or C4a; 128·9, d, C6′,2′; 130·3, d, C8; 146·2, s, C8a; 159·5, s, C4′; 164·2, s, C6; 195·6, s, C1; 199·9, d, CHO.

(*e*) *Preparation of 6-Methoxy-2-*(p-*methoxyphenyl*)*-3,4-dihydronaphthalen-1*(2H)*-one* (*14b*) *by Deformylation of the 2-Formyl Ketone* (*14a*)

The 2-formyl ketone (14a) (6·3 g, 0·02 mol) was adsorbed onto basic alumina (grade II, 100 g) from light petroleum. Elution with light petroleum containing dichloromethane (10%), and recrystallization from ethanol, afforded colourless crystals of 6-methoxy-2-(*p*-methoxyphenyl)-3,4-dihydronaphthalen-1(2*H*)-one (14b) (4·6 g, 81%), m.p. 126–127° (lit.[15] 124–126°). ν_{max} (Nujol) 1670m, 1600s, 1275s, 1255s, 1230m, 1025s cm^{-1}. ^{1}H n.m.r. δ (90 MHz, $CDCl_3$) 2·37, t, *J* 6 Hz, H3,3; 3·00, coincident t's, *J* 6 Hz, H2,3,3; 3·77, s, OMe; 3·85, s, OMe; 6·60–7·30, m, 6 aromatic H; 8·05, d, *J* 9 Hz, H8. ^{13}C n.m.r. δ ($CDCl_3$) 29·1, t, C3; 31·4, t, C4; 53·5, d, C2; 55·3, q, OMe;

* The melting points of several preparations were consistently 190–200°; the difference between this and the reported value[10] remains unexplained.

† This signal would be expected to be a singlet; the small splitting of 5·8 Hz observed in the off-resonance spectrum (decoupling frequency off-set at 370 Hz downfield from $SiMe_4$ with a power of 3 W, c.w.) is apparently due to β-coupling with the formyl hydrogen.

55·5, q, OMe; 112·5, d, C5 or C7; 113·3, d, C7 or C5; 114·0, d, C3′,5′; 126·6, s, C4a; 129·4, d, C2′,6′; 130·3, d, C8; 132·1, s, C1′; 146·6, s, C8a; 158·5, s, C4′; 163·7, s, C6; 197·3, s, C1. Mass spectrum: *m/z* 282 (30%), 161 (34), 148 (100), 122 (10), 121 (21), 91 (17), 77 (10).

(*f*) *6-Methoxy-2-*(p-*methoxyphenyl*)*-2-methyl-3,4-dihydronaphthalen-1*(2H)*-one* (*17*)

A slurry of sodium hydride (0·38 g, 16 mmol) in dry dimethyl sulfoxide (10 ml) was stirred under nitrogen at 70° for 1·5 h. The mixture was cooled to room temperature, then a solution of the ketone (14b) (4·0 g, 14 mmol) in dry dimethyl sulfoxide (5 ml) was added. The mixture was stirred for a further 2 h, resulting in a deep yellow solution. Methyl iodide (2·0 g, 14 mmol) was added, and stirring was continued until the yellow colour had faded (1–1·5 h). After the addition of water (500 ml) the mixture was extracted with ether (3 × 100 ml), and washed with water (3 × 250 ml), dried (Na_2SO_4) and evaporated. Recrystallization of the residue from ethanol gave *6-methoxy-2-*(p-*methoxyphenyl*)*-2-methyl-3,4-dihydronaphthalen-1*(2H)*-one* (17) as colourless needles (3·19 g, 74%), m.p. 74–76° (Found: C, 77·3; H, 6·6. $C_{19}H_{20}O_3$ requires C, 77·0; H, 6·8%). ν_{max} (Nujol) 1670m, 1600s, 1465s, 1380s, 1350m, 1310w, 1300w, 1280m, 1262m, 1230m, 1190m, 1100m, 1020m cm^{-1}. ^1H n.m.r. δ (90 MHz, $CDCl_3$) 1·50, s, Me; 2·0–3·0, m, CH_2CH_2; 3·75, s, OMe; 3·80, s, OMe; 6·4–7·3, m, 6 aromatic H; 8·10, d, *J* 9 Hz, 1 aromatic H. ^{13}C n.m.r. δ ($CDCl_3$) 26·5, t, C3; 27·2, q, Me; 36·5, t, C4; 49·5, s, C2; 55·2, q, OMe, 55·4, q, OMe; 112·4, d, C5 or C7; 113·4, d, C7 or C5; 114·0, d, C3′,5′; 126·5, s, C5a; 127·5, d, C2′,6′; 130·5, d, C8; 134·5, s, C1′; 146·2, s, C8a; 158·3, s, C4′; 163·5, s, C6; 200·2, s, C1. Mass spectrum: *m/z* 296 (19%), 161 (10), 148 (100), 120 (10).

(*g*) *Preparation of 6-Methoxy-2-methyl-3,4-dihydronaphthalen-1*(2H)*-one* (*15*) *by Catalytic Reduction of the 2-Benzoyloxymethylene Ketone* (*13b*)

Platinum(II) oxide (0·1 g) was suspended in isopropyl alcohol (50 ml) and pre-reduced with hydrogen. A suspension of the 2-benzoyloxymethylene ketone (13b) (4·6 g, 15 mmol) in isopropyl alcohol (50 ml) containing triethylamine (4 ml) was added, and the mixture was hydrogenated at room temperature and atmospheric pressure. The filtered solution was concentrated to 20 ml, added to water (200 ml), and extracted with ether (2 × 50 ml). The extract was washed with saturated sodium bicarbonate solution (2 × 200 ml), 1 M sulfuric acid (2 × 200 ml), then dried (Na_2SO_4). Evaporation followed by bulb-to-bulb distillation gave the pure 2-methyl ketone (15) as a colourless oil (2·91 g, 99%), b.p. 150°/1·1 mm (lit.[11] 110·112°/0·6 mm). ν_{max} (film) 2920s, 2860m, 1660s, 1595s, 1480m, 1440m, 1340m, 1245bs, 1125m, 1020m, 960m, 915m, 720 cm^{-1}. ^1H n.m.r. δ (60 MHz, $CDCl_3$) 1·26, d, *J* 7·2 Hz, Me; 1·5–3·1, m, H2,3,3,4,4; 3·90, s, OMe; 6·6–7·0, m, H5,7; 8·13, d, *J* 9 Hz, H8. ^{13}C n.m.r. δ ($CDCl_3$) 15·5, q, Me; 29·2, t, C3; 31·5, t, C4; 42·3, d, C2; 55·4, q, OMe; 112·5, d, C5 or C7; 113·1, d, C7 or C5; 126·1, s, C4a; 129·9, d, C8; 146·7, s, C8a; 163·4, s, C6; 199·7, s, C1.

(*h*) *2-Chloro-6-methoxy-2-methyl-3,4-dihydronaphthalen-1*(2H)*-one* (*16*)

A solution of sulfuryl chloride (0·82 g, 6·1 mmol) in dry carbon tetrachloride (10 ml) was added dropwise during 1 h to a stirred solution of the 2-methyl ketone (15) (1·1 g, 5·6 mmol) in dry carbon tetrachloride (10 ml) kept at 0°. The reaction mixture was then allowed to warm up to room temperature and stirred for a further 12 h. The solvent was removed in vacuum, and crystallization of the residue from ethanol gave *2-chloro-6-methoxy-2-methyl-3,4-dihydronaphthalen-1*(2H)*-one* (16) as colourless prisms (1·2 g, 99%), m.p. 67–69° (Found: C, 64·3; H, 6·0; Cl, 15·7. $C_{12}H_{13}ClO_2$ requires C, 64·2; H, 5·8; Cl, 15·8%). ν_{max} (film) 2950m, 1845w, 1680s, 1600s, 1280s, 1260s, 1235s, 1100m, 1090m, 865w cm^{-1}. ^1H n.m.r. δ (60 MHz), ($CDCl_3$) 1·80, s, Me; 2·0–3·5, m, H3,3,4,4; 3·87, s, OMe; 6·7–7·1, m, H5,7; 8·14, d, *J* 9 Hz, H8. ^{13}C n.m.r. δ ($CDCl_3$) 26·4, q, Me; 26·8, t, C3; 38·7, t, C4; 55·5, q, OMe; 67·6, s, C2; 112·4, d, C5 or C7; 113·9, d, C7 or C5; 123·2, s, C4a; 131·5, d, C8; 145·7, s, C8a; 164·0, s, C6; 190·3, s, C1. Mass spectrum: *m/z* 224/226 (18%), 188 (11), 140 (100), 120 (15).

(*i*) *Preparation of 6-Methoxy-2-*(p-*methoxyphenyl*)*-2-methyl-3,4-dihydronaphthalen-1*(2H)*-one* (*17*) *from 2-Chloro-6-methoxy-2-methyl-3,4-dihydronaphthalen-1*(2H)*-one* (*16*)

A solution of *p*-methoxyphenylmagnesium bromide in tetrahydrofuran 0·53 M, 8·45 ml) was added during 1 h to a solution of 2-chloro-6-methoxy-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one

(16) (1·0 g, 4·5 mmol) in dry benzene (25 ml) cooled to 0°. The solution was refluxed for 3 h, treated with dilute ammonium chloride solution (100 ml), washed with water (2 × 100 ml), then dried (Na_2SO_4) and evaporated. The ^1H n.m.r. spectrum and analytical t.l.c. (alumina, ether/light petroleum, 1 : 1) indicated the presence of approximately 50% of the unchanged 2-chloro ketone (16), 25% of 6-methoxy-2-(*p*-methoxyphenyl)-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one (17), and two other unidentified products.

(*j*) *6-Methoxy-2-*(p-*methoxyphenyl*)*-2-methyl-1,2,3,4-tetrahydronaphthalen-1ξ-ol* (*19*)

A solution of the 2-anisyl-2-methyl ketone (17) (1·0 g, 3·4 mmol) in dry diethyl ether (50 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (80 mg, 2·1 mmol) in dry diethyl ether (50 ml) in a nitrogen atmosphere and the mixture was refluxed for 15 h. Potassium hydroxide solution (100 ml) was added and the washed and dried (Na_2SO_4) extract was evaporated. Recrystallization of the residue from ethanol containing a trace of pyridine yielded colourless crystals of *6-methoxy-2-*(p-*methoxyphenyl*)*-2-methyl-1,2,3,4-tetrahydronaphthalen-1ξ-ol* (19) (1·0 g, 99%), m.p. 126–128° (Found: C, 76·2; H, 7·4. $C_{19}H_{22}O_3$ requires C, 76·5; H, 7·4%). ν_{max} (Nujol) 3560–3280bm, 1610s, 1510s, 1460s, 1250s, 1185m, 1160m, 1030m cm^{-1}. ^1H n.m.r. δ (90 MHz, $CDCl_3$) 1·20, s, Me; 1·53, s, OH (exch.); 2·0–3·0, m, H3,3,4,4; 3·79, s, OMe; 3·81, s, OMe; 4·64, s, H1; 6·7–7·5, m, 7 aromatic H. ^{13}C n.m.r. δ ($CDCl_3$) 23·9, q, Me; 26·3, t, C3 or C4; 26·5, t, C4 or C3; 41·0, s, C2; 55·2, q, 2 × OMe; 75·4, d, C1; 112·6, d, C5 or C7; 113·2, d, C7 or C5; 114·0, d, C3′,5′; 127·4, d, C2′,6′; 129·3, s, C1′; 131·9, d, C8; 137·1, s, C8a or C5a; 138·6, s, C5a or C8a; 158·0, s, C6; 159·2, s, C4′. Mass spectrum: *m/z* 298 (13%), 150 (100), 149 (71), 135 (11), 101 (10).

(*k*) *Attempted Bromination of 6-Methoxy-2-*(p-*methoxyphenyl*)*-2-methyl-1,2,3,4-tetrahydronaphthalen-1ξ-ol* (*19*)

(i) *With phosphorus tribromide in diethyl ether.*—A mixture of the alcohol (19) (1·1 g, 3·7 mmol) and phosphorus tribromide (1·1 g, 4·1 mmol) in diethyl ether (100 ml) was refluxed overnight. Water (100 ml) was added and the washed ether solution was dried (Na_2SO_4), and evaporated. Column chromatography of the residue on alumina (50 g, ethyl acetate/light petroleum, 1 : 1), followed by recrystallization from ethanol, gave a product (350 mg), m.p. 99·5–100·5°, which contained no bromine, and was shown to be 6-methoxy-1-(*p*-methoxyphenyl)-2-methyl-3,4-dihydronaphthalene (21) by direct comparison with an authentic specimen prepared by treatment of 6-methoxy-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one (15) with *p*-methoxyphenylmagnesium bromide. Recrystallization of the product from ethanol gave pure *compound* (*21*), m.p. 100·5–110·5°, undepressed on admixture with the above material (Found: C, 81·3; H, 7·3. $C_{19}H_{20}O_2$ requires C, 81·4; H, 7·2%). ν_{max} (Nujol) 1605s, 1505s, 1460s, 1245s, 1185s, 1030s, 870m, 840m cm^{-1}. λ_{max} (EtOH) 274·5 nm (4·23). ^1H n.m.r. δ (90 MHz, $CDCl_3$) 1·72, s, Me; 2·2–2·8, m, H3,3,4,4; 3·76, s, OMe; 3·84, s, OMe; 6·5–7·3, m, 7 aromatic H. ^{13}C n.m.r. δ ($CDCl_3$) 21·2, q, Me; 28·7, t, C3 or C4; 30·2, t, C4 or C3; 55·2, q, 2 × OMe; 110·6, d, C5 or C7; 113·3, d, C7 or C5; 113·7, d, C3′,5′; 114·2, s, C2; 126·3, d, C8; 130·6, 131·3, 132·4, 136·7, all s, C1,1′,4a,8a; 157·8, s, C6 or C4′; 158·3, s, C4′ or C6. Mass spectrum: *m/z* 281 (M+1, 83%), 280 (100), 279 (30), 278 (25), 267 (15), 266 (30), 265 (4), 253 (10), 252 (28), 251 (42), 250 (20), 249 (14), 235 (12), 234 (10), 140 (10), 121 (10).

(ii) *With phosphorus tribromide in benzene.*—A mixture of the alcohol (19) (300 mg, 1·1 mmol) and phosphorus tribromide (300 mg, 1·1 mmol), in dry benzene (50 ml), was stirred at room temperature for 5 h. After the addition of water (100 ml), the benzene layer was washed with water (2 × 100 ml), dried (Na_2SO_4) and evaporated. The ^1H n.m.r. spectrum showed that the product was mainly compound (21), as obtained in (i).

(iii) *With phosphorus tribromide in benzene with pyridine.*—A mixture of the alcohol (19) (300 mg, 1·0 mmol), phosphorus tribromide (300 mg, 1·1 mmol) and dry pyridine (0·1 ml) in dry benzene (50 ml) was stirred at room temperature for 5 h. Workup in the usual way gave a product whose ^1H n.m.r. spectrum indicated that it was probably a mixture of starting material and the corresponding bromide in the ratio of 5 : 3. The mixture gave a positive Beilstein test for halogen. Reaction for a further 5 h gave only 6-methoxy-1-(*p*-methoxyphenyl)-2-methyl-3,4-dihydronaphthalene (21), identified by its ^1H n.m.r. spectrum.

(*l*) *Preparation of 6-Methoxy-2-*(p-*methoxyphenyl)-1-methyl-3,4-dihydronaphthalene* (*22*)

A solution of the 2-(*p*-methoxyphenyl) ketone (14b) (500 mg, 1·77 mmol) in dry diethyl ether (190 ml) was added slowly with stirring to the cooled Grignard reagent prepared from magnesium (50 mg, 2·1 mmol) and methyl iodide (260 mg, 1·8 mmol) in dry diethyl ether (10 ml). The mixture was stirred at room temperature for 1 h, then refluxed overnight. The cooled mixture was treated with 1 M HCl (100 ml), and the product was extracted with ether. The washed, dried (Na_2SO_4) extract gave a white solid, recrystallization of which from acetone gave 6-methoxy-2-(*p*-methoxyphenyl)-1-methyl-3,4-dihydronaphthalene (211 mg, 43%), m.p. 136–137° (lit.[15] 136°). ν_{max} (EtOH) 201·5 (4·51), 225·0 (4·14), 289 (4·36) nm. ν_{max} (Nujol) 1600s, 1565m, 1495s, 1460s, 1440m, 1370m, 1305m, 1295m, 1275m, 1250s, 1175m, 1165m, 1120m, 1110w, 1060w, 1025s, 950w, 855w, 830s, 740w cm^{-1}. ^1H n.m.r. δ (60 MHz, $CDCl_3$) 2·00, t, *J* 2 Hz,* CH_3; 2·3–3·2, m, H 3,3,4,4; 3·80, s, 2 × OMe; 6·5–7·3, m, 7 aromatic H. ^{13}C n.m.r. ($CDCl_3$) 16·1, q, Me; 29·4, t, C 3 or C 4; 30·8, t, C 4 or C 3; 55·3, q, 2 × OMe; 111·1, d, C 5 or C 7; 113·5, d, C 2′,6′, C 7 or C 5; 124·6, d, C 8; 126·8, s, C 2 or C 1; 130·0, d, C 3′,5′; 130·3, 134·2, 135·9, all s, C 4a,8a,1′; 137·6, s, C 1 or C 2; 158·3, s, C 6,4′. Mass spectrum: *m/z* 281 (M+1, 20%), 280 (100), 264 (27), 159 (12), 140 (15), 121 (77).

(*m*) *Preparation of 1ξ-Acetoxy-6-methoxy-2-*(p-*methoxyphenyl)-2-methyl-1,2,3,4-tetrahydronaphthalene* (*23*)

Acetic anhydride (1 ml) was added with stirring to a cooled solution of the alcohol (19) (2·0 g, 6·7 mmol) in dry pyridine (20 ml). The mixture was allowed to warm to room temperature and stirred for a further 12 h. Water (500 ml) was added and the mixture was extracted with diethyl ether. The combined extracts were washed with 1 M hydrochloric acid (2 × 200 ml), saturated copper sulfate solution (2 × 100 ml) and water (2 × 100 ml). Evaporation of the dried (Na_2SO_4) extract and recrystallization of the residue from ethanol gave *1ξ-acetoxy-6-methoxy-2-*(p-*methoxyphenyl)-2-methyl-1,2,3,4-tetrahydronaphthalene* (23) as colourless needles (1·85 g, 81%), m.p. 115–117° (Found: C, 73·8; H, 7·1. $C_{21}H_{24}O_4$ requires C, 73·9; H, 7·3%). ν_{max} (Nujol) 1725s, 1620m, 1580w, 1505s, 1470bm, 1380m, 1280s, 1260s, 1190m, 1120m, 1040s, 1000m, 970m, 940m, 935, 920m cm^{-1}. ^1H n.m.r. δ (60 MHz, $CDCl_3$) 1·25, s, Me; 1·61, s, $MeCO_2$; 3·80, s, 2 × OMe; 6·20, s, H 1; 6·7–7·6, m, 7 aromatic H. ^{13}C n.m.r. δ ($CDCl_3$) 20·8, q, $MeCO_2$; 23·6, q, Me; 26·2, t, C 3 or C 4; 27·4, t, C 4 or C 3; 39·9, s, C 2; 55·2, q, 2 × OMe; 75·7, d, C 1; 112·6, d, C 5 or C 7; 113·4, d, C 3′,5′ and C 7 or C 5; 127·1, d, C 2′,6′; 132·0, s, C 1′; 132·2, d, C 8; 137·6, s, C 8a or C 4a; 138·7, s, C 4a or C 8a; 157·8, s, C 6; 159·6, s, C 4′; 170·4, CO. Mass spectrum: *m/z* 340 (7%), 280 (17), 265 (17), 232 (10), 192 (21), 151 (20), 150 (100), 149 (19), 135 (13), 133 (10), 121 (17), 43 (10).

(*n*) *Preparation of Ethyl* (*1*SR,*2*RS)-*2-Methyl-2-*[*6′-methoxy-2′-*(p-*methoxyphenyl)-2′-methyl-1′,2′,3′,4′-tetrahydronaphthalen-1′ξ-yl*]*propanoate* (*26a*)

(i) *Preparation of 2,2-dimethylketene ethyl trimethylsilyl acetal* (*24*).—A solution of butyllithium (1·47 M, 13·6 ml) in hexane was added to a stirred solution of diisopropylamine (2·0 g, 2·0 mmol) in dry tetrahydrofuran under nitrogen at 0°, during 5 min and allowed to stand for a further 15 min. Ethyl 2-methylpropanoate (2·4 g, 2·0 mmol) was added to the cold mixture. After a further 30 min at 0°, trimethylchlorosilane (5 ml) was added dropwise during 5 min, then the mixture was allowed to warm to room temperature and stirred for an additonal 30 min. The mixture was filtered, concentrated in vacuum, and diluted with dry diethyl ether (50 ml), then filtered and evaporated. Care was taken to exclude oxygen and moisture during all processes. The residue was distilled from a nitrogen atmosphere under reduced pressure to give the silyl ketene acetal (24) as a colourless liquid (2·4 g, 70%), b.p. 61–64°/19 mm. ν_{max} (film) 2960m, 2910m, 2850m, 1740w, 1705s, 1255s, 1190s, 1165s, 1040m, 980w, 880s, 870s, 850s, 760w cm^{-1}. ^1H n.m.r. δ (90 MHz, $CDCl_3$) 0·20, s, $SiMe_3$, 1·20, t, *J* 7·2 Hz, OCH_2**Me**; 1·50, s, =CCH_3; 1·55, s, =CMe_2; 3·72, q, *J* 7·2 Hz, OCH_2Me.

(ii) *Alkylation reaction.*—Zinc iodide (958 mg, 3 mmol), which had been vacuum dried (140°/1 mm over phosphorus pentoxide) for 12 h, was added to a stirred mixture of the silyl ketene acetal (22) (564 mg, 3 mmol) and the acetate (23) (1·02 g, 3 mmol) in dry dichloromethane (50 ml) at 5° under nitrogen. The stirred mixture was kept cold for 2 h, allowed to warm to room temperature, then stirred for a further 3 h. After addition of saturated sodium bicarbonate solution (150 ml), the mixture was filtered, separated, and the aqueous phase was washed with dichloromethane (50 ml).

* Homoallylic coupling with H 3.

The combined extract was dried (Na_2SO_4), and the solvent was removed to give a yellow oil which showed two spots on t.l.c. (silica, ethyl acetate/light petroleum 1 : 1). Flash chromatography (10% ethyl acetate in light petroleum) gave 6-methoxy-1-(*p*-methoxyphenyl)-2-methyl-3,4-dihydronaphthalene (21) as a solid (159 mg, 23%), followed by a colourless oil which was identified as a mixture of the two diastereoisomeric esters (25) and (26a) (852 mg, 71%). Further flash chromatography (5% ethyl acetate in light petroleum) gave the pure major isomer of *ethyl (1*SR,*2*RS)-*2-methyl-2-[6′-methoxy-2′-*(p-*methoxyphenyl)-2′-methyl-1′,2′,3′,4′-tetrahydronaphthalen-1′ξ-yl]propanoate* (26a) (790 mg, 66%), m.p. 74–76° (Found: C, 76·1; H, 8·3. $C_{25}H_{32}O_4$ requires C, 75·7; H, 8·1%). ν_{max} (Nujol), 1720s, 1605m, 1580w, 1510m, 1500m, 1450bm, 1375m, 1295m, 1240bm, 1220m, 1185m, 1130m, 1100m, 1030bm, 825m cm^{-1}. ^1H n.m.r. δ (90 MHz, $CDCl_3$) 0·76, s, Me (*gem*); 0·82, s, Me (*gem*); 0·95, s, angular Me; 0·98, t, *J* 7 Hz, OCH_2**Me**; 1·51–3·19, m, H3′,3′,4′,4′; 3·39, s, H1′; 3·43, q, *J* 7 Hz, OCH_2Me; 3·70, s, 2×OMe; 6·4–7·5, m, 7 aromatic H. ^{13}C n.m.r. δ ($CDCl_3$) 13·8, q, OCH_2**Me**; 23·3, q, angular Me; 26·0, t, C3′; 27·2, t, C4′; 29·1, q, Me (*gem*); 32·2, q, Me (*gem*); 40·1, s, CMe_2; 47·4, s, C2′; 54·7, d, C1′; 55·1, q, 2×OMe; 60·0, t, OCH_2Me; 110·3, d, C7′ or C5′; 112·9, d, C3″,5″; 113·2, d, C5′ or C7′; 128·2, d, C2″,6″; 129·2, s, C1″; 132·7, d, C8′; 138·0, s, C4a′ or C8a′; 140·1, s, C8a′ or C4a′; 157·6, s, C4″ or C6′; 158·2, s, C6′ or C4″; 177·5, s, C=O. Mass spectrum: (*m/z*) 396 (5%), 282 (25), 281 (100), 175 (15), 173 (10), 135 (75), 133 (25), 121 (30). The minor diastereoisomer of ethyl 2-methyl-2-[6′-methoxy-2′-(*p*-methoxyphenyl)-2′-methyl-1′,2′,3′,4′-tetrahydronaphthalen-1′ξ-yl]propanoate (25) crystallized from ethanol as colourless needles (50 mg, 4%), m.p. 115–116° (Found: C, 75·5; H, 7·9. $C_{25}H_{32}O_4$ requires C, 75·7; H, 8·1%). ν_{max} (Nujol) 1710s, 1610m, 1580m, 1500s, 1460bs, 1380s, 1300m, 1270s, 1230s, 1170w, 1110s, 830m cm^{-1}. ^1H n.m.r. δ (90 MHz, $CDCl_3$) 1·05, s, Me (*gem*); 1·09, s, Me (*gem*); 1·18, s, angular Me; 1·29, t, *J* 7·2 Hz, OCH_2**Me**; 2·21, t, *J* 7·8 Hz, H3′,3′; 2·85, t, *J* 7 Hz, H4′ 4′; 3·60, s, OMe; 3·62, s, OMe; 3·72, s, H1′; 4·14, q, *J* 6·8 Hz, OCH_2Me; 6·3–7·2, m, 7 aromatic H. ^{13}C n.m.r. δ ($CDCl_3$) 14·2, q, OCH_2**Me**; 20·7, q, angular Me; 26·7, t, C3′; 29·9, t, C4′; 29·7, q, Me (*gem*); 31·5, q, Me (*gem*); 41·9, s, CMe_2; 46·6, s, C2′; 53·9, d, C1′; 55·0, q, 2×OMe; 60·7, t, OCH_2Me; 110·3, d, C7′ or C5′; 113·1, d, C3″,5″ and C5′ or C7′; 126·5, d, C2″,6″; 128·3, s, C1″; 133·7, d, C8′; 138·4, s, C4a′ or C8a′; 143·0, s, C4a′ or C8a′; 157·0, s, C4″ or C6′; 157·9, s, C6′ or C4″; 179·7, s, C=O. Mass spectrum: (*m/z*) 396 (5), 282 (14), 281 (100), 175 (21), 173 (10), 135 (30), 133 (22), 121 (30).

(*o*) *Preparation of 2-Methyl-2-[6′-methoxy-2′-*(p-*methoxyphenyl)-2′-methyl-1′,2′,3′,4′-tetrahydronaphthalen-1′ξ-yl]propanoic Acid (26b)*

A mixture of the ethyl ester (26a) (100 mg, 0·25 mmol) and potassium hydroxide (1·0 g, 25 mmol) in ethane-1,2-diol (20 ml) was refluxed under nitrogen for 12 h. The cooled mixture was poured into a slurry of 1 M hydrochloric acid (50 ml) and ice (50 g), and the precipitate was filtered, dried under vacuum (60°/10 mm) and recrystallized from ethanol to give *2-methyl-2-[6′-methoxy-2′-*(p-*methoxyphenyl)-2′-methyl-1′,2′,3′,4′-tetrahydronaphthalen-1′ξ-yl]propanoic acid* (26b) (76 mg, 83%), m.p. 225–227° (Found: C, 74·6; H, 7·7. $C_{23}H_{28}O_4$ requires C, 75·0; H, 7·7%). ν_{max} (Nujol) 1700s, 1610s, 1510s, 1470s, 1260s, 1040s, 840 cm^{-1}. ^1H n.m.r. δ (90 MHz, CD_3SOCD_3) 0·62, s, Me (*gem*); 0·72, s, Me (*gem*); 0·82, s, angular Me; 1·6–3·2, m, H3′,3′,4′,4′; 3·58, s, H1′; 3·76, s, OMe; 3·79, s, OMe; 6·5–7·8, m, 7 aromatic H; 8·66, bs, OH (exch). Mass spectrum: (*m/z*) 368 (6%), 282 (20), 281 (100), 175 (15), 173 (10), 135 (37), 133 (22), 121 (43).

When the hydrolysis was attempted in methanol as solvent there was no appreciable reaction.

(*p*) *Preparation of 2,8-Dimethoxy-5,5,10b-trimethyl-*cis*-4b,10b,11,12-tetrahydrochrysen-6(5*H*)-one (27a)*

(i) *From the acid (26b).*—A solution of the acid (26b) (100 mg, 0·27 mmol) in methanesulfonic acid (3 ml) containing phosphorus pentoxide (0·3 g) was stirred for 5 h at 5° under nitrogen. Water (50 ml) and ice (50 g) were added, and the mixture was extracted with ether (2×25 ml). The extract was washed with saturated sodium bicarbonate (2×50 ml), water (2×50 ml), then dried (Na_2SO_4) and evaporated. Recrystallization from ethanol gave *2,8-dimethoxy-5,5,10b-trimethyl-*cis*-4b,10b,11,12-tetrahydrochrysen-6(5*H*)-one* (27a) (78 mg, 82%), m.p. 130–131° (Found: C, 78·8; H, 7·6. $C_{23}H_{26}O_3$ requires C, 78·8; H, 7·5%). ν_{max} (Nujol) 1690m, 1680m, 1610s, 1580w, 1500s, 1470bs, 1410w, 1380m, 1290s, 1260s, 1040m cm^{-1}. ν_{max} (CCl_4) 1678 cm^{-1}. ^1H n.m.r. δ (60 MHz, $CDCl_3$) 0·89, s, angular Me; 1·31, s, Me (*gem*); 1·37, s, Me (*gem*); 2·70–3·17, m, H11,11,12,12; 3·42, s, H4b; 3·83, s, OMe; 3·90, s, OMe; 6·70–7·60, m, 6 aromatic H. ^{13}C n.m.r. δ ($CDCl_3$) 23·2, q, angular

Me; 26·2, t, C11; 26·9, q, Me (*gem*); 28·2, q, Me (*gem*); 34·1, t, C12; 35·8, s, C10b; 46·7, s, C5; 52·2, d, C4b; 55·1, q, OMe; 55·4, q, OMe; 109·9, d, C3; 110·0, d, C1 or C7; 113·3, d, C7 or C1; 122·0, d, C9; 127·5, d, C10 or C4; 130·6, s, C4a; 132·4, d, C4 or C10; 137·3, s, C12a,6a; 144·7, s, C10a; 158·1, s, C8 or C2; 158·3, s, C2 or C8; 203·6, s, C6. Mass spectrum: (*m*/*z*) 350 (100%), 335 (35), 307 (60), 298 (17), 203 (20), 202 (18), 189 (35), 175 (10).

(ii) *From the ester* (*26a*).—A solution of the ester (1·0 g, 2·5 mmol) in methanesulfonic acid (5 ml) was stirred at 10–15° under nitrogen for 4 h. The resulting orange-red solution was worked up in the usual manner to give the ketone (25a) (600 mg, 68%), m.p. 130–131°.

(*q*) *Reduction of 2,8-Dimethoxy-5,5,10b-trimethyl*-cis-*4b,10b,11,12-tetrahydrochrysen-6*(5H)-*one* (27*a*)

Clemmensen procedure.—Powdered zinc metal (10 g, 0·15 mol) was amalgamated by the use of mercuric chloride (1 g, 3·7 mmol) in water (100 ml) and concentrated hydrochloric acid (25 ml). The amalgam was washed with water (3 × 100 ml), and to it was added the ketone (0·5 g, 1·4 mmol), toluene (20 ml), glacial acetic acid (2 ml) and water (50 ml). This mixture was heated under reflux with efficient stirring, and additional concentrated hydrochloric acid (240 ml) was added in portions during 24 h. The aqueous phase was washed with ether (3 × 50 ml) and the organic phase was washed with saturated sodium hydrogen carbonate solution (2 × 100 ml), water (2 × 100 ml), dried (Na_2SO_4), and evaporated. Crystallization of the residue from ethanol gave *2,8-dimethoxy-5,5,10b-trimethyl*-cis-*4b,5,6,10b,11,12-hexahydrochrysene* (27b) (300 mg, 62%), m.p. 158·5–160·5° (Found: C, 82·4; H, 8·5. $C_{23}H_{28}O_2$ requires C, 82·1; H, 8·4%). ν_{max} (Nujol) 1605s, 1570m, 1495s, 1460bs, 1420m, 1375m, 1280m, 1265s, 1245m, 1235m, 1155m, 1110m, 1035m, 815m cm^{-1}. ^1H n.m.r. δ (90 MHz, $CDCl_3$) 0·70, s, angular Me; 1·10, s, Me (*gem*); 1·21, s, Me (*gem*); 2·04–2·92, m, H11,11,12,12; 2·62, s, H6,6; 3·79, s, 2 × OMe; 6·60–7·34, m, 6 aromatic H. ^{13}C n.m.r. δ ($CDCl_3$) 23·2, q, angular Me; 26·7, t, C11; 29·6, q, Me (*gem*); 33·3, q, Me (*gem*); 33·7, t, C12; 34·7, s, C10b; 36·7, s, C5; 46·9, t, C6; 54·2, d, C4b; 55·0, q, 2 × OMe; 110·6, d, C3 or C9; 112·3, d, C9 or C3; 112·7, d, C1 or C7; 113·3, d, C7 or C1; 127·7, d, C4 or C10; 128·2, s, C4a or C10a; 133·7, d, C10 or C4; 136·0, s, C4a or C10a; 137·6, s, C6a or C12a; 138·2, s, C12a or C6a; 157·2, s, C2 or C8; 157·7, s, C8 or C2. Mass spectrum: (*m*/*z*) 336 (62%), 321 (63), 293 (30), 201 (40), 174 (16), 159 (10), 147 (15), 134 (100), 91 (11).

(*r*) *Preparation of 5,5,10b-Trimethyl*-cis-*4b,5,6,10b,11,12-hexahydrochrysene-2,8-diol* (*7a*)

To a refluxing solution of the dimethyl ether (27b) (500 mg, 1·92 mmol) in glacial acetic acid (5·9 ml) was added concentrated hydrobromic acid (48%, 3·5 ml) over a 3 h period under nitrogen. The orange solution was poured into ice/water (80 ml). The solid was filtered, dissolved in ether/toluene and extracted with 1 M sodium hydroxide (2 × 25 ml). Acidification of the alkaline extract gave a precipitate which was collected and recrystallized from chloroform to give *5,5,10b-trimethyl*-cis-*4b,5,6,10b,11,12-hexahydrochrysene-2,8-diol* (7a) (428 mg, 79%) as colourless prisms, m.p. 201–205° (dec.) (Found: $M^{+\cdot}$, 308·177 ± 0·002, $C_{21}H_{24}O_2$ requires 308·190). ν_{max} (Nujol) 3580–3080s, 1670m, 1600m, 1500s, 1470s, 1380s, 1270m, 1230m, 1160w, 1110w, 970w, 860w, 830w cm^{-1}. ^1H n.m.r. δ (90 MHz, CD_3SOCD_3) 0·61, s, angular Me; 1·02, s, Me (*gem*); 1·10, s, Me (*gem*); 1·5–3·5, m, H11,11,12,12; 2·51, s, H6,6; 3·43, s, H4b; 6·2–7·3, m, 6 aromatic H; 9·00, s, 2 × OH (exch.). ^{13}C n.m.r. δ (CD_3SOCD_3) 23·0, q, angular Me; 26·0, t, C11; 29·4, q, Me (*gem*); 33·0, q, Me (*gem*); 33·6, s, C10b; 34·2, t, C12; 36·1, s, C5; 46·2, t, C6; 53·5, d, C4b; 111·8, d, C3 or C9; 113·7, d, C9 or C3; 114·3, d, C1 or C7; 114·6, d, C7 or C1; 125·9, s, C10a; 127·4, d, C10; 133·4, d, C4; 135·1, s, C4a; 136·0, s, C6a or C12a; 136·9, s, C12a or C6a; 154·7, s, C2 or C8; 155·3, s, C8 or C2. Mass spectrum: (*m*/*z*) 308 (64%), 293 (70), 265 (51), 250 (14), 187 (48), 173 (17), 160 (16), 159 (10), 147 (16), 145 (16), 135 (10), 134 (12), 133 (25), 120 (100), 107 (17).

(*s*) *Attempted Cyclization of the Minor Diastereoisomer of Ethyl 2-Methyl-2-*[*6′-methoxy-2′-*(*p-methoxyphenyl*)*-2′-methyl-1′,2′,3′,4′-tetrahydronaphthalen-1′ξ-yl*]*propanoate* (*25*)

A solution of the ester (25) (50 mg, 0·13 mmol) in methanesulfonic acid (1·0 ml) was frozen (0°), then allowed to warm to 10° with magnetic stirring under nitrogen. After 8 h the red-orange solution was worked up in the usual manner. The i.r. spectrum (CCl_4) of the crude product showed absorbances at 1760 and 1720 cm^{-1}. Preparative t.l.c. (silica/10% ethyl acetate in light petroleum) gave two fractions (R_F 0·21, 0·35), the least polar of which was shown to be starting material (40 mg) by its ^1H n.m.r. spectrum. More severe reaction conditions resulted in a complex mixture (10 spots on analytical t.l.c.) which was not examined further.

(*t*) *Preparation of Ethyl 2-Methyl-2-[6'-methoxy-2'β-(p-methoxyphenyl)-2'α-methyl-1',2',3',4'-tetrahydronaphthalen-1'β-yl]propanoate (26a) from a 1 : 1-Epimeric Mixture of the Acetates (23a) and (23b)*

(i) *Preparation of a mixture of the epimers (23a) and (23b).*—A solution of 1ξ-hydroxy-6-methoxy-2-(*p*-methoxyphenyl)-2-methyl-1,2,3,4-tetrahydronaphthalene (19) (0·9 g, 3·0 mmol) in ethanol (50 ml) containing a trace of hydrochloric acid was brought to the boil on a steam bath, allowed to cool and the alcohol recovered in the usual fashion to give a colourless oil. The ^{1}H n.m.r. spectrum of the recovered alcohol showed it to be an approximately 1 : 1 mixture of the epimers. The oil was dissolved in dry pyridine (5 ml), acetic anhydride (2 ml) was added to the cooled (0°) solution, then the mixture was allowed to stand at room temperature for 24 h. The crude product, obtained by the usual workup, was filtered through a short silica column (10% ethyl acetate in light petroleum) to give a colourless oil (1·01 g, 98%). The important signals in the ^{1}H n.m.r. spectrum ($CDCl_3$) were δ (integral ratio): 1·25 and 1·20 (3 : 2·2), angular Me; 1·59 and 2·01 (3 : 2·4), MeCOO; 6·05 and 4·40 (1 : 1), H 1. This corresponds to an approximate ratio of 4 : 3, the isomer which was previously obtained pure in (*m*), slightly predominating.

(ii) *Reaction of the epimeric mixture of acetates (23a) and (23b) with 1-ethoxy-1-trimethylsilyloxy-2-methylprop-1-ene (24).*—The epimeric mixture of acetates (1·16 g, 3·4 mmol) was alkylated as described previously in (*n*)(ii) with the silyl ketene acetal (0·64 g, 3·4 mmol) in dry dichloromethane (50 ml). The product, isolated in the usual way, was identical (i.r., ^{1}H n.m.r., and m.p.) with (24a) obtained previously from epimerically pure acetate.

Crystallography of the Hexahydrochrysene Derivative (27b)

Crystal Data

$C_{23}H_{28}O_2$, M 336·5, triclinic, a 11·621(8), b 11·528(8), c 7·911(6) Å, α 114·4(8), β 97·9(6), γ 100·5(7)°, U 921·9 Å^3, D_c 1·21 (Z = 2), D_m 1·20(2) g cm^{-3} (flotation). F(000) 364, μ 5·1 cm^{-1} for Cu Kα radiation (λ 1·5418 Å). Space group $P\bar{1}$ from successful refinement. Cell parameters were determined from 24 medium to high angle reflections.

Intensity Measurements

Intensity measurements were made on a Philips PW1100 computer-controlled diffractometer with graphite-monochromated Cu Kα radiation with $6° \leqslant 2\theta \leqslant 120°$, operating in an ω-scan mode with a symmetric scan range of $(1·44+0·3\tan\theta)°$ in ω from the calculated Bragg scattering angle at a scan rate of 0·05°/s. A total of 2723 unique data were collected, 1127 of which were considered to be observed [$I \geqslant 3\sigma(I)$]. Three, nearly orthogonal, standard reflections monitored every 4 h showed no significant variation of intensity over the data collection period.

Intensity data were processed as described previously.[20] An absorption correction was applied, The atomic scattering factors for neutral atoms were those given by Cromer *et al.*,[21] and were corrected for anomalous dispersion by using the published values.[21] All calculations were performed on the Monash University VAX11/780 computer. The program used for least-squares refinement was that due to Sheldrick.[22]

Structure Solution and Refinement

The structure was solved by direct methods with the help of the program MULTAN.[23] The best E map gave sites for all non-hydrogen atoms, except the methyl group, which was located in a subsequent difference-Fourier synthesis. Full-matrix least-squares refinement employing isotropic temperature factors for carbon and oxygen reduced R from 0·261 to 0·115. Geometrically idealized hydrogen atom coordinates were calculated for all hydrogen atoms, and a riding model was employed

[20] Bandaranayake, W. M., Banfield, J. E., Black, D. St.C., Fallon, G. D., and Gatehouse, B. M., *Aust. J. Chem.*, 1981, **34**, 1655.

[21] Cromer, D. T., and Waber, J. T., Cromer, D. T., and Ibers, J. A., in 'International Tables for X-Ray Crystallography' Vol. 4 (Kynoch Press: Birmingham 1974).

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for refinement: the C–H vectors were held constant in magnitude (1·08 Å) and direction, but the carbon atoms were free to move. All hydrogen atoms were given the same isotropic thermal parameter which was allowed to refine. With the data weighted as $1/\sigma^2(F)$ the refinement converged at

$$R^1 = \sum\omega^{1/2}(||F_o|-|F_c||)/\sum\omega^{1/2}|F_o| = 0{\cdot}068$$

and a corresponding unweighted R index of 0·071. Final atomic parameters are given in Table 1 and selected interatomic distances in Table 2.*

Table 1. Non-hydrogen positional and thermal parameters for compound (27b)

Atom	$10^4x/a$	$10^4y/b$	$10^4z/c$	10^3U	Atom	$10^4x/a$	$10^4y/b$	$10^4z/c$	10^3U
C(1)	5716(6)	−982(7)	2356(9)	43(2)	C(10a)	7557(6)	4652(7)	5116(9)	39(2)
C(2)	6441(6)	−1816(7)	1755(9)	48(2)	C(10b)	7074(6)	3160(7)	3952(9)	40(2)
C(3)	7637(6)	−1337(7)	1848(9)	49(2)	C(11)	5890(6)	2715(6)	4445(9)	49(2)
C(4)	8103(6)	22(7)	2652(9)	47(2)	C(12)	5316(6)	1229(7)	3390(10)	53(2)
C(4a)	7424(6)	912(6)	3323(8)	35(2)	C(12a)	6190(6)	383(6)	3083(8)	35(2)
C(4b)	7998(5)	2400(6)	4227(9)	39(2)	C(13)	9733(6)	2250(7)	6449(10)	52(2)
C(5)	8755(6)	2978(6)	6321(9)	41(2)	C(14)	8009(6)	2935(7)	7769(9)	50(2)
C(6)	9430(6)	4411(6)	6900(9)	45(2)	C(15)	6809(6)	2824(7)	1790(9)	53(2)
C(6a)	8657(6)	5229(7)	6518(9)	38(2)	C(16)	6560(7)	−4073(8)	191(11)	73(3)
C(7)	9064(6)	6596(7)	7536(9)	44(2)	C(17)	8297(7)	9618(7)	8006(11)	69(2)
C(8)	8426(6)	7394(7)	7166(10)	46(2)	O(2)	8954(4)	8736(5)	8226(6)	58(2)
C(9)	7349(6)	6866(7)	5840(9)	51(2)	O(1)	5875(4)	−3157(5)	1040(6)	61(2)
C(10)	6940(6)	5505(7)	4826(10)	53(2)					

Table 2. Bond lengths (Å) for compound (27b)

Atoms	Distance	Atoms	Distance	Atoms	Distance
C(1)–C(2)	1·37(1)	C(5)–C(6)	1·54(1)	C(10)–C(10a)	1·39(1)
C(1)–C(12a)	1·40(1)	C(5)–C(13)	1·55(1)	C(10a)–C(10b)	1·52(1)
C(2)–C(3)	1·38(1)	C(5)–C(14)	1·54(1)	C(10b)–C(11)	1·54(1)
C(2)–O(1)	1·39(1)	C(6)–C(6a)	1·50(1)	C(10b)–C(15)	1·56(1)
C(3)–C(4)	1·39(1)	C(6a)–C(7)	1·39(1)	C(11)–C(12)	1·53(1)
C(4)–C(4a)	1·38(1)	C(6a)–C(10a)	1·41(1)	C(12)–C(12a)	1·51(1)
C(4a)–C(4b)	1·53(1)	C(7)–C(8)	1·37(1)	O(1)–C(16)	1·44(1)
C(4a)–C(12a)	1·40(1)	C(8)–C(9)	1·37(1)	O(2)–C(17)	1·43(1)
C(4b)–C(5)	1·56(1)	C(8)–O(2)	1·38(1)		
C(4b)–C(10b)	1·55(1)	C(9)–C(10)	1·38(1)		

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* Tables of structure factor amplitudes and bond angles can be obtained on request from the Editor-in-Chief, Editorial and Publications Service, CSIRO, 314 Albert Street, East Melbourne, Vic. 3002.