Thromboxane A_2 Receptor Antagonists. II. Synthesis and Pharmacological Activity of 6,6-Dimethylbicyclo[3.1.1]heptane Derivatives with the Benzenesulfonylamino Group

Kaoru SENO and Sanji HAGISHITA*

Shionogi Research Laboratories, Shionogi & Co., Ltd., Fukushima-ku, Osaka 553, Japan. *Received July 27, 1988*

Various stereoisomers based on the α- and ω-side chain ring junctions of 6,6-dimethylbicyclo[3.1.1]heptane were synthesized. Their sodium salts 12, 18, 20, 30 and 37 were examined *in vitro* for their inhibitory activity toward aggregation of rabbit platelet-rich plasma and rat washed platelets. Their potency was very high and the partial agonist effect was small. The differences of the side chain ring junctions did not affect the activity very much. Homologation in the ω-side chain (as in 47) decreased the activity.

Keywords prostaglandin; thromboxane A_2; receptor antagonist; pinane; benzenesulfonylamino group; stereoisomer; optical activity; platelet aggregation

New therapeutic agents acting as receptor antagonists of the thromboxane A_2 (TXA_2) system have been the target of much development activity. Several drugs, such as S-145,[1] SQ-29548[2] and ONO-3708,[3] possess the characteristics of TXA_2 receptor antagonists and are under preclinical evaluation. In a previous paper,[4] we reported the synthesis and *in vitro* inhibitory activity toward platelet aggregation of 7-oxa-bicyclo[2.2.1]heptane derivatives which were mimics of S-145 with oxygen in place of carbon at the 7-position (Fig. 1). In terms of the bicyclic skeleton, they are prostaglandin H_2 (PGH_2) analogues. Although PGH_2 itself fits the TXA_2 receptor and acts as an agonist, the TXA_2 ring system remains a desirable target. The instability of the ring has led to the preparation of a number of more stable analogues.[5] Since both enantiomers of pinane derivatives are readily available as starting materials, we chose the pinane framework as the bicyclic skeleton. There are four stereoisomers based on the combinations of the directions of the α- and ω-side chains (Fig. 1). The Squibb group[6] reported that prostaglandin activity was very sensitive to stereoisomerism at side chain ring junctions. We also reported[4] that the stereoisomerism of the ring junction of the α-side chain and the benzenesulfonylamino group affected the platelet aggregation–inhibitory activity.

In an attempt to find more active TXA_2 receptor antagonists which lack the partial agonist effect (causing shape change of the platelets before their aggregation), we synthesized four stereoisomers and investigated their platelet aggregation–inhibitory activity. The 1*S*,2*S*,3*S*,5*R*-isomer showed potent *in vitro* inhibitory activity against aggregation of rat washed platelets and did not show the partial agonist effect. We then synthesized the one-carbon homologated compound in the ω-side chain.

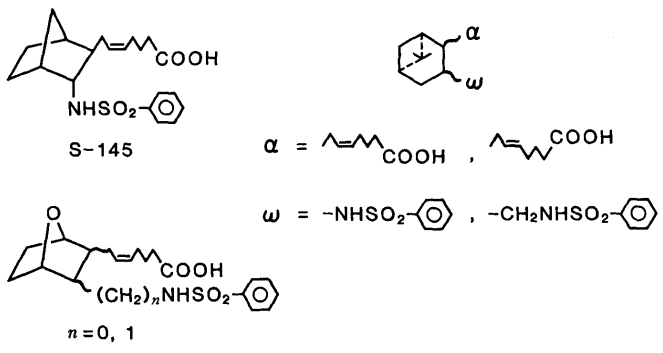


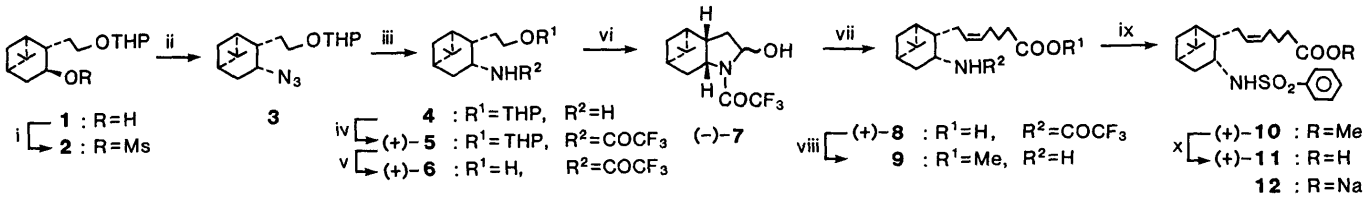
Fig. 1

Synthesis

Several groups have exploited the naturally chiral pinane derivatives to obtain optically active prostaglandin analogues.[3,4,7,8] We chose commercially available (−)-nopol and (−)-myrtenol as starting materials.

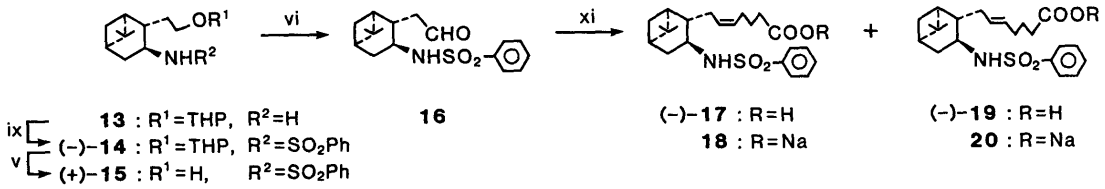
(1*S*,2*S*,3*S*,5*R*)-2-[2-(Tetrahydropyran-2-yloxy)ethyl]-3-hydroxy-6,6-dimethylbicyclo[3.1.1]heptane,[3] **1**, obtained *via* two steps from (−)-nopol, was converted to the methanesulfonyl derivative **2**, which was then treated with sodium azide in hexamethylphosphoric triamide to give **3** with inversion of the configuration. The azide **3** was reduced with lithium aluminum hydride and the amine was purified by converting it to the trifluoroacetamide derivative (+)-**5**. Removal of the tetrahydropyranyl protecting group and Swern oxidation of the alcohol (+)-**6** afforded the cyclized aldehyde equivalent (−)-**7** as crystals, which must have been one isomer and showed mutarotation in methanol. Wittig reaction of (−)-**7** with (4-carboxybutyl)-triphenylphosphonium bromide and sodium hydride-dimethylsulfoxide gave the condensed product (+)-**8** in good yield. This reaction was carried out with potassium *tert*-butoxide in tetrahydrofuran at room temperature and gave a *ca.* 1 : 1 mixture of (+)-**8** and the 5(*E*)-isomer. The latter was identified from the infrared (IR) absorption at 970 cm^{-1} and two kinds of signals in 1 : 1 ratio attributable to one of the methyl groups in the nuclear magnetic resonance (NMR) spectrum of the hydrolyzed compound. Hydrolysis of (+)-**8** with aqueous sodium hydroxide gave the amino acid, which was difficult to purify and gave **9** after being esterified with diazomethane. Condensation of benzenesulfonyl chloride gave the ester (+)-**10** which was hydrolyzed to (+)-**11**. The sodium salt **12** was lyophilized for use in biological tests.

(1*S*,2*S*,3*S*,5*R*)-2-[2-(Tetrahydropyran-2-yloxy)ethyl]-3-amino-6,6-dimethylbicyclo[3.1.1]heptane,[3] **13**, which was also obtained from (−)-nopol was condensed with benzenesulfonyl chloride to give (−)-**14**. Removal of the tetrahydropyranyl group, followed by Swern oxidation gave the aldehyde **16** in good yield. Wittig reaction using potassium *tert*-butoxide as above furnished a 4.4 : 1 mixture of 5(*Z*)- and 5(*E*)-isomers, (−)-**17** and (−)-**19**, which were separated by flash chromatography. The target 5(*Z*)-



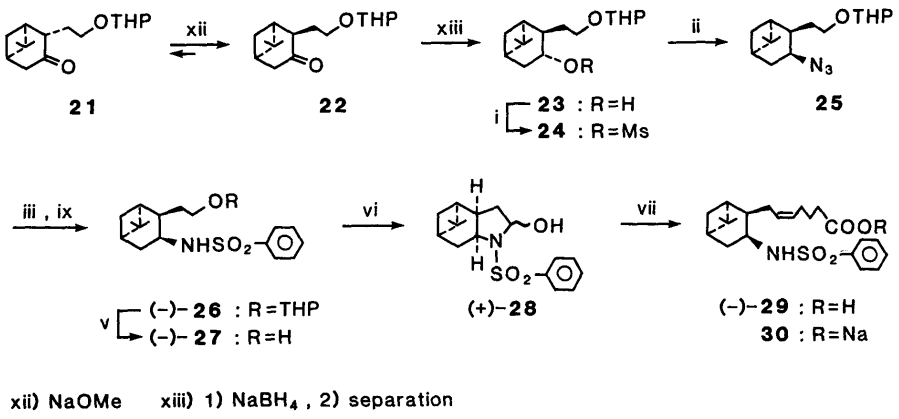
i) MsCl, Et_3N ii) NaN_3, HMPA iii) $LiAlH_4$ iv) $(CF_3CO)_2O$, Py. v) *p*-TsOH, MeOH
vi) 1) DMSO, $(COCl)_2$, 2) Et_3N vii) NaH-DMSO, $Ph_3\overset{+}{P}(CH_2)_4COOH\bar{B}r$
viii) 1) 10%KOH, 2) CH_2N_2 ix) $PhSO_2Cl$, Et_3N x) 10%NaOH

Chart 1



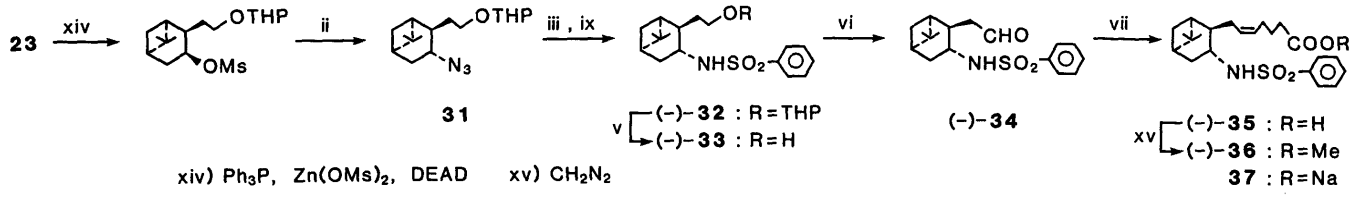
xi) *tert*-BuOK, $Ph_3\overset{+}{P}(CH_2)_4COOH\bar{B}r$

Chart 2



xii) NaOMe xiii) 1) $NaBH_4$, 2) separation

Chart 3



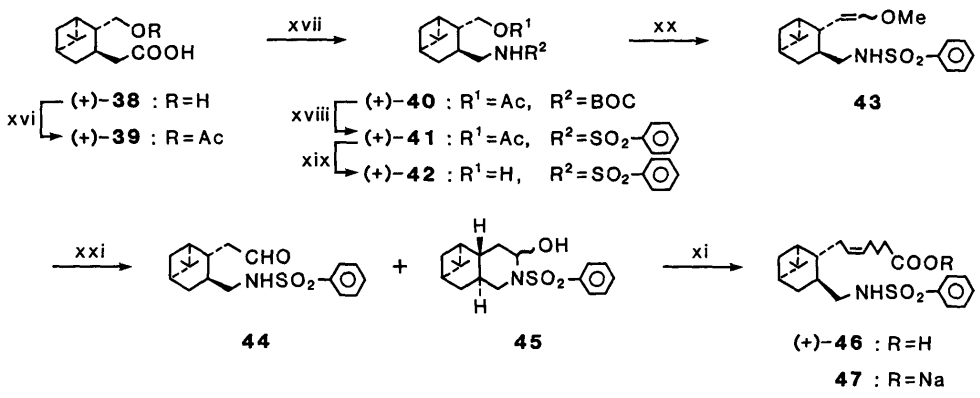
xiv) Ph_3P, $Zn(OMs)_2$, DEAD xv) CH_2N_2

Chart 4

isomer (−)-**17** was further purified by crystallization of its dicyclohexyl amine salt.

The ketone **21**, which was obtained by oxidation of **1**,[3] was treated with a 1.1 M solution of sodium methoxide in methanol to afford a 11 : 1 mixture of the epimerized ketone **22** and the starting material **21**. The mixture was reduced with sodium borohydride and separated by flash chromatography to give the *trans*-alcohol **23** in 90% yield. According to the same treatment as in Chart 1, **23** was converted with inversion of the configuration to the amine, which was purified by condensing it with benzenesulfonyl chloride. Furthermore, as in Chart 1, (−)-**26** was deprotected and oxidized to give the cyclized aldehyde equivalent (+)-**28** as an oil. Wittig reaction using sodium hydride-dimethylsulfoxide as above furnished the target 5(*Z*)-isomer (−)-**29**, which was also purified by crystallizing the dicyclohexyl amine salt.

The fourth compound is the *trans*-configuration form, and can be obtained by epimerizing the alcohol group at the C-3 position of **23**. However, Galynker and Still reported an efficient method for producing a tosylate with inversion of the configuration under the Mitsunobu conditions.[9] Zinc mesylate was used under the same conditions and the mesylate was treated with sodium azide as above. Thus, the azide **31** was prepared from **23** with retention of the configuration by double inversion of the configuration in



xvi) Ac_2O, Py. xvii) 1) Curtius, 2) *tert*-BuOH, Δ xviii) 1) CF_3COOH, 2) ix xix) KOH
xx) 1) vi, 2) $Ph_3\overset{+}{P}CH_2OCH_3\bar{C}l$, *tert*-BuOK xxi) 20%$CF_3COOH$

Chart 5

31% overall yield. The desired compound (−)-**35** was synthesized as described for (−)-**29** and was purified by converting it to the methyl ester (−)-**36** with diazomethane.

(+)-(1*S*,2*R*,3*R*,5*S*)-2-Hydroxymethyl-3-carboxymethyl-6,6-dimethylbicyclo[3.1.1]heptane,[7] prepared from (−)-myrtenol, was acylated and submitted to Curtius reaction. The obtained isocyanate derivative was heated with *tert*-butanol to give the *tert*-butoxycarbonyl (Boc) derivative (+)-**40**. Removal of the Boc group with trifluoroacetic acid furnished the amine, which was purified by converting it to the benzenesulfonylamino derivative (+)-**41**. Hydrolysis of the acetate followed by Swern oxidation of the alcohol (+)-**42** gave the aldehyde, which was not purified and was directly homologated by one carbon by means of the Wittig reaction with methoxymethyltriphenylphosphonium chloride and potassium *tert*-butoxide, followed by hydrolysis. The product was a *ca.* 1:2 mixture of **44** and **45** and was converted to the desired compound (+)-**46** by means of the Wittig reaction as above.

Biological Results and Discussion

The compounds prepared were examined *in vitro* for their inhibitory activity toward aggregation of rabbit platelet-rich plasma (PRP) induced by arachidonic acid and aggregation of rat washed platelets (WP) induced by collagen. S-145 was reported to be a good TXA_2 receptor antagonist. The IC_{50} value of S-145 was found to vary from 0.9—1.2 μM and 1.5—4.3 nM for rabbit PRP and rat WP, respectively. Thus each IC_{50} measured in a single experiment for the prepared compounds was corrected for the value obtained for the sodium salt of S-145, which was measured as the reference. IC_{50} values are shown in Table I. A few isomers showed a partial agonistic effect (shape change of platelets) and the relative values with respect to S-145 are listed in the table for rat WP. All four stereoisomers, (+)-**12**, (−)-**18**, (−)-**30** and (−)-**37**, showed potent inhibitory activity against aggregation of rat WP, but were more than 100 times weaker than S-145 in the case of rabbit PRP. The large difference hence arose from the species difference, as found for compounds with a pinane skeleton, such as ONO-3708 and ONO-11120.[10] From the results with rat WP, the latter three stereoisomers were similar in potency to S-145 and SQ-29548 and superior to ONO-3708. We and the Squibb group reported that the stereoisomerism at both side chain ring junctions of 7-oxabicyclo[2.2.1]heptane derivatives affected the inhibitory activity toward platelet aggregation.[4,6] But the activity of these pinane isomers seemed to be independent of the side chain stereochemistry. The partial agonistic effect was very weak and (−)-**18** did not exhibit any such effect. The 5(*E*)-isomer, (−)-**20**, had the same inhibitory potency as the 5(*Z*)-isomer (−)-**18** but the partial agonist activity was increased. Further, as shown by (+)-**47**, homologation in the ω-side chain decreased the potency of the inhibition, though no partial agonist activity was observed. As a result, in the compounds in which the nitrogen atom was bound directly to the bicyclic skeleton, the potency was very high and was less dependent on the side chain ring junction than that of the 7-oxabicyclo-[2.2.1]heptane derivatives.[4]

Table I. Inhibitory Concentration for Platelet Aggregation

Compound	IC_{50} Platelet aggregation		Partial agonist[c]
	Rabbit PRP[a] (μM)	Rat WP[b] (nM)	
(±)-S-145 Na salt	1.0[d]	2.9[e]	100
(+)-**12**	440	5.8	0
(−)-**18**	110	2.9	0
(−)-**20**	220	2.9	17
(−)-**30**	700	2.9	5
(−)-**37**	700	2.9	15
(+)-**47**	Negative	81	0
SQ-29548	8	2.9	0
ONO-3708	800	3.8	0
ONO-11120	400	150	0

a) Induced by 500 μM arachidonic acid. *b*) Induced by 4 μg/ml of collagen. *c*) Relative values (the value of S-145 is 100). *d*) The value varied from 0.9—1.2 μM in various measurements as the reference compound, so each IC_{50} of a test compound measured in a single experiment was corrected for the value for S-145 Na salt. *e*) The value varied from 1.5—4.3 nM in various measurements as the reference compound, so each IC_{50} of a test compound measured in a single experiment was corrected for the value for S-145 Na salt.

Experimental

Melting points are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Varian EM 390 spectrometer. IR spectra were recorded with a JASCO A-702 infrared spectrophotometer. Optical rotations were determined with a Perkin-Elmer Model 141 polarimeter using a 1-dm microcell. Circular dichroism curves were obtained using a JASCO Model J-40C spectropolarimeter. Mass spectra (MS) were

taken with a Hitachi M-68 mass spectrometer.

(1*S*,2*S*,3*S*,5*R*)-2-[2-(Tetrahydropyran-2-yloxy)ethyl]-3-methanesulfonyloxy-6,6-dimethylbicyclo[3.1.1]heptane (2) Methanesulfonyl chloride (6.16 g) was added dropwise to a solution of (1*S*,2*S*,3*S*,5*R*)-2-[2-(tetrahydropyran-2-yloxy)ethyl]-3-hydroxy-6,6-dimethylbicyclo[3.1.1]heptane[3] (**1**, 13 g) and triethylamine (9.9 ml) in dichloromethane (130 ml) at −20 °C under nitrogen. The mixture was stirred for 15 min at −20 °C, washed with aqueous ammonium chloride and water, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give **2** (16 g). NMR ($CDCl_3$) δ: 0.92 (3H, s), 1.12 (1H, d, J=10 Hz), 1.22 (3H, s), 1.36—2.86 (14H), 3.03 (3H, s), 3.30—3.63 (2H, m), 3.67—3.93 (2H, m), 4.57 (1H, m), 5.06 (1H, m).

(1*S*,2*S*,3*R*,5*R*)-2-[2-(Tetrahydropyran-2-yloxy)ethyl]-3-azido-6,6-dimethylbicyclo[3.1.1]heptane (3) A mixture of **2** (16 g) and sodium azide (4.73 g) in hexamethylphosphoric triamide (60 ml) was stirred at 50 °C for 2 h under nitrogen. Ether was added. The mixture was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was submitted to flash chromatography on silica gel in hexane–ethyl acetate (20 : 1) to give **3** (8.64 g). NMR ($CDCl_3$) δ: 0.96 (3H, s), 1.12 (1H, d, J=10 Hz), 1.16 (3H, s), 1.36—2.68 (14H), 3.21—3.97 (4H), 4.22 (1H, td, J=10, 6 Hz), 4.54 (1H, m).

(1*S*,2*S*,3*R*,5*R*)-2-[2-(Tetrahydropyran-2-yloxy)ethyl]-3-amino-6,6-dimethylbicyclo[3.1.1]heptane (4) A solution of **3** (8.64 g) in ether (100 ml) was added to a slurry of lithium aluminum hydride (1.2 g) in ether (200 ml) at 0 °C and the mixture was heated under reflux for 1 h. Ice (10 g) and then 10% aqueous sodium hydroxide (300 ml) were added with cooling in ice, and the organic phase was separated. The aqueous phase was extracted with ether. The combined organic phases were washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give **4** (7.56 g). NMR ($CDCl_3$) δ: 0.93 (3H, s), 1.16 (3H, s), 1.28 (1H, d, J=9 Hz), 1.30—2.47 (16H), 3.16—3.97 (5H), 4.56 (1H, m).

(+)-(1*S*,2*S*,3*R*,5*R*)-2-[2-(Tetrahydropyran-2-yloxy)ethyl]-3-trifluoroacetylamino-6,6-dimethylbicyclo[3.1.1]heptane (+)-(5) Trifluoroacetic acid was added dropwise to a solution of **4** (7.56 g) in dichloromethane (200 ml) and pyridine (23 ml) with cooling in ice. The mixture was stirred at 0 °C for 15 min and washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was submitted to flash chromatography in hexane–ethyl acetate (9 : 1) to give (+)-**5** (9.9 g). $[\alpha]_D^{25}$ +63.8° (c=2.241, MeOH). IR (film): 3310, 1697, 1554 cm^{-1}. NMR ($CDCl_3$) δ: 0.97 (3H, s), 1.21 (3H, s), 1.38 (1H, d, J=9 Hz), 1.40—2.78 (14H), 3.13—4.00 (4H), 4.45—4.93 (2H), 6.62 (1H, s). MS m/z: 364 (MH^+). *Anal.* Calcd for $C_{18}H_{28}F_3NO_3$: C, 59.49; H, 7.77; F, 15.68; N, 3.85. Found: C, 59.30; H, 7.84; F, 15.59; N, 3.80.

(+)-(1*S*,2*S*,3*R*,5*R*)-2-(2-Hydroxyethyl)-3-trifluoroacetylamino-6,6-dimethylbicyclo[3.1.1]heptane (+)-(6) A mixture of *p*-toluenesulfonic acid (115 mg) and (+)-**5** (9.7 g) in methanol (270 ml) was stirred at room temperature for 2 h. Triethylamine (5 ml) was added. The mixture was concentrated under reduced pressure. The residue was dissolved in chloroform. The solution was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Crystallization of the residue from chloroform–hexane gave needles (6.62 g). mp 143—144 °C. $[\alpha]_D^{25}$ +69.3° (c=2.639, MeOH). IR (KBr): 3450, 3220, 3080, 1695, 1566 cm^{-1}. NMR ($CDCl_3$) δ: 0.95 (3H, s), 1.21 (3H, s), 1.38 (1H, d, J=10 Hz), 2.21 (3H, s), 1.50—2.85 (9H), 3.61 (2H, m), 4.67 (1H, m), 6.25 (1H, s). MS m/z: 280 (MH^+). *Anal.* Calcd for $C_{13}H_{20}F_3NO_2$: C, 55.90, H, 7.22; F, 20.41; N, 5.02. Found: C, 56.22; H, 7.29; F, 20.34; N, 4.99.

(−)-(2*RS*,3a*S*,4*S*,6*R*,7a*R*)-2-Hydroxy-5,5-dimethyl-*N*-trifluoroacetyl-4,6-methanooctahydroindole (−)-(7) A solution of dimethylsulfoxide (3.4 ml) in dichloromethane (5 ml) was added dropwise to a stirred solution of oxalyl chloride (2 ml) in dichloromethane (25 ml) at −50 °C under nitrogen. The mixture was stirred at −50 °C for 2 min. A solution of (+)-**6** (2.79 g) in dichloromethane (20 ml) and dimethylsulfoxide (2 ml) was added to the solution at −50 °C. The mixture was stirred at −15 °C for 20 min and cooled to −50 °C. Triethylamine (10 ml) was added and the mixture was stirred for 5 min. Water (50 ml) was added. The mixture was extracted with ether–ethyl acetate (1 : 1). The extracts were washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was submitted to flash chromatography on silica gel in hexane–ethyl acetate (9 : 1) and recrystallized from dichloromethane–hexane to give (−)-**7** (1.9 g). mp 90—91 °C. $[\alpha]_D^{24}$ −63.8° (c=1.208, MeOH), (mutarotation, measured after standing for 1 h). IR (KBr): 3500, 1672 cm^{-1}. NMR ($CDCl_3$) δ: 0.89 (3H, s), 1.15 (1H, d, J=10 Hz), 1.21 (3H, s), 1.60—3.60 (9H), 4.23—4.80 (1H, m), 5.75—6.10 (1H, m). *Anal.* Calcd for $C_{13}H_{18}F_3NO_2$: C, 56.31; H, 6.54; F, 20.55; N, 5.05. Found: C, 56.25; H, 6.53; F, 20.73; N, 5.14.

(+)-(*Z*)-7-[(1*S*,2*S*,3*R*,5*R*)-3-(Trifluoroacetylamino)-6,6-dimethylbicyclo[3.1.1]hept-2-yl]hept-5-enoic Acid (+)-(8) A mixture of 50% sodium hydride (2.4 g) in dimethylsulfoxide (50 ml) was stirred at 70 °C for 1.5 h under nitrogen. A solution of (4-carboxybutyl)triphenylphosphonium bromide (1.08 g) in dimethylsulfoxide (25 ml) was added at room temperature. The mixture was stirred at room temperature for 15 min. A solution of (−)-**7** (1.664 g) in dimethylsulfoxide (20 ml) was added dropwise and the mixture was stirred at room temperature for 1 h. Ice water (100 ml) was added. The mixture was washed with ether, acidified with dilute hydrochloric acid and extracted with ether. The extracts were washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was submitted to flash chromatography on silica gel in hexane–ethyl acetate (4 : 1) to give (+)-**8** (2.107 g). $[\alpha]_D^{25}$ +94.0° (c=0.957, MeOH). IR (film): 3300, 3100, 1705, 1558 cm^{-1}. NMR ($CDCl_3$) δ: 0.97 (3H, s), 1.20 (3H, s), 1.32 (1H, d, J=10 Hz), 1.46—2.75 (14H), 4.70 (1H, m), 5.30 (2H, m), 6.31 (1H, br d, J=7 Hz), 7.20 (1H, br s).

Methyl (*Z*)-7-[(1*S*,2*S*,3*R*,5*R*)-3-Amino-6,6-dimethylbicyclo[3.1.1]hept-2-yl]hept-5-enoate (9) A mixture of (+)-**8** (1.995 g) and 10% aqueous sodium hydroxide (20 ml) was heated under reflux for 2 h, made neutral with acetic acid and concentrated under reduced pressure. The residue was dissolved in methanol (40 ml). The insoluble materials were removed by filtration. Again methanol (40 ml) was added and the insoluble materials were removed by filtration. Excess diazomethane in ether was added to the filtrate at 0 °C. The solution was concentrated under reduced pressure and the residue was submitted to flash chromatography on silica gel in chloroform–methanol (10 : 1) to give **9** (1.06 g). NMR ($CDCl_3$) δ: 0.99 (3H, s), 1.16 (3H, s), 1.22 (1H, d, J=10 Hz), 1.40—2.65 (16H), 3.5—3.9 (1H, m), 3.66 (3H, s), 5.36 (2H, m).

A Mixture of 5(*Z*)- and 5(*E*)-Isomers of 8 and 9 Potassium *tert*-butoxide (4.12 g) was added to a stirred suspension of (4-carboxybutyl)-triphenylphosphonium bromide (6.79 g) in tetrahydrofuran (60 ml). The mixture was stirred at room temperature for 30 min. A solution of (−)-**7** (1.7 g) in tetrahydrofuran (50 ml) was added at room temperature. The mixture was stirred at room temperature for 1 h. Water was added. The mixture was washed with ether, acidified with dilute hydrochloric acid and extracted with ether. The extracts were washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was submitted to flash chromatography on silica gel in hexane–ethyl acetate (4 : 1 to 2 : 1) to give a mixture of 5(*Z*)- and 5(*E*)-isomers of **8** but the NMR spectrum was identical with that of the 5(*Z*)-isomer (+)-**8**.

The mixture was hydrolyzed to **9** as described above. NMR showed it to be a *ca.* 1 : 1 mixture of 5(*Z*)- and 5(*E*)-isomers. NMR ($CDCl_3$) δ: 0.96 (1/2 × 3H, s), 1.00 (1/2 × 3H, s), 1.15 (3H, s), 1.23 (1H, d, J=10 Hz), 1.40—2.62 (16H), 3.66 (3H, s), 3.40—3.90 (1H, m), 5.38 (2H, m).

Methyl (+)-(*Z*)-7-[(1*S*,2*S*,3*R*,5*R*)-3-Benzenesulfonylamino-6,6-dimethylbicyclo[3.1.1]hept-2-yl]hept-5-enoate (+)-(10) A solution of **9** (1.06 g), benzenesulfonyl chloride (1.25 g) and triethylamine (10 ml) in dichloromethane (100 ml) was stirred at room temperature for 1 h, washed successively with dilute hydrochloric acid, 5% aqueous sodium carbonate and water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was submitted to flash chromatography on silica gel in hexane–ethyl acetate (10 : 1 to 4 : 1) to give (+)-**10**, (1.36 g). $[\alpha]_D^{25}$ +48.2° (c=1.826, MeOH). IR (film): 3285, 1737, 1322, 1160 cm^{-1}. NMR ($CDCl_3$) δ: 0.93 (3H, s), 1.13 (3H, s), 1.15 (1H, d, J=10 Hz), 1.43—2.53 (14H), 3.66 (3H, s), 4.02 (1H, m), 4.92 (1H, d, J=9 Hz), 5.26 (2H, m), 7.37—7.68 (3H), 7.85—7.96 (2H). MS m/z: 419 (M^+). CD (MeOH) λ nm ($\Delta\varepsilon$): 269 (+0.300), 262 (+0.390), 257 (+0.358), 221 (+4.63). *Anal.* Calcd for $C_{23}H_{33}NO_4S$: C, 65.84; H, 7.93; N, 3.34; S, 7.64. Found: C, 65.42; H, 7.91; N, 3.36; S, 7.52.

(+)-(*Z*)-7-[(1*S*,2*S*,3*R*,5*R*)-3-Benzenesulfonylamino-6,6-dimethylbicyclo[3.1.1]hept-2-yl]hept-5-enoic Acid (+)-(11) and Its Sodium Salt (12) A mixture of (+)-**10** (1.273 g), 40% potassium hydroxide (1.5 ml) and methanol (10 ml) was stirred at room temperature for 4 h, acidified with dilute hydrochloric acid and extracted with ethyl acetate. The extracts were washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was submitted to flash chromatography on silica gel in hexane–ethyl acetate (2 : 1) to give (+)-**11** (1.224 g). $[\alpha]_D^{25}$ +46.0° (c=1.620, MeOH). IR (film): 3285, 1708, 1320, 1160 cm^{-1}. NMR ($CDCl_3$) δ: 0.92 (3H, s), 1.11 (3H, s), 1.15 (1H, d, J=10 Hz), 1.43—2.53 (14H), 4.03 (1H, m), 5.06—5.48 (3H, m), 7.35—7.67 (3H), 7.84—7.96 (2H), 8.50 (1H, br s). MS m/z: 405 (M^+).

A 0.21 M solution of sodium methoxide in methanol (12.7 ml) was added to a solution of (+)-**11** (1.144 g) in methanol (15 ml). The volatile materials were removed by distillation under reduced pressure. The residue was dissolved in water (20 ml). The solution was treated with charcoal and

lyophilized to give **12** (1.143 g). IR (KBr): 3280, 1560, 1320, 1160 cm^{-1}.

(−)-(1*S*,2*S*,3*S*,5*R*)-2-[2-(Tetrahydropyran-2-yloxy)ethyl]-3-benzenesulfonylamino-6,6-dimethylbicyclo[3.1.1]heptane (−)-(14) (1*S*,2*S*,3*S*,5*R*)-2-[2-(Tetrahydropyran-2-yloxy)ethyl]-3-amino-6,6-dimethylbicyclo[3.1.1]-heptane[3] was treated as described for the preparation of (+)-**10** from **9**, to give (−)-**14** in 94.7% yield as needles. mp 116—117 °C. $[\alpha]_D^{26}$ −14.1° (*c*= 1.034, MeOH). IR (KBr): 3435, 3250, 1320, 1164 cm^{-1}. NMR ($CDCl_3$) δ: 0.77—0.97 (4H), 1.16 (3H, s), 1.33—2.53 (14H), 3.10—4.20 (5H), 4.47 (1H, m), 4.85 (1/2H, d, *J*=6 Hz), 5.12 (1/2H, d, *J*=6 Hz), 7.38—7.69 (3H), 7.82—8.08 (2H). *Anal.* Calcd for $C_{22}H_{33}NO_4S$: C, 64.83; H, 8.16; N, 3.44; S, 7.87. Found: C, 64.84; H, 8.16; N, 3.47; S, 7.73.

(+)-(1*S*,2*S*,3*S*,5*R*)-2-(2-Hydroxyethyl)-3-benzenesulfonylamino-6,6-dimethylbicyclo[3.1.1]heptane (+)-(15) The pyranyl ether (−)-**14** was converted to (+)-**15** as described for the preparation of (+)-**6**, in quantitative yield, mp 82—83 °C. $[\alpha]_D^{26}$ +0.88°, $[\alpha]_{365}^{26}$ −34.0° (*c*=1.359, MeOH). IR (KBr): 3385, 3170, 1318, 1152 cm^{-1}. NMR ($CDCl_3$) δ: 0.85 (1H, d, *J*=9 Hz), 0.86 (3H, s), 1.13 (3H, s), 1.42—2.47 (9H), 3.42—3.76 (3H), 5.28 (1H, d, *J*=7 Hz), 7.40—7.63 (3H), 7.86—7.97 (2H). *Anal.* Calcd for $C_{17}H_{25}NO_3S$: C, 63.13; H, 7.79; N, 4.33; S, 9.91. Found: C, 63.00; H, 7.77; N, 4.39; S, 9.81.

(1*S*,2*S*,3*S*,5*R*)-2-Formylmethyl-3-benzenesulfonylamino-6,6-dimethylbicyclo[3.1.1]heptane (16) The alcohol (+)-**15** was converted to **16** as described for the preparation of (−)-**7**, in 82.7% yield. IR (film): 3285, 1722, 1331, 1160 cm^{-1}. NMR ($CDCl_3$) δ: 0.89 (3H, s), 0.92 (1H, d, *J*= 10 Hz), 1.14 (3H, s), 1.47—2.74 (8H), 3.56 (1H, m), 5.18 (1H, d, *J*=6 Hz), 7.38—7.66 (3H), 7.86—7.98 (2H), 9.61 (1H, s).

(−)-(*Z*)-7-[(1*S*,2*S*,3*S*,5*R*)-3-Benzenesulfonylamino-6,6-dimethylbicyclo-[3.1.1]hept-2-yl]hept-5-enoic Acid (−)-(17), Its Sodium Salt (18), (−)-(*E*)-7-[(1*S*,2*S*,3*S*,5*R*)-Benzenesulfonylamino-6,6-dimethylbicyclo[3.1.1]-hept-2-yl]hept-5-enoic Acid (−)-(19) and Its Sodium Salt (20) Potassium *tert*-butoxide (22 g) was added to a suspension of (4-carboxybutyl)triphenylphosphonium bromide (36 g) in dry tetrahydrofuran (250 ml) under nitrogen at room temperature. The mixture was stirred at room temperature for 1 h. A solution of the aldehyde **16** (9.76 g) in tetrahydrofuran (130 ml) was added dropwise to the mixture at room temperature. The mixture was stirred at room temperature for 1 h, then water was added. The mixture was washed with ether, acidified with dilute hydrochloric acid and extracted with ether. The extracts were washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was submitted to flash chromatography on silica gel in hexane–ethyl acetate (2 : 1) to give (−)-**17** (8.46 g) and then (−)-**19** (1.91 g).

(−)-**17**: $[\alpha]_D^{26}$ −9.4° (*c*=1.928, MeOH). IR (film): 3270, 1709, 1325, 1156 cm^{-1}. NMR ($CDCl_3$) δ: 0.79 (1H, d, *J*=10H), 0.92 (3H, s), 1.14 (3H, s), 1.40—2.53 (14H), 3.60 (1H, m), 5.10—5.50 (3H), 7.40—7.70 (3H, m), 7.89—8.00 (2H, m), 8.86 (1H, br s).

(−)-**19**: $[\alpha]_D^{26}$ −5.0°, $[\alpha]_{365}^{26}$ −43.7° (*c*=1.562, MeOH). IR (film): 3275, 1709, 1328, 1155, 970 cm^{-1}. NMR ($CDCl_3$) δ: 0.81 (1H, d, *J*=10 Hz), 0.88 (3H, s), 1.13 (3H, s), 1.41—2.53 (14H), 3.55 (1H, m), 5.02—5.44 (3H), 7.35—7.70 (3H), 7.86—7.97 (2H), 9.20 (1H, s).

Both (−)-**17** and (−)-**19** were treated as described for the preparation of **12**. **18**: IR (KBr); 3275, 1565, 1324, 1157 cm^{-1}. **20**: IR (KBr): 3280, 1562, 1326, 1153, 968 cm^{-1}.

Dicyclohexylamine Salt of (−)-17 A solution of dicyclohexylamine (3.06 g) in ether (20 ml) was added to a solution of (−)-**17** (7.2 g) in ether (180 ml). The salt was collected by filtration, washed with ether and dried, giving a powder (9.8 g). mp 129—131 °C. IR (KBr): 3435, 1618, 1555, 1324, 1165, 1155 cm^{-1}. NMR ($CDCl_3$) δ: 0.83 (1H, d, *J*=6 Hz), 0.90 (3H, s), 1.13 (3H, s), 1.00—2.60 (34H), 2.92 (2H, m), 3.47 (1H, m), 5.10—5.50 (2H), 7.18 (1H, br s), 7.35—7.66 (3H), 7.85—8.11 (2H), 8.71 (2H, br s). *Anal.* Calcd for $C_{34}H_{54}N_2O_4S$: C, 69.58; H, 9.27; N, 4.77; S, 5.46. Found: C, 69.40; H, 9.34; N, 4.66; S, 5.53.

(1*S*,2*R*,3*S*,5*R*)-2-[2-(Tetrahydropyran-2-yloxy)ethyl]-3-hydroxy-6,6-dimethylbicyclo[3.1.1]heptane (23) (1*S*,2*R*,5*R*)-2-[2-(Tetrahydropyran-2-yloxy)ethyl]-3-oxo-6,6-dimethylbicyclo[3.1.1]heptane[3] (15.4 g) was dissolved in a 1.11 M solution of sodium methoxide in methanol (160 ml). The solution was stirred at room temperature for 2 h. the NMR spectrum showed it to be a mixture of *ca.* 11 : 1 of the epimerized ketone **22** and the starting material **21**. Sodium borohydride (11 g) was added in small portions to the cold solution. The mixture was stirred for 18 h, then dilute acetic acid was added. The mixture was extracted with ether. The extracts were washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was submitted to flash chromatography on silica gel in hexane–ethyl acetate (10 : 1) to give **23** in 90.3% yield. NMR ($CDCl_3$) δ: 0.92 (3H, s), 1.19 (3H, s), 1.25 (1H, d, *J*= 10 Hz), 1.35—2.53 (14H), 3.35—4.15 (6H), 4.63 (1H, m).

(1*S*,2*R*,3*S*,5*R*)-2-[2-(Tetrahydropyran-2-yloxy)ethyl]-3-(methanesulfonyloxy)-6,6-dimethylbicyclo[3.1.1]heptane (24) The alcohol **23** was converted to **24** as described for the preparation of **2** from **1**, in 97.7% yield. NMR ($CDCl_3$) δ: 0.91 (3H, s), 1.22 (3H, s), 1.27 (1H, d, *J*=10 Hz), 1.37—2.73 (14H), 3.03 (3H, s), 3.25—4.00 (4H), 4.48—4.88 (2H).

(1*S*,2*R*,3*S*,5*R*)-2-[2-(Tetrahydropyran-2-yloxy)ethyl]-3-azido-6,6-dimethylbicyclo[3.1.1]heptane (25) The mesyl derivative **24** was converted to **25** as described for the preparation of **3** from **2**, in 83.2% yield. IR (film): 2100 cm^{-1}. NMR ($CDCl_3$) δ: 0.79 (3H, s), 1.21 (3H, s), 1.34—2.60 (15H), 3.24—4.05 (5H), 4.55 (1H, m).

(−)-(1*S*,2*R*,3*S*,5*R*)-2-[2-(Tetrahydropyran-2-yloxy)ethyl]-3-benzenesulfonylamino-6,6-dimethylbicyclo[3.1.1]heptane (−)-(26) The azide compound **25** was converted to the amino derivative as described for the preparation of **4** and then the amino derivative was converted to (−)-**26** as described for the preparation of (+)-**10** from **9**, in 76.3% yield. mp 152—154 °C. $[\alpha]_D^{25}$ −48.9° (*c*=0.791, MeOH). IR (KBr): 3275, 1325, 1312, 1168 cm^{-1}. NMR ($CDCl_3$) δ: 0.76 (3H, s), 1.01 (1/2H, d, *J*=10 Hz), 1.04 (1/2H, d, *J*=10 Hz), 1.15 (3H, s). 1.30—2.70 (14H), 3.15—4.03 (5H), 4.51 (1H, br s), 5.14 (1/2H, d, *J*=9 Hz), 5.28 (1/2H, d, *J*=9 Hz), 7.34—7.68 (3H), 7.80—8.00 (2H). *Anal.* Calcd for $C_{22}H_{33}NO_4S$: C, 64.83; H, 8.16; N, 3.44; S, 7.87. Found: C, 64.77; H, 8.05; N, 3.37; S, 7.57.

(−)-(1*S*,2*R*,3*S*,5*R*)-2-(2-Hydroxyethyl)-3-benzenesulfonylamino-6,6-dimethylbicyclo[3.1.1]heptane (−)-(27) The tetrahydropyranylether (−)-**26** was converted to (−)-**27** as described for the preparation of (+)-**6**, in 89.3% yield. mp 129—131 °C. $[\alpha]_D^{25}$ −52.1° (*c*=1.041, MeOH). IR (KBr): 3460, 3110, 1324, 1306, 1156 cm^{-1}. NMR ($CDCl_3$) δ: 0.76 (3H, s), 1.07 (1H, d, *J*=10 Hz), 1.15 (3H, s), 1.30—2.66 (9H), 3.45—3.96 (3H), 5.68 (1H, d, *J*=9 Hz), 7.35—7.67 (3H), 7.86—7.97 (3H). *Anal.* Calcd for $C_{17}H_{25}NO_3S$: C, 63.13; H, 7.79; N, 4.33; S, 9.91. Found: C, 62.97; H, 7.69; N, 4.22; S, 9.78.

(+)-(2*RS*,3a*R*,4*S*,6*R*,7a*S*)-*N*-Benzenesulfonyl-2-hydroxy-5,5-dimethyl-4,6-methanooctahydroindole (+)-(28) The alcohol (−)-**27** was converted to (+)-**28** as described for the preparation of (−)-**7**, in 78.1% yield. $[\alpha]_D^{24}$ +51.4° (*c*=3.371, MeOH). IR ($CHCl_3$): 3570, 1348, 1329, 1318, 1310, 1160, 1152 cm^{-1}. NMR ($CDCl_3$) δ: 0.77 and 0.83 (total 3H, s and s), 1.06 (1H, d, *J*=9 Hz), 1.18 (3H, s), 1.50—4.30 (10H), 5.30 and 5.59 (total 1H, m and m), 7.38—7.70 (3H), 7.77—8.00 (2H).

(−)-(*Z*)-7-[(1*S*,2*R*,3*S*,5*R*)-3-Benzenesulfonylamino-6,6-dimethylbicyclo-[3.1.1]hept-2-yl]hept-5-enoic Acid (−)-(29), Its Dicyclohexylamine and Sodium Salt (30) This acid was prepared from (+)-**28** as described for the preparation of (−)-**8**, in 82.0% yield. $[\alpha]_D^{23}$ −31.3° (*c*=3.452, MeOH). IR ($CDCl_3$): 3525, 3400, 3280, 1721, 1352, 1330, 1310, 1161, 1095 cm^{-1}. NMR ($CDCl_3$) δ: 0.73 (3H, s), 1.02 (1H, d, *J*=10 Hz), 1.14 (3H, s), 1.33—2.60 (14H), 3.83 (1H, m), 5.12—5.51 (3H), 7.37—7.73 (3H), 7.87—7.98 (2H), 8.86 (1H, br s).

The dicyclohexylamine salt: mp 122—124 °C. $[\alpha]_D$ −17.6° (*c*=1.051, MeOH). IR (KBr): 3440, 3180, 3080, 1624, 1553, 1310, 1154, 1096 cm^{-1}. NMR ($CDCl_3$) δ: 0.73 (3H, s), 1.14 (3H, s), 0.88—2.43 (35H), 2.70—3.13 (2H), 3.78 (1H, br s), 5.03—5.56 (2H), 5.85 (1H, br d, *J*=6 Hz), 7.36—7.67 (3H), 7.77—8.03 (2H), 8.24 (2H, br s). *Anal.* Calcd for $C_{34}H_{54}N_2O_4S$: C, 69.58; H, 9.27; N, 4.77; S, 5.46. Found: C, 69.55; H, 9.21; N, 4.63; S, 5.29.

The sodium salt **30**: IR (KBr): 1560, 1327, 1309, 1160, 1093 cm^{-1}. *Anal.* Calcd for $C_{22}H_{30}NNaO_4S$: C, 61.81; H, 7.07; N, 3.28; S, 7.50. Found: C, 61.50; H, 7.03; N, 3.37; S, 7.47.

(1*S*,2*R*,3*R*,5*R*)-2-[2-(Tetrahydropyran-2-yloxy)ethyl]-3-azido-6,6-dimethylbicyclo[3.1.1]heptane (31) Diethyl azodicarboxylate (20 g) was added dropwise to a suspension of the alcohol **23** (6.11 g), triphenylphosphine (30 g) and zinc dimethanesulfonate (5.83 g) in benzene (350 ml) at room temperature in nitrogen. The mixture was stirred at room temperature for 3 h, washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was submitted to flash chromatography on silica gel in hexane–ethyl acetate to give the crude mesylate (6.7 g). The *trans*-azide compound **31** was prepared from the tosylate as described for the preparation of **3** from **2** in 31.3% yield. NMR ($CDCl_3$) δ: 0.86 (3H, s), 1.21 (3H, s), 1.28 (1H, d, *J*=10 Hz), 1.40—2.50 (14H), 3.22—4.00 (5H), 4.57 (1H, m).

(−)-(1*S*,2*R*,3*R*,5*R*)-2-[2-(Tetrahydropyran-2-yloxy)ethyl]-3-benzenesulfonylamino-6,6-dimethylbicyclo[3.1.1]heptane (−)-(32) The azide compound **31** was converted to (−)-**32** as described for the preparation of (−)-**26** from **25**, in 85.6% yield. mp 119—121 °C. $[\alpha]_D^{25}$ −26.3° (*c*=0.883, MeOH). IR (KBr): 3270, 1322, 1168 cm^{-1}. NMR ($CDCl_3$) δ: 0.80 (3H, s), 1.13 (3H, s), 1.20 (1H, d, *J*=10 Hz), 1.35—2.30 (14H), 2.90—4.10 (5H), 4.40—4.60 (1H, m), 5.03 and 5.21 (total 1H, d, *J*=6 Hz), 7.35—7.68 (3H), 7.86—7.97 (2H). *Anal.* Calcd for $C_{22}H_{33}NO_4S$: C, 64.83; H, 8.16; N, 3.44;

S, 7.87. Found: C, 64.89; H, 8.12; N, 3.42; S, 7.77.

(−)-(1*S*,2*R*,3*R*,5*R*)-2-(2-Hydroxyethyl)-3-benzenesulfonylamino-6,6-dimethylbicyclo[3.1.1]heptane (−)-(33) The tetrahydropyranyl ether (−)-**32** was converted to (−)-**33** as described for the preparation of (+)-**6** from (+)-**5**, in 90.6% yield. $[\alpha]_D^{23}$ −31.6° (c=1.094, MeOH). IR ($CHCl_3$): 3625, 3530, 3385, 3275, 1327, 1310, 1160, 1091 cm^{-1}. NMR ($CDCl_3$) δ: 0.80 (3H, s), 1.14 (3H, s), 1.21 (1H, d, J=10 Hz), 1.35—2.18 (8H), 2.30 (1H, br s), 3.20 (1H, q, J=9 Hz), 3.57 (2H, t, J=6 Hz), 5.65 (1H, d, J=7 Hz), 7.36—7.63 (3H), 7.88—7.99 (2H).

(−)-(1*S*,2*R*,3*R*,5*R*)-2-Formylmethyl-3-benzenesulfonylamino-6,6-dimethylbicyclo[3.1.1]heptane (−)-(34) The alcohol (−)-**33** was converted to (−)-**34** as described for the preparation of (−)-**7** from (+)-**6**, in 95.9% yield. $[\alpha]_D^{24}$ −19.8° (c=2.754, MeOH). IR ($CHCl_3$): 3390, 3280, 1723, 1330, 1161, 1091 cm^{-1}. NMR ($CDCl_3$) δ: 0.82 (3H, s), 1.13 (3H, s), 1.22 (1H, d, J=10 Hz), 1.49—2.78 (8H), 3.24 (1H, m), 5.51 (1H, d, J=9 Hz), 7.38—7.73 (3H), 7.88—7.99 (2H), 9.65 (1H, d, J=2 Hz).

(−)-(*Z*)-7-[(1*S*,2*R*,3*R*,5*R*)-3-Benzenesulfonylamino-6,6-dimethylbicyclo-[3.1.1]hept-2-yl)hept-5-enoic Acid (−)-(35), (−)-Methyl Ester (−)-(36) and Sodium Salt (37) The aldehyde (−)-**34** was converted to (−)-**35** and (−)-**36** as described for the preparation of (+)-**9** from (−)-**7**, in 95.1% yield. $[\alpha]_D^{23}$ −2.4°, $[\alpha]_{365}^{23}$ +17.6° (c=2.154, MeOH). IR (film): 3280, 1710, 1325, 1310, 1160, 1093 cm^{-1}. NMR ($CDCl_3$) δ: 0.76 (3H, s), 1.13 (3H, s), 1.22 (1H, d, J=10 Hz), 1.35—2.50 (14H), 3.20 (1H, m), 5.30 (2H, m), 5.42 (1H, d, J=9 Hz), 7.35—7.63 (3H), 7.86—7.97 (2H).

(−)-**36**: $[\alpha]_D^{23}$ −1.6°, $[\alpha]_{365}^{23}$ +24.8° (c=2.498, MeOH). IR (film): 3290, 1740, 1329, 1161, 1096 cm^{-1}. NMR ($CDCl_3$) δ: 0.76 (3H, s), 1.13 (3H, s), 1.23 (1H, d, J=10 Hz), 1.40—2.43 (14H), 3.23 (1H, m), 3.69 (3H, s), 5.30 (2H, m), 5.62 (1H, d, J=9 Hz), 7.36—7.70 (3H), 7.92—8.03 (2H). CD (MeOH) λ nm ($\Delta\varepsilon$): 268.5 (+0.085), 261 (+0.112), 258 sh (+0.155), 225 (+2.52). *Anal.* Calcd for $C_{23}H_{33}NO_4S$: C, 65.84; H, 7.93; N, 3.34; S, 7.64. Found: C, 65.78; H, 7.98; N, 3.42; S, 7.49.

37: IR (KBr): 1560, 1323, 1308, 1160, 1093 cm^{-1}.

(+)-(1*S*,2*R*,3*R*,5*S*)-2-Acetoxymethyl-3-carboxymethyl-6,6-dimethylbicyclo[3.1.1]heptane (+)-(39) Acetic anhydride (18 ml) was added to a solution of (+)-(1*S*,2*R*,3*R*,5*S*)-2-hydroxymethyl-3-carboxy-6,6-dimethylbicyclo[3.1.1]heptane[7] (4.6 g) in pyridine (25 ml). The mixture was stirred at room temperature for 1 h. Methanol (20 ml) was added and the mixture was stirred. Ether was added, then the solution was washed with dilute hydrochloric acid and water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was submitted to flash chromatography on silica gel (120 g) in hexane–ethyl acetate to give (+)-**39** (4.77 g) as an oil. $[\alpha]_D^{24}$ +31.8° (c=1.360, MeOH). IR (film): 1743, 1710 cm^{-1}. NMR ($CDCl_3$) δ: 0.85 (1H, d, J=10 Hz), 1.00 (3H, s), 1.20 (3H, s), 1.4—2.9 (9H), 4.08 (2H, d, J=7 Hz), 10.39 (1H, br s). *Anal.* Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.19; H, 8.66.

(+)-(1*S*,2*S*,3*S*,5*R*)-2-Acetoxymethyl-3-*tert*-butoxycarbonylaminomethyl-6,6-dimethylbicyclo[3.1.1]heptane (+)-(40) A solution of ethyl chloroformate (3 g) in acetone (4 ml) was added dropwise to a mixture of (+)-**39** (4.77 g), water (4 ml), triethylamine (4.2 ml) and acetone (20 ml) at 0 °C. The mixture was stirred at 0 °C for 1 h. A solution of sodium azide (3 g) in water (11 ml) was added dropwise. The mixture was stirred at 0 °C for 1 h, then water was added. The mixture was extracted with ether. The extracts were washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Benzene (50 ml) was added to the residue. The solution was heated under reflux for 1 h and concentrated under reduced pressure. *tert*-Butanol (60 ml) was added. The solution was heated under reflux for 10 h and concentrated under reduced pressure. The residue was submitted to flash chromatography (120 g) in hexane–ethyl acetate (6:1) to give (+)-**40** (3.40 g). $[\alpha]_D$ +21.3° (c=1.516, MeOH). IR (film): 3365, 1742, 1715 cm^{-1}. NMR ($CDCl_3$) δ: 0.83 (1H, d, J=10 Hz), 0.97 (3H, s), 1.21 (3H, s), 1.35—2.53 (7H), 1.47 (9H, s), 2.10 (3H, s), 3.13 (2H, t, J=6 Hz), 4.06 (2H, d, J=6 Hz), 5.05 (1H, br s). *Anal.* Calcd for $C_{18}H_{31}NO_4$: C, 66.43; H, 9.60; N, 4.30. Found: C, 66.30; H, 9.64; N, 4.24.

(+)-(1*S*,2*S*,3*S*,5*R*)-2-Acetoxymethyl-3-benzenesulfonylaminomethyl-6,6-dimethylbicyclo[3.1.1]heptane (+)-(41) A solution of (+)-**40** (3.35 g) in trifluoroacetic acid (15 ml) was stirred at room temperature for 30 min and concentrated under reduced pressure. Triethylamine (10 ml) and then benzene-sulfonyl chloride (2.4 g) were added dropwise to a solution of the residue in dichloromethane (30 ml) at 0 °C. The mixture was stirred at room temperature for 1 h and washed with water, dilute hydrochloric acid and water, then dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was submitted to flash chromatography on silica gel (70 g) in hexane–ethyl acetate (4:1) to give (+)-**41** (3.431 g). $[\alpha]_D^{25}$ +25.3° (c=1.032, MeOH). IR (film): 3290, 1740, 1329, 1160 cm^{-1}. NMR ($CDCl_3$) δ: 0.71 (1H, d, J=10 Hz), 0.90 (3H, s), 1.18 (3H, s), 1.30—2.50 (7H), 2.07 (3H), 2.93 (2H, t, J=6 Hz), 3.99 (2H, m), 5.53 (1H, t, J=6 Hz), 7.36—7.65 (3H, m), 7.83—7.94 (2H, m). *Anal.* Calcd for $C_{19}H_{27}NO_4S$: C, 62.44; H, 7.45; N, 3.83; S, 8.77. Found: C, 62.56; H, 7.54; N, 3.85; S, 8.73.

(+)-(1*S*,2*S*,3*S*,5*R*)-2-Hydroxymethyl-3-benzenesulfonylaminomethyl-6,6-dimethylbicyclo[3.1.1]heptane (+)-(42) The acetate (+)-**41** was hydrolyzed with potassium hydroxide in methanol as usual and the crude product was submitted to flash chromatography on silica gel in hexane–ethyl acetate (2:1) to give (+)-**42** in 96.1% yield. $[\alpha]_D^{25}$ +20.0° (c=1.721, MeOH). IR (film): 3495, 3285, 3160, 1323, 1155 cm^{-1}. NMR ($CDCl_3$) δ: 0.68 (1H, d, J=10 Hz), 0.83 (3H, s), 1.13 (3H, s), 1.23—2.42 (7H), 2.59—3.17 (3H), 3.39—3.73 (2H), 6.99 (1H, br s), 7.34—7.63 (3H, m), 7.83—7.94 (2H, m). *Anal.* Calcd for $C_{17}H_{25}NO_3S$: C, 63.13; H, 7.79; N, 4.33; S, 9.91. Found: C, 62.97; H, 7.84; N, 4.37; S, 9.81.

(1*S*,2*S*,3*S*,5*R*)-2-(2-Methoxyethenyl)-3-benzenesulfonylaminomethyl-6,6-dimethylbicyclo[3.1.1]heptane (43) The alcohol (+)-**42** (2.833 g) was converted to the aldehyde as described for the preparation of (−)-**7** and the aldehyde was used for the next procedure without further purification.

Potassium *tert*-butoxide (3.0 g) was added to a suspension of (methoxymethyl)triphenylphosphonium chloride (8.57 g) in dry tetrahydrofuran (50 ml) at room temperature in nitrogen. The mixture was stirred at room temperature for 15 min and a solution of the aldehyde in tetrahydrofuran (15 ml) was added dropwise. The mixture was stirred at room temperature for 1 h, then water was added. The mixture was extracted with ether. The extracts were washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was submitted to flash chromatography in hexane–ethyl acetate (4:1) to give **43** (2.811 g). NMR ($CDCl_3$) δ: 0.67 (3/4H, d, J=10 Hz), 0.71 (1/4H, d, J=10 Hz), 0.93 (3H, s), 1.16 (3H, s), 1.1—3.2 (9H), 3.45 (3×1/4H, s), 3.67 (3×3/4H, s), 4.50 (3/4H, dd, J=6, 11 Hz), 4.78 (1/4H, dd, J=9, 12 Hz), 5.6—5.9 (1H, m), 5.76 (3/4H, d, J=6 Hz), 6.17 (1/4H, d, J=12 Hz), 7.33—7.63 (3H, m), 7.78—7.93 (2H, m).

(1*S*,2*S*,3*S*,5*R*)-2-Formylmethyl-3-benzenesulfonylaminomethyl-6,6-dimethylbicyclo[3.1.1]heptane (44) and (4a*S*,5*S*,7*R*,8a*S*)-*N*-Benzenesulfonyl-3-hydroxy-6,6-dimethyl-5,7-methanoperhydroisoquinoline (45) A solution of the ether **43** (2.811 g) in 20% trifluoroacetic acid (100 ml) was stirred at room temperature for 2 h. Aqueous sodium hydrogencarbonate was added. The mixture was extracted with ether. The extracts were washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was submitted to flash chromatography on silica gel (100 g) in hexane–ethyl acetate (4:1) to give a mixture of **44** and **45** (1.284 g). IR ($CHCl_3$): 3695, 3610, 1723, 1348, 1334, 1161 cm^{-1}. NMR ($CDCl_3$) δ: 0.78 (1H, d, J=9 Hz), 0.93 (3×1/3H, s), 1.00 (3×2/3H, s), 1.17 (3×1/3H, s), 1.24 (3×2/3H, s), 1.2—3.2 (11H), 3.64 (2/3H, dd, J=3, 11 Hz), 5.02 (1/3H, t, J=6 Hz), 5.63 (2/3H, m), 7.36—7.68 (3H, m), 7.81—7.92 (2H, m), 9.68 (1/3H, t, J=2 Hz).

(+)-(*Z*)-7-[(1*S*,2*S*,3*S*,5*R*)-3-Benzenesulfonylaminomethyl-6,6-dimethylbicyclo[3.1.1]heptan-2-yl]hept-5-enoic Acid (+)-(46) and Its Sodium Salt (47) The above mixture, **44** and **45** (1.259 g), was converted to (+)-**46** as described for the preparation of (+)-**8**. The crude carboxylic acid was submitted to flash chromatography on silica gel (60 g) in hexane–ethyl acetate (1:1) to give (+)-**45**, 1.177 g. $[\alpha]_D^{26}$ +23.5° (c=1.425, MeOH). CD (MeOH) λ nm ($\Delta\varepsilon$): 269 (−0.070), 262.5 (−0.10), 227 (−0.89), 202 (+0.99). IR (film): 3280, 1709, 1323, 1158 cm^{-1}. NMR ($CDCl_3$) δ: 0.66 (1H, d, J=10 Hz), 0.94 (3H, s), 1.16 (3H, s), 1.31—2.42 (15H), 2.59—3.15 (2H, m), 5.10—5.50 (3H), 7.37—7.67 (3H, m), 7.83—7.94 (2H, m), 9.37 (1H, br s).

47: IR (KBr): 3295, 1562, 1324, 1158 cm^{-1}.

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, i.v.), blood was withdrawn from the carotid artery through an annulation tube using a syringe containing sodium citrate (3.8%, 1/10 volume). The sample was left standing for 20 min at room temperature 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,[11] using an AUTO-RAM61 type aggregometer (Rika-Denki Co., Ltd., Tokyo) as reported previously.[12] 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 alone 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 transmissions were recorded, with the light transmissions for PRP and PPP taken as 0% and 100%, respectively, and the maximum

light transmissions after addition of sodium arachidonate as the maximum aggregations. 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 interpolation on the regression line of the concentration–inhibition relationship based on 12—16 points of α covering three concentrations and ranging from 20 to 80%. The IC_{50} values obtained were calibrated with respect to the IC_{50} value (standard: 1.0 μM) of S-145 obtained with the same PRP sample.

Preparation of WP From the abdominal artery of a male rat (Sprague-Dawley, 8 weeks old), 10 ml of blood was collected with a syringe containing 1.5 ml of acid citrate dextrose (85 mM sodium citrate 70 mM citric acid, 110 mM glucose) and 20 μg of PG E_1. The blood was placed in a plastic test tube, mixed by moderate turning and centrifuged for 10 min at $160 \times g$ to give PRP. The prepared PRP was treated with apyrase (25 μg/ml) and the mixture was layered on 40% bovine serum albumin. The resulting mixture was centrifuged at $1200 \times g$ for 25 min. Platelets were suspended in a small amount of buffer (137 mM NaCl, 2.7 mM KCl, 1.0 mM $MgCl_2$, 3.8 mM NaH_2PO_4, 3.8 mM Hepes, 5.6 mM glucose, 0.035% bovine serum albumin, pH 7.35) and separated from plasma protein by gel filtration through a column of Sepharose 2B in the buffer.

Measurement of Inhibition of Platelet Aggregation The platelet aggregation was measured by an aggregometer (NKK HEMA TRACER 1 MODEL PAT-6A, Niko Bioscience). WP (245 μl) was placed in a measuring cuvette after adjustment of the platelet number to $5 \times 10^5/\mu$l and the cuvette was placed in the aggregometer. WP was stirred (1000 rpm) at 37 °C and 3.8 μl of 0.1 M of $CaCl_2$ was added. After 1 min, 0.5 μl of a solution of test compound in dimethylsulfoxide (DMSO) and after 2 min, 1 μl of collagen (Hormon-Chemie, Munchen, final concentration, 4 μg/ml) as a platelet aggregating agent were added. The aggregation was monitored with the aggregometer in terms of decrease in light transmittance. The concentration giving 50% inhibition of aggregation was calculated, based on measurements at 3 min after addition of a platelet aggregating agent.

Acknowledgement The authors are grateful to Dr. Masayuki Narisada for his helpful discussions and Dr. Kiyohisa Uchida, Dr. Hitoshi Arita, Mr. Hisato Kakushi and Mrs. Ayako Terawaki for their helpful discussions and for measurements of the IC_{50} values of inhibitory activity toward platelet aggregation.

References

1) M. Narisada, M. Ohtani, F. Watanabe, K. Uchida, H. Arita, M. Doteuchi, K. Hanasaki, H. Kakushi, K. Otani, and S. Hara, *J. Med. Chem.*, **31**, 1847 (1988).
2) A. M. Lefer and H. Darius, *Drugs Future*, **12**, 367 (1987).
3) *Drugs Future*, **12**, 446 (1987).
4) S. Hagishita and K. Seno, *Chem. Pharm. Bull.*, **37**, 327 (1989).
5) N. H. Wilson and R. L. Jones, *Adv. Prostaglandin, Thromboxane, Leukotriene Res.*, **14**, 393 (1985).
6) P. W. Sqrague, J. E. Heike, J. Z. Gougoutas, M. F. Malley, D. N. Harris, and R. Greenberg, *J. Med. Chem.*, **28**, 1580 (1985).
7) Y. Bounameaux, J. W. Coffey, M. O'Donnell, K. Kling, R. J. Quinn, P. Schönhelzer, A. Szente, L. D. Tobias, T. Tschopp, A. F. Welton, and A. Fischli, *Helv. Chim. Acta*, **66**, 989 (1983).
8) K. C. Nicolaou, R. L. Magolda, and D. A. Clameron, *J. Am. Chem. Soc.*, **102**, 1404 (1980); M. F. Ansell, M. P. L. Carton, M. N. Palfreyman, and K. A. J. Stuttle, *Tetrahedron Lett.*, **1979**, 37; J. Fried, J. Barton, S. Kittisopikul, P. Needleman, and A. Wyche, *Adv. Prostaglandin Thromboxane Res.*, **6**, 427 (1980); M. F. Ansell, M. P. L. Carton, and K. A. J. J. Stuttle, *J. Chem. Soc., Perkin Trans. I*, **1984**, 1069.
9) I. Galynker and W. C. Still, *Tetrahedron Lett.*, **23**, 4461 (1982).
10) S. Narumiya, M. Okuma, and F. Ushikubi, *Br. J. Pharmacol.*, **88**, 323 (1986); K. Hanasaki and H. Arita, *Thromb. Res.*, **50**, 365 (1988).
11) G. V. R. Born, *Nature* (London), **194**, 927 (1962).
12) K. Uchida, M. Nakamura, M. Konishi, T. Ishigami, and T. Komeno, *Jpn. J. Pharmacol.*, **43**, 9 (1987).