1,6-Asymmetric Induction Utilizing Asymmetric Desymmetrization by Diastereoselective C–O Bond Fission of the 4-Substituted Bicyclic Acetal: Application to a Synthesis of (−)-Frontalin

Naoyoshi MAEZAKI, Takeshi SHOGAKI, Masashi UCHIDA, Katsuya TOKUNO, Tsuneaki IMAMURA, Tetsuaki TANAKA, and Chuzo IWATA*

Faculty of Pharmaceutical Sciences, Osaka University, 1–6 Yamadaoka, Suita, Osaka 565, Japan.
Received August 6, 1997; accepted September 17, 1997

1,6-Asymmetric induction was achieved in the acid-induced diastereoselective acetal cleavage reaction of a 4-substituted bicyclic acetal 8 bearing a chiral sulfinyl group. On treatment with titanium tetrachloride and 2,6-disubstituted pyridine bases, 8 gave a synthetically versatile 3,3-disubstituted dihydropyran derivative 9a with moderate diastereoselectivity. The utility of this chiral synthon was successfully demonstrated by a formal synthesis of (−)-frontalin.

Key words 1,6-asymmetric induction; asymmetric desymmetrization; sulfinyl chirality; prochiral 2-substituted glycerol; diastereoselective acetal cleavage reaction

Asymmetric desymmetrization of σ-symmetric compounds is an extremely powerful methodology for creating optically active molecules.[1] We have already developed a novel asymmetric desymmetrization of the prochiral 1,3-diol *via* C–O bond fission of the bicyclic acetal (R = H), in which a chiral sulfinyl group induces a new chirality at the remote prochiral center through four carbons, thereby achieving 1,6-asymmetric induction (Chart 1).[2] In the course of this study, we turned our interest toward the diastereoselective acetal fission of a further functionalized bicyclic acetal (R = BnO), since this transformation is formally equivalent to asymmetric desymmetrization of the 2-substituted glycerol, which is a useful chiral building block[3] for diverse natural products having *tert*-alcohol structures, *e.g.* frontalin,[4] bicyclomycin,[5] and α-tocopherol.[6]

In this paper, we describe a 1,6-asymmetric induction *via* the diastereoselective acetal cleavage reaction of the bicyclic acetal (R = OBn) on treatment with a mixture of $TiCl_4$ and bases, and the application of the resulting dihydropyran-type chiral synthon to a formal synthesis of (−)-frontalin.[7]

Results and Discussion

The prochiral 2-substituted glycerol moiety was synthesized by homoallylation of the ketone **1**, which was readily prepared from commercially available dihydroxyacetone in a single step.[8] After protection of the *tert*-alcohol **2** as the benzyl ether, the olefin **3** was converted with Lemieux–Johnson reagent[9,10] into the aldehyde **4**, which was condensed with the lithium salt of methyl *p*-tolyl sulfoxide prepared by Solladié's procedure.[11] The resulting diastereomeric alcohols **5** were oxidized to the ketone **6** with Dess–Martin periodinane[12] without separation. On treatment of **6** with pyridinium *p*-toluenesulfonate in refluxing benzene, hydrolysis of the tetrahydropyran-2-yl (THP) ether and subsequent intermolecular acetalization of the resulting prochiral 1,3-diol proceeded to give the bicyclic acetal **8**. Unfortunately, unexpected racemization of the sulfinyl chirality occurred under these conditions. The problem was overcome by stepwise acetalization at room temperature. Thus, the bis-THP ether **6** was treated with *p*-TsOH·H_2O at room temperature to give the diastereomeric monocyclic acetals **7**, which can be converted without racemization on sulfur into the bicyclic acetal **8** with zinc chloride.[13]

With the bicyclic acetal **8** in hand, we investigated the diastereoselective acetal cleavage under acidic conditions. The results are shown in Table 1. According to our previous results,[2a,b] the bicyclic acetal **8** was treated with titanium tetrachloride ($TiCl_4$) in tetrahydrofuran (THF). However, the reaction was sluggish.

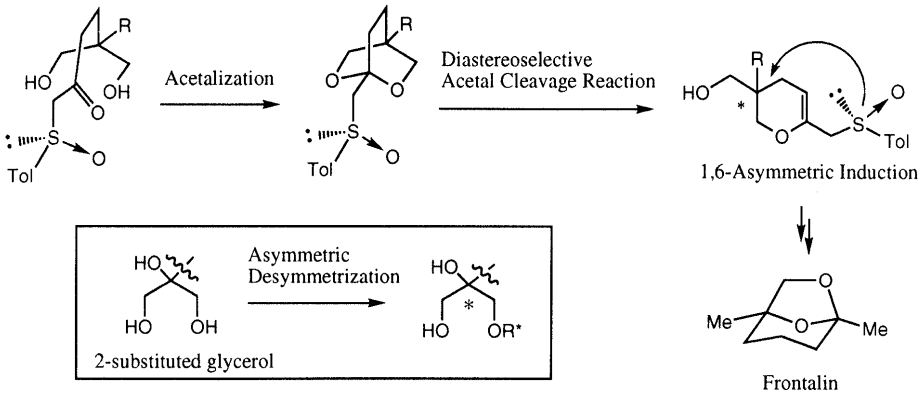
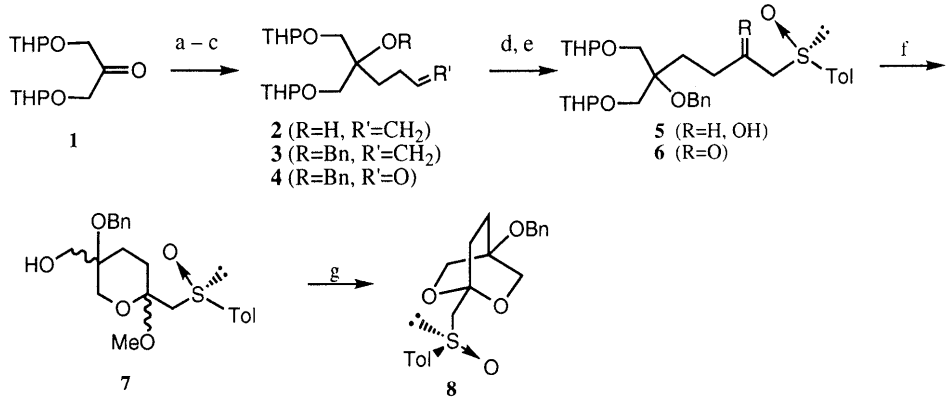


Chart 1

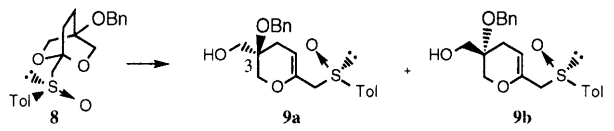
* To whom correspondence should be addressed.



a: 3-butenylmagnesium bromide, ether, 0°C (83%); b: NaH, BnBr, *n*-Bu_4NI, DMF, room temp. (91%); c: OsO_4, $NaIO_4$, aq. ether, room temp. (87%); d: LDA, (*R*)-methyl *p*-tolyl sulfoxide, THF, −78°C (99%); e: Dess-Martin periodinane. CH_2Cl_2, room temp. (96%); f: *p*-TsOH•H_2O, MeOH, room temp. (90%); g: $ZnCl_2$, CH_2Cl_2, room temp. (75%)

Chart 2

Table 1. Diastereoselective Acetal Cleavage of **8**



Conditions[a]	Time (h)	Yield (%)[b]	Ratio[c] **9a**:**9b**
$TiCl_4$, no base	19	Complex mixture	—
$TiCl_4$, 2,6-lutidine	15	82	75:25
$TiCl_4$, 2,6-di-*tert*-butylpyridine	22	89	71:29
$TiCl_4$, pyridine	22	42	67:33
$TiCl_4$, Et_3N	20	Complex mixture	—
$TiCl_4$, iso-Pr_2NEt	20.5	Complex mixture	—
$TiBr_4$, 2,6-lutidine	19.5	Complex mixture	—
BF_3·ether, 2,6-lutidine	21	No reaction	—

a) All reactions were performed with 5 eq of Lewis acid and 5 eq of base in dry THF at −78°C to 5°C. *b*) Combined yield. *c*) Determined by 200 MHz ^{1}H-NMR spectroscopy.

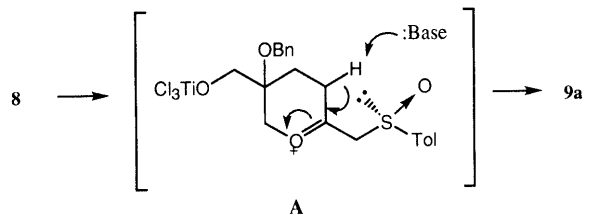


Chart 3

To promote the acetal cleavage reaction, the reaction was carried out in the presence of various bases, which were expected to promote conversion of the initially formed oxonium intermediate A into the dihydropyran structure (Chart 3).

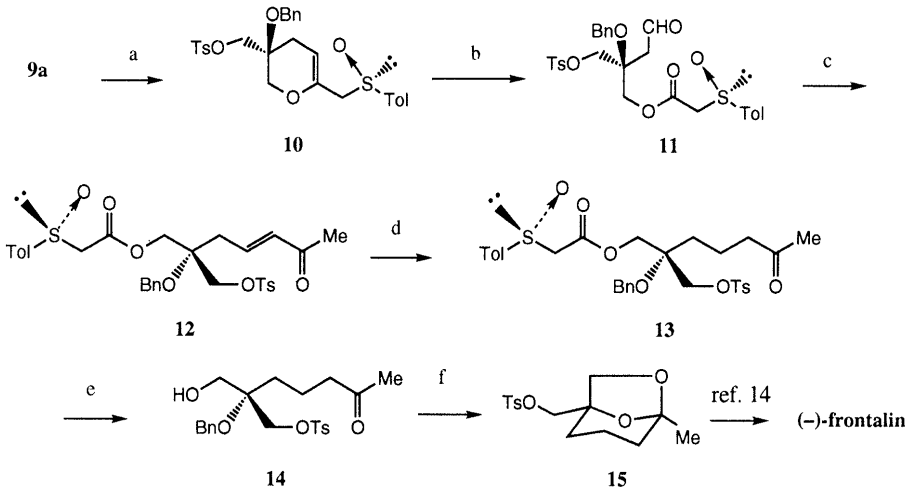
Among them, the combinations of $TiCl_4$ and pyridine derivatives afforded the dihydropyrans **9a** and **9b** with moderate diastereoselectivity. In particular, 2,6-disubstituted pyridine gave products in better yield and with higher selectivity than pyridine. Other Lewis acids ($TiBr_4$ or BF_3·ether) or other *tert*-amine bases (Et_3N or iso-Pr_2NEt) did not give the desired products. These diastereomeric isomers **9a** and **9b** could be separated by column chromatography. By analogy with the previous results,[2a,b] the major product **9a** was tentatively assigned as the (3*R*)-isomer, and this was later confirmed by the formal synthesis of (−)-frontalin.

The conversion of **9a** into (−)-frontalin is illustrated in Chart 4. After tosylation of the major product **9a**, the dihydropyran ring of **10** was cleaved by ozonolysis to afford the aldehyde **11**, which was converted into the enone **12** with 1-triphenylphosphoranylidene-2-propanone in refluxing THF. After reduction of the double bond, the ester **13** was hydrolyzed to the alcohol **14** with potassium hydroxide in isopropanol. Finally, hydrogenolysis of the benzyl ether (10% Pd–C, H_2, 1 atom) resulted in intramolecular acetalization to give the bicyclic acetal **15**, which has already been converted into (−)-frontalin by Monneret *et al.*[14] The spectroscopic data and the specific rotation $\{[\alpha]_D^{27}$ −20.5° (*c*=0.43, $CHCl_3$)} were consistent with the reported data $\{[\alpha]_D^{20}$ −20° (*c*=1, $CHCl_3$)}.

In conclusion, the $TiCl_4$-induced acetal cleavage reaction of the 4-benzyloxy bicyclic acetal **8** was carried out in the presence of 2,6-disubstituted pyridine, and 1,6-asymmetric induction was achieved to give the 3,3-disubstituted dihydropyran-type chiral synthon **9a** with moderate diastereoselectivity. The utility of this chiral synthon was demonstrated by a formal synthesis of (−)-frontalin.

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. ^{1}H-NMR spectra were measured with a Varian VXR-200 spectrometer (200 MHz) or a JEOL JNM-GX500 spectrometer (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). Electron impact mass spectra (EI-MS) were taken with a Shimadzu QP-1000 mass spectrometer or a JEOL JMS-D300 mass spectrometer. High-resolution (HR)-EI-MS were obtained with a JEOL JMS-D300 mass spectrometer. HR-FAB-MS were recorded on a JEOL JMS-SX 102A QQ mass spectrometer. Unless otherwise stated, all moisture-sensitive reactions were performed with anhydrous solvent and extracts were dried over $MgSO_4$. Merck Kieselgel



a: *p*-TsCl, Et_3N, DMAP, CH_2Cl_2, room temp. (87%); b: O_3, CH_2Cl_2, –78°C then Me_2S, room temp. (66%); c: $Ph_3P{=}CHCOCH_3$, THF, reflux (43%); d: H_2, 10% Pd-C, MeOH, room temp. (quant); e: 1 N KOH, iso-PrOH, room temp. (65%); f: H_2, 10% Pd-C, MeOH, room temp. (95%).

Chart 4

60 was used as an adsorbent for column chromatography.

1-(Tetrahydropyran-2-yloxy)-2-(tetrahydropyran-2-yloxymethyl)-5-hexen-2-ol (2) 3-Butenylmagnesium bromide (0.50 M ether solution) (3.0 ml, 1.50 mmol) was added dropwise to a solution of the ketone **1** (272 mg, 1.05 mmol) in ether (3 ml) with stirring at 0 °C under N_2. Stirring was continued at 0 °C for 2.5 h, then the reaction was quenched with saturated NH_4Cl and the whole was extracted with ether. The extract was washed with brine and then dried. The solvent was evaporated and the residue was chromatographed on silica gel with hexane–AcOEt (5 : 1) to give **2** (273 mg, 83%) as a colorless oil. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.40—1.90 (m, 14H), 2.10—2.28 (m, 2H, 4-H), 2.90—4.00 (m, 8H, 4 × CH_2O), 4.54—4.66 (m, 2H, anomeric H), 4.94 (dd, 1H, J = 10.4, 1.8 Hz, 6-H), 5.04 (dd, 1H, J = 17.4, 1.8 Hz, 6-H), 5.86 (ddt, 1H, J = 17.4, 10.4, 6.2 Hz, 5-H). IR (KBr): 3450, 1641, 1124, 1074 cm^{-1}. EI-MS *m/z* (%): 229 (M^+ – THP + 1, 1.2), 85 (THP – 1, 100). HR-EI-MS Calcd for $C_{12}H_{21}O_4$: 229.1437. Found: 229.1434.

2-Benzyloxy-1-(tetrahydropyran-2-yloxy)-2-(tetrahydropyran-2-yloxymethyl)-5-hexene (3) Sodium hydride (308 mg, 7.70 mmol) was added portionwise to a solution of the alcohol **2** (1.62 g, 5.14 mmol) and tetra-*n*-butylammonium iodide (28.5 mg, 0.077 mmol) in *N*,*N*-dimethylformamide (DMF) (20 ml) with stirring at room temperature under N_2. After 10 min, benzyl bromide (0.90 ml, 7.57 mmol) was added dropwise to the mixture and the whole was stirred at room temperature for 5 h. After cooling, the reaction was quenched with saturated $NaHCO_3$ and the whole was extracted with ether. The extract was washed with water and brine, and then dried. The solvent was evaporated and the residue was chromatographed on silica gel with hexane–AcOEt (10 : 1) to give **3** (1.90 g, 91%) as a pale yellow oil. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.40—1.90 (m, 14H), 2.12—2.30 (m, 2H, 4-H), 3.40—3.98 (m, 8H, 4 × CH_2O), 4.48—4.76 (m, 4H, benzylic-H, anomeric-H), 4.84—5.14 (m, 2H, 6-H), 5.75—5.98 (m, 1H, 5-H), 7.21—7.42 (m, 5H, Ar-H). IR (KBr): 3029, 1641, 1124, 1070 cm^{-1}. EI-MS *m/z* (%): 319 (M^+ – THP + 1, 1.6), 85 (THP – 1, 100). *Anal.* Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.08; H, 8.85.

4-Benzyloxy-5-(tetrahydropyran-2-yloxy)-4-(tetrahydropyran-2-yloxymethyl)pentanal (4) Osmium tetroxide (120 mg, 0.472 mmol) was added to a mixture of the benzyl ether **3** (3.87 g, 9.59 mmol) in ether–water (3 : 1) (40 ml) with stirring at room temperature. Stirring was continued at room temperature for 5 min, then the reaction mixture was cooled to 0 °C, sodium periodate (4.10 g, 19.2 mmol) was added over 30 min, and the whole was stirred at room temperature for 3 h. It was extracted with ether and the extract was dried over Na_2SO_4. The solvent was evaporated and the residue was chromatographed on silica gel with hexane–AcOEt (5 : 1) to give **4** (3.39 g, 87%) as a colorless oil. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.40—1.90 (m, 12H), 1.96—2.10 (m, 2H, 3-H), 2.55—2.68 (m, 2H, 2-H), 3.42—3.98 (m, 8H, 4 × CH_2O), 4.57—4.66 (m, 4H, benzylic-H, anomeric-H), 7.21—7.32 (m, 5H, Ar-H), 9.78 (br s, 1H, 1-H). IR (KBr): 3029, 1720, 1124, 1072 cm^{-1}. EI-MS *m/z* (%): 235 (M^+ – 2THP – 1, 2.3), 85 (THP – 1, 100). HR-EI-MS Calcd for $C_{18}H_{25}O_5$: 321.1699. Found: 321.1699.

(*Rs*)-5-Benzyloxy-6-(tetrahydropyran-2-yloxy)-5-(tetrahydropyran-2-yloxymethyl)-1-(*p*-toluenesulfinyl)hexan-2-ol (5) Lithium diisopropylamide (LDA) (THF solution) [prepared from *n*-BuLi (1.6 M in hexane; 19.6 ml, 31.4 mmol) and diisopropylamine (4.40 ml, 31.4 mmol) in THF (16 ml)] was added dropwise to a solution of (*Rs*)-methyl tolyl sulfoxide (4.60 g, 29.8 mmol) in THF (350 ml) with stirring at –78 °C under N_2. Stirring was continued at 0 °C for 15 min, then the aldehyde **4** (13.3 g, 32.8 mmol) was added and the whole was stirred at –78 °C for 30 min. The reaction was quenched with saturated NH_4Cl and the whole was extracted with AcOEt. The extract was washed with water and brine, and then dried. The solvent was evaporated and the residue was chromatographed on silica gel with hexane–AcOEt (1 : 1) to give **5** (16.6 g, 99%) as a pale yellow oil. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.44—1.90 (m, 16H), 2.42 (s, 3H, Ar-CH_3), 2.67 (br d, 3/7H, J = 13.1 Hz, 1-H), 2.77 (br dd, 4/7H, J = 13.1, 2.7 Hz, 1-H), 2.90—3.07 (m, 1H, 1-H), 3.38—3.58 (m, 4H), 3.72—3.94 (m, 5H), 4.10—4.20 (m, 1H), 4.52—4.68 (m, 4H, benzylic-H, anomeric-H), 7.20—7.52 (m, 9H, Ar-H). IR (KBr): 3376, 3030, 1124, 1031 cm^{-1}. EI-MS *m/z* (%): 559 (M^+ – 1, 0.33), 85 (THP – 1, 100). HR-EI-MS Calcd for $C_{26}H_{36}O_6S$: 476.2232. Found: 476.2232.

(*Rs*)-5-Benzyloxy-6-(tetrahydropyran-2-yloxy)-5-(tetrahydropyran-2-yloxymethyl)-1-(*p*-toluenesulfinyl)hexan-2-one (6) A solution of Dess–Martin periodinane (4.00 g, 9.43 mmol) in CH_2Cl_2 (30 ml) was added to a solution of the alcohol **5** (4.50 g, 8.03 mmol) in CH_2Cl_2 (100 ml) with stirring at 0 °C and the whole was stirred at room temperature for 45 min. It was diluted with ether, then saturated $NaHCO_3$ and saturated $Na_2S_2O_3$ were added. After becoming homogeneous, the mixture was extracted with ether. The extract was washed with water and brine, and then dried. The solvent was evaporated and the residue was chromatographed on silica gel with hexane–AcOEt (1 : 1) to give **6** (4.31 g, 96%) as a pale yellow oil. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.40—2.02 (m, 12H), 1.96 (t, 2H, J = 7.4 Hz, 3-H), 2.39 (s, 3H, Ar-CH_3), 2.56—2.69 (m, 2H, 3-H), 3.36—3.96 (m, 10H, 1-H, 4 × CH_2O), 4.48—4.67 (m, 4H, benzylic-H, anomeric-H), 7.22—7.37 (m, 7H, Ar-H), 7.44 (d, 1H, J = 1.6 Hz, Ar-H), 7.45 (d, 1H, J = 2.0 Hz, Ar-H). IR (KBr): 3029, 1712, 1124, 1070, 1033 cm^{-1}. EI-MS *m/z* (%): 558 (M^+, 1.1), 85 (THP – 1, 100). *Anal.* Calcd for $C_{31}H_{42}O_7S$: C, 66.64; H, 7.58; S, 5.74. Found: C, 66.44; H, 7.41; S, 5.90.

(*Rs*)-5-Benzyloxy-5-hydroxymethyl-2-methoxy-2-(*p*-toluenesulfinyl-methyl)tetrahydropyran (7) A solution of the ketone **6** (105 mg, 0.19 mmol) in MeOH (10 ml) was added to *p*-TsOH · H_2O (1.8 mg, 9.5 μmol) with stirring at room temperature and the whole was stirred at room temperature for 3 h. The reaction was quenched with saturated $NaHCO_3$ and most of MeOH was evaporated off. The residue was diluted with water and the whole was extracted with AcOEt. The extract was washed with brine, and then dried. The solvent was evaporated and the residue was chromatographed on silica gel with hexane–AcOEt (1 : 2) to give **7**

(68.5 mg, 90%) as a colorless oil. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.70—2.13 (m, 4H, 3-H, 4-H), 2.41 (s, 3H, Ar-CH_3), 3.16 (d, 3/5H, J=14.2 Hz, $CH_2S(O)$), 3.05 (d, 3/5H, J=14.2 Hz, $CH_2S(O)$), 3.00 (d, 2/5H, J=13.8 Hz, $CH_2S(O)$), 3.13 (d, 2/5H, J=13.8 Hz, $CH_2S(O)$), 3.25 (s, 6/5H, OCH_3), 3.28 (s, 9/5H, OCH_3), 3.38—3.68 (m, 3H, 6-H_{ax}, CH_2OH), 3.86—3.98 (m, 1H, 6-H_{eq}), 4.52—4.62 (m, 2H, benzylic-H). IR (KBr): 3375, 3031, 1157, 1103, 1045 cm^{-1}. EI-MS m/z (%): 373 (M^+-OCH_3, 0.59), 91 (Bn, 100). HR-EI-MS Calcd for $C_{21}H_{25}O_4S$: 373.1710. Found: 373.1456.

(*Rs*)-4-Benzyloxy-1-(*p*-toluenesulfinylmethyl)-2,6-dioxabicyclo[2.2.2]-octane (8) Anhydrous $ZnCl_2$ (230 mg, 1.68 mmol) was added to a solution of the monocyclic acetal **7** (135 mg, 0.33 mmol) in CH_2Cl_2 (10 ml) with stirring at room temperature under N_2 and the whole was stirred at room temperature for 10 h. After addition of cold water, the mixture was extracted with $CHCl_3$. The extract was washed with water and brine, and then dried. The solvent was evaporated and the residue was chromatographed on silica gel with benzene–AcOEt (3:1) to give **8** (92.3 mg, 75%) as a colorless powder, along with recovered **7** (24.8 mg, 18%). mp 135 °C (iso-PrOH). $[\alpha]_D^{26}$ +82.1° (c=1.03, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.04—2.54 (m, 4H, 7-H, 8-H), 2.41 (s, 3H, Ar-CH_3), 2.89 (d, 1H, J=13.6 Hz, $CH_2S(O)$), 3.05 (d, 1H, J=13.6 Hz, $CH_2S(O)$), 3.99 (br s, 2H, 3-H or 5-H), 4.04 (dd, 1H, J=8.0, 1.8 Hz, 3-H or 5-H), 4.11 (br d, 1H, J=8.0 Hz, 3-H or 5-H), 4.50 (s, 2H, benzylic-H), 7.24—7.37 (m, 7H, Ar-H), 7.55 (d, 2H, J=8.2 Hz, Ar-H). IR (KBr): 3031, 1144, 1059 cm^{-1}. EI-MS m/z (%): 372 (M^+, 3.7), 91 (Bn, 100). *Anal.* Calcd for $C_{21}H_{24}O_4S$: C, 67.72; H, 6.49; S, 8.61. Found: C, 67.66; H, 6.47; S, 8.54.

(3*R*,*Rs*)- and (3*S*,*Rs*)-3-Benzyloxy-3,4-dihydro-3-hydroxymethyl-6-(*p*-toluenesulfinylmethyl)-2*H*-pyran (9a, 9b) 2,6-Lutidine (0.156 ml, 1.34 mmol) and $TiCl_4$ (0.147 ml, 1.34 mmol) were added to a solution of the bicyclic acetal **8** (100 mg, 0.27 mmol) in THF (10 ml) with stirring at −78 °C under N_2. The temperature was raised to 5 °C over 5 h and stirring was continued for 15 h. The mixture was diluted with CH_2Cl_2 and quenched with saturated $NaHCO_3$. The whole was extracted with ether and the extract was washed with brine, and then dried. The solvent was evaporated and the residue was chromatographed on silica gel (35 g) with hexane–AcOEt (1:4) to give a mixture of **9a** (51.6 mg, 52%; Rf=0.26) as a colorless powder and **9b** (20.6 mg, 21%; Rf=0.18) as a pale yellow oil. **9a**: mp 117—118 °C (from benzene). $[\alpha]_D^{29}$ +116° (c=0.82, MeOH). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.95 (m, 3H, Ar-CH_3), 2.01 (d, 2H, J=3.6 Hz, 4-H), 2.46 (t, 1H, J=5.1 Hz, OH), 3.15 (d, 1H, J=12.8 Hz, $CH_2S(O)$), 3.23 (d, 1H, J=12.8 Hz, $CH_2S(O)$), 3.56 (d, 2H, J=5.1 Hz, CH_2OH), 3.83 (d, 1H, J=10.8 Hz, 2-H), 3.99 (d, 1H, J=10.8 Hz, 2-H), 4.37 (d, 1H, J=11.4 Hz, benzylic-H), 4.47 (d, 1H, J=11.4 Hz, benzylic-H), 4.54 (t, 1H, J=3.6 Hz, 5-H), 6.84 (d, 2H, J=8.1 Hz, Ar-H), 7.04—7.33 (m, 5H, Ar-H), 7.40 (d, 2H, J=8.1 Hz, Ar-H). IR (KBr): 3377, 3057, 1678, 1111, 1038 cm^{-1}. EI-MS m/z (%): 372 (M^+, 0.45), 91 (Bn, 100). *Anal.* Calcd for $C_{21}H_{24}O_4S$: C, 67.72; H, 6.49; S, 8.61. Found: C, 67.77; H, 6.45; S, 8.62. **9b**: $[\alpha]_D^{29}$ +107° (c=0.96, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.02—2.08 (m, 1H, OH), 2.15 (d, 1H, J=3.5 Hz, 4-H), 2.33 (d, 1H, J=3.5 Hz, 4-H), 2.41 (s, 3H, Ar-CH_3), 3.37 (d, 1H, J=12.9 Hz, CH_2OH), 3.50 (d, 1H, J=12.9 Hz, CH_2OH), 3.55 (d, 1H, J=12.1 Hz, $CH_2S(O)$), 3.66 (d, 1H, J=12.1 Hz, $CH_2S(O)$), 3.88 (d, 1H, J=10.6 Hz, 2-H_{ax}), 3.98 (dd, 1H, J=10.6, 0.6 Hz, 2-H_{eq}), 4.56 (s, 2H, benzylic-H), 4.78 (t, 3H, J=4.0 Hz, 5-H), 7.26—7.55 (m, 9H, Ar-H). IR (KBr): 3377, 3030, 1678, 1128, 1053 cm^{-1}. EI-MS m/z (%): 372 (M^+, 0.59), 91 (Bn, 100). HR-EI-MS Calcd for $C_{21}H_{24}O_4S$: 372.1396. Found: 372.1413.

(3*S*,*Rs*)-[4-Benzyloxy-3,4-dihydro-6-(*p*-tolylsulfinylmethyl)-2*H*-pyran-3-yl]methyl *p*-Toluenesulfonate (10) *p*-Tolenesulfonyl chloride (*p*-TsCl) (355 mg, 1.86 mmol) was added to a mixture of **9a** (346 mg, 0.93 mmol) and 4-dimethylaminopyridine (DMAP) (227 mg, 1.86 mmol) in CH_2Cl_2 (35 ml) with stirring at room temperature. After 10.5 h, DMAP (56.9 mg, 0.47 mmol) and *p*-TsCl (88.7 mg, 0.47 mmol) were added and stirring was continued at room temperature for 3 h. The reaction was quenched by the addition of saturated NH_4Cl and the whole was extracted with CH_2Cl_2. The extract was washed with water and brine, and then dried. The solvent was evaporated and the residue was chromatographed on silica gel with hexane–AcOEt (1:1) to give **10** (424 mg, 87%) as a colorless powder. $[\alpha]_D^{24}$ +103° (c=1.01, $CHCl_3$). mp 83—85 °C (from hexane–AcOEt). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.15—2.26 (m, 2H, 4-H), 2.40 (s, 3H, ArCH_3), 2.42 (s, 3H, ArCH_3), 3.30 (d, 1H, J=12.8 Hz, $CH_2S(O)$), 3.40 (d, 1H, J=12.8 Hz, $CH_2S(O)$), 3.76 (d, 1H, J=11.0 Hz, 2-H), 3.91 (d, 1H, J=11.0 Hz, 2-H), 4.03 (d, 1H, J=10.9 Hz, TsOCH_2), 4.17 (d, 1H, J=10.9 Hz, TsOCH_2), 4.45 (d, 1H, J=11.0 Hz, OCH_2Ph), 4.50 (d, 1H, J=11.0 Hz, OCH_2Ph), 4.61 (t, 1H, J=3.7 Hz, 5-H), 7.22—7.34 (m, 9H, Ar-H), 7.46 (d, 2H, J=8.5 Hz, Ar-H), 7.79 (d, 2H, J=8.5 Hz, Ar-H). IR (KBr): 1361, 1176 cm^{-1}. HR-FAB-MS m/z: 527.1572 (Calcd for $C_{28}H_{30}O_6S_2+H^+$: 527.1562).

(2*S*,*Rs*)-2-Benzyloxy-4-oxo-2-(*p*-toluenesulfonylmethyl)butyl (*p*-Toluenesulfinyl)acetate (11) Ozone was bubbled through a solution of **10** (50 mg, 0.095 mmol) in a solution of CH_2Cl_2 (5 ml) with stirring at −78 °C until a blue color appeared. About 1 min thereafter, the flow of ozone was stopped. The reaction mixture was purged with N_2 and then treated with Me_2S (70 μl, 0.95 mmol). The temperature was raised to room temperature and stirring was continued for 1 h. The solvent was evaporated and the residue was chromatographed on silica gel with hexane–AcOEt (1:1) to give **11** (35 mg, 63%) as a colorless oil. $[\alpha]_D^{27}$ +68.1° (c=0.74, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.40 (s, 3H, ArCH_3), 2.43 (s, 3H, ArCH_3), 2.73 (d, 2H, J=1.8 Hz, CH_2CHO), 3.63 (d, 1H, J=13.4 Hz, $CH_2S(O)$), 3.73 (d, 1H, J=13.4 Hz, $CH_2S(O)$), 4.22 (s, 2H, J=12.0 Hz, TsOCH_2), 4.31 (d, 1H, J=12.0 Hz, CH_2OCO), 4.36 (d, 1H, J=12.0 Hz, CH_2OCO), 4.48 (s, 2H, OCH_2Ph), 7.23—7.38 (m, 9H, Ar-H), 7.52 (d, 2H, J=8.5 Hz, Ar-H), 7.78 (d, 2H, J=8.5 Hz, Ar-H), 9.72 (t, 1H, J=1.8 Hz, CHO). IR (KBr): 1743, 1724, 1363, 1176 cm^{-1}. HR-FAB-MS m/z: 559.1475 (Calcd for $C_{28}H_{30}O_8S_2+H^+$: 559.1460).

(2*S*,*Rs*)-2-Benzyloxy-6-oxo-2-(*p*-tolylsulfonylmethyl)-4-heptenyl (*p*-Toluenesulfinyl)acetate (12) 1-Triphenylphosphoranylidene-2-propanone (140 mg, 0.44 mmol) was added to a solution of **11** (197 mg, 0.35 mmol) in THF (7 ml) and the mixture was refluxed for 18.5 h. The solvent was evaporated and residue was chromatographed on silica gel with hexane–AcOEt (1:1) to give **12** as a colorless oil (90 mg, 43%). $[\alpha]_D^{27}$ +60.3° (c=0.83, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.17 (s, 3H, $COCH_3$), 2.40 (s, 3H, ArCH_3) 2.43 (s, 3H, ArCH_3), 2.50—2.63 (m, 2H, $CH_2CH=$), 3.63 (d, 1H, J=14.0 Hz, $CH_2S(O)$), 3.72 (d, 1H, J=14.0 Hz, $CH_2S(O)$), 4.03 (d, 1H, J=10.4 Hz, TsOCH_2), 4.12 (d, 1H, J=10.4 Hz, TsOCH_2), 4.19 (d, 1H, J=11.6 Hz, CH_2OCO), 4.30 (d, 1H, J=11.6 Hz, CH_2OCO), 4.48 (s, 2H, OCH_2Ph), 6.11 (d, 1H, J=16.5 Hz, =CHCO), 6.65 (dt, 1H, 7.3, 16.5 Hz, =CHCH$_2$), 7.20—7.39 (m, 9H, Ar-H), 7.53 (d, 2H, J=8.5 Hz, Ar-H), 7.77 (d, 2H, J=7.9 Hz, Ar-H). IR (KBr): 1741, 1674, 1363, 1176 cm^{-1}. HR-FAB-MS m/z: 599.1760 (Calcd for $C_{31}H_{34}O_8S_2+H^+$: 599.1773).

(2*S*,*Rs*)-2-Benzyloxy-6-oxo-2-(*p*-toluenesulfonylmethyl)heptyl (*p*-Toluenesulfinyl)acetate (13) A mixture of **12** (24 mg, 0.04 mmol) and 10% Pd–C (12 mg) in MeOH (1.5 ml) was stirred under hydrogen (1 atom) for 10 min. The mixture was filtered, and the filtrate was evaporated to give **13** (24 mg, quant.). $[\alpha]_D^{27}$ +47.9° (c=1.00, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.48—1.65 (m, 4H, $(CH_2)_2CH_2CO$), 2.11 (s, 3H, $COCH_3$), 2.40 (s, 3H, ArCH_3), 2.42 (s, 3H, ArCH_3), 2.38—2.47 (m, 2H, CH_2CO), 3.60 (d 1H, J=13.4 Hz, $CH_2S(O)$), 3.73 (d 1H, J=13.4 Hz, $CH_2S(O)$), 4.02 (d, 1H, J=10.4 Hz, TsOCH_2), 4.07 (d, 1H, J=10.4 Hz, TsOCH_2), 4.15 (d, 1H, J=12.2 Hz, CH_2OCO), 4.27 (d, 1H, J=12.2 Hz, CH_2OCO), 4.42 (s, 2H, OCH_2Ph), 7.22—7.35 (m, 9H, Ar-H), 7.53 (d, 2H, J=7.9 Hz, Ar-H), 7.78 (d, 2H, J=7.9 Hz, Ar-H). IR (KBr): 1743 1362, 1265, 1176 cm^{-1}. HR-FAB-MS m/z: 601.1918 (Calcd for $C_{31}H_{36}O_8S_2+H^+$: 601.1930).

(2*S*)-2-Benzyloxy-2-hydroxymethyl-6-oxoheptyl *p*-Toluenesulfonate (14) A mixture of **13** (53 mg, 0.09 mmol) and 1 N KOH (0.23 ml, 0.23 mmol) in iso-PrOH (2.8 ml) was stirred at room temperature for 10 min. After neutralization with 0.1 N HCl, the aqueous phase was extracted with CH_2Cl_2. The extract was washed with brine and dried. The solvent was evaporated and the residue was purified by preparative TLC ($CHCl_3$:MeOH=97:3) to give **14** (24.2 mg, 65%) as a colorless oil. $[\alpha]_D^{25}$ −6.73° (c=1.13, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.50—1.68 (m, 4H, $(CH_2)_2CH_2CO$), 2.06 (t, 1H, J=7.3 Hz, OH), 2.13 (s, 3H, $COCH_3$), 2.44 (s, 3H, ArCH_3), 2.40—2.51 (m, 2H, CH_2CO), 3.60 (dd, 1H, J=7.3, 12.0 Hz, HOCH_2), 3.67 (dd, 1H, J=7.3, 12.0 Hz, HOCH_2), 4.03 (d, 1H, J=10.4 Hz, TsOCH_2), 4.12 (d, 1H, J=10.4 Hz, TsOCH_2), 4.47 (s, 2H, OCH_2Ph), 7.34—7.36 (m, 7H, Ar-H), 7.78 (d, 2H, J=8.5 Hz, Ar-H). IR (KBr): 3552, 1712, 1360, 1176 cm^{-1}. HR-FAB-MS m/z: 421.1695 (Calcd for $C_{22}H_{28}O_6S+H^+$: 421.1685).

(1*S*,5*R*)-(5-Methyl-6,8-dioxabicyclo[3.2.1]octan-1-yl)methyl *p*-Toluenesulfonate (15) A solution of **14** (8.0 mg, 0.019 mmol) in MeOH (0.4 ml) was hydrogenated over 10% Pd–C (6 mg) at 1 atmosphere for 3 d. After filtration, the solvent was evaporated and the residue was chromatographed on silica gel with $CHCl_3$–MeOH (97:3) to give **15** (5.6 mg, 95%) as a colorless powder. mp 111—112 °C (from hexane). $[\alpha]_D^{27}$ −20.5° (c=0.43, $CHCl_3$). [lit.[14] mp 110 °C; $[\alpha]_D^{27}$ −20° (c=1,

$CHCl_3$)]. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.37 (s, 3H, CH_3), 1.48—1.73 (m, 5H), 1.80—1.87 (m, 1H, 3-H), 2.46 (s, 3H, $ArCH_3$), 3.52 (dd, 1H, J=6.7, 1.8 Hz, 7-H), 3.89 (d, 1H, J=6.7 Hz, 7-H), 4.03 (d, 1H, J=10.1 Hz, $TsOCH_2$), 4.06 (d, 1H, J=10.1 Hz, $TsOCH_2$), 7.35 (d, 2H, J=7.9 Hz, Ar-H), 7.79 (d, 2H, J=7.9 Hz, Ar-H). IR (KBr): 1599, 1362, 1176, 1030, 984 cm^{-1}. HR-FAB-MS m/z: 313.1116 (Calcd for $C_{15}H_{20}O_5S+H^+$: 313.1110).

References and Notes

1) Reviews on chemical asymmetric desymmetrization, see: Maier M., "Organic Synthesis Highlights II," ed. by Waldmann H., VCH, New York, 1995, pp. 203—222; Ward R. S., *Chem. Soc. Rev.*, **19**, 1—19 (1990).
Reviews on enzymatic asymmetric desymmetrization, Schoffers E., Golebiowski A., Johnson C. R., *Tetrahedron*, **52**, 3769—3826 (1996) and references cited therein. Theil F., *Chem. Rev.*, **95**, 2203—2227 (1995); Altenbach H.-J., "Organic Synthesis Highlights," ed. by Mulzer J., Altenbach H.-J., Braun M., Krohn K., Reissig H.-U., VCH, New York, 1991, pp. 224—231.

2) *a*) Maezaki N., Murakami M., Soejima M., Tanaka T., Imanishi T., Iwata C., *Chem. Pharm. Bull.*, **44**, 1146—1151 (1996); *b*) Iwata C., Maezaki N., Murakami M., Soejima M., Tanaka T., Imanishi T., *J. Chem. Soc., Chem. Commun.*, **1992**, 516—518. For related work, see: Maezaki N., Matsumori Y., Shogaki T., Soejima M., Tanaka T., Ohishi H., Iwata C., *Chem. Commun.*, **1997**, 1755—1756; Maezaki N., Sakamoto A., Soejima M., Sakamoto I., Li Y.-X., Tanaka T., Ohishi H., Sakaguchi K., Iwata C., *Tetrahedron: Asymmetry*, **7**, 2787—2790 (1996); Maezaki N., Soejima M., Takeda M., Sakamoto A., Matsumori Y., Tanaka T., Iwata C., *Tetrahedron*, **52**, 6527—6546 (1996) and references cited therein.

3) Itoh T., Ohara H., Takagi Y., Kanda N., Uneyama K., *Tetrahedron Lett.*, **34**, 4215—4218 (1993); Seu Y.-B., Kho Y.-H., *ibid.*, **33**, 7015—7016 (1992); Prasad K., Estermann H., Chen C.-P., Repic O., Hardtmann G. E., *Tetrahedron: Asymmetry*, **1**, 421—424 (1990).

4) Mori K., *Tetrahedron*, **31**, 1381—1384 (1975).

5) Dung J.-S., Armstrong R. W., Anderson O. P., Williams R. M., *J. Org. Chem.*, **48**, 3592—3594 (1983).

6) Olson G. L., Cheung H.-C., Morgan K., Saucy G., *J. Org. Chem.*, **45**, 803—805 (1980).

7) Isolation, see: Kinzer G. W., Fentiman A. F., Jr., Page T. F., Jr., Foltz R. L., Vite J. P., Pitman G. B., *Nature (London)*, **221**, 477—478 (1969). Enantioselective synthesis, see: Chen S.-T., Fang J.-M., *J. Org. Chem.*, **62**, 4349—4357 (1997); Takemoto Y., Takeuchi J., Morio K., Nakamoto T., Iwata C., *Chem. Pharm. Bull.*, **44**, 940—947 (1996) and references cited therein.

8) Uesato S., Kobayashi K., Inouye H., *Chem. Pharm. Bull.*, **30**, 927—940 (1982).

9) Pappo R., Allen D. S., Jr., Lemieux, R. U., Johnson W. S., *J. Org. Chem.*, **21**, 478—479 (1956).

10) The ozonolysis also gave the aldehyde, but the yield was poor (40%).

11) Solladié G., Hutt J., Girardin A., *Synthesis*, **1987**, 173.

12) Dess D. B., Martin J. C., *J. Am. Chem. Soc.*, **113**, 7277—7287 (1991); Ireland R. E., Liu L., *J. Org. Chem.*, **58**, 2899 (1993).

13) The optical purity of **8** was determined as >98% e.e. by ^{1}H-NMR spectroscopic examination using $Eu(tfc)_3$ as a chiral shift reagent.

14) Trinh M.-C., Florent J.-C., Monneret C., *Tetrahedron*, **44**, 6633—6644 (1988); *idem*, *J. Chem. Soc., Chem. Commun.*, **1987**, 615—616.