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PREPARATION OF E- AND Z-5-DEUTERIOADAMANTAN-2-OL

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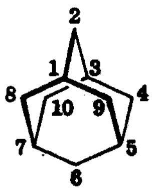
SUMMARY

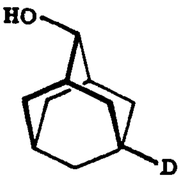
The title synthesis can readily be carried out on a 50 mg scale or more, starting with the 54/46 *mixture* of E- and Z-5-bromoalcohols obtained from the sodium borohydride reduction of the ketone. The key feature on which the synthesis depends is the fact that the Z-trimethylsilyl bromoether is reduced by zinc borohydride (and -deuteride) in benzene much faster than the E- epimer.

Key words: geometric mimics of enantiomers.

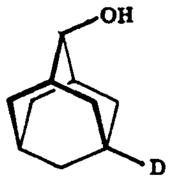
INTRODUCTION

E- and Z-5-Deuterioadamantan-2-ol (E-1 and Z-1) are of interest in that they can serve as the prototype geometric analogs of enantiomers. As such, they combine all the advantages in stereochemical studies that are usually attributed to geometric *and* to enantiomeric pairs. As geometric isomers, these alcohols have the special advantages of ease of preparation, proof of purity, and analysis: resolution, optical rotation measurements and the use of chiral auxiliary reagents are all avoided. Yet these compounds also have the principal advantage of enantiomers in that they have equal free energies; stereorandomness is indicated by a 50/50 composition of products. One application has been reported so far: the tosylate of the E- alcohol was shown to solvolyze with retention, this fact being readily demonstrated by means of ^{2}H NMR in the presence of Eu(fod)$_3$.[1]





E-1



Z-1

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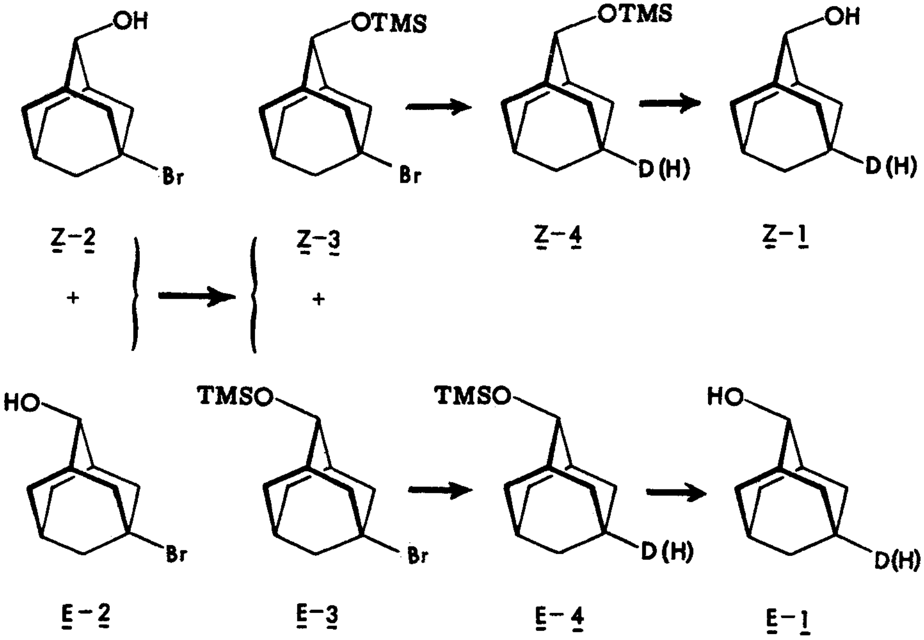
The main drawback is a series of difficulties encountered in the preparation of these compounds. A mixture of E- and Z-5-chloroalcohols obtained by $NaBH_4$ reduction of the chloroketone was trimethylsilylated (TMS), and the ethers were separated by means of GC. Since the R_f values proved to be very similar under all conditions tried, only very small quantities of the pure chloroethers could be laboriously obtained. Their reduction required a huge excess (35-fold) of lithium aluminum deuteride (98%). The reaction in THF apparently involves a SET mechanism;[2] in any case, the 2-adamantanol product contained only 20-30% deuterium at the desired position. Even use of the rather expensive THF-d_8 as solvent did not completely solve the problem; tunnelling apparently occurs, and the very large k_H/k_D ratio led to products which still contained only 75% deuterium in the Z- isomer (94% in the E-).

We now wish to report a preparative procedure that uses the more easily available 5-bromoadamantan-2-one,[3] that avoids the needs for GC and THF-d_8 altogether, that requires modest amounts of inexpensive zinc borodeuteride, and that furnishes both isomers in more than 90% isotopic and epimeric purity (see Scheme).

Scheme



The preparation is based on our observation that the Z-bromoether (Z-3) is reduced much faster than the E- epimer with zinc borohydride and -deuteride. Thus, when 350 mg of a 54/46 E-/Z- mixture of bromoethers is exposed to zinc borodeuteride in benzene at room temperature for 24 hours, 50 mg of the deuterioether Z-4 can be isolated with an isotopic content of 96% and epimeric purity of 90%. The unreacted part is correspondingly enriched in the bromoether E-3. Further reduction of this remaining mixture with zinc borohydride at room temperature in benzene for 24 hours is then employed to increase this enrichment. The bromoether still remaining is now highly enriched E-isomer; this is then in turn reduced with zinc borodeuteride in benzene, but now at reflux for 24 hours to give 61 mg of ether E-4, with a 94% isotopic and 93% epimeric purity.

The reduction of the Z- bromoether probably owes its much faster rate to the greater proximity of the anion to the bromo function in a species in which the zinc is coordinated with oxygen. A similar explanation has long been favored to account for the syn- cyclopropanation of unsaturated alcohols in the Smith-Simmons reaction.[4]

Our earlier procedure for preparing these deuterioalcohols, expensive and cumbersome as it was, did have one minor advantage over the present one: it provided them in epimeric (though not isotopic) purity. Where this issue is important, that procedure (or some combination) may still be preferred; however, the scale and ease of the new preparation are such that it should essentially always be chosen, especially since ^{2}H NMR provides a convenient and accurate analysis.

EXPERIMENTAL

General. A Perkin-Elmer 900 GC instrument was used to monitor the progress of the reactions and the purity of the products; it was equipped with a 10' x 1/8" column (3% DEGS on Chromosorb W). The helium flow was 50 mL/min and the oven temperature was programmed (80°C x 2 min, 6°C/min). A Varian 3400 GC instrument with a DB-5 (30 m/0.26 mm) capillary column and an Hp-3380A integrator were used to measure isomer ratios; the helium pressure was 40 psi and the oven temperature was programmed (120°C x 3 min, 10°C/min). TLC was done with Macherey-Nagel Polygram Sil G/UV 254 plates with ethyl acetate in hexanes (2:98) as eluant. Pure hexanes and silica gel were used in flash column chromatography. Mass spectra were taken with a Hewlett Packard 5980-A spectrometer. ^{1}H, ^{13}C and ^{2}H NMR spectra were measured on a NT-300 spectrometer. $CDCl_3$ ($CHCl_3$ for ^{2}H NMR) were used to prepare NMR samples; chemical shifts are reported in ppm relative to $\delta_{(TMS)} = 0$ ppm.

5-Bromoadamantan-2-ols (2). 5-Bromoadamantan-2-one[3] (700 mg, 3.057 mmol) was reduced as described previously[1] to give 685 mg (97%) of 5-bromoadamantan-2-ols. Capillary GC analysis (R.T.(E-) = 16.7 min., R.T.(Z) = 17.1 min.) showed the E-/Z- ratio to be 54/46.

5-Bromoadamantan-2-yl trimethylsilyl ethers (3). Dissolution of 2 (588 mg, 2.55 mmole) in 10 mL of dry THF followed by the addition of 7 mL of triethylamine and slow injection of chlorotrimethylsilane (4 mL, Aldrich) under an argon atmosphere led to a milky solution. After 15 hours of stirring at room temperature, TLC (R_f(2) = 0.03, R_f(3) = 0.47) and GC (R.T.'s: E-2 = 13.4, Z-2 = 14.2, E-3 = 2.24 and Z-3 = 2.56 minutes, respectively) showed the reaction to be complete. Addition of 1 g of powdered sodium bicarbonate and 2 mL of water was followed by ether extraction (2 x 100 mL). Washing, drying and evaporation was followed by flash chromatography to give a colorless liquid mixture (727 mg, 94%) with an E-/Z- ratio of 54/46 by capillary GC (R.T.'s: E-3 = 8.65 and Z-3 = 8.85 minutes, respectively). ^{1}H NMR: δ3.843 (bs, E-3 CHOTMS), 3.704 (bs, Z-3 CHOTMS), 2.8-1.4 (m), 0.088 (s, E-3 OTMS), 0.082 (s, Z-3 OTMS).

Zinc borodeuteride. This was prepared as described[5] from 840 mg of sodium borodeuteride (Aldrich, 98 atom % D) and 2.2 g of zinc bromide (Aldrich, 98%) in 20 mL of dry THF, followed by syringe filtration of the sodium bromide. The solvent was thoroughly removed by pumping overnight.

Z-5-Deuterio-2-trimethylsilyloxyadamantane (Z-4). Zinc borodeuteride (140 mg) in a 25 mL flask in dry benzene (5 mL) was treated under argon with 346 mg of the neat mixture of ethers 3 described above. After 24 hours stirring at room temperature, GC analysis showed that about half of the Z- ether and essentially all of the E- epimer was still left. Saturated aqueous ammonium chloride (2 mL) was slowly added followed by ethyl ether (100 mL) and triethylamine (2 mL). After washing with water and brine, drying over sodium sulfate, filtration and evaporation, the residue was separated by means of flash column chromatography (hexane) to give 50 mg of Z-4 (R_f = 0.71); the 268 mg of 3 (R_f = 0.47) recovered had an E-/Z- ratio of 64/36.

E-5-Bromo-2-trimethylsilyloxyadamantane (E-3). Part of this lattere mixture of 3 (210 mg) was dissolved in 4.5 mL of dry benzene, 190 mg of zinc borohydride was added with stirring at room temperature. GC was used to monitor the reaction; after 24 hours, Z-3 could no longer be detected. Quenching, workup and flash column chromatography as described above gave 120 mg of E-3 (R_f = 0.47) as white crystals; ^{1}H NMR: 3.843 (bs, 1H, CHOTMS), 2.4-1.3 (m, 13H), 0.088 (s, 9H, OTMS). About 50 mg of 2-trimethylsilyloxyadamantane (R_f = 0.71) was also obtained.

E-5-Deuterio-2-trimethylsilyloxyadamantane (E-4). Zinc borodeuteride (305 mg) in a 25 mL flask in 4 mL of dry benzene was mixed under argon with a solution of 101 mg of the E-3 dissolved in 4 mL of dry benzene. Reflux with vigorous stirring for 28 hours completed the reduction. Workup as above gave 77 mg of residue from which 61 mg of E-4 (R_f = 0.71) was obtained (83%) and as well as 2.4 mg of unreacted E-3.

Hydrolysis of the TMS ethers. This was affected by the reaction of dilute mineral acid (2 mL aqueous HCl (1M) in 5 mL methanol) for 30 minutes at room temperature with E-4 and with Z-4. Essentially no epimerization occurred; this was checked by the use of tetra-n-butylammonium fluoride in THF for six hours at room temperature.

Analysis: Excellent agreement was obtained in all cases concerning natural abundance and epimeric composition whether mass spectrometry, ^{2}H NMR with Eu(fod)$_3$ or ^{13}C NMR was used. For MS analysis, we used the base peak at 210 (M^+ - 15) rather than the weak parent peak region. Comparison of the 209 and 210 peaks of natural abundance and monodeuterated ethers served to reveal contamination by the D-free ether. The NMR analyses have been described previously.[6]

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REFERENCES AND NOTES

1. Cheung C. K., Tseng L. T., Lin M.-H., Srivastava S. and le Noble W. J. - J. Am. Chem. Soc. 108: 1598 (1986).
2. Srivastava S. and le Noble W. J. - Tetrahedron Lett. 25: 4871 (1984).
3. Klein H. and Wiartalla, R. - Syn. Commun. 9: 825 (1979). Use of t-butyl bromide instead of t-butanol as the catalyst was found to lead to a much smoother and more easily controlled reaction.
4. Winstein, S., Sonnenberg J. and de Vries L. - J. Am. Chem. Soc. 85: 1782 (1963).
5. Gensler, W. J., Johnson, F. and Sloan, A. D. B. - J. Am. Chem. Soc. 82: 6074 (1960).
6. Srivastava S., Cheung C. K. and le Noble W. J. - Magn. Res. Chem. 23: 232 (1985).