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STEREOSELECTIVE REDUCTION OF ACETALS. A METHOD FOR REDUCTIVE GENERATION OF HETEROCYCLIC RING SYSTEMS†

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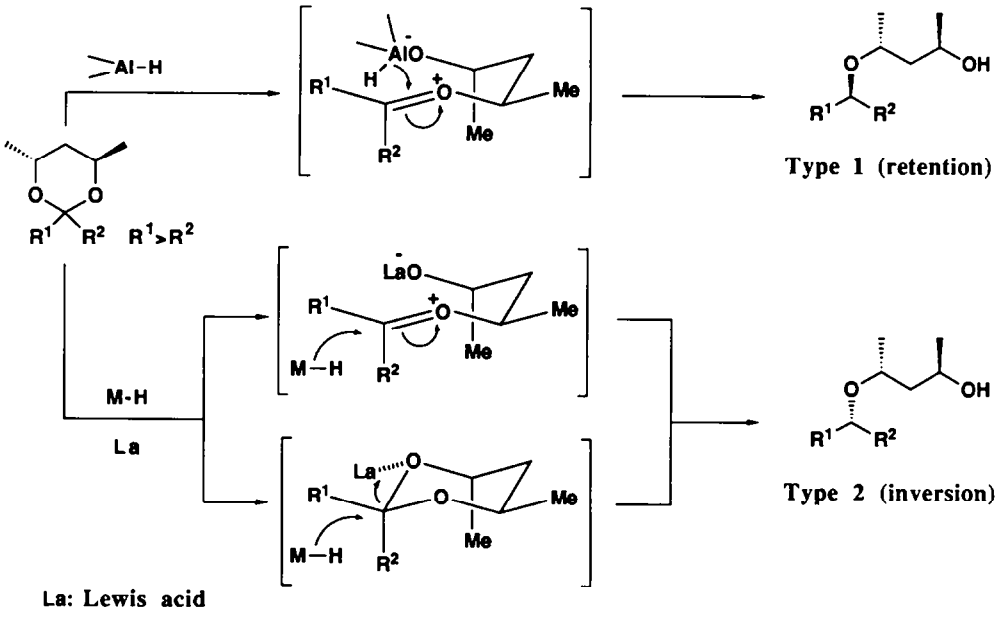
Abstract: A new synthetic process for the construction of oxygen-containing heterocyclic systems starting from bicyclic acetals is described. We have investigated the mechanism and the stereochemical course of the reductive cleavage of acetals.

Introduction

We previously described the diastereoselective cleavage of chiral acetals derived from the condensation of unsymmetrical ketones and (-)-(2*R*,4*R*)-2,4-pentanediol to give, after removal of chiral auxiliary, optically active alcohols with high enantiomeric purities.[1] The observed high stereoselective conversion of acetals to hydroxy ethers has been reported to follow the stereochemical course shown below (Scheme 1).

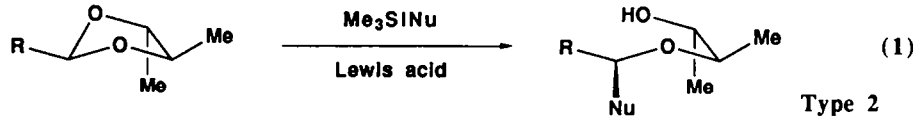
Reductive cleavage of acetals with organoaluminum hydride reagents affords stereoselectively *syn* reduced products. The observed high diastereoselectivity was ascribed to the stereospecific coordination of the organoaluminum reagent to one of the acetal oxygens followed by the hydride attack *syn* to the cleaved carbon-oxygen bond. This reaction probably proceeds by a tight ion paired S_N1 like mechanism (type 1). On the other hand, exposure of the acetal with a silane in the presence of Lewis acid gave an *anti* reduced product selectively *via* an invertive S_N2-type substitution on an intermediate Lewis acid complex or ion pair in which the breaking bond was attached to the sterically most accessible oxygen (type 2). We have developed a method to give both enantiomers from a single chiral starting acetal using these two reagent-systems.

†Dedicated to Professor W. David Ollis on the occasion of his 65th birthday.

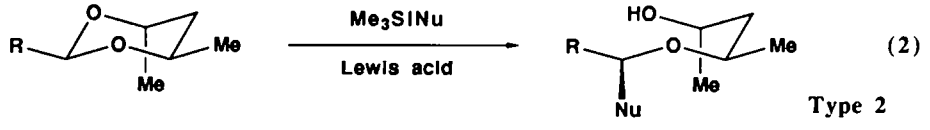


Scheme 1

Similar observations are reported by other groups:[2] Based on Johnson's landmark studies of acetal-initiated cationic polyolefin cyclizations,[3] both Kishi's group[4] and the Johnson and Bartlett group[5] reported remarkable levels of stereoselection in the Lewis acid promoted, opening of chiral acetals derived from optically active 2,3-butanediol and 2,4-pentanediol with silicon-containing nucleophiles (allylsilanes,[6] enol silanes,[7] cyanotrimethylsilane,[8] silylacetylenes[9]) (eqs 1 and 2). The rationale proposes that the reaction occurs through an invertive S_N2-type substitution (type 2).

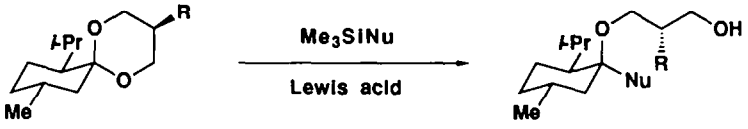


(1)



(2)

In contrast, Oku *et al.*[10] reported that the aldol type reaction of chiral acetal which was prepared from *l*-menthone and 2-substituted 1,3-propanediols promoted by titanium tetrachloride proceeds unambiguously with the selective cleavage of the equatorial carbon-oxygen bond followed by the attack of nucleophile with retention of conformation (type 1) (eq 3). Moreover, reduction of the same acetal with Et_3SiH in the presence of titanium tetrachloride also took place with similar stereoselectivity. Oku and his colleagues rationalize the stereoselectivity as follows: "Coordination of titanium tetrachloride with a less hindered equatorial oxygen may be preferred and, in a similar sense, the equatorial attack of a nucleophile on the positively charged sp^2-hybridized C(1) carbon of the menthone skeleton becomes highly preferable."[10]

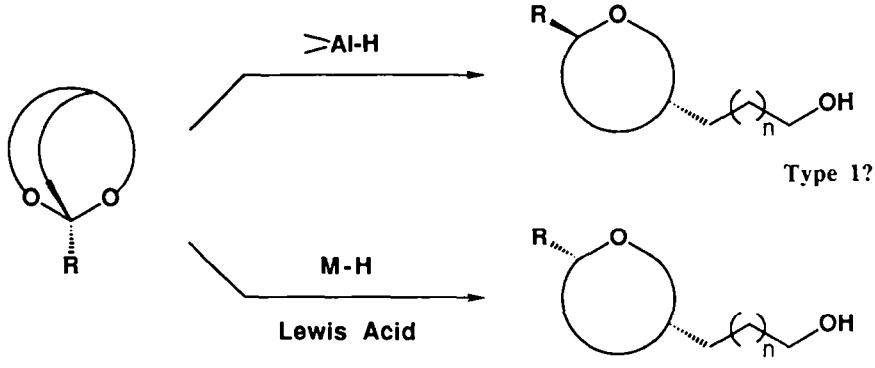


(3)

Type 1

In view of the growing interest in selective addition of nucleophiles to chiral acetal we have been investigating the detailed mechanism and stereochemical course of the reductive cleavage of acetals. The questions which have been the focus of our studies are as follows: (1) does the reaction *via* Lewis acid-metal hydride system proceed by an S_N1 (tight ion paired type)- or S_N2-like mechanism; (2) what factors (acetal structure, metal hydride, Lewis acid, and solvent) affect the mechanism of the reaction?

Scheme 2 outlines the general concept that led to the development of the present technology. In view of their ready availability and structural unambiguity, bicyclic acetals may be considered as an excellent potential precursors. Unfortunately, however, stereoselective reductive cleavage of the acetal group has never been developed to a useful level, while the most important aspects of diastereoselective reduction of the carbonyl group have already been assimilated by the chemical community. Nevertheless, stereocontrolled reduction of bicyclic acetals, if successful, is expected to generate specifically either a *cis* or *trans* cyclic ether depending on the choice of reagent.



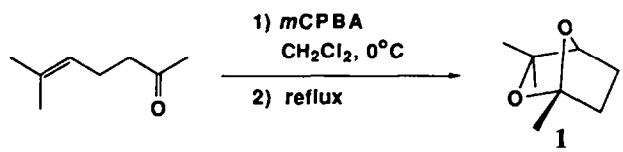
Scheme 2

In fact, oxygen containing heterocyclic ring frameworks are broadly distributed in nature and are of considerable interest as a key synthetic element of polyether antibiotics.[11] While a plethora of methods are now available for the synthesis of such ring systems,[11,12] technology for the stereospecific approach is still lacking. This paper describes promising results (Scheme 2) for effecting such transformations in a flexible way.[13]

Preparation of Bicyclic Acetal

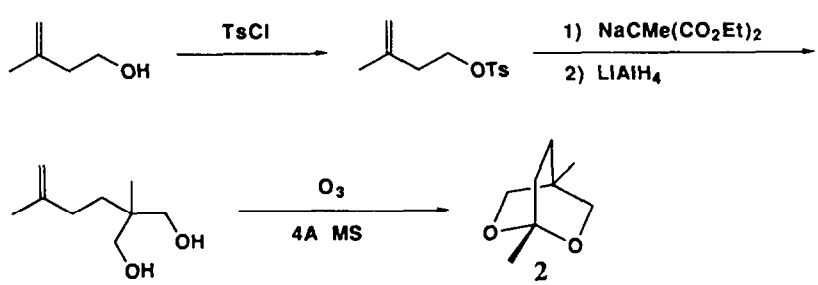
Bicyclic acetals have been well studied as a monomer of ring opening polymerization to give synthetic analogs of polysaccharides.[14] Four kinds of acetals used as starting materials of reductive cleavages were synthesized as shown below.

Preparation of 1,3,3-trimethyl-2,7-dioxabicyclo[2.2.1]heptane (1):[15] Oxidation of 2-methyl-2-hepten-6-one with *m*-chloroperoxybenzoic acid in dichloromethane at 0°C yielded the epoxyketone, which was refluxed in the presence of *m*-chlorobenzoic acid in dichloromethane to give the bicyclic acetal **1** in good yield (Scheme 3).



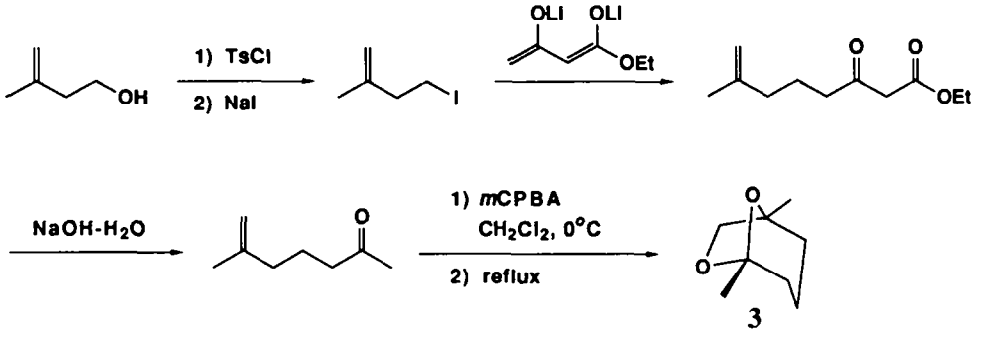
Scheme 3

Preparation of 1,4-dimethyl-2,6-dioxabicyclo[2.2.2]octane (2): Alkylation of diethyl methylmalonate anion with tosylate of 3-methyl-3-buten-1-ol followed by lithium aluminum hydride reduction afforded 2,5-dimethyl-2-hydroxymethyl-5-hexen-1-ol, which was treated with ozone in the presence of 4A molecular sieves to give **2** in good yield (Scheme 4).



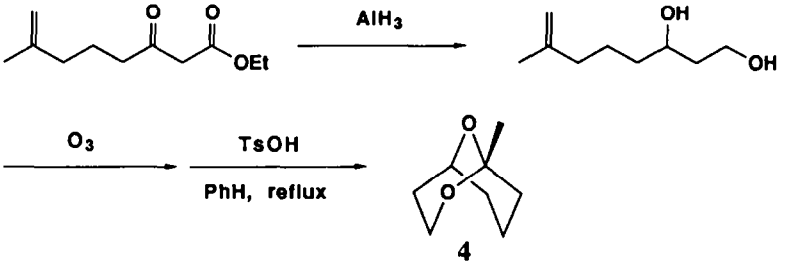
Scheme 4

Preparation of (±)-Frontalin (1,5-dimethyl-7,8-dioxabicyclo[3.2.1]octane) (3):[16] Alkylation of ethyl acetoacetate dianion with 4-iodo-2-methylbut-1-ene derived from 3-methyl-3-buten-1-ol followed by decarboxylation under a basic condition afforded 2-methyl-1-hepten-6-one, which was oxidated with *m*-chloroperoxybenzoic acid and refluxed in the presence of *m*-chlorobenzoic acid in dichloromethane to give **3** in good yield (Scheme 5).



Scheme 5

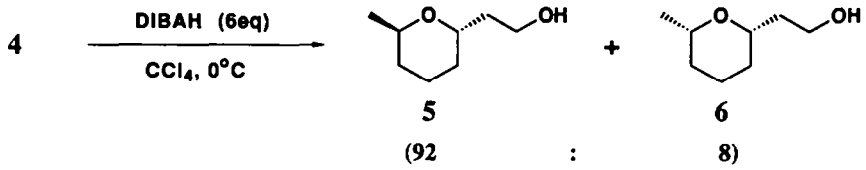
Preparation of 1-methyl-2,9-dioxabicyclo[3.3.1]nonane (4): Reduction of ethyl 7-methyl-3-oxo-7-octenate which was the intermediate of the synthesis of **3** with aluminum hydride afforded 7-methyl-7-octene-1, 3-diol, which was treated with ozone and refluxed in benzene with a catalytic amount of *p*-toluenesulfonic acid to give **4** (Scheme 6).



Scheme 6

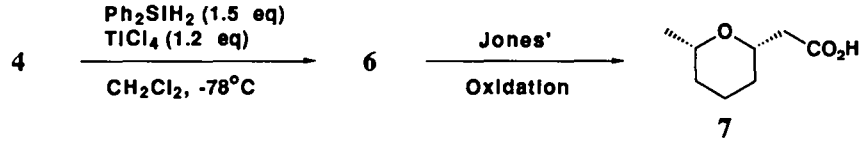
Results and Discussion

Reaction of a solution of bicyclic acetal **4** in carbon tetrachloride at 0°C with diisobutylaluminum hydride (DIBAH) for 1.5 h produced, after workup followed by short path column chromatography, the reduced alcohols (**5** and **6**) in 84% yield (Scheme 7). Analysis by gas chromatography (gc) of the products showed them to contain the *trans* and *cis* isomers in a ratio 92 : 8.



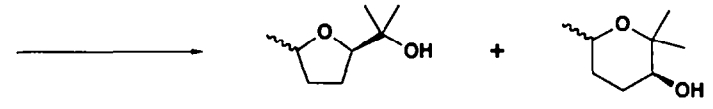
Scheme 7

Surprisingly, the reductive rupture of the same acetal with titanium tetrachloride in the presence of diphenylsilane followed a different stereochemical course. Thus, dropwise addition of titanium tetrachloride into a solution of acetal **4** and diphenylsilane at -78°C for 4 h afforded as major product (82% yield) the *cis* isomer **6**, the stereochemistry of which was determined by conversion (CrO_3) to the known carboxylic acid **7**, a constituent of civet[17](Scheme 8). Gc analysis of the alcohol which had been isolated simply by passage over silica gel showed >99% stereochemical purity.



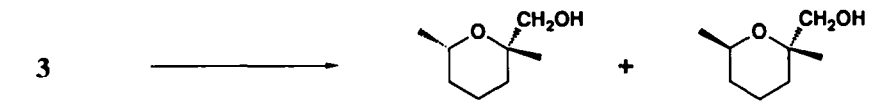
Scheme 8

To explore the generality and scope of this method in terms of ring size and substitution pattern, some bicyclic ethers were prepared and subjected to the described sequence leading to a series of substituted of oxocyclic systems in good to excellent yields (eqs 4 and 5).



(4)

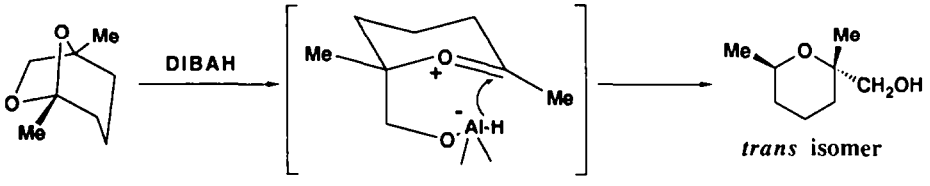
Condition	Yield (%)	*cis*	*trans*		*cis*	*trans*
DIBAH (6 eq) CH_2Cl_2, 0°C	61	0.6	55.5	:	2.1	41.8
Et_3SiH (1.5 eq) $TiCl_4$ (1.2 eq) CH_2Cl_2, -78°C	61	42.6	0.8	:	48.7	7.9



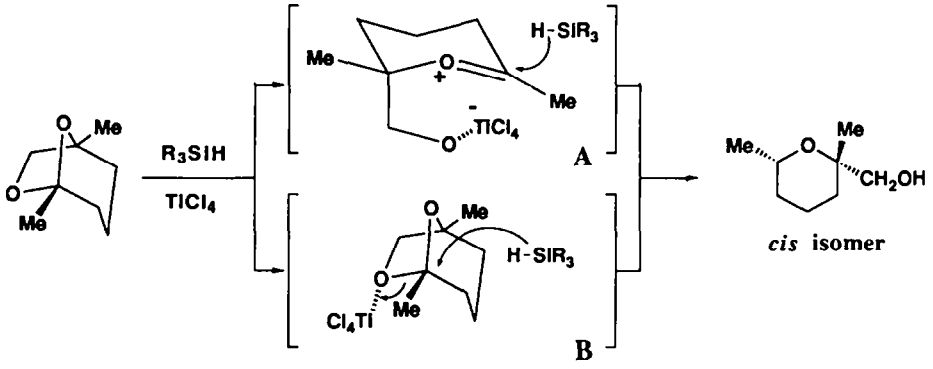
(5)

Conditioin	Yield (%)	*cis*		*trans*
DIBAH (6 eq) CH_2Cl_2, rt	82	3	:	97
Et_3SiH (1.5 eq) $TiCl_4$ (1.2 eq) CH_2Cl_2, -78°C	82	99	:	1
Ph_2SiH_2 (1.2 eq) $TiCl_4$ (1.2 eq) CH_2Cl_2, -78 ~ -21°C	76	93	:	7

Taking together the present and the previous results (for the reaction of chiral acetal derived from (-)-(2*R*,4*R*)-2,4-pentanediol), reduction of acetal with DIBAH in nonpolar solvent affords stereoselectively a *syn* reduced product. Most of the experimental data can be accommodated by Scheme 9. The key feature of the mechanism of DIBAH is the intermediacy of the ion paired species from which the *trans* isomeric product can be formed stereospecifically by rapid hydride attack from aluminum reagent to cationic center. On the other hand, exposure of the acetal with a silane in the presence of Lewis acid catalyst gave an *anti* reduced product selectively. The dramatic difference of these experimental results strongly suggests that aluminum reaction proceeds *via* an S_N1-type mechanism (Scheme 9), while the other cases of the titanium catalyzed process consist of a coupled attack on the acetal ring by an external electrophile ($TiCl_4$) and a nucleophile (R_3SiH), the overall results being *anti* attack on the tight ion paired intermediate (**A**) or S_N2 inversion (**B**) (Scheme 10).



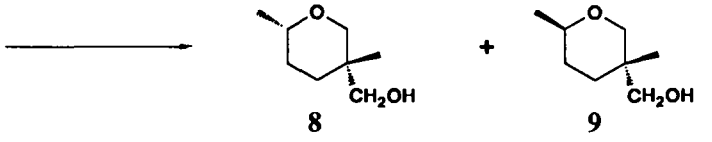
Scheme 9



Scheme 10

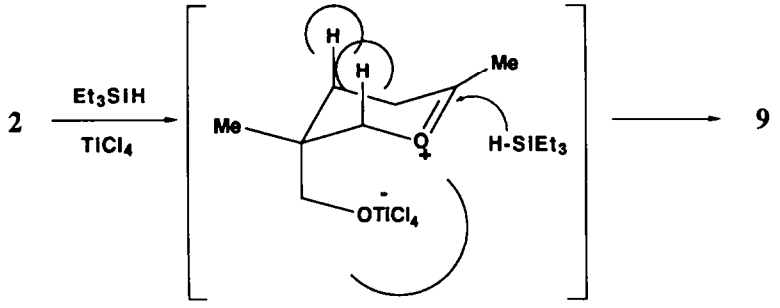
To further confirm the generality of these diverse selectivities, we next turned our attention to the symmetrical acetal **2**. The results (eq 6) were rather surprising and could not be explained as above. The usual selectivity of eq 6 may also be explained as Scheme 11, namely silane reagent should attack from the less hindered equatorial site for the cationic center (type 1).

We then examined the solvent effect on the stereochemical course of aluminum hydride reaction of bicyclic acetal **2**. In contrast with the result on the reductive cleavage of the acetal of (-)-(2*R*,4*R*)-2,4-pentanediol, the stereoselectivity was significantly affected by the nature of solvent. Table 1 summarizes the results.



(6)

Condition	Yield (%)	*cis*		*trans*
DIBAH (6 eq) CH_2Cl_2, rt	56	17	:	83
Et_3SiH (1.2 eq) $SnCl_4$ (1.2 eq) CH_2Cl_2, -78°C	72	24	:	76
Et_3SiH (1.2 eq) $TiCl_4$ (1.2 eq) CH_2Cl_2, -78°C	71	36	:	63



Scheme 11

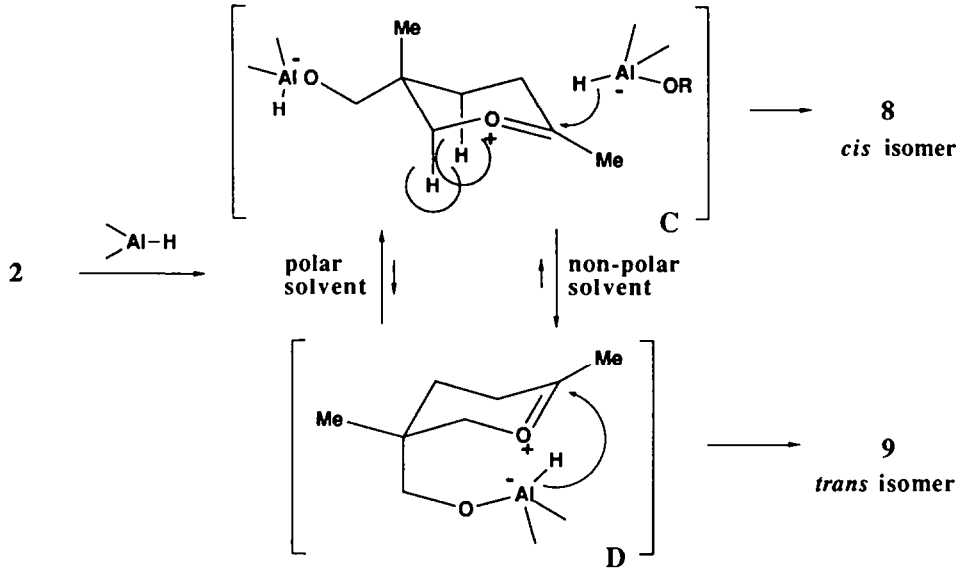
Table 1. Reductive Cleavage of 2 with Aluminum Hydride Reagents.

Reagent[a]	Solvent	Temp. (°C)	Time (h)	Yield (%)	Ratio[b] 8 : 9
DIBAH	$CHCl_3$	rt	20	36	8 : 92
DIBAH	CH_2Cl_2	rt	12	56	17 : 83
DIBAH	toluene	rt	20	38	17 : 83
DIBAH	CCl_4	rt	15	45	19 : 81
DIBAH	hexane	rt	20	33	44 : 56
DIBAH	ether	-20	3	81	79 : 21
DIBAH	THF	rt	15	51	82 : 18
Cl_2AlH	ether	-20	0.25	71	89 : 11
Br_2AlH	ether	-20	0.25	72	97 : 3

[a]6 equiv of aluminum reagent was used. [b]The ratio was determined by GC analysis.

The reactions in non-polar solvents such as toluene and dichloromethane gave the coresponding *trans* alcohol **9** *via* the syn attack of hydride, while, in polar solvents such as ether and THF the reaction afforded the *cis* alcohol **8** *via* the *anti* attack of hydride. By dibromoaluminum hydride in ether the selectivity of **8**

was increased dramatically (**8**/**9**=97:3). The reaction in hexane, however, gave almost no stereoselectivity. In order to explain the above results, we propose two kinds of ionic species, **C** and **D**, as intermediates (Scheme 12). Conformations of both **C** and **D** were drastically different from that of substrate **2** due to relief strain. The key feature of the mechanism of the reaction in non-polar solvents is the intermediacy of tight ion paired species **D** from which product **9** can be formed stereospecifically by rapid *syn* attack of hydride from aluminum reagent to cationic center. On the other hand, in the reaction in polar solvents the tight ion species **D** is in equilibrium with the relatively stably opened ionic species **C** from which product **8** can be formed stereospecifically by an *anti* attack of hydride. The low selectivity in hexane could not be examined by this simple mechanism probably due to the complex association of the aluminum reagent.



Scheme 12

We have not yet given any attention to the regioselectivity of the cleaved carbon-oxygen bond of bicyclic acetals. Figure 1 shows a view of each Lewis acid-bicyclic acetal complex in what appears to be the energetically favorable structure. Thus, the steric effect apparently influences the stabilities of Lewis acid-acetal complex, hence the relative ease of coordination of oxygen atom to Lewis acid; consequently, the least sterically congested of several possible structures would appear to be each one of these in Figure 1.

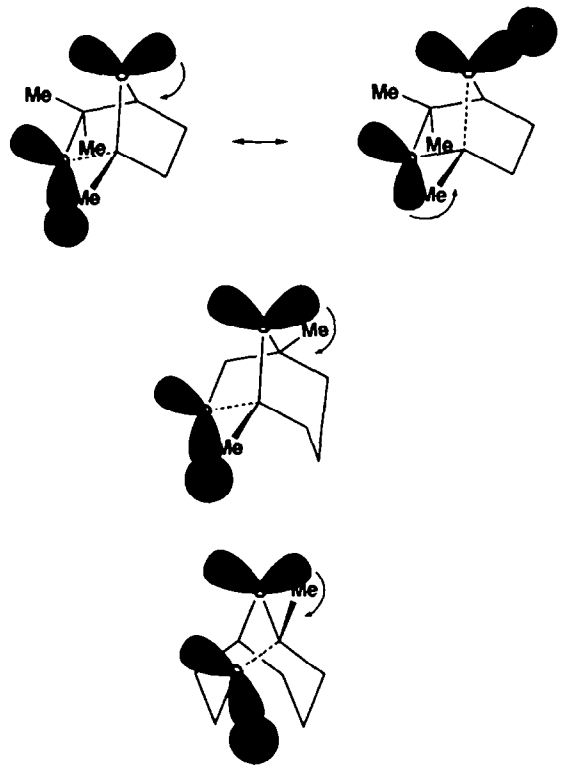


Figure 1

In summary, this study revealed that reductive cleavage of acetal may proceed *via* an S_N1-like mechanism. However, the reaction is heavily dependent on the structure of the acetal moiety. We also conclude that the relative stabilities and the steric conjugation of the intermediate oxonium ion may control the orientation of hydride attack.

Experimental Section

General. Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrometer. ^1H NMR spectra were mesured on a JNM-PMX-60 (60 MHz) or GX-270 (270 MHz) spectrometer. ^{13}C NMR spectra were determined on a FX-90Q (90 MHz) spectrometer. Chemical shifts of ^1H NMR are expressed in parts per million downfield relative to internal tetramethylsilane (δ=0) or chloroform (δ=7.26) and of ^{13}C NMR relative to chloroform-*d* (δ=77.1). Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q,

quartet; m, multiplet; br, broad peak. GC/MS spectra were determined on a JEOL D 300 mass spectrometer. Analytical gas-liquid phase chromatography (GLC) was performed on Simadzu Model 8A instrument with a flame-ionization detector and a capillary column of PEG-20M Bonded (25 m) using nitrogen as carrier gas. High-performance liquid chromatography (HPLC) was done with Shimadzu Model 6A liquid chromatograph. For thin layer chromatographic (TLC) analyses through this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used. The products were purified by preparative column chromatography on silica gel Fuji-Davison BW-300. Microanalyses were accomplished at the Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University. Reaction involving air- or moisture- sensitive compounds were conducted in appropriate round-bottomed flasks with magnetic stirring bars under an atmosphere of dry argon.

In experiments requiring dry solvents, ether, and tetrahydrofuran (THF) were dried over sodium metal. Dichloromethane was distilled from phosphorus pentoxide and stored over 4A molecular sieves. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification.

Preparation of Bicyclic Acetal

Preparation of 1,3,3-Trimethyl-2,7-dioxabicyclo[2.2.1]heptane (1).

To a solution of 2-methyl-2-hepten-6-one (7.4 mL, 50 mmol) in dichloromethane (100 mL) was added *m*-chloroperoxybenzoic acid (8.6 g, 50 mmol) at 0°C. Then the solution was stirred at 0°C for 1 h and then refluxed for 2 h. The solution was quenched with aqueous sodium bicarbonate and the organic layer was extracted with dichloromethane twice, dried over anhydrous sodium sulfate, concentrated *in vacuo*, and distilled to give **1** in 75% yield as a colorless oil: bp 48-53°C (25 torr); TLC, R_f=0.88 (Et_2O); IR (neat) 3000, 1400, 1160, 1150, 1000, 960, 880 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ 1.01 (s, 3H, $OCCH_3$), 1.17 (s, 3H, $OCCH_3$), 1.45 (s, 3H, O_2CCH_3), 1.30-2.28 (m, 4H, $(CH_2)_2$), 4.04 (d, J=4.2 Hz, 1H, OCH).

Preparation of 1,4-Dimethyl-2,6-dioxabicyclo[2.2.2]octane (2).

3-Methyl-3-buten-1-ol tosylate: To a mixture of 3-methyl-3-buten-1-ol (8.61 g, 100 mmol) and pyridine (9.49 g, 120 mmol) in 100 mL of dichloromethane was added *p*-toluenesulfonyl chloride (19.0 g, 100 mmol) at 0°C. The resulting mixture was stirred at room temperature for 12 h. The product was poured into 2 N HCl and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. Chromatography on silica gel (hexane-ether, 10:1-5:1) afforded 19.0 g of 3-methyl-3-buten-1-ol tosylate as a colorless liquid (79%). IR (film) 2950, 1600, 1360, 1175, 900 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ 1.70 (s, 3H, CH_3), 2.43 (s, 3H, CH_3Ar), 4.07 (t, J=6.4 Hz, 2H, CH_2O), 4.70 (br, 2H, CH_2=C).

2,5-Dimethyl-2-hydroxymethyl-5-hexen-1-ol: To a suspension of sodium hydride (oil free, 20.0 mmol) in THF was added ethyl methylmalonate (2.44 mL, 20.0 mmol) at 0°C. After stirring for 30 min, the tosylate (4.80 g, 20.0 mmol) was added and stirring was continued for 24 h under reflux. The product was poured into 2 N HCl and extracted with ether. Removal of the dried solvent left a crude which was treated with lithium aluminum hydride (1.52 g, 40.0 mmol) in 100 mL of THF under reflux for 24 h. After the excess LAH was destroyed by ethanol, the product was poured into 2 N HCl and extracted with

ether. The organic layers were dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give a crude oil. Purification by column chromatography on silica gel (hexane-ethyl acetate, 1:1) afforded a white solid (2.53 g, 80%). mp 53.8-54.5°C; IR (CCl_4, 60 MHz) 3100-3700 (br), 2920, 2870, 1550, 1120, 885 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ 0.80 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 3.40 (s, 4H, $2CH_2O$), 3.73 (brs, 2H, 2OH), 4.63 (brs, 2H, CH_2=C); Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 68.61; H, 11.17.

2: To a solution of the diol (1.58 g, 10.0 mmol) in dichloromethane and methanol (50 mL-50 mL) was babbled ozone for 1 h at -78°C. After the excess ozone was purged, was added methyl sulfide (1.68 mL, 25.0 mmol) and stirring was continued at room temperature for 24 h followed by treatment of 4A molecular sieves (3 g) for 24 h. After the removal of solvent, the product was purified by column chromatography on silica gel (hexane-ether, 1:1) to give **2** (1.03 g, 73%). TLC, R_f=0.72 (Et_2O); IR (film) 2930, 2860, 1450, 1390, 1155, 1055, 1020, 845 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ 0.73 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 3.63 (s, 4H, $2CH_2O$); MS, m/e=142.

Preparation of (±)-Frontalin (1,5-Dimethyl-7,8-dioxabicyclo[3.2.1]octane) (3).

4-Iodo-2-methylbut-1-ene: To a solution of 3-methyl-3-buten-1-ol tosylate (24 g, 0.10 mol) in acetone (300 mL) was added sodium iodide (30 g, 0.20 mol) at room temperature. Then the exothermic reaction took place, and the mixture was refluxed for 10 h. After being cooled to 0°C, the precipitated sodium toluene-*p*-sulfonate was filtered off and washed with hexane, and the solvents were evaporated. The residue was washed with excess of 10% sodium thiosulfate solution, and water, dried ($MgSO_4$), and purified by column chromatography to yield a light violet oil (7.8 g, 40% yield). TLC, R_f=0.70 (hexane-EtOAc, 5:2); ^1H NMR (CCl_4, 60 MHz) δ 1.73 (s, 3H, Me), 2.55 (t, 2H, CH_2I), 3.20 (t, 2H, CCH_2), 4.80 (d, 2H, CH_2=C).

Ethyl 7-methyl-3-oxo-7-octenate: To a solution of LDA (44 mmol) in THF (40 mL) was added dropwise ethyl acetoacetate (0.51 mL, 20 mmol) at 0°C and the solution was stirred at that temperature for 1 h. Then to the solution of the dianion of ethyl acetoacetate was added 4-iodo-2-methylbut-1-ene at 0°C. The reaction solution was stirred at room temperature for 2 h. The reaction was quenched with 2 N HCl aqueous solution. The organic layer was extracted with hexane twice, dried over sodium sulfate, and concentrated *in vacuo*. The crude product was given to ca. 80% yield. TLC, R_f=0.54 (hexane-EtOAc, 5:2).

Hydrolysis of Ethyl 7-Methyl-3-oxo-7-octenate and Decarboxylation of the Acid.

2-Methyl-1-hepten-6-one: A crude solution of ethyl 7-methyl-3-oxo-7-octenate (ca. 20 mmol) in 10 mL of 50% aqueous NaOH was refluxed for 2 h, then cooled, acidified with aqueous HCl, and extracted several times with Et_2O. The organic layer was dried over sodium sulfate, concentrated *in vacuo*, and purified by column chromatography to yield 1.7 g (ca. 70%) of 2-methyl-1-hepten-6-one.

Epoxidation of 2-Methyl-1-hepten-6-one and Cyclization to 3.

A solution of 1.26 g (10.0 mmol) of 2-methyl-1-hepten-6-one in 25 mL dry CH_2Cl_2 was cooled to 0°C and treated with 1.73 g (10.0 mmol) of *m*-chloroperoxybenzoic acid. The reaction mixture was stirred at room temperature for 12 h and then refluxed for 10 h. The solution was quenched with saturated $NaHCO_3$. The organic layer was extracted with dichloromethane. The extracts were combined and worked up to yield 725 mg (51%) of Frontalin **3** which was distilled (Kugelrohr) at 66°C/39 torr: TLC, R_f=0.52 (hexane-EtOAc=5:2); IR (neat) 2950, 1390, 1380, 1120, 1030, 850 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ 1.23 (s, 3H,

CH_3), 1.30 (s, 3H, CH_3), 1.27-1.90 (m, 6H, $(CH_2)_3$), 3.31 (d, J=7.2 Hz, 1H, CH_2O), 3.76 (d, J=7.2 Hz, 1H, CH_2O).

Preparation of 1-Methyl-2,9-dioxabicyclo[3.3.1]nonane (4).

7-Methyl-7-octene-1,3-diol: To the AlH_3 (0.25 mol) solution in ether (180 mL), prepared from lithium aluminum hydride (7.1 g, 0.19 mol) and aluminum chloride (8.3 g, 0.63 mol) in Et_2O (20 mL) at 0°C for 19 min. The reaction solution was stirred at 0°C for 8 min. Then the solution was stirred at room temperature for 3 h. The reaction mixture was quenched with water (8 mL), aqueous 2 N NaOH (14 mL), and water (16 mL). The alumina precipitate was removed by filtration, and organic layer was concentrated at reduced pressure. The product was purified by column chromatography to yield 7-methyl-7-octene-1,3-diol (8.1 g, 64%). TLC, R_f=0.2 (Et_2O).

Cyclization of 7-Methyl-7-octene-1,3-diol.

To a solution of 7-methyl-7-octene-1,3-diol (7.9 g, 50 mmol) in dichloromethane and methanol (100 mL-100 mL) was babbled ozone for 2 h at -78°C. After the removal solvent, the product was solved by benzene (200 mL) and to the solution was added toluene-*p*-sulfonate (50 mg) and 4A molecular sieves (20 g). The solution was refluxed for 11 h. The product was poured into aqueous sodium bicarbonate and extracted with hexane. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by distillation with a Kugelrohr apparatus (95°C, 25 torr) to give a clear colorless liquid **4** (ca. 20%): TLC, R_f=0.47 (hexane-EtOAc, 5:2); IR (neat) 2950, 1460, 1445, 1380, 1240, 1155, 1100, 1075 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ 1.00 (s, 3H, CH_3), 1.00-2.47 (m, 8H, $4CH_2$), 3.64 (d, J=4.2 Hz, 1H, CH_2O), 3.77 (d, J=4.2 Hz, 1H, CH_2O), 3.93-4.40 (m, 1H, CHO); Anal. Calcd for $C_8H_{14}O_2$: C, 67.56; H, 9.94. Found: C, 67.30; H, 10.29.

General Procedure A and B for the Reductive Cleavage of Bicyclic Acetal.

Reduction of Acetal 4 using Diisobutylaluminum hydride (DIBAH) (A).

To a solution acetal **4** (142 mg, 1.00 mmol) in carbon tetrachloride (6 mL) was added DIBAH (6.0 mL of an 1.0 M hexane solution) at 0°C. After being stirred for 1.5 h, the mixture was poured into ice cold dilute hydrochloric acid and the product was extracted with ether. Removal of the dried solvent left a crude oil which was purified by column chromatography on silica gel (hexane-EtOAc, 5:1) to afforded 2-(6-methyltetrahydropyran-2-yl)ethanol as an oil (yield 84%). The diastereomeric ratio was determined by glc (**5**/**6**=92:8).

***cis* Isomer (6)**: Glc (100°C), t_R=12.2 min; TLC, R_f=0.18 (hexane-EtOAc, 5:2); IR (neat) 3500 (br), 2950, 1085 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.15 (d, J=6.6 Hz, 3H, CH_3), 0.57-2.33 (m, 8H, $4CH_2$), 3.12 (br, 1H, OH), 3.12-4.16 (m, 2H, 2CHO), 3.76 (t, J=6.0 Hz, 2H, CH_2OH).

***trans* Isomer (5)**: Glc (100°C), t_R=20.3 min; TLC, R_f=0.10 (hexane-EtOAc, 5:2); IR (CCl_4) 3400 (br), 2950, 1450, 1380, 1210, 1060, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.20 (d,J=6.0 Hz, 3H, CH_3), 0.68-2.32 (m, 8H, $4CH_2$), 3.08 (br, 1H, OH), 3.73 (t, J=5.4 Hz, 2H, CH_2O), 3.50-4.33 (m, 2H, 2CHO).

Reduction of Acetal 4 using Ph_2SiH_2-$TiCl_4$ (B).

To a solution of the acetal **4** (1.00 mmol, 142 mg) in 6 mL of dichloromethane was added diphenylsilane (1.50 mmol, 0.278 mL) at -78°C. After that, titanium tetrachloride (1.2 mmol, 0.6 mL of 1.0 M dichloromethane solution) was added dropwise and stirring was for 15 min. The product was poured into 2 N hydrochloric acid and extracted with ether twice. The combined organic layers were dried over anhydrous sodium sulfate, concentrated *in vacuo* and purified by column chromatography on silica gel (hexcane-EtOAc, 5:1) to give 2-(*cis*-6-methyltetrahydropyran-2-yl)ethanol (**6**) in 82% yield as a colorless oil. The diastereomeric ratio was determined by glc (**5/6**=<1:99).

Reductive cleavage of the other acetals was carried out in the similar manners. The physical properties and analytical data of the alcohols thus obtained are listed below.

***cis*-2-(2-Hydroxy-2-propyl)-5-methyltetrahydrofuran**: Glc (80°C), t_R=5.69 min; TLC, R_f=0.26 (hexane-EtOAc, 5:2); ^{1}H NMR (CCl_4, 60 MHz) δ 1.03 (s, 3H, $HOCH_3$), 1.13 (s, 3H, $HOCCH_3$), 1.19 (d, J=6.6 Hz, 3H, $OCHCH_3$), 1.48-2.22 (m, 5H, $2CH_2$ and OH), 3.54 (t, J=7.2 Hz, 1H, C(2)H), 3.70-4.22 (m, 1H, C(5)H).

***trans*-2-(2-Hydroxy-2-propyl)-5-methyltetrahydrofuran**: Glc (80°C), t_R=6.84 min; TLC, R_f=0.26 (hexane-EtOAc, 5:2); IR (CCl_4, 60 MHz) 3450 (br, OH), 2980, 1390, 1090 cm^{-1}; ^{1}H NMR (CCl_4, 60 MHz) δ 1.03 (s, 3H, $OCHCH_3$), 1.37-2.20 (m, 4H, $2CH_2$), 3.50 (br, 1H, OH), 3.70 (t, J=7.2 Hz, 1H, C(2)H), 3.72-4.32 (m, 1H, C(5)H).

***cis*-3-Hydroxy-2,2,6-trimethyltetrahydropyran**: Glc (80°C), t_R=13.6 min; TLC, R_f=0.16 (hexane-EtOAc, 5:2); IR (CCl_4) 3450 (br, OH), 2940, 1450, 1385, 1080 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.13 (d, J=6.0 Hz, 3H, $CHCH_3$), 1.25 (s, 6H, $C(CH_3)$), 1.33-2.33 (m, 5H, $(CH_2)_2$ and OH), 3.35 (t, J=3.0 Hz, 1H, CHOH), 3.47-4.08 (m, 1H, CHO).

***trans*-3-Hydroxy-2,2,6-trimethyltetrahydropyran**: Glc (80°C), t_R=25.7 min; TLC, R_f=0.23 (hexane-EtOAc, 5:2); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.12 (d, J=6.0 Hz, 3H, $CHCH_3$), 1.17 (s, 3H, CCH_3), 1.27 (s, 3H, CCH_3), 140-2.02 (m, 4H, $(CH_2)_2$), 2.17 (s, 1H, OH), 3.39 (dd, J=4.2 and 9.0 Hz, 1H and HOCH), 3.43-3.95 (m, 1H, CHO); IR (neat) 3820 (br, OH), 2990, 2940, 2880, 1455, 1380, 1360, 1085, 1075, 975 cm^{-1}.

***cis*-2,5-Dimethyl-5-hydroxymethyltetrahydropyran (8)**: Glc (120°C), t_R=7.56 min; TLC, R_f=0.50 (Et_2O); IR (CCl_4) 3050-3650 (br), 2910, 2840, 1440, 1020, 850 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.80 (s, 3H, CH_3), 1.18 (d, J=6.5 Hz, 3H,CH_3), 1.29-1.88 (m, 2H, $C(3)H_2$), 1.64 (br, 1H, OH), 1.64-1.80 (m, 2H, $C(4)H_2$), 3.18 (d, J=13.5 Hz, 1H, CH_2OH), 3.31-3.44 (m, 1H, $C(6)H_2$), 3.78 (dd, J=13.5 and 1.8 Hz, 1H, CH_2OH); Anal. Calcd for $C_8H_{10}O_2$: C, 66.63; H, 11.18. Found: C, 66.62; H, 11.19.

***trans*-2,5-Dimethyl-5-hydroxymetyltetrahydropyran (9)**: Glc (120°C), t_R=10.9 min; TLC, R_f=0.50 (Et_2O); ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.05 (s, 3H, CH_3), 1.20 (d, J=6.6 Hz, 3H, CH_3).

***cis*-2,6-Dimethyl-5-hydroxymethyltetrahydropyran**: Glc (80°C), t_R=9.23 min, TLC, R_f=0.28 (hexane-EtOAc, 5:2); IR (neat) 3455 (br, OH), 3000, 2955, 2890, 1380, 1090, 1050 cm^{-1}; ^{1}H NMR (CCl_4, 60 MHz) δ 1.07 (d, J=6.0 Hz, 3H, $CHCH_3$), 1.12 (s, 3H, CCH_3), 1.12-1.85 (m, 6H, $(CH_2)_3$), 1.97 (br, 1H, OH), 3.22 (br, 2H, CH_2OH), 3.28-3.95 (m, 1H, CHO); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 17.4, 18.9, 21.9, 19.7, 33.1, 66.0, 71.0, 73.7.

***trans*-2,6-Dimethyl-2-hydroxymethyltetrahydropyran**: Glc (80°C), t_R=9.23 min; TLC, R_f=0.28 (hexane-EtOAc, 5:2); IR (neat) 3440 (br, OH), 2990, 2940, 2890, 1440, 1380, 1080, 1040 cm^{-1};

^{1}H NMR (CCl_4, 60 MHz) δ 1.08 (d, *J*=6.0 Hz, 3H, $CHCH_3$), 1.10 (s, 3H, CCH_3), 1.20-1.88 (m, 7H, $(CH_2)_3$ and OH), 3.09 (d, *J*=10.8 Hz, 1H, CH_2OH), 3.79 (d, *J*=10.8 Hz, 1H, CH_2OH), 3.28-3.80 (m, 1H, CHO); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 19.8, 22.6, 26.8, 32.1, 32.8, 62.9, 66.9, 73.6.

The Structural Assignment for 2-(6-Methyltetrahydropyran-2-yl)ethanol. (*cis*-6-Methyltetrahydropyran-2-yl)acetic acid (a constituent of civet) (7).

To a solution of **6** (115 mg, 0.800 mmol) in acetone (3 mL) was added the chromic acid oxidizing reagent persisted for 1 min. The mixture solution was stirred for 10 h. Isopropyl alcohol (1 mL) was added to the acetone solution until the excess chromic acid was destroyed. The solution was neutralized with saturated aqueous sodium bicarbonate and the suspension was filtered. After evaporation of acetone, saturated brine solution was added, and the mixture was extracted with ether repeatedly. The separated organic layers were concentrated *in vacuo* and chromatography on silica gel (hexane-EtOAc, 2:1) furnished **7** in 85% yield as a white crystalline solid: mp 51-52.5°C after recrystallization from pentane (lit.[18] mp 52-53°C); TLC, R_f=0.39 (Et_2O); IR (CCl_4) 3450 (br, OH), 2930, 1710 (C=O), 1070 cm^{-1}; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.17 (d, *J*=6.6 Hz, 3H, CH_3), 0.79-2.00 (m, 6H, $(CH_2)_3$), 2.52 (ab part of abx system with δ_a 2.67 ppm and δ_b 2.36 ppm, J_{ab}=15.6 Hz, J_{ax}=6.6 Hz, J_{bx}=6.0 Hz, 2H, CH_2CO_2), 3.22-4.04 (m, 2H, 2CHO), 10.67 (br, 1H, OH). These spectral data are identical with those reported in the literature.[18]

(*trans*-6-Methyltetrahydropyan-2-yl)acetic acid: In a similar experiment, 2-(*trans*-6-methyltetrahydropyran-2-yl)ethanol was oxidated to (trans-6-methyltetrahydropyran-2-yl)acetic acid in 79% yield as a colorless oil: TLC, R_f=0.39 (Et_2O); IR (neat) 3050 (br, OH), 2940, 1710 (C=O), 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 0.81-1.98 (m, 6H, $(CH_2)_3$), 1.21 (d, *J*=6.6 Hz, 3H, CH_3), 2.57 (ab part of abx system with δ_a 2.41 ppm and δ_b 2.74 ppm, J_{ab}=20.1 Hz, J_{ax}=6.0 Hz, J_{bx}=7.8 Hz, 2H, CH_2COO), 3.65-4.51 (m, 2H, CHO), 9.80 (br, 1H, OH).

The Structural Assignment for 2-(2-Hydroxy-2-propyl)-5-methyltetrahydrofuran.

The structural assignment was based on the comparison with the authentic *cis* isomer which was prepared by the hydrogenation of 2-acetyl-5-methylfuran over a rhodium on charcoal catalyst,[19] followed by the treatment with methyl lithium.

Preparation of the Authentic *cis*-2-(2-Hydroxy-2-propyl)-5-methyltetrahydrofuran.

2-Acetyl-5-methylfuran (1.16 mL, 10.0 mmol) in ethyl acetate (50 mL) was hydrogenated over 100 mg of rhodium on charcoal for 24 h. After the catalyst was filtrated, removal of the solvent left a colorless oil. The residual oil was purified by column chromatography on silica gel to afford *cis*-2-acetyl-5-methyltetrahydrofuran (280 mg, 22%) and *cis*-2-(1-hydroxyethyl)-5-methyltetrahydrofuran (296 mg, 23%) respectively; *cis*-2-acetyl-5-methyltetrahydrofuran: TLC, R_f=0.34 (hexane-EtOAc, 5:2); ^{1}H NMR (CCl_4, 60 MHz) δ 1.25 (d, *J*=6.0 Hz, 3H, CH_3), 2.12 (s, 3H, CH_3), 1.1-2.3 (m, 4H, $(CH_2)_2$), 3.73-4.33 (m, 2H, CHOCH).

To a solution of *cis*-2-acetyl-5-methyltetrahydrofuran (2.20 mmol, 280 mg) in THF (6 mL) was added dropwise methyl lithum (2.3 mmol, 1.6 mL of 1.4 M solution in Et_2O) at -78°C, and the reaction mixture was stirred for 15 min at that temperature. The solution was allowed to room temperature and was stirred for 3 h. The reaction was quenched with brine solution. The organic layers were extracted with ether twice, dried (Na_2SO_4) and filtered. Removal of solvent *in vacuo* gave a crude oil which was purified by column

chromatography on silica gel to afford 2-(2-hydroxy-2-propyl)-5-methyltetrahydrofuran as a colorless oil (yield 88%). The diastereomeric ratio of the products was determined by glc (*trans/cis*=8:92).

The Structural Assignment for 3-Hydroxy-2,2,6-trimethyltetrahydropyran.

The structural assignment was based on the comparison with the spectral values reported in the literature.[20]

The Structural Assignment for 2,5-Dimethyl-5-hydroxymethyltetrahydropyran.

The *cis* isomer (8): δ 0.80 (s, 3H, equatorial CH_3) ppm; **the *trans* isomer (9)**: δ 1.05 (s, 3H, axial CH_3) ppm. The structural assignments for each products were based on the comparison with the reported homologus alcohols:[21] 2-isopropyl-5-hydroxymethyl-5-methyl-1,3-dioxane; the *cis* isomer δ 0.72 (equatorial CH_3) ppm; the *trans* isomer δ 1.16 (axial CH_3) ppm.

The structural Assignment for 2,6-Dimethyl-2-hydroxymethyltetrahydropyran.

The structural assignments for each products were by examination of chemical shifts for the hydroxyethyl carbon and two methyl carbons: the *cis* isomer δ 71.0 (equatorial CH_2OH), 17.4 and 21.9 ($2CH_3$) ppm; the *trans* isomer δ 62.9 (axial CH_2OH), 22.6 and 22.8 ($2CH_3$) ppm. These spectral deta were compared with those reported in the literature.[22]

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