1,6-Asymmetric Induction by Reductive Acetal Cleavage of a Bicyclic Acetal Using a Sulfinyl Chiral Auxiliary

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A new synthetic route to a chiral 2,5-disubstituted tetrahydropyran has been achieved by asymmetric reductive acetal cleavage of a bicyclic acetal having a chiral sulfinyl group as a chiral auxiliary. It was found that the (5*S*)-tetrahydropyran was obtained preferentially (up to 96:4) with an *R*-sulfinyl chiral auxiliary by an efficient 1,6-asymmetric induction from sulfinyl chirality to the prochiral center on the bicyclic ring.

Key words 1,6-asymmetric induction; asymmetric desymmetrization; sulfinyl chirality; prochiral 1,3-diol; reductive acetal cleavage reaction

In the preceding paper,[1] we reported the asymmetric nucleophilic acetal cleavage of the bicyclic acetal **1** with allyltrimethylsilane and titanium tetrachloride ($TiCl_4$) using a chiral sulfoxide auxiliary. The reaction exhibited a high degree of diastereotopic group selectivity (1,6-asymmetric induction) and diastereofacial selectivity to give a (2*S*,5*S*)-isomer as a major product. In connection with this, we turned our attention to asymmetric reductive acetal fission (Chart 1) since this reaction would afford a chiral 2,5-disubstituted tetrahydropyran, which is found in many natural products, *e.g.* (+)-restricticin[2] and (+)-rhopaloic acid A.[3]

In this paper, we describe the results of our study of the stereochemistry of acid-promoted reductive acetal cleavage of the bicyclic acetal **1** using a sulfoxide as a chiral auxiliary, in which efficient 1,6-asymmetric induction was achieved.

Results and Discussion

The bicyclic acetal **1**[4] was prepared according to the previously reported procedure and the enantiomeric excess (>98% e.e.) was determined by ^{1}H-NMR spectroscopy with tris[3-(trifluoromethylhydroxymethylene-(+)-camphorato] europium(III) [Eu(tfc)$_3$] as a chiral shift reagent. Then, we investigated the reductive acetal cleavage of **1**. The results are shown in Table 1. A mixture of the bicyclic acetal **1** and triethylsilane was treated with $TiCl_4$ with stirring at −78 °C. Nucleophilic acetal cleavage took place rapidly to provide mainly the alcohols **2a** and **2b** along with their C_5-epimers, **2c** and **2d**. The main products, *cis*-isomer **2a** and *trans*-isomer **2b**, were formed *via* cleavage of the pro-*R* acetal oxygen (cleavage *a*). The ratio of cleavage *a* to *b* was 9:1, but the *cis*/*trans* selectivity (**2a**/**2b**) was poor (run 1).[5] On raising or lowering the reaction temperature, the selectivity of acetal fission was reduced and the *trans*-isomer was mainly formed (runs 2, 3). The same tendency was observed when $TiCl_4$ was added prior to triethylsilane (run 4) or when the amount of $TiCl_4$ was increased (runs 5, 6). On the other hand, increasing the amount of triethylsilane resulted in an improvement in the selectivity of acetal fission and the *cis*-isomer was mainly formed with moderate selectivity (runs 7, 8). In run 7, the selectivity of acetal fission was improved up to 96:4 and the *cis*-isomer was mainly formed with moderate selectivity. Use of a less polar solvent, toluene, gave lower selectivity than CH_2Cl_2 (run 9). Etherial solvents did not afford the desired products (runs 10, 11).[6]

To determine the absolute configuration of products **2a**—**d**, analytical samples were synthesized from *p*-methoxybenzoyl esters (PMBz) **3a** and **3b**[4,7] with known absolute configuration (Chart 2). The vinyl ether of **3a** was reduced with triethylsilane and $TiCl_4$ to give tetrahydropyrans **4a** (*cis*) and **4b** (*trans*) in a ratio of about 4:1. In a similar manner, **3b** was converted into **4c** (*cis*)

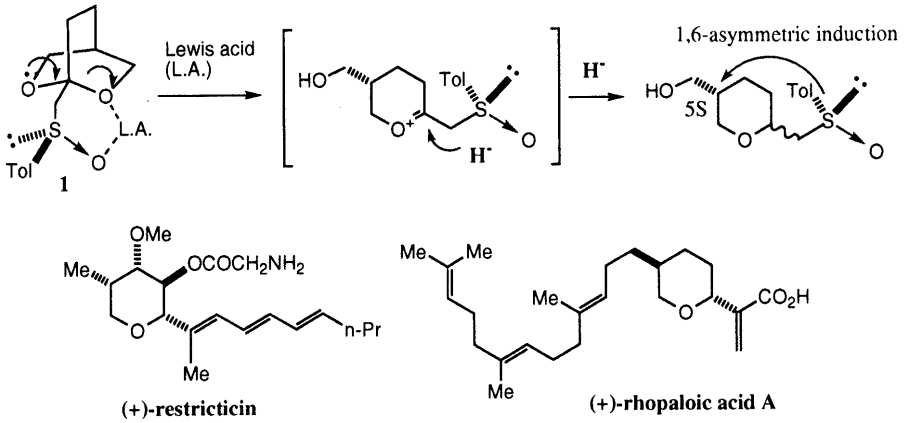

Chart 1

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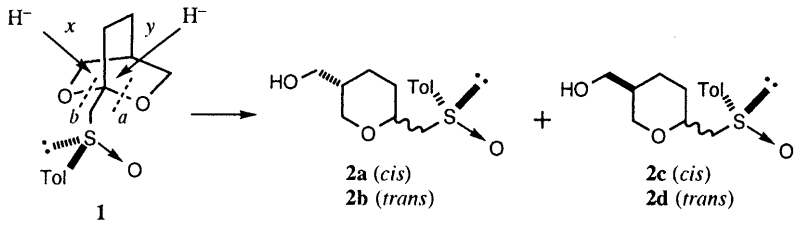
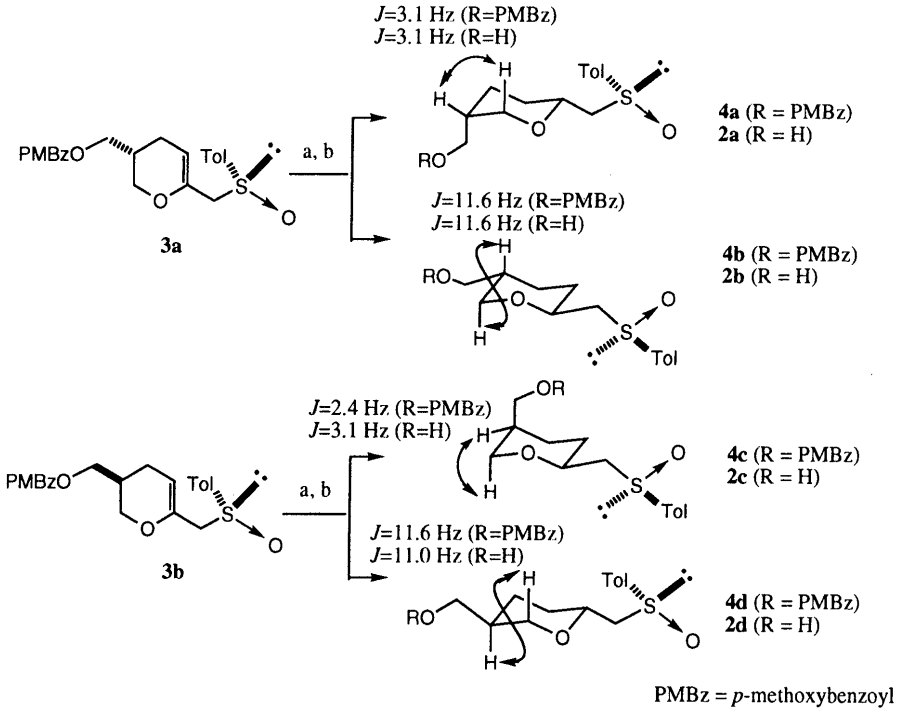
Table 1. Reductive Acetal Cleavage of the Bicyclic Acetal **1**



Run	Conditions[a]	Yield (%)[c]	Ratio[d] 2a : 2b : (2c + 2d)	Cleavage *a* : *b*
1	$TiCl_4$ (3), Et_3SiH (1.5) CH_2Cl_2, −78 °C	86	50 : 40 : 10	90 : 10
2	$TiCl_4$ (3), Et_3SiH (1.5), CH_2Cl_2, −20 °C	75	28 : 34 : 38	62 : 38
3	$TiCl_4$ (3), Et_3SiH (1.5), CH_2Cl_2, −100 °C	86	14 : 67 : 19	81 : 19
4	$TiCl_4$ (3), Et_3SiH (1.5), CH_2Cl_2, −78 °C[b]	85	16 : 58 : 26	74 : 26
5	$TiCl_4$ (5), Et_3SiH (1.5), CH_2Cl_2, −78 °C	81	19 : 58 : 23	77 : 23
6	$TiCl_4$ (10), Et_3SiH (1.5), CH_2Cl_2, −78 °C	69	19 : 55 : 26	74 : 26
7	$TiCl_4$ (3), Et_3SiH (5), CH_2Cl_2, −78 °C	92	58 : 38 : 4	96 : 4
8	$TiCl_4$ (3), Et_3SiH (10), CH_2Cl_2, −78 °C	86	56 : 38 : 6	94 : 6
9	$TiCl_4$ (3), Et_3SiH (1.5), toluene, −78 °C	89	60 : 18 : 22	78 : 22
10	$TiCl_4$ (3), Et_3SiH (1.5), Et_2O, −78 °C	0	—	—
11	$TiCl_4$ (3), Et_3SiH (1.5), THF, −78 °C	0	—	—

a) All reactions were performed by the addition of $TiCl_4$ to a mixture of triethylsilane and **1** unless mentioned. *b*) Triethylsilane was added to a mixture of the bicyclic acetal **1** and $TiCl_4$. *c*) Combined yield of **2a—d**. *d*) Determined by 500 MHz ^{1}H-NMR spectroscopy.



a: $TiCl_4$, Et_3SiH, −78°C to room temp. (**4a**, 15%; **4b**, 57%; **4c**, 18%; **4d**, 50%);
b: 1% NaOH, MeOH, room temp. (**2a**, 82%; **2b**, 83%; **2c**, 86%; **2d**, 91%).

Chart 2

and **4d** (*trans*) (*ca.* 3 : 1). After their separation by PTLC, the esters **4a—d** were hydrolyzed with 1% NaOH to give the corresponding **2a—d**, respectively. Assignment of the relationship between the C_2- and C_5-positions in the tetrahydropyrans **2a—d** and **4a—d** was achieved by using the coupling constants between each C_5 methine and C_6 axial protons, which are 11.0—11.6 Hz (axial–axial coupling) in the *trans*-isomer and 2.4—3.1 Hz (equatorial–axial coupling) in the *cis*-isomer.

The stereochemical outcome of this reaction may be rationalized as follows. Complexation to $TiCl_4$ of the sulfinyl oxygen and the pro-*R* acetal oxygen affords the most favorable six-membered ring chelation intermediate A (Chart 3).[4] The coordinated C–O bond was lengthened and led to the bond cleavage *a* (intermediate B). When the hydride attacks this intimate ion-pair B synchronous-

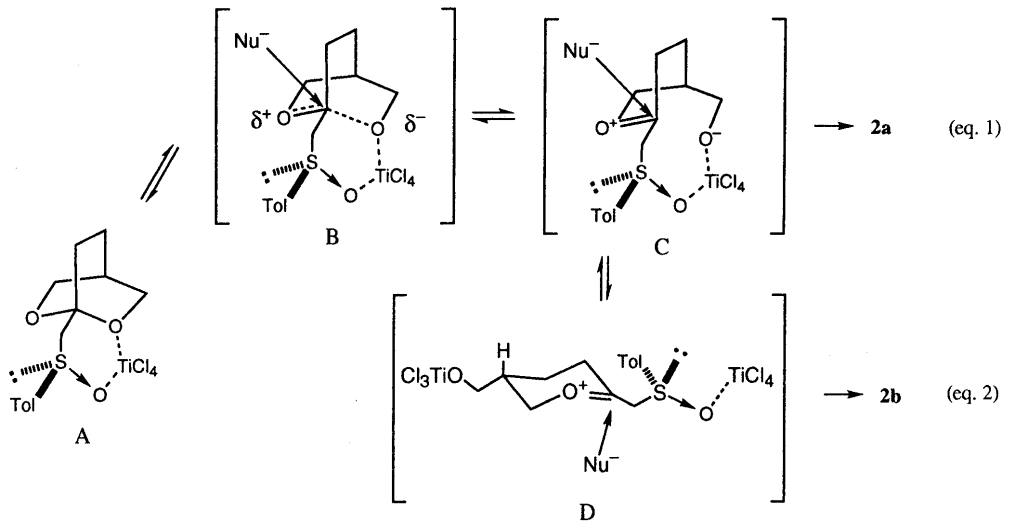


Chart 3

ly or a dissociative tight ion-pair intermediate C, the reaction proceeds stereospecifically to give the *cis*-isomer **2a** (eq. 1).[8] On the other hand, reduction of an open oxocarbenium ion intermediate D proceeded *via* stereoelectronically-favored axial attack of the hydride to give mainly the *trans*-isomer **2b** (eq. 2).[9]

In summary, on treatment of the bicyclic acetal **1** with triethylsilane and $TiCl_4$, reductive acetal fission proceeded diastereoselectively in good yield. Cleavage of the pro-*R* C–O oxygen (cleavage *a*) proceeded preferentially using a chiral sulfoxide with *R*-configuration, thereby achieving highly diastereoselective 1,6-asymmetric induction, although the diastereofacial selectivity was moderate.

Experimental

Melting points are uncorrected. Optical rotations were measured using a JASCO DIP-360 digital polarimeter. IR spectra were measured with a Horiba FT-210 IR spectrometer. NMR spectra were measured with a Varian Gemini-300 spectrometer (^{13}C: 75 MHz), JEOL JMN-AL 300 (^{13}C: 75 MHz) or a JEOL JNM-GX500 spectrometer (^{1}H: 500 MHz). All signals are expressed as ppm downfield from tetramethylsilane used as an internal standard (δ value). The following abbreviations are used: singlet (s), doublet (d), triplet (t), multiplet (m), and broad (br). HR-FAB-MS were recorded on a JEOL JMS-700 mass spectrometer. Merck Kieselgel 60 was used as an adsorbent for column chromatography. For preparative TLC (PTLC), Kieselgel 60 F_{254} (Merck) was used. For medium-pressure chromatography, a Lobar column (Merck LiChroprep Si 60) was used.

General Procedure for Reductive Acetal Cleavage of 1 Titanium tetrachloride (1.0 M CH_2Cl_2 solution) (0.56 ml, 0.56 mmol) was added to a solution of **1** (49.6 mg, 0.188 mmol) and triethylsilane (0.15 ml, 0.939 mmol) in dry CH_2Cl_2 (10 ml) with stiring at −78 °C. After 1 h, the mixture was quenched with 10% HCl and the aqueous layer was extracted with ether. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was evaporated and the residue was chromatographed on silica gel with AcOEt→$CHCl_3$–MeOH (95 : 5) to give a mixture of **2a**—**d** (45.8 mg, 92%) as a colorless oil.

(3*R*,*Rs*)- and (3*S*,*Rs*)-[3,4-Dihydro-6-(*p*-toluenesulfinylmethyl)-2*H*-pyran-3-yl]methyl *p*-Methoxybenzoate (3a and 3b) *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA) (0.078 ml, 0.52 mmol) was added to a stirred LDA solution [prepared from diisopropylamine (0.073 ml, 0.52 mmol) and *n*-BuLi (1.6 M hexane solution; 0.32 ml, 0.52 mmol) in dry THF (2 ml)] at −78 °C for 5 min. A solution of **1** (46.0 mg, 0.173 mmol) in dry THF (0.5 ml) was added dropwise to the mixture at −78 °C with stirring which was continued for 30 min. The reaction was quenched with saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with water and brine, and then dried over $MgSO_4$. The solvent was evaporated and the residue was chromatographed on silica gel with AcOEt–hexane (2 : 1) to give a mixture of the diastereoisomeric alcohols (42.0 mg, 92%). *p*-Methoxybenzoyl chloride (23 mg, 0.13 mmol) was added to a mixture of the diastereoisomeric alcohols (30 mg, 0.11 mmol) as well as 4-dimethylaminopyridine (16 mg, 0.13 mmol) in CH_2Cl_2 (1 ml) with stirring at 0 °C under N_2. The ice-bath was removed and the stirring was continued for 2 h. The reaction was quenched with $NaHCO_3$ followed by extraction with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. After filtration, the solvent was evaporated and the residue was chromatographed on silica gel with hexane–AcOEt (1 : 1) to give a mixture of **3a** and **3b** (53 mg), which was separated by medium pressure column chromatography with hexane–AcOEt (1 : 1, flow rate 3.2 ml/min) to give **3a** (minor) (11.4 mg, 23% from **1**) and **3b** (major) (29.0 mg, 59% from **1**) each as a colorless powder. **3a**: $[\alpha]_D^{27}$ +97.9° (c=0.52, EtOH). ^{1}H-NMR ($CDCl_3$) δ: 1.97 (ddd, 1H, J=17.7, 7.9, 3.7 Hz, 4-H_{ax}), 2.15 (ddd, 1H, J=17.7, 5.5, 4.0 Hz, 4-H_{eq}), 2.26—2.36 (m, 1H, 3-H), 2.41 (s, 3H, Ar-C$\underline{H}_3$), 3.33 (d, 1H, J=12.8 Hz, $CH_2S(O)$), 3.51 (d, 1H, J=12.8 Hz, $CH_2S(O)$), 3.84 (dd, 1H, J=10.4, 8.5 Hz, 2-H_{ax}), 3.87 (s, 3H, OCH_3), 4.10—4.20 (m, 1H, 2-H_{eq}), 4.17 (dd, 1H, J=11.3, 7.9 Hz, CH_2OCO), 4.31 (dd, 1H, J=11.3, 6.1 Hz, CH_2OCO), 4.74 (dd, 1H, J=4.0, 3.7 Hz, CH=), 6.93 (d, 2H, J=9.2 Hz, MeO-Ar$\underline{H}$), 7.31 (d, 2H, J=7.9 Hz, Me-Ar$\underline{H}$), 7.53 (d, 2H, J=7.9 Hz, Me-Ar$\underline{H}$), 7.99 (d, 2H, J=9.2 Hz, MeO-Ar$\underline{H}$). ^{13}C-NMR ($CDCl_3$) δ: 21.4, 23.4, 31.7, 55.5, 63.4, 64.6, 67.8, 102.1, 113.7 (2C), 122.4, 124.2 (2C), 129.7 (2C), 131.6 (2C), 140.7, 141.6, 144.7, 163.5, 166.1 IR (KBr): 2926, 1713, 1606, 1512, 1257 cm^{-1}. HR-FAB-MS m/z: 401.1415 (Calcd for $C_{22}H_{24}O_5S+H^+$: 401.1423). **3b**: $[\alpha]_D^{27}$ +89.2° (c=1.34, EtOH). ^{1}H-NMR ($CDCl_3$) δ: 1.86—1.94 (m, 1H, 4-H_{ax}), 2.27 (ddd, 1H, J=17.1, 4.9, 4.0 Hz, 4-H_{eq}), 2.32—2.42 (m, 1H, 3-H), 2.41 (s, 3H, Ar-C$\underline{H}_3$), 3.35 (d, 1H, J=12.8 Hz, $CH_2S(O)$), 3.48 (d, 1H, J=12.8 Hz, $CH_2S(O)$), 3.83 (dd, 1H, J=10.4, 7.3 Hz, 2-H_{ax}), 3.87 (s, 3H, OCH_3), 4.13 (ddd, 1H, J=10.4, 3.1, 1.2 Hz, 2-H_{eq}), 4.17 (dd, 1H, J=11.2, 7.9 Hz, CH_2OCO), 4.28 (dd, 1H, J=11.2, 6.1 Hz, CH_2OCO), 4.74 (dd, 1H, J=4.0, 3.7 Hz, CH=), 6.93 (d, 2H, J=8.5 Hz, MeO-Ar$\underline{H}$), 7.31 (d, 2H, J=7.9 Hz, Me-Ar$\underline{H}$), 7.52 (d, 2H, J=7.9 Hz, Me-Ar$\underline{H}$), 7.98 (d, 2H, J=8.5 Hz, MeO-Ar$\underline{H}$). ^{13}C-NMR ($CDCl_3$) δ: 21.4, 23.3, 31.5, 55.5, 63.3, 64.5, 67.5, 102.0, 113.7 (2C), 122.4, 124.2 (2C), 129.8 (2C), 131.6 (2C), 140.7, 141.6, 144.6, 163.5, 166.2. IR (KBr): 2926, 1713, 1606, 1512, 1259 cm^{-1}. HR-FAB-MS m/z: 401.1426 (Calcd for $C_{22}H_{24}O_5S+H^+$: 401.1423).

(2*R*,5*R*,*Rs*)- and (2*S*,5*R*,*Rs*)-[2-(*p*-Toluenesulfinylmethyl)tetrahydropyran-5-yl]methyl *p*-Methoxybenzoate (4a and 4b) Titanium chloride (1.0 M CH_2Cl_2 solution) (0.13 ml, 0.13 mmol) was added to a solution of **3a** (9.8 mg, 0.025 mmol) and triethylsilane (20 μl, 0.125 mmol) in CH_2Cl_2 (2 ml) with stirring at −78 °C under N_2. After 30 min., the temperature was raised to room temperature over 4.5 h. The reaction was quenched with 10% HCl (7 ml), and the mixture was extracted with CH_2Cl_2. The extracts were washed with brine and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by PTLC with

hexane–AcOEt (1 : 1) to give **4a** (1.5 mg, 15%) as a colorless oil and **4b** (5.6 mg, 57%) as a colorless powder. **4a**: $[\alpha]_D^{26}$ +45.9° (c = 1.01, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.53—1.79 (m, 3H, 3-H, 4-H_{ax}), 1.85—1.92 (m, 1H, 4-H_{eq}), 1.97—2.05 (m, 1H, 5-H), 2.43 (s, 3H, Ar-C$\underline{H}_3$), 2.74 (dd, 1H, J = 12.8, 5.5 Hz, $CH_2S(O)$), 3.25 (dd, 1H, J = 12.8, 6.8 Hz, $CH_2S(O)$), 3.47—3.56 (m, 1H, 2-H), 3.54 (dd, 1H, J = 11.6, 3.1 Hz, 6-H_{ax}), 3.86 (s, 3H, OCH_3), 3.98 (d, 1H, J = 11.6 Hz, 6-H_{eq}), 4.44 (d, 2H, J = 7.9 Hz, CH_2OCO), 6.91 (d, 2H, J = 8.5 Hz, MeO-Ar$\underline{H}$), 7.33 (d, 2H, J = 7.9 Hz, Me-Ar$\underline{H}$), 7.56 (d, J = 7.9 Hz, Me-Ar$\underline{H}$), 7.99 (d, J = 8.5 Hz, MeO-Ar$\underline{H}$). ^{13}C-NMR ($CDCl_3$) δ: 21.4, 23.8, 26.6, 32.5, 55.4, 63.2, 64.0, 68.2, 73.0, 113.5 (2C), 122.5, 124.3 (2C), 129.9 (2C), 131.5 (2C), 140.3, 141.6, 163.3, 166.2. IR (KBr): 2937, 1711, 1606, 1512, 1257 cm^{-1}. HR-FAB-MS m/z: 403.1587 (Calcd for $C_{22}H_{26}O_5S+H^+$: 403.1579). **4b**: mp 76—78 °C (from hexane). $[\alpha]_D^{28}$ +128.4° (c = 0.82, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.40—1.51 (m, 2H, 3-H_{ax}, 4-H_{ax}), 1.68—1.75 (m, 1H, 3-H_{eq}), 1.93—2.01 (m, 1H, 4-H_{eq}), 2.07—2.23 (m, 1H, 5-H), 2.41 (s, 3H, Ar-C$\underline{H}_3$), 2.75 (dd, 1H, J = 13.4, 7.1 Hz, $CH_2S(O)$), 2.87 (dd, 1H, J = 13.4, 2.4 Hz, $CH_2S(O)$), 3.45 (dd, 1H, J = 11.6, 11.0 Hz, 6-H_{ax}), 3.87 (s, 3H, OCH_3), 3.94 (br t, 1H, J = 11.6 Hz, 2-H), 4.08 (dd, 1H, J = 11.0, 7.3 Hz, CH_2OCO), 4.21 (m, 2H, 6-H_{eq}, CH_2OCO), 6.93 (d, 2H, J = 8.5 Hz, MeO-Ar$\underline{H}$), 7.32 (d, 2H, J = 7.9 Hz, Me-Ar$\underline{H}$), 7.54 (d, 2H, J = 7.9 Hz, Me-Ar$\underline{H}$), 7.97 (d, 2H, J = 8.5 Hz, MeO-Ar$\underline{H}$). ^{13}C-NMR ($CDCl_3$) δ: 21.4, 26.5, 30.9, 35.6, 55.5, 65.0, 65.6, 70.9, 71.4, 113.7 (2C), 122.4, 123.9 (2C), 130.0 (2C), 131.6 (2C), 141.2, 141.5, 163.5, 166.1. IR (KBr): 2939, 1712, 1606, 1511, 1257 cm^{-1}. HR-FAB-MS m/z: 403.1595 (Calcd for $C_{22}H_{26}O_5S+H^+$: 403.1579).

(2*S*,5*S*,*Rs*)- and (2*R*,5*S*,*Rs*)-[2-(*p*-Toluenesulfinylmethyl)tetrahydropyran-5-yl]methyl *p*-Methoxybenzoate (4c and 4d) By the same procedure as **4a** and **4b** were obtained from **3a**, **3b** (20 mg, 0.05 mmol) was converted into **4c** (3.7 mg, 18%) and **4d** (10.0 mg, 50%), each colorless oils. **4c**: $[\alpha]_D^{24}$ +53.0° (c = 0.50, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.46—1.62 (m, 2H, 3-H), 1.83—1.95 (m, 2H, 4-H), 2.04—2.13 (m, 1H, 5-H), 2.41 (s, 3H, Ar-C$\underline{H}_3$), 2.76 (dd, 1H, J = 13.4, 8.6 Hz, $CH_2S(O)$), 2.80 (dd, 1H, J = 13.4, 4.3 Hz, $CH_2S(O)$), 3.80 (dd, 1H, J = 12.2, 2.4 Hz, 6-H_{ax}), 3.87 (s, 3H, OCH_3), 3.97—4.04 (m, 1H, 2-H), 4.13 (d, 1H, J = 12.2 Hz, 6-H_{eq}), 4.44 (dd, 1H, J = 10.4, 7.9 Hz, CH_2OCO), 4.46 (dd, 1H, J = 10.4, 7.9 Hz, CH_2OCO), 6.89—6.95 (m, 2H, MeO-Ar$\underline{H}$), 7.32 (d, 2H, J = 8.5 Hz, Me-Ar$\underline{H}$), 7.54 (d, 2H, J = 8.5 Hz, Me-Ar$\underline{H}$), 7.97—8.01 (m, 2H, MeO-Ar$\underline{H}$). ^{13}C-NMR ($CDCl_3$) δ: 21.4, 24.2, 27.0, 32.5, 55.4, 64.0, 65.0, 68.5, 71.7, 113.6 (2C), 122.6, 123.8 (2C), 130.0 (2C), 131.6 (2C), 141.3, 141.4, 163.4, 166.3. IR (KBr): 2927, 1711, 1606, 1512, 1257 cm^{-1}. HR-FAB-MS m/z: 403.1587 (Calcd for $C_{22}H_{26}O_5S+H^+$: 403.1579). **4d**: $[\alpha]_D^{24}$ +16.6° (c = 1.14, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.18—1.38 (m, 1H, 4-H_{ax}), 1.52—1.64 (m, 1H, 3-H_{ax}), 1.77—1.83 (m, 1H, 3-H_{eq}), 1.90—1.97 (m, 1H, 4-H_{eq}), 2.07—2.18 (m, 1H, 5-H), 2.43 (s, 3H, Ar-C$\underline{H}_3$), 2.76 (dd, 1H, J = 12.8, 5.5 Hz, $CH_2S(O)$), 3.16 (dd, 1H, J = 11.6, 11.0 Hz, 6-H_{ax}), 3.22 (dd, 1H, J = 12.8, 7.3 Hz, $CH_2S(O)$), 3.37—3.45 (m, 1H, 2-H), 3.87 (s, 3H, OCH_3), 4.02 (dd, 1H, J = 11.0, 7.3 Hz, CH_2OCO), 4.11 (ddd, 1H, J = 11.6, 4.3, 2.4 Hz, 6-H_{eq}), 4.15 (dd, 1H, J = 11.0, 5.5 Hz, CH_2OCO), 6.89—6.94 (m, 2H, MeO-Ar$\underline{H}$), 7.34 (d, 2H, J = 7.9 Hz, Me-Ar$\underline{H}$), 7.56 (d, 2H, J = 7.9 Hz, Me-Ar$\underline{H}$), 7.94—7.98 (m, 2H, MeO-Ar$\underline{H}$). ^{13}C-NMR ($CDCl_3$) δ: 21.4, 26.2, 30.4, 35.3, 55.4, 63.3, 65.6, 70.8, 72.8, 113.6 (2C), 122.3, 124.3 (2C), 129.9 (2C), 131.5 (2C), 140.4, 141.7, 163.4, 166.1. IR (KBr): 2931, 1713, 1606, 1512, 1257 cm^{-1}. HR-FAB-MS m/z: 403.1581 (Calcd for $C_{22}H_{26}O_5S+H^+$: 403.1579).

(2*R*,5*S*,*Rs*)-5-Hydroxymethyl-2-(*p*-toluenesulfinylmethyl)tetrahydropyran (2a) A mixture of **4a** (19 mg, 0.047 mmol) and 1% NaOH in MeOH (3 ml) was stirred at room temperature for 4 h. After most of the MeOH had been evaporated, water (5 ml) was added to the residue followed by extraction with CH_2Cl_2; the extract was dried over Na_2SO_4. The solvent was evaporated and the residue was purified by PTLC with AcOEt to give **2a** (10.3 mg, 82%) as a colorless powder. mp 53—55 °C (from hexane–AcOEt). $[\alpha]_D^{24}$ +88.5° (c = 0.34, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.51—1.73 (m, 6H, 3-H, 4-H_{ax}, 5-H, OH), 1.80—1.86 (m, 1H, 4-H_{eq}), 2.43 (s, 3H, CH_3), 2.73 (dd, 1H, J = 12.8, 4.9 Hz, $CH_2S(O)$), 3.21 (dd, 1H, J = 12.8, 7.3 Hz, $CH_2S(O)$), 3.43—3.53 (m, 1H, 2-H), 3.50 (dd, 1H, J = 11.6, 3.1 Hz, 6-H_{ax}), 3.68—3.75 (m, 1H, C$\underline{H}_2$OH), 3.83—3.90 (m, 1H, C$\underline{H}_2$OH), 3.97 (d, 1H, J = 11.6 Hz, 6-H_{eq}), 7.33 (d, J = 8.6 Hz, ArH), 7.56 (d, J = 8.6 Hz, ArH). ^{13}C-NMR ($CDCl_3$) δ: 21.4, 23.7, 26.8, 35.4, 62.4, 63.3, 68.3, 73.0, 124.4 (2C), 129.9 (2C), 140.2, 141.7. IR (KBr): 3404, 2926, 2856, 1032 cm^{-1}. HR-FAB-MS m/z: 269.1210 (Calcd for $C_{14}H_{20}O_3S+H^+$: 269.1211). *Anal.* Calcd for $C_{14}H_{20}O_3S \cdot 1/2H_2O$: C, 60.62; H, 7.63. Found: C, 60.75; H, 7.69.

(2*S*,5*S*,*Rs*)-5-Hydroxymethyl-2-(*p*-toluenesulfinylmethyl)tetrahydropyran (2b) By the same procedure **2a** was obtained from **4a**, **4b** (19 mg, 0.047 mmol) was converted into **2b** (10.5 mg, 83%). Colorless powder: mp 147—149 °C (from hexane–AcOEt). $[\alpha]_D^{24}$ +201.8° (c = 0.40, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.24—1.46 (m, 3H, 4-H_{ax}, 3-H_{ax}, OH), 1.65—1.72 (m, 1H, 3-H_{eq}), 1.80—1.94 (m, 2H, 4-H_{eq}, 5-H), 2.41 (s, 3H, CH_3), 2.75 (dd, 1H, J = 13.4, 9.8 Hz, $CH_2S(O)$), 2.81 (dd, 1H, J = 13.4, 3.1 Hz, $CH_2S(O)$), 3.33 (dd, 1H, J = 11.6, 11.0 Hz, 6-H_{ax}), 3.44—3.61 (m, 2H, C$\underline{H}_2$OH), 3.85—3.92 (m, 1H, 2-H), 4.18 (ddd, 1H, J = 11.0, 4.3, 1.8 Hz, 6-H_{eq}), 7.32 (d, 2H, J = 8.5 Hz, ArH), 7.54 (d, 2H, J = 8.5 Hz, ArH). ^{13}C-NMR ($CDCl_3$) δ: 21.3, 26.3, 31.0, 38.4, 64.4, 65.0, 71.2, 71.3, 123.8 (2C), 130.0 (2C), 141.2, 141.4. IR (KBr): 3363, 2943, 2856, 1085 cm^{-1}. HR-FAB-MS m/z: 269.1208 (Calcd for $C_{14}H_{20}O_3S+H^+$: 269.1211). *Anal.* Calcd for $C_{14}H_{20}O_3S$: C, 62.66; H, 7.51. Found: C, 62.41; H, 7.48.

(2*S*,5*R*,*Rs*)-5-Hydroxymethyl-2-(*p*-toluenesulfinylmethyl)tetrahydropyran (2c) By the same procedure **2a** was obtained from **4a**, **4c** (9.2 mg, 0.023 mmol) was converted into **2c** (5.6 mg, 91%). Colorless oil: $[\alpha]_D^{26}$ +106.7° (c = 0.46, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.43—1.93 (m, 6H, 3-H, 4-H, 5-H, OH), 2.41 (s, 3H, CH_3), 2.73 (dd, 1H, J = 13.5, 9.8 Hz, $CH_2S(O)$), 2.79 (dd, 1H, J = 13.5, 3.1 Hz, $CH_2S(O)$), 3.70—3.78 (m, 1H, 2-H), 3.75 (dd, 1H, J = 12.2, 3.1 Hz, 6-H_{ax}), 3.84—3.91 (m, 1H, C$\underline{H}_2$OH), 3.94—4.01 (m, 1H, C$\underline{H}_2$OH), 4.09 (d, 1H, J = 12.2 Hz, 6-H_{eq}), 7.32 (d, 2H, J = 8.5 Hz, ArH), 7.54 (d, 2H, J = 8.5 Hz, ArH). ^{13}C-NMR ($CDCl_3$) δ: 21.4, 24.0, 27.2, 35.4, 62.8, 65.0, 68.7, 71.6, 123.8 (2C), 130.0 (2C), 141.2, 141.4. IR (KBr): 3394, 2924, 1063 cm^{-1}. HR-FAB-MS m/z: 269.1209 (Calcd for $C_{14}H_{20}O_3S+H^+$: 269.1211).

(2*R*,5*R*,*Rs*)-5-Hydroxymethyl-2-(*p*-toluenesulfinylmethyl)tetrahydropyran (2d) By the same procedure **2a** was obtained from **4a**, **4d** (15 mg, 0.037 mmol) was converted into **2d** (8.5 mg, 86%). Colorless oil: $[\alpha]_D^{26}$ +55.5° (c = 0.38, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.18 (ddd, 1H, J = 12.8, 12.8, 4.3 Hz, 4-H_{ax}), 1.33 (t, 1H, J = 4.9 Hz, OH), 1.53 (ddd, 1H, J = 12.8, 12.3, 3.6 Hz, 3-H_{ax}), 1.73—1.79 (m, 1H, 3-H_{eq}), 1.79—1.89 (m, 2H, 5-H, 4-H_{eq}), 2.42 (s, 3H, CH_3), 2.75 (dd, 1H, J = 13.4, 4.9 Hz, $CH_2S(O)$), 3.07 (dd, 1H, J = 11.5, 11.0 Hz, 6-H_{ax}), 3.22 (dd, 1H, J = 13.4, 7.3 Hz, $CH_2S(O)$), 3.31—3.38 (m, 1H, 2-H), 3.38—3.45 (m, 1H, C$\underline{H}_2$OH), 3.45—3.53 (m, 1H, C$\underline{H}_2$OH), 4.06 (ddd, 1H, J = 11.0, 3.7, 2.4 Hz, 6-H_{eq}), 7.33 (d, 2H, J = 7.9 Hz, ArH), 7.56 (d, 2H, J = 7.9 Hz, ArH). ^{13}C-NMR ($CDCl_3$) δ: 21.5, 26.0, 30.6, 38.1, 63.4, 64.6, 71.0, 72.8, 124.4 (2C), 129.9 (2C), 140.3, 141.7. IR (KBr): 3394, 2923, 1063 cm^{-1}. HR-FAB-MS m/z: 269.1218 (Calcd for $C_{14}H_{20}O_3S+H^+$: 269.1211).

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References and Notes

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5) The ratio of **2a** : **2b** : (**2c** + **2d**) was determined from 500 MHz ^{1}H-NMR spectroscopic data based on the signal due to the equatorial proton at the C_6-position.
6) Other Lewis acids ($SnCl_4$, $BF_3 \cdot Et_2O$) and organoaluminum reagents (H_2AlCl, $HAlCl_2$) were also examined, but they afforded

complex mixtures. No reaction was observed with DIBAL as a reductant.
7) The PMBz esters of **3a** and **3b** were prepared from the bicyclic acetal **1** by base-promoted acetal cleavage followed by esterification. Since the stereochemistry of the base-promoted acetal cleavage of **1** is known, the absolute configurations at the C_3-position of **3a** (minor) and **3b** (major) were assigned as *R* and *S*, respectively.
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