Synthesis of Metabolites of S-1452, an Orally Active Thromboxane A_2 Receptor Antagonist

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The synthesis of 16 metabolites of S-1452, an orally active thromboxane A_2 (TXA_2) receptor antagonist, is described. Regioselective hydroxylation at C-5 or C-6 of the bicyclo[2.2.1]heptane skeleton of the optically active intermediate 16 was attempted by using 9-borabicyclo[3.3.1]nonane followed by H_2O_2 or *m*-chloroperbenzoic acid (*m*-CPBA) and then $LiAlH_4$, to obtain the hydroxylated product 17a or 17b, respectively. Modification of the C-2 substituent of 17a and 17b afforded eight metabolites of S-1452. Eight non-hydroxylated metabolites were synthesized by using a similar reaction sequence.

Keywords thromboxane; TXA_2 receptor antagonist; S-1452 metabolite; enantioselective synthesis; regioselective hydroxylation

Thromboxane A_2 (TXA_2), which has potent platelet aggregation, vasoconstriction, and bronchoconstriction activities, is one of the major mediators causing problems in circulatory disorders and asthmatic conditions.[1] S-1452, calcium (1*R*,2*S*,3*S*,4*S*)-(5′*Z*)-7-(phenylsulfonylaminobicyclo[2.2.1]hept-2-yl)hept-5′-enoate, has been established as a chemically stable and orally active TXA_2 receptor antagonist.[2] The metabolism of S-145, the racemic acid form of S-1452,[3] in isolated rat hepatocytes was preliminarily examined by using high-performance liquid chromatography (HPLC) and gas chromatography/mass spectrometry (GC/MS).[4] Extensive studies have been done on the metabolism of S-1452 in rats in these laboratories, and 16 metabolites were isolated[5] (Fig. 1). The structures of these metabolites were first proposed on the basis of HPLC, proton nuclear magnetic resonance (^{1}H-NMR) and GC/MS findings, and then confirmed by direct comparison with authentic synthetic samples. Described herein is the enantio- and regioselective synthesis of these compounds.

Results and Discussion

The possibility that a hydroxy group is introduced at the C-5 or C-6 position of the bicyclo[2.2.1]heptane skeleton in living tissues was suggested on the basis of GC/MS spectroscopy[6] of eight metabolites. This led us to try regioselective hydroxylation of a common synthetic intermediate **16**, which could be converted to metabolites of S-1452, by employing two different types of reactions. Although the stereochemistry of the hydroxy group of the metabolites, *i.e.*, *exo* or *endo*, could not be ascertained from the physicochemical data, the production of *exo* hydroxy metabolites was presumed from the steric preference in bicyclo[2.2.1]heptane chemistry. Moreover, as the conversion from "*exo*" to "*endo*" was well established by the oxidation–reduction procedure, the synthesis of C-5 or C-6 *exo* hydroxy compounds could be designed as required.

For the present purpose, (1*S*,2*S*,3*S*,4*R*)-3-carboxy-2-methoxycarbonylbicyclo[2.2.1]hept-5-ene (**13**) was considered to be a very suitable starting material. It was prepared by the highly enantioselective synthesis of half-esters of bicyclo[2.2.1]heptane-2,3-dicarboxylic acid from bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride in 50% overall yield (99.8% ee).[7] Transformation of **13** into the sulfonamide **15** was carried out by the reported procedure[3,8] in 59% yield. Reduction of **15** with lithium aluminum hydride ($LiAlH_4$) followed by protection of the resulting alcohol using dihydropyran gave the tetrahydropyranyl (THP) ether **16** in 74% yield. As described above, **16** was a key intermediate for the introduction of a hydroxy group in the bicyclo[2.2.1]heptane skeleton, and

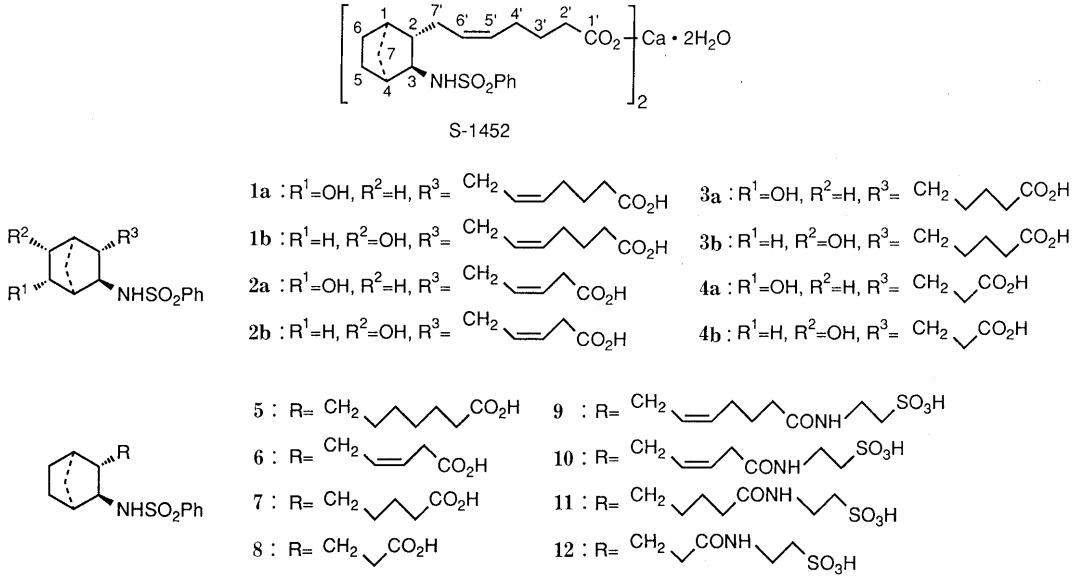


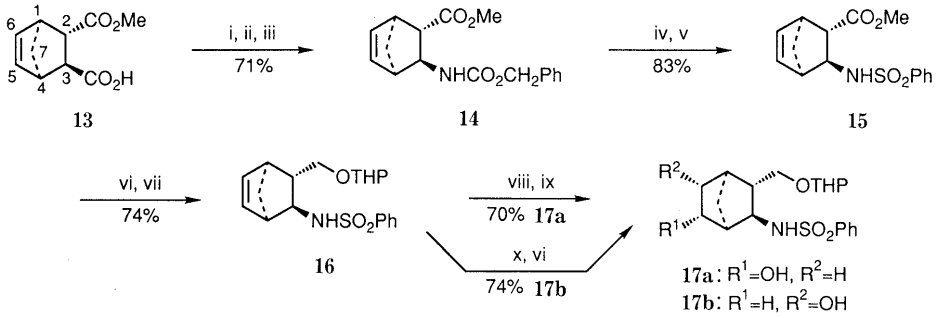
Fig. 1. Metabolites of S-1452 in Rat

regioselective hydroxylation at C-5 or C-6 was attempted.

Treatment of **16** with 9-borabicyclo[3.3.1]nonane (9-BBN) in tetrahydrofuran (THF) at 20 °C followed by oxidation with aqueous NaOH–H_2O_2 at 60 °C afforded a mixture of the hydroxy products in 85% yield in a ratio of 82 : 18 (determined by HPLC analysis). Chromatographic separation gave the major product **17a** as crystals and the minor one **17b** as an oil. Each compound, **17a** or **17b**, was a mixture of diastereomers concerning the THP protecting group and showed two peaks in HPLC identical with those of the major component or the minor one of the crude product, respectively. Epoxidation of **16** with *m*-chloroperbenzoic acid (*m*-CPBA) in CH_2Cl_2 at 0 °C gave the *exo* epoxide exclusively, and subsequent reduction with $LiAlH_4$ produced a mixture of **17a** and **17b** (2 : 98) in 86% yield (Chart 1). The major product, in this case, was identical with **17b** formed as the minor product in the 9-BBN procedure.

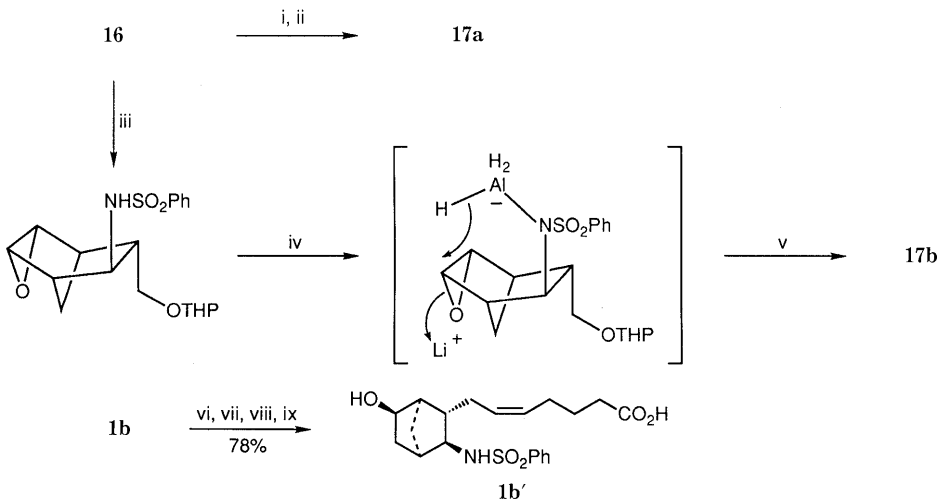
The position and stereochemistry of hydroxy groups of these compounds were determined by ^{1}H-NMR spectroscopy using the decoupling method because the values of the chemical shift (ppm) and the proton-proton coupling constant had already been well studied for bicyclo[2.2.1]-heptane derivatives.[9] ^{1}H-NMR spectroscopy of the hydroxymethyl derivatives **18a** and **18b** derived from **17a** and **17b**, respectively, as described in the next step, revealed a coupling constant corresponding to *endo-endo* coupling (J = 6—7 Hz) between the C-5 and C-6 proton at δ 4.13 (J = 6.2 Hz, 5-H) and δ 3.71 (J = 6.5 Hz, 6-H), respectively. Thus, the *exo* configuration of these compounds was determined and the structure of the major product in the 9-BBN procedure was found to be **17a**, and that of the minor one to be **17b**. Epoxidation of **16** also occurred from the less-hindered *exo* side, while $LiAlH_4$ reduction of the *exo* epoxide occurred from the *endo* side by intramolecular hydride transfer *via* formation of a complex between $LiAlH_4$ and the nitrogen atom[10] of the C-3 sulfonamide as depicted in Chart 2, giving the 6-hydroxy isomer **17b** with high regioselectivity.

To obtain chemical evidence of the *exo* configuration of the C-6 hydroxy compounds, **1b**, derived from **17b** as described later, was converted to the *endo* isomer **1b′** by a four-step procedure (esterification, pyridinium chlorochromate (PCC) oxidation, $NaBH_4$ reduction and hydrolysis) in 78% yield. The stereochemistry of **1b′** could easily be predicted from the course of the hydride reduction of the C-6 keto derivative prepared by PCC oxidation of **1b**. Clearly, the hydride reduction occurs from the *exo* face and gives the *endo* alcohol **1b′**. ^{1}H-NMR spectroscopy of **1b′** also supported the stereochemistry, based on a comparison of the coupling constant[9] of the C-6 proton ($J_{C5exo\text{-}C6exo}$ 10.4 Hz) with that of the C-6 *exo* hydroxy



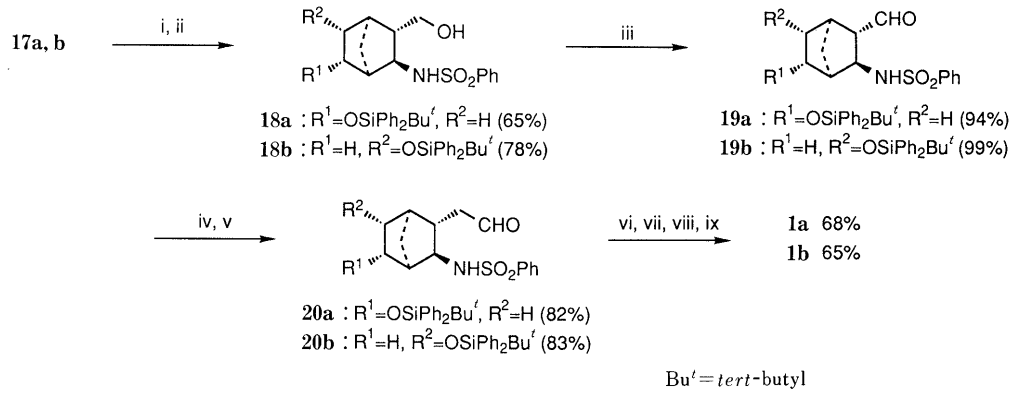
i, $ClCO_2Et$, Et_3N, NaN_3; ii, benzene, 80°C; iii, $PhCH_2OH$, Et_3N, benzene, 80°C; iv, TFA, anisole; v, $PhSO_2Cl$, Et_3N; vi, $LiAlH_4$; vii, dihydropyran, *p*-Ts-OH; viii, 9-BBN; ix, H_2O_2-NaOH; x, *m*-CPBA

Chart 1



i, 9-BBN; ii, H_2O_2-NaOH; iii, *m*-CPBA; iv, $LiAlH_4$; v, H^+; vi, CH_2N_2; vii, PCC; viii, $NaBH_4$; ix, 1 N NaOH

Chart 2. Presumed Transition State of Regioselective Hydroxylation



i, Bu^tPh_2SiCl, DMAP; ii, AcOH-H_2O-THF; iii, PCC; iv, Ph_3P=CHOMe; v, 90%HCO_2H; vi, Ph_3P=$CH(CH_2)_3CO_2K$; vii, CH_2N_2; viii, n-Bu_4NF; ix, 1 N NaOH

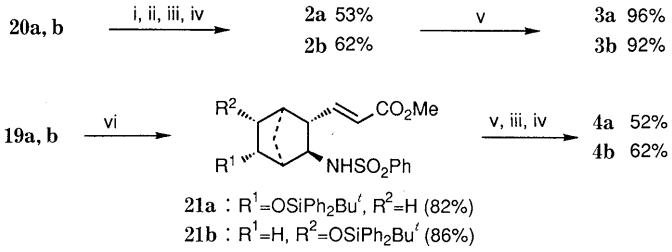
Chart 3

isomer **1b** ($J_{C5endo\text{-}C6endo}$ 6.2 Hz).

For the differentiation of the secondary alcohol of **17a** or **17b** from the C-1 primary alcohol, *tert*-butyldiphenylsilyl ether was used as a protecting group. It was stable to mild acid hydrolysis, which gave rise to effective deprotection of the C-1 THP ether. Treatment of **17a** with *tert*-butyldiphenylsilyl chloride and dimethylaminopyridine in dimethylformamide (DMF) and deprotection of the primary alcohol with aqueous AcOH at 50 °C gave the hydroxymethyl derivative **18a**, which, when oxidized with PCC, afforded the secondary aldehyde **19a** in 61% yield from **17a**.

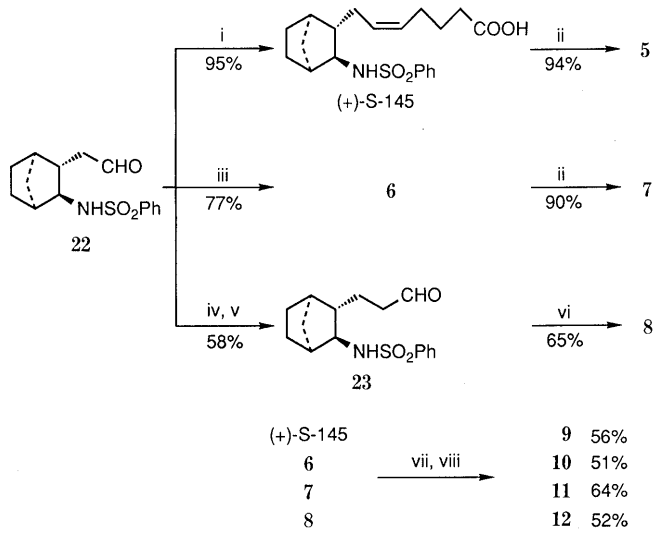
Methylene homologation of the aldehyde **19a** was accomplished by the Wittig reaction using methoxymethylenetriphenylphosphorane followed by acid treatment, to obtain the primary aldehyde **20a** in 82% yield. Compound **20a** was converted to the 5-hexenoic acid **1a** as follows. The Wittig reaction using (4-carboxybutyl)-triphenylphosphorane and the usual esterification with diazomethane afforded the methyl 5-hexenoate derivative. Deprotection of the silyl ether at C-5 with n-Bu_4NF followed by hydrolysis with 1 N KOH gave the objective compound **1a** in 68% yield from **20a**. The 6-hydroxy isomer **1b** was also derived from **17b** in the same manner as **1a** in 45% overall yield.

3-Pentenoic acid derivatives **2a** and **2b** were obtained from **20a** and **20b** in a similar manner to those of **1a** and **1b**, except that the Wittig reaction was performed using 2-carboxyethyltriphenylphosphorane, in 53 and 62% yields, respectively. In these cases, the 3-pentenoic acid derivatives were unstable under the Wittig reaction conditions, and double bond migration occurred, causing a decrease in the yield.[11] Catalytic hydrogenation of **2a** and **2b** using 10% Pd–C in methanol gave the saturated pentanoic acids **3a** and **3b** in 96 and 92% yields, respectively. The propionic acid derivatives **4a** and **4b** were obtained by four-step conversion as depicted in Chart 4. Transformation of **19a** into the α,β-unsaturated ester **21a** by application of the Wittig–Horner reaction using methyl diethylphosphonoacetate followed by catalytic reduction gave the saturated ester. Deprotection of the silyl ether and subsequent hydrolysis afforded **4a** in 43% overall yield. The 6-hydroxy isomer **4b** was also derived from **19b** by the same procedure.



i, Ph_3P=$CHCH_2CO_2K$; ii, CH_2N_2; iii, n-Bu_4NF; iv, 1 N NaOH; v, H_2, Pd/C; vi, $(MeO)_2P(O)CH_2CO_2Me$, NaH

Chart 4



i, Ph_3P=$CH(CH_2)_3CO_2K$; ii, H_2, Pd/C; iii, Ph_3P=$CHCH_2CO_2K$; iv, Ph_3P=CHOMe; v, 90%HCO_2H; vi, Jones oxidation; vii, DCC, HOSu; viii, $H_2N(CH_2)_2SO_3H$, Et_3N

Chart 5

Among the four non-hydroxylated metabolites (**5**—**7** and **8**), **5** could be prepared easily by catalytic reduction of (+)-S-145 and the other three compounds were synthesized from a common intermediate, (1*R*,2*S*,3*S*,4*S*)-(3-phenylsulfonylaminobicyclo[2.2.1]hept-2-yl)acetaldehyde (**22**),[2] which was derived from the saturated analog of **13**.

Two kinds of Wittig reaction of **22** afforded the β,γ-

unsaturated carboxylic acid **6** and the methoxymethylene derivative. Hydrogenation of **6** gave **7** in 69% yield from **22**. Acid treatment of the methoxymethylene derivative gave the propionyl aldehyde **23**, and subsequent Jones oxidation afforded the propionic acid derivative **8** in 38% yield from **22**. Taurine derivatives of non-hydroxylated compounds, **9**—**11** and **12** were prepared by the coupling reaction of (+)-S-145, **6**, **7** and **8** with taurine, respectively, using the active ester method (DCC–HOSu; dicyclohexylcarbodiimide–*N*-hydroxysuccinimide).

Sixteen metabolites of S-1452 were identified by comparison with authentic synthetic samples based on HPLC, MS and ^{1}H-NMR findings, and the structures of the metabolites were definitely established.

All the synthesized compounds were tested for their biological activities as TXA_2 receptor antagonists. Among them, the C-5 hydroxy derivative **1a** and the C-6 hydroxy derivative **1b** inhibited platelet aggregation in guinea pigs induced by U-46619,[12] exhibiting higher IC_{50} values (**1a**, 1.80 μM; **1b**, 0.68 μM) than that of S-1452 (0.07 μM).[13] These values correspond to 1/25 and 1/10 of the TXA_2 antagonistic activity of S-1452, respectively. Details of the biological activity will be reported elsewhere.[14]

Experimental

Reactions using anhydrous solvents that had been dried over type 4A molecular sieves were carried out in a nitrogen atmosphere. Melting points were determined on a Yanagimoto apparatus and were not corrected. Infrared (IR) spectra were recorded on a JASCO A702 spectrometer. The value of $[\alpha]_D$ was determined with a Perkin–Elmer 241 polarimeter. Unless otherwise stated, ^{1}H-NMR spectra were obtained in $CDCl_3$ with a Varian VXR-200 spectrometer using tetramethylsilane as an internal reference. HPLC analysis was carried out on a Shimadzu LC-6A chromatograph equipped with a C-6A integrator and an SPD-6A variable-wavelength ultraviolet monitor. Mass spectrometry (MS) was conducted on a Hitachi M-68 spectrometer. To dry organic solutions, anhydrous magnesium sulfate was used. For column chromatography, silica gel (Merck Silica gel 60) or a Merck Lobar column was used.

The hydroxylated products, **1a**, **1b**, **2a**, **2b**, **4a** and **4b**, were highly purified by preparative HPLC using Develosil (Nomura Chemical, Japan) ODS-15/30; column size, 50/500 (mm); mobile phase, CH_3CN–MeOH–H_2O–AcOH (200 : 200 : 450 : 1); flow rate, 80 ml/min; detection, 225 nm.

(1*S*,2*S*,3*S*,4*R*)-3-Carbobenzoxyamino-2-carbomethoxybicyclo[2.2.1]-hept-5-ene (14) Triethylamine (7.74 ml, 42.7 mmol × 1.3) and $ClCO_2Et$ (4.08 ml, 42.7 mmol) were added to a solution of **13** (7.70 g, 42.7 mmol) in acetone (120 ml) at 0 °C, and the mixture was stirred for 30 min. Next, a solution of NaN_3 (8.33 g, 42.7 mmol × 3) in H_2O (46 ml) was added and the mixture was stirred for 1 h, then poured into cold H_2O and extracted with ethyl acetate. The extract was washed with 5% aqueous $NaHCO_3$, dried, and concentrated *in vacuo* to obtain an oily residue, which was dissolved in benzene (90 ml) and heated to reflux for 1 h. After the gas evolution ceased, benzyl alcohol (8.70 ml, 42.7 mmol × 2) and triethylamine (7.7 ml, 42.7 mmol × 1.3) were added, and the mixture was stirred for 1 h under reflux and then poured into cold 2 N HCl. The organic solution was washed with aqueous 5% $NaHCO_3$ and H_2O, dried, and concentrated *in vacuo*. Chromatography on silica gel with toluene–ethyl acetate (10 : 1) as the eluent gave the carbobenzoxy derivative **14** (9.0 g, 71%), mp 81—82 °C. *Anal.* Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.78; H, 6.42; N, 4.62. $[\alpha]_D^{24}$ +138.3 ± 0.9° (c = 2.013, $CHCl_3$). IR ($CHCl_3$): 3442 (NH), 1730 (CO) cm^{-1}. ^{1}H-NMR δ: 1.52 (1H, ABq, A part, J = 8.0 Hz, 7-H), 1.83 (1H, ABq, B part, J = 8.0 Hz, 7-H), 1.93 (1H, dd, J = 1.4, 3.6 Hz, 2-H), 3.02 (2H, brs, 1-H, 4-H), 3.74 (3H, s, Me), 4.55 (2H, brs, 3-H, NH), 5.10 (2H, s, CH_2), 6.17 (1H, dABq, A part, J = 3.0, 5.4 Hz, olefinic H), 6.43 (1H, dABq, B part, J = 2.6, 5.4 Hz, olefinic H), 7.35 (5H, s, aromatic H).

(1*S*,2*S*,3*S*,4*R*)-2-Carbomethoxy-3-phenylsulfonylaminobicyclo[2.2.1]-hept-5-ene (15) A solution of **14** (8.0 g, 26.5 mmol) in a mixture of anisole (25 ml) and trifluoroacetic acid (100 ml) was stirred for 6 h at 45 °C, then concentrated *in vacuo*, and the residue was rinsed with *n*-hexane. To a solution of the residue in CH_2Cl_2 (50 ml), triethylamine (14.8 ml, 26.5 mmol × 4) and phenylsulfonyl chloride (4 ml, 26.5 mmol × 1.2) were added at 0 °C, and the mixture was stirred for 30 min at the same temperature. The reaction mixture was washed with 2 N HCl, aqueous 5% $NaHCO_3$ and H_2O, and then dried and concentrated *in vacuo*. Chromatography on silica gel with *n*-hexane–ethyl acetate (2 : 1) as the eluent gave the sulfonamide **15** (6.75 g, 83%), mp 128—129 °C. *Anal.* Calcd for $C_{15}H_{17}NO_4S$: C, 58.61; H, 5.58; N, 4.56; S, 10.43. Found: C, 58.60; H, 5.57; N, 4.52; S, 10.23. $[\alpha]_D^{25}$ +100.9 ± 0.5° (c = 3.005, $CHCl_3$), IR ($CHCl_3$): 3275 (NH), 1730 (CO) cm^{-1}. ^{1}H-NMR δ: 1.38—1.47 (1H, m, 7-H), 1.59—1.68 (1H, m, 7-H), 1.87 (1H, dd, J = 3.0, 2.8 Hz, 2-H), 2.88 (1H, s, 4-H), 2.91 (1H, s, 1-H), 3.58 (3H, s, Me), 4.23 (1H, ddd, J = 9.6, 3.7, 3.6 Hz, 3-H), 4.35 (1H, d, J = 9.6 Hz, NH), 6.10 (1H, dd, J = 2.6, 5.6 Hz, olefinic H), 6.41 (1H, dd, J = 2.6, 5.6 Hz, olefinic H), 7.46—7.65 (3H, m, aromatic H), 7.84—7.92 (2H, m, aromatic H).

(1*S*,2*S*,3*S*,4*R*)-3-Phenylsulfonylamino-(2-tetrahydropyranyloxymethyl)-bicyclo[2.2.1]hept-5-ene (16) A solution of **15** (6.54 g, 21.3 mmol) in a mixture of THF (30 ml) and ether (90 ml) was added to a suspension of $LiAlH_4$ (3.88 g, 21.3 mmol × 4.8) in ether (120 ml) over 40 min at 0 °C, and the reaction mixture was stirred for 30 min at the same temperature. Next, 2 N HCl was added carefully, and the mixture was partitioned between ethyl acetate and H_2O. The organic solution was washed with aqueous 5% $NaHCO_3$ and H_2O, and then dried and concentrated *in vacuo*. Dihydropyran (3.35 ml) and *p*-toluenesulfonic acid hydrate (100 mg) were added to a solution of the residue in CH_2Cl_2 (50 ml), and the mixture was stirred for 1.5 h at room temperature, then washed with aqueous 5% $NaHCO_3$ and H_2O, dried, and concentrated *in vacuo*. Chromatography of the residue on silica gel with *n*-hexane–ethyl acetate (4 : 1) as the eluent yielded the THP ether **16** (5.73 g, 74%), which was dissolved in benzene, and the solution was concentrated *in vacuo*. By repeating the procedures, contaminating solvents, except benzene, were removed, giving a colorless oil. *Anal.* Calcd for $C_{19}H_{25}NO_4S \cdot 0.3C_6H_6$: C, 64.57; H, 6.98; N, 3.62; S, 8.29. Found: C, 64.59; H, 6.99; N, 3.69; S, 8.03. $[\alpha]_D^{24}$ +61.8 ± 1.0° (c = 1.003, $CHCl_3$). IR ($CHCl_3$): 3380 (NH), 1345 (SO_2), 1158 (SO_2) cm^{-1}. ^{1}H-NMR δ: 1.30—1.88 (9H, m, 2-H, 7-H, methylene H of THP), 2.62—2.84 (2H, m, 1-H, 4-H), 3.13—3.87 (5H, m, 3-H, methylene H of THP), 4.30—4.60 (2H, m, NH, O–CH(C)–O), 5.90—6.00 (1H, m, olefinic H), 6.35—6.45 (1H, m, olefinic H), 7.37 (s, contaminated benzene), 7.46—7.65 (3H, m, aromatic H), 7.84—7.95 (2H, m, aromatic H). MS m/z: 364 $(M+H)^+$ (PILSIMS).

(1*S*,2*S*,3*S*,4*S*,5*R*)-5-Hydroxy-3-phenylsulfonylamino-(2-tetrahydropyranyloxymethyl)bicyclo[2.2.1]heptane (17a) A solution of 9-BBN (0.5 N, 50.6 ml, 25.3 mmol) was added to a solution of **16** (4.6 g, 12.7 mmol) in THF (23 ml) at room temperature, and the mixture was stirred for 1.5 h. To this solution, 6 N NaOH (6.3 ml, 38.0 mmol) and 30% H_2O_2 (5.0 ml, 44.3 mmol) were added, and the mixture was stirred for 1 h at 60 °C. The reaction mixture was poured into cold H_2O and extracted with ethyl acetate. The extract was washed with 2 N HCl and aqueous 5% $NaHCO_3$, dried, and evaporated to dryness to give 4.83 g of the crude product (**17a** : **17b** = 82 : 18). The ratio of the regioisomer was determined by HPLC analysis using Nucleosil 100-5: Mobile phase, *n*-hexane–THF (4 : 1); flow rate, 7 ml/min; detection, 225 nm. Chromatography on silica gel with *n*-hexane–ethyl acetate (2 : 1) as the eluent gave **17a** (3.4 g, 70%), mp 155—160 °C. *Anal.* Calcd for $C_{19}H_{27}NO_5S$: C, 59.82; H, 7.13; N, 3.67; S, 8.41. Found: C, 59.56; H, 7.00; N, 3.69; S, 8.45. ^{1}H-NMR δ: 1.17—1.90 (12H, m, 2-H, 6-H, 7-H, methylene H of THP, OH), 1.94—2.10 (1H, m, 4-H), 2.35—2.49 (1H, m, 1-H), 2.83—3.19 (2H, m, methylene H of THP), 3.29—3.62 (2.5H, m, 3-H, methylene H of THP), 3.79—3.95 (0.5H, m, 3-H), 4.27—4.48 (2H, m, 5-H, O–CH(C)–O), 4.87 (0.5H, d, J = 5 Hz, NH), 5.40 (0.5H, d, J = 3 Hz, NH), 7.47—7.67 (3H, m, aromatic H), 7.85—7.97 (2H, m, aromatic H). Polar fractions gave **17b** (0.65 g, 14%) as an oil, which was identical with the major product described in the next reaction.

(1*R*,2*S*,3*S*,4*R*,6*S*)-6-Hydroxy-3-phenylsulfonylamino-(2-tetrahydropyranyloxymethyl)bicyclo[2.2.1]heptane (17b) A solution of **16** (3.75 g, 10.3 mmol) in CH_2Cl_2 (80 ml) was treated with *m*-CPBA (80% purity, 3.33 g, 15.5 mmol) at 0 °C, and the mixture was stirred for 2.5 h at room temperature. The resulting crystals were removed by filtration and the filtrate was washed with aqueous 5% $Na_2S_2O_3$ solution, 5% $NaHCO_3$, and H_2O, and then dried and concentrated *in vacuo*. Chromatography on silica gel with *n*-hexane–ethyl acetate (1 : 1) as the eluent gave 3.55 g of the *exo* epoxide, which was dissolved in ether (20 ml) and reduced with $LiAlH_4$ (1.4 g) suspended in a mixture of ether (40 ml) and THF (20 ml) at room temperature. After the reaction mixture had been stirred for 30 min, H_2O was added carefully, and the mixture was partitioned

between ethyl acetate and 2 N HCl. The organic solution was washed with H_2O and aqueous 5% $NaHCO_3$, dried, and concentrated to dryness. Chromatography on silica gel with *n*-hexane–ethyl acetate (1 : 1) as the eluent gave **17b** (3.0 g, 74%), colorless oil. *Anal.* Calcd for $C_{19}H_{27}NO_5S \cdot 0.3H_2O$ (hygroscopic): C, 58.99; H, 7.19; N, 3.62; S, 8.29. Found: C, 58.84; H, 6.96; N, 3.68; S, 8.00. ^{1}H-NMR δ: 1.02—2.46 (14H, m, 1-H, 2-H, 4-H, 5-H, 7-H, methylene H of THP, OH), 2.82—3.20 (2H, m, methylene H of THP), 3.34—3.69 (2.5H, 3-H, methylene H of THP), 3.75—3.93 (1.5H, m, 3-H, 6-H), 4.33—4.46 (1H, m, O–CH(C)–O), 4.83 (0.5H, d, J=5 Hz, NH), 5.25 (0.5H, d, J=4.8 Hz, NH), 7.25—7.66 (3H, m, aromatic H), 7.84—7.95 (2H, m, aromatic H). MS m/z: 382 $(M+H)^+$ (PILSIMS).

(1*R*,2*S*,3*S*,4*R*,6*R*)-(5′*Z*)-7-(6-Hydroxy-3-phenylsulfonylaminobicyclo-[2.2.1]hept-2-yl)hept-5′-enoic Acid (1b′) Compound **1b** was esterified with diazomethane and the methyl ester was oxidized with PCC, in the same manner as **19a**, reduced with $NaBH_4$ in the usual way, and hydrolyzed with 1 N NaOH, giving **1b′** (78%), a colorless gum. *Anal.* Calcd for $C_{20}H_{27}NO_5S$: C, 61.65; H, 6.93; N, 3.49. Found: C, 61.90; H, 7.05, N, 3.35. IR ($CHCl_3$): 3600—2400 (COOH), 3270 (NH), 1710 (COOH), 1322 (SO_2), 1157 (SO_2) cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 1.23—2.17 (13H, m, 1-H, 2-H, 4-H, 5-H, 7-H, 3′-H, 4′-H, 7′-H), 2.23 (2H, t, J=5.5 Hz, 2′-H), 2.96—3.08 (1H, m, 3-H), 4.13 (1H, td, J=4.2, 10.4 Hz, 6-H), 5.10—5.29 (2H, m, olefinic H), 7.49—7.69 (3H, m, aromatic H), 7.80—7.94 (2H, m, aromatic H).

(1*S*,2*S*,3*R*,4*S*,5*R*)-5-*tert*-Butyldiphenylsilyloxy-2-hydroxymethyl-3-phenylsulfonylaminobicyclo[2.2.1]heptane (18a) and (1*R*,2*S*,3*S*,4*R*,6*S*)-6-*tert*-Butyldiphenylsilyloxy-2-hydroxymethyl-3-phenylsulfonylaminobicyclo-[2.2.1]heptane (18b) Dimethylaminopyridine (865 mg, 3.5 mmol × 2) and *tert*-butyldiphenylchlorosilane (1.4 ml, 3.5 mmol × 1.5) were added to a solution of **17a** (1.35 g, 3.5 mmol) in DMF (17 ml), and the mixture was stirred overnight at 50 °C, then poured into cold water and extracted with ethyl acetate. The extract was washed with aqueous 5% $NaHCO_3$ and H_2O, dried, and evaporated to dryness. Chromatography of the residue on silica gel with *n*-hexane–ethyl acetate (9 : 1)—(4 : 1) as the eluent gave 2.15 g of silylated product, which was dissolved in a mixture of THF (5 ml), acetic acid (15 ml), and H_2O (5 ml). The mixture was warmed overnight at 50 °C, then poured into H_2O and extracted with CH_2Cl_2. The extract was washed with aqueous 5% $NaHCO_3$ and H_2O, dried, and evaporated to dryness. Chromatography on silica gel with *n*-hexane–ethyl acetate (2 : 1) as the eluent gave the primary alcohol **18a** (1.18 g, 65%), mp 131—133 °C. *Anal.* Calcd for $C_{30}H_{37}NO_4SSi$: C, 67.25; H, 6.96; N, 2.61. Found: C, 67.22; H, 6.98; N, 2.75. $[\alpha]_D^{24}$ −6.9±0.5° (c=1.011, $CHCl_3$). IR ($CHCl_3$): 3510 (OH), 1324 (SO_2), 1162 (SO_2) cm^{-1}. ^{1}H-NMR δ: 1.04 (9H, s, *tert*-Bu), 1.15—1.30 (2H, m, 2-H, 7-H), 1.54—1.80 (6H, m, 6-H, 7-H, OH), 1.98—2.10 (2H, m, 1-H, 4-H), 2.80 (1H, q, J=8.0 Hz, 3-H), 3.29 (1H, dABq, A part, J=7.6, 11.0 Hz, CH_2O), 3.35 (1H, dABq, B part, J=7.6, 11.0 Hz, CH_2O), 4.03 (1H, d, J=5.2 Hz, NH), 4.08—4.18 (1H, m, 5-H), 7.34—7.77 (15H, m, aromatic H). ^{1}H-NMR (400 MHz; $CDCl_3$) δ: 4.13 (1H, d, J=6.2 Hz, 5-H).

18b: 78% yield; colorless oil. *Anal.* Calcd for $C_{30}H_{37}NO_4SSi$: C, 67.25; H, 6.96; N, 2.61. Found: C, 67.39; H, 7.11; N, 2.71. $[\alpha]_D^{24}$ +21.7±0.6° (c=1.014, $CHCl_3$). IR ($CHCl_3$): 3620 (OH), 3380 (NH), 1322 (SO_2), 1160 (SO_2) cm^{-1}. ^{1}H-NMR δ: 0.71—1.96 (7H, m, 1-H, 2-H, 5-H, 7-H, OH), 1.03 (9H, s, *tert*-Bu), 2.16 (1H, br s, 4-H), 2.90—3.02 (1H, m, 3-H), 3.22 (1H, dABq, A part, J=4.0, 10.0 Hz, CH_2O), 3.29 (1H, dABq, B part, J=4.0, 10.0 Hz, CH_2O), 3.71 (1H, d, J=6.5 Hz, 6-H), 4.62 (1H, d, J=6.0 Hz, NH), 7.30—7.70 (13H, m, aromatic H), 7.78—7.90 (2H, m, aromatic H).

(1*S*,2*S*,3*S*,4*S*,5*R*)-5-*tert*-Butyldiphenylsilyloxy-2-formyl-3-phenylsulfonylaminobicyclo[2.2.1]heptane (19a) and (1*R*,2*S*,3*S*,4*R*,6*S*)-6-*tert*-Butyldiphenylsilyloxy-2-formyl-3-phenylsulfonylaminobicyclo[2.2.1]heptane (19b) PCC (724 mg, 1.1 mmol × 3) and molecular sieves (type 4A, powder, 1.0 g) were added to a solution of **18a** (600 mg, 1.1 mmol) in CH_2Cl_2 (45 ml), and the mixture was stirred for 1 h at room temperature. The reaction mixture was passed through silica gel with CH_2Cl_2 and then *n*-hexane–ethyl acetate (4 : 1) as the eluents, and the secondary aldehyde **19a** (564 mg, 94%), a colorless oil was obtained. ^{1}H-NMR δ: 1.05 (9H, s, *tert*-Bu), 1.10 (1H, m, 2-H), 1.60—2.00 (4H, m, 6-H, 7-H), 2.27 (1H, br s, 4-H), 2.41—2.49 (1H, m, 2-H), 3.35—3.46 (2H, m, 3-H, NH), 4.00—4.11 (1H, m, 5-H), 7.37—7.73 (15H, m, aromatic H), 9.20 (1H, s, CHO).

19b: 99% yield, colorless oil. ^{1}H-NMR δ: 1.04 (9H, s, *tert*-Bu), 1.07—2.37 (7H, m, 1-H, 2-H, 4-H, 5-H, 7-H), 3.65—3.74 (1H, m, 3-H), 3.80—3.90 (1H, m, 6-H), 4.42 (1H, d, J=5.4 Hz, NH), 7.34—7.86 (15H, m, aromatic H), 9.20 (1H, s, CHO). These aldehydes **19a** and **19b** were found to be unstable and were used for the next reaction without further purification.

(1*S*,2*S*,3*R*,4*S*,5*R*)-5-*tert*-Butyldiphenylsilyloxy-2-formylmethyl-3-phenylsulfonylaminobicyclo[2.2.1]heptane (20a) and (1*R*,2*S*,3*S*,4*R*,6*S*)-6-*tert*-Butyldiphenylsilyloxy-2-formylmethyl-3-phenylsulfonylaminobicyclo[2.2.1]-heptane (20b) A suspension of methoxymethyltriphenylphosphonium chloride (19.27 g, 18.7 mmol × 3) in THF (190 ml) was treated with *tert*-BuOK (6.0 g, 18.7 mmol × 2.9) at 0 °C, and the mixture was stirred for 1 h at the same temperature. Then a solution of **19a** (10.0 g, 18.7 mmol) in THF (60 ml) was added. The reaction mixture was stirred for 20 min at 0 °C and poured into a mixture of toluene and H_2O. The organic solution was washed with H_2O, dried, and concentrated *in vacuo*. The residue was dissolved in a mixture of 90% formic acid (20 ml) and THF (2 ml), and the mixture was stirred for 1.5 h at room temperature, then poured into a mixture of aqueous 5% $NaHCO_3$ and CH_2Cl_2. The organic solution was washed with H_2O, dried, and concentrated *in vacuo*. Chromatography of the residue on silica gel with *n*-hexane–ethyl acetate (2 : 1) as the eluent gave the primary aldehyde **20a** (8.43 g, 82%), mp 137—139 °C. *Anal.* Calcd for $C_{31}H_{37}NO_4SSi$: C, 67.97; H, 6.81; N, 2.56. Found: C, 68.07; H, 6.77; N, 2.65. $[\alpha]_D^{24}$ +7.9±0.5° (c=1.004, $CHCl_3$). IR ($CHCl_3$): 3380 (NH), 1722 (CHO) cm^{-1}. ^{1}H-NMR δ: 1.05 (9H, s, *tert*-Bu), 1.14—1.82 (5H, m, 2-H, 6-H, 7-H), 1.88 (1H, br s, 1-H), 2.04 (1H, br s, 4-H), 2.26 (1H, dd ABq, A part, J=1.6, 18.0, 6.2 Hz, $CH_2(O)$, 2.42 (1H, dABq, B part, J=18.0, 6.2 Hz, CH_2CO), 2.61 (1H, q, J=4.0 Hz, 3-H), 4.15—4.30 (1H, m, 5-H), 4.34 (1H, d, J=4.0 Hz, NH), 7.34—7.80 (15H, m, aromatic H), 9.50 (1H, s, CHO).

20b: 83% yield, colorless foam. *Anal.* Calcd for $C_{31}H_{37}NO_4SSi \cdot 0.1H_2O$: C, 67.75; H, 6.82; N, 2.55. Found: C, 67.55; H, 6.76; N, 2.56. $[\alpha]_D^{24}$ +42.2±0.8° (c=1.004, $CHCl_3$). IR ($CHCl_3$): 3310 (NH), 1722 (CO), 1335 (SO_2), 1168 (SO_2) cm^{-1}. ^{1}H-NMR δ: 0.93—1.16 (1H, m, 2-H), 1.02 (9H, s, *tert*-Bu), 1.19 (1H, d, J=10.7 Hz, 7-H), 1.42 (1H, dd, J=4.8, 14.0 Hz, 5-H), 1.64 (1H, br s, 1-H), 1.80 (1H, dd, J=1.7, 10.7 Hz, 7-H), 2.05 (1H, ddd, J=2.2, 6.6, 14.0 Hz, 5-H), 2.29 (2H, d, J=7.2 Hz, CH_2CO), 2.33—2.40 (1H, m, 4-H), 2.50—2.61 (1H, m, 3-H), 3.74 (1H, d, J=6.6 Hz, 6-H), 5.07 (1H, d, J=3.9 Hz, NH), 7.28—7.67 (13H, m, aromatic H), 7.75—7.86 (2H, m, aromatic H), 9.40 (1H, s, CHO). MS m/z: 548 $(M+H)^+$ (PILSIMS).

(1*S*,2*S*,3*R*,4*S*,5*R*)-(5′*Z*)-7′-(5-Hydroxy-3-phenylsulfonylaminobicyclo-[2.2.1]hept-2-yl)hept-5′-enoic Acid (1a) General Procedure for the Preparation of **1b**, **2a**, **2b** and **6**: A suspension of 4-carboxybutyltriphenylphosphonium bromide (1.43 g, 1.1 mmol × 3) in THF (60 ml) was treated with *tert*-BuOK (654 mg, 1.1 mmol × 5.4) at 0 °C, and the mixture was stirred for 1 h at room temperature. To this solution of the phosphorane, a solution of **20a** (590 mg, 1.1 mmol) in THF (5 ml) was added at −15 °C, and the mixture was stirred for 1 h (−15 °C→0 °C), then poured into a mixture of 2 N HCl and ethyl acetate. The organic solution was washed with H_2O, dried, and concentrated *in vacuo*. The residue was treated with diazomethane in ether as usual, giving the crude product. Chromatography on silica gel with *n*-hexane–ethyl acetate (9 : 1)—(2 : 1) as the eluent gave the methyl 5-pentenoate derivative (647 mg), which was treated with *n*-Bu_4NF (1 mol solution in THF, 30 ml) in THF (5 ml) overnight at 60 °C. The reaction mixture was poured into aqueous saturated NH_4Cl solution and extracted with ethyl acetate. The extract was washed with H_2O, dried and evaporated to dryness. Chromatography of the residue on silica gel with *n*-hexane–ethyl acetate (9 : 1)—(1 : 1) as the eluent gave 360 mg of the desilylated product. Usual hydrolysis of the product with 1 N KOH (2.6 ml) in MeOH (3 ml) for 2 h at 40 °C gave the desired product **1a** (281 mg, 68%), colorless foam. *Anal.* Calcd for $C_{20}H_{27}NO_5S \cdot 0.25H_2O$ (hygroscopic): C, 60.36; H, 6.96; N, 3.52; S, 8.06. Found: C, 60.26; H, 6.92; N, 3.57; S, 7.99. $[\alpha]_D^{24}$ +46.0±0.8° (c=1.039, MeOH). IR (KBr): 3680—2400 (COOH), 3260 (OH), 1705 (COOH), 1315 (SO_2), 1155 (SO_2) cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.93—1.07 (1H, m, 2-H), 1.27—1.98 (11H, m, 1-H, 6-H, 7-H, 3′-H, 4′-H, 7′-H), 2.15—2.30 (3H, m, 4-H, 2′-H), 2.80—2.91 (1H, m, 3-H), 4.06—4.17 (1H, m, 5-H), 5.00—5.24 (2H, m, olefinic H), 7.51—7.69 (3H, m, aromatic H), 7.84—7.95 (2H, aromatic H). MS m/z: 394 $(M+H)^+$ (PILSIMS).

(1*R*,2*S*,3*S*,4*R*,6*S*)-(5′*Z*)-7′-(6-Hydroxy-3-phenylsulfonylaminobicyclo-[2.2.1]hept-2-yl)hept-5′-enoic Acid (1b) 65% yield, mp 127—128 °C. *Anal.* Calcd for $C_{20}H_{27}NO_5S$: C, 61.05; H, 6.92; N, 3.56; S, 8.15. Found: C, 61.02; H, 6.95; N, 3.57; S, 8.04. $[\alpha]_D^{24}$ +28.5±0.7° (c=1.013, MeOH). IR (KBr): 3650—2400 (COOH), 3430 (OH), 3210 (NH), 1710 (COOH), 1308 (SO_2), 1145 (SO_2) cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.80—0.96 (1H, m, 2-H), 1.01—2.17 (12H, m, 1-H, 4-H, 5-H, 7-H, 3′-H, 4′-H, 7′-H), 2.23 (2H, t, J=7.4 Hz, 2′-H), 2.82—2.91 (1H, m, 3-H), 3.63

(1H, d, J=6.2 Hz, 6-H), 5.09—5.31 (2H, m, olefinic H), 7.50—7.69 (3H, m, aromatic H), 7.83—7.92 (2H, m, aromatic H).

The pentenoic derivatives **2a**, **2b** and **6** were obtained by using 2-carboxyethyltriphenylphosphonium bromide, in place of 4-carboxybutyltriphenylphosphonium bromide, in the same manner.

(1*S*,2*S*,3*R*,4*S*,5*R*)-(3′*Z*)-5′-(5-Hydroxy-3-phenylsulfonylaminobicyclo[2.2.1]hept-2-yl)pent-3′-enoic Acid (2a) 53% yield, colorless foam. *Anal.* Calcd for $C_{18}H_{23}NO_5S$: C, 59.16; H, 6.34; N, 3.83; S, 8.77. Found: C, 58.95; H, 6.52; N, 3.84; S, 8.59. $[\alpha]_D^{24}$ +44.2±0.8° (c=1.008, MeOH). IR (KBr): 3760—2280 (COOH), 3260 (NH), 1710 (COOH), 1320 (SO_2), 1158 (SO_2) cm^{-1}. ^{1}H-NMR δ: (CD_3OD) 0.93—1.07 (1H, m, 2-H), 1.26—1.98 (7H, m, 1-H, 6-H, 7-H, 5′-H), 2.27 (1H, d, J=5.0 Hz, 4-H), 2.71—2.98 (3H, m, 3-H, 2′-H), 4.16—4.26 (1H, m, 5-H), 5.12—5.43 (2H, m, olefinic H), 7.52—7.68 (3H, m, aromatic H), 7.84—7.94 (2H, m, aromatic H).

(1*R*,2*S*,3*S*,4*R*,6*S*)-(3′*Z*)-5′-(6-Hydroxy-3-phenylsulfonylaminobicyclo[2.2.1]hept-2-yl)pent-3′-enoic Acid (2b) 62% yield, colorless foam. *Anal.* Calcd for $C_{18}H_{23}NO_5S \cdot 0.2H_2O$ (hygroscopic): C, 58.84; H, 6.42; N, 3.81; S, 8.73. Found: C, 58.63; H, 6.42; N, 3.88; S, 8.80. $[\alpha]_D^{24}$ +28.5±0.7° (c=1.017, MeOH). IR (KBr): 3700—2320 (COOH), 3280 (NH), 1710 (COOH), 1320 (SO_2), 1157 (SO_2) cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.84—2.19 (9H, m, 1-H, 2-H, 4-H, 5-H, 7-H, 5′-H), 2.77—3.03 (3H, m, 3-H, 2′-H), 3.64 (1H, d, J=6.0 Hz, 6-H), 5.23—5.50 (2H, m, olefinic H), 7.50—7.67 (3H, m, aromatic H), 7.82—7.91 (2H, m, aromatic H). MS m/z: 366 $(M+H)^+$ (PILSIMS).

(1*R*,2*S*,3*S*,4*S*)-(3′*Z*)-5′-(3-Phenylsulfonylaminobicyclo[2.2.1]hept-2-yl)-pent-3′-enoic Acid (6) 77% yield, mp 68—69 °C. *Anal.* Calcd for $C_{18}H_{23}NO_4S$: C, 61.87; H, 6.63; N, 4.01; S, 9.17. Found: C, 61.65; H, 6.72; N, 4.22; S, 8.93. $[\alpha]_D^{24}$ +11.2±0.5° (c=1.004, $CHCl_3$). IR (KBr): 3720—2200 (COOH), 3290 (NH), 1710 (COOH), 1325 (SO_2), 1165 (SO_2) cm^{-1}. ^{1}H-NMR δ: 0.80—1.65 (7H, m, 2-H, 5-H, 6-H, 7-H), 1.75—2.04 (3H, m, 1-H, 5′-H), 2.17 (1H, br s, 4-H), 2.85—3.14 (3H, m, 3-H, 2′-H), 5.09 (1H, d, J=6.8 Hz, NH), 5.27—5.56 (2H, m, olefinic H), 7.43—7.64 (3H, m, aromatic H), 7.83—7.97 (2H, m, aromatic H).

(1*S*,2*S*,3*R*,4*S*,5*R*)-5′-(5-Hydroxy-3-phenylsulfonylaminobicyclo[2.2.1]-hept-2-yl)pentanoic Acid (3a) General Procedure for the Preparation of **3b**, **5** and **7**: A solution of **2a** (288 mg) in MeOH (5 ml) containing 10% Pd–C (100 mg) was stirred for 20 min under a hydrogen atmosphere at room temperature. The solid was removed by filtration, and concentration of the filtrate *in vacuo* gave the saturated product **3a** (279 mg, 96%), a colorless oil. *Anal.* Calcd for $C_{18}H_{25}NO_5S$: C, 58.83; H, 6.85; N, 3.81. Found: C, 58.95; H, 6.93; N, 3.47. IR ($CHCl_3$): 3600—2400 (COOH), 3270 (NH), 1710 (COOH), 1322 (SO_2), 1161 (SO_2) cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.74—1.80 (11H, m, 2-H, 6-H, 7-H, 3′-H, 4′-H, 5′-H), 1.84—1.92 (1H, m, 1-H), 2.07 (2H, dd, J=7.8, 16.0 Hz, 2′-H), 2.20 (1H, d, J=5.0 Hz, 4-H), 2.84 (1H, t, J=4.0 Hz, 3-H), 4.14—4.26 (1H, m, 5-H), 7.52—7.70 (3H, m, aromatic H), 7.85—7.95 (2H, m, aromatic H).

(1*R*,2*S*,3*S*,4*R*,6*S*)-5′-(6-Hydroxy-3-phenylsulfonylaminobicyclo[2.2.1]-hept-2-yl)pentanoic Acid (3b) 92% yield, colorless oil. *Anal.* Calcd for $C_{18}H_{25}NO_5S$: C, 58.83; H, 6.86; N, 3.81. Found: C, 59.01; H, 6.87; N, 3.54. IR ($CHCl_3$): 3600—2270 (COOH), 3260 (NH), 1710 (COOH), 1324 (SO_2), 1159 (SO_2) cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.76—1.57 (10H, m, 2-H, 5-H, 7-H, 3′-H, 4′-H, 5′-H), 1.79 (1H, s, 1-H), 1.96—2.20 (4H, m, 4-H, 5-H, 2′-H), 2.81—2.90 (1H, m, 3-H), 3.64 (1H, d, J=6.0 Hz, 6-H), 7.51—7.70 (3H, m, aromatic H), 7.82—7.92 (2H, m, aromatic H).

(1*R*,2*S*,3*S*,4*S*)-7′-(3-Phenylsulfonylaminobicyclo[2.2.1]hept-2-yl)heptanoic Acid (5) 94% yield, mp 89—90 °C. *Anal.* Calcd for $C_{20}H_{29}NO_4S$: C, 63.30; H, 7.70; N, 3.69; S, 8.45. Found: C, 63.09; H, 7.62; N, 3.63; S, 8.22. $[\alpha]_D^{24}$ +16.3±0.6° (c=1.013, $CHCl_3$). IR (KBr): 3720—2280 (COOH), 3280 (NH), 1705 (CO), 1323 (SO_2), 1159 (SO_2) cm^{-1}. ^{1}H-NMR δ: 0.73—1.73 (17H, m, 2-H, 5-H, 6-H, 7-H, 3′-H, 4′-H, 5′-H, 6′-H, 7′-H), 1.84 (1H, br s, 1-H), 2.07 (1H, br s, 4-H), 2.35 (2H, t, J=7.2 Hz, 2′-H), 2.94—3.10 (1H, m, 3-H), 5.21 (1H, d, J=7.4 Hz, NH), 7.40—7.70 (3H, m, aromatic H), 7.80—8.06 (2H, m, aromatic H).

(1*R*,2*S*,3*S*,4*S*)-5′-(3-Phenylsulfonylaminobicyclo[2.2.1]hept-2-yl)pentanoic Acid (7) 90% yield, mp 84—86 °C. *Anal.* Calcd for $C_{18}H_{25}NO_4S$: C, 61.51; H, 7.17; N, 3.99; S, 9.12. Found: C, 61.71; H, 7.53; N, 4.19; S, 8.84. $[\alpha]_D^{24}$ +13.2±0.5° (c=1.002, $CHCl_3$). IR (KBr): 3720—2300 (COOH), 3275 (NH), 1706 (COOH), 1325 (SO_2), 1162 (SO_2) cm^{-1}. ^{1}H-NMR δ: 0.80—1.66 (13H, m, 2-H, 5-H, 6-H, 7-H, 3′-H, 4′-H, 5′-H), 1.84 (1H, br s, 1-H), 2.06 (1H, br s, 4-H), 2.26 (2H, t, J=7.1 Hz, 2′-H), 2.95—3.08 (1H, m, 3-H), 5.25 (1H, d, J=7.0 Hz, NH), 7.45—7.64 (3H, m, aromatic H), 7.84—7.98 (2H, m, aromatic H).

(1*S*,2*R*,3*R*,4*S*,5*R*)-Methyl (5-hydroxy-3-phenylsulfonylaminobicyclo[2.2.1]hept-2-yl)propenylate (21a) and (1*R*,2*S*,3*S*,4*R*,6*S*)-Methyl (6-hydroxy-3-phenylsulfonylaminobicyclo[2.2.1]hept-2-yl)propenylate (21b) A solution of methyl diethylphosphonoacetate (706 mg, 1.1 mmol × 3) in THF (10 ml) was treated with NaH (60% in mineral oil, 130 mg, 1.1 mmol × 2.9) at −10 °C and the mixture was stirred for 35 min at −5 °C. Next, a solution of **19a** (598 mg, 1.1 mmol) in THF (3 ml) was added at the same temperature. The mixture was stirred for 1 h at room temperature, then poured into a mixture of 2 N HCl and ethyl acetate. The organic solution was washed with aqueous 5% $NaHCO_3$ and H_2O, dried, and concentrated *in vacuo*. Chromatography on silica gel with *n*-hexane–ethyl acetate (2:1) as the eluent gave **21a** (540 mg, 82%), mp 178—184 °C. *Anal.* Calcd for $C_{33}H_{39}NO_5SSi$: C, 67.20; H, 6.67; N, 2.38. Found: C, 67.10; H, 6.90; N, 2.31. IR ($CHCl_3$): 1720 (COOMe) cm^{-1}. ^{1}H-NMR δ: 1.05 (9H, s, *tert*-Bu), 1.24—1.39 (2H, m, 2-H, 7-H), 1.63—1.84 (3H, m, 6-H, 7-H), 2.04—2.17 (2H, m, 1-H, 4-H), 2.94 (1H, q, J=5.0 Hz, 3-H), 3.69 (3H, s, Me), 3.90 (1H, d, J=5.4 Hz, NH), 4.05—4.16 (1H, m, 5-H), 5.47 (1H, dd, J=2.0, 15.6 Hz, olefinic H), 6.56 (1H, dd, J=15.6, 8.4 Hz, olefinic H), 7.34—7.74 (15H, m, aromatic H).

21b: 86% yield, mp 64—66 °C. *Anal.* Calcd for $C_{33}H_{39}NO_5SSi$: C, 67.20; H, 6.67; N, 2.38. Found: C, 67.46; H, 6.82; N, 2.58. IR ($CHCl_3$): 1721 (COOMe) cm^{-1}. ^{1}H-NMR δ: 0.84—0.95 (1H, m, 2-H), 1.02 (9H, s, *tert*-Bu), 1.20—1.48 (3H, m, 5-H, 7-H), 1.75—1.90 (2H, m, 1-H, 5-H), 2.20—2.30 (1H, m, 4-H), 3.10—3.21 (1H, m, 3H), 3.64—3.73 (1H, m, 6-H), 3.69 (3H, s, Me), 4.48 (1H, d, J=7.0 Hz, NH), 5.32 (1H, dd, J=1.2, 15.6 Hz, olefinic H), 6.48 (1H, dd, J=15.6, 8.2 Hz, olefinic H), 7.30—7.68 (13H, m, aromatic H), 7.72—7.83 (2H, m, aromatic H).

(1*S*,2*S*,3*R*,4*S*,5*R*)-(5-Hydroxy-3-phenylsulfonylaminobicyclo[2.2.1]hept-2-yl)propionic Acid (4a) and (1*R*,2*S*,3*S*,4*R*,6*S*)-(6-Hydroxy-3-phenylsulfonylaminobicyclo[2.2.1]hept-2-yl)propionic Acid (4b) Catalytic reduction of **21a** using 10% Pd–C gave the saturated product, which was subjected to silyl group deprotection and hydrolysis, in the same manner as **1a**, to obtain **4a** in 52% yield, colorless pillars, mp 187—189 °C. *Anal.* Calcd for $C_{16}H_{21}NO_5S$ (hygroscopic): C, 56.62; H, 6.24; N, 4.13; S, 9.45. Found: C, 56.40; H, 6.33; N, 4.06; S, 9.17. $[\alpha]_D^{26}$ +36.3±0.8° (c=1.011, MeOH). IR (Nujol): 3560—2200 (COOH), 3290 (NH), 1732 (COOH) cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.86—1.06 (1H, m, 2-H), 1.10—2.25 (10H, m, 1-H, 4-H, 6-H, 7-H, 2′-H, 3′-H), 2.86 (1H, t, J=5.0 Hz, 3-H), 4.10—4.24 (1H, m, 5-H), 7.50—7.73 (3H, m, aromatic H), 7.84—8.03 (2H, m, aromatic H).

4b: 62% yield, mp 182—185 °C. *Anal.* Calcd for $C_{16}H_{21}NO_5S$: C, 56.62; H, 6.24; N, 4.13; S, 9.45. Found: C, 56.31; H, 6.22; N, 4.24; S, 9.13. $[\alpha]_D^{23}$ +30.9±0.7° (c=1.008, MeOH). IR (Nujol): 3500—2360 (COOH), 3435 (OH), 3265 (NH), 1714 (COOH), 1328 (SO_2), 1160 (SO_2) cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.77—1.01 (2H, m, 2-H, 7-H), 1.21—1.61 (4H, m, 5-H, 7-H, 3′-H), 1.80 (1H, s, 1-H), 1.92—2.25 (4H, m, 4-H, 5-H, 2′-H), 2.82—2.94 (1H, m, 3-H), 3.64 (1H, d, J=6.0 Hz, 6-H), 7.49—7.68 (3H, m, aromatic H), 7.80—7.94 (2H, m, aromatic H).

(1*R*,2*S*,3*S*,4*S*)-(3-Phenylsulfonylaminobicyclo[2.2.1]hept-2-yl)propionic Acid (8) Wittig reaction of **22** with methoxymethylenetriphenylphosphorane, in the same manner as **20a**, gave the enol ether (100%). A solution of the enol ether (6.55 g) in 90% formic acid (6.5 ml) was allowed to stand for 1.5 h at room temperature, and the mixture was poured into aqueous 10% $NaHCO_3$, and extracted with ethyl acetate. The extract was washed with H_2O, dried and evaporated to dryness. Chromatography on silica gel with toluene–ethyl acetate (9:1) as the eluent gave **23** (3.6 g, 58%), mp 99—101 °C. *Anal.* Calcd for $C_{16}H_{21}NO_3S$: C, 62.52; H, 6.89; N, 4.56; S, 10.43. Found: C, 62.32; H, 6.79; N, 4.60; S, 10.14. $[\alpha]_D^{24}$ +6.3±0.5° (c=1.010, $CHCl_3$). IR (KBr): 3290 (NH), 1725 (CHO), 1312 (SO_2), 1162 (SO_2) cm^{-1}. ^{1}H-NMR δ: 0.85—1.00 (1H, m, 2-H), 1.06—1.68 (6H, m, 5-H, 6-H, 7-H), 1.83—1.91 (1H, br s, 1-H), 1.98—2.08 (1H, br s, 4-H), 2.33 (2H, d, J=7.3 Hz, CH_2CO), 3.00—3.12 (1H, m, 3-H), 4.81 (1H, d, J=7.6 Hz, NH), 7.45—7.65 (3H, m, aromatic H), 7.83—7.97 (2H, m, aromatic H), 9.66 (1H, s, CHO). A solution of **23** (4.46 g, 14.5 mmol) in acetone (44 ml) was oxidized with Jones' reagent (14.4 mmol) at room temperature for 1.5 h. The mixture was poured into H_2O and extracted with ethyl acetate. The extract was washed with brine, dried, and evaporated to dryness. The residue was partitioned between toluene and 1 N NaOH, and the aqueous solution was acidified with 2 N HCl, and extracted with ethyl acetate. The extract was washed with H_2O, dried, and evaporated to dryness. Recrystallization of the crude product from a mixture of MeOH–ethyl acetate gave the title compound **8** (3.03 g, 65%), mp 174—177 °C. *Anal.* Calcd for $C_{16}H_{21}NO_4S$: C, 59.42; H, 6.54; N, 4.33; S, 9.91. Found: C, 59.20; H, 6.54; N, 4.32; S, 9.73. $[\alpha]_D^{25}$ +19.6±0.6° (c=1.008, MeOH). IR (KBr): 3680—2600 (COOH), 3240 (NH), 1728 (COOH), 1318 (SO_2),

1156 (SO_2) cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.94—1.70 (9H, m, 2-H, 5-H, 6-H, 7-H, 3′-H), 1.82—1.92 (1H, br s, 1-H), 1.92—2.24 (3H, m, 4-H, 2′-H), 2.87—2.99 (1H, m, 3-H), 7.50—7.68 (3H, m, aromatic H), 7.83—7.96 (2H, m, aromatic H).

(1*R*,2*S*,3*S*,4*S*)-(5′*Z*)-(3-Phenylsulfonylaminobicyclo[2.2.1]hept-2-yl)-hept-5′-enamidoethylsulfonic Acid (9) General Procedure for Preparation of the Taurine Derivatives (**10**, **11** and **12**): DCC (274 mg, 1.3 mmol) and HOSu (153 mg, 1.3 mmol) were added to a solution of (+)-S-145 (500 mg, 1.3 mmol) in DMF (7.5 ml) at 0 °C, and the mixture was stirred for 1.5 h at room temperature. Then taurine (168 mg, 1.3 mmol) and triethylamine (370 μl, 2.7 mmol) were added, and the mixture was stirred overnight at the same temperature. The resulting crystals were removed by filtration and the filtrate was partitioned between ethyl acetate and 2 N HCl. The aqueous solution was washed with ethyl acetate and concentrated *in vacuo* (<40 °C). Purification with HP-20 resin using H_2O, and then H_2O–MeOH (1 : 1) as the eluent gave **9** (359 mg, 56%), colorless powder. *Anal.* Calcd for $C_{22}H_{32}N_2O_6S_2 \cdot 0.5H_2O$ (hygroscopic): C, 53.53; H, 6.74; N, 5.67; S, 12.99. Found: C, 53.86; H, 6.74; N, 5.97; S, 12.64. $[\alpha]_D^{23}$ +37.3±0.8° (c=1.002, H_2O). IR (KBr): 1650 (CO), 1320 (SO_2), 1155 (SO_2) cm^{-1}; ^{1}H-NMR (D_2O–DSS) δ: 1.00—1.96 (13H, m, 2-H, 5-H, 6-H, 7-H, 3′-H, 4′-H, 7′-H), 2.06—2.23 (3H, m, 1-H, 2′-H), 2.84—2.96 (1H, br s, 4-H), 3.05 (2H, t, J=6.8 Hz, CH_2S), 3.55 (2H, t, J=6.5 Hz, CH_2N), 4.97—5.27 (2H, br s, olefinic H), 7.55—7.78 (3H, m, aromatic H), 7.80—7.93 (2H, m, aromatic H). MS m/z: 483 $(M-H)^-$ (NILSIMS), 485 $(M+H)^+$ (PILSIMS).

(1*R*,2*S*,3*S*,4*S*)-(3′*Z*)-(3-Phenylsulfonylaminobicyclo[2.2.1]hept-2-yl)-pent-3′-enamidoethylsulfonic Acid (10) 51% yield (a mixture of double bond isomers), purified by preparative HPLC, colorless powder. ^{1}H-NMR (D_2O–DSS) δ: 1.02—1.97 (9H, m, 2-H, 5-H, 6-H, 7-H, 5′-H), 1.84—1.92 (1H, br s, 1-H), 2.10—2.21 (1H, br s, 4-H), 2.65—2.88 (2H, m, 2′-H), 2.88—2.97 (1H, m, 3-H), 3.04 (2H, t, J=6.7 Hz, CH_2S), 3.54 (2H, t, J=6.8 Hz, CH_2N), 5.28 (1H, td, J=7.2, 10.8 Hz, olefinic H), 5.41 (1H, td, J=7.2, 10.8 Hz, olefinic H), 7.55—7.76 (3H, m, aromatic H), 7.83—7.95 (2H, m, aromatic H). MS m/z: 455 $(M-H)^-$ (NILSIMS), 457 $(M+H)^+$ (PILSIMS).

(1*R*,2*S*,3*S*,4*S*)-(3-Phenylsulfonylaminobicyclo[2.2.1]hept-2-yl)pentamidoethylsulfonic Acid (11) 64% yield, colorless powder. *Anal.* Calcd for $C_{20}H_{30}N_2O_6S_2 \cdot 0.1H_2O$ (hygroscopic): C,52.18; H, 6.58; N, 6.08; S, 13.93. Found: C, 51.92; H, 6.67; N, 6.47; S, 13.59. $[\alpha]_D^{23}$ +17.9±0.6° (c=1.003, H_2O). IR (KBr): 1670 (CO), 1315 (SO_2), 1155 (SO_2) cm^{-1}. ^{1}H-NMR (D_2O–DSS) δ: 0.70—1.63 (13H, m, 2-H, 5-H, 6-H, 7-H, 3′-H, 4′-H, 5′-H), 1.82—1.91 (1H, br s, 1-H), 1.97—2.14 (1H, br s, 4-H), 2.07 (2H, t, J=7.2 Hz, 2′-H), 2.89—3.00 (1H, m, 3-H), 3.07 (2H, t, J=6.9 Hz, CH_2S), 3.56 (2H, t, J=6.8 Hz, CH_2N), 7.57—7.78 (3H, m, aromatic H), 7.85—7.94 (2H, m, aromatic H). MS m/z: 457 $(M-H)^-$ (NILSIMS), 459 $(M+H)^+$ (PILSIMS).

(1*R*,2*S*,3*S*,4*S*)-(3-Phenylsulfonylaminobicyclo[2.2.1]hept-2-yl)propionamidoethylsulfonic Acid (12) 52% yield, colorless powder. *Anal.* Calcd for $C_{18}H_{26}N_2O_6S_2 \cdot 0.2H_2O$ (hygroscopic): C, 49.80; H, 6.13; N, 6.45; S, 14.77. Found: C, 49.68; H, 6.15; N, 6.70; S, 14.49. $[\alpha]_D^{23}$ +12.3±0.5° (c=1.005, H_2O). IR (Nujol): 1675 (CO), 1322 (SO_2), 1155 (SO_2) cm^{-1}. ^{1}H-NMR (D_2O–DSS) δ: 0.89—1.63 (9H, m, 2-H, 5-H, 6-H, 7-H, 3′-H), 1.70—1.95 (2H, m, 1-H, 2′-H), 1.95—2.17 (2H, m, 4-H, 2′-H), 2.94—3.04 (1H, m, 3-H), 3.05 (2H, t, J=6.8 Hz, CH_2S), 3.52 (2H, t, J=6.8 Hz, CH_2N), 7.57—7.77 (3H, m, aromatic H), 7.87—7.95 (2H, m, aromatic H). MS m/z: 429 $(M-H)^-$ (NILSIMS), 431 $(M+H)^+$ (PILSIMS).

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