APPLICATION OF CHIRAL CYCLIC DIOLS TO ASYMMETRIC INDUCTION

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APPLICATION OF CHIRAL CYCLIC DIOLS TO ASYMMETRIC INDUCTION

A Dissertation
for
the Degree of Doctor of Pharmaceutical Sciences
Institute of Pharmaceutical Chemistry
Faculty of Pharmaceutical Sciences
Kyushu University

Keisuke Kato
1994

PREFACE

This dissertation has been carried out during four years from 1990 to 1994 under the direction of

Professor Dr. Kiyoshi Sakai

at the Institute of Pharmaceutical Chemistry, Faculty of Pharmaceutical Sciences, Kyushu University.
This thesis presents the **APPLICATION OF CHIRAL CYCLIC DIOLS TO ASYMMETRIC INDUCTION.**

The author would like to express his sincerest gratitude to Professor Dr. Kiyoshi Sakai for his kind and fruitful suggestion and encouragement throughout the course of his research.

He would like to make a grateful acknowledgment to Dr. Kazuhisa Funakoshi, Dr. Hiroshi Suemune, and Dr. Masakazu Tanaka for their profound and helpful discussions.

He extends his thankfulness to Mr. Kenji Watanabe and the rest of members in the Laboratory of Professor Sakai for their occasional discussions and hearty cooperation with him.

Finally, an acknowledgment must be made to his parents and brother for their patience and understanding, without which this work would not have been possible.

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February 1994

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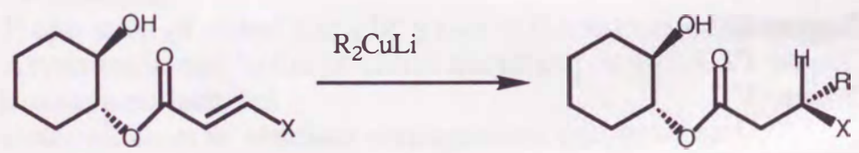
INTRODUCTION

The development of methodologies to effect on chiral synthesis efficiently, economically and in high enantiomeric purity is vital importance, because of the emergence of a number of chiral drugs.[1] For above purpose, a large number of chiral auxiliaries from natural and synthetic origins have been prepared[2] and studied.

Recently, the chemo-enzymatic approach[3] has proven its high potential in asymmetric synthesis. Lipase-catalyzed hydrolysis of esters or acetates is a convenient and useful method to obtain chiral building blocks and valuable auxiliaries.[4] In recent years, the stereochemical outcome of *Pseudomonas fluorescens lipase* (PFL)-catalyzed enantioselective hydrolysis have been systematically studied by Sakai *et al.*,[5] and chiral cyclic 1,2-diols were practically prepared in >99% e.e. For application of these diols to asymmetric synthesis and the development of promising auxiliaries, these chiral diols have been utilized as a chiral ester for asymmetric conjugate addition (Scheme 1).[6]

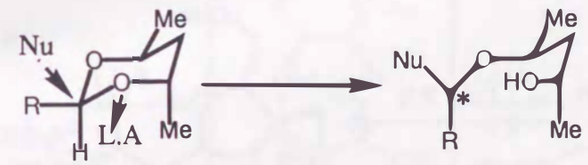


Scheme 1

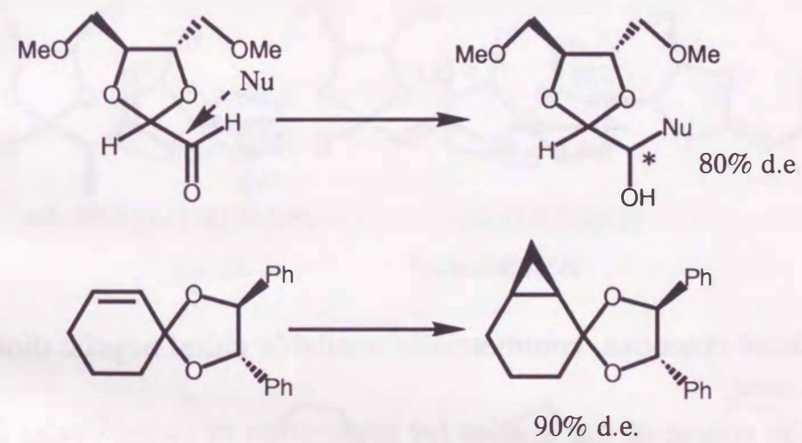
It is well known that the selection of a protective group plays an important role in organic synthesis, and many protective groups have been developed for this purpose.[7] Recently, chiral diols having a C_2 axis of symmetry have attracted much attention from the standpoint of asymmetric synthesis, because a single acetal can be derived from a simple carbonyl compound without any other chiral center, and chiral

acetal is capable of differentiating between the *re*- and *si*- faces of a neighboring prochiral group.[8]

On this point of view, several approaches have been recently reported,[8] which are divided into two classes. One is asymmetric reaction accompanied with cleavage of acetal ring by nucleophilic substitution reactions in the presence of strong Lewis acid (Scheme 2).

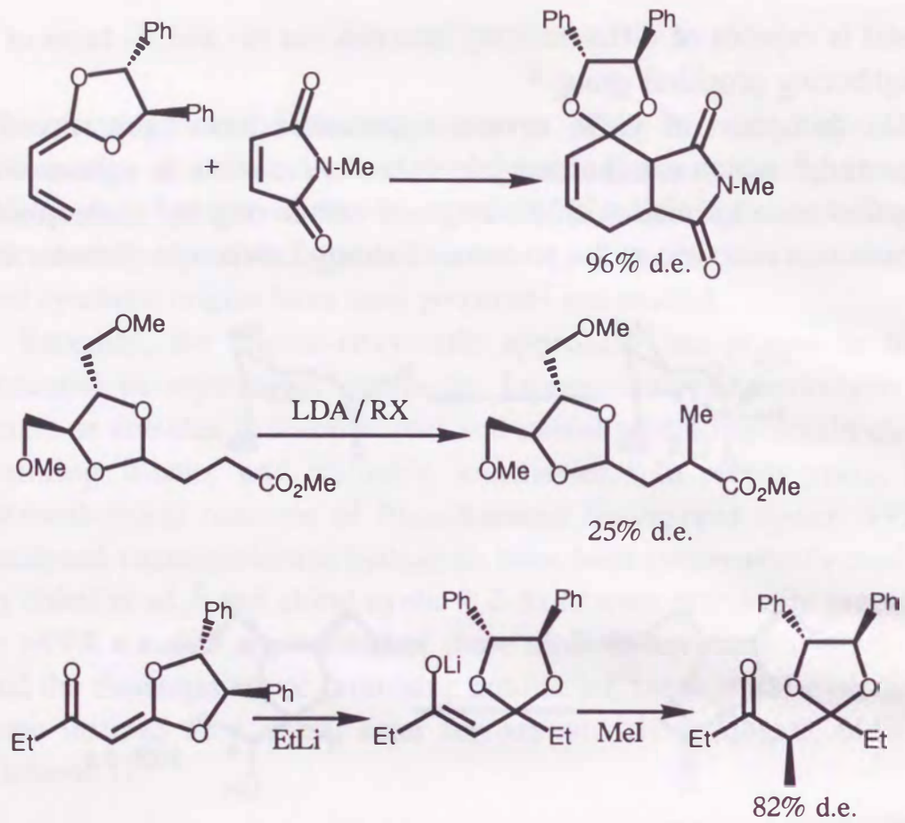


Scheme 2



Scheme 3

The other is asymmetric reactions without ring cleavage. The latter reactions are classified into two types ; i) Combination of electrophile with chiral acetal (Scheme 3), ii) Combination of nucleophile with chiral acetal (Scheme 4).[9]



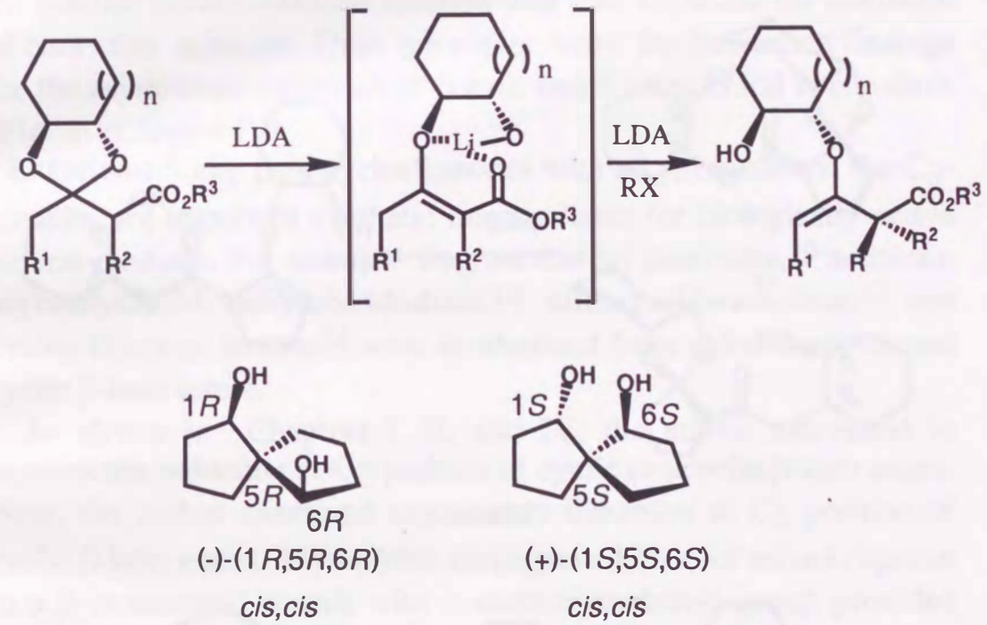
Scheme 4

In these reactions, commercially available chiral acyclic diols were often used.

In the course of our studies for application of chiral cyclic diols to asymmetric synthesis, the author succeeded in development of following asymmetric reactions. The molecular models reveal that chiral cyclic diols possess the conformational rigidity as well as molecular dissymmetry necessary for effective diastereofacial selectivity. The author found that asymmetric alkylation of chiral 1,2-cycloheptanedioxy (or 1,2-cyclohexanedioxy) acetals of five or six-membered ring (or acyclic) β-keto esters proceeded in a highly

diastereoselective manner *via* the base-promoted ring opening of chiral acetal to afford a quaternary carbon.

As a synthetic application of this reaction, enantio- and diastereo-selective syntheses of (+)- and (-)-spiro [4.4] nonane-1,6-diols were achieved (Chapter I) (Scheme 5).



Scheme 5

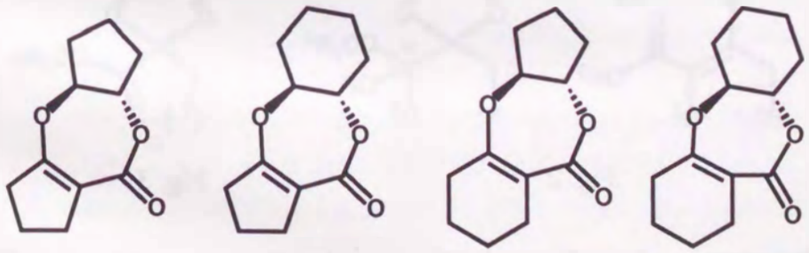
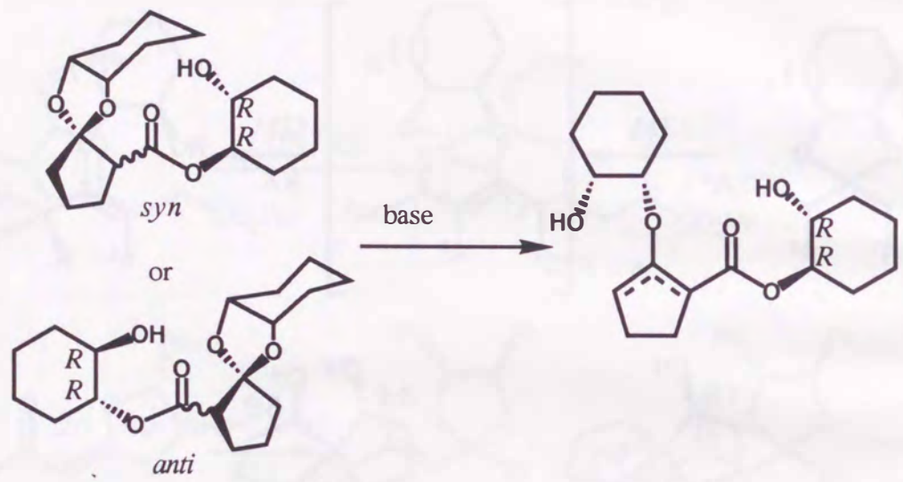


Fig. 1

In general, acetals are routinely prepared by treatment of aldehyde or ketone with the diol in the presence of acid under azeotropic conditions.[7] The author has also developed a preparation of chiral tricyclic 1,4-dioxepin-5-one derivatives under azeotropic conditions and its application to asymmetric alkylation (Chapter II) (Fig. 1).



Scheme 6

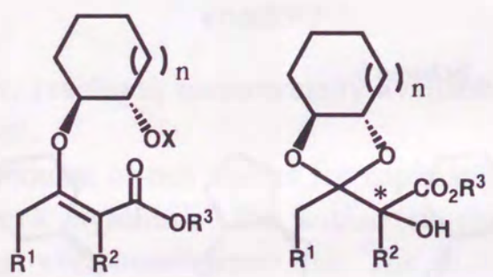


Fig. 2

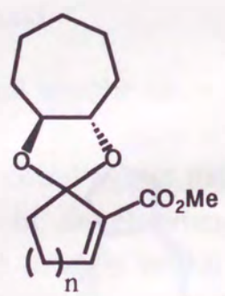


Fig. 3

In the course of studies on asymmetric alkylation (Chapter I), the author found that the acetal of β-keto esters is easily cleaved by treatment with LDA to afford the corresponding enol ether (Scheme 5). On the basis of this finding, he examined asymmetric induction to *meso*-cyclohexane-1,2-diol moiety (Scheme 6) (Chapter III).

In Chapter I, the author found that the chiral enol ether plays an important role on the asymmetric induction in terms of the formation of chelation complex among three oxygens and lithium cation (Scheme 5). Similar stereocontrolled reaction was also expected for oxidation of enol ether substrate. Thus, the author found the interesting findings for the asymmetric oxidation of β-keto esters using chiral cyclic diols (Fig. 2) (Chapter IV).

Enantiomerically pure cycloalkanones with alkyl function at the C_3-position are important synthetic intermediates for biologically active natural products. For example, fragrant methyl jasmonate,[10] antibiotic sarkomycin,[11] dehydroiridodiols,[12] mitsugashiwalactone,[13] and Prelog-Djerassi lactone[14] were synthesized from chiral 3-substituted cyclic β-keto esters.

As shown in Chapters I, II, and IV, the author succeeded in asymmetric induction at C_2 position of cyclic or acyclic β-keto esters. Next, the author examined asymmetric induction at C_3 position of cyclic β-keto esters. Asymmetric conjugate addition of mixed cuprates to α,β-unsaturated acetals with α-methoxycarbonyl group provided the new type of asymmetric double Michael reaction, induced by chiral acetal (Chapter V) (Fig. 3).

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1) Application of Chiral Cyclic Diols to Asymmetric Alkylation
Keisuke Kato, Hiroshi Suemune, and Kiyoshi Sakai
Tetrahedron Lett., **1992**, 33, 247.

2) Asymmetric Alkylation Using Chiral Cyclic Diols to Prepare a Quaternary Carbon
Keisuke Kato, Hiroshi Suemune, and Kiyoshi Sakai
submitted to *Tetrahedron*.

3) Stereoselective Synthesis of Chiral Spiranes
Hiroshi Suemune, Kazunori Maeda, Keisuke Kato, and Kiyoshi Sakai
in preparation.

4) Asymmetric Alkylation of Chiral α,β-Unsaturated Lactones
Keisuke Kato, Hiroshi Suemune, and Kiyoshi Sakai
Tetrahedron Lett., **1992**, 33, 3481.

5) Preparation of Optically Active Tricyclic 1,4-Dioxepin-5-one Derivatives and Its Application to Asymmetric Alkylation
Keisuke Kato, Hiroshi Suemune, and Kiyoshi Sakai
Heterocycles., in press.

6) Asymmetric Induction to *meso*-Cyclohexane-1,2-diol Based on Diastereoselective Elimination
Hiroshi Suemune, Kenji Watanabe, Keisuke Kato, and Kiyoshi Sakai
Tetrahedron : Asymmetry., **1993**, 4, 1767.

7) Asymmetric Oxidation of β-Keto Esters Using Chiral Cyclic Diols
Keisuke Kato, Hiroshi Suemune, and Kiyoshi Sakai
submitted to *Tetrahedron Lett.*

8) New Type of Asymmetric Double Michael Reaction Induced by Chiral Acetal
Keisuke Kato, Hiroshi Suemune, and Kiyoshi Sakai
Tetrahedron Lett., **1993**, 34, 4979.

CHAPTER I
ASYMMETRIC ALKYLATION OF CHIRAL ACETALS PREPARED FROM CYCLIC OR ACYCLIC β-KETO ESTERS AND CHIRAL CYCLIC DIOLS

1. Introduction

The alkylation of β-keto esters under basic conditions represents widely used and synthetically flexible process. Much effort has been devoted to solve several problems associated with this reaction. Consequently, synthetically trouble problems such as O-alkylation and dialkylation were successfully clarified.[15] The asymmetric alkylation of β-keto esters is important, and the success of this process seems to offer new entry for the synthesis of highly functionalized and enantiomerically pure substrates. On these points of view, several approaches have been recently reported.[16] These reactions are classified to six classes: 1) Use of chiral phase transfer catalysts (Fig. 4).[16a]

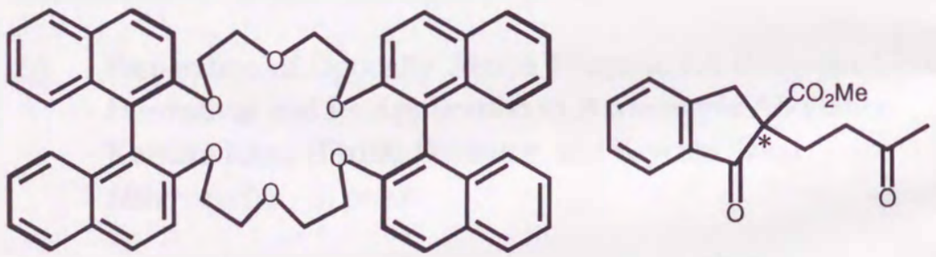
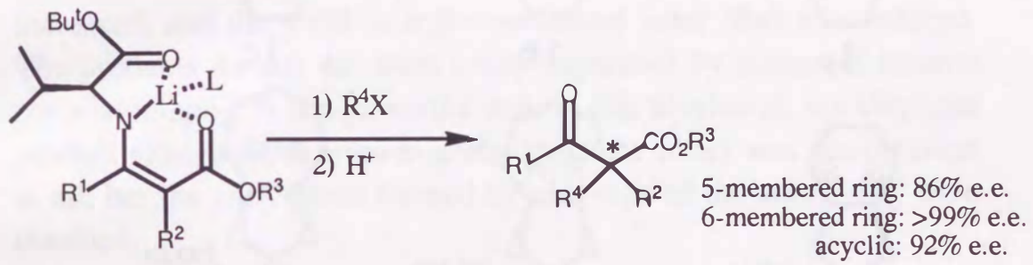


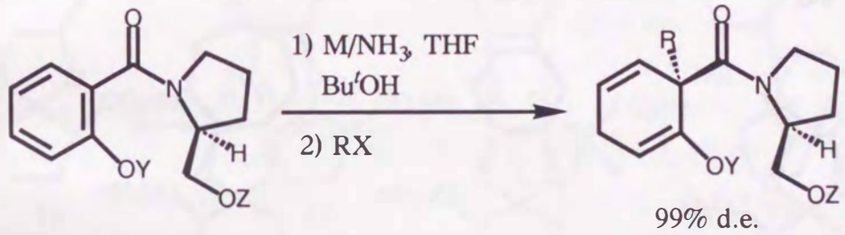
Fig. 4

2) Use of lithiated enamines (Scheme 7).[16b] 3) Reductive alkylation of benzoic acid derivatives (Scheme 8).[16c] 4) Use of chiral alkylating agents.[16d] 5) Lewis acid-promoted alkylation of enamines.[16e] 6) Use of ester-bound chiral auxiliaries.[9f] In the course of our studies for

application of chiral cyclic diols to asymmetric synthesis, the author found that asymmetric alkylation of chiral 1,2-cycloheptanedioxy (or 1,2-cyclohexanedioxy) acetal of five or six-membered ring (or acyclic) β-keto esters proceeds in a highly diastereoselective manner *via* the base-promoted cleavage of chiral acetal to afford a quaternary carbon.



Scheme 7



Scheme 8

2. Preparation of acetal substrates

Acetalization of cyclic (or acyclic) β-keto esters with chiral diols such as (*R, R*)-2,3-butanediol, (*R, R*)-1,4-dibenzyloxy-2,3-butanediol, (*R, R*)-2,4-pentanediol, (*S, S*)-1,2-cyclohexanediol, and (*R, R*)-1,2-cyclo-heptanediol under azeotropic conditions using *p*-TsOH (0.1 eq.) / benzene afforded the corresponding acetals, in 70-99% yields, which are an inseparable mixture of two diastereomers at C_2 position in

ratio of 1:1 to 2:1. Acetal (**1d**) was prepared from the chiral tricyclic lactone (**38**), and the detail of this reaction is described in Chapter II.

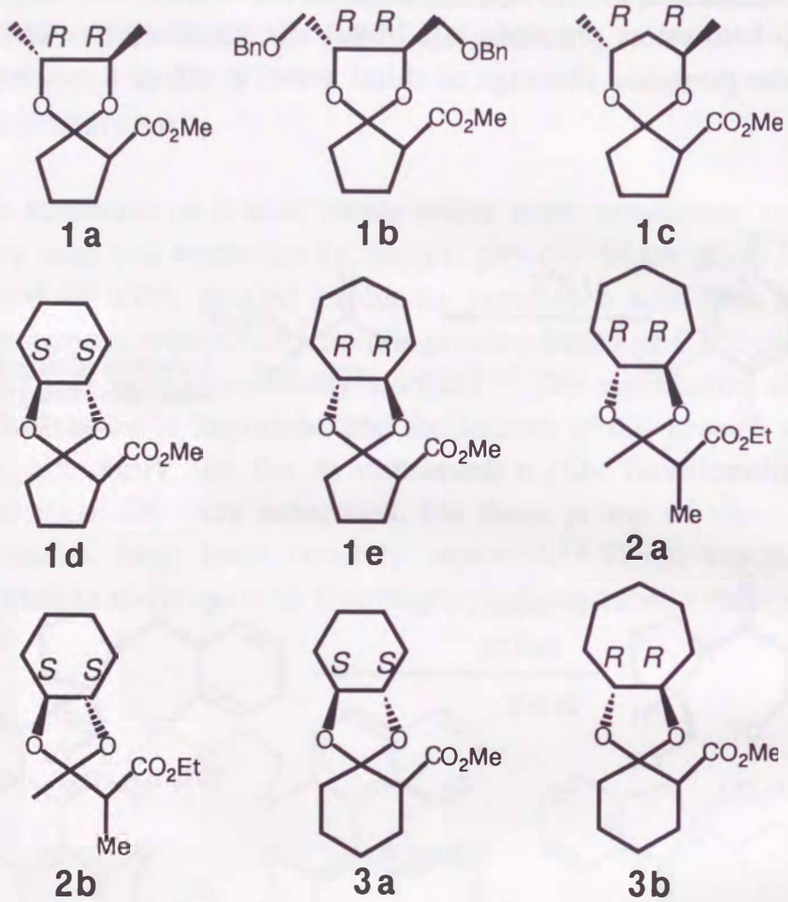
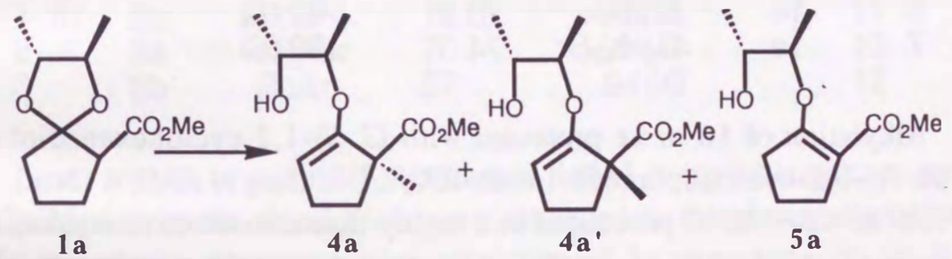


Fig. 5

3. Alkylation of five-membered ring and acyclic substrates

As a preliminary study for reaction conditions, effects of base species were studied on methylation of **1a** using LDA, $NaN(TMS)_2$, Bu^tOK and NaH. Among them, LDA gave the best result in chemical yield. As shown in Table 1, methylation of **1a** with MeI at -78°C afforded better yield of **4a** and **4a'** as the ratio of LDA was increased, and the yield of α,β-unsaturated ester (**5a**) was reduced. The products **4a** and **4a'** were easily separated by silica-gel column chromatography. It is noteworthy that, in this alkylation, the alkylated product retaining the original acetal structure intact was not obtained at all, but the enol ethers formed by cleavage of the acetal ring were obtained.

Table 1. Effect of the ratio of LDA to alkylation.



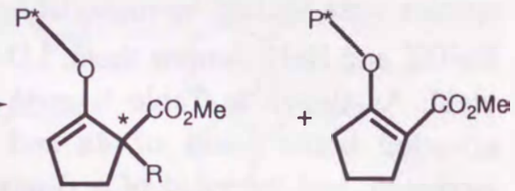
Entry	Eq. (LDA)	Products (%)			Recovery of **1a** (%)
		4a	**4a'**	**5a**	
1	1.0	11	7	28	46
2	2.5	43	21	14	0
3	5.0	59	32	0	0

Reaction conditions: MeI/LDA in THF at -78 °C under an Ar atmosphere.

Next, asymmetric alkylation of **1b-e** was examined. In each reaction, HMPA(5eq.) was added. Addition of HMPA did not affect on the diastereoselectivity, but effectively increased the chemical yield of the

products.

Table 2. Asymmetric alkylation of five-membered ring substrates **(1a-e)**



4a-e **5a-e**

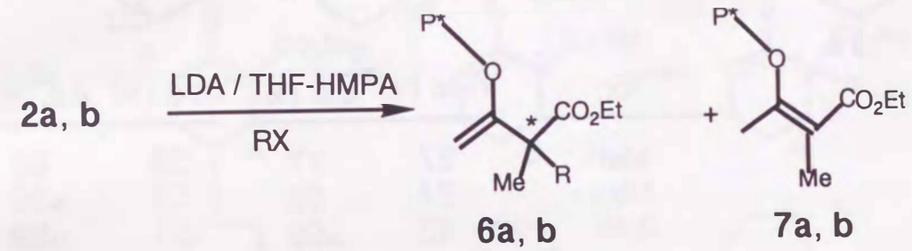
Entry	Substrate	RX	4a-e Yield (%)	4a-e d.e. (%) (abs.config)	5a-e Yield (%)
1	**1a**	MeI	91	29 (*S*)	-
2	**1b**	MeI	55	32 (*S*)	-
3	**1c**	MeI	57	73 (*S*)	6
4	**1d**	MeI	57	92 (*R*)	8
5	**1d**	$C_9H_{19}Br$	66	>99 (*R*)	7
6	**1e**	MeI	73	>99 (*S*)	18
7	**1e**	$C_9H_{19}Br$	74	>99 (*S*)	-

Alkylation of **1d** or **1e** protected with (*S, S*)-1,2-cyclohexanediol or (*R, R*)-1,2-cycloheptanediol with RX/LDA (5eq.)/HMPA (5eq.) in THF at -78 ~ -40 °C proceeded in a highly diastereoselective fashion, as shown in Table 2 (entries 4-7), while alkylation of **1b,c** protected with (*R, R*)-1,4-dibenzyloxy-2,3-butanediol, or (*R, R*)-2,4-pentanediol under the same conditions resulted in 32% d.e. (entry 2), and 73% d.e. (entry 3), respectively. The structure of alkylated enol ethers (**4a-e**) was determined by spectroscopic analysis. For example, the mass spectrum of **4e** (R=Me) showed a molecular ion peak at *m/z* 268. The IR absorption suggested the existence of hydroxyl group (3480 cm^{-1}), ester carbonyl (1720 cm^{-1}), and double bond (1640 cm^{-1}), respectively. The ^{1}H-NMR spectrum exhibited signals for olefinic proton at δ 4.52, C_1' and C_2' at δ 3.81-3.64, methyl ester at δ 3.70, and C_2-Me at δ 1.35. The ^{13}C-NMR spectrum indicated the presence of ester carbonyl (δ

176.8), olefinic carbons (δ 158.5 and δ 95.9), and newly generated quaternary carbon (δ 54.0).

The above results suggest that cyclic chiral diols, in particular, (*R, R*)-1,2-cycloheptanediol are superior as temporary chiral auxiliaries to acyclic chiral diols such as chiral 2,3-butanediols and 2,4-pentanediol.

Table 3. Asymmetric alkylation of acyclic substrates **(2a, b).**



6a, b **7a, b**

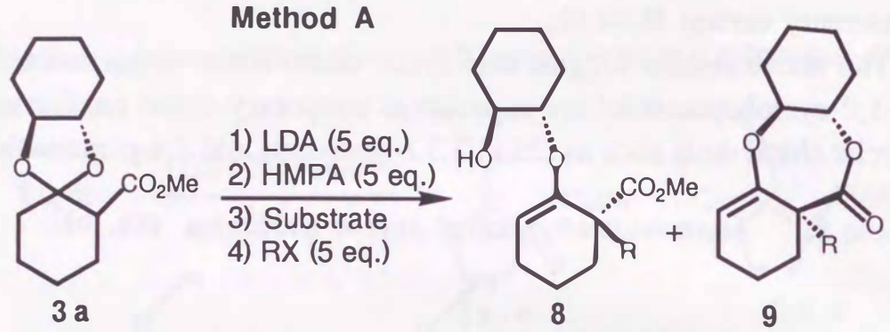
Entry	Substrate	RX	6a, b Yield (%)	6a, b d.e. (%) (abs.config)	7a, b Yield (%)
1	**2a**	BnBr	78	>99 (*R*)	11
2	**2a**	AllylBr	70	>99 (*R*)	10
3	**2b**	BnBr	57	94 (*S*)	12

Next, acyclic α-methyl-β-keto esters (ethyl α-methylacetoacetate) (**2a,b**) with cyclic chiral diols were subjected to the above alkylation. In accord with our expectation, alkylation of **2a** protected with (*R, R*)-1,2-cycloheptanediol afforded excellent results , as shown in Table 3.

4. Alkylation of six-membered ring substrate.

Alkylation of substrates (**3a,b**) prepared from six-membered β-keto ester proceeded in a different manner from the case of five-membered β-keto ester. Alkylation of **3a** protected with (*S, S*)-1,2-cyclohexanediol with RX/LDA (5eq.)/HMPA (5eq.) in THF at -78 ~ -40 °C (Method A)

Table 4. Alkylation of six-membered ring substrates.

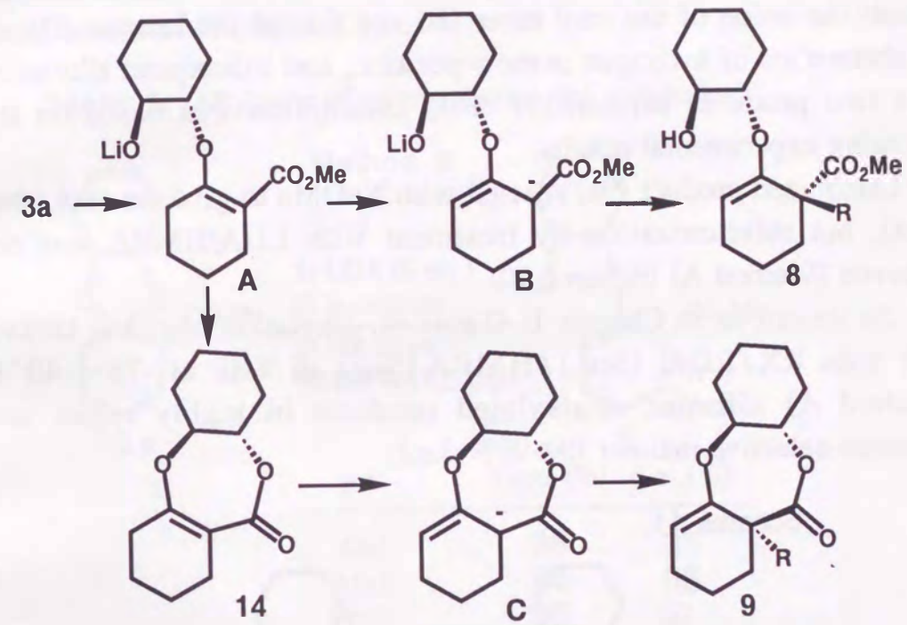


RX	Yield (%)	d.e. (%)	Yield (%)	d.e. (%)
MeI	37	77	59	95
Allyll	27	92	53	>99
BnBr	43	>99	51	>99

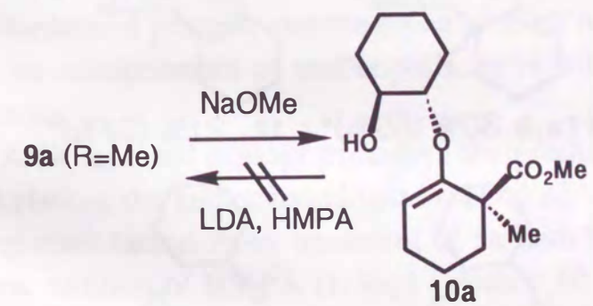
afforded a mixture of the lactonized products (**9**) (51-59% yield, 95-99% d.e.) and the alkylated products (**8**) (27-43% yield, 77-99% d.e.) (Table 4). The structure of alkylated products was determined by spectroscopic analysis. For example, the mass spectrum of **8a (R=Me)** showed a molecular ion peak at *m/z* 268. The IR absorption suggested the existence of hydroxyl group (3450 cm^{-1}), ester carbonyl (1710 cm^{-1}) and double bond (1660 cm^{-1}), respectively. The ^{1}H-NMR spectrum exhibited signals for olefinic proton at δ 4.81, diol moiety at δ 3.78, 3.49 and C_2-Me at δ 1.37. The ^{13}C-NMR spectrum indicated the presence of ester carbonyl (δ 177.4), olefinic carbons (δ 154.0 and δ 96.2), and newly generated quaternary carbon (δ 47.2). The structure of lactones (**9a-c**) was also determined by spectroscopic analysis. For example, the mass spectrum of **9a** (R=Me) showed a molecular ion peak at *m/z* 236. The IR absorption suggested the existence of lactone carbonyl (1720 cm^{-1}) and double bond (1650 cm^{-1}), respectively. The ^{1}H-NMR spectrum exhibited signals for olefinic proton at δ 5.31, diol moiety at δ 4.49, 3.92 and C_2-Me at δ 1.52. The ^{13}C-NMR spectrum indicated the presence of lactone carbonyl (δ 175.9), olefinic carbons

(δ 150.2 and δ 115.1), and newly generated quaternary carbon (δ 47.7).

Scheme 9



Scheme 10



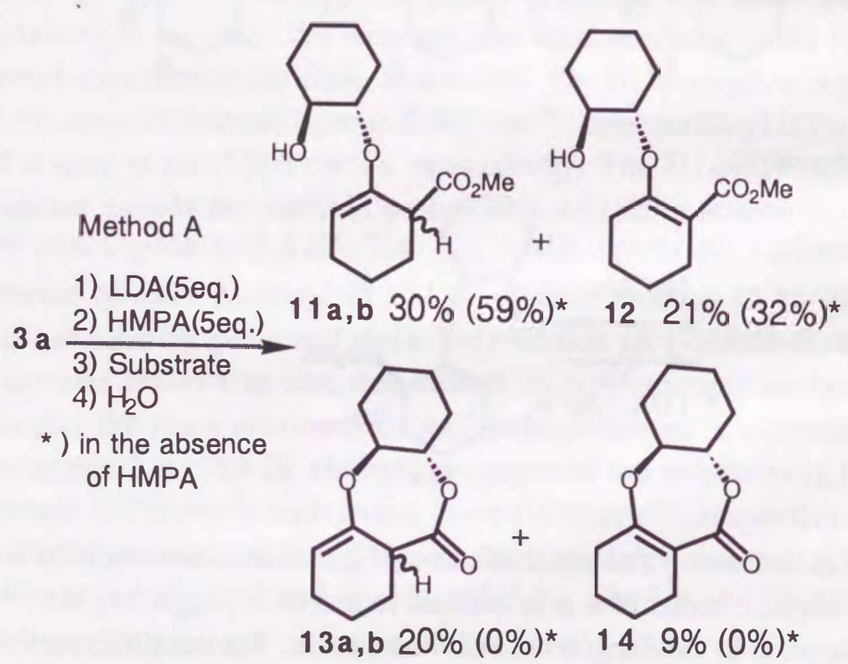
It is interesting that the absolute configuration of the newly generated stereogenic center of **8** is in contrast to that of **9**, suggesting the difference in the steric course of the reaction. The possible reaction

pathway was considered to be as follows (Scheme 9). At first, the enol ether (**A**) might be formed by acetal-ring opening of the substrate (**3a**) under basic conditions, followed by lactonization to give the lactone (**14**). In the next step, it is reasonable that the excess of base (5eq.) affords the anion of the enol ether (**B**) and that of the lactone (**C**) *via* the abstraction of hydrogen at the γ-position, and subsequent alkylation gave two products (**8**) and (**9**). This assumption was based on the following experimental results.

1) Lactonized product (**9a**) reacted with NaOMe to give the enol ether (**10a**), but relactonization by treatment with LDA/HMPA was not observed (Method A) (Scheme 10).

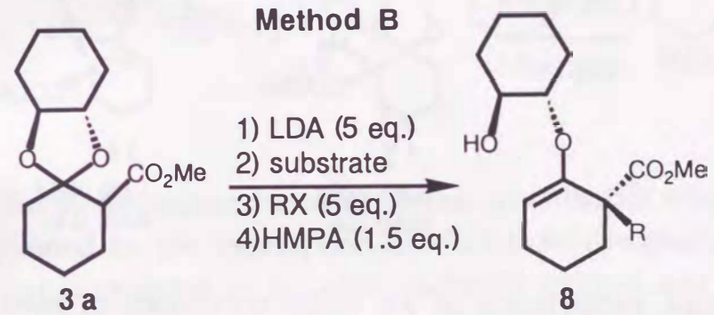
2) As described in Chapter II (Table 9), alkylation of chiral lactone (**14**) with RX/LDA (5eq.)/HMPA (5eq.) in THF at -78 ~ -40 °C (Method A) afforded α-alkylated products in highly regio- and diastereo-selective manner (94-99% d.e.).

Scheme 11



3) Treatment of **3a** with LDA (5eq.)/HMPA (5eq.) in THF at -78 °C and usual work-up gave a mixture of the enol ethers (**11,12**) and the lactones (**13, 14**). On the other hand, the same reaction without HMPA afforded exclusively the enol ethers (**11, 12**), and no lactone formation could be observed (Scheme 11).

Table 5. Alkylation of six-membered ring substrates.



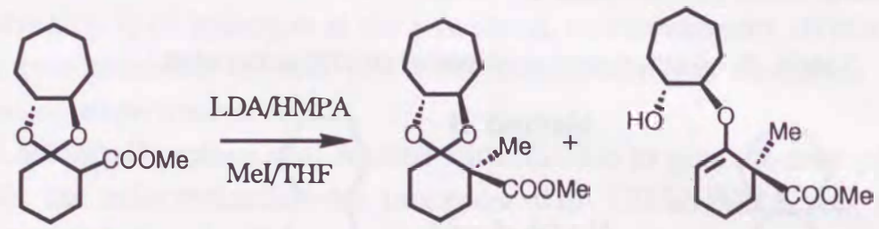
RX	Yield (%)	d.e. (%)
MeI	96	85
AllylI	84	96
BnBr	90	97

These result suggested that HMPA plays an important role in above lactonization process, and the effect of HMPA (5 eq.) was considered to be an enhancement of nucleophilicity of alkoxide anion to form the lactone.

After repeated attempt to control the product selectivity in the above alkylation, the author found that order of adding the reagent is the most important factor. After treatment of **3a** with LDA (5eq.)/RX at -78 °C, final addition of HMPA (1.5eq.) (Method B) gave exclusively the enol ether product (**8**), in 84-96% yields, in highly diastereoselective manner (85-97% d.e.) (Table 5). When the above reaction was performed in the absence of HMPA, the yield of the products decreased (MeI, 95%, 69% d.e.; AllylI, 43%, 96% d.e.; BnBr, 0%), because of the formation of complex mixture except for the case of methylation.

The effect of HMPA (1.5 eq.) was rationalized by assuming rapid alkylation of enolate anion prior to lactonization into **14** (Scheme 9). Actually, the reactions shown in Table 5 almost completed within 0.5 h.

Scheme 12



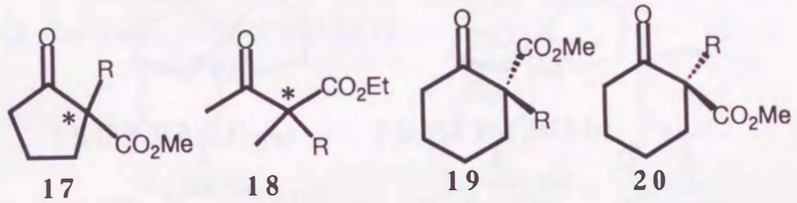
3b **15** 84% yield 66% d.e. **16** 12% yield 63% d.e.

Furthermore, methylation of **3b** under conditions of method A resulted in unsatisfactory diastereoselectivity to afford the acetal (**15**) (84% yield, 66% d.e.) as a major product, in addition to **16** (12% yield, 63% d.e.) as a minor product. On methylation of **3b**, it was confirmed that the substrate was firstly converted into enol ether (A-type in Scheme 9) by TLC detection before addition of MeI. Reconstruction of acetal ring in **15** might take place after alkylation. These different behavior such as lactone formation of **3a** and acetal formation of **3b** might be based on thermodynamic stabilities of individual ring systems.

5. Determination of absolute configuration and proposed mechanism.

Absolute configuration of each product (**4**, **6**, **8**, **15**, **16**) was determined by conversion to the corresponding keto esters (**17-20**) by acid treatment (Fig 6). Absolute configuration of the lactone (**9**) was also determined by conversion to the corresponding keto ester (**20**),

and the detail is described in Chapter II. Diastereomeric excess of these products was determined by the examination of 270MHz ^{1}H-NMR spectroscopy of the keto esters (**17-20**) using a chiral shift reagent ((+)-Eu(hfc)$_3$).[16b]

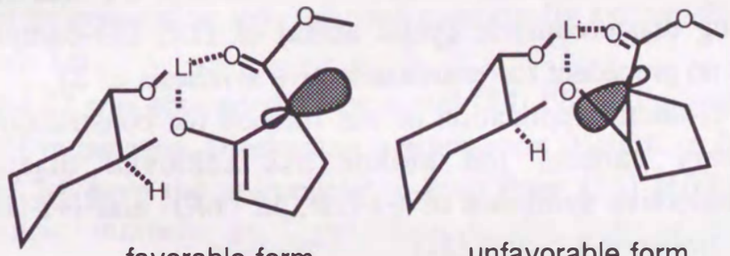


17 **18** **19** **20**

Fig. 6

The stereochemical course of this asymmetric alkylation could be explained by the assumption of chelation intermediate. The lithium cation is chelated to the ester carbonyl oxygen and two oxygens in chiral cyclic diol. As shown in Fig. 7, examination using the stereomodel (Dreiding) indicates that A is the preferable form to B, because the resulted anion lobe in B occupies a sterically crowded space. Thus, high diastereoselectivity in the alkylation of acetals may be rationally explained by considering the intermediate shown in A.

In conclusion, it has been found that chiral 1,2-cyclohexanediol and cycloheptanediol are useful auxiliaries for asymmetric alkylation of chiral acetals.



favorable form A unfavorable form B

Fig. 7

6. Stereoselective synthesis of (+)- and (-)-spiro[4.4]-nonane-1,6-diols

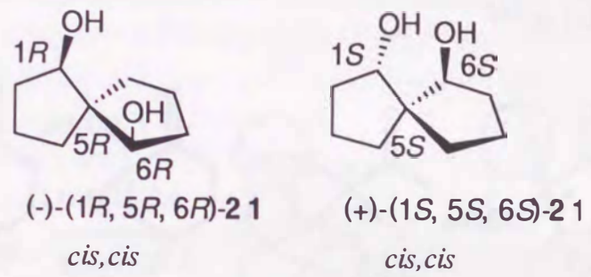


Fig 8

The synthesis of chiral auxiliaries as useful ligands in metal catalyzed asymmetric synthesis has been the target of many research groups in the last decade, and a large number of chiral auxiliaries from natural and synthetic origins have been developed.[2] In 1992, Kumar *et al.* reported[17] that (+)-(1*R*, 5*R*, 6*R*)- and (-)-(1*S*, 5*S*, 6*S*)-spiro[4.4]nonane-1,6-diol (**21**) were effective chiral ligand for asymmetric reduction of aromatic ketones when complexed with lithium aluminium hydride. The molecular model reveals that the enantiomer of *cis,cis*-spiro[4.4]nonane-1,6-diol (**21**) possesses the conformational rigidity as well as molecular dissymmetry necessary for effective diastereofacial selectivity. Recently, **21** was resolved by preparing diastereomeric cyclic acetal of (1*R*)-(+)-camphor.[18] But there is no precedent for enantioselective synthesis of **21**.

As a synthetic application of our method for construction of chiral quaternary carbon, the author has achieved diastereo- and enantioselective synthesis of (-)-(1*R*, 5*R*, 6*R*)- and (+)-(1*S*, 5*S*, 6*S*)-spiro[4.4]nonane-1,6-diol (**21**).

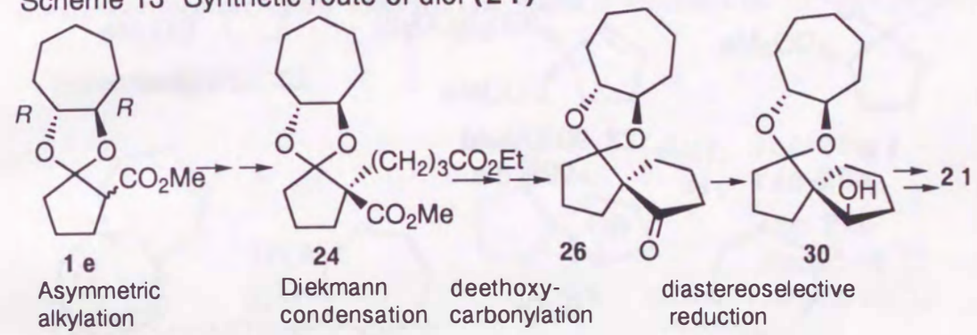
The author planned a construction of the spiro diol (**21**) employing the asymmetric alkylation of chiral acetals as a key step. The characteristics in our synthetic route are as follows.

1) Chiral cycloheptane-1,2-diol fully works as chiral auxiliary not only

for asymmetric alkylation, but also for diastereoselective reduction of **26** (Scheme 13).

2) Above diol acts as a protective group of ketone for Dieckmann condensation and subsequent deethoxycarbonylation (Scheme 13).

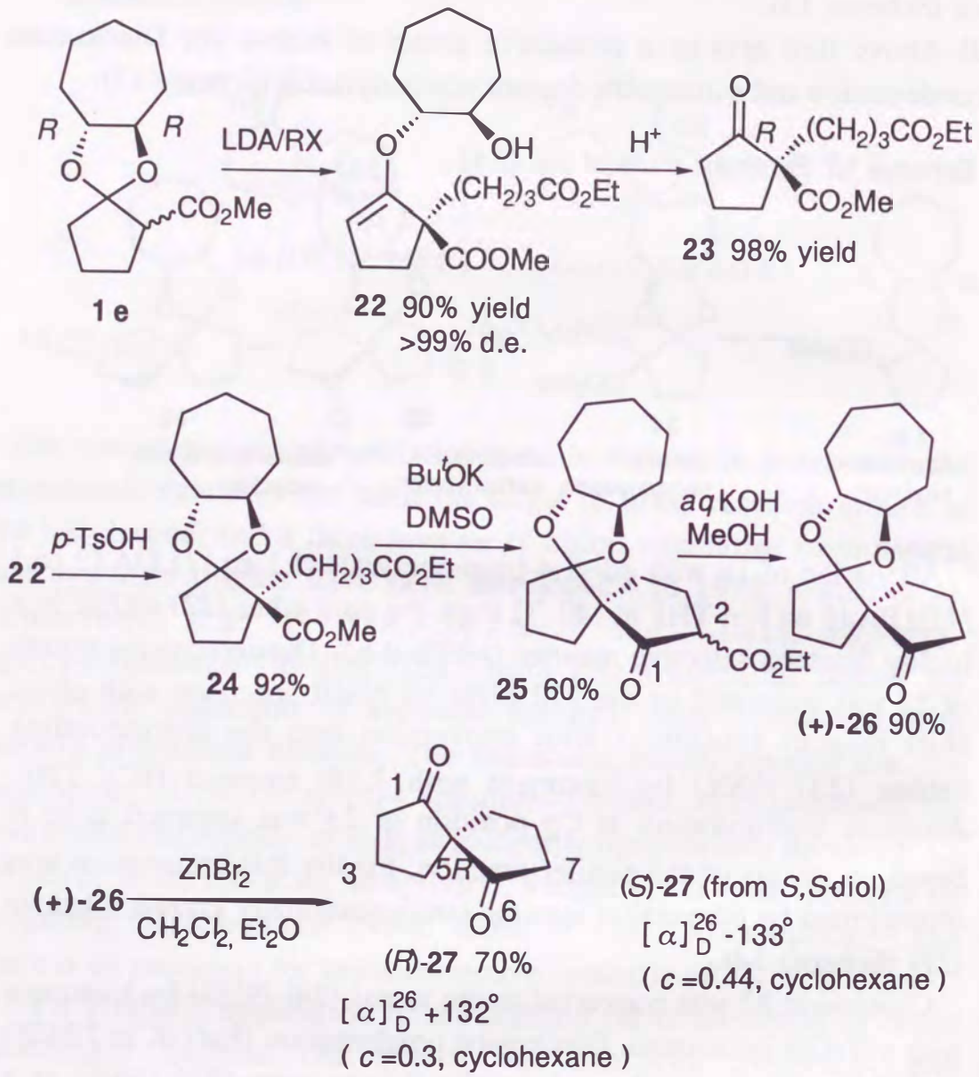
Scheme 13 Synthetic route of diol (**21**)



Alkylation of **1e** with ethyl 4-bromobutyrate (1.1 eq.) / LDA (2 eq.) / HMPA (5 eq.) in THF at -40 °C gave the enol ether (**22**) (90%) in a highly diastereoselective manner (>99% d.e.). Diastereomeric excess of **22** was estimated by the 270 MHz ^{1}H NMR spectrum with chiral shift reagent ($Eu(hfc)_3$) after conversion into the corresponding ketone (**23**) (98%) by treatment with 3.5% aqueous HCl/ THF. Absolute configuration at C_2-position of **23** was assumed to be *R* based on results of the similar reaction. Finally this assumption was reconfirmed by conversion into the configurationally known diketone (**27**) (Scheme 14).

Compound **22** was converted to the acetal (**24**) (92%) by treatment with *p*-TsOH in benzene. Dieckmann condensation (Bu^tOK in DMSO at 95 °C) of **24** gave the spirocyclic β-keto ester (**25**) (60%) as a diastereomeric mixture at C_2-position in the ratio of 3 to 1. Deethoxycarbonylation of **25** was achieved by treatment with aqueous KOH-MeOH at 95 °C to afford the intermediary keto-acetal **(+)-(26)** (90%). Deacetalization of **(+)-26** with $ZnBr_2$ / CH_2Cl_2 / THF

Scheme 14

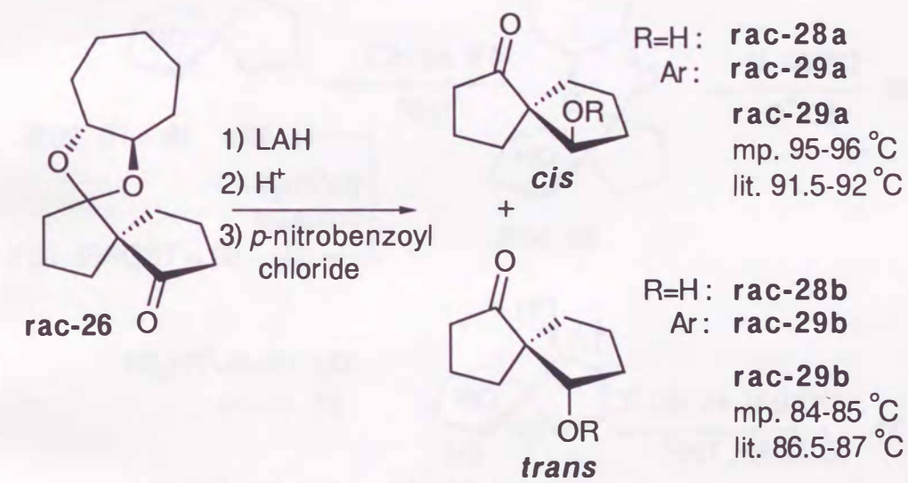


afforded the stereochemically known diketone **(+)-(27)** ($[\alpha]_D^{26}$ +132° (c=0.3, cyclohexane)) in 70% yield (lit.[19] $[\alpha]_D^{20}$ +135° (cyclohexane)). The ^{13}C-NMR spectrum of **27** showed one carbonyl carbon at δ 216.7, three methylene carbons at δ 38.5, 34.3 and 19.8 to support the C_2-symmetry, in addition to one quaternary carbon at δ

64.4.

According to Cram,[20] reduction of *dl*-**27** with $LiAlH_4$ affords a mixture of *cis,cis*-, *cis,trans*- or *trans,trans*-diols in a low diastereoselective manner. Reduction of **rac-26** with $LiAlH_4$, and subsequently acid treatment gave rac-**28a** (65%) and its C_6-diastereomer (rac-**28b**) (32%). The stereochemistry of rac-**28a,b** was

Scheme 15



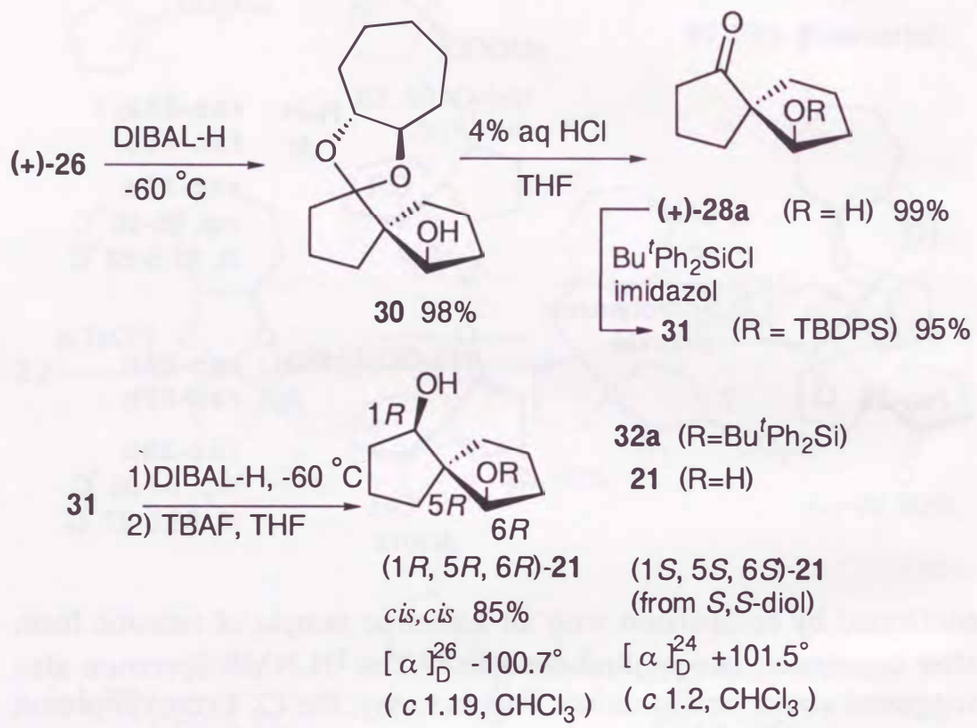
confirmed by comparison with an authentic sample of racemic form after conversion into *p*-nitrobenzoate.[20] The ^{1}H-NMR spectrum also suggested above configuration. That is to say, the C_6-hydroxyl proton of **28a** was observed at lower field (δ 3.44) than that of C_6 diastereomer of **28b** (δ 2.29), suggesting the presence of intramolecular hydrogen bond in **28a**.

Highly diastereoselective reduction of **(+)-26** was achieved by treatment with DIBAL-H in THF at -60 °C to afford **30** in 98% yield as a sole product. Deacetalization of **30** with 4% aqueous HCl / THF gave **(+)-28a** in quantitative yield (Scheme 15).

Reduction of **(+)-28a** with DIBAL-H in THF at -60 °C afforded an inseparable mixture of **21** (*cis,cis*) and its C_1-diastereomer (*cis,trans*),

in 77% yield, in the ratio of 1 to 2. After conversion of **(+)-28a** into *tert*-butyldiphenylsilyl ether **31** (95%) in usual manner, reduction of **31** with DIBAL-H in THF at -60 °C proceeded in a diastereoselective manner to afford **32a** (85%) and **32b** (9%), which could be easily

Scheme 16



separated by column chromatography on silica gel. Treatment of **32a** with tetrabutylammonium fluoride in THF gave **(-)-21** ($[\alpha]_D^{26}$ -100.7° (*c*=0.5, $CHCl_3$)) in quantitative yield.

The structure of **(-)-21** was determined by spectroscopic analysis. The mass spectrum showed a molecular ion peak at *m/z* 156. The IR absorption suggested the existence of hydroxyl group (3350 cm^{-1}). The ^{13}C-NMR spectrum of **(-)-21** showed one carbinol carbon at δ 79.6, three methylene carbons at δ 34.3, 33.9 and 21.2 (C_2-

symmetry), in addition to one quaternary carbon at δ 58.3.

Enantiomers of **(-)-21** and **(+)-27** were also synthesized by the same procedure utilizing (*S*, *S*)-cycloheptane-1,2-diol. Spectral data of compounds in this chapter are summarized in Table 6.

Table 6 (1). Spectral Data of **4a-e**

compound	IR cm^{-1} (neat)	^{1}H-NMR ($CDCl_3$) δ	Ms *m/z*
4a (Major)	3500 1730 1647	4.56 (1H, br-s), 3.82 (1H, m), 3.70 (3H, s) 3.67 (1H, m) 3.34 (1H, br-s), 2.40-2.26 (3H, m) 1.79 (1H, m), 1.35 (3H, s), 1.18 (3H, d, *J*=10 Hz), 1.16 (3H, d, *J*=10 Hz)	228 (M^+) 156 127
4a' (Minor)	3500 1740 1650	4.58 (1H, br-s), 3.80 (1H, m), 3.69 (1H, m) 3.68 (3H, s), 2.43-2.26 (4H, m),1.80 (1H, m) 1.37 (3H, s), 1.18 (3H, d, *J*=6Hz) 1.17 (3H, d, *J*=6Hz)	228 (M^+) 156 127
4b (32% d.e.)	3460 1725 1645	7.34-7.26 (10H, m), 4.65 (1H, br-s), 4.65-4.45 (4H, m), 4.29-4.05 (2H, m), 3.81-3.54 (4H, m) 3.65, 3.61 (total 3H, each-s, ratio=1:2), 2.38- 2.26 (3H, m), 1.85-1.72 (1H, m), 1.37, 1.38 (total 3H, each-s, ratio=1:2)	426 (M^+) 339 249 159
4c (Major)	3430 1735 1645	4.57 (1H, br-s), 4.30 (1H, m), 4.09 (1H, m) 3.68 (3H, s), 2.75 (1H, br-s), 2.43-2.25 (3H, m) 1.77-1.66 (3H, m), 1.34 (3H, s), 1.24 (3H, d, *J*=6 Hz), 1.20 (3H, d, *J*=6 Hz)	242 (M^+)
4c' (Minor)	3430 1735 1645	4.57 (1H, br-s), 4.34 (1H, m), 3.99 (1H, m) 3.69 (3H, s), 2.50 (1H, br-s), 2.37-2.29 (3H, m) 1.77-1.67 (3H, m), 1.33 (3H, s), 1.24 (3H, d, *J*=6Hz), 1.18 (3H, d, *J*=6Hz)	242 (M^+)
4d (R=Me) (92% d.e.)	3500 1730 1650	4.62 (1H, br-s), 3.70, 3.68 (3H, each-s, ratio=96:4), 3.72 (1H, m), 3.52 (1H, m), 3.50 (1H, br-s), 2.36-2.01 (4H, m), 1.83-1.65 (4H, m), 1.36 (3H, s) 1.32-1.27 (4H, m)	254 (M^+) (FD)
4d' (R=nonyl) (>99% d.e.)	3550 1740 1665	4.64 (1H, br-s), 3.69 (3H, s), 3.63 (1H, br-s) 3.70-3.48 (2H, m), 2.33-2.05 (6H, m), 1.88- 1.59 (6H, m),1.26 (16H, br-s), 0.88 (3H, t, *J*=7Hz)	366 (M^+) 191 142 110
4e (R=Me) (>99% d.e.)	3480 1720 1640	4.52 (1H, br-s), 3.81-3.64 (2H, m), 3.70 (3H, s), 3.38 (1H, br-s), 2.41-2.27 (3H, m), 1.98- 1.50 (11H, m), 1.35 (3H, s)	268(M^+) 156

Table 6 (2). Spectral Data of **4e'-8c**

compound	IR cm^{-1} (neat)	^{1}H-NMR ($CDCl_3$) δ	Ms *m/z*
4e' (R=Nonyl) (>99% d.e.)	3500 1720 1640	4.53 (1H, br-s), 3.78-3.63 (2H, m), 3.69 (3H, s), 3.55 (1H, br-s), 2.39-2.24 (3H, m), 1.98- 1.48 (11H, m),1.26 (16H, br-s), 0.88 (3H, t, *J*=7Hz)	380 (M^+) 254 167 142
6a (R=Bn) (>99% d.e.)	3475 1720 1660	7.26-7.10 (5H, m), 4.27-4.14 (2H, m), 3.99 (1H, d, *J*=3Hz), 3.93 (1H, d, *J*=3Hz), 3.89 (1H, m), 3.74 (1H, m), 3.25 (1H, d, *J*=13Hz), 3.20 (1H, s), 3.03 (1H, d, *J*=13Hz), 2.03-1.47 (10H, m), 1.27 (3H, t, *J*=7Hz), 1.21 (3H, s)	331 (M^+-15) 241 115
6a' (R=Allyl) (>99% d.e.)	3450 1720 1660	5.68-5.58 (1H, m), 5.08 (1H, d, *J*=4Hz), 5.30 (1H, s), 4.22-4.10 (2H, m), 4.11 (1H, d, *J*=3Hz) 4.04 (1H, d, *J*=3Hz), 3.85 (1H, m), 3.68 (1H, m) 3.01 (1H, s), 2.65 (1H, d-d, *J*=14, 6Hz) 2.43 (1H, d-d, *J*=14, 8Hz), 1.97-1.46 (10H, m) 1.30 (3H, s), 1.25 (3H, t, *J*=7)	296 (M^+) 281 142 155 114
6b (R=Bn) (94% d.e.)	3450 1710 1640	7.26-7.10 (5H, m), 4.27-4.15 (2H, m), 4.14 (1H, d, *J*=3Hz), 3.90 (1H, d, *J*=3Hz), 3.84 (1H, m) 3.59 (1H, m), 3.29 (1H, s), 3.27 (1H, d, *J*=14Hz), 3.00 (1H, d, *J*=14Hz), 2.24-2.04 (2H, m), 1.82-1.73 (2H, m), 1.41-1.29 (4H, m), 1.28 (3H, t, *J*=7Hz), 1.21 (3H, s)	332 (M^+) 234
8a (R=Me) (85% d.e.)	3450 1710 1660	4.81 (1H, br-s), 3.78 (1H, m), 3.70 (3H, s) 3.63 (1H, br-s), 3.49 (1H, m), 2.15-1.50 (10H, m), 1.37 (3H, s), 1.32-1.25 (4H, m)	268 (M^+) 153
8b (R=Allyl) (96% d.e.)	3500 1720 1660	5.72 (1H, m), 5.08 (1H, d, *J*=6 Hz), 5.03 (1H, s) 4.88 (1H, t, *J*=4 Hz), 3.86 (1H, br-s), 3.77 (1H, m), 3.71, 3.68 (total 3H, s each ratio=100:3.9), 3.51 (1H, m), 2.65 (1H, d-d *J*=13, 6 Hz), 2.38 (1H, d-d, *J*=13, 8 Hz) 2.29-2.03 (6H, m), 1.85-1.27 (8H, m)	294 (M^+) 164 137
8c (R=Bn) (>99% d.e.)	3450 1720 1660	7.27-7.18 (5H, m), 4.87 (1H, t, *J*=3 Hz), 4.20 (1H, s), 3.82 (1H, m), 3.72 (3H, s), 3.62 (1H, m) 3.32 (1H, d, *J*=13 Hz), 3.13(1H, d, *J*=13 Hz) 2.23-1.77 (7H, m), 1.54-1.27 (7H, m)	344 (M^+) 186 143 123

Table 6 (3). Spectral Data of **9a-c, 15, 16, 21-24**

compound	IR cm^{-1} (neat)	^{1}H-NMR ($CDCl_3$) δ	Ms *m/z*
9a	1720 1650 (nujol)	5.31 (1H, br.s), 4.49 (1H, m), 3.92 (1H, m) 2.19-1.65 (9H, m), 1.52 (3H, s) 1.53-1.18 (5H, m).	236 (M^+) 111
9b	1720 1660	5.87 (1H, m), 5.43 (1H, t, *J*=4 Hz), 5.11 (1H, d, *J*=8 Hz), 5.05 (1H, s), 4.46 (1H, m) 3.92 (1H, m), 2.73 (1H, dd, *J*=13, 6 Hz), 2.47 (1H, dd, *J*=13, 8 Hz), 2.20-2.07 (5H, m) 1.86-1.73 (4H, m), 1.61-1.17 (5H, m).	262 (M^+) 163 123
9c	1750 1690	7.29-7.21 (5H, m), 5.47 (1H, t, *J*=4Hz), 4.57-4.48 (1H, m), 3.85 (1H, m), 3.39 (1H, d, *J*=13Hz) 2.96 (1H, d, *J*=13Hz), 2.24-1.86 (5H, m), 1.78-1.68 (2H, m), 1.57-1.18 (7H, m).	312 (M^+) 180 107
15	1720	3.78 (1H, m), 3.68 (3H, s) 3.59 (1H, m) 2.26-2.15 (2H, m), 2.12-1.38 (16H, m) 1.27, 1.25 (total 3H, s each, ratio=13.6:68)	282 (M^+) 268 154
16	3480	4.66 (1H, t, *J*=4 Hz), 4.20 (1H, m) 3.70 (3H, s), 3.83-3.58 (2H, m) 2.26-1.38 (16H, m), 1.36 (3H, s)	282 (M^+)
21	3350	4.14 (2H, dd, *J*=5, 3Hz), 2.73 (2H, br.s) 1.98-1.81 (4H, m), 1.73-1.58 (6H, m) 1.38-1.25 (2H, m)	156 (M^+) 154 138
22	3500 1738 1650	4.56 (1H, t, J=3 Hz), 4.12 (2H, q, *J*=7 Hz) 3.77-3.61 (2H, m), 3.69 (3H, s), 3.48 (1H, br-s), 2.39-2.26 (5H, m), 2.01-1.83 (4H, m) 1.77-1.45 (11H, m), 1.26 (3H, t, *J*=7 Hz)	368 (M^+) 267 254 181
23	1750 1730	4.12 (2H, q, *J*=7 Hz), 3.71 (3H, s), 2.62-2.28 (4H, m), 2.05-1.89 (4H, m), 1.71-1.52 (4H, m) 1.25 (3H, t, *J*=7 Hz)	256 (M^+) 228 224
24	1730	4.11 (2H, q, *J*=7 Hz), 3.77 (1H, m), 3.68 (3H, s), 3.59 (1H, m), 2.45-2.27 (3H, m) 2.21-2.30 (3H, m), 2.0-1.73 (3H, m) 1.72-1.45 (13H, m), 1.25 (3H, t, *J*=7 Hz)	368 (M^+) 267 181

Table 6 (4). Spectral Data of **25-32a**

compound	IR cm^{-1} (neat)	^{1}H-NMR ($CDCl_3$) δ	Ms *m/z*
25	1750 1730	4.25-4.15 (2H, m), 3.74-3.58 (2H, m) 3.33, 3.21 (total 1H, m each, ratio=3:1) 2.39-2.03 (8H, m), 1.99-1.46 (12H, m) 1.28 (3H, t, *J*=7 Hz)	336 (M^+) 178 167
26	1740	3.73 (1H, m), 3.60 (1H, m), 2.45-2.05 (6H, m) 2.0-1.70 (6H, m), 1.69-1.45 (10H, m)	264 (M^+) 168
27	1739	2.48-2.33 (4H, m), 2.32-2.19 (4H, m) 2.17-1.78 (4H, m)	152 (M^+)
28a	3450	4.00 (1H, dd, *J*=4, 3 Hz), 3.44 (1H, d, *J*=4 Hz) 2.39-2.27 (2H, m), 2.08-1.75 (8H, m) 1.74-1.57 (2H, m)	154 (M^+) 136 110
28b	3450 1720	4.22 (1H, t, *J*=6 Hz), 2.29 (1H, m) 2.18-1.93 (2H, m), 1.92-1.69 (8H, m) 1.68-1.58 (2H, m)	154 (M^+) 136 110
29a	1730 1715 (nujol)	8.27 (2H, d, *J*=9 Hz), 8.14 (2H, d, *J*=9 Hz) 5.24 (1H, d-d, *J*=3, 2 Hz), 2.45-2.20 (4H, m) 2.18-1.93 (4H, m), 1.88-1.74 (2H, m) 1.53-1.45 (2H, m)	303 (M^+) 285 259 154
29b	1730 1715 (nujol)	8.30 (2H, d, *J*=9 Hz), 8.17 (2H, d, *J*=9 Hz) 5.40 (1H, d-d, *J*=3, 2 Hz), 2.45-2.28 (3H, m) 2.21-2.04(1H, m), 2.0-1.73 (8H, m)	303 (M^+) 285 259
30	3500	4.38 (1H, s), 3.97 (1H, d, *J*=3 Hz), 3.83-3.7 (2H, m), 2.24-2.14 (2H, m), 2.11-1.77 (5H, m), 1.73-1.43 (15H, m)	266 (M^+) 248 136
31	1740	7.77-7.67 (4H, m), 7.45-7.35 (6H, m), 4.05 (1H, t, *J*=6 Hz), 2.31-2.15 (2H, m), 2.12-1.92 (3H,m), 1.89-1.72 (4H, m), 1.57-1.23 (3H, m) 1.02 (9H, s)	392 (M^+)
32a	3500	7.75-7.65 (4H, m), 7.48-7.38 (6H, m), 4.21 (1H, d, *J*=4 Hz), 4.17 (1H, t, *J*=5 Hz), 3.95 (1H, s), 1.89-1.80 (2H, m), 1.74-1.49 (6H, m) 1.45-1.15 (4H, m), 1.07 (9H, s)	393 (M^+-1) 376 339

Table 6 (5). Spectral Data of **32b**

compound	IR cm^{-1} (neat)	^{1}H-NMR ($CDCl_3$) δ	Ms *m/z*
32b	3450	7.78-7.70 (4H, m), 7.47-7.35 (6H, m), 4.36 (1H, t, *J*=7 Hz), 3.79 (1H, br.s), 2.78 (1H, br.s), 2.33-2.20 (1H, m), 1.96-1.74 (2H, m), 1.72-1.53 (3H, m), 1.48-1.38 (4H, m), 1.37-1.19 (2H, m), 1.05 (9H, s)	394 (M^+) 393 376 339

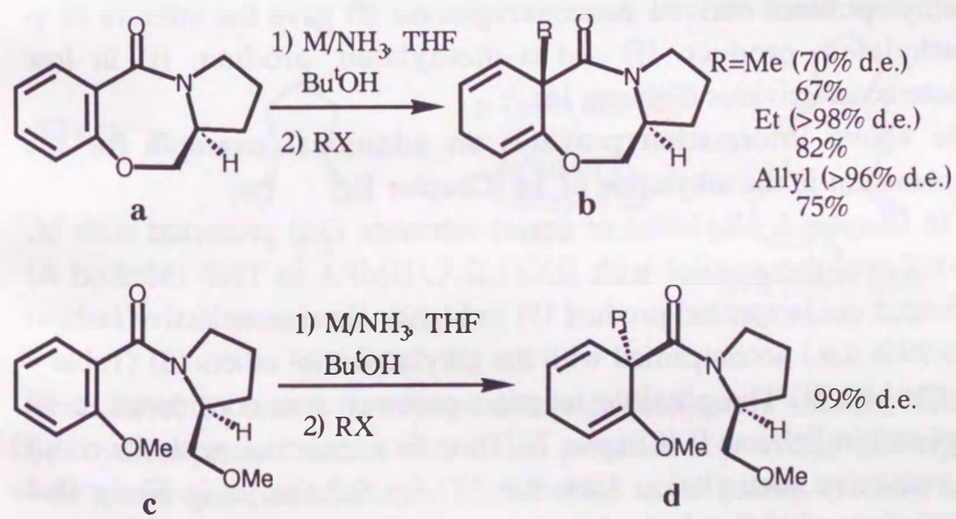
CHAPTER II

PREPARATION OF CHIRAL TRICYCLIC 1,4-DIOXEPIN-5-ONE DERIVATIVES AND ITS APPLICATION TO ASYMMETRIC ALKYLATION

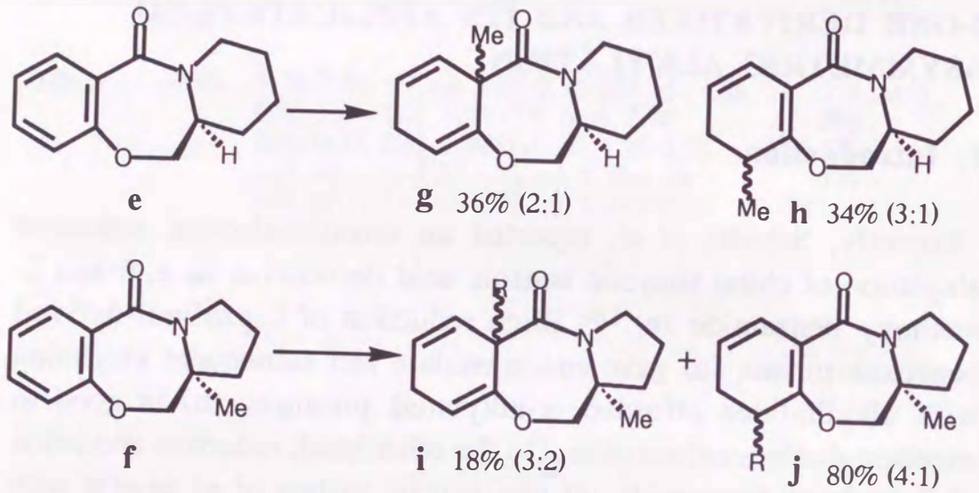
1. Introduction

Recently, Schultz *et al.* reported an enantioselective reductive alkylation of chiral tricyclic benzoic acid derivatives (**a**, **e**, **f**) and 2-methoxy benzamide (**c**).[16c] Birch reduction of L-prolinol-derived benzoxazepinone (**a**) gave amide enolate and subsequent alkylation with alkylhalides afforded α-alkylated products (**b**) in good to excellent diastereoselectivities. On the other hand, reductive alkylation of 2-methoxy benzamide (**c**) (the acyclic variant of **a**) gave **d** with excellent diastereoselectivity, and absolute configuration of newly generated quaternary carbon in **d** is contrary to that in the case of reductive alkylation of **a**.

Scheme 17



Scheme 18



In their reductive alkylation, structural effect of chiral auxiliary on regio- and diastereoselectivities was also examined. That is to say, reductive methylation of **e** with the chiral piperidine ring gave the mixture of α-methylated product (**g**) and γ-methylated product (**h**) in low diastereoselectivities. Similarly, reductive methylation of (*S*)-2-methyl prolinol-derived benzoxazepinone (**f**) gave the mixture of γ-methylated product (**j**) and α-methylated product (**i**) in low diastereoselectivities (Scheme 18).

The above information provides an additional example for the explanation in the alkylation of **3a** (Chapter I).

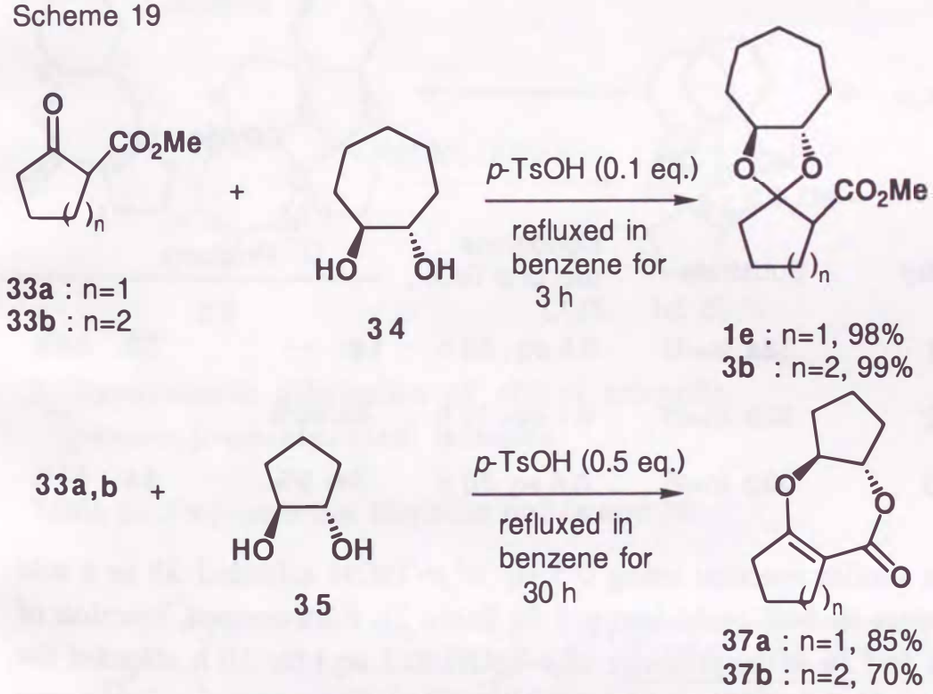
In Chapter I, alkylation of acetal substrate (**3a**) protected with (*S, S*)-1,2-cyclohexanediol with RX/LDA/HMPA in THF (Method A) afforded the lactonized product (**9**) in highly diastereoselective fashion (95-99% d.e.) accompanied with the alkylated enol ethers (**8**) (Table 4 in Chapter I). The possible reaction pathway was considered to be depicted in Scheme 9 (Chapter I). Thus, in connection with the result of reductive methylation (Scheme 17) by Schultz, it is likely that alkylation of the chiral tricyclic lactone (**14**) might proceed in a

highly diastereoselective manner to afford a chiral quaternary carbon, and the absolute configuration of the newly generated stereogenic center might be contrary to that in the case of alkylation of acetal substrate (**3a**) (Method B, Table 5 in Chapter I).

Next, the author developed preparation method of chiral tricyclic 1,4-dioxepin-5-one derivatives, and studied its application to asymmetric alkylation.

2. Preparation of chiral tricyclic γ-oxa-α,β-unsaturated lactones

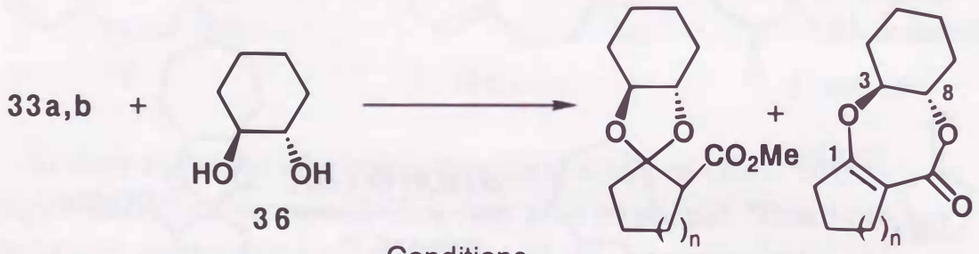
Scheme 19



Reaction of 5- and 6-membered cyclic β-keto esters (**33a,b**) with (*S,S*)-cycloheptane-1,2-diol (**34**) in the presence of *p*-TsOH (0.1 eq.) under azeotropic conditions for 3 h afforded usual acetals (**1e,3b**), in quantitative yields, as a diastereomeric mixture at C_1. On the other

hand, reaction of **33a,b** with (*S, S*)-cyclopentane-1,2-diol (**35**) in the presence of *p*-TsOH (0.5eq.) under the same conditions for 30 h afforded exclusively the tricyclic α,β-unsaturated lactones (**37a,b**), in 85 and 70% yields (Scheme 19). Reaction of **33a,b** with (*S, S*)-cyclohexane-1,2-diol (**36**) gave the product-selectivity depending on the mole ratio of employed *p*-TsOH. That is to say, reaction of **33a** and **36** under the above reaction conditions using 0.1eq. of *p*-TsOH resulted in recovery of the substrate (75%).

Table 7. Reaction of (*S,S*)-cyclohexanediol (**36**) with cyclic β-keto esters (**33a,b**)

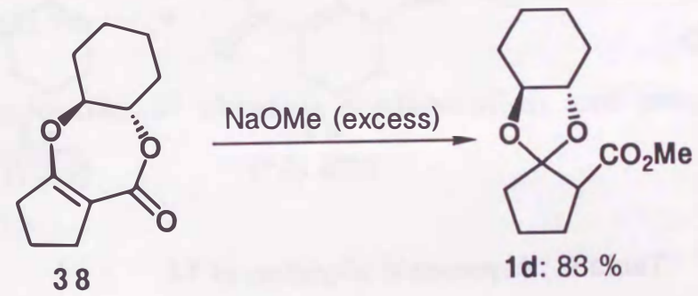


Entry	Substrate	Conditions (eq. of *p*-TsOH, R.T.)	Products	
1	**33a** (n=1)	0.5 eq., 53 h	**1d**: ---	**38**: 84%
2	**33b** (n=2)	0.1 eq., 10 h	**3a**:80%	---
3	**33b** (n=2)	0.5 eq.,70 h	**3a**: 5%	**14**: 51%

The similar reaction using 0.5 eq. of *p*-TsOH afforded **38** as a sole product in 84% yield (entry 1 in Table 7). Furthermore, reaction of **33b** and **36** in the presence of *p*-TsOH (0.1 eq.) for 10 h afforded the acetal (**3a**) in 80% yield (entry 2). When this reaction mixture was refluxed for additional 60 h with occasional addition of *p*-TsOH (total amount: 0.5 eq.), the tricyclic lactone (**14**) was obtained in 51% yield with a small amount of **3a** (entry 3). The structure of lactones (**14,37a,b,38**) was determined by spectroscopic analysis. For

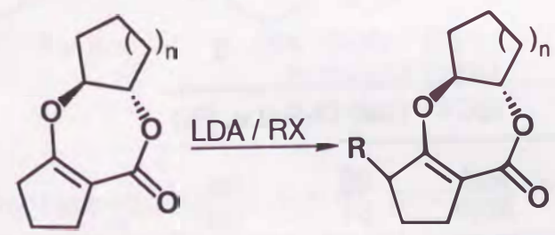
example, the mass spectrum of **38** showed a molecular ion peak at *m/z* 208. The IR absorption (1670 and 1615 cm^{-1}) suggested the existence of α,β-unsaturated carbonyl group. The ^{13}C-NMR spectrum indicated the presence of ester carbonyl (δ 166.4 (s)) and two olefinic carbons (δ 166.3 (s), 101.4 (s)). The ^{1}H-NMR spectrum showed C_3-H at δ 4.13 and C_8-H at δ 4.25. In addition, chemical conversion from **38** to the acetal (**1d**, 83%) by treatent with NaOMe in MeOH at room temperature also supported the structure of **38** (Scheme 20). Above results of product-selectivity shown in Scheme 19 and Table 7 might be rationalized based on thermodynamically stability of products.

Scheme 20



3. Asymmetric alkylation of chiral tricyclic γ-oxa-α,β-unsaturated lactones

Table 8. Regioselective alkylation of **37a** and **38**



37a (n=1), **38** (n=2) **39** (n=1), **40** (n=2)

Product	RX	Yield(%)	d.s.
39a	MeI	65	3:1
39b	BnBr	67	3:2
40a	MeI	70	3:1
40b	BnBr	63	3:2

Alkylation of **37a** and **38** with RX (5 eq.) /LDA (5 eq.) in THF at -78 to -40 °C afforded γ-alkylated products **39** and **40**, respectively (Table 8). Each reaction resulted in low diastereoselectivity (3:1 to 3:2), but it is noteworthy that the alkylation took place in a highly regioselective manner at γ-position of lactone carbonyl, and that no α-alkylated products could be detected.

Scheme 21

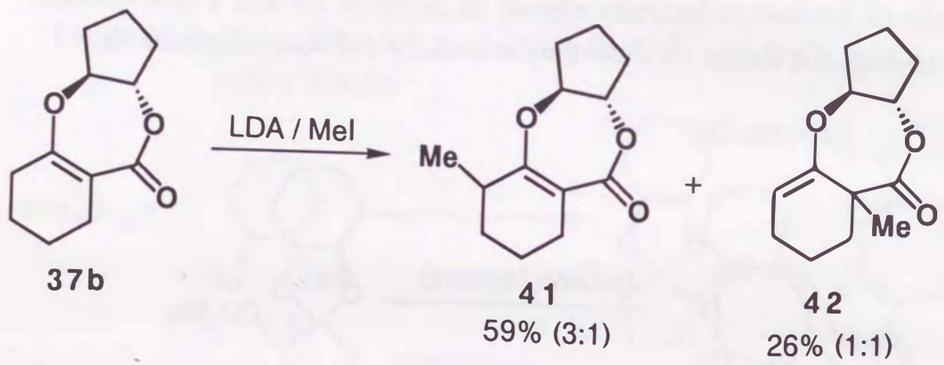
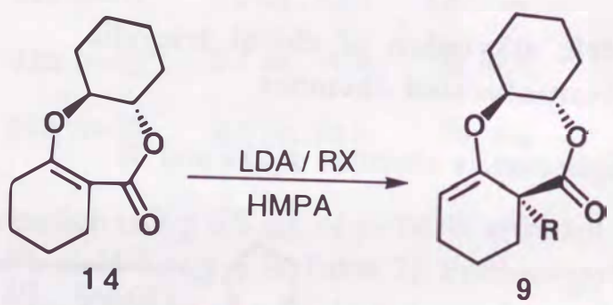


Table 9. Asymmetric alkylation of **14**



Product	RX	Yield (%)	d.e. (%)
9a	MeI	86	94
9b	Allyll	51	94
9c	BnBr	52	>99

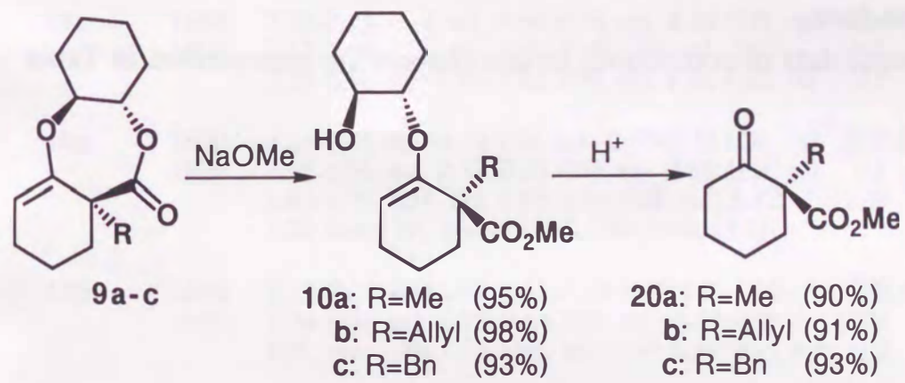
Alkylation of **37b** under the same reaction conditions gave a mixture of γ-alkylated product (**41**) and α-alkylated product (**42**) in 59% (diastereomeric ratio= 3:1) and 26% (1:1) yields, respectively (Scheme 21). Diastereomeric ratio of **39-42** was estimated by 270MHz ^{1}H-NMR spectra, and absolute configuration of these products (**39-42**) was not determined.

On the other hand, alkylation of **14** showed quite different behavior from the cases of **37a,b** and **38** to afford α-alkylated products (**9a-c**), in highly regio- and diastereoselective manner (94-99% d.e.), as shown in Table 9. The structure of alkylated products (**9a-c**) was confirmed by comparison with an authentic sample (Chapter I).

Above results were quite similar to that observed by Schultz (Scheme 17).

4. Determination of absolute configuration and proposed mechanism.

Scheme 22



Absolute configuration of products (**9a-c**) was determined by conversion to the corresponding keto esters (**20a-c**)[16b] *via* two-step sequence [i) NaOMe / MeOH ii) BF_3-Et_2O /H_2O / MeOH] (Scheme 22).

Diastereomeric excess of **9a-c** was determined by the examination of 270MHz ^{1}H-NMR spectroscopy of keto esters (**20a-c**) using a chiral shift reagent ((+)-Eu(hfc)$_3$)[16b].

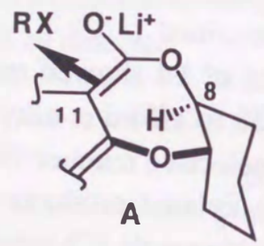


Fig . 9

The reaction mechanism is tentatively proposed as follows. The reaction presumably starts with abstraction of allylic hydrogen to form a dienolate anion **A**. Dreiding stereomodel suggests that the conformation of 7-membered ring as depicted in Fig. 9 might be favorable because of little ring strain. The axial(α) hydrogen atom at C_8 shielded *si*-face at C_{11}, so alkylation might occur predominantly from *re*-face.

Spectral data of compounds in this chapter are summarized in Table 10.

Table 10 (1). Spectral Data of **14, 37-41**

compound	IR cm^{-1} (neat)	^{1}H-NMR ($CDCl_3$) δ	Ms *m/z*
14	1690 1630 (nujol)	4.26 (1H, m), 4.12 (1H, m), 2.59 (1H, m) 2.33-2.18 (5H, m), 1.83-1.19 (10H, m).	222 (M^+) 141
37a	1680 1600	4.62 (1H, m), 4.48 (1H, m), 2.83 (1H, m) 2.75-2.63 (3H, m), 2.38-2.26 (2H, m) 1.97-1.81 (6H, m).	194 (M^+) 127
37b	1680 1600	4.57 (1H, m), 4.41 (1H, m), 2.68 (1H, m) 2.33-2.18 (5H, m), 1.94-1.78 (3H, m) 1.73-1.57 (5H, m).	208 (M^+) 141 125
38	1670 1615 (nujol)	4.25 (1H, dt, *J*=11, 7 Hz), 4.13 (1H, dt, *J*=11, 7 Hz), 2.83-2.54 (4H, m) 2.37-2.22 (2H, m), 1.93-1.75 (4H, m) 1.58-1.24 (4H, m).	208 (M^+) 111
39a	1680 1600	4.58 (1H, m), 4.43 (1H, m), 2.93-2.78 (2H, m), 2.64 (1H, m), 2.40-2.25 (2H, m) 2.15-1.83 (5H, m), 1.48 (1H, m) 1.14, 1.12 (total 3H, d each, *J*=7 Hz, ratio=3:1).	208 (M^+) 151 141
39b	1690 1618	7.33-7.15 (5H, m), 4.56 (1H, m), 4.44 (1H, m) 3.17-2.97 (2H, m), 2.82-2.48 (3H, m), 2.37- 2.25 (2H, m), 1.97-1.83 (5H, m), 1.68 (1H, m)	284 (M^+) 201 111
40a	1670 1620	4.24 (1H, m), 4.14 (1H, m), 2.87-2.72 (2H, m) 2.55 (1H, m), 2.37-2.25 (2H, m), 2.06 (1H, m) 1.83-1.75 (2H, m), 1.57-1.19 (5H, m), 1.12 1.10 (total 3H, d each, *J*=7, 7Hz, ratio=3:1).	222 (M^+) 141 125
40b	1680 1620	7.33-7.14 (5H, m), 4.31-4.19 (2H, m), 3.12- 2.94 (2H, m), 2.70-2.44 (3H, m), 2.38-2.21 (2H, m), 1.98-1.75 (3H, m), 1.64-1.24 (5H, m)	298 (M^+) 201 109
41	1680 1600	4.55 (1H, m), 4.41 (1H, m), 2.70 (1H, m) 2.52-2.19 (4H, m), 1.94-1.73 (5H, m) 1.69-1.39 (3H, m), 1.20, 1.13 (total 3H, d each, *J*=7, 7 Hz, ratio=3:1).	222 (M^+) 139

Table 10 (2). Spectral Data of **42, 10a-c**

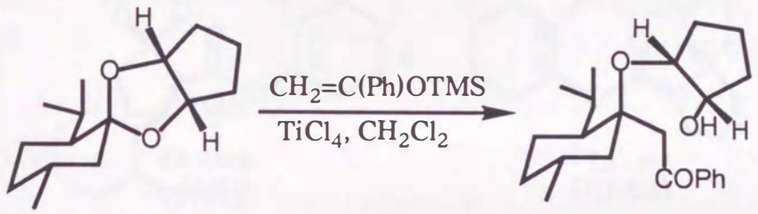
compound	IR cm^{-1} (neat)	^{1}H-NMR ($CDCl_3$) δ	Ms *m/z*
42	1725 1665	5.55, 5.42 (total 1H, t each, *J*=4 Hz, ratio=1:1) 4.90 (1H, m), 4.51, 3.83 (total 1H, m each, ratio=1:1), 2.58 (1H, m), 2.24-2.04 (5H, m) 1.84-1.55 (6H, m), 1.52, 1.48 (total 3H s each, ratio=1:1).	222 (M^+) 135 111
10a	3400 1720 1660	4.81 (1H, t, *J*=4 Hz), 3.78-3.68 (1H, m), 3.67 (3H, s), 3.51 (1H, m), 2.35 (1H, br.s), 2.23-2.01 (5H, m), 1.74-1.56 (5H, m), 1.40 (3H, s) 1.33-1.20 (4H, m).	268 (M^+) 170 153 138
10b	3500 1720 1660	5.88 (1H, m), 5.24-5.40 (2H, m), 4.88 (1H, t, *J*=4 Hz), 3.72 (1H, m), 3.68 (3H, s), 3.54 (1H, m), 2.70 (1H, dd, *J*=14, 6 Hz), 2.46 (1H, dd, *J*=14, 7 Hz), 2.51 (1H, br.s), 2.23-1.91 (5H, m), 1.82-1.55 (5H, m), 1.38-1.22 (4H, m).	294 (M^+) 164 136
10c	3450	7.27-7.20 (5H, m), 4.91 (1H, t, *J*=4 Hz), 3.75 (1H, m), 3.70 (3H, s), 3.46 (1H, m), 3.36 (1H, d, *J*=13 Hz), 3.04 (1H, d, *J*=13 Hz) 2.23-1.85 (6H, m), 1.74-1.66 (3H, m) 1.55-1.20 (6H, m).	344 (M^+) 228 186 107

Chapter III
ASYMMETRIC INDUCTION TO *meso*-CYCLOHEXANE-1,2-DIOL, BASED ON DIASTEREOSELECTIVE ELIMINATION

1. Introduction

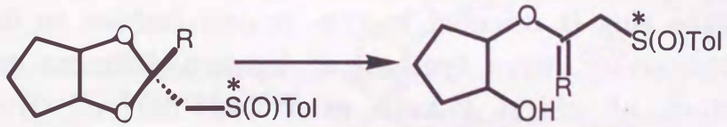
Enantioselective differentiation of prochiral functional group in bifunctionalyzed symmetric compound is one of the efficient preparation methods for new chiral compounds. While asymmeric induction for symmetric compound is achieved by enzymatic procedure, examples by the chemical transformation are rare.[21]

Scheme 23



>95% d.e.

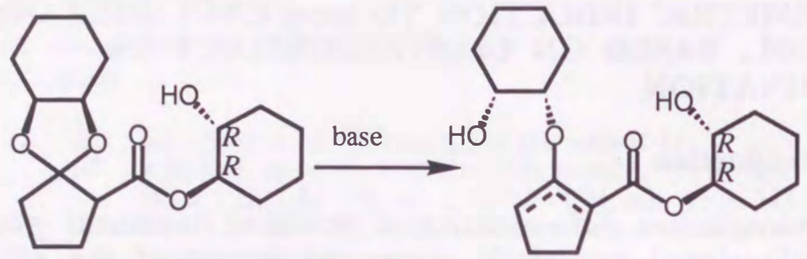
Scheme 24



Recently, Oku[22] and Iwata[23] reported an enantio-differentiation of *cis*-cycloalkane-1,2-diols *via* cleavage reaction of chiral acetals (Scheme 23 and 24).

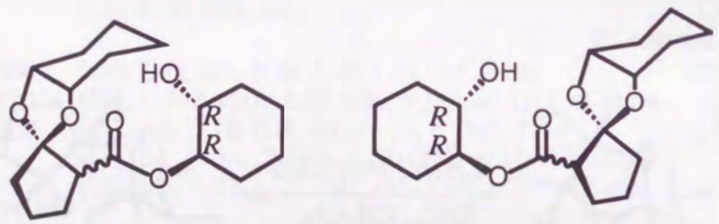
In the course of asymmetric alkylation described in Chapter I, the author found that the acetal of β-keto esters is easily cleaved by treatment with LDA to afford the corresponding enol ethers. On the basis of this finding, the author planned asymmetric induction to *meso*-cyclohexane-1,2-diol moiety in **43** (Scheme 25).

Scheme 25



43 47a and b

2. Preparation of substrates



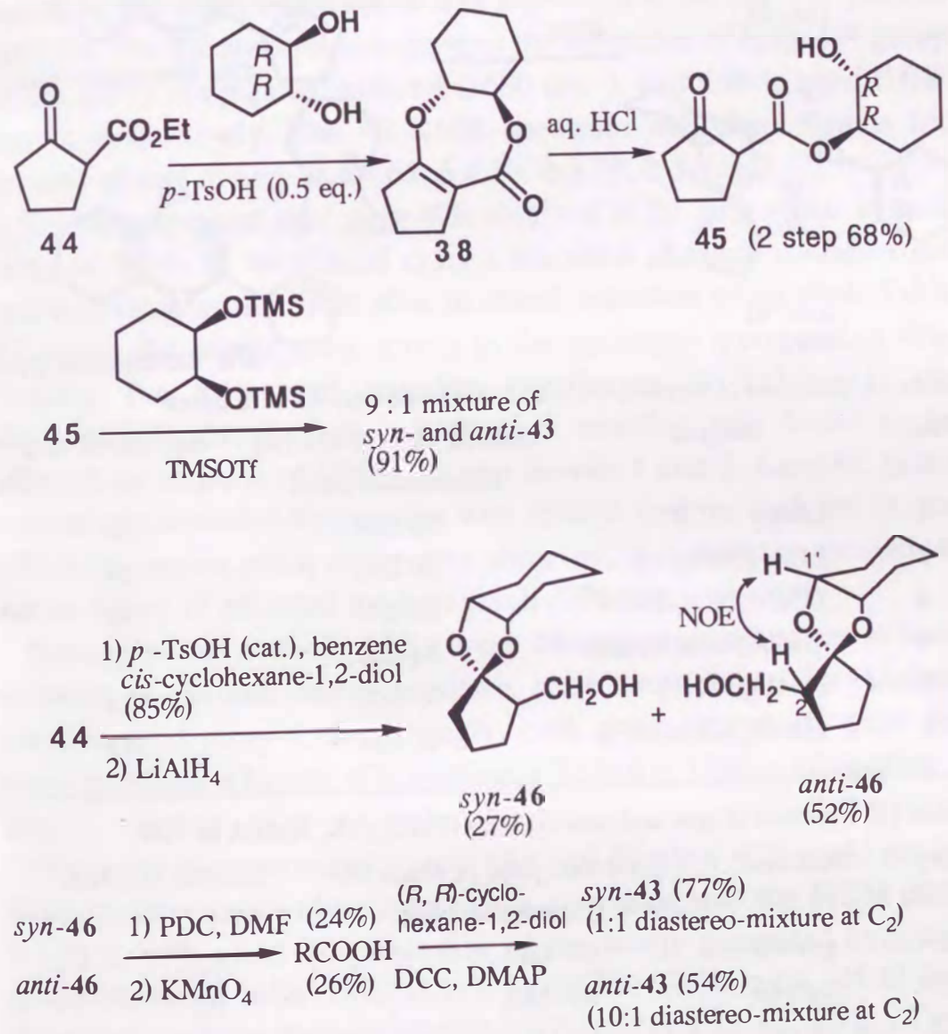
syn- 43 (3:2-1:1) *anti*- 43 (10:1)

Fig 10

Starting substrates *syn*- and *anti*-**43**, in which the ring fused to the 1,3-dioxolane ring is oriented in *syn*- or *anti*-fashion to the ester group, respectively, were synthesized by two different methods. Acetalization of chiral β-keto ester (**45**) derived from the corresponding ethyl ester (**44**) *via* a tricyclic lactone, with *cis*-1,2-bis(trimethylsilyloxy)-cyclohexane by Noyori's method[24] afforded an inseparable mixture (9:1) of *syn*- and *anti*-**43** in 91% yield. Another method for preparation of pure substrate is as follows. Acetalization of **44** with *cis*-cyclohexane-1,2-diol under azeotropic conditions (*p*-TsOH, benzene) and subsequent $LiAlH_4$ reduction of the ester function afforded separable alcohols (*syn*- and *anti*-**46**) in 27 and 52% yields from **44**, respectively. The relative stereochemistry was confirmed by $^1H,^1H$-NOESY spectra, in which the NOE was observed between C_2-H

and C_1'-H of *anti*-**46**. Each isolated alcohol was converted to the corresponding *syn*- and *anti*-**43** (24 and 26% yields) *via* two-step oxidation (i. PDC, DMF; ii. $KMnO_4$) and subsequent esterification with (*R*, *R*)-cyclohexane-1,2-diol (DCC, DMAP) in 77 and 54% yields, respectively (Scheme 26).

Scheme 26



3. Asymmetric induction to *meso*-cyclohexane-1,2-diol

Scheme 27

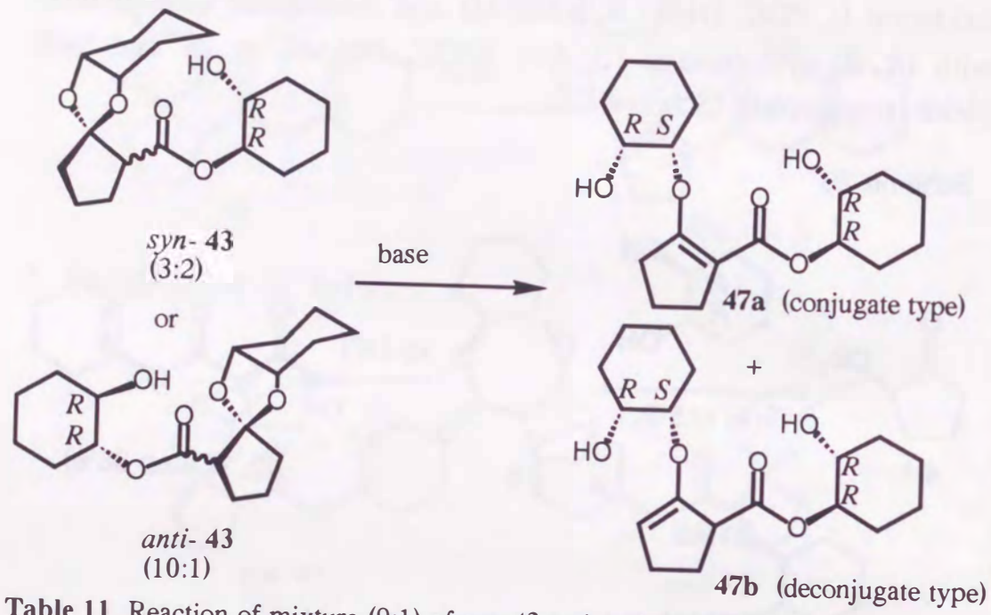


Table 11. Reaction of mixture (9:1) of *syn*-**43** and *anti*-**43** with bases

Entry	Reagent	Isolated yield of **47a** (%) (Conversion yield)	d.e. (%) of **47a**
1	LDA	30 (33)	29
2	LDA, HMPA	30 (34)	61
3	$(TMS)_2NLi$, HMPA	20 (60)	41
4	$(TMS)_2NNa$, HMPA	34 (65)	62
5	$(TMS)_2NK$	55 (63)	54
6	$(TMS)_2NK$, HMPA	41 (65)	72

Table 12. Reaction of *syn*- and *anti*-**43** with $(TMS)_2NK$, HMPA in THF

Entry	Substrate	Combined yield of **47a,b** (%) (Conversion yield)	d.e. (%) of **47a,b**
1	*syn*-**43**	67 (88)	72
2	*anti*-**43**	65 (90)	72

Starting substrates (*syn*- and *anti*-**43**) having the *cis*-cyclohexane-1,2-dioxy group were prepared as a 3 to 2 diastereomeric mixture at C_1. Reaction conditions were studied using a 9 to 1 mixture of *syn*- and *anti*-**43**. Treatment of the substrate (1 eq.) with a base (5 eq.) at -78 °C in THF under an Ar atmosphere for 0.5-1 h afforded the conjugated enol ether (**47a**) and the deconjugated enol ether (**47b**). The structure of **47a,b** were determined by spectroscopic data. For example, the mass spectrum of **47a** showed a molecular ion peak at *m/z* 324. The IR absorption suggested the existence of hydroxyl group (3400 cm^{-1}), conjugated carbonyl (1680 cm^{-1}), and double bond (1640 cm^{-1}), respectively. The ^{1}H-NMR spectrum exhibited signals for protons of diol moiety at δ 4.62, δ 4.15, δ 3.79, δ 3.59.

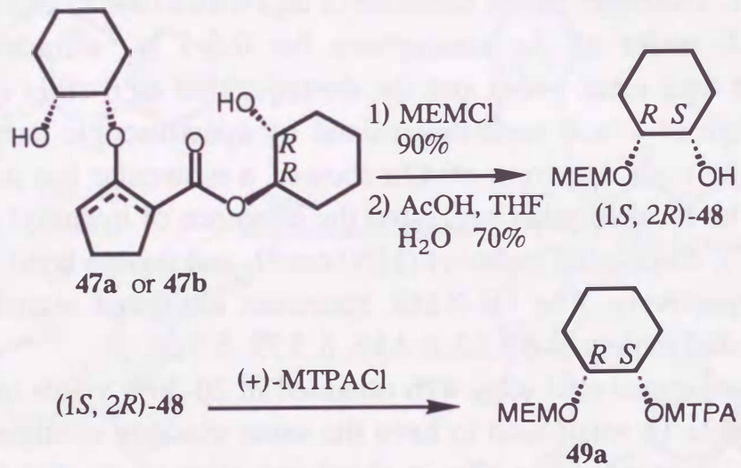
The deconjugated enol ether **47b** obtained in 20-30% yields in each entry of Table 11 was found to have the same absolute configuration and e.e. value as that from **47a**, in chiral induction of *cis*-diol. Table 11 shows the results relative only to the conjugate type product **47a**. Among the attempted reaction conditions in Table 11, the diastereoselectivity of the elimination reaction was found to be affected by addition of HMPA (5 eq.) (entries 1 and 2, 5 and 6). In the case of bis(trimethylsilyl)amides with HMPA (entries 3, 4 and 6), the effect of counter metal cation was observed, that is to say, potassium cation (entry 6) afforded the best result (72% d.e.).

Next, *syn*- and *anti*-**43**, which were diastereomerically pure at least in terms of *syn/anti* stereochemistry, were subjected to the reaction conditions of entry 6. Surprisingly, both *syn*- and *anti*-**43** gave the same products **47a** and **47b** with each 72% d.e. (Table 12, entries 1 and 2).

Since the diastereomeric excess (d.e.) of **47a** and **47b** could not be directly determined, these compounds converted into the MEM ether (-)-**48** in 63% yield *via* protection of the newly generated hydroxyl group as MEM ether (MEMCl / $(i\text{-Pr})_2NEt$ / CH_2Cl_2, r.t., 24 h) and subsequent acid-hydrolysis (AcOH-THF-H_2O (1:1:1), r.t., 24 h) of the enol ether function. The enantiomeric excess (e.e.) of (-)-**48** was

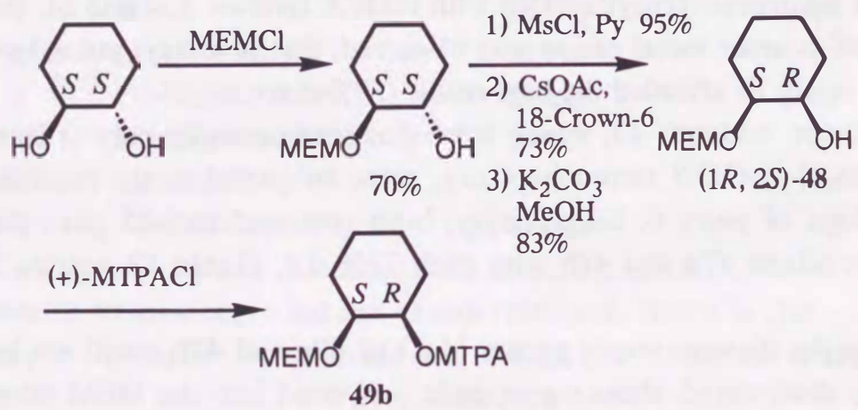
determined by 270MHz ^{1}H-NMR spectroscopy after conversion to corresponding (+)-MTPA ester (**49a**) (Scheme 28).

Scheme 28



4. Determination of absolute configuration and proposed mechanism

Scheme 29

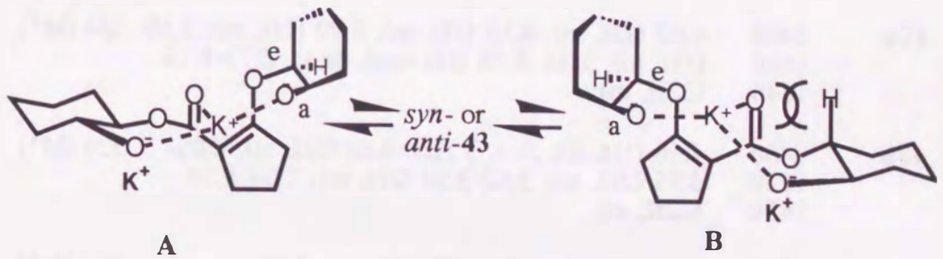


The absolute configuration of (-)-**48** ($[\alpha]_D^{24}$ -20.1° (c=0.7, $CHCl_3$)) was unambiguously determined to be (1*S*, 2*R*) by comparison of its specific rotation with an authentic sample. The authentic (1*R*, 2*S*)-**48**

($[\alpha]_D^{24}$ +27.1° (c=0.7, $CHCl_3$)) was synthesized from (*S*, *S*)-cyclohexane-1,2-diols *via* monoprotection of the hydroxy group and subsequent inversion of the hydroxy function by Ikegami's method[25] (Scheme 29).

The possible reaction pathway was considered to be as follows. An equilibrium between chelated enol ethers (**A** and **B** in Scheme 30) *via* acetal substrates was assumed judging from the following experimental results. 1) *Syn*- and *anti*-substrates gave the same products as regards absolute configuration and e.e. value. 2) In all cases of reaction in Tables 11 and 12, starting material was recovered in 5-25% yields. 3) Treatment of **47a** with NaH in THF gave a mixture of *syn*- and *anti*-**43**. The chelation intermediate **B** might be unfavorable because of steric hindrance between the carbonyl function and C_1'-axial-H. That is to say, the reaction might proceed *via* the favorable intermediate **A** in thermodynamically controlled fashion to afford finally (1*S*, 2*R*)-**47a** predominantly.

Scheme 30



In conclusion, it is remarkable that the product **48** could be obtained from a mixture of four possible diastereomers (C_1-diastereomeric mixture of *syn*- and *anti*-**43**) in 72% e.e.

Spectral data of compounds in this chapter are summarized in Table 13.

Table 13 (1). Spectral Data of **43, 45-48**

compound	IR cm^{-1} (neat)	^{1}H-NMR ($CDCl_3$) δ	Ms *m/z*
***syn*-43** (3:2)	3500 1725	4.77, 4.66 (total 1H, m each), 4.16-4.00 (2H, m) 3.77, 3.68 (total 1H, br s, ratio=3:2), 3.52 (1H, m), 3.05, 2.89 (total 1H, t each, *J*=8 Hz) 2.15-1.48 (16H, m), 1.43-1.15 (6H, m)	324 (M^+)
***anti*-43** (10:1)	3500 1725	4.75 (1H, m), 4.20-4.12 (2H, m), 3.50 (1H, s) 3.48 (1H, m), 2.84 (1H, m), 2.17-1.55 (16H, m) 1.54-1.19 (6H, m)	324 (M^+)
45	3475 1750 1720	4.63 (1H, m), 3.63-3.54 (2H, m), 3.21 (1H, dd, *J*=18, 5 Hz), 2.51-1.25 (14H, m)	226 (M^+)
***syn*-46**	3450	4.07 (2H, dt, *J*=10, 3 Hz), 3.78-3.59 (2H, m) 3.00 (1H, t, *J*=6 Hz), 2.18 (1H, m), 1.96-1.22 (14H, m)	212 (M^+)
***anti*-46**	3450	4.13-4.03 (1H, m), 3.65-3.55 (2H, m), 2.89 (1H, t, *J*=6 Hz), 2.03 (1H, m), 1.96-1.17 (14H, m)	212 (M^+)
47a	3400 1680 1640	4.62 (1H, m), 4.15 (1H, m), 3.79 (1H, m), 3.59 (1H, m), 3.35, 3.25 (1H each, br s), 2.72-1.15 (22H, m)	324 (M^+)
47b	3450 1720 1650	4.66 (1H, dd, *J*=4, 3 Hz), 4.64 (1H, m), 4.05-3.95 (2H, m), 3.62-3.50 (2H, m), 2.54-1.14 (22H, m)	324 (M^+)
48	3500	4.80 (2H, s), 3.85-3.77 (2H, m), 3.73 (1H, t, *J*=4), 3.68 (1H, m), 3.57 (2H, t, *J*=4) 3.40 (3H, s), 2.72 (1H, br s), 2.00-1.20 (8H, m)	204 (M^+)

Table 13 (2). ^{1}H-NMR Spectra of **49a** and **49b**

compound	^{1}H-NMR ($CDCl_3$) δ
49a (72% d.e.) From (1*S*, 2*R*)-**48**	7.58 (2H, m), 7.42-7.34 (3H, m), 5.35 (1H, m) 4.78, 4.76 (7/50 H each, d, *J*=15 Hz), 4.69, 4.66 (43/50H each, d, *J*=15 Hz), 3.76 (1H, m), 3.67 (2H, m), 3.56 (3H, d, *J*=1 Hz), 3.52 (2H, m) 3.39, 3.38 (total 3H, s each, ratio=7:43) 2.01-1.25 (8H, m)
49b (100% d.e.) From (1*R*, 2*S*)-**48**	7.64 (2H, m), 7.41-7.34 (3H, m), 5.43 (1H, m) 4.78 (1 H , d, *J*=15 Hz), 4.76 (1H, d, *J*=15 Hz) 3.77 (1H, m), 3.69 (2H, m), 3.59 (3H, d, *J*=1 Hz) 3.54 (2H, m), 3.39 (3H, s), 2.01-1.25 (8H, m)

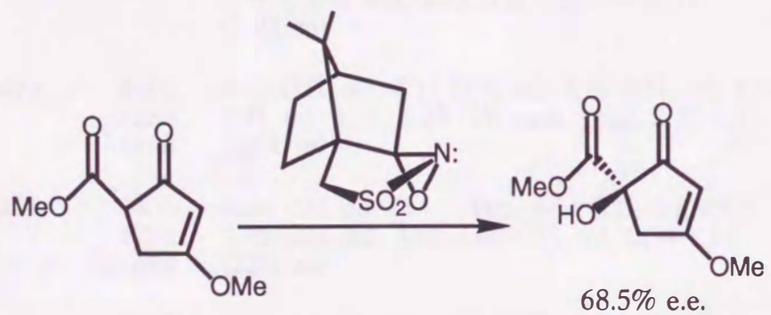
Chapter IV
ASYMMETRIC OXIDATION OF β-KETO ESTERS USING CHIRAL CYCLIC DIOLS

1. Introduction

The α-hydroxy carbonyl unit is commonly found in many natural products. Enantiomerically pure α-hydroxy carbonyl compounds are also important synthons for asymmetric synthesis of natural products[26] and are useful stereo-directing group.[27] Consequently, numerous studies have been aimed at developing methodology for the synthesis of this structural unit in optical active form. The usual method for introducing a hydroxy moiety into β-keto ester is the enolate[28] (or silyl enol ether[29]) oxidation.

Davis *et al.* and Smith *et al.* reported that in enantioselective synthesis of (+)-kjellmanianone, the key step entail enantioselective hydroxylation of the prochiral sodium enolate of β-keto ester with chiral N-sulfonyloxaziridine[30] (Scheme 31).

Scheme 31

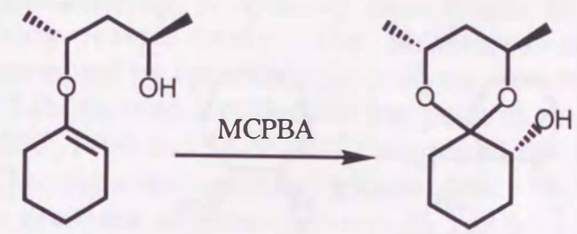


Recently, oxidation of the enol ether derived from cyclohexanone and 2,4-pentanediol were reported, and excellent diastereoselectivity was observed[31] (Scheme 32).

In Chapter I, the author have found that the chiral enol ether plays an important role on the asymmetric induction in terms of the formation of chelation complex (**A**) between three oxygen atoms (one carbonyl oxygen, one etheric oxygen and one alcoholic oxygen) and lithium cation (Scheme 33).

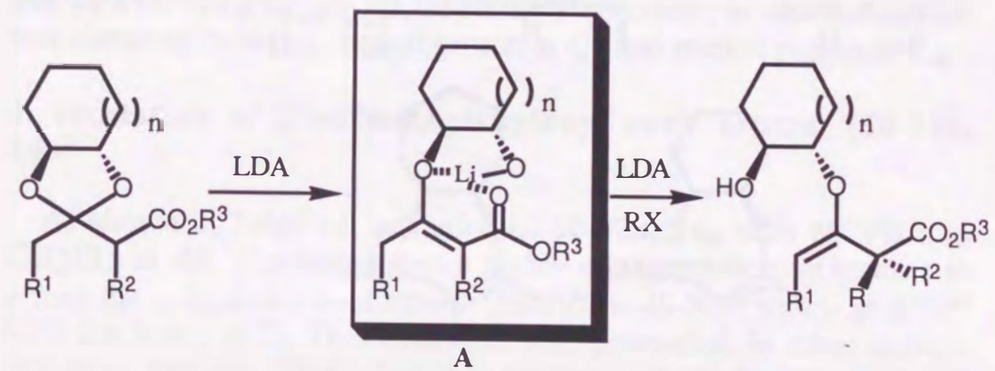
Similar stereo controled reaction is also expected for oxidation of the enol ether substrates (**5e, 12, 50-54**).

Scheme 32



>99% d.e.

Scheme 33



2. Preparation of substrates.

β'-Trimethylsilyloxy enol ethers (**50-54a**) were prepared by treatment of chiral 1,2-cyclohexanedioxy (or chiral 1,2-cycloheptane-dioxy) acetals with LDA in THF at -50 °C followed by silylation with trimetylsilyl chloride (TMSCl). The acetals derived from cyclic (five or six-membered ring) β-keto esters easily cleaved by treatment with 2 eq. of LDA. On the other hand, the similar reaction of the acetals derived from acyclic β-keto esters required 4 eq. of LDA. When 2 eq. of LDA were used in this reaction, starting acetals were recovered in >50% yield.

Desilylation of cyclic β'-trimethylsilyloxy enol ethers (**50-52a**) was performed by treatment with $ZnBr_2$ at room temperature to afford the corresponding β'-hydroxy enol ethers (**5e, 12, 52b**).

However, desilylation of acyclic β'-trimethylsilyloxy enol ethers (**53a, 54a**) under above conditions did not afford the desired β'-

hydroxy enol ethers (**53b, 54b**), but the corresponding acetals were quantitatively obtained.

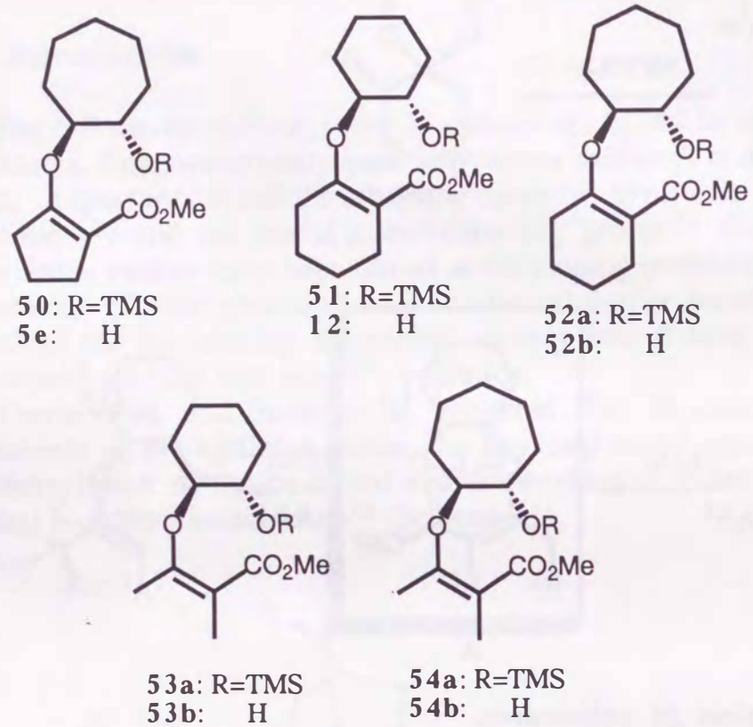
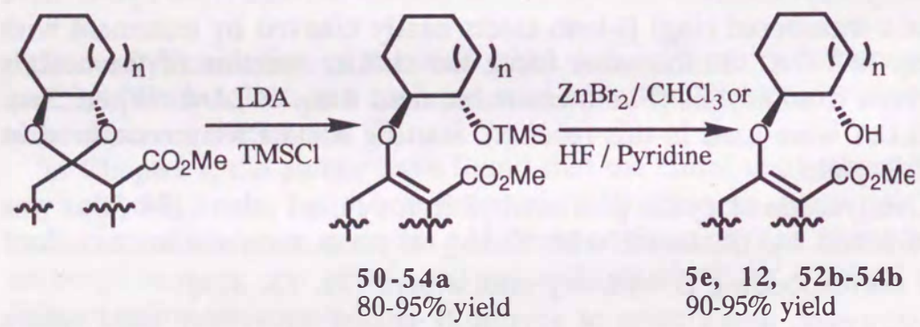


Fig. 10

Scheme 34



Desilylation of **53a** and **54a** with HF/pyridine afforded the corresponding β'-hydroxy enol ethers (**53b, 54b**) in 90 and 93% yields, respectively. The structures of **5e, 12, 50-54** were determined by spectroscopic analysis. For example, the mass spectrum of **54b** showed a molecular ion peak at *m/z* 242. The IR absorption (3450, 1700 and 1620 cm^{-1}) suggested the existence of hydroxyl and α,β-unsaturated carbonyl groups. The ^{13}C-NMR spectrum indicated the presence of ester carbonyl (δ 169.6 (s)), two olefinic carbons (δ 163.4 (s), 108.8 (s)) and two methyl carbons (δ 16.1 (q), 12.4 (q)). The ^{1}H-NMR spectrum showed the diol moiety at δ 4.06, δ 3.75 and two methyl groups at δ 2.42 and δ 1.82. The olefinic geometry of **53** and **54** was confirmed by $^{1}H,^{1}H$-NOESY spectrum, in which the NOE was observed between methyl proton at C_2 and methyl proton at C_4.

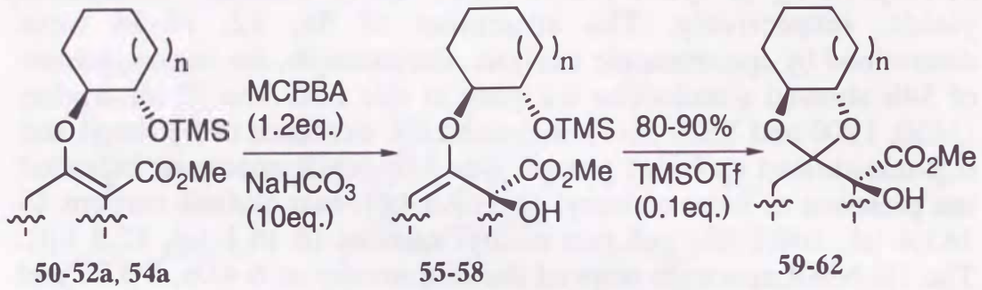
3. Oxidation of β'-trimethylsilyloxy enol ethers (50-52a, 54a)

As shown in Table 14, oxidation of **50-52a, 54a** with MCPBA in CH_2Cl_2 at -60 °C proceeded in a highly diastereoselective manner to afford the α-hydroxy enol ethers (**55-58**) in 46-70% yields with 82-99% d.e.(entry 4-7). This oxidation also proceeded in other solvent (toluene, hexane, THF) but the diastereoselectivity was reduced (entries 1-3).

All of the entries in Table 14 were carried out in the presence of excess (10eq.) amount of $NaHCO_3$ to avoid deacetalization. In the absence of $NaHCO_3$ deacetalization reaction was observed, and yield of the product (**56**) was reduced (40%), but the diastereoselectivity was not changed(>99% d.e.). This fact suggested that $NaHCO_3$ did not affect on diastereoselectivity of this oxidation.

The structure of α-hydroxy ethers (**55-58**) was determined by spectroscopic analysis. For example, the mass spectrum of **57** showed a molecular ion peak at *m/z* 356. The IR absorption suggested the existence of hydroxyl group (3530 cm^{-1}), ester carbonyl (1740 cm^{-1}), and double bond (1663 cm^{-1}), respectively. The ^{1}H-NMR spectrum exhibited signals for olefinic proton at δ 4.99, diol moiety at δ 4.00, δ 3.78, and methyl ester at δ 3.77. The ^{13}C-NMR spectrum indicated the presence of ester carbonyl (δ 175.9), olefinic carbons (δ 151.1 and δ 100.9), and newly generated quaternary carbon (δ 74.2).

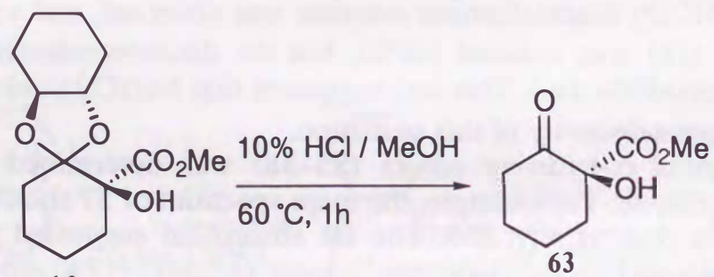
Table 14. Oxidation of β'-trimethylsilyloxy enol ether **(50-52a, 54a)**



Entry	Substrate	Condition	Product	Solvent	Yield (%)	d.e. (%)	Hydroxy acetal
1	**50**	c	**55**	Toluene	90	53	**59**
2	**50**	b	**55**	Hexane	79	53	**59**
3	**50**	a	**55**	THF	82	50	**59**
4	**50**	d	**55**	CH_2Cl_2	70	90	**59**
5	**51**	d	**56**	CH_2Cl_2	53	>99	**60**
6	**52a**	d	**57**	CH_2Cl_2	56	>99	**61**
7	**54a**	c	**58**	CH_2Cl_2	46	82	**62**

Conditions: a) r.t. 8 h b) 0 °C, 8 h c) -40~ -50 °C, 48~70 h
d) -50~ -60 °C, 48 h

Scheme 35



90% yield (>99% e.e.)

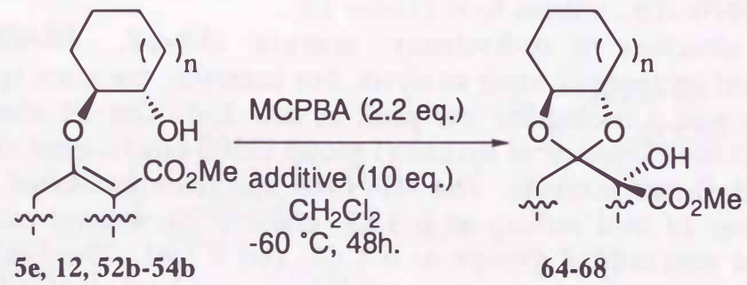
$[\alpha]_D^{26}$ -138.8° (c=1.19, $CHCl_3$)

Above products (**55-58**) were converted to the corresponding α-hydroxy acetals(**59-62**) by treatment with TMSOTf at -50 °C, and the diastereomeric excess of **55, 57, 58** was determined by the analysis

of ^{1}H-NMR spectroscopy of **59, 61, 62**. Diastereomeric excess of **56** could not be determined by ^{1}H-NMR spectroscopy of **60**. So, after conversion into α-hydroxy-β-keto ester **63**, the enantiomeric excess was determined by examination of ^{1}H-NMR spectroscopy using chiral shift reagent ($Eu(hfc)_3$) (Scheme 35).

4. Oxidation of enol ethers with free hydroxy group (5e, 12, 52b-54b)

Table 15. Oxidation of β'-hydroxy enol ether **(5e, 12, 52b-54b)**



Entry	Substrate	Product	Additive	Yield (%)	d.e. (%)
1	**5e**	**64**	none	85	67
2	**5e**	**64**	$NaHCO_3$	95	85
3	**5e**	**64**	LiOH	56	85
4	**5e**	**64**	K_2CO_3	85	84
5	**5e**	**64**	Li_2CO_3	85	89
6	**12** [1]	**65**	Li_2CO_3	94	83
7	**52b** [1]	**66**	Li_2CO_3	93	73
8	**53b**	**67**	Li_2CO_3	90	>99
9	**54b**	**68**	Li_2CO_3	96	>99

1) The reaction was performed at -40~ -45 °C for 70h.

As shown in Table 15, oxidation of **5e** with MCPBA proceeded in a moderately diastereoselective manner to afford the α-hydroxy acetal (**64**) (67% d.e.) (entry 1).

Interestingly, when this oxidation reaction was carried out in the presence of $NaHCO_3$ (10 eq.), diastereomeric excess of **64** increased

to 85% d.e. (entry 2). In the case of β'-trimethylsilyloxy enol ethers (**50**), $NaHCO_3$ had no influence on diastereoselectivity of this oxidation reaction. On the other hand, oxidation of enol ethers (**5e**) with free hydroxyl group was remarkably influenced by the basic additives. So, effects of several basic additives were studied in entries 2-5, and the best result was obtained in the presence of Li_2CO_3 (85% yield, 89% d.e., entry 5) (Table 15).

Oxidation of six-membered ring and acyclic substrates (**12, 52b-54b**) under above reaction conditions proceeded with moderate to high diastereoselectivities (**52b** and **12** in 73-83% d.e.) (**53b** and **54b** in >99% d.e., entries 6-9) (Table 15).

The structure of α-hydroxy acetals (**59-62, 64-68**) was determined by spectroscopic analysis. For example, the mass spectrum of **68** showed a molecular ion peak at *m/z* 258. The IR absorption suggested the existence of hydroxyl group (3500 cm^{-1}), ester carbonyl (1735 cm^{-1}), respectively. The ^1H-NMR spectrum exhibited signals for protons of diol moiety at δ 3.83, and δ 3.70, methyl ester at δ 3.80, and two methyl groups at δ 1.46, and δ 1.41. The ^{13}C-NMR spectrum indicated the presence of ester carbonyl (δ174.8), two methyl carbons (δ 21.5, δ 20.6), and newly generated quaternary carbon (δ 79.2).

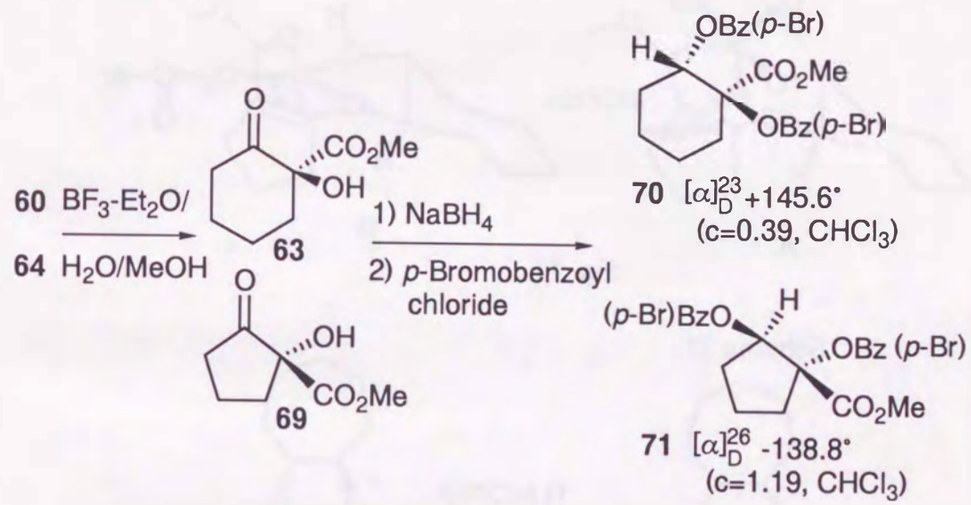
Diastereomeric excess of **64-68** was determined by analysis of ^1H-NMR spectroscopy.

In striking contrast to the oxidation of β'-trimethylsilyloxy enol ethers (**50-52a, 54a**), the oxidation of **5e, 12,** and **52b-54b** with MCPBA dramatically changed the stereochemical course of the reaction to give the α-hydroxy acetals (**64-68**) in a highly diastereoselective manner.

5. Determination of absolute configuration and proposed mechanism

Absolute configuration of α-hydroxy acetal (**60, 64**) was determined by CD spectra after conversion into the corresponding di-*p*-bromobenzoate (**70, 71**) *via* three-step sequence [i) BF_3-Et_2O /H_2O /MeOH ii) $NaBH_4$, -60 °C iii) *p*-bromobenzoyl chloride / pyridine]. The relative stereochemistry of **70** was unambiguously determined to be trans by comparison with an authentic sample. The authentic **racemic-70** was

Scheme 36



synthesized from methyl cyclohexene-1-carboxylate *via* three step sequence[32] [i) MCPBA ii) $HClO_4$ iii) *p*-bromobenzoylchloride / pyridine]. The relative stereochemistry of **71** was confirmed by the analysis of two-dimensional NOESY and COSY spectra.

The CD spectrum of **70** (>99% e.e.) showed a positive first Cotton effect ($\Delta\varepsilon_{250}$ + 14.2), and that of **71** (89% e.e.) displayed a negative first Cotton effect ($\Delta\varepsilon_{250}$ -20.1). The exciton chirality method therefore confirmed that the absolute configurations of **70** and **71** were assigned to be (1*S*, 2*S*) and (1*R*, 2*R*), respectively.

Though the absolute configuration of acyclic products (**58, 67, 68**) has not been determined, on the basis of above results of 5 or 6-

membered ring substrates, we tentatively assumed that the absolute configuration of **61, 62, 66-68** are as depicted in Table 14 and 15.

These results might be explained by assumption of the intermediates **A** and **B** (Fig 11). In the case of **A**, trimethylsilyl group would coordinate to the carbonyl oxygen, and MCPBA might attack from the opposite side (convex face). This assumption was supported by the following result. Oxidation and subsequent acid treatment of *tert*-butyldiphenylsilyl (TBDPS) ether (**72**) afforded **59** (50% yield) of 40% d.e. (Scheme 37). This decrease of d.e. might be ascribed to

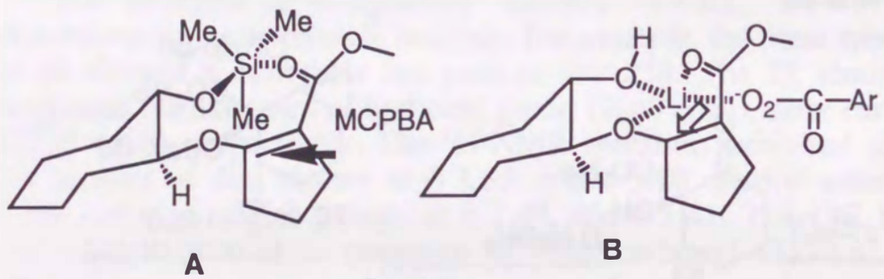
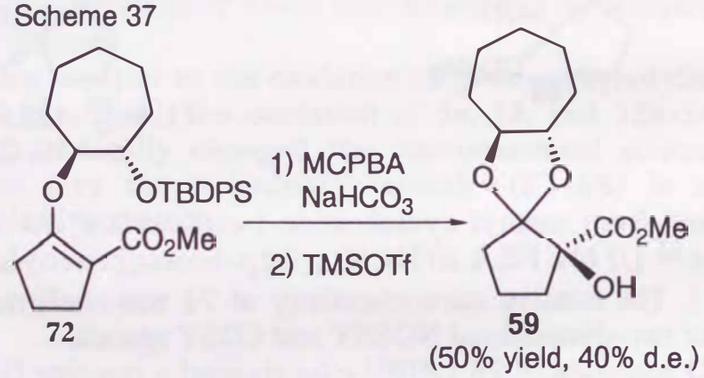


Fig. 11

Scheme 37



the difficulty of coordination between silicon atom and carbonyl group because of bulky substituents on silicon atom.

In the case of the oxidation of β'-hydroxy enol ethers, the lithium cation of peroxybenzoate chelated to the ester carbonyl oxygen and two oxygens (one is free hydroxyl and another is etheric oxygen) to

form intermediate **B.** Thus, peroxybenzoate anion could be attack from concave face.

In conclusion, this new method for the preparation of optically active α-hydroxy-β-keto esters was found to be applicable to both cyclic and acyclic substrates, and the absolute configuration of newly generated stereogenic center depends on the chirality of protective group.

Spectral data of compounds in this chapter are summarized in Table 16.

Table 16 (1). Spectral Data of **50-54b**

compound	IR cm^{-1} (neat)	^{1}H-NMR ($CDCl_3$) δ	Ms *m/z*
50	1700 1630	4.03 (1H, m), 3.84 (1H, m), 3.68 (3H, s), 2.67 (1H, m), 2.58-2.45 (3H, m), 1.90-1.62 (8H, m) 1.58-1.42 (4H, m), 0.08 (9H, s)	326 (M^+) 199
5e	3400 1680 1610	4.15 (1H, br-s), 3.79-3.71 (2H, m), 3.71 (3H, s), 2.72-2.52 (4H, m), 2.02-1.82 (4H, m) 1.76-1.49 (8H, m)	254 (M^+) 142 110
51	1685 1620	3.94 (1H, m), 3.69 (3H, s), 3.60 (1H, m) 2.46-2.16 (4H, m), 1.96-1.85 (2H, m), 1.73-1.53 (6H, m), 1.48-1.17 (4H, m), 0.08 (9H, s)	326 (M^+) 228 171
12	3400 1670 1610	5.37 (1H, br-s), 3.72 (3H, s), 3.64-3.57 (2H, m), 2.55-2.38 (2H, m), 2.32-1.97 (4H, m) 1.77-1.27 (10H, m)	254 (M^+) 222 124
52a	1682 1620	4.13 (1H, m), 3.83 (1H, m), 3.69 (3H, s) 2.36-2.14 (4H, m), 1.77-1.64 (6H, m), 1.63-1.38 (8H, m), 0.08 (9H, s)	340 (M^+) 213 185
52b	3400 1680 1620	5.18 (1H, br-s), 3.79-3.73 (2H, m), 3.71 (3H, s), 2.52-2.41 (2H, m), 2.22-2.12 (2H, m) 2.01-1.86 (2H, m), 1.73-1.48 (12H, m)	268 (M^+) 225 167
53a	1700 1620	4.02 (1H, m), 3.69 (3H, s), 3.51 (1H, m), 2.37 (3H, s), 1.92-1.85 (2H, m), 1.82 (3H, s), 1.70-1.66 (2H, m), 1.43-1.21 (4H, m), 0.07 (9H, s)	300 (M^+) 187 171
53b	3450 1698 1617	3.69 (1H, m), 3.50 (3H, s), 3.35 (1H, m), 2.35 (3H, s), 2.08 (3H, s), 2.0 (1H, br-s), 1.87 (1H, m), 1.53 (1H, m), 1.39-1.07 (3H, m) 1.04-0.74 (3H, m)	228 (M^+) 130
54a	1700 1620	4.15 (1H, m), 3.79 (1H, m), 3.69 (3H, s), 2.34 (3H, s), 1.82 (3H, s), 1.78-1.59 (5H, m) 1.58-1.39 (5H, m), 0.08 (9H, s)	314 (M^+) 185
54b	3450 1700 1620	4.06 (1H, m), 3.75 (1H, m), 3.71 (3H, s), 2.42 (1H, br-s), 2.33 (3H, s), 1.92 (1H, m), 1.82 (3H, s), 1.77-1.52 (3H, m), 1.59-1.41 (6H, m)	242 (M^+) 155

Table 16 (2). Spectral Data of **55-64**

compound	IR cm^{-1} (neat)	^{1}H-NMR ($CDCl_3$) δ	Ms *m/z*
55	3550 1740 1653	4.74 (1H, t, *J*=2 Hz), 3.92 (1H, m), 3.80 (1H, m), 3.77 (3H, s), 3.56 (1H, s, OH), 2.50-2.32 (3H, m), 2.02 (1H, m), 1.85-1.58 (5H, m) 1.56-1.35 (5H, m), 0.07 (9H, s)	342 (M^+) 185
56	3530 1740 1665	5.10 (1H, t, *J*=4 Hz), 3.77 (3H, s), 3.75 (1H, m), 3.64 (1H, s, OH), 3.59 (1H, m) 2.19-1.94 (4H, m), 1.88 (1H, m), 1.79-1.53 (4H, m), 1.42-1.17 (5H, m), 0.09 (9H, s)	342 (M^+) 171
57	3530 1740 1663	4.99 (1H, t, *J*=4 Hz), 4.00 (1H, m), 3.78 (1H, m), 3.77 (3H, s), 3.60 (1H, s, OH), 2.20-1.99 (3H, m), 1.94-1.61 (6H, m), 1.58-1.35 (7H, m), 0.08 (9H, s)	356 (M^+) 185
59	3550 1735	3.78 (3H, s), 3.75 (1H, m), 3.55 (1H, m), 3.48 (1H, s, OH), 2.46 (1H, m), 2.24-2.05 (2H, m) 2.03-1.72 (5H, m), 1.77-1.39 (8H, m)	270 (M^+) 154
60	3500 1735	3.79 (3H, s), 3.33 (1H, s, OH), 3.29 (1H, m) 3.05 (1H, m), 2.22-2.12 (3H, m), 1.98 (1H, m) 1.86-1.76 (4H, m), 1.69-1.57 (3H, m) 1.45-1.18 (5H, m)	270 (M^+) 182 172
61	3550 1732	3.79 (3H, s), 3.78 (1H, m), 3.53 (1H, m) 3.33 (1H, s, OH), 2.22-2.11 (3H, m), 1.96 (1H, m), 1.79-1.52 (10H, m),1.49-1.35 (4H, m)	284 (M^+) 196
62	3520 1735	3.79 (3H, s), 3.86-3.72 (2H, m), 3.48 (1H, s, OH), 2.22-2.13 (2H, m), 1.47 (3H, s) 1.41 (3H, s), 1.72-1.35 (8H, m)	257 (M^+- 1) 155
63	3450 1718	4.35 (1H, s), 3.79 (3H, s), 2.73-2.52 (2H, m) 2.22-1.67 (6H, m)	172 (M^+)
64	3500 1730	3.76 (3H, s), 3.77-3.68 (2H, m), 3.45 (1H, s, OH), 2.63-2.40 (2H, m), 2.25-1.99 (4H, m), 1.91-1.70 (4H, m), 1.59-1.27 (6H, m)	270 (M^+) 154

Table 16 (3). Spectral Data of **65-72**

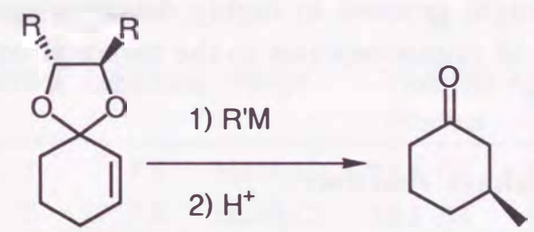
compound	IR cm^{-1} (neat)	^{1}H-NMR ($CDCl_3$) δ	Ms *m/z*
65	3500 1720	3.78 (3H, s), 3.50 (1H, s, OH), 3.29 (1H, m) 2.97 (1H, m), 2.22-2.09 (3H, m), 1.97 (1H, m) 1.88-1.52 (5H, m), 1.38-1.20 (7H, m)	270 (M^+) 269 154
66	3550 1725	3.78 (3H, s), 3.76 (1H, m), 3.49 (1H, m), 3.47 (1H, s, OH), 2.22-2.06 (3H, m), 1.98-1.77 (2H, m), 1.65-1.26 (13H, m)	284 (M^+) 196
67	3520 1735	3.80 (3H, s), 3.41 (1H, s, OH), 3.30 (2H, m) 2.18-2.11 (2H, m), 1.86-1.73 (2H, m), 1.49 (3H, s), 1.44 (3H, s), 1.41-1.18 (4H, m)	244 (M^+) 141
68	3500 1735	3.83 (1H, m), 3.80 (3H, s), 3.70 (1H, m) 3.40 (1H, s, OH), 2.22-2.10 (2H, m), 1.46 (3H, s), 1.41 (3H, s), 1.70-1.38 (8H, m)	258 (M^+) 155
69	3450 1740 (br)	3.81 (3H, s), 2.54-2.43 (3H, m), 2.17-2.04 (3H, m)	158 (M^+) 126 102
70	1730 (br)	7.90 (2H, d, *J*=9 Hz), 7.89 (2H, d, *J*=9 Hz) 7.62 (2H, d, *J*=9 Hz), 7.61 (2H, d, *J*=9 Hz) 5.50 (1H, t, *J*=3 Hz), 3.65 (3H, s), 2.48 (2H, m), 2.10 (2H, m), 1.82-1.39 (4H, m)	540 (M^+) 270
71	1725 (br)	7.90 (2H, d, *J*=9 Hz), 7.85 (2H, d, *J*=9 Hz) 7.61 (2H, d, *J*=9 Hz), 7.59 (2H, d, *J*=9 Hz) 5.72 (1H, t, *J*= 5 Hz), 3.66 (3H, s), 3.03 (1H, dt, *J*=15, 8 Hz), 2.36 (1H, m), 2.20 (1H, ddd, *J*=15, 9, 4 Hz), 2.11-1.95 (2H, m) 1.89 (1H, m)	526 (M^+) 262
72	1695	7.69 (4H, m), 7.39 (6H, m), 4.05 (2H, m) 3.64 (3H, s), 2.47 (2H, m), 2.33-2.00 (3H, m) 1.90-1.38 (11H, m), 1.07 (3H, s), 1.05 (6H, s)	492 (M^+) 199

CHAPTER V
NEW TYPE OF ASYMMETRIC DOUBLE MICHAEL REACTION, INDUCED BY CHIRAL ACETAL

1. Introduction

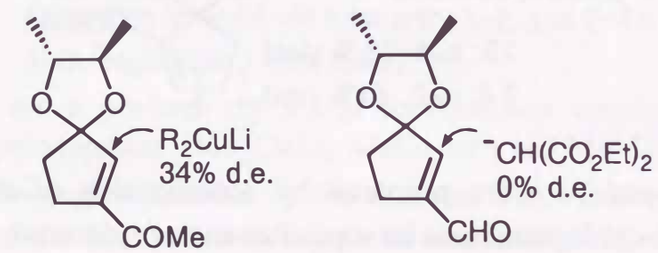
Enantio- and diastereo-selective conjugate addition reactions of organometallic reagents to α,β-unsaturated carbonyl and their analogues have been the subject of recent asymmetric synthesis and have provided potent methodologies for asymmetric C-C bond formation.[33]

Scheme 38



R=Me R'M=Me_2CuLi, BF_3 (23% e.e.) or Me_3Al (26% e.e.)
R=$CONH_2$ R'M=Me_3Al (78% e.e.)

Scheme 39



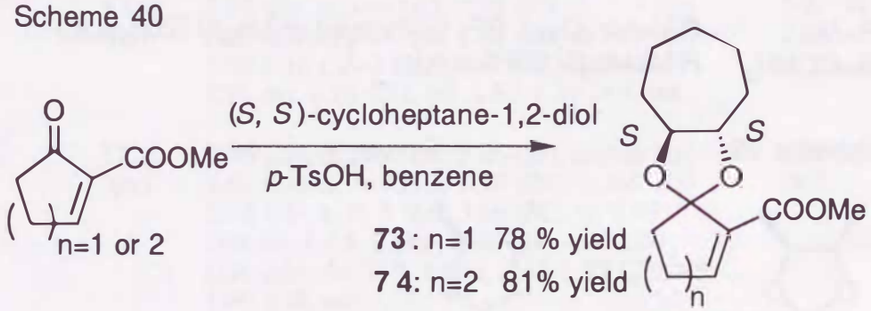
Among them, one that has recently received significant attention is the use of chiral acetals in diastereoselective process.[34] The conjugate addition of organocopper reagent to chiral cyclohexanone acetals followed by acid hydrolysis afforded 3-alkylcyclohexanone with low to moderate diastereoselectivity[35] (Scheme 38).

Double bond, activated by an electron-withdrawing group, is another kind of prochiral center. However, conjugate additions to enones bearing an acetal auxiliary in various relative positions met with little success[36] (Scheme 39).

In this Chapter, the author planned asymmetric conjugate addition of organocuprates to chiral acetals(**73** and **74**) derived from 2-methoxy-carbonyl-2-cycloalkenone and (*S, S*)-cycloheptane-1,2-diol. The author expected that the reaction might proceed in highly diastereoselective manner *via* the coordination of organocuprates to the carbonyl oxygen and selected one acetal oxygen.

2. Asymmetric double Michael reaction

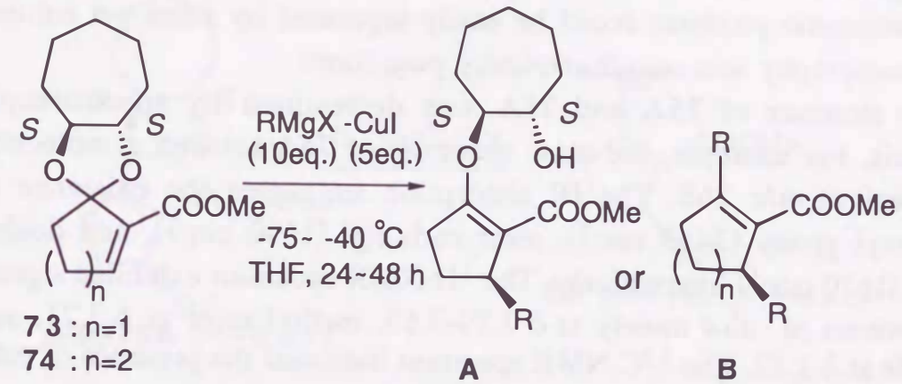
Scheme 40



Compounds **73** and **74** were prepared by acetalization of the 2-methoxycarbonyl-2-cyclopentenone(or-cyclohexenone) derived from corresponding β-keto esters[37] with (*S, S*)-cycloheptane-1,2-diol under

usual azeotropic conditions (*p*-TsOH, benzene) in 78 and 83% yields, respectively.

Table 17. Reaction of homochiral acetals **(73 and 74)** with mixed cuprates.



Entry	Substrate	RMgX	Yield(%) Product	d.e.(%)		Yield (%) Product	e.e. (%)	
1	**73**	MeMgBr	**75A**	85	89	---	---	---
2	**73**	Bu^tMgCl	**76A**	83	81	---	---	---
3	**73**	PhMgBr	---	---	---	**77B**	69	93
4	**73**	Bu^nMgCl	---	---	---	**78B**	81	81
5[a]	**73**	Bu^nMgCl	---	---	---	**78B**	83	76
6	**74**	Bu^nMgCl	---	---	---	**79B**	79	63

* Reaction time: 24~48 h for entry 1~2, and 2~4 h for entry 3~6.

a) Bu^nMgCl (5eq.) / CuI (5eq.).

As a preliminary study for reaction conditions, three kinds of organocuprates (Me_2CuLi, $MeCu\text{-}BF_3$ and MeMgBr-CuI) were studied on conjugate addition to chiral acetal (**73**). Among them, MeMgBr-CuI gave the best result in regard to chemical yield of methylated product. Another two kinds of cuprates gave a complex mixture.

Reaction of **73** with MeMgBr (10 eq.) / CuI (5 eq.) in THF at -78 to -40 °C afforded the enol ether (**75A**) (85% yield) of 89% d.e. with 3*S*-configuration (Table 17, entry 1). Reaction of **73** with Bu^tMgCl /CuI also gave (3*R*)-**76A** (83% yield) of 81% d.e. In the latter case, two diastereomeric products could be easily separated by silica-gel column chromatography into enantiomerically pure form.

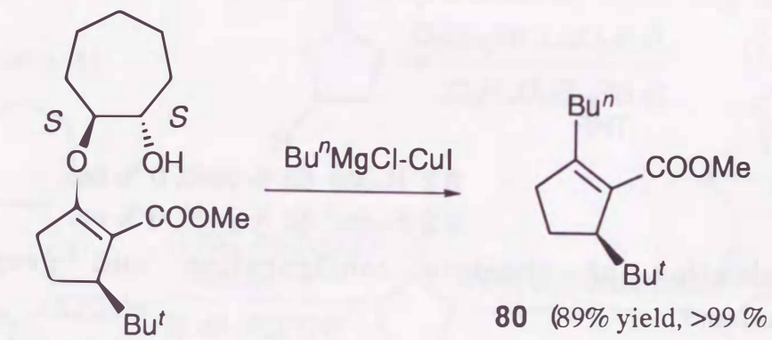
The structure of **75A** and **76A** was determined by spectroscopic analysis. For example, the mass spectrum of **75A** showed a molecular ion peak at *m/z* 268. The IR absorption suggested the existence of hydroxyl group (3450 cm^{-1}), ester carbonyl (1690 cm^{-1}), and double bond (1610 cm^{-1}), respectively. The ^{1}H-NMR spectrum exhibited signals for protons of diol moiety at δ 3.79-3.69, methyl ester at δ 3.71, and C_5-Me at δ 1.12. The ^{13}C-NMR spectrum indicated the presence of ester carbonyl (δ 168.9), olefinic carbons (δ 166.1 and δ 113.0), and newly generated tertiary carbon (δ 36.0).

Reaction of **73** with PhMgBr and Bu^nMgCl / CuI (entries 3 and 4) in a similar manner gave unexpected results. The reactions afforded the β, β'-disubstituted cycloalkenecarboxylates (**77B**) (69% yield, 93% e.e.) and (**78B**) (81% yield, 81% e.e.), respectively. When the ratio of Bu^nMgCl:CuI (2:1) was changed to (1:1) in the above reaction, similar result was obtained and slightly decreasing of e.e. was observed (entry 5).

Reaction of the six-membered substrate (**74**) with Bu^nMgCl / CuI also afforded **79B** (79% yield) of 63% e.e. The structure of **77B-79B** was determined by spectroscopic analysis. For example, the mass spectrum of **77B** showed a molecular ion peak at *m/z* 278. The IR absorption suggested the existance of ester carbonyl (1707 cm^{-1}), and double bond (1630 cm^{-1}), respectively. The ^{1}H-NMR spectrum exhibited signals for protons of phenyl group at δ 7.44-7.19, and methyl ester at δ 3.44. The

^{13}C-NMR spectrum indicated the presence of ester carbonyl (δ 166.4), and olefinic carbons (δ 153.3 and δ 132.3).

Scheme 41



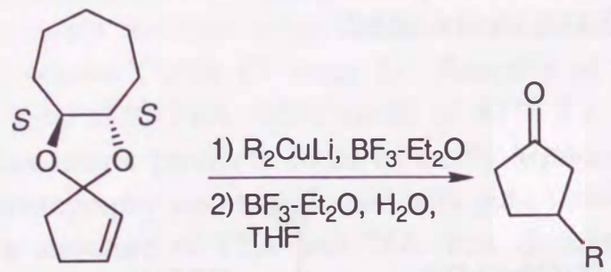
(3*R*)-**76A** (>99% d.e.)

80 (89% yield, >99 % e.e.)

Diastereomerically pure (3*R*)-**76A** did not react with Bu^tMgCl / CuI, but the reaction with Bu^nMgCl / CuI afforded **80** (89% yield) of >99% e.e. These results suggest that the formation of **B** proceeds *via* **A** by addition-elimination process[38] without epimerization at the stereogenic center of **A**. That is to say, e.e. of **B** should be reflected in the d.e. of intermediary **A**. Furthermore, the selection of product (**A** or **B**) might be attributable to the nucleophilicity of mixed cuprates.

Reaction of the substrate without methoxycarbonyl function (**81**) with R_2CuLi / BF_3-Et_2O (R=Me and Bu^t) in THF at -60 °C and subsequent acid hydrolysis afforded the 3-alkylcyclopentanones (**82** and **83**) with no diastereoselectivity (0% e.e.). These results suggested that C_2-methoxycarbonyl group in substrate (**73**) plays an important role in asymmetric induction (Scheme 42).

Scheme 42



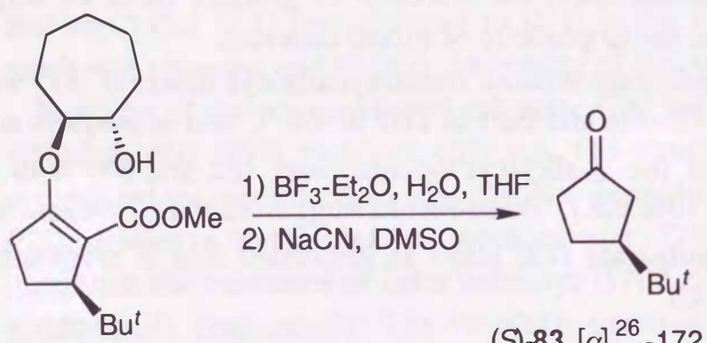
81

82 R=Me 65 % yield, 0 % ee.
83 R=Bu^t 82 % yield, 0 % ee.

3. Determination of absolute configuration and proposed mechanism.

The absolute configuration of **76A** was determined after conversion into the corresponding (*S*)-3-*tert*-butylcyclopentanone (**83**) by hydrolysis of enol ether and subsequent removal of the methoxycarbonyl group. On the basis of this result, the absolute configuration of **80** was assumed to be (*R*).

Scheme 43



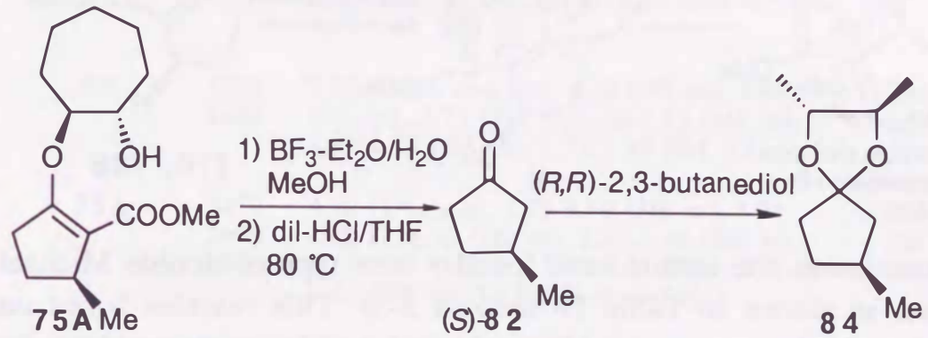
76A (>99 % d.e.)

(*S*)-**83** $[\alpha]_D^{26}$ -172.7° (c 0.74, $CHCl_3$)

authentic sample: $[\alpha]_D^{26}$ -172.3° (c 1.75, $CHCl_3$)

The d.e. value and absolute configuration of **75A** were determined by 270 MHz ^{13}C-NMR spectrum after conversion into the corresponding (*R,R*)-2,4-pentanediol acetal (**84**) *via* three step sequence [i) BF_3-Et_2O / H_2O / MeOH ii) H^+ iii) (*R, R*)-2,4-pentanediol, TsOH (0.1 eq.)].

Scheme 44

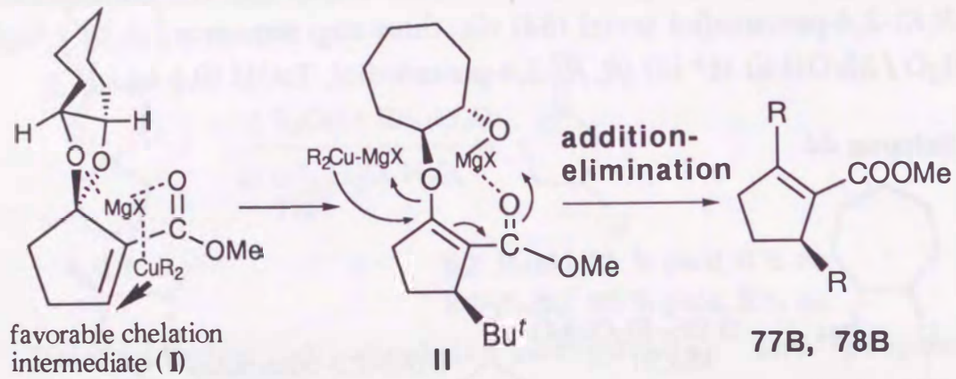


75A Me (*S*)-**82** **84**

The e.e. values of **77-79B** were estimated by 270 MHz ^{1}H-NMR spectra with (+)-Eu(hfc)$_3$. Absolute configuration of **77-79B** was tentatively assumed as depicted in Table 17 on the basis of that of **75A**, **76A** and **80**.

These experimental results permit us to account for the observed high e.e.'s in terms of the formation of chelation intermediate (**I**) between R_2Cu-MgX and chiral acetal as shown in Scheme 45, which resulted in the *si*-face attack of the reagent at β-position of carboxylate. The formation of chelation intermediate at the opposite diastereoface might be unfavorable because of steric hindrance. The resultant chelated enol ether intermediate (**II**) which was activated by intramolecular chelation of magnesium cation to ester carbonyl oxygen, might be converted to β,β'-disubstituted cyclopentene carboxyrates (**77B** and **78B**) *via* the subsequent conjugate addition-elimination process.

Scheme 45



In conclusion, the author have found a new type of double Michael reaction as shown in Table 17 (entries 3-5). This reaction based on diastereoselective conjugate addition showed the highest stereoselectivity among the related reports of chiral acetal-induced asymmetric conjugate addition (ref. 8, 34-36). Furthermore, this reaction is considered to be useful for preparation of optically active β,β'-disubstituted cyclopentene-carboxylates.

Spectral data of compounds in this chapter are summarized in Table 18.

Table 18 (1). Spectral Data of **73-78B**

compound	IR cm^{-1} (neat)	^{1}H-NMR ($CDCl_3$) δ	Ms *m/z*
73	1720 1630	7.07 (1H, t, J=3 Hz), 4.20 (1H, m), 3.76 (1H, m), 3.75 (3H, s), 2.45 (2H, d, J=7 Hz) 2.20 (2H, t-d, J=7, 6 Hz), 2.17-2.07 (2H, m) 1.75-1.41 (8H, m)	252 (M^+) 141
74	1720 1640	7.09 (1H, t, J=4 Hz), 4.20 (1H, m), 3.88 (1H, m), 3.73 (3H, s), 2.28-2.13 (4H, m) 1.95-1.73 (4H, m), 1.71-1.39 (8H, m)	266 (M^+) 238
75A	3450 1690 1610	4.12 (1H, br-s), 3.79-3.69 (2H, m), 3.71 (3H, s), 2.92 (1H, m), 2.70-2.48 (2H, m) 2.13-1.87 (3H, m), 1.75-1.63 (3H, m), 1.61-1.41 (6H, m), 1.12 (3H, d, J=7 Hz)	268 (M^+) 167 141
76A (Major)	3450 1695 1605	3.81-3.67 (2H, m), 3.69 (3H, s), 2.76 (1H, d, J=8 Hz), 2.64-2.40 (2H, m), 2.02-1.80 (4H, m), 1.79-1.64 (5H, m), 1.60-1.45 (4H, m), 0.85 (9H, s)	310 (M^+) 253 141
76A (Minor)	3450 1693 1607	4.37 (1H, br-s), 3.82-3.64 (2H, m), 3.70 (3H, s), 2.77 (1H, d, J=9 Hz), 2.66 (1H, m) 2.28 (1H, m), 2.12-1.83 (5H, m), 1.74-1.41 (7H, m), 0.84 (9H, s)	310 (M^+) 253 141
77B	1707 1630	7.44-7.19 (10H, m), 4.41-4.35 (1H, m), 3.44 (3H, s), 3.07 (1H, d-d-d-d, J=17, 9, 6, 2 Hz) 2.84 (1H, d-d-d-d, J=17, 9, 6, 1 Hz), 2.61-2.47 (1H, m), 1.98-1.85 (1H, m)	278 (M^+) 219
78B	1708 1633	3.72 (3H, s), 2.94 (1H, m), 2.62-2.44 (2H, m) 2.43 (1H, d-d-d, J=17, 9, 4 Hz), 2.03 (1H, m) 1.68-1.47 (2H, m), 1.45-1.19 (10H, m), 0.91 (3H, t, J=7 Hz), 0.88 (3H, t, J=6 Hz)	238 (M^+) 181

Table 18 (2). Spectral Data of **79B-84**

compound	IR cm^{-1} (neat)	^{1}H-NMR ($CDCl_3$) δ	Ms *m/z*
79B	1733 1640	3.72 (3H, s), 2.51 (1H, m), 2.19-2.12 (2H, m) 2.10-2.01 (2H, m), 1.67-1.47 (4H, m), 1.38 1.18 (10H, m), 0.89 (3H, t, J=7 Hz) 0.87 (3H, t, J=7 Hz)	252 (M^+) 195
80	1715 1640	3.72 (3H, s), 2.90 (1H, d, J=10 Hz) 2.57-2.43 (2H, m), 2.36-2.19 (2H, m) 1.93 (1H, m), 1.80 (1H, m), 1.49-1.26 (4H, m), 0.91 (3H, t, J=7 Hz), 0.83 (9H, s)	238 (M^+) 182
81	1620	6.70 (1H, t-d, J=6, 2 Hz), 5.73 (1H, t-d, J=6, 2 Hz), 3.78-3.67 (2H, m), 2.43-2.36 (2H, m), 2.21-2.07 (4H, m) 1.71-1.43 (8H, m)	194 (M^+)
83	1742	2.35-1.80 (6H, m), 1.60 (1H, m), 0.92 (9H, s)	140 (M^+)
		^{13}C-NMR ($CDCl_3$) δ	
(3*S*)-**84** (89% d.e.)		117.58 (s), {78.39 (d, major), 78.23 (d, minor)}, {78.19 (d, minor), 78.12 (d, major)}, {46.43 (t, major), 46.72 (t, minor)}, {38.03 (t, major), 38.51 (t, minor)}, {32.20 (d, major), 32.63 (d, minor)}, {32.17 (t, major), 32.58 (t, minor)}, {20.67 (q, major), 20.31 (q, minor)}, {17.26 (q, major), 16.99 (q, minor)}, {17.17 (q, major) 16.95 (q, minor)}	170 (M^+) 141 127
(3*R*)-**84** authentic data		117.53 (s), 78.23 (d), 78.19 (d), 46.73 (t), 38.55 (t) 32.68 (d), 32.60 (t), 20.32 (q), 17.01 (q), 16.97 (q)	

SUMMARY OF THE ORIGINAL WORK

This dissertation deals with application of chiral cyclic diols to asymmetric induction.

1. Asymmetric alkylation of chiral 1,2-cycloheptanedioxy (or 1,2-cyclohexanedioxy) acetals of five or six-membered ring (or acyclic) β-keto esters proceeded in a highly diastereoselective manner *via* the base-promoted opening of chiral acetal to afford the enol ether with a chiral quaternary carbon. This new reaction is practical and efficient method to prepare a chiral quaternary carbon. Stereoselective syntheses of (+)- and (-)-spiro[4.4]nonane 1,6-diols have been successively achieved on the basis of this asymmetric alkylation (Chapter I).

2. Chiral tricyclic α,β-unsaturated lactones (**14, 37, 38**) were easily synthesized from chiral cyclic diols and cyclic β-keto esters. Alkylation of **14** proceeded in a highly diastereoselective manner to afford a chiral quaternary carbon (Chapter II).

3. Cleavage of *cis*-1,2-cyclohexanedioxy acetal of chiral five-membered ring β-keto ester under basic conditions proceeded in a moderately diastereoselective manner to afford the enol ether (**2a**) of 72% d.e. (Chapter III).

4. Asymmetric oxidation of β'-trimethylsilyloxy enol ethers proceeded in a highly diastereoselective manner to afford the α-hydroxy enol ethers. On the contrary, oxidation of enol ethers with free hydroxyl group dramatically changed the stereochemical course of the reaction to give the α-hydroxy acetals (Chapter IV).

5. Reaction of α,β-unsaturated homochiral acetal (**73**) with RMgX-CuI afforded the enol ether (**75A**) and (**76A**) in highly diastereoselective manner in the case of R=Me, Bu^t. In the case of R=Ph, Bu^n, diastereoselective conjugate addition and subsequent addition-elimination afforded β,β'-disubstituted cycloalkene-carboxylate (**77B**) and (**78B**) of high enantiomeric excess. This new type of double Michael reaction is considered to be useful for preparation of optically active β,β'-disubstituted cyclopentenecarboxylates (Chapter V).

EXPERIMENTAL SECTION

IR spectra were measured with a JASCO A-202 spectrometer, and ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL JNM-GX-270 or JEOL JNM-FX-100 spectrometer. Mass spectra (Ms) were taken on a JEOL JMS-D 300 spectrometer. Optical rotations were measured on a JASCO DIP-360 polarimeter at the sodium line. For column chromatography, silica gel (Merck, Kieselgel 60, 70-230 mesh) was used. Thin layer chromatography (TLC) was performed on Silica gel 60F-254 plates (Merck). The melting points were measured with Yanagimoto micromelting point apparatus.

All solvents were purified before use: ether and THF were distilled from sodium benzophenone ketyl; CH_2Cl_2 and dimethylsulfoxide were distilled from calcium hydride; benzene was distilled from phosphorus pentoxide.

CHAPTER I

General procedure for preparation of acetals (1-5, 13, 14, 18 and 21).

To a solution of β-keto esters (3 mmol) and chiral diols (2 mmol) in benzene (30 ml) was added *p*-TsOH- H_2O (38 mg, 0.2 mmol), and the resulting mixture was refluxed with azeotropic removal of water for 3-10 h. Reaction was quenched with $NaHCO_3$ (504 mg, 6 mmol) and aqueous saturated $NaHCO_3$ (20 ml) at 0 °C. The whole was extracted with ethyl acetate. The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford an oily residue, which was purified by silica-gel column chromatography. The fraction eluted with hexane/ethyl acetate (40:1-30:1) afforded **1a-c,1e**, **2a,b**, **3a,b** as a colorless oil.

Methyl (1*RS*)-2,2-[(*R,R*)-Butane-2,3-dioxy]cyclopentanecarboxylate (1a)

Compound **1a** was obtained as a diastereomeric mixture (2:3) at C_1 in 85% yield. ^{1}H-NMR ($CDCl_3$) δ 3.71 (1H, m), 3.70, 3.69 (total 3H, s each, ratio=2:3) 3.57 (1H, m), 2.91 (1H, d-d, *J*=11, 7 Hz), 2.37-2.07 (2H, m), 1.98-1.58 (4H, m),

1.27, 1.24 (total 3H, d each, *J*=6, 6 Hz, ratio=2:3), 1.21, 1.19 (total 3H, d each, *J*=6, 6 Hz, ratio=2:3); MS *m/z* (EI) 214 (M^+), 185, 127; IR (neat, cm^{-1}) 2980, 1740, 1100.

Methyl (1*RS*)-2,2-[(*R,R*)-1,4-Dibenzyloxybutane-2,3-dioxy] cyclopentanecarboxylate (1b)

Compound **1b** was obtained as a diastereomeric mixture (1:1) at C_1 in 70% yield. ^{1}H-NMR ($CDCl_3$) δ 7.35-7.26 (10H, m), 4.54 (4H, d, *J*=11 Hz), 4.09-3.96 (2H, m), 3.67-3.56 (4H, m), 3.64, 3.57 (total 3H, s each, ratio=1:1), 2.98 (1H, m), 2.12-1.64 (6H, m); MS *m/z* (EI) 426 (M^+), 339, 249, 159, 105, 91; IR (neat, cm^{-1}) 2970, 1730, 1455, 1220, 740, 700.

Methyl (1*RS*)-2,2-[(*R,R*)-Pentane-2,4-dioxy]cyclopentanecarboxylate (1c)

Compound **1c** was obtained as a diastereomeric mixture (1:1) at C_1 in 80% yield. ^{1}H-NMR ($CDCl_3$) δ 4.16, 4.05 (total 1H, m each, ratio=1:1), 3.91 (1H, m), 3.69 (3H, s), 2.99 (1H, d-d, *J*=14, 9 Hz), 2.09-1.53 (8H, m), 1.21 (3H, d, *J*=6 Hz), 1.21 (3H, d, *J*=6 Hz); MS *m/z* (EI) 228 (M^+), 199, 69; IR (neat, cm^{-1}) 2970, 1740, 1435.

Methyl (1*RS*)-2,2-[(*R,R*)-Cycloheptane-1,2-dioxy]cyclopentane-carboxylate (1e)

Compound **1e** was obtained as a diastereomeric mixture (3:4) at C_1 in 98% yield. ^{1}H-NMR ($CDCl_3$) δ 3.81-3.68 (2H, m), 3.71, 3.70 (total 3H, s each, ratio=3:4), 2.92 (1H, dd, *J*=16, 8 Hz), 2.19-1.82 (7H, m), 1.68-1.43 (9H, m). Ms m/z (EI) 254 (M^+) 167. IR (neat, cm^{-1}) 1730, 1440, 1100.

Ethyl (2*RS*)-3,3-[(*R,R*)-Cycloheptane-1,2-dioxy]-2-methylbutanoate (2a)

Compound **2a** was obtained as a diastereomeric mixture (1:1) at C_1 in 98% yield. ^{1}H-NMR ($CDCl_3$) δ 4.23-4.10 (2H, m), 3.81-3.73 (2H,m), 2.77, 2.73 (total 1H, d-d each, *J*= 14, 7 Hz, ratio=1:1), 2.24-2.12 (2H, m), 1.63-1.45 (8H, m), 1.43 (3H, d, *J*=4 Hz), 1.29-1.19 (6H, m); MS *m/z* (EI) 241 (M^+-15), 155, 95, 43; IR (neat, cm^{-1}) 2920, 1720, 1440, 1100.

Ethyl (2*RS*)-3,3-[(*S,S*)-Cyclohexane-1,2-dioxy]-2-methylbutanoate (2b)

Compound **2b** was obtained as a diastereomeric mixture (1:1) at C_1 in 58% yield. ^{1}H-NMR ($CDCl_3$) δ 4.19-4.21 (2H, m), 3.36-3.22 (2H,m), 2.82, 2.74 (total 1H, d-d each, *J*=14, 7 Hz, ratio=1:1), 2.15-2.10 (2H, m), 1.85-1.78 (2H, m), 1.47 (3H, d, *J*=5 Hz), 1.44-1.21 (10H, m); MS *m/z* (FD) 242 (M^+), 198, 141; IR (neat, cm^{-1}) 2930, 1725, 1440, 1100.

Methyl (1*RS*)-2,2-[(*S,S*)-Cyclohexane-1,2-dioxy]cyclohexane-carboxylate (3a)

Compound **18** was obtained as a diastereomeric mixture (1:1) at C_1 in 80% yield.^{1}H-NMR ($CDCl_3$) δ 3.70, 3.69 (total 3H, s each, ratio=1:1), 3.32-3.05 (2H, m), 2.72 (1H, m), 2.17-1.45 (11H, m), 1.43-1.24 (5H, m). Ms m/z (EI) 254 (M^+) 153. IR (neat, cm^{-1}) 2930, 1725, 1430, 1100.

Methyl (1*RS*)-2,2-[(*R,R*)-Cycloheptane-1,2-dioxy]cyclohexane-carboxylate (3b)

Compound **21** was obtained as a diastereomeric mixture (2:1) at C_1 in 99% yield.^{1}H-NMR ($CDCl_3$) δ 3.83-3.69 (2H, m), 3.69, 3.68 (total 3H, s each, ratio=2:1), 2.69 (1H, m), 2.23-2.14 (2H, m), 1.93-1.42 (16H, m). Ms m/z (EI) 268 (M^+) 167. IR (neat, cm^{-1}) 2940, 1740, 1440.

General procedure for asymmetric alkylation of acetals (Method A).

A solution of *n*-BuLi (15% hexane solution, 1.4 ml, 2.25 mmol) was added dropwise to a stirred solution of diisopropylamine (223 mg, 2.25 mol) in THF (8 ml) at -78 °C under an Ar atmosphere. After 10 min, HMPA (403 mg, 2.25 mmol) in THF (0.5 ml) and substrate (0.45 mmol) in THF (2 ml) were added. The whole was stirred for 10 min, then alkyl halide (2.25 mmol) in THF (1 ml) was added. After being stirred for 3-5 h at -78 °C and for additional 12-24 h at -40 °C, the reaction mixture was diluted with aqueous saturated NH_4Cl, and extracted with ethyl acetate. The extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel.

Methyl (1*S*)-2-[(2*R*,3*R*)-3-Hydroxybutan-2-yl]oxy-1-methyl-2-cyclopenten-1-carboxylate (4a)

Colorless oil, 11-59% yield. ^{13}C-NMR ($CDCl_3$) δ 176.7 (s), 158.4 (s), 95.7 (d), 81.0 (d), 71.2 (d), 53.9 (s), 52.2 (q), 35.6 (t), 26.2 (t), 21.9 (q), 18.1 (q), 15.5 (q); $[\alpha]_D^{24}$ -79.8° (c=0.61, $CHCl_3$).

Methyl (1*R*)-2-[(2*R*,3*R*)-3-Hydroxybutan-2-yl]oxy-1-methyl-2-cyclopenten-1-carboxylate (4a')

Colorless oil , 7-32% yield. ^{13}C-NMR ($CDCl_3$) δ 176.2 (s), 158.4 (s), 96.2 (d), 79.5 (d), 70.3 (d), 54.1 (s), 51.9 (q), 35.7 (t), 26.4 (t), 21.6 (q), 18.3 (q), 14.5 (q); $[\alpha]_D^{24}$ +9.9° (c=0.92, $CHCl_3$).

Methyl 2-[(2*R*,3*R*)-3-Hydroxybutan-2-yl]oxy-1-cyclopenten-1-carboxylate (5a)

Colorless oil , 14-28% yield. ^{1}H-NMR($CDCl_3$) δ 4.23 (1H, m), 3.74 (1H, m), 3.71 (3H, s), 2.69-2.27 (4H, m),2.03-1.69 (3H, m), 1.26 (3H, d, *J*=10 Hz), 1.19 (3H, d, *J*=10 Hz); Ms, *m/z* (EI) 214 (M^+), 142, 127, 111, 110; IR (neat, cm^{-1}) 3450, 2955, 1690, 1620, 1440, 1235, 1150, 770; $[\alpha]_D^{25}$ -156.6° (c=0.83, $CHCl_3$).

Methyl (1*S*)-2-[(2*R*,3*R*)-1,4-Dibenzyloxy-3-hydroxybutan-2-yl]oxy-1-methyl-2-cyclopenten-1-carboxylate (4b)

Compound **4b** was obtained as a diastereomeric mixture (2:1) at C_1 in 55% yield. Colorless oil. $[\alpha]_D^{26}$ +1.41° (c=0.85, $CHCl_3$).

Methyl (1*R*)-2-[(2*R*,4*R*)-4-Hydroxypentan-2-yl]oxy-1-methyl-2-cyclopenten-1-carboxylate (4c)

Colorless oil, 49% yield. ^{13}C-NMR ($CDCl_3$) δ 176.3 (s), 158.6 (s), 95.7 (d), 72.7 (d), 64.6 (d), 54.0 (s), 52.0 (q), 45.0 (t), 35.5 (t), 26.5 (t), 23.8 (q), 21.7 (q), 18.7 (q); $[\alpha]_D^{24}$ -83.8° (c=0.75, $CHCl_3$).

Methyl (1*S*)-2-[(2*R*,4*R*)-4-Hydroxypentan-2-yl]oxy-1-methyl-2-cyclopenten-1-carboxylate (4c')

Colorless oil, 7.6% yield. ^{13}C-NMR ($CDCl_3$) δ 176.6 (s), 158.6 (s), 95.5 (d), 72.7 (d), 64.2 (d), 54.0 (s), 52.1 (q), 44.8 (t), 35.6 (t), 26.4 (t), 23.2 (q), 21.7 (q), 19.1 (q); $[\alpha]_D^{24}$ +3.9° (c=0.93, $CHCl_3$).

Methyl 2-[(2*R*,4*R*)-4-Hydroxypentan-2-yl]oxy-1-cyclopenten-1-carboxylate (5c)

Colorless oil, 5.8% yield. ^{1}H-NMR($CDCl_3$) δ 4.60 (1H, m), 4.30 (1H, m), 4.01 (1H, br-s), 3.69 (3H, s), 2.66-2.50 (4H, m), 1.94-1.63 (4H, m), 1.35 (3H, d, *J*=6Hz) 1.20 (3H, d, *J*=6Hz); ^{13}C-NMR($CDCl_3$) δ 168.0 (s), 165.1 (s), 105.5 (s), 75.4 (d), 63.1 (d), 50.8 (q), 44.2 (t), 31.1 (t), 28.7 (t), 19.5 (t), 23.6 (q), 20.4 (q); Ms, *m/z* (EI) 228(M^+), 142, 110; IR (neat, cm^{-1}) 3500, 2960, 1693, 1620, 1440, 1108; $[\alpha]_D^{23}$ -60.2° (c=1.49, $CHCl_3$).

Methyl (1*R*)-2-[(1*S*,2*S*)-2-Hydroxycyclohexan-1-yl]oxy-1-methyl-2-cyclopenten-1-carboxylate (4d)

Colorless oil, 57% yield, 92% d.e. at C_1. ^{13}C-NMR ($CDCl_3$) δ 176.9 (s), 159.0 (s), 96.0 (d), 84.1 (d), 73.8 (d), 54.1 (s), 52.2 (q), 35.7 (t), 31.9 (t), 29.4 (t), 26.2 (t), 24.2 (t), 23.9 (t), 21.9 (q); $[\alpha]_D^{21}$ +71.5° (c=1.02, $CHCl_3$).

Methyl (1*R*)-2-[(1*S*,2*S*)-2-Hydroxycyclohexan-1-yl]oxy-1-nonyl-2-cyclopenten-1-carboxylate (4d')

Colorless oil, 66% yield, >99% d.e. at C_1. ^{13}C-NMR ($CDCl_3$) δ 176.6 (s), 157.3 (s), 96.9 (d), 84.4 (d), 73.7 (d), 58.1 (s), 52.1 (q), 35.2 (t), 32.9 (t), 32.5 (t), 31.9 (t), 31.8 (t), 30.0 (t), 29.5 (t), 29.4 (t), 26.4 (t), 25.8 (t), 24.4 (t), 24.3 (t), 23.9 (t), 22.7 (t), 14.1 (q); $[\alpha]_D^{25}$ +55.6° (c=1.0, $CHCl_3$).

Methyl 2-[(1*S*,2*S*)-2-Hydroxycyclohexan-1-yl]oxy-1-cyclopenten-1-carboxylate (5d)

Colorless oil , 7-8% yield. ^{1}H-NMR($CDCl_3$) δ 4.17 (1H, br-s), 3.71 (3H, s), 3.67-3.60 (2H, m), 2.73-2.46 (5H, m), 2.10-1.70 (5H, m), 1.39-1.25 (4H, m); ^{13}C-NMR($CDCl_3$) δ 169.5 (s), 166.2 (s), 107.8 (s), 85.5 (d), 73.1 (d), 51.0 (q), 31.9 (t), 31.2 (t), 28.7 (t), 24.2 (t), 23.8 (t), 23.6 (t), 19.4 (t); Ms, *m/z* (EI) 240(M^+); IR (neat, cm^{-1}) 3400, 2950, 1690, 1620, 1440, 1230, 1150; $[\alpha]_D^{26}$ +152.7° (c=1.18, $CHCl_3$).

Methyl (1*S*)-2-[(1*R*,2*R*)-2-Hydroxycycloheptan-1-yl]oxy-1-methyl-2-cyclopenten-1-carboxylate (4e)

Colorless oil , 73% yield, >99% d.e. at C_1. ^{13}C-NMR ($CDCl_3$) δ 176.8 (s), 158.5 (s), 95.9 (d), 86.5 (d), 75.8 (d), 54.0 (s), 52.2 (q), 35.7 (t), 31.6 (t), 28.5 (t), 27.4 (t), 26.2 (t), 22.5 (t), 22.2 (t), 21.9 (q); $[\alpha]_D^{25}$ -63.6° (c=0.33, $CHCl_3$). HRms m/z 268.1665 (M^+, calcd for $C_{15}H_{24}O_4$ 268.1674).

Methyl (1*S*)-2-[(1*R*,2*R*)-2-Hydroxycycloheptan-1-yl]oxy-1-nonyl-2-cyclopenten-1-carboxylate (4e')

Colorless oil, 74% yield, >99% d.e. at C_1. ^{13}C-NMR ($CDCl_3$) δ 176.3 (s), 156.9 (s), 96.9 (d), 86.6 (d), 75.8 (d), 58.0 (s), 52.1 (q), 35.3 (t), 32.5 (t), 31.9 (t), 31.9 (t), 30.0 (t), 29.5 (t), 29.4 (t), 29.3 (t), 28.4 (t), 27.3 (t), 26.4 (t), 24.4 (t),

22.7 (t), 22.4 (t), 22.2 (t), 14.2 (q); $[\alpha]_D^{25}$ -24.1° (c=0.46, $CHCl_3$). HRms m/z 380.2935 (M^+, calcd for $C_{23}H_{40}O_4$ 380.2926).

Methyl 2-[(1*R*,2*R*)-2-Hydroxycycloheptan-1-yl]oxy-1-cyclopenten-1-carboxylate (5e)

Colorless oil, 7-18% yield. ^{1}H-NMR($CDCl_3$) δ 4.15 (1H, br-s), 3.79-3.71 (2H, m), 3.71 (3H, s), 2.72-2.52 (4H, m), 2.02-1.82 (4H, m), 1.76-1.49 (8H, m); ^{13}C-NMR($CDCl_3$) δ 169.2 (s), 166.1 (s), 107.6 (s), 87.5 (d), 75.2 (d), 51.0 (q), 31.9 (t), 31.7 (t), 30.9 (t), 28.7 (t), 26.8 (t), 22.3 (t), 22.1 (t), 19.5 (t); Ms, *m/z* (EI) 254 (M^+), 142, 110, 55 ; IR (neat, cm^{-1}) 3400, 2900, 1680, 1610, 1430, 1040; $[\alpha]_D^{25}$ -150.3° (c=0.23, $CHCl_3$).

Ethyl (2*R*)-2-Benzyl-3-[(1*R*,2*R*)-2-hydroxycycloheptan-1-yl]oxy-3-butenoate (6a)

Colorless oil , 78% yield, >99% d.e. at C_2. ^{13}C-NMR ($CDCl_3$) δ 175.6 (s), 160.8 (s), 137.0 (s), 130.6 (d), 127.7 (d), 126.4 (d), 84.2 (t), 84.2 (d), 83.7 (d), 61.4 (t), 52.1 (s), 41.0 (t), 31.7 (t), 28.0 (t), 27.8 (t), 22.5 (t), 22.3 (t), 20.9 (q), 14.1 (q); $[\alpha]_D^{25}$ -65.3° (c=1.4, $CHCl_3$). HRms m/z 346.2153 (M^+, calcd for $C_{21}H_{30}O_4$ 346.2144).

Ethyl (2*R*)-2-Allyl-3-[(1*R*,2*R*)-2-hydroxycycloheptan-1-yl]oxy-3-butenoate (6a')

Colorless oil, 70% yield, >99% d.e. at C_2. ^{13}C-NMR ($CDCl_3$) δ 175.3 (s), 161.2 (s), 133.7 (d), 118.1 (t), 83.3 (d), 83.0 (t), 75.6(d), 61.2 (t), 50.8 (s), 40.3 (t), 31.8 (t), 27.8 (t), 27.8 (t), 22.5 (t), 22.3 (t), 20.9 (q), 14.2 (q); $[\alpha]_D^{25}$ -69.6° (c=0.77, $CHCl_3$). HRms m/z 296.1979 (M^+, calcd for $C_{17}H_{28}O_4$ 296.1987).

Ethyl *cis*-3-[(1*R*,2*R*)-2-Hydroxycycloheptan-1-yl]oxy-2-butenoate (7a)

Colorless oil , 10-11% yield. ^{1}H-NMR($CDCl_3$) δ 5.20 (1H, br-s), 4.26-4.15 (2H, m), 3.77-3.69 (2H, m), 1.98 (3H, s), 2.61-2.47 (10H, m), 1.79 (3H, s), 1.29 (3H, t, J=7 Hz); ^{13}C-NMR($CDCl_3$) δ 169.5 (s), 160.1 (s), 106.4 (s), 85.5 (d), 75.3 (d), 60.3 (t), 31.8 (t), 31.4 (t), 26.8 (t), 22.3 (t), 22.1 (t), 15.9 (q), 14.3 (q), 14.1 (q); Ms, *m/z* (EI) 256 (M^+), 241, 144, 43; IR (neat, cm^{-1}) 3400, 2900, 1680, 1610, 1440, 1100; $[\alpha]_D^{26}$ -172.3° (c=0.29, $CHCl_3$).

Ethyl (2*S*)-2-Benzyl-3-[(1*S*,2*S*)-2-hydroxycyclohexan-1-yl]oxy-3-butenoate (6b)

Colorless oil, 70% yield, >94% d.e. at C_2. ^{13}C-NMR ($CDCl_3$) δ 175.6 (s), 161.0 (s), 137.0 (s), 130.6 (d), 127.6 (d), 126.4 (d), 84.0 (t), 81.5 (d), 73.5 (d), 61.3 (t), 52.2 (s), 41.0 (t), 32.0 (t), 29.2 (t), 24.2 (t), 23.8 (t), 20.8 (q), 14.1 (q); $[\alpha]_D^{25}$ -73.8° (c=0.68, $CHCl_3$).

Ethyl *cis*-3-[(1*S*,2*S*)-2-Hydroxycyclohexan-1-yl]oxy-2-butenoate (7b)

Colorless oil , 12% yield. ^{1}H-NMR($CDCl_3$) δ 4.16 (2H, q, J=7 Hz), 3.93 (1H, m), 3.74 (1H, m), 2.42 (1H, br-s), 2.35 (3H, s), 2.12-1.70 (4H, m), 1.83 (3H, s), 1.39-1.27 (4H, m), 1.28 (3H, t, J=7 Hz); ^{13}C-NMR($CDCl_3$) δ 169.5 (s), 162.7 (s), 108.9 (s), 80.6 (d), 73.5 (d), 59.8 (t), 32.1 (t), 30.9 (t), 24.0 (t), 23.8 (t), 16.1 (q), 14.4 (q), 12.1 (q); Ms, *m/z* (EI) 242 (M^+), 144, 98, 43; IR (neat, cm^{-1}) 3400, 2900, 1670, 1610, 1440, 1100; $[\alpha]_D^{26}$ -24.0° (c=0.52, $CHCl_3$).

Methyl (1*R*)-2-[(1*S*,2*S*)-2-Hydroxycyclohexan-1-yl]oxy-1-methyl-2-cyclohexen-1-carboxylate (8a)

Colorless oil, 37% yield, 77% d.e. at C_1. ^{13}C-NMR ($CDCl_3$) δ 177.4 (s), 154.0 (s), 96.2(d), 80.5 (d), 73.7 (d), 52.2 (q), 47.2 (s), 35.8 (t), 32.1 (t), 29.6 (t), 24.3 (t), 24.1 (t), 23.9 (t), 15.6 (t), 23.0 (q); $[\alpha]_D^{25}$ +61.9° (c=0.3, $CHCl_3$). HRms m/z 268.1665 (M^+, calcd for $C_{15}H_{24}O_4$ 268.1674).

(3*S*,8*S*,11*S*)-11-Methyl-2,9-dioxa-10-oxotricyclo[9,4,0,0^{3,8}] pentadec-1(15)-ene (9a)

Colorless needles, 59% yield, mp 95 °C. 95% d.e. at C_{11}. ^{13}C-NMR ($CDCl_3$) δ 175.9 (s), 150.2 (s), 115.1 (d), 81.6 (d), 76.9 (d), 47.7(s), 34.6 (t), 31.2 (t), 31.1 (t), 31.1 (t), 23.6 (t), 23.5 (t), 18.2 (t), 26.0 (q); $[\alpha]_D^{24}$ -8.9° (c=0.56, $CHCl_3$). HRms m/z 236.1426 (M^+, calcd for $C_{14}H_{20}O_3$ 236.1412).

(1*R*)-1-Allyl-2-[(1*S*,2*S*)-2-hydroxycyclohexan-1-yl]oxy-2-cyclohexen-1-carboxylate (8b)

Colorless oil, 27% yield, 92% d.e. at C_1. ^{13}C-NMR ($CDCl_3$) δ 176.5 (s), 150.2 (s), 136.5 (d), 118.0 (t), 97.9 (d), 80.8 (d), 73.7 (d), 52.3 (q), 50.6 (s), 40.1 (t), 32.0 (t), 31.9 (t), 29.7 (t), 24.3 (t), 23.9 (t), 23.8 (t), 19.7 (t); $[\alpha]_D^{30}$ +52.3° (c=0.60, $CHCl_3$). HRms m/z 294.1841 (M^+, calcd for $C_{17}H_{26}O_4$ 294.1831).

(3*S*,8*S*,11*R*)-11-Allyl-2,9-dioxa-10-oxotricyclo[9,4,0,0^{3,8}]pentadec-1(15)-ene (9b)

Colorless oil, 53% yield, >99% d.e. at C_{11}. ^{13}C-NMR ($CDCl_3$) δ 174.6 (s), 148.5 (s), 134.1 (d), 117.8 (t), 117.2 (d), 81.4 (d), 77.0 (d), 51.7 (s), 44.1 (t), 33.2 (t), 31.5 (t), 31.3 (t), 23.8 (t), 23.6 (t), 23.4 (t), 18.7 (t); $[\alpha]_D^{30}$ -0.8° (c=0.50, $CHCl_3$). HRms m/z 262.1553 (M^+, calcd for $C_{16}H_{22}O_3$ 262.1569).

(1*R*)-1-Benzyl-2-[(1*S*,2*S*)-2-hydroxycyclohexan-1-yl]oxy-2-cyclohexen-1-carboxylate (8c)

Colorless oil, 43% yield, >99% d.e. at C_1. ^{13}C-NMR ($CDCl_3$) δ 176.6 (s), 151.5 (s), 137.3 (s), 130.7 (d), 127.7 (d), 126.4 (d), 99.1 (d), 81.7 (d), 73.7 (d), 52.4 (q), 52.2 (s), 40.8 (t), 32.1 (t), 31.6 (t), 30.0 (t), 24.4 (t), 24.0 (t), 23.7 (t), 19.7 (t); $[\alpha]_D^{27}$ +64.0° (c=0.40, $CHCl_3$). HRms m/z 344.1978 (M^+, calcd for $C_{21}H_{28}O_4$ 344.1987).

(3*S*,8*S*,11*R*)-11-Benzyl-2,9-dioxa-10-oxotricyclo[9,4,0,0^{3,8}] pentadec-1(15)-ene (9c)

Colorless oil , 51% yield, >99% d.e. at C_{11}. ^{13}C-NMR ($CDCl_3$) δ 175.0 (s), 147.4 (s), 136.8 (s), 130.8 (d), 128.4 (d), 126.5 (d), 118.8 (d), 80.9 (d), 77.3 (d), 53.4 (s), 44.4 (t), 33.2 (t), 31.8 (t), 31.5 (t), 23.9 (t), 23.6 (t), 23.3 (t), 19.1 (t); $[\alpha]_D^{27}$ +17.6° (c=0.76, $CHCl_3$). HRms m/z 312.1711 (M^+, calcd for $C_{20}H_{24}O_3$ 312.1725).

Methyl (1*S*)-2,2-[(*R*,*R*)-Cycloheptane-1,2-dioxy]-1-methyl-cyclohexanecarboxylate (15)

Colorless oil, 84% yield, 66% d.e. at C_1. ^{13}C-NMR($CDCl_3$) δ 175.4 (s), 110.0 (s), 82.3 (d), 80.0 (d), 51.6 (q), 51.4 (s), 37.1 (t), 34.5 (t), 33.6 (t), 30.9 (t), 28.8 (t), 25.2 (t), 25.0 (t), 23.3 (t), 21.5 (t), 19.3 (q); $[\alpha]_D^{25}$ -8.2° (c=0.83, $CHCl_3$).

Methyl (1*S*)-2-[(1*R*,2*R*)-2-Hydroxycycloheptan-1-yl]oxy-1-methyl-2-cyclohexen-1-carboxylate (16)

Colorless oil, 12% yield, 63% d.e. at C_1. ^{13}C-NMR($CDCl_3$) δ 177.2 (s), 153.6 (s), 96.2(d), 82.6 (d), 75.8 (d), 52.2 (q), 47.2 (s), 35.7 (t), 31.7 (t), 28.5 (t), 27.6 (t), 23.9 (t), 23.1 (q), 22.5 (t), 22.3 (t), 19.5 (t); $[\alpha]_D^{27}$ +9.4° ($CHCl_3$, c=0.42).

Methyl (1*R*,*S*)-2-[(1*S*,2*S*)-2-Hydroxycyclohexan-1-yl]oxy-2-cyclohexen-1-carboxylate (11)

Compound **11** was obtained as a diastereomeric mixture (2:1) at C_1 in 59% yield. Colorless oil. ^{1}H-NMR ($CDCl_3$) δ 4.91 (1H, t, J=4 Hz), 3.79 (1H, m), 3.78 (1H, br. s), 3.72 (3H, s), 3.50 (1H, m), 3.16 (total 1H, t each, J=5 Hz, ratio=1:2), 2.13-1.70 (7H, m), 1.57-1.24 (7H, m); ^{13}C-NMR ($CDCl_3$) δ 175.1 (s), 150.2 (s), 97.8 (d), 81.1 (d), 73.8 (d), 52.2 (q), 44.6 (d), 32.0 (t), 29.9 (t), 26.9 (t), 24.3 (t), 23.9 (t), 23.2 (t), 20.4 (t); MS *m/z* (EI) 254 (M^+), 211, 156, 153, 124; IR (neat, cm^{-1}) 3500, 2900, 1720, 1660, 1440, 1170.

Methyl 2-[(1*S*,2*S*)-2-Hydroxycyclohexan-1-yl]oxy-1-cyclohexen-1-carboxylate (12)

Colorless oil, 32% yield. ^{1}H-NMR ($CDCl_3$) δ 5.37 (1H, br. s), 3.72 (3H, s), 3.64-3.57 (2H, m), 2.55-2.38 (2H, m), 2.32-1.97 (4H, m), 1.77-1.27 (10H, m); ^{13}C-NMR ($CDCl_3$) δ 169.7 (s), 164.2 (s), 109.4 (s), 84.5 (d), 73.9 (d), 52.0 (q), 32.3 (t), 32.1 (t), 27.5 (t), 25.2 (t), 24.5 (t), 24.0 (t), 22.4 (t), 22.0 (t); MS *m/z* (EI) 254 (M^+), 222, 156, 153, 124, 96; IR (neat, cm^{-1}) 3400, 2900, 1680, 1610, 1430, 1050; ; $[\alpha]_D^{26}$ +169.6° (c=0.57, $CHCl_3$).

(3*S*,8*S*)-(11*R*,*S*)-2,9-Dioxa-10-oxotricyclo[9,4,0,0^{3,8}]pentadec-1(15)-ene (13)

Compound **13** was obtained as a diastereomeric mixture (4:3) at C_{11} in 20% yield. Colorless oil. ^{1}H-NMR ($CDCl_3$) δ 5.45 (1H, t, J=4 Hz), 4.37 (1H, m), 3.55 (1H, m), 3.35 (total 1H, d each, J=5 Hz, ratio=3:4), 2.31 (1H, m), 2.21-2.02 (4H, m), 1.84-1.65 (4H, m), 1.59-1.20 (5H,m); ^{13}C-NMR ($CDCl_3$) δ 172.2 (s), 146.3 (s), 113.7 (d), 81.8 (d), 81.4 (d), 41.3 (d), 31.8 (t), 31.3 (t), 25.0 (t), 23.6 (t), 23.4 (t), 23.4 (t), 18.5 (t); MS *m/z* (EI) 222 (M^+), 141, 124, 123, 96, 79, 68; IR (neat, cm^{-1}) 2920, 1723, 1663, 1455, 1378, 1222, 1160, 1020.

(3*S*,8*S*)-2,9-Dioxa-10-oxotricyclo[9,4,0,0^{3,8}]pentadec-1(11)-ene (14)

Colorless needles, 9% yield. mp 96 °C. ^{13}C-NMR ($CDCl_3$) δ 169.1 (s), 161.3 (s), 101.9 (s), 82.1 (d), 76.8 (d), 32.1 (t), 31.2 (t), 31.0 (t), 29.7 (t), 27.0 (t), 23.1 (t), 23.1 (t), 22.4 (t); $[\alpha]_D^{27}$ -199.2° (c=0.25, $CHCl_3$). HRms m/z 222.1268 (M^+, calcd for $C_{13}H_{18}O_3$ 222.1256).

General procedure for asymmetric alkylation of 3a (Method B).

A solution of *n*-BuLi (15% hexane solution, 1.4 ml, 2.25 mmol) was added dropwise to a stirred solution of diisopropylamine (223 mg, 2.25 mol) in THF (8 ml) at -78 °C under an Ar atmosphere. After 10 min, **3a** (0.45 mmol) in THF (2 ml) and alkyl halide (2.25 mmol) in THF (1 ml) were added. The whole was stirred for 10 min, then HMPA (121 mg, 0.68 mmol) in THF (0.5 ml) was added. After being stirred for 1-3 h at -40 °C, the reaction mixture was diluted with aqueous saturated NH_4Cl, and extracted with ethyl acetate. The extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel .The fraction eluted with 20:1 hexane/ethyl acetate gave the alkylated enol ether (**8a**) in 96% yield (85% d.e.), (**8b**) in 90% yield (97% d.e.) and (**8c**) in 84% yield (96% d.e.).

General Procedure for deprotection of enol ethers (4,6,8,10).

To a mixture of BF_3-etherate (0.5 ml, 4 mmol) and H_2O (0.5 ml) was added a solution of enol ether (0.2 mmol) in MeOH (4 ml) at room temperature, the reaction mixture was heated at 60-70 °C for 3-5 h, then diluted with saturated aqueous NaCl (20 ml), and extracted with ethyl acetate. The extracts were washed with saturated aqueous $NaHCO_3$, and dried over $MgSO_4$, then concentrated in vacuo to afford an oily residue, which was purified by silica-gel column chromatography. The fraction eluted with 40:1-30:1 hexane/ethyl acetate afforded **17-19** as a colorless oil.

Methyl (*R*)- and (*S*)-1-Methyl-2-oxocyclopentanecarboxylate (17a)

70-85% yield. ^{1}H-NMR ($CDCl_3$) δ 3.71 (3H, s), 2.59-2.24 (3H, m), 2.12-1.78 (3H, m), 1.32 (3H, s); MS *m/z* (EI) 156(M^+), 128, 125, 113, 101, 69, 41; IR (neat, cm^{-1}) 2950, 1735(br), 1720, 1450, 1270, 1150, 1060, 940. (*R*)-**17a** (>99% e.e.) $[\alpha]_D^{22}$ -10.7° (c=1.1, $CHCl_3$), (*S*)-**17a** (>99% e.e.) $[\alpha]_D^{27}$ +10.5° (c=0.41, $CHCl_3$). lit[16g] for (*R*)-**17a** (>96% e.e.) $[\alpha]_D^{23}$ -10.6° (c=1.15, $CHCl_3$).

Methyl (*R*) and (*S*)-1-Nonyl-2-oxocyclopentanecarboxylate (17b)

80-95% yield. ^{1}H-NMR ($CDCl_3$) δ 3.71 (3H, s), 2.61-2.20 (3H, m), 2.01-1.87 (3H, m), 1.25 (16H, s), 0.88(3H, t, J=7 Hz); MS *m/z* (EI) 268 (M^+), 237, 143, 142, 110, 98; IR (neat, cm^{-1}) 2950, 1755, 1720, 1460, 1230, 1160. (*R*)-**17b** (>99% e.e.) $[\alpha]_D^{26}$ +20.5° (c=0.65, $CHCl_3$), (*S*)-**17b** (>99% e.e.) $[\alpha]_D^{28}$ -21.0° (c=0.4, $CHCl_3$). lit[16g] for (*R*)-**17b** (>96% e.e.) $[\alpha]_D^{23}$ +20.9° (c=1.13, $CHCl_3$).

Ethyl (*R*) and (*S*)-2-Benzyl-2-methylacetoacetate (18a)

85-90% yield. ^{1}H-NMR ($CDCl_3$) δ 7.28-7.03 (5H, m), 4.19 (2H, q, J=7 Hz), 3.29 (1H, d, J=14 Hz), 3.04 (1H, d, J=14 Hz), 2.17 (3H, s), 1.28 (3H, s), 1.25 (3H, t, J=7 Hz); MS *m/z* (EI) 234 (M^+), 191, 145, 91, 78; IR (neat, cm^{-1}) 2980, 1720, 1710, 1605, 1500, 1450, 1360, 1270, 1100, 1020, 860, 745, 700. (*R*)-**18a** (>99% e.e.) $[\alpha]_D^{25}$ +62.5° (c=0.42, $CHCl_3$), (*S*)-**18a** (>99% e.e.) $[\alpha]_D^{24}$ -58.5° (c=0.75, $CHCl_3$). lit[16b] for (*S*)-**18a** (92% e.e.) $[\alpha]_D^{22}$ -58.2° ($CHCl_3$).

Ethyl (*R*)-2-Allyl-2-methylacetoacetate (18b)

92% yield. ^{1}H-NMR ($CDCl_3$) δ 5.83-5.63 (1H, m), 5.17 (1H, m), 5.0 (1H, m), 4.20 (2H, q, *J*=7 Hz), 2.61 (1H, d, *J*=7 Hz), 2.55 (1H, d, *J*=7 Hz), 2.15 (3H, s), 1.33 (3H, s), 1.26 (3H, t, *J*=7 Hz); MS *m/z* (EI) 184(M^+), 142, 114, 97, 69, 43; IR (neat, cm^{-1}) 2980, 1740, 1708, 1640, 1450, 1240, 1140, 1100. (*R*)-**18b** (>99% e.e.) $[\alpha]_D^{27}$ +29.3° (c=0.36, $CHCl_3$). lit[16b] for (*R*)-**18b** (95% e.e.) $[\alpha]_D^{22}$ +28.2° ($CHCl_3$).

Methyl (*R*) and (*S*)-1-Methyl-2-oxocyclohexanecarboxylate (19a, 20a)

85-90% yield. ^{1}H-NMR ($CDCl_3$) δ 3.73 (3H, s), 2.60-2.39 (3H, m), 2.10-1.40 (5H, m), 1.30 (3H, s). Ms m/z (EI) 170 (M^+), 142, 127, 110. IR (neat, cm^{-1}) 1720 (br), 1450, 1375, 1300, 1250, 1150, 1180. (*R*)-**19a** (85% e.e.) $[\alpha]_D^{26}$ -91.0° (c=0.43, ethanol), (*S*)-**20a** (95% e.e.) $[\alpha]_D^{25}$ +103.9° (c=1.1, ethanol). lit[16b] for (*R*)-**19a** (>99% e.e.) $[\alpha]_D^{25}$ -108° (ethanol).

Methyl (*R*) and (*S*)-1-Allyl-2-oxocyclohexanecarboxylate (19b, 20b)

85-91% yield. ^{1}H-NMR ($CDCl_3$) δ 5.75 (1H, m), 5.06 (1H, br.s), 5.02 (1H, br.s), 3.71 (3H, s), 2.63 (1H, dd, *J*=14, 7 Hz), 2.53-2.43 (3H, m), 2.33 (1H, dd, *J*=14, 8 Hz), 2.14 (1H, m), 1.82-1.57 (3H, m), 1.47 (1H, m). Ms m/z (EI) 196 (M^+), 137, 136, 119. IR (neat, cm^{-1}) 1710 (br), 1640, 1435, 1270, 1150, 1000. (*R*)-**20b** (>99% e.e.) $[\alpha]_D^{25}$ +133.8° (c=1.12, ethanol), (*S*)-**19b** (96% e.e.) $[\alpha]_D^{27}$ -128.5° (c=1.1, ethanol). lit[16b] for (*S*)-**19b** (76% e.e.) $[\alpha]_D^{25}$ -102° (ethanol).

Methyl (*R*) and (*S*)-1-Benzyl-2-oxocyclohexanecarboxylate (19c, 20c)

93% yield. ^{1}H-NMR ($CDCl_3$) δ 7.2-7.0 (5H, m), 3.64 (3H, s), 3.33 (1H, d, *J*=14 Hz), 3.86 (1H, d, *J*=14 Hz), 2.53-2.24 (3H, m), 2.17-1.37 (5H, m). Ms m/z (EI) 246 (M^+), 228, 187, 186, 117. IR (neat, cm^{-1}) 1708 (br), 1600, 1500, 1450, 1430. (*R*)-**20c** (>99% e.e.) $[\alpha]_D^{26}$ +110.7° (c=0.45, ethanol), (*S*)-**19c** (>99% e.e.) $[\alpha]_D^{26}$ -110.5° (c=0.42, ethanol). lit[16b] for (*S*)-**19c** (>99% e.e.) $[\alpha]_D^{25}$ -111° (ethanol).

Asymmetric alkylation of 1e: (22)

A solution of *n*-BuLi (15% hexane solution, 5.3 ml, 8.4 mmol) was added dropwise to a stirred solution of diisopropylamine (852 mg, 8.4 mol) in THF (30 ml) at -78 °C under an Ar atmosphere. After 10 min, HMPA (3.75 g, 21 mmol) and **1e** (1.07 g, 4.2 mmol) in THF (2 ml) were added. The whole was stirred for 10 min, then 4-bromobutylate (900 mg, 4.62 mmol) in THF (1 ml) was added. After being stirred for 0.5 h at -78 °C and for additional 5 h at -40 °C, the reaction mixture was diluted with aqueous saturated NH_4Cl, and extracted with ethyl acetate. The extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (10:1 hexane/ethyl acetate). Colorless oil, 90% yield. ^{13}C-NMR ($CDCl_3$) δ 175.9 (s), 173.3 (s), 156.5 (s), 97.2 (d), 86.7 (d), 75.5 (d), 60.2 (t), 57.7 (s), 52.1 (q), 34.7 (t), 34.5 (t), 32.5 (t), 31.5 (t), 28.4 (t), 27.3 (t), 26.4 (t), 22.3 (t), 22.2 (t), 20.1 (t), 14.3 (q); (*S*)-**22** (>99% d.e.) $[\alpha]_D^{23}$ -48.3° (c=1.2, $CHCl_3$), (*R*)-**22** (>99% d.e.) $[\alpha]_D^{23}$ -47.8° (c=1.1, $CHCl_3$).

Deprotection of 22: (23)

To a mixture of 3.5% HCl (2 ml) and THF (3 ml) was added a solution of **22** (73.6 mg, 0.2 mmol) in THF (1 ml) at room temperature, the reaction mixture was heated at 60-70 °C for 4 h, then diluted with saturated aqueous NaCl (20 ml), and extracted with ethyl acetate. The extracts were washed with saturated aqueous $NaHCO_3$, and dried over $MgSO_4$, then concentrated *in vacuo* to afford an oily residue, which was purified by silica-gel column chromatography. The fraction eluted with 30:1 hexane/ethyl acetate afforded **23** as a colorless oil in 98% yield. (*R*)-**23** (>99% e.e.) $[\alpha]_D^{27}$ -25.3° (c=0.12, $CHCl_3$), (*S*)-**23** (>99% e.e.) $[\alpha]_D^{25}$ +24.8° (c=0.13, $CHCl_3$).

Acetalization of 22: (24)

To a solution of **22** (368mg, 1mmol) in benzene (15 ml) was added *p*-TsOH-H_2O (38 mg, 0.2 mmol), and the resultig mixture was refluxed with azeotropic removal of water for 0.5 h. Reaction was quenched with $NaHCO_3$ (504 mg, 6 mmol) and aqueous saturated $NaHCO_3$ (20 ml) at 0 °C. The whole was extracted with ethyl acetate. The combined extracts were dried over $MgSO_4$ and

concentrated *in vacuo* to afford an oily residue, which was purified by silica-gel column chromatography. The fraction eluted with hexane/ethyl acetate (30:1) afforded **24** as a colorless oil in 92% yield. ^{13}C-NMR($CDCl_3$) δ 174.0 (s), 173.4 (s), 118.1 (s), 81.6 (d), 81.3 (d), 60.2 (t), 59.1 (s), 55.1 (q), 37.7 (t), 34.7 (t), 32.9 (t), 31.0 (t), 30.3 (t), 28.8 (t), 25.2 (t), 25.0 (t), 24.9 (t), 21.0 (t), 19.7 (t), 14.3 (q); *(R)*-**23** $[\alpha]_D^{23}$ -32.6° (c=0.8, $CHCl_3$), *(S)*-**23** $[\alpha]_D^{24}$ +32.9° (c=1.3, $CHCl_3$).

Dieckmann condensation of 24: (25)

To a solution of **24** (1.25 g, 3.4 mmol) in DMSO (20 ml) was added Bu^tOK (762 mg, 6.8 mmol), and the resultig mixture was heated at 90-100°C for 2.5h. The reaction mixture was diluted with saturated aqueous NH_4Cl (30 ml) at 0 °C, and extracted with $CHCl_3$. The extracts were washed with saturated aqueous NaCl, and dried over $MgSO_4$, then concentrated *in vacuo* to afford an oily residue, which was purified by silica-gel column chromatography. The fraction eluted with 20:1 hexane/ethyl acetate afforded **25** as a colorless oil in 60% yield.

Deethoxycarbonylation of 25: (26)

To a mixture of 2N KOH (12 ml) and MeOH (30 ml) was added a solution of **25** (1.68 g, 5 mmol) in MeOH (1ml) at room temperature, the reaction mixture was heated at 100 °C for 3 h, then diluted with saturated aqueous NaCl (20 ml), and extracted with ethyl acetate. The extracts were washed with saturated aqueous $NaHCO_3$, and dried over $MgSO_4$, then concentrated *in vacuo* to afford an oily residue, which was purified by silica-gel column chromatography. The fraction eluted with 30:1 hexane/ethyl acetate afforded **26** as a colorless oil in 90% yield. ^{13}C-NMR ($CDCl_3$) δ 220.3 (s), 117.9 (s), 81.6 (d), 80.0 (d), 59.9 (s), 38.8 (t), 36.1 (t), 33.3 (t), 32.1 (t), 30.4 (t), 28.7 (t), 25.2 (t), 25.0 (t), 25.0 (t), 19.6 (t), 19.4 (t); *(R)*-**26** $[\alpha]_D^{25}$ +63.3° (c=0.38, $CHCl_3$), *(S)*-**26** $[\alpha]_D^{24}$ -65.5° (c=1.57, $CHCl_3$).

(*R*) and (*S*)-Spiro[4.4]nonane-1,6-dione(27)

To a suspended mixture of $ZnBr_2$ (171 mg, 0.76 mmol) and CH_2Cl_2 / THF (100/1) (5 ml) was added a solution of **26** (100 mg, 0.38 mmol) in CH_2Cl_2 (1 ml) at room temperature. The reaction mixture was stirred for 24 h, and $ZnBr_2$ (85.5 mg, 0.38 mmol) was added. After being stirred for 24 h, the reaction mixture was diluted

with saturated aqueous $NaHCO_3$ (20 ml), and extracted with ethyl acetate. The extracts were dried over $MgSO_4$, then concentrated *in vacuo* to afford an oily residue, which was purified by silica-gel column chromatography. The fraction eluted with 30:1 hexane/ethyl acetate afforded **27** as a colorless needles in 90% yield. mp 65 °C; ^{13}C-NMR ($CDCl_3$) δ 216.7 (s), 64.4 (s), 38.5 (t), 34.3 (t), 19.8 (t); *(R)*-**27** $[\alpha]_D^{26}$ +132° (c=0.3, cyclohexane), *(S)*-**27** $[\alpha]_D^{26}$ -133° (c=0.44, cyclohexane).

LAH reduction of racemic-26: (28a,b)

To a suspended solution of LAH (100 mg, 2.6 mmol) in THF (20 ml) was added dropwise a solution of **raccemic-26** (268 mg, 1 mmol) at 0 °C and the resultig mixture was stirred for 1 h. Reaction was quenched with ethyl acetate (1 ml) and saturated aqueous NH_4Cl (0.2 ml) at 0 °C, and filtered.The filtrate was dried over $MgSO_4$, then concentrated *in vacuo* to afford an oily residue. To a solution of the oily residue in THF (3 ml) was added 3.5 % HCl (1 ml), and stirred for 0.5 h at room temperature. The reaction mixture was diluted with saturated aqueous NaCl (10 ml), and extracted with ethyl acetate. The extracts were dried over $MgSO_4$, then concentrated *in vacuo* to afford an oily residue, which was purified by silica-gel column chromatography. The fraction eluted with 10:1 hexane/ethyl acetate afforded **racemic-28b** as a colorless oil in 32% yield, and the latter fraction eluted with 5:1 hexane/ethyl acetate afforded **racemic-28a** as a colorless oil in 65% yield.

racemic-*cis*-28a

^{13}C-NMR($CDCl_3$) δ 225.1 (s), 80.5 (d), 58.9 (s), 39.0 (t), 35.7 (t), 34.5 (t), 33.9 (t), 21.4 (t), 19.3 (t).

racemic-*trans*-28b

^{13}C-NMR($CDCl_3$) δ 223.5 (s), 76.7 (d), 60.3 (s), 38.4 (t), 34.4 (t), 33.8 (t), 30.3 (t), 20.8 (t), 19.6 (t).

DIBAL-H reduction of (+) and (-)-26

To a solution of **26** (264 mg, 1 mmol) in THF (5 ml) was added DIBAL-H: 1M in THF (2 ml, 2 mmol) at -78 °C, and the resulting mixture was stirred for 3 h at -60 °C. The reaction mixture was diluted with ethyl acetate (10 ml) and aqueous saturated NH_4Cl (0.5 ml) at -60 °C, and filtered. The filtrate was dried over $MgSO_4$, then concentrated *in vacuo* to afford an oily residue, which was purified by silica-gel column chromatography. The fraction eluted with 30:1 hexane/ethyl acetate afforded

cis-**30** as a colorless oil in 98% yield. ^{13}C-NMR ($CDCl_3$) δ 118.9 (s), 82.0 (d), 79.7 (d), 78.9 (d), 56.8 (s), 36.1 (t), 34.6 (t), 33.1 (t), 30.5 (t), 29.8 (t), 28.7 (t), 25.2 (t), 24.9 (t), 24.9 (t), 20.2 (t), 18.4 (t); (5*R*)-**30** $[\alpha]_D^{22}$ -33.0° (c=1.1, $CHCl_3$), (5*S*)-**30** $[\alpha]_D^{25}$ +33.8° (c=1.25, $CHCl_3$).

(+) and (-)-*cis*-Ketol (28)

To a solution of **30** (266 mg, 1 mmol) in THF (3 ml) was added 3.5 % HCl (1 ml), and stirred for 2 h at room temperature. The reaction mixture was diluted with saturated aqueous NaCl (10 ml), and extracted with ethyl acetate. The extracts were dried over $MgSO_4$, then concentrated *in vacuo* to afford an oily residue, which was purified by silica-gel column chromatography. The fraction eluted with 5:1 hexane/ethyl acetate afforded ***cis*-28** as a colorless oil in 99% yield. ^{13}C-NMR($CDCl_3$) δ 225.1 (s), 80.5 (d), 58.9 (s), 39.0 (t), 35.7 (t), 34.5 (t), 33.9 (t), 21.4 (t), 19.3 (t); (5*R*)-**28** $[\alpha]_D^{22}$ +47.7° (c=2.0, $CHCl_3$), (5*S*)-**28** $[\alpha]_D^{25}$ -48.8° (c=0.9, $CHCl_3$).

TBDPS ether (+) and (-)-(31)

To a mixture of **28** (154 mg, 1 mmol) and imidazol (272 mg, 4 mmol) was added a solution of *tert*-butylchlorodiphenylsilane (550 mg, 2 mmol) in DMF (1 ml) at room temperature. After being stirred for 48 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ (20 ml), and extracted with ethyl acetate. The extracts were dried over $MgSO_4$, then concentrated *in vacuo* to afford an oily residue, which was purified by silica-gel column chromatography. The fraction eluted with 50:1 hexane/ethyl acetate afforded **31** as a colorless oil in 95% yield. ^{13}C-NMR ($CDCl_3$) δ 220.5 (s), 135.9 (d), 129.7 (d), 129.6 (d), 127.6 (d), 127.4 (d), 134.2 (s), 133.6 (s), 83.1 (d), 58.8 (s), 39.0 (t), 36.8 (t), 33.9 (t), 33.1 (t), 21.0 (t), 19.6 (t), 26.9 (q), 19.2 (s); 5-(*R*)-**31** $[\alpha]_D^{23}$ -14.6° (c=0.5, $CHCl_3$), 5-(*S*)-**28** $[\alpha]_D^{23}$ +14.5° (c=1.2, $CHCl_3$).

DIBAL-H reduction of (+) and (-)-31: (32a and 32b)

Compounds **32a, b** were obtained as a colorless oil by a similar manner to that described for the preparation of **30**.

32a : 85% yield. ^{13}C-NMR ($CDCl_3$) δ 135.9 (d), 129.9 (d), 129.8 (d), 127.8 (d), 127.6 (d), 134.0 (s), 133.0 (s), 81.8 (d), 78.9 (d), 33.9 (t), 33.1 (t), 32.9 (t), 32.9

(t), 27.0 (q), 21.0 (t), 19.9 (t), 19.0 (s); (5*R*)-**32a** $[\alpha]_D^{25}$ -34.8° (c=0.54, $CHCl_3$), (5*S*)-**32a** $[\alpha]_D^{25}$ +33.7° (c=1.0, $CHCl_3$).

32b : 9% yield.

(1R,5R,6R) and (1S,5S,6S)-Spiro[4.4]nonane-1,6-diol (21)

To a solution of **32a** (394 mg, 1 mmol) in THF (2 ml) was added tetra-*n*-butylammonium fluoride: 1M in THF (2 ml, 2 mmol), and stirred for 2 h at room temperature. The reaction mixture was diluted with saturated aqueous NaCl (4 ml), and extracted with ethyl acetate. The extracts were dried over $MgSO_4$, then concentrated *in vacuo* to afford an oily residue, which was purified by silica-gel column chromatography. The fraction eluted with 3:1 hexane/ethyl acetate afforded **21** as a colorless oil in 100% yield. ^{13}C-NMR($CDCl_3$) δ 79.6 (d), 58.3 (s), 34.3 (t), 33.9 (t), 21.2 (t); **(1R,5R,6R)-21** $[\alpha]_D^{26}$ -100.7 (c=1.19, $CHCl_3$), **(1S,5S,6S)-21** $[\alpha]_D^{24}$ +101.5° (c=1.2, $CHCl_3$).

CHPTER II

General procedure for preparation of lactones (14, 37a,b and 38).

To a solution of **33a** or **33b** (3 mmol) and **35** or **36** (2 mmol) in benzene (30 ml) was added *p*-TsOH•H_2O (38 mg, 0.2 mmol), and the resultig mixture was refluxed with azeotropic removal of water for 6-18 h. After four times addition of *p*-TsOH•H_2O (38 mg x 4) with an interval of 6-13 h under above conditions, the reaction was quenched with $NaHCO_3$ (504 mg, 6 mmol) and aqueous saturated $NaHCO_3$ (20 ml) at 0 °C, and extracted with ethyl acetate. The extracts were dried over $MgSO_4$, then concentrated *in vacuo* to afford an oily residue, which was purified by silica-gel column chromatography. The fraction eluted with hexane/ethyl acetate (10:1) afforded the lactones (**14, 37a,b** and **38**).

(3*S*,7*S*)-2,8-Dioxa-9-oxotricyclo[8,3,0,0^{3,7}]tridec-1(10)-ene (37a)

Compound **37a** was obtained as a colorless oil in 85% yield. ^{13}C-NMR ($CDCl_3$) δ 166.5 (s) , 166.5 (s), 103.5 (s), 87.1 (d), 80.9 (d), 35.4 (t), 33.2 (t), 30.5 (t), 30.2 (t), 20.8 (t), 19.5 (t). $[\alpha]_D^{22}$ -289.7° (c=0.53, $CHCl_3$). HRMS m/z 194.0932 (M^+, calcd for $C_{11}H_{14}O_3$ 194.0943).

(3*S*,7*S*)-2,8-Dioxa-9-oxotricyclo[8,4,0,0^{3,7}]tetradec-1(10)-ene (37b)

Compound **37b** was obtained as a colorless oil in 70% yield. ^{13}C-NMR ($CDCl_3$) δ 168.9 (s), 161.9 (s), 102.4 (s), 85.9 (d), 80.6 (d), 30.6 (t), 30.4 (t), 30.1 (t), 28.3 (t), 22.8 (t), 22.1 (t), 21.2 (t). $[\alpha]_D^{19}$ -200.7° (c=1.1, $CHCl_3$). HRMS m/z 208.1113 (M^+, calcd for $C_{12}H_{16}O_3$ 208.1099).

(3*S*,8*S*)-2,9-Dioxa-10-oxotricyclo[9,3,0,0^{3,8}]tetradeca-1(11)-ene (38)

Compound **38** was obtained as colorless needles in 84% yield. mp 87 °C. ^{13}C-NMR ($CDCl_3$) δ 166.4 (s) , 166.3 (s), 101.4 (s), 82.1 (d), 76.8 (d), 35.9 (t), 32.1 (t), 31.6 (t), 31.2 (t), 23.0 (t), 22.9 (t), 19.2 (t). $[\alpha]_D^{25}$ -219.1° (c=0.59, $CHCl_3$). HRMS m/z 208.1087 (M^+, calcd for $C_{12}H_{16}O_3$ 208.1099).

(3*S*,8*S*)-2,9-Dioxa-10-oxotricyclo[9,4,0,0^{3,8}]pentadec-1(11)-ene (14)

Compound **14** was obtained as colorless needles in 51% yield. mp 96 °C. ^{13}C-NMR ($CDCl_3$) δ 169.1 (s), 161.3 (s), 101.9 (s), 82.1 (d), 76.8 (d), 32.1 (t), 31.2 (t), 31.0 (t), 29.7 (t), 27.0 (t), 23.1 (t), 23.1 (t), 22.4 (t). $[\alpha]_D^{27}$ -199.2° (c=0.25, $CHCl_3$). HRMS m/z 222.1268 (M^+, calcd for $C_{13}H_{18}O_3$ 222.1256).

Methyl (1*RS*)-2,2-[(*S*,*S*)-Cyclohexane-1,2-dioxy]cyclopentane-carboxylate (1d)

To a solution of NaOMe prepared from Na (460 mg, 20 mmol) in MeOH (5 ml) was added (3*S*,8*S*)-2,9-dioxa-10-oxotricyclo[9,3,0,0^{3,8}]tetradeca-1(11)-ene (104 mg, 0.5 mmol) under an Ar atmosphere. The mixture was stirred at room temperature for 48 h, then dilluted with saturated aqueous NH_4Cl (20 ml), and extracted with ethyl acetate. The extracts were dried over $MgSO_4$, then concentrated *in vacuo* to afford an oily residue, which was purified by silica-gel column chromatography. The fraction eluted with hexane/ethyl acetate (30:1) afforded **1d** (99.5 mg, 83%) as a diastereomeric mixture (1:1) at C_1. ^{1}H-NMR ($CDCl_3$) δ 3.70, 3.69 (total 3H, s each, ratio=1:1), 3.44-3.15 (2H, m), 2.98 (1H, dd, *J*=17, 7 Hz), 2.15-1.78 (9H, m), 1.46-1.26 (5H, m). Ms m/z (EI) 240 (M^+) 153, 114; IR (neat, cm^{-1}) 1740, 1435, 1100.

General procedure for asymmetric alkylation of lactones (37a,b, 38, and 14).

A solution of *n*-BuLi (15% hexane solution, 1.4 ml, 2.25 mmol) was added dropwise to a stirred solution of diisopropylamine (223 mg, 2.25 mol) in THF (8 ml) at -78 °C under an Ar atmosphere. After 10 min, HMPA (403 mg, 2.25 mmol) in THF and lactone substrate (0.45 mmol) in THF (1ml) were added. The whole was stirred for 10 min, then alkyl halide (2.25 mmol) in THF (0.5 ml) was added. After being stirred for 3-5 h at -78 °C and for additional 12-24 h at -40 °C, the reaction mixture was diluted with aqueous saturated NH_4Cl, and extracted with ethyl acetate. The extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel .

(3*S*,7*S*,13*RS*)-13-Methyl-2,8-dioxa-9-oxotricyclo[8,3,0,0^{3,7}]tridec-1(10)-ene (39a)

Compound **39a** was obtained as a diastereomeric mixture (3:1) at C_{13} in 65% yield. Colorless oil. ^{13}C-NMR ($CDCl_3$) δ 169.5 (s), 166.7 (s), 102.4 (s), 87.2 (d), 80.9 (d), 47.1 (d), 30.7 (t), 30.2 (t), 30.1 (t), 28.3 (t), 20.8 (t), 18.0 (q).

(3*S*,7*S*,13*RS*)-13-Benzyl-2,8-dioxa-9-oxotricyclo[8,3,0,0^{3,7}]tridec-1(10)-ene (39b)

Compound **39b** was obtained as a diastereomeric mixture (3:2) at C_{13} in 67% yield. Colorless oil. ^{13}C-NMR($CDCl_3$) δ 167.8 (s), 166.5 (s), 139.4 (s), 129.0 (d), 128.4 (d), 126.3 (d), 103.7 (s), 87.1 (d), 80.8 (d), 48.6 (d), 38.3 (t) , 30.7 (t), 30.2 (t), 25.9 (t), 25.1 (t), 20.8 (t).

(3*S*,8*S*,14*RS*)-14-Methyl-2,9-dioxa-10-oxotricyclo[9,3,0,0^{3,8}] tetradec-1(11)-ene (40a)

Compound **40a** was obtained as a diastereomeric mixture (3:1) at C_{14} in 70% yield by the similar manner to that described for the general procedure without HMPA. ^{13}C-NMR ($CDCl_3$) δ 169.2 (s), 166.5 (s), 100.5 (s), 82.3 (d), 76.7 (d), 42.1 (d), 31.5 (t), 31.2 (t), 29.5 (t), 28.1 (t), 23.1 (t), 22.8 (t),18.0 (q).

(3*S*,8*S*,14*RS*)-14-Benzyl-2,9-dioxa-10-oxotricyclo[9,3,0,0^{3,8}] tetradec-1(11)-ene (40b)

Compound **40b** was obtained as a diastereomeric mixture (3:2) at C_{14} in 63% yield by the similar manner to that described for the general procedure without HMPA. Colorless oil. ^{13}C-NMR ($CDCl_3$) δ 167.2 (s), 166.2 (s), 139.5 (s), 129.0 (d),

128.3 (d), 126.2 (d), 101.6 (s), 82.3 (d), 76.8 (d), 48.6 (d), 38.4 (t), 31.5 (t), 31.2 (t), 29.4 (t), 25.8 (t), 23.1 (t), 22.8 (t).

(3*S*,7*S*,14*RS*)-14-Methyl-2,8-dioxa-9-oxotricyclo[8,4,0,$0^{3,7}$] tetradec-1(10)-ene (41)

Compound **41** was obtained as a diastereomeric mixture (3:1) at C_{14} in 59% yield. Colorless oil. ^{13}C-NMR ($CDCl_3$) δ 169.4 (s), 165.6 (s), 102.1 (s), 85.8 (d), 80.7 (d), 34.7 (d), 30.4 (t), 30.1 (t), 29.3 (t), 29.0 (t), 21.2 (t), 19.9 (t), 20.1 (q).

(3*S*,7*S*,10*RS*)-10-Methyl-2,8-dioxa-9-oxotricyclo[8,4,0,$0^{3,7}$] tetradec-1(14)-ene (42)

Compound **42** was obtained as a diastereomeric mixture (1:1) at C_{10} in 26% yield. Colorless oil.

(3*S*,8*S*,11*S*)-11-Methyl-2,9-dioxa-10-oxotricyclo[9,4,0,$0^{3,8}$] pentadec-1(15)-ene (9a)

Colorless needles, 86% yield, 94% d.e. at C_{11}.

(3*S*,8*S*,11*R*)-11-Allyl-2,9-dioxa-10-oxotricyclo[9,4,0,$0^{3,8}$]pentadec-1(15)-ene (9b)

Colorless oil , 51% yield, 94% d.e. at C_{11}.

(3*S*,8*S*,11*R*)-11-Benzyl-2,9-dioxa-10-oxotricyclo[9,4,0,$0^{3,8}$] pentadec-1(15)-ene (9c)

Colorless oil, 52% yield, >99% d.e. at C_{11}.

Enol ethers (10a-c)

Compounds **10a-c** were obtained as a colorless oil by a similar manner to that described for the preparation of **1d**.

10a: 95% yield. ^{13}C-NMR($CDCl_3$) δ 176.7 (s), 153.5 (s), 96.5(d), 79.3 (d), 73.3 (d), 51.9 (q), 47.1 (s), 35.5 (t), 31.9 (t), 28.1 (t), 23.9 (t), 23.9 (t), 23.7 (t), 19.2 (t), 22.6 (q). $[\alpha]_D^{24}$ +11.7° (c=0.29, $CHCl_3$) .

10b: 98% yield. ^{13}C-NMR ($CDCl_3$) δ 175.9 (s), 151.3 (s), 135.8 (t), 116.8 (d), 97.9 (d), 80.6 (d), 79.7 (d), 51.8 (q), 50.2 (s), 39.8 (t), 32.6 (t), 31.9 (t), 28.1 (t), 27.9 (t), 23.9 (t), 23.6 (t), 19.1 (t). $[\alpha]_D^{28}$ -10.1° (c=0.73, $CHCl_3$).

10c: 93% yield. ^{13}C-NMR ($CDCl_3$) δ 176.1 (s), 150.8 (s), 138.4 (s), 130.5 (d), 128.0 (d), 126.3 (d), 99.3 (d), 79.3 (d), 73.2 (d), 51.9 (q), 51.8 (s), 40.5 (t), 32.4

(t), 32.0 (t), 27.8 (t), 23.9 (t), 23.9 (t), 23.5 (t), 19.0 (t). $[\alpha]_D^{26}$ -4.7° (c=0.45, $CHCl_3$).

Methyl (*S*)-1-Methyl-2-oxocyclohexanecarboxylate (20a)

90% yield. (*S*)-**20a** (94% e.e.) $[\alpha]_D^{25}$ +104.0° (c=1.19, ethanol).

Methyl (*R*)-1-Allyl-2-oxocyclohexanecarboxylate (20b)

91% yield. (*R*)-**20b** (94% e.e.) $[\alpha]_D^{25}$ +127.3° (c=1.12, ethanol).

Methyl (*R*)-1-Benzyl-2-oxocyclohexanecarboxylate (20c)

93% yield. (*R*)-**20c** (>99% e.e.) $[\alpha]_D^{26}$ +109.3° (c=0.45, ethanol).

Chapter III

(1'*R*,2'*R*)-2'-Hydroxycyclohexyl 2-oxocyclopentanecarboxylate (45)

To a solution of **38** (5 g, 24 mmol) in THF (25ml) was added 10 % HCl (10 ml), and stirred for 24 h at room temperature. The reaction mixture was diluted with saturated aqueous NaCl (30 ml), and extracted with ethyl acetate. The extracts were washed with 10% aqueous $NaHCO_3$, dried over $MgSO_4$, then concentrated *in vacuo* to afford an oily residue, which was purified by silica-gel column chromatography. The fraction eluted with 10:1 hexane/ethyl acetate afforded **45** as a diastereomeric mixture (3:1) at C_1. Colorless oil, 99% yield. ^{13}C-NMR ($CDCl_3$) δ 213.8 (s), 168.2 (s), 79.9 (d), 72.6 (d), 55.5 (d), 37.9 (t), 32.0 (t), 30.0 (t), 25.8 (t), 24.0 (t), 23.8 (t), 20.5 (t); $[\alpha]_D^{25}$ -53.4° (c=0.85, $CHCl_3$).

1,1-(*cis*-Cyclohexane-1,2-dioxy)-2-[(1*R*,2*R*)-2-hydroxycyclohexyl] oxycarbonylcyclopentane (43)

To a mixture of **45** (1.0 g, 4.4 mmol) in CH_2Cl_2 (30 ml) and *meso*-1,2-bis(trimethylsilyloxy)cyclohexane (1.7 g, 6.7 mmol) was added a solution of trimethylsilyl trifluoromethanesulfonate (10 mg, 0.045 mmol) in CH_2Cl_2 (1 ml) at -78 °C. The reaction mixture was stirred for 10 h at -60 °C, then diluted with saturated aqueous NaCl (20 ml), and extracted with CH_2Cl_2. The extracts was dried over $MgSO_4$, then concentrated *in vacuo* to afford an oily residue, which was purified by silica-gel column chromatography. **43** was obtained as 9:1 (syn:anti) mixture of diastereomers. Colorless needles, 91% yield. mp 52 °C.

1,1-(*cis*-Cyclohexane-1,2-dioxy)-2-hydroxymethylcyclopentane (46)

To a mixture of β-keto ester **44** (1.46 g, 10.3 mmol) and *cis*-cyclohexane-1,2-diol (1.2 g, 10.3 mmol) in benzene (30 ml) was added *p*-TsOH•H_2O (152 mg, 0.8 mmol), and the resultig mixture was refluxed with azeotropic removal of water for 3 h. The reaction mixture was diluted with $NaHCO_3$ (504 mg, 6 mmol) and aqueous saturated $NaHCO_3$ (20 ml) at 0 °C. The whole was extracted with ethyl acetate. The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford an oily residue. To a suspended solution of LAH (750 mg, 20 mmol) in THF (20 ml) was added dropwise a solution of above oily residue in THF (5 ml) at 0°C and the resultig mixture was stirred for 1 h. The reaction mixture was diluted with ethyl acetate (1 ml) and saturated aqueous NH_4Cl (0.2 ml) at 0 °C, and filtered.The filtrate was dried over $MgSO_4$, then concentrated *in vacuo* to afford an oily residue, which was purified by silica-gel column chromatography. *syn*-**46** (27%) and *anti*-**46** (52%) were obtained as a colorless oil, respectively.

syn and anti-1,1-(*cis*-Cyclohexane-1,2-dioxy)-2-formyl-cyclopentane

To a solution of pyridinium dichromate (PDC) (2.84 g, 7.5 mmol) in CH_2Cl_2 (50 ml) was added **46** (320 mg, 1.5 mmol) at room temperature. After being stirred at room temperature for 72 h, the reaction mixture was diluteded with isopropyl alchohol and ether, then filtered through a short pad of Florisil. The filtrate was concentrated *in vacuo* to afford an oily residue, which was purified by silica-gel column chromatography. Colorless oil. *syn*-aldehyde (60%), *anti*-aldehyde (63%). *anti*-aldehyde: ^{1}H-NMR ($CDCl_3$) δ 9.67 (1H, d, *J*=4 Hz), 4.31-3.88 (2H, m), 3.01-2.67 (1H, m), 2.30-1.26 (14H, m); IR (neat, cm^{-1}) 1720.

***syn* and *anti*-2,2-(*cis*-Cyclohexane-1,2-dioxy)-cyclopentanecarboxylic acid**

To a mixture of *syn* or *anti*-aldehyde (250 mg, 1.2 mmol) in Bu^tOH (10 ml) and 5% aqueous NaH_2PO_4 (5 ml) was added $KMnO_4$ (570 mg, 3.6 mmol) at room temperature. After being stirred at room temperature for 8 h, the reaction mixture was diluted with ether, and washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford an oily residue, which was purified by silica-gel column chromatography. *syn*-carboxylicacid (40%) and *anti*-carboxylicacid (41%).

***syn* and *anti*-1,1-(*cis*-Cyclohexane-1,2-dioxy)-2-[(1*R*,2*R*)-2-hydroxycyclohexyl] oxycarbonylcyclopentane (43)**

To a mixture of *syn* or *anti*-carboxyricacid (111 mg, 0.5 mmol) and (*R, R*)-cyclohexane-1,2-diol (57 mg, 0.5 mmol) in CH_2Cl_2 (10 ml) was added 4-dimethylaminopyridine (30 mg, 0.25 mmol) and N,N'-dicyclohexylcarbodiimide (DCC) at room temperature. After being stirred at room temperature for 5 h, the reaction mixture was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford an oily residue, which was purified by silica-gel column chromatography.

***syn*-43** was obtained as a diastereomixture (1:1) in 77% yield. ^{13}C-NMR ($CDCl_3$) δ 172.2 (s), 117.5 (s), 78.4 (d), 74.8 (d), 73.5 (d), 73.1 (d), 52.9 (d), 38.4 (t), 34.8 (t), 31.9 (t), 30.1 (t), 28.3 (t), 27.4 (t), 24.3 (t), 23.9 (t), 21.5 (t), 21.1 (t), 20.4 (t). ***anti*-43** was obtained as a diastereomixture (10:1) in 54% yield. ^{13}C-NMR ($CDCl_3$) δ 172.9 (s), 117.9 (s), 78.2 (d), 74.8 (d), 73.7 (d), 73.3 (d), 52.7 (d), 36.7 (t), 32.1 (t), 30.1 (t), 28.3 (t), 27.4 (t), 25.9 (t), 24.2 (t), 23.9 (t), 21.3 (t), 21.2 (t), 20.4 (t).

Reaction of 43 with LDA: (47a,b)

A solution of *n*-BuLi (15% hexane solution, 1.45ml, 2.3 mmol) was added dropwise to a stirred solution of diisopropylamine (223.8 mg, 2.3 mol) in THF (15 ml) at -78 °C under an Ar atmosphere. After 10 min, HMPA (405 mg, 2.3 mmol) was added. The whole was stirred for 5 min, then **43** (150 mg, 0.46 mmol) in THF (0.5 ml) was added. After being stirred at -78 °C for 0.5 h, the reaction mixture was diluted with aqueous saturated NH_4Cl, and extracted with ethyl acetate. The extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel.

47a was obtained as a colorless oil in 30 % yield. $[\alpha]_D^{20}$ -14.2° (c=0.90, $CHCl_3$).

47b was obtained as a colorless oil in 50 % yield.

Methoxyethoxymethylation of 47

A mixture of **47a** (45.7 mg, 0.14 mmol) in CH_2Cl_2 (5 ml), diisopropylethylamine (364 mg, 2.8 mmol), and β-methoxyethoxymethyl chloride (0.16 ml, 1.4 mmol) was stirred at room temperature for 24 h. The reaction mixture

was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel.

Colorless oil, 90% yield. ^{1}H-NMR ($CDCl_3$) δ 4.89-4.74 (6H, m), 4.39 (1H, m) 3.79-3.56 (5H, m), 3.53 (4H, t, *J*=4 Hz), 3.39 (3H, s), 3.38 (3H, s), 2.70-2.49 (4H, m), 2.09-1.23 (18H, m); MS *m/z* (EI) 500 (M^+), 424, 238; IR (neat, cm^{-1}) 1680, 1620.

(1*S*,2*R*)-2-Methoxyethoxymethoxycyclohexanol (48)

A mixture of above product (60 mg, 0.12 mmol) and AcOH:THF:H_2O=1:1:1 (5 ml) was stirred at room temperature for 24 h. The reaction mixture was diluted with brine, and extracted with ethyl acetate. The extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel. **48** was obtained as a colorless oil in 70% yield. $[\alpha]_D^{24}$ -20.1° (c=0.7, $CHCl_3$).

Chapter IV

General procedure for preparation of β'-trimethylsilyloxy enol ethers (50-54a)

A solution of *n*-BuLi (15% hexane solution, 1.4 ml, 2.25 mmol) was added dropwise to a stirred solution of diisopropylamine (223 mg, 2.25 mol) in THF (8 ml) at -78 °C under an Ar atmosphere. After 10 min, acetal substrate **(1e, 3a,b)** (1.13 mmol) in THF (2 ml) were added. The whole was stirred for 10 min, then trimethylsilyl chloride (TMSCl) (353 mg, 3.25 mmol) in THF (1 ml) was added. After being stirred for 0.5 h at -60 °C , the reaction mixture was diluted with aqueous saturated $NaHCO_3$, and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel. In the case of preparation of **53a,b**, LDA (4eq) and TMSCl (5eq) were used in the above reaction. The fraction eluted with 50:1-40:1 hexane/ethyl acetate afforded **50-54a** as a colorless oil in 85-95 % yield.

Methyl 2-[(1*S*,2*S*)-2-Trimethylsilyloxycycloheptan-1-yl]oxy-1-cyclopenten-1-carboxylate (50)

93% yield. ^{13}C-NMR($CDCl_3$) δ 168.5 (s), 165.7 (s), 104.0 (s), 86.5 (d), 76.5 (d), 50.4 (q), 33.3 (t), 31.9 (t), 30.5 (t), 29.1 (t), 27.9 (t), 22.2 (t), 22.1 (t), 19.4 (t), 0.0 (q); $[\alpha]_D^{20}$ +36.5° (c=1.0, $CHCl_3$).

Methyl 2-[(1*S*,2*S*)-2-Trimethylsilyloxycyclohexan-1-yl]oxy-1-cyclohexen-1-carboxylate (51)

95% yield. ^{13}C-NMR($CDCl_3$) δ 168.6 (s), 161.5 (s), 107.0 (s), 78.5 (d), 73.7 (d), 50.8 (q), 33.5 (t), 30.2 (t), 26.9 (t), 25.6 (t), 23.4 (t), 23.3 (t), 22.6 (t), 22.3 (t), 0.2 (q); $[\alpha]_D^{24}$ +43.5° (c=1.1, $CHCl_3$).

Methyl 2-[(1*S*,2*S*)-2-Trimethylsilyloxycycloheptan-1-yl]oxy-1-cyclohexen-1-carboxylate (52a)

95% yield. ^{13}C-NMR($CDCl_3$) δ 168.7 (s), 160.7 (s), 107.9 (s), 82.2 (d), 76.6 (d), 50.8 (q), 33.8 (t), 30.0 (t), 28.4 (t), 26.8 (t), 25.6 (t), 22.6 (t), 22.4 (t), 22.3 (t), 22.2 (t), 0.3 (q); $[\alpha]_D^{21}$ +7.8° (c=0.48, $CHCl_3$).

Methyl *cis*-3-[(1*S*,2*S*)-2-Trimethylsilyloxycyclohexan-1-yl]oxy-2-butenoate (53a)

87% yield. ^{13}C-NMR($CDCl_3$) δ 170.3 (s), 164.5 (s), 105.8 (s), 79.0 (d), 73.9 (d), 51.0 (q), 33.9 (t), 31.0 (t), 23.6 (t), 23.5 (t), 15.9 (q), 12.0 (q), 0.2 (q); $[\alpha]_D^{20}$ -9.2° (c=0.50, $CHCl_3$).

Methyl *cis*-3-[(1*S*,2*S*)-2-Trimethylsilyloxycycloheptan-1-yl]oxy-2-butenoate (54a)

85% yield. ^{13}C-NMR($CDCl_3$) δ 170.2 (s), 163.9 (s), 106.6 (s), 82.8 (d), 76.9 (d), 51.0 (q), 33.8 (t), 30.5 (t), 28.4 (t), 22.8 (t), 22.4 (t), 15.9 (q), 12.0 (q), 0.2 (q); $[\alpha]_D^{25}$ -38.6° (c=1.60, $CHCl_3$).

Desilylation of 50-52a: (5e,12,52b)

To a solution of trimethylsilyl enol ether **(50-52a)** (1 mmol) in $CHCl_3$ (10 ml) was added $ZnBr_2$ (900 mg, 4 mmol) at room temperature. After being stirred at room temperature for 5-20 min, the reaction mixture was diluted with aqueous saturated $NaHCO_3$ (10 ml), and filtered. The filtrate was dried over $MgSO_4$, then concentrated *in vacuo* to afford an oily residue. The crude product was purified by

flash column chromatography on silica gel. The fraction eluted with 5:1 hexane/ethyl acetate afforded **5e,12,52b** as a colorless oil in 90-95 % yield.

Methyl 2-[(1*S*,2*S*)-2-Hydroxycycloheptan-1-yl]oxy-1-cyclopenten-1-carboxylate ((+)-5e)

95% yield. $[\alpha]_D^{25}$ +151.1° (c=0.50, $CHCl_3$).

Methyl 2-[(1*S*,2*S*)-2-Hydroxycyclohexan-1-yl]oxy-1-cyclohexen-1-carboxylate (12)

95% yield.

Methyl 2-[(1*S*,2*S*)-2-Hydroxycycloheptan-1-yl]oxy-1-cyclohexen-1-carboxylate (52b)

90% yield. ^{13}C-NMR($CDCl_3$) δ 169.0 (s), 163.4 (s), 108.1 (s), 84.1 (d), 75.3 (d), 51.3 (q), 31.8 (t), 31.7 (t), 27.3 (t), 26.9 (t), 25.2 (t), 22.5 (t), 22.4 (t), 22.1 (t), 22.1 (t); $[\alpha]_D^{21}$ +186.5° (c=1.20, $CHCl_3$).

Desilylation of 53a,54a: (53b,54b)

To a mixture of pyridine (316 mg, 4 mmol) and aqueous 47% HF (340 mg, 8 mmol) in CH_2Cl_2 (10 ml) was added trimethylsilyl enol ether **(53a,52a)** (1 mmol) in CH_2Cl_2 (1 ml) at room temperature. After being stirred at room temperature for 10 min, the reaction mixture was washed with brine (5 ml) and aqueous saturated $NaHCO_3$ (5 ml), dried over $MgSO_4$ and concentrated *in vacuo* to afford an oily residue. The crude product was purified by flash column chromatography on silica gel. The fraction eluted with 6:1 hexane/ethyl acetate afforded **53b,54b** as a colorless oil in 90-93 % yield.

Methyl *cis*-3-[(1*S*,2*S*)-2-Hydroxycyclohexan-1-yl]oxy-2-butenoate (53b)

90% yield. ^{13}C-NMR(C_6D_6) δ 169.5 (s), 163.7(s), 108.4 (s), 80.4 (d), 73.2 (d), 50.8 (q), 32.5 (t), 30.8 (t), 23.9 (t), 23.7 (t), 16.1 (q), 12.4 (q); $[\alpha]_D^{25}$ -34.7° (c=0.84, $CHCl_3$) .

Methyl *cis*-3-[(1*S*,2*S*)-2-Hydroxycycloheptan-1-yl]oxy-2-butenoate (54b)

93% yield. ^{13}C-NMR($CDCl_3$) δ 169.6 (s), 163.4 (s), 108.8 (s), 83.3 (d), 75.9 (d), 50.8 (q), 32.5 (t), 30.2 (t), 27.9 (t), 22.7 (t), 22.5 (t), 16.1 (q), 12.4 (q); $[\alpha]_D^{24}$ -82.5° (c=0.88, $CHCl_3$).

General procedure for oxidation of β'-trimethylsilyloxy enol ethers 50-54a : (55-58)

To a mixture of β'-trimethylsilyloxy enol ether **(50-54a)** (0.5 mmol) and $NaHCO_3$ (420 mg, 5 mmol) in CH_2Cl_2 (7 ml) was added MCPBA (80%) (129.2 mg, 0.6 mmol) at -78 °C. After being stirred at -50- -60 °C for 48 h, the reaction mixture was diluted with aqueous saturated Na_2CO_3 (20 ml) and extracted with CH_2Cl_2. The extracts were dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel. The fraction eluted with 30:1 hexane/ethyl acetate afforded **55-58** as a colorless oil.

Methyl (1*S*)-2-[(1*S*,2*S*)-2-Trimethylsilyloxycycloheptan-1-yl]oxy-1-hydroxy-2-cyclopenten-1-carboxylate (55)

70% yield. ^{13}C-NMR($CDCl_3$) δ 175.5 (s), 155.9(s), 100.5 (d), 85.9 (d), 82.8 (s), 75.5 (d), 52.9 (q), 35.3 (t), 34.0 (t), 28.9 (t), 27.8 (t), 25.7 (t), 23.0 (t), 22.5 (t), 0.2 (q); $[\alpha]_D^{21}$ +69.0° (c=1.0, $CHCl_3$).

Methyl (1*S*)-2-[(1*S*,2*S*)-2-Trimethylsilyloxycyclohexan-1-yl]oxy-1-hydroxy-2-cyclohexen-1-carboxylate (56)

53% yield. ^{13}C-NMR($CDCl_3$) δ 175.9 (s), 151.9(s), 101.6 (d), 79.3 (d), 74.1 (s), 71.5 (d), 52.8 (q), 34.7 (t), 32.8 (t), 28.2 (t), 23.6 (t), 22.7 (t), 22.5 (t), 18.4 (t), 0.2 (q); $[\alpha]_D^{24}$ +23.5° (c=0.80, $CHCl_3$).

Methyl (1*S*)-2-[(1*S*,2*S*)-2-Trimethylsilyloxycycloheptan-1-yl]oxy-1-hydroxy-2-cyclohexen-1-carboxylate (57)

56% yield. ^{13}C-NMR($CDCl_3$) δ 175.9 (s), 151.1(s), 100.9 (d), 82.2 (d), 74.9 (d), 74.2 (s), 52.8 (q), 34.8 (t), 33.6 (t), 28.8 (t), 28.0 (t), 26.4 (t), 23.6 (t), 22.2 (t), 18.5 (t), 0.2 (q); $[\alpha]_D^{24}$ +26.7° (c=0.65, $CHCl_3$).

Methyl (1*S*)-3-[(1*S*,2*S*)-2-Trimethylsilyloxycycloheptan-1-yl]oxy-2-hydroxy-2-methyl-3-butenoate (58)

IR (neat, cm^{-1}) 3500, 2950, 1740, 1630. The crude product was subjected to following acetalization.

General procedure for acetalization of α-hydroxy enol ethers 55-58 : (59-62)

To a solution of α-hydroxytrimethylsilyl enol ethers **(55-58)** (0.5 mmol) in CH_2Cl_2 (7 ml) was added a solution of trimethylsilyl trifluoromethane-

sulfonate (10 mg, 0.045 mmol) at -78 °C. After being stirred at -60 °C for 1 h, the reaction mixture was diluted with aqueous saturated $NaHCO_3$ (20 ml), and extracted with CH_2Cl_2. The extracts were dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel. The fraction eluted with 8:1 hexane/ethyl acetate afforded **59-62** as a colorless oil.

Methyl (1*S*)-2,2-[(*S,S*)-Cycloheptane-1,2-dioxy]-1-hydroxy-cyclopentanecarboxylate (59)

90% yield. ^{13}C-NMR($CDCl_3$) δ 173.6 (s), 116.9 (s), 83.0 (s), 81.8 (d), 81.7 (d), 52.3 (q), 36.4 (t), 34.5 (t), 29.5 (t), 29.1 (t), 25.1 (t), 24.8 (t), 24.7 (t), 19.7 (t); $[\alpha]_D^{23}$ +16.3° (c=1.20, $CHCl_3$).

Methyl (1*S*)-2,2-[(*S,S*)-Cyclohexane-1,2-dioxy]-1-hydroxy-cyclohexanecarboxylate (60)

80% yield. ^{13}C-NMR($CDCl_3$) δ 173.7 (s), 109.3 (s), 81.8 (d), 79.9 (d), 77.9 (s), 52.7 (q), 33.5 (t), 33.3 (t), 39.4 (t), 28.8 (t), 23.7 (t), 23.6 (t), 22.4 (t), 20.2 (t); $[\alpha]_D^{28}$ +4.5° (c=0.55, $CHCl_3$).

Methyl (1*S*)-2,2-[(*S,S*)-Cycloheptane-1,2-dioxy]-1-hydroxy-cyclohexanecarboxylate (61)

95% yield. ^{13}C-NMR($CDCl_3$) δ 173.9 (s), 109.2 (s), 82.3 (d), 80.7 (d), 78.0 (s), 52.7 (q), 33.7 (t), 32.9 (t), 30.4 (t), 29.1 (t), 25.2 (t), 24.9 (t), 24.9 (t), 22.4 (t), 20.1 (t); $[\alpha]_D^{26}$ +59.8° (c=0.80, $CHCl_3$).

Methyl (2*S*)-3,3-[(*R,R*)-Cycloheptane-1,2-dioxy]-2-hydroxy-2-methylbutanoate (62)

46% yield (from **54**). ^{13}C-NMR($CDCl_3$) δ 174.9 (s), 110.4 (s), 82.3 (d), 81.4 (d), 79.6 (s), 52.7 (q), 30.2 (t), 28.9 (t), 25.2 (t), 24.9 (t), 24.8 (t), 21.9 (q), 20.1 (q); $[\alpha]_D^{25}$ +51.0° (c=0.40, $CHCl_3$).

General procedure for oxidation of β'-hydroxy enol ethers 5e,12,52b-54b : (64-68)

To a mixture of β'-hydroxy enol ether **(5e,12,52b-54b)** (0.5 mmol) and Li_2CO_3 (370 mg, 5 mmol) in CH_2Cl_2 (7 ml) was added MCPBA (80%) (236.9 mg, 1.1 mmol) at -78 °C. After being stirred at -60 °C for 48 h, the reaction mixture was quenched with aqueous saturated Na_2CO_3 (20 ml), and extracted with CH_2Cl_2. The extracts were dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was

purified by flash column chromatography on silica gel. The fraction eluted with 8:1 hexane/ethyl acetate afforded **64-68** as a colorless oil.

Methyl (1*R*)-2,2-[(*S,S*)-Cycloheptane-1,2-dioxy]-1-hydroxy-cyclopentanecarboxylate (64)

85% yield. ^{13}C-NMR($CDCl_3$) δ 174.2 (s), 117.4 (s), 82.6 (s), 81.6 (d), 81.6 (d), 52.1 (q), 35.7 (t), 33.1 (t), 29.4 (t), 29.0 (t), 25.2 (t), 24.7 (t), 24.7 (t), 19.1 (t); $[\alpha]_D^{20}$ +6.8° ($CHCl_3$, c=1.05).

Methyl (1*R*)-2,2-[(*S,S*)-Cyclohexane-1,2-dioxy]-1-hydroxy-cyclohexanecarboxylate (65)

94% yield. ^{13}C-NMR($CDCl_3$) δ 174.5 (s), 109.6 (s), 80.7 (d), 80.4 (d), 77.2 (s), 52.5 (q), 32.4 (t), 31.9 (t), 29.3 (t), 28.9 (t), 23.6 (t), 23.6 (t), 22.8 (t), 19.8 (t); $[\alpha]_D^{24}$ -29.1° ($CHCl_3$, c=0.95).

Methyl (1*R*)-2,2-[(*S,S*)-Cycloheptane-1,2-dioxy]-1-hydroxy-cyclohexanecarboxylate (66)

93% yield. ^{13}C-NMR($CDCl_3$) δ 174.6 (s), 109.3 (s), 81.3 (d), 81.2 (d), 77.6 (s), 52.4 (q), 33.0 (t), 31.7 (t), 30.2 (t), 29.0 (t), 25.2 (t), 24.9 (t), 24.8 (t), 22.8 (t), 19.8 (t); $[\alpha]_D^{22}$ -9.8° ($CHCl_3$, c=0.90).

Methyl (2*R*)-3,3-[(*S,S*)-Cyclohexane-1,2-dioxy]-2-hydroxy-2-methylbutanoate (67)

90% yield. ^{13}C-NMR($CDCl_3$) δ 174.5 (s), 110.5 (s), 82.0 (d), 80.2 (d), 79.1 (s), 52.9 (q), 29.5 (t), 28.6 (t), 23.7 (t), 23.7 (t), 21.4 (q), 20.8 (q); $[\alpha]_D^{23}$ +17.8° ($CHCl_3$, c=0.83).

Methyl (2*R*)-3,3-[(*S,S*)-Cycloheptane-1,2-dioxy]-2-hydroxy-2-methylbutanoate (68)

96% yield. ^{13}C-NMR($CDCl_3$) δ 174.8 (s), 110.6 (s), 82.5 (d), 81.0 (d), 79.2 (s), 52.8 (q), 30.4 (t), 28.8 (t), 25.1 (t), 25.0 (t), 24.9 (t), 21.5 (q), 20.6 (q); $[\alpha]_D^{26}$ +48.2° ($CHCl_3$, c=1.0).

Deprotection of α-hydroxyacetal 60 and 64: (63 and 69)

To a mixture of BF_3-etherate (1 ml, 8 mmol) and H_2O (0.5 ml) was added a solution of enol ether (0.2 mmol) in MeOH (4 ml) at room temperature, the reaction mixture was heated at 60-70 °C for 0.5-2 h, then diluted with saturated aqueous NaCl (20 ml), and extracted with $CHCl_3$. The extracts were washed with saturated

aqueous $NaHCO_3$, and dried over $MgSO_4$, then concentrated *in vacuo* to afford an oily residue, which was purified by silica-gel column chromatography. The fraction eluted with 8:1 hexane/ethyl acetate afforded **63** (85 %), **69** (48%) as a colorless oil.

Methyl (*S*)-1-Hydroxy-2-oxocyclohexanecarboxylate (63)

>99% e.e. $[\alpha]_D^{26}$ -138.8° ($CHCl_3$, c=1.19).

Methyl (*R*)-1-Hydroxy-2-oxocyclopentanecarboxylate (69)

89% e.e. ^{13}C-NMR($CDCl_3$) δ 213.1 (s), 172.0 (s), 79.9 (s), 53.2 (q), 35.8 (t), 34.8 (t), 18.4 (t); $[\alpha]_D^{28}$ +7.9° ($CHCl_3$, c=1.1).

Preparation of dibenzoate (70,71)

To a solution of α-hydroxy-β-keto ester **(63,69)** (0.5 mmol) in MeOH (5 ml) was added $NaBH_4$ (20 mg, 0.53 mmol) at -78 °C. After being stirred at -60 °C for 1 h, the reaction mixture was diluted with 3.5% HCl (0.2 ml), and filtered through a short column chromatography on silica gel. The filtrate was concentrated in *vacuo to* afford the crude diol. To a mixture of the crude diol and DMAP (366.6 mg, 3 mmol) in CH_2Cl_2 (5 ml) was added *p*-bromobenzoylchloride (329.3 mg, 1.5 mmol) at room temperature. After being stirred for 48 h, the reaction mixture was diluted with brine, and extracted with $CHCl_3$. The extracts were dried over $MgSO_4$, then concentrated *in vacuo* to afford an oily residue, which was purified by silica-gel column chromatography. The fraction eluted with 50:1 hexane/ethyl acetate afforded **70** (70 %), **71** (53%) as a colorless needles.

(2*S*,3*S*)-70

^{13}C-NMR($CDCl_3$) δ 170.3 (s), 164.3 (s), 163.9 (s), 132.0 (d), 131.9 (d), 131.3 (d), 131.2 (d), 128.8 (s), 128.7 (s), 128.5 (s), 128.3 (s), 80.3 (s), 72.4 (d), 52.6 (q), 26.9 (t), 26.7 (t), 29.5 (t), 19.9 (t); $[\alpha]_D^{23}$ +145.6° ($CHCl_3$, c=0.39) (>99% e.e.). mp. 157 °C

(2*R*,3*R*)-71

^{13}C-NMR($CDCl_3$) δ 169.1 (s), 164.6 (s), 164.4 (s), 131.9 (d), 131.8 (d), 131.4 (d), 131.2 (d), 128.7 (s), 128.6 (s), 128.5 (s), 128.3 (s), 89.5 (s), 80.7 (d), 52.6 (q), 33.5 (t), 30.5 (t), 21.4 (t); $[\alpha]_D^{24}$ -96.5° ($CHCl_3$, c=0.5) (89% e.e.); mp.120 °C

Methyl *trans*-1,2-Dihydroxycyclohexanecarboxylate (racemic)

To a solution of methyl 1-cyclohexenecarboxylate (400 mg, 2.86 mmol) in CH_2Cl_2 (7 ml) was added MCPBA (50%) (1 g, 3.0 mmol) at room temperature. After being stirred at room temperature for 48 h, the reaction mixture was diluted with aqueous saturated Na_2CO_3 (30 ml) and extracted with CH_2Cl_2. The extracts were dried over $MgSO_4$, and concentrated *in vacuo.* A mixture of the crude product and 10% $HClO_4$ (5 ml) was stirred at room temperature for 8 h, the reaction mixture was neutralized with Na_2CO_3, and extracted with $CHCl_3$. The extracts were dried over $MgSO_4$, and concentrated *in vacuo* to afford an oily residue, which was purified by silica-gel column chromatography. The fraction eluted with 3:1 hexane/ethyl acetate afforded methyl *trans*-1,2-dihydroxycyclohexanecarboxylate (51%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ 3.83 (3H, s), 3.66 (1H, dd, *J*=9, 4 Hz), 3.44 (1H, br.s), 2.80 (1H, br.s), 2.11-1.34 (8H, m); ^{13}C-NMR ($CDCl_3$) δ 175.4 (s), 77.3 (s), 74.7 (d), 52.6 (q), 33.4 (t), 29.8 (t), 22.4 (t), 21.8 (t); Ms m/z (EI) 174 (M^+).

Racemic-70

Racemic-70 was obtained as a colorless needles by a similar manner to that described for the preparation of **(2*S*,3*S*)-70**. mp.145°C.

Methyl 2-[(1*S*,2*S*)-2-*tert*-Butyldiphenylsilyloxycycloheptan-1-yl]oxy-1-cyclopenten-1-carboxylate (72)

A mixture of β'-hydroxy enol ether **(5e)** (127 mg, 0.5 mmol), imidazol (272 mg, 4 mmol) and *tert*-butyldiphenylsilyl chloride (550 mg, 2 mmol) in DMF (2 ml) was stirred at room temperature for 12 h, then diluted with brine, and extracted with CH_2Cl_2. The extracts were dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by flash column chromatography on silica gel. The fraction eluted with 40:1 hexane/ethyl acetate afforded **72** as a colorless oil. 90% yield. $[\alpha]_D^{22}$ +15.3° ($CHCl_3$, c=1.1).

CHAPTER V

General procedure for preparation of α,β–unsaturated acetals (73, 74)

To a solution of 2-carbomethoxy-2-cyclopenten-1-one (or -cyclohexen-) (2 mmol) and (*S,S*)-cycloheptane-1,2-diol (2 mmol) in benzene (30 ml) was added *p*-TsOH•H_2O (19 mg, 0.1 mmol), and the resultig mixture was refluxed with azeotropic removal of water for 1 h. The reaction was quenched with $NaHCO_3$ (504 mg, 6 mmol) and aqueous saturated $NaHCO_3$ (20 ml) at 0 °C. The whole was extracted with ethyl acetate. The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford an oily residue, which was purified by silica-gel column chromatography. The fraction eluted with hexane/ethyl acetate (40:1) afforded **73,74** as a colorless oil.

Methyl 2,2-[(*S,S*)-Cycloheptane-1,2-dioxy]-1-cyclopentene carboxylate (73)

^{13}C-NMR($CDCl_3$) δ 163.6 (s), 149.9 (d), 136.1 (s), 117.6 (s), 81.6 (d), 81.6 (d), 51.2 (q), 38.1 (t), 30.1 (t), 28.7 (t), 28.1 (t), 25.3 (t), 25.0 (t), 24.9 (t); $[\alpha]_D^{26}$ +19.5° ($CHCl_3$, c=0.8).

Methyl 2,2-[(*S,S*)-Cycloheptane-1,2-dioxy]-1-cyclohexene carboxylate (74)

^{13}C-NMR($CDCl_3$) δ 165.7 (s), 145.3 (d), 132.2 (s), 105.2 (s), 81.8 (d), 81.0 (d), 51.3 (q), 36.2 (t), 30.9 (t), 28.5 (t), 25.8 (t), 25.5 (t), 25.1 (t), 25.1 (t), 19.9 (t); $[\alpha]_D^{28}$ +58.4° ($CHCl_3$, c=1.13).

3,3-[(*S,S*)-Cycloheptane-1,2-dioxy]-1-cyclopentene carboxylate (81)

Compounds **(81)** was obtained as a colorless oil in 93% yield by a similar manner to that described for the preparation of **73,74**.

^{13}C-NMR($CDCl_3$) δ 136.7 (d), 131.7 (d), 119.9 (s), 81.4 (d), 81.0 (d), 35.7 (t), 29.7 (t), 29.7 (t), 29.5 (t), 25.3 (t), 24.9 (t), 24.9 (t); $[\alpha]_D^{20}$ -44.2° ($CHCl_3$, c=1.63).

General procedure for conjugate addition of cuplates to α,β-unsaturated acetals (73, 74)

A solution of RMgX (1M-2M THF solution, 5 mmol) was added dropwise to a stirred solution of CuI (476.3 mg, 2.5 mol) in THF (3 ml) at -75°C under an Ar atmosphere. The mixture was stirred at -40°C for 0.5-2 h, re-cooled at -50°C, then acetal substrate (0.5 mmol) in THF (1 ml) was added. After being stirred for 3-5 h at -50°C and for additional 24-48 h at -40 °C, the reaction mixture was diluted with aqueous saturated NH_4Cl, and extracted with ethyl acetate. The combined extracts

were dried over $MgSO_4$ and concentrated *in vacuo* to afford an oily residue, which was purified by silica-gel column chromatography.

Methyl (5*S*)-2-[(1*S*,2*S*)-2-Hydroxycycloheptan-1-yl]oxy-5-methyl-1-cyclopenten-1-carboxylate (75A)

Colorless oil, 85% yield (89% d.e.).^{13}C-NMR($CDCl_3$) δ 168.9 (s), 166.1 (s), 113.0 (s), 87.3 (d), 75.2 (d), 50.8 (q), 36.0 (d), 31.6 (t), 30.9 (t), 30.2 (t), 28.3 (t), 26.8 (t), 22.3 (t), 22.1 (t), 20.7 (q); $[\alpha]_D^{24}$ +151.8° ($CHCl_3$, c=0.79).

Methyl (5*R*)-2-[(1*S*,2*S*)-2-Hydroxycycloheptan-1-yl]oxy-5-*tert*-butyl-1-cyclopenten-1-carboxylate (76A, major)

Colorless oil, 75.1% yield.^{13}C-NMR($CDCl_3$) δ 169.4 (s), 166.7 (s), 110.1 (s), 87.1 (d), 75.0 (d), 50.8 (d), 50.7 (q), 36.3 (s), 31.7 (t), 31.6 (t), 30.7 (t), 26.9 (t), 23.6 (t), 22.2 (t), 22.1 (t), 27.3 (q); $[\alpha]_D^{28}$ +144.5° ($CHCl_3$, c=0.92).

Methyl (5*S*)-2-[(1*S*,2*S*)-2-Hydroxycycloheptan-1-yl]oxy-5-*tert*-butyl-1-cyclopenten-1-carboxylate (76A', minor)

Colorless oil, 7.8% yield.^{13}C-NMR($CDCl_3$) δ 168.1 (s), 167.7 (s), 110.5 (s), 87.2 (d), 75.6 (d), 51.2 (d), 50.8 (q), 36.0 (s), 31.5 (t), 31.0 (t), 30.9 (t), 26.8 (t), 24.2 (t), 22.3 (t), 22.1 (t), 27.3 (q); $[\alpha]_D^{27}$ +100.5° ($CHCl_3$, c=1.67).

Methyl (5*R*)-2,5-Diphenyl-1-cyclopenten-1-carboxylate (77B)

Colorless oil, 69% yield (93% e.e.).^{13}C-NMR($CDCl_3$) δ 166.4 (s), 153.3 (s), 144.9 (s), 136.5 (s), 132.3 (s), 128.4 (d), 128.2 (d), 127.9 (d), 127.7 (d), 127.1 (d), 126.3 (d), 53.7 (d), 51.1 (q), 28.4 (t), 22.9 (t); $[\alpha]_D^{25}$ -55.8° ($CHCl_3$, c=1.25).

Methyl (5*R*)-2,5-di-*n*-Butyl-1-cyclopenten-1-carboxylate (78B)

Colorless oil, 81% yield (81% e.e.).^{13}C-NMR($CDCl_3$) δ 166.8 (s), 159.1 (s), 131.3 (s), 50.7 (q), 46.1 (d), 36.4 (t), 33.7 (t), 30.3 (t), 29.9 (t), 29.7 (t), 27.7 (t), 22.9 (t), 22.8 (t), 14.1 (q), 14.0 (q); $[\alpha]_D^{24}$ +15.0° ($CHCl_3$, c=1.10).

Methyl (5*R*)-2,5-di-*n*-Butyl-1-cyclohexen-1-carboxylate (79B)

Colorless oil, 79% yield (63% e.e.).^{13}C-NMR($CDCl_3$) δ 170.6 (s), 145.1 (s), 130.3 (s), 51.0 (q), 35.2 (d), 35.3 (t), 33.9 (t), 30.9 (t), 30.4 (t), 29.5 (t), 26.5 (t), 22.8 (t), 22.8 (t), 19.2 (t), 14.1 (q), 14.0 (q); $[\alpha]_D^{26}$ -29.0° ($CHCl_3$, c=1.00).

Methyl (5*R*)-2-*n*-Butyl-5-*tert*-butyl-1-cyclopenten-1-carboxylate (80)

Colorless oil, 89% yield (>99% e.e.). ^{13}C-NMR($CDCl_3$) δ 168.4 (s), 157.1 (s), 130.2 (s), 56.5 (d), 50.7 (q), 37.0 (t), 35.8 (s), 30.4 (t), 29.8 (t), 25.7 (t), 22.8 (t), 27.4 (q), 13.9 (q); $[\alpha]_D^{25}$ -28.6° ($CHCl_3$, c=0.90).

Deprotection of 75A and 76A

Methyl (3*S*)-3-*tert*-butyl-2-oxo-cyclopentane-1-carboxylate and methyl (3*S*)-3-methyl-2-oxo-cyclopentane-1-carboxylate were obtained as a colorless oil by a similar manner to that described for the preparation of **63** and **69**.

Methyl (3*S*)-3-Methyl-2-oxo-cyclopentane-1-carboxylate

92 % yield. ^{1}H-NMR ($CDCl_3$) δ 3.77 (3H, s), 2.79 (1H, d, *J*=11 Hz), 2.71-2.15 (4H, m), 1.50 (1H, m), 1.19 (3H, d, *J*=7 Hz); Ms m/z (EI) 156 (M^+), 141, 128, 125; IR (neat, cm^{-1}) 1750, 1725; $[\alpha]_D^{27}$ -89.7° ($CHCl_3$, c=0.7).

Methyl (3*S*)-3-*tert*-Butyl-2-oxo-cyclopentane-1-carboxylate

98 % yield. ^{1}H-NMR ($CDCl_3$) δ 3.74 (3H, s), 3.04 (1H, d, *J*=12 Hz), 2.65-1.98 (4H, m), 1.55 (1H, m), 0.92 (9H, s, *J*=7 Hz); Ms m/z (EI) 198 (M^+), 141, 109; IR (neat, cm^{-1}) 1760, 1735; $[\alpha]_D^{25}$ -98.6° (c=1.03, $CHCl_3$).

(3*S*)-*tert*-Butylcyclopentanone (*S*)-83

A mixture of methyl (3*S*)-3-*tert*-butyl-2-oxo-cyclopentane-1-carboxylate (100 mg, 0.5 mmol), NaCN (272 mg, 4 mmol) in DMSO (5 ml) was heated at 110-120°C for 6 h. The reaction mixture was diluted with brine, and extracted with CH_2Cl_2. The extracts were dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel. The fraction eluted with 40:1 hexane/ethyl acetate afforded **(*S*)-83** as a colorless oil.
57% yield. $[\alpha]_D^{26}$ -172.7° (c=0.74, $CHCl_3$).

(3*S*)-3-*tert*-Butyl-1,1-[(*R,R*)-butane-1,2-dioxy]cyclopentane (84)

A mixture of methyl (3*S*)-3-methyl-2-oxo-cyclopentane-1-carboxylate (100 mg, 0.5 mmol), 10% HCl (3 ml) and THF (6 ml) was heated at 80°C for 6 h, the reaction mixture was diluted with brine, and extracted with CH_2Cl_2. The extracts were dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel. The fraction eluted with 2:1 hexane/ether afforded **(*S*)-82** as a colorless oil. **84** was obtained as a colorless oil by a similar manner to that described for preparation of acetals **(73** and **74).** 50%

yield. ^{1}H-NMR ($CDCl_3$) δ 4.22 (2H, m), 2.27-1.74 (7H, m), 1.25 (3H, d, *J*=6 Hz), 1.24 (3H, d, *J*=6 Hz), 1.01 (3H, d, *J*=6 Hz); Ms m/z (EI) 170 (M^+), 141, 127.

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