Stereoselective Total Synthesis (±)-Trimethylsequirin-B

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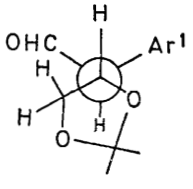
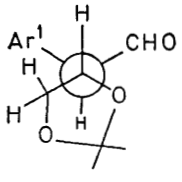
Summary Stereoselective total synthesis of (±)-trimethylsequirin-B (**16**) and the formation (±)-trimethylsequirin-C (**14**) in an intermediate stage is described.

A SMALL number of norlignans of novel skeletal type, exemplified by sequirin-B (**15**) and sequirin-C (**13**) (*Sequoia sempervirens*[1,2]) have recently been recognised as heartwood constituents of members of the *Coniferae*. Study of this group[1-5] has so far been confined to structure elucidation and no syntheses have been described. We report a total stereoselective synthesis of (±)-trimethylsequirin-B (**16**) (Scheme).

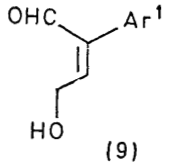
3,4-Dimethoxyacetophenone (**1**) was treated with formaldehyde and dimethylamine hydrochloride. The methiodide of the resulting Mannich base decomposed when shaken with aqueous $NaHCO_3$ to the vinyl ketone (**2**) (60%), which gave, on epoxidation with alkaline H_2O_2, the diol (**3**) (80%). This was converted into its acetonide (**4**) (92%) which yielded a benzyl glycidic ester (**5**) (61%) when treated with benzyl chloroacetate in base, and the free epoxy-acid (**6**) (95%) was obtained by hydrogenolysis. Stereoselective rearrangement and decarboxylation of the glycidic acid was effected by heating acetone solutions at 100° in a sealed tube affording a mixture (*ca.* 80%) of the aldehydes (**7**) and (**8**). The desired stereoisomer (**7**) was predominant (*ca.* 5:1). Comparison of Newman projections of the staggered conformers (**7a**) and (**8a**) of the two aldehydes suggests that the latter is destabilised by an aryl–methylene interaction. Aldehydes (**7**) and (**8**) decompose very readily in polar or protic media to the unsaturated aldehyde (**9**) and the furan (**10**).



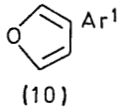
(7a)



(8a)

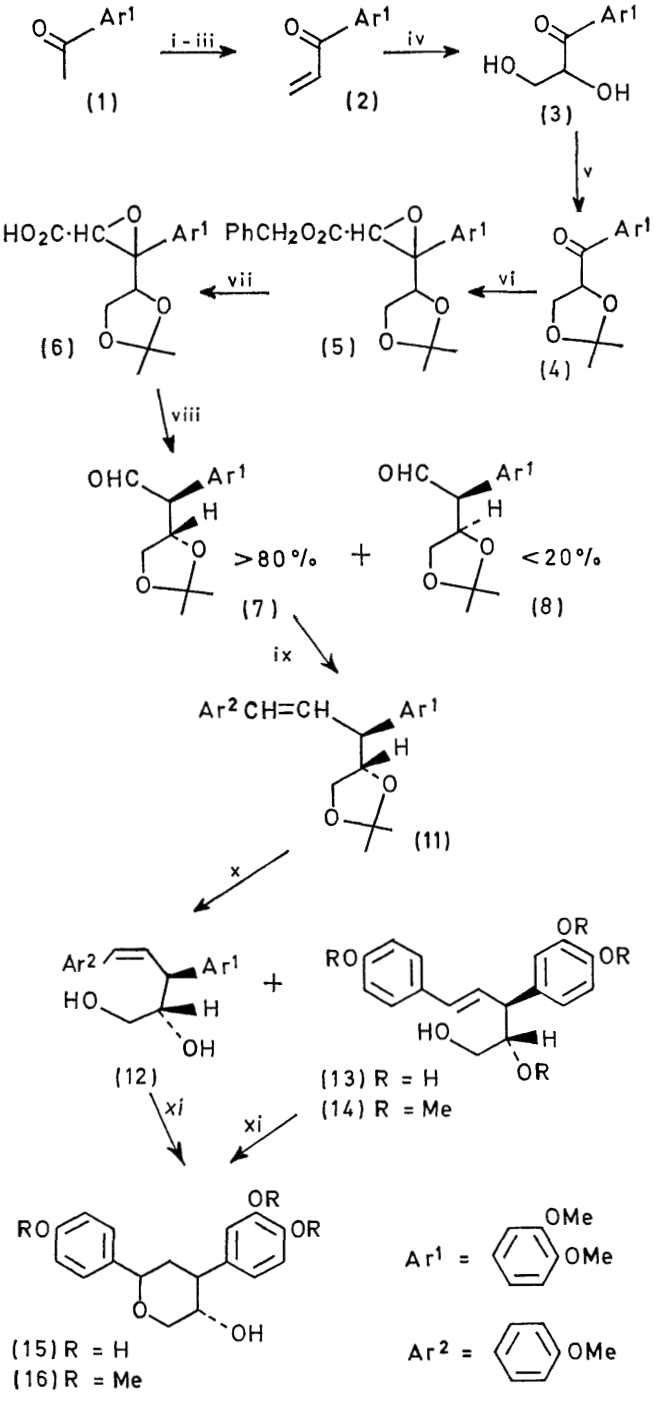


(9)



(10)

The mixture of compounds (**7**) and (**8**) was treated with *p*-methoxybenzylidenetriphenylphosphorane to yield the *cis*- and *trans*-isomers of the olefin (**11**). Traces of minor stereoisomers were removed at this stage by p.l.c. The yield of olefin (**11**), overall from glycidic acid (**6**), was *ca.* 50%. Removal of the acetonide function by brief acid treatment then gave a mixture (95%) of (±)-trimethylsequirin-C (**14**) and its *cis*-isomer (**12**), the latter predominating. Both isomers cyclised essentially quantitatively and stereospecifically when heated under reflux



i, CH_2O,Me_2NH,HCl, heat; ii, MeI; iii, aq. $NaHCO_3$; iv, H_2O_2, NaOH, then H^+,H_2O; v, Me_2CO,H^+; vi, $ClCH_2CO_2CH_2Ph$,$KOBu^t$; vii, H_2,Pd; viii, Me_2CO, heat; ix, $Ar^2CH{=}PPh_3$; x, H_2O,MeOH, H^+; xi, HCl,MeOH.

SCHEME

with methanolic HCl for 72 h, to form (±)-trimethylsequirin-B (**16**), m.p. 121—123°, spectroscopically and chromatographically identical with the trimethyl ether of natural (−)-sequirin-B. P.l.c. of the intermediate mixture (**12**) and (**14**) gave (±)-trimethylsequirin-C also, m.p. 116—118°, with spectroscopic properties in accordance with those of the methyl ether of the natural (−)-phenol.

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