ASYMMETRIC SYNTHESIS USING HOMOCHIRAL ACETAL

ATSUNORI MORI

Department of Applied Chemistry

Nagoya University

1987

ASYMMETRIC SYNTHESIS USING HOMOCHIRAL ACETAL

ATSUNORI MORI

Department of Applied Chemistry
Nagoya University

1987

CONTENTS

CHAPTER 1

INTRODUCTION AND GENERAL SUMMARY

The synthesis of enantiomerically pure compounds is becoming increasingly important for chemists. This is due to the fact that all biological systems interact differently with chiral molecule and their mirror images. For example, while S-configuration asparagine tastes bitter, its R-enantiomer tastes sweet. Only one of the enantiomers of estrone shows hormonal activity. The narcotic properties of the barbituric acid derivative are tied to one stereoisomer; its mirror image causes cramps. The thalidomide tragedy was caused by consumption of the racemic drug, for it was recently demonstrated that , at least in animals, teratogenic activity comes only from the S-configurated Contergan; the R-form leads to no deformities. Thus, for all applications of chemicals, it is essential to have access to either enantiomer. Generally, the synthetic methods include the

four main areas accessible for acquiring enantiomerically pure compounds:

(1) Resolution via enzyme and selective bond formation

(2) Use of chiral starting materials (chiral pool)

(3) Catalytically promoted asymmetric induction

(4) Chiral auxiliary to induce asymmetry and later removed

Among various methodologies as shown above, asymmetric synthesis (3 and 4) has recently become a powerful method in obtaining enantiomerically pure compound because of its high efficiency and selectivity.[1] Especially, it has explosively developed in the last decade. In connection with the area of (3), hydroboration, hydrogenation and epoxidation to prochiral olefins, asymmetric addition to prochiral carbonyl compounds, and various types of C-C bond formation reactions have been extensively studied. Concerning the area of (4), a wide variety of chiral auxiliaries such as oxazolines, hydrazones and sulfoxides are well known. However, the asymmetric reactions using protective group as a chiral auxiliary have not intensely studied. The author has, thus, been interested in the possibility to apply the protective group for a chiral auxiliary.

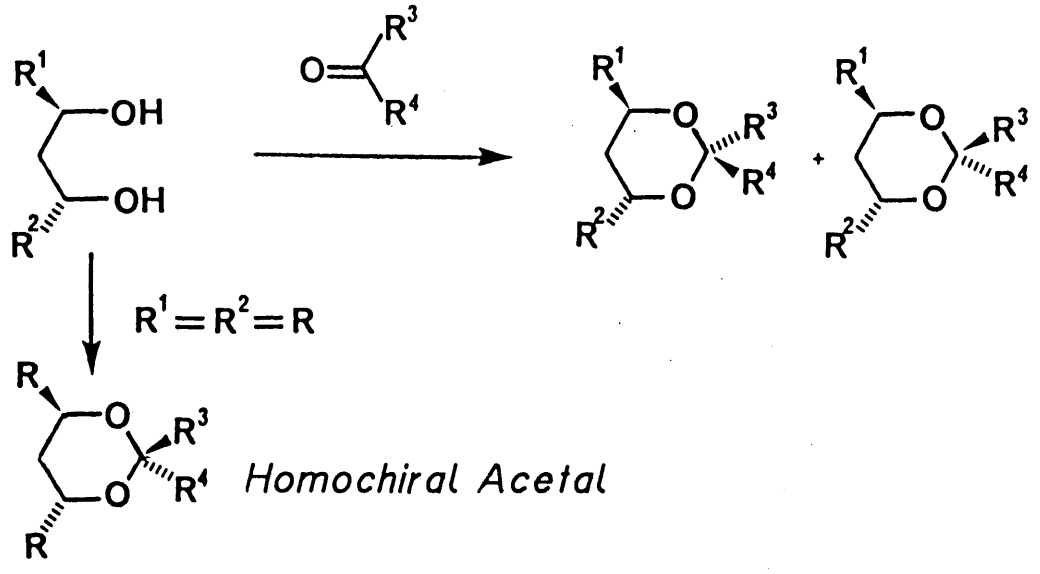
Protective group always plays an essential role in organic synthesis.[2] When a chemical reaction is to be carried out

selectively at one reactive site in a multifunctional compound, other reactive site must be temporarily blocked. Many protective groups have been and being developed for this purpose. A protective group must fulfill a number of requirements. It must react selectively in good yield to give a protected substrate that is stable to the projected reactions. The protected group must be selectively removed in good yield by readily available reagents that do not attack the regenerated functional group. Therefore, the protective group into which the chirality is introduced seems to involve a great potential as a chiral auxiliary.

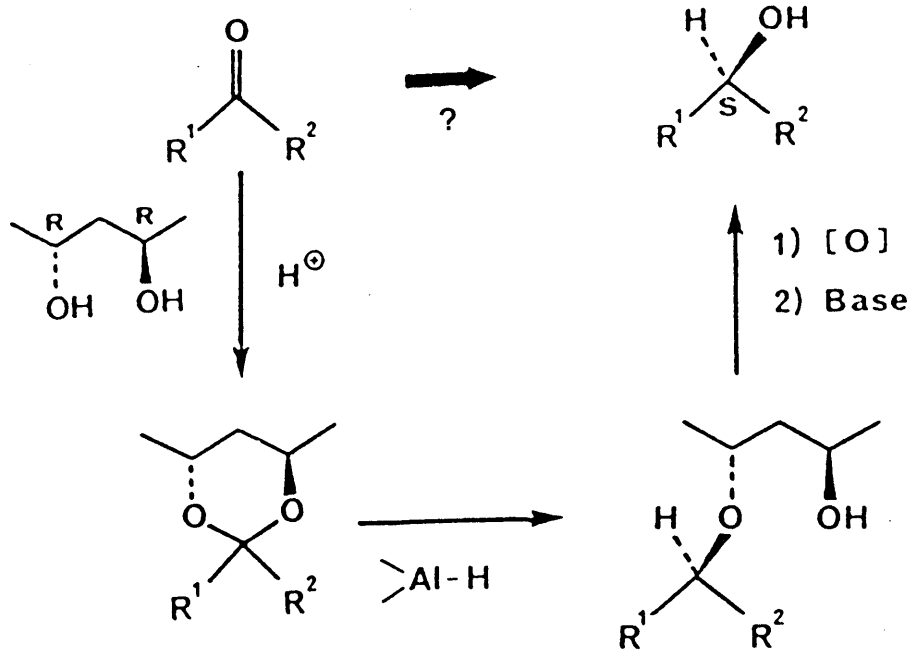
One of the most widely studied processes in asymmetric synthesis is the enantiofacial selection of the prochiral carbonyl compounds via nucleophilic attack.[3] Considerable success has been achieved in obtaining high asymmetric inductions in this process, particularly with modified nucleophilic reagents. However, there still remains a major challenge in obtaining a general methodology. The author's interest of protective groups as a tool for asymmetric synthesis was first focused on the chiral acetal which could be regarded as a chiral synthon of carbonyl compounds.

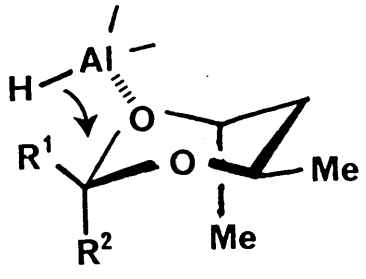
The starting chiral diol should have a C_2-axis symmetry in the molecule. When a cyclic acetal is formed from an unsymmetrical carbonyl compound and a chiral diol, it usually gives a diastereomeric mixture. In contrast, the employment of a chiral diol which has C_2 axis symmetry would results to give a homochiral[4], enantiomerically pure acetal, thus avoiding

troublesome separation of diastereoisomers. This thesis is devoted to the development on new asymmetric synthesis using homochiral acetal.



An initial approach to the asymmetric synthesis using homochiral acetal is focused on the reductive cleavage of the acetal of unsymmetrical ketones. Treatment of the acetal derived from (-)-(2R,4R)-2,4-pentanediol[5] with aluminum hydride reagent which is well known to act as an acid-base complexed reagent,[6] afforded a reduced hydroxyl ether diastereoselectively. Removal of the chiral auxiliary is carried out as follows: Swern oxidation[7] of the hydroxyl group followed by the treatment of the resulting ketone with potassium carbonate to yield the optically active secondary alcohol with high enantiopurity. The high selectivity was observed in the cleavage not only of aromatic ketone acetals but also of aliphatic saturated ketone acetals such as 2-octanone and 1-cyclohexyl ethanone which have been

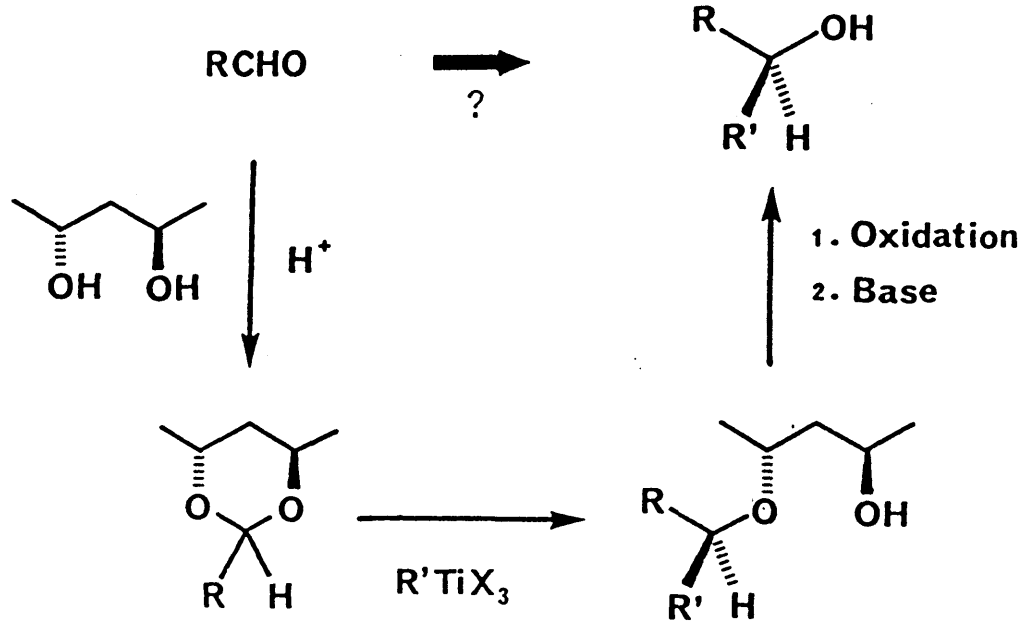


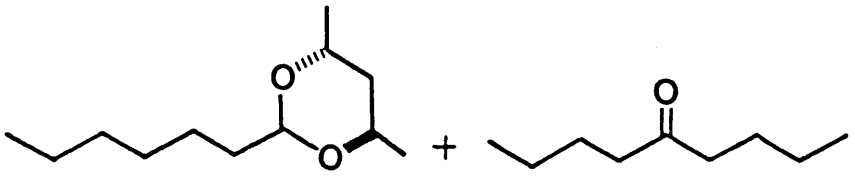


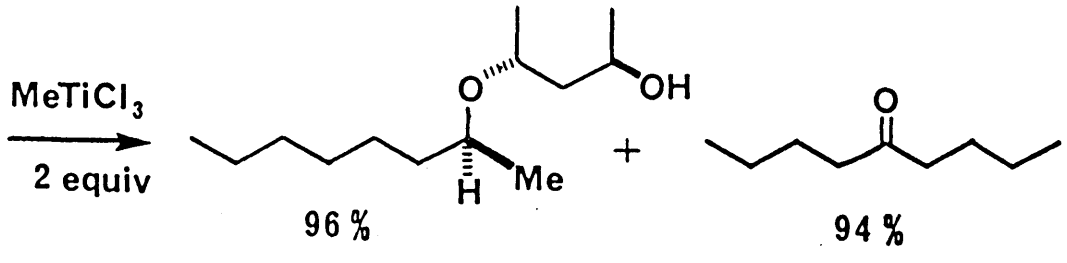
$R^1 > R^2$

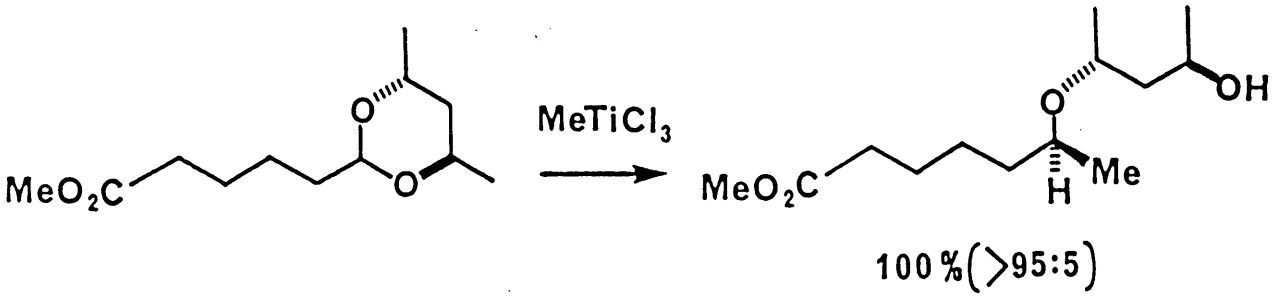
difficult to reduce asymmetrically by previous methods.[3] The observed high selectivity of this process is ascribed to a stereospecific coordination of the organoaluminum reagent to one of the acetal oxygen followed by the hydride attack <u>syn</u> to the cleaved C-O bond. The alkylative cleavage of the acetal of aldehyde with high diastereoselectivity is also realized by the use of alkyltitanium reagent.[8] It is also noteworthy that the

reaction shows a remarkable chemoselectivity[8] between acetal and keto or ester groups. The details of these new asymmetric reactions are summarized in chapter 2.[9]

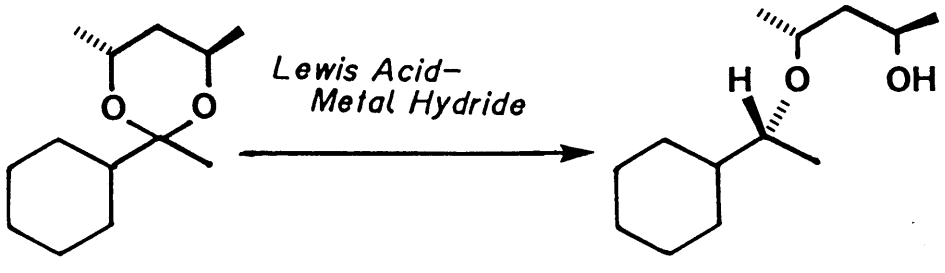


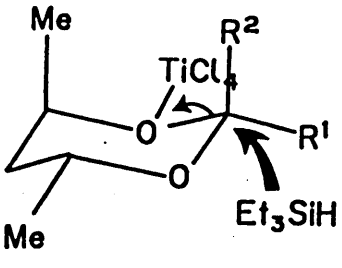




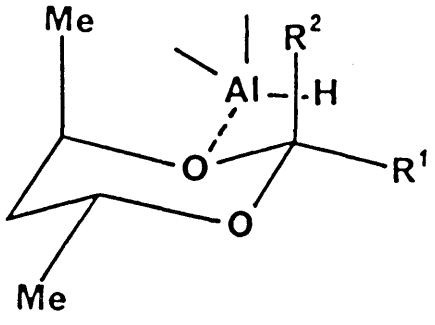


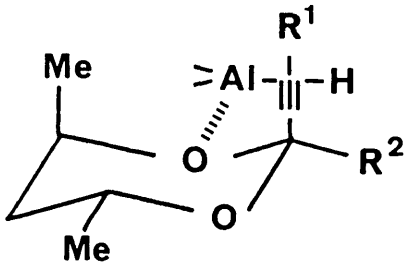
Chapter 3 deals with two independent methods for achieving the different stereochemical outcomes of the reductive cleavage of homochiral acetals compared with the result described in chapter 2. Treatment of the acetal with hydride reagent in the presence of Lewis acid produces the cleaved hydroxyl ether with high diastereoselectivity. In contrast with the result of aluminum hydride reduction in chapter 2, the stereochemistry of the product is found to be the opposite and the reaction is





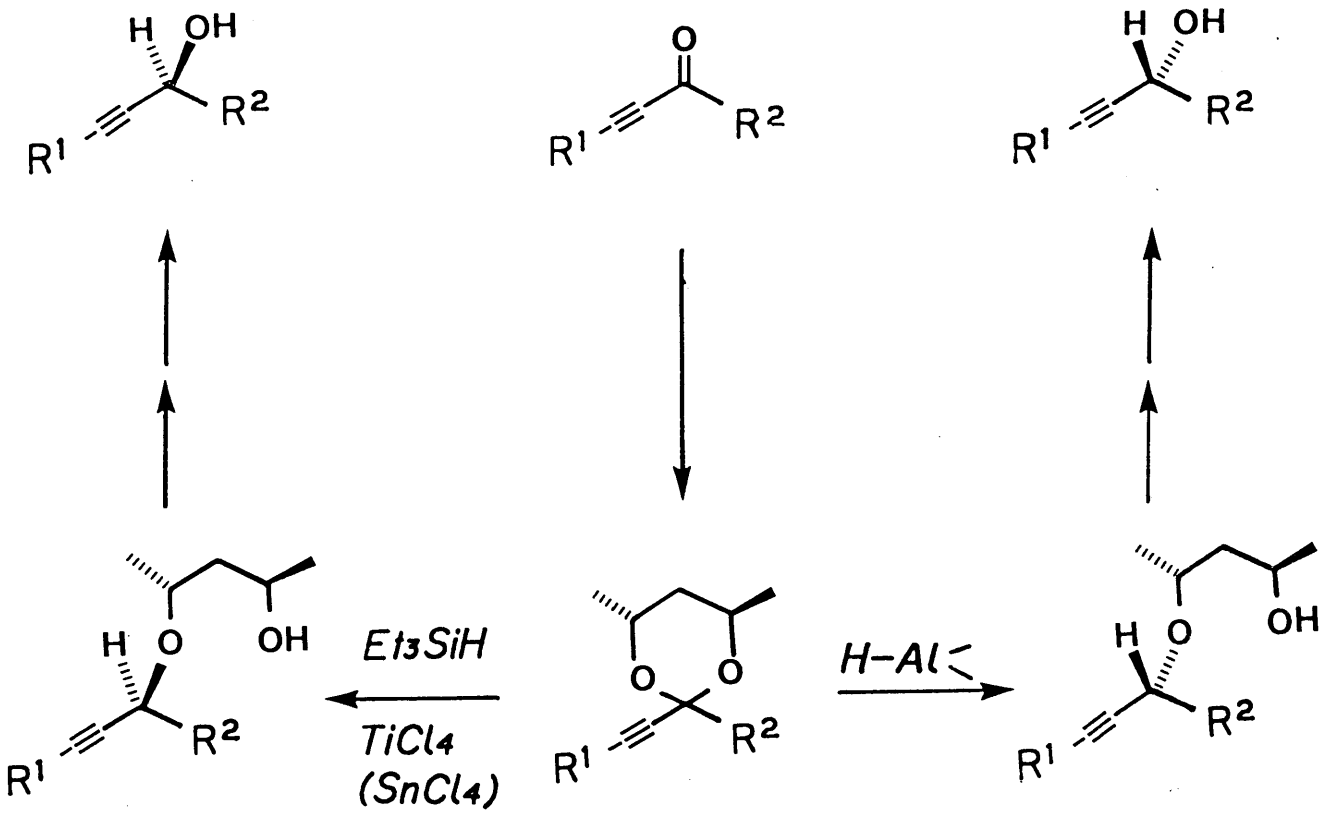
ascribed to proceed via anti attack toward the departing C-O bond of the acetal. Another indirect approach to the same stereochemical result is based on the employment of the acetylenic group in the substrate. The acetal of 2,4-pentanediol would exist as shown below where R^1 is sterically larger than



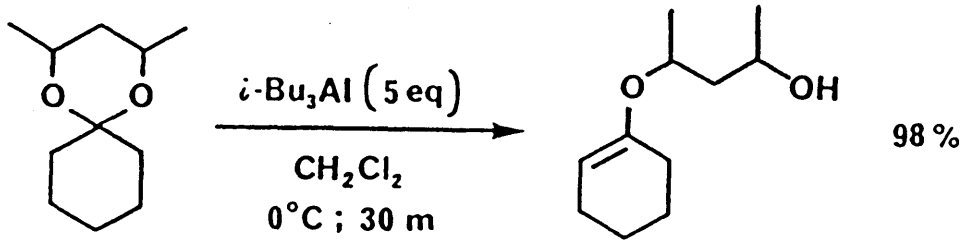


$R^1 > R^2$

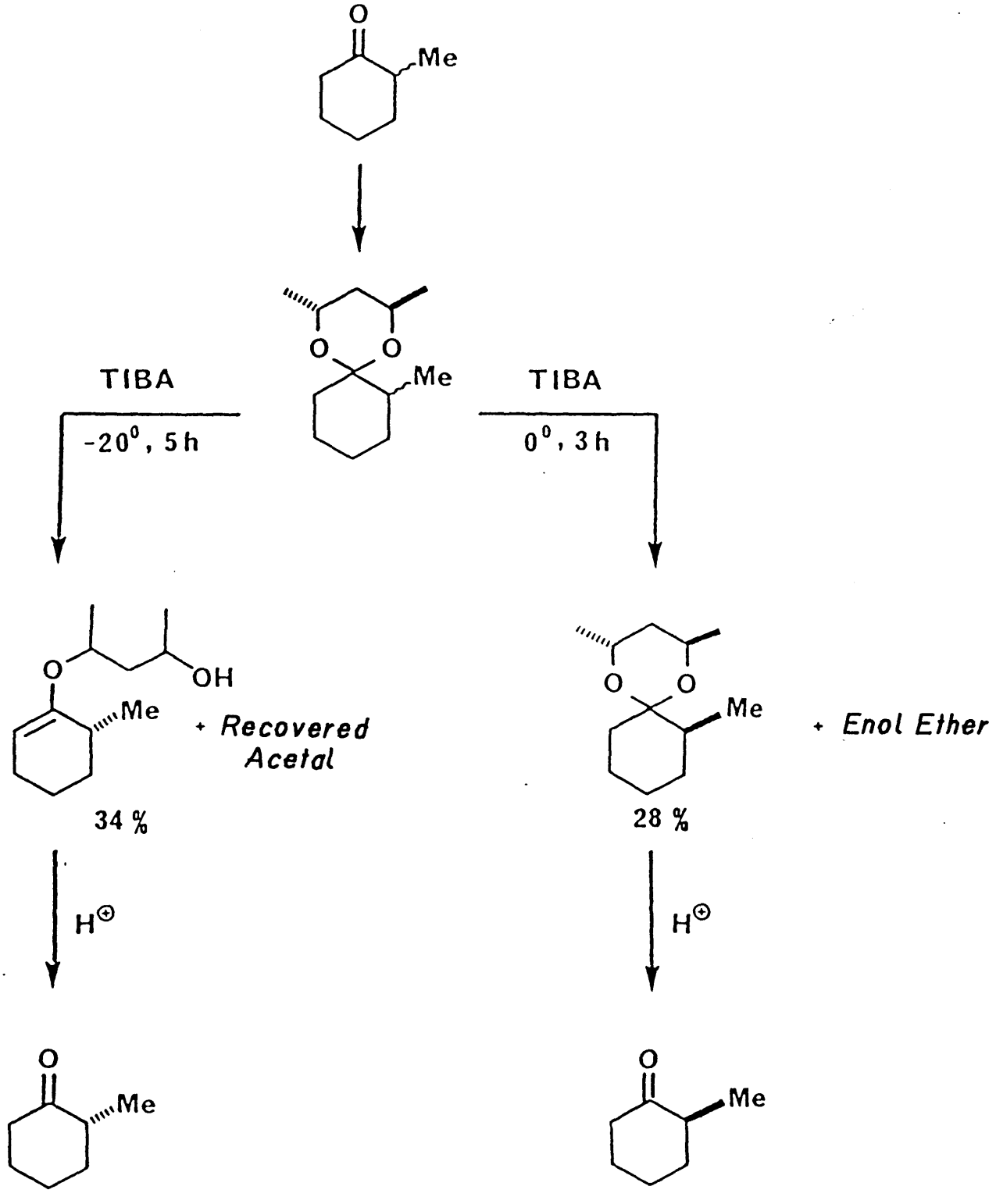
R^2. Whereas the sterically less hindered acetylenic group would occupy the axial position even R^2 is methyl. Indeed, the reaction of acetylenic acetal with aluminum hydride reagent afforded, after removal of chiral auxiliary, the R-alcohol with high stereoselectivity. Therefore, a new method for the preparation of optically active propargylic alcohol is now provided.[10] Furthermore, the reaction of the acetylenic acetal with Lewis acid-hydride system has also afforded the reduced acetal with inversion of the stereoselectivity. Thus, both enantiomer of the propargylic alcohols can be synthesized from the same intermediate.

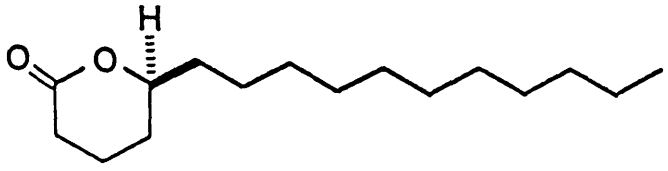


For the aforementioned reactions, it is impossible to recover the auxiliary reagent (immorative process). The following two chapters describe the reactions which enable to regenerate the chiral auxiliary after the asymmetric induction. In chapter 4, a kinetic resolution of racemic ketones via the homochiral acetals using organoaluminum reagent is described.[11] In studying the detail of the cleavages of homochiral acetals, it has been found that the treatment of the acetal of cyclohexanone with excess triisobutylaluminum (TIBA) produces the corresponding



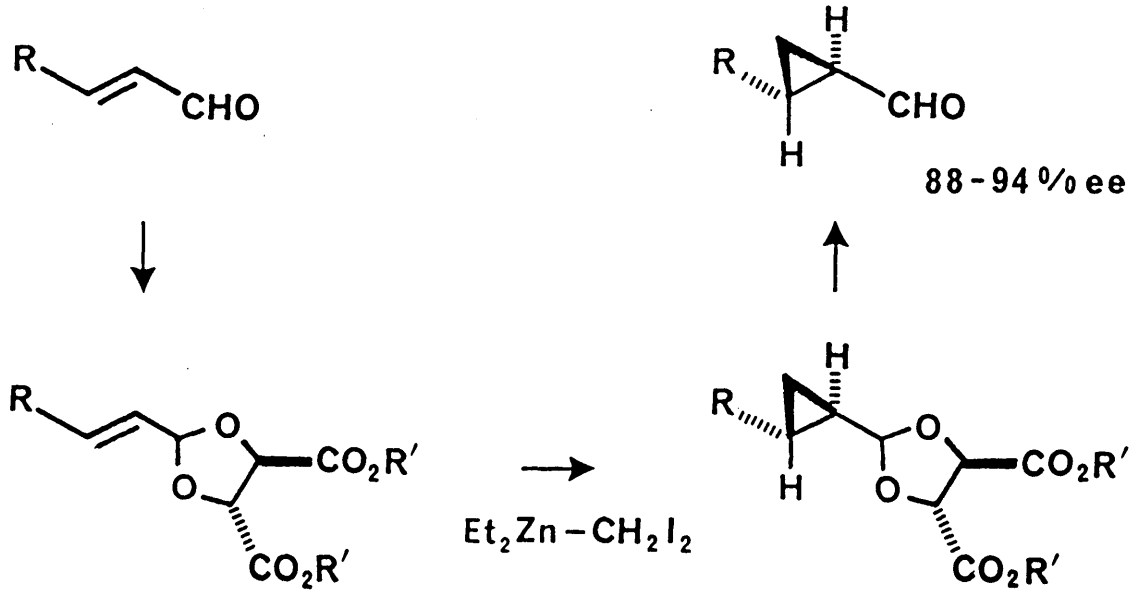
enol ether via abstraction of the hydrogen atom at α-position of the acetal in good yield. When the reaction is carried out in the acetal of the racemic α-substituted ketones, it has also been found that the large rate difference is observed between two diastereoisomers on the stereochemistry at α-position. Thus, when the reaction is carried to some degree of conversion, an enol ether is obtained diastereoselectively along with the recovered acetal. Hydrolysis of the enol ether thus obtained affords the optically pure ketone. Furthermore, by controlling the reaction condition, the recovered acetal is also found to be diastereomerically pure, which is transformed to the corresponding optical pure isomer after mild hydrolysis. The efficiency of this type of kinetic resolution is successfully applied to a short synthesis of optically active (-)-(S)-5-hexadecanolide, feromone of Vespa orientalis.[12]


O
Me
O
O
Me
TIBA
-20°, 5h
TIBA
0°, 3h
O
OH
Me
+ Recovered Acetal
34 %
H⊕
O
Me
O
O
Me
+ Enol Ether
28 %
H⊕
O
Me

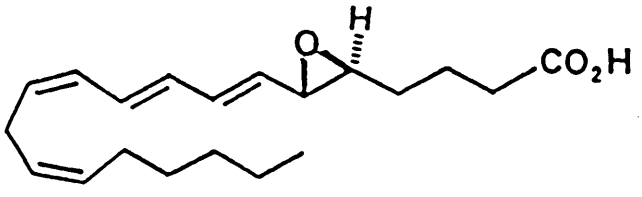


(−)-(S)-5-Hexadecanolide

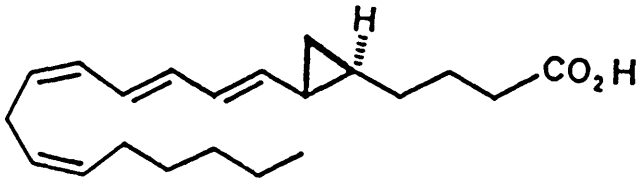
In chapter 5, new asymmetric Simmons-Smith reactions of α,β-unsaturated acetals derived from chiral dialkyl tartrate or (2R,4R)-pentanediol are described.[13] Treatment of the α,β-unsaturated acetal with excess diethylzinc and methylene iodide[14] under mild condition affords the cyclopropane in a reasonable yield with high diastereoselectivity. The acetal group is



readily transformed to the aldehyde (hydrolysis) or to the ester (ozonolysis).[15] Since both enantiomers of tartaric acid esters are readily available in optically pure form, this method allows the synthesis of both enantiomers of cyclopropanes from α,β-unsaturated aldehyde in a predictable manner.[16] An enantioselective synthesis of 5,6-methanoleukotriene A_4, a stable and selective inhibitor of leukotriene biosynthesis is also described.[17,18,19]



Leukotriene A_4



(5R,6R)-5,6-Methanoleukotriene A_4

In conclusion, the present author has contributed to the following points:

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

(2) A novel kinetic resolution of the racemic ketones is explored. The method is based on the selective enolization of the homochiral acetal by triisobutyl-aluminum.

(3) Asymmetric Simmons-Smith reactions using homochiral acetal of tartaric acid derivatives or 2,4-pentanediol are developed. It opened a new route to chiral cyclopropanes.

Additionally, it is remarkable that after the first discovery of the utility of homochiral protective group there are continuous and explosive publications on the asymmetric synthesis using homochiral acetals. For example, Tamura has developed the asymmetric alkylation of α-keto acetal by Grignard reagent. This reaction shows high selectivity in both cyclic and acyclic systems.[20] Similar reactions are also reported by Mioskowski.[21] Asymmetric synthesis of anthracycline antibiotics by Terashima has been realized by using the acetal of tartaric acid derivatives.[22] Seebach and Schreiber have developed the nucleophilic cleavage reaction of acetal derived from β-hydroxy carboxylic acid.[23] In short, present asymmetric reactions using homochiral acetal are going to become one of the important area in organic asymmetric synthesis.[24]

References

1. (a) "Asymmetric Synthesis", Morrison, J. D., Ed.; Academic Press: New York, 1983-1985.
   (b) Seebach, D.; Imwinkelried, R.; Weber, T., In "Modern Synthetic Method, Vol 4"; Schefford, R., Ed.; Springer-Verlag: Berlin, **1986**; p125.
2. For reviews, see: McOmie, J. F. W. "Protective Group in Organic Chemistry"; Plenum Press: New York, 1973; Greene, T. W. "Protective Groups in Organic Synthesis"; Wiley; New York, 1981.
3. For reviews, see: Morrison, J. D.; Mosher, H. S. "Asymmetric Organic Reactions", Prentice-Hall: Englewood Cliffs, N. J., 1971; pp 160-218; Valentine, D.; Scott, J. W. Synthesis, **1978**, 329; Kagan, H. B.; Fiaud, J. C. Top. Stereochem., **1978**, 10, 175; ApSimon, J. W.; Seguin, R. P. Tetrahedron, **1979**, 35, 2797; Noyori, R. Pure & Appl. Chem., **1981**, 53, 2315.
4. Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R., Angew. Chem., Int. Ed. Engl. **1985**, 24, 1; Anet, F. A. L.; Miura, S. S.; Siegel, J.; Mislow, K., J. Am. Chem. Soc., **1983**, 105, 1419.

5. Ito, K.; Harada, T.; Tai, A., Bull. Chem. Soc. Jpn., **1980**, 53, 3367.

6. For reviews, see: Yamamoto, H.; Nozaki, H, Angew. Chem., Int. Ed. Engl., **1978**, 17, 169.; Maruoka, K.; Yamamoto, H.; Ibid., **1985**, 24, 668.

7. Mancuso, A. J.; Swern, D., Synthesis, **1981**, 165.

8. Reviews of organotitanium reagents in organic synthesis: Reetz, M. T., Top. Curr. Chem., **1982**, 106, 1; see also Wiedmann, B.; Seebach, D., Angew. Chem., Int. Ed. Engl., **1983**, 22, 31.

9. Related works on nucleophilic cleavages of homochiral acetals by other groups, see: (a) McNamara, J. M.; Kishi, Y., J. Am. Chem. Soc., **1982**, 104, 7371; (b) Bartlett; P. A., Johnson; W. S., Elliott, J. D., J. Am. Chem. Soc., **1983**, 105, 2088; Johnson; W. S., Elliott; R., Elliott; J. D., Ibid, **1983**, 105, 2904; Elliott, J. D.; Choi, V. M. F.; Johnson, W. S., J. Org. Chem., **1983**, 48, 2294; Choi, V. M. F.; Elliott, J. D.; Johnson, W. S., Tetrahedron Lett., **1984**, 25, 591; Lindell, S. D.; Elliott, J. D.; Johnson, W. S., Ibid., **1984**, 25, 3947; Johnson, W. S.; Crackett, P. H.; Elliott, J. D.; Jagodzinski, J. J.; Lindell, S. D.; Natarajan, S., Ibid., **1984**, 25, 3951; Johnson, W. S.; Edington, C.; Elliott, J. D.; Silverman, I. R., J. Am. Chem. Soc., **1984**, 106, 7588; Johnson, W. S.; Chan, M. F., J. Org. Chem., **1985**, 50, 2600; Elliott, J. D.; Steele, J.; Johnson, W. S., Tetrahedron Lett., **1985**, 26, 2535. (c) Ghribi, A.; Alexakis, A.; Normant, J. F., Tetrahedron Lett., **1984**, 25,

3083. See also: (d) Richter, W. J., J. Org. Chem., **1981**, 46, 5119; Hiyama, T.; Saito, K.; Sato, K.; Wakasa, N.; Inoue, M., Chem. Lett., **1986**, 1471; Yamamoto, Y.; Nishii, S.; Yamada, J., J. Am. Chem. Soc., **1986**, 108, 7116.

10. (a) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M., J. Am. Chem. Soc., **1984**, 106, 6717. (b) Johnson, W. S.; Brinkmeyer, R. S.; Kappor, V. M.; Yarnell, T. M., J. Am. Chem. Soc., **1977**, 99, 8341. (c) Cohen, N.; Lopresti, R. S.; Newkom, C.; Saucy, G., J. Org. Chem., **1980**, 45, 582. (d) Brinkmeyer, R. S.; Kappor, V. M., J. Am. Chem. Soc., **1977**, 99, 8339. (e) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A., J. Am. Chem. Soc., **1980**, 102, 867; Midland, M. M.; Tramontano, A.; Kazubski, A.; Graham, R. S., Tetrahedron, **1984**, 40, 1371.

11. This type of enolization reaction is successfully applied to the asymmetrization of meso ketals: Naruse, Y.; Yamamoto, H., Tetrahedron Lett., **1986**, 27, 1363.

12. Ikan, R.; Gottlieb, R.; Bergmann, E. D.; Ishay, J., J. Insect Physiol., **1969**, 15, 1709.

13. Simmons, H. E.; Cairns, T. L.; Vlauduchick, S. A.; Hoiness, C. M., Org. React., **1973**, 20, 1.

14. Furukawa, J.; Kawabata, N.; Nishimura, J., Tetrahedron, **1968**, 24, 53.

15. Deslongchamps, P.; Atlani, P.; Frèhel, D.; Malaval, A.; Moreau, C., Can. J. Chem., **1974**, 52, 3651.

16. Recent asymmetric synthesis using dialkyl tartrate: (a) Katsuki, T.; Sharpless, K. B., J. Am. Chem. Soc., **1980**, 102, 5976; (b) Haruta, R.; Ishiguro, M.; Ikeda, N.; Yamamoto, H., Ibid., **1982**, 104, 7667; Ikeda, N.; Arai, I.; Yamamoto, H., Ibid., **1986**, 108, 483; See also (c) Seebach, D. in "Modern Synthetic Methods 1980"; Scheffold, D., Ed., Otto Salle Verlag, Frankfurt.

17. Nicolaou, K. C.; Petasis, N. A.; Seitz, S. P., J. Chem. Soc., Chem. Commun., **1981**, 1195.

18. For asymmetric reaction of α,β-unsaturated acetals, see: (a) Fujiwara, J.; Fukutani, Y.; Hasegawa, M.; Maruoka, K.; Yamamoto, H., J. Am. Chem. Soc., **1984**, 106, 5004; Fukutani, Y.; Maruoka, K.; Yamamoto, H., Tetrahedron Lett., **1984**, 25, 5911; Maruoka, K., Nakai, S., Sakurai, M.; Yamamoto, H., Synthesis, **1986**, 129. (b) Mangeney, P.; Alexakis, A.; Normant, J. F., Tetrahedron Lett., **1986**, 27, 3143.

19. The similar cyclopropanation reaction using cyclic ketone acetals is reported independently: Mash, E. A.; Nelson, K. A., J. Am. Chem. Soc., **1985**, 107, 8256; Idem, Tetrahedron Lett., **1986**, 27, 1441; J. Org. Chem., **1986**, 51, 2721.

20. Tamura, Y.; Kondo, H.; Annoura, H.; Takeuchi, R.; Fujioka, H., Tetrahedron Lett., **1986**, 27, 81; Tamura, Y.; Ko, T.; Kondo, H.; Annoura, H.; Fuji, M.; Takeuchi, R.; Fujioka, H., Ibid., **1986**, 27, 2117; see also: Matsumoto, T.; Matsuda, F.; Hasegawa, K.; Yanagiya, M., Tetrahedron, **1984**, 40, 2343.

21. Heitz, M. P.; Gellibert, F.; Mioskowski, C., Tetrahedron Lett, **1986**, 27, 3859.

22. Suzuki, M.; Kimura, Y.; Terashima, S., Chem. Lett., **1985**, 367; Idem, Tetrahedron Lett., **1985**, 26, 6481.

23. Seebach, D.; Imwinkelried, R.; Stucky, G., Angew. Chem., Int. Ed. Engl., **1986**, 25, 178; Schreiber, S. L.; Regan, J., Tetrahedron. Lett., **1986**, 27, 2945; see also Mashraqui, S. H.; Kellogg, R. M., J. Org. Chem., **1984**, 49, 2516.

24. Other papers using homochiral protective groups: Hosokawa, T.; Ohta, T.; Murahashi, S.-I., J. Chem. Soc., Chem. Commun., **1983**, 848; Masaki, Y.; Serizawa, Y.; Nagata, K.; Oda, H.; Nagashima, H.; Kaji, H., Tetrahedron Lett., **1986**, 27, 231; Utaka, M.; Fujii, Y.; Takeda, A., Chem. Lett., **1986**, 1103; Zibuck, R.; Liverton, N. J.; Smith III, A. B., J. Am. Chem. Soc., **1986**, 108, 2451.

CHAPTER 2

NUCLEOPHILIC CLEAVAGE OF HOMOCHIRAL ACETAL USING ORGANOMETALLIC REAGENTS

Abstract - A highly chemo- and stereo-selective cleavage of acetals derived from (-)-(2R,4R)-2,4-pentanediol with organoaluminum and organotitanium reagents has been demonstrated. The reactions proceed under mild conditions with excellent yields and high chemoselectivities to give, after removal of the auxiliary, chiral alcohols of high enantiomeric purities.

The problem of devising general methods for the asymmetric synthesis of chiral, optically active alcohols via nucleophilic additions to carbonyl compounds which are efficient both with regard to the optical and material yield remains a major challenge despite extensive studies in this area for many years.[1] The direct formation of such alcohols with high enantiomeric purities is not possible using classical synthetic reactions, and consequently indirect approaches have been required, e.g. a sequence employing the nucleophilic addition of Main Group organometallics to chiral acetals.[2] Indeed, a number of method for the cleavage of simple acetals have been investigated previously. These include: (a) the reaction that proceeds via the free ketone produced by proton abstraction from a ketal methylene[3]; (b) the nucleophilic opening of a cyclic acetal which takes place in the presence of reagents that can function as Lewis acids.[4,5]

The derivation of the present approach to asymmetric synthesis was based on the following conditions: (1) that the starting chiral alcohol be readily available; (2) that the carbonyl compound be combined with a chiral diol to form a ring of a single diastereoisomer; (3) that the cleavage product be readily convertible by a simple operation to a chiral alcohol. Thus, the acetals of type **1** formed by the reaction of ketones and aldehydes with readily available (-)-(2<u>R</u>,4<u>R</u>)-2,4-pentanediol as potential chiral synthetic equivalents of carbonyl compounds were chosen to investigate.

Reductive cleavage of acetals using aluminum reagents

One of the most widely studied processes for the asymmetric induction of a chiral center into a molecule is the asymmetric reduction of a prochiral ketone. Considerable success has been achieved in obtaining high asymmetric inductions in this process, particularly with modified lithium aluminum hydride reagents.[6] However, one of the major drawbacks of existing methods is that they are effective only for aromatic or α,β-unsaturated ketones. This lack of generality is rather disappointing in view of the importance of the process in organic synthesis. For some time, the supposition that the optically active acetal may be cleaved regio- and stereo-selectively by organoaluminum reagent under proper conditions[7] has been intrigued. Were this found to be the case, this might provide a practical solution to this problem. Scheme 1 illustrates how such a process would proceed.

Table 1 illustrates the results obtained with four different ketone systems under various conditions. Thus, reagent, temperature, and solvent, the three variables in the reduction were explored in detail. Although almost every readily available aluminum hydride was tried, only diisobutylaluminum hydride (DIBAH), Cl_2AlH, and Br_2AlH have satisfactory results.[8] Tetrahydrofuran and other basic solvents were generally found to be unsatisfactory for the reaction. A low reaction temperature gave slightly better selectivities.

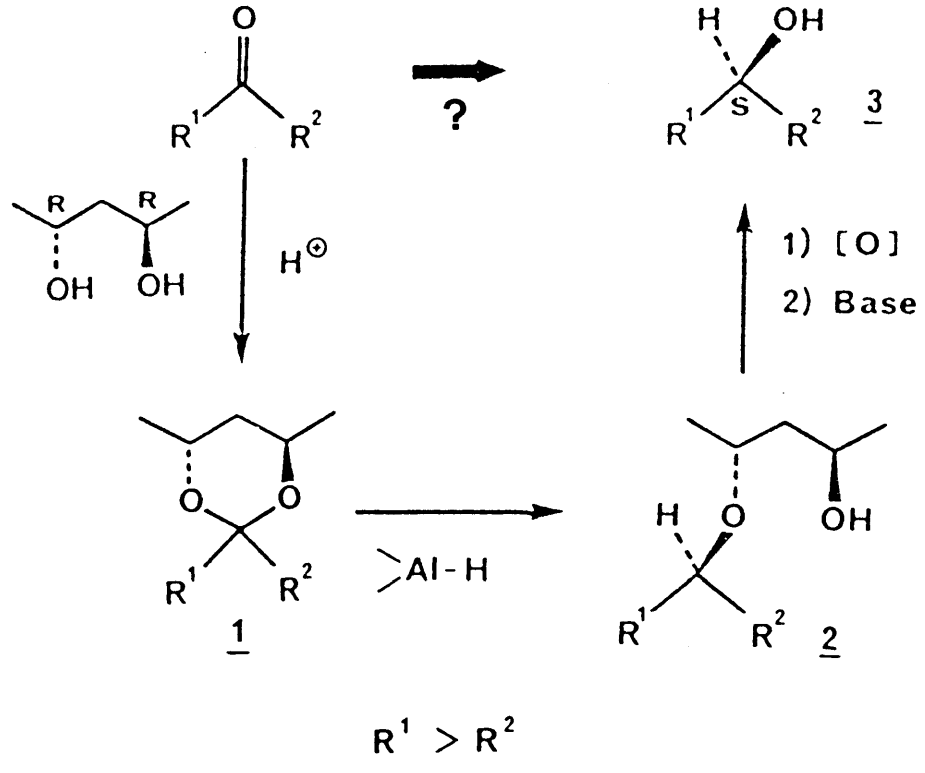
Table 1 Reduction of Chiral Acetals with Hydride Reagents[a]

Acetal 1		Hydride Reagent	Conditions	2		% ee of 3[c,d]
			solvent	Yield	Ratio[b]	
R^1	R^2	(equiv)	(°C, h)		(%)	(confign)
c-Hexyl	Me	DIBAH (5)	CH_2Cl_2 (0, 0.5)	88	13:1	88
		DIBAH (2)	CH_2Cl_2 (0, 1.5)	65	7:1	
		DIBAH (5)	Ether (0, 6)	76	8:1	76
		DIBAH (5)	Toluene (0, 0.5)	74	9:1	
		DIBAH (5)	Hexane (0, 1)	87	12:1	
		Et_2AlH (5)	Toluene (0, 0.5)	88	3:1	
		Et_2AlH (5)	Ether (0, 1.5)	81	8:1	
		Cl_2AlH (6)	Ether (0, 0.5)	98	19:1	92 (S)[f]
		Br_2AlH (6)	Ether (-20, 0.5)	99	23:1	95
n-Hexyl	Me	DIBAH (5)	CH_2Cl_2 (0, 2)	58	3.5:1	55[e]
		Cl_2AlH (6)	Ether (0, 1.5)	73	2:1	
		Br_2AlH (6)	Ether (0, 0.75)	69	4:1	
		Br_2AlH (20)	Ether (-40, 2)	87	4:1	58[e](S)[f]
		Br_2AlH (20)	Ether (-78, 1)	64	8:1	78[e]
Ph	Me	DIBAH (5)	CH_2Cl_2 (0, 1.5)	88	28:1	93
		Br_2AlH (6)	Ether (-78, 1; 0, 0.5)	94	57:1	96 (S)[f]
Ph	n-Pr	DIBAH (5)	CH_2Cl_2 (0, 0.5)	72	20:1	
		Br_2AlH (6)	Ether (-20, 0.5)	92	42:1	94 (S)[f,g]

Legend of the Table 1

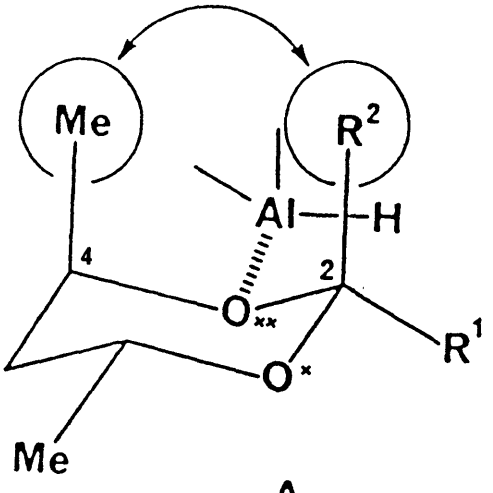
[a]Reduction of the chiral acetal was carried out as described in experimental section. [b]The diastereomeric ratio was determined by GLC on a 20 m PEG-HT capillary column. The reduction product **2** (R^1 = cyclohexyl, R^2 = Me) was also converted into the trimethylsilyl ether, which showed clean separation on GLC. [c]Unless otherwise specified, the optical yield was determined by GLC analysis of (S)-(-)-MTPA esters. See, Dale, J. A.; Dull, D. L.; Mosher, H. S. J. Org. Chem., **1969**, 34, 2543. [d]The alcohols **3** were obtained by the two step sequence from **2** in yields of 70-83%. [e]Determined by ^{1}H NMR analysis of the MTPA derivative in the presence of Eu(fod)$_3$. [f]Optical rotation values of **3** were $[\alpha]^{25}_D$ +4.58° (neat, d = 0.92) for R^1 = cyclohexyl, R^2 = Me; $[\alpha]^{25}_D$ -55.36° (c 0.98, cyclopentane) for R^1 = Ph, R^2 = Me; $[\alpha]^{25}_D$ +5.34° (neat, d = 0.82) for R^1 = n-hexyl, R^2 = Me; $[\alpha]^{25}_D$ -38.41° (c 2.90, benzene) for R^1 = Ph, R^2 = n-Pr. [g]Optical yield after correction for (-)-(2R,4R)-2,4-pentanediol of 93% optical purity.

Scheme 1



Swern oxidation[9] of the resulting alcohol **2** followed by base-catalyzed β-elimination gave the optically pure alcohol **3** in good yield.

Structure **A** shows a view of the aluminum reagent-acetal complex in what appears to be the energetically favorable structure. Thus, the steric effect should influence the reactivity of the oxygen atoms of the acetal function, hence their relative ease of coordination to aluminum metal, and consequently the least sterically congested of several possible

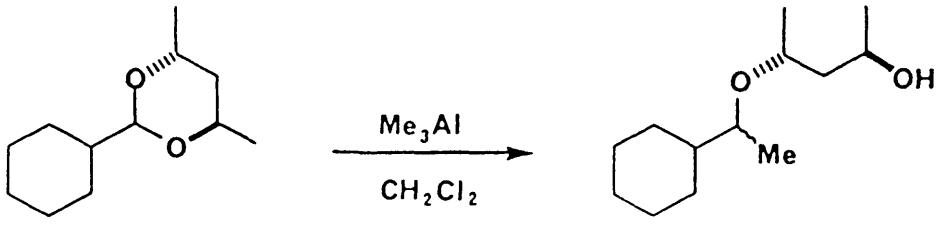


A

structure would appear to be **A.** Furthermore, the C-O* bond in conformer **A** should be shorter than a normal C-O ether bond because it has a partial double-bond character due to the anomeric effect[10], whereas the C-O** bond should be longer than usual because of electron donation from the other oxygen. Such lengthening of the C-O** bond should relieve at least part of the severe 2,4-diaxial interaction of **A.**[11] This transient species can undergo smooth cleavage of the C-O** bond by the attack of hydride ion of aluminum metal from the direction <u>syn</u> to this departing oxygen, which would lead to the <u>S</u> configuration at the resulting ether carbon, as observed.[12]

Alkylic cleavage of acetals

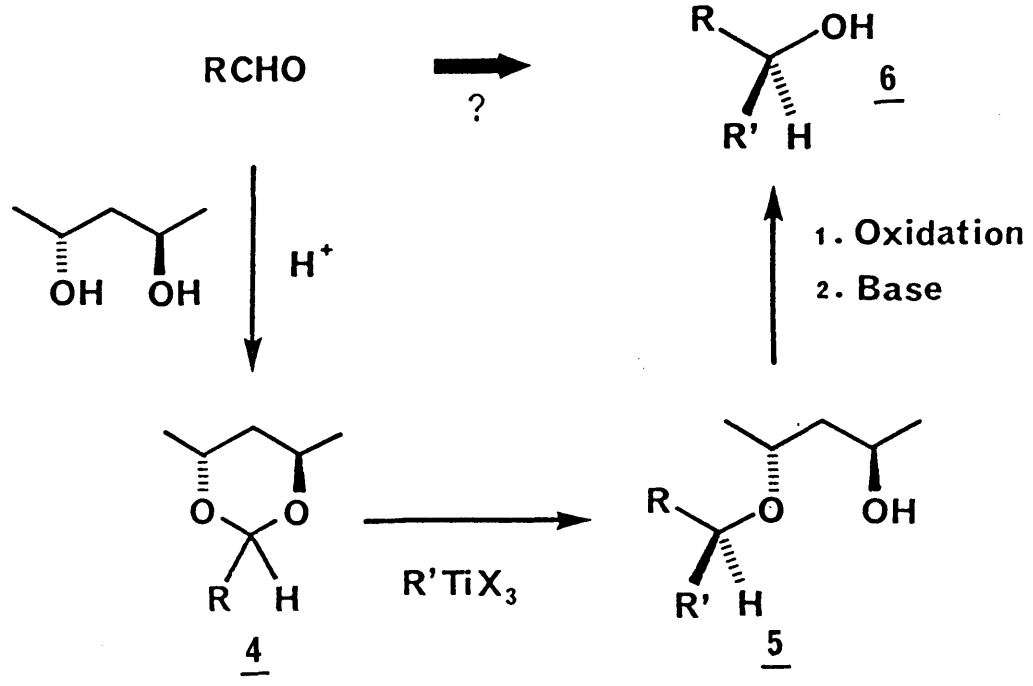
In view of the efficiency of the mild and stereospecific cleavage of chiral acetals by aluminum reagents, the behavior of trialkylaluminum has been studied systematically. It was soon realized that treatment of acetals in dichloromethane with trialkylaluninum leads to a mixture of diastereoisomers. These rather disappointing results are consistent with a common S_N2-type alkylation of organoaluninum reagents in non-polar solvents such as hexane or dichloromethane.[13] The results may be attibuted to the aggregated form of the aluninum reagent.



64% (2:3)

In view of the inefficiency of the aluminum reagent, the behavior of certain anionic organometallic reagents having Lewis acidic character was studied. Of these reagents, the titanium reagent prepared by the reaction of dialkylzinc with titanium tetrachloride was clearly the most effective.[14] The new process is illustrated in Scheme 2.

Scheme 2



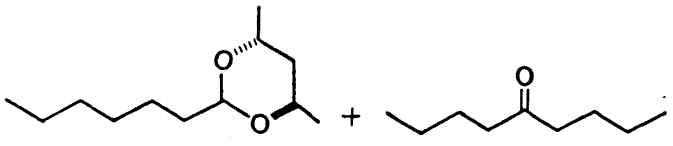
When the chiral acetal **4** was exposed to equimolar amounts of CH_3TiCl_3[15] at -78°C, the corresponding methylated product **5** (R' = Me) was obtained quantitatively. The chiral auxiliary was removed in the manner described previously. Several examples of this transformation are given in Table 2.

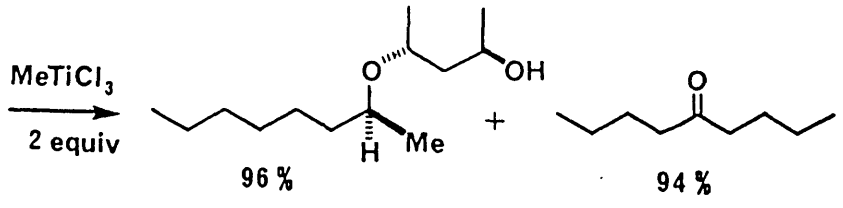
Table 2 Nucleophilic Cleavage of Acetals using Organotitanium Reagents[a]

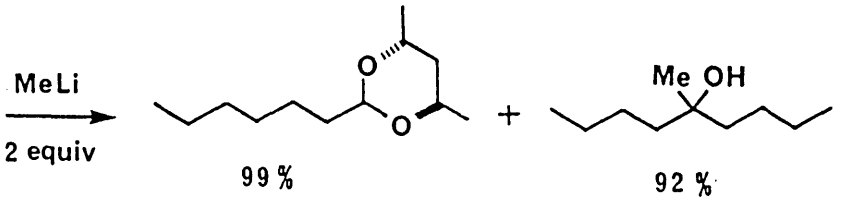
Acetal **4** R	Method	R'	**5** Yield	Ratio[b]	**6** Confign
c-Hexyl	A	Me	100	24:1	S[c]
	B	Me	100	24:1	S[c]
	C	Me	91	32:1	S[c]
	D	n-Bu	92	8:1	S[d]
n-Hexyl	A	Me	93	16:1	S[c]
	C	Me	77	32:1	S[c]
	E	Et	100	4:1	S[e]
	F	Et	100	4:1	S[e]
	D	n-Bu	47	10:1	-
n-Bu	A	Me	81	32:1	-
	E	Et	86	3.5:1	-
Et	D	n-Bu	45	7:1	-
Me	D	n-Bu	34	24:1	-

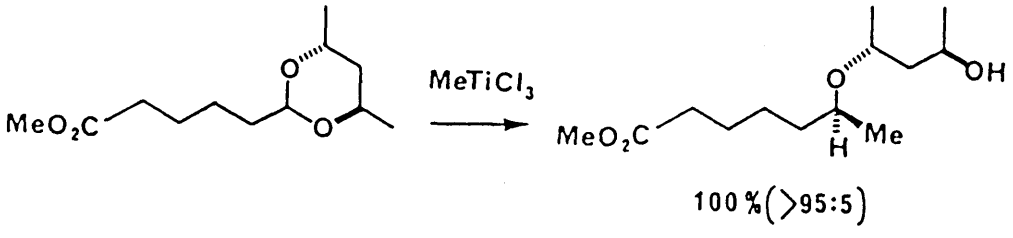
[a]For method A-F, see experimental section. [b]The diastereomeric ratio was determined by GLC on a 25 m PEG-HT capillary column. [c]Determined by comparison with authentic samples which were prepared by reductive cleavage of chiral acetals. [d]$[\alpha]_D$ -8.85° (c 1.10, benzene), see ref 17. [e]$[\alpha]_D$ +6.17° (c 2.35, $CHCl_3$), see ref 18.

It has also been possible to show that the reaction between acetal and titanium reagent is highly chemeoselective[14] and that this is a factor of considerable importance in organic synthesis. Indeed, essentially complete chemoselectivity is observed in the following reactions.



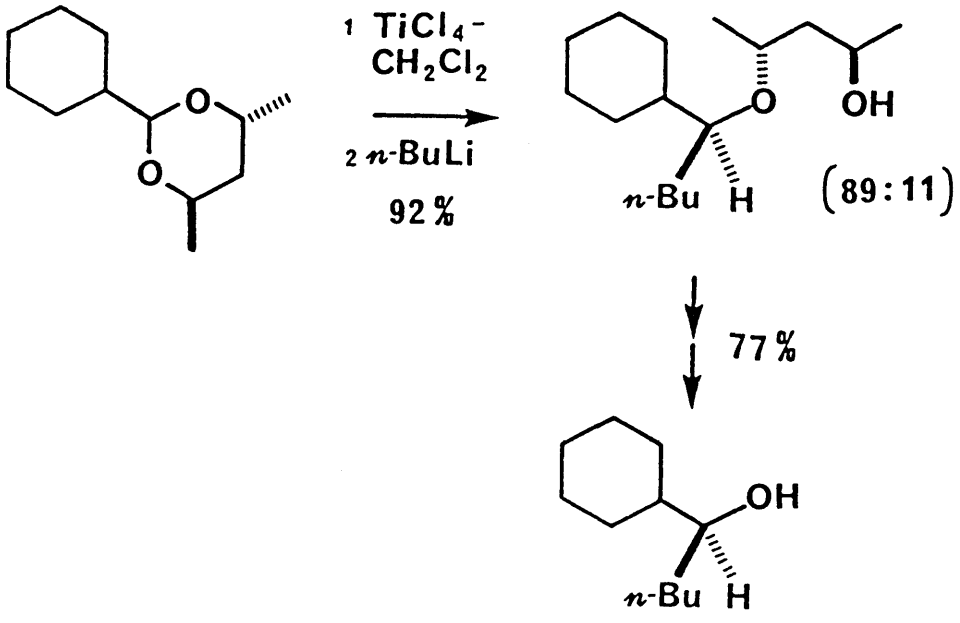






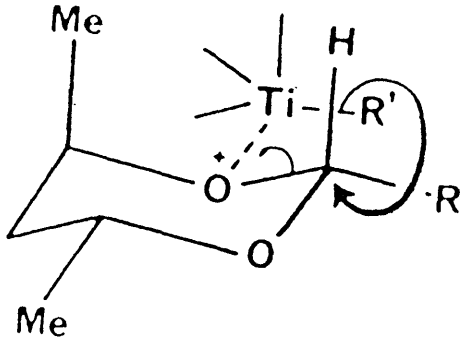
It should also be noted that treatment of **4** (R = c-hexyl) with titanium tetrachloride at low temperature followed by the addition of n-butyllithium at -78°C results in stereoselectivity of 89% with a high chemical yield. The method involves in situ

butyltitanium formation in the presence of dichloromethane and acetal, thus avoiding the troublesome procedure with the preformed butyltitanium trichloride.[16]



A feasible mechanistic explanation for these titanium reagents must be very similar to that of reductive cleavage of acetal as shown in structure **A**. Unfortunately, however, it is not clear that the same model suggested for the transition state of the aluminum reagent is applicable to titanium cases. Thus, the nucleophile approaches the alkyl group from the si-face of the carbonyl (inversion), while hydride was shown to approach from the re-face of the carbonyl, i. e. anti-addition[12]: It should also be pointed out that only one equivalent of titanium

reagent was used in the reaction, thus an intermolecular reaction mechanism may be unlikely. Further study is required before the mechanistic details of these reactions can be fully understood.



In summary, the process described above opens up a practical and highly chemo- and stereo-selective methodology to nucleophilic addition to carbonyl compounds.

Experimental

General: Infrared (IR) spectra were recorded on a Hiachi 260-10 spectrometer. ^{1}H NMR spectra were measured on a JNM-PMX 60 spectrometer. 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. Gas liquid phase chromatographic (GLC) analyses were performed on Hitachi Model 163, 164 or Gasukuro Kogyo Model 370 instruments equipped with a flame ionization detector, using nitrogen as the carrier gas. Mass spectra (MS) were recorded on a Hitachi MU-6L

spectrometer, and exact mass on a Hitachi M-80 spectrometer. Optical rotations were measured on a JASCO DIP-140 digital polarimeter. All experiments were carried out under an atmosphere of dry argon. For thin layer chromatographic (TLC) analysis throughout 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 E, Merck Art 9385. Microanalyses were done at the Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University. In experiments requiring dry solvents, ether and tetrahydrofuran (THF) were distilled from sodium-benzophenone. Benzene, hexane, and toluene were dried over sodium metal. Dichloromethane was distilled from phosphorus pentoxide and stored over 4A molecular sieves. The optical purity of (-)-(2R,4R)-2,4-pentanediol from Wako Pure Chemical Industries Ltd. should be checked before use.[19] Other chemicals were purchased and used as such.

1-cyclohexylethanone: To a solution of cyclohexanecarboxylic acid (25.6 g, 0.200 mol) in dry ether (100 mL) was added methyllithium (312 mL of a 1.28 M ethereal solution, 0.400 mol) dropwise at 0°C. After stirring for 1 h at room temperature, the mixture was poured into 2 N HCl (200 mL). The aqueous layer was extracted twice with ether (100 mL). The combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo* to give the crude product, which was distilled to yield the ketone as a colorless oil (20.4 g): b.p. 73°C (20 Torr); IR (film) 1705 cm^{-1}; ^1H NMR (CCl_4) δ 2.10 (s, 3 H).

Preparation of chiral acetals: *Method I.* A mixture of ketone

(20 mmol), (-)-(2R,4R)-2,4-pentanediol (2.08 g, 20 mmol), and pyridinium p-toluenesulfonate (20 mg) in benzene (20 mL) was heated at reflux for 10 h with continuous azeotropic removal of water. After cooling to room temperature, the mixture was poured into aq. $NaHCO_3$ (20 mL), and the product was extracted twice with ether (20 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Chromatography on silica gel afforded chiral acetal as a colorless oil. 1 (R^1 = c-hexyl, R^2 = Me): 77% yield; TLC, R_f = 0.61 (hexane-ethyl acetate, 5:1); IR (film) 2960, 2915 cm^{-1}; ^1H NMR (CCl_4) δ 3.50-4.27 (m, 2 H), 1.04-1.17 (m, 9 H). Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.21; H, 11.72. 1 (R^1 = n-hexyl, R^2 = Me): 87% yield; TLC, R_f = 0.76 (hexane-ethyl acetate, 5:1); IR (film) 2980, 2950, 2870 cm^{-1}; ^1H NMR (CCl_4) δ 3.57-4.12 (m, 2 H); Anal. Calcd for $C_{13}H_{26}O_2$: C, 72.84; H, 12.23. Found: C, 72.57; H, 12.50.

Method II. A mixture of ketone (10 mmol), triethyl orthoformate (2.12 g, 20 mmol) and p-toluenesulfonic acid (10 mg) in methanol (10 mL) was stirred at 0°C for 2 h. The mixture was poured into aq. $NaHCO_3$ and the product was extracted with ether twice. The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Chromatography on silica gel afforded dimethyl acetal as a colorless oil. The mixture of dimethyl acetal (2.0 mmol), (-)-(2R,4R)-2,4-pentanediol (0.23 g, 2.2 mmol) and pyridinium tosylate (2 mg) in benzene was heated with continuous removal of methanol for 30 min. After cooling to room temperature, the mixture was poured into aq. $NaHCO_3$ and the

product was extracted with ether twice. The organic layers were dried over sodium sulfate and concentrated *in vacuo*. Chromatography on silica gel afforded chiral acetal as a colorless oil. **1** (R^1 = Ph, R^2 = Me): 77% yield from acetophenone; TLC, R_f = 0.62 (hexane-ethyl acetate, 5:10); IR (film) 750, 690 cm^{-1}; ^1H NMR (CCl_4) δ 7.16 (m, 5 H, ArH), 3.16-4.33 (m, 2 H), 1.40 (s, 3 H), 1.13 (m, 6 H); Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.45; H, 9.03. **1** (R^1 = Ph, R^2 = *n*-Pr): 80% yield from butyrophenone; TLC, R_f = 0.63 (hexane-ethyl acetate, 3:1); IR (film) 770, 750, 695 cm^{-1}; ^1H NMR (CCl_4) δ 7.23 (m, 5 H, ArH), 3.30-4.36 (m, 2 H); Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.65; H, 7.69.

Reduction of Chiral Acetal 1 (R^1 = *c*-hexyl, R^2 = Me) using DIBAH: To a solution of diisobutylaluminum hydride (DIBAH, 2.5 mL of a 1 *M* hexane solution) in dry dichloromethane (5 mL) was added dropwise at 0°C the acetal **1** (R^1 = *c*-hexyl, R^2 = Me) (106 mg, 0.50 mmol) and the mixture was stirred there for 30 min. After the excess aluminum reagent was destroyed with cold *dil*. HCl, 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-ethyl acetate, 5:1) to afford the alcohol **2** (R^1 = *c*-hexyl, R^2 = Me) as an oil (94 mg). The diastereomeric ratio was determined by GLC (13:1). TLC, R_f = 0.37 (hexane-ethyl acetate, 3:1); IR (film) 3100-3600 cm^{-1} (br); ^1H NMR (CCl_4) δ 3.03-4.30 (m, 3 H), 2.95 (br, 1 H OH), 0.97-1.20 (m, 9 H); Anal. Calcd for $C_{13}H_{26}O_2$: C, 72.85; H, 12.23. Found: C, 72.72; H, 12.36.

Reduction of 1 (R^1 = c-hexyl, R^2 = Me) using Br_2AlH: Lithium aluminum hydride (57 mg, 1.50 mmol) was added to a solution of aluminum bromide (1.20 g, 4.5 mmol) in dry ether (10 mL) at 0°C for 10 min. To the resulting suspension was added dropwise at -20°C the acetal **1** (212 mg, 1.00 mmol) in dry ether (1 mL), and the mixture was stirred there for 30 min. After the excess of aluminum reagent was decomposed with cold dil. HCl, the product was extracted with ether. Removal of dried solvent left a crude oil which was purified by column chromatography on silica gel (hexane-ethyl acetate, 5:1) to afford the alcohol **2** (R^1 =c-hexyl, R^2 = Me) (212 mg). The diastereomeric ratio of the product was determined by GLC.

The reductive cleavage of other chiral acetals were carried out in a manner described above. The physical properties and analytical data of the alcohols, thus obtained are listed below:

2 (R^1 = n-hexyl, R^2 = Me): TLC, R_f =0.39 (hexane-ethyl acetate, 3:1); IR (film) 3070-3700 cm^{-1} (br); ^1H NMR (CCl_4) δ 3.16-4.23 (m, 3 H), 2.47 (br, 1 H, OH); Anal. Calcd for $C_{13}H_{28}O_2$: C, 72.17; H, 13.04. Found: C, 72.01: H, 13.20.

2 (R^1 = Ph, R^2 = Me): TLC, R_f = 0.33 (hexane-ethyl acetate, 3:1); IR (film) 3100-3700 (br), 750, 690 cm^{-1}; ^1H NMR (CCl_4) δ 7.13 (s, 5H, ArH), 3.10-4.56 (m, 3 H), 2.43 (br, 1 H, OH); Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.11; H, 9.53.

2 (R^1 = Ph, R^2 = n-Pr): TLC, R_f = 0.36 (hexane-ethyl acetate, 3:1); IR (film) 3100-3580 (br), 690 cm^{-1}; ^1H NMR (CCl_4) δ 7.20 (s, 5H, ArH), 3.17-4.50 (m, 3 H), 2.00 (br, 1 H, OH);

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.07; H, 10.40.

Removal of Chiral Auxiliary; Preparation of 1-cyclohexylethanol: To a solution of oxalyl chloride (0.20 mL, 2.2 mmol) in dichloromethane (2 mL) was added DMSO (0.34 mL, 4.8 mmol) in dichloromethane (0.35 mL) at -78°C. The mixture was stirred for 2 min and the alcohol **2** (R^1 = c-hexyl, R^2 = Me) (174 mg, 0.81 mmol) was added. Stirring was continued for an additional 15 min. Triethylamine (0.48 mL, 5.0 mL) was added and the mixture was stirred at -78°C for 5 min and at room temperature for 30 min. Water (10 mL) was added and aqueous layer was extracted with dichloromethane. The dried organic layers were concentrated *in vacuo*. The crude ketone thus obtained was dissolved in methanol (10 mL) and treated with K_2CO_3 (1.38 g, 10 mmol) and the suspension was stirred at room temperature for 12 h. The mixture was diluted with water and the product was purified by column chromatography on silica gel (hexane-ethyl acetate, 5:1) to give 1-cyclohexylethanol as a colorless oil (84 mg, 81 %), identical with an authentic sample.

Preparation of Chiral Acetals from Aldehydes. The acetal 4 (R = c-hexyl): The mixture of cyclohexanecarbaldehyde (2.24 g, 20 mmol), (-)-(2*R*,4*R*)-2,4-pentanediol (2.29 g, 22 mmol) and *p*-toluenesulfonic acid (20 mg) in benzene (20 mL) was heated at reflux for 3 h with continuous azeotropic removal of water. After cooling to room temperature, the mixture was poured into aqueous $NaHCO_3$ (20 mL) and extracted with ether. Organic layer was dried over sodium sulfate and concentrated *in vacuo*.

Chromatography on silica gel (hexane-ethyl acetate, 30:1) afforded the chiral acetal **4** (R = c-hexyl) as a colorless liquid (3.72 g, 94%): bp 50-53°C (0.9 torr); IR (film) 2990, 2950, 2870 cm^{-1}; ^1H NMR δ 3.53-4.57 (m, 3 H), 1.07-1.33 (m, 6 H); Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.52; H, 11.34.

Synthesis of other chiral acetals from the corresponding aldehydes and (-)-(2R,4R)-2,4-pentanediol were carried out in a manner described above. The physical properties and analytical data of these acetals were listed below.

4 (R = n-hexyl): 79% yield; TLC, R_f = 0.58 (hexane-ethyl acetate, 3:1); IR (film) 2920, 2840 cm^{-1}; ^1H NMR (CCl_4) δ 4.73 (m, 1H), 3.50-4.45 (m, 2 H); Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 71.62; H, 12.41.

4 (R = n-Bu): 68% yield; TLC, R_f = 0.58 (hexane-ethyl acetate, 3:1); IR (film) 2920, 2840 cm^{-1}; ^1H NMR (CCl_4) δ 4.47 (m, 1 H), 3.50-4.46 (m, 2 H); MS Found: m/z 172.1433. Calcd for $C_{10}H_{20}O_2$: M 172.1463.

4 (R = Et): 73% yield; bp 59-62°C (28 Torr); IR (film) 2970, 2925, 2850 cm^{-1}; ^1H NMR (CCl_4) δ 4.62 (t, J = 5 Hz, 1 H), 3.50-4.45 (m, 2 H); MS Found: m/z 144,1152. Calcd for $C_8H_{16}O_2$: M 144.1150.

4 (R = $(CH_2)_4$COOMe): 61% yield; TLC, R_f = 0.54 (hexane-ethyl acetate, 1:1); IR 1730 cm^{-1}; ^1H NMR (CCl_4) δ 4.70 (br, 1 H), 3.45-4.40 (m, 2 H), 3.57 (s, 3 H, OCH_3); Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.70; H, 9.51.

Preparation of chiral acetal 4 (R = Me): The mixture of

ethyl vinyl ether (0.96 mL, 10 mmol), (-)-(2R,4R)-2,4-pentanediol (1.04 g, 10 mmol) and p-toluenesulfonic acid (10 mg) in dry ether (10 mL) was stirred at room temperature for 1 h. The mixture was poured into aq. $NaHCO_3$ and the product was extracted with pentane. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. Chromatography on silica gel (pentane-ether, 10:1) afforded the chiral acetal **4** (R = Me) as a colorless oil (0.87 g, 67%): bp 138°C (760 Torr); IR 2960, 2950, 2850 cm^{-1}; ^1H NMR (CCl_4) δ 4.83 (q, J = 5 Hz, q), 3.40-4.40 (m, 2 H); MS Found: m/z 130.0963. Calcd for $C_7H_{14}O_2$: 130.0994.

Reaction of chiral acetal 4 (R = c-hexyl) using trimethylaluminum: To a solution of trimethylaluminum (1.25 mL of 2 M hexane solution) in dichloromethane (2.5 mL) was added a solution of **4** (R = c-hexyl) (99 mg, 0.5 mmol) in dichloromethane (0.5 mL) at 0°C. The resulting mixture was stirred at 0°C for 30 min, at room temperature for 3.5 h, and at 40°C for 1.5 h. The mixture was then poured into cold dil. HCl and extracted with dichloromethane. Evaporative concentration followed by column chromatography on silica gel (hexane-ethyl acetate, 5:1) furnished the alcohol **5** (R = c-hexyl, R' = Me) (69 mg). The diastereomeric ratio was substantiated by GLC to be 2:3.

General Methods for Nucleophilic Cleavages of Chiral Acetals Using Organotitanium Reagents:

Method A: To a solution of dimethylzinc (0.18 mL of a 1.4 M hexane solution, 0.25 mmol) in dry dichloromethane (5 mL) was added $TiCl_4$ (0.50 mL of 1 M dichloromethane solution, 0.50 mmol) at -78°C. The chiral acetal (0.50 mmol) was added at -78°C and

the mixture was stirred there for 30 min. The solution was poured into water and the product was extracted with ether. Organic layers were dried over sodium sulfate and concentrated *in vacuo*. Chromatography on silica gel afforded the product as an oil. The diastereomeric ratio was determined by GLC.

Method B: To a solution of dimethylzinc (0.50 mmol) in dichloromethane was added $TiCl_4$ (0.50 mmol) at -78°C. The chiral acetal (0.50 mmol) was added at -78°C and the mixture was stirred there for 30 mim.

Method C: To a solution of dimethylzinc (0.25 mmol) in dichloromethane was added $TiBr_4$ (0.183 g, 0.50 mmol) at -78°C. The acetal was added at -78°C and the mixture was stirred there for 30 min.

Method D: To a solution of acetal (0.50 mmol) in dichloromethane was added $TiCl_4$ (0.50 mmol) at -78°C. *n*-butyllithium (0.62 mL of a 1.61 M hexane solution, 1.00 mmol) was added at the same temperature and the mixture was stirred there for 30 min.

Method E: To a solution of acetal (0.50 mmol) in dichloromethane was added a solution of $TiCl_4$ (0.50 mmol) at -78°C. Diethylzinc (0.45 mL of a 1.1 *M* hexane solution, 0.50 mmol) was added at -78°C and the mixture was stirred there for 30 min.

Method F: To a solution of acetal (0.50 mmol) in dry dichloromethane was added a solution of $TiBr_4$ (0.50 mmol) at -78°C. Diethylzinc (0.50 mmol) was added and the mixture was stirred there for 30 min.

The physical property and analytical data of **5** were listed below.

5 (R = c-hexyl, R' = n-Bu): TLC, R_f = 0.37 (hexane-ethyl acetate, 5:1); IR (film) 3030-3630 cm^{-1} (br); ^1H NMR (CCl_4) δ 3.40-4.30 (m, 2 H), 3.03 (m, 1 H), 2.58 (br, 1 H, OH); Anal. Calcd for $C_{16}H_{32}O_2$: C, 77.58; H, 13.02. Found: C, 77.42; H, 13.18.

5 (R = n-hexyl, R' = Et): TLC, R_f = 0.45 (hexane-ethyl acetate, 3:1); IR (film) 3050-3610 cm^{-1} (br); ^1H NMR (CCl_4) δ 3.00-4.23 (m, 3 H), 2.27 (br, 1 H, OH); Anal. Calcd for $C_{14}H_{30}O_2$: C, 72.99; H, 13.13. Found: C, 72.72; H, 13.40.

5 (R = n-hexyl, R' = n-Bu): TLC, R_f = 0.52 (hexane-ethyl acetate, 3:1); IR(film) 3050-3610 cm^{-1} (br); ^1H NMR (CCl_4) δ 3.03-4.27 (m, 3 H), 2.60 (br, 1 H, OH); Anal. Calcd for $C_{16}H_{34}O_2$: C, 74.36; H, 13.26. Found: C, 74.25; H, 13.37.

5 (R = n-Bu, R' = Me): TLC, R_f = 0.31 (hexane-ethyl acetate, 3:1); IR (film) 3030-3600 cm^{-1} (br); ^1H NMR (CCl_4) δ 3.20-4.27 (m, 3 H), 2.47 (br, 1 H, OH); Anal. Calcd for $C_{11}H_{24}O_2$: C, 70.16; H, 12.85. Found: 69.93; H, 13.08.

5 (R = n-Bu, R' = Et): TLC, R_f = 0.44 (hexane-ethyl acetate, 3:1); IR (film) 3040-3610 cm^{-1} (br); ^1H NMR (CCl_4) δ 2.97-4.13 (m, 3 H), 2.37 (br, 1 H, OH); Anal. Calcd for $C_{12}H_{26}O_2$: C, 71.23; H, 12.95. Found: C, 70.96; H, 13.22.

Chemoselective Reaction of Acetal 4 (R = n-hexyl) in the Presence of 5-Nonanone: To a solution of $MeTiCl_3$ (2.0 mmol) in dichloromethane was added a mixture of the acetal **4** (R = n-hexyl) (0.20 g, 1.0 mmol) and 5-nonanone (0.142 g, 1.00 mmol) at -78°C.

The mixture was stirred there for 30 min. Extractive isolation, removal of the dried solvent, and chromatography on silica gel (hexane-ethyl acetate, 5:1) afforded 0.207 g of 5 (R = n-hexyl, R' = Me) (96%) and 0.133 g of 5-nonanone (94%).

To the mixture of **4** (R = n-hexyl) (0.50 mmol) and 5-nonanone (0.5 mmol) in ether (5 mL) was added methyllithium (0.78 mL of a 1.28 M ether solution, 1.00 mmol) at 0°C. The mixture was stirred at 0°C for 15 min. Extractive workup and chromatography on silica gel gave **4** (R = n-hexyl) (99 mg, 99%) and 5 methyl-5-nonanol (73 mg, 92 %).

Chemoselective Reaction of Acetal in the Presence of Ester Function: To a solution of $MeTiCl_3$ (1.00 mmol) in dichloromethane (5 mL) was added the acetal **4** (R = $(CH_2)_4COOMe$) at -78°C. The mixture was stirred there for 30 min. Extractive isolation, removal of the dried solvent and chromatography on silica gel (hexane-ethyl acetate, 1:1) afforded **5** (R = $(CH_2)_4COOMe$, R' = Me) (0.127 g, 100%) as a sole product. TLC, R_f = 0.37 (hexane-ethyl acetate, 1:1); IR (film) 3070-3700 (br), 1730 cm^{-1}; ^1H NMR (CCl_4) δ 3.57 (s, 3 H), 3.16-4.27 (m, 3 H), 2.43 (br, 1 H, OH); Anal. Calcd for $C_{13}H_{26}O_4$: C, 63.37; H, 10.66. Found: C, 63.26; H, 10.77. The diastereomeric ratio was substantiated by GLC to be 20:1.

References

1. Solladié, G. In Asymmetric Synthesis, Vol. 2, J. D. Morrison Ed., pp 157-199, Academic Press, New York, 1983.
2. A part of this work was published in a communication form: Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. Tetrahedron Lett., **1983**, 24, 4581.; Mori, A.; Maruoka, K.; Yamamoto, H. Ibid., **1984**, 25, 4421. For other recent result in this area, see (a) McNamara, J. M.; Kishi, Y. J. Am. Chem. Soc., **1982**, 104, 7371. (b) Bartlett, P. A.; Johnson, W. S.; Elliott, J. D. Ibid., **1983**, 105, 2088.; Johnson, W. S.; Elliott, R.; Elliott, J. D. Ibid., **1983**, 105, 2904.; Elliott, J. D.; Choi, V. M. F.; Johnson, W. S. J. Org. Chem., **1983**, 48, 2294.; Choi, V. M. F.; Elliott, J. D.; Johnson, W. S. Tetrahedron Lett., **1984**, 25, 591.; (c) Ghribi, A.; Alexakis, A.; Normant, J. F. Ibid., **1984**, 25, 3083.
3. Holland, H. L.; Jahngir Tetrahedron Lett., **1983**, 24, 1577.; Ho, T.-L. Synthetic Commun., **1983**, 13, 769.
4. Barbot, F.; Miginiac, P. J. Organomet. Chem., **1979**, 170, 1.; Mallory, R. A.; Rovinski, S.; Kohen, F.; Scheer, I. J. Org. Chem., **1967**, 32, 1417.; Zakharkin, L. I.; Knorlina, I. M. Bull. Acad. Sci. USSR Engl. Transl., **1959**, 2156.
5. Normant and his co-worker reported their elegant results of acetal cleavages using BF_3 associated organocopper and cuprate reagents, see Ghribi, A.; Alexakis, A.; Normant, J. F. Tetrahedron Lett., **1984**, 25, 3075, 3079, 3083.

6. For a general review, see Grandbois, E. R.; Howard, S. I.; Morrison, J. D. In Asymmetric Synthesis, Vol. 2, Morrison, J. D. Ed., pp 71-91, Academic Press, New York, 1983; see also Morrison, J. D.; Mosher, H. S., Asymmetric Organic Reactions, Prentice-Hall, Englewood Cliffs, N. J., 1971; Valentine, D.; Scott, J. W. Synthesis, **1978**, 329.; Kagan, H. B.; Fiaud, J. C. Top. Stereochem., **1978**, 10, 175.; ApSimon, J. W.; Seguin, R. P. Tetrahedron, **1979**, 35, 2797.; Noyori, R. Pure & App. Chem., **1981**, 53, 2315.

7. Yamamoto, H.; Maruoka, K. J. Am. Chem. Soc., **1981**, 103, 4186.

8. Aluminum hydrides, especially dichloroaluminum hydride were shown to be an excellent reagent for the cleavage of acetals, see Eliel, E. L. Record of Chemical Progress, **1961**, 22, 129.; Eliel, E. L.; Martin, R. J. L.; Nasipuri, D. Org. Synth., **1973**, Coll. Vol. 5, 175.; Daignault, R. A.; Eliel, E. L. Ibid., **1973**, Coll. Vol. 5, 303.

9. Mancuso, A. J.; Swern, D. Synthesis, **1981**, 165.

10. Deslongchamps, P., "Stereoelectronic Effects in Organic Chemistry" Pergamon Press, Oxford, 1983.

11. The use of 1,3-dioxanes as the acetal substrate is essential for obtaining excellent diastereoselectivity in the present study. For example, the reduction of other acetals, 2-phenyl-2,4,5-trimethyl-1,3-dioxolane and 2-cyclohexyl-2,4,5-trimethyl-1,3-dioxolane, with $LiAlH_4/AlCl_3$ was previously reported to give the corresponding hydroxyl ethers in 5 and 50 % diastereomeric excess, respectively; Richter, W. J., J.

Org. Chem., 1981, 46, 5119. See also ref. 2b.

12. The reaction should proceed via a planar, sp^2-hybridized oxocarbonium ion.

13. Ozawa, S.; Itoh, A.; Oshima, K.; Nozaki, H. Tetrahedron Lett., 1979, 2909.

14. Reviews of organotitanium reagents in organic synthesis: Reetz, M. T. Top. Curr. Chem., 1982, 106, 1.; Wiedmann, B.; Seebach, D. Angew. Chem., Int. Ed. Engl., 1983, 22, 31.

15. Reetz, M. T.; Westermann, J.; Steinbach, R. Angew. Chem., Int. Ed. Engl., 1980, 19, 900.

16. Prepared from $TiCl_4$ and Bu_2Zn, see Reetz, M. T.; Steinbach, R.; Wenderoth, B. Synth. Commun., 1981, 11, 261.

17. (R)-(+)-1-cyclohexyl-1-pentanol, 22.5% ee, was reported to give $[\alpha]_D$ +2.7° (c, 10.7, benzene), Seebach, D.; Klinowski, H.-O.; Bastani, B.; Crass, G.; Daum, H.; Dorr, H.; DuPreez, N. P.; Ehrig, V.; Langer, W.; Nussler, C.; Oei, H.-A.; Schmidt, M. Helv. Chim. Acta, 1977, 60, 301.

18. Lit. $[\alpha]_D$ = +9.6° (c 8.3, $CHCl_3$) for (S)-(+)-3-nonanol; Mukaiyama, T.; Hojo, K. Chem. Lett., 1976, 893.

19. In some cases, the diol should be recrystallized from ether, see Ito, K.; Harada, T.; Tai, A. Bull. Chem. Soc. Jpn., 1980, 53, 3367.

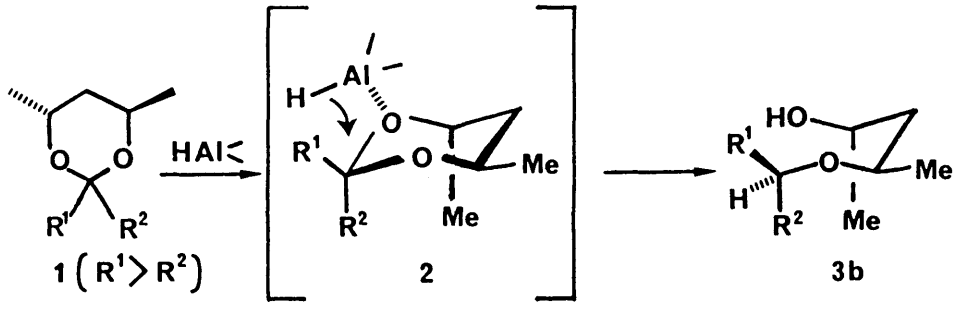
CHAPTER 3

REDUCTIVE CLEAVAGES OF HOMOCHIRAL ACETALS: INVERSION OF THE STEREOSELECTIVITY

ABSTRACT - Reductive cleavages of homochiral acetals using Lewis acid-hydride systems and of alkynyl acetals using organoaluminum reagents are described. Stereochemical outcomes are found to be the opposite compared with results on the aluminum hydride reduction of the acetal described in chapter 2.

In chapter 2, the diastereoselective cleavages of homochiral acetals derived from the condensation of unsymmetrical ketones and (-)-(2R,4R)-2,4-pentanediol to give, after removal of chiral auxiliary, optically active alcohols with high enantiopurities are demonstrated. The observed high diastereoselectivity was ascribed to a stereospecific coordination of the organoaluminum reagent to one of the acetal oxygen followed by the hydride attack syn to the cleaved carbon-oxygen bond (Scheme 1).[1]

Scheme 1



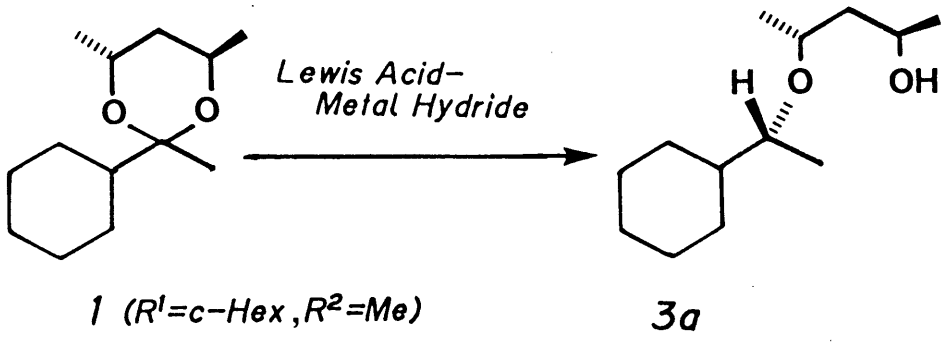
From the beginning of the studies on the acetal cleavage reaction, the author has been interested in the possibility to achieve for inverting the stereochemical outcome of hydride attack to the acetal group, which, if successful, would provide a method to give both enantiomers from a single chiral starting acetal. The approach to this enterprise was first focused on the Lewis acid catalyzed hydride attack anti to the departing oxygen atom. In fact, Johnson and his co-workers reported that the cleavage of the homochiral acetal with organosilicon reagents in the presence of Lewis acids such as titanium(IV) chloride was

taken place via anti attack of the reagent.[2] Thus, the combination of Lewis acid and hydride reagent should also result the desired anti selectivity. Another indirect approach to this problem came from the consideration that homochiral acetal **1** would exist as conformer **2** where R^1 is sterically larger than R^2, whereas the employment of the sterically less hindered acetylenic group would result to occupy the axial position even R^1 is methyl. Furthermore, since the optically pure propargylic alcohols have been recognized as important synthetic intermediates for a variety of natural products, it is synthetically important to provide a general method for the preparation of this class of compounds.[3] Herein, reductive cleavages of homochiral acetals by the combined use of Lewis acids and silyl hydride reagents are described and the selective cleavage of acetals of alkynyl ketones which provide a new method for the synthesis of optically pure propargylic alcohols after removal of chiral auxiliary is also disclosed.[4]

Reductive cleavages of homochiral acetal using Lewis acid-hydride systems: In 1962 the reagent combination of triethylsilane-zinc chloride was reported to reduce noncyclic acetals and ketals to ethers.[5] It was also reported that the reaction of the acetal with trimethylsilane in the presence of catalytic amount of trimethylsilyltrifluoromethane sulfonate gave a reduced ether by Noyori.[6] These papers encouraged the author to explore the possibility on the selective cleavage of the homochiral acetal of 2,4-pentanediol by using Lewis acid-hydride system.

Some results of the reactions of the acetal derived from 1-cyclohexyl ethanone and (-)-(2R,4R)-2,4-pentanediol with various Lewis acids and hydride reagents were shown in Table 1 (Scheme 2). In dramatic contrast to the previous results with

Scheme 2



1 (R^1=c-Hex, R^2=Me) *3a*

dibromoaluminum hydride reagent, the stereochemical outcome of the reaction was found to be the opposite: the reaction proceeds from the Si-face of the carbonyl. The diastereomeric ratio was determined by gc analysis of the cleaved ether which showed a clear base line separation of the two peaks. The minor peak was identical with the previously obtained (S)-isomer from aluminum method. Among the various combination of Lewis acids and hydride reagents examined, the addition of triethylsilane to the mixture of the acetal and titanium (IV) chloride at low temperature found to be the most effective. The inverse addition (titanium (IV) chloride to the mixture of acetal and triethylsilane) also gives a similar diastereoselectivity, however, almost a 1:1 diastereomeric mixture was obtained from the reaction using the premixed reagent of trietylsilane and titanium (IV) chloride.

Boron trifluoride etherate also showed the high diastereoselectivity with high chemical yield. The use of aluminum chloride or tin (IV) chloride as a Lewis acid gave the low selectivities. Interestingly, the reaction with t-butylmagnesium chloride in the presence of titanium (IV) chloride was also effective as a hydride source.[7]

Table 1. Reductive cleavage of the acetal **1**

(R^1 = c-Hex, R^2 = Me)

Lewis acid (equiv)	Hydride reagent (equiv)	Condition °C , h	3 Yield (%)	3 Ratio **3a:3b**
$TiCl_4$ (1.2)	Et_3SiH (1.2)	-78 , 0.5	85	98:2
$SnCl_4$ (1.0)	Et_3SiH (1.0)	-78 , 0.5 -20 , 2.0	93	65:35
$AlCl_3$ (1.2)	Et_3SiH (1.2)	-78 , 8.0	69	66:34
BF_3OEt_2 (1.0)	Et_3SiH (1.0)	-78 , 5.0 -20 , 15.0	93	93:7
$TiCl_4$ (1.2)	^tBuMgCl(5.0)[a]	-78 , 1.0	76	94:6

[a] A 0.82 M ether solution titrated prior to use.

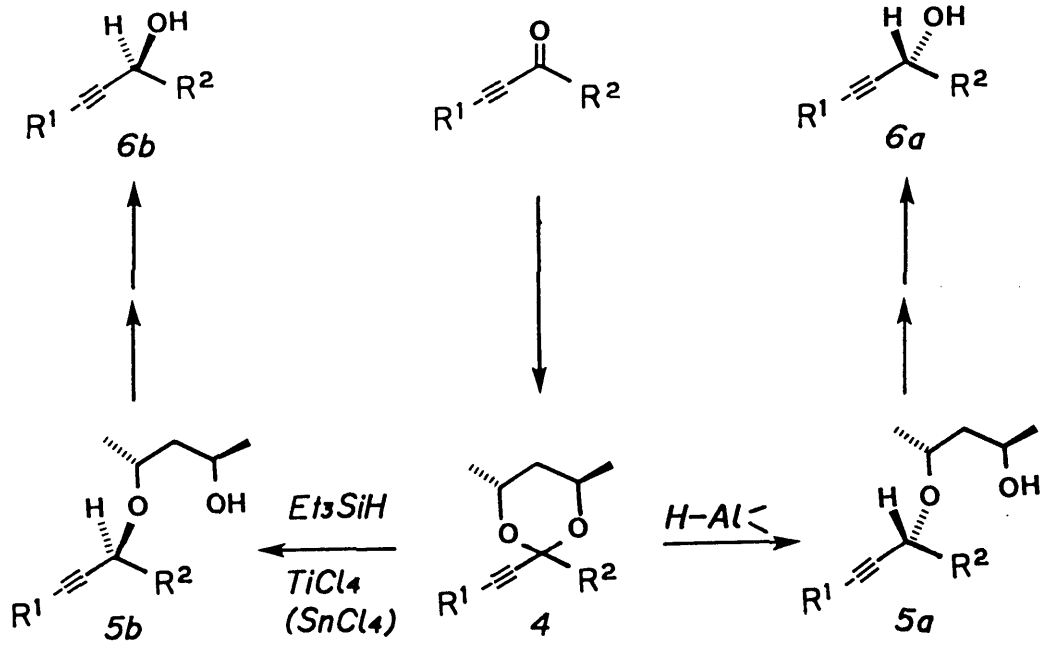
The reactions of the acetals of other ketones are summarized in Table 2. The selectivity was improved by lowering the reaction temperature. The reaction of aromatic acetal, however, afforded a complex mixture. The moderate selectivities were realized by the use of tin (IV) chloride as a Lewis acid. It should be noted that the reaction is highly chemoselective.[8] Thus, the acetal of ethyl levulinate which has acetal and ester group in the molecule, gave the corresponding ether in good yield with high chemo- and diastereoselectivities.

Table 2. Cleavage of various acetals with triethylsilane

1		Lewis acid	Condition	3	
R^1	R^2	(equiv)	^oC , h	Yield (%)	Ratio **3a:3b**
Hex	Me	$TiCl_4$ (1.2)	-78 , 1.5	97	88:12
		$TiCl_4$ (1.2)	-90 , 0.5	76	93:7
Ph	Me	$SnCl_4$ (1.2)	-78 , 0.5	24	81:19
			-40 , 1.5		
$(CH_2)_2$-COOEt	Me	$TiCl_4$ (1.2)	-78 , 1.0	85	94:6

Reductive cleavage of α,β-alkynyl acetal: The sequence of the reaction was summarized in Scheme 3. Reduction of the acetal was carried out with excess organoaluminum reagents such as

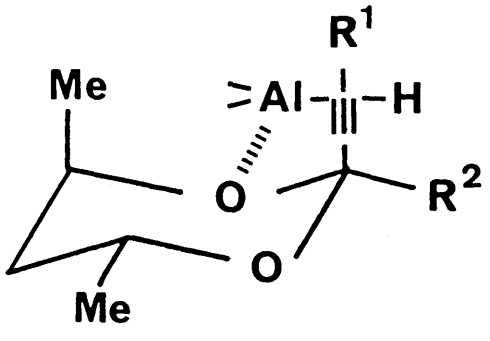
Scheme 3



diisobutylaluminum hydride (DIBAH) and dibromoaluminum hydride (Br_2AlH). The diastereomeric ratio of the cleaved ether 5 was determined by gc analysis, which showed a baseline separation of two isomers. Especially noteworthy is the easy separation of isomers by simple column chromatography on silica gel. Thus, the optically pure propargylic alcohol was obtained after removal of

chiral auxiliary by the previously reported manner (oxidation followed by the base treatment). The optical purity of the obtained propargylic alcohols was confirmed to be pure by the measurement of specific rotation and gc analysis of the corresponding (+)-MTPA esters.[9]

Table 3 shows the results of the cleavage of some alkynyl acetals. Both DIBAH and Br_2AlH were equally effective for the cleavage reaction. It should be noted that the carbinol **6a** shows (R)-configuration. Thus, sterically less hindered alkynyl group should occupy the axial position in the six-membered transition state **7** as shown below. As the steric bulkness of R^2 group is getting larger, diastereoselectivity of the cleavage reaction was improved.



The reaction of the acetal **4** with triethylsilane in the presence of Lewis acid ($TiCl_4$ or $SnCl_4$) could also inverse the streoselectivity compared with the case using aluminum hydrides to afford the corresponding ether **5b** with the ratio of 96:4.

Table 3. Reduction of the alkynyl acetals **4**

4		Reagent	Conditions	5	
R^1	R^2	(equiv)	°C , h	Yield (%)	Ratio **5a:5b**
Bu	Me	DIBAH (2)	0 , 6	68	85:15
		DIBAH (4)	0 , 1	80	93:7
		DIBAH (6)	0 , 1	90	96:4
		Br_2AlH (2)	-20 , 5	53	50:50
		Br_2AlH (4)	-20 , 3	99	68:32
		Br_2AlH (6)	-20 , 3	100	93:7
Bu	Et	DIBAH (4)	0 , 1	93	97:3
		Br_2AlH (6)	-20 , 5	98	98:2
Me	^{i}Bu	Br_2AlH (6)	-20 , 4	99	98:2
Ph	Me	DIBAH (6)	0 , 2	86	90:10
		Br_2AlH (6)	-20 , 2	92	90:10
Ph	Et	Br_2AlH (6)	-20 , 2	99	95:5
Me	^{c}Hex	Br_2AlH (6)	-20 , 1	98	99:1

In conclusion, two independent methods were now established to achieve the stereoselective route to the (R)-alcohol. The method described herein provides methodology for the synthesis of optically active alcohols which have never been synthesized by the previous procedure. Taken together with the previous procedure, selective synthesis of either (R)- or (S)-alcohols from the same acetal was realized. Furthermore, a new method is established for the stereocontrolled sythesis of optically active propargylic alcohols and the resulting (R)-alcohol **6** may be converted to the corresponding saturated (R)-alcohol after hydrogenation of triple bond.

Experimental Section

General. Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrometer. ^{1}H NMR spectra were measured on a JNM-PMX 60 spectrometer. 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. Optical rotations were measured on a JASCO DIP-140 digital polarimeter. Gas liquid phase chromatographic (GC) analyses were performed on Hitachi164 instruments equipped with 25-m PEG-HT capillary column and a flame ionization detector, using nitrogen as a carrier gas. All experiments were carried out under an atmosphere of dry argon. For thin layer chromatographic (TLC) analyses throughout

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 E, Merck Art 9385. Microanalyses were accomplished at the Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University. In experiments requiring dry solvents, ether and tetrahydrofuran (THF) were distilled from sodium-benzophenone. Benzene, hexane, and toluene were dried over sodium metal. Dichloromethane was distilled from phosphorus pentoxide and stored over 4A molecular sieves. (-)-(2R,4R)-2,4-pentanediol was purchased and used after recrystallization from dry ether[10]; $[\alpha]^{24}_{D}$ -41.2° (c 9.99, $CHCl_3$). Other chemicals were purchased and used as such.

Preparation of the chiral acetal 1: The acetals 1 were synthesized in the manner described previously.[1] The physical property and analytical data of the acetal 1 (R^1 = $(CH_2)_2COOEt$, R^2 = Me) is as follows: $[\alpha]^{23}_{D}$-36.73° (c 1.05, $CHCl_3$); IR (neat) 2960, 2930, 1730, 1435, 1050, 905 cm^{-1}; ^1H NMR (CCl_4) δ 3.73 (q, J = 6.8 Hz, 2 H), 0.90 (s, 3 H), 0.83 (t, J = 6.8 Hz, 3 H); Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.58; H, 9.63.

General procedure for the reductive cleavage of the acetal 1 with Et_3SiH-$TiCl_4$: To a solution of the acetal 1 (0.5 mmol, 0.099 g) in 3 mL of dichloromethane was added titanium (IV) chloride (0.6 mmol, 0.6 mL of 1 M dichloromethane solution) at -78°C. After stirring there for 10 min, triethylsilane (0.6 mmol, 0.096 mL) was added and stirring was continued for 30 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. Removal of the solvent in vacuo afforded the crude product which was treated with potassium fluoride (0.2 g) in 3 mL of methanol for 2 h to remove the silyl group of the product. The resulting mixture was poured into water and the product was extracted with ether. The organic layers were dried over anhydrous sodium sulfate, concentrated in vacuo and purified by column chromatography on silica gel (hexane-ether, 5:1) to give **3** in 85% yield as a colorless oil. Gc analysis (130°C) showed two peaks with the ratio of 98:2, and the minor peak was identical with previously obtained (S)-isomer: t_R = 15.0 (minor) and 15.8 (major) min. The reactions of the acetal **1** with other Lewis acids were carried out in the similar manner described above. The results of gc analyses of acetals **3** were listed below: **3** (R^1 = n-hexyl, R^2 = Me; 115°C); t_R = 11.4 (minor) and 12.3 (major) min. **3** (R^1 = Ph, R^2 = Me; 150°C); t_R = 10.9 (minor) and 14.0 (major) min. The physical property and analytical data of **3** (R^1 = $(CH_2)_2COOEt$, R^2 = Me) is as follows; Gc (180°C) t_R = 9.4 (minor) and 10.2 (major) min; IR (neat) 3760-3000 (br), 2960, 2920, 1720, 1470, 975 cm^{-1}; ^1H NMR (CCl_4) δ 4.03 (q, J = 6.8 Hz, 2 H), 1.20 (t, J = 6.8 Hz, 3 H), 1.12 (d, J = 6.0 Hz, 3 H); Anal. Calcd for $C_{12}H_{24}O_4$: C, 62.04; H, 10.04. Found: C, 62.26; H, 10.19.

Preparation of α,β-alkynyl acetal 4: Acetals **4** were prepared from α,β-alkynyl ketones[3] and (-)-(2R,4R)-2,4-pentanediol in the

presence of catalytic amount of pyridinium tosylate.[1] The physical properties and analytical data of the acetal **4** were listed below.

4 (R^1 = Me, R^2 = n-Bu): 78% yield. $[\alpha]^{25}_D$ +8.86° (c 1.10, $CHCl_3$) TLC, R_f = 0.55 (hexane-EtOAc, 5:1); IR (neat) 2930, 2860, 2230, 1363 cm^{-1}; ^1H NMR (CCl_4) δ 3.80-4.58 (m, 2 H), 2.03-2.60 (m, 2 H), 1.43 (s, 3 H); Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.00; H, 10.78.

4 (R^1 = n-Bu, R^2 = Et): 81% yield; $[\alpha]^{25}_D$ +10.1° (c 1.01, $CHCl_3$); TLC, R_f = 0.56 (hexane-EtOAc, 5:1) ; IR (neat) 2970, 2930, 2870, 2210 cm^{-1}; ^1H NMR (CCl_4) δ 3.73-4.57 (m, 2 H), 2.00-2.67 (m, 2 H); Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.76; H, 10.97.

4 (R^1 = Ph, R^2 = Me): 91% yield; $[\alpha]^{24}_D$ +10.3° (c 1.14, $CHCl_3$); TLC, R_f = 0.53 (hexane-EtOAc, 5:1); IR (neat) 2980, 2940, 2230, 1140 cm^{-1}; ^1H NMR (CCl_4) δ 7.07-7.64 (m, 5 H, ArH), 3.87-4.67 (m, 2 H), 1.57 (s, 3 H); Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.19; H, 7.92.

4 (R^1 = Ph, R^2 = Et): 92% yield; $[\alpha]^{25}_D$ +9.41° (c 1.06, $CHCl_3$); TLC, R_f = 0.65 (hexane-EtOAc, 5:1); IR (neat) 2980, 2930, 2880, 2230 cm^{-1}; ^1H NMR (CCl_4) δ 7.07-7.57 (m, 5 H, ArH), 3.87-4.64 (m, 2 H); Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.57; H, 8.33.

4 (R^1 = Me, R^2 = i-Bu): 38% yield; $[\alpha]^{25}_D$ +2.41° (c 1.02, $CHCl_3$); TLC, R_f = 0.63 (hexane-EtOAc, 5:1); IR (neat) 2950, 2890, 2270, 1380 cm^{-1}; ^1H NMR (CCl_4) δ 3.70-4.54 (m, 2 H), 1.84 (s, 3 H); Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.04; H,

10.74.

4 (R^1 = Me, R^2 = cyclohexyl): 63% yield; $[\alpha]^{25}_D$ +7.07° (c 1.03, $CHCl_3$); TLC, R_f = 0.57 (hexane-EtOAc, 5:1); IR (neat) 2930, 2860, 2250, 1140 cm^{-1}; ^1H NMR (CCl_4) δ 3.67-4.57 (m, 2 H), 1.83 (s, 3 H); Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23. Found: C, 76.15; H, 10.31.

General procedure for the reduction of chiral acetal 4 (R^1 = n-Bu, R^2 = Me) using DIBAH. To a solution of the acetal **4** (105.2 mg, 0.5 mmol; R^1 = n-Bu, R^2 = Me) in dry dichloromethane (3 mL) was added diisobutylaluminum hydride (DIBAH, 3 mL of an 1 M hexane solution) at 0°C. After being stirred for 1 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, 8:1) to afford the alcohol **5** (R^1 = n-Bu, R^2 = Me) as an oil (yield 90%). The diastereomeric ratio was determined by Gc (**5a/5b** = 96/4); t_R = 9.4 (**5b**), 13.7 (**5a**) min (150°C); TLC, R_f(**5b**) = 0.22, R_f(**5a**) = 0.30 (hexane-EtOAc, 5:1); IR (neat) 3410 (br), 2960, 2940, 2870, 2250, 1450, 1370, 1330, 1080 cm^{-1}; ^1H NMR (CCl_4) δ 3.60-4.43 (m, 3 H), 1.97-2.63 (m, 3 H); Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.59; H, 11.34.

Reduction of chiral acetal 4 (R^1 = n-Bu, R^2 = Me) using Br_2AlH: Lithium aluminum hydride (29 mg, 0.75 mmol) was added to a solution of aluminum bromide (0.60 g, 2.25 mmol) in dry ether

(3 mL) at 0°C. After stirring the resulting suspension for 10 min, was added dropwise at -20°C the acetal **4** (0.5 mmol) in dry ether (3 mL). After being stirred for 3 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, 8:1) to afford the alcohol **5** (R^1 = n-Bu, R^2 = Me) as an oil (yield >99%). The diastereomeric ratio of the product was determined by Gc (93:7). Reductive cleavages of other acetals were carried out in the similar manner. The physical properties and analytical data of the alcohols thus obtained are listed below.

5 (R^1 = n-Bu, R^2 = Et): Gc (150°C) t_R = 12.1 (**5b**), 18.4 (**5a**) min; TLC, R_f(**5b**) = 0.27, R_f(**5a**) = 0.22 (hexane-EtOAc, 5:1); IR (neat) 3450 (br), 2970, 2940, 2250, 1460, 1380, 1330, 1130 cm^{-1}; ^1H NMR (CCl_4) δ 3.64-4.30 (m, 3 H), 2.30-2.40 (m, 3 H); Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58. Found: C, 74.02; H, 11.85.

5 (R^1 = Ph, R^2 = Me): Gc (200°C) t_R = 11.8 (**5b**), 15.7 (**5a**) min; TLC, R_f(**5b**) = 0.27, R_f(**5a**) = 0.19 (hexane-EtOAc, 5:1); IR (neat) 3430 (br), 2980, 2940, 1610, 1100, 760 cm^{-1}; ^1H NMR (CCl_4) δ 7.03-7.53 (m, 5 H, ArH), 3.73-4.67 (m, 3 H), 1.97 (s, 1 H, OH); Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.56; H, 8.67.

5 (R^1 = Ph, R^2 = Et): Gc (200°C) t_R = 15.3 (**5b**), 20.7 (**5a**) min; TLC, R_f(**5b**) = 0.19, R_f(**5a**) = 0.11 (hexane-EtOAc, 5:1); IR (neat) 3450 (br), 2980, 2950, 1610, 1100, 1070, 760 cm^{-1}; ^1H NMR (CCl_4)

δ 7.00-7.57 (m, 5 H, ArH), 3.67-4.43 (m, 3 H), 2.37 (s, 1 H, OH); Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.00; H, 9.00. Found: C, 78.00; H, 9.00.

5 (R^1 = Me, R^2 = i-Bu): Gc (150°C) t_R = 7.1 (**5b**), 9.4 (**5a**) min; TLC, R_f(**5b**) = 0.36, R_f(**5a**) = 0.22 (hexane-EtOAc, 5:1); IR (neat) 3400 (br), 2950, 2100, 1640 cm^{-1}; ^1H NMR (CCl_4) δ 3.50-4.40 (m, 3 H), 2.60 (s, 1 H, OH), 1.80 (d, J = 1.9 Hz, 3 H); Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.49; H, 11.44.

5 (R^1 = Me, R^2 = cyclohexyl): Gc (180°C) t_R = 7.1 (**5b**), 9.0 (**5a**) min; TLC, R_f(**5b**) = 0.26, R_f(**5a**) = 0.21 (hexane-EtOAc, 5:1); IR (neat) 3430 (br), 2930, 2860, 1450, 1380, 1330, 1060 cm^{-1}; ^1H NMR (CCl_4) δ 3.60-4.30 (m, 3 H), 2.60 (s, 1 H, OH), 1.83 (d, J = 2.0 Hz, 3 H); Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10,99. Found: C, 75.53; H, 11.04.

Reductive cleavage of the acetal 4 with Et_3SiH in the presence of $TiCl_4$: To a solution of the acetal **4** (0.105 g, 0.5 mmol) and triethylsilane (0.080 mL, 0.5 mmol) in 3 mL of dichloromethane was added $TiCl_4$ (0.5 mL of 1 M dichloromethane solution, 0.5 mmol) at -78°C. The mixture was stirred there for 2 h. 0.5 mL of methanol was added and the resulting mixture was raised to room temperature and the product was poured into 2 N hydrochloric acid. Extraction of the product with ether twice followed by the removal of dried solvent to give a crude oil which was treated with KF-MeOH in a similar manner as carried out in the reduction of the acetal **1** to give a 61.2 mg of **5b** (58%). Gc analysis showed the ratio of 94:6; t_R = 9.4 (major) and 13.7

(minor) min (150°C) which was identical with those of the product of aluminum hydride reduction. The reaction of **4** with $SnCl_4$ was also carried out similarly to afford **5b** in 67% yield with the ratio of 95:5.

Removal of chiral auxiliary. Preparation of 3-octyn-2-ol (R^1 = n-Bu, R^2 = Me). Oxidation of **5a** (R^1 = n-Bu, R^2 = Me), was carried out with pyridinium chlorochromate (215.6 mg, 1.0 mmol) in dichloromethane (3 mL) at room temperature for 14 h. A saturated aqueous sodium bisulfite (10 mL) was poured into the resulting suspension and the separated organic layers were concentrated in vacuo to give the crude oil which was subsequently treated with potassium carbonate (0.7 g) in methanol (5 mL) at room temperature for 2 h. The mixture was diluted with water and the product was extracted with hexane twice, concentration in vacuo and chromatography on silica gel (hexane-ether, 10 : 1) furnished the optically pure (R)-3-octyn-2-ol (**6a**, R^1 = Bu, R^2 = Me) in 71% yield from **5a** as a colorless liquid. TLC, R_f = 0.22 (hexane-EtOAc, 5:1); IR (neat) 3350 (br), 2950, 2930, 2860, 2250, 1150, 1080 cm^{-1}; ^1H NMR (CCl_4) δ 4.37 (q, J = 7.0 Hz, 1 H), 2.63 (s, 1 H, OH), 1.93-2.50 (m, 2 H), 1.33 (d, J = 7.0 Hz, 3 H); $[\alpha]^{24}_D$ +39.11° (c 1.63, ether); lit. $[\alpha]^{23}_D$ +33.0 (c 1.62, ether).[3a]

4-Nonyn-3-ol (6a, R^1 = n-Bu, R^2 = Et): TLC, R_f = 0.41 (hexane-EtOAc, 5:1); IR (neat) 3350 (br), 2970, 2950, 2890, 2270, 1460 cm^{-1}; ^1H NMR (CCl_4) δ 4.00-4.44 (m, 1 H), 1.90-2.47 (m, 3 H); $[\alpha]^{26}_D$ +21.60° (c 1.03, ether).

4-Phenyl-3-butyn-2-ol (6a, R^1 = Ph, R^2 = Me): TLC, R_f = 0.10 (hexane- EtOAc, 5:1); IR (neat) 3330 (br), 2990, 2250, 1610, 1100, 750 cm^{-1}; ^1H NMR (CCl_4) δ 6.93-7.87 (m, 5 H, ArH), 4.67 (q, J = 6.0 Hz, 1 H), 3.23 (s, 1 H, OH), 1.50 (d, J = 6.0 Hz, 3 H); $[\alpha]^{21}_D$ +36.68° (c 0.81, $CHCl_3$); lit. $[\alpha]^{25}_D$ +51.8° (neat).[3e]

1-Phenyl-1-pentyn-3-ol (6a, R^1 = Ph, R^2 = Et): TLC, R_f = 0.16 (hexane-EtOAc, 5:1); IR (neat) 3330 (br), 2970, 2940, 2880, 2240, 1660, 1490, 1440, 760, 690 cm^{-1}; ^1H NMR (CCl_4) δ 6.97-7.50 (m, 5 H, ArH), 4.43 (t, J = 6.0 Hz, 1 H), 2.67 (s, 1 H, OH), 1.50-2.10 (m, 2 H), 1.03 (t, J = 6.0 Hz, 3 H); $[\alpha]^{21}_D$ +21.97° (c 1.27, ether).

6-Methyl-2-heptyn-4-ol (6a, R^1 = Me, R^2 = i-Bu): TLC, R_f = 0.21, (hexane-EtOAc, 5:1); IR (neat) 3350 (br), 2960, 2940, 2880, 2250, 1460, 1030 cm^{-1}; ^1H NMR (CCl_4) δ 4.00-4.44 (m, 1 H), 2.27 (s, 1 H, OH), 1.80 (d, J = 1.8 Hz, 3 H), 0.90 (d, J = 6.0 Hz, 6 H); $[\alpha]^{24}_D$ +15.10° (c 2.47, $CHCl_3$); lit. $[\alpha]^{25}_D$ +13.48° (c 4.9, $CHCl_3$).[3d]

References

1. Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H., Tetrahedron Lett., **1983**, 24, 4581; Idem, J. Organometal. Chem., **1985**, 285, 83.
2. Bartlett, P. A.; Johnson, W. S.; Elliott, J. D., J. Am. Chem. Soc., **1983**, 105, 2088.
3. (a) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M., J. Am.

Chem. Soc., **1984**, 106, 6717. (b) Johnson, W. S.; Brinkmeyer, R. S.; Kappor, V. M.; Yarnell, T. M., J. Am. Chem. Soc., **1977**, 99, 8341. (c) Cohen, N.; Lopresti, R. S.; Newkom, C.; Saucy, G., J. Org. Chem., **1980**, 45, 582. (d) Brinkmeyer, R. S.; Kappor, V. M., J. Am. Chem. Soc., **1977**, 99, 8339. (e) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A., J. Am. Chem. Soc., **1980**, 102, 867; Midland, M. M.; Tramontano, A.; Kazubski. A.; Graham. R. S., Tetrahedron, **1984**, 40, 1371. (f) Reviews: Morrison, J. D.; Mosher, H. S. "Asymmetric Organic Reactions", Prentice-Hall: Englewood Cliffs, N. J., **1971**; pp 160-218; Valentine, D.; Scott, J. W., Synthesis, **1978**, 329.; Kagan, H. B.; Fiand, J. C. Top. Stereochem., **1978**, 10, 175; ApSimon, J. W.; Seguin, R. P. Tetrahedron, **1979**, 35, 2797; Noyori, R. Pure & Appl. Chem., **1981**, 53, 2315; Haubenstock, H., Top. Stereochem., **1983**, 14, 231.

4. Preliminary communication: Ishihara, K.; Mori, A.; Arai, I.; Yamamoto H., Tetrahedron Lett., **1986**, 27, 983; Mori, A.; Ishihara, K.; Yamamoto, H., Ibid., **1986**, 27, 987.
5. Frainnet, E.; Esclamadon, C., Compt. Rend., **1962**, 254, 1814.
6. Tsunoda, T.; Suzuki, M.; Noyori, R., Tetrahedron Lett., **1979**, 4679.
7. Maruoka, K.; Sakurai, M.; Yamamoto, H., Tetrahedron Lett., **1985**, 26, 3853.
8. Reetz, M. T.; Westermann, J.; Steinbach, R., Angew. Chem., Int. Ed. Engl., **1980**, 19, 900; Mori, A.; Maruoka, K.; Yamamoto H., Tetrahedron Lett., **1984**, 25, 4421.

9. Dale, J. A.; Dull, D. L.; Mosher, H. S., J. Org. Chem., 1969, 34, 2543.

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

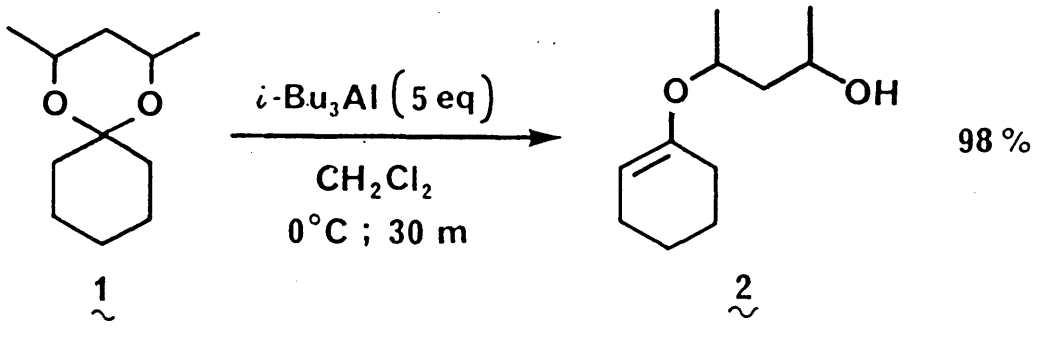
CHAPTER 4

RESOLUTION OF KETONES VIA CHIRAL ACETAL KINETIC APPROACH

Abstract A practical resolution of ketone is described. The method depends on kinetic resolution of chiral acetals. When the chiral acetal is treated with triisobutylaluminum at low temperature, one diastereoisomer reacts much faster than the other. The resulting enol ether thus obtained is transformed to optically pure ketnone. Meanwhile, the recovered acetal is also transformed to ketone of the opposite stereochemistry. The similar reaction is performed with diisobutylaluminum hydride and optically pure ketone or alcohol are obtained. The method is successfully applied to the synthesis of (-)-(S)-5-hexadecanolide, pheromone of Vespa orientalis.

In contrast to the generation of optically active carbonyl compounds by asymmetric alkylation, which is now used with great frequency in synthesis and for which many selective reagents are known,[1] methods for the efficient resolution of carbonyl compounds are still quite limited. Classical approaches to the optical activation of ketones are not always reliable.[2,3] This chapter describes the successful development of a new type of resolution for ketones based on a kinetic approach.

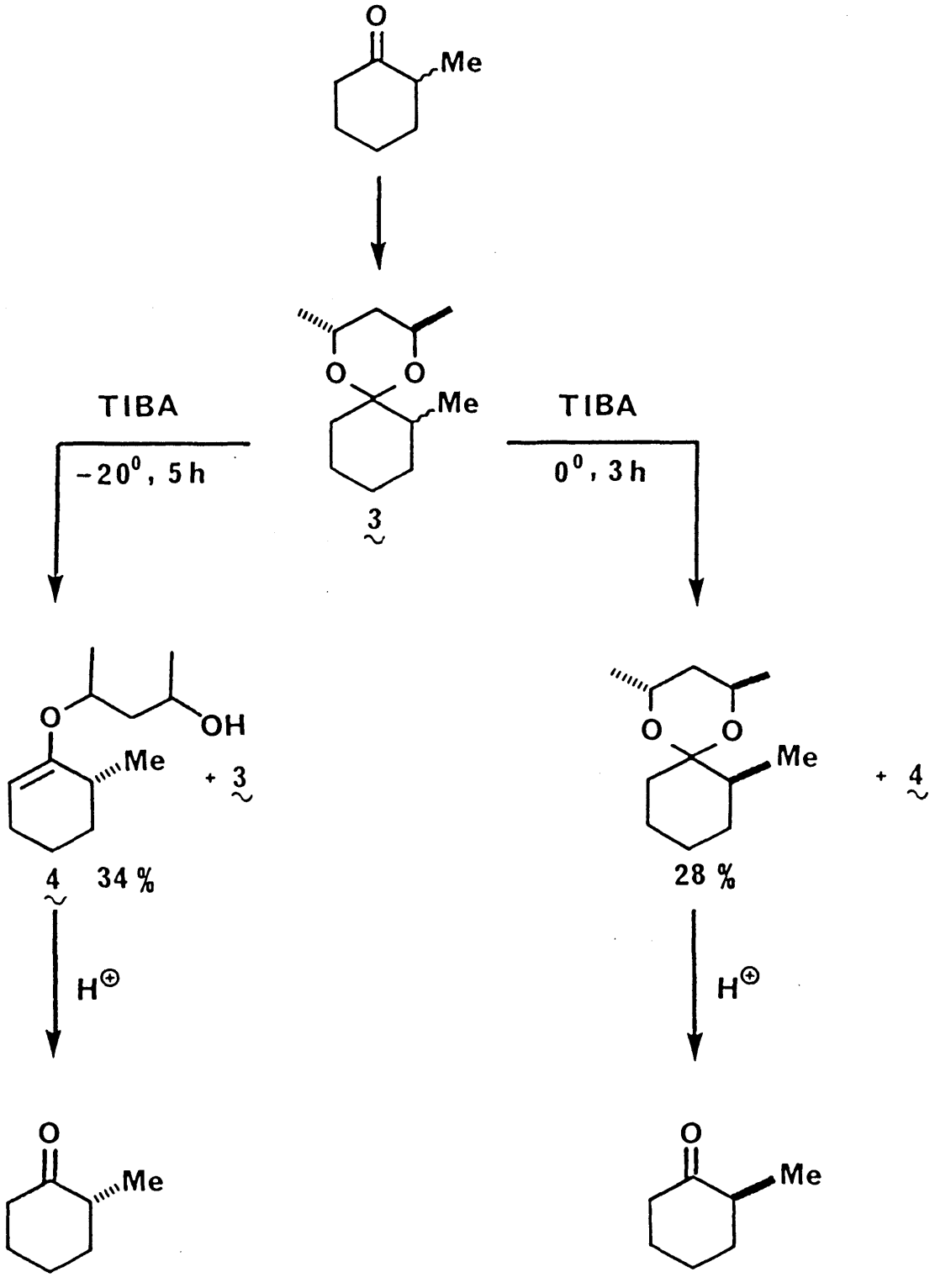
The nucleophilic cleavage of homochiral acetal derived from (-)-(2R,4R)-2,4-pentanediol using organoaluminum reagents was described in chapter 2 and 3.[4] By studying these reactions in detail, it was discovered that an enol ether was formed under certain conditions. Thus, treatment of acetal 1 with triisobutylaluminum (TIBA) in dichloromethane at 0°C for 30 min produced the enol ether 2 in 98% yield.[5]



1 2

The availability of enol ether from acetals under mild conditions attracted the author's attention as a potential means of ketone resolution. Scheme 1 illustrates the realization of such a process. The chiral acetal **3** was prepared in >95% yield from the reaction of racemic 2-methylcyclohexanone and (-)-(2R,4R)-2,4-pentanediol[6] in the presence of a catalytic amount of pyridinium tosylate. Treatment of the diastereomers **3** with 2 equiv of TIBA at -20°C for 5 h furnished enol ether **4** (34%) along with recovered acetal (62%).[7] Simple chromatographic separation of the enol ether **4** followed by mild acid treatment in benzene regenerated the diastereomerically pure acetal (2R,4R,7R)-**3** (>99% diastereomerically pure by GC analysis). Mild hydrolysis of **4** (0.1 N HCl-acetone, 0°C, 1.5 h) produced (R)-2-methylcyclohexanone, $[\alpha]^{24}_{D}$ -15.9° (neat),[8] with an enantiomeric excess of >95%.[9] When the reaction was carried out about 70% completion (0°C, 3 h), the recovered acetal was separated chromatographically and shown to be >99% pure by GC analysis. From this acetal (S)-2-methylcyclohexanone was prepared in 78% yield: $[\alpha]^{24}_{D}$ +14.9° (neat).[8,10]

Scheme 1



The stereochemical outcome of the reaction of diisobutylaluminum hydride (DIBAH) with diastereomers **3** is illustrated in Scheme 2. Here, the recovered acetal **3** (42%) was diastereomerically pure (>99%) and the reduced ether **5** (49%) was obtained in 90% diastereomeric purity by GC analysis.[11,12] Furthermore, pure **5** was readily prepared by terminating the reaction at 30% completion (-20°C, 3 h). Oxidation followed by basic treatment of **5** gave (+)-(1S,2R)-2-methylcyclohexanol (**6**),[13] $[\alpha]^{24}_{D}$ +20.3°,[14] in 74% yield with >99% de and 98% ee.[15]

Scheme 2

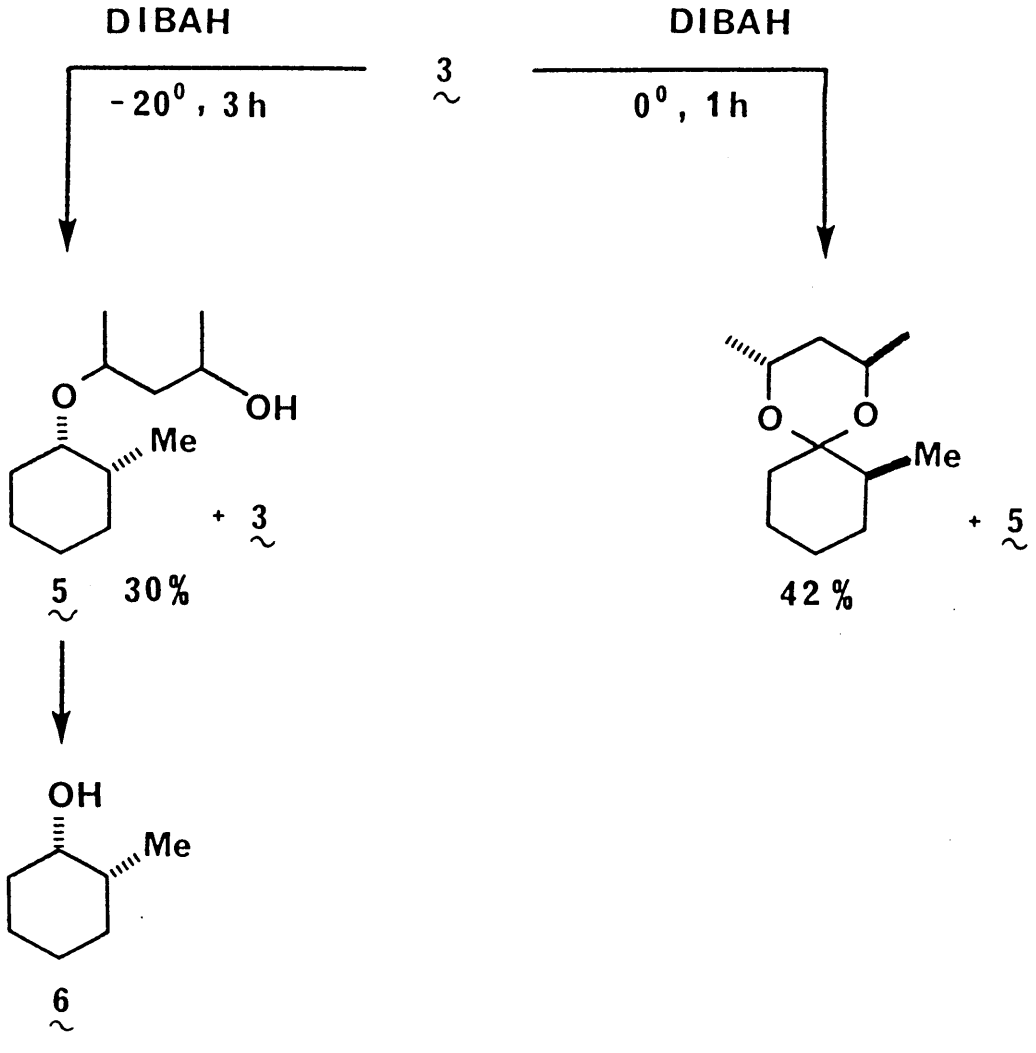
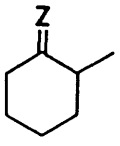
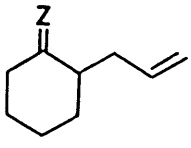
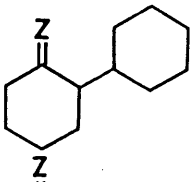
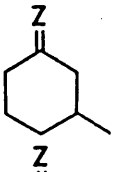
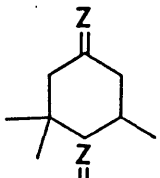
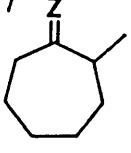
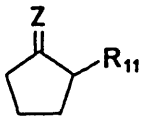
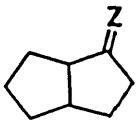
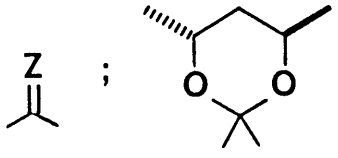


Table 1. Resolution of Ketones Using Chiral Acetals

Entry	Acetal[a]	Aluminum Reagent (equiv)	Reaction Condn. °C, h	Enol Ether Yield(%)[b] (ratio)[c]	Recovered Acetal Yield(%)[b] (ratio)[d]
1		TIBA(2)	0, 3		28 (<1:99)
2		TIBA(2)	-20, 5	34 (>99:1)	
3		DIBAH(2)	-20, 3		42 (<1:99)
4		TIBA(4)	-20, 2		35 (1:99)[e]
5		TIBA(2)	-20, 1	33 (97:3)[e]	
6		TIBA(4)	-20, 3		25 (<1:99)
7		TIBA(4)	-20, 1		49 (36:64)
8		TIBA(6)	-20, 1		20 (26:74)
9		TIBA(4)	-20, 0.5		36 (12:88)
10		TIBA(4)	-20, 3		18 (1:99)
11		DIBAH(4)	-20, 0.5		27 (2:98)
12		DIBAH(1.5)	0, 0.5		37 (2:98)
13		DIBAH(4)	-20, 1.5		18 (<1:99)

Legend of the Table 1

a 

b Isolated pure product.

c GC analyses were carried out after the transformation to the corresponding acetal by treatment with a catalytic amount of pyridinium tosylate in anhydrous benzene.

d The diastereoselectivity was determined by GC analyses of the product.

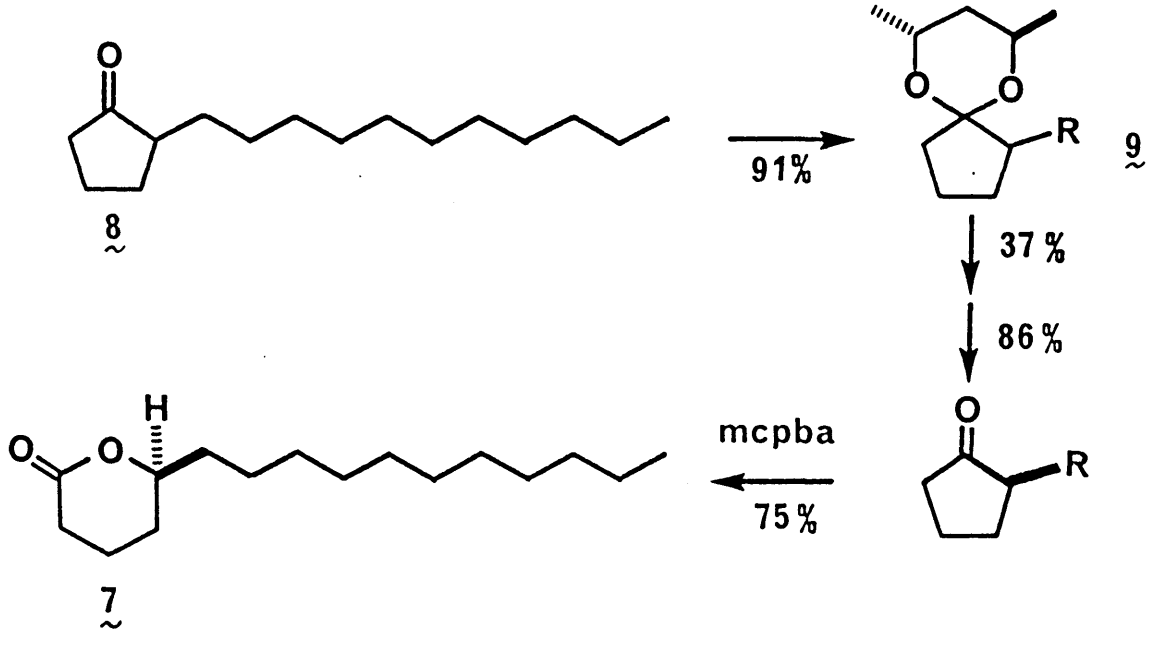
e The ratio was determined after hydrogenation of the olefin.

Table 1 summarizes the generality of the reaction which is effective not only six-membered ring but five-, seven-, and bicyclic ring system. It should also be noted that the resolution of β-substituted ketones are effective although the selectivity of the reactions are slightly lower.

The efficiency of the present method is highlighted by a rapid and convenient synthesis of (-)-(S)-5-hexadecanolide (**7**), pheromone of Vespa orientalis.[16] The sequence of the reaction utilized is outlined in Scheme 3. Acetalization of the readily available ketone **8**[17] with (-)-(2R,4R)-2,4-pentanediol gave, diastereomers **9**. Treatment of **9** with 1.5 equiv of DIBAH at 0°C for 30 min gave, after chromatographic purification, optically

pure acetal (2R,4R,7S)-9 in 37% yield with 97% de. Mild hydrolysis in 0.1 N HCl-acetone furnished pure (S)-8 in 86% yield. Baeyer-Villiger oxidation of (S)-8 with m-chloroperbenzoic acid in chloroform at 25°C for 24 h yielded the lactone 7 in 75% yield.

Scheme 3



As implied above, the process is remarkably general and should in many cases provide a practical, if not unique, route to optically pure ketones. Another noteworthy aspect of this approach to chiral material is that the enol ether itself may provide a point of departure for further transformations.

Experimental

General. Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrometer. ^1H NMR spectra were measured on a JNM-PMX 60 spectrometer. The chemical shifts are expressed in part per million downfield from internal tetramethylsilane ($\delta = 0$). 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 digital polarimeter. Gas liquid phase chromatography (GC) analyses were performed on Hitachi Model 164 instrument equipped with 25-m PEG-HT capillary column and a flame ionization detector using nitrogen as a carrier gas. All experiments were carried out under an atmosphere of dry argon. For thin layer chromatography (TLC) analyses throughout 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 E. Merck Art 9385. Microanalyses were accomplished at the Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University. In experiments requiring dry solvents, ether and tetrahydrofuran (THF) were distilled from sodium-benzophenone. Benzene, hexane, and toluene were dried over sodium metal. Dichloromethane was distilled from phosphorus pentoxide and stored over 4A molecular sieves. (-)-(2R,4R)-2,4-pentanediol was purchased and used after recrystallization from dry ether; $[\alpha]^{24}_D$ -41,2° (c 9.99, chloroform). Other chemicals were

purchased and used as such.

General Method for Preparation of Chiral Acetals. The mixture of a ketone (10.0, mmol), pyridinium tosylate (10 mg) and (-)-(2R,4R)-2,4-pentanediol (1.14 g, 11.0 mmol) in 10 mL of benzene was refluxed with continuous removal of water for 5 h. The resulting mixture was poured into saturated sodium bicarbonate and the product was extracted with hexane twice. The organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification of the crude oil by column chromatography on silica gel (hexane-ethyl acetate, 30-50:1) afforded a corresponding acetal. The physical properties and analytical data of acetals are listed below.

Acetal derived from cyclohexanone **(1)**: 85% yield; IR (neat) 2980, 2950, 2880, 1455, 1020, 950 cm^{-1}; ^1H NMR (CCl_4) δ 3.60-4.17 (m, 2 H), 1.30-1.83 (m, 12 H), 1.12 (d, J = 8.4 Hz, 6 H); Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.45; H, 11.22.

Acetal derived from 2-methylcyclohexanone **(3)**: 99% yield; IR (neat) 2980, 2930, 2860, 1445, 1275, 980 cm^{-1}; ^1H NMR (CCl_4) δ 3.63-4.30 (m, 2 H); Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.48; H, 11.38; GC analysis (100°C) revealed two separate peaks (t_R = 8.4 and 8.6 min).

Acetal derived from 2-allylcyclohexanone (Table 1, Entry 4 and 5): 85% yield; IR (neat) 2970, 2930, 2860, 1640, 910 cm^{-1}; ^1H NMR (CCl_4) δ 5.07 (m, 1 H), 4.80 (m, 1 H), 3.63-4.27 (m, 2 H); Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.96;

H, 10.77. An aliquot of the sample was hydrogenated using Pd/C as a catalyst in ether at room temperature for 10 h and the resulting acetal of 2-propylcyclohexanone was analyzed by GC: t_R = 8.4 and 8.6 min (120°C).

Acetal derived from 2-cyclohexylcyclohexanone (Table 1, Entry 6): 45% yield; IR (neat) 2930, 2850, 1445, 985, 940 cm^{-1}; ^1H NMR (CCl_4) δ 3.80-4.40 (m, 2 H); Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.65; H, 11.34. GC: t_R = 22.5 and 23.8 min (150°C).

Acetal derived from 3-methylcyclohexanone (Table 1, Entry 7 and 8): 94% yield; IR (neat) 2920, 1440, 1375, 990, 900 cm^{-1}; ^1H NMR (CCl_4) δ 3.60-4.17 (m, 2 H), 1.66 (d, J = 6.0 Hz, 6 H), 0.87 (d, J = 6.0 Hz, 3 H); Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.38; H, 11.43. GC: t_R = 7.8 and 8.2 min (100°C).

Acetal derived from 3,3,5-trimethylcyclohexanone (Table 1, Entry 9 and 10): 96% yield; IR (neat) 2940, 2920, 1450, 1345, 1140, 950 cm^{-1}; ^1H NMR (CCl_4) δ 3.53-4.23 (m, 2 H), 0.80 (d, J = 4.0 Hz, 3 H); Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58. Found: C, 74.11; H, 11.76. GC: t_R = 8.8 and 10.4 min (100°C).

Acetal derived from 2-methylcycloheptanone (Table 1, Entry 11): 59% yield; IR (neat) 2970, 2930, 2860, 1440, 1375, 925 cm^{-1}; ^1H NMR (CCl_4) δ 3.60-4.23 (m, 2 H); Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.40; H, 11.53. GC: t_R = 12.7 and 13.2 min (100°C).

Acetal derived from cis-Bicyclo[3.3.1]octane-2-one (Table 1, Entry 13): 89% yield; IR (neat) 2950, 2870, 1445, 1380, 1160,

980 cm^{-1}; ^1H NMR (CCl_4) δ 3.83-4.13 (m, 2 H), 1.08 (d, J = 6.2 Hz, 6 H); Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.15; H, 10.63. GC: t_R = 12.6 and 14.2 min (100°C).

Reaction of the acetal 1 with triisobutylaluminum. To a solution of acetal **1** (0.184 g, 1.00 mmol) in dry dichloromethane (5 mL) was added 2.5 mL of 2.0 M hexane solution of triisobutylaluminum (5.0 mmol) at 0°C. The mixture was stirred there for 1 h. The product was poured into 2 N NaOH and extracted with ether twice. The organic layers were dried over sodium sulfate and concentrated in vacuo. Purification by column chromatography on silica gel using hexane-ethyl acetate (5 : 1) as an eluant afforded 0.181 g of the corresponding enol ether **2** in 98% yield. IR (neat) 3000-3700 (br), 2980, 2945, 2850, 1675, 1380, 960 cm^{-1}; ^1H NMR (CCl_4) δ 4.50-4.73 (m, 1 H), 3.67-4.47 (m, 2 H); Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.34; H, 11.25.

General Procedure for the Resolution of the Acetals with Triisobutylaluminum or Diisobutylaluminum Hydride. To a solution of the acetal (10.0 mmol) in dry dichloromethane (50 mL) was added triisobutylaluminum (2.0 M hexane solution) or diisobutylaluminum hydride (1.0 M hexane solution) at the conditions as shown in Table 1. The mixture was poured into 2 N NaOH and the product was extracted with ether twice. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. Chromatography on silica gel (hexane-

ethyl acetate, 5:1) gave the recovered acetal and the enol ether (the reduced product). The recovered acetal was analyzed by GC. The physical properties and analytical data of the enol ethers are listed below.

Enol ether derived from 2-methylcyclohexanone **4**. IR (neat) 3100-3700 (br), 2980, 2940, 2860, 1665, 1380, 970 cm^{-1}; ^1H NMR (CCl_4) δ 3.63-4.70 (m, 3 H), 2.33 (br, 1 H, OH); Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.47; H, 11.39.

Enol ether derived from 2-allylcyclohexanone (Table 1, Entry 5): IR (neat) 3030-3650 (br), 2970, 2930, 1660, 1445, 915, 795 cm^{-1}; ^1H NMR (CCl_4) δ 5.07 (m, 1 H), 4.80 (m, 1 H), 4.57 (m, 1 H); Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.81; H, 10.92.

Regeneration of the Acetal (2R,4R,7R)-3. To a solution of the enol ether **4** (0.033 g, 0.16 mmol) in benzene (3 mL) was treated with a catalytic amount of pyridinium tosylate (5 mg) for 2 h. The mixture was poured into saturated sodium bicarbonate and the product was extracted with hexane twice. After removal of dried solvent, chromatography on silica gel (hexane-ether, 10:1) afforded the 0.024 g of the **(2R,4R,7R)-3** in 73% yield. GC peak was identical with one of the two diastereomers of **3** (t_R = 8.4 min, 100°C).

Hydrolysis of the Acetal 3. A mixture of the acetal **3** (0.28 g, 1.4 mmol), 0.4 mL of 0.1 N HCl and 1.0 mL of acetone was stirred at 0°C for 2 h. The product was poured into cold water

and extracted with pentane twice. The organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by column chromatography on silica gel (pentane-ether, 5:1) afforded 0.12 g of (*S*)-(+)-2-methylcyclohexanone in 78% yield. $[\alpha]^{25}_{D}$ +14.88° (neat, d = 0.924); lit. $[\alpha]^{20}_{D}$ -16.6°.[8]

Hydrolysis of the Enol Ether 4. The mixture of the enol ether **4** (0.68 g, 3.4 mmol), 1 mL of 0.1 *N* HCl and 2 mL of acetone was stirred at 0°C for 1.5 h. The product was poured into cold water and extracted with pentane twice. The organic layers were dried over anhydrous and sodium sulfate and concentrated *in vacuo*. Purification by column chromatography on silica gel afforded 0.23 g of (*R*)-(-)-2-methylcyclohexanone in 61% yield. $[\alpha]^{25}_{D}$ -15.87° (neat, d = 0.924); lit. $[\alpha]^{20}_{D}$ -16.6° (neat).[8]

(+)-(1*S*,2*R*)-2-Methylcyclohexanol (6). To a solution of the acetal **3** (1.98 g, 10.0 mmol) in dry dichloromethane (50 mL) was added 20 mL of 1 *M* hexane solution of diisobutylaluminum hydride (20.0 mmol) at -20°C. The mixture was stirred there for 3 h. The product was poured into 2 *N* NaOH and extracted with ether twice. The organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo*. Chromatography on silica gel (hexane-ethyl acetate, 5:1) afforded 0.59 g of the reduced ether **5** (30%) along with 1.30 g of the recovered acetal **3** (66%). For **5**: IR (neat) 3100-3600 (br), 2960, 2920, 2850, 1440, 1120 cm^{-1}; ^{1}H NMR (CCl_4) δ 3.23-4.33 (m, 3 H), 2.73 (br, 1 H, OH); Anal.

Calcd for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 71.88; H, 12.15. GC analysis showed the >98% diastereomeric purity: t_R = 17.5 min (130°C). The mixture of **5** (0.59 g, 3.0 mmol) and PCC (1.30 g, 6.0 mmol) in 10 mL of dry dichloromethane was stirred at room temperature for 24 h. To the resulting mixture was added saturated solution of sodium bisulfite and stirred for 3 h. The product was extracted with ether and concentration of the dried solvent afforded the crude ketone which was treated with potassium carbonate (2.10 g, 15.0 mmol) in 10 mL of methanol for 12 h. The resulting mixture was poured into water and the product was extracted with pentane repeatedly. After removal of the dried solvent, chromatography on silica gel (pentane-ether, 5:1) gave a 0.24 g of **6** (74%). $[\alpha]^{24}_D$ +20.29° (c 3.21, ethanol); lit. $[\alpha]^{25}_D$ +15.7° (c 3.4, ethanol).[14]

Acetalization of 2-Undecylcyclopentanone 8. Acetalization of **8** with (-)-(2R,4R)-2,4-pentanediol was carried out in a similar manner to give 5.88 g of the acetal **9** in 91% yield: IR (neat) 2930, 2860, 1460, 1380, 1200, 1155, 1120 cm^{-1}; ^1H NMR (CCl_4) δ 3.63-4.27 (m, 2 H); Anal. Calcd for $C_{21}H_{40}O_2$: C, 77.72; H, 12.42. Found: C, 77.67; H, 12.47. GC: t_R = 15.5 and 16.2 min (180°C).

Resolution of the Diastereomers 9 by Diisobutylaluminum Hydride. To a solution of the acetal **9** (1.62 g, 5.0 mmol) in 25 mL of dry dichloromethane was added 7.5 mL of diisobutylaluminum hydride (1.0 M of hexane solution, 7.5 mmol)

at 0°C in 10 min. The mixture was stirred there for 30 min. The reaction mixture was poured into NaOH. Extraction with ether, evaporation of dried solvent and chromatography on silica gel (hexane-ethyl acetate, 30:1) afforded 0.60 g of **(2R,4R,7S)-9** in 37% yield. GC analysis showed the ratio of 98.3:1.7 (97% de): t_R (major isomer) = 16.2 min (180°C).

Hydrolysis of the Acetal (2R,4R,7S)-9. To a solution of the acetal **9** (1.85 mmol, 0.601 g) in 1 mL of acetone was added dropwise 0.1 N hydrochloric acid at 0°C. The mixture was stirred there for 3 h. The product was poured into ice water and extracted with hexane. The organic layer was concentrated and purified by column chromatography on silica gel (hexane-ethyl acetate, 10:1) to give 0.379 g of **(S)-8** in 86% yield: $[\alpha]^{24}_D$ +81.02° (c 1.04, ether).

Baeyer-Villiger oxidation of (S)-8. The mixture of **(S)-8** (0.38 g, 1.6 mmol) and 70% m-chloroperbenzoic acid (0.74 g, 3.0 mmol) in 10 mL of chloroform was stirred at room temperature for 24 h. The product was washed with sodium bisulfite and sodium bicarbonate. The organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. Chromatography on silica gel (hexane-ethyl acetate, 4:1) afforded the 0.31 g of (-)-(S)-5-hexadecanolide **(7)** in 75% yield: IR (neat) 2920, 2850, 1735, 1460, 930 cm^{-1}; ^1H NMR (CCl_4) δ 3.83-4.43 (m, 1 H); $[\alpha]^{24}_D$ -38.29° (c 1.17, THF); lit. $[\alpha]_D$ -39.2 (THF).[16e]

References

1. For reviews, see: "Asymmetric Synthesis, Vol. 2 and 3"; Morrison, J. D. Ed.; Academic Press: New York, 1983 and 1984.
2. For review, see: Wilen, S. H. In "Topics in Stereochemistry"; Eliel, E. L., Allinger, N. L., Eds.; Wiley-Interscience: New York, 1971; Vol 6, p 107. See also: Newman, P.; "Optical Resolution Procedures for Chemical Compounds"; Optical Resolution Information Center, Manhattan College, New York, 1984; Vol 3, p 479.
3. Recently Johnson reported an elegant resolution technique of ketone based on the addition of an optically pure sulfoximine: Johnson, C. R.; Zeller, J. R. J. Am. Chem. Soc. **1982**, 104, 4021; Tetrahedron **1984**, 40, 1225.
4. (a) Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. J. Organometal. Chem., **1985**, 285, 83; Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. Tetrahedron Lett., **1983**, 24, 4581; Mori, A.; Maruoka, K.; Yamamoto, H. Ibid., **1984**, 25, 4421; Ishihara, K.; Mori, A.; Arai, I.; Yamamoto, H., Ibid., **1986**, 27, 983; Mori, A.; Ishihara, K.; Yamamoto, H., Ibid., **1986**, 987. See also, (b) Bartlett, P. A.; Johnson, W. S.; Elliott, J. D. J. Am. Chem. Soc., **1983**, 105, 2088; Johnson, W. S.; Elliott, R.; Elliott, J. D. Ibid., **1983**, 105, 2904; Elliott, J. D.; Choi, V. M. F.; Johnson, W. S. J. Org. Chem., **1983**, 48, 2294; Choi, V. M. F.; Elliott, J. D.; Johnson, W. S. Tetrahedron Lett., **1984**, 25, 591; Ghribi, A.;

Alexakis, A.; Normant, J. F. Ibid., **1984**, 25, 3083; Lindell, S. D.; Elliott, J. D.; Johnson, W. S. Ibid., **1984**, 25, 3947; Johnson, W. S.; Crackett, P. H.; Elliott, J. D.,; Jagodzinski, J. J.; Lindell, S. D.; Natarajan, S. Ibid., **1984**, 25, 3951; Johnson, W. S.; Edington, C.; Elliott, J. D.; Silverman, I. R. J. Am. Chem. Soc., **1984**, 106, 7588.

5. It should be noted that the effective elimination of the acetal was only observed with the acetal from 2,4-pentanediol. Thus, treatment of the ethylene acetal of cyclohexanone with excess TIBA at 25°C for 24 h gave the reduced cleavage product $(CH_2)_5CH\text{-}O\text{-}(CH_2)_2OH$ in 38% yield.
6. (-)-(2R,4R)-2,4-pentanediol was purchased from Wako Pure Chemical Industries Ltd. and recrystallized from ether: Ito, K.; Harada, T.; Tai, A. Bull. Chem. Soc. Jpn., **1980**, 53, 3367.
7. GC analysis (25-m PEG-HT capillary column) of this product revealed a mixture of two diastereoisomers of the ratio of ca. 3 : 7.
8. Lit. $[\alpha]^{20}_D$ -16.6° (neat): Enders, D. Chemtech., **1981**, 504; Enders, D.; Eichenauer, H. Chem. Ber., **1979**, 112, 2933.
9. Optical purity was determined by conversion to cis-2-methylcyclohexanol (L-selectride at -78°C) and GC analysis of its MTPA ester.
10. Optical purity was >95% ee by the method of ref. 9.
11. 1R,2R : 1R,2S : 1S,2R : 1S,2S = 0.7 : 3.0 : 89.6 : 6.7 by GC analysis.

12. The recovered acetal was further reduced with excess DIBAH (5 equiv) at 25°C for 6 h to give the cleavage product in 83% yield with low selectivity: 1R,2R : 1R,2S : 1S,2R : 1S,2S = 0 : 64 : 0 : 36.

13. The cis : trans ratio was >99:1 by GC analysis.

14. Lit. $[\alpha]^{25}_{D}$ +15.7° (c 3.4, EtOH): Jones, J. R.; Takemura, T. Can. J. Chem. **1982**, 60, 2950.

15. Optical purity was determined by GC analysis of the MTPA ester.

16. (a) Ikan, R.; Gottlieb, R.; Bergmann, E. D.; Ishay, J. J. Insect Physiol., **1969**, 15, 1709. For the synthesis of **7**: (b) Coke, J. L.; Richon, A. B. J. Org. Chem., **1976**, 41, 3516; (c) Pirkle, W. H.; Adams, P. E. Ibid. **1979**, 44, 2169; (d) Solladié, G.; Moghadam, F. M. Ibid., **1982**, 47, 91; (e) Servi, S. Tetrahedron Lett., **1983**, 24, 2023; (f) Fujisawa, T.; Itoh, T.; Nakai, M.; Sato, T. Ibid., **1985**, 26, 771.

17. Hájek, M.; Málek, J. Coll. Czech., Chem. Commun., **1976**, 41, 746.

CHAPTER 5

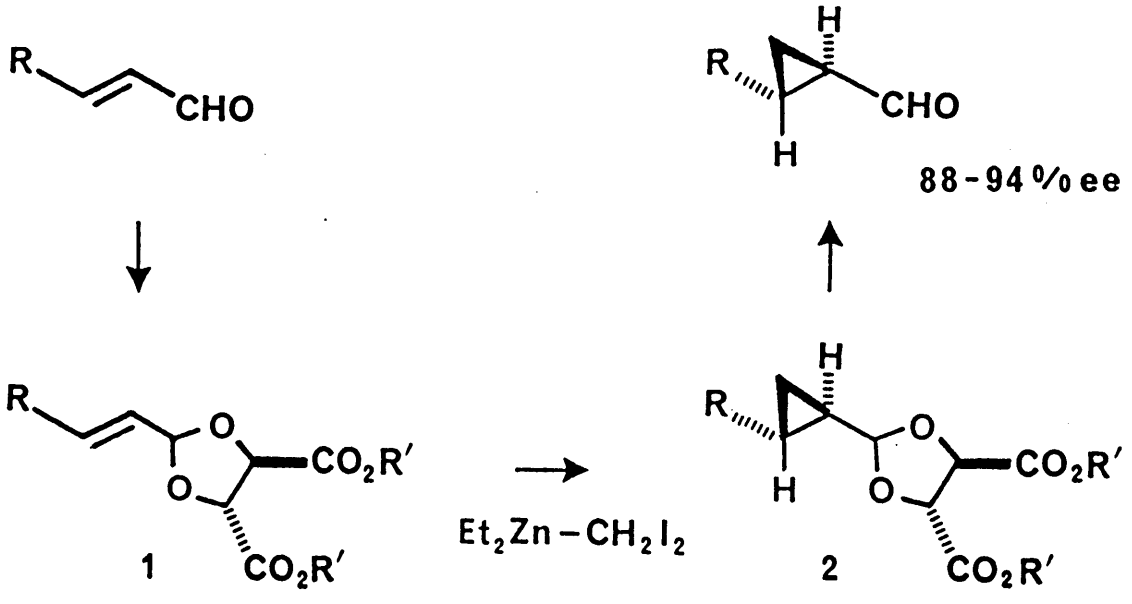
ASYMMETRIC SIMMONS-SMITH REACTIONS USING HOMOCHIRAL PROTECTIVE GROUPS[1]

ABSTRACT Asymmetric Simmons-Smith reactions of α,β-unsaturated acetals derived from chiral dialkyl tartrate or (2R,4R)-2,4-pentanediol are described. Treatment of the acetal with diethylzinc and methylene iodide gives a cyclopropane with high diastereoselectivity. The acetal group is readily transformed to the aldehyde or the ester group. In addition, the method is successfully applied to the enantioselective synthesis of 5,6-methanoleukotriene A_4, a stable and selective inhibitor of leukotriene biosynthesis.

Introduction of the cyclopropane ring to organic molecule in enantiomerically pure manner is one of the most important problem in organic synthesis. Although Simmons-Smith reaction is the powerful method for cyclopropanation of the olefin and its scope and mechanism have been widely studied,[2] there have been little studied on its application to the asymmetric reactions. Recent studies of asymmetric syntheses using homochiral protective groups[3] encouraged the author to explore possibility of the asymmetric Simmons-Smith reactions using homochiral acetals. In this chapter, a new method for asymmetric cyclopropanation and its application to the synthesis of chiral 5,6-methanoleukotriene A_4, a stable and selective inhibitor of leukotriene biosynthesis is described.[4]

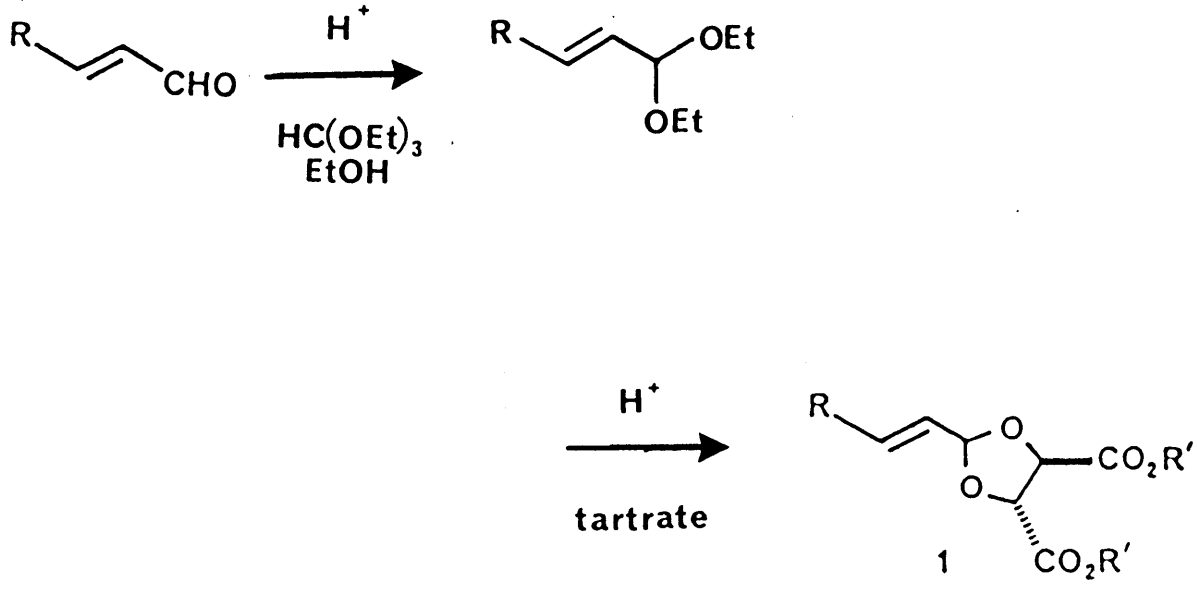
Asymmetric Simmons-Smith Reactions: When an α,β-unsaturated acetal dissolved in hydrocarbon was treated with excess methylene iodide and diethylzinc,[5] the corresponding cyclopropane was obtained in a reasonable yield with high diastereoselectivity. The acetal group was readily transformed to the aldehyde (hydrolysis) or to the ester (ozonolysis).[6] The process is illustrated in Scheme 1.

Scheme 1



The starting acetal was readily synthesized from the corresponding aldehyde as shown in Scheme 2. The direct preparation of **1** from their aldehyde gave rise to rather low yield. It should be noted that a single isomer of the starting acetal was formed from dialkyl tartrate which has C_2 axis symmetry, thus avoiding troublesome separation of diastereoisomer.

Scheme 2



Results are given in Table 1. Since both (R,R)- and (S,S)-tartaric acid esters are readily available in optically pure form,[7] this method allows the synthesis of both enantiomers of cyclopropanes from α,β-unsaturated aldehyde in a predictable manner. Generally the acetal derived from diisopropyl tartrate (DIPT) gave a slightly higher diastereomeric excess than that of diethyl tartrate (DET) (**2b**, **2c** and **2d**, **2e**). The reactions of **1h** and **1i** indicated that the asymmetric inductions are totally controlled by the auxiliary tartrate ligand and are independent of the chirality of isopropenyl group. The diastereomeric ratio

was determined by ^{1}H NMR analysis of the acetal of (2R,4R)-2,4-pentanediol obtained by transacetalization of **2**. Thus, a base-line separation of the two doublets of C<u>H</u>$(OR)_2$ was obtained in the presence of the shift reagent, Eu$(fod)_3$ (90 or 60 MHz) or in the absence of the shift reagent (500 MHz). The absolute configuration has proven by the measurement of $[\alpha]_D$ value after transformation to the corresponding aldehyde or carboxylic acid.

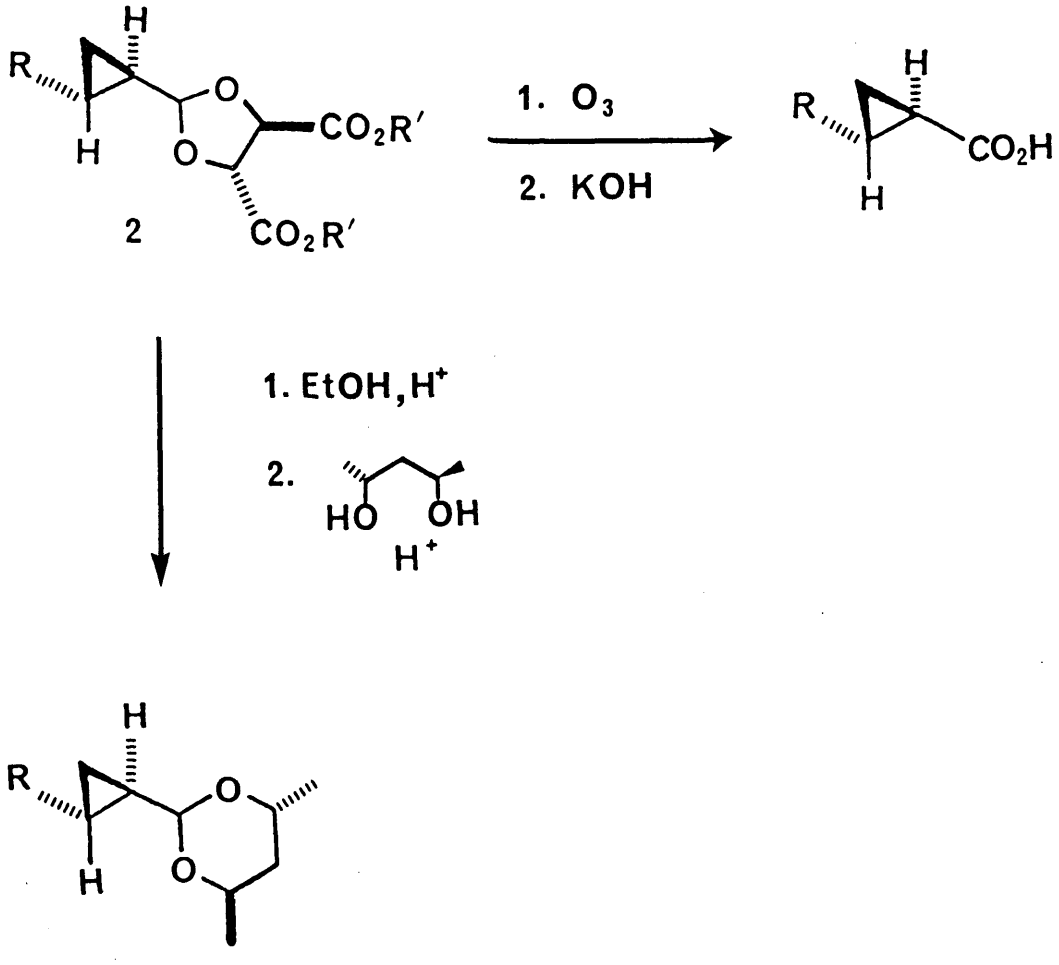
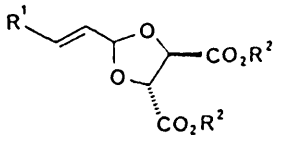
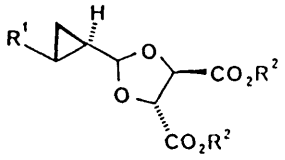
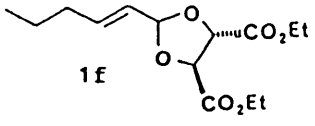
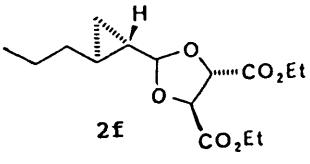
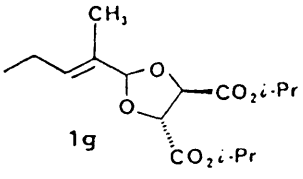
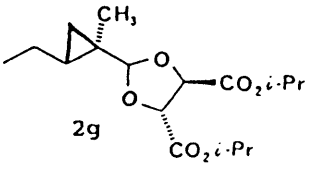
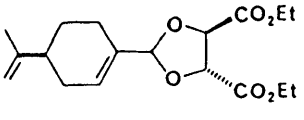
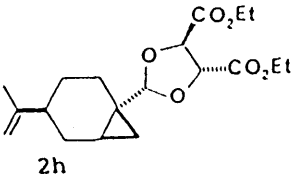
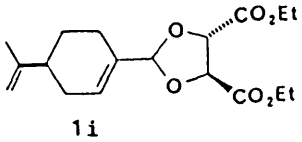
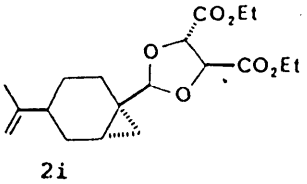


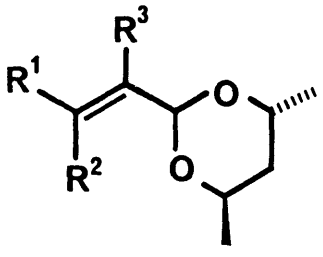
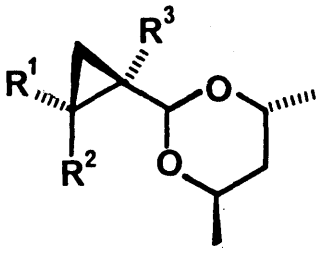
Table 1. Asymmetric Simmons-Smith Reaction of 1

Acetal	Conditions (°C, h)	Product	Yield of 2[a] (%)	%de[b]
				
R^1 R^2				
Me i-Pr (1a)	-20, 1; 0, 4	2a	90	94
n-Pr Et (1b)	-20, 3	2b	95	88
n-Pr i-Pr (1c)	-20, 1; 0, 5	2c	80	91
Ph Et (1d)	-20, 6; 0, 6	2d	82	87
Ph i-Pr (1e)	-20, 1; 0, 3	2e	92	91
 1f	-20, 5	 2f	94	89
 1g	-20, 1; 0, 4	 2g	81	89
 1h	-20, 7; 20, 10	 2h	61	88[c]
 1i	-20, 7; 20, 10	 2i	50	85[c]

[a] Isolated yield. [b] Diastereomeric excess (de). Unless otherwise specified, the diastereoselectivity was determined as described in text. [c] The diastereomeric ratio and absolute configuration were tentatively assigned by ^1H NMR spectra ($CDCl_3$) of the corresponding aldehyde after the mild hydrolysis.

Chiral acetals derived from (2R,4R)-2,4-pentanediol was also studied and results are shown in Table 2. The (R,R)-stereochemistry of the produced cyclopropane was established by the conversion to the corresponding acid.

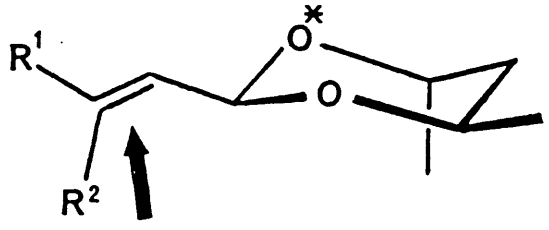
Table 2. Asymmetric Simmons-Smith Reaction of 3

Acetal				Product		
					Yield of 4[a] (%)	%de[b]
	R^1	R^2	R^3			
						
3a	Me	H	H	**4a**	74	69
3b	n-Pr	H	H	**4b**	95	71
3c	Ph	H	H	**4c**	85	68
3d	Me	Me	H	**4d**	81	-29[c]
3e	Et	H	Me	**4e**	69	75

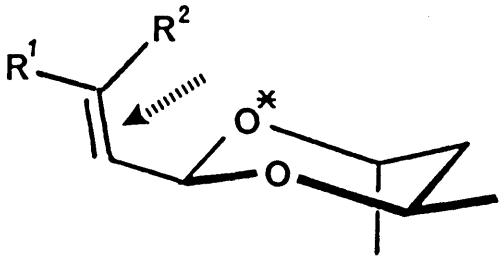
[a] Isolated yield. [b] Diastereomeric excess determined by ^1H NMR analysis of the product in the presence of shift reagent, $Eu(fod)_3$. [c] The absolute configuration was confirmed by the transformation to the corresponding carboxylic acid.

Apparently the observed selectivity is ascribed to the eminent affinity of zinc reagent for ethereal oxygen. Complex formation between the oxygen atom and the organozinc reagent, followed by methylene transfer to the nearest face of the neighboring double bond, has been proposed to account for the stereoselectivity and the large rate enhancement found for methylene addition to allylic alcohols and ethers relative to simple olefins.[2,8] The stereochemical outcome of Table 2 was surprising because it is in contrast to the regioselectivity reported for the previous reaction of acetal with (2R,4R)-2,4-pentanediol[3] in which one of the ether oxygen, O^* in **5**, should be coordinated preferentially by Lewis acid of the system. The same oxygen therefore should function as a syn director for the transfer of methylene: However, the observed stereochemical course is the opposite and this might be the result, inter alia, of different geometry relating olefinic linkage during cyclopropanation process (**5b** rather than **5a**).[9] Indeed, the trisubstituted olefin **3d**, $R^1 = R^2 = Me$, $R^3 = H$, for which the corresponding **5b** may be rather unlikely from the steric interaction of R^2 and the ring, gave the corresponding cyclopropane with the opposite stereochemistry. Thus, the substitution pattern of the starting trisubstituted double bond can have a pronounced effect on diastereoselectivities of the reaction: R^2 should be H for the selective reaction. In the reaction of the acetal **1**, the similar structure is also a responsible conformer. Although the exact mechanism of the cyclopropanation is not clear, at least O^* in **5c** should be a

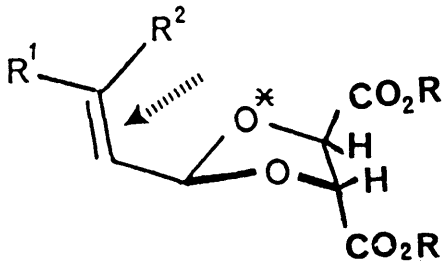
preferable coordination site of the Lewis acid.



5a

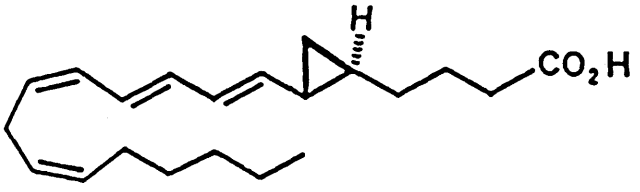


5b



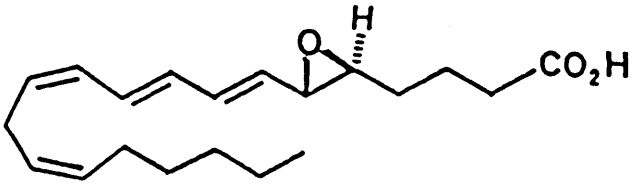
5c

Synthesis of (5R,6R)-5,6-methanoleukotriene A_4: It seems clear that the present method can encompass an availability of chiral cyclopropanes, increasingly important class of biologically active functionalities. One attractive target was (5R,6R)-5,6-methanoleukotriene A_4 (**6**), a stable and selective inhibitor of leukotriene A_4 (**7**) biosynthesis.[10]



(5R,6R)-5,6-Methanoleukotriene A_4

6

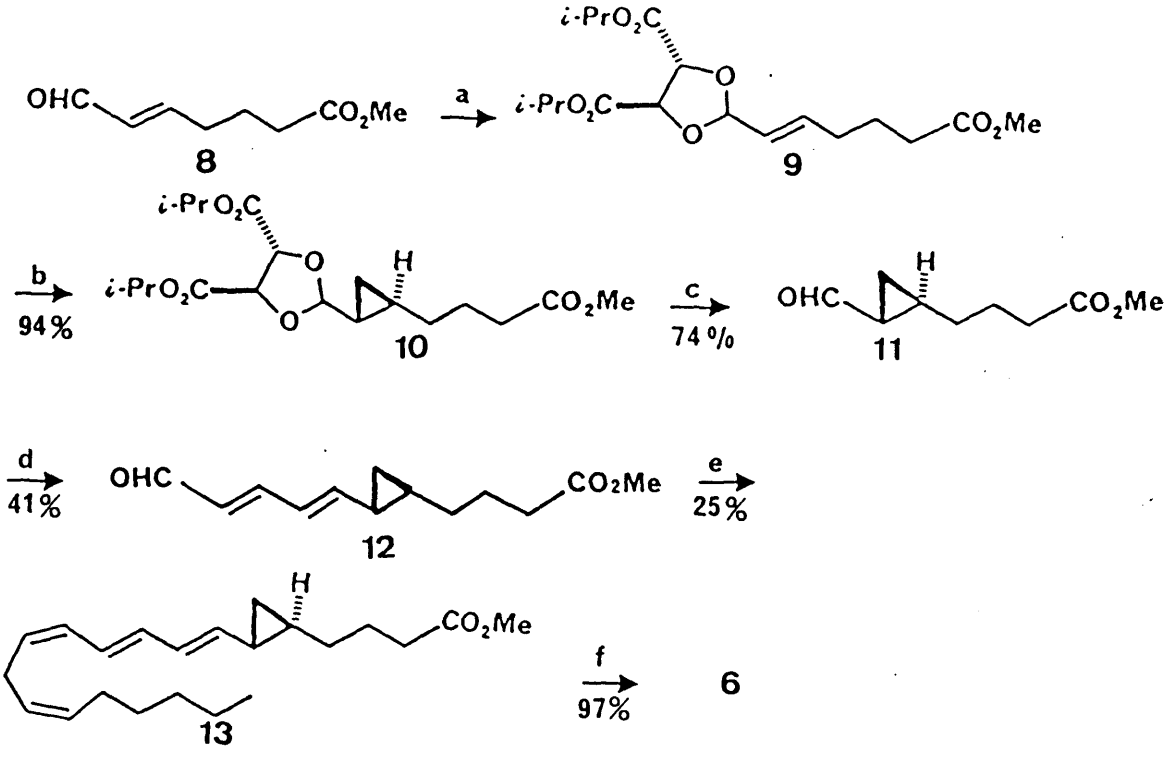


Leukotriene A_4

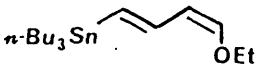
7

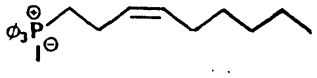
An enantioselective route of **6** is shown in Scheme 3. Acetalization of the α,β-unsaturated aldehyde **8** afforded the corresponding chiral acetal **9**, which was treated with methylene iodide and diethylzinc to give the cyclopropane **10**. Mild hydrolysis of **10** by p-toluenesulfonic acid in methanol-water gave **11**. The enantiomeric ratio of **11** was determined by conversion to the corresponding acetal of (-)-(2R,4R)-2,4-pentanediol whose 500 MHz ^{1}H NMR spectrum showed the purity of 90% ee. Reaction of aldehyde **11** with 1-lithio-4-ethoxybutadiene gave a dienal ester **12**. Selective Wittig reaction of **12** followed by mild hydrolysis of the methyl ester **13** afforded the desired inhibitor **6**. Some biological results of **6** compared with its racemate were shown in Table 3.

Scheme 3



a) 1) $HC(OEt)_3$-EtOH, NH_4NO_3, 78% 2) L-(+)-DIPT, TsOH-Py. 50%;

b) CH_2I_2-Et_2Zn; c) TsOH, MeOH-H_2O; d) 1)  , n-BuLi;

2) TsOH, THF-H_2O; e)  , n-BuLi- HMPA

f) NaOH, MeOH-THF-H_2O

Table 3 % Inhibition for 5-lipoxygenase

	100μM	50μM	5μM	IC_{50} (μM)
(-)-6	100	100	31.0	9.3
(±)-6	100	100	21.0	10.3

In conclusion the asymmetric Simmons-Smith reaction described herein appears to offer special advantages including high efficiency, procedural simplicity, predictable chirality of the product, and mildness of the conditions. Further application of the process to the synthesis of biologically active compounds and its derivatives is in progress.

Experimental

General. Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrometer. ^{1}H NMR spectra were measured on a JNM-PMX 60 (60 MHz), JNM-FX 90 QE (90 MHz) or JNM-GX 500 (500 MHz) spectrometer. 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. Optical rotations were measured on a JASCO DIP-140 digital polarimeter. All experiments were carried out under an atmosphere of dry argon. For thin layer chromatography (TLC) analyses throughout 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-200 MH. Microanalyses were accomplished at the Institute of Applied Chemistry, Faculty of Engineering, Nagoya University. In experiments requiring dry solvents, ether and THF were distilled from sodium-benzophenone. Hexane and benzene were dried over

sodium metal. Dichloromethane, chloroform, and carbon tetrachloride was dried over 4A molecular sieves. (-)-(2R,4R)-2,4-pentanediol was purchased and used after recrystallization from ether; $[\alpha]^{24}_{D}$ -41.2° (c 9.99, $CHCl_3$). Diethylzinc available as a 3.1 M hexane solution was used as such or after dilution to 2 M solution.[11] Other chemicals were purchased and used as such.

General procedure for the preparation of α,β-unsaturated acetal 1a-i and 3a-e. The mixture of the aldehyde, triethyl orthoformate (1.2 equiv) and a catalytic amount of ammonium nitrate in ethanol was stirred at room temperature until the consumption of the most of the starting aldehyde was confirmed by tlc. The product was washed with aqueous sodium bicarbonate and the organic layers were dried over anhydrous sodium sulfate. Removal of the dried solvent left the corresponding diethylacetal which was used for the next reaction without further purification. The mixture of the aldehyde diethylacetal (3.0 mmol), pyridinium tosylate (30 mg), and dialkyl tartrate (3.3 mmol) or (-)-(2R,4R)-2,4-pentanediol (344 mg, 3.3 mmol) in 30 mL of benzene was heated for 1 h to distill off the solvent and the producing ethanol. After cooling to room temperature, the residue was purified by column chromatography on silica gel (hexane-ether, 3-5:1) to give the corresponding acetal. The physical properties and analytical data of the acetal thus obtained were listed in Table 4a and 4b.

General procedure for the cyclopropanation of 1a-i. Small scale: To a solution of the acetal (1.0 mmol) in 10 mL of dry

hexane was added diethylzinc (5.0 mmol, 2.5 mL of a 2 M hexane solution) at -20°C. Methylene iodide (0.86 mL, 10 mmol) was added dropwise to the resulting vigorously stirred solution and the mixture was stirred under the condition as shown in Table 1. The reaction mixture was poured into cold aqueous ammonium chloride and the product was extracted with ether repeatedly. The organic layers were washed with sodium thiosulfate, dried over sodium

Table 4a. Spectral Data of α,β-Unsaturated Acetals 1 and 3

acetal[a]	IR (cm^{-1})[a]	^1H NMR (δ; ppm)[b]
1a	2970, 2920, 1735, 1365, 935	5.30-6.17 (m, 3 H), 5.03 (m, 2 H), 4.37-4.57 (m, 2 H), 1.78 (d, J = 6.0 Hz, 3 H), 1.28 (d, J = 6.0 Hz, 12 H)
1b	2970, 1750, 1210, 1095	5.30-6.33 (m, 3 H), 4.51 (m, 2 H), 4.29 (q, J = 7.5 Hz, 4 H), 1.32 (t, J = 7.5 Hz, 6 H)
1c	2970, 1740, 1215, 1100	5.30-6.23 (m, 3 H), 5.03 (m, 2 H), 4.47 (m, 2 H), 1.30 (d, J = 7.5 Hz, 4 H)
1d	2990, 1760, 1205, 1150, 1115, 795	7.30 (m, 5 H, ArH), 6.80 (d, J = 16.0 Hz, 1 H), 6.13 (dd, J = 16.0, 6.0 Hz, 1 H), 5.68 (d, J = 6.0 Hz, 1 H), 4.61 (m, 2 H) 4,29 (q, J = 7.6 Hz, 4 H), 1.33 (t, J = 7.6 Hz, 6 H)
1e	2980, 2930, 1745, 1680, 970, 750	7.13-7.63 (m, 5 H), 6.82 (d, J = 16.0 Hz, 1 H), 6.14 (dd, J = 16.0 Hz, 6.0 Hz, 1 H), 5.68 (d, J = 6.0 Hz, 1 H), 1.30 (d, J = 6.0 Hz, 12 H)
1g	2960, 2920, 1730, 1450, 950	5.43-5.63 (m, 1 H), 5.27 (s, 1 H), 5.03 (m, 2 H), 4.47 (m, 2 H), 1.30 (d, J = 6.5 Hz, 12 H)
1h	2970, 2900, 1735, 1640, 945	5.93 (br, 1 H), 5.33 (s, 1 H), 4.67 (br, 2 H), 4.20 (q, J = 6.4 Hz, 4 H), 1.73 (s, 3 H), 1.30 (t, J = 6.4 Hz, 6 H)
3a	2970, 2920, 2850, 1680, 1375	5.43-6.20 (m, 2 H), 5.17-5.33 (m, 1 H), 3.70-4.53 (m, 2 H), 1.72 (d, J = 6.0 Hz, 3 H)
3b	2970, 2920, 1455, 995,	5.33-6.00 (m, 2 H), 5.10 (d, J = 5.0 Hz, 1 H), 3.64-4.50 (m, 2 H)
3c	2985, 2935, 1370, 1130	7.30 (m, 5 H), 6.64 (d, J = 16.0 Hz, 1 H), 6.00 (dd, J = 16.0 Hz, 4.0 Hz, 1 H), 5.31 (d, J = 4.0 Hz, 1 H), 3.67-4.57 (m, 2 H)
3d	2980, 2950, 1690, 1380, 980	5.27 (d, J = 6.0 Hz, 1 H), 1.63 and 1.70 (s, 3 H each), 1.14 and 1.34 (d, J = 7.4 Hz, 3 H each)
3e	2970, 2920, 2860, 1680, 1370, 980	5.20-5.57 (m, 1 H), 4.87 (s, 1 H), 3.60-4.27 (m, 2 H), 1.53 (s, 3 H)

[a] Film. [b] ^1H NMR spectra were taken in CCl_4 solution.

Table 4b. Elemental Analyses of the acetals **1** and **3**

acetal	Yield (%)	Formula	Calcd C	Calcd H	Found C	Found H
1a	79	$C_{14}H_{22}O_6$	58.73	7.75	58.76	7.72
1b	53	$C_{14}H_{22}O_6$	58.73	7.75	58.69	7.79
1c	48	$C_{16}H_{26}O_6$	61.13	8.34	61.13	8.28
1d[a]	63	$C_{17}H_{20}O_6$	63.74	6.29	63.56	6.36
1e[b]	93	$C_{19}H_{24}O_6$	65.50	6.94	65.66	7.00
1g	61	$C_{16}H_{26}O_6$	61.13	8.34	61.14	8.33
1h	70	$C_{18}H_{26}O_6$	63.87	7.76	63.93	7.72
3a	77	$C_9H_{16}O_2$	69.19	10.32	68.89	10.62
3b	91	$C_{11}H_{20}O_2$	71,70	10.94	71.59	11.05
3c	99	$C_{14}H_{18}O_2$	77.03	8.31	76.95	8.28
3d	78	$C_{10}H_{18}O_2$	70.55	10.66	70.36	10.85
3e	78	$C_{11}H_{20}O_2$	71.70	10.94	71.51	11.13

[a] Mp 55.5-56.0°C. [b] Mp 56.0-57.5°C

sulfate and concentrated *in vacuo*. Chromatography of the residual oil on silica gel (hexane-ether, 3-5:1) afforded the corresponding cyclopropane **2a-i**.

For larger scale (20 mmol): To a solution of the acetal **1d**, R^1 = Ph, R^2 = Et (6.4 g, 20 mmol), in dry hexane (220 mL) was added diethylzinc (100 mmol, 32.3 mL of a 3.1 M hexane solution)

at -20°C. Methylene iodide (16.2 mL, 0.20 mol) was added dropwise to the resulting mechanically stirred solution and the mixture was mechanically stirred vigorously at -20°C for 6 h and 0°C for 6 h.[12] Treatment of the reaction mixture with aqueous ammonium chloride, sodium thiosulfate and water followed by the purification of the concentrated residue by column chromatography on silica gel (hexane-ether, 5:1) afforded the pure cyclopropane **2d**, R^1 = Ph, R^2 = Et, as a colorless oil (6.08 g, 91%).

The physical properties and analytical data of the cyclopropanes obtained are shown in Table 5a and 5b.

Table 5a. Spectral data of the acetal **2**.

Acetal	IR (cm^{-1})[a]	^1H NMR (δ; ppm)[b]
2a	2930, 1740, 1215, 1200	4.34-4.50 (m, 5 H), 1.30 (d, J = 6.0 Hz, 12 H)
2b	2930, 1750, 1205, 1115	3.93-4.83 (m, 7 H)
2c	2975, 2920, 1730, 1275, 1100	4.17-5.17 (m, 5 H), 1.17 (d, J = 6.0 Hz, 12 H)
2d	3000, 2960, 1755, 1620, 1380, 1160, 870, 760	7.07 (br s, 5 H, ArH), 5.03 (d, J = 5.6 Hz, 1 H), 4.47-4.67 (m, 2 H), 4.20 (q, J = 8 Hz, 4 H), 1.87-2.37 (m, 1 H), 1.27, 1.30 (2t, J = 8 Hz, 3 H each), 0.67-1.87 (m, 3 H)
2e	2970, 1735, 1215, 1100	7.03 (s, 5 H), 4.73-5.27 (m, 3 H), 4.50 (m, 2 H), 1.27 (d, J = 6.5 Hz, 6 H), 1.22 (d, J = 6.5 Hz, 2 H)
2g	2975, 2930, 2870, 1735, 1370, 1215, 1100	5.00 (m, 2 H), 4.27-4.60 (m, 3 H), 1.28 (d, J = 6.0 Hz, 12 H), 1.07 (s, 3 H)
2h	3070, 2990, 2920, 2860, 1740, 1210, 1115	4.63 (s, 1 H), 4.48 (m, 2 H), 4.21 (q, J = 7.5 Hz, 4 H), 1.30 (t, J = 7.5 Hz, 6 H), 0.83 (s, 3 H)

[a] Film. [b] Taken in CCl_4 solution.

Table 5b $[\alpha]_D$ and elemental analyses of the acetal **2**.

acetal	$[\alpha]_D$[a] degree	(c, °C)	Formula	Calcd C	Calcd H	Found C	Found H
2a	-56.1	(1.10, 24)	$C_{15}H_{24}O_6$	59.98	8.05	60.01	8.12
2b	-45.8	(1.26, 24)	$C_{15}H_{24}O_6$	59.98	8.05	60.12	8.04
2c	-49.3	(1.05, 25)	$C_{17}H_{28}O_6$	62.17	8.59	62.31	8.65
2d	-94.2	(1.03, 25)	$C_{18}H_{22}O_6$	64.66	6.63	64.66	6.63
2e	-84.5	(0.98, 23)	$C_{20}H_{26}O_6$	66.28	7.23	66.05	7.34
2f	+47.8	(1.02, 28)					
2g	-43.6	(0.97, 24)	$C_{17}H_{28}O_6$	62.17	8.59	62.13	8.63
2h	-44.8	(1.13, 26)	$C_{20}H_{30}O_6$	65.55	8.25	65.56	8.24
2i	+15.6	(1.00, 25)					

[a] Measured in ethanol solution

General procedure for the cyclopropanation of 3a-e. To a solution of the acetal **3** (1.0 mmol) in dry hexane (10 mL) was added diethylzinc (5.0 mmol, 2.5 mL of a 2 M hexane solution) at -20°C. Methylene iodide was added dropwise to the vigorously stirred solution[12] and the stirring was continued for 2 h at -20°C. The reaction mixture was poured into 1 N NaOH and extracted with ether repeatedly. The organic layers were dried over sodium sulfate and concentrated *in vacuo*. Purification of

the residual oil by column chromatography on silica gel (hexane-ether, 3-4:1) afforded the cyclopropane **4**.

The physical properties and analytical data of the cyclopropanes thus obtained are listed in Table 6a and 6b.

Table 6a Spectral data of the acetal **4**

acetal	IR (cm^{-1})[a]	^1H NMR (δ; ppm)[b]
4a	2910, 2850, 1370, 1140, 995	4.53 (d, J = 3.5 Hz, 1 H), 3.53-4.43 (m, 2 H)
4b	2960, 2920, 1155, 1140, 1000	4.40 (d, J = 4.0 Hz, 1 H), 3.47-4.30 (m, 2 H)
4c	3030, 2970, 2920, 2850, 1600, 1495, 1370, 995	7.00 (m, 5 H, ArH), 4.57 (d, J = 4.5 Hz, 1 H), 3.50-4.40 (m, 2 H)
4d	2970, 2930, 1450, 1380, 1000	3.43-4.47 (m, 3 H), 1.03 (s, 6 H)
4e	2950, 2920, 2850, 1370, 1150, 1130, 1100	3.67-4.67 (m, 3 H), 1.17 (s, 3 H)

[a] Film. [b] Taken in CCl_4 solution.

Table 6b. $[\alpha]_D$ and elemental analyses of the acetal **4**.

Acetal	$[\alpha]_D$[a] degree	(c, °C)	Formula	Calcd C	Calcd H	Found C	Found H
4a	-4.5	(1.06, 25)	$C_{10}H_{18}O_2$	70.55	10.66	70.30	10.91
4b	-13.5	(1.08, 32)	$C_{12}H_{22}O_2$	72.68	11.18	72.65	11.21
4c	-76.5	(0.98, 29)	$C_{15}H_{20}O_2$	77.55	8.68	77.52	8.71
4d			$C_{11}H_{20}O_2$	71.70	10.94	71.58	11.06
4e	-12.8	(1.00, 26)	$C_{12}H_{22}O_2$	72.58	11.18	72.44	11.42

[a] Measured in ethanol solution

The transacetalization of the acetal 2: The mixture of the acetal **2** (0.5 mmol) and p-toluenesulfonic acid (30 mg) in methanol (15 mL) was stirred at 25°C for 24 h. The reaction mixture was poured into saturated sodium bicarbonate and the product was extracted with hexane twice. The organic layers were dried over sodium sulfate and concentrated *in vacuo*. The residue was dissolved in 10 mL of benzene. To the mixture was added (2*R*,4*R*)-2,4-pentanediol (52 mg, 0.5 mmol) and pyridinium tosylate (10 mg). The resulting reaction mixture was heated for 1 h to distill off the solvent. The resulting mixture was poured into saturated sodium bicarbonate and the product was extracted with hexane twice. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. Purification by column

chromatography on silica gel (hexane-ether, 3-5:1) afforded the corresponding acetal in ca. 60-70% yield. IR and ^{1}H NMR spectra of the acetal obtained were identical with those of the acetal **4**.

Hydrolysis of the acetal 2d: A mixture of the acetal **2d** (1.67 g) and p-toluenesulfonic acid (1.0 g) in THF-water (50 mL-10 mL) was heated with reflux for 7 h. The reaction mixture was poured into saturated sodium bicarbonate and the product was extracted with hexane twice. The organic layers were dried over sodium sulfate and concentrated in vacuo. Bulb to bulb distillation of the residue afforded a colorless oil (450 mg, 62% yield): bp (bath temp) 120°C (1 torr); IR (neat) 3040, 2850, 2730, 1695, 760, 700 cm^{-1}; ^{1}H NMR (CCl_4) δ 9.33 (d, J = 3.8 Hz, 1 H, CHO), 7.10 (m, 5 H, ArH); $[\alpha]^{25}_D$ -378° (c 0.378, $CHCl_3$); lit. $[\alpha]^{25}_D$ -340° (c 0.363, $CHCl_3$).[4c]

Hydrolysis of the acetal 2h: A mixture of the acetal **2h** (100 mg, 0.27 mmol) and p-toluenesulfonic acid (50 mg) in ethanol (3 mL)-water (3 mL) was stirred at 25°C for 36 h. The product was washed with saturated sodium bicarbonate. Concentration of the dried solvent left a crude oil, which was purified by column chromatography on silica gel (hexane-ether, 5:1) to give the corresponding aldehyde as a colorless oil in 75% yield: IR (neat) 3070, 2980, 2920, 2850, 2700, 1700, 1440, 1005, 925 cm^{-1}; ^{1}H NMR (CCl_4) δ 8.66 (s, CHO of the axial aldehyde), 8.59 (s, equatorial isomer), 0.75 (s, 3 H).[13] Hydrolysis of **2i** was also carried out in the similar manner (79% yield).

(1R,2R)-2-Phenylcyclopropanecarboxylic acid: A solution of the acetal **2d** (1.67 g, 5.0 mmol) in 50 mL of carbon tetrachloride

was treated with the excess ozone at 0°C for 5 h.[6] The solvent and the remaining ozone was removed *in vacuo* and the residue was dissolved in ethyl acetate and washed with brine. The separated organic layers were dried over sodium sulfate and concentrated *in vacuo* to give the crude oil. The ester thus obtained was dissolved in ethanol (25 mL) - 10 N KOH (5 mL) and stirred at 0°C for 2 h to complete the hydrolysis of the ester. The mixture was poured into cold 2 N hydrochloric acid (50 mL) and the product was extracted with ethyl acetate repeatedly. The concentration of the dried organic layers followed by the purification by column chromatography on silica gel (hexane-ethyl acetate, 1:2) afforded (1R,2R)-2-Phenylcyclopropanecarboxylic acid as a colorless oil (0.44 g, 43%): $[\alpha]^{26}_{D}$ -287.6° (c 1.21, ethanol); lit. 1S,2S isomer: $[\alpha]^{25}_{D}$ +311.7° (c 1.776, 1 dm, ethanol).[14] The $[\alpha]_{D}$ of other carboxylic acid thus obtained are listed below.

(1R,2R)-2-Methylcyclopropanecarboxylic acid: $[\alpha]^{24}_{D}$-71.9° (c 1.00, ethanol); lit. 1R,2R isomer (51% ee): $[\alpha]^{24}_{D}$-39.7 (ethanol)[15]

1-(S)-2,2-dimethylcyclopropanecarboxylic acid: 4d was transformed to the carboxylic acid in the manner as described above in 85% yield: $[\alpha]^{27}_{D}$ +38.89° (c 1.01, $CHCl_3$); lit. 1S isomer: $[\alpha]^{25}_{D}$ +146° (c 1.06, $CHCl_3$).[16]

L-Diisopropyl-2,3-O-*trans*-6'-carbomethoxy-1'-pentenylidene-tartrate (9): The mixture of methyl *trans*-7-oxo-5-heptenoate **8** (1.56 g, 10 mmol),[17] triethyl orthoformate (1.80 g, 12 mmol) and 10 mL of ethanol was stirred at room temperature for 12 h. The reaction mixture was poured into saturated sodium bicarbonate and

the product was extracted with hexane twice. The organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The product was purified by column chromatography on silica gel (hexane-ether, 5:1) to give the diethylacetal (1.80 g, 78%). The mixture of the diethylacetal (1.80 g, 7.8 mmol), L-(+)-diisopropyl tartrate (1.76 g, 7.5 mmol) and pyridinium tosylate (10 mg) in 50 mL of benzene was heated for 30 min to distill off the solvent and resultant ethanol. The residue was purified by column chromatography on silica gel (hexane-ethyl acetate, 10:1-5:1, gradient elution) to give the acetal **9** as a colorless oil (1.44 g, 50% yield): IR (neat) 2980, 2950, 1750, 1735, 1220, 965 cm^{-1}; ^1H NMR (CCl_4) δ 3.60 (s, 3 H), 1.18 (d, J = 6.2 Hz, 12 H); Anal. Calcd for $C_{18}H_{28}O_8$: C, 58.05; H, 7.58. Found: C, 58.27; H, 7.70.

Asymmetric Simmons-Smith reaction of the acetal 9 : To a solution of the acetal **9** (0.744 g, 2 mmol) in 20 mL of dry hexane was added diethylzinc (10 mmol, 5 mL of 2.0 *M* hexane solution) at -20°C. Methylene iodide (1.62 mL, 20 mmol) was added dropwise to the resulting stirred solution and the mixture was vigorously stirred at -20°C for 4 h and at 0°C for 4 h. The reaction mixture was poured into cold aqueous ammonium chloride and the product was extracted with ether repeatedly. The ether layers were washed with sodium thiosulfate and water. The combined ether layers were dried over sodium sulfate and concentrated *in vacuo*. Purification by chromatography on silica gel (hexane-ethyl acetate, 3:1) afforded the pure cyclopropane **10** as a colorless oil (0.726 g, 94% yield): IR (neat) 3000, 2950, 1750,

1735, 1375, 1220, 1105, 905 cm^{-1}; ^1H NMR (CCl_4) δ 4.75 (d, J = 5.8 Hz, 1 H), 3.57 (s, 3 H), 1.28 (d, J = 6.2 Hz, 12 H), 0.17-1.17 (m, 4 H); Anal. Calcd for $C_{19}H_{30}O_8$: C, 59.05; H, 7.83. Found: C, 59.07; H, 7.81.

(2R,3R)-6-Carbomethoxy-2,3-methanohexanal (11): A mixture of the acetal **10** (292 mg, 0.76 mmol) and p-toluenesulfonic acid (100 mg) in methanol-water (8 mL - 3 mL) was stirred at room temperature for 72 h. The reaction mixture was poured into saturated sodium bicarbonate and the product was extracted with ether repeatedly. The organic layers were dried over sodium sulfate and concentrated in vacuo. Purification by chromatography on silica gel (hexane-ethyl acetate, 5:1) afforded the aldehyde **11** (95.5 mg, 74%), spectral data of which was identical with the reported racemic aldehyde: $[\alpha]^{27}_D$ -51.2° (c 1.05, $CHCl_3$); Stereochemical purity (90% ee) of the product was determined after the following: Treatment of **11** (94 mg, 0.56 mmol) and (2R,4R)-2,4-pentanediol (104 mg, 1.0 mmol) in the presence of pyridinium tosylate (5 mg) in benzene at reflux for 1 h gave the corresponding acetal (125 mg, 87% yield): ^1H NMR ($CDCl_3$) (500 MHz) δ 4.31 (d, J = 5.65 Hz); the S isomer 4.35 (d, J = 5.65 Hz).

(5R,6R)-Methyl-5,6-methano-11-oxo-undeca-7,9-dienoate (12): To a solution of tributylstannyl-4-ethoxy-1,3-butadiene (542 mg, 1.40 mmol)[17] in 5 mL of THF was added n-butyllithium (0.9 mL of 1.45 N hexane solution, 1.31 mmol) at -78°C under argon. The temperature was raised to -40°C in 15 min. The reaction mixture was cooled to -78°C, and the aldehyde **11** (188 mg, 1.10 mmol)

dissolved in 5 mL of THF was added. After being stirred at -78°C for 1 h, the resulting mixture was poured into aq. sodium bicarbonate and the product was extracted with ether repeatedly. The combined organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo* to give a crude oil, which was dissolved in THF-water (4.5 mL-0.5 mL) and exposed with catalytic amount of *p*-toluenesulfonic acid at room temperature for 15 min. The mixture was poured into aq. sodium bicarbonate 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 (ether-hexane, 1:2) to give unstable **12** (100 mg, 41%): ^{1}H NMR ($CDCl_3$) δ 9.47 (1 H, d, J = 8 Hz), 7.01 (1 H, dd, J = 16 and 12 Hz), 6.34 (1 H, dd, J = 16 and 10 Hz), 6.03 (1 H, dd, J = 16 and 8 Hz), 5.77 (1 H, dd, J = 16 and 10 Hz), 3.33 (3 H, s), 2.34 (2 H, t, J = 7 Hz), 1.00-0.74 (4 H, m)

(5*R*,6*R*)-5,6-Methanoleukotriene A_4 (6): To a solution of *cis*-3-nonenyltriphenylphosphonium iodide (450 mg, 0.88 mmol)[17] in 5 mL of THF was added *n*-butyllithium (0.58 mL of 1.5 *N* hexane solution, 0.87 mmol) followed by addition of HMPA (1.5 mL) at -78°C under argon. After being stirred for 5 min, the freshly prepared aldehyde **12** (162 mg, 0.73 mmol) dissolved in 5 mL of THF was added and stirring was continued for 15 min. The resulting mixture was poured into aq. sodium bicarbonate and the product was extracted with ether. The dried organic layer was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (ether-hexane, 1:40) to give **13** (60 mg, 25%)[18]. To a solution of **13** (60 mg, 0.18 mmol) in methanol-

THF (5 mL- 5 mL) was added 1 mL of 2 N NaOH and the mixture was stirred at 40°C for 5 h under argon. After being recooled to 0°C, the mixture was acidified by 1 N hydrochloric acid and the product was extracted with ether. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give **6** (55 mg, 97%): $[\alpha]^{22}_{D}$ -19.3° (c 2.55, $CHCl_3$); IR(neat) 3700-2200, 1710, 1630, 995 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.44-6.26 (1 H, m), 6.24-6.05 (2 H, m), 6.05-5.90 (1 H, m), 5.50-5.20 (4 H, m), 2.98 (2 H, t, J = 7 Hz), 2.39 (2 H, t, J = 7 Hz), 0.70-0.50 (2 H, m); MS m/e 316 (M^+: $C_{21}H_{32}O_2$).

References

1. Part of this paper was reported preliminary: Arai, I.; Mori, A.; Yamamoto, H. J. Am. Chem. Soc., **1985**, 107, 8254. The similar reaction using cyclic ketone acetals was also reported independently: (a) Mash, E. A.; Nelson, K. A. Ibid., **1985**, 107, 8256. (b) Idem, Tetrahedron Lett., **1986**, 27, 1441.
2. Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A.; Hoiness, C. M. Org. React. **1973**, 20, 1.
3. (a) Mori, A.; Ishihara, K.; Yamamoto, H. Tetrahedron Lett., **1986**, 27, 987 and references cited therein; (b) Elliott, J. D.; Steele, J.; Johnson, W. S. Tetrahedron Lett., **1985**, 26, 2535 and references cited therein.

4. Asymmetric cyclopropanation of α,β-unsaturated carbonyl derivatives: (a) Johnson, C. R.; Schroeck, C. W. J. Am. Chem. Soc., **1968**, 90, 6852; Ibid., **1973**, 95, 7418; (b) Johnson, C. R.; Barbachyn, M. R. Ibid., **1982**, 104, 4290; (c) Abdallah, H.; Cree, R.; Carrie, R. Tetrahedron Lett., **1982**, 23, 503.

5. Furukawa, J.; Kawabata, N.; Nishimura, J. Tetrahedron, **1968**, 24, 53.

6. Deslongchamps, P.; Atlani, P.; Frèhel, D.; Malaval, A.; Moreau, C. Can. J. Chem., **1974**, 52, 3651.

7. Recent asymmetric syntheses using dialkyl tartrate: (a) Katsuki, T.; Sharpless, K. B.; J. Am. Chem. Soc., **1980**, 102. 5976; (b) Haruta, R.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. Ibid., **1982**, 104, 7667; Ikeda, N.; Arai, I.; Yamamoto, H. Ibid., **1986**, 108, 483; See also (c) Seebach, D. In "Modern Synthetic Methods 1980"; Scheffold, D. Ed., Otto Salle Verlag, Frankfurt.

8. Poulter, C, D.; Friedrich, E. C.; Winstein, S. J. Am. Chem. Soc., **1969**, 91, 6892.

9. Similar effect was also observed in the Simmons-Smith reaction of (-)-menthyl cinnamate; Morrison J. D.; Mosher, H. S. "Asymmetric Organic Reactions"; p 248, Prentice-Hall, N. J. (1971).

10. Nicolaou, K. C.; Petasis, N. A.; Seitz, S. P. J. Chem. Soc., Chem. Commun., **1981**, 1195.

11. Diethylzinc was kindly donated by Toyo Staufer Chemical Co., Ltd.

12. Vigorous stirring is very important during these operations: otherwise the reaction sometimes occurs explosively. see ref. 5.

13. The CHO of trans-4-tert-butylcyclohexanecarbaldehyde, δ 9.61; the corresponding cis isomer, δ 9.70. Accrombessi, G.; Geneste, P.; Olive, J. L.; Pavia, A. A. Bull. Soc. Chim. Fr. **1981**, II-19.

14. Inouye, Y.; Sugita, T.; Walborsky, H. M. Tetrahedron, **1964**, 20, 1695.

15. Sugita, T.; Inouye, Y. Bull. Chem. Soc. Jpn., **1966**, 39, 1075

16. Aratani, T. Private communication.

17. Corey, E. J.; Clark, D. A.; Goto, G.; Marfat, A.; Mioskowski, C.; Samüelsson, B.; Hammarstrom, S. J. Am. Chem. Soc., **1980, 102**, 1436.

18. Degassed solvent was used for extraction and column chromatography.

PUBLICATION LIST

I. Part of the present thesis have been published in the following journals.

CHAPTER 2 Tetrahedron Lett., **1983**, 24, 4581.
Ibid., **1984**, 25, 4421.
J. Organometal. Chem., **1985**, 285, 83.

CHAPTER 3 Tetrahedron Lett., **1986**, 27, 983.
Ibid., **1986**, 27, 987.
Tetrahedron, in press.

CHAPTER 4 J. Org. Chem., **1985**, 50, 5444.
and supplementary material.

CHAPTER 5 J. Am. Chem. Soc., **1985**, 107, 8254.
Tetrahedron, in press.

II. Following publications are not included in this thesis.

Stereoselective Carbonyl Olefination via Organosilicon Compounds. Boron and Titanium Reagents.
Haruta, R.; Ishiguro, M.; Furuta, K.; Mori, A.; Ikeda, N.; Yamamoto, H. Chem. Lett., **1982**, 1093.

A New Cyclopentanone Annulation of α-Bromomethylacrylates.
Furuta, K.; Misumi, A.; Mori, A.; Ikeda, N.; Yamamoto, H. Tetrahedron Lett., **1984**, 25, 669.

Palladium-Catalyzed Dimerization of Allenes to 2,3-Bis(chloromethyl)butadienes. Synthesis of Conjugate Exocyclic Dienes.
Hegedus, L. S.; Kambe, N.; Ishii, Y.; Mori, A. J. Org. Chem., **1985**, 50, 2240.

Palladium (0)-Catalyzed Synthesis of Indoloquinones.
Hegedus, L. S.; Mulhern, T. A.; Mori, A. J. Org. Chem., **1985**, 50, 4282.

Reviews:

Selective Synthetic Reactions Using Organotitanium Reagents.
Yamamoto, H.; Mori, A. Kagaku Zokan, **1985**, 105, 63.

Asymmetric Syntheses Using Homochiral Acetals.
Mori, A.; Yamamoto, H. Kagaku, **1987**, in press.

ACKNOWLEDGMENTS

The author would like to express his grateful acknowledgment to Professor Hisashi Yamamoto whose encouragements and helpful suggestion have been indispensable to the completion of the present thesis. He is also indebted to Drs. Keiji Maruoka, Kyoji Furuta and Nobuo Ikeda for practical guidance and fruitful discussion. Furthermore he would like to thank Professor Takeshi Nishiguchi for informative suggestion. It is pleasure to express his appreciation to the colleagues, especially Messers. Junya Fujiwara, Isao Arai and Kazuaki Ishihara for valuable contribution.

Finally, the author wishes to express his special acknowledgment to Professor Louis S. Hegedus who gave him an opportunity to study at Colorado State University, U.S.A. for the period of June to September 1984. He is also indebted to colleagues of Professor Hegedus' research group.