165. An Efficient Synthesis of α,β-Unsaturated Aldehydes by a Four-Carbon Unit Extension of *Grignard* Reagents[1])

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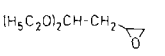
Summary

Copper-catalyzed addition of organomagnesium halides to 2-(2,2-diethoxyethyl)oxirane (**1**) affords aldol acetals **2** which upon acid treatment undergo hydrolysis and dehydration to give α,β-unsaturated aldehydes **7** with high yields.

The problem of synthesizing α,β-unsaturated aldehydes (enals) by chain extension appears to be solved. An exhaustive literature survey would produce an almost infinite variety of methods. A closer look, however, reveals some important restrictions: in general, the building blocks used for the chain extension do not have more than three carbon atoms and in most cases these are introduced as nucleophiles.

A particularly simple approach is based on ylid reactions. An α,β-unsaturated aldehyde can easily be converted into its next higher homolog by condensation with (triphenylphosphonio)methoxymethanide [2] and hydrolysis of the resulting diene-ether. (Triphenylphosphonio)formylmethanide [3] and its acetals [4] confer two C-atoms, (triphenylphosphonio)3-methoxyallylide [5] three C-atoms together with the proper functionality. Instead of ylids, organolithium reagents may serve the same purpose. Dichloromethyllithium [6] allows submission of carbonyl compounds to a *Darzens*-related reaction sequence leading to enals. Synthetic equivalents of the impractible acetaldehyde α-anion such as α-deprotonated *Schiff* bases [7] or (*Z*)-2-ethoxyvinyllithium [8] offer the possibility of performing component-controlled ('directed') aldol condensations. Despite some difficulties in achieving regiocontrol, metalated allyl ethers [9–12] or allenyl ethers [13] may be combined with aldehydes or, respectively, alkyl halides to afford again precursors to enals.

For reasons that become clear later, we envisaged a novel CC-linking pattern. We wanted to elongate organometallic reagents by an *electrophilic four-carbon unit* carrying all the required functionality to generate ultimately the enal group. The readily accessible 2-(2,2-diethoxyethyl)oxirane (**1**) was devised as the key reagent.



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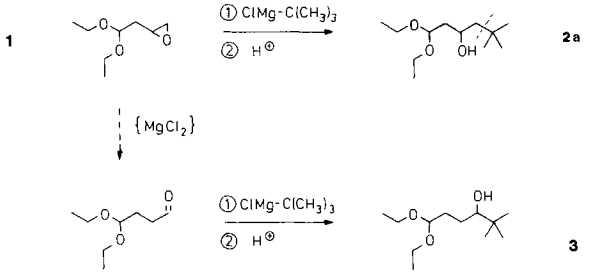
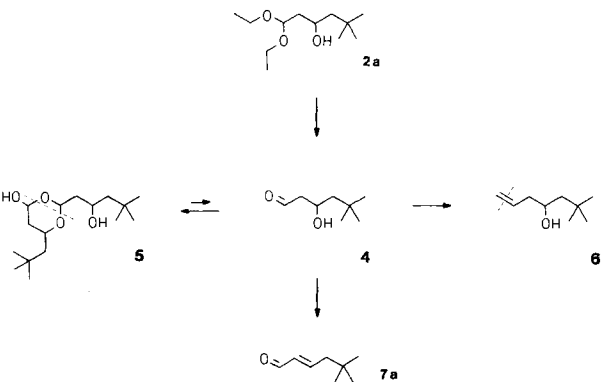
[1]) Part XI of the series 'Selective Syntheses with Organometallics'; part X: [1].

[2]) Ph.D. Thesis, Ecole Polytechnique Fédérale, Lausanne, 1983.

When the epoxide **1** was treated at 25°C with a solution of *tert*-butylmagnesium chloride in tetrahydrofuran, two products were obtained in a 2:1 ratio. The expected 3-hydroxyacetal **2a** was accompanied by a constitutional isomer **3** which carried the hydroxy group in position 4. Apparently this by-product must arise from an intermediate succinic dialdehyde monoacetal which may result from a magnesium-salt-catalyzed [14] isomerization of epoxide **1**.



Addition of catalytic amounts (8 mol-%) of CuBr [15] and lowering the temperature to −50°C efficiently prevented the side reaction. Under these conditions 88% of **2a** was isolated. Very mild hydrolysis removed the acetal protective group without elimination of the hydroxy group. The aldol **4** thus obtained dimerizes upon standing at room temperature to a 4-hydroxy-1,3-dioxane derivative **5**. To provide additional structural evidence, aldol **4** was converted to the homoallyl alcohol **6** by means of a *Wittig* reaction. If the hydrolysis is performed less carefully, aldol **4** appeared only as a transient species that immediately dehydrated to give the stable enal **7a**.

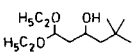
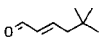
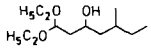
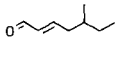
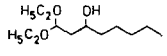
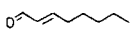
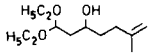
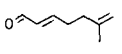
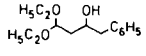
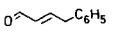
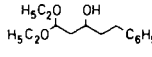
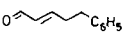
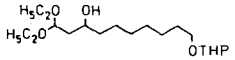
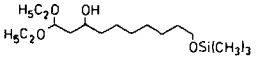
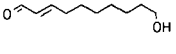


The reaction sequence was applied to several other compounds thus demonstrating the scope of the new method. Unsaturated or oxygen-functionalized *Grignard* reagents proved to be fully compatible with the general scheme. The adducts **2** were obtained in approximately 85% yield; the yield of isolated enals averaged 70% (see *Table 1*).

By adding a *Grignard* reagent derived from 1,6-hexanediol to epoxide **1** we prepared large quantities of 10-hydroxy-2-decenal which we needed for work on pheromone analogs. If we had chosen a C_1-, C_2- or C_3-building block rather than **1**, we

would have been obliged to use a longer diol derivative. The 1,7-, 1,8- and 1,9-diol homologs, however, are 60, 40 and 150 times, respectively, more expensive than 1,6-hexanediol.

Table 1. *Addition of Organomagnesium Reagents to Oxirane* **1**: *Yields of β-Hydroxyacetals and, after Hydrolysis, of Enals*

Series No.	*Grignard* reagent	Adduct **2**	Yield[a] [%]	Enal **7**	Yield[a] [%]
a	$ClMg\text{-}C(CH_3)_3$		88		75
b	$ClMg\text{-}CH(CH_3)C_2H_5$		80		83
c	$BrMg\text{-}C_4H_9$		84		75
d	$ClMg\text{-}CH_2\text{-}C(CH_2)CH_3$		82		66
e	$BrMg\text{-}C_6H_5$		83		50
f	$ClMg\text{-}CH_2\text{-}C_6H_5$		92		74
g	$ClMg\text{-}(CH_2)_6\text{-}OTHP$		81	[b]	–
h	$ClMg\text{-}(CH_2)_6\text{-}OSi(CH_3)_3$		78		85

[a]) Yield of distilled, pure compound.
[b]) Hydrolysis not attempted.

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Experimental Part

General Remarks. See [11].

Starting Materials. – *1,1-Diethoxy-3-butene.* To a vigorously stirred slurry of 0.37 kg (15 mol) Mg turnings in 1.26 kg (8.5 mol) triethyl orthoformate, 0.57 kg (7.5 mol) allyl chloride were added in the course of 15 h. After 5 h additional stirring, the mixture was cooled in an ince bath and treated with 0.5 l of a sat. NH_4Cl solution. After extraction with Et_2O (4 × 250 ml), the org. layers were combined and concentrated. The residue was shaken for 90 min with a mixture of 80 ml AcOH, 40 g AcONa and 200 ml H_2O to destroy all remaining orthoformate. The product was again extracted with Et_2O and, after drying and evaporation of the org. phases, destilled under reduced pressure; b.p. 73–74°/60 Torr; 0.75 kg (70%). ^{1}H-NMR ($CDCl_3$, 360 MHz): 5.81 (*ddt*, J = 17.5, 10.4, 7.0, 1H); 5.15 (*ddt*, J = 17.5, 3.4, 2.0, 1H); 5.09 (*ddt*, J = 10.4, 3.4, 2.0, 1H); 4.52 (*t*, J = 6, 1H); 3.66 (*dq*, J = 9.4, 7.0, 2H); 3.51 (*dq*, J = 9.4, 7.0, 2H); 2.41 (*t*, with fine structure; J = 6.8, 2H); 1.23 (*t*, J = 6.8, 6H). Anal. calc. for $C_8H_{16}O_2$ (144.2): C 66.63, H 11.18; found: C 66.74, H 11.06.

2-(2,2-Diethoxyethyl)oxirane (**1**). To an ice-cooled mixture of 72 g (0.50 mol) 1,1-diethoxy-3-butene in 0.50 l of a 13% aq. solution of NaOCl (1.1 mol), 0.50 l of 10% aq. AcOH were slowly added. Afterwards the stirring was continued 1 h at 0° and 3 h at 25°. The chlorohydrin was extracted with Et_2O (4 × 100 ml) and, after drying, filtration and evaporation of the org. phase, used without further purification. The oily product was allowed to

drop slowly into a flask containing 0.10 kg (2.5 mol) NaOH pellets and heated to 100°. Under reduced pressure (12 Torr), the reaction product was removed, as it formed, through a distillation bridge connected to the flask. After drying ($CaSO_4$) the product was distilled through a *Widmer* column of 30 cm length: 40 g **1** (50%); b.p. 73–74°/12 Torr[3]); n_D^{20} 1.4240. IR: 3010*s*, 1135*s*, 1070*s*, 850*m*. ^{1}H-NMR ($CDCl_3$, 360 MHz): 4.69 (*dd*, *J* = 7, 0, 4.8, 1H); 3.74 (*dq*, *J* = 9.5, 7.3, 1H); 3.70 (*dq*, *J* = 9.5, 7.1, 1H); 3.57 (*dq*, *J* = 9.5, 7.3, 1H); 3.54 (*dq*, *J* = 9.5, 7.1, 1H); 3.05 (*dddd*, *J* = 6.9, 5.0, 4.1, 2.5, 1H); 2.79 (*dd*, *J* = 5.0, 4.0, 1H); 2.51 (*dd*, *J* = 5.0, 2.7, 1H); 1.92 (*ddd*, *J* = 14.4, 6.9, 4.5, 1H); 1.76 (*ddd*, *J* = 14.3, 6.9, 4.8, 1H); 1.21 (*dt*, *J* = 7.0, 5.0, 6H). Anal. calc. for $C_8H_{16}O_3$ (160.2): C 59.97, H 10.07; found: C 59.98, H 10.12.

6-Chloro-1-trimethylsilyloxyhexane (see [17]). A solution of 30 g (0.28 mol) chlorotrimethylsilane in 40 ml Et_2O was added dropwise to a cooled mixture of 34 g (0.25 mol) 6-chloro-1-hexanol and 30 g (0.30 mol) Et_3N in 90 ml Et_2O. After additional 15 min of stirring, sufficient H_2O (40 ml) was added to dissolve the white precipitate and the org. product was extracted with Et_2O (2 × 50 ml). After drying (K_2CO_3), filtration and evaporation, 48.5 g (93%) of the pure silyl ether were isolated by distillation; b.p. 63–64°/1 Torr; n_D^{20} 1.4329. ^{1}H-NMR (C_6D_6): 3.68 (*t*, *J* = 6, 2H); 3.34 (*t*, *J* = 6, 2H); 1.5 (*m*, 8H); 0.33 (*s*, 9H).

β-Hydroxyacetals and their Derivatives. – *1,1-Diethoxy-5,5-dimethyl-3-hexanol* (**2a**). Solutions of 30 mmol *tert*-butylmagnesium chloride in 24 ml THF and 0.3 g (1 mmol) CuBr in 10 ml THF were mixed at −75° and kept 15 min at −60°. After addition of 4.00 g (25.0 mmol) oxirane **1**, the mixture was left 15 h at −50°. Addition of 60 ml sat. aq. NH_4Cl solution, extraction with Et_2O (2 × 50 ml), drying, evaporation and distillation afforded 4.75 g (88%) **2a**; b.p. 59–60°/0.01 Torr. ^{1}H-NMR (C_6D_6, 360 MHz): 4.57 (*dd*, *J* = 6.3, 4.5, 1H); 4.07 (*tt*, *J* = 9.2, 2.2, 1H); 3.51 (*dq*, *J* = 9.2, 7.0, 1H); 3.42 (*dq*, *J* = 9.2, 7.1, 1H); 3.3 (*m*, 1H); 3.24 (*dq*, *J* = 9.2, 7.1, 1H); 2.92 (*s*, 1H); 1.82 (*ddd*, *J* = 14.1, 4.5, 2.5, 1H); 1.62 (*ddd*, *J* = 14.1, 9.2, 6.2, 1H); 1.53 (*dd*, *J* = 14.0, 8.5, 1H); 1.19 (*dd*, *J* = 14.3, 3.0, 1H); 1.06 (*s*, 9H); 1.0 (*m*, 6H). MS (CI): 217 (2, $M^+ - 1$), 173 (20), 73 (100). Anal. cal. for $C_{12}H_{26}O_3$ (218.3): C 66.01, H 12.00; found: C 66.00, H 12.12.

The other *β-hydroxyacetals* are obtained in the same way (see *Table 2*). IR, NMR, and mass spectra as well as elemental analysis confirm the identity and purity of the products.

Table 2. *Yields, Boiling Ranges ('bp') and Elemental Analyses of β-Hydroxy-acetals* **2b–2h**

Compound		Yield [%]	B.p. °C/mmHg	C	H
				Calc. (Found) [%]	Calc. (Found) [%]
2b	1,1-Diethoxy-5-methyl-3-heptanol	80	65–67/0.03	66.01 (65.44)	12.00 (11.73)
2c	1,1-Diethoxy-3-octanol	84	73–74/0.03	66.01 (66.22)	12.00 (11.87)
2d	1,1-Diethoxy-6-methyl-6-hepten-3-ol	82	63–65/0.03	66.01 (–)	12.00 (–)
2e	4,4-Diethoxy-1-phenyl-2-butanol	83	95–98/0.08	70.56 (70.76)	9.30 (9.30)
2f	1,1-Diethoxy-5-phenyl-3-pentanol	92	98–100/0.02	71.39 (71.07)	9.59 (9.41)
2g	1,1-Diethoxy-10-(2-tetrahydropyranyloxyl)-3-decanol[a])	81	[b])	65.86 (65.78)	11.05 (11.44)
2h	1,1-Diethoxy-10-trimethyl-silyloxy-3-decanol	78	126–128/0.06	73.03 (–)	6.30 (–)

[a]) The *Grignard* reagent is prepared from 2-(6-chlorohexyloxytetrahydropyrane [17].
[b]) Purified by chromatography on alumina (*Brockmann* activity III).

5,5-Dimethyl-3-hydroxyhexanal (**4**) *and its Dimer.* A mixture of 2.18 g (10.0 mmol) acetal **2a**, 5 ml of 1N HCl and 25 ml THF was allowed to stand 3 h at 25°. After neutralization with 100 ml of sat. $NaHCO_3$ solution, the solution was extracted with Et_2O (3 × 50 ml). After careful drying of the org. phase, the solvent was completely removed from a 15-ml portion under reduced pressure (0.02 Torr). The remaining viscous oil has the properties required for dimer **5**. IR: 3440*m*, 2970*s*, 2880*m*, 1730*w*, 1370*m*, 1130*s*, 1070*m*, 1015*m*, 950*m*. MS: 287 (0.2, $M_2^+ - 1$), 217 (3.0), 187 (0.3), 173 (20), 145 (28), 57 (100).

To the greater part of the organic solution 9 mmol of (triphenylphosphonio)methanide [19] in 12 ml of THF were added. After 2 h at 25°, the solvent was evaporated and the residue distilled under reduced pressure. In the boiling range 58–61°/12 Torr, 0.94 g (67%) of *6,6-dimethyl-1-hepten-4-ol* (**6**) are collected; n_D^{20} = 1.4383. ^{1}H-NMR ($CDCl_3$ 360 MHz): 5.82 (*dddd*, *J* = 16.0, 11.4, 7.3, 6.5, 1H); 5.13 (*ddt*, *J* = 16.5, 2.5, 1.5, 1H); 5.13

[3]) So far, oxirane **1** has only been mentioned in a patent application [16].

(*ddt*, J = 11.5, 1.8, 0.5, 1H); 3.79 (*dq*, J = 7.5, 5.2, 1H); 2.24 (*dddt*, J = 14.5, 11.8, 6.0, 1.5, 1H); 2.15 (*dddt*, J = 14, 7, 6.5, 0.5, 1H); 1.57 (*s*, 1H); 1.38 (*d*, J = 5.5, 2H); 0.97 (*s*, 9H). MS: 124 (2, $M^+ - 18$), 101 (18), 57 (100). Anal. calc. for $C_9H_{18}O$ (142.2): C 76.00, H 12.76; found C 75.58, H 12.78.

α,β-Unsaturated Aldehydes. – *5,5-Dimethyl-2-hexenal* (**7a**). A mixture of 2.18 g (10.0 mmol) acetal **2a**, 5 ml of 1N HCl and 25 ml THF was heated 4 h under reflux. The acid was neutralized with 60 ml of sat. aq. $NaHCO_3$ solution. The enal **7a** was extracted with Et_2O (3 × 25 ml) and, after drying and evaporation of the org. phase, distilled under reduced pressure; b.p. 56–58°/12 Torr; 0.96 g (75%). IR: 2960*s*, 1690*s*, 975*s*. ^{1}H-NMR: 9.48 (*d*, J = 8, 1H); 6.91 (*dt*, J = 17, 8, 1H); 6.08 (*dd*, J = 17, 8, 1H); 2.23 (*d*, J = 8, 2H); 0.96 (*s*, 9H). MS: 126 (0.1, M^+), 71 (5), 70 (100). Anal. calc. for $C_8H_{14}O$ (126.3): C 76.14, H 11.18; found: C 75.96. H 10.98.

The other enals, listed below, are prepared in an identical manner.

5-Methyl-2-heptenal (**7b**). B.p. 67–68°/12 Torr; 83%; n^{20} = 1.4542. ^{1}H-NMR: 9.51 (*d*, J = 8, 1H); 6.82 (*dt*, J = 16, 8, 1H); 6.09 (*dd*, J = 16, 8, 1H); 2.3 (*m*, 2H); 1.3 (*m*, 3H); 0.9 (*m*, 6H). MS: 126 (0.3, M^+), 111 (4), 97 (9), 70 (100). Anal. calc. for $C_8H_{14}O$ (126.3): C 76.14, H 11.18; found: C 75.95, H 11.08.

2-Octenal (**7c**) [20]. B.p. 73–75°/12 Torr; 75%. ^{1}H-NMR: 9.53 (*d*, J = 8, 1H); 6.84 (*dt*, J = 15, 8, 1H); 6.09 (*dd*, J = 15, 7, 1H); 2.31 (*q*, J = 7, 2H); 1.4 (*m*, 6H); 0.88 (*t*, J = 6, 3H). MS: 126 (0.2, M^+), 111 (4), 108 (5), 97 (16), 83 (67), 70 (94), 55 (100).

6-Methyl-2,6-heptadienal (**7d**). B.p. 70–71°/12 Torr; 66%. ^{1}H-NMR: 9.47 (*d*, J = 8, 1H); 6.82 (*dt*, J = 16, 6, 1H); 6.10 (*dd*, J = 16, 8, 1H); 4.74 (*d*, J = 4, 2H); 2.4 (*m*, 4H); 1.75 (*s*, 3H). MS: 124 (4, M^+, 109 (43), 95 (36), 55 (100). Anal. calc. for $C_8H_{12}O$ (124.2): C 77.38, H 9.74; found: C 77.21, H 9.79.

4-Phenyl-2-butenal (**7e**) [21]. B.p. 56–60°/0.06 Torr; 50%. ^{1}H-NMR: 9.47 (*d*, J = 8, 1H); 7.2 (*m*, 5H); 6.89 (*dt*, J = 15, 7, 1H); 6.03 (*dd*, J = 15, 8, 1H); 3.58 (*d*, J = 7, 2H). MS: 146 (51, M^+), 128 (20), 117 (89), 115 (100).

5-Phenyl-2-pentenal (**7f**) [22]. B.p. 77–78°/0.15 Torr; 74%. ^{1}H-NMR: 9.50 (*d*, J = 7, 1H); 7.2 (*m*, 5H); 6.82 (*dt*, J = 16, 6, 1H); 6.10 (*dd*, J = 16, 7, 1H); 2.7 (*m*, 4H). MS: 160 (1, M^+), 91 (100).

10-Hydroxy-2-decenal (**7h**). 85% after purification by chromatography on silica with AcOEt/hexane (1:1). IR: 3420*s*, 2940*s*, 2870*s*, 1695*s*, 1135*m*, 1075*m*, 975*m*. ^{1}H-NMR: 9.48 (*d*, J = 8, 1H); 6.83 (*dt*, J = 16, 6.5, 1H); 6.08 (*dd*, J = 16, 8, 1H); 3.59 (*t*, J = 6, 2H); 2.33 (*q*, J = 6.5, 2H); 1.80 (*s*, 1H); 1.3 (*m*, 10H). MS: 169 (2, $M^+ - 1$), 128 (5), 115 (7), 111 (17), 97 (35), 70 (88), 55 (100). Anal. calc. for $C_{10}H_{18}O_2$ (170.3): C 70.55, H 10.66; found: C 70.19, H 10.75.

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