Tetrahedron Letters No. 16, pp 1615 - 1617, 1972. Pergamon Press. Printed in Great Britain.

A CONVENIENT SYNTHESIS OF LUNULARIC ACID

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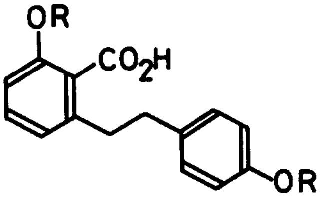
(Received in Japan 23 February 1972; received in UK for publication 14 March 1972)

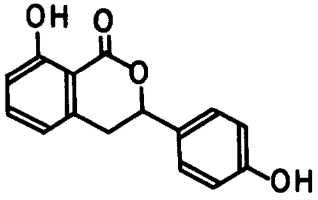
Recently lunularic acid (lb), a new growth inhibitor from Lunularia cruciata (L) Dum., has been isolated and characterized.[1] Final proof of the structure was provided by the derivation of lb from hydrangenol (2).[1,2] The synthesis of 2, via 7,4'-dimethoxybenzalphthalide (3), has already been reported. Hydrogenolysis of 3 would give dimethoxy lunularic acid (la), but the yield of 3 from 3-methoxyphthalic anhydride was only 1.5% at best.[3]

We wish to describe an efficient four-step synthesis of lunularic acid in 21% overall yield. Several methods have been investigated for the preparation of 3-arylisocoumarins, which would be converted into lb by hydrogenolysis. Of the methods available, the condensation of a homophthalic acid with a phenol[4] seemed attractive. The required homophthalic acid (7c) has been prepared by longer sequence of reactions.[5] However, the poor overall yield caused this route to be rejected. By applying the novel synthesis of 3-methoxyphthalic acid from 1-methoxycyclohexa-1,3-diene (4),[6] we have obtained 3-methoxyhomophthalic acid.

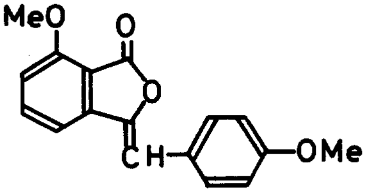
Heating the mixture of 4 and dimethyl allene-1,3-dicarboxylate (5)[7] in a sealed tube at 180° for 17 hours gave dimethyl 3-methoxyhomophthalate (7a), identical with the authentic sample, in 42% yield in one step. This represents an excellent synthesis of homophthalic acids. The minor product, 5% in yield, of the Diels-Alder reaction was assigned the structure (6) on the basis of NMR evidence. $\delta(CCl_4)$ 1-2.2 (4H, m), 3.06 (1H, m, H_e), 3.40, 3.56 and 3.62 (each 3H, s), 3.72 (1H, t, J=3 Hz, H_d), 5.62 (1H, d, J=3 Hz, H_c), 6.08 (1H, dd, J=6,



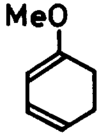
(1a) R = Me
(1b) R = H



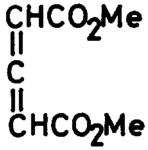
(2)



(3)

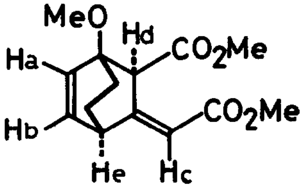


(4)

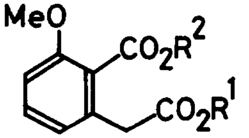


$$\begin{array}{l}\mathrm{CHCO_2Me}\\ \| \\ \mathrm{C}\\ \| \\ \mathrm{CHCO_2Me}\end{array}$$

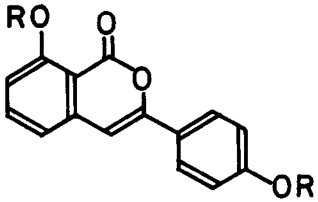
(5)



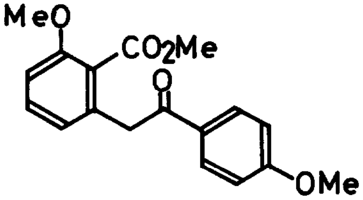
(6)



(7a) $R^1 = R^2 = Me$
(7b) $R^1 = H; R^2 = Me$
(7c) $R^1 = R^2 = H$



(8a) R = Me
(8b) R = H



(9)

9 Hz, H_b) and 6.36 ppm (1H, d, J=9 Hz, H_a).

Mild alkaline hydrolysis of 7a gave the half ester (7b). More vigorous hydrolysis (acid or base) of 7a gave 3-methoxyhomophthalic acid (7c), identical with the authentic sample.[5] Condensation of 7c with anisole in PPA at 90° gave the isocoumarin (8a), mp 161-162°, in 81% yield with the expected spectroscopic data. When 7b was condensed with anisole, the keto ester (9) together with 8a was obtained depending on the condition used. Catalytic hydrogenation of 8a gave the acid 1a in quantitative yield, which afforded, on treatment with BBr_3, 1b in 63% yield, mp 195-196° (lit. mp 192°).[1] The IR spectrum is identical with that of the natural acid and the UV and mass spectra are in accord with the published data.

Preliminary tests for the biological activity of the synthetic 1b were carried out using *Avena* straight growth. At concentrations 10-30 mg/l it inhibited IAA-induced (5 mg/l) elongation of coleoptile segments excised from 4 day-old etiolated seedlings. Kinetic studies, however, appear to show that the inhibition was elicited not in a competitive manner. Detailed information will appear elsewhere.

We thank Professor W. W. Schwabe, Department of Horticulture, University of London, for the supply of the IR spectrum of lunularic acid and Professor Y. Masuda, Department of Biology, Osaka City University, for biological tests.

References

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