One-Pot Synthesis of Substituted Homoallylic Alcohols (3-Alkenols) and 1-Deuterio-3-alkenols; II.[1] Extension to Ketone Enolates

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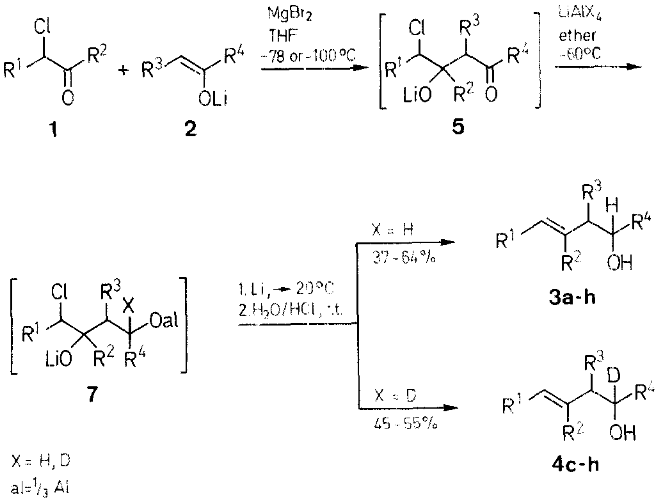
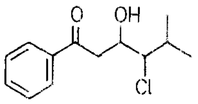
The reaction of different lithium ketone enolates with α-chloro carbonyl compounds followed by *in situ* reduction with lithium aluminium hydride or deuteride and final lithiation with ltihium powder leads to the corresponding homoallylic or 1-deuterio homoallylic alcohols in a regioselective manner.

In a recent paper[1] we described the preparation of homoallylic and 1,1-dideuteriohomoallylic alkenols (**3**, $R^3 = R^4 = H$; **4**, $R^3 = H$, $R^4 = D$) by successive treatment of different α-chloro carbonyl compounds **1** with the lithium enolate of ethyl acetate (**2**, $R^3 = H$, $R^4 = OC_2H_5$), lithium aluminium hydride or deuteride and final lithiation with lithium powder. We extend here this reaction to the use of lithium enolates derived from ketones (**2**).

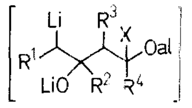
When several α-chloroaldehydes (**1**, $R^2 = H$) or ketones (**1**, $R^2 \neq H$) were allowed to react successively with different ketone enolates **2**[2] (obtained *in situ* from the corresponding ketone and lithium diisopropylamine[3]), lithium aluminium hydride (X = H) and lithium powder, the corresponding homoallylic alcohols **3** were isolated. The use of lithium aluminium deuteride (X = D) instead of lithium aluminium hydride led to the expected deuterated alkenols **4**.



The first intermediate in the reaction is the corresponding alcoholate **5**, since when the reaction mixture was hydrolyzed after this addition the corresponding chlorohydrin could be isolated. Thus, in the reaction of the lithium acetophenone enolate with 2-chloro-3-methylbutanal the corresponding chlorohydrin **6g** was isolated after acid hydrolysis. The *in situ* reduction of the remaining carbonyl group in **5** led to the corresponding intermediate **7**, which through lithiation afforded a β-substituted organolithium compound **8**.[4] The final spontaneous β-elimination[5] from the unstable species **8** yields, after hydrolysis, the product **3** or **4**.



6g



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When the same process was tried with lithium enolates derived from aldehydes (**2**, $R^4 = H$) an intractable mixture of reaction products was obtained, probably due to (a) the difficulty of obtaining the enolate[6] or/and (b) the low stability of the corresponding alcoholate **5**.

3-Alkenols 3 and 4; General Procedure:

To a stirred solution of lithium diisopropylamide (1.93 g, 18 mmol) in tetrahydrofuran (30 ml) is added the corresponding ketone at −78 °C under argon, and stirring is continued for 30 min. Anhydrous magnesium bromide (1.84 g, 10 mmol) and the α-chlorocarbonyl compound **1** (10 mmol) in tetrahydrofuran (10 ml) are successively added at −100 °C (bath temperature) for aldehydes or −78 °C for ketones. The mixture is stirred for 1 h, an ether solution of lithium aluminium hydride or deuteride (4.5 mmol) is added, and stirring is continued for 4 h at −60 °C. Lithium powder (0.25 g, 35 mmol) is added and the mixture stirred overnight, allowing the temperature to rise to 20 °C. The mixture is then hydrolyzed with 2 normal hydrochloric acid (10 ml), and extracted with ether (2 × 15 ml). The organic layer is washed with water (10 ml), dried with sodium sulfate, and evaporated (15 torr). The residue is distilled at reduced pressure to afford the alcohol **3** or **4**.

Table 1. 3-Alkenols 3 and 4 Prepared

Product	R^1	R^2	R^3	R^4	Yield[a] (%)	b.p. (°C)/torr[b]	Molecular Formula[c] or Lit. b.p. (°C)/torr
3a	CH_3	CH_3	H	CH_3	40 (1/1.3)	28–30/0.1	$C_7H_{14}O$ (114.2)
3b	C_2H_5	H	H	CH_3	37 (1/2.3)	46–50/15	45/6[7]
3c	i-C_3H_7	H	H	CH_3	55 (1/6)	33–36/0.1	–[8,e]
3d	–$(CH_2)_3$–		H	CH_3	52	39–41/0.1	–[9,e]
3e	–$(CH_2)_4$–		H	CH_3	49	46–50/0.1	56/1.75[10]
3f	C_2H_5	H	H	C_6H_5	50 (1/2.5)	43–47/0.01	–[8,e]
3g	i-C_3H_7	H	H	C_6H_5	60 (1/5)	40–44/0.01	$C_{13}H_{18}O$ (190.3)
3h	–$(CH_2)_4$–		–$(CH_2)_4$–		64 (1/2.5)[d]	35–39/0.01	139/15[11]
4c	i-C_3H_7	H	H	CH_3	45 (1/4)	33–36/0.1	$C_8H_{15}DO$ (129.2)
4e	–$(CH_2)_4$–		H	CH_3	50	38–42/0.1	$C_9H_{15}DO$ (141.2)
4f	C_2H_5	H	H	C_6H_5	49 (1/2.5)	43–47/0.01	$C_{12}H_{15}DO$ (177.3)
4h	–$(CH_2)_4$–		–$(CH_2)_4$–		55 (1/2.6)[d]	35–39/0.01	$C_{12}H_{19}DO$ (181.3)

[a] Yield of isolated product, based on the starting α-chlorocarbonyl compound **1**. In parentheses the *Z/E* ratio from ^{13}C-NMR analysis.
[b] Distillation interval.
[c] Satisfactory microanalyses obtained: C ±0.24, H/D ±0.26.
[d] *anti/syn* Ratio from ^{13}C-NMR analysis.
[e] No data reported.

Table 2. Spectral Data of 3-Alkenols **3** and **4**

Product	IR (film)[a] ν (cm^{-1})	^{1}H-NMR ($CCl_4 + D_2O_{capillary}$)[b] δ (ppm)	^{13}C-NMR (neat + $D_2O_{capillary}$)[b] δ (ppm)	MS (E.I.)[c] m/e (% rel. int.)
3a	3460 (OH); 3020, 1620 (HC=C)	1.0 (d, 3H, J = 7 Hz, $C\underline{H}_3CHO$); 1.4–1.8 (m, 6H, $2CH_3C$=C); 1.8–2.2 (m, 2H, CH_2); 2.8 (s, 1H, OH); 3.5–4.1 (m, 1H, OCH); 5.0–5.5 (m, 1H, CH=C)	14.7, 24.3, 42.8, 51.2, 66.3, 122.8, 134.2[d,e]	114 (M$^+$, 1.2), 81 (11), 70 (100), 55 (69), 53 (11), 41 (17), 39 (15), 32 (13)
3b	3350 (OH); 3020, 1650 (HC=C)	1.0 (t, 3H, J = 7 Hz, $C\underline{H}_3CH_2$); 1.1 (d, 3H, J = 7 Hz, $C\underline{H}_3CH$); 1.7–2.3 (m, 4H, $2CH_2C$=C); 3.6–3.9 (m, 1H, O–CH); 3.7 (s, 1H, OH); 5.4–5.6 (m, 2H, 2CH=C)	14.3, 22.8, 26.2, 42.9, 68.2, 126.5, 135.0[d]	114 (M$^+$, 1.2), 96 (12), 81 (17), 70 (100), 55 (84), 53 (11), 45 (67), 43 (26), 42 (17), 39 (29), 28 (16), 27 (11)
3c	3350 (OH); 3020, 1650 (HC=C)	1.0 (d, 6H, J = 7 Hz, $2C\underline{H}_3CH$); 1.1 (d, 3H, J = 7 Hz, CH_3CO); 1.7–2.7 (m, 3H, CH_2 and $C\underline{H}CH_3$); 3.5–3.8 (m, 1H, OCH); 3.6 (s, 1H, OH); 5.3–5.5 (m, 2H, 2CH=C)	23.2, 23.7, 31.7, 43.2, 68.0, 124.2, 140.5[d]	128 (M$^+$, 2), 95 (17), 84 (45), 69 (100), 55 (20), 45 (40), 41 (25), 39 (15)
3d	3370 (OH); 3050, 1640 (HC=C)	1.1 (d, 3H, J = 7 Hz, CH_3); 1.5–2.8 (m, 8H, $4CH_2$); 2.2 (s, 1H, OH); 3.7–4.0 (m, 1H, OCH); 5.3–5.6 (m, 1H, CH=C)	23.5, 24.2, 33.1, 36.0, 41.8, 66.7, 126.3, 142.2	126 (M$^+$, 7), 93 (16), 82 (34), 79 (18), 67 (100), 45 (16)
3e	3370 (OH); 3030, 1660 (HC=C)	1.1 (d, 3H, J = 7 Hz, CH_3); 1.5–2.3 (m, 10H, $5CH_2$); 2.3–2.6 (m, 1H, OH); 3.6–3.9 (m, 1H, OCH); 5.4–5.6 (m, 1H, CH=C)	23.2, 23.5, 23.7, 26.0, 29.4, 48.9, 66.1, 124.1, 135.6	140 (M$^+$, 6), 122 (16), 107 (18), 96 (32), 81 (100), 68 (22), 67 (30), 55 (10), 45 (12)
3f	3450 (OH); 3050, 3020, 1670, 1600, 1490, 790, 700 (HC=C)	0.9 (t, 3H, J = 7 Hz, CH_3); 1.7 (s, 1H, OH); 1.8–2.4 (m, 4H, $2CH_2$); 4.4 (t, 1H, J = 7 Hz, OCH); 5.0–5.6 (m, 2H, 2CH=C); 6.8–7.5 (m, 5H_{arom})[f]	14.4, 26.2, 43.3, 74.4, 125.8, 126.6, 127.5, 128.5, 135.4, 145.3[d]	176 (M$^+$, 1), 107 (100), 79 (51), 77 (32)
3g	3420 (OH); 3070, 3020, 1680, 1600, 1490, 790, 700 (HC=C)	1.0 (t, 6H, J = 8 Hz, $2CH_3$); 1.2–2.5 (m, 4H, CH_2, $C\underline{H}CH_3$, and OH); 4.8 (t, 1H, J = 7 H, OCH); 5.2–5.6 (m, 2H, 2CH=C); 7.0–7.6 (m, 5H_{arom})[f]	23.2, 31.7, 43.2, 74.6, 123.7, 126.8, 127.7, 128.7, 141.2, 145.6[d]	172 (M$^+$–H_2O, 1), 107 (100), 79 (42), 77 (24)
3h	3460 (OH); 3020, 1660 (HC=C)	1.1–1.7 (m, 12H, $6CH_2$); 1.7–2.3 (m, 6H, $2CH_2C$=C, OH, and CHC=C); 3.2–3.8 (m, 1H, OCH); 5.2–5.5 (m, 1H, CH=C)[f]	23.7, 24.0, 26.1, 26.3, 27.0, 31.6, 35.8, 55.7, 71.5, 123.9, 140.0[d,e]	180 (M$^+$, 10), 162 (64), 147 (18), 135 (38), 133 (78), 119 (46), 95 (54), 91 (56), 81 (84), 79 (100), 67 (64), 55 (30), 41 (28)
4c	3350 (OH); 3020, 1650 (HC=C)	1.0 (d, 6H, J = 7 Hz, $2C\underline{H}_3CH$); 1.1 (s, 3H, CH_3CD); 1.7–2.3 (m, 3H, CH_2 and $C\underline{H}CH_3$); 3.8 (s, 1H, OH); 5.3–5.5 (m, 2H, 2CH=C)	22.9, 23.2, 24.6, 31.7, 43.0, 67.5 (t, CD, J_{CD} = 21 Hz), 124.2, 140.4[d]	129 (M$^+$, 2), 96 (16), 84 (44), 69 (100), 55 (12), 46 (28), 41 (16)
4e	3370 (OH); 3030, 1660 (HC=C)	1.1 (s, 3H, CH_3); 1.5–2.3 (m, 10H, $5CH_2$); 2.3–2.6 (m, 1H, OH); 5.4–5.6 (m, 1H, CH=C)	23.3, 23.8, 26.0, 29.4, 48.8, 65.9 (t, CD, J_{CD} = 21 Hz), 124.0, 135.8	141 (M$^+$, 6), 123 (14), 108 (24), 96 (30), 81 (100), 79 (22), 68 (22), 67 (26), 46 (20)
4f	3450 (OH); 3060, 3020, 1670, 1600, 1490, 750, 700 (HC=C)	0.9 (t, 3H, J = 7 Hz, CH_3); 1.8–2.4 (m, 5H, $2CH_2$ and OH); 5.0–5.6 (m, 2H, 2CH=C); 6.8–7.5 (m, 5H_{arom})[f]	14.4, 26.3, 43.2, 74.0 (t, CD, J_{CD} = 19 Hz), 125.8, 126.7, 127.7, 128.7, 135.5, 145.3[d]	177 (M$^+$, 1), 108 (100), 80 (48), 78 (25), 77 (15)
4h	3450 (OH); 3030, 1640 (HC=C)	1.1–1.7 (m, 12H, $6CH_2$); 1.7–2.3 (m, 6H, $2CH_2C$=C, OH, and CHC=C); 5.2–5.5 (m, 1H, CH=C)[f]	23.5, 24.0, 25.9, 26.2, 27.0, 31.7, 35.8, 55.8, 71.6 (t, CD, J_{CD} = 21 Hz), 123.8, 140.0[d]	181 (M$^+$, 18), 163 (99), 135 (36), 131 (72), 121 (30), 119 (24), 107 (20), 103 (40), 92 (31), 91 (77), 80 (54), 79 (100), 77 (39), 67 (51), 55 (22), 41 (27)

[a] Recorded on a Perkin-Elmer 298 infrared spectrometer.
[b] Recorded on a Varian FT-80A spectrometer.
[c] Recorded on a HP-5987A spectrometer.
[d] For the major isomer.
[e] In $CCl_4 + D_2O_{capillary}$.
[f] In $CCl_4 + TMS_{capillary}$; recorded on a Varian EM-390 spectrometer.

(2-Hydroxy-3-chloro-4-methyl)pentyl Phenyl Ketone (6g).

To a stirred solution of lithium diisopropylamide (1.93 g, 18 mmol) in tetrahydrofuran (30 ml) is added acetophenone (1.62 g, 15 mmol) at –78 °C under argon and stirring is continued for 30 min. Anhydrous magnesium bromide (1.84 g, 10 mmol) and 2-chloro-3-methylbutanal (**1g**; 1.21 g, 10 mmol) in tetrahydrofuran (10 ml) are successively added at –78 °C and stirring is continued for 1 h. The mixture is then hydrolyzed with 2 normal hydrochloric acid (10 ml), and extracted with ether (2 × 15 ml). The organic layer is washed with water (10 ml), dried with sodium sulfate, and evaporated (15 torr). The residue is purified by removing of the excess acetophenone *in vacuo* (0.01 torr); yield: 1.92 g (80 %); isomer ratio 5.3:1 (GLC analysis); m.p. 78–80 °C (hexane/ether).

$C_{13}H_{17}ClO_2$ (240.7)	calc.	C 64.86	H 7.12
	found	64.5	7.3

IR (Nujol): ν = 3480 (OH); 3080, 1600, 1480 (C_6H_5); 1680 cm^{-1} (C=O).

^{1}H-NMR ($CDCl_3$ + D_2O capillary): δ = 1.0, 1.05 (2d, 6H, J = 6 Hz, $2CH_3$); 1.3–1.7 (m, 1H, $C\underline{H}$–CH_3); 2.3–2.6 (m, 2H, CH_2); 3.3–4.3 (m, 3H, CH–Cl, CH–O, and OH); 7.55, 8.0 ppm (2 m, 5H, H_{arom}).

^{13}C-NMR ($CDCl_3$ + D_2O capillary) for the major isomer: δ = 16.7, 21.6, 29.9, 43.3, 70.1, 72.8, 129.1, 129.5, 134.4, 137.5, 201.2 ppm.

MS: m/e (% rel. int.) = 204 (M$^+$ –Cl, 1), 187 (7), 149 (10), 120 (8), 105 (100), 77 (24), 51 (8).

This paper is dedicated to Prof. Rafael Usón of the University of Zaragoza, Spain, on the occasion of his 60th birthday.

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(1) Part I: Barluenga, J., Alvarez, F., Concellón, J.M., Yus, M. *Synthesis* **1986**, 654.
(2) The best results were obtained when this first step was carried out in the presence of a stoichiometric amount of magnesium bromide (see procedure).
(3) The use of other basic agents such as potassium or sodium hydride, or sodium amide led to lower yields.
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(5) See, for example: Barluenga, J., Yus, M., Concellón, J.M., Bernad, P. *J. Org. Chem.* **1981**, *46*, 2721.
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