Facile Synthesis of Basic Skeletons of Naturally Occurring Lactonic Terpenes

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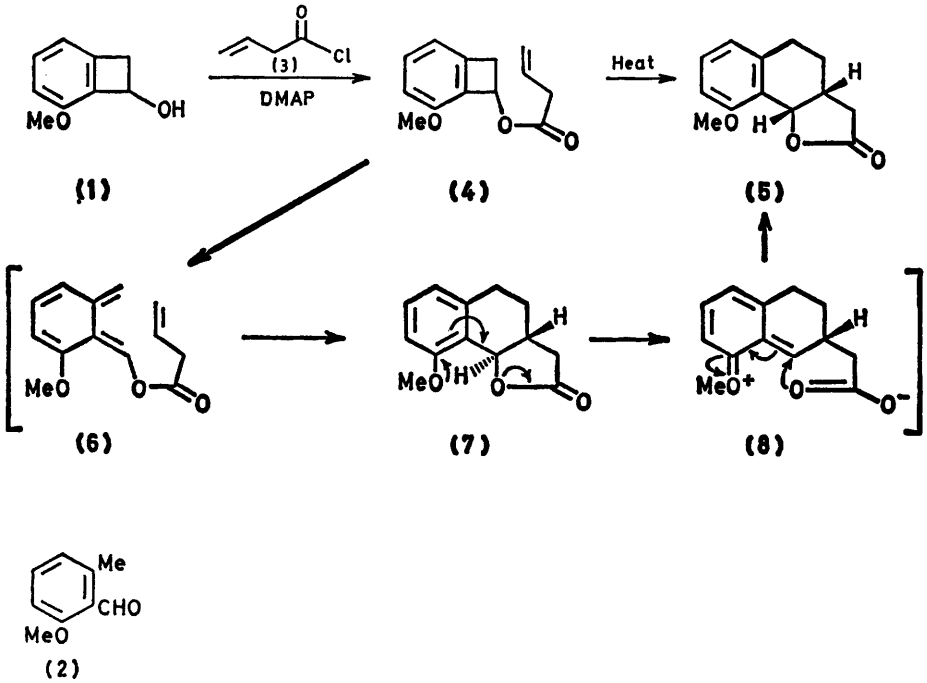
Simple syntheses of the basic skeletons of some naturally occurring terpenes possessing lactone moieties are described. Thermolysis of 1,2-dihydro-6-methoxybenzocyclobuten-1-yl but-3-enoate (4) in a sealed tube at 180—200 °C afforded the cyclised lactone (5) in moderate yield. On similar treatment, the benzocyclobutenes (11) and (14) gave the corresponding fused lactones (12) and (15) respectively.

In continuation of our work on the chemistry on benzocyclobutenes, we have investigated simple syntheses of the basic skeletons of naturally occurring lactonic terpenes which are known to display interesting biological activities, *e.g.* as fungitoxics, allergenics, and antimitotics. Efficient construction of these skeletons is a synthetic challenge which has received considerable attention during the past few years.[1-4] Since we had demonstrated that benzocyclobutenes were attractive starting materials for constructing complicated molecules stereo- and regio-selectively,[5-9] we considered that a fused lactone ring could also be synthesised in a similar manner. We here report the facile synthesis of three lactones *via* benzocyclobutene thermolysis.

We first planned to use 1,2-dihydro-6-methoxybenzocyclobuten-1-ol (1)[10] in a synthesis of the santonin-type lactone (5). However, attempted intermolecular cycloaddition by heating (1) with methyl but-3-enoate in a sealed tube at 200 °C for 26 h gave no cyclised product, the isomeric aldehyde (2) being the sole isolated product. As various other attempts to induce the intermolecular cycloaddition reaction also failed, our attention turned to a synthetic route involving an intramole cular cycloaddition. Thus, compound (1) was treated with but-3-enoyl chloride (3) in the presence of *NN*-dimethylaminopyridine (DMAP) in methylene dichloride at 0 °C to afford the ester (4), *m/e* 218 (M^+), which showed resonances for three olefinic protons in its n.m.r. spectrum and a carbonyl absorption at 1 725 cm^{-1} in its i.r. spectrum. The ester (4) was thermolysed by heating a toluene solution in a sealed tube at 180—200 °C for 48 h, to furnish the lactone (5) [*m/e* 218 (M^+), i.r. 1 770 cm^{-1} (five-membered lactone)] in 61% yield, *via* the well established *o*-quinodimethane intermediate (6). The stereochemistry of the BC-ring junction of (5) was determined to be *cis* on the basis of n.m.r. data,[11,12] in particular a benzylic methine proton resonance at δ 5.63, *J* 5 Hz. On consideration of the reaction mechanism, in which the *o*-quinodimethane intermediate (generated *in situ* by benzocyclobutene thermolysis) has the

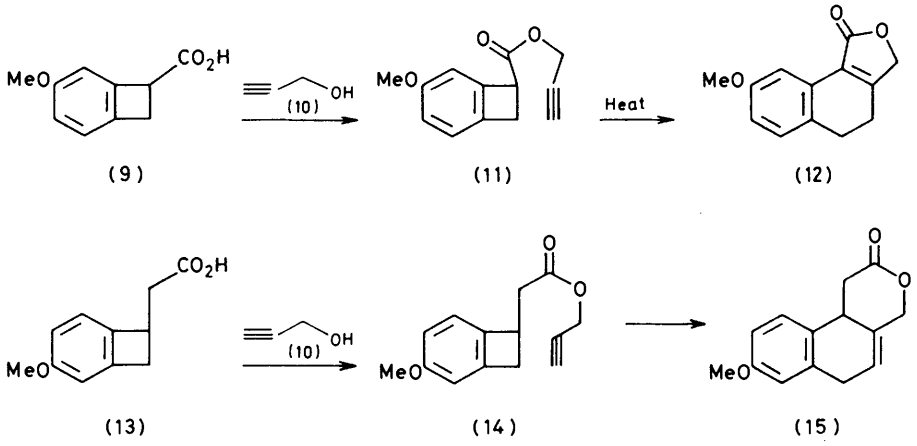


Scheme 1

E-configuration, this intramolecular cycloaddition is expected to produce the *trans*-BC-ring system (7). The fact that only the *cis*-product (5) was obtained can most reasonably be explained by assuming that the initially formed kinetically controlled product (7) is isomerised to (8), and that recyclisation then occurs to produce the thermodynamically more stable *cis*-BC-lactone (5). This lactone is expected to be a useful synthetic precursor for various natural santonin-type lactonic terpenes, such as frullanolide [13] and α- and β-cyclocostunolides.[14]

proton at δ 6.05 in its n.m.r. spectrum and a carbonyl absorption at 1 725 cm^{-1} in its i.r. spectrum.

Thus, intramolecular cycloaddition of *o*-quinodimethanes, *via* benzocyclobutene thermolysis, has been shown to provide a useful synthetic route to fused lactones, as demonstrated by our synthesis of the three terpenoidal (5), (12), and (15), which may exhibit pharmacological activity, and which are expected to be key intermediates in the synthesis of the known natural analogues.



SCHEME 2

For our synthesis of isodrimane-type lactonic terpenes, the acid [15] (9) was prepared from the corresponding nitrile by basic hydrolysis. Conversion into the acid chloride was carried out using oxalyl dichloride in methylene dichloride, and this product was treated with prop-2-ynyl alcohol (10) in the presence of *NN*-dimethylaminopyridine in methylene dichloride at 0 °C, to afford the ester (11) [*m/e* 216 (M^+), i.r. 3 310, and 1 730 cm^{-1} (acetylene and ester respectively)] in 98% yield. The ester (11) in toluene solution was heated in a sealed tube at 180—200 °C for 40 h to furnish the lactone (12), *m/e* 216 (M^+), which showed a conjugated five-membered lactone absorption at 1 745 cm^{-1} in its i.r. spectrum and did not show olefinic proton resonances in its n.m.r. spectrum. The structure of this fused lactone (12) was readily deduced from the spectroscopic data. Lactones of this type, *e.g.* isodrimenine and warburganal,[16] are known to exhibit interesting biological activities, and our synthetic lactone (12) is expected to be a key intermediate in syntheses of the above terpenes.

Finally, synthesis of the abietane-type [17] lactone (15) was carried out *via* the ester (14), *m/e* 230 (M^+), which was prepared in 96% yield by treatment of the acid chloride [derived from the acid [18] (13) with oxalyl dichloride in methylene dichloride] with prop-2-ynyl alcohol (10) in the presence of *NN*-dimethylaminopyridine in methylene dichloride at 0 °C. Thermolysis of the ester (14) in toluene solution in a sealed tube at 180—200 °C for 40 h gave the cyclised product (15), *m/e* 230 (M^+), in 76.5% yield, which exhibited one olefinic

EXPERIMENTAL

I.r. spectra were obtained with a Hitachi 260—10 spectrophotometer, n.m.r. spectra with a JEOL-PMX-60 spectrometer (tetramethylsilane as internal reference), and mass spectra with Hitachi M-52G and JEOL-JMS-2 spectrometers.

1,2-Dihydro-6-methoxybenzocyclobuten-1-yl But-3-enoate (4).—To a stirred solution of the cyclobutenol (1) (900 mg) and *NN*-dimethylaminopyridine (880 mg) in methylene dichloride (15 ml) at 0 °C was added but-3-enoyl chloride (570 mg) dropwise over 10 min. The mixture was then stirred at 0 °C for 1 h. The organic solution was washed with water, saturated sodium hydrogencarbonate solution, and water, and dried (Na_2SO_4). Evaporation gave a yellow oil which was purified by silica gel (30 g) column chromatography, using methylene dichloride as eluant, to afford the ester (4) as an oil (1.05 g, 73%); $\nu_{max.}$ ($CHCl_3$) 1 725 (C=O) cm^{-1}; δ($CDCl_3$) 3.83 (3 H, s, OMe), 5.20 br (2 H, d, *J* 15 Hz, CH=CH_2), and 6.12 (1 H, m, ArC*H*–O); *m/e* 218 (M^+).

Thermolysis of the Ester (4).—A solution of the ester (4) (1 g) in dry toluene (5 ml) was heated in a sealed tube at 180—200 °C for 48 h. After evaporation, the crystalline product was recrystallised to give the *lactone* (5) (610 mg, 61%) as needles, m.p. 167—168 °C (methanol) (Found: C, 71.8; H, 6.45. $C_{13}H_{14}O_3$ requires C, 71.55; H, 6.45%); $\nu_{max.}$ ($CHCl_3$) 1 770 cm^{-1} (C=O); δ($CDCl_3$) 3.88 (3 H, s, OMe) and 5.63 (1 H, d, *J* 5 Hz, ArC*H*–O–); *m/e* 218 (M^+).

Prop-2-ynyl 1,2-Dihydro-5-methoxybenzocyclobutene-1-carboxylate (11).—To a solution of the acid (9) (1 g) in dry methylene dichloride was added oxalyl dichloride (1 ml) and the mixture refluxed for 1 h. Excess of reagent and the solvent were removed *in vacuo* to give the acid chloride, which, without further purification, was added to a stirred

solution of prop-2-ynyl alcohol (380 mg) and *NN*-dimethylaminopyridine (750 mg) in methylene dichloride (10 ml) at 0 °C. The mixture was stirred at 0 °C for 1 h, washed with water, saturated sodium hydrogencarbonate solution, 10% hydrochloric acid solution, and water, and dried (Na_2SO_4). The solvent was removed to give a reddish oil which was chromatographed on silica gel (30 g), using methylene dichloride as eluant, to afford the ester (11) (1.2 g, 98%) as a colourless oil; $\nu_{max.}$ ($CHCl_3$) 3 310 (C≡CH) and 1 730 cm^{-1} (C=O); δ($CDCl_3$) 2.42 (1 H, t, *J* 2 Hz, C≡CH), 3.38 (2 H, d, *J* 4 Hz, ArCH_2), 3.73 (3 H, s, OMe), 4.23 (1 H, t, *J* 4 Hz, ArC*H*–CO–), and 4.70 (2 H, d, *J* 2 Hz, CO_2CH_2); *m/e* 216 (M^+).

Thermolysis of the Ester (11).—A solution of the ester (11) (1 g) in dry toluene (5 ml) has heated in a sealed tube at 180—200 °C for 40 h. Removal of the solvent gave a yellow oil which was chromatographed on silica gel (20 g), using methylene dichloride as eluant, to afford the *lactone* (12) (420 mg, 42%) as prisms, m.p. 123—124 °C (methanol) (Found: C, 72.2; H, 5.7. $C_{13}H_{12}O_3$ requires C, 72.2; H, 5.6%); $\nu_{max.}$ ($CHCl_3$) 1 745 cm^{-1} (C=O); δ($CDCl_3$) 2.33—3.02 (4 H, m, ArCH_2CH_2), 3.80 (3 H, s, OMe), 4.85 (2 H, s, CH_2OCO), 6.77 (1 H, dd, *J* 2 and 8 Hz, ArH), 7.12 (1 H, d, *J* 8 Hz, ArH), and 7.70 (1 H, d, *J* 2 Hz, ArH); *m/e* 216 (M^+).

Prop-2-ynyl 1,2-Dihydro-4-methoxybenzocyclobuten-1-ylacetate (14).—A mixture of the benzocyclobutenylacetic acid (13) (2 g), oxalyl dichloride (2 ml), and dry methylene dichloride (20 ml) was refluxed for 1 h. Excess of reagent and the solvent were distilled off to afford the acid chloride, which was then treated with prop-2-ynyl alcohol (700 mg), in a similar manner to the preparation of (11), to give the ester (14) (2.3 g, 96%) as a colourless oil; $\nu_{max.}$ ($CHCl_3$) 3 325 (C≡CH) and 1 740 cm^{-1} (C=O); δ($CDCl_3$) 2.50 (1 H, t, *J* 2 Hz, C≡CH), 2.70 (2 H, d, *J* 8 Hz, ArCHCH_2CO), 3.73 (3 H, s, OMe), 4.73 (2 H, d, *J* 2 Hz, CO_2CH_2), 6.72 (1 H, s, ArH), 6.78 (1 H, dd, *J* 2 and 9 Hz, ArH), and 7.50 (1 H, d, *J* 9 Hz, ArH); *m/e* 230 (M^+).

Thermolysis of the Ester (14).—Thermolysis of the ester (14) (1 g) was carried out as for the ester (11), to furnish the *lactone* (15) (765 mg, 76.5%) as prisms, m.p. 136—137 °C (methanol) (Found: C, 72.75; H, 6.3. $C_{14}H_{14}O_3$ requires C, 73.0; H, 6.15%); $\nu_{max.}$ ($CHCl_3$) 1 725 cm^{-1} (C=O); δ($CDCl_3$) 2.47 [1 H, dd, *J* 12 and 17 Hz, ArCHC(H)*H*–CO–], 3.27 [1 H, dd, *J* 5 and 17 Hz, ArCHC(H)*H*–CO–], 3.30—3.70 (3 H, m, ArCH_2C=C and Ar$CH$$CH_2$), 3.80 (3 H, s, OMe), 4.88 (2 H, s, CO_2CH_2), 6.05 br (1 H, s, olefinic H), 6.73 br (1 H, s, ArH), 6.82 (1 H, dd, *J* 2 and 8 Hz, ArH), and 7.10 (1 H, d, *J* 8 Hz, ArH); *m/e* 230 (M^+).

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