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A METHOD FOR THE SYNTHESIS OF BRIDGED TERPENOIDS

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We have been engaged for some time in the development of methods (1,2) for the synthesis of compounds of the type 1. While these studies were in progress we have simultaneously tested various approaches which might serve for the further development of the intermediate 1 to songorine 2. In the present communication we wish to report a simple and stereospecific new method for the conversion of the phenol 3 to the two tetracyclic diketones 4 and 5 and an X-ray structure determination of compound 4. We believe that this method will not only be useful in the synthesis of songorine but also in the synthesis of many other terpenoids. Thus, for instance, a very facile synthesis of tricyclovetivene has made good progress in our laboratory.

The starting material 3 [m.p. 119°] was prepared from the corresponding methoxy derivative (3) by demethylation with pyridine hydrobromide. The phenol 3 was converted to the allyl ether 6 in a 93% yield by refluxing with allyl chloride, potassium carbonate and potassium iodide in acetone. Compound 6 [b.p. 94°/0.05 mm. Hg] was characterized by n.m.r. and mass spectrometry.* The ether 6 was rearranged to the allyl phenol 7 in a 91% yield by heating *in vacuo* to 180-185° [b.p. 110°/0.05 mm. Hg]. Compound 7 was methylated with aqueous sodium hydroxide and dimethylsulphate to the methyl ether 8 in a yield

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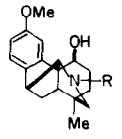
* I.r., n.m.r. and mass spectra of all compounds were recorded but are discussed only in specially relevant cases. All crystalline compounds gave satisfactory elemental analyses.

of 92% [b.p. 100°/0.03 mm. Hg; n.m.r.: 2 singlets (1H each) τ = 3.2, 3.4 p.p.m. (aromatic H), multiplet (3H) τ = 5.0-5.21 p.p.m. (vinylic H), singlet (3H) τ = 6.31 p.p.m. (-OMe)]. Compound 8 was subjected to a catalytic osymylation with osmic acid and sodium chlorate in aqueous tetrahydrofuran. The corresponding diol 9 [m.p. 84.5-85.5°, benzene-hexane] was obtained in a yield of 75%.

The cleavage of 9 with sodium periodate in the same solvent mixture gave the aldehyde 10 in a quantitative yield. [I.r. (CCl_4): 1725 cm^{-1} (aldehyde); n.m.r.: triplet (1H) τ = 0,5 p.p.m. (-C$\overset{H}{\underset{O}{\lessgtr}}$), two singlets (1H each) τ = 3.16, 3.25 p.p.m. (aromatic hydrogen), singlet (3H) τ = 6.25 p.p.m. (-OMe).] Ketalization of compound 10 with ethylene glycol-p-toluenesulphonic acid in benzene gave the corresponding oily ketal 11 in a yield of 97%. Compound 11 was reduced with lithium in liquid ammonia-t-butanol and the Birch product 12 obtained in a 90% yield was purified by chromatography. The Birch product was then treated with oxalic acid in aqueous methanol at room temperature and the oily compound 13 was obtained in a yield of 99%. [I.r. (CCl_4): 1710 cm^{-1} (ketone); n.m.r.: no vinylic hydrogen, triplet (1H) τ = 5.09, 5.17, 5.25 p.p.m. (-CH$\overset{O-}{\underset{O-}{\lessgtr}}$).] An isomerization of compound 13 to the conjugated ketone 14 may be achieved by reflux in 0.1% methanolic potassium hydroxide for 30 minutes. The yield of the oily product 14 was 93%. [I.r. (CCl_4): 1670 cm^{-1} (conjugated ketone); n.m.r.: singlet (1H) τ = 4.27 p.p.m. (vinylic hydrogen), triplet (1H) τ = 4.88, 4.97, 5.05 p.p.m. (-CH$\overset{O-}{\underset{O-}{\lessgtr}}$).]

A deketalization of 14 was achieved by heating with 70% acetic acid to 70° for 45 minutes. The oily keto aldehyde 15 was obtained in a yield of 94%. [I.r. (CCl_4): 1665, 1725 cm^{-1} (conjugated ketone, aldehyde); n.m.r.: narrow triplet (1H) τ = 0.28 p.p.m. (-C$\overset{H}{\underset{O}{\lessgtr}}$), singlet (1H) τ = 4.34 p.p.m. (vinylic hydrogen).] The keto aldehyde 15 was allowed to stand at room temperature in a 1% methanolic potassium hydroxide solution for 18 hours. The presumably thermodynamically controlled product 16 was then subjected to an acetylation with acetic anhydride and pyridine. Crystallization from hexane gave the acetate 17 in a 47% yield [m.p. 108-109°; i.r. (CCl_4): 1675 (conjugated ketone), 1740 cm^{-1} (acetate); n.m.r.: singlet (1H) τ = 4.46 p.p.m. (vinylic hydrogen), narrow



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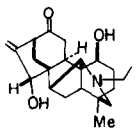

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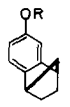
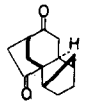


3 R=H

6 R=-CH_2-CH=CH_2



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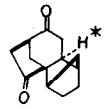

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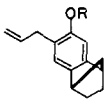
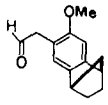


7 R=H

8 R=OMe



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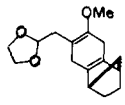

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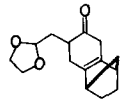

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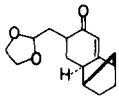

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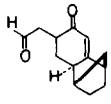

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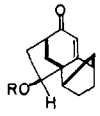
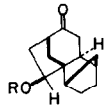


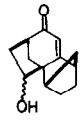
16 R=H

17 R=OAc



18 R=OAc

19 R=H



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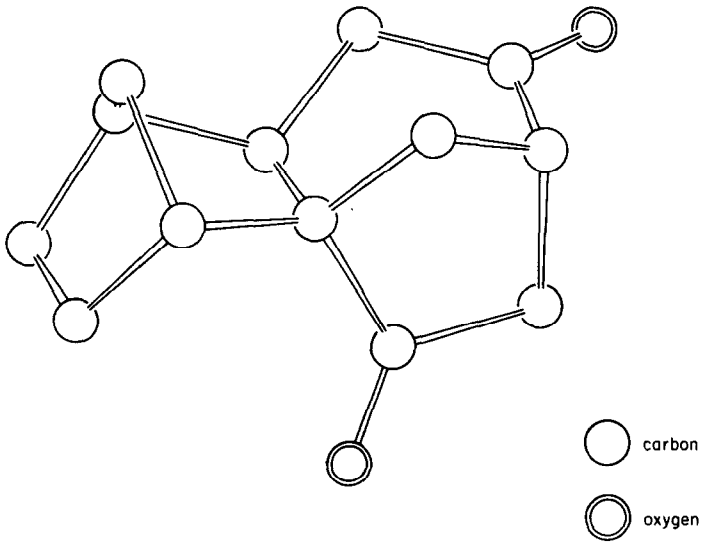

Figure 1.The structure of the tetracyclic diketone 4 along the b axis.

triplet (1H) τ = 5.17 p.p.m. (hydrogen unshielded by acetate), singlet (3H) τ = 7.9 p.p.m. (-OAc)].

The acetate 17 was hydrogenated in ethanol with 10% palladium on charcoal. A quantitative yield of the dihydro derivative 18 [m.p. 98° (hexane)] was obtained. The same compound was prepared in a lower yield by reduction of 17 with lithium in liquid ammonia followed by acetylation. Saponification of 18 by 5% methanolic potassium hydroxide gave the corresponding alcohol 19 [m.p. 119-120°] in a quantitative yield. Finally, Jones' oxidation of this last compound yielded the diketone 4 [m.p. 124°; i.r. (CCl_4): 1720, 1740 cm^{-1} (6- and 5-membered ketones)]. The configuration of compound 4 was determined rigorously by an X-ray structure analysis. The view of the molecule along the b axis is presented in Figure 1. A full account of this investigation will be published elsewhere.

Compound 13 was heated in 75% aqueous acetic acid to 90° for 5 hours. The oily product 20 with a unique but undetermined configuration of the hydroxyl was obtained stereospecifically in a yield of 30%. Compound 20 was now converted to the diketone 5 by exactly the same route which was employed for the isomer 16. [Acetate m.p. 92-93°, dihydroacetate m.p. 66-67°.] The diketone 5 crystallized from hexane [m.p. 108-109°; i.r. (CCl_4): 1720, 1740 cm^{-1} (ketones)]. The configuration of the hydrogen marked by the asterisk is not proved, but may be safely assumed to be as shown in the formula by analogy with the diketone 4. The stereospecificity of the acid-catalyzed cyclization 13 → 20 may be understood as a kinetically controlled electrophilic attack of the protonated aldehyde group on the endocyclic double bond. Such reactions are known (4) to proceed preferentially exo with respect to the bicycloheptane system.

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