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Synthesis and Biological Activity of 1-Phenylsulfonyl-4-Phenylsulfonylaminopyrrolidine Derivatives as Thromboxane A_2 Receptor Antagonists

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Abstract—The synthesis and biological activity of novel 1-phenylsulfonyl-4- phenylsulfonylaminopyrrolidine analogues are described. All compounds were produced through modification of the substituent formally corresponding to the 1,3-dioxane ring system and the ω-octenol side chain of thromboxane A_2 (TXA_2), in reference to the structure of Daltroban. Several compounds were found to be potent TXA_2 receptor antagonists. Compound **51a** was the most effective inhibitor of 9,11-epoxymethano PGH_2 (U-46619)-induced rat aortic strip contraction ($IC_{50} = 0.48$ nM).

Introduction

Thromboxane A_2 (TXA_2) **1**[1] is recognized as an important and potent mediator of acute life threatening disorders. TXA_2 displays potent platelet aggregation,[2] vasoconstriction[3] and bronchoconstriction[4] activities, and is a mediator that can cause problems in various circulatory disorders[5] and in asthmatic conditions.[6] Efforts to modulate the actions of TXA_2 have focused on agents that inhibit the biosynthesis of TXA_2 or alternatively block the action of TXA_2 at the receptor level. An example of the former approach is cyclooxygenase inhibition. However, cyclooxygenase inhibitors such as aspirin block not only TXA_2 synthesis on platelets, but also the synthesis of vascular prostaglandin I_2 (PGI_2),[7] a powerful antiaggregatory and vasodilatory substance.[8] Several thromboxane synthase inhibitors, for example Dazoxiben **2**,[9,10] have been introduced, however such compounds display possible proaggregatory activity of prostaglandin endoperoxides accumulating after blockage of thromboxane synthase, which are believed to interact at a common receptor[11] for TXA_2. Blocking the action of TXA_2 at the receptor level is TXA_2 receptor antagonism. TXA_2 receptor antagonists present the advantage[12] of inhibiting the proaggregatory action of both TXA_2 and prostaglandin endoperoxides and of antagonizing the effects of various agonists on smooth muscle cells, thus TXA_2 receptor antagonists are becoming an established method for treating asthma and various cardiovascular diseases in the clinic.[12–15]

Several drugs and development candidates with prostanoid structures such as SQ29548 **3**,[16,17] Domitroban **4**,[18,19] and with non-prostanoid structures, for example sulfonamide derivatives such as Daltroban **5**,[20,21] Seratrodast **6**[22,23] and Ramatroban **7**,[24,25] have been found to be selective TXA_2 receptor antagonists.

We recently reported synthesis and biological activity of 4-methyl-3,5-dioxane derivatives as thromboxane A_2 receptor antagonists. Among these compounds, sodium (*Z*)-7-{(1*S*,2*R*,4*R*)-2-[2-aza-2-(((phenyamino)thioxomethyl)amino)vinyl]-4-methyl-3,5-dioxanyl}hept-5-enoate was the most potent in vitro antagonist,[26] but there was a need to improve the in vivo duration of action. In order to achieve this, we next aimed to discover a new chemical skeleton with a non-prostanoid structure and focused on the conformational similarities of TXA_2 and Daltroban.

Inspection for the conformational similarities between their structures with an accurate 3-D molecular model suggested that the sulfonamides, exemplified by Daltroban, might interact with the thromboxane receptor in

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one of two ways, as shown in Scheme 1. In the first model, the oxygen atoms of the sulfonamide might mimic the two oxygen atoms in the 1,3-dioxane ring system of TXA_2. In this conformation, Daltroban could be viewed as lacking an ω-octenol side chain. Alternatively, in the second model the sulfonamide might mimic the allylic alcohol of TXA_2. In this case, the conformation of Daltroban would indicate a structure without the nuclear interaction of the 1,3-dioxane ring system. These observations suggested that the sulfonamide moiety of Daltroban might tentatively play a role as mimics of both the nuclear oxygen atoms and the allylic alcohol. On the basis of this prediction, we designed a new scaffold with two sulfonamide groups in the same molecule. After examining various possibilities for a new ring system and its stereochemistry for the sulfonamide groups in reference to the conformation and the distance between the nuclear oxygen atoms and allylic alcohol in TXA_2, amino pyrrolidine compound **18a** was finally chosen as a lead. Herein, we report a series of new pyrrolidine compounds as highly potent and long-acting TXA_2 receptor antagonists.

Chemistry

All possible stereoisomers were synthesized, as shown in Schemes 2 and 3, in order to find the appropriate configurations at the 2- and 4-positions in the pyrrolidine ring.

Commercially available *trans*-4-hydroxy-L-proline **8** was esterified with $SOCl_2$ in MeOH, treated with di-*tert*-butyldicarbonate, then mesylated at the free hydroxy group to afford **9**. S_N2 substitution of the mesylate group of **9** with benzoate in DMSO followed by debenzoylation of **10** using K_2CO_3 in MeOH, gave alcohol **11**. Alcohol **11** was mesylated again to afford **12**. The mesyl group of **12** was substituted by an azide group in DMSO with inversion of configuration at the 4-position to give **13**. Catalytic hydrogenation of the azide group in **13** in MeOH, followed by acylation with $PhSO_2Cl$ gave sulfonamide **14**. Aldehyde **15**, obtained from **14** by DIBAL reduction, was subjected to a Wittig reaction with the ylide prepared from (4-carboxybutyl)-triphenylphosphonium bromide and *t*-BuOK in dimethylacetamide and afforded the desired acid **16** as the major product together with approximately 5% of the trans isomer. The acid **16** was then treated with aqueous TFA to remove the Boc group to yield **17**. Sulfonylation of the nitrogen atom in the pyrrolidine ring with $PhSO_2Cl$ and Et_3N in CH_2Cl_2 followed by treatment with NaOH in MeOH afforded the desired sodium salt **18a**. Stereoisomer **18b** was obtained in a similar manner to the methods shown above, starting from azide **19**, which was obtained from **9** by inversion of configuration of the position 4 of the pyrrolidine ring. Each S_N2 reaction employed for the preparation of **18a** and **18b** occurred stereospecifically, as confirmed by the observation of no diastereoisomers by 200 MHz NMR. The other two isomers **18c** and **18d** were prepared starting from commercially available *cis*-4-hydroxy-D-proline **24** using a related strategy, as shown in Scheme 3.

For comparison of the biological activity, 1-alkylsulfonyl **35** and 1-carbamoyl **36** derivatives were prepared from **8** as follows. Sulfonylation of **17**, prepared by the method showed in Scheme 2, with *n*-butylsulfonylchloride and triethylamine in CH_2Cl_2 followed by treatment with NaOH in MeOH gave **35**. On the other hand, **36** was obtained by carbamoylation of **15** with phenylisocyanate and Et_3N in CH_2Cl_2 followed by treatment with NaOH in MeOH. Various bis-sulfonyl compounds **37a–g** and **50a–55** were prepared in a similar manner to that for the synthesis of **18a**, as described in Schemes 4 and 5.

Furthermore, in order to investigate the effect of the side chain at 2-position, different analogues **58a–58d** were synthesized from **42** as shown in Scheme 6. The aldehyde **42** was prepared from **8** and was subjected to Wittig reaction with an appropriate ylide. In addition, the saturated form **55** was also obtained by catalytic hydrogenation of the mixture of **51a** and **51b**.

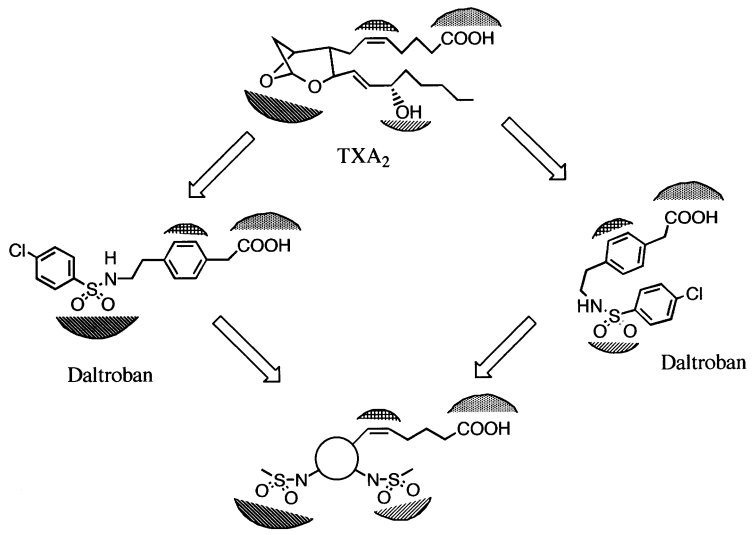
Results and Discussion

In reference to the possible binding conformations shown in Scheme 1, we first assumed that a molecule with two sulfonamides moiety might mimic both the nuclear oxygen atoms and the allylic alcohol, and may possess more potent TXA_2 receptor antagonistic activity

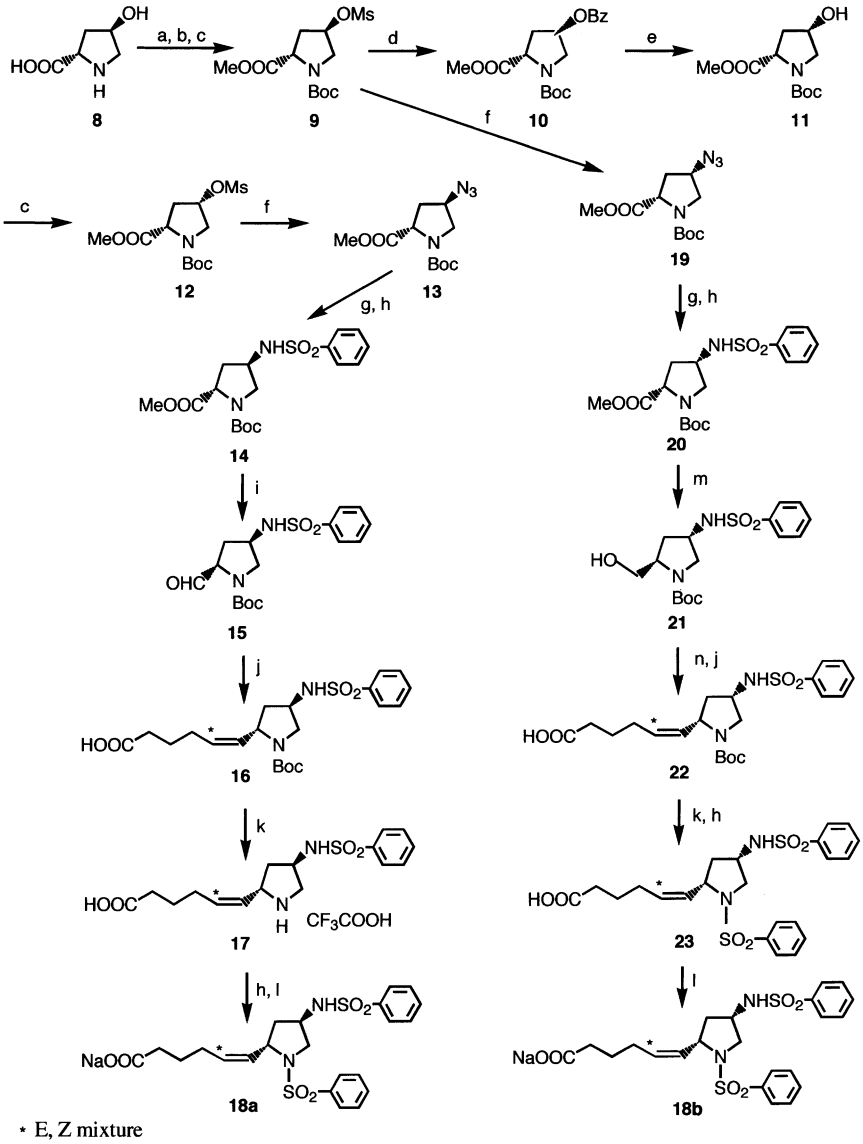
Table 1. In vitro activity on platelet aggregation

Compound	Inhibition of rabbit platelet aggregation (IC_{50}, μM[a])	
	9,11-azo PGH2	ADP
18a	0.57	> 100
18b	100	> 100
18c	2.3	> 100
18d	100	> 100
35	2.4	> 100
16	30	> 100
36	29	> 100
37a	0.17	> 100
37b	0.26	> 100
37c	0.36	> 100
37d	0.66	> 100
37e	0.34	> 100
37f	0.23	> 100
37g	0.16	> 100
50a	0.13	
50b	0.68	> 100
51a	0.055	> 100
51b	0.056	> 100
52	0.14	> 100
53	0.12	> 100
54	0.12	> 100
55	0.23	> 100
58a	0.032	> 100
58b	0.37	> 100
58c	0.31	> 100
58d	3.4	> 100
Daltroban	0.16	> 100

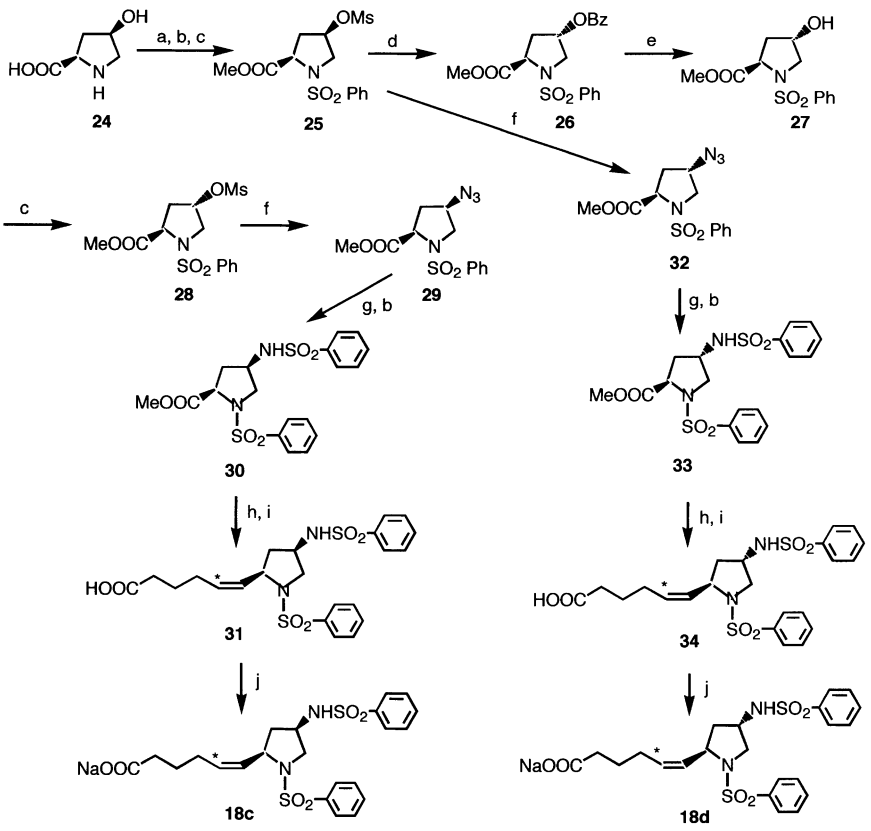
[a]IC_{50} value were calculated by regression analysis from three dose groups, using three different preparations.



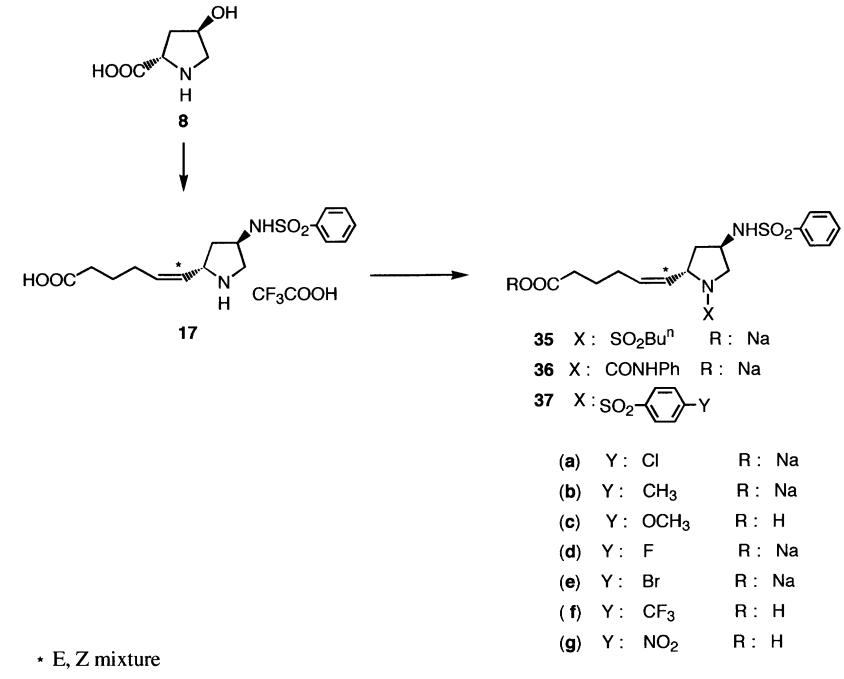
Scheme 1.



Scheme 2. (a) SOCl2, MeOH; (b) Boc_2O, Et_3N, CH_2Cl_2; (c) MsCl, Et_3N, CH_2Cl_2; (d) BzONa, DMSO; (e) K_2CO_3, MeOH; (f) NaN_3, DMSO; (g) H_2-Pd/C, MeOH; (h) $PhSO_2Cl$, Et_3N, CH_2Cl_2; (i) DIBAL, toluene, −78 °C; (j) $HOOC(CH_2)_4P^+Ph_3Br^-$, *t*-BuOK, DMAC; (k) 75% TFA; (l) 1N-NaOH, MeOH; (m) DIBAL, toluene, −25 °C; (n) CrO_3, pyridine, CH_2Cl_2.

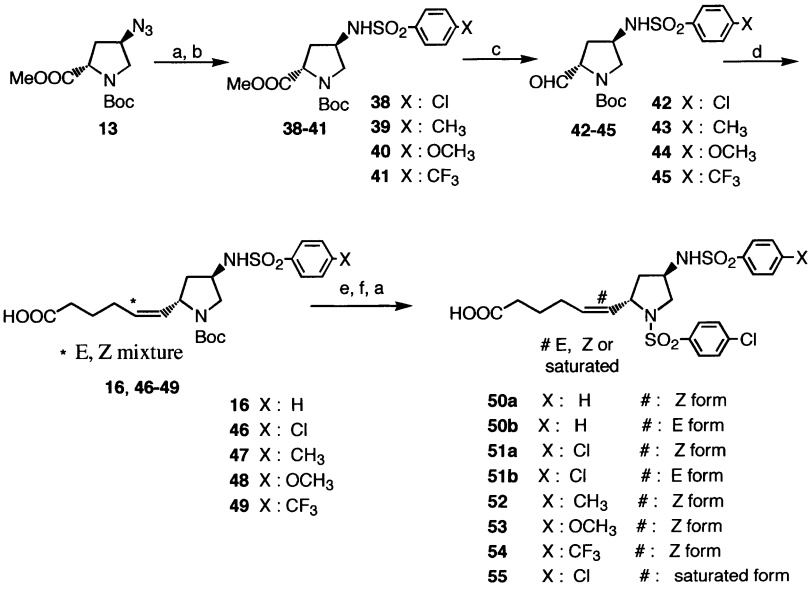


Scheme 3. (a) $SOCl_2$, MeOH; (b) $PhSO_2Cl$, Et_3N, CH_2Cl_2; (c) MsCl, Et_3N, CH_2Cl_2; (d) BzONa, DMSO; (e) K_2CO_3, MeOH; (f) NaN_3, DMSO; (g) H_2-Pd/C, MeOH; (h) DIBAL, toluene, −78 °C; (i) $HOOC(CH_2)_4P^+Ph3Br^-$, *t*-BuOK, DMAC; (j) 1N-NaOH, MeOH.

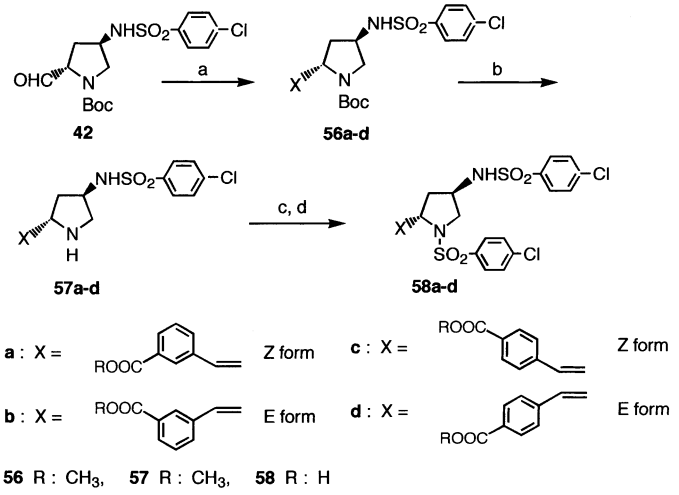


Scheme 4.

than Daltroban. We attempted to design a new compound with a ring system in reference to the conformation and the distance between the nuclear oxygen atoms and allylic alcohol in TXA_2. As a result, we designed the 2-alkenyl-4-aminopyrrolidine skeleton which has two centers of asymmetry at the 2- and 4-positions of the pyrrolidine ring system. Since we cannot predict which stereoisomer would be the most



Scheme 5. (a) H_2-Pd/C, MeOH; (b) *p*-XPhSO2Cl, Et_3N, CH_2Cl_2; (c) DIBAL, CH_2Cl_2; (d) $HOOC(CH_2)_4P^+Ph_3Br^-$, *t*-BuOK, DMAC; (e) 75% TFA; (f) *p*-$ClPhSO_2Cl$, Et_3N, CH_2Cl_2.



Scheme 6. (a) $Ph_3P^+Cl^-CH_2Ph^-$(*m*- or *p*-)COOMe, NaH, THF; (b) 90% TFA; (c) *p*-Cl–$PhSO_2Cl$, Et_3N, CH_2Cl_2; (d) 1N-NaOH, MeOH.

potent TXA_2 receptor antagonist, even in reference to the proposed common spatial pharmacophore[27] for TXA_2 receptor antagonists, we first synthesized all four stereoisomers (**18a**–**18d**) as shown in Scheme 2 and 3.

The target compounds described in Schemes 2 and 3 were evaluated for their ability to inhibit platelet aggregation of rabbit platelet-rich plasma (PRP) induced by 9,11-azo PGH_2[28] (5 μL, final concentration 1.0 μM) or adenosine diphosphate (ADP, 5 μL, final concentration 2.5 μM). The concentrations (IC_{50}) that caused 50% inhibition of platelet aggregation induced by 9,11-azo PGH_2 are shown in Table 1. Consistent with their mechanism of action, none of the compounds was effective in inhibiting ADP induced platelet aggregation.

We confirmed that both **18a** and **18c** displayed TXA_2 receptor antagonistic activity and that the 4*R* form is essential and 2*S* form is preferable for antagonistic activity. Therefore, we fixed the stereochemistry at the 2- and 4-positions of the pyrrolidine ring as 2*S* and 4*R*, respectively, and first synthesized derivatives (**16**, **35**, **36**) with different 1-position substituents on the pyrrolidine ring. As shown in Table 1, the sulfonamide derivative is the most potent and demonstrates that our hypothesis that a molecule with two sulfonamide moieties on a 2-alkenyl-4-aminopyrrolidine skeleton may possess potent TXA_2 receptor antagonistic activity is reasonable.

Since **18a** demonstrated more potent TXA_2 receptor antagonistic activity than **35**, we investigated the substituent group effect in the *para* position of the 1-phenylsulfonamide moiety in **18a** in reference to Daltroban, as shown in Table 1. All compounds (**37a**–**37g**) showed TXA_2 receptor antagonistic activity, but **37a** (*p*-chloro) and **37g** (*p*-nitro) were clearly the most potent. Taking the other biological activities of **37a** and **37g** into consideration, we fixed the 1-phenylsulfonamide moiety as p-chloro and investigated the substituent group effect in the para position of the 4-phenylsulfonamide moiety as

Table 2. Potencies of **51a** for inhibition of [^{3}H]-U-46619 binding to washed guinea-pig platelets

Compound	**51a**
IC_{50}[a]	1.7×10^{-9} M

[a]IC_{50} value were calculated by regression analysis from five dose groups, using three different preparations.

Table 3. In vitro activities of **51a** in various species

Species	Agonist	IC_{50}, M[a]
Human PRP	U-46619	5.8×10^{-8}
	Collagen	3.6×10^{-8}
Monkey PRP	U-46619	4.5×10^{-8}
Dog PRP	Collagen	3.2×10^{-9}
Guinea-pig PRP	U-46619	1.8×10^{-9}
	Collagen	1.5×10^{-9}
Rat aortic strips	U-46619	4.8×10^{-10}

[a]IC_{50} values were calculated by regression analysis from three dose groups, using four different preparations.

shown in Table 1. All compounds (**50a**–**55**) showed TXA_2 receptor antagonistic activity, but **51a** (*p*-chloro) was the most potent among them.

Finally, we fixed the two phenylsulfonamide moieties as p-chloro and then modified the nature of the substituent formally corresponding to the α-heptenoic acid chain. We first evaluated the potency of *cis*- and *trans*- forms (**51a** and **51b**), respectively, and synthesized the saturated form **55**. The activity of **51a** was almost equal to **51b**, whilst the saturated form **55** was less potent than the unsaturated forms. Next, we examined benzoic acid derivatives as a means to fix the conformation of the carboxylic acid. As shown in Table 1, **58a** had the most potent TXA_2 receptor antagonist activity among all compounds, whilst the other compounds (**58b**–**58d**) had decreased potency. These results demonstrated that there is a region which recognizes a double bond in the TXA_2 receptor and that the conformational relationship between the two phenylsulfonamide moieties and the carboxylic acid in **58a** is the most suitable for binding to the TXA_2 receptor.

From these studies, we discovered that 1-phenylsulfonyl-4-phenylsulfonylaminopyrrolidine derivatives based on the structure of Daltroban possess high TXA_2 receptor antagonistic activity and finally selected compound **51a** as a potential drug candidate from in vivo experiments. We examined the biological activities of **51a** as shown in Tables 2–6. In a radioligand binding assay with guinea-pig platelets, we confirmed **51a** inhibited the binding of U-46619,[29] which possesses almost the same agonistic activity[30] as 9,11-azo PGH_2, with an IC_{50} value of 1.7×10^{-9} M and demonstrated high affinity for the TXA_2 receptor (Table 2).

We next evaluated in vitro inhibitory activities against U-46619- and collagen-induced platelet aggregation and aortic strip contraction in various species. As shown in Table 3, **51a** displayed highly specific inhibitory activity, especially against rat aortic strip contraction ($IC_{50}=4.8\times10^{-10}$ M). In addition, we evaluated inhibitory activity against ex vivo platelet aggregation induced by U-46619 or collagen, following oral administration of **51a** to guinea-pigs, and confirmed the potent activity, as shown in Table 4. Especially for 0.32 mg/kg p.o. administration, the inhibitory activity after 6 h is the same as that after 1 h and we confirmed the stability of **51a** in vivo. Furthermore, compound **51a** was effective in the arachidonic acid- induced pulmonary infarction mouse model which is well known for evaluating TXA_2 receptor antagonists and improved the mortality rate apparently (Table 5). In addition, compound **51a** also prevents thrombus formation in the extracorporeal shunt rat model (Table 6). The in vivo stability of the 1-phenylsulfonyl-4-phenylsulfonylaminopyrrolidine skeleton was also demonstrated through these oral administration experiments.

Table 4. Inhibition of ex vivo platelet aggregation by oral administration of **51a** in guinea-pig

mg/kg po	1 h (%)[a]		6 h (%)[a]	
	U-46619	Collagen	U-46619	Collagen
0.032	21	10	NT[b]	NT[b]
0.1	97**	51*	NT[b]	NT[b]
0.32	100**	96**	100**	95**

[a] $*p<0.05$ and $**p<0.01$, compared with control group. Data represents the average percent of inhibition in a group of five animals.

Table 5. Effects of **51a** in the arachidonic acid-induced pulmonary infarction mice model

Compound	**51a**			
Dose (mg/kg, po)	0	0.32	1.0	3.2
Survival rate (%)[a]	0	20	70**	80**

[a] $**p<0.01$, compared with control group. Data represent the survival percent in a group of 10 mice.

Table 6. Effects of **51a** on thrombus formation in extracorporeal shunt in rat

Compound	**51a**			
Dose (mg/kg, po)	0.01	0.032	0.1	0.32
Inhibition (%)[a]	19.5	34.8**	49.7***	63.4***

[a] $**p<0.01$ and $***p<0.005$, compared with control group. Data represent the average percent of inhibition in a group of 10 animals.

Conclusion

We designed a series of1-phenylsulfonyl-4-phenylsulfonylaminopyrrolidines as potent TXA_2 receptor antagonists, and investigated stereochemistry and various modifications of the substituent groups on the two phenylsulfonylamide moieties. Through evaluation of these derivatives, compound **51a** was found to be the most effective inhibitor of 9,11-epoxymethano PGH_2

(U-46619)-induced rat aortic strip contraction ($IC_{50} = 4.8 \times 10^{-10}$ M). Further studies on optimizing this activity will be the subject of subsequent papers.

Experimental

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AM-200 Spectrometer using tetramethylsilane (TMS) or 3-(trimethylsilyl)propionic acid-d_4 sodium salt (TSP-d_4) as an internal reference. The ESI mass spectra (MS) were recorded on a Plateform LC-MS Spectrometer (Micromass) and the ESI-TOF mass spectra were recorded on a Micromass LCT Mass Spectrometer (Micromass). The optical rotations ($[\alpha]_D^{20}$) were recorded on a Jasco automatic photoelectric polarimeter model p-1020. Column chromatography was carried out on Silica gel 60 (E. Merck, 70–200 mesh).

1-*tert*-Butyl 2-methyl (2*S*,4*R*)-4-((methylsulfonyl)oxy)-1,2-pyrrolidinedicarboxylate (9). Methanol (175 mL) was cooled in a dry ice-acetone bath and to the solution was added dropwise thionyl chloride (21.4 mL, 293 mmol) over 30 min. After stirring at the same temperature, to the solution was added portionwise **8** (35.0 g, 267 mmol) and the dry ice–acetone bath was removed. The reaction mixture warmed to room temperature then refluxed gently for 6 h. The solvent was evaporated in vacuo and the residue was filtrated and washed with ether to give 2-methyl (2*S*,4*R*)-4-hydroxy-1,2-pyrrolidinecarboxylate hydrochloride that was dissolved in dichloromethane (350 mL). The solution was cooled in an ice bath then triethylamine (75 mL, 538 mmol) and di-*tert*-butyl dicarbonate (61.4 g, 267 mmol) were added. The reaction mixture was stirred at the same temperature for 4 h. The mixture was washed with diluted hydrochloric acid, water, saturated aqueous sodium hydrogenecarbonate and brine, and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was filtered and washed with n-hexane to give 53.4 g (81.5% from **8**) of 1-*tert*-butyl 2-methyl (2*S*,4*R*)-4-hydroxy-1,2-pyrrolidinedicarboxylate that was dissolved in dichloromethane (500 mL). The solution was cooled in an ice bath then triethylamine (36 mL, 258 mmol) and methanesulfonyl chloride (20.7 mL, 257 mmol) were added and the reaction mixture was stirred at the same temperature for 3 h. The solution was washed successively with diluted hydrochloric acid, saturated aqueous sodium hydrogenecarbonate and brine, and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was crystallized from *n*-hexane to give 56.2 g (65.0% from **8**) of **9** as colorless crystals: mp 73–75 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.43 (6H, s), 1.47 (3H, s), 2.28 (1H, ddd, $J = 5, 8, 14$Hz), 2.63 (1H, m), 3.05 (3H, s), 3.7–3.9 (2H, m), 3.77 (3H, s), 4.41 (0.67H, t, $J = 8$Hz), 4.48 (0.33H, t, $J = 8$Hz), 5.28 (1H, m). ESI-MS m/z 324 $(M+H)^+$. ESITOF-MS m/z 346.0955 $(M+Na)^+$, calcd for $C_{12}H_{21}NO_7SNa$ 346.0936.

1-*tert*-Butyl 2-methyl (2*S*,4S)-4-((benzoyl)oxy)-1,2-pyrrolidinedicarboxylate (10). A mixture of **9** (32.3 g, 100 mmol) and sodium benzoate (28.8 g, 200 mmol) in dimethylsulfoxide (320 mL) was stirred at 90 °C overnight and cooled to room temperature. The mixture was diluted with ethyl acetate (600 mL) and washed successively with water and brine. The organic phase was dried over magnesium sulfate and the solvent was evaporated in vacuo to give an oil. The oil was crystallized from n-hexane to give 31.0g (88.7%) of **10** as colorless crystals: mp 89–90 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.45 (4.5H, s), 1.48 (4.5H, s), 2.4–2.7 (2H, m), 3.68 (1.5H, s), 3.69 (1.5H, s), 3.69 (1H, m), 3.82 (1H, m), 4.48 (0.5H, dd, $J = 2, 11$ Hz), 4.61 (0.5H, dd, $J = 4, 11$ Hz), 5.53 (1H, m), 7.43 (1H, t, $J = 7.5$ Hz), 7.57 (2H, t, $J = 7.5$ Hz), 7.98 (2H, d, $J = 7.5$ Hz). ESI-MS m/z 350 $(M+H)^+$. ESITOF-MS m/z 372.1513 $(M+Na)^+$, calcd for $C_{18}H_{23}NO_6Na$ 372.1423.

1-*tert*-Butyl 2-methyl (2*S*,4S)-4-hydroxy-1,2-pyrrolidinedicarboxylate (11). To a solution of **10** (30 g, 85.9 mmol) in methanol (600 mL) was added potassium carbonate (11.9 g, 86.1 mmol) and the mixture was stirred at room temperature for 1 h. The solution was diluted with ethyl acetate (1 L) and washed with water. The organic phase was washed with brine. The aqueous phase was saturated with sodium chloride, extracted with chloroform and washed with brine. The combined organic extracts were dried over magnesium sulfate and evaporated in vacuo to give an oil. The oil was chromatographed on a silica gel (500 g) column with a mixture of *n*-hexane and ethyl acetate (1:1) as an eluent to give 20.7g (98.4%) of **11** as colorless crystals: mp 59–62 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.45 (5.4H, s), 1.47 (3.6H, s), 2.10 (1H, m), 2.33 (1H, m), 3.5–3.7 (3H, m), 3.78 (1.8H, s), 3.80 (1.2H, s), 4.35 (1H, m). ESI-MS m/z 246 $(M+H)^+$. ESITOF-MS m/z 268.1123 $(M+Na)^+$, calcd for $C_{11}H_{19}NO_5Na$ 268.1161.

1-*tert*-Butyl 2-methyl (2*S*,4S)-4-((methylsulfonyl)oxy)-1,2-pyrrolidinedicarboxylate (12). To a solution of **11** (20.0 g, 81.5 mmol) in dichloromethane (500 mL) were added triethylamine (13.5 mL, 96.9 mmol) and methanesulfonyl chloride (7.4 mL, 95.6 mmol) with stirring in an ice bath and the mixture was stirred at the same temprature for 4 h. The solution was washed successively with diluted hydrochloric acid, saturated aqueous sodium hydrogencarbonate and brine, and dried over magnesium sulfate. The solvent was evaporated in vacuo to give 26.4 g (100%) of **12** as a pale brown oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.43 (5.4H, s), 1.46 (3.6H, s), 2.53 (2H, m), 3.03 (3H, s), 3.76 (3H, s), 3.80 (2H, m), 4.4–4.6 (1H, m), 5.75 (1H, m). ESI-MS m/z 324 $(M+H)^+$.

1-*tert*-Butyl 2-methyl (2*S*,4*R*)-4-azido-1,2-pyrrolidinedicarboxylate (13). A mixture of **12** (26.4 g, 81.5 mmol) and sodium azide (10.6 g, 163 mmol) in dimethyl sulfoxide (350 mL) was stirred at 90 °C overnight and the solution was diluted with ethyl acetate (600 mL). The solution was washed successively with water and brine. The solution was dried over magnesium sulfate and the solvent was evaporated in vacuo to give 20.0 g (90.8%)

of **13** as a pale brown oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.41 (6H, s), 1.47 (3H, s), 2.20 (1H, m), 2.32 (1H, m), 3.4–3.7 (3H, m), 3.76 (3H, s), 4.20 (1H, m), 4.36 (1H, m). ESI-MS *m*/*z* 271 $(M+H)^+$.

1-*tert*-Butyl 2-methyl (2*S*,4*R*)-4-((phenylsulfonyl)amino)-1,2-pyrrolidinedicarboxylate (14). A solution of **13** (19.5 g, 72.1 mmol) in methanol (150 mL) was shaken under hydrogen (3 atm) with 10% palladium on carbon (3.0g) at room temperature for 3 h. After removal of the catalyst by filtration, the solvent was evaporated in vacuo to give 1-*tert*-butyl 2-methyl (2*S*,4*R*)-4-amino-1,2-pyrrolidinedicarboxylate that was dissolved in pyridine (150 mL). The solution was cooled in an ice bath then benzenesulfonyl chloride (11.0 mL, 86.2 mmol) added. The reaction mixture was stirred at the same temperature for 5 h. The solvent was evaporated in vacuo and the residure was dissolved in ethyl acetate (300 mL). The solution was washed successively with water, diluted hydrochloric acid, saturated aqueous sodium hydrogencarbonate and brine, and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was chromatographed on a silica gel column with a mixture of *n*-hexane and ethyl acetate (1:1) as eluent to give 22.5 g (81.2% from **13**) of **14** as colorless crystals: mp 110–111 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.40 (9H, s), 2.0–2.3 (2H, m), 3.17 (1H, dd, J = 5, 11 Hz), 3.59 (1H, m), 3.98 (1H, m), 4.30 (1H, m), 4.82 (1H, m), 7.5–7.7 (3H, m), 8.8–8.9 (2H, m). ESI-MS *m*/*z* 385 $(M+H)^+$. ESITOF-MS *m*/*z* 385.1423 $(M+H)^+$, calcd for $C_{17}H_{25}N_2O_6S$ 385.1433.

1-*tert*-Butyl (2*S*,4*R*)-2-formyl-4-((phenylsulfonyl)amino)-1,2-pyrrolidinecarboxylate (15). To a solution **14** (10.0 g, 26.0 mmol) in toluene (70 mL) was added dropwise 1.0 M solution of diisobutylaluminum hydride in toluene (80 mL, 80.0 mmol) at −78 °C. After the resulting mixture was stirred at the same temperature for 5 h, saturated aqueous potassium sodium tartrate was added to the reaction mixture and the mixture was filtered through Celite. The solid was washed with ethyl acetate and the combined organic solution was washed with brine and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was chromatographed on a silica gel column with a mixture of *n*-hexane and ethyl acetate (2:1–1:2) as eluent to give 8.75 g (95.0%) of **15** as a pale yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.34 (5.4H, s), 1.37 (3.6H, s), 1.94 (2H, m), 3.17 (1H, m), 3.38 (1H, m), 3.67 (1H, m), 4.15 (1H, m), 7.6–7.7 (3H, m), 7.8–7.9 (2H, m), 8.12 (1H, broad), 9.36 (1H, broad). ESI-MS *m*/*z* 355 $(M+H)^+$.

(5*E* and 5*Z*)-6-((2*S*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-((phenylsulfonyl)amino)pyrrolidinyl)-5-hexenoic acid (16). To a solution of (4-carboxybutyl)triphenylphosphonium bromide (18.8 g, 42.4 mmol) in dimethyl sulfoxide (50 mL) was added sodium methylsulfinylmethide [84.8 mmol, prepared from sodium hydride 3.39 g, 60% in oil, 84.8 mmol) and dimethyl sulfoxide (50 mL)] and the solution was stirred at room temperature for 30 min. To the resulting solution was added **15** (5.0 g, 14.1 mmol) in dimethyl sulfoxide (50 mL) and the mixture was stirred at room temperature for 6 h. To the reaction mixture was added water and the aqueous solution was washed with ethyl acetate. The aqueous phase was adjusted to pH 2 with 1 N hydrochloric acid and extracted with ethyl acetate. The organic phase was washed successively with water and brine, and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was chromatographed on a silica gel column with a mixture of chloroform and methanol (25:1) as eluent to give 1.70 g (27.6%) of **16** as a pale yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.36 (9H, s), 1.6–1.8 (3H, m), 2.0–2.2 (3H, m), 2.3–2.4 (2H, m), 3.2–3.5 (2H, m), 3.85 (1H, m), 4.57 (1H, m), 5.1–5.5 (2H, m), 5.72 (1H, broad), 7.3–7.4 (2H, m), 7.4–7.6 (3H, m). ESI-MS *m*/*z* 437 $(M-H)^-$.

(5*E* and 5*Z*)-6-((2*S*,4*R*)-4-((Phenylsulfonyl)amino)pyrrolidinyl)-5-hexenoic acid trifluoroacetate (17). A solution of **16** (1.6 g, 3.65 mmol) in 75% aqueous trifluoroacetic acid (10 mL, 97.4 mmol) was stirred at room temperature for 1 h and the solvent was evaporated in vacuo. To the residue was added toluene (10 mL) and the solvent was evaporated in vacuo to give 1.65 g of **17** (100%) as a brown oil: ^{1}H NMR (200 MHz, D_2O) δ 1.7–1.9 (4H, m), 2.1–2.3 (2H, m), 2.3–2.4 (2H, m), 3.3–3.6 (2H, m), 4.07 (1H, m), 4.46 (1H, m), 4.80 (1H, m), 5.80 (1H, m), 7.5–7.7 (3H, m), 7.8–7.9 (2H, m). ESI-MS *m*/*z* 337 $(M-H)^-$.

Sodium (5*E* and 5*Z*)-6-((2*S*,4*R*)-1-(phenylsulfonyl)-4-((phenylsulfonyl)amino) - 2 - pyrrolidinyl) - 5 - hexenoate (18a). To a solution of **17** (322 mg, 0.712 mmol) in dichloromethane (5.0 mL) was added triethylamine (0.44 mL, 3.15 mmol) and benzenesulfonyl chloride (126 mg, 0.713 mmol) and the mixture was stirred at room temperature for 2 h. The solution was washed successively with diluted hydrochloric acid and brine, and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was chromatographed on a silica gel column with a mixture of chloroform and methanol (40:1) as eluent to give 100 mg of (5*E* and 5*Z*)-6-((2*S*,4*R*)-1-(phenylsulfonyl)-4-((phenylsulfonyl)amino)-pyrrolidinyl)-5-hexenoic acid that was dissolved in a mixture of 1 N sodium hydroxide (0.2 mL, 0.2 mmol) and water (20 mL). The solution was stirred at room temperature for 30min and washed with dichloromethane. The aqueous phase was applied to a column of Diaion HP-20 (trademark, sold by Mitsubishi Chemical Industries Ltd.). The column was washed with water and the object compound was eluted with a mixture of water and methanol (1:1). The organic solvent was removed in vacuo and the aqueous residue was lypholyzed to give 94 mg (26.5% from **17**) of **18a** as a pale yellow powder: ^{1}H NMR (200 MHz, D_2O) δ 1.5–1.7 (2H, m), 1.7–1.8 (2H, m), 1.9–2.1 (2H, m), 2.15 (2H, m), 3.33 (1H, m), 3.57 (1H, m), 3.70 (1H, m), 4.38 (1H, m), 5.3–5.6 (2H, m), 7.5–7.9 (10H, m). ESI-MS *m*/*z* 477 $(M-H)^-$.

1-*tert*-Butyl 2-methyl (2*S*,4S)-4-azido-1,2-pyrrolidinedicarboxylate (19). By the procedure used for **13**, **9** (16.2 g, 50 mmol) and sodium azide (6.5 g, 100 mmol) gave 14.3g (100%) of **19** as a pale brown oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.43 (5.4H, s), 1.48 (3.6H, s), 2.14 (0.4H, t, J = 4 Hz), 2.21 (0.6H, t, J = 4 Hz), 2.47 (1H,

m), 3.50 (1H, m), 3.73 (1H, m), 3.76 (3H, s), 4.14 (1H, m), 4.33 (0.6H, dd, J = 4, 9 Hz), 4.43 (0.4H, dd, J = 4, 9 Hz). ESI-MS m/z 271 $(M+H)^+$.

1-*tert*-Butyl 2-methyl (2*S*,4*S*)-4-((phenylsulfonyl)amino)-1,2-pyrrolidinedicarboxylate (20). By the procedure used for **14**, **19** (14.0 g, 51.8 mmol), 10% palladium on carbon (1.4 g) and benzenesulfonyl chloride (6.61 mL, 51.8 mmol) gave 10.55 g (53.0%) of **20** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.37 (9H, s), 1.7–1.9 (1H, m), 2.81 (1H, m), 3.3–3.5 (2H, m), 3.74 (3H, s), 4.03 (1H, m), 4.20 (1H, m), 5.93 (1H, broad), 7.5–7.6 (3H, m), 7.8–7.9 (2H, m). ESI-MS m/z 385 $(M+H)^+$.

1-*tert*-Butyl (2*S*,4*S*)-2-hydroxymethyl-4-((phenylsulfonyl)-amino)-1,2-pyrrolidinecarboxylate (21). To a solution **20** (10.0 g, 26.0 mmol) in toluene (70 mL) was added dropwise 1.0 M solution of diisobutylaluminum hydride in toluene (70 mL, 70.0 mmol) at −25 °C and the resulting mixture was stirred at the same temperature for 4 h. After saturated aqueous ammonium chloride was added to the reaction mixture and the mixture was stirred at room temperature for 1 h. The mixture was filtered and filtrate was extracted with ethyl acetate. The organic phase was washed with brine and dried over magnesium sulfate. The solvent was evaporated in vacuo to give 9.44 g (100%) of **21** as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.82 (1H, m), 2.23 (1H, m), 3.24 (1H, dd, J = 3, 12 Hz), 3.47 (1H, dd, J = 3.5, 12 Hz), 3.53 (1H, m), 3.8–3.9 (2H, m), 4.03 (1H, dd, J = 2.5, 11 Hz), 7.4–7.6 (3H, m), 7.8–7.9 (2H, m). ESI-MS m/z 357 $(M+H)^+$.

(5*E* and 5*Z*)-6-((2*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-((phenylsulfonyl)amino)pyrrolidinyl)-5-hexenoic acid (22). To a solution of pyridine (8.5 mL, 106 mmol) in dichloromethane (150 mL) was added chromium trioxide (5.55 g, 55.5 mmol) in an ice bath and the mixture was stirred at room temperature for 1 h. To the solution were added Celite and a solution of **21** (3.4 g, 9.54 mmol) in dichloromethane (20 mL) and the mixture was stirred at room temperature for 1 h. After being diluted with a mixture of *n*-hexane and ethyl acetate (1:1, 150 mL), the solution was passed through silica gel and the solvent was evaporated in vacuo to give 3.38 g (100% from **21**) of 1-*tert*-butyl (2*S*,4*S*)-2-formyl-4-((phenylsulfonyl)amino)-1,2-pyrrolidinedicarboxylate. By the procedure used for **16**, 1-*tert*-butyl (2*S*,4*S*)-2-formyl-4-((phenylsulfonyl)amino)-1,2-pyrrolidinedicarboxylate (3.38 g, 9.54 mmol), (4-carboxybutyl)triphenylphosphonium bromide (12.7 g, 28.6 mmol), sodium hydride (2.29 g, 60% in oil, 57.3 mmol) and dimethyl sulfoxide (35 mL) gave 2.20 g (52.7% from **21**) of **22** as a pale brown oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.38 (9H, s), 1.5–1.8 (3H, m), 2.0–2.1 (3H, m), 2.3–2.4 (2H, m), 3.08 (1H, dd, J = 6.5, 10.5 Hz), 3.6–3.8 (2H, m), 4.44 (1H, m), 5.2–5.5 (2H, m), 7.4–7.6 (3H, m), 7.8–7.9 (2H, m). ESI-MS m/z 437 $(M-H)^-$.

(5*E* and 5*Z*)-6-((2*S*,4*S*)-1-(phenylsulfonyl)-4-((phenylsulfonyl)amino)-2-pyrrolidinyl)-5-hexenoic acid (23). By the procedure used for **17**, **22** (264 m g, 0.663 mmol) and 75% aqueous trifluoroacetic acid (2.7 mL, 26.3 mmol) gave 300 mg (100%) of (5*E* and 5*Z*)-6-((2*S*,4*R*)-4-((phenylsulfonyl)amino)pyrrolidinyl) - 5 - hexenoic acid trifluoroacetate. To a solution of (5*E* and 5*Z*)-6-((2*S*,4*R*)-4-((phenylsulfonyl)amino)pyrrolidinyl)-5-hexenoic acid trifluoroacetate (300 mg, 0.663 mmol) in dichloromethane (10 mL) was added triethylamine (0.5 mL, 3.59 mmol) and benzenesulfonyl chloride (0.1 mL, 0.784 mmol) and the mixture was stirred at room temperature for 6 h. The solution was washed successively with diluted hydrochloric acid and brine, and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was chromatographed on a silica gel column with a mixture of chloroform and methanol (30:1) as eluent to give 114 mg (35.9% from **22**) of **23** as an oil: ^{1}H NMR (200 MHz, D_2O) δ 1.5–1.9 (3H, m), 2.0–2.3 (3H, m), 2.39 (2H, t), 3.1–3.2 (1H, m), 3.4–3.6 (1H, m), 4.32 (1H, m), 4.89 (1H, m), 5.3–5.5 (2H, m), 7.5–7.7 (6H, m), 7.7–7.9 (4H, m). ESI-MS m/z 477 $(M-H)^-$.

Sodium (5*E* and 5*Z*)-6-((2*S*,4*S*)-1-(phenylsulfonyl)-4-((phenylsulfonyl)amino) - 2 - pyrrolidinyl) - 5 - hexenoate (18b). By the procedure used for **18a**, **23** (114 mg, 0.238 mmol) and 1 N sodium hydroxide (1 mL, 1.0 mmol) gave 80 mg (67.2%) of **18b** as a pale yellow powder: ^{1}H NMR (200 MHz, D_2O) δ 1.4–1.7 (4H, m), 2.0–2.2 (4H, m), 2.9–3.2 (3H, m), 3.37 (1H, dd, J = 6, 12 Hz), 4.28 (1H, m), 5.4–5.5 (2H, m), 7.6–7.8 (10H, m). ESI-MS m/z 477 $(M-H)^-$.

2-Methyl (2*R*,4*R*)-4-((methylsulfonyl)oxy)-1-(phenylsulfonyl)-2-pyrrolidinecarboxylate (25). Methanol (10 mL) was cooled in a dry ice-acetone bath and to the solution was added dropwise thionyl chloride (1.22 mL, 16.7 mmol) over 10 min. After stirring at the same temperature, to the solution was added portionwise **24** (2.0 g, 15.2 mmol) and the dry ice-acetone bath was removed. The reaction mixture warmed to room temperature then refluxed gently for 6 h. The solvent was evaporated in vacuo and the residue was filtrated and washed with ether to give 2-methyl (2*R*,4*R*)-4-hydroxy-1,2-pyrrolidinecarboxylate hydrochloride that was dissolved in dichloromethane (20 mL). The solution was cooled in an ice bath then triethylamine (4.22 mL, 30.4 mmol) and benzenesulfonyl chloride (1.94 mL, 15.2 mmol) were added. The reaction mixture was stirred at the same temperature for 3 h. The mixture was washed with diluted hydrochloric acid, water, saturated aqueous sodium hydrogenecarbonate and brine, and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was filtered and washed with *n*-hexane to give 1-*tert*-butyl 2-methyl (2*R*,4*R*)-4-hydroxy-1,2-pyrrolidinedicarboxylate that was dissolved in dichloromethane (20 mL). The solution was cooled in an ice bath then triethylamine (2.11 mL, 15.2 mmol) and methanesulfonyl chloride (1.18 mL, 15.2 mmol) were added and the reaction mixture was stirred at the same temperature for 30 min. The solution was washed successively with diluted hydrochloric acid, saturated aqueous sodium hydrogenecarbonate and brine, and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was crystallized from *n*-hexane to give 5.10g (94.4% from **24**) of **25** as white crystals: mp 114–116 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.32 (1H, ddd, J = 4.5, 9, 13.5 Hz), 2.58 (1H, m), 2.84 (3H, s), 3.79 (3H, s), 3.7–3.8 (2H, m), 4.46 (1H, t, J = 12

Hz), 5.23 (1H, m), 7.5–7.7 (3H, m), 7.9–8.0 (2H, m). ESI-MS m/z 364 $(M+H)^+$. ESITOF-MS m/z 386.0262 $(M+Na)^+$, calcd for $C_{13}H_{17}NO_7S_2Na$ 386.0344.

2-Methyl (2*R*,4*S*)-4-(benzoyloxy)-1-(phenylsulfonyl)-2-pyrrolidinecarboxylate (26). By the procedure used for **10**, **25** (2.42 g, 6.65 mmol) and sodium benzoate (1.92 g, 13.3 mmol) gave 1.84 g (71.1%) of **26** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.35 (1H, ddd, J = 4, 9.5, 14 Hz), 2.52 (1H, dt, J = 14, 3 Hz), 3.78 (1H, m), 3.80 (3H, s), 3.89 (1H, dd, J = 3.5, 12.5 Hz), 4.42 (1H, dd, J = 8, 9.5 Hz), 5.41 (1H, m), 7.3–7.4 (5H, m), 7.5–7.6 (3H, m), 7.8–7.9 (2H, m). ESI-MS m/z 390 $(M+H)^+$.

2-Methyl (2*R*,4*S*)-4-hydroxy-1-(phenylsulfonyl)-2-pyrrolidinecarboxylate (27). By the procedure used for **11**, **26** (1.84 g, 4.72 mmol) and potassium carbonate (654 mg, 4.72 mmol) gave 1.11 g (82.5%) of **27** as colorless crystals: mp 114–117 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.12 (1H, ddd, J = 4.5, 9, 13.5 Hz), 2.24 (1H, m), 3.43 (1H, dt, J = 11.5, 2 Hz), 3.62 (1H, dd, J = 4, 11.5 Hz), 3.75 (3H, s), 4.45 (1H, t, J = 9 Hz), 4.47 (1H, m), 7.5–7.7 (3H, m), 7.9–8.0 (2H, m). ESI-MS m/z 286 $(M+H)^+$. ESITOF-MS m/z 308.0516 $(M+Na)^+$, calcd for $C_{12}H_{15}NO_5SNa$ 308.0569.

2-Methyl (2*R*,4*S*)-4-((methylsulfonyl)oxy)-1-(phenylsulfonyl)-2-pyrrolidinecarboxylate (28). By the procedure used for **12**, **27** (1.09 g, 3.82 mmol), triethylamine (0.54 mL, 3.87 mmol) and methanesulfonyl chloride (0.3 mL, 3.88 mmol) gave 1.73 g (100%) of **28** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.30 (1H, ddd, J = 4.5, 9, 13.5 Hz), 2.58 (1H, m), 3.82 (3H, s), 3.7–3.9 (2H, m), 3.77 (3H, s), 4.45 (1H, t, J = 8 Hz), 5.23 (1H, m), 7.5–7.7 (3H, m), 7.9–8.0 (2H, m). ESI-MS m/z 364 $(M+H)^+$. ESITOF-MS m/z 364.0458 $(M+H)^+$, calcd for $C_{13}H_{18}NO_7S_2$ 364.0524.

2-Methyl (2*R*,4*R*)-4-azido-1-(phenylsulfonyl)-2-pyrrolidinecarboxylate (29). By the procedure used for **13**, **28** (1.39 g, 3.82 mmol) and sodium azide (497 mg, 7.64 mmol) gave 1.15 g (97.0%) of **29** as a pale yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.2–2.4 (2H, m), 3.35 (1H, dd, J = 4, 11 Hz), 3.67 (1H, dd, J = 5.5, 11 Hz), 3.73 (3H, s), 4.10 (1H, m), 4.56 (1H, dd, J = 4, 8.5 Hz), 7.5–7.7 (3H, m), 7.9–8.0 (2H, m). ESI-MS m/z 311 $(M+H)^+$. ESITOF-MS m/z 311.0841 $(M+H)^+$, calcd for $C_{12}H_{15}N_4O_4S$ 311.0814.

2-Methyl (2*R*,4*R*)-1-(phenylsulfonyl)-4-((phenylsulfonyl)-amino)-2-pyrrolidinecarboxylate (30). By the procedure used for **14**, **29** (1.0 g, 3.22 mmol), 10% palladium on carbon (200 mg) and benzenesulfonyl chloride (0.41 mL, 3.22 mmol) gave 1.05 g (76.8%) of **30** as white crystals: mp 110–111 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.83 (1H, m), 2.18 (1H, ddd, J = 6, 10, 15 Hz), 3.2–3.3 (2H, m), 3.77 (3H, s), 4.04 (1H, m), 4.23 (1H, dd, J = 2, 6 Hz), 5.97 (1H, d, J = 10 Hz), 7.4-7.7 (6H, m), 7.7-7.9 (4H, m). ESI-MS m/z 425 $(M+H)^+$. ESITOF-MS m/z 425.0797 $(M+H)^+$, calcd for $C_{18}H_{21}N_2O_6S_2$ 425.0763.

(5*E* and 5*Z*)-6-((2*R*,4*R*)-1-(phenylsulfonyl)-4-((phenylsulfonyl)amino)pyrrolidinyl)-5-hexenoic acid (31). By the procedure used for **15** and **16**, **30** (1.0 g, 2.36 mmol), 1.0 M solution of diisobutylaluminum hydride in toluene (3 mL, 3.0 mmol), (4-carboxybutyl)triphenylphosphonium bromide (566 mg, 7.08 mmol) and sodium methylsulfinylmethide [14.2 mmol, prepared from sodium hydride 3.39 g, 60% in oil, 14.2 mmol) and dimethyl sulfoxide (10 mL)] gave 207 mg (18.3%) of **31** as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.4–1.8 (3H, m), 2.0–2.2 (3H, m), 2.38 (2H, m), 3.13 (1H, m), 3.50 (2H, m), 4.30 (1H, m), 4.92 (1H, d, J = 6.5 Hz), 5.3–5.5 (2H, m), 7.4–7.7 (6H, m), 7.7–7.9 (4H, m). ESI-MS m/z 477 $(M-H)^-$.

Sodium (5*E* and 5*Z*)-6-((2*R*,4*R*)-1-(phenylsulfonyl)-4-((phenylsulfonyl)amino) - 2 - pyrrolidinyl) - 5 - hexenoate (18c). By the procedure used for **18a**, **31** (200 mg, 0.418 mmol) and 1 N sodium hydroxide (1 mL, 1.0 mmol) gave 112 mg (54.5%) of **18c** as a pale yellow powder: ^{1}H NMR (200 MHz, D_2O) δ 1.4–1.7 (4H, m), 2.0–2.2 (4H, m), 2.9–3.2 (2H, m), 3.37 (1H, m), 4.28 (1H, m), 5.4–5.6 (2H, m), 7.5–7.8 (10H, m). ESI-MS m/z 477 $(M-H)^-$.

2-Methyl (2*R*,4S)-4-azido-1-(phenylsulfonyl)-2-pyrrolidinecarboxylate (32). By the procedure used for **13**, **25** (2.42 g, 6.65 mmol) and sodium azide (865 mg, 13.3 mmol) gave 1.88 g (91.0%) of **32** as pale yellow crystals: mp 97–99 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.23 (2H, m), 3.47 (1H, dd, J = 3, 12 Hz), 3.76 (1H, dd, J = 5, 12 Hz), 3.78 (3H, s), 4.25 (1H, m), 4.35 (1H, t, J = 7 Hz), 7.5–7.7 (3H, m), 7.9–8.0 (2H, m). ESI-MS m/z 311 $(M+H)^+$. ESITOF-MS m/z 333.0630 $(M+Na)^+$, calcd for $C_{12}H_{14}N_4O_4SNa$ 333.0633.

2-Methyl (2*R*,4S)-1-(phenylsulfonyl)-4-((phenylsulfonyl)amino)-2-pyrrolidinecarboxylate (33). By the procedure used for **14**, **32** (1.80 g, 5.80 mmol), 10% palladium on carbon (500 mg) and benzenesulfonyl chloride (0.74 mL, 5.80 mmol) gave 1.02 g (41.4%) of **33** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.1–2.2 (2H, m), 3.18 (1H, dd, J = 3, 12 Hz), 3.50 (1H, dd, J = 5, 12 Hz), 3.77 (3H, s), 3.99 (1H, m), 4.42 (1H, dd, J = 5, 8 Hz), 4.75 (1H, d, J = 7 Hz), 7.5–7.7 (6H, m), 7.8–7.9 (4H, m). ESI-MS m/z 425 $(M+H)^+$.

(5*E* and 5*Z*)-6-((2*R*,4*S*)-1-(phenylsulfonyl)-4-((phenylsulfonyl)amino)pyrrolidinyl)-5-hexenoic acid (34). By the procedure used for **15** and **16**, **33** (1.0 g, 2.36 mmol), 1.0 M solution of diisobutylaluminum hydride in toluene (4 mL, 4.0 mmol), (4-carboxybutyl)triphenylphosphonium bromide (3.14 g, 7.08 mmol) and sodium methylsulfinylmethide [14.2 mmol, prepared from sodium hydride 566 mg, 60% in oil, 14.2 mmol) and dimethyl sulfoxide (10 mL)] gave 542 mg (48.0%) of **34** as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.5–1.8 (2H, m), 1.9–2.0 (1H, m), 2.12 (1H, m), 2.2–2.4 (2H, m), 3.4–3.5 (2H, m), 3.68 (1H, m), 4.45 (1H, m), 5.2–5.5 (2H, m), 6.27 (1H, d, J = 6 Hz), 7.4–7.6 (6H, m), 7.6–7.9 (4H, m). ESI-MS m/z 477 $(M-H)^-$.

Sodium (5*E* and 5*Z*)-6-((2*R*,4S)-1-(phenylsulfonyl)-4-((phenylsulfonyl)amino) - 2 - pyrrolidinyl) - 5 - hexenoate (18d). By the procedure used for **18a**, **34** (500 mg, 1.04 mmol) and 1 N sodium hydroxide (2 mL, 2.0 mmol) gave 100 mg (19.1%) of **18d** as a pale yellow powder: ^{1}H NMR (200 MHz, D_2O) δ 1.5–1.7 (2H, m), 1.81 (1H, m),

2.03 (1H, m), 2.1–2.2 (2H, m), 3.40 (1H, m), 3.56 (1H, dd, J = 4.5, 11.5 Hz), 3.70 (1H, m), 4.38 (1H, m), 5.3–5.6 (2H, m), 7.5–7.9 (10H, m). ESI-MS m/z 477 $(M-H)^-$.

Sodium (5*E* and 5*Z*)-6-((2*S*,4*R*)-1-(*n*-butylsulfonyl)-4-((phenylsulfonyl)amino)-2-pyrrolidinyl)-5-hexenoate (35). By the procedure used for **18a**, **17** (368 mg, 0.813 mmol), triethylamine (0.26 mL, 1.87 mmol), *n*-butylsulfonyl chloride (0.117 mL, 0.902 mmol) and 1 N sodium hydroxide (0.91 mL, 0.91 mmol) gave 32 mg (8.2%) of **35** as a white powder: mp 96–98 °C. ^{1}H NMR (200 MHz, D_2O) δ 0.78 (3H, t, J = 7 Hz), 1.2–1.4 (2H, m), 1.4–1.7 (5H, m), 1.8–2.1 (5H, m), 2.86 (1H, m), 3.03 (2H, m), 3.24 (1H, m), 3.56 (1H, m), 4.50 (1H, m), 5.2–5.4 (2H, m), 7.4–7.5 (3H, m), 7.6–7.7 (2H, m). ESI-MS m/z 457 $(M-H)^-$.

Sodium (5*E* and 5*Z*)-6-((2*S*,4*R*)-1-(anilinocarbonyl)-4-((phenylsulfonyl)amino)-2-pyrrolidinyl)-5-hexenoate (36). By the procedure used for **18a**, **17** (226 mg, 0.50 mmol), triethylamine (0.153 mL, 1.1 mmol), phenyl isocyanate (0.06 mL, 0.55 mmol) and 1 N sodium hydroxide (0.55 mL, 0.55 mmol) gave 51 mg (21.3%) of **36** as a pale yellow powder: mp 214–218 °C. ^{1}H NMR (200 MHz, D_2O) δ 1.5–1.7 (2H, m), 1.78 (1H, m), 2.0–2.2 (5H, m), 3.28 (1H, dd, J = 5, 11 Hz), 3.57 (1H, dd, J = 6, 11 Hz), 3.88 (1H, m), 4.72 (1H, m), 5.3–5.6 (2H, m), 7.1–7.3 (3H, m), 7.3–7.4 (2H, m), 7.5–7.6 (3H, m), 7.8–7.9 (2H, m). ESI-MS m/z 456 $(M-H)^-$.

Sodium (5*E* and 5*Z*)-6-((2*S*,4*R*)-1-((4-chlorophenyl)sulfonyl)-4-((phenylsulfonyl)amino)-2-pyrrolidinyl)-5-hexenoate (37a). By the procedure used for **18a**, **17** (441 mg, 0.975 mmol), triethylamine (0.30 mL, 2.15 mmol), 4-chlorobenzenesulfonyl chloride (211 mg, 1.00 mmol) and 1 N sodium hydroxide (1.1 mL, 1.1 mmol) gave 90.5 mg (17.4%) of **37a** as a white powder: mp 103–110 °C. ^{1}H NMR (200 MHz, D_2O) δ 1.4–1.6 (2H, m), 1.74 (1H, m), 1.89 (1H, m), 1.9–2.1 (2H, m), 2.12 (2H, m), 3.2–3.5 (2H, m), 3.62 (1H, m), 4.42 (1H, m), 5.1–5.3 (1H, m), 5.3–5.6 (1H, m), 7.4–7.7 (9H, m). ESI-MS m/z 511 $(M-H)^-$.

Sodium (5*E* and 5*Z*)-6-((2*S*,4*R*)-1-((4-methylphenyl)sulfonyl)-4-((phenylsulfonyl)amino)-2-pyrrolidinyl)-5-hexenoate (37b). By the procedure used for **18a**, **17** (606 mg, 1.34 mmol), triethylamine (0.56 mL, 4.02 mmol), *p*-toluenesulfonyl chloride (256 mg, 1.34 mmol) and 1 N sodium hydroxide (1.47 mL, 1.47 mmol) gave 96 mg (13.9%) of **37b** as a white powder: mp 109–113 °C. ^{1}H NMR (200 MHz, D_2O) δ 1.5–1.7 (3H, m), 1.7–1.9 (2H, m), 1.9–2.1 (2H, m), 2.1–2.2 (2H, m), 2.47 (3H, s), 3.53 (1H, m), 3.68 (1H, m), 4.33 (1H, m), 5.3–5.6 (2H, m), 7.4–7.8 (9H, m). ESI-MS m/z 491 $(M^-H)^-$.

(5*E* and 5*Z*)-6-((2*S*,4*R*)-1-((4-methoxyphenyl)sulfonyl)-4-((phenylsulfonyl)amino)-2-pyrrolidinyl)-5-hexenoic acid (37c). By the procedure used for **23**, **17** (665 mg, 1.47 mmol), triethylamine (0.62 mL, 4.45 mmol), 4-methoxybenzenesulfonyl chloride (304 mg, 1.47 mmol) gave 333 mg (44.5%) of **37c** as colorless crystals: mp 130–131 °C. ^{1}H NMR (200 MHz, D_2O–NaOD) δ 1.3–1.4 (4H, m), 1.7–2.0 (4H, m), 2.58 (1H, m), 3.19 (1H, m), 3.47 (1H, m), 3.76 (3H, s), 4.20 (1H, m), 4.9–5.2 (2H, m), 6.9–7.0 (2H, m), 7.3–7.4 (2H, m), 7.5–7.6 (4H, m). ESI-MS m/z 507 $(M-H)^-$.

Sodium (5*E* and 5*Z*)-6-((2*S*,4*R*)-1-((4-fluorophenyl)sulfonyl)-4-((phenylsulfonyl)amino)-2-pyrrolidinyl)-5-hexenoate (37d). By the procedure used for **18a**, **17** (995 mg, 2.20 mmol), triethylamine (0.62 mL, 4.45 mmol), 4-fluorobenzenesulfonyl chloride (428 mg, 2.20 mmol) and 1 N sodium hydroxide (2.42 mL, 2.42 mmol) gave 289 mg (25.4%) of **37d** as a white powder: mp 94–98 °C. ^{1}H NMR (200 MHz, D_2O) δ 1.3–1.6 (4H, m), 1.72 (1H, m), 1.8–2.1 (3H, m), 2.70 (1H, m), 3.22 (1H, m), 3.47 (1H, m), 4.36 (1H, m), 5.3–5.7 (2H, m), 7.3–7.4 (5H, m), 7.5–7.6 (2H, m), 7.7–7.8 (2H, m). ESI-MS m/z 495 $(M-H)^-$.

Sodium (5*E* and 5*Z*)-6-((2*S*,4*R*)-1-((4-bromophenyl)sulfonyl) - 4 - ((phenylsulfonyl)amino)-2-pyrrolidinyl)-5-hexenoate (37e). By the procedure used for **18a**, **17** (990 mg, 2.20 mmol), triethylamine (0.62 mL, 4.45 mmol), 4-bromobenzenesulfonyl chloride (562 mg, 2.20 mmol) and 1 N sodium hydroxide (2.42 mL, 2.42 mmol) gave 308 mg (24.3%) of **37e** as a white powder: mp 108–112 °C. ^{1}H NMR (200 MHz, D_2O) δ 1.4–1.7 (3H, m), 1.8–2.2 (6H, m), 3.51 (1H, m), 3.64 (1H, m), 4.37 (1H, m), 5.3–5.6 (2H, m), 7.6–7.9 (5H, m). ESI-MS m/z 556 $(M-H)^-$.

(5*E* and 5*Z*)-6-((2*S*,4*R*)-4-((phenylsulfonyl)amino)-1-((4-(trifluoromethyl)phenyl)sulfonyl) - 2 - pyrrolidinyl)-5-hexenoic acid (37f). By the procedure used for **23**, **17** (904 mg, 2.00 mmol), triethylamine (0.62 mL, 4.45 mmol), 4-(trifluoromethyl)benzenesulfonyl chloride (489 mg, 2.00 mmol) gave 215 mg (19.7%) of **37f** as colorless crystals: mp 108–110 °C. ^{1}H NMR (200 MHz, D_2O–NaOD) δ 1.5–1.7 (3H, m), 1.7–1.9 (2H, m), 1.9–2.2 (4H, m), 3.34 (1H, m), 3.49 (1H, m), 4.43 (1H, m), 5.3–5.6 (2H, m), 7.3–7.5 (3H, m), 7.6–8.0 (6H, m). ESI-MS m/z 545 $(M-H)^-$.

(5*E* and 5*Z*)-6-((2*S*,4*R*)-1-((4-nitrophenyl)sulfonyl)-4-((phenylsulfonyl)amino)-2-pyrrolidinyl)-5-hexenoic acid (37g). By the procedure used for **23**, **17** (998 mg, 2.20 mmol), triethylamine (0.62 mL, 4.45 mmol), 4-nitrobenzenesulfonyl chloride (488 mg, 2.20 mmol) gave 193 mg (16.7%) of **37g** as colorless crystals: mp 132–134 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.6–1.9 (3H, m), 1.9–2.1 (2H, m), 2.1–2.2 (2H, m), 2.3–2.4 (2H, m), 3.42 (1H, m), 3.63 (1H, m), 4.57 (1H, m), 5.3–5.6 (2H, m), 7.4–7.6 (3H, m), 7.7–7.8 (2H, m), 7.9–8.0 (2H, m), 8.3–8.4 (2H, m). ESI-MS m/z 522 $(M-H)^-$.

1-*tert*-Butyl 2-methyl (2*S*,4*R*)-4-(((4-chlorophenyl)sulfonyl)amino)-1,2-pyrrolidinedicarboxylate (38). By the procedure used for **14**, **13** (7.27 g, 26.9 mmol), 10% palladium on carbon (1.12 g) and 4-chlorobenzenesulfonyl chloride (6.26 g, 29.7 mmol) gave 9.13 g (81.0%) of **38** as a pale yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.37 (6H, s), 1.40 (3H, s), 2.0–2.4 (2H, m), 3.20 (1H, m), 3.63 (1H, m), 3.72 (3H, s), 3.95 (1H, m), 4.30 (1H, m), 5.0–5.2 (1H, m), 7.52 (2H, d, J = 10 Hz), 7.83 (2H, d,J = 10 Hz). ESI-MS m/z 419 $(M+H)^+$.

1-*tert*-Butyl 2-methyl (2*S*,4*R*)-4-(((4-methylphenyl)sulfonyl)amino)-1,2-pyrrolidinedicarboxylate (39). By the procedure used for **14**, **13** (5.12 g, 18.9 mmol), 10% palladium on carbon (787 mg) and p-toluenesulfonyl chloride (3.98 g, 20.9 mmol) gave 5.38 g (%) of **39** as a pale yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.40 (9H, s), 2.1–2.3 (2H, m), 2.45 (3H, s), 3.19 (1H, m), 3.60 (1H, dd, J = 6, 11 Hz), 3.71 (3H, s), 3.94 (1H, m), 4.30 (1H, m), 5.20 (1H, m), 7.34 (2H, d, J = 8 Hz), 7.77 (2H, d, J = 8 Hz). ESI-MS m/z 399 $(M+H)^+$.

1-*tert*-Butyl 2-methyl (2*S*,4*R*)-4-(((4-methoxyphenyl)sulfonyl)amino)-1,2-pyrrolidinedicarboxylate (40). By the procedure used for **14**, **13** (7.00 g, 25.9 mmol), 10% palladium on carbon (1.5 g) and 4-methoxybenzenesulfonyl chloride (6.42 g, 31.1 mmol) gave 8.60g (80.1%) of **40** as a pale yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.48 (9H, s), 2.1–2.3 (2H, m), 3.18 (1H, m), 3.59 (1H, dd, J = 6, 11 Hz), 3.70 (3H, s), 3.88 (3H, s), 3.90 (1H, m), 4.28 (1H, m), 5.40 (1H, m), 6.98 (2H, d, J = 8 Hz), 7.80 (2H, d, J = 8 Hz). ESI-MS m/z 415 $(M+H)^+$.

1-*tert*-Butyl 2-methyl (2*S*,4*R*)-4-(((4-(trifluoromethyl)-phenyl)sulfonyl)amino)-1,2-pyrrolidinedicarboxylate (41). By the procedure used for **14**, **13** (6.00 g, 22.2 mmol), 10% palladium on carbon (1.0g) and 4-(trifluoromethyl)benzenesulfonyl chloride (6.51 g, 26.6 mmol) gave 6.40 g (63.7%) of **41** as a pale yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.39 (9H, s), 2.0–2.2 (2H, m), 2.30 (1H, m), 3.2–3.4 (1H, m), 3.73 (3H, s), 3.98 (1H, m), 4.33 (1H, m), 7.82 (2H, d, J = 8 Hz), 8.04 (2H, d, J = 8 Hz). ESI-MS m/z 453 $(M+H)^+$.

1-*tert*-Butyl (2*S*,4*R*)-2-formyl-4-(((4-chlorophenyl)sulfonyl)amino)-1,2-pyrrolidinecarboxylate (42). By the procedure used for **15**, **38** (9.01 g, 21.5 mmol) and 1.0M solution of diisobutylaluminum hydride in toluene (38.7 mL, 38.7 mmol) gave 5.51 g (65.9%) of **42** as pale yellow crystals: mp 120–122 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.43 (9H, s), 2.16 (2H, m), 3.33 (1H, m), 3.60 (1H, m), 3.85 (1H, m), 4.26 (1H, m), 4.87 (1H, m), 7.53 (2H, d, J = 10 Hz), 7.82 (2H, d, J = 10 Hz), 9.4–9.6 (1H, m). ESI-MS m/z 389 $(M+H)^+$.

1-*tert*-Butyl (2*S*,4*R*)-2-formyl-4-(((4-methylphenyl)sulfonyl)amino)-1,2-pyrrolidinecarboxylate (43). By the procedure used for **15**, **39** (5.00 g, 12.6 mmol) and 1.0M solution of diisobutylaluminum hydride in toluene (25.2 mL, 25.2 mmol) gave 3.42 g (74.0%) of **43** as a pale yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.40 (9H, s), 2.13 (1H, m), 2.47 (3H, s), 3.32 (1H, m), 3.57 (1H, m), 3.82 (1H, m), 4.25 (1H, m), 5.10 (1H, m), 7.34 (2H, d, J = 8 Hz), 7.75 (2H, d, J = 8 Hz), 9.50 (1H, broad). ESI-MS m/z 369 $(M+H)^+$.

1-*tert*-Butyl (2*S*,4*R*)-2-formyl-4-(((4-methoxyphenyl)sulfonyl)amino)-1,2-pyrrolidinecarboxylate (44). By the procedure used for **15**, **40** (8.00 g, 22.9 mmol) and 1.0 M solution of diisobutylaluminum hydride in toluene (45.8 mL, 45.8 mmol) gave 6.00 g (80.9%) of **44** as a pale yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.42 (9H, s), 1.88 (1H, m), 2.12 (1H, m), 3.15 (1H, m), 3.7-4.0 (2H, m), 3.88 (3H, s), 4.93 (1H, m), 5.38 (1H, m), 7.02 (2H, d, J = 8 Hz), 7.25–7.35 (2H, m), 9.44 (1H, broad). ESI-MS m/z 385 $(M+H)^+$.

1-*tert*-Butyl (2*S*,4*R*)-2-formyl-4-(((4-(trifluoromethyl)-phenyl)sulfonyl)amino)-1,2-pyrrolidinecarboxylate (45). By the procedure used for **15**, **41** (6.00 g, 13.3 mmol) and 1.0 M solution of diisobutylaluminum hydride in toluene (30.9 mL, 30.9 mmol) gave 5.20 g (92.8%) of **45** as a pale yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.42 (9H, s), 2.1–2.3 (2H, m), 3.3–3.6 (1H, m), 3.83 (1H, m), 4.05 (1H, m), 4.22 (1H, m), 5.47 (1H, m), 7.81 (2H, d, J = 8 Hz), 8.00 (2H, d, J = 8 Hz), 9.47 (1H, m). ESI-MS m/z 423 $(M+H)^+$.

(5*E* and 5*Z*)-6-((2*S*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-(((4-chlorophenyl)sulfonyl)amino)pyrrolidinyl) - 5 - hexenoic acid (46). By the procedure used for **16**, **42** (5.06 g, 13.0 mmol), (4-carboxybutyl)triphenylphosphonium bromide (17.3 g, 39.0 mmol), sodium hydride (3.12 g, 60% in oil, 78.0 mmol) and dimethyl sulfoxide (45 mL) gave 6.15 g (100%) of **46** as a pale brown oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.38 (6H, s), 1.39 (3H, s), 1.7–1.8 (2H, m), 2.0–2.2 (4H, m), 2.3–2.5 (2H, m), 3.30 (1H, m), 3.45 (1H, dd, J = 5, 12 Hz), 3.86 (1H, m), 4.58 (1H, m), 5.2–5.5 (3H, m), 7.52 (1H, d, J = 10 Hz), 7.83 (1H, d, J = 10 Hz). ESI-MS m/z 471 $(M-H)^-$.

(5*E* and 5*Z*)-6-((2*S*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-(((4-methylphenyl)sulfonyl)amino)pyrrolidinyl) - 5 - hexenoic acid (47). By the procedure used for **16**, **43** (3.00 g, 8.17 mmol), (4-carboxybutyl)triphenylphosphonium bromide (10.9 g, 24.5 mmol), sodium hydride (1.96 g, 60% in oil, 49.0 mmol) and dimethyl sulfoxide (30 mL) gave 2.90 g (68.5%) of **47** as a pale brown oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.41 (9H, s), 1.65–1.85 (3H, m), 2.05–2.25 (2H, m), 2.3–2.45 (3H, m), 2.45 (3H, s), 3.25–3.5 (1H, m), 3.6–3.9 (1H, m), 4.4–4.65 (1H, m), 5.25–5.5 (2H, m), 7.34 (2H, J = 8 Hz), 7.78 (1H, d, J = 8 Hz). ESI-MS m/z 451 $(M-H)^-$.

(5*E* and 5*Z*)-6-((2*S*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-(((4-methoxyphenyl)sulfonyl)amino)pyrrolidinyl) - 5 - hexenoic acid (48). By the procedure used for **16**, **44** (5.50 g, 14.3 mmol), (4-carboxybutyl)triphenylphosphonium bromide (19.0 g, 42.9 mmol), sodium hydride (3.43 g, 60% in oil, 85.8 mmol) and dimethyl sulfoxide (50 mL) gave 5.24 g (78.2%) of **48** as a pale brown oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.39 (9H, s), 1.6–1.8 (3H, m), 2.0–2.2 (2H, m), 2.25–2.45 (3H, m), 3.35–3.5 (1H, m), 3.75–3.9 (1H, m), 3.87 (3H, s), 4.55 (1H, m), 5.2–5.5 (2H, m), 6.99 (2H, J = 9 Hz), 7.81 (1H, d, J = 9 Hz). ESI-MS m/z 467 $(M-H)^-$.

(5*E* and 5*Z*)-6-((2*S*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-(((4-(trifluoromethyl)phenyl)sulfonyl)amino)pyrrolidinyl) - 5 - hexenoic acid (49). By the procedure used for **16**, **45** (5.00 g, 11.8 mmol), (4-carboxybutyl)triphenylphosphonium bromide (15.7 g, 35.5 mmol), sodium hydride (2.84 g, 60% in oil, 71.0 mmol) and dimethyl sulfoxide (40 mL) gave 5.30 g (88.4%) of **49** as a pale brown oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.38 (9H, s), 1.6–1.8 (3H,

m), 2.0–2.2 (2H, m), 2.25–2.45 (3H, m), 3.3–3.5 (1H, m), 3.86 (1H, m), 4.59 (1H, m), 5.3–5.5 (2H, m), 6.10 (1H, m), 7.78 (2H, J = 8 Hz), 8.02 (1H, d, J = 8 Hz). ESI-MS m/z 505 $(M-H)^-$.

(5*Z*)-6-((2*S*,4*R*)-1-((4-Chlorophenyl)sulfonyl)-4-((phenylsulfonyl)amino)pyrrolidinyl) - 5 - hexenoic acid (50a). By the procedure used for **18a**, **17** (29.9 g, 66.1 mmol), triethylamine (40.9 mL, 293 mmol) and 4-chlorobenzenesulfonyl chloride (14.0 g, 66.3 mmol) gave crude (5*E* and 5*Z*)-6-((2*S*,4*R*)-1-((4-chlorophenyl)sulfonyl)-4-((phenylsulfonyl)amino)pyrrolidinyl) - 5 - hexenoic acid that was dissolved in chloroform and chromatographed on a silica gel (Wakogel C300, 700 g) column with chloroform as an eluent. **50a** (10.5 g, 31.0%) was obtained from the first fractions as crystals: mp 121–123 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.5–1.8 (3H, m), 1.92 (1H, m), 2.11 (2H, q, J = 6.5 Hz), 2.33 (2H, t, J = 6.5 Hz), 3.4–3.6 (2H, m), 3.68 (1H, m), 4.46 (1H, q, J = 8 Hz), 5.37 (1H, dd, J = 10.5, 10 Hz), 5.45 (1H, dt, J = 10.5, 7 Hz), 7.5–7.7 (5H, m), 7.7–7.9 (4H, m). ESI-MS m/z 511 $(M-H)^-$.

(5*E*)-6-((2*S*,4*R*)-1-((4-Chlorophenyl)sulfonyl)-4-((phenylsulfonyl)amino)pyrrolidinyl) - 5 - hexenoic acid (50b). By the procedure used for **50a**, **50b** (1.55 g, 4.6%) was obtained from the second fractions as crystals: mp 155–156 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.6–1.7 (2H, m), 1.7–1.8 (2H, m), 1.9–2.1 (2H, m), 2.28 (2H, t, J = 7.5 Hz), 3.18 (1H, dd, J = 5.5, 10.5 Hz), 3.47 (1H, m), 3.76 (1H, m), 4.28 (1H, q, J = 6.5 Hz), 5.20 (1H, dd, J = 8, 15.5 Hz), 5.54 (1H, dt, J = 15.5, 6.5 Hz), 7.4–7.6 (5H, m), 7.6–7.7 (2H, m), 7.75–7.85 (2H, m). ESI-MS m/z 511 $(M-H)^-$.

(5*Z*)-6-((2*S*,4*R*) - 1 - ((4 - Chlorophenyl)sulfonyl) - 4 - (((4 - chlorophenyl)sulfonyl)amino)pyrrolidinyl) - 5 - hexenoic acid (51a). By the procedure used for **17**, **18a** and **50a**, **46** (8.14 g, 18.0 mmol), 90% aqueous trifluoroacetic acid (50 mL, 584 mmol), triethylamine (12.5 mL, 89.7 mmol) and 4-chlorobenzenesulfonyl chloride (3.80 g, 18.0 mmol) gave 2.50 g (25.4%) of **51a** as colorless crystals: mp 150.5–151.5 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.5–1.8 (3H, m), 2.03 (1H, m), 2.1–2.2 (2H, m), 2.41 (2H, t, J = 6.5 Hz), 3.4–3.5 (2H, m), 3.74 (1H, m), 4.56 (1H, q, J = 7 Hz), 5.25 (1H, dd, J = 10.5, 9 Hz), 5.48 (1H, dt, J = 10.5, 7.5 Hz), 7.4–7.5 (4H, m), 7.7–7.8 (4H, m). ESI-MS m/z 545 $(M-H)^-$. ESITOF-MS m/z 547.0562 $(M+H)^+$, calcd for $C_{22}H_{25}Cl_2N_2O_6S_2$ 547.0531. $[\alpha]_D^{20} = +7.3°$ (0.1 g, 1 mol/L NaOH, 10 mL, 100 mm).

(5*E*)-6-((2*S*,4*R*) - 1 - ((4 - Chlorophenyl)sulfonyl) - 4 - (((4 - chlorophenyl)sulfonyl)amino)pyrrolidinyl) - 5 - hexenoic acid (51b). By the procedure used for **51a**, **51b** (650 mg, 6.6%) was obtained from the second fractions as crystals: mp 111–113 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.6–1.8 (2H, m), 1.8–1.9 (2H, m), 1.9–2.1 (2H, m), 2.31 (2H, t, J = 7.5 Hz), 3.22 (1H, dd, J = 5, 10 Hz), 3.42 (1H, dd, J = 5.5, 10 Hz), 3.83 (1H, m), 4.23 (1H, q, J = 6 Hz), 5.17 (1H, dd, J = 7.5, 15.5 Hz), 5.53 (1H, dt, J = 15.5, 6.5 Hz), 7.4–7.5 (4H, m), 7.65–7.8 (4H, m). ESI-MS m/z 545 $(M-H)^-$.

(5*Z*)-6-((2*S*,4*R*)-1-((4-Chlorophenyl)sulfonyl)-4-(((4-methylphenyl)sulfonyl)amino)pyrrolidinyl) - 5 - hexenoic acid (52). By the procedure used for **17**, **18a** and **50a**, **47** (3.60 g, 7.72 mmol), 75% aqueous trifluoroacetic acid (25 mL, 243 mmol), triethylamine (5.38 mL, 38.6 mmol) and 4-chlorobenzenesulfonyl chloride (1.81 g, 8.58 mmol) gave 630 mg (15.5%) of **52** as colorless crystals: mp 98–101 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.5–1.8 (5H, m), 1.98 (1H, m), 2.1–2.2 (2H, m), 2.43 (3H, s), 3.4–3.5 (2H, m), 3.69 (1H, m), 4.52 (1H, q, J = 7.5 Hz), 5.2–5.5 (3H, m), 7.32 (2H, d, J = 8 Hz), 7.50 (2H, d, J = 8 Hz), 7.68 (2H, d, J = 8 Hz), 7.75 (2H, d, J = 8 Hz). ESI-MS m/z 525 $(M-H)^-$.

(5*Z*) - 6 - ((2*S*,4*R*) - 1 - ((4 - Chlorophenyl)sulfonyl) - 4 - (((4 - methoxyphenyl)sulfonyl)amino)pyrrolidinyl) - 5 - hexenoic acid (53). By the procedure used for **17**, **18a** and **50a**, **48** (5.10 g, 10.9 mmol), 75% aqueous trifluoroacetic acid (32 mL, 312 mmol), triethylamine (6.06 mL, 43.5 mmol) and 4-chlorobenzenesulfonyl chloride (2.30 g, 10.9 mmol) gave 1.25g (21.1%) of **53** as colorless crystals: mp 90 °C (dec.). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.5–1.8 (3H, m), 2.02 (1H, m), 2.17 (2H, q, J = 7.5 Hz), 2.49 (2H, t, J = 6.5 Hz), 3.4–3.5 (2H, m), 3.66 (1H, m), 3.88 (3H, s), 4.50 (1H, q, J = 7 Hz), 5.2–5.5 (3H, m), 6.98 (2H, d, J = 8 Hz), 7.50 (2H, d, J = 8 Hz), 7.75 (4H, d, J = 8 Hz). ESI-MS m/z 541 $(M-H)^-$.

(5*Z*)-6-((2*S*,4*R*)-1-((4-Chlorophenyl)sulfonyl)-4-(((4-(trifluoromethyl)phenyl)sulfonyl)amino)pyrrolidinyl)-5-hexenoic acid (54). By the procedure used for **17**, **18a** and **50a**, **49** (4.60 g, 9.08 mmol), 75% aqueous trifluoroacetic acid (28 mL, 273 mmol), triethylamine (6.33 mL, 45.4 mmol) and 4-chlorobenzenesulfonyl chloride (1.91 g, 9.05 mmol) gave 1.08 g (20.5%) of **54** as colorless crystals: mp 140–141 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.5–1.8 (3H, m), 2.05 (1H, m), 2.18 (2H, q, J = 7.5 Hz), 2.40 (2H, t, J = 6.5 Hz), 3.41 (1H, dd, J = 4.5, 11 Hz), 3.53 (1H, dd, J = 3, 11 Hz), 3.79 (1H, m), 4.65 (1H, q, J = 7 Hz), 5.22 (1H, dd, J = 11, 10 Hz), 5.44 (1H, dt, J = 11, 7.5 Hz), 5.78 (1H, d, J = 6.5 Hz), 7.45 (2H, d, J = 8 Hz), 7.72 (2H, d, J = 8 Hz), 7.89 (2H, d, J = 8 Hz), 7.98 (2H, d, J = 8 Hz). ESI-MS m/z 581 $(M+H)^+$. ESITOF-MS m/z 603.0549 $(M+Na)^+$, calcd for $C_{23}H_{24}ClF_3N_2O_6S_2Na$ 603.0614.

6-((2*S*,4*R*)-1-((4-Chlorophenyl)sulfonyl)-4-(((4-chlorophenyl)sulfonyl)amino)pyrrolidinyl)-5-hexanoic acid (55). A solution of (5*Z* and 5*E*)-6-((2*S*,4*R*)-1-((4-chlorophenyl)sulfonyl) - 4 - (((4 - chlorophenyl)sulfonyl)amino)-pyrrolidinyl)-5-hexenoic acid (400 mg, 0.731 mmol) in methanol (15 mL) was hydrogenated under medium presure (2 atm) in the presence of 10% palladium carbon for 7 h. After removal of the catalyst, the solvent was evaporated in vacuo and the residue was triturated with diethyl ether to give 164 mg (41.0%) of **55** as a white powder: mp 124–125 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.2–1.4 (4H, m), 1.5–1.7 (3H, m), 1.7–1.9 (3H, m), 2.35 (2H, t, J = 7.5 Hz), 3.09 (1H, m), 3.38 (1H, m), 3.6–3.9 (2H, m), 7.4–7.6 (4H, m), 7.7–7.9 (4H, m). ESI-MS m/z 547 $(M-H)^-$.

1-*tert*-Butyl (2*S*,4*R*)-4-(((4-chlorophenyl)sulfonyl)amino)-2-((Z)-2-(3-(methoxycarbonyl)phenyl)ethenyl)-1-pyrrolidinecarboxylate (56a). To a suspension of triphenyl (4-methoxycarbonylbenzyl)phosphonium chloride (1.26 g, 2.81 mmol) in tetrahydrofuran (10 mL) was added sodium hydride (113 mg, 60% in oil, 2.83 mmol) by portions under an ice bath cooling and the mixture was stirred in an ice bath for 1 h. To the resultiing yellow suspension was added dropwise a solution of **42** (995 mg, 2.56 mmol) in tetrahydrofuran (4 mL) under ice bath cooling and the mixture was stirred in an ice bath for 1 h. To the mixture were added saturated aqueous ammonium chloride (1 mL) and ethyl acetate (30 mL), and the organic layer was washed successively with water and brine. The organic solution was dried over magnesium sulfate and the solvent was evaporated in vacuo to give a crude 1-*tert*-butyl (2*S*,4*R*)-4-(((4-chlorophenyl)sulfonyl)amino)-2-((*E* and *Z*)-2-(3-(methoxycarbonyl)phenyl)ethenyl)-1-pyrrolidinecarboxylate. The crude product was separated by using a silica gel column with a mixture of *n*-hexane and ethyl acetate (4:1–2:1) as an eluent. **56a** (500 mg, 37.5%) was obtained from the first fractions (less polar) as crystals: mp 154–156 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.28 (9H, s), 1.8–2.1 (2H, m), 3.30 (1H, dd, J = 5, 12 Hz), 3.56 (1H, dd, J = 6, 12 Hz), 3.89 (1H, m), 3.93 (3H, s), 4.79 (1H, m), 4.93 (1H, d, J = 7 Hz), 5.58 (1H, dd, J = 9, 12.5 Hz), 6.48 (1H, d, J = 12.5 Hz), 7.3–7.5 (4H, m), 7.83 (2H, d, J = 8.5 Hz), 7.92 (2H, m). ESI-MS m/z 521 $(M+H)^+$. ESITOF-MS m/z 521.1625 $(M+H)^+$, calcd for $C_{25}H_{30}ClN_2O_6S$ 521.1513.

1-*tert*-Butyl (2*S*,4*R*)-4-(((4-chlorophenyl)sulfonyl)amino)-2-((E)-2-(3-(methoxycarbonyl)phenyl)ethenyl)-1-pyrrolidinecarboxylate (56b). By the procedure used for **56a**, **56b** (572 mg, 42.9%) was obtained from the second fractions (more polar) as crystals: mp 126–128 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.40 (9H, s), 1.8–2.1 (2H, m), 3.24 (1H, dd, J = 5.5, 11 Hz), 3.57 (1H, dd, J = 6, 11 Hz), 3.92 (3H, s), 3.97 (1H, m), 4.49 (1H, m), 4.88 (1H, m), 6.09 (1H, dd, J = 6.5, 16 Hz), 6.43 (1H, d, J = 16 Hz), 7.33 (2H, d, J = 8.5 Hz), 7.49 (1H, t, J = 7.5 Hz), 7.4–7.6 (3H, m), 7.92 (1H, d, J = 7 Hz), 8.03 (1H, s). ESI-MS m/z 521 $(M+H)^+$. ESITOF-MS m/z 521.1527 $(M+H)^+$, calcd for $C_{25}H_{30}ClN_2O_6S$ 521.1513.

1-*tert*-Butyl (2*S*,4*R*)-4-(((4-chlorophenyl)sulfonyl)amino)-2-((Z)-2-(4-(methoxycarbonyl)phenyl)ethenyl)-1-pyrrolidinecarboxylate (56c). By the procedure used for **56a**, triphenyl (4 - methoxycarbonylbenzyl)phosphonium chloride (88.5 g, 198 mmol), sodium hydride (7.92 g, 60% in oil, 198 mmol) and **42** (70.0 g, 180 mmol) gave 16.0 g (17.1%) of **56c** as colorless crystals: mp 178–179 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29 (9H, s), 1.8–2.3 (2H, m), 3.26 (1H, m), 3.51 (1H, dd, J = 6, 11 Hz), 3.89 (1H, m), 3.93 (3H, s), 4.78 (1H, m), 5.10 (1H, m), 5.60 (1H, dd, J = 9, 11.5 Hz), 6.48 (1H, d, J = 11.5 Hz), 7.2–7.4 (2H, m), 7.48 (2H, d, J = 8.5 Hz), 7.82 (2H, d, J = 8.5 Hz), 8.02 (2H, d, J = 8.5 Hz). ESI-MS m/z 521 $(M+H)^+$. ESITOF-MS m/z 543.1280 $(M+Na)^+$, calcd for $C_{25}H_{29}ClN_2O_6SNa$ 543.1333.

1-*tert*-Butyl (2*S*,4*R*)-4-(((4-chlorophenyl)sulfonyl)amino)-2-((E)-2-(4-(methoxycarbonyl)phenyl)ethenyl)-1-pyrrolidinecarboxylate (56d). By the procedure used for **56c**, **56d** (21.9 g, 23.3%) was obtained from the second fractions as crystals: mp 164–165 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.39 (9H, s), 1.9-2.2 (2H, m), 3.24 (1H, dd, J = 5, 11 Hz), 3.55 (1H, dd, J = 6, 11.5 Hz), 3.91 (3H, s), 3.8–4.0 (1H, m), 4.49 (1H, m), 4.91 (1H, m), 6.12 (1H, dd, J = 6.5, 15.5 Hz), 7.37 (2H, d, J = 8.5 Hz), 7.50 (2H, d, J = 8.5 Hz), 7.82 (2H, d, J = 8.5 Hz), 7.97 (2H, d, J = 8.5 Hz). ESI-MS m/z 521 $(M+H)^+$.

Methyl 3-((*Z*)-2-((2*S*,4*R*)-4-(((4-chlorophenyl)sulfonyl)-amino) pyrrolidinyl)ethenyl)benzoate (57a). A solution of **56a** (447 mg, 0.858 mmol) in 90% aqueous trifluoroacetic acid (3 mL, 35.1 mmol) was stirred at room temperature for 30 min and the solvent was evaporated in vacuo. The residue was suspended in chloroform (10 mL) and the solution was adjusted to pH 8 with saturated aqueous sodium bicarbonate. The organic phase was separated, washed with brine and dried over magnesium sulfate. The solvent was evaporated in vacuo to give 330 mg (91.4%) of **57a** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.75 (1H, dd, J = 7.5, 14 Hz), 1.91 (1H, m), 2.74 (1H, dd, J = 5, 12 Hz), 3.26 (1H, dd, J = 6, 12 Hz), 3.90 (1H, m), 3.92 (3H, s), 4.13 (1H, m), 5.62 (1H, dd, J = 9.5, 12 Hz), 6.51 (1H, d, J = 12 Hz), 7.3–7.5 (5H, m), 7.7–8.0 (3H, m). ESI-MS m/z 421 $(M+H)^+$.

Methyl 3-((*E*)-2-((2*S*,4*R*)-4-(((4-chlorophenyl)sulfonyl)-amino)pyrrolidinyl)ethenyl)benzoate (57b). By the procedure used for **57a**, **56b** (570 mg, 1.09 mmol) and 90% aqueous trifluoroacetic acid (10 mL, 117 mmol) gave 450 mg (98.1%) of **57b** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.8--2.0 (2H, m), 2.93 (1H, dd, J = 4.5, 11.5 Hz), 3.32 (1H, dd, J = 6, 11.5 Hz), 3.90 (1H, m), 3.93 (3H, s), 4.05 (1H, m), 6.28 (1H, dd, J = 7.5, 16.5 Hz), 6.52 (1H, d, J = 16.5 Hz), 7.36 (1H, t, J = 7.5 Hz), 7.4--7.5 (3H, m), 7.7--7.9 (3H, m), 8.00 (1H, m). ESI-MS m/z 421 $(M+H)^+$.

Methyl 4-((*Z*)-2-((2*S*,4*R*)-4-(((4-chlorophenyl)sulfonyl)-amino)pyrrolidinyl)ethenyl)benzoate (57c). By the procedure used for **57a**, **56c** (15.5 g, 29.8 mmol) and 90% aqueous trifluoroacetic acid (100 mL, 1.17mol) gave 11.9 g (95.0%) of **57c** as a white powder: mp 189–190 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.7–2.2 (2H, m), 2.66 (1H, dd, J = 4.5, 11.5 Hz), 3.18 (1H, dd, J = 6, 11.5 Hz), 3.88 (1H, m), 3.93 (3H, s), 4.08 (1H, m), 5.61 (1H, dd, J = 9.5, 11.5 Hz), 6.52 (1H, d, J = 11.5 Hz), 7.28 (2H, d, J = 8.5 Hz), 7.49 (2H, d, J = 8.5 Hz), 7.80 (2H, d, J = 8.5 Hz), 8.00 (2H, d, J = 8.5 Hz). ESI-MS m/z 421 $(M+H)^+$.

Methyl 4-((E)-2-((2*S*,4*R*)-4-(((4-chlorophenyl)sulfonyl)-amino)pyrrolidinyl)ethenyl)benzoate (57d). By the procedure used for **57a**, **56d** (16.0 g, 30.7 mmol) and 90% aqueous trifluoroacetic acid (100 mL, 1.17 mol) gave 12.9 g (100%) of **57d** as an oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.7–2.1 (2H, m), 2.85 (1H, dd, J = 4, 11 Hz), 3.27 (1H, dd, J = 6, 11 Hz), 3.86 (1H, m), 3.90 (3H, s), 4.09 (1H, m), 6.21 (1H, dd, J = 7, 16 Hz), 6.50 (1H, d, J

= 16 Hz), 7.34 (2H, d, J = 8.5 Hz), 7.49 (2H, d, J = 8.5 Hz), 7.83 (2H, d, J = 8.5 Hz), 7.95 (2H, d, J = 8.5 Hz). ESI-MS m/z 421 $(M+H)^+$.

3-((*Z*)-2-((2*S*,4*R*)-1-((4-Chlorophenyl)sulfonyl)-4-(((4-chlorophenyl)sulfonyl)amino)pyrrolidinyl)ethenyl)benzoic acid (58a). By the procedure used for **18a**, **57a** (329 mg, 0.782 mmol), triethylamine (0.11 mL, 0.790 mmol) and 4-chlorobenzenesulfonyl chloride (165 mg, 0.782 mmol) gave 378 mg (81.2% from **57a**) of methyl 3-((*Z*)-2-((2*S*,4*R*)-1-((4-chlorophenyl)sulfonyl) - 4 - (((4 - chlorophenyl)sulfonyl)amino)pyrrolidinyl)ethenyl)benzoate. A solution of methyl 3-((*Z*) - 2 - ((2*S*,4*R*) - 1 - ((4 - chlorophenyl)sulfonyl)-4-(((4-chlorophenyl)sulfonyl)amino)-pyrrolidinyl)ethenyl)benzoate (378 mg, 0.635 mmol) in a mixture of methanol (2.5 mL) and 1 N aqueous sodium hydroxide (2.5 mL, 2.5 mmol) was stirred at 50 °C for 4 h and the volatile solvent was evaporated in vacuo. The residual aqueous solution was adjusted to pH 1 with concentrated hydrochloric acid. The white precipitate was collected by filtration and washed with water to give 359 mg (79.0% from **57a**) of **58a** as a white powder: mp 127–130 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.8–1.9 (2H, m), 3.23 (1H, dd, J = 4.5, 10.5 Hz), 3.50 (1H, dd, J = 5, 10.5 Hz), 3.63 (1H, m), 4.41 (1H, m), 5.67 (1H, dd, J = 9.5, 12 Hz), 6.54 (1H, d, J = 12 Hz), 7.4–8.0 (12H, m). ESI-MS m/z 579 $(M-H)^-$. ESITOF-MS m/z 581.0354 $(M+H)^+$, calcd for $C_{25}H_{23}Cl_2N_2O_6S_2$ 581.0374. $[\alpha]_D^{20}$ −126.6° (0.05 g, 1 mol/L NaOH, 10 mL, 100 mm).

3-((E)-2-((2*S*,4*R*)-1-((4-Chlorophenyl)sulfonyl)-4-(((4-chlorophenyl)sulfonyl)amino)pyrrolidinyl)ethenyl)benzoic acid (58b). By the procedure used for **18a** and **58a**, **57b** (420 mg, 1.00 mmol), triethylamine (0.14 mL, 1.01 mmol), 4-chlorobenzenesulfonyl chloride (211 mg, 1.00 mmol) and 1 N aqueous sodium hydroxide (2.3 mL, 2.3 mmol) gave 312 mg (53.8%) of **58b** as a white powder: mp 119–121 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.7–1.9 (2H, m), 3.12 (1H, dd, J = 5, 9.5 Hz), 3.50 (1H, dd, J = 6.5, 9.5 Hz), 3.79 (1H, m), 4.31 (1H, m), 6.23 (1H, dd, J = 7.5, 16 Hz), 6.57 (1H, d, J = 16 Hz), 7.4–8.0 (12H, m). ESI-MS m/z 579 $(M-H)^-$. ESITOF-MS m/z 581.0358 $(M+H)^+$, calcd for $C_{25}H_{23}Cl_2N_2O_6S_2$ 581.0374. $[\alpha]_D^{20}$ −55.8° (0.05 g, 1 mol/L NaOH, 10 mL, 100mm).

4-((Z)-2-((2*S*,4*R*)-1-((4-Chlorophenyl)sulfonyl)-4-(((4-chlorophenyl)sulfonyl)amino)pyrrolidinyl)ethenyl)benzoic acid (58c). By the procedure used for **18a** and **58a**, **57c** (11.5 g, 27.3 mmol), triethylamine (3.80 mL, 27.3 mmol), 4-chlorobenzenesulfonyl chloride (5.77 g, 27.3 mmol) and 1 N aqueous sodium hydroxide (78.5 mL, 78.5 mmol) gave 15.2g (95.7%) of **58c** as a white powder: mp 206–208 °C (dec). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.8–2.0 (2H, m), 3.31 (1H, dd, J = 3.5, 10.5 Hz), 3.51 (1H, dd, J = 5.5, 10.5 Hz), 4.40 (1H, m), 5.68 (1H, dd, J = 9.5, 11.5 Hz), 6.54 (1H, d, J = 11.5 Hz), 7.32 (2H, d, J = 8 Hz), 7.40 (2H, d, J = 8 Hz), 7.47 (2H, d, J = 8 Hz), 7.67 (2H, d, J = 8 Hz), 7.78 (2H, d, J = 8 Hz), 7.95 (2H, d, J = 8 Hz). ESI-MS m/z 579 $(M-H)^-$. ESITOF-MS m/z 581.0358 $(M+H)^+$, calcd for $C_{25}H_{23}Cl_2N_2O_6S_2$ 581.0374. $[\alpha]_D^{20}$ −87.5° (0.1 g, 1 mol/L NaOH, 10 mL, 100 mm).

4-((*E*)-2-((2*S*,4*R*)-1-((4-Chlorophenyl)sulfonyl)-4-(((4-chlorophenyl)sulfonyl)amino)pyrrolidinyl)ethenyl)benzoic acid (58d). By the procedure used for **18a** and **58a**, **57d** (12.5 g, 29.7 mmol), triethylamine (4.13 mL, 29.7 mmol), 4-chlorobenzenesulfonyl chloride (6.27 g, 29.7 mmol) and 1 N aqueous sodium hydroxide (83.0 mL, 83.0 mmol) gave 15.9 g (92.1%) of **58d** as a white powder: mp 168–171 °C (dec.). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.7–1.9 (2H, m), 3.08 (1H, dd, J = 6, 11 Hz), 3.46 (1H, m), 3.78 (1H, m), 4.32 (1H, m), 6.30 (1H, dd, J = 7, 16 Hz), 6.53 (1H, d, J = 16 Hz), 7.47 (2H, d, J = 8.5 Hz), 7.6–7.7 (4H, m), 7.7–7.8 (4H, m), 7.88 (2H, d, J = 8.5 Hz), 8.00 (1H, d, J = 6 Hz). ESI-MS m/z 579 $(M-H)^-$. ESITOF-MS m/z 581.0468 $(M+H)^+$, calcd for $C_{25}H_{23}Cl_2N_2O_6S_2$ 581.0374. $[\alpha]_D^{20}$ −40.8° (0.1 g, 1 mol/L NaOH, 10 mL, 100 mm).

Biological methods

Inhibitory effects on 9,11-azo PGH_2-induced platelet aggregation in rabbit. Blood was collected from the carotid artery of male rabbits into plastic vessels containing 0.1 volume of 3.8% aqueous sodium citrate. Platelet-rich plasma (PRP) was then prepared by centrifugation at 150*g* for 15 min. Platelet-poor plasma (PPP) was prepared from the remaining blood after removing PRP, by centrifugation at 1500*g* for 10min. PRP was then adjusted to a concentration of 6.0×10^5 cells/μL by using PPP. Platelet aggregation was investigated using the turbidometric method with an aggregometer (NKK Hematracer 1 Model 4A). To 225 μL of PRP, 25 μL of the test compound solution or vehicle solution (0.1 N NaOH) was added, and the whole stirred at 1000rpm for 2 min at 37 °C. Next, 5 μL of 9,11-azo PGH_2 (final concentration 1.0 μM) or ADP (final concentration 2.5 μM, Sigma) was added as an aggregating inducer. The concentration which caused 50% inhibition (IC_{50}) of 9,11-azo PGH_2-induced maximum aggregation was obtained by regression analysis of the concentration versus inhibition of aggregation curve.

Inhibitory effects of 51a on ^{3}H-U46619 binding to washed guinea-pig platelets. This was carried out according to the modified method of Kattelman et al.[31] PRP was prepared as described above from male Hartley strain guinea-pigs and treated with aspirin (final concentration 1 mM), then centrifuged at 150*g* for 15 min to remove residual contaminating red blood cells. PGI_2 (final concentration 40 nM, Funakoshi) was added to aid in resuspension of the platelets. The PRP was then spun at 1100*g* for 15 min to pellet the cells. The platelet free plasma was discarded, and the platelet pellets were gently resuspended in buffer [sodium chloride (138 mM), potassium chloride (5 mM), magnesium chloride (5 mM), glucose (5.5 mM) and Tris–HCl (25 mM), PH 7.4] to a final cell count of approximately 1.0×10^9 cells. Aliquots of platelet suspension (1.0 mL) were incubated with approximately 5 nM (final concentration) [^{3}H]-U46619 ([15-^{3}H(N)]-9,11-epoxymethano PGH_2, 22.4 Ci/mmol, NEN) plus various concentrations of **51a** for 5 min at 37 °C with stirring. In order to block U-46619-induced platelet activation, the cells were treated with PGI_2 (final concentration 250 nM) for

45 s prior to mixing them with drugs. After mixin g, a 0.4 mL aliquot of the binding assay mixture was transferred to a 1.5 mL Eppendorf tube, and the incubation was terminated at the appropriate time by centrifugation at 15,000 rpm for 1 min in a Eppendorf 5414 centrifuge. The supernatant was quickly removed by aspiration, and the inside of the Eppendorf tubes, as well as the surface of the pellet was rinsed twice with 0.4 mL of ice-cold resuspension buffer, which was immediately removed by aspiration. The tip of the tube was cut off, and placed in a polyethylene vial (Wheaton) including 0.4 mL of tissue solubilizer (NCS, Amersham). The mixture was incubated for 3–4 h at 50 °C, then 5 mL of toluene scintilator (Omnifluor 4 g/L toluene) was added to the mixture. The radioactivity was measured in a liquid scintillation counter.

Inhibitory effect of 51a on U-46619- or collagen-induced platelet aggregation in human, monkey, dog or guinea-pig. These tests were performed by a similar procedure to the test for platelet aggregation in rabbits. In this case, the final concentration of U-46619 (Cyman Chemical) was 1 μM (human), 2 M (monkey) or 0.5 μM (guinea-pig), and that of collagen (Horm) was 0.5 μg/mL (human or guinea-pig) or 20 μg/mL (dog). The concentration of PRP was adjusted to 3.0×10^5 cells/ mL in the case of human, monkey and dog.

Inhibitory effect of 51a on U-46619-induced contractile response in rat aorta. Male Sprague–Dawley rats (200–220 g) were killed and their thoracic aorta were placed in Tyrode solution. Adhering fat and connective tissues were removed and spiral strips of the aorta were prepared. Each strip (2 mm in width and 15 mm in length) were mounted in an organ bath containing 25 mL of Tyrode solution bubbled with 95% O_2 and 5% CO_2 gas at 37 °C. After 1 h of incubation period under 0.5 g resting tension, U-46619 (3.2×10^{-8} mol/L) was added to induce TXA_2 receptor-mediated contraction. The contractile response was isometrically recorded on a polygraph via a force-displacement transducer. After obtaining the maximum contractile response by U-46619, **51a** in water was then cumulatively added. Finally, papaverine (1.0×10^{-4} mol/L) was added to obtain the maximum relaxation. The concentration which induce 50% of the maximum relaxation was determined graphically and indicated as an IC_{50} value.

Inhibitory effect of 51a on ex vivo platelet aggregation in guinea-pig. Male Hartley strain guinea-pigs weighing about 300 g were used after overnight fasting. Blood was collected from the abdominal artery at 1 and 6 h after oral administration of **51a** or vehicle (0.1 N NaOH). PRP was prepared as described before, and platelet aggregation was induced by adding 5 μL of U-46619 (final concentration, 0.5 μM) or collagen (final concentration, 5 μg/mL) to 250 μL of PRP.

Protective effects of 51a against arachidonic acid-induced pulmonary infarction in mice. Male ddY mice weighing about 30 g were used after overnight fasting. **51a** was orally administered in saline at doses from 0.32 to 3.2 mg/kg. Control animals were given only saline. At 1 h after administration of **51a** or saline, arachidonic acid (90 mg/kg, Sigma) was injected intravenously for 20 s. The effect of **51a** was evaluated by measuring the incidence of death within 5 min of injection. Results are expressed as percent survival. Each group was comprised of 10 mice.

Inhibitory effect of 51a on thrombus formation in extracorporeal shunt in rat.[32] Male Sprague–Dawley rats weighing 390–530 g were anesthetized with sodium pentobarbital (50 mg ip). A silk thread (5 cm; Tire No. 50, Fujix Co., Osaka, Japan) was placed in a polyethylene tube (6 cm; Hibiki Size 7, Kunii Co., Tokyo, Japan). Both ends of this tubing were connected to other polyethylene tubing (10 cm; Hibiki Size 4, Kunii Co.). An extracorporeal shunt filled with heparin solution (50 IU/mL) was introduced between the right carotid artery and the left jugular vein, and after this, blood circulation was established. After 20 min, the blood flow was stopped on the artery side with a pinch-cock. The middle tubing was then taken away and the thread coated with thrombus was carefully pulled out of the tubing. The wet weight of the thrombus was measured immediately. Another new polyethylene tubing containing a silk thread and filled with heparin solution was inserted between the arterial and venous tubing ends. Blood circulation was re-established by opening the pinch-cock. After 20 min, the wet weight of the silk thread was measured as before. The third blood circulation was then performed. Thrombus weight was determined by subtracting the weight of a silk thread immersed in heparinized blood from that of the thread coated with thrombus. The total thrombus weight obtained from three blood circulation was taken as net thrombus weight in one experiment. **51a** at doses from 0.01 to 0.32 mg/kg or vehicle (water) was given orally 60 min before the first blood circulation. The effect of **51a** were expressed as percent inhibition of thrombus formation compared with vehicle treatment. Each group was comprised of 10 mice.

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