Synthesis of Some Cyclopropyl-γ-lactones as Analogues of Cytotoxic α-Methylene-γ-lactones

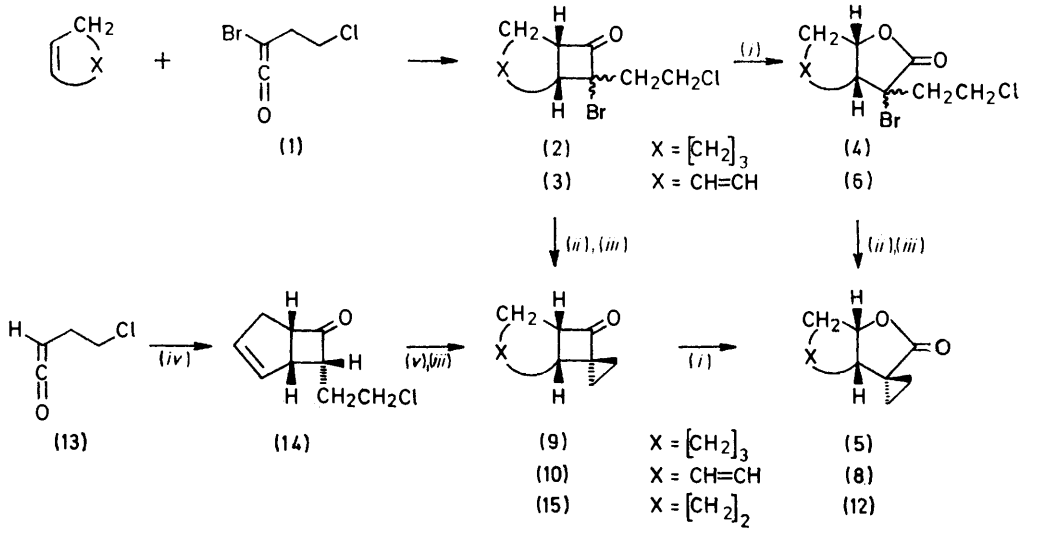
By S. Mubarik Ali, Thomas V. Lee, and Stanley M. Roberts,* The Ramage Laboratories, Department of Chemistry and Applied Chemistry, University of Salford, Salford M5 4WT
Roger F. Newton,* External Projects Department, Allen and Hanburys Ltd., Ware, Herts., SG12 ODJ

Five novel α-cyclopropyl-γ-lactones [(5), (8), (12), (18), and (19)] have been prepared. The spirocyclopropyl lactones (5), (8), and (12) were prepared by addition of a keten to an alkene followed by a series of reactions involving reduction, 1,4-dehydrohalogenation, and Baeyer–Villiger oxidation. The optimum order for the last three steps depends upon the structure of the final product. The 2-oxatricyclo[3.3.0.0^{4,6}]octanones (18) and (19) were prepared in high yield from the corresponding 2-bromobicycloheptanone by Baeyer–Villiger oxidation and dehydrobromination.

A LARGE number of naturally occurring terpenes that display anti-tumour activity have been found to possess an α-methylene-γ-lactone unit as part of their structure.[1] The presence of this unit has been shown to be vital for marked biological activity and it is suggested that the α-methylene-γ-lactone moiety acts as an electrophilic trap for the reactive thiol groups in macromolecular species that are essential for tumour growth.[2]

RESULTS AND DISCUSSION

Our most successful routes to the required α-spirocyclopropyl-γ-lactones involve the initial cycloaddition of the dihalogenoketen (1) to cyclohexene or cyclopentadiene to give a mixture of bicyclic compounds (2) and (3), respectively (Scheme 1). Baeyer–Villiger oxidation of the dihalogeno-ketones (2) gave the corresponding dihalogeno-lactones (4) (70%) from which the desired



SCHEME 1 (*i*) *m*-chloroperoxybenzoic acid; (*ii*) Zn–HOAc; (*iii*) diazabicyclo[4.3.0]non-5-ene; (*iv*) cyclopentadiene; (*v*) H_2,Pd

Notable syntheses of the complex naturally occurring α-methylene lactones have been achieved [3] but they are inevitably multi-stage processes and provide only limited quantities of material. On the other hand, simpler, more readily available molecules possessing the α-methylenebutyrolactone system have been prepared by a number of research groups [4] but, unfortunately, these simple analogues of the naturally occurring compounds proved to be as toxic to normal cells as to lymphoblastic leukaemia cells.[5]

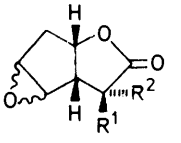
We considered that a greater selectivity of biological action for the simpler molecules might be achieved by substitution of a cyclopropyl ring for the *exo*-methylene group since such a mono-activated cyclopropyl system is known to undergo homoconjugate addition with only the more highly reactive nucleophiles, *e.g.* thiols.[6]

spirocyclopropyl lactone (5) was obtained by dehalogenation and base-treatment in quantitative yield.

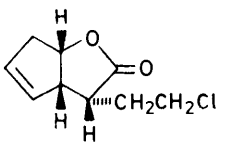
The isomeric ketones (3) were separated by column chromatography and fractional distillation. The *endo*-bromo-isomer gave only the *endo*-4-bromo-lactone (6) on peracid oxidation; Baeyer–Villiger oxidation of the *exo*-bromo-isomer (identified by the relatively low-field position of the signal due to H-5 in the n.m.r. spectrum [7]), proceeded more slowly and a mixture of the *exo*-4-bromo-lactone (6) (50%) and the epoxy-lactones (7) (25%) was obtained. The two bromo-lactones (6) were independently debrominated and dehydrochlorinated to give the spiro-lactone (8) in near quantitative yield in both cases.

In an alternative procedure the dihalogeno-ketones (2) and (3) afforded the tricyclic ketones (9) and (10),

respectively, in almost quantitative yield on dehalogenation and cyclization. Peracid oxidation of the ketone (9) gave the α-spirocyclopropyl-γ-lactone (5) only, as expected, while oxidation of the unsaturated ketone (10) yielded a mixture of the lactone (8) (20%) and the epoxy-lactone (11) (40%).



(7) R^1 = Br; R^2 = CH_2CH_2Cl
(11) R^1;R^2 = $-CH_2CH_2-$



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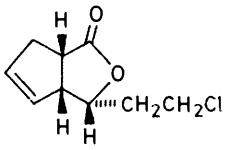
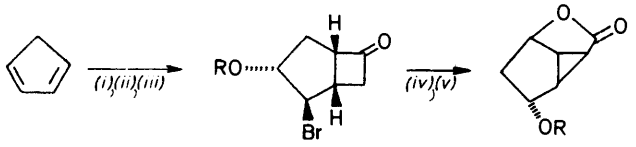


(17)

The tricyclic lactone (12) was prepared in the following way. The halogenoketen (13) did not react with cyclopentene, but with the more receptive cyclopentadiene reaction did take place, and a modest yield (25%) of the ketone (14) was obtained. Catalytic reduction of the alkene unit followed by base-induced cyclization gave the ketone (15) which was oxidized selectively by *m*-chloroperoxybenzoic acid to furnish the desired lactone (12). Note that Baeyer–Villiger oxidation of the ketone (14) was non-selective forming a mixture of the 2- and 3-oxabicyclo-octanones [(16) and (17), respectively] in the



(20) R = Me (18)
(21) R = MeCO (19)

SCHEME 2 (*i*) $Cl_2C{=}C{=}O$; (*ii*) Zn–HOAc; (*iii*) *N*-bromoacetamide, ROH; (*iv*) $MeCO_3H$; (*v*) $KOBu^t$

ratio 2 : 3. The lactone (16) was purified by chromatography and was converted into the spiro-lactone (8) in quantitative yield using diazabicyclononene.

We have recently shown that tricyclo[3.2.0.$0^{2,7}$]-heptan-6-ones are attacked rapidly by thiolates and other nucleophiles.[8] The related lactones (18) and (19) should be less susceptible to attack by nucleophiles since the inherent strain present in the tricycloheptanones is lessened by the inclusion of the ring-oxygen atom. Hence the lactones (18) and (19) might be expected to show selectivity when acting as electrophilic traps through homoconjugate addition reactions. A high-yield route to the lactones (18) and (19) is illustrated in Scheme 2. The bromobicycloheptanones (20) and (21) were prepared as described previously,[9] and were converted into the corresponding 2-oxatricyclo-octanones (18) and (19) by Baeyer–Villiger oxidation and t-butoxide-promoted dehydrohalogenation.

Ready access to the cyclopropyl-γ-lactones (5), (8), (12), (18), and (19) will allow an evaluation of the biological activity and chemical reactivity of these systems. The results of these studies will be reported elsewhere.

EXPERIMENTAL

^1H N.m.r. spectra were recorded with a Varian EM-360 spectrometer using deuteriochloroform as solvent. I.r. spectra were obtained with a Perkin-Elmer 257 spectrometer for neat films unless otherwise stated. M.p.s were taken by the capillary-tube method; b.p.s reported are oven temperatures at distillation. Silica gel MFC was used for column chromatography. Anhydrous sodium sulphate was used as a drying agent for solutions in organic solvents.

General Procedures.—(*i*) *Preparation of the bicyclic ketones.* To a solution of the appropriate acid chloride (1 mol equiv.) and freshly distilled cyclopentadiene or cyclohexene (6 mol equiv.) in dry hexane was added dropwise a solution of triethylamine (1.1 mol equiv.) in dry hexane with cooling and stirring. After the addition was complete the reaction mixture was stirred at room temperature for 2 h. Filtration, evaporation of the solvent followed by purification by column chromatography yielded the required bicyclic ketone.

(*ii*) *Baeyer–Villiger oxidation.* To a solution of the bicyclic ketone in chloroform was slowly added equimolar quantities of *m*-chloroperoxybenzoic acid and sodium hydrogencarbonate. The reaction mixture was stirred at room temperature overnight, unless otherwise stated. The mixture was washed with sodium sulphite solution (10%) and then saturated sodium hydrogencarbonate solution. The organic fraction was dried, the solvent was evaporated off, and purification was carried out by column chromatography.

(*iii*) *Debromination.* The α-bromobicyclic ketone or lactone in diethyl ether was stirred with powdered zinc in a few drops of glacial acetic acid. After 4 h at room temperature the reaction mixture was filtered. The ether solution was washed with water, dried, and evaporation of the solvent yielded the corresponding debrominated bicyclic ketone or lactone.

(*iv*) *Dehydrochlorination leading to spirocyclopropyl bicyclic ketones or lactones.* A solution of the bicyclic ketone or lactone in dry acetonitrile was treated with an equimolar amount of 1,5-diazabicyclo[4.3.0]non-5-ene and the reaction mixture was refluxed for 5 h. The solvent was evaporated off, and the residue was extracted with diethyl ether. The ether extract was washed with water, dried, and the solvent evaporated off. The product was purified by t.l.c.

(*v*) *Preparation of 2-oxatricyclo*[3.3.0.$0^{4,6}$]*octan-3-ones.* To a solution of freshly prepared potassium t-butoxide (1.66 equiv.) in benzene at 0 °C was slowly added, with stirring, the 2-oxabicyclo[3.3.0]octan-3-one (1 equiv.) in benzene. This formed a brown solution which was stirred at ambient temperature for 18 h. Ether was then added, the solution was stirred for a further 2 h, and filtration gave a colourless solution which on evaporation of the solvent furnished the product.

8-Bromo-8-(2-chloroethyl)bicyclo[4.2.0]*octan-7-ones* (2).—These were obtained from cyclohexene (100 g) and 2-bromo-4-chlorobutyryl chloride (45 g) as a colourless oil (5%).

7-Bromo-7-(2-chloroethyl)bicyclo[3.2.0]*hept-2-en-6-ones* (3).

—From the reaction of cyclopentadiene (170 g) and 2-bromo-4-chlorobutyryl chloride (87 g) was obtained a mixture of the two isomeric *bicyclic ketones* (3), (70%, 55 : 45 ratio). Separation was achieved by column chromatography to give 7-exo-*bromo*-7-endo-(2-*chloroethyl*)*bicyclo*[3.2.0]*hept*-2-*en*-6-*one* as a colourless oil, b.p. 78—82 °C (0.5 mmHg); $\nu_{max.}$ 2 940, 1 780, 1 450, and 1 160 cm^{-1}; δ 6.0 (2 H, m, H-2 and H-3), 4.4 (1 H, ddd, *J* 7, 7, and 2 Hz, H-5), 3.9 (1 H, m, H-1), 3.8 (2 H, t, *J* 8 Hz, CH_2Cl), 2.6 (2 H, m, H_2-4), and 2.2 (2 H, t, *J* 8 Hz, CH_2CH_2Cl). (Found: C, 43.0; H, 4.1. $C_9H_{10}BrClO$ requires C, 43.3; H, 4.0%): and 7-endo-*bromo*-7-exo-(2-*chloroethyl*)*bicyclo*[3.2.0]*hept*-2-*en*-6-*one* as a colourless oil, b.p. 84—86 °C (0.5 mmHg); $\nu_{max.}$ 2 950, 1 775, and 1 450 cm^{-1}, δ 5.8 (2 H, m, H-2 and H-3), 4.1 (1 H, ddd, *J* 8, 8, and 2 Hz, H-5), 3.7 (3 H, m, H-1 and CH_2Cl), and 2.6 (4 H, m, H_2-4 and CH_2CH_2Cl) (Found: C, 43.0; H, 4.0. $C_9H_{10}BrClO$ requires C, 43.3; H, 4.0%).

4-exo-*Bromo*-4-endo-(2-*chloroethyl*)-2-*oxabicyclo*[3.3.0]*oct*-6-*en*-3-*one* (6).—This was obtained by the Baeyer–Villiger oxidation of the corresponding bicyclic ketone (3) (1.0 g), as a colourless oil (4 days, 50%), b.p. 89—91 °C (0.3 mmHg); $\nu_{max.}$ 1 780, 1 250, and 1 190 cm^{-1}; δ 6.0 (2 H, m, H-6 and H-7), 5.25 (1 H, m, H-1), 4.0 (3 H, m, H-5 and CH_2Cl), and 2.5 (4 H, m, H_2-4 and CH_2CH_2Cl) (Found: C, 40.35; H, 3.8. $C_9H_{10}BrClO_2$ requires C, 40.7; H, 3.8%). The above reaction also yielded the *epoxy-lactones* (7) as a colourless oil (25%); $\nu_{max.}$ 2 950, 1 775, 1 430, and 1 180 cm^{-1}; δ 5.1 (1 H, m, H-1), 4.2—3.6 (4 H, m, H-6, H-7, and CH_2Cl), 3.4 (1 H, d, *J* 5 Hz, H-5), and 2.8—2.1 (4 H, m, H_2-8 and CH_2CH_2Cl).

4-endo-*Bromo*-4-exo-(2-*chloroethyl*)-2-*oxabicyclo*[3.3.0]*oct*-6-*en*-3-*one* (6).—This was obtained from the corresponding bicyclic ketone (1.0 g) as a colourless oil (70%), b.p. 92—95 °C (0.2 mmHg); $\nu_{max.}$ 2 950, 1 770, and 1 450 cm^{-1}; δ 5.8 (2 H, m, H-6 and H-7), 5.25 (1 H, m, H-1), 3.7 (3 H, m, H-5 and CH_2Cl), and 2.6 (4 H, m, H_2-8 and CH_2CH_2Cl).

7-endo-(2-*Chloroethyl*)*bicyclo*[3.2.0]*hept*-2-*en*-6-*one* (14).—(*a*) The reaction of cyclopentadiene (66.0 g) and 4-chlorobutyryl chloride (71.0 g) yielded the required *bicyclic ketone* (14) as a colourless oil (25%), b.p. 92—93 °C (0.7 mmHg); $\nu_{max.}$ 2 940, 1 750, and 1 445 cm^{-1}; δ 6.0 (2 H, m, H-2 and H-3), 3.8 (5 H, m, H-1, H-5, H-7, and CH_2Cl), 2.6 (2 H, m, H_2-4), and 2.0 (2 H, m, CH_2CH_2Cl) (Found: M^+, 170.0490. $C_9H_{11}ClO$ requires *M*, 170.0498). (*b*) Debromination of the bicyclic ketones (3) (1.0 g), with Zn–acetic acid, gave the above bicyclic ketone in quantitative yield.

4-endo-(2-*Chloroethyl*)-2-*oxabicyclo*[3.3.0]*oct*-6-*en*-3-*one* (16).— (*a*) From the oxidation of the bicyclic ketone (14) (1.5 g) the *lactone* (16) was obtained as a colourless oil (40%), b.p. 98—100 °C (0.5 mmHg); $\nu_{max.}$ 2 950, 1 730, and 1 180 cm^{-1}; δ 5.8 (2 H, m, H-6 and H-7), 5.0 (1 H, m, H-1), 3.8 (2 H, t, *J* 6 Hz, CH_2Cl), 3.6 (1 H, m), 3.0 (1 H, m), 2.7 (2 H, m, H_2-8), and 2.1 (2 H, m, CH_2CH_2Cl) (Found: M^+, 186.0450. $C_9H_{11}ClO_2$ requires *M*, 186.0447). From the above reaction the isomeric *lactone* (17) was also obtained as a colourless oil (60%), b.p. 125—127 °C (0.7 mmHg); $\nu_{max.}$ 2 920, 1 740, and 1 180 cm^{-1}; δ 6.1—5.5 (2 H, m, H-6 and H-7), 4.8 (1 H, dt, *J* 7 and 7 Hz, H-4), 3.8 (2 H, t, *J* 7 Hz, CH_2Cl), 3.65 (1 H, m, H-1), 3.4 (1 H, dt, *J* 7 and 3 Hz, H-5), 2.7 (2 H, m, H_2-8), 2.1 (2 H, dt, *J* 7 and 7 Hz, CH_2CH_2Cl) (Found: M^+, 186.0446. $C_9H_{11}ClO_2$ requires *M*, 186.0447). (*b*) Debromination of the lactones (6) (0.6 g) gave the *lactone* (16) in quantitative yield.

8-*Oxo*-7-*oxabicyclo*[4.3.0]*nonane*-9-*spirocyclopropane* (5).—(*a*) Debromination and dehydrochlorination of the ketones (2) (0.8 g) yielded the *tricyclic ketone* (9) as a colourless oil (90%); $\nu_{max.}$ 2 920, 2 840, 1 760, 1 450, and 1 030 cm^{-1}; δ 3.4 (1 H, m, H-6), 2.5 (1 H, m, H-1), 1.6 (8 H, m, H_2-2, H_2-3, H_2-4, and H_2-5), and 1.2 (4 H, m, cyclopropane). Baeyer–Villiger oxidation of the ketone (9) (0.15 g) gave the *ketone* (5) as a colourless oil (95%), b.p. 108—110 °C (0.7 mmHg); $\nu_{max.}$ (Nujol) 3 060, 2 990, 1 750, and 1 160 cm^{-1}; δ 4.7 (1 H, m, H-6), 2.3—1.3 (9 H, m, H-1, H_2-2, H_2-3, H_2-4, and H_2-5), and 1.1 (4 H, m, cyclopropane) (Found: M^+, 166.0993. $C_{10}H_{14}O_2$ requires *M*, 166.0993). (*b*) Baeyer–Villiger oxidation of the ketone (2) (1.0 g) gave the lactone (4) (70%). These lactones were debrominated, and dehydrochlorinated to give the *ketone* (5) (95%).

3-*Oxo*-2-*oxabicyclo*[3.3.0]*oct*-6-*ene*-3-*spirocyclopropane* (8).—(*a*) Dehydrochlorination of 4-*endo*-(2-chloroethyl)-2-oxabicyclo[3.3.0]oct-6-en-3-one (16) (0.4 g) yielded the required *lactone* (8) as a colourless oil (95%), b.p. 104 °C (0.4 mmHg), $\nu_{max.}$ 2 950, 1 710, 1 360, and 1 130 cm^{-1}; δ 5.8 (2 H, m, H-6 and H-7), 5.2 (1 H, m, H-1), 3.2 (1 H, m, H-5), 2.75 (2 H, m, H_2-8), and 1.1 (4 H, m, cyclopropane) (Found: M^+, 150.0679. $C_9H_{10}O_2$ requires *M*, 150.0680). (*b*) Dehydrochlorination of the bicyclic ketone (14) (0.3 g) yielded the *tricyclic ketone* (10) as a colourless oil (95%), b.p. 40 °C (0.08 mmHg); $\nu_{max.}$ 2 910, 2 830, 1 760, 1 340, and 1 065 cm^{-1}; δ 5.9 (2 H, m, H-2 and H-3), 3.9 (1 H, ddd, *J* 8, 7, and 4 Hz, H-5), 3.5 (1 H, m, H-1), 2.6 (2 H, m, H_2-4), and 1.1 (4 H, m, cyclopropane) (Found: M^+, 134.0731. $C_9H_{10}O$ requires *M*, 134.0731). The tricyclic ketone (10) (0.3 g) on Baeyer–Villiger oxidation gave the *lactone* (8) (20%), and the *epoxy-lactone* (11) as a colourless oil (40%), b.p. 105 °C (0.5 mmHg); $\nu_{max.}$ 3 090, 3 030, 1 760, and 1 100 cm^{-1}; δ 5.0 (1 H, ddd, *J* 8, 8, and 3 Hz, H-1), 3.5 (2 H, m, H-6 and H-7), 3.0 (1 H, d, *J* 8 Hz, H-5), 2.2 (2 H, m, H_2-8), and 1.1 (4 H, m, cyclopropane) (Found: M^+, 166.0626. $C_9H_{10}O_3$ requires *M*, 166.0629).

3-*Oxo*-2-*oxabicyclo*[3.3.0]*octane*-4-*spirocyclopropane* (12).—Catalytic hydrogenation of the bicyclic ketone (14) (1.1 g) in the presence of Pd–C (5%) yielded 7-endo-(2-*chloroethyl*)*bicyclo*[3.2.0]*heptan*-6-*one* as a colourless oil (96%), b.p. 95—100 °C (0.4 mmHg); $\nu_{max.}$ 2 950, 2 860, 1 740, and 1 450 cm^{-1}; δ 3.65 (2 H, t, *J* 7 Hz, CH_2Cl), 3.5 (1 H, m, H-5), 3.0 (1 H, m, H-7), 2.2—1.2 (9 H, m, H-1, H_2-2, H_2-3, H_2-4 and CH_2CH_2Cl) (Found: M^+, 172.0652. $C_9H_{13}ClO$ requires *M*, 172.0654). This ketone (0.9 g) on dehydrochlorination gave the *tricyclic ketone* (15) as a colourless oil (95%); $\nu_{max.}$ 2 950, 2 830, 1 765, 1 445, and 1 350 cm^{-1}; δ 3.6 (1 H, m, H-5), 2.9 (1 H, m, H-1), 1.8 (6 H, m, H_2-2, H_2-3, and H_2-4), and 1.2 (4 H, m, cyclopropane). Baeyer–Villiger oxidation of the ketone (15) (0.5 g) yielded the *ketone* (12) as a colourless oil (96%), b.p. 92—95 °C (0.8 mmHg); $\nu_{max.}$ 3 000, 2 870, 1 760, 1 380, 1 150, and 990 cm^{-1}; δ 5.1 (1 H, m, H-1), 2.7 (1 H, m, H-5), 1.8 (6 H, m, H_2-6, H_2-7, and H_2-8), and 1.0 (4 H, m, cyclopropane) (Found: M^+, 152.0837. $C_9H_{12}O_2$ requires *M*, 152.0837).

7-endo-*Methoxy*-2-*oxatricyclo*[3.3.0.$0^{4,6}$]*octan*-3-*one* (18).—Baeyer–Villiger oxidation of 2-*exo*-bromo-3-*endo*-methoxybicyclo[3.2.0]heptan-6-one (20) (1.5 g) yielded 6-exo-*bromo*-7-endo-*methoxy*-2-*oxabicyclo*[3.3.0]*octan*-3-*one* as white crystals from light petroleum–chloroform (10 : 1) (98%), m.p. 93—95 °C; $\nu_{max.}$ (Nujol) 2 960, 1 780, 1 200, and 1 090 cm^{-1}; δ 5.1 (1 H, dt, *J* 2 and 8 Hz, H-1), 4.18 (1 H, m, H-6), 4.0 (1 H, m, H-7), 3.35 (1 H, m, H-5), 3.3 (3 H, s, OMe), and 2.95—2.25 (4 H, m, H_2-4 and H_2-8) (Found: C, 40.7; H, 4.8. $C_8H_{11}BrO_3$ requires C, 40.9; H, 4.7%).

This lactone (1.0 g) on dehydrobromination using potassium t-butoxide gave the required 7-endo-*methoxy*-2-*oxatricyclo*[3.3.0.0^{4,6}]*octan*-3-*one* (18) as a white solid (95%), b.p. 90 °C (0.001 mmHg); $\nu_{max.}$(Nujol) 2 920 and 1 760 cm^{-1}; δ 5.3 (1 H, m, H-1), 4.0 (1 H, m, H-7), 3.3 (3 H, s, OMe), 3.12 (1 H, m, H-5), 2.55 (2 H, m, H-4 and H-6), and 2.15 (2 H, m, H_2-8) (Found: C, 62.15; H, 6.5. $C_8H_{10}O_3$ requires C, 62.3; H, 6.5%).

7-endo-*Acetoxy*-2-*oxatricyclo*[3.3.0.0^{4,6}]*octan*-3-*one* (19).—The bicyclic ketone (21) (1.5 g) on oxidation gave 7-endo-*acetoxy*-6-exo-*bromo*-2-*oxabicyclo*[3.3.0]*octan*-3-*one* as white crystals (97%), m.p. 81—83 °C; $\nu_{max.}$(Nujol) 2 960, 1 770, and 1 740 cm^{-1}; δ 5.15 (2 H, m, H-1 and H-7), 4.11 (1 H, d, *J* 2 Hz, H-6), 3.32 (1 H, m, H-5), 2.95—2.2 (4 H, H_2-4 and H_2-8), and 2.05 (3 H, s, COMe) (Found: C, 41.2; H, 4.4. $C_9H_{11}BrO_3$ requires C, 41.1; H, 4.2%).

Dehydrobromination of the above lactone (1.0 g) with potassium t-butoxide yielded the required 7-endo-*acetoxy*-2-*oxatricyclo*[3.3.0.0^{4,6}]*octan*-3-*one* (19) as a white solid (98%), m.p. 80—82 °C, $\nu_{max.}$(Nujol) 2 960, 1 770, and 1 750 cm^{-1}; δ 5.4 (1 H, m, H-1), 4.88 (1 H, m, H-7), 3.1 (1 H, m, H-5), 2.5 (2 H, m, H-4 and H-6), 2.12 (2 H, m, H_2-8), and 1.95 (3 H, s, COMe) (Found: C, 59.1; H, 5.6. $C_9H_{10}O_4$ requires C, 59.3; H, 5.5%).

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