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Synthetic Studies on Spiroketal Natural Products. I. A Stereoselective Synthesis of (2*R**,5*R**)- and (2*R**,5*S**)-2-Methyl-1,6-dioxaspiro[4.5]decane[1)]

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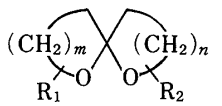
A stereoselective and novel method for construction of the spiroketal moiety is described, as illustrated by a synthesis of (2*R**,5*R**)- and (2*R**,5*S**)-2-methyl-1,6-dioxaspiro[4.5]decane (**2A** and **2B**).

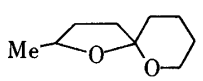
The sulfide (**7**), prepared from a lactone (**4**), was oxidized with sodium metaperiodate followed by treatment with an acid to provide the two sulfoxide products (**3A** and **3B**) in a 1 : 1 ratio. Acid-catalyzed cyclization of both compounds gave the corresponding dioxaspiro derivatives (**9** and **10**) without significant stereoselectivity, while their intramolecular bromohydrin formation reactions exhibited moderate stereoselection. Upon treatment with *N*-bromosuccinimide (NBS) followed by reductive operations, **3A** gave **9a** and **3B** afforded **10d** as major products. On the other hand, base-catalyzed intramolecular Michael reactions of **3A** and **3B** yielded **9b** and **10c** with extremely high stereoselectivity. These two dioxaspiro products were found to isomerize to the corresponding more stable isomers **9d** and **10a** on acidic treatment. Desulfurization of **9b** or **10a** afforded **2A** and that of **9d** or **10c** gave **2B** without any isomerization at the spiro center.

Keywords——1,6-dioxaspiro[4.5]decane; insect pheromone; vinylic sulfoxide; intramolecular Michael addition; sulfinyl chirality; desulfurization; total synthesis

The spiroketal framework represented by structure **1** plays a very important role as a complete or partial structural unit for many kinds of biologically active natural products such as calcimycin,[2)] monensin,[3)] milbemycins,[4)] talaromycins,[5)] and insect pheromones.[6)] Because of their valuable biological activities and the structural feature, spiroketals have been the focus of intense synthetic interest in recent years. Consequently, some sophisticated methods for construction of spiroketals, *e.g.*, acid-catalyzed intramolecular ketalization,[7)] hetero Diels–Alder reaction,[8)] the nitrile oxide cyclization (NOC) approach,[9)] cation-olefin cyclization,[10)] and organoselenium-mediated cyclization,[11)] have been developed to date. In most



1 $m, n = 2, 3$
R_1, R_2 = H, Me, Et



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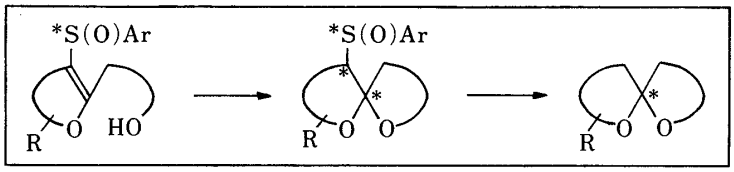


Chart 1

of these previous methods, however, no attempt has been made to control the stereochemistry at the spiro center. From the viewpoint of studies on the correlation between biological activities and stereochemistry,[12] the development of a novel construction method for spiroketal compounds with stereocontrol at the spiro center seems to be of great value. We have developed a stereoselective synthesis of spiroketal natural products with the aid of sulfinyl stereochemistry, as illustrated by the equation in Chart 1. We describe here its application to a diastereoselective total synthesis of two isomers of (±)-2-methyl-1,6-dioxaspiro[4.5]decane (**2**), which were isolated as insect pheromones of a common wasp, *Paravespula vulgaris*.[13]

Preparation and Structural Elucidation of 2,3-Dihydro-5-(4-hydroxybutyl)-2-methyl-4-phenylsulfinylfuran (3)

At first, the dihydrofuran (**3**) was prepared as follows, as a substrate to be cyclized according to the equation in Chart 1. The lactone (**4**)[14] was allowed to react with the Grignard reagent (**5**) generated from 4-[(tetrahydropyran-2-yl)oxy]butyl chloride[15] in tetrahydrofuran (THF) to afford the alcohol (**6**) in 73% yield as a diastereomeric mixture. Treatment of **6** with *p*-toluenesulfonic acid (TSA) in ether at 0 °C afforded the dihydrofuran (**7**) in 98% yield. Its proton nuclear magnetic resonance (^{1}H-NMR) spectrum exhibited two signals at 2.27 (dd, $J=14$, 8 Hz) and 2.83 ppm (dd, $J=14$, 10 Hz), and their signals were easily assignable to H_A and H_B attached on C-3, respectively, based on the coupling constants and chemical shifts. On oxidation with sodium metaperiodate[16] in methanol, the sulfide (**7**) gave the sulfoxide (**8**) as a diastereomeric mixture in 93% yield. The isomers (**8A** and **8B**) was separable by column chromatography, and the ratio of **8A**/**8B** was almost 1/1. Compared with the parent compound (**7**), isomer **8A** displayed lower-shifted H_A and higher-shifted H_B signals in the ^{1}H-NMR spectrum while the isomer **8B** showed reverse behavior (see the values depicted in Chart 2). These phenomena may be attributable to anisotropies of the phenyl

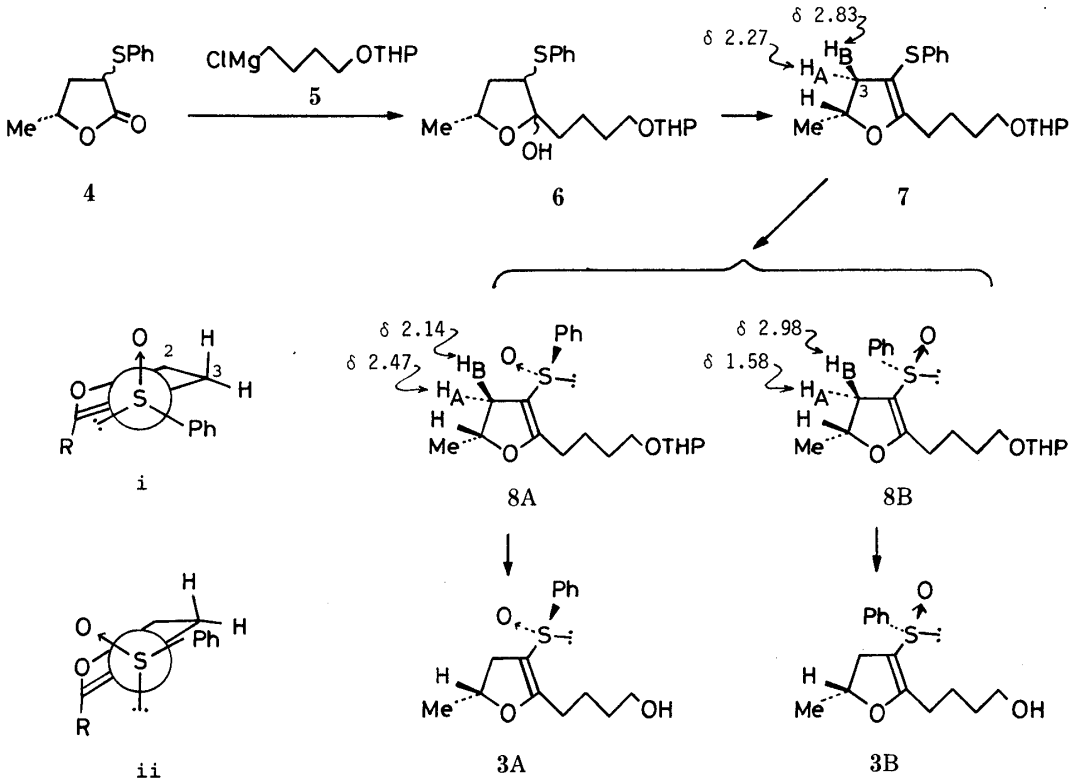


Chart 2

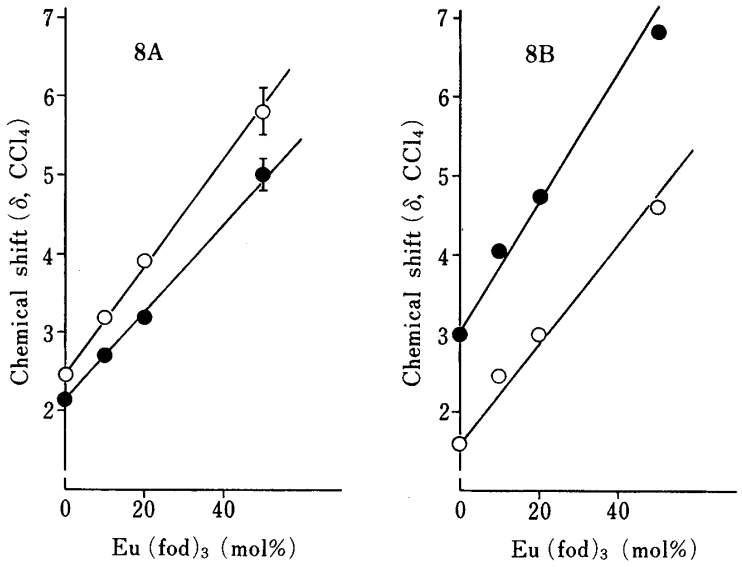


Fig. 1. Lanthanide-Induced Chemical Shifts of C_3-Protons (H_A and H_B) in **8A** and **8B**

—○—, H_A; —●—, H_B.

group and sulfinyl oxygen atom. Lanthanide-induced shift experiments clarified the situation. The result is shown in Fig. 1, which indicates that the H_A in isomer **8A** is closer to the sulfinyl oxygen than the H_B, and isomer **8B** has the opposite relation. Based on a consideration of $A^{1,3}$-strain and dipole repulsion, the most stable conformation of the sulfinyl group in the R^*_S isomer is assumed to be conformer i, in which the lone pair on the sulfur atom is situated near the bulky C-5 alkyl substituent, rather than the 'zig-zag' conformer ii.[17,18] From the above considerations, the two diastereomers, **8A** and **8B**, were decided to have the stereochemistry shown in Chart 2.

By acidic hydrolysis under mild conditions, the ethers (**8A** and **8B**) were converted into the corresponding alcohols (**3A** and **3B**).

Stereoselective Formation of the 1,6-Dioxaspiro[4.5]decanes (9 and 10)

Initially, for transformation of **3** into the dioxaspirodecanes (**9** and **10**), acidic conditions were employed. On treatment of **3A** with TSA in methanol at room temperature, the cyclization slowly proceeded and after 24 h the cyclized product (**9**) was obtained in 87% yield as a diastereomeric mixture. The same treatment of **3B** also gave the cyclized product (**10**) in 84% yield. Employment of other conditions afforded similar results, which are summarized in Tables I and II. Each of the four isomers of **9** and **10** was separated and the stereochemistry was confirmed by ^{1}H-NMR spectral considerations and chemical transformations as mentioned later.

As shown in the Tables, almost all runs with **3A** gave mainly **9a** and **9c**, epimeric at the spiro center, while **3B** predominantly afforded **10a** and **10d**, epimeric at C-2. The reaction may proceed *via* protonation at C-4, formation of the spiroketal system by intramolecular acetalization, and then acidic isomerization at the spiro center. Therefore, the direction of protonation and the thermodynamic stability under the conditions employed seem to control the stereochemistry at C-4 and at the spiro center, respectively. Consequently, the stereoselectivities of acidic cyclizations were found to be relatively low.

Next, a halohydrin method was tried. Tsuchihashi *et al.* previously reported a highly stereoselective conversion of a chiral vinyl sulfoxide to α-bromo-β-hydroxysulfoxide derivatives by an intermolecular reaction.[18] The treatment of **3A** with *N*-bromosuccinimide (NBS) in THF at 0 °C afforded a diastereomeric mixture of the brominated spiroketal (**11**),

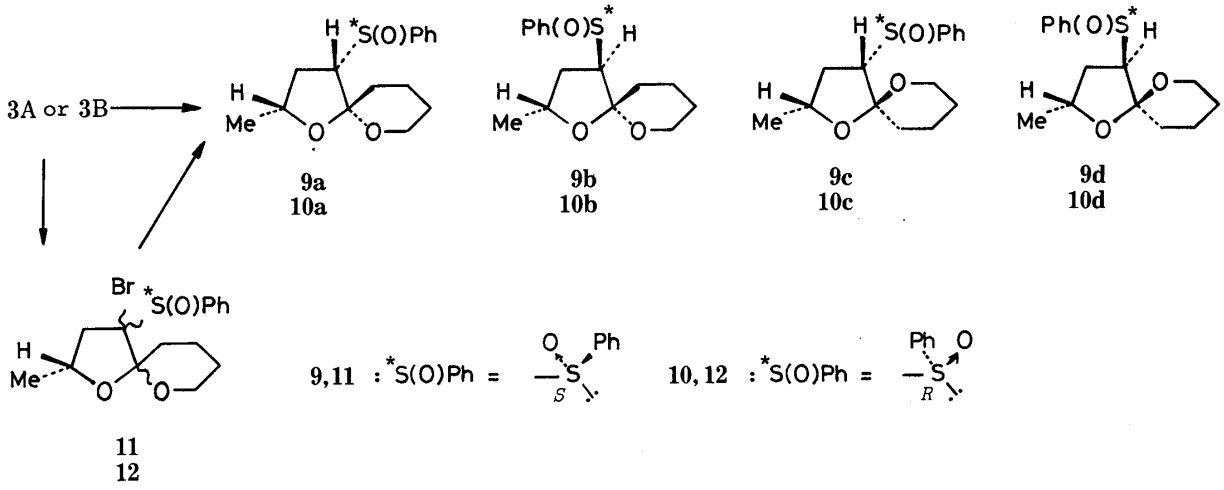


Chart 3

TABLE I. Acid-Catalyzed Cyclization of **3A**

Reaction conditions	Yield of **9**[a] (%)	Composition[b] (%)			
		9a	**9b**	**9c**	**9d**
TSA/MeOH, r.t., 24 h	87	36	0	51	13
TSA/CH_2Cl_2, r.t., 24 h	100	46	0	51	3
$ZnCl_2$/CH_2Cl_2, r.t., 24 h	85	73	0	16	11
$ZnBr_2$/CH_2Cl_2, r.t., 24 h	77	73	0	22	11
$MgCl_2$/CH_2Cl_2, r.t., 24 h	83	24	0	74	2
$HgCl_2$/CH_2Cl_2, r.t., 24 h	—[c]	36	5	51	8

a) Isolated yield. *b*) Determined by means of HPLC analysis. *c*) Not isolated.

TABLE II. Acid-Catalyzed Cyclization of **3B**

Reaction conditions	Yield of **10**[a] (%)	Composition[b] (%)			
		10a	**10b**	**10c**	**10d**
TSA/MeOH, r.t., 24 h	84	37	11	10	42
TSA/CH_2Cl_2, r.t., 24 h	100	13	6	1	80
$ZnCl_2$/CH_2Cl_2, r.t., 24 h	83	38	1	5	56
$ZnBr_2$/CH_2Cl_2, r.t., 24 h	80	52	3	6	38
$MgCl_2$/CH_2Cl_2, r.t., 24 h	86	1	45	1	53
$HgCl_2$/CH_2Cl_2, r.t., 24 h	—[c]	18	22	23	37

a) Isolated yield. *b*) Determined by means of HPLC analysis. *c*) Not isolated.

which was reduced with sodium borohydride in aqueous methanol to give **9a—d** in a ratio of 82:6:2:10 in 75% yield (total) from **3A**. The same treatment of **3B** provided **10a—d** *via* intermediate **12** in a ratio of 23:3:7:67 in 75% yield (total). Although the mechanism is not entirely clear at present, the intramolecular bromohydrin method resulted in predominant formations of **9a** and **10d** from **3A** and **3B**, respectively (Chart 3).

Alternatively, Tsuchihashi *et al.* also reported that base-catalyzed Michael addition of ethyl malonate to a vinylic sulfoxide gave a high stereoselectivity.[19] Abbott *et al.* demonstrated that piperidine reacted with a vinylic sulfinyl moiety stereoselectively, yielding a

Michael adduct.[20] In spite of the intermolecular nature of the reactions, highly effective asymmetric inductions were achieved. In our substrates (**3A** and **3B**), possessing both the Michael acceptor (vinylic sulfinyl group) and the nucleophile (hydroxyl group) in the molecules, a much higher stereoselectivity is expected. Thus, we examined the intramolecular Michael reactions of **3A** and **3B**. *n*-Butyllithium, sodium hydride, and potassium hydride

TABLE III. Base-Catalyzed Cyclization of **3A**

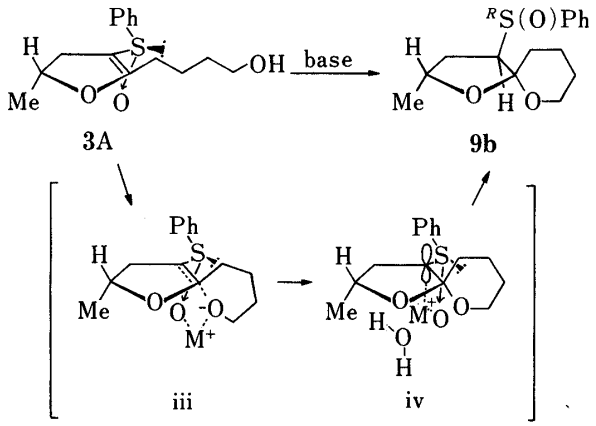
Reaction conditions	Yield of **9**[a] (%)	Composition[b] (%)			
		9a	**9b**	**9c**	**9d**
n-BuLi/THF, reflux, 2 h	82	0	86	14	0
NaH/THF, reflux, 2 h	93	0	94	6	0
KH/THF, r.t., 30 min	90	0	100	0	0
NaH/THF–hexane (1 : 1), reflux, 2 h	92	0	98	2	0
NaH/DME, reflux, 2 h	90	0	94	6	0
NaH/DMF, reflux, 2 h	80	31	38	21	10
NaH/DMSO, reflux, 2 h	85	18	4	36	42

a) Isolated yield. *b*) Determined by means of HPLC analysis.

TABLE IV. Base-Catalyzed Cyclization of **3B**

Reaction conditions	Yield of **10**[a] (%)	Composition[b] (%)			
		10a	**10b**	**10c**	**10d**
n-BuLi/THF, reflux, 2 h	81	0	4	96	0
NaH/THF, reflux, 2 h	92	0	2	98	0
KH/THF, reflux, 2 h	90	0	0	100	0
NaH/THF–hexane (1 : 1), reflux, 2 h	92	0	0	100	0
NaH/DME, reflux, 2 h	89	0	3	97	0
NaH/DMF, reflux, 2 h	78	22	11	8	59
NaH/DMSO, reflux, 2 h	83	37	13	6	44

a) Isolated yield. *b*) Determined by means of HPLC analysis.



3B $\xrightarrow{\text{base}}$ **10c**

Chart 4

were used as the base and THF, THF–hexane, 1,2-dimethoxyethane (DME), *N*,*N*-dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) as the solvent. The results are summarized in Tables III and IV. The reactions in polar solvents (DMF and DMSO) resulted in formation of all diastereoisomers of the cyclized products (**9a—d** or **10a—d**) without significant selection. On the other hand, all the runs in nonpolar solvents gave a quite satisfactory stereoselectivity. Isomers **3A** and **3B** afforded exclusively **9b** and **10c**, respectively. Practically 100% stereoselection was achieved by the use of potassium hydride in THF.

This observed stereoselectivity can be interpreted as follows, taking the reaction of **3A** as an example. A possible transition state (iii), in which the sulfinyl oxygen and the terminal oxido anion are chelated by the metal cation, would severely restrict the direction of the newly formed C–O bond. In the second step, protonation of the α-sulfinyl carbanion would take place from the same side of the sulfinyl oxygen *via* an intermediate (iv). Isomerization at the spiro center could not occur under the basic conditions employed.

Synthesis of (2*R,5*R**)- and (2*R**,5*S**)-2-Methyl-1,6-dioxaspiro[4.5]decane (2A and 2B)**

The sulfinylated dioxaspiro products (**9b** and **10c**), both predominantly obtained by a base-catalyzed cyclization of **3A** and **3B**, were treated with TSA to examine their thermodynamic stability. On reaction of **9b** with 1 eq of TSA in methanol at room temperature for 24 h, **9d** was obtained quantitatively *via* an exclusive steric inversion only at the spiro center, while the same reaction of **10c** gave **10a** along with the unchanged starting material (**10a**/**10c** = 80/20). The isomerization experiments revealed that **9b** (**10a**) and **9d** (**10c**) are epimers at the spiro center. It is noteworthy that **10a**, in which the methyl group is *cis* to the C_5–O_6 bond, is thermodynamically more stable than its *trans* isomer **10c**, although in the parent compounds (**2A** and **2B**) the reverse was observed.[13,21]

The four isomers (**9b**, **9d**, **10a**, and **10c**) were subjected to desulfurization reaction using Raney nickel (W-2) in methanol under basic conditions. Isomer **9b** or **10a** afforded the volatile dioxaspiroketal (**2A**) as a diastereomerically pure form, and the other spiroketal (**2B**) was also

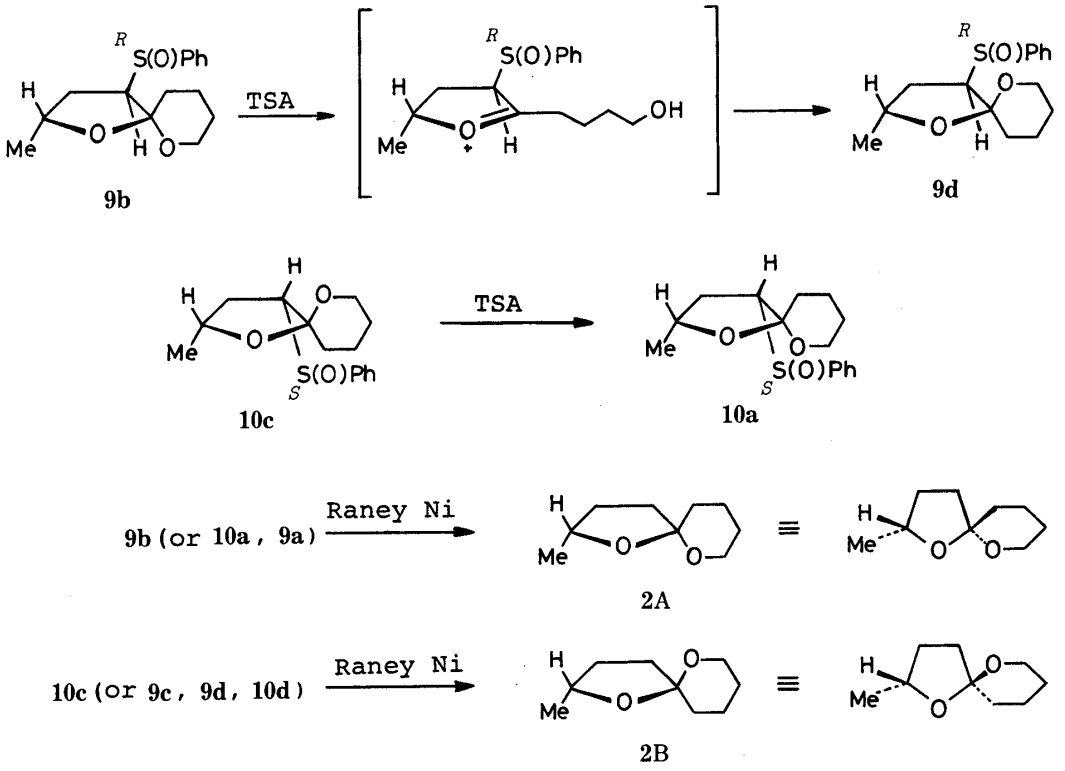


Chart 5

obtained in a pure form from **9d** or **10c**.

In conclusion, we have developed a novel construction method for the spiroketal framework by means of an intramolecular Michael addition of a hydroxy group to the vinylic sulfinyl moiety. According to this method, not only a thermodynamically stable dioxaspiro compound (**2B**) but also the less stable one (**2A**) were synthesized diastereoselectively. It is noteworthy that the non-volatile precursors (**9** and **10**), which are easily handled, are efficiently convertible into volatile parent dioxaspiro compounds (**2**) in a pure state by a catalytic hydrogenation procedure under basic conditions.

Experimental

All melting points 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-20 (60 MHz), a Hitachi R-22 (90 MHz), a JEOL JNM-FX-90Q (90 MHz), or a JEOL JNM-GX500 instrument, and the chemical shifts are given as δ (ppm) values with tetramethylsilane as an internal standard. The mass spectra (MS) and high-resolution MS (High MS) were obtained with a Shimadzu QP-1000 or a JEOL JMS-D300 mass spectrometer. Aluminiumoxide 90 and Kieselgel 60 (E. Merck) were used for column chromatography and preparative thin-layer chromatography (TLC), respectively. After drying over anhydrous sodium sulfate or magnesium sulfate, all organic extracts were concentrated under reduced pressure.

2-Hydroxy-5-methyl-3-phenylthio-2-[4-[(tetrahydropyran-2-yl)oxy]butyl]tetrahydrofuran (6)——A solution of **5** in dry THF [prepared from 4-[(tetrahydropyran-2-yl)oxy]butyl chloride[15] (22.3 g, 0.12 mol) and Mg (3.6 g, 0.15 mol) in dry THF (150 ml)] was added to a stirred solution of **4**[14] (4.6 g, 0.023 mol) in dry THF (50 ml) at 60°C over 30 min, and stirring at the same temperature was continued for 3 h. After cooling of the reaction mixture, saturated NH_4Cl was added and the organic layer was separated. The aqueous layer was extracted with ether. The combined extracts were washed with brine, dried, and concentrated. The oily residue was chromatographed on alumina with ether–petr. ether (1 : 1) to afford **6** (9.2 g, 73%) as a colorless oil. An analytical sample was obtained by distillation under reduced pressure, bp 170°C (0.002 mmHg). *Anal.* Calcd for $C_{20}H_{30}O_4S$: C, 65.55; H, 8.25. Found: C, 65.44; H, 8.43. IR (CCl_4) cm^{-1}: 3300, 1710, 1580, 1480. ^{1}H-NMR (CCl_4) δ: 2.42—2.75 (1H, m, C_3-H), 3.10—4.05 (6H, m, OH, C_5-H, and $OCH_2 \times 2$), 4.45 (1H, br s, anomeric H), 7.00—7.38 (5H, m, aromatic H × 5). MS *m/z*(%): 366 (M^+, 1.2), 348 (1.3), 85 (100).

2,3-Dihydro-2-methyl-4-phenylthio-5-[4-[(tetrahydropyran-2-yl)oxy]butyl]furan (7)——A mixture of **6** (135 mg, 0.37 mmol), TSA (5 mg), and dry ether (20 ml) was stirred at room temperature for 45 min. The mixture was neutralized by addition of saturated $NaHCO_3$ and then washed with brine. The dried organic layer was concentrated to leave an oil, which was chromatographed on alumina with benzene to give **7** (126 mg, 98%) as a colorless oil. bp 150°C (0.002 mmHg). *Anal.* Calcd for $C_{20}H_{28}O_3S$: C, 68.94; H, 8.10. Found: C, 68.74; H, 8.13. IR (CCl_4) cm^{-1}: 1640, 1580, 1480. ^{1}H-NMR (CCl_4) δ: 1.35 (3H, d, J=6 Hz, C_2-CH_3), 2.20–2.46 (2H, m, C_5-CH_2), 2.27 (1H, dd, J=14, 8 Hz, C_3-H_A), 2.83 (1H, dd, J=14, 10 Hz, C_3-H_B), 3.19—3.88 (4H, m, $OCH_2 \times 2$), 4.44 (1H, br s, anomeric H), 4.45—4.89 (1H, m, C_2-H), 6.88—7.22 (5H, m, aromatic H × 5). MS *m/z* (%): 348 (M^+, 37), 85 (100).

(2*R,*S**$_S$)- and (2*R**,*R**$_S$)-2,3-Dihydro-2-methyl-4-phenylsulfinyl-5-[4-[(tetrahydropyran-2-yl)oxy]butyl]furan (8A and 8B)**——A solution of $NaIO_4$ (84 mg, 0.39 mmol) in water (5 ml) was added to a stirred solution of **7** (105 mg, 0.30 mmol) in dry MeOH (20 ml) at 0 °C and the resulting mixture was further stirred at room temperature for 36 h. The reaction mixture was neutralized with saturated $NaHCO_3$ and then extracted with $CHCl_3$. The extract was washed with brine, dried, and concentrated. The oily residue was chromatographed on alumina with $CHCl_3$ to give a mixture of **8A** and **8B** (103 mg, total 93% yield), which was rechromatographed by the use of a Lobar column, LiChroprep Si 60, with AcOEt-hexane (4 : 3) to afford **8A** (53 mg) from the first eluate and **8B** (48 mg) from the second one.

8A: A colorless oil. IR ($CHCl_3$) cm^{-1}: 1640, 1590, 1040. ^{1}H-NMR ($CDCl_3$) δ:1.33 (3H, d, J=6 Hz, C_2-CH_3), 2.14 (1H, dd, J=14, 10 Hz, C_3-H_B), 2.47 (1H, dd, J=14, 8 Hz, C_3-H_A), 2.45—2.70 (2H, m, C_5-CH_2), 3.20—3.92 (4H, m, $OCH_2 \times 2$), 4.37—4.78 (1H, m, C_2-H), 4.49 (1H, br s, anomeric H), 7.20—7.52 (5H, m, aromatic H × 5). MS *m/z* (%): 364 (M^+, 0.4), 85 (100). High MS Calcd for $C_{20}H_{28}O_4S$: 364.171. Found: 364.171.

8B: A colorless oil. IR ($CHCl_3$) cm^{-1}: 1640, 1590, 1040. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, d, J=6 Hz, C_2-CH_3), 1.58 (1H, dd, J=14, 8 Hz, C_3-H_A), 2.46—2.72 (2H, m, C_5-CH_2), 2.98 (1H, dd, J=14, 10 Hz, C_3-H_B), 3.20—3.92 (4H, m, $OCH_2 \times 2$), 4.50 (1H, br s, anomeric H), 4.52–4.95 (1H, m, C_2-H), 7.20—7.52 (5H, m, aromatic H × 5). MS *m/z* (%): 364 (M^+, 0.5), 85 (100). High MS Calcd for $C_{20}H_{28}O_4S$: 364.171. Found: 364.170.

(2*R,*S**$_S$)-2,3-Dihydro-5-(4-hydroxybutyl)-2-methyl-4-(phenylsulfinyl)furan (3A)**——A mixture of **8A** (0.10 g, 0.27 mmol), TSA (trace), and dry MeOH (5 ml) was stirred at room temperature for 2 h and neutralized with saturated $NaHCO_3$. The methanol was evaporated off and the residue was taken up in $CHCl_3$. The $CHCl_3$ solution was washed with brine, dried, and concentrated to leave an oil, which was chromatographed on alumina with AcOEt to give **3A**

(71 mg, 92%) as a colorless oil. IR ($CHCl_3$)cm^{-1}: 3400, 1635, 1590, 1030. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, d, J=7 Hz, C_2-CH_3), 3.57—3.83 (2H, m, OCH_2), 4.46—4.89 (1H, m, C_2-H), 7.30—7.62 (5H, m, aromatic H×5). MS m/z (%): 280 (M^+, 3.0), 232 (100). High MS Calcd for $C_{15}H_{20}O_3S$: 280.113. Found: 280.111.

(2*R,*R**$_S$)-2,3-Dihydro-5-(4-hydroxybutyl)-2-methyl-4-(phenylsulfinyl)furan (3B)**——**8B** (0.10 g) was treated as described for **3A** to give **3B** (0.70 g, 92%) as a colorless oil. IR ($CHCl_3$)cm^{-1}: 3400, 1635, 1590, 1035. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, d, J=6 Hz, C_2-CH_3), 3.02 (1H, dd, J=14, 10 Hz, C_3-H), 3.56–3.78 (2H, m, OCH_2), 4.50—4.98 (1H, m, C_2-H), 7.30—7.66 (5H, m, aromatic H×5). MS m/z (%): 280 (M^+, 3.2), 262 (3.6), 232 (100). High MS Calcd for $C_{15}H_{20}O_3S$: 280.113. Found: 280.110.

The Spiroketalization of 3A and 3B. Preparation of (2*R,4*S**,5*R**,*R**$_S$)-, (2*R**,4*R**,5*R**,*R**$_S$)-, (2*R**,4*S**,5*S**,*R**$_S$)-, (2*R**,4*R**,5*S**,*R**$_S$)-, (2*R**,4*S**,5*R**,*S**$_S$)-, (2*R**,4*R**,5*R**,*S**$_S$)-, (2*R**,4*S**,5*S**,*S**$_S$)-, and (2*R**,4*R**,5*S**,*S**$_S$)-2-Methyl-4-phenylsulfinyl-1,6-dioxaspiro[4.5]decane (9a—d, 10a—d)**——a) With Acids: TSA (1 eq) or a Lewis acid (7 eq) was added to a solution of **3A** or **3B** (0.1 mmol) in dry CH_2Cl_2 (10 ml) at 0 °C and the resulting mixture was stirred at room temperature for 24 h. After neutralization with saturated $NaHCO_3$, the reaction mixture was washed with brine, dried and concentrated. The crude product was chromatographed on alumina with $CHCl_3$ to give a diastereomeric mixture of **9** or **10**, respectively.

b) With NBS: Sodium bicarbonate (45 mg, 0.56 mmol) and NBS (41 mg, 0.28 mmol) were added to a solution of **3A** (0.040 g, 0.14 mmol) in dry THF (5 ml) at 0 °C and the mixture was stirred at 0 °C for 1 h. The solvent was evaporated off and the residue was taken up in $CHCl_3$. The $CHCl_3$ solution was washed with brine, dried, and concentrated. Sodium borohydride (53 mg, 1.4 mmol) was added to a solution of the crude bromohydrin (**11**) in wet CH_3CN (5 ml) and the mixture was heated under reflux for 2 h. Evaporation of the solvent followed by the usual work-up afforded a crude product, which was chromatographed on alumina with $CHCl_3$ to give **9** (31.2 mg, 78%) as a diastereomeric mixture. The same treatment of **3B** (0.040 mg) afforded **10** (0.030 mg, 75%) as a diastereomeric mixture.

c) With Bases: A solution of **3A** or **3B** (0.1 mmol) in dry THF, THF–hexane (1 : 1), DME, DMF, or DMSO (5 ml) was treated with BuLi (1.5 M in hexane, 1.2 eq), or KH (5 eq), or NaH (5 eq) at 0 °C and the resulting mixture was stirred at room temperature (or under reflux) until the starting material had disappeared on TLC (30 min–2 h). Under ice cooling, wet ether was added and the whole was washed with brine. The dried organic layer was concentrated to leave a crude product, which was purified by preparative TLC (ether–petr. ether (1 : 2)).

Isolation and Ratio Determination of Each of the Four Isomers of 9 and 10——The diastereomeric mixture of **9** or **10**, obtained by the above cyclization reactions a) and b), was subjected to preparative TLC (ether–petr. ether (2 : 1)) to give **9a—d** or **10a—d**. The ratio of **9a—d** or **10a—d** was determined by high perfomance liquid chromatographic (HPLC) analysis with a column for separation of enantiomers (pump, Shimadzu LC-5A; 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). Retention times for the diastereomers are as follows. t_R=13.4 and 13.9 min (for **9a**), 16.9 and 18.5 min (for **9b**), 8.3 and 8.8 min (for **9c**), 18.5 and 19.9 min (for **9d**), 13.7 and 14.3 min (for **10a**), 10.5 and 11.3 min (for **10b**), 16.8 and 19.2 min (for **10c**), and 19.2 and 20.5 min (for **10d**).

9a: IR ($CHCl_3$)cm^{-1}: 1090, 1070, 1040, 980. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (2H, d, J=7 Hz, C_2-CH_3), 2.87 (1H, dd, J=10, 9 Hz, C_4-H), 3.61—4.05 (2H, m, C_7-H×2), 4.05—4.42 (1H, m, C_2-H), 7.32—7.68 (5H, m, aromatic H×5). MS m/z (%): 280 (M^+, 6.1), 83 (100). High MS Calcd for $C_{15}H_{20}O_3S$: 280.113. Found: 280.116.

9b: mp 86.5—87.5 °C. *Anal.* Calcd for $C_{15}H_{20}O_3S$: C, 64.25; H, 7.19. Found: C, 63.95; H, 7.36. IR ($CHCl_3$)cm^{-1}: 1080 1070, 1035, 980. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, d, J=6 Hz, C_2-CH_3), 3.34 (1H, dd, J=7, 3 Hz, C_4-H), 3.43—4.20 (3H, m, C_2-H and C_7-H×2), 7.35—7.72 (5H, m, aromatic H×5). MS m/z (%): 280 (M^+, 1.2), 155 (100).

9c: IR ($CHCl_3$)cm^{-1}: 1090, 1080. 1040, 980. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, d, J=6 Hz, C_2-CH_3), 3.02 (1H, dd, J=9, 7 Hz, C_4-H), 3.43—4.22 (3H, m, C_2-H and C_7-H×2), 7.29—7.53 (5H, m, aromatic H×5). MS m/z (%): 280 (M^+, 2.4), 155 (100). High MS Calcd for $C_{15}H_{20}O_3S$: 280.113. Found: 280.111.

9d: IR ($CHCl_3$)cm^{-1}: 1090, 1060, 1040, 980. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, d, J=6 Hz, C_2-CH_3), 3.01 (1H, dd, J=11, 9 Hz, C_4-H), 3.73—4.43 (3H, m, C_2-H and C_7-H×2), 7.37—7.77 (5H, m, aromatic H×5). MS m/z (%): 280 (M^+, 1.9), 55 (100). High MS Calcd for $C_{15}H_{20}O_3S$: 280.113. Found: 280.116.

10a: IR ($CHCl_3$)cm^{-1}: 1120, 1090, 1040, 980.^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, d, J=6 Hz, C_2-CH_3), 2.99 (1H, dd, J=12, 8 Hz, C_4-H), 3.61—4.27 (3H, m, C_2-H and C_7-H×2), 7.39—7.73 (5H, m, aromatic H×5). MS m/z (%): 280 (M^+, 11), 155 (100). High MS Calcd for $C_{15}H_{20}O_3S$: 280.113. Found: 280.113.

10b: IR ($CHCl_3$)cm^{-1}: 1080, 1070, 1040, 990. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, d, J=6 Hz, C_2-CH_3), 3.08 (1H, dd, J=9, 3 Hz, C_4-H), 3.46—4.20 (2H, m, C_7-H×2), 4.20—4.62 (1H, m, C_2-H), 7.38—7.58 (5H, m, aromatic H×5).

10c: mp 116—117 °C. *Anal.* Calcd for $C_{15}H_{20}O_3S$: C, 64.25; H, 7.19. Found: C, 63.93; H, 7.26. IR ($CHCl_3$)cm^{-1}: 1160, 1080, 1040, 980. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, d, J=6 Hz, C_2-CH_3), 3.31 (1H, dd, J=8.5, 7.5 Hz, C_4-H), 3.48—4.10 (3H, m, C_2-H and C_7-H×2), 7.32—7.77 (5H, m, aromatic H×5). MS m/z (%): 280 (M^+, 0.7), 55 (100).

10d: IR ($CHCl_3$)cm^{-1}: 1115, 1090, 1070, 1040, 980. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, d, J=6 Hz, C_2-CH_3), 2.97 (1H, t, J=6 Hz, C_4-H), 3.66—3.92 (2H, m, C_7-H×2), 4.10—4.56 (1H, m, C_2-H), 7.34—7.73 (5H, m, aromatic H). MS m/z (%): 280 (M^+, 1.7), 55 (100). High MS Calcd for $C_{15}H_{20}O_3S$: 280.113. Found: 280.114.

Isomerization at the Spiro Center of 9b and 10c——TSA (20.6 mg, 0.11 mmol) was added to a solution of **9b**

(0.030 g, 0.11 mmol) in dry MeOH (5 ml) at 0 °C and the mixture was stirred at room temperature for 24 h. After neutralization of the mixture with saturated $NaHCO_3$, the solvent was evaporated off and the residue was taken up in $CHCl_3$. The $CHCl_3$ solution was washed with brine, dried, and concentrated to leave an oil, which was chromatographed on alumina with $CHCl_3$ to give **9d** (0.030 g, 100%), which was identical with an authentic sample (**9d**) obtained by the acidic treatment of **3A**.

The same treatment of **10c** (0.030 g, 0.11 mmol) afforded a crude product (0.030 g), which consisted of a 4:1 mixture of **10a** and **10c** (based on the HPLC analysis).

(2*R,5*R**)-2-Methyl-1,6-dioxaspiro[4.5]decane (2A)**——Raney Ni (W-2; *ca.* 0.8 g) was added to a stirred solution of **9b** (136 mg, 0.49 mmol) and NaOH (39 mg, 1.0 mmol) in dry MeOH (10 ml) at 50 °C and stirring was continued for 1 h at the same temperature. After cooling, the reaction mixture was diluted with ether and the inorganic substances were filtered off. The filtrate was carefully evaporated under atmospheric pressure to leave an oil, which was chromatographed on alumina with pentane–ether (9:1) to give **2A** (67 mg, 89%) as a colorless volatile oil. IR ($CHCl_3$) cm^{-1}: 1160, 1120, 1080, 1070. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, d, J=6 Hz, 2-CH_3), 1.35—2.32 (10H, m), 3.30—4.28 (3H, m, 2-H and 7-H). The product was identical with an authentic sample[22] (optically active **2A**) (IR, ^{1}H-NMR, TLC, HPLC analysis).

The same treatment of **10a** (or **9a**) similarly gave **2A**.

(2*R,5*S**)-2-Methyl-1,6-dioxaspiro[4.5]decane (2B)**——Raney Ni (W-2; *ca.* 0.80 g) was added to a stirred solution of **9d** (140 mg, 0.50 mmol) and NaOH (40 mg, 1.0 mmol) in dry MeOH (10 ml) at 50 °C. After stirring of the mixture at the same temperature for 1 h, work-up as described for **2A** gave **2B** (62 mg, 79%) as a colorless volatile oil. IR ($CHCl_3$) cm^{-1}: 1160, 1125, 1090, 1075. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, d, J=6 Hz, 2-CH_3), 1.35—2.31 (10H, m), 3.33—3.95 (2H, m, 7-H), 4.09 (1H, sex, J=6 Hz, 2-H). The product was identical with an authentic sample[22] (optically active **2B**) (IR, ^{1}H-NMR, TLC, HPLC analysis).

The same treatment of **10c** (or **9c** or **10d**) similarly gave **2B**.

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References and Notes

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