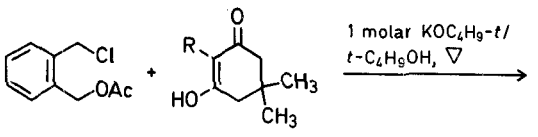
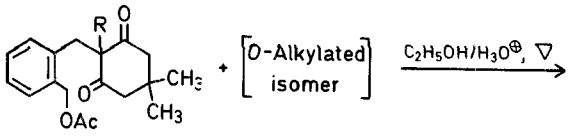
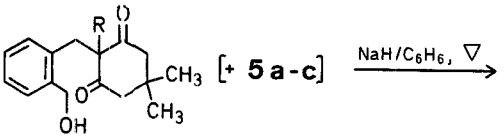


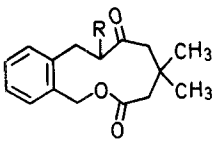
4 5a-c



6a-c



7a-c



8a-c

a R = CH_2=CH−CH_2
b R = C_6H_5−CH_2
c R = CH_3

Synthesis of 6-Alkyl-3,3-dimethyl-5-oxo-8,9-benzodecenolides by Intramolecular Reverse Dieckmann Reaction

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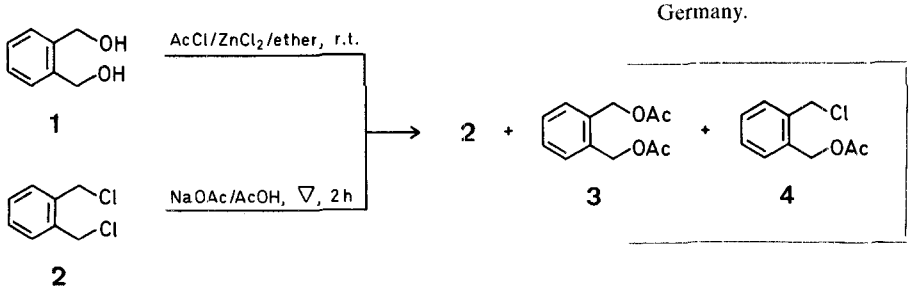
In connection with our work on the synthesis of medium ring and macrocyclic ketolactones, we recently developed a novel lactonization procedure by the intramolecular reverse Dieckmann reaction of the suitably substituted cyclohexane-1,3-diones[2]. This method has been successfully extended to the synthesis of 5-oxooctanolides[3], 5,9-dioxodecanolides[4], and 5-oxo-8,9-benzodecenolides[1]. We hereby report our results for the preparation of the title lactones **8a–c** from 2-alkyldimedones **5a–c** by alkylation with 2-(acetoxymethyl)-benzyl chloride (**4**), followed by acid hydrolysis, and subsequent intramolecular reverse Dieckmann reaction of the resulting hydroxy diketones **7a–c**.



1 2 3 4

2-(Acetoxymethyl)-benzyl chloride (**4**) has not been reported; we prepared it either from 1,2-bis[hydroxymethyl]benzene (**1**), by reaction with acetyl chloride and zinc chloride in anhydrous ether[5], or from 1,2-bis[chloromethyl]benzene (**2**) by displacement reaction with sodium acetate in refluxing acetic acid; the latter alone did not cause any solvolysis of the substrate **2**. Both reactions resulted in a mixture of products from which the desired 2-(acetoxymethyl)-benzyl chloride (**4**) was obtained after chromatographic separation and subsequent distillation under reduced pressure in a moderate yield of 38–43%. The rest of the procedure, reaction of **4** with the dimedone **5** in the presence of potassium *t*-butoxide, hydrolysis in ethanol, and sodium hydride-induced ring closure is similar to that already outlined in our original report[2] and the experimental conditions for the present preparations are described below.

1,2-Bis[dichloromethyl]benzene (**2**) was purchased from the Aldrich Chemical Co. Thin layer chromatograms (T.L.C.) were carried out on glass plates coated with silica gel G (Merck) and eluted with benzene containing 1–5% ethanol. The dried plates were exposed to iodine vapours. I.R. spectra were recorded on a Perkin Elmer 137 instrument; ^{1}H-N.M.R. spectra were measured at 60 MHz with a Varian A-60D spectrometer; microanalyses were performed by Analytische Laboratorien, D-5250 Engelskirchen, Germany.

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2-(Acetoxymethyl)-benzyl Chloride (4):
Method A: From 1,2-Bis[hydroxymethyl]benzene (**1**): Acetyl chloride (15.7 g, 14.3 ml, 200 mmol) dissolved in anhydrous ether (130 ml) is added dropwise during 1 h, with stirring at room temperature, to a mixture of diol **1** (13.8 g, 100 mmol) and anhydrous zinc chloride (18.7 g, 140 mmol) in the same solvent (100 ml). After further stirring for 5 h, the reaction mixture is carefully decomposed with crushed ice and the ethereal layer washed with water and brine. Drying with sodium sulfate and evaporation of solvent gives the crude product (19.2 g) consisting of three components (T.L.C.). The mixture is chromatographed over silica gel (Merck; 300 g) and eluted with petroleum ether (40–60°), containing a successively increasing amount of benzene (0–80 %), and benzene containing ethanol (0–20 %). After combining similar fractions (T.L.C.), further purification by recrystallization or distillation under reduced pressure yields the following pure compounds:

1,2-Bis[chloromethyl]benzene (**2**); yield: 4.4 g (25%); m.p. 53–55°; mixture m.p. 53–55°.

^{1}H-N.M.R. (CCl_4): $\delta = 4.68$ (s, 4H, $2CH_2Cl$); 7.45 ppm (s, 4 H_{arom}).

2-(Acetoxymethyl-benzyl Chloride (**4**); yield: 8.6 g (43 %); colorless viscous liquid; b.p. 92–94°/0.5 torr.

$C_{10}H_{11}ClO_2$	calc.	C 60.45	H 5.54	Cl 17.88
(198.5)	found	60.28	5.67	17.73

I.R. (neat): $\nu_{max} = 1745, 1227\,cm^{-1}$.

^{1}H-N.M.R. (CCl_4): $\delta = 2.03$ (s, 3H, AcO); 4.63 (s, 2H, CH_2Cl); 5.16 (s, 2H, H_2COAc); 7.2–7.4 ppm (m , 4 H_{arom}).

1,2-Bis[acetoxymethyl]benzene (**3**); yield: 4.6 g (21 %); colorless thick liquid; b.p. 112–116°/0.5 torr; Lit. [6] m.p. 35–36°.

I.R. (neat): $\nu_{max} = 1745, 1232\,cm^{-1}$.

^{1}H-N.M.R. (CCl_4): $\delta = 2.01$ (s, 6H, 2 AcO); 5.13 (s, 4H, 2 H_2COAc); 7.3 ppm (s, 4 H_{arom}).

Method B: From 1,2-Bis[chloromethyl]benzene (**2**): A mixture of the dichloride **2** (17.5 g, 100 mmol) and fused sodium acetate (9.0 g, 110 mmol) in glacial acetic acid (40 ml) is heated under reflux for 2 h, then the cooled reaction mixture is taken up in ether, and washed with water and brine. Work up as above gives the crude product (19.6 g) which is chromatographed (SiO_2) and purified as in the previous case to furnish the unreacted dichloride **2** (5.4 g; 31 %), the desired 2-(acetoxymethyl)-benzyl chloride (**4**; 7.6 g; 38 %), and the diacetate **3** (5.3 g; 24 %).

6-Allyl-3,3-dimethyl-5-oxo-8,9-benzodecenolide (8a):
To a solution of 2-allyldimedone[7] (**5a**; 1.8 g, 10 mmol) in 1 molar potassium *t*-butoxide in *t*-butyl alcohol (11 ml) is added 2-(acetoxymethyl)-benzyl chloride (**4**; 2.18 g, 11 mmol) and potassium iodide (166 g, 1 mmol). The mixture is heated gently under reflux on a water bath for 8–12 h, then the cooled reaction mixture is diluted with ether, and successively washed with water, 0.5 normal sodium hydroxide, water, and brine. Drying and evaporation of solvent gives a mixture (T.L.C.) of *C*- and *O*-alkylated products (3.4 g; ~100%); I.R. (neat): $\nu_{max} = 1748, 1704, 1658\,cm^{-1}$; which is hydrolysed by heating under reflux (~5 h) in ethanol (95 %; 10 ml), containing 0.5 normal hydrochloric acid (5 ml). After evaporation of excess ethanol, the residue is dissolved in ether and successively washed with water, 0.5 normal sodium hydroxide, water, and brine. Drying and evaporation of solvent yields the crude hydroxy diketone **7a** (2.75 g; 85%) as a thick liquid; I.R. (neat): $\nu_{max} = 3413, 1724, 1692\,cm^{-1}$; which is lactonized by heating under reflux (6–8 h) in dry benzene (100 ml), containing a catalytic amount of sodium hydride (80% suspension; 20 mg). The cooled reaction mixture is washed with water and brine. Evaporation of solvent affords a brown, thick liquid (2.27 g; 88%), which is crystallized from benzene containing charcoal. Recrystallization from methanol produces colorless, fine plates; yield: 1.22 g (40% from 2-allyldimedone); m.p. 61–63°.

$C_{19}H_{24}O_3$	calc.	C 75.97	H 8.05
(300.4)	found	75.82	8.04

I.R. (KBr): $\nu_{max} = 1745, 1715\,cm^{-1}$.

^{1}H-N.M.R. (CCl_4): $\delta = 0.72$ (s, 3H, CH_3); 1.13 (s, 3H, CH_3); 1.5–3.1 (m, 9H, 4 CH_2 and CH); 4.5–6.5 (5H, AB quartet of H_2C—OCO, $J_{AB} = 13$ Hz, superimposed on the H_2C=CH— multiplet); 7.0–7.4 ppm (m, 4 H_{arom}).

6-Benzyl-3,3-dimethyl-5-oxo-8,9-benzodecenolide (8b):
Alkylation of 2-benzyldimedone[7] (**5b**; 2.3 g, 10 mmol) with chloride **4** (2.18 g, 11 mmol), in the manner described above and acid hydrolysis of the crude product (3.8 g; ~100 %) furnishes the hydroxy diketone **7b** (2.9 g; 83%), which on isomerization in boiling benzene (100 ml), containing sodium hydride (80 % suspension; 20 mg), gives the desired benzolactone **8b** (2.48 g; 70 %). Crystallization from benzene containing charcoal followed by recrystallization from 95% ethanol yields the analytical sample as a colorless solid; yield: 1.45 g (40% from 2-benzyldimedone); m.p. 98–100°.

$C_{23}H_{26}O_3$	calc.	C 78.83	H 7.48
(350.5)	found	78.77	7.57

I.R. (KBr): $\nu_{max} = 1739, 1718\,cm^{-1}$.

^{1}H-N.M.R. (CCl_4): $\delta = 0.68$ (s, 3H, CH_3); 1.08 (s, 3H, CH_3); 1.5–3.2 (m, 9H, 4 CH_2 and CH); 5.0 (q_{AB}, $J_{AB} = 12$ Hz, 2H, H_2C—OCO); 6.9–7.4 ppm (m, 9 H_{arom}).

5-Oxo-3,3,6-trimethyl-8,9-benzodecenolide (8c):
Alkylation of 2-methyldimedone[7] (**5c**; 4.62 g, 30 mmol) with chloride **4** (6.54 g, 33 mmol) gives a semi-crystalline crude product (8.5 g; 90 %), which on recrystallization from 95 % ethanol furnishes the pure *C*-alkylated compound **6c**; yield: 3.6 g (38 %); colorless rods; m.p. 93–95°.

$C_{19}H_{24}O_4$	calc.	C 72.13	H 7.65
(316.4)	found	72.01	7.71

I.R. (KBr): $\nu_{max} = \sim 1750, 1721, 1692\,cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 0.91$ (s, 6H, $2CH_3$); 1.25 (s, 3H, CH_3); 2.07 (s, 3H, AcO); 2.45 (s, 4H, $2CH_2CO$); 3.20 (s, 2H, $H_2CC_6H_4$); 5.12 (s, 2H, H_2C—OAc); 7.0–7.4 ppm (m, 4 H_{arom}).

Acid hydrolysis of the pure *C*-alkylated compound **6c** (10 mmol, 3.16 g) affords the hydroxy diketone **7c** (2.4 g; 88 %), a pale-yellow gum; I.R. (film): $\nu_{max} = 3460, 1724, 1695\,cm^{-1}$; which is transformed into the corresponding ketolactone **8c**, under the usual intramolecular reverse Dieckmann conditions, in a quantitative yield. Short-path distillation (120°/0.25 torr) furnishes a colorless, viscous liquid, yield: 2.1 g (76 % from intermediate **6c**).

$C_{17}H_{22}O_3$	calc.	C 74.42	H 8.08
(274.4)	found	74.30	8.10

I.R. (neat): $\nu_{max} = 1739, 1709\,cm^{-1}$.

^{1}H-N.M.R. (CCl_4): $\delta = 0.72$ (s, 3H, CH_3); 1.13 (s, 3H, CH_3); 1.19 (d, $J = 7$ Hz, 3H, CH_3); 1.65–3.1 (m, 7H, 3 CH_2 and CH); 5.0 (q_{AB}, $J_{AB} = 13$ Hz, 2H, H_2C—OCO); 7.1–7.4 ppm (m, 4 H_{arom}).

Preparation of this ketolactone (**8c**) directly from the crude alkylation product, as in the previous two examples, resulted in 31 % yield based on 2-methyldimedone.

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