Tetrahedron Letters,Vol.24,No.1,pp 101-102,1983 0040-4039/83/010101-02$03.00
Printed in Great Britain

CANNABIS XXVI.[1] TOTAL SYNTHESIS OF CANNABIFURAN

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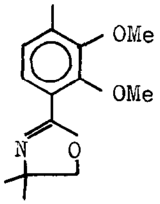
Summary: The naturally occurring dibenzofuran cannabifuran (10) has been synthesized from 2,3-dimethoxy-p-toluic acid and 2-bromoolivetol dimethyl ether. In the key step, the aryl-aryl bond has been formed via a methoxy displacement in the aryloxazoline (1). The final furan ring closure in (8) to (10) was accomplished by the HI/Ac_2O reagent.

We wish to report the total synthesis of cannabifuran (10), a naturally occurring dibenzofuran, isolated as a minor constituent of Cannabis sativa L. in 1975[2]. A very recent communication[3] on a different total synthesis of (10) prompts us to publish our results now.

As an extension and as a further test of our recently published method[4] of synthesis of sterically hindered biphenyls, coupled with our interest in the total synthesis of cannabinoids, the synthesis of cannabifuran was undertaken. The starting compound in our synthetic sequence was the known[5] 2,3-dimethoxy-p-toluic acid which was converted to the new oxazoline (1), m.p. 48-49° (cyclohexane), in 78% yield by the procedure of Meyers et al.[6] In the key step of our approach this oxazoline reacted with the Grignard reagent[4] (2) from 2-bromoolivetol dimethyl ether (2 equiv.) in boiling tetrahydrofuran for 22 h to afford the highly hindered biphenyloxazoline (3) in 83% yield. The cleavage of the oxazoline moiety to the carboxylic acid (4) under standard conditions[6] (boiling 4.5 N hydrochloric acid, 16 h) was accompanied by a partial ether cleavage leading to a mixture of the acid (4) (major product) and the lactone (9) in 100% yield. Performing the reaction on larger scale promoted more lactone formation. This mixture was methylated by dimethyl sulphate and aqueous NaOH to the methyl ester (5), m.p. 79-80° (cyclohexane), in 83% yield. The ester function was transformed quantitatively to the hydroxyisopropyl group in (6) by excess of methylmagnesium iodide. This carbinol was directly and quantitatively dehydrated by trifluoroacetic acid (3 h, 20°) and the resulting styrene (7) was reduced catalytically (H_2, 1 atm, PtO_2, EtOAc) to the isopropylbiphenyl (8), m.p. 75-76° (hexane), in 92% yield. In the final, remarkably smooth synthetic operation, (HI/Ac_2O, 5 h reflux), the cleavage of the three methoxy groups in compound (8) and the dehydration leading to cyclization took place simultaneously to afford the crystalline cannabifuran[7] (10), m.p. 80-81° (hexane) (lit.[3] 78-79°), in 90% yield identical with the natural oily[2] material.



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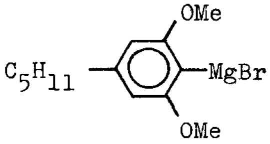

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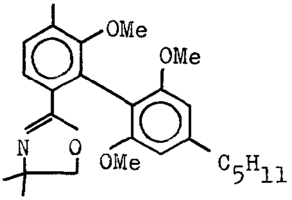

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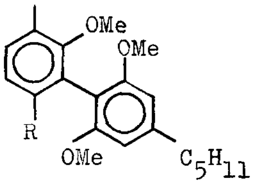

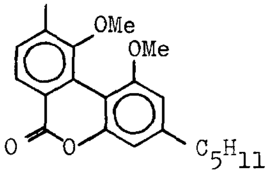

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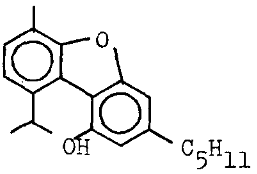
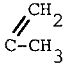


10

4 R = COOH

5 R = COOMe

6 R = $CH(OH)(CH_3)_2$



7 R = $C(=CH_2)-CH_3$

8 R = $CH(CH_3)_2$

References and Notes

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7. ^{13}C NMR ($CDCl_3$) of 10: δ 14.0, 15.0, 22.5, 24.3, 30.4, 31.0, 31.4, 35.8, 104.1, 109.7, 110.7, 118.3, 118.8, 121.4, 127.4, 142.0, 143.2, 149.8, 154.4, 158.3 ppm.

(Received in UK 25 October 1982)