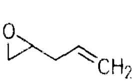
A Short and Efficient Synthesis of 4,5-Disubstituted-1-pentenes

Ann De Camp Schuda, Paul H. Mazzocchi*, Gregory Fritz, Tina Morgan

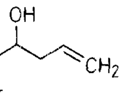
Department of Chemistry and Biochemistry, University of Maryland, College Park, Maryland 20742, U.S.A.

A one step synthesis of 5-chloro-4-hydroxy-1-pentene (65 %) and 5-bromo-4-hydroxy-1-pentene (81 %) was developed. Treatment of epibromohydrin or epichlorohydrin at −73 °C with a reagent prepared from vinylmagnesium bromide and a catalytic amount of copper(I) bromide gave the desired products. 5-Bromo-4-hydroxy-1-pentene was cleanly converted to 4,5-epoxy-1-pentene in 99 % yield by treatment with potassium hydroxide. A number of derivatives of 5-bromo-4-hydroxy-1-pentene are described.

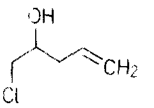
In conjunction with our studies on the synthesis of several pyrrolo[1,4]benzodiazepine antitumor antibiotics, we required various highly functionalized five carbon alkylating agents. Although 4,5-epoxy-1-pentene (**1**)[1–3], 5-bromo-4-hydroxy-1-pentene (**2**), and 5-chloro-4-hydroxy-1-pentene (**3**)[2,3] appeared to be ideally suited for our purposes, there was no simple route to **1**, **2**, or **3** reported in the literature.



1

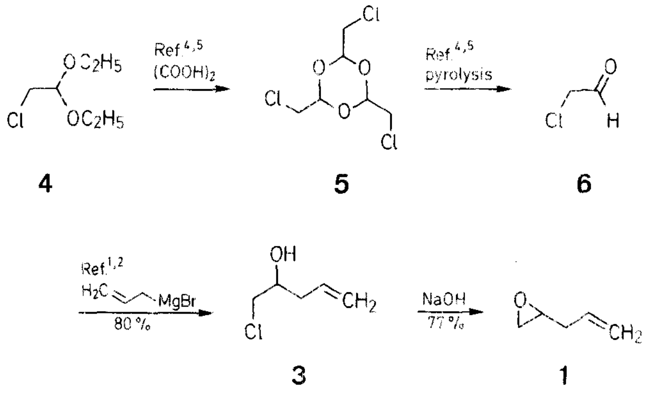


2



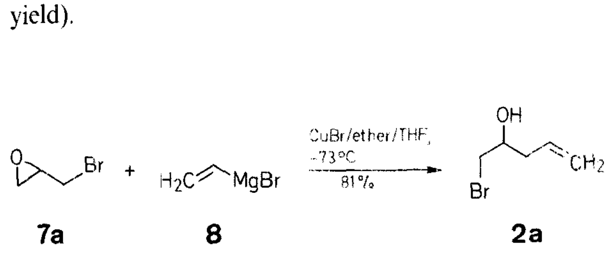
3

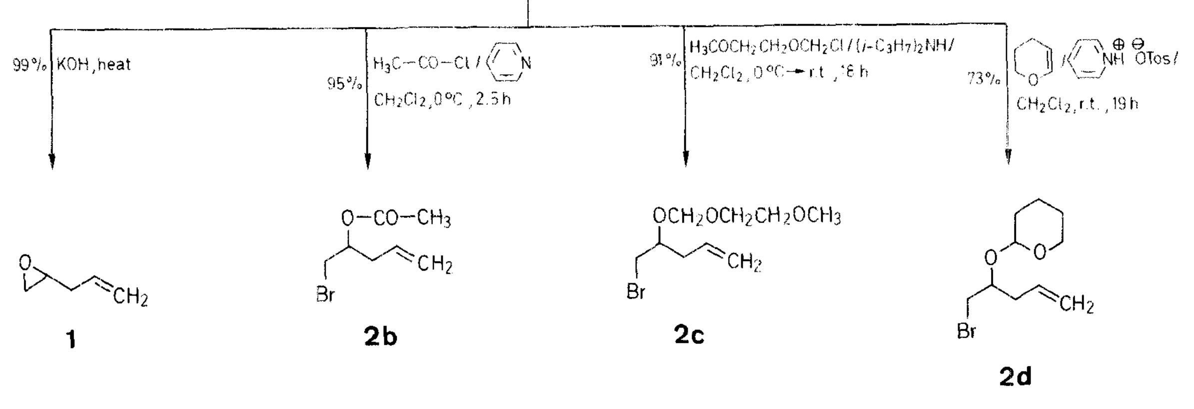
Indeed, we found that the preferred preparation of **1** via **3** was somewhat tedious (Scheme **A**). In it, chloroacetaldehyde diethyl acetal (**4**) was hydrolyzed in the presence of oxalic acid to give the trimer **5** which was pyrolyzed to the unstable and highly lachrymatory anhydrous chloroacetaldehyde (**6**)[4,5]. The reaction of **6** with allylmagnesium bromide[1,2] afforded **3** (80 % yield) which was converted to **1** with sodium hydroxide (77% yield). It became clear that a facile alternative route suitable for the large scale preparation of **1**, **2**, and **3** was desirable. We report here a one step synthesis of **2** and **3** from commercially available starting materials.

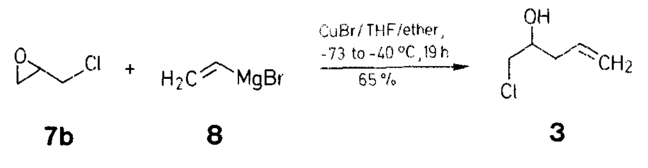


Scheme A

We found that the reaction of vinylmagnesium bromide (**8**) with epibromohydrin (**7a**) in anhydrous ether at −73 °C in the presence of 0.1 equivalents of copper(I) bromide[6] afforded the desired **2a** (81% yield). It was found that the presence of the copper(I) catalyst was crucial to the success of the reaction[7-10] as the absence of this catalyst invariably led to the extensive formation of 1,3-dibromo-2-propanol[7]. Compound **2a** was cleanly converted to **1** with potassium hydroxide (99% yield). A number of oxygen protected derivatives of **2a** were prepared and are shown in Scheme **B**. Similarly, **3** was prepared from epichlorohydrin (**7b**) (65% yield).

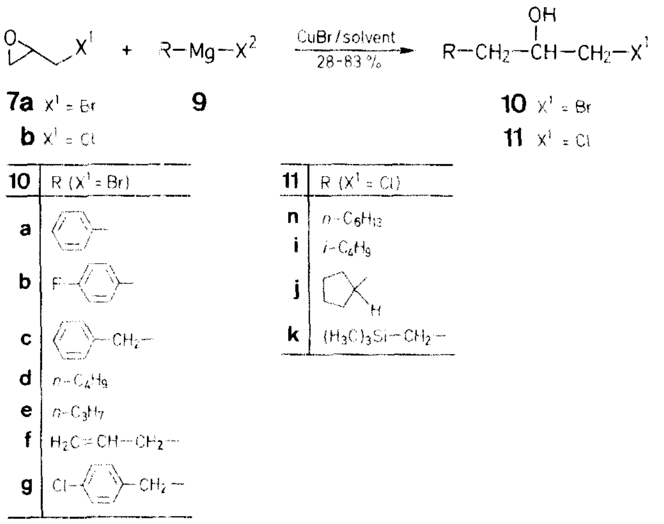






Scheme B

We have found that this reaction of **7a, b** is successful in generally moderate yields with a variety of Grignard reagents **9** using diethyl ether and tetrahydrofuran as solvents to give the substituted halohydrins **10,11** (Scheme **C** and Table).



Scheme C

G.L.C. analyses were performed with a Hewlett-Packard 5750 Gas Chromatograph with a 6 ft UC-W98 column. I.R. spectra were recorded on a Perkin-Elmer Model 281 spectrophotometer. ^{1}H- and ^{13}C-N.M.R. spectra were recorded with an IBM WP-200 spectrometer and deuterochloroform as solvent; TMS as internal reference for ^{1}H- and deuterochloroform as internal reference for ^{13}C-N.M.R. spectra. Mass spectra were determined on a Bell and Howell 21-492 (70eV) or a VG 7070E mass spectrometer. Microanalyses were performed by Dr. Franz Kasler of the University of Maryland. Flash chromatography refers to the procedure of Still[12] and was done on E. Merck silica gel of particle size 40–63 μm. Copper(I) bromide (purum grade, Fluka Chemical Corp.) was used without further purification.

4,5-Epoxy-1-pentene (1):

Potassium hydroxide (85%, 1.6 g) is added to the bromohydrin **2a** (4.0 g, 0.024 mol) in a flask fitted with a distillation head. The mixture is heated and the epoxide **1** distills over as a colorless liquid; yield: 2.0 g (99%); b.p. 80–82 °C (Ref.[1], b.p. 92–94 °C); n_D^{24}: 1.4170 (Ref.[1], n_D^{20}: 1.4191).

5-Bromo-4-hydroxy-1-pentene (2a):

A 1 molar solution of vinylmagnesium bromide (**8**) in tetrahydrofuran (200 ml, 0.20 mol) is added to a suspension of copper(I) bromide (2.86 g, 0.02 mol) in anhydrous diethyl ether (500 ml) at −73 °C under nitrogen. Epibromohydrin (**7a**; 28.6 g, 0.210 mol) is added over a period of 5 min and the mixture stirred at −73 °C for 23 h. The progress of the reaction is monitored by G.L.C. as the yellow reaction mixture is warmed to −30 °C over a period of 5 h. The mixture is poured into water (1200 ml), extracted with diethyl ether (3 × 1000 ml), the extract is washed with water (1000 ml), dried with anhydrous sodium sulfate, and evaporated in vacuo to give a pale yellow liquid. Vacuum distillation of the crude product gives the bromohydrin **2a** as a colorless liquid; yield: 26.7 g (81 %); b.p. 61–75 °C/4.0 torr.

C_5H_9BrO calc. C 36.39 H 5.50
(165.0) found 36.27 5.80

Table 1. Substituted Halohydrins **10**, **11** prepared (Scheme **C**)

Product	Yield [%] in THF	Yield [%] in ether	b.p. [°C]/torr	Molecular Formula[a] or Lit. b.p. [°C]/torr
10a	56	35	80–84°/0.25	–[b]
10b	67	–	110–114°/0.2	$C_9H_{10}BrFO$ (233.9)
10c	61	–	84–90°/0.05	–[c]
10d	28	43	44–48°/0.3	102–103°/12[17]
10e	25	83	32–36°/0.15	93–95°/17[19]
10f	60	–	36–38°/0.5	75–78°/3[20]
10g	60	–	90–95°/0.2	$C_9H_{10}ClBrO$ (249.5)
11h	–	55	70–73°/0.25	114.5–116.5°/13[18]
11i	–	63	70–74°/3.5	85–87°/15[17]
11j	–	77	104–108°/7	$C_8H_{15}ClO$ (162.7)
11k	–	58	116–120°/3.5	103–104°/20[21]

[a] Satisfactory microanalyses obtained: C ±0.29, H ±0.28.
[b] Spectral data identical to those given in Ref.[16].
[c] Not analyzed.

5-Chloro-4-hydroxy-1-pentene (3):
A 1 molar solution of vinylmagnesium bromide (**8**) in tetrahydrofuran (20 ml, 0.02 mol) is added to a suspension of copper(I) bromide (0.286, 0.002 mol) in anhydrous diethyl ether (50 ml) at −73 °C under nitrogen. Epichlorohydrin **7b** (1.94 g, 0.021 mol) is added, the mixture stirred at −73 to −40 °C for 19 h, poured into water (120 ml), extracted with diethyl ether (3 × 100 ml), the extracts are washed with water (100 ml), and dried with anhydrous sodium sulfate. Diethyl ether and tetrahydrofuran are removed by distillation and the residue vacuum distilled to afford the chlorohydrin **3** as a colorless liquid; yield: 1.57 g (65 %): b.p. 66–69 °C/21 torr (Ref.[1], b.p. 65–70 °C/16–17 torr).

4-Acetoxy-5-bromo-1-pentene (2b):
Acetyl chloride (11.62 g, 0.148 mol) is added dropwise to a solution of anhydrous pyridine (11.78 g, 0.149 mol) in anhydrous dichloromethane (23 ml) at 0 °C under nitrogen[13]. The bromohydrin **2a** (7.0 g, 0.042 mol) in dichloromethane (46 ml) is added, the mixture is stirred at 0 °C for 2.5 h, poured into diethyl ether (700 ml), and carefully washed with saturated aqueous sodium hydrogen carbonate solution (2 × 600 ml). The combined aqueous washings are extracted with diethyl ether (300 ml). The combined organic phases are dried with anhydrous sodium sulfate and evaporated in vacuo to give a dark yellow liquid (14.8 g) which is vacuum distilled to give the acetate **2b** as a colorless liquid; yield: 8.4 g (95 %); b.p. 77.5–79.5 °C/3.75 torr.

$C_7H_{11}BrO_2$ calc. C 40.60 H 5.36
(207.1) found 40.64 5.53

Table 2. Spectroscopic Data for Compounds **1–3**, **10b**, **c**, **g**, and **11j**

Product	I.R. (neat) ν[cm^{-1}]	^{1}H-N.M.R. (CDCl$_3$/TMS) δ[ppm]	^{13}C-N.M.R. (CDCl$_3$) δ[ppm]	M.S. [m/e]
1	2995, 1647, 1410, 920[a]	2.23–2.37 (m, 2H); 2.48 (dd, J = 5.0 Hz, 2.6 Hz, 1H); 2.73 (dd, J = 5.0 Hz, 4.0 Hz, 1H); 2.91–3.03 (m, 1H); 5.03–5.22 (m, 2H); 5.68–5.92 (m, 1H)	36.4; 46.4; 51.1; 117.5; 133.0	83 (M$^+$ − 1); 55 (base); 43, 41
2a	3400 (br), 2920, 1645, 1420, 920	2.29–2.37 (m, 3H, 1H exchanges with D_2O); 3.36 (dd, J = 10.0 Hz, 6.5 Hz, 1H); 3.49 (dd, J = 10.0 Hz, 3.8 Hz, 1H); 3.83 (m, 1H); 5.08–5.19 (m, 2H); 5.67–5.88 (m, 1H)	38.8; 39.4; 70.2; 118.2; 133.2	—
3	3380 (br), 3085, 2960, 1646, 1432, 920	2.30–2.41 (m, 2H); 2.50 (br. s, 1H, exchanges with D_2O); 3.51 (dd, J = 6.5 Hz, 10.9 Hz, 1H); 3.63 (dd, J = 4.0 Hz, 10.9 Hz, 1H); 3.80–3.97 (m, 1H); 5.09–5.25 (m, 2H); 5.70–5.94 (m, 1H)	—	—
2b	2950, 1745, 1475, 1035	2.08 (s, 3H); 2.42–2.50 (m, 2H); 3.39–3.60 (m, 2H); 4.99–5.23 (m, 3H); 5.63–5.84 (m, 1H)	20.8; 33.1; 36.8; 71.7; 118.8; 132.2; 169.8	—
2c	3095, 2900, 1648, 1040	2.35–2.54 (m, 2H); 3.40 (s, 3H); 3.42–3.94 (m, 7H); 4.81 (s, 2H); 5.03–5.25 (m, 2H); 5.60–5.95 (m, 1H)	35.1; 37.6; 58.9; 67.3; 71.8; 76.1; 94.8; 118.2; 133.4	—
2d	3090, 2950, 1648, 1445, 1135, 1025	2.30–2.96 (m, 6H); 2.26–2.57 (m, 2H); 3.32–3.61 (m, 3H); 3.77–4.05 (m, 2H); 4.72 (t, J = 3.3 Hz, 1H); 4.77 (t, J = 3.3 Hz, 1H); 5.02–5.24 (m, 2H); 5.65–5.97 (m, 1H)	19.5; 25.5; 30.7; 30.8; 34.4; 35.5; 36.9; 38.4; 62.4; 62.5; 74.7; 76.2; 97.7; 98.6; 117.8; 118.0; 133.5; 133.8	—
10b	3400 (br), 2940, 1515, 1225, 1025, 840, 820	2.35 (s, 1H, exchanges with D_2O); 2.45–2.83 (m, 2H); 2.87–3.42 (m, 2H); 3.45–3.93 (m, 1H); 6.30–6.98 (m, 4H)	—	—
10c	3410 (br), 3040, 2930, 1500, 1460, 1045, 750, 700	1.55–2.15 (m, 2H); 2.22–3.03 (m, 3H; 1H exchanges with D_2O); 3.18–4.05 (m, 4H); 6.87–7.43 (m, 5H)	—	230 (M$^+$, ^{81}Br); 228 (M$^+$, ^{79}Br); 148 (M − Br); 131 (base), 105, 91, 77
10g	3400 (br), 2930, 1495, 1090, 1020, 830, 805	2.33–3.00 (m, 3H, 1H exchanges with D_2O); 3.02–4.13 (m, 3H); 6.83–7.47 (m, 4H)	—	—
11j	3380 (br), 2960, 2870, 1455, 1435, 1045, 740	1.70–2.70 (m, 12H, 1H exchanges with D_2O); 3.15–3.98 (m, 3H)	—	—

[a] In CCl_4 solution.

5-Bromo-4-(2-methoxyethoxymethoxy)-1-pentene (2c):
A mixture of diisopropylamine (9.70 g, 0.075 mol) and 2-methoxyethoxymethyl chloride[14] (9.35 g, 0.075 mol) in dichloromethane (50 ml) is stirred at 0 °C under nitrogen for 1 h. A solution of the bromohydrin **2a** (12.5 g, 0.075 mol) in dichloromethane (50 ml) is added and the mixture allowed to warm to room temperature and stirred for 18 h. The amber-colored mixture is poured into water (700 ml) and the aqueous phase extracted with dichloromethane (2 × 250 ml). The combined organic phases are washed with water (400 ml), dried with anhydrous sodium sulfate, and evaporated in vacuo. The residue is vacuum distilled to afford the product **2c** as a colorless liquid; yield: 11.5 g (91 %); b.p. 105–115 °C/2.25 torr.

H.R.M.S.: $m/e = 252.0373$ (calc. for $C_9H_{17}\,{}^{79}BrO_3$, 252.0361).

5-Bromo-4-(2-tetrahydropyranyloxy)-1-pentene (2d):
A mixture of the bromohydrin **2a** (0.980 g, 5.9 mol), dihydropyran (0.75 g, 8.9 mmol), pyridinium p-toluenesulfonate (0.15 g, 0.59 mmol), and dichloromethane (42 ml) is stirred for 19 h[15]. Diethyl ether (60 ml) is added and the mixture washed with half saturated sodium chloride solution, dried with anhydrous sodium sulfate, and evaporated in vacuo. The residue is purified by flash chromatography (25 % ether in Skelly F) to give a mixture of the diastereomeric tetrahydropyranyloxy compounds **2d** as a colorless liquid; yield: 1.08 g (73 %).

$C_{10}H_{17}BrO_2$	calc.	C 48.18	H 6.88
(249.2)	found	48.41	7.10

Substituted Halohydrins 10,11; General Procedure:
The procedure used for the preparation of **3** is employed except that a 1 molar solution of the appropriate Grignard reagent **9** (20 ml) is substituted for **8**. Products either gave properties identical to those reported in the literature or gave N.M.R. I.R., and analytical data consistent with their structures.

We thank the USDA, Agricultural Research Center, Beltsville, Maryland for partial support of this work.

Received: January 10, 1985

---

[1] Brown, H.C., Lynch, G. *J. Org. Chem.* **1981**, *46*, 930.

[2] Bergkvist, T. *Sven. Kem. Tidskr.* **1947**, *41, 59*, 27; *C.A.* **1947**, *41*, 5095.

[3] Zaidlewicz, M., Sarnowski, R. *Heterocycles* **1982**, *18*, 281.

[4] House, H.O., Jones, V.K., Frank, G.A. *J. Org. Chem.* **1964**, *29*, 3327.

[5] De Bièvre, P.J., Van der Kelen, G.P., Cornille, G., Eeckhaut, Z. *Bull. Soc. Chim. Belg.* **1959**, *68*, 550.

[6] Huynh, G., Derguini-Boumechal, F., Linstrumelle, G. *Tetrahedron Lett.* **1979**, 1509.

[7] Gaylord, N.G., Becker, I.E. *Chem. Rev.* **1951**, *49*, 413.

[8] Wege, P.M., Clark, R.D., Heathcock, C.H. *J. Org. Chem.* **1976**, *41*, 3144.

[9] Normant, J.F., Alexakis, A. *Synthesis* **1981**, 841.

[10] Lipshutz, B.H., Koslowski, J.A. *J. Org. Chem.* **1984**, *49*, 1149.

[11] Fritz, G., unpublished results.

[12] Still, W.G., Kahn, M., Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

[13] Trost, B.M., Chan, D.M.T. *J. Am. Chem. Soc.* **1983**, *105*, 2315. The yield of the reaction was increased dramatically (54 to 95 %) when the literature procedure was modified as given here.

[14] Corey, E.J., Gras, J.L., Ulrich, P. *Tetrahedron Lett.* **1976**, 809.

[15] Myashita, M., Yoshikoshi, A., Grieco, P.A. *J. Org. Chem.* **1977**, *42*, 3772.

[16] Dalton, D.R., Dutta, V.P. *J. Chem. Soc.* [*B*] **1971**, 85.

[17] Rothstein, B. *Bull. Soc. Chim. Fr.* **1935**, *2*, 1936.

[18] Major, R.T., Bonnett, H.T. *J. Am. Chem. Soc.* **1936**, *58*, 23.

[19] Levene, P.A., Haller, H.L. *J. Biol. Chem.* **1928**, *79*, 474.

[20] Torsell, K. *Ark. Kemi.* **1965**, *23*, 543.

[21] Brynolf, S. *Acta Chem. Scand.* **1956**, *10*, 883.