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SYNTHESIS OF 1,3-DIOXIN-4-ONES HAVING CHIRAL HYDROXYALKYL GROUPS AT THE 6-POSITION BY MEANS OF BAKER'S YEAST REDUCTION AND THEIR USES FOR EPC SYNTHESIS[1,2]

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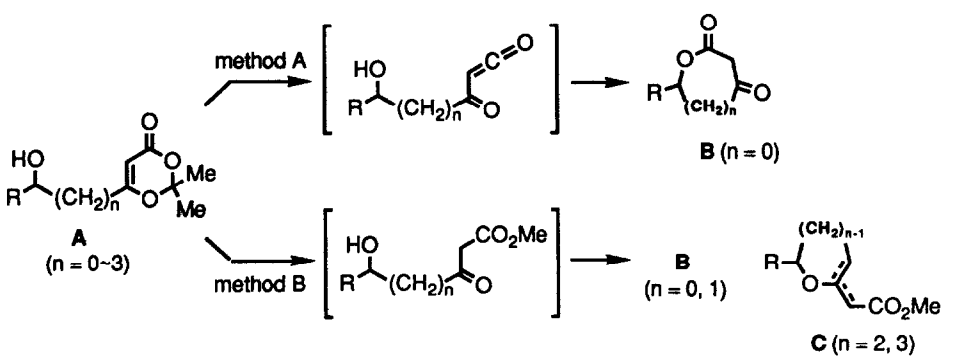
Abstract: Prochiral methyl ketones connected with 6-(4-oxo-1,3-dioxinyl) group directly or through methylene chain (1-3) gave, by treatment with fermenting baker's yeast, the corresponding (S)-alcohols which served as synthons for a variety of enantiomerically pure compounds.

Introduction

In the previous paper,[1] we have reported two different methods for the synthesis of lactones (**B**) and/or cyclic ethers (**C**) from 1,3-dioxin-4-ones having 1- ∿ 4-hydroxyalkyl group at the 6-position (**A**: n=0-3).



Scheme 1. Method A: toluene, Δ; method B: K_2CO_3 / MeOH

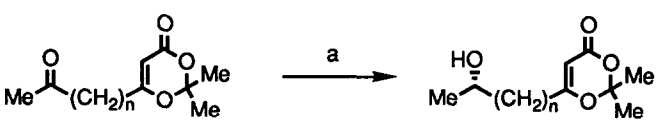
Keeping in mind that a dioxinone ring is also manipulatable in a variety of ways,[3] it seems to be an important project to find a new and efficient method to prepare the chiral alcohols (**A**). Though several papers dealing with this kind of researches have been reported, necessary uses of chiral dioxinones (e.g. an optically active 2-tert-butyl-1,3-dioxin-4-one derived from (R)-3-hydroxybutyric acid) as the starting materials and unsatisfactory diastereomeric excesses observed for the reactions employed made the methods far from ideal.[4,5]

We have reported in a communication form[5] that methyl ketone group connected with 6-(4-oxo-1,3-dioxinyl) group through methylene chain could be reduced to the corresponding alcohol (**A**: n=0-2) by fermenting baker's yeast and reasoned the high enantiomeric excesses of the reactions by marked steric requirement of the dioxinone ring.[6,7] Since the reduction by baker's yeast is simple to handle and extendable to a large scale, we applied this biochemical reduction to prepare the higher methylene homologue (**A**: n=3) as well as several new derivatives of **A**.

This paper reports in detail the baker's yeast mediated reduction of the dioxinones having 1- ∿ 4-oxoalkyl groups at the 6-position (**1-4**) to the corresponding alcohols (**5-8**), determination of both enantiomeric excesses (e.e.s) of the reactions and absolute structures of the products, and uses of these alcohols to the EPC (enantiomerically pure compounds) synthesis of some natural products. The results of these bioreductions using some related prochiral ketones are reported at the same time.

Results and Discussion

Reduction with baker's yeast——The prochiral methyl ketones (**1-4**) having 6-(4-oxo-1,3-dioxinyl) groups as the terminal units were prepared accord-



	n
1	0
2	1
3	2
4	3

	n
5	0
6	1
7	2
8	3

Scheme 2. a: baker's yeast, 32 °C

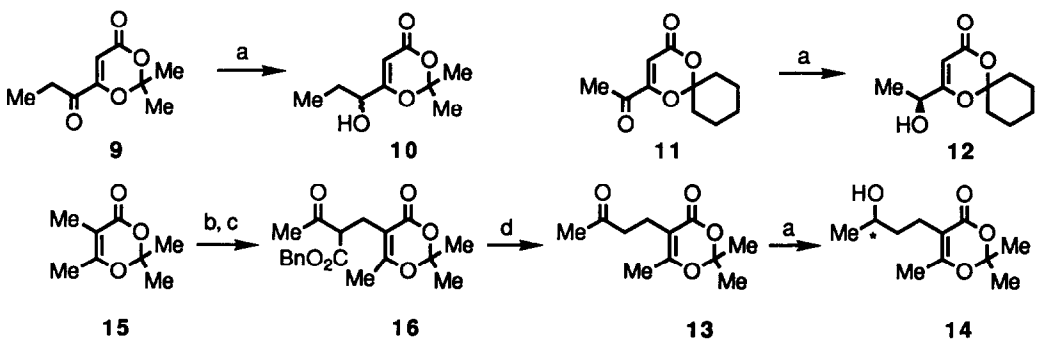
Table 1. Bioreduction of 6-Oxoalkyl-1,3-dioxin-4-ones (1 - 4) with Fermenting Yeast

Compd	n	Reaction time / d	Yield (%)	$[\alpha]_D^{\circ}$ ($CHCl_3$)	e.e. (%)	Absolute config.
1	0	1	90	-5.4	91	*S*
2	1	2	44 (55)[a]	+25.2	90	*S*
3	2	2	58 (97)[a]	+16.8	>99[b]	*S*
4	3	2	15 (64)[a]	+5.8	94	*S*

a) Yields in parenthesis are based on the consumed ketones.
b) No other enantiomer could be detected.

ing to the methods described in the precedent paper.[1] These ketones, when subjected to baker's yeast reduction, gave the expected alcohols (5-8).

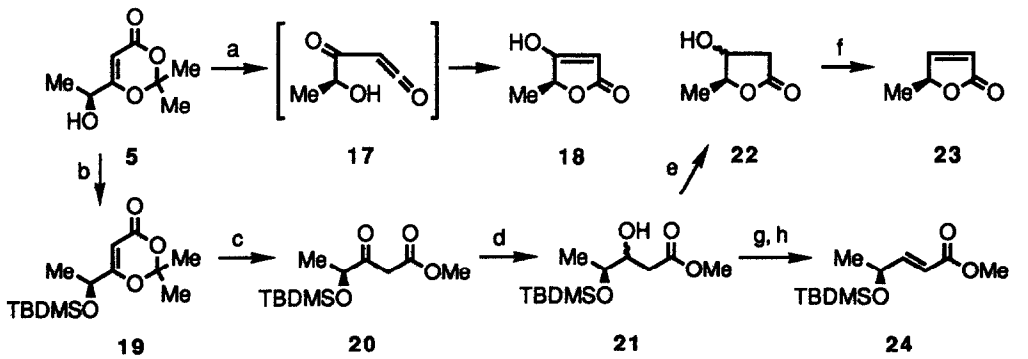
E.e.s of these reactions (determined by 500 MHz ^{1}H-NMR analysis of the corresponding MTPA-esters) were all high and the results are summarized in Table I. The absolute structures of the products were determined by their conversions to the known chiral compounds (vide infra). The following experiments were carried out in order to clarify the scope of this bioreduction: 1) When **9** was used, e.e. of the product (**10**) became much lower (43%). 2) Using **11**, e.e. became almost 100% (no other enantiomer



Scheme 3. a: baker's yeast, 32 °C; b: NBS, AIBN, *hν*; c: $CH_3COCH_2CO_2Bn$, NaH, DMF; d: H_2/Pd-C

could be detected by the 500 MHz NMR of the corresponding Mosher ester), and 3) The fact that 13 was also reduced by baker's yeast in almost 100% e.e. shows that the dioxinylethyl group is especially fitted to highly enantioselective reduction by this organism, irrespective of the position of the dioxinone ring.

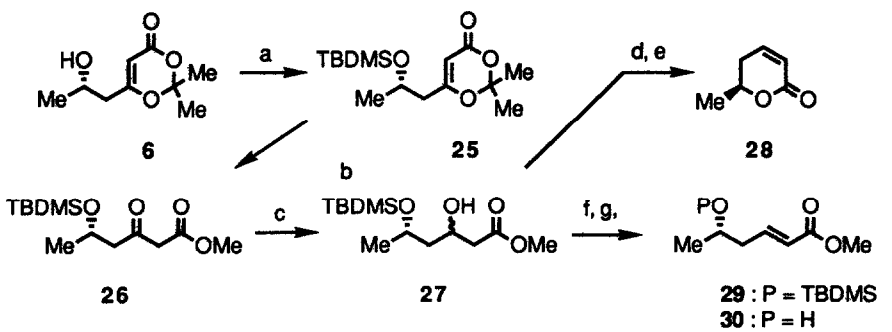
Determination of absolute structures of the products and their uses for the synthesis of natural products——The reactions of 5 derived from 1 are summarized in Scheme 4. Almost all of these reactions were already carried out in racemic series and the results were published in the original paper.[8] As expected, all reactions proceeded exactly the same as those in racemic series and, due to mild reaction conditions employed, no racemization was observed in all steps.



Scheme 4. a: toluene, Δ; b: TBDMSCl, imidazole, DMF; c: toluene-MeOH, Δ; d: $NaBH_4$, MeOH; e: *n*-$Bu_4N^+F^-$, THF; f: MsCl, Et_3N; g: MsCl, pyridine; h: DBU, benzene, Δ

Since (S)-(+)-γ-methyltetronic acid (18)[9] and (+)-β-angelica lactone (23)[10] were obtained, it is obvious that 5 has (S)-configuration.

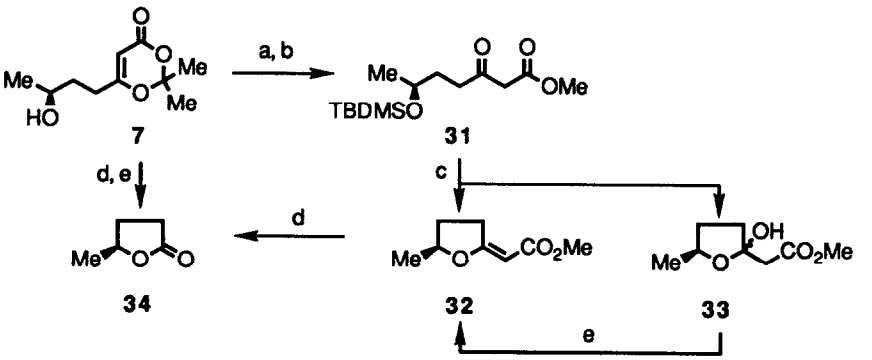
In Scheme 5, the transformations from 6 are summarized. Successful conversion of 6 to (S)-(+)-parasorbic acid (28)[11] showed that it has also (S)-configuration. Thus, it is evident that 30 has (S)-structure. This



Scheme 5. a: TBDMSCl, imidazole, DMF; b: toluene-MeOH, Δ; c: $NaBH_4$, MeOH; d: *n*-$Bu_4N^+F^-$, THF; e: *p*-TsOH, benzene, Δ; f: MsCl, pyridine; g: DBU, benzene, Δ

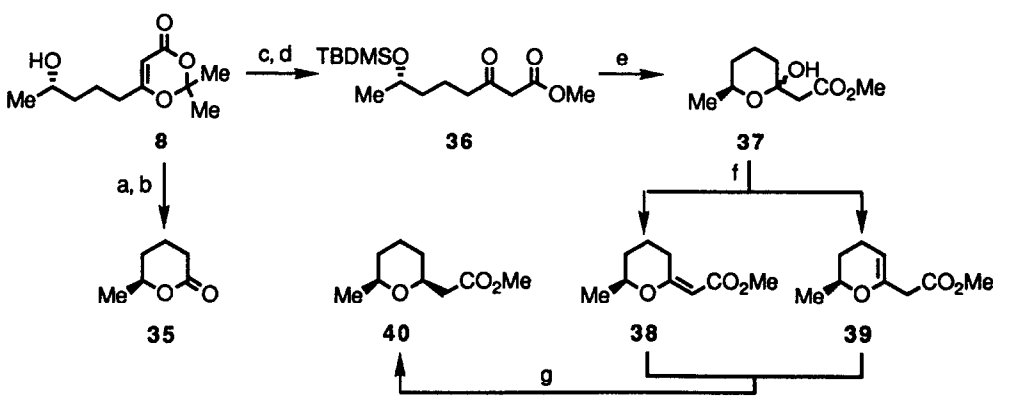
ester (30) was used previously as EPC synthesis of colletodiol through inversion of the alcohol function by Mitsunobu method.[12]

As reported in the precedent paper,[1] racemic 7 was converted into the tetrahydrofuran derivative (32). The same reactions using optically active 7 also proceeded smoothly to give the corresponding ester (32) as an EPC. Ozonolysis of 32 afforded γ-lactone (34).[13] The same lactone was also obtained by direct ozonolysis of 7 and subsequent acid-catalyzed lactonization.



Scheme 6. a: TBDMSCl, imidazole, DMF; b: toluene-MeOH, Δ; c: aq. AcOH, THF; d: O_3, MeOH, -78 °C, then Me_2S; e: *p*-TsOH, benzene

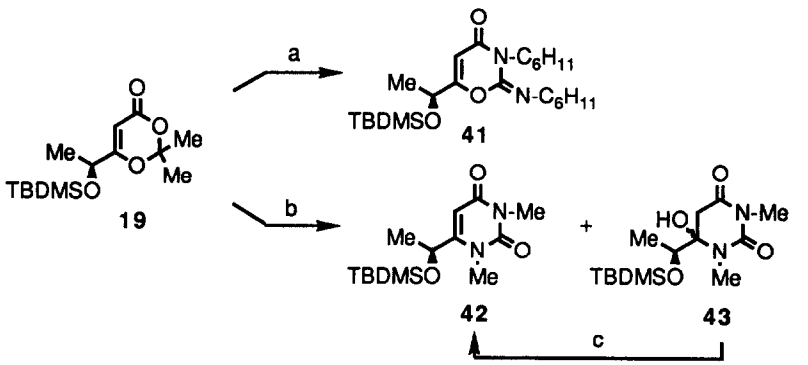
The same conversion of 8 to δ-lactone (35)[14] was also realized. The cyclic ether (40),[15] a component contained in the glandular secretion of



Scheme 7. a: O_3, MeOH, -78 °C, then Me_2S; b: *p*-TsOH, benzene, Δ; c: TBDMSCl, imidazole, DMF; d: toluene-MeOH, Δ; e: aq. AcOH, THF; f: *p*-TsOH, benzene; g: H_2/Pd-C

civet cat, was synthesized as an EPC as shown in Scheme 7. The identity of specific rotation data (sign and magnitude) of these two products with those of the respective natural products demonstrated that the reduction of **4** again proceeded with high e.e. to give (S)-alcohol (**8**).

EPC Synthesis of six-membered heterocycles having a 1-hydroxyethyl group at the 6-position——Due to facile 6π-electrocyclic ring opening to the acylketene species, the dioxinone ring could serve as alternatives for a variety of heterocycles. Knowing that the yeast-mediated reduction of heterocycles carrying an acetyl group gave in general poor results,[16]



Scheme 8. a: DCC, toluene, Δ; b: $(MeHN)_2CO$, toluene, Δ; c: *p*-TsOH, benzene, Δ

manipulation of the dioxinone ring in **5** to oxazine and uracil rings was examined. Thus, the protected alcohol (**19**), when refluxed in toluene containing dicyclohexylcarbodiimide (DCC), afforded the oxazine (**41**) in 88% yield.

By the use of N,N'-dimethylurea instead of DCC in the above reaction, the uracil (**42**) and its hydrated derivative (**43**) were obtained in 20% and 70% yields, respectively. It is obvious that the latter product was the primary product, hence it is the cyclized tautomer of the product formed from the acylketene species (cf. 17) derived from **19** and the urea. The dehydration of **43** to **42** was accomplished in a high yield by heating the former in benzene containing a small amount of p-toluenesulphonic acid.

Conclusion

6-Oxoalkyl-1,3-dioxin-4-ones were found to be reduced by fermenting baker's yeast in high enantioselectivities, so long as methyl group

attached directly to the carbonyl group. It should be noted that even if two methylene unit is present as in 3, e.e. of the reduction is almost 100%. The same e.e. was also observed when one used the isomeric ketone (13). This showed that the enzyme responsible to this reduction fits well with these dioxinones especially when acetyl and dioxinyl groups are connected by two methylene units.

Chiral alcohols having the dioxinone ring at the terminal unit served as synthons for EPC in two ways: 1) synthesis of chiral lactones and related compounds and 2) synthesis of chiral alcohols containing a variety of heterocyclic rings. The thorough researches of this laboratory so far done in racemic series[3] indicate that these two lines of works in a chiral series are very prospecive and applicable to the synthesis of a variety of EPC which are not included in this paper.[17]

Experimental Section

All physical data were measured as described in the preceding paper.[1]

6-Acetyl-2,2-dimethyl-1,3-dioxin-4-one (1)

PCC (414 mg, 1.92 mmol) was added to a solution of 6-(1-hydroxyethyl)-2,2-dimethyl-1,3-dioxin-4-one[8] (110 mg, 0.64 mmol) in CH_2Cl_2 (3 ml) under ice-cooling. The reaction mixture was stirred for 30 min at the same temperature and further for 15 h at room temperature. The whole was once passed through a short silica gel column (elution by CH_2Cl_2) to remove a tarry insoluble material. After evaporation of CH_2Cl_2 *in vacuo*, the residue was purified by silica gel column chromatography (hexane:AcOEt= 10:1) to give colorless needles **1** (90 mg, 83%). mp 55.5-57 °C (hexane-ether). *Anal*. Calcd for $C_8H_{10}O_5$: C, 56.45; H, 5.93. Found: C, 56.41; H, 5.64. IR ($CHCl_3$): 1735, 1720(sh), 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.77 (6H, s, Me x 2), 2.39 (3H, s, COMe), 6.05 (1H, s, C_5-H).

Prochiral Ketones (2-4)

Prochiral ketones (**2-4**: n=1-3) were prepared according to the procedure reported in the precedent paper.[1]

General Procedure of Bioreduction with Baker's Yeast

A mixture of baker's yeast (Oriental Yeast Co.; 10 g), sucrose (5 g), and water (15 ml) was shaken at 32 °C for 30 min and prochiral ketone (**1-4**) (100 mg) was added. The reaction mixture was shaken at the same temperature. After 12 h, baker's yeast (10 g) and sucrose (5 g) were added to this mixture and the resulting mixture was shaken for additional 12 h. Most of water was evaporated *in vacuo*. Salt (*ca*. 5 g) and celite (*ca*. 5

g) were added to the residue. The pasty mixyure was extracted repeatedly with CH_2Cl_2. The combined extracts were dried over anhydrous $MgSO_4$ and then evaporated. The residue was purified by silica gel column chromatography (hexane:AcOEt= 5:1).

(S)-6-(1-Hydroxyethyl)-2,2-dimethyl-1,3-dioxin-4-one (5)

According to the general procedure, prochiral ketone (1) was reduced with baker's yeast to give alcohol **5**. Colorless oil. Yield, 90%. $[\alpha]_D^{25}$ -5.4° (c=1.03, $CHCl_3$). High-resolution MS m/z Calcd $C_8H_{12}O_4$ (M^+): 172.0735. Found: 172.0725. IR ($CHCl_3$): 3450, 1725, 1635 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, d, J=6.6 Hz, CHMe), 1.71 (6H, s, Me x 2), 3.18 (1H, br s, OH), 4.30 (1H, q, J= 6.6 Hz, OCH), 5.54 (1H, s, C_5-H).

(S)-6-(2-Hydroxypropyl)-2,2-dimethyl-1,3-dioxin-4-one (6)

According to the general procedure, prochiral ketone (2) was reduced with baker's yeast to give alcohol **6**. Colorless oil. Yield, 41% (55%; based on the consumed ketone). $[\alpha]_D^{23}$ +25.2° (c=1.20, $CHCl_3$). High-resolution MS m/z Calcd $C_9H_{14}O_4$ (M^+): 186.0891. Found: 186.0897. IR ($CHCl_3$): 1725, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, d, J=6.0 Hz, CHMe), 1.69 (6H, s, Me x 2), 2.37 (2H, d, J= 7.0 Hz, CH_2), 2.51-3.01 (1H, br s, OH), 3.77-4.44 (1H, m, CHOH), 5.33 (1H, s, C_5-H).

(S)-6-(3-Hydroxybutyl)-2,2-dimethyl-1,3-dioxin-4-one (7)

According to the general procedure, prochiral ketone (3) was reduced with baker's yeast to give alcohol **7**. Colorless oil. Yield, 23% (33%; based on the consumed ketone). $[\alpha]_D^{22}$ +16.8° (c=1.05, $CHCl_3$). High-resolution MS m/z Calcd $C_{10}H_{17}O_4$ (M^++1): 201.1126. Found: 201.1130. IR ($CHCl_3$): 3450, 1715, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, d, J=6.4 Hz, CHMe), 1.69 (6H, s, Me x 2), 2.05-2.62 (5H, m, OH, CH_2CH_2), 3.85 (1H, q, J=6.4 Hz, CHOH), 5.67 (1H, s, C_5-H).

(S)-6-(4-Hydroxypentyl)-2,2-dimethyl-1,3-dioxin-4-one (8)

According to the general procedure, prochiral ketone (4) was reduced with baker's yeast to give alcohol **8**. Colorless oil. Yield, 15% (64%; based on the consumed ketone). $[\alpha]_D^{27}$ +5.8° (c=1.75, $CHCl_3$). High-resolution MS m/z Calcd $C_{11}H_{19}O_4$ (M^++1): 215.1282. Found: 215.1274. IR ($CHCl_3$): 3500, 1715, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, d, J=6.2 Hz, CHMe), 1.20-1.90 (4H, m, CH_2CH_2), 1.68 (6H, s, Me x 2), 1.90-2.50 (3H, m, OH, $C{=}CCH_2$), 3.52-4.26 (1H, m, CHOH), 5.24 (1H, s, C_5-H).

2,2-Dimethyl-6-(1-oxopropyl)-1,3-dioxin-4-one (9)

Prochiral ketone (9) was prepared from the corresponding alcohol (racemic **10**) by the PCC oxidation mentioned above (74% yield). This race-

mic alcohol was prepared from 2,2-dimethyl-6-propyl-1,3-dioxin-4-one by the three-step procedure[7] (bromination under irradiation, substitution by acetoxyl group, and then hydrolysis). **9**: colorless oil. High-resolution MS m/z Calcd $C_6H_6O_3$ (M^+-Me_2CO): 126.0317. Found: 126.0293. IR ($CHCl_3$): 1730, 1720(sh), 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.14 (3H, d, J=7.0 Hz, $CH_2\underline{Me}$), 1.76 (6H, s, Me x 2), 2.79 (2H, q, J=7.0 Hz, $C\underline{H}_2Me$), 6.03 (1H, s, C_5-H).

6-(1-Hydroxypropyl)-2,2-dimethyl-1,3-dioxin-4-one (10)

According to the general procedure, prochiral ketone (**9**) was reduced with baker's yeast to give alcohol **10**. Colorless oil. Yield, 53%. $[\alpha]_D^{20}$ +7.5° (c=3.40, $CHCl_3$). High-resolution MS m/z Calcd $C_9H_{14}O_4$ (M^+): 186.0892. Found: 186.0920. IR ($CHCl_3$): 3420, 1725, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, t, J=7.0 Hz, $CH_2\underline{Me}$), 1.60-1.90 (2H, m, $C\underline{H}_2Me$), 1.70 (6H, s, Me x 2), 3.27 (1H, br s, OH), 4.12 (1H, t, J=7.0 Hz, OCH), 5.55 (1H, s, C_5-H).

2-Acetyl-4-oxo-1,5-dioxaspiro[5.5]undec-2-one (11)

Prochiral ketone (**11**) was prepared from the corresponding alcohol (racemic **12**) by PCC oxidation (81% yield). This racemic alcohol was prepared from 2-ethyl-4-oxo-1,5-dioxaspiro[5.5]undec-2-ene[8] by the three-step procedure mentioned above. **11**: colorless oil. High-resolution MS m/z Calcd $C_{11}H_{14}O_4$ (M^+): 210.0891. Found: 210.0892. IR ($CHCl_3$): 1735, 1720(sh), 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.10-2.40 [10H, m, $(CH_2)_5$], 2.41 (3H, s, Me), 6.02 (1H, s, C_5-H).

2-(1-Hydroxyethyl)-4-oxo-1,5-dioxaspiro[5.5]undec-2-ene (12)

According to the general procedure, prochiral ketone (**11**) was reduced with baker's yeast to give alcohol **12**. Colorless oil. Yield, 20%. $[\alpha]_D^{27}$ -7.4° (c=1.03, $CHCl_3$). High-resolution MS m/z Calcd $C_{11}H_{16}O_4$ (M^+): 212.1048. Found: 212.1036. IR ($CHCl_3$): 3420, 1720, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.10-2.35 [10H, m, $(CH_2)_5$], 1.41 (3H, d, J=6.4 Hz, $CH\underline{Me}$), 3.18 (1H, br s, OH), 4.30 (1H, q, J=6.4 Hz, $C\underline{H}OH$), 5.51 (1H, s, C_5-H).

5-(2-Benzyloxycarbonyl-3-oxobutyl)-2,2,6-trimethyl-1,3-dioxin-4-one (16)

A solution of 2,2,5,6-tetramethyl-1,3-dioxin-4-one[18] (**15**) (3.12 g, 0.02 mol), N-bromosuccinimide (3.56 g, 0.02 mol), and α,α'-azobisisobutyronitrile (200 mg, 1.22 mmol) in CCl_4 (200 ml) was irradiated externally with a RIKO 1 kw high-pressure mercury lamp equipped with Pyrex filter for 1 h with vigorous stirring at room temperature. The reaction mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was added to a solution of benzyl acetoacetate sodium salt [prepared

from benzyl acetoacetate (3.84 g, 0.02 mol) and NaH (0.8 g, 0.02 mol)] in DMF (20 ml) under ice-cooling. After stirring for 15 h at room temperature, ice-water was added to this reaction mixture. The whole was extracted with ether and the organic layer was dried over $MgSO_4$. After evaporation of the solvent *in vacuo*, the residue was purified by silica gel column chromatography (hexane:AcOEt= 5:1) to give colorless oil **16** (4.704 g, 68%). High-resolution MS m/z Calcd $C_{19}H_{22}O_6$ (M^+): 346.1415. Found: 346.1420. IR ($CHCl_3$): 1745, 1715, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.55 (3H, s, C_2-Me), 1.61 (3H, s, C_2-Me), 1.97 (3H, s, C_6-Me), 2.22 (3H, s, MeCO), 2.77 (2H, d, J= 7.2 Hz, C=CC$\underline{H}_2$), 4.06 (1H, t, J= 7.2 Hz, CH), 5.15 (2H, s, C$\underline{H}_2$Ph), 7.35 (5H, s, Ph).

2,2,6-Trimethyl-5-(3-oxobutyl)-1,3-dioxin-4-one (13)

A mixture of compound **16** (3.46 g, 0.01 mol), 10% Pd-C (300 mg), and MeOH (25 ml) was shaken in hydrogen under atmospheric pressure for 1 h at room temperature. After filtration to remove the catalyst, the filtrate was concentrated. The residue was purified by silica gel column chromatography (hexane:AcOEt= 4:1) to give colorless oil **13** (1.541 g, 73%). High-resolution MS m/z Calcd $C_{11}H_{16}O_4$ (M^+): 212.1048. Found: 212.1057. IR ($CHCl_3$): 1715, 1645 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.65 (6H, s, C_2-Me_2), 2.06 (3H, s, C_6-Me), 2.14 (3H, s, MeCO), 2.33-2.83 (4H, m, CH_2CH_2).

5-(3-Hydroxybutyl)-2,2,6-trimethyl-1,3-dioxin-4-one (14)

According to the general procedure, prochiral ketone (**13**) was reduced with baker's yeast to give alcohol **14** as a colorless oil. Yield, 39% (62%; based on the consumed ketone). $[\alpha]_D^{23}$ +20.1° (c=1.48, $CHCl_3$). High-resolution MS m/z Calcd $C_{11}H_{18}O_4$ (M^+): 214.1204. Found: 214.1203. IR ($CHCl_3$): 3500, 1705, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, d, J= 6.2 Hz, $\underline{Me}$CH), 1.31-1.80 (2H, m, CHC$\underline{H}_2$), 1.63 (6H, s, C_2-Me_2), 2.02 (3H, s, C_6-Me), 2.25-2.55 (2H, m, C=CC$\underline{H}_2$), 2.80 (1H, br s, OH), 3.50-4.10 (1H, m, CH).

(S)-5-Methyltetronic Acid (18)

A solution of **5** (120.4 mg, 0.7 mmol) in toluene (30 ml) was added portionwise to refluxing toluene (30 ml) over 10 min. The reaction mixture was refluxed for an additional 5 min. The solvent was evaporated off *in vacuo* and the residue was recrystallized from AcOEt to give **18** (70 mg, 88%) as prisms of mp 110-112 °C. $[\alpha]_D^{20}$ +12.9° (c=0.59, H_2O) [lit.[9] mp 109-111 °C. $[\alpha]_D^{25}$ +14.7° (c=0.193, H_2O)].

(S)-6-(1-*tert*-Butyldimethylsilyloxyethyl)-2,2-dimethyl-1,3-dioxin-4-one (19)

tert-Butyldimethylchlorosilane (868 mg, 5.76 mmol) and imidazole (392 mg, 5.76 mmol) were added to a solution of compound 5 in DMF (6 ml) under ice-cooling. After stirring for 5 h at room temperature, ice-water was added to this reaction mixture and the whole was extracted with ether. The ethereal layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane:AcOEt= 40:1) to give colorless oil **19** (1.082 g, 99%). $[\alpha]_D^{24}$ -17.1° (c=0.97, $CHCl_3$). High-resolution MS m/z Calcd $C_{14}H_{27}O_4Si$ (M^++1): 287.1677. Found: 287.1652. IR ($CHCl_3$): 1720, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.09 (6H, s, $SiMe_2$), 0.93 (9H, s, t-Bu), 1.33 (3H, d, J=6.8 Hz, CHMe), 1.68 (6H, s, Me x 2), 4.25 (1H, q, J= 6.8 Hz, CHO), 5.55 (1H, s, C_5-H).

Methyl (S)-4-tert-Butyldimethylsilyloxy-3-oxopentanoate (20)

A solution of compound **19** (474 mg, 1.66 mmol) and abs. MeOH (265 mg, 8.3 mmol) in toluene (6 ml) was refluxed for 1.5 h. After the solvent was evaporated in vacuo, the residue was purified by silica gel column chromatography (hexane:AcOEt= 30:1) to give colorless oil **20** (410 mg, 95%). $[\alpha]_D^{26}$ -0.38° (c=3.14, $CHCl_3$). High-resolution MS m/z Calcd $C_{12}H_{25}O_4Si$ (M^++1): 261.1488. Found: 261.1491. IR ($CHCl_3$): 1745, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) (keto form:enol form=ca. 14:1) δ: 0.09 (6H, s, $SiMe_2$), 0.93 (9H, s, t-Bu), 1.33 (3H, d, J=7.0 Hz, CHMe), 3.62 (2H x 14/15, s, $COCH_2$), 3.72 (3H, s, OMe), 4.22 (1H, q, J= 7.0 Hz, CHMe), 5.34 (1H x 1/15, s, C=CH), 11.94 (1H x 1/15, s, OH).

Methyl (S)-4-tert-Butyldimethylsilyloxy-3-hydroxypentanoate (21)

$NaBH_4$ (53 mg, 1.4 mmol) was added to a solution of ketoester **20** (364 mg, 1.4 mmol) in MeOH (15 ml) under ice-cooling. After stirring for 30 min at the same temperature, the solvent was evaporated in vacuo. The residue was diluted with water, neutralized by 10% HCl, and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane:AcOEt= 30:1) to give colorless oil **21** (166 mg, 45%). $[\alpha]_D^{24}$ +15.6° (c=1.87, $CHCl_3$). High-resolution MS m/z Calcd $C_{12}H_{27}O_4Si$ (M^++1): 263.1677. Found: 263.1721. IR ($CHCl_3$): 3550, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.09 (6H, s, $SiMe_2$), 0.90 (9H, s, t-Bu), 1.14 (3H, d, J=6.2 Hz, CHMe), 2.43-2.65 (2H, s, $COCH_2$), 2.80 (1H, br s, OH), 3.71 (3H, s, OMe), 3.72-4.02 (2H, m, CHOH, CHMe).

(4S)-3-Hydroxypentan-4-olide (22)

n-$Bu_4N^+F^-$ (1.0 M THF solution) (0.612 ml, 0.612 mmol) was added to a solution of hydroxyester **21** (134 mg, 0.51 mmol) in THF (3 ml) under ice-

cooling. The reaction mixture was stirred for 30 min at the same temperature and then for 30 min at room temperature. After the solvent was evaporated *in vacuo*, the residue was diluted with water and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane:AcOEt= 3:1) to give colorless oil **22** (50 mg, 85%). $[\alpha]_D^{23}$ -12.6° (*c*=1.30, $CHCl_3$). High-resolution MS *m/z* Calcd $C_5H_8O_3$ (M^+): 116.0473. Found: 116.0490. IR ($CHCl_3$): 3400, 1775 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, d, *J*=6.0 Hz, Me), 2.26 (1H, dd, *J*=18.0, 4.2 Hz, C_2-H), 2.85 (1H, dd, *J*=18.0, 6.2 Hz, C_2-H), 3.31 (1H, br s, OH), 4.02-4.32 (1H, m, C*H*CO), 4.32-4.76 (1H, m, C*H*Me).

(*S*)-(+)-β-Angelica Lactone (23)

Et_3N (523 mg, 5.17 mmol) and MsCl (355 mg, 3.1 mmol) were successively added to a solution of hydroxylactone **22** (300 mg, 2.59 mmol) in CH_2Cl_2 (10 ml) under ice-cooling. After stirring for 1 h, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with 5% HCl, then with water, and dried over $MgSO_4$. The residue obtained by evaporation of the solvent was purified by distillation to give colorless oil **23** (233 mg, 92%). bp 68 °C (3 torr). $[\alpha]_D^{22}$ +90.9° (*c*=2.6, $CHCl_3$). [lit.[10a] bp 98-100 °C (15 torr). lit.[10b] $[\alpha]_D$ +101.4° (*c*=0.64, $CHCl_3$)]. High-resolution MS *m/z* Calcd $C_5H_6O_2$ (M^+): 98.0367. Found: 98.0370. IR ($CHCl_3$): 1785, 1760, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (3H, d, *J*=7.2 Hz, Me), 5.15 (1H, ddq, *J*=7.2, 2.2, 1.8 Hz, C_4-H), 6.08 (1H, dd, *J*=6.0, 2.2 Hz, C_2-H), 7.46 (1H, dd, *J*=6.0, 1.8 Hz, C_3-H).

Methyl (*S*, *E*)-4-*tert*-Butyldimethylsilyoxypent-2-enoate (24)

MsCl (26.2 mg, 0.23 mmol) was added to a solution of hydroxyester **21** (40 mg, 0.15 mmol) in pyridine (3 ml) under ice-cooling. After stirring for 12 h at room temperature, the solvent was evaporated *in vacuo*. The residue was diluted with water and neutralized with 10% HCl. The mixture was extracted with CH_2Cl_2 and the organic layer was dried over $MgSO_4$. After evaporation of the solvent *in vacuo*, the residue was purified by silica gel column chromatography (hexane:AcOEt= 30:1) to give the mesylate (31 mg, 60%). $[\alpha]_D^{24}$ +33.8° (*c*=0.59, $CHCl_3$). High-resolution MS *m/z* Calcd $C_{12}H_{15}O_6Si$ (M^+-*t*-Bu): 283.0637. Found: 283.0664. IR ($CHCl_3$): 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.09 (6H, s, $SiMe_2$), 0.91 (9H, s, *t*-Bu), 1.17 (3H, d, *J*=6.2 Hz, CH*Me*), 1.35 (2H, d, *J*=6.2 Hz, $COCH_2$), 3.08 (3H, s, Ms), 3.75 (3H, s, OMe), 3.95-4.43 (1H, m, C*H*Me), 4.47-5.10 (1H, m, C*H*OMs).

DBU (12.4 mg, 0.08 mmol) was added to a solution of the mesylate (23

mg, 0.07 mmol) in benzene (3 ml) and the whole was refluxed for 30 min. After evaporation of the solvent *in vacuo*, the residue was diluted with water and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue obtained was purified by silica gel column chromatography (hexane:AcOEt= 30:1) to give colorless oil **24** (12 mg, 72%). $[\alpha]_D^{25}$ +4.7° (*c*=1.14, $CHCl_3$). High-resolution MS *m/z* Calcd $C_{12}H_{24}O_3Si$ (M^+): 244.1493. Found: 244.1494. IR ($CHCl_3$): 1710, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.06 (3H, s, SiMe), 0.07 (3H, s, SiMe), 0.91 (9H, s, *t*-Bu), 1.26 (3H, d, *J*=6.1 Hz, CHMe), 3.74 (3H, s, OMe), 4.45-4.47 (1H, m, CHMe), 6.01 (1H, dd, *J*=15.3, 1.84 Hz, COCH), 6.94 (1H, dd, *J*=15.6, 4.0 Hz, MeCHCH).

(*S*)-6-(2-*tert*-Butyldimethylsilyloxypropyl)-2,2-dimethyl-1,3-dioxin-4-one (25)

tert-Butyldimethylchlorosilane (226 mg, 1.5 mmol) and imidazole (102 mg, 1.5 mmol) were added to a solution of compound **6** (186 mg, 1 mmol) in DMF (2 ml) under ice-cooling. After stirring for 5 h at room temperature, ice-water was added to the mixture and the whole was extracted with ether. The ethereal layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane:AcOEt= 20:1) to give colorless oil **25** (297 mg, 99%). $[\alpha]_D^{25}$ +28.0° (*c*=2.02, $CHCl_3$). High-resolution MS *m/z* Calcd $C_{12}H_{22}O_3Si$ (M^+-Me_2CO): 242.1337. Found: 242.1313. IR ($CHCl_3$): 1725, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.06 (6H, s, $SiMe_2$), 0.89 (9H, s, *t*-Bu), 1.21 (3H, d, *J*=6.0 Hz, CHMe), 1.69 (6H, s, Me_2), 2.36 (2H, d, *J*=6.0 Hz, C=CCH_2), 4.15 (1H, tq, *J*= 6.0, 6.0 Hz, CHO), 5.29 (1H, s, C_5-H).

Methyl (*S*)-5-*tert*-Butyldimethylsilyloxy-3-oxohexanoate (26)

A solution of compound **25** (297 mg, 0.99 mmol) and abs. MeOH (47.5 mg, 1.49 mmol) in toluene (8 ml) was refluxed for 1.5 h. After the solvent was evaporated *in vacuo*, the residue was purified by silica gel column chromatography (hexane:AcOEt= 20:1) to give colorless oil **26** (219.7 mg, 81%). $[\alpha]_D^{22}$ +27.3° (*c*=1.39, $CHCl_3$). High-resolution MS *m/z* Calcd $C_9H_{17}O_4Si$ (M^+-*t*-Bu): 217.0895. Found: 217.0847. IR ($CHCl_3$): 1750, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$)(keto form:enol form=*ca.* 3:1) δ: 0.05 (6H, s, $SiMe_2$), 0.85 (9H, s, *t*-Bu), 1.16 (3H, d, *J*=6.0 Hz, CHMe), 2.26 (2H x 1/4, d, *J*=6.2 Hz, C=CCH_2), 2.38-2.94 (2H x 3/4, m, $CHCH_2$), 3.46 (2H x 3/4, s, $COCH_2CO$), 3.71 (3H, s, OMe), 3.91-4.54 (1H, m, OCH), 4.97 (1H x 1/4, s, C=CH), 11.98 (1H x 1/4, s, OH).

Methyl (5*S*)-5-*tert*-Butyldimethylsilyloxy-3-hydroxyhexanoate (27)

$NaBH_4$ (30.3 mg, 0.8 mmol) was added to a solution of ketoester **26** (219.2 mg, 0.8 mmol) in MeOH (4 ml) under ice-cooling. After stirring for 30 min at the same temperature, the solvent was evaporated *in vacuo*. The residue was diluted with water, neutralized by 10% HCl, and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane:AcOEt= 20:1) to give colorless oil **27** (198.7 mg, 90%). $[\alpha]_D^{25}$ +20.4° (*c*=2.85, $CHCl_3$). High-resolution MS *m/z* Calcd $C_9H_{19}O_4Si$ (M^+-*t*-Bu): 219.1151. Found: 219.1034. IR ($CHCl_3$): 3500, 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.11 (6H, s, $SiMe_2$), 0.92 (9H, s, *t*-Bu), 1.15 (3H, d, *J*=6.2 Hz, CH*Me*), 1.37-1.87 (3H, m, $CHCH_2CH$, OH), 2.46 (2H, d, *J*=6.2 Hz, CH_2CO_2Me), 3.71 (3H, s, OMe), 3.93-4.51 (2H, m, CH x 2).

(*S*)-(+)-Parasorbic Acid (28)

n-$Bu_4N^+F^-$ (1.0 *M* THF solution) (0.3 ml, 0.3 mmol) was added to a solution of hydroxyester **27** in THF (1 ml) under ice-cooling. The reaction mixture was stirred for 30 min at the same temperature and then for 4 h at room temperature. After the solvent was evaporated *in vacuo*, the residue was diluted with water and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane:AcOEt= 1:1) to give dihydroxyester (19.8 mg, 61%). $[\alpha]_D^{25}$ +24.1° (*c*=0.34, $CHCl_3$). High-resolution MS *m/z* Calcd $C_7H_{15}O_4$ (M^++1): 163.0969. Found: 163.0950. IR ($CHCl_3$): 3450, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (3H, d, *J*=6.0 Hz, Me), 1.45-1.75 (2H, m, $CHCH_2CH$), 2.50 (2H, d, *J*=6.4 Hz, CH_2CO_2Me), 3.75 (3H, s, OMe), 3.91-4.45 (2H, m, CH x 2).

A mixture of this diol (162 mg, 1.0 mmol) and *p*-toluenesulfonic acid (17.2 mg, 0.1 mmol) in benzene (8 ml) was refluxed for 4 h. After evaporation of the solvent, the residue was diluted with water and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue obtained was purified by silica gel column chromatography (hexane:AcOEt= 6:1) to give colorless oil **28** (90.7 mg, 81%). $[\alpha]_D^{26}$ +150.8° (*c*=0.52, EtOH). [lit.[11] $[\alpha]_D$ +160° (*c*=0.15, EtOH)].

Methyl (*S*,*E*)-5-*tert*-Butyldimethylsilyoxyhex-2-enoate (29)

MsCl (91.6 mg, 0.80 mmol) was added to a solution of hydroxyester **27** (168.4 mg, 0.61 mmol) in pyridine (3 ml) under ice-cooling. After stirring for 3 h at room temperature, the solvent was evaporated *in vacuo*. The residue was diluted with water and neutralized with 10% HCl, and then extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evapo-

rated in vacuo. The residue was purified by silica gel column chromatography (hexane:AcOEt= 20:1) to give mesylate (198.7 mg, 92%). $[\alpha]_D^{25}$ +19.4° (c=1.35, $CHCl_3$). High-resolution MS m/z Calcd $C_{10}H_{21}O_6SiS$ (M^+-t-Bu): 297.0827. Found: 297.0837. IR ($CHCl_3$): 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (6H, s, $SiMe_2$), 0.90 (9H, s, t-Bu), 1.04-1.41 (3H, m, Me), 1.79-2.20 (2H, m, $CHCH_2CH$), 2.81 (2H, d, J=6.0 Hz, CH_2CO_2Me), 3.03 (3H, s, Ms), 3.71 (3H, s, OMe), 3.82-4.26 (1H, m, C_5-H), 4.96-5.43 (1H, m, C_3-H).

A solution of this mesylate (90 mg, 0.254 mmol) and DBU (46.5 mg, 0.38 mmol) in benzene (8 ml) was refluxed for 30 min. After evaporation of the solvent in vacuo, the residue was diluted with water and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue obtained was purified by silica gel column chromatography (hexane:AcOEt= 20:1) to give colorless oil **29** (62.3 mg, 95%). $[\alpha]_D^{26}$ +7.5° (c=1.31, $CHCl_3$). High-resolution MS m/z Calcd $C_9H_{17}O_3Si$ (M^+-t-Bu): 201.0946. Found: 201.0954. IR ($CHCl_3$): 1720, 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.04 (6H, s, SiMe), 0.88 (9H, s, t-Bu), 1.16 (3H, d, J=6.1 Hz, CHMe), 2.32 (2H, m, CH_2), 3.73 (3H, s, OMe), 3.87-3.98 (1H, m, C_2-H), 5.84 (1H, dt, J=15.9, 1.2 Hz, C_3-H), 6.93-6.99 (1H, m, C_5-H).

Methyl (S,E)-5-Hydroxyhex-2-enoate (30)

n-$Bu_4N^+F^-$ (1.0 M THF solution) (0.3 ml, 0.3 mmol) was added to a solution of **29** (51.6 mg, 0.2 mmol) in THF (1 ml) under ice-cooling. The reaction mixture was stirred for 30 min at the same temperature and then for 30 min at room temperature. After evaporation of the solvent, the residue was diluted with water and extracted with AcOEt. Organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane:AcOEt= 3:1) to give colorless oil **30** (20.3 mg, 71%). $[\alpha]_D^{26}$ +16.4° (c=0.39, $CHCl_3$). [lit.[12] 5R-isomer: $[\alpha]_D$ -16.9° (c=1.05, $CHCl_3$).

Preparation of 31-33 (n=2 Series) and 36-39 (n=3 Series)

Since synthetic procedures and spectroscopic data of title compounds were reported in the preceding paper[1] in their racemic series, their specific rotation values are recorded as below.

	$[\alpha]_D^\circ$	c ($CHCl_3$)		$[\alpha]_D^\circ$	c ($CHCl_3$)
31	+20.8	1.44	**36**	+11.6	2.79
32	-51.4	1.72	**37**	-31.6	2.19
33	+5.2	1.11	**38+39**	-82.3	1.66

(S)-Pentan-4-olide (34)

(i) From **32**: A solution of **32** (156 mg, 1 mmol) in MeOH (10 ml) was

cooled to -78 C, and O_3 was passed into the solution with stirring until the spot of **32** was no longer observed on TLC (3 h). Me_2S (0.5 ml) was added to this solution at -78° C. After stirring for 1 h at the same temperature and then for 3 h at room temperature, the solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane:AcOEt= 5:1) to give colorless oil **34** (66 mg, 66%). $[\alpha]_D^{20}$ -32.8° (c=0.34, CH_2Cl_2) [R-isomer: lit.[13] $[\alpha]_D^{20}$ +30.1° (c=0.85, CH_2Cl_2)].

(ii) From **7**: Alcohol (**7**) (160 mg, 0.8 mmol) was treated with O_3 by the usual way. The residue obtained by evaporation of the solvent in vacuo was dissolved in benzene (5 ml) and TsOH (15 mg, 0.08 mmol) was added to this solution. The whole was refluxed for 20 min. After evaporation of benzene in vacuo, the residue was purified by silica gel column chromatography (hexane:AcOEt= 5:1) to give colorless oil **34** (58.4 mg, 73%).

(S)-Hexan-5-olide (35)

According to the above procedure (ii), lactone **35** was prepared from **8** in 65% yield. $[\alpha]_D^{24}$ -40.0° (c=0.39, EtOH) [lit.[14] $[\alpha]_D^{24}$ -40.0° (c=1.0, EtOH)].

Methyl (S,S)-cis-6-Methyltetrahydropyran-2-yl)acetate (40)

A mixture of **38** and **39** (85 mg, 0.05 mol) was hydrogenated over 10% Pd-C (15 mg) in AcOEt (2 ml) under atmospheric pressure for 15 h at room temperature. After filtration to remove the catalyst, the filtrate was concentrated. The residue was purified by silica gel column chromatography (hexane:AcOEt= 20:1) to give colorless oil (**40**) (72.2 mg, 84%). $[\alpha]_D^{24}$ +31.6° (c=1.76, benzene) [lit.[15b] $[\alpha]_D^{22}$ +32.86° (c=1.05, benzene); lit.[15c] $[\alpha]_D$ +41.2° (benzene)].

Reaction of Compound 19 with DCC

A solution of **19** (143 mg, 0.5 mmol) and DCC (103 mg, 0.5 mmol) in toluene (5 ml) was refluxed for 20 min. After evaporation of the solvent, the residue was purified by silica gel column chromatography (hexane:AcOEt= 7:1) to give colorless oil **41** (190 mg, 88%). $[\alpha]_D^{26}$ -13.7° (c=1.62, $CHCl_3$). High-resolution MS m/z Calcd $C_{24}H_{42}O_3N_2Si$ (M^+): 434.2962. Found: 434.3000. IR ($CHCl_3$): 1685, 1640 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.09 (6H, s, $SiMe_2$), 0.93 (9H, s, t-Bu), 1.08-1.89 (22H, m, cyclohexyl), 1.39 (3H, d, J=6.6 Hz, CHMe), 4.30 (1H, q, J=6.6 Hz, CHMe), 5.61 (1H, s, C_5-H). UV λ_{max} (MeOH) nm: 205.

Reaction of Compound 19 with N,N'-Dimethylurea

A solution of **19** (143 mg, 0.5 mmol) and N,N'-dimethylurea (44 mg, 0.5 mmol) in toluene (5 ml) was refluxed for 20 min. After evaporation of the

solvent, the residue was purified by silica gel column chromatography (hexane:AcOEt= 7:1) to give colorless oil **42** (30 mg, 20%). $[\alpha]_D^{26}$ -33.5° (c=3.76, $CHCl_3$). High-resolution MS m/z Calcd $C_{14}H_{26}O_3N_2Si$ (M^+): 298.1711. Found: 298.1695. IR ($CHCl_3$): 1700, 1660, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.10 (6H, s, $SiMe_2$), 0.93 (9H, s, t-Bu), 1.14 (3H, d, J=6.8 Hz, CHMe), 3.37 (3H, s, NMe), 3.48 (3H, s, NMe), 4.70 (1H, q, J=6.8 Hz, CHMe), 5.88 (1H, s, C_5-H). UV λ_{max} (MeOH) nm: 265, 205.

Elution with the same solvents gave colorless oil **43** (110 mg, 70%). $[\alpha]_D^{26}$ -0.45° (c=5.73, $CHCl_3$). High-resolution MS m/z Calcd $C_{10}H_{19}O_4N_2Si$ (M^+): 259.1114. Found: 259.1127. IR ($CHCl_3$): 3350, 1710, 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.09 (6H, s, $SiMe_2$), 0.88 (9H, s, t-Bu), 1.24 (3H, d, J=6.2 Hz, CHMe), 2.70 (1H, d, J=16.8 Hz, CH_2), 3.03 (3H, s, NMe), 3.12 (1H, d, J=16.8 Hz, CH_2), 3.14 (3H, s, NMe), 3.99 (1H, q, J=6.2 Hz, CHMe), 4.58 (1H, br s, OH).

Dehydration of 43 to 42

A mixture of **43** (259 mg, 1 mmol) and TsOH (19 mg, 0.1 mmol) in benzene (10 ml) was refluxed for 30 min. After evaporation of the solvent, the residue was diluted with water and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated off in vacuo. The residue was purified by silica gel column chromatography (hexane:AcOEt= 7:1) to give **42** (259 mg, 87%).

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