Thromboxane A_2 Receptor Antagonists. III. Synthesis and Pharmacological Activity of 6,6-Dimethylbicyclo[3.1.1]heptane Derivatives with a Substituted Sulfonylamino Group at C-2

Kaoru SENO and Sanji HAGISHITA*

Shionogi Research Laboratories, Shionogi & Co., Ltd., Fukushima-ku, Osaka 553, Japan. *Received November 10, 1988*

Four stereoisomers of the title compounds based on side chain ring junctions, (+)-7a, (+)-7b, (−)-7c and (−)-24, were synthesized from (−)-myrtenol and (+)-nopinone. The (1*R*,2*R*,3*S*,5*S*)-isomer (+)-7b had the most potent inhibitory activity against platelet aggregation and did not show partial agonist activity (shape change of platelets). We also synthesized the antipode, (−)-7b, and derivatives of (+)-7b with various kinds of substituents at the sulfonylamino group, 34a—n and p. The one-carbon homologated compound, (+)-58, was also prepared. The inhibitory activities of these compounds against platelet aggregation were measured.

Keywords thromboxane A_2; receptor antagonist; pinane; benzenesulfonylamino group; platelet aggregation

Recently, we reported on the synthesis and inhibitory activity of 7-oxabicyclo[2.2.1]heptane[1] and 6,6-dimethylbicyclo[3.1.1]heptane derivatives[2] with a benzensulfonylamino group against aggregation of rabbit platelet-rich plasma (PRP) and of rat washed platelets (WP). These compounds are expected to be therapeutic agents which can act as receptor antagonists of the thromboxane A_2 (TxA_2) system. One of the latter derivatives, (−)-(5*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, had potent inhibitory activity and did not act as a partial agonist or cause platelet shape change, thus encouraging us to search for more active TxA_2 receptor antagonists among 6,6-dimethylbicyclo[3.1.1]heptane derivatives. We focused our attention on regio isomers of 6,6-dimethylbicyclo[3.1.1]heptane derivatives, in which the α- and ω-side chains were interchanged (Fig. 1). Four stereoisomers of the title compound based on side chain ring junctions were prepared and their *in vitro* inhibitory activities against aggregation of rabbit PRP and of rat WP were measured. The 1*R*,2*R*,3*S*,5*S*-isomer, (+)-**7b**, showed very potent *in vitro* inhibitory activity and did not act as a partial agonist. We thus established a synthetic pathway capable of supplying (+)-**7b** in multigram quantities without need for chromatographic separations. We also prepared the antipode of (+)-**7b**, several derivatives with different kinds of substituents on the sulfonylamino group and the homologated compound with one methylene in the ω-side chain and investigated their inhibitory activity against platelet aggregation.

Synthesis Commercially available (−)-myrtenol, used as the starting material, was converted to (−)-(4a*R*,6*S*,8*S*,8a*S*)- and (+)-(4a*R*,6*S*,8*S*,8a*R*)-7,7-dimethyl-6,8-methanoperhydroisochroman-3-ol (−)-**1a** and (+)-**1b** *via* three and four steps, respectively, by a method developed by the Hoffman–LaRoche group.[3] The hemiacetals (−)-**1a** and (+)-**1b** were subjected to Wittig reaction with (4-carboxybutyl)triphenylphosphonium bromide and sodium hydride–dimethyl sulfoxide (DMSO) and subsequent treatment with diazomethane gave (−)-**2a** and (+)-**2b**, respectively. The alcohols (−)-**2a** and (+)-**2b** were oxidized with Jones' reagent to the carboxylic acids **3a** and (+)-**3b**. However, the (1*S*,2*R*,3*R*,5*S*)-isomer (−)-**2c**, obtained by the Hoffman–LaRoche method from (−)-myrtenol,[3] did not afford the carboxylic acid in the same way. The alcohol (−)-**2c** was converted by Swern oxidation to an aldehyde, which was then oxidized with Jones' reagent, but the required carboxylic acid could not be obtained. The aldehyde was epimerized with sodium methoxide and oxidized with Jones' reagent to furnish the (−)-carboxylic acid (−)-**3c**. Carboxylic acid derivatives **3a**, (+)-, (−)-**3b** and (−)-**3c** were subjected to Curtius reaction and the resulting isocyanates were heated with *tert*-butanol to obtain the BOC derivatives (+)-**4a**, (+)-**4b** and (−)-**4c**. The BOC group was removed with trifluoroacetic acid and the obtained amine was condensed with benzenesulfonyl chloride to afford **5a**—**c**. By flash chromatography of the product from (+)-**4a**, the (5*E*)-isomer (−)-**8** was isolated as an oil. After **5a**—**c** and (−)-**8** had been hydrolyzed with aqueous sodium hydroxide to **6a**—**c**, the sodium salts **7a**—**c** and **10** were lyophilized for biological testing.

Alternatively, compounds (+)-**6b** and (−)-**6c** were synthesized by treating the lithium enolate of (+)-nopinone with one equivalent of allyl bromide at 35 °C. The products were a mixture of the starting material, the monosubstituted mixture **15** and the disubstituted compound (+)-**14** in an isolated ratio of 1.7 : 14.5 : 1. The mixture of epimers **15** was converted to the *O*-methyl oximes, which were separated by flash chromatography to give three isomers. At this stage, the configuration at C-3 could not be determined but the final products **6b** and **6c** could be identified in comparison with the above mentioned products **6b**—**c**. The first eluate with the largest *Rf* value had the 3*R* configuration and the 2nd and the last eluates were of the 3*S* configuration, though the orientation of the methoxy group at N was uncertain. The N-methoxide (+)-**16a** was reduced by dissolving sodium metal in ethanol to an amine, which was treated with benzenesulfonyl chloride and triethyl-

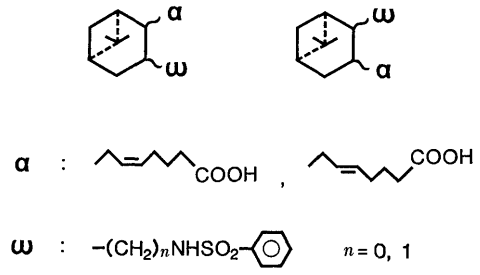
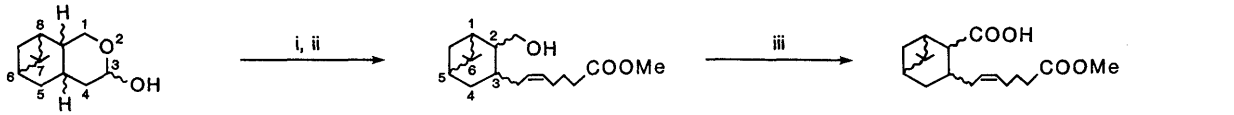
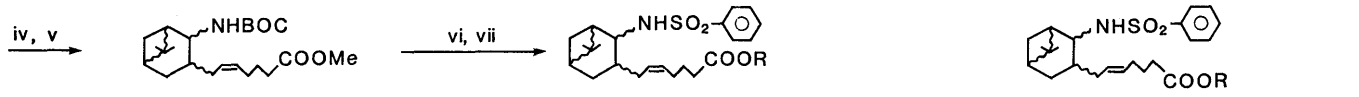


Fig. 1



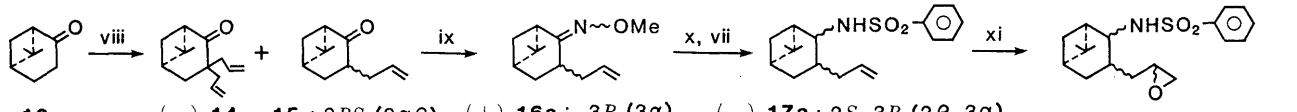
(−)-**1a** : 4a*R*, 6*S*, 8*S*, 8a*S* (4aα, 6α, 8α, 8aα) (−)-**2a** : 1*S*, 2*S*, 3*S*, 5*S* (1α, 2β, 3β, 5α) **3a** : 1*S*, 2*S*, 3*S*, 5*S* (1α, 2β, 3β, 5α)
(+)-**1b** : 4a*R*, 6*S*, 8*S*, 8a*R* (4aα, 6α, 8α, 8aβ) (+)-**2b** : 1*S*, 2*R*, 3*S*, 5*S* (1α, 2α, 3β, 5α) (+)-**3b** : 1*S*, 2*R*, 3*S*, 5*S* (1α, 2α, 3β, 5α)
(−)-**1b** : 4a*S*, 6*R*, 8*R*, 8a*S* (4aβ, 6β, 8β, 8aα) (−)-**2b** : 1*R*, 2*S*, 3*R*, 5*R* (1β, 2β, 3α, 5β) (−)-**3b** : 1*R*, 2*S*, 3*R*, 5*R* (1β, 2β, 3α, 5β)
(−)-**2c** : 1*S*, 2*R*, 3*R*, 5*S* (1α, 2α, 3α, 5α) (−)-**3c** : 1*S*, 2*S*, 3*R*, 5*S* (1α, 2β, 3α, 5α)



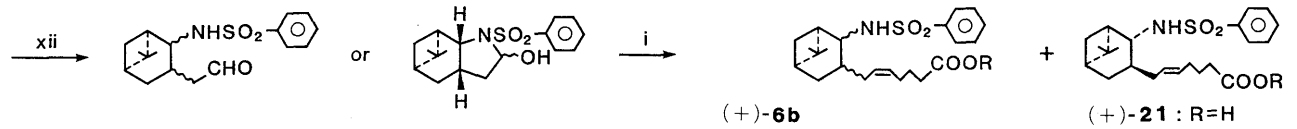
(+)-**4a** : 1*R*, 2*S*, 3*S*, 5*S* (1α, 2β, 3β, 5α) **5a-c** : R=Me , **6a-c** : R=H , **7a-c** : R=Na (−)-**8** : R=Me ,(−)-**9** : R=H , **10** : R=Na
(+)-**4b** : 1*R*, 2*R*, 3*S*, 5*S* (1α, 2α, 3β, 5α) **a** : 1*R*, 2*S*, 3*S*, 5*S* (1α, 2β, 3β, 5α) 1*R*, 2*S*, 3*R*, 5*S* (1α, 2β, 3α, 5α)
(−)-**4b** : 1*S*, 2*S*, 3*R*, 5*R* (1β, 2β, 3α, 5β) **b** : 1*R*, 2*R*, 3*S*, 5*S* (1α, 2α, 3β, 5α) (−)-**11** : R=H , **12** : R=Na
(−)-**4c** : 1*R*, 2*S*, 3*R*, 5*S* (1α, 2β, 3α, 5α) *anti*-**b** : 1*S*, 2*S*, 3*R*, 5*R* (1β, 2β, 3α, 5β) 1*S*, 2*S*, 3*R*, 5*R* (1β, 2β, 3α, 5β)
c : 1*R*, 2*S*, 3*R*, 5*S* (1α, 2β, 3α, 5α)

i) $Ph_3\overset{+}{P}(CH_2)_4COOH\bar{B}r$, NaH–DMSO ii) CH_2N_2 iii) Jones' oxidation or 1) $(COCl)_2$–DMSO, 2) Jones' oxidation iv) Curtius reaction
v) *tert*-BuOH vi) CF_3COOH vii) $PhSO_2Cl$, Et_3N

Chart 1



13 (−)-**14** **15** : 3*RS* (3αβ) (+)-**16a** : 3*R* (3α) (−)-**17a** : 2*S*, 3*R* (2β, 3α) (−)-**18a** : 2*S*, 3*S* (2β, 3α)
(+)-**16b** : 3*S* (3β) (−)-**17b** : 2*R*, 3*R* (2α, 3α) **18b** : 2*R*, 3*R* (2α, 3β)
(+)-**17c** : 2*R*, 3*S* (2α, 3β) **18c** : 2*R*, 3*S* (2α, 3α)



(−)-**19a** : 2*S*, 3*S* (2β, 3α) **20** (+)-**6b** (+)-**21** : R=H
19b : 2*R*, 3*R* (2α, 3β) (−)-**6c** **22** : R=Na
(−)-**23** : R=H, 2*R*, 3*R* (2α, 3α)
24 : R=Na, 2*R*, 3*R* (2α, 3α)

viii) LDA, ⁄⁄Br ix) $NH_2OMe \cdot HCl$, Py x) Na, EtOH xi) MCPBA xii) HIO_4

Chart 2

amine, followed by flash chromatography to give two stereoisomers, (−)-**17a** and (−)-**17b** in a ratio of 4.4 : 1. The same treatment of (+)-**16b** gave only one isomer (+)-**17c**. The double bond of (−)-**17a** was oxidized with *m*-chloroperbenzoic acid and the crystalline mixture of the epoxide (−)-**18a** was cleaved with periodic acid, giving the aldehyde (−)-**19a**. Isomers (−)-**17b** and (+)-**17c** were also treated in the same manner. The former (−)-**17b** furnished **19b** and the latter (+)-**17c** gave the cyclized hemiacetal **20** as an oil. Wittig reaction of (+)-**19a** and **19b** was carried out as in the preparation of **2** from **1** and gave the above-described (+)-**6b** and (−)-**6c**. The (5*E*)-isomer (+)-**21** was isolated by flash chromatography of the product of (+)-**6b**. The hemiacetal **20** was converted in the same manner to the required condensation product (−)-**23** in low yield.

Since the (1*R*,2*R*,3*S*,5*S*)-isomer (+)-**6b** was potent in biological screening, the antipode was prepared by converting (+)-α-pinene by the procedure of Harwood and Julia[4] to (+)-myrtenol which was treated as in the preparation of (+)-**6b** depicted in chart 1. The (5*E*)-isomer (−)-**11** could be isolated by flash chromatography of (−)-**6b**.

To modify the sulfonylamino group of (+)-**6b**, the intermediate (+)-**31** was prepared as follows. Ethyl 6,6-dimethyl-2-methylidenebicyclo[3.1.1]hept-3-ylacetate, (+)-**25**, obtained from (−)-myrtenol[3] was converted to the ketone **26** by ozonolysis. The crude ketone **26** was treated with *O*-methylhydroxylamine. The *O*-methyl oxime was purified by distillation and reduced by dissolving sodium metal in *n*-propanol at 90 °C to give amino alcohols, which were purified by recrystallization of the benzoic acid salt from acetone. The amino group of (+)-**28** was protected with a BOC group and the alcohol (+)-**29** was subjected to Swern oxidation. The crude aldehyde **30** was treated with (4-carboxybutyl)triphenylphosphonium bromide and potassium *tert*-butoxide in tetrahydrofuran, followed by flash chromatography to give a common intermediate (+)-**31** in

good yield. Esterification of the carboxylic acid (+)-**31** and subsequent removal of the BOC group with trifluoroacetic acid as described above gave the amino ester, which was condensed with alkyl- and arylsulfonyl chlorides to furnish the esters **32a**—**o** as depicted in Chart 3. The esters **32a**—**n** were hydrolyzed to the carboxylic acids **33a**—**n**. The diester **32o** gave **33p**.

A *p*-toluenesulfonylamino group was also effective in the biological screening and the *cis*-isomer (+)-**36** was prepared from (+)-**4a** by the same method.

The (1*R*,2*R*,3*S*,5*S*)-isomer (+)-**6b** seems promising for development as a therapeutic reagent. We established a synthetic pathway capable of furnishing (+)-**6b** in multigram quantities without need for chromatographic separation. The free amine of (+)-**28** was condensed with benzenesulfonyl chloride. Recrystallization from ether–diisopropyl ether afforded (+)-**38**. The alcohol (+)-**38** was submitted to Swern oxidation and Wittig reaction of the aldehyde was carried out as in the preparation of (+)-**31** from (+)-**29**. The crude product was purified by the preparation of the crystalline salt of *p*-methoxybenzylamine. Though recrystallization could not decrease the content of the contaminating (5*E*)-isomer, it could be decreased to 0.6% by converting the compound to the free acid and subsequently preparing the *p*-methoxybenzylamine salt.

A one-carbon homologated compound (+)-**57** of (+)-**6b** was synthesized from (+)-(1*S*,2*R*,3*R*,5*S*)-3-carboxy-2-hydroxymethyl-6,6-dimethylbicyclo[3.1.1]heptane, (+)-**49**.[3] Esterification of (+)-**49**, followed by Swern oxidation of the resulting alcohol (+)-**50** gave an aldehyde (−)-**51**, which was then converted to the benzenesulfonylamino compound (+)-**53** by the procedure used to prepare **17a** from **15**. Swern oxidation of (+)-**53** gave a mixture of an aldehyde **55**, a cyclized aldehyde equivalent (−)-**56** and its dehydrated compound **54**. The last one (20%) was removed by flash chromatography. The cyclized hemiacetal (−)-**56** was isolated from **55** by crystallization, but the mixture of

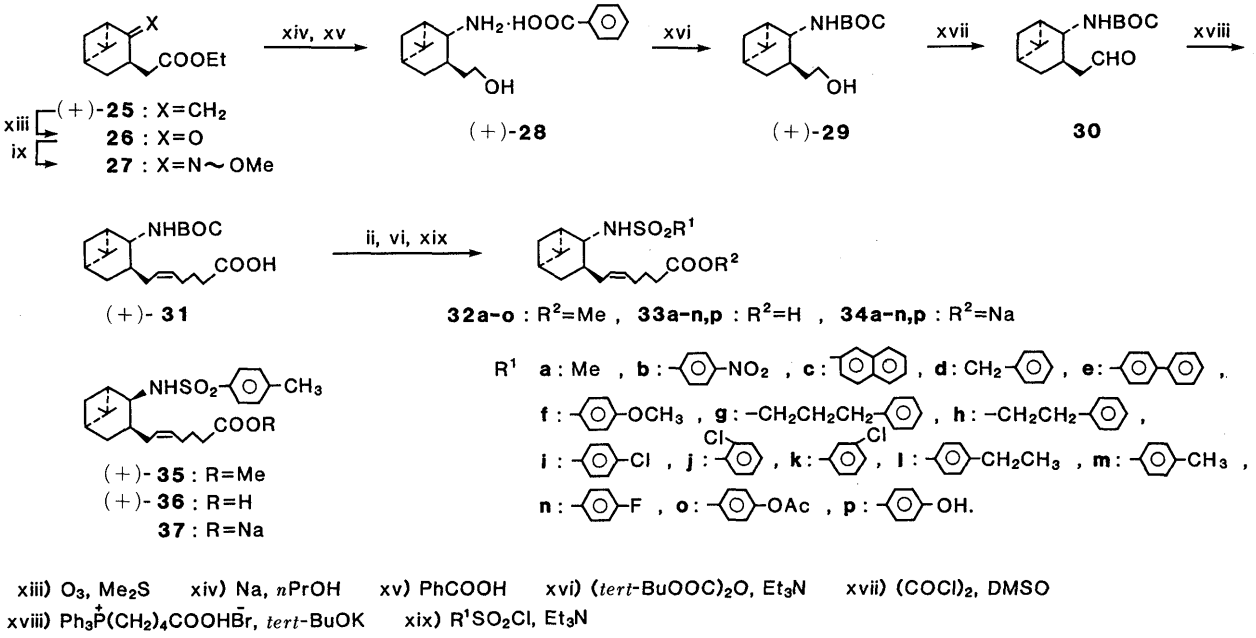


Chart 3

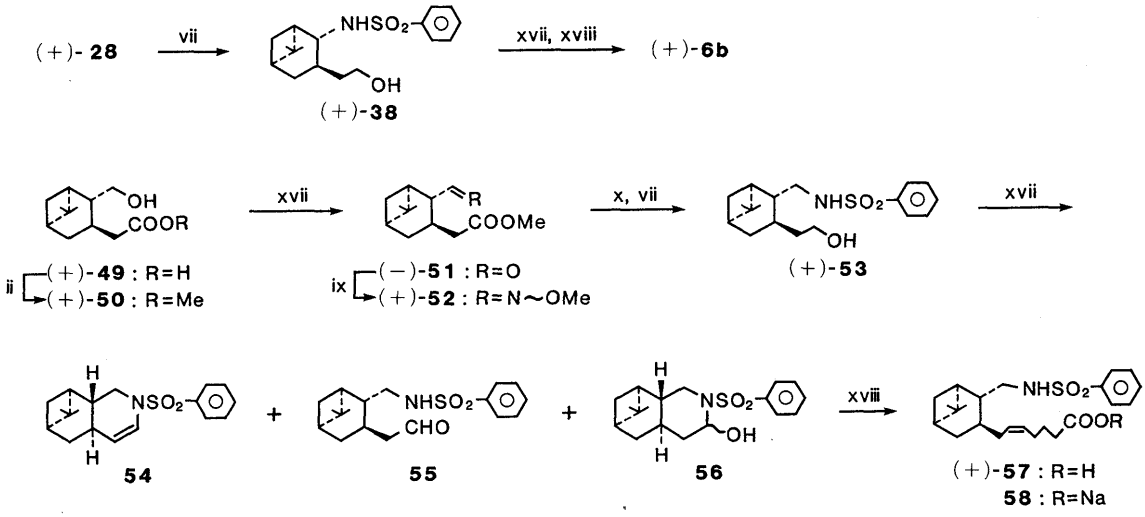


Chart 4

55 and (−)-**56** was used for the next Wittig reaction and furnished the required product (+)-**57**.

Biological Results and Discussion

The compounds prepared were examined *in vitro* for their inhibitory activity against aggregation of rabbit PRP induced by arachidonic acid and of rat WP induced by collagen. (+)-(5*Z*)-7-(3-*endo*-Benzenesulfonylaminobicyclo[2.2.1]hept-2-*exo*-yl)hept-5-enoic acid, S-145, was reported to be a good thromboxane A_2 receptor antagonist.[5] 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. Thus, each IC_{50} value measured by a single experiment for the compounds prepared 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 the Table with the values of SQ-29548,[6] ONO-3708[7] and ONO-11120. Partial agonistic effect (shape change of platelets) for rat WP was measured and the values relative to S-145 are also listed in Table I.

Of the four stereoisomers based on the side chain ring junctions, (+)-**7a**, (+)-**7b**, (−)-**7c** and (−)-**24**, the *trans*-isomer (+)-**7b** was found to be the most potent for rat WP. The orientation of the α- and ω-side chains affects the inhibitory activity in the 2-benzensulfonylamino series more remarkably than in the 3-benzenesulfonylamino series.[2] These isomers did not show a partial agonistic effect. The inhibitory activity was weaker for rabbit PRP than for rat WP. Thus, there was a large species difference, though S-145 and 7-oxabicyclo[2.2.1]heptane derivatives were reported not to exhibit a species difference.[1,5] The (5*E*)-isomer (+)-**22** had the same order of potency and its antipode, (−)-**7b** had very weak activity.

The above biological results indicate that rat WP could be used as an index of the activity for modified compounds. The potency was affected by the substituent at the sulfonylamino group according to the results of (+)-**34a**—**n** and **p**. We can not clearly explain the relative potency of the compounds, but the following tendencies were observed. An aromatic group attached to the sulfonylamino group is desirable from the results with (+)-**34a**, **d**, **h** and **g**. Introduction of a halogen group brings about a partial agonistic effect and the *meta*-position is better than the others, as observed in (+)-**34i**, **k**, **n** and (−)-**34j**. Increasing the length of methylene chain at the *para*-position decreases the potency gradually, as found in (+)-**7a**, (+)-**34m** and (+)-**341**. One-carbon homologation of the ω-side chain decreased the activity, as observed in (+)**58**. Three compounds synthesized by other groups, SQ-29548, ONO-3708 and ONO-11120, have been studied against a variety of agonists under different experimental conditions. This makes direct comparison of the antagonists quite difficult. These compounds were studied in the same way as above. We concluded that (+)-**7b** showed the most potent inhibitory activity among the derivatives investigated and the compounds reported by other groups. We plan to examine other biological effects in detail.

TABLE I

Compd.	IC_{50} Platelet aggregation Rabbit PRP[a] (μM)	Rat WP[b] (nM)	Partial agonist[c]
(±)-S-145 Na	1.0[d]	2.9[e]	100
(+)-**7a**	Negative	14.5	0
(+)-**7b**	275	0.97	0
(−)-**7b**	317	183	0
(−)-**7c**	Negative	270	0
(−)-**10**	270	1000	0
(−)-**12**	185	170	0
(+)-**22**	800	1.6	0
(−)-**24**		43	0
(+)-**34a**		580	0
(+)-**34b**		32	18
(+)-**34c**		5.2	14
(+)-**34d**		290	0
(+)-**34e**		12	0
(+)-**34f**		4.1	0
(+)-**34g**		14	0
(+)-**34h**		16	0
(+)-**34i**		6.4	20
(−)-**34j**		7.7	8
(+)-**34k**		1.6	8
(+)-**34l**		12	8
(+)-**34m**		2.0	0
(+)-**34n**		2.2	20
(+)-**34p**		2.2	33
(+)-**37**		147	0
(+)-**58**		150	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 μM/ml of collagen. *c*) Relative values (the value of S-145 is 100). *d*) The value varied from 0.9—1.2 μM for measurements as the reference compound, and thus each IC_{50} measured by a single experiment for the other compounds was corrected for the value obtained for S-145 Na salt. *e*) The value varied from 1.5—4.3 nM for measurements as the reference compound, and thus each IC_{50} measured by a single experiment for the other compounds was corrected for the value obtained for S-145 Na salt.

Experimental

Melting points were not corrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Varian EM 390 spectrometer. Infrared (IR) spectra were recorded with a JASCO A-702 infrared spectrophotometer. Optical rotations were determined with a Perkin-Elmer Model 141 polarimeter using a l-dm microcell. Circular dichroism (CD) curves were obtained using a JASCO Model J-40C spectropolarimeter. Mass spectra (MS) were taken with a Hitachi M-68 mass spectrometer.

(−)-Methyl (5*Z*)-7-((1*S*,2*S*,3*S*,5*S*)-2-Hydroxymethyl-6,6-dimethylbicyclo[3.1.1]hept-3-yl)hept-5-enoate ((−)-2a) A mixture of 60% sodium hydride (4 g, 0.1 mol) in dry DMSO (100 ml) was warmed at 80 °C for 1 h in nitrogen. A solution of (4-carboxybutyl)triphenylphosphonium bromide (22.15 g, 50 mmol) in DMSO (60 ml) was added at room temperature. The mixture was stirred for 15 min. A solution of (−)-(4a*R*,6*S*,8*S*,8a*S*)-7,7-dimethyl-6,8-methanoperhydroisochroman-3-ol ((−)-**1a**, 3.73 g, 19 mmol) in DMSO (50 ml) was added. The mixture was stirred at room temperature for 2.5 h. Ice water was added and the mixture was washed with ether. The aqueous phase was acidified with dilute hydrochloric acid to *ca.* pH 3 and extracted with ether. The extracts were washed with water and dried over anhydrous sodium sulfate. Excess diazomethane in ether was added with cooling in ice. After stirring for 10 min, the solution was concentrated under reduced pressure. Flash chromatography of the residue on silica gel (240 g) in hexane–ethyl acetate (4 : 1 to 2 : 1) gave (−)-**2a**, 4.01 g, 71.7%; $[\alpha]_D^{23}$ −3.5 (*c*=1.060, MeOH). IR (film): 3430, 1740 cm^{-1}. NMR ($CDCl_3$) δ: 0.87 (3H, s), 1.11 (1H, d, *J*=9 Hz), 1.20 (3H, s), 1.32—2.70 (16H), 3.54 (1H, dd, *J*=6, 10 Hz), 3.66 (3H, s), 3.86 (1H, dd, *J*=6, 10 Hz). *Anal.* Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.17; H, 10.06.

(+)-(1*S*,2*R*,3*S*,5*S*)- and (−)-(1*R*,2*S*,3*R*,5*R*)-Isomers ((+)-2b) and ((−)-2b) (+)-(4a*R*,6*S*,8*S*,8a*R*)- and (−)-(4a*S*,6*R*,8*R*,8a*S*)-7,7-Dimethyl-6,8-methanoperhydroisochroman-3-ol,[3] (+)- and (−)-**1b** were converted to (+)- and (−)-**2b** as described above with yields of 91.7 and 75.6%; $[\alpha]_D^{23}$ +34.1 (*c*=1.309, MeOH) and −32.3 (1.042, MeOH), respectively. IR (film): 3440, 1742 cm^{-1}. NMR ($CDCl_3$) δ: 0.85 (1H, d, *J*=9 Hz), 0.94 (3H,

s), 1.19 (3H, s), 1.35—2.5 (16H), 3.57 (2H, d, J=7 Hz), 3.65 (3H, s), 5.43 (2H, m). *Anal.* Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.38. Found ((+)-**2b**): C, 73.22; H, 10.38.

Methyl (5*Z*)-7-((1*S*,2*S*,3*S*,5*S*)-, (1*S*,2*R*,3*S*,5*S*)- and (1*R*,2*S*,3*R*,5*R*)-2-Carboxy-6,6-dimethylbicyclo[3.1.1]hept-3-yl)-hept-5-enoate (3a,b) Jones' reagent (3.8 ml) was added to a solution of the alcohol (−)-**2a** (2.10 g, 7.13 mmol) in acetone (20 ml) at 0 °C. The mixture was stirred for 1 h. Water was added and the mixture was extracted with ether. The extracts were washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give **3a**. Both enantiomers of **3b** were prepared as described above.

(−)-**3a**: 96.6% yield. IR (film): 1740, 1706 cm^{-1}. NMR ($CDCl_3$) δ: 0.90 (3H, s), 1.22 (3H, s) 1.4—2.7 (15H), 3.18 (1H, m), 3.65 (3H, s), 5.35 (2H, m), 8.95 (1H, br s).

(+)-**3b**: 93.4%. IR (film): 1740, 1700 cm^{-1}. NMR ($CDCl_3$) δ: 0.88 (3H, s), 0.97 (1H, d, J=10 Hz), 1.20 (3H, s), 1.4—2.9 (15H), 3.64 (3H, s), 5.43 (2H, m), 9.70 (1H, br s).

(−)-**3b**: 97.7% yield.

Methyl (5*Z*)-7-((1*S*,2*S*,3*R*,5*S*)-2-Carboxy-6,6-dimethylbicyclo[3.1.1]-hept-3-yl)hept-5-enoate ((−)-3c) A solution of DMSO (1.7 ml) in dichloromethane (15 ml) was added to a solution of oxalyl chloride (1.0 ml) in dichloromethane (25 ml) at −60 °C. The mixture was stirred for 10 min. A solution of (−)-(5*Z*)-7-((1*S*,2*R*,3*R*,5*S*)-2-hydroxymethyl-6,6-dimethylbicyclo[3.1.1]hept-3-yl)hept-5-enoate[3] ((−)-**2c**) (3.0 g, 10.2 mmol) in dichloromethane (30 ml) was added dropwise at −60 °C. The mixture was stirred at −60 °C for 1 h. Triethylamine (9 ml) in dichloromethane (15 ml) was added. The reaction mixture was brought to room temperature and poured into water. The organic phase was separated and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude aldehyde, which was dissolved in 0.38 M sodium methoxide in methanol (40 ml). The solution was allowed to stand at room temperature for 1 h, acidified with dilute hydrochloric acid and extracted with dichloromethane. The extracts were washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was oxidized as described above, and when subjected to flash chromatography on silica gel in hexane–ethyl acetate (4:1 to 1:1), gave (−)-**3c**: 70.1%; $[\alpha]_D^{20}$ −47.4 (c=1.474, MeOH). IR (film): 1741, 1702 cm^{-1}. NMR ($CDCl_3$) δ: 0.82 (3H, s), 1.22 (3H, s), 1.4—2.2 (16H), 3.67 (3H, s), 5.43 (2H, m), 9.73 (1H, br s). *Anal.* Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 69.74; H, 9.14.

General Procedure for the Preparation of *N*-BOC Derivatives 4a—c from Carboxylic Acid Derivatives 3a—c. A Typical Example: Methyl (+)-(5*Z*)-7-((1*R*,2*S*,3*S*,5*S*)-2-(*tert*-Butoxycarbonylamino)-6,6-dimethylbicyclo[3.1.1]hept-3-yl)hept-5-enoate ((+)-4a) A solution of triethylamine (1.4 ml) in acetone (3 ml) and then a solution of ethyl chloroformate (1.0 g, 9.2 mmol) in acetone (2 ml) were added dropwise to a solution of **3a** (2.063 g, 6.69 mmol) in acetone (8 ml) and water (1.5 ml) at 0 °C. The mixture was stirred at 0 °C for 1 h. A solution of sodium azide (1.0 g, 15.3 mmol) in water (4 ml) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 1 h. Water was added and the mixture was extracted with ether. The extracts were washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. A solution of the residue in benzene (50 ml) was heated under reflux for 30 min and concentrated under reduced pressure. A solution of the residue in *tert*-butanol (30 ml) was heated under reflux for 72 h and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (45 g) in hexane–ethyl acetate (6:1) gave (+)-**4a**.

(+)-**4a**: 44.1% yield; $[\alpha]_D^{22}$ +43.3 (c=1.191, MeOH). IR (film): 3460, 3390, 1741, 1713, 1512, 1504 cm^{-1}. NMR ($CDCl_3$) δ: 0.94 (3H, s), 0.94 (1H, d, J=10 Hz), 1.20 (3H, s), 1.43 (9H, s), 1.3—2.6 (14H), 3.68 (3H, s), 4.30 (1H, t, J=9 Hz), 4.80 (1H, d, J=9 Hz), 5.40 (2H, m). *Anal.* Calcd for $C_{22}H_{27}NO_4$: C, 69.62; H, 9.83; N, 3.69. Found: C, 69.69; H, 9.86; N, 3.24.

(+)-**4b**: 38.6% yield; $[\alpha]_D^{22}$ +33.0 (c=1.302, MeOH). IR (film): 3460, 3400, 1740, 1723, 1499 cm^{-1}. NMR ($CDCl_3$) δ: 0.82 (1H, d, J=10 Hz), 1.01 (3H, s), 1.20 (3H, s), 1.43 (9H, s), 1.3—2.6 (14H), 3.65 (3H, s), 3.73 (1H, m), 4.09 (1H, d, J=9 Hz), 5.40 (2H, m). *Anal.* Calcd for $C_{22}H_{27}NO_4$: C, 69.62; H, 9.83; N, 3.69. Found: C, 69.31; H, 9.86; N, 3.64.

(−)-**4c**: 70.7% yield; $[\alpha]_D^{24}$ −43.2 (c=0.975, MeOH). IR (film); 3390, 1741, 1715 cm^{-1}. NMR ($CDCl_3$) δ: 0.83 (3H, s), 1.20 (3H, s), 1.42 (9H, s), 1.2—2.55 (15H), 3.67 (3H, s), 3.73 (1H, s), 4.55 (1H, d, J=9 Hz), 5.43 (2H, m). *Anal.* Calcd for $C_{22}H_{27}NO_4$: C, 69.62; H, 9.83; H, 3.69. Found: C, 69.33; H, 9.80; N, 3.71.

(−)-**4b**: 45.7% yield: $[\alpha]_D^{22}$ −31.7 (c=1.036, MeOH).

General Procedure for the Preparation of Sulfonylamino Derivatives 5a—c from *N*-BOC Derivatives 4a—c. A Typical Example: Methyl (+)-(5*Z*)-7-((1*R*,2*S*,3*S*,5*S*)-2-Benzenesulfonylamino-6,6-dimethylbicyclo-[3.1.1]hept-3-yl)hept-5-enoate ((+)-5a) A solution of the *N*-BOC derivative (+)-**4a** (1.25 g, 0.745 mmol) in trifluoroacetic acid (10 ml) was stirred at room temperature for 30 min. The volatile materials were removed by distillation under reduced pressure. Benzenesulfonyl chloride (600 mg, 3.40 mmol) and triethylamine (3 ml) were added to a solution of the residue in dichloromethane (15 ml). The mixture was stirred at room temperature for 20 min, washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was chromatographed on silica gel (45 g) in hexane–ethyl acetate (4:1) and crystallized from hexane to give (+)-**5a**.

Methyl (−)-(5*E*)-7-((1*R*,2*S*,3*R*,5*S*)-2-benzenesulfonylamino-6,6-dimethylbicyclo[3.1.1]hept-3-yl)hept-5-enoate ((−)-**8**) was separated by flash chromatography of (−)-**5c**.

(+)-**5a**: 78.6% yield; mp 55 °C; $[\alpha]_D^{23}$ +52.7 (c=1.094, MeOH). IR (KBr): 3280, 1735, 1337, 1320, 1167, 1157 cm^{-1}. NMR ($CDCl_3$) δ: 0.84 (3H, s), 0.96 (1H, d, J=10 Hz), 1.07 (3H, s), 1.2—2.5 (14H), 3.66 (3H, s), 3.90 (1H, m), 4.86 (1H, d, J=10 Hz), 5.23 (2H, m), 7.35—7.66 (3H, m), 7.80—7.91 (2H, m). CD (MeOH) λnm ($\Delta\varepsilon$): 269.5 (+0.297), 262.5 (+0.358), 255.5 (+0.345), 222 (+5.03). *Anal.* Calcd for $C_{23}H_{33}NO_4S$: C, 65.84; H, 7.93; N, 3.34; S, 7.64. Found: C, 65.77; H, 7.85; N, 3.34; S, 7.59.

(+)-**5b**: 73.6% yield; $[\alpha]_D^{23}$ +29.5 (c=1.263, MeOH). IR (film): 3300, 1740, 1328, 1164 cm^{-1}. NMR ($CDCl_3$) δ: 0.72 (1H, d, J=10 Hz), 0.99 (3H, s), 1.08 (3H, s), 1.25—2.45 (14H), 3.37 (1H, m), 3.69 (3H, s), 4.94 (1H, d, J=8 Hz), 5.31 (2H, m), 7.36—7.68 (3H, m), 7.86—7.97 (2H, m). CD (MeOH) λnm ($\Delta\varepsilon$): 279 (+0.333), 270 (+0.085), 264 (+0.115), 257 (+0.082), 247 (+0.091), 225 (+1.35), 200! (−2.89). *Anal.* Calcd for $C_{23}H_{33}NO_4S$: C, 65.84; H, 7.93; N, 3.34; S, 7.64. Found: C, 65.63; H, 7.71; N, 3.36; S, 7.45.

(−)-**5c**: 73.6% yield; $[\alpha]_D^{23}$ −24.6 (c=1.276, MeOH). IR (film): 3280, 1738, 1323, 1161 cm^{-1}. NMR ($CDCl_3$) δ: 0.72 (3H, s), 1.07 (3H, s), 1.2—2.45 (15H), 3.34 (1H, t, J=8 Hz), 3.69 (3H, s), 4.85 (1H, d, J=9 Hz), 5.34 (2H, m), 7.37—7.65 (3H, m), 7.83—7.94 (2H, m). CD (MeOH) λnm ($\Delta\varepsilon$) 269 (+0.070), 262 (+0.106), 257 sh (+0.118), 220 (+3.15). *Anal.* Calcd for $C_{23}H_{33}NO_4S$: C, 65.84; H, 7.93; N, 3.34; S, 7.64. Found: C, 65.93; H, 7.93; N, 3.36; S, 7.56.

(−)-**5b**: 71.4% yield; $[\alpha]_D^{23}$ −29.0 (c=0.978, MeOH). *Anal.* Calcd for $C_{23}H_{33}NO_4S$: C, 65.84; H, 7.93; N, 3.34; S, 7.64. Found: C, 65.74; H, 8.01; N, 3.36; S, 7.52.

(−)-**8**: 4.1% yield; mp 101—102 °C; $[\alpha]_D^{23}$ −21.4 (c=0.980, MeOH). IR (KBr): 3270, 1732, 1324, 1167 cm^{-1}. NMR ($CDCl_3$) δ: 0.68 (3H, s), 1.06 (3H, s), 1.20—2.50 (15H), 3.31 (1H, t, J=8 Hz), 3.66 (3H, s), 4.79 (1H, d, J=9 Hz), 5.32 (2H, m), 7.37—7.70 (3H, m), 7.83—7.98 (2H, m). CD (MeOH) λnm ($\Delta\varepsilon$): 269 (+0.064), 262 (+0.091), 256 sh (+0.109), 222 (+2.55). *Anal.* Calcd for $C_{23}H_{33}NO_4S$: C, 65.84; H, 7.93; N, 3.34; S, 7.64. Found: C, 65.64; H, 7.88; N, 3.29; S, 7.52.

General Procedure for the Preparation of Carboxylic Acid Derivatives 6a—c and (−)-9 and Their Sodium Salts. A Typical Example: (+)-(5*Z*)-7-((1*R*,2*S*,3*S*,5*S*)-2-Benzenesulfonylamino-6,6-dimethylbicyclo-[3.1.1]hept-3-yl)hept-5-enoic Acid ((+)-6a) and Its Sodium Salt (7a) A mixture of 10% aqueous sodium hydroxide (8 ml) and a solution of the ester (+)-**5a** (1.58 g, 0.406 mmol) in methanol (20 ml) was stirred at room temperature for 2 h, 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. Flash chromatography of the residue on silica gel (20 g) in hexane–ethyl acetate (2:1) gave (+)-**6a**.

(−)-(5*E*)-7-((1*S*,2*S*,3*R*,5*R*)-2-Benzenesulfonylamino-6,6-dimethylbicyclo[3.1.1]hept-3-yl)hept-5-enoic acid ((−)-**11**) was isolated by flash chromatography of (−)-**6b**.

(+)-**6a**: 95.3%; $[\alpha]_D^{23}$ +48.7 (c=1.513, MeOH). IR ($CHCl_3$): 3520, 3395, 3265, 1710, 1342, 1158 cm^{-1}. NMR ($CDCl_3$) δ: 0.85 (3H, s), 0.98 (1H, d, J=10 Hz), 1.07 (3H, s), 1.3—2.5 (14H), 3.91 (1H, m), 5.23 (1H, d, J=7 Hz), 5.33 (2H, m), 7.33—7.63 (3H, m), 7.80—7.91 (2H, m), 8.15 (1H, br s).

(+)-**6b**: 92.8% yield; $[\alpha]_D^{23}$ +32.9 (c=1.278, MeOH); IR ($CHCl_3$): 3520, 3395, 3275, 1710, 1331, 1160 cm^{-1}. NMR ($CDCl_3$) δ: 0.71 (1H, d, J=10 Hz), 0.99 (3H, s), 1.07 (3H, s), 1.3—2.45 (14H), 3.35 (1H, m), 5.23 (1H, d, J=7 Hz), 5.32 (2H, m), 7.35—7.63 (3H, m), 7.83—7.94 (2H, m).

(−)-**6c**: 77.9% yield; $[\alpha]_D^{23}$ −23.4 (c=1.252, MeOH). IR (film): 3280, 1709, 1324, 1163 cm^{-1}; NMR ($CDCl_3$) δ: 0.71 (3H, s), 1.07 (3H, s), 1.2—2.5 (15H), 3.31 (1H, m), 5.17 (1H, d, J=9 Hz), 5.35 (2H, m), 7.4—7.6 (3H,

m), 7.7—8.0 (2H, m).

(−)-**9**: Quantitative yield; $[\alpha]_D^{23}$ −29.6 (c=0.945, MeOH). NMR ($CDCl_3$) δ: 0.69 (3H, s), 1.06 (3H, s), 1.2—2.5 (15H), 3.32 (1H, t, J=8 Hz), 5.08 (1H, d, J=9 Hz), 5.33 (2H, m), 7.37—7.69 (3H, m), 7.83—7.94 (2H, m), 8.53 (1H, br s).

(−)-**6b**: 77.9% yield; $[\alpha]_D^{23}$ −30.5 (c=0.798, MeOH).

(−)-**11**: 1.8% yield; $[\alpha]_D^{23}$ −29.4 (c=0.640, MeOH).

A 0.221 M solution of sodium methoxide in methanol (18.2 ml) was added to a solution of the carboxylic acid (+)-**6a** (1.676 g, 0.446 mmol) in methanol (10 ml). The solution was concentrated under reduced pressure. Water (30 ml) was added. The solution was treated with charcoal and lyophilized to give **7a**.

IR spectra of sodium salts (KBr); **7a**: 3300, 1560, 1338, 1308, 1153 cm^{-1}. **7b**: 3295, 1563, 1325, 1162 cm^{-1}. **7c**: 3280, 1565, 1323, 1162 cm^{-1}. **10**: 3280, 1560, 1322, 1161, 967 cm^{-1}. **12**: 3280, 1564, 1322, 1161, 967 cm^{-1}.

(1*R*,3*RS*,5*R*)-3-(2-Propenyl)-6,6-dimethylbicyclo[3.1.1]heptan-2-one (15) A 1.6 M solution of *n*-butyllithium in hexane (115 ml, 0.184 mol) was added dropwise to a solution of diisopropylamine (30 ml) in dry tetrahydrofuran (THF) (40 ml) at −30 °C under nitrogen. The mixture was stirred at −20 °C for 5 min. A solution of (+)-nopinone (18.9 g, 0.136 mol) in THF (20 ml) was added dropwise to the solution at −30 °C. The mixture was stirred at 0 °C for 10 min and cooled to −30 °C. A solution of allyl bromide (17.5 ml, 0.202 mol) in THF (10 ml) was added. The mixture was stirred at 35 °C for 30 min, poured into ice-cold dilute hydrochloric acid and extracted with ether. The extracts were washed with aqueous sodium hydrogencarbonate and water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was distilled through a 10-cm column. After nopinone (1.90 g, 10.1%) had been recovered at 61—65 °C at 8 mmHg, **15** was distilled at 60—78 °C at 5 mmHg; 16.1 g, 66.0%. The NMR spectrum showed it to be a mixture of epimers. *Anal.* Calcd for $C_{12}H_{18}O$: C, 80.85; H, 9.96. Found: C, 80.59; H, 9.96.

Flash chromatography of the residue on silica gel (60 g) in hexane–ethyl acetate (10:1) gave (+)-**14**, 1.10 g, 3.7%; $[\alpha]_D^{23}$ +56.4 (c=1.172, $CHCl_3$). IR (film): 1704 cm^{-1}. NMR ($CDCl_3$) δ: 0.85 (3H, s), 1.35 (3H, s), 1.8—2.9 (10H), 4.8—5.3 (4H, m), 5.5—6.2 (2H, m). *Anal.* Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 81.69; H, 9.91.

***O*-Methyl Oxime of (+)-(1*R*,3*R*,5*S*)- and (+)-(1*R*,3*S*,5*S*)-3-(2-Propenyl)-6,6-dimethylbicyclo[3.1.1]heptan-2-one ((+)-16a,b)** A mixture of **15** (22.6 g, 0.127 mol), *O*-methylhydroxylamine hydrochloride (23.8 g, 0.285 mol), pyridine (25 ml) and ethanol (300 ml) was heated under reflux for 18 h and concentrated to one-third of the initial volume. Ice water was added, and the mixture was acidified with dilute hydrochloric acid and extracted with ethyl acetate. The extracts were washed with aqueous sodium hydrogencarbonate and water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (450 g) in hexane–ether (20:1 to 10:1) gave three isomeric products.

1st Eluate (+)-**16a**: 43.4% yield; $[\alpha]_D^{24}$ +23.4 (c=1.054, $CHCl_3$). IR (film): 1641, 1064 cm^{-1}. NMR ($CDCl_3$) δ: 0.71 (3H, s), 1.29 (3H, s), 1.4—1.7 (2H, m), 1.8—2.4 (4H, m), 2.5—3.0 (2H, m), 3.41 (1H, t, J=6 Hz), 4.9—5.3 (2H, m), 5.7—6.2 (1H, m). *Anal.* Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 74.91; H, 10.41; N, 6.76.

2nd Eluate (+)-**16b**: 11.8%; $[\alpha]_D^{24}$ +122.0 (c=1.388, $CHCl_3$). IR (film): 1641, 1060 cm^{-1}. NMR ($CDCl_3$) δ: 0.80 (3H, s), 1.30 (3H, s), 1.31 (1H, d, J=10 Hz), 1.5—2.9 (7H), 3.45 (1H, t, J=6 Hz), 3.79 (3H, s), 4.9—5.2 (2H, m), 5.6—6.1 (1H, m). *Anal.* Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.32; H, 10.39; N, 6.38.

The Last Eluate (+)-**16b**: 16.0% yield; $[\alpha]_D^{24}$ +65.2 (c=2.127, $CHCl_3$). IR ($CHCl_3$): 1640, 1055 cm^{-1}. NMR ($CDCl_3$) δ: 0.78 (3H, s), 1.28 (3H, s), 1.46 (1H, d, J=10 Hz), 1.5—3.1 (8H, m), 3.72 (3H, s), 4.9—5.2 (2H, m), 5.6—6.1 (1H, m). *Anal.* Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 74.97; H, 10.21; N, 6.76.

(−)-(1*R*,2*S*,3*R*,5*S*)- and (−)-(1*R*,2*R*,3*R*,5*S*)-2-Benzenesulfonylamino-3-(2-propenyl-6,6-dimethylbicyclo[3.1.1]heptanes ((−)-17a,b) Sodium metal (1.0 g, 43 mg atm) was added in small portions to a solution of (+)-**16a** (11.4 g, 55.0 mmol) in 99% ethanol (160 ml) at the refluxing temperature over 3 h. After the metal had been dissolved by heating under reflux, the mixture was cooled and poured into water. The mixture was extracted with ether. The extracts were washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure.

A mixture of the residue, benzenesulfonyl chloride (10 ml), triethylamine (26 ml) and dichloromethane (165 ml) was allowed to stand at room temperature overnight and poured into ice-cold dilute hydrochloric acid. The organic phase was separated and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed with aqueous sodium hydrogencarbonate and water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (300 g) in hexane–ethyl acetate (4:1) gave (−)-**17a** and (−)-**17b**.

The isomer (+)-**16b** was converted as described above but only one stereoisomer (+)-**17c** was obtained.

1st Eluate (−)-**17a**: 17.1% yield; $[\alpha]_D^{22}$ −32.0 (c=1.233, $CHCl_3$). IR (film): 3330, 1342, 1162 cm^{-1}. NMR ($CDCl_3$) δ: 0.93 (3H, s), 1.04 (3H, s), 0.7—2.8 (9H), 3.95 (1H, m), 4.82 (1H, d, J=9 Hz), 4.90 (1H, s), 5.00 (1H, s), 5.11 (1H, s), 5.75 (1H, m), 7.4—7.6 (3H, m), 7.7—8.0 (2H, m).

2nd Eluate (−)-**17b**: 75.5% yield; mp 93 °C (benzene); $[\alpha]_D^{22}$ −33.9 (c=1.144, $CHCl_3$). IR (Nujol): 3260, 1327, 1173 cm^{-1}. NMR ($CDCl_3$) δ: 0.72 (3H, s), 1.08 (3H, s), 1.2—2.5 (9H), 3.36 (1H, t, J=8 Hz), 4.71 (1H, d, J=9 Hz), 4.89 (1H, s), 5.03 (1H, m), 5.70 (1H, m), 7.4—7.7 (3H, m), 7.8—8.0 (2H, m). *Anal.* Calcd for $C_{18}H_{25}NO_2S \cdot 1/2(C_6H_6 \cdot H_2O)$: C, 68.63; H, 7.95; N, 3.81; S, 8.72. Found: C, 68.53; H, 7.61; N, 3.95; S, 8.89.

(+)-**17c**: mp 57—58 °C (hexane); $[\alpha]_D^{22}$ +22.6 (c=1.353, ($CHCl_3$). IR (Nujol): 3295, 1330, 1163 cm^{-1}. NMR ($CDCl_3$) δ: 0.69 (1H, d, J=10 Hz), 1.00 (3H, s), 1.08 (3H, s), 1.3—1.6 (1H, m), 1.7—2.3 (7H, m), 3.35 (3H, m), 4.80 (1H, dd, J=9, 3 Hz), 4.96 (1H, s), 5.14 (1H, d, J=9 Hz), 5.4—5.9 (1H, m), 7.4—7.6 (3H, m), 7.8—8.2 (2H, m). *Anal.* Calcd for $C_{18}H_{25}NO_2S$: C, 67.68; H, 7.89; N, 4.38; S, 10.04. Found: C, 67.44; H, 7.94; N, 4.43; S, 9.85.

(−)-(1*R*,2*S*,3*S*,5*S*)-2-Benzenesulfonylamino-3-(2,3-epoxypropyl)-6,6-dimethylbicyclo[3.1.1]heptane ((−)-18a) *m*-Chloroperbenzoic acid (1.2 g, 8.75 mmol) was added in small portions to a solution of (−)-**17a** (0.955 g, 2.98 mmol) in dichloromethane (13 ml) with cooling in ice. The mixture was stirred at room temperature for 5 h. The insoluble materials were removed by filtration. The filtrate was washed successively with aqueous sodium thiosulfate, aqueous sodium hydrogencarbonate and water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Recrystallization from benzene gave a mixture of epimers (−)-**18a**, 0.95 g; mp 127—131 °C; $[\alpha]_D^{22}$ −34.7 (c=1.027, $CHCl_3$). IR (Nujol): 3260, 1328, 1172 cm^{-1}. NMR ($CDCl_3$) δ: 0.72 (3H, s), 1.05 and 1.07 (total 3H, s), 1.3—2.2 (9H), 2.38 (1H, m), 2.72 (1H, m), 2.86 (1H, m), 3.33 (1H, m), 4.80 and 4.88 (total 1H, d, J=8 Hz), 7.4—7.6 (3H, m), 7.7—8.0 (2H, m). *Anal.* Calcd for $C_{21}H_{27}NO_3S \cdot 1/2C_6H_6$: C, 67.53; H, 7.28; N, 3.75; S, 8.58. Found: C, 67.13; H, 7.51; N, 3.85; S, 8.57.

The olefins (−)-**17b** and (+)-**17c** were converted to **18b** and **18c** as described above, respectively, and the oily products were used for the next preparation step without further purification.

(−)-(1*R*,2*S*,3*S*,5*S*)-2-Benzenesulfonylamino-3-formylmethyl-6,6-dimethylbicyclo[3.1.1]heptane ((−)-19a) An aqueous solution of periodic acid (1.2 g, 6.25 mmol in 3 ml) was added to a solution of (−)-**18a** (0.938 g, 2.80 mmol) in dioxane (10 ml) at room temperature. The mixture was stirred for 4 h and extracted with ethyl acetate. The extracts were washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Flash chromatography of the residue on silica gel in hexane–ethyl acetate (3:2) and recrystallization from hexane gave (−)-**19a**, 445 mg, 49.5%; mp 108—110 °C. IR (Nujol): 3215, 1704, 1328, 1151 cm^{-1}. NMR ($CDCl_3$) δ: 0.70 (3H, s), 1.06 (3H, s), 1.3—2.9 (9H), 3.33 (1H, t, J=9 Hz), 4.87 (1H, d, J=9 Hz), 7.4—7.6 (3H, m), 7.7—7.9 (2H, m), 9.70 (1H, s). *Anal.* Calcd for $C_{17}H_{23}NO_3S$: C, 63.52; H, 7.21; N, 4.36; S, 9.97. Found: C, 63.21; H, 7.23; N, 4.29; S, 9.73.

Epoxides **18b** and **18c** were converted to **19b** and **20**, respectively, as described above.

(−)-(5*Z*)-7-((1*R*,2*R*,3*R*,5*S*)-2-Benzenesulfonylamino-6,6-dimethylbicyclo[3.1.1]hept-3-yl)hept-5-enoic Acid ((−)-23) and Its Sodium Salt (24) By the procedure used to prepare (−)-**2a** from (−)-**1a**, compound **20** was converted to (−)-**23**; $[\alpha]_D^{20}$ −4.7 (c=0.706, MeOH). IR (film): 3300, 1708, 1341, 1156 cm^{-1}. NMR ($CDCl_3$) δ: 0.81 (3H, s), 1.03 (3H, s), 1.2—2.7 (15H), 3.96 (1H, m), 5.43 (2H, m), 7.4—7.6 (3H, m), 7.7—7.9 (2H, m), 8.68 (1H, br s).

The aldehydes **19a** and **19b** were converted to (+)-**6b** and (−)-**6c**, respectively, as described above.

(+)-(5*E*)-7-((1*R*,2*R*,3*S*,5*S*)-2-Benzenesulfonylamino-6,6-dimethylbicyclo[3.1.1]hept-3-yl)hept-5-enoic acid ((+)-**21**) was isolated by chromatography in the preparation of (+)-**6b**; $[\alpha]_D^{20}$ +26.5 (c=1.208, MeOH). IR (film): 3285, 1708, 1323, 1160 cm^{-1}. NMR ($CDCl_3$) δ: 0.70 (1H, d, J=8 Hz), 1.00 (3H, s), 1.08 (3H, s), 1.2—2.5 (14H), 3.37 (1H, m), 4.89 (1H, d, J=8 Hz), 5.27 (2H, m), 7.3—7.7 (3H, m), 7.8—8.0 (2H, m).

IR spectra of **22** and **24** (KBr); **22**: 3290, 1565, 1322, 1159, 967 cm^{-1}. **24**: 3290, 1565, 1322, 1159 cm^{-1}.

Ethyl ((1*R*,3*R*,5*S*)-2-Oxo-6,6-dimethylbicyclo[3.1.1]hept-3-yl)acetate (26) and the *O*-Methyl Oxime (27) Ozonized oxygen was introduced into a solution of ethyl (1*R*,3*R*,5*S*)-2-methylidene-6,6-dimethylbicyclo[3.1.1]-

hept-3-yl)acetate[3] (111.2 g, 0.5 mol) in methanol (450 ml) at −78 °C until the characteristic blue color persisted. Dimethylsulfide (100 ml) was added dropwise. The mixture was gradually warmed from −10 °C to room temperature over 3 h. The volatile materials were removed by distillation under reduced pressure. The residue was dissolved in ether. The solution was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain **26** (107.0 g, 95.4%). NMR ($CDCl_3$) δ: 0.94 (3H, s), 1.26 (3H, t, J=7 Hz), 1.33 (3H, s), 1.1—3.15 (9H), 4.18 (2H, q, J=7 Hz).

The crude ketone **26** (107.0 g, 0.477 mol), *O*-methylhydroxylamine hydrochloride (50.1 g, 0.6 mol), ethanol (500 ml) and pyridine (47.5 g, 0.6 mol) were heated under reflux for 3 h and concentrated under reduced pressure. Water was added and the mixture was extracted with ether. The extracts were washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Distillation of the residue at 118—123 °C at 1.2 mmHg gave **27**, 106.1 g, 87.8%. IR (film): 1738, 1630 cm^{-1}. NMR ($CDCl_3$) δ: 0.79 and 0.85 (total 3H, s), 1.20—1.73 (8H), 1.94—3.65 (7H), 3.76 and 3.83 (total 3H, s), 4.18 (2H, q, J=7 Hz). *Anal.* Calcd for $C_{14}H_{23}NO_4$: C, 66.37; H, 9.15; N, 5.53. Found: C, 65.92; H, 9.13; N, 5.60.

(+)-2-((1*R*,2*R*,3*R*,5*S*)-2-Amino-6,6-dimethylbicyclo[3.1.1]hept-3-yl)-ethanol-benzoic Acid Salt ((+)-28) Sodium metal (35 g, 1.52 g atm) was added in small portions to a solution of **27** (35.0 g, 0.138 mol) in *n*-propyl alcohol (420 ml) at 90 °C (bath temperature) over 30 min under nitrogen. The mixture was heated under reflux until the metal had dissolved (*ca.* 1 h). After cooling, the mixture was poured into ice water. The organic phase was separated and the aqueous phase was extracted with ether. The combined organic phases were concentrated under reduced pressure. The residue was dissolved in ether. The extracts were washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure, giving the crude amino alcohol, 20.1 g, 79.5%.

A solution of benzoic acid (13.5 g) in ether (100 ml) was added to a solution of the residue in ether (200 ml). The crystals (26.8 g, 63.6%) were collected by filtration and recrystallization from acetone gave (+)-**28**, 16.7 g, 39.6%; mp 180—183 °C; $[\alpha]_D^{26}$ +27.1 (c=1.083, MeOH). IR (KBr): 1522, 1383 cm^{-1}. NMR ($CDCl_3$) δ: 0.71 (1H, d, J=10 Hz), 1.07 (3H, s), 1.13 (3H, s), 1.30—2.50 (8H), 3.27 (1H, m), 3.45—3.90 (2H), 6.62 (4H, s), 7.30—7.47 (3H), 7.95—8.05 (2H). *Anal.* Calcd $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.60; H, 8.76; N, 4.62.

(+)-2-((1*R*,2*R*,3*R*,5*S*)-2-*tert*-Butoxycarbonylamino-6,6-dimethylbicyclo[3.1.1]hept-3-yl)ethanol ((+)-29) Triethylamine (20 ml) was added to a solution of (+)-**28** (13.7 g, 44.9 mmol) in dichloromethane (60 ml) with cooling in ice and the mixture was stirred for 20 min. A solution of di-*tert*-butyl dicarbonate (13.5 g, 61.8 mmol) in dichloromethane (25 ml) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 3 h. Water was added. The organic phase was separated and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (240 g) in hexane–ethyl acetate (4:1) gave (+)-**29**, 12.7 g, 99.8%; $[\alpha]_D^{26}$ +35.5 (c=1.182, MeOH). IR (film): 3460, 3360, 1690 cm^{-1}. NMR ($CDCl_3$) δ: 0.84 (1H, d, J=10 Hz), 1.05 (3H, s), 1.22 (3H, s), 1.44 (9H, s), 1.40—2.38 (8H), 3.60—3.90 (3H), 4.73 (1H, d, J=7 Hz). *Anal.* Calcd for $C_{16}H_{29}NO_3$: C, 67.81; H, 10.31; N, 4.94. Found: C, 67.31; H, 10.40; N, 5.02.

(+)-(5*Z*)-7-((1*R*,2*R*,3*S*,5*S*)-2-(*tert*-Butoxycarbonylamino)-6,6-dimethylbicyclo[3.1.1]hept-3-yl)hept-5-enoic Acid ((+)-31) A solution of DMSO (10.2 ml) in dichloromethane (30 ml) was added dropwise at −70 °C to a stirred solution of oxalyl chloride (6 ml) in dichloromethane (150 ml). The mixture was stirred at −78 °C for 10 min. A solution of (+)-**29** (12.7 g, 44.8 mmol) in dichloromethane (30 ml) was added dropwise and the mixture was stirred for 20 min. Triethylamine (42 ml) was added. The mixture was stirred at −70 °C for 15 min and at room temperature and then poured into water. The organic phase was separated and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude aldehyde **30** was used for the next preparation step without further purification.

Potassium *tert*-butoxide (31.2 g, 0.278 mol) was added to a suspension of (4-carboxybutyl)triphenylphosphonium bromide (61.5 g, 0.139 mol) in dry THF (250 ml) under nitrogen. The mixture was stirred at room temperature for 1 h. A solution of **30** in THF (60 ml) was added dropwise at 0 °C. The mixture was stirred for 1 h. Water was added. The mixture was washed with ether and acidified with dilute hydrochloric acid. Ether was added. The mixture was allowed to stand at room temperature and solids were removed by filtration. The organic phase was separated and 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. Flash chromatography of the residue on silica gel (200 g) in hexane–ethyl acetate (3:2 to 1:1) and recrystallization from hexane gave (+)-**31**, 11.76 g (71.7%) mp 92—93 °C; $[\alpha]_D^{26}$ +34.6 (c=1.204, MeOH). IR (KBr): 3320, 1720, 1650 cm^{-1}. NMR ($CDCl_3$) δ: 0.84 (1H, d, J=10 Hz), 1.03 (3H, s), 1.21 (3H, s), 1.45 (9H, s), 1.39—2.50 (14H), 3.74 (1H, m), 4.71 (1H, d, J=10 Hz), 5.31—5.64 (2H). *Anal.* Calcd for $C_{21}H_{35}NO_4$: C, 69.01; H, 9.65; N, 3.83. Found: C, 68.99; H, 9.64; N, 3.95.

General Procedure for the Preparation of Methyl (5*Z*)-7-((1*R*,2*R*,3*S*,5*S*)-2-(Substituted Sulfonylamino)-6,6-dimethylbicyclo[3.1.1]hept-3-yl)hept-5-enoates (32a—o) Excess diazomethane in ether was added to a solution of (+)-**31** (500 mg, 1.49 mmol) in ether (5 ml). After 10 min, the volatile materials were removed by distillation under reduced pressure.

A solution of trifluoroacetic acid (1 ml) in dichloromethane (0.5 ml) was added. The solution was stirred at room temperature for 30 min and concentrated under reduced pressure. The residue was dissolved in ether. The solution was washed with 10% sodium carbonate and water, dried over anhydrous sodium sulfate and concentrated under reduced pressure.

The sulfonyl chloride (1.2—2.0 eq) was added to a solution of the residue in triethylamine (1 ml) and dichloromethane (10 ml). The mixture was stirred at room temperature for 1 h. Ether was added and the mixture was washed with water, dilute hydrochloric acid, aqueous sodium hydrogencarbonate and water, then dried over anhydrous sodium sulfate and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (25 g) in hexane–ethyl acetate (4:1) gave **32a—o**.

(+)-**32a**, R=Me: 76.7% yield; $[\alpha]_D^{25}$ +37.7 (c=1.285, MeOH). IR (film): 3300, 1738, 1322, 1152 cm^{-1}. NMR ($CDCl_3$) δ: 0.85 (1H, d, J=10 Hz), 1.06 (3H, s), 1.24 (3H, s), 1.49 (1H, ddd, J=3, 5, 13 Hz), 1.70 (2H, m), 1.83—2.39 (8H), 2.34 (2H, t, J=7 Hz), 2.48 (1H, td, J=5, 14 Hz), 2.97 (3H, s), 3.51 (1H, ddd, J=3, 6, 9 Hz), 3.68 (3H, s), 4.55 (1H, d, J=9 Hz), 5.46 (2H, m).

(+)-**32b**, R=*p*-Nitrophenyl: 97.6% yield; $[\alpha]_D^{25}$ +33.4 (c=1.070, MeOH). IR (film): 3295, 1739, 1531, 1350, 1165 cm^{-1}, NMR ($CDCl_3$) δ: 0.75 (1H, d, J=10 Hz), 1.02 (3H, s), 1.11 (3H, s), 1.30—2.50 (14H), 3.40 (1H, m), 3.69 (3H, s), 5.10—5.50 (3H, s), 8.05 (2H, d, J=9 Hz), 8.35 (2H, d, J=9 Hz). *Anal.* Calcd for $C_{23}H_{32}N_2O_6S$: C, 59.46; H, 6.94; N, 6.03; S, 6.90. Found: C, 59.15; H, 7.00; N, 6.07; S, 6.62.

(+)-**32c**, R=2-Naphthyl: 96.3% yield; $[\alpha]_D^{25}$ +12.4 (c=1.810, MeOH). IR (film): 3295, 1738, 1327, 1160 cm^{-1}. NMR ($CDCl_3$) δ: 0.71 (1H, d, J=10 Hz), 1.03 (3H, s), 1.07 (3H, s), 1.30—2.40 (14H), 3.40 (1H, m), 3.67 (3H, s), 5.05 (1H, d, J=8 Hz), 5.22 (2H, m), 7.50—8.10 (6H), 8.45 (1H, s). *Anal.* Calcd for $C_{27}H_{35}NO_4S$: C, 69.05; H, 7.51; N, 2.98; S, 6.83. Found: C, 68.68; H, 7.56; N, 3.03; S, 6.60.

(+)-**32d**, R=Benzyl: 57.8% yield; $[\alpha]_D^{25}$ +18.0 (c=1.991, MeOH). IR (film): 3305, 1738, 1320, 1153 cm^{-1}. NMR ($CDCl_3$) δ: 0.81 (1H, d, J=10 Hz). 0.93 (3H, s), 1.22 (3H, s), 1.30—2.60 (14H), 3.52 (1H, m), 3.63 (3H, s), 4.21 (2H, s), 4.38 (1H, d, J=9 Hz), 5.42 (2H, m), 7.39 (5H, s). *Anal.* Calcd for $C_{24}H_{35}NO_4S$: C, 66.48; H, 8.14; N, 3.23; S, 7.40. Found: C, 66.22; H, 8.19; N, 3.36; S, 7.26.

(+)-**32e**, R=*p*-Biphenyl: 95.3% yield; mp 86—87 °C; $[\alpha]_D^{25}$ +32.9 (c=1.024, MeOH). IR (KBr): 3280, 1731, 1325, 1160 cm^{-1}. NMR ($CDCl_3$) δ: 0.75 (1H, d, J=10 Hz), 1.03 (3H, s), 1.11 (3H, s), 1.42 (1H, m), 1.55—2.31 (11H), 2.27 (2H, t, J=7 Hz), 3.40 (1H, m), 3.67 (3H, s), 4.85 (1H, d, J=8 Hz), 5.32 (2H, m), 7.38—7.64 (5H), 7.72 (2H, d, J=9 Hz), 7.93 (2H, d, J=9 Hz). *Anal.* Calcd for $C_{27}H_{37}NO_4S$: C, 70.27; H, 7.52; N, 2.83; S, 6.47. Found: C, 70.38; H, 7.58; N, 2.93; S, 6.40.

(+)-**32f**, R=*p*-Methoxyphenyl: 96.7% yield; $[\alpha]_D^{25}$ +27.9 (c=1.218, MeOH). IR (film): 3285, 1738, 1324, 1156 cm^{-1}. NMR ($CDCl_3$) δ: 0.71 (1H, d, J=10 Hz), 1.00 (3H, s), 1.10 (3H, s), 1.27—2.50 (14H), 3.33 (1H, m), 3.68 (3H, s), 3.87 (3H, s), 4.91 (1H, d, J=8 Hz), 5.32 (2H, m), 6.96 (2H, d, J=9 Hz), 7.82 (2H, d, J=9 Hz). *Anal.* Calcd for $C_{24}H_{35}NO_5S$: C, 64.11; H, 7.85; N, 3.12; S, 7.13. Found: C, 63.61; H, 7.86; N, 3.17; S, 7.05.

(+)-**32g**, R=3-Phenylpropyl: 60.1% yield; $[\alpha]_D^{26}$ +27.7 (c=1.890, MeOH). IR (film): 3295, 1739, 1322, 1148 cm^{-1}. NMR ($CDCl_3$) δ: 0.78 (1H, d, J=10 Hz), 1.01 (3H, s), 1.19 (3H, s), 1.30—3.10 (20H), 3.44 (1H, m), 3.65 (3H, s), 4.48 (1H, d, J=9 Hz), 5.41 (2H, m), 7.06—7.45 (5H). *Anal.* Calcd for $C_{26}H_{39}NO_4S$: C, 67.64; H, 8.52; N, 3.03; S, 6.95. Found: C, 67.34; H, 8.46; N, 3.19; S, 6.89.

(+)-**32h**, R=2-Phenylethyl: 78.9% yield; $[\alpha]_D^{26}$ +33.0 (c=1.313, MeOH). IR (film): 3300, 1738, 1320, 1149 cm^{-1}. NMR ($CDCl_3$) δ: 0.82 (1H, d, J=10 Hz), 1.03 (3H, s), 1.21 (3H, s), 1.33—2.70 (14H), 2.96—3.40 (4H), 3.50 (1H, m), 3.65 (3H, s), 4.54 (1H, d, J=9 Hz), 5.44 (2H, m), 7.10—7.46 (5H). *Anal.* Calcd for $C_{25}H_{37}NO_4S$: C, 67.08; H, 8.33; N, 3.13;

S, 7.16. Found: C, 66.92; H, 8.36; N, 3.28; S, 7.01.

(+)-**32i**, R=*p*-Chlorophenyl: 93.4% yield; $[\alpha]_D^{26}$ +31.2 (*c*=1.308, MeOH). IR (film): 3300, 1739, 1322, 1163 cm^{-1}. NMR ($CDCl_3$) δ: 0.72 (1H, d, *J*=10 Hz), 0.98 (3H, s), 1.09 (3H, s), 1.28—2.43 (14H), 3.33 (1H, m), 3.67 (3H, s), 5.12 (1H, d, *J*=8 Hz), 5.30 (2H, m), 7.48 (2H, d, *J*=8 Hz), 7.84 (2H, d, *J*=8 Hz).

(−)-**32j**, R=*o*-Chlorophenyl: 96.8% yield; $[\alpha]_D^{25}$ −9.3 (*c*=1.684, MeOH). IR (film): 3310, 1738, 1341, 1167 cm^{-1}. NMR ($CDCl_3$) δ: 0.69 (1H, d, *J*=10 Hz), 1.05 (3H, s), 1.08 (3H, s), 1.29—2.45 (14H), 3.39 (1H, m), 3.67 (3H, s), 5.10—5.53 (3H), 7.30—7.63 (3H), 8.11 (1H, m). *Anal.* Calcd for $C_{23}H_{32}ClNO_4S$: C, 60.84; H, 7.10; Cl, 7.81; N, 3.09; S, 7.06. Found: C, 60.55; H, 7.14; Cl, 8.02; N, 3.33; S, 6.77.

(+)-**32k**, R=*m*-Chlorophenyl: 93.9% yield; $[\alpha]_D^{25}$ +30.5 (*c*=1.233, MeOH). IR (film): 3295, 1739, 1334, 1162 cm^{-1}. NMR ($CDCl_3$) δ: 0.74 (1H, d, *J*=10 Hz), 1.00 (3H, s), 1.11 (3H, s), 1.30—2.45 (14H), 3.37 (1H, m), 3.70 (3H, s), 5.02 (1H, d, *J*=8 Hz), 5.33 (2H, m), 7.35—7.95 (4H). *Anal.* Calcd for $C_{23}H_{32}ClNO_4S$: C, 60.84; H, 7.10; Cl, 7.81; N, 3.09; S, 7.06. Found: C, 60.67; H, 7.14; Cl, 8.09; N, 3.11; S, 6.89.

(+)-**32l**, R=*p*-Ethylphenyl: 89.1% yield; $[\alpha]_D^{25}$ +28.8 (*c*=1.945, MeOH). IR (film): 3300, 1740, 1327, 1161 cm^{-1}. NMR ($CDCl_3$) δ: 0.72 (1H, d, *J*=10 Hz), 1.01 (3H, s), 1.10 (3H, s), 1.25 (3H, t, *J*=8 Hz), 1.40—2.42 (14H), 2.71 (2H, q, *J*=8 Hz), 3.35 (1H, m), 3.69 (3H, s), 4.82 (1H, d, *J*=8 Hz), 5.29 (2H, m), 7.31 (2H, d, *J*=8 Hz), 7.77 (2H, d, *J*=8 Hz). *Anal.* Calcd for $C_{25}H_{37}NO_4S$: C, 67.08; H, 8.33; N, 3.13; S, 7.17. Found: C, 66.92; H, 8.44; N, 3.16; S, 6.86.

(+)-**32m**, R=*p*-Methylphenyl: 80.8% yield; $[\alpha]_D^{25}$ +30.7 (*c*=1.157, MeOH). IR (film): 3290, 1740, 1325, 1162 cm^{-1}. NMR ($CDCl_3$) δ: 0.72 (1H, d, *J*=10 Hz), 1.01 (3H, s), 1.10 (3H, s), 1.26—2.5 (12H), 2.28 (2H, t, *J*=7 Hz), 2.41 (3H, s), 3.32 (1H, m), 3.68 (3H, s), 4.78 (1H, d, *J*=8 Hz), 5.30 (2H, m), 7.29 (2H, d, *J*=8 Hz), 7.75 (2H, d, *J*=8 Hz).

(+)-**32n**, R=*p*-Fluorophenyl: 20.6% yield; $[\alpha]_D^{23}$ +28.8 (*c*=1.760, MeOH). IR ($CHCl_3$): 3395, 1730, 1340, 1165, 1154 cm^{-1}. NMR ($CDCl_3$) δ: 0.72 (1H, d, *J*=10 Hz), 1.00 (3H, s), 1.10 (3H, s), 1.1—2.6 (14H), 3.35 (1H, m), 2.69 (3H, s), 4.91 (1H, d, *J*=8 Hz), 5.33 (2H, m), 7.23 (2H, d, *J*=9 Hz), 7.90 (2H, dd, *J*=9, 5 Hz).

32o, R=*p*-Acetoxyphenyl: 12.2% yield. IR (film): 3290, 1774, 1738, 1330, 1195, 1157 cm^{-1}. NMR ($CDCl_3$) δ: 0.72 (1H, d, *J*=10 Hz), 1.01 (3H, s), 1.11 (3H, s), 1.26—2.50 (14H), 2.33 (3H, s), 3.33 (1H, m), 3.67 (3H, s), 5.16 (1H, d, *J*=8 Hz), 5.30 (2H, m), 7.22 (2H, d, *J*=9 Hz), 7.88 (2H, d, *J*=9 Hz). *Anal.* Calcd for $C_{25}H_{35}NO_6S$: C, 62.87; H, 7.39; N, 2.93; S, 6.71. found: C, 62.74; H, 7.46; N, 3.26; S, 6.35.

(5*Z*)-7-((1*R*,2*R*,3*S*,5*S*)-2-(Substituted Sulfonylamino)-6,6-dimethylbicyclo[3.1.1]hept-3-yl)hept-5-enoic Acids (33a—n, p) and Their Sodium Salts (34a—n, p) The esters **32a—o** were hydrolyzed according to the procedure for hydrolysis of **5**.

(+)-**33a**: 92.2% yield; $[\alpha]_D^{25}$ +36.5 (*c*=0.896, MeOH). IR (film): 3285, 1709, 1320, 1151 cm^{-1}. NMR ($CDCl_3$) δ: 0.83 (1H, d, *J*=10 Hz), 1.07 (3H, s), 1.24 (3H, s), 1.52 (1H, ddd, *J*=3, 6, 13 Hz), 1.58—2.39 (10H), 2.38 (2H, t, *J*=7 Hz), 2.56 (1H, m), 2.98 (3H, s), 3.52 (1H, ddd, *J*=3, 6, 8 Hz), 5.10 (1H, d, *J*=8 Hz), 5.48 (2H, m). *Anal.* Calcd for $C_{17}H_{29}NO_4S$: C, 59.45; H, 8.51; N, 4.08; S, 9.34. Found: C, 58.93; H, 8.42; N, 4.06; S, 8.92.

(+)-**33b**: 95.6% yield; mp 75—78 °C; $[\alpha]_D^{25}$ +33.2 (*c*=1.060, MeOH). IR (KBr): 3285, 1705, 1533, 1350, 1309, 1165 cm^{-1}. NMR ($CDCl_3$) δ: 0.73 (1H, d, *J*=10 Hz), 0.99 (3H, s), 1.06 (3H, s), 1.46 (1H, ddd, *J*=3, 5, 13 Hz), 1.56—2.32 (11H), 2.39 (2H, t, *J*=7 Hz), 3.44 (1H, ddd, *J*=3, 6, 8 Hz), 5.40 (2H, m), 5.65 (1H, d, *J*=8 Hz), 8.07 (2H, d, *J*=9 Hz), 8.37 (2H, d, *J*=9 Hz). CD (MeOH) λnm ($\Delta\varepsilon$): 291 (+0.409), 242 (−0.133), 222 (+0.267). *Anal.* Calcd for $C_{22}H_{30}N_2O_6S$: C, 58.65; H, 6.71; N, 6.22; S, 7.12. Found: C, 58.66; H, 6.83; N, 6.12; S, 7.09.

(+)-**33c**: 99.0% yield; $[\alpha]_D^{25}$ +13.0 (*c*=1.117, MeOH). IR ($CHCl_3$): 3390, 3260, 1710, 1332, 1156 cm^{-1}. NMR ($CDCl_3$) δ: 0.69 (1H, d, *J*=10 Hz), 1.02 (6H, s), 1.42 (1H, ddd, *J*=2, 5, 13 Hz), 1.52—2.35 (11H), 2.31 (2H, t, *J*=7 Hz), 3.41 (1H, ddd, *J*=2, 6, 8 Hz), 5.21—5.40 (2H), 5.45 (1H, d, *J*=8 Hz), 7.62 (2H, m), 7.82—7.99 (4H), 8.44 (1H, d, *J*=1.5 Hz). CD (MeOH) λnm ($\Delta\varepsilon$): 321.5 (+0.203), 307.5 (+0.161), 292.5 (+0.382), 268 (−0.773), 228 (−4.73), 224 (−5.30).

(+)-**33d**: 96.1% yield; $[\alpha]_D^{25}$ +18.3 (*c*=1.162, MeOH). IR (film): 3290, 1708, 1318, 1152 cm^{-1}. NMR ($CDCl_3$) δ: 0.80 (1H, d, *J*=10 Hz), 0.93 (3H, s), 1.21 (3H, s), 1.48 ((1H, ddd, *J*=3, 6, 13 Hz), 1.56—2.40 (10H), 2.35 (2H, t, *J*=7 Hz), 2.55 (1H, d, *J*=3, 7, 13 Hz), 3.57 (1H, m), 4.21 (1H, d, *J*=14 Hz), 4.29 (1H, d, *J*=14 Hz), 4.86 (1H, d, *J*=8 Hz), 5.46 (2H, m), 7.39 (5H, m). CD (MeOH) λnm ($\Delta\varepsilon$) 262 (−0.00303), 257 (−0.00424), 251.5 (−0.00424), 245 (−0.00364), 210 (−0.424).

(+)-**33e**: 95.3% yield; mp 111—113 °C; $[\alpha]_D^{25}$ +33.0 (*c*=1.048, MeOH). IR (KBr): 3275, 1712, 1323, 1161 cm^{-1}. NMR ($CDCl_3$) δ: 0.72 (1H, d, *J*=10 Hz), 1.01 (3H, s), 1.06 (3H, s), 1.45 (1H, m), 1.52—2.40 (11H), 2.36 (2H, t, *J*=7 Hz), 3.42 (1H, ddd, *J*=2, 6, 8 Hz), 5.27—5.50 (3H), 7.37—7.53 (3H), 7.58—7.67 (2H), 7.72 (2H, d, *J*=9 Hz), 7.94 (2H, d, *J*=9 Hz). CD (MeOH) λnm ($\Delta\varepsilon$): 262 (−0.252), 255 (−0.300), 216 (+5.00). *Anal.* Calcd for $C_{28}H_{35}NO_4S$: C, 69.82; H, 7.32; N, 2.91; S, 6.66. Found: C, 69.50; H, 7.28; N, 2.83; S, 6.39.

(+)-**33f**: 93.1% yield; $[\alpha]_D^{25}$ +30.3 (*c*=1.503, MeOH). IR (film): 3285, 1708, 1322, 1154 cm^{-1}. NMR ($CDCl_3$) δ: 0.70 (1H, d, *J*=10 Hz), 1.00 (3H, s), 1.08 (3H, s), 1.44 (1H, m), 1.55—2.30 (11H), 2.37 (2H, t, *J*=7 Hz), 3.32 (H, m), 3.87 (3H, s), 5.28 (1H, d, *J*=8 Hz), 5.29—5.48 (2H), 6.97 (2H, d, *J*=9 Hz), 7.80 (2H, d, *J*=9 Hz). CD (MeOH) λnm ($\Delta\varepsilon$): 277 (+0.221), 270.5 (+0.245), 240 (+0.455), 208 (+2.72).

(+)-**33g**: 46.3% yield; $[\alpha]_D^{25}$ +30.6 (*c*=0.900, MeOH). IR (film): 3290, 1710, 1320, 1148 cm^{-1}. NMR ($CDCl_3$) δ: 0.78 (1H, d, *J*=10 Hz), 1.05 (3H, s), 1.20 (3H, s), 1.50 (1H, ddd, *J*=2, 6, 13 Hz), 1.58—2.42 (12H), 2.36 (2H, t, *J*=7 Hz), 2.59 (1H, t, *J*=9 Hz), 2.76 (2H, t, *J*=7 Hz), 2.99 (2H, m), 3.47 (1H, m), 5.25 (1H, d, *J*=8 Hz), 5.33—5.61 (2H), 7.15—7.35 (5H). CD (MeOH) λnm ($\Delta\varepsilon$): 260 (−0.00515), 253 (−0.00455), 245 (−0.00303).

(+)-**33h**: 89.3% yield; $[\alpha]_D^{25}$ +30.5 (*c*=1.133, MeOH). IR (film): 3290, 1709, 1318, 1150 cm^{-1}. NMR ($CDCl_3$) δ: 0.82 (1H, d, *J*=10 Hz), 1.07 (3H, s), 1.23 (3H, s), 1.51 (1H, ddd, *J*=3, 5, 13 Hz), 1.61—2.42 (10H), 2.37 (2H, t, *J*=7 Hz), 2.60 (1H, m), 3.07—3.36 (4H), 3.54 (1H, ddd, *J*=3, 6, 8 Hz), 5.09 (1H, d, *J*=8 Hz), 5.35—5.60 (2H), 7.28—7.38 (5H). CD (MeOH) λnm ($\Delta\varepsilon$): 280 (+0.00364), 209 (+0.555).

(+)-**33i**: 95.2% yield; $[\alpha]_D^{25}$ +32.0 (*c*=1.158, MeOH). IR (film): 3285, 1709, 1330, 1162 cm^{-1}. NMR ($CDCl_3$) δ: 0.71 (1H, d, *J*=10 Hz), 0.99 (3H, s), 1.07 (3H, s), 1.45 (1H, ddd, *J*=2, 5, 13 Hz), 1.57—2.42 (11H), 2.38 (2H, t, *J*=7 Hz), 3.38 (1H, ddd, *J*=2, 6, 8 Hz), 5.29—5.48 (3H), 7.48 (2H, d, *J*=9 Hz), 7.82 (2H, d, *J*=9 Hz). CD (MeOH) λnm ($\Delta\varepsilon$): 276 (+0.139), 268.5 (+0.170), .235 (+1.548).

(−)-**33j**: 99.1% yield; $[\alpha]_D^{25}$ −5.6 (*c*=1.965, MeOH). IR (film): 3295, 1708, 1333, 1162 cm^{-1}. NMR ($CDCl_3$) δ: 0.69 (1H, d, *J*=10 Hz), 1.07 (6H, s), 1.43 (1H, ddd, *J*=3, 5, 13 Hz), 1.58—2.42 (11H), 2.37 (2H, d, *J*=7 Hz), 3.41 (1H, ddd, *J*=3, 5, 9 Hz), 5.36 (2H, m), 5.53 (1H, d, *J*=9 Hz), 7.36—7.55 (3H), 8.09 (1H, m). CD (MeOH) λnm ($\Delta\varepsilon$): 277.5 (−0.188), 270 (−0.215), 261.5 (−0.194), 226 (−2.03).

(+)-**33k**: 98.5% yield; $[\alpha]_D^{25}$ +34.2 (*c*=1.238, MeOH). IR (film): 3285, 1709, 1332, 1162 cm^{-1}. NMR ($CDCl_3$) δ: 0.72 (1H, d, *J*=10 Hz), 1.00 (3H, s), 1.08 (3H, s), 1.45 (1H, ddd, *J*=2, 5, 13 Hz), 1.57—2.32 (11H), 2.38 (2H, t, *J*=7 Hz), 3.40 (1H, ddd, *J*=2, 6, 8 Hz), 5.29—5.50 (3H), 7.45 (1H, t, *J*=8 Hz), 7.54 (1H, td, *J*=2, 8 Hz), 7.76 (1H, td, *J*=1, 8 Hz), 7.87 (1H, t, *J*=2 Hz). CD (MeOH) λnm ($\Delta\varepsilon$): 276 (−0.0242), 269 (−0.0273), 232 (+2.336).

(+)-**33l**: 87.9% yield; $[\alpha]_D^{25}$ +30.8 (*c*=0.941, MeOH). IR (film): 3280, 1710, 1322, 1160 cm^{-1}. NMR ($CDCl_3$) δ: 0.70 (1H, d, *J*=10 Hz), 0.99 (3H, s), 1.04 (3H, s), 1.25 (3H, t, *J*=8 Hz), 1.43 (1H, ddd, *J*=2, 5, 14 Hz), 1.56—2.42 (11H), 2.37 (2H, t, *J*=7 Hz), 2.72 (2H, q, *J*=8 Hz), 3.38 (1H, ddd, *J*=2, 6, 8 Hz), 5.27 (1H, d, *J*=8 Hz), 5.28—5.46 (2H), 7.32 (2H, d, *J*=9 Hz), 7.78 (2H, d, *J*=9 Hz). CD (MeOH) λnm ($\Delta\varepsilon$): 271.5 (+0.118), 265 (+0.136), 258 (+0.115), 230 (+1.336).

(+)-**33m**: 90.0% yield; mp 79—80 °C; $[\alpha]_D^{25}$ +33.7 (*c*=0.891). IR ($CHCl_3$): 3400, 3270, 1335, 1159 cm^{-1}. NMR ($CDCl_3$) δ: 0.70 (1H, d, *J*=10 Hz), 1.00 (3H, s), 1.06 (3H, s), 1.42 (1H, m), 1.55—2.45 (11H), 2.37 (2H, t, *J*=7 Hz), 2.42 (3H, s), 3.36 (1H, m), 5.29 (1H, d, *J*=8 Hz), 5.37 (2H, m), 7.29 (2H, d, *J*=8 Hz), 7.75 (2H, d, *J*=8 Hz). CD (MeOH) λnm ($\Delta\varepsilon$): 273 (+0.106), 266 (+0.118), 261 (+0.103), 230 (+1.69). *Anal.* Calcd for $C_{23}H_{33}NO_4S$: C, 65.84; H, 7.93; N, 3.34; S, 7.64. Found: C, 65.61; H, 7.95; N, 3.60; S, 7.39.

(+)-**33n**: Quantitative yield. NMR ($CDCl_3$) δ: 0.70 (1H, d, *J*=10 Hz), 0.99 (3H, s), 1.08 (3H, s), 1.2—2.5 (14H), 3.35 (1H, m), 5.24 (1H, d, *J*=9 Hz), 5.34 (2H, m), 7.21 (2H, d, *J*=9 Hz), 7.50 (1H, br s), 7.87 (2H, dd, *J*=9, 6 Hz).

(+)-**33p**: 64.6% yield; mp 95—96 °C; $[\alpha]_D^{25}$ +34.3 (*c*=0.865, MeOH). IR (KBr): 1708, 1318, 1152, 1144 cm^{-1}. NMR ($CDCl_3$) δ: 0.71 (1H, d, *J*=10 Hz), 1.01 (3H, s), 1.12 (3H, s), 1.42 (1H, ddd, *J*=2, 5, 13 Hz), (1.58—2.29 (11H), 2.36 (2H, t, *J*=7 Hz), 3.25 (1H, ddd, *J*=2, 6, 8 Hz), 5.14 (1H, d, *J*=8 Hz), 6.92 (2H, d, *J*=9 Hz), 7.74 (2H, d, *J*=9 Hz). CD (MeOH) λnm ($\Delta\varepsilon$): 278 sh (+0.324), 274 (+0.376), 241 (+0.439), 208.5 (+1.99). *Anal.* Calcd for $C_{22}H_{31}NO_5S$: C, 62.68; H, 7.41; N, 3.32; S, 7.61. Found: C, 62.59; H, 7.45; N, 3.41; S, 7.39.

IR (KBr); **34a**: 3300, 1564, 1318, 1150 cm^{-1}. **34b**: 3300, 1565, 1530, 1350, 1165 cm^{-1}. **34c**: 3290, 1565, 1328, 1258 cm^{-1}. **34d**: 3295, 1564, 1317, 1151 cm^{-1}. **34e**: 3295, 1562, 1320, 1157 cm^{-1}. **34f**: 3285, 1565, 1320, 1301, 1155 cm^{-1}. **34g**: 3295, 1565, 1319, 1303, 1148 cm^{-1}. **34h**: 3300, 1567, 1319, 1307, 1149 cm^{-1}. **34i**: 3290, 1563, 1325, 1160 cm^{-1}. **34j**: 3320, 1561, 1333,

1162 cm^{-1}. **34k**: 3295, 1564, 1331, 1162 cm^{-1}. **34l**: 3290, 1565, 1320, 1159 cm^{-1}. **34m**: 3290, 1564, 1321, 1159 cm^{-1}. **34n**: 3300, 1591, 1566, 1330, 1165, 1153 cm^{-1}. **34p**: 3295, 1555, 1302, 1153 cm^{-1}.

(+)-Methyl (5*Z*)-7-((1*R*,2*S*,3*S*,5*S*)-2-(*p*-Toluenesulfonylamino-6,6-dimethylbicyclo[3.1.1]hept-3-yl)hept-5-enoate ((+)-35), the Carboxylic Acid ((+)-36) and the Sodium Salt (37) The BOC derivative (+)-**4a** was converted to (+)-**35**, (+)-**36** and **37** as described above.

(+)-**35**: 44.8% yield; mp 92—93 °C; $[\alpha]_D^{23}$ +58.3 (c=0.978, MeOH). IR ($CHCl_3$): 3395, 1732, 1341, 1155 cm^{-1}. NMR ($CDCl_3$) δ: 0.84 (3H, s), 0.95 (1H, d, J=10 Hz), 1.07 (3H, s), 1.2—2.6 (14H), 2.41 (3H, s), 3.67 (3H, s), 3.90 (1H, m), 4.88 (1H, d, J=9 Hz), 5.35 (2H, m), 7.28 (2H, d, J=8 Hz), 7.74 (2H, d, J=8 Hz).

(+)-**36**: Quantitative yield. NMR ($CDCl_3$) δ: 0.84 (3H, s), 0.97 (1H, d, J=10 Hz), 1.07 (3H, s), 1.2—2.65 (14H), 2.40 (3H, s), 3.90 (1H, m), 5.18 (1H, d, J=9 Hz), 5.34 (2H, m), 7.26 (2H, d, J=8 Hz), 7.71 (2H, d, J=8 Hz), 8.40 (1H, br s).

37: IR (KBr): 3295, 1565, 1339, 1318, 1303, 1157 cm^{-1}.

(+)-2-((1*R*,2*R*,3*R*,5*S*)-2-Benzenesulfonylamino-6,6-dimethylbicyclo[3.1.1]hept-3-yl)ethanol ((+)-38) A mixture of 5.2% aqueous potassium hydroxide (40 ml), the salt (+)-**28** (15.5 g, 50.7 mmol) and ether (40 ml) was stirred for 15 min. Triethylamine (15 ml) and then a solution of benzenesulfonyl chloride (8.96 g, 50.7 mmol) in ether (30 ml) were added to the mixture with cooling in ice. The mixture was stirred at 0 °C for 1.5 h. The organic phase was separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed successively with water, dilute hydrochloric acid, aqueous sodium hydrogencarbonate and water, then dried over anhydrous sodium sulfate and concentrated under reduced pressure. Recrystallization of the residue from ether–diisopropyl ether (30 ml : 5 ml) gave **38**, 7.42 g (45.2%); mp 113—115 °C; $[\alpha]_D^{25}$ +34.7 (c=1.495, MeOH). IR (KBr): 3480, 3275, 1321, 1160 cm^{-1}. NMR ($CDCl_3$) δ: 0.66 (1H, d, J=10 Hz), 0.97 (3H, s), 1.01 (3H, s), 1.25—2.7 (9H), 3.41 (1H, m), 3.62 (2H, m), 5.58 (1H, d, J=8 Hz), 7.38—7.70 (3H), 7.80—8.00 (2H). *Anal.* Calcd for $C_{17}H_{25}NO_3S$: C, 63.13; H, 7.79; N, 4.33; S, 9.91. Found: C, 63.21; H, 7.55; N, 4.34; S, 9.72.

***p*-Methoxybenzylamine Salt of (+)-6b** The alcohol (+)-**38** (9.5 g, 29.4 mmol) was submitted to Swern oxidation and then Wittig reaction in the same manner as in the preparation of (+)-**31** from (+)-**29**. A solution of *p*-methoxybenzylamine (4.03 g, 29.4 mmol) in ethyl acetate (10 ml) was added to a solution of crude (+)-**6b** in ethyl acetate (40 ml). The solution was allowed to stand overnight at room temperature. The crystals (10.9 g, 72.3%) collected by filtration were contaminated with *ca.* 2% of the *E*-isomer according to high performannce liquid chromatography (HPLC) analysis. The crude salt (41.9 g) was shaken 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 carboxylic acid was again treated with *p*-methoxybenzylamine and gave the salt, 35.2 g, which was contaminated with *ca.* 0.6% of the *E*-olefin. mp 125—127 °C; $[\alpha]_D^{24}$ +27.7 (c=1.083, MeOH). IR (KBr): 1542, 1517, 1309, 1151 cm^{-1}, NMR ($CDCl_3$) δ: 0.69 (1H, d, J=10 Hz), 1.02 (3H, s), 1.11 (3H, s), 1.32—2.37 (14H), 3.18 (1H, m), 3.78 (3H, s), 3.91 (1H, d, J=14 Hz), 3.95 (1H, d, J=14 Hz), 5.34 (2H, m), 5.65 (3H, br s), 6.40 (1H, br s), 6.86 (2H, d, J=9 Hz), 7.29 (2H, d, J=9 Hz), 7.42—7.58 (3H), 7.90 (2H, m). *Anal.* Calcd for $C_{30}H_{42}N_2O_5S$: C, 66.39; H, 7.80; N, 5.16; S, 5.91. Found: C, 66.28; H, 7.76; N, 5.15; S, 5.94.

(+)-Methyl (1*S*,2*R*,3*R*,5*S*)-2-Hydroxymethyl-6,6-dimethylbicyclo[3.1.1]heptan-3-ylacetate ((+)-50) (+)-(1*S*,2*R*,3*R*,5*S*)-3-Carboxy-2-hydroxymethyl-6,6-dimethylbicyclo[3.1.1]heptane[3] (2.1 g, 10 mmol) was esterified with diazomethane as described above; 2.163 g, 96.6%; $[\alpha]_D^{24}$ +43.0 (c=1.135, MeOH). NMR ($CDCl_3$) δ: 0.84 (1H, d, J=10 Hz), 0.97 (3H, s), 1.20 (3H, s), 1.40—2.75 (10H), 3.60 (2H, d, J=6 Hz), 3.66 (3H, s). IR (film): 3430, 1740 cm^{-1}. *Anal.* Calcd for $C_{18}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.72; H, 9.80.

(−)-Methyl (1*S*,2*R*,3*R*,5*S*)-2-Formyl-6,6-dimethylbicyclo[3.1.1]heptan-3-ylacetate ((−)-51) By the procedure used to prepare **30** from (+)-**29**, the alcohol (+)-**50** (2.163 g, 9.56 mmol) was converted to (−)-**51** in 95% yield; $[\alpha]_D^{24}$ −23.7 (c=1.834, CH_2Cl_2). IR (film): 1737 cm^{-1}. NMR $CDCl_3$) δ: 0.77 (3H, s), 1.03 (1H, d, J=8 Hz), 1.20 (3H, s), 1.42—3.27 (9H), 3.66 (3H, s), 9.76 (1H, s).

(+)-Methyl (1*S*,2*R*,3*R*,5*S*)-2-Methoxyiminomethyl-6,6-dimethylbicyclo[3.1.1]heptan-3-ylacetate ((+)-52) By the procedure used to prepare **16** from **15**, the aldehyde (−)-**51** was converted to (+)-**52** in 97.4% yield; $[\alpha]_D^{23}$ +17.8 (c=1.179, MeOH). IR (film): 1742 cm^{-1}. NMR ($CDCl_3$) δ: 0.89 (1H, d, J=10 Hz), 1.00 (3H, s), 1.19 (3H, s), 1.40—2.75 (9H), 3.65 (3H, s), 3.78 (5/7×3H, s), 3.81 (2/7×3H, s), 6.74 (2/7H, d, J=7 Hz), 7.42 (5/7H, d, J=7 Hz). *Anal.* Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.34; H, 9.22; N, 5.24.

(+)-2-((1*S*,2*R*,3*R*,5*S*)-2-Benzenesulfonylaminomethyl-6,6-dimethylbicyclo[3.1.1]heptan-3-yl)ethanol ((+)-53) By the procedure used to prepare **17** from **16**, the *O*-methyl oxime (+)-**52** was converted to (+)-**53** in 36.2% yield; $[\alpha]_D^{25}$ +36.1 (c=0.938, MeOH). IR (film): 3500, 3285, 1322, 1155 cm^{-1}. NMR ($CDCl_3$) δ: 0.74 (1H, d, J=10 Hz), 0.80 (3H, s), 1.09 (3H, s), 1.30—2.45 (10H), 2.96 (2H, t, J=6 Hz), 3.67 (2H, br t, J=6 Hz), 5.44 (1H, t, J=6 Hz), 7.36—7.67 (3H), 7.83—7.95 (2H).

2-((1*S*,2*R*,3*R*,5*S*)-2-Benzenesulfonylaminomethyl-6,6-dimethylbicyclo[3.1.1]heptan-3-yl)ethanol (55) and the Tautomer (−)-(56) The alcohol (+)-**53** (991 mg, 3.06 mmol) was oxidized by Swern oxidation as described above. Flash chromatography of the crude product on silica gel (40 g) in hexane–ethyl acetate (4 : 1 to 1 : 1) gave a mixture of **55** and **56**, 683 mg. Recrystallization of the mixture from dichloromethane–hexane gave pure (−)-**56**, 394 mg. The mother liquor contained a mixture of **55** and **56** in the ratio of *ca.* 2 : 1.

(−)-**56**: mp 119—121 °C; $[\alpha]_D^{25}$ −25.8 (c=0.971, MeOH). IR (KBr): 3480, 1329, 1312, 1164, 1151, 1145 cm^{-1}. NMR ($CDCl_3$) δ: 0.72 (1H, d, J=10 Hz), 1.11 (3H, s), 1.23 (3H, s), 1.32—2.85 (10H), 3.16 (1H, t, J=12 Hz), 3.56 (1H, dd, J=11, 4 Hz), 5.63 (1H, m), 7.37—7.70 (3H), 7.81—7.93 (2H). *Anal.* Calcd for $C_{18}H_{25}NO_3S$: C, 64.45; H, 7.51; N, 4.18; S, 9.56. Found: C, 64.31; H, 7.40; N, 4.12; S, 9.37.

By chromatography, the olefin **54**, 183 mg (19.6%), was isolated.

(+)-(5*Z*)-((1*S*,2*R*,3*S*,5*S*)-2-Benzenesulfonylaminomethyl-6,6-dimethylbicyclo[3.1.1]heptan-3-yl)hept-5-enoic Acid ((+)-57) and the Sodium Salt (58) By the procedure used to prepare (+)-**31** from **30**, the mixture of **55** and **56** (661 mg) was converted to (+)-**57** in 62.6% yield; $[\alpha]_D^{25}$ +37.8 (c=1.256, MeOH). IR (film): 3285, 1708, 1325, 1159 cm^{-1}. NMR ($CDCl_3$) δ: 0.74 (1H, d, J=10 Hz), 0.80 (3H, s), 1.07 (3H, s), 1.30—2.50 (13H), 2.94 (2H, d, 6 Hz), 5.10 (1H, t, J=6 Hz), 5.39 (2H, m), 7.38—7.72 (3H), 7.82—7.94 (2H), 8.50 (1H, br s). CD (MeOH) λ nm ($\Delta\varepsilon$): 269 (−0.0455), 263 (−0.0577), 215 (+0.915). *Anal.* Calcd for $C_{23}H_{31}NO_4S$: C, 65.84; H, 7.93; N, 3.34; S, 7.64. Found: C, 65.46; H, 7.91; N, 3.44; S, 7.25.

58: IR (KBr): 3290, 1563, 1321, 1156 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 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 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,[8] using an Auto-RAM61 type aggregometer (Rika-Denki Co., Ltd., Tokyo) as reported previously.[9] A pair of samples of PRP (400 μl) placed in cuvettes 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 transmissions for PRP and PPP being 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 regression analysis of the concentration–inhibition relationship for 12—16 values of α covering three concentrations and ranging from 20 to 80%. The IC_{50} values obtained were calibrated based on 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 prostaglandin E_1. The blood was placed in a plastic test tube, mixed by moderate turing and centrifuged for 10 min at 160×***g*** to obtain PRP. Apyrase (25 μg/ml) was added to the prepared PRP and the mixture was layered on 40% bovine serum albumin. The resulting mixture was centrifuged at 1200×***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 6M, Niko Bioscience). A 245 μl aliquot of the WP, the platelet

number of which had been adjusted to $5 \times 10^5/\mu l$, was placed in a measuring cuvette, which was set in the aggregometer. WP was stirred (1000 rpm) at 37 °C and 3.8 μl of 0.1 M $CaCl_2$ was added. After 1 min, 0.5 μl of a solution of test compound in DMSO was added and after 2 min, 1 μl of collagen (Hormon-Chemie, Munchen, final concentration 4 μg/ml) was added as a platelet aggregating agent. The aggregation was monitored with the aggregometer in terms of the decrease in light transmittance. The 50% aggregation inhibitory rate was calculated from the aggregation inhibitory rate measured 3 min after addition of a platelet aggregating agent.

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

References and Notes

1) S. Hagishita and K. Seno, *Chem. Pharm. Bull.*, **37**, 327 (1989).
2) K. Seno and S. Hagishita, *Chem. Pharm. Bull.*, **37**, 948 (1989).
3) Y. Bounameaux, J. W. Coffey, M. O'Donnell, K. Kling, R. J. Quinn, P. Schönholzer, A Szente, L. D. Tobias, T. Tschopp, A. F. Welton and A. Fischli, *Helv. Chim. Acta*, **66**, 989 (1983).
4) L. M. Harwood and M. Julia, *Synthesis*, **1980**, 456.
5) 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).
6) A. M. Lefer and H. Darius, *Drugs of the Future*, **12**, 367 (1987).
7) *Drugs of the Future*, **12**, 446 (1987).
8) G. V. R. Born, *Nature* (London), **194**, 927 (1962).
9) K. Uchida, M. Nakamura, M. Konishi, T. Ishigami and T. Komeno, *Jpn. J. Pharmacol.*, **43**, 9 (1987).