Interphenylene 7-Oxabicyclo[2.2.1]heptane Oxazoles. Highly Potent, Selective, and Long-Acting Thromboxane A_2 Receptor Antagonists†

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A series of interphenylene 7-oxabicyclo[2.2.1]heptane oxazoles (2) were prepared and evaluated for their thromboxane (TxA_2) antagonistic activity in vitro and duration of action in vivo. Examination of the carboxyl side chain indicated that the interphenylene ring substitution pattern and, to a lesser extent, chain length were important factors in determining TxA_2 antagonistic potency. For the carboxyl side chain, ortho substitution, a single methylene spacer between the interphenylene and oxabicycloheptane rings, and a propionic acid side-chain length were determined to be optimal. With respect to the oxazole side chain a wide range of amide substituents with diverse structures and lipophilicities were compatible with potent antagonistic activity. Finally, an acidic functional group on the α-chain and a hydrogen bond acceptor on the 4-position of the oxazole ring were critical for potent activity. From the analogs prepared **42** {BMS-180,291: [(+)-1*S*-(1α,2α,3α,4α)]-2-[[3-[4-[(*n*-pentylamino)carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]benzenepropanoic acid} was found to be a potent, selective, and orally-active TxA_2 antagonist with a long duration of action and has been selected as a candidate for clinical development. In human platelet-rich plasma, **42** inhibited arachidonic acid (800 μM) and U-46,-619 (10 μM) induced aggregation with I_{50} values of 7 and 21 nM, respectively. Radioligand binding studies of **42** with [^{3}H]-SQ 29,548 showed a K_d value of 4.0 ± 1.0 nM in human platelet membranes. Both in vitro and in vivo studies indicated **42** was devoid of direct agonistic activity. In vivo **42** (0.2 mg/kg, po) showed extended protection (T_{50} = 14.4 h) from U-46,619 (2 mg/kg, iv) induced death in mice, and a single oral dose of **42** (3 mg/kg) abolished U46,619-induced platelet aggregation ex vivo in African green monkeys for >24 h.

Introduction

Thromboxane A_2 (TxA_2)[1] is an extremely potent, short-lived endogenous mediator which induces both platelet activation and aggregation and smooth muscle contraction. It has been implicated as a potential contributor in the pathogenesis of thrombotic, renal, and vasospastic diseases.[2] Preclinical studies employing stable, selective TxA_2 agonists and antagonists have suggested that TxA_2 antagonists may be useful in the treatment of these disorders and that antagonists possessing suitable pharmacokinetic and pharmacodynamic properties may serve as useful therapeutic agents.[2b,3]

As part of an effort to develop a potent, selective, and orally-active TxA_2 antagonist with a clinically useful duration of action, we previously described a novel series of interphenylene 7-oxabicyclo[2.2.1]heptane TxA_2 antagonists, **1** (Figure 1), with semicarbazone ω chains.[4] From this series we identified orally-active analogs which exhibited potent antagonistic activity and a long duration of action. However, we were reluctant to pursue further development of this series due to the potential toxicity associated with semicarbazones. We describe here the synthesis and biological evaluation of a related series of potent, long-acting interphenylene 7-oxabicyclo[2.2.1]-heptane analogs, **2** (Figure 1), in which a heterocyclic semicarbazone surrogate, the 4-amido oxazole,[5] has replaced the semicarbazone functionality in the ω chain.[6,7]

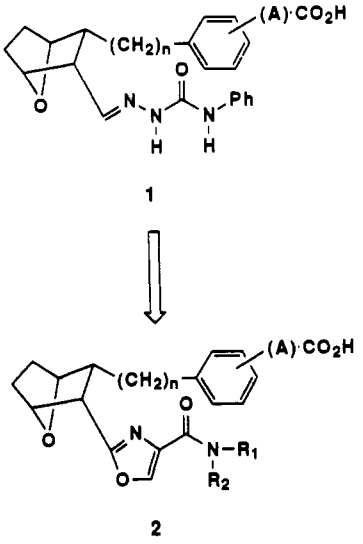

Figure 1.

Synthesis

Interphenylene 7-oxabicyclo[2.2.1]heptane oxazoles **2** were available through the intermediate alcohol–esters, as shown in Scheme I, by elaboration of 7-oxabicyclo-[2.2.1]heptane tetrahydrofuranol **3a**.[8]

Alcohol–Esters. The general methodology for the preparation of alcohol–ester intermediates for interphenylene 7-oxabicycloheptane oxazoles in Tables I and II from lactols **3a** and **3b** by addition of the appropriate aryllithium (2.2 equiv) followed by carboxyl side chain (α-chain) elaboration has been described previously[4] and is shown in Scheme II. Although this methodology was

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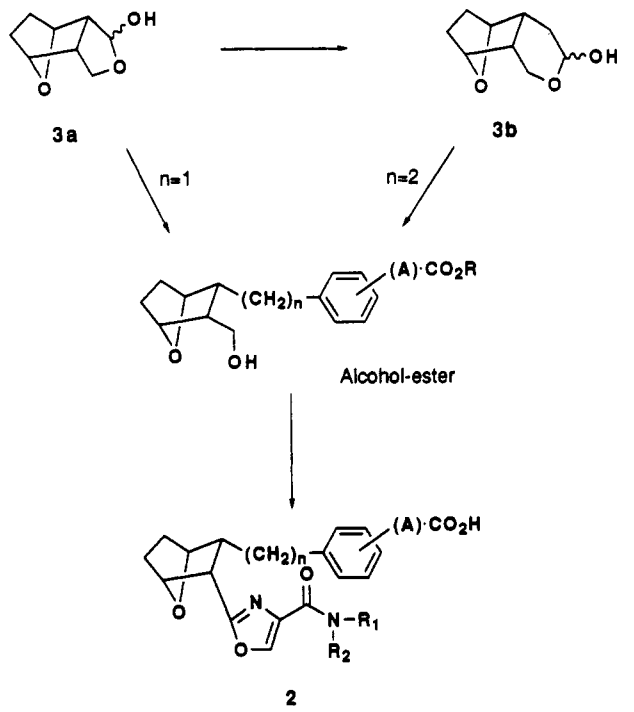
Scheme I



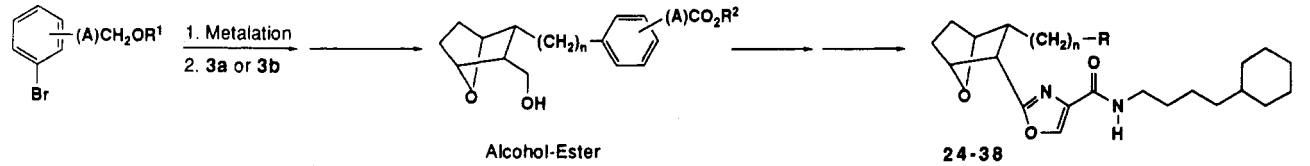
2

viable for early explorations of interphenylene substitution pattern and carboxyl side chain length, it carried the liability of requiring 2.2 equiv of aryllithium reagent to introduce a single phenyl ring and in the case of the optimal substitution pattern, the ortho-substituted propionic acid analogs, the additional disadvantage of affording an intermediate diol addition product **5**/**epi-5** (1:1 mixture of alcohol epimers) which underwent hydrogenolysis to **6** in low yield. The overall yield of alcohol–ester **8** from lactol **3a** based on lactol was 40% and based on aryl bromide **4** was only 16%. Alternatively we have explored the use of Grignard reagents in this sequence and found that we could successfully employ only 1.3 equiv of arylmagnesium bromide **4a** if we initially deprotonated lactol **3a** with ethylmagnesium bromide (0.95 equiv). In contrast to the aryllithium additions, the diol addition product was obtained as single crystalline alcohol epimer **5** in 88% yield which was smoothly reduced to **6**. The overall yield from lactol **3a** to alcohol–ester **8** was 60–65% based on lactol and 46% yield based on aryl bromide **4**. This sequence for preparing key intermediate **8** is shown in Scheme III. The alcohol–ester for benzoic acid analog **29** (Table I) was prepared by a modified route employing an ortho-metalated oxazoline. As shown in Scheme IV lactol **3a** was added to lithiated oxazoline **9**[9] to afford oxazoline **10**. Acid hydrolysis of **10** to give **11** followed by hydrogenolysis and Fisher esterification of the resulting acid afforded alcohol–ester **12**. Finally, one of the early examples, meta-substituted analog **26**, was prepared by similar methodology but in a substantially different sequence of steps involving elaboration of the oxazole side chain (ω chain) prior to the oxidation of the α side chain (see supplementary material).

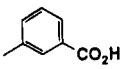
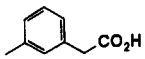
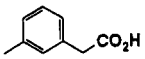
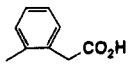
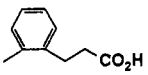
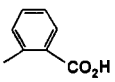
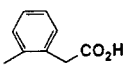
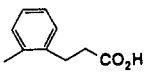
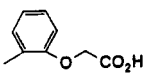
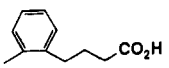
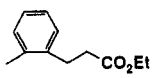
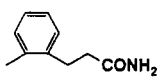
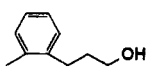
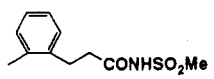
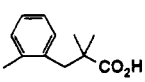
Oxazole Synthesis. The carbinol side chains of the intermediate alcohol–esters were elaborated to 4-amido-substituted oxazoles as exemplified for the conversion of alcohol–ester **8** to **31** (SQ 33,961) by the two routes shown in Schemes V and VI. Scheme V shows a convergent route in which the carbons required for the oxazole side chain were introduced as acyclic serine amide **14**. Alternatively, Scheme VI shows a more flexible route in which the carbons for the oxazole chain were introduced in two steps employing L-serine benzyl ester then coupling with 4-cyclohexylbutylamine. Both routes form the oxazole ring from an acyclic precursor by intramolecular cyclization to an intermediate oxazoline followed by oxidation to the oxazole. The route shown in Scheme VI facilitated the preparation and examination of a number of *N*-amide-substituted analogs (see Table II) employing advanced intermediate oxazole acid **21**. For both, alcohol–ester **8** was oxidized under Jones conditions to afford acid–ester **13** in 83% yield. In Scheme V, acid–ester **13** was coupled with serine amide **14** using water-soluble carbodiimide (WSC)/HOBT conditions to afford N-acylated serine amide **15** in quantitative yield. Amide **15** was cyclized to acid-sensitive oxazoline **16** using diisopropyl azodicarboxylate/triphenylphosphine/carbon tetrachloride and employing diisopropylethylamine as a base in acetonitrile. Oxazoline formation was relatively clean with a minor amount (<5%) of acrylate formation as a result of β-elimination. On larger scale serine amide **15** was more conveniently derivatized as the mesylate ($MsCl/Et_3N/CH_2Cl_2$, 0 or −20 °C) and then refluxed with excess powdered potassium carbonate in acetone to cleanly afford oxazoline **16**. In some cases, it was also possible to cyclize the crude mesylate by simple treatment with excess triethylamine (2 equiv, CH_2Cl_2, 25 °C). Oxazoline **16** was oxidized to oxazole **17** in 66% yield employing a novel oxidation protocol which involved treatment of **16** with a mixture of copper(II) bromide and DBU in 1:1 ethyl acetate/chloroform at room temperature. Experimentally, a solution of the oxazoline (1 equiv) in chloroform was added to a mixture of copper(II) bromide (2 equiv) and DBU (4 equiv) in ethyl acetate under argon at room temperature.[7,10] In general the reactions were sluggish and required the introduction of additional portions of both copper(II) bromide and DBU after 18–24 h. Heating to 45 °C resulted in a marked reduction in yield. In most cases 4–5 equiv of copper(II) bromide and 8–10 equiv of DBU were necessary to consume oxazoline, and yields of oxazole were 50–75%. Base hydrolysis of **17** followed by recrystallization from acetonitrile afforded desired acid **31** as a stable white solid. The ^1H NMR ($CDCl_3$) spectrum of oxazole **31** exhibited a characteristic downfield resonance at δ 8.12 (s, 1 H), and the ^{13}C NMR ($CDCl_3$) spectrum exhibited resonances at 160.8, 140.9, 136.0 for the oxazole ring.

In Scheme VI oxabicycloheptane acid **13** was coupled with L-serine benzyl ester to afford N-acylated serine ester **18**. Cyclization under Mitsunobu conditions gave oxazoline **19** in 75% yield. In contrast to the conversion of **15** to **16**, attempts to prepare oxazoline **19** by mesylation followed by base-induced cyclization led predominately to acrylate formation. Unlike the oxidation of amide-substituted oxazoline **16** with copper(II) bromide/DBU, the oxidation of ester-substituted oxazoline **19** was relatively rapid (<24 h) at room temperature and required only 2–3 equiv of copper(II) bromide and 4–6 equiv of DBU. Although the oxidation was seemingly more facile, the yield of oxazole **20** (65%) was comparable to the yields for the oxidations of amide-substituted oxazolines. Alternatively, oxazoline **19** was converted to oxazole **20** in methylene chloride by the addition of excess nickel peroxide reagent[11] (4–5 wt equiv) at room temperature in 48% yield.[12] Nickel peroxide was added portionwise while monitoring disappearance of starting material by TLC. Generally the reactions were rapid and afforded a single nonpolar product although the isolated yields were only

Table I. Synthesis of Interphenylene 7-Oxabicycloheptane Oxazoles: Carboxyl Side-Chain Modifications



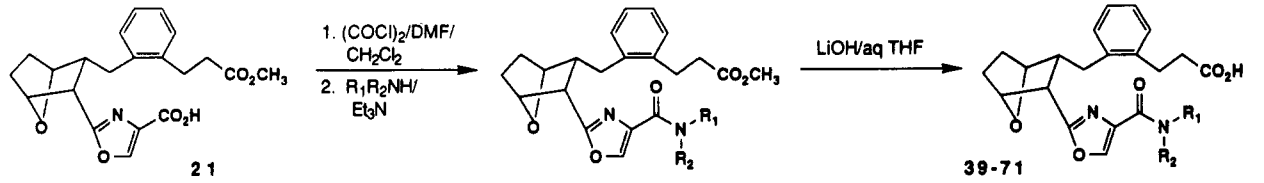
Alcohol-Ester 24-38

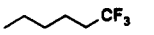
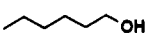
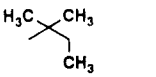
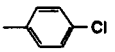
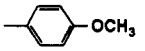
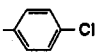
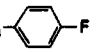
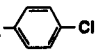
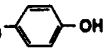
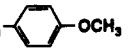
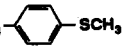
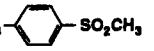
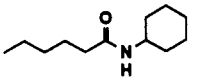
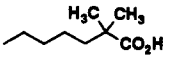
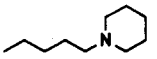
			lactol **3a** or **3b** to alcohol–ester		alcohol–ester to oxazole			
no.	R	*n*	method[a]	% yield	method[b]	% yield	mp, °C	formula[c]
24		2	A	30	A	23	160–161	$C_{29}H_{38}N_2O_5 \cdot 0.5H_2O$
25		2	A	37	A	44	50–58	$C_{30}H_{40}N_2O_5 \cdot 0.75H_2O$
26		1	B	48	*d*	*d*	141–145	$C_{29}H_{38}N_2O_5$
27		2	A	37	A	42	58–63	$C_{30}H_{40}N_2O_5 \cdot 0.5H_2O$
28		2	B	46	A	11	120–122	$C_{31}H_{42}N_2O_5 \cdot 0.7H_2O$
29		1	C	44	B	28	139–141	$C_{28}H_{36}N_2O_5 \cdot 0.43H_2O$
30		1	D	35	A	19	130–132	$C_{29}H_{38}N_2O_5 \cdot 0.75H_2O$
31		1	E	61	A	45	164–165	$C_{30}H_{40}N_2O_5$
32		1	F	33	C	18	190–191	$C_{29}H_{28}N_2O_6$
33		1	F	10	D	22	130–132	$C_{31}H_{42}N_2O_5$
34		1					130–131	$C_{32}H_{44}N_2O_5 \cdot 0.35H_2O$
35		1					173–174	$C_{30}H_{41}N_3O_4$
36		1					119–121	$C_{30}H_{42}N_2O_5$
37		1					154–156	$C_{31}H_{43}N_3S \cdot 0.30H_2O$
38		1	D	53	C[e]	17	133–135	$C_{32}H_{44}N_2O_5$

[a] Method A: (1) tBu/Li/ether, −78 or −100 °C then lactol **3a** or **3b**/THF, −78 to 0 °C; (2) Ac_2O/py, 0–25 °C; (3) CrO_3/H_2SO_4/acetone, 25 °C; (4) CH_2N_2/ether, 0 °C; (5) 10% Pd–C/H_2 (1 atm)/aqueous $HClO_4$/MeAc, 25 °C; (6) K_2CO_3/acetone/MeOH, 0 °C or tBuOK (1.1 equiv)/MeOH, 0–25 °C then CH_2N_2/ether, 25 °C. Method B: (1) tBuLi/ether, −78 °C then lactol **3a**/THF, −78 to 0 °C; (2) 20% $Pd(OH)_2$–C/H_2 (1 atm)/HOAc; (3) Ac_2O/DMAP/py, 25 °C; (4) CrO_3/H_2SO_4/acetone, 0–25 °C; (5) NaOH/aqueous THF, 25 °C; (6) HCl/MeOH, 0 °C. Method C: see Scheme IV. Method D: (1) Mg/THF, reflux then lactol **3a**/EtMgBr, 0–25 °C; (2) 20% $Pd(OH)_2$–C/H_2 (1 atm)/HOAc; (3) Ac_2O/py, 0–25 °C; (4) *n*-Bu_4NF/THF, 25 °C; (5) Dess-Martin periodinane/CH_2Cl_2, 25 °C; (6) K_2CO_3/NIS/MeOH, 25 °C; (7) K_2CO_3/MeOH, 25 °C. Method E: see Scheme III. Method F: see ref 4. [b] Method A: (1) CrO_3/H_2SO_4/acetone, 25 °C; (2) WSC/HOBT/Et_3N/serine amide **14**/DMF, 0–25 °C; (3) MsCl/$(iPr)_2NEt$/CH_2Cl_2, 0 °C; (4) K_2CO_3 (3 equiv)/acetone, 65 °C; (5) $CuBr_2$/DBU/EtOAc/$CHCl_3$, 25 °C; (6) LiOH/aqueous THF, 25 °C. Method B: (1) CrO_3/H_2SO_4/acetone, 25 °C; (2) WSC/HOBT/Et_3N/serine amide **14**/DMF, 0–25 °C; (3) MsCl/$(iPr)_2NEt/CH_2Cl_2$, 0 °C; (4) K_2CO_3 (3 equiv)/acetone, 65 °C; (5) NiO_2/CH_2Cl_2, 25 °C; (6) NaOH/aqueous THF, 25 °C. Method C: (1) CrO_3/H_2SO_4/acetone, 25 °C; (2) WSC or DCC/HOBT/Et_3N/L-serine benzyl ester·HCl/THF, 0–25 °C; (3) $PPh_3/CCl_4/(iPr)_2NEt/CH_3CN/CH_2Cl_2$, 25 °C; (4) NiO_2/CH_2Cl_2, 25 °C; (5) 20% $Pd(OH)_2$–C/H_2 (1 atm)/EtOAc; (6) $(COCl)_2$/cat. DMF/CH_2Cl_2, 25 °C then cyclohexylbutylamine hydrochloride/Et_3N, 0 °C; (7) LiOH/aqueous THF, 25 °C. Method D: (1) CrO_3/H_2SO_4/acetone, 25 °C; (2) WSC/HOBT/Et_3N/serine amide **14**/DMF, 0–25 °C; (3) $PPh_3/CCl_4/(iPr)_2NEt/CH_3CN/CH_2Cl_2$, 25 °C; (4) $CuBr_2$/DBU/EtOAc/$CHCl_3$, 25 °C; (5) LiOH, aqueous THF, 25 °C. [c] Acceptable C, H, N and where applicable S combustion analyses were obtained for **24–38**; water content was not experimentally determined. [d] See supplementary material. [e] Oxazoline oxidation performed using $CuBr_2$/DBU/EtOAc/$CHCl_3$, 25 °C.

35–60%. The benzyl ester of oxazole **10** was selectively cleaved by hydrogenolysis in the presence of palladium hydroxide on carbon to afford key intermediate oxazole acid–ester **21** in near quantitative yield. Oxazole acid **21** was converted to the corresponding acid chloride by treatment with oxalyl chloride and catalytic DMF in methylene chloride then coupled to 4-cyclohexylbutylamine in the presence of triethylamine to give ester–amide **17** in 85% yield. In general, the oxazole amides in Table II were available from oxazole acid **21** and the appropriate amine in 60–95% yields using this procedure. As described previously, base hydrolysis of the esters provided the

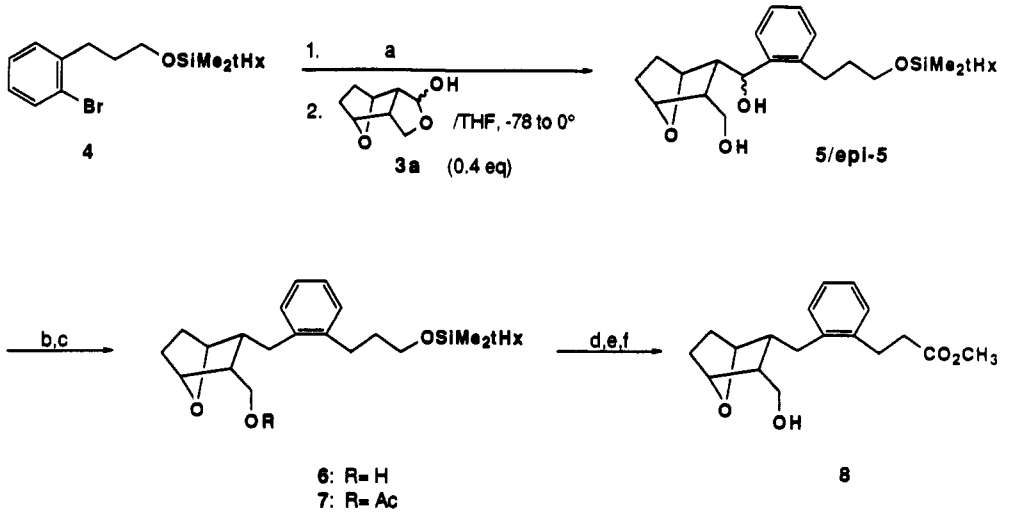
Table II. Synthesis and Lipophilicity of Interphenylene 7-Oxabicycloheptane Oxazoles: ω Side-Chain Amide Substitutions



no.	R_1	R_2	% yield ester	% yield acid	mp, °C	formula[a]	log P[b]
39	H	H	61	62	>200	$C_{20}H_{22}N_2O_5$	-0.78
40	H	CH_3	58	100	194-195	$C_{21}H_{24}N_2O_5$	-0.11
41	H	*n*-C_3H_5	86	84	165-168	$C_{23}H_{28}N_2O_5$	0.40
42	H	*n*-C_5H_{11}	84	85	148-150	$C_{25}H_{32}N_2O_5$	1.61
43	CH_3	*n*-C_5H_{11}	66	97	oil	$C_{26}H_{34}N_2O_5$	1.00
44	H	*n*-C_7H_{15}	76	84	134-137	$C_{27}H_{36}N_2O_5$	2.88
45	H	*n*-$C_{10}H_{21}$	77	96	145-147	$C_{30}H_{42}N_2O_5 \cdot 0.10H_2O$	3.86
46	H	$-(CH_2)_5-C\equiv C-H$	82	54	143-144	$C_{27}H_{32}N_2O_5$	0.87
47	H		78	63	161-162	$C_{25}H_{29}F_3N_2O_5$	1.59
48	H		79	86	136-139	$C_{25}H_{32}N_2O_6 \cdot 0.10H_2O$	1.07
49	H		85	85	128-132	$C_{25}H_{32}N_2O_5$	0.51
50	H	iPr	51	92	100-102	$C_{23}H_{28}N_2O_5$	0.05
51	H	tBu	92	83	155-156	$C_{24}H_{30}N_2O_5$	-0.02
52	H	$(CH_2)_2$tBu	84	81	160-162	$C_{26}H_{34}N_2O_5$	1.23
53	H	$(CH_2)_4$tBu	77	78	147-149	$C_{28}H_{38}N_2O_5 \cdot 0.25H_2O$	3.41
54	H		91	98	solid foam	$C_{26}H_{32}N_2O_5 \cdot 0.45H_2O$	0.89
55	H	$-(CH_2)_2-$ 	39	97	158-161	$C_{28}H_{36}N_2O_5$	1.03
31	H	$-(CH_2)_4-$ 	85	97	162-165	$C_{30}H_{40}N_2O_5$	3.93
56	CH_3	$-(CH_2)_4-$ 	72	79	solid foam	$C_{31}H_{42}N_2O_5 \cdot 0.25H_2O$	3.89
57	H		78	98	170-172	$C_{26}H_{26}N_2O_5$	1.19
58	H		66	98	220-221	$C_{26}H_{25}ClN_2O_5$	2.52
59	H		82	98	solid foam	$C_{27}H_{28}N_2O_5 \cdot 0.39H_2O$	0.95
60	H	$-(CH_2)_2-$ 	90	82	181-183	$C_{28}H_{30}N_2O_5$	0.98
61	H	$-(CH_2)_2-$ 	80	91	187-188	$C_{28}H_{29}ClN_2O_5$	1.55
62	H	$-(CH_2)_4-$ 	93	74	151-153	$C_{30}H_{34}N_2O_5$	1.80
63	H	$-(CH_2)_4-$ 	73	82	141-143	$C_{30}H_{33}FN_2O_5$	2.17
64	H	$-(CH_2)_4-$ 	83	98	133-135	$C_{30}H_{33}ClN_2O_5$	3.52
65	H	$-(CH_2)_4-$ 	99[c]	53[d]	212 dec	$C_{30}H_{34}N_2O_6$	1.49
66	H	$-(CH_2)_4-$ 	81	81	125-127	$C_{31}H_{36}N_2O_5$	2.49
67	H	$-(CH_2)_4-$ 	82	80	155-158	$C_{31}H_{36}N_2O_5S$	1.66
68	H	$-(CH_2)_4-$ 	91[e]	78	159-161	$C_{31}H_{36}N_2O_7S$	0.32
69	H		59	69	168-169	$C_{31}H_{41}N_3O_6$	1.18
70	H		71	53	123-125	$C_{28}H_{36}N_2O_7 \cdot 0.85H_2O$	0.50
71	H	 (Li salt)	74	95	lyophylate	$C_{29}H_{38}N_3O_5Li \cdot 2.05H_2O$	0.53

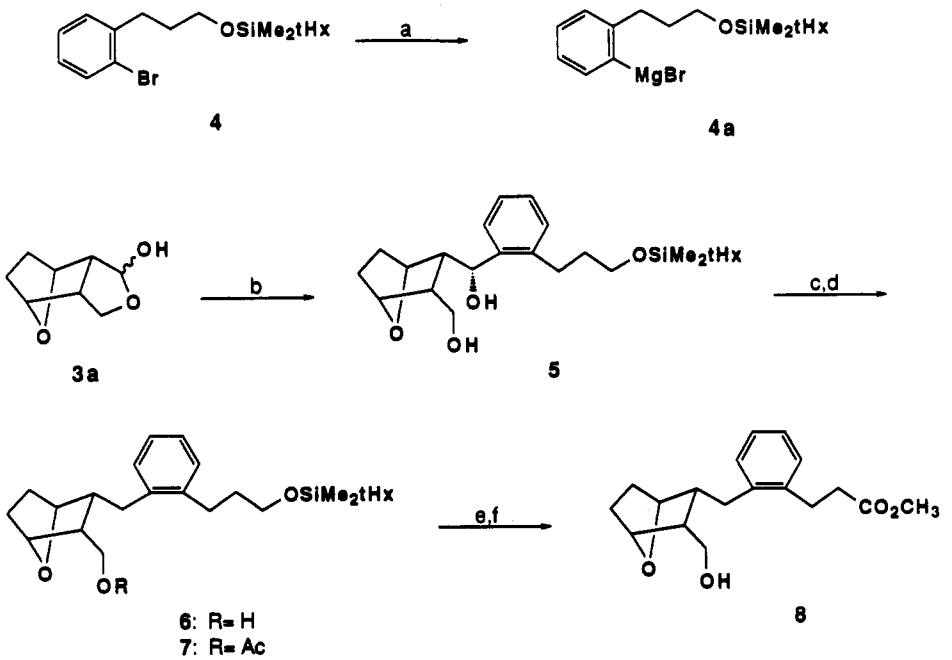
[a] Acceptable C, H N and where applicable S combustion analyses were obtained for 31, 39-71; water content was not experimentally determined. [b] Determined by RP-TLC at pH = 7 (see Experimental Section). [c] Coupled with the *O*-benzyl-protected phenol. [d] Ester hydrolysis followed by removal of the *O*-benzylphenol protecting group (10% Pd-C/H_2(1 atm)/MeOH/EtOAc). [e] Prepared from 67 methyl ester by oxone oxidation (aqueous THF/MeOH, 25 °C).

Scheme II[a]



[a] (a) tBuLi (1.7 equiv)/ether, −100 to 0 °C, 97%; (b) 20% $Pd(OH)_2$–C/H_2 (1 atm)/HOAc, 55%; (c) Ac_2O/DMAP/py, 25 °C; (d) CrO_3/H_2SO_4/acetone, 0 °C; (e) aqueous NaOH/THF, 25 °C; (f) HCl/MeOH, 0 °C, 74% from **6**.

Scheme III[a]



[a] (a) Mg/THF, reflux; (b) EtMBr (0.95 equiv)/THF, 0 °C then **4a** (1.3 equiv), 0–25 °C, 88%; (c) 20% $Pd(OH)_2$–C/H_2 (1 atm)/HOAc, 25 °C; (d) Ac_2O/py, 25 °C; (e) CrO_3/H_2SO_4/acetone, 25 °C; (f) HCl/MeOH, 0 °C, 70% from **5**.

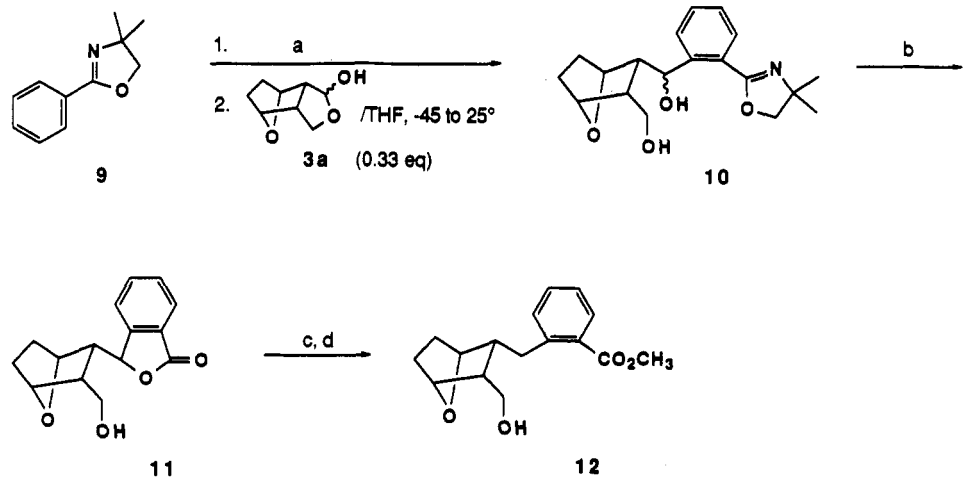
corresponding acids. Compounds **34–37** in which the α-chain carboxyl group has been modified were obtained from **31** by literature methods as described in the Experimental Section.

4-Amidooxazole Modifications. Shown in Table V are the 4-thioamide (**72**), 4-ester (**73**), 4-keto (**74**), and 4-alkenyl (**75**) oxazole analogs of **31** (SQ 33,961). The 4-thioamide analog **72** was obtained by treatment of ester **17** with phosphorus pentasulfide (2 equiv, pyridine (1.2 equiv), CH_2Cl_2, reflux, 84%) followed by base hydrolysis of the α-chain methyl ester (LiOH, aqueous THF, 25 °C, 88%). The 4-ester analog **73** was prepared as shown in Scheme VII by initial conversion of acid **31** to benzyl ester **22**. Treatment of **22** with dinitrogen tetraoxide afforded a stable isolable crude *N*-nitrosoamide as a bright yellow oil which upon thermolysis in dioxane gave rearranged diester **23**.[13] Selective cleavage of the α-chain benzyl ester yielded desired acid–ester **73**. The 4-keto analog **74** was prepared in low yield by addition of (5-cyclohexylpentyl)-zinc chloride (1 equiv) to the acid chloride generated from oxazole acid **21** (benzene/ether, 25–80 °C, 10%) followed by base hydrolysis of the α-chain methyl ester (LiOH, aqueous THF, 25 °C, 81%). The 4-alkenyl analog **75** was obtained by a straightforward but lengthy sequence which involved Wittig olefination of an oxazole-4-carboxaldehyde intermediate (see supplementary material). Finally, carbinol **76** was prepared by lithium tri-*tert*-butoxyaluminum hydride (2.5 equiv, THF, 0 °C, 94%) reduction of the acid chloride generated from acid–ester **21** followed by base hydrolysis of the α-chain methyl ester (LiOH, aqueous THF, 25 °C, 51%).

Structure–Activity and Discussion

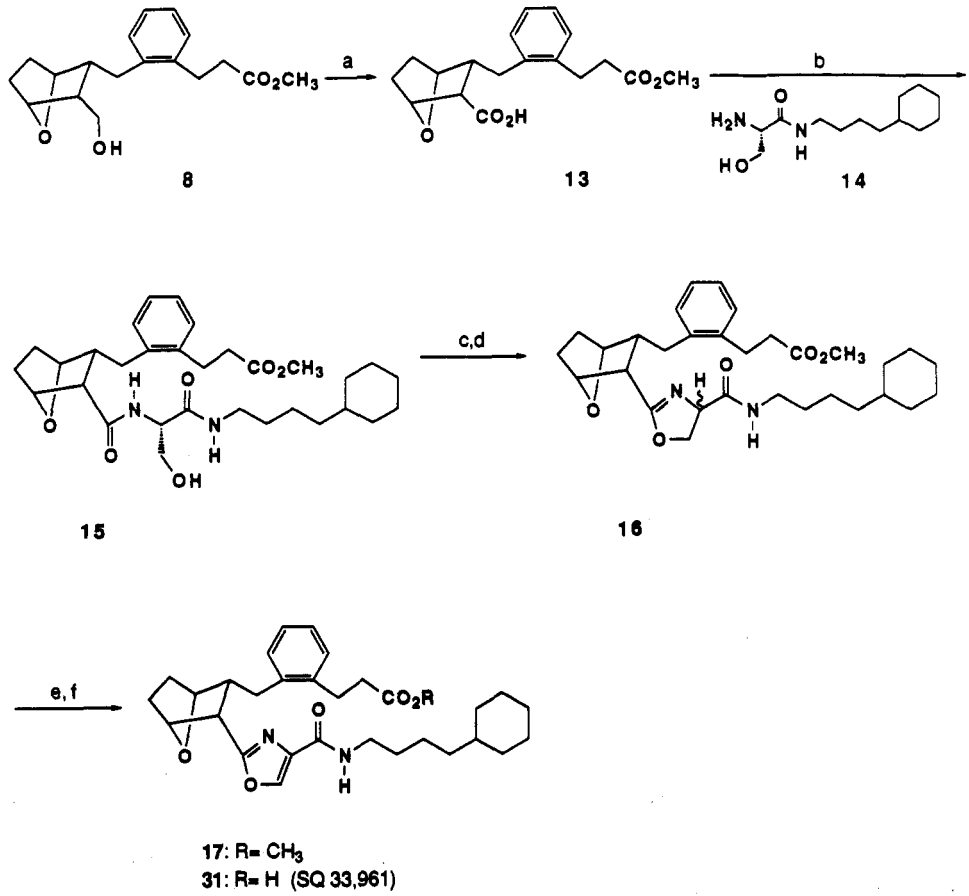
In Vitro. Interphenylene 7-oxabicycloheptane oxazoles were evaluated for their ability to inhibit platelet aggregation of human platelet-rich plasma in response to exogenous arachidonic acid (AAIPA, 800 μM) and/or TxA_2 mimetic U-46,619 (UIPA, 10 μM).[14] The data are summarized in Tables III–V and are expressed as I_{50} (nM) values, the concentration of antagonist required for 50%

Scheme IV[a]



[a] (a) BuLi/THF, −45 °C, 45%; (b) aqueous oxalic acid/THF, 25 °C, 98%; (c) 20% $Pd(OH)_2$–C/H_2 (1 atm)/HOAc; (d) HCl/MeOH, 25 °C, 51% from 11.

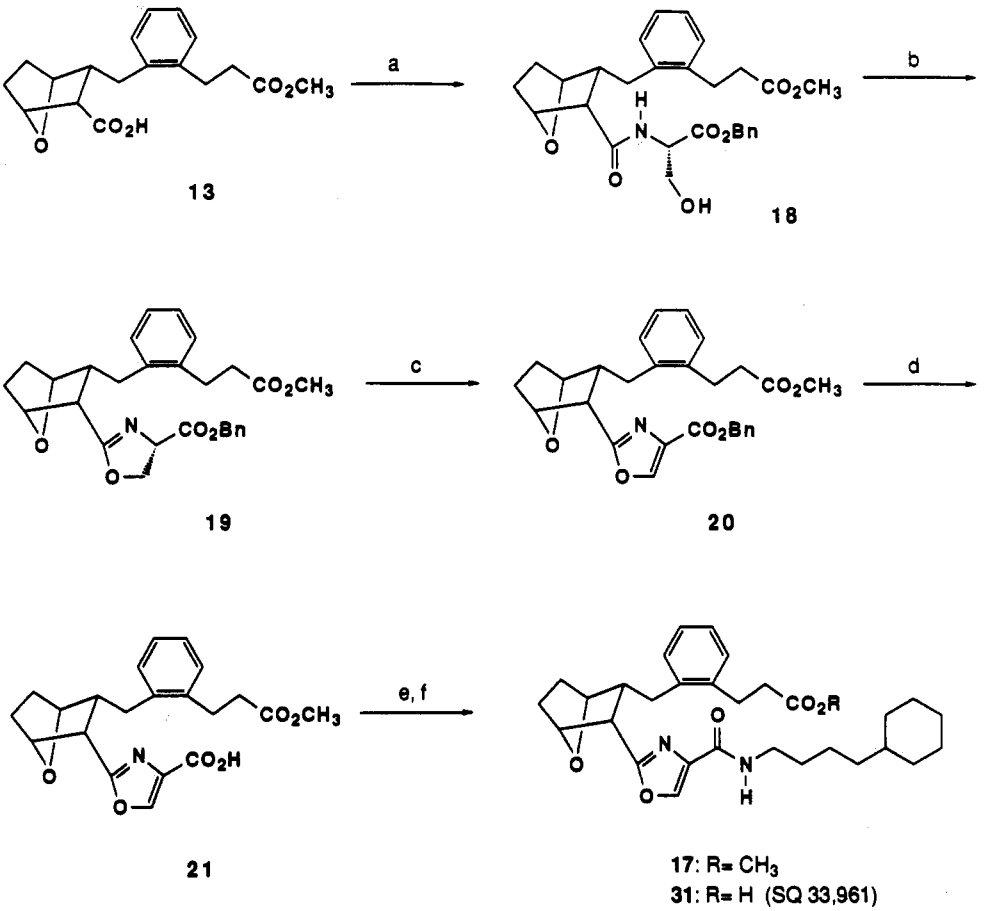
Scheme V[a]



[a] (a) CrO_3/H_2SO_4/acetone, 25 °C, 83%; (b) WSC/4-methylmorpholine/HOBT/DMF, 0–25 °C, 100%; (c) MsCl/Et_3N/CH_2Cl_2, 0 °C; (d) K_2CO_3 (4 equiv)/acetone, 65 °C, 90% from 15: (e) $CuBr_2$/DBU/$CHCl_3$/EtOAc, 25 °C, 66%; (f) aqueous NaOH/MeOH/THF, 25 °C, 89%.

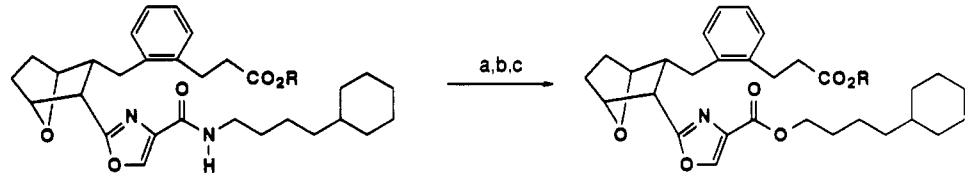
inhibition of platelet aggregation. For comparison purposes, GR32191[15] and BM13.505[16] showed AAIPA I_{50} values of 33 and 730 nM and UIPA I_{50} values of 59 and 1600 nM, respectively. In addition, all oxazoles were evaluated for their ability to inhibit platelet aggregation in response to exogenous adenosine diphosphate (ADP, 20 μM) and exhibited I_{50} values greater than 1000 μM. In most cases oxazoles with reasonable platelet inhibitory activity were also evaluated for their ability to inhibit the specific binding of [^{3}H]-SQ 29,548 to TxA_2 receptors in human platelet membranes.[17] The data are expressed as inhibition constants (K_d, nM) calculated from their individual I_{50} values and establish that platelet inhibitory activity is the result of binding to the TxA_2 receptor. For comparison purposes, GR32191 and BM13.505 showed K_d values of 2.0 and 11.3 nM with slope factors of 1.1 and 1.0, respectively. Table III shows the effect of carboxyl side-chain modifications in the interphenylene oxabicycloheptane oxazole series on TxA_2 antagonistic potency in vitro. In particular, compounds **24–33** examine the effect of interphenylene substitution pattern and carboxyl side-chain length on potency. The data establish that ortho substitution is generally preferable to meta substitution and that a single methylene spacer rather than an ethylene spacer between the oxabicycloheptane and interphenylene rings provides an increase in potency (**25** vs **26**, **27** vs **30**,

Scheme VI[a]



[a] (a) DCC/HOBT/Et_3N/DMF, 0–25 °C, 81%; (b) Ph_3P/CCl_4/DIPEA/CH_3CN, 25 °C, 77%; (c) $CuBr_2$/DBU/$CHCl_3$/EtOAc, 25 °C, 65%; (d) 20% $Pd(OH)_2$–C/H_2(1 atm)/EtOAc, 94%; (e) $(COCl)_2$/cat DMF/CH_2Cl_2, 25 °C then cyclohexylbutylamine/Et_3N/CH_2Cl_2, 0 °C, 85%; (f) LiOH/aqueous THF, 25 °C, 97%.

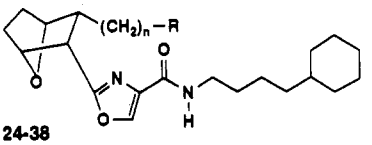
Scheme VII[a]



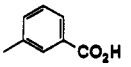
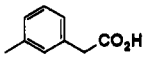
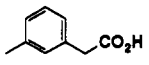
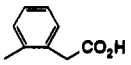
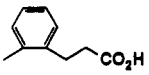
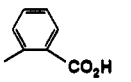
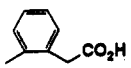
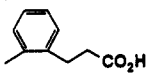
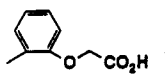
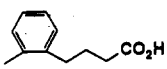
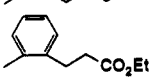
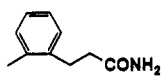
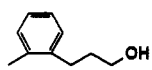
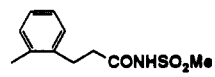
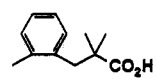
[a] (a) K_2CO_3/BnBr/DMF, 25 °C, 85%; (b) $NaNO_2$/HOAc/Ac_2O, 25 °C then dioxane, 95 °C, 56%; (c) 10% Pd–C/H_2 (1 atm)/EtOAc, 79%.

28 vs 31). Within the ortho-substituted series the propionic acid side-chain length was found to maximize antagonistic activity although a surprisingly small 26-fold difference in potency was observed in carboxyl side-chain lengths ranging from C_1 to C_4. Phenoxyacetic acid **32** established that an oxygen was tolerated in the carboxyl side chain with only a minimal loss in potency. These results are consistent with the structure–activity relationships reported previously in the interphenylene oxabicycloheptane semicarbazone series.[4] Compounds **34–37** in which the carboxylic acid functionality in the α-chain was modified demonstrated the requirement for an acidic group to maintain potent antagonistic activity. Finally, in contrast to previous results in the oxabicycloheptane series,[18] α,α-dimethyl analog **38** showed that substitution was tolerated adjacent to the carboxyl group and resulted in only a 2-fold loss of potency. The effects of modifying the 4-amido substituent on platelet TxA_2 antagonistic potency and receptor binding are summarized in Table IV. Examples **39–71** establish that a wide range of lipophilic amide substitution was tolerated with *n*-alkyl, branched alkyl, cyclic alkyl, unsaturated alkyl, and aromatic rings exhibiting potent antagonistic activity. Lipophilicity measurements (see Table II) showed that antagonistic potency showed only modest variations over an unusually large lipophilicity range with the more lipophilic analogs generally showing greater potency. For example, the *n*-alkyl series **41–45** exhibited only an 8-fold difference in antagonistic activity while the measured *P* values spanned nearly 4 orders of magnitude. In addition, moderately polar substituents such as hydroxy, methoxy, and thiomethyl on the ω side chain were compatible with potent antagonistic activity. A decrease in activity relative to **31** (SQ 33,961) was seen for the less lipophilic analogs; for example, unsubstituted 4-amido analog **39** or analogs **68–71** containing more polar sulfone, amide, acid, or amine functionalities in the ω side chain. Finally, examples **43** and **56** established that N,N-disubstituted amides were nearly equipotent with their monosubstituted analogs. Shown in Table V are the platelet TxA_2 antagonistic and receptor

Table III. Pharmacological Evaluation of Interphenylene 7-Oxabicycloheptane Oxazoles: α-Chain Modifications



24-38

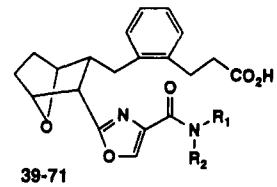
			in vitro			
			I_{50}, nM[a]			
no.	R	n	AAIPA	UIPA	K_d, nM:[b] platelet	slope factor
24		2	110		18.4	1.4
25		2	146		16.3	1.8
26		1	12	34	1.2	0.8
27		2	1575			
28		2	63	616		
29		1	52	171		
30		1	14	97	19	1.7
31		1	2	6	0.1	2.0
32		1	7	8	3.2	3.3
33		1	6		0.85	0.77
34		1	290			
35		1	1067			
36		1	1540		112	1.5
37		1	2		1.6	1.7
38		1	4	13	36	2.8

[a] Inhibition of arachidonic acid (800 μM) or U-46,619 (10 μM) induced platelet aggregation in human platelet-rich plasma (PRP), see ref 14. [b] Determined by measurement of the inhibition of specific binding of [^{3}H]-SQ 29,548 in human platelet membranes, see ref 17.

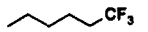
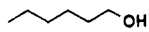
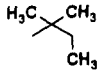
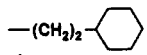
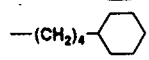
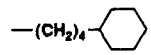
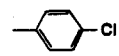
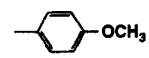
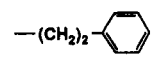
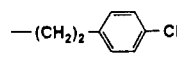
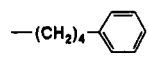
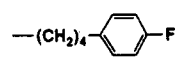
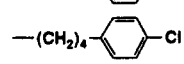
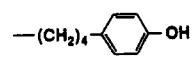
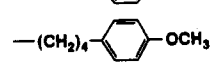
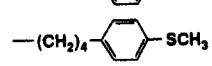
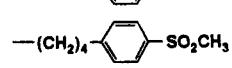
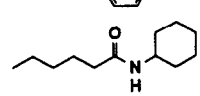
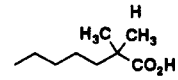
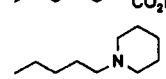
binding activities of a series of compounds, **72–75**, in which the amide in the ω side chain of **31** has been replaced by a thioamide, ester, ketone, and *trans*-ethylene bridge. The platelet results show that amide, thioamide, ester, and ketone are nearly equipotent; however, removal of the hydrogen bond acceptor as in **75** results in a >150-fold loss in potency. This is further supported by the poor antagonistic activity of carbinol analog **76** which is >700-fold less potent than unsubstituted 4-amido analog **39**. The data from this series clearly establish the requirement of a carbonyl or carbonyl-like hydrogen bond acceptor at the 4-position of the oxazole ring.

In Vivo. Interphenylene 7-oxabicycloheptane oxazoles exhibiting potent TxA_2 antagonistic activity in vitro were evaluated for their oral potency and duration of action in vivo by their ability to inhibit U-46,619 (2.0 mg/kg, iv) induced lethality in conscious mice as a function of time.[19] The data are summarized in Table IV and are expressed as a T_{50} (h) value, the calculated time for which half of the population survived at a given oral dose, 10 and/or 0.2 mg/kg. For comparison purposes, GR32191 and BM13.505 showed T_{50} values of 0.5 and 7.1 h at 0.2 mg/kg and 9.3 and 34.6 h at 10 mg/kg, respectively. The data established that carboxyl side-chain modifications affording potent interphenylene oxabicycloheptane oxazoles gave analogs which also exhibited oral activity and that propionic acid analog **31** in particular exhibited an exceptionally long duration of action, 22.5 and 49.6 h, at the 0.2 and 10 mg/kg doses, respectively. The analogs in Table IV show the effect on duration of action of ω-side chain amide substitution in the optimal ortho-substituted propionic acid series. In clear contrast to the results in vitro, no discernible trends were apparent in vivo based on overall lipophilicity or structure of the ω side chain amide

Table IV. Pharmacological Evaluation of Interphenylene 7-Oxabicycloheptane Oxazoles: ω-Side-Chain Amide Modifications

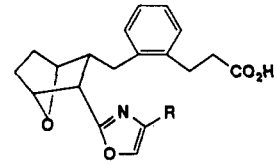


39-71

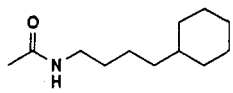
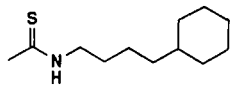
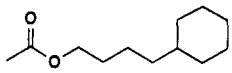
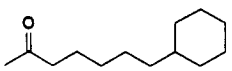
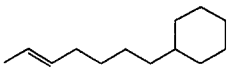
			in vitro					
			I_{50}, nM[a]				in vivo duration of action: T_{50}, h[c]	
no.	R_1	R_2	AAIPA	UIPA	K_d, nM:[b] platelet	slope factor	10 mg/kg po	0.2 mg/kg po
39	H	H	44	258				
40	H	CH_3	20	81	45	1.0		7.5
41	H	n-C_4H_9	8	53	10	0.9		2.3
42	H	n-C_5H_{11}	7	21	4.0	1.1	29.4	14.4
43	CH_3	n-C_5H_{11}	9		11	0.7		11.3
44	H	n-C_7H_{15}	2	13	0.2	1.5	27.4	9.5
45	H	n-$C_{10}H_{21}$	1	6	5.8	2.3		4.3
46	H	$-(CH_2)_5-C\equiv C-H$	14	31	4.7	1.3		11.1
47	H		12	29	4.8	1.4		
48	H		15	35	20	1.1		
49	H		12	30	0.8	1.1		8.8
50	H	-iPr	7	63	26	1.0		10.0
51	H	-tBu	12	61	19	1.0		7.4
52	H	$-(CH_2)_2$tBu	8	28	2.9	1.3		13.5
53	H	$-(CH_2)_4$tBu	8	35	0.6	1.3		36.5
54	H		3	25	4.5	1.0		8.3
55	H		2		0.7	1.0		8.3
31	H		2	6	0.1	2.0	49.6	22.5
56	CH_3		2					
57	H		12					
58	H		6					25.8
59	H		6					
60	H		9	30	0.7	0.9		4.0
61	H		4	14	1.3	1.3	38.7	22.7
62	H		4	13	0.3	1.3		20.0
63	H		4	11	3.9	2.9		22.5
64	H		4	13	0.2	1.7		18.6
65	H		12		0.5	1.5		
66	H		16	62	0.3	1.3		
67	H		6		2.9	2.3		
68	H		26					
69	H		27	82	22	1.2		
70	H		64					
71	H	 (Li salt)	30	137	22	1.2		

[a] Inhibition of arachidonic acid (800 μM) or U-46,619 (10 μM) induced platelet aggregation in human platelet-rich plasma (PRP), see ref 14. [b] Determined by measurement of the inhibition of specific binding of [^{3}H]-SQ 29,548 in human platelet membranes, see ref 17. [c] Protection from U-46,619-induced (2.0 mg/kg iv) death in mice as a function of time, see ref 19.

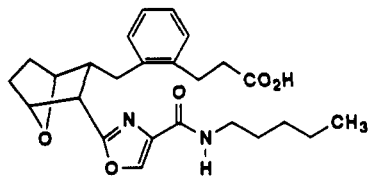
Table V. Interphenylene 7-Oxabicycloheptane Oxazoles: ω Side-Chain 4-Amide Modifications



72-76

no.	R	mp, °C	formula[a]	in vitro I_{50}, nM[b] AAIPA	in vitro I_{50}, nM[b] UIPA	in vitro K_d, nM:[c] platelet	in vitro slope factor
31		164–165	$C_{30}H_{40}N_2O_5$	2	6	0.1	2.0
72		135–137	$C_{30}H_{40}N_2O_4S$	2	9	10.6	3.2
73		135–137	$C_{30}H_{39}NO_6$	2	10	1.0	1.0
74		155–158	$C_{31}H_{41}NO_5$	4	11	0.05	0.62
75		solid foam	$C_{31}H_{41}NO_4 + 1.55H_2O$	320	2760		
76		137–138	$C_{20}H_{23}NO_5$	31000			

[a] Acceptable C, H, N and where applicable S combustion analyses were obtained for **31**, **72–76**; water content was not experimentally determined. [b] Inhibition of arachidonic acid (800 μM) or U-46,619 (10 μM) induced platelet aggregation in human platelet-rich plasma (PRP), see ref 14. [c] Determined by measurement of the inhibition of specific binding of [^{3}H]-SQ 29,548 in human platelet membranes, see ref 17.



42 (BMS-180,291)

Figure 2.

substituent. Relatively minor structural modifications, for example in the *n*-alkyl series **40–45**, seemed to affect the duration of action in an unpredictable manner. In some cases minor modifications resulted in large changes in duration. For example, for *tert*-butyl analogs **52** and **53** the introduction of two methylene groups resulted in a nearly 3-fold increase in T_{50} while in the case of phenyl analogs **60** and **61** a chloro substituent afforded a nearly 6-fold increase in T_{50}. In the absence of structural guidelines with which to predict duration of action, it was particularly critical to identifying analogs with a suitable pharmacokinetic profile that a wide number of amide substitution modifications were compatible with potent in vitro antagonistic activity. Evaluation of these analogs for TxA_2 agonist activity as measured by their ability to elicit airway and blood pressure responses in guinea pigs (10 mg/kg iv) and subsequent metabolism studies in vitro in rat liver microsomes and in vivo in rats and monkeys resulted in the selection of **42** for further development.

Pharmacological evaluation of **42** {BMS-180,291: [(+)-1*S*-(1α,2α,3α,4α)]-2-[[3-[4-[(*n*-pentylamino)carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]benzenepropanoic acid} showed it was a potent, selective, and orally-active TxA_2 receptor antagonist with a long duration of action.[7,20–22] In human PRP, **42** inhibited arachidonic acid-induced (800 μM) and U46,619-induced (10 μM) platelet aggregation with I_{50} values of 7 ± 1 and 22 ± 5 nM, respectively. The platelet aggregation response to U-46,-619 was antagonized in a noncompetitive manner while the platelet shape change response was antagonized competitively with a K_B = 11 ± 2 nM. At 1 mM **42** produced no inhibition of ADP (20 μM) or human α-thrombin (1 unit/mL) induced platelet aggregation in human PRP, TxA_2 synthase in human PRP, or cyclooxygenase activity in platelets or bovine seminal vesicles. Radioligand binding studies in human platelet membranes with the specific TxA_2 receptor radioligand [^{3}H]-SQ 29,-548 showed a K_d value of 4.0 ± 1.0 nM for **42** with a slope factor of 1.1. In rat aortas **42** competitively antagonized U-46,619-induced contractions with a K_B = 0.6 ± 0.1 nM. Importantly, **42** was devoid of direct agonistic activity in rat stomach and bovine coronary artery strips (10 μM) and produced no significant cardiovascular or pulmonary changes in vivo in rats (10 mg/kg iv), guinea pigs (10 mg/kg iv), and domestic pigs (3 mg/kg iv). Duration studies in conscious mice showed that **42** provided extended protection (T_{50} = 14.4 h, 0.2 mg/kg po) from U46,619-induced (2 mg/kg iv) death and a single oral dose of **42** (3 mg/kg) abolished U46,619-induced platelet aggregation ex vivo in African green monkeys for >24 h.

Conclusions

Interphenylene 7-oxabicyclo[2.2.1]heptane oxazoles were found to be potent, orally-active TxA_2 receptor antagonists with a long duration of action. Examination of the carboxyl side chain indicated that the interphenylene ring substitution pattern and to a lesser extent chain length were important factors in determining TxA_2 antagonistic potency. Ortho substitution, a single methylene spacer between the interphenylene and oxabicycloheptane rings, and a propionic acid side-chain length were determined to be optimal. On the ω-chain a wide range of amide substituents with diverse structures and lipophilicities

were compatible with potent antagonistic activity. Finally, an acidic functional group on the α-chain and a hydrogen bond acceptor on the 4-position of the oxazole ring were critical for potent activity. From the compounds examined **42** was found to be a potent, selective, and orally-active TxA_2 receptor antagonist with a long duration of action and has been selected as a candidate for clinical development.

Experimental Section

^1H NMR spectra reported were measured at 270 MHz and ^{13}C NMR spectra were measured at 67.5 MHz on JOEL CPF-270 or GX-270 spectrometers unless noted otherwise; 400-MHz ^1H NMR spectra were measured on a JOEL GX-400 spectrometer. Chemical shifts are reported in δ units and are relative to internal $(CH_3)_4Si$ assigned at δ 0.00 and/or $CHCl_3$ assigned at δ 7.24 or $CDCl_3$ assigned to δ 77.0. Infrared spectra (IR) were recorded on a Perkin-Elmer Model 983 infrared spectrophotometer and were calibrated with the 1601-cm^{-1} polystyrene absorption. Mass spectra (MS) were measured with a Finnigan TSQ mass spectrometer in chemical ionization (CI) mode. All compounds exhibited spectra consistent with their structure. Elemental combustion analyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer. All final compounds showed acceptable (±0.4%) elemental analysis. Melting points (mp) were measured on a Thomas-Hoover capillary melting point apparatus and are uncorrected. log *P* values were calculated from R_M values obtained using Whatman KC18F TLC plates eluting with acetone in 0.5 M aqueous potassium bromide buffered with 0.25 N triethylammonium phosphate to pH 7.3. The partition coefficients for seven oxabicycloheptane compounds with a range of lipophilicities were obtained by the traditional shake flask method at pH 7.0 and used to construct a calibration curve which was subsequently used to calculate log *P* values from R_M values.[23]

All reactions excluding hydrogenations were conducted under an argon atmosphere. All reagents and starting materials were obtained from commercial sources and used without further purification unless indicated; copper(II) bromide and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were obtained from Aldrich Chemical Co., chloroform (ethanol free), and ethyl acetate employed in oxazoline oxidations were Burdick and Jackson brand, tetrahydrofuran (THF), and ether were distilled under argon from benzophenone ketyl; methylene chloride was distilled under nitrogen from phosphorus pentoxide, triethylamine and HMPA were distilled from calcium hydride, WS-carbodiimide refers to ethyl (3-(3-dimethylamino)propyl)carbodiimide hydrochloride, aryl bromides were prepared from the appropriate bromobenzaldehydes as described previously[4] except in the case of **38** (see below). Flash chromatography[24] was performed using Merck silica gel 60. Thin-layer chromatography (TLC) was performed using E. Merck Kieselgel 60 F_{254} (0.25-mm) plates which were visualized with acidic aqueous ammonium molybdate/ceric sulfate stain and/or under UV_{254} illumination unless otherwise indicated.

Preparation of Aryl Bromide for 38. [3-(2-Bromophenyl)-2,2-dimethylpropoxy]dimethyl(1,1,2-trimethylpropyl)silane. To a solution of 17 mL (120 mmol) of diisopropylamine in 100 mL of THF cooled to −78 °C was added dropwise 44 mL (2.5 M in hexanes, 110 mmol) of *n*-butyllithium solution over ~15 min. The reaction mixture was stirred for an additional 30 min and then a solution of 10.2 g (100 mmol) of methyl isobutyrate in 10 mL of THF was added dropwise over 15 min. After 30 min 17 mL (98 mmol) of HMPA was added followed by a solution of 25.0 g (100 mmol) of 2-bromobenzyl bromide in 10 mL of THF over ~5 min. The reaction mixture was stirred at −78 °C for 1 h and then stored at 0 °C for 18 h. The resulting solution was quenched by addition of 5 mL of water and then concentrated in vacuo. The residue was partitioned between 150 mL of 1 M aqueous HCl solution and 150 mL of ether. The organic layer was separated, washed with two 150-mL portions of water and 50 mL of brine, dried (magnesium sulfate), and concentrated in vacuo to give a yellow oil. The crude material was purified by flash chromatography (12 × 10 cm, 1:19 ether/hexane) to afford 22.2 g (82%) of 3-(2-bromophenyl)-2,2-dimethylpropanoic acid methyl ester as a pale yellow liquid. TLC: R_f (silica gel, 1:9 ether/hexane) = 0.31.

A solution of 21.3 g (78.6 mmol) of methyl ester from above in 50 mL of THF and 50 mL of 3 M aqueous NaOH solution was stirred at 65 °C for 18 h and then cooled and concentrated in vacuo. The residue was cooled in an ice bath and acidified by slow addition of 15 mL of concentrated HCl. The resulting slurry was partitioned between 100 mL of water and 50 mL of ether. The aqueous layer was separated and extracted with an additional 50 mL of ether. The combined ether extracts were washed with 50 mL of brine, dried (magnesium sulfate), and concentrated in vacuo to give 19.8 g of 3-(2-bromophenyl)-2,2-dimethylpropanoic acid as a white solid, mp 84–86 °C. TLC: R_f (silica gel, 1:9 methanol/methylene chloride) = 0.56.

To a solution of the crude acid from above in 100 mL of dry THF cooled in an ice bath was added dropwise 44 mL (2.0M in THF, 88 mmol) of borane–dimethyl sulfide solution over 20 min. The reaction mixture was stirred at 0 °C for 2 h and then at room temperature for 20 h. The resulting solution was quenched by addition of 5 mL of water, stirred for 30 min, and then concentrated in vacuo. The residue was partitioned between 100 mL of 1 M aqueous HCl solution and 100 mL of ether. The organic layer was separated, washed with two 100-mL portions of 1 M aqueous NaOH solution and 50 mL of brine, dried (magnesium sulfate), and concentrated in vacuo to give an oil. The oil was dissolved in 50 mL of anhydrous methanol and concentrated in vacuo; the process was repeated with an additional 50 mL of methanol to afford 18.6 g (97%, two steps) of 3-(2-bromophenyl)-2,2-dimethylpropanol as a colorless oil. TLC: R_f (silica gel, 1:9 methanol/methylene chloride) = 0.70.

To a solution of 18.6 g (76.5 mmol) of the above alcohol, 15.0 g (84.3 mmol) of dimethylethylsilyl chloride, and 14 mL (100 mmol) of triethylamine in 100 mL of methylene chloride was added 1.84 g (15.1 mmol) of 4-(dimethylamino)pyridine at room temperature. The reaction mixture was stirred for 20 h then cooled in an ice bath and diluted with 100 mL of hexane to precipitate triethylamine hydrochloride. After 15 min the slurry was filtered. The filtrate was concentrated in vacuo and the residue partitioned between 10 mL of hexane and 100 mL of 1 M aqueous HCl solution. The organic layer was separated, washed with an additional 100 mL of 1 M aqueous HCl solution and 100 mL of water, dried (magnesium sulfate), and concentrated in vacuo to give an oil. The crude material was purified by flash chromatography (12 × 10 cm, 1:99 ether/hexane) to afford 23.9 g (81%) of [3-(2-bromophenyl)-2,2-dimethylpropoxy]dimethyl(1,1,2-trimethylpropyl)silane as a colorless liquid. TLC: R_f (silica gel, 1:4 ethyl acetate/hexane) = 0.69. IR (film): 2957, 1470, 1252, 1089, 848, 829 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.00 (s, 6 H), 0.78, 0.79, 0.81, 0.83 (overlapping s, 18 H), 1.56 (m, 1 H), 2.70 (s, 3 H), 3.16 (s, 3 H), 6.93 (dd, *J* = 7, 7, 1 H), 7.09 (dd, *J* = 7, 7, 1 H), 7.17 (dd, *J* = 2, 8, 1 H), 7.43 (d, *J* = 8 1 H). ^{13}C NMR ($CDCl_3$): δ −3.54, 18.6, 20.4, 23.9, 24.1, 25.2, 34.3, 37.9, 42.4, 71.0, 126.2, 126.6, 127.4, 132.5, 132.9, 139.2. MS (CI): *m/z* 386 ($M + H^+$). Anal. ($C_{19}H_{33}BrOSi$) C, H.

Preparation of Nickel Peroxide Oxidant.[11] To a solution of 130 g (490 mmol) of nickel(II) sulfate hexahydrate in 240 mL of water was added dropwise over ~45 min a solution of 360 mL of aqueous sodium hypochlorite (min. 5%) containing 42 g of sodium hydroxide. The reaction was mildly exothermic, and the temperature was maintained between 20 and 25 °C with a cool water bath. The catalyst formed as a black precipitate upon addition. The reaction mixture was stirred for an additional 2 h and then divided into two centrifuge bottles. The black solid was separated by centrifugation (2500 rpm/10 min), and the supernatant was decanted. The solid was slurried with 400 mL of ice-cold water and centrifuged. This washing procedure was repeated four additional times (pH = 10), and then the resulting black solid was collected on a Buchner funnel with the aid of a latex dam. The solid cake (144 g) was dried in a vacuum oven (25 °C) for 2 d. The resulting material (56.5 g) was crushed and then dried under oil pump vacuum for 24 h to afford 48.3 g (108%) of active nickel peroxide oxidant as a black powder.

Preparation of [1-Bromo-2-[3-[[dimethyl(1,1,2-trimethylpropyl)silyl]oxy]propyl]phenyl]magnesium (4a). To 19.0 g (782 mmol) of hammer-crushed magnesium turnings covered with 440 mL of THF at room temperature was added a crystal of iodine and then 2 mL of 1,2-dibromoethane. After several min 207 g (94% pure, 546 mmol) of aryl bromide **4**[4] was added in a single portion. Upon initiation the reaction mixture warmed

to reflux. The reaction mixture was intermittently cooled in a water bath to control foaming. An additional 120 mL of THF was introduced to insure product solubility, and then when the exotherm subsided the mixture was heated to reflux for 1 h. The resulting clear brown solution of Grignard **4a** was cooled to room temperature and used without further characterization.

Preparation of [1*S*-(1α,2α,3α,(*S),4α)]-α-[2-[3-[[Dimethyl-(1,1,2-trimethylpropyl)silyl]oxy]propyl]phenyl]-7-oxabicyclo[2.2.1]heptane-2,3-dimethanol (5).** To a solution of 63.1 g (405 mmol) of lactol **3a**[8] in 400 mL of THF cooled to 0 °C was added 192 mL (2.0 M in THF, 385 mmol, 0.95 equiv) of ethylmagnesium bromide solution over 30 min. The reaction mixture was stirred for 1 h at 0 °C, and then a solution of Grignard **4a** (~546 mmol, 1.3 equiv) was introduced via cannula over 1 h. The temperature was maintained at 0 °C for several hours and then warmed to room temperature, and an additional 50 mL of THF was introduced. After 6 d the reaction mixture was quenched by slow addition of 290 mL of saturated aqueous ammonium chloride solution.[25] The mixture was stirred for 2 h; the inorganic salts formed a white paste. To the mixture was added 1.0 L of methylene chloride, and the organic supernatant was decanted. The paste was washed with two 500-mL portions of methylene chloride, and then the organic layers were combined, dried (sodium sulfate), and concentrated in vacuo to give an oil.[26] The oil was quickly solubilized in 2.0 L of hexane and the solution refrigerated. The solid which formed was collected by filtration, washed with cold hexane, and dried under vacuum to afford 145.9 g (83%) of **5** as large white crystals, mp 99.5–100.5 °C. A second crop yielded an additional 8.7 g (5%) of **5**. The two crops were combined to give a total of 154.6 g (88%) of **5**. TLC: R_f (silica gel, 1:1 ethyl acetate/hexane) = 0.29. IR (KBr): 3393, 3327, 2957, 1464, 1250, 1092, 1030, 828 cm^{-1}. OR: $[\alpha]_D$ = +31° (c = 0.50 in chloroform). ^{1}H NMR ($CDCl_3$): δ 0.00, 0.01 (overlapping s, 6 H), 0.77, 0.79, 0.82 (overlapping s, 12 H), 1.20–1.85 (m, 8 H), 2.03 (dt, J = 5, 9, 1 H), 2.17 (broad s, 1 H), 2.22 (dd, J = 5, 9, 1 H), 2.53 (dt, J = 7, 14, 1 H), 2.69 (dt, J = 7, 14, 1 H), 3.55 (m, 5 H), 4.51 (d, J = 4, 1 H), 4.73 (d, J = 5, 1 H), 5.01 (broad s, 1 H), 7.12 (m, 3 H), 7.50 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ −3.3, 18.5, 20.3, 25.2, 28.0, 29.7, 29.7, 34.1, 34.2, 49.0, 51.7, 61.7, 62.2, 67.4, 77.3, 79.5, 125.5, 126.2, 127.3, 129.5, 138.7, 141.8. MS (CI): m/z 435 (M + H$^+$). Anal. ($C_{25}H_{42}O_4Si$) C, H.

Preparation of [1*S*-(1α,2α,3α,4α)]-2-[[3-(Hydroxymethyl)-7-oxabicyclo[2.2.1]hept-2-yl]methyl]benzenepropanoic Acid, Methyl Ester (8). A mixture of 140.5 g (324 mmol) of diol **5** and 28.1 g of 20% palladium hydroxide on activated carbon catalyst in 2.2 L of glacial acetic acid was stirred under an atmosphere of hydrogen (balloon) at room temperature for 24 h. The reaction mixture was filtered and the filtrate concentrated in vacuo to give an oil. The oil was solubilized in 500 mL of toluene and then concentrated in vacuo to remove residual acetic acid; this process was repeated two additional times to afford 150.9 g of crude alcohol **6** as an oil. TLC: R_f (silica gel, 1:1 ethyl acetate/hexane) = 0.46.

To a solution of 150.8 g of crude **6** in 200 mL of pyridine was added in one portion at room temperature 50 mL (530 mmol) of acetic anhydride. The addition was mildly exothermic. The reaction mixture was stirred for 16 h and then concentrated in vacuo to give a yellow oil. The oil was solubilized with 500 mL of toluene and then concentrated in vacuo to remove residual volatiles; this was repeated two additional times to afford 154.7 g of crude acetate **7** as a yellow oil. TLC: R_f (silica gel, 2:1 ethyl acetate/hexane) = 0.52; the R_f of **6** was 0.19.

To a solution of 154.7 g of crude **7** in 2.0 L of acetone was added at room temperature a total of 240 mL of Jones reagent[27] in ~50-mL portions at 10-min intervals. The reaction was exothermic, but cooling was not required. The reaction mixture was stirred for an additional 45 min and then quenched by addition of 50 mL of 2-propanol and stirring for 15 min. The chromium salts were separated by filtration through a pad of Celite and then rinsed with 1.0 L of acetone. The filtrate was concentrated in vacuo and the residue partitioned between 800 mL of chloroform and 400 mL of 3:1 water/brine. The organic layer was separated, and the aqueous layer was extracted with two 300-mL portions of chloroform. The organic layers were combined, dried (sodium sulfate), and concentrated in vacuo to give a yellow oil. The oil was solubilized at room temperature in 1.0 L of acidic methanol (prepared by slow addition of 10 mL of acetyl chloride to 1.0 L of methanol at room temperature). The solution was stirred for 15 h and then neutralized by addition of 30 g of solid sodium bicarbonate. The resulting mixture was dried (sodium sulfate) and concentrated in vacuo to give crude **8** as an oil. The crude material was purified by flash chromatography (1.5 kg, 2:1 ethyl acetate/hexane) followed by recrystallization (ethyl acetate/hexane) to afford 68.5 g (70% from **5**) of alcohol–ester **8** in two crops as large white crystals, mp 100–101 °C. TLC: R_f (silica gel, 2:1 ethyl acetate/hexane) = 0.23. IR (KBr): 3404, 2978, 2953, 2882, 1732, 1435, 1371, 1296, 1190, 1170 cm^{-1}. OR: $[\alpha]_D$ = +24° (c = 1.0 in chloroform). ^{1}H NMR ($CDCl_3$): δ 1.25–1.85 (m, 4 H), 2.17 (m, 3 H), 2.58 (m, 3 H), 2.82 (dd, J = 4, 14, 1 H), 2.97 (dd, J = 8, 8, 2 H), 3.67 (s, 3 H), 3.75 (m, 2 H), 4.23 (d, J = 5, 1 H), 4.53 (d, J = 5, 1 H), 7.17 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ 27.6, 29.5, 30.4, 35.0, 46.9, 49.1, 51.7, 61.8, 79.5, 126.4, 126.5, 128.9, 129.6, 138.5, 139.2, 173.4. MS (CI): m/z 305 (M + H)$^+$. Anal. ($C_{18}H_{24}O_4$) C, H.

Preparation of [1*S*-(1α,2α,3α,4α)]-2-[[3-(Hydroxymethyl)-7-oxabicyclo[2.2.1]hept-2-yl]methyl]benzoic Acid, Methyl Ester (12). To a solution of 7.22 g (41.3 mmol) of oxazoline **9**[9] in 70 mL of THF cooled to −45 °C was added dropwise 15 mL (2.5M in hexanes, 38 mmol) of n-butyllithium solution over 10 min. The reaction mixture was stirred for 3.5 h, and 2.15 g (13.8 mmol) of lactol **3a** was added in one portion. The resulting solution was stirred at −45 °C for 1 h and then at room temperature for 15 h. A portion (25 mL) of the reaction solution was removed and quenched by slow addition into 40 mL of saturated ammonium chloride solution. The resulting mixture was extracted with four 50-mL portions of ethyl acetate. The organic extracts were combined, dried (magnesium sulfate), and concentrated in vacuo to give crude **10**. The crude material was purified by flash chromatography (180 g, 1–2% methanol/methylene chloride) to yield 2.26 g (45% based on aliquot proportion removed) of diol **10**. TLC: R_f (silica gel, 4:96 methanol/methylene chloride) = 0.38.

To a solution of 1.26 g (3.81 mmol) of diol **10** in 5 mL of THF was added at room temperature 25 mL of 5% aqueous oxalic acid solution. The reaction mixture was stirred for 75 h, diluted with 200 mL of saturated sodium bicarbonate solution, and extracted with four 250-mL portions of ethyl acetate. The combined organic extracts were dried (magnesium sulfate) and concentrated in vacuo to afford 910 mg (98%) of crude lactone **11** as an oil. TLC: R_f (silica gel, 4:96 methanol/methylene chloride) = 0.40.

A mixture of 980 mg (4.02 mmol) of lactone **11** and 1.00 g of 20% palladium hydroxide on activated carbon catalyst in 18 mL of glacial acetic acid was stirred at room temperature under an atmosphere of hydrogen (balloon) for 4 d. The reaction mixture was filtered through a pad of Celite and the filtrate concentrated in vacuo to give an oil. The crude material was solubilized at room temperature in 100 mL of acidic methanol (prepared from 100 mL of methanol and 1 mL of acetyl chloride) and stirred for 16 h. The resulting solution was concentrated in vacuo and the residue purified by flash chromatography (45 g, 3:2 ethyl acetate/hexane) to afford 490 mg of **12** and 200 mg of the corresponding acid. The acid was esterified in acidic methanol (16 h, 25 °C) as above and purified by flash chromatography to afford a total of 570 mg (51% from **11**) of alcohol–ester **12** as a colorless oil. TLC: R_f (silica gel, 4:96 methanol/methylene chloride) = 0.50. IR (KBr): 3442 (broad), 2977, 2951, 1720, 1434, 1295, 1261, 1080, 1030, 1016, 739 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.20–1.80 (m, 4 H), 2.10–2.20 (m, 2 H), 2.50–2.70 (m, 2 H), 3.37 (d, J = 8, 1 H), 3.72 (m, 1 H), 3.81 (m, 1 H), 3.88 (s, 3 H), 4.25 (d, J = 5, 1 H), 4.52 (d, J = 5, 1 H), 7.25–7.31 (m, 2 H), 7.44 (dd, J = 8, 8, 1 H), 7.94 (d, J = 7, 1 H). ^{13}C NMR ($CDCl_3$): δ 29.2, 29.7, 33.0, 47.9, 49.5, 51.9, 61.8, 79.1, 79.3, 126.1, 128.9, 131.2, 131.7, 132.0, 143.8, 167.7. MS (CI): m/z 277 (M + H$^+$).

Preparation of [1*S*-(1α,2α,3α,4α)]-2-[(3-Carboxy-7-oxabicyclo[2.2.1]hept-2-yl)methyl]benzenepropanoic Acid, Methyl Ester (13). To a solution of 20.0 g (65.8 mmol) of alcohol–ester **8** in 500 mL of acetone at room temperature was added rapidly ~1/2 of a 50-mL portion of Jones reagent. The addition was exothermic, but external cooling was not required. After 10 min the remaining Jones' reagent was added. The reaction mixture was stirred for 30 min, and then the excess reagent was quenched by addition of 15 mL of 2-propanol. The slurry was stirred for 15 min and then filtered to remove the chromium salts. The salts were rinsed with an additional 250 mL of acetone.

The filtrate was concentrated in vacuo and the oily residue partitioned between 250 mL of chloroform and 150 mL of 1 M aqueous HCl solution. The organic layer was separated, and the aqueous layer was extracted with two 75-mL portions of chloroform. The combined organic layers were dried (sodium sulfate) and concentrated in vacuo to give 19.6 g of a colorless oil. The oil was crystallized (ethyl acetate/hexane) to afford 17.1 g (82%) of **13** as large colorless crystals, mp 90–92 °C. TLC: R_f (silica gel, 1:9 methanol/methylene chloride) = 0.46. IR (KBr): 3121, 2994, 2955, 1738, 1439, 1410, 1375, 1296, 1171 cm^{-1}. OR: $[\alpha]_D$ = +47° (c = 1.0 in chloroform). ^{1}H NMR ($CDCl_3$): δ 1.15–1.85 (m, 4 H), 2.55 (m, 4 H), 2.75 (dd, J = 3, 13, 1 H), 2.95 (m, 3 H), 3.65 (s, 3 H), 4.30 (d, J = 4, 1 H), 4.88 (d, J = 4, 1 H), 7.15 (m, 4 H), 8.8 (br s, 1 H). ^{13}C NMR ($CDCl_3$): δ 27.4, 28.8, 29.2, 32.0, 34.9, 48.5, 51.6, 52.3, 77.7, 78.5, 126.5, 126.7, 128.9, 130.2, 138.0, 138.6, 173.7, 176.9. MS (CI): m/z 319 (M + H)$^+$. Anal. ($C_{18}H_{22}O_5$) C, H.

Preparation of *N*-(4-Cyclohexylbutyl)-L-serinamide (14). To a mixture of 14.3 g (74.7 mmol) of 4-cyclohexylbutylamine hydrochloride,[28] 16.1 g (78.4 mmol) of *N*-Boc-L-serine, 10.1 g (74.7 mmol) of 1-hydroxybenzotriazole monohydrate, and 7.9 g (78 mmol) of 4-methylmorpholine in 200 mL of DMF at 0 °C was added 15.0 g (78.4 mmol) of WS carbodiimide in one portion. The reaction was allowed to warm to room temperature, stirred overnight, and then concentrated in vacuo to give an oily solid. This material was diluted with 400 mL of ethyl acetate and then washed with two 200-mL portions of 0.3 M aqueous HCl solution followed by two 200-mL portions of 1 M aqueous sodium bicarbonate solution. The organic layer was diluted with 500 mL of toluene, dried (sodium sulfate), and concentrated in vacuo to give a thick oily solid. The crude material was dissolved in 150 mL of methylene chloride, and then added at room temperature was 100 mL of trifluoroacetic acid (gas evolution). The reaction mixture was stirred for 4 h, concentrated in vacuo, and then coevaporated with chloroform to afford crude **14**. The crude material was purified by flash chromatography (1.0 kg, 1:9 (1:9 concentrated ammonium hydroxide/methanol)/methylene chloride) to afford 12.7 g (70%) of **14** as a white solid. TLC: R_f (silica gel, 1:9 (concentrated aqueous ammonium hydroxide/methanol)/methylene chloride) = 0.17 (anisaldehyde). ^{1}H NMR ($CDCl_3$): δ 0.50–1.80 (m, 17 H), 2.10 (broad s, 3 H), 3.24 (dt, J = 7, 7, 2 H), 3.42 (t, J = 7, 1 H), 3.70 (dd, J = 7, 12, 1 H), 3.85 (dd, J = 7, 12, 1 H), 7.38 (broad s, 1 H). ^{13}C NMR ($CDCl_3$): δ 24.0, 26.2, 26.5, 29.6, 33.1, 36.9, 37.3, 39.1, 56.3, 64.6, 173.4.

[1*S*-(1α,2α,3α,(*R),4α)]-2-[[3-[[[2-[(4-Cyclohexylbutyl)amino]-1-(hydroxymethyl)-2-oxoethyl]amino]carbonyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]benzenepropanoic Acid, Methyl Ester (15).** To a solution of 16.7 g (52.5 mmol) of alcohol–acid **13**, 12.7 g (52.5 mmol) of serinamide **14**, 7.8 g (58 mmol) of 1-hydroxybenzotriazole monohydrate, and 5.8 g (58 mmol) of 4-methylmorpholine in 250 mL of DMF cooled to 0 °C was added 11.1 g (57.8 mmol) of WS carbodiimide. The reaction mixture was allowed to warm to room temperature, stirred overnight, and then concentrated in vacuo to remove DMF. The residue was diluted with 700 mL of ethyl acetate (solids remaining) and then washed with two portions of 0.3 M aqueous HCl solution followed by two 250-mL portions of 1.0 M aqueous sodium bicarbonate solution; added was a total of 700 mL of methylene chloride to solubilized the remaining solids, which were dried (sodium sulfate) and concentrated in vacuo to give 30.7 g (100%) of crude **15** as a white solid which used in the next step. TLC: R_f (silica gel, 1:1 (1:19 acetic acid/ethyl acetate)/hexane) = 0.12; the R_f of **13** was 0.34.

[1*S*-(1α,2α,3α,4α)]-2-[[3-[4-[[(4-Cyclohexylbutyl)amino]carbonyl]-4,5-dihydro-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]benzenepropanoic Acid, Methyl Ester (16) via Mesylate. To a solution of 30.7 g (52.5 mmol) of crude **15** in 800 mL of methylene chloride cooled to 0 °C was added 12.1 g (120 mmol) of triethylamine followed by 6.9 g (60 mmol) of methanesulfonyl chloride. The reaction mixture was stirred for 40 min, warmed to room temperature, and after 30 min concentrated in vacuo. The residue was diluted with 1.0 L of acetone, 27.6 g (200 mmol) of potassium carbonate was added, and the mixture was refluxed for 2 h. The mixture was refrigerated overnight, the resulting slurry was filtered, and the solids were extensively rinsed with acetone followed by methylene chloride. The filtrate was concentrated in vacuo and the residue purified by flash chromatography (500 g, 1:4 acetone/toluene) to afford 24.9 g (90%) of oxazoline **16** as a white solid which was used in the next step. TLC: R_f (silica gel, 1:4 acetone/toluene) = 0.34; the R_f of **15** was 0.13 and the intermediate mesylate was 0.21. ^{1}H NMR indicated **16** was a mixture of diastereomers.

Preparation of [1*S*-(1α,2α,3α,4α)]-2-[[3-[4-[[(4-Cyclohexylbutyl)amino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]benzenepropanoic Acid, Methyl Ester (17). To a stirred suspension of 22.3 g (100 mmol) of copper(II) bromide in 250 mL of ethyl acetate was added at room temperature 30.4 g (200 mmol) of DBU. The resulting dark mixture was stirred for 15 min, and then a solution of 24.9 g (47.0 mmol) of oxazoline **16** in 250 mL of chloroform was added. The reaction mixture warmed to ~45 °C. After 18 h, a second 22.3-g portion of copper(II) bromide and 15.2-g portion of DBU were added. The reaction was stirred for 25 h (TLC showed the reaction was nearly complete), and then final portions of 11.2 g of copper(II) bromide an 7.6 g of DBU were introduced. The reaction mixture was stirred for 4 h and then partitioned between 1.0 L of ethyl acetate and 1.4 L of 1:1 (saturated aqueous ammonium chloride/concentrated ammonium hydroxide); 750 mL of ether was added to facilitate phase separation. The organic layer was separated, and the aqueous layer was extracted with two 800-mL portions of ethyl acetate. The organic extracts were combined, dried (sodium sulfate), and concentrated in vacuo to give an oil. The crude material was purified by flash chromatography (750 g, 1:3 to 2:5 ethyl acetate/hexane gradient) to afford 16.5 g (66%) of oxazole **17** as a white solid which was used in the next step. TLC: R_f (silica gel, 1:4 acetone/toluene) = 0.47.

Preparation of [1*S*-(1α,2α,3α,4α)]-2-[[3-[4-[[(4-Cyclohexylbutyl)amino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]benzenepropanoic Acid (31). A solution of 16.5 g (31.6 mmol) of methyl ester **17** in 100 mL of THF, 500 mL of methanol, and 200 mL of 1 M aqueous sodium hydroxide solution was stirred at room temperature for 5 h and then acidified by addition of 300 mL of 1 M HCl solution. The resulting mixture was extracted with one 500-mL then two 250-mL portions of methylene chloride. The combined organic extracts were dried (sodium sulfate) and concentrated in vacuo to give a solid. The crude product was recrystallized from 1.8 L of hot acetonitrile to afford 14.3 g (89%) of acid **31** as a white solid, mp 167.5–168.5 °C. TLC: R_f (silica gel, 1:9 methanol/methylene chloride) = 0.57. IR (KBr): 3420 (broad), 2923, 1724, 1648, 1603, 1520, 1107 cm^{-1}. OR: $[\alpha]_D$ = +14° (c = 2.9 in chloroform). ^{1}H NMR ($CDCl_3$): δ 0.70–1.90 (m, 21 H), 2.21 (dd, J = 2, 9, 1 H), 2.39 (dd, J = 9, 9, 1 H), 2.55 (t, J = 7, with overlapping 1 H m, 3 H total), 2.91 (t, J = 8, 2 H), 3.38 (m, 3 H), 4.39 (d, J = 5, 1 H), 4.98 (d, J = 5, 1 H), 7.05 (crude t, 1 H), 7.14 (m, 4 H), 8.12 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 24.3, 26.4, 26.7, 27.5, 28.9, 29.9, 32.4, 33.4, 34.6, 37.1, 37.6, 39.2, 47.0, 50.0, 78.7, 79.7, 126.6, 126.7, 129.1, 129.7, 136.0, 137.8, 138.5, 140.9, 160.8, 163.9, 175.7. MS (CI): m/z 509 (M + H$^+$). Anal. ($C_{30}H_{40}N_2O_5$) C, H, N.

Preparation of [1*S*-(1α,2α,3α,4α)]-2 -[[3-[[[1-(Hydroxymethyl)-2-oxo-2-(phenylmethoxy)ethyl]amino]carbonyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]benzenepropanoic Acid, Methyl Ester (18). To a solution of 23.5 g (73.9 mmol) of acid–ester **13** in 300 mL of THF cooled to 0 °C was added 13.1 g (85.6 mmol) of 1-hydroxybenzotriazole hydrate, 18.0 g (77.6 mmol) of L-serine benzyl ester hydrochloride, and 22 mL (160 mmol) of triethylamine. The slurry was stirred for 5 min, and then 16.0 g (77.6 mmol) of dicyclohexylcarbodiimide was added rapidly. The reaction mixture was stirred for 4 h at 0 °C and then at room temperature for 16 h. The resulting slurry was cooled to 0 °C, diluted with 300 mL of ethyl acetate, stirred for 15 min, and then filtered. The filtrate was concentrated in vacuo to give a yellow oil. The oil was purified by flash chromatography (1 kg, ethyl acetate) to give **18** as a white solid. Recrystallization (ethyl acetate/hexane) afforded 29.5 g (81%) of **18** as small white crystals, mp 123–124 °C. TLC: R_f (silica gel, ethyl acetate) = 0.32. IR (film): 3365 (broad), 2949, 1735, 1650, 1526, 1193 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.10–2.20 (m, 6 H), 2.30–2.88 (m, 6 H), 2.94 (t, J = 7, 2 H), 3.62 (s, 3 H), 3.80–4.10 (m, 2 H), 4.30 (d, J = 5, 1 H), 4.73 (dt, J = 5, 8, 1 H), 5.19 (d, J = 4, 2 H), 7.00–7.45 (m, 10 H). ^{13}C NMR ($CDCl_3$): δ 27.6, 28.7, 29.7, 31.9, 35.0, 48.4, 51.7, 54.6, 55.0, 63.3, 67.3, 78.5, 79.6, 126.5, 128.1, 128.4, 128.5, 129.0, 129.8, 135.2, 138.5, 138.8, 170.2, 172.4, 173.8. MS (CI): m/z 496 (M + H$^+$). Anal. ($C_{28}H_{33}NO_7$) C, H, N.

Preparation of [1S-(1α,2α,3α,4α)]-2-[[3-[4,5-Dihydro-4-[(phenylmethoxy)carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]-hept-2-yl]methyl]benzenepropanoic Acid, Methyl Ester (19). A mixture of 29.4 g (59.4 mmol) of 18 in 200 mL of sieve-dried acetonitrile and 50 mL of methylene chloride was warmed until homogeneous and then cooled in an ambient water bath. To the resulting solution was added 23.3 g (89.1 mmol) of triphenylphosphine and then 12.2 g (95.0 mmol) of diisopropylethylamine. The mixture was stirred until homogeneous, and then 13.7 g (89.1 mmol) of carbon tetrachloride was added dropwise over 5 min. The reaction mixture was stirred for 2.5 h, cooled to 0 °C, and diluted with 500 mL of ethyl acetate followed by 150 mL of saturated aqueous sodium bicarbonate solution. After being stirred for 10 min the mixture was poured into 350 mL of water, and the organic layer was separated, washed with 200 mL of brine, dried (sodium sulfate), and concentrated in vacuo to give a yellow oil. The oil was purified by flash chromatography (20 × 10 cm, 2:1 ethyl acetate/hexane) to yield 21.8 g (77%) of oxazoline **19** as a white solid, mp 85–87 °C. TLC: R_f (silica gel, ethyl acetate) = 0.47. IR (film): 2950, 1736, 1655, 1175, 996 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.30–1.80 (m, 4 H), 2.45 (m, 1 H), 2.58 (m, 3 H), 2.95 (m, 3 H), 3.65 (s, 3 H), 4.29 (d, J = 5, 1 H), 4.37 (dd, J = 8, 10, 1 H), 4.49 (d, J = 8, 9, 1 H), 4.78 (dd, J = 7, 10, 1 H), 4.86 (d, J = 5, 1 H), 5.18 (d, J = 3, 2 H), 7.15 (s, 5 H), 7.30 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ 27.6, 28.8, 29.8, 31.6, 34.9, 46.7, 48.9, 51.5, 67.2, 68.0, 69.5, 78.1, 79.0, 126.5, 128.3, 128.3, 128.5, 128.9, 129.8, 135.3, 138.4, 138.8, 169.7, 171.0, 173.2. MS (CI): m/z 478 (M + H$^+$). Anal. ($C_{28}H_{31}NO_6$) C, H, N.

Preparation of [1S-(1α,2α,3α,4α)]-2-[[3-[4-[(Phenylmethoxy)carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]-methyl]benzenepropanoic Acid, Methyl Ester (20) via Copper Bromide Oxidation. To a solution of 29.0 (191 mmol) of DBU in 200 mL of ethyl acetate was added 21.3 g (95.6 mmol) of copper(II) bromide at room temperature. The mixture was stirred for 10 min, and then a solution of 21.7 g (45.5 mmol) of oxazoline **19** in 200 mL of chloroform was added dropwise over 1 h. The addition was mildly exothermic, and the reaction mixture was cooled in an ambient water bath. After 6 h an additional 5.80 g (38.2 mmol) of DBU and 4.26 g (19.1 mmol) of copper(II) bromide were added, and the reaction mixture was stirred for 16 h. The resulting thick, dark mixture was transferred to a separatory funnel and added was 1.0 L of 1:1 (saturated aqueous ammonium chloride/concentrated ammonium hydroxide solution) and then 1.0 L of ether. The mixture was shaken, and the organic layer was separated. The aqueous layer was extracted with 500 mL of ether. The organic layers were combined, washed with 500 mL of brine, dried (magnesium sulfate), and concentrated in vacuo to give an oil. The crude material was purified by flash chromatography (20 × 10 cm, 3:2 ethyl acetate/hexane) to afford 14.1 g (65%) of oxazole **20** as a white solid, mp 84–85 °C. TLC: R_f (silica gel, 2:1 ethyl acetate/hexane) = 0.46. IR (film): 2950, 1735, 1577, 1446, 1454, 1312, 1133, 1108, 1003 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.20–1.90 (m, 4 H), 2.20 (dd, J = 5, 9, 1 H), 2.35 (dd, J = 9, 9, 1 H), 2.51 (m, 3 H), 2.90 (t, J = 7, 2 H), 3.51 (d, J = 9, 1 H), 3.63 (s, 3 H), 4.34 (d, J = 5, 1 H), 4.91 (d, J = 5, 1 H), 5.35 (s, 2 H), 7.11 (s, 5 H), 7.40 (m, 4 H), 8.19 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 27.4, 28.8, 29.8, 32.3, 34.8, 47.2, 50.2, 51.5, 66.6, 78.2, 79.4, 126.4, 126.5, 128.3, 128.4, 128.5, 128.8, 129.7, 132.8, 135.5, 137.8, 138.5, 144.0, 160.9, 164.8, 172.9. MS (CI): m/z 476 (M + H$^+$). Anal. ($C_{28}H_{29}NO_6$) C, H, N.

Preparation of [1S-(1α,2α,3α,4α)]-2-[[3-[4-[(Phenylmethoxy)carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]-methyl]benzenepropanoic Acid, Methyl Ester (20) via Nickel Peroxide Oxidation. To a solution of 375 mg (0.79 mmol) of oxazoline **19** in 10 mL of methylene chloride was added 750 mg of nickel peroxide oxidant at room temperature. The reaction mixture was stirred for 1 h, and then an additional 190 mg of nickel peroxide was added. After 30 min the reaction mixture was diluted with 20 mL of ethyl acetate followed by 10 mL of 3 M aqueous sodium bisulfite solution. The mixture was stirred rapidly for 20 min, 10 mL of water was added, and the organic layer was separated. The aqueous layer was extracted with an additional 20 mL of ethyl acetate. The combined organic layers were washed with 25 mL of 1 M aqueous sodium citrate solution, dried (magnesium sulfate), and concentrated in vacuo to yield an oil. The oil was purified by flash chromatography (15 × 1.5 cm, 2:3 ethyl acetate/petroleum ether) to afford 180 mg (48%) of oxazole **20**.

Preparation of [1S-(1α,2α,3α,4α)]-2-[[3-(4-Carboxy-2-oxazolyl)-7-oxabicyclo[2.2,1]hept-2-yl]methyl]benzenepropanoic Acid, Methyl Ester (21). A mixture of 14.0 g (29.5 mmol) of oxazole benzyl ester **20** and 1.40 g of 20% palladium hydroxide on activated carbon catalyst in 200 mL of ethyl acetate was stirred under an atmosphere of hydrogen (balloon) for 1.5 h during which time a precipitate formed. An additional 100 mL of ethyl acetate was added to facilitate stirring, and the reaction continued for a total of 3 h. The resulting thick slurry was added to ~500 mL of ethyl acetate and warmed to solubilize the precipitated product. The warmed mixture was filtered rapidly to remove the catalyst and the filtrate concentrated in vacuo to give a white solid. The crude material was slurried with ~250 mL of ethyl acetate, and then the solids were collected on a Buchner funnel. The filtrate was concentrated in vacuo to ~1/4 volume, and the additional solid material which formed was collected. The solids were combined and dried in vacuo to afford 10.7 g (94%) of oxazole acid **21** as a white solid, mp 171–173 °C. TLC: R_f (silica gel, 1:10:90 acetic acid/methanol/methylene chloride) = 0.25. IR (KBr): 3432 (broad), 2953, 1733, 1635, 1585, 1154, 1109 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.20–1.90 (m, 4 H), 2.20 (dd, J = 5, 9, 1 H), 2.35 (dd, J = 9, 9, 1 H), 2.51 (m, 3 H), 2.90 (t, J = 7, 2 H), 3.59 (d, J = 9, 1 H), 3.65 (s, 3 H), 4.38 (d, J = 5, 1 H), 4.95 (d, J = 4, 1 H), 7.12 (s, 4 H), 8.28 (s, 1 H), 9.15 (br s, 1 H). ^{13}C NMR ($CDCl_3$): δ 27.5, 28.9, 29.8, 32.4, 34.9, 47.1, 50.2, 51.6, 78.4, 79.5, 126.5, 126.6, 128.9, 129.7, 132.5, 137.7, 138.5, 144.7, 164.2, 165.2, 173.2. MS (CI): m/z 383 (M + H$^+$). Anal. ($C_{21}H_{23}NO_6$) C, H, N.

General Procedure for Preparation of 39-71 from Oxazole Acid 21. Preparation of [1S-(1α,2α,3α,4α)]-2-[[3-[4-[(Pentylamino)carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]-methyl]benzenepropanoic Acid (42). To a solution of 1.50 g (3.90 mmol) of oxazole acid **21** in 15 mL of methylene chloride were added at room temperature a small drop of DMF and then dropwise a solution of 600 mg (4.72 mmol) of oxalyl chloride in 3 mL of methylene chloride. The solution was stirred until gas evolution ceased, ~40 min, and then concentrated in vacuo to give the crude acid chloride as a pale yellow solid.

To a solution of the crude acid chloride (~3.9 mmol) in 20 mL of methylene chloride cooled to 0 °C was added 0.70 mL (5.0 mmol) of triethylamine followed by a solution of 407 mg (4.68 mmol) of *n*-amylamine in 3 mL of methylene chloride dropwise over 5 min. The reaction mixture was stirred for 15 min and then partitioned between 50 mL of 1 M aqueous HCl solution and 75 mL of ethyl acetate. The organic layer was separated and concentrated in vacuo to give a solid. The crude material was purified by flash chromatography (12 × 5.0 cm, 3:2 ethyl acetate/hexane) to afford 1.48 g (84%) of **42** methyl ester as a white solid, mp 137–138 °C. TLC: R_f (silica gel, 2:1 ethyl acetate/hexane) = 0.30.

To a solution of 1.45 g (3.19 mmol) of **42** methyl ester in 15 mL of 2:1 THF/water was added 535 mg (12.7 mmol) of lithium hydroxide monohydrate at room temperature. The mixture was stirred rapidly for 2 h, acidified by addition of 15 mL of 1 M aqueous HCl solution, and partitioned between 50 mL of water and 50 mL of ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with an additional 50 mL of ethyl acetate. The combined organic layers were dried (magnesium sulfate) and concentrated in vacuo to give a solid. The crude material was recrystallized (acetonitrile) to afford 1.20 g (85%) of **42** as a white solid, mp 148–150 °C. TLC: R_f (silica gel, 1:9 methanol/methylene chloride) = 0.44. IR (KBr): 3406 (broad), 2955, 1726, 1709, 1649, 1603, 1522, 1217 cm^{-1}. OR: $[\alpha]_D$ = +23° (c = 0.50 in chloroform). ^{1}H NMR ($CDCl_3$): δ 0.87 (t, J = 7, 3 H), 1.20–1.95 (m, 10 H), 2.22 (dd, J = 5, 14, 1 H), 2.33 (dd, J = 14, 14, 1 H), 2.56 (t, J = 7, with overlapping 1 H m, 3 H total), 2.91 (t, J = 8, 2 H), 3.38 (m, 3 H), 4.41 (d, J = 5, 1 H), 4.98 (d, J = 5, 1 H), 7.14 (m, 5 H), 8.16 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 13.9, 22.3, 27.3, 28.8, 29.0, 29.2, 29.8, 32.5, 34.8, 39.1, 46.9, 49.9, 78.6, 79.7, 126.5, 126.7, 128.9, 129.7, 135.8, 137.7, 138.4, 141.0, 160.8, 163.9, 176.7. MS (CI): m/z 441 (M + H$^+$). Anal. ($C_{25}H_{32}N_2O_5$) C, H, N.

Preparation of [1S-(1α,2α,3α,4α)]-2-[[3-[4-[[(4-Cyclohexylbutyl)amino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]-hept-2-yl]methyl]benzenepropanoic Acid, Ethyl Ester (34).

To 20 mL of absolute ethanol was added at room temperature slowly 0.25 mL of acetyl chloride. The solution was stirred for 90 min, and then 353 mg (0.69 mmol) of acid **31** was added and after 1.5 h diluted with methylene chloride and concentrated in vacuo. The residue was dissolved in 40 mL of methylene chloride, washed with 20 mL of saturated sodium bicarbonate solution, dried (magnesium sulfate), and concentrated in vacuo to give a white solid. The crude material was triturated with ether and then diluted with an equal volume of hexane. The resulting slurry was chilled and the solid collected to afford 280 mg (76%) of **34** as a white solid, mp 130–131 °C. TLC: R_f (silica gel, 3:97 methanol/methylene chloride) = 0.65, vanillin. IR (KBr): 3416, 2922, 1732, 1653, 1601, 1516, 1294 cm^{-1}. OR: $[\alpha]_D$ = +3.7 (c = 1.4 in methanol). ^{1}H NMR ($CDCl_3$): δ 0.80–1.8 (m), 2.23 (dd, J = 9, 5, 1 H), 2.35 (dd, J = 11, 14, 1 H), 2.52 (m, 2 H), 3.40 (m, 2 H), 4.13 (q, J = 7, 2 H), 4.40 (d, J = 5, 1 H), 4.94 (d, J = 5, 1 H), 7.09 (m, 4 H), 8.06 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 14.2, 24.2, 26.4, 26.4, 26.7, 27.6, 28.8, 29.9, 32.5, 33.2, 33.3, 35.1, 37.1, 37.5, 39.1, 50.0, 60.4, 78.6, 79.7, 126.4, 126.6, 128.9, 129.7, 136.2, 137.8, 138.5, 140.5, 160.5, 163.7. MS (CI): m/z 537 (M + H$^+$). Anal. ($C_{32}H_{44}N_2O_5$·0.35H_2O) C, H, N.

Preparation of [1*S*-(1α,2α,3α,4α)]-2-[[3-[4-[[(4-Cyclohexylbutyl)amino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]benzenepropanamide (35). To a solution of 110 mg (0.57 mmol) of WS carbodiimide and 80 mg (0.59 mmol) of 1-hydroxybenzotriazole monohydrate in 30 mL of DMF was added at room temperature 32 mg (0.59 mmol) of ammonium chloride, 120 mg (1.2 mmol) of triethylamine, and 300 mg (0.59 mmol) of acid **31**. The reaction mixture was stirred for 2.5 d and then added to 15 mL of water and extracted with three 50-mL portions of ethyl acetate. The combined organic extracts were dried (magnesium sulfate) and concentrated in vacuo to give a solid. The crude material was purified by a combination of flash chromatography and recrystallization (ethyl acetate/hexane/chloroform) to afford 30 mg (10%) of amide **35** as a white solid, mp 173–174 °C. TLC: R_f (silica gel, ethyl acetate) = 0.20. IR (KBr): 3420, 2924, 2851, 1657, 1603, 1526 cm^{-1}. OR: $[\alpha]_D$ = +15° (c = 1.4 in methanol). ^{1}H NMR ($CDCl_3$): δ 0.80–2.00 (m, 21 H), 2.20–2.80 (m, 5 H), 3.00 (t, J = 8, 2 H), 3.48 (m, 3 H), 4.45 (d, J = 4, 1 H), 5.08 (d, J = 4, 1 H), 5.35 (br s, 1 H), 5.61 (br s, 1 H), 7.20 (sharp m, 5 H), 8.18 (s, 1 H). MS (CI): m/z 508 (M + H$^+$). Anal. ($C_{30}H_{41}N_3O_4$) C, H, N.

Preparation of [1*S*-(1α,2α,3α,4α)]-*N*-(4-Cyclohexylbutyl)-2-[2-[[2-(3-hydroxypropyl)phenyl]methyl]-7-oxabicyclo[2.2.1]hept-3-yl]-4-oxazolecarboxamide (36). To a slurry of 450 mg (0.77 mmol) of ester **34** in 20 mL of ether at room temperature was added 56 mg (2.5 mmol) of lithium borohydride. The reaction mixture was stirred for 5 min, and then 5 mL of THF was added. After 24 h the reaction mixture was quenched by slow addition of 1 M aqueous HCl solution until gas evolution ceased (pH = 1). The resulting mixture was concentrated in vacuo, and the residue was diluted with 20 mL of water and then extracted with 25 mL of ether and two 25-mL portions of methylene chloride. The combined organic extracts were dried (magnesium sulfate) and concentrated in vacuo, and the residue was purified by flash chromatography (40 g, 3:97 methanol/methylene chloride) to afford 280 mg of impure **36**. The impure material was dissolved in 1–2 mL of methylene chloride, diluted with ether and then hexane, and cooled to 0 °C. The solid which formed was collected and dried in vacuo to give 120 mg (32%) of pure alcohol **36** as fine white crystals, mp 119–121 °C. TLC: R_f (silica gel, 3:97 methanol/methylene chloride) = 0.35, vanillin. IR (KBr): 3418, 2922, 2851, 1657, 1601, 1522, 1449 cm^{-1}. OR: $[\alpha]_D$ = +4.0 (methanol). ^{1}H NMR ($CDCl_3$): δ 0.80–2.00 (m), 2.04 (dd, J = 4, 10, 1 H), 2.29 (dd, J = 12, 14, 1 H), 2.55 (m, 2 H), 3.30 (m, 4 H), 3.57 (dt, J = 3, 6, 2 H), 4.29 (d, J = 5, 1 H), 4.91 (d, J = 5, 1 H), 7.06 (m, 4 H), 8.02 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 24.2, 26.4, 26.7, 28.8, 29.9, 32.1, 33.4, 34.1, 37.1, 37.5, 39.2, 47.0, 50.1, 62.1, 78.6, 79.8, 126.1, 126.5, 129.4, 129.6, 136.3, 137.8, 140.3, 140.5, 160.6, 163.9. MS (CI): m/z 495 (M + H$^+$). Anal. ($C_{30}H_{42}N_2O_4$) C, H, N.

Preparation of [1*S*-(1α,2α,3α,4α)]-2-[[3-[4-[[(4-Cyclohexylbutyl)amino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]-*N*-(methylsulfonyl)benzenepropanamide (37). To 250 mg (0.49 mmol) of acid **31**, 70 mg (0.6 mmol) of 4-(dimethylamino)pyridine, 130 mg (1.4 mmol) of methanesulfonamide, and 130 mg (0.68 mmol) of WS carbodiimide was added at room temperature 2 mL of DMF. The reaction mixture was stirred for 24 h, diluted with ethyl acetate, washed with three portions of 1 M aqueous HCl solution, dried (sodium sulfate), and concentrated in vacuo. The residue was purified by flash chromatography (1:3 to 1:1 (5% acetic acid/ethyl acetate)/hexane gradient) and then crystallized from ether to afford 260 mg (90%) of **37** as a white solid, mp 154–156 °C. TLC: R_f (silica gel, 2.5:47.5:50 acetic acid/ethyl acetate/hexane) = 0.33 (anisaldehyde). IR (film): 2922, 1715, 1649, 1601, 1524, 1449, 1339 cm^{-1}. OR: $[\alpha]_D$ = +20° (c = 1.7 in chloroform). ^{1}H NMR ($CDCl_3$): δ 0.60–1.95 (m, 21 H), 2.00–2.75 (m, 5 H), 2.90 (t, J = 8, 2 H), 3.24 (s, 3 H with 2 H m overlapping), 3.40 (d, J = 8, 1 H), 4.32 (d, J = 4, 1 H), 5.04 (d, J = 4, 1 H), 7.12 (s with overlapping m, 6 H total), 8.15 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 24.1, 26.3, 26.6, 27.6, 28.6, 29.7, 29.9, 31.9, 33.3, 37.0, 37.4, 37.6, 39.2, 41.2, 46.7, 49.8, 78.7, 79.8, 126.7, 129.3, 129.5, 135.9, 137.5, 138.2, 141.0, 160.8, 163.7, 172.1. MS (CI): m/z 586 (M + H$^+$). Anal. ($C_{31}H_{43}N_3O_6S$·0.30H_2O) C, H, N, S.

Preparation of [1*S*-(1α,2α,3α,4α)]-2-[[3-[4-[[(4-Cyclohexylbutyl)amino]thioxomethyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]benzenepropanoic Acid (72). A solution of 410 mg (0.74 mmol) of **31** methyl ester, 70 μL (0.87 mmol) of pyridine, and 685 mg (1.54 mmol) of phosphorus pentasulfide in 25 mL of methylene was refluxed for 16 h. The reaction mixture was cooled and filtered through a pad of Celite, and the filtrate was partitioned between 20 mL of methylene chloride and 20 mL of 1 M aqueous NaOH solution. The organic layer was separated, dried (magnesium sulfate), and concentrated in vacuo to give an oil. The crude material was purified by flash chromatography (15 × 3.0 cm, 1:3 ethyl acetate/hexane) to afford 344 mg (84%) of **72** methyl ester as a yellow glass. TLC: R_f (silica gel, 1:2 ethyl acetate/hexane) = 0.38; the R_f of **72** methyl ester was 0.10.

A solution of 340 mg (0.62 mmol) of **72** methyl ester and 100 mg (2.38 mmol) of lithium hydroxide monohydrate in 7.5 mL of 2:1 THF/water was stirred rapidly at room temperature for 6 h. The reaction was acidified by addition of 2.6 mL of 1 M aqueous HCl solution and then partitioned between 20 mL of ethyl acetate and 20 mL of water. The aqueous layer was separated and extracted with an additional 20 mL of ethyl acetate. The organic extracts were combined, dried (magnesium sulfate), and concentrated in vacuo to give a solid. The crude solid was recrystallized (ethyl acetate/hexane) to afford 286 mg (88%) of **72** as a pale yellow solid, mp 135–137 °C. TLC: R_f (silica gel, 1:9 methanol/methylene chloride) = 0.56. IR (KBr): 3276 (broad), 2923, 2850, 1709, 1591, 1522, 1448, 1397, 1307 cm^{-1}. OR: $[\alpha]_D$ = +25° (c = 0.25 in chloroform). ^{1}H NMR ($CDCl_3$): δ 0.70–2.00 (m, 20 H), 1.95 (dd, J = 5, 14, 1 H), 2.33 (dd, J = 12, 12, 1 H), 2.58 (t, J = 8, 3 H), 2.91 (t, J = 7, 2 H), 3.49 (d, J = 9, 1 H), 3.81 (m, 2 H), 4.40 (d, J = 4, 1 H), 4.99 (d, J = 4, 1 H), 7.15 (sharp m, 4 H), 8.24 (s, 1 H), 8.82 (t, 1 H). ^{13}C NMR ($CDCl_3$): δ 24.3, 26.3, 26.7, 27.2, 28.4, 28.8, 29.9, 32.5, 33.3, 34.7, 37.1, 37.5, 44.7, 46.9, 50.0, 78.6, 79.8, 126.6, 126.8, 128.9, 129.8, 137.7, 138.2, 141.1, 142.2, 163.7, 177.7, 184.5. MS (CI): m/z 525 (M + H$^+$). Anal. ($C_{30}H_{40}N_2OS$) C, H, N, S.

Preparation of [1*S*-(1α,2α,3α,4α)]-2-[[3-4-[[(4-Cyclohexylbutyl)oxo]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]benzenepropanoic acid (73). To a mixture of 200 mg (0.39 mol) of acid **31** and 80 mg (0.58 mmol) of anhydrous granular potassium carbonate in 4 mL of sieve-dried DMF was added 60 mL (0.50 mmol) of benzyl bromide at room temperature. The reaction was stirred for 3 h and then partitioned between 25 mL of water and 25 mL of ethyl acetate. The organic layer was separated, washed with three 25-mL portions of water, dried (magnesium sulfate), and concentrated in vacuo to give a solid. The crude solid was recrystallized (ethyl acetate/hexane) to afford 198 mg (85%) of benzyl ester **22** as a white solid, mp 114–116 °C. TLC: R_f (silica gel, ethyl acetate) = 0.61.

A mixture of 190 mg (0.32 mmol) of **22** in 5 mL of 1:4 glacial acetic acid/acetic anhydride was warmed until homogeneous and then cooled in an ice bath. To the resulting solution was added in one portion 480 mg (6.96 mmol) of sodium nitrite. The reaction was stirred for 45 min during which time a precipitate formed. The mixture was warmed to room temperature, an additional 480 mg (6.96 mmol) of sodium nitrite was added, and stirring continued for 2.5 h. The resulting mixture was diluted with 25 mL of ethyl acetate and then added to 50 mL of water. The organic layer was separated, washed with two 50-mL portions of

ice-cold 1 M aqueous NaOH solution, 20 mL of brine, dried (magnesium sulfate), and concentrated in vacuo to afford the crude *N*-nitrosoamide as a yellow oil. The R_f (silica gel, 1:1 ethyl acetate/hexane) of the *N*-nitrosoamide was 0.48 and of **22** was 0.21. A solution of the crude *N*-nitrosoamide in 3 mL of dioxane was heated to 95 °C for 2 h and then cooled to room temperature. The solution color changed from yellow to colorless during this time. The resulting solution was concentrated in vacuo to give an oil. The crude oil was purified by flash chromatography (12 × 3.0 cm, 1:2 ethyl acetate/hexane) to afford 105 mg (56%) of diester **23** as a colorless glass. TLC: R_f (silica gel, 1:2 ethyl acetate/hexane) = 0.28; the *N*-nitrosoamide showed the same R_f.

A mixture 100 mg (0.17 mmol) of diester **23** and 20 mg of 10% palladium on activated carbon catalyst in 5 mL of reagent ethyl acetate was stirred rapidly under an atmosphere of hydrogen (balloon) for 5 h then passed through a 0.4 μM polycarbonate membrane. The filtrate was concentrated in vacuo to give a solid. The crude solid was recrystallized (ethyl acetate/hexane) to afford 68 mg (79%) of **74** as a white solid, mp 135–137 °C. TLC: R_f (silica gel, 1:9 methanol/methylene chloride) = 0.54. OR: $[\alpha]_D$ = +44° (*c* = 0.27 in chloroform). ^{1}H NMR ($CDCl_3$): δ 0.70–1.90 (m, 17 H), 2.23 (dd, *J* = 4, 10, 1 H), 2.35 (t, *J* = 13, 1 H), 2.55 (crude t, 3 H), 2.95 (t, *J* = 8, 2 H), 3.54 (d, *J* = 9, 1 H), 4.30 (t, *J* = 7, 2 H), 4.36 (d, *J* = 5, 1 H), 4.92 (d, *J* = 5, 1 H), 7.15 (sharp m, 4 H), 8.17 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 23.1, 26.4, 26.7, 27.4, 28.9, 29.9, 32.4, 33.3, 34.7, 37.0, 37.5, 47.3, 50.4, 65.4, 78.3, 79.5, 126.6, 126.7, 128.9, 129.9, 133.1, 137.9, 138.4, 143.7, 161.3, 164.9, 176.6. MS (CI): *m/z* 510 (M + H$^+$). Anal. ($C_{30}H_{39}NO_6$) C, H, N.

Preparation of [1*S*-(1α,2α,3α,4α)]-2-[[3-[4-(6-Cyclohexyl-1-oxohexyl)-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]benzenepropanoic Acid (75). To 2.08 g (85.8 mmol) of magnesium turnings covered with 20 mL of ether was added three drops 1,2-dibromoethane and a small iodine crystal followed by the slow dropwise addition of 10.0 g (42.9 mmol) of 5-cyclohexylpentyl bromide. The reaction was slightly exothermic. After addition of bromide, the reaction mixture was refluxed for 3 h and then cooled to room temperature to afford a solution of (5-cyclohexylpentyl)magnesium bromide.

To a solution of 1.8 mL (1 M in ether, 1.8 mmol) of zinc chloride solution in 5 mL of ether at room temperature was added dropwise 1.1 mL (1.6 M in ether, 1.8 mmol) of the Grignard reagent from above over 10 min. The reaction mixture was refluxed for 1.5 h, and then a solution of **21** acid chloride (~1.3 mmol, see **42** for preparation) in 25 mL of benzene was added dropwise over 15 min. The mixture was stirred for 12 h at room temperature and then refluxed for 8 h. The reaction mixture was cooled and partitioned between 150 mL of methylene chloride and 150 mL of 1 M aqueous HCl solution. The organic layer was separated, washed with 100 mL of saturated $NaHCO_3$ solution, dried (magnesium sulfate), and concentrated in vacuo to give a crude yellow oil. The crude oil was purified by flash chromatography (1:4 ethyl acetate/hexane) to give 130 mg of an impure white solid (TLC). The impure solid was recrystallized (ethyl acetate/hexane) to give 69 mg (10%) of **75** methyl ester as a white solid, mp 105–107 °C. TLC: R_f (silica gel, 1:2 ethyl acetate/hexane) = 0.67.

To a solution of 66 mg (0.13 mmol) of **75** methyl ester in 5 mL of 4:1 THF/water was added 11 mg (0.25 mmol) of lithium hydroxide monohydrate at room temperature. The reaction mixture was stirred vigorously for 2.5 h and then acidified by the addition of 0.5 mL of 1 M aqueous HCl solution. The mixture was partitioned between 15 mL of ethyl acetate and 15 mL of water. The water layer was separated and extracted with an additional 15-mL portion of ethyl acetate. The combined ethyl acetate layers were dried (magnesium sulfate) and concentrated in vacuo to give 52 mg (81%) of acid **75** as a white solid, mp 155–158 °C. TLC: R_f (silica gel, 1:9 methanol/methylene chloride) = 0.61. IR (KBr): 3433, 3076, 2922, 2850, 1710, 1689, 1579 cm^{-1}. OR: $[\alpha]_D$ = +31° (*c* = 0.50 in methylene chloride). ^{1}H NMR ($CDCl_3$): δ 0.70–1.90 (m, 23 H), 2.21 (dd, *J* = 5, 14, 1 H), 2.56 (crude t, 3 H), 2.90 (m, 4 H), 3.48 (d, *J* = 9, 1 H), 4.38 (d, *J* = 5, 1 H), 4.96 (d, *J* = 5, 1 H), 7.14 (s, 4 H), 8.14 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 23.8, 26.4, 26.7, 26.8, 27.4, 28.9, 29.6, 29.9, 32.4, 33.4, 34.6, 37.3, 37.6, 39.9, 47.2, 50.2, 78.5, 79.6, 126.6, 126.7, 129.0, 129.8, 137.9, 138.4, 140.4, 142.0, 164.4, 176.3, 195.5. MS (CI): *m/z* 508 (M + H$^+$). Anal. ($C_{31}H_{41}NO_5$) C, H, N.

Preparation of [1*S*-(1α,2α,3α,4α)]-2-[[3-[4-(Hydroxymethyl)-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]benzenepropanoic Acid (76). To a solution of 500 mg (1.3 mmol) of acid **31** in 10 mL of dry methylene chloride was added 1 small drop of DMF followed by 780 μL (2 M in methylene chloride, 1.6 mmol) of oxalyl chloride solution. The reaction was stirred at room temperature until gas evolution ceased (about 30 min), and then the mixture was concentrated in vacuo and azeotroped with two 5-mL portions of toluene to give the crude acid chloride as a pale yellow solid. To a mixture of 661 mg (2.6 mmol) of lithium tri-*tert*-butoxyaluminohydride in 5 mL of THF at 0 °C was added dropwise over 10 min a solution of the crude acid chloride in 20 mL of THF. The reaction mixture was stirred at 0 °C for 3.5 h, and then an additional portion of 164 mg (0.7 mmol) of lithium tri-*tert*-butoxyaluminohydride was added. The reaction mixture was stirred at 0 °C for an additional 40 min and then quenched by the addition of 5 mL of water. The resulting mixture was partitioned between 100 mL of ethyl acetate and 100 mL of 1 M aqueous HCl solution. The organic layer was separated, and the water layer was extracted with two 50-mL portions of ethyl acetate. The combined ethyl acetate layers were dried (magnesium sulfate) and concentrated in vacuo to give a crude oil. The crude oil was purified by flash chromatography (ethyl acetate) to give 448 mg (94%) of **76** methyl ester as a clear oil. TLC: R_f (silica gel, ethyl acetate) = 0.22.

To a solution of 448 mg (1.20 mmol) of **76** methyl ester in 10 mL of 4:1 THF/water was added 102 mg (2.43 mmol) of lithium hydroxide monohydrate at room temperature. The reaction was stirred vigorously for 2.5 h and then acidified by the addition of 4.8 mL of 1 M aqueous HCl solution. The mixture was partitioned between 50 mL of ethyl acetate and 50 mL of water; the water layer was separated and extracted with two 30-mL portions of ethyl acetate. The combined ethyl acetate layers were dried (magnesium sulfate) and concentrated in vacuo to give 397 mg of a crude white solid. The crude solid was purified by two recrystallizations (ethyl acetate) to afford 220 mg (51%) of **76** as a white solid, mp 137–138 °C. TLC: R_f (silica gel, 1:9 methanol/methylene chloride) = 0.20. IR (KBr): 3828, 3126, 2953, 2880, 1712, 1699, 1634, 1567 cm^{-1}. OR: $[\alpha]_D$ = +57° (*c* = 0.50 in chloroform). ^{1}H NMR ($CDCl_3$): δ 1.40–1.90 (m, 3 H), 2.09 (dd, *J* = 4, 14, 1 H), 2.26 (dd, *J* = 13, 13, 1 H), 2.48 (m, 3 H), 2.90 (t, *J* = 8, 2 H), 3.50 (d, *J* = 9, 1 H), 4.44 (d, *J* = 5, 1 H), 4.56 (s, 2 H), 4.92 (d, *J* = 4, 1 H), 7.13 (sharp m, 4 H), 7.54 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 27.9, 28.8, 29.9, 32.6, 35.5, 47.1, 50.7, 55.6, 78.5, 79.2, 126.5, 126.7, 129.4, 129.8, 135.3, 138.3, 139.1, 139.6, 165.1, 176.2. MS (CI): *m/z* 358 (M + H$^+$). Anal. ($C_{20}H_{23}NO_5$) C, H, N.

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Supplementary Material Available: Synthetic routes to **26** and **75** (3 pages). Ordering information is given on any current masthead page.

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