

Synthesis of 3,3-Dimethyl-5-oxo-6-alkyloctanolides by Ring Expansion of Appropriately Substituted Cyclohexane-1,3-diones¹

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Descreve-se a síntese de algumas cetolactonas de 9-membros (5a-c) a partir de 2-alil-2-alkyldimedonas (2-alil-2-alkil-5,5-dimetilcicloexano-1,3-dionas; 1a-c), através de ozonólise, seguida de redução seletiva dos aldeídos obtidos, com boroidreto ou, melhor, cianoboroidreto de sódio, e subsequente lactonização dos hidroxi-compostos (3a-c/4a-c), catalizada por hidreto de sódio em benzeno sob refluxo.

Three examples of the 9-membered keto-lactones (5 a-c) have been prepared from 2-allyl-2-alkyl-5,5-dimethylcyclohexane-1,3-diones (2-allyl-2-alkyldimedones; 1a-c), by ozonolysis to the corresponding diketo-aldehydes 2a-c, followed by the selective reduction of the formyl group with sodium borohydride or sodium cyanoborohydride, and lactonization of the resulting hemi-ketals 4a-c, catalized with sodium hydride in refluxing benzene.

Key Words: octanolides; ketolactones, synthesis of; cyclohexane-1,3-diones

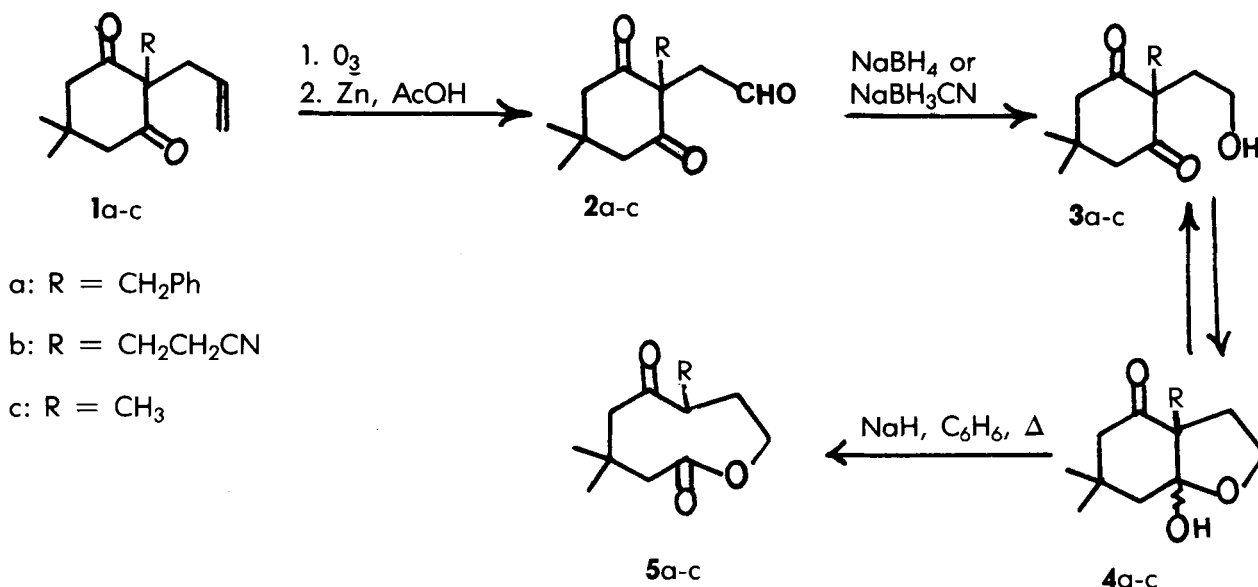
Introduction

In connection with our studies on the synthesis of medium ring and macrocyclic ketolactones², we hereby describe the preparation of the 9-membered title lactones (5a-c) by the sequence depicted below.

Materials and Methods

Easily available 2-allyl-2-alkyldimedones (1a-c)³ were ozonized following the established procedure⁴, affording the desired aldehydes 2a-c in 70-90% yield. Initially, the selective reduction of the formyl group of these diketoalde-

hydes was attempted with sodium borohydride in *t*-butyl alcohol. However, this procedure was efficient only with the benzyl substituted derivative (2a), affording the desired hydroxy-compound (3a/4a) in 55-65% yield; other substrates (2b, c) undergo substantial over-reduction to the more polar products (diol, triol; TLC) as well as partial lactonization of the mono-ol, provoked by the basic reaction medium. Consequently, chromatographic separation of the reaction mixture was needed and eventually furnished 44% of 4b and only ~ 5% of slightly impure 4c. We thus explored



the desired selective reduction with sodium cyanoborohydride under acidic conditions^{5,6}, as already reported for the homologous compounds^{1d}. The procedure worked nicely and furnished the expected products in one of the more stable diastereoisomeric hemi-ketal forms (4a-c), as evidenced by the isolation of pure crystalline compounds in 60, 50, and 34% yield, respectively; the mother liquors still contain appreciable quantities of the desired mono-ol (TLC), which on chromatographic separation (silica gel and benzene, containing 1-5% ethanol) can afford further amounts of the same or isomeric hemi-ketal, or the purified product may be lactonized to the corresponding ketolactone (5a-c).

Attempted improvement by the reduction of 2c with tetra-n-butylammonium cyanoborohydride - a specific reducing agent for aldehydes^{5,7} - gave only comparable yield of 4c and, in addition, required chromatographic elimination of the accompanying tetra-n-butylammonium salts.

Lactonization of the hemi-ketals 4a-c, induced with sodium hydride in refluxing benzene, either by the high-dilution technique^{1d} or in the conventional manner^{8,9}, produced similar results (TLC) and furnished the crude product in almost quantitative yield, from which the desired octanolides could be isolated by crystallization (5a) or column chromatography (5b,c), in 50-80% yield. These results compare very favourably with the poor yields furnished by the cyclization techniques for forming the 9-membered lactones, which are known to be difficult due to their inherent strain and unfavourable entropy of formation^{10,11}.

IR spectra were recorded on a Perkin Elmer 137 Infracord Instrument, ¹H-NMR spectra were measured at 60MHz with a Varian A-60D spectrometer; routine experimental procedures are those reported in our earlier publications^{9,12}, other pertinent details are given below.

Ozonolysis of 2-allyl-2-alkyldimedones (1a-c); general procedure⁴: a slow stream of ozone/oxygen mixture is

bubbled through a solution of the substrate (10 mmol) in dichloromethane (100 ml), cooled by an ice-NaCl bath, till an excess of ozone can be detected by its odour and/or KI-starch paper (2-3h). After flushing the reaction mixture with oxygen for 15 min, zinc dust (2 g) and acetic acid (4 ml) are added and stirring continued at room temperature for 4h. The solid material is filtered and the filtrate washed successively with water, 10% aq. NaHCO₃ solution, and brine. Drying (Na₂SO₄) and evaporation of the solvent furnishes the crude product, which is recrystallized from benzene/petroleum ether to obtain the pure diketoaldehydes 2a-c (Table 1).

Selective Reduction of 2-alkyl-2-(2-oxoethyl)-dimedones (2a-c) with NaBH₄ (Method A); general procedure: to a stirred solution (N₂) of the substrate (10 mmol) in *t*-butyl alcohol (150 ml), at room temperature, NaBH₄ (120 mg, 3.15 mmol) is added in two equal portions (60 mg each) after an interval of 4h. The reaction mixture is further stirred for 4-8h, till the disappearance (TLC) of the starting material, after which it is washed with water, dried (Na₂SO₄), and evaporated to afford the crude product. Crystallization from benzene or benzene / petroleum ether furnishes the hemi-ketals 4a-c (Table 2).

Selective Reduction of diketo-aldehydes 2c with NaBH₃CN (Method B); typical procedure^{1d}:

NaBH₃CN (630 mg, 10 mmol) is added at room temperature to a stirred solution of 2c (1.96 g, 10 mmol) in *t*-butyl alcohol (50 ml), containing formic acid (99%; 1.9 ml, 2.32g, 50 mmol). Stirring is maintained (8-12h) till there is no more starting material (TLC), after which benzene (80 ml) is added and the reaction mixture washed successively with water, aq. NaOH (0.1N), water, and brine. Drying and evaporation affords the crude product, which is crystallized from benzene to obtain the hemi-ketal 4c (667 mg; 34% yield), as colorless needles, mp 90-92 °C (Table 2).

The mother liquor (1.3 g) is chromatographed on sili-

Table 1. 2-Alkyl-2-(oxoethyl)-dimedones (2a-c)

Product	Yield (%)	mp (°C)	Molecular Formula ^a	IR(KBr) ν (cm ⁻¹)	¹ H-NMR(CDCl ₃ /TMS) δ , J(Hz)
2a	87	106-107	C ₁₇ H ₂₀ O ₃ (272.3)	1730 1718 1692	1.20(s,6H,CM ₂); 2.73 (qAB, 4H, J=15, ν_{AB} 21.2Hz, 2CH ₂); 2.86 (s,2H,CH ₂ Ph); 3.10(s,2H,CH ₂ CHO); 6.85-7.35(m,5H arom); 9.51 (s,1H,HCO).
2b	72	102-104	C ₁₃ H ₁₇ NO ₃ (235.3)	2262 1730 1720 1690	1.20, 1.23(2s,6H,CM ₂); 2.15-2.40 (m,4H,CH ₂ CH ₂ CN); 2.72(qAB,4H,J=15, ν_{AB} 17.4Hz,2CH ₂); 3.05 (s,2H,CH ₂ CHO); 9.82 (s,1H, HCO).
2c	90	100-102	C ₁₁ H ₁₆ O ₃ (196.2)	1739 1721 1701	1.15,1.20(2s,6H,CM ₂); 1.40 (s,3H,CH ₃); 2.65(qAB, 4H,J=15, ν_{AB} 22.5Hz,2CH ₂); 3.02(s,2H,CH ₂ CHO); 8.80(s,1H,HCO).

^a Satisfactory microanalyses obtained: C \pm 0.12, H \pm 0.10

Table 2. Selective reduction of Diketo-aldehydes 2a-c to Hemi-ketals 4a-c

Product	Method	Yield (%) ^a	mp (°C)	Molecular Formula ^c	IR(KBr) $\nu(\text{cm}^{-1})$	¹ H-NMR(CDCl ₃ /TMS) δ , J(Hz)
4a	A	55-65	137-139	C ₁₇ H ₂₂ O ₃ (274.3)	3356, 1701	0.93, 1.07(2s, 3H each, CMe ₂); 1.75-2.80(m, 6H, 3CH ₂); 3.11 (s, 2H, CH ₂ Ph); 3.4-4.2(m, 2H, CH ₂ O); 4.60(s, 1H, OH) 6.95-7.40(m, 5H arom).
	B	60				
4b	A	20 44 ^b	112-113	C ₁₃ H ₁₉ NO ₃ (237.3)	3448, 2268, 1701	0.81, 0.91, 1.20-minor singlets-, 0.95, 1.12-major singlets (6H, 2CH ₃); 1.55-3.15 (m, 11H, 5CH ₂ , OH); 3.35- 4.25(m, 2H, CH ₂ O).
	B	50 55-75 ^b				
4c	B	34 55 ^b	90-92	C ₁₁ H ₁₈ O ₃ (198.2)	3400, 1698	0.92, 1.07, 1.27(3s, 3H each, 3CH ₃); 1.5-3.0(m, 7H, 3CH ₂ , OH), 3.5- 4.1(m, 2H, CH ₂ O).
	B ^d	50 ^b				
	A	5 ^c				

^a Yield of the crystalline product obtained without chromatographic purification.

^b Total yield augmented by chromatographic separation of the mother liquor.

^c A pure compound could not be isolated by this method.

^d *n*-Bu₄NBH₃CN used instead of NaBH₃CN.

^e Satisfactory microanalyses obtained: C ± 0.15, H ± 0.10

ca gel (50g) and eluted with benzene, containing 1-5% ethanol. After elution of the less polar components (~175 mg), slightly contaminated (TLC) 4c (622 mg; 31% yield) is eluted with benzene/ethanol (4%). Although crystallization of this product is difficult, it is lactonized in the conventional manner (see below) to afford the ketolactone 5c in 70% yield. Consequently, the total yield of the reduced product (4c) is raised to ~55%.

3, 3-Dimethyl-5-oxo-6-benzyl-octanolide (5a); dilution technique^{1d}: the hemi-ketal 4a (1.37 g, 5 mmol) dissolved in anhydrous benzene (40 ml) is added dropwise during 4-6h, through a dilution device^{1d}, to magnetically stirred and vigorously refluxing benzene (50 ml), containing sodium hydride (80% suspension; 15 mg, 0.5 mmol). The dropping funnel is rinsed with benzene (10 ml) and the reaction mixture further stirred and refluxed for 2-3h, till TLC shows only traces of the starting material and an upper spot corresponding to the desired ketolactone. The cooled reaction mixture is successively washed with 0.1 normal hydrochloric acid (10 ml), water, and brine. Drying (Na₂SO₄) and evaporation furnishes the crude product, a translucent solid, in a quantitative yield (1.37 g), which on recrystallization from petroleum ether gives white needles; yield: 1.1 g (80%); mp 68-69 °C.

C ₁₇ H ₂₂ O ₃ (274.3)	calc. found	C 74.42 74.50	H 8.08 8.12
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IR(KBr): $\nu = 1738, 1710 \text{ cm}^{-1}$.

¹H-NMR(CDCl₃): $\delta = 0.98, 1.15$ (2s, 3H each, CMe₂); 1.7-3.0 (m, 9H, 4CH₂ and CH); 3.67-4.37 (m, 2H, CH₂O); 7.39 (s, 5H arom).

3,3-Dimethyl-5-oxo-6-(2-cyanoethyl)-octanolide (5b): the hemi-ketal 4b (1.19 g, 5 mmol) is lactonized as described above and yields 1.18 g (99%) of a viscous liquid, which is chromatographed on silica gel (50g), eluted with benzene / ethanol (0-4%). After elution of the less polar impurities (~120 mg), the desired ketolactone 5b, yield: 793 mg (66.6%), is eluted with benzene/ethanol (2-3%); it is preceded and followed by slightly less pure product (107 mg and 76 mg, respectively). Short-path distillation (110-120 °C / ~10 torr) affords the analytical sample as a colorless, viscous liquid.

C ₁₃ H ₁₉ NO ₃ (237.3)	calc. found	C 65.80 65.66	H 8.07 8.15
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IR(neat): $\nu = 2268, 1739, 1718 \text{ cm}^{-1}$.

¹H-NMR (CCl₄): $\delta = 1.05, 1.18$ (2s, 3H each, CMe₂); 1.6-2.7 (m, 11H, 5CH₂ and CH); 3.8-4.3 (m, 2H, CH₂O).

Lactonization of the hemi-ketal 4b carried out in the conventional manner (see below) gives similar results.

5-Oxo-3,3,6-trimethyloctanolide (5c); conventional procedure^{8,9}: hemi-ketal 4c (792 mg, 4 mmol) is lactonized by heating under reflux (10-12h) in dry benzene (80 ml), containing NaH (80% suspension; 12 mg). The cooled reaction mixture is worked up as described above and furnishes the crude product in a quantitative yield. Short-path distillation (110-120 °C / ~10 torr) affords a colorless, viscous liquid yield: 730 mg (92%), which still contains some impurities (TLC). Chromatographic purification, as described above, gives the analytical sample in about 50% yield.

$C_{11}H_{18}O_3$	calc.	C66.64	H 9.15
(198.2)	found	66.56	8.99

IR(neat): $\nu = 1739, 1709 \text{ cm}^{-1}$.

$^1\text{H-NMR}$ (CDCl_3): $\delta = 1.07$ (d, 3H, $J=7$, CH_3); 1.22, 1.32 (2s, 3H each, CMe_2); 1.75-2.85 (m, 7H, 3CH_2 and CH); 4.23 (t, 2H, $J=6$, CH_2O).

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