Asymmetric Synthesis by the Intramolecular Haloetherification Reaction of Ene Acetal: Discrimination of Prochiral Dienes in Cyclohexane Systems

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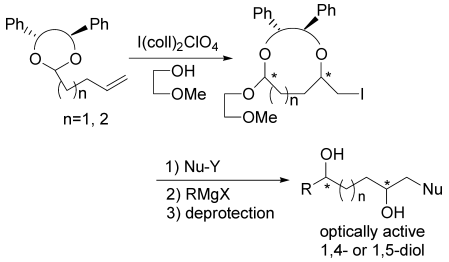
Received March 10, 2005; accepted May 7, 2005; published online May 13, 2005

A novel asymmetric synthesis of the cyclohexane derivative functionalized by some substituents has been developed from the diene acetals (1), prepared from the corresponding diene aldehyde and (+)-hydrobenzoin. The treatment of 1 with NBS in the presence of $MeOCH_2CH_2OH$ predominantly afforded 2 in a stereoselective manner. Subsequent alkylation of the methoxyethoxy group produced the optically active cyclohexene compounds (3) in good yields. The stereoselective chemical modification of the remaining olefin in 3 was made by OsO_4-oxidation.

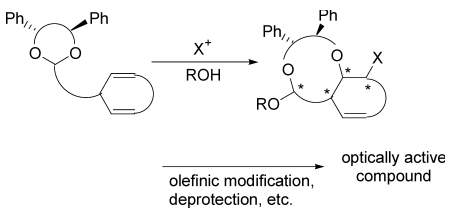
Key words desymmetrization; cyclohexa-1,4-diene; intramolecular haloetherification; (+)-hydrobenzoin; ene acetal

Asymmetric synthesis based on the desymmetrization of symmetric compounds is one of the most powerful ways to get optically pure compounds, especially for the substrates having prochiral carbon atom(s), and many methodologies by chemical reactions, for examples refs. 1—4,[1—4] and enzymatic ones, for examples refs. 5—9,[5—9] have already been developed. Recently, we have developed a new asymmetric synthesis of 1,4- and 1,5-diols from the ene aldehydes involving the intramolecular haloetherification reaction of their C_2-symmetric acetals as a key step (Eq. 1).[10,11]



(1)

We then planned to extend this methodology to the symmetric compounds with two prochiral olefins. If the reaction can successfully discriminate the diastereotopic groups and their faces, it will be quite useful for constructing optically active compounds because it can produce chiral non-racemic compounds bearing multichiral centers and the remaining olefin can be used for further transformations (Eq. 2). (For examples of discrimination of prochiral two olefinic groups by halocyclization using chiral auxiliary, see refs 12—18.)[12—18]



(2)

Based on this idea, we studied the intramolecular haloetherification reaction of cyclohexa-1,4-dienes **1** having the C_2-symmetric acetal on the side chain and found that the reaction discriminated the two prochiral olefins in a highly diastereoselective manner to give **2** as the major product (Chart 1).[19] The alkoxy group of the mixed acetals was then converted to an alkyl group. The obtained alkylated compounds **3** were subjected to several transformation reactions forming optically active cyclohexane derivatives with multichiral centers. We now present the full details of our study.

Results and Discussion

The optically active monosubstituted cyclohexadiene acetals (**1a**, **b**) were synthesized as follows (Chart 2). The cyclohexadiene acetals (**4**, **5**) were prepared from benzoic acid according to a literature procedure.[20] Their transacetalization with (+)-hydrobenzoin[21] gave **1a** and **1b** in good yields. The disubstituted cyclohexadiene acetals (**1c**, **d**) were synthesized from compound **6**, which was obtained by reductive alkylation[22] of methyl benzoate followed by reduction with DIBAL-H (Chart 3). Protection of the hydroxy group of **6** by the *tert*-butyldiphenylsilyl (TBDPS) group and selective deprotection of the resulting disilyl ether afforded **7** in good yield. The Swern oxidation[23] of **7** followed by acetalization with (+)-hydrobenzoin produced the optically active 3,3-disubstituted cyclohexadiene acetal silyl ether **1c**. The desilyla-

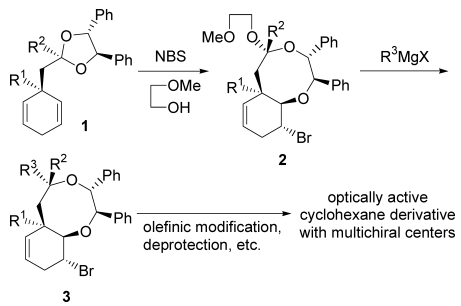


Chart 1

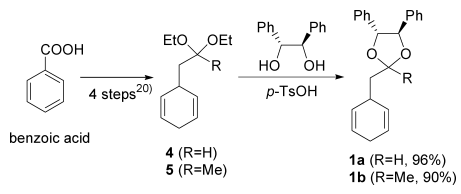


Chart 2

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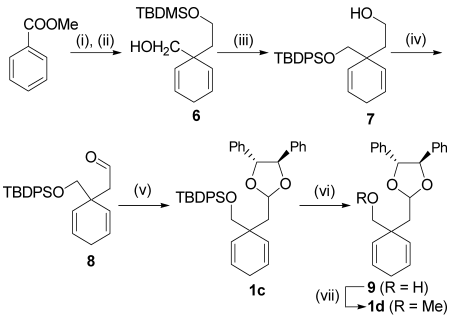
tion of **1c** followed by methylation of the resulting hydroxy group gave the methyl ether **1d**.

The haloetherification reaction of **1a** with $I(coll)_2ClO_4$, which was the best choice of an electrophile in our previous work,[10,11] in the presence of $MeOCH_2CH_2OH$ as a nucleophile in CH_2Cl_2 did not give the desired product at all (Chart 4). The only aromatic compound **10** was obtained in 43% yield. This disappointing result must be due to the basicity of 2,4,6-collidine, which coexisted with the reagent. That is, it must have worked as a base for deprotonation from the iodonium ion intermediate (**A**) before the oxygen atom of the acetal attacked the cationic part, then hydrogen iodide was eliminated *via* **B** leading to the aromatization.



(i) Li, liq.NH_3, $TBDMSOCH_2CH_2I$, (ii) DIBAL-H (67% over 2 steps), (iii) TBDPSCl, $^iPr_2EtN$ then 80% AcOH aq., reflux (81%), (iv) $(COCl)_2$, DMSO, CH_2Cl_2, then Et_3N (85%), (v) (+)-hydrobenzoin, *p*-TsOH, reflux (93%), (vi)TBAF (99%), (vii) MeI, Ag_2O (90%).

Chart 3

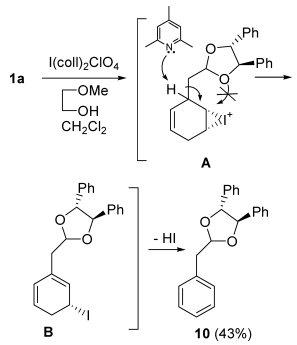


Chart 4

Therefore, we studied the reaction in detail. The results are summarized in Table 1. A change in the reaction solvent from CH_2Cl_2 to CH_3CN was not effective (entry 1). We then used *N*-iodosuccinimide (NIS), a rather more neutral reagent than $I(coll)_2ClO_4$ (entry 2). In this case, the desired product **2a** (R^1=R^2=H, X=I) was obtained as a mixture of stereoisomers, but the yield was low. When *N*-bromosuccinimide (NBS) was used as the electrophile, the reactions successfully proceeded to give **2a** (R^1=R^2=H, X=Br) having the newly formed four chiral centers and other stereoisomers in good yields with fairly good diastereoselective manners (entries 3—5). A lower reaction temperature also gave better results (entries 3 *vs.* 4) and CH_3CN was a better choice than CH_2Cl_2 in terms of chemical yield (entries 3 *vs.* 5). For the ketal **1b**, the chemical yield was pretty low due to steric hindrance of the methyl group preventing the attack of $MeOCH_2CH_2OH$ on the acetal carbon in the intermediate (**C**) (entry 6). The disubstituted cyclohexadiene acetals **1c** and **1d** reacted with NBS in a similar diastereoselective manner to give **2c** (R^1=$CH_2OTBDPS$, R^2=H, X=Br) and **2d** (R^1=CH_2OMe, R^2=H, X=Br) as the major products in fairly good yields (entries 7, 8). Mixed solvent (CH_3CN/CH_2Cl_2=4/1) was used in entry 7 due to low solubility of **1c** to CH_3CN. The stereochemistries of the major stereoisomers, **2a** and **2c**, were determined by NOE experiments (Fig. 1). The stereochemistries of the major stereoisomers, **2b** and **2d**, were deduced from the stereochemistries of **2a** and **2c**, and a mechanistic consideration (Chart 5).

The plausible reaction mechanism of the haloetherification reaction in the case of **1a** is shown in Chart 5. First, the addition of the bromonium ion to one of the double bonds followed by attack of one of the acetal oxygen atoms forms the tricyclic oxonium ion intermediates (possible intermediates

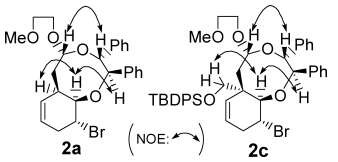
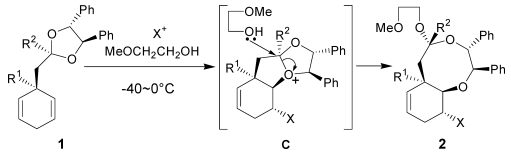


Fig. 1. NOE Experiments of **2a** and **2c**

Table 1. Haloetherification Reaction of **1**



Entry	1	Electrophile	Solvent	2	Yield (%)[a]	Selectivity[b]
1	**1a**	$I(coll)_2ClO_4$	CH_3CN	**2a** (R^1=R^2=H, X=I)	Trace	
2	**1a**	NIS	CH_3CN	**2a** (R^1=R^2=H, X=I)	39	[c]
3	**1a**	NBS	CH_3CN	**2a** (R^1=R^2=H, X=Br)	75	**76** : (**19**+**5**)
4	**1a**	NBS	CH_3CN	**2a** (R^1=R^2=H, X=Br)	54[d]	73 : (22+5)
5	**1a**	NBS	CH_2Cl_2	**2a** (R^1=R^2=H, X=Br)	41	73 : (19+8)
6	**1b**	NBS	CH_3CN	**2b** (R^1=H, R^2=Me, X=Br)	44	**79** : (**12**+**9**)
7	**1c**	NBS	CH_3CN/CH_2Cl_2 (4/1)	**2c** (R^1=$CH_2OTBDPS$, R^2=H, X=Br)	77	**82** : (**14**+**4**)
8	**1d**	NBS	CH_3CN	**2d** (R^1=CH_2OMe, R^2=H, X=Br)	76	**75** : (**17**+**8**)

a) Isolated yield involving minor isomers (≤10%). *b*) Major isomer (**2**) *vs.* minor ones. The presence of two minor isomers was detected by ^{1}H-NMR. The ratio was determined from the crude product by ^{1}H-NMR and HPLC (chiral OD). *c*) Not determined. *d*) Carried out at 0 °C.

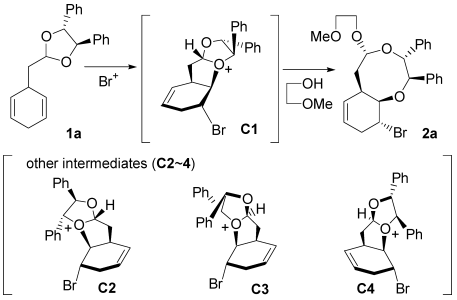


Chart 5

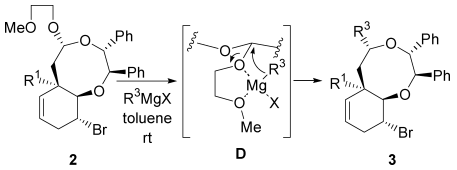


Chart 6

Table 2. Nucleophilic Replacement with Grignard Reagent

Entry	Substrate[a)]	Product	Yield (%)[b)]
1	R^1=H (**2a**)	R^3=Me (**3a**)	81
2	R^1=H (**2a**)	R^3=allyl (**3b**)	77
3	R^1=H (**2a**)	R^3=$PhCH_2CH_2$ (**3c**)	89
4	R^1=OTBDMS (**2c**)	R^3=Me (**3d**)	78

a) Substrates involving minor isomers (≤10%) were used. *b*) Isolated yield of only main isomer.

are **C1**, **C2**, **C3** or **C4**). Among the four intermediates, **C1** is most preferable because **C2** has a steric repulsion between the phenyl ring and cyclohexene ring, **C3** has repulsion between the dioxolane ring and cyclohexene ring, and **C4** has repulsion between the phenyl group and cyclohexene ring in addition to the one between the dioxolane ring and cyclohexene ring. The subsequent *SN*2-type attack of an alcohol on the intermediate **C1** would then occur to give the 8-membered mixed acetal **2a** having four newly formed chiral centers. This result fitted the experimental fact well and corresponded to the MO calculations for intermediates by SPARTAN (ver. 3.1.2) using the AM1 Hamiltonian (Energy: 165.00 kcal/mol for **C1**, 166.28 kcal/mol for **C2**, 169.90 kcal/mol for **C3**, 178.43 kcal/mol for **C4**). These results suggested that the reaction mainly proceeded via the tricyclic intermediate (**C1**).

The obtained mixed acetals **2** were converted to **3** by the Grignard reaction controlled by chelation of Mg^{2+} to two oxygen atoms of the methoxyethoxy group (Chart 6). This nucleophilic replacement reaction has already been reported to proceed in a retentive stereospecific manner.[11,12)] The results are shown in Table 2. The reactions of **2a** and **2c** with Grignard reagents afforded the alkyl substituted compounds **3a**—**d** in good yields. At this stage, **3a**—**c** were obtained with purity by recrystallization and the yields shown in Table 2 are those of the pure compounds.

Removal of the diphenylethylene unit was also examined as follows using **3a** as the substrate (Chart 7). The catalytic hydrogenolysis of **3a** smoothly proceeded to give the bromo diol **11** with four chiral centers in good yield. On the other

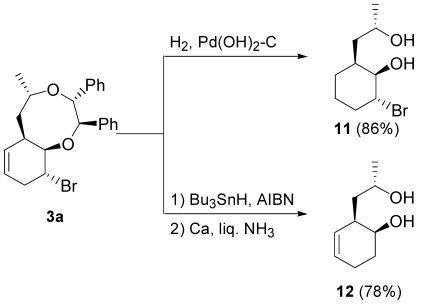


Chart 7

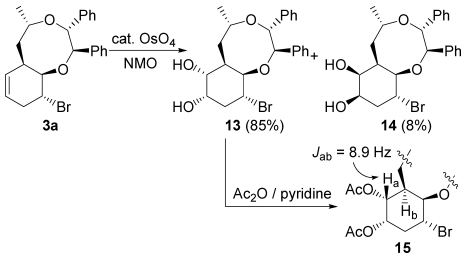


Chart 8

hand, although the Birch reduction of **3a** itself resulted in the formation of a complex mixture, the reaction of the debrominated compound obtained by the reduction with tri-*n*-butyltin hydride proceeded without any problems to afford the cyclohexene diol derivative **12** with an olefin, which can be used for further transformations.

We also examined the chemical modification of the remaining olefin. Dihydroxylation of **3a** with OsO_4 stereoselectively proceeded in high yields to produce the α-dihydroxylated compound **13** as the major product (Chart 8). The stereochemistries of **13** and **14** were determined from the coupling patterns. The methine proton H_a of compound **15**, the diacetate of **13**, appears as a dd, J=8.9 and 3.0 Hz (δ 5.40 ppm). The large coupling constant between H_a and H_b in **15** suggested the configurations of the diol as α.

In conclusion, we have developed a novel asymmetric synthesis of the cyclohexane derivatives with multichiral centers using the haloetherification reaction. Since optically active cyclohexane ring units with multichiral centers are found in many natural products, the applications of this work to their asymmetric synthesis are now under investigation.

Experimental

All melting points are uncorrected. The NMR spectra were measured using 270 and 500 MHz spectrometers with $CDCl_3$ as the solvent and with $SiMe_4$ as the internal standard. The infrared (IR) absorption spectra were recorded as a KBr pellet. All solvents were dried and distilled according to standard procedures.

Preparation of Diene Acetal (4, 5) Diene acetal (**4**) was prepared according to a known procedure.[20)] **5** was also prepared in a similar procedure.

Preparation of 1a and 1b To a solution of (+)-hydrobenzoin (1.0 mmol) and diene acetal (**4** or **5**, 1.0 mmol) in C_6H_6 (20 ml) was added a catalytic amount of *p*-toluenesulfonic acid (0.05 mmol) under a nitrogen atmosphere. The reaction mixture was refluxed for 1 h under azeotropic conditions. K_2CO_3 was added to the mixture at r.t. After stirring for 15 min, the solution was filtered through Celite and concentrated *in vacuo*. The residue was purified by SiO_2 column chromatography with hexane–AcOEt as the eluent to give the ene acetal (**1**).

(4*R*,5*R*)-2-(2,5-Cyclohexadienylmethyl)-4,5-diphenyl-1,3-dioxolane (**1a**): Eluent hexane–AcOEt (50/1); colorless oil; bp 185—195 °C (bath temp.)/0.2 mmHg; $[\alpha]_D^{25}$ +31° (c=1.0, $CHCl_3$); IR ν_{max} (KBr) 1605, 1497,

1456 cm^{-1}; ^{1}H-NMR δ 2.02 (2H, dd, J=6.7, 4.8 Hz), 2.6—2.7 (2H, m), 3.1—3.2 (1H, m), 4.77 (2H, s), 5.63 (1H, t, J=4.8 Hz), 5.7—5.9 (4H, m), 7.2—7.4 (10H, m); *Anal.* Calcd for $C_{22}H_{22}O_2$: C, 82.99; H, 6.96. Found: C, 82.93; H, 7.04.

(4*R*,5*R*)-2-(2,5-Cyclohexadienylmethyl)-2-methyl-4,5-diphenyl-1,3-dioxolane (**1b**): Eluent hexane–AcOEt (20/1); colorless oil; $[\alpha]_D^{20}$ −51° (c=0.51, $CHCl_3$); IR ν_{max} (KBr) 1605, 1497, 1456 cm^{-1}; ^{1}H-NMR δ 1.68 (3H, s), 2.05 (2H, d, J=6.3 Hz), 2.6—2.7 (2H, m), 3.1—3.3 (1H, m), 4.75 (1H, d, J=8.6 Hz), 4.78 (1H, d, J=8.6 Hz), 5.6—5.8 (2H, m), 5.8—6.0 (2H, m), 7.1—7.3 (10H, m); FAB-MS m/z 333 (M+H$^+$); FAB-HR-MS Calcd for $C_{23}H_{25}O_2$ (M+H$^+$) 333.1855, Found 333.1847.

1-(2-*tert*-Butyldimethylsilyloxyethyl)-1-hydroxymethyl-2,5-cyclohexadiene (6) To a solution of methyl benzoate (7.0 g, 51.4 mmol), MeOH (2.3 ml, 56.8 mmol) and THF (30 ml) in liq. NH_3 (300 ml) was added lithium wire (1.2 g, 170 mmol) at −78 °C under a nitrogen atmosphere. After being stirred for 10 min, $TBDMSOCH_2CH_2I$ (15.6 g, 54.5 mmol) was added at the same temperature. After additional 20 min, the reaction mixture was quenched with saturated aqueous NH_4Cl. After removal of NH_3 at r.t., the solution was extracted with AcOEt. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was dissolved in THF (100 ml). DIBAL-H (0.95 M in hexane, 118 ml) was slowly added to the mixture at −78 °C for 30 min. After being stirred for 30 min, the reaction mixture was poured into water. To the solution was added saturated aqueous NH_4Cl, then the resultant solution was extracted with AcOEt. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by SiO_2 column chromatography with hexane–AcOEt (20/1→10/1) as an eluent to give **6** (8.4 g, 67%). Colorless oil; bp 185—190 °C (bath temp.)/15 mmHg; IR ν_{max} (KBr) 3350, 1471, 1464 cm^{-1}; ^{1}H-NMR δ 0.04 (6H, s), 0.88 (9H, s), 1.58 (2H, t, J=7.0 Hz), 2.0 (1H, br s), 2.6—2.7 (2H, m), 3.3 (2H, br s), 3.62 (2H, t, J=7.0 Hz), 5.49 (2H, dt, J=10, 2.0 Hz), 5.90 (2H, dt, J=10, 3.3 Hz); MS (EI) m/z 268 (M$^+$); *Anal.* Calcd for $C_{15}H_{28}O_2Si$: C, 67.11; H, 10.51. Found: C, 67.06; H, 10.36.

1-(*tert*-Butyldiphenylsilyloxymethyl)-1-(2-hydroxyethyl)-2,5-cyclohexadiene (7) To a solution of **6** (1.4 g, 5.3 mmol) and ^{i}Pr$_2$EtN (2.0 ml) was added TBDPSCl (1.5 ml, 5.7 mmol) at 0 °C under a nitrogen atmosphere. Slowly warming to r.t., the reaction mixture was stirred for 5 h, then was poured into water. The solution was extracted with hexane for only one time. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Eighty percent aqueous acetic acid was added to the residue, and the mixture was refluxed for 2 h. The reaction mixture was directly concentrated *in vacuo*. The residue was purified by SiO_2 column chromatography with hexane–AcOEt (4/1) as an eluent to give **7** (1.7 g, 4.3 mmol, 81%). Colorless oil; IR ν_{max} (KBr) 3400, 1589, 1487, 1464 cm^{-1}; ^{1}H-NMR δ 1.05 (9H, s), 1.77 (2H, t, J=6.4 Hz), 2.6—2.7 (2H, m), 3.43 (2H, s), 3.67 (2H, t, J=6.4 Hz), 5.58 (2H, dt, J=10, 2.0 Hz), 5.85 (2H, dt, J=10, 3.6 Hz), 7.3—7.5 (6H, m), 7.6—7.7 (4H, m); FAB-MS m/z 393 (M+H$^+$); FAB-HR-MS Calcd for $C_{25}H_{33}O_2Si$ (M+H$^+$) 393.2250, Found 393.2226.

(1-*tert*-Butyldiphenylsilyloxymethyl-2,5-cyclohexadienyl) Acetaldehyde (8) To a solution of oxalyl chloride (0.35 ml, 4.0 mmol) in CH_2Cl_2 (9.0 ml) was carefully added a solution of dimethyl sulfoxide (0.57 ml, 8.0 mmol) in CH_2Cl_2 (9.0 ml) at −78 °C under a nitrogen atmosphere. After being stirred for 5 min, the reaction mixture was warmed to −20 °C. To the resulting solution was added a solution of **7** (718 mg, 1.83 mmol) in CH_2Cl_2 (10.0 ml). After being stirred for 15 min at the same temperature, the reaction mixture was cooled to −78 °C, then quenched with Et_3N (1.28 ml, 9.2 mmol). The solution was warmed to 0 °C, then poured into water. The solution was extracted with AcOEt. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by SiO_2 column chromatography with hexane–AcOEt (20/1) as an eluent to give **8** (606 mg, 85%). Colorless oil; IR ν_{max} (KBr) 1722, 1589, 1471 cm^{-1}; ^{1}H-NMR δ 1.06 (9H, s), 2.49 (2H, d, J=3.2 Hz), 2.6—2.7 (2H, m), 3.48 (2H, s), 4.67 (2H, dt, J=10, 2.0 Hz), 5.87 (2H, dt, J=10, 3.3 Hz), 7.3—7.5 (6H, m), 7.6—7.7 (4H, m), 9.66 (1H, t, J=3.2 Hz); FAB-MS m/z 391 (M+H$^+$); *Anal.* Calcd for $C_{25}H_{30}O_2Si$: C, 76.88; H, 7.74. Found: C, 76.67; H, 7.77.

(4*R*,5*R*)-2-[(1-*tert*-Butyldiphenylsilyloxymethyl-2,5-cyclohexadienyl)-methyl]-4,5-diphenyl-1,3-dioxolane (1c) **1c** was prepared by the same procedure for **1a** and **1b**. **8** (296 mg, 0.76 mmol), (+)-hydrobenzoin (162 mg, 0.76 mmol), C_6H_6 (7.5 ml), **1c** (414 mg, 93%). Eluent hexane–AcOEt (30/1); colorless oil; $[\alpha]_D^{21}$ +17° (c=1.3, $CHCl_3$); IR ν_{max} (KBr) 1605, 1497, 1456 cm^{-1}; ^{1}H-NMR δ 1.07 (9H, s), 2.16 (1H, dd, J=14, 4.6 Hz), 2.19 (1H, dd, J=14, 4.6 Hz), 2.6—2.7 (2H, m), 3.53 (2H, s), 4.68 (1H, d, J=7.3 Hz), 4.74 (1H, d, J=7.3 Hz), 5.45 (1H, t, J=4.6 Hz), 5.7—5.8 (2H, m), 5.8—5.9 (2H, m), 7.1—7.4 (16H, m), 7.6—7.7 (4H, m); FAB-MS (EI) m/z 587 (M+H$^+$); FAB-HR-MS Calcd for $C_{39}H_{43}O_3Si$ (M+H$^+$) 587.2982, Found 587.2958.

(4*R*,5*R*)-2-[(1-Hydroxymethyl-2,5-cyclohexadienyl)methyl]-4,5-diphenyl-1,3-dioxolane (9) To a solution of **1c** (507 mg, 0.86 mmol) in THF (4.3 ml) was added Bu_4NF (TBAF) (1.0 M in THF, 1.7 ml) at r.t. After being stirred for 2 h, H_2O was added to the solution. The reaction mixture was extracted with AcOEt. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by SiO_2 column chromatography with hexane–AcOEt (8/1) as an eluent to give **9** (300 mg, 99%). Colorless oil; $[\alpha]_D^{22}$ +25° (c=1.3, $CHCl_3$); IR ν_{max} (KBr) 3480, 1605, 1497, 1456 cm^{-1}; ^{1}H-NMR δ 1.8—1.9 (1H, br s), 2.02 (2H, d, J=4.5 Hz), 2.7—2.8 (2H, m), 3.50 (2H, d, J=4.6 Hz), 4.73 (1H, d, J=7.6 Hz), 4.75 (1H, d, J=7.6 Hz), 5.53 (1H, t, J=4.5 Hz), 5.6—5.7 (2H, m), 5.9—6.1 (2H, m), 7.1—7.4 (10H, m); FAB-MS m/z 349 (M+H$^+$); FAB-HR-MS Calcd for $C_{23}H_{25}O_3$ (M+H$^+$) 349.1804, Found 349.1815.

(4*R*,5*R*)-2-[(1-Methoxymethyl-2,5-cyclohexadienyl)methyl]-4,5-diphenyl-1,3-dioxolane (1d) To a solution of **9** (185 mg, 0.53 mmol) in MeI (5.3 ml) was added Ag_2O (1.23 g, 5.3 mmol) at r.t. The reaction mixture was stirred for 20 h in the dark. The solution was filtered through Celite and concentrated *in vacuo*. The residue was purified by SiO_2 column chromatography with hexane–AcOEt (20/1) as an eluent to give **1d** (173 mg, 90%). Colorless oil; $[\alpha]_D^{22}$ +32° (c=0.9, $CHCl_3$); IR ν_{max} (KBr) 1605, 1497, 1456 cm^{-1}; ^{1}H-NMR δ 2.06 (1H, dd, J=14, 4.6 Hz), 2.09 (1H, dd, J=14, 4.6 Hz), 2.6—2.8 (2H, m), 3.29 (2H, s), 3.36 (3H, s), 4.70 (1H, d, J=7.6 Hz), 4.73 (1H, d, J=7.6 Hz), 5.46 (1H, t, J=4.6 Hz), 5.6—5.8 (2H, m), 5.8—6.0 (2H, m), 7.2—7.4 (10H, m); *Anal.* Calcd for $C_{24}H_{26}O_3Si$: C, 79.53; H, 7.23. Found: C, 79.27; H, 7.19.

General Procedure for Haloetherification Reaction in Table 1 To a solution of the diene acetal **1** (1.0 mmol) and $MeOCH_2CH_2OH$ (5.0 mmol) in CH_3CN (10.0 ml) was added an electrophile (1.3 mmol) at −40 °C under a nitrogen atmosphere. The reaction mixture was allowed to warm to 0 °C, then stirred for over 4 h. The solution was quenched with saturated aqueous $Na_2S_2O_3$, then extracted with AcOEt. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by SiO_2 column chromatography with hexane–AcOEt to give the products **2** in the yields shown in Table 1. The products **2** involving impurities (≤10%) were used for the next nucleophilic substitution by Grignard reagent (Table 2). We supposed the contained impurities as minor stereoisomers by considering the fact that they show the same polarity on TLC using various developing solvent systems (hexane–AcOEt, benzene–AcOEt, CH_2Cl_2–Et_2O) and the result of the intramolecular haloetherification of more simple ene acetals previously reported by us (see Eq. 1).[10,11]

The NMR data showed the signals of the major products (**2a**—**d**).

(1*R*,3*R*,4*R*,6*R*,8*R*,12*R*)-12-Bromo-6-methoxyethoxy-2,5-dioxa-3,4-diphenylbicyclo[6.4.0]dodec-9-ene (2a) The ratio of the diastereoisomers [**2a** : others=76 : (19+5)] was determined by HPLC analysis [Chiralcel OD, hexane–iPrOH (99/1), 0.7 ml/min flow rate]. Eluent hexane–AcOEt (4/1); colorless oil; IR ν_{max} (KBr) 1495, 1454 cm^{-1}; ^{1}H-NMR δ 2.05 (2H, dd, J=6.4, 5.5 Hz), 2.5—2.6 (1H, m), 2.8—2.9 (1H, m), 3.31 (3H, s). 3.3—3.6 (4H, m), 3.6—3.8 (1H, m), 4.03 (1H, dd, J=9.0, 5.5 Hz), 4.32 (1H, dt, J=9.0, 6.1 Hz), 4.42 (1H, d, J=9.2 Hz), 4.43 (1H, d, J=9.2 Hz), 5.38 (1H, t, J=5.5 Hz), 5.5—5.6 (1H, m), 5.6—5.7 (1H, m), 6.9—7.3 (10H, m); ^{13}C-NMR δ 35.46, 35.62, 37.67, 47.80, 58.94, 66.56, 71.68, 81.94, 87.90, 88.50, 104.17, 124.42, 127.40, 127.48, 127.55, 127.75, 127.82, 129.18, 137.93, 138.10; FAB-MS m/z 473 (M+H$^+$); FAB-HR-MS Calcd for $C_{25}H_{30}BrO_4$ (M+H$^+$) 473.1727, Found 473.1334.

(1*R*,3*R*,4*R*,6*R*,8*R*,12*R*)-12-Bromo-6-methoxyethoxy-6-methyl-2,5-dioxa-3,4-diphenylbicyclo[6.4.0]dodec-9-ene (2b) The ratio of the diastereoisomers [**2b** : others=79 : (12+9)] was determined by HPLC analysis [Chiralcel OD, hexane–iPrOH (99/1), 0.7 ml/min flow rate]. Eluent hexane–AcOEt (10/1); colorless oil; IR ν_{max} (KBr) 1493, 1455 cm^{-1}; ^{1}H-NMR δ 1.26 (3H, s), 1.84 (1H, dd, J=14, 3.5 Hz), 2.2—2.4 (3H, m), 2.8—3.0 (1H, m), 3.46 (3H, s), 3.3—3.5 (1H, m), 3.5—3.7 (2H, m), 3.9—4.0 (1H, m), 4.2—4.3 (1H, m), 4.36 (1H, d, J=8.6 Hz), 4.43 (1H, d, J=8.6 Hz), 4.94 (1H, t, J=4.3 Hz), 5.4—5.5 (1H, m), 5.6—5.7 (1H, m), 6.8—6.9 (4H, m), 7.0—7.2 (6H, m); FAB-MS m/z 487 (M+H$^+$); FAB-HR-MS Calcd for $C_{26}H_{32}BrO_4$ (M+H$^+$) 487.1484, Found 487.1469.

(1*R*,3*R*,4*R*,6*R*,8*S*,12*R*)-12-Bromo-8-*tert*-butyldiphenylsilyloxymethyl-6-methoxyethoxy-2,5-dioxa-3,4-diphenylbicyclo[6.4.0]dodec-9-ene (2c) The reaction was carried out in CH_3CN–CH_2Cl_2 (v/v=4/1) within 2 h. The ratio of the diastereoisomers [**2c** : others=82 : (14+4)] was determined by HPLC analysis [Chiralcel OD, hexane–iPrOH (99/1), 0.7 ml/min flow rate]. Eluent hexane–AcOEt (10/1→8/1); colorless oil; IR ν_{max} (KBr) 1495, 1455 cm^{-1}; ^{1}H-NMR δ 1.14 (9H, s), 1.84 (1H, dd, J=15.5, 7.6 Hz), 2.10

(1H, dd, J=15.5, 4.6 Hz), 2.5—2.9 (2H, m), 3.27 (3H, s), 3.3—3.5 (3H, m), 3.5—3.7 (1H, m), 3.68 (1H, d, J=10 Hz), 4.28 (1H, dt, J=10, 5.6 Hz), 4.41 (1H, d, J=10 Hz), 4.46 (1H, d, J=9.2 Hz), 4.62 (1H, d, J=9.2 Hz), 4.94 (1H, d, J=10 Hz), 5.20 (1H, dd, J=7.6, 4.6 Hz), 5.5—5.6 (2H, m), 6.84 (2H, d, J=6.9 Hz), 6.9—7.3 (18H, m); FAB-MS m/z 741 ($M+H^+$); FAB-HR-MS Calcd for $C_{42}H_{50}BrO_5Si$ ($M+H^+$) 741.2611, Found 741.2609.

(1*R*,3*R*,4*R*,6*R*,8*R*,12*R*)-12-Bromo-6-methoxyethoxy-8-methoxymethyl-2,5-dioxa-3,4-diphenylbicyclo[6.4.0]dodec-9-ene (2d) The ratio of the diastereoisomers [**2d** : others=75 : (17+8)] was determined by HPLC analysis [Chiralcel OD, hexane–iPrOH (99/1), 0.7 ml/min flow rate]. Eluent hexane–AcOEt (6/1); colorless oil; IR ν_{max} (KBr) 1603, 1495, 1455 cm^{-1}; ^{1}H-NMR δ 2.05 (1H, dd, J=15.5, 6.9 Hz), 2.11 (1H, dd, J=15.5, 4.6 Hz), 2.5—2.7 (1H, m), 2.7—2.9 (1H, m), 3.31 (3H, s). 3.45 (3H, s), 3.3—3.8 (3H, m), 4.2—4.3 (2H, m), 4.4—4.6 (3H, m), 5.4—5.7 (3H, m), 6.9—7.2 (10H, m); FAB-MS m/z 539 ($M+Na^+$); FAB-HR-MS Calcd for $C_{27}H_{32}BrNaO_5$ ($M+Na^+$) 539.1409, Found 539.1401.

General Procedure for the Grignard Reaction in Table 2 To a solution of the acetal [**2a** or **2c**, 1.0 mmol, involving minor isomers (≤10%)] in toluene (50.0 ml) was added RMgX (5.0 mmol) at r.t. under a nitrogen atmosphere. The reaction mixture was stirred for 12 h at r.t., then quenched with saturated aqueous NH_4Cl. The resulting solution was extracted with AcOEt. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by SiO_2 column chromatography with hexane–AcOEt as an eluent to give **3** involving minor isomers derived from those in substrates. Minor isomers of **3a**—**d** were successfully removed by recrystallization (hexane) to give **3a**—**d** in the pure state.

(1*R*,3*R*,4*R*,6*S*,8*R*,12*R*)-12-Bromo-6-methyl-2,5-dioxa-3,4-diphenylbicyclo[6.4.0]dodec-9-ene (**3a**): Eluent hexane–AcOEt (20/1); colorless crystal; mp 98.5—99 °C (hexane); $[\alpha]_D^{24}$ −402° (c=0.56, $CHCl_3$); IR ν_{max} (KBr) 1493, 1454 cm^{-1}; ^{1}H-NMR δ 1.32 (3H, d, J=6.3 Hz), 1.53 (1H, dt, J=14, 3.0 Hz), 2.3—2.4 (1H, m), 2.44 (1H, ddd, J=14, 4.6, 2.0 Hz), 2.8—3.0 (1H, m), 3.1—3.3 (1H, m), 4.0—4.2 (1H, m), 4.27 (1H, q, J=4.8 Hz), 4.42 (2H, s), 4.76 (1H, t, J=4.8 Hz), 5.4—5.7 (2H, m), 6.8—7.2 (10H, m); MS (EI) m/z 412 (M^+), 414 ($M+2^+$); HR-MS Calcd for $C_{23}H_{25}BrO_2$ 412.1039 (M^+), 414.1019 ($M+2^+$), Found 412.1042 (M^+), 414.1027 ($M+2^+$); *Anal.* Calcd for $C_{23}H_{25}BrO_2$: C, 66.83; H, 6.10; Br, 19.33. Found: C, 66.97; H, 6.09; Br, 18.94.

(1*R*,3*R*,4*R*,6*S*,8*R*,12*R*)-6-Allyl-12-bromo-2,5-dioxa-3,4-diphenylbicyclo[6.4.0]dodec-9-ene (**3b**): Eluent hexane–AcOEt (20/1); colorless crystal; mp 74—74.5 °C (hexane); $[\alpha]_D^{23}$ −215° (c=0.57, $CHCl_3$); IR ν_{max} (KBr) 1495, 1455 cm^{-1}; ^{1}H-NMR δ 1.66 (1H, dt, J=15, 3.8 Hz), 2.2—2.6 (4H, m), 2.8—3.0 (1H, m), 3.1—3.3 (1H, m), 4.0—4.1 (1H, m), 4.29 (1H, q, J=5.0 Hz), 4.41 (1H, d, J=9.0 Hz), 4.42 (1H, d, J=9.0 Hz), 4.63 (1H, t, J=5.0 Hz), 4.9—5.1 (2H, m), 5.5—5.7 (2H, m), 5.7—5.9 (1H, m), 6.8—7.2 (10H, m); MS (EI) m/z 438 (M^+), 440 ($M+2^+$); *Anal.* Calcd for $C_{25}H_{27}BrO_2$: C, 68.34; H, 6.19. Found: C, 68.16; H, 6.09.

(1*R*,3*R*,4*R*,6*S*,8*R*,12*R*)-12-Bromo-2,5-dioxa-3,4-diphenyl-6-(2-phenylethyl)bicyclo[6.4.0]dodec-9-ene (**3c**): Eluent hexane–AcOEt (30/1); colorless crystal; mp 160—161 °C (hexane); $[\alpha]_D^{24}$ −187° (c=1.1, $CHCl_3$); IR ν_{max} (KBr) 1603, 1495, 1454 cm^{-1}; ^{1}H-NMR δ 1.5—1.6 (1H, m), 1.6—1.8 (1H, m), 2.0—2.2 (1H, m), 2.3—2.4 (2H, m), 2.5—2.7 (1H, m), 2.7—3.0 (2H, m), 3.1—3.3 (1H, m), 3.87 (1H, ddt, J=9.2, 5.0, 5.0 Hz), 4.28 (1H, q, J=4.5 Hz), 4.39 (1H, d, J=8.9 Hz), 4.45 (1H, d, J=8.9 Hz), 4.72 (1H, t, J=4.5 Hz), 5.4—5.7 (2H, m), 6.8—7.3 (15H, m); *Anal.* Calcd for $C_{30}H_{31}BrO_2$: C, 71.57; H, 6.21; Br, 15.87. Found: C, 71.47; H, 6.31; Br, 15.78.

(1*R*,3*R*,4*R*,6*S*,8*S*,12*R*)-12-Bromo-8-*tert*-butyldiphenylsilyloxymethyl-6-methyl-2,5-dioxa-3,4-diphenylbicyclo[6.4.0]dodec-9-ene (**3d**): Eluent hexane–AcOEt (30/1); colorless oil; $[\alpha]_D^{20}$ −155° (c=0.50, $CHCl_3$); IR ν_{max} (KBr) 1590, 1493, 1455 cm^{-1}; ^{1}H-NMR δ 1.09 (12H, s), 1.82 (2H, d, J=6.3 Hz), 2.5—2.7 (1H, m), 2.8—2.9 (1H, m), 3.78 (1H, d, J=10 Hz), 4.28 (1H, dt, J=2.8, 8.4 Hz), 4.41 (2H, t, J=8.8 Hz), 4.6—4.8 (3H, m), 5.2—5.3 (1H, m), 5.5—5.6 (1H, m), 6.7—6.8 (2H, m), 6.9—7.0 (2H, m), 7.0—7.2 (6H, m), 7.3—7.5 (6H, m), 7.6—7.8 (4H, m); FAB-MS m/z 681 ($M+H^+$); FAB-HR-MS Calcd for $C_{40}H_{46}BrO_3Si$ ($M+H^+$) 681.2400, Found 681.2405.

(1*R*,2*R*,6*S*)-2-Bromo-6-[(2*S*)-2-hydroxypropyl]cyclohexanol (11) To a solution of **3a** (33.8 mg, 0.082 mmol) in EtOH–THF (3.5 ml, v/v=6/1) was added a catalytic amount of $Pd(OH)_2$–C at r.t. under a medium pressure of H_2 (4 kgf/cm^2). After the completion of the reaction, the product was purified by SiO_2 column chromatography with hexane–AcOEt (2/1) as an eluent to give **11** (16.5 mg, 86%). Colorless crystal; mp 71—71.5 °C (AcOEt–hexane); $[\alpha]_D^{16}$ −23° (c=0.66, $CHCl_3$); IR ν_{max} (KBr) 3330, 1456 cm^{-1}; ^{1}H-NMR δ 1.22 (3H, d, J=6.2 Hz), 1.3—1.9 (7H, m), 2.2—2.5 (2H, m), 2.55 (2H, br s), 3.87 (1H, dd, J=6.6, 3.5 Hz), 3.9—4.1 (1H, m), 4.27 (1H, dt, J=3.8, 6.6 Hz); *Anal.* Calcd for $C_9H_{17}BrO_2$: C, 45.59; H, 7.23; Br, 33.70. Found: C, 45.60; H, 7.02; Br, 33.39.

(1*S*,2*R*)-2-[(2*S*)-2-Hydroxypropyl]-3-cyclohexen-1-ol (12) To a solution of **3a** (95 mg, 0.22 mmol) in toluene (2.2 ml) was added Bu_3SnH (0.092 ml, 0.34 mmol) and a catalytic amount of AIBN under a nitrogen atmosphere. The reaction mixture was refluxed for 1 h. The resultant solution was directly concentrated *in vacuo*. To a solution of Ca (26 mg, 0.66 mmol) in liq. NH_3 (6.0 ml) was added the obtained residue at −78 °C under a nitrogen atmosphere. After being stirred for 15 min, a solution of EtOH (0.04 ml, 0.66 mmol) in THF (1.0 ml) was added at the same temperature. The solution was quenched with saturated aqueous NH_4Cl. After removal of NH_3 at r.t., the resultant solution was extracted with AcOEt. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by SiO_2 column chromatography with hexane–AcOEt (2/1→1/1) as an eluent to give **12** (28.0 mg, 78%). Colorless oil; $[\alpha]_D^{20}$ +35° (c=0.56, $CHCl_3$); IR ν_{max} (KBr) 3300, 1641 cm^{-1}; ^{1}H-NMR δ 1.21 (3H, d, J=5.9 Hz), 1.5—1.7 (6H, m), 2.0—2.5 (3H, m), 3.6—3.7 (1H, m), 3.8—3.9 (1H, m), 4.9—5.1 (2H, m), 5.8—5.9 (1H, m); MS (EI) m/z 156 (M^+).

(1*R*,3*R*,4*R*,6*S*,8*R*,9*R*,10*S*,12*R*)-12-Bromo-9,10-dihydroxy-6-methyl-2,5-dioxa-3,4-diphenylbicyclo[6.4.0]dodecane (13) To a solution of **3a** (74 mg, 0.17 mmol) and 4-methylmorpholine *N*-oxide (NMO) (50% in H_2O, 0.04 ml) in acetone–H_2O (v/v=1/1, 2.0 ml) was added a catalytic amount of OsO_4 at r.t. The reaction mixture was stirred for 1.5 h. The solution was quenched with saturated aqueous Na_2SO_3, then stirred for 15 min at r.t. The resultant solution was extracted with AcOEt. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by SiO_2 column chromatography with hexane–AcOEt (3/1) as an eluent to give **13** (68.3 mg, 85%) and **14** (6.0 mg, 8%). **13**: colorless oil; $[\alpha]_D^{26}$ −59.6° (c=2.36, $CHCl_3$); IR ν_{max} (KBr) 1493, 1453, 1437 cm^{-1}; ^{1}H-NMR δ 1.23 (3H, d, J=6.0 Hz), 1.8—2.0 (1H, m), 2.2—2.7 (5H, m), 2.84 (1H, br s), 3.9—4.2 (3H, m), 4.4—4.7 (3H, m), 4.7 (1H, br s), 6.8—7.2 (10H, m); FAB-MS m/z 447 ($M+H^+$); FAB-HR-MS Calcd for $C_{23}H_{28}BrO_4$ ($M+H^+$) 447.1171, Found 447.1173. **14**: $[\alpha]_D^{27}$ −48.7° (c=0.48, $CHCl_3$); IR ν_{max} (KBr) 3499, 2922, 1088, 1069 cm^{-1}; ^{1}H-NMR δ 1.30 (3H, d, J=6.6 Hz), 1.8—1.9 (1H, m), 2.0—2.2 (2H, m), 2.46 (1H, br s), 2.6—2.8 (3H, m), 3.60 (1H, d, J=10.0 Hz), 3.83 (1H, d, J=10.0 Hz), 3.9—4.1 (1H, m), 4.2—4.4 (3H, m), 4.62 (1H, d, J=9.0 Hz), 5.10 (1H, s), 6.8—7.2 (10H, m); FAB-HR-MS Calcd for $C_{23}H_{28}BrO_4$ (MH^+) 447.1171, Found 447.1171.

(1*R*,3*R*,4*R*,6*S*,8*R*,9*R*,10*S*,12*R*)-12-Bromo-9,10-diacetoxy-6-methyl-2,5-dioxa-3,4-diphenylbicyclo[6.4.0]dodecane (15) A mixture of **13** (160 mg, 0.36 mmol), Ac_2O (0.18 ml), and pyridine (0.36 ml) was stirred for 3 h at r.t. Under a nitrogen atmospher. The resulting solution was evaporated *in vacuo* to give crude product, which was purified by SiO_2 column chromatography with hexane–AcOEt (5/1) as an eluent to give **15** (173 mg, 87%). **15**: white amorphous; $[\alpha]_D^{24}$ −20.4° (c=2.6, $CHCl_3$); IR ν_{max} (KBr) 1738, 1245 cm^{-1}; ^{1}H-NMR δ 1.18 (3H, d, J=6.0 Hz), 1.7—1.9 (1H, m), 1.9—2.1 (1H, m), 2.08 (3H, s), 2.10 (3H,s), 2.31 (1H, dt, J=13.5, 5.4 Hz), 2.49 (1H, dt, J=13.5, 4.1 Hz), 3.0—3.1 (1H, m), 4.0—4.2 (1H, m), 4.3—4.5 (1H, m), 4.39 (1H, A part in ABq), 4.43 (1H, B part in ABq), 5.21 (1H, br s), 5.38 (1H, dd, J=8.9, 3.0 Hz), 6.8—7.2 (10H, m); FAB-MS m/z 530 (M^+); FAB-HR-MS Calcd for $C_{27}H_{31}BrO_6$ (M^+) 530.1303, Found 530.1314.

Acknowledgment This research was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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