SYNTHESIS OF THE ENANTIOMERS OF ERYTHRO-2-OXIRANYL-1,4-BENZODIOXAN[1]

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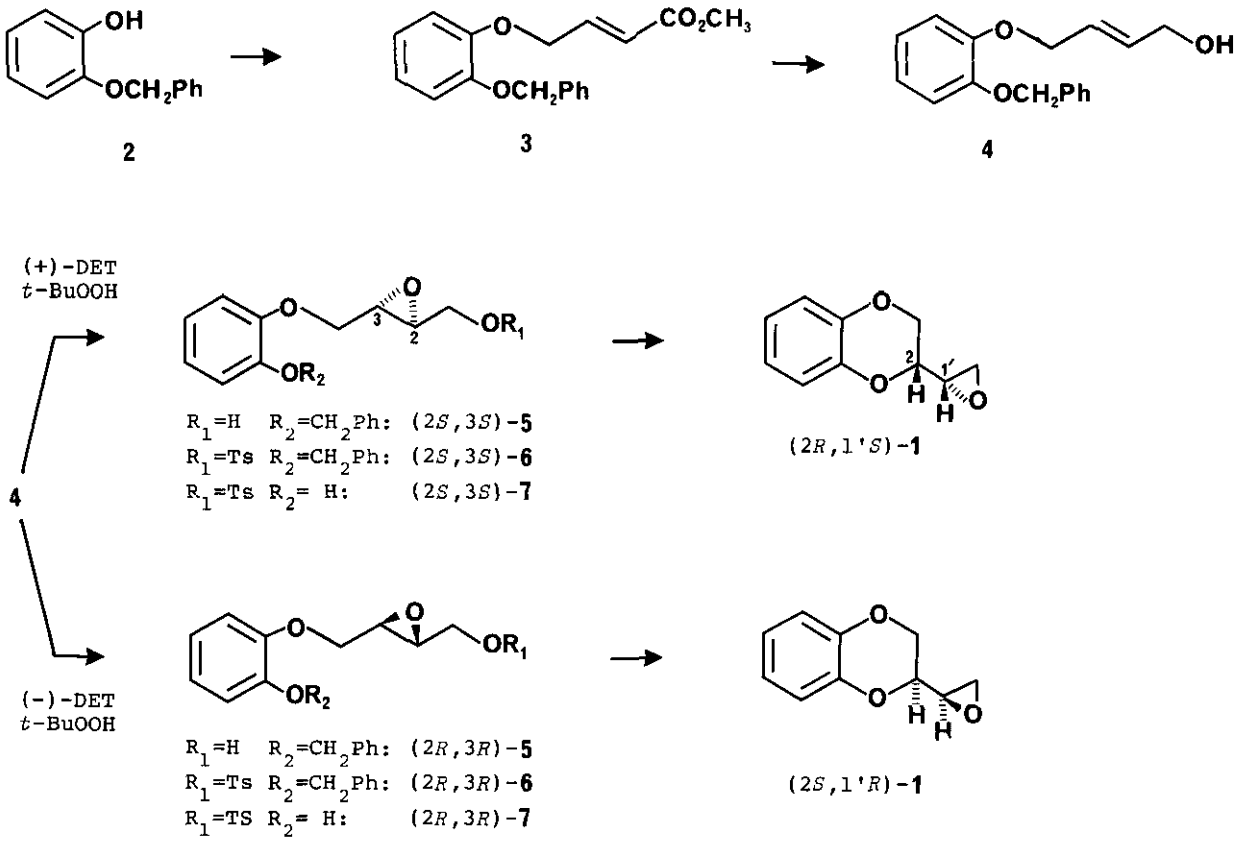
Abstract - (2R, 1'S) and (2S, 1'R)-2-Oxiranyl-1-4-benzodioxan (2R, 1'S-1 and 2S, 1'R-1) were prepared in six steps from 2-benzyloxyphenol. The key step in each synthesis was the enantioselective Sharpless epoxidation of allylic alcohol 4.

A number of cardiovascular agents, including beta-antagonists[2] and centrally active antihypertensives[3,4], can be derived from erythro-2-oxiranyl-1,4-benzodioxan (1). A direct synthesis of this racemic intermediate by condensation of catechol with trans-bis-chloromethyloxirane has been described.[5] Our need to prepare the enantiomers of several antihypertensive agents required that we have available both enantiomeric forms of this key intermediate. Reported herein are asymmetric syntheses of (2R,1'S) and (2S.1'R)-1 in which enantioselectivity is derived from the Sharpless asymmetric epoxidation.[6]

Alkylation of 2-benzyloxyphenol (2) with methyl trans-4-bromocrotonate in 2-butanone in the presence of potassium carbonate afforded ester 3 in 78% yield (Scheme I). Although treatment of 3 with lithium aluminum hydride gave a mixture of products, use of diisobutylaluminum hydride in ether at -20°C gave allylic alcohol 4 in 83% yield. Asymmetric epoxidation of 4 using the Sharpless procedure[6] was then carried out. Thus, reaction of 4 with 1.0 equivalent of (+)-diethyl tartrate and 1.0 equivalent of titanium tetraisopropoxide and excess tert-butylhydroperoxide at -20°C afforded an 86% yield of (2S,3S)-epoxide 5. Under identical conditions, using (-)-diethyl

tartrate, an 86% yield of (2R,3R)-5 was obtained. The optical purities of 5 were determined by the Mosher method[7] (^{1}H-NMR analysis of the derived 2-methoxy-2-trifluoromethylphenyl acetates). An enantiomeric excess (ee) of >92% was found for (2S,3S)-5 while an ee of >96% was found for (2R,3R)-5. The absolute configurations of these enantiomers were initially assigned on the basis of the empirical Sharpless model[6]. Confirmation of these assignments was made by degradation of the derived epoxide 1 to a material of known absolute configuration (vida infra).

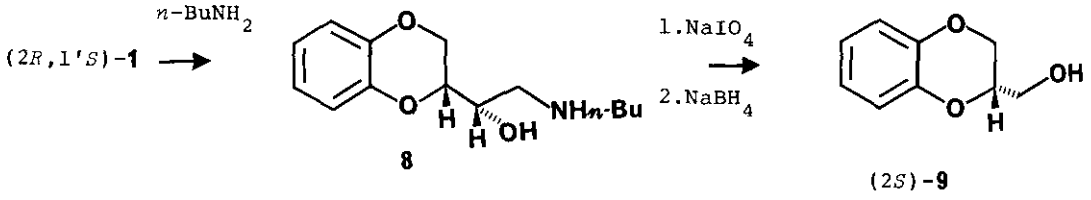
Scheme I.



The epoxy alcohols 5 were converted to tosylates 6 which were debenzylated to the phenols 7. Base promoted cyclization then provided the erythro-epoxides (2R,1'S)-1 and (2S,1'R)-1 in overall yields of 77% and 73%, respectively for the three steps. The enantiomeric purities of the epoxides were determined using $Eu(hfc)_3$ chiral ^1H-NMR shift reagent at 300 MHz (experimental section). The (2R,1'S)-1 was found to contain approximately 4% of the 2S,1'R enantiomer (92% ee) while (2S,1'R)-1 was enantiomerically pure within the limits of detectability (>96% ee). Thus, the enantiomeric purities were the same as those of the epoxy alcohol precursors 5.

Assignment of the absolute configuration of the benzodioxan C-2 of (2R,1'S)-1 was made by degradation to 2-hydroxymethyl-1,4-benzodioxan (9) (Scheme II). The material thus obtained ($[\alpha]_D$ = -33°; mp 74-74.5°C) can be assigned as (2S)-9 since Nelson (8) has reported data for its enantiomer; (2R)-9, $[\alpha]_D$ = +34°; mp 71-73°C). The absolute configuration of the oxirane C-1' follows from the erythro configuration.

Scheme II.



EXPERIMENTAL

Proton magnetic resonance spectra were recorded with a Bruker WM 300 instrument and are reported in ppm δ downfield from an internal standard of TMS. Silica gel chromatography was performed using 70-230 mesh (Merck) silica gel. Medium pressure (flash) chromatography was performed using 230-400 mesh Merck Kieselgel. Melting points are uncorrected. Analyses indicated by

elemental symbols were within ± 0.4% of the theoretical values and were done by Syntex Analytical Department.

Methyl trans-4-(2-benzyloxyphenoxy)-2-butenoate 3

A mixture of 2-benzyloxyphenol (20 g, 0.1 mol), methyl 4-bromocrotonate (21.4 g, 0.12 mol), and potassium carbonate (27.6 g, 0.2 mol) in 180 mL of 2-butanone was stirred mechanically at reflux temperature for 16 h. The mixture was filtered, diluted with ether, washed with water and brine, dried (Na_2SO_4) and evaporated. Medium pressure chromatography (25% ether-hexane) afforded 23.3 g (78.2%) of 3, mp 44-45°C; ^1H NMR ($CDCl_3$) δ 3.73 (3H, s, OCH_3), 4.74 (2H, dd, J = 2,3 Hz, H-4), 5.12 (2H, s, OCH_2 Ph), 6.24 (1H, dt, J = 16, 2 Hz, H-2), 6.87 (4H, m, aromatics), 7.08 (1H, td, J = 16, 3 Hz, H-3), 7.26-7.46 (5H, m, benzyl aromatics). Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.23; H, 6.20.

4-(2-Benzyloxyphenoxy)-2-buten-1-ol 4

A solution of ester 3 (22 g, 0.073 mol) in ether (500 ml) was cooled to -20°C and diisobutylaluminum hydride (107 mL of 1.4 M in hexane, 0.15 mol) was added slowly. Methanol (10 mL) was added and the resulting solution was diluted with water, washed with 5% HCl and brine, and dried (Na_2SO_4). Evaporation followed by medium pressure chromatography of the crude product (50% ether-hexane) gave 16.6 g (83.4%) of 4, mp 38-39°C; ^1H NMR ($CDCl_3$) δ 2.00 (1H, s, OH), 4.12 (2H, m, H-1a,1b), 4.58 (2H, m, H-4a,4b), 5.12 (2H, s, OCH_2Ph), 5.95 (2H, m, H-2,3), 6.86 (4H, m, aromatics), 7.26-7.46 (5 H, m, benzyl aromatics). Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.80; H, 6.73.

(2S,3S)-4-(2-Benzyloxyphenoxy)-2,3-epoxybutan-1-ol (2S,3S)-5

The Sharpless procedure[6] was used: Dry dichloromethane (200 mL) was cooled to -20°C with a dry ice-CCl_4 bath and titanium tetraisopropoxide (5.94 mL, 0.02 mol) and (+)-diethyl tartrate (3.47 mL, 0.02 mol) were added sequentially. The mixture was stirred for 5 min and a solution of alcohol 4 (5.5 g, 0.024 mol) in dichloromethane (5 mL) was added. A solution of tert-butyl hydroperoxide in dichloromethane, prepared as described[6] (35 mL,

1.3 M), was added and the resulting solution was stored overnight in a freezer at -20°C. The mixture was returned to a -20°C bath and an aqueous solution of 10% tartaric acid (50 mL) was added. After 0.5 h the layers were separated and the organic phase was washed with water and evaporated. The residue was dissolved in ether (200 mL), cooled to 5°C, and 1M NaOH (60 mL) was added. The mixture was stirred at 5°C for 30 min and the ether layer was separated, washed with brine, dried (Na_2SO_4), and evaporated. Chromatography on silica gel (75% ether-hexane) gave 4.8 g (85.7%) of (2S,3S)-5, mp 42-43°C; $[\alpha]_D^{25}$ = -15.8° (c = 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.24 (1H, s, OH), 3.18 (1H, m, H-2), 3.38 (1H, m, H-3), 3.62 (1H, dd, J = 12, 5 Hz, H-1a), 3.88 (1H, dd, J = 12, 3 Hz, H-1b), 4.08 (1H, dd, J = 11.5, 5.3 Hz, H-4a), 4.27 (1H, dd, J = 11.5, 3.3 Hz, H-4b), 5.11 (2H, s, OCH_2Ph), 6.90 (4H, m, aromatics), 7.26-7.46 (5H, m, benzyl aromatics). Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.24; H, 6.59.

(2R,3R)-4-(2-Benzyloxy)-2,3-epoxybutan-1-ol (2R,3R)-5

Substitution of (-)-diethyl tartrate in the above procedure gave (2R,3R)-5 in 85.7% yield, mp 42-43°C; $[\alpha]_D^{25}$ = +16.4° (c = 1.1, $CHCl_3$). Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.14; H, 6.22.

Determination of the enantiomeric purities of (2R,3R)-5 and (2S,3S)-5

The 5 enantiomers were converted to MTPA esters with (-)-2-methoxy-2-trifluoromethylphenylacetyl chloride[7] in dichloromethane with dimethylaminopyridine catalysis. ^1H NMR analysis indicated that the downfield double doublet for the H-1a proton of the two esters occurred at different chemical shifts. The ester from (-)-5 had δ 4.68 (J = 12.3, 3 Hz) and the ester from (+)-5 had δ 4.60 (J = 12.2, 2.9 Hz) for this proton. In the spectrum of the (2R,3R)-5 ester, none of the double doublet corresponding to the (2S,3S)-5 ester was detected (>96% ee). In the spectrum of the (2S,3S)-5 ester, ~4% of the (2R,3R)-5 ester was detected (92% ee).

(2S,3S)-4-(2-Benzyloxyphenoxy)-2,3-epoxy-1-(p-toluenesulfonyloxy)-butane (2S,3S)-6

p-Toluenesulfonyl chloride (4.3 g, 0.023 mol) was added to a 5°C solution of

(2S,3S)-5 in pyridine (50 mL) and the solution was refrigerated for 16 h (~5°C). The mixture was added to water (300 mL) and filtered to afford 5.8 g (88%) of crude 2S,3S-6 which was of >95% purity by tlc analysis. An analytical sample was obtained by crystallization from cold ether, mp 84-85°C; $[\alpha]_D^{25}$ = -23.9° (c = 0.2, $CHCl_3$). Anal. Calcd for $C_{24}H_{24}SO_6$: C, 65.44; H, 5.49. Found: C, 65.54; H, 5.63.

(2R,3R)-4-(2-Benzyloxyphenoxy)-2,3-epoxy-1-(p-toluene-sulfonyloxy)-butane (2R,3R)-6

This compound was obtained in the same manner (~100% yield), mp 84-85°C; $[\alpha]_D^{25}$ = +23.3° (c = 0.6, $CHCl_3$). Anal. Calcd for $C_{24}H_{24}SO_6$: C, 65.44; H, 5.49. Found: C, 65.55; H, 5.53.

(2R,1'S)-2-Oxiranyl-1,4-benzodioxan (2R,1'S)-1

A solution of (2S,3S)-6 (1.82 g, 0.004 mol) and 10% Pd-C (0.45 g) in methanol (50 mL) was hydrogenated at 50 psi for 6 h. The mixture was filtered and 10% aqueous potassium hydroxide (2.7 mL) was added to the filtrate. The resulting solution was stirred at room temperature for 30 min and then added to water. Ether extraction afforded an oil which was purified by silica gel chromatography (20% ether-hexane) to give 0.67 g (88%) of (2R,1'S)-1, mp 63-64°C (lit mp for racemic 1:51-52°C[5]; $[\alpha]_D^{25}$ = -46.3° (c = 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.82 (1H, dd, J = 5, 2.6 Hz, H-2'a), 2.92 (1H, dd, J = 5, 3.8 Hz, H-2'b), 3.16 (1H, ddd, J = 6, 3.8, 2.6 Hz, H-1'), 3.96 (1H, ddd, J = 6, 6, 2.4 Hz, H-2), 4.15 (1H, dd, J = 11,6 Hz, H-3a), 4.36 (1H, dd, J = 11, 2.4 Hz, H-3b), 6.86 (4H, m, aromatics). Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.51; H, 5.64.

(2S,1'R)-2-Oxiranyl-1,4-benzodioxan (2S,1'R)-1

This compound was prepared in 73% yield from (2R,3R)-6, mp 62-64°C; $[\alpha]_D^{25}$ = +48.1° (c = 1.1, $CHCl_3$). Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.32; H, 5.58.

Determination of the enantiomeric purities of (2R,1'S)-1 and (2S,1'R)-1

The enantiomers were analyzed by ^1H NMR in $CDCl_3$ using $Eu(hfc)_3$ shift

reagent at 300 MHz. The best separation of signals occurred on the epoxide $-OCH_2$ where a difference of 40 Hz was observed between the two enantiomers at a molar ratio of epoxide to $Eu(hfc)_3$ of 1.5:1. Under these conditions, a broad singlet was observed for the $-OCH_2$ of the (+)-1 at δ 3.18 whereas two broad singlets were observed for the $-OCH_2$ of (-)-1 at δ 3.30 and δ 3.40. Control experiments with racemic 1 showed a 50:50 ratio between these signals. The areas under the $-OCH_2$ peaks were analyzed at the same molar ratios of epoxide to $Eu(hfc)_3$ and (-)-(2R,1'S)-1 was found to contain ~4% of the other enantiomer (92% ee). The (+)-(2S,1'R)-1 was found to be pure within the ~2% detection limits.

Degradation of (-)-1 to (2S)-2-Hydroxymethyl-1,4-benzodioxan (2S)-9

A mixture of (-)-1 (0.25 g) and n-butylamine (5 mL) was stirred at reflux temperature for 2 h. The solvent was evaporated to afford the crystalline amino alcohol 8. A solution of this material (0.32 g, 0.0012 mol) in ethanol (5 mL) and water (2 mL) was treated with a solution of sodium periodate (0.32 g, 0.0015 mol) in water (3 mL). After 10 min the mixture was filtered and sodium borohydride (0.25 g) was added to the filtrate. After an additional 10 min the mixture was diluted with water and extracted with dichloromethane. The dichloromethane was evaporated and the residue was purified by chromatography on silica gel (40% ether-hexane) to give 0.13 g of (2S)-9 mp 74-74.5°C; $[\alpha]_D^{25}$ = -33.0° (c = 0.7, ethanol). Reported for the (2R) isomer (8): mp 71-73°C; $[\alpha]_D$ = 34.0 (c = 0.1, ethanol).

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