A Convenient Synthesis of Cyclic Ether-lactones from Olefinic Hydroxy-acids

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Silver salts of the unsaturated hydroxy-acids (4)—(7) were converted directly into the cyclic ether-lactones (9)—(13), respectively, on treatment with iodine followed by silver acetate.

We have previously reported the regio- and stereo-specific cyclisation of olefinic dicarboxylic acids upon treatment of their silver salts with iodine followed by silver ion, leading to di-γ-lactones.[1] We also described [1] the total synthesis of canadensolide (1), an antifungal mould metabolite,[2] which involved stereospecific cyclisation of the olefinic dicarboxylic acid (2) as the key step. We were then interested in extending this reaction to olefinic hydroxy-acids, anticipating that the reaction would give cyclic ether-lactones directly.

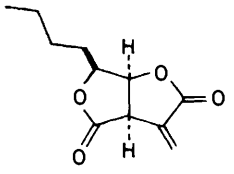
The reaction might be expected to occur as shown in the Scheme. Our previous discussion on the double lactonisation of olefinic dicarboxylic acids [1] allowed us to presume that with iodine, the olefinic hydroxy-carboxylate anion (A) would give the intermediate hydroxy-iodolactone (B), which would then cyclise stereospecifically

[1] M. Kato, M. Kageyama, R. Tanaka, K. Kuwahara, and A. Yoshikoshi, *J. Org. Chem.*, 1975, **40**, 1932.

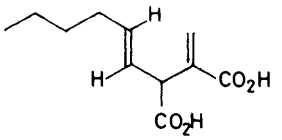
[2] N. J. McCorkindale, J. L. C. Wright, P. W. Brian, S. M. Clarke, and S. A. Hutchinson, *Tetrahedron Letters*, 1968, 727.

(S_N2) to the cyclic ether-lactone (C) on treatment with a halogen abstractor such as silver ion. Such a cyclic ether-lactone structure has been found in certain natural products, *e.g.* corianin [3] (3), and a reaction of the foregoing type would be applicable to the synthesis of such a compound from an appropriate unsaturated hydroxy-acid.

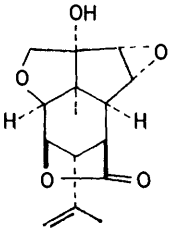
In conventional iodo-lactonisation reactions the alkali



(1)

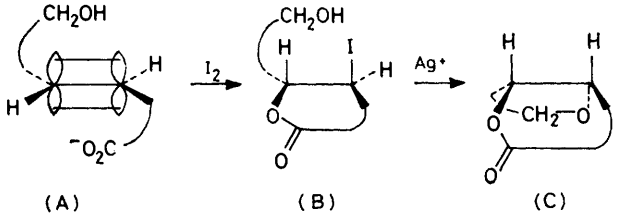


(2)



(3)

metal salt of the olefinic hydroxy-acid is used in the initial step (A) ⟶ (B).[4] However, we used silver carboxylates since silver salts of the olefinic dicarboxylic acids afforded better yields of dilactones than did their sodium salts.[1] Dimethylformamide was selected as the solvent for similar reasons.



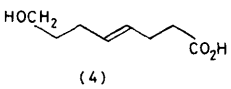
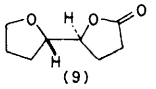
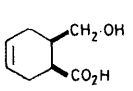
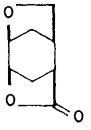
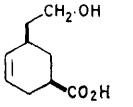
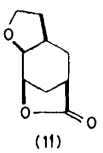
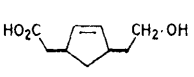
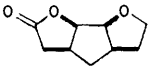
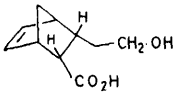
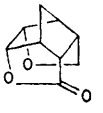
(A) (B) (C)

SCHEME

The hydroxy-acids (4)—(7) listed in the Table [of which (4), (5), and (7) were characterized] were subjected to this reaction. Compounds (4) and (7) were obtained by partial reduction of the corresponding diesters (14a) [5] and (15a) [6] with lithium aluminium hydride to the hydroxy-esters (14b) and (15b), followed by alkaline hydrolysis, and (6) was prepared from the formyl ester (16a) [1] by reduction ($NaBH_4$) to (16b) and hydrolysis. Compounds (5) and (8) were derived from the lactones (17) [7] and (18) obtained by reduction ($NaBH_4$) of the corresponding anhydrides.

Iodine was added to the dried silver salts of these hydroxy-acids suspended in dimethylformamide at room temperature; after a while silver acetate was added and the mixture was warmed. Work-up followed by recrystallisation or chromatographic separation gave the cyclic ether-lactones (9)—(13) in moderate to high yields (Table).

The reaction proceeded highly stereospecifically as

Hydroxy-acid	Cyclic ether-lactone	Yield (%)
 (4)	 (9)	58
 (5)	 (10)	37 (58 [a])
 (6)	 (11)	41 [b]
 (7)	 (12)	44 (55 [a])
 (8)	 (13)	61 [b]

[a] Values in parentheses represent yields based on the silver salts. [b] Based on the hydroxy-ester (16b) or the hydroxy-lactone (15b).

exemplified by the lack of formation of the diastereoisomer of (9) in the reaction of (4). Compound (11) has a structure identical with that of the cyclic ether-lactone portion of the structure of corianin (3).

EXPERIMENTAL

I.r. spectra were recorded on a Hitachi EPI-32 spectrophotometer, and unless otherwise indicated a JEOL C-60-HL (60 MHz) spectrometer was used for n.m.r. measurements (solvent $CDCl_3$; Me_4Si as internal standard).

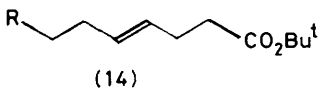
General Procedure for the Preparation of Cyclic Ether-lactones.—A methanolic solution of the hydroxy-acid [(4), (5), or (7)] was neutralized with aqueous sodium hydroxide, and a small excess of aqueous silver nitrate was added. The precipitated silver salt was filtered off, washed with a small quantity of cold water and ether, and then dried *in vacuo* at room temperature in the dark. The silver salts of (6) and

[3] T. Okuda and T. Yoshida, *Tetrahedron Letters*, 1971, 4499.
[4] H. O. House, 'Modern Synthetic Reactions,' 2nd edn., Benjamin, Menlo Park, California, 1972, pp. 443—444.
[5] K. Shindo, K. Sei, and N. Nozaki, *J. Org. Chem.*, 1962, **27**, 2681.
[6] P. G. Gassman and X. Creary, *J.C.S. Chem. Comm.*, 1972, 1214.
[7] B. Belleau and J. Puranen, *Canad. J. Chem.*, 1965, **43**, 2551; see also H. Christol, A. Douche, and F. Plenat, *Bull. Soc. chim. France*, 1966, 2535.

(8) were prepared directly, without isolation of the hydroxy-acids, by alkaline hydrolysis of (16b) and (18), respectively, followed by addition of aqueous silver nitrate.

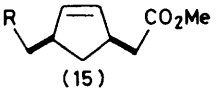
The silver salts (1—2 mmol) thus obtained were suspended in dry dimethylformamide (3 ml per mmol), and iodine (2.4 atom equiv.) was added with stirring at room temperature in the dark. After stirring for 0.5—1 h, silver acetate (1.33 equiv.) was added, and the mixture was stirred at 60—70° for *ca.* 20 h,* and then filtered. The filtrates were concentrated *in vacuo* at 60 °C. The residues were dissolved in chloroform and washed with water, and dried. The products obtained by evaporation were purified by recrystallisation or chromatography.

4-(*Tetrahydrofuran-2-yl*)*butan-4-olide* (9), purified by preparative t.l.c. (ether) had m.p. 35—36° (needles), $\nu_{max.}$ (KBr)



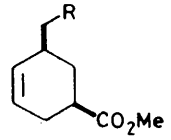
(14)

a; R = CO_2Bu^t
b; R = CH_2·OH

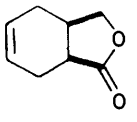


(15)

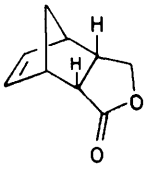
a; R = CO_2Me
b; R = CH_2·OH



(16)



(17)



(18)

a; R = CHO
b; R = CH_2·OH

1 770 and 1 170 cm^{-1}, δ 1.8—2.8 (8 H, m), 3.33 (3 H, m, CH_2·O·CH), and 4.50 (1 H, m, CH·O·CO) (Found: C, 61.4; H, 7.6. $C_8H_{12}O_8$ requires C, 61.5; H, 7.75%).

3,8-*Dioxatricyclo*[4.2.1.$1^{2,5}$]*decan-4-one* (10), recrystallised from ethyl acetate–ether (1 : 2) after filtration of the crude product through a short silica gel column, had m.p. 89—90° (needles), $\nu_{max.}$ (KBr) 1 750 cm^{-1}, δ 2.7—2.8 (6 H, m), 3.12 (2 H, finely split s, O·CH_2), 4.00 (1 H, dd, *J* 4.0 and 1.8 Hz, O·CH), and 4.40 (1 H, t, *J* 4.0 Hz, CH·O·CO) (Found: C, 62.4; H, 6.6. $C_8H_{10}O_3$ requires C, 62.3; H, 6.5%).

3,10-*Dioxatricyclo*[6.2.1.$0^{2,6}$]*decan-9-one* (11), purified by preparative t.l.c. (methylene chloride) was an oil, $\nu_{max.}$ (film) 1 776 cm^{-1}, δ 1.1—3.1 (8 H, m), 3.5—4.4 (3 H, m, CH_2·O·CH), and 4.8 (1 H, m, CH·O·CO) (Found: C, 63.9; H, 7.0. $C_9H_{12}O_3$ requires C, 64.3; H, 7.2%).

3,11-*Dioxatricyclo*[6.3.0.$0^{2,6}$]*undecan-4-one* (12), purified by filtration through a short silica gel column (ether as eluant), had m.p. 47—48° (needles), $\nu_{max.}$ (KBr) 1 765 and 1 170 cm^{-1}, δ 1.0—3.2 (8 H, m), 4.02 (2 H, m, O·CH_2), 4.43 (1 H, t, *J* 4.8 Hz, O·CH), and 4.92 (1 H, dd, *J* 6.7 and 4.8 Hz, CH·O·CO) (Found: C, 64.5; H, 7.4. $C_9H_{12}O_3$ requires C, 64.3; H, 7.2%).

3,11-*Dioxatetracyclo*[6.3.0.$0^{2,6}$.$0^{5,9}$]*undecan-4-one*(13), recrystallised from ethyl acetate, had m.p. 187—189° (needles), $\nu_{max.}$ (KBr) 1 790sh and 1 770 cm^{-1}, δ 1.5—2.1 (2 H, m), 2.5—3.6 (4 H, m), and 4.0—4.7 (4 H, m, CH·O·CH_2 and CH·O·CO) (Found: C, 65.2; H, 6.6. $C_9H_{10}O_3$ requires C, 65.05; H, 6.1%).

t-Butyl 8-*Hydroxyoct-4-enoate* (14b).—A solution of lithium aluminium hydride (247 mg, 6.5 mmol) in dry ether (30 ml) was added to a stirred solution of the diester (14a) [5] (2.84 g, 10 mmol) in dry ether (10 ml) at room temperature under nitrogen, and then the mixture was gently refluxed for 8 h with stirring. The usual work-up gave a pale yellow oil (2.3 g), which was chromatographed on a silica gel column. Light petroleum–ether (1 : 1) eluted the diester (14a) (1.45 g) and then the *hydroxy-ester* (14b) (660 mg, 31%) as an oil, $\nu_{max.}$ (liquid) 3 400 and 1 730 cm^{-1}, δ 1.40 (9 H, s), 1.3—2.2 (4 H + OH, m), 2.27br (4 H, s), 3.65 (2 H, t, *J* 7 Hz, CH_2OH), and 5.48 (2 H, m, =CH–) (Found: C, 67.1; H, 10.3. $C_{12}H_{22}O_3$ requires C, 67.25; H, 10.35%). Further elution with ether gave the corresponding diol [8] (200 mg).

Methyl 4-(2-*Hydroxyethyl*)*cyclopent-2-enylacetate* (15b).—A solution of lithium aluminium hydride (175 mg, 4.6 mmol) in dry ether (20 ml) was added to a stirred solution of the diester (15a) [6] (1.48 g, 7 mmol) in the same solvent (5 ml) at −78 °C under nitrogen. The mixture was gradually allowed to warm to room temperature and worked up. The resulting oil (*ca.* 1.4 g) was chromatographed on a silica gel column; light petroleum–ether (1 : 1) eluted the diester (15a) (800 mg) and then the *hydroxy-ester* (15b) (226 mg, 21%) as an oil, $\nu_{max.}$ (liquid) 3 300 and 1 730 cm^{-1}, δ 1.1—2.9, (8 H + OH, m), 3.70 (3 H ,s), 3.78 (2 H, t, *J* 7 Hz, CH_2OH), and 5.68 (2 H, m, =CH–) (Found: C, 65.4; H, 8.6. $C_{10}H_{16}O_3$ requires C, 65.2; H, 8.75%).

Further elution with the same solvent gave the corresponding *diol*, m.p. 57—58°, $\nu_{max.}$ (KBr) 3 400, 3 010w, 1 060, 1 040, 1 010, and 740 cm^{-1}, δ 0.9—3.0 (8 H + 2 × OH, m), 3.75 (4 H, t, *J* 7 Hz, CH_2OH), and 5.75 (2 H, s, =CH–) (Found: C, 69.3; H, 10.7. $C_9H_{16}O_2$ requires C, 69.2; H, 10.3%).

8-*Hydroxyoct-4-enoic Acid* (4).—A mixture of the ester (14b) (642 mg, 3 mmol), sodium hydroxide (68 mg, 4.2 mmol), ethanol (4 ml), and water (1 ml) was gently refluxed for 4 h under nitrogen. Work-up in the usual manner gave the *acid* (4) (338 mg, 70%) as an oil, $\nu_{max.}$ (liquid) 3 500—2 400, 1 705, and 970 cm^{-1}, δ 1.4—2.6 (8 H, m), 3.65 (2 H, t, *J* 7 Hz, CH_2OH), 5.50 (2 H, m, =CH–), and 6.69br (2 H, s, OH and CO_2H) (Found: C, 60.8; H, 9.3. $C_8H_{14}O_3$ requires C, 60.7; H, 8.9%).

4-(2-*Hydroxyethyl*)*cyclopent-2-enylacetate* (7).—A mixture of the ester (15b) (274 mg, 1.5 mmol), sodium hydroxide (92 mg, 2.3 mmol), and water (1 ml) was heated at 60 °C for 2 h with stirring. Work-up gave crystals (191 mg, 73%), which were recrystallised from light petroleum–ether (1 : 1) to give the *hydroxy-acid*, m.p. 60—61.5°, $\nu_{max.}$ (KBr) 3 400, 3 300—2 500, and 1 705 cm^{-1}, δ 0.9—3.3 (8 H, m), 3.73 (2 H, t, *J* 7, CH_2·OH), 5.72 (2 H, s, =CH–), and 5.95 (2 H, m, OH + CO_2H) (Found: C, 63.2; H, 8.4. $C_9H_{14}O_3$ requires C, 63.5; H, 8.3%).

Methyl 5-(2-*Hydroxyethyl*)*cyclohex-3-enecarboxylate* (16b).—A solution of the formyl ester (16a) [1] (516 mg, 2.84 mmol) and sodium borohydride (37 mg) in methanol (5 ml) was stirred for 4 h at room temperature under nitrogen. A small quantity of acetic acid was added to remove the excess of reagent, and the mixture was evaporated at 40 °C *in vacuo*. The residue was added to water and extracted with methylene chloride, and the extract was washed with water and

* To improve the yield, the silver salt of (7) was treated with 1.73 equiv. of silver acetate after the addition of iodine, and the mixture was heated at 85 °C for 48 h.

[8] R. Lukes, *Chem. listy*, 1958, **52**, 1926 (*Chem. Abs.*, 1959, **53**, 3055c).

brine, and dried. Removal of the solvent left an oil, which was passed through a short silica gel column with ether to give the *hydroxy-ester* (16b) (485 mg, 94%) as an oil, which was distilled; b.p. 120° (bath temp.) at 1 mmHg, $\nu_{max.}$ (liquid) 3 350 and 1 727 cm^{-1}, δ 1.0—2.9 (8 H + OH, m), 3.70 (3 H, s), 3.78 (2 H, t, *J* 7 Hz), and 5.70 (2 H, m, =CH–) (Found: C, 64.85; H, 8.7. $C_{10}H_{16}O_3$ requires C, 65.2; H, 8.75%).

4-*Oxatricyclo*[5.2.1.$0^{2,6}$]*dec*-8-*en*-3-*one* (18).[9]—A solution of norborn-5-ene-*endo*-2,3-dicarboxylic anhydride [10] (492 mg, 3 mmol) in dry tetrahydrofuran (5 ml) was added dropwise to a stirred suspension of sodium borohydride (114 mg, 3 mmol) under nitrogen in an ice-bath. Stirring was continued for an additional 1 h at room temperature, then the mixture was cooled in an ice-bath and acidified with 6N-hydrochloric acid. The mixture was concentrated at 50 °C *in vacuo*, and the residue was extracted with methylene chloride. The combined extracts were washed with water and brine, and dried. Removal of the solvent left an oil, which crystallised when kept in an ice-bath. Recrystallisation from ether gave the *lactone* (18) (239 mg, 57%) as cubes, m.p. 129—130°, $\nu_{max.}$ (KBr) 1 770 and 1 130 cm^{-1}, δ 1.9—3.0 (6 H, m), 4.05 and 4.37 (1 H each dd, *J* 10.5, 4.5, and 1.5 Hz, CH·CH_2·O·CO), and 5.82 (2 H, m) (Found: C, 72.2; H, 7.0. $C_9H_{10}O_2$ requires C, 72.0; H, 7.0%).

[6/2061 *Received*, 8*th November*, 1976]

[9] For another synthesis of this lactone, see U. Scheidegger, J. E. Baldwin, and J. D. Roberts, *J. Amer. Chem. Soc.*, 1976, **89**, 894; R. D. Miller, D. L. Dolce, and V. Y. Merritt, *Tetrahedron Letters*, 1974, 3347; G. E. Pacey and K. E. Kolb, *ibid.*, p. 4547; M. Fetizon, M. Goldfier, and J. M. Louis, *Tetrahedron*, 1975, **31**, 171.

[10] O. Dielsand K. Alder, *Annalen*, 1928, **460**, 98; R. M. Roberts, J. C. Gilbert, L. B. Rodewald, and A. Wingrove, ' Modern Experimental Organic Chemistry,' Holt, Rinehart, and Winston, New York, 1969, p. 145.