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SYNTHESIS OF THE (±)-DIMETHYLETHERS OF AGATHARESINOL, SEQUIRIN-A, AND HINOKIRESINOL, RELATED NORLIGNANS OF CONIFERAE.

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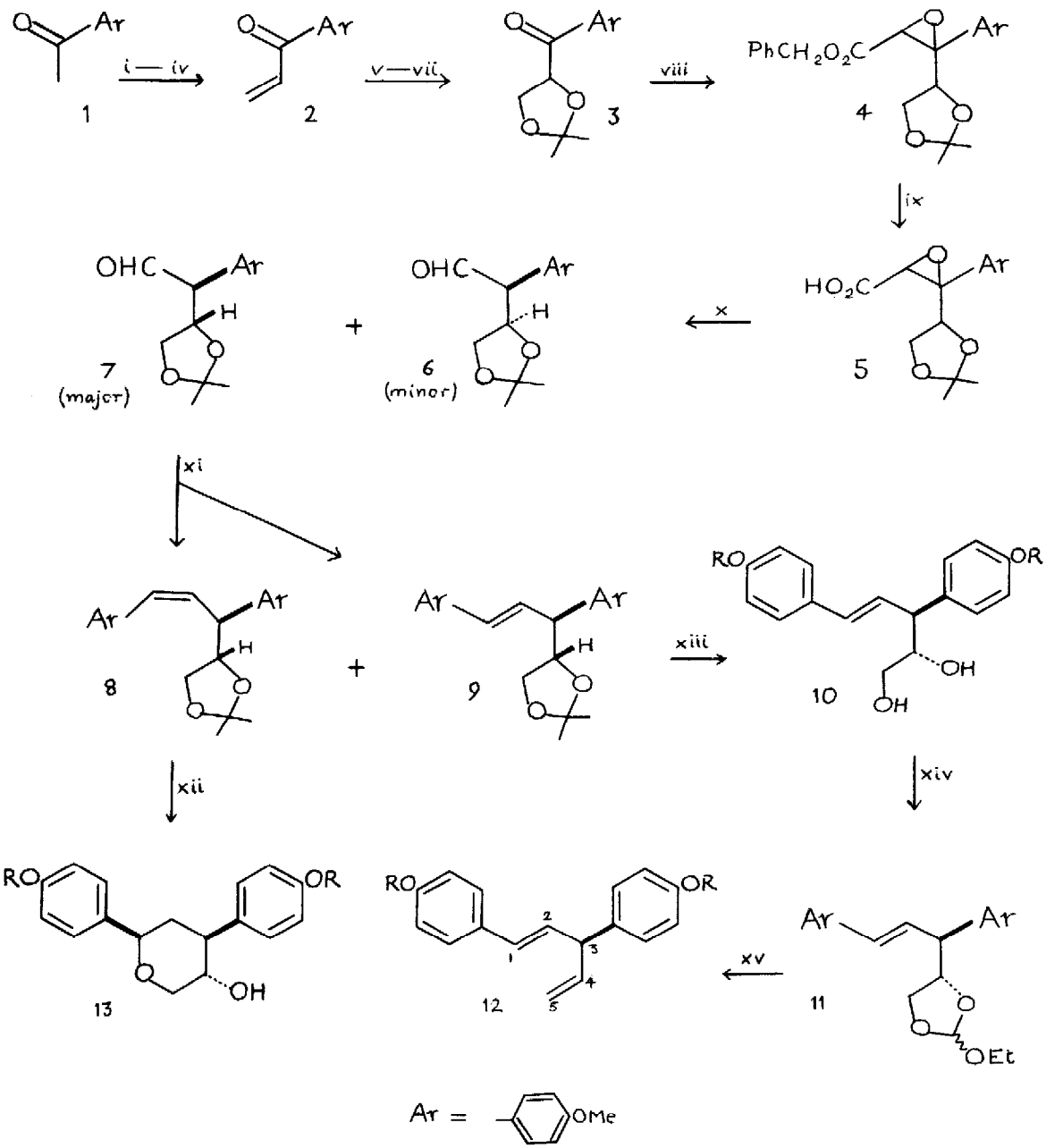
Norlignans are a small group of phenolic extractives, characteristic of the Coniferae, whose biosynthesis represents an interesting variation on the normal lignan pattern.[1] Agatharesinol[2] (10;R=H) (Agathis australis), sequirin-A[3] (13;R=H) (A.australis and other spp.[4,5]), and hinokiresinol[5,6] (12;R=H) (Chamaecyparis obtusa) form a group likely to be related in a biosynthetic sequence (12→10→13), although not yet reported to occur together in one species. In this paper we report the stereoselective syntheses of the (±)-dimethyl ethers (10,12,13;R=Me) of these norlignans using a common route.

The key synthon was the arylacetaldehyde (7). This was prepared from p-methoxyacetophenone (1), converted to the vinylketone (2) by alkaline decomposition of the methiodide of its Mannich base. Epoxidation of the ketone (2) with hydrogen peroxide was followed by aqueous acid hydrolysis and subsequent reaction with acetone to provide the p-methoxybenzoyl dioxolane (3). Ketone (3) was transformed into the benzylglycidic ester (4) by benzylchloroacetate and base, and hydrogenolysis afforded the free epoxyacid (5). All these steps proceeded with yields in the range 60-90%.

Stereoselective rearrangement and decarboxylation of the glycidic acid was effected by heating acetone solutions at 100° in a sealed tube to give the aldehydes (6) and (7). The desired stereoisomer (7) predominated (ca. 5:1). In this reaction, decarboxylation of the epoxyacid (5) (of unknown, but for the present purpose inconsequential, stereochemistry) yields an enol intermediate whose ketonisation controls product stereochemistry: examination of molecular models suggests that the isomer (6) is destabilised by an aryl-methylene interaction, in the staggered conformation. The mixture of (6) and (7) were treated with p-methoxybenzylidene triphenylphosphorane to yield cis- and trans-



Reagents: i, $Me_2NH.HCl$, CH_2O; ii, aq. Na_2CO_3; iii, CH_3I; iv, aq. $NaHCO_3$-Et_2O; v, H_2O_2, NaOH, -20°C; vi, H_3O^+; vii, HCl, Me_2CO; viii, $PhCH_2O.COCH_2Cl$, KO^tBu, C_6H_6; ix, H_2-Pd/C; x, Me_2CO, 100°C; xi, $ArCH{=}PPh_3$, C_6H_6; xii, HCl, MeOH, 72h; xiii, aq. HCl, MeOH, 0.5h; xiv, $H(OEt)_3$, H^+; xv, Δ, 150-160°, 1h.

acetonides (8) and (9) (overall yield from glycidic acid, ca. 40%); traces of minor stereoisomers were removed at this stage by chromatography. The cis olefinic acetonide (8) (which slowly isomerised to (9) on standing) was refluxed with methanolic hydrochloric acid when removal of acetone was followed by cyclisation, essentially quantitatively and stereospecifically, to afford (±)-dimethylsequirin-A(13,R=Me), m.p. 108-110°; spectroscopically and chromatographically indistinguishable from the ether of natural sequirin-A. The trans isomer (9) was treated briefly with acid to provide (±)-dimethyl-agatharesinol (10;R=Me) m.p. 124-126°, also with parallel spectroscopic and chromatographic properties to the methylated natural product. The trans-diol (10,R=Me) was then transformed, using triethylorthoformate, into the mixed orthoformate (11), finally pyrolysed cleanly at 150-160° to yield (±)-dimethylhinokiresinol (12;R=Me) as a clear oil. The cis-isomer of (12;R=Me) could not be obtained by this method; pyrolysis of the orthoester of the cis-isomer of diol (10) proceeded with stereomutation to yield only trans-(12;R=Me). Limited light absorption data are recorded for natural hinokiresinol, but our product was authenticated by detailed n.m.r. analysis. The salient features are the trans 1-H, 2-H (τ 3.4, 4.2; $J_{1,2}$ 12 Hz), the methine 3-H (τ 5.4; $J_{2,3}$ 10, $J_{3,4}$ 6 Hz), and terminal vinyl protons 4-H, 5-H_2 (τ 3.9, 4.8; $J_{5,5'}$ 5, $J_{4,5}$ 10, $J_{4,5'}$ 18 Hz). Electron-impact fragmentation followed the pattern described for the natural phenol.[7] Trans (12;R=Me), the thermodynamically stable isomer, and displaying[6] ν_{max} 967cm^{-1} (trans disubstituted ethylene) shows a vic ethylenic coupling constant (12 Hz) at the low end of the range; this value is lower than $J_{1,2}$ for (9), 16 Hz, (cf. (8), 9 Hz). Few close models are available to assist an understanding of this difference.

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