Facile Conversion of Epoxides to Chlorohydrins with Titanium(IV) Chloride/1,8-Diazabicyclo[5.4.0]undec-7-ene

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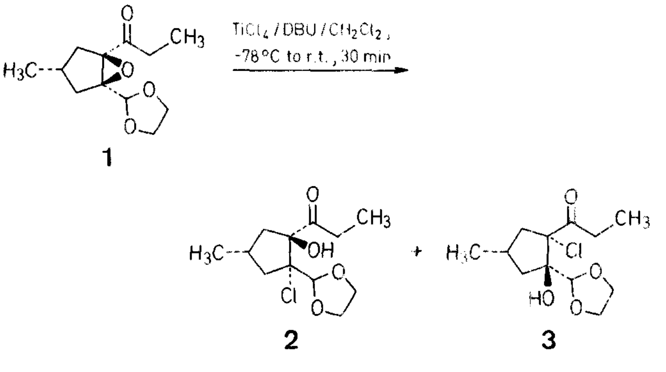
A series of epoxides has been converted to the analogous chlorohydrins by treatment with titanium(IV) chloride and 1,8-diazabicyclo[5.4.0]undec-7-ene. This procedure tolerates acetal protecting groups normally labile to aqueous acids, and, when used in conjunction with the Sharpless epoxidation protocols, it allows the preparation of chiral chlorodiols selectively protected at one hydroxy group.

During the course of our studies directed toward the total synthesis of (+)-jatrophone[1], we prepared the acetal epoxide **1**, and were forced to consider methods for its conversion to chlorohydrin **2**. Survival of the acetal function appeared unlikely under most standard conditions for this transformation. Accordingly, we sought a new procedure for converting epoxides to chlorohydrins which would tolerate such acid labile groups as this acetal.

Although there is precedent for the Lewis acid-assisted conversion of epoxides to halohydrins[2] [e.g. with iron(III) chloride[3]], these reactions often afford only modest yields. We hypothesized that use of a stronger Lewis acid might result in a better yield, but when compound **1** was treated with titanium(IV) chloride in dichloromethane at −78 °C, conversion to the chlorohydrins (**2** and **3**) was observed only to a limited extent (25%). Furthermore, use of excess titanium(IV) chloride or higher temperatures did not significantly improve the yield. However, treatment of epoxide **1** with titanium(IV) chloride and diazabicycloundecene (DBU) in dichloromethane at room temperature resulted in an efficient conversion (84%) to the desired chlorohydrins **2** and **3**.



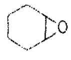
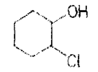
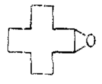
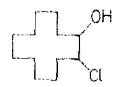
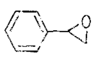
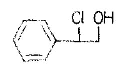
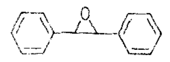
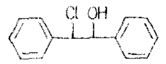
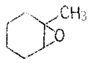
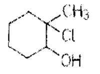
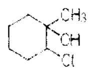
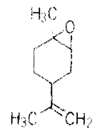
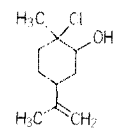
1

2 **3**

Other amine bases (e.g. 4-dimethylaminopyridine) can be used in place of DBU, but yields are slightly diminished.

To explore further the value of this procedure we examined this reaction with a series of epoxides, most of which had previously been converted to chlorohydrins with other reagents[3,4]. The results of these studies are given in Table 1. For mono- and disubstituted epoxides, the $TiCl_4$/DBU combination results in good yields of the expected chlorohydrins. Perhaps especially significant are the yields obtained with compounds **8** and **10** (Table 1). When these epoxides are treated with other Lewis acids they readily rearrange to carbonyl compounds[3], but treatment with $TiCl_4$/DBU affords good yields of the chlorohydrins **9** and **11**. With trisubstituted epoxides, the yields isolated were more mod-

Table 1. Chlorohydrins from Epoxides

Epoxide		Product		Yield [%]	b.p. [°C]/torr (reported)
4		**5**		87	67–72°/0.25 (93–94°/30)[4]
6		**7**		72	78–81°/0.6 (–)
8		**9**		94	62°/0.2 (86°/1)[7]
10		**11**		87	viscous oil (m.p. 42–43°)[8]
12		**13**  + **14** 		40	85–90°/1.5 (–)[9]
15		**16**		46	78–80°/0.7 (–)

est. However, the procedure may still be useful in these cases because selectivity for the tertiary chloride, secondary alcohol is quite good.

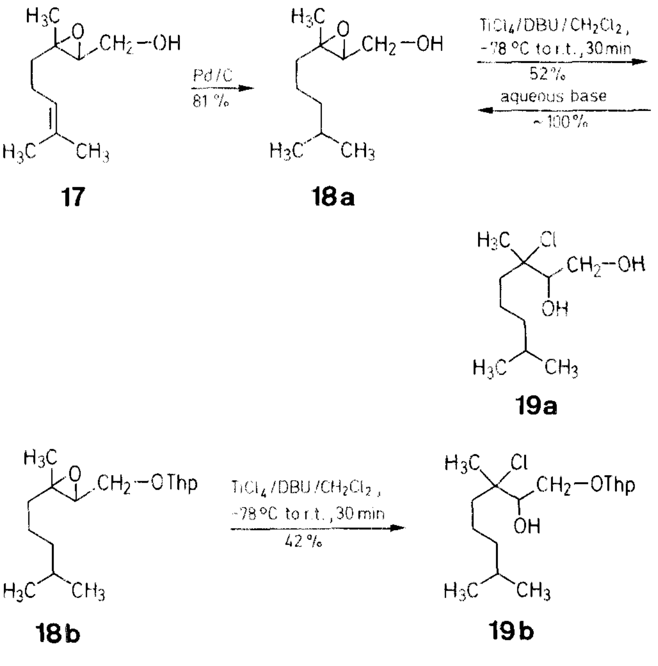


Table 2. Physical and Spectral Data of Products

Compound	$[\alpha]_D$	Molecular Formula[a]	^{1}H-N.M.R. δ [ppm]	^{13}C-N.M.R. δ [ppm]	M.S. *m/e* (relative intensity)
2	–	–	5.34 (s, 1H); 4.0–3.8 (m, 4H); 3.0–1.9 (m, 7H); 1.54 (s, 1H); 1.13 (d, 3H, J = 6.2 Hz); 1.02 (t, 3H, J = 7.0 Hz)	211.8; 104.0; 88.1; 83.4; 65.9; 48.1; 41.2; 34.7; 29.2; 21.5; 7.9	*m/e* = 226.1215 (calc. for $C_{12}H_{18}O_4$: 226.1204)
3	–	–	5.32 (s, 1H); 4.0–3.8 (m, 4H); 3.0–1.9 (m, 7H); 1.54 (s, 1H); 1.13 (d, 3H, J = 6.2 Hz); 1.02 (t, 3H, J = 7.0 Hz)	200.4; 104.0; 88.8; 82.1; 65.9; 48.1; 42.3; 34.7; 29.7; 22.1; 7.9	–
7	–	–	4.0–3.6 (m, 2H); 2.5 (br. s, 1H); 2.4–1.2 (m, 20H)	74.0; 66.6	*m/e* = 200.1329 (calc. for $C_{12}H_{21}O$: 200.1331)
9	–	–	7.38 (m, 5H); 4.99 (t, 1H, J = 6.6 Hz); 3.93 (d, 2H, J = 6.6 Hz); 1.97 (s, 1H)	137.9; 128.4; 127.3; 67.4 (CH_2OH); 64.2 (CHCl)	156 (M^+, 5%); 158 (M^+ + 2,2%); 138 ($M^+ - H_2O$, 0,5%); 120 (M^+ − HCl, 15%); 102 ($M^+ - H_2O$ − HCl, 3%); 127 (17%); 126 (20%); 125 (49%)
16	–	–	4.7 (s, 2H); 4.0–3.5 (m, 2H); 1.73 (s, 3H); 1.63 (s, 3H)	149.0; 109.3; 77.6; 74.0; 43.3; 37.2; 35.1; 28.6; 26.7; 20.8	*m/e* = 188.0965 (calc. for $C_{10}H_{17}ClO$: 188.0967)
18a	−5.32° ($CDCl_3$)	$C_{10}H_{20}O_2$ (172.3)	3.74 (t, 1H, J = 6 Hz); 3.47 (q, 1H, J = 7 Hz); 3.0 (t, 1H, J = 6 Hz); 1.5–1.1 (m, 7H); 1.3 (s, 3H); 0.9 (d, 6H, J = 6 Hz)	63.0; 61.1; 60.8; 38.6; 38.4; 30.7; 27.6; 22.5; 22.2; 16.4	–
19a	−4.57°	$C_{10}H_{21}ClO_2$ (208.7)	3.9–3.0 (m, 3H); 1.7–1.2 (m, 7H); 1.5 (s, 3H); 0.85 (d, 6H, J = 6 Hz)	77.5; 76.9; 62.7; 44.1; 40.4; 39.0; 27.8; 22.5; 21.9	–
18b	−3.80°	–	4.6 (br. s, 1H); 3.8–3.4 (m, 4H); 3.0 (t, 1H, J = 5 Hz); 1.6–1.2 (m, 14H); 1.3 (s, 3H); 0.85 (d, 6H, J = 6 Hz)	97.7; 62.5; 61.0; 60.7; 60.4; 38.2; 30.0; 27.3; 24.9; 22.2; 18.5; 16.1	–
19b	–	–	3.8–3.5 (m, 6H); 1.6–1.2 (m, 12H); 1.5 (s, 3H); 0.85 (d, 6H, J = 6 Hz)	93.8; 76.7; 74.8; 62.3; 53.8; 53.1; 48.1; 40.7; 31.9; 28.3; 27.2; 24.7; 22.0; 18.8	–

[a] Satisfactory microanalyses obtained: C ±0.35, H ±0.28.

With emergence of the Sharpless methodology for asymmetric epoxidation[5], chiral epoxyalcohols are now readily available. To determine whether this reagent would afford chlorohydrins with stereospecificity, we prepared (−)-geraniol epoxide **(17)**[5]. However, treatment of this epoxide with $TiCl_4$/DBU gives a complex mixture, presumably because of participation of the remaining double bond. Accordingly, (−)-dihydrogeraniol epoxide **(18a)** was prepared by catalytic hydrogenation of compound **17**. When this epoxide was treated with $TiCl_4$/DBU we obtained an optically active product, chlorohydrin **19a**, in yields comparable to those obtained with other trisubstituted epoxides. The stereospecificity of this process was confirmed by converting this chlorohydrin **(19a)** back to the original epoxide **18a**, with no loss of optical activity. Finally, the stability of acetal groups to these conditions was again demonstrated by conversion of the tetrahydropyranyl protected (−)-dihydrogeraniol **18b** into the analogous chlorohydrin **19b** (42 %) with no observable cleavage of the acetal group.

The generally high yields, mild reaction conditions, and tolerance of acetal groups normally labile to aqueous acids, combine to make this an attractive procedure for conversion of at least mono- and disubstituted epoxides to chlorohydrins. By combination of this procedure with the Sharpless epoxidation protocols, it is now possible to prepare chiral chlorodiols, selectively protected at one hydroxy group[6].

Chlorohydrins from Epoxides; General Procedure:
1,8-Diazabicyclo[5.4.0]undec-7-ene (0.79 g, 5.12 mmol) is added via a syringe to a solution of the epoxide (2.56 mmol) in anhydrous dichloromethane (20 ml). This solution is cooled to −78 °C (Dry Ice/isopropyl alcohol bath) prior to addition of titanium(IV) chloride (7.7 mmol as a 2 molar solution in dichloromethane). The cooling bath is removed and the mixture is allowed to warm to room temperature over 30 min. The reaction is then monitored by T. L. C. (usually using ~ 15 % ethyl acetate/hexane as eluent) until starting material has been consumed. After treatment with 5 % aqueous sodium carbonate solution (10 ml) the two-phase mixture is partitioned and the aqueous phase is extracted with dichloromethane (4 × 10 ml). The combined organic layers are dried with sodium sulfate, concentrated in vacuo, and the product isolated by Kugelrohr vacuum distillation (Tables 1 and 2).

2-Chloro-2-phenylethanol (9):
Prepared from **8** (100 mg, 0.8 mol) in dichloromethane (7.5 ml) following the general procedure given above. This reaction is monitored by T. L. C. using 20 % ethyl acetate/hexane as eluent. The crude oil is vacuum distilled (Kugelrohr) to afford a colorless oil, identified as 2-chloro-2-phenylethanol **(9)** on the basis of its oxidation (pyridinium chlorochromate) to 2-chloro-2-phenylacetaldehyde, and on spectral data; yield: 122.3 mg (94 %); b.p. 62 °C/0.2 torr.

Chlorohydrin 19a from (−)-Dihydrogeraniol Epoxide (18a):
Geraniol epoxide[5] (**17**; 8.75 g, 53 mmol) is hydrogenated over palladium on carbon catalyst (260 mg) until uptake of hydrogen is complete. *The product* ***18a*** *is obtained after simple distillation;* yield: 7.3 g (81 %).

This epoxide (2.99 g, 17.43 mmol) is then converted to the chlorohydrin by application of the general procedure to give a dark yellow oil; yield: 1.88 g (52 %). An analytical sample of **19a** is obtained by flash chromatography.

When treated with dilute aqueous base, this chlorohydrin **19a** is converted to the starting epoxide **18a** in quantitative yield, providing material with an optical rotation identical to that of the starting epoxide.

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