Synthesis and Biological Activity of Various Derivatives of a Novel Class of Potent, Selective, and Orally Active Prostaglandin D_2 Receptor Antagonists. 2. 6,6-Dimethylbicyclo[3.1.1]heptane Derivatives

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In an earlier paper, we reported that novel prostaglandin D_2 (PGD_2) receptor antagonists having the bicyclo[2.2.1]heptane ring system as a prostaglandin skeleton were a potent new class of antiallergic agents and suppressed various allergic inflammatory responses such as those observed in conjunctivitis and asthma models. In the present study, we synthesized PGD_2 receptor antagonists having the 6,6-dimethylbicyclo[3.1.1]heptane ring system. These derivatives have the amide moiety, in contrast to those with the bicyclo[2.2.1]heptane ring system, which have the sulfonamide group. The derivatives having the 6,6-dimethylbicyclo[3.1.1]heptane ring also exhibited strong activity in PGD_2 receptor binding and cAMP formation assays. In in vivo assays such as allergic rhinitis, conjunctivitis, and asthma models, these series of derivatives showed excellent pharmacological profiles. In particular, compound **45** also effectively suppressed eosinophil infiltration in allergic rhinitis and asthma models. This compound (**45**, S-5751) is now being developed as a promising alternative antiallergic drug candidate.

Introduction

In an earlier paper,[1] we reported that novel prostaglandin D_2 (PGD_2) receptor antagonists having the bicyclo[2.2.1]heptane ring system as a prostaglandin skeleton were synthesized as a potential new class of antiallergic agents. These compounds exhibited selective antagonism of the PGD_2 receptor in radioligand binding and cAMP formation assays with IC_{50} values below 50 nM and exhibited much less antagonism of TXA_2 and PGI_2 receptors. Furthermore, they suppressed various allergic inflammatory responses such as those in rhinitis, conjunctivitis, and asthma models. Clearly, PGD_2 plays an important role in the pathogenesis of allergic diseases,[1,2] and support for this comes from a study of DP knockout mice recently reported by Narumiya et al.[3]

We have been trying to develop PGD_2 receptor antagonists having other prostaglandin skeletons in order to enhance the biological activities. As described in an earlier paper,[1a] the bicyclo[2.2.1]heptane ring system was derived from a TXA_2 receptor antagonist.[4] At that time, we obtained two different types of prostaglandin (PG) skeletons, both of which exhibited strong TXA_2 antagonism. One (S-1452) is the bicyclo[2.2.1]heptane ring system, and the other (S-6877) is the 6,6-dimethylbicyclo[3.1.1]heptane ring system[5] (Figure 1). In the case of the bicyclo[2.2.1]heptane ring system, compounds having the enantiomer skeleton of S-1452, which is a strong TXA_2 antagonist, exhibited strong PGD_2 inhibitory activities. This suggested that 6,6-dimethylbicyclo-[3.1.1]heptane ring derivatives having the enantiomer structure of S-6877, which also displays strong TXA_2 antagonism, would have PGD_2 inhibitory activity. However, the enantiomer skeleton of S-6877 was unsuitable for an SAR study and as a drug candidate because of its synthetic difficulty. We have therefore tried to investigate types of the 6,6-dimethylbicyclo[3.1.1]heptane ring system that are regio- and stereoisomeric to S-6877 to find a new seed compound for PGD_2 antagonists. Examination of the three types of regio- and stereoisomers having the sulfonamide moiety (**2**, **5**, and **6**) showed that compound **2** with a (1*R*,2*R*,3*S*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptane ring skeleton exhibited PGD_2 antagonist activity (Table 1). Several sulfonamides with this stereo structure were synthesized as done in the SAR study on the bicyclo[2.2.1] heptane ring system, but no better results were obtained. However, evaluation of compounds having the amide moiety revealed that the simple compound **7** having the benzoyl group and its analogues of the ω-chain (**8** and **9**) showed strong activity especially in the in vivo assay. No improvement of the antagonistic activity was noted for the other regio- and stereoisomers having the amide moiety (**10** and **11**), despite the conversion of the sulfonamide. We therefore initiated further SAR studies of the (1*R*,2*R*,3*S*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptane

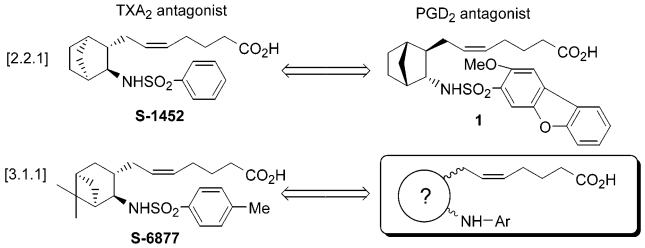

Figure 1. Relation between TXA_2 and PGD_2 antagonists.

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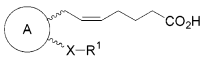
Table 1. Inhibition of PGD_2 Receptor Binding, Biological Activity in Human Platelets, and Antigen-Induced Nasal Blockage in Guinea Pigs



Compd	A	X	R^1	IC_{50} (μM)[a] DP binding	IC_{50} (μM)[a] DP cAMP	in vivo[b] (rhinitis model) inhibn at 1 mg/kg (iv)
2		-SO_2-	*p*-biphenyl	1.2	0.53	nd[c]
3		-SO_2-	4-(phenylazo)benzene	1.3	>1.0	nd[c]
4		-SO_2-	2-dibenzofurane	0.78	>1.0	nd[c]
5		-SO_2-	*p*-biphenyl	1.3	>1.0	nd[c]
6		-SO_2-	*p*-biphenyl	1.3	>1.0	nd[c]
7		-CO-	Ph	5.2	0.36	52±5[d]
8		-CO-	*p*-biphenyl	0.047	0.47	30±8
9		-CO-	4-(phenylazo)benzene	0.54	0.38	60±10[d]
10		-CO-	*p*-biphenyl	5.1	>1.0	nd[c]
11		-CO-	*p*-biphenyl	3.6	>1.0	nd[c]

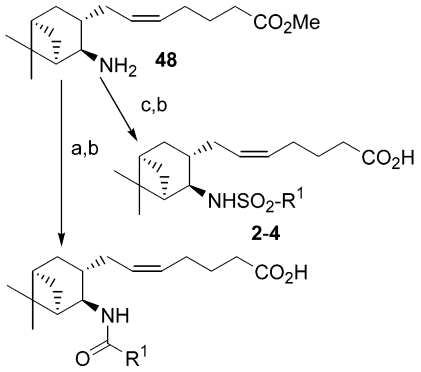
[a] PGD_2 receptor (DP) assay.[1] Inhibition of [^{3}H]PGD_2 specific binding to human platelet membranes[4c] and cAMP formation evoked by PGD_2 in human platelets.[25] IC_{50} represents the mean value of two or three measurements. [b] Inhibition of antigen-induced increase in intranasal pressure in actively sensitized guinea pigs. Compounds were administered iv 10 min before the antigen challenge. Values represent the mean ± SEM. [c] Not done. [d] Significantly different from each control; $p < 0.01$ (Student's *t*-test).

ring system having the amide moiety. The results revealed that the compound with the benzothiophene-3-carbonyl moiety as the *ω*-chain exhibited fairly strong antagonistic activity against the PGD_2 receptor. In this paper, we describe the synthesis and development of a new class of PGD_2 receptor antagonists with the 6,6-dimethylbicyclo[3.1.1]heptane ring system having the benzothiophene-3-carbonyl moiety.

Synthetic Chemistry

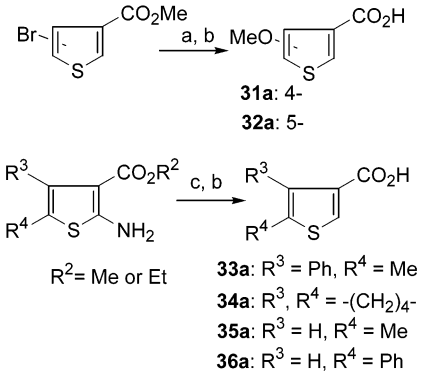
(1*R*,2*R*,3*S*,5*S*)-(5*Z*)-7-(2-Amino-6,6-dimethylbicyclo-[3.1.1]hept-3-yl)hept-5-enoic acid methyl ester (**48**) was prepared by methods described in the literature.[5a] Most of the target compounds were synthesized in the following manner. Coupling of amine **48** with the readily prepared sulfonyl and acyl chloride or carboxylic acid by using Et_3N or water-soluble carbodiimide (WSCD) produced the desired ester in good yield.[6] Hydrolysis of the corresponding ester using aqueous potassium hydroxide in methanol produced the target molecule in almost quantitative yield (Scheme 1). Other regio- and

Scheme 1[a]



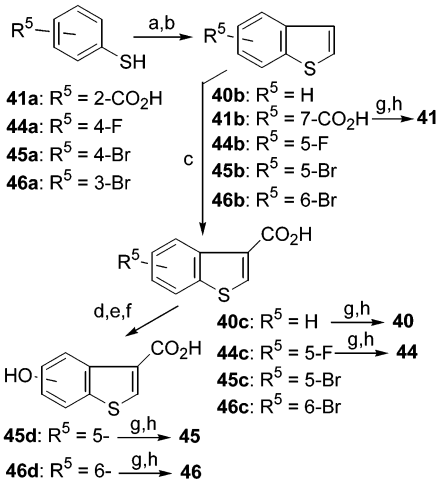
[a] Reagents: (a) R^1CO_2H, WSCD, HOBt, THF; or R^1COCl, Et_3N; (b) KOH; (c) R^1SO_2Cl, Et_3N.

Scheme 2[a]



[a] Reagents: (a) (1) NaOMe, NaI, CuO, MeOH, (2) CH_2N_2, Et_2O; (b) NaOH; (c) (1) $NaNO_2$, HCl, (2) H_3PO_2.

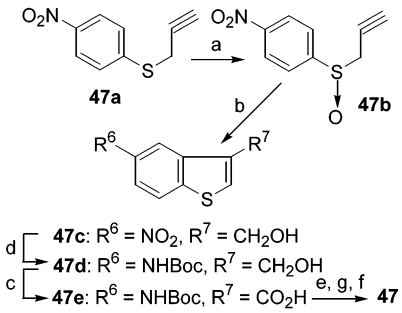
Scheme 3[a]



[a] Reagents: (a) $BrCH_2CH(OMe)_2$, NaOMe; (b) PPA, PhCl; (c) (1) AcCl, $SnCl_4$, (2) NaOCl or NaOBr; (d) NaOMe, CuBr, Cu; (e) CH_2N_2; (f) BBr_3; (g) **48**, WSCD, HOBt, THF; (h) KOH.

stereoisomers (**5**, **6**, **10**, and **11**) were also synthesized, as done for the (1*R*,2*R*,3*S*,5*S*)-isomer.[5] The substituted thiophene or benzothiophene carboxylic acids were prepared from the appropriately substituted compounds as shown in Schemes 2−4. Briefly, reaction of the substituted thiophene with $NaNO_2$ or NaOMe, deamination[7] or methoxy substitution,[8] followed by suitable treatment afforded the corresponding 3-substituted

Scheme 4[a]

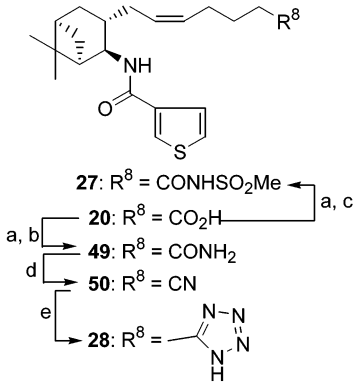


[a] Reagents: (a) H_2O_2, HCO_2H; (b) (1) dioxane, reflux, (2) *p*-TsOH, H_2O; (c) (1) NaOCl, TEMPO, (2) H_2O_2, $NaClO_2$; (d) (1) $SnCl_2$, EtOH, H_2O, (2) Boc_2O, K_2CO_3; (e) **48**, WSCD, HOBt; (f) aqueous NaOH; (g) (1) TFA, (2) MsCl, Et_3N.

carboxylic acids such as **31a**−**36a** (Scheme 2). Benzothiophene carboxylic acid, which is an important synthon because of expression of the fairly good inhibitory activity as the *ω*-chain, can be synthesized from the substituted benzenethiol by two synthetic routes. One is the cyclization of (2,2-dimethoxyethylsulfanyl)-benzene in the presence of polyphosphoric acid (PPA), which readily gave the desired benzothiophene in good yield.[9] Friedel−Crafts acylation of benzothiophene derivatives using $SnCl_4$ followed by oxidation with NaOCl[10] produced the target molecules (**40c**, **44c**, **45d**, and **46d**)[11] in moderate yields (Scheme 3). **47e** was prepared by the other method: tandem [2,3]/[3,3] thio-Claisen rearrangement[12] of propargyl sulfoxide and cyclization to hydroxymethylbenzothiophene (Scheme 4). Propargylphenylsulfoxide (**47b**) prepared by the oxidation of **47a** with H_2O_2/HCO_2H gave the 3-hydroxymethylbenzothiophene derivative **47c** on application of heat in 1,4-dioxane and successive treatment with *p*-TsOH.[12c] The obtained 3-hydroxymethylbenzothiophene (**47d**) was oxidized to the corresponding carboxylic acid in two steps; that is, the hydroxymethyl substituent was changed to an aldehyde using the 2,2,6,6-tetramethylpiperidine 1-oxide (TEMPO) catalyst,[13] and the resulting aldehyde was further oxidized to the desired benzothiophene carboxylic acid by a general method.[14] This synthetic route involving oxidation steps can be used for industrial-scale synthesis for its safety and efficiency.

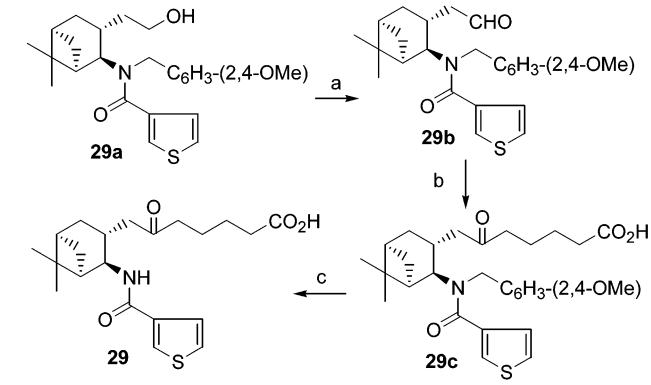
The modifications of the α-chain at the prostaglandin skeleton containing methanesulfonamide and tetrazole moieties are presented in Scheme 5. Compound **20** was reacted with $ClCO_2Et$ to give the corresponding mixed anhydride. Methanesulfonamide or ammonia was coupled with this acyl chloride to afford **27**[15] or **49**, respectively. Compound **49** was further treated with thionyl choride to give the corresponding nitrile,[16] which was converted into the tetrazole derivative by reaction with $TMSN_3$.[17] 5-Ketoheptanoic acid derivative **29** was synthesized from **29a** protected by the 2,4-dimethoxybenzyl moiety.[18] Swern oxidation of **29a** gave an aldehyde **29b**, which was successively oxidized by Jones reagent,[19] followed by coupling with the corresponding α-chain Grignard reagent to give the N-protected 5-keto derivative **29c**. Deprotection of **29c** occurred smoothly in the presence of *m*-dimethoxybenzene by treatment of TFA to give **29** (Scheme 6).

Scheme 5[a]



[a] Reagents: (a) $ClCO_2Et$, Et_3N; (b) aqueous NH_3; (c) $MeSO_2NH_2$, DBU; (d) $SOCl_2$; (e) $TMSN_3$, Bu_2SnO.

Scheme 6[a]

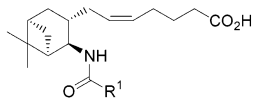


[a] Reagents: (a) (1) $(COCl)_2$, DMSO then Et_3N; (b) (1) TBDMSO-$(CH_2)_5MgBr$, (2) Jones oxidation; (c) TFA, *m*-dimethoxybenzene.

Biological Results and Discussion

As reported before, novel PGD_2 receptor antagonists having the bicyclo[2.2.1]heptane ring system showed promise as a potential new class of antiallergic agents. In the present study, we tried to synthesize another series of PGD_2 antagonists having the 6,6-dimethylbicyclo-[3.1.1]heptane ring system as a PG skeleton. Study of several isomers of the 6,6-dimethylbicyclo[3.1.1]heptane ring system as a PG skeleton revealed that only the (1*R*,2*R*,3*S*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptane derivative exhibited moderate antagonistic activity in the cAMP assay. At first, many kinds of sulfonamide derivatives (**2**−**4**) were synthesized and studied, as was done for the bicyclo[2.2.1]heptane ring system,[1a] but similar modifications of the *ω*-chain, which led to strong activity in the case of the bicyclo[2.2.1]heptane ring system, did not improve the inhibitory activity (Table 1). We next tried to find other types of *ω*-chains having the amide instead of the sulfonamide moiety. To our surprise, it turned out that the very simple amide **7** having the benzoyl group exhibited fairly strong activity in the in vivo assay rather than the sulfonamide ones, which exhibited some activity in vitro. Other amide derivatives (**8** and **9**) also had fairly good activities similar to the activity of **7**. Strong activity was exhibited by compound **9** in the in vivo assay, but the azo structure is thought to be unsuitable for a drug candidate because of the possibility of pharmacological instability and toxicology. Thus, benzoyl derivative **8**, which is thought to be pharmacologically stable and

Table 2. Inhibition of PGD_2 Receptor Binding, Biological Activity in Human Platelets, and Antigen-Induced Nasal Blockage in Guinea Pigs



		IC$_{50}$ (μM)[a]	
		DP	
compd	R^1	binding	cAMP
12	4-NO_2-C_6H_4	4.4	0.11
13	4-MeO-C_6H_4	3.9	0.19
14	2-MeO-C_6H_4	4.6	0.32
15	4-OH-C_6H_4	3.4	0.24
16		2.1	0.17
17	[c]hexyl	>10	>1.0
18	benzyl	>10	>1.0
19	2-thienyl	3.3	0.015
20	3-thienyl	1.6	0.038
21	3-furfuryl	0.56	0.017
22	2-pyrrolyl	nd[b]	0.037
23	N-methyl-3-pyrrolyl	0.42	0.11
24	3-pyridyl	0.33	nd[b]
25	5-thiazolyl	>10	0.50
26	2-naphthyl	nd[b]	0.073

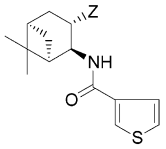
[a] PGD_2 receptor (DP) assay.[1] Inhibition of [^{3}H]PGD_2 specific binding to human platelet membranes[4c] and cAMP formation evoked by PGD_2 in human platelets.[25] IC$_{50}$ represents the mean value of two or three measurements. [b] Not done.

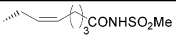
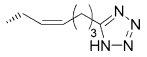
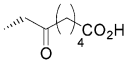
flexible for modification, was selected for the lead compound to be further modified.

Study of the biological activities of the compounds by introducing various kinds of substituents to the phenyl ring and other types of aromatics or alkyl moieties (**12**−**26**) showed that derivatives replacing the phenyl group with other aromatic rings, such as 2- or 3-thienyl, 3-furfuryl, and 2-pyrrolyl (**19**−**22**), gave fairly good activity in the cAMP assay (Table 2). In particular, compound **20**, having the 3-thienyl group as a benzene ring equivalent, effectively inhibited the antigen-induced increase in intranasal pressure in actively sensitized guinea pigs, with the percent inhibition at 1 mg/kg (iv) being 77% ($p < 0.01$). On the other hand, compound **19** having the 2-thienyl group exhibited weak activity in vivo, with the percent inhibition at 1 mg/kg (iv) being 38%. Thus, further evaluation was performed with **20** as the next lead compound to obtain more favorable derivatives for drug candidates.

At this stage, α-chain modification was performed for compound **20** having the 3-thienyl group as the ω-chain as shown in Table 3. However, these transformations dramatically decreased the inhibitory activity in comparison with the normal ω-chain except for **28**, which has a tetrazole moiety as the bioisoster of the carboxylic acid group. This suggested that the spatial position and acidity of the carboxylic acid are very important for the inhibitory activity (**27**−**29**) and the normal type of ω-chain, the heptenoic acid structure, is the most suitable for expression of the biological activity.

Table 3. Inhibition of PGD_2 Receptor Binding and Biological Activity in Human Platelets

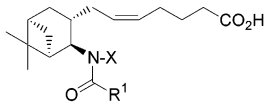


		IC$_{50}$ (μM)[a]	
		DP	
compd	Z	binding	cAMP
27		6.0	0.41
28		nd[b]	0.093
29		>10	>1.0

[a] PGD_2 receptor (DP) assay.[1] Inhibition of [^{3}H]PGD_2 specific binding to human platelet membranes[4c] and cAMP formation evoked by PGD_2 in human platelets.[25] IC$_{50}$ represents the mean value of two or three measurements. [b] Not done.

Methylation of the amide moiety of compounds **7** and **20** significantly diminished the activity (**37** and **38**), indicating that the acidic proton of the amide moiety played an important role in the PGD_2 inhibitory activity in the case of the 6,6-dimethylbicyclo[3.1.1]heptane ring system as well as the bicyclo[2.2.1]heptane derivatives[1a,20] and the introduction of methyl, methoxy, and phenyl groups at the 5-position in the thiophene moiety (**32**−**36**) tended to enhance the activity in comparison with other transformations (Table 4). In our previous report,[1a] we suggested that a rigid and planar conformation of the ω-chain would be important for strong PGD_2 antagonism, so we linked each aromatic ring of **36** as a benzothiopene moiety in order to further enhance the activity. In accord with our expectation, compound **40** showed very good activity in in vitro and in vivo assays (Table 5). The substitution patterns of the benzothoiphene derivaives (**39**−**41**) indicated fairly good results, but replacement of the sulfur atom of the benzothiophene moiety with a nitrogen or oxygen atom considerably decreased the inhibitory activity (**42** and **43**). Study of the substitution groups in the benzothiophene-3-carbonyl derivative showed that introduction of a hydroxyl or fluoro substituent at the 5-position (**44** and **45**) increased the inhibitory activities of PGD_2 receptor binding and cAMP assay about 1 or more orders of magnitude over the compound **40**. This suggests the existence of a hydrogen bonding site at the 5-position. These compounds also exhibited strong inhibitory activity in vivo at 3 mg/kg (po), and we now had two highly active compounds as drug candidates against allergic diseases.

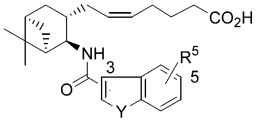
Table 4. Inhibition of PGD_2 Receptor Binding, Biological Activity in Human Platelets, and Antigen-Induced Nasal Blockage in Guinea Pigs



			IC_{50} (μM)[a]	
			DP	
compd	X	R^1	binding	cAMP
30	H	2-Me-3-thienyl	0.18	0.02
31	H	4-MeO-3-thienyl	4.5	0.23
32	H	5-MeO-3-thienyl	0.52	0.056
33	H	5-Me-4-Ph-3-thienyl	0.59	0.074
34	H		0.15	0.035
35	H	5-Me-3-thienyl	0.013	0.025
36	H	5-Ph-3-thienyl	0.042	0.10
37	Me	Ph	>10	>1.0
38	Me	3-thienyl	>10	>1.0

[a] PGD_2 receptor (DP) assay.[1] Inhibition of [^{3}H]PGD_2 specific binding to human platelet membranes[4c] and cAMP formation evoked by PGD_2 in human platelets.[25] IC_{50} represents the mean value of two or three measurements.

Table 5. Inhibition of PGD_2 Receptor Binding, Biological Activity in Human Platelets, and Antigen-Induced Nasal Blockage in Guinea Pigs



				IC_{50} [a] (μM) DP		
compd	position	Y	R^5	binding	cAMP	in vivo[b] (rhinitis model) % inhibition
39	2	S		0.019	0.39	nd[c]
40	3	S		0.032	0.022	82 ± 8[d,e,g]
41	7	S		0.026	0.0056	70 ± 6[d,e]
42	3	NH		0.52	0.11	nd[c]
43	2	O		0.69	0.076	nd[c]
44	3	S	5-F	0.00042	0.0032	nd[c] (86 ± 8[d,f])
45	3	S	5-OH	0.0019	0.0009	96 ± 5[d,e] (64 ± 7[d,f])
46	3	S	6-OH	0.0022	0.018	88 ± 3[d,e]
47	3	S	5-NHMs	7.5	0.030	nd[c]

[a] PGD_2 receptor (DP) assay.[1] Inhibition of [^{3}H]PGD_2 specific binding to human platelet membranes[4c] and cAMP formation evoked by PGD_2 in human platelets.[25] IC_{50} represents the mean value of two or three measurements. [b] Inhibition of antigen-induced increase in intranasal pressure in actively sensitized guinea pigs. Compounds were administrated po 10 min before the antigen challenge. [c] Not done. [d] Significantly different from each control; $p < 0.01$ (Student's *t*-test). [e] % inhibition at 10 mg/kg (po). [f] % inhibition at 3 mg/kg (po). [g] Na salt was used.

Further evaluation was performed for the selected compounds (**20**, **44**, and **45**) that markedly inhibited PGD_2- and antigen-induced increase in conjunctival microvascular permeability (Table 6). In the asthma model, compounds **44** and **45** also inhibited antigen-induced increase in specific airway resistance at 10 mg/kg (po). Since PGD_2 has been thought to exert a contractile response of airway smooth muscle by directly acting on the TXA_2 receptor not via the PGD_2 receptor,[21] there is a possibility that the antiasthmatic activity of these compounds arises from their TXA_2 receptor antagonistic activity. However, this possibility was ruled out by our finding that none of these three compounds had a significant effect on the bronchoconstriction induced by intravenous injection of U-46619, a TXA_2 mimic, at 10 mg/kg (po) in the guinea pig model.[1b,21b] Thus, the PGD_2 receptor mediated component may have a role in the antigen-induced increase in specific airway resistance.[2a,3,22] We also evaluated the effect of compound **45** on antigen-induced eosinophil infiltration in allergic rhinitis and asthma models. Compound **45** effectively reduced the increase in the eosinophil number in nasal lavage fluid at 5 h after intranasal antigen challenge in actively sensitized guinea pig[2b,23] and in bronchoalveolar lavage fluid at 72 h after inhalation of aerosol antigen,[22] the percent inhibition at 10 mg/kg (po) being 80% ($p < 0.01$) and 43% ($p < 0.05$), respectively.

Table 6. Effect of Orally Administered DP Antagonists on PGD_2- and Antigen-Induced Increase in Vascular Permeability in Conjunctiva and Antigen-Induced Increase in Airway Resistance in Guinea Pigs

	conjunctivitis model ED_{50} [a] (mg/kg)		
compd	PGD_2	antigen	asthma model % inhibition at 10 mg/kg[b] antigen
20	3.5	9.5	15 ± 21
44	3.5	8.9	69 ± 9[c]
45	0.12	2.0	70 ± 5[c]

[a] Dose required to inhibit 50% of conjunctival microvascular permeability caused by topical application of 0.1% PGD_2 or antigen in guinea pigs. [b] Inhibition of increase in specific airway resistance by antigen inhalation in conscious guinea pigs. All antagonists were administered po 1 h before the challenge. Values represent the mean ± SEM. [c] Significantly different from each control; $p < 0.01$ (Student's *t*-test).

Conclusion

We have described here novel PGD_2 receptor antagonists containing the 6,6-dimethylbicyclo[3.1.1]heptane ring system with the characteristic carbonylamino group, which were originally synthesized in our laboratories. Although there have been several reports on the contribution of PGD_2 to the pathogenesis of allergic diseases on the basis of local production of PGD_2 after antigen challenge,[3,24] only a small number of PGD_2 antagonists have been synthesized, even as experimental agents. In this study, we obtained PGD_2 antagonists that were effective in rhinitis, conjunctive, and asthma models in the guinea pig. Among them, compound **45**, designated as S-5751, was considered to be a promising candidate for development as a drug against diseases caused by excess PGD_2 production. It is now being developed as an alternative antiallergic drug.

Experimental Section

Chemistry. Melting points were uncorrected. ^{1}H NMR spectra were taken with a Varian VXR-200 or Gemini-200, 300 FT-NMR spectrometer using tetramethylsilane as an internal standard. IR spectra were recorded on a Nicolet 20SXB FT-

IR spectrometer. Mass spectra were measured on a JEOL JMS-SX/S102A or a HITACHI M-90 mass spectrometer. Unless otherwise stated, all reactions were carried out under a nitrogen atmosphere with commercial grade solvents that had been dried over type 4A molecular sieves. Drying of organic extracts over anhydrous sodium sulfate is simply indicated by the word "dried". Column chromatography using Merck silica gel 60 (70−230 or 230−400 mesh) or a Merck Lobar column is referred to as "chromatography on silica gel".

Typical Procedures. (1*R*,2*R*,3*S*,5*S*)-(5*Z*)-(6,6-Dimethyl-2-((thiophene-3-carbonyl)amino)bicyclo[3.1.1]hept-3-yl)-hept-5-enoic Acid Methyl Ester. A mixture of 0.256 g (2.00 mmol) of 3-thiophene carboxylic acid, one drop of DMF, and 0.43 mL (6 mmol) of $SOCl_2$ in 4 mL of toluene was refluxed for 1 h. The reaction mixture was concentrated in vacuo to obtain the corresponding acid chloride. The prepared acid chloride was dissolved in 2 mL of THF and added to a stirred solution of 0.279 g (1.00 mmol) of **48** and 0.50 mL (0.360 mmol) of triethylamine in 3 mL of THF. After being stirred for 2 h, the reaction mixture was diluted with water and extracted with AcOEt. The organic layer was washed with 1 N HCl, water, and a saturated $NaHCO_3$ solution, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel to give the title compound (0.362 g, 93%).

(1*R*,2*R*,3*S*,5*S*)-(5*Z*)-(6,6-Dimethyl-2-((thiophene-3-carbonyl)amino)bicyclo[3.1.1]hept-3-yl)hept-5-enoic Acid (20). To a solution of 0.224 g (0.575 mmol) of the methyl ester prepared above in 2.5 mL of methanol was added 0.36 mL (1.45 mmol) of 4 N NaOH, and the mixture was stirred for 6 h. The reaction mixture was neutralized with 1 N HCl and extracted with AcOEt. The organic layer was washed with water, dried over $MgSO_4$, and evaporated. The residue was dissolved in a small amount of AcOEt and diluted with hexane. The resulting precipitate was filtered with glass filter and dried to give **20** (0.206 g, 95%) as a colorless solid. Mp 87−88 °C. ^{1}H NMR ($CDCl_3$): δ 0.96 (d, J = 10.5 Hz, 1H), 1.11 (s, 3H), 1.23(s, 3H), 1.52−2.46 (m, 14H), 4.25 (m, 1H), 5.34−5.56 (m, 2H), 6.14 (d, J = 8.7 Hz, 1H), 7.34 (d, J = 2.0 Hz, 2H), 7.85 (t, J = 2.0 Hz, 1H). IR ($CHCl_3$): 3452, 3114, 3030, 3013, 2925, 2870, 1708, 1649, 1535, 1498, 1471 cm^{-1}. $[\alpha]^{24}_D$ +51.6° (*c* 1.01, MeOH). Anal. ($C_{21}H_{29}NO_3S$) C, H, N, S.

(1*R*,2*R*,3*S*,5*S*)-(5*Z*)-7-(2-((Benzo[*b*]thiophene-3-carbonyl)amino)-6,6-dimethylbicyclo[3.1.1]hept-3-yl)hept-5-enoic Acid (40). To a mixture of 1.00 g (3.36 mmol) of **48**, 0.718 g (4.03 mmol) of 3-benzothiophene carboxylic acid (**40c**), and 45 mg (0.336 mmol) of HOBT in 6 mL of THF was added 0.678 g (4.37 mmol) of WSCD in 4 mL of THF. After being stirred for 14 h at room temperature, the mixture was poured into 10 mL of water, treated with 5 mL of 1 N HCl, and extracted with Et_2O twice. The organic layer was washed with water and saturated $NaHCO_3$ solution, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel to give 1.718 g of the ester compound. This compound was dissolved with 8 mL of MeOH and 4 mL of THF, and 2.0 mL (8 mmol) of 4 N NaOH solution was added. After being stirred for 3 h, the mixture was concentrated in vacuo and the residue was dissolved with 25 mL of H_2O. The mixture was treated with 1 N HCl and extracted with Et_2O. The organic layer was washed with water, dried over $MgSO_4$, and evaporated. The residue was crystallized from a small portion of Et_2O and washed with hexane to give a colorless solid (1.36 g, 98%). Mp 112−113 °C. ^{1}H NMR ($CDCl_3$): δ 0.99 (d, J = 10.2 Hz, 1H), 1.11 (s, 3H), 1.24 (s, 3H), 1.52−2.53 (m, 14H), 4.34 (m, 1H), 5.33−5.57 (m, 2H), 6.21 (d, J = 8.6 Hz, 1H), 7.35−7.50 (m, 2H), 7.83 (s, 1H), 7.86 (m, 1H), 8.31 (m, 1H). IR ($CHCl_3$): 3443, 3067, 3013, 2925, 2870, 2665, 1708, 1651, 1515, 1493 cm^{-1}. $[\alpha]^{23}_D$ +58.1° (*c* 1.01, MeOH). Anal. ($C_{25}H_{31}NO_3S$) C, H, N, S.

Thiophene-3-carboxylic Acid [(1*R*,2*R*,3*S*,5*S*)-3-((*Z*)-6-Carbamoyl-hex-2-enyl)-6,6-dimethylbicyclo[3.1.1]hept-2-yl]amide (49). To a mixture of 0.376 g (1.00 mmol) of **20** and 0.146 mL (1.05 mmol) of Et_3N in 1.5 mL of THF was added 0.10 mL (1.05 mmol) of $ClCO_2Et$ at 0 °C. After being stirred for 30 min, this solution was poured into 0.7 mL (5.00 mmol) of 28% NH_4OH in 6 mL of THF and allowed to warm to ambient temperature. The mixture was stirred for 1 h, poured into water, and extracted with AcOEt. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel to give the title compound (0.32 g, 89%) as an amorphous compound. ^{1}H NMR ($CDCl_3$): δ 0.96 (d, J = 10.2 Hz, 1H), 1.12 (s, 3H), 1.22 (s, 3H), 1.54−2.44 (m, 14H), 4.20 (m, 1H), 5.26 (br, 1H), 5.34−5.50 (m, 2H), 6.21 (d, J = 8.7 Hz, 1H), 6.43 (br, 1H), 7.34−7.35 (m, 2H), 7.83 (dd, J = 2.1 and 1.8 Hz, 1H). IR ($CHCl_3$): 3523, 3451, 3407, 3375, 3198, 2940, 1677, 1645, 1603, 1598, 1538, 1500, 1471, 1386, 1320 cm^{-1}. $[\alpha]^{26}_D$ +57.2° (*c* 1.02, MeOH). Anal. ($C_{21}H_{30}N_2O_2S\cdot0.3H_2O$) C, H, N, S.

Thiophene-3-carboxylic Acid [(1*R*,2*R*,3*S*,5*S*)-3-((*Z*)-6-Cyanohex-2-enyl)-6,6-dimethylbicyclo[3.1.1]hept-2-yl]amide (50). To a mixture of 0.595 g (1.59 mmol) of **49** in 13 mL of toluene and 6.5 mL of THF was added 0.173 mL (2.39 mmol) of thionyl chloride, and this solution was heated at 75 °C. After being stirred for 2.5 h, the mixture was poured into ice/water and extracted with AcOEt. The organic layer was washed with water, 2 N NaOH, and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel to give **50** (0.565 g, 99%) as an amorphous compound. ^{1}H NMR ($CDCl_3$): δ 0.85 (d, J = 10.2 Hz, 1H), 1.10 (s, 3H), 1.23 (s, 3H), 1.57−2.28 (m, 11H), 2.35 (t, J = 7.2 Hz, 1H), 2.51 (m, 1H), 4.27 (m, 1H), 5.30−5.60 (m, 2H), 6.12 (d, J = 8.7 Hz, 1H), 7.34−7.35 (m, 2H), 7.83 (m, 1H). IR ($CHCl_3$): 3678, 3452, 3012, 2922, 2244, 1647, 1533, 1497, 1470 cm^{-1}.

Thiophene-3-carboxylic Acid {(1*R*,2*R*,3*S*,5*S*)-6,6-Dimethyl-3-[(*Z*)-6-(1*H*-tetrazol-5-yl)hex-2-enyl]bicyclo[3.1.1]-hept-2-yl}amide (28). To a solution of 0.327 g (0.917 mmol) of **50** in 1.8 mL of toluene were added 0.243 mL (1.83 mmol) of $TMSN_3$ and 23 mg (0.092 mmol) of Bu_2SnO, and this mixture was heated at 110 °C. After being stirred for 45 h, the mixture was evaporated and the residue was purified by column chromatography on silica gel to give **28** (0.315 g, 86%) as an amorphous compound. ^{1}H NMR ($CDCl_3$): δ 0.85 (d, J = 10.2 Hz, 1H), 1.14 (s, 3H), 1.26 (s, 3H), 1.61 (m, 1H), 1.83 (m, 1H), 1.91−2.14 (m, 5H), 2.20−2.38 (m, 5H), 2.90−3.10 (m, 2H), 4.09 (m, 1H), 5.46 (m, 2H), 6.29 (d, J = 8.7 Hz, 1H), 7.35−7.42 (m, 2H), 7.94 (dd, J = 1.5 and 3.0 Hz, 1H). IR ($CHCl_3$): 3451, 3117, 2925, 2871, 2753, 2621, 1631, 1538, 1500, 1471, 1415, 1386, 1367, 1320, 1260, 1236, 1078, 1058, 988 cm^{-1}. $[\alpha]^{26}_D$ +60.6° (*c* 1.01, MeOH). Anal. ($C_{21}H_{29}N_5OS\cdot0.2H_2O$) C, H, N, S.

Thiophene-3-carboxylic Acid (2,4-Dimethoxybenzyl)-[(1*R*,2*R*,3*R*,5*S*)-6,6-dimethyl-3-(2-oxo-ethyl)bicyclo[3.1.1]-hept-2-yl]amide (29b). To a solution of 0.274 mL (3.87 mmol) of DMSO in 1.3 mL of CH_2Cl_2 was added 0.162 mL (1.81 mmol) of $(COCl)_2$ in 3.8 mL of CH_2Cl_2 over a period of 30 min at −78 °C. After being stirred for 30 min, 0.536 g (1.21 mmol) of **29a** in 2 mL of CH_2Cl_2 was added dropwise to the mixture, the mixture was stirred for 40 min at −50 °C, then 1.13 mL (8.09 mmol) of Et_3N was added, and the mixture was allowed to reach ambient temperature. After being stirred for 1 h, the mixture was poured into ice/water and extracted with AcOEt. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated to give **29b** (0.564 g, 100%) as an amorphous compound. ^{1}H NMR ($CDCl_3$): δ 0.90 (m, 1H), 1.06 (s, 3H), 1.17 (s, 3H), 1.82 (m, 1H), 2.18−2.89 (m, 7H), 3.77 (s, 3H), 3.79 (s, 3H), 4.56−4.65 (m, 3H), 6.40 (d, J = 2.4 Hz, 1H), 6.44 (dd, J = 8.4 and 2.4 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 7.16 (dd, J = 1.2 and 5.1 Hz, 1H), 7.23 (m, 1H), 7.42 (dd, J = 1.2 and 3.0 Hz, 1H), 9.61 (s, 1H).

{(1*R*,2*R*,3*R*,5*S*)-[(2,4-Dimethoxybenzyl)(1-thiophen-3-yl-methanoyl)amino]dimethylbicyclo[3.1.1]hept-3-yl}-oxoheptanoic Acid (29c). To a mixture of 44 mg (1.81 mmol) of magnesium turnings and a catalytic amount of I_2 in 0.2 mL of dry Et_2O was added dropwise 0.544 g (1.93 mmol) of 5-bromo-1-(*tert*-butyldimethylsiloxy)pentane in 2 mL of Et_2O with gentle refluxing. After being stirred for 2 h, the mixture was cooled to 0 °C and 0.564 g (1.21 mmol) of **29b** was added.

This reaction mixture was allowed to reach ambient temperature, stirred for 18 h, poured into saturated NH_4Cl solution, and extracted with AcOEt. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel to give 0.597 g (0.826 mmol) of an alcohol derivative. This compound was successively dissolved with 12 mL of acetone and 0.96 mL (27.81 mmol) of Jones reagent at 0 °C. The reaction mixture was allowed to reach ambient temperature, stirred for 1.5 h, and quenched with several drops of MeOH. The mixture was poured into ice/water and extracted with AcOEt. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated to give **29c** (0.450 g, 69%) as an amorphous compond. ^{1}H NMR ($CDCl_3$): δ 0.10 (s, 3H), 0.91 (s, 3H), 1.32 (m, 1H), 1.88 (m, 1H), 2.17−2.62 (m, 13H), 2.79 (m, 2H), 3.76 (s, 3H), 3.78 (s, 3H), 4.51−4.77 (m, 3H), 6.39 (s, 1H), 6.42 (m, 1H), 7.06−7.22 (m, 3H), 7.43 (s, 1H). IR ($CHCl_3$): 3664, 3572, 3010, 2924, 2852, 1710, 1613, 1503, 1462, 1418, 1300, 1283, 1254 cm^{-1}.

7-{(1*R*,2*R*,3*R*,5*S*)-6,6-Dimethyl-2-[(1-thiophen-3-ylmethanoyl)amino]bicyclo[3.1.1]hept-3-yl}-6-oxoheptanoic Acid (29). To a solution of 0.450 g (0.83 mmol) of **29c** and 0.218 mL (1.66 mmol) of 1.3-dimethoxybenzene in 4 mL of CH_2Cl_2 was added 1.92 mL (24.9 mmol) of trifluoroaceetic acid at 0 °C. After being stirred for 15 h, the mixture was poured into water and extracted with AcOEt. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel to give **29** (0.188 g, 58%). ^{1}H NMR ($CDCl_3$): δ 0.93 (d, J = 10.2 Hz, 1H), 1.15 (s, 3H), 1.24 (s, 3H), 1.36 (m, 1H), 1.56−1.62 (m, 3H), 1.99 (m, 1H), 2.17 (m, 1H), 2.30−2.65 (m, 9H), 3.00 (dd, J = 4.2 and 16.8 Hz, 1H), 4.19 (m, 1H), 6.19 (d, J = 8.4 Hz, 1H), 7.31−7.36 (m, 2H), 7.84 (dd, J = 1.5 and 2.7 Hz, 1H). IR ($CHCl_3$): 3452, 2925, 1710, 1649, 1535, 1498, 1471, 1412, 1387, 1367, 1284, 1267, 1159, 1133, 1096, 1017, 874, 841 cm^{-1}. $[\alpha]^{25}_D$ +20.7° (*c* 1.01, MeOH). Anal. ($C_{21}H_{29}NO_4S\cdot0.2H_2O$) C, H, N, S.

4,5,6,7-Tetrahydrobenzo[*b*]thiophene-3-carboxylic Acid (34a). To a solution of 4.00 g (17.75 mmol) of ethyl 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate in 20 mL of 1,4-dioxane and 14 mL of concentrated HCl solution was slowly added 1.35 g (19.53 mmol) of $NaNO_2$ in 2.0 mL of water at 0 °C. The reaction mixture was stirred for 15 min at −5 °C and then added portionwise to 36 mL of 50% H_3PO_4 solution and 36 mL of Et_2O at 0 °C with vigorous stirring. After being stirred for 30 min, the mixture was poured into ice/water and extracted with Et_2O. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel to give an ester (2.00 g, 54%). This compound (2.00 g, 9.51 mmol) was dissolved with 21 mL of EtOH and 21 mL of 1 N NaOH and refluxed. After being stirred for 30 min, the mixture was cooled to ambient temperature and treated with 4.2 mL of 5 N HCl. The precipitate was collected with a glass filter and dried under reduced pressure to give **34a** (1.68 g, 97%) as a colorless solid. Mp 181−183 °C. ^{1}H NMR ($CDCl_3$): δ 1.80−1.86 (m, 4H), 2.71−2.96 (m, 4H), 8.06 (s, 1H).

4-Methoxythiophene-3-carboxylic Acid (31a). To a mixture of 2.16 g (93.9 mmol) of Na in 40 mL of MeOH was added 2.00 g (9.05 mmol) of methyl 3-bromo-4-thiophenecarboxylate, 0.51 g (3.40 mmol) of NaI, and 0.31 g (3.90 mmol) of CuO, and the mixture was refluxed. After being stirred for 68 h, the mixture was filtered through Hyflo Super-Cell and evaporated. The residue was treated with 2 N HCl and extracted with AcOEt. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was dissolved with Et_2O, and 25 mL of CH_2N_2 in Et_2O solution (ca. 0.5 M) was added at 0 °C. The mixture was quenched with AcOH and evaporated. The residue was purified by column chromatography on silica gel to give methyl 4-methoxy-3-thiophenecarboxylate (1.30 g, 83%). This compound was dissolved in 15 mL of MeOH, 15 mL of 1 N NaOH was added, and the mixture was refluxed. After being stirred for 15 min, the mixture was concentrated in vacuo, treated with 2 N HCl, and diluted with water. The precipitate was collected with a glass filter and dried under reduced pressure to give **31a** (1.05 g, 81%) as a colorless solid. Mp 100−105 °C. ^{1}H NMR ($CDCl_3$): δ 4.00 (s, 3H), 6.41 (d, J = 3.6 Hz, 1H), 8.20 (d, J = 3.6 Hz, 1H). IR (Nujol): 3514, 3398, 1705, 1666, 1554, 1467, 1294, 1208, 1181, 1081 cm^{-1}. Anal. ($C_6H_6O_3S\cdot1.0H_2O$) C, H, S.

5-Bromobenzo[*b*]thiophene (45b). To a solution of 9.99 g (0.434 mmol) of Na in 250 mL of MeOH was added 50.95 g (0.269 mmol) of 4-bromothiophenol and 35 mL (0.296 mmol) of bromoacetoaldehyde dimethylacetal at 0 °C, and the mixture was refluxed. After being stirred for 3.5 h, the mixture was evaporated and cool water was added to the residue. The aqueous layer was extracted with Et_2O, and the combined organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was distilled under reduced pressure to give a thioether ($bp_{0.5}$ 118−123 °C). To a mixture of 140 g of PPA and 600 mL of chlorobenzene was slowly added 70.0 g (0.253 mmol) of this crude material with gentle refluxing. After being stirred for 15 h, the supernatant of the reaction mixture was separated and the residue was washed with toluene. The combined organic phase was evaporated, and the residue was purified by column chromatography on silica gel to give **45b** (42.35 g, 79%) as a colorless solid. Mp 45−46 °C. ^{1}H NMR ($CDCl_3$): δ 7.27 (d, J = 5.0 Hz, 1H), 7.41−7.49 (m, 2H), 7.74 (d, J = 8.6 Hz, 1H), 7.96 (d, J = 1.6 Hz, 1H).

5-Bromobenzo[*b*]thiophene-3-carboxylic Acid (45c). To a solution of 20.0 g (93.9 mmol) of **45b** and 8.0 mL (0.113 mol) of acetyl chloride in 200 mL of 1,2-dichloroethane was slowly added 13.0 mL (0.113 mol) of $SnCl_4$ in 30 mL of 1,2-dichloroethane at 0 °C, and the mixture was allowed to reach ambient temperature. After being stirred for 20 h, the mixture was poured into ice/water and extracted with $CHCl_3$. The organic layer was washed with saturated $NaHCO_3$ solution, water, and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel to give 3-acetyl-5-bromobenzo[*b*]thiophene (21.52 g, 90%). To a solution of 29.4 g (0.734 mol) of NaOH in 200 mL of water was slowly added 15.2 mL (0.295 mol) of Br_2 at 0 °C. After the mixture was stirred for 15 min, 21.52 g (84.3 mmol) of an acetyl derivative in 160 mL of 1,4-dioxane was added dropwise, and the mixture was allowed to reach ambient temperature and stirred for 1.5 h. The reaction mixture was quenched with 10.0 g (96.1 mmol) of $NaHSO_3$ and 19 mL of concentrated HCl. The precipitate was collected with a glass filter, washed with water, and dried to give **45c** (16.6 g, 77%) as a colorless solid. Mp 292−293 °C. ^{1}H NMR (DMSO-d_6): δ 7.61 (dd, J = 8.6 and 2.0 Hz, 1H), 8.09 (d, J = 8.6 Hz, 1H), 8.66 (d, J = 2.0 Hz, 1H), 8.72 (s, 1H).

5-Hydroxybenzo[*b*]thiophene-3-carboxylic Acid (45d). To a solution of 4.37 g (0.19 mol) of Na in 100 mL of MeOH was added 5.00 g (19.5 mmol) of **45c** and 0.279 g (1.95 mmol) of CuBr, and the mixture was refluxed. After the mixture was stirred for 2 h, 0.124 g (19.5 mmol) of Cu was added and the mixture was stirred for 42 h. The reaction mixture was filtered through Hyflo Super-Cell and evaporated. To the residue was added ice/water, and the mixture was treated with concentrated HCl solution and extracted with Et_2O. The organic layer was washed with water and brine, and 20 mL (ca. 20.0 mmol) of CH_2N_2 solution was added at 0 °C. After being stirred for 30 min, the mixture was quenched with AcOH and water and extracted with AcOEt. The organic layer was washed with water and saturated $NaHCO_3$ solution, dried over $MgSO_4$, and evaporated to give a methyl ester (4.53 g, 71%). A portion of the methyl ester (2.06 g, 9.27 mmol) was dissolved with 20 mL of CH_2Cl_2, and 2.0 mL (21.2 mmol) of BBr_3 in 5 mL of CH_2Cl_2 was added at 0 °C under N_2. After being stirred for 20 min, the mixture was allowed to reach ambient temperature and was stirred for another 3.5 h. The reaction mixture was poured into ice/water, and the precipitate was collected with a glass filter and dried. To the obtained solid was added 22 mL (22.0 mmol) of 1 N NaOH, and the mixture was heated at 100 °C. After being stirred for 20 min, the mixture was cooled to room

temperature, treated with 2 N HCl, and extracted with AcOEt. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated to give **45d** (1.64 g, 91%) as a colorless solid. Mp 264−265 °C. ^{1}H NMR (DMSO-d_6): δ 6.93 (dd, J = 2.6 and 8.6 Hz, 1H), 7.83 (d, J = 8.6 Hz, 1H), 7.93 (d, J = 2.6 Hz, 1H), 8.55 (s, 1H), 9.59 (br, 1H), 12.80 (br, 1H).

Compounds **40c**,[11a] **41b**,[11b] **44c**,[11a] and **46d**[11c] were prepared by procedures similar to those used for **45b**−**d**.

Nitro-4-prop-2-ynylsulfanylbenzene (47b). To a solution of 28.23 g (0.146 mmol) of **47a** in 168 mL of HCO_2H and 9.2 mL of water was slowly added 15.3 mL (0.148 mmol) of 30% H_2O_2 at 0 °C, and the mixture was allowed to reach room temperature. After being stirred for 5 h, the mixture was poured into water and extracted with AcOEt. The organic layer was washed with water and saturated $NaHCO_3$ solution, dried over Na_2SO_4, and evaporated to give **47b** (27.96 g, 91%) as a pale-yellow solid. Mp 139−140 °C. ^{1}H NMR ($CDCl_3$): δ 2.40 (dd, J = 2.4 and 2.7 Hz, 1H), 3.72 (d, J = 2.4 Hz, 1H), 3.74 (d, J = 2.7 Hz, 1H), 7.92 (d, J = 8.4 Hz, 2H), 8.40 (d, J = 8.4 Hz, 2H).

1-Nitro-4-(prop-2-yne-1-sulfinyl)benzene (47c). A solution of 27 67 g (0.132 mmol) of **47b** in 810 mL of 1,4-dioxane was refluxed. After the mixture was stirred for 3 h, 7.54 g (39.68 mmol) of *p*-TsOH·H_2O and 75 mL of water were added, followed by refluxing for a further 2 h. The mixture was cooled to ambient temperature and evaporated. The residue was treated with saturated $NaHCO_3$ solution and extracted with AcOEt. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel to give **47c** (20.0 g, 72%) as a pale-yellow solid. Mp 155−156 °C. ^{1}H NMR ($CDCl_3$): δ 1.87 (t, J = 5.4 Hz, 1H), 5.02 (d, J = 5.1 Hz, 2H), 7.60 (s, 1H), 7.97 (d, J = 9.0 Hz, 1H), 8.22 (dd, J = 2.4 and 9.0 Hz, 1H), 8.77 (d, J = 2.4 Hz, 1H).

(5-Nitrobenzo[*b*]thiophen-3-yl)methanol (47d). To a solution of 10.0 g (47.85 mmol) of **47c** in 100 mL of EtOH was added 64.59 g (0.287 mmol) of $SnCl_2$·H_2O, and the mixture was heated at 80 °C. After being stirred for 40 min, the mixture was treated with 2 N NaOH solution and extracted with AcOEt. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel to give an amine compound (6.55 g, 76%). To a solution of 6.55 g (36.59 mmol) of amine in 66 mL of THF and 6.6 mL of water were added 10.6 g (76.70 mmol) of K_2CO_3 and 15.95 g (73.17 mmol) of Boc_2O. After being stirred for 19 h, the mixture was poured into ice/water and extracted with AcOEt. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel to give **47d** (8.88 g, 87%) as a colorless solid. Mp 124−126 °C. ^{1}H NMR ($CDCl_3$): δ 1.54 (s, 9H), 1.58 (br, 1H), 4.92 (s, 2H), 6.58 (br, 1H), 7.30 (dd, J = 2.1 and 9.0 Hz, 1H), 7.40 (s, 1H), 7.74 (d, J = 9.0 Hz, 1H), 7.95 (d, J = 2.1 Hz, 1H).

5-*tert*-Butoxycarbonylaminobenzo[*b*]thiophene-3-carboxylic Acid (47e). To a solution of 8.88 g (31.83 mmol) of **47d** and 49.7 mg (0.319 mmol) of 2,2,6,6-tetramethylpiperidine 1-oxide (TEMPO) in 266 mL of MeCN was added dropwise 60 mL (37.98 mmol) of 0.633 N NaClO solution at 0 °C. After the mixture was stirred for 30 min, 5.44 g (47.75 mmol) of 79% $NaClO_2$ and 4.34 mL (43.53 mmol) of 31% H_2O_2 solution were added, and the reaction mixture was allowed to reach ambient temperature. After being stirred for 1 h, the mixture was diluted with water and the precipitated solid was collected. The precipitate was washed with water and dried under reduced pressure to give **47e** (5.28 g, 57%) as a colorless solid. Mp 203−205 °C. ^{1}H NMR (DMSO-d_6): δ 1.50 (s, 9H), 7.47 (dd, J = 2.1 and 9.0 Hz, 1H), 7.91 (d, J = 9.0 Hz, 1H), 8.58 (s, 1H), 8.74 (d, J = 2.1 Hz, 1H), 9.48 (s, 1H), 12.82 (br, 1H).

(*Z*)-7-((1*R*,2*R*,3*S*,5*S*)-2-{[1-(5-Methoxysulfinylaminobenzo[*b*]thiophen-3-yl)methanoyl]amino}-6,6-dimethylbicyclo[3.1.1]hept-3-yl)hept-5-enoic Acid (47). To a solution of 0.558 g (2.00 mmol) of **48** and 0.586 g (2.00 mmol) of **47e** in 6 mL of THF was added 27 mg (0.20 mmol) of HOBT and 0.403 g (2.60 mmol) of WSCD in 2 mL of THF, and the mixture was stirred at room temperature. After being stirred for 19 h, the mixture was poured into 1 N HCl and extracted with toluene. The combined organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel to give the crude product (1.03 g, 93%). A portion of this compound (0.768 g, 1.39 mmol) was dissolved with CH_2Cl_2, and 1.07 mL (13.9 mmol) of TFA was added at room temperature. After being stirred for 6 h, the mixture was evaporated, treated with saturated $NaHCO_3$ solution, and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to afford the amine product (0.628 g, 100%). To a solution of this amine product (0.178 g, 0.392 mol) in 1.7 mL of pyridine was added 36 μL (0.470 mmol) of methanesulfonyl chloride at 0 °C, and this mixture was allowed to reach ambient temperature. After being stirred for 1 h, the mixture was quenched with 1 N HCl and extracted with AcOEt. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel and hydrolyzed by 4 N NaOH in MeOH at room temperature to afford **47** (0.184 g, 91%) as an amorphous compound. ^{1}H NMR ($CDCl_3$): δ 1.12 (m, 1H), 1.22−1.33 (m, 2H), 1.42−1.54 (m, 2H), 1.61−1.76 (m, 4H), 2.01−2.33 (m, 5H), 2.40 (t, J = 7.2 Hz, 2H), 2.57 (m, 1H), 2.96 (s, 3H), 3.91 (m, 1H), 5.31−5.47 (m, 2H), 6.19 (d, J = 7.2 Hz, 1H), 7.51 (dd, J = 2.4 and 9.0 Hz, 1H), 7.81 (d, J = 9.0 Hz, 1H), 7.88 (s, 1H), 8.20 (d, J = 2.4 Hz, 1H). IR ($CHCl_3$): 3509, 3438, 3366, 3223, 3100, 3031, 3023, 3017, 3012, 2955, 2876, 1709, 1645, 1606, 1518, 1475, 1329 cm^{-1}. $[\alpha]^{23}_D$ +37.8° (*c* 1.01, MeOH). Anal. ($C_{26}H_{34}N_2O_5S_2$·$0.2H_2O$) C, H, N, S.

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Supporting Information Available: Experimental details with spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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