Enantiospecific Synthesis and Gas Chromatographic Resolution of (R)-(-)- and (S)-(+)-1,2-Dibromo-3-chloropropane

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Introduction

The haloalkane nematocide 1,2-dibromo-3-chloropropane (DBCP) is a persistent environmental pollutant that was used extensively as a soil fumigant in California's San Joaquin Valley and the Southern Atlantic Coast states. In 1979 the use of DBCP was restricted by regulatory agencies.[1] It is a carcinogen and a mutagen and displays target-organ toxicity to the testes and the kidneys.[2] Two distinct metabolic pathways have been shown in the bioactivation of DBCP to reactive genotoxic and cytotoxic intermediates: An oxidative pathway[3] involving cytochrome P-450 is responsible for the activation of DBCP to mutagenic metabolites, and contributes to DNA damage in isolated hepatocytes while a glutathione *S*-transferase-dependent pathway[4] and the sequential formation of reactive episulfonium ion intermediates from glutathione conjugates of DBCP appear to account for DBCP-induced DNA damage in extrahepatic target organs and contribute to DBCP-induced DNA damage observed in isolated hepatocytes.

Because little is known about effects of stereochemistry on the metabolism and toxicity of halogenated alkyl compounds and DBCP may show enantioselectivity in its metabolism and/or toxicities, it was necessary to prepare the enantiomers of DBCP for comparative studies of mutagenicity and cytotoxicity. In the present study, we report the enantiospecific synthesis of (*R*)-(-)- and (*S*)-(+)-DBCP starting from the commercially available (*R*)-(-)- and (*S*)-(+)-epichlorohydrin (1) as well as an analytical chiral gas chromatographic procedure that was developed to resolve the DBCP enantiomers.

Results and Discussion

In our retrosynthetic analysis, (*R*)-DBCP can be obtained via an S_N2-type reaction with inversion of configuration from (*S*)-1-bromo-3-chloro-2-propanol (2) which can be prepared from (*S*)-(+)-1 by regioselective opening of the epoxide with an appropriate brominating agent. Similarly, (*S*)-DBCP can be prepared from (*R*)-(-)-1 via the key intermediate (*R*)-2. To carry on this analysis, a synthetic procedure was first developed to prepare racemic DBCP from racemic epichlorohydrin. After optimizing conditions and yields, the procedure was then utilized to prepare the enantiomers of DBCP from optically pure (*R*)-(-)-1 and (*S*)-(+)-1 as shown in Scheme I.

Starting with (*R*)-(-)-1 or (*S*)-(+)-1, the regioselective opening of the epoxide from the less hindered side was accomplished by utilizing Li_2NiBr_4 as a nonaqueous source of "soft" nucleophilic bromide according to the procedure of Dawe et al.[5] to yield (*R*)-(+)-2 or (*S*)-(-)-2, the key intermediates in this synthesis, in 95% yield. Attempts to convert the bromochlorohydrin intermediate 2 directly into DBCP by utilizing NBS/triphenylphosphine[6] or 1,2-bis(diphenylphosphino)ethane/Br_2,[7] which are commonly used procedures for the conversion of alcohols into bromides, were very low yielding and resulted in a mixture of mainly three products which were characterized by GC-MS as DBCP, 1,3-dibromo-2-propanol, and 1,3-dibromopropan-2-one. An alternative approach was then carried out in which the secondary alcohol in the key intermediate 2 was first converted into a better leaving group followed by reaction with LiBr. The mesylate of racemic 2 was first prepared. However, the low yield and harsh conditions of the LiBr reaction (LiBr/acetonitrile, 100 °C reflux; 40% yield by GC) prompted us to prepare the triflate which afforded a better leaving group.

Reacting (*R*)-(+)-2 or (*S*)-(-)-2 with triflic anhydride and pyridine yielded the triflates (*R*)-(-)-3 or (*S*)-(+)-3 in 97% yield as shown in Scheme I. The triflate (*R*)-(-)-3 was then converted to (*S*)-(+)-DBCP with LiBr/acetonitrile in 90% yield of vacuum-distilled product. Similarly, the triflate (*S*)-(+)-3 was converted to (*R*)-(-)-DBCP (Scheme I). The overall yield of DBCP enantiomers from this synthetic procedure was 83%. **CAUTION**: Compounds 1, 2, 3, and DBCP are highly toxic substances and should be handled with utmost care.

Following the preparation of DBCP enantiomers, it was necessary to determine the optical purity of these products. Since no analytical method for resolving the commercially available racemic DBCP has been reported and the use of chiral NMR shift reagents in resolving related racemic haloalkanes has been unsuccessful,[8] a chiral GC procedure was developed to resolve DBCP enantiomers utilizing a (trifluoroacetyl)-β-cyclodextrin capillary column as shown in Figure 1. This procedure was then utilized to determine percent ee of (*R*)-(-)-DBCP and (*S*)-(+)-DBCP which were 97% and 94.4%, respectively.

Experimental Section

General. Gas chromatography was performed on a fused silica capillary column (30-m × 0.32-mm i.d.) coated with DB-5 (J and W Scientific, Folsom, CA). Helium was used as a carrier gas (head pressure 10 psi), and the injector and the flame ionization detector blocks were maintained at 250 °C except for the analysis of the triflate 3 which required maintaining the injector block at 90 °C. The oven was held at 100 °C isothermal following splitless injection. ^1H- and ^{13}C-NMR spectra were obtained in

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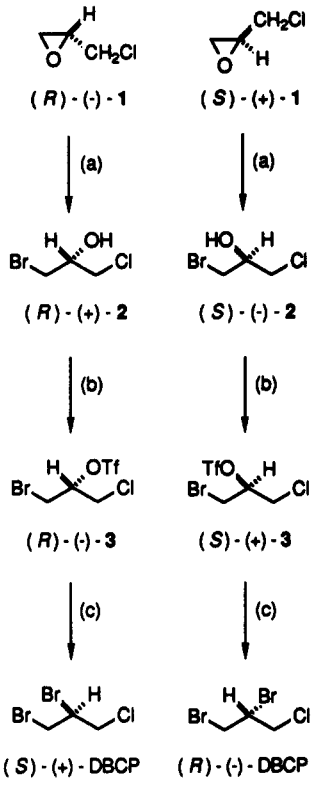
Scheme I[a]



[a] Key: (a) Li_2NiBr_4, THF, 0 °C; (b) triflic anhydride, pyridine, CH_2Cl_2, -10 °C; (c) LiBr, acetonitrile, rt.

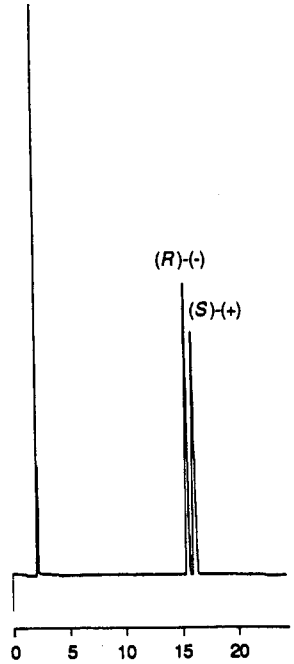


Figure 1. Enantiomeric resolution of DBCP by chiral GC on a 40-m × 0.25-mm (trifluoroacetyl)-β-cyclodextrin capillary column. Retention times are in min. CH_2Cl_2 was used as solvent. Conditions: oven temperature, 90 °C; helium (1.7 mL/min) as carrier gas; split (100/1) injection; flame ionization detection.

$CDCl_3$ at 300 and 75 MHz, respectively. TMS was utilized as internal reference. Standard Varian attached proton test (APT) pulse sequence was utilized to determine multiplicities of ^{13}C-NMR signals. (±)-Epichlorohydrin (1), (*R*)-(-)-1 ($[\alpha]^{20}_D = -34°$ (*c* = 1, methanol); 98.3% ee, chiral GC by Aldrich) and (*S*)-(+)-1 ($[\alpha]^{20}_D = +34°$ (*c* = 1, methanol); 97.8% ee, chiral GC by Aldrich) were purchased from Aldrich Chemical Co., Inc. (Milwaukee, WI). All other chemicals were obtained from Aldrich or J. T. Baker Chemical Co. (Phillipsburg, NJ). THF was predried over KOH and then distilled over Na with benzophenone as indicator. Pyridine and CH_2Cl_2 were distilled from CaH_2 and stored over 4-Å molecular sieves. Acetonitrile was distilled from P_2O_5 and CaH_2 and stored over 4-Å molecular sieves. The term in vacuo refers to removal of solvent with rotary evaporator under water aspirator vacuum (15–30 mmHg).

GC–MS. GC conditions were the same as described for GC analysis. EI MS conditions utilizing a VG7070H mass spectrometer were as follows: ion source temperature, 200 °C; emission current, 100 μA; accelerating voltage, 4 kV. Spectra were recorded at a nominal resolution of $M/\Delta M = 1000$ (10% valley). Magnetic field scanning from *m/z* 50 to 450 was repeated at 1.5 s/decade.

Chiral GC. Enantiomeric resolution of DBCP by GC was performed on a (trifluoroacetyl)-β-cyclodextrin (Chiraldex B-TA) capillary column (40-m × 0.25-mm i.d.; Advanced Separation Technologies Inc., Whippany, NJ). Helium (1.7 mL/min, head pressure 25 psi) was used as carrier gas, and the injector and the flame ionization detector blocks were maintained at 200 and 250 °C, respectively. The oven was held at 90 °C isothermal following split (100/1) injection.

(*R*)-(+)-1-Bromo-3-chloro-2-propanol [(*R*)-(+)-2]. The (*R*)-(+)-bromochlorohydrin was prepared from (*R*)-(-)-1 according to the procedure of Dawe et al.[5] To a solution of 1.89 g (20.45 mmol) of (*R*)-(-)-1 in 2 mL of dry THF was added an excess (1.6 equiv) of Li_2NiBr_4 (82 mL, 32.8 mmol), and the mixture was stirred for 2 h at 0 °C in an ice bath. The reaction mixture was then warmed to rt (~25 °C) and allowed to stir for 1 h. The mixture was then treated with 100 mL of phosphate buffer (pH 7) and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and the solvent evaporated in vacuo. Residual THF was removed in vacuo at 40 °C for 2 h followed by drying overnight under high vacuum (0.3 mmHg) at rt to yield 3.34 g (95% yield) of (*R*)-(+)-2 as an oil (>99% pure by GC) which was stored at -20 °C: $[\alpha]^{28}_D = +1°$ (*c* = 1, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}) 3385.4 (OH); GC–MS (EI) *m/z* (relative intensity) 123 (25), 125 (23) [M - CH_2Cl]$^+$; 79 (69), 81 (21) [M - CH_2Br]$^+$; ^1H-NMR ($CDCl_3$) δ 4.01–4.11 (m, 1 H, C*H*OH), 3.71 (d, 2 H, *J* = 5.2 Hz), 3.57 (d, 2 H, *J* = 5.1 Hz), 3.27 (d, 1 H, *J* = 6.5 Hz, exchangeable with D_2O, CHO*H*); ^{13}C-NMR ($CDCl_3$) δ 70.4 (CHOH), 46.4 (CH_2Cl), 34.7 (CH_2Br).

(*S*)-(-)-1-Bromo-3-chloro-2-propanol [(*S*)-(-)-2]. This was prepared from (*S*)-(+)-1 following the same procedure that was utilized to prepare (*R*)-(+)-2. $[\alpha]^{28}_D = -1°$ (*c* = 1, $CHCl_3$); IR, GC–MS, and NMR data were identical to those of the (*R*)-(+)-2 enantiomer.

Triflate of (*R*)-(+)-2 [(*R*)-(-)-3]. A total of 5 mL of CH_2Cl_2 was added under argon to a flask which had been cooled to -10 °C in an ice/acetone bath followed by 0.118 g (1.5 mmol) of pyridine and 0.25 g (1.45 mmol) of (*R*)-(+)-2. The mixture was allowed to stir for 15 min. A chilled (4 °C) solution of 0.42 g (1.5 mmol) of trifluoromethanesulfonic anhydride in 2 mL of CH_2Cl_2 was then added dropwise, and the resulting white suspension was stirred at -10 °C for 4 h under argon. The suspension was then filtered and the organic layer was evaporated in vacuo at rt. The oily residue was extracted with hexane which was evaporated in vacuo at rt to yield 0.43 g (97% yield) of (*R*)-(-)-3 as an oil (>99% pure by GC) which was stored at -20 °C: $[\alpha]^{28}_D = -5.1°$ (*c* = 1, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}) 1414.3 (OSO_2), 1140.1 (OSO_2), 1213.1 (CF); GC–MS (EI) *m/z* (relative intensity) 255 (14.9), 257 (15.3) [M - CH_2Cl]$^+$; 211 (4), 213 (1) [M - CH_2Br]$^+$; 154 (25), 156 (33), 158 (8) [M - CF_3SO_3H]$^+$; 75 (100), 77 (33) [M - (CF_3SO_3H, Br)]$^+$; 69 (100) [CF_3]$^+$; ^1H-NMR ($CDCl_3$) δ 5.12–5.19 (m, 1 H, C*H*OSO_2CF_3), 3.92 (d, 2 H, *J* = 4.9 Hz), 3.71–3.74 (m, 2 H); ^{13}C-NMR ($CDCl_3$) δ 118.3 (q, $^1J_{^{13}C-F}$ = 315 Hz, CF_3), 84.3 (*C*HOSO_2CF_3), 42.8 (CH_2Cl), 28.6 (CH_2Br).

Triflate of (*S*)-(-)-2 [(*S*)-(+)-3]. This triflate was prepared from (*S*)-(-)-2 following the same procedure that was utilized to prepare (*R*)-(-)-3. $[\alpha]^{28}_D = +5.3°$ (*c* = 1, $CHCl_3$); IR, GC–MS, and NMR data were identical to those of the (*R*)-(-)-3 enantiomer.

(*R*)-(-)-1,2-Dibromo-3-chloropropane [(*R*)-(-)-DBCP]. A total of 5 mL of acetonitrile was added under argon to a flask containing 0.068 g (0.8 mmol) of anhydrous LiBr. The mixture was stirred at rt for 15 min. A solution of 0.125 g (0.4 mmol) of (*S*)-(+)-3 in 2 mL of acetonitrile was then added dropwise. The

reaction mixture was allowed to stir at rt for 1 h. The mixture was then poured into ice–water and extracted with hexane. The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The oily residue was vacuum-distilled (82 °C (18 mmHg); lit.[9] 78 °C (16 mmHg)) to yield 0.084 g (90% yield) of (*R*)-(−)-DBCP as a colorless liquid (>99% pure by GC; 97% ee by chiral GC): $[\alpha]^{28}_D = -9.2°$ ($c = 1$, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}) 3032.9 (CH_2Cl, CH_2Br), 2951.8 ($-CH_2-$), 1425.1 (CH), 724.8 (CCl), 654.0 (CBr); GC–MS (EI) *m/z* (relative intensity) 234 (0.15), 236 (0.3), 238 (0.24), 240 (0.06) $[M]^+$; 199 (0.3), 201 (0.6), 203 (0.3) $[M - Cl]^+$; 185 (1.3), 187 (2.4), 189 (1.2) $[M - CH_2Cl]^+$; 155 (83), 157 (100), 159 (25) $[M - Br]^+$; 141 (0.9), 143 (1.2), 145 (0.3) $[M - CH_2Br]^+$; 119 (9), 121 (8) $[M - (Br, HCl)]^+$; 105 (8), 107 (8) $[M - (HCl, CH_2Br)]^+$; 93 (13), 95 (12) $[CH_2Br]^+$; 75 (100), 77 (34) $[M - (Br, HBr)]^+$; ^{1}H-NMR ($CDCl_3$) δ 4.33–4.41 (m, 1 H, CHBr), 3.80–4.08 (m, 4 H); ^{13}C-NMR ($CDCl_3$) δ 48.7 (CHBr), 46.5 (CH_2Cl), 33.4 (CH_2Br).

(S)-(+)-1,2-Dibromo-3-chloropropane [(*S*)-(+)-DBCP]. The (*S*)-(+)-DBCP enantiomer (94.4% ee by chiral GC) was prepared from (*R*)-(−)-**3** following the same procedure utilized to prepare (*R*)-(−)-DBCP: $[\alpha]^{28}_D = +9.0°$ ($c = 1$, $CHCl_3$); IR, GC–MS, and NMR data were identical to those of the (*R*)-(−)-DBCP enantiomer.

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