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SYNTHESIS OF (±)-TRIMETHYLSEQUIRIN C: ALTERNATIVE ACID-CATALYSED CYCLISATION PATHWAYS FOR (±)-TRIMETHYLSEQUIRIN C RELATIVES

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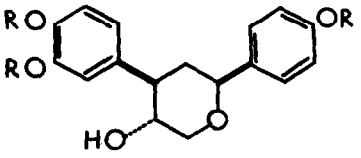
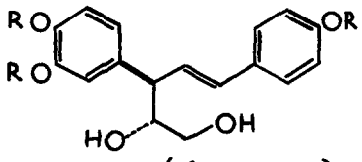
A group of norlignans, all possessing a 1,3-diaryl pentane skeleton[1-5] are found in heartwood of various members of the Coniferae. These are typified by sequirin B (1) and sequirin C (2){Sequoia sempervirens[4].} Recently we reported[6] a total synthesis of (±)-sequirin B trimethyl ether (3)*, by a route involving cyclisation of the 1,2-cis and 1,2-trans isomers of (±)-trimethylsequirin C (4). The latter isomer, with the natural 1,2-trans geometry, was the minor component in the synthetic product. We now describe an alternative synthesis for (±)-trimethylsequirin C which provides only the trans form, and include some observations on the acid-catalysed cyclisation mode of this product and a derivative.

2,2-Dimethyl-4-veratroyl-1,3-dioxolane[6] (5) was condensed with anisylacetylene in liquid ammonia with sodamide, affording the acetylenic alcohol (6) as a mixture (58%) of diastereoisomers. Reduction with lithium aluminium hydride gave the olefinic alcohol (7) (99%) as a mixture of two diastereomers, both 1,2-trans ($J_{1,2}$ 16Hz). Further reduction with lithium aluminium hydride of the sulphate (8), prepared from (7) with pyridine-sulfur trioxide[8], afforded (±)-trimethylsequirin C acetonide (9) and a diastereomer. The former was isolated (33% from 7) by chromatography and hydrolysed to (±)-trimethylsequirin C (4) (99%). This product was spectroscopically identical with the trimethyl ether of the natural (-)-phenol[4].

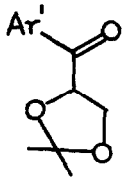
*Another synthetic route to this compound has now been described[7].



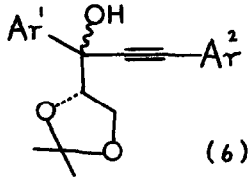
(1; R = H)
(3; R = CH_3)



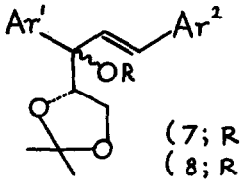
(2; R = H)
(4; R = CH_3)



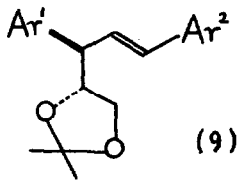
(5)



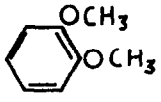
(6)

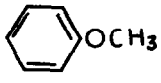


(7; R = H)
(8; R = SO_3H)

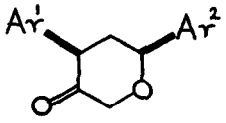


(9)

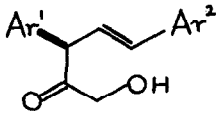
Ar^1 = 

Ar^2 = 

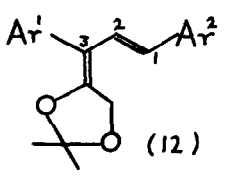
Trimethylsequirin C (4) cyclises to trimethylsequirin B (3) on treatment with dilute acid. The latter alcohol is not readily oxidised[4] to ketone (10), and it was hoped to prepare the latter by cyclisation of the ketol (11) in analogy with the (4) → (3) conversion. The enol acetonide (12) of ketol (11) was the major product of pyridine-p-toluenesulphonyl chloride dehydration of (7). The 1E, 3Z stereochemistry probably follows from the mode of preparation and from further reactions.



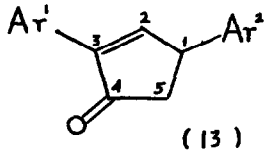
(10)



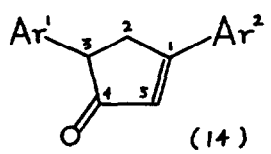
(11)



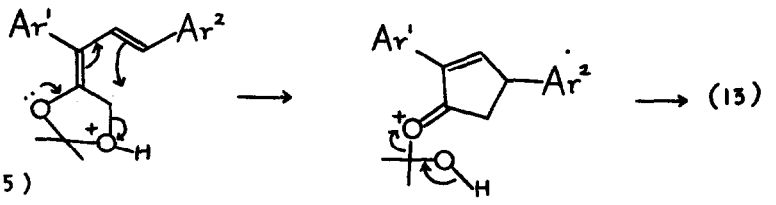
(12)



(13)



(14)



(15)

Treatment of enolacetonide (12) under various acidic conditions (acetone -5M hydrochloric acid (5:1), methanol-0.25M hydrochloric acid (2:1), ethylene glycol-p-toluenesulphonic acid) did not produce tetrahydropyranone (10). Instead, the major products proved to be the cyclopentenones (13) and (14). The former, $C_{20}H_{20}O_4$, had $\lambda_{max.}$ 285nm and $\nu_{max.}$ 1700cm^{-1}. N.m.r. signals were observed at τ 2.32 d (J 3Hz, 2-H), 5.93 (J 7,3 and 1 Hz, 1-H), 6.91q (J 18 and 7Hz, 5-H), and 7.57q (J 18 and 3Hz, 5-H), as well as resonances for aromatic and methoxyl protons. Cyclopentenone (14), $C_{20}H_{20}O_4$, had, in comparison, λ_{max} 317nm (log ε 4.00), ν_{max} 1685cm^{-1}, and τ 3.46s (5-H), 6.1 - 6.9m (2-H_2, 3-H). Cyclisation of (12), in acid, does not therefore involve opening to the ketol (11), protonation of the double bond and capture of the resulting carbonium ion, as in the (4) → (3) transformation. Instead, protonation at 5-oxygen initiates cyclisation as rationalised in (15), the product collapsing to acetone and (13). The latter then equilibrates by prototropic shift with the more conjugated ketone (14).

Satisfactory analytical and spectroscopic data were collected for all compounds described.

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