Thromboxane A_2 Receptor Antagonists. I. Synthesis and Pharmacological Activity of 7-Oxabicyclo-[2.2.1]heptane Derivatives with the Benzenesulfonylamino Group

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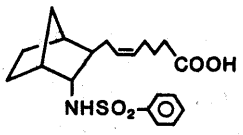
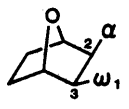
Four stereoisomers of 7-oxabicyclo[2.2.1]heptane derivatives with the benzenesulfonylamino group, 11, 14, 23 and 33, were synthesized and their sodium salts were examined *in vitro* for inhibitory activity against aggregation of rabbit platelet-rich plasma and of rat washed platelets. The *trans*-isomer 23 exhibited high potency but showed a partial agonistic effect. Compound 11 did not show a partial agonistic effect, though it was a less active inhibitor. The following *trans* compounds were synthesized and their IC_{50} values were measured: homologated *trans*-isomers with one methylene chain (47 and 53), an olefin derivative (58), and optically active derivatives ((−)-11 and (+)-23).

Keywords thromboxane A_2; receptor antagonist; 7-oxabicyclo[2.2.1]heptane; benzenesulfonylamine; stereoisomer; enzymatic resolution; platelet aggregation

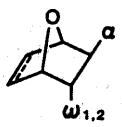
A proper balance between prostaglandin I_2 (PGI_2) and thromboxane A_2 (TXA_2) formation seems to be essential for the functioning of cardio- and cerebrovascular systems. Any imbalance caused either by the biosynthesis of too much TXA_2 or too little PGI_2 may lead to thromboembolic disease. The search continues for therapeutic agents for cardiovascular and circulatory disorders. Recent research has mainly focused on i) the synthesis of stable PGI_2 analogues,[1] ii) the search for TXA_2 synthetase inhibitors[2] and iii) studies on TXA_2 (PGH_2) receptor antagonists. Many TXA_2 receptor antagonists have been reported,[3] and one of them, S-145, (±)-(5*Z*)-7-(3-*endo*-benzenesulfonylaminobicyclo[2.2.1]hept-2-*exo*-yl)hept-5-enoic acid, has demonstrated potential activity for inhibiting platelet aggregation and vascular constriction.[4] Over the past few years, several 7-oxabicyclo[2.2.1]heptane derivatives have been reported to be potent TXA_2 receptor antagonists.[5] We have been interested in synthesizing stereoisomers with the 7-oxabicyclo[2.2.1]heptane skeleton with the hope of finding more active TXA_2 receptor antagonists. This skeleton is a type of PGH_2 with four possible isomers having different combinations of directions of the α- and ω-side chains. Since the differences in configuration have been reported to be reflected in the biological activities,[5] we synthesized four stereoisomers with an ordinary hept-5-enoic acid and benzenesulfonylamino groups as the α- and ω-chains, *i.e.*, *exo-cis*-, natural *trans*-, unnatural *trans*- and *endo-cis*-isomers (Fig. 1).



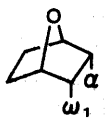
S-145



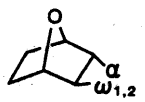
exo-cis



natural *trans*



exo-cis



unnatural *trans*

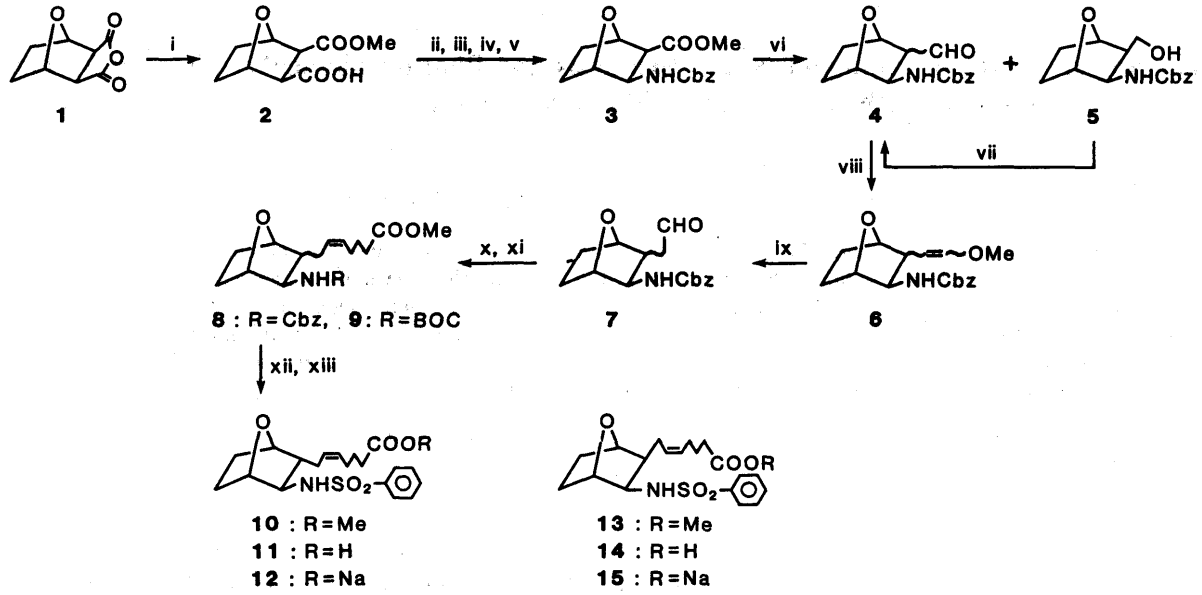
α : COONa, ω1 : -NHSO2-⬡, ω2 : -CH2NHSO2-⬡

Fig. 1

The two isomers with the *trans*-configuration turned out to have encouraging biological activities, leading us to synthesize them in the optically pure state, together with two homologated *trans*-isomers with one methylene group in the ω-chain. We also prepared the 7-oxabicyclo[2.2.1]-heptene derivative of the natural *trans*-form to investigate the effect of the unsaturated group.

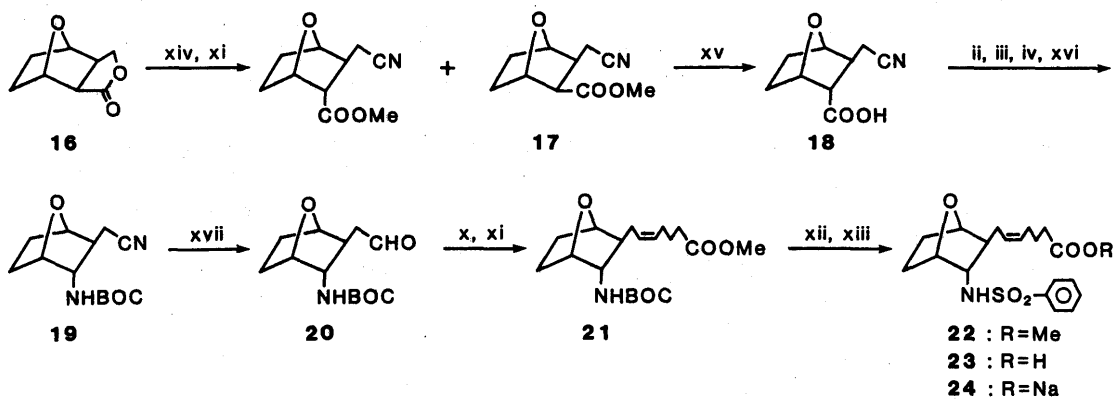
Synthesis The stereochemistry at positions 2 and 3 is important in the synthesis of these compounds. The *exo-cis*-half ester **2** could be prepared easily from furan and maleic anhydride, based on by the anti-*endo*-rule[6] of the Diels–Alder reaction, followed by hydrogenation and methanolysis. Curtius reaction of **2** gave the protected amino compound **3** with retention of the configuration in 66% yield from **2**. The ester **3** could not be reduced to the aldehyde **4** with diisobutylaluminumhydride but gave **4** and a small amount of the alcohol derivative **5** with sodium bis(methoxyethoxy)aluminum hydride upon addition of 1 eq of *N*-methylpiperazine.[7] The aldehyde **4** was a *ca.* 1 : 1 mixture of the epimers according to the nuclear magnetic resonance (NMR) spectrum, but the alcohol **5** was the *exo*-isomer. The pure *exo*-aldehyde **4** was obtained by oxidation of **5** with pyridinium chlorochromate. Wittig reaction of **4** gave **6**, which was composed of mainly the *endo*-isomer. After hydrolysis of **6** with 90% formic acid, Wittig reaction was carried out with potassium *tert*-butoxide and carboxybutyltriphenylphosphonium bromide to give a *ca.* 1 : 1 mixture of the Cbz derivative **8** and the BOC derivative **9**. The latter resulted from ester exchange. Deprotection of the BOC and Cbz groups followed by condensation with benzenesulfonyl chloride gave the unnatural *trans*-isomer **10** and a small amount of the *exo-cis*-compound **13**. They were separated by flash chromatography and **13** was isolated as crystals. After hydrolysis of **10** and **13**, the sodium salts **12** and **15** were lyophilized for biological testing.

The *exo*-lactone **16**[6,8] was treated with potassium cya-



i) MeOH, Δ; ii) ClCOOEt, Et_3N; iii) NaN_3; iv) Δ; v) $C_6H_5CH_2OH$; vi) SMEAH + *N*-methylpiperazine; vii) P.C.C.; viii) $Ph_3\overset{+}{P}CH_2OCH_3\bar{Cl}$, LDA; ix) 90% HCOOH; x) $Ph_3\overset{+}{P}(CH_2)_4COOH\bar{Br}$, *tert*-BuOK; xi) CH_2N_2; xii) CF_3COOH; xiii) benzenesulfonylchloride, Et_3N.

Chart 1



xiv) KCN, DMSO; xv) KOH; xvi) *tert*-BuOH; xvii) 2eq. DiBAL, $-20\,^{\circ}C$, 6h.

Chart 2

nide in dimethylsulfoxide (DMSO) at 185 °C for 2 h and gave a mixture of *cis*-cyanocarboxylic acid and a small amount of *trans*-cyanocarboxylic acid.[9] The mixture was esterified with diazomethane. The major isomer **17** was separated by recrystallization and the epimerized *trans*-isomer was isolated by chromatography of the mother liquor. Epimerization of **17** to **18** proceeded by hydrolysis of **17**. The *trans*-carboxylic acid **18** was submitted to the Curtius reaction and the isocyanate derivative was treated with *tert*-butanol to afford the BOC derivative **19** in 54% yield. After several examinations, it was found that the cyano group of **19** could be reduced to **20** with two equivalents of diisobutylaluminum hydride at $-20\,^{\circ}C$ for 6 h. Extension of the α-side chain followed by introduction of a benzenesulfonyl group were carried out as described above to give the natural *trans*-derivative **23**.

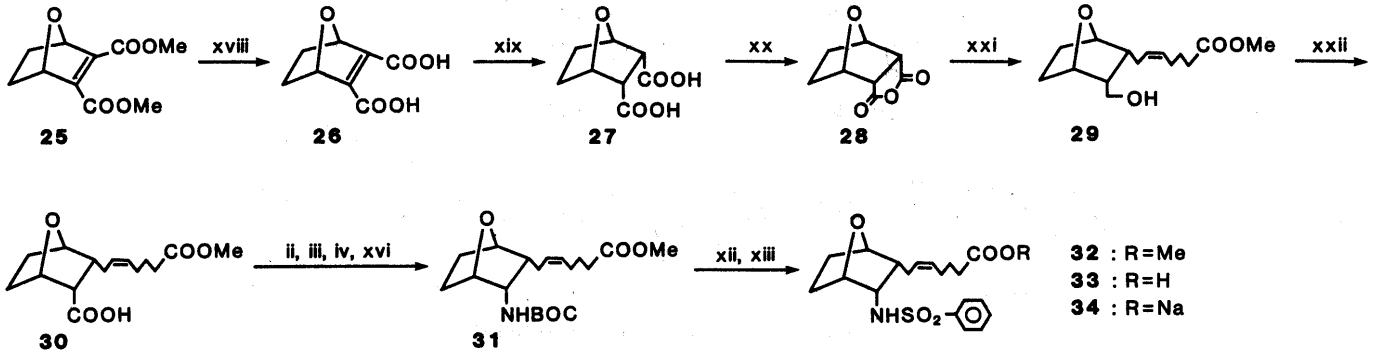
Diels–Alder reaction of furan and maleic acid has been reported to give the *endo-cis*-adduct[5,6] but it was not as easy to isolate by crystallization as reported.[10] Therefore, we prepared **27** by hydrogenation of **26**, which was prepared from furan and dimethyl acetylenedicarboxylate *via* three steps.[11] The alcohol **29** was prepared from the anhydride **28** by the method of Sprague *et al.*[5] The carboxylic acid **30**, obtained by Jones' oxidation, was derived to the *endo-cis*-compound **33** by Curtius reaction followed by introduction of a benzenesulfonyl group as described above.

Homologues of the *trans*-isomer, **47** and **53**, were prepared as follows. Wittig reaction of the *exo*-hemiacetal **35a** gave a mixture of stereoisomers of the enolether **36a**. Hydrolysis with 20% trifluoroacetic acid furnished the *trans*-isomer **37a**, the methylether of hemiacetal **38a** and the hemiacetal **39a** in 4.8, 12.4 and 27% yields, respectively. The methyl ether **38a** was easily converted to **39a** with 10% hydrochloric acid. The *exo*-hemiacetal **39a** was subjected to Wittig reaction to construct the α-side chain. Swern oxidation of the alcohol **40a**[12] gave the aldehyde **41a**, which was then epimerized to the *trans*-isomer **42a** with sodium methoxide at room temperature. The alcohol **43**, obtained by reduction with sodium borohydride of **42a**, was converted to the azide derivative **45** *via* the mesyl derivative **44**. The natural *trans*-isomer **47** was prepared by treatment of **45** with triphenylphosphine, followed by water and then the benzenesulfonyl group was introduced as described above.

The unnatural *trans*-isomer **53** was prepared from **37a** by the same method as used for **47**.

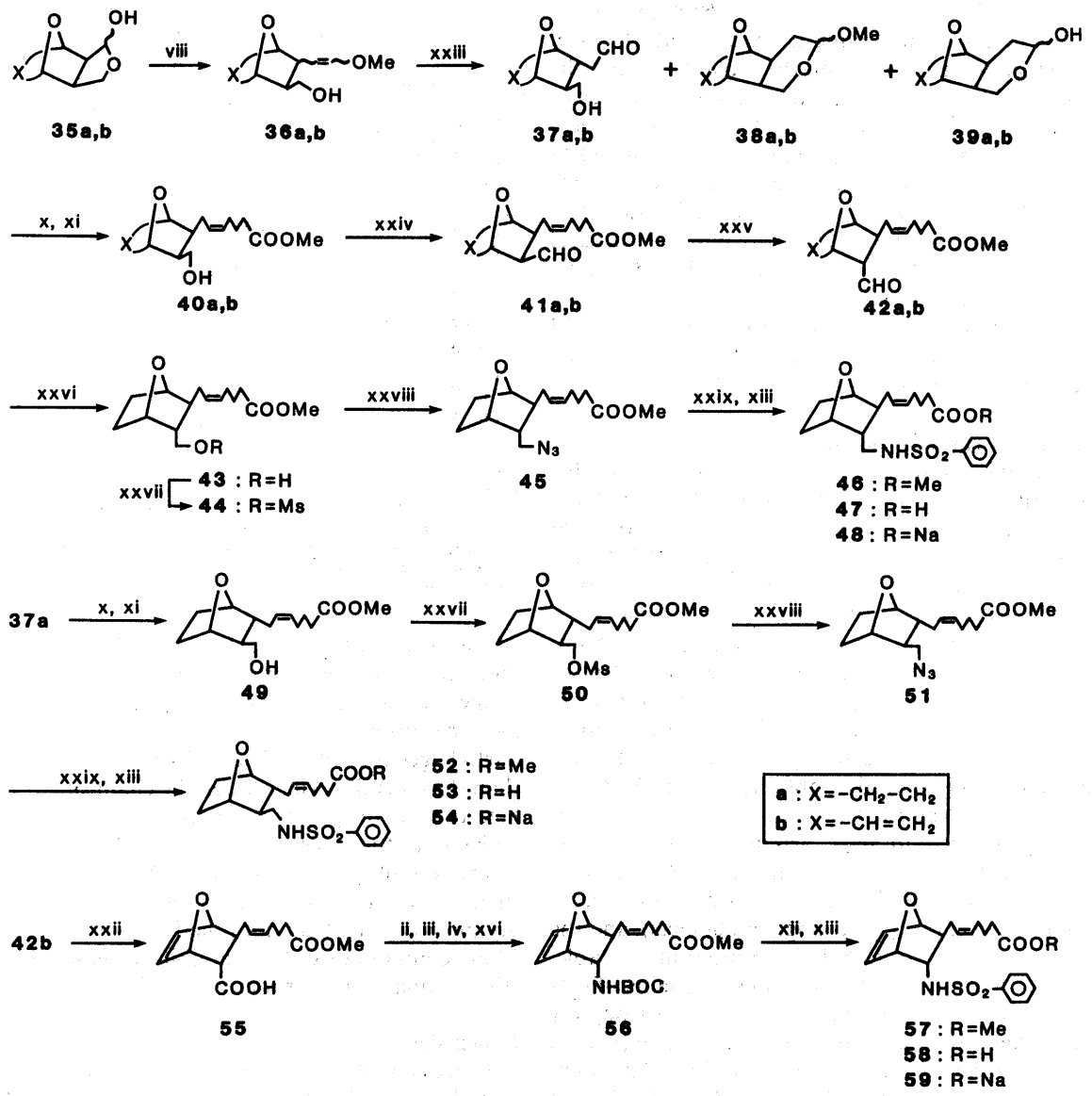
An analogue containing an unsaturated group, **58**, was prepared as follows. The epimerized aldehyde **42b** was obtained from **35b** by the same route as used for **42a** and gave the carboxylic acid **55** by Jones' oxidation. Curtius reaction of **55** gave **56**, but the yield was not good (26.5%), owing to retro-Diels–Alder reaction in the thermolysis of the acid azide. The BOC derivative **56** was converted to the desired olefin **58** by the introduction of the benzenesulfonyl group as described above.

An optically active half ester, (−)-**2** was recently pre-



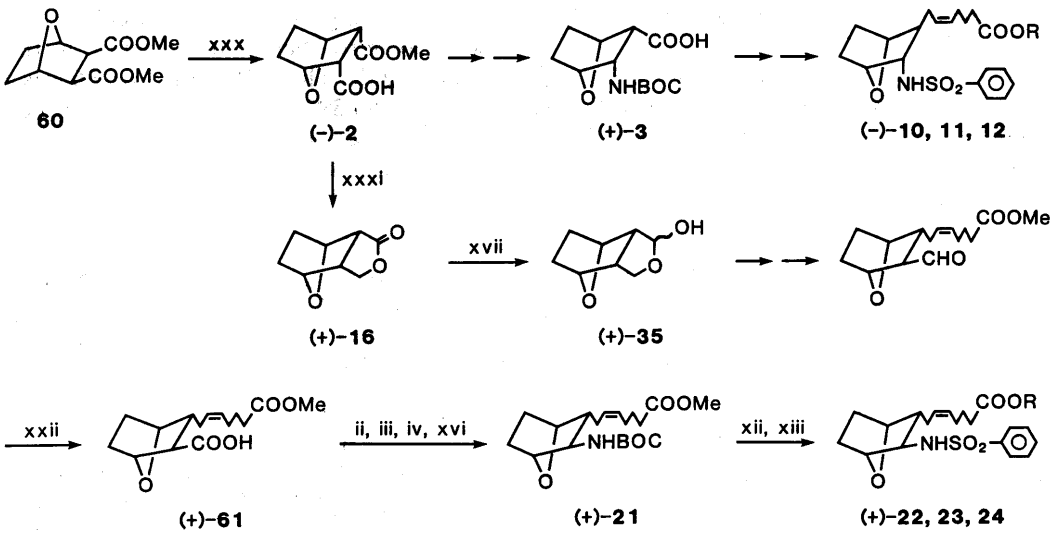
xviii) 1) LiOH, 2) Amberlite IR 120BH$^+$; xix) H_2, 10% Pd–C, MeOH; xx) AcCl; xxi) ref. 5); xxii) Jones' reagent.

Chart 3



xxiii) 20% CF_3COOH; xxiv) 1) $(COCl)_2$, DMSO 2) Et_3N; xxv) NaOMe; xxvi) $NaBH_4$; xxvii) MsCl, Et_3N; xxviii) NaN_3; xxix) 1) Ph_3P, 2) H_2O.

Chart 4



xxx) P.L.E., 30 °C, ≤pH 6; xxxi) 1) ii, 2) $NaBH_4$.

Chart 5

pared by selective hydrolysis of the diester **60** with porcine liver esterase in good enantiomeric excess and chemical yield.[13] The reaction proceeded on the molar scale and the *meso*-diester could be used to produce the (−)-half ester without discarding half of the substrate as in the optical resolution. The carboxylic acid group of (−)-**2** was selectively reduced *via* the mixed anhydride to give the lactone (+)-**16**, the absolute configuration and optical rotation of which were reported recently.[14] Optically pure (−)-natural *trans*-isomer (−)-**11** was prepared from (−)-**2** by the route described for the racemic compound.

The optically pure (+)-unnatural *trans*-isomer (+)-**23** was prepared from the (+)-lactone (+)-**16** by the route used to prepare racemic **58**, as described above.

Biological Results and Discussion

The compounds prepared were examined *in vitro* for inhibitory activity against aggregation of rabbit platelet-rich plasma (PRP) induced by arachidonic acid and of rat washed platelets (WP) induced by collagen. S-145 was reported to be a good TXA_2 receptor antagonist.[4] The IC_{50} value of S-145 was found to vary from 0.9—1.2 and 1.5—4.3 nM for rabbit PRP and for rat WP, respectively. Thus, each IC_{50} value measured by a single experiment for the prepared compounds was corrected for the value for S-145 which was measured as the reference. IC_{50} values are shown in the table. The relative inhibitory activity obtained for rabbit PRP agreed well with that obtained for rat WP. The large differences between the two kinds of IC_{50} values (μM *vs.* nM) are considered to have arisen mostly from the probable binding of the test compounds to serum proteins and not from the species difference. Some isomers showed a partial agonistic effect (a shape change of platelets), and the relative values with respect to S-145 are listed in the table. Clearly, the orientation of the α- and ω-side chains affects the inhibitory activity, as observed by the Squibb group for eight stereoisomers with a natural ω-chain.[5] Compounds with the *endo*-benzenesulfonylamino group, **24** and **34**, were more potent than those with *exo*-ones, **12** and **15**, but showed a partial agonistic effect. The natural *trans*-isomer

TABLE

Compound	IC_{50} Platelet aggregation Rabbit PRP[a] (μM)	Rat WP[b] (nM)	Partial agonist (Rat WP)[c]
(±)-S-145 Na salt	1.0[d]	2.9[e]	100
(±)-**12**	45	62	0
(−)-**12**	200	200	0
(±)-**15**	20	260	0
(±)-**24**	1.0	1.5	>100
(+)-**24**	0.23	0.63	>100
(±)-**34**	2.0	17	100
(±)-**48**	51	17	14
(±)-**54**	260	149	0
(±)-**59**	2.7	21	93
SQ-29548	8.0	2.9	0
ONO-3708	800	3.8	0

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

24 was more active than S-145,[4] ONO-3708,[15] SQ-29548[16] and other prepared compounds. Both the (+)- and (±)-isomers of **24** were measured using the same WP and the (+)-enantiomer was more active, although **24** showed a partial agonistic effect. The (−)-isomer of **12** was less active than the racemic form, though the enantiomers in which the heterocyclic oxygen is in α-orientation are usually more active than their isomers.[5]

The homologated compounds **48** and **54** were less potent than those with the same configuration, **24** and **34**. The double bond in **59** did not function to increase the potency. These compounds did not inhibit synthesis of TXA_2 in rat WP stimulated by thrombin.

Conclusion

Stereoisomers of 7-oxabicyclo[2.2.1]heptane derivatives with the benzenesulfonylamino group were synthesized and their IC_{50} values for the inhibition of platelet aggregation

were measured. Study of the structure–activity relationship of four stereoisomers, **12**, **15**, **24** and **34**, revealed that the isomers with the *trans*-configuration of the α- and ω-side chains were more active. The natural *trans*-isomer **24** was the most potent but showed a partial agonistic effect. The unnatural *trans*-isomer **12** did not show a partial agonistic effect, but the activity was not high. Thus, to improve the biological activity, the homologated *trans*-isomers **48** and **54**, the olefin **59** and the optically active compounds (−)-**12** and (+)-**24** were synthesized and assayed. Among them, the (+)-natural *trans*-isomer (+)-**24** had the strongest inhibitory activity.

Experimental

Melting points were not corrected. ^{1}H-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 1-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.

3-*exo*-(Methoxycarbonyl)-7-oxabicyclo[2.2.1]heptane-2-*exo*-carboxylic Acid (2) A mixture of *exo*-hexahydro-4,7-epoxyisobenzofuran-1,3-dione[6] (**1**) (24.3 g) and absolute methanol (200 ml) was heated under reflux for 18 h. The volatile materials were removed by distillation under reduced pressure. Recrystallization of the crystalline residue from ethyl acetate gave **2** (27.5 g, 95.1%), mp 144—146 °C. IR (Nujol): 1737, 1697 cm^{-1}. NMR (DMSO-d_6) δ: 1.52 (4H, s), 2.93 (2H, s), 3.50 (3H, s), 4.66 (2H, s). *Anal.* Calcd for $C_9H_{12}O_5$: C, 54.00; H, 6.04. Found: C, 54.04; H, 5.93.

Methyl 3-*exo*-(Benzyloxycarbonylamino)-7-oxabicyclo[2.2.1]heptane-2-*exo*-carboxylate (3) Acetone was added to a suspension of **3** (46.8 g) in water (42 ml) until it became clear. A solution of triethylamine (27.8 g) in acetone (490 ml) was added to the above solution with cooling in ice. A solution of ethyl chloroformate (34.1 g) in acetone (120 ml) was added to the solution with cooling in ice over 30 min. The mixture was stirred at 0 °C for 30 min. A solution of sodium azide (23.2 g) in water (80 ml) was added with cooling in ice over 30 min. The mixture was stirred at 3 °C for 1 h, poured into ice water and extracted with ether. When the extracts were washed with water, dried (Na_2SO_4) and concentrated under reduced pressure, an oil was obtained. IR (Nujol): 2130 cm^{-1}. A solution of the acid azide in dry benzene (200 ml) was heated under reflux for 2 h. The reaction was monitored by measuring the IR spectrum: (Nujol) 2230 cm^{-1}.

Benzyl alcohol (25 ml) was added. The solution was heated under reflux for 4 h and the volatile materials were removed by distillation. Recrystallization of the residue from ether gave **3** (47.2 g, 66.1% from **2**), mp 108 °C. IR (Nujol): 3350, 1728, 1716 cm^{-1}. NMR ($CDCl_3$) δ: 1.3—2.0 (4H, m), 2.95 (1H, d, J=10 Hz), 3.55 (3H, s), 4.2—4.5 (2H, m), 4.79 (1H, d, J=3 Hz), 5.09 (2H, d, J=10 Hz), 7.36 (5H, s). *Anal.* Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.74; H, 6.09; N, 4.37.

2-*exo*-(Benzyloxycarbonylamino)-3-*endo*- and *exo*-formyl-7-oxabicyclo-[2.2.1]heptane (4) *N*-Methylpiperazine (5.5 ml) in benzene (14 ml) was added to 35% sodium bis(methoxyethoxy)aluminum hydride in benzene (26 ml) with cooling in ice under nitrogen. The mixture was stirred at 0 °C for 10 min and added to a suspension of **3** (12.3 g) in benzene (20 ml) at 0 °C. The solution was stirred at room temperature for 2.5 h. Water and then dilute hydrochloric acid were added with cooling in ice. The organic phase was separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (150 g) in ethyl acetate–hexane (1 : 1) gave the starting substance **3** (0.622 g, 5.1%). Elution with ethyl acetate gave a mixture of *ca.* 1 : 1 of the epimers **4** (4.7 g, 43.8%) contaminated with *ca.* 10% of **3**. Next, **5** (0.222 g, 2.0%) was eluted and recrystallized from ether, mp 174—175 °C. IR (Nujol): 3330, 1685 cm^{-1}. NMR ($CDCl_3$) δ: 1.48 (4H, s), 1.95 (1H, m), 3.19 (1H, d, J=4 Hz), 3.79 (1H, t, J=10 Hz), 4.20 (1H, s), 4.39 (1H, s), 4.50 (1H, t, J=2 Hz), 5.01 (2H, s), 7.11 (1H, d, J=10 Hz), 7.35 (5H, s). *Anal.* Calcd for $C_{15}H_{17}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.73; H, 6.70; N, 5.06.

The alcohol **5** (190.5 mg) was added in one portion to a suspension of pyridinium chlorochromate (301 mg) in dichloromethane (5 ml). The mixture was stirred at room temperature and then ether was added. The mixture was chromatographed on a short column of Florisil in ether, and recrystallization from benzene gave the *exo-cis*-derivative **4** (138 mg, 73%), mp 117—119 °C. IR (Nujol): 3300, 1706 cm^{-1}. NMR ($CDCl_3$) δ: 1.2—2.0 (4H, m), 2.90 (1H, d, J=9 Hz), 4.3—4.6 (2H, m), 4.93 (1H, m), 5.07 (2H, s), 5.30 (1H, m), 7.36 (5H, s), 9.56 (1H, d, J=2 Hz). *Anal.* Calcd for $C_{15}H_{19}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.55; H, 6.17; N, 4.96.

2-*exo*-(Benzyloxycarbonylamino)-3-*endo*- and *exo*-(2-methoxyethenyl)-7-oxabicyclo[2.2.1]heptane (6) (Methoxymethyl)triphenylphosphonium chloride (36.6 g) was dried by distillation of toluene from its suspension. A solution of lithium diisopropylamide, prepared from 1.6 M *n*-butyllithium in hexane (70 ml), diisopropylamine (11.0 g) and dry tetrahydrofuran (40 ml) at 0 °C under nitrogen, was added dropwise to the above suspension at 0 °C over 30 min. The mixture was stirred at 0 °C for 2 h. A solution of **4** (9.1 g) in tetrahydrofuran (20 ml) and toluene (20 ml) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 2.5 h and poured into ice water. The organic phase was separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was submitted to flash chromatography on silica gel (160 g) in hexane–ethyl acetate (1 : 1) and gave **6** (6.5 g), which was used for the next preparation without further purification.

2-*exo*-(Benzyloxycarbonylamino)-3-*endo*- and *exo*-(formylmethyl)-7-oxabicyclo[2.2.1]heptane (7) A solution of **6** (3.07 g) in 90% formic acid (10 ml) was allowed to stand at room temperature for 2 h, poured into aqueous sodium hydrogencarbonate and extracted with dichloromethane. The extracts were washed with water, dried (Na_2SO_4) and concentrated under reduced pressure to obtain **7** (2.8 g). IR (film): 3320, 1720 cm^{-1}. The residue was used for the next preparation without further purification.

Methyl (5*Z*)-7-(3-*exo*-*tert*-Butyloxycarbonylamino-7-oxabicyclo[2.2.1]-heptan-2-*endo*- and *exo*-yl)hept-5-enoate (8) and the Benzyloxycarbonyl-amino Derivative (9) Potassium *tert*-butoxide (13.9 g) was added in one portion to a suspension of carboxybutyltriphenylphosphonium bromide (27.5 g) in dry tetrahydrofuran (50 ml) at room temperature under nitrogen. The mixture was stirred at room temperature for 30 min. A solution of **7** (6.0 g) in dry tetrahydrofuran (20 ml) was added to the mixture at room temperature. The whole was stirred at room temperature for 1 h and poured into aqueous oxalic acid. The organic phase was separated and the aqueous phase was extracted with ethyl acetate. The extracts were washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel in hexane–ethyl acetate (1 : 1).

Excess diazomethane in ether was added to a solution of the carboxylic acid (3.2 g) in ether (10 ml). The volatile materials were removed by distillation under reduced pressure. Flash chromatography of the residue on silica gel (90 g) in hexane–ethyl acetate (2 : 1) gave the BOC derivative (**8**, 0.95 g, 13.0% from **7**) and the Cbz derivative (**9**, 1.25 g, 15.6%). NMR of **8**: ($CDCl_3$) δ: 1.45 (9H, s), 1.5—1.9 (5H, m), 1.9—2.4 (6H, m), 3.25 (1H, dd, J=10, 3 Hz), 3.69 (3H, s), 4.29 (1H, d, J=5 Hz), 4.43 (1H, t, J=5 Hz), 4.75 (1H, m), 5.3—5.5 (2H, m). NMR of **9**: ($CDCl_3$) δ: 1.3—1.9 (6H, m), 1.9—2.5 (5H, m), 3.30 (1H, dd, J=9, 4 Hz), 3.62 (3H, s), 4.26 (1H, d, J=4 Hz), 4.41 (1H, t, J=4 Hz), 5.06 (2H, s), 4.9—5.2 (1H, m), 5.31 (2H, m), 7.31 (5H, s).

Methyl (5*Z*)-7-(3-*exo*- and *endo*-Benzenesulfonylamino-7-oxabicyclo-[2.2.1]heptan-2-*endo*-yl)hept-5-enoate (10 and 13) Trifluoroacetic acid (3 ml) was added to **8** (0.675 g) and the solution was allowed to stand at room temperature for 1 h. The volatile materials were removed by distillation under reduced pressure. Hexane was added and the volatile materials were again removed by distillation under reduced pressure. These procedures were repeated again to remove excess trifluoroacetic acid. Triethylamine (0.7 g) and then benzenesulfonyl chloride (0.35 g) were added to the solution of the salt in dichloromethane (10 ml). The solution was allowed to stand at room temperature for 1 h. Ice-cold dilute hydrochloric acid was added. 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 (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (25 g) in hexane–ethyl acetate (2 : 1) gave **13** and **10**.

The *cis*-compound **13** was crystallized from benzene–hexane, 15 mg (2%), mp 93—94 °C. IR (KBr): 3420, 3195, 1734, 1165 cm^{-1}. NMR ($CDCl_3$) δ: 1.2—2.4 (13H, m), 3.60 (1H, m), 3.70 (3H, s), 3.93 (1H, t, J=2 Hz), 4.16 (1H, t, J=2 Hz), 4.89 (1H, d, J=10 Hz), 5.48 (2H, m), 7.58 (3H, m), 7.89 (2H, m). *Anal.* Calcd for $C_{20}H_{27}NO_5S$: C, 61.05; H, 6.91; N, 3.56; S, 8.15. Found: C, 60.85; H, 6.93; N, 3.58; S, 8.01.

The *trans*-isomer **10**: 417 mg (55.5%). IR (film): 3270, 1735, 1162 cm^{-1}.

NMR ($CDCl_3$) δ: 1.1—2.4 (13H, m), 2.92 (1H, dd, J=9, 3 Hz), 3.69 (3H, s), 4.12 (1H, d, J=6 Hz), 4.40 (1H, t, J=6 Hz), 5.0—5.4 (3H, m), 7.60 (3H, m), 7.90 (2H, m).

(5*Z*)-7-(3-*exo*-Benzenesulfonylamino-7-oxabicyclo[2.2.1]heptan-2-*endo*-yl)hept-5-enoic Acid (11) and Its Na Salt (12) Aqueous sodium hydroxide (10%, 7 ml) was added to a solution of **10** (366 mg) in methanol (7 ml). The solution was allowed to stand at room temperature overnight. Dilute hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The extracts were washed with water, dried (Na_2SO_4) and concentrated under reduced pressure and crystallized from hexane–ether, giving **11** (348 mg, 98.6%), mp 91—95 °C. IR (film): 3220, 1708, 1162 cm^{-1}. NMR ($CDCl_3$) δ: 1.1—2.5 (13H, m), 2.93 (1H, d, J=10 Hz), 4.13 (1H, d, J=3 Hz), 4.43 (1H, t, J=2 Hz), 5.20 (2H, m), 5.45 (1H, d, J=10 Hz), 7.56 (3H, m), 7.90 (2H, m), 9.00 (1H, s). MS *m/z*: 379 (M^+). *Anal.* Calcd for $C_{19}H_{25}NO_5S$: C, 60.14; H, 6.64; N, 3.69; S, 8.45. Found: C, 59.92; H, 6.64; N, 3.61; S, 8.45.

Sodium methoxide (0.263 M) in methanol (2.80 ml) was added to **11** (311 mg) in methanol and the volatile materials were removed by distillation under reduced pressure. Water (5 ml) was added. The solution was treated with active carbon and lyophilized to give **12**. IR (KBr): 3420, 3260, 1565, 1324, 1159 cm^{-1}.

(5*Z*)-7-(3-*exo*-Benzenesulfonylamino-7-oxabicyclo[2.2.1]heptan-2-*exo*-yl)hept-5-enoic Acid (14) and Its Na Salt (15) **14**: NMR ($CDCl_3$) δ: 1.2—2.5 (13H), 3.60 (1H, d, J=2 Hz), 3.99 (1H, d, J=2 Hz), 4.19 (1H, d, J=2 Hz), 5.36 (2H, m), 5.48 (1H, m), 7.58 (3H, m), 7.90 (2H, m).

15: IR (KBr): 3415, 3270, 1563, 1317, 1157 cm^{-1}.

Methyl *exo*-3-(Cyanomethyl)-7-oxabicyclo[2.2.1]heptane-*exo*-2-carboxylate (17) A mixture of *exo*-hexahydro-4,7-epoxyisobenzofuran-1(3*H*)-one[6,8] (**16**, 10 g), pulverized potassium cyanide (5.85 g) and dimethylsulfoxide (70 ml) was heated at 185 °C for 2 h. Water and then dilute hydrochloric acid were added carefully. The mixture was extracted with ethyl acetate. The extracts were washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. Excess diazomethane in ether was added dropwise to a suspension of the residue in ether. The volatile materials were removed by distillation under reduced pressure. Crystallization of the residue from ether gave **17** (3.78 g), mp 88—89 °C. IR (Nujol): 2320, 1724 cm^{-1}. NMR ($CDCl_3$) δ: 1.3—2.1 (4H, m), 2.42 (2H, s), 2.4—2.8 (1H, m), 2.83 (1H, d, J=8 Hz), 3.71 (3H, s), 4.50 (1H, d, J=5 Hz), 4.85 (1H, d, J=3 Hz). *Anal.* Calcd for $C_{10}H_{13}NO_3$: C, 61.84; H, 6.23; N, 7.21. Found: C, 61.35; H, 6.67; N, 7.23.

The mother liquor was concentrated under reduced pressure and subjected to flash chromatography on silica gel in ethyl acetate–hexane (1 : 2). Recrystallization of the product from ether gave the methyl ester of **18** (0.428 g), mp 67—68 °C. IR (Nujol): 2225, 1735 cm^{-1}. NMR ($CDCl_3$) δ: 1.5—2.0 (4H, m), 2.40 (2H, m), 2.60 (2H, m), 3.75 (3H, s), 4.79 (1H, t, J=5 Hz), 4.91 (1H, d, J=3 Hz). *Anal.* Calcd for $C_{10}H_{13}NO_3$: C, 61.84; H, 6.23; N, 7.21. Found: C, 61.35; H, 6.69; N, 7.26.

***exo*-3-(Cyanomethyl)-7-oxabicyclo[2.2.1]heptane-*exo*-2-carboxylic Acid (18)** A mixture of **17** (5.5 g) and 10% potassium hydroxide in methanol (50 ml) was stirred at room temperature for 1 h, acidified with dilute hydrochloric acid and extracted with ethyl acetate. The extracts were washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was recrystallized from benzene and then ether, 3.95 g (77%), mp 103 °C. IR (Nujol): 2240, 1702 cm^{-1}. NMR ($CDCl_3$) δ: 1.4—2.1 (4H, m), 2.2—2.8 (4H, m), 4.41 (1H, d, J=3 Hz), 4.85 (1H, d, J=5 Hz), 10.9 (1H, s). *Anal.* Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.62; H, 6.11; N, 7.77.

2-*endo*-(*tert*-Butoxycarbonylamino)-3-*exo*-(cyanomethyl)-7-oxabicyclo-[2.2.1]heptane (19) The preparation of **19** (53.9%) from **18** was done according to the procedure described for the synthesis of **3**, except that *tert*-butanol was used instead of benzyl alcohol. IR (film): 3345, 2250, 1703 cm^{-1}. NMR ($CDCl_3$) δ: 1.43 (9H, s), 1.5—2.0 (5H, m), 2.4—2.8 (2H, m), 3.50 (1H, m), 4.37 (1H, d, J=5 Hz), 4.63 (1H, t, J=4 Hz), 4.80 (1H, s).

2-*endo*-(*tert*-Butoxycarbonylamino)-3-*exo*-formylmethyl-7-oxabicyclo-[2.2.1]heptane (20) A 1 M solution of diisobutylaluminum hydride in hexane (13 ml) was added dropwise to a stirred solution of **19** (2.94 g) in dry toluene (50 ml) at −20 °C under nitrogen. The solution was stirred at −20 °C for 6 h. Aqueous ammonium chloride and then dilute hydrochloric acid were added. The organic phase was separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was found to be a mixture of **20** and the starting material **19**. A small portion of the residue was submitted to flash chromatography on silica gel in hexane–ethyl acetate (2 : 1). NMR ($CDCl_3$) δ: 1.40 (9H, s), 1.5—2.0 (5H, m), 2.71 (2H, d, J=7 Hz), 3.46 (1H, m), 4.10 (1H, d, J=4 Hz), 4.63 (1H, t, J=4 Hz), 4.96 (1H, s), 9.76 (1H, s). The mixture was used for the next preparation without further purification.

Methyl (5*Z*)-7-(3-*endo*-*tert*-Butoxycarbonylamino-7-oxabicyclo-[2.2.1]heptan-2-*exo*-yl)hept-5-enoate (21) and (+)-Isomer (+)-(21) Crude **20** (813 mg) was treated by the procedure described for the preparation of **8** to obtain the carboxylic acid (300 mg). NMR ($CDCl_3$) δ: 1.45 (9H, s), 1.2—1.9 (7H, m), 1.9—2.5 (6H, m), 3.49 (1H, m), 4.14 (1H, d, J=5 Hz), 4.61 (1H, t, J=3 Hz), 5.39 (2H, m), 8.35 (1H, s). This product was esterified with diazomethane in the same way as in the preparation of **8**. IR (film): 3340, 1740, 1713, 1170 cm^{-1}. NMR ($CDCl_3$) δ: 1.42 (9H, s), 1.1—1.9 (6H, m), 1.9—2.4 (7H, m), 3.47 (1H, m), 4.11 (1H, d, J=5 Hz), 4.61 (1H, t, J=3 Hz), 4.82 (1H, d, J=6 Hz), 5.37 (2H, m).

(+)-**21**: $[\alpha]_D$ +42.9 (c=1.038, MeOH).

Methyl (5*Z*)-7-(3-*endo*-Benzenesulfonylamino-7-oxabicyclo[2.2.1]-heptan-2-*exo*-yl)hept-5-enoate (22) and (+)-Isomer (+)-(22) Using the same procedure as for the preparation of **10**, **22** was synthesized in 67.9% yield. IR (film): 3270, 1735, 1160 cm^{-1}. NMR ($CDCl_3$) δ: 1.0—2.4 (13H, m), 3.02 (1H, m), 3.69 (3H, s), 4.09 (1H, d, J=4 Hz), 4.46 (1H, t, J=3 Hz), 5.17 (2H, m), 5.64 (1H, d, J=5 Hz), 7.60 (3H, m), 7.93 (2H, m).

(+)-**22**: $[\alpha]_D^{24}$ +44.2 (c=1.363, MeOH). MS *m/z*: 394 (MH^+).

(5*Z*)-7-(3-*endo*-Benzenesulfonylamino-7-oxabicyclo[2.2.1]heptan-2-*exo*-yl)hept-5-enoic Acid (23) and Its Na Salt (24) This was prepared from **22** by the procedure described for the preparation of **11**. **23**: IR (film): 3260, 1706, 1157 cm^{-1}. NMR ($CDCl_3$) δ: 1.2—2.4 (13H), 3.01 (1H, m), 4.07 (1H, d, J=4 Hz), 4.41 (1H, t, J=5 Hz), 5.16 (2H, ml), 5.64 (1H, d, J=6 Hz), 7.55 (3H, m), 7.88 (2H, m). MS *m/z*: 379 (M^+).

24: IR (KBr): 3410, 3260, 1560, 1320, 1155 cm^{-1}.

***endo*-Hexahydro-4,7-epoxyisobenzofuran-1,3-dione (28)** A solution of dimethyl 7-oxabicyclo[2.2.1]hept-2-ene-2,3-dicarboxylate[11] (**25**, 41.2 g) in methanol (420 ml) was added to a solution of lithium hydroxide (33.0 g) in water (420 ml). The mixture was warmed at 50 °C for 2 h and treated with charcoal. The filtrate was acidified with Amberlite IR 120BH^+. The volatile materials were distilled under reduced pressure. NMR (DMSO-d_6) δ: 1.25 (2H, dd, J=5, 11 Hz), 1.78 (2H, dd, J=3, 8 Hz), 5.08 (2H, m).

The carboxylic acid **26**, 10% palladium–charcoal (3.0 g) and methanol (500 ml) were stirred under a hydrogen atmosphere and 4.4 l of hydrogen was absorbed. The catalyst was filtered off and washed with methanol. The filtrate and washing were combined and concentrated under reduced pressure. Acetyl chloride (200 ml) was added. The mixture was heated under reflux for 1 h. The volatile materials were finally removed by distillation under reduced pressure. The residue was dissolved in dichloromethane, the insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure. Crystallization of the residue from benzene gave **28** (13.5 g, 41.3%). NMR ($CDCl_3$) δ: 1.7—2.1 (4H, m), 3.70 (2H, m), 4.96 (2H, m). *Anal.* Calcd for $C_8H_8O_4$: C, 57.14; H, 4.80. Found: C, 57.00; H, 4.91.

Methyl (5*Z*)-7-(3-*endo*-Carboxy-7-oxabicyclo[2.2.1]heptan-2-*endo*-yl)-hept-5-enoate (30) Jones' reagent was added dropwise to a solution of **29** (1.47 g) in acetone (15 ml) with cooling in ice until the brown color persisted. Ice water was added, and the mixture was extracted with ethyl acetate. The extracts were washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel (50 g) in hexane–ethyl acetate (1 : 3) (0.877 g, 56.7%). NMR ($CDCl_3$) δ: 1.4—2.6 (13H), 3.09 (1H, dd, J=5, 11 Hz), 3.68 (3H, s), 4.52 (1H, t, J=3 Hz), 5.35 (2H, m), 8.1 (1H, br s).

Methyl (5*Z*)-7-(3-*endo*-(*tert*-Butoxycarbonylamino)-7-oxabicyclo[2.2.1]-heptan-2-*endo*-yl)hept-5-enoate (31) The procedure for preparing **19** was used to obtain **31** (49.6%). IR (film): 3370, 1739, 1716, 1698 cm^{-1}. NMR ($CDCl_3$) δ: 1.44 (9H, s), 1.5—2.5 (13H, m), 3.67 (3H, s), 4.05 (1H, m), 4.47 (1H, m), 4.57 (1H, m), 5.34 (2H, m).

Methyl (5*Z*)-7-(3-*endo*-Benzenesulfonylamino-7-oxabicyclo[2.2.1]hep-tan-2-*endo*-yl)hept-5-enoate (32) The procedure used to prepare **10** was employed to obtain **32** from **27** in 56.4% yield. IR (film): 3300, 1737, 1343, 1163 cm^{-1}. NMR ($CDCl_3$) δ: 1.4—2.4 (13H), 3.60 (1H, m), 3.69 (3H, s), 4.33 (2H, m), 5.25 (2H, m), 5.35 (1H, m), 7.55 (3H, m), 7.88 (2H, m).

(5*Z*)-7-(3-*endo*-Benzenesulfonylamino-7-oxabicyclo[2.2.1]heptan-2-*endo*-yl)hept-5-enoic Acid (33) and Its Sodium Salt (34) The ester **32** was hydrolyzed by the same method as used to prepare **11**, 94.0%. IR (film): 3290, 1709, 1340, 1162 cm^{-1}. NMR ($CDCl_3$) δ: 1.4—2.5 (13H, m), 3.66 (1H, m), 4.27 (1H, m), 4.38 (1H, m), 5.27 (2H, m), 5.65 (1H, d, J=9 Hz), 7.58 (3H, m), 7.90 (2H, m), 8.14 (1H, br s).

The salt **34**: IR (KBr): 3430, 1558, 1339, 1158 cm^{-1}.

2-(2-Methoxyethenyl)-3-*exo*-(hydroxymethyl)-7-oxabicyclo[2.2.1]hep-tane (36a) and -hept-5-ene (36b) The procedure for preparing **6** was used to obtain **36a** and **36b** from **35a** and **35b**[5] as oils in 68.0 and 72.1% yields,

respectively. The NMR showed a mixture of four stereoisomers due to the configuration of the methoxyethenyl group. The mixture was used for the next preparation without further purification.

2-*endo*-(Formylmethyl)-3-*exo*-(hydroxymethyl)-7-oxabicyclo[2.2.1]heptane (37a), 4-Methoxy-5,11-dioxatricyclo[6.2.1.0^{2,7}]undecane (33a) and 4-Hydroxy-5,11-dioxatricyclo[6.2.1.0^{2,7}]undecane (39a) Under a nitrogen atmosphere, **36a** (7.7 g) was dissolved in 20% trifluoroacetic acid (50 ml), and the solution was allowed to stand at room temperature for 2 h. Sodium hydrogen carbonate (11.3 g) was added carefully in small portions to the solution. The mixture was extracted with dichloromethane. The extracts were dried (Na_2SO_4), concentrated under reduced pressure and subjected to flash chromatography on silica gel (150 g) in hexane–ethyl acetate (1 : 1) to give **38a** (0.88 g, 12.4%) and in ethyl acetate to give **37a** (0.342 g, 4.8%) and **39a** (1.90 g, 26.7%). NMR of **38a**: ($CDCl_3$) δ: 1.3—2.3 (8H), 3.46 (3H, s), 3.5—3.8 (2H, m), 4.18 (2H, m), 4.5—4.9 (1H, m). NMR of **37a**: ($CDCl_3$) δ: 1.3—2.2 (7H), 2.51 (2H, m), 3.0—3.8 (2H), 4.0—4.8 (3H), 9.75 (1H, t, J=1 Hz). NMR of **39a**: ($CDCl_3$) δ: 1.3—2.4 (8H), 3.2—3.8 (3H, m), 4.1—4.3 (2H, m), 4.9—5.4 (1H, m).

(−)-(**38a**): $[\alpha]_D^{24}$ −73.7 (c=2.263, MeOH).

(−)-(**39a**): $[\alpha]_D^{24}$ −42.3 (c=1.385, $CHCl_3$). Mutarotation, −18.5 after standing for 8 h. *Anal.* Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.71; H, 8.29.

2-*endo*-(Formylmethyl)-3-*exo*-(hydroxymethyl)-7-oxabicyclo[2.2.1]hept-5-ene (37b) and 4-Methoxy-5,11-dioxatricyclo[6.2.1.0^{2,7}]undec-9-ene (38b) and 3-Hydroxy Derivative (39b) The ether derivative **36b** was treated as described above. The crude products were submitted to flash chromatography on silica gel in hexane–ethyl acetate (1 : 1), giving **38b** in 7.8% yield, and in ethyl acetate, giving **37b** in 1.9% yield and **39b** in 35.0% yield.

37b: oil. NMR ($CDCl_3$) δ: 1.3—2.5 (4H), 3.3—4.0 (2H), 4.56 (1H, s), 4.75 (1H, s), 6.2—6.6 (2H, m), 9.74 (1H, s).

38b: oil. NMR ($CDCl_3$) δ: 1.6—2.7 (4H), 3.38 (3H, s), 3.4—3.9 (2H, m), 4.06 (2H, s), 4.4—4.9 (1H, m), 6.30 (2H, m).

39b: mp 86—88 °C. IR (Nujol): 3400, 1038, 1015 cm^{-1}. NMR ($CDCl_3$) δ: 1.5—2.3 (4H), 3.2—4.0 (4H), 4.54 (1H, d, J=5 Hz), 4.61 (1H, s), 5.0—5.4 (1H, m), 6.30 (2H, m). *Anal.* Calcd for $C_{10}H_{14}O_3$: C, 64.27; H, 7.19. Found: C, 64.12; H, 7.25.

Methyl (5*Z*)-7-(3-*exo*-(Hydroxymethyl)-7-oxabicyclo[2.2.1]heptan-2-*exo*-yl)hept-5-enoate (40a), (+)-Isomer (+)-(40a) and Methyl (5*Z*)-7-(3-*exo*-(Hydroxymethyl)-7-oxabicyclo[2.2.1]hept-5-en-2-*exo*-yl)hept-5-enoate (40b) These compounds were prepared by the same procedure as used to synthesize **8**.

40a: oil, 62% yield. IR (film): 3445, 1737 cm^{-1}. NMR ($CDCl_3$) δ: 1.3—2.4 (15H), 3.60 (2H, m), 3.66 (3H, s), 4.19 (1H, m), 4.46 (1H, m), 5.36 (2H, m).

(−)-**40a**: $[\alpha]_D^{40}$ −12.5 (c=1.021, MeOH).

40b: oil, 27.5% yield. IR (film): 3440, 1737 cm^{-1}. NMR ($CDCl_3$) δ: 1.5—2.5 (10H), 3.70 (3H, s), 3.82 (2H, m), 4.60 (1H, s), 4.90 (1H, s), 5.45 (2H, m), 6.36 (2H, s).

Methyl (5*Z*)-7-(3-*exo*-Formyl-7-oxabicyclo[2.2.1]heptan-2-*exo*-yl)hept-5-enoate (41a) and Methyl (5*Z*)-7-(3-*exo*-Formyl-7-oxabicyclo[2.2.1]hept-5-en-2-*exo*-yl)hept-5-enoate (41b) A solution of dimethylsulfoxide (1.5 ml) in dichloromethane (4 ml) was added to a solution of oxalyl chloride (0.75 ml) in dichloromethane (20 ml) at −60 °C. The mixture was stirred at −60 °C for 10 min. A solution of **40a** (2.02 g) in dichloromethane (20 ml) was added dropwise. The mixture was stirred at −60 °C for 1 h. Triethylamine (5.3 ml) was added and the mixture was stirred at room temperature. 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 (Na_2SO_4) and concentrated under reduced pressure to give **41a** as an oil. NMR ($CDCl_3$) δ: 1.4—2.7 (14H), 3.69 (3H, s), 4.36 (4H, m), 4.76 (1H, m), 5.41 (2H, m), 9.12 (1H, d, J=5 Hz).

By the same procedure, **41b** was prepared. NMR ($CDCl_3$) δ: 1.5—2.5 (10H), 3.67 (3H, s), 4.76 (1H, s), 5.13 (1H, s), 5.46 (2H, m), 6.31 (1H, dd, J=6, 2 Hz), 6.45 (1H, dd, J=6, 2 Hz), 9.70 (1H, d, J=5 Hz). These compounds were used for the next preparation without further purification.

Methyl (5*Z*)-7-(3-*endo*-Formyl-7-oxabicyclo[2.2.1]heptan-2-*exo*-yl)-hept-5-enoate (42a), (+)-Isomer (+)-(42a) and Methyl (5*Z*)-7-(3-*endo*-Formyl-7-oxabicyclo[2.2.1]hept-5-en-2-*exo*-yl)hept-5-enoate (42b) The crude aldehyde **41a** was dissolved in 0.068 M sodium methoxide in methanol (30 ml) at 0 °C. The solution was stirred at room temperature for 2 h, poured into aqueous ammonium chloride and extracted with ether. The extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give **42a** as an oil in 85.0% yield from **40a**. NMR ($CDCl_3$) δ: 1.4—1.7 (14H), 3.69 (3H, s), 4.31 (1H, m), 4.80 (1H, m), 5.40 (2H, m), 9.72 (1H, d, J=2 Hz).

(+)-**42a**: $[\alpha]_D^{24}$ +43.2 (c=1.258, benzene).

42b: 88.2% yield from **40b**, oil. NMR ($CDCl_3$) δ: 1.5—2.5 (9H), 2.63 (1H, m), 3.68 (3H, m), 4.69 (1H, d, J=1 Hz), 5.11 (1H, d, J=3 Hz), 5.43 (2H, m), 6.33 (1H, dd, J=6, 2 Hz), 6.50 (1H, dd, J=6, 2 Hz), 9.40 (1H, d, J=2 Hz).

Methyl (5*Z*)-7-(3-*endo*-(Hydroxymethyl)-7-oxabicyclo[2.2.1]heptan-2-*exo*-yl)hept-5-enoate (43) Sodium borohydride (0.4 g) was added in small portions to a solution of **42** (1.605 g) in methanol (15 ml) with cooling in ice. The mixture was stirred at 0 °C for 30 min. Dilute hydrochloric acid was added dropwise. The mixture was extracted with ether. The extracts were washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (50 g) in hexane–ethyl acetate (1 : 2) gave **43** (1.455 g, 90.0%). IR (film): 3440, 1737 cm^{-1}. NMR ($CDCl_3$) δ: 1.0—2.5 (15H), 3.3—3.9 (2H, m), 3.68 (3H, s), 4.18 (1H, m), 4.57 (1H, m), 5.39 (2H, m). *Anal.* Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 66.91; H, 9.11.

Methyl (5*Z*)-7-(3-*endo*-(Methanesulfoxymethyl)-7-oxabicyclo[2.2.1]-heptan-2-*exo*-yl)hept-5-enoate (44) A solution of methanesulfonyl chloride (0.7 g) in dichloromethane (1 ml) was added to a solution of **43** (1.45 g) and triethylamine (1.2 ml) in dichloromethane (15 ml) at −20 °C. The mixture was stirred at −20 °C for 20 min, poured into ice-cold dilute hydrochloric acid and extracted with dichloromethane. The extracts were washed with water, dried (Na_2SO_4) and concentrated under reduced pressure to give **44** (1.52 g, 81.1%). NMR ($CDCl_3$) δ: 1.1—2.5 (14H), 3.03 (3H, s), 3.66 (3H, s), 4.23 (1H, m), 4.59 (1H, s), 5.41 (2H, m). This was used for the next preparation without further purification.

Methyl (5*Z*)-7-(3-*endo*-(Azidomethyl)-7-oxabicyclo[2.2.1]heptan-2-*exo*-yl)hept-5-enoate (45) A mixture of **44** (1.51 g), sodium azide (0.45 g) and hexamethylphosphoric triamide (6 ml) was stirred at 50 °C for 2 h. Water was added. The mixture was extracted with ether. The extracts were washed with water, dried (Na_2SO_4), concentrated under reduced pressure and subjected to flash chromatography on silica gel (50 g) in hexane–ethyl acetate (2 : 1) to give **45** (1.26 g, 79.4%). IR (film): 2090, 1736 cm^{-1}. NMR ($CDCl_3$) δ: 1.0—2.5 (14H), 3.0—3.6 (2H, m), 3.68 (3H, s), 4.16 (1H, m), 4.52 (1H, s), 5.39 (2H, m).

Methyl (5*Z*)-7-(3-*endo*-Benzenesulfonylaminomethyl-7-oxabicyclo-[2.2.1]heptan-2-*exo*-yl)hept-5-enoate (46) A mixture of **45** (1.16 g) and triphenylphosphine (1.25 g) in tetrahydrofuran (35 ml) was stirred at room temperature overnight. Water (7 ml) was added. The mixture was heated under reflux for 30 min and concentrated under reduced pressure. The residue was dissolved in dichloromethane. The solution was dried (Na_2SO_4) and crystallized from ether. The filtrate was concentrated to dryness.

Benzenesulfonyl chloride (1.5 ml) was added to a solution of the residue and triethylamine (6 ml) in dichloromethane (30 ml) at room temperature. The mixture was stirred at room temperature for 1.5 h and poured into ice water. The organic phase was separated and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed with dilute hydrochloric acid, aqueous sodium hydrogencarbonate and water, dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (70 g) in hexane–ethyl acetate (1 : 2) gave **46** (639 mg, 40.0%). IR (film): 3260, 1736, 1328, 1160 cm^{-1}. NMR ($CDCl_3$) δ: 1.0—2.5 (14H), 2.8—3.1 (2H, m), 3.70 (3H, s), 4.13 (1H, m), 4.44 (1H, m), 4.96 (1H, t, J=6 Hz), 5.35 (2H, m), 7.4—7.7 (3H, m), 7.8—8.0 (2H, m). *Anal.* Calcd for $C_{21}H_{29}NO_3S$: C, 61.89; H, 7.17; N, 3.44; S, 7.87. Found: C, 61.42; H, 7.29; N, 3.21; S, 7.70.

(5*Z*)-7-(3-*endo*-Benzenesulfonylaminomethyl-7-oxabicyclo[2.2.1]heptan-2-*exo*-yl)hept-5-enoic Acid (47) and Its Na Salt (48) Compound **46** was allowed to react as described for the preparation of **10**. **47**: 91.5%. IR (film): 3265, 1708, 1327, 1160 cm^{-1}. NMR ($CDCl_3$) δ: 1.0—2.5 (14H), 2.8—3.1 (2H, m), 4.18 (1H, d, J=4 Hz), 4.46 (1H, m), 5.2—5.6 (3H, m), 7.4—7.7 (3H, m), 7.8—8.0 (2H, m), 8.96 (1H, s). MS m/z: 394 (MH^+).

48: IR (KBr): 3280, 1565, 1324, 1158 cm^{-1}.

Methyl (5*Z*)-7-(3-*exo*-(Hydroxymethyl)-7-oxabicyclo[2.2.1]heptan-2-*endo*-yl)hept-5-enoate (49) This was prepared from **37** in the same manner as described for the preparation of **8**. IR (film): 3445, 1737 cm^{-1}. NMR ($CDCl_3$) δ: 1.2—2.4 (14H), 3.47 (2H, d, J=7 Hz), 3.68 (3H, s), 4.41 (2H, m), 5.36 (2H, m).

Methyl (5*Z*)-7-(3-*exo*-(Methanesulfonylmethyl)-7-oxabicyclo[2.2.1]-heptan-2-*endo*-yl)hept-5-enoate (50) This was prepared from **49** by the method used to obtain **44**. NMR ($CDCl_3$) δ: 1.2—1.9 (8H), 1.9—2.5 (6H), 3.01 (3H, s), 3.69 (3H, s), 3.99 (2H, d, J=7 Hz), 4.40 (2H, m), 5.36 (2H, m).

Methyl (5*Z*)-7-(3-*exo*-(Azidomethyl)-7-oxabicyclo[2.2.1]heptan-2-*endo*-yl)hept-5-enoate (51) This was prepared from **50** by the method used to

obtain **45**, in 75.4% yield. IR (film): 2300, 1730 cm^{-1}. NMR ($CDCl_3$) δ: 1.2—2.0 (8H, m), 2.0—2.5 (6H, m), 3.17 (2H, d, J=8 Hz), 3.69 (3H, s), 4.29 (1H, d, J=5 Hz), 4.42 (1H, t, J=5 Hz), 5.37 (2H, m).

Methyl (5*Z*)-7-(3-*exo*-Benzenesulfonylaminomethyl-7-oxabicyclo-[2.2.1]heptan-2-*endo*-yl)hept-5-enoate (52) This was prepared by the method used to obtain **46**. IR (film): 3280, 1734, 1328, 1160 cm^{-1}. NMR ($CDCl_3$) δ: 1.0—2.9 (14H), 2.89 (2H, m), 3.67 (3H, s), 4.16 (1H, d, J= 4 Hz), 4.41 (1H, t, J=4 Hz), 5.11 (1H, m), 5.33 (2H, m), 7.4—7.7 (3H, m), 7.8—8.0 (2H, m).

(5*Z*)-7-(3-*exo*-Benzenesulfonylaminomethyl-7-oxabicyclo[2.2.1]heptan-2-*endo*-yl)hept-5-enoic Acid (53) and Its Na Salt (54) This was prepared by the method used to obtain **46**. IR (film): 3270, 1707, 1327, 1158 cm^{-1}. NMR ($CDCl_3$) δ: 1.1—2.5 (14H), 2.85 (2H, m), 4.15 (1H, m), 4.42 (1H, t, J=5 Hz), 5.33 (2H, m), 5.58 (1H, t, J=7 Hz), 7.4—7.6 (3H, m), 7.7—8.0 (2H, m), 8.85 (1H, s).

54: IR (KBr): 3280, 1566, 1325, 1155 cm^{-1}.

Methyl (5*Z*)-7-(3-*endo*-Carboxy-7-oxabicyclo[2.2.1]hept-5-en-2-*endo*-yl)hept-5-enoate (55) 42.1% yield. IR (film): 1736 cm^{-1}. NMR ($CDCl_3$) δ: 1.5—2.5 (9H), 2.66 (1H, m), 3.66 (3H, s), 4.66 (1H, s), 5.12 (1H, d, J= 5 Hz), 5.45 (2H, m), 6.31 (1H, dd, J=6, 2 Hz), 6.48 (1H, dd, J=6, 2 Hz), 8.50 (1H, s).

Methyl (5*Z*)-7-(3-*endo*-(*tert*-Butoxycarbonylamino)-7-oxabicyclo-[2.2.1]hept-5-en-2-*endo*-yl)hept-5-enoate (56) The procedure for preparing **19** was used to obtain **56** in 26.5% yield. IR (film): 3365, 1739, 1713, 1513 cm^{-1}. NMR ($CDCl_3$) δ: 1.0—2.5 (9H), 1.43 (9H, s), 3.68 (3H, s), 3.79 (1H, m), 4.25 (1H, m), 4.59 (1H, s), 4.99 (1H, d, J=3 Hz), 5.46 (2H, m), 6.36 (1H, dd, J=6, 2 Hz), 6.56 (1H, dd, J=6, 2 Hz).

Methyl (5*Z*)-7-(3-*endo*-Benzenesulfonylamino-7-oxabicyclo[2.2.1]hept-5-en-2-*endo*-yl)hept-5-enoate (57) The procedure for preparing **10** was used to prepare **57** from **52** in 62.9% yield. IR (film): 3260, 1734, 1325, 1156 cm^{-1}. NMR ($CDCl_3$) δ: 1.0—2.5 (9H), 3.30 (1H, m), 3.69 (3H, s), 4.53 (1H, s), 4.77 (1H, s), 4.82 (1H, m), 5.26 (2H, m), 6.28 (1H, dd, J=6, 2 Hz), 6.53 (1H, dd, J=6, 2 Hz), 7.5—7.7 (3H, s), 7.8—8.1 (2H, m).

(5*Z*)-7-(3-*endo*-Benzenesulfonylamino-7-oxabicyclo[2.2.1]hept-5-en-2-*endo*-yl)hept-5-enoic Acid (58) and Its Na Salt (59) The ester **57** was hydrolyzed as described above. IR (film): 3265, 1707, 1323, 1158 cm^{-1}. NMR ($CDCl_3$) δ: 1.0—1.9 (3H, m), 1.4—2.5 (7H), 3.25 (1H, m), 4.51 (1H, s), 4.76 (1H, d, J=5 Hz), 5.15 (1H, m), 5.23 (2H, m), 6.25 (1H, dd, J=6, 2 Hz), 6.50 (1H, dd, J=6, 2 Hz), 7.4—7.7 (3H, m), 7.8—8.0 (2H, m).

The salt **59**: IR (KBr): 3270, 1570, 1325, 1160 cm^{-1}.

(−)-2-*exo*-(Methoxycarbonyl)-7-oxabicyclo[2.2.1]heptane-3-*exo*-carboxylic Acid (2) The diester **60** (63.0 g) was incubated with porcine liver esterase (200 units, 6.25 ml + 260 units, 3.56 ml) in 0.1 M phosphate buffer (1.5 l) at 30 °C for 20 h at pH 6.5, which was maintained throughout the entire reaction by continuous addition of 1 N sodium hydroxide. The mixture was acidified to pH 3 with 1 N hydrochloric acid and concentrated under reduced pressure at 40 °C. The residue was extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was crystallized from ethyl acetate to give the racemic half-ester 4.4 g (7.5%) and the (−)-isomer 37.6 g (63.8%) as the second crop; mp 111—114 °C. $[\alpha]_D^{24}$ −4.5 (c=2.132, MeOH), lit. −3.9.[13]

(+)-Methyl 2-*exo*-(Benzyloxycarbonylamino)-7-oxabicyclo[2.2.1]-heptane-3-*exo*-carboxylate (+)-(3) The carboxylic acid ((−)-**2**) was treated by the procedure described for the preparation of **21**. mp 67—68 °C, $[\alpha]_D^{24}$ +44.0±0.5 (c=1.286, $CHCl_3$). *Anal.* Calcd for $C_{16}H_{19}NO_4$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.54; H, 7.85; N, 5.32.

(−)-3-*exo*-(Benzyloxycarbonylamino)-2-*endo*-(formylmethyl)-7-oxabicyclo[2.2.1]heptan (−)-(7) mp 119—122 °C, $[\alpha]_D^{24}$ −19.6 (c=1.089, $CHCl_3$). *Anal.* Calcd for $C_{16}H_{19}NO_3$: C, 61.15; H, 8.29; N, 5.49. Found: C, 61.05; H, 8.09; N, 5.47.

(−)-(5*Z*)-7-(3-*exo*-Benzenesulfonylamino-7-oxabicyclo[2.2.1]heptan-2-*endo*-yl)hept-5-enoic Acid (−)-(11) $[\alpha]_D^{24}$ −27.7 (c=1.168, MeOH). CD (MeOH) λ nm ($\Delta\varepsilon$): 269.5 (−0.103), 262.5 (−0.121), 256.5 (−0.091), 220 (−0.712), 213 (−1.12), 202 (+1.63).

(+)-*exo*-Hexahydro-4,7-epoxyisobenzofuran-1(3*H*)-one (+)-(16) A solution of triethylamine (23.3 g) in acetone (32 ml) was added to a solution of (−)-**2** (38.3 g) in water (32 ml) and acetone (100 ml) with cooling in ice. A solution of ethyl chloroformate (28.7 g) in acetone (65 ml) was added dropwise to the solution during 30 min with cooling in ice. The mixture was stirred at 0 °C for 30 min. Ice water was added. The mixture was extracted with dichloromethane. The extracts were washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. Benzene was added. The volatile materials were removed by distillation under reduced pressure. These procedures were repeated twice to remove acetone.

Sodium borohydride (23.0 g) was added in small portions to a solution of the residue in methanol (200 ml) at −30 °C to −40 °C over 30 min. The mixture was stirred at −20 °C for 1 h, poured into ice-cold dilute hydrochloric acid and extracted with dichloromethane. The aqueous phase was concentrated under reduced pressure to dryness. The residue was extracted with dichloromethane. The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was crystallized from ether. The mother liquor was submitted to flash chromatography on silica gel (130 g) in hexane–ethyl acetate (1 : 2). The combined crystals were recrystallized from ether, 19.4 g (65.8%), mp 66—67 °C, $[\alpha]_D^{24}$ +115.4 (c=1.262, $CHCl_3$) lit.[14] +114.2. IR (Nujol): 1765, 1753 cm^{-1}. *Anal.* Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.19; H, 6.52.

(+)-*exo*-Hexahydro-4,7-epoxyisobenzofuran-1-ol (35a) A 1.0 M solution of diisobutyl aluminum hydride in hexane (160 ml) was added dropwise to a suspension of (+)-**16** (21.7 g) in dry toluene (400 ml) at −60 to −70 °C. The solution was stirred at −70 °C for 1.5 h. Water (100 ml) was added dropwise. The mixture was then stirred at room temperature. The solid was filtered off and extracted with ethanol. The combined filtrates were concentrated under reduced pressure and crystallized from ether to give (+)-**35a** (17.4 g, 79.1%), $[\alpha]_D^{24}$ +53.6 (c=1.232, $CHCl_3$).

(+)-Methyl (5*Z*)-7-(3-*endo*-Carboxy-7-oxabicyclo[2.2.1]heptan-2-*exo*-yl)hept-5-enoate (+)-(61) Jones' reagent (1.5 ml) was added dropwise to a solution of (+)-**42** (1.47 g) in acetone (15 ml) with cooling in ice. The mixture was stirred at 0 °C for 10 min. Water was added. The mixture was extracted with ether. The extracts were washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (50 g) in ethyl acetate–hexane (1 : 1) and in ethyl acetate gave **57** (1.22 g, 78.3%), $[\alpha]_D^{24}$ +55.7 (c=1.248, MeOH). IR (film): 1738, 1710 cm^{-1}. NMR ($CDCl_3$) δ: 1.5—2.5 (13H), 4.63 (1H, m), 3.69 (3H, s), 4.26 (1H, d, J=4 Hz), 4.74 (1H, d, J=6 Hz), 5.40 (2H, m), 8.30 (1H, s). *Anal.* Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.02; H, 8.00.

Inhibitory Effect on Rabbit PRP Aggregation. Preparation of Rabbit PRP Mature male rabbits (NIBS-JW) weighing 2.2—2.6 kg were used. With the animal under sodium pentobarbital anesthesia (Somnopentyl, Pitman Moore, *ca.* 20 mg/kg, 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,[17] using an AUTO-RAM61 type aggregometer (Rika-Denki Co., Ltd., Tokyo) as reported previously.[18] A pair of sample of PRP (400 μl) placed in a cuvette were warmed at 37 °C for 1 min with stirring (1200 rpm), and then a saline solution of the test compound (50 μl) or saline was added. Exactly 2 min later, a solution of sodium arachidonate (50 μl) was added to each of the samples and the changes in light transmission were recorded, with the light transmission for PRP and PPP taken as 0% and 100%, respectively, and the maximum light 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 into 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 turning and centrifuged for 10 min at 160 × *g* to give 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-6M, Niko bioscience). A 245 μl aliquot of the WP, the platelet number of which had been adjusted to 5 × 10^5/μl, 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 a test compound in DMSO and after 2 min, 1 μl of collagen (Hormon-Chemie, Munich, 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 50% aggregation inhibitory rate was calculated from the aggregation inhibitory rate measured 3 min after addition of a platelet-aggregating agent.

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References

1) Reviews: R. C. Nickolson, M. H. Town and H. Vorbruggen, *Med. Res. Rev.*, **5**, 1 (1985); R. F. Newton, S. M. Roberts and R. J. K. Taylor, *Synthesis*, **1984**, 449.
2) P. W. Manley, D. P. Tuffin, N. M. Allanson, P. E. Buckle, N. Lad, S. M. F. Lai, D. O. Lunt, R. A. Porter and P. J. Wade, *J. Med. Chem.*, **30**, 1812 (1987); R. A. Johnson, E. G. Nidy and J. W. Crittenden, *ibid.*, **29**, 1461 (1986) and references cited therein.
3) A review: A. M. Lefer, *Drugs Today*, **21**, 283 (1985).
4) 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).
5) P. W. Sprague, J. E. Heikes, J. Z. Gougoutas, M. F. Malley, D. N. Harris and R. Greenberg, *J. Med. Chem.*, **28**, 1580 (1985); P. W. Sprague, J. E. Heikes, D. N. Harris and R. Greenberg, *Adv. PG TX Res.*, **6**, 493 (1980); *idem, ibid.*, **11**, 337 (1983).
6) T. A. Eggelte, H. deKoning and H. O. Huisman, *Tetrahedron*, **29**, 2445, 2491 (1973).
7) R. Kanazawa and T. Tokoroyama, *Synthesis*, **1976**, 526.
8) R. McCrindle, K. H. Overton and R. A. Raphael, *J. Chem. Soc.*, **1962**, 4798.
9) T. Kametani, T. Suzuki, A. Tomino, S. Kamada and K. Unno, *Chem. Pharm. Bull.*, **30**, 796 (1982).
10) H. Stockmann, *J. Org. Chem.*, **26**, 2025 (1961).
11) G. Storks, E. van Tamelen, L. T. Friedman and A. W. Burgstahler, *J. Am. Chem. Soc.*, **75**, 384 (1953).
12) S. E. Hall, W.-C. Han, M. F. Haslanga, D. N. Harris and M. L. Ogletree, *J. Med. Chem.*, **29**, 2335 (1986).
13) R. Bloch, E. G.-Jampel and C. Girard, *Tetrahedron Lett.*, **26**, 4087 (1985).
14) J. Das, M. F. Haslanger, J. Z. Gougoutas and M. F. Malley, *Synthesis*, **1987**, 1100.
15) *Drugs of the Future*, 446 (1987).
16) A. M. Lefer and H. Darius, *Drugs of the Future*, **12**, 367 (1987).
17) G. V. R. Born, *Nature* (London), **194**, 927 (1962).
18) K. Uchida, M. Nakamura, M. Konishi, T. Ishigami and T. Komeno, *Jpn. J. Pharmacol.*, **43**, 9 (1987).