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Synthetic Studies on Spiroketal Natural Products. III.[1] Enantioselective Synthesis of 1,6-Dioxaspiro[4.5]decane Compounds[2]

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Two enantiomers of 1,6-dioxaspiro[4.5]decane (**1**) and all four stereoisomers of 2-methyl-1,6-dioxaspiro[4.5]decane (an insect pheromone) (**9**) were successfully synthesized *via* a crucial step, an asymmetric five-membered ring cyclization induced by a sulfinyl chirality.

The alcohol (**6**), prepared from the optically active sulfoxide (**2**), was treated with potassium hydride to give the spiroketal (**7**), which was transformed into the isomer (**8**) by acid. Reductive desulfurization of these products furnished *R*-1 and *S*-1, respectively.

The ketone (**10**), also prepared from **2**, was reduced with diisobutylaluminum hydride (DIBAL) or DIBAL–$ZnCl_2$ to afford selectively **15a** or **15b**, respectively. Base-catalyzed cyclization gave **21a** and **21b**, which were convertible to **22a** and **22b** under acidic conditions. The four isomers (**21a**, **21b**, **22a**, and **22b**) were efficiently transformed into **9a**, **9b**, **9c**, and **9d** by removal of the chiral auxiliary.

Keywords——asymmetric synthesis; spiroketal; sulfinyl chirality; 1,6-dioxaspiro[4.5]decane; 2-methyl-1,6-dioxaspiro[4.5]decane; Michael reaction; insect pheromone; diisobutylaluminum hydride; diisobutylaluminum hydride–zinc chloride; asymmetric reduction

In the preceding paper, we reported an enantioselective synthesis of (*R*)- and (*S*)-isomers of 1,7-dioxaspiro[5.5]undecane (an insect pheromone).[1,3] In the synthesis, an extremely high-grade asymmetric six-membered ring cyclization was accomplished by means of an intramolecular Michael addition of a hydroxyl group to a chiral vinylic sulfoxide moiety. It seemed to be important to examine whether this novel method for asymmetric construction of the 6,6-spiroketal framework (1,7-dioxaspiro[5.5]undecane) is applicable to other spiroketal ring systems or not, since few general synthetic methods for chiral spiroketal compounds have been reported to date.[4] In this paper, as an application of this method for construction of spiroketals we describe an enantioselective synthesis of 1,6-dioxaspiro[4.5]decanes (5,6-spiroketal framework) by asymmetric five-membered ring cyclization.

Enantioselective Synthesis of (*R*)- and (*S*)-1,6-Dioxaspiro[4.5]decane

Although 1,6-dioxaspiro[4.5]decane (**1**) has not been identified as a naturally occurring product at the present time, it has been attracting much attention among organic chemists because of its structural resemblance to many volatile spiroketal-type insect pheromones. There have been several reports concerning its racemic synthesis.[5]

Treatment of the readily available optically active sulfoxide (**2**)[1] with lithium diethylamide in tetrahydrofuran (THF) followed by condensation with γ-butyrolactone at room temperature gave the ketol (**3**) in 90.4% yield. Its acetate (**4**) (81.0%) was successively reacted with pyridinium *p*-toluenesulfonate (PPTS) in methanol and *p*-toluenesulfonic acid (TSA) in benzene, affording the optically active dihydropyran derivative (**5**) (70.3%), which was converted into the alcohol (**6**) in 92.4% yield by the action of potassium carbonate in aqueous methanol.

In accordance with our previous finding,[1] on exposure of **6** to a large excess (*ca.* 10 molar eq) of potassium hydride in THF at room temperature, the desired intramolecular Michael reaction smoothly took place and the single cyclized product (**7**) [mp 126—128 °C, $[\alpha]_D^{17}$ +62.6° (c=1.87, $CHCl_3$)] was obtained in 81.2% yield. The proton magnetic resonance (^{1}H-NMR) spectrum of **7** exhibited a C_{10} proton signal at 2.75 ppm (dd, J=3.0 and 3.0 Hz), indicating that the sulfinyl group is axially situated and *trans* to the C_5–O_1 bond (anomeric effect). As the intramolecular Michael reaction would be stereochemically controlled by the sulfinyl chirality, the absolute configuration of the product must be 5*R*; 10*R*. On reaction with TSA in methanol, more than 94% of **7** was found to isomerize at the spiro center, affording the thermodynamically more stable 5*S*; 10*R* isomer **8** [mp 84—86 °C, $[\alpha]_D^{19}$ +95.9° (c=0.73, $CHCl_3$)]. A reductive desulfurization of each of the isomers (**7** and **8**) afforded the corresponding parent dioxaspiro compounds (*R*-1 and *S*-1). The present preparation of *R*-1 and *S*-1 is the first successful synthesis of 1,6-dioxaspiro[4.5]decane (**1**) in optically active form. The absolute values of specific optical rotations for the two enantiomers (*R*-1 and *S*-1) are well coincident and both **7** and **8** were considered to be diastereoisomerically pure. Since no racemization should take place during reductive desulfurization under basic conditions,[1] the optical purity of the products (*R*-1 and *S*-1) should be extremely high.

Stereoselective Synthesis of All Four Isomers of 2-Methyl-1,6-dioxapiro[4.5]decane

The next target for synthesis is 2-methyl-1,6-dioxaspiro[4.5]decane (**9**), which has been characterized as a component of insect pheromones isolated from the common wasp, *Papavespula vulgaris*.[6] There have been several syntheses of **9** in racemic or optically active form.[7] In order to synthesize **9** stereoselectively, it is necessary to control the other chiral

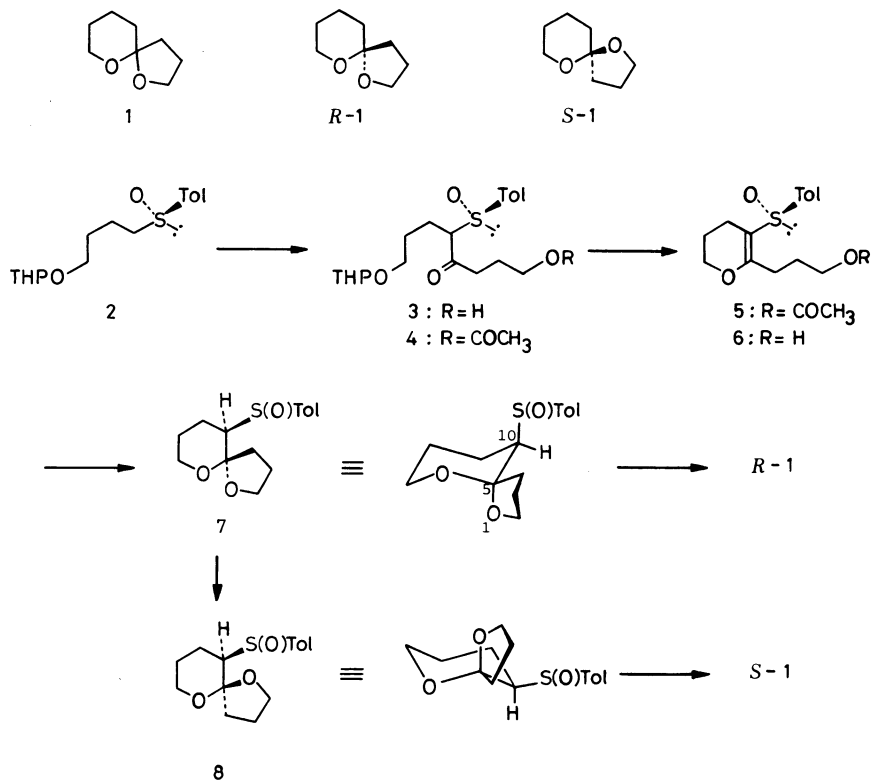


Chart 1

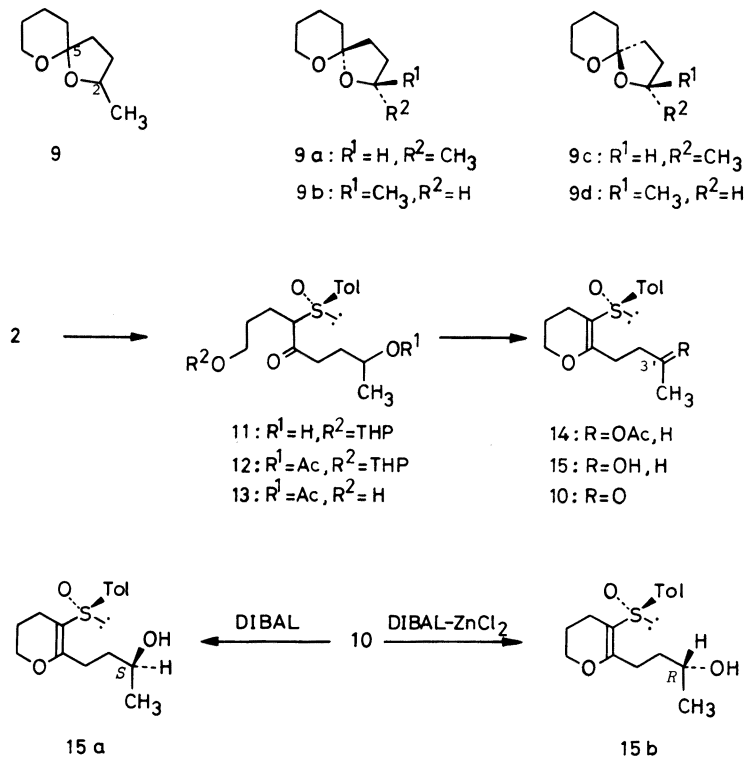
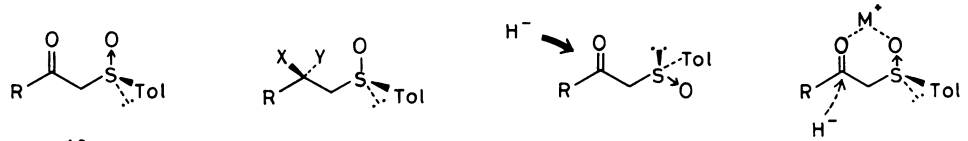


Chart 2

center (C_2) besides the spiro center. For introduction of the chirality at C_2, an asymmetric reduction of the ketone (**10**) was employed, and **10** was prepared as follows.

The anion generated from the sulfoxide (**2**) was allowed to react with (±)-γ-valerolactone in THF to afford a diastereoisomeric mixture of the alcohol (**11**) in 91.4% yield. By a 4-step sequence, **11** was transformed into the dihydropyran derivative (**15**) as an inseparable 1 : 1 diastereoisomeric mixture of **15a** (3′*R* configuration) and **15b** (3′*S* configuration) in 67% overall yield *via* **12**, **13**, and **14**. Pyridinium chlorochromate (PCC) oxidation of the mixture gave the desired ketone (**10**) [mp 135—136 °C, $[\alpha]_D^{23}$ −38.0° (c=1.54, $CHCl_3$)].

Recently, Solladié *et al.*[8] reported highly stereoselective reductions of chiral β-keto sulfoxide (**16**) *via* 1,3-asymmetric induction. The reduction with diisobutylaluminum hydride (DIBAL) in THF at low temperature gives the alcohol (**17**) exclusively and that with lithium aluminum hydride (LAH) or DIBAL–$ZnCl_2$ affords the isomer **18**, both in 90—95% diastereoisomeric excess.[9] They have proposed two possible transition states; a dipole model (**19**) for **17** and a chelate model (**20**) for **18**. Under the same conditions, reductions of **10** were examined, and the results are summarized in Table I. Although the chiral center in **10** is so far from the reaction center, it is very noteworthy that moderate diastereoselectivities were gained *via* 1,6-asymmetric induction (runs 1 and 2). The (3′*S*)-isomer (**15a**) mainly formed in the case of DIBAL and the (3′*R*)-isomer (**15b**) in the reaction with DIBAL–$ZnCl_2$. A chelate model (A), similar to **20**, is reasonable for explanation of the stereoselectivity in the case of DIBAL–$ZnCl_2$. The absence of stereoselection in the LAH reduction may be attributable to a somewhat weak Li-mediated chelating ability compared with that of Zn. On the other hand, any kinds of dipole models, similar to **19**, could not explain the relative high diastereoselection in the case of DIBAL only. The emergence of the diastereoselection seems



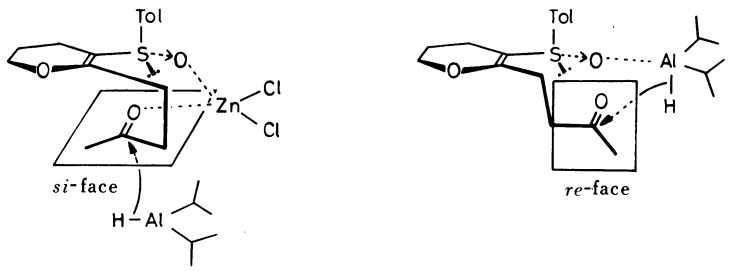
16 17 : X=H, Y=OH 18 : X=OH, Y=H 19 20

Chart 3

TABLE I. Synthesis of the Dioxaspiro[4.5]decanes (**21a** and **21b**) [**10**→**15**→**21**]

Run	Reduction of **10**			Cyclization of **15**[a]	
	Conditions	Yield of **15** (%)[b]	Ratio of **15a** : **15b**[c]	Yield of **21** (%)[b]	Ratio of **21a** : **21b**[c]
1	DIBAL/THF, −78 °C	94.4	85 : 15	84.5	82 : 18
2	DIBAL–$ZnCl_2$/THF, −78 °C	98.4	24 : 76	74.1	27 : 73
3	LAH/THF, −78 °C	99.0	42 : 58	85.7	45 : 55

a) Cyclization conditions: KH/THF, room temperature. *b*) Isolated yield. *c*) Determined by HPLC analysis.



A B

Fig. 1. Possible Intermediates in the Reduction of **10**

to be attributable to substrate-bound aluminum hydride, as illustrated by B (shown in Fig. 1). Namely, the tricoordinated aluminum atom in DIBAL is initially coordinated with the sulfinyl oxygen atom to form a tetracoordinated species, which has a much stronger hydride-donor character than DIBAL itself, and the activated hydride intramolecularly attacks the carbonyl function from the *re*-face to result in predominant formation of **15a**. A similar argument has appeared in a recent paper,[10] which dealt with a diastereoselective reduction of β-hydroxy ketones with a borane reductant. Although isolation of the epimeric alcohols (**15a** and **15b**) was hardly achieved, the ratio of **15a** and **15b** could be obtained by high performance liquid chromatography (HPLC) analysis (see Experimental). The stereochemistry of the products was confirmed by their cyclization as follows. A diastereomeric mixture of **15** was allowed to react with potassium hydride in THF at room temperature to give a readily separable mixture of two cyclized diastereoisomers (**21a** and **21b**) (see Table I). The C_2 configuration of **21a** and **21b** was determined to be *R* and *S*, respectively, on the basis of their ^{1}H-NMR signals: 1.33 ppm (a somewhat down-field shift due to anisotropy of the tetrahydropyranyl oxygen atom) for C_2-methyl of **21a** and 1.13 ppm for C_2-methyl of **21b**.

On treatment with TSA in methanol, the initially obtained dioxaspiro compounds (**21a** and **21b**) were easily converted into the corresponding C_5-epimers (**22a** and **22b**) *via* retro-

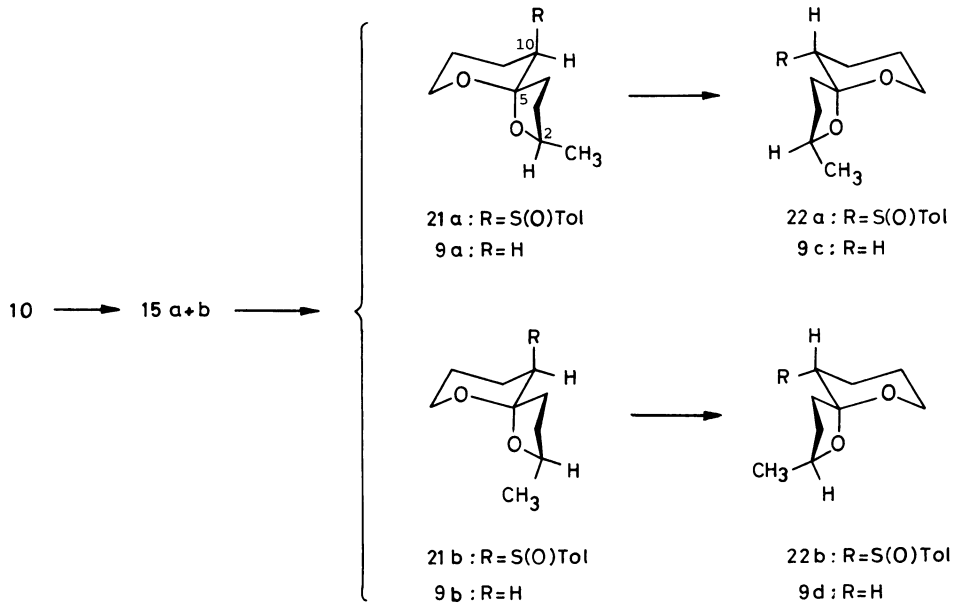


Chart 4

TABLE II. Physical Properties of **21a**, **21b**, **22a**, and **22b**

Compound No.	mp (°C)	$[\alpha]_D$ (deg., concentration)[a]	Analysis[b] (Found)		
			C	H	S
21a	132—133	+47.5, 1.04	65.07	7.67	10.84
21b	102—103	+34.1, 1.08	65.03	7.45	10.88
22a	111—113	+90.1, 1.07	65.41	7.35	10.86
22b	91—92.5	+87.9, 1.11	65.36	7.54	11.09

a) Measured in $CHCl_3$ at 13 °C (for **21a** and **21b**) or 15 °C (for **22a** and **22b**). *b*) Calcd for $C_{16}H_{22}O_3S$: C, 65.27; H, 7.53; S, 10.89.

TABLE III. Spectral Data of **21a**, **21b**, **22a**, and **22b**

Compound No.	IR (cm^{-1})	MS (*m/z*; %)	^{1}H-NMR [chemical shift (δ); *J* (Hz)]			
			C_2-CH_3	Ar-CH_3	C_{10}-H	Ar-H
21a	1600 1025	295 (M^+, 0.42) 155 (100)	1.18 d, J=6	2.40 s	2.76 dd, J=3, 3	7.26, 7.56 d, J=8
21b	1600 1025	295 (M^+, 0.55) 155 (100)	1.31 d, J=6	2.40 s	2.74 dd, J=3, 3	7.25, 7.57 d, J=8
22a	1600 1030	295 (M^+, 0.39) 155 (100)	1.35 d, J=6	2.41 s	2.98 dd, J=11, 7	7.24, 7.53 d, J=8
22b	1600 1025	295 (M^+, 0.47) 155 (100)	1.38 d, J=6	2.41 s	2.93 dd, J=12, 5	7.24, 7.54 d, J=8

Michael and Michael reactions. Physical and spectral data of the four stereoisomers (**21a**, **21b**, **22a**, and **22b**) are summarized in Tables II and III. As mentioned above, these four stereoisomers are all stereoselectively obtainable from the same key intermediate (**10**) by using

suitable combinations of conditions for ketone reduction and acid-catalyzed isomerization at the spiro center (or not).

Finally, by reductive desulfurization under basic conditions, all four stereoisomers (**9a**, **9b**, **9c**, and **9d**) of 2-methyl-1,6-dioxaspiro[4.5]decane were synthesized. Although some of them have already been obtained as optically active forms,[7a,d,h] the present synthesis of all the isomers of **9** seems to be of great value from the viewpoint that all the isomers were able to be prepared stereoselectively from the common starting material. Thus, the novel stereoselective method for construction of spiroketals has been found to be very useful not only for six-membered ring cyclization but also for five-membered ring closure in the course of this investigation.

Experimental

All melting and boiling points are uncorrected. Infrared (IR) spectra were recorded with a Hitachi 260-10 spectrometer. ^{1}H-NMR spectra were measured with a Hitachi R-60 (60 MHz), a Hitachi R-22 (90 MHz), a JEOL JNM-FX-90Q (90 MHz), or a JEOL JNM-GX-500 instrument. The chemical shifts are given as δ (ppm) values with tetramethylsilane as an internal standard. Optical rotations were recorded with a JASCO DIP-360 polarimeter. Mass spectra (MS) and high-resolution MS (High MS) were obtained with a Shimadzu QP-1000 or a JEOL JMS D-300 mass spectrometer. For column chromatography, Aluminiumoxid 90 or Kieselgel 60 (E. Merck) was used. After being dried over anhydrous sodium sulfate or magnesium sulfate, all organic extracts were concentrated under reduced pressure.

(R_S)-1-Hydroxy-8-(tetrahydropyran-2-yl)oxy-5-(*p*-tolyl)sulfinyloctan-4-one (3)——A solution of **2** (1.50 g, 4.59 mmol) in dry THF (10 ml) was added to a stirred $LiNEt_2$ solution [prepared from *n*-BuLi (1.6 M in hexane; 6.5 ml, 10.2 mmol) and diethylamine (1.05 ml, 10.2 mmol) in THF (15 ml)] at −60 °C over 20 min, and the mixture was further stirred at −40 °C for 30 min. A solution of γ-butyrolactone (1.30 g, 15.1 mmol) in dry THF (10 ml) was added to the stirred mixture at −78 °C over *ca.* 30 min and stirring was continued at the same temperature for 1 h. After addition of saturated NH_4Cl aqueous solution, the reaction mixture was extracted with $CHCl_3$. The extract was washed with brine, dried, and concentrated. The oily residue was chromatographed on silica gel with hexane–AcOEt (1 : 4) to afford **3** (1.75 g, 90.4%) as a colorless oil. $[\alpha]_D^{19}$ +81.0° (c = 0.99, $CHCl_3$). *Anal.* Calcd for $C_{20}H_{30}O_5S$: C, 62.80; H, 7.90; S, 8.38. Found: C, 62.78; H, 7.95; S, 8.02. IR ($CHCl_3$) cm^{-1}: 3400, 1710, 1600, 1030. ^{1}H-NMR ($CDCl_3$) δ: 1.34—2.24 (12H, m), 2.38 (3H, s, $ArCH_3$), 2.59 (2H, t, J = 7 Hz, C_3-H × 2), 2.82 (1H, br s, OH), 3.11—4.14 (7H, m), 4.58 (1H, br s, anomeric H), 7.13—7.42 (4H, m, Ar-H × 4). MS m/z (%): 382 (M^+, 0.05), 139 (13), 85 (100).

(R_S)-1-Acetoxy-8-(tetrahydropyran-2-yl)oxy-5-(*p*-tolyl)sulfinyloctan-4-one (4)——A mixture of **3** (1.08 g, 2.83 mmol), acetic anhydride (4 ml), and dry pyridine (4 ml) was allowed to stand at room temperature for 30 min and then concentrated *in vacuo* to give an oily residue, which was taken up in ether. The ethereal solution was washed with saturated $NaHCO_3$, saturated $CuSO_4$, and then brine. The dried organic layer was evaporated off and the residue was chromatographed on silica gel with hexane–AcOEt (1 : 3) to give **4** (972 mg, 81.0%) as a colorless oil. $[\alpha]_D^{19}$ +68.8° (c = 1.16, $CHCl_3$). *Anal.* Calcd for $C_{22}H_{32}O_6S$: C, 62.24; H, 7.61; S, 7.55. Found: C, 62.02; H, 7.64; S, 7.03. IR ($CHCl_3$) cm^{-1}: 1735, 1600, 1040. ^{1}H-NMR ($CDCl_3$) δ: 1.35—1.97 (12H, m), 2.01 (3H, s, $COCH_3$), 2.38 (3H, s, $ArCH_3$), 2.52 (2H, t, J = 7 Hz, C_3-H × 2), 3.15—4.04 (7H, m), 4.49 (1H, br s, anomeric H), 7.13—7.50 (4H, m, Ar-H × 4).

(R_S)-6-(3-Acetoxypropyl)-3,4-dihydro-5-(*p*-tolyl)sulfinyl-2*H*-pyran (5)——A mixture of **4** (157 mg, 0.368 mmol), PPTS (93.7 mg, 0.368 mmol), and dry MeOH (10 ml) was stirred at 50 °C for 6 h. After neutralization with saturated $NaHCO_3$ aqueous solution, the MeOH was evaporated off and the residue was extracted with $CHCl_3$. The extract was washed with brine, dried, and concentrated to dryness to leave an oil, which was taken up in dry benzene (30 ml) and treated with TSA (a catalytic amount; *ca.* 10 mg). The whole mixture was stirred at room temperature for 12 h. The reaction mixture was washed with saturated $NaHCO_3$ and brine, dried, and concentrated. The crude product was purified by chromatography on silica gel with hexane–AcOEt (1 : 3) to give **5** (83.3 mg, 70.3%) as a colorless oil. $[\alpha]_D^{19}$ +17.5° (c = 1.32, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 1730, 1630, 1600, 1040. ^{1}H-NMR ($CDCl_3$) δ: 1.30—2.25 (6H, m), 2.04 (3H, s, $COCH_3$), 2.37 (3H, s, $ArCH_3$), 2.75 (2H, t, J = 7 Hz, C_6-CH_2), 3.45—4.05 (2H, m), 4.11 (2H, t, J = 7 Hz, C_2-H × 2), 7.24, 7.40 (each 2H, d, J = 8 Hz, Ar-H × 4). MS m/z (%): 322 (M^+, 4.2), 141 (100). High MS Calcd for $C_{17}H_{22}O_4S$: 322.1236. Found: 322.1225.

(R_S)-3,4-Dihydro-5-(*p*-tolyl)sulfinyl-2*H*-pyran-6-propanol (6)——A mixture of **5** (325 mg, 1.01 mmol), K_2CO_3 (34.4 mg, 0.50 mmol), H_2O (10 ml), and MeOH (40 ml) was stirred at room temperature for 6 h. After neutralization with dilute HCl, the MeOH was evaporated off and the residue was extracted with $CHCl_3$. The extract was washed with brine, dried, and concentrated to leave an oil, which was chromatographed on silica gel with AcOEt to give **6** (0.300 g, 92.4%) as a colorless oil. $[\alpha]_D^{18}$ +14.9° (c = 0.74, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 1630, 1600, 1030. ^{1}H-NMR

($CDCl_3$) δ: 1.25—2.15 (6H, m), 2.37 (3H, s, $ArCH_3$), 2.59—2.99 (2H, m, C_6-CH_2), 3.22 (1H, br s, OH), 3.70 (2H, t, J=7 Hz, CH_2OH), 3.82—4.25 (2H, m, C_2-H × 2), 7.19, 7.38 (each 2H, d, J=7 Hz, Ar-H × 4). MS m/z (%): 280 (M^+, 1.6), 141 (17.9), 140 (100). High MS Calcd for $C_{15}H_{20}O_3S$: 280.1131. Found: 280.1118.

(5*R*,10*R*,*R*$_S$)-10-(*p*-Tolyl)sulfinyl-1,6-dioxaspiro[4.5]decane (7)——A solution of **6** (150 mg, 0.536 mmol) in dry THF (1 ml) was added to a stirred suspension of KH (*ca.* 200 mg, 5 mmol) in THF (5 ml) under ice cooling. The mixture was further stirred at room temperature for 1 h and treated with wet ether (*ca.* 20 ml) to decompose the excess KH. The resulting mixture was washed with brine, dried, and concentrated to leave a crude product, which was purified by chromatography on silica gel (ether–petr. ether = 2 : 1) and recrystallization from hexane–benzene to give **7** (122 mg, 81.2%) as colorless needles, mp 126—128 °C. $[\alpha]_D^{17}$ +62.6° (c = 1.87, $CHCl_3$). *Anal.* Calcd for $C_{15}H_{20}O_3S$: C, 64.26; H, 7.19; S, 11.43. Found: 63.97; H, 7.14; S, 11.29. IR ($CHCl_3$) cm^{-1}: 1600, 1500, 1150, 1085, 1030. ^{1}H-NMR ($CDCl_3$) δ: 1.80—2.32 (8H, m), 2.39 (3H, s, $ArCH_3$), 2.75 (1H, dd, J=3, 3 Hz, C_{10}-H), 3.50—4.18 (4H, m), 7.24, 7.54 (each 2H, d, J=9 Hz, Ar-H × 4). MS m/z (%): 280 (M^+, 1.3), 141 (100).

(5*S*,10*R*,*R*$_S$)-10-(*p*-Tolyl)sulfinyl-1,6-dioxaspiro[4.5]decane (8)——A mixture of **7** (150 mg, 0.536 mmol), TSA (82 mg, 0.536 mmol), and dry MeOH (16 ml) was stirred at room temperature for 24 h. After neutralization with saturated $NaHCO_3$ aqueous solution, the MeOH was evaporated off and the residue was taken up in $CHCl_3$. The $CHCl_3$ layer was washed with brine, dried, and concentrated to leave a crude product, which was purified by chromatography on silica gel (ether–petr. ether = 2 : 1) to give a crude **8** (141 mg, 94.1%), which was recrystallized from hexane to afford pure **8** (112 mg, 74.9%) as colorless plates, mp 84—86 °C. $[\alpha]_D^{19}$ +95.9° (c = 0.73, $CHCl_3$). *Anal.* Calcd for $C_{15}H_{20}O_3S$: C, 64.26; H, 7.19; S, 11.43. Found: C, 64.02; H, 7.26; S, 11.25. IR ($CHCl_3$) cm^{-1}: 1600, 1500, 1150, 1085, 1030. ^{1}H-NMR ($CDCl_3$) δ: 1.11—1.65 (4H, m), 1.85—2.23 (3H, m), 2.40 (3H, s, $ArCH_3$), 2.71—3.15 (1H, m), 2.98 (1H, dd, J=12, 5 Hz, C_{10}-H), 3.35—4.22 (4H, m), 7.22, 7.51 (each 2H, d, J=9 Hz, Ar-H × 4). MS m/z (%): 280 (M^+, 17), 141 (100).

(*R*)-1,6-Dioxaspiro[4.5]decane (*R*-1)——Raney Ni (W-2, *ca.* 1 g) was added to a mixture of **7** (62.0 mg, 0.221 mmol), NaOH (17.7 mg), and dry MeOH (10 ml). The whole mixture was stirred at 50 °C for 3 h. The catalyst was removed by filtration and the filtrate was concentrated carefully. The oily residue was chromatographed on alumina with pentane–ether (3 : 1) to give *R*-1 (27.1 mg, 86.2%) as a colorless oil, bp 110—120 °C (bath temperature)/30 mmHg. $[\alpha]_D^{25}$ −44.4° (c = 0.635, pentane). IR ($CHCl_3$) cm^{-1}: 1160, 1110, 1080. ^{1}H-NMR ($CDCl_3$) δ: 1.33—2.20 (10H, m), 3.41—4.10 (4H, m). MS m/z (%): 142 (M^+, 24), 98 (100). High MS Calcd for $C_8H_{14}O_2$: 142.0991. Found: 142.0984.

(*S*)-1,6-Dioxaspiro[4.5]decane (*S*-1)——Raney Ni (W-2, *ca.* 1.4 g) was added to a mixture of **8** (119.6 mg, 0.427 mmol), NaOH (34 mg), and dry MeOH (15 ml). The whole mixture was stirred at 50 °C for 3 h and work-up as described for *R*-1 gave *S*-1 (48.3 mg, 79.6%) as a colorless oil, bp 110—120 °C (bath temperature)/30 mmHg. $[\alpha]_D^{25}$ +43.9° (c = 0.760, pentane). High MS Calcd for $C_8H_{14}O_2$: 142.0991. Found: 142.0990. The IR, ^{1}H-NMR, and MS of *S*-1 were found to be identical with those of *R*-1.

(*R*$_S$)-8-Hydroxy-1-(tetrahydropyran-2-yl)oxy-4-(*p*-tolyl)sulfinylnonan-5-one (11)——The anion of **2** was prepared from **2** (1.86 g, 5.69 mmol), diethylamine (1.3 ml, 12.6 mmol), 1.6 M *n*-BuLi in hexane (8.1 ml, 12.6 mmol), and dry THF (20 ml) according to the procedure for preparation of **3**. A solution of (±)-γ-valerolactone (1.26 g, 12.6 mmol) in dry THF (10 ml) was added dropwise to the above mixture with stirring at −78 °C over 10 min and the whole mixture was further stirred for 1 h under cooling. Work-up as described for **3** gave a crude product, which was chromatographed on silica gel with hexane–AcOEt (1 : 3) to afford **11** (2.28 g, 91.4%) as a colorless oil. $[\alpha]_D^{13}$ +73.5° (c = 1.17, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 1710, 1600, 1500, 1030. ^{1}H-NMR ($CDCl_3$) δ: 1.08, 1.10 (total 3H, each d, J= 6 Hz, $CHCH_3$), 1.21—2.27 (12H, m), 2.41 (3H, s, $ArCH_3$), 2.51—2.79 (2H, m), 3.06—4.07 (6H, m), 4.31—4.61 (2H, m), 7.15—7.56 (4H, m, Ar-H × 4). MS m/z (%): 378 (M^+ − 18, 0.7), 139 (19), 91 (15), 85 (100).

(*R*$_S$)-8-Acetoxy-1-(tetrahydropyran-2-yl)oxy-4-(*p*-tolyl)sulfinylnonan-5-one (12)——A mixture of **11** (2.28 g, 5.76 mmol), Ac_2O (8 ml), and dry pyridine (8 ml) was allowed to stand at room temperature for 3 h. Work-up as described for **4** gave an oily residue, which was chromatographed on silica gel with hexane–AcOEt (1 : 2) to afford **12** (2.09 g, 81.0%) as a colorless oil. $[\alpha]_D^{13}$ +48.9° (c = 3.29, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 1730, 1600, 1500, 1375, 1030. ^{1}H-NMR ($CDCl_3$) δ: 1.12, 1.17 (total 3H, each d, J = 6 Hz, $CHCH_3$), 1.32—1.92 (12H, m), 1.97 (3H, s, $COCH_3$), 2.18—2.66 (2H, m), 2.39 (3H, s, $ArCH_3$), 3.14—4.02 (5H, m), 4.49 (1H, br s, anomeric H), 4.57—4.93 (1H, m, $CHCH_3$), 7.16—7.53 (4H, m, Ar-H × 4).

(*R*$_S$)-6-(3-Acetoxybutyl)-3,4-dihydro-5-(*p*-tolyl)sulfinyl-2*H*-pyran (14)——A mixture of **12** (2.08 g, 4.64 mmol), TSA (a catalytic amount; *ca.* 20 mg), and dry MeOH (80 ml) was stirred at room temperature for 4 h. After neutralization with saturated $NaHCO_3$ aqueous solution, the MeOH was evaporated off and the residue was taken up in $CHCl_3$. The $CHCl_3$ layer was washed with brine, dried, and concentrated to give a crude **13**, which was used in the next step without purification. A mixture of the crude **13**, TSA (*ca.* 20 mg), and dry benzene (80 ml) was stirred at room temperature for 10 h. Work-up as usual gave an oily residue, which was chromatographed on silica gel with hexane–AcOEt (1 : 1) to afford **14** (1.28 g, 82.1% from **12**) as a colorless oil. $[\alpha]_D^{13}$ −27.9° (c = 2.07, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 1730, 1630, 1600, 1500, 1375, 1030. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, d, J = 6 Hz, $CHCH_3$), 1.65—2.02 (4H, m), 2.01, 2.03 (total 3H, each s, $COCH_3$), 2.14—2.53 (2H, m), 2.38 (3H, s, $ArCH_3$), 2.74 (2H, t-like, J = 7 Hz, C_6-CH_2), 3.64—4.28 (2H, m, C_2-H × 2), 4.92 (1H, sex, J = 7 Hz, $CHCH_3$), 7.21, 7.38 (each 2H, d, J = 9 Hz, Ar-H × 4). MS

m/z (%): 336 (M^+, 37), 259 (100), 139 (25). High MS Calcd for $C_{18}H_{24}O_4S$: 336.1395. Found: 336.1416.

(R_S)-3,4-Dihydro-6-(3-oxobutyl)-5-(*p*-tolyl)sulfinyl-2*H*-pyran (10)——A mixture of **14** (1.14 g, 3.39 mmol), K_2CO_3 (130 mg, 0.94 mmol), H_2O (20 ml), and MeOH (80 ml) was stirred at room temperature for 6 h. Work-up as usual and chromatography of the crude product on silica gel with AcOEt gave **15** (823 mg, 82.5%) as a *ca.* 1 : 1 mixture of **15a** and **15b**, as a colorless oil. $[\alpha]_D^{15}$ −20.3° (*c* = 1.50, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 1635, 1600, 1500, 1030. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, d, *J* = 6 Hz, $CHCH_3$), 1.40—2.01 (5H, m), 2.16—2.53 (1H, m), 2.36 (3H, s, $ArCH_3$), 2.65—2.92 (2H, m, C_6-CH_2), 3.54—4.28 (4H, m), 7.21 (2H, d, *J* = 8 Hz, Ar-H × 2), 7.39, 7.40 (total 2H, each d, *J* = 8 Hz, Ar-H × 2).

A mixture of **15** (124 mg, 0.423 mmol), PCC (185 mg, 0.846 mmol), NaOAc (35.0 mg, 0.423 mmol), and dry CH_2Cl_2 (10 ml) was stirred at room temperature for 30 min. The reaction mixture was passed through a short column packed with Florisil and the column was washed thoroughly with CH_2Cl_2–ether (1 : 1). The combined eluates were evaporated and the residue was chromatographed on silica gel with hexane–AcOEt (1 : 3) to give **10** (83.0 mg, 66.9%) as colorless crystals, mp 135—136 °C. $[\alpha]_D^{23}$ −38.0° (*c* = 1.54, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 1715, 1635, 1030. ^{1}H-NMR ($CDCl_3$) δ: 1.41—1.97 (4H, m), 2.17 (3H, s, $COCH_3$), 2.37 (3H, s, $ArCH_3$), 2.57—3.09 (4H, m), 3.55—4.22 (2H, m, C_2-H × 2), 7.23, 7.44 (each 2H, d, *J* = 8 Hz, Ar-H × 4). MS *m/z* (%): 292 (M^+, 5.2), 249 (100), 139 (4.3). High MS Calcd for $C_{16}H_{20}O_3S$: 292.1134. Found: 292.1156.

Reduction of 10——a) With DIBAL: A DIBAL–hexane solution (2.0 M solution; 0.10 ml, 0.20 mmol) was added to a stirred solution of **10** (45.0 mg, 0.154 mmol) in dry THF (1 ml) at −78 °C and the reaction mixture was stirred at the same temperature for 10 min. After treatment with saturated NH_4Cl aqueous solution, the whole mixture was extracted with $CHCl_3$. The extract was washed with brine, dried, and concentrated to leave an oil, which was chromatographed on silica gel with AcOEt to give a mixture of **15a** and **15b** (42.5 mg, 94.4%) as a colorless oil.

b) With DIBAL–$ZnCl_2$: A solution of $ZnCl_2$ (28.7 mg, 0.209 mmol) in dry THF (1 ml) was added to a solution of **10** (61.0 mg, 0.209 mmol) in dry THF (1 ml) at −78 °C. After stirring under cooling for 5 min, a DIBAL–hexane solution (2.0 M solution; 0.26 ml, 0.54 mmol) was added and the resulting mixture was further stirred at the same temperature for 10 min. Work-up as described above gave a mixture of **15a** and **15b** (60.0 mg, 98.4%) as a colorless oil.

c) With LAH: A solution of **10** (14.0 mg, 0.048 mmol) in dry THF (1 ml) was added to a suspension of LAH (1.00 mg, 0.024 mmol) in dry THF (1 ml) at −78 °C and the mixture was stirred at the same temperature for 10 min. After addition of saturated potassium sodium tartrate aqueous solution, work-up as usual gave a mixture of **15a** and **15b** (14.0 mg, 100%) as a colorless oil.

The ratio of **15a** and **15b** was determined by means of HPLC analysis (pump, Shimadzu LC-5A; chiral column, SUMIPAC OA-2000A 4 mm × 25 cm; solvent hexane–diisopropyl ether (29 : 1); flow rate, 1 ml/min; column pressure, 40 kg/cm^2; detector, Sohma S-301A UV detector).

(2*S*,5*S*,10*R*,R_S)- and (2*R*,5*S*,10*R*,R_S)-2-Methyl-10-(*p*-tolyl)sulfinyl-1,6-dioxaspiro[4.5]decane (21a and 21b)——General Procedure: A solution of **15** (1.00 mmol) in dry THF (3 ml) was added to a suspension of KH (*ca.* 10 mmol) in dry THF (10 ml) and the resulting mixture was stirred at room temperature for 1 h. After addition of wet ether, the whole mixture was separated. The aqueous layer was extracted with ether thoroughly and the combined ether layer was washed with brine. The dried extract was concentrated to leave a crude cyclized product, which was chromatographed on silica gel with hexane–AcOEt (1 : 2) to give a mixture of **21a** and **21b**. The mixture was subjected to medium-pressure chromatography (a Lobar column: Merck LiChroprep Si 60) with benzene–AcOEt (2 : 1) to give **21a** from the first eluate and **21b** from the second one. The results are summarized in Table I. The physical and spectral data for **21a** and **21b** are summarized in Tables II and III.

(2*S*,5*R*,10*R*,R_S)-2-Methyl-10-(*p*-tolyl)sulfinyl-1,6-dioxaspiro[4.5]decane (22a)——A mixture of **21a** (104 mg, 0.350 mmol), TSA (66.6 mg, 0.350 mmol), and dry MeOH (15 ml) was stirred at room temperature for 24 h. Work-up as described for **8** afforded a crude product, which was chromatographed on silica gel with hexane–AcOEt (1 : 1) to give a mixture of **22a** and **21a** (103 mg, quantitative yield), the ratio of which was found to be 86 : 14 by means of HPLC analysis as described in the case of the reduction of **10**. A pure sample of **22a** was obtained by recrystallization from benzene. The physical and spectral data for **22a** are summarized in Tables II and III.

(2*R*,5*R*,10*R*,R_S)-2-Methyl-10-(*p*-tolyl)sulfinyl-1,6-dioxaspiro[4.5]decane (22b)——The same treatment of **21b** (110 mg, 0.370 mmol) as that for **22a** gave a mixture of **22b** and **21b** (92 : 8) (110 mg, quantitative yield). A pure sample of **22b** was obtained by recrystallization from hexane–benzene. The physical and spectral data for **22b** are summarized in Tables II and III.

Four Isomers of 2-Methyl-1,6-dioxaspiro[4.5]decane (9) (Reductive Desulfurization of 21a, 21b, 22a, and 22b)——Each of the diastereoisomeric sulfoxides (**21a**, **21b**, **22a**, and **22b**) was desulfurized by the same procedure as described for **1**. The physical and spectral data for the products are as follows.

(2*S*,5*R*)-2-Methyl-1,6-dioxaspiro[4.5]decane (**9a**): 81.2% from **21a**. bp 100—110 °C (bath temperature)/20 mmHg. $[\alpha]_D^{20}$ −79.1° (*c* = 0.392, pentane). IR ($CHCl_3$) cm^{-1}: 1160, 1125, 1090, 1075. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, d, *J* = 6 Hz, C_2-CH_3), 1.35—2.31 (10H, m), 3.33—3.95 (2H, m, C_7-H × 2), 4.09 (1H, sex, *J* = 6 Hz, C_2-H). MS *m/z* (%): 156 (M^+, 15), 111 (8.6), 101 (40), 98 (100). High MS Calcd for $C_9H_{16}O_2$: 156.1149. Found: 156.1167.

(2*R*,5*R*)-2-Methyl-1,6-dioxaspiro[4.5]decane (**9b**): 73.8% from **21b**. bp 100—110 °C (bath temperature)/

20 mmHg. $[\alpha]_D^{20}$ −83.4° (c=0.728, pentane). IR ($CHCl_3$) cm^{-1}: 1160, 1120, 1080, 1070. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, d, J=6 Hz, C_2-CH_3), 1.35—2.32 (10H, m), 3.30—4.28 (3H, m, C_2-H and C_7-H × 2). MS m/z (%): 156 (M^+, 29), 111 (69), 101 (35), 55 (100). High MS Calcd for $C_9H_{16}O_2$: 156.1149. Found: 156.1149.

(2*S*,5*S*)-2-Methyl-1,6-dioxaspiro[4.5]decane (**9c**): 77.8% from **22a**. bp 100—110 °C (bath temperature)/20 mmHg. $[\alpha]_D^{20}$ +84.2° (c=0.101, pentane). High MS Calcd for $C_9H_{16}O_2$: 156.1149. Found: 156.1128. IR, ^{1}H-NMR, and MS of **9d** were identical with those of **9b**.

(2*R*,5*S*)-2-Methyl-1,6-dioxaspiro[4.5]decane (**9d**): 79.2% from **22b**. bp 100—110 °C (bath temperature)/20 mmHg. $[\alpha]_D^{20}$ +79.2° (c=0.725, pentane). High MS Calcd for $C_9H_{16}O_2$: 156.1149. Found: 156.1161. IR, ^{1}H-NMR, and MS of **9c** were identical with those of **9a**.

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