

### 3,3-Diethoxypropyl-lithium: A Masked Lithium Propanal Homoenoate in Organic Synthesis<sup>1</sup>

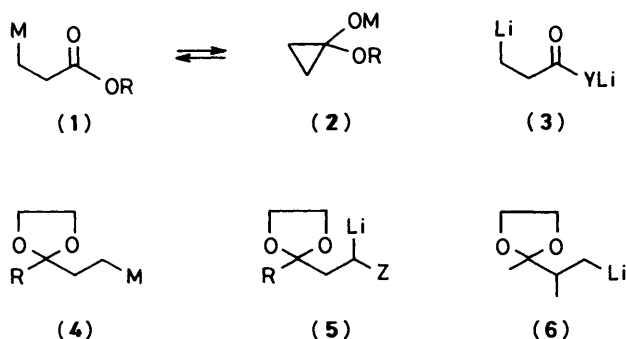
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3,3-Diethoxypropyl-lithium is prepared by lithiation of the corresponding chlorinated precursor with lithium naphthalenide at  $-78^{\circ}\text{C}$ ; the reaction of this masked propanal homoenoate with different electrophilic reagents [ $\text{H}_2\text{O}$ ,  $\text{D}_2\text{O}$ ,  $(\text{PhCH}_2)_2\text{S}_2$ ,  $\text{PrCHO}$ ,  $\text{Bu}^t\text{CHO}$ ,  $\text{PhCHO}$ ,  $n\text{-C}_7\text{H}_{15}\text{CHO}$ ,  $\text{PhCH}=\text{CHCHO}$ ,  $[\text{CH}_2]_5\text{CO}$ ,  $[\text{CH}_2]_7\text{CO}$ ,  $\text{PhCOMe}$ ,  $\text{PhCH}=\text{NPh}$ ,  $\text{PhCONEt}_2$ ,  $\text{PhCN}$ ,  $c\text{-C}_6\text{H}_{11}\text{CN}$ ,  $4\text{-MeC}_6\text{H}_4\text{CN}$ ] leads to the corresponding mono- and bi-functionalized compounds. In the case of the reaction with aldehydes or ketones the prepared crude products are oxidized with *m*-chloroperbenzoic acid, yielding directly the  $\gamma$ -substituted butyrolactones.

The chemistry of homoenoate derivatives has been the subject of attention recently,<sup>2</sup> mainly in relation to the homoaldol reaction. In the literature have been described either stable ( $\text{M} = \text{TiCl}_3$ ,<sup>3a,b,4</sup>  $\frac{1}{2}\text{Zn}$  or  $\text{ZnI}_2$ ,<sup>3c-g</sup>  $\text{GaCl}_2$ ,<sup>3c</sup>  $\text{NbCl}_4$ ,<sup>3c</sup>  $\text{CdCl}_2$ ,<sup>3c</sup>  $\text{SnCl}_3$  or  $\text{SnBu}_3$ ,<sup>3b,c,h</sup>  $\text{SbCl}_4$ ,<sup>3c</sup>  $\text{TeCl}_3$ ,<sup>3c</sup>  $\text{HgOAc}$  or  $\text{HgCl}_2$ ,<sup>3c</sup>  $\text{BiCl}_2$ ,<sup>3c</sup>) or transient<sup>5</sup> [iron(III),<sup>6</sup> copper(II),<sup>7</sup> silver,<sup>5</sup> lead(IV),<sup>8</sup> palladium(II),<sup>5</sup> or lanthanoid metal (La, Ce, Nd, Sm)<sup>9</sup> species] systems of type (1), siloxycyclopropanes being the most important starting materials.† However, the corresponding derivatives of the main-group metals are very unstable species and decompose spontaneously after formation yielding metallic cyclopropanolates (2).<sup>2</sup> In our hands, there are only two examples of such a type of stable lithium homoenoate (3) ( $\text{Y} = \text{O}$ ,<sup>10</sup>  $\text{PnN}$ ;<sup>11</sup> prepared by lithiation or Sn/Li-transmetalation starting from the adequate bromo or tributyltin derivatives), in which the intramolecular addition to the carbonyl group is inhibited due to the presence of the anionic carboxylate or amide moiety. Another possible way to overcome the above mentioned decomposition is the use of a 'defensive' strategy;<sup>2c</sup> thus, intermediates (4) ( $\text{M} = \text{MgBr}$ <sup>12</sup>) and (5) ( $\text{Z} = \text{PhSO}_2$ ,<sup>2c</sup>  $\text{NO}_2$ ,<sup>13</sup>  $\text{Ph}_3\text{P}^+$ ,<sup>14</sup> or  $\text{Ph}_2\text{PO}$ <sup>15</sup>) have been described. There is only one non-stabilized lithium derivative (6) of the type (4) with  $\text{M} = \text{Li}$  described very recently,<sup>16</sup> which is prepared by reaction of the corresponding brominated system with *t*-butyl-lithium at  $-78^{\circ}\text{C}$ .

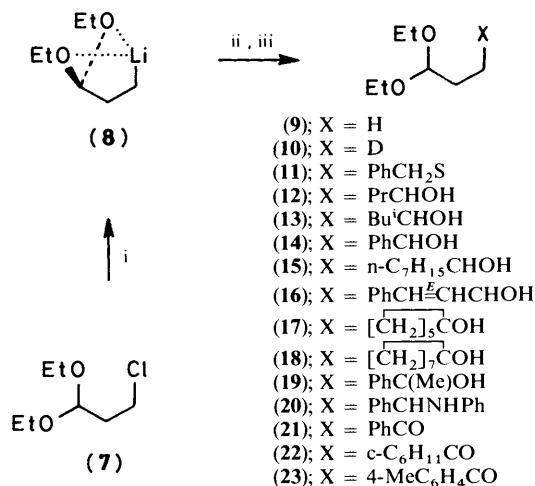
In this paper we describe the first preparation and synthetic application of a masked lithium homoenoate derived from propanal (8), that is a new lithium  $d^3$ -reagent<sup>17</sup> of type (4) with  $\text{R} = \text{H}$ .



† For an excellent review on this subject see ref. 5. We thank Professor E. Nakamura for sending a copy of this manuscript to us prior to publication.

### Results and Discussion

The reaction of 3-chloropropanal diethyl acetal (7) with lithium naphthalenide<sup>‡</sup> at  $-78^{\circ}\text{C}$  led to the corresponding 3,3-diethoxypropyl-lithium (8). The *in situ* treatment of this intermediate with different electrophilic reagents (water, deuterium oxide, dibenzyl disulphide, aldehydes or ketones, benzylideneaniline, *N,N*-diethylbenzamide, or nitriles) yielded, after hydrolysis, the expected 3-substituted propanal diethyl acetals (9)–(23) (Scheme 1 and Table 1). In the case of the



**Scheme 1. Reagents and conditions:** i,  $\text{Li}^+ \text{C}_{10}\text{H}_8^-$   $-78^{\circ}\text{C}$ ; ii,  $\text{E}^+ = \text{H}_2\text{O}$ ,  $\text{D}_2\text{O}$ ,  $(\text{PhCH}_2)_2\text{S}_2$ ,  $\text{PrCHO}$ ,  $\text{Bu}^t\text{CHO}$ ,  $\text{PhCHO}$ ,  $n\text{-C}_7\text{H}_{15}\text{CHO}$ ,  $\text{PhCH}=\text{CHCHO}$ ,  $[\text{CH}_2]_5\text{CO}$ ,  $[\text{CH}_2]_7\text{CO}$ ,  $\text{PhCOMe}$ ,  $\text{PhCH}=\text{NPh}$ ,  $\text{PhCONEt}_2$ ,  $\text{PhCN}$ ,  $c\text{-C}_6\text{H}_{11}\text{CN}$ ,  $4\text{-MeC}_6\text{H}_4\text{CN}$ ;  $-78$  to  $20^{\circ}\text{C}$ ; iii,  $\text{HCl-H}_2\text{O}$

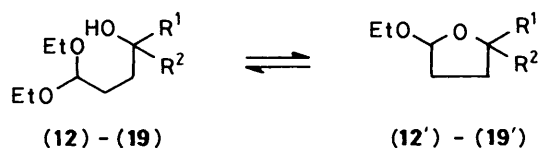
products (12)–(19) (Table 1, entries 4–11) derived from carbonyl compounds, they undergo intramolecular cyclization<sup>18</sup> at room temperature (after a time) or on distillation<sup>19</sup> under reduced pressure, affording a mixture of (12)–(19) and the cyclic acetals (12')–(19') (Scheme 2). When *N,N*-diethylbenzamide or benzonitrile (Table 1, entries 13 and 14) were used as electrophiles the same product (21) was obtained, the yield being higher in the second case.

‡ The metallation with lithium powder at low temperature failed (J. Barluenga, J. Flórez, and M. Yus, *J. Chem. Soc., Chem. Commun.*, 1982, 1153).

**Table 1.** Formation of 3,3-diethoxypropyl-lithium (8) and reaction with electrophiles; preparation of compounds (9)—(23)

Entry	Electrophile	Product	% Yield <sup>a</sup>
1	H <sub>2</sub> O	(9)	80
2	D <sub>2</sub> O	(10)	82
3	(PhCH <sub>2</sub> ) <sub>2</sub> S <sub>2</sub>	(11)	85
4	PrCHO	(12)	54
5	Bu <sup>i</sup> CHO	(13)	68
6	PhCHO	(14)	63
7	n-C <sub>7</sub> H <sub>15</sub> CHO	(15)	56
8	PhCH=CHCHO	(16)	77
9	[CH <sub>2</sub> ] <sub>5</sub> CO	(17)	71
10	[CH <sub>2</sub> ] <sub>7</sub> CO	(18)	81
11	PhCOMe	(19)	69
12	PhCH=NPh	(20)	70
13	PhCONEt <sub>2</sub>	(21)	41
14	PhCN	(21)	52
15	c-C <sub>6</sub> H <sub>11</sub> CN	(22)	49
16	4-MeC <sub>6</sub> H <sub>4</sub> CN	(23)	44

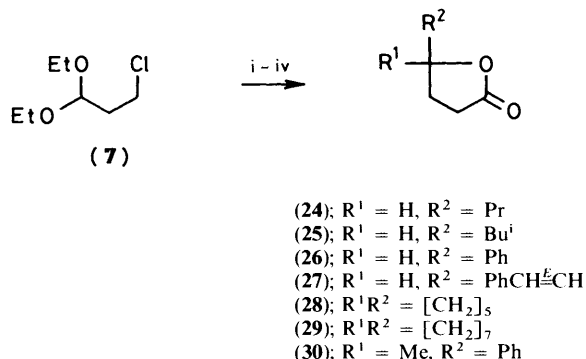
<sup>a</sup> Isolated yield based on initial amount of starting material (7).



Scheme 2.

In general, products (9)—(23) should be considered as 3-functionalized protected propanal derivatives, whose acid hydrolysis easily yields the corresponding deprotected carbonyl systems.

Finally, the *in situ* oxidation of the initially obtained crude products (12)—(19) with *m*-chloroperbenzoic acid (MCPBA) led to  $\gamma$ -substituted butyrolactones (24)—(30) as reaction products (Scheme 3 and Table 2). This class of compounds is



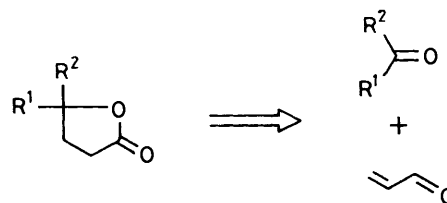
**Scheme 3.** Reagents and conditions: i, Li<sup>+</sup> C<sub>10</sub>H<sub>8</sub><sup>-</sup>, -78 °C; ii, R<sup>1</sup>R<sup>2</sup>C=O, -78 to 20 °C; iii, NH<sub>4</sub>Cl; iv, MCPBA-BF<sub>3</sub>·OEt

important not only because they are present in many natural products,<sup>20</sup> but also because they may be easily transformed into the corresponding butenolides.<sup>21</sup> Since the starting material (7) can be easily prepared from acrylaldehyde by addition of hydrogen chloride in ethanol, the tandem process described in Scheme 3 represents a reasonable route to butyrolactones<sup>22</sup> starting from acrylaldehyde and carbonyl compounds (Scheme 4).

**Table 2.**  $\gamma$ -Substituted butyrolactones (24)—(30) from 3-chloropropanal diethyl acetal (7) and carbonyl compounds

Entry	Carbonyl compound	Product	% Yield <sup>a</sup>
1	PrCHO <sup>b</sup>	(24)	44
2	Bu <sup>i</sup> CHO <sup>b</sup>	(25)	52
3	PhCHO	(26)	51
4	PhCH=CHCHO	(27)	62
5	[CH <sub>2</sub> ] <sub>5</sub> CO	(28)	53
6	[CH <sub>2</sub> ] <sub>7</sub> CO	(29)	66
7	PhCOMe	(30)	59

<sup>a</sup> Isolated yield based on initial amount of starting material (7). <sup>b</sup> In Table 1 of our preliminary communication (ref. 1b), these compounds were mistakenly written as EtCHO, Pr<sup>i</sup>CHO respectively (error in R<sup>2</sup> column).



Scheme 4.

## Experimental

The experimental techniques and spectroscopic instrumentation employed in the course of this work were as described in ref. 23.

*Preparation of 3,3-Diethoxypropyl-lithium and Reaction with Electrophiles. Isolation of Compounds (9)—(23). General Procedure.*—To a solution of 3-chloropropanal diethyl acetal (7) (Aldrich, 15 mmol) in tetrahydrofuran (THF) (30 ml) was added a solution of lithium naphthalene in THF (33 mmol) at -78 °C under argon and the mixture was stirred for 6 h at the same temperature. The corresponding electrophile (15 mmol)\* was then added and the mixture was stirred for 2 h, allowing the temperature to rise to 20 °C. The resulting mixture was hydrolysed with water, neutralized with aqueous hydrochloric acid, and extracted with diethyl ether. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated (15 mmHg). Naphthalene was removed under reduced pressure (10<sup>-4</sup> mmHg; 60 °C bath temperature)\* to give an oily residue of pure products (11)—(20); products (21)—(23) were purified by distillation under reduced pressure.

Propanal diethyl acetal (9), b.p. 20—22 °C (10<sup>-1</sup> mmHg) [lit.,<sup>24</sup> 122.8 °C (760 mmHg)];  $\nu$ (neat) 1 100 and 1 020 (C—O) cm<sup>-1</sup>;  $\delta_{\text{H}}$ (CCl<sub>4</sub>) 0.85 (3 H, t, *J* 8 Hz, MeCH<sub>2</sub>CH<sub>2</sub>), 1.1 (6 H, t, *J* 8 Hz, 2  $\times$  MeCH<sub>2</sub>O), 1.65—1.95 (2 H, m, CH<sub>2</sub>CH), 3.35—3.6 (4 H, m, 2  $\times$  CH<sub>2</sub>O), and 4.3 (1 H, t, *J* 6 Hz, CH);  $\delta_{\text{C}}$ (CCl<sub>4</sub>) 8.6 (q, CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>), 15.0 (q, 2  $\times$  CH<sub>3</sub>CH<sub>2</sub>O), 26.5 (t, CH<sub>2</sub>CH<sub>2</sub>OO), 60.2 (t, 2  $\times$  CH<sub>2</sub>O), and 103.8 (d, CH); *m/z* 132 (*M*<sup>+</sup>, <1%), 103 (100), 88 (31), 87 (89), 75 (61), 60 (30), 59 (82), 57 (12), and 17 (31).

3-Deuteriopropanal diethyl acetal (10), b.p. 20—22 °C (10<sup>-1</sup> mmHg);  $\nu$ (neat) 1 120 and 1 020 (C—O) cm<sup>-1</sup>;  $\delta_{\text{H}}$ (CCl<sub>4</sub>) 0.6—0.9 (2 H, m, CH<sub>2</sub>D), 1.1 (6 H, t, *J* 6 Hz, 2  $\times$  MeCH<sub>2</sub>O), 1.8 (2 H, m, CH<sub>2</sub>CH), 3.2—3.6 (4 H, m, 2  $\times$  CH<sub>2</sub>O), and 4.2 (1 H, t, *J* 6 Hz, CH);  $\delta_{\text{C}}$ (CCl<sub>4</sub>) 7.75 (tt, *J*<sub>CD</sub> 19.3 Hz, CH<sub>2</sub>D), 14.5 (q, 2  $\times$  Me), 25.8 (t, CH<sub>2</sub>CD), 59.6 (t, 2  $\times$  CH<sub>2</sub>O), and 103.1 (s, CH); *m/z* 133

\* When H<sub>2</sub>O or D<sub>2</sub>O was used as an electrophile a large excess (ca. 100 mmol) was added. In the final work up, the isolation of products (9) and (10) was carried out by condensation under reduced pressure (10<sup>-1</sup> mmHg) prior to removing naphthalene.

( $M^+$ , <1%), 131 (26), 116 (11), 88 (79), 87 (11), 75 (81), 60 (100), 59 (20), 58 (19), 57 (31), 47 (33), 42 (11), and 41 (26).

**3-Benzylthiopropional diethyl acetal (11)** (Found: C, 66.5; H, 9.0.  $C_{14}H_{22}O_3$  requires C, 66.10; H, 8.72%), oil;  $\nu(\text{neat})$  1 130 and 1 070 (C–O)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}(\text{CCl}_4)$  0.85–1.15 (6 H, m, 2  $\times$  Me), 1.5–1.8 (2 H, m,  $\text{CH}_2\text{CH}$ ), 2.1–2.35 (2 H, m,  $\text{CH}_2\text{CH}_2\text{S}$ ), 3.15–3.65 (6 H, m, 2  $\times$   $\text{CH}_2\text{O}$ ,  $\text{PhCH}_2\text{S}$ ), 4.2–4.5 (1 H, m, CH), and 7.0–7.3 (5 H, m, Ph);  $\delta_{\text{C}}(\text{CCl}_4)$  15.1 (q, 2  $\times$  Me), 26.3, 33.3 (2 t,  $\text{CH}_2\text{CH}_2\text{S}$ ), 35.0 (t,  $\text{CH}_2\text{Ph}$ ), 60.7 (t, 2  $\times$   $\text{CH}_2\text{O}$ ), 101.1 (d, CH), 125.5, 126.6, and 127.7 (3 d, 5  $\times$  ArC), and 129.1 (s, Ar  $C_{\text{ipso}}$ );  $m/z$  208 ( $M^+$  – EtOH, 19%), 162 (10), 137 (12), 103 (15), 91 (100), 89 (16), 85 (63), 75 (29), 65 (17), 61 (11), 57 (51), 17 (25), 45 (14), 40 (10), and 32 (50).

**4-Hydroxyheptanal diethyl acetal (12)** (Found: C, 64.4; H, 11.4.  $C_{11}H_{24}O_3$  requires C, 64.66; H, 11.84%), oil;  $\nu(\text{neat})$  3 440 (OH), 1 120, and 1 060 (C–O)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}(\text{CCl}_4)$  0.8–1.7 (17 H, m, 3  $\times$  Me, 4  $\times$   $\text{CCH}_2\text{C}$ ), 3.2–3.6 (6 H, m, 2  $\times$   $\text{CH}_2\text{O}$ , CHOH), and 4.2–4.5 (1 H, m, CH);  $\delta_{\text{C}}(\text{CCl}_4)$  13.5 (q,  $\text{MeCH}_2\text{CH}_2$ ), 15.45 (q, 2  $\times$   $\text{MeCH}_2\text{O}$ ), 19.1, 29.5, 32.5, and 39.9 (4 t, 4  $\times$   $\text{CCH}_2\text{C}$ ), 60.6 (t, 2  $\times$   $\text{CH}_2\text{O}$ ), 70.8 (d, CHOH), and 103.0 (d, CH);  $m/z$  158 ( $M^+$  – EtOH, <1%), 115 (100), 113 (37), 95 (56), 87 (78), 75 (26), 69 (60), 58 (43), 57 (35), 56 (29), 55 (33), 47 (20), 45 (12), 43 (46), 41 (52), and 39 (25).

**4-Hydroxy-6-methylheptanal diethyl acetal (13)** (Found: C, 65.7; H, 12.2.  $C_{12}H_{26}O_3$  requires C, 66.01; H, 12.02%), oil;  $\nu(\text{neat})$  3 400 (OH), 1 100, and 1 015 (C–O)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}(\text{CCl}_4)$  0.9 (6 H, d,  $J$  8 Hz,  $\text{Me}_2\text{CH}$ ), 1.0–1.35 (6 H, m, 2  $\times$   $\text{MeCH}_2\text{O}$ ), 1.4–2.0 (7 H, m,  $\text{CH}_2\text{CHMe}$ ,  $\text{CH}_2\text{CH}_2\text{CH}$ ), 3.1–3.8 (6 H, m, 2  $\times$   $\text{CH}_2\text{O}$ , CHOH), and 4.3–4.6 (1 H, m, CH);  $\delta_{\text{C}}(\text{CCl}_4)$  15.2 (q, 2  $\times$   $\text{Me}_2\text{CH}_2\text{O}$ ), 22.1, 23.4 (2 q,  $\text{Me}_2\text{CH}$ ), 24.4 (d,  $\text{CHMe}_2$ ), 29.6, 32.9, 43.0 (3 t,  $\text{CH}_2\text{CH}_2\text{CHO}$ ,  $\text{CH}_2\text{CHOH}$ ), 60.1 (t, 2  $\times$   $\text{CH}_2\text{O}$ ), 68.7 (d, CHOH), and 102.6 (d, CH);  $m/z$  172 ( $M^+$  – EtOH, <1%), 87 (100), 85 (28), 71 (13), 69 (89), 57 (17), 45 (18), 43 (23), and 41 (16).

**4-Hydroxy-4-phenylbutanal diethyl acetal (14)** (Found: C, 70.0; H, 9.2.  $C_{14}H_{22}O_3$  requires C, 70.55; H, 9.31%), oil;  $\nu(\text{neat})$  3 440 (OH), 1 040, and 1 020 (C–O)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}(\text{CCl}_4)$  0.8–1.1 (6 H, m, 2  $\times$   $\text{MeCH}_2\text{O}$ ), 1.3–1.7 and 1.75–2.0 (4 H, 2 m,  $\text{CH}_2\text{CH}_2$ ), 3.1–3.7 (6 H, m, 2  $\times$   $\text{CH}_2\text{O}$ , CHOH), 4.2–4.5 (1 H, m, CH), and 6.9–7.4 (5 H, m, Ph);  $\delta_{\text{C}}(\text{CCl}_4)$  14.9 (q, 2  $\times$  Me), 2.95 and 34.1 (2 t,  $\text{CH}_2\text{CH}_2$ ), 60.1 (t, 2  $\times$   $\text{CH}_2\text{O}$ ), 73.1 (d, CHOH), 102.0 (d, CH), 125.6, 127.0, and 127.75 (3 d, 5  $\times$  ArC), and 145.2 (s, Ar  $C_{\text{ipso}}$ );  $m/z$  192 ( $M^+$  – EtOH, 10%), 148 (10), 147 (55), 129 (33), 120 (54), 117 (16), 107 (26), 105 (24), 104 (13), 103 (100), 91 (38), 86 (79), 79 (41), 78 (15), 77 (51), 75 (72), 73 (30), 58 (51), 57 (21), 47 (48), and 29 (19).

**4-Hydroxyundecanal diethyl acetal (15)** (Found: C, 69.3; H, 12.8.  $C_{15}H_{32}O_3$  requires C, 69.20; H, 12.40%), oil;  $\nu(\text{neat})$  3 440 (OH), 1 130, and 1 070 (C–O)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}(\text{CCl}_4)$  0.7–0.9 (3 H, m,  $\text{MeCH}_2\text{CH}_2$ ), 0.9–1.75 (22 H, m, 2  $\times$   $\text{MeCH}_2\text{O}$ ,  $\text{CH}_2\text{CH}_2$ ,  $[\text{CH}_2]_6$ ), 3.2–3.7 (6 H, m, 2  $\times$   $\text{CH}_2\text{O}$ , CHOH), and 4.2–4.4 (1 H, m, CH);  $\delta_{\text{C}}(\text{CCl}_4)$  13.6 (q,  $\text{MeCH}_2\text{CH}_2$ ), 14.9 (q, 2  $\times$   $\text{MeCH}_2\text{O}$ ), 22.4, 29.15, 29.4, and 31.6 (4 t,  $[\text{CH}_2]_6$ ), 25.5 and 38.4 (2 t,  $\text{CH}_2\text{CH}_2$ ), 60.0 (t, 2  $\times$   $\text{CH}_2\text{O}$ ), 70.5 (d, CHOH), and 102.5 (d, CH);  $m/z$  214 ( $M^+$  – EtOH, <1%), 115 (100), 103 (43), 87 (52), 86 (18), 75 (20), 69 (32), 58 (13), 57 (25), 55 (23), 47 (15), 43 (25), and 41 (33).

**(E)-4-Hydroxy-6-phenylhex-5-enal diethyl acetal (16)** (Found: 72.2; H, 8.8.  $C_{16}H_{24}O_3$  requires C, 72.69; H, 9.15%), oil;  $\nu(\text{neat})$  3 410 (OH), 1 100, and 1 025 (C–O)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}(\text{CCl}_4)$  1.0–1.3 (6 H, m, 2  $\times$  Me), 1.4–1.9 (5 H, m,  $\text{CH}_2\text{CH}_2$ , OH), 3.15–3.7 (4 H, m, 2  $\times$   $\text{CH}_2\text{O}$ ), 4.05–4.7 (2 H, m, OCHO, CHOH), 6.1–6.65 (2 H, m,  $\text{CH}=\text{CH}$ ), and 6.9–7.5 (5 H, m, Ph);  $\delta_{\text{C}}(\text{CCl}_4)$  15.0 (q, 2  $\times$   $\text{MeCH}_2\text{O}$ ), 29.0 and 32.0 (2 t,  $\text{CH}_2\text{CH}_2$ ), 60.5 (t, 2  $\times$   $\text{CH}_2\text{O}$ ), 72.0 (d, CHOH), 102.5 (d, OCHO), 127.0 and 133.0 (2 d,  $\text{CH}=\text{CH}$ ), 126.5, 128.5, and 130.0 (3 d, 5  $\times$  ArC), and 137.5 (s, Ar  $C_{\text{ipso}}$ );  $m/z$  218 ( $M^+$  – EtOH, 32%), 173 (17), 155 (11), 146 (22), 139 (19), 130 (11), 129 (53), 128 (24), 127 (10), 117

(10), 115 (25), 105 (31), 104 (15), 103 (10), 91 (37), 86 (22), 85 (100), 77 (14), 58 (27), and 57 (27).

**3-(1-Hydroxycyclohexyl)propanal diethyl acetal (17)** (Found: C, 67.4; H, 11.6.  $C_{13}H_{26}O_3$  requires C, 67.78; H, 11.38%), oil;  $\nu(\text{neat})$  3 440 (OH), 1 110, and 1 045 (C–O)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}(\text{CCl}_4)$  0.8–1.9 (21 H, m, 2  $\times$  Me, 7  $\times$   $\text{CH}_2$ , OH), 3.1–3.75 (4 H, m, 2  $\times$   $\text{CH}_2\text{O}$ ), and 4.75–4.95 (1 H, m, CH);  $\delta_{\text{C}}(\text{CCl}_4)$  14.5 (q, 2  $\times$   $\text{MeCH}_2\text{O}$ ), 22.0, 25.5, 27.0, 28.0, and 37.0 (5 t, 7  $\times$   $\text{CCH}_2\text{C}$ ), 60.0 (t, 2  $\times$   $\text{CH}_2\text{O}$ ), 70.0 (s, COH), and 103.0 (d, CH);  $m/z$  184 ( $M^+$  – EtOH, 16%), 142 (20), 141 (100), 128 (36), 121 (36), 113 (15), 110 (18), 99 (11), 97 (14), 95 (43), 93 (11), 86 (35), 85 (27), 83 (10), 82 (16), 81 (40), 79 (16), 71 (19), 69 (10), 67 (30), 58 (22), 57 (24), 43 (11), and 41 (17).

**3-(1-Hydroxycyclo-octyl)propanal diethyl acetal (18)** (Found: C, 69.3; H, 11.8.  $C_{15}H_{30}O_3$  requires C, 69.72; H, 11.70%), oil;  $\nu(\text{neat})$  3 440 (OH), 1 105, and 1 040 (C–O)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}(\text{CCl}_4)$  0.8–1.2 (6 H, m, 2  $\times$  Me), 1.2–2.0 (19 H, m, 9  $\times$   $\text{CCH}_2\text{C}$ , OH), 3.15–3.7 (4 H, m, 2  $\times$   $\text{CH}_2\text{O}$ ), and 4.7–4.95 (1 H, m, CH);  $\delta_{\text{C}}(\text{CCl}_4)$  16.0 (t, 2  $\times$  Me), 22.5, 25.0, 29.0, and 36.5 (4 t, 9  $\times$   $\text{CCH}_2\text{C}$ ), 60.5 (t, 2  $\times$   $\text{CH}_2\text{O}$ ), 74.0 (s, COH), and 103.0 (d, CH);  $m/z$  212 ( $M^+$  – EtOH, 8%), 169 (12), 167 (15), 149 (18), 142 (11), 141 (100), 128 (51), 127 (10), 113 (13), 110 (13), 109 (13), 97 (13), 95 (22), 86 (39), 85 (32), 83 (15), 82 (15), 81 (29), 79 (12), 71 (15), 69 (14), 67 (13), 58 (18), 57 (25), 55 (32), 43 (11), and 41 (19).

**4-Hydroxy-4-phenylpentanal diethyl acetal (19)** (Found: C, 71.0; H, 9.6.  $C_{15}H_{24}O_3$  requires C, 71.39; H, 9.59%), oil;  $\nu(\text{neat})$  3 440 (OH), 1 095, and 1 000 (C–O)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}(\text{CCl}_4)$  0.85–1.2 (6 H, m, 2  $\times$   $\text{MeCH}_2\text{O}$ ), 1.2–2.2 (7 H, m, with s at  $\delta$  1.5,  $\text{MeCPh}$ ,  $\text{CH}_2\text{CH}_2$ ), 2.4–2.8 (1 H, br, OH), 3.2–3.9 (4 H, m, 2  $\times$   $\text{CH}_2\text{O}$ ), 5.0–5.25 (1 H, m, CH), and 6.9–7.55 (5 H, m, Ph);  $\delta_{\text{C}}(\text{CCl}_4)$  16.0 (q, 2  $\times$   $\text{MeCH}_2\text{O}$ ), 29.0 and 31.0 (2 t,  $\text{CH}_2\text{CH}_2$ ), 39.5 (q,  $\text{MeCPh}$ ), 61.0 and 61.5 (2 t, 2  $\times$   $\text{CH}_2\text{O}$ ), 74.5 (s, COH), 103.5 (d, CH), 126.0, 127.0, 129.0 (3 d, 5  $\times$  ArC), and 150.0 (s, Ar  $C_{\text{ipso}}$ );  $m/z$  206 ( $M^+$  – EtOH, <1%), 192 (14), 191 (100), 161 (23), 145 (10), 143 (21), 131 (10), 117 (10), 115 (14), 105 (19), 91 (26), 86 (16), 77 (18), and 58 (22).

**4-Anilino-4-phenylbutanal diethyl acetal (20)** (Found: C, 76.1; H, 8.9; N, 4.5.  $C_{20}H_{27}NO_2$  requires C, 76.64; H, 8.68; N, 4.47%), oil;  $\nu(\text{neat})$  3 400 (NH), 1 160, and 1 070 (C–O)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}(\text{CCl}_4)$  1.0–1.45 (6 H, m, 2  $\times$  Me), 1.4–2.0 (5 H, m,  $\text{CH}_2\text{CH}_2$ , NH), 3.35–3.7 (4 H, m, 2  $\times$   $\text{CH}_2\text{O}$ ), 4.2–4.55 (2 H, m, CH, CHN), and 7.0–7.5 (10 H, m, 2  $\times$  Ph);  $\delta_{\text{C}}(\text{CCl}_4)$  15.3 (q, 2  $\times$   $\text{MeCH}_2\text{O}$ ), 30.9 and 33.35 (2 t,  $\text{CH}_2\text{CH}_2$ ), 60.4 (t, 2  $\times$   $\text{CH}_2\text{O}$ ), 60.8 (d, CHN), 102.15 (d, CH), 126.2, 126.7, 128.3, and 128.8 (4 d, 10  $\times$  ArC), and 143.0 and 147.3 (2 s, 2  $\times$  Ar  $C_{\text{ipso}}$ );  $m/z$  313 ( $M^+$ , 7%), 222 (25), 183 (15), 182 (100), 129 (17), 104 (17), 91 (14), 77 (23), and 32 (11).

**3-Benzoylpropanal diethyl acetal (21)** (Found: C, 71.0; H, 8.6.  $C_{14}H_{20}O_3$  requires C, 71.15; H, 8.53%), b.p. 79–81 °C (10<sup>–4</sup> mmHg);  $\nu(\text{neat})$  1 675 (C=O), 1 120, and 1 050 (C–O)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}(\text{CCl}_4)$  1.0 (6 H, t,  $J$  8 Hz, 2  $\times$  Me), 1.8–2.1 (2 H, m,  $\text{CH}_2\text{CH}$ ), 3.95 (2 H, t,  $J$  8 Hz,  $\text{CH}_2\text{CO}$ ), 3.2–3.7 (4 H, m, 2  $\times$   $\text{CH}_2\text{O}$ ), 4.4–4.5 (1 H, m, CH), and 7.2–7.6 (5 H, m, Ph);  $\delta_{\text{C}}(\text{CCl}_4)$  16.0 (q, 2  $\times$  Me), 29.0 and 34.0 (2 t,  $\text{CH}_2\text{CH}_2$ ), 62.0 (t, 2  $\times$   $\text{CH}_2\text{O}$ ), 102.5 (d, CH), 129.0, 130.0, and 134.0 (3 t, 5  $\times$  ArC), 138.5 (s, Ar  $C_{\text{ipso}}$ ), and 199.0 (s, C=O);  $m/z$  191 ( $M^+$  – EtO, 30%), 117 (29), 116 (25), 105 (39), 103 (100), 85 (10), 77 (38), 75 (49), 51 (10), and 47 (24).

**3-Cyclohexylcarbonylpropanal diethyl acetal (22)** (Found: C, 69.1; H, 10.8.  $C_{14}H_{26}O_3$  requires C, 69.38; H, 10.81%), b.p. 80–81 °C (10<sup>–4</sup> mmHg);  $\nu(\text{neat})$  1 710 (C=O), 1 110, and 1 050 (C–O)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}(\text{CCl}_4)$  0.9 (6 H, t,  $J$  8 Hz, 2  $\times$  Me), 1.2–1.8 (12 H, m,  $\text{CH}_2\text{CO}$ , 5  $\times$  ring  $\text{CH}_2$ ), 1.95–2.15 (3 H, m,  $\text{CHCOCH}_2$ ), 3.15–3.45 (4 H, m, 2  $\times$   $\text{CH}_2\text{O}$ ), and 4.15 (1 H, t,  $J$  8 Hz, CH);  $\delta_{\text{C}}(\text{CCl}_4)$  15.5 (q, 2  $\times$  Me), 26.0, 26.5, 28.0, 29.0, and 35.0 (5 t, 7  $\times$   $\text{CCH}_2\text{C}$ ), 51.0 (d,  $\text{CHC}=\text{O}$ ), 61.0 (t, 2  $\times$   $\text{CH}_2\text{O}$ ), 102.5 (d, CH), and 210.0 (s, C=O);  $m/z$  241 ( $M^+$  – 1, <1%), 197

(39), 116 (51), 103 (100), 89 (14), 87 (12), 86 (10), 85 (74), 83 (29), 75 (39), 67 (10), 58 (13), 57 (20), 55 (39), 47 (22), and 41 (19).

3-(*p*-Toluoyle)propanal diethyl acetal (**23**) (Found: C, 71.6; H, 9.0.  $C_{15}H_{22}O_3$  requires C, 71.96; H, 8.86%), b.p. 82–84 °C ( $10^{-4}$  mmHg);  $\nu$ (neat) 1 680 (C=O), 1 125, and 1 070 (C–O)  $cm^{-1}$ ;  $\delta_H$ ( $CCl_4$ ) 0.7–1.0 (6 H, m,  $2 \times MeCH_2$ ), 1.6–1.9 (2 H, m,  $CH_2CH$ ), 2.1 (3 H, s,  $MeC_6H_4$ ), 2.5–2.8 (2 H, m,  $CH_2C=O$ ), 2.9–3.4 (4 H, m,  $2 \times CH_2O$ ), 3.9–4.3 (1 H, m, CH), and 6.7–7.1 and 7.4–7.7 (4 H, 2 m, ArH);  $\delta_C$ ( $CCl_4$ ) 16.5 (q,  $2 \times MeCH_2O$ ), 22.0 (q, MePh), 28.5 and 33.5 (2 t,  $CH_2CH_2$ ), 61.5 (t,  $2 \times CH_2O$ ), 102.5 (d, CH), 129.0 and 130.0 (2 d,  $4 \times ArC$ ), 136.0 and 144.0 (2 s,  $2 \times ArC_{ipso}$ ), and 199.0 (s, C=O);  $m/z$  250 ( $M^+$ , 3%), 205 (36), 175 (10), 159 (12), 134 (10), 131 (41), 119 (74), 117 (19), 116 (37), 103 (100), 91 (52), 89 (19), 85 (13), 75 (54), 65 (19), and 47 (28).

*Tandem Reaction of Intermediate (8) with Carbonyl Compounds and Further Oxidation with MCPBA. Isolation of  $\gamma$ -Butyrolactones (24)–(30). General Procedure.*—Once products (**12**)–(**19**) were isolated as described above (here the final hydrolysis was carried out with aqueous ammonium chloride instead of hydrochloric acid), the corresponding crude product (15 mmol scale) was dissolved in dichloromethane (40 ml). To the resulting solution was added MCPBA (17 mmol) and boron trifluoride–diethyl ether (3 mmol). After being stirred overnight, the resulting suspension was hydrolysed with water, neutralized with sodium hydrogen carbonate, and extracted with diethyl ether. The extract was washed with water and dried ( $Na_2SO_4$ ). The solvents were evaporated off (15 mmHg) and the residue was distilled *in vacuo* to afford the product (**24**)–(**30**).

4-Propylbutanolide (**24**) (Found: C, 65.4; H, 9.7.  $C_7H_{12}O_2$  requires C, 65.59; H, 9.44%), b.p. 50–52 °C ( $10^{-1}$  mmHg);  $\nu$ (neat) 1 765 (C=O)  $cm^{-1}$ ;  $\delta_H$ ( $CCl_4$ ) 0.65–0.95 (3 H, m, Me), 1.1–1.55 (4 H, m,  $CH_2CH_2Me$ ), 1.9–2.45 (4 H, m,  $CH_2CH_2C=O$ ), and 4.1–4.4 (1 H, m, CH);  $\delta_C$ ( $CCl_4$ ) 12.8 (q, Me), 17.7, 26.9, 27.6, and 36.65 (4 t,  $4 \times CH_2$ ), 79.3 (d, CH), and 175.6 (s, C=O);  $m/z$  128 ( $M^+$ , <1%), 85 (100), and 56 (10).

4-Isobutylbutanolide (**25**) (Found: C, 67.7; H, 9.9.  $C_8H_{14}O_2$  requires C, 67.57; H, 9.93%), b.p. 57–60 °C ( $10^{-1}$  mmHg);  $\nu$ (neat) 1 765 (C=O)  $cm^{-1}$ ;  $\delta_H$ ( $CCl_4$ ) 0.9 (6 H, d,  $J$  8 Hz,  $2 \times Me$ ), 1.25–1.9 (5 H, m,  $CH_2CHMe$ ,  $CH_2CH$ ), 2.15–2.5 (2 H, m,  $CH_2C=O$ ), and 4.25–4.55 (1 H, m, CH);  $\delta_C$ ( $CCl_4$ ), 22.15 (q,  $2 \times Me$ ), 24.25 (d, CHMe), 21.4, 27.65, and 43.9 (3 t,  $3 \times CH_2$ ), 77.9 (d, CH), and 175.2 (s, C=O);  $m/z$  142 ( $M^+$ , <1%) and 85 (100).

4-Phenylbutanolide (**26**) (Found: C, 73.8; H, 6.0.  $C_{10}H_{10}O_2$  requires C, 74.05; H, 6.21%), b.p. 96–98 °C ( $10^{-1}$  mmHg);  $\nu$ (neat) 1 765 (C=O)  $cm^{-1}$ ;  $\delta_H$ ( $CCl_4$ ) 2.1–2.5 (4 H, m,  $2 \times CH_2$ ), 5.1–5.4 (1 H, m, CH), and 7.0–7.3 (5 H, m, Ph);  $\delta_C$ ( $CCl_4$ ) 28.5 and 30.5 (2 t,  $2 \times CH_2$ ), 80.6 (d, CH), 125.2, 128.0, and 128.4 (3 d,  $5 \times ArC$ ), 137.7 (s,  $ArC_{ipso}$ ), and 176.1 (s, C=O);  $m/z$  162 ( $M^+$ , 100%), 161 (18), 118 (18), 117 (36), 115 (12), 107 (99), 106 (10), 105 (70), 91 (18), 79 (21), 78 (18), 77 (42), 56 (65), 51 (22), and 50 (10).

(E)-4-Styrylbutanolide (**27**) (Found: C, 76.5; H, 6.5.  $C_{12}H_{12}O_2$  requires C, 76.57; H, 6.43%), b.p. 62–63 °C ( $10^{-4}$  mmHg);  $\nu$ (neat) 1 770 (C=O)  $cm^{-1}$ ;  $\delta_H$ ( $CCl_4$ ) 1.0–1.3 (2 H, m,  $CH_2CH$ ), 2.15–2.6 (2 H, m,  $CH_2C=O$ ), 3.2–3.6 (1 H, m,  $CHCH_2$ ), 6.15–6.55 (2 H, m, CH=CH), and 7.0–7.6 (5 H, m, Ph);  $\delta_C$ ( $CCl_4$ ) 28.0 and 28.5 (2 t,  $2 \times CH_2$ ), 80.5 (d,  $CHCH_2$ ), 126.5 and 133.0 (2 d, CH=CH), 127.0, 128.5, and 129.0 (3 d,  $5 \times ArC$ ), 136.0 (s,  $ArC_{ipso}$ ), and 177.0 (s, C=O);  $m/z$  188 ( $M^+$ , 97%), 166 (40), 159 (34), 146 (40), 145 (24), 143 (11), 135 (13), 133 (48), 131 (49), 129 (42), 128 (35), 127 (10), 118 (12), 117 (19), 115 (44), 105 (60), 104 (100), 103 (40), 102 (14), 99 (11), 92 (10), 91 (54), 89 (10), 85 (11), 78 (27), 77 (47), 65 (14), 63 (16), 55 (21), 51 (30), 50 (10), and 39 (12).

4,4-Pentamethylenebutanolide\* (**28**),<sup>9</sup> b.p. 44–46 °C ( $10^{-4}$

mmHg);  $\nu$ (neat) 1 760 (C=O)  $cm^{-1}$ ;  $\delta_H$ ( $CCl_4$ ) 1.1–1.7 (10 H, m,  $5 \times$  ring  $CH_2$ ), 1.75–2.1 (2 H, m,  $CH_2CH_2C=O$ ), and 2.3–2.7 (2 H, m,  $CH_2C=O$ );  $\delta_C$ ( $CCl_4$ ) 22.5, 25.0, 28.0, 32.5, and 37.0 (5 t,  $7 \times CH_2$ ), 85.0 (s, C-4), and 176.0 (s, C=O);  $m/z$  154 ( $M^+$ , 18%), 112 (16), 111 (100), 99 (11), 98 (24), 83 (10), and 55 (15).

4,4-Heptamethylenebutanolide† (**29**) (Found: C, 72.3; H, 10.0.  $C_{11}H_{18}O_2$  requires C, 72.49; H, 9.95%), b.p. 60–62 °C ( $10^{-4}$  mmHg);  $\nu$ (neat) 1 760 (C=O)  $cm^{-1}$ ;  $\delta_H$ ( $CCl_4$ ) 1.3–2.2 (16 H, m,  $7 \times$  ring  $CH_2$ ,  $CH_2CH_2C=O$ ), and 2.2–2.6 (2 H, m,  $CH_2C=O$ );  $\delta_C$ ( $CCl_4$ ) 22.0, 24.5, 28.0, 28.5, 33.0, and 35.5 (6 t,  $9 \times CH_2$ ), 89.0 (s, C-4), and 176.0 (s, C=O);  $m/z$  182 ( $M^+$ , 2%), 139 (10), 122 (21), 112 (10), 111 (100), 98 (42), 83 (13), 82 (11), 67 (13), 56 (11), 55 (22), and 41 (13).

4-Methyl-4-phenylbutanolide (**30**),<sup>9</sup> b.p. 55–57 °C ( $10^{-4}$  mmHg);  $\nu$ (neat) 1 770 (C=O)  $cm^{-1}$ ;  $\delta_H$ ( $CCl_4$ ) 1.6 (3 H, s, Me), 2.2–2.5 (4 H, m,  $2 \times CH_2$ ), and 7.1–7.6 (5 H, m, Ph);  $\delta_C$ ( $CCl_4$ ) 29.0 and 36.0 (2 t,  $2 \times CH_2$ ), 29.5 (q, Me), 86.5 (s, C-4), 125.5, 128.5, and 129.5 (3 t,  $5 \times ArC$ ), 145.5 (s,  $ArC_{ipso}$ ), and 176.5 (s, C=O);  $m/z$  176 ( $M^+$ , 12%), 162 (10), 161 (100), 121 (34), 117 (12), 115 (10), 105 (43), 77 (27), 51 (10), and 43 (13).

\* Cyclohexanespiro-4'-butanolide.

† Cyclo-octanespiro-4'-butanolide.

## References

- 1 Preliminary communications: (a) J. Barluenga, C. Rubiera, J. R. Fernández, and M. Yus, *J. Chem. Soc., Chem. Commun.*, 1987, 425; (b) J. Barluenga, J. R. Fernández, and M. Yus, *ibid.*, p. 1534.
- 2 For recent reviews see: (a) N. H. Werstiuk, *Tetrahedron*, 1983, **39**, 205; (b) J. C. Stowell, *Chem. Rev.*, 1984, **84**, 409; (c) D. Hoppe, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 932.
- 3 (a) E. Nakamura and I. Kuwajima, *J. Am. Chem. Soc.*, 1983, **105**, 651; (b) E. Nakamura, H. Oshino, and I. Kuwajima, *ibid.*, 1986, **108**, 3745; (c) E. Nakamura, J. Shimada, and I. Kuwajima, *Organometallics*, 1985, **4**, 641; (d) E. Nakamura, K. Sekiya, and I. Kuwajima, *Tetrahedron Lett.*, 1987, **28**, 337; (e) E. Nakamura and I. Kuwajima, *J. Am. Chem. Soc.*, 1984, **106**, 3368; (f) Y. Tamaru, H. Ochiai, T. Nakamura, K. Tsubaki, and Z. Yoshida, *Tetrahedron Lett.*, 1985, **26**, 5559; (g) Y. Tamaru, H. Ochiai, T. Nakamura, and Z. Yoshida, *ibid.*, 1986, **27**, 955; (h) E. Nakamura and I. Kuwajima, *J. Am. Chem. Soc.*, 1977, **99**, 7360.
- 4 R. Goswami, *J. Org. Chem.*, 1985, **50**, 5907.
- 5 I. Kuwajima and E. Nakamura, *Top. Curr. Chem.*, in the press.
- 6 Y. Ito, S. Fujii, and T. Saegusa, *J. Org. Chem.*, 1976, **41**, 2073; Y. Ito, T. Sugaya, M. Nakatsuka, and T. Saegusa, *J. Am. Chem. Soc.*, 1977, **99**, 8366.
- 7 I. Ruy, M. Ando, A. Ogawa, S. Murai, and N. Sohoda, *J. Am. Chem. Soc.*, 1983, **105**, 7192; G. Stork, J. E. Davies, and A. Mersels, *ibid.*, 1963, **85**, 3419.
- 8 G. M. Rubotton, R. Marrero, D. S. Krueger, and J. L. Schreiner, *Tetrahedron Lett.*, 1977, 4013.
- 9 S. Fukuzawa, T. Fujinami, and S. Sakai, *J. Chem. Soc., Chem. Commun.*, 1987, 475.
- 10 D. Caine and A. S. Frobese, *Tetrahedron Lett.*, 1978, 883.
- 11 R. Goswami and D. E. Corcoran, *Tetrahedron Lett.*, 1982, **23**, 1463.
- 12 J. I. Levin and S. M. Weinreb, *J. Am. Chem. Soc.*, 1983, **105**, 1397.
- 13 R. L. Crumble, J. S. Nimitz, and H. S. Mosher, *J. Org. Chem.*, 1983, **47**, 4040.
- 14 E. J. Corey and K. Shimoji, *J. Am. Chem. Soc.*, 1983, **105**, 1662.
- 15 A. Bell, A. H. Davidson, C. Earnshaw, H. K. Norrish, R. S. Torr, and S. Warren, *J. Chem. Soc., Chem. Commun.*, 1978, 988.
- 16 C. Neukom, D. P. Richardson, J. H. Myerson, and P. A. Bartlett, *J. Am. Chem. Soc.*, 1986, **108**, 5559.
- 17 For a review see: D. Seebach, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 239.
- 18 W. R. Roush, H. R. Gillis, and A. I. Ko, *J. Am. Chem. Soc.*, 1982, **104**, 2269.
- 19 G. Büchi and H. Wüest, *J. Org. Chem.*, 1969, **34**, 1122.
- 20 For a review see: S. Kano, S. Shibuya, and T. Ebata, *Heterocycles*, 1980, **14**, 661.

- 21 See for instance: C. C. Price and J. M. Judge, *Org. Synth.*, 1973, Coll. Vol. 5, p. 255; K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, *J. Am. Chem. Soc.*, 1973, **95**, 6137; B. M. Trost, T. N. Salzmann, and K. Hiroi, *ibid.*, 1976, **98**, 4887.
- 22 For other routes to butyrolactones see for instance: P. Canonne and M. Akssira, *Tetrahedron Lett.*, 1984, **25**, 3453 and references cited therein.

- 23 J. Barluenga, F. Foubelo, F. J. Fañanás, and M. Yus, *J. Chem. Soc., Perkin Trans. 1*, in the press.
- 24 Beilstein Handbuch der organischen Chemie, Hauptwerk, 1928, vol. 1, p. 630.

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