STUDIES ON STEREOSELECTIVE REACTIONS OF ACETALS

KAZUAKI ISHIHARA

アセタールを用いた立体選択的反応の研究

石原一彰

報告番号	甲 第 2442 号

Dedicated to my wife Chise Ishihara
this thesis in token of affection and gratitude.

CONTENTS

Chapter 1

Introduction and General Summary

1. Introduction

Acetals and *ketals* are important functional groups that find use in the preparation of novel heterocyclic compounds, in polymers, and in the protection of carbonyl compounds or alcohols. *Acetals* and *ketals* are stable under basic conditions but hydrolyze easily under acidic conditions to the starting carbonyl compound and alcohol. Notice the structural features that define *acetals* and *ketals*. In place of the carbonyl group of the aldehyde or ketone from which they are formed, *acetals* and *ketals* have a tetrahedral carbon to which two ether groups are attached.

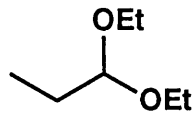
Acetals and *ketals* are similar in both structure and mechanism of formation. Whenever we refer to properties, like mechanism, that are shared by both these derivatives, we shall refer to them collectively as acetals.

Acetal (new): *Acetal* (old) or *ketal* (old).

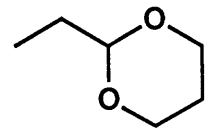
Acetal (old): A composite functional group in which two ether functions are joined to a carbon bearing a hydrogen and an alkyl group.

Ketal (old): A composite functional group in which two ether functions are joined to a carbon bearing two alkyl groups.

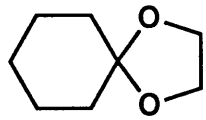
The *Chemical Abstracts* nomenclature is used for most of the acetals described in this thesis. The compounds are named either as dialkoxy derivatives or as derivatives of acetals. Examples are shown below:



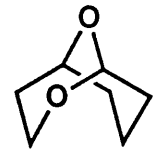
1,1-Diethoxypropane or
Propionaldehyde diethyl acetal



2-Ethyl-1,3-dioxane



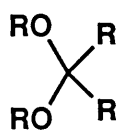
1,4-Dioxaspiro[4.5]decane



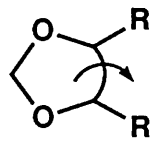
2,9-Dioxabicyclo[3.3.1]nonane

The principal reactions and properties of acetals are summarized in Scheme 1. Acetals can undergo most of the functional group reactions on their side chains as long as those reactions are carried out under neutral or basic conditions. The inertness of acetals, like ethers, under these conditions has important consequences. Nature uses acetals to protect biologically important aldehydes and ketones from unwanted reactions. The synthetic chemist finds a similar use of acetals as protective groups for carbonyl groups or for hydroxy groups (**A**). For instance, under certain conditions they do not react with Grignard reagents. An acetal is a reversibly "hidden" carbonyl compound. Acetal derivatives are also utilized to protect two OH groups of 1,2- or 1,3-diol in a rigid form with restricted rotation around the bonds between the OH substituted carbons (**B**). The more stable conformer of acetal can be prepared under equilibrating conditions (thermodynamic control), in which steric or stereoelectronic effects play a major role for the

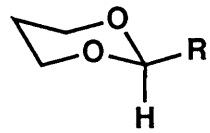
stability of the conformers (**C** and **D**). Under acidic conditions, acetals are reactive centers of molecules: (1) in the presence of Lewis acids they are amenable to nucleophilic substitution (**E**); (2) they are precursors to enol derivatives (**F**), and (3) the leaving group ability of the RO group can lead to vinylogous substitutions (S_N2' type; (**G**)); (4) a deprotonation is possible (especially with thioacetals) for use in nucleophilic acylations (**H**).



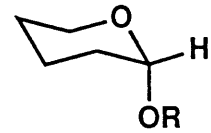
A. Protection



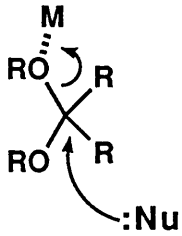
B. To Prevent Rotation



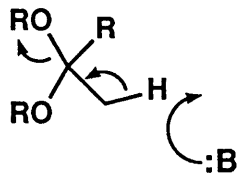
C. Equatorial Preference of **R**



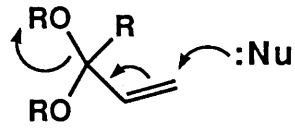
D. Axial Preference of **OR**



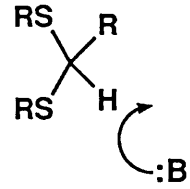
E. Substitution by Nucleophile



F. Elimination



G. Substitution with Double Bond Shift



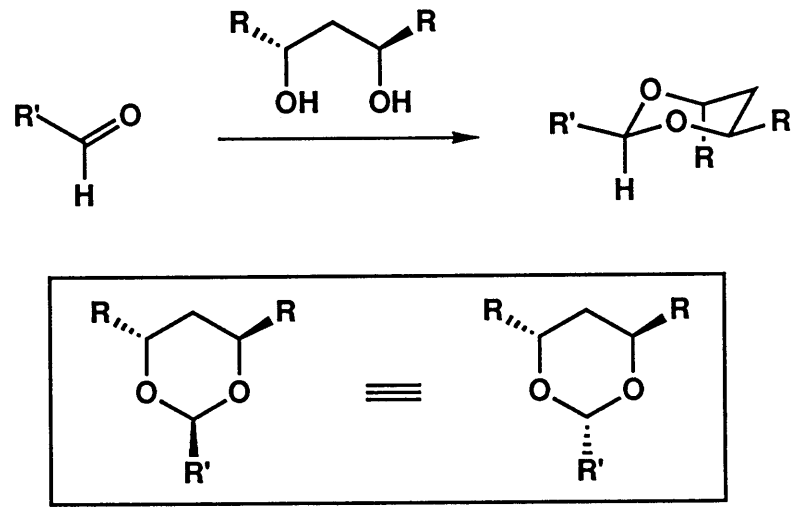
H. Substitution by Deprotonation

Scheme 1

Acetals as protective groups have already played an important role in organic synthesis. For instance, a key step in the synthesis of vitamin C involves selective oxidation of sorbose. To achieve this, all but one of the hydroxy groups are protected by conversion to a double acetal. The author has been interested in the properties of acetals as functional groups rather than as protective groups. There still remains a major challenge in obtaining a general methodology for stereoselective cleavage reactions of acetals and developing a variety of useful methods using acetal synthons in organic synthesis. This thesis is devoted to the development of new

stereoselective reactions using acetal auxiliaries and to studies on the mechanism of nucleophilic cleavage reactions of acetals.

During recent years, a growing number of papers dealing with chiral acetals have demonstrated the usefulness of these auxiliaries in asymmetric synthesis.[1] Of particular interest to the author are acetals prepared with diols having a C_2 axis of symmetry.[2] In these cases, the acetal carbon is prochiral rather than chiral. In a simple aldehyde, without any other stereogenic center, there is no differentiation between the *si* and *re* face of its carbonyl group. By reaction with a C_2 axially symmetric chiral diol a single acetal is formed. However, in its most stable conformation, for example, in the case of a dioxane ring , this acetal now has one axial and one equatorial R substituent. It is by these subtle effects that the *si* and *re* faces of what was a carbonyl group are now differentiated (Scheme 2).[3]



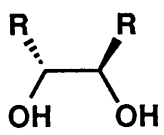
C_2 Axis Symmetry

Scheme 2

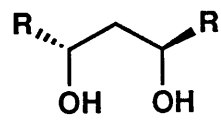
These acetals may undergo cleavage reactions of the acetal ring, or they may be used near a prochiral center to control its reactivity and stereoselectivity.

Chiral acetals are routinely prepared by reacting an aldehyde or a ketone with the chiral diol with azeotropic removal of water in a Dean-Stark trap.[4] Alternatively, Noyori's procedure[5] with desilylated diols can be applied when migration of the double bond of α,β-enones is a serious problem. Finally, transacetalization[4] is also a useful process when an acyclic acetal is the starting material and the corresponding carbonyl compound rather unstable.

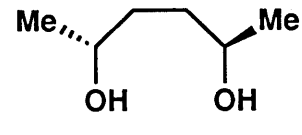
Most of the chiral diols are commercially available. The prices go from the very cheap tartaric acid or mannitol, to the more expensive 2,4-pentanediol. Several simple methods exist for their easy preparative synthesis. Scheme 3 summarizes the most commonly encountered diols and their method of preparation.



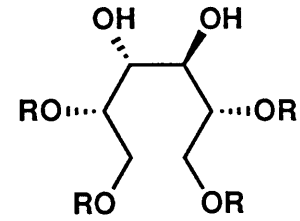
1, R=CO_2R'
2, R=$CONR'_2$
3, R=CH_2OR'
4, R=CH_2SR'
5, R=Me
6, R=*i*-Pr
7, R=*c*-Hex
8, R=Ph



9, R=Me
10, R=*i*-Pr
11, R=Ph



12



13

From tartaric acid: **1, 2, 3, 4, 5** ref 6
From microbial transformation: **5** ref 7, **11** ref 8, **12** ref 9
From asymmetric hydrogenation: **9, 10** ref 10
From Sharpless osmylation: **7, 8** ref 11

Scheme 3

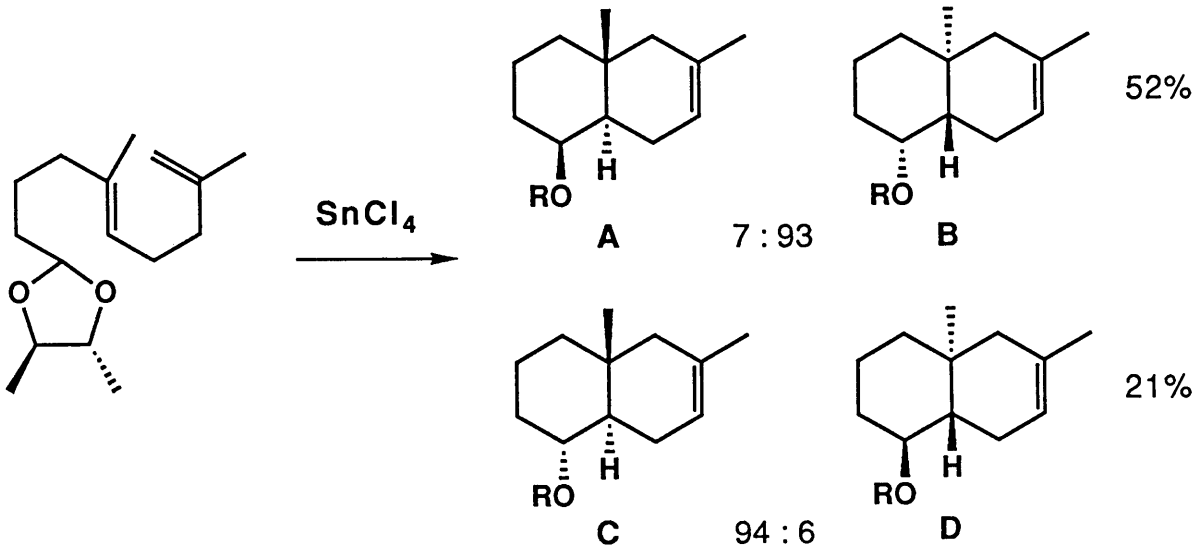
There are also other general methods[12] and some of more specific interest. Thus, **7** was prepared by hydrogenation of **8**,[13] which, in turn, was obtained by reduction of benzoin or benzil, followed by resolution.[14] Matteson *et al.* prepared **6** through borane chemistry.[15] Chiral or racemic diepoxybutane may be opened twice by an organometallic reagent.[16] Finally, a large

array of chiral racemic *d,l*-1,2-diols may be obtained by pinacol type reductive dimerization.[17] These are useful for test studies and may be resolved by standard methods.[18]

2. Cleavage of Acetals

Acetals are among the most popular protective groups for aldehydes and ketones.[4] However, under appropriate conditions, particularly in the presence of Lewis acid, they may be attacked by nucleophiles or they may undergo electrophilic substitution reactions.[19]

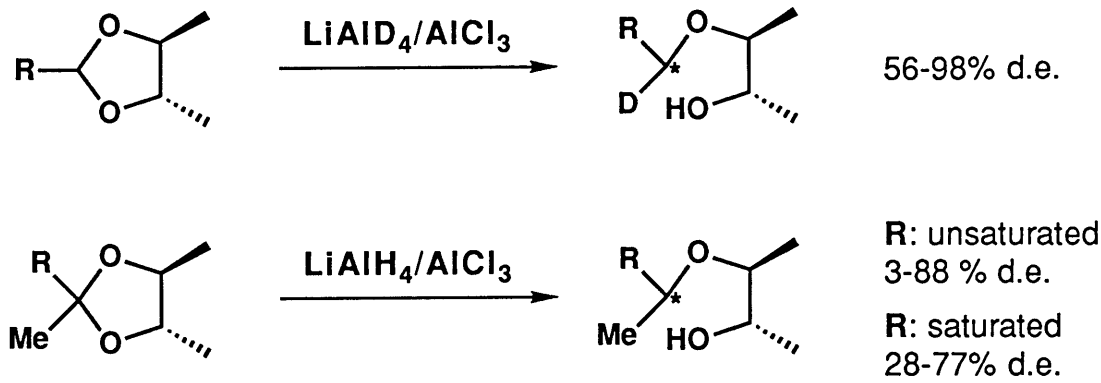
Pioneering in the field of chiral acetals, W. S. Johnson's group[20] used an acetal of *R,R*-2,3-butanediol in their cationic biomimetic cyclization in 1976. Of the four stereoisomers obtained in this $SnCl_4$ catalyzed reaction, the two major ones, **B** and **C** have the same absolute configuration at what was the acetal carbon (Scheme 4). That represents a very high degree of diastereoselectivity in the reaction process (86% d.e.). Removal of the chiral auxiliary, by degradation, allowed the determination of the absolute configuration.



Scheme 4

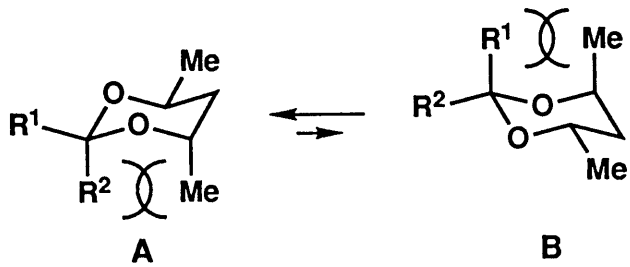
Acetals are easily cleaved and reduced by hydrides having a Lewis acid character such as aluminum or boron hydrides. This methodology is routinely used in carbohydrate chemistry[21] for monodeprotection of vicinal diols. However, in these examples the interest lies in the diol part of

the acetal and not in the aldehyde part. Chiral acetals with a C_2 axial symmetry were first studied by Richter in 1981.[22] Acetals and ketals of 2,3-butanediol were cleaved by $LiAlD_4/AlCl_3$ reagent. Since the diol was racemic, the stereochemical outcome of the reaction was not ascertained; however, the d.e. could be measured and summarized as in Scheme 5.



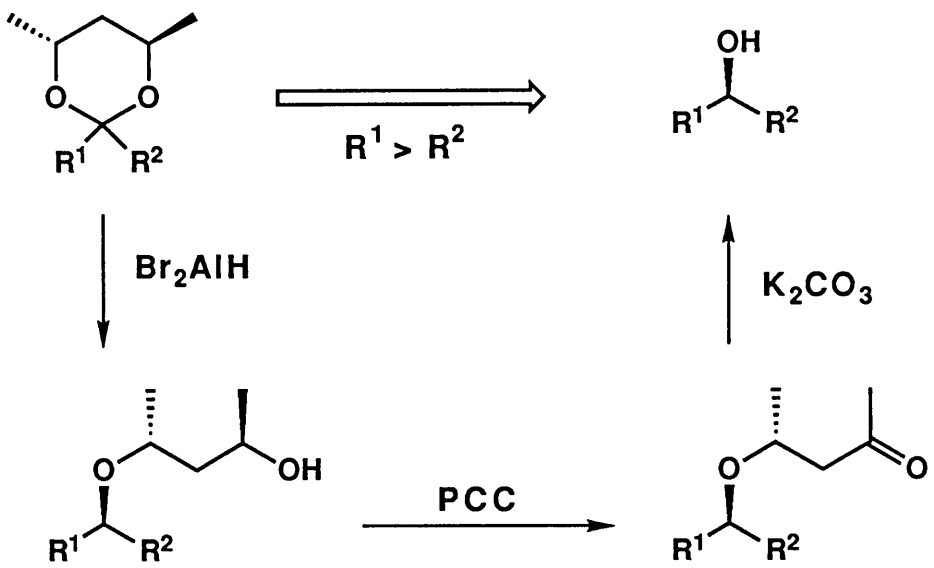
Scheme 5

The two conformers **A** and **B** of *ketal* differ much less energetically, and both conformers may react with equal rate (Scheme 6). That might explain the considerable decrease in diastereoselectivity (28-77% d.e.) as compared to *acetals*. More importantly, with unsaturated methyl ketones as starting carbonyl compounds, the d.e. is almost negligible, the lowest being with R: HC≡C-.



Scheme 6

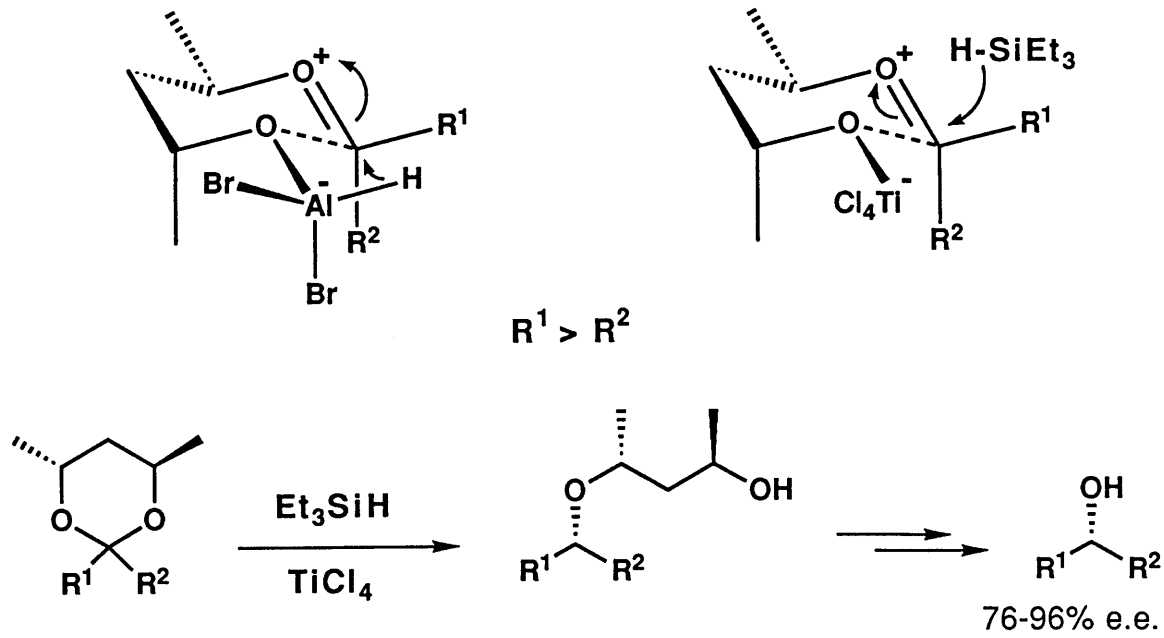
In the case of *ketals* the ring size becomes of crucial importance for the diastereoselectivity of the reaction. With *ketals* of 2,4-pentanediol the diastereoselectivity is boosted to 78-96%.[23] Not only can aryl-alkyl ketones be used, but also dialkyl[24] and, more interestingly, alkynyl-alkyl ketones[25] as shown in Scheme 7. The stereochemical outcome of these reductions was determined by the usual oxidation-β-elimination sequence.



R^1, R^2: alkyl or aryl 78-96% e.e.
R^1: alkyl or aryl; R^2: alkynyl 80-98% e.e.

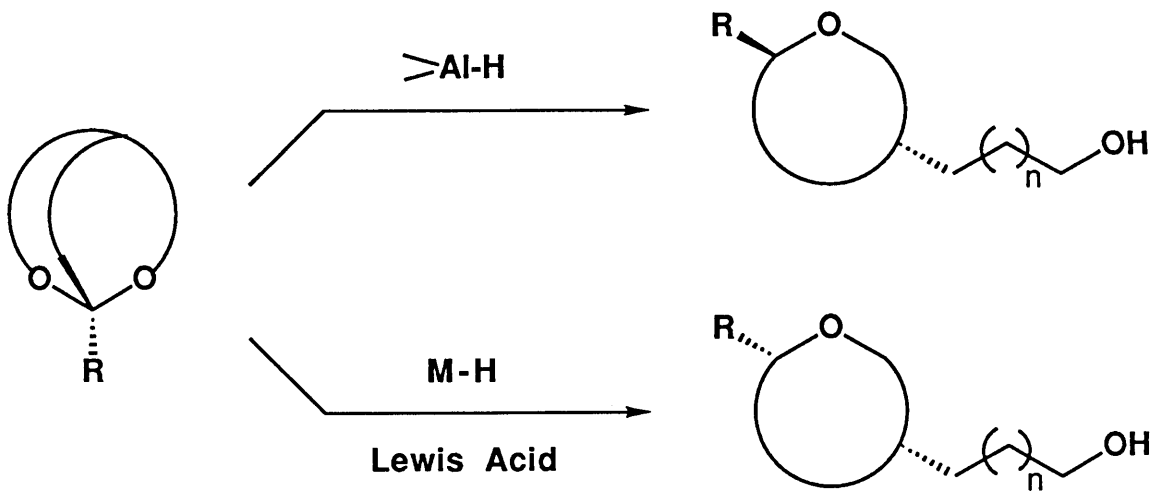
Scheme 7

Interestingly, in these reductions with X_2AlH, the stereochemistry of the final chiral secondary alcohol was found to be completely reversed to what was expected. In fact this result can be easily explained if one takes into account the fact that the Lewis acid and the nucleophile are the same reagent. Thus, the stereospecific coordination of organoaluminum reagent to the oxygen next to the axial methyl group is followed by the attack of the hydride *syn* to the cleaved carbon-oxygen bond (Scheme 8). We also reported that the normal stereochemical outcome can be restored with a binary reagent, R_3SiH/Lewis acid.[26,27] This last reaction is also highly diastereoselective with acetals of dialkyl ketones and of alkynyl-alkyl ketones (Scheme 8).



Scheme 8

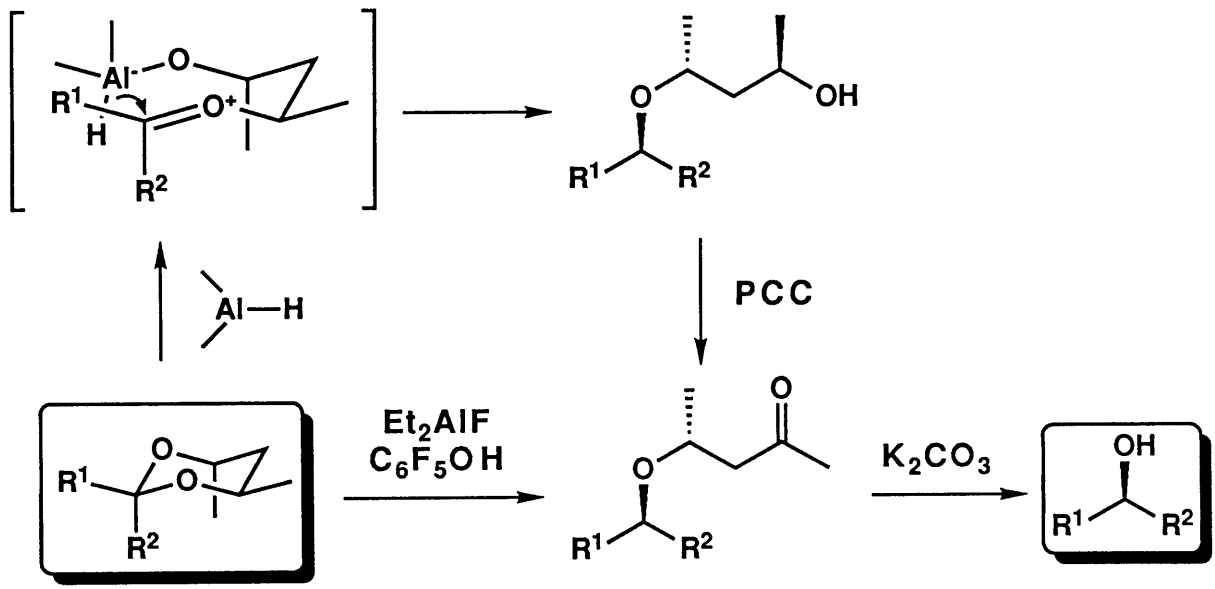
In the course of our studies in this field we have been interested in the stereoselectivity of bicyclic acetals.[28] In chapter 2, the stereoselective reduction of bicyclic acetals and its application to the total synthesis of one of the constituents of civet cat were described. Scheme 9 outlines the general concept that led to the development of the present technology. In view of the growing interest in selective additions of nucleophiles to chiral acetals we investigated 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 an S_N2-like mechanism; (2) what factors (acetal structure, metal hydride, Lewis acid, or solvent) affect the mechanism of the reaction?



Scheme 9

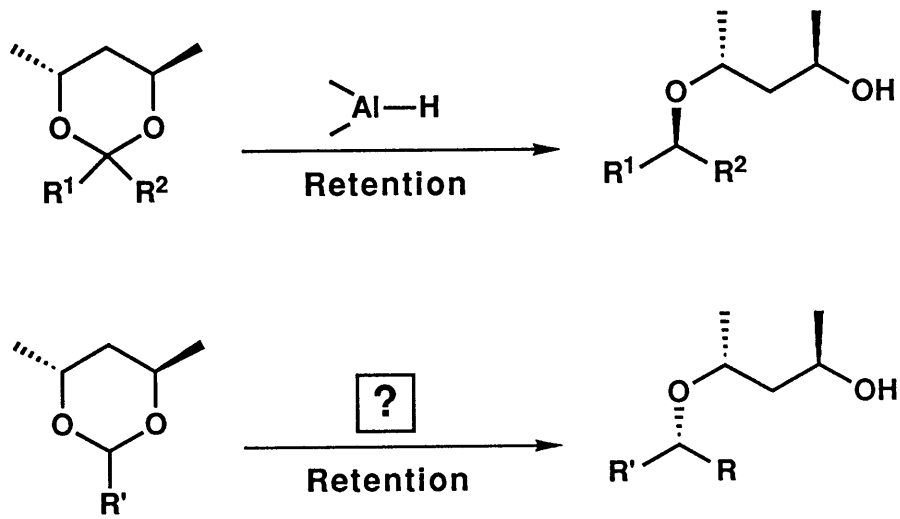
In view of their ready availability and structural unambiguity, bicyclic acetals may be considered as excellent potential precursors. In fact, the above results permit stereocontrolled reduction of bicyclic acetals generating specifically either a *cis* or *trans* cyclic ether depending on the choice of reagent.

Reductive cleavages of acetals with organoaluminum hydride reagents (e.g. Br_2AlH, Cl_2AlH, DIBAH) affords stereoselectively syn reduced products.[23,24,25,27] The observed high diastereoselectivity was ascribed to the stereospecific coordination of the organoaluminum reagent with one of the acetal oxygens followed by the hydride attack syn on the cleaved carbon-oxygen bond. The reaction probably proceeds by a tight ion paired S_N1-like mechanism. In chapter 3, we describe the reductive cleavages of chiral acetals by the combined use of diethylaluminum fluoride and pentafluorophenol reagents. This is a new reaction for acetals, an intramolecular Meerwein-Ponndorf-Verley reductive and Oppenauer oxidative reaction of acetal template. Removal of the chiral auxiliary, followed by base-catalyzed β-elimination of the resulting β-alkoxy ketone, easily give the optically pure alcohol in good yield. We have also demonstrated that pentafluorophenol is a more useful additive for this novel hydride-transfer reaction (Scheme 10).



Scheme 10

Stereoselective alkylative cleavage of chiral acetals *via* syn attack of the reagents, however, has not yet been reported, although we did report the reductive cleavage of chiral acetals by aluminum hydride reagents (e.g. DIBAH, Br_2AlH, Cl_2AlH).[23,24,25,27] Since the beginning of these studies, we have been interested in the possibility of achieving the retention of the stereochemical outcome of alkyl anion attack on the acetal group, which, if successful, would provide a method to obtain both enantiomers from a single chiral starting acetal (Scheme 11).



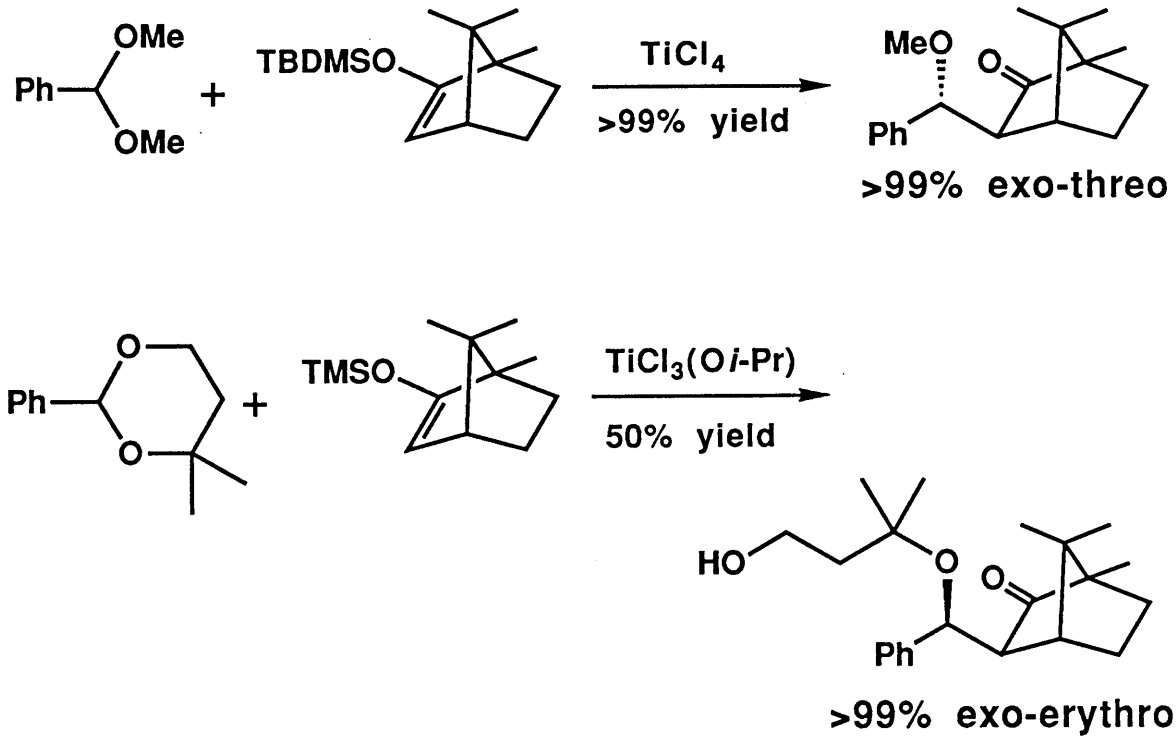
Scheme 11

In chapter 4, we describe the highly stereoselective alkylative cleavage of chiral acetals derived from (-)-(2*R*,4*R*)-2,4-pentanediol by the combined use of trialkylaluminum and pentafluorophenol, and also describe the selective cleavages of acetals derived from 1,3-butanediol and (-)-(2*R*,3*R*)-2,3-butanediol respectively.

The results of our investigations on unprecedented selectivities in the reaction of enol silyl ethers with a variety of acetal templates are described in chapter 5.

Aldol reactions are usually divided into two categories depending on the method of activation of the enolates and carbonyl substrates. Most reactions proceed *via* a six-membered chelated transition state assembled by a metal enolate and carbonyl compound.[29] In this case, the aldol stereoselectivity is heavily dependent on the geometry of the enolate double bond: (*E*)-enolates generally giving threo aldols and (*Z*)-enolates giving erythro products. The other reactions proceed through acyclic transition states, and both (*E*)- and (*Z*)- enolates give the erythro adducts selectively.[29,30] Very little is known, however, of the stereochemistry of the titanium mediated coupling of enol silyl ethers with aldehydes (Mukaiyama reaction),[31] despite its broad utility in organic synthesis.

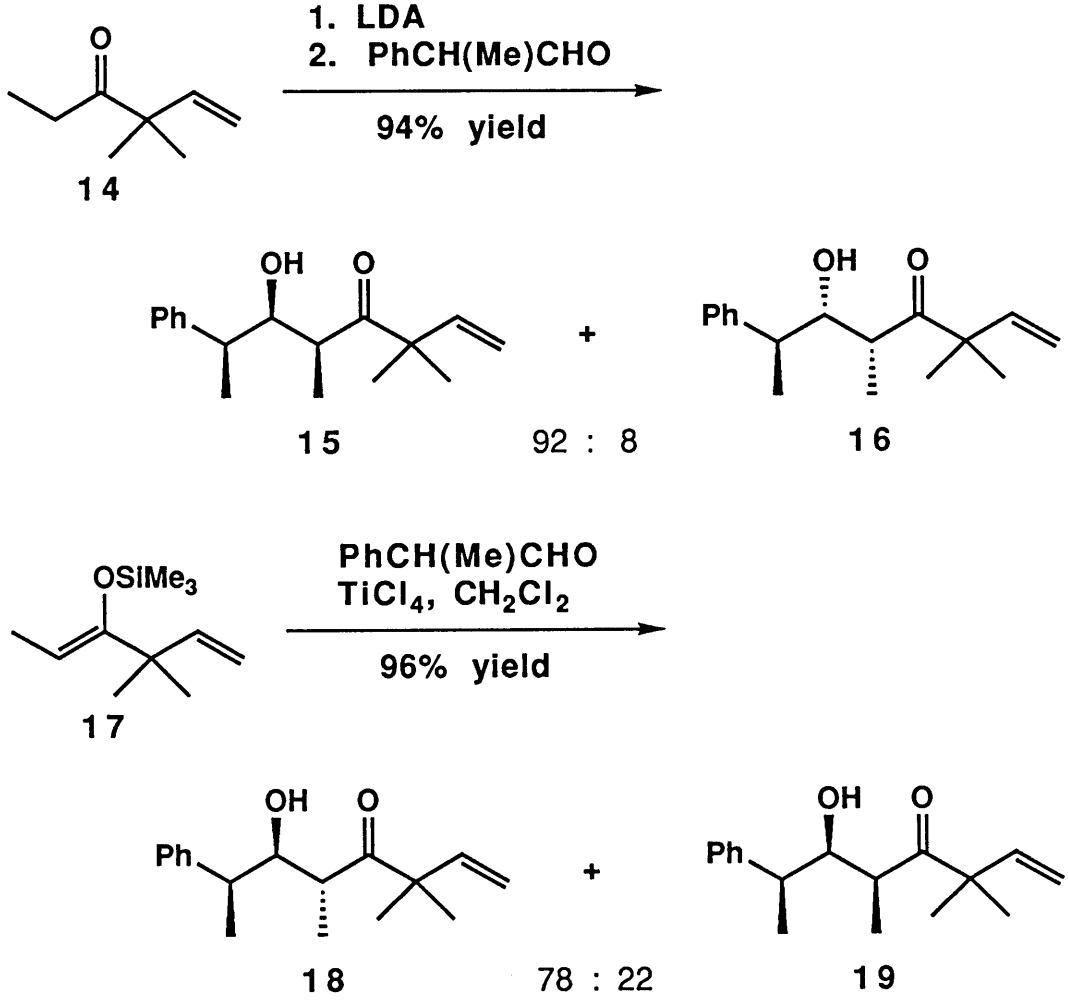
We chose to investigate the stereoselectivity of the aldol formation from benzaldehyde acetal and the enol silyl ether of *D*-camphor, an enol silane of high steric demand (Scheme 12). In the reaction of benzaldehyde dimethyl acetal with the enol silyl ether of *D*-camphor, the exo-threo product was obtained almost exclusively. In dramatic contrast, however, similar reaction conditions but with benzaldehyde acetal of 3-methyl-1,3-butanediol gave the exo-erythro isomer exclusively. This reversal strongly suggests a crucial role for the acetal structure on the selectivity of the reaction and prompted us to investigate the course of the reaction with a wide variety of acetals under various reaction conditions. Details of these reactions are summarized in chapter 5.



Scheme 12

Chapter 6 contains description of the double stereoselective aldol reaction of α-chiral aldehyde with silyl enol ether using a pinacol acetal template. This stereoselective reaction is essentially similar to the diastereoselective aldol reaction using 3-methyl-1,3-butanediol acetal template described in the previous chapter.

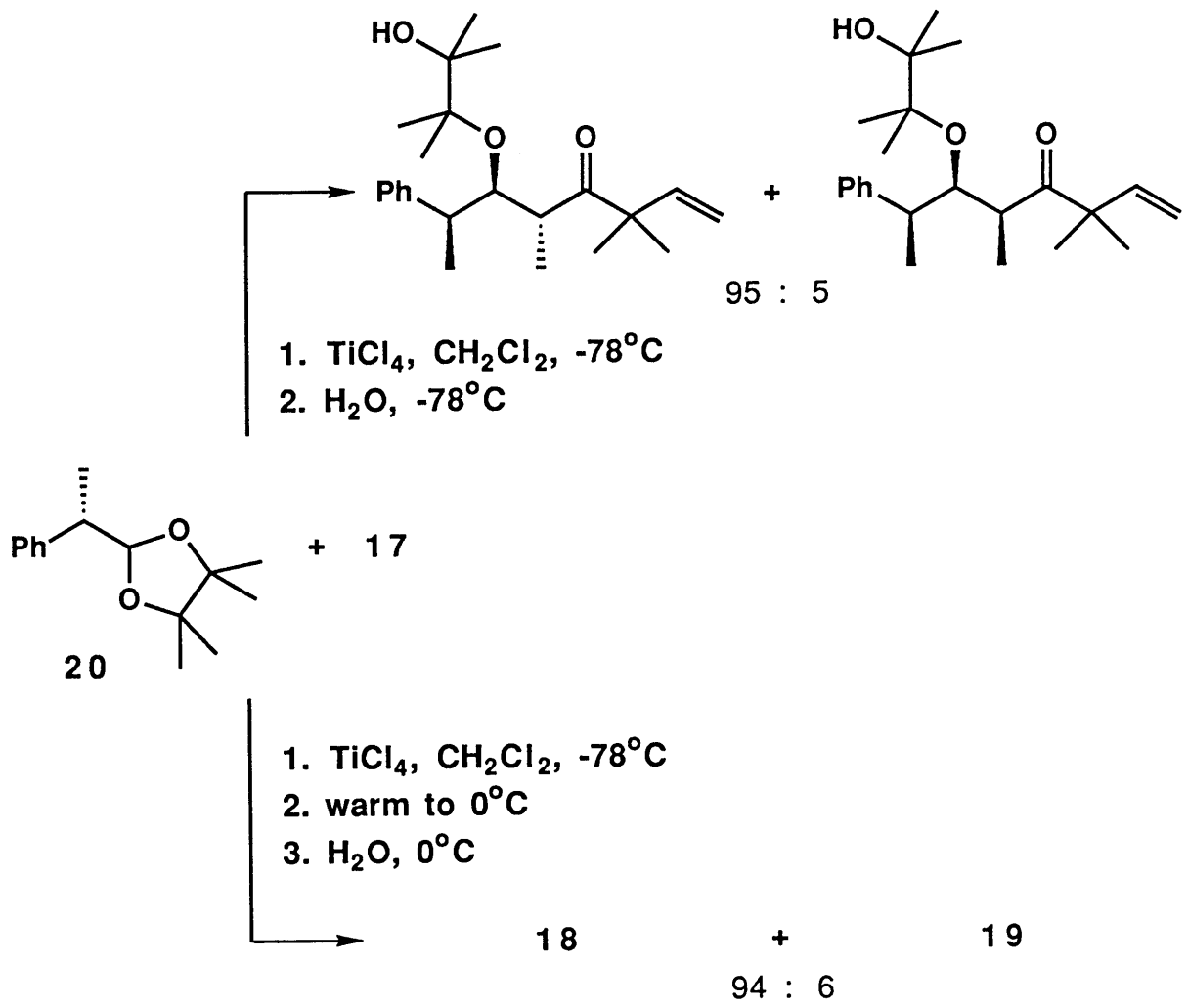
2-Phenylpropanal was used to examine the stereoselectivity of the aldol reactions of reagents **14** and **17** with a typical chiral aldehyde (Scheme 13). The reaction of the lithium enolate of **14** with 2-phenylpropanal gives only the two *syn* aldols, and a rather high Cram/*anti*-Cram ratio of 92:8 is observed. In the $TiCl_4$-mediated reaction of **17** with the same aldehyde, the Cram/*anti*-Cram ratio is >97:3,[32] but the simple diastereoselectivity is usually low; aldols **18** and **19** are produced in a ratio of 3.5:1.



Scheme 13

Because it has been previously shown by Heathcock and his colleaques[33] that diastereofacial selectivity in addition to α-chiral thionium ions is enhanced when the sulfur substituent is more bulky, the author investigated the Lewis acid mediated nucleophilic substitution reactions of the pinacol acetal **20** of 2-phenylpropanal. As shown in Scheme 14, use of the pinacol ether is essential to obtain high diastereofacial selectivity in a ratio of 95:5; when the dimethyl acetal corresponding to **20** is used in this reaction, three β-methoxy ketones are obtained in a ratio of 5:4:1. To our pleasant surprise, we discovered that aldols **18** and **19** were produced in 96% yield in a ratio of 94:6 if the aldol reaction mixture was warmed for -78°C to 0°C prior to the aqueous

quench. The loss of the pinacol group presumably occurs by $TiCl_4$-promoted pinacol rearrangement of the intermediate ethers.

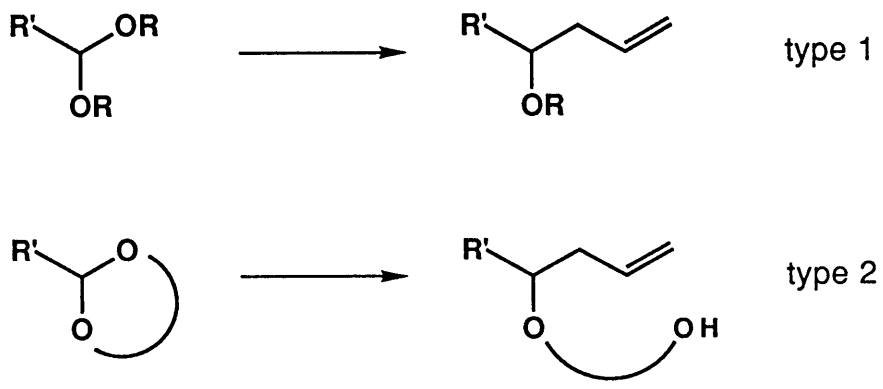


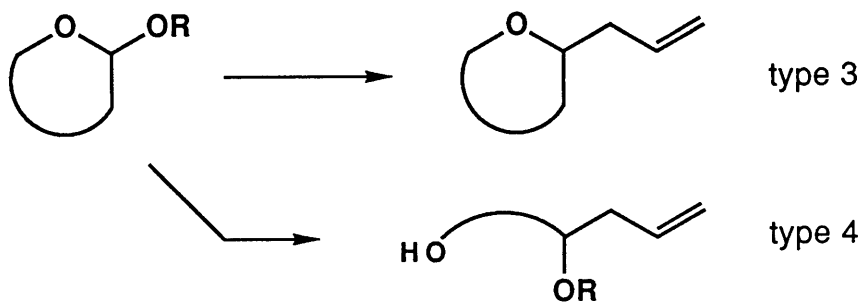
Scheme 14

The Lewis acid-mediated reaction of acetals with nucleophiles such as silyl enol ethers is a powerful method for carbon-carbon bond formation and has proven to be highly stereoselective in many cases.[34] Detailed mechanistic studies are scarce, although some mechanistic rationales have been put forward for these and related reactions.[34a,34c,35-40] Recent communications from Denmark and coworkers provide strong evidence for a mechanistic divergence in an intramolecular version of the reaction[41] and give information pertaining to the structures of complexes of cyclic

acetals with BF_3 in various solvents.[42] In chapter 7, two sets of experiments that provide information about the mechanism of the intermolecular reaction are described.[43]

Intermolecular substitution reactions of acetals can be classified to four groups, depending on the structure of the acetal and which alkoxy group is replaced. These are illustrated in Scheme 15 for hypothetical reactions with allyltrimethylsilane. In this study, we examined reactions of type 1 and type 2. Our results indicate a mechanistic divergence; acetal substitution can occur by an S_N1 (oxocarbenium ion) or S_N2 mechanism. The operative mechanism depends on the size of the acetal alkoxy group and the polarity of the solvent. Greater steric bulk in the acetal alkoxy group and more polar solvent promote ionization to the oxocarbenium ion. With acyclic acetals, stereoselectivity increases with increasing steric bulk of the alkoxy group and increasing polarity of the reaction medium. The enhanced stereoselectivity observed with acetals of secondary and tertiary alcohols is explained by perturbation of the approach trajectory of the nucleophilic alkene as it attacks the oxocarbenium ion. Highest stereoselectivity is seen in the reaction of 2-(1-phenylethyl)-4,4,5,5-tetramethyl-1,3-dioxolane with enol silane; only one diastereomeric product is obtained, even in the relatively non-polar solvent CH_2Cl_2. The $TiCl_4$-mediated reactions of cyclic acetals with silyl enol ether show that in these systems the substitution does not occur by the S_N2 mechanism.

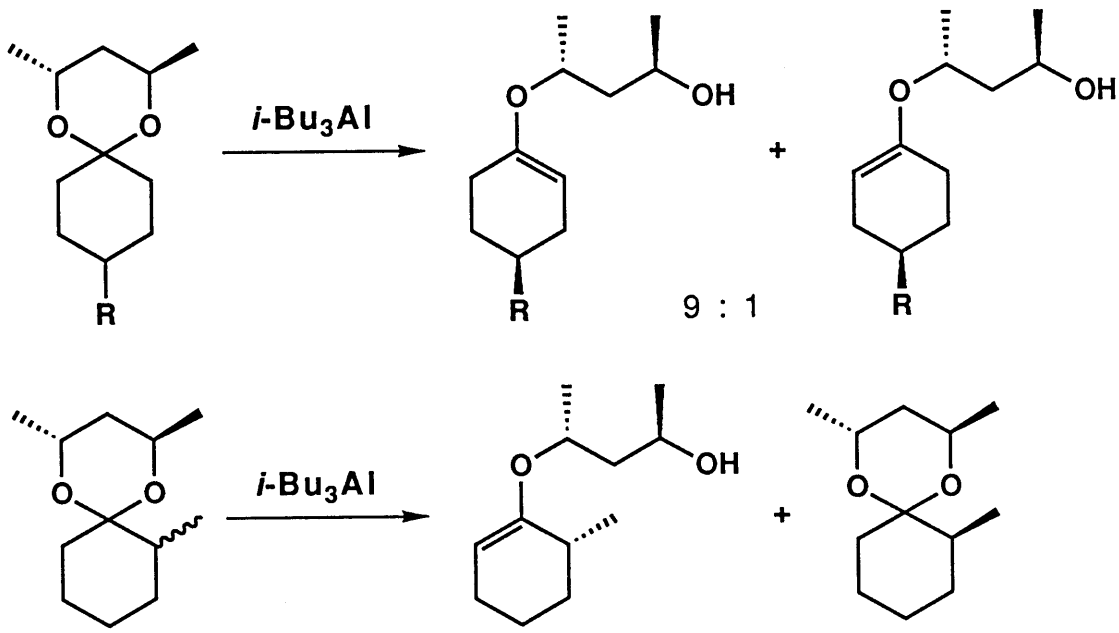




Scheme 15

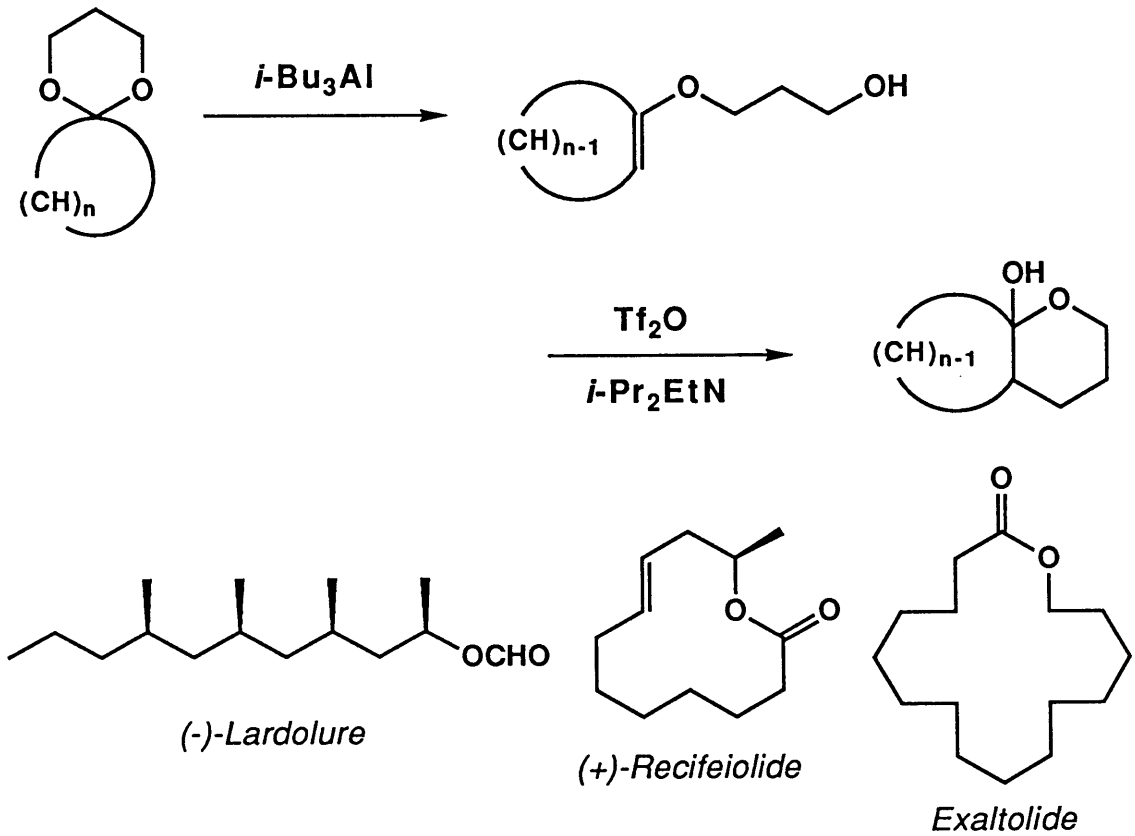
3. Synthetic Application for Cleaved Products of Acetals

Another example of cleavage of an acetal by elimination rather than by substitution was observed in the reaction between cyclic acetals and triisobutylaluminum or an aluminum amide by H. Yamamoto *et al.* Asymmetrization of meso ketones was, thus, achieved.[44] The same kind of reagent also serves for the kinetic resolution of substituted spiro acetals (Scheme 16).[45] In these cases, *i*-Bu_3Al acts as Lewis acid and as a base for the abstraction of a proton to afford the enol ether.



Scheme 16

It thus seemed to us that the possibility of forming rings by intramolecular addition of a terminal alcohol to a double bond, as shown in Scheme 17, deserved to explored.[46] This appeared particularly true because such a process would result in the formation of a ring that would have a variety of appendages with predictable stereochemistry. An efficient and stereospecific ring formation from unsaturated alcohols, which in turn are prepared by regio- and stereospecific ring opening of acetals, is described in chapter 8. (-)-Lardolure has been synthesized by intramolecular cyclization of vinyl ether alcohol derived from spiro acetal *via* triisobutylaluminum and further ring enlargement of the afforded bicyclic hemiacetals. The same method was utilized for new stereospecific ring enlargement to yield medium and large rings ((+)-recifeiolide, exaltolide, etc) from simple cycloketones.

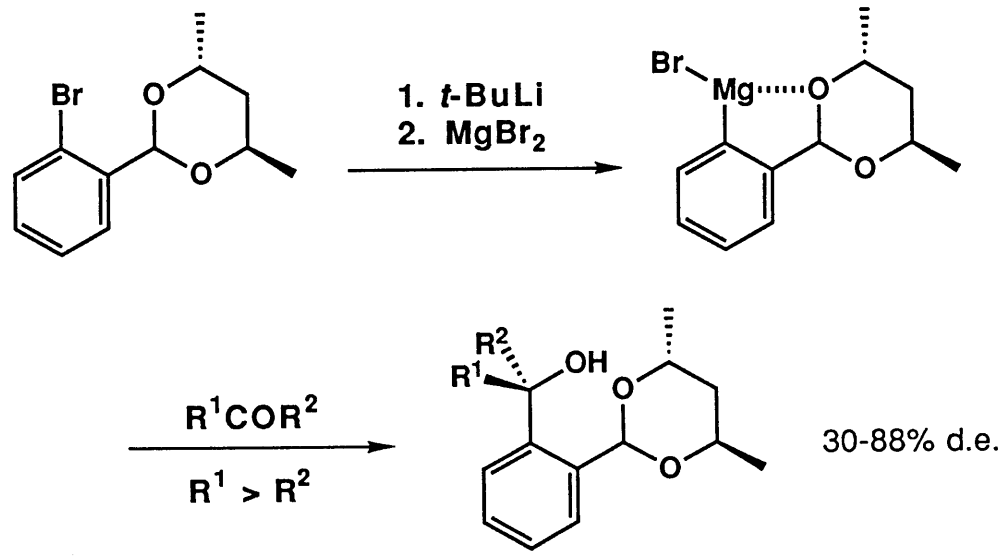


Scheme 17

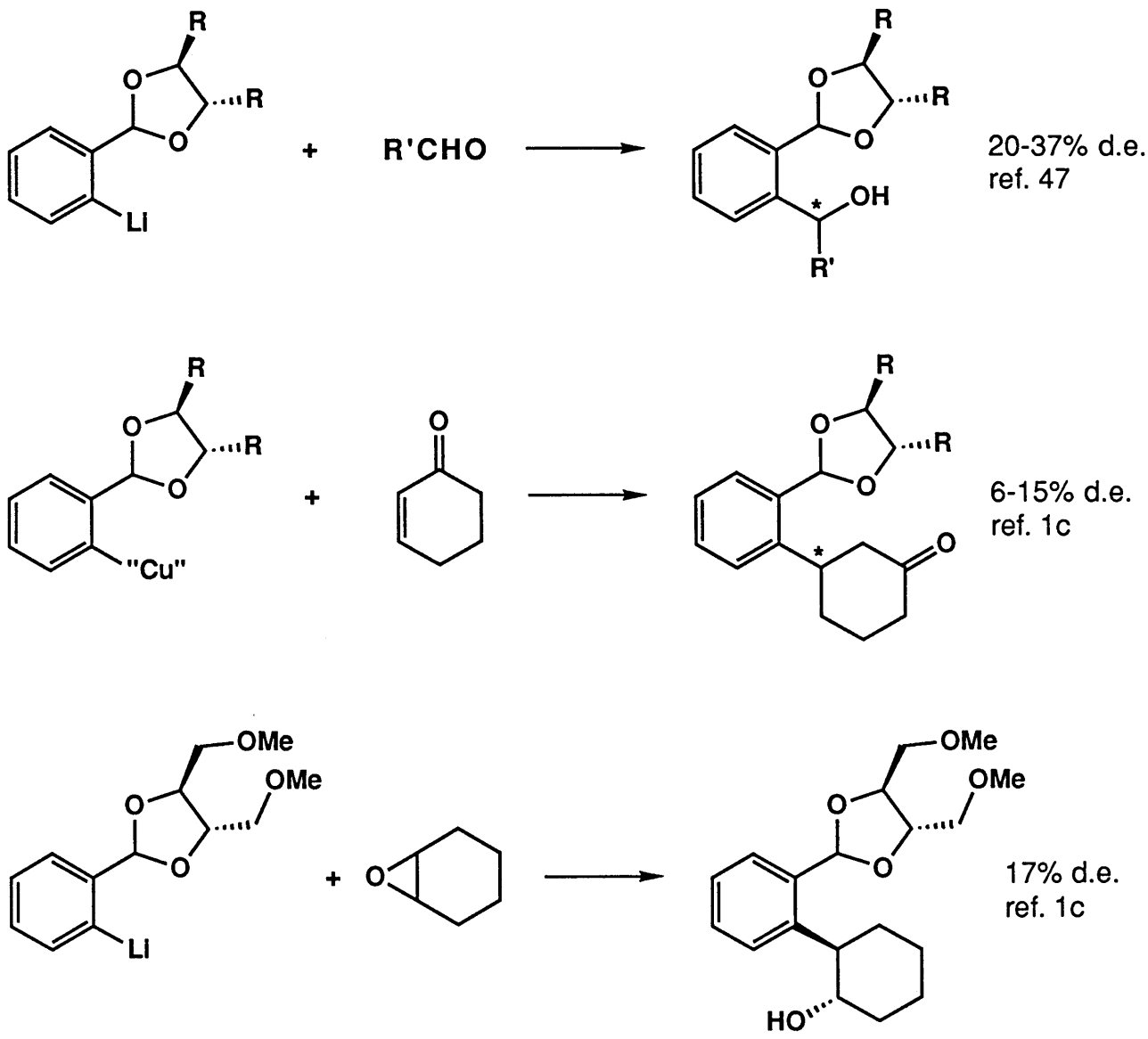
4. Reactions without Ring Cleavage

The formation of a cyclic chiral acetal may serve other purposes than a diastereoselective cleavage reaction. The chiral environment, thus created, should influence the face selectivity of a proximal prochiral center. Steric as well as chelation factors account for the observed selectivities, and the nature of the diol plays a crucial role. A large array of chemical transformations have been investigated, with the acetal auxiliary in various relative positions to the prochiral center, either on the nucleophile or the electrophile. However, the diastereoselective reaction of a chiral nucleophile having an acetal appendage is very scarce.

In chapter 9, we describe diastereoselective addition of Grignard reagents which have an adjacent chiral acetal auxiliary (Scheme 18). Chiral aryl Grignard reagents are generated *in situ* from chiral 2-halobenzaldehyde 2,4-pentanediol acetal, *t*-butyllithium, and magnesium bromide. These reagents react with aromatic aldehydes to moderate diastereoselectivities. The diastereoselectivity now depends not only on the type of acetal, but also on the substrate (generally an aldehyde) and the kind of metal. Similar examples[1c,47] reported by the other groups are shown in Scheme 19.



Scheme 18



Scheme 19

5. Conclusion

In conclusion, the author has proposed several methodologies for the stereoselective construction of acyclic as well as cyclic carbon frameworks. These methods are heavily dependent on the unusual reactivities of an acetal template. The major contributions of the present work may be summarized as follows:

(1) Nucleophilic cleavages of chiral acetals using various organometallic reagents are realized. The method provides general routes for the preparation of optically active alcohols.

(2) Reductive cleavages of bicyclic acetals using various organometallic reagents are also realized. The method provides a new process for the construction of oxygen-containing heterocyclic systems.

(3) A novel diastereoselective aldol-type reaction using a wide variety of achiral acetal templates is explored. These results suggest a crucial role for the acetal structure in the stereoselectivity of aldol-tye reaction under various reaction conditions.

(4) The mechanism of Lewis acid-mediated nucleoplilic substitution reactions of acetals has been studied in detail. These results indicate that the operative mechanism depends on size of the acetal alkoxy group and polarity of the solvent.

(5) An efficient and stereospecific ring formation from unsaturated alcohols which, in turn, are prepared by regio- and stereospecific ring opening of acetals has been developed. (-)-Lardolure has been synthesized in short steps by this method.

(6) Diastereoselective addition of a phenyl magnesium derivative bearing, in the ortho position, a chiral acetal auxiliary has been developed. The chiral Grignard reagent approach was verified as a powerful methodology for the synthesis of optically active diaryl alcohols.

References

1. There are already some partial reviews on this topic:

   (a) Seebach, D.; Imwinkelried, R.; Weber, T.; in "*Modern Synthetic Methods*"; Scheffold, R. (ed.), Vol. 4; p. 125; Springer-Verlag, Berlin, **1986**.

   (b) Mash, A. E. in "*Studies in Natural Product Synthesis*", Atta-Ur Rahman (ed.), Vol. 1, p. 577; Elsevier, Amsterdam, **1988**.

   (c) Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**,*1*, 477.

2. A recent review deals with C_2 symmetry and asymmetric induction: Whitesell, J. K. *Chem. Review* **1989**, *89*, 1581.

3. Eliel, E. L. *Acc. Chem. Res.* **1970**, *3*, 1.

4. Greene, T. W. in "*Protective Groups in Organic Synthesis*", Wiley, J. (ed.), New York, **1981**.

5. Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.

6. Seebach, D; Hungerbuhler, E. in "*Modern Synthetic Methods*", Scheffold, R. (ed.) Vol. 2; p. 91; Salle+Sauerlander, **1980**.

7. Ledingham, G. A.; Adams, G. A. *Can. Chem. Process Inds.* **1944**, *28*, 742 and 801.

8. Yamamoto, K.; Ando, H.; Chikamatsu, H. *J. Chem. Soc., Chem. Comm.* **1987**, 334.

9. Lieser, J. K. *Synthetic Comm.* **1983**, *13*, 764.

10. (a) Ito, K.; Harada, T.; Tai, A. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3367.

    (b) Tai, A.; Ito, K.; Harada, T. *Ibid.* **1981**, *54*, 223.

    (c) Sugimura, T.; Futagawa, T.; Yoshikawa, M.; Tai, A. *Tetrahedron Lett.* **1989**, *30*, 3807.

11. (a) Jacobsen, E. N.; Marks, I.; Mungall, W. S.; Schroder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.

    (b) Lohray, B. B.; Kalantar, T. H.; Kim, B. M.; Park, C. Y.; Shibata, T.; Wai, J. S. M.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 2041.

12. For example, the stereocontrolled *syn* or *anti* reactions of α, β or γ hydroxy carbonyl compounds. Among the dozens of papers on this topic see, for example, the following articles and the references cited therein:

    (a) Maier, G.; Roth, C.; Schmitt, R. K. *Chem. Ber.* **1985**, *118*, 704.

    (b) Maier, G.; Schmitt, R. K.; Seipp, U. *Ibid.* **1985**, *118*, 722.

    (c) Kiyooka, S.; Kuroda, H.; Shimasaki, Y. *Tetrahedron Lett.* **1986**, *27*, 3009.

    (d) Evans, D. A.; Chapman, K. T. *Ibid.* **1986**, *27*, 5939.

    (e) Handa, Y.; Inanaga, J. *Ibid.* **1987**, *28*, 5717.

13. Ditrich, K.; Bube, T.; Sturmer, R.; Hoffman, R. W. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 160.

14. (a) Brugidou, J.; Christol, H.; Sales, R. *Bull. Soc. Chim. Fr.* **1974**, 2033.
(b) Collet, A. *Synthesis*, **1973**, 664.

15. (a) Matteson, D. S.; Beedle, E. C.; Kandil, A. A. *J. Org. Chem.* **1987**, *52*, 5034.
(b) Matteson, D. S.; Tripathy, P. B.; Sarkar, A.; Sadhu, K. M. *J. Am. Chem. Soc.* **1989**, *111*, 4399.

16. Hatakeyama, S.; Sakurai, K.; Saijo, K.; Takano, S. *Tetrahedron Lett.* **1985**, *26*, 1333.

17. (a) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S. *Tetrahedron Lett.* **1985**, *26*, 1333.
(b) Raubenheimer, H. G.; Seebach, D. *Chimia* **1986**, *40*, 12.

18. (a) Kagan, H. in "*Stereochemistry: Fundamental and Methods*", Vol. 1-3, Thieme, G. (ed.), Stuttgart, **1977**.
(b) Morisson, J. D. in "*Asymmetric Synthesis*" Vol. 1, Academic Press, New York, **1983**.
(c) Whitesell, J. K.; Reynolds, D. *J. Org. Chem.* **1983**, *48*, 3548.
(d) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M. *Ibid.* **1986**, *51*, 2370.

19. (a) Schmitz, E.; Eichhorn, I. in "*The Chemistry of the Ether Linkage*" Chapt. 7, p. 309, "*Acetals and Ketals*", Patai, S. (ed.), Interscience Pub., London, **1967**.
(b) Mukaiyama, T. *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 817.

20. (a) Johnson, W. S.; Harbert, C. A.; Stipanovic, R. D. *J. Am. Chem. Soc.* **1968**, *90*, 5279.
(b) Johnson, W. S.; Harbert, C. A.; Ratcliffe, B. E.; Stipanovic, R. D. *Ibid.* **1976**, *98*, 6188.

21. See, for example, the following articles and the references cited therein:

(a) Takano, S.; Kurotaki, A.; Sekigushi, Y.; Satoh, S.; Hirama, M.; Ogasawara, K. *Synthesis*, **1986**, 811.

(b) ref. 12a.

(c) Nutaitis, C. F.; Gribble, G. W. *Org. Prep. Proc. Int.* **1985**, *17*, 11.

(d) Winterfeldt, E. *Synthesis* **1975**, 617.

22. Richter, W. J. *J. Org. Chem.* **1981**, *46*, 5119.
23. Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4581.
24. Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *J. Organomet. Chem.* **1985**, *285*, 83.
25. Ishihara, K.; Mori, A.; Arai, I.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 983.
26. Mori, A.; Ishihara, K.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 987.
27. Mori, A.; Ishihara, K.; Arai, I.; Yamamoto, H. *Tetrahedron* **1987**, *43*, 755.
28. (a) Kotsuki, H.; Ushio, Y.; Kadota, I.; Ochi, H. *Chem. Lett.* **1988**, 927.

    (b) Kotsuki, H.; Ushio, Y.; Kadota, I.; Ochi, H. *J. Org. Chem.* **1989**, *54*, 5153.
29. (a) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066 and references cited therein.

    (b) Evans, D. A.; Nelson, J. R.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099 and references cited therein.
30. Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1981**, *103*, 2106.
31. Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503.
32. Lewis acid mediated addition of silyl enol ethers to a-chiral aldehydes have previously been shown to give enhanced Cram/*anti*-Cram ratios:

    Heathcock, C. H.; Flippin, L. A. *J. Am. Chem. Soc.* **1983**, *105*, 1667.
33. Mori, I.; Bartlett, P. A.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 7199.
34. (a) Bartlett, P. A.; Johnson, W. S.; Elliot, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2088.

    (b) Choi, V. M. F.; Elliot, J. D.; Johnson, W. S. *Tetrahedron Lett.* **1984**, *25*, 591.

    (c) Maruoka, K.; Yamamoto, H. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 668.

(d) Berlan, J.; Besace, J.; Prat, D.; Pourcelot, G. *J. Organomet. Chem.* **1984**, *264*, 399.

35. Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *44*, 4259.
36. Silverman, R.; Edington, C.; Elliot, J. D.; Johnson, W. S. *J. Am. Chem. Soc.* **1987**, *52*, 180 and refernces therein.
38. (a) Imwinkelried, R.; Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 765.
(b) ref. 1a.
39. Mukaiyama, T.; Ohshima, M.; Miyoshi, N. *Chem. Lett.* **1987**, 1121.
40. Yamamoto, Y.; Nishii, S.; Yamada, J. *J. Am. Chem. Soc.* **1986**, *108*, 7116.
41. Denmark, S. E.; Wilson, T. M. *J. Am. Chem. Soc.* **1989**, *111*, 3475.
42. Denmark, S. E.; Wilson, T. M.; Almstead, N. G. *J. Am. Chem. Soc.* **1989**, *111*, 9258.
43. Denmark and coworkers have also reached essentially the same mechanistic conclusions. Their results will be published separately.
44. Naruse, Y.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 1363.
45. Mori, A.; Yamamoto, H. *J. Org. Chem.* **1985**, *50*, 5445.
46. Previous examples for cationic cyclization of vinyl ethers, see:
(a) Hashimoto, S.; Itoh, A.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 4192.
(b) Boeckman, Jr., R. K.; Bruza, K. J.; Heinrich, G. R. *Ibid.* **1978**, *100*, 7101.
47. Commercon, M.; Mangeney, P.; Tejero, T.; Alexakis, A. *Tetrahedron : Asymmetry* **1990**, *1*, 287.

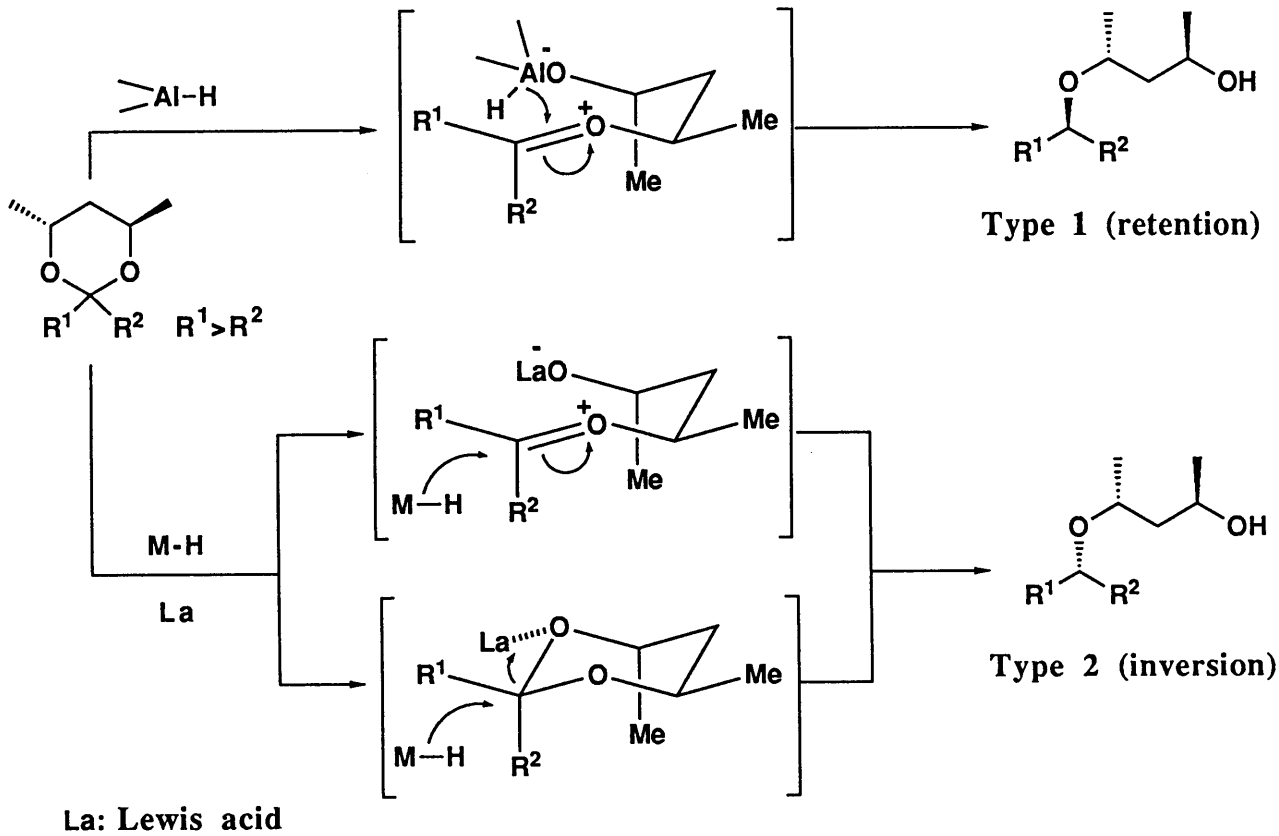
Chapter 2

Stereoselective Reduction of Acetals.
A Method for Reductive Generation of Heterocyclic Ring Systems

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).

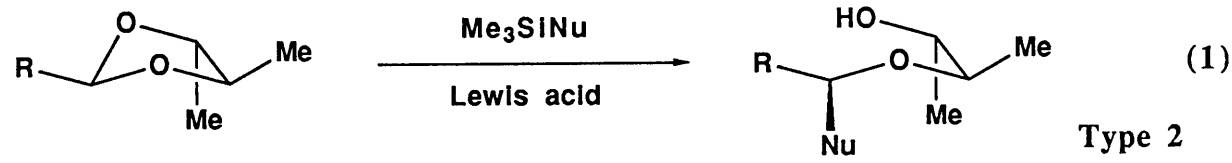


Scheme 1

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-

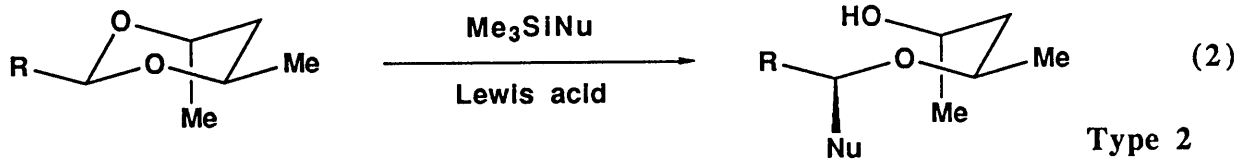
type substitution on an intermediate Lewis acid complex or ion pair in which the breaking bond was attached to the sterically most accessible oxygen (type 2). We have developed a method to give both enantiomers from a single chiral starting acetal using these two reagent-systems.

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)

Type 2

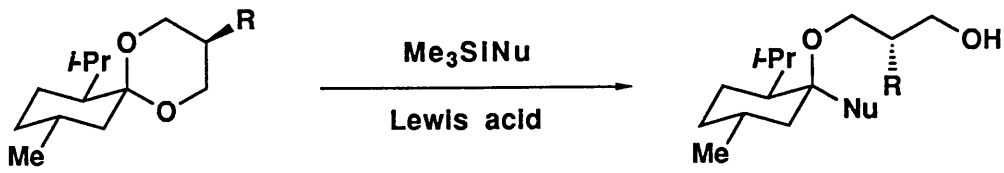


(2)

Type 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

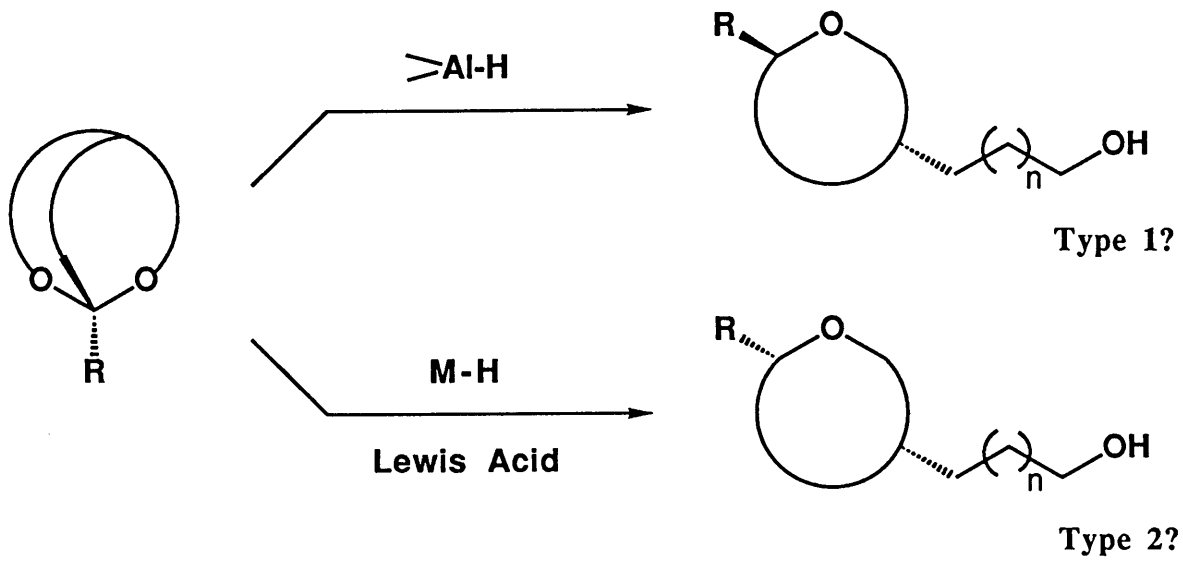
and, in a similar sense, the equatorial attack of a nucleophile on the positively charged sp^2-hybridized C(1) carbon of the menthone skeleton becomes highly preferable."[10]



(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

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

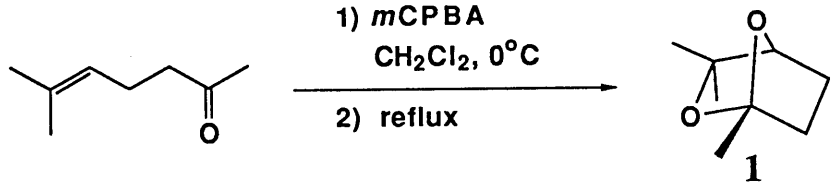
cleavage of the acetal group has never been developed to a useful level, while the most important aspects of diastereoselective reduction of the carbonyl group have already been assimilated by the chemical community. Nevertheless, stereocontrolled reduction of bicyclic acetals, if successful, is expected to generate specifically either a *cis* or *trans* cyclic ether depending on the choice of reagent.

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

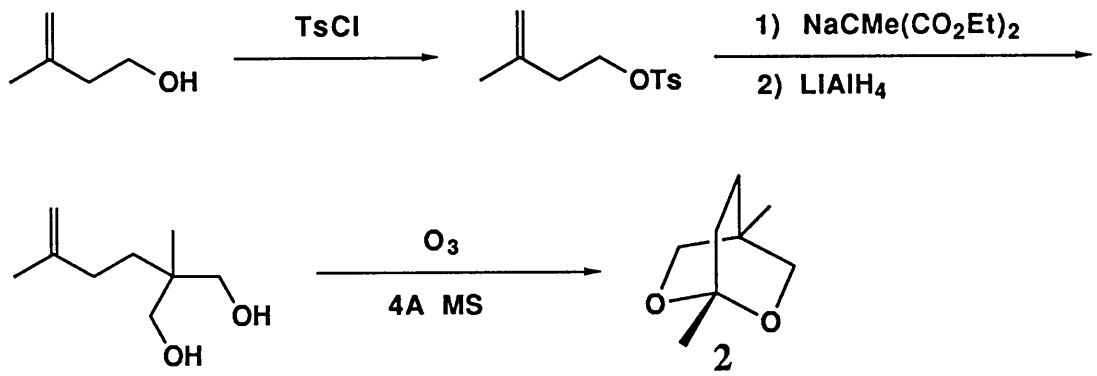
Bicyclic acetals have been well studied as a monomer of ring opening polymerization to give synthetic analogs of polysaccharides.[14] Four kinds of acetals used as starting materials of reductive cleavages were synthesized as shown below.

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).



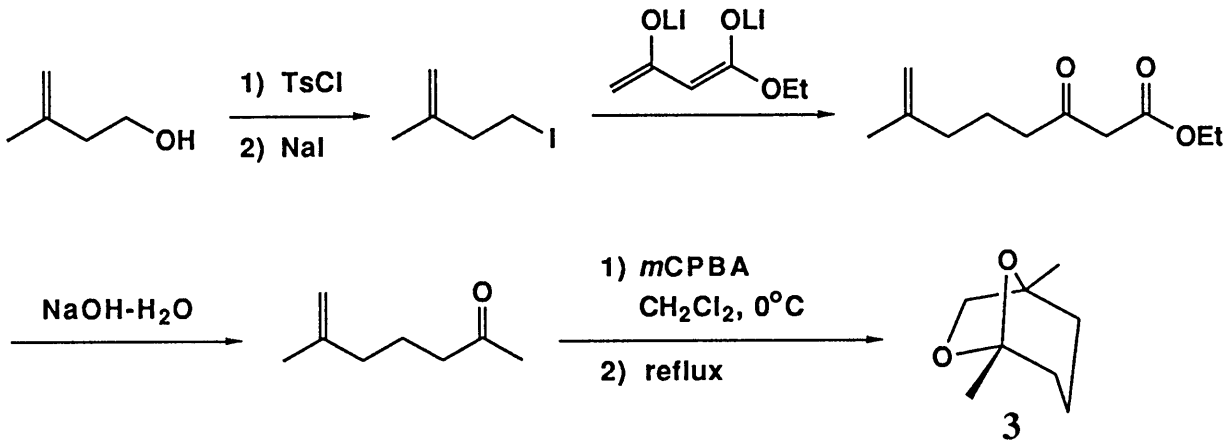
Scheme 3

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).



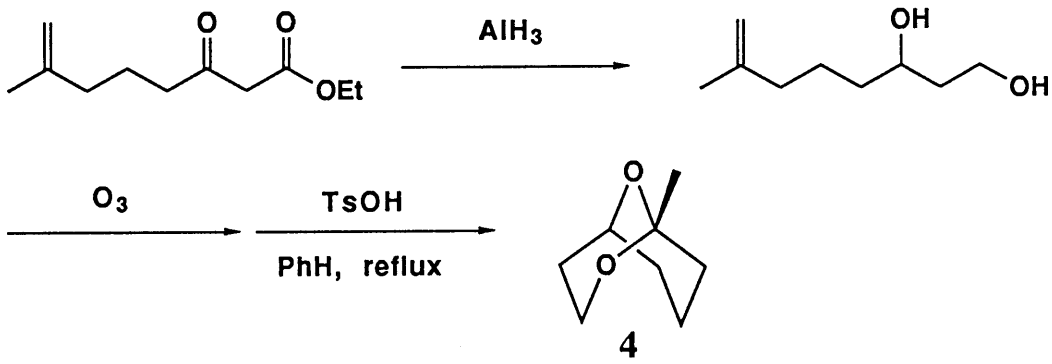
Scheme 4

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

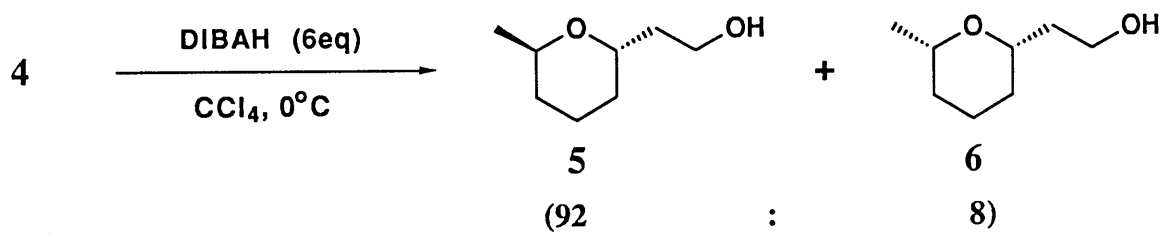
Preparation of 1-methyl-2,9-dioxabicyclo[3.3.1]nonane (4): Reduction of ethyl 7-methyl-3-oxo-7-octenate which was the intermediate of the synthesis of **3** with aluminum hydride afforded 7-methyl-7-octene-1, 3-diol, which was treated with ozone and refluxed in benzene with a catalytic amount of *p*-toluenesulfonic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



Scheme 6

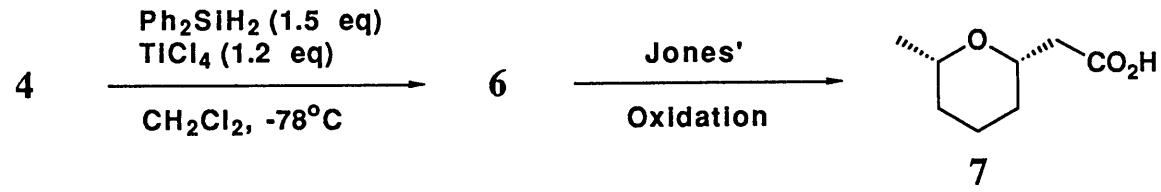
Results and Discussion

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.



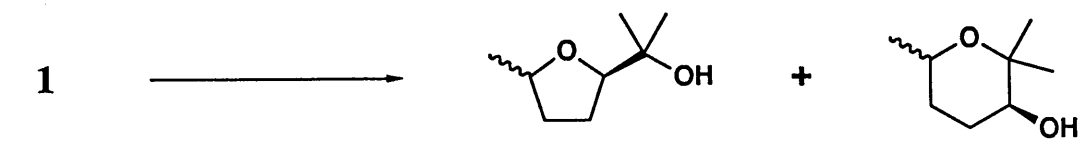
Scheme 7

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.



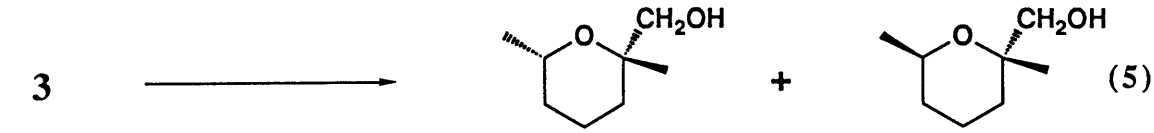
Scheme 8

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)

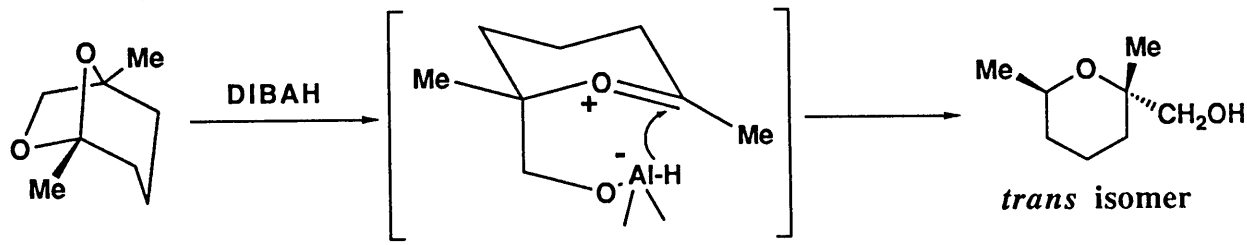
Condition	Yield (%)	*cis*	*trans*		*cis*	*trans*
DIBAH (6 eq) CH_2Cl_2, 0°C	61	0.6	55.5	:	2.1	41.8
Et_3SiH (1.5 eq) $TiCl_4$ (1.2 eq) CH_2Cl_2, -78°C	61	42.6	0.8	:	48.7	7.9



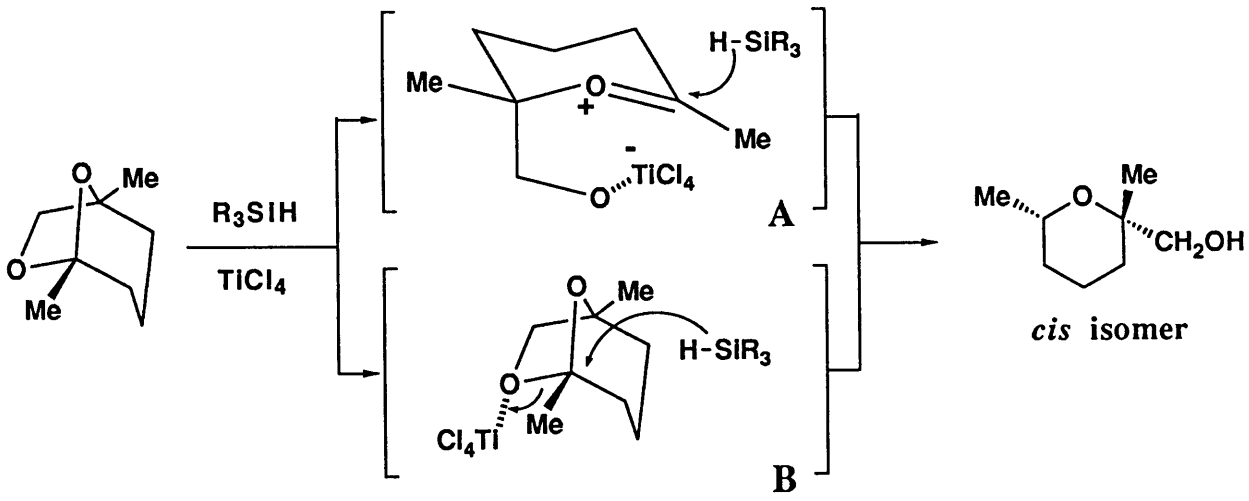
(5)

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).

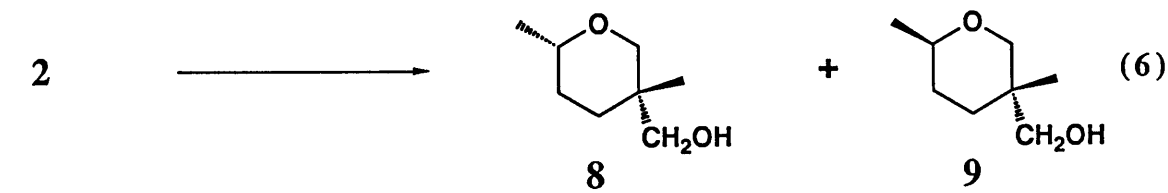


Scheme 9



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).

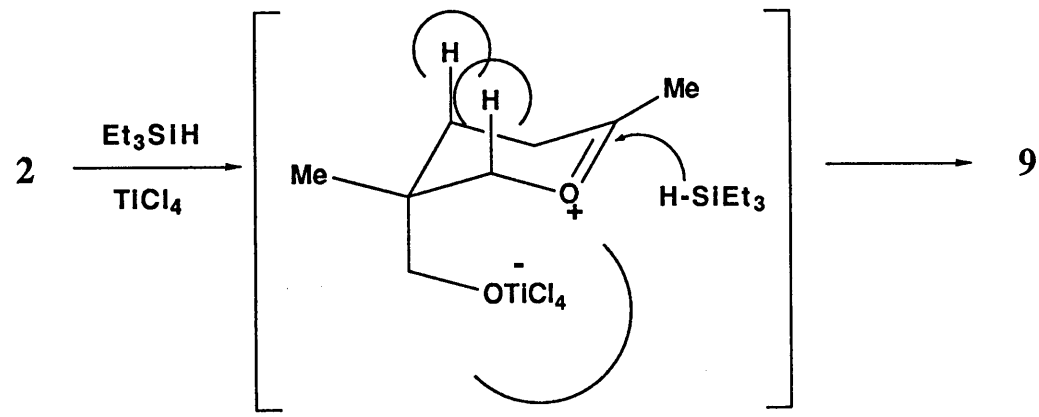


(6)

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

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.



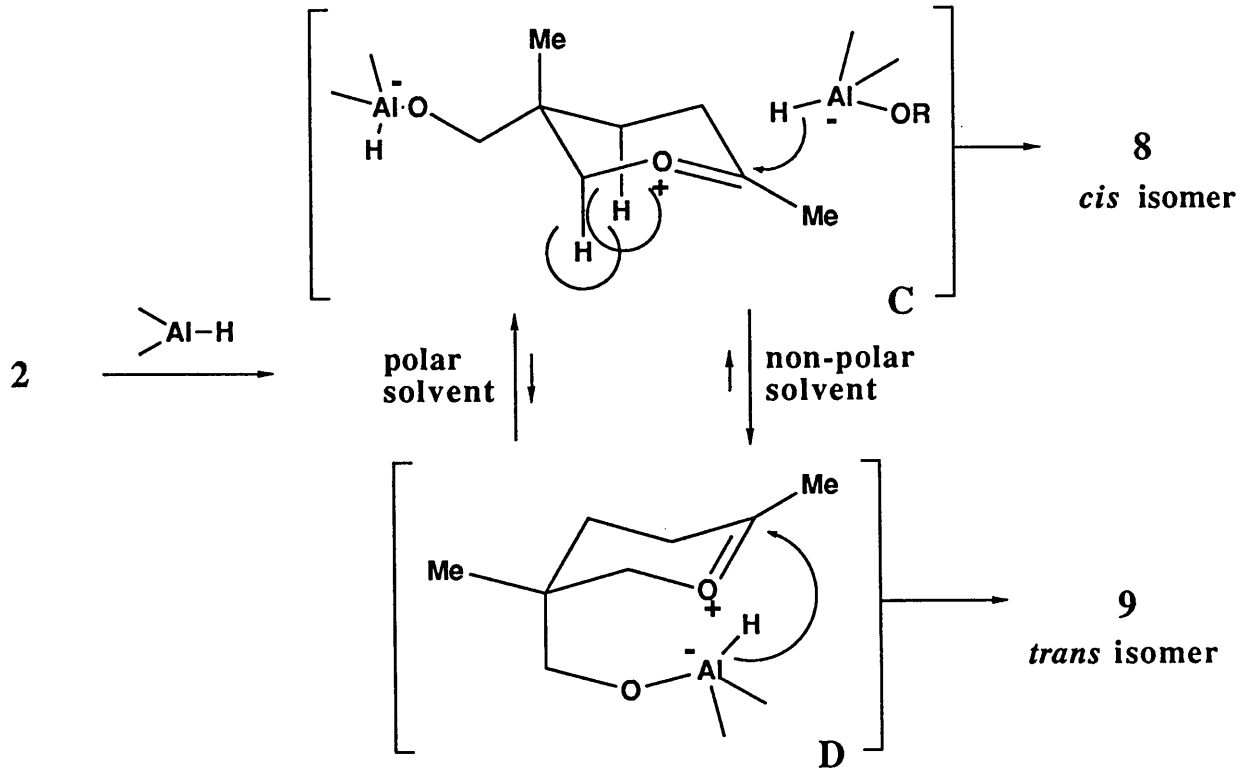
Scheme 11

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 corresponding *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).



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.

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.

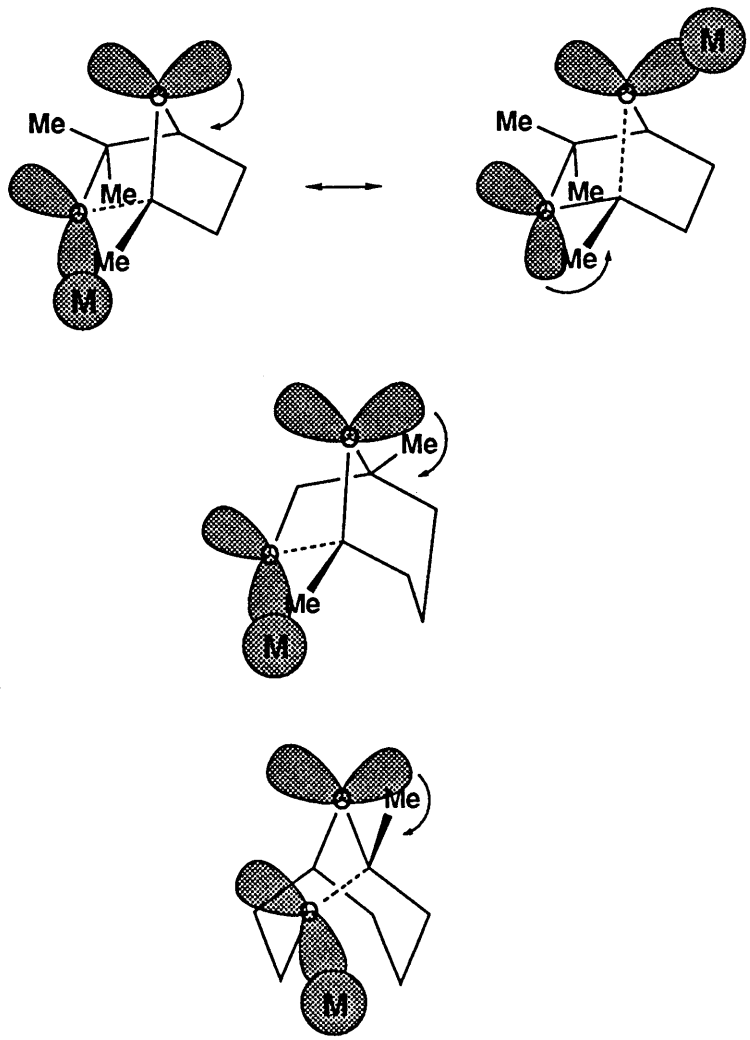


Figure 1

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); ^1H 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}; ^1H 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}; ^1H 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); ^1H 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}; ^1H 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, $C\underline{H}_2OH$), 3.31-3.44 (m, 1H, $C(6)H_2$), 3.78 (dd, J=13.5 and 1.8 Hz, 1H, $C\underline{H}_2OH$); 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); ^1H 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}; ^1H 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}; ^1H 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, $C\underline{H}_2OH$), 3.79 (d, J=10.8 Hz, 1H, $C\underline{H}_2OH$), 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}; ^1H 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}; ^1H 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); ^1H 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]

References and Notes

1. (a) Mori, A; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4581.

   (b) Idem, *J. Organometal. Chem.* **1985**, *285*, 83.

   (c) Ishihara, K.; Mori, A.; Arai, I.;Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 983.

   (d) Mori, A.; Ishihara, K.; Yamamoto, H. *Ibid.*, **1986**, *27*, 987.

(e) Mori, A.; Ishihara, K.; Arai, I.; Yamamoto, H. *Tetrahedron* **1987**, *43*, 755.

2. For extensive references, see:

   Seebach, D.; Imwinkelried, R.; Weber, T. *"Modern Synthetic Methods 1986, Vol. 4"* ed by R. Scheffold, Springer-Verlag Berlin Heidelberg (1986), pp. 191-216.

3. (a) Johnson, W. S.; Harbert, C. A.; Stipanovic, R. D. J. *Am. Chem. Soc.* **1968**, *90*, 5279.

   (b) Johnson, W. S.; Harbert, C. A.; Ratcliffe, B. E.; Stipanovic, R. D. *Ibid.* **1976**, *98*, 6188.

   (c) Hughes, L. R.; Schmid, R.; Johnson, W. S. *Bioorg. Chem.* **1979**, *8*. 513.

4. (a) McNamara, J. M.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7371.

   (b) Sekizaki, H.;Jung, M.; McNamara, J. M.; Kishi, Y. *Ibid.* **1982**, *104*, 7372.

5. Bartlett, P. A.; Johnson, W. S.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2088.

6. (a) Johnson, W. S.; Crackett, P. H.; Elliott, J. D.

   (b) Jagodzinski, J. J.; Lindell, S. D.; Natarajan, S. *Tetrahedron Lett.* **1984**, *25*, 3951.

7. Johnson, W. S.; Edington, C.; Elliott, J. D.; Silverman, I. R. *J. Am. Chem. Soc.* **1984**, *106*, 7588.

8. Elliott, J. D.; Choi, V. M. F.; Johnson, W. S. *J. Org. Chem.* **1983**, *48*, 2294.

9. Johnson, W. S., Elliott, R.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2904.

10. Harada, T.; Hayashiya, T.; Wada, I; Iwa-ake, N.; Oku, A. *J. Am. Chem. Soc.* **1987**, *109*, 527.

11. Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2.

12. Recent methods:

   (a) Okada, M.; Sumitomo, H.; Irii, S. *Makromol. Chem.* **1976**, *177*, 2331.

   (b) Bloodworth, A. J.; Khan, J. A. *J. Chem. Soc. Perkin Trans. I* **1980**, 2450.

   (c) Williams, D. R.; Phillips, J. G.; Barner, B. A. *J. Am. Chem. Soc.* **1981**, *103*, 7398.

(d) Walba, D. M.; Stoudt, G. S. *Tetrahedron Lett.* **1982**, *23*, 727.

(e) Porter, N. A.; Zuraw, P. J. *J. Org. Chem.* **1984**, *49*, 1345.

(f) Winstead, R. C.; Simpson, T. H.; Lock, G. A.; Schiavelli, M. D.; Thompson, D. W. *Ibid.* **1986**, *51*, 275.

(g) Bartlett, P. A.; Chapuis, C. *Ibid.* **1986**, *51*, 2799 and references cited therein; Overman, L. E.; Castaneda, A.; Blumenkopf, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 1303 and references cited therein.

(h) Nicolaou, K. C.; Ladduawahetty, T.; Randall, J. L.; Chuchowski, A. *Ibid.* **1986**, *108*, 2466 and references cited therein.

(i) Babirad, S. A.; Wang, Y.; Kishi, Y. *J. Org. Chem.* **1987**, *52*, 1370.

13. Preliminary communication:

(a) Ishihara, K; Mori, A.; Yamamoto, H. *Tetrahedron Lett.* **1987**, *28*, 6613.

The similar reports were disclosed by Kotsuki et al.

(a) Kotsuki, H.; Ushio, Y.; Kadota, I.; Ochi, M. *Chem. Lett.* **1988**, 927.

(b) Idem, *J. Org. Chem.* **1989**, *54*, 5153.

14. Hall, Jr. H. K.; DeBlauwe, F.; Carr, L. J.; Rao, V. S.; Reddy, G. S. *J. Polymer Sci.* **1976**, *56*, 101.

15. Wasserman, H. H.; Wolff, S.; Oku, T. *Tetrahedron Lett.* **1986**, *27*, 4909.

16. Joshi, N. N.; Mamdapur, V. R.; Chadha, M. S. *J. Chem. Soc. Perkin. Trans. I* **1983**, 2963.

17. Nussabaumer, C.; Frater, G. *Helv. Chim. Acta* **1987**, *70*, 396 and references cited therein.

18. Maurer, B.; Grieder, A.; Thommen, W. *Helv. Chim. Acta* **1979**, *62*, 44; The *trans* isomer was found to be an oil.

19. Arco, M. J.; Trammell, M. H.; White, J. D. *J. Org Chem.* **1976**, *41*, 2075.

20. Trost, B. M.; Masuyama, Y. *Isr. J. Chem.* **1984**, *24*, 134.

21. Eliel, E. L.; Banks, H. D. *J. Am. Chem. Soc.* **1972**, *94*, 171.

22. (a) Eliel, E. L.; Manoharan, M.; Pietrusiewicz, K. M.; Hargrave, K. D. *Org. Mag. Reson.* **1983**, *21*, 94.

(b) Utaka, M.; Makino, H.; Oota, Y.; Tsuboi, S.; Takeda, A. *Tetrahedron Lett.* **1983**, *24*, 2567.

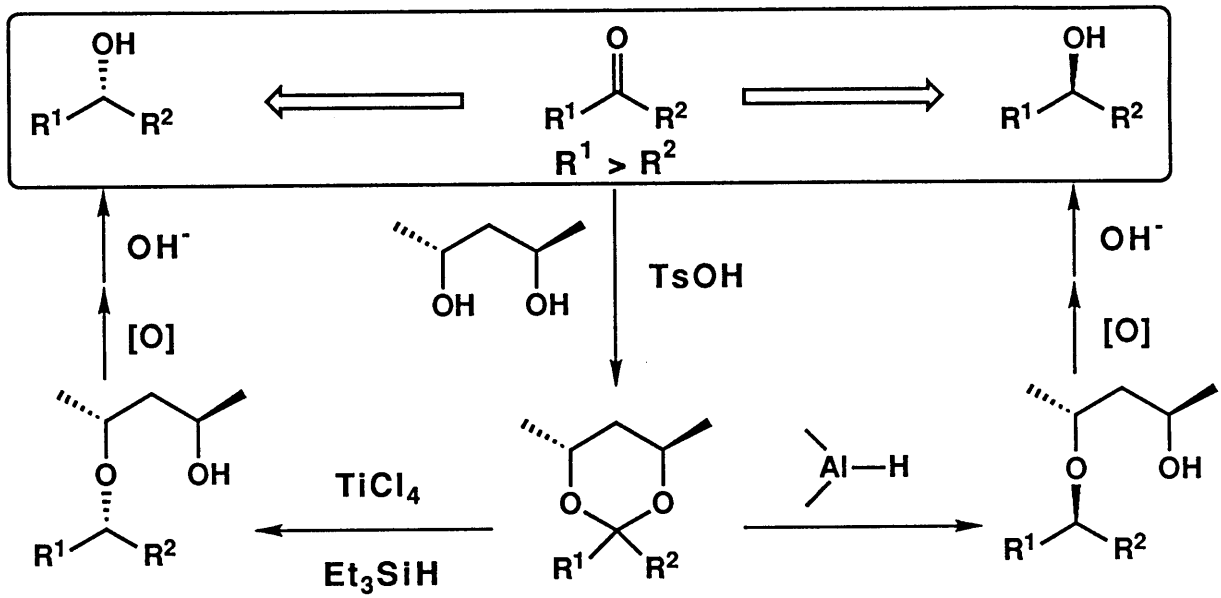
Chapter 3

Reductive Cleavage of Chiral Acetals Using Diethylaluminum Fluoride-Pentafluorophenol System

Abstract: The reaction of acetal derived from (-)-(2*R*,4*R*)-2,4-pentanediol and a ketone with a diethylaluminum fluoride-pentafluorophenol system produces reductively cleaved products with high diastereoselectivity. The reaction is a new method for diastereoselective cleavage of acetals: an intramolecular Meerwein-Ponndorf-Verley reductive and Oppenauer oxidative reaction of acetal template.

Introduction

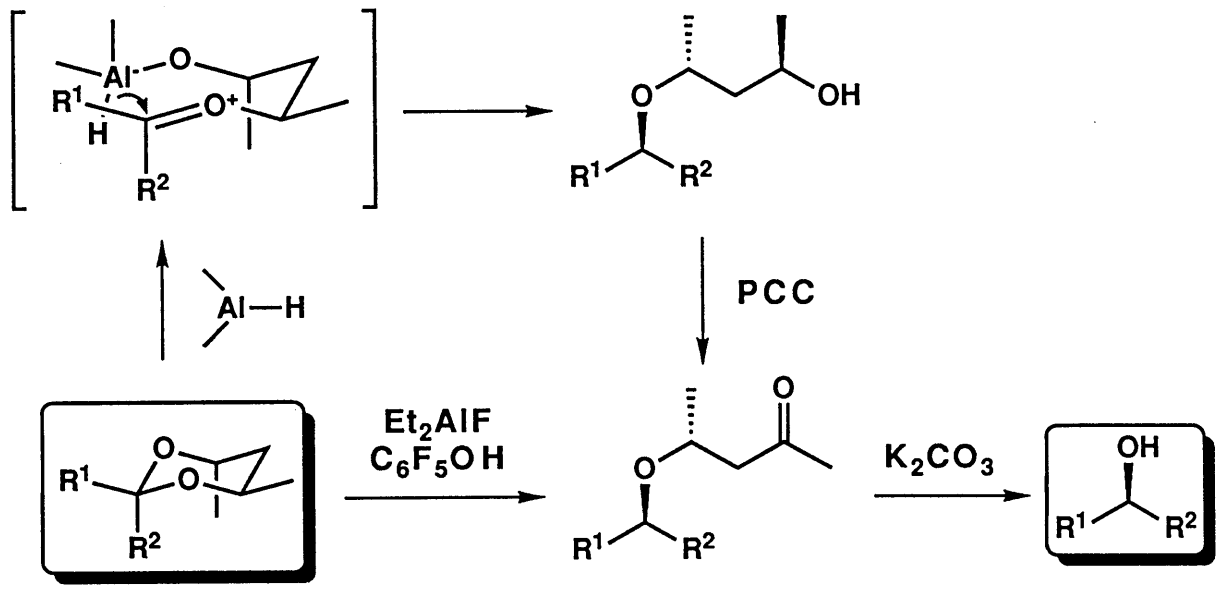
We previously described the diastereoselective cleavage of chiral acetals derived from the condensation of unsymmetrical ketones and (-)-(2*R*,4*R*)-2,4-pentanediol to give, after removal of chiral auxiliary, optically active alcohols with high enantiopurities.[1] The observed high stereoselective conversion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



Scheme 1

Reductive cleavages of acetals with organoaluminum hydride reagents (e.g. Br_2AlH, Cl_2AlH, DIBAH) affords stereoselectively syn reduced products. The observed high diastereoselectivity was ascribed to the stereospecific coordination of the organoaluminum reagent with one of the acetal oxygens followed by the hydride attack syn on the cleaved carbon-oxygen bond. The reaction probably proceeds by a tight ion paired S_N1-like mechanism. Herein, we report the reductive cleavages of chiral acetals by the combined use of diethylaluminum fluoride and pentafluorophenol reagents. This is a new reaction for acetals, an intramolecular Meerwein-Ponndorf-Verley reductive and Oppenauer oxidative reaction of acetal template. Removal of the chiral auxiliary, followed by base-catalyzed β-elimination of the resulting β-alkoxy ketone, easily

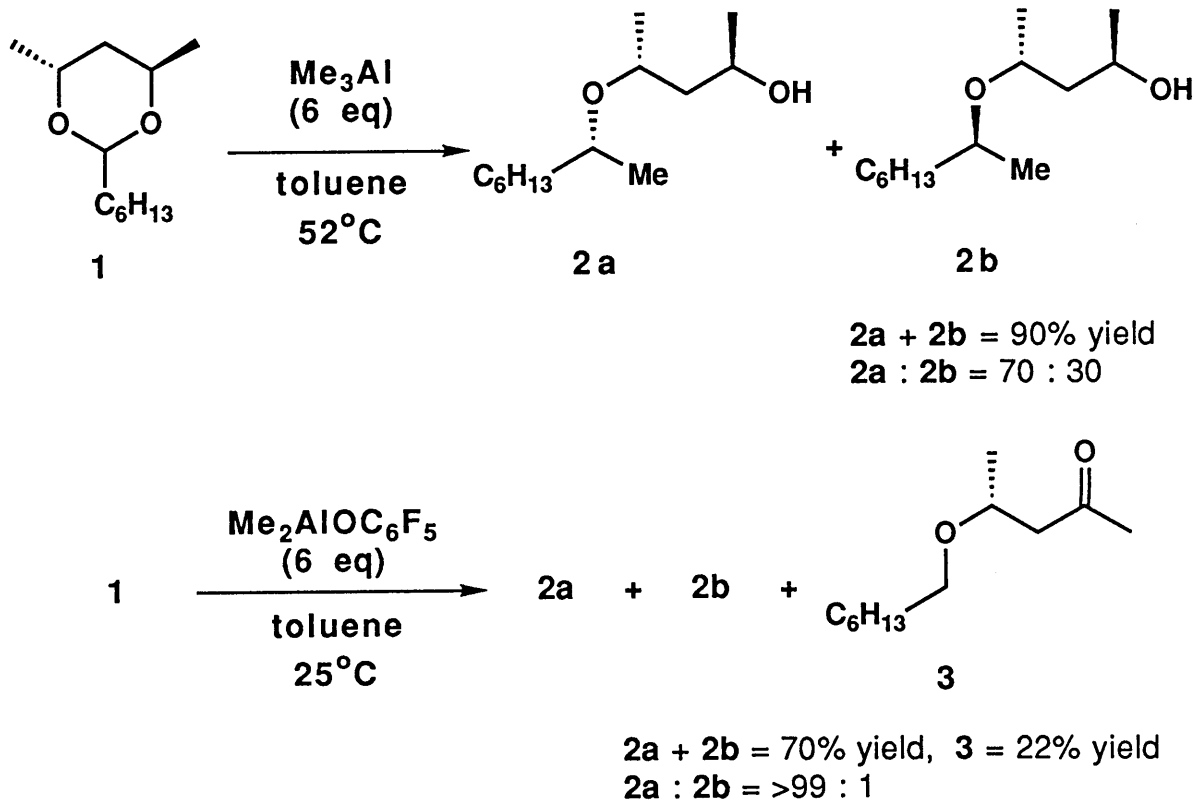
give the optically pure alcohol in good yield. In this paper we have also demonstrated that pentafluorophenol is a more useful additive for this novel hydride-transfer reaction (Scheme 2).



Scheme 2

Results and Discussion

In view of the efficiency of the mild and stereospecific cleavage of chiral acetals by organoaluminum hydride reagents, the behavior of trialkylaluminum was studied systematically. It was soon realized, however, that treatment of acetals with trialkylaluminum led to a mixture of diastereomers. Our initial studies found these rather disappointing results. We recently discovered that diastereoselectivities of conversion of chiral acetals derived from aldehyde and (-)-(2*R*,4*R*)-pentanediol to hydroxy ethers were increased by the combined use of trialkylaluminum and pentafluorophenol. In this case, a reductive β-alkoxyketone was always produced as a minor product (Scheme 3).



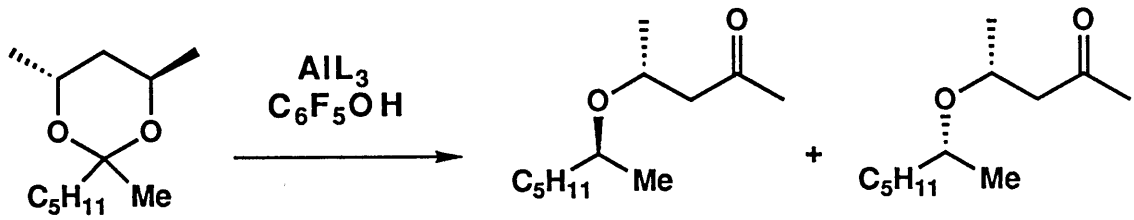
Scheme 3

During the course of our continuing study, our interests have focused on direct preparation of β-alkoxy ketones from chiral acetal and its stereoselectivity in the case of chiral acetals derived from unsymmetrical ketones. This reaction is, so to speak, an intramolecular Meerwein Ponndorf-Verley reductive and Oppenauer oxidative reaction of acetal template.

The conversion of chiral acetal **4** derived from 2-heptanone and (-)-(2*R*,4*R*)-pentanediol to β-alkoxyketone was initially chosen as a model, and the effect of pentafluorophenol was studied. The results, of examining various reaction conditions and of using several aluminum reagents as Lewis acid, are summarized in Table 1. Treatment of **4** with trimethylaluminum and pentafluorophenol gave rather reductively cleaved β-alkoxy ketones **5** as main products and alkylic cleaved β-alkoxy alcohol was not almost given (Entries 1 and 2). The combined use of 1.2 equivalent of diethylaluminum fluoride and 2.4 equivalent of pentafluorophenol was found to be effective for new diastereoselective reductive cleavage reaction (Entries 6 and 7). When

dichloromethane was used as a solvent, **5** was obtained in good yield (91%) and its diastereomeric ratio was 81 : 19 (Entry 6). When the reaction medium was changed from dichloromethane to toluene, the diastereomeric ratio of **5** was raised to 86 : 14 (Entry 7). The major isomer afforded syn reduced products, and the observed high diastereoselectivity was similar to that of reductive cleavages of acetals with organoaluminum hydride reagents. In addition, it was noted that, in the presence of a catalytic amount of diethylaluminum fluoride (10 mol%) and pentafluorophenol (20 mol%) this reaction did not proceed even with heating to 80°C.

Table 1. Reductive Cleavage of 4 with the Combined Use of AlL_3 and C_6F_5OH



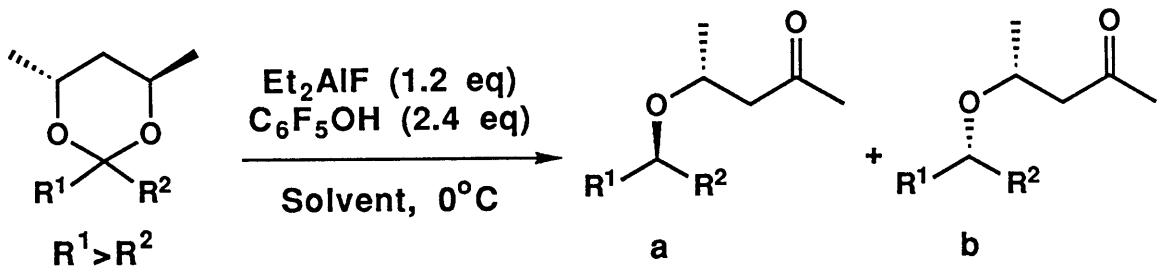
4 5a 5b

Entry	Al reagent (eq)	Equivqlent of C_6F_5OH	Solvent	Temp. (°C)	Yield (%)	Ratio 5a : 5b
1	Me_3Al (6)	6	toluene	0→25	23	85 : 15
2	Me_3Al (6)	12	toluene	0→25	34	76 : 24
3	Me_2AlCl (6)	6	toluene	0→25	12	68 : 32
4	Et_2AlF (1.2)	-	CH_2Cl_2	0→25	trace	-
5	Et_2AlF (1.2)	1.2	CH_2Cl_2	0	62	82 : 18
6	Et_2AlF (1.2)	2.4	CH_2Cl_2	0	91	81 : 19
7	Et_2AlF (1.2)	2.4	toluene	0	61	86 : 14

As shown in Table 2, several chiral acetals derived from aliphatic or aromatic ketones are applicable in good yields and with high diastereoselectivities in this reaction. These

diastereoselectivities tend to be similar to that in the reductive cleavage using organoaluminum hydride. In all cases, when toluene was used as a solvent instead of dichloromethane, diastereoselectivity was improved, but the yield was rather low.

Table 2. Reductive Cleavage of Acetals with the Combined use of Et_2AlF and C_6F_5OH

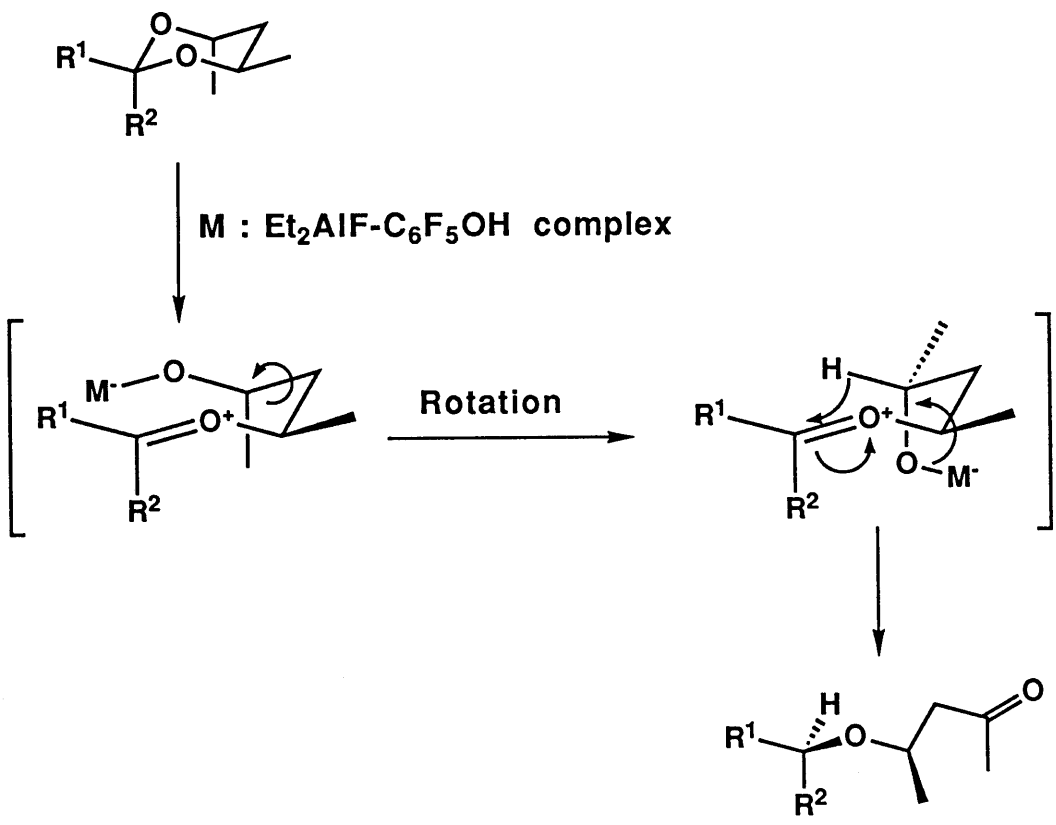


R^1	R^2	Solvent	Yield (%)	Ratio a : b
C_5H_{11}	Me	CH_2Cl_2	91	81 : 19
		toluene	61	86 : 14
i-Bu	Me	CH_2Cl_2	81	72 : 28
		toluene	69	77 : 23
i-Pr	Me	CH_2Cl_2	71	97 : 3
		toluene	62	98 : 2
Ph	Me	CH_2Cl_2	81	95 : 5
		toluene	68	>99 : 1
Ph	Et	CH_2Cl_2	92	90 : 10
		toluene	84	93 : 7

Each acetal derived from several differential alcohols was next examined for this transformation. Acetals derived from 1,3-propanediol and (-)-(2*R*,3*R*)-butanediol were not

converted even at room temperature. Acyclic acetals derived from 2-propanol were only hydrized to aldehyde after the usual work-up. Therefore, the structure of acetal derived from (-)-(2*R*,4*R*)-pentanediol was found to be a suitable substrate in the present intramolecular hydride transfer reaction.

Although the detailed mechanism is not yet clear, it is assumed that energetically stable tight ion-paired intermediate is generated by stereospecific coordination of the Et_2AlF-C_6F_5OH complex to one of the oxygens of acetal: the hydrogen atom of alkoxide as hydride is then transferred from the direction syn to this departing oxygen which leads to the *S* configuration at the resulting ether carbon, as observed (Scheme 4).



Scheme 4

The precise structure of the Et_2AlF-C_6F_5OH complex is also not yet clear. However, it should be noted that, when Et_2AlF and C_6F_5OH were mixed at room temperature, ethane gas was not generated. Further investigations to elucidate the present reaction should be made.

Experimental Section

General. Infrared (IR) were recorded on a Hitachi 260-10 spectrometer. ^1H NMR spectra were measured on a Varian Gemini 200 (200 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). Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; br, broad peak. Analytical gas-liquid phase chromatography (GC) was performed on Shimadzu Model 8A instrument with a flame-ionization detector and a capillary column of PEG-20M Bonded (25 m) using nitrogen as carrier gas. 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 purified by preparative column chromatography on silica gel 60 E. Merck Art 9385. 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 flsks with magnetic stirring bars under an atomosphere of dry argon.

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

Preparation of Acetals. Acetals were prepared in excellent yield from the corresponding ketone and (-)-(2*R*,4*R*)-2,4-pentanediol in the presence of a catalytic quantity of *p*-toluenesulfonic acid.

(4*R*,6*R*)-2-Pentyl-2,4,6-trimethyl-1,3-dioxane: ^{1}H NMR ($CDCl_3$) δ 0.90 (t, *J*=6.5 Hz, 3H, CH_3), 1.19 (d, *J*=6.2 Hz, 6H, $2CH_3$), 1.31 (s, 3H, CH_3), 1.24-1.80 (m, 10H, $(CH_2)_4$ and C(5)H_2), 3.85-4.10 (m, 2H, 2CHO).

(4*R*,6*R*)-2-(2-Methylpropyl)-2,4,6-trimethyl-1,3-dioxane: ^{1}H NMR ($CDCl_3$) δ 0.94 (d, *J*=6.4 Hz, 3H, Me), 0.95 (d, *J*=6.4 Hz, 3H, CH_3), 1.17 (d, *J*=6.2 Hz, 6H, 2Me), 1.33 (s, 3H, Me), 1.40-1.86 (m, 5H, C(5)H_2 and Me_2CHCH_2), 3.83-4.07 (m, 2H, 2OCH).

(4*R*,6*R*)-2-(1-Methylethyl)-2,4,6-trimethyl-1,3-dioxane: ^{1}H NMR ($CDCl_3$) δ 0.90 (d, *J*=7.0 Hz, 3H, Me), 0.94 (d, *J*=6.6 Hz, 3H, Me), 1.13-1.21 (complex of d and s, 9H, 3Me), 1.52-1.62 (m, 2H, C(15)H_2), 2.04 (septet, *J*=7.0 Hz, 1H, Me_2CH), 3.86-4.09 (m, 2H, 2CHO).

(4*R*,6*R*)-2-Phenyl-2,4,6-trimethyl-1,3-dioxane: ^{1}H NMR ($CDCl_3$) δ 1.23 (d, *J*=6.4 Hz, 3H, Me), 1.25 (d, *J*=6.4 Hz, 3H, Me), 1.55 (s, 3H, Me), 1.44-1.74 (m, 2H, C(5)H_2), 3.60-3.78 (m, 1H, CHO), 4.11-4.30 (m, 1H, CHO), 7.25-7.45 (m, 3H, Ph), 7.50-7.60 (m, 2H, Ph).

(4*R*,6*R*)-4,6-Dimethyl-2-ethyl-2-phenyl-1,3-dioxane: ^{1}H NMR ($CDCl_3$) δ 0.73 (t, *J*=7.4 Hz, 3H, CH_3), 1.19 (d, *J*=6.4 Hz, 3H, CH_3), 1.21 (d, *J*=6.4 Hz, 3H, CH_3), 1.40-2.00 (m, 4H, C(5)H_2 and CH_2CH_3), 3.59-3.78 (m, 1H, CHO), 4.07-4.25 (m, 1H, CHO).

General Procedure for Reductive Cleavage of Acetals with the Combined Use of Diethylaluminum Fluoride and Pentafluorophenol. To a solution of pentafluorophenol (2.0 M in toluene or dichloromethane, 0.6 mL, 1.2 mmol) in toluene (9 mL) or dichloromethane (9 mL) was added dropwise diethylaluminum fluoride (1.0 M in hexane, 0.6 mL, 0.6 mmol) at 0°C and the solution was stirred at that temperature for 10 min. Then a solution of acetal (0.5 mmol) in toluene (1 mL) or dichloromethane (1 mL) was added dropwise to the

solution at 0°C. After stirring for 1 h, the resulting mixture was poured into 2 N aqueous sodium hydroxide (20 mL), and extracted with hexane for three times (20 mL X 3). The combined organic layers were dried over magnesium sulfate, concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluant: hexane-EtOAc) to give the diastereomeric mixture of the corresponding β-alkoxy ketones as a colorless oil. The diastereomeric ratio was determined by capillary GC analysis by comparison with the authentic samples, which were prepared by reductive cleavages of the corresponding acetals using titanium tetrachloride-triethylsilane system or using diisobutylaluminum hydride and subsequent oxidation with pyridinium chlorochromate.

The physical properties and analytical data of the β-alkoxy ketones thus obtained are listed below.

(2*S*,1'*R*)-2-(1'-Methyl-3'-oxabutoxy)heptane: GC (100°C), t_R=10.8 min; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, *J*=6.3 Hz, 3H, CH_3), 1.11 (d, *J*=6.2 Hz, 3H, CH_3), 1.16 (d, *J*=6.2 Hz, 3H, CH_3), 1.20-1.50 (m, 8H, $(CH_2)_4$), 2.17 (s, 3H, CH_3), 2.40 (dd, *J*=5.8, 15.8 Hz, 1H, C*H*HC=O), 2.72 (dd, *J*=6.9, 15.8 Hz, 1H, CH*H*C=O), 3.34-3.52 (m, 1H, CHO), 3.95 (sixtet, *J*=6.2 Hz, 1H, CHO).

(2*R*,1'*R*)-2-(1'-Methyl-3'-oxabutoxy)heptane: GC (100°C), t_R=11.8 min; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, *J*=6.5 Hz, 3H, CH_3), 1.06 (d, *J*=6.0 Hz, 3H, CH_3), 1.13 (d, *J*=6.0 Hz, 3H, CH_3), 1.20-1.49 (m, 8H, $(CH_2)_4$), 2.17 (s, 3H, CH_3), 2.40 (dd, *J*=5.4, 15.4 Hz, 1H, C*H*HC=O), 2.70 (dd, *J*=7.4, 15.4 Hz, 1H, CH*H*C=O), 3.32-3.53 (m, 1H, CHO), 3.94 (sixtet, *J*=6.0 Hz, 1H, CHO).

(2*S*,1'*R*)-4-Methyl-2-(1'-methyl-3'-oxabutoxy)pentane: GC (90°C), t_R=7.5 min; ^{1}H NMR ($CDCl_3$) δ 0.88 (d, *J*=6.6 Hz, 3H, CH_3), 0.89 (d, *J*=6.6 Hz, 3H, CH_3), 1.12 (d, *J*=6.0 Hz, 3H, CH_3), 1.10-1.22 (m, 1H, Me_2CHCHH), 1.18 (d, *J*=6.2 Hz, 3H, CH_3), 1.33-1.80 (m, 2H, Me_2CHCHH), 2.18 (s, 3H, CH_3), 2.42 (dd, *J*=5.8, 15.8 Hz, 1H, C*H*HC=O), 2.73 (dd, *J*=6.6, 15.8 Hz, 1H, CH*H*C=O), 3.43-3.61 (m, 1H, CHO), 3.87-4.05 (m, 1H, CHO).

(2*R*,1'*R*)-4-Methyl-2-(1'-methyl-3'-oxabutoxy)pentane: GC (90°C), t_R=8.0 min; ^{1}H NMR ($CDCl_3$) δ 0.887 (d, *J*=6.6 Hz, 3H, CH_3), 0.895 (d, *J*=6.6 Hz, 3H, CH_3), 1.06 (d, *J*=6.2 Hz, 3H, CH_3), 1.09-1.22 (m, 1H, Me_2CHCHH), 1.15 (d, *J*=6.0 Hz, 3H, CH_3), 1.41 (ddd, *J*=6.0, 7.6, 13.8 Hz, 1H, Me_2CHCHH), 1.58-1.82 (m, 1H, Me_2CH), 2.18 (s, 3H, CH_3), 2.41 (dd, *J*=5.4, 15.4 Hz, C*H*HC=O), 2.70 (dd, *J*=7.3, 15.4 Hz, CH*H*C=O), 3.53 (dquintet, *J*=7.6, 6.0 Hz, 1H, CHO), 3.88-4.05 (m, 1H, CHO).

(2*S*,1'*R*)-3-Methyl-2-(1'-methyl-3'-oxabutoxy)butane: GC (40°C), t_R=33.8 min; ^{1}H NMR ($CDCl_3$) δ 0.82 (d, *J*=6.0 Hz, 3H, Me), 0.85 (d, *J*=6.8 Hz, 3H, Me), 1.05 (d, *J*=6.4 Hz, 3H, Me), 1.16 (d, *J*=6.0 Hz, 3H, Me), 1.55-1.77 (m, 1H, Me_2CH), 2.18 (s, 3H, Me), 2.40 (dd, *J*=5.8, 15.8 Hz, 1H, C*H*HC=O), 2.74 (dd, *J*=6.9, 15.8 Hz, 1H, CH*H*C=O), 3.22 (quintet, *J*=6.0 Hz, 1H, CHO), 3.85-4.03 (m, 1H, CHO).

(2*R*,1'*R*)-3-Methyl-2-(1'-methyl-3'-oxabutoxy)butane: GC (40°C), t_R=32.9 min; ^{1}H NMR ($CDCl_3$) δ 0.86 (d, *J*=6.8 Hz, 3H, Me), 0.88 (d, *J*=6.8 Hz, 3H, Me), 1.01 (d, *J*=6.4 Hz, 3H, Me), 1.13 (d, *J*=6.2 Hz, 3H, Me), 1.65 (septet, *J*=6.8 Hz, 1H, Me_2CH), 2.18 (s, 3H, CH_3), 2.40 (dd, *J*=5.4, 15.0 Hz, 1H, C*H*HC=O), 2.70 (dd, *J*=7.3, 15.0 Hz, 1H, CH*H*C=O), 3.14-3.29 (m, 1H, CHO), 3.84-4.02 (m, 1H, CHO).

(1*S*,1'*R*)-1-(1'-Methyl-3'-oxabutoxy)-1-phenylethane: GC (120°C), t_R=26.6 min; ^{1}H NMR ($CDCl_3$) δ 1.21 (d, *J*=6.2 Hz, 3H, Me), 1.42 (d, *J*=6.4 Hz, 3H, Me), 2.04 (s, 3H, CH_3), 2.41 (dd, *J*=6.1, 15.4 Hz, 1H, C*H*HC=O), 2.66 (dd, *J*=7.0, 15.4 Hz, 1H, CH*H*C=O), 3.74-3.92 (m, 1H, CHO), 4.55 (q, *J*=6.4 Hz, 1H, CHO).

(1*R*,1'*R*)-1-(1'-Methyl-3'-oxabutoxy)-1-phenylethane: GC (120°C), t_R=29.7 min; ^{1}H NMR ($CDCl_3$) δ 1.06 (d. *J*=6.2 Hz, 3H, CH_3), 2.21 (s, 3H, CH_3). Other resonances could not be discerned for this minor isomer.

(1*S*,1'*R*)-1-(1'-Methyl-3'-oxabutoxy)-1-phenylpropane: GC (130°C), t_R=22.1 min; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, *J*=7.4 Hz, 3H, Me), 1.20 (d, *J*=6.2 Hz, 3H, CH_3), 1.50-1.90 (m, 2H, CH_2CH_3), 2.02 (s, 3H, CH_3), 2.40 (dd, *J*=6.0, 15.3 Hz, 1H, C*H*HC=O),

2.63 (dd, *J*=6.8, 15.3 Hz, 1H, CH*H*C=O), 3.81 (sixtet, *J*=6.2 Hz, 1H, OC*H*Me), 4.24 (dd, *J*=6.2, 7.2 Hz, 1H, PhC*H*), 7.20-7.40 (m, 5H, Ph).

(1*R*,1'*R*)-1-(1'-Methyl-3'-oxabutoxy)-1-phenylpropane: GC (130°C), t_R=23.7 min; ^{1}H NMR ($CDCl_3$) δ 1.01 (d, *J*=6.2 Hz, 3H, Me), 2.20 (s, 3H, Me), 2.47 (dd, *J*=6.0, 15.6 Hz, 1H, C*H*HC=O), 2.82 (dd, *J*=6.4, 15.6 Hz, 1H, CH*H*C=O), 3.91 (sixtet, *J*=6.2 Hz, 1H, OCHMe). Other resonances could not be discerned for this minor isomer.

References and Notes

1. (a) Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4581.

   (b) Idem, *J. Organometal. Chem.* **1985**, *285*, 83.

   (c) Ishihara, K.; Mori, A.; Arai, I.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 983.

   (d) Mori, A.; Ishihara, K.; Yamamoto, H. *Ibid.*, **1986**, *27*, 983.

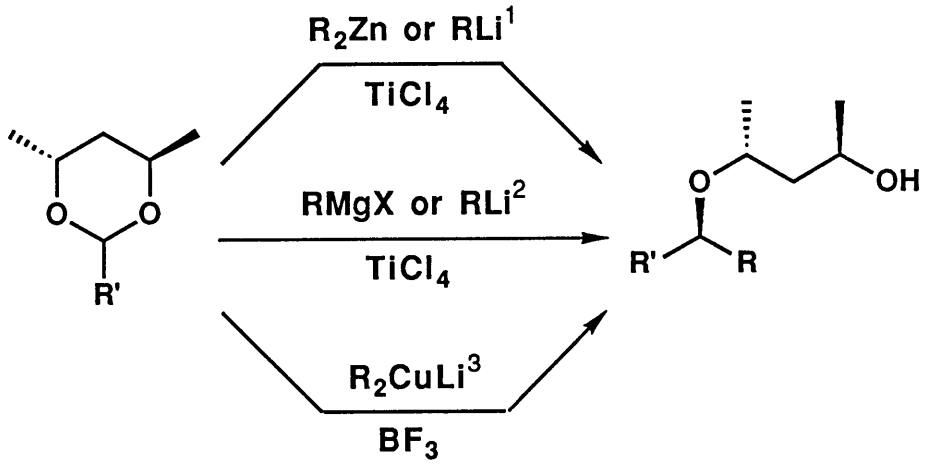
   (e) Mori, A.; Ishihara, K.; Arai, I.; Yamamoto, H. *Tetrahedron* **1987**, *43*, 755.

Chapter 4

Stereoselective Alkylative Cleavage of Chiral Acetals: Retention of the Stereochemistry

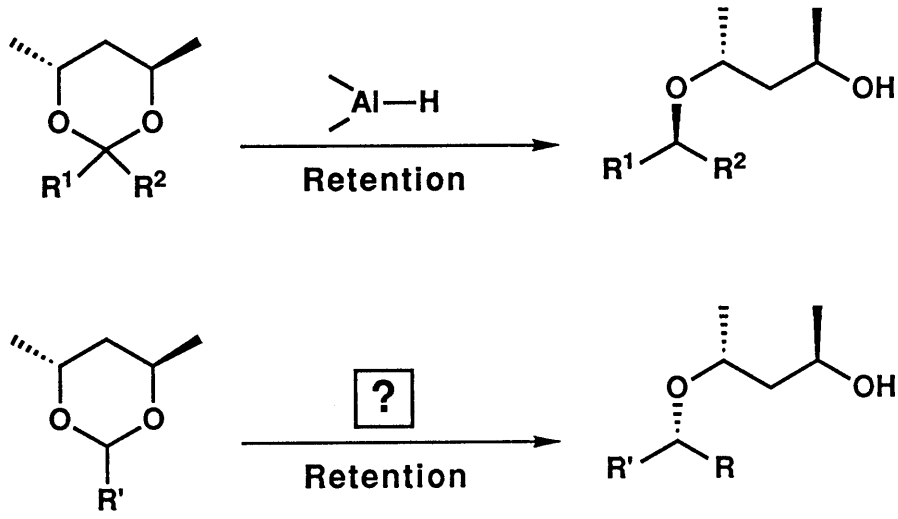
Abstract: The reaction of acetal derived from (-)-(2*R*,4*R*)-2,4-pentanediol and an aldehyde with a trialkylaluminum-pentafluorophenol system produces alkylatively cleaved products with high diastereoselectivity. The observed stereochemical outcome is followed by the alkyl anion attack syn to the cleaved carbon oxygen bond.

We previously described a highly chemo- and stereoselective cleavage of acetals derived from (-)-(2*R*,4*R*)-2,4-pentanediol with organotitanium reagents.[1] The reaction proceeds under mild conditions in excellent yield and high chemoselectivity to give, after removal of auxiliary, chiral alcohols of high enantiopurities. In addition, complexation of chiral acetals and titanium tetrachloride followed by treatment with *n*-butyllithium also results in formation of the corresponding *n*-butylated alcohols with high stereoselectivity. Johnson's group disclosed similar results with organolithium and Grignard reagents in the presence of titanium tetrachloride.[2] Closely related reactions with dialkylcopper lithium in the presence of boron trifluoride were also published by Alexakis' group.[3] All the above reactions took place *via* anti attack of the alkylmetallic reagents to the cleaved carbon-oxygen bond (Scheme 1).



Scheme 1

Stereoselective alkylative cleavage of chiral acetals *via* syn attack of the reagents, however, has not yet been reported, although we did report the reductive cleavage of chiral acetals by aluminum hydride reagents (e.g. DIBAH, Br_2AlH, Cl_2AlH).[1b,4] Since the beginning of these studies, we have been interested in the possibility of achieving the retention of the stereochemical outcome of alkyl anion attack on the acetal group, which, if successful, would provide a method to obtain both enantiomers from a single chiral starting acetal (Scheme 2).

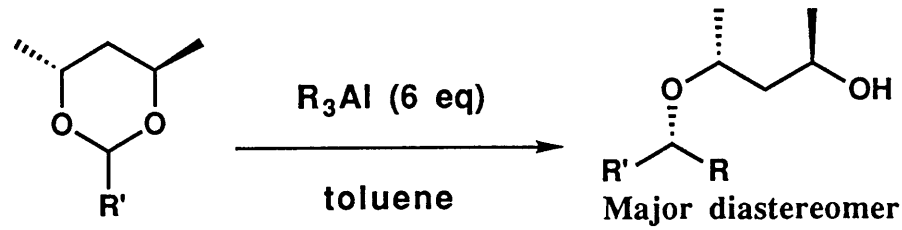


Scheme 2

Herein, we report the highly stereoselective alkylative cleavage of chiral acetals derived from (-)-(2*R*,4*R*)-2,4-pentanediol by the combined use of trialkylaluminum and pentafluorophenol, and also describe the selective cleavages of acetals derived from 1,3-butanediol and (-)-(2*R*,3*R*)-2,3-butanediol respectively.

In view of the efficiency of the mild and stereospecific cleavage of chiral acetals by aluminum reagents, the behavior of trialkylaluminum has been studied systematically. It was soon realized that treatment of acetals in toluene with trialkylaluminum led to a mixture of diastereomers. Several examples of this reaction are given in Table 1. These rather disappointing results are consistent with a common inversion-type alkylation of organoaluminum reagents in non-polar or less polar solvents such as hexane, toluene, or dichloromethane. The results may be attributed to the aggregated form of the aluminum reagent.

Table 1. Alkylative Cleavage of Acetals Using R_3Al.



R'	R	Temp (°C)	Yield (%)	Ratio
C_6H_{13}	Me	52	90	70 : 30
		[40	76	77 : 23][a]
		[53	92	46 : 54][b]
	Et	52	99	87 : 13
c-C_6H_{11}	Me	52	87	78 : 22
		[49	95	66 : 34][a]
	Et	50	85	94 : 6
Ph	Me	25	—[c]	60 : 40
	Et	25	86	91 : 9
Bu–C≡C	Me	50	88	51 : 49
	Et	50	66	82 : 18

[a]Dichloromethane was used as a solvent.

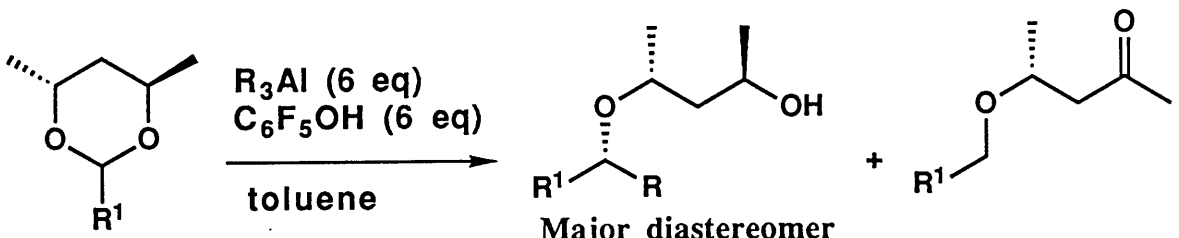
[b]Hexane was used as a solvent.

[c]In this case the desired product could not be separated with by-products by column chromatography.

We found incidentally that the combined use of trialkylaluminum and pentafluorophenol was effective on the stereoselective cleavage of chiral acetal derived from (-)-(2*R*,4*R*)-2,4-pentanediol. The new process is illustrated and several examples of this transformation are given in Table 2. This reaction was clearly more reactive and stereoselective than the above reaction

without pentafluorophenol. In this reaction the β-hydroxyketone was given in low yield as a by-product. In the case of aromatic acetal the desirable coupling product was given as a low yield. While, on the contrary, the side-reaction was increased. The by-product was presumably produced by an intramolecular Meerwein-Ponndorf-Verley reductive cleavage.[5]

Table 2. Alkylative Cleavage of Acetals Using R_3Al-C_6F_5OH System.

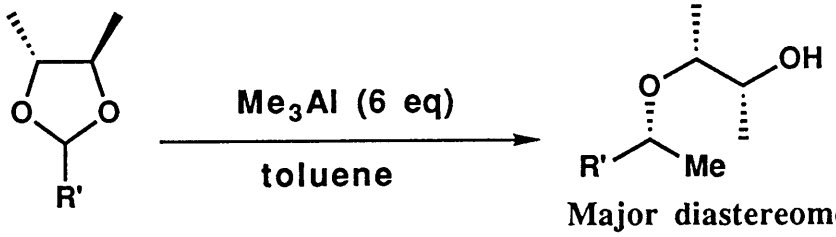


R^1	R	Temp (°C)	1 Yield (%)	1 Ratio	2 Yield (%)
C_6H_{13}	Me	25	70	>99 : 1	22
	Et	25	70	93 : 7	18
c-C_6H_{11}	Me	25	70	>99 : 1	21
	Et	25	87	>99 : 1	0
Ph	Me	0	49	82 : 18	37
	Et	0	41	97 : 3	34
Bu–C≡C	Me	25	57	>99 : 1	37
	Et	25	64	97 : 3	0

Next, we examined the reaction of acetals derived from (-)-(2*R*,3*R*)-2,3-butanediol for the purpose of reducing the side reaction of an intramolecular hydride transfer. Some of our results are summarized in Table 3. The use of 2,3-butanediol instead of 2,4-pentanediol clearly did depress the side reaction. However, this reaction of the acetal of dioxolane type was a slower

process than reaction of the above acetal of dioxane type. The stereoselectivity on the reaction was raised by the addition of pentafluorophenol in the same way as acetal derived from 2,4-pentanediol.

Table 3. Alkylative Cleavage of Acetals Derived from 2,3-Butanediol.



Major diastereomer

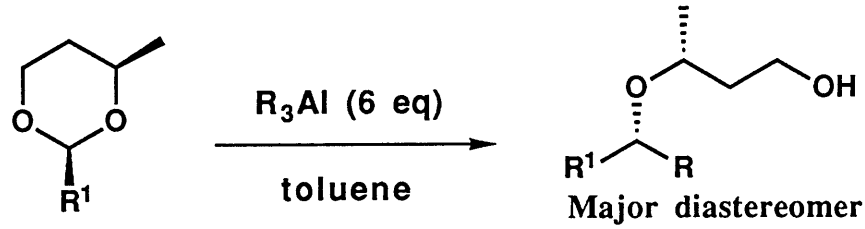
R'	Additive[a]	Temp (°C)	Yield (%)	Ratio
C_6H_{13}	C_6F_5OH	51	21	>99 : 1
	—	51	62	86 : 14
Ph	C_6F_5OH	25	70	82 : 18
	—	25	70	65 : 35

[a] Me_3Al (6 eq) and C_6F_5OH (6 eq) were premixed before addition of the acetal.

Finally, we examined the reaction of acetals derived from 1,3-butanediol with trialkylaluminum or the trialkylalumiun-pentafluorophenol system. This type of acetal represents an especially interesting situation, because the 2-position (derived from the aldehyde carbon) becomes chiral in the acetalization, and if the acetal can exist in the more stable diequatorial form of 2*SR*,4*RS*-cis-compound, trialkylaluminum would be expected to have stereospecific coordination to that of the acetal oxygens which is less hindered;[6] hence the stereoselectivity on this reaction should genuinely represent syn or anti directional selectivity on attack of alkyl anion to cleaved carbon-oxygen bond. The results are summarized in Table 4. In this type of acetal, the stereoselectivity on this reaction with trialkylaluminum is preferable to that with the trialkylaluminum-pentafluorophenol system. As a result, the lower stereoselectivity of the reaction

in the presence of C_6F_5OH can be adequately understood in terms of a slightly extended oxocarbenium ion pair intermediate *via* a polarity of C_6F_5OH. The reaction did not produce β-hydroxyketone as a by-product.

Table 4. Alkylative Cleavage of Acetals Derived from 1,3-Butanediol.



R^1	R	Temp (°C)	Yield (%)	Ratio
c-C_6H_{11}	Me	0	[69	>99 : 1][a]
			57	>99 : 1
	Et	25	[47	>99 : 1][a]
			92	94 : 6
Ph	Me	0	[81	83 : 17][a]
			91	96 : 4
	Et		[58	93 : 7][a]
		25	87	96 : 4

[a] In this case, R_3Al and C_6F_5OH were premixed before addition of the acetal.

The precise structure of the R_3Al-C_6F_5OH complex is also not yet clear. However, it should be noted that, when R_3Al and C_6F_5OH were premixed at room temperature, an equivalent gas of RH was generated in toluene, but was not generated in CH_2Cl_2. Further investigations to elucidate the present reaction should be made.

Experimental Section

General. Infrared (IR) were recorded on a Hitachi 260-10 spectrometer. ^1H NMR spectra were measured on a Varian Gemini 200 (200 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). Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; br, broad peak. Analytical gas-liquid phase chromatography (GC) was performed on Shimadzu Model 8A instrument with a flame-ionization detector and a capillary column of PEG-20M Bonded (25 m) using nitrogen as carrier gas. 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 purified by preparative column chromatography on silica gel 60 E. Merck Art 9385. 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 flsks with magnetic stirring bars under an atomosphere of dry argon.

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

Preparation of Acetals. Acetals were prepared in excellent yield from the corresponding aldehydes and chiral diols, e.g. (-)-(2*R*,4*R*)-2,4-pentanediol, (-)-(2*R*,3*R*)-2,3-butanediol, 1,3-butanediol, in the presence of a catalytic quantity of *p*-toluenesulfonic acid or pyridinium *p*-toluenesulfonate.

The physical properties and analytical data of the thus are listed below.

(4*R*,6*R*)-4,6-Dimethyl-2-hexyl-1,3-dioxane: Physical properties were identical with those of reported.[1b]

(4*R*,6*R*)-2-Cyclohexyl-4,6-dimethyl-1,3-dioxane: Physical properties were identical with those of reported.[1b]

(4*R*,6*R*)-4,6-Dimethyl-2-phenyl-1,3-dioxane: Physical properties were identical with those of reported.[3b]

(4*R*,6*R*)-4,6-Dimethyl-2-(1'-hexnyl)-1,3-dioxane: IR (film) 2980, 2950, 2880, 2270, 1400, 1380, 1180, 1155, 1140, 1110, 1035, 1000, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, *J*=7.5 Hz, 3H, CH_3CH_2), 1.02-2.03 (m, 6H, $CH_3CH_2CH_2$ and $CHCH_2CH$), 1.26 (d, *J*=6.2 Hz, 3H, CH_3), 1.39 (d, *J*=7.2 Hz, 3H, CH_3), 2.24 (dt, *J*=1.5, 7.2 Hz, 2H, $CH_2C{\equiv}C$) , 3.93-4.11 (m, 1H, C*H*Me), 4.38 (m, 1H, C*H*Me), 5.56 (t, *J*=1.5 Hz, 1H, CHC≡C).

(4*R*,5*R*)-2-Cyclohexnyl-4,5-dimethyl-1,3-dioxolane: Physical properties were identical with those of reported.[3b]

(4*R*,5*R*)-4,5-Dimethyl-2-phenyl-1,3-dioxolane: Physical properties were identical with those of reported.[3b]

(2*SR*,4*RS*)-2-Cyclohexyl-4,5-dimethyl-1,3-dioxane: IR (film) 2980, 2930, 2870, 1460, 1380, 1330, 1175, 1135, 1115, 1040, 1010, 985 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80-1.85 (m, 13H, *c*-C_6H_{11} and OCH_2CH_3), 1.18 (d, *J*=6.2 Hz, 3H, CH_3), 3.58-3.75 (m, 2H, OC*H*Me and OC*H*H), 4.05 (ddd, *J*=1.4, 5.0, 11.4 Hz, 1H, OCH*H*), 4.19 (d, *J*=5.4 Hz, 1H, OCHO).

(2*SR*,4*RS*)-4,5-Dimethyl-2-phenyl-1,3-dioxane: Physical properties were identical with those of reported.[3b]

General Procedure for Alkylative Cleavage of Acetals with Trialkylaluminum. To a solution of acetal (0.5 mmol) in solvent (15 mL) was added dropwise trialkylaluminum (2.0 M in hexane, 1.5 mL, 3.0 mmol) at 0°C. The reaction mixture was stirred at the suitable temperature. After complete conversion, the resulting mixture was poured into 2N aqueous sodium hydroxide (20 mL), and extracted with hexane for three times (20 mL X 3). The combined organic layers were dried over magnesium sulfate, concentrated *in vacuo*. The residue

was purified by column chromatography on silica gel (eluant: hexane-EtOAc) to give the diastereomeric mixture of the corresponding alcohols as a colorless oil.

General Procedure for Alkylative Cleavage of Acetals with the Combined Use of Trialkylaluminum and Pentafluorophenol. To a solution of pentafluorophenol (2.0 M in toluene or dichloromethane, 1.5 mL, 3.0 mmol) in toluene (15 mL) or dichloromethane (15 mL) was added dropwise trialkylaluminum (2.0 M in hexane, 1.5 mL, 3.0 mmol) at 0°C. The solution was warmed to room temperature and stirred at that temperature for 1 h. Then a solution of acetal (0.5 mmol) in toluene (1 mL) or dichloromethane (1 mL) was added dropwise to the solution at 0°C. The reaction mixture was stirred at the suitable temperature. After complete conversion, the resulting mixture was poured into 2N aqueous sodium hydroxide (20 mL), and extracted with hexane for three times (20 mL X 3). The combined organic layers were dried over magnesium sulfate, concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluant: hexane-EtOAc) to give the diastereomeric mixture of the corresponding alcohols as a colorless oil.

The diastereomeric ratios were determined by GC analysis by comparison with the authentic samples, which were prepared by alkylative cleavage of the corresponding acetals using a titanium tetrachloride-dialkylzinc system[1] or a titanium tetrachloride-dialkylcopper lithium system.[3] In the case of some adducts it was necessary to prepare the corresponding acetates in order to obtain a base-line separation of the two peaks.

The physical properties and analytical data of the alcohol thus are listed below.

(2*R*,1'*R*,3'*R*)-2-(3'-Hydroxy-1'-methylbutoxy)octane:[4c] TLC, R_f=0.39 (hexane-EtOAc, 5 : 2); GC (110°C), t_R=18.3 min (Alcohol form); IR (film) 3750-3100, 2970, 2930, 2870, 1465, 1380, 1340, 1160, 1120, 1080, 1060, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, *J*=6.5 Hz, 3H, CH_3), 1.14 (d, *J*=6.0 Hz, 3H, CH_3), 1.18 (d, *J*=6.2 Hz, 3H, CH_3), 1.20 (d, *J*=6.2 Hz, 3H, CH_3), 1.20-1.70 (m, 12H, $CH_3(CH_2)_5$ and $CHCH_2CH$), 3.36 (br, 1H, OH), 3.42-3.60 (m, 1H, CHO), 3.80-3.98 (m, 1H, CHO), 4.04-4.23 (m, 1H, CHO).

(2*S*,1'*R*,3'*R*)-2-(3'-Hydroxy-1'-methylbutoxy)octane:[1b] TLC, R_f=0.39 (hexane-EtOAc, 5 : 2); GC (110°C), t_R=16.9 min (Alcohol form).

(3*R*,1'*R*,3'*R*)-3-(3'-Hydroxy-1'-methylbutoxy)nonane: TLC, R_f=0.44 (hexane-EtOAc, 5 ; 2); GC (130°C), t_R=12.2 min (Acetate form); IR (film) 3750-3100, 2970, 2930, 2870, 1465, 1380, 1340, 1160, 1120, 1080, 1060, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, *J*=7.4 Hz, 6H, $2CH_3$), 1.19 (d, *J*=6.4 Hz, 6H, $2CH_3$), 1.22-1.75 (m, 14H, $CH_3(CH_2)_5$, CH_2CH_3 and $CHCH_2CH$), 3.20-3.44 (m, 2H, OH and OCH), 3.77-3.93 (dquintet, *J*=4.1, 6.2 Hz, 1H, OCH), 4.05-4.23 (m, 1H, OCH).

(3*S*,1'*R*,3'*R*)-3-(3'-Hydroxy-1'-methylbutoxy)nonane:[1b] TLC, R_f=0.49 (hexane-EtOAc, 5 : 2); GC (130°C), t_R=10.3 min (Acetate form).

(1*R*,1'*R*,3'*R*)-1-Cyclohexyl-1-(3'-hydroxy-1'-methylbutoxy)ethane:[4c] TLC, R_f=0.45 (hexane-EtOAc, 5 : 2); GC (130°C), t_R=15.4 min (Acetate form); IR (film) 3750-3100, 2980, 2930, 2860, 1460, 1380, 1335, 1345, 1160, 1130, 1100, 1080, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80-1.80 (m, 13H, *c*-C_6H_{11} and $CHCH_2CH$), 1.06 (d, *J*=6.2 Hz, 3H, CH_3), 1.13 (d, *J*=6.2 Hz, 3H, CH_3), 1.16 (d, *J*=6.2 Hz, 3H, CH_3), 3.23 (quintet, *J*=6.2 Hz, 1H, CHO), 3.48 (d, *J*=3.0 Hz, 1H, OH), 3.72-3.92 (m, 1H, CHO), 4.01-4.18 (m, 1H, CHO).

(1*S*,1'*R*,3'*R*)-1-Cyclohexyl-1-(3'-hydroxy-1'-methylbutoxy)ethane:[1b] TLC, R_f=0.45 (hexane-EtOAc, 5 : 2); GC (130°C), t_R=12.9 min (Acetate form); ^1H NMR ($CDCl_3$) δ 0.80-1.80 (m, 13H, *c*-C_6H_{11} and $CHCH_2CH$), 1.05 (d, *J*=6.4 Hz, 3H, CH_3), 1.15 (d, *J*=6.2 Hz, 3H, CH_3), 1.17 (d, *J*=6.2 Hz, 3H, CH_3), 3.18-3.33 (m, 2H, OH and CHO), 3.70-3.86 (m, 1H, CHO), 4.02-4.21 (m, 1H, CHO).

(1*R*,1'*R*,3'*R*)-1-Cyclohexyl-1-(3'-hydroxy-1'-methylbutoxy)propane: TLC, R_f=0.49 (hexane-EtOAc, 5 : 2); GC (140°C), t_R=13.8 min (Alcohol form); IR (film) 3750-3100, 2980, 2940, 2870, 1460, 1430, 1380, 1345, 1315, 1280, 1165, 1125, 1105, 1080, 1065, 1025, 1000, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80-1.85 (m, 15H, *c*-C_6H_{11}, CH_2CH_3 and $CHCH_2CH$), 0.85 (t, *J*=7.4 Hz, 3H, CH_2CH_3), 1.13 (d, *J*=6.2 Hz, 3H, CH_3), 1.15 (d, *J*=6.2

Hz, 3H, CH_3), 1.15 (d, J=6.2 Hz, 3H, CH_3), 3.03 (q, J=5.4 Hz, 1H, c-$C_6H_{11}CHO$), 3.56 (d, J=2.8 Hz, 1H, OH), 3.73-3.89 (m, 1H, CHO), 4.03-4.21 (m, 1H, CHO).

(1*S*,1'*R*,3'*R*)-1-Cyclohexyl-1-(3'-hydroxy-1'-methylbutoxy)propane: TLC, R_f=0.49 (hexane-EtOAc, 5 : 2); GC (140°C), t_R=12.9 min (Alcohol form).

(1*R*,1'*R*,3'*R*)-1-(3'-Hydroxy-1'-methylbutoxy)-1-phenylethane:[4c] TLC, R_f=0.35 (hexane-EtOAc, 5 : 2); GC (170°C), t_R=7.8 min (Alcohol form); IR (film) 3750-3150, 2980, 2950, 1460, 1380, 1165, 1125, 1095, 1060, 1040, 1030, 765, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (d, J=6.4 Hz, 3H, CH_3), 1.18 (d, J=6.6 Hz, 3H, CH_3), 1.40 (d, J=6.4 Hz, 3H, CH_3), 1.44-1.54 (m, 1H, CHC*H*HCH), 1.66-1.84 (m, 1H, CHCH*H*CH), 3.26 (br, 1H, OH), 3.68-3.84 (m, 1H, MeC*H*), 4.08-4.26 (m, 1H, MeC*H*), 4.57 (q, J=6.4 Hz, 1H, PhC*H*), 7.20-7.40 (m, 5H, Ph); Anal. Found. C, 73.71; H, 12.72. $C_{13}H_{20}O_2$ calcd.: C, 73.63; H, 12.36%.

(1*S*,1'*R*,3'*R*)-1-(3'-Hydroxy-1'-methylbutoxy)-1-phenylethane:[1b,3b] TLC, R_f=0.35 (hexane-EtOAc, 5 : 2); GC (170°C), t_R=6.5 min (Alcohol form); ^1H NMR ($CDCl_3$) δ 1.07 (d, J=6.2 Hz, 3H, CH_3), 1.18 (d, J=6.2 Hz, 3H, CH_3), 1.42 (d, J=6.2 Hz, 3H, CH_3), 1.49 (t, J=5.7 Hz, 2H, CHCH_2CH), 2.65 (d, J=3.0 Hz, 1H, OH), 3.48-3.64 (m, 1H, MeC*H*O), 3.94-4.13 (m, 1H, MeC*H*OH), 4.52 (q, J=6.2 Hz, 1H, PhC*H*), 7.20-7.40 (m, 5H, Ph).

(1*R*,1'*R*,3'*R*)-1-(3'-Hydroxy-1'-methylbutoxy)-1-phenylpropane: TLC, R_f=0.39 (hexane-EtOAc, 5 : 2); GC (170°C), t_R=8.6 min (Alcohol form); IR (film) 3750-3150, 2980, 2940, 2890, 1470, 1460, 1380, 1160, 1125, 1110, 1090, 1060, 1020, 760, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (t, J=7.4 Hz, 3H, CH_3), 1.02 (d, J=6.4 Hz, 3H, CH_3), 1.18 (d, J=6.2 Hz, 3H, CH_3), 1.40-1.90 (m, 4H, CH_3CH_2 and CHCH_2CH), 3.25 (d, J=2.2 Hz, 1H, OH), 3.65-3.80 (m, 1H, CH_3C*H*O), 4.05-4.25 (m, 1H, CH_3C*H*OH), 4.28 (t, J=6.6 Hz, 1H, PhC*H*), 7.20-7.40 (m, 5H, Ph); Anal. Found. C, 75.67; H, 9.67. $C_{14}H_{22}O_2$ calcd.: C, 75.63; H, 9.97%.

(1*S*,1'*R*,3'*R*)-1-(3'-Hydroxy-1'-methylbutoxy)-1-phenylpropane: TLC, R_f=0.39 (hexane-EtOAc, 5 : 2); GC (170°C), t_R=7.0 min (Alcohol form); ^1H NMR ($CDCl_3$) δ 0.86 (t, J=7.3 Hz, 3H, CH_3), 1.06 (d, J=6.4 Hz, 3H, CH_3), 1.18 (d, J=6.0 Hz, 3H, CH_3),

1.44-1.90 (m, 4H, CH_3CH_2 and $CHCH_2CH$), 2.76 (d, J=3.2 Hz, 1H, OH), 3.50-3.65 (m, 1H, CH_3CHO), 3.95-4.14 (m, 1H, CH_3CHOH), 4.22 (dd, J=6.0, 7.4 Hz, 1H, PhCH), 7.20-7.40 (m, 5H, Ph).

(1*R*,1'*R*,3'*R*)-2-(3'-Hydroxy-1'-methylbutoxy)-3-octyne:[4c] TLC, R_f=0.44 (hexane-EtOAc, 5 : 2); GC (130°C), t_R=14.9 min; IR (film) 3750-3130, 2980, 2940, 2890, 1460, 1380, 1330, 1160, 1130, 1080, 1050, 1020, 950 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, J=7.1 Hz, 3H, CH_3), 0.90-1.73 (m, 6H, $CH_3(CH_2)_2$ and $CHCH_2CH$), 1.15 (d, J=5.8 Hz, 3H, CH_3), 1.26 (d, J=6.2 Hz, 3H, CH_3), 1.36 (d, J=6.8 Hz, 3H, CH_3), 2.17 (dt, J=1.8, 6.8 Hz, 2H, $CH_2C{\equiv}C$), 2.70-2.80 (br, 1H, OH), 3.87-4.18 (m, 2H, $CH(CH_3)OH$ and $OCHCH_3$), 4.27 (tq, J=1.8, 6.4 Hz, 1H, $C{\equiv}CCHCH_3$).

(1*S*,1'*R*,3'*R*)-2-(3'-Hydroxy-1'-methylbutoxy)-3-octyne:[4c] TLC, R_f=0.47 (hexane-EtOAc, 5 : 2); GC(130°C), t_R=8.8 min (Alcohol form); ^1H NMR ($CDCl_3$) δ 1.15 (d, J=6.0 Hz, 3H, CH_3), 1.21 (d, J=6.4 Hz, 3H, CH_3). Other resonances could not be discerned for this minor isomer.

(1*R*,1'*R*,3'*R*)-3-(3'-Hydroxy-1'-methylbutoxy)-4-nonyne:[4c] TLC, R_f=0.33 (hexane-EtOAc, 5 : 2); GC (130°C), t_R=19.1 min (Alcohol form); IR (film) 3750-3100, 2980, 2950, 2900, 1470, 1390, 1340, 1160, 1130, 1105, 1085, 1060, 1020, cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, J=7.0 Hz, 3H, CH_3), 0.98 (t, J=7.2 Hz, 3H, CH_3), 1.18 (d, J=6.2 Hz, 3H, CH_3), 1.30 (d, J=6.4 Hz, 3H, CH_3), 1.10-1.76 (m, 8H, $CH_3(CH_2)_2$, $CHCH_2CH$, and $C{\equiv}CCHCH_2CH_3$), 2.22 (dt, J=2.0, 6.8 Hz, 2H, $CH_2C{\equiv}C$), 2.30-3.00 (br, 1H, OH), 3.90-4.20 (m, 3H, $CC{\equiv}CHO$, $OCHCH_3$, and $CH(CH_3)OH$).

(1*S*,1'*R*,3'*R*)-3-(3'-Hydroxy-1'-methylbutoxy)-4-nonyne:[4c] TLC, R_f=0.44 (hexane-EtOAc, 5 : 2); GC (130°C), 10.9 min (Alcohol form); ^1H NMR ($CDCl_3$) δ 1.15 (d, J=6.2 Hz, 3H, CH_3), 1.21 (d, J=6.4 Hz, 3H, CH_3). Other resonances could not be discerned for this minor isomer.

(2*R*,1'*R*,2'*R*)-2-(2'-Hydroxy-1'-methylpropoxy)octane:[3b] TLC, R_f=0.41 (hexane-EtOAc, 5 : 2); GC (100°C), t_R=21.0 min (Acetate form); IR (film) 3750-3100, 2990,

2940, 2870, 1460, 1380, 1120, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.67-1.63 (m, 10H, $CH_3(CH_2)_5$), 0.89 (t, *J*=6.8 Hz, 3H, CH_3), 1.07 (d, *J*=6.0 Hz, 3H, CH_3), 1.12 (d, *J*=6.0 Hz, 3H, CH_3), 1.14 (d, *J*=6.2 Hz, 3H, CH_3), 2.35-2.87 (br, 1H, OH), 3.20 (quintet, *J*=6.2 Hz, 1H, $CH(CH_3)OH$), 3.38-3.60 (m, 2H, $C_6H_{13}CH$ and $OCHCH_3$).

(2*S*,1'*R*,2'*R*)-2-(2'-Hydroxy-1'-methylpropoxy)octane:[3b] TLC, R_f=0.41 (hexane-EtOAc, 5 : 2); GC (100°C); t_R=19.2 min; ^1H NMR ($CDCl_3$) δ 0.88 (t, *J*=6.8 Hz, 3H, CH_3), 1.11 (d, *J*=8.0 Hz, 3H, CH_3), 1.14 (d, *J*=8.0 Hz, 3H, CH_3), 1.15 (d, *J*=6.2 Hz, 3H, CH_3), 1.20-1.70 (m, 10H, $CH_3(CH_2)_5$), 1.85-2.60 (br, 1H, OH), 3.21 (quintet, *J*=6.0 Hz, 1H, $CH(CH_3)OH$), 3.36-3.59 (m, 2H, $C_6H_{13}CH$ and $OCHCH_3$).

(1*R*,1'*R*,2'*R*)-1-(2'-Hydroxy-1'-methylpropoxy)-1-phenylethane:[3b] TLC, R_f=0.31 (hexane-EtOAc, 5 : 2); GC (130°C), t_R=17.2 min (Alcohol form); IR (film) 3800-3050, 3000, 2960, 2920, 1460, 1385, 1100, 770, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (d, *J*=6.2 Hz, 3H, CH_3), 1.17 (d, *J*=6.4 Hz, 3H, CH_3), 1.47 (d, *J*=6.6 Hz, 3H, CH_3), 1.83-2.80 (br, 1H, OH), 3.33 (quintet, *J*=6.2 Hz, 1H, $CHCH_3$), 3.61 (quintet, *J*=7.0 Hz, 1H, $CHCH_3$), 4.53 (q, *J*=6.4 Hz, 1H, $PhCHCH_3$), 7.20-7.40 (m, 5H, Ph).

(1*S*,1'*R*,2'*R*)-1-(2'-Hydroxy-1'-methylpropoxy)-1-phenylethane:[3b] TLC, R_f=0.31 (hexane-EtOAc, 5 : 2); GC (130°C), 14.6 min (Alcohol form); ^1H NMR ($CDCl_3$) δ 1.05 (d, *J*=6.4 Hz, 3H, CH_3), 1.12 (d, *J*=6.0 Hz, 3H, CH_3), 1.46 (d, *J*=6.6 Hz, 3H, CH_3), 1.60-2.45 (br, 1H, OH), 3.09 (dq, *J*=7.2, 6.2 Hz, 1H, $CHCH_3$), 3.54 (quintet, *J*=6.6 Hz, 1H, $CHCH_3$), 4.57 (q, *J*=6.4 Hz, 1H, $PhCHCH_3$), 7.25-7.45 (m, 5H, Ph).

(1*RS*,1'*RS*)-1-Cyclohexyl-1-(3'-hydroxy-1'-methylpropyl)ethane: TLC, R_f=0.28 (hexane-EtOAc, 5 : 2); GC (130°C), t_R=17.8 min (Acetate form); ^1H NMR ($CDCl_3$) δ 1.07 (d, *J*=6.0 Hz, 3H, CH_3), 1.10 (d, *J*=6.2 Hz, 3H, CH_3), 0.75-1.90 (m, 13H, *c*-C_6H_{11} and $CH(CH_3)CH_2CH_2OH$), 2.20-2.85 (br, 1H, OH), 3.22 (quintet, *J*=6.2 Hz, 1H, *c*-$C_6H_{11}CH$), 3.57-3.90 (m, 3H, $OCHCH_3$ and CH_2OH); Anal. Found: C, 71.91; H, 12.12. $C_{12}H_{24}O_2$ calcd.: C, 71.95; H, 12.08%.

(1*SR*,1'*RS*)-1-Cyclohexyl-1-(3'-hydroxy-1'-methylpropyl)ethane: TLC, R_f=0.28 (hexane-EtOAc, 5 : 2); GC (130°C), t_R=16.3 min (Acetate form); ^{1}H NMR ($CDCl_3$) δ 0.50-1.95 (m, 13H, *c*-C_6H_{11} and CH_2CH_2OH), 1.05 (d, *J*=6.4 Hz, 3H, CH_3), 1.15 (d, *J*=6.0 Hz, 3H, CH_3), 1.95-2.65 (br, 1H, OH), 3.12 (quintet, *J*=6.0 Hz, 1H, *c*-$C_6H_{11}CH$), 3.43-3.86 (m, 3H, $OCHCH_3$ and CH_2OH).

(1*RS*,1'*RS*)1-Cyclohexyl-1-(3'-hydroxy-1'-methylpropyl)propane: TLC, R_f=0.44 (hexane-EtOAc, 5 : 2); GC (130°C), t_R=24.2 min (Acetate form); ^{1}H NMR ($CDCl_3$) δ 0.60-1.85 (m, 15H, *c*-C_6H_{11}, CH_3CH_2 and CH_2CH_2OH), 0.84 (t, *J*=7.4 Hz, 3H, CH_3CH_2CH), 1.09 (d, *J*=6.2 Hz, 3H, CH_3), 2.55-3.30 (br, 1H, OH), 3.40 (q, *J*=5.4 Hz, 1H, *c*-$C_6H_{11}CH$), 3.60-3.90 (m, 3H, $OCHCH_3$ and CH_2OH); Anal. Found: C, 72.92; H, 12.09. $C_{13}H_{26}O_2$ calcd.: C, 72.85; H, 12.23%.

(1*SR*,1'*RS*)1-Cyclohexyl-1-(3'-hydroxy-1'-methylpropyl)propane: TLC, R_f=0.44 (hexane-EtOAc, 5 : 2); GC (130°C), t_R=21.9 min; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, *J*=7.4 Hz, 3H, CH_3CH_2CH), 1.13 (d, *J*=6.2 Hz, 3H, CH_3). Other resonances could not be discerned for this minor isomer.

(1*RS*,1'*RS*)-1-(3'-Hydroxy-1'-methylpropyl)-1-phenylethane: TLC, R_f=0.16 (hexane-EtOAc, 5 : 2); GC (170°C), t_R=10.0 min (Alcohol form); IR (film) 3750-3050, 3110, 3080, 3060, 3000, 2950, 2900, 1500, 1460, 1380, 1360, 1335, 1315, 1290, 1220, 1150, 1100, 1075, 1060, 1040, 1025, 1010, 760 705 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.04 (d, *J*=6.4 Hz, 3H, CH_3), 1.42 (d, *J*=6.6 Hz, 3H, CH_3), 1.55-1.95 (m, 2H, CH_2CH_2OH), 2.60 (t, *J*=5.3 Hz, OH), 3.65-3.95 (m, 3H, $OCHCH_3$ and CH_2OH), 4.55 (q, *J*=6.4 Hz, 1H, $PhCHCH_3$), 7.15-7.40 (m, 5H, Ph); Anal. Found: C, 74.19; H, 9.34. $C_{12}H_{18}O_2$ calcd.: C, 74.19; H, 9.34%.

(1*SR*,1'*RS*)-1-(3'-Hydroxy-1'-methylpropyl)-1-phenylethane:[3b] TLC, R_f=0.16 (hexane-EtOAc, 5 : 2); GC (170°C), t_R=8.4 min (Alcohol form); ^{1}H NMR ($CDCl_3$) δ 1.16 (d, *J*=6.2 Hz, 3H, CH_3), 1.42 (d, *J*=6.6 Hz, 3H, CH_3). Other resonances could not be discerned for this minor isomer.

(1*RS*,1'*RS*)-1-(3'-Hydroxy-1'-methylpropyl)-1-phenylpropane: TLC, R_f=0.27 (hexane-EtOAc, 5 : 2); GC (170°C), t_R=11.5 min (Alcohol form); IR (film) 3770-3050, 3100, 3075, 3050, 2975, 2950, 2890, 1500, 1460, 1390, 1345, 1140, 1095, 1060, 1020, 760, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (t, *J*=7.4 Hz, 3H, CH_2CH_3), 0.98 (d, *J*=6.4 Hz, 3H, CH_3), 1.45-1.90 (m, 4H, CH_2CH_2OH and CH_3CH_2), 2.55-3.10 (br, 1H, OH), 3.40-3.95 (m, 3H, $OCHCH_3$ and CH_2OH), 4.25 (t, *J*=6.6 Hz, 1H, PhCHO), 7.10-7.45 (m, 5H, Ph); Anal Found: C, 74.91; H, 9.64. $C_{13}H_{20}O_2$ calcd.: C, 74.96; H, 9.68%.

(1*SR*,1'*RS*)-1-(3'-Hydroxy-1'-methylpropyl)-1-phenylpropane: TLC, R_f=0.27 (hexane-EtOAc, 5 : 2); GC (170°C), t_R=9.3 min (Alcohol form); ^1H NMR ($CDCl_3$) δ 1.32 (d, *J*=6.4 Hz, 3H, CH_3), 4.10 (t, *J*=6.6 Hz, 1H, PhCHO). Other resonances could not be discerned for this minor isomer.

References and Notes

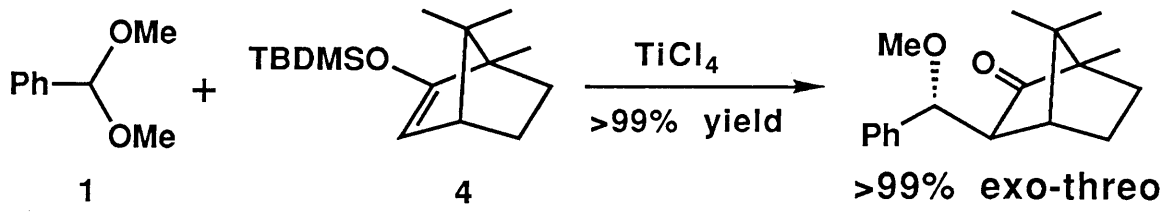
1. (a) Mori, A.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1984**, *25*, 4421.
   (b) Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *J. Organomet. Chem.* **1985**, *285*, 83.
2. Lindell, S. D.; Elliott, J. D.; Johnson, W. S. *Tetrahedron Lett.* **1984**, *25*, 3947.
3. (a) Ghribi, A.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1984**, *25*, 3083.
   (b) Normant, J. F.; Alexakis, A.; Ghribi, A.; Mangeney, P. *Tetrahedron* **1989**, *45*, 507.
4. (a) Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4581.
   (b) Ishihara, K.; Mori, A.; Arai, I.; Yamamoto, H. *Ibid.* **1986**, *27*, 983.
   (c) Mori, A.; Ishihara, K.; Arai, I.; Yamamoto, H. *Tetrahedron* **1987**, *43*, 755.
5. We have studied in detail concerning "Reductive Cleavage of Chiral Acetals Using Diethylaluminum Fluoride-Pentafluorophenol System". See: Chapter 3.
6. Choi, V. M. F.; Elliott, J. D.; Johnson, W. S. *Tetrahedron Lett*, **1984**, *25*, 591.

Chapter 5

Diastereoselective Aldol Synthesis Using Acetal Templates

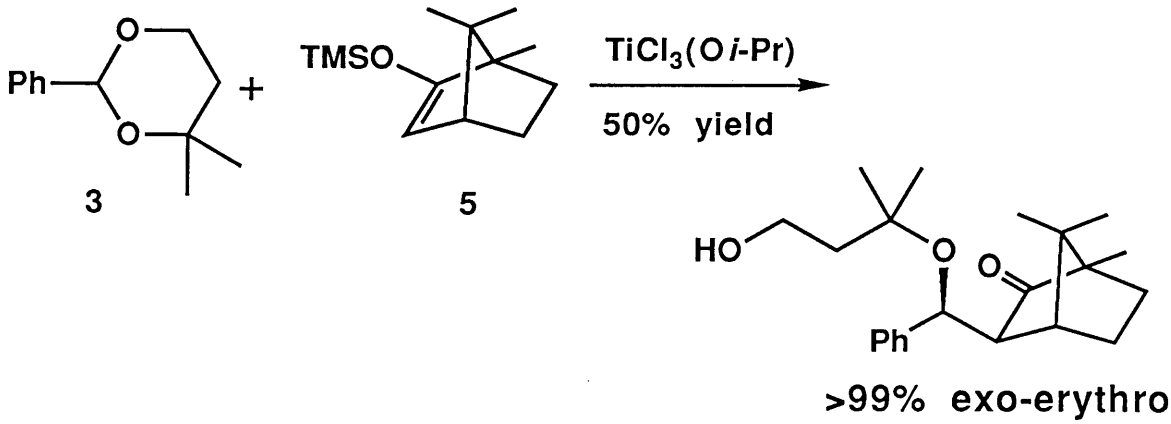
Abstract: Stereoselectivity of the Mukaiyama reaction is dramatically changed by the steric features of acetal structures. In the reaction of benzaldehyde dimethyl acetal with the enol silyl ether of *D*-camphor, the exo-threo product is obtained almost exclusively. In dramatic contrast, however, similar reaction conditions but with benzaldehyde acetal of 3-methyl-1,3-butanediol give the exo-erythro isomer exclusively.

Aldol reaction are divided into two categories depending on the method of activation of the enolates and carbonyl substrates. Most reactions proceed *via* a six-membered chelated transition state assembled by a metal enolate and carbonyl compound.[1] In this case, the aldol stereoselectivity is heavily dependent on the geometry of the enolate double bond: (*E*)-enolates giving, generally, threo aldols and (*Z*)-enolates give erythro products. The other reactions proceed through acyclic transition states, and both (*E*)- and (*Z*)-enolates give the erythro adducts selectively.[1,2] Very little is known, however, of the stereochemistry of the titanium mediated coupling of enol silyl ethers with aldehydes (Mukaiyama reaction),[3] despite its broad utility in organic synthesis. We report herein results of our investigations on unprecedented selectivities in the reaction of enol silyl ethers with a variety of acetal templates.



1 4 >99% exo-threo

(eq. 1)



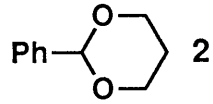
3 5 >99% exo-erythro

(eq. 2)

We chose to investigate the stereoselectivity of the aldol formation from benzaldehyde acetal and the enol silyl ether of *D*-camphor, an enol silane of high steric demand. Thus, a

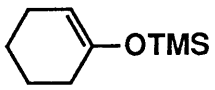
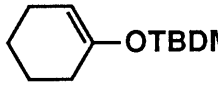
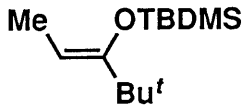
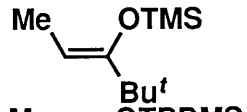
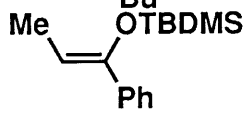
solution of benzaldehyde dimethyl acetal **1** in dichloromethane was cooled to -78°C and titanium tetrachloride was added dropwise. Enol silane **4** was then added, and the mixture was stirred for 15 min. After usual workup, the exo-threo product was obtained almost exclusively (eq. 1).[4] In dramatic contrast, however, similar reaction conditions but with the acetal of type **3** gave the exo-erythro isomer exclusively (eq. 2)![4] This reversal strongly suggests a crucial role for the acetal structure on the selectivity of the reaction and promoted us to investigate the course of the reaction with a wide variety of acetals under various reaction conditions. Some of our results are summarized in Table 1.

Table 1. Condensation of Enol Silanes of *D*-Camphor with Benzaldehyde Acetals

Acetal[a]	Enol Silane[a]	Lewis Acid[a]	Temp. (°C)	Product (% Yield)[b]	Isomer Ratio[c] E : T[d]
1	**4**	**$TiCl_4$**	-78	>99	<1 : 99
1	**5**	**$TiCl_3(Oi\text{-}Pr)$**	-78	99	24 : 76[e]
$PhCH(OCH_2)_2$	**5**	**$TiCl_3(Oi\text{-}Pr)$**	-78	72	27 : 73
 **2**	**4**	**$TiCl_4$**	0	61	9 : 91
2	**5**	**$TiCl_3(Oi\text{-}Pr)$**	-78	87	33 : 67
2	**5**	**$TiCl_3(Oi\text{-}Pr)$**	-90	43	37 : 63
3	**5**	**$TiCl_3(Oi\text{-}Pr)$**	-78	50[f]	>99 : 1[g]

[a]Acetal : Enol Silane : Lewis Acid = 1.0 : 1.2 : 1.2. [b]Isolated yield. [c]The structural assignment was based on ^1H NMR analysis and ratios were determined by HPLC assay. [d]E=erythro, T=threo. [e]The ratio was determined by the isolation of each isomer by chromatography. [f]28% yield of the aldol product was also produced in this case. [g]Ratio was determined by ^1H NMR analysis.

Table 2. Condensation of Enol Silanes with Acetals

Acetal[a]	Enol Silane[a]	Lewis Acid[a]	Product[b] (% Yield)[c]	Isomer Ratio[d] E : T[g]	A[e] E : T[g]	B[f] E : T[g]
1		9-BBNOTf	95	78 : 22	92 : 8	
		$TiCl_4$	95	76 : 24		
2		9-BBNOTf	83	73 : 27		
		$TiCl_4$	39	54 : 46		
3		9-BBNOTf	59	15 : 85		25 : 75[h]
		$TiCl_4$	73	14 : 86		
1		9-BBNOTf	99	6 : 94[f]	5 : 95[i]	
2		$TiCl_4$	73	3 : 97		
3		$TiCl_3(O\textit{i}\text{-Pr})$	43	3 : 97		5 : 95
1		9-BBNOTf	99	86 : 14	84 : 16	
2		9-BBNOTf	64	79 : 21		
3		9-BBNOTf	55	73 : 27		47 : 53

[a]Acetal : Enol Silane : 9-BBNOTf = 1.0 : 1.2 : 1.0 or Acetal : Enol Silane : $TiCl_4$ = 1.0 : 1.2 : 1.2. [b]Reaction at -78°C. [c]Isolated yield. [d]In the reaction of **1**, the stereochemistry was determined by an independent synthesis of each isomer. For other cases, the ether bond was cleaved by oxidation-elimination sequence to produce the corresponding aldols which were analyzed by ^1H NMR. Isomer ratio was determined by HPLC analysis. [e]ref. 6. [f]ref. 7. [g]E=erythro, T=threo. [h]ref. 3. [i]ref. 5.

In order to explore the generality and scope of the above reversal stereoselectivity on aldol-type synthesis based on acetal structures, some enol silyl ethers were prepared and their reactions examined with various acetals. The results are shown in Table 2. In the acetals of type **1**, most reactions[5] stereoselectively afforded an erythro product independent of the geometry of the enolate double bond.[6] These results are consistent with the reaction of enol silyl ether and aldehyde dimethyl acetal in the presence of trimethylsilyl trifalte developed by Noyori et al.[6] On the other hand, the results from acetal **3** showed a trend similar to that discussed by Heathcock et al. for the reaction of titanium catalyzed coupling of enol silyl ethers with aldehyde.[7]

The question of why each acetal reacts with enol silyl ethers with such diverse selectivity is most intriguing but far from answerable at present in view of the lack of knowledge of the nature of coordinated acetals in solution.[8]

Experimental Section

General. Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrometer. ^1H NMR spectra were measured on JNM-PMX 60 or Varian Gemini-200 spectrometers. The chemical shifts are expressed in parts per million downfield from internal tetramethylsilane (δ=0). Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. 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 a 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 Enol Silanes. Enol silanes were prepared by quenching the corresponding lithium enolate with trimethylchlorosilane or *tert*-butyldimethylsilylchlorosilane. Representative procedures follow:

Procedure A (Preparation of Trimethylsilyl Enol Ether). A solution of lithium diisopropylamide in 50 mL of THF was prepared in the usual way from 1.7 mL (12 mmol) of diisopropylamine and 7.0 mL of a 1.58 M solution of *n*-butyllithium in hexane. To this solution was added 1.52 g (10.0 mmol) of (1*R*)-(+)-camphor at -78°C. The resulting solution was allowed to stand at -78°C for 1 h, 1.3 mL (10.0 mmol) of trimethylsilyl chloride was added in one portion, and the reaction mixture was allowed to warm to room temperature and stirred for 1 h. The solvent of the reaction mixture was removed with a rotary evaporator and the crude product was distilled through with a short-path distillation apparatus under reduced pressure to afford 1.86 g (83%) of a colorless liquid, bp 80°C (5.0 torr).

2-Trimethylsilyloxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-ene (5): TLC, R_f=0.92 (hexane-EtOAc, 5 : 2); IR (film) 2900, 2350, 1620, 1330, 1250, 1140, 920, 900, 840 cm^{-1}; ^1H NMR (CCl_4) δ 0.53 (s, 3H, CH_3), 0.67 (s, 6H, $2CH_3$), 0.73-2.10 (m, 5H, CH_2CH_2CH), 4.40 (d, *J*=3.4 Hz, C=CH).

Procedure B (Preparation of *tert*-Butyldimethylsilyl Enol Ether). A solution of 1.10 mmol of lithium diisopropylamide in 30 mL of dry THF was cooled to -78°C and added 9 mL of HMPA was added. To this rapidly stirred solution was added 1.52 g (10.0 mmol) of (1*R*)-(+)-camphor. After an additional 30 min at -78°C, 3.2 mL (11 mmol) of *t*-$BuMe_2SiCl$ was added.

This mixture was stirred for 2 min at -78°C and then allowed to warm to room temperature over 1 h. The reaction mixture was poured into 20 mL of pentane in a separatory funnel and washed with 60 mL of water, the layers were separated, and the pentane layer was dried ($MgSO_4$). The solvent was removed with a rotary evaporator and the crude product thus obtained was distilled through a short-path still to afford a quantitative yield of the purified product.

2-*tert*-Butyldimethylsilyloxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-ene (4): bp 180°C (11 torr); IR (film) 2950, 2350, 1620, 1330, 890, 840 cm^{-1}; ^1H NMR (CCl_4) δ 0.00 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$), 0.62 (s, 3H, CH_3), 0.77 (s, 6H, $2CH_3$), 0.83 (s, 9H, *t*-Bu), 1.0-2.2 (m, 5H, CH_2CH_2CH), 4.4 (d, *J*=3.6 Hz, 1H, C=CH).

Preparation of the other enol silanes was carried out in the similar manners. The physical properties and analytical data of the enol silanes thus obtained are listed below.

1-Trimethylsiloxy-1-cyclohexene: bp 74°C (20 torr); IR (film) 2930, 2350, 1670, 1190, 890, 850 cm^{-1}; ^1H NMR (CCl_4) δ 0.00 (s, 9H, $3CH_3$), 1.2-2.2 (m, 8H, $CH_2CH_2CH_2CH_2$), 4.73 (m, 1H, C=CH).

1-*tert*-Butyldimethylsilyloxy-1-cyclohexene: bp 120°C (8 torr); TLC, R_f=0.78 (hexane-EtOAc, 5 : 2); IR (film) 2910, 2850, 1670, 1250, 1190, 1180, 890, 840, 770 cm^{-1}; ^1H NMR (CCl_4) δ 0.00 (s, 6H, $2CH_3$), 0.80 (s, 9H, *t*-Bu), 1.2-2.2 (m, 8H, $CH_2CH_2CH_2CH_2$), 4.5-4.8 (m, 1H, C=CH).

(*Z*)-4,4-Dimethyl-3-trimethylsilyloxy-2-pentene: bp 80-100°C (22 torr); IR (film) 2970, 2370, 1670, 1260, 1150, 850 cm^{-1}; ^1H NMR (CCl_4) δ 0.00 (s, 9H, $3CH_3$), 0.82 (s, 9H, *t*-Bu), 1.30 (d, *J*=7 Hz, 3H, $CHCH_3$), 4.30 (q, *J*=7 Hz, 1H, *CH*Me).

(*Z*)-4,4-Dimethyl-3-*tert*-butyldimethylsilyloxy-2-pentene: bp 100-110°C (5 torr); IR (film) 2950, 2350, 1670, 1320, 1150, 770 cm^{-1}; ^1H NMR (CCl_4) δ 0.00 (s, 6H, $2CH_3$), 0.82 (s, 9H, *t*-Bu), 0.87 (s, 9H, *t*-Bu), 1.3 (d, *J*=7 Hz, 3H, $CHCH_3$), 4.3 (q, *J*=7 Hz, 1H , *CH*Me).

(Z)-1-Phenyl-1-trimethylsilyloxy-1-propene: bp 140°C (6 torr); IR (film) 2450, 1250, 1060, 880, 840 cm^{-1}; ^1H NMR (CCl_4) δ 0.00 (s, 9H, $3CH_3$), 1.6 (d, J=7 Hz, 3H, $CHCH_3$), 5.1 (q, J=7 Hz, 1H, CHMe), 6.8-7.4 (m, 5H, Ph).

(Z)-1-Phenyl-1-*tert*-butyldimethylsilyloxy-1-propene: bp 180°C (20 torr); IR (film) 2975, 2950, 2880, 1660, 1330, 1260, 1060, 880, 850, 790 cm^{-1}; ^1H NMR (CCl_4) δ 0.00 (s, 6H, $2CH_3$), 1.1 (s, 9H, *t*-Bu). 1.8 (d, J=7 Hz, 3H, $CHCH_3$), 5.1 (q, J=7 Hz, 1H, CHMe), 7.1-7.6 (m, 5H, Ph).

Preparation of Benzaldehyde Acetal.

Benzaldehyde dimethyl acetal (1): The mixture of benzaldehyde (3.0 mL, 30 mmol), orthoformic acid dimethyl acetal (4.4 mL, 40 mmol), and ammonium nitrate (160.1 mg, 2 mmol) in methanol (2 mL) was stirred at room temperature for 1 day. The solution was quenched with saturated aqueous sodium bicarbanate. The organic layers were extracted with hexane twice, dried (Na_2SO_4) and filtered. Removal of solvent *in vacuo* gave a crude oil which was purified by distillation with a Kugelrohr apparatus (87°C, 18 torr) to give benzaldehyde dimethyl acetal as a colorless oil (a quantitative yield). TLC, R_f=0.60 (hexane-EtOAc, 5 : 2); IR (film) 2400, 1100, 1050, 700 cm^{-1}; ^1H NMR (CCl_4) δ 3.2 (s, 6H, $2CH_3$), 5.4 (s, 1H, OCHO), 7.1-7.5 (m, 5H, Ph).

2-Phenyl-1,3-dioxane (2): The mixture of benzaldehyde (1.02 mL, 10 mmol), 1.3-propanediol (0.94 mL, 13 mmol), and *p*-toluenesulfonic acid (10 mg) in benzene (20 mL) was heated at reflux for 2.5 h with continuous azeotropic removal of water. After cooling to room temperature, the mixture was poured into aq. $NaHCO_3$ extracted with hexane twice. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. Distillation with a Kugelrohr apparatus afforded 2-phenyl-1,3-dioxane as a white crystalline solid in a quantitative yield. TLC, R_f=0.46 (hexane-EtOAc, 5 : 2); IR (CCl_4) 2370, 2350, 1120 cm^{-1}; ^1H NMR (CCl_4) δ 1.1-1.6 (m, 1H, CH_2), 1.7-2.6 (m, 1H, CH_2), 3.6-4.4 (m, 4H, $2OCH_2$), 5.3 (s, 1H, OCHO), 7.1-7.6 (m, 5H, Ph).

Preparation of the other acetals were carried out in the similar manner. The physical properties and analytical data of the acetals thus obtained are listed below.

2-Phenyl-1,3-dioxolane: TLC, R_f=0.54 (hexane-EtOAc, 5 : 2); ^{1}H NMR (CCl_4) δ 3.92 (s, 4H, $2CH_2O$), 5.70 (s, 1H, CHO_2), 7.13-7.60 (m, 5H, Ph).

4,4-Dimethyl-2-phenyl-1,3-dioxane (3): bp 180°C (9 torr); TLC, R_f=0.56 (hexane-EtOAc, 5 : 2); IR (film) 2980, 2360, 2330, 1150, 1090 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.3 (s, 3H, CH_3); 1.4 (s, 3H, CH_3), 1.6-2.5 (m, 2H, CCH_2), 4.0 (dd, J=2, 9 Hz, 2H, OCH_2), 5.5 (s, 1H, OCHO), 7.0-7.5 (m, 5H, Ph).

General Procedure for the Reaction of Enol Silanes with Acetals. To a stirring solution of 1.0 mmol of acetal and 15 mL of CH_2CH_2 at -78°C was added dropwise titanium tetrachloride (1.2 mmol, 1.2 mL of 1.0 M solution in dichloromethane) or 9-BBN triflate (1.0 mmol, 0.5 mL of 2.0 M solution in hexane). The complex was stirred for 3 min and 1.2 mmol of enol silane was added by syringe over a 20 sec period. After 15 min, the reaction was quenched with by rapidly injecting 15 mL of water. The mixture was warmed to room temperature and the aqueous layer was separated and extracted with two 30 mL portions of ether. The combined organic layers were dried over $MgSO_4$ and the solvent was removed with a rotary evaporator. The crude product was purified by column chromatography on silica gel to give the pure aldol-type adducts. The product was examined by HPLC to determine the ratio of isomers.

(1*R*,3*S*,α*S*)-3-(α-Methoxybenzyl)-1,7,7-trimethyl[2.2.1]bicycloheptan-2-one (exo-erythro isomer): Hplc, t_R=5.6 min (hexane-EtOAc, 30 : 1); TLC, R_f=0.60 (hexane-EtOAc, 5 : 2); IR (CCl_4) 2370, 1750, 1100 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.82 (s, 3H, CH_3), 0.94 (s, 6H, $2CH_3$), 1.1-2.6 (m, 6H, CH_2CH_2CH, CH=O), 4.1 (d, J=8 Hz, 1H, CHO), 7.0-7.5 (br, 5H, Ph).

(1*R*,3*S*,α*R*)-3-(α-Methoxybenzyl)-1,7,7-trimethyl[2.2.1]bicycloheptan-2-one (exo-threo isomer): A white crystalline; Hplc, t_R=2.58 min (hexane-EtOAc, 30 : 1); TLC, R_f=0.48 (hexane-EtOAc, 5 : 2); IR (CCl_4) 2370, 1750, 1110 cm^{-1}; 1H NMR (CCl_4) δ 0.80

(s, 6H, $2CH_3$), 0.87 (s, 3H, CH_3), 1.1-2.0 (m,5H, CH_2CH_2CH), 2.3 (d, *J*=8 Hz, 1H, CHC=O), 3.1 (s, 3H, OCH_3), 4.1 (d, *J*=8 Hz, 1H, CHO), 6.9-7.5 (m, 5H, Ph).

(1*R*,3*S*,α*S*)-3-(α-(3-Hydroxyethanoxy)benzyl)-1,7,7-trimethyl[2.2.1]bicycloheptan-2-one (exo-erythro isomer): Hplc, t_R=12.4 min (hexane-EtOAc, 78 : 22); TLC, R_f=0.24 (hexane-EtOAc, 5 : 2); ^1H NMR (CCl_4) δ 2.25 (d, *J*=8 Hz, 1H, CHC=O), 4.33 (d, *J*=8 Hz, CHO).

(1*R*,3*S*,α*R*)-3-(α-(3-Hydroxyethanoxy)benzyl)-1,7,7-trimethyl[2.2.1]bicycloheptan-2-one (exo-threo isomer): Hplc, t_R=7.79 min (hexane-EtOAc, 78 : 22); TLC, R_f=0.24 (hexane-EtOAc, 5 : 2); ^1H NMR (CCl_4) δ 0.83 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 0.93 (s, 3H, CH_3), 1.10-2.12 (m, 5H, CH_2CH_2CH), 2.38 (d, *J*=10 Hz, 1H, CHC=O), 3.00-3.77 (m, 4H, $2CH_2O$), 4.27 (d, *J*=10 Hz, 1H, CHO), 7.03-7.53 (m, 5H, Ph).

(1*R*,3*S*,α*S*)-3-(α-(3-Hydroxypropanoxy)benzyl)-1,7,7-trimethyl[2.2.1]bicycloheptan-2-one (exo-erythro isomer): Hplc, t_R=5.4 min (hexane-EtOAc, 5 : 2); IR (CCl_4) 3450, 2400, 1760 cm^{-1}; ^1H NMR (CCl_4) δ 0.83 (s, 3H, CH_3), 1.0 (s, 6H, $2CH_3$), 1.2-2.6 (m, 7H, CH_2CH_2CHCH and OH), 3.2-3.8 (m, 4H, $2OCH_2$), 4.2 (d, *J*=8 Hz, 1H, CHO), 7.1-7.4 (br, 5H, Ph).

(1*R*,3*S*,α*R*)-3-(α-3-Hydroxypropanoxy)benzyl)-1,7,7-trimethyl[2.2.1]bicycloheptan-2-one (exo-threo isomer): Hplc, t_R=11.2 min (hexane-EtOAc, 2 : 1); TLC, R_f=0.17 (hexane-EtOAc, 5 : 2); IR (CCl_4) 3540, 2980, 2380, 1750 cm^{-1}; ^1H NMR (CCl_4) δ 0.82 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 1.1-2.1 (m, 7H, CH_2CH_2CH and CH_2), 2.3 (d, *J*=9 Hz, CHC=O), 3.1-4.0 (m, 3H, CH_2OH), 3.4 (t, 2H, CH_2O), 4.2 (d, *J*=9.6 Hz, 1H, CHO), 7.0-7.6 (br, 5H, Ph).

(1*R*,3*S*,α*S*)-3-(α-(1,1-Dimethyl-3-hydroxypropanoxy)benzyl)-1,7,7-trimethyl[2.2.1]bicycloheptan-2-one (exo-erythro isomer): TLC, R_f=0.23 (hexane-EtOAc, 5 : 2); IR (CCl_4) 3400, 2980, 1740, 1040 cm^{-1}; ^1H NMR (CCl_4) δ 0.7-2.7 (m, 24H, $5CH_3$, CH_2CH_2CHCH, CH_2C, and OH), 3.65 (t, *J*=6 Hz, 2H, CH_2O), 4.6 (d, *J*=8 Hz, 1H, CHO), 7.0-7.5 (br, 5H, Ph).

erythro-2-Methoxybenzylcyclohexanone: Hplc, t_R=8.6 min (hexane-EtOAc, 20 : 1); TLC, R_f=0.50 (hexane-EtOAc, 5 : 2); IR (film) 2940, 1700, 1440, 1100 cm^{-1}; ^1H NMR (CCl_4) δ 1.1-2.6 (m, 9H, $CH_2CH_2CH_2CH_2CH$), 3.2 (s, 3H, OCH_3), 4.7 (d, J=4 Hz, CHO), 6.8-7.4 (m, 5H, Ph).

threo-Methoxybenzylcyclohexanone: Hplc, t_R=19.1 min (hexane-EtOAc, 20 : 1); TLC, R_f=0.40 (hexane-EtOAc, 5 : 2); IR (film) 2930, 1720, 1460, 1100, 700 cm^{-1}; ^1H NMR (CCl_4) δ 0.7-2.9 (m, 9H, $CH_2CH_2CH_2CH_2CH$), 3.1 (s, 3H, CH_3), 4.5 (d, J=8 Hz, 1H, CHO), 6.8-7.6 (m, 5H, Ph).

erythro-2-(3-Hydroxypropanoxy)benzylcyclohexanone: Hplc, t_R=9.7 min (hexane-EtOAc, 2 : 1); TLC, R_f=0.12 (hexane-EtOAc, 5 : 2); IR (film) 3450, 2950, 2870, 1710, 1080, 700 cm^{-1}; ^1H NMR (CCl_4) δ 1.1-2.7 (m, 13H, $CH_2CH_2CH_2CH_2CH$ and CH_2CH_2OH), 3.5 (t, J=5.6 Hz, 2H, CH_2OH), 3.6 (t, J=5.6 Hz, 2H, CH_2O), 4.8 (d, J=3.6 Hz, 1H, CHO), 6.9-7.5 (m, 5H, Ph).

threo-2-(3-Hydroxypropanoxy)benzylcyclohexanone: Hplc, t_R=20.1 min (hexane-EtOAc, 2 : 1); TLC, R_f=0.07 (hexane-EtOAc, 5 : 2); IR (film) 3450, 2950, 2870, 1720, 1110, 710 cm^{-1}; ^1H NMR (CCl_4) δ 0.8-2.9 (m, 12H, $CH_2CH_2CH_2CH_2CH$ and CH_2CH_2OH), 3.4 (t, J=6 Hz, 2H, CH_2OH), 3.6 (t, J=6 Hz, 2H, CH_2O), 4.5 (d, J=8 Hz, 1H, CHO), 7.1-7.5 (m, 5H, Ph).

erythro-2-(1,1-Dimethyl-3-hydroxypropanoxy)benzylcyclohexanone: Hplc, t_R=8.6 min (hexane-EtOAc, 5 : 2); TLC, R_f=0.15 (hexane-EtOAc, 5 : 2); IR (CCl_4) 3450, 2950, 1710, 1030 cm^{-1}; ^1H NMR (CCl_4) d 0.9 (s, 3H, CH_3), 1.2 (s, 3H, CH_3), 1.3-2.8 (m, 12H, $CH_2CH_2CH_2CH_2CH$ and CH_2CH_2OH), 3.6 (t, J=6 Hz, CH_2O), 5.1 (d, J=3.6 Hz, CHO), 6.8-7.5 (m, 5H, Ph).

threo-2-(1,1-Dimethyl-3-hydroxypropanoxy)benzylcyclohexanone: Hplc, t_R=15.0 min (hexane-EtOAc, 5 : 2); TLC, R_f=0.10 (hexane-EtOAc, 5 : 2); IR (film) 3470, 2950, 1720, 1060, 1030 cm^{-1}; ^1H NMR (CCl_4) δ 0.89 (s, 3H, CH_3), 1.2 (s, 3H, CH_3), 1.4-3.0 (m,

12H, $CH_2CH_2CH_2CH_2CH$ and CH_2CH_2OH), 3.6 (t, J=6 Hz, 2H, CH_2O), 5.0 (d, J=6 Hz, 1H, CHO), 6.8-7.4 (m, 5H, Ph).

erythro-1-Methoxy-2,4,4-trimethyl-1-phenylpentan-3-one: Hplc, t_R=17.6 min (hexane-EtOAc, 200 : 1); TLC, R_f=0.63 (hexane-EtOAc, 5 : 2); IR (film) 2980, 2370, 1707, 1460, 1103 cm^{-1}; ^1H NMR (CCl_4) δ 0.66 (d, J=7 Hz, 3H, CH_3), 1.2 (s, 9H, t-Bu), 2.9-3.4 (m, 1H, C*H*Me), 3.0 (s, 3H, OCH_3), 4.1 (d, J=9.6 Hz, CHO), 7.0-7.4 (br, 5H, Ph).

threo-1-Methoxy-2,4,4-trimethyl-1-phenylpentan-3-one: Hplc, t_R=15.3 min (hexane-EtOAc, 5 : 1); TLC, R_f=0.63 (hexane-EtOAc, 5 : 2).

erythro-1-(3-Hydroxypropanoxy)-2,4,4-trimethyl-1-phenylpentan-3-one: t_R=16.4 min (hexane-EtOAc, 5 : 1); TLC, R_f=0.25 (hexane-EtOAc, 5 : 2).

threo-1-(3-Hydroxypropanoxy)-2,4,4-trimethyl-1-phenylpentan-3-one: Hplc, t_R=12.5 min (hexane-EtOAc, 5 : 1); TLC, R_f=0.25 (hexane-EtOAc, 5 : 2); IR (film) 3470, 2980, 1720, 1490, 1460, 1100, 710 cm^{-1}; ^1H NMR (CCl_4) δ 0.71 (d, J=7.5 Hz, 3H, CH_3), 1.2 (s, 9H, $3CH_3$), 1.5-1.9 (m, 2H, CH_2CH_2OH), 2.1 (br, 1H, OH), 4.3 (d, J=10 Hz, PhC*H*O), 7.2-7.5 (m, 5H, Ph).

erythro-1-(1,1-Dimethyl-3-hydroxypropanoxy)-2,4,4-trimethyl-1-phenylpentan-3-one: Hplc, t_R=17.6 min (hexane-EtOAc, 10 : 1), TLC, R_f=0.32 (hexane-EtOAc, 5 : 2); IR (CCl_4) 3500, 2930, 1420, 1310 cm^{-1}; ^1H NMR (CCl_4) δ 0.67 (d, J=7 Hz, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.1 (s, 3H, CH_3), 1.2 (s, 9H, t-Bu), 1.55 (t, J=6 Hz, 2H, CCH_2), 2.3 (br, 1H, OH), 2.9-3.6 (m, 3H, CH_2O and MeO*H*), 4.3 (d, J=10 Hz, 1H, PhC*H*), 7.1-7.5 (m, 5H, Ph).

threo-1-(1,1-Dimethyl-3-hydroxypropanoxy)-2,4,4-trimethyl-1-phenylpentan-3-one: Hplc, t_R=26.8 min (hexane-EtOAc, 10 : 1), TLC, R_f=0.27 (hexane-EtOAc, 5 : 2); IR (film) 3450, 2970, 1700, 1360, 1020, 695 cm^{-1}; ^1H NMR (CCl_4) δ 0.62 (d, J=7 Hz, 3H, CH_3), 0.81 (s, 3H, CH_3), 1.0 (s, 3H, CH_3), 1.2 (s, 9H, t-Bu), 1.4-1.8 (m, 2H, CH_2C), 2.8 (br, 1H, OH), 2.9-3.8 (m, 3H, CH_2OH), 4.55 (d, J=10 Hz, 1H, PhCH), 7.0-7.4 (m, 5H, Ph).

erythro-3-Methoxy-2-methyl-1,3-diphenyl-1-propanone: Hplc, t_R=15.3 min (hexane-EtOAc, 15 : 1); TLC, R_f=0.48 (hexane-EtOAc, 5 : 2); IR (film) 3480, 1680, 1610, 1460, 1230, 980, 700 cm^{-1}; ^1H NMR (CCl_4) δ 1.1 (d, J=7.6 Hz, 3H, CH_3), 3.0-3.9 (m, 2H, C*H*Me and O*H*), 4.9-5.2 (m, 1H, CHO), 6.9-8.1 (m, 10H, 2Ph).

threo-3-Methoxy-2-methyl-1,3-diphenyl-1-propanone: Hplc, t_R=22.3 min (hexane-EtOAc, 15 : 1); TLC, R_f=0.46 (hexane-EtOAc, 5 : 2); ^1H NMR (CCl_4) δ 0.9 (d, J=7.6 Hz, 3H, CH_3), 4.6-4.9 min (m, 1H, CHO).

erythro-3-(3-Hydroxypropanoxy)-2-methyl-1,3-diphenyl-1-propanone: Hplc, t_R=12.3 min (hexane-EtOAc, 3 : 1); TLC, R_f=0.15 (hexane-EtOAc, 5 : 2); IR (film) 3400, 1650, 1440, 1080, 960, 690 cm^{-1}; ^1H NMR (CCl_4) δ 1.3 (d, J=7 Hz, 3H, CH_3), 1.4-2.0 (m, 2H, C*H*$_2$CH$_2$OH), 2.4 (br, 1H, OH), 3.0-4.1 (m, 4H, OC*H*$_2$CH$_2$C*H*$_2$OH), 4.5 (d, J=7 Hz, 1H, CHO), 6.7-8.1 (m, 10H, 2Ph).

threo-3-(3-Hydroxypropanoxy)-2-methyl-1,3-diphenyl-1-propanone: Hplc, t_R=10.5 min (hexane-EtOAc, 3 : 1); TLC, R_f=0.15 (hexane-EtOAc, 5 : 2); ^1H NMR (CCl_4) δ 0.82 (d, J=7 Hz, 3H, CH_3), 2.2 (br, 1H, OH), 4.4 (d, J=8 Hz, 1H, CHO).

erythro-3-(1,1-Dimethyl-3-hydroxypropanoxy)-2-methyl-1,3-diphenyl-1-propanone: Hplc, t_R=32.0 min (hexane-EtOAc, 7 : 1); TLC, R_f=0.20 (hexane-EtOAc, 5 : 2); IR (film) 3450, 2970, 2930, 1680, 1445, 965, 895 cm^{-1}; ^1H NMR (CCl_4) δ 0.53-2.2 (m, 11H, 3C*H*$_3$ and C*H*$_2$CH$_2$OH), 2.9 (br, 1H, OH), 3.15-4.10 (m, 3H, C*H*$_2$OH and C*H*Me), 4.8 (d, J=7.4 Hz, 1H, CHO), 6.8-8.2 (m, 10H, 2Ph).

threo-3-(1,1-Dimethyl-3-hydroxypropanoxy)-2-methyl-1,3-diphenyl-1-propanone: Hplc, t_R=29.1 min (hexane-EtOAc, 7 : 1); TLC, R_f=0.20 (hexane-EtOAc, 5 : 2); ^1H NMR (CCl_4) δ 4.75 (d, J=9 Hz, 1H, CHO).

The Structural Assignment for Aldol-Type Adducts. The stereochemistries (erythro or threo) of the aldol-type adducts, formed by the reaction of enol silanes and

benzaldehyde dimethyl acetal, were determined by comparison with the authentic samples prepared stereoselectively by Noyori's method.

The stereochemistries (exo or endo, erythro or threo) of (1*R*,3*S*)-3-(α-methoxybenzyl)-1,7,7-trimethyl[2.2.1]bicycloheptan-2-one were determined by ^{1}H NMR analysis: the exo-erythro isomer δ 2.16 (d, *J*=8 Hz, 1H, C(3)H), 2.50 (d, *J*=4 Hz, 1H, C(4)H); the exo-threo isomer δ 2.30 (d, *J*=8 Hz, 1H, C(3)H), 1.1-2.0 (m, 5H, $CH_2CH_2C(3)H$).

The stereochemistries (erythro or threo) of the other aldol-type adducts were determined by its transformation into the aldol products (: a removal of auxiliary from aldol ethers).

Removal of Auxiliary. Preparation of Aldol. (1*R*,3*S*)-3-(α-Hydroxybenzyl)-1,7,7-trimethyl[2.2.1]bicycloheptan-2-one. The diastereoisomeric mixture of (1*R*,3*S*)-3-[α-(3-hydroxypropanoxy)benzyl]-1,7,7-trimethyl[2.2.1]bicycloheptan-2-ones (exo-erythro/exo-threo, 33 : 67) (269 mg, 0.85 mmol) was dissolved in dichloromethane (5 mL) and pyridinium chlorochromate (647 mg, 3 mmol) added. The mixture was stirred at room temperature under argon for 2 h in a flask protected from light. A saturated aqueous sodium bisulfite (10 mL) was poured into the resulting suspension and the separated organic layers were concentrated *in vacuo*. Column chromatography gave keto aldehydes as a colorless oil (217 mg, 81%).

To a solution of *N*-benzylmethylammonium trifluoroacetate (2.8 mmol) in benzene (10 mL), which was prepared from *N*-benzylmethylamine (0.36 mL, 2.8 mmol) and trifluoroacetic acid (0.22 mL, 2.8 mmol), was added the mixture of keto aldehydes (217 mg, 0.69 mmol) dissolved in benzene (2 mL) at 50°C. After 10 min the solution was washed with water. The organic layers were extracted with ether twice, dried over $MgSO_4$, concentrated *in vacuo*, and chromatography on silica gel afforded 114 mg (83%) of a 31 : 69 mixture of exo-erythro and exo-threo isomers, respectively.

exo-erythro Isomer: TLC, R_f=0.39 (hexane-EtOAc, 5 : 2); IR (CCl_4) 3480, 2980, 1750, 1460, 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.86 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.01 (s,

3H, CH_3), 1.34-1.71 (m, 3H, C(5)H(endo)C(6)H_2), 1.92 (sbr, 1H, OH), 1.98-2.15 (m, 1H, C(5)H(exo)), 2.40 (d, J=8 Hz, 1H, C(3)H(endo)), 2.52 (d, J=6 Hz, 1H, C(4)H), 4.76 (d, J=8 Hz, 1H, OCH), 7.25-7.64 (m, 5H, Ph).

exo-threo Isomer: A white crystalline; TLC, R_f=0.45 (hexane-EtOAc, 5 : 2); IR (CCl_4) 3500, 2950, 1720, 1460, 1410, 1030, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.17-1.74 (m, 4H, C(5)H_2C(6)H_2), 1.80-1.93 (m, 1H, C(4)H), 2.25 (d, J=10 Hz, 1H, C(3)H(endo)), 4.55 (s, 1H, OH), 4.90 (d, J=10 Hz, 1H, CHO), 7.32-7.37 (m, 5H, Ph).

Nuclear Overhauser enhancement experiments were carried out with exo-erythro and exo-threo isomers respectively at 500 MHz. With each isomer the doublet for the hydrogen of benzyl position was irradiated. For exo-erythro isomer enhancement was observed of hydrogen signal of methyl group (δ 1.01 (s, 3H, CH_3) ppm). For exo-threo isomer enhancement was observed of hydrogen signal of methyl group (δ 1.05 (s, 3H, CH_3) ppm).

Removal of auxiliary of the other aldol ethers were carried out in the similar manner. The physical properties and analytical data of the aldols thus obtained are listed below.

erythro-2-Hydroxybenzylcyclohexanone: Hplc, t_R=5.7 min (hexane-EtOAc, 5 : 1); TLC, R_f=0.34 (hexane-EtOAc, 5 : 2); IR (CCl_4) 3510, 2950, 1710, 1570, 1550 cm^{-1}; ^1H NMR (CCl_4) δ 1.2-2.7 (m, 9H, $CH_2CH_2CH_2CH_2CH$), 2.8 (d, J=3 Hz, 1H, OH), 5.25 (dd, J=3, 3 Hz, 1H, CHO), 6.9-7.5 (m, 5H, Ph).

threo-2-Hydroxybenzylcyclohexanone: Hplc, t_R=8.7 min (hexane-EtOAc, 5 : 1); TLC, R_f=0.24 (hexane-EtOAc, 5 : 2); IR (CCl_4) 3500, 2950, 1710, 1460, 1140, 1050 cm^{-1}; ^1H NMR (CCl_4) δ 0.77-2.8 (m, 9H, $CH_2CH_2CH_2CH_2CH$), 3.65 (d, J=3 Hz, OH), 4.65 (dd, J=3, 8 Hz, CHO), 6.8-7.6 (m, 5H, Ph).

erythro-1-Hydroxy-2,4,4-trimethyl-1-phenylpentan-3-one: Hplc, t_R=10.7 min (hexane-EtOAc, 15 : 1); TLC, R_f=0.47 (hexane-EtOAc, 5 :2); IR (film) 3430, 2980, 2370, 1705, 990, 665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (d, J=2.2 Hz, 3H, CH_3), 1.08 (s, 9H, t-Bu),

3.19-3.31 (m, 1H, C*H*Me), 3.51 (d, *J*=1.4 Hz, 1H, OH), 4.91 (dd, *J*=1.4, 3.9 Hz, 1H, CHO), 7.15-7.36 (m, 5H, Ph).

threo-1-Hydroxy-2,4,4-trimethyl-1-phenylpentan-3-one: Hplc, t_R=9.5 min (hexane-EtOAc, 5: 2); TLC, R_f=0.47 (hexane-EtOAc, 5 : 2); IR (CCl_4) 3500, 3000, 1710, 1480, 1460, 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (d, *J*=7 Hz, 3H, CH_3), 1.03 (s, 9H, *t*-Bu), 3.19 (d, *J*=5.8 Hz, 1H, OH), 3.21-3.39 (m, 1H, C*H*Me), 4.77 (dd, *J*=5.8, 7.0 Hz, 1H, CHO), 7.17-7.39 (m, 5H, Ph).

erythro-3-Hydroxy-2-methyl-1,3-diphenyl-1-propanone: Hplc, t_R=15.3 min (hexane-EtOAc, 15 : 1); TLC, R_f=0.48 (hexane-EtOAc, 5 : 2); IR (film) 3480, 1680, 1610, 1460, 1230, 980, 700 cm^{-1}; ^1H NMR (CCl_4) δ 1.1 (d, *J*=7.6 Hz, 3H, CH_3), 3.0-3.9 (m, 2H, C*H*Me and O*H*), 4.9-5.2 (m, 1H, CHO), 6.9-8.1 (m, 10H, 2Ph).

threo-3-Hydroxy-2-methyl-1,3-diphenyl-1-propanone: Hplc, t_R=23.3 min (hexane-EtOAc, 15 : 1); TLC, R_f=0.48 (hexane-EtOAc, 5 : 2); ^1H NMR (CCl_4) δ 0.9 (d, *J*=7.6 Hz, 3H, CH_3), 4.6-4.9 (m, 1H, CHO).

References and Notes

1. (a) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066 and references cited therein.
   (b) Evans, D. A.; Nelson, J. R.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099 and references cited therein.
2. Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1981**, *103*, 2106.
3. Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503.
4. The aldol reaction of the *D*-camphor enolate with benzaldehyde was reported to proceed with an unusual stereoselectivity, see:

Harlow, R. L.; Simonsen, S. H. *Cryst. Struct. Comm.* **1976**, *5*, 471. In fact, under the reaction conditions of Noyori (ref. 6) the exo-threo product was the major product (78 : 22). On the other hand, the reactioon conditions of Heathcock (ref. 7) gave the exo-erythro product almost exclusively (<1 : 99). Thus, these results are consistent with the mechanism of the scheme in the text.

5. The anti configuration (threo) of this particular reaction was reported by Heathcock. See:

Heathcock, C. H., In "*Asymmetric Synthesis*, Vol. 3 Part B," Ed by Morrison, J. D., Academic Press, **1984**, pp 138-139.

6. Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248.

7. Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3027.

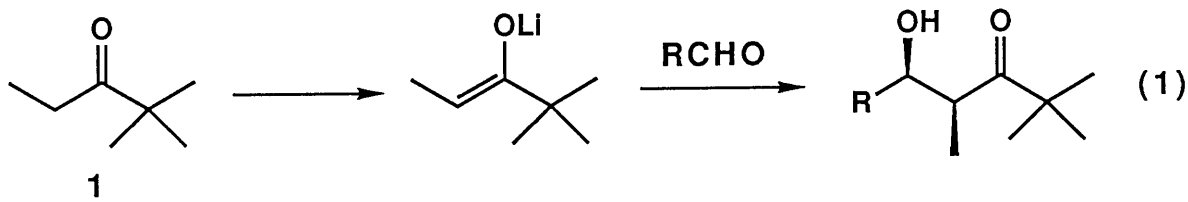
8. The mechanistic studies of these reactions will be published in due course.

Chapter 6

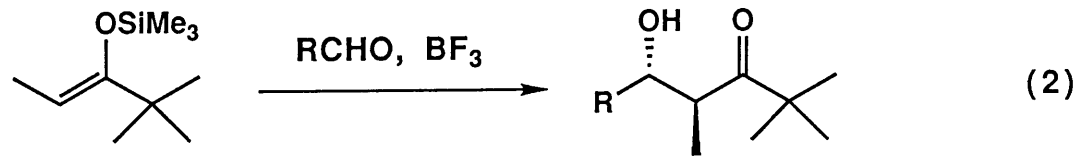
New Stereoselective Propanal/Propanoic Acid Synthons for Aldol Reactions[1]

Abstract: We have developed short, convenient syntheses of 4,4-dimethyl-5-hexen-3-one (**6**) and the derived trimethylsilyl enol ether **7**, which may be used for stereoselective formation of syn and anti β-hydroxy carbonyl compounds. The obvious limitation of the new reagents is that other groups that react with lithium aluminum hydride or lead tetraacetate could provide avenues for side reactions.

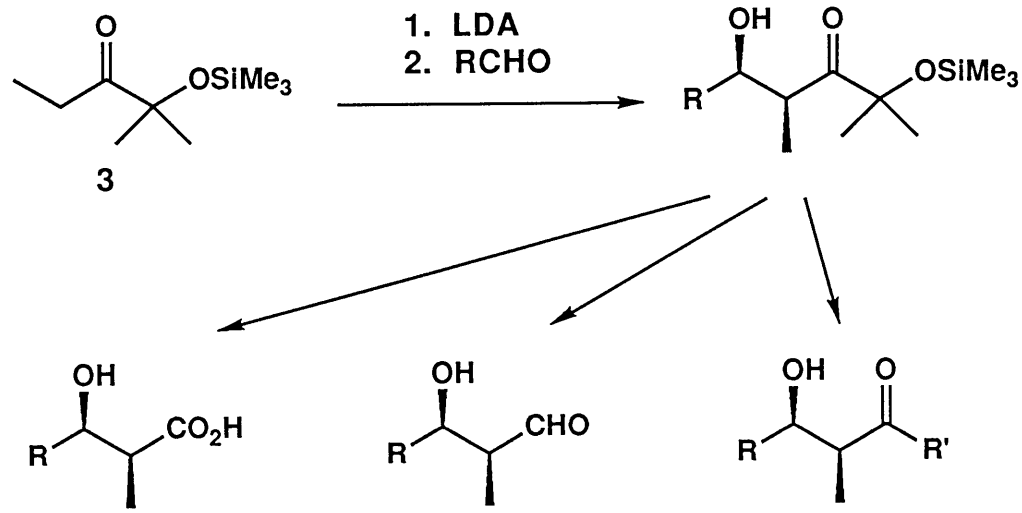
It has been well established that reactions of performed main-group metal enolates with aldehydes show a correlation between enolate geometry and aldol relative configuration if the nonreacting carbonyl ligand is sterically bulky.[2] For example, 2,2-dimethyl-3-pentanone undergoes deprotonation to give a *Z* enolate, which reacts with aldehydes to given syn aldols of high stereochemical purity (eq 1).[3] Conversely, the trimethylsilyl enol ethers of such ketones undergo anti-selective Lewis acid mediated aldol reactions (eq 2).[4]



1 (1)



2 (2)



3

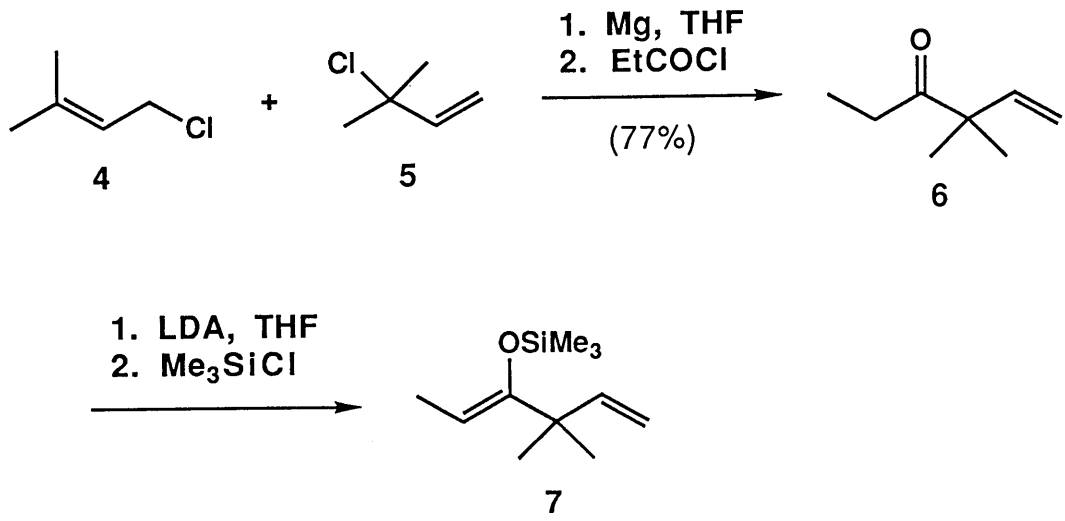
Scheme 1

To capitalize on this high aldol stereoselectivity, we developed aldol reagent **3**.[3,5,6] Like 2,2-dimethyl-3-pentanone, ketone **3** gives a *Z* enolate that reacts with a variety of aldehydes to

give syn aldols that can be cleaved by periodic acid to give β-hydroxy acids,[7] reduced and then cleaved by periodate to give β-hydroxy aldehydes,[8] or treated sequentially with an alkyllithium reagent and periodate to provide β-hydroxy ketones (Scheme 1).[9]

Reagent **3** and its relatives have been employed in several syntheses as syn-selective propanal or propanoic acid synthons.[10] A structurally related synthon, ethyl trityl ketone, also undergoes highly syn-selective aldol reactions; the resulting trityl aldols may be reductively cleaved with lithium triethylborohydride, after protection of the secondary alcohol.[11]

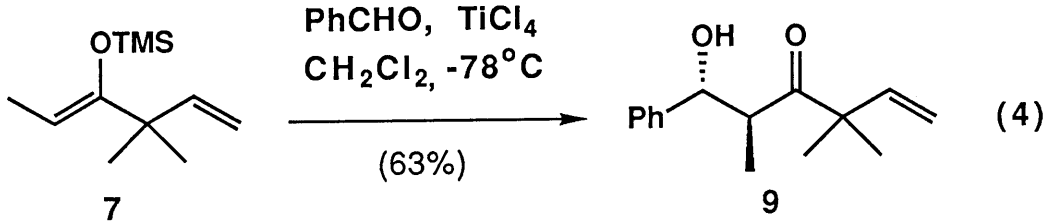
In spite of its utility, however, ketone **3** has limitations. A case in point is in Lewis acid mediated additions of its (Z)-trimethylsilyl enol ether to aldehydes. Although this reagent is highly anti-selective with sample aldehydes, it is less selective with α-alkoxy aldehydes, perhaps because of unwanted coordination of the Lewis acid by the α-(trimethylsilyl)oxy group.[12] To remedy this deficiency, we have developed another 2,2-dimethyl-3-pentanone analogue that has all of the desirable properties of **3**, without the undesirable feature of a (trialkylsilyl)oxy group. The new reagent, ketone **6**, is simply prepared as shown in Scheme 2 by reaction of the Grignard reagent derived from prenyl chloride[13] with propanoyl chloride; ketone **6** is obtained in 77% yield.[14] Treatment of the derived lithium enolate with trimethylsilyl chloride affords the trimethylsilyl enol ether **7** in 75% yield.



Scheme 2

The reactions summarized in eq 3 and 4 were carried out to assess the simple diastereoselectivity of reagents **6** and **7**. As expected, reaction of the lithium enolate with benzaldehyde affords syn aldol **8**, whereas the $TiCl_4$-mediated reaction of **7** with the same aldehyde provides the anti aldol **9**. Both aldols are obtained in a diastereomeric purity of >97 : 3 (high-field ^1H NMR).

6 8 (3)

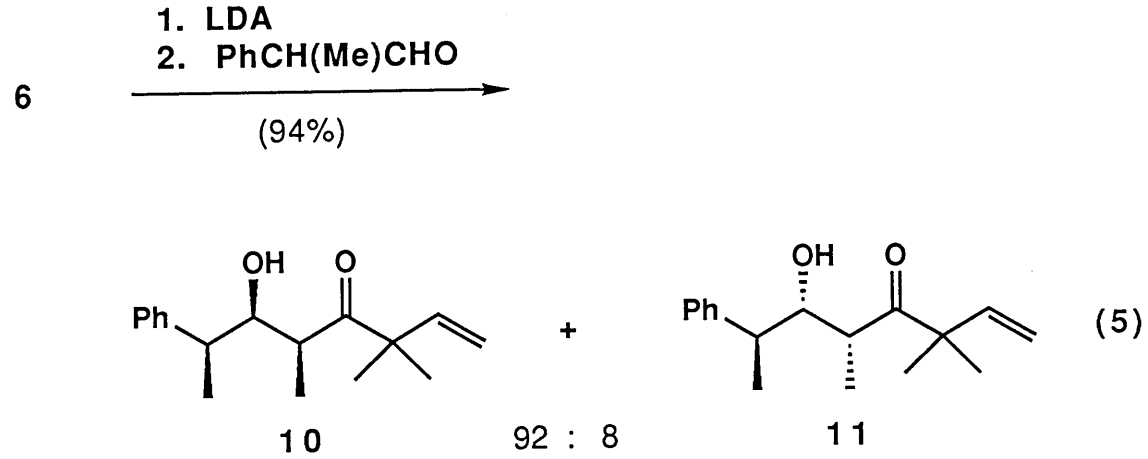


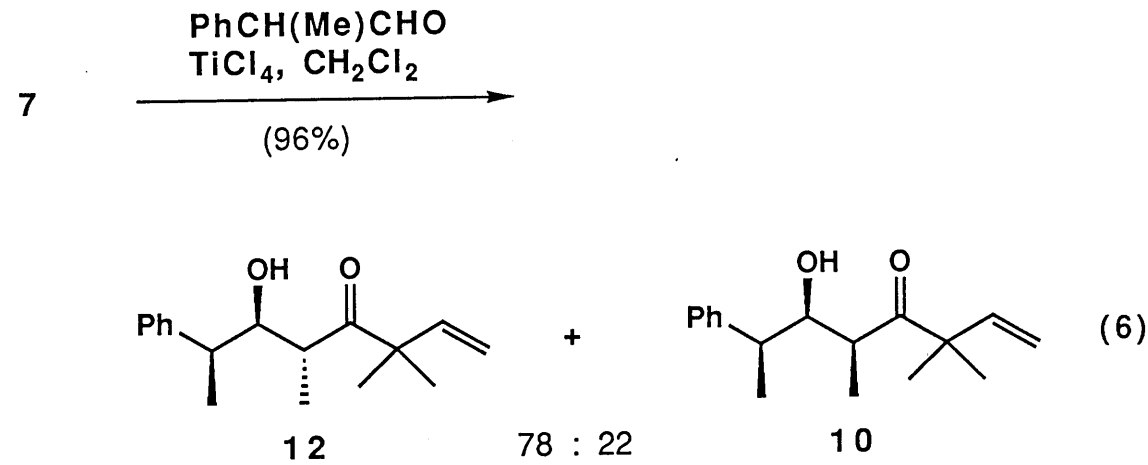
7 9 (4)

2-Phenylpropanal was used to examine the stereoselectivity of the aldol reactions of reagents **6** and **7** with a typical aldehyde. The reaction of the lithium enolate of **6** with 2-phenylpropanal gives only the two syn aldols, and a rather high Cram/anti-Cram ratio of 92 : 8 is observed (eq 5). In the $TiCl_4$-mediated reaction of **7** with the same aldehyde (eq 6), the Cram/anti-Cram ratio is >97 : 3,[15] but the simple diastereoselectivity is unusually low; aldols **12** and **10** are produced in a ratio of 3.5 : 1.

Because it has been found that diastereofacial selectivity in additions to α-chiral thionium ions is enhanced when the sulfur substituent is more bulky,[16] we investigated the Lewis acid mediated nucleophilic substitution reactions of the pinacol acetal (**13**) of 2-phenyl-2-propanal. As shown in Scheme 3, $TiCl_4$-mediated reaction of **13** with reagent **7** provides a 95 : 5 mixture of **14** and **15** if the reaction is carried out and quenched at -78°C. To our pleasant surprise, we discover that aldols **12** and **10** are produced in 96% yield in a ratio of 94 : 6 if the aldol reaction mixture is

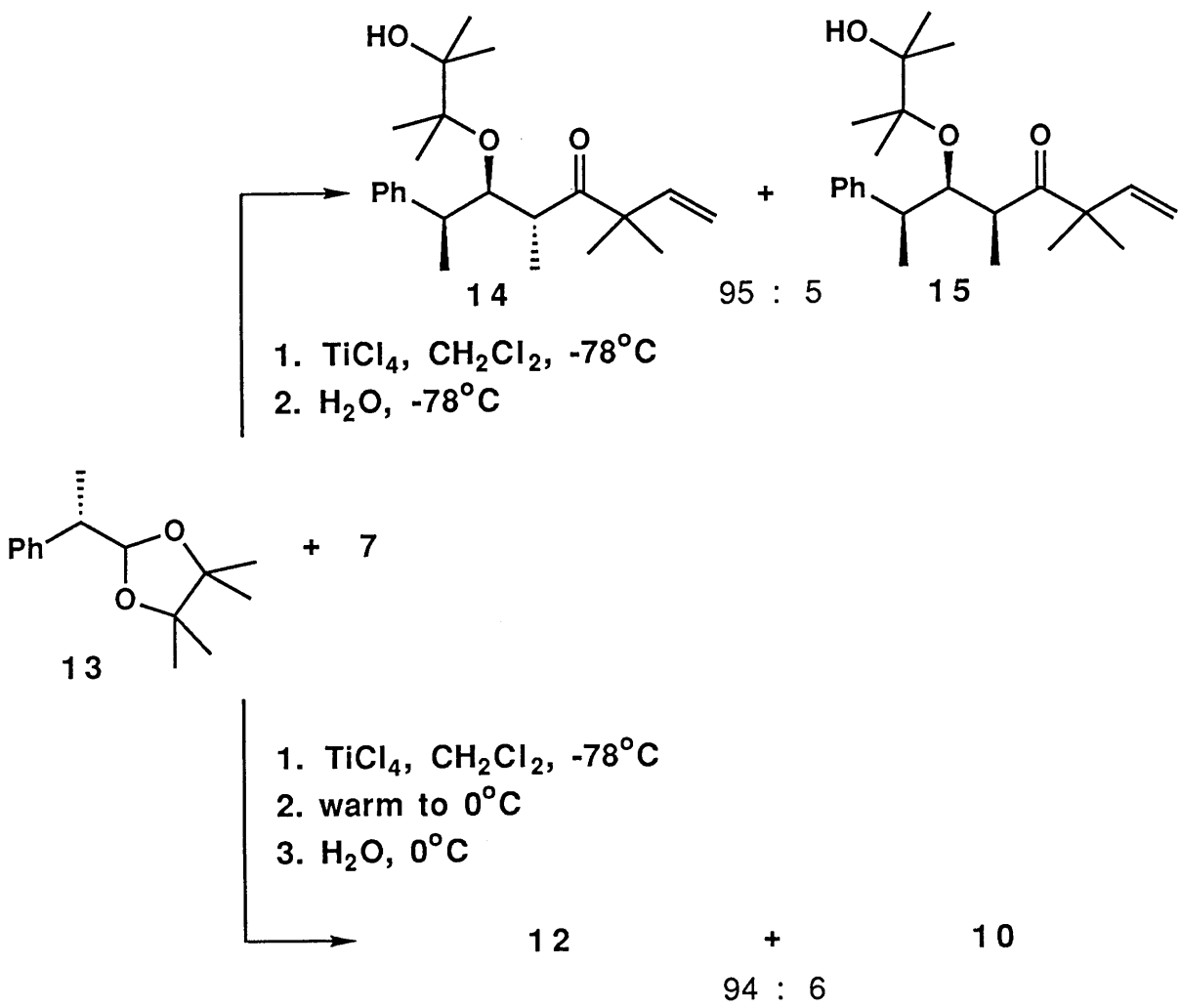
warmed for -78°C to 0°C prior to the aqueous quench. The loss of the pinacol group presumably occurs by $TiCl_4$-promoted pinacol rearrangement of the intermediate ethers. Use of the pinacol ether is essential to obtain high diastereofacial selectivity; when the dimethyl acetal corresponding to **13** is used in this reaction, three β-methoxy ketones are obtained in a ratio of 5: 4 : 1.





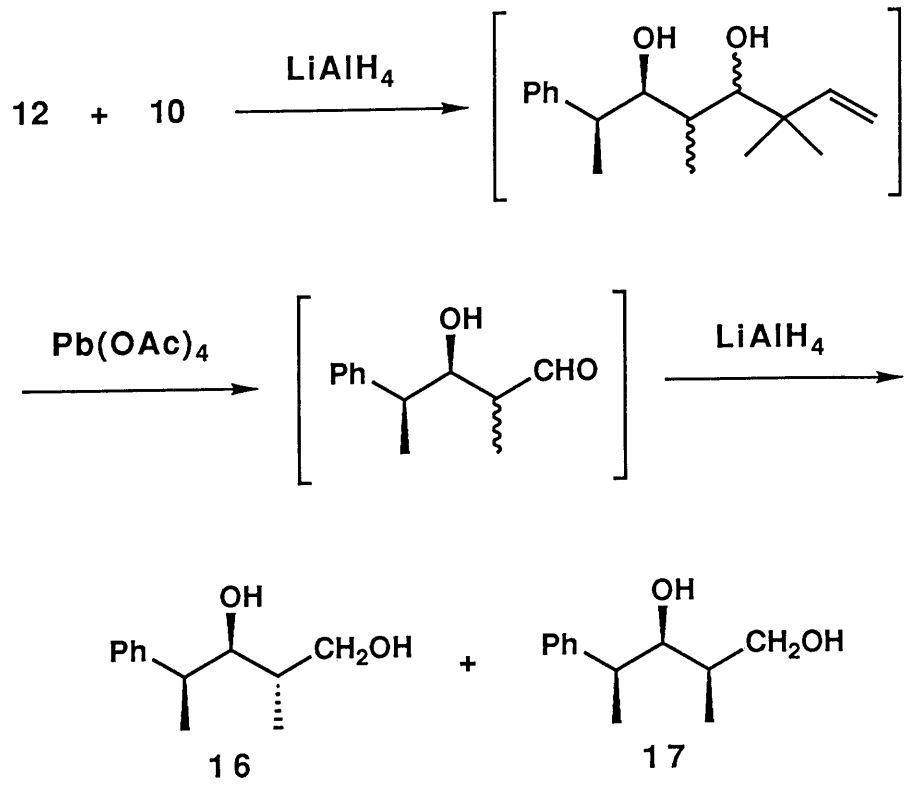
Finally, we have demonstrated the conversion of the new aldols to more useful β-hydroxy carbonyl compounds as shown in Scheme 4. Reduction of a 24 : 1 mixture of aldols **12** and **10** with lithium aluminum hydride provides a mixture of diols that is oxidized with lead tetraacetate to a mixture of β-hydroxy aldehydes.[17] Reduction of the latter mixture provides a mixture of diols **16** (57%) and **17** (5%). The transformation depicted in Scheme 4 is impressively chemoselective, considering the fact that one of the secondary hydroxy groups is homoallylic and

the other is homobenzylic. Other examples of the $Pb(OAc)_4$-mediated conversion of such homoallylic alcohols to aldehydes will be reported in connection with a paper detailing the use of **7** for an iterative ion extension process.[18]



Scheme 3

In conclusion, we have developed short, convenient syntheses of ketone **6** and the derived trimethylsilyl enol ether **7**, which may be used for stereoselective formation of syn and anti β-hydroxy carbonyl compounds. The obvious limitation of the new reagents is that other groups that react with lithium aluminum hydride or lead tetraacetate could provide avenues for side reactions.



Scheme 4

Experimental Section

General. Unless otherwise noted, materials were obtained from commercial sources and used without further purification. All reactions were performed under a dry N_2 atmosphere. Tetrahydrofuran (THF), diethyl ether, and benzene were distilled from sodium/benzophenone ketyl immediately prior to use. Dichloromethane was distilled from calcium hydride. Chromatography was performed with silica gel 60 (E. Merk, Darmstadt), 100-120 mesh, with the indicated solvents. Analytical thin-layer chromatography was performed on precoated glass plates (250 m, silica gel 60, E. Merk, Darmstadt). ^1H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ solution. *J* values are in hertz.

4,4-Dimethyl-5-hexen-3-one (6).[14] In a 500-mL, three-necked, round-bottomed flask equipped with a thermometer, a reflux condenser, and a magnetic stirring bar were placed magnesium turnings (21.6 g, 0.9 mol) and 100 mL of THF under N_2. A small piece of iodine and ca. 0.2 mL of prenyl chloride[13] were added at 25°C. After 10 min, the disappearance of iodine color indicated the initiation of the reaction. The reaction mixture was cooled to -10 to-15°C and then was diluted with 60 mL of THF. A solution of prenyl chloride (31.5 g, 0.3 mol) in 200 mL of THF was added dropwise over a period of 3 h with vigorous stirring. The reaction mixture was allowed to warm to room temperature and was stirred for 30 min. The solution of the Grignard reagent was transferred dropwise over a period of 1 h at -78°C, *via* cannula, into a 1000-mL flask containing 52.5 mL (0.6 mol) of propanoyl chloride in 200 mL of THF. The resulting mixture was allowed to warm to room temperature, stirred for 2 h, and poured into 1 L of water. The organic layer was removed and the aqueous layer was extracted with two 100-mL portions of ether. The combined organic layers were washed with 1 L of 2 M NaOH and 500 mL of brine. After drying, the solvent was removed by distillation through a 10-in. Vigreux column at atmospheric pressure. The residual oil was distilled at reduced pressure to give 29.0 g (77% yield) of ketone **6** as a colorless oil, bp 72-74°C/40 Torr. IR (film): 3100, 2980, 1720, 1630, 1460, 1100, 980, 920 cm^{-1}. ^1H NMR (250 MHz): δ 5.93 (dd, 1, *J*=10.5, 17.4), 5.14 (dd, 1, *J*=17.4, 0.7), 5.13 (d, 1, *J*=10.5, 0.7), 2.49 (q, 2, *J*=7.2), 1.23 (s, 6), 1.00 (t, 3, *J*=7.2). ^{13}C NMR (50.78 MHz): δ 213.6, 142.6, 113.8, 50.6, 30.4, 23.5, 8.1. Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 75.95; H, 11.27.

(Z)-3,3-Dimethyl-4-[(trimethylsilyl)oxy]-1,4-hexadiene (7). To a solution of diisopropylamine (15.4 mL, 110 mmol) in 200 mL of THF was added 53 mL of BuLi (105 mmol, 1.98 M in hexane) in 10 min at 0°C. After being stirred for 15 min, the solution was cooled to -78°C and 12.6 g (100 mmol) of ketone **6** was added over a period of 10 min. After being stirred for 1.5 h, $(CH_3)_3SiCl$ (13.9 mL, 110 mmol) was added at -78°C, and the mixture was allowed to warm to 25°C and stirred overnight. The reaction mixture was poured into 400 mL of pH 7 phosphate buffer and extracted with three 50-mL portions of pentane. The combined organic

layers were washed with two 200-mL portions of the phosphate buffer, dried over $MgSO_4$, concentrated with a rotary evaporator, and distilled to give 17.8 g (90% yield) of ether **7**, bp 103-106°C/45 Torr. IR (film): 3090, 2960, 1660, 1640, 1250, 1140, 1080, 900, 905, 845 cm^{-1}. ^1H NMR (250 MHz): δ 5.87 (dd, 1, *J*=10.6, 17.5), 5.05 (dd, 1, *J*=17.5, 1.3), 4.98 (dd, 1, *J*=10.6, 1.3), 4.64 (q, 1, *J*=6.7), 1.52 (d, 3, *J*=6.7), 1.13 (s, 6), 0.21 (s, 9). ^{13}C NMR (50.78 MHz): δ 157.1, 146.3, 111.2, 99.4, 42.6, 25.5, 11.7, 1.1. Anal. Calcd for $C_{11}H_{22}OSi$: C, 66.60; H, 11.80. Found: C, 66.64; H, 11.54.

(1*S,2*S**)-1-Hydroxy-2,4,4-trimethyl-1-phenylhex-5-en-3-one (8).** To a stirring solution of 1.55 mL (11 mol) of diisopropylamine in 35 mL of THF was added 5.5 mL (11 mmol) of a 2 M solution of BuLi in hexane at 0°C. After 15 min, the solution was cooled to -78°C and 1.26 g (10 mmol) of ketone **6** was added over 5 min. After being stirred for 30 min, 1.06 g (10 mmol) of benzaldehyde was added dropwise, and the solution was stirred for 30 min. The reaction was quenched with 50 mL of saturated NH_4Cl and extracted with three 20-mL portions of ether. The combined ether layers were dried over Na_2SO_4 and concentrated to give 2.21 g (95%) of the title compound as a colorless oil. ^1H NMR (250 MHz): δ 7.28 (m, 5), 5.76 (dd, 1, *J*=10.5, 17.5), 5.18 (dd, 1, *J*=17.5, <1.0), 5.16 (dd, 1, *J*=10.5, <1.0), 4.84 (d, 1, *J*=4.2), 3.48 (br s, 1), 3.20 (dq, 1, *J*=4.2, 6.9), 1.17 (s, 3), 1.08 (s, 3), 1.02 (d, 3, *J*=6.9). ^{13}C NMR (50.78 MHz): δ 217.4, 141.1, 140.4, 127.4, 126.6, 125.4, 114.6, 51.0, 46.4, 22.2, 22.0, 11.6.

(1*S,2*R**)-1-Hydroxy-2,4,4-trimethyl-1-phenylhex-5-en-3-one (9).** To a mixture of 106 mg (1.0 mmol) of benzaldehyde and 291 mg (1.5 mmol) of ether **7** in 5 mL of CH_2Cl_2 at -78°C was added dropwise 0.11 mL (1.0 mmol) of $TiCl_4$. After 30 min the reaction mixture was poured into 20 mL of 1 N HCl, the organic layer was separated, and the aqueous layer was washed with two 10-mL portions of CH_2Cl_2. The combined organic layers were washed with 20 mL of brine, dried over ($MgSO_4$), and concentrated to give an oil. This crude product was chromatographed on silica gel, using 5 : 1 hexane/ethyl acetate as eluant, to obtain 136 mg (63%) of aldol **9** as a colorless oil. IR (film): 3500, 2980, 1710, 1635, 1500, 1015, 995,

925, 775, 710 cm^{-1}. ^1H NMR (250 MHz): δ 7.28 (m, 5), 5.80 (dd, 1, *J*=17.4, 0.8), 5.14 (dd, 1, *J*=10.6, 0.8), 5.11 (dd, 1, *J*=10.6, 0.8), 4.71 (d, 1, *J*=7.4), 3.27 (dq, 1, *J*=7.4, 7.0), 3.05 (br s, 1), 1.16 (s, 3), 0.94 (d, 3, *J*=7.0). ^{13}C NMR (50.78 MHz): δ 217.7, 142.8, 141.6, 128.2, 127.6, 126.4, 114.4, 72.2, 51.5, 47.5, 22.9, 22.8, 16.6. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.17; H, 8.66.

Reaction of the Lithium Enolate of Ketone 6 with 2-Phenylpropanal. A solution of LDA, prepared from 0.24 mL (1.70 mmol) of diisopropylamine and 0.62 mL of a 2.42 M solution of BuLi (1.50 mmol) in hexane, in 10 mL of THF was cooled to -78°C and 189 mg (1.5 mmol) of ketone **6** was slowly added. After stirring for 30 min at -78°C, 0.134 g (1.0 mmol) of 2-phenylpropanal was added. After 15 min at -78°C, water was added and the solution was worked up in the usual manner to provide 249 mg (95%) of a 92 : 8 mixture of aldols **10** and **11**, as shown by ^1H NMR spectroscopy. The pure aldols were isolated by gravity chromatography on silica gel.

(2*R,3*S**,4*R**)-3-Hydroxy-4,6,6-trimethyl-2-phenyloct-7-en-5-one (10).** TLC: R_f=0.44 (5.1 hexane/ethyl acetate). ^1H NMR (250 MHz): δ 5.61 (dd, 1, *J*=10.5, 17.3), 5.01 (d, 1, *J*=10.5), 4.89 (d, 1, *J*=17.3), 3.69 (dd, 1, *J*=0.8, 9.8), 3.50 (d, 1, *J*=0.8), 2.68-2.84 (m, 2), 1.36 (d, 3, *J*=6.8), 1.06 (s, 3), 1.00 (d, 3, *J*=7.0). ^{13}C NMR (50.78 MHz): δ 219.1, 143.9, 140.5, 128.3, 127.3, 126.4, 115.2, 75.7, 51.3, 42.8, 40.1, 22.5, 18.7, 10.1.

(2*R,3*R**,4*S**)-3-Hydroxy-4,6,6-trimethyl-2-phenyloct-7-en-5-one (11).** TLC: R_f=0.38 (5.1 hexane/ethyl acetate). ^1H NMR (250 MHz): δ 7.21-7.34 (m, 5), 5.93 (dd, 1, *J*=10.0, 17.8), 5.26 (d, 1, *J*=10.5), 5.25 (d, 1, *J*=17.0), 3.77 (d, 1, *J*=9.0), 3.31 (dq, 1, *J*=1.8, 7.3), 3.25 (s, 1), 2.76-2.83 (m, 1), 1.25 (s, 3), 1.19 (d, 3, *J*=7.3), 1.09 (d, 3, *J*=7.0).

$TiCl_4$-Promoted Reaction of Ether 7 with 2-Phenylpropanal. To a mixture of 0.134 g (1.0 mmol) of 2-phenylpropanal and 0.238 g (1.2 mmol) of ether **7** in 11 mL of CH_2Cl_2 was added 0.13 mL (1.2 mmol) of $TiCl_4$ slowly at -78°C. After being stirred for 15 min, the

bright yellow reaction mixture was quenched at -78°C by rapid addition of 10 mL of saturated $NaHCO_3$. The mixture was extracted with two 50-mL portions of ether and the combined ether layers were dried and concentrated to obtain 251 mg (96%) of a 78 : 22 mixture of aldols **12** and **10**, as judged from the ^1H NMR spectrum. The pure aldols were obtained by chromatography on silica gel.

(2*R,3*S**,4*S**)-3-Hydroxy-4,6,6-trimethyl-2-phenyloct-7-ene-5-one (12).** TLC: R_f=0.38 (5.1 hexane/ethyl acetate). IR (film): 3520, 2950, 1710, 1460, 1000, 715 cm^{-1}. ^1H NMR (250 MHz): δ 7.16-7.34 (m, 5), 5.88 (dd, 1, *J*=10.5, 17.5), 5.12 (d, 1, *J*=16.5), 5.11 (d, 1, *J*=11.5), 3.75 (dd, 1, *J*=6.8, 12.3), 3.00-3.14 (m, 1), 2.79-2.93 (m, 1), 2.38 (d, 1, *J*=6.8), 1.30 (d, 3, *J*=7.0), 1.19 (s, 3), 1.17 (s, 3), 1.10 (d, 3, *J*=7.0). ^{13}C NMR (50.78 MHz): δ 218.2, 144.5, 128.3, 127.6, 126.2, 113.9, 51.1, 42.9, 23.5, 16.0, 14.5. Anal. Calcd for $C_{14}H_{24}O_2$: C, 78.40; H, 9.31. Found: C, 78.12; H, 8.99.

(2*R,3*S**,4*R**)-3-Hydroxy-4,6,6-trimethyl-2-phenyloct-7-en-5-one (10).** TLC: R_f=0.44 (5.1 hexane/ethyl acetate). This material was identical by ^1H NMR with the sample obtained as the major product in the foregoing lithium enolate reaction.

2-(1-Phenylethyl)-4,4,5,5-tetramethyl-1,3-dioxolane (13). A mixture of 0.670 g (5.0 mmol) of 2-phenylpropanal and 0.590 g (5 mmol) of pinacol in 25 mL of benzene was heated under reflux while water was continuously removed with a Dean-Stark trap. After 1 h the solution was cooled to room temperature and 0.2 g of $NaHCO_3$ was added. The solvent was removed under vacuum and the residue purified by flash chromatography[19] on silica gel, eluting with 20 : 1 hexane/ethyl acetate, to obtain 1.02 g (87%) of the pure acetal. IR (film): 2980, 1605, 1500, 1450, 1370, 1100, 980, 770, 700 cm^{-1}. ^1H NMR (250 MHz): δ 7.27 (m, 5), 5.08 (d, 1, *J*=5.4), 2.87 (dq, 1, *J*=5.4, 7.2), 1.32 (d, 3, *J*=7.2), 1.18 (s, 3), 1.14 (s, 3), 1.08 (s, 6). ^{13}C NMR (50.78 MHz): δ 142.4, 128.5, 127.9, 126.4, 103.6, 81.7, 81.6, 45.1, 24.11, 24.06, 22.2, 22.1, 16.2. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.04; H, 9.34.

$TiCl_4$-Promoted Reaction of Acetal 13 with 2-Phenylpropanal. To a stirring solution of 0.234 g (1.0 mmol) of acetal **13** and 0.238 g (1.2 mmol) of ether **7** in 11 mL of CH_2Cl_2 was added dropwise 0.13 mL (1.2 mmol) of $TiCl_4$ at -78°C. After 15 min, the mixture was allowed to warm to 0°C and stirred 30 min, and the bright yellow mixture was quenched by rapid addition of 10 mL of saturated $NaHCO_3$ at 0°C. The mixture was extracted with two 50-mL portions of ether. The combined organic layers were dried and concentrated to obtain 251 mg (96%) of a 94 : 6 mixture of aldols **12** and **10**, as judged by ^1H NMR. The pure aldols were obtained by chromatography on silica gel.

Conversion of Aldols 12 and 10 to Diols 16 and 17. To a solution of 260 mg (1.0 mmol) of a 94 : 6 mixture of aldols **12** and **10** in 10 mL of ether was added 38 mg (1.0 mmol) of $LiAlH_4$ at 0°C. The solution was stirred for 38 mg (1.0 mmol) of $LiAlH_4$ at 0°C. The solution was stirred for 5 min and allowed to warm to room temperature. After 30 min, the mixture was quenched at 0°C by the slow addition of 10 mL of 1N HCl. The mixture was extracted with two 20-mL portions of ether, and the combined ether layers were dried ($MgSO_4$) and concentrated to obtain 253 mg (96%) of a diastereomeric mixture of diols. To a solution of this material in 10 mL of CH_2Cl_2 was added 443 mg (1.0 mmol) of $Pb(OAc)_4$ at -78°C under N_2. The mixture was stirred for 2 h at -78°C and allowed to warm to room temperature. After 1.5 h, ca. 0.5 g of silica gel was added (for filtration aid), the mixture was filtered, and the filtrate was concentrated to obtain a diastereomeric mixture of β-hydroxy aldehydes as an oil. This crude material was dissolved in 10 mL of ether and 38 mg (1.0 mmol) of $LiAlH_4$ was added at 0°C. This solution was stirred for 5 min and allowed to warm to room temperature. After 30 min the mixture was quenched at 0°C by the slow addition of 10 mL of 1 N HCl. The resulting mixture was extracted with two 20-mL portions of ether and the combined organic layers were dried and concentrated to obtain a solid. Flash chromatography on silica gel, using 5 : 2 hexane/ethyl acetate as eluent, gave 111 mg (57%) of diol **16**, mp 54-55°C, and 10 mg (5%) of diol **17**, oil.

(2*R,3*S**,4*R**)-2-Methyl-4-phenylpentane-1,3-diol (16).** TLC: R_f=0.14 (2 : 1 hexane/ethyl acetate). ^{1}H NMR (250 MHz): δ 7.21-7.32 (m, 5), 3.73-3.77 (m, 1), 3.56-3.61 (m, 2), 3.12 (br s, 1), 3.01 (dq, 1, *J*=4.6, 7.0), 2.47 (br s, 1), 1.71-1.88 (m, 1), 1.31 (d, 3, *J*=7.0), 0.96 (d, 3, *J*=7.0).

(2*R,3*S**,4*S**)-2-Methyl-4-phenylpentane-1,3-diol (17).** TLC: R_f=0.09 (2 : 1 hexane/ethyl acetate). ^{1}H NMR (250 MHz): δ 7.16-7.30 (m, 5), 3.96 (dd, 1, *J*=1.9, 9.6), 3.57-3.70 (m, 2), 2.82 (dq, 1, *J*=9.8, 6.8), 2.48 (br s, 1), 1.65 (br s, 1), 1.35-1.50 (m, 1), 1.37 (d, 3, *J*=6.8), 0.94 (d, 3, *J*=7.0).

The spectral data for these two diols are in agreement with data reported by Matsumoto and co-workers[20] and were found to be identical with the spectra of samples previously prepared in this laboratory.[21]

Registry No. 4, 503-60-6; **5**, 2190-48-9; **6**, 78186-80-8; (*Z*)-**7**, 124400-14-2; **8**, 124400-15-3; **9**, 124400-16-4; **10**, 124400-17-5; **11**, 124509-16-6; **12**, 124509-17-7; **13**, 124400-18-6; **14**, 124400-19-7; **15**, 124508-29-8; **16**, 1245080-30-1; **17**, 124508-31-2; $CH_3CH_2C(O)Cl$, 79-03-8; $CH_3CH(Ph)CHO$, 93-53-8; $PhCH(CH_3)CH(OH)CH(CH_3)CH(OH)$-$C(CH_3)_2CH{=}CH_2$, 124400-20-0; $PhCH(CH_3)CH(OH)CH(CH_3)CHO$ (stereoisomer 1), 124400-21-1; $PhCH(CH_3)CH(OH)CH(CH_3)CHO$ (stereoisomer 2), 124508-32-3; pinacol, 76-09-5.

References and Notes

1. Paper 50 in the series Acyclic Stereoselection. For paper 49, see: Montgomery, S. H.; Pirrung, M. C.; Heathcock, C. H. *Carbohyd. Res.*, in press.
2. (a) Kleschick, W. A.; Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 247.

(b) Heathcock, C. H. In *Asymmetric Synthesis, Volume 3*; Morrison, J. D., Ed.; Academic Press: New York, 1984; p 111, and references contained therein.

3. Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.
4. Heathcock, C. H.; Hug, K. T.; Flippin, L. A. *Tetrahedron Lett.* **1984**, *25*, 5793.
5. Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 2337.
6. Buse, C. T. Ph. D. Dissertation, University of California, Berkeley, 1978.
7. (a) Young, S. D.; Buse, C. T.; Heathcock, C. H. *Org. Synth.* **1985**, *63*, 79.

   (b) Bal, B.; Buse, C. T.; Smith, K.; Heathcock, C. H. *Ibid.* **1983**, *63*, 89.
8. Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pilli, R.; Badertscher, U. *J. Org. Chem.* **1985**, *50*, 2095.
9. White, C. T.; Heathcock, C. H. *J. Org. Chem.* **1981**, *46*, 191.
10. (a) Collum, D. B.; McDonald, J. H.; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2118.

    (b) Dauben, W. G.; Saugier, R. K.; Fleischhauer, I. *J. Org. Chem.* **1985**, *50*, 3767.

    (c) Heathcock, C. H.; Montgomery, S. H. *Tetrahedron Lett.* **1983**, *24*, 4637.

    (d) Brooks, D. W.; Kellogg, R. P. *Tetrahedron Lett.* **1982**, *23*, 4991.

    (e) Heathcock, C. H.; Finkelstein, B. L. *J. Chem. Soc., Chem. Commun.* **1983**, 919.

    (f) Heathcock, C. H.; Finkelstein, B. L.; Jarvi, E. T.; Radel, P. A.; Hadley, C. R. *J. Org. Chem.* **1988**, *53*, 1922.

    (g) Heathcock, C. H.; Jarvi, E. T. *Tetrahedron Lett.* **1982**, *23*, 2825.

    (h) Heathcock, C. H.; Radel, P. A. *J. Org. Chem.* **1986**, *51*, 4322.
11. (a) Seebach, D.; Ertas, M.; Locher, R.; Schweizer, W. B. *Helv. Chim. Acta* **1985**, *68*, 264.

    (b) Ertas, M.; Seebach, D. *Ibid.* **1985**, *68*, 961.

12. Heathcock, C. H.; Dasidsen, S. K.; Hug, K. T.; Fillipin, L. A. *J. Org. Chem.* **1986**, *51*, 3027.

13. Prenyl chloride is obtained as a 5 : 1 mixture of **4** and **5** by reaction of 3-methylbut-1-en-3-ol with concentrated HCl:
Mayer, H.; Klein, H.; Sippel, H. *Chem. Ber.* **1983**, *116*, 3624.

14. For a precedent for this reaction, see:
Sato, F.; Inoue, M.; Oguro, K.; Sato, M. *Tetrahedron Lett.* **1979**, 4303.

15. Lewis acid mediated additions of silyl enol ethers to α-chiral aldehydes have previously been shown to give enhanced Cram/anti-Cram ratios:
Heathcock, C. H.; Flippin, L. A. *J. Am. Chem. Soc.* **1983**, *105*, 1667.

16. Mori, I.; Bartlett, P. A.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 7199.

17. The oxidative cleavage of homoallylic alcohols by lead tetraacetate is well-precedented.
(a) Braude, E. A.; Wheeler, O. H. *J. Chem. Soc.* **1955**, 320.
(b) Amorosa, M.; Caglioti, L.; Cainelli, G.; Immer, H.; Keller, J.; Wehrli, H.; Mihaiolovic, M. L.; Schaffner, K.; Arigoni, D.; Jeger, O. *Helv. Chim. Acta* **1962**, *45*, 2674.
(c) Heusler, D.; Kalvoda, J. *Angew. Chem., Int. Ed. Engl.* **1964**, 525.
For reviews, see:
(d) Criegee, R. In *Oxidation in Organic Chemistry, Part A*; Academic Press: New York, 1965; Chapter V.
(e) Rubottom, G. M. In *Oxidation in Organic Chemistry, Part D*; Academic Press: New York, 1982; Chapter I.

18. Mori, I; Bartlett, P. A.; Heathcock, C. H., manuscript in preparation.

19. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

20. Matsumoto, T.; Hosoda, K.; Mori, K.; Fukui, K. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3156.

21. Buse, C. T.; Heathcock, C. H. *Tetrahedron Lett.* **1978**, 1685.

Chapter 7

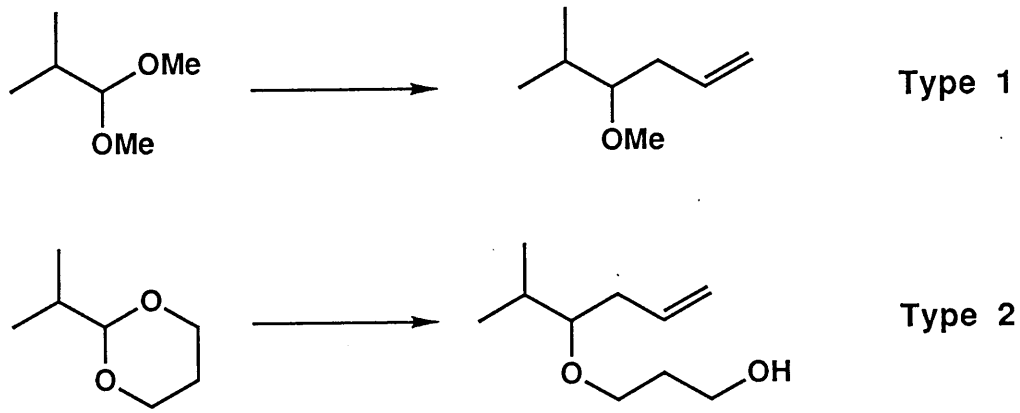
On the Mechanism of Lewis-Acid-Mediated Nucleophilic Substitution Reactions of Acetals[1]

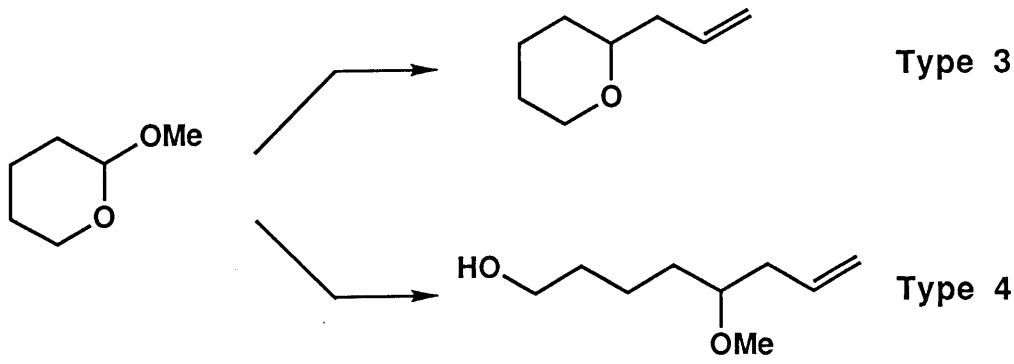
Abstract: Lewis-acid-mediated nucleophilic substitution of acetals can occur by direct displacement (S_N2) or oxocarbenium ion (S_N1) mechanisms. With acyclic acetals, stereoselectivity increases with increasing steric bulk of the alkoxy group and with increasing polarity of the reaction medium. The enhanced stereoselectivity observed with acetals of secondary and tertiary alcohols is explained by perturbation of the approach trajectory of the nucleophilic alkene as it attacks the oxocarbenium ion. Highest stereoselectivity is seen in the reaction of 2-(1-phenylethyl)-4,4,5,5-tetramethyl-1,3-dioxolane (**4**) with enolsilane **5**; only one diastereomeric product (**9s**) is obtained, even in the relatively non-polar solvent CH_2Cl_2. The $TiCl_4$-mediated reactions of cyclic acetals **18c**, **18t**, **25**, and **28** with silyl enol ether **5** show that in these systems the substitution dose not occur by the S_N2 mechanism.

Introduction

The Lewis-acid-mediated reaction of acetals with nucleophiles such as silyl enol ethers and allylsilanes is a powerful method for carbon-carbon bond formation[2] and has proven to be highly stereoselective in many cases.[3] Detailed mechanistic studies are scare, although some mechanistic rationales have been put forward for these and related reactions.[2o,3a,3c,4,5,6,7,8] Recent communications from Denmark and coworkers provide strong evidence for a mechanistic divergence in an intramolecular version of the reaction[9] and give information pertaining to the structures of complexes of cyclic acetals with BF_3 in various solvents.[10] In this paper, we report two sets of experiments that provide information about the mechanism of the intermolecular reaction.[11]

Intermolecular substitution reactions of acetals can be classified in four groups, depending on the structure of the acetal and which alkoxy group is replaced. These are illustrated in Scheme 1 for hypothetical reactions with allyltrimethylsilane. In this study, we have examined reactions with of Type 1 and Type 2. Our results also indicate a mechanistic divergence; acetal substitution can occur by S_N1 (oxocarbenium ion) or S_N2 mechanisms. The operative mechanism depends on the size of the acetal alkoxy group and more polarity of the solvent. Greater steric bulk in the acetal alkoxy group and more polar solvent promote ionization to the oxocarbenium ion.

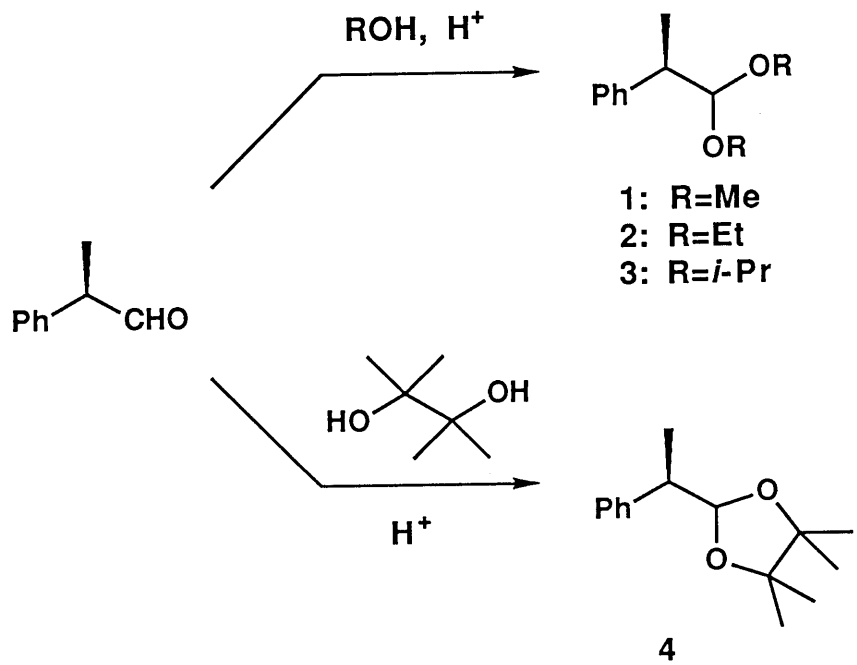




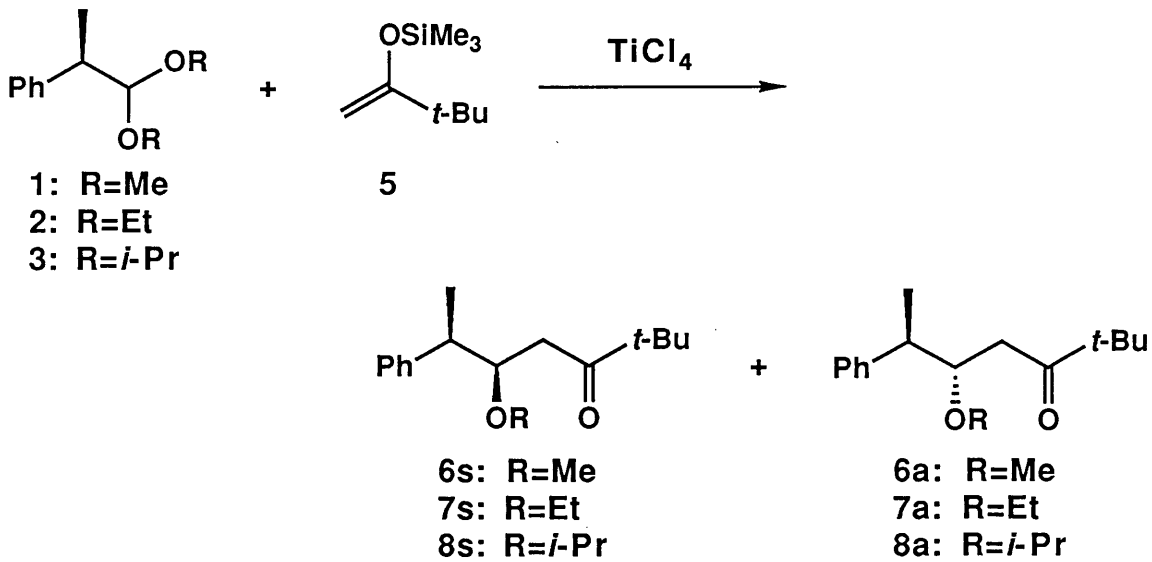
Scheme 1

Results. A. Effect of Alkoxy Group on Stereochemistry of Type 1 Acetal Reactions

Acetals **1-3** were prepared by reaction of 2-phenylpropanal with methanol, ethanol, 2-propanol, respectively. The *t*-butyl acetal cannot be prepared by this method because of elimination to give an enol ether. However 2-phenylpropanal reacts with pinacol to give acetal **4**, a reasonable substitute for the di-*t*-butyl acetal.



Reactions of acetals **1-4** were carried out with the trimethylsilyl enol ether derived from pinacolone. Reactions were carried out in methylene chloride with $TiCl_4$ as catalyst. Results are summarized in Table 1.



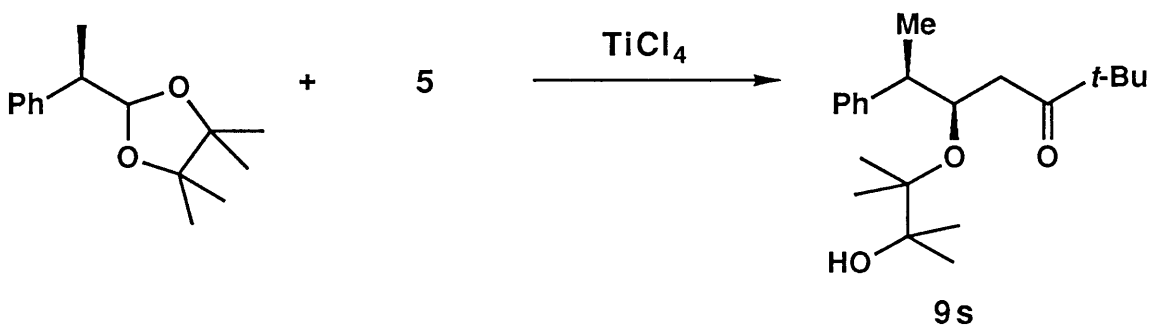
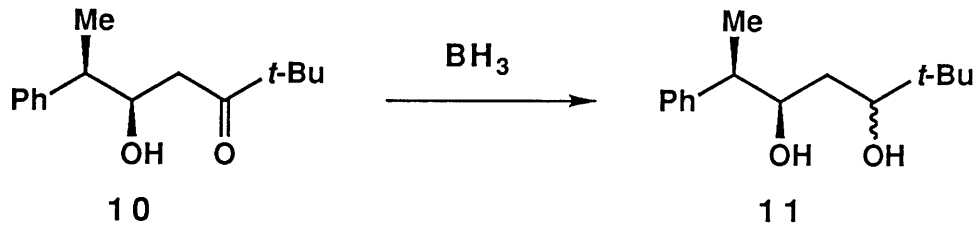


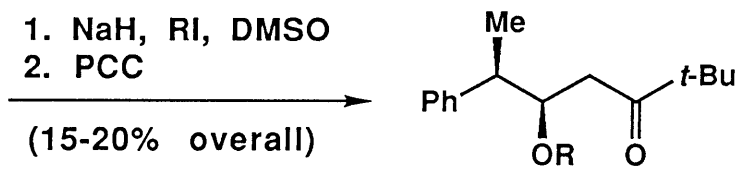
Table 1. Stereochemistry of Acetal Substitution Reactions (Scheme 4)

Entry	Acetal	Conc., *M*	Solvent	Temp., °C	syn/anti	Products	Yield, %
1	**1**	0.2	CH_3CN	-40 to 0	4.4 : 1	**6s : 6a**	92
2	**1**	0.2	CH_3CN	0	2.9 : 1	**6s : 6a**	100
3	**1**	0.2	CH_2Cl_2	-78	2.5 : 1	**6s : 6a**	84
4	**1**	0.02	CH_2Cl_2	-78	2.6 : 1	**6s : 6a**	89
5	**1**	0.2	toluene	-78	1.3 : 1	**6s : 6a**	83
6	**1**	0.2	hexane	-78	1.3 : 1	**6s : 6a**	31
7	**2**	0.2	CH_2Cl_2	-78	3.6 : 1	**7s : 7a**	90
8	**3**	0.2	CH_2Cl_2	-78	7.3 : 1	**8s : 8a**	82
9	**3**	0.2	toluene	-78	2.2 : 1	**8s : 8a**	82
10	**4**	0.2	CH_2Cl_2	-78	>50 : 1	**9s**	94

The major isomers from reaction of acetals **1** and **2** with **5** were shown to be the syn isomers **6s** and **7s** by independent synthesis from aldol **10**. An attempt to prepare alkoxy ether **8s** by this method failed, so the structure of the major isomer from reaction of acetal **3** with **5** is assigned by analogy.

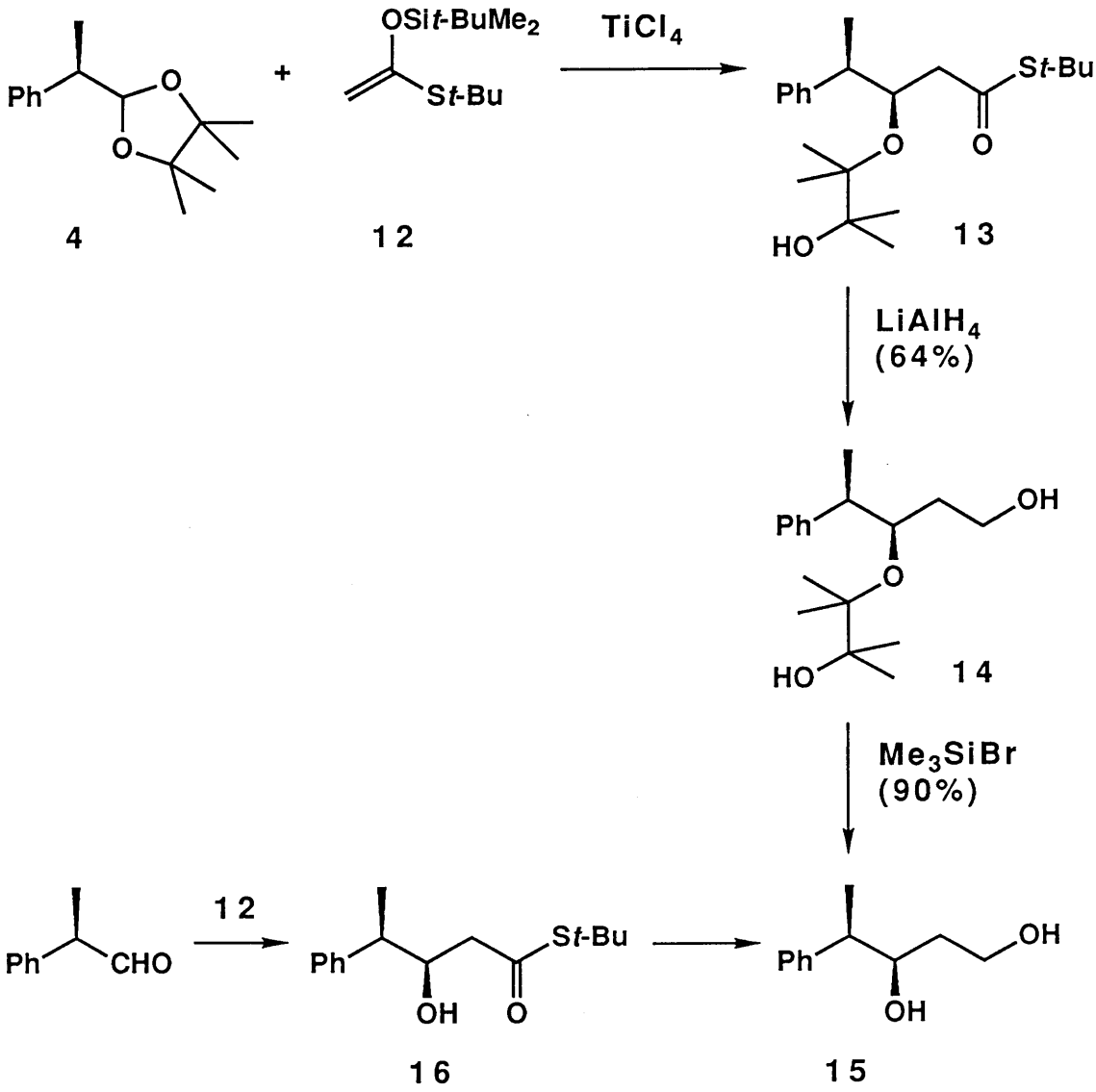


10 **11**



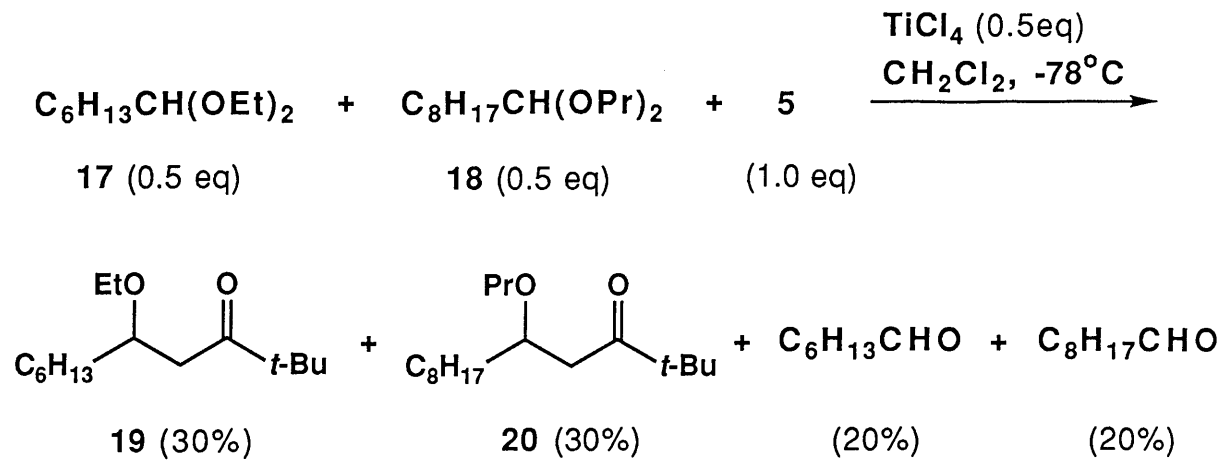
6s: R=Me
7s: R=Et

The stereochemistry of the sole isomer from the reaction of acetal **4** with **5** is inferred to be syn on the basis of the following. As shown in Scheme 2, **4** reacts with **12** to give a mixture of diastereomeric products in a ratio of 10 : 1. This mixture was reduced to a diol, which was treated with trimethylsilyl bromide to remove the pinacol group. This major product of this mixture was identical to the diol (**15**) produced from authentic syn β-hydroxy thioester **16**, obtained by the $TiCl_4$-mediated reaction of **12** with 2-phenylpropanal.



Scheme 2

One further experiment was carried out. As shown in Scheme 3, an equimolar mixture of acetals **17** and **18** was treated with silyl enol ether **5** and $TiCl_4$ in methylene chloride. Under these conditions, β-alkoxy ketones **19** and **20** were each obtained in 30% yield; heptanal and nonal were each obtained in 20% yield. Crossover products in which ethoxy is associated with C_6H_{13} or propoxy with C_8H_{17} were not observed.



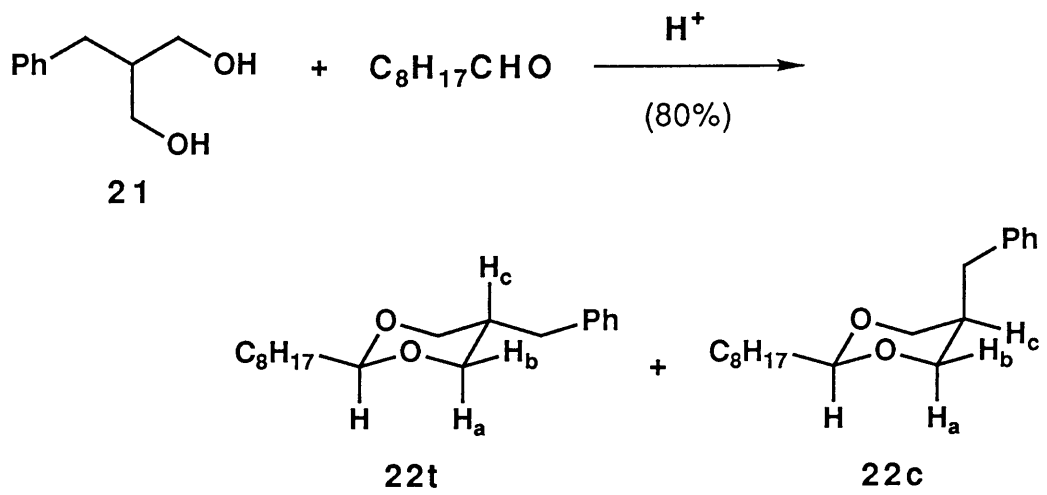
Scheme 3

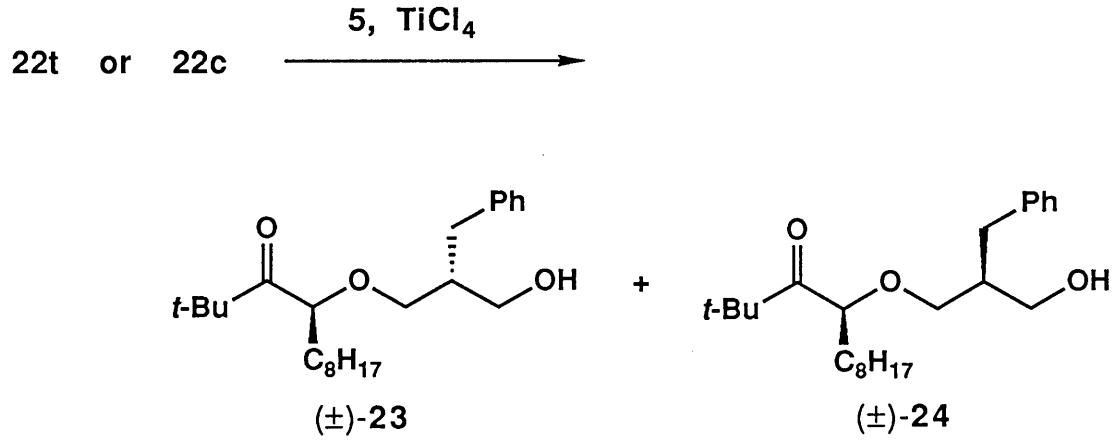
Results. B. Stereochemistry of Type 2 Acetal Reactions

Acetals **22t** and **22c** were prepared by reaction of diol **21** with nonal. The configurations of the two acetals were readily established by the vicinal ^1H NMR coupling constants; J_{ac} is 10.5 Hz in **22t** and <1.0 in **22c**.

The $TiCl_4$-promoted reactions of both **22t** and **22c** with silyl enol ether **5** occurred in good yield to give 1 : 1 mixtures of diastereomers (±)-**23** and (±)-**24**. To fully interpret this result, it was necessary to carry out control experiments to show that the observed 1 : 1 ratio of products was not the result of acetal equilibration. In fact, reaction of **22c** with $TiCl_4$ in CH_2Cl_2 at -78°C for 15 minutes followed by $NaHCO_3$ quench at the same temperature gave rise to a 1 : 1 mixture of **22c** and **22t**. When **22t** was treated with 2 equivalents of **5** and 0.2 equivalents of

$TiCl_4$ under the same conditions, there was obtained in 50% yield a 1 : 1 mixture of the ***R*,S**** and ***S*,S**** diastereomeric products [(±)-**23** and (±)-**24**] along with 50% of unchanged **22t**. Similar treatment of **22c** afforded in 33% yield a 1 : 1 mixture of (±)-**23** and (±)-**24** along with 67% yield of unchanged **22c**. These controls show that, although **22t** and **22c** *are* equilibrated under the reaction conditions (presumably *via* the oxocarbenium ion), the equilibration is slower than reaction with **5**.[12]

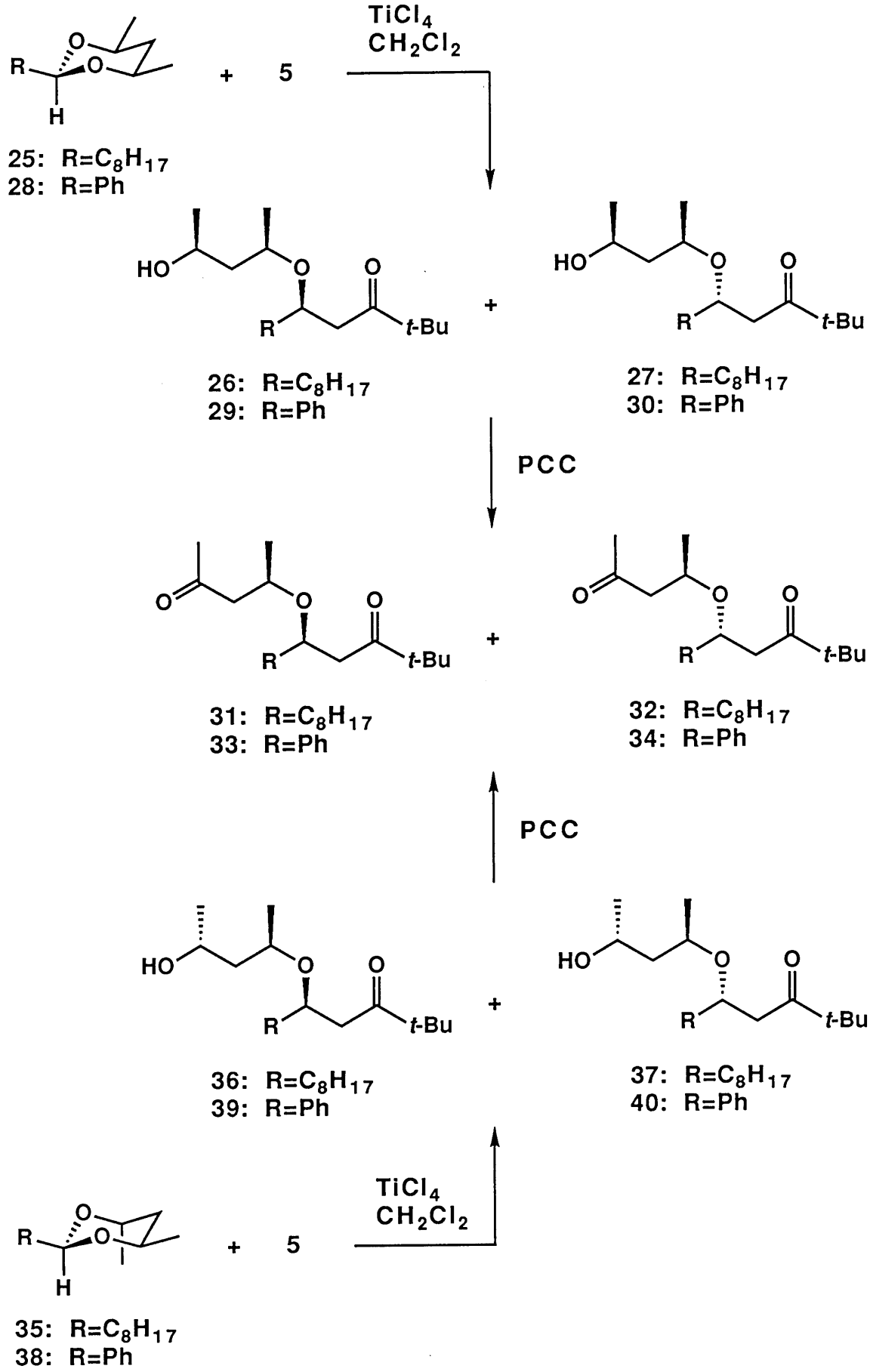




Similar experiments were carried out with acetals **25** and **28**, derived from meso-2,4-pentanediol, (Scheme 4). For comparison, identical experiments were carried out with acetals **35** and **38**, derived from (*R**,*R**)-2,4-pentanediol and the same two aldehydes. In all four experiments the initial hydroxy ketones were oxidized to diketones. Mixtures **26/27** and **36/37** each gave diketones **31** and **32**, whereas mixtures **29/30** and **39/40** gave diketones **33** and **34**. For each of the four experiments, diastereomer ratios were determined by ^{1}H NMR and GC. Results are summarized in Table 2.

Table 2. Stereochemistry of Acetal Substitution Reactions (Scheme 10 and 11)

Entry	Acetal	**26:27**	**29:30**	**36:37**	**39:40**	Yield (%)	**31:32**	**33:34**	Yield (%)
1	**25**	83 : 17	-	-	-	69	82 : 18	-	97
2	**28**	-	70 : 30	-	-	86	-	71 : 29	86
3	**35**	-	-	95 : 5	-	94	95 : 5	-	>99
4	**38**	-	-	-	89 : 11	>99	-	89 : 11	84


TiCl4
CH2Cl2
+ 5
25: R=C8H17
28: R=Ph
26: R=C8H17
29: R=Ph
27: R=C8H17
30: R=Ph
PCC
31: R=C8H17
33: R=Ph
32: R=C8H17
34: R=Ph
PCC
36: R=C8H17
39: R=Ph
37: R=C8H17
40: R=Ph
TiCl4
CH2Cl2
+ 5
35: R=C8H17
38: R=Ph

Scheme 4

Discussion

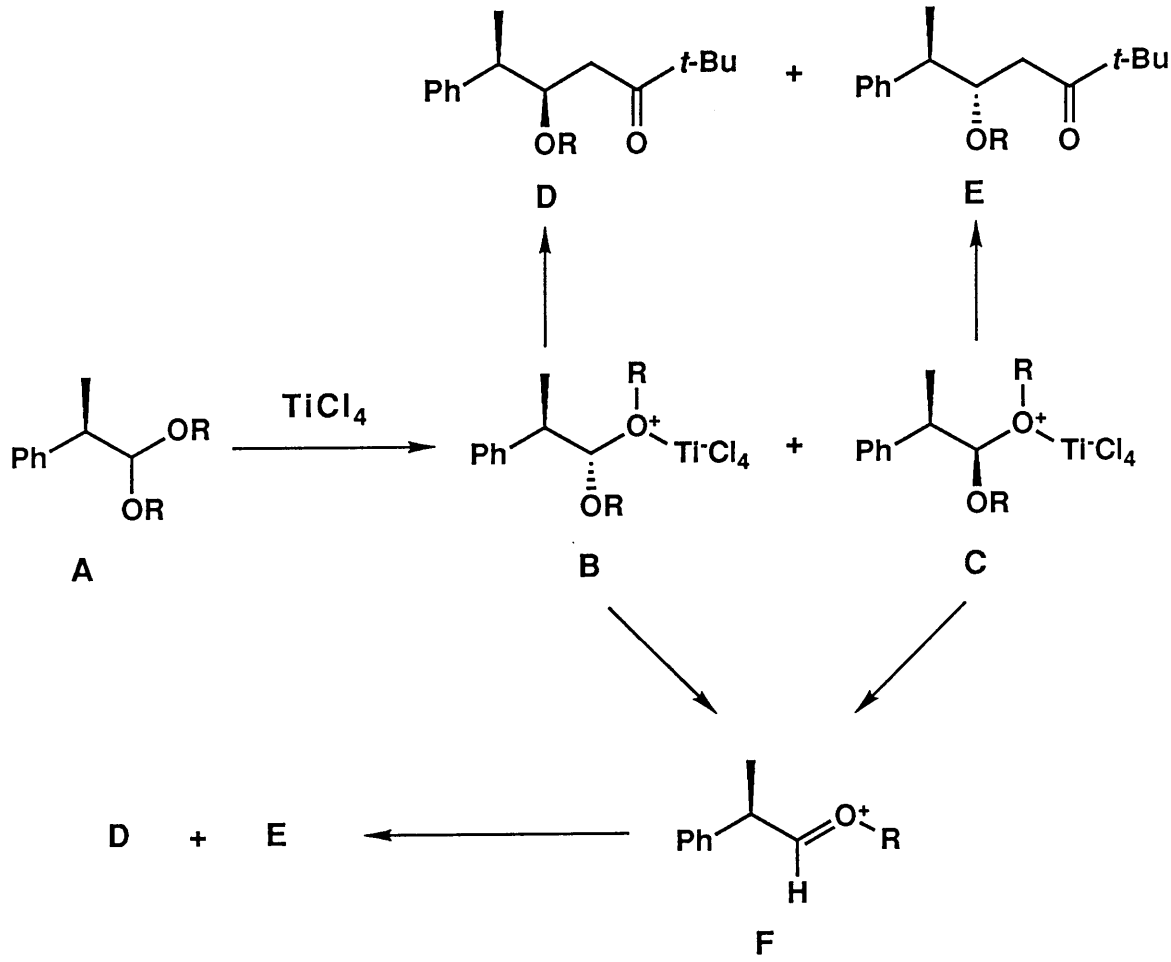
A general mechanistic scheme for type 1 acetal reactions is put forth in Scheme 5 for acetals of 2-phenylpropanal (**A**). If products **D** and **E** result from S_N1 attack on an oxocarbenium ion our previous work suggests that the diastereofacial preference of **F** should increase with increasing steric bulk of R.[13] If **D** and **E** arise from **B** and **C** by the S_N2 mechanism, the effect of R on the stereochemistry of the substitution reaction is harder to predict. If the decomplexation of **B** and **C** is slower than substitution, the **D/E** ratio would depend on the relative rates of complexation of the diastereotopic alkoxy groups and it is likely that the stereoisomer ratio would be approximately 1 : 1 and independent of the nature of R. If the equilbrium between **A** and **B** is fast, the **D/E** ratio would depend on the relative heats of formation of the diastereomeric complexes and on their rates of reaction to give **D** and **E**.

The experiment summarized in Scheme 3 rules out reversible formation of free oxocarbenium ions under the reaction conditions. Substitution could occur by the S_N2 mechanism or by the S_N1 mechanism by way of free oxocarbenium ions provided reaction of the intermediate oxocarbenium ions with **5** are faster than reaction with Cl_4TiOR. Reaction *via* oxocarbenium ion pairs are also not ruled out by this experiment.

The results in Table 1 (cf. entries 3, 7, 8, 10) show that there *is* an effect of the steric bulk of the alkoxy group on the stereochemistry of the acetal substitution reaction in the direction expected for the S_N1 mechanism. There is also a solvent effect; with methyl acetal **1** and isopropyl acetal **3** the product syn/anti ratio increases with increasing solvent polarity (cf. entries 1, 3, 5, 6 and entries 8, 9). The 4 : 1 ratio of isomers obtained in the reaction of acetal **1** with **5** in acetonitrile is a normal Cram/anti-Cram ratio for 2-phenylpropanal and may represents the intrinsic diastereofacial preference of the oxocarbenium ion (Scheme 5, **F**, R=Me). The nearly 1 : 1 ratio of stereoisomers resulting from this reaction in the nonpolar solvents hexane and toluene suggests that **1** reacts by the S_N2 mechanism or *via* oxocarbenium ion pairs in these solvents. The 2.5 : 1 ratio observed in CH_2Cl_2 is most consistent with a mixture of S_N2 and oxocarbenium ion pair

mechanisms. The absence of an effect of concentration on stereochemistry (Table 1, entries 3 and 4) would seem to rule out S_N1 reaction through dissociated ions in this solvent.[14]

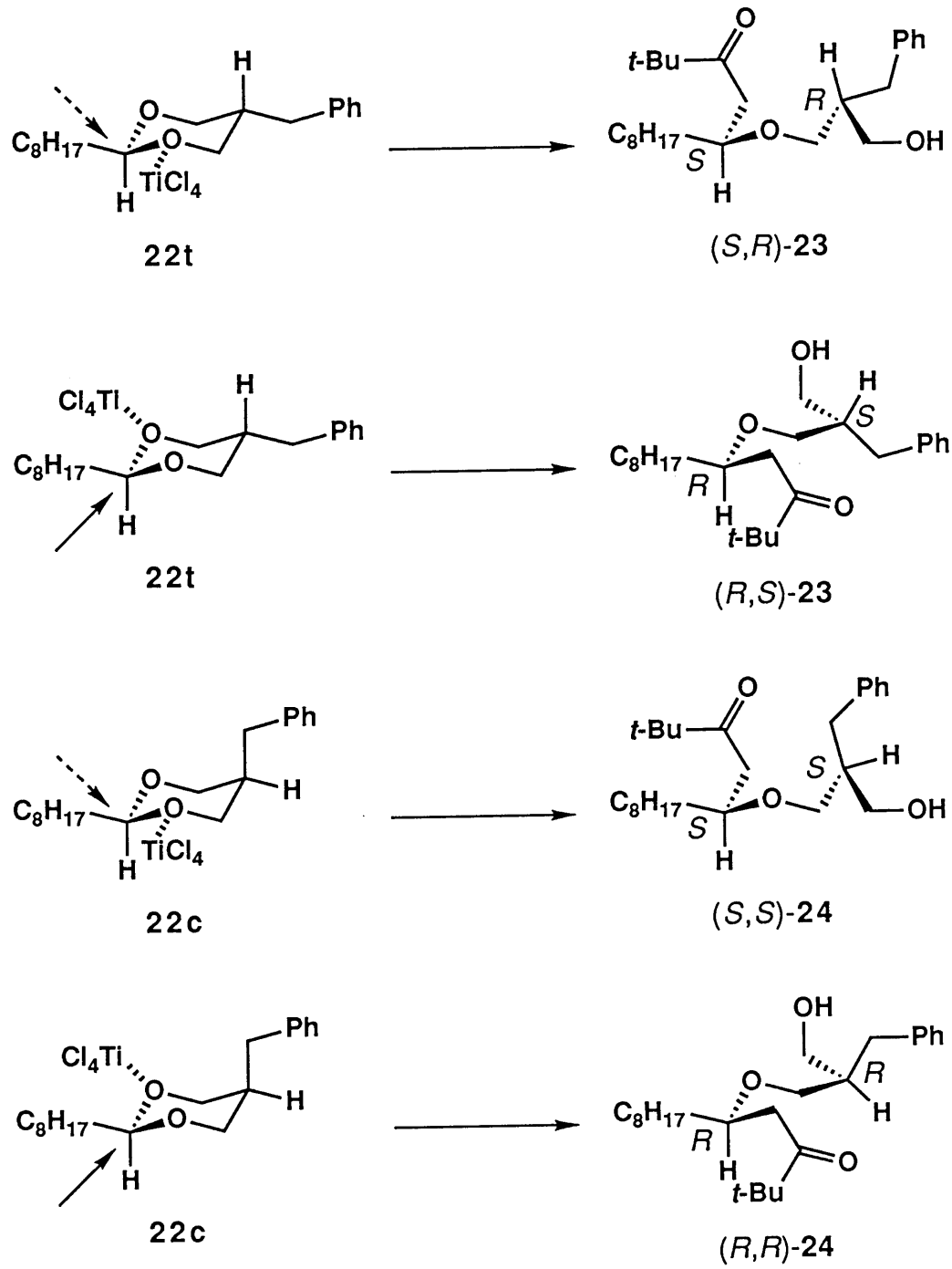
The simplest explanation of the data is that acetals **3** and **4** react essentially completely by the S_N1 mechanism in CH_2Cl_2, and acetal **2** reacts partly by this mechanism. It is reasonable that dissociation to an oxocarbenium ion would be favored by steric repulsion of the alkoxy groups in complexes **B** and **C** (Scheme 5).



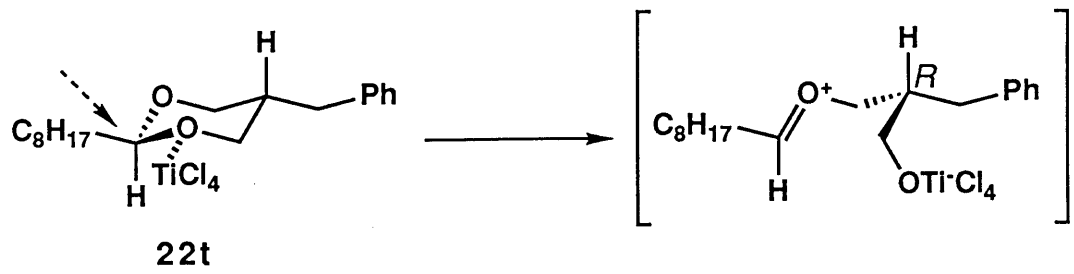
Scheme 5

The experimental design for the type 2 acetal study is shown in Schemes 6 and 7. The acetal oxygens in acetals **22t** and **22c** are enantiotopic. Thus, as shown in Scheme 6, if substitution occurs by the S_N2 mechanism, **22t** would give the *R*,S** diastereomer (±)–**23** and

22c would give the *S**,*S** diastereomer (±)-**24**. On the other hand, if substitution occurs by the S_N1 mechanism both acetals should give both diastereomeric products (Scheme 7). Although the faces of the oxocarbenium ion are diastereotopic, little 1,4-asymmetric induction is expected and a nearly 1 : 1 mixture of *R**,*S** and *S**,*S** diastereomers is expected by this mechanism.

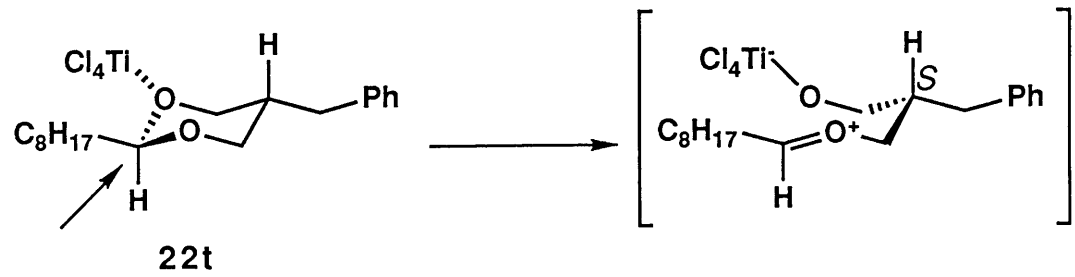


Scheme 6



22t

(*S*,*R*)-**23** + (*R*,*R*)-**24**



22t

(*R*,*S*)-**23** + (*S*,*S*)-**24**

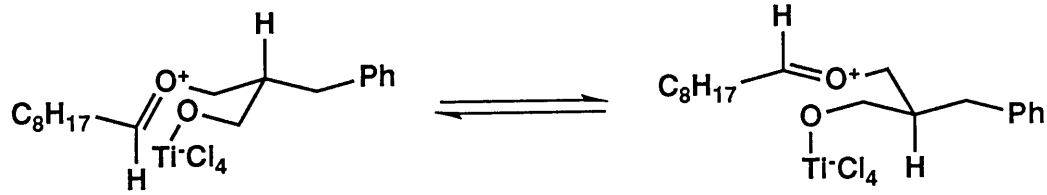
The same situation holds for **22c**; an approximate 1 : 1 mixture of diastereomers should result.

Scheme 7

The results of the study of cyclic acetals **22c** and **22t** are quite definitive and only consistent replacement by the S_N1 (oxocarbenium ion) mechanism. With the meso acetals **25** and **28** the situation is identical to that described for **22t** and **22c**. Thus, if reaction occurs by the S_N2 mechanism, both **25** and **28** should give a 1 : 1 mixture of the *S**,*R**,*S** and *R**,*S**,*R** enantiomers. On the other hand, if substitution occurs by the S_N1 mechnism both acetals should give a mixture both diastereomeric products. The results in Table 2 indicate that the reaction mechanism must be completely or largely S_N1.

The results of this study, particularly those obtained from **25** and **28**, raise an interesting question about the origin of stereoselectivity in Johnson's chiral acetal substitutions, which have been explained by invoking the S_N2 mechanism.[4,5] It was for this reason that acetals **35** and **38** were examined. As seen in Table 2, the results obtained with these two acetals were qualitatively similar to those obtained with **25** and **28**. In both the nonal and benzaldehyde series, the meso acetal gives slightly lower diastereomer ratios than dose the chiral acetal.

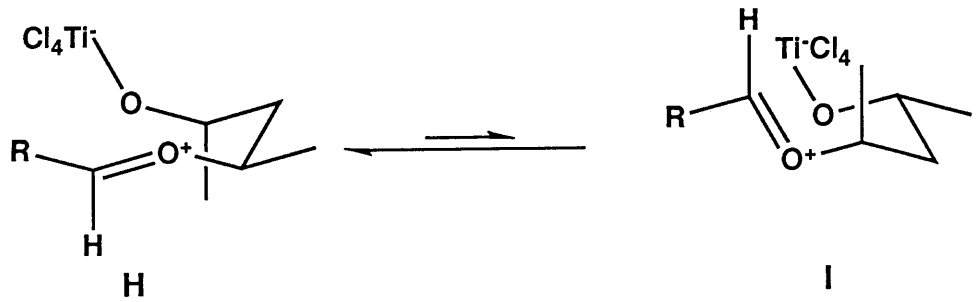
In summary, the bulk of our evidence, especially the behavior of cyclic acetals **22t**, **22c**, **25**, and **28**, points to the S_N1 mechanism for acetal substitution. How, then, do we account for the results observed for acetals **35** and **38**, and for high stereoselectivity seen in substitution reactions of Johnson-type acetal in general? The answer to this question may be that the reactions, at least of the type 2 acetals in CH_2Cl_2, occur through oxocarbenium ion pairs, and that in some cases, these tight ion pairs behave very much as though the six-membered ring is still intact. Under the acidic conditions of their formation, acetals **22c** and **22t** exist in an equilibrium ratio of 1 : 1 and it is not likely that complexation with $TiCl_4$ complexes would perturb this ratio. If the geometries of the two ion pairs **G** and **F** closely resemble those of **22c** and **22t**, it is expected that attack on the oxocarbenium ion would be stereorandom.



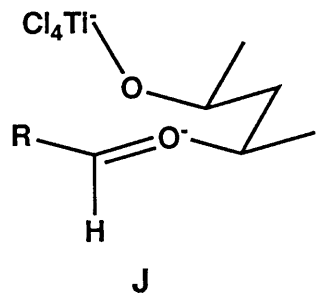
F **G**

On the other hand, the comparable ion pairs **H** and **I** derived from chiral acetals **35** and **38** are likely to differ significantly in energy, since it has been shown that is a strong preference for complexation of the dioxane oxygen next to the axial methyl group.[11] In these cases, attack of nucleophile on the more exposed *si* face of **H** would be quite reasonable, and would approximate the results expected from the S_N2 mechanism. The slightly lower stereoselectivity seen with the

benzaldehyde acetal **38** would be consistent with some reaction through an extended conformer of H/I.



With meso acetals **25** and **28** the Lewis acid has no choice but to complex an oxygen next to an equatorial methyl group. As a result, the pseudo-cyclic ion pair **J** might be sufficiently disfavored that some reaction occurs through some extended, non ion-paired conformer. Again, the lower stereoselectivity seen with the benzaldehyde-derived acetal **28** is consistent with this notion.



Thus, the stereochemistry observed in substitutions of type 2 acetals in CH_2Cl_2 under $TiCl_4$ catalysis can be adequately understood in terms of a predominate oxocarbenium ion pair mechanism. With type 1 acetals of tertiary and secondary alcohols the stereochemical trends observed argue strongly for a substitution mechanism involving either free oxocarbenium ions or ion pairs. For type 1 acetals of methanol and primary alcohols the evidence is not quite so definitive, and substitutions may occur partly by the S_N2 mechanism.

Experimental Section

General. Unless otherwise noted, materials were obtained from commercial sources and used without further purification. All reactions were performed under a dry nitrogen atmosphere. Tetrahydrofuran, diethyl ether, and benzene were distilled from sodium/benzophenone ketyl, dichloromethane and acetonitrile from calcium hydride, and dimethylformamide from calcium sulfate. Melting and boiling points are uncorrected. Chromatography was performed with Silica Gel 60 (E. Merk, Darmstadt) 100-120 mesh. Analytical thin-layer chromatography was performed on precoated glass plates (250 m, Silica Gel 60, E. Merk, Darmstadt). The 200 MHz ^1H NMR spectra were obtained on a Varian Gemini 200 spectrometer in $CDCl_3$ and are reported as follows: chemical shift (relative to internal tetramethylsilane as 0.0 ppm (multiplicity, number of protons, coupling constants in hertz). IR spectra were measured as thin films on NaCl unless otherwise indicated. Capillary GC was performed with a Simadzu model 8A gas chromatograph equipped with a flame-ionization detector and nitrogen (0.75 kg/cm^2) as a carrier gas using a 0.2 mm X 25 m bonded PEG-HT capillary column. High performance liquid chromatography (HPLC) was done with a Simadzu 6A instrument using a 4.6 mm X 25 cm Jasco Finepak Sil column. Microanalyses were accomplished at the Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University.

1,1-Diethoxyheptane (17). A mixture of 1.4 mL (10 mmol) of heptanal, 2.49 mL (15 mmol) of triethyl orthoformate, and 10 mg of NH_4NO_3 in 1 mL of ethanol was stirred for 10 h at 0°C. The mixture was poured into 20 mL of $NaHCO_3$ solution and the resulting mixture was extracted with three 20-mL portions of ether. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 50 : 1 hexane/ethyl acetate. The combined product fractions were distilled with a Kugelrohr apparatus (bath temperature 90°C, 8 torr) to give 1.32 g (70%) of **17** as a clear, colorless oil. The product was more than 98% pure by GC (130°C, t_R=2.9 min). TLC, R_f=0.35

(hexane-EtOAc, 19 : 1); IR (film) 2950, 1465, 1380, 1140, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, *J*=6.0 Hz, 3H, CH_3), 1.20-1.40 (m, 8H, $(CH_2)_4$), 1.21 (t, *J*=7.1 Hz, 6H, $2OCH_2CH_3$), 1.53-1.70 (m, 2H, CH_2), 3.50 (dq, *J*=9.4, 7.1 Hz, 2H, $2OCHHCH_3$), 3.65 (dq, *J*=9.4, 7.1 Hz, 2H, $2OCHHCH_3$), 4.49 (t, *J*=5.7 Hz, 1H, $CH(OEt)_2$). Anal. Calcd for $C_{11}H_{24}O_2$: C, 70.16; H, 12.85. Found: C, 70.02; H, 13.20.

1,1-Dipropoxynonane (18). A mixture of 1.72 mL (10 mmol) of nonanal, 1.87 mL (25 mmol) of propanol, and 10 mg of pyridinium *p*-toluenesulfonate in 50 mL of benzene was refluxed with continuous azeotropic removal of water for 2 h. After cooling to room temperature the mixture was poured into 20 mL of $NaHCO_3$ solution. The benzene layer was dried and evaporated and the resulting crude product was purified first by flash chromatography on silica gel, eluting with 25 : 1 hexane/ethyl acetate, and then by distillation using a Kugelrohr apparatus (bath temperature 150°C, 7 torr). There was obtained 1.78 g (73%) of acetal as a colorless oil, more than 98% pure by GC (130°C, t_R=6.2 min). TLC, R_f=0.57 (hexane-EtOAc, 5 : 2); IR (film) 2980, 2950, 2890, 2870, 1460, 1130, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, *J*=6.5 Hz, 3H, CH_3), 0.95 (t, *J*=7.3 Hz, 6H, $2OCH_2CH_2CH_3$), 1.20-1.40 (br, 12H, $(CH_2)_6$), 1.50-1.70 (m, 6H, $2OCH_2CH_2CH_3$ and CH_2), 3.39 (dt, *J*=9.2, 6.8 Hz, 2H, $2OCHH$), 3.55 (dt, *J*=9.2, 6.8 Hz, 2H, $2OCHH$), 4.49 (t, *J*=5.8 Hz, 1H, $CH(OPr)_2$). Anal. Calcd for $C_{15}H_{32}O_2$: C, 73.71; H, 13.20. Found: C, 73.71; H, 13.57.

Reaction of Acetals 17 and 18 with Silyl Enol Ether 5. To a mixture of 94.2 mg (0.50 mmol) of acetal **17**, 122 mg (0.50 mmol) of acetal **18**, and 172 mg (1.00 mmol) of silyl enol ether **5** in 8.0 mL of CH_2Cl_2 was added $TiCl_4$ (0.50 mL of a 1.00 *M* CH_2Cl_2 solution, 0.50 mmol), dropwise at -78°C. After stirring for 30 min at -78°C the resulting yellow solution was poured into 20 mL of $NaHCO_3$ solution and extracted with three 10-mL portions of ether. The combined organic layers were dried over $MgSO_4$, concentrated, and chromatographed on silica gel eluting with 40 : 1 hexane/ethyl acetate. Keto ethers **19** and **20** (159 mg, 60%) were obtained as a colorless oil. ^1H NMR and capillary GC analysis of the crude product showed the presence of

19, **20**, heptanal, and nonal in a ratio of 3 : 3 : 2 : 2. Neither starting acetals nor other keto ethers were present by GC (130°C). Authentic samples of **19** and **20** were obtained from the reactions of silyl enol ether **5** with acetals **17** and **18**, respectively.

2,2-Dimethyl-5-ethoxyundecan-3-one (19). GC, 130°C, t_R=7.6 min; TLC, R_f=0.62 (hexane-EtOAc, 5 : 2); IR (film) 3000, 2950, 2900, 1720, 1490, 1470, 1380, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, J=6.4 Hz, 3H, CH_3), 1.10-1.18 (m, 3H, OCH_2CH_3), 1.14 (s, 9H, *t*-Bu), 1.20-1.54 (m, 10H, $(CH_2)_5$), 2.44 (dd, J=5.4, 16.8 Hz, C*H*HC=O), 2.83 (dd, J=7.0, 16.8 Hz, 1H, CH*H*C=O), 3.49 (dq, J=2.2, 7.0 Hz, 2H, CH_2O), 3.76-3.90 (m, 1H, EtOC*H*). Anal. Calcd for $C_{15}H_{30}O_2$: C, 74.33; H, 12.47. Found: C, 74.21; H, 12.63.

2,2-Dimethyl-5-propyltridecan-3-one (20). GC, 130°C, t_R=22.1 min; TLC, R_f=0.64 (hexane-EtOAc, 5 : 2); IR (film) 2990, 2950, 2880, 1720, 1480, 1270, 1380, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, J=7.4 Hz, 6H, $2CH_3$), 1.14 (s, 9H, *t*-Bu), 1.20-1.62 (m, 14H, $(CH_2)_7$), 2.43 (dd, J=5.4, 16.8 Hz, 1H, C*H*HC=O), 2.83 (dd, J=6.9, 16.8 Hz, 1H, CH*H*C=O), 3.30-3.47 (m, 2H, OCH_2), 3.75-3.88 (m, 1H, OCH). Anal. Calcd for $C_{18}H_{36}O_2$: C, 76.00; H, 12.75. Found: C, 75.98; H, 12.93.

Heptanal. GC, 130°C, t_R=2.5 min.

Nonanal. GC, 130°C, t_R=3.2 min.

General Procedure for the Preparation of Acetals 25, 28, 35, and 38. A mixture of 10.0 mmol of the appropriate aldehyde, 1.15 g (11.0 mmol) of 2,4-pentanediol (mixture of meso and chiral isomers), and a small amount of pyridinium *p*-toluenesulfonate in 25 mL of benzene are refluxed under a Dean-Stark trap for 4 h. To the cooled solution was added 50 mL of $NaHCO_3$ solution and the resulting mixture was extracted with three 20-mL portions of hexane. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The diastereomeric acetals were separated by flash chromatography on silica gel, eluting with hexane/ether. The products were obtained as colorless oils in a total yield that was nearly quantitative.

(4*R,6*S**)-4,6-Dimethyl-2-octyl-1,3-dioxane (25).** TLC, R_f=0.44 (hexane-EtOAc, 10 : 1); IR (film) 2970, 2900, 1470, 1390, 1190, 1180, 1140, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, *J*=6.4 Hz, 3H, CH_2CH_3), 1.20-1.68 (m, 16H, $(CH_2)_7$ and C(5)H_2), 1.22 (d, *J*=6.2 Hz, 6H, $2CH_3$), 3.71 (ddq, *J*=2.6, 12.4, 6.2 Hz, 2H, 2OC*H*Me), 4.52 (t, *J*=5.2 Hz, 1H, CHO_2). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.98; H, 8.39.

(2*S,4*R**,6*R**)-4,6-Dimethyl-2-octyl-1,3-dioxane (35).** TLC, R_f=0.35 (hexane-EtOAc, 10 : 1); IR (film) 2940, 2880, 1460, 1380, 1160, 1150, 1110, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, *J*=6.5 Hz, 3H, CH_3), 1.18-1.64 (m, 15H, $(CH_2)_7$ and C(5)*H*H), 1.22 (d, *J*=6.2 Hz, 3H, CH_3(equatorial)), 1.36 (d, *J*=7.0 Hz, 3H, CH_3(axial)), 1.84 (ddd, *J*=6.2, 11.6, 13.2 Hz, 1H, C(5)H*H*), 3.95 (ddq, *J*=2.4, 12.2, 6.2 Hz, 1H, C*H*(axial)Me), 4.31 (dq, *J*=6.2, 7.0 Hz, 1H, C*H*(equatorial)Me). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.97; H, 8.33.

(4*R,6*S**)-4,6-Dimethyl-2-phenyl-1,3-dioxane (28).** TLC, R_f=0.31 (hexane-Et_2O, 10 : 1); IR (film) 2970, 1380, 1340, 1180, 1120, 1060, 1030, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (d, *J*=6.2 Hz, 6H, $2CH_3$), 1.30-1.50 (m, 1H, C*H*H(axial)), 1.60 (dt, *J*=13.0, 2.7 Hz, 1H , CH*H*(equatorial)), 3.93 (ddq, *J*=2.7, 12.6, 6.2 Hz, 2H, 2C*H*Me), 5.51 (s, 1H, PhC*H*), 7.25-7.40 (m, 3H, ArH), 7.45-7.55 (m, 2H, ArH). Anal. Calcd for $C_{14}H_{28}O_2$: C, 73.63; H, 12.36. Found: C, 73.63; H, 12.70.

(2*S,4*R**,6*R**)-4,6-Dimethyl-2-phenyl-1,3-dioxane (38).** TLC, R_f=0.22 (hexane-Et_2O, 10 : 1); IR (film) 2980, 1380, 1160, 1140, 1050, 1000, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (d, *J*=6.0 Hz, 3H, CH_3(equatorial)), 1.44 (ddd, *J*=1.0, 2.4, 13.2 Hz, 1H, C*H*H(equatorial)), 1.49 (d, *J*=7.0 Hz, 3H, CH_3(axial)), 2.00 (ddd, *J*=6.0, 11.7, 13.2 Hz, 1H, CH*H*(axial)), 4.20 (ddq, *J*=2.4, 11.7, 6.0 Hz, 1H, C*H*(axial)Me), 4.74 (dq, *J*=6.0, 7.0 Hz, C*H*(equatorial)Me), 5.84 (s, 1H, CHO_2), 7.25-7.40 (m, 3H, ArH), 7.45-7.55 (m, 2H, ArH). Anal. Calcd for $C_{14}H_{28}O_2$: C, 73.63; H, 12.36. Found: C, 73.63; H, 12.68.

General Procedure for the Reactions of Acetals 25, 28, 35, and 38 with Silyl Enol Ether 5. To a mixture of 0.50 mmol of the acetal and 129 mg (0.75 mmol) of silyl enol ether **5** in 8.5 mL of CH_2Cl_2 was added $TiCl_4$ (0.50 mL of a 1.00 *M* CH_2Cl_2 solution, 0.50 mmol), dropwise at -78°C. After stirring for 30 min at -78°C, the resulting yellow solution was poured into 20 mL of $NaHCO_3$ solution and extracted with three 20-mL portions of ether. The combined organic layers were dried ($MgSO_4$), concentrated under reduced pressure, and chromatographed on silica gel with hexane/ethyl acetate as eluent. The resulting diastereomeric mixture of hydroxy ketones was analyzed by HPLC or GC; individual isomers were not separated.

(5*R,1'*R**,3'*S**)-2,2-Dimethyl-5-(3'-hydroxy-1'-methylbutoxy)tridecan-3-one (26).** GC (190°C), t_R=16.6 min; TLC, R_f=0.46 (hexane-EtOAc, 5 : 2); ^{1}H NMR ($CDCl_3$) δ 0.89 (t, *J*=6.5 Hz, 3H, C*H*$_3$CH$_2$), 1.08 (d, *J*=6.0 Hz, 3H, CH$_3$), 1.12 (s, 9H, *t*-Bu), 1.14 (d, *J*=6.2 Hz, 3H, CH$_3$), 1.20-1.70 (m, 17H, (CH$_2$)$_7$, C(2')H$_2$, and OH), 2.38 (dd, *J*=4.5, 16.5 Hz, 1H, C*H*HC=O), 2.80 (dd, *J*=7.9, 16.5 Hz, 1H, CH*H*C=O), 3.70-4.08 (m, 3H, C(3')*H*C(2')H$_2$C(1')*H*OC(5)*H*). Anal. Calcd for $C_{20}H_{40}O_3$: C, 73.12; H, 12.27. Found: C, 72.97; H, 12.48.

(5*S,1'*R**,3'*S**)-2,2-Dimethyl-5-(3'-hydroxy-1'-methylbutoxy)tridecan-3-one (27).** GC (190°C), t_R=15.0 min; TLC, R_f=0.41 (hexane-EtOAc, 5 : 2); ^{1}H NMR ($CDCl_3$) δ 1.15 (s, 9H, *t*-Bu), 2.62 (dd, *J*=6.6, 17.6 Hz, 1H, C*H*HC=O). Other resonances could not be discerned for this minor isomer.

(5*S,1'*R**,3'*S**)-2,2-Dimethyl-5-(3'-hydroxy-1'-methylbutoxy)-5-phenylpentan-3-one (29).** HPLC, t_R=13.4 min (hexane-EtOAc, 15 : 2; 2.0 mL/min); TLC, R_f=0.28 (hexane-EtOAc, 5 : 2); ^{1}H NMR ($CDCl_3$) δ 1.03 (d, *J*=5.2 Hz, 3H, CH$_3$), 1.039 (s, 9H, *t*-Bu), 1.12 (d, *J*=6.0 Hz, 3H, CH$_3$), 1.30-1.75 (m, 2H, MeCHC*H*$_2$), 2.54 (dd, *J*=4.5, 16.5 Hz, 1H, PhCHC*H*H), 3.11 (dd, *J*=8.5, 16.5 Hz, 1H, PhCHCH*H*), 3.40-3.60 (m, 1H, C*H*OH), 3.60-4.00 (m, 2H, MeC*H* and O*H*), 5.05 (dd, *J*=4.6, 8.4 Hz, 1H, PhC*H*), 7.20-7.40 (m, 5H, C$_6$H$_5$). Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.93; H, 9.97.

(5*S,1'*S**,3'*R**)-2,2-Dimethyl-5-(3'-hydroxy-1'-methylbutoxy)-5-phenylpentan-3-one (30).** HPLC, t_R=16.3 min (hexane-EtOAc, 15 : 2); ^{1}H NMR ($CDCl_3$) δ 0.89 (d, *J*=6.2 Hz, 3H, CH_3), 1.047 (s, 9H, *t*-Bu), 1.14 (d, *J*=6.2 Hz, 3H, CH_3), 2.63 (dd, *J*=4.6, 17.6 Hz, 1H, PhCHC*H*H), 3.04 (dd, *J*=8.4, 17.6 Hz, 1H, PhCHCH*H*), 4.94 (dd, *J*=4.5, 8.5 Hz, 1H, PhC*H*). Other resonances could not be discerned for this minor isomer.

(5*R,1'*R**,3'*R**)-2,2-Dimethyl-5-(3'-hydroxy-1'-methylbutoxy)tridecan-3-one (36).** GC (190°C), t_R=16.0 min; TLC, R_f=0.43 (hexane-EtOAc, 5 : 2); IR (film) 3700-3200 (br), 3000, 2950, 2900, 1720, 1470, 1390, 1140, 1090 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, *J*=6.4 Hz, 3H, C*H*$_3$CH$_2$), 1.13 (s, 9H, *t*-Bu), 1.14 (d, *J*=6.2 Hz, 3H, CH_3), 1.18 (d, *J*=6.2 Hz, 3H, CH_3), 1.20-1.74 (m, 17H, $(CH_2)_7$, C(2')H_2, and OH), 2.41 (dd, *J*=4.8, 16.8 Hz, 1H, C*H*HC=O), 2.79 (dd, *J*=7.6, 16.8 Hz, 1H, CH*H*C=O), 3.78-4.18 (m, 3H, C(3')*H*C(2')H$_2$C(1')*H*OC(5)*H*). Anal. Calcd for $C_{20}H_{40}O_3$: C, 73.12; H, 12.27. Found: C, 73.13; H, 12.50.

(5*S,1'*R**,3'*R**)-2,2-Dimethyl-5-(3'-hydroxy-1'-methylbutoxy)tridecan-3-one (37).** GC (190°C), t_R=14.3 min.

(5*S,1'*R**,3'*R**)-2,2-Dimethyl-5-(3'-hydroxy-1'-methylbutoxy)-5-phenylpentan-3-one (39).** HPLC, t_R=12.3 min (hexane-EtOAc, 15 : 2; 2.0 mL/min); TLC, R_f=0.29 (hexane-EtOAc, 5 : 2); ^{1}H NMR ($CDCl_3$) δ 1.04 (s, 9H, *t*-Bu), 1.06 (d, *J*=6.2 Hz, 3H, CH_3), 1.17(d, *J*=6.2 Hz, 3H, CH_3), 1.38-1.53 (m, 2H, C*H*$_2$CHMe), 2.55 (dd, *J*=4.6, 16.7 Hz, 1H, PhCHC*H*H), 2.63 (s, 1H, OH), 3.09 (dd, *J*=8.4, 16.7 Hz, 1H, PhCHCH*H*), 3.47-3.63 (m, 1H, C*H*OH), .393-4.10 (m, 1H, CHOC*H*Me), 4.96 (dd, *J*=4.6, 8.4 Hz, 1H, PhC*H*), 7.20-7.40 (m, 5H, C_6H_5). Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.93; H, 9.95.

(5*R,1'*R**,3'*R**)-2,2-Dimethyl-5-(3'-hydroxy-1'-methylbutoxy)-5-phenylpentan-3-one (40).** HPLC, t_R=11.8 min (hexane-EtOAc, 15 : 2; 2.0 mL/min); ^{1}H NMR ($CDCl_3$) δ 4.88 (dd, *J*=3.4, 9.4 Hz, 1H, PhC*H*). Other resonances could not be discerned for this minor isomer.

General Procedure for the Oxidation of Hydroxy Ketones 26/27, 29/30, 36/37, and 39/40. A solution of 0.40 mmol of the hydroxy ketone and 172 mg (0.80 mmol) of pyridinium chlorochromate in 2.0 mL of CH_2Cl_2 was kept at room temperature for 12 h. After the addition of 10 mL of $NaHSO_3$ solution the mixture was extracted with three 10-mL portions of ether. The combined organic layers were dried ($MgSO_4$), concentrated, and chromatographed on silica gel using hexane/ethyl acetate as eluant to give a mixture of the hydroxy ketones as a colorless oil. The diastereomeric ratio was determined by HPLC or GC.

(5*R,1'*R**)-2,2-Dimethyl-5-(1'-methyl-3'-oxobutoxy)-5-phenylpentan-3-one (33).** HPLC, t_R=10.3 min (hexane-EtOAc, 10 : 1; 2.0 mL/min); TLC, R_f=0.35 (hexane-EtOAc, 5 : 2); ^{1}H NMR ($CDCl_3$) δ 1.067 (s, 9H, *t*-Bu), 1.16 (d, *J*=6.0 Hz, 3H, CHC*H*$_3$), 1.98 (s, 3H, CH_3CO), 2.33 (dd, *J*=5.6, 15.0 Hz, 1H, MeCHC*H*H), 2.50 (dd, *J*=4.5, 16.4 Hz, 1H, PhCHCH*H*), 2.56 (dd, *J*=7.2, 15.0 Hz, 1H, MeCHC*H*H), 3.09 (dd, *J*=8.8, 16.4 Hz, 1H, PhCHCH*H*), 3.70-3.87 (m, 1H, MeC*H*), 4.97 (dd, *J*=4.5, 8.8 Hz, 1H, PhC*H*), 7.20-7.40 (m, 5H, C_6H_5). Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.44; H, 9.21.

(5*S,1'*R**)-2,2-Dimethyl-5-(1'-methyl-3'-oxobutoxy)-5-phenylpentan-3-one (34).** HPLC, t_R=9.8 min (hexane-EtOAc, 10 : 1, 2.0 mL/min); ^{1}H NMR ($CDCl_3$) δ 1.073 (s, 9H, *t*-Bu), 1.01 (d, *J*=6.2 Hz, 3H, CH_3), 2.17 (s, 3H, CH_3CO), 4.90 (dd, *J*=4.0, 8.6 Hz, 1H, PhC*H*). Other resonances could not be discerned for this minor isomer.

(5*R,1'*R**)-2,2-Dimethyl-5-(1'-methyl-3'-oxobutoxy)-5-tridecan-3-one (31).** GC (190°C), t_R=13.0 min; TLC, R_f=0.50 (hexane-EtOAc, 5 : 2); IR (film) 2980, 2950, 2870, 1720, 1470, 1460, 1370, 1140, 1090 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, *J*=6.5 Hz, 3H, CH_2CH_3), 1.10 (d, *J*=6.2 Hz, 3H, CHC*H*$_3$), 1.135 (s, 9H, *t*-Bu), 1.20-1.50 (m, 14H, $(CH_2)_7$), 2.38 (dd, *J*=5.7, 15.4 Hz, 1H, C*H*HCOMe), 2.41 (dd, *J*=5.2, 16.6 Hz, 1H, C*H*HCOBu^t), 2.68 (dd, *J*=7.0, 15.4 Hz, 1H, CH*H*COMe), 2.77 (dd, *J*=7.0, 16.6 Hz, 1H, CH*H*COBu^t), 3.84-4.04 (m, 2H, C*H*OC*H*Me). Anal. Calcd for $C_{20}H_{38}O_3$: C, 73.57; H, 11.73. Found: C, 73.55; H, 12.01.

(5*S,1'*R**)-2,2-Dimethyl-5-(1'-methyl-3'-oxobutoxy)-5-tridecan-3-one (32).** GC (190°C), t_R=11.4 min; ^{1}H NMR ($CDCl_3$) δ 1.147 (s, 9H, *t*-Bu). Other resonances could not be discerned for this isomer.

References and Notes

1. Paper 52 in the series "Acyclic Stereoselection." For paper 51, see: Mori, I.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 0000.
2. For example, see:

   (a) Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1976**, 941.

   (b) Tsunoda, T.; Suzuki, M.; Noyori, R. *Ibid.* **1980**, *21*, 71.

   (c) Sakurai, H.; Sasaki, K.; Hosomi, A. *Tetrahedron Lett.* **1981**, *22*, 745.

   (d) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899.

   (e) Sakurai, H. *Pure. Appl. Chem.* **1982**, *54*, 1.

   (f) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4876.

   (g) Kozikowski, A. P.; Sorgi, K. L. *Tetrahedron Lett.* **1982**, *23*, 2281.

   (h) Danishefsky, S.; Kerwin, J. F. *J. Org. Chem.* **1982**, *37*, 3803.

   (i) Hosomi, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett.* **1984**, *25*, 2383.

   (j) Keck, G. E.; Enholm, E. J.; Kachensky, D. F. *Tetrahedron Lett.* **1984**, *25*, 1867.

   (k) Mukaiyama, T.; Nagaoka, H.; Murakami, M.; Oshima, M. *Chem Lett.* **1985**, 977.

   (l) Hosomi, A.; Ando, M.; Sakurai, H. *Tetrahedron Lett.* **1986**, 365.

   (m) Danishefsky, S. J.; DeNinno, S.; Lartey, P. *J. Am. Chem. Soc.* **1987**, *109*, 2082.

   (n) Danishefsky, S. J.; Armistead, D. M.; Wincott, F. E.; Selnick, H. G.; Hungate, R. *J. Am. Chem. Soc.* **1987**, *109*, 8117.

(o) Murata, S.; Suzuki, M.; Noyori, R. *Ibid.* **1988**, *44*, 4259.

3. (a) Bartlett, P. A.; Johnson, W. S.; Elliot, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2088.

   (b) Choi, V. M. F.; Elliot, J. D.; Johnson, W. S. *Tetrahedron Lett.* **1984**, *25*, 591.

   (c) Maruoka, K.; Yamamoto, H. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 668; *Angew. Chem.* **1985**, *97*, 670.

   (d) Berlan, J.; Besace, J.; Prat, D.; Pourcelot, G. *J. Organomet. Chem.* **1984**, *264*, 399.

4. Silverman, R.; Edington, C.; Elliot, J. D.; Johnson, W. S. *J. Am. Chem. Soc.* **1987**, *52*, 180 and references therein.

5. Mori, A.; Fujiwara, J.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4581.

6. (a) Imwinlelried, R.; Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 765.

   (b) Seebach, D. in "Modern Synthetic Methods", Ed Sceffold, R., **1986**, p191, Springer-Verlag.

7. Mukaiyama, T.; Oshima, M.; Miyoshi, N. *Chem. Lett.* **1987**, 1121.

8. Yamamoto, Y.; Nishii, S.; Yamada, J. *J. Am. Chem. Soc.* **1986**, *108*, 7116.

9. Denmark, S. E.; Wilson, T. M. *J. Am. Chem. Soc.* **1989**, *111*, 3475.

10. Denmark, S. E.; Wilson, T. M.; Almstead, N. G. *J. Am. Chem. Soc.* **1989**, *111*, 9258.

11. In the course of the review and revision of this manuscript, we became aware that Denmark and coworkers have carried out similar experiments and reached essentially the same mechanistic conclusions as are set forth in this paper. Professor Denmark's results will be published separately.

12. Identical results were obtained in the reactions of **18t** and **18c** with allyltrimethylsilane.

13. (a) Heathcock, C. H.; Flippin, L. A. *J. Am. Chem. Soc.* **1983**, *105*, 1667.

   (b) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 2819.

(c) Mori, I.; Bartlett, P. A.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 7199.

(d) Mori, I.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 0000.

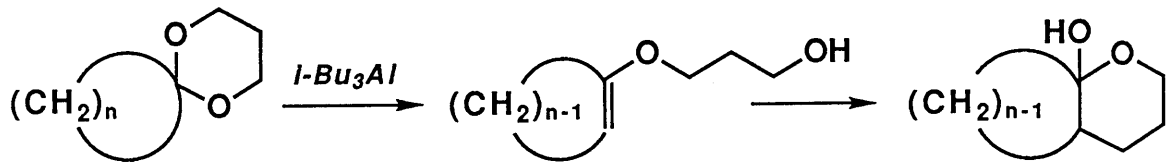
14. If the reaction of acetal **1** is carried out by premixing the acetal with $TiCl_4$ in CH_2Cl_2 prior to addition of silyl enol ether **5**, the **6s** : **6a** ratio is 1.4 : 1. Although we have not studied this reaction in detail. It is possible that **1** reacts with $TiCl_4$ under these conditions to form an α-chloro ether.

Chapter 8

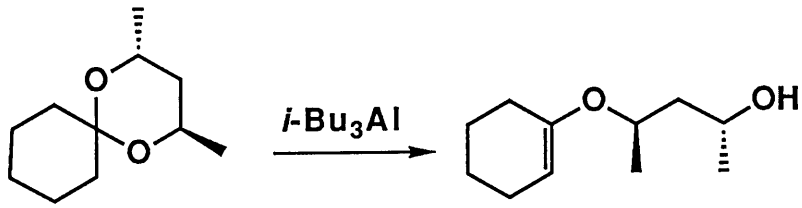
Stereospecific Cyclization of Vinyl Ether Alcohols. Facile Synthesis of (-)-Lardolure

Abstract: An efficient stereospecific ring formation from unsaturated alcohols, which in turn are prepared by regio- and stereospecific ring opening of acetals, is described. (-)-Lardolure has been synthesized by intramolecular cyclization of vinyl ether alcohol derived from spiroacetal *via* triisobutylaluminum and further ring enlargement of the afforded bicyclic hemiacetals. The same method was utilized for new stereospecific ring enlargement to yield medium and large rings from simple ketones.

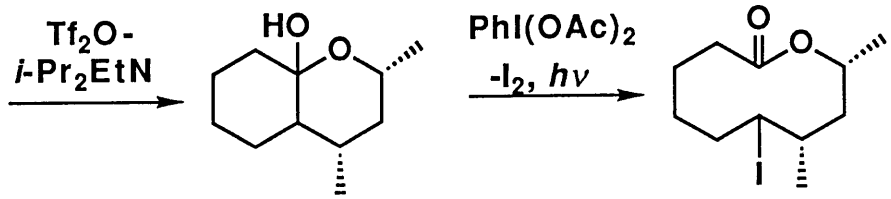
We report here a new method of ring formation that we believe has considerable potential in organic synthesis. We previously described that triisobutylaluminum is a powerful reagent for the transformation of acetal to vinyl ether (**1** → **2**).[1] It thus seemed to us that the possibility of forming rings by intramolecular addition of a terminal alcohol to a double bond, as shown in **2** → **3**, deserved to be explored.[2] This appeared particularly true because such a process would result in the formation of a ring that would have a variety of appendages with predictable stereochemistry.



1 **2** **3**



4 **5**

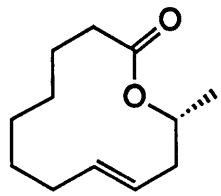


6 **7**

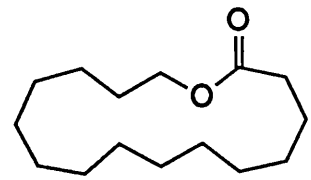
Reaction of a solution of the acetal **4** with excess triisobutylaluminum at -78°C for 0.5 h and 0°C for 5 h produced the elimination product **5** in an essentially quantitative yield.[1] The crude vinyl ether thus obtained after extractive workup was exposed to triflic anhydride in

dichloromethane in the presence of excess diisopropylethylamine at -78°C for 3 h to produce, after workup with aqueous acetic acid, the cyclized hemiacetal **6** in >95% yield. Some of the results are summarized in Table 1.

The produced hemiacetals were easily converted to lactones by the method of Suginome,[3] Suarez,[4] or Nagao.[5] For example, hemiacetal **6** was quantitatively transformed to the medium ring iodo lactone **7** (1.1 equiv of iodobenzene diacetate, 1.0 equiv of iodine in cyclohexane under irradiation at room temperature).[4] The method thus provides a facile route to large and medium ring lactones in a stereospecific way, which was demonstrated by the synthesis of (+)-recifeiolide (**12**)[6,7] from **10** (entry 8 of Table 1) (photochemical ring opening followed by treatment with DBU) and exaltolide (15-pentadecanolide, **13**)[8] from **11** (entry 9) (photochemical ring opening followed by reduction with tributyltin hydride).



12

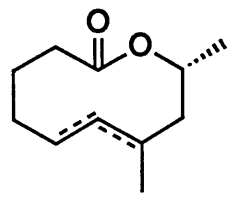


13

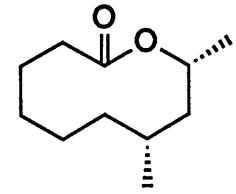
We draw attention to the fact that in elimination of acetals derived from prochiral ketones (entries 6 and 7) with triisobutylaluminum, an asymmetric deprotonation reaction takes place (selectivity: >9:1),[9] thus leading to optically pure hemiacetal after the cyclization process: Addition of triisobutylaluminum to the acetal **8** prepared from prochiral ketone followed by cyclization as above gave hemiacetal **9** (entry 6 of Table 1). After one recrystallization of the crude product, all of the chiral centers of the molecule were found to be homogeneous (see also entry 7).

It is presumed that the annulation reaction proceeds through a pure S_N2-like mechanism, namely inversion of stereochemistry at the hydroxy function. Evidence for the complete inversion was obtained upon elimination (with DBU at 90°C) followed by hydrogenation (Pd/C) from iodo

lactone **7**. In this case, it was assumed that hydrogenation should give a mixture of diastereoisomers. Indeed, the crude reaction mixture from hydrogenation of **14** revealed two peaks on GC analysis, while exposure of the iodo lactone with tributyltin hydride-AIBN in THF under reflux furnished quantitatively lactone **15** as a sole product.

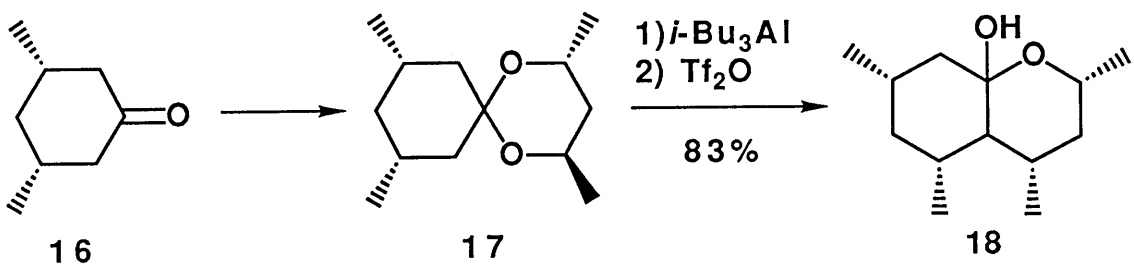


14

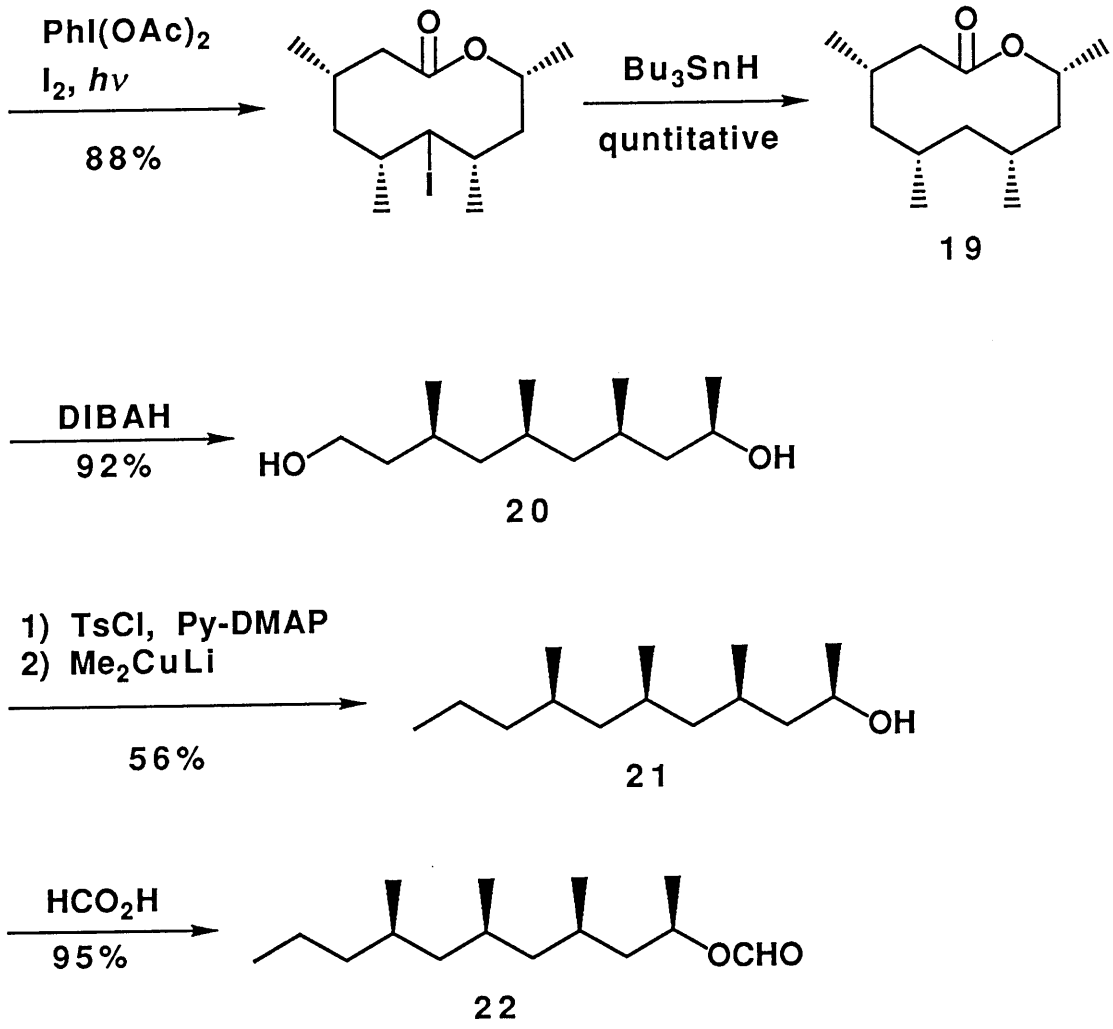


15

We now demonstrate the effectiveness of this approach starting with simple ketone **16**[10] which can be transformed into (-)-Lardolure (**22**),[11] the aggregation pheromone of the acarid mite, *Lardoglyphus Konoi*, in short steps (Scheme 1). Under standard cyclization conditions the hemiacetal **18** was obtained in 83% yield, mp 78-80°C after one recrystallization. Ring opening with iodobenzene diacetate gave the iodo lactone (88%), which was further transformed to lactone **19** quantitatively with tributyltin hydride. Addition of an excess of DIBAH at -78°C produced the diol **20** (92%). Selective monotosylation (64%; 1.2 equiv of TsCl, pyridine-DMAP at -20°C) followed by exposure of the monotosylate with excess dimethyl copper lithium in ether gave **21** in 92% yield with the desired carbon framework and desired stereochemistry. Formylation of **21** (95%; formic acid at 65°C) then led to pheromone **22**,[12] which was identical with the authentic material kindly provided by Professor Kenji Mori.



16 **17** **18**

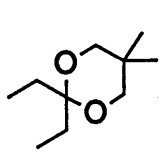
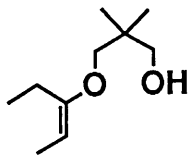
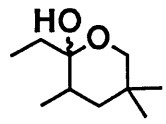
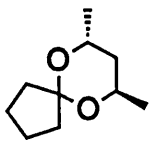
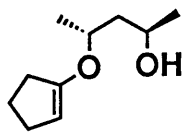
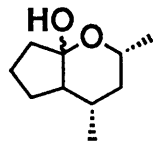
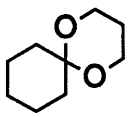
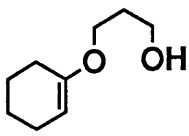
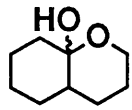
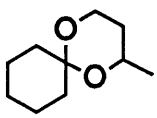
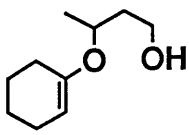
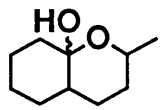
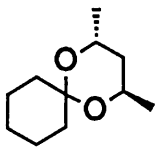
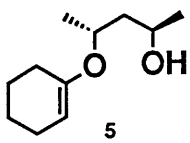
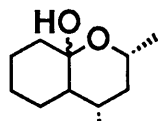
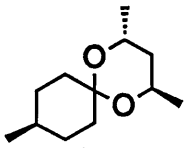
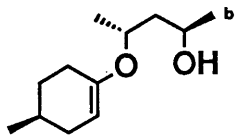
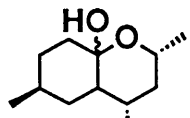
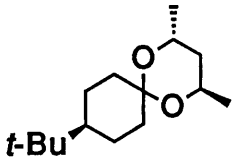
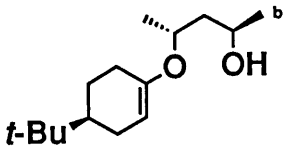
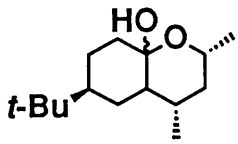
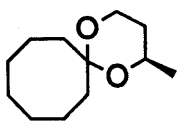
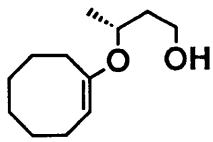
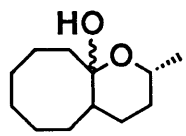
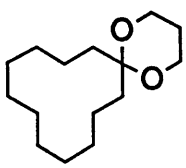
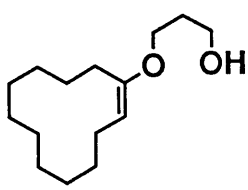
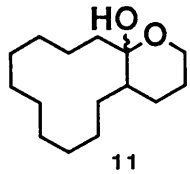


Scheme 1

The synthesis of **22** described herein is straightforward with full stereocontrol. Its brevity stems from the effective dovetailing of new annulation process.

Acknowledgment. A part of this work was financially supported by a Grant-in Aid for Scientific Study from the Ministry of Education, Science and Culture of the Japanese Government. One of us (K.I.) is also acknowledged for the JSPS Fellowships for Japanese Junior Scientists. We also especially thank Professor Kenji Mori for the authentic sample of (-)-Lardolure.

Table 1 Intramolecular Cyclization of Vinyl Ether Alcohols

entry	acetal	vinyl ether[a]	hemiacetal[c]	yield (%)
1				79
2				68
3				75
4				87
5	 4	 5	 6	>95
6	 8	 b	 9	>95
7	 t-Bu	 b t-Bu	 t-Bu	87
8			 10	85
9			 11	83

a) The crude products were used for the next reaction without purification. b) Diastereoratio of >9:1. See ref.9. c) Mixture of anomers.

Experimental Section

General. Melting points were taken on a Shimadzu MM-2 apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrometer. The 200 MHz ^{1}H NMR and the 50 MHz ^{13}C NMR spectra were obtained on a Varian Gemini 200 spectrometer. Chemical shifts of ^{1}H 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. Optical rotations were measured on a Jasco DIP 140 polarimeter. Analitical gas-liquid phase chromatography (GLC) was performed on a Gasukuro Kogyo Model 370 or Simadzu Model 8A instrument with a flame-ionization detector and a capillary column of PEG-20M Bonded (0.25 mm X 25 m), PEG-HT Bonded (0.25 mm X 25 m), or OV-101 (0.25 mm X 25 m) using nitrogen as carrier gas. 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 60 E. Merck Art 9385. 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 atomosphere of dry argon.

In experiments requiring dry solvents, ether, and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Toluene and benzene were dried over sodium metal. Dichloromethane was distilled from phosphorus pentoxide and stored over 4A molecular sieves. (-)-(2*R*,4*R*)-2,4-Pentanediol was purchased from Wako Pure Chemical Industries Ltd. and after checking the optical purity; $[\alpha]^{23}_{D}$=-41.2° (*c* 9.99, chloroform). (-)-(3*R*)-1,3-Butanediol was purchased from Aldrich Chemical Company, Inc. and after checking the optical purity; $[\alpha]^{24}_{D}$=-29.6° (*c* 1.00, ethanol). Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification.

Preparation of Acetals. Acetals were prepared in excellent yield from the corresponding ketone and 1,3-diol in the presence of a catalytic quantity of *p*-toluenesulfonic acid or pyridinium *p*-toluenesulfonate.

2,2-Diethyl-5,5-dimethyl-1,3-dioxane: TLC, R_f=0.61 (hexane-EtOAc, 5 : 2); IR (film) 2950, 2880, 1470, 1460, 1160, 1140, 1105, 960, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, *J*=7.6 Hz, 6H, $2CH_2C\underline{H}_3$), 0.97 (s, 6H, $2CH_3$), 1.73 (q, *J*=7.6 Hz, 4H, $2C\underline{H}_2CH_3$), 3.49 (s, 4H, $2CH_2O$).

(7*R*,9*R*)-7,9-Dimethyl-6,10-dioxaspiro[4.5]decane: TLC, R_f=0.53 (hexane-EtOAc, 10 : 3); IR (film) 2990, 2960, 2900, 1385, 1355, 1335, 1200, 1155, 1130, 1110, 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (d, *J*=6.4 Hz, 6H, 2Me), 1.58-1.96 (m, 10H), 3.98 (septet, *J*=6.6 Hz, 2H, 2OCH).

1,5-Dioxaspiro[5.5]undecane[13]: TLC, R_f=0.47 (hexane-EtOAc, 5 : 2); IR (film) 2970, 2900, 1180, 1160, 1120, 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35-1.95 (m, 12H, $(CH_2)_5$ and CH_2), 3.92 (t, *J*=5.6 Hz, 4H, $2(CH_2O)$).

2-Methyl-1,5-dioxaspiro[5.5]undecane[13]: TLC, R_f=0.47 (hexane-EtOAc, 10 : 3); IR (film) 2950, 2880, 2370, 2340, 1450, 1370, 1170, 1160, 1115, 940 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (d, *J*=6.2 Hz, 3H, Me), 1.30-2.06 (m, 12H, $(CH_2)_5$ and CH_2), 3.79 (ddd, *J*=1.7, 5.5, 11.5 Hz, 1H, CH_2O), 3.98 (dt, *J*=3.1, 11.5 Hz, 1H, CH_2O), 3.94-4.12 (m, 1H, CHO).

(2*R*,4*R*)-2,4-Dimethyl-1,5-dioxaspiro[5.5]undecane (4)[1]: TLC, R_f=0.58 (hexane-EtOAc, 10 : 3); IR (film) 2980, 2950, 2880, 2380, 2340, 1540, 1160, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (d, *J*=6.4 Hz, 6H, 2Me), 1.30-1.73 (m, 12H, $(CH_2)_5$ and CH_2), 3.99 (septet, *J*=6.4 Hz, 2H, 2CHO).

(2*R*,4*R*)-2,4,9-Trimethyl-1,5-dioxaspiro[5.5]undecane (8): Physical properties were identical with those of reported.[9b]

(2*R*,4*R*)-2,4-Dimethyl-9-(1,1-dimethylethyl)-1,5-dioxaspiro[5.5]undecane: Physical properties were identical with those of reported.[9b]

(2*R*,4*R*)-2,4,8,10-Tetramethyl-1,5-dioxaspiro[5.5]undecane (17): Physical properties were identical with those of reported.[9b]

(2*R*)-2-Methyl-1,5-dioxaspiro[5.7]tridecane: 82% yield. TLC, R_f=0.50 (hexane-EtOAc, 5 : 2); IR (film) 3000, 2950, 2890, 1480, 1460, 1395, 1175, 1155, 1120, 990, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (d, *J*=6.0 Hz, 3H, CH_3), 1.36-1.70 (m, 12H, $6CH_2$), 1.76-1.86 (m, 2H, CH_2), 1.92-2.18 (m, 2H, CH_2), 3.79 (ddd, *J*=1.8, 5.6, 11.7 Hz, 1H, OC<u>H</u>H), 3.97 (dt, *J*=3.4, 11.7 Hz, 1H, OCH<u>H</u>), 3.93-4.08 (m, 1H, C<u>H</u>Me); Anal. Found: C, 72.63; H, 11.19. $C_{12}H_{22}O_2$ calcd.: C, 72.68; H, 11.18%.

1,5-Dioxaspiro[5.11]heptadecane: 88% yield. TLC, R_f=0.53 (hexane-EtOAc, 5 : 2); IR (film) 2950, 2880, 1470, 1120, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23-1.50 (m, 18H, $(CH_2)_9$), 1.65-1.85 (m, 6H, $3CH_2$), 3.90 (t, *J*=5.7 Hz, 4H, $2CH_2O$); Anal. Found: C, 75.05; H, 11.84. $C_{15}H_{28}O_2$ calcd.: C, 74.95; H, 11.74%.

General Procedure for the Deprotonation of Acetals. To a solution of acetal (1.0 mmol) in dichloromethane (10 mL) was added triisobutylaluminum (2.0 M in hexane, 2.0 mL, 4.0 mmol) at -78°C. Stirred was the solution at that temperature for 30 min, and at 0°C for 6 h. It was poured into 2 N aqueous sodium hydroxide (60 mL), and extracted with ether (20 mL). The water layer was saturated with sodium chloride, and extracted with ether twice (20 mL X 2). The combined organic layers were dried over magnesium sulfate. Concentrated *in vacuo* gave a crude product of vinyl ether alcohol. This product was used for the next step without further purification.

General Procedure for the Intramolecular Cyclization of Vinyl Ether Alcohols. A crude product of vinyl ether alcohol prepared as detailed above was diluted in dichloromethane (10 mL) and *N*,*N*-diisopropylethylamine (1 mL). After cooling at -78°C, trifluoromethanesulfonic anhydride (210 uL, 1.2 mmol) was added to this solution. After stirring for 3 h, the resulting mixture was poured into sat. aqueous sodium hydrogen carbonate (50 mL),

and extracted with ether for three times (20 mL X 3). The combined ether extracts were washed successively with 1 N sodium hydrogen sulfate and concentration *in vacuo* afforded a crude product, which was diluted in 50% aqueous acetic acid (1.2 mL) and acetone (15 mL). After stirring at ambient temperature overnight, the solution was diluted with water (30 mL), and extracted with ether (30 mL X 3). The combined ether extracts were washed with sat. aqueous sodium hydrogen carbonate and brine, dried over sodium sulfate-potassium carbonate, concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give a colorless solid or oil, which can be recrystalized from petroleum ether.

2-Ethyl-2-hydroxy-3,5,5-trimethyltetrahydropyran: 79% yield. TLC, R_f=0.45 (hexane-EtOAc, 5 : 2); IR (film) 3700-3200 (br), 2980, 2900, 1475, 1468, 1080, 1065, 1005, 955 cm^{-1}; 0.83 (s, 3H, Me); 0.90 (d, J=6.8 Hz, 3H, Me), 0.97 (t, J=7.6 Hz, 3H, Me), 1.03 (s, 3H, Me), 1.05-2.00 (m, 6H, $CH_2C(OH)C(3)HC(4)CH_2$), 3.12 (dd, J=2.6, 10.8 Hz, 1H, OC<u>H</u>H), 3.65 (d, J=10.8 Hz, 1H, OCH<u>H</u>).

(3*R*,5*S*)-3,5-Dimethyl-1-hydroxy-2-oxabicyclo[4.3.0]nonane: 68% yield. TLC, R_f=0.23 (hexane-EtOAc, 10 : 3); IR (film) 3700-3150 (br), 2990, 2950, 2380, 1120, 1070, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (d, J=6.8 Hz, 3H, Me), 0.99-2.16 (m, 10H), 1.16 (d, J=6.4 Hz, 3H, Me), 2.28-2.29 (br, 1H, OH), 3.89-4.05 (m, 1H, OCH); $[\alpha]^{26}_D$=-3.58° (*c* 1.00, ether).

1-Hydroxy-2-oxabicyclo[4.4.0]decane: 75% yield. Physical properties were identical with those of reported.[3,14]

1-Hydroxy-3-methyl-2-oxabicyclo[4.4.0]decane[3,14]: 87% yield. TLC, R_f=0.31 (hexane-EtOAc, 10 : 3); IR (CCl_4) 3610, 3000, 2950, 2930, 2890, 2370, 2350, 1560, 1550, 1530, 1080, 1070, 1060, 990, 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14-2.01 (m, 10H), 1.16 and 1.20 (d and d, J=6.2 and 6.4 Hz, 3H, Me), 1.90 (s, 1H, OH), 2.01-2.46 (m, 3H, $C\underline{H}_2C(OH)C\underline{H}$), 3.69-3.78 and 4.03-4.18 (m and m, 1H, OC<u>H</u>Me)

(3*R*,5*S*)-3,5-Dimethyl-1-hydroxy-2-oxabicyclo[4.4.0]decane (6): >95% yield. TLC, R_f=0.30 (hexane-EtOAc, 4 : 1); mp: 52-53°C; IR (nujol mull) 3600-3300 (br), 1460,

1380, 1215, 1105, 975 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (d, *J*=6.5 Hz, 3H, Me), 1.40 (d, *J*=6.3 Hz, 3H, $OCHC\underline{H}_3$), 0.90-1.78 (13H), 4.06-4.19 (m, 1H, $CH_3C\underline{H}O$); $[\alpha]^{23}_D$=37.2° (*c* 1.00, ether).

(3*R*,5*S*,8*S*)-1-Hydroxy-3,5,8-trimethyl-2-oxabicyclo[4.4.0]decane (9): >95% yield. TLC, R_f=0.28 (hexane-EtOAc, 4 : 1); mp: 97-98°C; IR (nujol mull) 3550-3300 (br), 1740, 1465, 1380, 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (d, *J*=6.4 Hz, 3H, Me), 0.93 (d, *J*=6.0 Hz, 3H, Me), 1.14 (d, *J*=6.3 Hz, 3H, $OCHC\underline{H}_3$), 0.90-1.79 (12H), 4.09-4.19 (m, 1H, $CH_3C\underline{H}O$); $[\alpha]^{23}_D$=27.5° (*c* 1.01, ether).

(3*R*,5*S*,8*S*)-3,5-Dimethyl-8-(1,1-dimethylethyl)-1-hydroxy-2-oxaspiro[4.4.0]decane: 87% yield. TLC, R_f=0.20 (hexane-EtOAc, 4 : 1); mp: 90-91°C; IR (nujol mull) 3600-3300 (br), 1460, 1385, 1220, 1160, 1090, 985, 935 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86-0.95 (complex of d and s, 12H, Me, and *t*-Bu), 0.90-2.40 (12H), 1.15 (d, *J*=6.2 Hz, 3H, $C\underline{H}_3CHO$), 4.10-4.20 (m, 1H, $CH_3C\underline{H}O$); $[\alpha]^{23}_D$=55.4° (*c* 1.07, ether).

(3*R*,5*S*,7*R*,9*S*)-1-Hydroxy-3,5,7,9-tetramethyl-2-oxaspiro[4.4.0]decane (18): 83% yield. TLC, R_f=0.45 (hexane-EtOAc, 4 : 1); mp: 78-80°C; IR (CCl_4) 3640, 2980, 2950, 2900, 2400, 2360, 1565, 1550, 1260, 1205, 1170, 1100, 1000, 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.71-1.33 (m, 4H), 0.88 (d, *J*=6.6 Hz, 3H, Me), 1.05 (d, *J*=6.6 Hz, 3H, Me), 1.06 (d, *J*=6.4 Hz, 3H, Me), 1.12 (d, *J*=6.4 Hz, 3H, Me), 1.45-1.99 (m, 7H), 4.04-4.20 (m, 1H, OCH); Anal. Found: C, 73.45; H, 11.54. $C_{13}H_{24}O_2$ calcd.: C, 73.52; H, 11.41%.

(11*R*)-1-Hydroxy-11-methyl-12-oxabicyclo[6.4.0]dodecane (10): 85% yield. TLC, R_f=0.12 (hexane-EtOAc, 5 : 2); IR (film) 3460, 2950, 2880, 1710, 1475, 1460, 1385, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (d, *J*=6.2 Hz, 3H, CH_3), 1.10-2.15 (m, 15H, $C(3)H_2C(4)H_2C(5)H_2C(6)H_2C(7)H_2$, $C(9)H_2C(10)H_2$ and OH), 2.25-2.70 (m, 3H, $C(2)H_2$ and C(8)H), 3.60-3.85 (m, 1H, $C\underline{H}Me$); Anal. Found: C, 72.44; H, 11.35. $C_{12}H_{22}O_2$ calcd.: C, 72.68; H, 11.18%.

1-Hydroxy-16-oxabicyclo[10.4.0]octadecane (11): 83% yield. TLC, R_f=0.11 (hexane-EtOAc, 5 : 2); IR (film) 3450, 2950, 2900, 1720, 1480, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ

1.12-1.86 (m, 23H, ($C\underline{H}_2$)$_2$CH($C\underline{H}_2$)$_9$ and O$\underline{H}$), 2.42 (ddd, J=4.6, 7.6, 17.0 Hz, 1H, CC$\underline{H}$H), 2.51-2.66 (m, 1H, CH), 2.63 (ddd, J=4.6, 7.6, 17.0 Hz, 1H, CCH$\underline{H}$), 3.54-3.72 (m, 2H, OCH_2); Anal. Found: C, 75.04; H, 11.94. $C_{15}H_{28}O_2$ calcd.: C, 74.95; H, 11.74%.

General Procedure for the Iodolactonization of Bicyclic Hemiacetals. The following procedure was modified upon the basis of Suarez's method[4] for the synthesis of medium-sized lactones. A solution of hemiacetal (1.0 mmol), iodobenzene diacetate (98%, 360 mg, 1.1 mmol), and iodine (250 mg, 1.0 mmol) in cyclohexane (20 mL) was irradiated with stirring by 250 W tungsten filament lamp for 90 min. The resulting solution was poured into aqueous sodium sulfite (30 mL), and extracted with ether (20 mL X 3). The combined organic layers were washed with aqueous sat. sodium hydrogen carbonate (30 mL) and brine (30 mL), dried over magnesium sulfate, concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluant: first with hexane, then hexane-EtOAc) to give a colorless oil of the corresponding iodolactone.

(7*S*,9*R*)-6-Iodo-7,9-dimethylnonanolide (7): >95% yield. TLC, R_f=0.48 (hexane-EtOAc, 10 : 3); IR (film) 2965, 2940, 2880, 2360, 2350, 1740, 1460, 1260, 1240 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.18 (d, J=6.6 Hz, 3H, Me); 1.29 (d, J=5.2 Hz, 3H, Me), 1.43-2.25 (m, 8H, ($C\underline{H}_2$)$_3$CHI and MeCHC$\underline{H}_2$)), 4.70-4.79 (m, 1H, CHI), 5.10-5.17 (m, 1H, OCH), 2.25-2.36 (m, 1H, CH_2CO_2), 2.58 (dt, J=15.6, 4.6 Hz, 1H, CH_2CO_2).

(3*S*,5*R*,7*S*,9*R*)-6-Iodo-3,5,7,9-tetramethylnonanolide: 88% yield. TLC, R_f=0.35 (hexane-EtOAc, 10:1); IR (CCl_4) 2970, 2930, 2355, 2340, 1725, 1560, 1540, 1520, 1510, 1455, 1230, 1110, 1000, 980 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.80-1.99 (m, 6H), 0.99 (d, J=6.4 Hz, 3H, Me), 1.00 (d, J=6.2 Hz, 3H, Me), 1.22 (d, J=6.2 Hz, 3H, Me), 1.22 (d, J=6.2 Hz, 3H, Me), 1.30 (d, J=6.6 Hz, 3H, Me), 2.04-2.40 (m, 3H), 4.91 (m, 1H, CHI), 5.19-5.29 (m, 1H, OCH); Anal. Found: C, 46.17; H, 6.96. $C_{13}H_{23}O_2I$ calcd.: C, 46.16; H, 6.87%.

(11*R*)-8-Iodo-11-methyl-11-undecanolide: 76% yield. TLC, R_f=0.58 (hexane-EtOAc, 5 : 2); IR (film) 2960, 2900, 1750, 1465, 1265, 1240, 1215, 1160 cm^{-1}; ^{1}H NMR

($CDCl_3$) δ 1.25 (d, J=6.4 Hz, 3H, CH_3 (major isomer)), 1.26 (d, J=6.2 Hz, 3H, CH_3 (minor isomer)), 1.10-2.57 (m, 16H, $8CH_2$), 4.16-4.32 (m, 1H, CHI (minor isomer)), 4.48 (quintet, J=6.4 Hz, 1H, CHI (major isomer)), 4.92-5.09 (m, 1H, CHMe (minor isomer)), 5.23 (dquintet, J=3.0, 6.4 Hz, 1H, CHMe (major isomer)); Anal. Found: C, 44.48; H, 6.61. $C_{12}H_{21}O_2I$ calcd.: C, 44.46; H, 6.53%.

12-Iodo-15-pentadecanolide: 81% yield. TLC, R_f=0.59 (hexane-EtOAc, 5 : 2), IR (film) 2950, 2900, 1750, 1470, 1460, 1250, 1190 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18-2.12 (m, 22H, $(CH_2)_2CHI(CH_2)_9$), 2.35 (t, J=7.0Hz, 2H, $CH_2C=O$), 4.03-4.31 (m, 3H, OCH_2 and CHI); Anal. Found C, 49.20; H, 7.53. $C_{15}H_{27}O_2I$ calcd.: C, 49.19; H, 7.43%.

General Procedure for the Deiodogenation of Iodolactones. A mixture of iodolactone (3.1 mmol), tributyltin hydride (2.5 mL, 9.3 mmol), AIBN (100 mg), and THF (65 mL) was refluxed for 40 min. The reaction mixture was diluted with reagent grade (undried) ether (100 mL). DBU (1.7 g, 11 mmol) was added to the reaction mixture and then titrated with 0.1 M iodine solution in ether. During this time, DBU-hydroiodide precipitated as a white solid. After the iodine color just persisted, the solution was transfered to a short column (SiO_2); after solution with ether (50 mL), the solvent was removed. The residue was almost tin-free. [This DBU workup procedure was suggested by D. P. Curran et al.[15]] The residue was purified by column chromatography on silica gel (eluent : first with hexane, then hexane-EtOAc) to give a colorless oil of the corresponding lactone.

(7*R*,9*R*)-7,9-Dimethylnonanolide (15): Quantitative yield. TLC, R_f=0.33 (hexane-EtOAc, 4 : 1); IR (film) 2950, 2890, 2370, 2350, 1735, 1455, 1252, 1095, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80-1.69 (m, 10H), 0.93 (d, J=6.0 Hz, 3H, Me), 1.26 (d, J=6.0 Hz, 3H, Me), 1.85-2.33 (m, 2H), 2.43-2.59 (m, 1H), 4.88-5.02 (m, 1H, $OCHCH_3$); Anal. Found: C, 71.65; H, 10.96. $C_{11}H_{20}O_2$ calcd.: C, 71.68; H, 10.96%.

(3*S*,5*S*,7*R*,9*R*)-3,5,7,9-Tetramethylnonanolide (19): Quantitative yield. TLC, R_f=0.43 (hexane-EtOAc, 10:1); IR (film) 2980, 2950, 2900, 2380, 2360, 1740, 1465, 1315,

1245, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77-2.25 (m, 10H), 0.87 (d, *J*=5.4 Hz, 3H, Me), 0.90 (d, *J*=6.6 Hz, 3H, Me), 0.95 (d, *J*=6.4 Hz, 3H, Me), 1.25 (d, *J*=6.4 Hz, 3H, Me), 2.31 (dd, *J*=1.1, 8.7 Hz, 2H, CH_2CO_2), 4.89-5.03 (m, 1H, OCH); Anal. Found: C, 73.42; H, 11.42. $C_{13}H_{24}O_2$ calcd.: C, 73.52; H, 11.41%.

Exaltolide (15-Pentadecanolide, 13)[8]: 95% yield. TLC, R_f=0.59 (hexane-EtOAc, 5 : 2); mp: 30.5-31.0°C; IR (film) 2950, 2890, 1750, 1470, 1360, 1245, 1180, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20-1.50 (m, 20H, $(CH_2)_{10}$), 1.55-1.75 (m, 4H, $2CH_2$), 2.34 (t, *J*=6.7Hz, 2H, CH_2C=O), 4.15 (t, *J*=5.4 Hz, 2H, CH_2O); Anal. Found: C, 75.06; H, 11.88. $C_{15}H_{28}O_2$ calcd.: C, 74.95; H, 11.74%.

Transformation of 19 into (-)-Lardolure (22).

(3*R*,5*R*,7*R*,9*R*)-3,5,7-Trimethyl-1,9-decanediol (20): To a solution of **19** (0.903g, 4.25 mmol) in toluene (30 mL) was added dropwise diisobutylaluminum hydride (1 M in hexane, 12.8 mL, 12.8 mmol) at -78°C. Stirring was continued for 3 h at that temperature. The reaction mixture was poured into ice 1 N hydrochloric acid, extracted with ether repeatedly, dried over magnesium sulfate, concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: hexane-EtOAc, 4 : 3) to give a colorless oil (846 mg, 92% yield). TLC, R_f=0.3 (hexane-EtOAc, 1 : 1); IR (film) 3570-3070 (br), 2975, 2940, 2375, 2350, 1460, 1185, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75-1.82 (m, 13H), 0.88 (d, *J*=6.6 Hz, 3H, Me), 0.907 (d, *J*=5.6 Hz, 3H, Me), 0.91 (d, *J*=6.8 Hz, 3H, Me), 1.21 (d, *J*=6.0 Hz, 3H, Me), 3.58-3.78 (m, 2H, $C\underline{H}_2OH$), 3.84-3.98 (m, 1H, $C\underline{H}OH$); Anal. Found: C, 71.85; H, 13.25. $C_{13}H_{24}O_2$ calcd.: C, 72.15; H, 13.07%.

(3*R*,5*R*,7*R*,9*R*)-1-*p*-Toluenesulfonyl-3,5,7-trimethyl-9-decanol: To a solution of **20** (0.60 g, 2.8 mmol), DMAP (50 mg), and pyridine (0.97 mL, 12 mmol) in dichloromethane (3 mL) was added TsCl (0.63 g, 3.3 mmol) at -20°C under argon. Stirring was continued for 5.5 h at the same temperature. It was worked up with water, extracted with ether. The organic layer was washed with hydrochloric acid (1N), dried over $MgSO_4$, concentrated *in*

vacuo and purified by column chromatography on silica gel (eluent: hexane-EtOAc, 3 : 1) to give a colorless oil (0.66 g, 1.8 mmol, 64% yield). TLC, R_f=0.55 (hexane-EtOAc, 1:1); IR (film) 3700-3150 (br), 2960, 2935, 2365, 2340, 1455, 1355, 1185, 1165, 1095, 945, 815, 665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.69-1.81 (m, 12H), 0.82 (d, *J*=6.6 Hz, 3H, Me), 0.83 (d, *J*=6.4 Hz, 3H, Me), 0.89 (d, *J*=6.6 Hz, 3H, Me), 1.21 (d, *J*=6.0 Hz, 3H, Me), 2.47 (s, 3H, ArC$\underline{H}_3$), 3.84-4.00 (m, 1H, C$\underline{H}$OH), 4.03-4.15 (m, 2H, C$\underline{H}_2$OTs), 7.37 (d, *J*=8.2 Hz, 2H, Ar), 7.81 (d, *J*=8.2 Hz, 2H, Ar); Anal. Found: C, 64.77; H, 9.31. $C_{20}H_{34}O_4S$ calcd.: C, 64.82; H, 9.27%.

(2*R*,4*R*,6*R*,8*R*)-Trimethyl-2-undecanol (21): To a solution of cuprous iodide (2.73 g, 14.3 mmol) in ether (18 mL) was added methyllithium (1.5 M solution, 19.1 mL, 28.6 mmol) at -78°C under argon. It was stirred at -20°C for 4 h. A solution of tosylate (0.656 g, 1.79 mmol) in ether (10 mL) was added to it at -78°C. Stirring was continued for 2 h at -20°C. The reaction mixture was worked up with aqueous ammonium chloride, extracted with ether, dried over magnesium sulfonate, concentrated *in vacuo*, and purified by column chromatography on silica gel (eluent: hexane-EtOAc, 6 : 1) to give a colorless oil (354 mg, 1.65 mmol, 92% yield). TLC, R_f=0.38 (hexane-EtOAc, 4:1); IR (film) 3600-3150, 2985, 2940, 2885, 2860, 2380, 2340, 1455, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.73-1.80 (m, 20H), 0.85 (d, *J*=6.2 Hz, 3H, Me); 0.91 (d, *J*=6.8 Hz, 3H, Me), 1.21 (d, *J*=6.2 Hz, 3H, Me), 3.88-3.98 (m, 1H, CHO); Anal. Found. C, 78.37; H, 14.25. $C_{14}H_{30}O$ calcd.: C, 78.41; H, 14.13%.

(1*R*,3*R*,5*R*,7*R*)-1,3,5,7-Tetramethyldecyl formate (22)[11]: A mixture of **21** (313 mg, 1.46 mmol) and formic acid (8.2 mL) was stirred for 1.5 h at 65°C. It was then poured into ice-sat. aq $NaHCO_3$ and extracted with hexane, dried over magnesium sulfate, concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: hexane-EtOAc, 50 : 1) to give a colorless oil (336 mg, 1.39 mmol, 95% yield). TLC, R_f=0.25 (hexane-EtOAc, 50 : 1); IR (film) 2975, 2950, 2900, 2380, 2350, 1740, 1465, 1390, 1190, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83-1.80 (m, 6H), 0.84 (d, *J*=1.2 Hz, 3H, Me), 0.87 (d, *J*=1.8 Hz, 3H, Me), 0.90 (d, *J*=2.2 Hz, 3H, Me), 1.28 (d, *J*=6.2 Hz, 3H, Me), 5.13-5.22 (m, 1H, MeC$\underline{H}$O), 8.08 (s, 1H, OCHO); ^{13}C NMR ($CDCl_3$) δ 14.55, 20.10, 20.34, 20.51, 20.71, 21.04, 26.60, 27.36, 29.83,

39.10, 43.15, 45.50, 45.67, 69.26, 161.42; $[\alpha]^{25}_{D}$=-3.64° (*c* 7.88, hexane); GLC (instrument, Gasukuro Kogyo Model 370; column, OV-101, 25 m X 0.25 mm at 100°C + 0.5°C/min; carrier gas, N_2, 5 kg/cm^2) R_t 66.35 min. Anal. Found: C, 74.24; H, 12.59. $C_{15}H_{30}O_2$ calcd.: C, 74.30; H, 12.50%. The ^{1}H NMR and ^{13}C NMR spectra and capillary GC retention time were identical with those of the natural pheromone.[11]

Conversion of 7 to a Diastereoisomeric Mixture of (7*S*,9*R*)-7,9-Dimethylnonanolide and 15. A mixture of **7** (1.10 mmol, 0.362 g) and DBU (1.10 mmol, 0.175 mL) was heated to 90°C. Stirring was continued for 30 min. The reaction mixture was worked up with aqueous ammonium chloride and extracted with ether, dried over magnesium sulfate, concentrated *in vacuo* and purified by column chromatography on silica gel (eluent: hexane-EtOAc, 20 : 1) to give **14** (isomeric mixture of 5-olefin and 6-olefin) as a colorless oil (70.7 mg, 35% yield). **14** (5-olefin): TLC, R_f=0.50 (hexane-EtOAc, 4 : 1); ^{1}H NMR ($CDCl_3$) δ 0.83-2.53 (m, 9H), 0.94 (d, *J*=5.0 Hz, 3H, Me), 1.18 (d, *J*=5.0 Hz, 3H, Me), 5.05-5.38 (m, 3H, OC<u>H</u>Me and C<u>H</u>=C<u>H</u>). **14** (6-olefin): TLC, R_f=0.50 (hexane-EtOAc, 4 : 1); ^{1}H NMR ($CDCl_3$) δ 0.83-2.53 (m, 10H), 1.34 (d, *J*=6.0 Hz, 3H, Me), 1.75 (s, 3H, CH=C<u>Me</u>), 5.05-5.38 (m, 2H, C<u>H</u>=C and OC<u>H</u>).

To a solution of **14** (70.7 mg, 0.39 mmol) in methanol (1.1 mL) was added 10% Pd-C (4 mg) and then the reaction atomosphere was substituted for hydrogen gas. Stirring was continued for 5 h at room temperature. The solution was filtrated. The filtrate was concentrated *in vacuo* and purified by column chromatography on silica gel (eluent: hexane-EtOAc, 50 : 1) to give a mixture of (7*S*,9*R*)-7,9-dimethylnonanolide and **15** as a colorless oil (47.6 mg, 66% yield). GLC analysis showed a mixture of (7*S*,9*R*)-7,9-dimethylnonanolide and **15** present in a 56 : 44 ratio, respectively. TLC, R_f=0.33 (hexane-EtOAc, 4 : 1); IR (film) 2960, 2885, 2375, 2345, 1730, 1460, 1245, 1145, 1100, 965 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.86-1.67 (m, 8H), 0.88 (d, *J*=6.8 Hz, 3H, Me (7*S*)), 0.93 (d, *J*=5.8 Hz, 3H, Me (7*R*)), 1.26 (d, *J*=6.2 Hz, 3H, Me (7*R*)), 1.30 (d, *J*=6.6 Hz, 3H, Me (7*S*)), 1.74-2.28 (m, 4H), 2.37-2.56 (m, 1H), 4.88-4.97 (m, 1H,

$CH_3C\underline{H}O$ (7*S*)), 5.03-5.14 (m, 1H, $CH_3C\underline{H}O$ (7*R*)). GLC (instrument, Gasukuro Kogyo Model 370; column, PEG-20M Bonded, 25 m X 0.25 mm at 100°C + 0.5°C/min; carrier gas, N_2, 5 kg/cm^2) R_t 32.8 min (44%, (7*R*)), 39.9 min (56%, (7*S*)). Anal. Found: C, 71.67; H, 10.86. $C_{11}H_{20}O_2$ calcd.: C, 71.68; H, 10.96%.

Transformation of (11*R*)-8-Iodo-11-methyl-11-undecanolide into (+)-Recifeiolide (12).

Procedure for Dehydroiodination. The hindered amidine DBU (5 mL) and (11*R*)-8-iodo-11-methyl-11-undecanolide (2.14 g, 6.59 mmol) were mixed together and heated in an oil bath at 85±5°C. Heating and stirring were continued for 40 min after the appearance (about 3 min) of a white precipitate or syrup. The reaction mixture was worked up with hexane, dried over magnesium sulfate, concentarated *in vacuo*, and purified by column chromatography on silica gel (eluent: hexane-EtOAc, 20 : 1) to give a 59 : 31 : 2 : 7 mixture of the four diastereoisomeric olefinic lactones ((8*E*)-11-methyl-8-undecen-11-olide (**12**), (7*E*)-11-methyl-7-undecen-11-olide, and two other minor cis isomers) as a colorless oil (1.26 g, 98% yield). Although we had no independent proof for the assigned stereochemistry of two minor cis isomers, (8*E*)-isomer **12**[7,16,17] and (7*E*)-isomer[17] were chromatographically and spectrally identical with the one reported in the literature. Chromatographic separation of the isomeric olefinic lactones, using silica gel impregnated with silver nitrate by immersing silica gel (E. Merck) into a 12.5% (w/v) solution of silver nitrate in acetonitrile and then dried for 1 day under reduced pressure (vacuum pump) and hexane-ethyl acetate (500 : 1) as the eluent, gave pure **12**. Silica gel TLC plates were immersed briefly in a 12.5% (w/v) solution of silver nitrate in acetonitrile and allowed to air-dry in the dark overnight. GLC (instrument, Simadzu Model 8A; column, PEG-HT Bonded, 25 m X 0.25 mm at 130°C+0.5°C/min; carrier gas, N_2, 0.75 kg/cm^2) R_t 11.6 min ((8*E*)-isomer **12**), 12.9 min ((7*E*)-isomer), 13.6 min ((*Z*)-isomer), 13.9 min ((*Z*)-isomer).

(8*E*)-isomer 12: TLC, R_f=0.17 (hexane-EtOAc, 20 : 1); IR (film) 3000, 2950, 2890, 1740, 1240, 1170 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.252 (d, *J*=6.2 Hz, 3H, CH_3), 1.04-2.48 (m,

14H, $(CH_2)_6$ and CH_2), 5.08-5.27 (m, 1H, C<u>H</u>Me), 5.24-5.36 (m, 2H, CH=CH); $[\alpha]^{24}_D$=+71.18° (*c* 1.03, $CHCl_3$); lit.[7b] $[\alpha]_D$=+70° (*c* 1, $CHCl_3$).

(7*E*)-Isomer: TLC, R_f=0.14 (hexane-EtOAc, 20 : 1); ^1H NMR ($CDCl_3$) δ 1.247 (d, *J*=6.2 Hz, 3H, Me), 4.78-4.94 (m, 1H, CHO), 5.08-5.36 (m, 1H, C<u>H</u>=CH), 5.47 (ddd, *J*=4.8, 9.2, 14.3 Hz, 1H, CH=C<u>H</u>).

References and Notes

1. Mori, A.; Yamamoto, H. *J. Org. Chem.* **1985**, *50*, 5444.
2. Previous examples for cationic cyclization of vinyl ethers, see:
   (a) Hashimoto, S.; Itoh, A.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 4192.
   (b) Boeckman, Jr., R. K.; Bruza, K. J.; Heinrich, G. R. *Ibid.* **1978**, *100*, 7101.
3. Suginome, H.; Yamada, S. *Tetrahedron* **1987**, *43*, 3371.
4. Freire, R.; Marrero, J. J.; Rodriguez, M. S.; Suarez, E. *Tetrahedron Lett.* **1986**, *27*, 383. **7** was mixture of two stereoisomers.
5. Ochiai, M.; Iwaki, S.; Ukita, T.; Nagao, Y. *Chemistry Lett.* **1987**, 133.
6. $[\alpha]^{24}_D$=+71.18° (*c* 1.03, $CHCl_3$); lit.[7b] $[\alpha]_D$=+70° (*c* 1, $CHCl_3$).
7. For (+)-recifeiolide, see:
   (a) Vesonder, R. F.; Stodola, F. H.; Wickerham, L. J.; Ellis, J. J.; Rohwedder, W. K. *Can. J. Chem.* **1971**, *49*, 2029.
   (b) Gerlach, H.; Oertle, K.; Thalmann, A. *Helv. Chim. Acta*, **1976**, *59*, 755.
   (c) Utimoto, K.; Uchida, K.; Yamaya, M.; Nozaki, H. *Tetrahedron Lett.* **1977**, *41*, 3641.
8. More recent examples for syntheses of exaltolide, see:

(a) Cossy, J.; Pete, J. P. *Bull. Soc. Chim. Fr.* **1988**, 989; Torra, N.; Urpi, F.; Vilarrasa, J. *Tetrahedron* **1989**, *45*, 863.

(b) Matsuyama, H.; Nakamura, T.; Kamigata, N. *J. Org. Chem.* **1989**, *54*, 5218.

(c) Bestmann, H. J.; Schobert, R. *Synthesis* **1989**, 419.

9. (a) Naruse, Y.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 1363.

(b) Idem *Tetrahedron* **1988**, *44*, 6021.

10. Burman, M. J. F.; Elliott, D. R.; Gordon, M. H.; Robinson, M. J. T. *Tetrahedron Lett.* **1976**, *18*, 1535.

11. For synthesis of Lardolure, see:

(a) Mori, K.; Kuwahara, S. *Tetrahedron* **1986**, *42*, 5539.

(b) Idem *Liebigs Ann. Chem.* **1987**, 555.

For stereochemistry of Lardolure, see:

(c) Mori, K.; Kuwahara, S. *Tetrahedron* **1986**, *42*, 5545.

12. $[\alpha]^{25}_D$ = -3.64° (*c* 7.88, hexane); lit.[11] $[\alpha]^{23}_D$ = -3.4° (*c* 7.86, hexane); Gc analysis reveals a single peak and identical with an authentic sample[11]; t_R = 66.53 min (OV-101, capillary column at 100°C), see ref. 11.

13. (a) Thuy, V. M.; Maitte, P. *Bull. Chim. Soc. Fr.* **1975**, 2558.

(b) Kantlehner, W.; Gutbrod, H. D. *Liebigs Ann. Chem.* **1979**, 1362.

(c) Meslard, J. C.; Subira, F.; Vairon, J. P.; Guy, A.; Garreau, R. *Bull. Soc. Chim. Fr.* **1985**, 84.

14. (a) Mahajan, J. R.; D. Araujo, H. C. *Synthesis* **1981**, 49.

(b) Suginome, H.; Yamada, S. *Tetrahedron Lett.* **1985**, *26*, 3715.

(c) Idem *Tetrahedron* **1987**, *43*, 3371.

15. Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140.

16. For (±)-recifeiolide, see:

(a) Corey, E. J.; Ulrich, P.; Fitzpatrick, J. M. *J. Am. Chem. Soc.* **1976**, *98*, 222.

(b) Narasaka, K.; Yamaguchi, M.; Mukaiyama, T. *Chem. Lett.* **1977**, 959.

(c) Takahashi, T.; Hashiguchi, S.; Kasuga, K.; Tsuji, J. *J. Am. Chem. Soc.* **1978**, *100*, 7424.

(d) Trost, B. M.; Verhoeven, T. R. *Ibid.* **1980**, *102*, 4743.

(e) Wasserman, H. H.; Gambale, R. J.; Pulwer, M. J. *Tetrahedron*, **1981**, *37*, 4059.

(f) Ahmed, A.; Taniguchi, N.; Fukuda, H.; Kinoshita, H.; Inomata, K.; Kotake, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 781.

(g) Hirano, T.; Hayashi, K.; Fujihara, Y.; Ohshiro, Y.; Agawa, T. *J. Org. Chem.* **1985**, *50*, 279.

(h) Bestmann , H. J.; Schobert, R. *Synthesis* **1989**, 419.

17. Schreiber, S. L.; Hulin, B.; Liew, W. *Tetrahedron* **1986**, *42*, 2945.

Chapter 9

Chiral Aryl Grignard Reagents-Generation and Reactions with Carbonyl Compounds

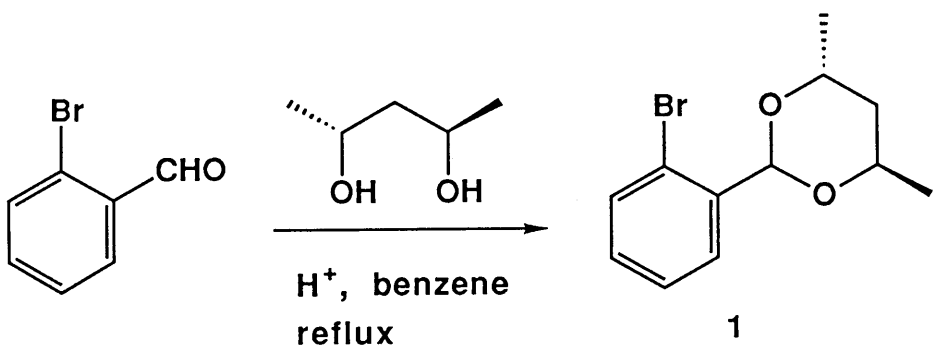
Abstract: Chiral aryl Grignard reagents are generated *in situ* from chiral 2-halobenzaldehyde acetal, *t*-butyllithium, and magnesium bromide. These reagents react with aromatic aldehydes to moderate diastereoselectivities.

The chiral acetal method plays an increasingly important role in asymmetric synthesis.[1] We have shown that the Lewis acid catalyzed coupling of chiral acetals with various nucleophilic organometallic reagents proceeds in a highly diastereoselective manner, ultimately providing a route for generating chiral secondary alcohols in high chemical and optical yields.[2,3] Especially six-membered ring acetals derived from (2*R*,4*R*)- or (2*S*,4*S*)-pentanediols react with excellent diastereoselectivities to give products from which the acetal auxiliary is easily removed.[3] Asymmetric induction produced by the acetal derived from (-)-(2*R*,4*R*)-2,4-pentanediol is ascribed to a stereospecific coordination of the Lewis acid to one of the acetal oxygens.

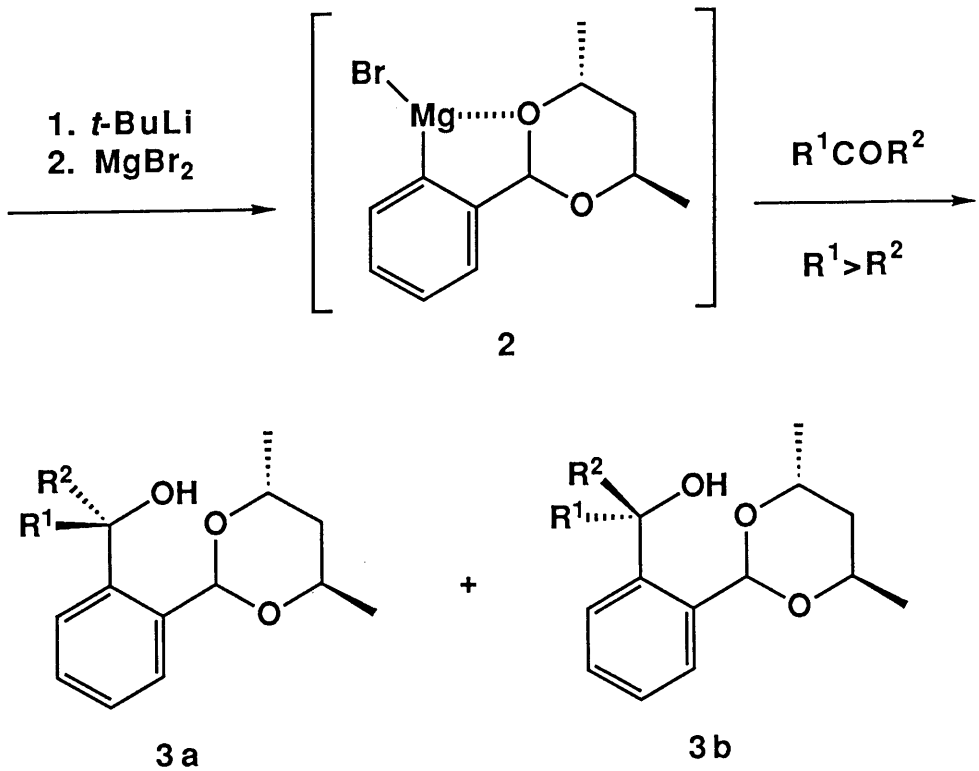
As part of a program aimed at exploring a scope and limitations of chiral acetal methodology, we now report diastereoselective addition of Grignard reagents which have an adjacent chiral acetal group.

Results and Discussion

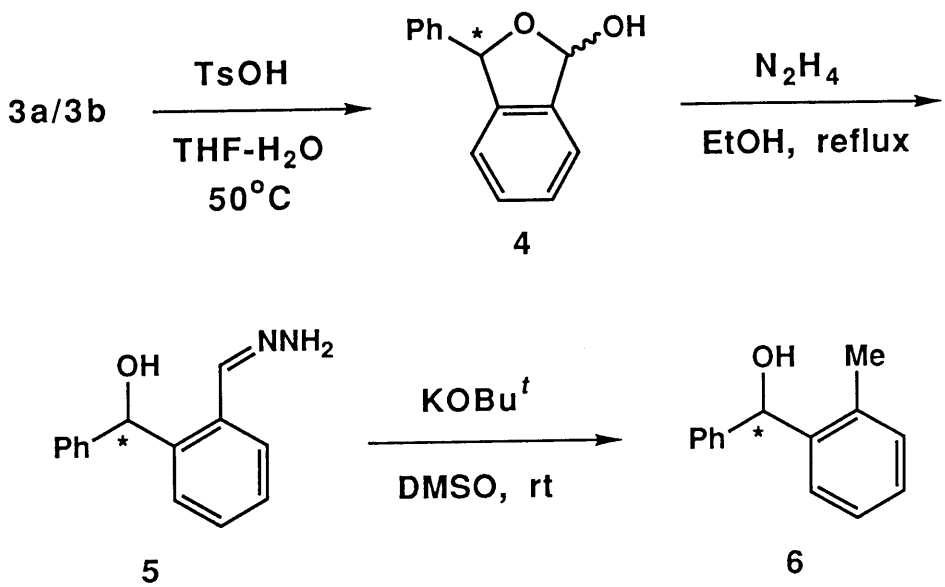
Chiral aryl Grignard reagent **2** was readily prepared as shown in Scheme 1: Acetalization of 2-bromobenzaldehyde with (-)-(2*R*,4*R*)-2,4-pentanediol, lithiation with *t*-butyllithium, and finally transmetallation with magnesium bromide. The reactions of the Grignard reagent **2** with various carbonyl compounds were carried out in toluene-ether at -78°C. Some of our results are listed in Table 1. Using an aromatic carbonyl compound as the electrophile, **2** gave high diastereoselectivity providing the predominant product **3a** (Entries 1, 4, and 5). The less stereoselectivity, on the other hand, was obtained in the reactions with the other organometallic reagents (Entries 2, 3, and 10) and the reactions with aliphatic aldehydes (Entries 6 and 8).



1



Scheme 1



Scheme 2

Evidence for the stereochemical course of the process depicted in Scheme 1 was obtained by the transformation shown in Scheme 2. The product **3a** (R^1=Ph, R^2=H; 88% de) in Entry 1 was converted into phenyl-*o*-tolylmeyhanol (**6**) whose stereochemistries were already established.[4] Thus, hydrolysis of **3a** with *p*-toluenesulfonic acid afforded hemiacetal **4**, which was further converted to hydrazone **5** by hydrazine. Treatment of **5** by pottasium *t*-butoxide gave the compound **6** ($[\alpha]^{23}_D$=-0.53°, *c* 1.0, benzene) having the *S*-configuration.[4] The stereochemistries of the major product **3a** of the other cases were tentatively assigned from mechanistic analogy.

Although the detailed stereochemical course is not ascertained, the formation of **3a** as predominant products may be reasonably explained by the attack of the Griganrd reagents from *re*-face side in the structure of organometallic reagent on the *re*-face of the carbonyl compounds as shown in Fig. 1. Namely, the magnesium metal is intramolecularly fixed by a stereospecific coordination to one of the acetal oxygen atoms leading to the formation of the five-membered ring structure. Then electrophiles approach to the less hindered side of the magnesium reagent as in the figure.

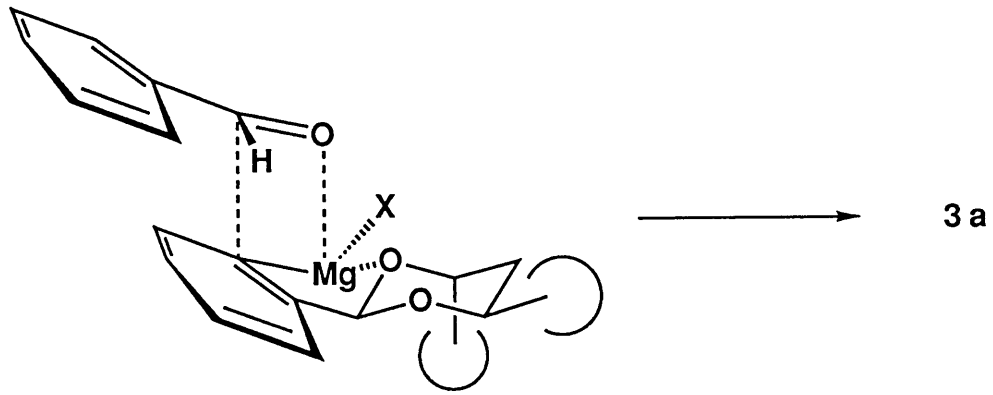


Fig. 1.

The study described above illustrates the suitability of optically active alcohols. One obvious advantage of our methodology is that product **3a** could be further transformed into other new chiral compounds by a diastereoselective cleavage of the remaining homochiral acetal group.

Table 1. Grignard Reaction *via* Homochiral Acetal

Entry	Substrate	R^1COR^2 R^1	R^2	Yield(%)	Ratio 3a : 3b
1	1	Ph	H	91	94 : 6
2[a)]				73	72 : 28
3[b)]				50	60 : 40
4		*p*-$CF_3C_6H_4$	H	72	89 : 11
5		Ph	Me	34	83 : 17
6		*t*-Bu	H	85	82 : 18
7		PhCH=CH	H	66	74 : 26
8		*c*-Hex	H	69	65 : 35
9		Ph	H	47	82 : 18
10[b)]				50	73 : 27

a) $Ti(O\textit{i}\text{-}Pr)_4$ was used instead of $MgBr_2$.
b) R^1COR^2 was added after lithiation.

Experimental Section

General. The IR spectra were determined on a Hitachi 260-10 spectrometer. The ^1H NMR spectra were recorded on a Varian Gemini-200 spectrometer, using TMS (tetramethylsilane) as an internal standard. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The microanalyses were performed at the Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University. Analytical gas-liquid phase chromatography (GLC) was performed on Gasukuro Kogyo model 370 instruments with a flame-ionization detector and a capillary column of PEG-HT (0.25X25000 mm) using nitrogen as the carrier gas. Ether and tetrahydrofuran (THF) were distilled from benzophenone ketyl. Toluene and benzene were dried over sodium metal. All experiments were carried out under an argon atmosphere. Purification of the product was carried out by column chromatography on silica gel Fuji-Davison BW-300. (-)-(2*R*,4*R*)-2,4-pentanediol was purchased from Wako Pure Chemical Industries Ltd. and used after checking the optical purity; $[\alpha]^{23}_D$=-41.2° (*c* 9.99, chloroform). Unless otherwise noted, other chemicals were purchased from commercial suppliers and used without further purification.

General Method for Preparation of Homochiral Acetals. The mixture of corresponding aldehyde or ketone (10.0 mmol), *p*-toluenesulfonic acid (10 mg) and (-)-(2*R*,4*R*)-2,4-pentanediol (1.14 g, 11.0 mmol) in 10 mL of benzene was refluxed with continuous azeotropic removal of water for 2 h. The resulting mixture was poured into saturated sodium hydrogen carbonate and the product was extracted with twice with hexane. The organic layers were dried over magnesium sulfate and concentrated *in vacuo*. Purification of the crude oil by column chromatography on silica gel (hexane/ethyl acetate as eluent) afforded the corresponding acetal. The physical data of acetals are listed below.

(4*R*,6*R*)-2-(2-Bromophenyl)-4,6-dimethyl-1,3-dioxane (1): Quantitative yield; IR (CCl_4) 2986, 1366, 1148, 1129, 996 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (d, *J*=6.2 Hz, 3H,

C(equatorial)H_3), 1.40-1.52 (m, 1H, *H*(equatorial)CH), 1.55 (d, *J*=6.8 Hz, 3H, C(axial)H_3), 1.92-2.10 (m, 1H, *H*(axial)CH), 4.24 (dqd, *J*=2.4, 5.9, 11.8 Hz, 1H, OC*H*(axial)CH_3), 4.48 (m, 1H, OC*H*(equatorial)CH_3), 6.13 (s, 1H, O_2CH), 7.19 (dt, 1H, *J*=1.8, 7.6 Hz, ArH), 7.35 (dt, 1H, *J*=1.3, 7.7 Hz, ArH), 7.53 (dd, 1H, *J*=1.3, 7.7 Hz, ArH), 7.74 (dd, 1H, *J*=1.8, 7.7 Hz, ArH). Anal. ($C_{12}H_{15}O_2Br$) C, H.

(4*R*,6*R*)-2-(2-Bromophenyl)-2,4,6-trimethyl-1,3-dioxane: Quantitative yield; IR (film) 3000, 2950, 2375, 2350, 1460, 1440, 1385, 1378, 1275, 1245, 1185, 1175, 1130, 1030, 970, 765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (d, *J*=2.6 Hz, 3H, C(equatotial)H_3), 1.29 (d, *J*=2.6 Hz, 3H, C(axial)H_3), 1.46-1.67 (m, 2H, CH_2), 1.70 (s, 3H, O_2CCH_3), 3.55-3.72 (m, 1H, OC*H*(axial)CH_3), 4.12-4.29 (m, 1H, OC*H*(equatorial)CH_3), 7.14 (dt, *J*=1.8, 7.6 Hz, 1H, ArH), 7.32 (dt, *J*=1.4, 7.6 Hz, 1H, ArH), .61 (dd, *J*=1.4, 7.8 Hz, 1H, ArH), 7.81 (dd, *J*=1.8, 7.8 Hz, 1H, ArH). Anal. ($C_{13}H_{17}O_2Br$) C, H.

General Procedure for the Grignard Type Coupling of the Homochiral Acetal. To a solution of the acetal (0.5 mmol) in toluene (3 mL) was added *t*-butyllithium (0.26 mL, 0.6 mmol, 2.32 mol dm^{-3} in pentane solution) at -78°C and the resulting yellow solution was stirred at 0°C for 30 min. After cooling to -78°C, a solution of magnesium bromide (1.0 mmol) in ether (3 mL) (prepared in another flask from magnesium turnings (29.2 mg, 1.2 mmol) and 1,2-dibromoethane (0.0862 mL, 1.0 mmol) at room temperature for 30 min) was added at -78°C, and after 30 min, the corresponding aldehyde (0.5 mmol) was added at the same temperature. The mixture was stirred at -78°C for 30 min, poured into aqueous ammonium chloride, extracted with ether, and dried over magnesium sulfate. Evaporation of solvents and purification of the residue by column chromatography on silica gel (hexane/ethyl acetate as eluent) gave the corresponding hydroxy acetals (**3a** and **3b**). The diastereomeric ratio of the adducts was determined by ^1H NMR. The physical properties and analytical data of the adducts obtained are listed below.

(4*R*,6*R*)-4,6-Dimethyl-2-[2-(α-hydroxybenzyl)phenyl]-1,3-dioxane (3, Entries 1, 2, and 3): IR (CCl_4) 3461 (OH), 2999, 2956, 1453, 1381, 1156, 1134, 1106, 1036,

1019, 996, 763, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (d, *J*=6.2 Hz, 3H, C(equatorial)H_3), 1.47 (d, *J*=7.0 Hz, 3H, C(axial)H_3), 1.97-2.12 (m, 1H, *H*(axial)CH), 1.33-1.43 (m, 1H, *H*(equatorial)CH), 3.72 (d, *J*=3.5 Hz, 1H, OH (**3a** isomer)), 3.95 (d, *J*=4.8 Hz, 1H, OH (**3b** isomer)), 4.21 (dqd, *J*=2.2, 6.2, 12.2 Hz, 1H, OC*H*(axial)CH_3), 4.48-4.60 (m, 1H, OC*H*(equatorial)CH_3), 5.92 (s, 1H, O_2CH (**3b** isomer)), 6.08 (s, 1H, O_2CH (**3a** isomer)), 6.34 (d, *J*=4.8 Hz, 1H, C*H*OH (**3b** isomer)), 6.43 (d, *J*=3.5 Hz, 1H, C*H*OH (**3a** isomer)), 7.10-7.65 (m, 9H, ArH). Anal. ($C_{19}H_{22}O_3$) C, H.

(4*R*,6*R*)-4,6-Dimethyl-2-[2-(4-trifluoromethyl-α-hydroxybenzyl)phenyl]-1,3-dioxane (**3**, Entry 4): IR (film) 3400 (OH), 2975, 2930, 2880, 1615, 1455, 1410, 1375, 1320, 1140, 1020, 925, 860, 810, 758 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (d, *J*=6.0 Hz, 3H, C(equatorial)H_3), 1.47 (d, *J*=7.2 Hz, 3H, C(axial)H_3), 1.39-1.53 (m, 1H, *H*(equatorial)CH), 1.95-2.10 (m, 1H, *H*(axial)CH), 3.91 (d, *J*=3.7 Hz, 1H, OH (**3a** isomer)), 3.93 (d, *J*=2.6 Hz, 1H, OH (**3b** isomer)), 4.13-4.28 (m, 1H, OC*H*(axial)CH_3), 4.44-4.57 (m, 1H, OC*H*(equatorial)CH_3), 5.92 (s, 1H, O_2CH (**3b** isomer)), 6.05 (s, 1H, O_2CH (**3a** isomer)), 6.44 (d, *J*=3.7 Hz, 1H, C*H*OH (**3b** isomer)), 6.51 (d, *J*=2.6 Hz, 1H, CHOH (**3a** isomer)),6.97-7.65 (m, 8H, ArH). Anal. ($C_{20}H_{21}O_3F_3$) C, H.

(4*R*,6*R*)-4,6-Dimethyl-2-[2-(1-hydroxy-1-phenylethyl)phenyl]-1,3-dioxane (**3**, Entry 5): IR (film) 3423, 2993, 2943, 1443, 1373, 1155, 1135, 1036, 985, 925, 758, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (d, *J*=8.0 Hz, 3H, C(equatorial)H_3), 1.28 (d, *J*=8.0 Hz, 3H, C(axial)H_3), 1.25-1.50 (m, 1H, *H*(equatorial)CH), 1.75-2.00 (m, 1H, *H*(axial)CH), 3.46-3.66 (m, 1H, OC*H*(axial)CH_3), 4.24-4.41 (m, 1H, OC*H*(equatorial)CH_3), 5.31 (s, 1H, O_2CH (**3b** isomer)), 5.61 (s, 1H, O_2CH (**3a** isomer)), 6.79-8.40 (m, 9H, ArH). Anal. ($C_{20}H_{24}O_3$) C, H.

(4*R*,6*R*)-4,6-Dimethyl-2-[2-(1-hydroxy-2,2-dimethylpropyl)phenyl]-1,3-dioxane (**3**, Entry 6): IR (film) 3450, 2970, 2950, 2880, 1372, 1125, 1031, 983, 753 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (s, 9H, *t*-Bu), 1.25 (d, *J*=6.2 Hz, 3H, C(equatorial)H_3), 1.46 (d, *J*=7.0 Hz, C(axial)H_3), 1.39-1.51 (m, 1H, *H*(axial)CH), 1.92-2.08 (m, *H*(equatorial)CH), 2.16 (d,

J=2.6 Hz, 1H, OH (**3a** isomer)), 2.27 (d, *J*=2.0 Hz, 1H, OH (**3b** isomer)), 4.16 (dqd, *J*=2.2, 6.2, 12.4 Hz, 1H, OC*H*(axial)CH_3), 4.40-4.54 (m, 1H, OC*H*(equatorial)CH_3), 4.83-4.86 (m, 1H, C*H*OH), 6.22 (s, 1H, O_2CH), 7.26-7.75 (m, 4H, ArH). Anal. ($C_{17}H_{16}O_3$), C. H.

(4*R*,6*R*)-4,6-Dimethyl-2-[2-(1-hydroxy-3-phenyl-2-propenyl)-phenyl]-1,3-dioxane (**3**, Entry 7): IR (film) 3450, 3040, 2980, 2945, 2880, 1500, 1450, 1408, 1380, 1159, 1135, 1108, 1041, 990, 928, 760, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (d, *J*=6.0 Hz, C(equatorial)H_3), 1.43-1.58 (m, 1H, *H*(equatorial)CH), 1.52 (d, *J*=6.8 Hz, 3H, C(axial)H_3), 1.98-2.14 (m, 1H, *H*(axial)CH), 3.58 (d, *J*=3.0 Hz, 1H, OH (**3a** isomer)), 3.66 (d, *J*=3.4 Hz, 1H, OH (**3b** isomer)), 4.26 (dqd, *J*=2.6, 6.0, 12.0 Hz, 1H, OC*H*(axial)CH_3), 4.53 (m, 1H, OC*H*(equatorial)CH_3), 5.94-5.99 (m, 1H, C*H*OH), 6.15 (s, 1H, O_2CH), 6.52 (dd, *J*=4.7, 16.0 Hz, C*H*=CHPh), 6.88 (dd, *J*=1.7 Hz, 16.0 Hz, CH=C*H*Ph), 7.21-7.63 (m, 9H, ArH). Anal. ($C_{21}H_{24}O_3$) C, H.

(4*R*,6*R*)-4,6-Dimethyl-2-[2-(cyclohexylhydroxymethyl)phenyl]-1,3-dioxane (**3**, Entry 8): IR (film) 3443, 2973, 2918, 2700, 1440, 1373, 1148, 1125, 1100, 1033, 980, 918, 753 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (d, *J*=6.0 Hz, 3H, C(equatorial)H_3), 1.49 (d, *J*=6.8 Hz, 3H, C(axial)H_3), 1.92-2.08 (m, 1H, *H*(axial)CH), 0.89-2.18 (m, 12H, C_6H_{11} and *H*(equatorial)CH_3), 4.20 (dqd, *J*=2.1, 6.0, 12.0 Hz, 1H, OC*H*(axial)CH_3), 4.40-4.54 (m, 1H, OC*H*(equatorial)CH_3), 4.72 (dd, *J*=2.6, 8.0 Hz, 1H, C*H*OH (**3b** isomer)), 4.80 (dd, *J*=2.6, 8.2 Hz, C*H*OH (**3a** isomer)), 6.08 (s, 1H, O_2CH (**3a** isomer)), 6.12 (s, 1H, O_2CH (**3b** isomer)), 7.24-7.67 (m, 4H, ArH). Anal. ($C_{19}H_{28}O_3$) C, H.

(4*R*,6*R*)-2,4,6-Trimethyl-2-[2-(α-hydroxybenzyl)phenyl]-1,3-dioxane (**3**, Entries 9 and 10): IR (film) 3500, 2980, 2948, 1450, 1382, 1248, 1178, 1162, 1121, 1039, 1019, 962, 921, 765, 739, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25-1.30 (m, 6H, 2CHC*H*$_3$), 1.52-1.82 (m, 2H, CH_2), 1.78 (s, 3H, O_2CCH_3), 3.70-3.81 (m, 1H, OC*H*(axial)CH_3), 4.02 (d, 1H, *J*=4.0 Hz, OH), 4.21-4.32 (m, 1H, OC*H*(equatorial)CH_3), 6.40 (d, *J*=3.8 Hz, 1H, C*H*OH (**3a** isomer)), 6.61 (d, *J*=5.0 Hz, 1H, C*H*OH (**3b** isomer)), 6.98-7.66 (m, 9H, ArH). Anal. ($C_{20}H_{24}O_3$) C, H.

Procedure for the Conversion of 3a/3b to 6. The mixture of **3a/3b** (94 : 6, 1.24 g, 4.2 mmol), *p*-toluenesulfonic acid (200 mg), water (15 mL), and THF (15 mL) was stirred at 50°C for 5h. Then the mixture was poured into saturated sodium hydrogen carbonate aqueous solution and extracted with ether. The combined extracts were dried over magnesium sulfate, filtered, and evaporated. Column chromatography (gradient elution, hexane/ethyl acetate, 5 : 2) gave **4** as a colorless oil (0.863 g, 98% yield).

To a solution of **4** (0.863 g, 4.1 mmol) prepared as detailed above in ethanol was added hydrazine monohydrate (0.971 mL, 20 mmol) at room temperature. After warming to 50-70°C, the mixture was stirred at the same temperature for 8 h. After cooling to room temperature, the resulting solution was concentrated *in vacuo*. Column chromatography (gradient elution, Et_2O) gave **5** as a colorless oil (0.731 g, 79% yield).

To a rapidly stirred mixture of sublimed potassium *t*-butoxide and anhydrous dimethyl sulfoxide (20 mL) was added a solution of **5** in anhydrous dimethyl sulfoxide (20 mL) in a very small portions over 1 h period. The solution turned deep green. Stirring was continued for 30 min. It was worked up with water and extracted with dichloromethane. The organic layer was washed with water, dried, and concentrated *in vacuo*. Column chromatography (gradient elution, benzene) gave **6** (455 mg, 71% yield).

3-Phenyl-2-oxaindan-1-ol (4): ^1H NMR ($CDCl_3$) δ 3.51 and 3.57 (d, *J*=7.4 Hz, 1H, OH), 6.13 (s, 1H, C*H*Ph (trans isomer)), 6.36 (d, *J*=7.4 Hz, 1H, C*H*Ph (cis isomer)), 6.61 (d, *J*=7.4 Hz, 1H, CHO_2 (trans isomer)), 6.72 (dd, *J*=1.7, 7.4 Hz, 1H, CHO_2), 7.05-7.53 (m, 9H, ArH).

2-(α-Hydroxybenzyl)benzaldehyde hydrazone (5): ^1H NMR ($CDCl_3$) δ 5.49 (br, 3H, NH_2 and OH), 5.99 (s, 1H, PhC*H*), 7.10-7.44 (m, 9H, ArH), 7.82 (s, 1H, CH=N).

Phenyl-*o*-tolylmethanol (6): ^1H NMR ($CDCl_3$) δ 2.30 (d, *J*=5.0 Hz, 1H, OH), 2.25 (s, 3H, CH_3), 6.00 (d, *J*=5.0 Hz, 1H, C*H*OH), 7.12-7.55 (m, 9H, ArH). The %ee of this

compound ($[\alpha]^{23}_D$=-0.53°, *c* 1.0, benzene), determined from ^{1}H NMR by a shift reagent Eu(hfc)$_3$, was 72%.

References and Notes

1. Seebach, D.; Imwinkelried, R.; Weber, T. "Modern Synthetic Methods 1986, Vol. 4" ed by Scheffold, R. Springer-Verlag Berlin Heidelberg (1986), pp. 191-216.
2. Fujiwara, J.; Fukutani, Y.; Hasegawa, M.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1984**, *106*, 5004.
3. (a) Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *J. Organomet. Chem.* **1983**, *285*, 83.
   (b) Ishihara, K.; Mori, A.; Arai, I.; Yamamoto, H. *Tetrahedron Lett.*, **1986**, *27*, 983; Mori, A.; Ishihara, K.; Yamamoto, H. *ibid.* **1986**, *27*, 987.
   (c) Mori, A.; Ishihara, K.; Arai, I; Yamamoto, H. *Tetrahedron*, **1987**, *43*, 755.
4. (*R*)-(+)-Phenyl-*o*-tolylmethanol, 85% ee, was reported to give $[\alpha]^{25}_D$=+0.38° (*c* 1.0, benzene):
   Seebach, D.; Beck, A. K.; Roggo, S.; Wonnacott, A. *Chem. Ber.* **1985**, *118*, 3673.

List of Publications

I. Parts of the present thesis have been, or to be, published in the following Journals.

Chapter 2. Stereoselective Reduction of Bicyclic Acetals.
A Method for Reductive Generation of Heterocyclic Ring Systems
Kazuaki Ishihara, Atsunori Mori, Hisashi Yamamoto
Tetrahedron Lett. **1987**, *28*, 6613.

Stereoselective Reduction of Bicyclic Acetals.
A Method for Reductive Generation of Heterocyclic Ring Systems
Kazuaki Ishihara, Atsunori Mori, Hisashi Yamamoto
Tetrahedron **1990**, *46*, 4595.

Chapter 3. Not to be published.

Chapter 4. Not to be published.

Chapter 5. Diastereoselective Aldol Synthesis Using Acetal Templates
Kazuaki Ishihara, Hisashi Yamamoto, Clayton H. Heathcock
Tetrahedron Lett. **1989**, *30*, 1825.

Chapter 6. New Stereoselective Propanal/Propanoic Acid Synthons for Aldol Reactions
Ichiro Mori, Kazuaki Ishihara, Clayton H. Heathcock
J. Org. Chem. **1990**, *55*, 1114.

Chapter 7. On the Mechanism of Lewis Acid-Mediated Nucleophilic Substitution Reactions of Acetals.

Ichiro Mori, Kazuaki Ishihara, Lee A. Flippin, Kyoko Nozaki, Hisashi Yamamoto, Paul A. Bartlett, Clayton H. Heathcock

J. Org. Chem. **1990**, in press.

Chapter 8. Stereospecific Cyclization of Vinyl Ether Alcohols.

Facile Synthesis of (-)-Lardolure

Makoto Kaino, Yuji Naruse, Kazuaki Ishihara, Hisashi Yamamoto

J. Org. Chem. **1990**, *55*, 5814.

Chapter 9. Chiral Aryl Grignard Reagents-Generation and Reactions with Carbonyl Compounds

Makoto Kaino, Kazuaki Ishihara, Hisashi Yamamoto

Bull. Chem. Soc. Jpn. **1989**, *62*, 3736.

II. Following publications are not included in this thesis.

1. Reductive Cleavages of α,β-Alkynyl Acetals.

New Route to Optically Pure Propargylic Alcohols

Kazuaki Ishihara, Atsunori Mori, Isao Arai, Hisashi Yamamoto

Tetrahedron Lett. **1986**, *27*, 983.

2. Reductive Cleavages of Chiral Acetals Using Lewis Acid-Hydride System

Atsunori Mori, Kazuaki Ishihara, Hisashi Yamamoto

Tetrahedron Lett. **1986**, *27*, 987.

3. Reductive Cleavages of Homochiral Acetals: Inversion of the Stereoselectivity

Atsunori Mori, Kazuaki Ishihara, Isao Arai, Hisashi Yamamoto

Tetrahedron **1987**, *43*, 755.

III. Review

1. Chiral Synthon and Asymmetric Synthesis

Kazuaki Ishihara, Hisashi Yamamoto

Kagaku **1990**, *45*, 56.

Acknowledgements

The author would like to express his sincere thanks and special gratitude to Professor Hisashi Yamamoto whose encouragement and helpful suggestion have been indispensable to the completion of the present thesis.

He is also indebted to Drs. Keiji Maruoka, Kyoji Furuta, Akira Yanagisawa for their encouragements, practical guidances, and fruitful discussions. Furthermore he would like to thank Dr. Atsunori Mori (Chapters 1 and 2) for informative suggestion.

It is pleasure to express his appreciation to the colleagues, especially Messrs. Ichiro Mori (Chapters 6 and 7), Yuji Naruse (Chapter 8), Isao Arai (Chapter 1), Kyoko Nozaki (Chapter 7), Makoto Kaino (Chapters 8 and 9), and Naoyuki Hanaki (Chapter 4) for their valuable contributions.

And also he wishes to express his special acknowledgement to Professor Clayton H. Heathcock who gave him an opportunity to study at University of California, Berkeley, U. S. A. for the period of June to September 1988. He is also indebted to colleagues of Professor Heathcock's research group.

He is very grateful to the Japan Society for the Promotion of Science for the fellowship of JAPS for Japanese Junior Scientists.

He would finally like to express special thanks to Professors Yusuke Izumi, Shoji Eguchi, Yasuhiko Sawaki, Minamoto Katsumaro for serving on his dissertation committee.