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THE ABSOLUTE CONFIGURATION OF SEQUIRIN-D, A BIOGENETICALLY NOVEL NORLIGNAN; SYNTHESIS OF (±)-DIMETHYLSEQUIRIN-D.

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The norlignan sequirin-D (6; $R^1 = R^2 = H$), a phenolic dihydronaphthalene, has a carbon skeleton arising from coupling of arylpropane units in a way not previously observed, either in Nature or _in vitro_. The structure of this novel natural product has been established by X-ray analysis[1] of its dimethyl ether. C.d. measurements have been made on solutions of this derivative but knowledge of the preferred conformation in the same solutions is required before a reliable deduction of absolute configuration can emerge. Such knowledge should be obtainable from ^{1}H.m.r. parameters; however, paucity of natural specimens prevented an adequately detailed study. We report here the total synthesis of (±)-di-_O_-methylsequirin-D(6; $R^1 = H$, $R^2 = Me$), the key H-H coupling constants, and consequent assignment of absolute stereochemistry: knowledge of the last is desired to establish biogenetic connections and as a reference for future natural relatives.

Deoxyanisoin (1) was treated with the Grignard reagent from 1-(2-bromethyl)-dioxolan to yield the acetal (2). The last proved unstable in methanol, converting to the cyclic acetal (3). Hydrogenolysis of (3) in acidic methanol gave the dimethyl acetal of aldehyde (4), whence the free aldehyde could be recovered. Hydrogenolysis of (2) and subsequent hydrolysis also gave (4). Direct cyclodehydration of (4) to dimethylsequirin-D (6; $R^1 = H$, $R^2 = Me$) could be induced directly (H_3PO_4) but in very poor yield. However the indirect route _via_ oxidation of (4) to the corresponding acid, cyclisation of the acid by hydrogen fluoride (directed entirely to formation of a new 6-membered ring) to ketone (5; R = H), followed by reduction and dehydration operations gave the desired dihydronaphthalene (6; $R^1 = H$, $R^2 = Me$) in 7% yield overall from (1) (average 68% perstep), with identical i.r., n.m.r., and chromatographic characteristics to the sample derived from Nature.

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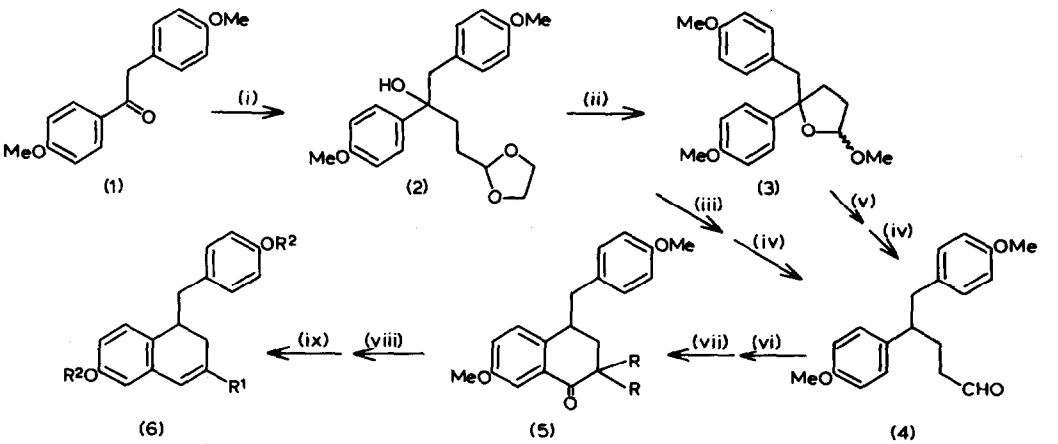
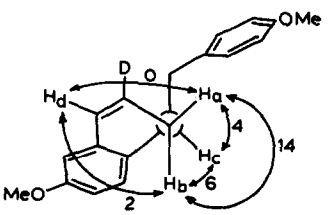
The ^{1}H.m.r. spectrum of (6; R^1 = H, R^2 = Me) showed extensive long-range coupling; accordingly the deuteriated derivative (6; R^1 = D, R^2 = Me) was prepared from the α-dideuterioketone (5; R = D). The ^{1}H.m.r. in $CDCl_3$ of (6; R^1 = D, R^2 = Me) provided the coupling constants (Hz) shown in (7). The benzylic methine proton H_c, with J_{ac}, J_{bc} = 4 and 6Hz is clearly quasi-eq rather than quasi-ax, with the torsion angle H_c-C-C-H_a greater than H_c-C-C-H_b. A solution conformation similar to that in the solid state is apparent, where these torsion angles are approx. 75° and 45°. Allylic couplings J_{ad}, J_{bd} of 0,2Hz were measured; these magnitudes are appropriate to the geometry. All the above couplings were maintained in spectra run in CD_3OD. The c.d. data[1] in methanol (Δε+10.3, 260nm) indicate that the skewed styrene chromophore adopts a right-handed helix.[3] Since the p-methoxybenzyl group takes an ax-orientation as just demonstrated, the absolute stereochemistry of di-O-methylsequirin-D is correctly shown in (7), i.e. it has the 1R configuration.



(i) BrMg[O,O]; (ii) MeOH; (iii) H_2–Pd; (iv) H_3O^+; (v) H_2–Pd, H^+, MeOH; (vi) Ag_2O; (vii) HF; (viii) $LiAlH_4$ (ix) TsOH, C_6H_6

(7)



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