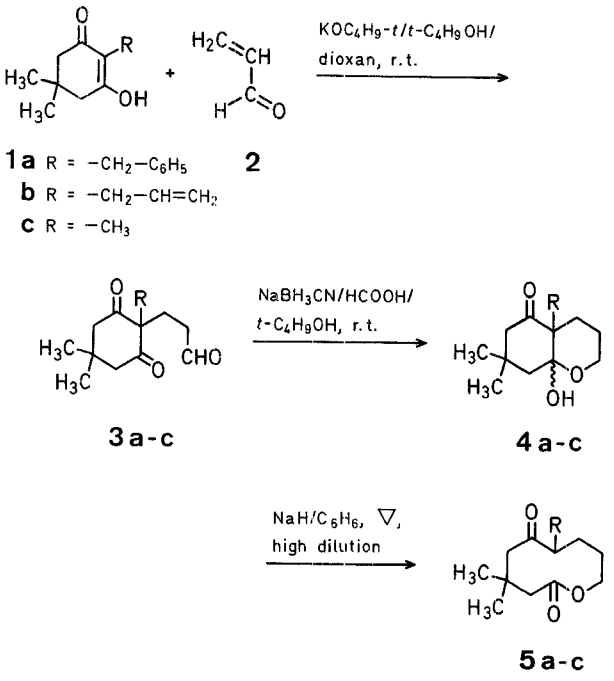

Synthesis of 6-Alkyl-3,3-dimethyl-5-oxononanolides by Intramolecular Reverse Dieckmann Reaction*,[1]

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We have recently synthesized several 9- and 11-membered ketolactones by a novel lactonization procedure involving the intramolecular reverse Dieckmann reaction of the suitably 2,2-disubstituted dimedones[3-6]. We here report the synthesis of the title lactones **5a-c** from the 2-alkyldimedones **1a-c** by alkylation with acrolein (**2**), followed by the selective reduction of the aldehydic carbonyl group of the adducts **3a-c** with sodium cyanoborohydride, and subsequent sodium hydride-induced lactonization of the hydroxy-ketones **4a-c** in boiling benzene.

Michael addition of 2-alkyldimedones[5,7,8] **1a-c** to acrolein (**2**) proceeded smoothly at room temperature in *t*-butanol/dioxan (1:1), containing a catalytic amount of potassium *t*-butoxide, and furnished the desired adducts **3a-c** in 70–90% yield. The selective reduction of the formyl group of these diketo-aldehydes **3a-c**, carrying the two ketonic functions in a relatively hindered position, was initially attempted with sodium borohydride in *t*-butanol—a process found to be moderately successful in the homologous series of 2-alkyl-2-(2′-oxoethyl)dimedones[6]. However, under these conditions, the adduct **3a** yielded a mixture of products (T.L.C.) from which small amounts of 2-benzyldimedone (**1a**) and ketolactone **5a** were isolated after a laborious purification. Evidently, the alkaline medium of the reaction mixture provoked the retro-Michael reaction of the adduct **3a**, while the reduction product **4a** was partially lactonized. Therefore, we investigated the acid-catalyzed reduction of these compounds with sodium cyanoborohydride[9] and found that the desired reduction could be effected in an excellent yield in *t*-butanol, acidified with formic acid, and using only one mol equivalent of the reducing agent.

The resulting hydroxy-diketones were entirely in the cyclic form **4a-c**, showing infrared absorptions for the hydroxy group between 3350–3450 cm^{-1} and only one peak in the carbonyl region (1680–1695 cm^{-1}), instead of the two bands (~1725 and ~1695 cm^{-1}) observed for the 2,2-dialkyldimedones[8]. The crude products **4a-c** were essentially pure as evidenced by only one major spot (T.L.C.), followed by small amounts of more polar impurities; their attempted crystallization was unsuccessful, probably due to the presence of diastereoisomeric cyclic forms **4a-c**. Therefore, after a brief treatment with a pinch of charcoal, these products were subjected to the intramolecular reverse Dieckmann reaction. However, owing to the formation of dimeric lactones in an analogous series[5], the sodium hydride-induced lactonization was carried out using a modified high-dilution technique[10], in the present case, and afforded the desired ketolactones **5a-c** in 60–64% yield.

Acrolein was freshly distilled from hydroquinone, the distillate protected from light and collected over hydroquinone (~1%). Other routine experimental procedures are those reported in our recent publications[4,5,11].

Michael Addition of 2-Alkyldimedones 1a-c to Acrolein (2); General Procedure:

To a stirred solution of 2-alkyldimedone **1** (40 mmol) in anhydrous dioxan (20 ml) and *t*-butanol (40 ml) containing potassium *t*-butoxide (1 molar in *t*-butanol; 0.5 ml), is added dropwise freshly distilled acrolein (**2**; 4.0 ml, 3.36 g, 50 mmol) diluted with dioxan (20 ml). After further stirring at room temperature for 1–2 h, the homogeneous reaction mixture is allowed to stand for 14–18 h; T.L.C. (silica gel/benzene/1–5% ethanol/iodine vapour) at this stage shows the absence of the starting material and a higher R_f spot for the adduct. Acetic acid (0.5 ml) is added and the solvent removed

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on a rotary evaporator. The resulting yellowish, thick liquid is taken up in benzene (80 ml) and successively washed with water, 0.1 normal sodium hydroxide, water again, and brine. Drying and evaporation affords the crude product in almost quantitative yield, which is purified and characterized as described below.

2-Benzyl-2-(3-oxopropyl)-dimedone **(3a):**
Recrystallization of the crude solid from *t*-butanol affords colorless needles; yield: 9.8 g (85%); m.p. 96–97 °C.

$C_{18}H_{22}O_3$	calc.	C 75.50	H 7.74
(286.4)	found	75.50	7.77

I.R. (KBr): $\nu = 1727, 1706, 1684\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 0.80$ (s, 3H, CH_3); 0.90 (s, 3H, CH_3); 2.21 (A_2B_2, 4H, CH_2CH_2CHO); 2.54 (s, 4H, $2CH_2CO$); 3.10 (s, 2H, $CH_2C_6H_5$); 7.2 (m, $5H_{arom}$); 9.75 ppm (t, $J \approx 1$ Hz, 1H, CHO).

2-Allyl-2-(3-oxopropyl)-dimedone **(3b):**
Crystallization of the crude viscous liquid from a mixture of benzene and petroleum ether gives colorless fine rods; yield: 8.6 g (91%); m.p. 40–41 °C.

$C_{14}H_{20}O_3$	calc.	C 71.16	H 8.53
(236.3)	found	70.85	8.31

I.R. (KBr): $\nu = 1730, 1704, 1650\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 0.95$ (s, 3H, CH_3); 1.09 (s, 3H, CH_3); 1.8–3.0 (m, 10H, $5CH_2$); 4.9–5.9 (m, 3H, CH_2-CH); 9.8 ppm (t, $J \approx 1$ Hz, 1H, CHO).

2-Methyl-2-(3-oxopropyl)-dimedone **(3c):**
Recrystallization of the crude solid from benzene/petroleum ether furnishes colorless needles; yield: 5.9 g (70%); m.p. 50–51 °C.

$C_{12}H_{18}O_3$	calc.	C 68.55	H 8.63
(210.3)	found	68.38	8.54

I.R. (KBr): $\nu = 1721, 1692\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.01$ (s, 6H, $2CH_3$); 1.30 (s, 3H, CH_3); 2.24 (A_2B_2, 4H, CH_2CH_2CHO); 2.64 (s, 4H, $2CH_2CO$); 9.85 ppm (t, $J \approx 1$ Hz, 1H, CHO).

Selective Reduction of Diketo-aldehydes 3a–c; General Procedure:
Sodium cyanoborohydride (630 mg, 10 mmol) is added to a stirred solution of the adduct **3a–c** (10 mmol) in *t*-butanol (50 ml; in case of the adduct **3a**, 2 ml of benzene are also added to obtain a complete solution), containing formic acid (99%; 1.9 ml, 2.32 g, 50 mmol). The resulting suspension, pH ~ 4, is stirred at room temperature for 1.5–2 h, T.L.C. (as above) at this stage shows the absence of the starting material. The reaction mixture is diluted with benzene (50 ml) and washed with water and saturated solution of sodium hydrogen carbonate. Drying and evaporation affords the crude product as a yellowish gum; yield: ~100%.

4a: I.R. (neat): $\nu = 3415, 1686\ cm^{-1}$.

4b: I.R. (neat): $\nu = 3460, 1695\ cm^{-1}$.

4c: I.R. (neat): $\nu = 3400, 1681\ cm^{-1}$.

Attempted crystallization from benzene containing charcoal, benzene/petroleum ether, and several other common solvents was unsuccessful. Therefore, the crude product was lactonized as described below.

Lactonization of Hydroxy-ketones 4a–c; General Procedure:
The above hydroxy-ketone **4a–c** (10–20 mmol) dissolved in anhydrous benzene (50–100 ml) is added very slowly during 5–10 h, through a dilution device[10], to magnetically stirred and vigorously refluxing benzene (100–200 ml), containing sodium hydride (80% suspension; 30–60 mg, 1–2 mmol). The reaction mixture is further stirred and refluxed for 1–2 h; T.L.C. (as above) shows only traces of the starting material and an upper spot corresponding to the desired ketolactone. The cooled reaction mixture is successively washed with water, 0.1 normal hydrochloric acid, and brine. Drying and evaporation furnishes the crude product; yield: 85–95%.

6-Benzyl-3,3-dimethyl-5-oxononanolide **(5a):**
Crystallization of the crude, viscous liquid (5.5 g; 95% from 20 mmol of the adduct **3a**) from petroleum ether gives colorless needles; yield: 3.7 g (64%); m.p. 65–66 °C.

$C_{18}H_{24}O_3$	calc.	C 74.97	H 8.39
(288.4)	found	75.18	8.39

I.R. (KBr): $\nu = 1739, 1706\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 0.98$ (s, 3H, CH_3); 1.31 (s, 3H, CH_3); 1.5–3.2 (m, 11H, $5CH_2$ and CH); 4.0 (m, 2H, CH_2OCO); 7.3 ppm (m, $5H_{arom}$).

6-Allyl-3,3-dimethyl-5-oxononanolide **(5b):**
The yellowish viscous liquid (4.4 g; 92% based on 20 mmol of the adduct **3b**) is chromatographed over silica gel (160 g) and eluted with benzene containing successively increasing amounts of ethanol (0–5%). After a few fractions eluted with benzene (360 mg; T.L.C. shows it to be a mixture of two superimposed components), the desired ketolactone **5b**; yield: 2.86 g (60%), is eluted with benzene/ethanol (1–4%). The last few fractions (315 mg), eluted with benzene/ethanol (5%), also contain the ketolactone **5b** contaminated with impurities. Short-path distillation (110–120 °C/1 torr) affords the analytical sample as a colorless, viscous liquid.

$C_{14}H_{22}O_3$	calc.	C 70.56	H 9.30
(238.3)	found	70.98	9.26

I.R. (film): $\nu = 1745, 1715, 1647\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.08$ (s, 3H, CH_3); 1.33 (s, 3H, CH_3); 1.5–3.0 (m, 11H, $5CH_2$ and CH); 3.95 (m, 2H, CH_2OCO); 4.8–6.1 ppm (m, 3H, $CH=CH_2$).

5-Oxo-3,3,6-trimethylnonanolide **(5c):**
Recrystallization of the crude solid product (1.8 g; 85% from 10 mmol of the adduct **3c**) from benzene/petroleum ether furnishes colorless rods; yield: 1.32 g (62%); m.p. 71–72 °C.

$C_{12}H_{20}O_3$	calc.	C 67.89	H 9.50
(212.3)	found	67.81	9.53

I.R. (KBr): $\nu = 1736, 1695\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.00$ (d, $J = 7$ Hz, 3H, CH_3); 1.07 (s, 3H, CH_3); 1.30 (s, 3H, CH_3); 1.5–2.9 (m, 9H, $4CH_2$ + CH); 3.92 ppm (m, 2H, CH_2OCO).

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* Although frequently used for this process, the term "intramolecular reverse Dieckmann reaction" is not strictly correct; alternative terms are: (a) lactonization of cyclic 1,3-diones or (b) intramolecular alcoholysis of cyclic 1,3-diones.

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