***N*-(2-Tetrazol-2-ylethyl)-4-[(carbomethoxyoxy)methyl]-4-(*N*-propionanilido)piperidine (4f)**: eluant EtOAc. NMR: δ 8.53 (s, 1 H), 7.37 (br s, 5 H), 4.98 (s, 2 H), 4.81–4.55 (m, 2 H), 3.84 (s, 3 H), 3.14–1.28 (complex, 12 H), 0.85 (t, 3 H, J = 7.0 Hz).

***N*-(Phthalamidoethyl)-4-[(propionyloxy)methyl]-4-(*N*-propionanilido)piperidine (5a)**: eluant EtOAc–hexane 3:2. NMR: δ 7.90 (br s, 4 H), 7.42 (br s, 5 H), 4.98 (br s, 2 H), 3.71 (t, 3 H, J = 6.0 Hz), 2.85–1.62 (complex, 14 H), 1.47–0.92 (m, 6 H).

Pharmacological Methods. Mouse Hot-Plate Determination of ED_{50} Dose. Ten male Swiss-Webster mice, weighing 18–26 g, purchased from Hilltop Laboratories were utilized. Animals were randomly selected and allowed to acclimate to the laboratory environment for at least 1 h prior to testing. Drugs were injected iv in the lateral tail vein. The animal was placed on a hot plate kept at constant temperature (55.0 ± 0.5 °C) and observed for occurrence of licking of hind or front paws.

A timer was simultaneously started as the animal was placed on the hot plate and stopped when a nociceptive response was elicited. The animal was immediately removed from the hot plate and the latency time was recorded. Mice control latency times in excess of 15 s were eliminated from the study.

Test latency times were determined 5 min after iv administration of the test drug. Analgesia is defined as test hot plate latency of 2 or more times greater than control latency times. No animal was permitted to remain on the hot plate longer than 30 s to prevent tissue damage. The number of mice exhibiting analgesia out of 10 was plotted as a percentage affected, thus generating a dose–response curve. At least three doses between 10 and 90% of responding animals were utilized. ED_{50} values with 95% confidence limits were calculated.[11]

Duration of Analgesia. Two times the ED_{50} dose was administered to 10 mice, and the hot-plate latencies were determined at various times after injection of the drug into the lateral tail vein. The mean maximum percent effect (% MPE) was calculated for each time period, and a time effect curve was generated. We have defined a test compound to be short acting if the duration to 50% MPE was less than 6 min, intermediate with a duration of 6.1–15 min, and long acting with a duration greater than 15.1 min.

Loss of Righting[12] (LOR). Male Swiss-Webster mice weighing 18–26 g with free access to food and water were marked, weighed, and allowed to acclimate for 1 h in the laboratory environment.

The starting dose was usually 15.5 mg/kg with use of three mice per dose. The range of doses tested was that dose that elicits death in 1/3 mice (lowest lethal dose LLD) decreasing to a dose that does not produce loss of righting (LOR) in 0/3 mice.

Immediately following a bolus injection into one of the lateral tail veins, a stopwatch was started and the mouse was placed on his dorsal side. Failure to return to the ventral side indicates LOR. Duration of LOR was recorded as the time from LOR until righting occurred. The lowest dose required to produce loss of righting in 3/3 mice (lowest effective dose 100, LED_{100}) was used as a standard for comparing the test compounds.

Opiate Receptor Binding. The method was based on that of Pasternak[13] et al. and used crude membrane fractions prepared from freshly harvested rat brains. Doses of 1, 10, and 100 nM were run in triplicate, and the data curve was fitted to the mean. The K_i for inhibition of [^{3}H]nalaxone binding was then calculated according to the method of Cheng and Prusoff.[14]

Acknowledgment. The technical assistance of Mark Benvenga, Thomas Jerrussi, Steve Waters, and Barry I. Gold (Anaquest Pharmacology Department, Murray Hill, NJ) and of the Dental School of the University of Maryland at Baltimore is gratefully acknowledged. We also thank the discussions and valuable insight of Dr. Jerome R. Bagley (Anaquest Chemistry Department) during the course of this investigation.

Supplementary Material Available: A listing of the NMR data for **1–5** (4 pages). Ordering information is given on any current masthead page.

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9,11-Epoxy-9-homo-14-thiaprost-5-enoic Acid Derivatives: Potent Thromboxane A_2 Antagonists

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A novel bicyclic prostaglandin analogue, (1*S*)-[1α,2α(*Z*),3α,4α]-7-[3-[(hexylthio)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid ((−)-**10**), and its cogeners were found to be potent antagonists at the TxA_2 receptor. Compound (−)-**10** was the only stereoisomer out of eight possible structures that was active. Thioether (−)-**10** was 30–40-fold more potent than another TxA_2 antagonist, BM 13.177, in inhibiting arachidonic acid (AA) induced aggregation of human platelet-rich plasma. Compound (−)-**10** was effective (I_{50} = 0.5 ± 0.4 μM) in inhibiting 9,11-azo-PGH_2-induced (0.1 μg/mL) contraction of guinea pig tracheal spirals. The bronchoconstriction in anesthetized guinea pigs induced by AA was also effectively antagonized by (−)-**10** (1 mg/kg, iv); however, in this assay (−)-**10** exhibited some direct agonist activity. Radioligand binding studies in washed (human) platelets revealed that (−)-**10** is one of the most potent ligands for the PGH_2/TxA_2 receptor yet described (K_d = 1.6 ± 0.4 nM).

The development of pharmacological agents that modulate the synthesis or actions of a variety of arachidonic acid (AA) metabolites continues to be an active area of research. Our interest in the AA manifold has focused on the least stable member of this family, namely thromboxane A_2 (TxA_2, **1**).[1] This compound, whose structural

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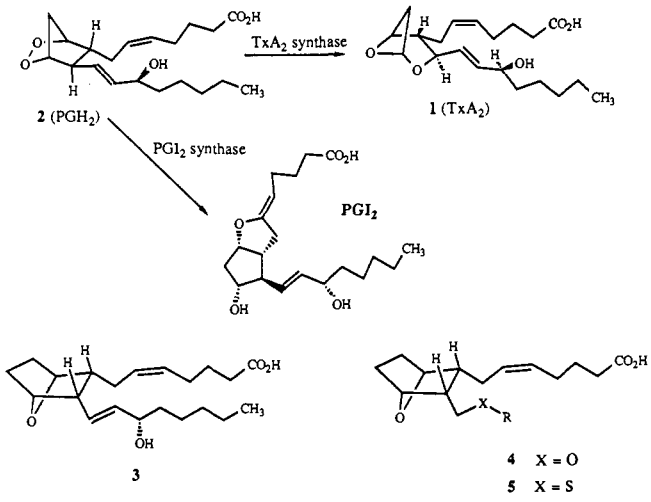
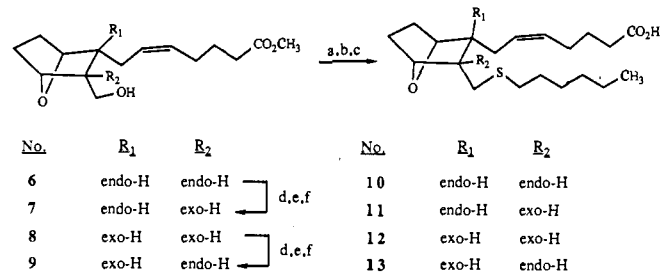
Scheme I



assignment has been supported by total synthesis,[2] is a potent stimulator of blood platelet aggregation and is also a potent smooth muscle spasmogen. Proof for a causative relationship between endogenous production of TxA_2 and the pathophysiology of disease remains elusive due in part to the lack of specific tools that block the pharmacological effects of these endogenous mediators. A number of research groups have investigated the development of TxA_2 synthetase inhibitors.[3] These agents block the conversion of the endoperoxide PGH_2 (**2**) to TxA_2 (Scheme I). Proponents of this approach have assumed that the PGH_2 produced on stimulation would diffuse out of the cell responsible for its production (i.e. platelets) and be converted to the antiaggregatory and vasodilatory prostacyclin (PGI_2) by other cell types (i.e. endothelium).[4] A major disadvantage of this approach is that PGH_2 possesses a similar pharmacological profile to that of TxA_2 and is only 10-fold less potent[2] than TxA_2. This may be responsible, in part, for the disappointing clinical trials with these agents.[5] An alternate approach is the pursuit of compounds that would block the actions of TxA_2 at the receptor level. This type of compound would also be expected to antagonize the effects of PGH_2 since these two agents appear to share a common receptor.[6] Sprague[7] and Nakane[8] from these

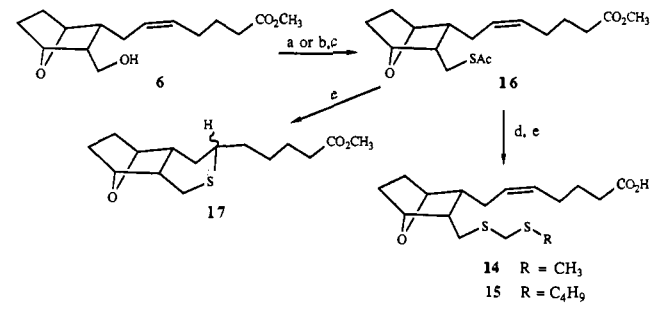
Scheme II[a]



No.	R_1	R_2	No.	R_1	R_2
6	endo-H	endo-H	10	endo-H	endo-H
7	endo-H	exo-H	11	endo-H	exo-H
8	exo-H	exo-H	12	exo-H	exo-H
9	exo-H	endo-H	13	exo-H	endo-H

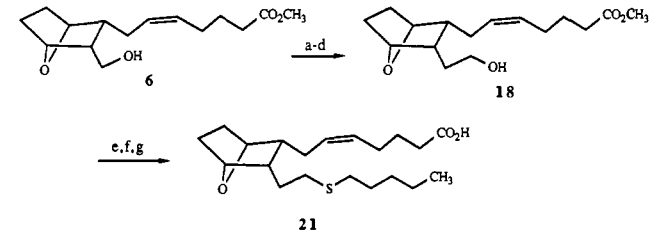
[a] (a) TsCl, Py, CH_2Cl_2, 23 °C; (b) KOtBu, RSH, THF, Δ; (c) 1 N LiOH, H_2O, THF, 23 °C; (d) PCC, NaOAc, CH_2Cl_2, Celite; (e) cat. $NaOCH_3$, CH_3OH, 0 → 23 °C; (f) $NaBH_4$, CH_3OH, 0 °C.

Scheme III[a]



[a] (a) DIAD, Ph_3P, HSAc, THF, 0 → 23 °C; (b) TsCl, Py, CH_2Cl_2; (c) KSAc, THF, DMSO, Δ; (d) KOH, $ClCH_2SR$, xylene, Δ; (e) 1 N LiOH, H_2O, THF.

Scheme IV[a]



[a] (a) PCC, NaOAc, Celite; (b) $Ph_3P^+CH_2OCH_3Br^-$, KOtAm, THF; (c) 20% TFA, THF; (d) $NaBH_4$, CH_3OH, $CeCl_3$; (e) TsCl, Py, CH_2Cl_2; (f) KOtBu, $C_5H_{11}SH$, THF, Δ; (g) 1 N LiOH, H_2O, THF.

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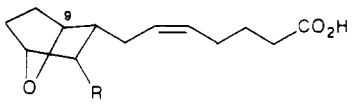
Table I. Synthesis and in Vitro Activity of Thia 7-Oxabicyclo[2.2.1]heptyl Acids



		synthesis						in vitro pharmacology[a]	
no.	R	RSH, equiv	KOtBu, equiv	reaction time, h	yield, %	config at C(9)	mp, °C	AAIPA:[c] I_{50}, μM	contraction of rat stomach strip A_{50},[b] μM
10	$CH_2S(CH_2)_5CH_3$	3.0	1.1	5.5	84	*R,S*	oil	3.8	39
21	$CH_2CH_2S(CH_2)_4CH_6$	*g*				*R,S*	oil	37	
24	$S(CH_2)_6CH_3$	*g*				*R,S*	oil	35	
25	(*endo*)-$S(CH_2)_6CH_3$	*g*				*R,S*	oil	230	
31	sulfoxide of **10** (FMI)	*d*				*R,S*	83–87	192	9%
32	sulfoxide of **10** (SMI)	*d*				*R,S*	39–43	63	21
33	sulfone of **10**	*d*				*R,S*	56–58	25	8
34	CH_2SCH_2-c-C_6H_{11}	3.0	1.1	7.0	94	*R,S*	47–50	20	
35	$CH_2S(CH_2)_2$-Ph	3.0	1.1	4.5	90	*R,S*	oil	5.5	23
36	$CH_2S(CH_2)_3$-Ph	3.0	1.1	6.5	98	*R,S*	oil	5.0	0.2
37	$CH_2S(CH_2)_2OPh$	3.0	1.1	4.5	84	*R,S*	oil	20	0.1
38	(*E*)-CH_2SCH_2CH=CH-Ph	2.6	1.2	4.0	79	*R,S*	oil	86	0.7
39	$CH_2S(CH_2)_7CH_3$	2.5	1.2	3.75	99	*R,S*	41–43.5	547	
(+)-**10**	$CH_2S(CH_2)_5CH_3$	3.4	1.2	2.5	81	*R*	31–35	83	6%
(−)-**10**	$CH_2S(CH_2)_5CH_3$	3.6	1.3	2.5	78	*S*	31–35	1.0	25
	Effect of Substitution								
40	(*S*)-$CH_2SCH(CH_3)(CH_2)_4CH_3$	5.0	1.1	7.6	86	*S*	oil	3.8	
41	(*R*)-$CH_2SCH(CH_3)(CH_2)_4CH_3$	5.0	1.1	10.0	89	*S*	oil	A_{50} = 22 μM	
42	$CH_2SCH_2CH(OH)(CH_2)_3CH_3$[e]	3.0	2.5	3.5	76	*S*	oil	10	
43	$CH_2SCH_2CH(OH)(CH_2)_3CH_3$[f]					*S*	oil	19	
44	$CH_2SCH_2C(O)NH(CH_2)_2CH_3$	3.0	2.2	7.5	74	*S*	oil	72	
15	$CH_2SCH_2S(CH_2)_3CH_3$[g]				72	*S*	oil	0.7	
	Effect of Chain Length								
45	CH_2SCH_3	2.0	2.0	7.5	50	*S*	67–68	38	30%
46	$CH_2SCH_2CH_3$	7.4	1.1	16	96	*S*	49–50	5.4	13%
47	$CH_2S(CH_2)_2CH_3$	5.0	1.2	8.6	96	*S*	oil	0.7	10%
48	$CH_2S(CH_2)_3CH_3$	5.0	1.1	17	88	*S*	oil	1.0	
49	CH_2SCH_2CH=CH_2	3.0	1.1	5	91	*S*	oil	0.5	26%
50	$CH_2S(CH_2)_2CH$=CH_2	15.6	1.1	16.25	81	*S*	oil	0.2	32
14	$CH_2SCH_2SCH_3$	*g*			81	*S*	oil	0.7	28%
51	$CH_2S(CH_2)_6CH_3$	10	1.5	8	94	*S*	oil	42	
52	CH_2SPh	5	1.1	7.5	98	*S*	110–112	13	0.8
	Effect of Unsaturation								
53	(*E*)-CH_2SCH_2CH=CHC_3H_7	3	1.1	6	73	*S*	oil	1.3	26
54	(*E*)-$CH_2SCH_2C(CH_3)$=CHC_3H_7	3	1.1	6	65	*S*	oil	1.1	46
55	(*Z*)-CH_2SCH_2CH=CHC_3H_7	5	1.1	8	60	*S*	oil	5.7	4.3
56	(*Z*)-$CH_2S(CH_2)_2CH$=CHC_2H_5	5	1.1	5.75	89	*S*	oil	0.2	0.2
57	(*E*)-$CH_2S(CH_2)_2CH$=CHC_2H_5	5	1.1	10	86	*S*	31–33	0.7	0.04

[a] For details of the methods used, see ref 17; none of the compounds was effective in inhibiting ADP (20 μM) induced platelet aggregation (PA) with the exception of sulfides **42** and **43**. [b] Concentration of test compound required to elicit 50% of the maximal contraction induced by 3×10^{-7} M serotonin; when given as a percentage, this is the maximum contraction observed; $n = 8$ for all compounds tested. [c] I_{50} vs 800 μM arachidonic acid in human platelet-rich plasma (PRP); values represent single determinations. [d] Prepared by $NaIO_4$ oxidation of (±)-**10**; see the Experimental Section. [e] FMI; refers to fast-moving isomer as determined on silica gel TLC; I_{50} vs ADP (20 μM) induced PA = 45 μM. [f] SMI; refers to slow-moving isomer as determined on silica gel TLC; I_{50} vs ADP (20 μM) induced PA = 59 μM. [g] Prepared as described in the Experimental Section.

laboratories have previously reported the synthesis of a series of 7-oxabicyclo[2.2.1]heptane analogue related to **3** that were found to be potent TxA_2 antagonists. Recently, we described a series of 7-oxabicyclo[2.2.1]heptane ether analogues (**4**) that were found to possess potent inhibitory action on PG synthetase.[9] As part of our continuing program to identify novel TxA_2 antagonists, we now describe the development of a new class of TxA_2 antagonists that employs a simple thioether moiety as the ω-chain. Some of these compounds (**5**) were also shown to have modest activity in inhibiting TxA_2 synthetase.

Chemistry

The preparation of the initial target thioethers proved to be straightforward given the availability of alcohol esters **6–9**. These intermediates were prepared from the exo and endo Diels–Alder adducts of furan and maleic anhydride as described by Sprague et al.[7] The majority of the thioethers were synthesized as outlined in Scheme II. Tosylation of the requisite alcohol ester followed by displacement with potassium hexanethiolate and hydrolysis provided the target acids **10–13** in good yield. Subsequent synthesis of additional thioethers followed this three-step procedure with few exceptions (Table I). In general, the required mercaptans were not commercially available but

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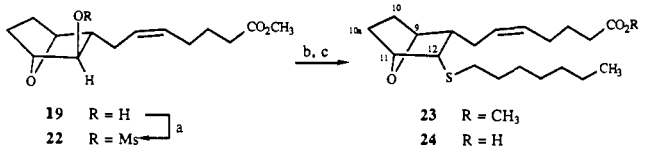
Scheme V[a]

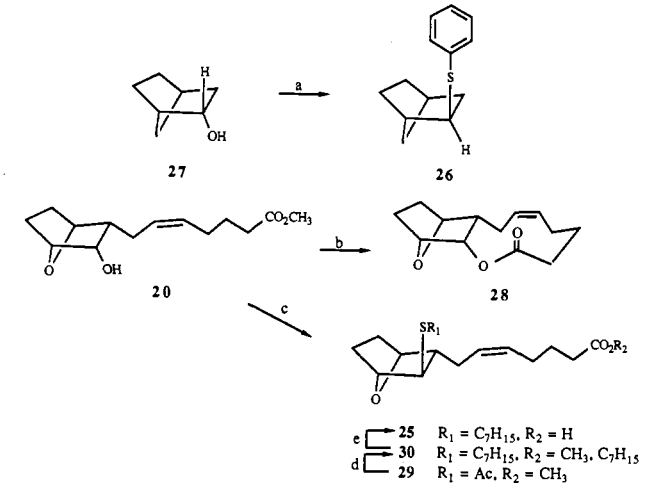


19 R = H
22 R = Ms

23 R = CH_3
24 R = H

[a] (a) MsCl, Py, CH_2Cl_2; (b) KOtBu, $C_7H_{15}SH$, DMSO/THF, Δ; (c) 1 N LiOH, H_2O, THF.

Scheme VI[a]



25 $R_1 = C_7H_{15}$, R_2 = H
30 $R_1 = C_7H_{15}$, $R_2 = CH_3$, C_7H_{15}
29 R_1 = Ac, $R_2 = CH_3$

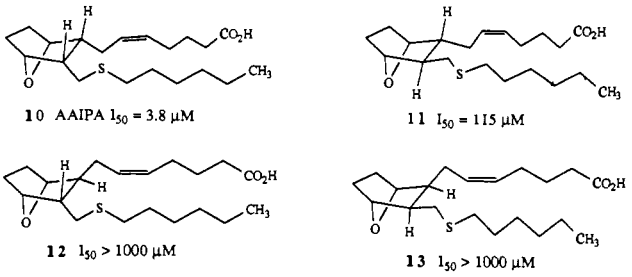
[a] (a) NaH, $Ph_3P^+N(CH_3)PhI^-$, PhSH; (b) NaH, $Ph_3P^+N(CH_3)$-PhI^-, $C_7H_{15}SH$; (c) DIAD, Ph_3P, HSAc, THF, 0 → 23 °C, 12 h; (d) KOH, xylene, $C_7H_{15}Br$, Δ; (e) 1 N LiOH, H_2O, THF.

were prepared by the method of Volante[10] (ROH → RSAc → RSH) and were employed in the displacement step without purification. The target compounds that contained an additional heteroatom β to the sulfur at position 14 (i.e. **14** and **15**) were necessarily prepared by an alternative route (Scheme III). The Mitsunobu style conversion of alcohol **6** to thioacetate **16** proceeded efficiently (90%) but purification proved to be troublesome. Thus, a two-step process was used (R–OH → R–OTs → R–SAc) to provide **16** in 74% overall yield. Attempts to hydrolyze the thioacetate were plagued with formation of the cyclic sulfide **17** as well as the desired mercaptan. Synthesis of **14** and **15** was realized, however, by subjecting thioacetate **16** to the alkylation conditions that we found to work well in the O-alkylation[9] of **6–9**. In this reaction, the liberated thiolate is alkylated before it has the opportunity to participate in unwanted side reactions.

A priori, it was not obvious what effect translocation of the sulfur atom might have with regard to TxA_2 antagonism. As such, we were interested in analogues of **10** wherein the sulfur atom at position 14 had been shifted to either the 13- or 15-position. At the outset, this appeared to be a simple task as we had recently synthesized the prerequisite alcohols **18**, **19**, and **20**.[9] Indeed, conversion of alcohol **18** to thioether **21** was accomplished without incident under the conditions described above for alcohols **6–9** (Scheme IV). Preparation of the epimeric 13-thia analogues was, as expected, more difficult due to the increased steric congestion of alcohols **19** (Scheme V) and **20** (Scheme VI). Displacement of mesylate **22** with heptyl mercaptan using the same conditions employed for the 14-thia analogues afforded only traces of **23**. Addition of DMSO led to a modest yield (26%) of the thioether along with 38% of recovered mesylate **22** and 26% of the precursor alcohol **19**. The NMR spectrum of **23** confirmed that the relative stereochemistry of the two side chains was

(10) Volante, R. P. *Tetrahedron Lett.* **1981**, *22*, 3119.

Scheme VII. Evaluation of Stereoisomers



10 AAIPA I_{50} = 3.8 μM

11 I_{50} = 115 μM

12 I_{50} > 1000 μM

13 I_{50} > 1000 μM

not scrambled as both H(9) and H(11) appeared as doublets (coupled only to H(10aα)). Had the trans isomer been formed, one of these resonances (H-11) would appear as a triplet (also coupled to H(12)). No further work on this reaction was performed as there was enough product for initial pharmacological evaluation. Synthesis of the trans isomer **25** proceeded as shown in Scheme VI. Murahashi et al.[11] had used a double-activation procedure to prepare the endo phenyl thioether **26** directly from the exo alcohol **27**. In our hands, treatment of **20** under these conditions resulted in extensive degradation with lactone **28** obtained as the only isolable product (10% yield). Introduction of the sulfur was achieved on treatment of **20** with excess Ph_3P/HSAc/diisopropyl azodicarboxylate.[10] Thioacetate **29** was obtained in 33% yield along with 56% of recovered **20**. Direct conversion of **29** to the desired thioether **30** was accomplished by treatment of **29** with KOH/heptyl bromide in refluxing xylene. Basic hydrolysis of the resulting mixture of methyl and heptyl esters afforded the target acid **25**.

Pharmacology

In Vitro. Initial efforts to prepare analogues of either PGH_2 or TxA_2 have focused on alteration of the nucleus while maintaining the natural α- and ω-chains. Nearly every combination of nitrogen, oxygen, sulfur, and carbon atoms that would lead to a stable [2.2.1] or [3.1.1] bicyclic framework has been synthesized and evaluated. In general, analogues that possessed the natural α- and ω-chains maintained proaggregatory/vasoconstrictor activity.[12] In contrast, analogues that possessed a saturated α-chain[13] or a modified ω-chain (mainly replacement of the allylic alcohol with a diene or simple olefin) led to compounds that possessed activity as either TxA_2 synthetase inhibitors[14,15d] or TxA_2 antagonists.[15] Many of these compounds

(11) Tanigawa, Y.; Kanamaru, H.; Murahashi, S. I. *Tetrahedron Lett.* **1975**, *16*, 4655.

(12) (a) Corey, E. J.; Nicolaou, K. C.; Machida, Y.; Malmsten, C. L.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 3355. (b) Corey, E. J.; Narasaka, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1976**, *98*, 6417. (c) Corey, E. J.; Shibasaki, M.; Nicolaou, K. C.; Malmsten, C. L.; Samuelsson, B. *Tetrahedron Lett.* **1976**, 737. (d) Miyake, H.; Iguchi, S.; Itoh, H.; Hiyashi, M. *J. Am. Chem. Soc.* **1977**, *99*, 3536. (e) Portoghese, P. S.; Larson, D. L.; Abatjoglou, A. G.; Dunham, E. W.; Gerrad, J. M.; White, J. G. *J. Med. Chem.* **1977**, *20*, 320. (f) Bundy, G. L. *Tetrahedron Lett.* **1975**, 1957.

(13) Raz, A.; Minkes, M. S.; Needleman, P. *Biochem. Biophys. Acta* **1977**, *488*, 305.

(14) (a) Barraclough, P. *Tetrahedron Lett.* **1980**, 1897. (b) Bundy, G. L.; Peterson, D. C. *Tetrahedron Lett.* **1978**, 41.

(15) (a) Kam, S.-T.; Portoghese, P. S.; Gerrad, J. M.; Dunham, E. W. *J. Med. Chem.* **1979**, *22*, 1402. (b) Gorman, R. R.; Bundy, G. L.; Peterson, D. C.; Sun, F. F.; Miller, O. V.; Fitzpatrick, F. A. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 4007. (c) Shimizu, K.; Kohli, J. D.; Goldberg, L. I.; Kittisopikul, S.; Freid, J. In *Advances in Prostaglandin and Thromboxane Research*; Samuelsson, B., Paoletti, R., Ramwell, P., Eds.; Raven: New York, 1983; Vol. 11, p 333. (d) Maxey, K. M.; Bundy, G. L. *Tetrahedron Lett.* **1980**, 445.

were only evaluated for their activity in the platelet; however, some of these analogues (i.e. carbo-TxA_2) possessed potent vasoconstrictor activity despite their antiaggregatory activity in the platelet.[16]

The compounds in the present study are similar to these analgoues in that the allylic alcohol has been replaced by a more lipophilic residue, namely, an alkyl sulfide. All of the thioethers were evaluated for their ability to inhibit both arachidonic acid induced and adenosine diphosphate induced platelet aggregation (AAIPA and ADPIPA, respectively) of human platelet-rich plasma (PRP).[17] These results are summarized in Table I. Initial evaluation of the four isomeric thioethers **10–13** established that only the cis-exo isomer possessed significant activity (Scheme VII). The poor activity of the trans-isomer **11** was surprising since the analogues prepared in the above studies possessed the same relative stereochemistry[12-15] as sulfide **11**. Translocation of the sulfur atom from position 14 to either 13 or 15 led to a 10-fold decrease in activity. As a result, our initial structure–activity relationships (SAR) were developed with a series of 14-thia cis-exo analogues (racemic). Oxidation at sulfur was not tolerated as evidenced by decreases in activity ranging from 10- to 50-fold for sulfoxides **31** and **32** as well as the sulfone **33**. Likewise, modification of the thioether alkyl residue led to dramatic attenuations in activity. For example, homologation of the alkyl group in the ω-chain from six to eight atoms (**10** vs **39**) resulted in a 100-fold drop in potency.

Evaluation of the individual enantiomers of **10** revealed that both antipodes possessed antiaggregatory activity. Further investigation revealed that (−)-**10** (absolute stereochemistry as shown in Scheme VII) derived its activity as a thromboxane antagonist. Its antipode (+)-**10**, in analogy to the related O-ether analogues,[9] was found to inhibit prostaglandin synthase. To avoid possible complications in the interpretation of the results from racemic mixtures, all subsequent thioethers were prepared as single enantiomers. As our initial studies suggested that the antiaggregatory activity of the thioethers was strongly influenced by the nature of the sulfide ω-chain, our SAR work focused on modification of the ω-chain tail. These compounds are grouped in Table I into three general categories representative of the following changes: substitution in the alkyl chain, length of the alkyl chain, or unsaturation in the alkyl chain. Within the first category, substitution α or β to the sulfur atom led to decreased activity. The stereochemistry of substitution in the α-position (C-15) was important; whereas methylated analogue **40** was just slightly less potent than (−)-**10**, the methyl epimer **41** was actually a stimulator of platelet aggregation.[18] Unlike the other thioethers prepared, alcohols **42** and **43** possessed inhibitory activity against ADP-induced aggregation of human PRP. Within this limited group of compounds, the only modification tolerated was the isosteric replacement of a methylene group with an additional sulfur atom (**15**).

Within a homologous series of alkyl thioethers some latitude in length was tolerated. Thioethers possessing alkyl chains of three to six carbons were equipotent, while alteration of the length beyond these limits led to sharp decreases in activity. In fact, the only modification that led to increased activity, albeit modest, was the introduction of unsaturation in the alkyl residue.[19] The allylic thioethers (**49**, **53–55**) were similar or slightly more potent that their corresponding saturated analogues. The homoallylic thioethers (**50**, **56**, **57**) were approximately 5-fold more potent than their saturated counterparts.

Given the effect of the related O-ethers[9] on AA metabolism, several of the more potent thioethers were evaluated for their effects on AA metabolism in a lysed platelet preparation (Table II). Some of these analogues possessed TxA_2 synthetase inhibitory activity, but only at concentrations at least 10-fold higher than the concentration necessary for effective inhibition of platelet aggregation. This was clearly not due to cyclooxygenase inhibition since PGE_2 production was stimulated by over 500% at the concentrations that inhibited TxA_2 synthesis by 50% (60–310 μM). This result was not completely unexpected as a number of PGH_2/TxA_2 analogues that possessed highly lipophilic ω-chains inhibited TxA_2 synthetase.[14,15d,16d] The prospects of a pharmaceutical agent with both TxA_2 antagonist activity and TxA_2 synthetase inhibitory activity are attractive as these compounds would not only block the effects of TxA_2 (as well as PGH_2) at the receptor level, but also might shunt PGH_2 from the platelet to the vasculature resulting in the conversion of PGH_2 to PGI_2.

Critical to the development of a TxA_2 receptor antagonist as a potential pharmaceutical agent is whether these agents possess any agonist activity. As a general screen for direct agonist activity, we evaluated the effects of the more potent thioethers on rat stomach strips.[20] This tissue

Table II. Effect of Thioethers on TxB_2 and PGE_2 Synthesis in a Lysed Platelet Preparation[a]

no.	drug concn, μM	inhib of TxB_2 synthesis, %	stimulation of PGE_2 synthesis, %
(−)-**10**	1.0	7	174
	3.1	3	137
	10	17	230
	31	29	404
	100	69	556
(+)-**10**	10	33	27
	100	45	44
	1000	75	−51[b]
21	10	33	13
	100	80	−45[b]
	1000	90	−75[b]
49	10		220
	33		380
	100	22.1	860
	333	51.8	1650
	1000	61.5	1820
56	10		210
	33		420
	100	24.4	900
	333	56.9	1340
	1000	91.2	1920

[a] Compounds **30–32** had no effect on either TxB_2 or PGE_2 synthesis. [b] PGE_2 synthesis was inhibited; these compounds apparently inhibit cyclooxygenase.

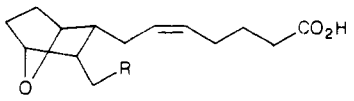
(16) (a) Corey, E. J.; Ponder, J. W.; Ulrich, P. *Tetrahedron Lett.* **1980**, 137. (b) Nicolaou, K. C.; Magolda, R. L.; Claremon, D. A. *J. Am. Chem. Soc.* **1980**, *102*, 1404. (c) Nicolaou, K. C.; Magolda, R. L.; Smith, J. B.; Aharony, A.; Smith, E. F.; Lefer, A. M. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 2566. (d) Wilson, N. H.; Jones, R. L. In *Advances in Prostaglandin and Thromboxane Research*; Samuelsson, B., Paoletti, R., Ramwell, P., Eds.; Raven: New York, 1985; Vol. 14, p 393. (e) Ansell, M. F.; Caton, M. P. C.; Palfreyman, M. N.; Stuttle, K. A. *Tetrahedron Lett.* **1979**, 4497.

(17) Arachidonic acid (800 μM) and ADP (20 μM) induced platelet aggregation in platelet-rich plasma as described: Harris, D. N.; Phillips, M. B.; Michel, I. M.; Goldenberg, H. J.; Sprague. P. W.; Antonaccio, M. J. *Prostaglandins* **1981**, *22*, 295.

(18) It is interesting to note that the antagonist/agonist profile observed for **40** and **41** parallels that found for allylic alcohol **3** (antagonist) and its carbinol epimer (agonist).

(19) It was anticipated that introduction of a double bond in the ω-chain might enhance the inhibitory activity of these thioethers toward TxA_2 synthetase, in analogy with the TxA_2 synthetase inhibitory activity exhibited by PGH_3.

Table III. Antagonist Activity of Thioethers in Guinea Pig Tracheal Spirals[a]



no.	R	I_{50}, μM histamine	I_{50}, μM 9,11-azo-PGH_2
(−)-**10**	SC_6H_{13}	>100	0.5 ± 0.4
49	$SCH_2CH{=}CH_2$	>100	3.8 ± 0.3
53	(*E*)-$SCH_2CH{=}CHC_3H_7$	>100	0.4 ± 0.04[b]
54	(*E*)-$SCH_2C(CH_3){=}CHC_3H_7$	>100	1.6 ± 0.1[b]
55	(*Z*)-$SCH_2CH{=}CHC_3H_7$	>100	1.6 ± 0.2
56	(*Z*)-$SCH_2CH_2CH{=}CHC_2H_5$	>100	0.38 ± 0.02[b]

[a] Contraction induced by either histamine (1 μg/mL) or 9,11-azo-PGH_2 (0.1 μg/mL). For comparison, BM, 13,177,[25] a structurally unrelated TxA_2 antagonist, had no effect on histamine-induced contraction and was weakly active against 9,11-azo-PGH_2 ($I_{50} \approx 100$ μM, 46% inhibition at 100 μM). [b] Antagonism of 9,11-azo-PGH_2 responses remained after "washout".

is unique in that it contracts to prostanoids with few exceptions. Almost all of these thioethers displayed some direct contractile activity on the stomach strips. At the outset it was assumed that the contractile activity was due to activation of the PGH_2/TxA_2 receptor, but evidence to support this assumption remained to be identified (vide infra). The concentration–effect curves for the majority of the thioethers evaluated in the rat stomach were consistent with them functioning as partial agonists in this tissue since the magnitude of the contraction seldom exceeded 50% of the control response. Although the lack of a correlation between the TxA_2 antagonist activities of the thioethers, as measured in the platelet screen, and their contractile potencies in the rat stomach strip suggested that these two activities might be dissected, we were unable to identify analogues of (−)-**10** that were completely free of contractile activity. Thus, (−)-**10** and its congeners were shown to be qualitatively similar to a growing number of PGH_2/TxA_2 analogues that, despite potent antagonist activity in the platelet, display varying amounts of PGH_2/TxA_2 agonist activity in a variety of smooth muscle preparations.[16]

As an alternative measure of TxA_2 antagonist activity, several of the thioethers were evaluated for their ability to block contractions of guinea pig trachea spirals induced by either 9,11-azo-PGH_2 (a stable PGH_2/TxA_2 mimetic)[12a,b] or histamine (Table III).[21] Consistent with their mechanism of action, all of the thioethers tested were effective in inhibiting 9,11-azo-PGH_2-induced but not histamine-induced contractions. In general, the potencies of the thioethers in this assay correlated well with their activity in the platelet screen. Unlike the contractile activity displayed by these thioethers on rat stomach strips, none of the sulfides tested exhibited any direct effect on the guinea pig tracheal spirals. One interesting yet unexplained observation is that the inhibitory effect of several thioethers (**54**, **56**) could not be readily washed from the trachea spirals.

Table IV. One-Site Analysis of Inhibition of Specific Binding of HSQ in Washed Platelets[a]

no.	K_d ± SEM, nM	slope factor ± SEM
(−)-**10**	1.6 ± 0.4	0.73 ± 0.03
47	97 ± 20	0.75 ± 0.04
49	76 ± 11	0.67 ± 0.01
50	49 ± 5	0.72 ± 0.01
53	3.1 ± 0.5	0.99 ± 0.05
56	0.4 ± 0.1	0.75 ± 0.06

[a] Inhibition of specific binding of HSQ (5,6-di-^{3}H-SQ 29,548), [1*S*-[1α,2α(*Z*),3α,4α]]-7-[3-[[2-[(phenylamino)carbonyl]hydrazino]-methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-[5,6-$^3H_2$]-5-heptenoic acid as described in ref 22b. Values reported are an average of four determinations.

Table V. Evaluation of Antagonist/Agonist Activities of Thioethers in Anesthetized Guinea Pigs[a]

no.	agonist activity, % R_L	agonist activity, % MABP	inhibition of AA responses R_L, %	inhibition of AA responses MABP, %	inhibition of AA responses duration, min
(−)-**10**	+349	+107	95	153	<60
47	+131	+50	97	177	<60
48	+136	+58	98	180	<60
49	+273	+115	98	165	>60
53	+535	+76	98	192	<60
55	+355	+98	95	194	<60
56	+245	+90	97	292	>60

[a] R_L = change in airway resistance. MABP = change in mean arterial blood pressure; inhibition > 100% indicates reversal of blood pressure response. All compounds were administered as a 1.0 mg/kg rapid iv infusion. All values for R_L and MABP, $n = 5$, $p < 0.005$ vs vehicle.

Further characterization of these compounds was obtained from radioligand binding studies in washed platelets. Several of the more potent thioethers were evaluated for their ability to inhibit the binding of 5,6-ditritiated-SQ 29,548 (HSQ), a recently described radioligand[22] which displays high levels (>90%) of specific binding. As shown in Table IV, these thioethers possessed high affinities for the PGH_2/TxA_2 receptor.[23] Compound **56** is the most potent ligand for the TxA_2 receptor yet described (for comparison, the affinities for several recently described TXA_2 antagonists in this assay were SQ 28,668,[24] $K_d = 31.8 \pm 1.2$ nM, and BM13,177,[25] $K_d = 1.4 \pm 0.1$ μM). All six compounds tested inhibited the specific binding of HSQ in a concentration-dependent manner. Analysis of the competition binding data using a one-site model yielded slopes of the concentration–effect curves that deviated from unity for most of these compounds. This result suggests that either the antagonism is not competitiv at a single class of receptors or alternatively that binding of the thioethers may occur at multiple classes of receptor sites.

(20) A_{50} determined as the concentration of test compound required to elicit 50% of the maximal contraction of rat fundic stomach strips induced by 3×10^{-7} M serotonin. For details see: (a) Ogletree, M. L.; Harris, D. N.; Greenberg, R.; Haslanger, M. F.; Nakane, M. *J. Pharmcol. Exp. Ther.* **1985**, *234*, 435. (b) Harris, D. N.; Greenberg, R.; Phillips, M. B.; Michel, I. M.; Goldenberg, H. J.; Haslanger, M. F.; Steinbacher, T. E. *Eur. J. Pharmacol.* **1984**, *103*, 9.

(21) Contraction induced by 9,11-azo-PGH_2 (0.1 μg/mL) or histamine (1.0 μg/mL) as described in ref 20.

(22) (a) Hedberg, A.; Hall, S. E.; Ogletree, M. L.; Carpenter, K. S.; Lui, E. C.-K. *Pharmacologist* **1987**, *29*, 167. (b) Hedberg, A.; Hall, S. E.; Ogletree, M. L.; Harris, D. N.; Lui, E. C.-K. *J. Pharmacol. Exp. Ther.* **1988**, *245*, 786. (c) This radioligand is now commercially available from New England Nuclear.

(23) The large discrepancy between the affinities of the thioethers for the TxA_2/PGH_2 receptor in the washed platelet and the I_{50} observed for the inhibition of platelet aggregation may be a consequence of a high degree of protein binding (expected for highly lipophilic molecules) in the aggregation assay since PRP is used instead of washed platelets. Despite this potential problem, the most potent analogue (**57**) in the platelet aggregation assay was also shown to possess the highest affinity in the radioligand binding assay.

(24) Harris, D. N.; Hall, S. E.; Hedberg, A.; Ogletree, M. L. *Drugs Future* **1988**, *13*, 153.

(25) Stegmeir, K.; Pill, J.; Muller-Beckman, B.; Schmidt, F. H.; Witte, C.; Wolff, H. P.; Patscheke, H. *Thromb. Res.* **1984**, *35*, 379.

In Vivo. A number of more potent thioethers were evaluated for their effects on changes in lung mechanics as well as blood pressure induced by AA in the anesthetized guinea pig.[26] Although these thioethers were potent inhibitors of AA-induced changes, administration of the compounds caused varying amounts of direct bronchoconstriction and systemic hypertension. These results, compiled in Table V, correlated well with the rank order of potency observed in the platelet screen. In contrast to the range of agonist activities displayed in the rat stomach strip, most thioethers induced a similar degree of bronchoconstriction. Preadministration of the selective TxA_2 antagonist SQ 28,053 (the racemate of SQ 29,548) completely blocked the bronchoconstrictor effects of SQ 28,913, (−)-**10**, confirming that this effect was due to activation of the PGH_2/TxA_2 receptor.[27] In contrast, SQ 28,053 was only partially effective in blocking the hypertensive response to SQ 28,913 (50% inhibition). That the agonist activity was not due to subsequent TxA_2 synthesis was demonstrated by the fact that indomethacin had no effect on either bronchoconstriction or systemic hypertension induced by (−)-**10**.

Conclusion

Replacement of the standard PG ω-chain with a simple thioether has led to a series of potent TxA_2 antagonists, some of which also possess inhibitory activity toward TxA_2 synthetase. The most potent analogue in this class of thioether antagonists possessed subnanomolar affinity for the PGH_2/TxA_2 receptor. All of the thioethers exhibited some level of direct TxA_2 agonist activity. This latter aspect will delay further development of this novel class of compounds until analogues that are free of the undesired agonist activity can be identified.

Experimental Section

^1H NMR spectra were measured at 270 MHz on a JEOL FX-270 and at 400 MHz on a JEOL GX-400. ^{13}C NMR spectra were measured at 15 MHz on a JEOL FX-60 and at 67.5 MHz on a JEOL FX-270. Chemical shifts are reported in δ units relative to internal Me_4Si, $CHCl_3$ assigned at δ 7.24 or $CDCl_3$ at δ 77.0. Infrared spectra were recorded on a Perkin-Elmer Model 983 infrared spectrophotometer and were calibrated with the 1601-cm^{-1} absorption of polystyrene. Mass spectra were measured with an Extranuclear Simulscan or Finnigan TSQ mass spectrometer in either CI or EI mode. High-resolution mass spectra and fast-atom-bombardment MS were measured on a VG-ZAB-2F instrument. All new compounds exhibited IR and MS spectra consistent with their assigned structure and for the sake of brevity will not be tabulated here. Melting points were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

All reactions were conducted in oven-dried glassware under atmospheres of argon. All solvents were purified before use unless otherwise indicated; THF and ether were distilled from sodium benzophenone ketyl, CH_2Cl_2 was distilled from P_2O_5, and toluene and xylene were distilled from sodium and stored over activated 4A molecular sieves. Flash chromatography was performed as described by Still[28] with J. T. Baker "Flash" grade silica gel.

General Procedure for the Synthesis of Thioethers. The synthesis of thioethers followed the procedure described below for **10** except for the variation in conditions as noted in Table I.

Methyl [1α,2α(*Z*),3α,4α]-(±)-7-[3-[[(*p*-Tolylsulfonyl)oxy]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoate (58). To a stirred solution of 2.10 g (7.83 mmol) of alcohol **6** in 28 mL of dry pyridine was added 3.01 g (15.7 mmol) of *p*-toluenesulfonyl chloride. This mixture was stirred at 23 °C for 5 h, diluted with 400 mL of ether, and washed with 1 N HCl (50 mL, 50 mL, 100 mL), saturated aqueous $NaHCO_3$ (100 mL), H_2O (100 mL), and saturated aqueous NaCl (75 mL). The ether layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to afford crude tosylate. Purification was effected by silica chromatography with 1% CH_3OH/CH_2Cl_2 as eluant to provide 2.44 g (74%) of pure **58**. TLC: silica gel, 4% CH_3OH/CH_2Cl_2, R_f 0.8, iodine. In practice, it was not necessary to purify this tosylate; the crude material could be employed without any effect on the yield of the next step. ^1H NMR ($CDCl_3$, 270 MHz): δ 7.78 (d, *J* = 9 Hz, 2 H), 7.35 (d, *J* = 9 Hz, 2 H), 5.35 (m, 2 H), 4.31 (d, *J* = 4 Hz, 1 H), 4.15 (d, *J* = 4 Hz 1 H), 4.06 (dd, *J* = 7, 12 Hz, 1 H), 3.91 (t, *J* = 12 Hz, 1 H), 3.67 (s, 3 H), 2.46 (s, 3 H), 2.30 (t, *J* = 7 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 15 MHz): δ 173.8, 144.7, 132.8, 130.1, 129.8, 129.8, 128.9, 127.7, 127.7, 80.0, 78.5, 69.6, 51.3, 45.9, 45.9, 33.3, 29.3, 28.9, 26.6, 25.7, 24.5, 21.5.

[1α,2α(*Z*),3α,4α]-(±)-7-[3-[(Hexylthio)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (10). To a solution of 132 mg (1.17 mmol) of potassium *tert*-butoxide in 10 mL of dry THF under argon was added 378 mg (3.21 mmol) of 1-hexanethiol. To this mixture was added a solution of 450 mg (1.07 mmol) of tosylate **58** in 5 mL of THF. The reaction mixture was stirred at room temperature under argon for 2.5 h and then heated to reflux for 5.5 h. The cooled reaction mixture was diluted with 300 mL of ether and poured into 100 mL of saturated $NaHCO_3$ solution. The aqueous layer was extracted with ether (2 × 100 mL). The combined ether extracts (500 mL) were washed with 0.5 N aqueous sodium hydroxide (2 × 100 mL) and brine (100 mL) and then dried ($MgSO_4$), filtered, and concentrated in vacuo to give 0.55 g of crude oil. Purification was effected by chromatography on 25.2 g of silica gel 60 with 5:1 petroleum ether/ether as eluant to give 328 mg of the methyl ester of **10** as an oil (84%). TLC: silica gel, 3:2 petroleum ether/ether, R_f 0.55, iodine. To a stirred solution of 328 mg (0.89 mmol) of the above methyl ester in 43.8 mL of THF and 6.67 mL of H_2O under argon was added 8.40 mL of 1 N aqueous lithium hydroxide solution. This mixture was purged with argon vigorously for 20 min and stirred at room temperature for 12.5 h. The reaction mixture was acidified to pH 4 by the addition of 1 N aqueous HCl solution and poured into 50 mL of saturated NaCl solution. The resulting solution was saturated with solid NaCl and extracted with EtOAc (4 × 50 mL). The combined EtOAc extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give 295 mg of crude acid. Purification was effected by flash chromatography on 25 g of siliCAR CC-7 with 2:3 petroleum ether/ether as eluant to give **10** (250 mg, 79%) as an oil. TLC: silica gel, 2:3 petroleum ether/ether, R_f 0.25, iodine. ^1H NMR ($CDCl_3$, 400 MHz): δ 5.58–5.31 (m, 2 H), 4.50 (d, *J* = 5 Hz, 1 H), 4.21 (d, *J* = 5 Hz, 1 H), 2.61–2.54 (dd, *J* = 8, 14 Hz, 1 H), 2.51 (t, *J* = 8 Hz, 2 H), 2.45–2.31 (m, 3 H), 2.13 (q, *J* = 8 Hz, 2 H), 2.05 (t, *J* = 8 Hz, 2 H), 2.00–1.90 (m, 1 H), 1.90–1.80 (q, *J* = 8 Hz, 1 H), 1.78–1.61 (m, 4 H), 1.60–1.50 (q, *J* = 8 Hz, 2 H), 1.49–1.20 (m, 8 H), 0.90 (t, *J* = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 15 MHz): δ 178.7, 129.8, 129.7, 80.6, 80.4, 47.5, 46.9, 33.4, 32.6, 32.1, 31.8, 31.3, 29.6, 29.4, 28.4, 26.7, 26.2, 24.4, 22.4, 13.9. Anal. ($C_{20}H_{34}O_3S$) C, H, S.

[1α,2α(*Z*),3β,4α]-(±)-7-[3-[(Hexylthio)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (11). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.48–5.38 (m, 2 H), 4.50 (t, *J* = 5 Hz, 1 H), 4.12 (d, *J* = 5 Hz, 1 H), 2.70–2.60 (dd, *J* = 9, 13 Hz, 1 H), 2.50–2.25 (m, 7 H), 2.20–1.10 (m, 18 H), 0.88 (t, *J* = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 179.2, 130.0, 128.6, 80.8, 79.5, 51.1, 48.6, 33.7, 33.4, 32.8, 32.4, 31.3, 29.9, 29.5, 28.5, 26.6, 24.5, 23.5, 22.5, 13.9. Anal. ($C_{20}H_{34}O_3S$) C, H, S.

[1α,2β(*Z*),3β,4α]-(±)-7-[3-[(Hexylthio)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (12). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.32 (m, 2 H), 4.57 (t, *J* = 4 Hz, 1 H), 4.45 (t, *J* = 4 Hz, 1 H), 2.58 (m, 1 H), 2.50 (t, *J* = 7 Hz, 2 H), 0.88 (t, *J* = 7 Hz). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 179.1, 129.3, 128.9, 80.6, 80.3, 42.9, 41.6, 33.3, 32.6, 31.4, 29.9, 29.6, 28.5, 26.7, 24.4, 24.0, 23.6, 22.5, 14.0. Anal. ($C_{20}H_{34}O_3S$) C, H, S.

[1α,2β(*Z*),3α,4α]-(±)-7-[3-[(Hexylthio)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (13). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.45–5.22 (m, 2 H), 4.40 (t, *J* = 5 Hz, 1 H), 4.41 (d,

(26) Greenberg, R.; Steinbacher, T. E.; Harris, D. N.; Haslanger, M. F. *Eur. J. Pharmacol.* **1984**, *103*, 19.

(27) SQ 28,053 (0.03 mg/kg, iv) administered 3 min prior to SQ 28,913 (1 mg/kg, iv) resulted in 89 ± 2% inhibition of the increase in lung resistance and 89 ± 4% inhibition of the decrease in dynamic compliance induced by SQ 28,913.

(28) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

J = 5 Hz, 1 H), 0.85 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 15 MHz): δ 179.3, 129.3, 128.6, 80.6, 79.7, 50.1, 49.9, 27.3, 33.3, 32.3, 31.3, 29.6, 29.6, 29.0, 28.5, 26.6, 24.5, 23.6, 22.5, 13.9. Anal. ($C_{20}H_{34}O_3S$) C, H, S.

[1α,2α(Z),3α,4α]-(±)-7-[3-[[(Cyclohexylmethyl)thio]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (34). ^1H NMR ($CDCl_3$, 400 MHz): δ 5.46–5.32 (m, 2 H), 4.50 (d, J = 5 Hz, 1 H), 4.18 (d, J = 5 Hz, 1 H), 2.60–2.51 (dd, J = 8, 14 Hz, 1 H), 2.44–2.30 (m, 5 H). ^{13}C NMR ($CDCl_3$, 15 MHz): δ 178.7, 129.9, 129.7, 80.7, 80.4, 47.6, 47.1, 40.4, 38.0, 33.4, 32.9, 32.9, 32.9, 29.5, 29.5, 29.5, 26.7, 26.3, 26.1, 26.1, 24.6. Anal. ($C_{21}H_{34}O_3S$) C, H, S.

[1α,2α(Z),3α,4α]-(±)-7-[3-[[(2-Phenylethyl)thio]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (35). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.31–7.15 (m, 5 H), 5.46–5.30 (m, 2 H), 4.50 (d, J = 5 Hz, 1 H), 4.20 (d, J = 5 Hz, 1 H), 2.95–2.88 (m, 2 H), 2.82–2.74 (m, 2 H), 2.62–2.52 (dd, J = 6, 12 Hz, 1 H), 2.42 (t, J = 12 Hz, 1 H), 2.32 (t, J = 8 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 15 MHz): δ 179.0, 140.5, 129.9, 129.7, 128.4, 128.4, 128.4, 128.4, 126.3, 80.6, 80.4, 47.5, 46.9, 36.4, 34.1, 33.4, 32.3, 29.5, 29.5, 26.7, 26.2, 24.5. Anal. ($C_{22}H_{30}O_3S$) C, H, S.

[1α,2α(Z),3α,4α]-(±)-7-[3-[[(3-Phenylpropyl)thio]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (36). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.31–7.25 (m, 3 H), 7.20–7.15 (m, 2 H), 5.46–5.30 (m, 2 H), 4.50 (d, J = 5 Hz, 1 H), 4.19 (d, J = 5 Hz, 1 H), 2.78–2.70 (t, J = 8 Hz, 2 H), 2.60–2.55 (dd, J = 6, 8 Hz, 1 H), 2.54–2.50 (t, J = 8 Hz, 2 H), 2.42 (d, J = 8 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 15 MHz): δ 179.0, 141.4, 129.8, 129.7, 128.4, 128.4, 128.4, 128.4, 125.8, 80.6, 80.4, 47.5, 46.9, 34.7, 33.4, 32.1, 31.9, 29.5, 29.5, 29.5, 26.7, 26.2, 24.7. Anal. ($C_{23}H_{32}O_3S$) C, H, S.

[1α,2α(Z),3α,4α]-(±)-7-[3-[[(2-Phenoxyethyl)thio]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (37). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.32–7.21 (m, 3 H), 7.00–6.86 (m, 2 H), 5.48–5.30 (m, 2 H), 4.51 (d, J = 5 Hz, 1 H), 4.21 (d, J = 5 Hz, 1 H), 4.16 (t, J = 8 Hz, 2 H), 2.99–2.82 (m, 2 H), 2.76–2.70 (dd, J = 6, 12 Hz, 1 H), 2.60–2.50 (t, J = 12 Hz, 1 H), 2.34 (t, J = 8 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 15 MHz): δ 178.9, 129.7, 129.7, 129.4, 129.4, 121.0, 114.6, 114.6, 80.5, 80.5, 67.8, 47.5, 47.0, 33.3, 32.7, 31.5, 29.5, 29.5, 27.7, 26.3, 24.5. Anal. ($C_{22}H_{30}O_4S$) C, H, S.

[1α,2α(Z),3α(E),4α]-(±)-7-[3-[[(3-Phenyl-2-propenyl)thio]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (38). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.4–7.2 (m, 5 H), 6.43 (d, J = 15 Hz, 1 H), 6.18 (dt, J = 15, 7 Hz, 1 H), 5.35 (m, 2 H), 4.48 (d, J = 4.5 Hz, 1 H), 4.20 (d, J = 4.5 Hz, 1 H), 3.30 (m, 2 H), 2.58 (dd, J = 12, 4 Hz, 1 H), 2.41 (dd, J = 12, 11 Hz, 1 H), 2.30 (t, J = 7 Hz, 2 H). Anal. ($C_{23}H_{30}O_3S$) C, H, S.

[1α,2α(Z),3α,4α]-(±)-7-[3-[(Octylthio)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (39). ^1H NMR ($CDCl_3$, 400 MHz): δ 5.38 (m, 2 H), 4.48 (d, J = 4.5 Hz, 1 H), 4.21 (d, J = 4.5 Hz, 1 H), 2.59 (dd, J = 12, 5 Hz, 1 H), 2.50 (t, J = 7 Hz, 2 H), 2.42 (dd, J = 12, 11 Hz, 1 H), 0.87 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 15 MHz): δ 178.8, 129.8, 129.7, 80.6, 80.4, 47.5, 46.9, 33.3, 32.6, 32.1, 31.7, 29.6, 29.3, 29.1, 28.8, 26.7, 26.2, 24.5, 22.5, 13.9. Anal. ($C_{22}H_{38}O_3S$) C, H, S.

[1S-[1α,2α(Z),3α(R*),4α]]-7-[3-[(2-Heptylthio)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (40). $[\alpha]_D$ = +7.8° (c = 1.43, $CHCl_3$). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.42–5.34 (m, 2 H), 4.48 (s, 1 H), 4.20 (s, 1 H), 2.80–2.70 (m, 1 H), 2.64–2.57 (dd, J = 6, 14 Hz, 1 H), 1.24 (d, J = 9 Hz, 3 H), 0.88 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 178.8, 130.0, 129.7, 80.9, 80.4, 47.6, 47.3, 40.9, 37.0, 33.4, 31.7, 30.3, 29.5, 29.4, 26.7, 26.6, 26.3, 24.5, 22.6, 21.6, 14.0. Anal. ($C_{21}H_{36}O_3S$) C, H, S.

[1S-[1α,2α(Z),3α(S*),4α]]-7-[3-[(2-Heptylthio)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (41). $[\alpha]_D$ = −7.9° (c = 1.65, $CHCl_3$). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.46–5.40 (m, 2 H), 4.50 (d, J = 5 Hz, 1 H), 4.20 (d, J = 5 Hz, 1 H), 2.78–2.63 (m, 1 H), 2.60–2.52 (dd, J = 8, 14 Hz, 1 H), 2.45 (d, J = 10 Hz, 1 H), 2.35 (t, J = 8 Hz, 3 H), 1.23 (d, J = 8 Hz, 3 H), 0.88 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 179.0, 130.0, 129.7, 80.8, 80.4, 47.6, 47.0, 40.5, 37.0, 33.4, 31.7, 30.0, 29.5, 29.4, 26.7, 26.7, 26.3, 24.5, 22.5, 21.5, 14.0. Anal. ($C_{21}H_{36}O_3S$) C, H, S.

[1S-[1α,2α(Z),3α,4α]]-7-[3-[[(2-Hydroxyhexyl)thio]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (FMI, Fast-Moving Isomer) (42). $[\alpha]_D$ = +11.8° (c = 3.15, $CHCl_3$). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.40 (m, 2 H), 4.46 (d, J = 5 Hz, 1 H), 4.22 (d, J = 5 Hz, 1 H), 3.67 (m, 1 H), 2.68 (m, 2 H), 2.35 (t, J = 7 Hz, 2 H), 0.89 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 129.8, 129.8, 80.5, 80.5, 69.6, 47.5, 47.0, 35.9, 33.2, 32.4, 29.5, 29.5, 27.8, 26.6, 26.3, 24.5, 22.7, 14.0. Anal. ($C_{20}H_{34}O_4S$) C, H, S: calcd, 8.65; found, 8.20.

[1S-[1α,2α(Z),3α,4α]]-7-[3-[[(2-Hydroxyhexyl)thio]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (SMI, Slow-Moving Isomer) (43). $[\alpha]_D$ = −21.1° (c = 2.03, $CHCl_3$). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.40 (m, 2 H), 4.48 (d, J = 4 Hz, 1 H), 4.23 (d, J = 4 Hz, 1 H), 3.67 (m, 1 H), 2.75 (dd, J = 15, 4 Hz, 1 H), 2.63 (dd, J = 15, 6 Hz, 1 H), 0.91 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 129.8, 80.5, 80.5, 69.6, 47.5, 47.0, 40.4, 35.9, 33.2, 32.4, 29.5, 27.8, 26.6, 26.2, 24.5, 22.7, 14.0. Anal. ($C_{20}H_{34}O_4S$) C, H, S.

[1S-[1α,2α(Z),3α,4α]]-7-[[[[2-Oxo-2-(propylamino)ethyl]thio]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (44). $[\alpha]_D$ = −38.0° (c = 1.31, $CHCl_3$). ^1H NMR ($CDCl_3$, 270 MHz): δ 6.92 (br S, 1 H), 5.47–5.32 (m, 2 H), 4.44 (d, J = 5 Hz, 1 H), 4.24 (d, J = 5 Hz, 1 H), 3.34–3.12 (m, 4 H), 2.68–2.58 (dd, J = 6, 15 Hz, 1 H), 2.51–2.40 (t, J = 15 Hz, 1 H), 2.32 (t, J = 8 Hz, 2 H), 0.94 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 177.0, 169.6, 129.9, 129.6, 80.4, 80.2, 47.6, 46.4, 41.5, 36.2, 32.9, 32.9, 29.5, 29.3, 26.5, 26.0, 24.5, 22.6, 11.3. Anal. ($C_{19}H_{31}NO_4S$) C, H, N, S.

Methyl [1S-[1α,2α(Z),3α,4α]]-7-[3-[[(2-Oxo-2-ethyl)thio]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoate (16). To a mixture of 200 mg (0.47 mmol) of chiral tosylate **58** and 220 mg (1.90 mmol) of potassium thioacetate in 2.5 mL of dry THF under argon was added 1.0 mL of dry DMSO. This dark brown reaction mixture was heated at 75 °C for 1.25 h. The cooled reaction mixture was diluted with 12 mL of one-third saturated $NaHCO_3$ solution and extracted with ether (4 × 20 mL). The combined ether extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give 155 mg (100%) of thioacetate **16** as an oil. TLC: silica gel, 2:1 hexane/ether, R_f 0.64, I_2. $[\alpha]_D$ = −6.7° (c = 1.03, $CHCl_3$). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 195.4, 173.6, 130.0, 129.5, 80.8, 80.4, 51.4, 47.5, 47.3, 33.5, 30.6, 29.5, 29.4, 29.2, 26.8, 26.4, 24.7.

[1S-[1α,2α(Z),3α,4α]]-7-[3-[[[(Butylthio)methyl]thio]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (15). A mixture of powdered KOH (0.38 g) in 30 mL of dry xylene was heated to reflux under argon atmosphere and 15 mL of xylene was removed by distillation. To this mixture was added a solution of 250 mg (0.77 mmol) of thioacetate **16** and 0.44 mL (3.81 mmol) of chloromethyl n-butyl sulfide in 15 mL of dry xylene. The volume of the reaction mixture was reduced 5 mL by distillative removal of xylene and an additional 0.44 mL of chloromethyl n-butyl sulfide was added. This mixture was refluxed for 35 min. The cooled reaction mixture was diluted with 120 mL of saturated NH_4Cl solution and extracted with 150 mL of ether. The aqueous layer was acidified to pH 3 by the addition of 1 N aqueous HCl solution and extracted with ether (2 × 150 mL). The combined ether extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. This was chromatographed on 30 g of silica gel 60 with 4:1 hexane/ether as eluant to give 120 mg (33%) of the (n-butylthio)methyl ester of **15** (**59**) and 140 mg (~39%) of a mixture of (butylthio)methyl ester **59**, the corresponding methyl ester (**60**), and chloromethyl n-butyl sulfide. TLC: silica gel, 2:1 hexane/ether, R_f 0.54, I_2. To a stirred solution of 120 mg (0.25 mmol) of (butylthio)methyl ester **59** in 12.1 mL of freshly distilled THF under argon were added 2.3 mL of H_2O and 2.6 mL of 1 N aqueous lithium hydroxide solution. The reaction mixture was purged with argon vigorously for 15 min and stirred at room temperature for 6 h and 30 min. The reaction mixture was acidified to pH 3 by the addition of 1 N aqueous HCl solution and poured into 50 mL of brine. The resulting solution was saturated with NaCl and extracted with EtOAc (4 × 80 mL). The combined EtOAc extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The mixture of (butylthio)methyl ester, methyl ester, and chloromethyl n-butyl sulfide was hydrolyzed and worked up in the same manner. These two crude products were combined and chromatographed on 30 g of silica gel 60 with 1:1 hexane/ether as eluant to give 170 mg of desired acid **15** with some contamination by chloromethyl n-butyl sulfide. Final purification was effected by flash chromatography on 25 g of silica gel 60 with 2:1 hexane/ether as eluant to give 50 mg (53%) of **15**. TLC: silica

gel, 1:2 hexane/ether, R_f 0.42, I_2. $[\alpha]_D = -31.9°$ (c = 0.46, $CHCl_3$). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.48–5.30 (m, 2 H), 4.48 (d, J = 5 Hz, 1 H), 4.22 (d, J = 5 Hz, 1 H), 3.64 (s, 1 H), 2.79–2.70 (dd, J = 8, 14 Hz, 1 H), 2.63 (t, J = 8 Hz, 2 H), 2.52 (t, J = 14 Hz, 1 H), 2.37 (t, J = 8 Hz, 2 H), 0.92 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 178.9, 129.8, 129.8, 80.7, 80.4, 47.6, 46.4, 35.8, 33.4, 31.1, 31.1, 30.6, 29.5, 29.5, 26.7, 26.3, 24.5, 22.0, 13.6. Anal. ($C_{19}H_{32}O_3S_2$) C, H, S.

[1*S*-[1α,2α(*Z*),3α,4α]]-7-[3-[(Methylthio)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (45). $[\alpha]_D = -21.8°$ (c = 0.41, $CHCl_3$). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.43–5.31 (m, 2 H), 4.50 (d, J = 5 Hz, 1 H), 4.20 (d, J = 5 Hz, 1 H), 2.60–2.50 (dd, J = 8, 14 Hz, 1 H), 2.41 (d, J = 14 Hz, 1 H), 2.34 (t, J = 8 Hz, 3 H), 2.10 (s, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 179.0, 129.8, 129.8, 80.6, 80.4, 47.5, 46.4, 34.3, 33.3, 29.5, 29.5, 26.6, 26.2, 24.5, 15.9. Anal. ($C_{15}H_{24}O_3S$) C, H, S.

[1*S*-[1α,2α(*Z*),3α,4α]]-7-[3-[(Ethylthio)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (46). $[\alpha]_D = -13.9°$ (c = 1.48, $CHCl_3$). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.42–5.34 (m, 2 H), 4.50 (d, J = 5 Hz, 1 H), 4.21 (d, J = 5 Hz, 1 H), 2.65–2.40 (m, 6 H), 2.35 (t, J = 7 Hz, 2 H), 1.25 (t, J = 8 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 179.1, 129.8, 129.6, 80.6, 80.4, 47.5, 46.8, 33.3, 31.6, 29.4, 29.4, 26.6, 26.4, 26.2, 24.4, 14.8. Anal. ($C_{16}H_{26}O_3S$) C, H, S.

[1*S*-[1α,2α(*Z*),3α,4α]]-7-[3-[(Propylthio)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (47). $[\alpha]_D = -11.6°$ (c = 0.55, $CHCl_3$). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.42–5.32 (m, 2 H), 4.48 (d, J = 5 Hz, 1 H), 4.21 (d, J = 5 Hz, 1 H), 2.62–2.52 (dd, J = 6, 15 Hz, 1 H), 0.98 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 178.9, 129.9, 129.7, 80.7, 80.4, 47.5, 46.9, 34.7, 33.4, 32.0, 29.4, 29.4, 26.7, 26.2, 24.5, 23.0, 13.4. Anal. ($C_{17}H_{28}O_3S$) C, H, S.

[1*S*-[1α,2α(*Z*),3α,4α]]-7-[3-[(Butylthio)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (48). $[\alpha]_D = -11.0°$ (c = 1.11, $CHCl_3$). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.43–5.32 (m, 2 H), 4.50 (d, J = 5 Hz, 1 H), 4.22 (d, J = 5 Hz, 1 H), 2.64–2.53 (dd, J = 6, 15 Hz, 1 H), 0.92 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 178.9, 129.9, 129.7, 80.7, 80.4, 47.5, 47.0, 33.4, 32.4, 32.2, 31.8, 29.5, 29.5, 26.7, 26.3, 24.5, 22.0, 13.6. Anal. ($C_{18}H_{30}O_3S$) C, H, S.

[1*S*-[1α,2α(*Z*),3α,4α]]-7-[3-[(2-Propenylthio)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (49). $[\alpha]_D = -8.5°$ (c = 1.24, $CHCl_3$). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.88–5.70 (m, 1 H), 5.48–5.30 (m, 2 H), 5.09 (d, J = 6 Hz, 1 H), 5.04 (s, 1 H), 4.48 (d, J = 5 Hz, 1 H), 4.20 (d, J = 5 Hz, 1 H), 3.12 (d, J = 9 Hz, 2 H), 2.60–2.50 (dd, J = 8, 14 Hz, 1 H), 2.40–2.30 (m, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 179.2, 134.4, 129.9, 129.7, 116.9, 80.7, 80.4, 47.5, 46.5, 35.2, 33.4, 30.7, 29.4, 29.4, 26.7, 26.2, 24.4. Anal. ($C_{17}H_{26}O_3S$) C, H, S.

[1*S*-[1α,2α(*Z*),3α,4α]]-7-[3-[(3-Butenylthio)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (50). $[\alpha]_D = -9.1°$ (c = 1.55, $CHCl_3$). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.91–5.75 (m, 1 H), 5.48–5.32 (m, 2 H), 5.13–4.98 (m, 2 H), 4.50 (d, J = 5 Hz, 1 H), 4.21 (d, J = 5 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 179.0, 136.9, 129.8, 129.7, 115.8, 80.6, 80.4, 47.5, 46.8, 33.9, 33.4, 32.1, 31.9, 29.4, 29.4, 26.6, 26.2, 24.4. Anal. ($C_{18}H_{26}O_3S$) C, H, S.

[1*S*-[1α,2α(*Z*),3α,4α]]-7-[3-[[[(Methylthio)methyl]thio]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (14). A mixture of powdered KOH (0.38 g) in 30 mL of dry xylene was heated to reflux under argon atmosphere and 15 mL of xylene was removed by distillation. To this mixture was added a solution of 250 mg (0.77 mmol) of chiral thioacetate **16** and 0.32 mL (3.82 mmol) of chloromethyl methyl sulfide in 15 mL of dry xylene. The volume of the reaction mixture was reduced 5 mL by distillative removal of xylene and an additional 0.32 mL of chloromethyl methyl sulfide was added. This mixture was refluxed for 40 min. The cooled reaction mixture was diluted with 100 mL of saturated NH_4Cl solution and extracted with 120 mL of ether. The aqueous layer was acidified to pH 3 by the addition of 1 N aqueous HCl solution and extracted with ether (2 × 120 mL). The combined ether extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was esterified by ethereal diazomethane. The excess diazomethane was destroyed by glacial acetic acid and concentrated in vacuo. The crude product was chromatographed on 30 g of silica gel 60 with 4:1 hexane/ether as eluant to give 74.7 mg (25%) of the (methylthio)methyl ester of 14 and 140 mg (56%) of the recovered starting thioacetate **16**. TLC: silica gel, 2:1 hexane/ether, R_f 0.44, iodine. To a stirred solution of 144 mg (0.37 mmol) of the above ester in 18 mL of freshly distilled THF under argon was added 3.4 mL of H_2O and 3.8 mL of 1 N aqueous lithium hydroxide solution. The reaction mixture was purged with argon vigorously for 15 min and stirred at room temperature for 8 h and 30 min. The reaction mixture was acidified to pH 3 by the addition of 1 N aqueous HCl solution and poured into 50 mL of brine. The resulting solution was saturated with NaCl and extracted with EtOAc (4 × 60 mL). The combined EtOAc extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. This was chromatographed on 24 g of silica gel 60 with 400 mL of 2:1 hexane/ether as eluant, followed by the elution with 1:1 hexane/ether, to give 57 mg (46%) of **14** as an oil. TLC: silica gel, 1:2 hexane/ether, R_f 0.40, I_2. $[\alpha]_D = -23.2°$ (c = 1.32, $CHCl_3$). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.48–5.34 (m, 2 H), 4.48 (d, J = 5 Hz, 1 H), 4.22 (d, J = 5 Hz, 1 H), 3.18 (m, 1 H, A of AB), 3.12 (m, 1 H, B of AB), 2.80–2.70 (dd, J = 8, 14 Hz, 1 H), 2.50 (t, J = 14 Hz, 1 H), 2.35 (t, J = 8 Hz, 2 H), 2.18 (s, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 178.9, 129.8, 129.8, 80.7, 80.4, 47.6, 46.4, 38.2, 33.4, 31.0, 29.5, 29.5, 26.7, 26.3, 24.5, 14.5. Anal. ($C_{16}H_{26}O_3S_2$) C, H, S.

[1*S*-[1α,2α(*Z*),3α,4α]]-7-[3-[(Heptylthio)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (51). $[\alpha]_D = -9.3°$ (c = 1.04, $CHCl_3$). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.47–5.32 (m, 2 H), 4.50 (d, J = 5 Hz, 1 H), 4.22 (d, J = 5 Hz, 1 H), 2.63–2.53 (dd, J = 6, 15 Hz, 1 H), 0.90 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 179.1, 129.9, 129.6, 80.7, 80.4, 47.5, 46.9, 33.4, 32.7, 32.1, 31.7, 29.7, 29.5, 29.5, 28.8, 28.8, 26.7, 26.2, 24.5, 22.5, 14.0. Anal. ($C_{21}H_{36}O_3S$) C, H, S.

[1*S*-[1α,2α(*Z*),3α,4α]]-7-[3-[(Phenylthio)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (52). $[\alpha]_D = +11.2°$ (c = 0.34, $CHCl_3$). ^1H NMR ($CDCl_3$, 270 MHz): δ 7.38–7.11 (m, 5 H), 5.48–5.30 (m, 2 H), 4.65 (d, J = 5 Hz, 1 H), 4.34 (d, J = 5 Hz, 1 H), 3.10–3.00 (dd, J = 6, 15 Hz, 1 H), 2.82 (t, J = 15 Hz, 1 H), 2.40 (t, J = 8 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 179.0, 136.5, 129.8, 129.7, 129.3, 129.3, 128.9, 128.9, 125.9, 80.6, 80.5, 47.5, 46.5, 33.7, 33.3, 29.5, 29.4, 26.7, 26.4, 24.5. Anal. ($C_{20}H_{26}O_3S$) C, H, S.

[1*S*-[1α,2α(*Z*),3α(*E*),4α]]-7-[3-[(2-Hexenylthio)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (53). $[\alpha]_D = -9.5°$ (c = 0.84, $CHCl_3$). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.58–5.30 (m, 4 H), 4.38 (s, 1 H), 4.31 (s, 1 H), 3.08 (d, J = 8 Hz, 2 H), 2.59–2.50 (dd, J = 6, 15 Hz, 1 H), 2.41–2.30 (m, 3 H), 0.90 (t, J = 8 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 179.0, 133.5, 130.0, 129.6, 126.2, 80.8, 80.4, 47.5, 46.7, 34.4, 34.3, 33.4, 30.7, 29.5, 29.5, 26.7, 26.3, 24.5, 22.5, 13.6. Anal. ($C_{20}H_{32}O_3S$) C, H, S.

[1*S*-[1α,2α(*Z*),3α(*E*),4α]]-7-[3-[[(2-Methyl-2-hexenyl)thio]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (54). $[\alpha]_D = -11.6°$ (c = 0.79, $CHCl_3$). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.46–5.38 (m, 2 H), 5.24 (t, J = 9 Hz, 1 H), 4.48 (d, J = 5 Hz, 1 H), 4.20 (d, J = 5 Hz, 1 H), 3.11 (m, 1 H, A of AB), 3.03 (m, 1 H, B of AB), 2.50–2.42 (dd, J = 8, 14 Hz, 1 H), 1.68 (s, 3 H), 0.90 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 179.0, 131.0, 130.0, 129.6, 128.4, 80.8, 80.4, 47.6, 46.6, 41.8, 33.4, 30.7, 30.2, 29.6, 29.4, 26.7, 26.3, 24.5, 22.8, 14.8, 13.8. Anal. ($C_{21}H_{34}O_3S$) C, H, S.

[1*S*-[1α,2α(*Z*),3α(*Z*),4α]]-7-[3-[(2-Hexenylthio)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (55). $[\alpha]_D = -2.5°$ (c = 0.64, $CHCl_3$). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.58–5.32 (m, 4 H), 4.48 (d, J = 5 Hz, 1 H), 4.20 (d, J = 5 Hz, 1 H), 3.20–3.08 (m, 2 H), 2.60–2.50 (dd, J = 6, 15 Hz, 1 H), 0.92 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 179.0, 132.5, 129.8, 129.7, 125.7, 80.7, 80.3, 47.5, 46.8, 33.4, 31.1, 29.5, 29.4, 29.4, 28.8, 26.6, 26.2, 24.5, 22.7, 13.7. Anal. ($C_{20}H_{32}O_3S$) C, H, S.

[1*S*-[1α,2α(*Z*),3α(*Z*),4α]]-7-[3-[(3-Hexenylthio)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (56). $[\alpha]_D = -8.6°$ (c = 1.82, $CHCl_3$). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.50–5.28 (m, 4 H), 4.48 (d, J = 5 Hz, 1 H), 4.20 (d, J = 5 Hz, 1 H), 0.98 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 179.1, 133.2, 129.9, 129.7, 126.8, 80.7, 80.4, 47.5, 46.9, 33.4, 32.7, 32.2, 29.5, 29.5, 27.5, 26.7, 26.3, 24.5, 20.6, 14.2. Anal. ($C_{20}H_{32}O_3S$) C, H, S.

[1*S*-[1α,2α(*Z*),3α(*E*),4α]]-7-[3-[(3-Hexenylthio)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (57). $[\alpha]_D = -7.2°$ (c = 1.90, $CHCl_3$). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.60–5.30 (m,

4 H), 4.48 (d, J = 5 Hz, 1 H), 4.20 (d, J = 5 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 179.0, 133.6, 129.8, 129.7, 127.0, 80.7, 80.4, 47.5, 46.9, 33.4, 32.9, 32.7, 32.1, 29.5, 29.5, 26.7, 26.2, 25.5, 24.5, 13.7. Anal. ($C_{20}H_{32}O_3S$) C, H, S.

[1α,2α(Z),3α,4α]-(±)-7-[3-[2-(Pentylthio)ethyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (21). ^{1}H NMR ($CDCl_3$, 270 MHz): δ 5.53–5.28 (m, 2 H), 4.23 (s, 1 H), 4.18 (s, 1 H), 2.68–2.30 (m, 8 H), 2.18–1.33 (m, 18 H), 0.88 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 15 MHz): δ 178.8, 130.2, 129.6, 80.2, 80.1, 47.4, 46.3, 33.4, 32.3, 31.7, 31.1, 29.8, 29.5, 29.4, 28.8, 26.7, 26.6, 24.5, 22.3, 14.0. Anal. ($C_{20}H_{34}O_3S$) C, H, S.

[1α,2α(Z),3α,4α]-(±)-7-[3-[(Hexylsulfinyl)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid, FMI (31), [1α,2α-(Z),3α,4α]-(±)-7-[3-[(Hexylsulfinyl)methyl]-7-oxabicyclo-[2.2.1]hept-2-yl]-5-heptenoic Acid, SMI (Slow Moving Isomer) (32), and [1α,2α(Z),3α,4α]-(±)-7-[3-[(Hexylsulfonyl)-methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (33). To a solution of 634 mg (1.72 mmol) of sulfide ester in 6.78 mL of methanol at 0 °C was added dropwise over 4 min 8.37 mL of 0.5 M aqueous sodium periodate solution. Tetrahydrofuran (2 mL) was then added and the resulting reaction mixture was stirred at room temperature for 15 h. The white precipitate was removed by filtration and washed with ether (3 × 50 mL). The filtrate was washed with 60 mL of saturated aqueous $NaHCO_3$ solution and dried over anhydrous magnesium sulfate. Concentration in vacuo afforded 648 mg of an oily crude product. This was chromatographed on 54.16 g of silica gel 60 with 0.5–1.0% CH_3OH in CH_2Cl_2 as eluant. This gave FMI sulfoxide (211 mg, 32%), SMI sulfoxide (142 mg, 21%) sulfone (165 mg, 24%). TLC: silica gel, 2% CH_3OH/CH_2Cl_2, R_f **32**, 0.28; **31**, 0.21; **33**, 0.74, iodine. The methyl esters were hydrolyzed as described in the preparation of (±)-**10** in yields of 85%, 85%, and 91% respectively. Data for **31**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.50–5.37 (m, 2 H), 4.48 (d, J = 5 Hz, 1 H), 4.28 (d, J = 5 Hz, 1 H), 2.90–2.80 (m, 2 H), 2.76–2.62 (m, 1 H), 2.60–2.48 (m, 2 H), 2.32 (t, J = 8 Hz, 2 H), 0.90 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 15 MHz): δ 130.3, 129.0, 81.7, 80.0, 52.8, 52.8, 47.3, 41.8, 33.4, 31.3, 29.4, 28.4, 27.1, 27.1, 26.7, 24.6, 22.4, 22.4, 13.8. Anal. ($C_{20}H_{34}O_4S$) C, H, S. Data for **32**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.50–5.36 (m, 2 H), 4.47 (d, J = 5 Hz, 1 H), 4.26 (d, J = 5 Hz, 1 H), 2.90–2.62 (m, 4 H), 0.92 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 15 MHz): δ 130.4, 129.0, 81.7, 80.0, 52.8, 47.3, 41.8, 33.4, 31.2, 28.4, 27.2, 26.7, 24.6, 22.4, 13.8. Anal. ($C_{20}H_{34}O_4S$) C, H, S. Data for **33**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.51–5.30 (m, 2 H), 4.73 (d, J = 5 Hz, 1 H), 4.22 (d, J = 5 Hz, 1 H), 3.0 (q, J = 8 Hz, 4 H), 2.57 (q, J = 8 Hz, 1 H), 2.34 (t, J = 8 Hz, 2 H), 0.90 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 15 MHz): δ 178.4, 130.3, 128.9, 80.9, 79.8, 54.1, 51.7, 47.0, 39.9, 33.1, 31.1, 29.4, 28.8, 28.0, 27.1, 26.7, 24.3, 22.2, 21.9, 13.7. Anal. ($C_{20}H_{34}O_5S$) C, H, S.

Methyl [1α,2α(Z),3β,4α]-(±)-7-[3-[(2-Oxo-2-ethyl)thio]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoate (29). To a stirred solution of 1.56 g (5.95 mmol) of triphenylphosphine in 15 mL of THF at 0 °C was added 1.20 mL (6.09 mmol) of diisopropyl azodicarboxylate over 7 min. This mixture was stirred at 0 °C for 30 min. To this mixture was then added dropwise over 10 min a solution of 520 mg (2.05 mmol) of alcohol **20** and 0.75 mL (10.5 mmol) of thiolacetic acid in 5 mL of THF. The reaction mixture was stirred at 0 °C for 1 h and then allowed to warm to room temperature overnight. The resulting solution was concentrated in vacuo and the residue was triturated with 1:1 hexane/ether. The filtrate was concentrated in vacuo to afford a semisolid product. This was chromatographed on 100 g of silica gel with 2:1 hexane/ether as eluant followed by ether (fractions 61–69). This afforded 210 mg (33%) of **29** and 290 mg (56%) of recovered alcohol **20**. TLC: silica gel, 1:1 hexane/ether, R_f 0.45. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 5.38 (m, 2 H), 4.67 (t, J = 5.5 Hz, 1 H), 4.22 (d, J = 5.5 Hz, 1 H), 3.67 (s, 3 H), 3.35 (dt, J = 2, 5 Hz, 1 H), 2.31 (s in t, 3 H), 2.31 (t, J = 7 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 130.6, 127.7, 80.4, 79.1, 51.4, 51.4, 50.1, 33.4, 32.0, 30.3, 29.6, 26.6, 24.8, 24.8.

[1α,2α(Z),3β,4α]-(±)-7-[3-(Heptylthio)-7-oxabicyclo-[2.2.1]hept-2-yl]-5-heptenoic Acid (25). A slurry of 0.50 g (8.93 mmol) of powdered KOH in 10 mL of xylene was heated to reflux. To this mixture was added a solution of 210 mg (0.67 mmol) of **29** and 0.70 mL (4.45 mmol) of heptyl bromide in 2 mL of xylene. The reaction mixture was refluxed for 3 h and then an additional 1.1 mL (7.0 mmol) of heptyl bromide was added. After being allowed to reflux for an additional 30 min, the reaction mixture was allowed to cool to room temperature. The cooled reaction mixture was partitioned between 25 mL of each of brine and ether. The aqueous layer was acidified by careful addition of 6 N HCl to pH ~4, shook with ether layer, and separated. The aqueous layer was extracted with 25 mL ether. The combined ether extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was esterified with excess ethereal CH_2N_2 at 0 °C. The product was chromatographed on 38 g of silica gel with 4:1 hexane/ether as eluant. This afforded 0.11 g (40%) of a mixture of the heptyl and methyl esters **30**. TLC: silica gel, 1:1 hexane/ether R_f methyl ester 0.5; R_f heptyl ester 0.75. To a stirred solution of 60 mg of heptyl ester in 6.0 mL of freshly distilled THF and 1.0 mL of H_2O was added 2.0 mL of 1 N LiOH solution. The mixture was purged with a stream of Ar for 30 min and then stirred at room temperature for 4.5 h. At this time, TLC analysis showed that very little of the ester had hydrolyzed so 1.0 mL of methanol was added, affording a nearly homogeneous solution. This was stirred at room temperature for 1.5 h and then placed in the refrigerator overnight. The methyl ester was hydrolyzed under the exact same conditions. The two reaction mixtures were combined and partitioned between 40 mL each of brine and ether. The aqueous layer was acidified to pH ~2 with 1 N HCl and extracted with two 40-mL portions of ether. The combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo to give 130 mg of crude product. Chromatography on 30 g of silica gel with 1:1 hexane/ether as eluant gave 34 mg (36%) of **25**. TLC: silica gel, 4% $MeOH/CH_2Cl_2$, R_f 0.5. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 5.43 (m, 2 H), 4.52 (t, J = 5 Hz, 1 H), 4.17 (d, J = 5 Hz, 1 H), 2.68 (m, 1 H), 2.47 (t, J = 7 Hz, 2 H), 2.36 (t, J = 7 Hz, 2 H), 0.86 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 178.7, 130.1, 128.4, 80.8, 80.2, 52.3, 52.0, 33.3, 32.7, 32.4, 31.7, 29.9, 28.8, 26.6, 24.6, 23.8, 22.6, 14.0. Anal. ($C_{20}H_{34}O_3S$) C, H, S.

Methyl [1α,2α(Z),3β,4α]-(±)-7-[3-[(Methylsulfonyl)-oxy]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoate (22). To a stirred solution of 900 mg (3.54 mmol) of endo alcohol **19** in 18 mL of dry pyridine at 0 °C under argon was added a solution of 1.63 g (14.2 mmol) of mesyl chloride in 18 mL of dry CH_2Cl_2. This mixture was allowed to warm to room temperature and stirred for 7 h. The mixture was diluted with 700 mL of ether and washed with 1 N HCl (2 × 180 mL), saturated $NaHCO_3$ solution (1 × 150 mL), and brine (1 × 200 mL). The ether solution was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification was effected by flash chromatography on 47 g of silica gel 60 with 1:1 hexane/ether as eluant to give 1.12 g (86%) of mesylate **22** as an oil. TLC: silica gel, 1:2 hexane/ether, R_f 0.30, $Ce(SO_4)_2$. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 5.45 (m, 2 H), 4.66 (t, J = 5 Hz, 1 H), 4.42 (m, 1 H), 4.21 (d, J = 5 Hz, 1 H), 3.67 (s. 3 H), 2.03 (s, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 173.7, 131.2, 127.0, 84.0, 80.9, 77.6, 51.3, 49.4, 37.8, 33.2, 30.4, 29.2, 26.5, 24.5, 22.5.

[1α,2α(Z),3α,4α]-(±)-7-[3-(Heptylthio)-7-oxabicyclo-[2.2.1]hept-2-yl]-5-heptenoic Acid (24). To a stirred solution of 134 mg (1.05 mmol) of potassium *tert*-butoxide in 1 mL of dry THF under argon was added 0.36 mL (2.11 mmol) of heptyl mercaptan. To this mixture was added a solution of 100 mg (0.30 mmol) of mesylate **22** in 1 mL of dry THF. The reaction mixture was diluted with 2 mL of dry DMSO and heated at 95 °C for 6 h and 20 min. The cooled reaction mixture was diluted with 30 mL of half-saturated NaCl solution and extracted with 40 mL of ether. The aqueous layer was acidified to pH 4.5 by the addition of 1 N aqueous HCl solution and extracted with ether (3 × 40 mL). The combined ether extracts were washed with 20 mL of water, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was treated with ethereal diazomethane at room temperature and the excess diazomethane was destroyed by the addition of glacial HOAc. Concentration in vacuo gave the crude product. Purification was effected by flash chromatography on 30 g of silica gel 60. A stepped solvent gradient was used for elution; hexane (120 mL), 4:1 hexane/ether (120 mL), 2:1 hexane/ether (120 mL) 1:1 hexane/ether (120 mL), and finally 2:1 ether/hexane. This gave 28.7 mg (25.6%) of thioether **24** as its methyl ester, 38.1 mg (38.1%) of recovered starting mesylate **22**, and 19.6 mg (25.9%) of endo alcohol **19**. TLC: silica gel, 1:2

hexane/ether, R_f 0.66, $Ce(SO_4)_2$. To a stirred solution of 101 mg (0.27 mmol) of the above methyl ester in 12.9 mL of freshly distilled THF was added 2.5 mL of H_2O and 2.9 mL of 1 N aqueous lithium hydroxide solution. The reaction mixture was purged with argon vigorously for 15 min and stirred at room temperature for 8 h and 30 min. Another batch of 25 mg of methyl ester was hydrolyzed separately in the same manner and then combined for workup. The combined reaction mixtures were acidified to pH 3 by the addition of 1 N aqueous HCl solution and poured into 70 mL of brine. The resulting solution was saturated with NaCl and extracted with EtOAc (4 × 100 mL). The combined EtOAc extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo to give 200 mg of crude product as an oil. Purification was effected by flash chromatography on 30 g of silica gel 60 with 1:1 hexane/ether as eluant to give 42 mg (35%) of acid **24**. TLC: silica gel, 1:1 hexane/ether, R_f 0.26, I_2. ^1H NMR ($CDCl_3$, 270 MHz): δ 5.47–5.33 (m, 2 H), 4.45 (s, 1 H), 4.22 (s, 1 H), 2.96 (d, J = 9 Hz, 1 H), 2.51 (t, J = 8 Hz, 2 H), 2.35 (t, J = 8 Hz, 2 H), 0.88 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 178.6, 129.9, 129.7, 82.9, 79.8, 53.5, 48.4, 33.4, 33.2, 31.7, 31.8, 29.6, 29.4, 29.2, 28.9, 28.0, 26.7, 24.6, 22.6, 14.0. Anal. ($C_{20}H_{34}O_3S$) H, S, C: calcd, 67.75; found, 67.30.

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Registry No. **1**, 57576-52-0; (±)-**6**, 104596-10-3; (9*R*)-**6**, 70120-34-2; (9*S*)-**6**, 94903-79-4; (±)-**7**, 104596-12-5; (±)-**8**, 104596-11-4; (±)-**9**, 104596-13-6; (±)-**10**, 119785-27-2; (+)-**10**, 110902-61-9; (−)-**10**, 119785-54-5; (±)-**10** (methyl ester), 119785-26-1; (±)-**10** (sulfoxide, isomer 1), 119785-43-2; (±)-**10** (sulfoxide, isomer 2), 119785-44-3; (±)-**10** (methyl ester; sulfoxide, isomer 1), 119785-40-9; (±)-**10** (methyl ester; sulfoxide, isomer 2), 119785-41-0; (±)-**11**, 119785-28-3; (±)-**12**, 119785-29-4; (±)-**13**, 119785-30-7; **14**, 119694-90-5; **14** (methylthiomethyl ester), 119694-89-2; **15**, 119694-84-7; **16**, 119785-38-5; (±)-**18**, 104596-27-2; (±)-**19**, 119785-50-1; (±)-**20**, 104506-57-2; (±)-**21**, 119694-94-9; (±)-**22**, 119785-51-2; (±)-**23**, 119785-52-3; (±)-**24**, 119785-53-4; (±)-**25**, 119785-49-8; (±)-**28**, 119694-93-8; (±)-**29**, 119785-46-5; (±)-**30** ($R_2 = CH_3$), 119785-47-6; (±)-**30** ($R_2 = C_7H_{15}$), 119785-48-7; (±)-**33**, 119785-45-4; (±)-**33** (methyl ester), 119785-42-1; (±)-**34**, 119785-31-8; (±)-**35**, 119785-32-9; (±)-**36**, 119785-33-0; (±)-**37**, 119786-24-2; (±)-**38**, 119785-34-1; (±)-**39**, 119785-35-2; **40**, 119694-80-3; **41**, 119785-36-3; (*R*)-**42**, 105616-83-9; (*S*)-**42**, 105551-88-0; **44**, 119694-81-4; **45**, 119694-85-8; **46**, 119694-86-9; **47**, 119694-87-0; **48**, 119694-88-1; **49**, 104108-78-3; **50**, 104108-86-3; **51**, 119694-91-6; **52**, 119694-92-7; **53**, 104108-76-1; **54**, 119785-39-6; **55**, 104154-31-6; **56**, 104108-71-6; **57**, 104154-29-2; (±)-**58**, 119785-25-0; **59**, 119694-82-5; **60**, 119694-83-6; $HS(CH_2)_5CH_3$, 111-31-9; $HS(CH_2)_4CH_3$, 110-66-7; $HS(CH_2)_6CH_3$, 1639-09-4; $HSCH_2$-c-C_6H_{11}, 2550-37-0; $HS(CH_2)_2Ph$, 4410-99-5; $HS(CH_2)_3Ph$, 24734-68-7; $HS(CH_2)_2OPh$, 6338-63-2; (*E*)-$HSCH_2CH{=}CHPh$, 95351-73-8; $HS(CH_2)_7CH_3$, 111-88-6; (*S*)-$HSCH(CH_3)(CH_2)_4CH_3$, 119785-37-4; (*R*)-$HSCH(CH_3)(CH_2)_4CH_3$, 119785-55-6; (±)-$HSCH_2CH(OH)(CH_2)_3CH_3$, 105551-87-9; $HSCH_2CONH(CH_2)_2CH_3$, 38042-20-5; $HSCH_3$, 74-93-1; $HSCH_2CH_3$, 75-08-1; $HS(CH_2)_2CH_3$, 107-03-9; $HS(CH_2)_3CH_3$, 109-79-5; $HSCH_2CH{=}CH_2$, 870-23-5; $HS(CH_2)_2CH{=}CH_2$, 5954-70-1; $ClCH_2SCH_3$, 2373-51-5; HSPh, 108-98-5; (*E*)-$HSCH_2CH{=}CHC_3H_7$, 89222-69-5; (*E*)-$HSCH_2C(CH_3){=}CHC_3H_7$, 104108-73-8; (*Z*)-$HSCH_2CH{=}CHC_3H_7$, 104108-89-6; (*Z*)-$HS(CH_2)_2CH{=}CHC_2H_5$, 89222-70-8; (*E*)-$HS(CH_2)_2CH{=}CHC_2H_5$, 104108-88-5; $ClCH_2S(CH_2)_3CH_3$, 42330-14-3; $Br(CH_2)_6CH_3$, 629-04-9.

Design and Synthesis of Inhibitors of N^8-Acetylspermidine Deacetylase

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Analogues of N^8-acetylspermidine (**1**) were synthesized as potential inhibitors of the cytoplasmic enzyme N^8-acetylspermidine deacetylase. The compounds were assayed for their ability to inhibit the deacetylation of **1** in a cytosolic fraction from rat liver. The apparent K_i values were determined by Dixon plots. The apparent K_m of **1** for this enzyme is 11.0 μM. It was found that compounds which lacked the N1 or the N4 of spermidine were less effective at competing for the enzyme than the substrate. All compounds with acyl substituents larger than acetyl were less potent inhibitors than the corresponding acetylated derivatives. Thus, the enzyme's selectivity as a deacetylase seems to be attributable to steric hindrance which occurs with larger acyl groups. The N8 of the substrate is not essential for its binding to the enzyme. Replacement of N8 with a CH_2 group gives the ketone **14**, which has an apparent K_i of 0.18 μM, 60-fold lower than the apparent K_m of **1**. The inhibitory potency of **14** is retained in compounds substituted at the N1 position. The N^1,N^1-dimethyl and the N^1,N^1-diethyl analogues (**15** and **16**) of **14** have apparent K_i values of 0.096 and 0.10 μM, respectively. These agents are the most potent inhibitors of N^8-acetylspermidine deacetylase reported, and they are promising tools for use in determining the physiological function of N^8-acetylspermidine deacetylation.

The polyamines are a group of compounds present in all higher organisms.[1,2] The polyamines are deemed essential for cell growth and proliferation; however, their function in regulating cell metabolism remains unknown.[1-4] These substances are polycationic at physiological pH and are found closely associated with DNA in the nuclei of the cells. The concentrations of polyamines are greatly increased within cells that are undergoing rapid growth. In mammalian tissues, the concentrations of polyamines are governed primarily by the activity of the enzyme ornithine decarboxylase (ODC), the first and a rate-limiting enzyme in the biosynthesis of polyamines (Figure 1).[5] ODC converts ornithine to putrescine. Putrescine is then converted, by the action of spermidine synthase, to spermidine via the transfer of an aminopropyl group from decarboxylated

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