Insight into Acid-Mediated Asymmetric Spirocyclization in the Presence of a Chiral Diol

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Asymmetric spirocyclization based on intramolecular conjugate addition using a combination of a Lewis acid and an optically active cyclohexane-1,2-diol has been studied in connection with 1) the effect of substituents on the cyclohexane-1,2-diol and 2) the effect of substituents on the substrate. This reaction was found to be both thermodynamically and kinetically controlled under restricted conditions.

Key words asymmetric spirocyclization; Lewis acid; 1,2-diol; kinetic control; thermodynamic control

We previously reported asymmetric spirocyclization of 3-(4-oxobutyl)-2-cyclohexenone **1** into spiro[5.5]undecane-2,8-dione **2** using the combination of a Lewis acid and an optically active cyclohexane-1,2-diol, in which the best result in terms of enantiomeric excess (ee) of **2** was up to 85% ee as shown in Chart 1.¹⁾ Our working hypothesis in the study of this reaction was an enol ether intermediate **A** as mentioned in the earlier paper. To further study the aspects of this reaction, we planned the following two approaches: 1) determination of the effects of substituents on the cyclohexane-1,2-diol, and 2) of the effects of geminal dimethyl substituents at the C5-position of the substrate.

Effects of Substituents on Cyclohexane-1,2-diol Preparation of Cyclohexane-1,2-diols: First, we planned to study this reaction of using several kinds of cyclohexane-1,2-diols, **4**, (*dl*)-**5**, (*dl*)-**6** and optically active **3**, **7**—**10**. Racemic *trans*-1,2-diols **5**, **6** were prepared by conventional methods from 1-methylcyclohexene and dimedone, respectively, according to reported procedures.²⁾

Optically active diols **7**—**10** were prepared from *l*-menthol via **11**, which was obtained by *trans*-elimination of the corresponding mesylate in 95% yield.³⁾ Diastereoselective *trans*-

dihydroxylation of **11** into **7** was performed by epoxidation with *m*-chloroperbenzoic acid (*m*CPBA) and subsequent epoxide ring cleavage under acidic conditions. Preparation of the minor *trans*-product **8** was established by another method as described below. The stereochemistry of **7** and **8** was determined based on ¹H-NMR spectra. In the case of **7**, signals at δ 3.98 and δ 3.68, attributable to C1-H and C2-H, respectively, were observed with a value of $W_H = 7.9$ Hz, which suggests that the hydroxy functions at the C1- and C2-positions are in an axial orientation. In the ¹H-NMR spectrum of **8**, the corresponding signals were observed at δ 3.20 ($J = 10.6$, 8.6 Hz) and δ 2.97 ($J = 9.9$, 8.6 Hz), which suggests all the substituents are in equatorial orientation.

Osmium-catalyzed *cis*-dihydroxylation of **11** gave an inseparable diastereomeric mixture of **9** and **10** in a ratio of 2 to 7 in 98% yield, which were separated after conversion into monobenzoates **12** and **13**. In this process, it was noted that a hydroxy group in equatorial orientation reacted regioselectively to afford the above products despite the use of 2 eq of benzoyl chloride (BzCl). The structure of **12** and **13** was determined by ¹H-¹H correlation spectroscopy (COSY) NMR

Chart 1. Asymmetric Spirocyclization Using **1**

Fig. 1. Cyclohexane-1,2-diols

Chart 2. Preparation of **7** and **8**

(a) methanesulfonyl chloride (MsCl), pyridine, CH₂Cl₂, r.t. (quant.); (b) *tert*-BuOK, dimethyl sulfoxide (DMSO), 70 °C (95%); (c) *m*-CPBA, CH₂Cl₂, 0 °C; (d) 3% H₂SO₄ aq., tetrahydrofuran (THF), 0 °C.

Chart 3. Preparation of **9** and **10**

(a) OsO₄, 4-methylmorpholine *N*-oxide (NMO), acetone, H₂O, r.t.; (b) BzCl, pyridine, CH₂Cl₂, r.t. and separation; (c) K₂CO₃, MeOH.

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Dedicated to the memory of Dr. Kyosuke Tsuda.

spectra. These compounds were easily converted into the corresponding diols **9**, **10** in quantitative yields.

Next, *trans*-diol **8** was prepared starting from compound **13**. For inversion of stereochemistry at the C2-position, mesylation of **13** in refluxing CHCl_3 gave a mesylate **14** in 67% yield. After solvolysis of **14** into **15**, reaction with CsOAc at 100°C in *N,N*-dimethylformamide (DMF) according to Ikegami's procedure⁴⁾ gave the desired products, a 1 to 1 mixture of **16** and **17** in 55% yield.⁵⁾ The acyl migration from **16** was believed to afford **17**. Further solvolysis of a mixture of **16** and **17** afforded **8** in 82% yield.

Results and Discussion of Spirocyclization of **1**: Reaction of **1** under acidic conditions in the presence of a diol was studied. The reaction conditions were based on our previous study,^{1b)} that is to say, $\text{BF}_3\text{-Et}_2\text{O}$ (2 eq) as a Lewis acid, 3 eq of a diol and CH_2Cl_2 as a solvent were used. The results are summarized in Table 1.

In entries 1 and 2, our previous results are shown. In entry 1, reaction without a diol proceeded slowly to give **2** (31%) and an intramolecular aldol-dehydration product **18** (30%) accompanied by recovery of **1** (28%). In entry 2, spirocyclization was highly accelerated by addition of **3** to afford (*R*)-(-)-**2** (86%) of 85% ee.

As a preliminary study, the effects of substituents at the C1- and C3,6-positions were studied using (*dl*)-**5**, **6**. In the case of entry 3 using (*dl*)-**5**, the reaction was not at all af-

fected by addition of a diol. Furthermore, in entry 4 using (*dl*)-**6**, the obtained result was similar to that of entry 1. This result of entry 4 prompted us to study what kind of substituents inhibited the roll of a diol such as **3** in entry 2.

When *trans*-diols **7**, **8** were used, the respective results were very different. As regards the effect on reactivity when using diol **7** in entry 5, the yield of **2** (86%) was evaluated as high as when **3** was used, but the effect of diol **8** was similar to that of **6**. These results suggest that alkyl substituents at the C3,6-positions which locate in vicinal *trans* orientation to the C1- or C2-hydroxy group might inhibit the acceleration of spirocyclization. In connection with asymmetric induction, the absolute stereochemistry of **2** was dependent on that of the C1,2-position of the *trans*-diols used (entries 2, 5, 6). However, ees of **2** in entries 5 and 6 were not as high as that in entry 2. Taking the configurational factor of **3** and **7** into consideration, both hydroxy groups of **3** were predominantly in equatorial orientation. On the other hand, those of **7** were in axial orientation as aforementioned. The relationship between this conformational aspect and ee of product **2** is still undetermined.

Next, spirocyclization of **1** using *cis*-cyclohexane-1,2-diol **4** was examined in entry 7, which afforded **2** in 53% yield and **18** in 16% yield. These results, which showed some acceleration of the reaction rate compared to entry 1, prompted us to study the reaction using optically active *cis*-diols **9** and **10**. As shown in entries 8—11 in Table 1, both diols gave similar results. That is to say, reactions at 0°C for 24 h gave the corresponding acetals **19** (60%) and **20** (65%), respectively (entries 8, 10).⁶⁾ In addition, reactions in refluxing CH_2Cl_2 for 48 h gave (*S*)-(+)-**2** of 13% ee (44% yield) and 16% ee (49% yield), respectively (entries 9, 11).

Throughout these studies, a more efficient diol than **3** to produce **2** of high ee was not found, but the effects of alkyl substituents at C3,6-positions were observed in connection with the reactivity of **1**.

Spirocyclization of 5,5-dimethyl-3-(4-oxobutyl)-2-cyclo-

Chart 4. Conversion from **13** to **8**

(a) MsCl , pyridine, 4-dimethylaminopyridine (DMAP), CHCl_3 , reflux (67%); (b) K_2CO_3 , MeOH , r.t. (99%); (c) CsOAc , DMF, 100°C (55%, **16**:**17**=1:1); (d) K_2CO_3 , MeOH , r.t. (82%).

Table 1. Reaction of **1** with Cyclohexane-1,2-diols

Entry	Diol	Temp.	Time (h)	Product 2			Recovery (%)	Other products (%)
				Yield (%)	Abs. config.	% ee		
1 ^{a)}	—	r.t.	72	31	—	—	28	18 (30)
2 ^{a)}	3	0°C	6	86	<i>R</i>	85	—	—
3	(<i>dl</i>)- 5	r.t.	96	27	—	—	68	—
4	(<i>dl</i>)- 6	r.t.	24	25	—	—	38	18 (15)
5	7	0°C	12	86	<i>S</i>	28	—	—
6	8	r.t.	24	31	<i>R</i>	26	44	18 (13)
7	4	r.t.	24	53	—	—	—	18 (16)
8	9	0°C	24	—	—	—	39	19 (60)
9	9	Reflux	48	44	<i>S</i>	13	—	—
10	10	0°C	24	—	—	—	33	20 (65)
11	10	Reflux	48	49	<i>S</i>	16	—	—

a) Previous result.¹⁾

18

19

20

Chart 5. Preparation of Substrate **22**

(a) iso-BuOH, *p*-toluenesulfonic acid (*p*-TsOH), benzene, reflux (quant.); (b) (i) BrMg(CH₂)₃CH=CH₂, THF, r.t., (ii) 10% HCl, THF, r.t. (78% 2 steps); (c) PdCl₂, CuCl, O₂, DMF, H₂O, r.t. (73%).

Table 2. Spirocyclization of **22**

Entry	Lewis acid	Temp.	Time	Yield (%)	% ee	Recovery (%)
1 ^{a)}	BF ₃ ·Et ₂ O	r.t.	3 d	0	—	98
2	BF ₃ ·Et ₂ O	r.t.	3 d	0	—	90
3 ^{a)}	TMSOTf	r.t.	3 d	20	—	36
4	TMSOTf	r.t.	3 h	56	33	9
5	TMSOTf	0 °C	5 h	41	64	15
6	TMSOTf	-20 °C	1 d	30	86	50
7	TMSOTf	-20 °C	7 d	36	91	48
8	TMSOTf	-30 °C	10 d	0	—	98

a) Reaction was performed without diol.

hexenone Next, compound **22** was prepared as a substrate by a similar sequence of reactions as for preparation of **1** as shown in Chart 5. The objective in setting up **22** was to investigate the effect of C-5 geminal dimethyl functions on asymmetric spirocyclization under the previously optimized conditions, using BF₃·Et₂O (2 eq) or trimethylsilyl trifluoromethanesulfonate (TMSOTf) (2 eq) as the Lewis acid, and **3** (3 eq) in CH₂Cl₂. The results are summarized in Table 2. In reactions using BF₃·Et₂O as the Lewis acid, the spirocyclized product **23** was not obtained at all, and most of the substrate was recovered, regardless of the absence or presence of **3** (entries 1, 2). The desired product **23** was obtained using TMSOTf (entries 3–7). This result was interesting, because when **1** was used as a substrate, BF₃·Et₂O was the first choice as Lewis acid.

Acceleration of the reaction by addition of **3** can be clearly observed by comparing entries 3 and 4. That is to say, reaction for 3 d at room temperature without a diol afforded (*dl*)-**23** in 20% yield (entry 3), while the reaction for 3 h at the same temperature in the presence of **3** gave (–)-**23** in 56% yield (33% ee) (entry 4). The ee of (–)-**23** was strongly influenced by the reaction temperature. Reaction at –20 °C for 1 d gave (–)-**23** of 86% ee and that at the same temperature for 7 d gave (–)-**23** of 91% ee, although chemical yields were unsatisfactory (30–36% yields) (entries 6, 7). This value of 91% ee was the best among our studies of asymmetric spirocyclization.⁷⁾

The ee of (–)-**23** was determined by ¹H-NMR spectroscopy after conversion into bisacetal of (*R,R*)-butane-2,3-diol **24** under azeotropic conditions (*p*-TsOH, benzene). This was the same procedure used for the determination of ee of **1**. In both cases, no decrease of ee was confirmed by repeating acetalization and deacetalization (5–10% aqueous HCl), which led us to believe that the asymmetric spirocyclization

Chart 6

proceeded in an irreversible manner (Chart 6). However, surprisingly, this assumption had to be corrected based on the following results.

Compound (–)-**23** (81% ee, 91% ee) was treated under the same reaction conditions of spirocyclization (TMSOTf, **3** in CH₂Cl₂) at room temperature and –20 °C, respectively. In the former case, the ee of recovered (–)-**23** (58% yield) was decreased from 81% ee to 28% ee and the formation of **22** (25%) was observed. In the latter case, the ee of (–)-**23** (84%) was slightly decreased from 91% ee to 86% ee and a small amount of **22** (5%) was obtained (Chart 6). Each ee was similar to that of the product at the corresponding reaction temperature in Table 2 (entries 4, 6). In addition, it is noteworthy that this reverse reaction from (–)-**23** to **22** proceeded in a regioselective manner, that is to say, formation of the other possible product **B** was not detected at all. These results suggest that this asymmetric spirocyclization might be both kinetically and thermodynamically controlled under restricted conditions.

Experimental

Melting points were measured on Yanaco micro melting point apparatus without correction. ¹H-NMR spectra were taken on a JEOL GX-270 (270 MHz) spectrometer. ¹³C-NMR were recorded on a JEOL GX-270 (67.8 MHz) spectrometer. IR spectra were measured on a JASCO IR A-100 IR spectrophotometer. Mass spectra (electron ionization (EI), FAB) were measured on a JEOL JMS-D300 or JEOL JMS-SX102 spectrometer, and specific rotations were measured on a JASCO DIP-360 digital polarimeter. The elemental analyses were performed on a Yanaco MT2 CHN recorder. Column chromatography were carried out on silica gel 70–230 mesh (Merck, Kieselgel 60). Solvents were distilled and dried before use. All the extracts were dried with Na₂SO₄.

(1*R*,2*R*,3*R*,6*S*)-3-Methyl-6-(methylethyl)cyclohexane-1,2-diol (7) and (1*S*,2*S*,3*R*,6*S*)-3-Methyl-6-(methylethyl)cyclohexane-1,2-diol (8) A solution of *m*-CPBA (11.6 g, 47.1 mmol) in CH₂Cl₂ (30 ml) was added dropwise to a solution of **11** (5.00 g, 36.2 mmol) in CH₂Cl₂ (200 ml) at 0 °C. The whole was stirred at the same temperature for 8 h. The reaction mixture was successively washed with 5% of aqueous sodium bisulfite, 5% of aqueous NaHCO₃ and brine, then dried. After removal of the solvent *in vacuo*, the residue was diluted with THF (20 ml), which was added to 3% of aqueous H₂SO₄ (150 ml) at 0 °C. The whole was stirred at 0 °C for 7 h. After neutralization by addition of NaHCO₃, the reaction mixture was extracted with AcOEt (50 ml×3). The combined extracts were washed with brine, and dried. The solvent was removed *in vacuo*, and the residue was purified by column chromatography (hexane:AcOEt=3:1) to afford **7** (4.49 g, 72%) and **8** (160 mg, 3%).

7: Colorless oil. [α]_D²⁶ 38.6° (*c*=1.01, CHCl₃). IR (neat) cm⁻¹: 3400, 2940, 2900, 2850, 1120, 1010, 970. ¹H-NMR (CDCl₃): δ 3.98 (br, 1H), 3.68 (br d, *J*=2.6 Hz, 1H), 1.88 (m, 1H), 1.65–1.18 (m, 8H), 0.97 (d, *J*=6.9 Hz, 3H), 0.96 (d, *J*=6.9 Hz, 3H), 0.95 (d, *J*=6.6 Hz, 3H). ¹³C-NMR (CDCl₃): δ 74.4 (d), 71.1 (d), 41.7 (d), 30.1 (d), 28.7 (d), 27.6 (t), 23.6 (t), 21.1 (q), 20.6 (q), 17.5 (q). MS *m/z*: 172 (M⁺). FAB-MS *m/z*: 172.1455 (Calcd for C₁₀H₂₀O₂ (M⁺): 172.1463).

8: A colorless solid. $[\alpha]_D^{25} -41.1^\circ$ ($c=0.99$, CHCl_3). IR (CHCl_3) cm^{-1} : 3400, 2950, 2920, 2860, 1450, 1200, 1050. $^1\text{H-NMR}$ (CDCl_3): δ 3.20 (m, 1H), 2.97 (m, 1H), 2.49 (brs, 1H), 2.44 (brs, 1H), 2.14 (m, 1H), 1.69 (m, 1H), 1.57 (m, 1H), 1.46–1.26 (m, 2H), 1.17–0.92 (m, 2H), 1.03 (d, $J=6.3$ Hz, 3H), 0.93 (d, $J=6.9$ Hz, 3H), 0.82 (d, $J=6.9$ Hz, 3H). $^{13}\text{C-NMR}$ (CDCl_3): δ 81.5 (d), 76.4 (d), 47.7 (d), 37.6 (d), 32.4 (t), 25.9 (d), 22.5 (t), 20.9 (q), 18.3 (q), 15.9 (q). MS m/z : 154 ($\text{M}^+ - \text{H}_2\text{O}$), 137, 136. FAB-MS m/z : 172.1469 (Calcd for $\text{C}_{10}\text{H}_{20}\text{O}_2$ (M^+): 172.1463).

(1S,2R,3S,6R)-2-Hydroxy-6-methyl-3-(methylethyl)cyclohexyl Benzoate (12) and (1S,2R,3R,6S)-2-Hydroxy-3-methyl-6-(methylethyl)cyclohexyl Benzoate (13) Aqueous 2% OsO_4 (5 ml, 0.394 mmol) was added to a mixed solution of aqueous 50% NMO (31 ml, 130 mmol) and **11** (6.00 g, 43.5 mmol) in acetone (200 ml) and H_2O (100 ml) at 0°C . The whole was stirred at room temperature for 16 h. After addition of 5% of aqueous sodium bisulfite (16 ml), the whole was stirred for 30 min, then concentrated *in vacuo* to remove acetone, and the residue was extracted with AcOEt (50 ml $\times$ 3). The combined extracts were washed with brine and dried. After removal of the solvent *in vacuo*, the residue was purified by column chromatography (hexane: AcOEt = 1:1) to afford a mixture of **9** and **10** (7.13 g; 95%; **9**:**10** = 2:7). Benzoyl chloride (9.59 ml, 82.8 mmol) was added dropwise to a mixed solution of a mixture of **9** and **10** (7.13 g, 41.4 mmol) and pyridine (13.4 ml, 165 mmol) in CH_2Cl_2 (200 ml) at 0°C . The whole was stirred at room temperature for 6 h. Reaction was quenched by addition of 5% of aqueous NaHCO_3 , then the organic layer was washed with 5% of aqueous HCl and brine, and dried. After removal of the solvent *in vacuo*, the residue was purified by column chromatography (hexane: AcOEt = 20:1) to give **12** (2.51 g, 22%) and **13** (8.79 g, 76%).

12: A colorless solid. mp $95-98^\circ\text{C}$ (hexane). $[\alpha]_D^{27} -50.1^\circ$ ($c=1.02$, CHCl_3). IR (CHCl_3) cm^{-1} : 3600, 2950, 2850, 1700, 1450, 1310, 1270, 1100. $^1\text{H-NMR}$ (CDCl_3): δ 8.16–8.04 (m, 2H), 7.65–7.43 (m, 3H), 4.72 (dd, $J=11.2$, 2.6 Hz, 1H), 4.19 (brd, $J=2.3$ Hz, 1H), 2.14 (m, 1H), 1.84 (m, 1H), 1.76–1.59 (m, 2H), 1.44 (m, 1H), 1.19–1.06 (m, 2H), 0.95 (d, $J=6.6$ Hz, 3H), 0.94 (d, $J=6.9$ Hz, 3H), 0.94 (d, $J=6.9$ Hz, 3H). $^{13}\text{C-NMR}$ (CDCl_3): δ 166.0 (s), 133.0 (d), 130.3 (s), 129.6 (d), 128.4 (d), 81.9 (d), 69.1 (d), 47.7 (d), 32.9 (t), 30.3 (d), 28.9 (d), 23.2 (t), 21.1 (q), 20.6 (q), 18.1 (q). MS m/z : 277 ($\text{M}^+ + \text{H}$), 137, 105, 77.

13: A colorless solid. mp $86-88^\circ\text{C}$ (hexane). $[\alpha]_D^{27} -57.2^\circ$ ($c=1.04$, CHCl_3). IR (CHCl_3) cm^{-1} : 3600, 2950, 2920, 2850, 1700, 1440, 1260, 1100, 1090. $^1\text{H-NMR}$ (CDCl_3): δ 8.11–8.04 (m, 2H), 7.61–7.43 (m, 3H), 4.99 (dd, $J=11.9$, 2.6 Hz, 1H), 4.00 (brt, $J=2.3$ Hz, 1H), 2.06 (m, 1H), 1.89 (dq, $J=6.9$, 6.9, 3.0 Hz, 1H), 1.76–1.60 (m, 2H), 1.49–1.41 (m, 2H), 1.12 (m, 1H), 1.03 (d, $J=6.6$ Hz, 3H), 0.93 (d, $J=6.9$ Hz, 3H), 0.79 (d, $J=6.9$ Hz, 3H). $^{13}\text{C-NMR}$ (CDCl_3): δ 165.8 (s), 133.0 (d), 130.3 (s), 129.6 (d), 128.4 (d), 77.6 (d), 72.4 (d), 39.5 (d), 35.6 (d), 26.9 (t), 26.2 (d), 23.3 (t), 20.6 (q), 17.7 (q), 16.3 (q). MS m/z : 277 ($\text{M}^+ + \text{H}$), 137, 105, 77.

(1R,2S,3R,6S)-3-Methyl-6-(methylethyl)cyclohexane-1,2-diol (9) K_2CO_3 (4.08 g, 29.6 mmol) was added to a solution of **12** (2.72 g, 9.86 mmol) in MeOH (40 ml) at room temperature, and the whole was stirred for 7 h at the same temperature. After neutralization by addition of 10% aqueous HCl, MeOH was removed *in vacuo*. The aqueous residue was extracted with AcOEt (40 ml $\times$ 4). The combined extracts were washed with brine and dried. After removal of the solvent, the residue was purified by column chromatography (hexane: AcOEt = 2:1) to give **9** (1.64 g, 97%) as a colorless solid. mp $78-80^\circ\text{C}$. $[\alpha]_D^{26} -26.3^\circ$ ($c=1.02$, CHCl_3). IR (CHCl_3) cm^{-1} : 3420, 3025, 2930, 2860, 1450, 1380, 1200, 940. $^1\text{H-NMR}$ (CDCl_3): δ 4.01 (brs, 1H), 3.06 (brd, $J=9.9$ Hz, 1H), 2.05 (brs, 1H), 1.90 (brs, 1H), 1.75–1.54 (m, 4H), 1.27 (m, 1H), 1.07–0.89 (m, 2H), 1.00 (d, $J=6.3$ Hz, 3H), 0.97 (d, $J=6.9$ Hz, 3H), 0.93 (d, $J=6.6$ Hz, 3H). $^{13}\text{C-NMR}$ (CDCl_3): δ 78.7 (d), 71.1 (d), 47.9 (d), 32.8 (t), 32.8 (d), 29.0 (d), 23.3 (t), 21.2 (q), 20.7 (q), 18.3 (q). MS m/z : 172 (M^+), 154, 137, 136. FAB-MS m/z : 172.1466 (Calcd for $\text{C}_{10}\text{H}_{20}\text{O}_2$ (M^+): 172.1463).

(1S,2R,3R,6S)-3-Methyl-6-(methylethyl)cyclohexane-1,2-diol (10) Solvolysis of **13** (1.55 g, 5.60 mmol) in a similar manner to that described for preparation of **9** gave **10** (944 mg; 98%) as a colorless solid. mp $69-70^\circ\text{C}$. $[\alpha]_D^{25} -32.1^\circ$ ($c=1.03$, CHCl_3). IR (CHCl_3) cm^{-1} : 3400, 2950, 2860, 1450, 1380, 1360, 1090, 960. $^1\text{H-NMR}$ (CDCl_3): δ 3.79 (brs, 1H), 3.37 (brd, $J=10.2$ Hz, 1H), 2.15–2.01 (m, 3H), 1.62–1.21 (m, 5H), 1.09 (m, 1H), 1.02 (d, $J=6.9$ Hz, 3H), 0.94 (d, $J=6.9$ Hz, 3H), 0.81 (d, $J=6.9$ Hz, 3H). $^{13}\text{C-NMR}$ (CDCl_3): δ 74.9 (d), 73.7 (d), 42.3 (d), 35.7 (d), 27.2 (t), 25.8 (d), 22.8 (t), 20.9 (q), 17.9 (q), 16.0 (q). MS m/z : 172 (M^+), 154, 136. FAB-MS m/z : 172.1478 (Calcd for $\text{C}_{10}\text{H}_{20}\text{O}_2$ (M^+): 172.1463).

(1S,2R,3R,6S)-3-Methyl-6-(methylethyl)-2-(methylsulfonyloxy)cyclohexyl Benzoate (14) MsCl (3.05 ml, 26.3 mmol) was added to a mixed solution of **13** (3.63 g, 13.2 mmol), pyridine (8.51 ml, 105 mmol) and small

amount of DMAP in CH_2Cl_2 (130 ml) at 0°C , and the whole was heated under reflux for 2 d. The whole was successively washed with 5% of aqueous NaHCO_3 , 5% of aqueous HCl, and brine, and dried. After concentration *in vacuo*, the residue was purified by column chromatography (hexane: AcOEt = 6:1) to afford **14** (3.12 g, 67%) as colorless needles. mp $133-135^\circ\text{C}$ (hexane). $[\alpha]_D^{30} -42.6^\circ$ ($c=1.08$, CHCl_3). IR (CHCl_3) cm^{-1} : 2950, 1720, 1340, 1280, 1180, 1100. $^1\text{H-NMR}$ (CDCl_3): δ 8.11–8.06 (m, 2H), 7.61–7.43 (m, 3H), 5.10 (brs, 1H), 4.99 (dd, $J=11.7$, 2.5 Hz, 1H), 2.95 (s, 3H), 2.12–1.73 (m, 4H), 1.58 (m, 1H), 1.41 (m, 1H), 1.20 (m, 1H), 1.07 (d, $J=6.9$ Hz, 3H), 0.95 (d, $J=6.9$ Hz, 3H), 0.77 (d, $J=6.9$ Hz, 3H). MS m/z : 355 ($\text{M}^+ + \text{H}$), 259, 137, 105, 77.

(1R,2S,3S,6R)-2-Hydroxy-6-methyl-3-(methylethyl)cyclohexyl Methylsulfonate (15) Solvolysis of **14** (103 mg, 0.291 mmol) in a similar manner to that described for preparation of **9** gave **15** (72 mg; 99%) as colorless needles. mp $83-84^\circ\text{C}$ (hexane). $[\alpha]_D^{30} -18.1^\circ$ ($c=1.03$, CHCl_3). IR (KBr) cm^{-1} : 3530, 2940, 1320, 1150, 1030. $^1\text{H-NMR}$ (CDCl_3): δ 4.94 (brs, 1H), 3.51 (ddd, $J=10.9$, 6.3, 2.3 Hz, 1H), 3.15 (s, 3H), 2.20–2.09 (m, 2H), 1.75–1.45 (m, 5H), 1.29 (m, 1H), 1.05 (d, $J=6.9$ Hz, 3H), 0.94 (d, $J=6.9$ Hz, 3H), 0.81 (d, $J=7.3$ Hz, 3H). MS m/z : 251 ($\text{M}^+ + \text{H}$), 155, 137.

8 from 15 A stirred solution of **15** (2.52 g, 10.1 mmol) and CsOAc (7.16 g, 37.3 mmol) in DMF (100 ml) was heated at 100°C for 5 h. The reaction mixture was poured into water, and the whole was extracted with AcOEt. The combined extracts were washed with brine, then dried. After removal of the solvent *in vacuo*, the residue was purified by column chromatography (hexane: AcOEt = 4:1) to afford a mixture of **16** and **17** (1.19 g, 55%; **16**:**17** = 1:1). The mixture (1.10 g) submitted to solvolysis by a similar manner to that described for preparation of **9** gave **8** (728 mg, 82%).

General Procedure for Spirocyclization Reaction without Diol: To a solution of substrate (2 mmol) in CH_2Cl_2 (10 ml) was added dropwise Lewis acid, and the mixture was stirred. The resulting mixture was washed with saturated aqueous NaHCO_3 and extracted with AcOEt. The combined organic layers were washed with brine, and dried. After removal of the solvent *in vacuo*, the residue was purified by column chromatography (hexane: AcOEt = 4:1 to 2:1).

Reaction with Diol: To a solution of substrate and diol in CH_2Cl_2 was added dropwise Lewis acid and the mixture was stirred. The reaction mixture was treated in a similar manner as above.

5,5-Dimethyl-3-(4-pentenyl)cyclohex-2-en-1-one (21) A solution of 5,5-dimethyl-3-(2-methylpropoxy)cyclohex-2-en-1-one (2.0 g, 10.2 mmol) in THF (7 ml) was added at 0°C to a solution of 4-pentenylmagnesium bromide prepared from magnesium (270 mg, 11.2 mmol) and 5-bromo-1-pentene (1.2 ml, 10.2 mmol) in THF (25 ml), and the mixture was stirred for 30 min at room temperature. The reaction was quenched with saturated aqueous NH_4Cl , and extracted with ethyl acetate. The combined organic layers were washed with brine, and dried. After removal of the solvent *in vacuo*, the residue was purified by column chromatography (hexane: AcOEt = 10:1) to give **21** (1.53 g, 78%) as a colorless oil. IR (neat) cm^{-1} : 2975, 2945, 1660, 1360, 1300, 1280. $^1\text{H-NMR}$ (CDCl_3): δ 5.89 (m, 1H), 5.80 (m, 1H), 5.07–4.94 (m, 2H), 2.28–2.05 (m, 6H), 1.65–1.07 (m, 4H), 1.04 (s, 6H). MS m/z : 193 ($\text{M}^+ + 1$).

5,5-Dimethyl-3-(4-oxopentyl)cyclohex-2-en-1-one (22) A solution of palladium(II) chloride (0.36 g, 2.04 mmol) and copper(I) chloride (0.5 g, 5.14 mmol) in DMF (21 ml) and water (7 ml) was stirred for 2 h at room temperature under an O_2 atmosphere. To the solution was added a solution of **21** (1.0 g, 5.14 mmol) in DMF (6 ml) and water (2 ml), and the mixture was stirred for 3 h at room temperature. The resulting mixture was washed with saturated NH_4Cl , and extracted with ether. The organic layer was washed with brine, and dried. After removal of solvent *in vacuo*, the residue was purified by column chromatography (hexane: AcOEt = 2:1) to give **22** (0.78 g, 73%) as a colorless oil. IR (neat) cm^{-1} : 2950, 1700, 1680, 1620, 1400, 1360, 1300. $^1\text{H-NMR}$ (CDCl_3): δ 5.87 (t, $J=1.32$ Hz, 1H), 2.53 (t, $J=7.3$ Hz, 2H), 2.22–2.16 (m, 6H), 2.15 (s, 3H), 1.78 (tt, $J=7.3$, 6.9 Hz, 2H), 1.03 (s, 3H). MS m/z : 209 ($\text{M}^+ + 1$).

4,4-Dimethylspiro[5.5]undecane-2,8-dione (23) A colorless oil. IR (neat) cm^{-1} : 2950, 1700, 1440, 1380, 1340, 1320. $^1\text{H-NMR}$ (CDCl_3): δ 2.36–2.17 (m, 8H), 1.95–1.85 (m, 2H), 1.80–1.54 (m, 4H), 1.07 (s, 3H), 1.06 (s, 3H). $^{13}\text{C-NMR}$ (CDCl_3): δ 210.0 (s), 209.9 (s), 55.1 (t), 54.0 (t), 51.7 (t), 47.8 (t), 43.7 (s), 40.6 (t), 37.2 (t), 35.8 (s), 31.9 (q), 30.7 (q), 21.7 (t). MS m/z : 209 ($\text{M}^+ + 1$). FAB-MS m/z : 209.1553 (Calcd for $\text{C}_{13}\text{H}_{22}\text{O}_2$ ($\text{M} + \text{H}$) $^+$: 209.1541). $[\alpha]_D^{25} -15.5^\circ$ ($c=1.0$, CHCl_3) (91% ee) (Table 2, entry 7).

Determination of the Enantiomeric Excess of 23 p -TsOH– H_2O (10 mg) was added to a solution of compound (–)-**23** (52.7 mg, 0.25 mmol)

and (*R,R*)-2,3-butanediol (68 mg, 0.76 mmol) in benzene (15 ml), and the whole was refluxed with azeotropic removal of water for 2 h. The resulting mixture was washed with saturated aqueous NaHCO_3 and extracted with AcOEt. The combined organic layers were washed with brine, and dried. After removal of solvent *in vacuo*, the residue was purified by column chromatography (hexane/AcOEt=9:1) to give the corresponding bisacetal (**24**) (87 mg, 98% yield) as a colorless oil. IR (neat) cm^{-1} : 2970, 2940, 2860, 1450, 1370, 1320, 1300, 1220, 1200. $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ 3.63—3.49 (m, 4H), 2.08—2.00 (m, 2H), 1.66—1.23 (m, 12H), 1.18—1.20 (m, 3H $\times$ 4), 1.03 [0.97] (s, 3H), 0.93 [0.99] (s, 3H). $^{13}\text{C-NMR}$ (125.7 MHz, CDCl_3): δ 109.5 (s), 109.4 (s), 77.81 [77.85] (d), 77.71 [77.56] (d), 77.48 [77.19] (d), 76.52 [76.68] (d), 51.90 [49.68] (t), 48.6 [48.2] (t), 46.1 [45.8] (t), 43.5 [43.9] (t), 40.2 [38.3] (t), 37.1 [37.0] (t), 36.9 (s), 33.4 [32.4] (q), 32.2 (s), 31.43 [30.40] (q), 19.3 [19.7] (t), 17.22 [17.21] (q), 17.14 [17.08] (q), 17.04 [16.96] (q), 16.9 [16.8] (q). Chemical shifts are those of the major diastereomer, bisacetal of (–)-**23**, and those in parentheses are based on the minor diastereomer, bisacetal of (+)-**23**. The ee of **23** was determined based on the average ratio of these peak intensities.

References and Notes

- 1) a) Suemune H., Takahashi Y., Sakai K., *J. Chem. Soc., Chem. Commun.*, **1993**, 1858—1859; b) Yamada S., Karasawa S., Takahashi Y., Aso M., Suemune H., *Tetrahedron*, **54**, 15555—15566 (1998) and references cited therein.
- 2) For compound (*dl*)-**4**: Von der Werf, M. De Bont J. A. M., Swarts H. J., *Tetrahedron: Asymmetry*, **10**, 4225—4230 (1999) and references cited therein.; For compound (*dl*)-**5**: Takeda T., Imamoto T., *ibid.*, **10**, 3209—3218 (1999) and references cited therein.
- 3) For compound **11**: Shimizu, T., Ohzeki T., Hiramoto K., Hori N., Nakata T., *Synthesis*, **1999**, 1373—1385; Corey, E. J., Posner G. H., Atkinson R. F., Wingard A. K., Halloran D. J., Razik, D. M., Nash J. J., *J. Org. Chem.*, **54**, 389—393 (1989). For compound **8**: Furuya T., Orihara Y., Miyatake H., *J. Chem. Soc., Perkin Trans. 1*, **1989**, 1711—1719. For compound **9**: Takahashi H., Noma Y., Toyota M., Asakawa Y., *Phytochemistry*, **35**, 1465—1467 (1994).
- 4) Torisawa Y., Okabe H., Ikegami S., *Chem. Lett.*, **1984**, 1555.
- 5) Reaction of **14** with CsOAc at 150 °C in DMF gave elimination product (1*S*,6*S*)-3-methyl-6-(methylethyl)cyclohex-2-enyl benzoate in 43% yield.
- 6) For compounds **19** and **20**, absolute stereochemistry of acetal carbons was not determined.
- 7) The absolute stereochemistry of (–)-**23** was not determined.