7-Oxabicyclo[2.2.1]heptyl Carboxylic Acids as Thromboxane A_2 Antagonists: Aza ω-Chain Analogues

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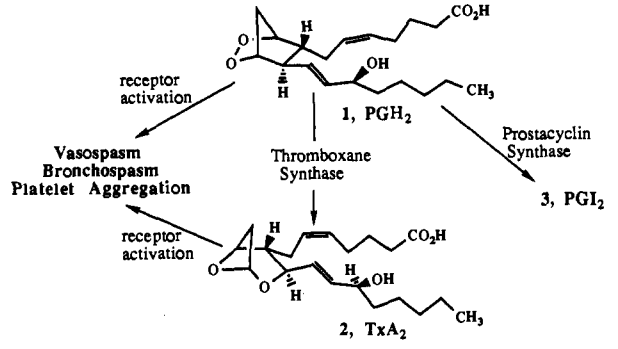
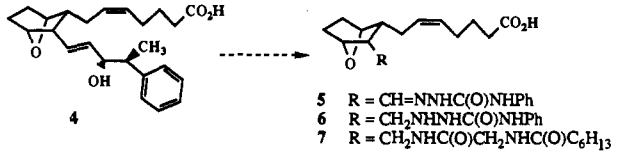
A novel bicyclic prostaglandin analogue, [1*S*-[1α,2α(*Z*),3α,4α]]-7-[3-[[[[(1-Oxoheptyl)amino]acetyl]amino]-methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid ((−)-**7**) was found to be a potent and selective thromboxane A_2 (TxA_2) receptor antagonist. Unlike the related series of ω-chain allylic alcohols, amide **7** and its congeners were uniformly free of direct contractile activity in vitro (bovine coronary) and in vivo (anesthetized guinea pig). Amide **7** was effective in the inhibition of (a) arachidonic acid induced platelet aggregation of human platelet-rich plasma (I_{50} = 0.18 ± 0.006 μM), (b) 11,9-epoxymethano-PGH_2 induced platelet aggregation of human platelet-rich plasma (I_{50} = 0.24 μM), (c) 11,9-epoxymethano-PGH_2 induced contraction of guinea pig trachea (K_b = 3.0 ± 0.3 nM) or rat aorta (K_b = 8.8 ± 1.1 nM), and (d) arachidonic acid induced bronchoconstriction in the anesthetized guinea pig (0.1–1.0 mg/kg iv). Amide **7** inhibited the binding of [5,6-$^3H_2$]-[1*S*-[1α,2α(*Z*),3α,4α)]-7-[3-[[2-[(Phenylamino)carbonyl]hydrazino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid to human platelet membranes in a specific and saturable manner with a K_d = 49.6 ± 1.4 nM.

Thromboxane A_2 (**1**), an unstable metabolite of arachidonic acid (AA), is a potent stimulator of platelet aggregation and elicits contraction of smooth muscle.[1] Efforts to modulate the actions of this eicosanoid have focused on agents which would either inhibit the biosynthesis of TxA_2 or alternatively block the actions of TxA_2 at the receptor level.[2] The former approach has received greater interest, due in part to the hypothesis that PGH_2 (**2**) produced in the platelet could be secreted and taken up by endothelial cells for conversion to the antiaggregatory and antispasmotic prostacyclin (PGI_2, **3**). A potential 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 than TxA_2.[1] Our interest in this area has centered around the discovery and development of compounds which would act at the receptor level. A compound of this type would not only inhibit the actions of TxA_2 but also block the effects of its biosynthetic precursor, PGH_2, as these two eicosanoids are believed to interact at a common receptor (Scheme I). Earlier studies[3] from these laboratories have described a series of 7-oxabicyclo[2.2.1]heptane analogues related to **4** which displayed TxA_2 antagonistic activity in both platelets and smooth-muscle preparations. Analogue **4** (SQ 28,668) was selected for clinical development due to its selective profile.[4] In particular, **4** was the only compound among an extensive group of allylic alcohols which was completely free of agonist activity. This study demonstrated that the allylic alcohol moiety was of critical importance in determining the agonist/antagonist profile of these analogues. As one approach toward the identification of new classes of TxA_2 receptor antagonists, we investigated analogues of **4** (Scheme II) in which the allylic alcohol group had been replaced with a stable imine functionality such as a hydrazone, semicarbazone, carbazone, or oxime. For example, semicarbazone **5** has been shown to be a potent TxA_2 receptor antagonist.[5] In contrast to the structure–activity relationships developed for a series of norbornane semicarbazones,[6] reduction of the imine functionality in **5** led to semicarbazide **6**, which was 10-fold more potent.[5] Semicarbazide **6** (SQ 29,548) has been studied in a number of laboratories and has been shown to be a selective TxA_2 antagonist, both in vitro[7] and in vivo.[8] Although its questionable safety profile precludes its further development as a potential clinical candidate,[9] it is one of the most potent TxA_2 antagonists described to date and remains an important tool in eicosanoid research. We therefore ini-

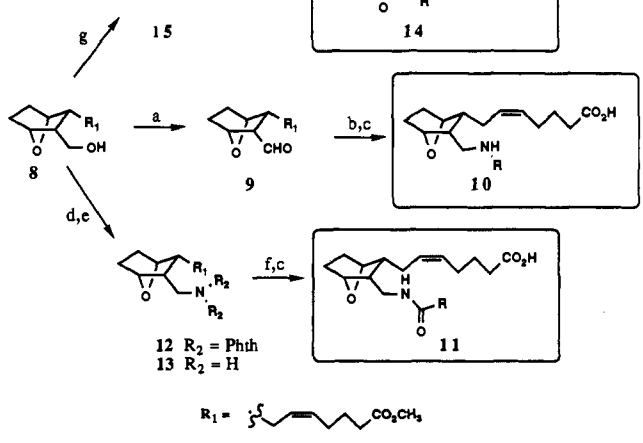
Scheme I



Scheme II



Scheme III.[a] Synthesis of 14-Aza-7-oxabicycloheptane Analogues



[a] (a) PCC, Celite, NaOAc, CH_2Cl_2, 23 °C; (b) RNH_2, HOAc, EtOH, $NaCNBH_3$, 23 °C; (c) LiOH, H_2O, THF, 23 °C; (d) H_3CPhSO_2Cl, Py, CH_2Cl_2; then PhthNK, DMSO, 95 °C; (e) H_2N-NH_2, toluene, 23 °C; CH_3OH, reflux; (f) carbonyldiimidazole, RCO_2H, Et_3N, THF, 23 °C; (g) CrO_3, H_2SO_4, acetone, 0 °C; (h) *N*,*N*′-carbonyldiimidazole, then RNH_2, Et_3N, THF, 23 °C.

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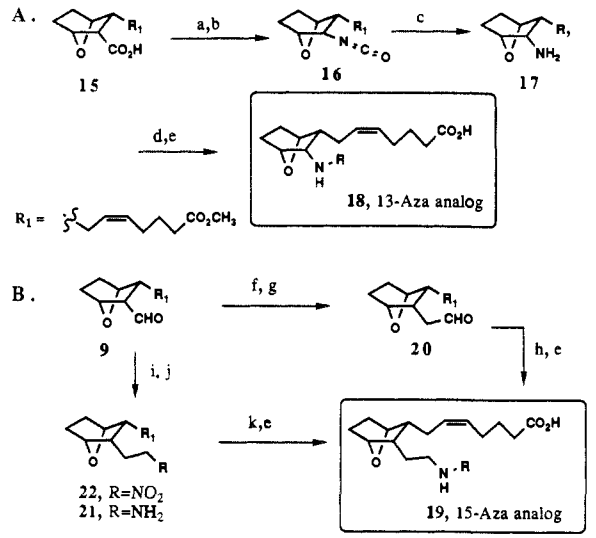
Scheme IV.[a] Synthesis of 13-Aza and 15-Aza Analogues



[a] (a) oxalyl chloride, benzene, cat. DMF; (b) $TMSN_3$, 90 °C; (c) 1 N HCl, THF, 23 °C; (d) $OHC(CH_2)_5CH_3$, CH_3OH, HOAc, $NaCNBH_3$; (e) LiOH, H_2O, THF, 23 °C; (f) $Cl^-Ph_3P^+CH_2OCH_3$, KOtAm; (g) TFA, THF, H_2O; (h) $H_2N(CH_2)_4CH_3$, $NaCNBH_3$, HOAc; (i) KF, H_3CNO_2, then Ac_2O, DMAP; (j) $NaBH_4$, EtOH; (k) PhNCO, CH_2Cl_2.

tiated studies to extract the important structural features responsible for the outstanding antagonistic activity of semicarbazide **6**. In this report, we describe the structure–activity relationships of ω-chain aza analogues related to **6** which have led to the identification of a new class of TxA_2 receptor antagonists. Double amide **7** (SQ 30,741) was found to be a potent and selective TxA_2 receptor antagonist and is currently in clinical trials.

Chemistry

The synthesis of three general types of 14-aza ω-chain analogues proceeded from the known alcohol **8**[3] and is outlined in Scheme III. Oxidation to the corresponding aldehyde **9** was accomplished with PCC.[10] Reductive amination was conveniently achieved by either a one-step (RNH_2, HOAc, EtOH, $NaCNBH_3$) or a two-step procedure ((a) RNH_2, EtOH, crushed sieves, (b) $NaBH_4$, EtOH). Hydrolysis of the intermediate amino ester provided the target acid **10**. Amides of general structure **11** were also prepared from alcohol **8**. Conversion of **8** to phthalimide **12** was accomplished by displacement of the corresponding tosylate with potassium phthalimide or alternatively by a one-step procedure via a Mitsunobu-type coupling.[11] Treatment of **12** with hydrazine afforded amine **13**, which was condensed with the appropriate acylimidazole followed by basic aqueous hydrolysis to provide amide **11**. The transposed amide **14** was prepared by a carbonyldiimidazole coupling of acid **15**, itself prepared by Jones oxidation[12] of alcohol **8**.

Analogues in which the nitrogen atom was located at the 13- or 15-position were synthesized as outlined in Scheme IV. Conversion of acid **15** to the corresponding acyl azide was accomplished by one of two procedures. Initially, this transformation was achieved by conversion of **15** to the acid chloride followed by treatment with $TMSN_3$.[13] Alternatively, acid **15** was treated with diphenyl phosphorazidate[14] at room temperature to provide the intermediate acyl azide. Rearrangement was effected at 80 °C and the resulting isocyanate **16** was captured with 2-(trimethylsilyl)ethanol.[15] Cleavage of the SEM carbamate proceeded with tetra-*N*-butylammonium fluoride in THF to afford amine **17**. Conversion of amine **17** to the target acid **18** where R is an acyl residue was accomplished by coupling **17** with the appropriate acylimidazole. The preparation of 13-aza analogues in which R is an alkyl residue was realized with the two-step reductive alkylation method. The one-step procedure described above led to varying amounts of tertiary amines due to the subsequent reaction

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(4) (a) Ogletree, M. L.; Harris, D. N.; Heran, C. L.; Phillips, M. B.; Michel, I. M.; Goldenberg, H. J. *Eicosanoids* **1988**, *1*, 85. (b) Ogletree, M. L.; Heran, C. L.; Harris, D. N. *Thrombos Haemostas* **1985**, *54*, 280. (c) Schumacher, W. A.; Goldenberg, H. J.; Harris, D. N.; Ogletree, M. L. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1987**, *46* (3), 423. (d) Ashton, J. H.; Schmitz, J. M.; Campbell, W. B.; Ogletree, M. L.; Raheja, S.; Taylor, A. L.; Fitzgerald, C.; Buja, L. M.; Willerson, J. T. *Circ. Res.* **1986**, *59*, 568. (e) Golino, P. Buja, M.; Ashton, J. H.; Kulkarni, P.; Taylor, A.; Willerson, J. T. *Circulation* **1988**, *78*, 701. (f) Schumacher, W. A.; Adams, H.; Ogletree, M. L. *Pharmacology* **1987**, *34*, 301. (g) Das, J.; Hall, S. E.; Nakane, M.; Haslanger, M. F.; Reid, J. A.; Garber, D.; Vu, C. T.; Harris, D. N.; Hedberg, A.; Ogletree, M. L. *J. Med. Chem.* **1990**, *33*, 1741. Analogues of **4** in which the ω-chain is in the endo orientation have recently been described and are the most potent PGH_2/TxA_2 mimetics identified to date. Synthesis and pharmacology of the *p*-F-derivative: Wilson, N. H.; Jones, R. L.; Marr, C. G.; Muir, G. *Eur. J. Med. Chem.* **1988**, *23*, 359. Pharmacology of the *p*-I-derivative: Morinelli, T. A.; Oatis, J. E., Jr.; Okwu, A. K.; Mais, D. E.; Mayeux, P. R.; Masuda, A.; Knapp, D. R.; Halushka, P. V. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 557.

(5) A communication describing the initial aza-analogues has been published: Nakane, M.; Reid, J. A.; Haslanger, M. F.; Garber, D. P.; Harris, D. N.; Ogletree, M. L.; Greenberg, R. In *Advances in Prostaglandin and Thromboxane Research*; Samuelsson, B., Paoletti, R., Ramwell, P., Eds.; Raven: New York, 1985; Vol. 15, p 291.

(6) Jones, R. L.; Wilson, N. H.; U.S. Patent 4,596,823, 1986.

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Table I. Synthesis and in Vitro Activity of Aza ω-Chain Analogues

9: $R^1 = CHO$
13: $R^1 = CH_2NH_2$
15: $R^1 = CO_2H$

		synthesis				in vitro pharmacology	
no.	R	% overall yield[a]	precursor	configuration at C(9)[b]	formula[c]	mp,[d] °C	AA-IPA[e] I_{50} μM
(±)-6	$CH_2NHNHC(O)NHPh$	43	9	*R,S*	$C_{21}H_{29}N_3O_4$	134–5	0.09
(+)-6	$CH_2NHNHC(O)NHPh$	53	9	*S*	$C_{21}H_{29}N_3O_4$	92–5	0.02 ± 0.007
23	$CH_2NHNHC(O)CH_2Ph$	32	9	*R,S*	$C_{22}H_{30}N_2O_4$	115–8	0.2
24	$CH_2NHCH_2C(O)NHPh$	23	9	*R,S*	$C_{22}H_{30}N_2O_4 \cdot 0.25H_2O$	139–41	5.3
25	$CH_2NHCH_2CH_2NHPh$	29	9	*R,S*	$C_{22}H_{32}N_2O_3 \cdot 0.3H_2O$	159–62	65
26	$CH_2CH_2NHC(O)NHPh$	3	9	*R,S*	$C_{22}H_{30}N_2O_4 \cdot 1.3CH_3OH$	oil	184
27	$CH_2NH(CH_2)_5CH_3$	48	9	*R,S*	$C_{20}H_{35}NO_3 \cdot 0.8H_2O$	foam	12
28	$NH(CH_2)_6CH_3$	5	15	*R,S*	$C_{20}H_{35}NO_3 \cdot 0.65H_2O$	oil	120
29	$CH_2CH_2NH(CH_2)_4CH_3$	33	9	*R,S*	$C_{20}H_{35}NO_3 \cdot 0.88H_2O$	oil	340
30	$CH_2NHC(O)CH_2CH_2Ph$	12	13	*R,S*	$C_{23}H_{31}NO_4 \cdot 0.2H_2O$	oil	3.3
31	$CH_2NHC(O)C(O)NHPh$	12	13	*R,S*	$C_{22}H_{28}N_2O_5$	153–5	5.5
32	$CH_2NHC(O)NHCH_2Ph$	63	13	*R,S*	$C_{22}H_{30}N_2O_4 \cdot 0.25H_2O$	oil	26
33	$NHC(O)(CH_2)_3Ph$	26	15	*R,S*	$C_{23}H_{31}NO_4$	oil	11
(−)-7	$CH_2NHC(O)CH_2NHC(O)(CH_2)_6CH_3$	50	13	*S*	$C_{23}H_{38}N_2O_5$	115–8	0.18 ± 0.006
34	$CH_2NHC(O)CH_2C(O)NHC_5H_{11}$	34	13	*S*	$C_{22}H_{36}N_2O_5$	94–6	0.5
35	$CH_2NHC(O)CH_2CH_2NHC(O)C_4H_9$	54	13	*S*	$C_{22}H_{36}N_2O_5$	113–5	14
36	$CH_2NHC(O)C_8H_{17}$	30	13	*S*	$C_{23}H_{39}NO_4$	78–81	15
37	$NHC(O)CH_2CH_2C(O)NHC_5H_{11}$	23	15	*R,S*	$C_{22}H_{36}N_2O_5$	oi	160
38	$NHC(O)CH_2C(O)NHC_6H_{13}$	11	15	*R,S*	$C_{22}H_{36}N_2O_5$	oil	125
39	$C(O)NHCH_2C(O)NHC_7H_{15}$	24	15	*S*	$C_{23}H_{38}N_2O_5 \cdot 0.7H_2O$	oil	30
40	$C(O)NHCH_2CH_2C(O)NHC_5H_{11}$	44	15	*S*	$C_{23}H_{38}N_2O_5 \cdot 0.2H_2O$	oil	14

[a] Overall yield of analytically pure product from precursor **9**, **13**, or **15** as noted. [b] Denotes whether the compound was prepared as a racemate (*R,S*) or as a single enantiomer. [c] Satisfactory elemental analysis (±0.4%) was obtained for all final products with the exception of compound **26**. Anal. ($C_{22}H_{30}N_2O_4 \cdot 1.3CH_3OH$) C; H: calcd, 8.26; found 7.70; N: calcd, 6.54; found 6.02. [d] Melting points are uncorrected. [e] Inhibition of arachidonic acid (800 μM) induced platelet aggregation of human platelet-rich plasma (PRP) as described in ref 17; for comparison, the activity of a standard antagonist 4-[2-(((4-Chlorophenyl)sulfonyl]amino]ethyl]phenylacetic acid[35] (BM13.505) is this assay was $I_{50} = 0.63 \pm 0.10$ μM. Consistent with their mechanism of action, none of the compounds was effective in inhibiting adenosine diphosphate (ADP) induced platelet aggregation of human PRP. Unless otherwise noted, the values reported are the result of a single determination.

of the initial product. The synthesis of the 15-aza derivative **19** employed the same routes as those described for the preparation of **10** and **11**, except the homologated aldehyde **20** or amine **21**, respectively, were employed as the starting materials. Aldehyde **20** was synthesized by homologation of **9** using (methoxymethyl)triphenylphosphorane followed by TFA cleavage of the vinyl ether. The corresponding amine **21** was prepared by Zn-dust reduction of nitro ester **22**, itself synthesized from aldehyde **9** using the one-pot procedure described by Wollenberg.[16] Side-chain amines and acids were synthesized in a straightforward manner with representative procedures described in the Experimental Section.

Pharmacology

In Vitro. All final acids were tested for their ability to inhibit platelet aggregation of human platelet-rich plasma (PRP) induced by either arachidonic acid (AA, 800 μM) or adenosine diphosphate (ADP, 20 μM).[17] Consistent with these compounds exerting their effects via antagonism of the TxA_2/endoperoxide receptor, none of the analogues was effective in preventing aggregation induced by ADP. The overall chemical yields and physical data of the target compounds along with their antiaggregatory activities are summarized in Table I. In an attempt to extract the important attributes of the semicarbazide group present in compound **6**, each of the nitrogens and the carbonyl group of (±)-**6** was replaced with a methylene spacer. A comparison of the activities within this group (**23–26**) revealed that the most important feature was the nitrogen at position 14.[18] Substitution of a methylene in this position (**26**) led to a 2000-fold drop in potency. In contrast, replacement of the aniline nitrogen led to an acyl hydrazide (**23**), which was only 2-fold less potent than semicarbazide (±)-**6**. The other substitutions (**24**, **25**) led to antagonists of intermediate potencies. The importance of the 14-aza substituent was confirmed in a series of simple amines (**27–29**) as the 14-aza amine **27** was 10–30 fold more potent than its positional isomers **28** and **29**. Acylated derivatives of **27** were found to be somewhat more potent, with the amide **30** and oxamide **31** being better than the urea **32**. In analogy with the results of the simple amines (compare **27** and **28**), the positional isomer of amide **30**, in which the nitrogen atom was attached directly to the oxabicycloheptane ring (**33**), was less potent. It was noteworthy that all of these compounds, like amine **27**, were completely free of PG agonist activity as determined by their lack of contractile activity in the rat stomach strip.[19]

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(18) Prostaglandin numbering used; i.e., the first atom of the ω-chain which is directly attached to the oxabicycloheptane ring is position 13.

Table II. Synthesis and in Vitro Activity of 14-Amido Analogues

13

		synthesis			in vitro pharmacology[i]				
					I_{50}, μM		K_d, nM:	K_b, nM	
no.	R	% overall yield[a]	formula	mp, °C	AA-IPA[d]	U-IPA[e]	platelet[f]	GPT[g]	RA[h]
(-)-7	$CH_2NHC(O)C_6H_{13}$	50	$C_{23}H_{38}N_2O_5$	115–8	0.18 ± 0.006	0.24	49.6 ± 1.4	3.0 ± 0.3	8.8 ± 1.1
41	CH_2NHPh-(4)-OCH_3	14	$C_{23}H_{32}N_2O_5$·HCl	126–8 dec	13.5				
42	CH_2SPh-(4)-OCH_3	40	$C_{23}H_{31}NO_5S$	oil	1.4				
43	$CH_2OC(O)C_6H_{13}$	21	$C_{23}H_{37}NO_6$	oil	0.66				
44	$CH_2NHC(O)NHC_4H_9$	39	$C_{21}H_{35}N_3O_5$·0.1H_2O	foam	1.0				
45	$CH_2NHC(O)OC_4H_9$	14	$C_{21}H_{34}N_2O_6$	104–6	1.1				
46	$CH_2NHC(O)Ph$	61	$C_{23}H_{30}N_2O_5$	162–3	2.6				
47	$CH_2N(CH_3)C(O)C_5H_{11}$	46	$C_{23}H_{38}N_2O_5$	oil	3.0				
48	(*R*)-$CH(CH_3)NHC(O)C_5H_{11}$	40	$C_{23}H_{38}N_2O_5$	101–3	53				
49	(*S*)-$CH(CH_3)NHC(O)C_5H_{11}$	31	$C_{23}H_{38}N_2O_5$	104–6	0.9				
50	$C(CH_3)_2NHC(O)C_5H_{11}$	36	$C_{24}H_{40}N_2O_5$	81–7	520				
51	$CH_2NHC(O)C_7H_{15}$	61	$C_{24}H_{40}N_2O_5$	129–31	0.22	0.43	17.5 ± 1.8	2.0 ± 0.4	3.4 ± 0.4
52	$CH_2NHC(O)C_8H_{17}$	52	$C_{25}H_{42}N_2O_5$	121–7	0.22	1.1	8.3 ± 1.7	1.4 ± 0.2	7.1 ± 1.0
53	$CH_2NHC(O)CH_2SPh$	68	$C_{24}H_{32}N_2O_5S$	126–8	0.021 ± 0.015	0.11	41.4 ± 4.5	2.4 ± 0.3	1.8 ± 0.2
54	$CH_2NHC(O)CH_2SPh$-(4)-*t*-C_4H_9	63	$C_{28}H_{40}N_2O_5S$	141–2	0.015 ± 0.001	0.15	4.2 ± 0.3	0.10 ± 0.02	1.8 ± 0.4
55	$CH_2NHC(O)(CH_2)_3C_6H_{12}$	78	$C_{26}H_{42}N_2O_5$	141–3	0.045 ± 0.02	0.12	1.1 ± 0.3[j]	0.07 ± 0.01	0.9 ± 0.1
56	$CH_2NHC(O)(CH_2)_4C_6H_{12}$	72	$C_{27}H_{44}N_2O_5$	137–8	0.16 ± 0.015	1.95	2.6 ± 0.3	0.07 ± 0.01	2.5 ± 0.8
57	$CH_2NC(S)C_6H_{13}$	55	$C_{23}H_{38}N_2O_4S$	117–9	0.04	0.23	12.4 ± 2.8	4.4 ± 0.9	1.1 ± 0.2
58[k]	$CH_2NC(S)C_6H_{13}$	24	$C_{23}H_{38}N_2O_3S_2$	oil	0.97	9.6	26.4 ± 3.4		
(+)-7[l]	$CH_2NHC(O)C_6H_{13}$	41	$C_{23}H_{38}N_2O_5$	114–5	6.6			174 ± 17	326 ± 83

[a] Overall yield of analytically pure product from precursor 13. Unless otherwise noted, all compounds were prepared as single enantiomers and possess the *S* configuration at C(9) as shown. [b] Satisfactory elemental analysis (±0.4%) for C, H, N, and where applicable S, was obtained for all final products. [c] Melting points are uncorrected. [d] Inhibition of arachidonic acid (800 μM) induced platelet aggregation of human platelet-rich plasma (PRP) as described in ref 17; for comparison, the activity of a standard antagonist 4-[2-[[(4-Chlorophenyl)sulfonyl]amino]ethyl]phenylacetic acid[35] (BM13.505) is this assay was I_{50} = 0.63 ± 0.10 μM. Consistent with their mechanism of action, none of the compounds was effective in inhibiting adenosine diphosphate (ADP) induced platelet aggregation of human PRP. [e] Inhibition of 11,9-epoxymethano-PGH_2 (**59**) induced platelet aggregation of human PRP. [f] K_d determined by the inhibition of [$^3H_2$]-**6** binding to human platelet membranes. [g] K_b determined by analysis of the rightward shift in the cumulative dose–response curves to **59**-induced contraction of guinea pig trachea spirals in the presence of increasing concentrations of the antagonist. [h] K_b determined by analysis of the rightward shift in the cumulative dose–response curves to **59**-induced contraction of rat aorta strips in the presence of increasing concentrations of the antagonist. [i] Unless otherwise noted, the values reported are the result of a single determination. [j] Slope = 0.61 ± 0.03. [k] Compound **58** is the bis-thioamide related to compound (-)-**7** which was prepared from the *tert*-butyl ester of (-)-**7** as described in the Experimental Section. [l] Possesses *R* configuration at C(9).

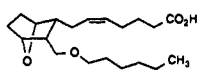
As noted in Table I, all of the initial analogue (**6**, **23–33**) were prepared as their racemates. Subsequent to the initiation of our efforts with the aza ω-chain analogues, we observed that both enantiomers of the related oxabicycloheptanes which possess ω-chain ethers[20] or thioethers[21] displayed antiplatelet activity. In the former example, the "inactive" enantiomer was shown to be a potent cyclooxygenase inhibitor.[20] As a result of these findings, additional aza analogues were prepared as single enantiomers wherein the oxabicycloheptane possessed the *S* configuration at C(9).

The structure–activity study on (±)-**6** suggested that the entire array of heteroatoms in the semicarbazide group was required for potent TxA_2 receptor antagonism; however, this study also established the 14-amido group as the most critical portion of this functionality. Further synthetic efforts were therefore focused on analogues of amide **30** which might be capable of additional receptor interactions, for example, via the introduction of additional groups capable of hydrogen-bond interactions. This concept led to the preparation of a series of double amide ω-chains. Within the group of 14,15-amides (**7**, **34–36**) optimal activity was realized only when there was a single methylene unit insulating the two amide groups (**7**, **34**). A spacer of two methylenes resulted in a double amide (**35**) which was not more potent than the parent monoamide **36**. The 13,14-amides (**37–40**), regardless of orientation, were uniformly less active than their 14,15-counterparts. In agreement with the importance of a nitrogen atom at position 14, **39** and **40** were more potent than the 13-aza analogues **37** and **38**.

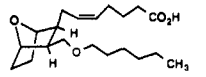
A more detailed pharmacological profile of additional 14-amido analogues related to **7** is compiled in Table II. Several analogues were prepared in which the external amide was replaced with other heteroatom arrays. Substitution with an amine (**41**), thioether (**42**), ester (**43**), urea (**44**), or carbamate (**45**) resulted in antagonists of reduced potency in vitro. Steric congestion in the vicinity of the external amide also resulted in a progressive loss of activity. Benzamide **46** and the *N*-methyl analogue **47** were ca. 10-fold less active than (-)-**7**. The double amide analogues

(19) 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. Pharmacol. 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. (c) Vane, J. R. *J. Pharmacol.* **1957**, *12*, 344.

(20) (a) Hall, S. E.; Han, W.-C.; Haslanger, M. F.; Harris, D. N.; Ogletree, M. L. *J. Med. Chem.* **1986**, *29*, 2335. (b) Harris, D. N.; Phillips, M. B.; Michel, I. M.; Goldenberg, H. J.; Steinbacher, T. E.; Ogletree, M. L.; Hall, S. E. *Prostaglandins* **1986**, *31*, 651.

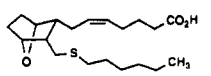


weak TxA_2 antagonist

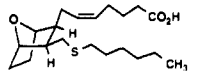


potent cyclooxygenase inhibitor

(21) Hall, S. E.; Han, W.-C.; Harris, D. N.; Hedberg, A.; Ogletree, M. L. *J. Med. Chem.* **1989**, *32*, 974.



potent TxA_2 antagonist



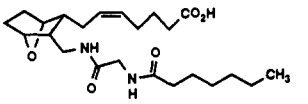
weak cyclooxygenase inhibitor

derived from *d*-alanine (**48**), *l*-alanine (**49**), and sarcosine (**50**) were 5–5000-fold less potent; this decrement in activity was stereospecific (compare **48** and **49**). In general, analogues of (−)-**7** in which the ω-chain alkyl group was replaced with a more lipophilic residue (**51–56**) displayed increased potency in vitro. Likewise, replacement of the external amide with a thioamide (**57**) resulted in a slight increase in activity although conversion of both amide groups to thioamides resulted in an analogue (**58**) of reduced activity. Finally, in contrast to our observations with **4**, the enantiomer of **7** was only 50-fold less potent than **7** itself. This level of activity cannot be attributed to contamination of (+)-**7** with (−)-**7** as the maximum amount of (−)-**7** present in (+)-**7** could not exceed 0.1%.[22,23]

A summary of additional in vitro data for (−)-**7** and its more potent analogues is included in Table II. These double amides were evaluated for their ability to inhibit platelet aggregation induced by 11,9-epoxymethano-PGH_2 (**59**, U-46,619), a stable PGH_2/TxA_2 mimic, as well as contraction of guinea pig trachea and rat aorta strips induced by this same agonist. A direct measure of their affinity for the TxA_2 receptor was obtained by using standard radioligand-binding techniques in human platelet membranes.[24] Using [$^3H_2$]-**6** as the radioligand, the affinities of (−)-**7** and **51–57** for the TxA_2 receptor ranged from 1 to 70 nM. Although the rank order potencies of these compounds in inhibiting aggregation induced by either AA or **59** were similar, there was not always a good correlation between this data and the K_d for the platelet. This may be due to the presence of plasma protein in the aggregation assay (PRP is used instead of washed platelets). As such, differences in protein binding due to varying lipophilicities could affect the I_{50} values. For example, the homologous series of *n*-alkylamides (−)-**7** (K_d = 50 nM), **51** (K_d = 17 nM), and **52** (K_d = 8 nM) displayed increasing affinities for the TxA_2 receptor, yet the latter two compounds were actually less potent in the platelet-aggregation assays. This same subset of double amides ((−)-**7**, **51–57**) was also effective in inhibiting contractions of guinea pig trachea spirals[19a] and rat aorta strips[19a] induced by **59**; K_b's ranged from 0.07 to 5.0 nM. Although the agreement was not complete, the rank order potencies followed the same general trends as those obtained in the platelet assays. The most potent compound, cyclohexyl analogue **55**, was 10-fold more potent in the guinea pig trachea than in the rat aorta. This variability is likely due to the pronounced species differences in TxA_2 receptors as described recently by Ogletree and Allen.[25]

Having established the efficacy of this class of thromboxane receptor antagonists, it was equally important to define the specificity of these agents. Amide (−)-**7** was effective in inhibiting platelet aggregation induced by collagen as well as the secondary phase of epinephrine-induced aggregation (Table III). Consistent with the primary phase of epinephrine-induced aggregation being independent of TxA_2, amide (−)-**7** had no effect. Since other oxabicycloheptane-derived analogues[20] have been shown previously to inhibit some of the enzymes in the AA cascade, we evaluated amide (−)-**7** for its effect on cyclooxygenase, TxA_2 synthase, and PGI_2 synthase. As summarized in Table III, (−)-**7** had no effect on these enzymes. In addition, (−)-**7** did not display any direct agonist activity in the rat stomach[19] or bovine coronary artery.[26] Additional information regarding the specificity of (−)-**7** has been published elsewhere.[27] Thus, (−)-**7** appeared to be a specific TxA_2 receptor antagonist.

Table III. In Vitro Characterization of Double Amide (−)-**7**



A. Effects of (−)-**7** on the Aggregation of Human Platelets

aggregating agent	concn, μM	I_{50}, μM
Arachidonic Acid	800	0.18 ± 0.006
U-46,619	5	0.22
U-46,619	10	0.24 ± 0.01
ADP	20	>1000
Epinephrine (1° Phase)	10	>1000
Epinephrine (2° Phase)	10	0.04
Collagen	10 μg/mL	0.19
Collagen	20 μg/mL	0.56

B. Effects of (−)-**7** on the Biosynthesis of Prostaglandins, Thromboxane, and Prostacyclin by Microsomal Enzymes

enzyme source	substrate	product measured	IC_{50}, μM
human platelet	AA	TxB_2	>1000
human platelet	AA	PGE_2	>1000
human platelet	PGH_2	TxB_2	>1000
human platelet	PGH_2	PGE_2	>1000
bovine seminal vesicles	AA	PGE_2	>1000
bovine aorta	AA	6-keto-$PGF_{1\alpha}$	>1000
bovine aorta	PGH_2	6-keto-$PGF_{1\alpha}$	>1000

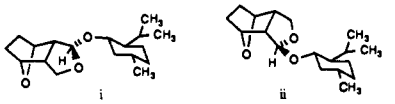
Table IV. Percent Inhibition of Arachidonate-Induced Responses at 3 and 60 min after Dosing (0.1 mg/kg iv) in the Anesthetized Guinea Pig[a]

	airways resistance		dynamic compliance		blood pressure[b]	
no.	3	60	3	60	3	60
(+)-**6**	97	42	96	56	151	59
(−)-**7**	96	23	86	22	195	90
51[c]	97	79	98	74	195	130
52[c]	99	31	98	39	252	138
53	98	53	92	42	287	235
54	98	43	95	26	191	184
55	99	84	97	59	289	289
57	97	51	94	56	178	158

[a] All values for airway resistance, dynamic compliance, and blood pressure had $n = 5$, $p < 0.005$ vs vehicle; none of the compounds had any direct effects on these parameters. For details of the method used, see ref 19. [b] Inhibition >100% refers to the reversal of AA-induced hypertension, resulting in decreases in blood pressure in response to AA. [c] 1.0 mg/kg iv dose.

In Vivo. Several of the more potent TxA_2 antagonists were evaluated for their ability to inhibit the bronchospastic and vasospastic responses to AA in the anesthetized

(22) This value is determined by the diastereomeric purity of the menthol acetal i. This is measured by careful integration of the 400-MHz ^1H NMR spectrum in which the acetal proton appears at δ 5.14 for i and at δ 4.99 for the oxabicycloheptane diastereomer ii.



(23) This result contrasts with the relative activities of **4** and its enantiomer which was 1000-fold less active than **4** itself.

(24) For details of the methods used, see: (a) Hedberg, A.; Hall, S. E.; Ogletree, M. L.; Harris, D. N.; Liu, E. C.-K. *J. Pharmacol. Exp. Ther.* **1988**, *245*, 786. (b) [$^3H_2$]-**6** is commercially available from New England Nuclear.

(25) Ogletree, M. L.; Allen, G. T. *J. Pharmacol. Exp. Ther.*, in press.

(26) A modification of the method described by Verheggen and Schror in which isometric tension was used instead of isotonic tension: Verheggen, R.; Schror, K. *J. Cardiovasc. Pharmacol.* **1986**, *8*, 483.

(27) Schumacher, W. A.; Heran, C. L.; Allen, G. T.; Ogletree, M. L. *Prostaglandin* **1989**, *38*, 335.

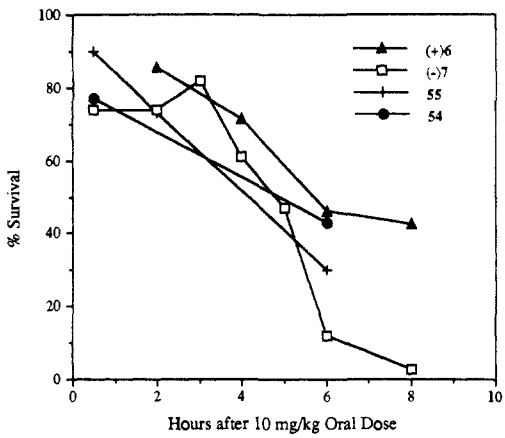


Figure 1. Inhibition of U-46,619-induced lethality in the conscious mouse. Each point represents the survival rate in a group of at least 20 mice following injection of 2 mg/kg U-46,619 into the tail vein at various times after oral administration of the thromboxane receptor antagonist. The 2- and 4-h time points with (+)-**6** represent groups of only 14 mice.

guinea pig.[28] As summarized in Table IV, all of the double amides tested were effective in preventing the increased lung resistance, decreased lung compliance, and systemic hypertension induced by the administration of AA (0.5 mg/kg, iv). Preadministration of the receptor antagonist reversed the hypertensive response to AA to a hypotensive response. This reversal is consistent with these compounds acting as TxA_2 receptor antagonists and results from the unmasking of the PGI_2 effect (exogenously added AA is metabolized to both TxA_2 and PGI_2). In contrast to the thioether receptor antagonists[21] described previously, none of the double amides displayed any direct activity, confirming that these compounds were acting as pure antagonists instead of partial agonists. Amides (-)-**7** and **51–57** compared favorably with the protection afforded by the semicarbazide (+)-**6**. The levels of protection observed in this assay were consistent with the ability of these compounds to inhibit contraction of guinea pig trachea spirals in vitro. For example, amide **55** displayed the most pronounced and long-lived reversal of blood pressure and was also the most potent analogue in vitro (Table II). Although the results shown in Table IV were obtained when the animals were dosed iv, these antagonists were also orally active. At a dose of 1 mg/kg po, amide (-)-**7** afforded >80% inhibition of the increased lung resistance and 70–110% inhibition of the hypertensive response for the entire duration of this model (2 h).

Inhibition of arachidonic acid induced lethality has been shown to be a useful model for evaluating TxA_2 receptor antagonists.[29] Compound (-)-**7** and several related double amides were shown to be effective in preventing the lethal response to the TxA_2/PGH_2 mimic **59** in the conscious mouse (Figure 1). Although double amide (-)-**7** was less potent than semicarbazide (+)-**6** when evaluated 30 min after oral administration of the antagonist, compounds (+)-**6**, (-)-**7**, **54**, and **55** afforded similar levels of protection (at least from 0 to 5 h after dosing) when administered at equal doses (10 mg/kg po).

Conclusion

Systematic modification of the potent semicarbazide TxA_2 antagonist (+)-**6** has led to the identification of a series of potent double amide ω-chain analogues. The structure–activity studies have revealed that the most important structural feature is the nitrogen at position 14, although both amides are required for optimal activity. These compounds, exemplified by amide (-)-**7**, were shown to be effective in blocking the deleterious effects of TxA_2 or stable TxA_2 mimetics in vitro (platelet aggregation, contraction of guinea pig trachea, contraction of rat aorta) and in vivo (AA-induced bronchoconstriction in the guinea pig, AA-induced systemic hypertension in the guinea pig, and **59**-induced lethality in the conscious mouse). Other studies with amide (-)-**7** have shown it to be effective in (a) inhibiting cyclical flow reductions in a model of renal thrombosis (cynomolgus monkey),[30] (b) limiting infarct size even when given only during reperfusion (dog),[31] and (c) limiting Forssman shock (guinea pig).[32] Equally important, (-)-**7** and its congeners did not display any agonist activity, a side effect which has plagued some of the earlier TxA_2 antagonists.[26,33] The selective profile of amide (-)-**7** in conjunction with a favorable toxicological evaluation has prompted the advancement of (-)-**7** into clinical trials.

Experimental Section

^{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 or the center resonances of $CDCl_3$ or CD_3OD at δ 77.0 and 49.0, respectively. ^1H NMR spectra were measured at 270 MHz on a JEOL FX-270 and at 400 MHz on a JEOL GX-400. Unless otherwise indicated, all NMR spectra were recorded in $CDCl_3$. 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 ^1H NMR, 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. Optical rotations were measured at 23 °C on a Perkin-Elmer Model 131 polarimeter.

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; toluene and xylene were distilled from sodium and stored over activated 4A molecular sieves. Flash chromatography was performed as described by Still[34] using J. T. Baker "Flash" grade silica gel. TLC was performed on 2.5 × 10 cm Kieselgel $60F_{254}$ plates purchased from E. Merck.

General Procedure for Compounds Prepared by Two-Step Reductive Amination. [1*S*-[1α,2α(*Z*),3α,4α]]-7-[3-[[2-

(28) Greenberg, R.; Steinbacher, T. E.; Harris, D. N.; Haslanger, M. F. *Eur. J. Pharmacol.* **1984**, *103*, 19.
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[(Phenylamino)carbonyl]hydrazino]methyl]-7-oxabicyclo-[2.2.1]hept-2-yl]-5-heptenoic Acid ((+)-6). Chiral aldehyde 9[4g] (24.6 g, 92.4 mmol) was dissolved in CH_3OH, and 4-phenylsemicarbazide (15.4 g, 102 mmol, recrystallized from water) dissolved in CH_3OH (250 mL) was added. A slight exotherm was noted and the mixture was cooled in an ice bath for 15 min. The cooling bath was removed and the mixture was stirred at room temperature for 6 h. The solvent was removed in vacuo, leaving 38.4 g of very viscous material. This was combined with material from a 4.09-mmol run and chromatographed on 1 kg of silica gel eluting with EtOAc/hexane (1:2 and 1:1) to give methyl[1*S*-[1α,2α(*Z*),3α,4α]]-7-[3-[[2-[(phenylamino)carbonyl]hydrazono]-methyl]-7-oxabicyclo[2.2.2]hept-2-yl]-5-heptenoate (**60**) as a mixture of syn and anti isomers. The faster moving isomer was solid, but the mixture was a very viscous oil (35.15 g, 83%). TLC: silica gel, Et_2O, UV and vanillin, R_f 0.29 and 0.42. ^{13}C NMR of anti isomer (67.5 MHz): δ 24.7, 26.8, 28.3, 29.1, 29.7, 33.4, 48.8, 50.4, 51.5, 79.8, 80.2, 119.3, 123.2, 128.9, 130.3, 138.1, 145.3, 153.3, 174.0.

To a solution of hydrazone **60** (85.1 g, 88.0 mmol) in CH_3OH (900 mL) was added sodium cyanoborohydride (5.55 g, 88.0 mmol) followed by the dropwise addition of glacial acetic acid (200 mL) over a period of 4 h. The reaction mixture was cooled in a water bath during much of the addition to control the slight exotherm. Following the completion of the addition (pH 3–3.5) the mixture was stirred overnight at room temperature. The pH was then adjusted to 1 by adding 3 N HCl solution (~125 mL). After stirring at room temperature for 30 min, the mixture was diluted with 800 mL of water and solid $NaHCO_3$ was added portionwise to pH 7–8. The product was extracted into EtOAc (3 × 1 L). The combined extracts were washed once with saturated NaCl solution, dried ($MgSO_4$), filtered, and freed of solvent in vacuo. The residue was dissolved in CH_2Cl_2 (a small amount of material was insoluble), dried ($MgSO_4$), and free of solvent in vacuo, leaving semisolid, gelatinous material. Trituration of this with isopropyl ether gave methyl [1*S*-[1α,2α(*Z*),3α,4α]]-7-[3-[[2-[(phenylamino)-carbonyl]hydrazino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoate (**61**) as a white solid (31 g, 88%). TLC: silica gel, 5% CH_3OH/CH_2Cl_2, UV and vanillin, R_f 0.31 with contamination by trace amounts of four or five other spots. Attempts to crystallize this material from several solvents gave gels.

Methyl ester **61** (29 g, 72.2 mmol) was dissolved in a solution of THF (270 mL) and water (70 mL) which had been purged with argon. A solution of argon-purged 1 N LiOH (145 mL) was added and the mixture was stirred at room temperature for 2 h. 1 N HCl (125 mL) was added to pH 6–6.5, followed by solid KCl to saturate the aqueous layer. The product was extracted into EtOAc (4 × 400 mL). The combined extracts were washed with saturated NaCl solution, dried ($MgSO_4$), and freed of solvent in vacuo, leaving 25 g of a solid foam. This was dissolved in 225 mL of hot acetonitrile. On cooling, a small amount of yellow gummy material was deposited followed by white, crystalline material. The white material was scraped off the sides of the flask, harvested, and washed with isopropyl ether to give (+)-**6** (11.68 g, 41.8%), mp 92–95 °C. An additional 8.45 g (30.2%) of (+)-**6** was obtained which was contaminated with a very small amount of yellow material. TLC: silica gel, 10% CH_3OH/CH_2Cl_2, UV and PMA, R_f 0.49. $[\alpha]_D$ = +19.2° (c = 1.4, CH_3OH). ^{13}C NMR (CD_3OD, 67.5 MHz): δ 25.9, 27.2, 27.8, 30.2, 30.5, 34.4, 45.6, 47.9, 81.3, 81.6, 120.5, 124.0, 129.8, 130.8, 131.0, 140.0, 159.5, 177.4. Anal. ($C_{21}H_{29}N_3O_4$) C, H, N.

General Procedure for Compounds Prepared by One-Step Reductive Amination. [1α,2α(*Z*),3α,4α]-7-[3-[(Hexylamino)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (27). Aldehyde **9** (1.06 g, 4 mmol) was dissolved in CH_3OH (50 mL) under an argon atmosphere. Hexylamine (1.1 mL, 810 mg, 8 mmol) and sodium cyanoborohydride (252 mg, 4 mmol) were added, and the resulting mixture was cooled to 0 °C. Glacial acetic acid (7 mL) was added dropwise (pH ~4). The cooling bath was removed and the mixture was stirred at room temperature for 4 h. The reaction mixture was acidified to pH 1 with 1 N HCl and then stirred for 45 min. A small amount of water was added and the solution was basified by the addition of solid $NaHCO_3$. The product was extracted into EtOAc (3 × 75 mL). The combined extracts were washed with saturated NaCl solution (75 mL), dried ($MgSO_4$), and freed of solvent in vacuo, leaving a very viscous oil which gave a positive boron flame test. This material was dissolved in methanol and treated with 1 N HCl (6.5 mL). The solvent was removed in vacuo. Methanol was added and removed in vacuo six times. The residue was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$) and freed of solvent in vacuo. The remaining oil gave a negative boron test. This was chromatographed on SiliCAR CC-7 (110 g), eluting with 10% CH_3OH/CH_2Cl_2 to give 1.031 g (73%) of methyl [1α,2α(*Z*),3α,4α]-7-[3-[(hexylamino)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoate (**62**) as a partial hydrate. ^{13}C NMR (15 MHz): δ 13.9, 22.5, 24.7, 26.0, 26.7, 26.9, 29.4, 29.4, 29.7, 30.0, 31.7, 33.4, 46.8, 47.5, 48.9, 50.2, 51.2, 79.7, 80.0, 129.4, 130.1, 173.8.

Methyl ester **62** (500 mg, 1.42 mmol) was dissolved in THF (50 mL) and H_2O (10 mL) under an argon atmosphere. A 1 N LiOH solution (14.2 mL) was added and the mixture was stirred overnight at room temperature. HCl (1 N, ~14.2 mL) was added (pH 6–6.5) and the solution was saturated with KCl. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 125 mL). The combined organic layers were dried ($MgSO_4$), filtered, and freed of solvent in vacuo, leaving a glassy material (390 mg). This was chromatographed on SiliCAR CC-7 (40 g), eluting with 5% CH_3OH/CH_2Cl_2 to give pure **27**, (58.2 mg) (TLC: silica gel, 15% CH_3OH/CH_2Cl_2 + trace NH_4OH, vanillin, R_f 0.26) along with a larger fraction of **27** (269.5 mg, total yield = 66%) which was contaminated with a small amount of faster moving material (R_f 0.31). ^{13}C NMR (CD_3OD, 15 MHz): δ 14.3, 23.4, 26.4, 27.2, 27.2, 27.2, 28.0, 29.9, 30.4, 32.4, 32.4, 45.4, 47.8, 48.8, 49.8, 80.2, 81.4, 130.0, 131.7. Anal. ($C_{20}H_{35}NO_3 \cdot 0.8H_2O$): C, H, N.

Methyl [1*S*-[1α,2α(*Z*),3α,4α]]-7-[3-Aminomethyl)-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoate (13). A mixture of 8.11 g (19.2 mmol) of methyl [1*S*-[1α,2α(*Z*),3α,4α]]-7-[3-[(tosyloxy)-methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoate[21] (**63**) and 6.4 of potassium phthalimide (34.6 mmol, purified by boiling 5 g in 9 mL of acetone for 15 min, filtering while hot, washing with 5 mL of acetone, and drying for 6 h at 100 °C in vacuo) in 70 mL of DMSO was heated to 90–100 °C for 2.5 h. The reaction mixture was cooled to room temperature and diluted with 90 mL of water. This mixture was then poured into ice water (~350 mL) and stirred for 30 min. The solid was collected by filtration and washed with water. The solid was dissolved in warm EtOAc (150 mL), washed with water (3 × 50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting solid was recrystallized from isopropyl ether (~150 mL) to afford the corresponding phthalimide **12** (6.45 g, 83%). TLC: silica gel, 2:1 Et_2O/hexane, UV and vanillin, R_f 0.35.

To a solution of 5.05 g (13.8 mmol) of **12** in 24 mL of CH_2Cl_2 and 104 mL of ethanol was added 0.78 mL (25.6 mmol) of anhydrous hydrazine. This mixture was stirred at room temperature for 8 h, at which time an additional 0.2 mL of hydrazine was added. The mixture was stirred for 15 h, and the resulting solids were removed by filtration. The filter cake was rinsed with CH_2Cl_2, and the combined filtrates were concentrated in vacuo. The residue was treated with 80 mL of cold 0.5 N HCl solution and a small amount of white precipitate was removed by filtration and washed with 0.5 N HCl solution (80 mL). The filtrate was washed with ether (2 × 100 mL) and then basified with solid K_2CO_3. Amine **13** was extracted into $CHCl_3$ (3 × 100 mL), which was then dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was treated with 100 mL of ether at 0 °C. A small amount of solid was removed by filtration and the filtrate was concentrated in vacuo to afford amine **13** (2.44 g, 71%), which was used without further purification. TLC: silica gel, 15% CH_3OH/CH_2Cl_2 + NH_4OH (3 drops/10 mL), UV and vanillin, R_f 0.42. ^{13}C NMR (15 MHz): δ 24.5, 25.9, 26.5, 29.4, 29.4, 33.2, 40.6, 46.6, 50.3, 51.2, 78.9, 79.9, 129.4, 129.9, 173.7.

General Procedure for Compounds Prepared by Acylation of Amine 13. [1*S*-[1α,2α(*Z*),3α,4α]]-7-[3-[[[[(1-Oxoheptyl)-amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid ((−)-7). A stirred solution of 173.2 mg (1 mmol) of *N*-heptanoylglycine (**64**) in 8.0 mL of THF was cooled to 0 °C. To this solution was added 162 mg (1 mmol) of *N,N'*-carbonyldiimidazole. The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 1 h. The reaction mixture was cooled in an ice bath and a solution of 267 mg (1.0 mmol) of amine **13** in 3.0 mL of THF was added. The reaction

mixture was allowed to warm to room temperature, stirred overnight, and then concentrated in vacuo. The residue was diluted with 35 mL of $CHCl_3$ and washed with 15 mL of 1 N HCl solution, 15 mL of 1 N NaOH solution, and 15 mL of water. The $CHCl_3$ layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 374 mg of crude product. This was chromatographed on 20 g of silica gel eluting with EtOAc and 2% CH_3OH/EtOAc to give methyl [1*S*-[1α,2α(*Z*),3α,4α]]-7-[3-[[[[(1-oxoheptyl)amino]-acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoate (**65**) (255 mg, 60%) as an oil. TLC: silica gel, 5% CH_3OH/EtOAc, vanillin, R_f 0.45.

Methyl ester **65** (250 mg, 0.59 mmol) was dissolved in 25 mL of THF and 5 mL of water and treated with 5.9 mL of 1 N LiOH solution. The reaction mixture was stirred at room temperature for 2.5 h and then neutralized by the addition of 5.9 mL of a 1 N HCl solution. Solid KCl was added, and the layers were separated. The aqueous layer was extracted with $CHCl_3$ (3 × 25 mL). The combined extracts were washed with 15 mL of saturated NaCl solution, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 234 mg of a white solid. Recrystallization from acetonitrile gave 187 mg (78%) of (−)-**7**, mp 114–116 °C. TLC: silica gel, 10% CH_3OH/CH_2Cl_2, vanillin, R_f 0.40. $[\alpha]_D = -6.6°$ (c = 1.15, CH_3OH). ^{13}C NMR (15 MHz): δ 14.0, 22.4, 24.4, 25.5, 26.1, 26.4, 28.9, 29.3, 29.7, 31.5, 32.7, 36.3, 39.4, 43.2, 46.0, 46.9, 79.9, 80.1, 129.8, 129.9, 169.7, 174.5, 176.5. Anal. ($C_{23}H_{38}O_5N_2$) C, H, N.

[1*R*-[1α,2α(*Z*),3α,4α]]-7-[3-[[[[(1-Oxoheptyl)amino]-acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid ((+)-**7**). $[\alpha]_D = +6.9°$ (c = 1.35, CH_3OH). ^{13}C NMR (67.5 MHz): δ 14.0, 22.4, 24.4, 25.5, 26.1, 26.4, 28.9, 29.3, 29.7, 31.5, 32.6, 36.4, 39.4, 43.2, 45.9, 47.0, 79.9, 80.1, 129.8, 129.9, 169.7, 174.5, 176.5. Anal. ($C_{23}H_{38}N_2O_5$): C, H, N.

Methyl [1*S*-[1α,2α(*Z*),3α,4α]]-7-[3-Carboxy-7-oxabicyclo-[2.2.1]hept-2-yl]-5-heptenoate (**15**). A solution of 5.00 g (18.7 mmol) of alcohol ester **8** in 500 mL of acetone was cooled in an ice bath. To the above stirred solution was added dropwise 11.4 mL of a 2.67 M solution of Jones's reagent. On this scale, the addition required 18 min and the reaction mixture was maintained at 0–5 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 1 h. Isopropyl alcohol (2 mL) was added to destroy excess oxidant. Sodium acetate (20 g) and $MgSO_4$ was then added to the reaction mixture. This mixture was filtered through a 2-in. pad of Celite and the filtrate was concentrated in vacuo to afford a two-phase residue. The residue was dissolved in ether, dried ($MgSO_4$), filtered, and concentrated in vacuo to give 5.42 g of crude **15** as an oil. Purification was effected by flash chromatography on 80 g of Florisil using ether as eluant. This gave 3.78 g (72%) of **15** which solidified on standing in a freezer. Further elution of the above column with ethyl acetate afforded an additional 0.68 g (12%) of **15**. TLC: silica gel, ether, iodine, R_f 0.30. ^{13}C NMR (15 MHz): δ 24.5, 26.4, 27.0, 28.6, 28.9, 33.2, 47.7, 51.7, 78.1, 78.3, 128.2, 130.4, 173.9, 176.9.

Methyl [1*S*-[1α,2α(*Z*),3α,4α]]-7-[3-Amino-7-oxabicyclo-[2.2.1]hept-2-yl]-5-heptenoate (**17**). To a solution of 5.31 g (18.8 mmol) of *cis*-carboxylic acid **15** in 25 mL of dry benzene containing 8 drops of dry DMF was added dropwise 5.38 mL (61.6 mmol) of oxalyl chloride over a period of 20 min. This mixture was stirred at room temperature for 45 min and then concentrated in vacuo to provide an orange residue. The residue was dissolved in 200 mL of dry toluene and the resultant solution was heated to 90 °C. To this solution was added 3.6 mL (27.1 mmol) of freshly distilled trimethylsilyl azide over a period of 25 min. The reaction was stirred for 3 h at 90 °C. The reaction mixture was cooled and concentrated in vacuo to provide an orange oil. This residue was dissolved in 125 mL of THF and then added to a stirred solution of 140 mL of 1 N aqueous HCl in 1200 mL of THF. The resulting solution was stirred for 12 h at room temperature and was then concentrated to a volume of 300 mL. The concentrated solution was diluted with 350 mL of distilled water and washed twice with 200 mL of ether. The aqueous layer was neutralized with solid $NaHCO_3$ and then saturated with solid NaCl. The aqueous layer was extracted with four 50-mL portions of EtOAc. The combined EtOAc extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo to give 1.9 g (40%) of **17** as an oil. TLC: silica gel, 10% CH_3OH/CH_2Cl_2, iodine, R_f 0.1. ^{13}C NMR (15 MHz): δ 24.2, 25.3, 26.0, 26.3, 28.9, 32.9, 48.0, 57.8, 79.5, 83.2, 129.1, 129.5, 173.3.

[1α,2α(*Z*),3α,4α]-7-[3-(Heptylamino)-7-oxabicyclo[2.2.1]-hept-2-yl]-5-heptenoic Acid (**28**). To a solution of 171 mg (1.50 mmol) of 1-heptanal and 315 mg (1.25 mmol) of amine **17** in 15 mL of CH_3OH was added 105 mg (1.67 mmol) of sodium cyanoborohydride. The above solution was cooled in an ice bath and 1.2 mL of HOAc was added dropwise. The reaction mixture was then warmed to room temperature and stirred for 3 h. The pH was adjusted to 1 by the addition of 1 N aqueous HCl solution (4.5 mL). After stirring at room temperature for an additional 30 min, the reaction mixture was diluted with 20 mL of H_2O and then basified with solid $NaHCO_3$. The reaction mixture was extracted with $CHCl_3$ (3 × 100 mL). The combined extracts were dried over $MgSO_4$ and concentrated in vacuo to give a viscous oil. This oil was chromatographed on 20 g of silica CC-7 using 1% CH_3OH/CH_2Cl_2 as eluant to give 106 mg (25%) of methyl [1α,2α(*Z*),3α,4α]-7-[(heptylamino)-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoate (**66**). TLC: silica gel, 4% CH_3OH/CH_2Cl_2, iodine, R_f 0.40. The low yield in this reaction was due in part to competing dialkylation.

To a stirred solution of 106 mg (0.30 mmol) of methyl ester **66** in 15 mL of THF and 2.3 mL of H_2O was added 2.9 mL of 1 N aqueous LiOH solution. The resulting mixture was stirred at room temperature for 7 h. The reaction mixture was then acidified to pH 4 by the addition of 1 N aqueous HCl solution. This solution was poured into 40 mL of saturated NaCl solution which was then extracted with EtOAc (3 × 80 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated in vacuo to give 110 mg of crude oil. This was chromatographed on 18.5 g of silica CC-7 using 4% CH_2OH/CH_2Cl_2 as eluant to give **28** (51 mg, 50%). TLC: silica gel, 10% CH_3OH/CH_2Cl_2, iodine, R_f 0.30. ^{13}C NMR (15 MHz): δ, 13.9, 22.5, 25.2, 27.0, 27.0, 27.6, 27.6, 28.9, 28.9, 28.9, 31.6, 35.0, 48.1, 48.1, 64.3, 77.9, 79.5, 128.3, 131.1, 178.2. Anal. ($C_{20}H_{35}NH_3 \cdot 0.65H_2O$) C, H, N.

Methyl [1*S*-[1α,2α(*Z*),3α,4α]]-7-[3-(Formylmethyl)-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoate (**20**). A mixture of 12.9 g (37.8 mmol, dried prior to use by heating in a vacuum oven at 80 °C for 2 h) of (methoxymethyl)triphenylphosphonium chloride and 235 mL of dry toluene was cooled in an ice bath. To this mixture was added dropwise 18.3 mL (28.3 mmol) of a 1.55 M KOtAm solution in toluene. The resulting red solution was stirred at 0 °C for an additional 35 min. A solution of 5.0 g (18.9 mmol) of aldehyde **9** in 60 mL of toluene was added dropwise over a period of 35 min. A few min after completion of the aldehyde addition, the reaction was quenched by the addition of a solution of 2.3 g (39.0 mmol) of HOAc in 5 mL of ether. The reaction mixture was immediately poured in 200 mL of saturated NH_4Cl solution and extracted with ether (4 × 200 mL). The combined ether extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to yield the crude product. Trituration with EtOAc removed most of the byproduct triphenylphosphine oxide. Purification was effected by flash chromatography using LPS-1 silica gel eluting with a gradient of hexane-EtOAc (90%–60%) gave a mixture of enol ether **67** and the hydrolyzed product **20**. Total product yield from the chromatography was 3.7 g (67%). The purified enol ether **67** (1.0 g, 3.4 mmol) was dissolved in 20 mL of distilled THF and to this solution was added 80 mL of 20% aqueous TFA solution. The resulting two-phase reaction mixture was stirred vigorously for 5 h. Solid $NaHCO_3$ was added portionwise until the pH ~7 (a small amount of H_2O was also added). The bulk of the THF was removed in vacuo and the remaining product was extracted with CH_2Cl_2 (4 × 95 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to yield 871 mg (91%) of **20**. ^{13}C NMR (15 MHz): δ 24.7, 26.7, 27.3, 29.3, 29.3, 33.4, 40.4, 44.1, 46.3, 51.3, 80.1, 81.5, 129.4, 130.0, 173.8, 201.8.

[1α,2α(*Z*),3α,4α]-7-[3-[2-(Pentylamino)ethyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (**29**). To a stirred solution of 336.4 mg (1.2 mmol) of aldehyde **9** in 20 mL of dry CH_3OH was added 0.29 mL (2.5 mmol) of distilled *n*-pentylamine and 90.9 mg (1.4 mmol) of sodium cyanoborohydride. The reaction mixture was cooled in an ice bath and then 1.7 mL of glacial HOAc was added (pH ~4). The reaction mixture was allowed to stir at room temperature for 5 h and was then acidified to pH ~1 with 1 N HCl. Stirring was continued for 40 min and then the mixture was basified by the addition of solid $NaHCO_3$. The product was extracted into EtOAc (4 × 75 mL). The combined extracts were

washed with 150 mL of brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography, using SiliCAR CC-7 (100 g), packed in CH_2Cl_2, and elution with a 2%–10% CH_3OH/CH_2Cl_2 gradient gave 321 mg (76%) of methyl [1α,2α(Z),3α,4α]-7-[3-[2-(pentylamino)ethyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoate (**68**). ^{13}C NMR (15 MHz): δ 13.7, 22.2, 24.7, 25.2, 26.0, 26.7, 26.7, 28.8, 29.4, 29.4, 33.4, 44.6, 47.1, 47.1, 47.3, 51.2, 79.9, 79.9, 129.4, 129.9, 173.8.

Methyl ester **68** (321.5 mg, 0.91 mmol) was dissolved in 35 mL of THF and to this solution was added 15 mL of 1 N LiOH solution. The resulting two-phase reaction mixture was stirred vigorously under argon for 23 h at room temperature. The reaction mixture was concentrated in vacuo to remove the THF before acidification to pH 6 with 1 N HCl. The solution was then saturated with KCl, extracted with EtOAc (4 × 125 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to leave a glassy solid. This was purified by flash column chromatography (SiliCAR CC-7, packed in CH_2Cl_2, eluting with 5% CH_3OH/CH_2Cl_2) to yield 241 mg (71%) of **29** as a partial hydrate. ^{13}C NMR (15 MHz): δ 13.7, 22.0, 24.4, 25.0, 25.4, 26.2, 28.7, 28.7, 29.4, 29.4, 32.9, 44.6, 47.1, 47.4, 47.6, 79.9, 79.9, 129.7, 129.9, 176.8. Anal. ($C_{20}H_{35}NO_3 \cdot 0.88H_2O$) C, H, N.

[1α,2α(Z),3α,4α]-7-[3-[[[[(Phenylmethyl)amino]carbonyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (32). Amine **13** (248 mg, 0.93 mmol) was dissolved in CH_2Cl_2 (20 mL). The solution was cooled in an ice bath and then benzyl isocyanate (0.135 mL, 1.1 mmol) was added. The mixture was stirred at 0–5 °C for 45 min and at room temperature for 4 h. The solvent was removed in vacuo and the remaining oil was chromatographed on silica gel 60 (20 g). The product was eluted with 1.5% CH_3OH in CH_2Cl_2 to give 275 mg (74%) of methyl [1α,2α(Z),3α,4α]-7-[3-[[[[(phenylmethyl)amino]carbonyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoate (**69**). TLC: silica gel, 5% CH_3OH/CH_2Cl_2, UV and vanillin, R_f 0.42. ^{13}C NMR (15 MHz): δ, 24.5, 26.0, 26.5, 29.3, 29.5, 33.2, 39.6, 44.1, 46.5, 46.7, 51.3, 79.4, 80.0, 126.9, 127.1, 128.3, 129.5, 129.7, 139.5, 158.6, 174.1.

Methyl ester **69** (260 mg, 0.65 mmol) was dissolved in THF (20 mL) and water (5 mL). A 1 N LiOH solution (6.5 mL) was added and the mixture was stirred at room temperature for 6 h and then neutralized by the addition of a 1 N HCl solution (6.5 mL). Solid NaCl was added to separate the layers. The aqueous layer was extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers (THF and $CHCl_3$) were washed with saturated NaCl solution (2 × 20 mL), dried ($MgSO_4$), and freed of solvent in vacuo, leaving a colorless oil. This was chromatographed on silica gel 60 (20 g) eluting with 5% CH_3OH/CH_2Cl_2 to give **32** as an oil (214 mg, 85%). TLC: silica gel, 8% CH_3OH/CH_2Cl_2, UV and vanillin, R_f 0.47. ^{13}C NMR (15 MHz): δ, 24.5, 26.0, 26.4, 29.3, 29.3, 33.2, 39.6, 44.3, 46.6, 46.6, 79.5, 80.3, 127.2, 127.2, 128.4, 129.7, 129.7, 139.1, 159.2, 177.0. Anal. ($C_{22}H_{30}N_2O_4 \cdot 0.25H_2O$) C, H, N.

[1α,2α(Z),3α,4α]-7-[3-[[3-(Hexylamino)-1,3-dioxopropyl]amino]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (38). Alternate Procedure for the Preparation of Amine 17. To a stirred solution of 1.02 g (4.29 mmol) of carboxylic acid **15** and 0.60 mL (4.29 mmol) of triethylamine in 2.9 mL of dry toluene was added dropwise 0.93 mL (4.29 mmol) of diphenyl phosphorazidate. The reaction mixture was heated at 80 °C for 2 h, at which time 1.23 mL (8.59 mmol) of 2-(trimethylsilyl)ethanol was added dropwise. The reaction mixture was heated at 80 °C for 5.5 h and cooled to room temperature. The mixture was stirred overnight and then concentrated in vacuo. The residue was dissolved in 100 mL of 1:1 ether/EtOAc and washed with a 0.1 N aqueous NaOH solution (2 × 45 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. This was chromatographed on 80 g of silica gel 60 by gradient elution from CH_2Cl_2 to 2% CH_3OH/CH_2Cl_2 to give 0.55 g (40%) of methyl [1α,2α(Z),3α,4α]-7-[3-[[[2-(trimethylsilyl)ethoxy]carbonyl]amino]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoate (**70**) as an oil. TLC: silica gel, 1% CH_3OH/CH_2Cl_2, $Ce(SO_4)_2$, R_f 0.30. ^{13}C NMR (67.5 MHz): δ 17.6, 24.7, 26.2, 26.3, 26.7, 29.2, 33.4, 48.2, 51.3, 57.5, 62.9, 79.5, 82.2, 128.8, 130.0, 156.4, 173.8.

To 540 mg (1.36 mmol) of (trimethylsilyl)ethyl carbamate **70** was added 6.0 mL of a 1 M solution of n-Bu_4NF in THF. The mixture was heated at 50 °C for 2.5 h. The cooled reaction mixture was diluted with 50 mL of brine and extracted with EtOAc (4 × 60 mL). The combined EtOAc extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was dissolved in 75 mL of a 1 N aqueous HCl solution and washed with ether (50 mL), CH_2Cl_2 (50 mL), and EtOAc (50 mL). The aqueous layer was basified to pH 9 by the addition of solid K_2CO_3 and then saturated with KCl. The resulting solution was extracted with EtOAc (4 × 80 mL). The combined EtOAc extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give 580 mg (>100%) of crude amine **17**, which was used without further purification. TLC: silica gel, 10% CH_3OH/CH_2Cl_2, $Ce(SO_4)_2$, R_f 0.11. ^{13}C NMR (67.5 MHz): δ, 24.3, 25.4, 26.0, 26.3, 29.0, 33.0, 48.3, 50.9, 58.1, 79.6, 83.7, 129.3, 173.4.

Amine **17** (338 mg, 1.33 mmol) and 3-(hexylamino)-3-oxopropanoic acid (324 mg, 1.73 mmol) were coupled as described above for amide **7**. Purification was effected by flash chromatography on 36 g of silica gel 60 using 100 mL of each 2%, 3%, 4%, 5%, 6%, and 10% of CH_3OH/ether as eluant to give 270 mg (48%) of methyl [1α,2α(Z),3α,4α]-7-[3-[[3-(hexylamino)-1,3-dioxopropyl]amino]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoate (**71**) as an oil. TLC: silica gel, 6% CH_3OH/CH_2Cl_2, $Ce(SO_4)_2$, R_f 0.7.

Methyl ester **71** (175 mg, 0.42 mmol) was hydrolyzed as described above for amide **7**. The crude compound was chromatographed on 24 g of silica gel 60 using 4% CH_3OH/CH_2Cl_2 with 0.25% HOAc as eluant to give 100 mg (59%) of pure acid **38** as an oil. TLC: silica gel, 4% CH_3OH in CH_2Cl_2 with 0.25% HOAc, $Ce(SO_4)_2$, R_f 0.30. ^{13}C NMR (67.5 MHz): δ 13.1, 22.4, 24.4, 26.2, 26.4, 26.4, 26.4, 29.1, 29.1, 31.3, 33.0, 39.7, 42.7, 48.2, 56.0, 79.4, 81.5, 128.9, 130.1, 167.5, 167.8, 176.6. Anal. ($C_{22}H_{36}N_2O_5$) C, H, N.

[1S-[1α,2α(Z),3α,4α]]-7-[3-[[[2-(Heptylamino)-2-oxoethyl]amino]carbonyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (39). To a solution of 100 mg of acid **15** (0.35 mmol) in 5 mL of THF at 0 °C was added 63 mg of N,N'-carbonyldiimidazole (0.39 mmol, 1.1 equiv). The mixture was stirred at 0 °C for 1 h and at 25 °C for 1 h and then cooled to 0 °C.

A mixture of 200 mg of 1-glycylheptylamine trifluoroacetic acid salt (0.7 mmol, 2 equiv) and 1 mL of triethylamine in 5 mL of THF was stirred at 25 °C for 30 min. This mixture was then added to the above 0 °C acylimidazole solution and the stirring was continued at 25 °C for 20 h. The mixture was concentrated. The residue was diluted with 30 mL of CH_2Cl_2 and washed with three 10-mL portions of a 1 N HCl solution, three 10-mL portions of a saturated aqueous $NaHCO_3$ solution, and 10 mL of H_2O. The organic layer was dried ($MgSO_4$), filtered, and concentrated to leave 110 mg of methyl [1S-[1α,2α(Z),3α,4α]]-7-[3-[[[2-(heptylamino)-2-oxoethyl]amino]carbonyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoate (**72**) as a white solid.

A mixture of 110 mg of crude **72** (ca. 0.25 mmol), 1 mL of 1 N LiOH, and 3 mL of THF was stirred at 25 °C for 6 h and then concentrated. The residue was diluted with 2 mL of H_2O, acidified to pH 3 with a saturated solution of oxalic acid and extracted with four 10-mL portions of ether. The combined organic layers were washed with two 10-mL portions of H_2O, dried ($MgSO_4$), filtered, and concentrated. The residue was purified on a silica gel column. Elution with a gradient from 2% CH_3OH/CH_2Cl_2 to 10% CH_3OH/CH_2Cl_2 afforded 36 mg of acid **39**, TLC: silica gel, 10% CH_3OH/CH_2Cl_2, $Ce(SO_4)_2$, R_f 0.42. $[\alpha]_D$ = +29.2° (c = 0.13, CH_3OH). ^{13}C NMR (67.5 MHz): δ, 14.0, 22.5, 24.6, 26.3, 26.8, 27.3, 28.7, 28.9, 29.3, 29.6, 31.7, 33.0, 39.8, 43.4, 48.1, 54.4, 79.0, 129.1, 130.3, 169.8, 173.4, 176.7. Anal. ($C_{23}H_{38}N_2O_5 \cdot 0.7H_2O$) C, H, N.

[1S-[1α,2α(Z),3α,4α]]-7-[3-[[[3-(Hexylamino)-3-oxopropyl]amino]carbonyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (40). A solution of 247 mg of acid **15** (0.87 mmol) was coupled with 500 mg of 1-β-alanylhexylamine trifluoroacetic acid salt (1.4 mmol, 2 equiv) and then hydrolyzed by using the procedure described for **39** to give 160 mg of **40** as a clear oil. TLC: silica gel, 10% CH_3OH/CH_2Cl_2, $Ce(SO_4)_2$, R_f 0.44. $[\alpha]_D$ = +40° (c = 0.12, CH_3OH). ^{13}C NMR (67.5 MHz): δ, 13.8, 22.4, 24.5, 263.5, 27.2, 28.6, 29.2, 29.5, 31.3, 33.0, 35.5, 35.7, 39.6, 47.8, 54.5, 78.9, 79.0, 128.9, 130.3, 171.9, 172.9, 176.2. Anal. ($C_{23}H_{38}N_2O_5 \cdot 0.2H_2O$) C, H, N.

[1S-[1α,2α(Z),3α,4α]]-7-[3-[[[[(1-Oxoheptyl)oxy]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (43). A solution of 2-acetoxyacetic acid (108 mg, 0.91 mmol) in $CHCl_3$ (5 mL) was cooled to 0 °C and treated with 1,1'-

carbonyldiimidazole (148 mg, 0.91 mmol). The mixture was stirred at 0 °C for 1 h and then at room temperature for 2 h. The hydrochloride salt of amine **13** (278 mg, 0.91 mmol) was added and the mixture was cooled to 0 °C. *n*-Butylamine (0.22 mL, 0.91 mmol) was added and the mixture was stirred overnight at room temperature. The mixture was then diluted with $CHCl_3$ (30 mL) and washed with a 1 N HCl solution (15 mL), a saturated $NaHCO_3$ solution (15 mL), and a saturated NaCl solution (15 mL). The $CHCl_3$ layer was dried ($MgSO_4$) and filtered, and the solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel (15 g) eluting with 2% CH_3OH in EtOAc to give methyl [1*S*-[1α,2α(*Z*),3α,4α]]-7-[3-[[[[(1-oxoethyl)-oxy]-acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoate (**73**) as an oil (299 mg, 89%). TLC: silica gel, 2% CH_3OH/EtOAc, vanillin, R_f 0.51. ^{13}C NMR (67.5 MHz): δ 20.4, 24.5, 26.1, 26.5, 28.9, 29.7, 33.2, 38.7, 45.4, 46.6, 51.2, 62.7, 79.5, 80.1, 129.3, 129.8, 166.9, 169.3, 173.7.

Methyl ester **73** (299 mg, 0.81 mmol) was dissolved in THF (35 mL) and water (2.5 mL) and treated with a 1 N LiOH solution (5 mL). The mixture was stirred at room temperature for 2 h and neutralized with a 1 N HCl solution (5 mL), and then solid KCl was added to separate the two phases. The aqueous layer was extracted with chloroform (3 × 25 mL). The combined organic layers (THF and chloroform) were washed with saturated NaCl solution (20 mL), dried ($MgSO_4$), filtered, and freed of solvent in vacuo, leaving [1*S*-[1α,2α(*Z*),3α,4α]]-7-[3-[[(2-hydroxy-acetyl)amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid (**74**) as a solid (241 mg, 99%). TLC: silica gel, 10% CH_3OH in EtOAc, vanillin, R_f 0.15.

Hydroxy acid **74** (241 mg, 0.77 mmol) was dissolved in pyridine (5 mL) and cooled to −25 ± 5 °C. Heptanoyl chloride (0.36 mL, 343 mg, 2.31 mmol) was then added dropwise over 30 min. The mixture was stirred at 25 °C for 1 h and left in a freezer (−20°) overnight. Ice (3 g) was added and the mixture was stirred at room temperature for 6 h before it was left overnight at 5 °C. EtOAc (90 mL) was added and the mixture was washed with a 1 N HCl solution (4 × 25 mL) and saturated NaCl solution (4 × 25 mL), dried ($MgSO_4$), filtered, and freed of solvent in vacuo, leaving an amber oil. This was chromatographed on silica gel (Baker for flash chromatography, 15 g), eluting with 2% CH_3OH in CH_2Cl_2 to give **43** (78.5 mg, 24%) as an oil. TLC: silica gel, 10% CH_3OH in CH_2Cl_2, vanillin, R_f 0.52. $[\alpha]_D$ = −6.6° (*c* = 0.9, CH_3OH). ^{13}C NMR (67.5 MHz): δ 13.9, 22.4, 24.4, 24.6, 26.2, 26.5, 28.7, 29.0, 29.8, 31.3, 33.0, 33.9, 38.9, 45.5, 46.8, 62.8, 79.7, 80.4, 129.6, 130.0, 167.7, 172.4, 177.3. Anal. ($C_{23}H_{37}NO_6$) C, H, N.

[1*S*-[1α,2α(*Z*),3α,4α]]-7-[3-[[[[(1-Thioxoheptyl)amino]-acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (57). To piperidine (8.5 g, 100 mmol) dissolved in Et_2O (50 mL) at 0 °C was added NaOH (4.4 g, 110 mmol) in H_2O (25 mL). The heterogeneous mixture was vigorously stirred and cooled to 0 °C. *n*-Heptanoyl chloride (14.9 g, 100 mmol) in Et_2O (25 mL) was then added dropwise at 0 °C over 1 h. The mixture was stirred at 0 °C for 30 min and at room temerature for 1 h. The layers were separated and the water layer was extracted with Et_2O (80 mL). The combined Et_2O layers were washed with saturated NH_4Cl (50 mL), H_2O, and dried over $MgSO_4$. Filtration and evaporation of solvent gave a slightly straw-colored oil, 1-heptanoylpiperidine (19.3 g, 98 mmol, 98%). The crude product was used for the subsequent reaction.

To a solution of 1-heptanoylpiperidine in benzene (50 mL) at room temperature was added P_2S_2 (13.0 g, 29.2 mmol). An exothermic reaction took place. The reaction was allowed to cool to room temperature and was then heated at reflux for 30 min. The reaction was poured into ice-cold $NaHCO_3$ (~100 mL) and stirred until CO_2 gas evolution subsided. The products were extracted with Et_2O (2 × 100 mL), The organic layers were combined and washed with saturated $NaHCO_3$ (20 mL) and H_2O (20 mL) and dried over $MgSO_4$. Filtration and removal of solvents gave a brown oil, which was distilled to give a pale straw-colored oil, 1-(1-thioxoheptyl)piperidine (**75**; 12.45 g, 58.4 mmol, 59%, bp: 149 °C/0.4 mmHg).

Bromoacetic acid (8.9 g, 64 mmol, solid) was dried under vacuum for 20 min and dissolved in benzene (30 mL). To this solution was added **75** (12.45 g, 58.4 mmol). The reaction was stirred overnight at room temperature. A layer of oil separated. The reaction was concentrated in vacuo to give a yellow viscous oil. This crude product was dissolved in EtOH (70 mL, dried over $Mg(OEt)_2$) and cooled to 0 °C. H_2S gas was slowly bubbled into the reaction for 4 h. The reaction became increasingly yellow and a precipitate formed. After stirring at 0 °C overnight, the reaction mixture was concentrated in vacuo to give a yellow oil which was partitioned between Et_2O (200 mL) and H_2O (50 mL). The Et_2O layer was washed with H_2O (70 mL). The combined H_2O layers were extracted with Et_2O (150 mL). The combined Et_2O layers were washed with H_2O (20 mL) and brine (100 mL) and dried over $MgSO_4$. Filtration and evaporation of solvent gave a yellow sludge (15 g), which was crystallized from petroleum ether. Bright yellow crystals of 2-[(1-thioxoheptyl)thio]acetic acid (**76**; 9.4 g, 42.7 mmol, 73% from **75**) were obtained.

A solution of **76** (2.2 g, 10 mmol) in Et_2O (20 mL) was added to a magnetically stirred solution of glycine (750 mg, 10 mmol) in 2 N NaOH (10 mL, 20 mmol). The reaction was stirred at room temperature for 5 h. 2 N NaOH (10 mL) was added to the reaction, and the layers were separated. The Et_2O layer was extracted with 2 N NaOH (5 mL). The aqueous layers were combined and washed with Et_2O (20 mL). The water layer was acidified with concentrated HCl, and the products were extracted with Et_2O (3 × 50 mL). The combined Et_2O layers were washed with brine (2 × 20 mL) and dried over $MgSO_4$. Filtration and evaporation of solvent gave a yellow solid which was crystallized from benzene/*n*-hexane to give colorless crystals of 2-[(1-thioxoheptyl)amino]acetic acid (**77**; 1.65 g, 8.1 mmol, 81%), mp 96–104 °C.

Acid **77** was coupled with amine **13** as described for **7** to give **57**. $[\alpha]_D$ = −5.8° (*c* = 0.88, CH_3OH). ^{13}C NMR (67.5 MHz): δ 14.0, 22.4, 24.4, 26.1, 26.5, 28.6, 29.3, 29.7, 31.4, 32.8, 39.4, 45.9, 46.3, 46.7, 49.1, 79.7, 80.2, 129.6, 129.9, 168.3, 177.1, 206.5. Anal. ($C_{23}H_{38}N_2O_4S$) C, H, N, S.

[1*S*-[1α,2α(*Z*),3α,4α]]-7-[3-[[[1-Thioxo-2-[(1-thioxoheptyl)amino]ethyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (58). Amide (−)-7 (507 mg, 1.2 mmol) was partially dissolved in benzene (10 mL). This mixture was heated to reflux and then *N*,*N*-dimethylformamide di-*tert*-butyl acetal (1.15 mL, ~970 mg, 4.8 mmol) was added dropwise over 45 min while heated under reflux. One hour after the addition was complete, additional *N*,*N*-dimethylformamide di-*tert*-butyl acetal (0.35 mL) was added dropwise over 30 min and heating was continued an additional 60 min. After cooling, the mixture was diluted with ether (30 mL) and washed with 1 N NaOH (15 mL) and a saturated NaCl solution (15 mL). The solution was dried ($MgSO_4$), filtered, and freed of solvent in vacuo, leaving *tert*-butyl [1*S*-[1α,2α(*Z*),3α,4α]]-7-[3-[[[1-oxo-2-[(1-oxoheptyl)-amino]ethyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoate (**78**; 508.5 mg, 88%). TLC: silica gel, 5% CH_3OH/ether, vanillin, R_f 0.34. ^{13}C NMR (67.5 MHz): δ 13.8, 22.3, 24.7, 25.4, 26.0, 26.6, 27.9, 28.7, 29.2, 29.5, 31.3, 34.8, 36.1, 38.8, 43.2,46.1, 46.4, 79.2, 79.8, 80.0, 128.1, 129.2, 130.0, 169.0, 172.8, 173.8.

To a solution of ester **78** (505 mg, 1.05 mmol) in THF (15 mL) was added Lawesson's reagent (286 mg, 0.7 mmol) and the mixture was heated under reflux for 2 h and 20 min. The reaction mixture was cooled to 0–5 °C and then a saturated $NaHCO_3$ solution (15 mL) was added slowly. The cooling bath was removed and stirring was continued for 15 min. Ether (60 mL) was added, and the layers were separated. The aqueous layer was extracted with Et_2O (30 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (20 mL) and water (20 mL), dried ($MgSO_4$), and freed of solvent in vacuo, leaving a yellow-orange oil (488 mg). This was chromatographed on 20 g of silica gel eluting with 1:4 EtOAc/hexane to give *tert*-butyl [1*S*-[1α,2α(*Z*),3α,4α]]-7-[3-[[[1-thioxo-2-[(1-thioxoheptyl)amino]ethyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoate (**79**, 239 mg, 45%) as a yellow oil. TLC: silica gel, 1:2 EtOAc/hexane, UV and vanillin, R_f 0.51. ^{13}C NMR (67.5 MHz): δ, 13.9, 22.4, 24.5, 26.5, 26.8, 28.9, 28.5, 29.0, 29.9, 31.4, 35.0, 44.6, 46.0, 46.5, 46.8, 55.2, 80.0, 80.2, 80.4, 129.0, 130.4, 173.2, 196.4, 206.1.

Ester **79** (239 mg, 0.468 mmol) was cooled in an ice bath and treated with precooled distilled trifluoroacetic acid (7 mL). The solution was stirred at 0–5 °C for 75 min. The TFA was removed in vacuo leaving an oil (252 mg). This was chromatographed on SiliCAR CC4 eluting with 1–2% CH_3OH in CH_2Cl_2 to give **58** (129 mg, 60%) as an amber oil. TLC: silica gel, 5% CH_3OH/CH_2Cl_2,

UV and vanillin, R_f 0.26. $[\alpha]_D = +7.7°$ (c = 1.7, CH_3OH). ^{13}C NMR (67.5 MHz): δ 13.9, 22.3, 24.3, 26.3, 26.5, 28.4, 28.9, 29.7, 31.3, 32.8, 44.5, 45.8, 46.4, 46.6, 55.0, 80.0, 80.3, 129.3, 130.0, 177.6, 196.4, 205.5. Anal. ($C_{23}H_{38}N_2O_3S$) C, H, N, S.

Representative Procedures for the Preparation of Side Chains. *N*-Phenyloxamic Acid[36] (80). A mixture of dimethyl oxalate (11.8 g, 0.1 M) and aniline (9.3 g, 0.1 M) in CH_3OH (20 mL) was heated under reflux for 12 h. The mixture was cooled to 0 °C and the resulting white solid (14.8 g) was removed by filtration. This material was partially dissolved in acetone. Insoluble material was removed by filtration. The filtrate was taken to dryness in vacuo. The white solid residue was crystallized from methanol to give methyl *N*-phenyloxamate as white crystals (6.9 g, 39%). Mp: 109–112 °C. TLC, silica gel, 1% CH_3OH/CH_2Cl_2, UV + PMA, R_f 0.63. The ester (1.79 g, 10 mmol) was dissolved in distilled THF (50 mL) and treated with a 1 N LiOH solution (20 mL). The mixture was left standing overnight at room temperature, at which time a white solid had precipitated from the reaction mixture. Water (20 mL) was added and the mixture was then poured into ether (50 mL). The organic layer that separated was extracted with 0.5 N NaOH (30 mL). The combined aqueous layers were washed with ether (50 mL) and then acidified to pH 1–2 with concentrated HCl. After saturation with NaCl, the aqueous solution was extracted with EtOAc (2 × 50 mL). The combined EtOAc extracts were washed with saturated NaCl solution, dried ($MgSO_4$), and freed of solvent in vacuo, leaving a white solid (1.52 g). This was crystallized from toluene/IPA to give **80** (1.13 g, 68%). Mp: 152–153 °C. ^{13}C NMR (CD_3OD, 15 MHz): δ 121.6, 126.3, 129.8, 138.2, 157.7, 162.8.

***N*-Glycylaniline Hydrochloride[37] (81).** A solution of *t*-BOC-glycine (4.38 g, 25 mmol) in dry THF (100 mL) was cooled to 0 °C. *N,N'*-carbonyldiimidazole (4.1 g, 25 mmol) was added and the mixture was stirred at 0 °C for 1 h. Aniline (2.73 mL, 2.79 g, 30 mmol) was then added and the mixture was allowed to warm slowly to room temperature overnight. The solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 (100 mL) and washed with a 10% $KHSO_4$ solution (100 mL), a saturated $NaHCO_3$ solution (100 mL), and H_2O (100 mL). After drying ($MgSO_4$), the solvent was removed in vacuo, leaving a tan solid (5.04 g, 81%). This sample was recrystallized from EtOAc/Et_2O to give 3.5 g (56%) of *N*-(*t*-BOC-glycyl)aniline (**82**) as white crystals. TLC: silica gel, Et_2O, PMA and UV, R_f 0.56. ^{13}C NMR (CD_3OD): δ 28.7, 44.7, 45.3, 46.1, 47.6, 49.0, 50.4, 51.9, 53.3, 80.8, 121.3, 125.2, 129.7, 139.5, 170.5. *t*-BOC derivative **82** (3.5 g, 14 mmol) was treated with cold (0 °C) distilled TFA. The solution was stirred at 0 °C for 50 min. The TFA was removed in vacuo and benzene was added and removed in vacuo. The residue was dissolved in CH_3OH and an excess of concentrated HCl solution was added. This solution was taken to dryness in vacuo. Ethanol was added and removed in vacuo (repeated), leaving a solid which was triturated with Et_2O and harvested by filtration to give hydrochloride **81** (2.61 g, 99%) as a white solid. ^{13}C NMR (CD_3OD, 67.5 MHz): δ 42.2, 121.0, 125.6, 129.9, 139.0, 165.4.

***N*-Butyl-*N'*-(carboxymethyl)urea[38] (83).** Glycine ethyl ester hydrochloride (5.58 g, 40 mmol) was suspended in distilled CH_2Cl_2 (20 mL) and cooled in an ice bath. To this was added distilled Et_3N (6.13 mL, 44 mmol) followed by distilled *n*-butyl isocyanate (4.95 mL, 44 mmol). The cooling bath was removed and the mixture was stirred overnight at room temperature. Additional Et_3N (3.05 mL) was added and the mixture was stirred for 3 h. After diluting with CH_2Cl_2, the solution was washed with water (50 mL), 1 N HCl (50 mL), a saturated $NaHCO_3$ solution (50 mL), and water (50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to afford *N*-butyl-*N'*-[(ethoxycarbonyl)methyl]urea (**84**; 7.641 g, 94.6%), which slowly crystallized. This was used without further purification. Ethyl ester **84** (3.378 g, 16.7 mmol) was dissolved in distilled THF (100 mL) and treated with a 1 N LiOH solution (40 mL). The reaction was stirred overnight at room temperature and then acidified with concentrated HCl. Solid KCl was added, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers (THF and EtOAc) were washed with saturated NaCl solution (25 mL), dried ($MgSO_4$), filtered, and freed of solvent in vacuo, leaving **83** as a white solid (2.81 g, 97%). ^{13}C NMR (CD_3OD, 67.5 MHz): δ 14.1, 21.0, 33.3, 40.8, 42.6, 161.0, 174.4.

3-Oxo-3-(pentylamino)propanoic Acid[39] (85). Dimethyl malonate (3.2 g, 24 mmol) and *n*-amylamine (2.1 g, 24 mmol) were mixed at room temperature. Solid began to precipitate after 1 h. Diisopropyl ether (10 mL) was added and the mixture was left overnight at room temperature. The reaction mixture was concentrated in vacuo. The residue was chromatographed on 100 g of silica gel eluting with CH_2Cl_2 and 2% CH_3OH/CH_2Cl_2 to give methyl 3-oxo-3-(pentylamino)propanoate (**86**) as an oil (1.97 g, 44%). Ester **86** (1.43 g, 7.6 mmol) was dissolved in CH_3OH (ca. 1 mL) and treated with a 1 N LiOH solution (20 mL). The heterogeneous solution was left stirring overnight at room temperature. During this time it became homogeneous. The solution was washed with ether (50 mL). The water layer was then acidified with concentrated HCl to pH ~1. The product was extracted into ether (2 × 50 mL). The combined ether extracts were washed with saturated NaCl solution, dried ($MgSO_4$), filtered, and freed of solvent in vacuo to give **85** (1.15 g, 87%). Mp: 67.5–68.5 °C. ^{13}C NMR (67.5 MHz): 13.8, 19.3, 22.1, 28.6, 38.9, 39.9, 168.0, 170.7.

***N*-(Butyloxycarbonyl)glycine (87).** Glycine ethyl ester hydrochloride (3.5 g, 25 mmol) was suspended in distilled CH_2Cl_2 (25 mL) and cooled to −40 °C. Distilled Et_3N (7.65 mL, 55 mmol) was added followed by dropwise addition of a solution of distilled *n*-butyl chloroformate (3.2 mL, ca. 25 mmol) in CH_2Cl_2 (10 mL). After stirring at −40 °C for 1 h, the mixture was left in a freezer (−5 °C) overnight. The mixture was stirred at −5 to −10° for 1 h. Additional CH_2Cl_2 was added and this mixture was washed with water (50 mL), a saturated $NaHCO_3$ solution (50 mL), and water (50 mL). The organic layer was dried ($MgSO_4$), filtered, and freed of solvent in vacuo, leaving 3.13 g of material. This was combined with material from a 5-mmol run and chromatographed on 100 g of silica gel eluting with 1:1 ether/hexane to give ethyl *n*-(butyloxycarbonyl)glycinate (**88**) as an oil (3.19 g, 52%). TLC: silica gel, 1:1 Et_2O/hexane, PMA, R_f 0.34. Ethyl ester **88** (3.14 g, 15.47 mmol) was dissolved in 100 mL of distilled THF and treated with a 1 N LiOH solution (40 mL). The mixture was stirred overnight at room temperature and then acidified with concentrated HCl. Solid KCl was added, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers (THF and EtOAc) were washed with saturated NaCl solution (25 mL), dried ($MgSO_4$), filtered, and freed of solvent in vacuo, leaving **87** (2.78 g) which slowly crystallized. ^{13}C NMR (CD_3OD, 67.5 MHz): δ, 14.0, 20.0, 32.2, 43.0, 66.0, 159.4, 173.6. Anal. ($C_7H_{13}NO_4$) C, H, N.

***N*-[[(4-*tert*-Butylphenyl)thio]acetyl]glycine (89).** Glycine (15 g, 0.2 M) was dissolved in 2.5 N NaOH solution (200 mL, 0.5 M), and ether (150 mL) was added. The mixture was stirred vigorously and cooled to 0 °C, and then a solution of chloroacetyl chloride (22.6 g, 15.9 mL, 0.2 M) in ether (100 mL) was added dropwise over a period of 30 min. The mixture was stirred an additional 30 min at 0 °C and then at room temperature for 75 min. The layers were separated. The aqueous layer was washed twice with ether and then acidified to pH 2 with concentrated HCl. The product was extracted into EtOAc (3 × 200 mL). The combined EtOAc extracts were washed with saturated NaCl solution, dried ($MgSO_4$), filtered, and freed of solvent in vacuo to give *n*-(chloroacetyl)glycine (**90**) as a white solid (15.68 g, 52%). A solution of the acid **90** (1.97 g, 13 mmol) in distilled CH_3OH (15 mL) was cooled to 0 °C and treated with $NaOCH_3$ (1.59 g, 29.5 mmol). 4-*tert*-Butylthiophenol (2.49 g, 15 mmol) was added dropwise and the mixture was allowed to warm to room temperature and left stirring overnight. A 1 N NaOH solution was added and the mixture was washed with ether (2 × 60 mL). The aqueous layer was acidified to pH 2 with concentrated HCl. The product was then extracted into ether (3 × 70 mL), washed with saturated NaCl solution (40 mL), dried ($MgSO_4$), filtered, and freed of solvent in vacuo, leaving partially solid material. This

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was crystallized from benzene (30 mL). The solid obtained (1.41 g, 38%) was recrystallized from acetonitrile (25 mL) to give the desired product **89** (0.98 g, 27%). ^{13}C NMR (CD_3OD, 67.5 MHz): δ 31.6, 35.3, 39.1, 42.1, 125.4, 127.1, 127.7, 131.0, 133.0, 151.4, 172.0, 172.6. Anal. ($C_{14}H_{19}NO_3S$) C, H, N, S.

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Synthesis of New (±)-3,5-Dihydroxypentyl Nucleoside Analogues from 1-Amino-5-(benzyloxy)pentan-3-ol and Their Antiviral Evaluation

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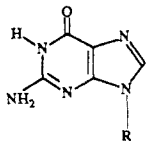
The synthesis and antiviral evaluation of a series of (±)-3,5-dihydroxypentyl nucleoside analogues related to acyclic nucleoside antiviral agents are reported. All purine and pyrimidine nucleoside analogues described in this paper have been obtained from 1-amino-5-(benzyloxy)pentan-3-ol. A synthesis of this amine is reported from 1-(benzyloxy)but-3-ene after epoxidation and regiospecific diethylaluminum chloride catalyzed opening of the epoxide by trimethylsilyl cyanide. The compounds were tested in vitro in infected MRC5 and CEM cells. None of the compounds exhibited antiviral activity against HSV-1, HCMV, and HIV-1 with the exception of the guanine derivative **7**, which inhibited the cytopathic effect of HSV-1 by 50% at 12.5 μg/mL.

The discovery of the potent and selective anti-HSV (herpes simplex virus) activity of acyclovir[1] (ACV) has stimulated extensive research in the synthesis of new acyclic nucleoside analogues in which the cyclic carbohydrate moiety has been replaced by acyclic chains mimicking the sugar portion of naturally occurring nucleosides.

Analogues **2–6** exhibit potent antiherpes virus activity in cell cultures[4,5,7-11] and some of them (DHPG, DHBG, BRL 39123) were found to be superior to ACV in infectious animal models.[2,3,7,12] ACV, DHPG, BRL 39123, and 2 HM-HBG are also inhibitory of varicella zoster virus (VZV).[5,8,10]



1 : R = $CH_2OCH_2CH_2OH$ (ACV)

2 : R = CH_2OCHCH_2OH (CH_2OH) (DHPG)

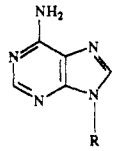
3 : R = $CH_2CH_2CHCH_2OH$ (OH) (R-DHBG)

4 : R = $CH_2CH_2CH_2CH_2OH$ (HBG)

5 : R = $CH_2CH_2CHCH_2OH$ (CH_2OH) (BRL 39123)

6 : R = $CH_2CHCH_2CH_2OH$ (CH_2OH) ((+/-)2HMHBG)

7 : R = $CH_2CH_2CHCH_2CH_2OH$ (OH)



8 : R = CH_2CHCH_2OH (OH) ((S)-DHPA)

9 : R = $CH{=}C{=}CHCH_2OH$ ((+/-)adenallene)

10 : R = $CH_2CHOCH_2PO_3H_2$ (CH_2OH) (S-HPMPA)

11 : R = $CH_2CH_2OCH_2PO_3H_2$ (PMEA)

12 : R = $CH_2CH_2CHCH_2CH_2OH$ (OH)

These acyclic nucleosides share the common property[10] of being preferentially phosphorylated by the virus-coded thymidine kinase.[18] A second level of selectivity is achieved through the inhibitory activity of their triphosphate form against the virus-coded DNA polymerase while cellular polymerases are much less affected.

However, activity of acyclic nucleosides is not restricted

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