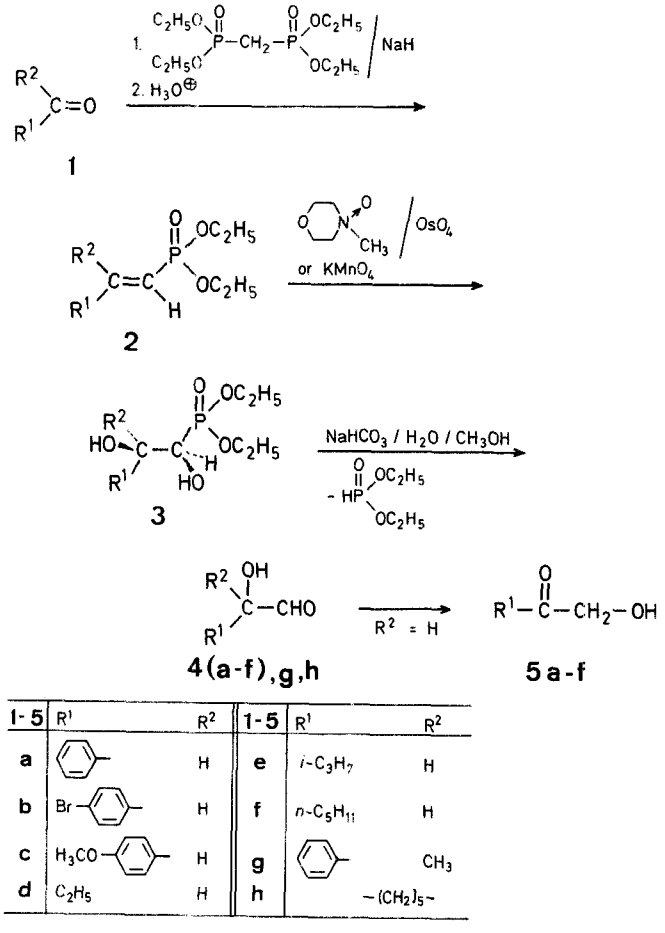
A Convenient Synthesis of α-Hydroxyaldehydes and Hydroxymethyl Ketones

Wiesław Waszkuć, Tomasz Janecki, Ryszard Bodalski*

Institute of Organic Chemistry, Technical Unversity, Żwirki 36, 90-924 Łódź, Poland

α-Hydroxyaldehydes (**4**) and the tautomeric hydroxymethyl ketones (**5**) have attracted considerable interest because of their use in organic synthesis[1,2] and their widespread occurrence in biological systems[3,4]. The preparation of compounds **4** and **5** can be accomplished in different ways[1,5-10]; much use has been made of a specific umpolung homologation of aldehydes or ketones **1** based on the addition of various formyl anion equivalents to the carbonyl group[7-10]. Herein we report a novel alternative, mild, and operationally simple synthetic approach to compounds **4** and **5** starting from various types of aldehydes or ketones (**1**).



1-5	R^1	R^2	1-5	R^1	R^2
a		H	e	i-C_3H_7	H
b		H	f	n-C_5H_{11}	H
c		H	g		CH_3
d	C_2H_5	H	h		$-(CH_2)_5-$

Standard carbonyl olefination of the aldehydes or ketones **1** with the sodio derivative of tetraethyl methanediphosphonate in benzene[11] affords the pure diethyl (*E*)-1-alkenephosphonates **2** in good yields. With aromatic aldehydes (**1**, R^1 = aryl, R^2 = H), equally convenient results are obtained using the phase-transfer catalysis technique[12]. Phosphonic esters **2** are converted into the *threo*-diols **3**, the key intermediates of the sequence **1** → **5**, by treatment with 4-methylmorpholine 4-oxide in *t*-butanol/water in the presence of osmium(VIII) oxide[13]. This stereoselective *syn*-hydroxylation affords compounds **3** in high yields and in an almost pure state (Method A). The same hydroxylation can be achieved with still satisfactory though lower yields of **3** by use of potassium permanganate as oxidizing agent in aqueous alkaline solution[14] (Method B). The crude hydroxylation products **3** are isolated from the reaction mixture by column chromatography on Florisil® and are finally recrystallized. Base-promoted cleavage of compounds **3** (retro-addition of diethyl phosphite[15]) proceeds smoothly in aqueous methanol containing sodium hydrogen carbonate to give the α-hydroxyaldehydes **4** which in the case $R^2 \neq H$ are isolated in good yields. In the case R^2 = H, compounds **4** undergo isomerization (Lobry de Bruyn – van Ekenstein rearrangement[16]) to give the hydroxymethyl ketones **5**, also in good yields.

Solvents and the commerically available aldehydes and ketones **1** (Aldrich Chemical Co.) were redistilled prior to use. 4-Methylmorpholine 4-oxide (Fluka A.G.) was used as supplied. Tetraethyl methanediphosphonate was prepared according to the reported procedure[17]. All melting and boiling points are uncorrected. T.L.C. analyses (to monitor the progress of the reactions) were conducted on silica gel plates (F-254, Merck A.G.) using chloroform/methanol (19/1) as eluent.

Table 1. Preparation of Diethyl 1-Alkenephosphonates (**2**)

2	Method	Yield [%]	b.p. [°C]/torr or m.p. [°C]	Molecular Formula or Lit. Data
a	D	83	b.p. 131–133°/0.2	b.p. 136–138°/0.3[12]
b	D	75	m.p. 68–69°	m.p. 69–70°[12]
c	D	85	b.p. 160–162°/0.2	$C_{13}H_{19}O_5P$ (270.2)[a]
d	C	80	b.p. 58–59°/0.1	b.p. 63–64°/0.25[18]
e	C	78	b.p. 47–49°/0.05	b.p. 45°/0.025[19]
f	C	86	b.p. 75–78°/0.2	b.p. 114–116°/3[20]
g	C	70	b.p. 112–113°/0.05	b.p. 110–111°/0.03[21]
h	C	82	b.p. 92–94°/0.05	b.p. 95–97°/0.03[21]

[a] calc. C 57.77 H 7.08 P 11.46
found 57.60 6.81 11.82

^{1}H-N.M.R. ($CDCl_3$)/TMS_{int}): δ = 1.28 (t, 6H, J_{HH} = 7.0 Hz); 3.76 (s, 3H); 4.25 (dq, 4H, $^3J_{HP}$ = 8.0 Hz, J_{HH} = 7.0 Hz); 6.04, 7.37 (ABx system, 2H, $J_{H_AH_B}$ = 17.0 Hz, $^2J_{H_AP}$ = 17.0 Hz, $^3J_{H_BP}$ = 22.0 Hz); 6.85, 7.45 ppm (AB system, $4H_{arom}$, $J_{H_AH_B}$ = 9.0 Hz).

Table 2. Preparation of Diethyl 1,2-Dihydroxyalkanephosphonates (**3**)

3	Method	Reaction time [h]	Yield [%]	m.p. [°C]	Molecular formula[a]
a	A	48	75	oil	$C_{12}H_{19}O_5P$ (274.2)
	B	0.05	58		
b	A	48	78	72–73°	$C_{12}H_{18}BrO_5P$ (353.1)
	B	0.05	45		
c	A	48	86	75–77°	$C_{13}H_{21}O_6P$ (304.3)
	B	0.05	51		
d	A	72	82	oil	$C_6H_{19}O_5P$ (226.2)
	B	0.05	45		
e	A	72	72	70–71°	$C_9H_{21}O_5P$ (240.2)
	B	0.05	43		
f	A	72	78	oil	$C_{11}H_{25}O_5P$ (268.3)
	B	0.05	48		
g	A	96	62	oil	$C_{13}H_{21}O_5P$ (288.2)
	B	0.05	41		
h	A	48	87	oil	$C_{11}H_{23}O_5P$ (266.3)
	B	0.05	48		

[a] The microanalyses were in satisfactory agreement with the calculated values: C ±0.41, H ±0.26, P ±0.40.

Table 3. N.M.R.-Spectral Data of Diethyl 1,2-Dihydroxyalkanephosphonates (**3**)

3	^{1}H-N.M.R. (solvent/TMS$_{int}$) δ [ppm], J [Hz]	^{31}P-N.M.R. (CH_3OH/H_3PO_{4ext}) δ [ppm]
a	($CDCl_3$): 1.22 (t, 3H, O—CH_2—CH_3, J_{HH} = 7.0); 1.28 (t, 3H, O—CH_2—CH_3, J_{HH} = 7.0); 3.70–4.15 (m, 1H, 1-H); 3.88 (dq, 2H, O—CH_2—CH_3, $^3J_{HP} = J_{HH}$ = 7.0); 4.02 (dq, 2H, O—CH_2—CH_3, $^3J_{HP} = J_{HH}$ = 7.0); 4.32 (br.s, 2H, 2OH); 5.01 (dd, 1H, 2-H, $^3J_{HP} = J_{HH}$ = 3.5); 7.08–7.62 (m, 5H$_{arom}$)	22.54
b	($CDCl_3$): 1.20 (t, 3H, O—CH_2—CH_3, J_{HH} = 7.0); 1.24 (t, 3H, O—CH_2—CH_3, J_{HH} = 7.0); 3.75–4.20 (m, 1H, 1-H); 4.03 (dq, 2H, O—CH_2—CH_3, $^3J_{HP} = J_{HH}$ = 7.0); 4.06 (dq, 2H, O—CH_2—CH_3, $^3J_{HP} = J_{HH}$ = 7.0); 4.56 (bs, 2H, 2OH); 4.97 (dd, 1H, 2-H, $^3J_{HP} = J_{HH}$ = 4.0); 7.21, 7.34 (AB system, 4H$_{arom}$, $J_{H_AH_B}$ = 7.0	22.52
c	($CDCl_3$): 1.24 (t, 3H, O—CH_2—CH_3, J_{HH} = 7.0); 1.28 (t, 3H, O—CH_2—CH_3, J_{HH} = 7.0); 3.76 (s, 3H, OCH_3); 3.90–4.25 (m, 1H, 1-H); 4.02 (dq, 2H, O—CH_2—CH_3, $^3J_{HP} = J_{HH}$ = 7.0); 4.05 (dq, 2H, O—CH_2—CH_3, $^3J_{HP} = J_{HH}$ = 7.0); 4.35 (br.s, 2H, 2OH); 4.98 (dd, 1H, 2-H, $^3J_{HP} = J_{HH}$ = 3.5); 6.80, 7.27 (AB system, 4H$_{arom}$, $J_{H_AH_B}$ = 9.0)	22.46
d	($CDCl_3$): 0.96 (t, 3H, CH_2—CH_3, J_{HH} = 7.0); 1.33 (t, 6H, 2O—CH_2—CH_3, J_{HH} = 7.0); 1.56 (qv, 2H, CH_2—CH_3, J_{HH} = 7.0); 3.41–3.85 (m, 2H, 1-H + 2H); 4.12 (dq, 2H, O—CH_2—CH_3, $^3J_{HP} = J_{HH}$ = 7.0); 4.15 (dq, 2H, O—CH_2—CH_3, $^3J_{HP} = J_{HH}$ = 7.0); 4.48 (bs, 2H, 2OH)	24.17
e	($CDCl_3$): 0.92 [d, 3H, $(CH_3)_2CH$, J_{HH} = 6.5); 1.02 [d, 3H, $(CH_3)_2CH$, J_{HH} = 6.5]; 1.33 (t, 6H, 2O—CH_2—CH_3, J_{HH} = 7.0); 1.88 [d sept, 1H, $(CH_3)_2CH$, J_{HH} = 6.5, J_{HH} = 7.5]; 3.47 (ddd, 1H, 2-H, J_{HH} = 7.5, $^3J_{HP}$ = 3.5, J_{HH} = 1.5); 3.82 (br.s, 2H, 2OH), 3.95 (dd, 1H, 1-H, $^2J_{HP}$ = 10.0, J_{HH} = 1.5); 4.14 (dq, 2H, O—CH_2—CH_3), $^3J_{HP} = J_{HH}$ = 7.0); 4.17 (dq, 2H, O—CH_2—CH_3, $^3J_{HP} = J_{HH}$ = 7.0)	24.16
f	(CCl_4): 0.89 [t, 3H, H_3C—$(CH_2)_4$, J_{HH} = 6.0]; 1.20–1.65 [m, 8H, H_3C—$(CH_2)_4$]; 1.31 (t, 6H, 2O—CH_2—CH_3, J_{HH} = 7.0); 3.48–3.85 (m, 2H, 1-H + 2-H); 4.17 (dq, 4H, 2O—CH_2—CH_3, $^3J_{HP} = J_{HH}$ = 7.0); 4.57 (bs, 2H, 2OH)	23.85
g	(CCl_4): 1.13 (t, 3H, O—CH_2—CH_3, J_{HH} = 7.0); 1.26 (t, 3H, O—CH_2—CH_3, J_{HH} = 7.0); 1.58 (s, 3H, CH_3); 3.65–4.20 (m, 1H, 1-H); 4.01 (dq, 2H, O—CH_2—CH_3, $^3J_{HP} = J_{HH}$ = 7.0); 4.03 (dq, 2H, O—CH_2—CH_3, $^3J_{HP} = J_{HH}$ = 7.0); 4.48 (br.s, 2H, 2OH); 7.02–7.53 (m, 5H$_{arom}$)	22.40
h	(CCl_4): 1.30 (t, 6H, 2O—CH_2—CH_3, J_{HH} = 7.0); 1.34–1.75 (m, 10 H$_{cyclohexyl}$); 3.62 (d, 1H, 1-H, $^2J_{HP}$ = 9.0); 4.13 (dq, 2H, O—CH_2—CH_3, $^3J_{HP} = J_{HH}$ = 7.0); 4.20 (dq, 2H, O—CH_2—CH_3, $^3J_{HP} = J_{HH}$ = 7.0); 4.45 (br.s, 2H, 2OH)	23.47

Table 4. Preparation of α-Hydroxyaldehydes (**4**) and Hydroxymethyl Ketones (**5**)

Product	Reaction Time [h]	Yield [%]	b.p. [°C]/torr or m.p. [°C] found	reported
4g	3	65	b.p. 105–108°/03	b.p. 116–120°/0.7[7]
4h	2	63	b.p. 87–90°/18	b.p. 80–82°/12[9]
5a	1.5	84	m.p. 85–86°	m.p. 86°[22]
5b	1.5	74	m.p. 144–145°	m.p. 146°[23]
5c	1.5	76	m.p. 102–103°	m.p. 103–104°[24]
5d	1	82	b.p. 82–85°/20	b.p. 70–80°/14[25]
5e	1	70	b.p. 60–62°/20	b.p. 64–66°/24[26]
5f	1	75	b.p. 93–96°/20	b.p. 95°/20[27]

^{1}H-N.M.R. and ^{31}P-N.M.R. spectra were recorded with a Bruker HFX-72 instrument operating at 90 MHz and 36.43 MHz, respectively.

Diethyl 1-Alkenephosphonates (2):

Method C: The phosphonates **2** are obtained by refluxing an equimolecular mixture of sodium tetraethyl methanediphosphonate and the aldehyde or ketone **1** in benzene following the known procedure[11].

Method D: The phosphonates **2** are prepared by adding the aldehyde **1** to a mixture of tetraethyl methanediphosphonate, 50% aqueous sodium hydroxide, and dichloromethane at 25°C as described earlier[12].

Diethyl 1,2-Dihydroxy-1-alkenephosphonates (3); General Procedures:

Method A: A solution of the appropriate 1-alkenephosphonate **2** (50 mmol) in acetone (5 ml) is added dropwise with efficient stirring to a mixture of 4-methylmorpholine 4-oxide dihydrate (9.1 g, 53 mmol), osmium tetroxide (0.04 g, 0.16 mmol), acetone (25 ml), and *t*-butanol (8 ml) at room temperature. Stirring and monitoring the consumption of **2** by T.L.C. are continued for 46–96 h. When compound **2** has completely disappeared a slurry of sodium sulfite (0.5 g, 4 mmol), magnesium silicate (6 g), and water is added and the resultant magnesol is filtered off. The filtrate is neutralized to pH 2 with 1 normal sulfuric acid and extracted with chloroform (3 × 200 ml). The chloroform layer is washed with water (2 × 100 ml), dried with magnesium sulfate, and evaporated in vacuo. The residue is chromatographed on a column (30 × 2 cm) containing Florisil® (100–200 mesh, Aldrich Chemical Co.). Tetrachloromethane (100 ml) is passed through the column to remove nonpolar impurities followed by chloroform/methanol mixture (99/1) (200 ml) to elute the crude product **3** which is further purified by recrystallization from ethanol/ethyl acetate (1/1).

Method B: To a stirred solution of the diethyl 1-alkenephosphonate **2** (30 mmol) in *t*-butanol (300 ml) and water (200 ml), a solution of potassium permanganate (7.02 g, 44.4 mmol) and sodium hydroxide (1.5 g, 37.5 mmol) in water (240 ml) is added quickly at 0°C. The resultant mixture is kept at 2–3°C for 3 min and then treated with sodium sulfite (3.78 g, 30 mmol) to ensure complete reduction of permanganate. Manganese dioxide is filtered off and the residual solution is extracted with chloroform (3 × 30 ml). The chloroform layer is dried with magnesium sulfate and evaporated in vacuo. The crude product is further worked up as described above.

α-Hydroxyaldehydes (4) and Hydroxymethyl Ketones (5); General Procedure:

A solution of the appropriate 1,2-dihydroxyalkanephosphonate **3** (30 mmol) and sodium hydrogen carbonate (12.6 g, 150 mmol) in water (150 ml) and methanol (150 ml) is refluxed for 1–3 h. After cooling, the mixture is extracted with dichloromethane (3 × 100 ml). The extract is washed with water (2 × 50 ml), dried

with magnesium sulfate, and evaporated in vacuo. The crude product is recrystallized from ethanol or distilled under reduced pressure.

Received: February 28, 1984

* Address for correspondence.

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