Synthesis of Thromboxane Receptor Antagonists with Bicyclo[3.1.0]hexane Ring Systems

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Thromboxane A_2 receptor antagonists **11a**, **15a**, **26a**, **30a**, **34a**, **36a**, **46a**, **52a**, **61a**, **72a**, and **82a**, which contain 6-oxabicyclo[3.1.0]hexane, 6-thiabicyclo[3.1.0]hexane, bicyclo[3.1.0]hexane, or 6,6-dimethylbicyclo[3.1.0]hexane ring systems with heptenoic and (phenylsulfonyl)amino side chains, and their corresponding sodium salts and methyl esters were synthesized. This study then examined the inhibitory effects of their sodium salts for the platelet aggregation induced by arachidonic acid with rabbit platelet-rich plasma and platelet aggregation induced by collagen with rat washed platelets.

Thromboxane A_2 (TXA_2) is a short-lived arachidonic acid metabolite[1] and a powerful inducer of platelet aggregation[2] and vascular[3] and respiratory smooth muscle constriction.[4] The structure of TXA_2 was originally proposed on the basis of structural studies carried out on its degradation products and metabolites, and was finally confirmed by the synthetic work of Still and co-workers.[5]

As the formation of TXA_2 plays a role in the pathogenesis of myocardial ischemia and thrombosis,[6] considerable efforts have been directed toward the synthesis of agents that would either inhibit TXA_2 biosynthesis[7] or block the action of TXA_2 at the receptor level.[7] As the inhibition of TXA_2 formation by thromboxane synthetase inhibitor would be considered to lead to accumulation of prostaglandin H_2 (PGH_2), which is also considered to exert TXA_2-like activity via the common receptor,[8] the latter approach has been considered to be more attractive and effective.[9]

Due to the short half-life of TXA_2 or PGH_2, the synthesis of several stable analogues of TXA_2 or PGH_2 with modified ring systems has been attempted to evaluate their biological characteristics.[10] For these purposes, one or both oxygen atoms have been replaced by carbon units or nitrogen or sulfur atoms, or the oxygen and carbon atoms have been transposed in their oxabicyclo[3.1.1]heptane or 2,2-dioxa[2.2.1]heptane ring systems. Further modification of these analogues led to the discovery of several derivatives that have been reported to be potent TXA_2 receptor antagonists and some of them have been evaluated in clinical studies.

Recently, the (phenylsulfonyl)amino function of the non-prostanoid TXA_2 antagonist BM-13,177[11] has been applied to PGH_2 or TXA_2 analogues with bicyclic ring systems of norbornane, pinane, and oxabicyclo[2.2.1]heptane, and extremely potent and effective TXA_2 antagonistic activity both in vitro and in vivo has been found.[12] Among a number of compounds, *dl*-7-[3-*endo*[(phenylsulfonyl)amino]bicyclo[2.2.1]hept-2-*exo*-yl]-5(*Z*)-heptenoic acid (S-145) has been reported to have remarkably high potency in the therapy of various TXA_2-mediated pathophysiological disorders and is presently undergoing extensive clinical trials.

In our attempt to design thromboxane receptor antagonists, we chose compounds with the bicyclo[3.1.0]hexane ring system that retains a certain structural similarity to TXA_2. Replacement of two oxygen functions of the 2,6-dioxabicyclo[3.1.1]heptane ring system of TXA_2 by their carbon equivalent and the subsequent elimination of either one of the bridged carbon atoms led to the bicyclo[3.1.0]hexane ring system. In the compounds designed, which can be represented by the general formula A, we

TXA_2 [A] X=O, S, CH_2, $C(CH_3)_2$

retained the α-heptenoic acid side chain and replaced the ω-octenol side chain by a (phenylsulfonyl)amino function. The carbon atom at the 6-position of the bicyclic ring system was further replaced by oxa, thia, and dimethylcarba functions. In each case, synthesis of the stereoisomers with respect to the stereochemical relationship of the α-carboxylic side chain to the (phenylsulfonyl)amino side chain or bicyclic ring juncture was attempted. From observations of the structure–activity relationships of the synthesized compounds, we also expected to obtain some information about the stereoelectronic requirement of the 6′-oxygen or 7-carbon function of the TXA_2 2,6-dioxabicyclo[3.1.1]heptane ring system for the affinity to the receptor.

Chemistry

Stereoisomers of 6-oxabicyclo[3.1.0]hex-2-yl-5(*Z*)-heptenoic acid derivatives, **11a** and **15a**, in which the (phenylsulfonyl)amino group was substituted at the 3-position and in the trans relation to the 2-heptenoic acid side chain, were synthesized according to the reaction sequences described in Scheme I. 2-(4-Hydroxycyclopenten-3-yl)ethanol (**1**)[13] was converted to its mono(triphenylmethyl

(1) Hamberg, M.; Svensson, J.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 2994.
(2) Svensson, J.; Hamberg, M.; Samuelsson, B. *Acta Phisiol. Scand.* **1976**, *98*, 285.
(3) Hamberg, M.; Hadquvist, P.; Strandberg, K.; Svensson, J.; Samuelsson, B. *Life Sci.* **1975**, *16*, 451.
(4) (a) Samuelsson, B.; Folco, G.; Granstrom, E.; Kindahl, H.; Malmsten, C. *Adv. Prostaglandin Thromboxane Res.* **1978**, *4*, 1. (b) Ogletree, M. L. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1987**, *46*, 133.
(5) Bhagwat, S. S.; Hamann, P. R.; Still, W. C. *J. Am. Chem. Soc.* **1985**, *107*, 6372.
(6) (a) Moncada, S.; Vane, J. R. *Pharmacol. Rev.* **1979**, *30*, 293. (b) Moncada, S.; Vane, J. R. In *Enzyme Inhibitors as Drugs*; Sander, M., Ed.; McMillan: London, 1980; p 249. (c) Lefer, A. H.; Darius, H. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1987**, *46*, 144.
(7) (a) Cross, P. E. *Annu. Rep. Med. Chem.* **1982**, *17*, 79. (b) Cross, P. E.; Dickinson, R. P. *Annu. Rep. Med. Chem.* **1987**, *22*, 95.
(8) (a) Charo, I. F.; Feinman, R.; Detwiler, T.; Smith, J. B.; Ingerman, C. M.; Silver, M. J. *Nature (London)* **1977**, *269*, 66. (b) Coleman, R. A.; Humphrey, P. P. A.; Kennedy, I.; Levy, G. P.; Lumley, P. *Br. J. Pharmacol.* **1981**, *73*, 773.
(9) A review: Lefer, A. M. *Drugs Today* **1985**, *21*, 283.
(10) A review: Newton, R. F.; Roberts, S. M.; Taylor, R. K. *Synthesis* **1984**, 449.
(11) Mannhold, R. *Drugs Future* **1984**, *9*, 804.
(12) 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. (b) Seno, K.; Hagishita, S. *Chem. Pharm. Bull.* **1989**, *37*, 327, 948, 1524.

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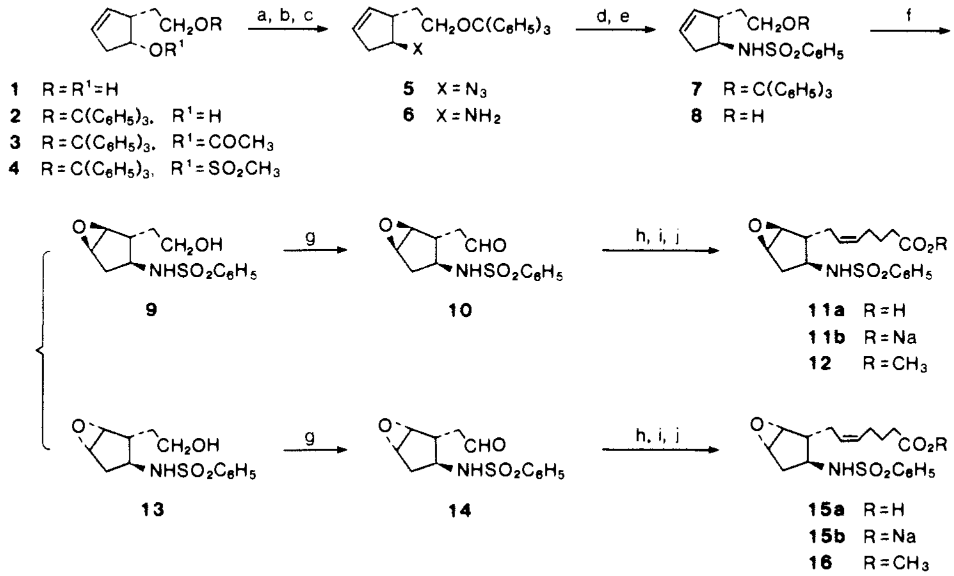
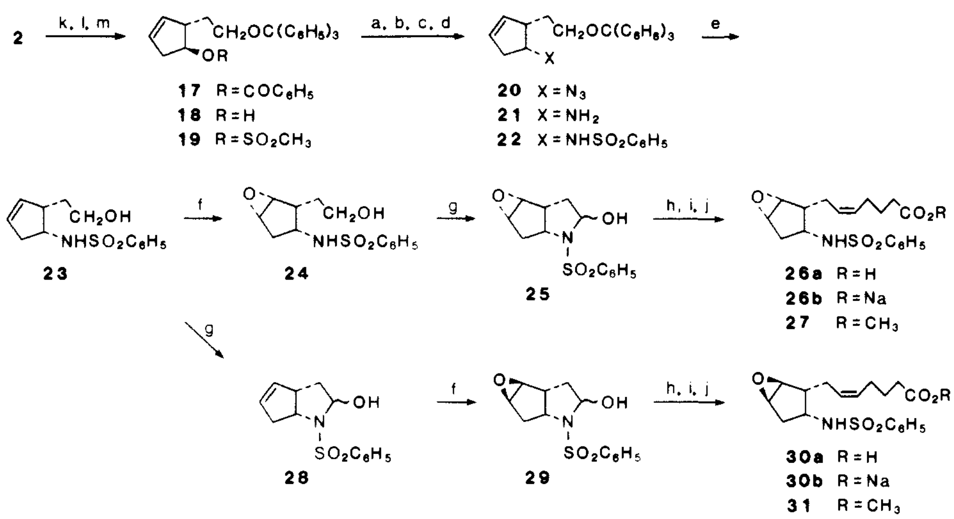
Scheme I[26]



Scheme II[26]

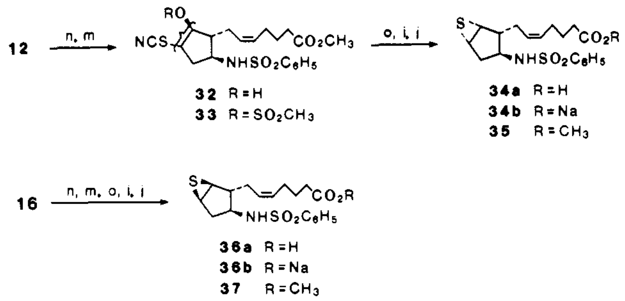


ether) derivative **2** and then transformed to the corresponding acetate **3** or methanesulfonate **4** by the usual reaction procedures. Compound **4** was converted to azide derivative **5** with sodium azide in *N*,*N*-dimethylformamide (DMF). Subsequent reduction of **5** with triphenylphosphine and hydrolysis of the resulting phosphine imino derivative with water gave the amine derivative **6**. Sulfonylation of **6** with benzenesulfonyl chloride and triethylamine gave the (phenylsulfonyl)amino derivative **7** whose triphenylmethyl substituent was subsequently hydrolyzed with acid to obtain **8**. Epoxidation of **7** with 3-chloroperbenzoic acid proceeded smoothly and gave preferentially the triphenylmethyl ether of **9** although the hydrolysis of the triphenylmethyl group with acid failed to give **9** due to the lability of the epoxide function to acid. The selectivity of the epoxidation was probably due to the steric effect of the (triphenylmethoxy)ethyl substituent and also to the interaction between the sulfonamide proton and the reagent.[14] On the other hand, stereocontrol by the directing effect of the free hydroxy group in **8** was not observed as expected and epoxidation of **8** provided a mixture of **9** and **13** in a 2:1 ratio (in 66% yield). The steric effect of the hydroxyethyl group or the directing effect of the (phenylsulfonyl)amino group might overcome the directing effect of the hydroxy group in this epoxidation. To secure the structure of **9** and **13**, the stereochemistry of **9** was confirmed by X-ray crystallographic analysis. Swern oxidation[15] of **9** yielded the aldehyde **10**. Wittig reaction of **10** with 3 equiv of ylide, prepared from (4-carboxybutyl)triphenylphosphonium bromide and dimsylsodium in dimethyl sulfoxide (DMSO) at room temperature produced the desired 5(*Z*)-heptenoic acid derivative **11a**. Treatment of **11a** with 1 equiv of aqueous NaOH and lyophilization gave **11b** for biological examination studies. Esterification of **11a** with diazomethane in ether gave methyl ester **12**. By the same procedure, the isomeric (phenylsulfonyl)amino alcohol derivatives **13** were converted to **15a,b** and **16**.

According to the reaction sequence described in Scheme II, the other two stereoisomers of 6-oxabicyclo[3.1.0]hex-2-yl-5(*Z*)-heptenoic acid derivatives, **26a** and **30a**, in which the (phenylsulfonyl)amino group and the 2-heptenoic acid side chain are in a cis relationship, were synthesized. Mitsunobu reaction[16] of **2** with diethyl azodicarboxylate,

(13) Corey, E. J.; Noyori, R. *Tetrahedron Lett.* **1970**, 311.
(14) (a) Pyne, S. G.; Hensel, M. J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1982**, *104*, 5719. (b) Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1984**, *25*, 1587.
(15) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
(16) A review: Mitsunobu, O. *Synthesis* **1981**, 1.

Scheme III[26]



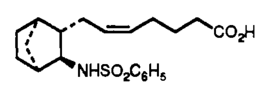
triphenylphosphine, and benzoic acid gave **17** accompanied by cyclopenta-1,3-dienylethanol trityl ether. The benzoyl group was hydrolyzed to obtain **18**, which was further converted to the (phenylsulfonyl)amino derivative **22** and the corresponding hydrolysis product **23** by the sequence used for the conversion of **2** to **7** and **8**. Epoxidation of **23** with 3-chloroperbenzoic acid gave **24** stereospecifically with no trace of the stereoisomer of the epoxide. The stereospecificity seems to result from the synergistic directing effects of the hydroxyethyl and (phenylsulfonyl)amino groups. Swern oxidation of **24** afforded the aldehyde derivative **25**, which mainly existed in a cyclic aminal form due to the cis relationship of the two side chains. To obtain the isomeric epoxide, compound **23** was converted to the cyclic animal derivative **28** by Swern oxidation. Epoxidation of **28** proceeded from the sterically less hindered side and compound **29** was obtained as the sole product. These compounds **25** and **29** were also converted to **26a,b** and **27** or **30a,b** and **31**, respectively, by the procedure described for the conversion of **10** to **11a,b** and **12**.

To obtain 6-thiabicyclo[3.1.0]hex-2-yl-5(*Z*)-heptenoic acid derivative **34a**, compound **12** was treated with thiocyanic acid to give a mixture of the regioisomers of the thiocyano alcohol derivatives **32** (Scheme III). The methanesulfonate (**33**) of **32**, treated with KOH in a methanol–dioxane mixture, gave **34a**. By the same procedure, compound **16** was converted to **36a**. Compounds **34a** and **36a** were also converted to their sodium salt or methyl ester derivatives, **34b**, **35**, **36b**, and **37**.

Table I. Inhibition of Platelet Aggregation by Bicyclo[3.1.0]hexane Analogues

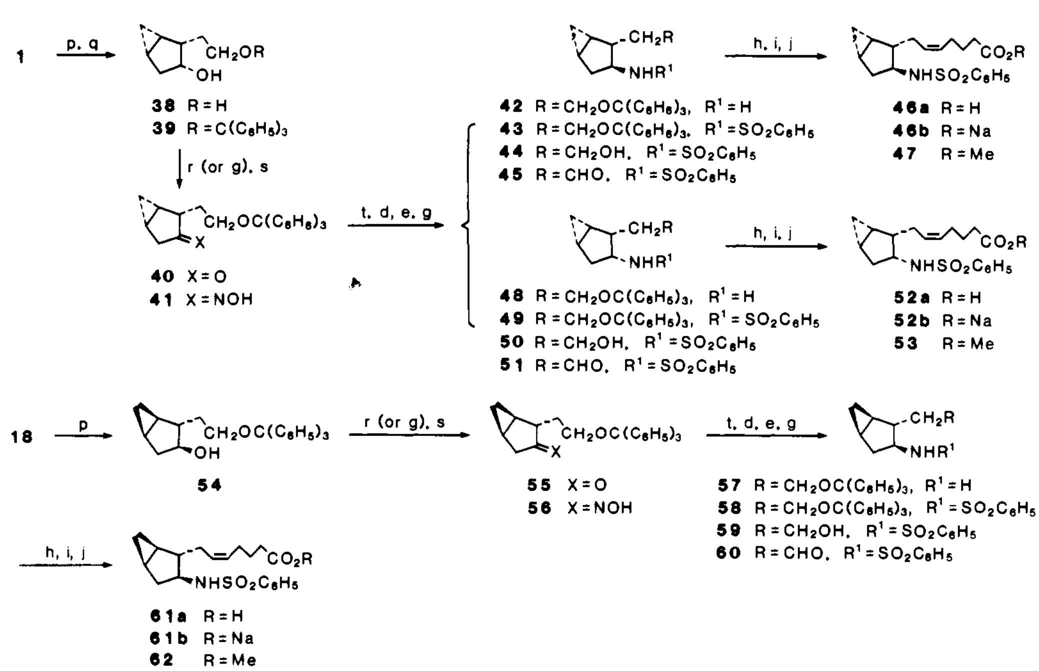
	rabbit PRP[a]	rat WP[b]	
compd	IC_{50}, μM	IC_{50}, nM	relative agonist activity[c]
S-145[f]	1.0[d]	1.0[e]	100
15b	2.6	4.0	82
26b	49.1	23.0	26
11b	391.1	100.0	0
34b	11.3	2.9	74
36b	178.1	10.0	0
46b	5.3	8.3	67
52b	37.8	25.0	33
61b	11.3	12.5	22
82b	44.0	4.3	22
72b	438.4	4.1	11

[a] Aggregation of platelet-rich plasma (PRP) was induced by 500 μM of arachidonic acid. [b] Aggregation of washed platelets (WP) was induced by 4 μg/mL of collagen. [c] The partial agonistic activity (shape change of rate WP) induced by test compound at 1 μM was calibrated for that of S-145. [d] The value varied from 0.9 to 1.9 μM for every measurement as the standard compound; thus, each IC_{50} measured by three experiments for the other compound was corrected for the value for S-145. The relative ranges of three values of IC_{50}'s to their average were approximately 20% for most of comparative compounds. [e] The value varied from 0.8 to 2.5 nM on every measurement as the standard compound; thus, each IC_{50} measured by three experiments for the other compound was corrected for the value for S-145. The relative ranges of three values of IC_{50}'s to their average were approximately 20% for most of comparative compounds. [f] *dl*-7-[3-*endo*-[(Phenylsulfonyl)amino]bicyclo[2.2.1]hept-2-*exo*-yl]-5(*Z*)-heptenoic acid:

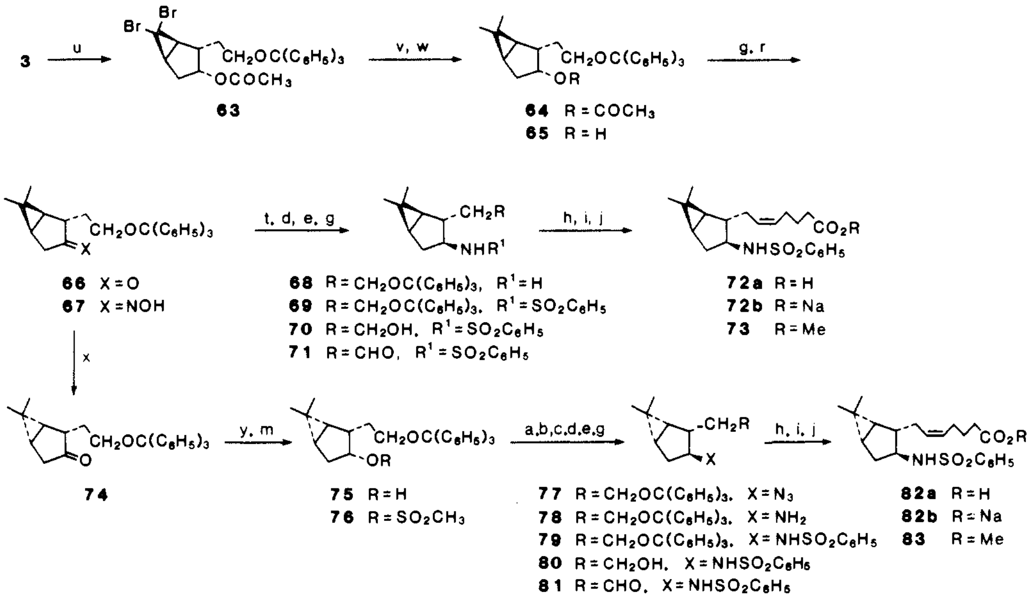


Next, we synthesized the stereoisomers of bicyclo[3.1.0]hex-2-yl-5(*Z*)-heptenoic acid derivatives, **46a**, **52a**, and **61a**, in which the (phenylsulfonyl)amino group was substituted at the 3-position and in the trans or cis relation to the heptenoic acid side chain. Stereocontrolled cyclopropanation of **1** by Simmons–Smith reagent prepared with a Zn(Ag) couple and diiodomethane gave **38** (Scheme IV). Compound **39**, the trityl ether of **38**, was oxidized with pyridinium dichromate (PDC) in DMF or by Swern oxidation to give keto derivative **40**. The corresponding

Scheme IV[26]



Scheme V[26]



oxime **41** was reduced to the mixture of amino derivatives by application of the method developed by Barton et al.[17] which includes the reaction with diphenyl disulfide and tri-*n*-butylphosphine in tetrahydrofuran (THF) followed by reduction of the resulting (phenylsulfonyl)imino intermediate with sodium cyanoborohydride in acetic acid (AcOH). After phenylsulfonylation of the reaction mixture, hydrolysis of the trityl ether and separation by column silica gel chromatography, compound **44** and its isomer **50** were isolated. On the other hand, stereocontrolled cyclopropanation of alcohol **18** by the same Simmons–Smith reagent gave **54**. Compound **54** was oxidized to the ketone derivative **55** with PDC in DMF and the corresponding oxime **56** was reduced by the same procedure as described for the reduction of **41**. After phenylsulfonylation of the amine and the following hydrolysis, only stereoisomer **59** was obtained in good total yield. These (phenylsulfonyl)amino alcohol derivatives **44**, **50**, or **59** were converted to their corresponding acid, sodium carboxylate, or ester derivatives **46a,b** and **47** or **52a,b** and **53** or **61a,b** and **62**, respectively by the procedure described for the conversion of **9** to **11a,b** and **12**.

Preparation of the stereoisomers of the 3-(phenylsulfonyl)amino derivative of 7-(6,6-dimethylbicyclo[3.1.0]hex-2-yl-5(*Z*)-heptenoic acid, **72a** and **82a**, was also examined. Addition of dibromocarbene occurred from the sterically less hindered side when **3** was allowed to react with bromoform and benzyltriethylammonium chloride in a refluxing mixture of 40% aqueous NaOH and dichloromethane, and **63** was obtained in 84% yield (Scheme V). Reaction of **63** with $Me_2CuSCNLi_2$ and hexamethylphosphoramide (HMPA) in ether followed by methylation with methyl iodide[18] gave the dimethyl derivative **64**. The stereochemistry of the introduced dimethylcyclopropyl function was confirmed by X-ray crystallographic analysis of **64**. Swern oxidation of hydrolysis product **65** gave the keto derivative **66**. The enolate of **66** produced under thermodynamically controlled conditions was protonated under kinetically controlled conditions and **74**, the isomer of **66**, was obtained in quantitative yield. Both isomers were converted to the corresponding (phenylsulfonyl)amino alcohol derivatives **70** and **80** by the procedure described for the conversion of **40** to **44**. Both isomers **70** and **80** were converted to their corresponding acid, sodium carboxylate, or ester derivatives **72a,b** and **73** or **82a,b** and **83**, respectively, by the procedure described for the conversion of **9** to **11a,b** and **12**.

Biological Results and Discussion

Sodium salt of the TXA_2 analogues described in this paper were examined for their inhibitory activity against platelet responses induced by TXA_2-dependent and TXA_2-independent aggregatory agents: (i) aggregation of rabbit platelet-rich plasma (PRP) induced by arachidonic acid (AA), (ii) aggregation of rat washed platelets (WP) induced by collagen, and (iii) aggregation of rat WP induced by thrombin or ADP. For comparison, the inhibitory activity of S-145 in these tests was examined at the same time. All compounds blocked both AA-induced aggregation of rabbit PRP and collagen-induced aggregation of rat WP, whereas they caused no inhibition when TXA_2-independent aggregatory stimuli (e.g., ADP and thrombin) were used (data not shown). The IC_{50} values of these compounds for aggregation of rabbit PRP and rat WP are shown in Table I. As these compounds showed partial agaonistic activity (occurrence of platelet shape change), the relative agonistic activity to S-145 was also listed in Table I.

Although none of them surpassed the inhibitory effect of S-145, all the compounds tested showed inhibitory effects with IC_{50} values of 2.6–4.38.4 μM in the rabbit PRP test and of 2.9–100 nM in rat WP test. Interestingly, these bicyclo[3.1.0]hexane TXA_2 analogues display the inhibitory effect depending on their relative stereochemistry of the molecule. In general, the compounds with trans-oriented α-heptenoic acid and (phenylsulfonyl)amino side chains like **15b** or **46b** exhibited lower IC_{50} values than the corresponding compounds with cis-oriented side chains like **26b** or **52b**. The effects of variation in the function of the 6-position of the bicyclo[3.1.0]hexane ring system was not so prominent especially in the rat WP test. And most interestingly, the relative stereochemistry of the α-heptenoic acid side chain and three-membered functions of the bicyclo[3.1.0]hexane ring system had strong effect on the biological activity. Thus, 2-endo-3-exo configured

(17) Barton, D. H. R.; Montehwewell, W. B.; Simon, E. S.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1984**, 337.

(18) Harayama, T.; Fukushi, H.; Ogawa, K.; Yoneda, F. *Chem. Pharm. Bull.* **1985**, *33*, 3564.

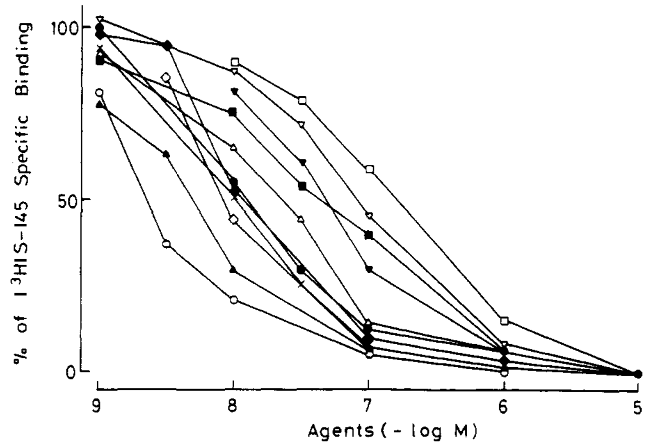


Figure 1. Competitive inhibition of the specific binding of [^{3}H]S-145 by various compounds. Rat WP (1.7×10^8) were incubated with 1.1 nM [^{3}H]S-145 in the presence of various concentrations of S-145 (○), **26b** (■), **34b** (▲), **46b** (×), **61b** (▼), **72b** (◆), **15b** (●), **11b** (□), **36b** (△), **52b** (▽), and **82b** (◇). Incubation was carried out at 24 °C for 60 min. The control value (100%) was defined as the specific binding of [^{3}H]S-145 in the absence of these compounds. Data are mean values for three experiments performed in triplicate.

derivatives **15b**, **34b**, **46b**, and **82b** exhibited lower IC_{50} values than the corresponding 2-exo-3-endo configured compounds **11b**, **36b**, **61b**, and **72b** in both tests except **82b**, which exhibited almost the same value as **72b** in rat WP test. And, the IC_{50} values of these 2-endo-3-exo configured derivatives in the inhibition for collagen-induced aggregation of rat WP ranged in almost the same order as S-145. From the diversity of the structures of TXA_2 antagonists hitherto synthesized, TXA_2 receptor has been thought to have considerable tolerance for structural change in the bicyclic ring system. But the structure–activity relationship in this series of specific TXA_2 antagonists might indicate that stereochemical factors of the 6-oxygen function of the TXA_2 2,6-dioxabicyclo[3.1.1]heptane ring system plays a more critical role for its binding to the receptor and the effect of this function seems to be more prominent than that of the corresponding 7-carbon function.

The IC_{50} values for collagen-induced aggregation of rat WP are regarded as more important indices than those for AA-induced aggregation of rabbit PRP from the recent observations that (a) the collagen-induced aggregation of rat platelets directly depended on the action of TXA_2[19,20] and (b) TXA_2 receptors on rat platelets have almost the same specificity as those on human platelets.[21,22] The binding characteristics of TXA_2 receptors on rabbit platelets has been reported to be somewhat different from those on humans.[22,23] The displacement of the specific (^{3}H)-S-145 binding by the compounds listed was done for further confirmation of receptor antagonism in rat WP (Figure 1). From log-log plots of IC_{50} (aggregation in rat WP) and the K_i values ((^{3}H)-S-145 binding; from Figure 1), highly linear correlations were observed for the inhibitory potencies of the compounds between collagen-induced aggregation and (^{3}H)-S-145 binding to rat WP

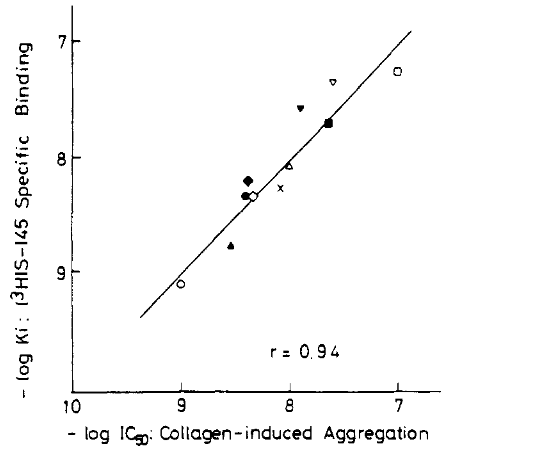


Figure 2. Graphic correlation of receptor affinity and antiaggregatory potency of S-145 (○), **26b** (■), **34b** (▲), **46b** (×), **61b** (▼), **72b** (◆), **15b** (●), **11b** (□), **36b** (△), **52b** (▽), and **82b** (◇). Each point represents a log–log plot of IC_{50} (collagen-induced aggregation of rat WP) versus K_i value ([^{3}H]S-145 binding to rat WP). The K_i values were determined by radioligand competition studies as described in Figure 1 and were calculated from the Cheng and Prusoff equations using the K_d value of [^{3}H]S-145 (0.67 nM) obtained by Scatchard analysis. The IC_{50} values were taken from the normalized concentration–response curves obtained from the inhibition by the respective compounds for the aggregation of rat WP induced by 4 μg/mL of collagen. The reported points were fitted with a least-squares linear regression ($r = 0.9394$).

(Figure 2). Biosynthesis of TXA_2 as well as 12-HETE in rabbit WP stimulated by thrombin was not inhibited by all the listed compounds at concentrations of up to 10 μM (data not shown). These data strongly imply the inhibitory mechanism on platelets of the compounds to be TXA_2 receptor antagonistic action. In conclusion, some compounds like **36b**, **82b**, and **72b**, which showed comparable activity to S-145 in the inhibition against aggregation of rat WP, lacked agonistic activity or showed relatively weaker agonistic activity than S-145. These compounds should be subjected to further biological evaluation.

Experimental Section

Unless otherwise stated, all reactions were carried out under a nitrogen atmosphere with dry solvents being used under anhydrous conditions and with anhydrous $MgSO_4$ being used as a drying agent for extracts. The organic solvents were removed by evaporation under reduced pressure with a rotary evaporator. Medium-pressure column chromatographies on Merck "Lobar" prepacked columns packed with LiChroprep Si 60 [size A (240-10 mm, 40–63 μm), size B (310-25 mm, 40–63 μm), and size C (440-37 mm, 40–63 μm)] were carried out for separation and purification of the products. Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were determined with a Hitachi Model 260-10 spectrophotometer, and NMR spectra were determined on a Varian EM-390 spectrometer.

***dl-cis*-2-(2-Hydroxycyclopent-4-enyl)ethanol Triphenylmethyl Ether (2).** To an ice-cooled and stirred solution of 14.0 g (109 mmol) of **1** in 500 mL of CH_2Cl_2 were added a solution of 32 g (114 mmol) of triphenylmethyl chloride in 100 mL of CH_2Cl_2, 19.8 mL (142 mmol) of triethylamine (Et_3N), and 300 mg of 4-(dimethylamino)pyridine, and the mixture was stirred at room temperature for 20 h. The product was isolated by CH_2Cl_2 extraction. The CH_2Cl_2 layer was washed with diluted aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl and then dried and evaporated. The product was purified by column silica gel chromatography using an ethyl acetate (AcOEt)–*n*-hexane (1:4) mixture as an eluent, and 38.63 g (96%) of **2** was obtained as an oily product: IR ($CHCl_3$) 3450 cm^{-1}; NMR ($CDCl_3$) δ 1.5–2.0 (2 H, m), 2.15–2.85 (3 H, m), 3.02–3.5 (2 H, m), 4.2–4.5 (1 H, m), 5.4–5.6 (1 H, m), 5.6–5.7 (1 H, m), 7.15–7.65 (15 H, m).

(19) Nakano, K.; Terawaki, A.; Arita, H. *J. Biochem.* **1987**, *101*, 1169.
(20) Hanasaki, K.; Nakano, T.; Arita, H. *Thrombosis Res.* **1987**, *46*, 425.
(21) Hanasaki, K.; Arita, H. *Biochem. Pharmacol.* **1988**, *37*, 3923.
(22) Hanasaki, K.; Arita, H. *Thrombosis Res.* **1988**, *50*, 365.
(23) Narumiya, S.; Okuma, M.; Ushikubi, F. *Br. J. Pharmacol.* **1986**, *88*, 323.

***dl-trans*-2-(2-Azidocyclopent-4-enyl)ethanol Triphenylmethyl Ether (5).** To an ice-cooled and stirred solution of 3.83 g (10.3 mmol) of **2** in 50 mL of CH_2Cl_2 were added 0.88 mL (11.3 mmol) of methanesulfonyl chloride and 1.72 mL (12.36 mmol) of Et_3N, and the mixture was stirred at 0 °C for another 30 min. The product was isolated by CH_2Cl_2 extraction. The CH_2Cl_2 layer was washed with 2 N aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried, and evaporated. The sample of crude *dl-cis*-2-[2-[(methylsulfonyl)oxy]cyclopent-4-enyl]ethanol triphenylmethyl ether (**4**) thus obtained was dissolved in 50 mL of DMF, and 12.05 g (185.4 mmol) of sodium azide was added. The mixture was then allowed to react at 75 °C for 5 h. After cooling, the product was isolated by AcOEt extraction. The AcOEt layer was washed with saturated aqueous NaCl, dried, and evaporated. The product was purified by column silica gel chromatography using an AcOEt–benzene (9:1) mixture containing 1% of triethylamine as an eluent, and 3.99 g (98%) of **5** was obtained: IR ($CHCl_3$) 2080 cm^{-1}; NMR ($CDCl_3$) δ 1.50–1.85 (2 H, m), 2.20–3.0 (3 H, m), 3.15 (2 H, t, *J* = 6 Hz), 3.50–3.80 (1 H, m), 5.59 (2 H, s), 7.20–7.60 (15 H, m). The product was subjected to the next reaction without further purification.

***dl-trans*-2-(2-Aminocyclopent-4-enyl)ethanol Triphenylmethyl Ether (6).** A solution of 3.99 g (10.1 mmol) of **5** and 3.54 g (13.5 mmol) of triphenylphosphine (Ph_3P) was allowed to react at room temperature for 15 h. To this solution was added 1 mL of water and the mixture was stirred at 45 °C for 2 h and then under reflux for 1 h. After cooling, the product was isolated by AcOEt extraction. The AcOEt layer was washed with saturated aqueous NaCl, dried, and evaporated. The residue was separated by column silica gel chromatography using an AcOEt–benzene (4:1) mixture as an eluent, and the crude product of **6**, which was contaminated with a small amount of Ph_3P, was obtained: NMR ($CDCl_3$) δ 1.31 (2 H, s), 1.57–1.82 (2 H, m), 1.83–2.17 (1 H, m), 2.23–2.80 (2 H, m), 3.00–3.27 (1 H, m), 3.15 (2 H, t, *J* = 6 Hz), 5.55 (2 H, s), 7.03–7.56 (15 H, m). The crude product was subjected to the next reaction without further purification.

***dl-trans*-2-[2-[(Phenylsulfonyl)amino]cyclopent-4-enyl]ethanol Triphenylmethyl Ether (7).** To an ice-cooled and stirred solution of the crude product **6** obtained in the previous reaction in 20 mL of CH_2Cl_2 were added 1.97 mL (14.23 mmol) of Et_3N and 1.45 mL (11.38 mmol) of benzenesulfonyl chloride. After stirring of the mixture at 0 °C for another 30 min, the excess reagent was decomposed by addition of diluted aqueous NH_4OH, and the product was isolated by CH_2Cl_2 extraction. The CH_2Cl_2 layer was washed with saturated aqueous NaCl, dried, and evaporated. The product was purified by column silica gel chromatography using an AcOEt–benzene (4:1) mixture as an eluent, and 2.84 g of **7** (55.2% from **5**) was obtained as a noncrystalline powder: IR ($CHCl_3$) 3360, 1335, 1320, 1155 cm^{-1}; NMR ($CDCl_3$) δ 1.33–1.83 (2 H, m), 1.85–2.20 (1 H, m), 2.33–2.82 (2 H, m), 3.03 (2 H, t, *J* = 6 Hz), 3.32–3.67 (1 H, m), 4.76 (1 H, d, *J* = 8 Hz), 5.49 (2 H, s), 7.17–7.57 (18 H, m), 7.70–7.90 (2 H, m). Anal. ($C_{32}H_{31}NO_3S$) C, H, N.

***dl-trans*-2-[2-[(Phenylsulfonyl)amino]cyclopent-4-enyl]ethanol (8).** A solution of 1.37 g (2.69 mmol) of **7** in a mixture of 5 mL of 1 N aqueous HCl, 10 mL of THF, and 10 mL of MeOH was allowed to react at 45 °C for 2 h. The solvents were evaporated, and the product was isolated by AcOEt extraction. The AcOEt layer was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried, and evaporated. The product was purified by column silica gel chromatography using an AcOEt–benzene (4:1) mixture as an eluent, and 2.16 g (99%) of compound **8** was obtained on recrystallization from ether: mp 112–113 °C; IR ($CHCl_3$) 3650–3100, 1340, 1320, 1155 cm^{-1}; NMR ($CDCl_3$ + CD_3OD) δ 1.40–1.70 (2 H, m), 1.90–2.23 (1 H, m), 2.30–2.80 (2 H, m), 3.50–3.70 (1 H, m), 3.60 (2 H, t, *J* = 6 Hz), 5.59 (2 H, s), 7.43–7.67 (3 H, m), 7.8–8.0 (2 H, m). Anal. ($C_{13}H_{17}O_3NS$) C, H, N, S.

***dl*-(1α,2α,3β,5α)- and -(1β,2α,3β,5β)-2-(Hydroxyethyl)-3-[(phenylsulfonyl)amino]-6-oxabicyclo[3.1.0]hexane (9 and 13).** A solution of 732 mg (2.74 mmol) of **8** and 650 mg (3.0 mmol) of 80% 3-chloroperoxybenzoic acid in 10 mL of CH_2Cl_2 was allowed to react at 0 °C for 15 h. The excess reagent was decomposed by addition of 5% aqueous sodium thiosulfate and stirring of the mixture, and the product was isolated by CH_2Cl_2 extraction. The CH_2Cl_2 layer was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried, and evaporated. The residue was separated by column silica gel chromatography using an AcOEt–benzene (1:1) mixture as an eluent. From the less polar fraction, 335 mg (43.4%) of **9** was obtained. A portion of the product was recrystallized from CH_2Cl_2–*n*-hexane: mp 124–125 °C; IR ($CHCl_3$) 3100–3650, 1345, 1155 cm^{-1}; NMR ($CDCl_3$) δ 1.00–1.53 (2 H, m), 1.62 (1 H, s), 1.77–2.06 (2 H, m), 2.10–2.43 (1 H, m), 3.30–3.80 (5 H, m), 5.08 (1 H, d, *J* = 10 Hz), 7.43–7.65 (3 H, m), 7.72–7.95 (2 H, m). Anal. ($C_{13}H_{17}NO_4S$) C, H, N, S. From the polar fraction 174 mg (22.6%) of **13** was obtained. A portion of the product was recrystallized from CH_2Cl_2–benzene: mp 101–103 °C; IR ($CHCl_3$) 3400–3200, 3360, 1320, 1155 cm^{-1}; NMR ($CDCl_3$) δ 1.23–2.35 (5 H, m), 2.42 (1 H, br s), 3.20 (1 H, m), 3.33–3.48 (2 H, m), 3.69 (2 H, t, *J* = 6 Hz), 5.68 (1 H, d, *J* = 8 Hz), 7.47–7.63 (3 H, m), 7.80–7.95 (2 H, m). Anal. ($C_{13}H_{17}NO_4S$) C, H, N, S.

***dl*-(1α,2α,3β,5α)-2-(Formylmethyl)-3-[(phenylsulfonyl)amino]-6-oxabicyclo[3.1.0]hexane (10).** To a cooled solution of 0.105 mL (1.2 mmol) of oxalyl chloride in 20 mL of CH_2Cl_2 with dry ice–acetone bath at −70 °C was added 0.19 mL (2.4 mmol) of DMSO dropwise, and the mixture was stirred at −70 °C for another 5 min. To the mixture was added a solution of 271 mg (0.96 mmol) of **9** in CH_2Cl_2 dropwise. After the reaction mixture had been allowed to react at −60 °C for 15 min, 1.67 mL (12 mmol) of Et_3N was added and the temperature of the reaction mixture was allowed to rise to room temperature. After stirring of the mixture at room temperature for an additional 1 h, the oxidation product was isolated by AcOEt extraction. The AcOEt layer was washed with water, 2 N aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, then dried, and evaporated. The crude product **10** thus obtained was subjected to the next reaction without further purification: IR ($CHCl_3$) 3360, 2820, 2720, 1725, 1345, 1160 cm^{-1}; NMR ($CDCl_3$) δ 1.67–2.17 (2 H, m), 2.20–2.67 (m, 3 H), 3.30–3.63 (3 H, m), 4.97–5.35 (1 H, m), 7.40–7.67 (3 H, m), 9.62 (1 H, s).

***dl*-(1α,2α,3β,5α)-7-[3-[(Phenylsulfonyl)amino]-6-oxabicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptenoic Acid (11a).** A suspension of 216 mg (5.6 mmol) of 60% sodium hydride in mineral oil in 10 mL of DMSO was heated at 70 °C for 2.5 h. To the cooled solution of sodium (methylsulfinyl)methide in DMSO at 12 °C was added 1.36 g (3 mmol) of (4-carboxybutyl)triphenylsulfonium bromide, and the mixture was stirred at room temperature for 20 min. A solution of 296 mg of the crude **10** in 3 mL of DMSO was added to this reagent solution, and the mixture was allowed to react at room temperature for 2 h. AcOEt and water were added to the reaction mixture, and after acidification of the aqueous layer with 2 N aqueous HCl, the product was isolated by AcOEt extraction. The AcOEt layer was washed with 2 N aqueous HCl and saturated aqueous NaCl, then dried, and evaporated. The product was separated by column silica gel chromatography using an AcOEt–benzene (2:1) mixture as an eluent. The crude product of **11a** thus obtained was subjected to the next reaction without further purification: IR ($CHCl_3$) 3360, 1705, 1345, 1160 cm^{-1}; NMR ($CDCl_3$) δ 1.50–2.20 (9 H, m), 2.33 (2 H, t, *J* = 6 Hz), 3.27–3.63 (2 H, m), 4.90–5.60 (3 H, m), 7.40–7.65 (3 H, m), 7.78–7.97 (2 H, m).

***dl*-(1α,2α,3β,5α)-7-[3-[(Phenylsulfonyl)amino]-6-oxabicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptenoic Acid Methyl Ester (12).** A solution of diazomethane in ether was added to an ice-cooled solution of the crude **11a** obtained in the previous reaction in 5 mL of CH_2Cl_2. The solvents were evaporated, and the residue was purified by column silica gel chromatography using an AcOEt–benzene (2:1) mixture as an eluent, and 153 mg of **12** (42% from **9**) was obtained: IR ($CHCl_3$) 3350, 1720, 1335, 1155, 1088 cm^{-1}; NMR ($CDCl_3$) δ 1.50–2.16 (9 H, m), 2.28 (2 H, t, *J* = 6 Hz), 3.27–3.60 (3 H, m), 3.66 (3 H, s), 5.00–5.60 (3 H, m), 7.47–7.66 (3 H, m), 7.80–7.97 (2 H, m).

***dl*-Sodium (1α,2α,3β,5α)-7-[3-[(Phenylsulfonyl)amino]-6-oxabicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptenoate (11b).** A sample of 67 mg (0.18 mmol) of **11a** was dissolved in 1.8 mL of 0.1 N aqueous NaOH, and the solution was lyophilized to obtain 69 mg of compound **11b**: Anal. ($C_{18}H_{22}O_5NSNa$) C, H, N, S, Na.

By the procedure described for the conversion of **9** to **11a,b** and **12**, **13** was converted to **15a,b** and **16**.

(1β,2α,3β,5β)-2-(Formylmethyl)-3-[(phenylsulfonyl)amino]-6-oxabicyclo[3.1.0]hexane (14). IR ($CHCl_3$) 3350, 2820, 2720, 1725, 1325, 1155 cm^{-1}; NMR ($CDCl_3$) δ 1.12–2.53 (5 H, m), 3.30–3.53 (3 H, m), 5.30 (1 H, d, J = 8 Hz), 7.37–7.67 (5 H, m), 7.70–8.00 (2 H, m), 9.78 (1 H, s).

***dl*-(1β,2α,3β,5β)-7-[3-[(Phenylsulfonyl)amino]-6-oxabicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptenoic Acid (15a).** IR ($CHCl_3$) 3350, 1705, 1325, 1155 cm^{-1}; NMR ($CDCl_3$) δ 1.20–2.40 (9 H, m), 2.33 (2 H, t, J = 6 Hz), 2.77–3.18 (1 H, m), 3.34 (2 H, m), 5.25–5.67 (3 H, m), 7.40–7.63 (3 H, m), 7.77–7.95 (2 H, m), 7.60–8.40 (1 H, m).

***dl*-Methyl (1β,2α,3β,5β)-7-[3-[(Phenylsulfonyl)amino]-6-oxabicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptenoate (16).** IR ($CHCl_3$) 3360, 1720, 1320, 1155 cm^{-1}; NMR ($CDCl_3$) δ 1.23–2.45 (9 H, m), 2.30 (2 H, t, J = 6 Hz), 2.80–3.23 (1 H, m), 3.35 (2 H, s), 3.69 (3 H, m), 5.10–5.65 (3 H, m), 7.43–7.70 (3 H, m), 7.80–8.00 (2 H, m).

***dl*-Sodium (1β,2α,3β,5β)-7-[3-[(Phenylsulfonyl)amino]-6-oxabicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptenoate (15b).** Anal. ($C_{18}H_{22}O_5NSNa$) C, H, N, S, Na.

***dl*-*trans*-2-[2-(Benzoyloxy)cyclopent-4-enyl]ethanol Triphenylmethyl Ether (17).** To an ice-cooled and stirred solution of 1.86 g (5 mmol) of **2**, 2.62 g, (10 mmol) of Ph_3P, and 1.22 g (10 mmol) of benzoic acid in 100 mL of THF was added 1.74 g (10 mmol) of diethyl azodicarboxylate, and the mixture was allowed to react at room temperature for 15 min. MeOH (1 mL) was added to the mixture and the solvent was evaporated. The residue was triturated with diethyl ether and insoluble material was filtrated and washed with diethyl ether. The solvent was evaporated and the residue was separated by column silica gel chromatography using an AcOEt–*n*-hexane (1:9) mixture as an eluent and 0.72 g (40.9%) of **17** was obtained as an oil. IR ($CHCl_3$) 1695 cm^{-1}; NMR ($CDCl_3$) δ 1.55–1.95 (2 H, m), 2.33 (1 H, dd, J = 12 and 2 Hz), 2.81 (1 H, dd, J = 12 and 5 Hz), 2.9–3.4 (3 H, m), 5.13–5.36 (1 H, m), 5.45–5.70 (2 H, m), 6.95–8.15 (20 H, m). From the less polar fraction 0.72 g (40.9%) of cyclopenta-1,4-dienylethanol triphenylmethyl ether was obtained.

***dl*-*trans*-2-(2-Hydroxycyclopent-4-enyl)ethanol Triphenylmethyl Ether (18).** A mixture of 1.32 g (2.8 mmol) of **17** and 0.8 g (5.79 mmol) of Na_2CO_3 in 4 mL of water and 10 mL of THF was stirred under reflux for 5 h. After cooling, the solvents were evaporated, and the product was isolated by CH_2Cl_2 extraction. The CH_2Cl_2 layer was washed with saturated aqueous NaCl, dried, and evaporated. The residue was purified by column silica gel chromatography using an AcOEt–benzene (1:2) mixture as an eluent and 0.98 g (95.0%) of **18** was obtained as an oil: IR ($CHCl_3$) 3450 cm^{-1}; NMR ($CDCl_3$) δ 1.50–1.83 (3 H, m), 2.06–2.40 (1 H, m), 2.47–2.83 (2 H, m), 3.05–3.40 (2 H, m), 4.0–4.23 (1 H, m), 5.43–5.7 (2 H, m), 7.10–7.65 (15 H, m).

By the procedure described for the conversion of **2** to **8**, **18** was converted to **23**.

***dl*-*cis*-2-(2-Azidocyclopent-4-enyl)ethanol Triphenylmethyl Ether (20).** IR ($CHCl_3$) 2080 cm^{-1}; NMR ($CDCl_3$) δ 1.55–2.10 (2 H, m), 2.27–3.40 (3 H, m), 3.18 (2 H, t, J = 6 Hz), 3.73–4.10 (1 H, m), 5.40–5.80 (2 H, m), 7.10–7.60 (15 H, m).

***dl*-*cis*-2-(2-Aminocyclopent-4-enyl)ethanol Triphenylmethyl Ether (21).** NMR ($CDCl_3$) δ 1.40–2.00 (2 H, m), 2.08–2.20 (1 H, m), 2.40–2.85 (2 H, m), 3.05–3.35 (2 H, m), 3.37–3.70 (1 H, m), 5.40–5.80 (2 H, m), 7.17–7.63 (15 H, m).

***dl*-*cis*-2-[2-[(Phenylsulfonyl)amino]cyclopent-4-enyl]ethanol Triphenylmethyl Ether (22).** Noncrystalline powder; IR ($CHCl_3$) 1335, 1160 cm^{-1}; NMR ($CDCl_3$) δ 1.47–1.88 (2 H, m), 1.90–2.07 (1 H, m), 2.12–2.48 (1 H, m), 2.57–2.90 (1 H, m), 2.92–3.17 (2 H, m), 3.78–4.17 (1 H, m), 5.11 (1 H, d, J = 9 Hz), 5.47 (2 H, s), 7.17–9.58 (18 H, m), 7.70–7.88 (2 H, m). Anal. ($C_{32}H_{31}NO_2S$) C, H, N.

***dl*-*cis*-2-[2-[(Phenylsulfonyl)amino]cyclopent-4-enyl]ethanol (23).** IR ($CHCl_3$) 3650–3100, 3360, 1325, 1155 cm^{-1}; NMR ($CDCl_3$) δ 1.45–1.90 (2 H, m), 1.92–2.57 (3 H, m), 2.65–3.00 (1 H, m), 3.65 (2 H, t, J = 6 Hz), 3.80–4.23 (1 H, m), 5.64 (2 H, s), 5.97 (1 H, d, J = 9 Hz), 7.43–7.70 (3 H, m), 7.85–8.10 (2 H, m).

***dl*-(1β,2α,3α,5β)-2-(Hydroxyethyl)-3-[(phenylsulfonyl)amino]-6-oxabicyclo[3.1.0]hexane (24).** A solution of 255 mg (0.95 mmol) of **23** and 226 mg (1.05 mmol) of 80% 3-chloroperoxybenzoic acid in 10 mL of CH_2Cl_2 was allowed to react at 0 °C for 4 h. The product was isolated and purified by the procedure described for the epoxidation of **8**, and 225 mg (83.0%) of **24** was obtained. A portion of the product was recrystallized from CH_2Cl_2–*n*-pentane; mp 109–111 °C: IR ($CHCl_3$) 3650–3100, 3350, 1330, 1150; NMR ($CDCl_3$) δ 1.58–2.05 (5 H, m), 2.20–2.50 (1 H, m), 3.30–3.53 (2 H, m), 3.55–3.90 (1 H, m), 3.75 (3 H, s), 4.92 (1 H, d, J = 11 Hz), 7.40–7.63 (3 H, m), 7.83–7.93 (2 H, m). Anal. ($C_{13}H_{17}NO_4S$) C, H, N.

By the procedure described for the conversion of **9** to **11a,b** and **12**, **24** was converted to **26a,b** and **27**.

***dl*-(1β,5β)-2-(Phenylsulfonyl)-3-hydroxy-6a,7α-epoxy-2-azabicyclo[3.3.0]octane (25).** IR ($CHCl_3$) 3600–3150, 3360, 1325, 1155 cm^{-1}; NMR ($CDCl_3$) δ 1.55–2.45 (4 H, m), 2.85–3.15 (1 H, m), 3.30–3.85 (2 H, m), 4.23–4.50 (1 H, m), 4.99 (1 H, d, J = 12 Hz), 5.38–5.67 (1 H, m), 7.36–7.65 (3 H, m), 7.75–8.05 (2 H, m).

***dl*-(1β,2α,3α,5β)-7-[3-[(Phenylsulfonyl)amino]-6-oxabicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptenoic Acid (26a).** IR ($CHCl_3$) 3350, 1700, 1340, 1155 cm^{-1}; NMR ($CDCl_3$) δ 1.50–1.90 (4 H, m), 1.93–2.50 (7 H, m), 3.41 (2 H, s), 3.55–3.90 (1 H, m), 4.94 (1 H, d, J = 11 Hz), 5.35–5.57 (2 H, m), 7.40–7.63 (3 H, m), 7.73–7.97 (2 H, m), 8.80–9.60 (1 H, m).

***dl*-Methyl (1β,2α,3α,5β)-7-[3-[(Phenylsulfonyl)amino]-6-oxabicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptenoate (27).** Mp 56–57 °C (CH_2Cl_2–*n*-pentane); IR ($CHCl_3$) 3350, 1720, 1335, 1155 cm^{-1}; NMR ($CDCl_3$) δ 1.50–1.87 (4 H, m), 1.92–2.45 (7 H, m), 3.39 (2 H, s), 3.50–3.87 (1 H, m), 3.66 (3 H, s), 4.70–4.98 (1 H, m), 5.33–5.52 (23 H, m), 7.40–7.60 (3 H, m), 7.75–7.93 (2 H, m). Anal. ($C_{19}H_{25}NO_5S$) C, H, N, S.

***dl*-Sodium (1β,2α,3α,5β)-7-[3-[(Phenylsulfonyl)amino]-6-oxabicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptenoate (26b).** Anal. ($C_{18}H_{22}O_5NSNa\cdot{}^1/_2H_2O$) C, H, N, S, Na.

***dl*-(1α,5α)-2-(Phenylsulfonyl)-3-hydroxy-2-azabicyclo-[3.3.0]oct-6-ene (28).** To a cooled solution of 0.28 mL (3.2 mmol) of oxalyl chloride in 35 mL of CH_2Cl_2 in a dry ice–acetone bath at −78 °C was added 0.45 mL of DMSO, and the mixture was stirred at −78 °C for 5 min. To the mixture was added a solution of 672 mg (2.51 mmol) of **23** in 5 mL of CH_2Cl_2. After the mixture was allowed to react at −60 °C for 15 min, 4.2 mL (30 mmol) of Et_3N was added and the temperature of the mixture was allowed to rise to room temperature. The reaction mixture was stirred at room temperature for an additional 1 h, then the oxidation product was isolated and purified by the procedure described for the preparation of **10**, and 456 mg (64.0%) of **28** was obtained: IR ($CHCl_3$) 3550, 3200–3450, 1345, 1155 cm^{-1}; NMR ($CDCl_3$) δ 1.50–2.20 (2 H, m), 2.50–3.00 (2 H, m), 3.15–3.65 (1 H, m), 4.10–4.45 (2 H, m), 5.10–6.40 (3 H, m), 7.35–7.70 (3 H, m), 7.75–8.05 (2 H, m).

***dl*-(1β,5β)-2-(Phenylsulfonyl)-3-hydroxy-6β,7β-epoxy-2-azabicyclo[3.3.0]octane (29).** A mixture of 265 mg (1.0 mmol) of **28** and 258 mg (1.2 mmol) of 80% 3-chloroperoxybenzoic acid in 10 mL of CH_2Cl_2 was stirred at room temperature for 3 h. The oxidation product was isolated and purified by the procedure described for the preparation of **10**, and 76 mg (27%) of **29** was obtained: IR ($CHCl_3$) 3580, 3360, 1350, 1160 cm^{-1}; NMR ($CDCl_3$) δ 1.5–3.0 (3 H, m), 3.2–3.65 (2 H, m), 3.65–4.0 (1 H, m), 4.5–4.9 (1 H, m), 5.4–5.75 (1 H, m), 7.3–7.65 (3 H, m), 7.75–8.2 (2 H, m).

By the procedure described for the preparation of **12** from **9**, **31** was prepared from **29**.

***dl*-Methyl (1α,2α,3α,5α)-7-[3-[(Phenylsulfonyl)amino]-6-oxabicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptenoate (31).** Mp 66–67 °C (CH_2Cl_2–*n*-pentane); IR ($CHCl_3$) 3375, 1728, 1150, 1095 cm^{-1}; NMR ($CDCl_3$) δ 1.5–1.9 (4 H, m), 1.9–2.5 (7 H, m), 3.33 (2 H, s), 3.45–3.8 (1 H, m), 3.67 (3 H, s), 4.82 (1 H, d, J = 9 Hz), 5.30–5.56 (2 H, m), 7.35–7.65 (3 H, m), 7.75–8.0 (2 H, m). Anal. ($C_{19}H_{25}NO_5S$) C, H, N, S.

***dl*-(1β,2α,3β,5β)-7-[3-[(Phenylsulfonyl)amino]-6-thiabicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptenoic Acid (34a).** A two-layer mixture of 4.5 g (0.6 mmol) of potassium thiocyanate in 5 mL of water, 6.75 g of phosphoric acid, and 15 mL of diethyl ether was stirred vigorously at room temperature and the ether layer was separated. The solution of thiocyanic acid in diethyl ether thus obtained was added to an ice-cooled and stirred solution of 568.5 mg (1.5 mmol) of **12** in 30 mL of diethyl ether. After the temperature of the reaction mixture had risen to room temperature, the mixture was allowed to react for another 2 h, and the product was isolated by ether extraction. The ether layer was washed with 2 N aqueous Na_2CO_3 and saturated aqueous NaCl, dried, and evaporated. To the ice-cooled and stirred solution of the product containing *dl*-methyl 7-[1β(or 2β)-hydroxy-2α(or 1α)-thiocyano-4β-[(phenylsulfonyl)amino]cyclohex-3α-yl]-5(*Z*)-heptenoate (**32**) obtained in the previous reaction in 10 mL of CH_2Cl_2 were added 0.128 mL (1.65 mmol) of methanesulfonyl chloride and 0.314 mL (82.25 mmol) of Et_3N. After the mixture had been allowed to react at 0 °C for 30 min, the product was isolated by CH_2Cl_2 extraction. The CH_2Cl_2 layer was washed with 2 N aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, then dried, and evaporated. The product containing *dl*-methyl-7-[1β(or 2β)-[(methylsulfonyl)oxy]-2α(or 1α)-thiocyano-4β-[(phenylsulfonyl)amino]cyclohex-3α-yl]-5(*Z*)-heptenoate (**33**) was then dissolved in 25 mL of dioxane and 15 mL of 5% NaOH solution in MeOH, and the mixture was stirred at room temperature for 12 h. After the solvents had been evaporated, AcOEt and water were added to the residue. The aqueous layer was acidified with 2 N aqueous hydrochloric acid, and the product was isolated by AcOEt extraction. The AcOEt layer was washed with 2 N aqueous HCl and saturated aqueous NaCl, dried, and evaporated. Crystallization of the residue from ether–*n*-hexane gave 444 mg (77.3% from **12**) of **34a**: mp 133–134 °C; IR ($CHCl_3$) 3360, 3350–3100, 1700, 1320, 1155, 1085 cm^{-1}; NMR ($CDCl_3$) δ 2.50–1.30 (11 H, m), 2.90–3.40 (3 H, m), 5.20–5.70 (3 H, m), 7.37–7.70 (3 H, m), 7.60–8.30 (1 H, m), 7.76–8.00 (2 H, m). Anal. ($C_{18}H_{23}NO_4S_2$) C, H, N, S.

***dl*-Methyl (1β,2α,3β,5β)-7-[3-[(Phenylsulfonyl)amino]-6-thiabicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptenoate (35).** IR ($CHCl_3$) 3370, 3100–3350, 1700, 1155, 1083 cm^{-1}; NMR ($CDCl_3$) δ 1.50–2.50 (11 H, m), 3.07–3.46 (3 H, m), 3.70 (3 H, s), 5.06 (1 H, d, J = 10 Hz), 5.36–5.57 (2 H, m), 7.43–7.70 (3 H, m), 7.80–7.97 (2 H, m).

***dl*-Sodium (1β,2α,3β,5β)-7-[3-[(Phenylsulfonyl)amino]-6-thiabicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptanoate (34b).** Anal. ($C_{18}H_{22}NO_4S_2Na\cdot{}^1/_2H_2O$) C, H, N, S, Na.

By the procedures described for the preparation of **34a,b** and **35** from **12**, **36a,b** and **37** were prepared from **16**.

***dl*-(1α,2α,3β,5α)-7-[3-[(Phenylsulfonyl)amino]-6-thiabicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptenoic Acid (36a).** IR ($CHCl_3$) 3370, 3100–3350, 1700, 1155, 1083 cm^{-1}; NMR ($CDCl_3$) δ 1.5–1.9 (4 H, m), 1.9–2.6 (7 H, m), 3.15 (2 H, m), 3.63–4.05 (1 H, m), 5.25 (1 H, d, J = 10 Hz), 5.25–5.60 (2 H, m), 7.4–7.7 (3 H, m), 7.8–8.0 (3 H, m).

***dl*-Methyl (1α,2α,3β,5α)-7-[3-[(Phenylsulfonyl)amino]-6-thiabicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptenoate (37).** IR ($CHCl_3$) 3370, 1720, 1155, 1088 cm^{-1}; NMR ($CDCl_3$) δ 1.50–2.50 (11 H, m), 3.14 (2 H, m), 3.66 (3 H, s), 3.73–4.10 (1 H, m), 5.14 (1 H, d, J = 10 Hz), 5.25–5.65 (2 H, m), 7.35–7.63 (3 H, m), 7.77–7.97 (2 H, m).

***dl*-Sodium (1α,2α,3β,5α)-7-[3-[(Phenylsulfonyl)amino]-6-thiabicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptenoate (36b).** Anal. ($C_{18}H_{22}NO_4S_2Na\cdot{}^1/_2H_2O$) C, H, N, S, Na.

***dl*-(1β,2α,3α,5β)-2-(Hydroxyethyl)-3-hydroxybicyclo[3.1.0]hexane (38).** To a hot stirred solution of 80 mg (0.49 mmol) of silver acetate in 200 mL of AcOH was added 13.1 g (200 mg-atom) of zinc powder in one portion. The mixture was stirred for 30 s, and the zinc–silver couple formed was isolated by decantation and was washed with ether (5 × 50 mL). A solution of 26.8 g (100 mmol) of diiodomethane in 80 mL of ether was added dropwise over 1 h to a suspension of zinc–silver couple product in 120 mL of ether so as to maintain a gentle refluxing of ether and then a solution of 6.4 g (53.3 mmol) of **1** in 10 mL of ether. The mixture was stirred under reflux for another 4 h. After cooling, the mixture was poured into saturated aqueous NH_4Cl and the product was isolated by AcOEt extraction. The AcOEt layer was washed with saturated aqueous NaCl, dried, and evaporated. The product was purified by column silica gel chromatography using an AcOEt–benzene (1:1) mixture as an eluent, and 3.98 g (56%) of **38** was obtained. A portion of the product was recrystallized from CH_2Cl_2–*n*-pentane: mp 72–73 °C; IR ($CHCl_3$) 3450 cm^{-1}; NMR ($CDCl_3$) δ 0.0–0.5 (1 H, m), 0.5–0.8 (1 H, m), 1.1–1.14 (2 H, m), 1.5–2.0 (3 H, m), 2.0–2.8 (4 H, m), 3.55–4.1 (2 H, m), 4.1–4.35 (1 H, m). Anal. ($C_8H_{14}O_2$) C, H.

***dl*-(1β,2α,3α,5β)-3-Hydroxy-2-[2-(triphenylmethoxy)ethyl]bicyclo[3.1.0]hexane (39).** To an ice-cooled and stirred solution of 2.1 g (14.8 mmol) of **39** and 4.36 g (15.6 mmol) of triphenylmethyl chloride in 50 mL of CH_2Cl_2 were added 2.5 mL (17.8 mmol) of Et_3N and 100 mg of 4-(dimethylamino)pyridine, and the mixture was allowed to react at 0 °C for 30 min and at room temperature for 20 h. The product was isolated and purified as described for the preparation of **2** and 5.46 g (95.7%) of **39** was obtained: IR ($CHCl_3$) 3450 cm^{-1}; NMR ($CDCl_3$) δ 0.1–0.4 (1 H, m), 0.5–0.8 (1 H, m), 1.0–1.35 (2 H, m), 1.4–2.5 (6 H, m), 2.95–3.28 (1 H, m), 3.28–3.55 (1 H, m), 4.10 (1 H, t, J = 6 Hz), 7.0–7.6 (15 H, m).

***dl*-(1β,2α,5β)-2-[2-(Triphenylmethoxy)ethyl]bicyclo[3.1.0]hexan-3-one (40).** A mixture of 5.62 g (14.8 mmol) of **39** and 11.1 g (29.5 mmol) of PDC in 30 mL of DMF was stirred at room temperature for 3 h. The mixture was poured into ice water and the product was isolated by AcOEt extraction. The AcOEt layer was washed with saturated aqueous NaCl, dried, and evaporated. The residue was purified by column silica gel chromatography using an AcOEt–benzene (1:9) mixture as an eluent and 3.21 g (56.8%) of **40** was obtained: IR ($CHCl_3$) 1725 cm^{-1}; NMR ($CDCl_3$) δ –0.35–0.0 (1 H, m), 0.45–0.80 (1 H, m), 0.9–1.8 (3 H, m), 1.95–2.4 (2 H, m), 2.47–3.0 (2 H, m), 3.0–3.4 (2 H, m), 7.1–7.6 (15 H, m).

***dl*-(1β,2α,5β)-3-(Hydroxyimino)-2-[2-(triphenylmethoxy)ethyl]bicyclo[3.1.0]hexane (41).** To an ice-cooled and stirred solution of 1.11 g (16.8 mmol) of KOH in 65 mL of MeOH were added 1.17 g (16.8 mmol) of hydroxyamine hydrochloride and then a solution of 3.21 g (8.4 mmol) of **40** in 35 mL of MeOH, and the mixture was stirred at room temperature for 3 h. The reaction mixture was poured into water and the product was isolated by AcOEt extraction. The AcOEt layer was washed with saturated aqueous NaCl, dried, and evaporated. The residue was purified by column silica gel chromatography using an AcOEt–benzene (1:9) mixture as an eluent and 3.30 g (99%) of **41** was obtained on recrystallization from benzene–*n*-hexane: mp 133–134 °C; IR ($CHCl_3$) 3560 cm^{-1}; NMR ($CDCl_3$) δ –0.4–0.2 (1 H, m), 1.23–1.60 (1 H, m), 1.13–1.67 (4 H, m), 1.95–2.30 (1 H, m), 2.4 (1 H, d, J = 18 Hz), 2.8 (1 H, d, J = 18 Hz), 3.0–3.4 (2 H, m), 7.2–7.64 (15 H, m), 8.08 (1 H, s). Anal. ($C_{27}H_{27}NO_2$) C, H, N.

***dl*-(1β,2α,3β,5β)- and (1β,2α,3α,5β)-3-[(Phenylsulfonyl)amino]-2-[2-(triphenylmethoxy)ethyl]bicyclo[3.1.0]hexane (43 and 49).** To an ice-cooled and stirred solution of 2.91 g (7.31 mmol) of **41** in 20 mL of THF were added 1.92 g (8.77 mmol) of diphenyl disulfide and 3.27 mL (13.16 mmol) of *n*-tributylphosphine and the mixture was allowed to react at room temperature for 1 h. The mixture was then cooled to –70 °C, and 10 mL of acetic acid and 1.65 g (26.32 mmol) of sodium cyanoborohydride were added. After the mixture was stirred at –70 °C for 10 min, the temperature of the mixture was allowed to rise gradually to room temperature. Saturated aqueous $NaHCO_3$ was added to the mixture and the product was isolated by AcOEt extraction. The AcOEt layer was washed with saturated aqueous NaCl, dried, and evaporated to obtain the crude product containing *dl*-(1β,2α,3β,5β)- and (1β,2α,3α,5β)-3-amino-2-[2-(triphenylmethoxy)ethyl]bicyclo[3.1.0]hexane (**42** and **48**). To an ice-cooled and stirred solution of the crude product containing **42** and **48** obtained in the previous reaction in 30 mL of CH_2Cl_2 was added 4.2 mL (32.9 mmol) of benzenesulfonyl chloride and 9.13 mL (65.8 mmol) of Et_3N, and the mixture was allowed to react at room temperature for 3 h. The product was isolated and purified as described for the preparation of **7** and 2.18 g of the mixture consisting of **43** and **49** was obtained.

***dl*-(1β,2α,3β,5β)- and (1β,2α,3α,5β)-2-(Hydroxyethyl)-3-[(phenylsulfonyl)amino]bicyclo[3.1.0]hexane (44 and 50).** A solution of 1.77 g (3.38 mmol) of the mixture containing **43** and **49** in 50 mL of 80% aqueous acetic acid was stirred under reflux for 15 h. The solvents were evaporated, and the product was isolated by AcOEt extraction. The AcOEt layer was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, then dried, and evaporated. The product containing **44**, **50**, and their corresponding acetates was dissolved in a solution of 716 mg of Na_2CO_3 in 60 mL of MeOH and 30 mL of water, and the mixture was stirred under reflux for 5 h. After cooling, the mixture was poured into water and the product was isolated by AcOEt extraction. The AcOEt layer was washed with saturated aqueous NaCl, dried, and evaporated. The residue was separated by column silica gel chromatography using AcOEt–benzene (1:2) mixture as an eluent. From the less polar fraction, 593 mg (63%) of **44** was obtained. A portion of the product was recrystallized from CH_2Cl_2–ether: mp 109–111 °C; IR ($CHCl_3$) 3650–3100, 3360, 1325, 1160 cm^{-1}; NMR ($CDCl_3$) δ –0.14–0.34 (2 H, m), 0.94–2.34 (8 H, m), 2.54–2.99 (1 H, m), 3.69 (2 H, t, J = 6 Hz), 5.39 (1 H, d, J = 8 Hz), 7.29–7.69 (3 H, m), 7.77–8.04 (2 H, m). Anal.

($C_{14}H_{19}NO_3S$) C, H, N. From the polar fraction, 154 mg (16%) of **50** was obtained. A portion of the product was recrystallized from CH_2Cl_2–ether: mp 109–113 °C; IR ($CHCl_3$) 3650–3100, 3360, 1335, 1150 cm^{-1}; NMR ($CDCl_3$) δ −0.98–0.5 (2 H, m), 0.94–2.22 (8 H, m), 2.3–2.67 (1 H, m), 3.44–3.92 (3 H, m), 5.08 (1 H, d, J = 8 Hz), 7.32–7.6 (3 H, m), 7.67–8.00 (2 H, m). Anal. ($C_{14}H_{19}NO_3S$) C, H, N.

By the procedure described for the conversion of **9** to **11a,b** and **12**, **44** was converted to **46a,b** and **47**.

***dl*-(1β,2α,3β,5β)-7-[3-[(Phenylsulfonyl)amino]bicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptenoic Acid (46a).** IR ($CHCl_3$) 3360, 3250, 1705, 1320, 1155 cm^{-1}; NMR ($CDCl_3$) δ −0.07–0.37 (2 H, m), 1.00–2.50 (13 H, m), 2.60–3.03 (1 H, m), 5.10 (1 H, d, J = 9 Hz), 5.20–5.70 (2 H, m), 7.47–7.68 (3 H, m), 7.83–8.05 (2 H, m), 8.00–9.00 (1 H, br s).

***dl*-Methyl (1β,2α,3β,5β)-7-[3-[(Phenylsulfonyl)amino]bicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptenoate (47).** IR ($CHCl_3$) 3360, 1725, 1325, 1155 cm^{-1}; NMR ($CDCl_3$) δ −0.14–0.3 (2 H, m), 0.93–2.36 (13 H, m), 2.43–2.96 (1 H, m), 3.61 (3 H, s), 4.46–4.73 (1 H, d, J = 9 Hz), 5.2–5.3 (2 H, m), 7.36–7.6 (3 H, m), 7.73–7.93 (2 H, m).

***dl*-Sodium (1β,2α,3β,5β)-7-[3-[(Phenylsulfonyl)amino]bicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptenoate (46b).** Anal. ($C_{19}H_{24}O_4NSNa\cdot{}^1/_4H_2O$) C, H, N, S, Na.

By the procedure described for the conversion of **9** to **11a,b** and **12**, **50** was converted to **52a,b** and **53**.

***dl*-(1β,2α,3α,5β)-2-(Formylmethyl)-3-[(phenylsulfonyl)amino]bicyclo[3.1.0]hexane (51).** IR ($CHCl_3$) 3520, 3360, 1155 cm^{-1}; NMR ($CDCl_3$) δ −0.1–0.5 (2 H, m), 0.8–2.40 (7 H, m), 2.9–4.1 (1 H, m), 5.17–5.33 (0.6 H, dd, J = 7 and 3 Hz), 5.47–5.6 (0.4 H, m), 7.3–7.57 (3 H, m), 7.57–7.88 (2 H, m).

***dl*-(1β,2α,3α,5β)-7-[3-[(Phenylsulfonyl)amino]bicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptenoic Acid (52a).** IR ($CHCl_3$) 3360, 3250, 1705, 1320, 1155 cm^{-1}; NMR ($CDCl_3$) δ −0.11–0.52 (2 H, m), 0.92–2.82 (13 H, m), 3.42–3.85 (1 H, m), 4.90 (1 H, d, J = 8 Hz), 5.07–5.62 (2 H, m), 7.30–7.67 (3 H, m), 7.67–8.02 (2 H, m).

***dl*-Methyl (1β,2α,3α,5β)-7-[3-[(Phenylsulfonyl)amino]bicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptenoate (53).** IR ($CHCl_3$) 3360, 1720, 1340, 1155 cm^{-1}; NMR ($CDCl_3$) δ −0.07–0.5 (2 H, m), 0.93–1.37 (2 H, m), 1.37–2.6 (11 H, m), 3.60 (3 H, s), 3.47–3.83 (1 H, m), 4.68 (1 H, d, J = 9 Hz), 5.1–5.6 (2 H, m), 7.4–7.63 (3 H, m), 7.7–8.0 (2 H, m).

***dl*-Sodium (1β,2α,3α,5β)-7-[3-[(Phenylsulfonyl)amino]bicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptenoate (52b).** Anal. ($C_{19}H_{24}O_4NSNa\cdot{}^1/_4H_2O$) C, H, N, S, Na.

***dl*-(1α,2α,3β,5α)-3-Hydroxy-2-[2-(triphenylmethoxy)ethyl]bicyclo[3.1.0]hexane (54).** To a hot stirred solution of 100 mg (0.61 mmol) of silver acetate in 80 mL of AcOH was added 11.5 g (176 mg-atom) of zinc powder in one portion. The mixture was stirred for 30 s, and the zinc–silver couple formed was isolated by decantation and was washed with ether (5 × 50 mL). A solution of 23.57 g (88 mmol) of diiodomethane in 50 mL of ether was added dropwise over 1 h to a suspension of zinc–silver couple product in 120 mL of ether so as to maintain a gentle refluxing of ether and then a solution of 8.2 g (22 mmol) of **18** in 10 mL of ether was added. The mixture was stirred under reflux for another 4 h. The product was isolated and purified by the procedure described for the preparation of **38**, and 7.50 g (87%) of **54** was obtained: IR ($CHCl_3$) 3450 cm^{-1}; NMR ($CDCl_3$) δ 0.33–0.66 (2 H, m), 0.86–1.30 (2 H, m), 1.34 (3 H, s), 1.43–1.77 (3 H, m), 1.81–2.27 (2 H, m), 3.28 (2 H, t, J = 6 Hz), 3.95 (1 H, d, J = 6 Hz), 7.2–7.63 (15 H, m).

By the procedure described for the conversion of **39** to **46a,b** and **47**, **54** was converted to **61a,b** and **62**.

***dl*-(1α,2α,5α)-2-[2-(Triphenylmethoxy)ethyl]bicyclo[3.1.0]hexan-3-one (55).** Mp 104–105 °C (from CH_2Cl_2–*n*-hexane); IR ($CHCl_3$) 1730 cm^{-1}; NMR ($CDCl_3$) δ 0.67–1.0 (1 H, m), 1.07–2.09 (5 H, m), 2.14–2.37 (2 H, m), 2.39–2.77 (1 H, m), 3.21 (2 H, t, J = 6 Hz), 7.17–7.67 (15 H, m). Anal. ($C_{27}H_{26}O_2$) C, H.

***dl*-(1α,2α,5α)-3-(Hydroxyimino)-2-[2-(triphenylmethoxy)ethyl]bicyclo[3.1.0]hexane (56).** IR ($CHCl_3$) 3580 cm^{-1}; NMR ($CDCl_3$) δ (mixture of syn and anti compounds) 0.40–0.77 (1 H, m), 0.90–3.40 (8 H, m), 3.23 (2 H, t, J = 6 Hz), 7.1–7.7 (16 H, m).

***dl*-(1α,2α,3β,5α)-3-[(Phenylsulfonyl)amino]-2-[2-(triphenylmethoxy)ethyl]bicyclo[3.1.0]hexane (58).** IR ($CHCl_3$) 3360, 1330, 1160 cm^{-1}; NMR ($CDCl_3$) δ 0.0–0.3 (1 H, m), 0.4–0.7 (m, 1 H), 0.7–2.27 (7 H, m), 3.0 (2 H, t, J = 6 Hz), 3.2–3.5 (1 H, m), 4.43 (1 H, d, J = 6 Hz), 7.17–7.65 (19 H, m), 7.7–7.9 (2 H, m).

***dl*-(1α,2α,3β,5α)-2-(Hydroxyethyl)-3-[(phenylsulfonyl)amino]bicyclo[3.1.0]hexane (59).** IR ($CHCl_3$) 3360, 3250, 1330, 1160 cm^{-1}; NMR ($CDCl_3$) δ 0.12–0.33 (1 H, m), 0.43–0.77 (1 H, m), 0.86–2.33 (9 H, m), 3.27–3.63 (1 H, m), 4.8–5.05 (1 H, d, J = 6 Hz), 7.43–7.67 (3 H, m), 7.8–8.0 (2 H, m).

***dl*-(1α,2α,3β,5α)-2-(Formylmethyl)-3-[(phenylsulfonyl)amino]bicyclo[3.1.0]hexane (60).** IR ($CHCl_3$) 3350, 1715, 1338, 1155 cm^{-1}; NMR ($CDCl_3$) δ 0.24–0.47 (1 H, m), 0.53–0.84 (1 H, m), 0.87–1.90 (3 H, m), 1.95–2.57 (4 H, m), 3.23–3.6 (1 H, m), 4.85 (1 H, d, J = 6 Hz), 7.4–7.8 (3 H, m), 7.89–8.0 (2 H, m), 9.68 (1 H, s).

***dl*-(1α,2α,3β,5α)-7-[3-[(Phenylsulfonyl)amino]bicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptenoic Acid (61a).** Mp 81–83 °C (AcOEt–*n*-pentane); IR ($CHCl_3$) 3360, 3250, 1705, 1320, 1160 cm^{-1}; NMR ($CDCl_3$) δ 0.08–0.33 (1 H, m), 0.36–0.73 (1 H, m), 0.74–1.3 (2 H, m), 1.3–2.43 (11 H, m), 3.13–3.53 (1 H, m), 4.92 (1 H, d, J = 6 Hz), 5.06–5.50 (2 H, m), 7.43–7.66 (3 H, m), 7.76–8.01 (2 H, m), 8.53–9.66 (1 H, m). Anal. ($C_{19}H_{25}NO_4S$) C, H, N, S.

***dl*-Methyl (1α,2α,3β,5α)-7-[3-[(Phenylsulfonyl)amino]bicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptenoate (62).** IR ($CHCl_3$) 3350, 1720, 1350, 1155 cm^{-1}; NMR ($CDCl_3$) δ 0.08–0.34 (1 H, m), 0.39–0.71 (1 H, m), 0.86–1.29 (2 H, m), 1.45–2.39 (11 H, m), 3.16–3.46 (1 H, m), 3.63 (3 H, s), 4.64 (1 H, d, J = 6 Hz), 5.03–5.49 (2 H, m), 7.43–7.66 (3 H, m), 7.76–7.99 (2 H, m).

***dl*-Sodium (1α,2α,3β,5α)-7-[3-[(Phenylsulfonyl)amino]bicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptenoate (61b).** Anal. ($C_{19}H_{24}O_4NSNa\cdot{}^1/_4H_2O$) C, H, N, S, Na.

***dl*-*cis*-2-(2-Acetoxycyclopent-4-enyl)ethanol Triphenylmethyl Ether (3).** A mixture of 15.3 g (41.3 mmol) of **1**, 40 mL of acetic anhydride, and 0.1 g of 4-(dimethylamino)pyridine in 60 mL of pyridine was allowed to react at room temperature for 2 h. The solvent and excess reagent were evaporated in vacuo, and the product was isolated by AcOEt extraction. The AcOEt layer was washed with diluted aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried, and evaporated. The residue was purified by column silica gel chromatography using an AcOEt–*n*-hexane (1:9) mixture as an eluent and 16.87 g (99.0%) of **3** was obtained: IR ($CHCl_3$) 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.5–3.05 (5 H, m), 1.9 (3 H, s), 3.14 (2 H, t, J = 6 Hz), 5.2–5.45 (1 H, m), 5.6 (2 H, s), 7.05–7.9 (15 H, m).

***dl*-(1α,2α,3α,5α)-6,6-Dibromo-3-acetoxy-2-[2-(triphenylmethoxy)ethyl]bicyclo[3.1.0]hexane (63).** A mixture of 16.5 g (40 mmol) of **3**, 14 mL (160 mmol) of bromoform, 1 g of benzyltriethylammonium chloride, and 50 mL of 40% aqueous NaOH in 80 mL of CH_2Cl_2 was stirred vigorously at 50 °C for 20 h. After cooling, the mixture was diluted with 200 mL of CH_2Cl_2, and the insoluble material was removed by filtration through a pad of Hyflo Super Cel. The filtrate was washed with water and saturated aqueous NaCl, then dried, and evaporated. The residue was purified by column silica gel chromatography using an AcOEt–*n*-hexane (1:9) mixture as an eluent and 19.6 g (84%) of **63** was obtained: IR ($CHCl_3$) 1735 cm^{-1}; NMR ($CDCl_3$) δ 1.5–2.55 (7 H, m), 1.92 (3 H, s), 3.16 (2 H, t, J = 6 Hz), 5.06–5.3 (1 H, m), 7.1–7.7 (15 H, m).

***dl*-(1α,2α,3α,5α)-3-Acetoxy-6,6-dimethyl-2-[2-(triphenylmethoxy)ethyl]bicyclo[3.1.0]hexane (64).** To a cooled suspension of 26.3 g (216 mmol) of cuprous thiocyanate in 250 mL of ether with dry ice-acetone bath at −60 °C was added 1.4 N methyllithium in ether, while the temperature was kept at −50 °C, and the mixture was gradually warmed to 0 °C in 30 min. Then the mixture was cooled to −20 °C, and a solution of 11.5 g (19 mmol) of **63** in 50 mL of ether and 8.56 mL (47.5 mmol) of HMPA were added dropwise and stirred at −20 °C for another 1 h. The mixture was cooled to −50 °C and a large excess of methyl iodide was added in one portion. After 10 min, the reaction mixture was quenched with aqueous NH_4Cl at −78°C and the insoluble material was removed by filtration through a pad of Hyflo Super Cel and washed with ether. The filtrate was washed with diluted aqueous NH_3 and saturated aqueous NaCl, dried, and evaporated to obtain a crude product of **64**. A portion of the product was recrystallized from MeOH: mp 89–90 °C; IR ($CHCl_3$) 1725 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (6 H, s), 0.8–1.4 (3 H, m), 1.4–2.2 (4 H, m), 1.92 (3 H, s), 3.12 (2 H, t, J = 6 Hz), 4.95–5.2 (1 H, m), 7.05–7.7 (15 H, m). Anal. ($C_{31}H_{34}O_3$) C, H. The product was subjected to the next reaction without further purification.

***dl*-(1α,2α,3α,5α)-6,6-Dimethyl-3-hydroxy-2-[2-(triphenylmethoxy)ethyl]bicyclo[3.1.0]hexane (65).** A mixture of the crude product **64** obtained in the previous reaction, 29 mL (58 mmol) of 2 N aqueous NaOH, 60 mL of MeOH, and 60 mL of THF was stirred under reflux for 3 h. The solvents were evaporated, and the product was isolated by AcOEt extraction. The AcOEt layer was washed with saturated aqueous NaCl, dried, and evaporated. The residue was purified by column silica gel chromatography using an AcOEt–*n*-hexane (1:5) mixture containing 2% of Et_3N as an eluent and 7.41 g (95.0% from **63**) of **65** was obtained as an oil: IR ($CHCl_3$) 3420 cm^{-1}; NMR ($CDCl_3$) δ 0.87 (3 H, s), 0.93 (3 H, s), 0.75–1.1 (1 H, m), 1.1–1.4 (1 H, m), 1.5–2.1 (1 H, m), 2.44 (1 H, br s), 3.0–3.43 (2 H, m), 4.12 (1 H, m), 7.0–7.8 (15 H, m).

***dl*-(1α,2α,5α)-6,6-Dimethyl-2-[2-(triphenylmethoxy)ethyl]bicyclo[3.1.0]hexan-3-one (66).** To a cooled and stirred solution of 0.74 mL (8.3 mmol) of oxalyl chloride in 20 mL of CH_2Cl_2 in a dry ice–acetone bath at −70 °C was added dropwise a solution of 1.2 mL (16.9 mmol) of DMSO in 1 mL of CH_2Cl_2, and the mixture was stirred for another 5 min. Next, a solution of 2.9 g (7.03 mmol) of **65** in 5 mL of CH_2Cl_2 was added dropwise. After the reaction mixture had been allowed to react at −60 °C for 20 min, 6.84 mL (49.2 mmol) of Et_3N was added and the temperature of the reaction mixture was allowed rise to room temperature. The oxidation product was isolated and purified as described for the preparation of **10** and 2.86 g (99%) of **66** was obtained as an oil: IR ($CHCl_3$) 1725 cm^{-1}; NMR ($CDCl_3$) δ 0.82 (3 H, s), 1.00 (3 H, s), 0.8–1.3 (2 H, m), 1.4–2.3 (4 H, m), 2.48 (1 H, dd, *J* = 20 and 6 Hz), 3.2 (2 H, t, *J* = 6 Hz), 7.1–7.6 (15 H, m). Anal. ($C_{29}H_{30}O_2$), C, H.

***dl*-(1β,2α,5β)-6,6-Dimethyl-2-[2-(triphenylmethoxy)ethyl]bicyclo[3.1.0]hexan-3-one (74).** A mixture of 4.5 g (11 mmol) of **66** and 10.86 g (96.8 mmol) of potassium *tert*-butoxide in 110 mL of DMF was stirred at room temperature for 8 h. The mixture was poured into a cooled and stirred solution of 12 g (0.2 mol) of acetic acid in 200 mL of CH_2Cl_2 with a dry ice–acetone bath at −20 °C, and the product was isolated by AcOEt extraction. The AcOEt layer was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried, and evaporated. The product was purified by column silica gel chromatography using an AcOEt–benzene (1:9) as an eluent and 3.37 g (75%) of **74** was obtained. A portion of the product was recrystallized from MeOH: mp 120–121 °C; IR ($CHCl_3$) 1725 cm^{-1}; NMR ($CDCl_3$) δ 0.80 (3 H, s), 0.93 (3 H, s), 1.0–1.68 (3 H, m), 2.0–2.93 (4 H, m), 3.03–3.48 (2 H, m), 7.10–7.60 (15 H, m). Anal. ($C_{29}H_{30}O_2$) C, H.

***dl*-(1β,2α,3α,5β)-6,6-Dimethyl-3-hydroxy-2-[2-(triphenylmethoxy)ethyl]bicyclo[3.1.0]hexane (75).** To a cooled solution of 1.64 g (4 mmol) of **74** in 164 mL of THF in an ice bath was added 2.03 g (8 mmol) of lithium tri-*tert*-butoxyaluminohydride, and the mixture was stirred at room temperature for 2.5 h. Excess reagent was decomposed by adding water and the product was isolated by AcOEt extraction. The AcOEt layer was washed with saturated aqueous NaCl, dried, and evaporated. The product was purified by column silica gel chromatography using benzene containing 1% of Et_3N as an eluent and 988 mg (60%) of **75** was obtained: IR ($CHCl_3$) 3430 cm^{-1}; NMR ($CDCl_3$) δ 0.77–1.13 (2 H, m), 0.88 (3 H, s), 1.30 (3 H, s), 1.44–1.80 (2 H, m), 1.80–2.22 (1 H, m), 2.23–2.6 (2 H, m), 2.77 (1 H, br s), 2.90–3.20 (1 H, m), 3.23–3.52 (1 H, m), 4.55 (1 H, t, *J* = 9 Hz), 7.1–7.6 (15 H, m).

By the procedure described for the conversion of **40** to **44**, **66** was converted to **70**.

***dl*-(1α,2α,5α)-6,6-Dimethyl-3-(hydroxyimino)-2-[2-(triphenylmethoxy)ethyl]bicyclo[3.1.0]hexane (67).** IR ($CHCl_3$) 3490, 3325 cm^{-1}; NMR ($CDCl_3$) δ (mixture of syn and anti compounds) 0.83 (3 H, s), 0.93 (3 H, s), 0.9–1.4 (2 H, m), 1.6–2.1 (2 H, m), 2.4–2.8 (3 H, m), 3.21 (3 H, m), 7.0–7.6 (15 H, m), 8.38 (1 H, br s), 0.83 (3 H, s), 0.9 (3 H, s), 0.95–2.25 (4 H, m), 2.27 (1 H, d, *J* = 18 Hz), 2.58 (1 H, dd, *J* = 18 and 5 Hz), 3.03 (1 H, m), 3.2 (2 H, t, *J* = 6 Hz), 7.0–7.7 (16 H, m).

***dl*-(1α,2α,3β,5α)-6,6-Dimethyl-3-[(phenylsulfonyl)amino]-2-[2-(triphenylmethoxy)ethyl]bicyclo[3.1.0]hexane (69).** Mp 163–165 °C (from MeOH); IR ($CHCl_3$) 3360, 1320, 1160 cm^{-1}; NMR ($CDCl_3$) δ 0.87 (3 H, s), 0.93 (3 H, s), 0.6–1.2 (5 H, m), 1.2–2.2 (5 H, m), 2.9–3.2 (2 H, m), 3.2–3.6 (1 H, m), 4.98 (1 H, d, *J* = 8 Hz), 7.1–7.95 (18 H, m), 7.7–7.95 (2 H, m). Anal. ($C_{35}H_{37}NO_3S$) C, H, N.

***dl*-(1α,2α,3β,5α)-6,6-Dimethyl-2-(hydroxyethyl)-3-[(phenylsulfonyl)amino]bicyclo[3.1.0]hexane (70).** IR ($CHCl_3$) 3550, 3370, 1325, 1165 cm^{-1}; NMR ($CDCl_3$) δ 0.9 (3 H, s), 0.94 (3 H, s), 0.6–1.3 (2 H, m), 1.4–2.15 (5 H, m), 2.35 (1 H, br s), 3.43 (1 H, br s), 3.62 (2 H, t, *J* = 6 Hz), 5.7–6.0 (1 H, d, *J* = 7 Hz), 7.4–7.7 (3 H, m), 7.8–8.1 (2 H, m).

By the procedure described for the conversion of **9** to **11a,b** and **12**, **70** was then converted to **72a,b** and **73**.

***dl*-(1α,2α,3β,5α)-6,6-Dimethyl-2-(formylmethyl)-3-[(phenylsulfonyl)amino]bicyclo[3.1.0]hexane (71).** NMR ($CDCl_3$) δ 0.9 (3 H, s), 0.99 (3 H, s), 0.55–1.45 (3 H, m), 1.7–2.2 (2 H, m), 2.4–2.9 (2 H, m), 3.2–3.7 (1 H, m), 5.67 (1 H, br s), 7.35–7.7 (3 H, m), 7.75–8.0 (2 H, m), 9.65 (1 H, s).

***dl*-(1α,2α,3β,5α)-7-[6,6-Dimethyl-3-[(phenylsulfonyl)amino]bicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptenoic Acid (72a).** IR ($CHCl_3$) 3360, 3250, 1705, 1320, 1160 cm^{-1}; NMR ($CDCl_3$) δ 0.9 (3 H, s), 0.92 (3 H, s), 0.6–2.25 (11 H, m), 2.34 (2 H, t, *J* = 6 Hz), 3.47 (1 H, m), 5.2–5.5 (1 H, m), 5.65 (1 H, d, *J* = 9 Hz), 7.35–7.7 (3 H, m), 7.8–8.0 (2 H, m), 9.09 (1 H, br s).

***dl*-Methyl (1α,2α,3β,5α)-7-[6,6-Dimethyl-3-[(phenylsulfonyl)amino]bicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptenoate (73).** IR ($CHCl_3$) 3360, 3270, 1720 cm^{-1}; NMR ($CDCl_3$) δ 0.65–1.10 (2 H, m), 0.93 (3 H, s), 0.94 (3 H, s), 1.3–2.35 (11 H, m), 3.35–3.55 (1 H, m), 3.71 (3 H, s), 4.99 (1 H, d, *J* = 8 Hz), 5.2–5.4 (2 H, m), 7.45–7.65 (3 H, m), 7.83–7.93 (2 H, m).

***dl*-Sodium (1α,2α,3β,5α)-7-[6,6-Dimethyl-3-[(phenylsulfonyl)amino]bicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptenoate (72b).** Anal. ($C_{21}H_{28}O_4NSNa{\cdot}H_2O$) C, H, N, S, Na.

By the procedure described for the conversion of **2** to **8**, **75** was converted to **80**.

***dl*-(1β,2α,3β,5β)-3-Azido-6,6-dimethyl-2-[2-(triphenylmethoxy)ethyl]bicyclo[3.1.0]hexane (77).** IR ($CHCl_3$) 2080 cm^{-1}; NMR ($CDCl_3$) δ 0.73–1.2 (2 H, m), 0.80 (3 H, s), 0.97 (3 H, s), 1.4–2.6 (5 H, m), 2.98–3.43 (3 H, m), 7.1–7.63 (15 H, m).

***dl*-(1β,2α,3β,5β)-6,6-Dimethyl-3-[(phenylsulfonyl)amino]-2-[2-(triphenylmethoxy)ethyl]bicyclo[3.1.0]hexane (79).** Mp 166–167 °C (MeOH); IR ($CHCl_3$) 3360, 1320, 1155 cm^{-1}; NMR ($CDCl_3$) δ 0.63–1.07 (2 H, m), 0.84 (3 H, s), 0.89 (3 H, s), 1.1–2.4 (5 H, m), 2.85–3.4 (3 H, m), 4.65 (1 H, d, *J* = 9 Hz), 7.1–7.62 (18 H, m), 7.78–7.98 (2 H, m). Anal. ($C_{35}H_{37}NO_3S$) C, H, N.

***dl*-(1β,2α,3β,5β)-6,6-Dimethyl-2-(hydroxyethyl)-3-[(phenylsulfonyl)amino]bicyclo[3.1.0]hexane (80).** IR ($CHCl_3$) 3100, 1325, 1155 cm^{-1}; NMR ($CDCl_3$) δ 0.63–1.3 (2 H, m), 0.88 (3 H, s), 0.95 (3 H, s), 1.3–2.7 (6 H, m), 3.0–3.38 (1 H, m), 3.68 (2 H, t, *J* = 6 Hz), 5.33–5.9 (1 H, m), 7.32–7.67 (3 H, m), 7.79–8.0 (2 H, m).

By the procedure described for the conversion of **9** to **11a,b** and **12**, **80** was then converted to **82a,b** and **83**.

***dl*-(1β,2α,3β,5β)-6,6-Dimethyl-2-(formylmethyl)-3-[(phenylsulfonyl)amino]bicyclo[3.1.0]hexane (81).** IR ($CHCl_3$) 3360, 2825, 2725, 1725, 1330, 1160 cm^{-1}; NMR ($CDCl_3$) δ 0.85–1.2 (2 H, m), 0.86 (3 H, s), 0.96 (3 H, s), 1.2–2.3 (3 H, m), 2.53–2.7 (2 H, m), 3.05–3.4 (1 H, m), 5.25–5.5 (1 H, m), 7.47–7.7 (3 H, m), 7.8–8.0 (2 H, m).

***dl*-(1β,2α,3β,5β)-7-[6,6-Dimethyl-3-[(phenylsulfonyl)amino]bicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptenoic Acid (82a).** IR ($CHCl_3$) 3350, 3240, 1700, 1315, 1150 cm^{-1}; NMR ($CDCl_3$) δ 0.73–1.10 (2 H, m), 0.87 (3 H, s), 0.99 (3 H, s), 1.3–2.3 (9 H, m), 2.35 (2 H, t, *J* = 6 Hz), 2.95–3.4 (1 H, m), 5.07 (1 H, d, *J* = 9 Hz), 5.2–5.55 (2 H, m), 7.39–7.68 (3 H, m), 7.77–7.97 (2 H, m), 7.9–8.9 (1 H, m).

***dl*-Methyl (1β,2α,3β,5β)-7-[6,6-Dimethyl-3-[(phenylsulfonyl)amino]bicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptenoate (83).** IR ($CHCl_3$) 3350, 1720, 1320, 1155 cm^{-1}; NMR ($CDCl_3$) δ 0.85–1.15 (2 H, m), 0.88 (3 H, s), 1.00 (3 H, s), 1.37–2.50 (11 H, m), 3.0–3.45 (1 H, m), 3.70 (3 H, s), 4.77 (1 H, d, *J* = 9 Hz), 5.2–5.6 (2 H, m), 7.43–7.7 (3 H, m), 7.8–8.03 (2 H, m).

***dl*-Sodium (1β,2α,3β,5β)-7-[6,6-Dimethyl-3-[(phenylsulfonyl)amino]bicyclo[3.1.0]hex-2-yl]-5(*Z*)-heptenoate (82b).** Anal. ($C_{21}H_{28}O_4NSNa{\cdot}H_2O$) C, H, N, S, Na.

Biological Methods. Materials. [^{3}H]S-145 was synthesized at Shionogi Research Laboratories, Osaka, Japan. Collagen (type IV, soluble), thrombin, arachidonic acid, ADP, and bovine serum albumin (BSA) were purchased from Sigma, St. Louis. Collagen was solubilized in isotonic saline before use.

Inhibitory Effect on Rabbit PRP Aggregation: Preparation of Rabbit PRP. Mature male rabbits (NIBS-JW) weighing 2.2–2.6 kg were used. With the animal under sodium pentobarbital anesthesia (Somnopentyl, Pitman Moore, ca. 20 mg/kg, iv), blood was withdrawn from the carotid artery through a cannulation tube using a syringe containing sodium citrate (3.8%, $^1/_{10}$ volume). The sample was left standing for 20 min at room temperature and then centrifuged at 210*g* for 10 min at 22 °C to obtain PRP. The remaining blood was centrifuged at 3000 rpm for 10 min to obtain platelet-poor plasma (PPP).

Measurement of Inhibition of Platelet Aggregation. Platelet aggregation was examined by the method of Born,[24] using an AUTO-RAM61 type aggregometer (Rika-Denki Co., Ltd., Tokyo) as reported previously.[25] A pair of samples of PRP (400 μL) placed in a cuvette were warmed at 37 °C for 1 min with stirring (1200 rpm), and then a saline solution of the test compound (50 μL) or saline was added. Exactly 2 min later, a solution of sodium arachidonate (50 μL) was added to each of the samples, and the changes in light transmission were recorded, with the light transmission for PRP and PPP taken as 0% and 100%, respectively, and the maximum light transmission after addition of sodium arachidonate as the maximum aggregation. The percent inhibition α was expressed as the difference between 1 and the ratio of the maximum aggregation with the test compound to that with the saline.

The IC_{50} value for each compound was obtained by regression analysis of the concentration–inhibition relationship among 12–16 points of α covering three concentrations and ranging from 20 to 80%, obtained by three experiments. The IC_{50} values obtained were calibrated for the IC_{50} value (standard: 1.0 μM) of S-145 obtained with the same PRP sample and are shown in Table I. The IC_{50} values for S-145 fluctuated [1.29 ± 0.42 (SD) μM, n = 21] for each sample of platelets, and thus the confidence limits of the IC_{50} values shown in Table I are believed to be of this level.

Inhibitory Effect on WP Aggregation: Preparation of WP. Rat blood was taken from the abdominal aorta with an injection syringe under sodium methylhexabarbital anesthesia and was collected into 0.15 volumes of acid citrate dextrose (85 mM disodium citrate, 70 mM citric acid, and 110 mM glucose) containing 12 μg/mL PGE_1. PRP obtained by centrifugation at 160*g* for 10 min was layered on 40% bovine serum albumin. Platelets were sedimented at 1200*g* for 25 min and resuspended in 0.5 mL of resuspension buffer (137 mM NaCl, 2.7 mM KCl, 1.0 mM $MgSO_4$, 3.8 mM NaH_2PO_4, pH 7.35). Platelets were separated from plasma proteins by gel filtration through a column of Sepharose 2B and suspended in the resuspension buffer.

Measurement of Inhibition of Platelet Aggregation. Rat WP (5×10^8 cells/mL) were preincubated with 1 mM $CaCl_2$ for 2 min at 37 °C in the presence of various concentrations of the test compounds dissolved in water, and then 4 μg/mL of collagen was added. The aggregation was monitored with the aggregometer in terms of the increase in light transmission. The IC_{50} values for each compound, calculated from the values of percent inhibition obtained by three experiments and calibrated (standard: 1.0 nM) in a similar way to that described above, are shown in Table I. The IC_{50} value of S-145 fluctuated for every experiment [1.56 ± 0.82 (SD) nM, n = 8].

Measurement of Platelet Shape Change. Rat WP (5×10^8 cells/mL) were preincubated with 1 mM Ca_2Cl_2 for 2 min at 37 °C, and then 1 μM test compounds dissolved in water were added. The response of platelet shape change induced by each compound was monitored with the aggregometer in terms of the increase in light transmission and were expressed as a percentage of that induced by 1 μM S-145.

Binding Experiments. The binding assays in rat WP were carried out according to the method used in the [^{3}H]U46619 binding as described previously.[22] The specific binding of [^{3}H]S-145 is defined as the differences between binding in the presence and absence of 10 μM unlabeled S-145.

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(24) Born, G. V. R. *Nature (London)* **1962**, *194*, 927.

(25) Uchida, K.; Nakamura, M.; Konishi, M.; Ishigami, T.; Komeno, T. *Jpn. J. Pharmacol.* **1987**, *43*, 9.

(26) Reagents (Schemes I–V): (a) sodium azide (NaN_3) in *N,N*-dimethylformamide (DMF), (b) triphenylphosphine (Ph_3P) in tetrahydrofuran (THF), (c) aqueous THF, (d) benzenesulfonyl chloride ($PhSO_2Cl$), triethylamine (Et_3N), in CH_2Cl_2, (e) 1 N HCl in THF–MeOH, (f) 3-chloroperoxybenzoic acid (*m*-CPBA) in CH_2Cl_2, (g) oxalyl chloride [$(COCl)_2$], dimethyl sulfoxide (DMSO, Me_2SO) in CH_2Cl_2–Et_3N, (h) sodium (methylsulfinyl)methide ($Na^+MeS({=}O)CH_2^-$), (4-carboxybutyl)triphenylphosphonium bromide ($Br^-Ph_3P^+(CH_2)_4CO_2H$), in DMSO, (i) diazomethane (CH_2N_2) in CH_2Cl_2–ether, (j) 0.1 N aqueous NaOH, (k) diethyl azodicarboxylate ($EtO_2CN{=}NCO_2Et$), Ph_3P, benzoic acid ($PhCO_2H$) in THF, (l) K_2CO_3 in MeOH–H_2O, (m) methanesulfonyl chloride ($MeSO_2Cl$), Et_3N, in CH_2Cl_2, (n) thiocyanic acid (HSCN) in ether, (o) KOH in MeOH–dioxane, (p) Zn(Ag), diiodomethane (CH_2I_2) in ether, (q) triphenylmethyl chloride (trityl chloride, TrCl, Ph_3CCl), Et_3N, 4-(dimethylamino)pyridine (4-$Me_2NC_6H_4N$), in CH_2Cl_2, (r) pyridinium dichromate (PDC) in DMF, (s) hydroxyamine hydrochloride ($NH_2OH{\cdot}HCl$), NaOH in MeOH, (t) diphenyl disulfide (Ph_2S_2), tributylphosphine (*n*-Bu_3P), in THF–sodium cyanoborohydride ($NaBH_3CN$), acetic acid (AcOH), (u) bromoform ($CHBr_3$), benzyltriethylammonium chloride ($PhCH_2N(Et)_3Cl$), 40% aqueous NaOH in CH_2Cl_2, (v) cuprous thiocyanate (CuSCN), methyllithium (MeLi), hexamethylphosphoramide (HMPA), in ether–methyl iodide (MeI), (w) NaOH in MeOH–THF–H_2O, (x) potassium *tert*-butoxide (Me_3COK) in DMSO–AcOH, (y) lithium tri-*tert*-butoxyaluminohydride [$LiAlH(OCMe_3)_3$] in THF.