124716-16-1; (2′S,4′R,2″S)-1, 124716-17-2; (2′R,4′S,2″S)-1, 124716-18-3; (DL-erythro)-2, 124688-42-2; DL-threo)-2, 124688-43-3; (DL-erythro)-3, 124688-44-4; (DL-threo)-3, 124688-45-5; (2′S,4′S,2″S)-4, 124688-46-6; (2′R,4′R,2″S)-4, 124815-52-7; (2′S,4′R,2″S)-4, 124815-53-8; (2′R,4′S,2″S)-4, 124815-54-9; (2′S,4′S,2″S)-5, 124688-47-7; (2′R,4′R,2″S)-5, 124688-48-8; (2′S,4′R,2″S)-5, 124688-49-9; (2′R,4′S,2″S)-5, 124688-50-2; ('S,4′S,2″S)-6, 124688-51-3; (2′R,4′R,2″S)-6, 124688-52-4; (2′S,4′R,2″S)-6, 124688-53-5; (2′R,4′S,2″S)-6, 124688-54-6; 7, 19741-14-1; FPGS, 63363-84-8; GH, 9074-87-7; (DL-erythro)-FGlu, 91383-48-1; (DL-threo)-FGlu, 91383-47-0; H-Glu(OBu-t)-OBu-t, 16874-06-9.

Synthesis and in Vitro Activity of Stereoisomers of a Novel Thromboxane Receptor Antagonist, (±)-(5*Z*)-7-[3-*endo*-[(Phenylsulfonyl)amino]bicyclo[2.2.1]hept-2-*exo*-yl]heptenoic Acid

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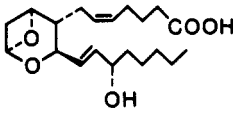
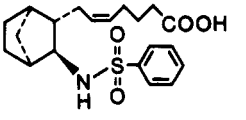
Three stereoisomers of S-145 (1) with variations at the side-chain junctions were synthesized. Endo-cis isomer **10** and *N*-exo-trans isomer **18** were obtained via the common intermediate **5** having an endo-fused ring structure. Exo-cis isomer **28** was prepared via exo-fused azetidino compound **21**. Inhibitory concentrations (IC_{50}) of the sodium salts newly obtained for platelet aggregation were measured using washed rat platelets (WP) and human platelet-rich plasma (PRP). The IC_{50} values of these compounds for contraction of the rat aorta were also measured. Compound **1** of *N*-endo-trans structure and *N*-exo-trans isomer **18** exhibited more potent inhibitory activity than cis-isomers **10** and **28** against responses induced by TXA_2-related substances for rat WP and rat thoracic aorta. However, these compounds exhibited almost comparable inhibitory activity for human PRP.

Thromboxane A_2 (TXA_2) is a very potent inducer of human platelet aggregation and vasoconstriction of bronchial and vascular smooth muscles. Therefore, TXA_2 has been considered to be an important mediator in a variety of circulatory diseases.[1] In the previous paper,[2] we described the synthesis and in vitro activity of a novel TXA_2 receptor antagonist, S-145 [(±)-(5*Z*)-7-[3-*endo*-[(phenylsulfonyl)amino]bicyclo[2.2.1]hept-2-*exo*-yl]heptenoic acid, **1**], and emphasized the importance of the aromatic sulfonylamino group as a side chain for exhibiting the potent inhibitory activity against responses induced by TXA_2-related substances. The effect of stereochemical variation in the attached ring system on the biological activity of the TXA_2 receptor antagonist is not yet understood completely, and one stereoisomer frequently shows a different character from another in biological examinations.[3] We were very interested in finding the dependence of the biological activity upon the variation in the stereochemical structure and directed our research toward the synthesis and evaluation of the in vitro activity of the racemic three stereoisomers of compound **1**.



TXA_2



1 (S-145)

Chemistry

Isomers having different stereochemistry from that of compound **1** at the junctions of the side chains were synthesized as depicted in Scheme I. Endo-cis isomer **10** and *N*-exo-trans isomer **18** were derived from a key intermediate (**5**), which was prepared from dicyclopentadiene (**2**). Catalytic hydrogenation of dicyclopentadiene (**2**) with a catalytic amount of nickel boride occurred regioselectively at the norbornene skeleton and gave **3** in 84.5% yield.[4] Ozonolysis of **3** followed by Zn–acetic acid treatment and subsequent Jones' oxidation afforded dicarboxylic acid **4** in 41.7% yield. Treatment of **4** with acetic anhydride gave cyclic anhydride which, without purification, was treated with methanol under reflux, regioselectively giving acid ester **5** in 93.5% yield. Curtius rearrangement of **5** and subsequent alcoholysis with benzyl alcohol afforded benzyl carbamate **6** in 59.1% yield. Diisobutylaluminum hydride (DIBAL) reduction of **6** gave an unstable product (**7**),[5] which was treated with Wittig reagent prepared from (4-carboxybutyl)triphenylphosphonium bromide and dimsyl sodium in DMSO, giving a crude acid. Esterification of the acid with diazomethane gave methyl ester **8** in 34.3% yield from **6**. Removal of the carbobenzoxy group[2] in **8** followed by phenylsulfonylation afforded sulfonylamino ester **9** in 80.4% yield. Hydrolysis of **9** with KOH in aqueous methanol gave **10**, which was transformed into its sodium salt **11** for biological assay in vitro by neutralizing with sodium methoxide in methanol in 88.8% yield. The

(1) See recent reviews: (a) Brezinski, M. E.; Yanagisawa, A.; Lefer, A. M. *J. Cardiovasc. Pharmacol.* **1987**, *9*, 65. (b) Ogletree, M. L. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1987**, *46*, 133. (c) Lefer, A. M.; Darius, H. *Ibid.* **1987**, *46*, 144. (d) Halushka, P. V.; Mais, D. E.; Saussy, D. L., Jr. *Ibid.* **1987**, *46*, 149.

(2) Narisada, M.; Ohtani, M.; Watanabe, F.; Uchida, K.; Arita, H.; Doteuchi, M.; Hanasaki, K.; Kakushi, H.; Otani, K.; Hara, S. *J. Med. Chem.* **1988**, *31*, 1847 and references therein.

(3) Sprague, P. W.; Heikes, J. E.; Gougoutas, J. Z.; Malley, M. F.; Harris, D. N.; Greenberg, R. *J. Med. Chem.* **1985**, *28*, 1580. (b) Hall, S. E.; Han, W.-C.; Haslanger, M. F.; Harris, D. N.; Ogletree, M. L. *Ibid.* **1986**, *29*, 2335. (c) Friedhoff, L. T.; Mannig, J.; Funke, P. T.; Ivashikiv, E.; Tu, J.; Cooper, W.; Willard, D. A. *Clin. Pharmacol. Ther.* **1986**, *40*, 634. (d) Sprague, P. W.; Heikes, J. E.; Harris, D. N.; Greenberg, R. *Advances in Prostaglandin, Thromboxane and Leukotriene Research*; Samuelsson, B., Paoletti, R., Ramwell, P., Ed.; Raven Press: New York, 1983; Vol. 11, p 337.

(4) Brown, H. C.; Rothberg, I.; Jagt, D. L. V. *J. Org. Chem.* **1972**, *37*, 4098.

(5) Cyclization occurred and gave 2-hydroxyoctahydroindole derivative **7**, which was unstable and used for the next reaction without purification. See the Experimental Section.

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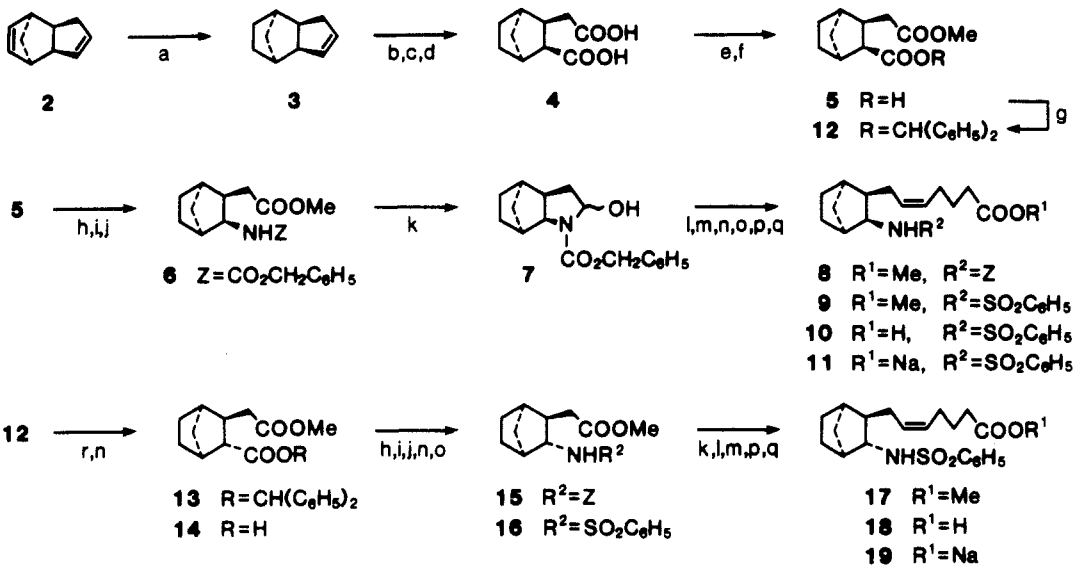
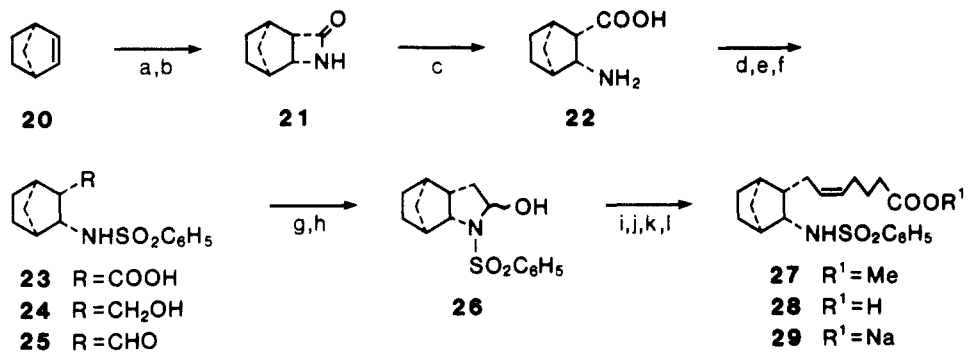
Scheme I[a]



[a] (a) H_2/Ni_2B; (b) O_3; (c) Zn, AcOH; (d) Jones' oxidation; (e) Ac_2O; (f) MeOH; (g) Ph_2CN_2; (h) $ClCO_2Et$, Et_3N; (i) NaN_3, Δ; (j) $PhCH_2OH$; (k) DIBAL; (l) $Ph_3P{=}CH(CH_2)_3COOK$; (m) CH_2N_2; (n) TFA, anisole; (o) $PhSO_2Cl$, Et_3N; (p) KOH; (q) NaOMe; (r) DBU, Δ.

Scheme II[a]



[a] (a) $ClSO_2NCO$; (b) Na_2SO_3, KOH; (c) HCl; (d) $PhSO_2Cl$, KOH; (e) B_2H_6; (f) CrO_3–Py; (g) $Ph_3P{=}CHOCH_3$; (h) HCOOH; (i) $Ph_3P{=}CH(CH_2)_3COOK$; (j) CH_2N_2; (k) KOH; (l) NaOMe.

N-exo-trans isomer **18** was also prepared from acid ester **5**. Esterification of **5** with diphenyldiazomethane gave *cis*-diester **12**. Epimerization of **12** with DBU in refluxing toluene to *trans*-diester **13**, followed by removal of the benzhydryl group (TFA, anisole) of the resulting *trans*-diester gave *trans*-acid ester **14** in 40.0% yield from **5**. Curtius rearrangement–alcoholysis, described above, gave benzyl carbamate derivative **15**, which was transformed into (phenylsulfonyl)amino ester **16** by deprotection of the carbobenzoxy group (TFA–anisole) and phenylsulfonylation (phenylsulfonyl chloride–triethylamine) in 57.3% yield. DIBAL reduction of **16** followed by Wittig reaction and esterification afforded **17** in 34.6% yield. Hydrolysis of **17** with KOH gave the desired acid **18** in 88.5% yield, which was converted to sodium salt **19** with sodium methoxide in 97.7% yield. The exo-cis isomer **28** was synthesized by an alternative route as shown in Scheme II starting from amino acid derivative **22** which was easily obtained by hydrolysis of β-lactam compound **21** prepared from norbornene and chlorosulfonyl isocyanate.[6] Sulfonylation of **22** with phenylsulfonyl chloride in 10% aqueous KOH solution gave (phenylsulfonyl)amino acid **23** in 38.6% yield. Reduction of **23** with diborane in THF afforded primary alcohol **24** in 62.3% yield, which was oxidized with PCC to the secondary aldehyde **25** in 62.7% yield. Wittig reaction of **25** with (methoxymethylene)triphenylphosphorane followed by acid treatment gave an unstable product (**26**), which was treated again with Wittig reagent prepared from (4-carboxybutyl)triphenylphosphonium bromide, giving crude acid. Esterification of the acid with diazomethane gave **27** in 30.8% yield from **25**. Hydrolysis and neutralization of **27** gave sodium salt **29** in 94.7% yield.

Biological Results and Discussion

Compounds **11**, **19**, **29**, and reference compounds were examined, using a previously described procedure,[2] for their inhibitory activity against biological responses induced by TXA_2-related substances. The IC_{50} values of these compounds obtained for aggregation of human PRP (platelet-rich plasma) induced by U-46619,[7] rat WP (washed platelets) induced by collagen and contraction of rat thoracic aorta induced by U-46619 are shown in Table I.

As the IC_{50} values varied substantially with each measurement, each value was corrected with the value for the

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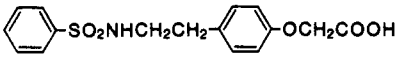
(7) (a) Bundy, G. L. *Tetrahedron Lett.* **1975**, 1957. (b) Coleman, R. A.; Humphrey, P. P. A.; Kennedy, I.; Levy, G. P.; Lumley, P. *Br. J. Pharmacol.* **1981**, *73*, 773.

Table I. Inhibitory Concentrations (IC_{50})

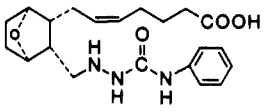
compound	human PRP,[a] μM	rat WP,[b] nM	rat aorta,[c] nM (confidence limit, $P < 0.05$)
1 (Na salt)	0.45[c]	2.9[d]	1.4 (1.1–1.7)
11	2.5	4.1	37.2 (29.4–48.2)
19	3.3	2.9	16.9 (12.3–26.4)
29	2.9	11.0	32.6 (23.9–45.0)
sulotroban	7.2	260	1800[f]
SQ-29548	0.06	3.0	14.5 (12.2–17.1)
ONO-3708	0.90	3.7	52.6 (42.2–65.3)

[a] Aggregation of platelet-rich plasma (PRP) was induced by 4 μM of U-46619. [b] Aggregation of washed platelets (WP) was induced by 4 μg/mL of collagen. [c] Each value represents the mean of triplicate measurements with the pooled PRP of five volunteers. [d] As the value varied from 1.5 to 4.3 nM with each measurement as the standard compounds, each IC_{50} measured by a single experiment for the other compound was corrected with the value for the sodium salt of compound 1. [e] Contraction of rat thoracic aorta induced by 30 nM of U-46619. IC_{50} values measured by three experiments and their confidence limits are indicated. [f] This IC_{50} value was measured in a single experiment.

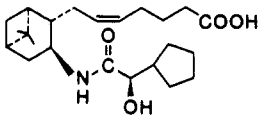
sodium salt of compound 1 as the standard compound. The IC_{50} values of sulotroban,[8] SQ-29548,[9] and ONO-3708[10]



Sulotroban



SQ-29548



ONO-3708

were also used as reference. The large differences between the two kinds of IC_{50} values (μM vs nM) are considered to have arisen mostly from the probable binding of the test compounds to serum proteins. These isomers were found to exhibit similar inhibitory activity against TXA_2-PGH_2 receptor though the potency varied in the range from 2.5 to 3.3 μM for human PRP, from 2.9 nM to 11 μM for rat WP, and from 17 to 37 μM for thoracic aorta. For the newly synthesized compounds, the relative inhibitory activity for rat WP agreed well with that obtained for rat thoracic aorta.[11]

The effects of these stereoisomers on aggregation for human PRP were almost comparable. All of these compounds having a (phenylsulfonyl)amino group as an ω-side chain were found to form intramolecular hydrogen bonding in the free-acid forms between the carboxylic acid and the sulfonylamino group in highly diluted, nonpolar solvents as shown in Table II.[12] Although the correlation of hydrogen bonding with biological activity is not obvious yet, the resulting U-shaped conformation may play an important role in the interaction with TXA_2-PGH_2 receptor. The slight difference of biological activity in these stereoisomers may have arisen from the variety of dihedral bond angles between the α- and ω-side chains and a change of the steric bulkiness in the macrocyclic structure.

Three stereoisomers of compound 1 exhibited higher IC_{50} values in the experiment using rat thoracic aorta than 1, but *N*-exo-trans isomer **19** exhibited an IC_{50} value comparable to that for SQ-29548 and a lower IC_{50} value than that for ONO-3708. In the experiment using human PRP, these stereoisomers exhibited higher IC_{50} values than SQ-29548 or ONO-3708. Although it is difficult to compare the biological activity of 1 and its stereoisomers with other TXA_2 receptor antagonists such as SQ-29548 or ONO-3708 because of their significant differences both in the nucleus and in the ω-side chain, within the limit of the stereoisomers of S-145, these stereoisomers exhibited almost comparable and potent antagonistic activity against responses induced by U-46619.

Conclusion

Three stereoisomers of S-145 1 with variations in the side chain were synthesized as racemates. Although none were as potent as 1, they exhibited efficient TXA_2 antagonistic activity. These stereoisomers exhibited almost comparable inhibitory activity for human PRP. All of these isomers form very similar conformations in the free acid forms in diluted nonpolar solvents by intramolecular hydrogen bonding and the slight difference of biological activity in these compounds may have arisen from the variety of dihedral bond angles between α- and ω-side chains and the change of steric bulkiness in macrocyclic structure.

Experimental Section

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. Measurements of intramolecular hydrogen-bonding in **10**, **18**, and **28** in carbon tetrachloride solution were carried out with a Nicolet 20 SXB Fourier transform infrared (FTIR) spectrometer. The curve-fitting calculations for peak separation of the FTIR spectra were also carried out with the FOCAS program. Proton magnetic resonance (^1H NMR) spectra were obtained on a Varian EM-390 spectrometer using deuteriochloroform unless otherwise stated, with tetramethylsilane as an internal reference. To dry the organic solution of the extraction, anhydrous magnesium sulfate was used. For column chromatography, silica gel (Merck silica gel 60) or Merck's Lobar column was used. Elemental analyses were within ±0.5% of the theoretical values.

2-*endo*-(Carboxymethyl)-3-*endo*-carboxybicyclo[2.2.1]heptane (4). Ozone gas was bubbled at −78 °C into a solution of 10.74 g (80 mmol) of compound **3** in 200 mL of methylene chloride until the solution turned blue. Acetic acid (50 mL) and zinc powder (25 g) were added to the reaction mixture at −78 °C. The mixture was gradually warmed to 20 °C and zinc was removed by decantation. The organic solution was washed with 1%

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(10) (a) Yui, Y.; Sakaguchi, K.; Susawa, T.; Hattori, R.; Takatsu, Y.; Yui, N.; Kawai, C. *Cardiovasc. Res.* **1987**, *21*, 119. (b) Toda, N.; Nakajima, M.; Okumura, T.; Miyazaki, M. *J. Cardiovasc. Pharmacol.* **1986**, *8*, 818. (c) Fujioka, M.; Nagao, T.; Kuriyama, H. *Naunyn-Schmiedeberg's Archiv. Pharmacol.* **1986**, *334*, 468.

(11) A correlation similar to that obtained for IC_{50} values between the aggregation of rat WP and a binding to rat WP has recently been found for the IC_{50} values between rat aorta contraction and binding to rat aorta smooth muscle cells in culture. See: (a) Hanasaki, K.; Nakano, K.; Kasai, H.; Arita, H.; Otani, K.; Doteuchi, M. *Biochem. Biophys. Res. Commun.* **1988**, *150*, 1170. (b) Hanasaki, K.; Nakano, K.; Kasai, H.; Arita, H. *Biochem. Pharmacol.* **1989**, *38*, 2967.

(12) The structural similarity of S-145 (1) with acyclic sulfonamide, sulotroban, and U-46619 is shown by measuring FTIR spectra of them in diluted nonpolar solvents. Takasuka, M.; Yamakawa, M.; Watanabe, F. *J. Chem. Soc., Perkin Trans. II* **1989**, 1173.

Table II. FTIR Spectral Data[a] in CCl_4 (5 cm Cell)

compd	assign[b]		ν, cm^{-1}	ϵ, mol^{-1} dm^3 cm^{-1}	$\Delta\nu_{1/2}$, cm^{-1}	10^8A, cm^2 s^{-1} $molecule^{-1}$	N,[c] %	10^5c,[d] mol dm^{-3}
10	ν_{OH}	F	3529.8	28.4	23.4	8.1		3.3695
		H	3232.2	85.7	227.1	231.5		
	$\nu_{C=O}$	F	1756.1	68.1	21.7	18.1	13.6	
		H	1725.5	69.0	41.5	34.9		
		H	1707.8	505.1	13.5	88.1		
	ν_{NH}	F	3394.4	13.1	22.8	4.1		
		H	3231.6	157.7	63.6	153.0		
18	ν_{OH}	F	3529.2	25.7	26.6	8.0		3.3695
		H	3244.4	88.3	229.5	235.8		
	$\nu_{C=O}$	F	1755.1	75.0	24.9	22.8	14.9	
		H	1720.8	264.9	17.8	67.5		
		H	1708.8	281.3	13.9	51.9		
	ν_{NH}	F	3394.4	14.3	22.8	4.5		
		H	3247.4	126.0	67.4	103.5		
28	ν_{OH}	F	3530.5	48.4	25.2	14.5		3.4437
		H	3235.1	78.1	219.2	205.1		
	$\nu_{C=O}$	F	1757.9	112.7	20.5	29.3	22.5	
		H	1729.9	81.9	42.2	42.1		
		H	1709.2	385.2	14.2	72.0		
	ν_{NH}	F	3394.4	21.6	22.8	6.8		
		H	3232.4	100.8	71.6	102.1		

[a] ν, ϵ, $\Delta\nu_{1/2}$, and A are the band frequency, the molar absorption coefficient, the band width at half-intensity, and the integrated intensity, respectively. [b] ν_{OH}, $\nu_{C=O}$, and ν_{NH} show OH, C=O, and NH stretching vibration bands, respectively, and F and H are free and intramolecular hydrogen bonded bands, respectively. [c] The percentage (N) of non-hydrogen-bonded molecules is the molar absorption coefficient ratio of the band to 100% free $\nu_{C=O}$ band of lauric acid.[12] [d] Concentration.

aqueous sodium bicarbonate and with water, dried, and concentrated in vacuo. The residue was oxidized with Jones' reagent (36 mL) at 0 °C in 200 mL of acetone. After stirring for 4 h at 23 °C, the mixture was allowed to stand overnight at the same temperature, concentrated in vacuo, and diluted with 200 mL of ethyl acetate. The resulting solids were removed by filtration. The filtrate was washed with water, dried, and concentrated in vacuo, giving crude crystals which were recrystallized from a mixture of ether and *n*-hexane to obtain **4** (6.6 g, 41.7%) as colorless prisms: mp 133–136 °C; IR ($CHCl_3$) 2450–3550, 1708 cm^{-1}; ^1H NMR δ 1.25–1.75 (m, 6 H), 2.05–2.70 (m, 4 H), 2.83–3.35 (m, 2 H), 10.32 (br s, 2 H). Anal. ($C_{10}H_{14}O_4$) C, H.

2-*endo*-(Carbomethoxymethyl)-3-*endo*-carboxybicyclo[2.2.1]heptane (5). A suspension of 7.2 g (36.3 mmol) of **4** in 40 mL of acetic anhydride was stirred for 10 min at 100 °C. The resulting solution was concentrated in vacuo, 30 mL of methanol was added, and the mixture was stirred for 20 min under reflux. Concentration of the mixture in vacuo, followed by chromatographic purification of the residue on silica gel ($CHCl_3$), afforded 7.2 g (93.5%) of **5** as a colorless oil: ^1H NMR δ 1.20–1.80 (m, 6 H), 2.15–2.67 (m, 4 H), 2.68–3.10 (m, 2 H), 3.63 (s, 3 H), 10.49 (br s, 1 H). Anal. ($C_{11}H_{16}O_4$) C, H.

2-*endo*-(Carbomethoxymethyl)-3-*endo*-(carbobenzoxyamino)bicyclo[2.2.1]heptane (6) and 2-*endo*-(Carbomethoxymethyl)-3-*exo*-(carbobenzoxyamino)bicyclo[2.2.1]heptane (15). Triethylamine (3.61 mL, 20 mmol × 1.3) and ethyl chloroformate (2.49 mL, 20 mmol × 1.3) were added to a solution of 4.25 g (20 mmol) of compound **5** in 40 mL of acetone at 0 °C. The mixture was stirred for 45 min at 0 °C, and a solution of 1.95 g (20 mmol × 1.5) of sodium azide in 20 mL of water was added to the reaction mixture at 0 °C. After being stirred for 1 h, the mixture was partitioned between ether and water. The organic solution was washed with 0.1 N HCl and with water, dried, and concentrated in vacuo. The residue dissolved in 50 mL of benzene was stirred for 1 h under reflux. Benzyl alcohol (5 mL) and triethylamine (3.6 mL) were added at 80 °C, and the reaction mixture was stirred for 3 h under reflux. After cooling, the mixture was washed with 0.1 N HCl and water, dried, and concentrated in vacuo, giving an oil which when chromatographed on silica gel (toluene–ethyl acetate, 95:5) gave 3.75 g (59.1%) of **6** as colorless prisms: mp 70 °C; ^1H NMR δ 1.25–1.63 (m, 6 H), 2.07–2.70 (m, 5 H), 3.58 (s, 3 H), 4.11 (t-d, J = 9, 5 Hz, 1 H), 4.90 (d, J = 9 Hz, 1 H), 5.07 (s, 2 H), 7.34 (s, 5 H). Anal. ($C_{18}H_{23}NO_4$) C, H, N.

Compound **15** was also prepared from **14** in a similar manner to that described above: colorless oil; ^1H NMR δ 1.05–1.70 (m, 6 H), 1.93 (m, 1 H), 2.22 (br s, 2 H), 2.34, 2.72 (ABq-d, J = 16, 8, 7 Hz, 2 H), 3.03 (m, 1 H), 3.64 (s, 3 H), 4.80 (br s, 1 H), 5.09 (s, 2 H), 7.38 (s, 5 H). Anal. ($C_{18}H_{23}NO_4$) C, H, N.

(5*Z*)-7-[3-*endo*-(Carbobenzoxyamino)bicyclo[2.2.1]hept-2-*endo*-yl]heptenoic Acid Methyl Ester (8) and (5*Z*)-7-[3-*exo*-[(Phenylsulfonyl)amino]bicyclo[2.2.1]hept-2-*endo*-yl]-heptenoic Acid Methyl Ester (17). DIBAL (1.0 M solution in hexane, 5.35 mL, 3.15 mmol × 1.7) was added to a solution of 1.00 g (3.15 mmol) of **6** in 10 mL of toluene at −78 °C. After being stirred for 45 min at the same temperature, the reaction mixture was poured into a mixture of ethyl acetate and 2 N HCl. The organic layer was washed with water, dried, and concentrated in vacuo, giving a colorless oil **7**: ^1H NMR δ 1.15–2.33 (m, 9 H), 2.33–2.75 (m, 2 H), 3.87 (br s, 1 H), 4.03 (d-d, J = 11, 6 Hz, 1 H), 5.14 (s, 2 H), 5.70 (t-d, J = 3, 8 Hz, 1 H), 7.36 (s, 5 H). In a separate flask, sodium hydride (60% in mineral oil, 907 mg, 3.15 mmol × 7.2) was suspended in 40 mL of DMSO and the mixture was stirred for 1.5 h at 75 °C. After cooling to 12 °C, a solution of 5.58 g (3.15 mmol × 4) of (4-carboxybutyl)triphenylphosphonium bromide in 10 mL of DMSO was added and the red mixture was stirred for 20 min at 20 °C. To this red solution was added a solution of the crude oil obtained above in 10 mL of DMSO at 20 °C. The reaction mixture was stirred for 2.5 h at the same temperature and partitioned between ethyl acetate and 0.2 N HCl. The organic solution was washed with water, dried, and concentrated in vacuo, giving the crude acid, which was treated with a solution of diazomethane in ether as usual. Concentration of the solution in vacuo, followed by chromatographic purification of the residue on silica gel (*n*-hexane–ethyl acetate, 9:1), gave 416 mg (34.3%) of **8** as a colorless oil: IR ($CHCl_3$) 3440, 1720, 1505 cm^{-1}; ^1H NMR δ 1.36 (br s, 6 H), 1.55–2.43 (m, 9 H), 2.36 (t, J = 7 Hz, 2 H), 3.62 (s, 3 H), 4.03 (m, 1 H), 4.90 (d, J = 9 Hz, 1 H), 5.06 (s, 2 H), 5.27 (m, 2 H), 7.31 (s, 5 H). Anal. ($C_{23}H_{31}NO_4$) C, H, N. Compound **17** was obtained from **16** in a similar manner to that described above: colorless pillars; mp 70 °C; ^1H NMR δ 0.75–2.40 (m, 15 H), 2.26 (t, J = 7 Hz, 2 H), 2.55 (m, 1 H), 3.68 (s, 3 H), 4.90 (d, J = 7 Hz, 1 H), 5.18 (m, 1 H), 7.36–7.75 (m, 3 H), 7.75–8.10 (m, 2 H). Anal. ($C_{21}H_{29}NO_4S$) C, H, N, S.

(5*Z*)-7-[3-*endo*-[(Phenylsulfonyl)amino]bicyclo[2.2.1]-hept-2-*endo*-yl]heptenoic Acid Methyl Ester (9) and 2-*endo*-(Carbomethoxymethyl)-3-*exo*-[(phenylsulfonyl)-amino]bicyclo[2.2.1]heptane (16). A mixture of compound **8** (200 mg, 0.51 mmol), trifluoroacetic acid (3 mL), and anisole (0.5 mL) was stirred for 4 h at 45 °C and concentrated in vacuo, giving an oily residue. A mixture of the residue, phenylsulfonyl chloride (99 μL, 0.51 mmol × 1.5), and triethylamine (215 μL, 0.51 mmol × 3) in methylene chloride (4 mL) was stirred for 15 min at 0 °C and then partitioned between ethyl acetate and 0.1 N HCl. The organic solution was washed with water and with 1% aqueous

sodium bicarbonate, dried, and concentrated in vacuo. Chromatography of the residue on silica gel (*n*-hexane–ethyl acetate, 9:1) gave compound **9** (160 mg, 80.4%) as colorless prisms: mp 79 °C; ^{1}H NMR δ 1.05–2.25 (m, 15 H), 2.29 (t, J = 8 Hz, 2 H), 3.60 (m, 1 H), 3.66 (s, 3 H), 5.03 (d, J = 9 Hz, 1 H), 5.26 (m, 2 H), 7.33–7.60 (m, 3 H), 7.70–8.00 (m, 2 H). Anal. ($C_{21}H_{29}NO_4S$) C, H, N, S.

Compound **16** was prepared from **15** in a similar manner to that described above: colorless oil; ^{1}H NMR δ 0.77–1.75 (m, 6 H), 1.75–2.40 (m, 5 H), 2.47 (t, J = 5 Hz, 1 H), 3.57 (s, 3 H), 5.35 (d, J = 5 Hz, 1 H), 7.36–7.67 (m, 3 H), 7.80–8.03 (m, 2 H). Anal. ($C_{16}H_{21}NO_4S$) C, H, N, S.

(5*Z*)-7-[3-*endo*-[(Phenylsulfonyl)amino]bicyclo[2.2.1]-hept-2-*endo*-yl]heptenoic Acid (10), (5*Z*)-7-[3-*exo*-[(Phenylsulfonyl)amino]bicyclo[2.2.1]hept-2-*endo*-yl]heptenoic Acid (18), and (5*Z*)-7-[3-*exo*-[(Phenylsulfonyl)amino]bicyclo[2.2.1]hept-2-*exo*-yl]heptenoic Acid (28). To a solution of compound **9** (120 mg, 0.306 mmol) in 2 mL of methanol was added 0.61 mL (0.61 mmol) of 1 N KOH at 0 °C, and the mixture was stirred for 8 h at the same temperature. The reaction mixture was partitioned between ether and water. The aqueous layer was acidified with 2 N HCl and extracted with ethyl acetate. The organic solution was washed with water, dried, and concentrated in vacuo, giving crude crystals, which were recrystallized from petroleum ether to obtain 109 mg (94.3%) of compound **10** as colorless pillars: mp 104–106 °C; ^{1}H NMR δ 1.05–2.25 (m, 15 H), 2.33 (t, J = 7 Hz, 2 H), 3.63 (t-d, J = 9, 3 Hz, 1 H), 5.25 (m, 2 H), 5.44 (d, J = 9 Hz, 1 H), 7.33–7.70 (m, 3 H), 7.75–8.03 (m, 2 H), 9.10 (br s, 1 H). Anal. ($C_{20}H_{27}NO_4S$) C, H, N, S. Compound **18** and **28** were also obtained in a similar way to that described above. Compound **18**: 88.5%; colorless pillars; mp 82–83 °C; ^{1}H NMR δ 0.83–2.27 (m, 15 H), 2.31 (t, J = 7 Hz, 2 H), 2.53 (m, 1 H), 5.00 (d, J = 7 Hz, 1 H), 5.17 (m, 2 H), 7.35–7.70 (m, 3 H), 7.80–8.05 (m, 3 H). Anal. ($C_{20}H_{27}NO_4S$) C, H, N, S. Compound **28**: 100%; colorless gum; ^{1}H NMR δ 0.85–2.23 (m, 15 H), 2.36 (t, J = 8 Hz, 2 H), 3.32 (t, J = 8 Hz, 1 H), 5.25 (d, J = 8 Hz, 1 H), 5.36 (m, 2 H), 7.40–8.03 (m, 5 H), 8.48 (br s, 1 H). Anal. ($C_{20}H_{27}NO_4S$) C, H, N, S. These acids **10**, **18**, and **28** were transformed into their sodium salts **11**, **19**, and **29**, respectively, for biological assay by neutralizing them with sodium methoxide in methanol at 0 °C, followed by freeze-drying of the aqueous solution.

2-*endo*-(Carbomethoxymethyl)-3-*endo*-[(diphenylmethoxy)carbonyl]bicyclo[2.2.1]heptane (12). To a solution of **5** (7.0 g, 33 mmol) in 30 mL of ethyl acetate was added 6.4 g (33 mmol) of diphenyldiazomethane at 0 °C. The mixture was stirred for 2.5 h at 45 °C and concentrated in vacuo, giving crude diester. Chromatography of the diester on silica gel (*n*-hexane–ethyl acetate, 98:2) gave 7.3 g (58.4%) of **12** as a colorless oil: ^{1}H NMR δ 1.15–1.75 (m, 6 H), 2.10–3.20 (m, 6 H), 3.46 (s, 3 H), 6.79 (s, 1 H), 7.32 (s, 10 H).

2-*endo*-(Carbomethoxymethyl)-3-*exo*-[(diphenylmethoxy)carbonyl]bicyclo[2.2.1]heptane (13). A mixture of **12** (5.30 g, 14 mmol) and DBU (2.09 mL, 14 mmol) in 50 mL of toluene was stirred for 3 days under reflux. After cooling, the reaction mixture was washed with 0.2 N HCl and with water, dried, and concentrated in vacuo. The crude crystals were recrystallized from petroleum ether, giving 3.70 g (69.8%) of compound **13**: colorless pillars; mp 65 °C; ^{1}H NMR δ 1.10–1.75 (m, 6 H), 1.98 (m, 1 H), 2.13–2.75 (m, 5 H), 3.49 (s, 3 H), 6.87 (s, 1 H), 7.35 (s, 10 H). Anal. ($C_{24}H_{26}O_4$) C, H.

2-*endo*-(Carbomethoxymethyl)-3-*exo*-carboxybicyclo[2.2.1]heptane (14). A mixture of **13** (3.70 g, 9.78 mmol), anisole (7.6 mL), and trifluoroacetic acid (7.6 mL) was stirred for 1 h at 0 °C. After concentration in vacuo, the residue was chromatographed on silica gel (chloroform–methanol, 95:5), giving 2.06 g (98.1%) of compound **14** as a colorless oil: ^{1}H NMR δ 1.05–2.00 (m, 7 H), 2.20–2.70 (m, 5 H), 3.67 (s, 3 H), 9.40 (br s, 1 H). Anal. ($C_{11}H_{16}O_4$) C, H.

2-*exo*-Carboxy-3-*exo*-[(phenylsulfonyl)amino]bicyclo[2.2.1]hexane (23). To a solution of **22** (12.42 g, 80 mmol) in 10% aqueous KOH (100 mL) was added 5.1 mL (40 mmol) of phenylsulfonyl chloride at 0 °C. The mixture was stirred for 20 min at 0 °C and 5.1 mL (40 mmol) of phenylsulfonyl chloride was added again at the same temperature. The mixture was diluted with ether, washed with 2 N HCl and water, dried, and concentrated in vacuo. The residue was purified by chromatography on silica gel (chloroform–methanol, 98:2) to obtain 9.10 g (38.6%) of **23** as colorless prisms: mp 148 °C; ^{1}H NMR δ 0.80–2.05 (m, 6 H), 1.86 (br s, 1 H), 2.49 (br s, 1 H), 2.73 (d, J = 8 Hz, 1 H), 3.66 (t, J = 8 Hz, 1 H), 6.70 (d, J = 8 Hz, 1 H), 7.70 (br s, 1 H), 7.37–8.05 (m, 5 H). Anal. ($C_{14}H_{17}NO_4S$) C, H, N, S.

2-*exo*-(Hydroxymethyl)-3-*exo*-[(phenylsulfonyl)amino]bicyclo[2.2.1]heptane (24). To a solution of **23** (3.40 g, 11.51 mmol) in 10 mL of THF was added a solution of diborane (1.0 M solution in THF, 80 mL, 80 mmol) at 0 °C. The mixture was stirred for 4 h at 20 °C and partitioned between ethyl acetate and 0.2 N HCl. The organic solution was washed with water, dried, and concentrated in vacuo. Chromatography of the residue on silica gel (toluene–ethyl acetate, 4:1) gave 3.22 g (99%) of **24** as a colorless gum: ^{1}H NMR δ 0.80–2.00 (m, 7 H), 2.04 (br s, 2 H), 2.40 (br s, 1 H), 3.30 (t, J = 8 Hz, 1 H), 3.66 (m, 2 H), 5.81 (d, J = 8 Hz, 1 H), 7.45–8.10 (m, 5 H). Anal. ($C_{14}H_{19}NO_3S$) C, H, N, S.

2-*exo*-Formyl-3-*exo*-[(phenylsulfonyl)amino]bicyclo[2.2.1]heptane (25). A mixture of **24** (3.5 g, 12.45 mmol) and PCC (16.1 g, 74.7 mmol) in 500 mL of methylene chloride was stirred for 1.5 h at 20 °C. The mixture was passed through silica gel (50 g, toluene–ethyl acetate, 2:1) and concentration of the eluate gave 1.96 g (56.3%) of **25** as a colorless gum: ^{1}H NMR δ 0.95–1.90 (m, 6 H), 2.01 (br s, 1 H), 2.50 (br s, 1 H), 2.60 (d-t, J = 8, 1 Hz, 1 H), 3.61 (t-d, J = 8, 1 Hz, 1 H), 5.62 (d, J = 8 Hz, 1 H), 7.35–8.00 (m, 5 H), 9.56 (d, J = 1 Hz, 1 H). Anal. ($C_{14}H_{17}NO_3S$) C, H, N, S.

(5*Z*)-7-[3-*exo*-[(Phenylsulfonyl)amino]bicyclo[2.2.1]-hept-2-*exo*-yl]heptenoic Acid Methyl Ester (27). To a suspension of methoxymethylphosphonium chloride (2.40 g, 7 mmol) in 20 mL of THF was added *n*-butyllithium (1.6 M solution in *n*-hexane, 3.75 mL, 6 mmol) at −78 °C. The mixture was stirred for 20 min at 0 °C and a solution of **25** (558 mg, 2 mmol) in 5 mL of THF was added to the mixture at −78 °C. After raising of the temperature of the reaction mixture to 20 °C over 30 min, the mixture was partitioned between ethyl acetate and water. The organic solution was washed with water, dried, and concentrated in vacuo, giving the crude methoxyvinyl derivative. After treatment of the crude product with 90% formic acid (0.5 mL) for 20 min at 20 °C, the mixture was neutralized with 5% aqueous sodium bicarbonate and extracted with ethyl acetate. The organic solution was washed with water, dried, and concentrated in vacuo, giving 270 mg of **26**, which was unstable and used immediately for the next reaction without further purification. The signal of the aldehyde proton of **26** was not observed in its ^{1}H NMR spectrum. Sodium hydride (60% in mineral oil, 460 mg, 0.92 mmol × 7 × 1.8) was suspended in 15 mL of DMSO and the mixture was stirred for 1.5 h at 70 °C. After cooling to 12 °C, 2.84 g (0.92 mmol × 7) of (4-carboxybutyl)triphenylphosphonium bromide was added and the red solution was stirred for 15 min at the same temperature. To the red solution was added a solution of **26** (270 mg, 9.92 mmol) in 5 mL of DMSO at 12 °C, and the mixture was stirred for 1.5 h at 20 °C and partitioned between ethyl acetate and 2 N HCl. The organic solution was washed with water, dried, and concentrated in vacuo, giving the crude acid, which was treated with a solution of diazomethane in ether as usual. Concentration of the solution in vacuo, followed by chromatographic purification of the residue on silica gel (*n*-hexane–ethyl acetate, 4:1) gave 241 mg (30.8% from **25**) of **27** as a colorless gum: ^{1}H NMR δ 0.80–2.20 (m, 15 H), 2.30 (t, J = 7 Hz, 2 H), 3.30 (t, J = 8 Hz, 1 H), 3.67 (s, 3 H), 4.80 (d, J = 8 Hz, 1 H), 5.33 (m, 2 H), 7.35–8.03 (m, 5 H). Anal. ($C_{21}H_{29}NO_4S$) C, H, N, S.

Biology. Tests, using methods described previously,[2] gave the results presented in Table I.[13]

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(13) IC_{50} values for platelet aggregation were measured by H. Kakushi and IC_{50} values for contraction of rat thoracic aorta were measured by K. Otani of Shionogi Laboratories. Their contribution to this study is gratefully acknowledged.