FACILE FORMATION OF THE BASIC SKELETONS OF NATURALLY OCCURRING TERPENOIDAL LACTONES

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Abstract —— Three lactones which should be important intermediates in the synthesis of the corresponding natural terpenoidal lactones have been synthesized via thermolysis of benzocyclobutenes. Heating the benzocyclobutenes (7), (8) and (13) afforded the cyclized products (9), (10) and (14) respectively, in reasonable yields.

An increasing number of terpenoidal lactones have been isolated from natural sources, and a considerable amount of synthetic effort has been made in this field.[1] Most of the interest in this area results from the fact that many of these lactones display fugitoxic, allergenic, antimitotic activity. Thus the development of a simple synthetic route to such compounds continues to be a very important area of research. We wish to report here the facile formation, via benzocyclobutene thermolysis, of three tricyclic lactones which are expected to be key intermediates in the synthesis of the abietane (1) diterpenes and the eudesman (2) and driman (3) sesquiterpenes.

Scheme 1

The acid chlorides (4) and (5), prepared from the corresponding acids[2,3] and oxalyl chloride in refluxing methylene chloride, were treated with propargyl alcohol (6) in the presence of N,N-dimethylaminopyridine in methylene chloride to afford the esters (7)[4] and (8)[5] respectively, as colorless oils in quantitative yields. Heating a toluene solution of the ester (7) in a sealed tube at 190 - 200°C for 40 h afforded the lactones (9) in 76.5 % yields; colorless prisms, mp 136 - 137°C (MeOH); δ ($CDCl_3$) 2.47 (1H, dd, J = 12 and 17 Hz, $ArCH(H)C(H)-CO-$), 3.27 (1H, dd, J = 5 and 17 Hz, $ArCH(H)C(H)-CO-$), 3.30 - 3.70 (3H, m, $ArCH_2-C(H)=C-$ and $ArCH-CH_2-$), 3.80 (3H, s, OCH_3), 4.88

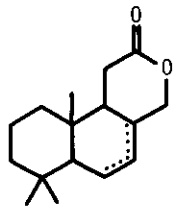
(2H, s, $CO_2C\underline{H}_2$-), 6.05 (1H, br s, olefinic proton) 6.73 (1H, br s, aromatic proton), 6.82 (1H, dd, J = 2 and 8 Hz, aromatic proton) and 7.10 (1H, d, J = 8 Hz, aromatic proton); ν_{max} ($CHCl_3$) 1725 (C=O) cm^{-1}; m/e 230 (M^+). The ester (8) on similar treatment gave the cyclized product, 10 in 42 % yield; colorless prisms, mp 123 - 124°C (MeOH); δ ($CDCl_3$) 2.33 - 3.02 (4H, m, $ArC\underline{H}_2C\underline{H}_2$-), 3.80 (3H, s, $OC\underline{H}_3$), 4.85 (2H, s, $CO_2C\underline{H}_2$-), 6.77 (1H, dd, J = 2 and 8 Hz, aromatic proton), 7.12 (1H, d, J = 8 Hz, aromatic proton) and 7.70 (1H, d, J = 2 Hz, aromatic proton); ν_{max} ($CHCl_3$) 1745 (C=O) and 1655 (C=C) cm^{-1}; m/e 216 (M^+). Isomerization of the double bond was observed during the thermolysis of the benzocyclobutene and the structure of the product was assigned on the basis of the above spectral data.

Scheme 2

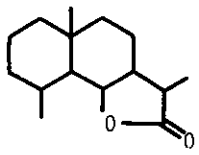
Finally, the benzocyclobutenol[6] (11) was esterified with vinylacetyl chloride (12) in the presence of N,N-dimethylaminopyridine in methylene chloride at 0°C to give the ester (13)[7] which on thermolysis in a sealed tube at 190 - 200°C for 48 h furnished the cyclized lactone (14) in 61 % yield; colorless needles, mp 167 - 168°C (MeOH); δ ($CDCl_3$) 3.88 (3H, s, $OC\underline{H}_3$) and 5.63 (1H, d, J = 5 Hz, $Ar\underline{C}\underline{H}$-O-), ν_{max} ($CHCl_3$) 1770 (C=O) cm^{-1}; m/e 218 (M^+). The stereochemistry of the B/C ring system is tentatively assigned as cis from the NMR spectral data.[8,9]

Thus thermolysis of benzocyclobutenes has been shown to provide a useful synthetic route to various lactone compounds which may show interesting biological activity. Now, the conversion of these aromatic lactones to natural products such as acrostalidic acid[10], α- and β-cyclocostunolide[11], iso-drimenin[12] and warburganal[12] is under progress in this laboratory.

Scheme 1



1



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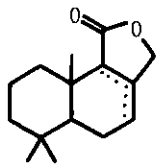

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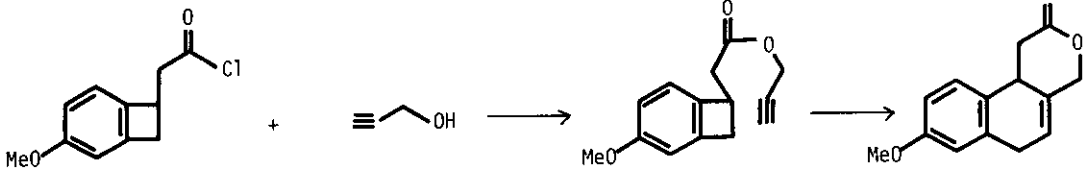
Scheme 2



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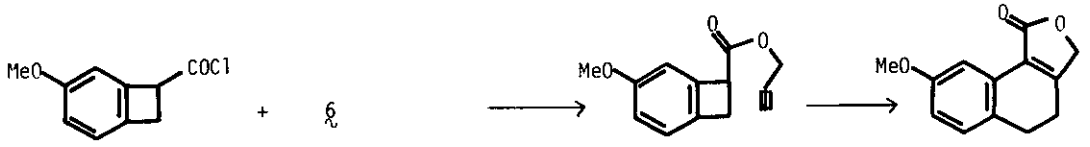
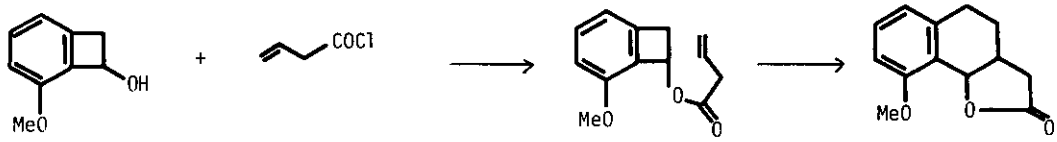


5 6 8 10



11 12 13 14

REFERENCES AND FOOTNOTES

1. J. ApSimon, "The Total Synthesis of Natural Produts", A Wiley-Interscience Publication, John Wiley & Sons, New York, 1973.

2. T. Kametanı, H. Nemoto, H, Ishikawa, K. Shiroyama, H. Matsumoto, and K. Fukumoto, J. Amer. Chem. Soc., 1977, 99, 3461.

3. T. Kametani, M. Kajiwara, and K. Fukumoto, Tetrahedron, 1974, 30, 1053.

4. δ ($CDCl_3$) 2.42 (1H, t, J = 2 Hz, -C≡C$\underline{H}$), 3.38 (2H, d, J = 4 Hz, ArC$\underline{H}_2$-), 3.73 (3H, s, OC$\underline{H}_3$), 4.23 (1H, t, J = 4 Hz, ArC$\underline{H}$·CO-), and 4.70 (2H, d, J = 2 Hz, $CO_2C\underline{H}_2$-); ν_{max} ($CHCl_3$) 3310 (C≡CH) and 1730 (C=O) cm^{-1}; m/e 216 (M^+).

5. δ ($CDCl_3$) 2.50 (1H, t, J = 2 Hz, -C≡C$\underline{H}$), 2.70 (2 H, d, J = 8 Hz, ArC$\underline{H}$-C$\underline{H}_2$CO-), 3.73 (3H, s, OC$\underline{H}_3$), 4.73 (2H, d, J = 2 Hz, $CO_2C\underline{H}_2$-), 6.72 (1H, br s aromatic proton), 6.78 (1H, dd, J = 2 and 9 Hz, aromatic proton) and 7.50 (1H, d, J = 9 Hz, aromatic proton); ν_{max} ($CHCl_3$) 3325 (C≡CH) and 1740 (C=O) cm^{-1}; m/e 230 (M^+).

6. T. Kametani, M. Takeshita, H. Nemoto, and K. Fukumoto, Chem. and Pharm. Bull. (Japan), 1978, 26, 556.

7. δ ($CDCl_3$) 3.83 (3H, s, OC$\underline{H}_3$), 5.20 (2H, br d, J = 15 Hz, CH=C$\underline{H}_2$) and 6.12 (1H, m, ArC$\underline{H}$-O-); ν_{max} ($CHCl_3$) 1725 (C=O) cm^{-1}; m/e 218 (M^+).

8. J. P. Pinhey and S. Sternhall, Austral. J. Chem., 1965, 18, 543.

9. A. Ahond, J. C. Coll, and J. D. Fourneron, Tetrahedron Letters, 1979, 1879.

10. M. Sato, T. Ruo, T. Hayashi, and H. Kakısawa, Tetrahedron Letters, 1974, 2183.

11. T. C. Jaın and J. E. McCloskey, Tetrahedron, 1975, 31, 2211.

12. a. S. P. Tanis and K. Nakanıshi, J. Amer. Chem. Soc., 1979, 101, 4398, and references cited therein.

b. T. Nakata, H. Akita, T. Naıto, and T. Oishi, J. Amer. Chem. Soc., 1979, 101, 4400.

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