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Efficient Synthesis of Optically Active *cis-endo*-2,3-Dihydroxymethyl-5-norbornene Monoacetate by Lipase-Catalyzed Transesterification

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Chiral *cis-endo*-2,3-dihydroxymethyl-5-norbornene monoacetate was produced by lipase-catalyzed asymmetric transesterification, and used to synthesize an optically active thromboxane A_2 (TXA_2) antagonist.

Keywords asymmetric synthesis; lipase; transesterification; norbornene derivative; thromboxane A_2 antagonist

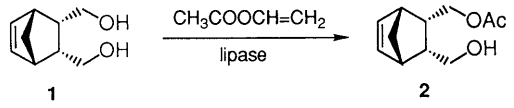
Optically active norbornene derivatives are valuable chiral building blocks for a variety of biologically active derivatives and natural products.[1] Several chemical and enzymatic syntheses of chiral norbornene derivatives have been reported.[2] For example, Zwanenburg *et al.* reported pig liver esterase (PLE)-catalyzed asymmetric hydrolysis of bicyclic esters.[3] However, *cis-endo*-5-norbornene-2,3-dicarboxylic acid dimethyl ester did not give any hydrolysis products. It may be resistant to hydrolysis because of steric hindrance. We have reported several lipase-catalyzed asymmetric reactions in organic media.[4] As a continuation of those studies, the lipase-catalyzed esterification of the hydroxymethyl moiety of norbornene (derived from its carboxylic acid group) was investigated. We describe here the asymmetric transesterification of *cis-endo*-2,3-dihydroxymethyl-5-norbornene (**1**) with vinyl acetate in organic solvents and the application of the resultant optically active building block to the synthesis of an optically pure thromboxane A_2 (TXA_2) antagonist.[5]

First, we surveyed several lipases for the transesterification of the meso diol (**1**) with vinyl acetate. The reaction was generally carried out by stirring a suspension of the meso diol, vinyl acetate, and a crude lipase in CH_2Cl_2 at room temperature.

This reaction needed a large amount of lipase, probably because of its steric factor, and the rate of esterification was generally slow except with lipase AY. Although lipase P showed high enantioselectivity for the transesterification of substrates such as 1,3-propanediols,[6] it gave a low optical yield in this case (entry 1 in Table I). In addition, lipase P showed no enantioselectivity in the case of *cis-endo*-2,3-dihydroxymethyl-5-norbornene as a substrate. Among the lipases tested, lipase GC showed the highest enantioselectivity with only moderate conversion to the monoacetate (**2**).

We further investigated the effect of solvents on the acylation catalyzed by lipase GC. The reaction in diethyl ether or without solvent gave satisfactory results as shown in Table II. Especially, lipase GC in diethyl ether gave the monoacetate (**2**) in high optical yield.

With lipase GC in diethyl ether, the enantiomer excess for esterification of the diol was 78% after 4 h. However,



1 2

Chart 1

TABLE I. Transesterification of *cis-endo*-5-Norbornene-2,3-dimethanol[a]

Entry	Lipase	Solvent	Reaction time (d)	Product		
				Diester (%)	Monoester (%)	% ee[b]
1	P	CH_2Cl_2	3	26	43	33
2	SAM-II	CH_2Cl_2	3	18	37	20
3	LP	CH_2Cl_2	3.5	6	26	27
4	AK	CH_2Cl_2	3	34	51	50
6	AY	CH_2Cl_2	3 (h)	88	11	72[c]
8	GC	CH_2Cl_2	3	0	54	71
9	GC[d]	CH_2Cl_2	3	12	80	80

a) All reactions were carried out with substrate (2 mmol), vinyl acetate (20 mmol), and lipase (200 mg) at room temperature unless otherwise noted. *b*) Optical yields were determined by HPLC analysis using a column packed with Chiralcel OD (iso-PrOH : *n*-hexane = 1 : 100) after tosylation of the hydroxy group. *c*) (−)-(2*S*,3*R*)-*cis*-3-(Acetoxymethyl)-2-(hydroxymethyl)bicyclo[2.2.1]hept-5-ene. *d*) Lipase GC (500 mg).

TABLE II. Effect of Organic Solvents[a] on Transesterification of **1**

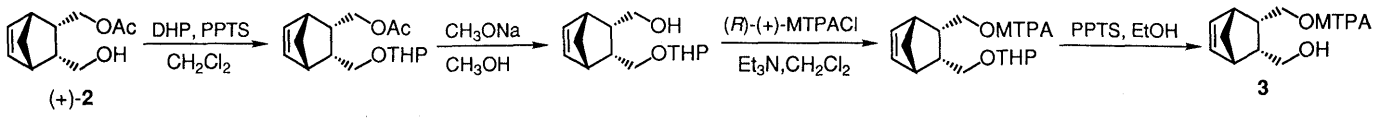
Entry	Lipase	Solvent	Reaction time (d)	Product		
				Diester (%)	Monoester (%)	% ee[b]
1	GC	CH_2Cl_2	3	12	80	80
2	GC	$(C_2H_5)_2O$	2	25	75	95
3	GC	C_6H_6	3	17	75	79
4	GC	*tert*-BuOH	3	0	35	63
5	GC	$(CH_3)_2CO$	3	3	58	84
6	GC	—	2	21	74	87

a) All reactions were carried out with substrate (2 mmol), vinyl acetate (20 mmol), and lipase (500 mg) at room temperature. *b*) Optical yields were determined by HPLC analysis using a column packed with Chiralcel OD (iso-PrOH : *n*-hexane = 1 : 100) after tosylation of the hydroxy group.

TABLE III. Time-Course of Transesterification[a] by Lipase GC in Diethyl Ether

Entry	Reaction time (h)	Product		
		Diacetate (%)	Monoacetate (%)	% ee[b]
1	6	0	20	78
2	12	2	38	80
3	24	5	63	82
4	36	9	79	85
5	48	25	75	95

a) All reactions were carried out with substrate (2 mmol), vinyl acetate (20 mmol), and lipase (500 mg) at room temperature. *b*) Optical yields were determined by HPLC analysis using a column packed with Chiralcel OD (iso-PrOH : *n*-hexane = 1 : 100) after tosylation of the hydroxy group.



(+)-2 3

Chart 2

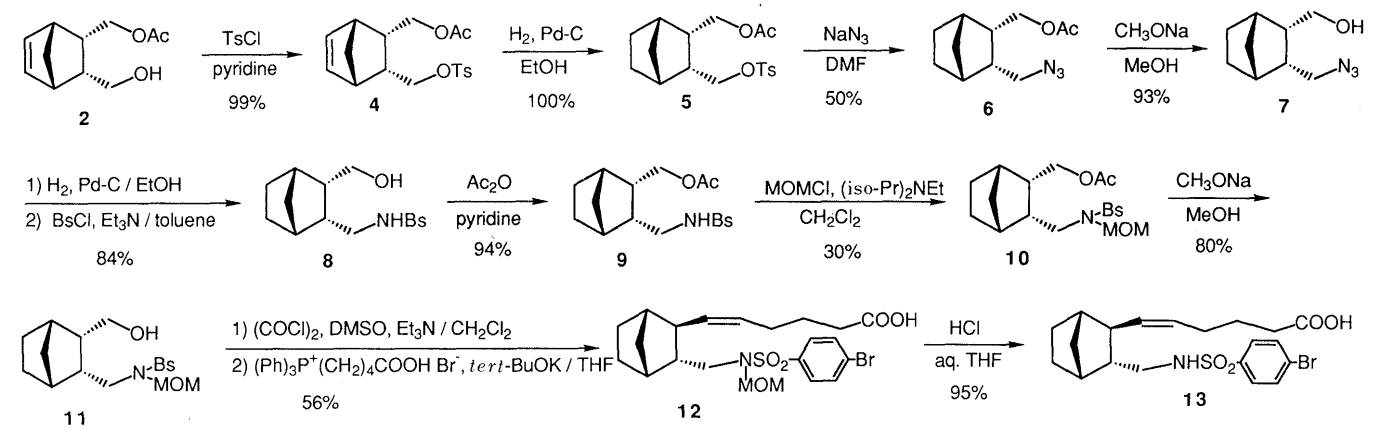


Chart 3

the further esterification of its second alcohol group proceeded with kinetic resolution of the monoacetate resulting in the 95% ee of the unreacted monoacetate after 48 h (Table III). Thus, lipase GC in ether was the most efficient catalyst for the esterification of this substrate. The absolute configuration of (+)-**2** was determined by the conversion of (+)-**2** into the corresponding (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl (MTPA) ester (**3**) (Chart 2).[7]

The utility of (+)-2,3-dihydroxymethyl-5-norbornene monoacetate (**2**) as a chiral building block was demonstrated by the synthesis of an optically active TXA_2 antagonist (**13**) (Chart 3), as developed by Hamanaka *et al.*[8]

Treatment of (+)-**2** (95% ee) with *p*-toluenesulfonyl chloride in pyridine at room temperature followed by recrystallization from petroleum ether gave optically pure **4**. The unsaturated tosylate **4** was hydrogenated in the presence of 5% Pd–C in ethanol to give 2-acetoxy-3-tosyloxynorbornane (**5**). Compound **5** was heated with sodium azide in *N*,*N*-dimethylformamide (DMF) at 100 °C to give the azide (**6**). After deacylation of **6** with sodium methoxide in methanol, hydrogenation of the resultant **7** over 5% Pd–C in ethanol followed by sulfonylation, without further purification, with *p*-bromobenzenesulfonyl chloride in the presence of triethylamine in toluene afforded a sulfonamide (**8**). Because the direct oxidation of **8** resulted in the formation of the undesired *cis*-*O*,*N*-acetal, the oxidation to an *exo* aldehyde was carried out after protection of the sulfonamide with chloromethyl methyl ether. Compound **8** was acetylated with acetyl chloride and triethylamine in dichloromethane. The sulfonamide group of the resulting compound was protected with chloromethyl methyl ether and diisopropylethylamine in dichloromethane followed by deacetylation with sodium methoxide to give **11**. Swern oxidation of **11** proceeded smoothly to give a crude aldehyde as a mixture of *exo* and *endo* isomers. The ratio was 5 : 1, but it was not clear whether the major product was *endo* or *exo*. When this mixture was treated with (4-carboxybutyl)triphenylphosphonium bromide and potassium *tert*-butoxide in dry tetrahydrofuran (THF), it gave an acid (**12**). Deprotection of the methoxymethyl (MOM) group of **12** with acid gave mainly *trans*-**13** (95%) which contained a small amount of *trans*-olefin. Therefore, the major aldehyde obtained by Swern oxidation was *exo*-form. This crude **13** was treated with cyclohexylamine in dichloromethane, and the resulting salt was treated with hydrogen chloride solution to give pure **13**. Thus, we have developed an efficient method for the preparation of the optically active norbornene derivative and have demonstrated its utility.

Experimental

Melting points were determined on a micro melting point apparatus, BY-1 (Yazawa), and are uncorrected. Optical rotations were measured on a JASCO DIP-140 digital polarimeter. IR spectra were taken on a JASCO IR-810 IR spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-GX270 FT-NMR spectrophotometer using tetramethylsilane (in $CDCl_3$) as an internal standard. Abbreviations are as follows; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. HPLC was carried out with a JASCO Trirotar-V (ultraviolet detection) equipped with a column of Chiralcel OD (*n*-hexane–isopropanol). Column chromatography was carried out on a silica gel (Kiesel gel-60, 70—230 mesh, Merck). Thin-layer chromatography was used to monitor the reaction and to ascertain the purity of the reaction products. Lipases were supplied by Amano Seiyaku Co., Ltd. and Toyo Jozo Co., Ltd. Sources of enzymes are as follows; lipases P, SAM-II, AK, *Pseudomonas* sp.; lipase AY, *Candida rugosa*; lipase GC, *Geotrichum candidum*; lipase LP, *Chromobacterium viscosum*.

Lipase-Catalyzed Transesterification of *cis-endo*-2,3-Dihydroxymethyl-5-norbornene A mixture of **1** (1.54 g, 10 mmol), vinyl acetate (8.6 g, 100 mmol), lipase GC (2.5 g), and diethyl ether (20 ml) was stirred at room temperature for 48 h. After removal of the lipase by filtration, the filtrate was concentrated under reduced pressure. The residue was chromatographed on a short silica gel column with AcOEt–hexane (1 : 1) to give the monoacetate (**2**). The optical purity of the product was determined by HPLC analysis after tosylation of the hydroxy group. Yield and optical purity are listed in Tables I, II and III. **2**: $[\alpha]_D^{23}$ +12.6° (c=1.0, $CHCl_3$). IR (neat) cm^{-1}: 3400 (OH), 1740 (CO). MS *m/z*: 196 (M^+). ^{1}H-NMR: 1.35 (H_A, d, J=8.1 Hz, CCH_2C), 1.51 (H_B, d, J=8.1 Hz, CCH_2C), 2.05 (3H, s, CH_3), 2.40—2.61 (2H, m, 2×CCHC), 2.91—2.96 (2H, m, 2×CCHC), 3.33 (H_A, dd, J=7.7, 10.5 Hz, CH_2O), 3.74 (H_B, dd, J=6.6, 10.5 Hz, CH_2O), 3.80—3.94 (2H, m, CH_2O), 6.12—6.19 (2H, m, 2×CH=C). ^{13}C-NMR: 21.04 (t), 40.64 (d), 44.66 (d), 45.50 (d), 45.73 (t), 49.20 (d), 62.77 (t), 65.03 (t), 135.09 (d), 135.52 (d), 170.95 (s).

Determination of the Absolute Configuration A solution of (+)-**2** (196 mg, 1 mmol), 3,4-dihydropyran (84 mg, 1 mmol), and pyridinium *p*-toluenesulfonate (PPTS) (25 mg, 0.1 mmol) in dichloromethane (10 ml)

was stirred at room temperature for 12 h. After usual work-up, followed by chromatography, the product was treated with NH_4OH–methanol (1 : 10) at room temperature for 12 h to give the corresponding alcohol (200 mg, 84%). ^{1}H-NMR: 1.15—1.80 (9H, m), 2.54 (2H, m), 2.82 (2H, m), 3.08—3.85 (6H, m), 4.56 (1H, br s), 6.03 (2H, m). This alcohol was allowed to react with (*R*)-(+)-MTPA chloride in the presence of triethylamine in dichloromethane, followed by removal of the THP group with PPTS in ethanol at 55 °C, giving the corresponding (*R*)-(+)-MTPA ester (**3**) (242 mg, 78%). **3**: ^{1}H-NMR: 1.31 (1H, br d, J=8.4 Hz), 1.49 (1H, br d, J=8.4 Hz), 2.35—2.63 (2H, m), 2.81 (1H, br s), 2.92 (1H, br s), 3.35 (2H, d, J=7.3 Hz), 3.54 (3H, s), 3.97—4.26 (2H, m), 6.07—6.20 (2H, m), 7.40—7.42 (3H, m), 7.50—7.57 (2H, m).

(−)-(2*S*,3*R*)-*cis*-3-(Tosyloxymethyl)-2-(acetoxymethyl)bicyclo[2.2.1]-hept-5-ene (4) *p*-Toluenesulfonyl chloride (1.7 g, 8.94 mmol) was added to a solution of **2** (1.46 g, 7.45 mmol) in pyridine at 0 °C. The mixture was stirred at room temperature for 12 h, then poured into ice-cooled water, and extracted with dichloromethane. The organic layer was washed with 1 N hydrochloride solution three times, washed with brine, and dried. After removal of the solvent, the residue was chromatographed on a short silica gel column with AcOEt–hexane (1 : 3) to give **4** (2.59 g, 99%) as a colorless solid. Single recrystallization from petroleum ether gave the optically pure product. **4**: mp 68—70 °C. $[\alpha]_D^{22}$ −38.0° (c=1.23, $CHCl_3$). ^{1}H-NMR: 1.31 (H_A, d, J=8.4 Hz, CCH_2C), 1.51 (H_B, d, J=8.4 Hz, CCH_2C), 2.01 (3H, s, CH_3), 2.46 (3H, s, CH_3), 2.40—2.57 (2H, m, 2×CCHC), 2.86—2.94 (2H, m, 2×CCHC), 3.56—3.94 (4H, m, 2×CH_2O), 5.89—5.92 (1H, m, CH=), 6.08—6.11 (1H, m, CH=), 7.36 (2H, d, J=8.1 Hz, Ar-H), 7.78 (2H, d, J=8.1 Hz, Ar-H); IR (KBr) cm^{-1}: 1740 (CO), 1350, 1175 (SO_2). *Anal.* Calcd for $C_{18}H_{22}O_5S$: C, 61.69; H, 6.33. Found: C, 61.40; H, 6.38.

(−)-(2*S*,3*R*)-*cis*-3-(Tosyloxymethyl)-2-(acetoxymethyl)bicyclo[2.2.1]-heptane (5) Compound **4** (2.5 g, 7.14 mmol) was hydrogenated over 5% Pd–C (300 mg) in ethanol at room temperature. The catalyst was filtered off and the filtrate was evaporated *in vacuo* to give **5** (2.5 g, 100%) as a colorless solid. **5**: mp 62—62 °C. $[\alpha]_D^{22}$ −19.5° (c=1.03, $CHCl_3$). ^{1}H-NMR: 1.21—1.48 (6H, m, 3×CCH_2C), 2.00 (3H, s, CH_3), 2.25—2.31 (4H, m, 4×CCHC), 2.46 (3H, s, CH_3), 3.96—4.02 (3H, m, CH_2O), 4.08—4.14 (1H, m, CH_2O), 7.35 (2H, d, J=8.1 Hz, Ar-H), 7.79 (2H, d, J=8.1 Hz, Ar-H). IR (KBr) cm^{-1}: 1730 (CO), 1350, 1170 (SO_2). *Anal.* Calcd for $C_{18}H_{24}O_5S$: C, 61.34; H, 6.86. Found: C, 61.15; H, 6.92.

(−)-(2*S*,3*R*)-*cis*-3-(Azidomethyl)-2-(acetoxymethyl)bicyclo[2.2.1]-heptane (6) A suspension of **5** (2.5 g, 7.10 mmol) and sodium azide (550 mg, 8.46 mmol) in dry *N*,*N*-dimethylformamide (DMF) (10 ml) was heated at 100 °C for 3 h. The reaction mixture was cooled, poured into water (100 ml), and extracted with ether (20 ml) three times. The combined extracts were washed with brine, dried and concentrated. The residual oil was chromatographed on a short silica gel column with AcOEt–hexane (1 : 10) to give **6** (792 mg, 50%). **6**: $[\alpha]_D^{22}$ −14.5° (c=1.0, $CHCl_3$). ^{1}H-NMR: 1.37—1.40 (6H, m, 3×CCH_2C), 2.01 (3H, s, CH_3), 2.06—2.32 (4H, m, 4×CCHC), 3.22 (H_A, dd, J=9.5, 12.5 Hz, CH_2O), 3.37 (H_B, dd, J=6.2, 12.5 Hz, CH_2O), 4.01—4.09 (2H, m, CH_2O). IR (neat) cm^{-1}: 2100 (N_3), 1740 (CO).

(−)-(2*S*,3*R*)-*cis*-3-(Azidomethyl)-2-(hydroxymethyl)bicyclo[2.2.1]-heptane (7) Sodium methoxide (191 mg, 3.54 mmol) was added to a solution of **6** (790 mg, 3.54 mmol) in a methanol (50 ml). The mixture was stirred at room temperature for 3 h. After removal of the solvent, the residue was partitioned between dichloromethane and water. The organic layer was washed with brine, dried and concentrated. The residue was chromatographed on a short silica gel column with AcOEt–hexane (1 : 5) to give **7** (596 mg, 93%). **7**: $[\alpha]_D^{22}$ −7.7° (c=1.1, $CHCl_3$). ^{1}H-NMR: 1.26—1.50 (6H, m, 3×CCH_2C), 2.03—2.30 (4H, m, 4×CCHC), 2.32 (1H, s, OH), 3.30 (H_A, dd, J=8.1, 12.5 Hz, CH_2O), 3.52 (H_B, dd, J=7.3, 12.5 Hz, CH_2O), 3.57 (H_A, dd, J=6.6, 11.0 Hz, CH_2O), 3.70 (H_B, dd, J=7.7, 11.0 Hz, CH_2O). IR (neat) cm^{-1}: 3350 (OH), 2100 (N_3).

(+)-(2*S*,3*R*)-*cis*-3-(4-Bromobenzenesulfonylaminomethyl)-2-(hydroxymethyl)-bicyclo[2.2.1]heptane (8) Compound **7** (590 mg, 3.26 mmol) was hydrogenated with 5% Pd–C in ethanol (20 ml) at room temperature. The catalyst was filtered off and filtrate was evaporated *in vacuo* to give the amino alcohol derivative (490 mg, 97%). A solution of the amino alcohol and triethylamine (320 mg, 3.16 mmol) in dry toluene (50 ml) was treated with *p*-bromobenzene sulfonyl chloride (808 mg, 3.16 mmol) at 0 °C. The mixture was stirred at room temperature for 12 h, washed with water, washed with brine, and dried. After removal of the solvent, the residue was chromatographed on a short silica gel column with AcOEt–hexane (1 : 2) to give **8** (1.03 g, 87%) as a colorless solid. **8**: mp 112—114 °C. $[\alpha]_D^{22}$ +16.6° (c=1.07, $CHCl_3$). ^{1}H-NMR: 1.23—1.38 (6H, m, 3×CCH_2C), 2.04—2.27 (4H, m, 4×CCHC), 2.99 (2H, m, CH_2O), 3.16 (1H, s, OH), 3.58 (2H, m, CH_2O), 6.53 (1H, s, NH), 7.65 (2H, d, J=8.4 Hz, Ar-H), 7.75 (2H, d, J=8.4 Hz, Ar-H). IR (KBr) cm^{-1}: 3500 (OH), 3150 (NH), 1320, 1150 (SO_2). *Anal.* Calcd for $C_{15}H_{20}BrNO_3S$: C, 48.13; H, 5.39; N, 3.74. Found: C, 48.20; H, 5.43; N, 3.61.

(−)-(2*S*,3*R*)-*cis*-3-(4-Bromobenzenesulfonylaminomethyl)-2-(acetoxymethyl)-bicyclo[2.2.1]heptane (9) Acetyl chloride (210 mg, 2.67 mmol) was added to a solution of **8** (1 g, 2.67 mmol) and triethylamine (303 mg, 3 mmol) in dichloromethane (50 ml) at 0 °C. The mixture was stirred for 3 h, then washed with water and brine, and dried. After removal of the solvent, the residue was chromatographed on a short silica gel column with AcOEt–hexane (1 : 3) to give **9** (1.05 g, 94%) as a colorless solid. **9**: mp 117—118 °C. $[\alpha]_D^{22}$ −14.2° (c=1.01, $CHCl_3$). ^{1}H-NMR: 1.20—1.45 (6H, m, 3×CCH_2C), 2.00—2.31 (4H, m, 4×CCHC), 2.03 (3H, s, CH_3), 2.85—3.11 (2H, m, CH_2O), 3.92—4.12 (2H, m, CH_2O), 4.68 (1H, s, NH), 7.67 (2H, d, J=8.8 Hz, Ar-H), 7.73 (2H, d, J=8.8 Hz, Ar-H); IR (KBr) cm^{-1}: 3250 (NH), 1720 (CO), 1330, 1170 (SO_2). *Anal.* Calcd for $C_{17}H_{22}BrNO_4S$: C, 49.04; H, 5.33; N, 3.36. Found: C, 48.65; H, 5.31; H, 3.21.

(−)-(2*S*,3*R*)-*cis*-3-(4-Bromobenzenesulfonyl)methoxymethylamino-methyl-2-(acetoxymethyl)bicyclo[2.2.1]heptane (10) A mixture of **9** (1 g, 2.4 mmol), *N*,*N*-diisopropylethylamine (370 mg, 2.86 mmol), and chloromethyl methyl ether (230 mg, 2.86 mmol) in dry dichloromethane (10 ml) was stirred at room temperature for 12 h. The reaction mixture was washed with water and brine, then dried. After removal of the solvent, the residue was chromatographed on a short silica gel column with AcOEt–hexane (1 : 3) to give **10** (332 mg, 30%). About 60% of **9** was recovered. **10**: $[\alpha]_D^{22}$ −9.9° (c=2.6, $CHCl_3$). ^{1}H-NMR: 1.32—1.52 (6H, m, 3×CCH_2C), 2.00 (3H, s, CH_3), 2.20—2.33 (4H, m, 4×CCHC), 3.12—3.21 (2H, m, CH_2O), 3.26 (3H, s, OCH_3), 3.94—4.06 (2H, m, CH_2O), 4.68 (2H, ABq, J=10.4 Hz, OCH_2O), 7.63 (2H, d, J=8.8 Hz, Ar-H), 7.72 (2H, d, J=8.8 Hz, Ar-H). IR (neat) cm^{-1}: 1740 (CO), 1360, 1170 (SO_2).

[(1*S*,2*S*,3*R*,4*S*)-3-[*N*,*N*-(4-Bromobenzenesulfonyl)methoxymethylamino-methyl]bicyclo[2.2.1]heptan-2-yl]methylalcohol (11) Sodium methoxide (39 mg, 0.72 mmol) was added to a solution of **10** (330 mg, 0.72 mmol) in methanol at 0 °C. The mixture was stirred at room temperature for 2 h, then treated with Amberlite IRC-50 for 1 h. The Amberlite was filtered off and filtrate was evaporated *in vacuo*. The residue was chromatographed on a short silica gel column with AcOEt–hexane (1 : 3) to give **11** (240 mg, 80%). **11**: $[\alpha]_D^{22}$ −13.9° (c=2.3, $CHCl_3$). ^{1}H-NMR: 1.26—1.46 (6H, m, 3×CCH_2C), 1.80 (1H, br s, OH), 2.04—2.33 (4H, m, 4×CCHC), 3.18 (H_A, dd, J=10.3, 13.9 Hz, CH_2O), 3.36 (H_B, dd, J=5.1, 13.9 Hz, CH_2O), 3.26 (3H, s, OCH_3), 3.52—3.65 (2H, m, CH_2O), 4.68 (2H, ABq, J=10.6 Hz, OCH_2O), 7.63 (2H, d, J=8.8 Hz, Ar-H), 7.72 (2H, d, J=8.8 Hz, Ar-H). IR (neat) cm^{-1}: 3400 (OH), 1340, 1160 (SO_2).

(5*Z*)-6-[(1*R*,2*R*,3*R*,4*S*)-3-[*N*,*N*-(4-Bromobenzenesulfonyl)methoxy-methylaminomethyl]bicyclo[2.2.1]heptan-2-yl]hex-5-enoic Acid (12) A solution of oxalyl chloride (180 mg, 1.41 mmol) in dichloromethane (2 ml) was added dropwise to a stirred solution of dimethylsulfoxide (259 mg, 3.31 mmol) in dichloromethane (20 ml) under an argon atmosphere at −78 °C. The solution was stirred for 15 min, and then a solution of **11** (240 mg, 0.57 mmol) in dichloromethane (2 ml) was added. Stirring was continued at −78 °C for 1 h, then triethylamine (430 mg, 4.26 mmol) was added and the whole was allowed to warm to 0 °C over 1 h. The reaction mixture was washed with water and brine, dried, and concentrated under reduced pressure to give the crude aldehyde. The aldehyde was employed without further purification. A suspension of (4-carbohydroxy-*n*-butyl)triphenylphosphonium bromide (800 mg, 1.8 mmol) in dry tetrahydrofuran was treated with potassium *tert*-butoxide (400 mg, 3.56 mmol) under an argon atmosphere. The mixture was stirred at room temperature for 1 h. The resulting red suspension was cooled to 0 °C and a solution of the crude aldehyde in dry tetrahydrofuran was added. The mixture was stirred for 1 h, poured into ice-water and extracted with ethyl ether. The organic layer was discarded. The aqueous layer was acidified to pH 2 with 6 N HCl solution. The product was extracted with ethyl acetate twice and the combined extracts were dried and concentrated *in vacuo*. The residue was chromatographed on a short silica gel column with CH_2Cl_2–MeOH (15 : 1) to give **12** (160 mg, 56%). **12**: $[\alpha]_D^{22}$ +7.9° (c=1.7, $CHCl_3$). ^{1}H-NMR: 1.10—1.91 (11H, m, 5×CCH_2C, CCHC), 2.00—2.20 (3H, m, CCHC), 2.30—2.41 (2H, m, CCH_2C), 3.08—3.18 (2H, m, CCH_2C), 3.24 (3H, s, OCH_3), 4.67 (2H, ABq, J=10.6 Hz, OCH_2O), 5.21—5.30 (2H, m, 2×CH=), 7.62 (2H, d, J=8.4 Hz, Ar-H), 7.71 (2H, d, J=8.4 Hz, Ar-H). IR (neat) cm^{-1}: 1710 (CO), 1330, 1160 (SO_2).

(5*Z*)-6-[(1*R*,2*R*,3*R*,4*S*)-3-[*N*-(4-Bromobenzenesulfonyl)aminomethyl]-bicyclo[2.2.1]heptan-2-yl]hex-5-enoic Acid (13) A solution of **12** (160 mg, 0.32 mmol) in 6 N hydrochloride and tetrahydrofuran was heated at 55 °C

for 6 h. The reaction mixture was extracted with dichloromethane, washed with brine, dried, and concentrated under reduced pressure. The residue was chromatographed on a short silica gel column with CH_2Cl_2–MeOH (15 : 1) to give **13** (139 mg, 95%). **13**: $[\alpha]_D^{22}$ +19° (c=1.5, EtOH). A stirred solution of **13** in dichloromethane (20 ml) was treated with cyclohexylamine (28 mg). The resulting salt was collected by filtration, treated with 4 N HCl solution, and extracted with ether twice. The combined extracts were dried and concentrated *in vacuo* to give **13**. **13**: $[\alpha]_D^{22}$ +21° (c=1.1, EtOH). ^{1}H-NMR: 1.06—1.91 (11H, m, 5×CCH_2C, CCHC), 1.92—2.23 (3H, m, CCHC), 2.30—2.41 (2H, m, CCH_2C), 2.81—3.06 (2H, m, CCH_2C), 4.82—4.91 (1H, m, NH), 5.15—5.30 (2H, m, 2×CH=), 7.63—7.75 (4H, m, Ar-H). IR (neat) cm^{-1}: 3300 (OH), 1710 (CO), 1330, 1160 (SO_2). (+)FABMS m/z: 456, 458 $(M+H)^+$. *Anal.* Calcd for $C_{20}H_{26}BrNO_4S \cdot C_6H_{13}N$: C, 56.21; H, 7.08; N, 5.04. Found: C, 56.17; H, 7.02; N, 5.04.

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