Table I. Preparation of Trans Vicinal Fluoro-Bromo Compounds

substrate	reactn conditions[f]	product	yield,[a] %	bp °C/mm (lit.)	δ(¹⁹F) NMR[d]	δ(¹³C) NMR[e]
	1, 0		35	41–44/21	160.6 (m)	C_2 = 100.2 (J_{C-F} = 179.4 Hz), C_1 = 52.7 (J_{C-C-F} = 27.7 Hz), C_4 or C_5 = 33.9, C_4 or C_5 = 21.2, C_3 = 29.7 (J_{C-C-F} = 20.7 Hz)
	15, −5		69	75–77/11 (30/11)[12]	169.3 (dd)	C_2 = 93.6 (J_{C-F} = 179.4 Hz), C_1 = 52.2 (J_{C-C-F} = 19.5 Hz), C_6 = 34.5 ($J_{C-C-C-F}$ = 3.7 Hz), C_5 = 24.6, C_4 = 22.4 ($J_{C-C-C-F}$ = 8.6 Hz), C_3 = 30.9 (J_{C-C-F} = 19.1 Hz)
	20, −5		39	70–73/3.5	161.3 (m)	C_2 = 98.1 (J_{C-F} = 175.1 Hz), C_1 = 56.1 (J_{C-C-F} = 23.6 Hz), C_7 = 33.8 ($J_{C-C-C-F}$ = 5.6 Hz), C_5 or C_6 = 27.2, C_5 or C_6 = 24.6, C_4 = 20.7 ($J_{C-C-C-F}$ = 4.4 Hz), C_3 = 31.3 (J_{C-C-F} = 22.0 Hz)
	5, 0		58[b]		171.6 (m), 175.6 (m)	C_4 = 19.5 (J_{C-C-F} = 19.4 Hz), 19.4 (J_{C-C-F} = 25.5 Hz), C_3 = 93.8 (J_{C-F} = 174.5 Hz), 93.1 (J_{C-F} = 175.5 Hz), C_2 = 52.4 (J_{C-C-F} = 23.4 Hz), C_1 = 22.8 ($J_{C-C-C-F}$ = 3.0 Hz), 22.5 ($J_{C-C-C-F}$ = 5.7 Hz)
	15, −5		60[c]		169.6 (m), 176.1 (m), 181.6 (cm)	too complex to assign
$CH_3(CH_2)_6CH_2Br$	no reaction		0			

[a] Isolated and purified product. [b] Mixture of diastereomers in 2:1 ratio. [c] Mixture of regioisomers with diastereomeric pairs. [d] In ppm (upfield) from external $CFCl_3$, dd = doublet of doublet, m = multiplet, cm = complex multiplet. [e] In ppm downfield from tetramethylsilane. [f] Time (h), temperature (°C).

NMR spectrometer. The boiling points reported are uncorrected. All manipulations were done in polyethylene ware since $(HF)_n$–pyridine is corrosive to glass.

1-Bromo-2-fluorocyclohexane (1) from 1-Bromocyclohexane. To a stirred solution of $NO_2^+BF_4^-$ (6.64 g, 50 mmol) in 30 mL of $(HF)_n$–pyridine (70:30) in a 200-mL polyethylene bottle at −5 °C under a dry nitrogen atmosphere was added dropwise 1-bromocyclohexane (6.52 g, 40 mmole) over a period of 10 min. The reaction mixture was stirred at −5 °C for 15 h and was then poured into ice–water (200 mL). The resulting mixture was extracted with ether (2 × 200 mL), and the combined ethereal extract was washed several times with 10% aqueous $NaHCO_3$ solution followed by brine solution until neutral. The neutral ether extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The remaining residue was distilled under vacuum to provide pure *trans*-1-bromo-2-fluorocyclohexane (1), bp 75–77 °C/11 mmHg[12] (5.0 g, 69%).

Preparation of 1-Bromo-1-deuteriocyclohexane (5). 1-Deuterio-1-cyclohexanol. A solution of cyclohexanone (9.82 g, 0.01 mol) in ether (15 mL) was added slowly to a suspension of lithium aluminum deuteride (2.31 g, 0.055 mol) in ether (100 mL) so as to maintain a gentle reflux. The reaction mixture was refluxed for 0.5 h and then poured into aqueous 10% H_2SO_4 solution and extracted with ether (200 mL). The extract was washed with water, aqueous saturated $NaHCO_3$ solution, water, and brine, dried over $MgSO_4$, and evaporated in vacuo. The crude product was distilled under reduced pressure to give the deuterio alcohol as a colorless oil, bp 61–63 °C/7 mmHg (7.9 g, 78%).

1-Deuterio-1-cyclohexyl *p*-Toluenesulfonate. To a solution of 1-deuterio-1-cyclohexanol (1.85 g, 18.3 mmol) in pyridine (75 mL) was added *p*-toluenesulfonyl chloride (3.49 g, 18.3 mmol). The mixture was stirred at room temperature for 24 h, poured into ice–water, and extracted with ether. The extract was washed with aqueous 10% HCl solution and water, dried over Na_2SO_4, and concentrated to give the *p*-toluenesulfonate as an oil, which was used in the next step without further purification (3.7 g, 81%).

1-Bromo-1-deuteriocyclohexane (5). A mixture of dry LiBr (1.22 g, 14.1 mmol) and 1-deuterio-1-cyclohexyl *p*-toluenesulfonate (3.0 g, 14.1 mmol) in hexamethylphosphoramide (18 mL) was heated at 150 °C under vacuum (25 mmHg) and the volatile product was trapped in an acetone–dry ice bath. Purification by redistillation gave **5** (300 mg) as a colorless oil: bp 53–54 °C/20 mmHg; ^{13}C NMR ($CDCl_3$, ambient) δ 53.2 (J_{C-D} = 23.1 Hz), 37.3, 25.8, and 25.0.

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(12) Bowers, A.; Ibanez, L. C.; Denot, E.; Becerra, R. *J. Am. Chem. Soc.* **1960**, *82*, 4001.

Chemical Behavior of (+)-(1*R*,3*S*)-1,2,2-Trimethyl-1,3-bis(hydroxymethyl)cyclopentane upon Attempted Halogenation. Formation of (+)-(1*S*,3*S*)-1-Bromo-3-(bromomethyl)-1,2,2-trimethylcyclohexane

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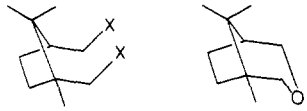
In an earlier report,[1] we pointed out the desirability of finding a convenient synthesis of (+)-(1*R*,3*S*)-1,2,2-trimethyl-1,3-bis(bromomethyl)cyclopentane (1) from the readily available glycol (+)-(1*R*,3*S*)-1,2,2-trimethyl-1,3-

(1) Erickson, G. W.; Fry, J. L. *J. Org. Chem.* **1980**, *45*, 970–972.

0022-3263/87/1952-0933$01.50/0

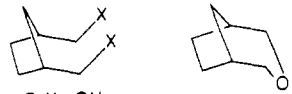


1, X = Br
2, X = OH
3, X = $OP^+Ph_3TfO^-$

bis(hydroxymethyl)cyclopentane (2) because metalation of 1 could provide an entree to the synthesis of a large number of chiral products with potential use in studies of asymmetric synthesis. We, and others,[2-4] also described the failure of many standard methods for the conversion of alcohols to halides to effect such a conversion in this system. In particular, we reported the nearly quantitative formation of the ring-closed ether (+)-(1*R*,5*S*)-1,8,8-trimethyl-3-oxabicyclo[3.2.1]octane (3) from 2 upon attempted halogenation by several means. We ascribed this to the extremely small propensity of the "neopentane-like" hydroxyl group to undergo substitution from external reagents and to the thermodynamic driving force for ring closure to 3.

Since our earier report, the synthesis of compound 1 by way of the bis(alkoxytriphenylphosphonium triflate) 4 has been published by Ramos and Rosen.[5] However, as the amount and yield of the product reported from this multistep synthesis were very small, we continued to seek alternative, more direct routes to this compound.

A simple route that seemed promising was the use of phosphorus tribromide in sulfolane (tetramethylene sulfone) solvent as reported by Anteunis et al.[6] They reported that when *cis*-1,3-bis(hydroxymethyl)cyclopentane (5) was treated with PBr_3 in CH_2Cl_2 solvent, the desired



5, X = OH
6, X = Br

cis-1,3-bis(bromomethyl)cyclopentane (6) was obtained in less than 50% yield as part of a mixture containing the cyclic ether 3-oxabicyclo[3.2.1]octane (7). However, when the reaction was modified simply by exchanging sulfolane for CH_2Cl_2 as solvent, the yield of 6 was reported to be cleanly quantitative.[7]

Considering the structural parallels between glycols 2 and 5, on the one hand, and cyclic ethers 3 and 7, on the other, it seemed a resonable experiment to attempt the bromination of glycol 2 by using PBr_3 in sulfolane solvent, even though an earlier attempt by us to form 1 by treatment of 2 with PBr_3 in anhydrous benzene solution had led only to an uncharacterized product mixture.[8]

Results

Treatment of glycol 2 with PBr_3 in sulfolane and workup as reported by Anteunis et al. for *cis*-1,3-bis(hydroxymethyl)cyclopentane[6,7] gave a 54% yield of a crude dibromide product. However, this product did not exhibit the spectral properties of the expected (+)-(1*R*,3*S*)-1,2,2-trimethyl-1,3-bis(bromomethyl)cyclopentane (1). Instead, purification by Kugelrohr distillation and recrystallization gave a single optically active product whose spectral and microanalytical data were consistent with the structure of 1-bromo-3-(bromomethyl)-1,2,2-trimethylcyclohexane (8).

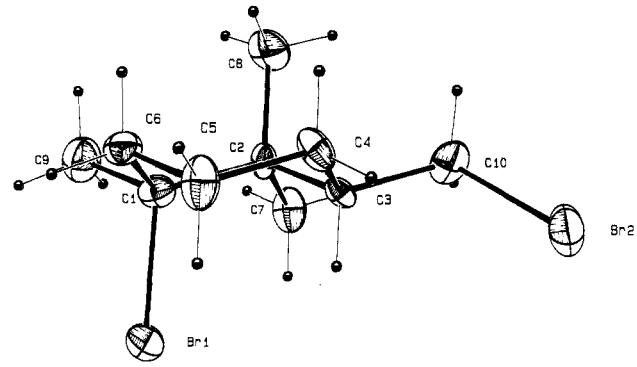
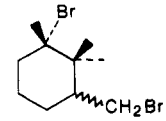


Figure 1. ORTEP plot showing the structure of dibromide 9 in the solid state from a single-crystal X-ray analysis.



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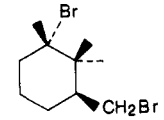
In particular, in the area of the ^1H NMR spectrum where the four methylene proton signals of the two bromomethyl groups should be found, viz. δ 3–4,[5] only an apparent triplet centered at δ 3.05 and integrating for 1 H and a doublet of doublets centered at δ 3.70 and also integrating for only 1 H were displayed by this product. Unfortunately, we were unable to distinguish the cis or trans disposition of the bromo and bromomethyl ring substituents on the basis of the NMR spectra. In order to do this, the structure was determined by single-crystal X-ray diffraction analysis. That structure, with correct absolute configuration, is shown in Figure 1. It clearly shows that the product isolated from this reaction is the trans compound, (+)-(1*S*,3*S*)-1-bromo-3-(bromomethyl)-1,2,2-trimethylcyclohexane (9) rather than the cis diastereomer.



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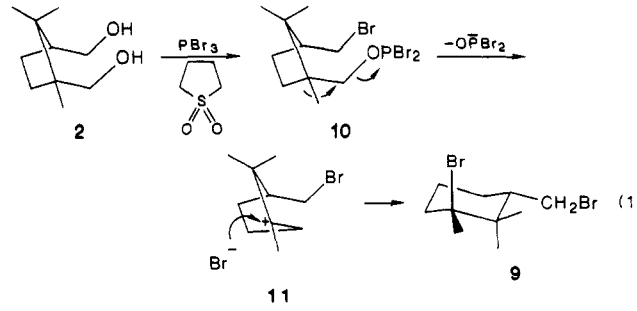
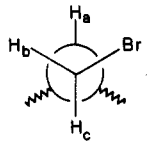
Discussion

The formation of this reaction product may be explained by the reaction sequence shown in eq 1. On the basis of



2 10 11 9 (1)

(2) Morrison, J. D.; Masler, W. F.; Neuberg, M. K. *Adv. Catal.* **1976**, *25*, 81–124.
(3) Morrison, J. D.; Masler, W. F.; Hathaway, S. In *Catalysis in Organic Syntheses—1976*; Rylander, P. N., Greenfield, H., Eds.; Academic: New York, 1976; pp 203–233.
(4) Masler, W. F. Ph.D. Dissertation, University of New Hampshire, 1974.
(5) Ramos, S.; Rosen, W. *Tetrahedron Lett.* **1981**, *22*, 35–38; *J. Org. Chem.* **1981**, *46*, 3530–3533.
(6) Carleer, R.; Hosten, N.; Anteunis, M. J. O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 709–716.
(7) We have repeated the synthesis of 6 from 5 in sulfolane as reported.[6] In our hands, the yields of pure product actually obtained averaged only 30–40%. However, as reported, 6 was the only product isolated; no 7 was found.
(8) Erickson, G. W.; Fry, J. L., unpublished observations.



dihedral angle, deg		J, Hz	
H_a-C-C-H_b	64	H_a-H_b	2.64
H_a-C-C-H_c	167	H_a-H_c	10.32
H_a-C-C-Br	51	H_b-H_c	(-)9.67

Figure 3. Dihedral angles and coupling constants of $CHCH_2Br$.

an earlier study of this system,[1] the differential S_N2 reactivity between the two hydroxyl groups of **2** would be expected to yield the monobromo dibromo phosphite ester **10**. The polarity of sulfolane is apparently sufficiently greater than that of either benzene or methylene chloride to permit the ionization and rearrangement of **10** to form the relatively stable tertiary carbocation **11**.

Stereospecific attack by bromide ion onto only one diastereotopic face of the sp^2-hybridized carbocation center seems rather amazing at first; however, upon examination of molecular models, it becomes quite understandable from both kinetic and thermodynamic grounds. The approach leading to *trans*-**9** is less sterically hindered than the path toward the other face, which would give cis product. In addition, product **9** has an axial bromine and larger methyl group equatorial, whereas the cis compound, which was not obtained, has the larger methyl group in the more congested axial position and the smaller bromine in the less sterically demanding equatorial position. Thus, the observed product seems favored regardless of whether the transition state for nucleophilic capture of carbocation **11** is "early" or "late".

One conclusion that follows from obtaining only product **9** to the exclusion of either its cis isomer or unrearranged dibromide **1** is that the Wagner–Meerwein shift that forms ion **11** must be concerted with the heterolytic cleavage of the C–O bond in **10**. In addition, it follows that carbocation **11** must be an open, "classical" tertiary cation without any vestige of σ-bond bridging; otherwise, bromide attack would be expected to lead to the cis product only.

The ^1H NMR spectrum of product **9** is shown in Figure 2 (supplementary material). The region above δ 2.8 where the two diastereotopic methylene proton signals of the C-10 bromomethyl group resonate is of particular interest. Analyses of the geminal and vicinal spin–spin couplings of the methylene protons with each other and with the axial ring proton on C-3 are summarized in Figure 3, together with relevant dihedral angles derived from the X-ray diffraction study.

Comparison of the vicinal coupling constants with the dihedral angles observed in the crystalline state is interesting. Attempts to calculate dihedral bond angles from vicinal spin–spin coupling constants by quantitative application of the Karplus equation or similar relationships are subject to many problems.[9] We have thus resisted doing this. Nevertheless, a qualitative comparison of the two very different vicinal coupling constants with the respective dihedral angles found in the crystalline state reveals a striking similarity between what would be the expected dihedral angles for the species in solution and those found in the solid. This suggests that the dissolved species are very likely restricted in their conformational freedom and that the preferred solution conformation may be quite close to that found in the crystalline state.

Experimental Section

General Methods. Proton nuclear magnetic resonance spectra were obtained by using Varian T-60A or JEOL FX-90Q spectrometers. Carbon-13 spectra were obtained on the latter. Unless otherwise indicated, the solvent used was $DCCl_3$, and chemical shifts were related to Me_4Si. Infrared spectra were obtained on a Nicolet 60 SX Fourier transform infrared spectrometer with CCl_4 solutions in 0.1-mm NaCl cells or with KBr pellets. X-ray intensity data collection was carried out with an Enraf-Nonius CAD4 automatic diffractometer. All calculations were performed on a VAX 11/750 using VAXSDP.[10] Scattering factors for the neutral atoms and anomalous scattering coefficients were taken from standard tabulations.[11] Gas chromatographic analyses were carried out on a Varian Aerograph 90-P instrument using 6.4 mm × 2 m columns. Optical rotations were measured on a Rudolph Research Autopol III automatic digital polarimeter using a 4 mm × 1 dm tube. Melting points (Thomas-Hoover apparatus) and boiling points are uncorrected. Elemental analyses were performed by MicAnal Organic Microanalysis, Tucson, AZ. Sulfolane (Aldrich) was purified before use by distillation first from NaOH and then from CaH_2, bp 113 °C (1 torr).[12]

Bromination of Glycol 2 with PBr_3 in Sulfolane. A 15.0-g (0.0871-mol) portion of glycol **2**, prepared as previously reported,[1,13] was dissolved in 40 mL of sulfolane in an oven-dried, 500-mL three-necked round-bottomed flask equipped with a mechanical stirrer, addition funnel, reflux condenser, and dry nitrogen bubbler. The reaction apparatus was cooled with an ice–water bath, and a solution of 14 mL (0.146 mol) of phosphorus tribromide dissolved in 40 mL of sulfolane was added dropwise with stirring. At the end of the addition period, there remained a white precipitate. After 20 min of warming of the reaction vessel with an infrared lamp, the precipitate had disappeared. The yellowish reaction mixture was stirred at room temperature for an additional 48 h before being poured over ca. 300 g of crushed ice. Saturated aqueous sodium carbonate solution was added to the mixture until the aqueous layer indicated pH 9 on pH paper. The mixture was extracted four times with 100-mL portions of pentane. The combined pentane portion was then washed twice with water to remove sulfolane and once with saturated aqueous $CaCl_2$ and dried (Na_2SO_4). Removal of pentane on a rotary evaporator gave 14.0 g (54%) of crude product. This was subjected to Kugelrohr distillation [85–100 °C (2 torr)] to yield 10.5 g of colorless product that crystallized upon cooling: mp 69–70.5 °C; $[\alpha]^{23}_D$ +53.0° (*c* 2.029, $CHCl_3$); ^1H NMR δ 0.87 (3 H, s), 1.21 (3 H, s), 1.81 (3 H, s), 1.85–2.42 (7 H, m), 3.05 (1 H, t), 3.70 (1 H, dd); ^{13}C NMR δ 16.30 (q), 22.71 (t), 25.66 (q), 26.09 (d), 29.38 (q), 36.75 (t), 39.79 (t), 43.25 (s), 45.85 (t), 82.17 (s); IR 2920, 1448, 1388, 1376, 1152, 642 cm^{-1}. Anal. Calcd for $C_{10}H_{18}Br_2$: C, 40.30; H, 6.07; Br, 53.62. Found: C, 40.14; H, 6.27; Br, 53.40.

Acknowledgment. We thank The University of Toledo Faculty Research Awards and Fellowships Program for support of this work (J.L.F.) and the College of Arts and Sciences of The University of Toledo for providing resources for the X-ray Diffraction Center.

Supplementary Material Available: Text of data collection and reduction, structure solution and refinement, and references, tables of crystal structure data, positional parameters, bond distances, bond angles, torsional angles, hydrogen positional parameters, and anisotropic temperature factors, and Figure 2 showing the ^1H NMR spectrum of **9** (14 pages); tables of calculated and observed structure factors (3 pages). Ordering information is given on any current masthead page.

(9) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon: New York, 1969; pp 280–301.

(10) Frenz, B. A. In *Computing in Crystallography*; Schenk, H., Olthof-Hazelkamp, R., van Konigsveld, H., Bassi, G. C., Eds.; Delft University: Delft, Holland, 1978; pp 64–71.

(11) Cromer, D. T.; Waber, J. T. In *International Tables for X-ray Crystallography*; Ibers, J. A., Hamilton, W. C., Eds.; Kynoch: Birmingham, England, 1974; Vol. IV, Table 2.2b. Cromer, D. T. *Ibid.*, Table 2.3.1.

(12) Arnett, E. M.; Douty, C. F. *J. Am. Chem. Soc.* **1964**, *86*, 409–412.

(13) Johnson, T. H.; Klein, K. C. *J. Org. Chem.* **1979**, *44*, 461–462.