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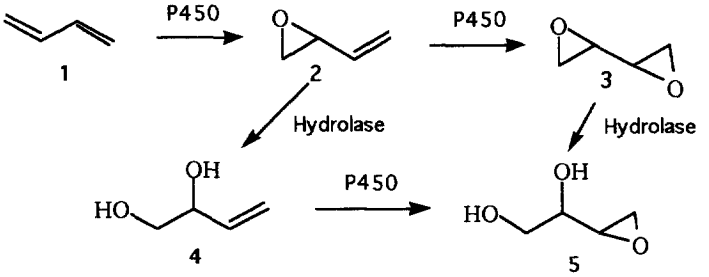
Synthetic Route to Optically-Pure Metabolites of Butadiene, and their Chiral GC Separation.

David J. Claffey and James A. Ruth*

School of Pharmacy, University of Colorado Health Sciences Center, Campus Box C-238, 4200 East Ninth Ave., Denver, Colorado 80262, USA.

Abstract: The four possible stereoisomers of 3,4-epoxybutane-1,2-diol were stereospecifically synthesized in excellent yields, and fully characterized, as part of a study on the stereochemical aspects of butadiene metabolism and toxicity. GC methodology was developed whereby baseline separation of the enantiomeric pairs was achieved. Copyright © 1996 Elsevier Science Ltd

3,4-Epoxybutane-1,2-diol is a metabolite of butadiene **1**, a monomer in the synthetic rubber industry. Several epidemiologic studies[1] have suggested an excess mortality for lymphatic and hematopoetic neoplasms in the 65,000 workers that are potentially exposed to butadiene in the United States[2]. Recent studies have demonstrated a stereoselective course for the metabolic activation of butadiene to R- and S- vinyloxirane **2**[3]. These epoxides can be hydrolyzed to 3,4-butene-1,2-diol **4**[4] and epoxidized (cytochrome P450) to 3,4-epoxybutane-1,2-diol **5**[5], or alternatively, they can be epoxidized to the bis-epoxide[6] **3** and hydrolyzed to **5**.

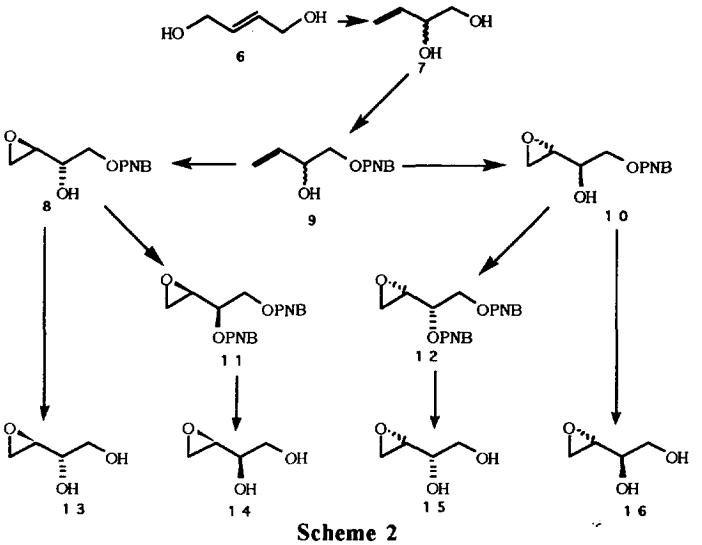


Scheme 1

Since observed dramatic species differences in sensitivity to butadiene toxicity[7] may involve differences in the stereochemical course of its metabolism, the elucidation of the stereochemical fate of butadiene is essential. Central to this work is the need for pure samples of (2R,3S), (2S,3R), (2R,3R), and (2S,3S)- 3,4-epoxybutane-1,2-diol, for use both as analytical standards and as substrates for toxicological and metabolic studies. No record in the literature of the synthesis of the full complement of these compounds could be found.

(2R,3S)-(-)- and (2S,3R)-(+)-1-tosyloxy-3,4-epoxybutan-2-ol were recently reported as co-products in the synthesis of enantiomerically pure 3-butene-1,2-diol derivatives[8]. Efforts in this laboratory to hydrolyze the tosyl ester invariably led to partial racemization of the resulting epoxydiol. This sensitivity substantially limits the synthetic usefulness of these derivatives. Furthermore, the procedure[8] did not provide one of the two required enantiomeric pairs of epoxydiols. Attempts to prepare **14** and **15** by treatment of the enantiomerically-pure olefinic starting materials of the Sharpless resolution with MCPBA resulted in low yields of diastereomeric mixtures, with the allylic hydroxyl failing to direct the epoxidation[9]. We decided that

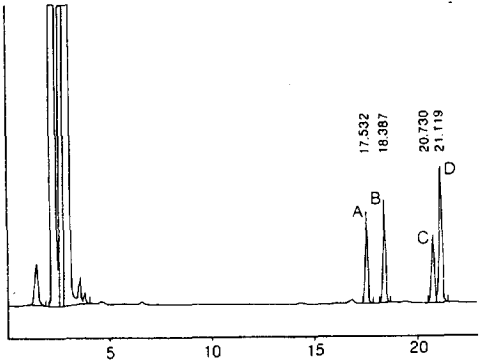
Mitsunobu chemistry[10] would provide access to all of the required stereoisomers. The *p*-nitrobenzoyl ester was envisioned as being a compatible protecting group for the Mitsunobu reaction and one that may be easily removed without loss of stereochemical integrity[11].



Scheme 2

3-Butene-1,2-diol **7** was produced in 60% yield by isomerization of *cis*-2-butene-1,4-diol **6** ($HgSO_4$, H_2SO_4, H_2O, Δ, 1.5h)[12]. Regioselective mono-esterification of **6** (1.05mol equiv. *p*-nitrobenzoyl chloride/ pyridine/ dichloromethane) gave the racemic **9** in 88% yield. Sharpless epoxidation[13] of **9** with D-diisopropyltartrate gave epoxide **8** in 91% theoretical yield with greater than 99% ee (and de)[14]. Transesterification of **8** with catalytic (0.5%) sodium ethoxide in ethanol gave the diol **13** in almost quantitative yields[15]. Epoxidation with L-diisopropyltartrate similarly produced **10** in 94% theoretical yield (>99% ee). Subsequent deprotection gave **16** in 95% yield and >99% ee (and de)[16].

Mitsunobu chemistry[10] provided an excellent route to **14** and **15**. The diester **11** was thus obtained[17] in 88% yield and in >99% ee from **8**. Epoxydiester **12** was produced in equally high yield and ee from **10**. Transesterifiaction of both enantiomers with sodium ethoxide gave **15**[18] and **14**[19] in almost quantitative yields and >99% ee (and de). The stereochemistry was established based on the rules of Sharpless[20] and by comparison of the residual 3-butene-1,2-diols from the kinetic resolution with authentic samples (Acros Chemical Co.) as described below.



A: **16** B: **13** C: **15** D: **14**

Figure 1

A routine methodology was needed for the analysis of the diastereomeric and enantiomeric composition of these compounds. NMR analysis of the Mosher ester derivatives[21] of the enantiomers proved unreliable and cumbersome. Chiral GC analysis proved to be a much more efficient method. Baseline separation of the diacetylated enantiomers was achieved (Figure 1) using a β-cyclodextrin (Supelco β-Dex 120) column (length, 60m; ID, 0.2mm; film 0.2μm) at 125°C, 30psi.

The four epoxydiols are currently being assessed for their relative toxicities. It is clear that the methodology described here is an extremely efficient, high yielding stereoselective route to these compounds. The compounds may have much wider importance, and could be used as chiral building blocks for the synthesis of numerous natural products[22].

Acknowledgment
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14. Diisopropyl-D-tartrate (0.518g, 1.82mmol) was added to a stirred mixture of dichloromethane (25ml) and 4Å molecular sieves (2g) at -5°C. Titanium (IV) isopropoxide (0.37g, 1.52mmol) was then added, followed by 5.5M *tert*-butyl hydroperoxide in decane (1.37ml, 6.83mmol), and the mixture was allowed to stir at -5°C. After four hours, the mixture was cooled to -15°C, and **9** (3.60g, 15.18mmol) in dichloromethane (30ml) was added dropwise with stirring over 90 minutes. After stirring at -15° C for 36 hours TLC (1:1 ethyl acetate-hexanes) showed the reaction to have gone to completion. The mixture was passed through a small plug of celite. Evaporation of the solvent under reduced pressure gave a yellow syrup, which was flash chromatographed on SiO_2 (100g), and 1:1 ethyl acetate-hexanes as eluant. The unreacted **9** emerged first, followed by the desired epoxide as a clear syrup which crystallized on standing. Recrystallization from dichloromethane-hexanes gave (2R, 3S)-1-*O*-(*p*-nitrobenzoyl)-3,4-epoxybutan-2-ol **10** as small white needles (1.75g, 91% yield) mp 78-79°C; $[\alpha]_D^{25}$ -0.78° (*c* 1, methanol); ^1H NMR (300 MHz, $CDCl_3$) δ 2.63 (d, J=3.17Hz, 1H), 2.77-2.85 (m, 2H), 3.13 (dt, J= 2.69, 3.90Hz, 1H), 4.11-4.15 (m, 1H), 4.44 (dd, J= 11.72, 5.86Hz, 1H), 4.54 (dd, J=11.72, 3.66Hz, 1H), 8.15-8.26 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.8, 51.6, 66.4 , 67.8, 123.5, 130.7, 134.9, 150.5, 164.6; MS *m/e* calc'd for $C_{11}H_{11}O_6N$ $(M+H)^+$: 253.0586, found 253.0559.

15. A sodium ethoxide solution (NaH (1.0mg, 0.042mmol) in ethanol (5ml)) was added dropwise to **10** (253mg, 1.0mmol) in ethanol (dried, distilled) (5ml), at -5°C. The mixture was allowed to reach room temperature. After 10 minutes TLC (1:1 ethyl acetate-hexanes) indicated that the reaction had gone to completion. The mixture was then allowed to stir for 10 minutes with amberlite H^+ ion-exchange resin (3g). The solution was decanted and the resin washed with 3x5ml volumes of ethanol. The combined alcoholic solutions were evaporated under reduced pressure to give a white syrup-solid. This was chromatographed on SiO_2 (20g) with ethyl acetate-acetone (2:1) as eluant. A fraction containing pure (2R,3S)-3-epoxybutane-1,2-diol **16** was obtained (97.0mg, 93% yield); $[\alpha]_D^{25}$ -2.54° (*c* 1, methanol); ^1H NMR (300 MHz, acetone-d6) δ 2.64-2.66 (2H, m), 2.90-2.97 (1H, m), 3.44-3.50 (1H, m), 3.53-3.66 (2H, m), 3.74 (1H, t), 3.95 (1H, d, J=4.6Hz); ^{13}C NMR (75 MHz, acetone d-6) δ 44.6, 52.6, 64.6, 72.2; MS *m/e* calc'd for $C_4H_8O_3$ $(M+H)^+$: 105.0551, found 105.0558.
16. Deacylation was carried out as described in reference 15, (2S,3R)-3-epoxybutane-1,2-diol **16** was obtained as a clear liquid $[\alpha]_D^{25}$ 2.49° (*c* 1, methanol); ^1H NMR (300 MHz, acetone-d6) δ 2.64-2.66 (2H, m), 2.90-2.97 (1H, m), 3.44-3.51 (1H, m), 3.53-3.67 (2H, m), 3.72 (1H, t), 3.94 (1H, d); ^{13}C NMR (75 MHz, acetone d-6) δ 44.5, 52.6, 64.6, 72.3; MS *m/e* calc'd for $C_4H_8O_3$ $(M+H)^+$: 105.0551, found 105.0571.
17. Diethyl azodicarboxylate (147mg, 0.134ml, 0.83mmol) was added dropwise over 45 minutes at -5°C to a stirred mixture of triphenylphosphine (217mg, 0.83mmol) and *p*-nitrobenzoic acid (138mg, 0.83mmol), and **10** (0.1760g, 0.69mmol) in toluene (12ml). The mixture was warmed to room-temperature and was allowed to stir for one hour, at which point TLC (2:1 hexanes-ethyl acetate) showed the reaction to be complete. The solvent was removed under reduced pressure giving a yellow syrup which was purified by flash chromatography on silica (50g), and 2:1 hexanes-ethyl acetate as eluant. A clear syrup was obtained which crystalized on standing to a white solid. Recrystalization from ethyl acetate-hexanes gave (2S,3S)-1,2-di-*O*-(*p*-nitro-benzoyl)-3-epoxybutane **12** as a white solid (244mg, 88% yield); mp 113-114°C; $[\alpha]_D^{25}$ +1.22° (*c* 1, chloroform); ^1H NMR (300 MHz, $CDCl_3$) δ 2.80 (m, 1H), 2.94 (m, 1H), 3.38-3.42 (m, 1H), 4.64 (dd, J=6.59, 11.96Hz, 1H), 4.79 (dd, J=3.91, 11.96Hz, 1H), 5.39-5.44 (m, 1H), 8.13-8.30 (m, 8H); ^{13}C (75 MHz, $CDCl_3$) δ 44.2, 50.4 , 64.0, 72.6, 123.6, 130.7, 130.9, 134.5, 134.5, 150.7, 150.7, 163.7, 164.1; MS *m/e* calc'd for $C_{18}H_{14}O_9N_2$ $(M+H)^+$: 402.0699, found 402.0697.
18. Deacylation was carried out as described reference 15. (2S,3S)-3,4-epoxy-butane-1,2-diol **15** was obtained as a clear liquid (99.1mg, 95% yield); $[\alpha]_D^{25}$ +1.29° (*c* 1, methanol); ^1H NMR (300 MHz, acetone-d6) δ 2.64 (m, 2H), 2.90-2.97 (m, 1H), 3.44-3.51 (m, 1H), 3.53-3.67 (m, 2H), 3.72 (t, 1H), 3.93 (d, J=4.39Hz, 1H); ^{13}C NMR (75 MHz, acetone-d6) δ 44.0, 53.8, 64.6, 73.3; MS *m/e* calc'd for $C_4H_8O_3$ $(M+H)^+$: 105.0551, found 105.0562.
19. Deacylation was carried out as described in reference 15. (2R,3R)-3,4-epoxy-butane-1,2-diol **14** was obtained as a clear liquid (98.5mg, 95% yield); $[\alpha]_D^{25}$ -1.32° (*c* 1, methanol); ^1H NMR (300 MHz, acetone d-6) δ 2.57-2.65 (m, 2H), 2.90-2.93 (m, 1H), 3.43-3.51 (m, 1H), 3.54 (m, 2H), 3.75 (t, 1H), 3.93 (d, J=4.39Hz, 1H); ^{13}C NMR (75 MHz, acetone-d6) δ 44.0, 53.8, 64.6, 73.4; MS *m/e* calc'd for $C_4H_8O_3$ $(M+H)^+$: 105.0551, found 105.0590.

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