Asymmetric Desymmetrization of Prochiral 1,3-Diols *via* Diastereoselective C–O Bond Fission of Bicyclic Acetal Using a Chiral Sulfoxide as a Chiral Auxiliary

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Asymmetric desymmetrization of a prochiral 1,3-diol was established by diastereoselective C–O bond fission of the chiral α-sulfinyl acetal 6. Treatment of 6 with titanium tetrachloride afforded mainly 7a *via* an oxonium intermediate, while with lithium diisopropylamide 7b was selectively obtained *via* diastereoselective β-elimination followed by an olefin isomerization.

Key words asymmetric desymmetrization; prochiral 1,3-diol; sulfinyl chirality; α-sulfinyl acetal; β-elimination

Chiral 1,3-diol moieties are widely found in many natural products[1] having interesting biological activities. Various strategies have been developed for chiral 1,3-diol construction.[2,3] Among the synthetic methods that have emerged, asymmetric desymmetrization of prochiral 1,3-diols has proved to be of considerable synthetic utility. While chirality induction by enzymatic reaction is well known,[2] approaches by chemical methods are rare.[3] Since the application of enzymatic methods is limited owing to the high specificity of enzymes for substrates, development of efficient chemical methods is very important. We have found a novel asymmetric induction of prochiral 1,3-diols controlled by a chiral sulfoxide *via* diastereoselective C–O bond fission of a bicyclic acetal[3a,c] and applied this reaction to a total synthesis of spiroketal fungal metabolites, (+)-talaromycin A and (−)-talaromycin B (Chart 1).[3b,d] This transformation is formally equivalent to the asymmetric desymmetrization of prochiral 1,3-diols.

In this conversion, however, the diastereoselectivity may be affected by both the chiral centers, including a chiral sulfinyl group. The usefulness of the sulfinyl group as a chiral auxiliary for acetal cleavages is of interest, so we planned to investigate the reaction of a bicyclic acetal with only one chirality. We designed the bicyclic acetal (Chart 2), which could be cleaved diastereoselectively in two different ways, by acid-promoted acetal cleavage based on diastereoselective complexation of a Lewis acid to an acetal oxygen (method A) or by diastereoselective β-elimination induced by the chiral α-sulfinyl carbanion (method B). There has been no report especially dealing with the stereochemistry of β-elimination, and therefore we investigated this reaction.

In this paper, we report two novel types of asymmetric desymmetrization based on diastereoselective acetal fission promoted by Lewis acids or bases. These reactions showed opposite selectivity.

Results and Discussion

The bicyclic acetal **6** was synthesized from the known alcohol **1** as shown in Chart 3. Swern oxidation of the alcohol **1** followed by Horner–Emmons olefination gave the α,β-unsaturated ester **3** in 87% yield. Then, the double bond was hydrogenated on palladium carbon to obtain the saturated ester **4** quantitatively. Introduction of the chiral auxiliary was carried out with lithiated (*R*)-methyl *p*-tolyl sulfoxide[4] to afford the β-ketosulfoxide **5** in 72% yield. In the reaction, *sec*-butyllithium was found to give better results than lithium diisopropylamide (LDA) for lithiation. The β-ketosulfoxide **5** was subjected to transacetalization in the presence of *p*-toluenesulfonic acid at room temperature for a day to give **6** in up to 96% yield.

Next, we investigated the diastereoselective acetal cleavage under acidic conditions. On treatment with trifluoroacetic acid or aluminum trichloride ($AlCl_3$), **6**

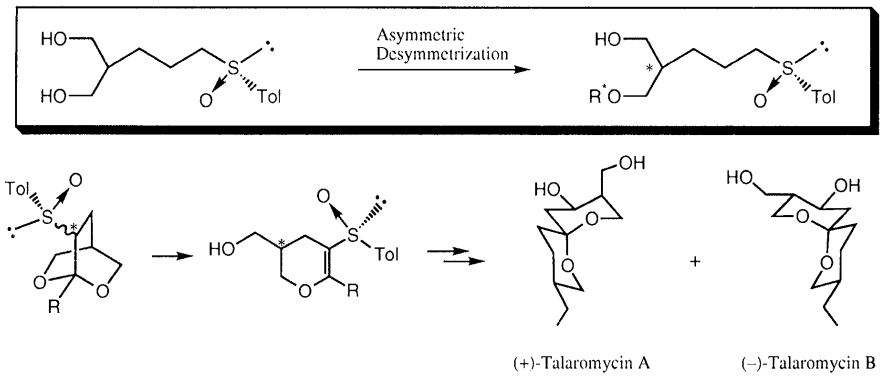

Chart 1

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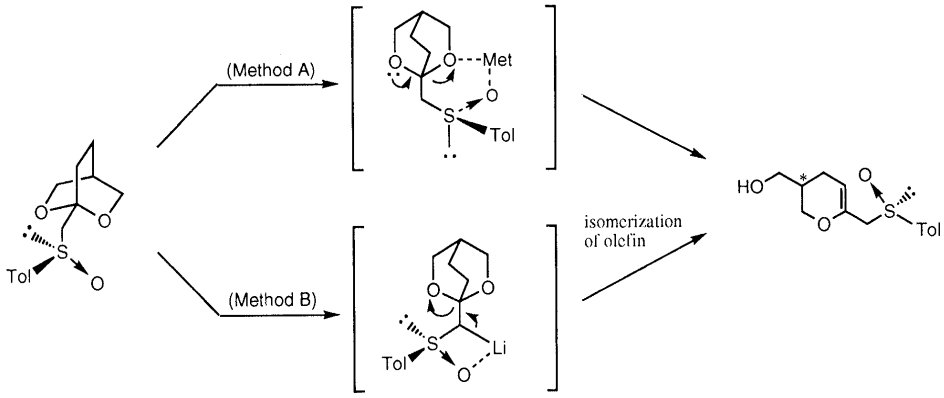
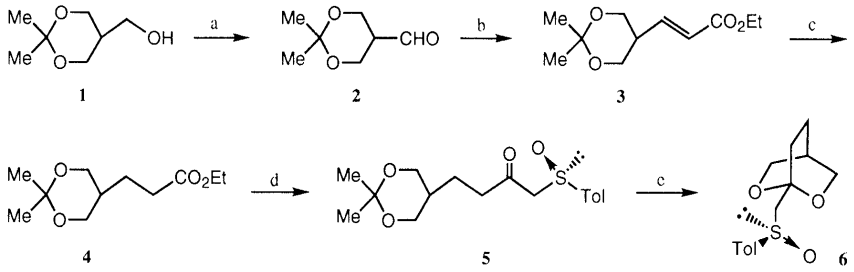


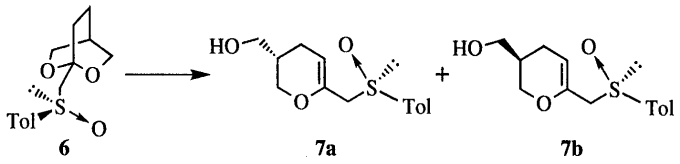
Chart 2



a: $(COCl)_2$, dimethylsulfoxide(DMSO), triethylamine, CH_2Cl_2, −58 °C; b: $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C (87% in 2 steps); c: H_2, Pd–C, MeOH, room temp. (quant.); d: Bu^tLi, (*R*)-methyl *p*-tolyl sulfoxide, THF, −78 °C (72%); e: *p*-$MeC_6H_4SO_3H \cdot H_2O$, benzene, room temp. (96%)

Chart 3

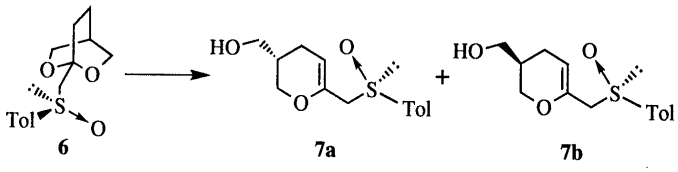
Table 1. Diastereoselective Acetal Cleavage of **6** under Acidic Conditions



Conditions (eq)	Yield (%)	Ratio[a] **7a**:**7b**
$TiCl_4$ (10), DME,[b] −50 °C	No reaction	—
$TiCl_4$ (10), DME, −20 °C	83	64:36
$TiCl_4$ (10), DME, room temp.	Complex mixture	—
$TiCl_4$ (10), Et_2O, −20 °C	80	53:47
$TiCl_4$ (10), CH_2Cl_2, −20 °C	No reaction	—
$TiCl_4$ (10), THF, −20 °C	81	72:28
$TiCl_4$ (2), THF, −20 °C	49	72:28
$TiCl_4$ (0.5), THF, −20 °C	27	74:26
CF_3CO_2H (10), THF, room temp.	48[c]	50:50
$AlCl_3$ (10), THF, room temp.	37	50:50

a) Determined by HPLC as the benzoate unless otherwise stated. *b*) DME = 1,2-dimethoxyethane. *c*) Isolated as a trifluoroacetate. The ratio was determined by 500 MHz ^{1}H-NMR spectroscopy.

Table 2. Diasteroselective Acetal Cleavage of **6** under Basic Conditions



Conditions (eq)	Yield (%)	Ratio[a] **7a**:**7b**
LDA (6), THF, −78 °C to room temp.	95	41:59
LDA (6), HMPA[b] (6), THF, −78 °C to room temp.	94	33:67
LDA (6), 12-crown-4 (6), THF, −78 °C to room temp.	92	28:72
LDA (6), DABCO[b] (6), THF, −78 °C to room temp.	81	28:72
LDA (6), TMEDA (6), THF, −78 °C to room temp.	92	25:75
$LiNEt_2$ (6), THF, −78 °C	91	35:65

a) Determined by HPLC as the benzoate. *b*) HMPA = hexamethylphosphoric triamide, DABCO = 1,4-diazabicyclo[2.2.2]octane.

afforded the dihydropyran derivatives **7a** and **7b**, but no selectivity was observed. The ratio of diastereomeric isomers was determined by ^{1}H-NMR spectroscopic analysis. In contrast, diastereoselective acetal cleavage proceeded with a large excess (10 eq) of titanium tetrachloride ($TiCl_4$) in tetrahydrofuran (THF) at −20 °C to give **7a** and **7b** with a moderate diastereoselectivity (**7a**:**7b** = 72:28) in 81% yield. With a smaller amount of $TiCl_4$, the yield was decreased but the diastereoselectivity did not change (Table 1). Temperature also affected the reaction. The best result was obtained at −20 °C.

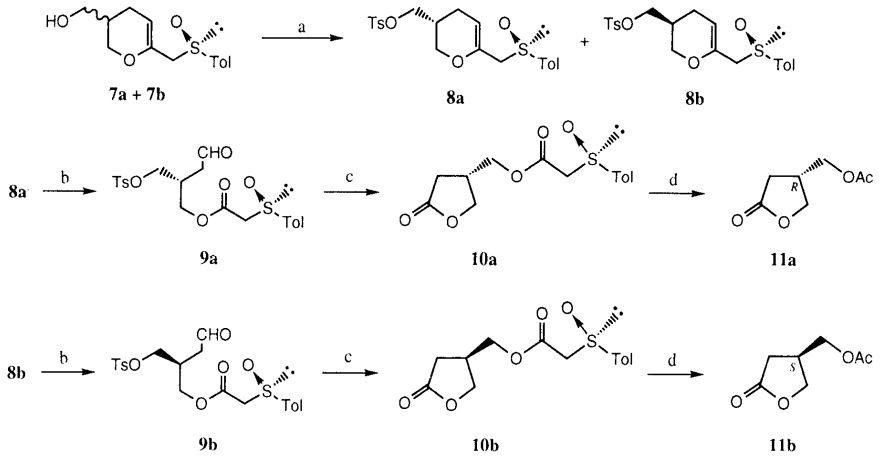
On the other hand, treatment of **6** with LDA in THF at −78 °C resulted in diastereoselective β-elimination followed by migration of the double bond to the β,γ-position. Interestingly, the diastereoselectivity was found to be reversed (**7a**:**7b** = 41:59) in this case. Addition of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) increased the selectivity (**7a**:**7b** = 25:75). The results are

summarized in Table 2.

Dihydropyran derivatives **7a** and **7b** were converted into the γ-lactone **11a** with known specific rotation and the enantiomeric isomer **11b**, respectively, as shown in Chart 4. After tosylation, the diastereomeric isomers were separated by high-performance liquid chromatography (HPLC) (column: Waters RCM 25×10, mobile phase: AcOEt–hexane, 1:1). The enol ether **8a** was converted into the aldehyde **9a** by reductive ozonolysis. Upon immediate oxidation of **9a** with sodium chlorite in phosphate buffer, the lactone **10a** was obtained in 96% yield from **8a**. In this reaction, the resulting carboxylate anion attacked the tosylate intramolecularly to give the γ-lactone **10a**. This was reduced to the γ-lactone **11a** with Raney Ni (W2) in EtOH quantitatively. The specific rotation of **11a** $[[\alpha]_D^{30}$ −33.0° (c=0.68, $CHCl_3$)] was consistent with the reported value $[[\alpha]_D^{23}$ −33.1° ($CHCl_3$)].[5] In the same manner, the other isomer **8b** was converted to **11b** $[[\alpha]_D^{29}$ +34.1° (c=0.57, $CHCl_3$)]. Thus, the stereochemistry of **7a** and **7b** was confirmed.

The mechanism of these cleavage reactions was speculated to be as follows. The bidentate $TiCl_4$ would coordinate between the acetal and sulfinyl oxygens. The bulky tolyl group would occupy an equatorial position in the chair-like six-membered chelation intermediates A and B, as shown in Chart 5. The sulfinyl group tends to become *anti* to the bulky 7-methylene group rather than the 6-oxygen owing to the unfavorable *gauche* interaction between these moieties and the favorable *gauche* interaction between the electron-positive sulfur atom and the electron-negative oxygens.[6] Therefore, the intermediate A is more stable than B. Since a protonic acid or monodentate Lewis acid can not form such a cyclic chelation intermediate due to random coordination of acids to both oxygens, no selectivity was observed.

Under the basic condition, the sulfinyl oxygen would coordinate to the adjacent lithium atom to form a four-membered chelation intermediate,[7] in which the tolyl group would be *trans* to the bulky bicyclic ring (intermediate C or D). Intermediate D is more stable than C because of the unfavorable and favorable *gauche* interactions between the sulfoxide and the bicyclic ring as argued above. As a result of favorable *anti* elimination, the dihydropyran derivative **7b** would be formed selec-



a: p-$MeC_6H_4SO_2Cl$, triethylamine, dimethylaminopyridine (DMAP), CH_2Cl_2, room temp. (89%); b: O_3, MeOH, −78°C then Me_2S, room temp. (quant.); c: $NaClO_2$, DMSO, NaH_2PO_4 buffer (**10a**: 96%, **10b**: 96%); d: Raney Ni (W2), EtOH, room temp. (**11a**: quant., **11b**: quant.)

Chart 4

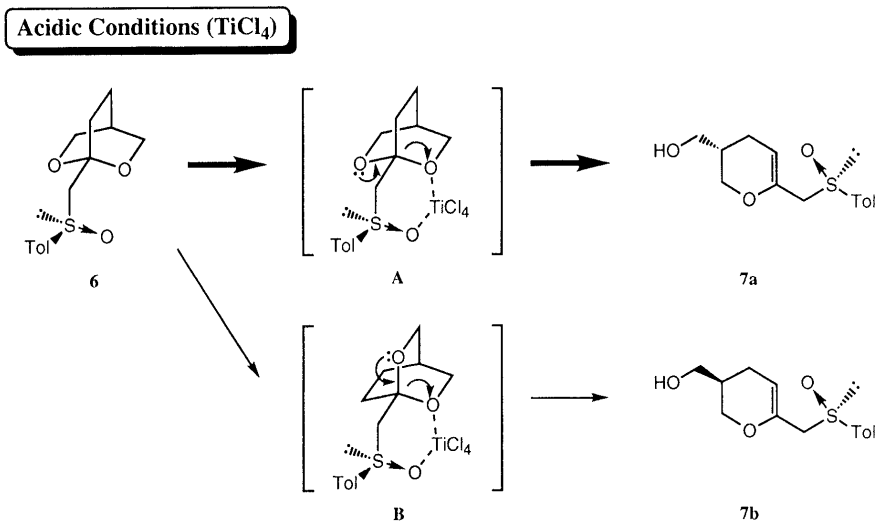


Chart 5

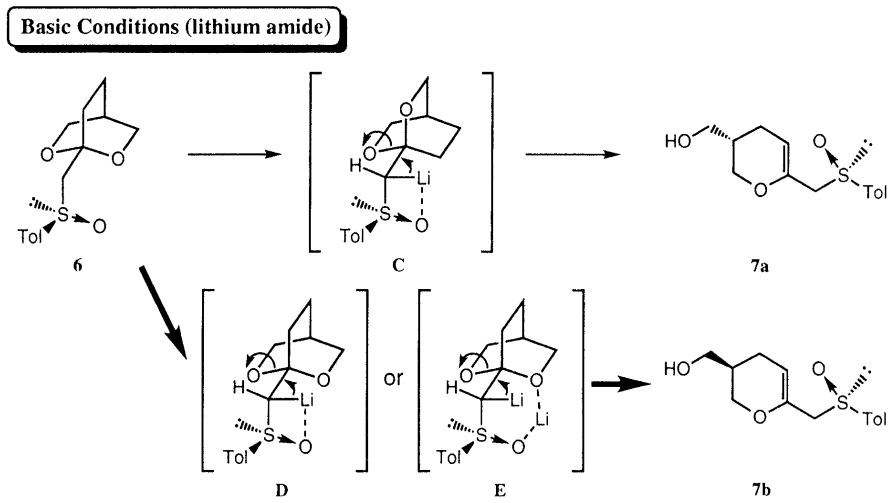


Chart 6

tively. The resulting α,β-unsaturated sulfoxide would isomerize to β,γ-unsaturated sulfoxide. Recently, we noted the possibility of a six-membered ring chelation intermediate as shown in intermediate E.[3e] Therefore, such a chelation may also contribute to the formation of **7b**.

In conclusion, we have found that the chiral sulfinyl group worked as a chiral auxiliary to differentiate the prochiral 1,3-diol under both acidic and basic conditions. Interestingly, the diastereoselectivity was reversed in these two conditions.

Experimental

Melting points are uncorrected. Optical rotations were measured using a JASCO DIP-360 digital polarimeter. IR spectra were measured with a Hitachi 260-10 IR spectrometer or a Horiba FT-210 IR spectrometer. ^{1}H-NMR spectra were measured with a Varian VXR-200 spectrometer (200 MHz) or a JEOL JNM-GX500 spectrometer (500 MHz). ^{13}C-NMR spectra were measured with a JEOL JNM-EX270 spectrometer (67.8 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), broad (br). Mass spectra were taken with a Shimadzu QP-1000 mass spectrometer and a JEOL JMS-D300 mass spectrometer. HPLC analyses were performed using a Waters 6000A pump, a Waters RCM 25 × 10 column, and a Soma S-310 UV detector (at 254 nm). Unless otherwise stated, all reactions were performed with anhydrous solvent. Merck Kieselgel 60 was used as an adsorbent for column chromatography.

(*E*)-5-[2-(Ethoxycarbonyl)ethenyl]-2,2-dimethyl-1,3-dioxane (3) Dimethyl sulfoxide (19.4 ml, 274 mmol) was added dropwise to a solution of oxalyl chloride (12.0 ml, 137 mmol) in dry CH_2Cl_2 (200 ml) with stirring at −58 °C. The stirring was continued at −58 °C for 5 min. A solution of **1** (10.0 g, 68.5 mmol) in dry CH_2Cl_2 was then added dropwise and the resulting solution was stirred at −58 °C for 15 min, at which time triethylamine (95.5 ml, 685 mmol) was added and the reaction mixture was allowed to warm to 25 °C. The stirring was continued for 1 h. The mixture was diluted with Et_2O, washed with water and brine, and then dried over $MgSO_4$. The solvent was evaporated and the residue was quickly chromatographed on silica gel with AcOEt–hexane (1 : 1) to give **2** (9.53 g), which was immediately used in the next step without further purification. Triethyl phosphonoacetate (10.3 ml, 51.4 mmol) was added dropwise to a suspension of NaH (2.06 g, 51.4 mmol) in dry THF (80 ml) with stirring at 0 °C and the stirring was continued at 0 °C for 1 h. A solution of **2** (3.70 g, 25.7 mmol) in dry THF (10 ml) was added dropwise to the reaction mixture and the whole was stirred at 20 °C for 1 h. The reaction was quenched with water. The organic layer was separated and the aqueous layer was extracted with Et_2O. 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 Et_2O–hexane (1 : 2) to give **3** (4.94 g, 87% in 2 steps) as colorless crystals, mp 43—44 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.29 (t, 3H, J = 7.3 Hz, $OCH_2C\underline{H}_3$), 1.43 (s, 3H, $CC\underline{H}_3$), 1.46 (s, 3H, $CC\underline{H}_3$), 2.65—2.74 (m, 1H, $CH_2C\underline{H}$), 3.78 (dd, 2H, J = 12.0, 9.4 Hz, $OC\underline{H}_2CH$), 3.92 (dd, 2H, J = 12.0, 4.7 Hz, $OC\underline{H}_2CH$), 4.20 (q, 2H, J = 7.3 Hz, $OC\underline{H}_2CH_3$), 5.92 (d, 1H, J = 10.8 Hz, CH = C$\underline{H}$CO), 6.81 (dd, 1H, J = 10.8, 7.9 Hz, CH = C$\underline{H}$CO). ^{13}C-NMR ($CDCl_3$) δ: 14.1, 20.7, 26.7, 37.6, 60.4, 63.0, 97.8, 123.3, 144.4, 165.9. IR (KBr): 2991, 2868, 1720, 1655, 1371, 1329, 1261, 1196, 1182, 1149, 1080, 1038 cm^{-1}. MS m/z (%): 199 ($M^+ - CH_3$, 41.7), 126 (100). *Anal.* Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.45; H, 8.30.

5-[2-(Ethoxycarbonyl)ethyl]-2,2-dimethyl-1,3-dioxane (4) A suspension of Pd–C (138 mg) in dry MeOH (15 ml) was stirred at 20°C under an H_2 atmosphere for 3 h. A solution of **3** (690 mg, 3.22 mmol) in dry MeOH (5 ml) was added to the stirred suspension at 20 °C. The stirring was continued at 20 °C for 8 h and then filtered. The solvent was evaporated and the residue was chromatographed on silica gel with Et_2O–hexane (1 : 1) to give **4** (696 mg, quant.) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (t, 3H, J = 7.3 Hz, $OCH_2C\underline{H}_3$), 1.40 (s, 3H, $CC\underline{H}_3$), 1.42 (s, 3H, $CC\underline{H}_3$), 1.59 (dd, 2H, J = 15.0, 7.3 Hz, $CHC\underline{H}_2CH_2$), 1.77—1.82 (m, 1H, $CH_2C\underline{H}$), 2.31 (t, 2H, J = 7.7 Hz, $C\underline{H}_2CO$), 3.59 (dd, 2H, J = 12.0, 9.0 Hz, $OC\underline{H}_2CH$), 3.87 (dd, 2H, J = 12.0, 4.7 Hz, $OC\underline{H}_2CH$), 4.13 (q, 2H, J = 7.3 Hz, $OC\underline{H}_2CH_3$). ^{13}C-NMR ($CDCl_3$) δ: 14.1, 21.1, 23.9, 26.7, 31.4, 33.7, 60.5, 64.4, 97.8, 173.1. IR (KBr): 2991, 2939, 2858, 1732, 1456, 1371, 1325, 1254, 1196, 1176, 1140, 1090, 1034 cm^{-1}. MS m/z (%): 201 ($M^+ - CH_3$, 100). *Anal.* Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found : C, 60.86; H, 9.08.

(*Rs*)-2,2-Dimethyl-5-[3-oxo-4-(*p*-tolylsulfinyl)butyl]-1,3-dioxane (5) *sec*-BuLi (1.08 M in cyclohexane, 3.74 ml, 4.03 mmol) was added dropwise to a solution of (*R*)-methyl *p*-tolyl sulfoxide (591 mg, 3.84 mmol) in dry THF (15 ml) at −78 °C and the whole was stirred at −78 °C for 30 min. A solution of **4** (415 mg, 1.92 mmol) in dry THF (4 ml) was added dropwise to the reaction mixture at −78 °C. The mixture was allowed to warm to 0 °C and stirred for 1 h. The reaction was quenched with saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, and then dried over $MgSO_4$. The solvent was evaporated and the residue was chromatographed on silica gel with AcOEt–$CHCl_3$ (1 : 2) to give **5** (450 mg, 72%) as colorless crystals, mp 107—108 °C (AcOEt–hexane), $[\alpha]_D^{26}$ +173.8° (c = 1.10, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.39 (s, 3H, $CC\underline{H}_3$), 1.39 (s, 3H, $CC\underline{H}_3$), 1.49 (q, 2H, J = 7.7 Hz, $CHC\underline{H}_2$), 1.63—1.72 (m, 1H, $C\underline{H}CH_2CH_2$), 2.43 (s, 3H, Ar-$C\underline{H}_3$), 2.45 (dt, 1H, J = 18.0, 7.7 Hz, $C\underline{H}_2CO$), 2.53 (dt, 1H, J = 18.0, 7.7 Hz, $C\underline{H}_2CO$), 3.52 (dd, 2H, J = 12.0, 8.6 Hz, $C\underline{H}_2O$), 3.75 (d, 1H, J = 13.7 Hz, $C\underline{H}_2SO$), 3.81 (dd, 2H, J = 12.0, 4.3 Hz, $C\underline{H}_2O$), 3.83 (d, 1H, J = 13.7 Hz, $C\underline{H}_2SO$), 7.34 (d, 2H, J = 8.1 Hz, Ar-$\underline{H}$), 7.52 (d, 2H, J = 8.1 Hz, Ar-$\underline{H}$). ^{13}C-NMR ($CDCl_3$) δ: 21.4, 21.4, 21.8, 26.2, 33.4, 42.1, 64.2, 67.7, 97.8, 123.9, 130.1, 139.4, 142.2, 200.8. IR (KBr): 2935, 2922, 2862, 1713, 1495, 1454, 1371, 1255, 1198, 1155, 1086, 1041 cm^{-1}. MS m/z (%): 309 ($M^+ - CH_3$, 43.3), 139 (100). *Anal.* Calcd for $C_{17}H_{24}O_4S$: C, 61.09; H, 9.32; S, 9.88. Found: C, 60.86; H, 9.08; S, 9.94.

(*Rs*)-1-(*p*-Tolylsulfinyl)methyl-2,6-dioxabicyclo[2.2.2]octane (6) A mixture of **5** (110 mg, 0.340 mmol) and a catalytic amount of *p*-toluenesulfonic acid monohydrate (3.2 mg, 0.020 mmol) in benzene

(8 ml) was stirred at 25 °C for 5 h. After the addition of saturated $NaHCO_3$, the whole was extracted with Et_2O. 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–benzene (1 : 1) to give **6** (87 mg, 96%) as colorless crystals, mp 100—101 °C (AcOEt–hexane), $[\alpha]_D^{28}$ +120.6° (c=1.05, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.86—1.90 (m, 3H), 2.04—2.12 (m, 1H), 2.32—2.40 (m, 1H), 2.40 (s, 3H, Ar-C$\underline{H}_3$), 2.86 (d, 1H, J=14.1 Hz, C$\underline{H}_2$SO), 3.01 (d, 1H, J=14.1 Hz, C$\underline{H}_2$SO), 4.01—4.06 (m, 1H, C$\underline{H}_2$O), 4.09—4.15 (m, 1H, C$\underline{H}_2$O), 4.18 (dt, 1H, J=8.5, 2.1 Hz, C$\underline{H}_2$O), 4.23 (dt, 1H, J=8.5, 2.1 Hz, C$\underline{H}_2$O), 7.30 (d, 2H, J=8.1 Hz, Ar-$\underline{H}$), 7.55 (d, 2H, J=8.1 Hz, Ar-$\underline{H}$). ^{13}C-NMR ($CDCl_3$) δ: 21.3, 22.8, 26.9, 32.4, 67.7, 69.3, 69.4, 93.9, 124.0, 129.8, 141.1, 141.9. IR (KBr): 2980, 2950, 2930, 2875, 1599, 1493, 1348, 1292, 1055, 1023, 1008 cm^{-1}. MS m/z (%): 266 (M^+, 15), 127 (100). *Anal.* Calcd for $C_{14}H_{18}O_3S$: C, 63.13; H, 6.81; S, 12.04. Found: C, 63.29; H, 6.81; S, 11.90.

(3*R*,*Rs*)- and (3*S*,*Rs*)-[3,4-Dihydro-6-(*p*-tolylsulfinyl)methyl-2*H*-pyran-3-yl]methyl *p*-Toluenesulfonate (8a and 8b) Method A: $TiCl_4$ (10.3 μl, 0.940 mmol) was added to a solution of **6** (25.0 mg, 0.0940 mmol) in dry THF (2 ml) at −20 °C. The stirring was continued at −20 °C for 30 min and then the mixture was poured into cold saturated $NaHCO_3$. After extraction with AcOEt, the organic layer was 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 **7a** and **7b** (20.1 mg, 81%). The diastereomeric mixture was used in the next step without further purification. 4-Dimethylaminopyridine (DMAP) (9.2 mg, 0.075 mmol) and triethylamine (21 μl, 0.15 mmol) were added to a solution of **7a** and **7b** (20 mg, 0.075 mmol) in dry CH_2Cl_2 (0.4 ml) at 0 °C. The stirring was continued at 0 °C for 10 min. A solution of *p*-toluenesulfonyl chloride (28.6 mg, 0.150 mmol) in dry CH_2Cl_2 (0.5 ml) was added to the stirred mixture and the stirring was continued at 0 °C for 5 h. After the addition of saturated $NaHCO_3$, the whole 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–benzene (1 : 4) to give a mixture of **8a** and **8b**. The mixture was separated by HPLC [AcOEt : hexane = 1 : 1, flow rate = 4 ml/min, t_R = 41.9 min (**8a**), t_R = 49.7 min (**8b**)] to afford **8a** (21.5 mg, 68%) as colorless crystals and **8b** (6.0 mg, 19%) as colorless crystals.

Method B: TMEDA (0.078 ml, 0.52 mmol) was added to a stirred LDA solution [prepared from *n*-BuLi (1.6 M in hexane; 0.32 ml, 0.52 mmol) and diisopropylamine (0.073 ml, 0.52 mmol) in dry THF (2 ml)] at −78 °C. The stirring was continued at −78 °C for 5 min. A solution of **6** (46.0 mg, 0.173 mmol) in dry THF (0.5 ml) was added dropwise to the stirred mixture at −78 °C and the whole was stirred at −78 °C 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 **7a** and **7b** (42.0 mg, 92%). The diastereomeric mixture was used in the next step without further purification. DMAP (9.2 mg, 0.075 mmol) and triethylamine (21 μl, 0.15 mmol) were added to a solution of **7a** and **7b** (20 mg, 0.075 mmol) in dry CH_2Cl_2 (0.4 ml) at 0 °C. The stirring was continued at 0 °C for 10 min. A solution of *p*-toluenesulfonyl chloride (28.6 mg, 0.150 mmol) in dry CH_2Cl_2 (0.5 ml) was added to the stirred mixture and the stirring was continued at 0 °C for 5 h. After the addition of saturated $NaHCO_3$, the whole 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–benzene (1 : 4) to give a mixture of **8a** and **8b**. The mixture was separated by HPLC to afford **8a** (7.0 mg, 22%) and **8b** (21.1 mg, 67%). **8a**: mp 94—96 °C (AcOEt–hexane), $[\alpha]_D^{24}$ +98.4° (c=1.26, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.74—1.84 (m, 1H), 2.04—2.14 (m, 1H), 2.18—2.26 (m, 1H), 2.41 (s, 3H, Ar-C$\underline{H}_3$), 2.45 (s, 3H, Ar-C$\underline{H}_3$), 3.27 (d, 1H, J=12.8 Hz, C$\underline{H}_2$SO), 3.39 (d, 1H, J=12.8 Hz, C$\underline{H}_2$SO), 3.74 (dd, 1H, J=10.7, 7.3 Hz, C$\underline{H}_2$O), 3.90—3.96 (m, 2H, C$\underline{H}_2$O), 3.99 (dd, 1H, J=9.8, 6.0 Hz, C$\underline{H}_2$O), 4.63 (t, 1H, J=3.8 Hz, C$\underline{H}$=C), 7.30 (d, 2H, J=8.1 Hz, Ar-$\underline{H}$), 7.36 (d, 2H, J=8.1 Hz, Ar-$\underline{H}$), 7.48 (d, 2H, J=8.1 Hz, Ar-$\underline{H}$), 7.79 (d, 2H, J=8.1 Hz, Ar-$\underline{H}$). ^{13}C-NMR ($CDCl_3$) δ: 21.3, 21.6, 22.6, 31.4, 63.1, 66.5, 69.8, 101.3, 124.0, 127.8, 129.7, 129.9, 132.6, 140.5, 141.5, 144.6, 144.9. IR ($CHCl_3$): 3000, 2900, 1582, 1162, 1023 cm^{-1}. MS m/z (%): 420 (M^+, 0.8), 109 (100). *Anal.* Calcd for $C_{21}H_{24}O_5S_2$: C, 59.98; H, 5.75; S, 15.25. Found: C, 59.80; H, 5.69; S, 14.98. **8b**: mp 120—122 °C (AcOEt—hexane), $[\alpha]_D^{24}$ +120.8° (c=0.83, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.74—1.82 (m, 1H), 2.10—2.30 (m, 2H), 2.41 (s, 3H, Ar-C$\underline{H}_3$), 2.45 (s, 3H, Ar-C$\underline{H}_3$), 3.27 (d, 1H, J=13.0 Hz, C$\underline{H}_2$SO), 3.40 (d, 1H, J=13.0 Hz, C$\underline{H}_2$SO), 3.74 (dd, 1H, J=10.7, 6.4 Hz, C$\underline{H}_2$O), 3.93 (dd, 1H, J=9.8, 7.7 Hz, C$\underline{H}_2$O), 3.95—4.01 (m, 2H, C$\underline{H}_2$O), 4.64 (t, 1H, J=3.8 Hz, C$\underline{H}$=C), 7.30 (d, 2H, J=8.1 Hz, Ar-$\underline{H}$), 7.36 (d, 2H, J=8.1 Hz, Ar-$\underline{H}$), 7.48 (d, 2H, J=8.1 Hz, Ar-$\underline{H}$), 7.79 (d, 2H, J=8.1 Hz, Ar-$\underline{H}$). ^{13}C-NMR ($CDCl_3$) δ: 21.4, 21.6, 22.6, 31.3, 63.1, 66.5, 69.8, 101.3, 124.0, 127.8, 129.7, 129.8, 132.6, 140.5, 141.6, 144.5, 144.9. IR ($CHCl_3$): 3000, 2940, 1603, 1180, 1042 cm^{-1}. MS m/z (%): 420 (M^+, 0.1), 109 (100). *Anal.* Calcd for $C_{21}H_{24}O_5S_2$: C, 59.98; H, 5.75; S, 15.25. Found: C, 59.83; H, 5.74; S, 15.12.

(3*S*,*Rs*)-3-[(*p*-Tolylsulfinyl)acetoxymethyl]butan-4-olide (10a) A stream of ozone was bubbled through a solution of **8a** (18.0 mg, 0.043 mmol) in dry MeOH (2 ml) at −78 °C until a pale blue color developed. Nitrogen was bubbled through the solution to remove excess ozone. Dimethyl sulfide (31 μl, 0.43 mmol) was added, the reaction mixture was allowed to warm to 25 °C, and the stirring was continued for 1 h. The solvent was evaporated to give **9a** (18.2 mg), which was used in the next step without further purification. To a solution of **9a** (18.2 mg) in dimethyl sulfoxide (DMSO) (0.7 ml) at 25 °C was added a solution of $NaClO_2$ (4.8 mg, 0.053 mmol) and $NaH_2PO_4 \cdot H_2O$ (16.0 mg, 0.116 mmol) in water (0.3 ml), and the mixture was stirred at 25 °C for 25 h. After dilution with CH_2Cl_2, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with 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 **10a** (12.2 mg, 92% in 2 steps) as a colorless oil, $[\alpha]_D^{25}$ +104.7° (c=0.86, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 2.27 (dd, 1H, J=18.0, 6.0 Hz, COC$\underline{H}_2$CH), 2.44 (s, 3H, Ar-C$\underline{H}_3$), 2.61 (dd, 1H, J=18.0, 8.6 Hz, COC$\underline{H}_2$CH), 2.82—2.92 (m, 1H, C$\underline{H}$), 3.71 (d, 1H, J=13.2 Hz, C$\underline{H}_2$SO), 3.81 (d, 1H, J=13.2 Hz, C$\underline{H}_2$SO), 4.03 (dd, 1H, J=9.4, 6.0 Hz, C$\underline{H}_2$O), 4.13 (dd, 1H, J=11.1, 6.0 Hz, C$\underline{H}_2$O), 4.16 (dd, 1H, J=11.1, 6.0 Hz, C$\underline{H}_2$O), 4.36 (dd, 1H, J=9.4, 7.7 Hz, C$\underline{H}_2$O), 7.37 (d, 2H, J=7.7 Hz, Ar-$\underline{H}$), 7.56 (d, 2H, J=7.7 Hz, Ar-$\underline{H}$). ^{13}C-NMR ($CDCl_3$) δ: 21.4, 30.8, 34.3, 61.0, 65.4, 69.8, 124.1, 130.2, 139.4, 142.7, 164.4, 175.6. IR ($CHCl_3$): 3000, 2926, 1781, 1742, 1600, 1498, 1180, 1048 cm^{-1}. MS m/z (%): 296 (M^+, 15.0), 139 (100). *Anal.* Calcd for $C_{14}H_{16}O_5S \cdot 1/2H_2O$: C, 55.07; H, 5.61; S, 10.50. Found: C, 55.21; H, 5.62; S, 10.12.

(3*R*,*Rs*)-3-[(*p*-Tolylsulfinyl)acetoxymethyl]butan-4-olide (10b) By a similar procedure to that used for the preparation of **10a**, **8b** (26.6 mg, 0.0633 mmol) was converted into **10b** (18.0 mg, 96% in 2 steps) as a colorless oil, $[\alpha]_D^{26}$ +161.5° (c=0.86, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 2.26 (dd, 1H, J=18.0, 6.8 Hz, COC$\underline{H}_2$CH), 2.44 (s, 3H, Ar-C$\underline{H}_3$), 2.61 (dd, 1H, J=18.0, 8.6 Hz, COC$\underline{H}_2$CH), 2.82—2.92 (m, 1H, C$\underline{H}$), 3.71 (d, 1H, J=13.3 Hz, C$\underline{H}_2$SO), 3.80 (d, 1H, J=13.3 Hz, C$\underline{H}_2$SO), 4.05 (dd, 1H, J=9.4, 5.2 Hz, C$\underline{H}_2$O), 4.09 (dd, 1H, J=11.1, 6.8 Hz, C$\underline{H}_2$O), 4.21 (dd, 1H, J=11.1, 6.0 Hz, C$\underline{H}_2$O), 4.36 (dd, 1H, J=9.4, 7.7 Hz, C$\underline{H}_2$O), 7.37 (d, 2H, J=7.7 Hz, Ar-$\underline{H}$), 7.56 (d, 2H, J=7.7 Hz, Ar-$\underline{H}$). ^{13}C-NMR ($CDCl_3$) δ: 21.4, 30.8, 34.3, 61.1, 65.5, 69.8, 124.1, 130.2, 139.5, 142.7, 164.4, 175.6. IR ($CHCl_3$): 2995, 2925, 1781, 1740, 1600, 1495, 1172, 1045 cm^{-1}. MS m/z (%): 296 (M^+, 7.9), 139 (100). *Anal.* Calcd for $C_{14}H_{16}O_5S \cdot 1/3H_2O$: C, 55.62; H, 5.56; S, 10.60. Found: C, 55.71; H, 5.65; S, 10.33.

(3*R*)-3-(Acetoxymethyl)butan-4-olide (11a) An excess of Raney Ni (W2) was added to a solution of **10a** (17.0 mg, 0.0574 mmol) in dry EtOH (1 ml) at 25 °C. The stirring was continued at 25 °C for 5 min. After filtration, the filtrate was evaporated and the residue was chromatographed on silica gel with AcOEt–hexane (1 : 1) to give **11a** (9.0 mg, quant.) as a colorless oil, $[\alpha]_D^{30}$ −33.0° (c=0.68, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 2.07 (s, 3H, COC$\underline{H}_3$), 2.36 (dd, 1H, J=17.9, 6.4 Hz, COC$\underline{H}_2$), 2.66 (dd, 1H, J=17.9, 9.4 Hz, COC$\underline{H}_2$), 2.86—2.95 (m, 1H, OCH$_2$C$\underline{H}$), 4.08 (dd, 1H, J=11.5, 6.4 Hz, C$\underline{H}_2$O), 4.13 (dd, 1H, J=9.4, 6.0 Hz, C$\underline{H}_2$O), 4.15 (dd, 1H, J=11.5, 6.0 Hz, C$\underline{H}_2$O), 4.42 (dd, 1H, J=9.4, 7.7 Hz, C$\underline{H}_2$O).

(3*S*)-3-(Acetoxymethyl)butan-4-olide (11b) By a similar procedure to that used for the preparation of **11a**, **10b** (15.6 mg, 0.0527 mmol) was converted into **11b** (8.3 mg, quant.) as a colorless oil, $[\alpha]_D^{29}$ +34.1° (c=0.57, $CHCl_3$).

References and Notes

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