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Efficient Routes To Isotopically Labelled Epichlorohydrins ((Chloromethyl) oxiranes)

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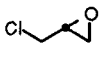
Summary: Efficient routes are developed for the synthesis of variously labelled ^{2}H- and ^{13}C- labelled epichlorohydrins prepared from appropriately labelled acetic acids and sodium borodeuteride. The route is versatile and can be used for strategic location of isotopes at C-1, C-2 and C-3 of epichlorohydrin. By way of demonstration [2-^{13}C]-, [2-^{2}H]-, [3-$^{2}H_2$] and [2-^{2}H, 3-$^{2}H_2$]- epichlorohydrins have been prepared. In addition the syntheses can be adapted for the preparation of enantiomerically pure and isotopically labelled epichlorohydrins.

Keywords: Epichlorohydrin, regiospecific labelling, multiple labelling.

Epichlorohydrin ((chloromethyl) oxirane) **1** has occupied a prominant role in the chemistry of materials [1], pharmaceuticals [2], and more generally in different aspects of the fine chemicals industry [3]. It's mutagenic properties are well known [4] and in this context radiolabelled epichlorohydrins have found use in metabolism and mutagenesis studies [5]. Its effects on cells is often complex [6,7] and not well understood and in these areas epichlorohydrin labelled with stable isotopes have provided useful investigative tools [8].



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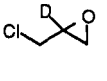

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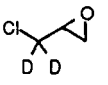

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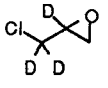

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We required to gain access to mmolar quantities of regiospecifically, and highly enriched (>95 mole %), isotopically labelled ^{13}C- and ^{2}H- epichlorohydrins **1a - 1d**. There was no straightforward and efficient route in the literature which allowed isotopic enrichment at the various sites in epichlorohydrin, and we now report details of the synthetic route shown in the Scheme which we have developed to solve this problem.

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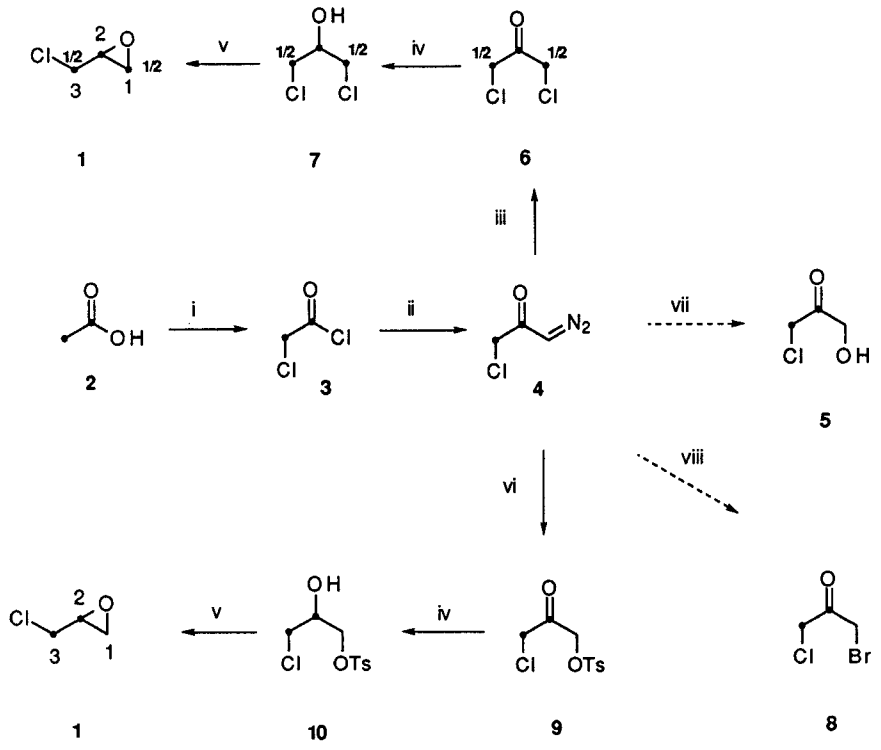


Scheme 1 i. $SOCl_2$, NCS; ii. CH_2N_2; iii. HCl; iv. $NaBH_4$; v. Na metal, ethylene glycol; vi. pTSA; vii. aq. HCl; viii. HBr.

We reasoned that a synthesis starting from acetic acid **2** would offer an accessible and relatively cheap source of isotope. At the outset our efforts focused on the conversion of chloroacetyl chloride **3** to its corresponding diazoketone **4** by treatment with diazomethane [9]. Hydrolysis of the diazoketone could then afford 1-chloro-3-hydroxyacetone **5** and provide an entry into epichlorohydrin **1** *via* 1-chloro-3-tosylpropanone **9**. Accordingly acetic acid was converted to chloroacetyl chloride **3** after treatment with thionylchloride and N-chlorosuccinamide [10]. Careful distillation of the chloroacetyl chloride followed by diazomethane treatment gave diazoketone **4** in good yield. Failure to remove all traces of thionyl chloride from the chloroacetyl chloride resulted in poor yields and lack of reproducibility at this stage. Diazoketone **4** was stable and could be characterised, however for routine synthesis the diazoketone was not normally isolated. Attempts to hydrolyse the diazoketone with dilute aqueous acid proved probematic. We became aware however that hydrolysis with dilute hydrochloric acid gave rise to trace amounts of 1,3-dichloropropanone **6** in the product mixture. Indeed if the diazoketone **4** is treated with a solution of dry HCl in diethyl ether then **6** is generated in almost quantative yield (>95%) [9]. This then became the more effective route towards epichlorohydrin. Sodium borohydride reduction of **6** gave 1,3-dichloropropan-2-ol **7** and

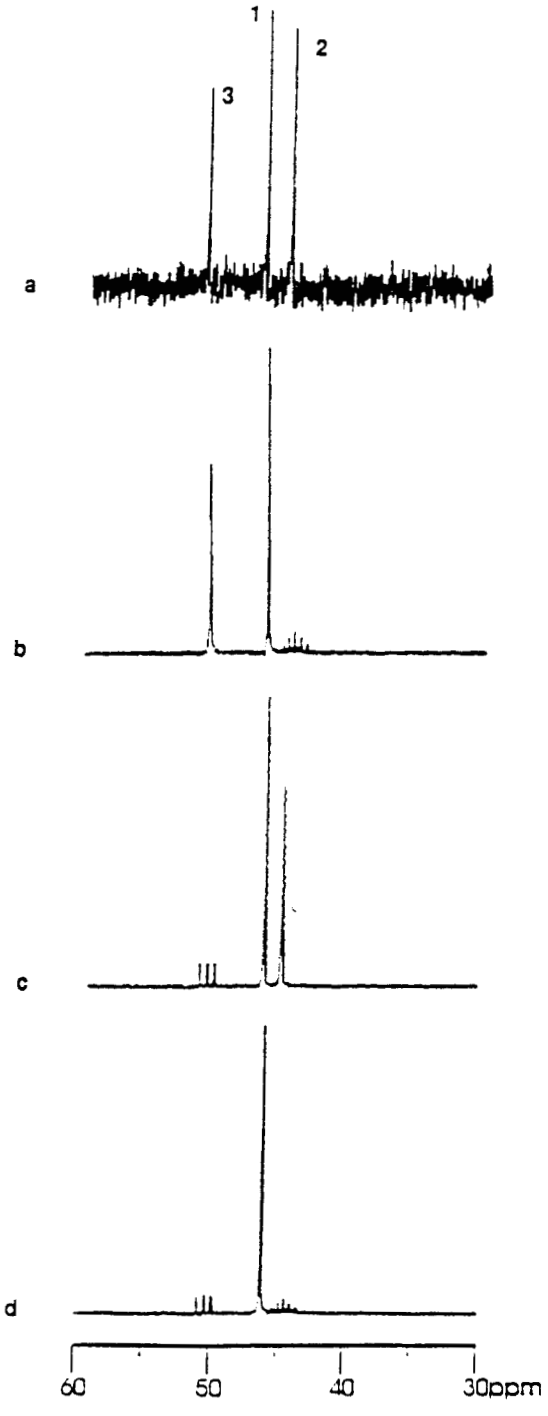
then treatment with sodium ethylene glycol, following a previously optimised protocol [11], afforded epichlorohydrin **1** in an overall yield of 33%.

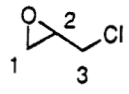
This route allows access to exclusively labelled [2-^{13}C]-epichlorohydrin **1a** from [1-^{13}C]-acetate. If sodium borodeuteride is used in the reduction step then deuterium can also be introduced at C-2 of epichlorohydrin eg **1b** and **1d**. A limitation however of this route is the intermediacy of 1,3-dichloropropanone **6**. Clearly if the isotope is introduced from C-2 of acetic acid **2** then the label will be scrambled equally between positions 1 and 3 in the resultant epichlorohydrin as illustrated in Scheme 1. This may be acceptable for some purposes, but for our study we required to control the regiochemistry.

In an attempt to differentiate the origins of C-1 and C-3 of epichlorohydrin, diazoketone **4** was quenched, in the first instance, with HBr. Although this gave rise to 1-bromo-3-chloroacetone **8**, the yield was poor and the reaction was not reproducible. Treatment of diazoketone **4** with *p*-toluenesulphonic acid however afforded the corresponding 3-chloro-2-oxopropyl-*p*-toluenesulfonate **9** in moderate yield (55%). The product is easily purified by recrystallisation and **9** provides an excellent intermediate at this stage of the synthesis. The reaction of *p*-toluenesulfonic acid with diazoketones to generate α-tosylketones was first reported many years ago [12,13] but it would appear that this reaction has received little attention since these early reports. Reduction of **9** to 3-chloro-2-hydroxypropyl-*p*-toluenesulfonate **10** with sodium borohydride, followed by epoxide ring closure, afforded epichlorohydrin without any trace of glycidyl tosylate [9]. Despite the moderate conversion of diazoketone **4** to **9** this route allows unique labelling at C-3 of epichlorohydrin from appropriately labelled C-2 acetic acids. For our purposes we have prepared [2-^{13}C]- **1a**, [2-^{2}H]- **1b**, [3-^{2}H$_2$]- **1c** and [2-^{2}H, 3-^{2}H$_2$]- **1d** epichlorohydrins by this route. The ^{13}C-NMR spectra of these samples are compared with unlabelled epichlorohydrin in Figure 1. It is obvious and interesting that the ^{13}C-^{2}H coupling significantly reduces the intensity of the ^{13}C-signals to which deuteriums are attached. Such a labelling strategy is analogous to the selective enrichment of specific carbons by carbon-13, and in cases where cost is an issue, strategic deuterium labelling could offer an alternative way of enhancing or depleting the relative ^{13}C-NMR sensitivity at specific sites in epichlorohydrin.

It is noteworthy that the route *via* 3-chloro-2-oxopropyl-*p*-toluenesulfonate **9** provides an entry into enantiomerically pure and isotopically labelled epichlorohydrins. Recently it has been demonstrated [14,15] that racemic 3-chloro-2-hydroxypropyl-*p*-toluenesulfonate **10** is efficiently resolved into its component enantiomers after selective acylation, or deacylation of the butyrate ester, of the S-enantiomer by the lipase from *Pseudomonas fluoresence*.

Finally the modified route illustrated in Scheme 2 has been developed for unique labelling at C-1 of epichlorohydrin. This route is initiated from bromoacetic acid **11** and proceeds *via* bromoacetyl chloride to the α-bromodiazoketone **12**. Treament of **12** with HCl again gave an efficient conversion to 1-bromo-3-chloropropanone **8**. Reduction with sodium borohydride to alcohol **13**, followed by base mediated epoxide ring closure, gave epichlorohydrin exclusively without any trace of epibromohydrin. The availability of ^{13}C-





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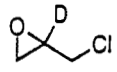

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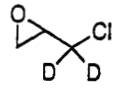

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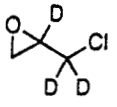
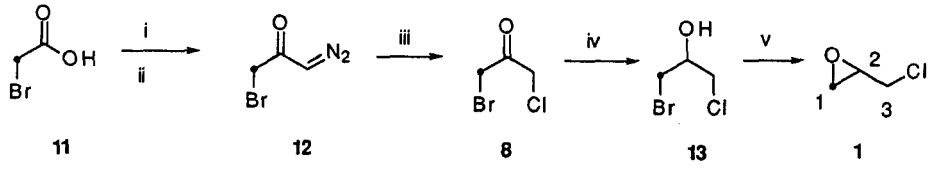


1d

Figure 1 ^{13}C-NMR Spectra of (a) epichlorohydrin **1**, (b) [2-^{2}H]-epichlorohydrin **1b**, (c) [3-$^{2}H_2$]-epichlorohydrin **1c** and (d) [2-^{2}H, 3-$^{2}H_2$]-epichlorohydrin **1d**.

and ^2H- isotopically labelled C-2 bromoacetic acids makes this an attractive route to C-1 labelled epichlorohydrins.



Scheme 2 i. $SOCl_2$; ii. CH_2N_2; iii. HCl; iv. $NaBH_4$; v. Na metal, ethylene glycol.

In summary we have developed an efficient and versatile route to isotopically labelled samples of epichlorohydrin which should allow mmolar quantities to be prepared easily and relatively cheaply from appropriately labelled acetic acids and sodium borodeuteride. Such materials should find use in the synthesis of isotopically enriched pharmaceuticals for metabolism studies as well as providing labelled epichlorohydrins for solution and solid state NMR investigations of relevant polymeric materials.

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Experimental

General. IR spectra were recorded on Perkin-Elmer F.T. 1720X or 1600 spectrometers. Low resolution mass spectra were recorded on a VG Analytical 7070E Organic mass spectrometer, while gas chromatography-mass spectra (GC-MS) were recorded using a Hewlett Packard 5890 Series II gas chromatograph connected to a VG Mass Lab Trio 1000. Chemical ionisation utilised NH_3 as the carrier gas. Solution state NMR spectra were recorded on Varian Gemini 200MHz (^1H at 199.975MHz, ^{13}C at 50.289MHz), Varian XL-200 (^1H at 200.057MHz) and Varian VXR 400(S) (^1H at 399.952MHz and ^{13}C at 100.577MHz) spectrometers. Chemical shifts are quoted relative to Me_4Si ($\delta = 0$) for ^1H and ^{13}C in $CDCl_3$.

Chloroacetyl chloride **3**. A solution of thionyl chloride (47.70g, 401mmol) in glacial acetic acid (6.0g, 99.9mmol) was heated at 70°C for 30 min. To this was added N-chlorosuccinimide (26.7g, 200mmol), thionyl chloride (33.0g, 277.4mmol) and conc HCl (6 drops), and the mixture heated at 85°C for a further 90 min. The volatile components were removed from the reaction mixture under reduced pressure, and collected in a liquid N_2 trap. The collected mixture was allowed to warm to room temperature, and then the thionyl chloride was removed by careful distillation. The residual liquid was flash distilled

to give **3** as a clear fuming liquid (6.55g, 58%); ν_{max}/cm^{-1} 3002, 2951, 1810, 1400, 979, 715; $\delta_H(CDCl_3)$, 4.52 (2H, s ,H-2); $\delta_C(CDCl_3)$ 49.2 (C-2), 167.9 (C-1); *m/z* 112 (M^+, 99%).

[1-^{13}C]-Chloroacetyl chloride. Following the procedure for **3** starting from [1-^{13}C]-acetic acid (5.06g, 82.9mmol), generated the title compound (4.14g, 44%); $\delta_H(CDCl_3)$ 4.54 (2H, d, $J_{^1H-^{13}C}$ 5.7, H-2); δ_C ($CDCl_3$) 49.2 (d, $J_{^{13}C-^{13}C}$ 60.2, C-2), 167.9 (C-1).

[2-$^2H_2$]-2-Chloroacetyl chloride. Following the procedure for **3**, starting from [2-$^2H_3$]-acetic acid (5.00g, 79.3mmol) generated the title compound (5.75g, 63%); $\delta_C(CDCl_3)$ 48.7 (d, J 23.6, C-2), 168.1 (C-1); *m/z* 51 (CD_2Cl, 64%), 79 (M-Cl, 100%).

1,3-Dichloropropanone **6** [16]. A mixture of 2-(2-ethoxyethoxy)-ethanol (12ml), potassium hydroxide (2.00g, 35.6mmol) in H_2O (4ml), and Et_2O (4ml) were heated up to 70°C. As soon as the ether began to evaporate, a solution of N-methyl-N-nitroso-*p*-toluenesulfonamide (7.20g, 33.6mmol) in Et_2O (50ml) was added dropwise, followed by a further portion of Et_2O (50ml). The vapours from the reaction were collected by bubbling them through two Et_2O traps maintained at 0°C. When the reaction mixture had become colourless, the diazomethane solutions in the two traps were combined, and a solution of chloroacetyl chloride (1.44g, 12.7mmol) in Et_2O (5ml) was added, and stirred at room temperature for 60 min to give diazoketone **4**; $\delta_H(CDCl_3)$ 4.03 (2H,s,H-3), 5.88(1H,s,H-1); *m/z* 118 (M^+, 58%). To this mixture was added 1M HCl in Et_2O (25ml, 25mmol), and the reaction heated under reflux for 4h. The solution was dried ($MgSO_4$), and the volatiles removed under reduced pressure to give **6** as a crystalline solid mp = 39-40°C, (1.49g, 92%);ν_{max}/cm^{-1} 2983, 2932, 1788, 1389, 1292, 1051, 734; δ_H ($CDCl_3$) 4.34 (4H, s, H-1,3); $\delta_C(CDCl_3)$ 46.6 (C-1, 3), 195.4 (C-2); *m/z* 126 (M^+, 13%).

1,3-Dichloropropan-2-ol **7**. Sodium borohydride (0.30g, 8.0mmol) was added to a solution of **6** (2.00g, 15.8mmol) in 1:1 MeOH: CH_2Cl_2 (40ml) and the mixture was stirred at room temperature for 1h. The reaction was then washed with H_2O (20ml), and the aqueous washings extracted into CH_2Cl_2 (20ml). The organic extract was dried ($MgSO_4$), and the solvent removed under reduced pressure to give **7** as a clear colourless oil (1.59g, 78%); ν_{max}/cm^{-1} 3400, 2963, 2919, 1432, 1077, 1053, 761, 703; $\delta_H(CDCl_3)$ 2.91 (1H, d, J 6.6, OH), 3.68 (4H, d, J 5.2, H-1,3), 4.06 (1H, dp, J 6.5 and 5.3, H-2); $\delta_C(CDCl_3;)$ 46.3(C-1,3), 71.3 (C-2); *m/z* 129 ($M+H^+$, 100%).

3-Chloro-2-oxopropyl-p-toluenesulfonate **9**. Chloroacetyl chloride **3** (6.20g, 54.9mmol) was added dropwise to a solution of excess diazomethane in Et_2O (250ml) and the reaction stirred at room temperature for 10 min to generate diazoketone **4**. *p*-Toluenesulfonic acid (25.0g, 145.2mmol) was then added to the mixture, and the reaction stirred with gentle heating until the yellow colour had disappeared. The solution was washed once with H_2O (100ml), the aqueous portion back extracted once into Et_2O (100ml), and the organic

solutions combined and dried ($MgSO_4$). The volatiles were removed under reduced pressure to give the crude product as a solid. Recrystallisation from Et_2O gave **9** as a white crystalline solid mp = 75.2-75.6°C, (7.76g, 54%); ν_{max}/cm^{-1} 2941, 1753, 1597, 1364, 1191, 1173, 1011, 850, 820, 772, 671, 567, 549; $\delta_H(CDCl_3)$ 2.46 (3H, s, H-5'), 4.27 (2H, s, H-3), 4.74 (2H, s, H-1), 7.38 (2H, m, H-3'), 7.80 (2H, m, H-2'); $\delta_C(CDCl_3)$ 22.2 (C-5'), 46.6 (C-3), 71.0 (C-1), 128.6 (C-2'), 130.7 (C-3'), 132.3 (C-4'), 146.4 (C-1'), 195.6 (C-2); *m/z* 281 ($M+NH_4^+$, 100%) (Found: C, 45.5; H, 4.1. $C_{10}H_{11}ClO_4S$ requires C, 45.7; H, 4.19%).

[2-^{13}C]-3-Chloro-2-oxopropyl-p-toluenesulfonate. Following the procedure for **9** starting from [1-^{13}C]-chloroacetyl chloride (4.14g, 36.3mmol), generated the title compound (4.98g, 52%); δ_H ($CDCl_3$) 2.47 (3H, s, H-5'), 4.28 (2H, d, $^2J_{13C-1H}$ 4.5, H-3), 4.74 (2H, d, $^2J_{13C-1H}$ 4.2, H-1), 7.39 (2H, m, H-3'), 7.83 (2H, m, H-2'); $\delta_C(CDCl_3)$ 21.7 (C-5'), 46.0 (d, $^1J_{13C-13C}$ 43.8, C-3), 70.4 (d, $^1J_{13C-13C}$ 46.4, C-1), 128.1 (C-2'), 130.2 (C-3'), 131.8 (C-4'), 145.9 (C-1'), 195.1 (C-2); *m/z* 281 ($M+NH_4^+$, 100%).

[3-$^2H_2$]-3-Chloro-2-oxopropyl-p-toluenesulfonate. Following the procedure for **9** starting from [2-$^2H_2$]-chloroacetyl chloride (5.38g, 46.8mmol), generated the title compound (6.43g, 52%); $\delta_H(CDCl_3)$ 2.47 (3H, s, H-5'), 4.75 (2H, s, H-1), 7.38 (2H, m, H-3'), 7.81 (2H, m, H-2'); $\delta_C(CDCl_3)$ 21.7 (C-5'), 45.5(p, J 23.2Hz, C-3), 70.5 (C-1), 128.1 (C-2'), 130.2 (C-3'), 131.8 (C-4'), 145.9 (C-1'), 195.2 (C-2); *m/z* 282 ($M+NH_4^+$, 100%).

3-Chloro-2-hydroxypropyl-p-toluenesulfonate **10** [14]. Sodium borohydride (0.36g, 9.5mmol) was added to a solution of **9** (5.00g, 19.0mmol) in 1:1 MeOH: CH_2Cl_2 (50ml) and the reaction was stirred at room temperature for 15 min. CH_2Cl_2 (50ml) was added and the reaction was washed once with H_2O (50ml). The aqueous washing was back extracted into CH_2Cl_2 (50ml) and the combined organic extracts were dried ($MgSO_4$), and the solvent removed under reduced pressure to give **10** as a clear colourless oil (4.47g, 89%); ν_{max}/cm^{-1} 3504, 2960, 1598, 1359, 1191, 1177, 1097, 990, 832, 815, 668, 556; $\delta_H(CDCl_3)$ 2.44 (3H, s, H-5'), 2.80(1H, d, J 6.0, OH), 3.57 (2H, d, J 5.1, H-3), 4.08 (1H, m, H-2), 4.09 (2H, m, H-1), 7.36 (2H, m, H-3'), 7.79 (2H, m, H-2'); $\delta_C(CDCl_3)$ 21.68 (C-5'), 44.96 (C-3), 69.00 (C-2), 69.98 (C-1), 128.01 (C-2'), 130.06 (C-3'), 132.17 (C-4'), 145.40(C-1'); *m/z* 282 ($M+NH_4^+$, 100%).

[2-^{13}C]-3-Chloro-2-hydroxypropyl-p-toluenesulfonate. Following the procedure for **10**, starting from [2-^{13}C]-3-chloro-2-oxopropyl-p-toluenesulfonate (4.98g, 18.9mmol) generated the title compound (4.00g, 80%); $\delta_H(CDCl_3)$ 2.45 (3H, s, H-5'), 2.96(1H, m, OH), 3.59 (2H, m, H-3), 4.10 (1H, m, H-2), 4.12 (2H, m, H-1), 7.37 (2H, m, H-3'), 7.80 (2H, m, H-2'); $\delta_C(CDCl_3)$ 21.7(C-5'), 44.9 (d, $^1J_{13C-13C}$ 40.1, C-3), 69.0 C-2), 70.5 (d, $^1J_{13C-13C}$ 33.0, C-1), 128.0 (C-2'), 130.1 (C-3'), 132.2 (C-4'), 145.4 (C-1').

[2-^{2}H]-3-Chloro-2-hydroxypropyl-p-toluenesulfonate. Following the procedure for **10**, starting with **9** (2.00g, 7.6mmol) but using sodium borodeuteride (0.16g, 3.8mmol), generated the

title compound (1.86g, 92%); $\delta_H(CDCl_3)$ 2.45 (3H, s, H-5'), 3.03 (1H, s, OH), 3.58 (2H, s, H-3), 4.11 (2H, s, H-1), 7.37 (2H, m, H-3'), 7.80 (2H, m, H-2'); $\delta_C(CDCl_3)$ 22.2 (C-5'), 45.3 (C-3), 69.1 (t, J 22.5, C-2), 70.5 (C-1), 128.5 (C-2'), 130.6 (C-3'), 132.6 (C-4'), 145.9 (C-1'); *m/z* 283 ($M+NH_4^+$, 100%).

[3-$^2H_2$]-3-Chloro-2-hydroxypropyl-p-toluenesulfonate. Following the procedure for **10**, starting with [3-$^2H_2$]-3-chloro-2-oxopropyl-p-toluenesulfonate (3.09g, 11.7mmol) generated the title compound (2.81g, 90%); $\delta_H(CDCl_3)$ 2.44 (3H, s, H-5'), 3.25 (1H, d, J 5.4Hz, OH), 4.09 (2H, m, H-2), 4.10 (2H, m, H-1), 7.36 (2H, m, H-3'), 7.79 (2H, m, H-2'); δ_C ($CDCl_3$) 22.1 (C-5'), 44.3 (p, 23.2, C-3), 69.2 (C-2), 70.7 (C-1), 128.5 (C-2'), 130.6 (C-3'), 132.5 (C-4'), 145.9 (C-1'); *m/z* 284 ($M+NH_4^+$, 100%).

[3-^2H,2-^2H]-3-Chloro-2-hydroxypropyl-p-toluenesulfonate. Following the procedure for [3-$^2H_2$]-3-chloro-2-hydroxypropyl-p-toluenesulfonate employing [3-$^2H_2$]-3-chloro-2-oxopropyl-p-toluenesulfonate (3.20g, 12.1mmol) but using sodium borodeuteride (0.25g, 6.0mmol) generated the title compound (2.92g, 91%); $\delta_H(CDCl_3)$ 2.43 (3H, s, H-5'), 3.46 (1H, s, OH), 4.10 (2H, s, H-1), 7.36 (2H, m, H-3'), 7.79 (2H, m, H-2'); $\delta_C(CDCl_3)$ 21.6 (C-5'), 44.2 (p, J 22.8, C-3), 68.3 (t, J 22.1, C-2), 70.1 (C-1), 127.9 (C-2'), 130.1 (C-3'), 132.0 (C-4'), 145.4 (C-1'); *m/z* 285 ($M+NH_4^+$, 100%).

Epichlorohydrin **1**. Sodium metal (0.78g, 33.9mmol) was added to ethylene glycol (30ml), and the mixture allowed to stir at 20°C for 15h to produce a solution of sodium ethylene glycolate in ethylene glycol. A solution of **10** (4.47g, 16.9mmol) in ethylene glycol (10ml) was then added, and the mixture stirred at 20°C for 15 min. The product was removed from the mixture under reduced pressure and collected in a liquid nitrogen cold finger as a clear liquid (1.23g, 79%); ν_{max}/cm^{-1} 3004, 2963, 1433, 1399, 1267, 1090, 962, 927, 854, 761, 723; $\delta_H(CDCl_3)$ 2.69 (1H, dd, J 4.8 and 2.6Hz, H-1), 2.90 (1H, dd, J 4.8 and 3.9Hz, H-1), 3.24 (1H, m, H-2), 3.59 (2H, m, H-3); $\delta_C(CDCl_3)$ 45.0 (C-3), 46.9 (C-1), 51.2 (C-2); *m/z* 49 (CH_2Cl, 30%), 57 (M-Cl, 100%), 62 (CH_2ClCH, 23%).

[2-^{13}C]-Epichlorohydrin **1a**. As for **1**, starting from [2-^{13}C]-3-chloro-2-hydroxypropyl-p-toluenesulfonate (4.00g, 15.1mmol) generated the title compound (1.00g, 71%); $\delta_H(CDCl_3)$ 2.69 (1H, m, H-1), 2.90 (1H, m, H-1), 3.24 (1H, m, H-2), 3.68 (2H, m, H-3); $\delta_C(CDCl_3)$ 45.5 (d, $^1J_{13C-13C}$ 48.1, C-3), 47.4 (d, $^1J_{13C-13C}$ 28.6, C-1), 51.7 (C-2); *m/z* 49 (CH_2Cl, 54%), 58 (M-Cl, 100%), 63 (CH_2ClCH, 32%), 93 (M^+, 1%).

[2-^2H]-Epichlorohydrin **1b**. As for **1**, starting from [2-^2H]-3-chloro-2-hydroxypropyl-p-toluenesulfonate (1.86g, 7.0mmol) generated the title compound (0.30g, 46%); $\delta_H(CDCl_3)$ 2.69 (1H, d, J 4.8, H-1), 2.89 (1H, d, J 4.8, H-1), 3.58 (2H, m, H-3); $\delta_C(CDCl_3)$ 44.8 (C-3), 46.1 (C-1), 50.4 (t, J 27.6, C-2); *m/z* 49 (CH_2Cl, 24%), 58 (M-Cl, 100%), 63 (CH_2ClCD, 17%).

[3-$^2H_2$]-Epichlorohydrin **1c**. As for **1**, starting from [3$^2H_2$]-3-chloro-2-hydroxypropyl-p-toluenesulfonate (2.00g, 7.5mmol) generated the title compound (0.49g, 69%); $\delta_H(CDCl_3)$

2.67 (1H, dd,J 4.8 and 2.5, H-1), 2.87 (1H, dd, J 4.8 and 3.9, H-1), 3.21 (1H, m, H-2); $\delta_C(CDCl_3)$ 45.2 (p, J 23.2, C-3), 47.2 (C-1), 51.5 (C-2); *m/z* 51 (CD_2Cl, 21%), 59 (M-Cl, 100%), 64 (CD_2ClCH, 17%).

[2-^2H, 3-$^2H_2$]-Epichlorohydrin **1 d**. As for **1**, starting from [3-$^2H_2$, 2-^2H]-3-chloro-2-hydroxypropyl-p-toluenesulfonate. (2.00g, 7.5mmol) generated the title compound (0.40g, 55%); $\delta_H(CDCl_3)$ 2.68 (1H, d, J 4.8, H-1), 2.87 (1H, d, J 4.8, H-1); $\delta_C(CDCl_3)$ 44.3 (p, J 23.4, C-3), 46.1 (C-1), 50.3 (t, J 27.6Hz, C-2); *m/z* 51 (CD_2Cl, 25%), 60 (M-Cl, 100%), 65 (CD_2ClCD, 22%).

1-Bromo-3-chloro-propanone **8** [16] from bromoacetyl chloride. Bromoacetyl chloride (6.64g, 42.2mmol), - which was prepared from bromoacetic acid in an analogous manner to **3** for labelled preparations - was added dropwise to a solution of excess diazomethane in Et_2O (150ml) and the reaction stirred at room temperature for 10 min to generate diazoketone **12**. A solution of HCl in Et_2O (50ml, 50mmol) was added and the reaction heated under reflux until the yellow colour had disappeared. The solution was washed once with H_2O (100ml), the aqueous portion extracted into Et_2O (100ml), and the two organic solutions combined and dried ($MgSO_4$). The volatiles were removed under reduced pressure to give **8** as a pale brown liquid (6.41g, 89%); This material was used directly for the next stage.ν_{max}/cm^{-1} 2937, 2850, 1735, 1396, 1182, 1115, 1078, 1046; $\delta_H(CDCl_3)$ 4.11 (2H, s, H-3), 4.35 (2H, s, H-1); $\delta_C(CDCl_3)$ 31.15 (C-3), 45.83 (C-1), 194.54 (C-2); *m/z* 188 ($M+NH_4^+$, 23%).

1-Bromo-3-chloropropan-2-ol **13**. Sodium borohydride (0.58g, 15.3mmol) was added to a solution of **8** (5.26g, 30.7mmol) in 1:1 MeOH:CH_2Cl_2 (50ml) and the mixture was stirred at room temperature for 15 min. The reaction was diluted with CH_2Cl_2 (50ml), washed with H_2O (50ml), and the aqueous portion extracted into CH_2Cl_2 (50ml). The organic extracts were combined, dried ($MgSO_4$), and the solvent removed under reduced pressure to give **13** as a clear pale brown oil (3.87g, 73%);ν_{max}/cm^{-1} 3386, 2961, 1428, 1191, 1176; $\delta_H(CDCl_3)$ 2.89 (1H, d, J 6.6 ,OH), 3.58 (2H, d, J 5.5 ,H-3), 3.71 (2H, d, J 5.6 ,H-1), 4.06 (1H, m, H-2); $\delta_C(CDCl_3)$ 34.80 (C-3), 46.51 (C-1), 70.47 (C-2); *m/z* 79 (M-$BrCH_2$, 29%), 93 (M-Br, 30%), 123 (M-$ClCH_2$, 31%), 137 (M-Cl, 12%), 155 (M-OH, 100%), 173 ($M+H^+$, 36%).

Epichlorohydrin **1** from **13**. The procedure was identical to that described above for **1** using sodium metal (1.0g, 43.5mmol), ethylene glycol (40ml) and **13** (3.87g, 22.6mmol) to afford epichlorohydrin as a clear liquid (1.2g, 58%). Spectroscopic data were identical with **1** as outlined above.

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