Synthesis and Biological Activity of Various Derivatives of a Novel Class of Potent, Selective, and Orally Active Prostaglandin D_2 Receptor Antagonists. 1. Bicyclo[2.2.1]heptane Derivatives

Susumu Mitsumori, Tatsuo Tsuri,* Tsunetoshi Honma, Yoshiharu Hiramatsu, Toshihiko Okada, Hiroshi Hashizume, Masanao Inagaki, Akinori Arimura, Kiyoshi Yasui, Fujio Asanuma, Junji Kishino, and Mitsuaki Ohtani

Shionogi Research Laboratories, Shionogi & Co., Ltd., 12-4, Sagisu 5-chome, Fukushima-ku, Osaka 553-0002, Japan

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Novel prostaglandin D_2 (PGD_2) receptor antagonists were synthesized as a potential new class of antiallergic agents having a bicyclo[2.2.1]heptane ring system with sulfonamide groups. Some of them exhibit extremely potent antagonism of the PGD_2 receptor in radioligand binding and cAMP formation assays with IC_{50} values below 50 nM and much less antagonism of TXA_2 and PGI_2 receptors. These potent PGD_2 receptor antagonists, when given orally, dramatically suppress various allergic inflammatory responses such as increased vascular permeability in allergic rhinitis, conjunctivitis, and asthma models. The excellent pharmacological profiles of PGD_2 receptor antagonists, originally synthesized in our laboratories, are of potentially great clinical significance. This study also provides experimental evidence suggesting that PGD_2 plays an important role in the pathogenesis of allergic diseases.

Introduction

Prostaglandins (PGs), formed by the actions of cyclooxygenase 1 and 2 on arachidonic acid, are important biological mediators of inflammation and cytoprotection in the stomach and intestine.[1a] Much effort has been devoted to the search for agonists or antagonists of PGs[1] such as PGE_2, PGI_2, and $PGF_{2\alpha}$ for their potential medical utility. Prostaglandin D_2 (PGD_2), the major cyclooxygenase metabolite produced by mast cells in response to IgE-dependent stimuli,[2] has a variety of inflammatory effects.[3] Thus, PGD_2 is considered to be an important mediator in various allergic diseases such as allergic rhinitis, atopic asthma, allergic conjunctivitis, and atopic dermatitis.[4] Despite much speculation about the roles of PGD_2, studies on its antagonists have only yielded BWA868C,[5] which is used as a tool for pharmacological examination of the PGD_2 receptor (Figure 1). There are also few reports on the efficacy of PGD_2 receptor antagonists in animal allergic models or against human allergic diseases.[6] We focused on the possible therapeutic value of selective PGD_2 receptor antagonists in the treatment of various allergic disorders.

As described previously,[4a] we have tried to develop PGD_2 receptor antagonists to obtain a seed compound by screening of our compound library. Screening of prostaglandin derivatives revealed that (±)-(5*Z*)-7-[3-(biphenyl-4-sulfonylamino)bicyclo[2.2.1]hept-2-yl]hept-5-enoic acid ((±)-**1**), previously reported to be a thromboxane (TX) A_2 receptor antagonist,[7] exhibited fairly strong binding to the PGD_2 receptor. With this seed compound in hand, we initiated structure−activity relationship (SAR) studies of α and *ω* side chains of the compounds. On the basis of our previous study on TXA_2 receptor antagonists, *ω* side chain modification seemed to be the most important for enhancing the biological activities against the PGD_2 receptor. These modifications pointed to the need for aromatic moieties linked with a proper spacer to be conjugated or the existence of a rigid structure. Since these studies revealed that compounds with the bicyclo[2.2.1]heptane ring system, which has fused aromatic rings, were effective for inhibiting PGD_2 receptor binding, we synthesized and investigated various types of compounds to obtain a drug candidate.

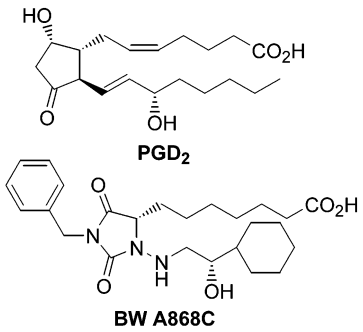

Figure 1. PGD_2 and PGD_2 antagonists reported previously.

Synthetic Chemistry

(1*S*,2*R*,3*R*,4*R*)-(5*Z*)-7-(3-Amino-bicyclo[2.2.1]hept-2-yl-)hept-5-enoic acid methyl ester (**2**) was prepared by methods described in the literature.[7a,b] Two synthetic routes were mainly used for the preparation of bicyclo-[2.2.1]heptane derivatives. One method of coupling amino derivative **2** with various types of sulfonyl chloride at the terminal stage readily gave the desired esters in good yield. Hydrolysis of these esters using aqueous potassium hydroxide in methanol produced the target molecules in almost quantitative yield (Scheme 1). Various types of sulfonyl chloride were synthesized by the following methods.[8,9] Typically, aryl compounds

* To whom correspondence should be addressed. Phone: +81-6-6458-5861. Fax: +81-6-6458-0987. E-mail: tatsuo.tsuri@shionogi.co.jp.

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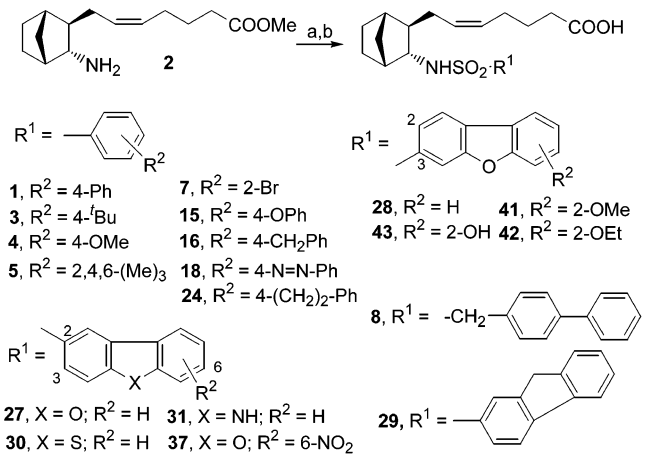
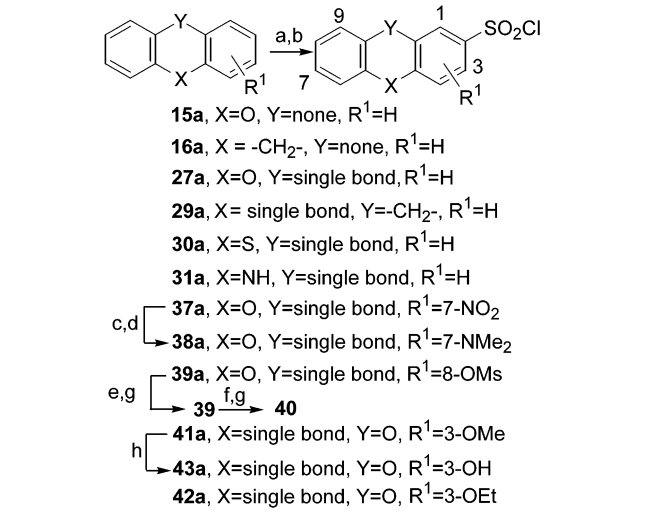
Scheme 1[a]



[a] Reagents: (a) R^1SO_2Cl, Et_3N; (b) KOH.

Scheme 2[a]

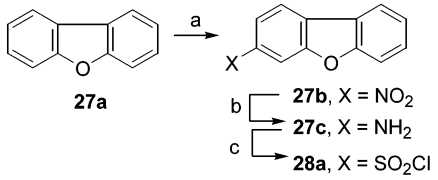


[a] Reagents: (a) $ClSO_3H$; (b) PCl_5; (c) Fe, NH_4Cl; (d) aqueous HCHO, $NaBH(OAc)_3$, AcOH; (e) **2**, Et_3N; (f) MeI, K_2CO_3; (g) KOH; (h) $AlCl_3$.

such as dibenzofuran, dibenzothiophene, carbazole, diphenylmethane, biphenyl ether, and their derivatives easily reacted with chlorosulfonic acid, and subsequent chlorination with phosphorus pentachloride gave the corresponding sulfonyl chlorides [8a−d,g] (Scheme 2). By using methoxydibenzofuran, we are able to convert many kinds of dibenzofuran derivatives (**39a**, **41a**−**43a**) by utilizing differences in the regioselectivity in the electrophilic attack, which was controlled by exchange of the substituent group from methoxy, an electron-donating group, to methanesulfonyloxy, an electron-withdrawing group. This transformation was very efficient for the syntheses of other derivatives when only a small variety of the desired sulfonyl chloride was commercially available. Other kinds of sulfonyl chloride, such as **28a**, for which electrophilic agents could not be used for conversion into the desired reagent, were synthesized from the corresponding nitro compound through diazonium salt derivatives[8e,f] as shown in Scheme 3. The nitration of **27a**, which was distinct from a normal type of electrophilic substitution, e.g., sulfonylation and bromination, occurred at the 3-position of the dibenzofuran skeleton to give **27b**.[10]

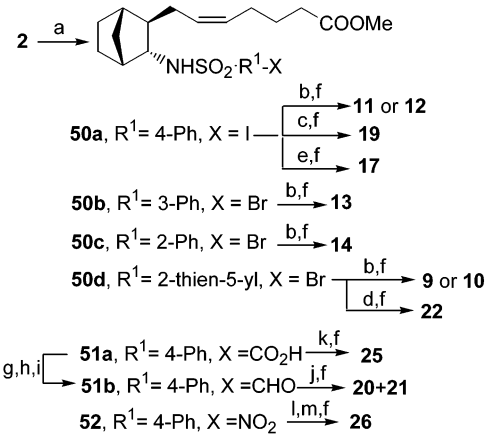
The other method to prepare bicyclo[2.2.1]heptane

Scheme 3[a]



[a] Reagents: (a) HNO_3, TFA; (b) Fe, NH_4Cl, H_2O; (c) $NaNO_2$, concentrated HCl, AcOH, then liquid SO_2, $CuCl_2$.

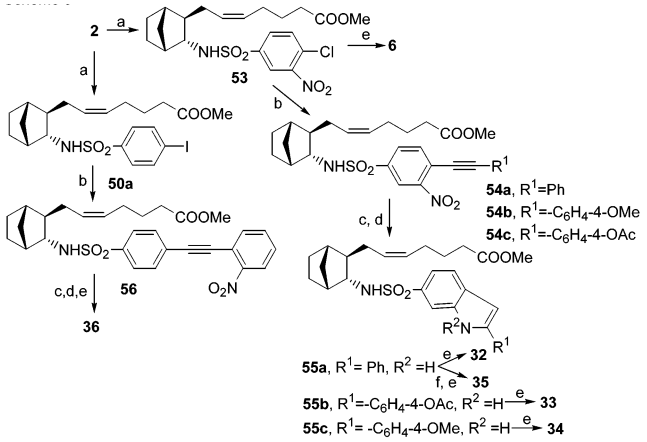
Scheme 4[a]



[a] Reagents: (a) X−R^1−SO_2Cl, Et_3N; (b) $Pd(PPh_3)_4$, aryl-$B(OH)_2$; (c) $Pd(PPh)_2Cl_2$, CuI, Et_3N, phenylacetylene; (d) $Pd(OAc)_2$, PPh_3, NaOAc, Bu_4NCl, styrene; (e) aniline, CuCl, Cu, K_2CO_3; (f) KOH; (g) ClCOOEt, Et_3N; (h) $NaBH_4$; (i) DMSO, $(COCl)_2$, Et_3N; (j) $Ph_3P^+(Cl^-)CH_2Ph$, ^{t}BuOK; (k) $(COCl)_2$, aniline, Et_3N; (l) Fe, NH_4Cl; (m) PhCOCl, Et_3N.

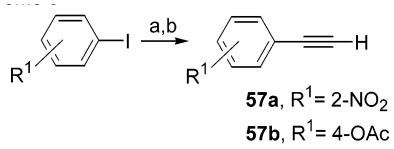
derivatives involved the conversion of sulfonamide synthesized from amine **2** and a commercially available or synthetic sulfonyl chloride described above. The sulfonamide synthesized as a key intermediate is transformed by a suitable reaction using methods[11] employing Pd catalysis. Syntheses of the derivatives containing biaryl, triple bond, and (*E*)-olefin moieties are shown in Scheme 4. The aryl halide intermediate synthesized from **2** and the corresponding sulfonyl chloride was modified by carbon−carbon bond formation methodologies: Suzuki,[11a] Sonogashira,[11b,c] or Heck reaction.[11d,e] For example, coupling of **50a**−**d** with arylboronic acid in the presence of $Pd(PPh_3)_4$ and K_2CO_3 produced the biaryl compounds **9**−**14** and reaction of **50a** with phenylacetylene in the presence of $PdCl_2(PPh_3)_2$, CuI(I), and triethylamine produced the acetylenic compound **19**. The Heck reaction proceeded smoothly in the presence of Bu_4NCl[12] but not under normal conditions, showing the need for addition of Bu_4NCl for the formation of (*E*)-olefin **22** in the reaction of **50d** with styrene. Syntheses of compounds containing the indolyl moiety (**32**−**36**) were done using the *o*-aminophenylacetylene compound prepared by the Sonogashira reaction (Scheme 5). In this case, aryl chloride, which was usually unreactive and unsuitable for palladium-catalyzed C−C bond formation, reacted smoothly with the phenylacetylene derivatives because of activation of halogen induced by the nitro group at the ortho position. Next, the reduction of the nitro group and palladium-catalyzed cyclization[13] of **56** or **54a**−**c** using $PdCl_2$ occurred smoothly, and 2-phenylindole derivatives were obtained in good yield despite the protection of the carboxylic acid group. The terminal alkyne compounds (**57a**,**b**) were easily pre-

Scheme 5[a]



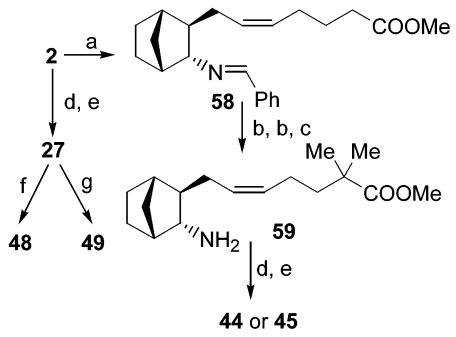
[a] Reagents: (a) Ar^1SO_2Cl, Et_3N; (b) $Pd(PPh_3)_2Cl_2$, Et_3N, phenylacetylene; (c) Fe, NH_4Cl; (d) $PdCl_2$; (e) KOH; (f) MeI, K_2CO_3.

Scheme 6[a]



[a] Reagents: (a) $Pd(PPh_3)_4$, CuI, trimethylsilylacetylene; (b) TBAF.

Scheme 7[a]

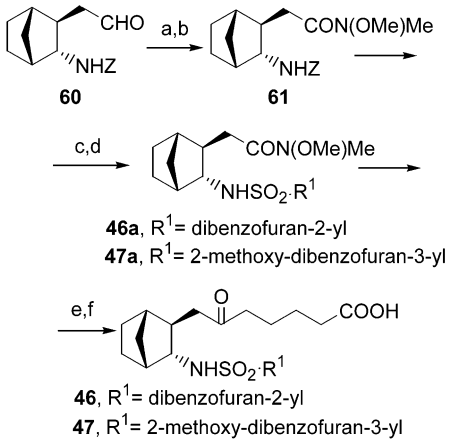


[a] Reagents: (a) PhCHO, PPTS; (b) LDA, MeI; (c) TFA; (d) R^1SO_2Cl, Et_3N; (e) KOH; (f) H_2, $Pd(OH)_2/C$; (g) $(COCl)_2$, $MeSO_2NH_2$, DBU.

pared from trimethylsilylacetylene and aryl iodide or bromide as shown in Scheme 6.

The modifications of the α-chain at the prostaglandin skeleton are presented in Schemes 7 and 8. The imine derivative **58** prepared from **2** and benzaldehyde was treated with LDA for deprotonation of the α-hydrogen of methyl ester and then allowed to react with MeI. This alkylation process was repeated twice, and removal of the protective group of the amino moiety by trifluoroacetic acid afforded the amine **59** containing α,α-dimethylcarboxylic acid methyl ester. This dimethyl derivative **59** also gave the target compounds by coupling of the corresponding sulfonyl chloride using general methods (Scheme 7). Compounds **46** and **47**, which have a 5-ketoheptanoic acid moiety as the α-chain, were synthesized by the following method.[14] Weinreb amide **61** derived from the corresponding aldehyde **60**[7a] was allowed to react with silylated Grignard reagent to transform the 5-ketoheptanol silyl ether derivative after deprotection of the benzyloxycarbonyl group and coupling with the corresponding sulfonyl chloride were

Scheme 8[a]



[a] Reagents: (a) $NaClO_2$, amylene, NaH_2PO_4; (b) MeONHMe·HCl, WSCD; (c) H_2, $Pd(OH)_2/C$; (d) R^1SO_2Cl, Et_3N; (e) Mg, $Br-(CH_2)_5-OTBS$; (f) Jones oxidation.

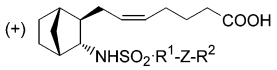
carried out. Deprotection of the TBDMS group and oxidation of the alcohol moiety occurred at the same time to afford the target compounds **46** and **47** (Scheme 8). The carbonyl-terminus-modified derivative **49** was prepared according to the cited literature.[15]

Biological Results and Discussion

All compounds described herein were evaluated by binding assays against the PGD_2 receptor and cAMP formation assays in human platelets.[4a,b] As previously described in our paper,[4a] the (1*S*,2*R*,3*R*,4*R*)-(+)-**1**-enantiomer was selected as a seed compound to further study the SAR of allergic disorders. The (+)-enantiomer was selected because it displayed selective PGD_2 receptor antagonist activity due to its weak activities at other prostaglandin receptors, particularly TXA_2 and PGI_2. We next focused on transforming of sulfonamide moieties to search for the selective PGD_2 antagonists (Table 1). Benzenesulfonamide derivatives (**3**−**7**), having simple substituents such as ^{t}Bu, OMe, Me, and NO_2, decreased the activities, compared with the seed compound **1**. Clearly, having two benzene units is a significant factor for the strong inhibitory activity of the PGD_2 receptor, and the arylsulfonamide structure is also essential in the comparison of **1** with aliphatic sulfonamide **8**. From this viewpoint, many biaryl derivatives such as **9**−**14** were examined, but no other improvements were found. Next, we tried to prepare some compounds having a spacer between the two phenyl rings of **1** to change their conformation, since the relative positions of the two aryl rings seemed to be important for the biological activities. Insertion of a suitable spacer such as a diazo, triple or double bond, and tetrazole resulted in enhancement of the activities (**18**−**23**), while insertion of methylene, ethylene, oxygen, or nitrogen atom or amide groups led to poor inhibitory activities (**15**−**17** and **24**−**26**). This suggests that compounds having two aryl rings lying in a coplanar position exhibit moderately strong PGD_2 antagonist activity, while those with the aryl rings lying in different planes do not.

At this stage, we also investigated the need for the sulfonamide proton that was regarded as a mimetic of the C-15 hydroxy group of PGD_2. Study of the amide compound, corresponding to sulfonamide **18**, and the

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



compd	R^1	R^2	Z	IC_{50} [a] (μM) DP binding	IC_{50} [a] (μM) DP cAMP
1	4-Ph	Ph		0.60	0.45
3	4-^{t}Bu−C_6H_4			>10	0.72
4	4-MeO−C_6H_4			>10	0.39
5	2,4,6-$(Me)_3$−C_6H_2			5.4	0.13
6	4-MeO−3-NO_2−C_6H_3			5.4	0.28
7	2-Br−C_6H_4			5.3	0.34
8	CH_2−(4-C_6H_4)	Ph		8.6	>1.0
9	2-thienyl-5-yl	2-thienyl		0.41	0.20
10	2-thienyl-5-yl	Ph		0.58	0.22
11	4-Ph	4-MeO−C_6H_4		0.45	0.20
12	4-Ph	4-CF_3−C_6H_4		0.66	0.35
13	3-Ph	Ph		0.67	0.28
14	2-Ph	Ph		8.6	nd[b]
15	4-Ph	Ph	−O−	0.68	0.57
16	4-Ph	Ph	$-CH_2-$	5.2	0.65
17	4-Ph	Ph	−NH−	0.33	0.16
18	4-Ph	Ph	−N=N−	0.025	0.32
19	4-Ph	Ph	−C≡C−	0.0085	0.21
20	4-Ph	Ph	(*E*)-C=C-	0.10	0.18
21	4-Ph	Ph	(*Z*)-C=C-	0.20	0.18
22	2-thienyl-5-yl	Ph	(*E*)-C=C-	0.090	0.10
23	4-Ph	Ph	tetrazolyl	0.062	0.38
24	4-Ph	Ph	$-(CH_2)_2-$	0.55	0.26
25	4-Ph	Ph	−CONH−	1.1	0.086
26	4-Ph	Ph	−NHCO−	6.0	0.12

[a] PGD_2 receptor (DP) assay.[4a,b] Inhibition of [^{3}H]PGD_2 specific binding to human platelet membranes[7c] and cAMP formation evoked by PGD_2 in human platelets.[17] IC_{50} represents the mean value of two or three measurements. [b] Not done.

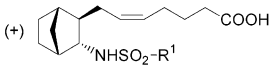
N-methylated compound of **19** revealed that PGD_2 receptor binding activities decreased by about 1 and 2 orders of magnitude, respectively. This observation agrees with the previous SAR study on platelet aggregation inhibitory activity of a PGD_2 analogue.[5d,e] Thus, the sulfonamide moiety seems to be indispensable for maintaining strong antagonist activities against the PGD_2 receptor.

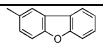
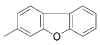
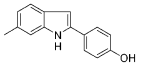
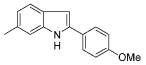
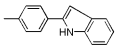
On the basis of our findings, we attempted to link each phenyl group of the sulfonamide moiety in order to form a rigid and planar conformation (Table 2). As expected, the dibenzofuran derivatives (**27** and **28**) exhibited higher activities in vitro and in vivo than **1** and **15**, which have benzene rings fixed only by an oxygen atom and carbon atom, respectively. Interestingly, the fluorene derivative **29**, having two phenyl rings that cannot be located in a planar conformation, shows less potent inhibitory activity in vitro regardless of its rigid structure, and the introduction of a sulfur or nitrogen atom in place of the oxygen (**30** and **31**) also does not lead to enhancement of the activity. The exceptions were 2-phenylindole derivatives, such as **32**−**34**, containing nitrogen atoms, which exhibited good activities in vitro and in vivo although other types of indole derivatives (**35** and **36**) showed no significant activity. Consequently, two different types of PGD_2 receptor antagonists, **27** and **32**, that were effective in animal allergic models were obtained. Among them, the dibenzofuran derivatives were selected for further modification because of their synthetic facility and generally high activity. The substituent and positional effects of the dibenzofuran ring in sulfonamide moieties were investigated, and an in vivo assay was also undertaken if the activities of the in vitro assay (cAMP formation and PGD_2 receptor binding) were both less than 0.1 μM (Table 3). The introduction of substituent groups at the 6- and 7-position in 2-sulfonamide derivatives did not enhance the inhibitory activities (**37**−**40**). In the case of 3-sulfonamide derivatives, a similar tendency of the substituent effect was also found. Next, the compounds, including alkyloxy or hydroxy at the 2-position, that could affect the adjacent sulfonamide function were investigated. The alkyloxy derivatives exhibited more potent inhibitory activities than those compounds having no or hydroxy substituent groups (**28** and **41**−**43**), and thus, the alkoxy substituent group at the 2-position seemed to be the most desirable for the inhibitory activities. When given po in the rhinitis model, compound **41** markedly inhibited an antigen-induced increase in intranasal pressure.

Finally, α-chain modifications were performed for the effective compounds (**27** and **41**) to try to the further increase the activity (Table 4). Compound **49** exhibited higher activities in vitro than **27**, but it showed less potent inhibitory activity in vivo, the percent inhibition at 1 mg/kg (iv) being 35%. Consequently, these transformations led to no significant improvement. This finding indicated that the spatial location of the carboxyl group is very important and the degree of freedom is very small, thus showing that α-chain modification is not an advantage for inhibitory activity.

The selected compound **41** was further evaluated to investigate its effect on other allergic diseases. It was found to meaningfully inhibit the PGD_2- and antigen-induced increases in conjunctival microvascular permeability and the antigen-induced increase in specific

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



		IC50 (μM)[a]		in vivo[b]
		DP		(rhinitis model)
compd	R^1	binding	cAMP	% inhibn at 1 mg/kg (iv)
27		0.13	0.070	82±4[d] (75±3[d,e,f])
28		0.022	0.16	nd[c]
29		nd[c]	>1.0	nd[c]
30		0.064	0.18	31±17
31		0.022	0.022	-9±27
32		0.047	0.071	60±7[d]
33		0.018	0.025	42±5
34		0.015	0.045	40±8
35		0.38	0.19	nd[c]
36		0.19	0.21	nd[c]

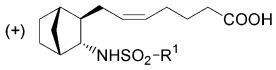
[a] PGD_2 receptor (DP) assay.[4a,b] Inhibition of [^{3}H]PGD_2 specific binding to human platelet membranes[7c] and cAMP formation evoked by PGD_2 in human platelets.[17] IC_{50} represents the mean value of two or three measurements. [b] Inhibition of antigen-induced increase in intranasal pressure in actively sensitized guinea pigs.[4a,b] Compounds were administered iv 10 min before the antigen challenge.[7d] Values represent the mean ± SEM. [c] Not done. [d] Significantly different from each control; $p < 0.01$ (Student's *t*-test). [e] % inhibition at 10 mg/kg (po). [f] Na salt was used.

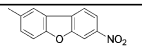
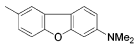
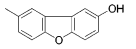
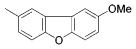
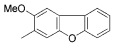
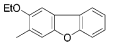
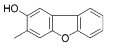
airway resistance in a guinea pig model[4b] (Table 5). Thus, the PGD_2-receptor-mediated component may have a role in the antigen-induced increase in the conjunctival microvascular permeability and specific airway resistance, and its receptor antagonist dramatically suppresses various allergic responses.

Conclusion

The novel PGD_2 receptor antagonist described here, having a bicyclo[2.2.1]heptane ring system with a characteristic sulfonamide group, was originally synthesized in our laboratories. PGD_2 has been implicated in the pathogenesis of allergic diseases because of its local production after antigen challenge.[3,4,16] The present study using our PGD_2 receptor antagonist provides experimental evidence suggesting its effectiveness for alleviating various allergic diseases. This is the first report of a promising drug candidate for diseases caused by excess production of PGD_2.

Table 3. Inhibition of PGD_2 Receptor Binding, Biological Activity in Human Platelets, and Antigen-Induced Nasal Blockage in Guinea Pigs



		IC50 (μM)[a]		in vivo[b]
		DP		(rhinitis model)
compd	R^1	binding	cAMP	% inhibn at 10 mg/kg (po)
37		0.55	0.057	nd[c]
38		0.036	0.17	nd[c]
39		0.20	0.25	nd[c]
40		0.034	0.33	nd[c]
41		0.024	0.052	81±4[d] (82±3[d,e])
42		0.032	0.034	53±11[d]
43		0.19	0.18	nd[c]

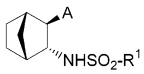
[a] PGD_2 receptor (DP) assay.[4a,b] Inhibition of [^{3}H]PGD_2 specific binding to human platelet membranes[7c] and cAMP formation evoked by PGD_2 in human platelets.[17] IC_{50} represents the mean value of two or three measurements. [b] Inhibition of antigen-induced increase in intranasal pressure in actively sensitized guinea pigs.[4a,b] Compounds were administrered iv 10 min before the antigen challenge.[7d] Values represent the mean ± SEM. [c] Not done. [d] Significantly different from each control; $p < 0.01$ (Student's *t*-test). [e] % inhibition at 1 mg/kg (iv).

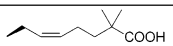
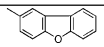
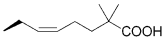
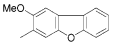
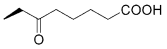
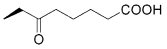
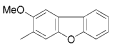
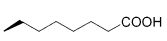
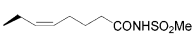
Experimental Section

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. The reaction mixture was filtered through a Hyflo Super-Cel as a filter agent if necessary. 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". The following starting materials were prepared as previously reported: **2**,[7a] 3-nitrodibenzofuran (**27b**),[10a] and **60**.[7a]

2-Methoxydibenzofuran-3-sulfonic Acid. A solution of 20.9 mL (0.315 mol) of $ClSO_3H$ in 20 mL of CH_2Cl_2 was added dropwise to a solution of 59.5 g (0.300 mol) of 2-methoxydibenzofuran in 280 mL of CH_2Cl_2 at 0 °C. The mixture was stirred for an additional 15 min and allowed to warm to room temperature. After being stirred for 2 h, the reaction mixture was cooled to 0 °C. The precipitate was filtered with glass filter, washed with 60 mL of CH_2Cl_2, and dried to give 72.0 g (86%) of the title compound as a colorless solid. Mp 178−179 °C. ^{1}H NMR (CD_3OD): δ 4.03 (s, 3H), 7.33−7.40 (m, 1H), 7.46−7.60 (m, 2H), 7.71 (s, 1H), 8.03−8.08 (m, 2H). IR ($CHCl_3$): 3432, 2644, 2226, 1635, 1469, 1453, 1414, 1232, 1218, 1189, 1173, 1157, 1077, 1032, 1010 cm^{-1}. Anal. ($C_{13}H_{10}O_5S \cdot 1.0H_2O$) C, H, N, S.

Table 4. Inhibition of PGD_2 Receptor Binding and Biological Activity in Human Platelets



			IC_{50} (μM)[a] DP	
compd	A	R^1	binding	cAMP
44			0.18	0.32
45			0.057	0.32
46			0.68	0.019
47			0.96	0.033
48			0.12	0.43
49			0.042	0.032

[a] PGD_2 receptor (DP) assay.[4a,b] Inhibition of [^{3}H]PGD_2 specific binding to human platelet membranes[7c] and cAMP formation evoked by PGD_2 in human platelets.[17] IC_{50} represents the mean value of two or three measurements.

Table 5. 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
41	1.6	6.6	42 ± 12[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.[4a,b] [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.[4a,b] Values represent the mean ± SEM. [c] Significantly different from each control; $p < 0.05$ (Student's *t*-test).

2-Methoxydibenzofuran-3-sulfonyl Chloride (41a). To a solution of 55.7 g (0.200 mol) of 2-methoxydibenzofuran-3-sulfonic acid in 50 mL of phosphoryl chloride was added 62.4 g (0.300 mol) of PCl_5. The resulting solution was heated at 90 °C and stirred for 1 h. The reaction mixture was poured into ice/water, and the precipitate was filtered with glass filter, washed with water, and dried in vacuo. The collected precipitate was recrystallized from toluene to give **41a** (18.7 g, 63%) as a colorless solid. Mp 176−178 °C. ^{1}H NMR ($CDCl_3$): δ 4.17 (s, 3H), 7.39−7.45 (m, 1H), 7.56−7.64 (m, 3H), 7.98−8.02 (m, 1H), 8.18 (s, 1H). IR ($CHCl_3$): 3434, 1636, 1580, 1473, 1452, 1438, 1414, 1370, 1243, 1221, 1187, 1166, 1149, 1015, 864 cm^{-1}. Anal. ($C_{13}H_9ClO_4S$) C, H, Cl, S.

(1*S*,2*R*,3*R*,4*R*)-(5*Z*)-7-(3-(2-Methoxydibenzofuran-3-sulfonylamino)bicyclo[2.2.1]hept-2-yl)hept-5-enoic Acid (41). To a solution of 5.22 g (20.0 mmol) of **2** and 5.60 mL (40.0 mmol) of Et_3N in 110 mL of CH_2Cl_2 was added 7.12 g (24.0 mmol) of 2-methoxydibenzofuran-3-sulfonyl chloride (**41a**) at 0 °C. After being stirred for an additional 10 min, the solution was warmed to room temperature and stood overnight. The reaction mixture was poured into water and extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel to give the methyl ester (5.04 g, 49%). A solution of 5.03 g (10.1 mmol) of the methyl ester prepared above in 40 mL of MeOH and 25 mL of THF was treated with 1 N KOH and allowed to stand overnight. The mixture was acidified with 10% HCl and extracted with AcOEt. The organic layer was washed with a saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and evaporated. The residue was recrystallized from CH_2Cl_2/hexane to give **41** (4.50 g, 89%) as a colorless solid. Mp 108−110 °C. ^{1}H NMR ($CDCl_3$): δ 0.96−1.98 (m, 14H), 2.02 (m, 1H), 2.25 (t, J = 7.2 Hz, 2H), 3.05 (m, 1H), 4.10 (s, 3H), 5.14−5.25 (m, 2H), 5.41 (d, J = 7.2 Hz, 1H), 7.35−7.42 (m, 1H), 7.51−7.64 (m, 3H), 7.94−8.00 (m, 1H), 8.16 (s, 1H). IR ($CHCl_3$): 3368, 3274, 3028, 2952, 2874, 1708, 1633, 1583, 1465, 1452, 1438, 1413, 1315, 1151, 1103, 1053, 1024 cm^{-1}. $[\alpha]^{23}_D$ +15.1° (*c* 1.01, $CHCl_3$). Anal. ($C_{27}H_{31}NO_6S$) C, H, N, S.

3-Aminodibenzofuran (27c). To a solution of 12.0 g (55.8 mmol) of **27b** in 200 mL of ^{i}PrOH and 30 mL of water was added 8.95 g (167 mmol) of NH_4Cl and 31.1 g (558 mmol) of Fe. The mixture was refluxed for 11 h and filtered through Hyflo Super-Cell. The filtrate was evaporated and purified by column chromatography on silica gel to give **27c** (6.85 g, 66%) as a colorless solid. Mp 83−84 °C. ^{1}H NMR ($CDCl_3$): δ 3.90 (br, 2H), 6.68 (dd, J = 8.1 and 1.8 Hz, 1H), 6.85 (d, J = 1.8 Hz, 1H), 7.24−7.35 (m, 2H), 7.47 (d, J = 8.1 Hz, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.79 (dd, J = 6.3 and 2.1 Hz, 1H).

Dibenzofuran-3-sulfonyl Chloride (28a). To a suspension of 6.00 g (32.4 mmol) of **27c** in 60 mL of concentrated HCl and 60 mL of AcOH was added slowly 2.68 g (38.8 mmol) of $NaNO_2$ in 20 mL of water at −20 °C to give a yellow suspension. After the mixture was stirred for 30 min, 30 mL of SO_2 and 11.5 g (67.2 mmol) of $CuCl_2 \cdot 2H_2O$ in 40 mL of 50% AcOH were added to the reaction mixture at −23 °C, and the mixture was slowly warmed to room temperature. After being stirred for 21 h, the reaction mixture was poured into water and extracted with AcOEt. The combined organic layer was washed with a saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and evaporated. The residue was washed with hexane to give **28a** (2.35 g, 27%) as a colorless solid. Mp 141−142 °C. ^{1}H NMR ($CDCl_3$): δ 7.46 (dd, J = 8.1 and 6.9 Hz, 1H), 7.61−7.71 (m, 2H), 8.04−8.08 (m, 2H), 8.16 (d, J = 8.1 Hz, 1H), 8.26 (d, J = 1.8 Hz, 1H). IR ($CHCl_3$): 3091, 3066, 1954, 1630, 1579, 1456, 1421, 1377, 1350, 1327, 1306, 1267, 1234, 1190, 1174, 1105, 1053, 1003 cm^{-1}. FABMS *m/z*: 266 [$M^{+\bullet}$, Cl = 35]$^+$. HRFABMS for $C_{12}H_7ClO_3S$: 265.9804. Found: 265.9809.

(1*S*,2*R*,3*R*,4*R*)-(5*Z*)-7-(3-(4-Phenylethynylbenzenesulfonylamino)bicyclo[2.2.1]hept-2-yl)hept-5-enoic Acid (19). Compound **50a** was prepared from **2** and 4-iodobenzensulfonyl chloride according to the procedure for **41**. To a solution of 0.300 g (0.580 mmol) of **50a** in 10 mL of DMF was added 20.3 mg (28.9 μmol) of $Pd(PPh_3)_2Cl_2$, 11.1 mg (58.3 μmol) of CuI, 64.0 μL (0.583 mmol) of phenylacetylene, and 0.240 mL (1.72 mmol) of triethylamine. The resulting solution was stirred under N_2 at 40 °C. After being stirred for 6 h, the mixture was diluted with water and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel to give a yellow oil. This yellow oil was hydrolyzed with aqueous KOH in MeOH to give **19** (0.101 g, 65%) as a colorless solid. Mp 117−118 °C. ^{1}H NMR ($CDCl_3$): δ 0.97−2.01 (m, 14H), 2.14 (m, 1H), 2.36 (t, J = 7.2 Hz, 2H), 3.02 (m,-1H), 5.23 (d, J = 5.4 Hz,1H), 5.26−5.30 (m, 2H), 7.37−7.39 (m, 3H), 7.54−7.58 (m, 2H), 7.63−7.66 (m, 2H), 7.85−7.88 (m, 2H). IR ($CHCl_3$): 3375, 3260, 3022, 2948, 2212, 1707, 1596, 1497, 1396, 1322, 1160 cm^{-1}. $[\alpha]^{24}_D$ +25.0° (*c* 1.02, $CHCl_3$). Anal. ($C_{28}H_{31}NO_4S \cdot 0.5H_2O$) C, H, N, S.

(*Z*)-7-{(1*S*,2*R*,3*R*,4*R*)-3-[5-((*Z*)-Styryl)thiophene-2-sulfonylamino]bicyclo[2.2.1]hept-2-yl}hept-5-enoic Acid (22). Compound **50d** was prepared from **2** and 5-bromothiophene-2-sulfonyl chloride according to the procedure for **41**. To a solution of 11.8 mg (52.6 μmol) of $Pd(OAc)_2$ in 15 mL of DMF was added 55.5 mg (0.212 mmol) of PPh_3, and this was stirred under N_2 for 5 min. To the resulting mixture was added 0.500 g (1.05 mmol) of **50d**, 0.240 mL (2.09 mmol) of styrene, 0.175

g of NaOAc (2.13 mmol), and 0.300 g (1.08 mmol) of Bu_4NI, and the mixture was heated at 110 °C. After being stirred for 9 h, the mixture was concentrated in vacuo and dissolved with AcOEt and water. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel to give a yellow oil, which was hydrolyzed with aqueous KOH in MeOH to give **22** (0.229 g, 45%) as an amorphous solid. ^{1}H NMR ($CDCl_3$): δ 0.98−2.00 (m, 14H), 2.11−2.36 (m, 3H), 3.12 (m, 1H), 5.10 (d, J = 6.6 Hz, 1H), 5.29−5.32 (m, 2H), 6.99−7.04 (m, 2H), 7.23 (d, J = 21.6 Hz, 1H), 7.32−7.49 (m, 6H). IR ($CHCl_3$): 3380, 3248, 3020, 2948, 2868, 1709, 1491, 1430, 1329, 1151 cm^{-1}. FABMS m/z: 508 $[M + Na]^+$. HRFABMS for $C_{26}H_{31}NO_4S_2Na$: 508.1605. Found: 508.1592. $[\alpha]^{25}_D$ +3.4° (c 1.03, $CHCl_3$).

(*Z*)-7-[(1*S*,2*R*,3*R*,4*R*)-3-(5-Phenylthiophene-2-sulfonylamino)bicyclo[2.2.1]hept-2-yl]hept-5-enoic Acid (10). To a solution of 0.224 g (0.194 mmol) of $Pd(PPh_3)_4$ and 0.236 g (1.94 mmol) of phenylboronic acid in 25 mL of toluene was added 0.500 g (0.966 mmol) of **50d** and 0.200 g (1.45 mmol) of K_2CO_3, and the mixture was heated at 60 °C under N_2. After being stirred for 3 h, the mixture was diluted with toluene and washed with 10% citric acid solution, a 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 a yellow oil. This yellow oil was hydrolyzed with aqueous KOH in MeOH to give **10** (0.319 g, 72%) as an amorphous solid. ^{1}H NMR ($CDCl_3$): δ 1.05−2.05 (m, 14H), 2.28−2.33 (m, 3H), 3.13 (m, 1H), 5.18 (d, J = 6.3 Hz, 1H), 5.27−5.31 (m, 2H), 7.24 (d, J = 4.2 Hz, 1H), 7.39−7.42 (m, 3H), 7.56 (d, J = 4.2 Hz, 1H), 7.58−7.62 (m, 2H). IR ($CHCl_3$): 3372, 3254, 3018, 2948, 2868, 1707, 1431, 1328, 1151 cm^{-1}. FABMS m/z: 482 $[M + Na]^+$. HRFABMS for $C_{24}H_{29}NO_4S_2Na$: 482.1436. Found: 482.1437. $[\alpha]^{21.5}_D$ +4.5° (c 1.01, $CHCl_3$).

(*Z*)-7-[(1*S*,2*R*,3*R*,4*R*)-3-(4-Phenylaminobenzenesulfonylamino)bicyclo[2.2.1]hept-2-yl]hept-5-enoic Acid (17). To a solution of 0.400 g (0.773 mmol) of **50a** and 0.138 g (1.00 mmol) of K_2CO_3 in 4 mL of aniline was added 63.0 mg (0.992 mmol) of copper and 85.0 mg (0.859 mmol) of CuCl, and the mixture was heated at 160 °C. After being stirred for 6 h, the mixture was poured into 1 N HCl solution and extracted with AcOEt. The organic layer was washed with water, a 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 a brown oil (0.205 g, 55%). This compound was hydrolyzed with aqueous KOH in MeOH to give **17** (0.191 g, 53%) as an amorphous solid. ^{1}H NMR ($CDCl_3$): δ 0.90−2.04 (m, 14H), 2.18 (m, 1H), 2.33 (t, J = 7.2 Hz, 2H), 2.96 (m, 1H), 5.04−5.35 (m, 3H), 6.98−7.12 (m, 3H), 7.12−7.20 (m, 2H), 7.28−7.38 (m, 2H), 7.66−7.74 (m, 2H). IR ($CHCl_3$): 3424, 3270, 3028, 2952, 2872, 1708, 1587, 1508, 1445, 1399, 1320, 1148, 1092 cm^{-1}. $[\alpha]^{23.0}_D$ +20.9° (c 1.06, $CHCl_3$). Anal. ($C_{26}H_{32}N_2O_4S\cdot 0.3H_2O$) C, H, N, S.

(*Z*)-7-{(1*S*,2*R*,3*R*,4*R*)-3-[4-Formylbenzenesulfonylamino]-bicyclo[2.2.1]hept-2-yl}hept-5-enoic Acid Methyl Ester (51b). (*Z*)-7-{(1*S*,2*R*,3*R*,4*R*)-3-[4-Carboxybenzenesulfonylamino]-bicyclo[2.2.1]hept-2-yl}hept-5-enoic acid methyl ester (**51a**) was prepared from **2** and 4-(chlorosulfonyl)benzoic acid using a procedure similar to that described for the preparation of **41** (79%). To a solution of 1.08 g (2.48 mmol) of **51a** and 0.400 mL (2.87 mmol) of Et_3N was added 0.270 mL (2.87 mmol) of $ClCO_2Et$ in an ice bath. After the mixture was stirred for 1 h, the resulting salt was removed and the filtrate was slowly added to a solution of 0.280 g (7.40 mmol) of $NaBH_4$ in 5.7 mL of water at 0 °C. After being stirred for 1 h, the mixture was evaporated and the residue was extracted with AcOEt. The combined organic layer was washed with 1 N HCl, a saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel to give an alcohol derivative (1.13 g, 78%). To a solution of 0.262 mL (3.07 mmol) of oxalyl chloride in 6 mL of CH_2Cl_2 was slowly added a solution of 0.437 mL (6.15 mmol) of DMSO in 2 mL of CH_2Cl_2 at −78 °C over a period of 15 min. A solution of 1.13 g (2.68 mmol) of an alcohol derivative prepared in 3 mL of CH_2Cl_2 was added dropwise to the reaction mixture. After the mixture was stirred for 15 min, 0.940 mL (6.74 mmol) of Et_3N was added and the mixture was warmed to room temperature. After the mixture was stirred for 1 h, the volatile materials were removed in vacuo to obtain a residue. The residue was dissolved with AcOEt and washed with water, 1 N HCl, a saturated $NaHCO_3$ solution, and brine, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel to give **51b** (1.11 g, 99%) as an amorphous solid. ^{1}H NMR ($CDCl_3$): δ 0.94−2.02 (m, 14H), 2.12 (m, 1H), 2.28 (t, J = 8.1 Hz, 2H), 3.05 (m, 1H), 3.69 (s, 3H), 4.98 (m, 1H), 5.12−5.32 (m, 2H), 7.99−8.09 (m, 4H), 10.11 (s, 1H).

(*Z*)-7-{(1*S*,2*R*,3*R*,4*R*)-3-[4-((*E*)-Styryl)benzenesulfonylamino]bicyclo[2.2.1]hept-2-yl}hept-5-enoic Acid (20) and (*Z*)-7-{(1*S*,2*R*,3*R*,4*R*)-3-[4-((*Z*)-Styryl)benzenesulfonylamino]bicyclo[2.2.1]hept-2-yl}hept-5-enoic Acid (21). To a solution of 1.11 g (2.65 mmol) of **51b**, 1.07 g (2.75 mmol) of benzyltriphenylphosphonium chloride, and 10.0 mg of 18-crown-6 in 11 mL of CH_2Cl_2 was added 0.456 g (4.06 mmol) of ^{t}BuOK, and the mixture was stirred at room temperature. After being stirred for 2 h, the mixture was evaporated and the brownish residue was purified by column chromatography on silica gel to give the (*E*)-olefin (0.372 g, 28%) and the (*Z*)-olefin (0.594 g, 45%). These compounds were hydrolyzed with aqueous KOH in MeOH to give **20** ((*E*)-product) (0.343 g, 95%) and **21** ((*Z*)-product) (0.566 g, 98%).

20. ^{1}H NMR ($CDCl_3$): δ 0.92−1.99 (m, 14H), 2.17 (m, 1H), 2.32 (t, J = 7.2 Hz, 2H), 3.02 (m, 1H), 5.23−5.29 (m, 3H), 7.11 (d, J = 16.2 Hz, 1H), 7.23 (d, J = 16.2 Hz, 1H), 7.28−7.41 (m, 3H), 7.52−7.55 (m, 2H), 7.61 (d, J = 8.7 Hz, 2H), 7.86 (d, J = 8.7 Hz, 2H). IR ($CHCl_3$): 3515, 3384, 3270, 3022, 3015, 2957, 2876, 2669, 1708, 1595, 1496, 1320, 1157 cm^{-1}. $[\alpha]^{24.0}_D$ +27.1° (c 1.02, $CHCl_3$). Anal. ($C_{28}H_{33}NO_4S\cdot 0.25H_2O$) C, H, N, S.

21. ^{1}H NMR ($CDCl_3$): δ 0.90−2.16 (m, 14H), 2.12 (m, 1H), 2.34 (t, J = 7.2 Hz, 2H), 3.02 (m, 1H), 5.16 (d, J = 6.9 Hz, 1H), 5.23−5.34 (m, 2H), 6.60 (d, J = 12.3 Hz, 1H), 6.74 (d, J = 12.3 Hz, 1H), 7.14−7.24 (m, 5H), 7.35 (d, J = 8.1 Hz, 2H), 7.72 (d, J = 8.1 Hz, 2H). IR ($CHCl_3$): 3515, 3384, 3269, 3025, 3021, 3014, 2957, 2876, 2668, 1709, 1595, 1322, 1162, 1147 cm^{-1}. $[\alpha]^{24.0}_D$ +26.4° (c 1.00, $CHCl_3$). Anal. ($C_{28}H_{33}NO_4S\cdot 0.25H_2O$) C, H, N, S.

(*Z*)-7-[(1*S*,2*R*,3*R*,4*R*)-3-(4-Phenylcarbamoylbenzenesulfonylamino)bicyclo[2.2.1]hept-2-yl]hept-5-enoic Acid (25). To a solution of 0.328 g (0.753 mmol) of **51a** and a small portion of DMF in 4 mL of toluene was added 99.0 μL (1.13 mmol) of oxalyl chloride in an ice bath, and the mixture was left standing at ambient temperature. After being stirred for 1 h, the mixture was evaporated, and the resulting residue was dissolved in 6 mL of CH_2Cl_2. To this solution was added 0.137 mL (1.51 mmol) of aniline and 0.262 mL (1.88 mmol) of Et_3N at 0 °C. After being stirred for 1 h at room temperature, the mixture was poured into water and extracted with AcOEt. The organic layer was washed with water, a saturated $NaHCO_3$ solution, and brine, then dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel to give a colorless solid, which was hydrolyzed with aqueous KOH in MeOH to give **25** (0.159 g, 43%) as a colorless solid. Mp 158−159 °C. ^{1}H NMR ($CDCl_3$/CD_3OD): δ 0.96−2.00 (m, 14H), 2.18−2.35 (m, 3H), 2.90 (m, 1H), 5.15−5.30 (m, 2H), 7.18 (m, 1H), 7.33−7.42 (m, 2H), 7.65−7.74 (m, 2H), 7.90−8.08 (m, 4H). IR (KBr): 3347, 3194, 3011, 2955, 2875, 1706, 1650, 1602, 1544, 1499, 1443, 1325, 1265, 1165, 1091 cm^{-1}. $[\alpha]^{24.0}_D$ −19.4° (c 1.00, MeOH). Anal. ($C_{27}H_{32}N_2O_5S\cdot 0.3H_2O$) C, H, N, S.

1-Ethynyl-2-nitrobenzene (57a). To a solution of 10.0 g (40.2 mmol) of 2-iodonitrobenzene in 70 mL of DMF was added 0.846 g (1.21 mmol) of $Pd(PPh_3)_2Cl_2$, 0.459 g (2.41 mmol) of CuI, 5.70 mL (40.3 mmol) of (trimethsilyl)acetylene, and 16.8 mL (154 mmol) of Et_3N, and the resulting solution was stirred under N_2 at 50 °C for 2 h. The mixture was diluted with water and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel to give trimethyl(2-nitrophenylethynyl)silane (8.41 g, 94%). To a

solution of 5.00 g (22.5 mmol) of (trimethylsilyl)acetylene derivative in 30 mL of THF was added 27.0 mL (27.0 mmol) of 1 N Bu_4NF in THF at 0 °C. After being stirred for 2 h, the mixture was poured into a saturated NH_4Cl solution and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel to give **57a** (2.12 g, 64%) as a pale-yellow solid. Mp 78−79 °C. ^{1}H NMR ($CDCl_3$): δ 3,53 (s, 1H), 7.48−7.74 (m, 3H), 8.06 (dd, J = 2.4 and 11.7 Hz, 1H). IR ($CHCl_3$): 3300, 2116, 1608, 1572, 1529, 1477, 1348 cm^{-1}. EIMS *m*/*z*: 147 [M$^+$].

(1*S*,2*R*,3*R*,4*R*)-(5*Z*)-7-(3-(3-Nitro-4-phenylethynylbenzenesulfonylamino)bicyclo[2.2.1]hept-2-yl)hept-5-enoic Acid Methyl Ester (54a). Compound **53** was prepared from **2** and 4-chloro-3-nitrobenzensulfonyl chloride using a procedure similar to that described for the preparation of **41**. To a solution of 1.94 g (4.75 mmol) of **53** in 20 mL of DMF was added 0.167 g (0.237 mmol) of $Pd(PPh_3)_2Cl_2$, 0.181 g (0.950 mmol) of CuI, 1.0 mL (9.00 mmol) of phenylacetylene, and 2.00 mL (14.4 mmol) of Et_3N, and the resulting solution was stirred under N_2 at 40 °C. After being stirred for 6 h, the mixture was diluted with water and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel to give **54a** (0.579 g, 72%) as a colorless solid. Mp 77−79 °C. ^{1}H NMR ($CDCl_3$): δ 0.96−1.97 (m, 14H), 2.24 (m, 1H), 2.31 (t, J = 6.9 Hz, 2H), 3.05 (m, 1H), 3.69 (s, 3H), 5.15 (d, J = 6.6 Hz, 1H), 5.25−5.27 (m, 2H), 7.40−7.43 (m, 3H), 7.61−7.64 (m, 2H), 7.85 (d, J = 8.1 Hz, 1H), 8.07 (dd, J = 8.1 and 1.8 Hz, 1H), 8.58 (d, J = 1.8 Hz, 1H). IR ($CHCl_3$): 3374, 3020, 2948, 2870, 2212, 1726, 1606, 1530, 1493, 1437, 1345, 1167 cm^{-1}. $[\alpha]^{25}_D$ +2.4° (*c* 1.03, $CHCl_3$). Anal. ($C_{29}H_{32}N_2O_6S\cdot 0.25H_2O$) C, H, N, S.

(1*S*,2*R*,3*R*,4*R*)-(5*Z*)-7-(3-(2-Phenyl-1*H*-indole-6-sulfonylamino)bicyclo[2.2.1]hept-2-yl)hept-5-enoic Acid Methyl Ester (55a). To a solution of 0.800 g (1.49 mmol) of **54a** in 60 mL of MeOH and 8 mL of water was added 0.830 g (14.9 mmol) of Fe and 0.240 g (4.49 mmol) of NH_4Cl, and the resulting solution was refluxed for 1.5 h. After cooling to room temperature, the mixture was filtered through Hyflo Super-Cell and evaporated. The residue was purified by column chromatography on silica gel to give the amine product (0.674 g, 89%). To a solution of 0.149 g (0.296 mmol) of the amine derivative prepared above in 5 mL of MeCN was added 5.2 mg (0.030 mmol) of $PdCl_2$, and the resulting solution was refluxed for 2 h. The mixture was evaporated and purified by column chromatography on silica gel to give **55a** (0.131 g, 87%) as a colorless solid. Mp 130−132 °C. ^{1}H NMR ($CDCl_3$): δ 0.96−1.87 (m, 14H), 2.20−2.25 (m, 3H), 2.95 (m, 1H), 3.66 (s, 3H), 4.74 (d, J = 6.6 Hz, 1H), 5.10−5.12 (m, 2H), 6.88 (d, J = 1.2 Hz, 1H), 7.37−7.50 (m, 3H), 7.56 (dd, J = 1.5 and 8.7 Hz, 1H), 7.68−7.77 (m, 3H), 8.06 (s, 1H), 9.44 (d, J = 1.2 Hz, 1H). IR ($CHCl_3$): 3462, 3374, 3026, 3006, 2952, 2872, 1724, 1610, 1580, 1484, 1452, 1358, 1309, 1147 cm^{-1}. $[\alpha]^{26}_D$ +16.4° (*c* 1.05, $CHCl_3$). Anal. ($C_{29}H_{34}N_2O_4S$) C, H, N, S.

(1*S*,2*R*,3*R*,4*R*)-(5*Z*)-7-(3-(2-Phenyl-1*H*-indole-6-sulfonylamino)bicyclo[2.2.1]hept-2-yl)hept-5-enoic Acid (32). A solution of 0.131 g (0.258 mmol) of **55a** in 8 mL of MeOH and 2 mL of THF was treated with 1 N KOH for 17 h. The mixture was acidified with 10% HCl and extracted with AcOEt. The organic layer was washed with a 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 **32** (0.127 g, 100%) as a colorless solid. Mp 160−161 °C. ^{1}H NMR ($CDCl_3$/CD_3OD): δ 1.00−2.02 (m, 14H), 2.23 (m, 1H), 2.29 (t, J = 6.9 Hz, 2H), 2.96 (m, 1H), 5.16−5.26 (m, 2H), 6.87 (s, 1H), 7.28−7.57 (m, 4H), 7.69 (d, J = 8.4 Hz, 1H), 7.75−7.78 (m, 2H), 7.99 (s, 1H). IR (KBr): 3254, 2944, 1704, 1484, 1358, 1305, 1147 cm^{-1}. $[\alpha]^{24}_D$ +13.0° (*c* 1.02, CH_3OH). Anal. ($C_{28}H_{32}N_2O_4S$) C, H, N, S.

(*Z*)-7-[(1*S*,2*R*,3*R*,4*R*)-3-(Benzylideneamino)bicyclo[2.2.1]-hept-2-yl]-hept-5-enoic Acid Methyl Ester (58). To a solution of 4.00 g (14.3 mmol) of **2** in 40 mL of toluene was added 1.46 mL (13.8 mmol) of benzaldehyde and 7.20 mg (28.6 μmol) of pyridinium *p*-toluenesulfonate, and the mixture was dehydrated by heating using the Dean−Stark apparatus. After being stirred for 1 h, the mixture was poured into a saturated $NaHCO_3$ solution and extracted with AcOEt. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated to give 5.26 g (100%) of **58** as an oil. ^{1}H NMR ($CDCl_3$): δ 1.28−2.08 (m, 14H), 2.23 (m, 1H), 2.32 (t, J = 7.2 Hz, 2H), 3.18 (m, 1H), 3.66 (s, 3H), 5.32−5.36 (m, 2H), 7.38−7.41 (m, 3H), 7.73−7.76 (m, 2H), 8.28 (s, 1H).

(*Z*)-7-((1*S*,2*R*,3*R*,4*R*)-3-Aminobicyclo[2.2.1]hept-2-yl)-2,2-dimethylhept-5-enoic Acid Methyl Ester (59). To a solution of 5.26 g (14.3 mmol) of **58** in 60 mL of THF was added 12.0 mL (21.6 mmol) of 1.8 M LDA in THF at −78 °C, and the mixture was stirred for 45 min at the same temperature. To the reaction mixture was added 4.46 mL of MeI (71.7 mmol), and the mixture was then warmed to ambient temperature. After being stirred for 1.5 h, the mixture was quenched with saturated NH_4Cl and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to give 5.81 g of a monomethyl derivative. The same procedure was again carried out to obtain 5.98 g of a dimethyl compound. This crude product was dissolved with 60 mL of CH_2Cl_2, and 1.65 mL of trifluoroacetic acid (21.4 mmol) was added at 0 °C. After being stirred for 2 h, the reaction mixture was concentrated in vacuo and treated with 4 N HCl in AcOEt and evaporated. The residue was dissolved with water and toluene, and the aqueous layer was washed with toluene, treated with a 15% NaOH solution, and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel to give 1.98 g (45%) of the crude material (**59**) that was used for the next step without further purification. ^{1}H NMR ($CDCl_3$): δ 0.80 (m, 1H), 1.05−2.09 (m, 14H), 1.18 (s, 6H), 1.49 (br, 2H), 2.72 (m, 1H), 3.66 (s, 3H), 5.34−5.40 (m, 2H).

{(1*R*,2*R*,3*R*,4*S*)-3-[(Methoxymethylcarbamoyl)methyl]-bicyclo[2.2.1]hept-2-yl}carbamic Acid Benzyl Ester (61). To a solution of 2.65 g (17.00 mmol) of $NaH_2PO_4\cdot 2H_2O$, 8.10 mL (76.45 mmol) of 2-methyl-2 butene and 4.88 g (16.98 mmol) of **60** in 60 mL of ^{t}BuOH and 18 mL of water was added 6.80 g (59.4 mmol) of 79% $NaClO_2$ at 0 °C, and this was left at room temperature. After being stirred for 45 min, the mixture was poured into 1 N $Na_2S_2O_3$ and extracted with AcOEt. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was dissolved with 40 mL of DMF, and 1.51 g (15.5 mmol) of MeONHMe·HCl, 2.40 g (15.5 mmol) of WSCDI, and a catalytic amount of HOBt were added at 0 °C. The reaction mixture was left at ambient temperature, stirred for 15 h, and diluted with AcOEt. This solution was washed with 0.7 N HCl, water, saturated $NaHCO_3$, and brine and then evaporated to give **61** (3.55 g, 60%) as an oil. ^{1}H NMR ($CDCl_3$): δ 1.23−1.59 (m, 7H), 1.98 (m, 1H), 2.42−2.63 (m, 3H), 3.15 (s, 3H), 3.46 (m, 1H), 3.66 (s, 3H), 5.02 (br, 1H), 5.08 (s, 2H), 7.27−7.36 (m, 5H).

***N*-Methoxy-2-[(1*S*,2*R*,3*R*,4*R*)-3-(2-methoxydibenzofuran-3-sulfonylamino)-bicyclo[2.2.1]hept-2-yl]-*N*-methylacetamide (47a).** To a solution of 4.35 g (12.6 mmol) of **61** in 50 mL of MeOH was added 0.40 g of $Pd(OH)_2$ on carbon, and the mixture was vigorously stirred under H_2 atmosphere for 2 h. The solution was filtered through Hyflo Super-Cell and evaporated to give 2.66 g as a colorless oil. To a solution of 0.527 g (2.48 mmol) of this colorless oil in 5 mL of THF was added 0.810 g (2.73 mmol) of 2-methoxydibenzofuran-3-sulfonyl chloride and 0.360 mL (2.98 mmol) of Et_3N at 0 °C. After the mixture was left at ambient temperature and stirred for 30 min, it was poured into water and extracted with AcOEt. The organic layer was washed with a 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 **47a** (0.937 g, 80%) as a pale-orange solid. ^{1}H NMR ($CDCl_3$): δ 1.15−1.78 (m, 7H), 1.89−2.17 (m, 4H), 2.97 (s, 3H), 3.00 (m, 1H), 3.44 (m, 3H), 4.12 (s, 3H), 5.56 (d, J = 6.3 Hz, 1H), 7.36−7.62 (m, 4H), 7.95 (d, J = 6.0 Hz, 1H), 8.15 (s, 1H).

7-[(1*S*,2*R*,3*R*,4*R*)-3-(2-Methoxydibenzofuran-3-sulfon-

ylamino)bicyclo[2.2.1]hept-2-yl]-6-oxoheptanoic Acid (47). To a solution of 1.04 g (3.70 mmol) of 1-bromo-5-(*tert*-butyldimethylsilyloxy)pentane in 6.5 mL of Et_2O and 9 mL of THF was added 90.0 mg (3.70 mmol) of Mg turnings and a catalytic amount of I_2. The mixture was refluxed for 1 h and cooled in an ice/water bath. To this solution was added a solution of 0.580 g (1.23 mmol) of **47a** in 9 mL of THF. The reaction mixture was stirred for 15 min at 0 °C and then was allowed to reach room temperature. After being stirred for 4.5 h, the mixture was quenched with a saturated NH_4Cl solution and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel to give 0.547 g (73%) of the alcohol derivative as a colorless solid. This alcohol derivative (0.300 g, 0.489 mmol) was treated with Jones reagent to give **47** (0.220 g, 88%) as an amorphous solid. ^{1}H NMR ($CDCl_3$): δ 1.10−2.25 (m, 19H), 2.94 (m, 1H), 4.12 (s, 3H), 5.53 (d, J = 7.2 Hz, 1H), 7.39 (m, 1H), 7.50−7.62 (m, 3H), 7.96 (d, J = 7.5 Hz, 1H), 8.13 (s, 1H). IR ($CHCl_3$): 3367, 3025, 2955, 1711, 1634, 1600, 1584, 1468, 1454, 1440, 1415, 1342, 1317, 1222, 1189, 1157 cm^{-1}. $[\alpha]^{25.0}_D$ +1.2° (*c* 1.00, $CHCl_3$). Anal. ($C_{27}H_{31}NO_7S\cdot 0.2H_2O$) 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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