A Simple Total Synthesis of Cyclopentanoid C_9-Terpene Lactones

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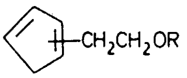
Summary The cyclopentanoid C_9-terpene lactones, onikulactone (**7**) and mitsugashiwalactone (**8**) have been synthesized by a novel intramolecular cyclization of a carbonate ester of cyclopentadienylethanol (**2**), followed by methylation and hydrogenation.

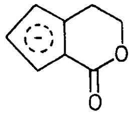
MANY compounds with a cyclopentanoid monoterpene lactone structure are known to be biologically active natural products.[1] The cyclopentanoid C_9-terpene lactones, onikulactone and mitsugashiwalactone, which were isolated by Sakan *et al.* as the biologically active principles of *Boschniakia rossica* Hult and *Menyanthes trifoliata* L, also have a highly attractive physiological action on the Felidae and Chrysopidae.[2] We now report a simple total synthesis of these C_9-terpene lactones by a route involving a novel intramolecular cyclization of a carbonate ester of cyclopentadienylethanol.

Treatment of cyclopentadienylethyl methyl carbonate (**2**), which was derived from cyclopentadienylethanol (**1**)[3] and methyl chloroformate in nearly quantitative yield, with sodium hydride at 45 °C in dimethoxyethane gave the corresponding cyclopentadienyl anion, which in turn cyclized *via* intramolecular attack on the carbonyl carbon to afford the anion (**3**). The structure of (**3**) was confirmed by spectral analyses of the acidified product, the cyclopentadieno-δ-lactone (**4**). Methylation of (**3**) with methyl fluorosulphonate at −70 °C gave a mixture of (**5**) (50%) [m.p. 52—54 °C (from ether), ν_{max} 1685, 1245, and 1070 cm^{-1}, δ ($CDCl_3$) 2·10 (3H, quartet), 2·72 (2H, t), 3·01 (2H, quartet), 4·34 (2H, t), and 5·78 (1H, m)] and (**6**) (17%), [m.p. 58—60 °C (from n-hexane–ether, 10:3), ν_{max} 1700, 1210, and 1090 cm^{-1}, δ ($CDCl_3$) 1·98 (3H, quartet), 2·64 (2H, sextet), 3·10 (2H, m), 4·36 (2H, t), and 6·30 (1H, m)].[4] Mass spectral and analytical data were in agreement with the presented structure, and the final elucidation of the position of the methyl group was achieved by n.m.r. analyses using a shift reagent; the methyl signal of (**5**) shifted 2·26 p.p.m. downfield and that of (**6**) shifted only 0·68 p.p.m., when $Eu(fod)_3$ was added. Hydrogenation of (**5**) on platinum oxide in ethanol at ambient pressure and temperature resulted in the formation of the racemic onikulactone (**7**) and mitsugashiwalactone (**8**) (1:1·8) in quantitative yield, which were separated by g.l.p.c. and identified by n.m.r., i.r. and mass spectral comparison with natural products.

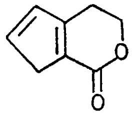
We thank Dr. Sakan and Dr. Murai of Osaka City University for supplying the spectral data of natural onikulactone and mitsugashiwalactone.



(1); R = H
(2); R = CO_2Me



(3)



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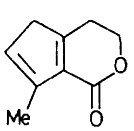

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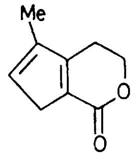

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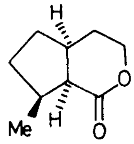
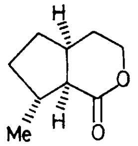


(7)



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(*Received*, 31*st December* 1975; *Com.* 1440.)

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[1] For reviews see 'Cyclopentanoid Terpene Derivatives,' eds. W. I. Taylor and A. R. Battersby, Marcel Dekker, New York, 1961; 'The Total Synthesis of Natural Products,' ed. J. ApSimon, vol. 2, Wiley-Interscience, New York, 1973, p. 62.

[2] T. Sakan, F. Murai, S. Isoe, S. Be Hyeon, and Y. Hayashi, *J. Chem. Soc. Japan*, 1969, **90**, 507.

[3] Cyclopentadienylethanol was synthesized by the modified method of the reaction of cyclopentadiene and ethylene oxide; R. Schröder, A. Striegler, G. Zimmerman, and M. Mühlstädt, *J. prakt. Chem.*, 1973, **315**, 958.

[4] N. m. r. analyses were performed on the basis of the data for methylcyclopentadiene; V. A. Korenevsky and N. M. Seigeyer, *J. Amer. Chem. Soc.*, 1972, **94**, 8586.