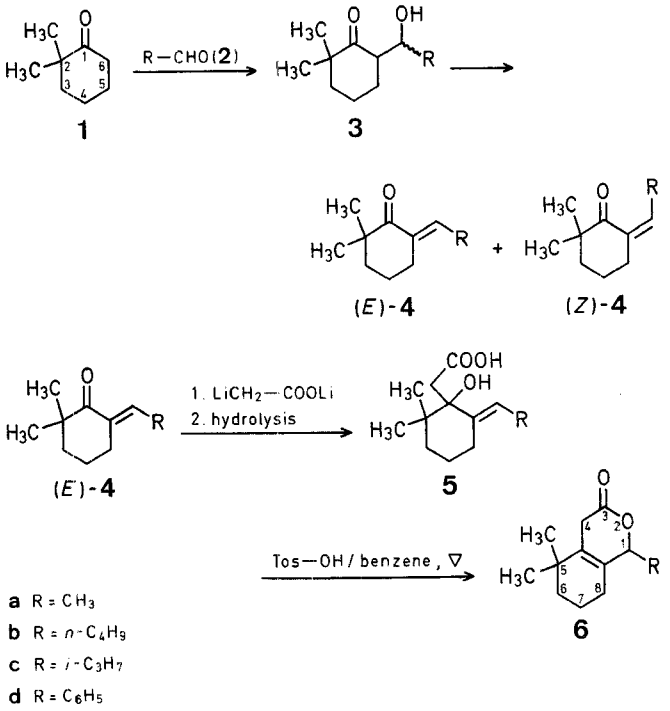

Introduction of a carboxymethyl group at C-1 to give the unsaturated hydroxy acids **5** could be achieved by 1,2-addition of lithium lithioacetate (dianion of acetic acid)[7] to the alkylidenecyclohexanones (*E*)-**4**. In all cases, N.M.R. investigation of the crude reaction mixtures revealed the presence of only small amounts (< 10%) of the 1,4-addition products [The 1,4-addition products show a slight difference in the chemical shift of the methylene protons adjacent to the carboxy moiety (—CH_2—COOH; 1,2-adduct: $\delta = 2.75$ ppm; 1,4-adduct: $\delta = 2.65$ ppm)]. The adducts **5** can be cyclized to the desired lactones **6** by treatment with *p*-toluenesulfonic acid in benzene.

The structures of all products obtained were confirmed by mass- and ^{1}H-N.M.R. spectroscopy and microanalysis or exact mass measurements.

Synthesis of δ-Substituted δ-Lactones

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For a planned total synthesis of podolactones[1,2] we required efficient methods for the anellation of a β,γ-unsaturated δ-substituted δ-lactone, starting from a ketone. Recently, we published one procedure for this anellation[3]; we have now developed a second method which complements the former one and in which the variation of substituents at the δ-position is accomplished by the choice of the aldehyde used in the aldol condensation.

The aldol condensation of 2,2-dimethylcyclohexanone[4] (**1**) with various aldehydes (**2**) according to Ref.[5] yielded mixtures of *threo*- and *erythro*-β-hydroxyketones (**3**). These mixtures were not purified, but dehydrated to the corresponding enones **4** using *p*-toluenesulfonic acid in benzene. After work-up, the crude reaction products were purified by column chromatography to give the pure (*Z*)- and (*E*)-isomers of **4**. The isomers (*E*)-**4** were the main products which implicates that the *erythro*-β-ketols were formed predominantly during the aldol condensation[6].

2-Alkylidene-6,6-dimethylcyclohexanones (4); General Procedure:
To a stirred solution of butyllithium (22 mmol) in hexane (14.7 ml) at 0 °C is added dropwise, over 10 min, a solution of diisopropylamine (2.42 g, 24 mmol) in dry tetrahydrofuran (75 ml) under a nitrogen atmosphere. After 15 min, the solution is cooled to −78 °C and then a solution of 2,2-dimethylcyclohexanone[4] (**1**; 2.53 g, 20 mmol) in dry tetrahydrofuran (25 ml) is added dropwise over 10 min. The solution is stirred for another 30 min and then a solution of the aldehyde (**2**; 22 mmol) in dry tetrahydrofuran (20 ml) is added dropwise. Stirring is continued for 45 min, 4 normal hydrochloric acid (5.5 ml) is added, and the mixture is allowed to warm to room temperature. Then, 0.5 normal hydrochloric acid (75 ml) is added and the mixture is extracted with ether (3 × 100 ml). The organic layer is washed with water (75 ml) and a saturated sodium chloride solution (75 ml), and dried with sodium sulfate. After evaporation of the solvent, the residue is dissolved in dry benzene (100 ml), *p*-toluenesulfonic acid (100 mg) is added, and the mixture is refluxed in a Dean-Stark apparatus for 90 min. After cooling, the reaction mixture is poured into saturated sodium hydrogen carbonate solution (75 ml). The aqueous layer is extracted with ether (2 × 50 ml) and the combined organic layers are washed with saturated sodium chloride solution (50 ml) and dried with sodium sulfate. The solvent is evaporated and the residue is chromatographed over silica gel (75 g; ether/petroleum ether 1/24 as eluent) to afford the isomeric alkylideneketones (*E*)-**4** and (*Z*)-**4** as oils of moderate stabilities.

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Table 1. 2-Alkylidene-6,6-dimethylcyclohexanones **(4)** prepared

Compound	Yield [%]	(*E*/*Z*)-Ratio	Properties	Molecular formula or Lit. Data	Mass-Spectral Fragmentation[a] (70 eV) *m/e* (intensity, %)	High-Resolution M.S.[b] (70 eV)	
						calculated	*m/e* found
(*E*)-**4a**			oil	$C_{10}H_{16}O$	152 (M^+, 12), 109 (57), 69 (100)	152.1201	152.1201
	81	87/13		(152.2)			
(*Z*)-**4a**			oil		152 (M^+, 51), 109 (77), 69 (100)		152.1203
(*E*)-**4b**			oil	$C_{13}H_{22}O$	194 (M^+, 13), 179 (11), 69 (100)	194.1671	194.1670
	60	82/18		(194.3)			
(*Z*)-**4b**			oil		194 (M^+, 100), 179 (81), 69 (90)		194.1668
(*E*)-**4c**			oil	$C_{12}H_{20}O$	180 (M^+, 52), 165 (38), 69 (100)	180.1514	180.1509
	74	89/11		(180.3)			
(*Z*)-**4c**			oil		180 (M^+, 70), 165 (100), 69 (60)		180.1509
(*E*)-**4d**	60	100/0	m.p. 76–77 °C	m.p. 79–80 °C[8]			

[a] Measured with a VG MM 70-70 instrument.

[b] Measured with an AEI-MS-902 instrument.

Table 2. 2-Alkylidene-6,6-dimethyl-1-hydroxycyclohexaneacetic Acids **(5)** prepared

5	Yield [%]	m.p.[a] [°C]	Molecular formula[b]	M.S.[c] *m/e* (intensity, %)
a	84	97–100°	$C_{12}H_{20}O_3$ (212.3)	212 (M^+, 13), 194 (54), 43 (100)
b	79	28–29°	$C_{15}H_{26}O_3$ (254.4)	254 (M^+, 4), 236 (18), 179 (100), 69 (46)
c	81	91.5–92.0°	$C_{14}H_{24}O_3$ (240.3)	240 (M^+, 1), 222 (8), 179 (100)
d	84	118.5–119.0°	$C_{17}H_{22}O_3$ (274.35)	274 (M^+, 3), 256 (40), 142 (100), 105 (96)

[a] Uncorrected.

[b] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.23; H, ±0.23.

[c] Measured with a VG MM 70-70 instrument at 70 eV.

Table 3. 1-Substituted 5,5-Dimethyl-3-oxo-3,4,5,6,7,8-hexahydro-1*H*-2-benzopyrans **(6)** prepared

6	Yield [%]	m.p.[a] [°C]	Molecular formula[b]	M.S.[c] *m/e* (relative intensity, %)
a	80	38.5–39.5°	$C_{12}H_{18}O_2$ (194.3)	194 (M^+, 40), 43 (100)
b	96	49.5–50.0°	$C_{15}H_{24}O_2$ (236.3)	236 (M^+, 15), 179 (100), 85 (48)
c	83	32.0–32.5°	$C_{14}H_{22}O_2$ (222.3)	222 (M^+, 7), 179 (100)
d	98	99.0–99.5°	$C_{17}H_{20}O_2$ (256.3)	256 (M^+, 30), 142 (27), 105 (100)

[a] Uncorrected.

[b] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.30; H, ±0.25.

[c] Measured with a VG MM 70-70 instrument at 70 eV.

2-Alkylidene-6,6-dimethyl-1-hydroxycyclohexaneacetic Acids (5); General Procedure:

To a stirred solution of butyllithium (25 mmol) in hexane (16.7 ml) at 0 °C is added dropwise, over 10 min, a solution of diisopropylamine (2.64 g, 26 mmol) in dry tetrahydrofuran (50 ml) under a nitrogen atmosphere. After 15 min, hexamethylphosphoric triamide (5.92 g, 33 mmol) is added. The solution is cooled to −20 °C and then a solution of acetic acid (0.67 g, 11 mmol) in dry tetrahydrofuran (60 ml) is added

Table 4. ^{1}H-N.M.R. Data[a] of Compounds **4, 5,** and **6**

Compound	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]
(*E*)-**4a**	1.11 (s, 6H, 2-CH_3); 1.6–1.8 (m, 7H); 2.45 (m, 2H, =C—CH_2—); 6.50 (tq, 1H, =C—H)
(*Z*)-**4a**	1.08 (s, 6H, 2-CH_3); 1.6–1.8 (m, 7H); 2.4 (m, 2H, =C—CH_2—); 5.60 (tq, 1H, =C—H)
(*E*)-**4b**	0.7–1.6 (m, 7H); 1.10 (s, 6H, 2-CH_3); 1.7 (m, 4H_{ring}); 2.1 (m, 2H, =C—CH_2—); 2.4 [m, 2H, =C—CH_2— (ring)]; 6.39 (tt, 1H, C=C—H)
(*Z*)-**4b**	0.7–1.6 (m, 7H); 1.08 (s, 6H, 2-CH_3); 1.7 (m, 4H_{ring}); 2.1 (m, 2H, =C—CH_2—); 2.4 [m, 2H, =C—CH_2— (ring)]; 5.45 (tt, 1H, C=C—H)
(*E*)-**4c**	0.98 [d, 6H, —CH(CH_3)$_2$]; 1.09 (s, 6H, 2-CH_3); 1.7 (m, 4H, —CH_2—CH_2—); 2.4 (m, 3H, —CH—C=C—CH_2—); 6.21 (dt, 1H, =C—H)
(*Z*)-**4c**	0.96 [d, 6H, —CH(CH_3)$_2$]; 1.08 (s, 6H, 2-CH_3); 1.6 (m, 4H, —CH_2—CH_2—); 2.4 (m, 3H, —CH—C=C—CH_2—); 5.22 (dt, 1H, =C—H)
(*E*)-**4d**	1.17 (s, 6H, 2-CH_3); 1.7 (m, 4H); 2.7 (m, 2H); 7.3 (m, 5H_{arom}, =C—H)
5a	0.88 (s, 3H, CH_3); 0.93 (s, 3H, CH_3); 1.3–1.9 (m, 4H); 1.60 (d, 3H, =C—CH_3); 2.0–2.5 (m, 2H); 2.73 (dd, 2H, —CH_2—COOH); 6.0–7.0 (2H[b])
5b	0.8–2.5 (m, 15H); 0.88 (s, 3H, CH_3); 0.93 (s, 3H, CH_3); 2.72 (dd, 2H, —CH_2—COOH); 5.36 (t, 1H, =CH); 6.0–7.0 (2H[b])
5c	0.88 (d, 3H, —CH—CH_3); 0.90 (s, 3H, —CH_3); 0.93 (s, 3H, —CH_3), 0.99 (d, 3H, —CH—CH_3); 1.4–1.8 (m, 4H); 1.8–2.8 (m, 3H), 2.74 (dd, 2H, —CH_2—COOH); 5.20 (d, 1H, C=C—H); 7.0–8.0 (2H[b])
5d	0.99 (s, 6H, 2-CH_3); 1.3–1.8 (m, 4H); 1.8–2.8 (m, 2H); 2.79 (dd, 2H, —CH_2—COOH); 6.45 (s, 1H, =C—H); 7.1 (m, 5H_{arom}); 6.5–7.5 (2H[b])
6a	1.01 (s, 6H, 2-CH_3); 1.3–1.9 (m, 6H); 1.41 (d, 3H, CH—CH_3); 2.96 (q, —CH_2—C=O); 4.80 (q, 1H, —CH—O—)
6b	0.8–2.1 (m, 15H); 1.00 (s, 3H, —CH_3); 1.02 (s, 3H, CH_3); 2.98 (q, 2H, —CH_2—C=O—); 4.6 (m, 1H, —CH—O—)
6c	0.82 (d, 3H, CH—CH_3); 1.01 (s, 6H, 2-CH_3); 1.09 (d, 3H, CH—CH_3); 1.3–1.9 (m, 6H); 2.93 (q, 2H, —CH_2—C=O); 4.48 (q, 1H, —CH—O—)
6d	1.07 (s, 6H, 2-CH_3); 1.3–1.9 (m, 6H); 3.01 (q, 2H, —CH_2—C=O); 5.51 (s, 1H, —CH—O—); 7.2 (m, 5H_{arom})

[a] Recorded on a Hitachi-Perkin Elmer R-24B instrument at 60 MHz.

[b] Exchangeable with D_2O.

dropwise over 10 min. The mixture is heated at 50 °C for a period of 1.5 h and then cooled to −78 °C. A solution of the alkylideneketone [(*E*)-**4**; 10 mmol] in dry tetrahydrofuran (10 ml) is added dropwise over a period of 15 min and this solution is stirred for 16 h under dry nitrogen during which time it is allowed to warm to room temperature. The mixture is poured into 1 normal hydrochloric acid (75 ml) and this mixture is extracted with chloroform (3 × 50 ml). The organic layer is washed with water (50 ml) and saturated sodium chloride solution (50 ml) and is dried with sodium sulfate. After evaporation of the solvent, the residue is chromatographed on silica gel (50 g; ether as eluent) and the condensation product **5** is isolated.

1-Substituted 5,5-Dimethyl-3-oxo-3,4,5,6,7,8-hexahydro-1*H*-2-benzopyrans (6); General Procedure:

A mixture of the 2-alkylidene-6,6-dimethyl-1-hydroxycyclohexaneacetic acid (**5**; 5 mmol) and *p*-toluenesulfonic acid (100 mg) in dry benzene (50 ml) is refluxed in a Dean-Stark apparatus for 2 h. After cooling, the mixture is poured into saturated sodium hydrogen carbonate solution (75 ml). The water layer is extracted with ether (2 × 25 ml) and the combined organic layers are washed with saturated sodium chloride solution (50 ml) and dried with sodium sulfate. The solvent is evaporated and the residual crude product **6** purified by column chromatography on silica gel (50 g) using ether/petroleum ether (1/19) as eluent.

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