Synthesis of (*E*)-4-Oxo-5-hexenals and Their Acetal Derivatives

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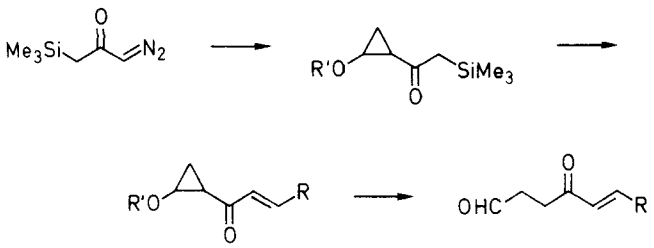
An effective synthesis of (*E*)-4-oxo-5-hexenals **6** and the acetals **5** starting from ethyl 2-alkoxy-1-cyclopropanecarboxylates **1a–d** is presented. The acid-induced ring opening of the cyclopropanecarboxylates **1a, b** followed by phosphorylmethylation or the phosphorylmethylation of the ester **1c** followed by ring opening leads to the 5-acetal of 2,5-dioxopentylphosphonate **4**. The Horner–Emmons olefination of **4** with various aldehydes produces the title compounds.

4-Oxo-5-hexenals are highly functionalized compounds, especially useful in the study of intramolecular dipolar cycloaddition reactions, since they bear a formyl moiety and a carbonyl-activated internal dipolarophile in the same molecule.[1] We have recently reported a new synthesis of 4-oxo-5-hexenals, by a sequence of cyclopropanation of vinyl ethers with 1-diazo-3-trimethylsilyl-2-propanone, Peterson olefination, and trifluoroacetic acid-induced ring opening of the cyclopropane ring (Scheme **A**).[2]



Scheme **A**

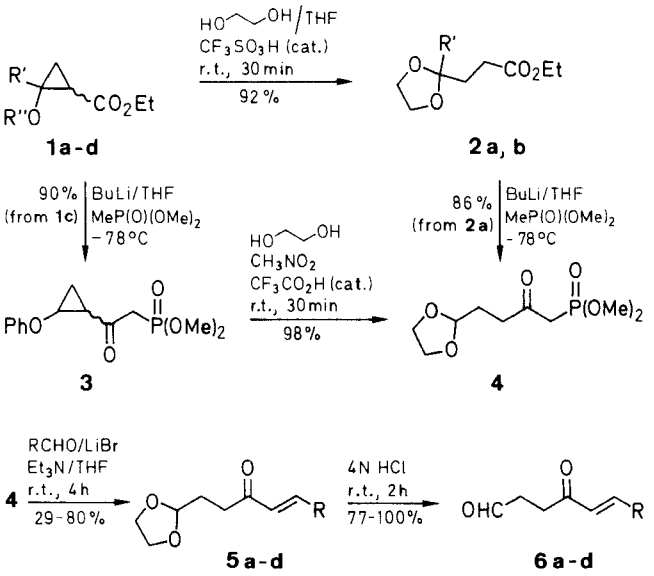
Herein we describe a revision of the previous method, where the rather cumbersome preparation of 1-diazo-3-silyl-2-propanone and the use of moisture-sensitive cyclopropyl silylmethyl ketones have been eliminated. The main synthetic advantages over the previous method are the use of readily available cyclopropanecarboxylates and the adoption of the *E*-selective Horner–Emmons olefination.

Ethyl 2-alkoxy-1-cyclopropanecarboxylates **1a–d**, which are readily available in multigram quantities by the cyclopropanation of the corresponding vinyl ethers with ethyl diazoacetate in the presence of copper(II) acetylacetonate,[3] were converted to either the ring-opened acetal esters **2a, b** or 2-phenoxycyclopropyl phosphorylmethyl ketone **3**.

Although the acid-catalyzed ring opening of 2-alkoxy-1-cyclopropanecarboxylates **1a–c** was totally unsuccessful under the previous reaction conditions using 1,2-ethanediol and trifluoroacetic acid in nitromethane,[2] trifluoromethanesulfonic acid in tetrahydrofuran, as a stronger acid, resulted in rapid ring opening to afford **2a, b** in excellent yield (Scheme **B**). A mixture of *cis*- and *trans* isomers of **1** can be used. Thus, the trifluoromethanesulfonic acid-induced ring opening of 2-alkoxy-1-cyclopropanecarboxylates offers an highly efficient short-step synthetic route to γ-oxo esters in an acetal-protected form, which are important multifunctionalized compounds in natural product synthesis.[4,5]

The phosphorylmethylation of **1c** gave **3** (90%), likewise **2a** gave **4** (86%), in a simple and high-yielding process, where two equivalents of dimethyl (lithiomethyl)phosphonate were used as usual. The ring opening of cyclopropyl ketone **3** was much easier than that of cyclopropyl esters **1**; the reaction was effected by trifluoroacetic acid in nitromethane in the presence of 1,2-ethanediol to give acetal phosphonate **4** in an almost quantitative yield (98%) (Scheme **B**).

The Horner–Emmons olefination of 2-oxoalkylphosphonate **4** was safely carried out by treatment with lithium bromide and triethylamine in tetrahydrofuran at 0°C, followed by the reaction with an aldehyde at room temperature.[6,7] A variety of aldehydes such as aryl, alkyl, α,β-unsaturated, and ester-functionalized aldehydes were used without trouble to give **5a–d** in satisfactory yields (Scheme **B**). In all cases, only the *E*-isomer of **5** was obtained.



1	R′	R″	2	R′	5, 6	R
a	H	Et	**a**	H	**a**	Ph
b	H	*i*-Bu	**b**	Me	**b**	Me
c	H	Ph			**c**	(*E*)-PhCH=CH
d	Me	Me			**d**	CO_2Me

Scheme **B**

Deacetalization of **5a–d** with dilute hydrochloric acid in tetrahydrofuran at room temperature afforded 4-oxo-5-hexenals **6a–d** in good yield (Scheme **B**). In the case of **5d**, the reaction time was carefully optimized by monitoring the reaction by TLC.

Since it is known that the Horner–Emmons olefination of **3** leads to 2-alkoxycyclopropyl vinyl ketones,[8] a direct synthetic route to **5a–d** and **6a–d** is now available, via the Horner–Emmons olefination of **3** followed by the acid-catalyzed cyclopropane ring-opening.[2]

Ethyl 3-(1,3-Dioxolan-2-yl)propionate (2a); Typical Procedure:
To a solution of **1a** (1.58 g, 10 mmol) in THF (10 mL) at 0 °C are added 1,2-ethanediol (1.1 mL, 20 mmol) and CF_3SO_3H (0.89 mL, 10 mmol). The mixture is stirred at 0 °C for 20 min, poured into sat. aq $NaHCO_3$, and extracted with CH_2Cl_2 (2 × 15 mL). The combined extracts are dried ($MgSO_4$) and concentrated *in vacuo*. The residue is distilled on a Kugelrohr apparatus to give **2a**; yield: 1.6 g (92%); bp 140 °C/3 mbar (oven temp). Yield of **2a** from **1b**: 87%. (Lit.[4] bp 117–122 °C/23 mbar).

2b (from **1d**); yield: 92%; bp 140 °C/3 mbar (oven temp) (Lit.[5] bp 104–105 °C/9–11 mbar).

Dimethyl [2-Oxo-2-(2-phenoxycyclopropyl)ethyl]phosphonate (3):
To a 1.6 M hexane solution of BuLi (1.46 mL, 2.4 mmol) in THF (3 mL), at − 78 °C under dry N_2 is added dimethyl methylphosphonate (0.26 mL, 2.4 mmol). After 1.5 h, **1b** (0.206 g, 1 mmol) in THF (2 mL) is added and the stirring is continued for 1.5 h. The mixture is treated with NH_4Cl and extracted with CH_2Cl_2 (2 × 10 mL). The combined extracts are dried ($MgSO_4$) and concentrated *in vacuo*. The residue is chromatographed on silica gel using EtOAc as eluent to give *trans* and *cis* isomers of **3**. The *cis*/*trans* mixture may be submitted, without separation, to the following transformation into **4**.

trans-**3**: yield: 166 mg (59%); oil.

$C_{13}H_{17}O_5P$	calc.	C 54.94	H 6.03
(284.3)	found	54.63	6.17

IR (neat): ν = 1690, 1245, 1045, 1025 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.57 (ddd, 1 H, J = 9.7, 6.0, 4.9 Hz, H-3), 1.67 (ddd, 1 H, J = 6.5, 6.5, 6.0 Hz, H-3), 2.46 (ddd, 1 H, J = 9.7, 6.5, 2.7 Hz, H-1), 3.28, 3.29 (d each, 2 H, $J_{H,P}$ = 22.3 Hz, PCH_2), 3.75, 3.79 (d each, 6 H, $J_{P,H}$ = 11.4 Hz, OCH_3), 4.10 (ddd, 1 H, J = 6.5, 4.9, 2.7 Hz, H-2), 6.9–7.3 (m, 5 H, C_6H_5).

^{13}C-NMR ($CDCl_3$): δ = 19.18 (C-3), 30.29 (C-1), 42.44 ($J_{C,P}$ = 128.1 Hz, PCH_2), 52.99 ($J_{C,P}$ = 6.8 Hz, OCH_3), 53.15 ($J_{C,P}$ = 5.8 Hz, OCH_3), 60.32 (C-2), 114.91, 121.85, 129.57, 157.79 (C_{arom}), 199.20 ($J_{C,P}$ = 6.8 Hz, CO).

MS (70 eV): m/z (%) = 284 (M^+, 1), 191 (77), 190 (21), 151 (20), 109 (100), 105 (27), 94 (45), 80 (93), 78 (44), 76 (91), 65, (34), 53 (30).

cis-**3**: yield: 88 mg (31%); oil.

$C_{13}H_{17}O_5P$	calc.	C 54.94	H 6.03
(284.3)	found	54.81	6.22

IR (neat): ν = 1700, 1245, 1050, 1025 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.39 (ddd, 1 H, J = 8.6, 6.0, 6.0 Hz, H-3), 1.94 (ddd, 1 H, J = 6.0, 6.0, 5.4 Hz, H-3), 2.62 (ddd, 1 H, J = 8.6, 6.0, 6.0 Hz, H-1), 3.02, 3.23 (d each, 2 H, $J_{H,P}$ = 22.7 Hz, PCH_2), 3.71, 3.74 (d each, 6 H, $J_{H,P}$ = 11.6 Hz, OCH_3), 4.12 (ddd, 1 H, J = 6.0, 6.0, 5.4 Hz, H-2), 6.9–7.3 (m, 5 H, C_6H_5).

^{13}C-NMR ($CDCl_3$): δ = 14.43 (C-3), 29.57 (C-1), 42.30 ($J_{C,P}$ = 129.1 Hz, PCH_2), 52.93 ($J_{C,P}$ = 5.8 Hz, OCH_3), 53.10 ($J_{C,P}$ = 7.0 Hz, OCH_3), 58.10 (C-2), 114.95, 121.82, 129.49, 158.09 (C_{arom}), 194.88 ($J_{C,P}$ = 5.9 Hz, CO).

Dimethyl [4-(1,3-Dioxolan-2-yl)-2-oxobutyl]phosphonate (4):
Method A, *from* **3**: To a solution of **3** (0.119 g, 0.42 mmol) in CH_3NO_2 (2 mL) at r.t. under dry N_2 are added 1,2-ethanediol (0.047 mL, 0.82 mmol) and CF_3CO_2H (0.031 mL, 0.42 mmol). The mixture is stirred for 30 min, poured into sat. aq $NaHCO_3$, and extracted with CH_2Cl_2 (2 × 10 mL). The combined extracts are dried ($MgSO_4$) and concentrated *in vacuo*. The residue is chromatographed on silica gel using EtOAc to give **4**; yield: 0.104 g (98%).

Method B, *from* **2a**: To a 1.6 M hexane solution of BuLi (2.48 mL, 4 mmol) in THF (5 mL) is added dimethyl methylphosphonate (0.54 mL, 4.96 mmol) at − 78 °C under dry N_2. After 1 h, **2a** (0.346 g, 2 mmol) is added. The mixture is stirred at − 78 °C for 3 h, poured into sat. aq NH_4Cl, and extracted with $CHCl_3$ (2 × 15 mL). The combined extracts are dried ($MgSO_4$) and concentrated *in vacuo*. The residue is distilled in a Kugelrohr apparatus to give **4**; yield: 0.433 g (86%); bp 45 °C/0.5 mbar.

HRMS: m/z calc. for $C_9H_{17}O_6P$: 252.0762; found: 252.0765 (M^+).

IR (neat): ν = 1715, 1400, 1255, 1020, 810 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.99 (ddd, 2 H, J = 7.3, 7.3, 4.4 Hz, H-4), 2.74 (t, 2 H, J = 7.3 Hz, H-3), 3.12 (d, 2 H, $J_{H,P}$ = 22.7 Hz, PCH_2), 3.77, 3.81 (d, 6 H, $J_{H,P}$ = 11.0 Hz, OCH_3), 3.8–4.0 (m, 4 H, OCH_2CH_2O), 4.92 (t, 1 H, J = 4.4 Hz, CH).

^{13}C-NMR ($CDCl_3$): δ = 27.47 (C-4), 37.98 (C-3), 41.19 ($J_{C,P}$ = 129.1 Hz, PCH_2), 53.06 ($J_{C,P}$ = 5.9 Hz, OCH_3), 65.01 (OCH_2CH_2O), 102.99 (CH), 201.06 (C-2, $J_{C,P}$ = 6.8 Hz).

MS (70 eV): m/z (%) = 252 (M^+, 2), 124 (12), 87 (28), 73 (100).

(*E*)-2-(3-Oxo-4-hexenyl)-1,3-dioxolane (5b); Typical Procedure:
To a mixture of **4** (1 g, 4 mmol) and LiBr (0.522 g, 6 mmol) in dry THF (15 mL) is added Et_3N (0.67 mL, 4.8 mmol) at 0 °C under dry N_2: After stirring for 30 min, acetaldehyde (0.89 mL, 16 mmol) is added. The mixture is stirred at r.t. for 4 h, poured into water, and extracted with Et_2O (2 × 20 mL). The combined extracts are dried ($MgSO_4$) and concentrated *in vacuo*. The residue is chromatographed on silica gel using hexane/Et_2O (1:1) to give **5b**; yield: 0.544 g (80%); oil.

HRMS: m/z calc. for $C_9H_{14}O_3$: 170.0942; found: 170.0939 (M^+).

IR (neat): ν = 1670, 1630, 1435, 1130, 1025 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.90 (dd, 3 H, J = 7.0, 1.5 Hz, H-6), 2.00 (ddd, 2 H, J = 7.3, 7.3, 4.4 Hz, H-1), 2.67 (t, 2 H, J = 7.3 Hz, H-2), 3.8–4.0 (m, 4 H, OCH_2H_2O), 4.92 (t, 1 H, J = 4.4 Hz, CH), 6.13 (dq, 1 H, J = 15.7, 1.5 Hz, H-4), 6.87 (dq, 1 H, J = 15.7, 7.0 Hz, H-5).

^{13}C-NMR ($CDCl_3$): δ = 18.23 (C-6), 27.88 (C-1), 33.75 (C-2), 64.97 (OCH_2CH_2O), 103.49 (OCHO), 131.87 (C-4), 142.59 (C-5), 199.35 (CO).

MS (70 eV): m/z (%) = 170 (M^+, 8), 110 (10), 87 (12), 86 (18), 73 (100), 69 (26).

5a: yield: 65%; oil (Lit.[2] oil).

5c: yield: 60%; mp 66–70 °C (Lit.[2] mp 66–70 °C).

5d: yield: 29%; oil (eluent for chromatography, hexane/EtOAc, 3:2).

HRMS: m/z calc. for $C_{10}H_{14}O_5$: 214.0840; found: 214.0843 (M^+).

IR (neat): ν = 1725, 1630, 1440, 1390, 1230, 1030 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 2.05 (ddd, 2 H, J = 7.2, 7.2, 4.4 Hz, H-6), 2.75 (t, 2 H, J = 7.2 Hz, H-5), 3.75 (s, 3 H, CO_2CH_3), 3.8–4.0 (m, 4 H, OCH_2CH_2O), 4.95 (t, 1 H, J = 4.4 Hz, OCHO), 6.03 (d, 1 H, J = 12.1 Hz, H-3), 6.53 (d, 1 H, J = 12.1 Hz, H-2).

^{13}C-NMR ($CDCl_3$): δ = 27.44 (C-6), 36.51 (C-5), 52.06 (CO_2CH_3), 65.01 (OCH_2CH_2O), 103.16 (OCHO), 124.32 (C-3), 141.92 (C-2), 165.73 (CO_2CH_3), 202.89 (C-4).

MS (70 eV): m/z (%) = 214 (M^+, 1), 182 (10), 87 (12), 86 (20), 73 (100).

(*E*)-4-Oxo-6-phenyl-5-hexenal (6a); Typical Procedure:
A solution of **5a** (0.256 g, 1.1 mmol) in THF (4 mL) containing 4 N HCl (2 mL) is stirred at r.t. for 2 h and extracted with CH_2Cl_2 (2 × 15 mL). The combined extracts are washed with aq $NaHCO_3$, dried ($MgSO_4$), and concentrated *in vacuo*. The residue is chroma-

tographed on silica gel using hexane/EtOAc (9:1) as eluent to give **6a**; yield: 207 mg (~100%); oil (Lit.[2] oil).

6c: reaction time 3 h; yield: 86%; mp 71–73°C (Lit.[2] mp 71–73°C).

6b: reaction time 24 h; yield 77%.

$C_7H_{10}O_2$ (126.2) calc. C 66.64 H 7.99 found 66.69 8.10

IR (neat): ν = 1730, 1680, 1640, 1450, 1200, 980 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.92 (dd, 3 H, J = 6.8, 1.8 Hz, H-7), 2.78, 2.88 (2 br t, 4 H, H-2, H-3), 6.16 (dq, 1 H, J = 15.7, 1.8 Hz, H-5), 6.92 (dq, J = 15.7, 6.8 Hz, H-6), 9.83 (s, 1 H, H-1).

^{13}C-NMR ($CDCl_3$): δ = 18.30 (C-7), 32.01 (C-3), 37.46 (C-2), 131.50 (C-5), 143.29 (C-6), 197.70 (C-4), 200.69 (C-1).

MS (70 eV): m/z (%) = 126 (M^+, 5), 84 (15), 83 (29), 73 (39), 69 (100).

6d: reaction time 0.5 h; yield: 89%; oil.

HRMS: m/z calc. for $C_8H_{10}O_4$: 170.0578; found: 170.0581.

IR (neat): ν = 1720, 1680, 1315, 1175 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 2.8–3.0 (m, 4 H, H-2, H-3), 3.83 (s, 3 H, CO_2CH_3), 6.73 (d, J = 16.0 Hz, H-5), 7.11 (d, 1 H, J = 16.0 Hz, H-6), 9.83 (br s, 1 H, H-1).

^{13}C-NMR ($CDCl_3$): δ = 33.53 (C-3), 37.25 (C-2), 52.42 ($CO_2\underline{C}H_3$)$_2$ 130.87 (C-5), 139.02 (C-6), 165.83 ($\underline{C}O_2Me$), 197.26 (C-4), 199.75 (C-1).

MS (70 eV): m/z (%) = 170 (M^+, 5), 142 (50), 139 (24), 138 (54), 128 (47), 114 (65), 113 (100), 111 (37), 110 (42), 83 (27).

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