Chemical Behavior of (+)-(1*R*,3*S*)-1,2,2-Trimethyl-1,3-bis(hydroxymethyl)cyclopentane upon Attempted Halogenation. Formation of (+)-(1*R*,5*S*)-1,8,8-Trimethyl-3-oxabicyclo[3.2.1]octane

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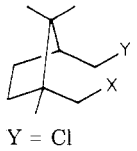
Attempts to effect the bis halogenation of the title glycol **3** by methods successful with neopentyl alcohol failed to produce either dichloride **1** or dibromide **2** because of extreme steric congestion and the opportunity for intramolecular cyclization to occur in this system. Treatment of **3** with either PPh_3/CCl_4 or $ZnBr_2/HBr$ reagents resulted in the formation of the cyclic ether **6**. Treatment of **6** with BBr_3 stereospecifically produced a bromoborate ester (**7**) derived from nucleophilic attack at the less hindered carbon. This ester produced the bromo alcohol **8** upon hydrolysis.

The metalation of (1*R*,3*S*)-1,2,2-trimethyl-1,3-bis(halomethyl)cyclopentanes **1** or **2** could serve as an attractive starting point for the synthesis of a large number of chiral compounds of potential interest in studies of asymmetric synthesis. This would be true if the dihalo compound could be obtained through halogenation of the corresponding glycol **3** since the glycol is easily obtained by lithium aluminum hydride reduction of (+)-camphoric acid, itself a relatively inexpensive compound which is commercially available in high optical purity. Unfortunately, this glycol does not lend itself to facile halogenation. Morrison, Masler, and co-workers recently reported that a large number of "standard" halogenation methods resulted only in the formation of unidentified product mixtures when applied to this glycol.[1-3]

At approximately the same time that Morrison and coworkers were engaged in their work, we too were independently attempting the synthesis of the dihalo compounds **1** and **2** from glycol **3**. Although we were also



1, X = Y = Cl
2, X = Y = Br
3, X = Y = OH
4, X = Y = OSO_2CH_3
5, X = Y = $OSO_2C_6H_4CH_3$
7, X = $OBBr_2$, Y = Br
8, X = OH, Y = Br
9, X = Br, Y = OH

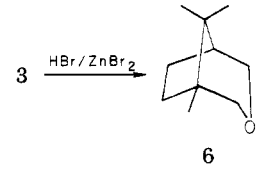
unable to effect the dihalogenation of this glycol, the studies which we now report have led to a better mechanistic understanding of the nature of the synthetic problems associated with this interesting system.

Results

The structural feature of glycol **3** which might make preparation of either of the corresponding dihalo compounds **1** or **2** difficult is the very sterically hindered "neopentyl-like" hydroxyl group β to C-1. Bearing this in mind, we (as did Morrison et al.[1-3]) attacked the problem by using synthetic methods previously proven effective in the halogenation of neopentyl-like alcohols.

Mosher and co-workers reported good yields of either neopentyl chloride or bromide when neopentyl tosylate was heated for several hours with lithium chloride or bromide in hexamethylphosphoramide (HMPA) solvent.[4] Accordingly, we prepared the dimesylate **4** by treatment of glycol **3** with methanesulfonyl chloride in pyridine and then heated it with lithium chloride in HMPA in an attempt to synthesize the dichloride **1**. Unhappily, only an ill-defined product mixture which exhibited proton NMR signals in the vinylic region was obtained. Related attempts to effect displacements on the corresponding ditosylate (**5**) are reported to give similar unsatisfactory results.[1,3]

Treatment of **3** with either thionyl chloride in pyridine or phosphorus tribromide did not yield **1** or **2**. However, when **3** was warmed and stirred overnight with 2 equiv of zinc(II) bromide dissolved in 2 equiv of concentrated hydrobromic acid, a single major product was formed. This product was not the expected dibromo compound **2**; rather, its spectral and microanalytical data were those entirely consistent with the structure of the cyclic ether (+)-1,8,8-trimethyl-3-oxabicyclo[3.2.1]octane (**6**) (eq 1).



(1)

6

The 60-MHz proton NMR spectrum of **6** is particularly diagnostic of its cyclic structure when compared with the spectra of the less rigid compounds such as **3**. Each of the three methyl groups in cyclic ether **6** gives rise to a well-resolved singlet (δ 0.72, 0.88, and 1.08), whereas only two methyl signals (ratio of 1:2 at δ 0.78 and 1.00) are seen in glycol **3**. Also, the two CH_2O groups in **6** show a distinct pattern of eight broad singlets in the region δ 2.9-4.1, and those in **3** display a broad singlet at δ 3.50 rising above a complex multiplet.

Many primary and secondary alcohols, when treated with triphenylphosphine and either carbon tetrachloride or carbon tetrabromide, yield the corresponding alkyl chlorides or bromides.[5] Even neopentyl alcohol gives

(1) Morrison, J. D.; Masler, W. F.; Neuberg, M. K. *Adv. Catal.* **1976**, *25*, 81-124.
(2) Morrison, J. D.; Masler, W. F.; Hathaway, S. In "Catalysis in Organic Syntheses-1976"; Rylander, P. N.; Greenfield, H., Eds.; Academic Press: New York, 1976; pp 203-33.
(3) Masler, W. F. Ph.D. Thesis, University of New Hampshire, 1974.
(4) Stephenson, B.; Solladie, G.; Mosher, H. S. *J. Am. Chem. Soc.* **1972**, *94*, 4184-8. Anderson, P. H.; Stephenson, B.; Mosher, H. S. *Ibid.* **1974**, *96*, 3171-7.

0022-3263/80/1945-0970$01.00/0

unrearranged halide under these mild conditions[6] through what must resemble a direct displacement mechanism.[4,7,8] However, when a carbon tetrachloride solution of glycol **3** and triphenylphosphine was heated, no chlorinated products were obtained. Instead, cyclic ether **6** was formed exclusively (eq 2). The reaction was easily followed by

$$3 + Ph_3P \xrightarrow[\Delta]{CCl_4} 6 + Ph_3PO \qquad (2)$$

proton NMR spectroscopy. The spectral changes were quite simple; the signals for the reactant **3** declined and were quantitatively replaced by those of the product ether **6**.[9] There was no spectral evidence for the accumulation of any reaction intermediates or other products. On a preparative scale, **6** was obtained cleanly in 80–90% isolated yield, regardless of whether 1 or 2 equiv of triphenylphosphine was used in the reaction.

As efforts to obtain compounds **1** or **2** directly from the open glycol **3** had failed, synthesis of dibromide **2** by ring cleavage of the cyclic ether **6** was attempted. The reaction of **6** with 4 equiv of boron tribromide[10] in chloroform-*d* was followed by proton NMR spectroscopy. At room temperature, the signals due to **6** disappeared within 1 h and were replaced quantitatively by a spectrum consistent with the formation of 1,2,2-trimethyl-1-[[(dibromoboro)oxy]-methyl]-3-(bromomethyl)cyclopentane (**7**) but not of **2** (eq 3). Passage of dry HBr into a solution of **7** produced, after 24 h, a solution whose complex NMR spectrum was indicative of a mixture.

$$3 + BBr_3 \rightarrow 7 \xrightarrow{H_2O} 8 \qquad (3)$$

Hydrolysis of the borate ester **7** cleanly produced a crystalline product whose spectral features were consistent only with the structure of 1,2,2-trimethyl-1-(hydroxymethyl)-3-(bromomethyl)cyclopentane (**8**). Distinction of the product structure between **8** and that of isomeric bromo alcohol **9** was made by the aid of an NMR LIS study. In CCl_4 solution, the diastereotopic CH_2O and CH_2Br proton signals of the product appeared as a complex multiplet (4 H) at δ 3.2–3.8. Increasing amounts of the lanthanide shift reagent $Eu(fod)_3$ caused the rapid downfield shift of a signal (2 H) which initially appeared as an approximate doublet centered at δ 3.48 and changed it into a broad singlet. A multiplet (2 H) of at least seven lines remained much less shifted by increasing amounts of shift reagent. This multiplet was assigned to the diastereotopic CH_2Br group of structure **8** which has vicinal as well as geminal coupling. The more shifted signal was assigned to the CH_2O group of structure **8** which has no vicinal coupling and which is nearest the site of europium coordination. These observations are not consistent with the expected spectral behavior of compound **9**.

Although bromo alcohol **8** can be stored for several weeks under nitrogen at −18 °C without decomposition, it suffers fairly rapid decomposition at room temperature or above either in the solid state or in solution. When a solution of **8** and carbon tetrabromide in dichloromethane was treated with triphenylphosphine, an exothermic reaction ensued, but, again, the very complex NMR spectrum of the product solution indicated the lack of clean conversion to dibromide **2**.

As expected, **8** proved to be quite sensitive to base. Treatment of a THF solution of **8** with a 10% excess of lithium diisopropylamide (LDA) yielded cyclic ether **6** as the major product (eq 4).

$$8 + LDA \rightarrow 6 \qquad (4)$$

Discussion

The results of our studies indicate that the anomalous chemical behavior of glycol **3** under conditions normally leading to halogenation of other alcohols is guided by both kinetic and thermodynamic factors imposed by the unique structure of **3**. Reagents appear to react much more rapidly at the less hindered hydroxymethyl group attached to C-3 than at the group at C-1. The effect of this disparity in hydroxyl group reactivity is often to produce reaction intermediates which possess good leaving groups close to a free, nucleophilic OH group. Kinetically favorable ring closure then leads to the thermodynamically accessible cyclic ether instead of the normal halogenated product.

These effects are particularly pronounced in the reaction of **3** with triphenylphosphine and carbon tetrachloride. The chlorination of alcohols with this reagent combination occurs by the sequence of reactions depicted in eq 5–7.[8]

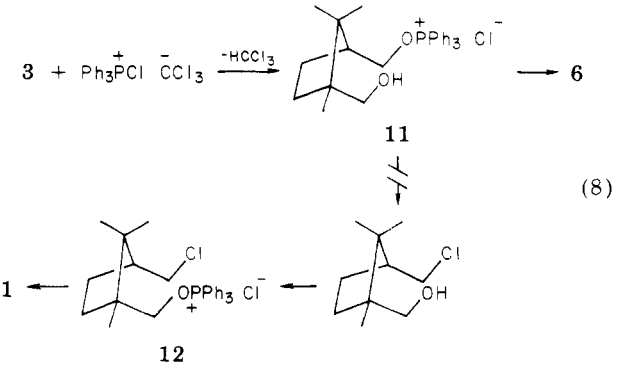
$$Ph_3P + CCl_4 \rightarrow Ph_3\overset{+}{P}Cl\ \overset{-}{C}Cl_3 \qquad (5)$$

$$Ph_3\overset{+}{P}Cl\ \overset{-}{C}Cl_3 + ROH \rightarrow \underset{\mathbf{10}}{RO\overset{+}{P}Ph_3}\ Cl^- + HCCl_3 \qquad (6)$$

$$\mathbf{10} \rightarrow RCl + Ph_3PO \qquad (7)$$

In the case of neopentyl alcohol, the buildup of intermediate **10** and its rate-determining decomposition to neopentyl chloride and triphenylphosphine oxide have been directly observed by NMR spectroscopy.[8]

The behavior of **3** under these conditions is consistent with the rapid intramolecular interception of intermediate **11** by the free proximate hydroxyl group to give **6** rather than displacement of triphenylphosphine oxide by chloride to give, eventually, **1** (eq 8). Apparently a reaction



(8)

pathway involving the sequential conversion of first the isobutyl-like and then the neopentyl-like hydroxyl groups to chlorides is not kinetically competitive. If it were, then one would expect not only to obtain dichloride **1** as final product but also to see the accumulation of its immediate precursor **12** as the reaction proceeded.[8]

The failure of the dimesylate **4** to form dichloride **1** upon treatment with lithium chloride in HMPA is not due to intramolecular cyclization. One is forced to conclude that in this system increased γ branching raises the reactivity difference at the two reaction sites above even the 10^3–10^4

(5) For a review of this method, see: Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801–11.
(6) Downie, I. M.; Holmes, J. B.; Lee, J. B. *Chem. Ind. (London)* **1966**, 900–1. Lee, J. B.; Nolan, T. J. *Can. J. Chem.* **1966**, *44*, 1331–4.
(7) Weiss, R. G.; Snyder, E. I. *J. Org. Chem.* **1971**, *36*, 403–6.
(8) Jones, L. A.; Sumner, C. E., Jr.; Franzus, B.; Huang, T. T.-S.; Snyder, E. I. *J. Org. Chem.* **1978**, *43*, 2821–7.
(9) As the reaction proceeded ($CDCl_3$), the OH signal originally at δ 1.75 shifted rapidly toward δ 6.8 and declined in intensity. Analogous observations have been reported with neopentyl alcohol.[8]
(10) BBr_3 rapidly cleaves aliphatic ethers to give, after hydrolysis, alcohols and alkyl bromides: Benton, F. L.; Dillon, T. E. *J. Am. Chem. Soc.* **1942**, *64*, 1128–9.

factor normally found for direct displacements at isobutyl vs. neopentyl positions.[11,12] It appears that the 1-[(mesyloxy)methyl] reaction site is so sterically shielded from external bimolecular displacements that rearrangement–elimination processes normally predominate under forcing conditions.[13]

The stereospecific ring opening of ether **6** to give bromo alcohol **8** with the exclusion of isomer **9** and the failure of **7** to yield dibromide **2** upon addition of hydrogen bromide are further demonstrations of the extreme reluctance of the sterically hindered primary center in this system to undergo direct displacement reactions. From this study, it is concluded that synthetic methods not dependent upon nucleophilic displacements should be sought for the bis halogenation of glycol **3**.

Experimental Section

General Methods. Proton nuclear magnetic resonance spectra were obtained on a Varian T-60A instrument using tetramethylsilane as an internal standard. A Varian CFT-20 spectrometer was used to obtain carbon-13 NMR spectra. Optical rotations were measured on samples in either 1.6 mm × 1 dm or 4.0 mm × 1 dm polarimeter tubes with a Rudolph Research Model 26202 automatic digital polarimeter. Infrared spectra were run by using either a Perkin-Elmer 137 or 621 spectrophotometer. Mass spectra were recorded on a Nuclide 12-90G mass spectrometer. Gas–liquid partition chromatographic analyses were conducted either on a Varian Aerograph 90-P instrument or on a Hewlett-Packard 5722A instrument equipped with an electronic integrating recorder. Melting points (Thomas-Hoover apparatus) and boiling points are uncorrected. Elemental analyses were performed by Spang Microanalytical Laboratories.

(+)-(1*R*,3*S*)-1,2,2-Trimethyl-1,3-bis(hydroxymethyl)cyclopentane (3). (+)-Camphoric acid, $[\alpha]^{24}_D$ +47.7° (*c* 10, EtOH), was reduced with lithium aluminum hydride to give glycol **3**:[14] mp 135.5–136.5 °C, $[\alpha]^{25}_D$ +63.81° (*c* 10, absolute EtOH) [lit.[15] mp 135–136 °C, $[\alpha]_D$ +61.25° ($CHCl_3$)]. The ^1H NMR spectrum was the same as that reported in the literature.[14] The ^{13}C NMR spectrum ($CDCl_3$) had signals at 18.65, 21.23, 24.81, 26.44, 34.71, 44.52, 49.66, 51.60, 64.54, and 68.84 ppm from Me_4Si.

Reaction of Glycol 3 with $ZnBr_2$/HBr. A mixture of 5 g (0.03 mol) of **2**, 13 g (0.06 mol) of $ZnBr_2$, and 7 mL of concentrated hydrobromic acid was placed in a 100-mL, three-necked flask fitted with a condenser and heated with magnetic stirring at 85 °C. At the end of 12 h, the heterogeneous reaction mixture was allowed to cool and was then extracted with pentane. The extract was washed first with water and then with saturated aqueous $NaHCO_3$ solution and dried (Na_2SO_4). Removal of the pentane followed by vacuum sublimation of the residue yielded 0.75 g of a white crystalline compound having a camphoraceous odor: mp 156–158 °C; $[\alpha]^{24}_D$ +26.37° (*c* 10, absolute EtOH). This compound was assigned the structure of (+)-(1*R*,5*S*)-1,8,8-trimethyl-3-oxabicyclo[3.2.1]octane (**6**) on the basis of its spectral characteristics: IR (CCl_4) 1150–1085 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.72 (s, 3 H), 0.88 (s, 3 H), 1.08 (s, 3 H), 1.37–2.0 (m, 5 H), 2.93–4.17 (8 br s, 4 H); ^{13}C NMR ($CDCl_3$) 15.1 (q), 18.0 (q), 24.6 (q), 25.8, 34.7, 41.2 (s), 43.4 (s), 46.6 (d), 69.2 (t), 74.4 (t) ppm from Me_4Si; mass spectrum (28 eV), *m/e* 154 (molecular ion).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.66. Found: C, 77.86; H, 11.66.

Reaction of Glycol 3 with Triphenylphosphine/Carbon Tetrachloride. Into a 300-mL, round-bottomed flask equipped with a magnetic stirring bar and reflux condenser fitted with a Drierite drying tube was placed a mixture of 15.0 g (87 mmol) of glycol **3** and 23.0 g (87 mmol) of triphenylphosphine (ROC/RIC) in 100 mL of carbon tetrachloride. The mixture was held at gentle reflux for 22.5 h. After the mixture cooled, 200 mL of pentane was added to the mixture, and the precipitated triphenylphosphine oxide was filtered off. The precipitate was then triturated with a total of 600 mL of pentane. The combined organic portions were concentrated in a rotary evaporator to yield 14.7 g of white solid. Sublimation of this solid [110 °C (20 torr)] produced 11.0 g (82%) of cyclic ether **6** which was pure by NMR and GLC (6.4 mm × 2 m column, 10% Apiezon L on 60/80 Chromosorb W, 180 °C) analyses. This reaction was rerun numerous times with either 1 or 2 equiv of triphenylphosphine and excess carbon tetrachloride with yields of **6** in the range 80–90%. The reaction was studied by ^1H NMR spectroscopy using $CDCl_3$ as the solvent, excess carbon tetrachloride, and 2 equiv of triphenylphosphine. The only spectral changes seen as the reaction progressed were those associated with the transition of **3** to **6** and of triphenylphosphine to triphenylphosphine oxide.[9]

Reaction of Ether 6 with BBr_3. To a solution of 0.26 g (1.7 mmol) of ether **6** in 8 mL of CH_2Cl_2 at −20 °C contained in a three-necked, 50-mL flask fitted with a condenser, dry-nitrogen inlet, magnetic stirring bar, and addition funnel was added dropwise a solution of 0.3 mL of BBr_3 (Alfa) in 5 mL of CH_2Cl_2. The resulting solution was allowed to warm to room temperature and was then held at reflux for 1.5 h. The solution was then stirred for 1.5 h at room temperature with 15 mL of 10% aqueous NaOH solution. The layers were separated, and the aqueous layer was extracted three times with small amounts of ether. The combined organic portions were washed once with saturated aqueous NaCl solution and dried (Na_2SO_4). Removal of the solvents by rotary evaporation left a pale yellow liquid which immediately began to crystallize upon standing. The solid was subjected to Kugelrohr distillation [50–60 °C (0.005 torr)] to yield 0.28 g (70%) of colorless crystals. Recrystallization twice from pentane yielded very white, fluffy crystals: mp 52–54 °C; $[\alpha]^{25}_D$ +68.01° (*c* 3.88, $CHCl_3$). This product gave an immediate white precipitate when added to an alcoholic solution of $AgNO_3$ and was identified as (+)-(1*R*,3*S*)-1,2,2-trimethyl-1-(hydroxymethyl)-3-(bromomethyl)cyclopentane (**8**) on the basis of its spectral properties: IR (between NaCl plates) 3590 (sh), 3300 (br), 2960, 2870, 1472, 1455, 1380, 1368, 1240, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.79 (s, 3 H), 1.03 (s, 6 H), 1.10–2.45 (m, 5 H), 2.25 (s, OH), 3.0–3.7 (overlapping multiplets, 4 H); ^{13}C NMR ($CDCl_3$) 18.0 (q), 20.6 (q), 23.5 (q), 27.8 (t), 33.0 (t), 36.2 (t), 45.4 (s), 48.9 (s), 51.0 (d), 69.2 (t) ppm from Me_4Si. Compound **8** was found to be stable for several weeks at −18 °C under nitrogen but suffered rapid decomposition at room temperature.

The course of the reaction between ether **6** and BBr_3 was followed in $CDCl_3$ solution by ^1H NMR spectroscopy. Addition of 30 mg (0.20 mmol) of **6** and 200 mg (0.80 mmol) of BBr_3 to 300 μL of $CDCl_3$ resulted in the total conversion of **6** into another species within 1 h at 30 °C. The product exhibited signals at δ 0.78 (s, 3 H), 1.02 (s, 6 H), 1.3–2.7 (m, 5 H), 2.9–3.7 (m, 2 H, CH_2Br), 4.13 (br s, 2 H, CH_2OB), consistent with the structure of 1,2,2-trimethyl-1-[[(dibromoboro)oxy]methyl]-3-(bromomethyl)cyclopentane (**7**). Addition of water to the solution immediately produced a spectrum identical with that of bromo alcohol **8**.

Base-Catalyzed Closure of 8 to 6. A solution of 86 mg (0.36 mmol) of bromo alcohol **8** in 6 mL of THF was placed in a three-necked flask equipped with a dry-nitrogen inlet and an addition funnel. Under a nitrogen atmosphere and with magnetic stirring, a solution of 0.396 mmol of LDA in 5 mL of THF was added dropwise. The resulting solution was stirred for 14 h before it was quenched with saturated aqueous NaCl solution and extracted three times with small portions of diethyl ether. The combined organic portion was dried (Na_2SO_4) and concentrated by rotary evaporation, and the residue was subjected to Kugelrohr distillation [60–90 °C (0.1 torr)]. There was obtained 50 mg of yellow liquid product. ^1H NMR and GLC (3.2 mm × 2 m 10% SE-30 column, 80–175 °C) analyses established that the predominant constituent of this product was cyclic ether **6**.

Registry No. **3**, 68510-42-9; **6**, 72777-11-8; **7**, 72726-98-8; **8**, 72726-99-9; (+)-camphoric acid, 124-83-4.

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(12) Ingold, C. K. *Q. Rev., Chem. Soc.* **1957**, *11*, 1–14.
(13) An exception to this is found in the reaction of **5** with 2 equiv of $KPPh_2$ to give the diphosphine CAMPHOS.[1-3]
(14) Johnson, T. H.; Klein, K. C. *J. Org. Chem.* **1979**, *44*, 461–2.
(15) Janczewski, M.; Bartnik, T. *Rocz. Chem.* **1962**, *36*, 1243.