ppm; IR (CCl_4) 2970, 1755, 1720, 1655, 1440 cm^{-1}; mass spectrum, m/e 182 (M^+), 150, 129, 105 (100%), 87, 81, 57, 55, 44, 41. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.87; H, 7.65.

Silyl Enol Ether 3. To a solution containing 24.9 g (137 mmol) of β-keto ester **10** and 60 mL (430 mmol) of triethylamine in 900 mL of ether was added 27.5 mL (217 mmol) of chlorotrimethylsilane at room temperature over 5 min. The reaction mixture was stirred for 3.5 h at room temperature and was filtered through a Celite pad with the aid of suction. The filtrate was concentrated in vacuo and taken up in 200 mL of ether. The ether solution was filtered as before and concentrated to 34.8 g (100%) of a very light yellow oil which was used without further purification: ^1H NMR (CCl_4) δ 5.00 (1 H, s), 4.73 (2 H, br s, $w_{1/2}$ = 8 Hz), 3.57 (3 H, s), 3.6–3.1 (1 H, m), 1.67 (3 H, br s), 1.3–0.7 (3 H, m), 0.25 (9 H, s); IR (CCl_4) 3090, 2960, 1715, 1610, 1145 cm^{-1}; mass spectrum, m/e 254 (M^+), 239, 186 (100%), 105, 89, 75, 73, 59, 45.

Cycloheptadiene 12. A 0.5 M solution prepared by combining 5.36 g (21.1 mmol) of silyl enol ether **3** and 40 mL of benzene was degassed and sealed under reduced pressure in a glass tube for reaction. The glass tube was placed in a stainless-steel bomb, surrounded with benzene and heated to 210 °C for 16 h. The crude reaction product was concentrated to 5.15 g (96%) and was used without further purification: ^1H NMR (CCl_4) δ 5.50 (1 H, m), 4.80 (1 H, t, J = 5 Hz), 3.62 (3 H, s), 3.3 (1 H, m), 2.9–2.2 (4 H, m), 1.70 (3 H, br s), 0.20 (9 H, s); IR (CCl_4) 2960, 1745, 1665, 1440, 1250, 1160, 880, 845 cm^{-1}; mass spectrum, m/e 254 (M^+), 157, 129, 89, 89, 82, 75, 73 (100%).

2-(Carbomethoxy)-4-methylcyclohept-4-en-1-one (2) from 12. A solution of 5.15 g (20.2 mmol) of cycloheptadiene **12** in 75 mL of methanol was combined with 1.74 g (30 mmol) of potassium fluoride and stirred for 3 h at room temperature. The crude reaction mixture was concentrated in vacuo and partitioned between 50 mL each of water and ether. The aqueous layer was extracted twice more with 40-mL portions of ether and the combined ether extracts were dried over anhydrous sodium sulfate. The dried ether solution was filtered through a pad of Celite and concentrated in vacuo to yield 3.60 g (98%) of an orange oil. The crude material was chromatographed on 100 g of silica. Elution with ether yielded 3.50 g (95%) of pure material that was identical spectroscopically with purified arising from thermal rearrangement of **10**.

Registry No. 2, 76757-71-6; **3**, 76833-06-2; **4**, 13949-95-6; **5**, 74857-26-4; **6**, 76833-07-3; **7**, 76833-08-4; **8**, 33383-61-8; **9**, 33383-66-3; **10**, 76833-09-5; **11**, 29684-56-8; **12**, 76833-10-8.

Preparation of Macrocyclic Lactones from Cyclohexane-1,3-diones[1]

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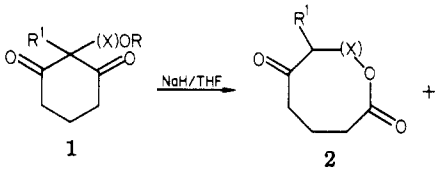
Received July 11, 1980

The dearth of general synthetic methods for the construction of macrocyclic lactones places severe restrictions on routes to the macrolide antibiotics.[2] Recent syntheses[3] have relied on the cyclization of hydroxy acids in the final stages. It would be of interest to have methods available by which the lactone function could be constructed at an early stage. Mahajan[4] has reported a novel synthesis of lactones **2** through a base-induced intramolecular rearrangement of 2,2-dialkylcyclohexane-1,3-diones (**1**, R = H).



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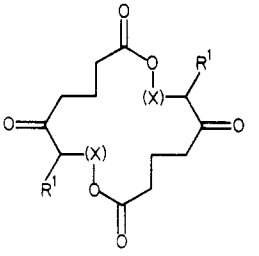

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This internal version of the retro-Dieckmann reaction was described for a limited number of precursors with short cyclizing side chains (X)OR. We show how a slight modification to the reaction conditions, the use of THF or THF–toluene as solvent in place of the benzene specified, broadens the scope of the Mahajan lactone synthesis, allowing yields greater than 50% to be obtained for 16-membered rings, the ring size of the leucomycin antibiotics.

The syntheses of the precursor 2,2-dialkylated cyclohexane-1,3-diones (**1a–d**, Table I) were accomplished by the consecutive alkylation of cyclohexane-1,3-dione.[5] Thus, **1c** was prepared by initial alkylation with 9-iodononanol followed by alkylation with allyl bromide. Since C-alkylation proceeds in poor yield with other than allylic halides, this step presently limits the utility of the lactone synthesis.

The cyclization of diketones **1a–d**, using catalytic amounts of sodium hydride in THF or THF–toluene, gave useful yields (Table I) of lactones **2a–d** which were easily separated by chromatography from the dimeric lactones

Table I. Synthesis of Cyclohexane-1,3-diones and 5-Oxo Lactones (R = H; R^1 = $CH_2CH{=}CH_2$)

compd[a]	X	lactone ring size	mp, °C	yield,[b] %
1a	$(CH_2)_4$		oil	20
1b	$(CH_2)_6$		oil	20
1c	$(CH_2)_9$		oil	19
1d	$(CH_2)_{20}$		66-67[c]	15
2a	$(CH_2)_4$	11	oil	49
2b	$(CH_2)_6$	13	20-21[d]	28
2c	$(CH_2)_9$	16	oil	56
2d	$(CH_2)_{20}$	27	oil	11
3a	$(CH_2)_4$	22	oil	15
3b	$(CH_2)_6$	26	77-78[c]	37
3c	$(CH_2)_9$	32	52[c]	12

[a] All new compounds were adequately characterized by proton NMR, IR, and mass spectroscopy and by elemental analysis (±0.4% for C and H). [b] Yields of **1a–d** from cyclohexane-1,3-dione. Yields of **2a–d** and **3a–c** for lactone formation. [c] From ethyl acetate–hexane. [d] From hexane at −20 °C.

(1) Contribution No. 556 from the Syntex Institute of Organic Chemistry.

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0022-3263/81/1946-1914$01.25/0

3a–c and higher oligomers. High dilution or slow addition techniques did not improve the yields of lactones or change the monomer–dimer ratios. Only part of the sodium hydride reacts and the reaction mixture remains heterogeneous. These facts suggest that lactonization occurs on the surface of the sodium hydride rather than in homogeneous solution. The use of benzene or toluene as solvent[4] decreased the reaction rate and gave only traces of lactone.

Experimental Section

Melting points were taken on a Mel-Temp apparatus and are uncorrected. Proton NMR chemical shifts were recorded with a Varian HA-100 spectrometer and are reported in parts per million downfield from internal Me_4Si. Mass spectra were measured on a Varian CH-4 spectrometer. Preparative TLC was performed with a Harrison Research Model 7924 centrifugal thin-layer chromatograph.

Standard Procedure for Alkylation of Cyclohexane-1,3-dione.[5] 2-Allyl-2-(9-hydroxynonyl)cyclohexane-1,3-dione (1c). Cyclohexane-1,3-dione (20 g, 0.178 mol) was dissolved in a solution of potassium hydroxide (10 g, 0.178 mol) in 250 mL of water containing a trace of copper powder (50 mg). The solution was heated on a steam bath, and 9-iodononanol (48 g, 0.178 mol) was added, followed by sufficient methanol to give a clear hot solution. After 4 h the methanol was removed under vacuum and 3 N sodium hydroxide solution was added until a pH of 11 was obtained. Neutral material was removed by six extractions with ether and the aqueous solution was then acidified with concentrated hydrochloric acid to pH 1. The oily suspension was allowed to solidify during 24 h of stirring. Filtration gave 10.4 g (23%) of 2-(9-hydroxynonyl)cyclohexane-1,3-dione: mp 123–124 °C after recrystallization from ethyl acetate–hexane; NMR ($CDCl_3$) δ 1.25 (s, 14 H, CH_2), 1.30–2.55 (m, 9 H, CH_2CO, $CH_2C{=}$, CH_2, OH exchanged by D_2O), 3.35 (s, 1 H, OH exchanged by D_2O), 3.62 (t, 2 H, CH_2O); mass spectrum, m/e 254 (M^+, 5%), 113 (100%). Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.80; H, 10.68.

A solution of this dione (6.2 g, 24 mmol, unpurified) in 25 mL of aqueous potassium hydroxide (1.5 g, 27 mmol) was stirred with excess allyl bromide (5 mL) for 18 h at room temperature. Ether (250 mL) was added and the solution was washed with small volumes of 1 N sodium hydroxide solution until the washings were strongly basic. After a further washing with water, the solution was dried ($MgSO_4$) and evaporated in vacuo. Chromatography of the residue on silica gel (ethyl acetate–hexane, 1:1) gave 6.0 g (84%) of 1c as an oil: NMR ($CDCl_3$) δ 1.25 (s) and 1.4–2.0 (m) (18 H, CH_2), 1.75 (s, 1 H, OH exchanged by D_2O), 2.5 (q, 6 H, CH_2CO, $CH_2C{=}$), 3.60 (t, 2 H, CH_2O), 4.85–5.10 (m, 2 H, $CH_2{=}$), 5.2–5.9 (m, 1 H, CH=); mass spectrum, m/e 294 (M^+, 15%), 152 (100%). Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.24; H, 10.59.

Standard Procedure for Formation of Lactones. 6-Allyl-5-oxopentadecanolide (2c). Sodium hydride (100 mg, 50% in oil, 2.1 mmol) was suspended in 2 mL of dry toluene and added in one portion to a stirred solution of diketone 1c (2.94 g, 10 mmol) in dry (molecular sieves) toluene–tetrahydrofuran (300 mL, 1:1) under a nitrogen atmosphere. The mixture was heated to reflux with a preheated oil bath and maintained at reflux for 45 min. The cooled mixture was treated with acetic acid (1 mL) and methanol (20 mL) to destroy unreacted sodium hydride and was then evaporated to dryness in vacuo. Preparative centrifugal TLC on silica gel (ethyl acetate–hexane, 1:19) gave the lactone 2c (1.65 g, 56%) as an oil: NMR ($CDCl_3$) δ 1.25 (s) and 1.4–2.1 (m) (18 H, CH_2), 2.1–2.7 (m, 7 H, CH_2CO, CHCO, CH_2CO_2, $CH_2C{=}$), 3.9–4.5 (m, 2 H, CH_2O), 4.85–5.15 (m, 2 H, $CH_2{=}$) 5.3–5.9 (m, 1 H, CH=); mass spectrum, m/e 294 (M^+, 40%), 152 (80%), 115 (100%). Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.47; H, 10.41.

Further elution with ethyl acetate–hexane (1:9) gave the dimeric lactone 3c (0.35 g, 12%): mp 52 °C from ethyl acetate–hexane; NMR ($CDCl_3$) δ 1.25 (s) and 1.4–2.1 (m) (36 H, CH_2), 2.1–2.7 (m, 14 H, CH_2CO, CHCO, CH_2CO_2, $CH_2C{=}$), 3.9–4.25 (t, 4 H, CH_2O), 4.85–5.15 (m, 4 H, $CH_2{=}$), 5.3–5.9 (m, 2 H, CH=); mass spectrum, m/e 588 (M^+, 80%), 152 (100%). Anal. Calcd for $C_{36}H_{60}O_6$: C, 73.43; H, 10.27. Found: C, 73.10; H, 10.54.

20-Acetoxy-1-bromoeicosane. A solution of 1,20-dibromoeicosane[6] (8.8 g, 20 mmol) in dimethylformamide (75 mL) containing sodium acetate (1.65 g, 20 mmol) was heated at 80 °C for 1 h. The solution was diluted with water and the products were extracted into ether. After the solution was washed with water and dried ($MgSO_4$), the solvent was removed in vacuo and the products were chromatographed on silica gel, using ethyl acetate–hexane. Crystallization from methanol gave 2.8 g (33%): mp 52 °C; mass spectrum, m/e 419 and 421 ($M^+ + H$). Anal. Calcd for $C_{22}H_{43}BrO_2$: C, 62.99; H, 10.33. Found: C, 63.13; H, 10.58.

2-Allyl-2-(4-hydroxybutyl)cyclohexane-1,3-dione (1a) and 2-Allyl-2-(20-hydroxyeicosyl)cyclohexane-1,3-dione (1d). The standard procedure for alkylation of cyclohexane-1,3-dione was modified for these preparations. Alkylation was performed first with allyl bromide then with the ω-acetoxyalkyl halide. The standard procedure gave only O-alkylated products. Hydrolysis of the acetoxy group was achieved by heating a solution in ethanol–0.5 N hydrochloric acid (2:1) at reflux for 2 h.

Registry No. 1a, 76334-20-8; 1b, 76346-75-3; 1c, 76334-21-9; 1d, 76334-22-0; 2a, 76334-23-1; 2b, 76334-24-2; 2c, 76334-25-3; 2d, 76334-26-4; 3a, 76334-27-5; 3b, 76334-28-6; 3c, 76334-29-7; cyclohexane-1,3-dione, 504-02-9; 9-iodononanol, 76334-30-0; allyl bromide, 106-95-6; 20-acetoxy-1-bromoeicosane, 76334-31-1; 1,20-dibromoeicosane, 14296-16-3.

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C(14) Configuration of 8,13-Epoxylabdan-14-ols

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Received September 22, 1980

Recently interest has been focused on ^{13}C NMR spectroscopy as a tool for the determination of C(15) configurations in pimarene- and isopimarene-15,16-diols.[1,2] The determination of the C(14) configuration of 8,13-epoxylabdanes with C(14)- or C(14),C(15)-oxygenated side chains by ^{13}C NMR spectroscopy is the subject of the present paper.

The natural diterpenoid borjatriol (1,[3,4] Chart I) was used as a representative of the 8,13-epoxylabdane diterpenes (manoyl oxide derivatives) and used as starting material for obtaining all the products here described. Compounds with a C(13),C(14)-threo configuration (13*R*,14*R*, 1–6) were directly synthetized from the natural product 1 by acetylation (2), acetone–anhydrous $CuSO_4$ treatment (3), selective C(15)-OH tosylation and subsequent reaction with Na_2CO_3–EtOH–H_2O (4),[5] $LiAlH_4$ reduction of compound 4 (5), and acetylation of product 5 to yield 6. The preparation of the C(14) epimeric series [13*R*,14*S*,C(13),C(14)-erythro compounds 7–13] was achieved as follows. The acetonide 3 was acetylated at its C(7) OH and then transformed into (14*R*)-7β-acetoxy-8,13-epoxylabdane-14,15-diol[3] by acid treatment. Selective C(15)-OH benzoylation and subsequent C(14)-OH tosyla-

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