Synthesis, Conformation, and Chirality of Di-*O*-Methylsequirin D, a Biogenetically Novel Metabolite of *Sequoia sempervirens*

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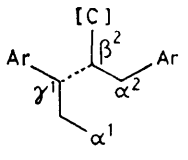
The synthesis of (±)-di-*O*-methylsequirin D (14; R = H) is reported. A Grignard reaction between 3,3-ethylenedioxypropylmagnesium bromide and deoxyanisoin gave the key alcohol (5), which was transformed into (14) by way of the acid (11) and the tetralone (12). Measurement of the 3-H_2,4-H coupling constants in (14; R = D) show the compound to have a 4-axial anisyl substituent, while c.d. data indicate a left-hand skewed styrene geometry in the dimethyl ether of the natural norlignan (2). The absolute configuration of (2) is hence deduced as 1*R*. The biosynthesis of sequirin-D and the origin of the *m*-hydroxycinnamate unit are discussed.

Sequoia is a monotypic genus, represented only by *S. sempervirens* (D. Don) Endl. In accord with its distinct taxonomic character the heartwood of this species has provided a biogenetically unusual set of norlignans (sequirins A—C, and E—G[1]) derived by γ^1—β^2 (1) linking of phenylpropanoid units, rather than the common β^1—β^2 union in lignans derived by oxidative coupling. Further, we have elucidated by *X*-ray analysis the structure of sequirin D[2] (2), from the same heartwood, a norlignan containing an α^1—β^2 bond (3). To the best of our knowledge sequirin D is the first reported example of this carbon skeleton in Nature.



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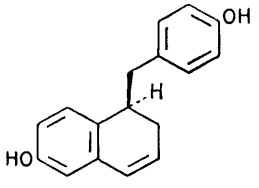

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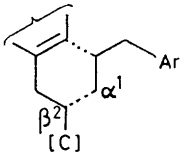


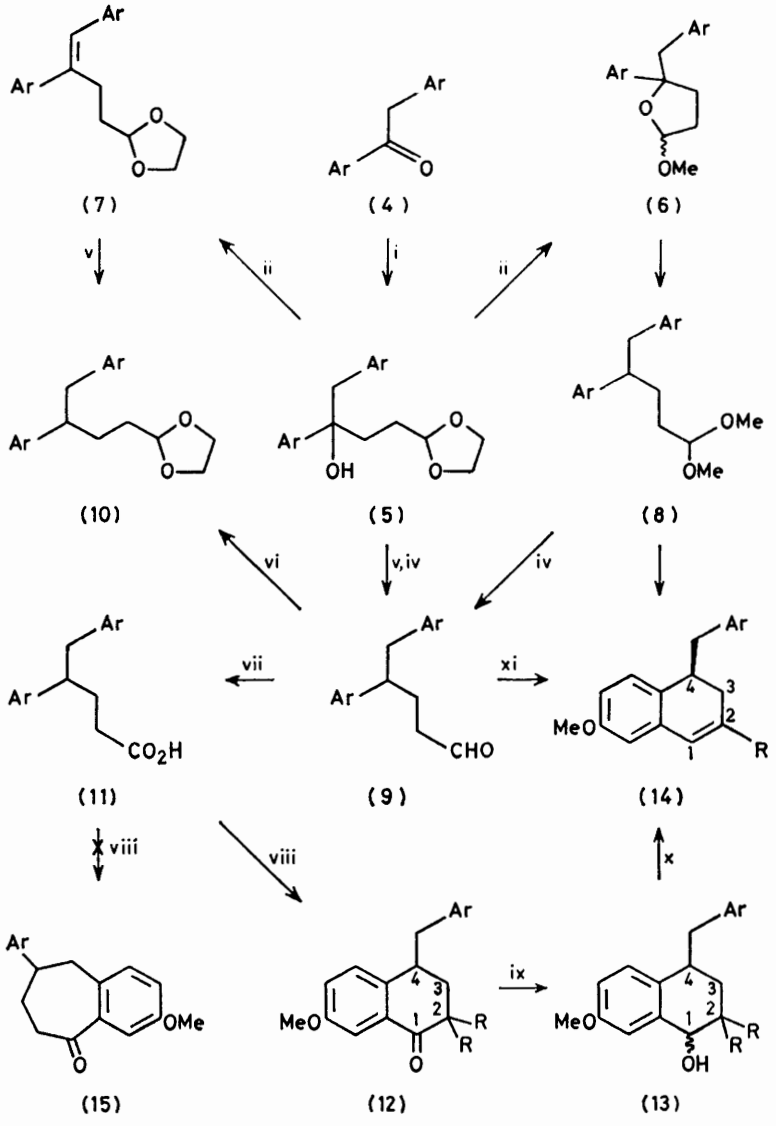
(3)

Sequirin D was isolated as the crystalline optically active dimethyl and diethyl ethers. Circular dichroism and optical rotatory dispersion data[2] were measured for the former. Since the correlation between sign of Cotton effect and absolute configuration in the inherently disymmetric skewed styrenes has been worked out,[3] the chirality of dimethylsequirin D could be deduced, provided that its conformation in solution was known. Although the molecular shape in the solid state is known, the preference in solution cannot be certainly inferred. Proton magnetic resonance measurements could solve the problem but insufficient natural material was available to collect spectra; a supply of synthetic material then became essential. In this paper we report a straightforward synthesis of (±)-dimethylsequirin D and its 2-deuterio-analogue, the preferred conformation of the compound in solution, and the absolute configuration of the natural product.

The carbon backbone required for sequirin D was assembled by reaction of the Grignard reagent from 2-(2-bromoethyl)-1,3-dioxolan (readily formed in tetrahydrofuran) with deoxyanisoin (4), providing the tertiary alcohol (5) in essentially quantitative yield. This product underwent further reaction in methanol, yielding a new cyclic acetal (6), one stereoisomer of which (configuration unassigned) was obtained crystalline. A minor by-product (4%) of this reaction was the *trans*-stilbene (7). Hydrogenolysis of the acetal (6) in acidic methanol gave the dimethyl acetal (8) of the pentanal (9); the free aldehyde was obtained after acidic hydrolysis. Alternatively, the aldehyde (9) was generated by hydrogenolysis of the tertiary alcohol (5), followed by hydrolysis. The aldehyde (9) with ethylene glycol gave the same acetal as was formed by hydrogenation of the olefin (7). Direct cyclodehydration of (9) to (±)-dimethylsequirin D (14; R = H) could be induced with phosphoric acid, but only in very poor yield. However the acid (11), prepared by silver oxide oxidation of the aldehyde (9), cyclised in hydrogen fluoride in satisfactory yield (40%) to form the α-tetralone (12; R = H) rather than the isomeric benzocycloheptanone (15). Reduction of the ketone (12) and acid-catalysed dehydration of the resulting alcohol (13; R = H) provided the desired dihydronaphthalene (14; R = H). The route (4) ⟶ (5) ⟶ (9) ⟶ (11) ⟶ (12) ⟶ (13) ⟶ (14) gave 13% overall yield † from (4) (effective mean yield 71% per step).

The ^{1}H n.m.r. spectrum of (14; R = H) was complicated by long-range couplings which hindered secure analysis. Accordingly, the ketone (12) was dideuteriated, in dioxan–deuterium oxide–sodium deuterioxide to yield (12; R = D), which was then converted into 2-deuteriodimethylsequirin D (14; R = D). The ^{1}H n.m.r. spectrum of the last-named compound in deuteriochloroform provided the coupling constant data shown in structure (16). The benzylic methine proton H_c, with $J_{ac} = 4$ and $J_{bc} = 6$ Hz, is clearly quasi-*eq* rather than quasi-*ax*, with the torsion angle H_c–C–C–H_a greater than H_c–C–C–

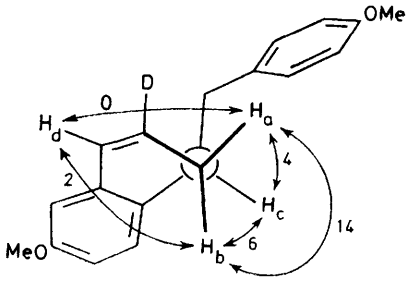
† Improved from that quoted in a preliminary communication.[4]



Reagents: i, 2-(1,3-dioxolan-2-yl)ethylmagnesium bromide; ii, MeOH; iii, H^+,MeOH; iv, H_3O^+; v, H_2–Pd; vi, $HOCH_2CH_2OH,H^+$; vii, Ag_2O; viii, HF; ix, $LiAlH_4$; x, $TsOH,C_6H_6$; xi, H_3PO_4

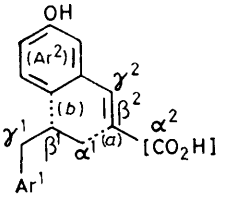
H_b. A solution conformation similar to that in the crystalline state [2] where these torsion angles are 75° and 45°, is apparent. Allylic couplings ($J_{ad} = 0$, $J_{bd} = 2$ Hz) were measured and their assignment confirmed by decoupling experiments: these magnitudes are appropriate [5] to the geometry in which the C(3)–H_a bond is approximately coplanar with the H_d–C(1)–C(2)–C(3) system, and the C(3)–H_b bond is roughly orthogonal to it. All these couplings were maintained in tetradeuteriomethanol solution. C.d. data for methanol solution have been measured ($\Delta\varepsilon$ + 10.3, 260 nm) and, as we have discussed before,[2] indicate that the non-planar styrene chromophore describes a left-handed helix: with a 4-axial *p*-methoxybenzyl group the absolute stereochemistry of di-*O*-methylsequirin D (and consequently of the natural phenol) is then correctly shown in diagrams (16) and (14), *i.e.* it has the 1*R* configuration. The ketone (12; R = D) also possesses a 4-axial anisyl group, shown by $J_{3eq,4eq}$, = $J_{3ax,4eq}$, = 4 Hz; the same 3,4-coupling constants were observed for the alcohol (13; R = D).

A plausible biosynthetic route to sequirin D involves the union of two ArC_3 units through two bonds, α^1—β^2 [bond *a*, see (17)] and Ar^2—β^1 (bond *b*), with loss of carbon α^2 (decarboxylation). Rearrangement of one ArC_3 unit from *p*-hydroxy-to *m*-hydroxy-substitution is also plausible. Various biogenetic hypotheses have been offered, differing essentially only in the sequences of bond formation and rearrangement. Thus Whiting *et al.*[2] suggested the possibility of a *m*-hydroxycinnamate precursor [which could be formed through dienone–phenol rearrangement of coumaric acid, (18) ⟶ (19)];



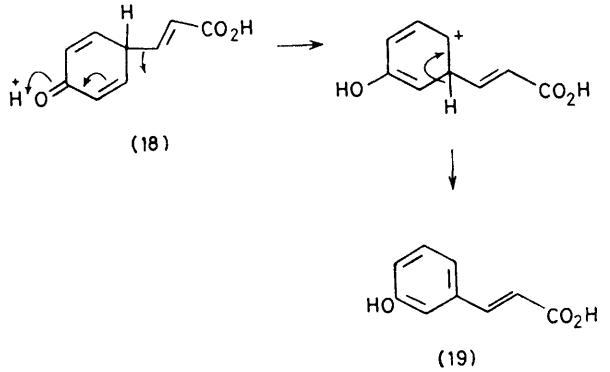
(16)

formation of bond *b* by oxidative coupling, and final formation of bond *a* through addition of an α^1-carbocation to the β^2—γ^2 double bond followed by decarboxylation induced by the new γ^2-carbocation. Erdtman *et al.*[6] have observed that bond *b* might be formed first,



(17)

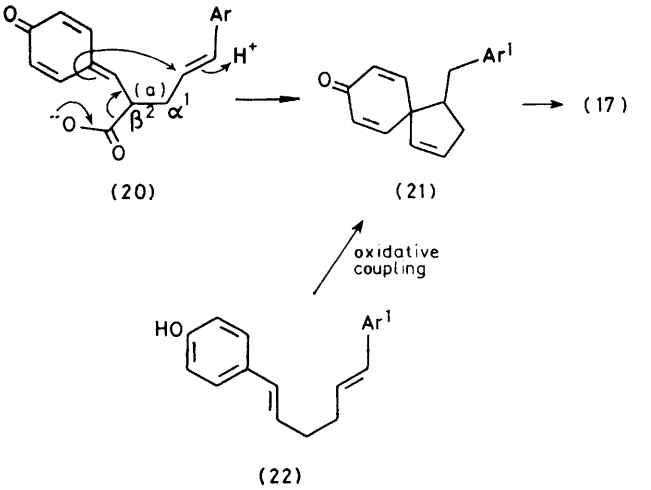
by oxidative coupling of coumarate with coumaryl alcohol; the dienone–phenol rearrangement follows, and bond *a* is finally constructed as above. Birch and Liepa[7] suggest a different order, with bond *a* as the initial link, formed in the manner we have proposed for hinokiresinol biosynthesis[8] (carbocation addition to cinnamic acid double bond with subsequent decarboxyl-



(18) (19)

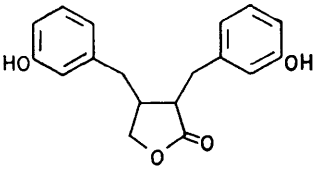
ation) but using the α^1-terminus of the allylic carbocation to form intermediate (20), which then cyclises as shown to the spirodienone (21) with final rearrangement to sequirin D. We note that an unbranched isomer (22) of himokiresinol could reorganise to sequirin D through a similar path.

Which of these possible biogenetic routes is correct is as yet undetermined. The matter is discussed here since the question of the origin of lignans containing *m*-



(20) (21) (22)

hydroxy ArC_3 moieties has assumed some importance in connection with the discovery of such lignans, *e.g.* (23), as constituents[9] of urinary extracts in humans, apes, and rats, in quantities comparable to those of steroid metabolites, and excreted in a cyclic pattern following, in females, the menstrual cycle.



(23)

EXPERIMENTAL

Unless otherwise stated, the following generalisations apply. M.p.s are corrected (Kofler block). I.r. spectra were collected using Nujol mulls. ^1H N.m.r. measurements were made on deuteriochloroform solutions at 100 MHz with tetramethylsilane as internal standard. Hydroxylic and carboxylic protons were identified by deuterium exchange. All compounds were purified to show only one spot on thin-layer chromatography (silica); benzene–ethyl acetate (8 : 2) and benzene–dioxan–acetic acid (85 : 15 : 0.5) solvent systems were employed. ' Drying ' refers to the use of magnesium sulphate; ' evaporation ' implies the use of reduced pressure. Mass spectra were recorded using the electron-impact method, probe temperature 150—200 °C.

Addition of 3,3-Ethylenedioxypropylmagnesium Bromide to Deoxyanisoin.—1-Bromo-3,3-ethylenedioxypropane (prepared[10] from acrylaldehyde, ethylene glycol, and hydrogen bromide; 28 g) in anhydrous tetrahydrofuran (100 cm^3) was added dropwise to clean magnesium (3.6 g) at 30—35 °C, with stirring. When the addition was complete, stirring of the mixture at the same temperature was continued for 1 h. A slurry of deoxyanisoin (from tin–acid reduction[11] of anisoin) (12.8 g) in tetrahydrofuran (50 cm^3) was added slowly, and the mixture set aside at ambient temperature overnight. The product was diluted with ice-cold saturated aqueous ammonium chloride and extracted with ether. The extracts were washed with water, dried, and evaporated. The residue crystallised on treatment with pentane;

recrystallisation from chloroform–light petroleum afford the *alcohol* (5) [1,1-ethylenedioxy-4-hydroxy-4,5-bis-(*p*-methoxyphenyl)pentane] (16 g, 90%), m.p. 95—96 °C (Found: C, 70.25; H, 7.15. $C_{21}H_{26}O_5$ requires C, 70.35; H, 7.3%); $\nu_{max.}$ 3 500, 1 605, and 1 580 cm^{-1}; τ 2.7—3.3 (8 H, ArH), 5.2 (1 H, t, *J* 6 Hz, 1-H), 6,0—6.3 (10 H, 2 × OCH_3, OCH_2CH_2O), 7.00 (2 H, *q*, *J* 12 Hz, 5-H_2), 7.68 (1 H, s, OH), and 7.8—8.6 (4 H, 2-H_2, 3-H_2); *m/z* 358 (M^+, 24%), 240 (20), 296 (15), 254 (20), 237 (20), 175 (100), 147 (20), and 121 (40).

In another experiment the immediate product was dissolved in methanol and set aside. A crystalline product separated and was recrystallised from methanol to yield the *acetal* (6) [2-methoxy-5-(*p*-methoxybenzyl)-5-(*p*-methoxyphenyl)tetrahydrofuran] (30%), m.p. 107—108 °C (Found: C, 73.2; H, 7.2. $C_{20}H_{24}O_4$ requires C, 73.15; H, 7.35%); $\nu_{max.}$ 1 610 and 1 580 cm^{-1}; τ 2.8—3.4 (8 H, ArH), 5.04 (1 H, dd, *J* 3 and 6 Hz, 2-H), 6.20 and 6.24 (both 3 H, s, OCH_3), 7.09 (2 H, q, *J* 14 Hz, $ArCH_2$) 7.84 (2 H, m, 3-H_2), and 8.4 (2 H, m, 4-H_2). The mother liquors were evaporated and chromatographed on a silica column. Elution with benzene afforded the *stilbene* (7) [(*E*)-1,1-ethylenedioxy-4,5-bis-(*p*-methoxyphenyl)pent-4-ene] (4%), m.p. 95 °C (from ethanol) (Found: C, 74.25; H, 6.7. $C_{21}H_{24}O_4$ requires C, 74.1; H, 7.1%); $\nu_{max.}$ 1 600 and 1 575 cm^{-1}; τ 2.28—2.92 (8 H, ArH), 3.16 (1 H, s, 5-H), 4.96 (1 H, t, *J* 4 Hz, 1-H), 5.9—6.1 (2 × OCH_3, OCH_2CH_2O), 7.04 (2 H, m, 3-H_2), and 8.16 (2 H, m, 2-H_2); $\lambda_{max.}$ 222infl (log ε 4.1) and 283 nm (4.32).

1,1-*Dimethoxy*-4,5-*bis*-(p-*methoxyphenyl*)*pentane* (8).—The cyclic acetal (6) (600 mg) was hydrogenated in methanol (40 cm^3) and sulphuric acid (5 mm^3) over 5% palladium–carbon (100 mg) until uptake of hydrogen ceased. The solution was filtered through alumina and evaporated to yield the *acetal* (8) (550 mg, 87%) as a colourless gum (single spot on t.l.c.) (Found: M^+, 344.194. $C_{21}H_{28}O_4$ requires *M*, 344.194); τ 2.95—3.3 (8 H, ArH), 5.78 (1 H, t, *J* 5 Hz, 1-H), 6.18 and 6.20 (both 3 H, s, $ArOCH_3$), 6.72 and 6.75 (both 3 H, s, OCH_3), 7.22 (3 H, 4-H, 5-H_2), and 8.2—8.8 (4 H, 2-H_2, 3-H_2).

4,5-*Bis*-(p-*Methoxyphenyl*)*pentanal* (9).—(*a*) The alcohol (5) (16 g) in ethanol (200 cm^3) was hydrogenated over 10% palladium–carbon (2.5 g) until uptake of hydrogen ceased (24 h). The catalyst was removed and the solvent was evaporated off. The residue was heated on steam in dioxan (150 cm^3) and dilute (5%) hydrochloric acid (40 cm^3) for 1 h. The product was concentrated and extracted with ether, and the combined extracts were stirred vigorously with saturated aqueous sodium disulphite for 24 h. The addition product was decomposed with aqueous sodium carbonate, and the precipitate collected in ether. Drying and evaporation provided the title *aldehyde* (9) (8 g, 75%) as a colourless oil (Found: M^+, 298.162. $C_{19}H_{22}O_3$ requires *M*, 298.157); $\nu_{max.}$ 1 720, 1 608, and 1 580 cm^{-1}; τ 0.48 (1 H, t, *J* 1.5 Hz, CHO), 3.0—3.4 (8 H, ArH), 7.2 (3 H, 4-H, 5-H_2), and 7.7—8.4 (4 H, m, 2-H_2, 3-H_2); 2,4-*dinitrophenylhydrazone*, m.p. 158—160 °C, *m/z* 478 (M^+).

(*b*) The acetal (8) (550 mg) was shaken overnight in dioxan (15 cm^3) with water (5 cm^3) and sulphuric acid (5 mm^3) at ambient temperature. The solution was concentrated and extracted with ether: the ethereal extracts were washed with aqueous sodium hydrogencarbonate, dried, and evaporated to yield the pentanal (9) (470 mg, 99%), identical with the above sample.

1,1-*Ethylenedioxy*-4,5-*bis*-(p-*methoxyphenyl*)*pentane* (10).—(*a*) The aldehyde (9) (2 g) in toluene (40 cm^3), ethylene glycol (6 g), and toluene-*p*-sulphonic acid (0.2 g) were refluxed for 3 h with azeotropic removal of water. The solution was then diluted with ether, washed with aqueous sodium hydrogencarbonate, dried, and evaporated. Chromatography of the residue on silica (chloroform elution) and crystallisation of the major fraction from ethanol afforded the *acetal* (10) (1 g, 44%), m.p. 62—64 °C (Found: C, 73.75; H, 8.05. $C_{21}H_{26}O_4$ requires C, 73.65; H, 7.65%); τ 2.96—3.24 (8 H, ArH), 5.20 (1 H, t, *J* 4 Hz, 1-H), 6.0—6.2 (10 H, 2 × OCH_3, OCH_2CH_2O), 7.1—7.4 (3 H, 4-H, 5-H_2), and 8.0—8.7 (4 H, m, 2-H_2, 3-H_2); *m/z* 342 (M^+), 222 (25%), 221 (100), 177 (25), 161 (35), 159 (50), 144 (15), 135 (30), and 121 (60).

(*b*) The unsaturated acetal (7) (500 mg) in anhydrous methanol (50 cm^3) was hydrogenated over 5% palladium–carbon (100 mg). Filtration and evaporation gave an oil, which was purified by p.l.c. (silica); the major fraction crystallised from ethanol to yield the acetal (10) (250 mg, 50%), m.p. 62—64 °C, spectroscopically identical with the above sample. The free aldehyde (9) was also isolated.

4,5-*Bis*-(p-*Methoxyphenyl*)*pentanoic Acid* (11).—To the aldehyde (9) (6 g) and silver nitrate (7.2 g) in ethanol (60 cm^3) was added sodium hydroxide (3.2 g) in water (60 cm^3), dropwise, with stirring, at room temperature, over 4 h. The product was filtered through Celite, washed with ether, and acidified. The precipitate was collected to provide the *acid* (11) (5.1 g, 80%), m.p. 113—114 °C (from aqueous ethanol) (Found: C, 72.2; H, 7.55. $C_{19}H_{22}O_4$ requires C, 72.6; H, 7.05%); $\nu_{max.}$ 3 200—2 500, 1 695, 1 610, and 1 580 cm^{-1}: τ 3.00—3.36 (8 H, ArH) *ca.* 3 (1 H, obscured, CO_2H), 6.24 and 6.28 (both 3 H, s, OCH_3), 7.24 (3 H, 4-H, 5-H_2), 7.8—8.3 (4 H, 2-H_2, 3-H_2); *m/z* 314 (M^+, 5%), 194 (10), 193 (100), 191 (50), 147 (60), and 121 (60).

7-*Methoxy*-4-(p-*Methoxybenzyl*)-1-*tetralone* (12; R = H).—Anhydrous hydrogen fluoride (5 g) was added to the acid (11) (1 g), and the solution was set aside for 48 h at room temperature. The product was poured onto ice, and the mixture extracted with ether. The extracts, after washing, drying, and evaporation, gave a gum which was treated with methanol. The methanolic solution was filtered, concentrated, and allowed to crystallise to yield the *ketone* (12; R = H) (400 mg, 42%), m.p. 53—55 °C (Found: M^+, 296.143. $C_{19}H_{20}O_3$ requires *M*, 296.141); $\nu_{max.}$ 1 680 and 1 610 cm^{-1}; τ 2.44 (1 H, s, 8-H), 2.8—3.2 (6 H, ArH), 6.16 and 6.20 (both 3 H, s, OCH_3), and 6.8—8.2 (7 H); *m/z* 296 (M^+, 3%), 175 (64), and 121 (100). Treatment of this ketone (100 mg) in dioxan (15 cm^3) with deuterium oxide (1 cm^3) and sodium deuterioxide (5 mg), at reflux for 24 h, yielded, after product isolation through ether extraction and crystallisation, the dideuterio-ketone (12; R = D); τ 6.8—7.4 (3 H, m, 4-H, 5-H_2), 7.8—8.2 (2 H, AB of ABX, $J_{3a,3b}$ 14, $J_{3a,4} = J_{3b,4}$ = 4 Hz); *m/z* 298 (M^+, 3%), 177 (59), and 121 (100).

1-*Hydroxy*-7-*Methoxy*-4-(p-*Methoxybenzyl*)*tetralin* (13; R = H).—The ketone (12; R = H) (300 mg) in ether (20 cm^3) was treated with lithium aluminium hydride (5 mol. excess) for 2 h at room temperature. After stirring the mixture with ethanol and dilute sulphuric acid, the ether layer was separated, washed, dried, and evaporated. The residue crystallised from benzene to give the *alcohol* (13; R = H) (250 mg, 83%), m.p. 87—88 °C (Found: M^+, 298.156, $C_{19}H_{22}O_3$ requires *M*, 298.157); $\nu_{max.}$ 3 250, 1 620, and 1 580 cm^{-1}; τ 2.8—3.3 (7 H, ArH), 5.32 (1 H, t, *J* 7 Hz, 1-H), 6.2 (6 H, s, 2 × OCH_3), 6.6—7.4 (3 H, 4-H, $ArCH_2$), 8.0—8.2 (4 H, 2-H_2, 3-H_2), and 8.16 (1 H, s, OH); *m/z* 298 (M^+,

1%), 177 (45), 159 (100), 144 (23), and 121 (21). Similar reduction of the dideuterio-ketone gave the 2,2-dideuterio-alcohol (13; R = D), τ 5.36 (1 H, s, 1-H) and 8.3 (2 H, d, *J* 4 Hz); *m/z* 300 (M^+).

(±)-*Di*-O-*methylsequirin D* (14; R = H).—The alcohol (13; R = H) (100 mg) in toluene (20 cm^3) was refluxed with toluene-*p*-sulphonic acid (25 mg) for 3 h, with azeotropic separation of water. The solution was then washed with aqueous sodium hydrogencarbonate and water, dried, and evaporated. The residue was crystallised from chloroform–hexane. Recrystallisation from methanol–chloroform gave *compound* (14; R = H) (80 mg, 85%), m.p. 89—90 °C (Found: C, 81.65; H, 7.4. $C_{19}H_{20}O_2$ requires C, 81.4; H, 7.2%); τ 3.00—3.4 (7 H, ArH), 3.12 (1 H, ddd, *J* 3, 6, and 9 Hz, 2-H), 3.56 (1 H, dd, *J* 2 and 9 Hz, 1-H), 6.20 (6 H, s, 2 × OCH_3), 7.0—7.4 (3 H, 4-H, $ArCH_2$), and 7.52—7.88 (2 H, m, 3-H_2); *m/z* 280 (M^+, 2%), 159 (100), and 145 (30). Treatment of the dideuterio-alcohol in a similar way afforded (±)-2-deuteriodimethylsequirin D (14; R = D), τ 3.52 (1 H, br, s, 1-H) and 7.48—7.96 (2 H, m, *J* 2, 4, 6, and 14 Hz, 3-H_2); *m/z* 281 (M^+).

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