Stereoselective Synthesis of Cyclic Ether Compounds *via* Reductive Cleavage of Bicyclic Ketals

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Bicyclic ketals in the 6,8-dioxabicyclo[3.2.1]octane system readily reacted with triethylsilane-boron trifluoride etherate at room temperature to give only the *cis*-tetrahydropyranol derivatives *via* C_5-O_6 bond cleavage. *Threo*- and *erythro*-alcohols were prepared selectively from the *endo*- and *exo*-ketal, respectively. Dehydrated products also formed when the tertiary alcohol was involved under these reaction conditions. However, the cleavage reaction with aluminum hydride gave the *trans*-tetrahydropyranol as the major product without dehydration.

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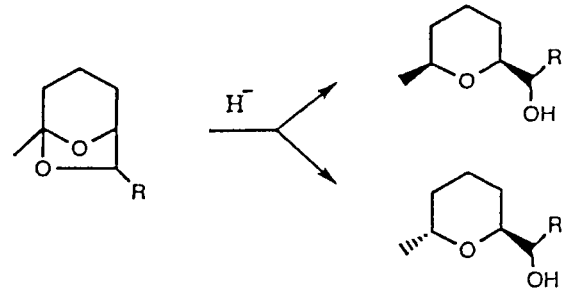
Aldehydes and ketones are usually protected from nucleophilic reagents, through formation of acetals and ketals which are one of the most useful functionalities in organic chemistry [1]. Acetals and ketals find application, for instance, in the protection of carbonyl groups (*e.g.* 1,3-dioxolanes), alcohols (*e.g.* 2-methoxyethoxymethyl ethers) and diols (*e.g.* isopropylidene ketals). As such, they represent a major component of the available protecting groups which can be used in the elaboration of complex or polyfunctional organic structures. The reductive cleavage of acetals and ketals to ethers is a synthetically useful method in asymmetric synthesis [2] and protective chemistry [3]. This protective group is normally stable towards various organometallic reagents, such as organolithium, Grignard or organocopper reagents [4]. On the other hand, organometallic reagents having a Lewis acid character are known to cleave them as well as some organoboron derivatives [5].

The most often used approach for the cleavage of acetals or ketals and the subsequent regeneration of the parent carbonyl compound involves treatment with acids or Lewis acids [1]. In some cases, the use of strong acids, depending on the stability or sensitivity of a given polyfunctional substrate to acidic media is a severe limiting factor. Until recently, a number of methods have been developed for this transformation involving various reagents such as lithium aluminum hydride-Lewis acids [6], trimethylsilane-trimethylsilyl trifluoromethanesulfonate [7], triethylsilane-acids [8], diisobutylaluminum hydride [9], sodium cyanoborohydride-hydrochloric acid [10], sodium borohydride-trifluoroacetic acid [11], and zinc borohydride-trimethylsilyl chloride [12]. We now wish to report a new synthetic route for cyclic ethers from bicyclic ketals.

In Scheme 1 is outlined the general concepts that led to the development of the present technology. In view of their ready availability and structural unambiguity, bicyclic ketals may be considered as one of the excellent potential precursors. Stereo-controlled reduction of bicyclic ketals was expected to generate specifically either a *cis*- or *trans*-cyclic ether depending on the choice of reagent.

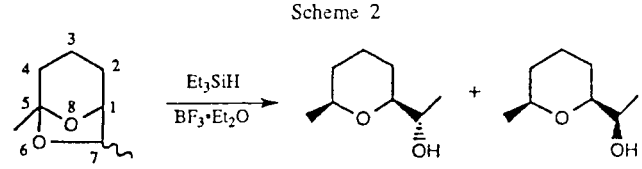
Scheme 1



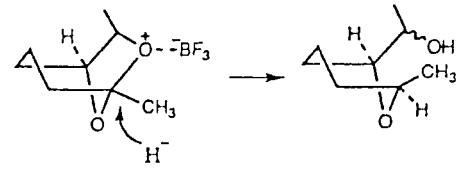
Results and Discussion.

The reductive cleavage of the carbon-oxygen bond of acetals and ketals can be accomplished by ionic hydrogenation, employing triethylsilane as the reducing agent and boron trifluoride etherate as the Lewis acid [13]. We applied this system to our bicyclic ketal in the 5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane (**1**) and obtained a high yield of C_5-O_6 bond cleavage to form alcohols (Scheme 2). The methyl ketal **1** (*endo:exo* = 40:60) gave only the

Scheme 2



1 **2** **3**



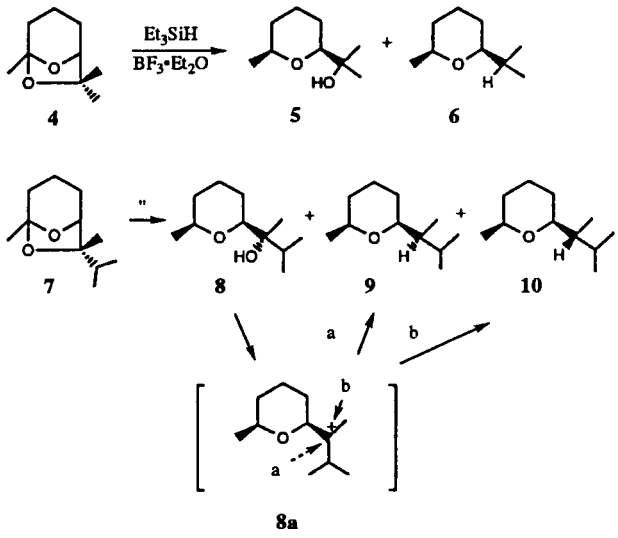
1a

cis-isomers as a 40:60 mixture of *threo*-alcohol **2** and *erythro*-alcohol **3** in 85% yield. These results indicate that the *threo*-alcohol **2** was obtained from the *endo*-ketal and the *erythro*-alcohol **3** from the *exo*-ketal. The formation of *cis* stereochemistry by this procedure is readily rationalized by considering an intermediate borane complex **1a** and S_N2 hydride displacement [14].

Brown's work on the hydrogenolysis of acetals and ketals by a mixture of lithium aluminum hydride and aluminum chloride in ether [15] has indicated that, as in the case for the hydrolysis of dioxabicyclooctanes, the rate controlling step of the hydrogenolysis reaction is the cleavage of the C_5-O_6 bond, weakened by the association of its oxygen atom with the Lewis acid. The association of O_6 with aluminum results in the hydride attacking C_5 from the opposite side of the complex rather than the hindered side.

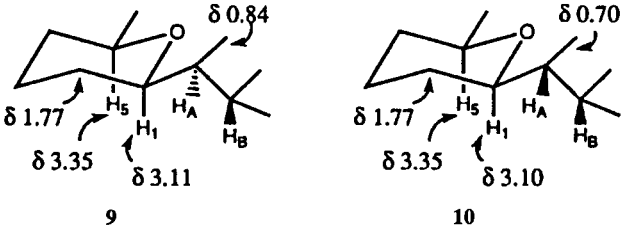
Other interesting results came from the cleavage of ketal **4** with triethylsilane, which gave the expected *cis*-alcohol **5** and the dehydrated product **6** in 21 and 45% yield, respectively (Scheme 3). Also, the *endo*-ketal **7** gave the expected *cis-threo*-alcohol **8** and dehydrated products **9** and **10** in 70, 11 and 13% yield, respectively. Again, this mechanism requires that boron trifluoride associates with O_6 and weaken the C_5-O_6 bond which is attacked by hydride from the opposite side of the complex to give *cis*-alcohol **8**. This was followed by loss of water and hydride attack of the carbonium ion **8a** by S_N1 which gave the dehydrated products **9** and **10**. The model of this compound indicates that the isopropyl group could not freely rotate because of steric bulkiness, which gives isomers **9** and **10**.

Scheme 3



The configurational assignments of **9** and **10** are based on the following (Scheme 4): (a) Isomers **9** and **10** should exist at room temperature as two rapidly equilibrating chair conformations, the two protons at C_1 and C_5 giving rise to an axial-equatorial time averaged signal in the proton nmr spectrum. Accordingly, the two axial methine protons of the *cis*-isomers resonate at higher field (3.10-3.35 ppm) than the corresponding protons of the *trans* isomers (4.01-4.12 ppm) [16]. The chemical shift of H_1 (3.11 and 3.10 ppm) and H_5 (3.35 ppm) for both isomers indicates the *cis*-stereochemistry. (b) To determine the configuration of the branched propane, irradiation of the methylene (C_2) protons at 1.77 ppm gave a doublet of the H_1 proton, which is coupled with H_A. Coupling constants obtained for **9** (7 Hz) and **10** (9.5 Hz), indicate 20° and 170° angles between H_1 proton and H_A, respectively. Irradiation of the methyl protons at 0.84 ppm of **9** gave a doublet of doublets for H_A, which coupled with H_1 and H_B and indicates a coupling constant of 10 Hz between H_A and H_B corresponding 180° angle. Also, irradiation of methyl protons at 0.70 ppm of **10** gave a doublet for H_A, which showed a 4 Hz coupling constant between H_A and H_B, corresponding to 45° between these two protons.

Scheme 4

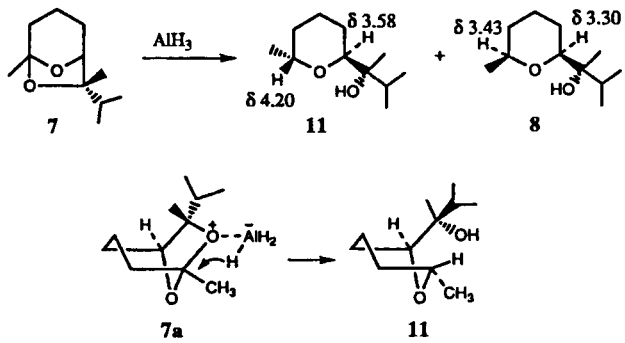


	H_{H1}-J_{HA}	J_{HA}-J_{HB}
9	7 Hz (20°)	10 Hz (180°)
10	9.5 Hz (170°)	4 Hz (45°)

When we used aluminum hydride, prepared by mixing an equimolar amount of lithium aluminum hydride and aluminum chloride in anhydrous ether solution for the reductive cleavage of *endo*-isopropyl bicyclic ketal **7**, we obtained an 83% yield of *trans-threo*-alcohol **11** and *cis-threo*-alcohol **8** in a 87:13 ratio (Scheme 5). The dehydrated products were not formed under these reaction conditions. The ^1H nmr spectrum of **8** shows the C_5 proton at 3.43 ppm while **11** shows the C_5 proton at 4.20 ppm. This indicates that **8** has an axial proton and **11** has an equatorial proton at C_5. The mechanism for the *trans*-alcohol can be explained by the intramolecular reduction through an intermediate like **7a** to result in the preferential formation of *trans*-product **11** [17].

In conclusion, the reductive cleavage of ketal derivatives by the use of triethylsilane-boron trifluoride etherate at room temperature gave only *cis*-tetrahydropyranol

Scheme 5



derivatives *via* C_5-O_6 bond cleavage through hydride attacks from the back side of the coordinated ketal oxygen. *Threo-* and *erythro*-alcohols were prepared selectively from *endo-* and *exo*-ketal, respectively. The tertiary alcohol formed under these reaction conditions could proceed further reaction to give dehydrated products. However, the cleavage reaction by using aluminum hydride gave the *trans*-tetrahydropyranol as a major product without dehydration.

EXPERIMENTAL

The nmr spectra were recorded on a Bruker 250 MHz FT-NMR, with the chemical shifts (δ) reported in parts per million (ppm) relative to TMS and the coupling constants (J) quoted in Hz. Deuteriochloroform was used as a solvent and an internal standard. Mass spectra were obtained using VG MM16 mass spectrometer and accurate mass data were obtained using a VG 7070 high resolution mass spectrometer. Analyses (glc) were performed using a Varian Aerograph series 2700 gas chromatograph equipped with a 11 ft x 1/4 in, 10% OV-17 column.

Materials.

Most of the chemicals used were purchased from Aldrich and were used without further purification unless noted otherwise. Bicyclic Ketals **1**, **4** and **7** were prepared from methyl vinyl ketone [18]. Flash chromatography was carried out using Merck 60 (230-400 mesh) silica gel. Thin-layer chromatography (tlc) was performed on DC-Plastikfolien 60, F_{254} (Merck, layer thickness 0.2 mm) plastic-backed silica gel plates with visualization by uv light (254 nm) or by treatment with *p*-anisaldehyde.

General Procedure for the Cleavage of Ketals by Using Triethylsilane-Boron Trifluoride Etherate.

Ten equivalents of triethylsilane (5.6 ml) and 10 equivalents of boron trifluoride etherate (4.3 ml) were added sequentially to 0.5 g (3.5 mmoles) of the bicyclic ketal **1** in 10 ml dry methylene chloride at 0° under nitrogen. After 24 hours stirring at room temperature, the reaction was quenched by adding 20 ml of saturated aqueous sodium bicarbonate. The reaction mixture was then extracted with several 30 ml portions of methylene chloride. The organic layers were combined, washed with brine, dried over anhydrous magnesium sulfate and evaporated *in vacuo* to give an oily residue. The residue was separated by column chromatography (ethyl acetate-hexane 3:7) to give pale yellow oils **2** and **3** in 34 and 51% yield, respectively.

Threo-1-(*cis*-6-methyltetrahydropyran-2-yl)ethanol (**2**).

This compound was obtained in 34% yield; ^{1}H nmr (deuteriochloroform): δ 3.54 (1H, m), 3.44 (1H, m), 3.05 (1H, m), 2.89 (1H, br s), 1.82 (2H, m), 1.65-1.41 (4H, m), 1.16 (3H, d, J = 6.3 Hz), 1.11 (3H, d, J = 6.4 Hz); ms: m/z 129 (M^+-15), 99, 81 (base), 71, 55, 43.

Anal. Calcd. for $C_8H_{16}O_2$ (114.11): C, 66.63; H, 11.18. Found: C, 66.51; H, 11.09.

Erythro-1-(*cis*-6-methyltetrahydropyran-2-yl)ethanol (**3**).

This compound was obtained in 51% yield; ^{1}H nmr (deuteriochloroform): δ 3.80 (1H, m), 3.45 (1H, m), 3.27 (1H, m), 2.15 (1H, br s), 1.83 (2H, m), 1.65-1.28 (4H, m), 1.14 (3H, d, J = 6.3 Hz), 1.11 (3H, d, J = 6.6 Hz); ms: m/z 129 (M^+-15), 99 (base), 81, 71, 55, 43.

Anal. Calcd. for $C_8H_{16}O_2$ (114.11): C, 66.63; H, 11.18. Found: C, 66.53; H, 11.08.

1-Methyl-1-(*cis*-6-methyltetrahydropyran-2-yl)ethanol (**5**).

This compound was obtained in 21% yield; ^{1}H nmr (deuteriochloroform): δ 3.44 (1H, m), 3.11 (1H, dd, J = 2, 11 Hz), 2.74 (1H, br s), 1.86-1.05 (6H, m), 1.15 (3H, s), 1.14 (3H, d, J = 6 Hz), 1.11 (3H, s); ms: m/z 158 (M^+), 143, 125, 99, 81 (base), 71, 59, 43.

Anal. Calcd. for $C_9H_{18}O_2$ (158.24): C, 68.31; H, 11.47. Found: C, 68.42; H, 11.39.

Cis-2-isopropyl-6-methyltetrahydropyran (**6**).

This compound was obtained in 45% yield; ^{1}H nmr (deuteriochloroform): δ 3.37 (1H, m), 2.93 (1H, m), 1.60 (1H, m), 1.82-1.05 (6H, m), 1.14 (3H, d, J = 6 Hz), 0.91 (3H, d, J = 6 Hz), 0.84 (3H, d, J = 6 Hz); ms: m/z 142 (M^+), 99 (base), 81, 73, 55, 43.

Anal. Calcd. for $C_9H_{18}O$ (142.24): C, 76.00; H, 12.76. Found: C, 75.91; H, 12.69.

1,2-Dimethyl-1-(*cis*-6-methyltetrahydropyran-2-yl)propanol (**8**).

This compound was obtained in 70% yield; ^{1}H nmr (deuteriochloroform): δ 3.43 (1H, m), 3.30 (1H, dd, J = 2, 11 Hz), 1.88 (1H, m), 1.87-1.28 (7H, m), 1.12 (3H, d, J = 6.3 Hz), 0.96 (3H, s), 0.90 (3H, d, J = 7 Hz), 0.87 (3H, d, J = 7 Hz); ms: m/z 186 (M^+), 171, 143, 125, 99, 87 (base), 81, 69, 55, 43.

Anal. Calcd. for $C_{11}H_{22}O_2$ (186.29): C, 70.92; H, 11.90. Found: C, 70.91; H, 11.93.

Erythro-1,2-Dimethyl-(*cis*-6-methyltetrahydropyran-2-yl) propane (**9**).

This compound was obtained in 11% yield; ^{1}H nmr (deuteriochloroform): δ 3.35 (1H, m), 3.11 (1H, m), 1.77 (2H, m), 1.70-1.35 (5H, m), 1.22 (1H, m), 1.12 (3H, d, J = 6.3 Hz), 0.88 (3H, d, J = 6.8 Hz), 0.84 (3H, d, J = 6.9 Hz), 0.76 (3H, d, J = 6.8 Hz); ms: m/z 99 (base, M^+-71), 81, 71, 66, 55, 43.

Anal. Calcd. for $C_{11}H_{22}O$ (170.29): C, 77.58; H, 13.02. Found: C, 77.64; H, 13.08.

Threo-1,2-Dimethyl-(*cis*-6-methyltetrahydropyran-2-yl)propane (**10**).

This compound was obtained in 13% yield; ^{1}H nmr (deuteriochloroform): δ 3.35 (1H, m), 3.10 (1H, m), 2.00 (1H, m), 1.84-1.45 (6H, m), 1.40 (1H, m), 1.14 (3H, d, J = 6.3 Hz), 0.86 (3H, d, J = 7 Hz), 0.75 (3H, d, J = 7 Hz), 0.70 (3H, d, J = 7 Hz); ms: m/z 170 (M^+), 110, 99 (base), 81, 71, 55, 43.

Anal. Calcd. for $C_{11}H_{22}O$ (170.29): C, 77.58; H, 13.02. Found: C, 77.63; H, 13.05.

1,2-Dimethyl-1-(*trans*-6-methyltetrahydropyran-2-yl)propanol (**11**).

To a gray suspension of 2 equivalents of aluminum chloride in 20 ml of anhydrous ether was added dropwise 0.5 equivalent of lithium aluminum hydride in 20 ml of anhydrous ether in an ice bath under nitrogen. Swirling with ether was repeated several times until all the hydride was added and the gray slurry was stirred for an hour. After this, 0.2 g (1.1 mmoles) of the ketal **7** in 10 ml ether was added at a rate sufficient for gentle refluxing. The mixture was refluxed for 3 hours. Excess hydride was destroyed by the dropwise addition of *ca.* 1 ml of water and 2*N* sulfuric acid was added carefully until no more reaction occurred in an ice bath. The ether layer was separated and the aqueous layer was extracted with ether three times. The combined ether solution was washed with water, brine, dried over anhydrous magnesium sulfate. Reduced in volume and column chromatograph (ethyl acetate-hexane 3:7) yielded 72% of **11** and 11% of **8** as pale yellow oils.

Compound **11** was obtained in 72% yield; ^{1}H nmr (deuteriochloroform): δ 4.20 (1H, m), 3.58 (1H, dd, J = 2.8, 11 Hz), 1.89 (1H, m, J = 7 Hz), 1.80-1.30 (7H, m), 1.23 (3H, d, J = 6.8 Hz), 0.92 (3H, s), 0.90 (3H, d, J = 7.9 Hz), 0.84 (3H, d, J = 6.9 Hz); ms: m/z 171 (M^+-15), 143, 125, 99, 87 (base), 81, 69, 55, 43.

Anal. Calcd. for $C_{11}H_{22}O_2$ (186.29): C, 70.92; H, 11.90. Found: C, 70.88; H, 11.79.

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