Structure−Activity Studies on Anticonvulsant Sugar Sulfamates Related to Topiramate. Enhanced Potency with Cyclic Sulfate Derivatives

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We have explored the structure−activity relationship (SAR) surrounding the clinically efficacious antiepileptic drug topiramate (**1**), a unique sugar sulfamate anticonvulsant that was discovered in our laboratories. Systematic structural modification of the parent compound was directed to identifying potent anticonvulsants with a long duration of action and a favorable neurotoxicity index. In this context, we have probed the pharmacological importance of several molecular features: (1) the sulfamate group (**6**−**8**, **22**−**25**, **27**, **84**), (2) the linker between the sulfamate group and the pyran ring (**9**, **10**, **21a**,**b**), (3) the substituents on the 2,3- (**58**−**60**, **85**, **86**) and 4,5-fused (**30**−**38**, **43**, **45**−**47**, **52**, **53**) 1,3-dioxolane rings, (4) the constitution of the 4,5-fused 1,3-dioxolane ring (**2**, **54**, **55**, **63**−**68**, **76**, **77**, **80**, **83a**−**r**, **84**−**87**, **90a**, **91a**, **93a**), (5) the ring oxygen atoms (**95**, **96**, **100**−**102**, **104**, **105**), and (6) the absolute stereochemistry (**106** and **107**). We established the C1 configuration as *R* for the predominant alcohol diastereomer from the highly selective addition of methylmagnesium bromide to aldehyde **15** (16:1 ratio) by single-crystal X-ray analysis of the major diastereomer of sulfamate **21a**. Details for the stereoselective syntheses of the hydrindane carbocyclic analogues **95**, **96**, **100**, and **104** are presented. We also report the synthesis of cyclic imidosulfites **90a** and **93a**, and imidosulfate **91a**, which are rare examples in the class of such five-membered-ring sulfur species. Imidosulfite **93a** required the preparation and use of the novel sulfur dichloride reagent, BocN=SCl_2. Our SAR investigation led to the impressive 4,5-cyclic sulfate analogue **2** (RWJ-37947), which exhibits potent anticonvulsant activity in the maximal electroshock seizure (MES) test (ca. 8 times greater than **1** in mice at 4 h, ED_{50} = 6.3 mg/kg; ca. 15 times greater than **1** in rats at 8 h, ED_{50} = 1.0 mg/kg) with a long duration of action (>24 h in mice and rats, po) and very low neurotoxicity (TD_{50} value of >1000 mg/kg at 2 h, po in mice). Cyclic sulfate **2**, like topiramate and phenytoin, did not interfere with seizures induced by pentylenetetrazole, bicucculine, picrotoxin, and strychnine; also, **2** was not active in diverse in vitro receptor binding and uptake assays. However, **2** turned out to be a potent inhibitor of carbonic anhydrase from different rat tissue sources (e.g., IC_{50} of 84 nM for the blood enzyme and 21 nM for the brain enzyme). An examination of several analogues of **2** (**83a**−**r**, **85**−**87**, **90a**, **91a**, **93a**) indicated that potent anticonvulsant activity is associated with relatively small alkyl substituents on nitrogen (Me/H, **83a**; Me/Me, **83m**; Et/H, **83b**; allyl/H, **83e**; c-Pr/H, **83j**; c-Bu/H, **83k**) and with limited changes in the cyclic sulfate group, such as 4,5-cyclic sulfite **87a**/**b**. The potent anticonvulsants **83a** and **83j** had greatly diminished carbonic anhydrase inhibitory activity; thus, inhibition of this enzyme may not be a significant factor in the anticonvulsant activity. The α-L-sorbopyranoses **67**, **68**, and **80**, which mainly possess a skew conformation (ref 29), were nearly twice as potent as topiramate (**1**). The L-fructose enantiomers of **1** (**106**) and **2** (**107**), synthesized from L-sorbose, were found to have moderate anticonvulsant activity, with eudysmic ratios (MES ED_{50} in mice at 4 h, po) of **1**:**106** = 1.5 and **2**:**107** = 3.5. The log *P* values for **1** and **2** were determined experimentally to be 0.53 and 0.42, respectively, which are less than the optimal 2.0 for CNS active agents. However, analogues with more favorable calculated log *P* (clogP) values, in conjunction with just minor steric perturbation according to the developed SAR profile, such as **47** (clogP = 2.09), **83m** (1.93), and **86** (1.50), did not display improved potency: **47** is less potent than **1**, **83m** is equipotent with **2**, and **86** is less potent than **2**. Although the measured log *P* value for diethyl analogue **31** is 1.52, this did not translate into enhanced potency relative to **1**. The 400-MHz ^{1}H NMR studies of **1** and **2** indicated that the skew $^3S_0$ conformer predominates at ambient temperature in nonaqueous and aqueous media; **95** strongly populates a skew $^3S_0$ conformer in benzene and (as reported in ref 29) **67** mainly adopts this skew conformation in various solvents. X-ray crystal structures for **1**, **2**, and **95** (as well as **67**) depict the skew $^3S_0$ conformer in the solid state. Solution IR studies with **1**, **2**, and **83b** showed an absence of intramolecular hydrogen bonding, in contrast to what has been observed for alcohol **4** (ref 73).

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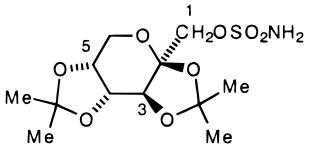
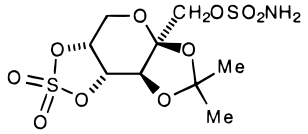
Epilepsy is a chronic neurological disorder characterized by seizures that result from the sudden, disorderly depolarization of neurons in the brain.[1] The constellation of seizure disorders that comprise "epilepsy" ranges from brief cessation of responsiveness (absence seizures) to severe tonic-clonic muscle spasms with a loss of consciousness (generalized seizures). Anticonvulsant drugs, which probably function by inhibiting initiation and/or propagation of the paroxysmal neuronal discharges, are employed to control epileptic symptoms. However, as far as therapeutic applications are concerned, the available drugs are limited in number, kind, and side-effect profile. This has inspired a broad-based search, including that spearheaded by the National Institute of Neurological Disorders and Stroke (NINDS), to find new, more effective, less toxic anticonvulsant agents.

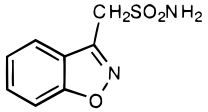
Because of the multiple etiologies of epilepsy, and our general lack of understanding about the responsible physiological mechanisms, the discovery of novel antiepileptic drugs is often an empirical exercise. Indeed, we discovered topiramate (**1**; TOPAMAX®) in our laboratories around 1980 by means of a standard in vivo screening protocol: the maximal electroshock seizure (MES) test.[2] Topiramate is orally active with rapid absorption, high bioavailability, and a long duration of action. Now, the antiepileptic efficacy of topiramate has been confirmed through clinical trials in patients refractory to commonly used drugs,[3] such as phenytoin and carbamazepine, and the drug development program has reached a very advanced stage, with several worldwide marketing approvals.



1 (topiramate)



2 (RWJ-37947)



zonisamide

Topiramate is especially interesting from a structural standpoint because it is derived from a monosaccharide and bears an unusual sulfamate functional group. By contrast, many well-known antiepileptic drugs, such as phenytoin, carbamazepine, and phenobarbital, contain a urea-type functionality accompanied by a benzenoid group, while other drugs contain an aryl-substituted benzodiazepine nucleus (e.g., diazepam), a backbone derived from γ-aminobutyric acid (e.g., vigabatrin and progabide), an amino- and aryl-substituted polyazaaromatic unit (e.g., lamotrigine), and carbamate groups (e.g., felbamate). The antiepileptic agent zonisamide (shown), a heterocyclic methanesulfonamide, is somewhat structurally related to topiramate. Topiramate's clinical success aptly supports a strategy of discovering new antiepileptic drugs predicated on structural uniqueness.

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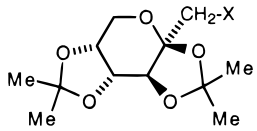
Although topiramate was one of the more interesting *O*-alkyl sulfamate anticonvulsants in our earlier paper,[2a] we did not explore the structure−activity characteristics of the sugar sulfamate pharmacophore in substantial detail. With respect to analogues of topiramate with a modified sulfamate group, monomethyl, monophenyl, or dimethyl substitution on nitrogen caused a significant attenuation in potency in the MES test in mice, while replacement of sulfamate with carbamate abolished activity. Additionally, linkage of the two methyl groups on the 4,5-ketal ring into a cyclohexane ring, or removal of the 4,5-ketal, abolished MES activity. Given our favorable clinical experience with topiramate, we continued to investigate this novel sugar sulfamate class, intent on identifying other potent, long-lived anticonvulsants devoid of neurological side effects and on defining the structure−activity relationship (SAR) for this series more thoroughly. In our follow-up work, we sought to determine the pharmacological importance of (1) the sulfamate group, (2) the linker between the sulfamate group and the pyran ring, (3) the substituents on the 2,3- and 4,5-fused 1,3-dioxolane rings, (4) the constitution of the 4,5-fused 1,3-dioxolane ring, (5) the ring oxygen atoms, and (6) the absolute stereochemistry. We now describe the systematic structural modification of parent compound **1**, which ultimately led to a cyclic sulfate analogue, RWJ-37947 (**2**), with potent anticonvulsant activity, a long duration of action, and an excellent neurotoxicity index.[4]

Structural Alterations and Synthetic Chemistry

The Sulfamate Group in 1 and Its Linker. Our previous report[2a] indicated that replacement of the OSO_2NH_2 group in topiramate (**1**) with $OC(O)NH_2$ (**3**) or OH (**4**) resulted in a loss of anticonvulsant activity, while the SO_2N_3 (**5**) group resulted in moderate activity. We have further examined isosteric analogues with $NHSO_2NH_2$ (**6**), $NMeSO_2NH_2$ (**7**), and $CH_2SO_2NH_2$ (**8**) groups, as well as homologues with an elongated linker by virtue of $CH_2OSO_2NH_2$ (**9**) and $CH_2CH_2OSO_2NH_2$ (**10**) groups (Table 1).



3 X = $OC(O)NH_2$
4 X = OH
5 X = OSO_2N_3
6 X = $NHSO_2NH_2$
7 X = $NMeSO_2NH_2$
8 X = $CH_2SO_2NH_2$
9 X = $CH_2OSO_2NH_2$
10 X = $(CH_2)_2OSO_2NH_2$
11 X = NH_2
12 X = I
13 X = NMeBzl
14 X = NHMe
19 X = CH_2OH
20 X = $(CH_2)_2OH$
26 X = OSO_2Cl
27 X = OSO_2Me

Aminodeoxyfructose **11**[5] was reacted with sulfamoyl chloride and NaH to give **6** in 20% yield. To obtain **7**, fructose bis-acetonide (**4**)[2a,6] was readily converted to iodide **12** (iodine, Ph_3P, and imidazole) in 80% yield[7] and then treated with *N*-methylbenzylamine for 2 days in the presence of sodium carbonate to give **13** in 98% yield. Hydrogenolysis of **13** (H_2, 10% Pd/C) afforded amine **14** (74% yield), which was reacted with sulfamoyl chloride and NaH to give **7** in 7% yield.

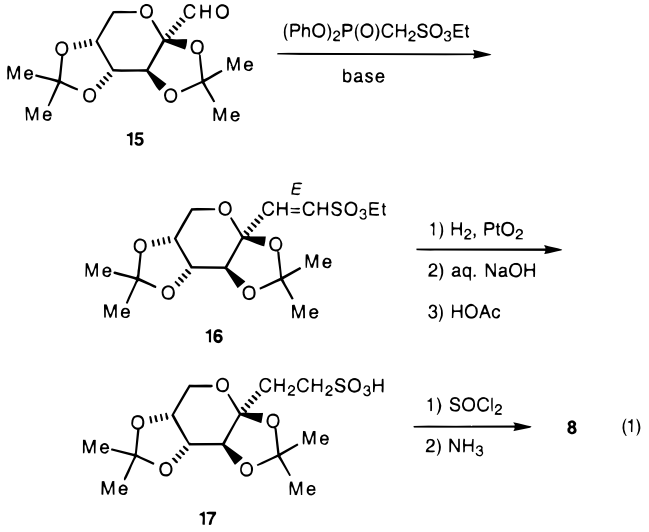
Table 1. Chemical Properties and Biological Data

compd[a]	% yield[b]	mp (purifcn)[c]	$[\alpha]_D$ (*c*)[d]	dosage po, mg/kg	MES test, 4 h % block (ED_{50})[e]
2	80	150−151 dec (E/W)[f]	−28.8 (1.17)	10, 35	80, 100% (6.3 mg/kg)
6	20	50−52 (foam, LC)	−25.9 (0.08)	75	0%
7[g]	7	foam (LC)	−18.2 (0.63)	75	0%
8	25	142−143 (LC)	−29.5 (1.00)	75	0%
9	41	syrup (LC)	−18.7 (1.01)	75	0%[h]
10	53	syrup (LC)	−19.6 (0.98)	75	0%
21a	43	syrup (LC)	−27.2 (0.97)	75	0%
21b	45	syrup (LC)	−24.2 (1.09)	75	0%
22[i]	59	syrup (LC)	−29.2 (1.06)	35, 75	0, 90%
23	67	48−50 (LC)	−11.7 (1.18)	10, 75	0, 80%
24	76	glass (LC)	−27.5 (1.04)	75	0%
25	98	152−154 (EA/M)	−44.7 (1.06)[j]	75	30%
27	76	125−127 (E)[k]	−35.1 (1.00)	75	0%
30	42	142−144 (LC)	−33.9 (1.00)	75	0%
31	34	127−130 (LC)	−25.6 (1.00)	75, 300	0, 80%
32	79	131−133 (EA/H)	−18.9 (1.00)	75	0%
33a	32	foam (LC)	−29.3 (1.20)	75	0%
33b	6	syrup (LC)	−18.1 (1.00)	10, 75	0, 100%
34	34	131−132 (EA/H)	−25.9 (1.00)	35, 75	10, 90%[l]
35	79	97−99 (LC)	−25.3 (1.00)	75	90%
36	45	164−165 (LC)	−19.3 (1.00)	75	0%
37[m]	55	130−133 (LC)	−19.5 (1.00)	75	0%
38	50	foam (LC)	−29.3 (1.00)	35, 75	0, 20%[n]
43	55	122−124 (LC)	+1.3 (0.74)	75	0%
45	42	glass (LC)	−10.6 (1.11)[j]	75	0%
46	44	syrup (LC)	−26.8 (1.00)	75	0%
47	81	109−112 (foam, LC)	−23.8 (1.00)	75	40%
52[o]			−45.5 (0.48)[j]	75, 300	0, 70%
53[o]			−75.1 (1.75)[j]	75	12.5%
54	50	88−89 (B/H)	−6.1 (1.03)[j]	75, 300	0, 50%
55	92	151−152 (B)	−9.7 (1.03)[j]	75	0%
58	73	foam (LC)	−31.7 (1.00)	75	0%
59	79	syrup (LC)	−19.7 (1.00)	75, 300	0, 70%
60	72	156−158 (AE/W)	−38.6 (1.00)	75	0%
63	58	135−138 (LC)	+27.0 (1.00)	75	0%
64	54	syrup (LC)	+28.4 (1.20)	75, 300	0, 40%
65	88	75−76 (B/H)	+27.1 (1.02)	75, 300	0, 100%
66[o]			−0.9 (1.13)	300	0%
67[o]			+39.4 (1.00)	10, 75	0, 90% (30 mg/kg)
68[o]			+20.1 (1.00)	10, 75	0, 100% (21 mg/kg)
76	50	syrup (LC)	−39.8 (1.26)	75	0%
77	53	115−116 (I)	−22.3 (1.00)	75	30%[h]
80[o]			+7.7 (1.00)	18.75, 37.5	50, 90% (24 mg/kg)
83a	90	151−153 (EA/H)	−25.3 (1.00)	10	100% (7.4 mg/kg)
83b	89	glass (LC)	−23.6 (1.00)	3, 35	0, 100% (14.4 mg/kg)
83c	79	125−127 (LC)	−24.3 (1.00)	10, 75	40, 90%
83d	74	111−113 (AE/W)	−25.1 (1.00)	10, 35	30, 100%
83e	55	75−77 (AE/W)	−31.1 (1.00)	1, 10	0, 70%
83f	48	syrup (LC)	−17.1 (1.00)	10, 75	0, 100%
83g	33	foam (LC)	−30.4 (0.96)	300	0%
83h	68	56−62 (foam, LC)	−28.4 (1.00)	75	0%
83i	70	foam (LC)	−22.8 (1.00)	10, 75	0, 100%
83j	94	foam (LC)	−24.3 (1.00)	1, 10	0, 90% (7.3 mg/kg)
83k	87	foam (LC)	−29.2 (1.00)	1, 10	0, 90%
83l	57	foam (LC)	−23.5 (1.00)	10, 75	0, 30%
83m	55	109−111 (AE/W)	−25.3 (1.00)	10, 35	70, 100% (6.9 mg/kg)
83n	44	foam (LC)	−26.3 (1.00)	10, 75	10, 100%
83o	93	foam (LC)	−22.0 (1.00)[p]	75	0%
83p	69	foam (LC)	−20.0 (0.82)	75	0%
83q	81	foam (LC)	−20.8 (1.00)	10, 75	0, 100%
83r	87	foam (LC)	−21.0 (1.00)	10, 35	0, 100%
84	71	powder (LC)	−35.5 (0.95)	75	0%
85	44	139−141 (E/W)	−31.5 (1.00)	75, 300	0, 10%
86	34	130−133 (EE/H)	−23.1 (1.00)	10, 75	0, 100%
87a/b	57	148−151 (E)	−19.8 (0.88)[n]	10	70% (5.7 mg/kg)
87a	40	151−153 (E)	−14.9 (1.00)	10	70% (6.3 mg/kg)
87b	18	197−199 dec (E)	−43.5 (1.00)	10	70% (6.5 mg/kg)
90a	56	68−73 (foam, LC)	+23.3 (1.00)	75, 300	0, 75%
91a	23	77−101 (foam, LC)	+4.1 (1.00)	300	80%
93a	27	175−176 (E)	+19.5 (1.00)	300	40%
95	24	168−170 (EA/H)		75	0%
96	40	152−154 (EA/H)		75	0%
100	55	70 dec (CC)		75	0%
101	41	wax (CC)		75	0%
102	68	50−52 (CC)		75	0%

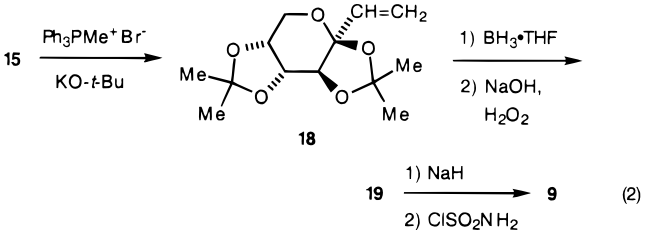
Table 1. (Continued)

compd[a]	% yield[b]	mp (purifcn)[c]	$[\alpha]_D$ (*c*)[d]	dosage po, mg/kg	MES test, 4 h % block (ED_{50})[e]
104	72	64−66 (EE/H)		75	0%
105[q]			+1.2 (0.50)	5, 35	30, 80% (16.6 mg/kg)
106	72	125−126 (AE/W)	+30.1 (1.85)	40, 80	20, 50% (82 mg/kg)
107	51	128−129 dec (AE/W)	+27.1 (1.18)	15, 30	30, 80% (22 mg/kg)
topiramate[r]				60	60% (53 mg/kg)
phenytoin[r]					(6.4 mg/kg)

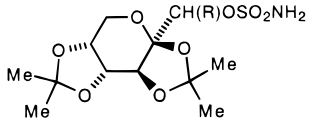
[a] All compounds were isolated and purified in unadducted form (i.e., no addition salts) unless indicated otherwise. They are represented by standard molecular formulas except for the following solvates: **6** (0.1 molar equiv of toluene), **7** (0.1 EtOAc, 0.1 DMF), **9** (0.3 H_2O), **10** (0.7 H_2O), **22** (0.15 EtOAc), **25** (1.0 imidazole), **33b** (0.1 EtOAc), **34** (0.1 EtOAc), **45** (0.1 H_2O), **64** (0.1 H_2O), **66** (0.15 $CHCl_3$), **83b** (0.25 EtOAc), **83f** (0.1 EtOAc), **91a** (0.2 CH_2Cl_2, 0.1 hexanes). Compounds are crystalline solids unless noted otherwise in the mp column. Microanalytical data (C, H, N; sometimes S; water where necessary) were within the accepted range (±0.4%) unless indicated otherwise. All new target compounds were characterized by high-field NMR and mass spectrometry. [b] The yields given are for the final synthetic step, as referred to in the text; they are for the product prior to final purification. [c] Mp values (in °C) are corrected to a set of standards. The purification method is indicated in parentheses: for compounds purified by recrystallization, a solvent is given in parentheses (AE = 95% EtOH, B = benzene, E = EtOH, EA = ethyl acetate, EE = ethyl ether, H = hexanes, I = 2-propanol, M = MeOH, W = water); "LC" or "CC" is given in parentheses for compounds purified by preparative HPLC or flash column chromatography; for noncrystalline compounds, a descriptor of physical form is indicated. [d] Optical rotations (in units of degrees) were measured at 25 °C in methanol, unless otherwise noted. The concentration, in g/100 mL, is given in parentheses. [e] Maximal electroshock seizure test in mice. Activity was measured at 4 h following administration of the oral dose, unless noted otherwise, and is reported as percent block at the given dose(s). ED_{50} values are given in parentheses for selected compounds. The 95% confidence limits for the ED_{50} values are contained in Supporting Information (see paragraph at the end of this paper). [f] For three batches, the mp varied from 150 to 151 (dec), 139−141 (dec), and 147−148 (dec) °C. Recrystallized from ethanol−water, 1:1. [g] %C: 44.65/45.30. [h] Activity of 70% at 75 mg/kg at 1 h. [i] %C: 46.07/46.54. [j] Determined at 20 °C. [k] Lit. mp 126−127 °C (ref 15). [l] Activity of 60% at 35 mg/kg at 1 h. [m] %C: 47.23/47.87. [n] Activity of 80% at 75 mg/kg at 1 h. [o] Reported in ref 29. [p] Determined in chloroform. [q] Reported in ref 58. [r] Reference compound.



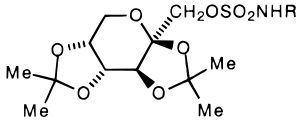
The synthesis of sulfonamide **8** began with a Wadsworth−Emmons olefination reaction between aldehyde **15**[8,9] and the phosphonate reagent depicted in eq 1, which was prepared by treating ethyl methanesulfonate with butyllithium (THF, −70 °C) followed by diphenyl phosphorochloridate.[10] Alkene **16**, which was obtained in 67% yield exclusively in the *E* configuration, was hydrogenated, hydrolyzed, and acidified to furnish **17** (48%), which was converted to **8** with thionyl chloride and ammonia (25%).



Wittig methylenation of aldehyde **15** afforded **18**[8b] (14% yield), which was subjected to standard hydroboration−oxidation to give alcohol **19**[8b] in 37% yield (eq 2). Reaction with NaH and sulfamoyl chloride provided homologue **9** in 41% yield. For homologue **10**, aldehyde **15** was converted with $Ph_3P{=}CHCO_2Me$ to the corresponding enoate (*E*:*Z* = 13:1; 95% yield),[11] which was hydrogenated (H_2, PtO_2), reduced with $LiAlH_4$ to alcohol **20**[12] (91%), and reacted with NaH and sulfamoyl chloride (53%).



21a R = Me
21b R = Et



22 R = Et **24** R = Bn
23 R = Bu **25** R = Ac

We also substituted the C1 methylene of **1** with methyl (**21a**) and ethyl (**21b**). Hence, aldehyde **15** was reacted with methyl- or ethylmagnesium bromide in ether to give the intermediate alcohols, each as a strongly biased mixture of two diastereomers, with respective isomer ratios of ca. 10:1 and 5:1, presumably in the same direction (*R* configuration; vide infra).[8c,13] Reaction of each alcohol with NaH and sulfamoyl chloride provided **21a** as virtually a single isomer and **21b** as a 5:1 mixture (ca. 45% yield for each). Because of the quaternary stereogenic center at C2, adjacent to the newly created stereogenic center at C1, it was not possible to assign the configuration at C1 from ^1H or ^{13}C NMR data. Thus, the direction of this highly diastereoselective addition to aldehyde **15** would have remained unknown.[8d] However, we were fortunately able to obtain a single crystal of the major diastereomer of **21a** and establish the configuration at C1 as *R* by X-ray analysis. By analogy with **21a**, we assign the *R* configuration at C1 in the major isomer of **21b**.

Our previous report[2a] indicated that substitution of the nitrogen of **1** resulted in attentuated anticonvulsant activity. The *N*-methyl analogue showed reasonable activity, being 50% less potent than **1**; however, the *N*-phenyl and *N*,*N*-dimethyl analogues were virtually

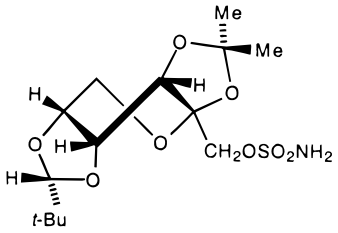
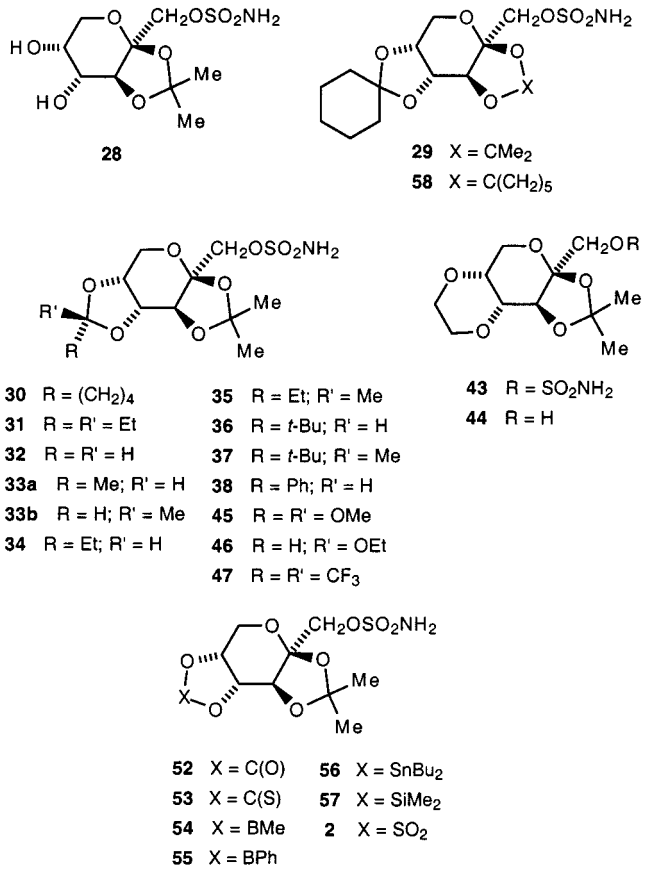


Figure 1. Compound **36** shown in the twist-boat (or skew) conformation.

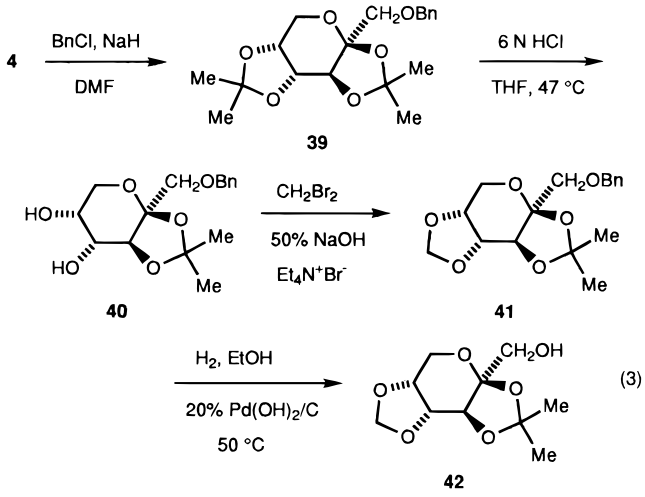
inactive. We synthesized four additional N-substituted compounds, **22**−**25**, to further define the SAR of **1**.[14] Treatment of alcohol **4** with sulfuryl chloride in the presence of pyridine (toluene, 0−10 °C) afforded a reasonably stable chlorosulfate[2a] (**26**) in 95% yield. Reaction of **26** with excess ethylamine, butylamine, or benzylamine provided **22**−**24** (yields: 59, 67, and 76%). Reaction of **1** with 1-acetylimidazole provided **25**, which was isolated and purified as a crystalline imidazole salt (78% yield). Mesylate **27**,[15] which is isosteric with **1** but lacks the acidic, hydrogen-bond donor group, was obtained by reacting **4** with methanesulfonyl chloride in the presence of triethylamine (76% yield).

The 4,5-Ring in 1. We were interested in modifying the 4,5-ketal of **1** by changing the ring substituents, size, and composition, as well as breaking the ring open and removing the ring. Data for the various target compounds are presented in Table 1. Earlier, we reported[2a] on 4,5-diol **28** and cyclohexylidene compound **29**, both of which are devoid of anticonvulsant activity. We have followed up on **29** with cyclopentylidene analogue **30**, which was prepared from **28** and the trimethylsilyl enol ether of cyclopentanone in 42% yield. A series of related ring-substituted analogues, **31**−**38**, were also synthesized from **28**. Ketone adduct **31** was produced via the silyl enol ether method (34% yield), while **35** and **37** were produced by using the relevant ketone in the presence of triethyl orthoformate (yields: 79 and 55%). We obtained **35** as an 85:15 mixture of diastereomers in favor of the *R* form, as shown, and **37** exclusively as the *R* isomer. Analogues **33**, **34**, **36**, and **38** were obtained via condensation of **28** with the relevant aldehyde diethyl acetal, generated in situ from the aldehyde and triethyl orthoformate (yields: 39, 34, 45, and 50%). We obtained **33** and **34** as a 90:10 mixture of diastereomers in favor of the *R* form, and **33a** and **33b** were separated by HPLC for independent biological testing; by contrast, we obtained **36** and **37** exclusively as the *R* isomer, and **38** as a 3:1 *R*:*S* mixture (which could not be readily separated by HPLC). It is interesting to note that there is a strong preference for the bulky substituent to occupy an endo position on the five-membered dioxolane ring of the cis-fused 5,6-ring system. Given a twist-boat conformation for the pyran ring,[2a,4] this suggests that the dioxolane ring fused to the 4,5-position of the sugar pyran ring is folded outward from the pyran ring with the large group favored in a pseudoequatorial orientation (endo), as opposed to a pseudoaxial orientation (exo). This structural disposition is illustrated for **36** in Figure 1.

To synthesize **32**, we resorted to a different approach, involving dibromomethane alkylation under phase-transfer conditions (eq 3),[16] because reactions of **28** with 37% formaldehyde[17a] (HCl, heat) or paraformaldehyde[17b]



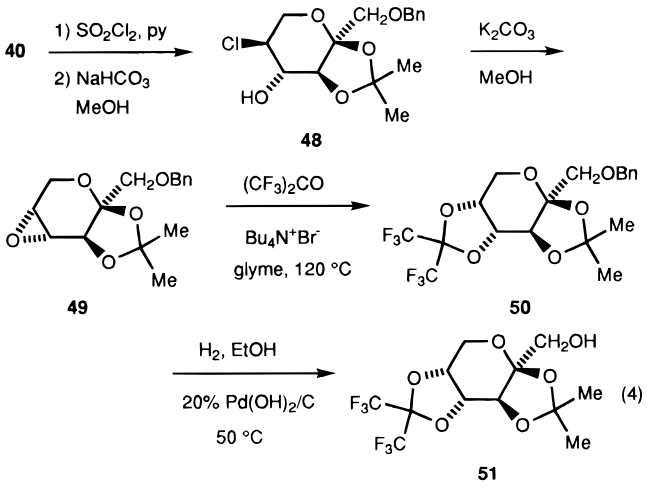
(H_2SO_4, heat) were unsuccessful.[18] Thus, **4** was benzylated in 87% yield to give **39**, which was carefully hydrolyzed to furnish diol **40** in 23% yield.[19] Phase-transfer alkylation at 60 °C yielded **41** (60%), which was subjected to hydrogen in the presence of Pearlman's catalyst to give **42** (99%).[20] Reaction of **42** with NaH and sulfamoyl chloride provided **32** in 79% yield. By the same token, fused 1,4-dioxane analogue **43** was synthesized by alkylating diol **40** with 1,2-dibromoethane in the presence of 50% NaOH (34% yield) and deprotecting the intermediate with hydrogen and Pearlman's catalyst to give **44** (98% yield). Reaction of **44** with sulfamoyl chloride and triethylamine supplied **43** in 55% yield.



(3)

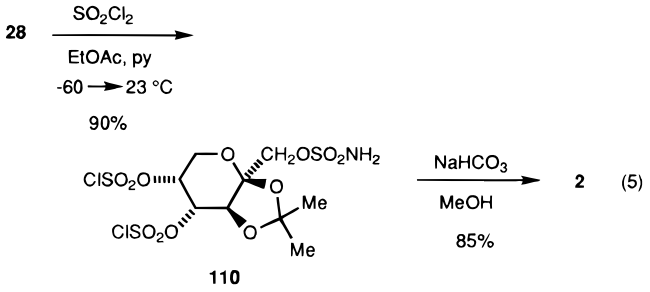
Reaction of diol **28** with tetramethyl orthocarbonate[21] or triethyl orthoformate (*p*-TsOH catalyst) afforded **45**

in 42% yield or **46** in 44% yield; the latter reaction also contained the ethyl imidate of **46** as a significant byproduct. Compound **46** was a 90:10 mixture of diastereomers with the major form being the *S* isomer, that is, having the ethoxy group in the exo position. This is the opposite stereochemical preference relative to the alkyl-substituted compounds and is probably reflective of a strong anomeric effect,[22] which would favor an ether group in the pseudoaxial position of a 1,3-dioxolane (see Figure 1).

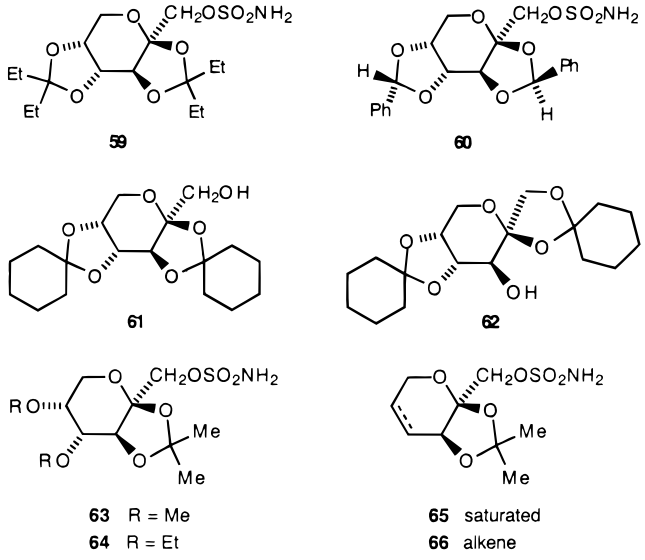


We wanted to synthesize bis-trifluoromethyl analogue **47** because it has a very favorable clogP value of 2.09 for effective transport across the blood−brain barrier, relative to a measured log *P* of 0.53 for **1** (vide infra);[23] additionally, the trifluoromethyl groups would impart little steric perturbation relative to the structure of **1**. Reaction of diol **28** with trifluoroacetaldehyde ethyl hemiacetal or chloral diethyl acetal under acidic conditions (sulfuric acid, triethyl orthoformate) led only to the formation of **1** (30% yield), presumably via disproportionation. Hexafluoroacetone was reacted with **28** to generate a 1:1 adduct that was subjected to dehydration with dicyclohexylcarbodiimide (DCC) at 90 °C; however, target **47** was not formed.[24] Cyclic carbonate **52** (vide infra) also failed to react with hexafluoroacetone ethyl hemiacetal at 100 °C for 18 h.[25] The successful synthesis started with diol **40**, which was converted[26] to chlorohydrin **48** in 47% yield (eq 4). Formation of epoxide **49** occurred in 100% yield, and condensation with hexafluoroacetone in the presence of iodide in a sealed vessel for 38 h provided ketal **50** in 89% yield.[27,28] Presumably, the reaction involves an intermediate iodohydrin that reacts with hexafluoroacetone to give an oxyanion adduct, which cyclizes to the desired product. Removal of the benzyl group (100% yield) and reaction of **51** with sulfamoyl chloride and triethylamine (DMF, 5 °C) supplied **47** in 81% yield.

We explored the introduction of other alterations into the 4,5-ring of **1** involving sp^2 carbons and noncarbon atom centers. Reaction of **28** with 1,1′-carbonyldiimidazole ($Im_2C{=}O$) or 1,1′-thiocarbonyldiimidazole ($Im_2C{=}S$) provided **52** (27%) or **53** (40%),[29] and with $MeB(OH)_2$ (in MeOH) or $PhB(OH)_2$[30] (in MeOH/water) provided **54** (50%) or **55** (92%). Although **28** with dibutyltin oxide[31] (refluxing MeOH) successfully generated **56**, the product was hydrolyzed back to **28** on attempted silica gel chromatography. Reaction of **28** with dimethyldichlorosilane (Et_3N, THF) led to decomposition products instead of **57**. A more chemically propitious result was realized in the reaction of **28** with sulfuryl chloride,[26] which afforded cyclic sulfate **2** in ca. 75% yield over two steps (eq 5).[4] The chemistry for obtaining diverse 4,5-cyclic sulfur compounds akin to **2** is discussed in the next section.

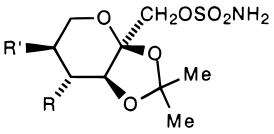


Some analogues of **1** with the 2,3-ring modified, along with the 4,5-ring, were prepared (viz. **58**−**60**). Thus, reaction of D-fructose with cyclohexanone in the presence of sulfuric acid, under conditions favoring the thermodynamic diketal, yielded a mixture of **61** and **62** in a 10:1 ratio, contaminated with oligomeric material from self-condensation of cyclohexanone. Alcohol **61**, isolated by Kugelrohr distillation followed by HPLC, was reacted with sulfuryl chloride and pyridine (toluene, 5 °C) to give the chlorosulfate (100% yield), which was reacted with anhydrous ammonia to give target **58** in 98% yield. The procedure for forming the sulfamate from an alcohol is generally superior to sulfamoyl chloride and base. In a similar manner, D-fructose was reacted with 3-pentanone to obtain the thermodynamic bis-ketal (ca. 10% yield), which was subjected to sulfuryl chloride/pyridine, then ammonia, to supply **59** in 96% yield.[32] Reaction of D-fructose with benzaldehyde and anhydrous zinc(II) chloride provided a mixture of at least three bis-acetal isomers,[33] from which one isomeric alcohol was isolated after chromatography and recrystallization in ca. 5% yield.[34] Reaction of the alcohol with sulfamoyl chloride and triethylamine (DMF, 5 °C) provided **60** in 72% yield.

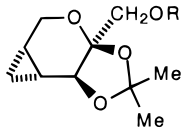


Although ring-opened diol **28** lacks anticonvulsant activity,[2a] its higher polarity than **1** detracts from a fair

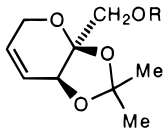
comparison of structure−activity for 4,5-ring cleavage. Thus, we studied other analogues of **1** missing the 4,5-ring, such as ethers **63** and **64** and dideoxy compounds **65** and **66**. Alkylation of **28** with dimsylsodium and MeI failed to provide **63**, the major product being the *N*,*N*-dimethyl derivative of **28**. However, diol **40** was alkylated with MeI or EtI (NaH, DMF) to furnish the corresponding bis-ethers, which were deprotected (H_2, 10% Pd/C) and treated with NaH and sulfamoyl chloride to yield **63** (58%) or **64** (54%). Proton NMR data for **63** and **64** indicate that these compounds prefer the chair conformation (vide infra).



67 R = I; R' = OC(O)SMe
68 R = Br; R' = Br



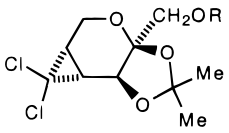
69 R = SO_2NH_2
70 R = H
72 R = Bn



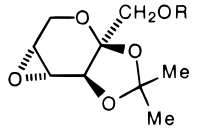
71 R = Bn
73 R = H

The Corey−Winter reaction[35] of cyclic thiocarbonate **53** in refluxing trimethyl or triethyl phosphite provided the *N*-methyl or *N*-ethyl version of alkene **66**,[36] while *N*,*N*′-dimethyl-2-phenyl-1,3,2-diazaphospholidine[37] was not satisfactory because of extensive decomposition. We were able to execute the elimination reaction by using distilled triisopropyl phosphite; however, the yield of **66** was poor. Reaction of **53** with $Fe(CO)_5$ in refluxing xylenes[38] or $Ni(COD)_2$ in refluxing THF[39] also failed to generate any **66**. By contrast, reaction of **53** with MeI[40] (DME, 90 °C, sealed tube) produced a mixture of iodo thiocarbonate **67** (74%) and cyclic carbonate **52** (23%),[29] and reduction of **67** with Zn powder in refluxing 95% ethanol supplied alkene **66** in 67% yield.[29] Catalytic hydrogenation of **66** with PtO_2 as catalyst furnished **65** in 88% yield. Addition of bromine to **66** furnished dibromosorbopyranose **68**, along with ca. 20% of the related β-D-tagatopyranose isomer (not shown), as reported earlier.[29]

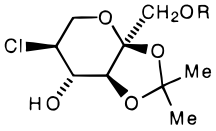
Alkene **66** failed to undergo Simmons−Smith cyclopropanation with diiodomethane to yield **69**, in the presence of zinc−copper couple, diethylzinc, or Zn/CuCl (all in ether).[41] A small amount of the alcohol **70** could be isolated from the assorted byproducts in the diethylzinc reaction. Presuming that the sulfamate group interfered with the cyclopropanation, we prepared alkene **71** for study by converting diol **40** to a cyclic thiocarbonate ($Im_2C{=}S$, THF; 93% yield) and heating that with trimethyl phosphite (83% yield). Simmons−Smith cyclopropanation of **71** with CH_2I_2/Et_2Zn gave a 5% yield of **72**, whereas the yield with CH_2I_2/Zn−Cu was somewhat better. Alcohol **73**, from hydrolysis of **66** with KOH in ethanol (15% yield), gave a cleaner reaction with CH_2I_2/Zn−Cu in a shorter amount of time, although the 7% yield of **70** was still quite poor.[42] As an alternative, we decided to examine dihalocarbene addition reactions. When **71** or **73** was heated with excess $PhHgCBr_3$ in DME at 150 °C,[43] no dibromocyclopropane adduct was detected among the numerous products; negative results were also found for reactions of **66** with $PhHgCBr_3$ and **71** with $PhHgCBrCl_2$.[43] Fortunately, reaction of **71** with $PhHgCCl_3$ at 150 °C for 4 days generated dichlorocyclopropane **74** in 25% yield; however, on a 6-g scale only a 10% yield of **74** was realized after extensive HPLC purification. Most favorably, reaction of **71** with chloroform and KOH under phase-transfer conditions ($BnNEt_3^+Cl^-$ catalyst) provided **74** in 44% yield.[44] Debenzylation of **74** was accomplished by free-radical bromination followed by hydrolysis (*N*-bromosuccinimide, CH_2Cl_2/water, *hν*; 21% yield),[45] and intermediate **75** was converted to target **76** with sulfamoyl chloride and triethylamine (50% yield). Since **76** was found to be devoid of anticonvulsant activity (vide infra), we discontinued the pursuit of **69**. Nevertheless, we were able to prepare isosteric epoxide **77**, as a related three-membered-ring analogue of **1**. Hence, sorbopyranose chlorohydrin **78**[26,29] was cleanly transformed by K_2CO_3 in methanol to epoxide **79** (99% yield), which was reacted with NaH and sulfamoyl chloride to give **77** (58% yield). We also converted **78** into sulfamate **80**, as disclosed previously.[29]



74 R = Bn
75 R = H
76 R = SO_2NH_2



77 R = SO_2NH_2
79 R = H



78 R = H
80 R = SO_2NH_2

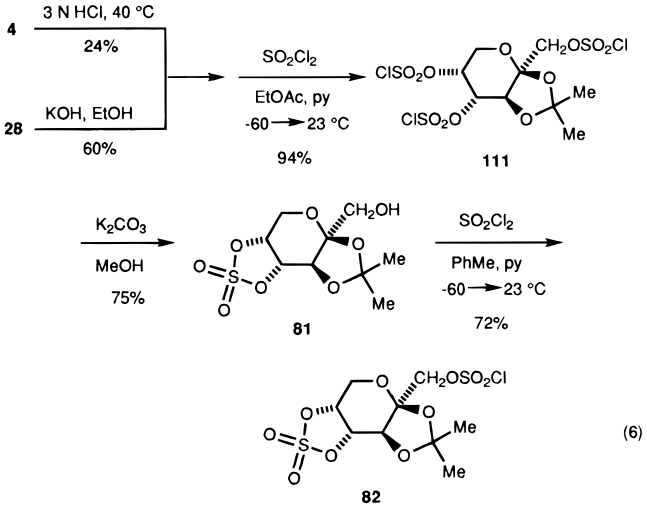
4,5-Cyclic Sulfur Derivatives Related to 2. Cyclic sulfate **2** was prepared from **28** by bis-chlorosulfate formation followed by base-induced 4,5-ring closure (eq 5; vide supra).[4] Owing to the exceptional biological activity found with **2** (vide infra),[4] we concentrated synthetic efforts on related compounds in order to define the SAR surrounding this series (Table 1). A collection of N-substituted analogues was generated from chlorosulfate **82**,[46] which was synthesized from bis-acetonide **4** or diol **28**, via alcohol **81**, according to the chemistry in eq 6.[4] Conversion of the tris-chlorosulfate to **81** with sodium bicarbonate, according to the literature,[26] resulted in a much lower yield (24%) than that obtained with potassium carbonate (75%); also, the reaction time for dechlorosulfation was shorter and formation of byproduct **78** was minimized. Reaction of **82** with diverse primary and secondary amines provided target sulfamates **83a**−**p** (see Table 2 for structural definition) in 40−90% yield.[4,47] Azido sulfate **83r** was obtained in 82% yield by reacting **82** with sodium azide (pyridine, MeCN). The carbamate analogue of **2**, **84**, was prepared

Table 2. Structures for 4,5-Cyclic Sulfate Derivatives **83**

compd	R	R′	compd	R	R′
83a	H	Me	**83j**	H	c-Pr
83b	H	Et	**83k**	H	c-Bu
83c	H	CH_2CF_3	**83l**	H	c-Oc
83d	H	Bu	**83m**	Me	Me
83e	H	allyl	**83n**	Et	Et
83f	H	octyl	**83o**[a]	$-(CH_2)_5-$	
83g	H	Ph	**83p**[b]	$-(CH_2)_2NBn(CH_2)_2-$	
83h	H	4-anisyl	**83q**[c]	$-CH=NCH=CH-$	
83i	H	benzyl	**83r**[d]	$-N_2-$	

[a] NRR′ = piperidide. [b] NRR′= 4-(benzyl)piperazide. [c] NRR′ = imidazolide. [d] NRR′ = azide.

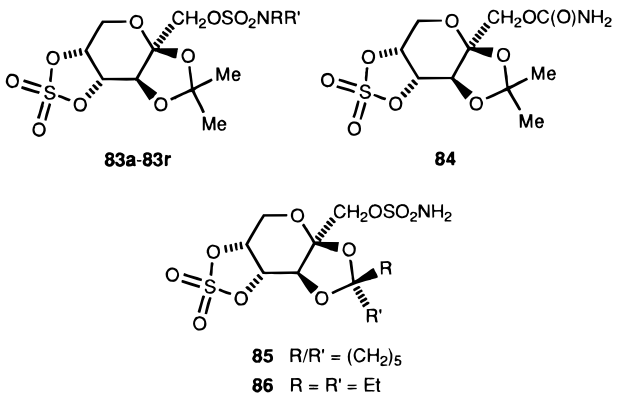
in 71% yield from alcohol **81** by treatment with $Cl_3CC(O)Cl$ (1 equiv) and pyridine, isolation of the intermediate chloroformate, and reaction of it with anhydrous ammonia.



Cyclic sulfates **85** and **86**, with a modified 2,3-ketal group, were synthesized from bis-ketals **58** and **59**. Thus, bis-cyclohexylidene sulfamate **58** was hydrolyzed under acidic conditions (6 N HCl, 50 °C) to the 4,5-diol (17% yield), which was reacted with sulfuryl chloride and pyridine, followed by methanolic $NaHCO_3$, to give **85** in 44% yield. Tetraethyl sulfamate **59** was hydrolyzed to the 4,5-diol (23%), which was converted to **86** in the same fashion (34%).

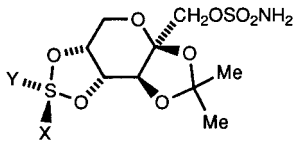
We sought to alter the cyclic sulfate moiety in **2** in terms of substitution on sulfur. Cyclic sulfite **87** was an obvious entity and we were interested in obtaining the *S* (**87a**, exo) and *R* (**87b**, endo) isomers independently for biological evaluation. Reaction of diol **28** with thionyl chloride produced a 5.3:1 mixture of **87a:87b** (THF at 23 °C).[4] The individual diastereomers were obtained starting with diol **40** according to the route that we described previously in our preliminary communication[4] (see the Experimental Section for details). This entailed the formation of benzyl cyclic sulfites **88a** and **88b** with thionyl chloride (12:1 in THF at 5 °C; 2:1 in 1,4-dioxane at 100 °C), separation of the 2:1 mixture, photodebenzylation of each isomer with *N*-bromosuccinimide, and sulfamoylation.[4]

Benzyl cyclic sulfite **88**[4] was reacted with *p*-tosyl azide and copper(0) (refluxing MeOH) in the hope of forming imidosulfate **89**,[48a] but no reaction was detected; reaction with $(BocN)OsO_3$ or $Se(NTs)_2$ also resulted in

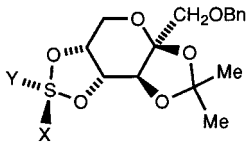


recovered starting material.[48b] Reaction of diol **28** with excess $TsN{=}SCl_2$[49] furnished imidosulfite **90a** (56% yield; stereochemistry tentatively assigned[50]), along with a some **87a**/**b**, which were difficult to separate away. Oxidation with sodium periodate and $RuCl_3$[51] gave imidosulfate **91a** (23% yield; presumably with retention of configuration[50]), along with **2** and *p*-$TsNH_2$ as byproducts. Attempted detosylation of **91a** with sodium naphthalenide in 1,2-dimethoxyethane (DME) at 5 °C[48c,52] afforded alkene **66** instead of **92a**, and under the same conditions, **90a** afforded diol **28**. *N*-Boc imidosulfite **93a** (stereochemistry tentatively assigned[50]) was synthesized from diol **28** and $BocN{=}SCl_2$[53] (pyridine, THF, 5 °C) in 27% yield, but oxidation of **93a** with sodium periodate and $RuCl_3$ only produced **2**. However, attempts to remove the Boc group of **93a** to obtain **94a** under acidic conditions was not successful. Treatment with trifluoroacetic acid generated target **94a**, but it appeared to be too hydrolytically unstable for isolation, while 3 N HCl (in ethyl acetate) provided diol **28** and trimethylsilyl iodide (CH_2Cl_2, 30 min) caused decomposition. It should be noted that **90a**, **91a**, and **93a** constitute rare examples of five-membered cyclic imidosulfur species.

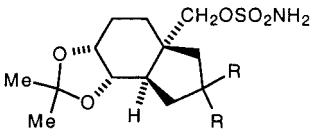
The Endocyclic Oxygen Atoms in 1 and 2. We were interested in assessing the relevance of various sugar-associated oxygen atoms, on C1−C6 of **1**, to achieving anticonvulsant activity. Some structures already mentioned (vide supra) serve to test this point: for **8**, O1 was replaced by CH_2; for **65** and **66**, O4 and O5 were removed; for **67** and **80**, O5 was replaced by halogen; for **68**, O4 and O5 were replaced by bromine; for **76**, O4 and O5 were replaced by a strained carbocycle; and for **77**, O4 and O5 were combined into a strained ring. In addition to the unsubtle changes wherein the 4,5-ring was either destroyed or severely strained (except for **8**), we endeavored to replace O2, O3, and O6 specifically with methylene groups and keep the tricyclic ring system intact. We have already communicated the stereoselective, multistep syntheses of hydrindan derivatives **95** and **96**, in which O2, O3, and O6 are replaced by CH_2.[54,55] We have also used intermediate alcohol **97**[54] to prepare 4,5-cyclic sulfate analogue **100**, according to the chemistry in eq 7. Crude **97** was benzylated, and the resulting ether was oxidized stereoselectively to diol **98** with catalytic OsO_4 and *N*-methylmorpholine *N*-oxide (NMO).[56] Sequential treatment with NaH and sulfuryl diimidazole[57] afforded the cyclic sulfate, which was debenzylated to give **99**.



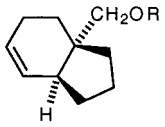
87a X = O; Y = :
87b X = : ; Y = O
90a X = NTs; Y = :
90b X = : ; Y = NTs
93a X = NBoc; Y = :
93b X = : ; Y = NBoc
91a X = NTs; Y = O
91b X = O; Y = NTs
92a X = NH; Y = O
92b X = O; Y = NH
94a X = NH; Y = :
94b X = : ; Y = NH



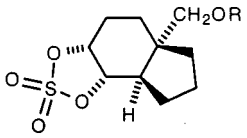
88a X = O; Y = :
88b X = : ; Y = O
89a X = O; Y = NTs
89b X = NTs; Y = O



95 R = H
96 R = Me

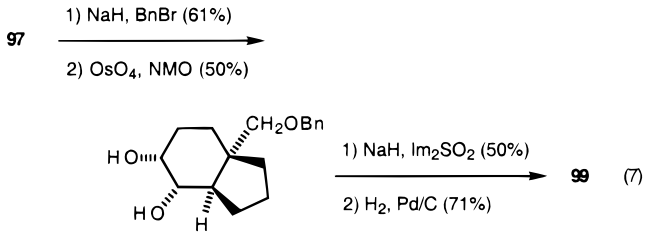


97 R = H
101 R = SO_2NH_2



99 R = H
100 R = SO_2NH_2

Treatment of **99** with NaH and sulfamoyl chloride resulted in a complex product mixture, from which **100** could not be isolated cleanly; reaction of **99** with sulfuryl chloride followed by ammonia also failed. The cyclic sulfate in this series, because of the absence of two neighboring, electron-attracting oxygen atoms, is more chemically reactive. Target **100** was ultimately obtained in 90% yield by reacting **99** with sulfamoyl chloride and triethylamine.

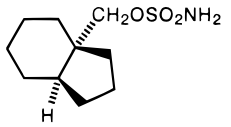


97 → (1) 1) NaH, BnBr (61%); 2) OsO_4, NMO (50%) → **98**

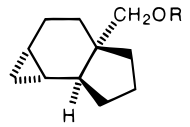
98 → (2) 1) NaH, Im_2SO_2 (50%); 2) H_2, Pd/C (71%) → **99**

Alcohol **97** was converted into sulfamate **101** with NaH and sulfamoyl chloride (15% yield) and into saturated sulfamate **102** (76% yield) by hydrogenation (10% Pd/C) followed by NaH and sulfamoyl chloride. Simmons−Smith cyclopropanation of alcohol **97** with diiodomethane and diethylzinc worked well, in comparison to cyclopropanation of **73** (vide supra), to provide **103** in 67% yield; reaction with NaH and sulfamoyl chloride gave target **104** in 72% yield.

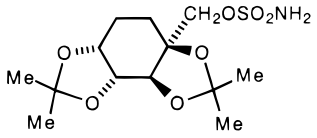
Compound **105** was synthesized as an analogue of **1** with the O6 replaced by a methylene group. This derivative of pseudo-β-D-fructose was obtained from (−)-quinic acid via a lengthy, multistep protocol that has been published in detail.[58]



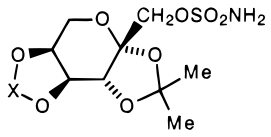
102



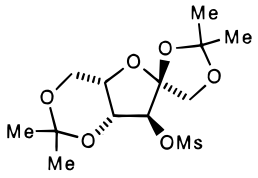
103 R = H
104 R = SO_2NH_2



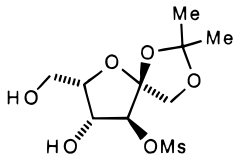
105



106 R = CMe_2
107 R = SO_2



108



109

L-Fructose Isomers of 1 and 2. The L-enantiomers of topiramate (**1**) and RWJ-37947 (**2**) were sought for biological evaluation (**106** and **107**). Consequently, we prepared L-fructose from L-sorbose via the four-step process developed by Chen and Whistler,[59] with one proviso. The single-pot conversion of **108** to **109** was problematic, with yields of L-fructose under 10%. As a remedy, we isolated diol **109** prior to treatment with hydroxide and thereby garnered a 60% yield of L-fructose. Following our established methodology, **106** was produced by bis-acetonide formation (56% yield) and sulfamoylation (72%),[2a] and **107** was produced, in analogy to **2** (eq 5),[4] by controlled hydrolysis of **106** (37%), bis-chlorosulfate formation (48%), and 4,5-ring closure (50%).

Biological Activity

Anticonvulsant activity for topiramate (**1**) and its analogues was generally evaluated by using the standard maximal electroshock seizure (MES) test.[60] Activity is indicated by a block of the hind-limb tonic-extensor seizure caused by application of an electric shock via corneal electrodes (percent of total animals dosed). From experience over many years, this assay is noted for being highly predictive of clinical efficacy for new anticonvulsant compounds in patients with partial-onset or generalized seizures. Data for the diverse topiramate analogues, tested 4 h after oral administration, are presented in Table 1.

Anticonvulsant Structure−Activity Relationships. In our earlier work on analogues of topiramate,

monomethyl, monophenyl, or dimethyl substitution on nitrogen of the sulfamate group caused a significant attenuation in potency in the MES test in mice, while replacement of the sulfamate with a carbamate abolished activity. Additionally, linkage of the two methyl groups on the 4,5-ketal ring into a cyclohexane ring, or removal of the 4,5-ketal to give a 4,5-diol, abolished MES activity. Further modifications of the sulfamate group were investigated.

The nitrogen and carbon isosteric analogues of OSO_2NH_2, **6**, **7**, and **8**, were devoid of activity, as were homologues with an elongated linker, **9** and **10**, and mesylate **27** (Table 1). Methyl and ethyl substitution of the side chain, **21a** and **21b**, also resulted in a total loss of activity. Substitution of the nitrogen of topiramate (**1**) with one methyl, ethyl, or butyl group did not have a major effect on potency (**1**, 60% block at 60 mg/kg;[4] N-Me **1**, 60% at 75 mg/kg;[4] **22**, 90% at 75 mg/kg; **23**, 80% at 75 mg/kg); however, phenyl (0% at 200 mg/kg[2a]) or benzyl substitution (**24**, 0% at 75 mg/kg) did. Substitution with acetyl (**25**, 30% at 75 mg/kg) and dimethyl (N,N-Me_2 **1**, 0% at 75 mg/kg and 80% at 200 mg/kg)[2a,4] groups caused a significant drop in potency.

The 4,5-ring turned out to be very sensitive to substitution. Although we already knew that a cyclohexylidene group is undesirable (**29**, 20% at 200 mg/kg),[2a] we looked at this area in some detail. The homologous cyclopentylidene analogue **30** was also found to be inactive. Removal of the two 4,5-ring methyl groups of topiramate drastically reduced potency (**32**, 0% at 75 mg/kg). Removal of one methyl from **1** was less critical if it is the endo methyl, which results in the *S* isomer (**33b**, 100% at 75 mg/kg), as the *R* isomer (exo methyl removed) was inactive (**33a**, 0% at 75 mg/kg). On the contrary, the monoethyl *R* isomer **34** had reasonable potency (90% at 75 mg/kg). Addition to the structure of **1** of one methyl group hardly affected potency (**35**, 90% at 75 mg/kg); however, addition of two methyl groups did (**31**, 0% at 75 mg/kg and 80% at 300 mg/kg). Bulkier compounds **36** and **37** were devoid of activity at 75 mg/kg, and phenyl analogue **38** was weak (20% at 75 mg/kg). The dimethoxy (**45**) and monoethoxy (**46**) analogues were inactive at 75 mg/kg. The bis-trifluoromethyl analogue showed moderate potency (40% at 75 mg/kg). Potency for the cyclic carbonate (**52**), thiocarbonate (**53**), methylboronate (**54**), phenylboronate (**55**), bis-cyclohexylidene (**58**), tetraethyl (**59**), and diphenyl (**60**) analogues was significantly attenuated. However, the 4,5-cyclic sulfate derivative **2** had remarkable potency, as discussed below.

Compounds **63** and **64** were inactive in the MES test at 75 mg/kg, although weak activity was observed for **64** at 300 mg/kg (40% block); fused six-membered-ring analogue **43** (a homologue of **32**) was also inactive (0% at 75 mg/kg); and analogues **65** (0% at 75 mg/kg and 100% at 300 mg/kg) and **66** (0% at 300 mg/kg) had attenuated potency. However, **67** gave a 90% block at 75 mg/kg with an ED_{50} of 30.1 mg/kg, which compares quite favorably with topiramate (**1**) (60% block at 60 mg/kg; ED_{50} = 53.5 mg/kg). The ED_{50} values for **80** and **68** were also a respectable 21 and 24 mg/kg. The good potency for the L-sorbopyranose analogues, **67**, **68**, and **80**, is believed to be connected with their preference for a skew conformation, which is the case for topiramate (vide infra).[29] The cyclopropane (**76**) and epoxide (**77**) analogues showed attenuated potency.

The high potency of 4,5-cyclic sulfate **2** is a noteworthy finding (ED_{50} = 6.3 mg/kg). Consequently, several analogues (**83a**−**r**, **85**−**87**, **90a**, **91a**, **93a**) were prepared and investigated (Table 1). To summarize, very potent anticonvulsant activity is associated with relatively small alkyl substituents on the nitrogen, i.e., Me/H, Me/Me, Et/H, allyl/H, c-Pr/H, c-Bu/H) and with limited changes in the sulfate group, such as cyclic sulfite **87a/b**. Compound **2** is approximately 8 times more potent than topiramate and the *N*,*N*-dimethyl analogue in the cyclic sulfate series, **83m** (70% at 10 mg/kg, ED_{50} = 6.9 mg/kg), is nearly 20 times more potent than the *N*,*N*-dimethyl analogue in the topiramate series (0% at 75 mg/kg and 80% at 200 mg/kg).[2a,4] The least potent compounds in this N-substituted series were phenyl (**83g**), 4-anisyl (**83h**), cyclooctyl (**83l**), piperidide (**83o**), and 4-(benzyl)piperazide (**83p**). The cyclic sulfite isomers **87a** and **87b** were potent anticonvulsants with no significant stereochemistry-based difference in activity. *N*-Tosylimido sulfate **90a** exhibited modest potency (75% block at 300 mg/kg), as did the other imidosulfur compounds, **91a** and **93a** (80% and 40% block at 300 mg/kg).

Exploration of the ring oxygen atoms was an interesting endeavor that required considerable synthetic chemistry. Replacement of O2, O3, and O6 of topiramate via **95** and **96** resulted in a loss of potency, which was not helped by introducing a cyclic sulfate group (**100**). Carbocyclic sulfamates **101**, **102**, and **103** were also lacking in potency. One bright spot was **105**, in which only O6 was replaced by CH_2; this analogue has a 4-h ED_{50} value of 17 mg/kg, making it 3 times more potent than topiramate.

The biological results with the L-fructose enantiomers of **1** and **2**, **106** and **107**, are surprising in that the anticonvulsant activity for each pair, **1** vs **106** and **2** vs **107**, is not dramatically different. The eudysmic ratios based on the ED_{50} values in Table 1 are **1**:**106** = 1.5 and **2**:**107** = 3.5. At 1 h in mice, orally, **1** had an ED_{50} of 44 (30−61) mg/kg and **106** had an ED_{50} of 160 (140−189) mg/kg for a eudysmic ratio of 3.5.

The structure−activity relationships for the topiramate analogues studied to date, for the attainment of reasonably good anticonvulsant activity, can be summarized as follows. It is necessary that the sulfamate nitrogen be unsubstituted or bear fairly small alkyl groups. In the cyclic sulfate series, a larger variety of nitrogen substituents is acceptable, including cyclobutyl (**83k**) and dimethyl (**83m**). The sulfamate group cannot be replaced by carbamate and the linker between the sulfamate group and the sugar unit (−CH_2O−) cannot be altered in terms of its constitution, length, or substitution. The fused 4,5-ring is important, with a five-membered-ring being preferred. This ring can have a tetrahedral carbon (ketal) or tetrahedral sulfur (cyclic sulfate or sulfite) group with very limited substitution; but a planar group, such as C=O or MeB, appears to be highly disfavored. In the case of the 4,5-ketal, the two carbon substituents have to be larger than hydrogen and smaller than ethyl, which certainly applies a great constraint on the SAR. Additionally, the two substituents on the carbon of the 2,3-ketal should not be larger

Table 3. Physicochemical Data for **1**, **2**, and **31**

compd	*D*	pH	pK_a	*P*	log *P*	*P*7.4	log *P*7.4	clogP
1	3.26	7.25	8.66	3.34	0.53	3.21	0.51	0.50
2	2.44	7.35	8.51	2.61	0.42	2.42	0.38	−1.01
31	30.4	7.61	8.62	33.4	1.52	31.5	1.50	1.55

than methyl, nor connected into a ring. The sugar oxygen atoms at C1, C2, and C3 are important, whereas the one at C6 can be replaced.

log *P* and pK_a Determinations. Octanol−water partition coefficients, via log *P* values, can be important for determining biological properties in vivo, particularly with respect to compounds affecting the central nervous system (CNS).[61] The transport of drugs across the blood−brain barrier, a key factor in the potency of CNS agents, appears to be optimal at a log *P* value of 2.0. For the most part, compounds with log *P* values that exceed this value by ±2, i.e., >4.0 or <0, do not readily cross the blood−brain barrier to enter the CNS by passive mechanisms and thus exhibit poor CNS activity, although some compounds may enter the CNS by means of an active transport process.

We determined the log *P* and pK_a values for **1**, **2**, and **31** (Table 3). The apparent octanol−water partition coefficients, *D*, were measured in unbuffered water (pH 7.2−7.6) because the pH 7.4 buffer interfered with the HPLC refractive index assay. The pK_a values at 25 °C, obtained by potentiometric titration, are the range of 8.5−8.7, reflecting the weak acidity of the sulfamate group. The true partition coefficients, *P*, which are independent of dissociation, and the apparent partition coefficients at pH 7.4 (*P*7.4) were calculated from the expressions: $P = D\{1 + 10^{(pH - pKa)}]$ and $P_{7.4} = P/[1 + 10^{(7.4 - pKa)}]$. Calculated log *P* values were obtained by using the MedChem (Daylight) clogP program.[62]

The experimentally determined log *P* value for **1** of 0.53 is less than optimal, but it is not outside of the acceptable range for CNS active drugs. Although the log *P* value for **31** is 1.52, which would have been predicted given ca. 0.5 units/CH_2 group, the potency of **31** relative to **1** is not enhanced, rather it is actually about 2-fold lower (Table 1). The log *P* values for **1** and **31** are in close agreement with the clogP values, whereas this is not the case for **2** (possibly due to a lack of parametrization in the program for the cyclic sulfate group). Indeed, the clogP value for **2** of −1.01 initially raised concern until we obtained the biological data, which showed **2** to be significantly more potent than **1**. The experimentally determined log *P* value was 0.42 for **2**, which is nearly the same as that for **1**. Thus, the increase in potency for **2** over **1** is probably due to *intrinsic activity of the 4,5-cyclic sulfate moiety*, and not to improved bioavailability. The well-known anticonvulsants phenytoin and carbamazepine have log *P* values close to 2.0: the log *P* of phenytoin is 2.47 and the clogP of carbamazepine is 1.98. Certain analogues were thought promising for increased potency because of their favorable clogP values in conjunction with minor steric perturbation according to the developed SAR profiles, namely **47** (clogP = 2.01), **83m** (1.47), and **86** (1.48). However, no enhancement in potency was obtained: **47** is less potent than **1**, **86** is less potent than **2**, and **83m** is equipotent with **2** (Table 1).

Additional Biological Studies on 2 and Related Analogues. Time-course studies were conducted on **1** and **2** in the MES test in mice, on oral administration. The comparative data (Table 4) clearly show that **2** retains significant anticonvulsant activity out past 24 h, while **1** does not, and suggest that **2** has about a 2-fold longer duration of action than **1**. Peak activity for both compounds was observed in the range of 1−4 h. Comparative data were also acquired in the MES test in rats, on oral administration (Table 4). Hence, **2** was found to have impressive potency, with an 8-h ED_{50} value of 1.0 mg/kg, and an impressive duration of action, with significant anticonvulsant activity out past 48 h! Peak activity for **1** occurred at 4 h, whereas that for **2** occurred in the range of 4−12 h. Four close analogues of **2**, **83a**, **83b**, **83j**, and **83m**, were also studied in the MES test in rats and found to be quite potent, with ED_{50} values (95% confidence limits) at 4 h, po, of 2.7 (1.9−3.4), 1.2 (1.0−1.4), 2.5 (1.5−3.4), and 2.1 (1.7−2.5) mg/kg. The ED_{50} values (mg/kg) for **1** and **2** on intraperitoneal dosing, respectively, were as follows: 47 (36−66; 2 h) and 7.6 (5.2−13.7; 1 h) in mice; 24 (16−43; 2 h) and 1.8 (0.9−2.8; 1 h) in rats (95% confidence limits; time).

Compound **2**, like **1**, showed no activity in mice against convulsions induced by pentylenetetrazole (>500 mg/kg), bicucculine (>500 mg/kg), and picrotoxin (>500 mg/kg). In vitro binding and uptake assays with ca. 25 various CNS receptor preparations (e.g., benzodiazepine/GABA-A, dopamine D-1 and D-2, adrenergic α-1 and α-2, serotonin S-1A and S-2, GABA uptake, glutamate uptake, adenosine uptake, and serotonin uptake) showed virtually no activity (IC_{50} > 10 μM). A similar lack of activity in the binding and uptake assays was observed with **1** and phenytoin. Thus, **2** appears to have an anticonvulsant profile similar to that of **1** and phenytoin.

The neurotoxicity of **2** was explored in a standard rotorod test in mice and rats, which assesses motor impairment.[63] The respective TD_{50} values of >1000 mg/kg and >500 mg/kg established excellent neurotoxicity indices (TD_{50}/ED_{50}) of >150 (2 h) in mice and >250 (4 h) in rats. These results compare favorably to the TD_{50}/ED_{50} ratios for **1** (mice, 9.3; rats, >115), phenytoin (mice, 4.2; rats, >50), and carbamazepine (mice, 7.1; rats, 21). The oral LD_{50} values for **2** in mice and rats were also quite favorable: >1000 and >500 mg/kg.

The importance of an SO_2NH_2 moiety for potent anticonvulsant activity in several compounds prompted us to be interested in carbonic anhydrase isozymes.[64] At least seven isozymes of carbonic anhydrase (EC 4.2.1.1) are now recognized:[64] erythrocytes contain CA-I and CA-II; kidney membranes contain CA-IV; myelin contains CA-II; mitochondria contain CA-V; skeletal muscle and adipose tissue contain CA-III; and parotid tissue and saliva contain CA-VI and CA-VII. Our earlier work demonstrated that topiramate is a weak inhibitor of erythrocyte carbonic anhydrase in several species.[2a] The present study was undertaken to evaluate selected compounds, particularly **2**, for carbonic anhydrase inhibitory activity in various rat tissues: erythrocytes (blood), kidney membranes, and subcellular fractions of the brain, i.e., myelin, synaptosomes, and brain supernatant (see experimental). The IC_{50} values for **2** in inhibition of carbonic anhydrase from blood, kidney membranes, myelin, high-density synaptosomes, and brain supernatant ranged from 21 to 130 nM,

Table 4. Comparative Time-Course Data for **1** and **2** in Mice and Rats (po)[a]

	time (h)							
no.	1	2	4	8	12	16	24	48
				Mice				
1	43.8 (31−61)	47.6 (33−66)	53.5 (36−77)		246 (197−303)	720 (592−928)	>1000	
2	8.6 (7.9−9.6)	6.6 (4.5−8.8)	6.3 (5.1−7.6)		23 (18−27)	ca. 50	72 (57−87)	
				Rats				
1	15 (0.1−??)	16 (12−51)	6.7 (5.1−8.1)	15 (6.4−19)	34 (20−51)	103 (64−137)	153 (76−473)	>1000
2	3.8 (1.2−6.7)	5.1 (2.2−7.7)	1.7 (1.1−2.5)	1.0 (0.6−1.4)	1.3 (1.0−1.8)	2.5 (1.7−3.0)	2.6 (1.5−3.5)	18 (10−26)

[a] Doses for each time point are reported as ED_{50} values (mg/kg); 95% confidence limits are given in parentheses.

Table 5. Inhibition of Carbonic Anhydrase by **1**, **2**, and Acetazolamide[a]

compd	blood	kidney	myelin	synaptosomes	brain
1	8890 (3600−21800)	8350 (4200−16600)	1360 (570−3230)	4840 (860−27400)	4550 (1170−17700)
2	84 (30−236)	130 (56−308)	52 (7−377)	21 (6−72)	27 (5−158)
azm[b]	37 (25−54)	650 (110−4080)	24 (10−58)	7 (3−15)	12 (3−44)

[a] Inhibition of carbonic anhydrase from blood, kidney membranes, myelin, high-density synaptosomes, and brain supernatant (see the Experimental Section). IC_{50} values are reported in nM units, followed by 95% confidence limits in parentheses. [b] azm = acetazolamide.

depending on the tissue preparation (Table 5). The potency range for **2** is generally comparable to that for acetazolamide (7−650 nM), a well-known reference inhibitor (Table 5). The results for topiramate (**1**) indicate that it is a markedly less potent carbonic anhydrase inhibitor (Table 5). Clearly, **2** is a more potent inhibitor than topiramate by a factor of 25−250 depending on the tissue source. We also determined IC_{50} values for several topiramate analogues for blood carbonic anhydrase (compound, IC_{50}): **31**, 56 000; **83a**, 1 310 000; **83j**, inactive; **86**, 120; **106**, 180 000; **107**, 6060 nM. It is noteworthy that **31**, with diethyl groups on the 4,5-ring, is 8 times weaker than **1**, but **86**, with diethyl groups on the 2,3-ring, is nearly equipotent with **2**; that L-topiramate (**106**) is ca. 20 times weaker than **1** and **107** is ca. 70 times weaker than **2**; and that monosubstitution of the nitrogen of **2** with small alkyl groups, which is still associated with potent anticonvulsant activity, strongly attenuates activity (cf. **83a** and **83j** with **2**). The greatly diminished carbonic anhydrase inhibition of **83a** and **83j** is most likely due to an inability of the substituted sulfamate group to interact with Zn(II) in the enzyme's active site.[65] Given the results with **83a** and **83j**, relative to **2**, potent anticonvulsant activity is probably independent of carbonic anhydrase inhibition, similar to what we experienced previously.[2a] Thus, inhibition of carbonic anhydrase may not be a critical mechanism of anticonvulsant action for **2** (vide infra).

We sent **2** to the National Institute of Neurological Disorders and Stroke (NINDS) for independent evaluation (ADD-182013).[66] It was found to have ED_{50} values in the MES test of 6.1 (4.6−7.2) mg/kg (2 h, ip, mice) and 1.06 (0.81−1.44) mg/kg (4 h, po, rats), compared to 33 and 11.4 mg/kg for **1**, respectively.[2a] Rotorod TD_{50} values for **2** were 400 (125−500) mg/kg (1 h, ip, mice) and >500 mg/kg (4 h, po, rats), reflecting excellent neurotoxicity indices of 66 and >472 (cf. phenytoin at 6.6 and >22). In mice, **2** was inactive (ED_{50} > 500 mg/kg) in blocking convulsions induced by pentylenetetrazole, bicucculine, picrotoxin, and strychnine.

Mechanism of Action of Topiramate (1) and 2. Topiramate is effective in blocking maximal electroshock seizures, but not chemically induced seizures, in analogy to phenytoin.[2b] The same can be said for **2**. Thus, the sugar sulfamates are probably much better in preventing the spread of seizures, rather than in raising the seizure threshold.[67] Topiramate has been found to block tonic and clonic seizures in spontaneous epileptic rats and mice genetically predisposed to epilepsy (DBA/2 mice).[68] Also, it blocks electrically kindled seizures in rats and clonic-tonic seizures in rats subjected to global ischemia.[67,69] Hence, topiramate appears to be broadly effective in animal models of epilepsy.[2b,67−69]

Clinical trials with topiramate have indicated that this antiepileptic drug is highly effective in adjunctive therapy and monotherapy for generalized, absence, and complex-partial seizures.[70] However, the pharmacological basis for topiramate's anticonvulsant activity has not yet been firmly established. Recent studies have revealed an intriguing combination of properties that may account for its seizure-blocking activity.[71] Topiramate significantly lowers glutamate and aspartate levels in spontaneous epileptic rats, while showing no effect on normal Wistar rats, suggesting that a reduction of abnormally high extracellular levels of these excitatory amino acid neurotransmitters in the hippocampus may be related to its anticonvulsant activity.[71a] Cellular biochemical and electrophysiological studies have identified several other properties that may contribute to the anticonvulsant activity. Topiramate (a) positively modulates some types of GABA-A receptors,[71b,c] (b) antagonizes kainate/AMPA receptors,[71d] and (c) inhibits generation of action potentials in neurons by exerting a state-dependent, voltage-sensitive antagonism of sodium ion channels.[71e,f] In the latter case, elevation of the action-potential threshold would block the spread of seizures. All of these biological actions are concentration-dependent and occur within a physiologically relevant concentration range of 1−100 μM. Topiramate inhibits some carbonic anhydrase isozymes, such as CA-II and CA-IV, in this concentration range, and **2** is even more potent as a carbonic anhydrase inhibitor. However, the very weak carbonic anhydrase inhibition of cyclic sulfate analogues **83a** and **83j**, relative to **2**, would serve to dissociate anticonvulsant activity from enzyme inhibition, deemphasizing carbonic anhydrase inhibition as a relevant mechanism of anticonvulsant action. Taking these observations together, it is reasonable to

speculate that **2** would share many of the mechanisms of action of **1**.

Structural and Conformational Aspects

Topiramate (**1**) adopts a skew conformation ($^3S_0$) for the tetrahydropyran ring in solution and in the solid state.[2a,29] This skew conformation is presumably favored over the possible chair conformations because of the two five-membered rings that are cis-fused onto the central pyranose ring. We have suggested that such a skew conformation may be critical for the potent anticonvulsant activity of topiramate.[2a,29] In our study of topiramate analogues, we have synthesized and biologically tested some compounds with the 4,5-isopropylidene ring absent, such as **63**−**68**. Diethers **63** and **64** are virtually devoid of anticonvulsant activity, but α-L-sorbopyranoses such as **67** and **68** are nearly twice as potent as topiramate (Table 1). This surprising observation can be explained by considering the conformations of these molecules.[29] As expected, **63** and **64** favor chair conformations ($^5C_2/^2C_5$), while **67** and **68** favor a skew conformation ($^3S_0$),[29] consistent with our structural hypothesis for topiramate's bioactivity.

The conformational preferences for 2,3-*O*-isopropylidene-α-L-sorbopyranose derivatives **67**, **68**, and **80** were determined by using high-field ^{1}H NMR data in combination with empirical force-field calculations.[29] A twist-boat (or skew) conformation ($^3S_0$) prevails over possible chair forms for each, with **67** being an ca. 4:1 mixture of the $^3S_0$ and $^2C_5$ conformers (good fit between calculated and observed NMR coupling values).[29] This conformational distribution for **67** was essentially constant with different solvents and temperatures, and the $^3S_0$ skew conformation for **67** was also manifested in the solid state.[29]

Proton NMR data for **63** and **64** (400 MHz) indicate that the compounds strongly prefer a chair conformation and predominantly adopt the one with the $CH_2SO_2NH_2$ group axial. In particular, the vicinal proton−proton coupling constants J_{56a} = 8.6 Hz and J_{56e} = 4.9 Hz, together with the characteristic long-range, W-pathway coupling constant J_{46e} = 0.9 Hz, indicate that **63** exists in $CDCl_3$ at 24 °C as a 3:1 mixture of $^5C_2/^2C_5$ chair forms (J_{34} = 3.7 Hz, J_{45} = 3.2 Hz).[72] Thus, for SAR purposes, a direct comparison of **63** or **64** with **1**, wherein the central pyran ring adopts a skew conformation, is not feasible.

Proton NMR spectra for **1** have indicated a skew conformation, which also exists in the solid state.[2a] We have now acquired 400-MHz ^{1}H NMR data for both **1** and **2** in different solvents. For **1** in $CDCl_3$, CD_3OD, and D_2O, the vicinal couplings J_{34}, J_{45}, J_{56a}, and J_{56e} were essentially unchanged (2.6, 8.0, 0.8, and 1.9 Hz, respectively). For **2** in DMSO-d_6, CD_3OD, and D_2O, the vicinal couplings J_{34}, J_{45}, J_{56a}, and J_{56e} were also essentially unchanged (2.7, 7.8, <0.3, and 2.0 Hz, respectively). The coupling constants for the tetrahydropyran ring protons confirm that the skew $^3S_0$ conformer predominates at room temperature in nonaqueous and aqueous media. The X-ray crystal structure of **2** (vide infra) also shows a skew conformation. Hydrindane analogue **95**, which also has a skew conformation in the solid state by X-ray analysis (vide infra), was examined by 400-MHz ^{1}H NMR in C_6D_6. Although many of the proton−proton coupling constants for **95** are not readily accessible because of fewer ether oxygen atoms than, say **1**, the vicinal coupling between H_3 and H_4 of 2.4 Hz is consistent with a skew cyclohexane ring for this compound.[54] Thus, the loss of potency for **95**, relative to **1**, is likely caused by electronic effects from three O → CH_2 replacements, not by conformational (steric) effects.

It is interesting to note that there is a consistency in optical rotations for compounds having the skew conformation, with no additional chromophore that could significantly perturb the ORD spectrum (Table 1). For example, **1**−**9** have $[\alpha]_D$ values in MeOH of −34.0°,[2a] −28.8°, −34.2°,[2a] −35.0°,[2a] −27.0°,[2a] −25.9°, −18.2°, −29.5°, −18.7°, despite different substitution at C1; **29**−**32** and **34**−**38** have $[\alpha]_D$ values in MeOH of −29.9°,[2a] −33.9°, −25.6°, −18.9°, −25.9°, −25.3°, −19.3°, −19.5, −29.3°, despite different substitution on the 4,5-ring. By contrast, compounds without the 4,5-ring that would principally adopt chair conformations, such as **28** and **63**−**65**, have consistent $[\alpha]_D$ values in MeOH of +25.7°, +27.0°, +28.4°, and +27.1°. In this vein, **76** (−39.8°) and **77** (−22.3°) appear to be mainly in the skew conformation, as would be expected from the constraint imposed by a three-membered-ring fused at the 4,5-position. However, **43** (+1.3°), with a less constrained six-membered-ring fusion, appears to be a mixture of skew and chair forms. Indeed, 400-MHz NMR spectral data for **43** and **77** are consistent with this interpretation (see the Experimental Section). The long-range W-pathway coupling for **43**, J_{46e} = 1.4 Hz, is especially noteworthy since it is diagnostic for the $^5C_2$ chair conformation in the β-fructopyranose system; the $^2C_5$ chair and $^3S_0$ skew conformations lack the proper geometry to manifest it.[73] This J_{46e} coupling is also observed for **28** (0.7 Hz)[2a] and for **63** (0.9 Hz) in $CDCl_3$, but it was unresolved for **64**. Proton NMR data (300 MHz, $CDCl_3$) for **77** show the absence of a J_{46e} coupling, as well as vicinal proton−proton couplings of less than 1 Hz for J_{34}, J_{56a} and J_{56e}, consistent with the $^3S_0$ conformation. Furthermore, it is interesting that alkene **66**, which should exist in a flattened half-chair conformation,[22] has an optical rotation (−0.9°) that is between the skew (−20° to −35°) and chair (+25° to +30°) extremes, as would be expected from the preceding analysis.

The optical rotations are also worth analyzing from a standpoint of orientation of substituents on the 4,5-ring, for the 4,5-ketals and the 4,5-cyclic sulfur derivatives. Compounds **1**, **29**, **30**, and **31**, in which the two substituents are identical, have fairly constant $[\alpha]_D$ values of −34.0°,[2a] −29.9°,[2a] −33.9°, and −25.6°, indicating minimal impact of the size of the substituents at this position. However, the optical rotations for **33a** (−29.3°; *R* isomer) and **33b** (−18.1°; *S* isomer) are distinctive for the orientation of the methyl substituent relative to the hydrogen. This configurational feature seems to apply, as well, to the 4,5-cyclic sulfite diastereomers **87b** (−43.5°; *R* isomer) and **87a** (−14.9°; *S* isomer), although a tetrahedral sulfur atom occupies the 4,5-ring and the substituent (oxygen) is quite polar. The 4,5-ketals **34** and **35**, with ca. 85−90% *R* isomer (NMR), have rotations that are consistent with this picture (−25.9° and −25.3°), whereas **36** and **37**, with 100% *R* isomer (NMR), have rotations that are not consistent

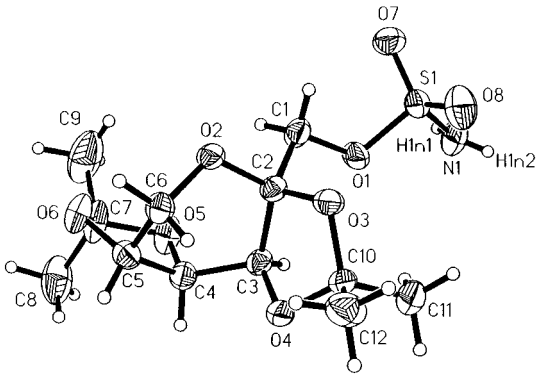


Figure 2. Perspective drawing of **1** from X-ray crystallography with non-hydrogen atoms represented by thermal ellipsoids drawn to encompass 50% of their electron density. Hydrogen atoms are arbitrarily represented by small spheres.

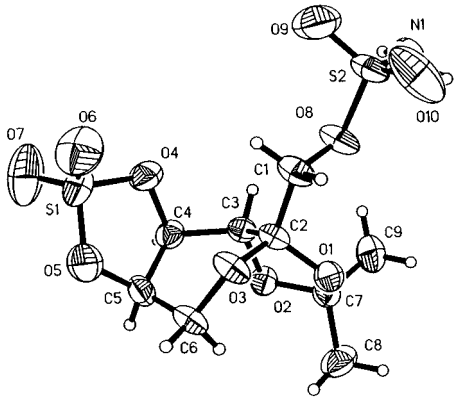


Figure 3. Perspective drawing of **2** from X-ray crystallography with non-hydrogen atoms represented by thermal ellipsoids drawn to encompass 50% of their electron density. Hydrogen atoms are arbitrarily represented by small spheres.

(−19.3° and −19.5°). Perhaps, the bulky *tert*-butyl group induces a change in the local conformation of the 1,3-dioxolane unit. Compound **46**, with 90% *S* isomer, has an optical rotation (−26.8°) that also seems to deviate from the pattern. Consequently, this parameter cannot be utilized as a stereochemical diagnostic for the 4,5-ring.

IR measurements of **4** in CD_3CN or $CHCl_3$ (at ca. 10% vs 0.3% concentrations) indicated that intramolecular hydrogen bonding exists, consistent with literature results for **4** in CCl_4.[73a] This presumably involves an interaction between the hydroxyl group and O4 in the skew conformation, to impose a constraint on the structure of the molecule. Consequently, we became interested in determining if there was a hydrogen-bonded structure for the active sulfamates. In CD_3CN or $CHCl_3$, alcohol **4** shows OH stretches (ν_{max}) at 3532 or 3493 cm^{-1} (intramolecular) and 3570 or 3597 cm^{-1} (free), whereas sulfamate **1** shows NH stretches at 3262 or 3290 cm^{-1} (intermolecular) and 3570 or 3353/3432 cm^{-1} (free) in $CHCl_3$.[74] Like **1**, **2** in CD_3CN shows intermolecular (3265 cm^{-1}) and free (3574 cm^{-1}) bands, with no intramolecular band. We could not examine **2** in $CHCl_3$ because of poor solubility; however, **83b** is a suitable surrogate. In $CDCl_3$, **83b** showed only intermolecular (3350 cm^{-1}) and free (3394 cm^{-1}) IR bands. Thus, neither **1** (in CD_3CN or $CHCl_3$) nor **2** (in CD_3CN) display a significant level of intramolecular hydrogen bonding.

We have determined crystal structures for topiramate (**1**) and four analogues: **2**, **21a**, **67**, and **95**;[75,76] details for the X-ray studies of **1**, **2**, and **95** are presented herein.[77] All five compounds (**1**, **2**, **21a**, **67**, and **95**) adopt a skew $^3S_0$ conformation in the solid state (see Figures 2−4), and a skew conformation is also observed for **1**, **2**, and **95** in solution by ^1H NMR (vide supra). Some specific methods and results for the X-ray studies on **1**, **2**, and **95** are provided in the Experimental Section.[75,76]

Conclusion

Structure−activity relationships surrounding the clinically efficacious antiepileptic drug topiramate (**1**), a unique sugar sulfamate anticonvulsant, were explored. Structural alterations were made to probe the importance of (1) the sulfamate group (**6**−**8**, **22**−**25**, **27**, **84**), (2) the linker between the sulfamate group and the pyran ring (**9**, **10**, **21a**,**b**), (3) the substituents on the 2,3- (**58**−**60**, **85**, **86**) and 4,5-fused (**30**−**38**, **43**, **45**−**47**, **52**, **53**) 1,3-dioxolane rings, (4) the constitution of the 4,5-fused 1,3-dioxolane ring (**2**, **54**, **55**, **63**−**68**, **76**, **77**, **80**, **83a**−**r**, **84**−**87**, **90a**, **91a**, **93a**), (5) the ring oxygen atoms (**95**, **96**, **100**−**102**, **104**, **105**), and (6) the absolute stereochemistry (**106** and **107**). This work led to the impressive cyclic sulfate analogue RWJ-37947 (**2**), which has potent anticonvulsant activity (ca. 8 times greater than **1** in mice at 4 h and ca. 15 times greater than **1** in rats at 8 h), a long duration of action (>24 h in mice and rats, po), and very low neurotoxicity (TD_{50} value of >1000 mg/kg, po in mice). The absence of activity for **2** against chemically induced seizures in mice, as well as in diverse in vitro receptor binding and reuptake assays, denotes an anticonvulsant profile similar to that of phenytoin and topiramate, although **2** also turned out to be a potent inhibitor of carbonic anhydrase (IC_{50} = 21−130 nM for enzymes from various rat tissues). Examination of analogues of the potent 4,5-cyclic sulfate **2**, namely **83a**−**r**, **85**−**87**, **90a**, **91a**, and **93a**, indicated that potent anticonvulsant activity is associated with relatively small alkyl substituents on the nitrogen (Me/H, **83a**; Me/Me, **83m**; Et/H, **83b**; allyl/H, **83e**; c-Pr/H, **83j**; c-Bu/H, **83k**) and with very limited changes in the cyclic sulfate group, such as cyclic sulfite **87a**/**b**. Interestingly, the potent anticonvulsants **83a** and **83j** had significantly diminished carbonic anhydrase inhibitory activity, suggesting that inhibition of this enzyme may not be responsible for the anticonvulsant activity.

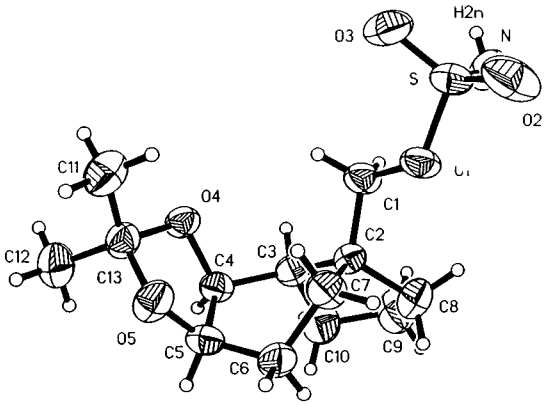


Figure 4. Perspective drawing of **95** from X-ray crystallography with non-hydrogen atoms represented by thermal ellipsoids drawn to encompass 50% of their electron density. Hydrogen atoms are arbitrarily represented by small spheres.

On the basis of 400-MHz ^{1}H NMR data, **1** and **2** predominantly adopt the $^3S_0$ skew conformation at ambient temperature in nonaqueous and aqueous media. From our earlier work,[29] α-L-sorbopyranose **67**, which is nearly twice as potent as **1**, also mainly adopts this skew conformation in solution. The X-ray structures for **1**, **2**, and **95** (as well as **21a** and **67**) depict the skew $^3S_0$ conformer in the solid state, as well. This skew conformation appears to be a critical structural feature relative to obtaining potent anticonvulsant activity. Considering all of the SAR results to date, we perceive **1** and **2** as possessing two key structural elements for interaction with relevant biological targets in the CNS: (1) a tetrahydropyran unit in a skew conformation with sterically unencumbered five-membered 1,3-dioxo rings, and (2) a polar sulfamate group spaced at a suitable distance from the monosaccharide nucleus and not burdened by oversized substituents. There seems to be a preferred topography for the hydrophobic skew 2,3-dioxolanopyran segment of **1**, **2**, and **67** that requires the 2,3-ether oxygen atoms and minimal steric bulk.

Clinical trials with topiramate have indicated that this drug is highly effective in adjunctive therapy and monotherapy for epilepsy. Although a pharmacological basis for topiramate's anticonvulsant activity has not yet been firmly established, some interesting biochemical mechanisms have been pinpointed to account for its seizure-blocking activity.[71] Topiramate has a positive modulatory effect on some types of GABA-A receptors,[71b,c] antagonizes kainate/AMPA receptors,[71d] and inhibits the generation of action potentials in neurons via antagonizing the activation of Na^+ channels.[71e,f] Presumably, **2** would function in a similar manner. Although **2** is a potent inhibitor of carbonic anhydrase isozymes, this is not viewed a being critical to its potent anticonvulsant activity. In the final analysis, topiramate analogue **2**, a novel sugar sulfamate cyclic sulfate, is a promising anticonvulsant that may be clinically useful in patients suffering from generalized tonic-clonic and/or complex partial seizures.

Experimental Section

General Methods. Reactions were generally conducted under argon or nitrogen in molecular sieve-dried solvents, unless noted otherwise. During concentration in vacuo, the materials were never heated above 40 °C unless otherwise noted. Amines were scrupulously dried (distilled from BaO) before use. Rigorously anhydrous conditions were used for chlorosulfate displacement reactions to prevent hydrolysis of the chlorosulfate. Melting points were determined on a Thomas-Hoover apparatus calibrated with a set of melting point standards. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at the sodium D line (λ = 589 nm). Infrared spectra were recorded on a Nicolet SX-60 spectrometer with a resolution of 4.0 cm^{-1} (s = strong, m = medium). ^{1}H NMR spectra (referenced to Me_4Si; s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad) were obtained at 400.13 MHz on a Bruker AM-400, at 300.13 MHz on a Bruker AC-300, at 600.13 MHz on a Bruker DMX-600, or at 90 MHz on a Varian EM-390 instrument, in $CDCl_3$ unless indicated otherwise. ^{13}C NMR spectra (referenced to Me_4Si) were obtained at 100.61 MHz on a Bruker AM-400 in $CDCl_3$; distortionless enhancement by polarization-transfer experiments with an editing pulse at 135° (DEPT-135) were used to assign carbon multiplicities. Chemical-ionization mass spectra (CI-MS) were recorded on a Finnigan 3300 mass spectrometer with ammonia as the reagent gas, unless methane is specifically indicated. Fast-atom-bombardment mass spectra (FAB-MS) were recorded on a VG 7070E high-resolution or Finnigan TSQ-70B triple-quadrupole mass spectrometer by using an argon beam at 7 kV and 2 mA of current in a thioglycerol matrix. The X-ray crystallography for **1**, **2**, **21a**, and **95** was performed by Crystalytics Co., Lincoln, NE. Elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA), Galbraith Laboratories, Inc. (Knoxville, TN), or Oneida Laboratories (Oneida, NY). TLC separations were conducted on 250-μm silica gel plates with visualization by iodine staining or by charring with ethanol/H_2SO_4 (95:5). Chromatographic separations were carried out by using HPLC-grade solvents on (1) a Waters Prep-500 HPLC equipped with two PrepPak cartridges (column, 47 × 300 mm; silica gel, 55−105 μm, 125 Å) connected in series and a refractive index detector ("LC"), or (2) flash-column chromatography with silica gel (40−63 μm; "CC"). Preparative TLC purification was performed with Analtech 1000-μm silica gel GF plates.

2,3-*O*-(Isopropylidene)-4,5-*O*-sulfonyl-β-D-fructopyranose Sulfamate (2). Diol **28**[2a] (50.0 g, 0.167 mol) was combined with ethyl acetate (1.7 L) and pyridine (31.7 g, 0.401 mol), heated to effect dissolution, and cooled to −60 °C. Sulfuryl chloride (49.6 g, 0.370 mol) was added dropwise with mechanical stirring under argon over 45 min (−60 to −50 °C). The resulting white slurry was stirred at −60 °C for 1 h, warmed to 23 °C, stirred for 2 h, and filtered through diatomaceous earth. The filtrate was rinsed sequentially with brine, 1 N HCl, saturated aqueous $NaHCO_3$, and brine, then dried ($MgSO_4$), and concentrated in vacuo to furnish 85.6 g (100%) of **110** (eq 5) as a white solid, which was used without further purification. A sample was purified by flash-column chromatography (CH_2Cl_2/ethyl acetate, 19:1): mp 119−121 °C dec; CI-MS *m*/*z* 513 $(M + NH_4)^+$. A solution of this material (83.1 g, 0.167 mol) in methanol (418 mL) was combined with $NaHCO_3$ (84.2 g, 1.0 mol) and stirred at 23 °C for 18 h, filtered through diatomaceous earth, and concentrated in vacuo. The residue was dissolved in ethyl acetate, rinsed twice with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by preparative HPLC (CH_2Cl_2/ethyl acetate, 9:1) and recrystallized from ethanol/water to afford **2** (31.4 g) as a white solid: mp 150−151 °C dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.38/1.53 (2 s, 6H, 2 Me) 3.90−4.10 (m, 4H, H_1 and H_6), 4.59 (d, 1H, J_{34} = 2.7 Hz, H_3), 5.49 (d, 1H, J_{45} = 7.8 Hz, H_5), 5.70 (dd, 1H, J_{34} = 2.7 Hz, J_{45} = 7.8 Hz, H_4), 7.75 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 25.0 (Me), 25.9 (Me), 59.2 (CH_2), 67.8 (CH_2), 68.1 (CH), 73.2, (CH), 77.7 (CH), 100.7 (C), 110.2 (C); IR (KBr) ν_{max} 3373 (s), 3267 (s), 1567 (m), 1377 (s), 1213 (s), 1189 (s) cm^{-1}; FAB-MS *m*/*z* 362 $(MH)^+$, 384 $(M + Na)^+$. Anal. ($C_9H_{15}NO_{10}S_2$) C, H, N.

1-[(Aminosulfonyl)amino]-1-deoxy-2,3:4,5-bis-*O*-(isopropylidene)-β-D-fructopyranose (6). A mixture of NaH (60% oil dispersion, 1.34 g, 0.033 mol) in DMF (50 mL) was treated with **11**[5] (6.67 g, 0.02 mol), and the reaction was stirred at 0 °C for 30 min. Sulfamoyl chloride (4.47 g, 0.039 mol) was added portionwise at 0−10 °C. After being stirred for 1 h, the mixture was poured into ice and extracted into ethyl acetate twice. The combined extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to a syrup, which was purified by preparative HPLC (hexane/ethyl acetate, 1:1) to give **6** (2.06 g, 20%) as a colorless solid: mp 50−52 °C; ^{1}H NMR (90 MHz) δ 1.29/1.35/1.48/1.50 (4 s, 12H, 4 Me), 2.40 (m, 2H, CH_2N), 3.84 (m, 2H, H_6), 4.22 (m, 2H, H_3 and H_5), 4.64 (dd, 1H, H_4), 4.70−4.90 (br s, 2H, NH_2), 5.00 (t, 1H, NH). Anal. ($C_{11}H_{22}N_2O_7S \cdot 0.1C_7H_8$) C, H, N.

1-[(Aminosulfonyl)methylamino]-1-deoxy-2,3:4,5-bis-*O*-(isopropylidene)-β-D-fructopyranose (7). A mixture of iodine (88 g, 0.35 mol), imidazole (26 g, 0.38 mol), and triphenylphosphine (151 g, 0.57 mol) in 1.5 L toluene/acetonitrile (9:1) was stirred for 30 min under nitrogen and then treated with fructose bis-acetonide (**4**, 50 g, 0.19 mol). The mixture was heated at reflux for 3 days, cooled to 23 °C, and concentrated to a syrup. The syrup was triturated with a mixture of petroleum ether and ethyl ether (1:1, 225 mL) and filtered. The filtrate was concentrated to a syrup that was

purified by preparative HPLC (hexane/ethyl acetate, 4:1) to give iodide **12** as a syrup. The iodide (6 g, 0.02 mol) was refluxed in DMF (45 mL) with *N*-methylbenzylamine (3.96 g, 0.032 mol) and Na_2CO_3 (3.13 g, 0.029 mol) for 2 days, cooled, poured into water, and extracted with ethyl acetate. The organic solution was washed with brine, dried (Na_2SO_4), and concentrated to syrupy **13**, which was dissolved in ethanol (60 mL), treated with 10% Pd/C (4.0 g), and shaken on a Paar apparatus with hydrogen (50 psig) for 16 h. After filtration, the solvent was concentrated in vacuo to give amine **14** as a syrup. To a cold solution of NaH (60% oil dispersion, 0.48 g, 0.012 mol) in DMF (10 mL) was added amine **14** (2.14 g, 0.008 mol). After the reaction stirred for 45 min, sulfamoyl chloride (2.12 g, 0.018 mol) was added portionwise at 0 °C and the mixture was stirred for 45 min. After 60 min more at 23 °C, it was poured into cold water and extracted with ethyl acetate. The organic solution was concentrated in vacuo, and the residue was purified by preparative HPLC (hexane/ethyl acetate, 1:1) to give **7** (0.25 g, 7%) as a pale yellow syrup: ^{1}H NMR (400 MHz) δ 1.34/1.42/1.50/1.60 (4 s, 12H, 4 Me), 3.05 (s, 3H, Me), 3.50−3.69 (dd, 2H, H_1), 3.75−3.91 (dd, 2H, H_6), 4.15−4.30 (m, 2H, H_3 and H_5), 4.51−4.65 (m, 1H, H_4), 4.80 (br s, 2H, NH_2). Anal. ($C_{13}H_{24}N_2O_7S\cdot0.1C_4H_8O_2\cdot0.1C_3H_7NO$) H, N; C: calcd, 44.65; found, 45.30.

2-[1,2:3,4-Bis-*O*-(isopropylidene)-β-D-arabinopyranos-1-yl]ethylsulfonamide (8). A mixture of ethyl methanesulfonate (17.7 g, 0.14 mol) in THF (350 mL) was treated with butyllithium (2.5 M in hexane, 65.5 mL, 0.16 mol) at −70 °C; after 45 min of stirring, the mixture was treated with diphenyl phosphorochloridate (44.1 g, 0.16 mol) and then stirred at −70 °C for 60 min more. The reaction was treated with brine, warmed to 23 °C, and extracted twice with CH_2Cl_2. The combined extract was washed with 4% aqueous NH_4Cl, dried (Na_2SO_4), and concentrated to a syrup, which was purified by preparative HPLC to give the phosphonate reagent as a solid. A mixture of this reagent (10.95 g, 0.03 mol) in THF (150 mL) was treated with butyllithium (2.5 M in hexane, 14.7 mL, 0.04 mol) at −70 °C. After 45 min of stirring, it was treated with a mixture of aldehyde **15** (10.46 g, 0.04 mol) in THF. The reaction was stirred at −70 °C for 45 min, stirred at 23 °C for 2 h, treated with brine, and extracted twice with ethyl acetate. The combined extract was dried (Na_2SO_4) and concentrated in vacuo to a semisolid, which was redissolved in CH_2Cl_2, washed with brine, dried (Na_2SO_4), and concentrated to a syrup. It was purified by preparative HPLC to give alkene **16** as a syrup, which crystallized on standing. A mixture of alkene (8.0 g, 0.022 mol) in ethanol (150 mL) and PtO_2 (4.0 g) was shaken on a Paar apparatus with hydrogen (40 psig) for 4 h, filtered, and concentrated in vacuo to a solid, which was recrystallized from ethanol−water to give pure sulfonate as a colorless solid. A solution of NaOH (2.28 g) in water (25 mL) was treated with sulfonate (2.80 g, 0.008 mol), and the mixture was refluxed for 90 min, cooled, treated with acetic acid (3.32 g), and stirred for 5 min. It was triturated with ethyl acetate and concentrated in vacuo to give the sulfonic acid as a white solid. The sulfonic acid (2.71 g, 0.008 mol) in a mixture of 10 mL of DMF and 20 mL of CH_2Cl_2 was treated with thionyl chloride (0.95 g, 0.008 mol) at −15 °C for 45 min, treated with ammonia-saturated chloroform (60 mL), stirred at 23 °C for 60 min, treated with water, and extracted with CH_2Cl_2. The organic solution was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to a thick syrup, which was purified by preparative HPLC (hexane/ethyl acetate, 1:1) to furnish sulfonamide **8** (0.80 g, 25%) as a white solid: mp 142−143 °C; ^{1}H NMR (400 MHz) δ 1.35/1.39/1.48/1.51 (4 s, 12H, 4 Me), 2.22−2.45 (m, 2H, CH_2), 3.39−3.52 (m, 2H, CH_2S), 3.70−3.1 (dd, 2H, H_6), 4.13 (m, 1H, H_3), 4.23 (m, 1H, H_5), 4.52−4.60 (m, 1H, H_4), 4.71 (br s, 2H, NH_2). Anal. ($C_{13}H_{23}NO_7S$) C, H, N.

1-[(Aminosulfonyloxy)methyl]-1-deoxy-2,3:4,5-bis-*O*-(isopropylidene)-β-D-fructopyranose (9). A solution of methyltriphenylphosphonium bromide (103.5 g, 0.29 mol) in anhydrous THF (470 mL) was treated with potassium *tert*-butoxide (32.5 g, 0.29 mol), and the mixture was stirred for 45 min. The reaction was treated dropwise with a solution of aldehyde **15** (30 g, 0.12 mol) in THF (300 mL), and the mixture was stirred for an additional 45 min. It was treated with cold water and extracted twice with ether. The combined extract was washed with 3% hydrogen peroxide solution, dried (Na_2SO_4), concentrated in vacuo, triturated with ether, filtered, and concentrated again to a syrup that was purified by preparative HPLC (ethyl acetate/hexanes, 1:9) to give pure olefin **18** as a colorless syrup. A solution of **18** (19.5 g, 0.076 mol) in THF (80 mL) was cautiously treated with $BH_3\cdot$THF (1 M in THF, 80 mL) dropwise, under 40 °C. After addition, the reaction was stirred for an additional 30 min, cooled to 5 °C, and cautiously treated with 3 N NaOH (28 mL), followed by hydrogen peroxide (30% aqueous solution, 28 mL). The mixture was refluxed for 15 min, cooled, and extracted twice with ethyl acetate. The combined extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give alcohol **19** as a syrup. A mixture of NaH (60% oil dispersion, 0.98 g, 0.025 mol) in DMF (20 mL) was treated with a solution of alcohol **19** (4.45 g, 0.016 mol) in DMF (20 mL), and the mixture was stirred for 15 min at 5 °C. Sulfamoyl chloride (3.0 g, 0.026 mol) was added portionwise, and the mixture was allowed to warm to 23 °C. After 2 h of stirring, the mixture was treated with cold water and extracted with ethyl acetate three times. The combined organic extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to a syrup, which was purified by preparative HPLC (hexanes/ethyl acetate, 1:1) to give **9** (2.30 g, 41%) as a colorless foam: ^{1}H NMR (400 MHz) δ 1.35/1.36/1.49/1.55 (4 s, 12H, 4 Me), 2.20−2.32 (m, 2H, CH_2), 3.64−3.82 (dd, 2H, H_6), 4.15 (m, 1H, H_3), 4.17−4.20 (m, 1H, H_5), 4.47−4.50 (m, 2H, CH_2O), 4.55−4.60 (m, 1H, H_4), 5.30 (br s, 2H, NH_2). Anal. ($C_{13}H_{23}NO_8S\cdot0.3H_2O$) C, H, N, H_2O.

1-[(Aminosulfonyloxy)ethyl]-1-deoxy-2,3:4,5-bis-*O*-(isopropylidene)-β-D-fructopyranose (10). A mixture of aldehyde **15** (26.3 g, 0.10 mol) and methyl (triphenylphosphoranylidene)acetate (65.9 g, 0.20 mol) in dry acetonitrile (536 mL) was refluxed for 2 h, cooled, and triturated with petroleum ether twice. The combined filtrate was concentrated to a syrup that was purified by preparative HPLC (hexanes/ethyl acetate, 2:1) to give the enoate as a 13:1 mixture of *E*:*Z* isomers. A mixture of alkene (18.5 g, 0.6 mol) in ethanol (180 mL) and PtO_2 (3.6 g) was shaken with hydrogen on a Paar apparatus (50 psig) for 4 h. After filtration, the solvent was evaporated in vacuo to give the ester as a colorless syrup. To a slurry of $LiAlH_4$ (2.09 g, 0.055 mol) in ether (150 mL) was added a solution of the ester (15.9 g, 0.05 mol) in ether (100 mL), dropwise. The reaction was stirred for 2 h, treated cautiously with water (2.2 mL), 15% NaOH (2.1 mL), and water (6.3 mL), stirred for 16 h, filtered, and concentrated to give alcohol **20** as a colorless syrup. A mixture of NaH (60% oil dispersion, 0.98 g, 0.025 mol) in DMF (40 mL) was treated with a solution of alcohol **20** (4.53 g, 0.016 mol) in DMF (40 mL), and the mixture was stirred for 15 min at 5 °C. Sulfamoyl chloride (3.50 g, 0.03 mol) was added portionwise and the reaction was allowed to warm to 23 °C. After 2 h of stirring, the mixture was treated with cold water and extracted with ethyl acetate three times. The combined extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by preparative HPLC (hexanes/ethyl acetate, 1:1) to give **10** (3.10 g, 53%) as a pale yellow syrup: ^{1}H NMR (400 MHz) δ 1.28/1.31/1.48/1.55 (4 s, 12H, 4 Me), 2.10 (m, 4H, 2 CH_2), 3.65−3.85 (dd, 2H, H_6), 4.10 (m, 1H, H_3), 4.16−4.21 (m, 1H, H_5), 4.22−4.30 (m, 2H, CH_2O), 4.51−4.60 (m, 1H, H_4), 5.15 (br s, 2H, NH_2). Anal. ($C_{14}H_{25}NO_8S\cdot0.7H_2O$) C, H, N, H_2O.

1-*C*-Methyl- and 1-*C*-Ethyl-2,3:4,5-bis-*O*-(isopropylidene)-β-D-fructopyranose Sulfamates (21a and 21b). A mixture of aldehyde **15** (10.45 g, 0.04 mol) in THF (150 mL) and ether (100 mL) was treated with methylmagnesium bromide (3 M in ether, 20 mL, 0.06 mol) at 25−40 °C and refluxed slowly for 3 h. After cooling, the reaction mixture was treated with cold water (50 mL) and 10% ammonium chloride (100 mL) and extracted twice with ethyl acetate. The combined extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to a mixture of diastereomeric alcohols (ca. 10:1), which was purified by preparative HPLC (hexanes/

ethyl acetate, 2:1). A mixture of sodium hydride (60% oil dispersion, 1.11 g, 0.028 mol) in DMF (45 mL) was treated with a solution of alcohols containing mainly the major isomer (4.90 g, 0.018 mol) in DMF (45 mL), and the reaction was stirred for 15 min at 10 °C. Sulfamoyl chloride (4.16 g, 0.036 mol) was added portionwise, and the mixture was warmed to 23 °C. After being stirred for 2 h, the mixture was treated with cold water and extracted three times with ethyl acetate. The combined extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The syrupy residue was purified by preparative HPLC (hexanes/ethyl acetate, 2:1) to give **21a** (2.43 g, 43%) as a waxy solid: ^{1}H NMR (400 MHz) δ 1.33/1.42/1.48/1.53 (4 s, 12H, 4 Me), 1.54 (d, 3H, Me), 3.84 (pair of d, 2H, H_6), 4.22 (dd, 1H, H_1), 4.43 (d, 1H, H_3), 4.6−4.7 (m, 2H, H_4 and H_5), 5.30 (br s, 2H, NH_2); the material was almost entirely one isomer; ^{13}C NMR (100 MHz) δ 15.4/15.5 (α/β), 24.2, 25.7, 26.1, 27.0, 61.5, 70.2, 70.5, 70.9, 80.2/80.3 (α/β), 102.9/103.5 (C2-α/C2-β), 108.8 (β),109.3, 109.6; the α/β ratio was estimated as ca. 20:1 from integration of the anomeric C2 resonances. Anal. ($C_{13}H_{23}NO_8S$) C, H, N. A sample was recrystallized from ethanol−water (1:3) to afford small colorless prisms of diastereomerically pure material, mp 152−153 °C. X-ray crystallographic analysis on a well-formed crystal served to establish the configuration at C1 in the major (α) isomer as *R*.[77]

Similarly, aldehyde **15** (9.75 g, 0.04 mol) in THF (150 mL) and ether (100 mL) was treated with ethylmagnesium bromide (3 M in ether, 23 mL, 0.06 mol) at 25−40 °C and refluxed for 3 h. The reaction was worked up to give a mixture of diastereomeric alcohols, which was purified by preparative HPLC (hexanes/ethyl acetate, 2:1). A mixture of sodium hydride (60% oil dispersion, 2.5 g, 0.06 mol) in DMF (100 mL) was treated with a solution of diastereomeric alcohols (11.33 g, 0.04 mol) in DMF (45 mL), and the reaction was stirred for 15 min at 10 °C. After addition of sulfamoyl chloride (9.31 g, 0.08 mol), as above, the mixture was worked up and the residue was purified by preparative HPLC (hexanes/ethyl acetate, 2:1) to give **21b** (6.60 g, 75%) as a syrup: ^{1}H NMR (400 MHz) δ 1.00−1.10 (2 t, 3H, Me), 1.34/1.43/1.49/1.54 (4 s, 12H, 4 Me), 1.75−1.90 (m, 1H, CH_2 of Et), 1.98−2.08 (m, 1H, CH_2 of Et), 3.78−3.93 (2 overlapping dd, 2H, H_6), 4.25 (dd, 1H, H_1), 4.39/4.48 (d, 1H, J = 2.3 Hz, H_3, α/β = 7.5:1), 4.60−4.70 (m, 2H, H_4 and H_5), 5.27/5.32 (br s, 2H, NH_2, β/α = 1:7.5); α/β ratio was estimated as ca. 7:1; ^{13}C NMR (100 MHz) δ 10.7/10.9 (α/β), 23.0/23.2 (β/α, CH_2 of Et), 24.1, 25.6, 25.82 (β), 25.88, 26.7 (β), 26.9, 61.1/61.3 (α/β, CH_2), 70.45, 70.54 (β), 70.7, 70.8, 72.1 (β), 87.4/87.6 (β/α) 103.6/103.8 (C2-β/C2-α), 109.0, 109.6; α/β ratio was estimated as ca. 5:1 from integration of the anomeric C2 resonances. Anal. ($C_{14}H_{25}NO_8S$) C, H, N. By analogy with **21a**, we assigned the *R* configuration to C1 in the major (α) isomer of **21b**.

2,3:4,5-Bis-*O*-(isopropylidene)-β-D-fructopyranose *N*-Ethylsulfamate (22), and Its *N*-Butyl (23) and *N*-Benzyl (24) Congeners. A saturated solution of ethylamine in THF (70 mL) at −78 °C was treated with chlorosulfate **26** (8.21 g, 0.023 mol). The mixture was stirred for 60 min in a pressure bottle, allowed to warm to 23 °C, stirred for 2 h, and concentrated in vacuo to a semisolid. The residue was dissolved in ethyl acetate and washed once with water, and the organic extract was dried (Na_2SO_4) and concentrated to a syrup, which was purified by preparative HPLC (hexanes/ethyl acetate, 3:1) to give **22** (5.0 g, 59%) as a syrup: ^{1}H NMR (400 MHz) δ 1.25 (t, 3H, Me), 1.40/1.41/1.50/1.58 (4 s, 12H, 4 Me), 3.20−3.30 (m, 2H, CH_2N), 3.71−3.98 (dd, 2H, H_6), 4.12−4.22 (dd, 2H, H_1), 4.25−4.28 (m, 1H, H_3), 4.48 (m, 1H, H_5), 4.55 (t, 1H, NH), 4.61−4.65 (m, 1H, H_4). Anal. ($C_{14}H_{25}NO_8S\cdot 0.15C_4H_8O_2$) C, H, N.

A mixture of chlorosulfate **26** (6.0 g, 0.016 mol) and butylamine (7.9 g, 0.11 mol) in THF (70 mL) was heated on a steam bath in a pressure bottle for 2 h, then cooled, concentrated, and redissolved in ethyl acetate. The solution was washed with water, dried (Na_2SO_4), and concentrated in vacuo to a syrup, which was purified by preparative HPLC (hexanes/ethyl acetate, 2:1) to give **23** (4.22 g, 67%) as a waxy solid: mp 48−50 °C; ^{1}H NMR (400 MHz) δ 0.95 (t, 3H, Me), 1.35/1.42/1.49/1.53 (4 s, 12H, 4 Me), 1.40 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 3.10−3.20 (m, 2H, CH_2N), 3.71−3.94 (dd, 2H, H_6), 4.12−4.22 (dd, 2H, H_1), 4.25 (m, 1H, H_3), 4.35 (m, 1H, H_5), 4.55 (t, 1H, NH), 4.60 (m, 1H, H_4). Anal. ($C_{16}H_{29}NO_8S$) C, H, N.

Chlorosulfate **26** (6.00 g, 16.7 mmol) was dissolved in 167 mL of THF and treated with benzylamine (5.38 g, 50.2 mmol) at 23 °C while being stirred under nitrogen. After 6 h, the reaction was treated with more benzylamine (5.38 g, 50.2 mmol), stirred for 18 h, and filtered through diatomaceous earth. The filtrate was concentrated in vacuo, and the residue was purified by preparative HPLC (hexanes/ethyl acetate, 7:3) to furnish **24** (4.01 g, 76%) as an amber glass: ^{1}H NMR (400 MHz) δ 1.34/1.41/1.46/1.53 (4 s, 12H, 4 Me), 3.70−3.95 (m, 2H, H_6), 4.10−4.35 (m, 6H, $2H_1$, H_3, H_5, NCH_2), 4.61 (dd, 1H, J_{34} = 2.6 Hz, J_{45} = 7.9 Hz, H_4), 4.94 (t, 1H, J = 5.2 Hz, NH), 7.34 (s, 5H, arom.); IR (KBr) ν_{max} 2994 (m), 2941 (m), 1567 (m), 1374 (s), 1173 (s), 910 (s) cm^{-1}; FAB-MS *m*/*z* 430 $(MH)^+$, 447 $(M + Na)^+$. Anal. ($C_{19}H_{27}NO_8S$) C, H, N.

2,3:4,5-Bis-*O*-(isopropylidene)-β-D-fructopyranose *N*-Acetylsulfamate (25). Topiramate (**1**, 3.39 g, 10 mmol) and 1-acetylimidazole (1.30 g, 12 mmol) were combined in 25 mL of dry toluene and heated on a steam bath for 5 h. Since the reaction was not completed (TLC), 1-acetylimidazole (0.4 g) was added and the mixture was heated for 2 h. After being cooled to 0 °C, the precipitate was collected, dried (4.40 g of off-white solid, 98%), and recrystallized (ethyl acetate/MeOH, 20:1) to furnish 3.50 g (78%) of TLC-homogeneous off-white crystals: mp 152−154 °C; ^{1}H NMR (400 MHz, $CDCl_3$/DMSO-d_6, 1:1) δ 1.32/1.38/1.43/1.50 (4 s, 12H, 4 Me), 2.04 (s, 3H, Ac), 3.67 (d, 1H, H_6), 3.86, (d, 1H, H_6), 4.1−4.3 (m, 3H, H_1 and H_3), 4.33 (d, 1H, J = ca. 2 Hz, H_5), 4.57 (dd, 1H, H_4), 7.12 (s, 2H, Im), 7.93 (s, 1H, Im), 7.43 (br s, 1H, exch H); IR (KBr) ν_{max} 3171/3160 (Im), 2993, 1614 (C=O, s), 1322, 1299, 1155, 1077, 843 cm^{-1}. Anal. ($C_{14}H_{23}NO_9S\cdot C_3H_4N_2$) C, H, N.

Reaction of Diol 28 with Trimethylsilyl Enol Ethers of Cyclopentanone (for 30) and 3-Pentanone (for 31). A mixture of diol **28** (6.88 g, 0.022 mol), 1-(trimethylsilyloxy)-cyclopentene (9.8 g, 0.062 mol) in THF (40 mL), and concentrated HCl (2 mL) was stirred for 90 min. It was reacted with water (1 mL), neutralized with solid Na_2CO_3, and filtered. The filtrate was concentrated in vacuo to a syrup, which was purified by preparative HPLC (hexanes/ethyl acetate, 2:1) to give **30** (2.46 g, 42%) as a solid: mp 142−144 °C; ^{1}H NMR (400 MHz) δ 1.48/1.60 (2 s, 6H, 2 Me), 1.75 (m, 6H, 3 CH_2), 1.98 (m, 2H, CH_2), 3.78−3.96 (dd, 2H, H_6), 4.19−4.28 (dd, 2H, H_1), 4.30−4.42 (m, 2H, H_3 and H_5), 4.50 (m, 1H, H_4), 4.95 (br s, 2H, NH_2). Anal. ($C_{14}H_{23}NO_8S$) C, H, N.

Similarly, a mixture of diol **28** (5.0 g, 0.016 mol), 3-(trimethylsilyloxy)pentene (8.15 g, 0.051 mol), THF (50 mL), and concentrated HCl (0.6 mL) yielded **31** (2.0 g, 34%) as white solid: mp 127−130 °C; ^{1}H NMR (400 MHz) δ 0.95 (2 t, 6H, 2 Me), 1.42/1.58 (2 s, 6H, 2 Me), 1.65 (q, 2H, CH_2), 1.75 (q, 2H, CH_2), 3.79−3.92 (dd, 2H, H_6), 4.22−4.30 (dd, 2H, H_1), 4.30−4.45 (m, 2H, H_3 and H_5), 4.70 (m, 1H, H_2), 5.00 (br s, 2H, NH_2). Anal. ($C_{14}H_{25}NO_8S$) C, H, N.

2,3-*O*-(Isopropylidene)-4,5-*O*-methylene-β-D-fructopyranose Sulfamate (32) and Diol Intermediate 40. A mixture of NaH (60% oil dispersion, 8.4 g, 0.21 mol) in DMF (100 mL) was cooled to 0 °C, treated with a solution of **4** (50 g, 0.19 mol) in DMF (100 mL), and stirred for 30 min. A solution of benzyl bromide (32.9 g, 0.19 mol) in DMF (25 mL) was added, and the reaction was stirred for 30 min, poured into cold water, and extracted twice with ethyl acetate. The combined extract was washed with brine, dried (Na_2SO_4), and concentrated to **39**, a thick syrup. Benzyl ether **39** (10.0 g, 0.29 mol) was treated with a mixture of 6 N HCl (90 mL) and THF (180 mL) and stirred at 38−50 °C for 3 h. It was cautiously neutralized with solid Na_2CO_3 and filtered. The filtrate was washed with brine, dried (Na_2SO_4), and concentrated to a syrup that was purified by preparative HPLC (hexanes/ethyl acetate, 1:1) to give diol **40** as a soft, light yellow solid, which was used without further manipulation: CI-MS

m/z 311 (MH^+); ^{1}H NMR (400 MHz) δ 1.34/1.55 (2 s, 6H, 2 Me), 3.15−3.20 (d, 1H, OH), 3.49−3.52 (d, 1H, J = 10 Hz, H_1), 3.76 (m, 1H, H_6), 3.85 (m, 1H, H_5), 3.96 (m, 1H, H_6), 4.15 (m, 1H, H_4), 4.29−4.30 (d, 1H, J_{34} = 2.7 Hz, H_3), 4.57−4.69 (pair of d, 2H, J = 12 Hz, CH_2Ph), 7.32−7.36 (m, 5H, arom).

A solution of diol **40** (4.00 g, 12.9 mmol) and tetrabutylammonium bromide (0.40 g, 1.24 mmol) in dibromomethane (124 g, 713 mmol) was combined with 50% aqueous NaOH (200 g, 2.5 mol) and vigorously stirred at 60 °C for 2 h. The layers were separated, and the aqueous layer was extracted twice with dichloromethane. The combined extracts were washed twice with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by preparative HPLC (hexanes/ethyl acetate, 9:1) to afford 2.48 g (60%) of **41** as a clear oil: ^{1}H NMR (400 MHz) δ 1.43/1.55 (2 s, 6H, 2 Me), 3.54/3.62 (pair of d, 2H, J_{ab} = 10.6 Hz, H_1), 3.75−4.00 (m, 2H, H_6), 4.18 (d, 1H, J_{45} = 7.9 Hz, H_5), 4.43 (dd, 1H, J_{34} = 2.1 Hz, J_{45} = 7.9 Hz, H_4), 4.53 (d, 1H, J_{34} = 2.1 Hz, H_3), 4.56/4.70 (pair of d, 2H, J = 13.2 Hz, CH_2Ph), 4.81 (s, 1H), 5.11 (s, 1H), 7.25−7.35 (m, 5H, arom). Compound **41** (2.72 g, 8.4 mmol) was combined with 20% $Pd(OH)_2$ on carbon (1.36 g) in anhydrous ethanol (42 mL), placed on a Parr apparatus under hydrogen (50 psig), and heated at 50 °C. After 2.5 h, the reaction was cooled to 23 °C, filtered through a Nylon-66 filter (0.45 μm), and concentrated in vacuo to afford 1.98 g (99%) of **42**, as an oil that crystallized on standing. A white solid was obtained from hexanes/ethyl acetate: mp 71−73 °C; $[\alpha]^{25}_D$ −27.4° (*c* 1.00, MeOH); ^{1}H NMR (400 MHz) δ 1.42/1.56 (2 s, 6H, 2 Me), 1.98 (dd, 1H, J = 5.9 Hz, J = 7.8 Hz, OH), 3.60−3.75 (m, 2H, H_1), 3.75−4.05 (m, 2H, H_6), 4.19 (d, 1H, J_{45} = 8.1 Hz, H_5), 4.40−4.50 (m, 2H, H_3 and H_4), 4.82 (s, 1H), 5.17 (s, 1H), 7.25−7.35 (m, 5H, arom.); IR (KBr) ν_{max} 3402 (s), 2998 (m), 2931 (m), 2856 (m), 1253 (m), 1374 (s), 1079 (s), 901 (s), 538 (m) cm^{-1}; CI-MS *m/z* 233 $(MH)^+$, 250 $(M + NH_4)^+$. To NaH (60% oil dispersion; 0.53 g, 8.0 mmol, washed with ether) suspended in 6 mL of DMF at 5 °C was added **42** (1.68 g, 6.31 mmol) with stirring. The reaction was stirred for 1 h, treated with sulfamoyl chloride (1.23 g, 10.6 mmol), slowly warmed to 23 °C over 1 h, diluted with water, and extracted three times with ethyl acetate. The organic solution was rinsed twice with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by preparative HPLC (hexanes/ethyl acetate, 7:3) and recrystallized from ethyl acetate/hexanes to yield **32** (1.21 g, 79%) as a white solid: mp 131−133 °C; ^{1}H NMR (400 MHz) δ 1.43/1.56 (2 s, 6H, 2 Me), 3.83−4.02 (m, 2H, H_6), 3.75−4.05 (m, 2H, H_6), 4.20 (d, 1H, J_{45} = 7.9 Hz, H_5), 4.26 (s, 2H, H_1), 4.40−4.48 (m, 2H, H_3 and H_4), 4.81 (s, 1H), 5.06 (s, 2H, NH_2), 5.19 (s, 1H); IR (KBr) ν_{max} 3377 (s), 3270 (s), 1564 (m), 1363 (s), 1076 (s), 904 (m) cm^{-1}; CI-MS *m/z* 312 $(MH)^+$, 329 $(M + NH_4)^+$. Anal. ($C_{10}H_{17}NO_8S$) C, H, N, S.

Reaction of Diol 28 with Carbonyl Compounds in the Presence of Triethyl Orthoformate. A. General Procedure. In a typical reaction, a mixture of ketone (excess, sometimes used as a solvent), concentrated sulfuric acid (0.5 mL), triethyl orthoformate (10.0 g, 0.07 mol), and ethanol (10 mL, used only when ketone could not be used as solvent) was stirred for 3 h and then treated with a mixture of diol **28** (10.0 g, 0.03 mol) in 20 mL of THF (only when ketone could not be used as solvent). After 24 h of stirring, the mixture was neutralized with Na_2CO_3 (to pH = 7), filtered, and concentrated in vacuo to the respective product, which was purified by preparative HPLC.

B. Compound 35. A mixture of diol **28** (8.0 g, 0.027 mol), 2-butanone (100 mL), triethyl orthoformate (10.0 g), and H_2SO_4 (0.4 mL) gave a syrup, which was purified by preparative HPLC (hexanes/ethyl acetate, 2:1) to give **35** (7.55 g, 79%) as a syrupy mixture of diastereomers. The material eventually crystallized on standing: mp 97−99 °C; ^{1}H NMR (400 MHz) δ 1.00 (t, 3H, Me), 1.29/1.45/1.58 (3 s, 9H, 3 Me), 1.75 (q, 2H, CH_2), 3.70−3.92 (dd, 2H, H_6), 4.20−4.30 (m, 2H, H_1), 4.31−4.35 (m, 2H, H_3 and H_5), 4.62 (m, 1H, H_4), 4.75 (br s, 2H, NH_2). Anal. ($C_{13}H_{23}NO_8S$) C, H, N.

C. Compound 37. In a similar way, a mixture of diol **28** (8.0 g, 0.027 mol), 3,3-dimethyl-2-butanone (100 mL), triethyl orthoformate (10 g), and H_2SO_4 (0.4 mL) gave a syrup, which was purified by preparative HPLC (hexanes/ethyl acetate, 2:1) to give **37** (5.60 g, 55%) as a syrup and a single isomer (*S*). The material eventually crystallized on standing: mp 130−133 °C; ^{1}H NMR (400 MHz) δ 1.10 (s, 9H, Me), 1.29/1.45/1.55 (3 s, 9H, 3 Me), 3.79−3.91 (dd, 2H, H_6), 4.21 (d, 1H, H_5), 4.30−4.36 (m, 3H, H_1 and H_3), 4.62 (m, 1H, H_4), 4.95 (br s, 2H, NH_2). Anal. ($C_{15}H_{27}NO_8S$) H, N; C: calcd, 47.23; found, 47.87.

D. Compounds 33a and 33b. A mixture of diol **28** (10.0 g, 0.033 mol), acetal (70 mL), and concentrated H_2SO_4 (0.5 mL) was stirred at 45 °C for 2 h and neutralized with solid Na_2CO_3. It was filtered and concentrated to a waxy solid, which was purified by preparative HPLC (hexanes/ethyl acetate, 2:1) to give diastereomers **33a** (3.34 g, 32%) and **33b** (0.69 g, 6.4%), each as a syrup. For **33a**: ^{1}H NMR (400 MHz) δ 1.40 (br s, 6H, 2 Me), 1.55 (s, 3H, Me), 3.70−3.80 (dd, 2H, H_6), 4.19 (d, 1H, H_5), 4.20−4.30 (m, 2H, H_1), 4.35 (d, 1H, H_3), 4.45 (m, 1H, H_4), 5.0 (m, 1H, *R*-CH), 5.15 (br s, 2H, NH_2). Anal. ($C_{11}H_{19}NO_8S$) C, H, N. For **33b**: ^{1}H NMR (400 MHz) δ 1.32/1.43/1.55 (3 s, 9H, 3 Me), 3.82−4.00 (dd, 2H, H_6), 4.20−4.30 (dd, 2H, H_1),4.19 (d, 1H, H_5), 4.40 (d, 1H, H_3), 4.60 (m, 1H, H_4), 5.15 (br s, 2H, NH_2), 5.45 (m, 1H, *S*-CH). Anal. ($C_{11}H_{19}NO_8S\cdot 0.1C_4H_8O_2$) C, H, N.

E. Compound 34. A mixture of diol **28** (10.0 g, 0.033 mol), propionaldehyde diethyl acetal (80 mL), and concentrated H_2SO_4 (0.5 mL) was stirred at 23 °C for 24 h and neutralized with solid Na_2CO_3. It was filtered and concentrated to a syrup, which was purified by preparative HPLC (hexanes/ethyl acetate, 2:1) to give **34** (3.77 g, 34%) as a syrupy mixture of diastereomers (*R*:*S* = 9:1). The material eventually crystallized on standing and was then recrystallized from ethyl acetate−hexanes: mp 131−132 °C; ^{1}H NMR (400 MHz) δ 0.90 (t, 3H, Me), 1.40/1.60 (2 s, 6H, 3 Me), 1.80 (q, 2H, CH_2), 3.80−3.95 (dd, 2H, H_6), 4.19 (d, 1H, H_5), 4.25−4.38 (dd, 2H, H_1), 4.40 (d, 1H, H_3), 4.50 (m, 1H, H_4), 4.85 (m, 0.9H, *R*-CH), 5.00 (br s, 2H, NH_2), 5.30 (t, 0.1H, *S*-CH). Anal. ($C_{12}H_{21}NO_8S\cdot 0.1C_4H_8O_2$) C, H, N.

F. Compound 36. A mixture of diol **28** (8.0 g, 0.027 mol), trimethylacetaldehyde diethyl acetal (9.0 g, 0.056 mol; prepared from trimethylacetaldehyde, triethyl orthoformate, ethanol, and *p*-TsOH), THF (20 mL), and concentrated H_2SO_4 (0.4 mL) was stirred at 23 °C for 6 h and neutralized with solid Na_2CO_3. It was filtered and concentrated to a solid, which was recrystallized from ethanol−water to give **36** (4.50 g, 45%), the *R*-isomer: mp 164−165 °C; ^{1}H NMR (400 MHz) δ 1.00 (s, 9H, Me), 1.45/1.55 (2 s, 6H, 2 Me), 3.80−3.95 (dd, 2H, H_6), 4.15 (d, 1H, H_5), 4.25−4.35 (dd, 2H, H_1), 4.40 (d, 1H, H_3), 4.50 (d, 1H, H_4), 4.52 (s, 1H, CH), 4.90 (br s, 2H, NH_2). Anal. ($C_{14}H_{25}NO_8S$) C, H, N.

G. Compound 38. A mixture of diol **28** (10.0 g, 0.033 mol), benzaldehyde dimethyl acetal (70 mL), and concentrated H_2SO_4 (0.5 mL) was stirred at 23 °C for 24 h, then neutralized with solid Na_2CO_3, filtered, and concentrated in vacuo to a syrup, which was purified by preparative HPLC (hexanes/ethyl acetate, 2:1) to give **38** (5.80 g, 45%) as a syrupy mixture of diastereomers (*R*:*S* = 3:1): ^{1}H NMR (400 MHz) δ 1.41/1.62 (2 s, 6H, 2 Me), 3.95−4.12 (m, 2H, H_6), 4.19−4.31 (dd, 1H, H_1), 4.35 (m, 1H, H_5), 4.45 (d, 1H, H_3), 4.65 (m, 1H, H_4), 4.72 (br s, 2H, NH_2), 5.25 (s, 0.75H, *R*-CH), 6.28 (s, 0.25H, *S*-CH). Anal. ($C_{16}H_{21}NO_8S$) C, H, N.

4,5-*O*-(1,2-Ethano)-2,3-*O*-(isopropylidene)-β-D-fructopyranose Sulfamate (43). A mixture of **40** (10.0 g, 0.032 mol), 1,2-dibromoethane (50 mL), and tetrabutylammonium bromide (2.0 g) was stirred at 50 °C while 50% aqueous NaOH (503 g) was added cautiously. The reaction was allowed to stand until gas evolution ceased, after which additional dibromoethane (210 mL, 2.5 mol total) was added while the temperature was kept under 60 °C. The mixture was stirred for 2 h at 55 °C, treated with ice−water, and extracted twice with ethyl acetate. The combined extract was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by preparative HPLC (hexanes/ethyl acetate, 1:1) to supply the 1,4-dioxane product as a syrup. A mixture of product (3.19 g, 0.087 mol) in ethanol (42 mL) was treated with $Pd(OH)_2$ on

carbon (1.36 g) and shaken with hydrogen at 50 °C for 3 h. It was cooled, filtered, and concentrated to **44**, as a syrup, which was used in the next step. A solution of alcohol **44** (2.19 g, 0.009 mol) in DMF (25 mL) with triethylamine (1.8 g, 0.018 mol) was stirred for 45 min at 5 °C, treated with sulfamoyl chloride (1.57 g, 0.013 mol), and stirred for 15 min at 5 °C and then 45 min at 23 °C. The mixture was poured into cold water and extracted twice with ethyl acetate. The combined extract was dried (Na_2SO_4) and concentrated in vacuo to a syrup, which was purified by preparative HPLC (hexane/ethyl acetate, 1:1) to give **43** (1.60 g, 55%) as a soft white solid: mp 122−124 °C; ^{1}H NMR (400 MHz) δ 1.40/1.55 (2 s, 6H, 2 Me), 3.50−3.72 (dd, 2H, H_6), 3.80−4.00 (m, 4H, 2 CH_2), 4.15 (m, 2H, H_1), 4.19 (d, 1H, H_5), 4.30 (d, 1H, H_3), 4.32−4.45 (dd, 1H, H_4), 5.15 (br s, 2H, NH_2); ^{1}H NMR (400 MHz, C_6D_6/D_2O) δ 1.35/1.45 (2 s, 6H, 2 Me), 3.00−3.13 (m, 1H, OCH_2), 3.20−3.35 (m, 2H, OCH_2), 3.40−3.57 (m, 1H, OCH_2), 3.85−3.95 (m, 2H, H_5 and H_{6a}), 3.95−4.05 (m, 1H, H_{6e}), 4.05−4.10 (m, 1H, H_4, decoupled at H_5: $J_{46e} = 1.4$ Hz, $J_{34} = 3.3$ Hz), 4.15 (d, 1H, $J_{34} = 3.3$ Hz, H_3), 4.32/4.42 (pair of d, 2H, $J_{ab} = 11.4$ Hz, H_1), 4.94 (br s, 2H, NH_2). Anal. ($C_{11}H_{19}NO_8S$) C, H, N.

4,5-*O*-(Dimethoxymethylene)-2,3-*O*-(isopropylidene)-*β*-D-fructopyranose Sulfamate (45). Diol **28**[2a] (6.00 g, 20 mmol), tetramethyl orthocarbonate (16.4 g, 120 mmol), and *p*-toluenesulfonic acid (0.60 g, 3.2 mmol) were dissolved in 1,4-dioxane (200 mL) and stirred at 23 °C for 22 h. The mixture was concentrated in vacuo, basified with $NaHCO_3$ (saturated aqueous), and extracted three times with ethyl acetate. The combined extracts were rinsed twice with $NaHCO_3$ (saturated aqueous), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by preparative HPLC (CH_2Cl_2/ethyl acetate, 9:1) to furnish **45** (2.60 g, 42%) as a glass: ^{1}H NMR (400 MHz) δ 1.46/1.60 (2 s, 6H, 2 Me), 3.41 (s, 3H, Me), 3.54 (s, 3H, Me), 3.90−4.05 (m, 2H, H_6), 4.28−4.43 (m, 1H, H_5), 4.74 (dd, 1H, $J_{34} = 2.4$ Hz, $J_{45} = 8.0$ Hz, H_4), 5.30 (s, 2H, NH_2), 5.19 (s, 1H); IR (KBr) ν_{max} 3435 (m), 3354 (m), 3264 (m), 1385 (s), 1133 (s), 1086 (s), 1015 (s), 910 (m) cm^{-1}; CI-MS *m*/*z* 372 $(MH)^+$. Anal. ($C_{12}H_{21}NO_{10}S\cdot 0.1H_2O$) C, H, N, H_2O.

4,5-*O*-[(*S*)-Ethoxymethylene]-2,3-*O*-(isopropylidene)-*β*-D-fructopyranose Sulfamate (46). A mixture of diol **28** (5 g, 0.017 mol), triethyl orthoformate (12.4 g, 0.08 mol), *p*-toluenesulfonic acid (0.14 g), and THF (20 mL) was stirred at 23 °C for 4 h and neutralized with solid Na_2CO_3. It was filtered and concentrated in vacuo to a residue, which was purified by preparative HPLC (hexanes/ethyl acetate, 2:1) to give **46** (2.67 g, 44%) as a syrupy mixture of diastereomers (*R*:*S* = 1:9): ^{1}H NMR (400 MHz) δ 1.20 (t, 3H, Me), 1.41/1.59 (2 s, 6H, 2 Me), 3.62 (q, 2H, CH_2), 3.8−3.95 (dd, 2H, H_6), 4.25 (m, 2H, H_1), 4.35 (d, 1H, H_3), 4.45 (m, 1H, H_5), 4.75 (m, 1H, H_4), 5.00 (br s, 2H, NH_2), 5.79 (s, 0.1H, *R*-CH), 5.92 (s, 0.9H, *S*-CH). Anal. ($C_{12}H_{21}NO_9S$) C, H, N.

2,3-*O*-(Isopropylidene)-4,5-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-*β*-D-fructopyranose Sulfamate (47). A solution of diol **40** (10.0 g, 32.2 mmol) and pyridine (10.4 mL, 129 mmol) in chloroform (133 mL) was cooled to −60 °C with mechanical stirring. Sulfuryl chloride (8.6 mL, 107 mmol) was added dropwise over 15 min, and the reaction was slowly warmed to 23 °C over 18 h. The reaction was stirred at 23 °C for 5 d, filtered through diatomaceous earth, washed sequentially twice with water, twice with $NaHCO_3$ (saturated aqueous), and twice with brine, then dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by preparative HPLC (hexanes/ethyl acetate, 9:1) to give **48** (5.01 g, 47%) as a white foam. A solution of **48** in methanol (114 mL) was treated with K_2CO_3 (4.72 g, 34 mmol), stirred at 23 °C for 16 h, filtered through diatomaceous earth, and concentrated in vacuo. The residue was partitioned between water and ethyl acetate, and the aqueous layer was extracted twice with ethyl acetate. The combined extract was washed twice with brine, dried ($MgSO_4$), and concentrated in vacuo to give **49** (3.48 g, 100%) as an amber oil, which was used without further purification. A screw-topped pressure tube containing a solution of **49** (3.18 g, 10.9 mmol) and tetrabutylammonium iodide (1.20 g, 3.3 mmol) in 1,2-dimethoxyethane (22 mL) was cooled to −60 °C, and hexafluoroacetone (18.0 g, 108 mmol) was condensed into the tube. The tube was sealed and heated at 120 °C in a silicone oil bath for 38 h. After being cooled to 23 °C, the mixture was filtered through diatomaceous earth and concentrated in vacuo. The residue was dissolved in ethyl acetate, washed sequentially twice with $NaHCO_3$ (saturated aqueous) and twice with brine, dried ($MgSO_4$), and concentrated in vacuo to give an orange oil, which was purified by preparative HPLC (hexanes/ethyl acetate, 9:1) to furnish **50** (3.48 g, 70%) as a clear viscous oil. Compound **50** (3.16 g, 6.9 mmol) was combined with 20% $Pd(OH)_2$ on carbon (0.32 g) in anhydrous ethanol (69 mL) and placed on a Parr apparatus with hydrogen (50 psig) at 23 °C. After 2 h, the reaction was filtered through diatomaceous earth and concentrated in vacuo to afford **51** (2.57 g, 100%) as a white solid, which was used without further purification. Sulfamoyl chloride (1.07 g, 9.3 mmol) was added to a solution of **51** (2.27 g, 6.2 mmol) and triethylamine (1.29 mL, 9.3 mmol) in dry DMF (31 mL) at 5 °C with stirring under argon. After 1 h, the reaction was diluted with brine and extracted three times with ethyl acetate. The combined extracts were rinsed twice with 3 N HCl, twice with $NaHCO_3$ (saturated aqueous), and twice with brine, then dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by preparative HPLC (hexanes/ethyl acetate, 7:3) to give **47** (2.23 g, 81%) as a white foam: ^{1}H NMR (400 MHz) δ 1.45/1.56 (2 s, 6H, 2Me), 4.15−4.35 (m, 2H, H_6), 4.49 (d, 1H, $J_{34} = 2.2$ Hz, H_3), 4.71 (d, 1H, $J_{45} = 7.9$ Hz), 4.90 (s, 2H, NH_2), 4.98 (d, 1H, $J_{45} = 7.9$ Hz); IR (KBr) ν_{max} 3363 (m), 3282 (m), 3264 (m), 1389 (m), 1235 (s), 1139 (s), 977 (s), 710 (m) cm^{-1}; CI-MS *m*/*z* 448 $(MH)^+$, 465 $(M + NH_4)^+$. Anal. ($C_{12}H_{15}F_6NO_8S$) C, H, N, S.

2,3-*O*-(Isopropylidene)-4,5-*O*-(methylboryl)-*β*-D-fructopyranose Sulfamate (54). Methylboronic acid (2.00 g, 33.4 mmol) was added to solution of diol **28**[2a] (5.00 g, 16.7 mmol) in methanol (100 mL) at 23 °C with stirring under argon. After 18 h, the reaction was concentrated in vacuo; the residue was dissolved in ethyl acetate, washed twice with $NaHCO_3$ (saturated aqueous), dried ($MgSO_4$), and concentrated in vacuo to an oil, which was crystallized (benzene/hexanes, 1:1) to furnish **54** (2.68 g, 50%) as a white solid: mp 88−89 °C; ^{1}H NMR (360 MHz, C_6D_6) δ 0.41 (s, 3H, Me), 1.21/1.30 (2 s, 6H, 2 Me), 3.50−3.75 (m, 2H, H_6), 3.85 (d, 1H, $J_{45} = 8.7$ Hz, H_5), 3.95−4.15 (br s, 2H, NH_2), 4.17/4.23 (pair of d, 2H, $J_{1a1b} = 10.6$ Hz, H_1), 4.29 (d, 1H, $J_{34} = 2.4$ Hz, H_3), 4.40 (dd, 1H, $J_{34} = 2.4$ Hz, $J_{45} = 8.7$ Hz, H_4); IR (KBr) ν_{max} 3348 (s), 3271 (m), 1364 (m), 1205 (s), 1053 (s), 912 (m), 816 (m) cm^{-1}; CI-MS *m*/*z* 324 $(MH)^+$, 341 $(M + NH_4)^+$. Anal. ($C_{10}H_{18}BNO_8S$) C, H, N.

2,3-*O*-(Isopropylidene)-4,5-*O*-(phenylboryl)-*β*-D-fructopyranose Sulfamate (55). A solution of phenylboronic acid (2.00 g, 33.4 mmol) in methanol (50 mL) was added to solution of diol **28**[2a] (4.07 g, 33.4 mmol) in water (100 mL) and stirred at 23 °C for 2 h. The white precipitate was isolated by filtration and purified by preparative HPLC (CH_2Cl_2/ethyl acetate, 9:1). Recrystallization from hot benzene furnished **55** (5.90 g, 92%) as a white solid: mp 151−152 °C; ^{1}H NMR (400 MHz) δ 1.10/1.21 (2 s, 6H, 2 Me), 2.47 (s, 0.8H, H_2O), 3.45−3.80 (m, 4H, H_1 and H_6), 4.19 (d, 1H, $J_{35} = 2.6$ Hz, H_3), 4.32 (d, 1H, $J_{45} = 8.5$ Hz, H_5), 4.61 (dd, 1H, $J_{34} = 2.6$ Hz, $J_{45} = 8.5$ Hz, H_4), 6.48 (bs, 2H, NH_2), 6.95−7.50 (m, 5H, Ph); IR (KBr) ν_{max} 3372 (s), 3292 (s), 2974 (m), 1362 (s), 1152 (s), 1035 (s), 913 (m) cm^{-1}; CI-MS *m*/*z* 403 $(M + NH_4)^+$. Anal. ($C_{15}H_{20}BNO_8S$) C, H, N.

2,3:4,5-Bis-*O*-(cyclohexylidene)-*β*-D-fructopyranose Sulfamate (58). Concentrated H_2SO_4 (75 mL) was added dropwise over 15 min to a suspension of D-fructose (150 g, 0.833 mol) in cyclohexanone (750 mL) at 23 °C. The reaction was warmed to 55 °C, stirred for 1 h, cooled to 23 °C, cautiously basified with a mixture of 50% NaOH (150 mL) and ice (200 g), diluted with water, and extracted with ether. The extract was washed with water, dried (Na_2SO_4), and concentrated in vacuo to an oil, which was concentrated on a Kugelrohr apparatus (130 °C, 0.15 mmHg) to yield a dark reddish-brown glass. Purification by preparative HPLC (hexanes/ethyl acetate, 9:1) afforded 2,3:4,5-bis-*O*-(cyclohexylidene)-*β*-D-fructopyranose (24.2 g, 8.5%)

as a tacky amber glass: ^{1}H NMR (300 MHz) δ 1.25−1.90 (m, 20H), 2.14 (dd, 1H, J = 4.3 Hz, 8.4 Hz, OH), 3.55−3.85 (m, 3H, 2 H_1 and H_{6a}), 3.94 (dd, J_{56e} = 1.6 Hz, J_{6a6e}= 13.1 Hz, 1H, H_{6e}), 4.24 (d, 1H, J_{45} = 7.9 Hz, H_5), 4.36 (d, 1H, J_{34} = 2.7 Hz, H_3), 4.64 (dd, 1H, J_{34} = 2.7 Hz, J_{45} = 7.9 Hz, H_4). Most of this material (22.6 g, 66.4 mmol) and pyridine (6.30 g, 79.7 mmol) were dissolved in toluene (150 mL) and added dropwise over 20 min to a vigorously stirred solution of sulfuryl chloride (8.75 g, 64.9 mmol) in toluene (150 mL) at −20 °C. The reaction was slowly warmed to 23 °C over 4 h and diluted with water. The toluene layer was washed three times with citric acid (10% aqueous), three times with $NaHCO_3$ (saturated aqueous), and twice with brine; it was dried ($MgSO_4$) and concentrated in vacuo to give 33.1 g of crude 2,3:4,5-bis-*O*-(cyclohexylidene)-β-D-fructopyranose chlorosulfate, which was dissolved in 132 mL of THF and reacted with anhydrous ammonia (30 psig) in a vigorously stirred autoclave for 18 h. The mixture was filtered through diatomaceous earth, concentrated in vacuo, and purified by preparative HPLC (hexanes/ethyl acetate, 7:3) to furnish 20.3 g (73%) of **58** as a hard white foam: ^{1}H NMR (400 MHz) δ 1.35−1.90 (m, 20H), 3.75−4.00 (m, 2H, H_6), 4.20−4.40 (m, 4H, 2 H_1, H_3 and H_5), 4.64 (dd, 1H, J_{34} = 2.3 Hz, J_{45} = 7.8 Hz, H_4), 5.03 (s, 2H, NH_2); IR (KBr) ν_{max} 3372 (m), 3277 (m), 2897 (s), 2859 (m), 1450 (m), 1372 (s), 1187 (s), 1087 (s), 935 (s) cm^{-1}; CI-MS *m*/*z* 420 $(MH)^+$, 437 $(M + NH_4)^+$. Anal. ($C_{18}H_{29}NO_8S$) C, H, N, S.

2,3:4,5-Bis-*O*-(ethylpropylidene)-β-D-fructopyranose Sulfamate (59). Concentrated H_2SO_4 (60 mL) was added dropwise at 40 °C over 20 min to a stirred suspension of d-fructose (100.0 g, 0.56 mol) in 3-pentanone (2.3 L, 1.13 mol). After 25 min, the reaction was cooled to 5 °C, cautiously basified to pH 11 with 3 N NaOH, concentrated in vacuo, diluted with water, and extracted three times with CH_2Cl_2. The extracts were washed twice with water, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by preparative HPLC (hexanes/ethyl acetate, 19:1) to give 9.4 g (5.3%) of 2,3:4,5-bis-*O*-(1-ethylpropylidene)-β-D-fructopyranose as a white crystalline solid: mp 46−48 °C; $[\alpha]^{25}_D$ −36.6° (*c* 1.00, MeOH); ^{1}H NMR (300 MHz) δ 0.60−1.10 (m, 12H), 1.50−1.80 (m, 8H); 2.02 (dd, 1H, J = 4.9 and 8.2 Hz, OH), 3.50−4.00 (m, 4H, H_1 and H_6), 4.15 (dd, 1H, J_{45} = 7.8 Hz, J_{56e} = 1.7 Hz), 4.25 (d, 1H, J_{34} = 2.6 Hz, H_3), 4.54 (dd, 1H, J_{34} = 2.6 Hz, J_{45} = 7.8 Hz, H_4); IR (KBr) ν_{max} 3510 (m), 2977 (m), 2944 (m), 1462 (m), 1176 (s), 1077 (s), 934 (s) cm^{-1}; CI-MS *m*/*z* 317$(MH)^+$, 334 $(M + NH_4)^+$. Anal. Calcd for $C_{16}H_{28}O_6$: C, 60.74; H, 8.92. Found: C, 60.77; H, 8.93. This material (17.2 g, 54.1 mmol) and pyridine (5.13 g, 64.9 mmol) were dissolved in toluene (73 mL) and added dropwise over 15 min at −20 °C to a vigorously stirred solution of sulfuryl chloride (8.75 g, 64.9 mmol) in 75 mL of toluene. The reaction was slowly warmed to 23 °C over 3 h and then diluted with water. The toluene layer was washed three times with citric acid (10% aqueous), three times with $NaHCO_3$ (saturated aqueous), and twice with brine; it was dried (Na_2SO_4) and concentrated in vacuo to afford 25.4 g of crude 2,3:4,5-bis-*O*-(1-ethylpropylidene)-β-D-fructopyranose chlorosulfate. The crude product was dissolved in THF (300 mL) and placed in a vigorously stirred autoclave under 30 psig of anhydrous ammonia for 18 h. The mixture was filtered through diatomaceous earth, concentrated in vacuo, and purified by preparative HPLC (hexanes/ethyl acetate, 3:1) to give **59** (2.48 g, 79%) as a clear syrup: ^{1}H NMR (400 MHz) δ 0.80−1.05 (m, 12H), 1.55−1.85 (m, 8H), 3.75−4.00 (m, 2H, H_6), 4.20−4.40 (m, 4H, 2 H_1, H_3 and H_5), 4.62 (dd, 1H, J_{34} = 2.4 Hz, J_{45} = 7.9 Hz, H_4), 4.93 (s, 2H, NH_2); IR ($CHCl_3$) ν_{max} 3435 (m), 3354 (m), 3293 (m), 1482 (s), 1377 (s), 1170 (m), 1083 (s), 909 (s) cm^{-1}; CI-MS *m*/*z* 396 $(MH)^+$, 413 $(M + NH_4)^+$. Anal. ($C_{16}H_{29}NO_8S$) C, H, N, S.

2,3-(*S*):4,5-(*R*)-Bis-*O*-(phenylmethylene)-β-D-fructopyranose Sulfamate (60). Anhydrous zinc chloride (80 g, 0.59 mol) was added over 20 min at 5 °C to a stirred suspension of D-fructose (100.0 g, 0.56 mol) in benzaldehyde (250 mL, 2.46 mol). After 60 min, the reaction was warmed to 23 °C, stirred for 5 d, and concentrated in vacuo. The residue was treated with ethyl acetate and washed three times with 1 N HCl, once with $NaHCO_3$ (saturated aqueous), and twice with brine, then dried ($MgSO_4$), and concentrated in vacuo. The excess benzaldehyde was removed by distillation on a Kugelrohr apparatus (70 °C, 0.35 Torr). The residue, which contained at least three bis-acetal isomers (two major) by GLC, was partially purified by preparative HPLC (hexanes/ethyl acetate, 4:1) to give 32.3 g of an isomeric mixture. This mixture was recrystallized once from hot carbon tetrachloride (350 mL), once from methanol (80 mL), and again from hot CCl_4 (180 mL) to afford 2,3-(*S*):4,5-(*R*)-bis-*O*-(phenylmethylene)-β-D-fructopyranose[33] as a white solid (9.13 g, 5%): $[\alpha]^{20}_D$ −20.7° (*c* 2.82, $CHCl_3$); ^{1}H NMR (400 MHz) δ 2.01 (dd, 1H, J = 5.2, 8.1 Hz, OH), 3.75−4.05 (m, 4H, H_1 and H_6), 4.35 (dd, 1H, J_{45} = 8.1 Hz, J_{56e} = 1.4 Hz, H_5), 4.55 (d, 1H, J_{34} = 2.4 Hz, H_3), 4.78 (dd, 1H, J_{34} = 2.4 Hz, J_{45} = 8.1 Hz, H_4), 5.79 (s, 1H), 5.90 (s, 1H), 7.35−7.65 (m, 10H, 2 Ph); ^{13}C NMR (100 MHz) δ 61.0 (CH_2), 65.4 (CH_2), 71.4 (CH), 71.8 (CH), 102.8 (CH), 103.0 (C), 103.8 (CH), 126.2 (CH), 127.0 (CH), 128.5 (CH), 128.6 (CH), 129.8 (CH), 130.0 (CH), 135.9 (C), 135.4 (C); CI-MS *m*/*z* 357 $(MH)^+$, 374 $(M + NH_4)^+$. A solution of this material (8.89 g, 25 mmol) and triethylamine (5.2 mL, 37.4 mmol) in dry DMF (125 mL) was cooled to 5 °C with stirring. Sulfamoyl chloride (4.32 g, 37.4 mmol) was added, and the mixture was stirred for 1 h at 5 °C and diluted with brine (300 mL). It was extracted three times with ethyl acetate, and the combined extracts were washed with 3 N HCl, twice with $NaHCO_3$ (saturated aqueous), and twice with brine, then dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (hexanes/ethyl acetate, 3:2) and recrystallized (EtOH/water, 5:1) to provide **60**[34] (7.84 g, 72%) as a white solid: mp 156−158 °C; ^{1}H NMR (400 MHz) δ 3.90−4.25 (m, 2H, H_6), 4.30−4.55 (m, 4H, 2 H_1, H_3 and H_5), 4.55 (d, 1H, J_{34} = 2.4 Hz, H_3), 4.61 (s, 2H, NH_2), 4.77 (dd, 1H, J_{34} = 2.4 Hz, J_{45} = 8.2 Hz, H_4), 5.79 (s, 1H), 5.90 (s, 1H), 7.35−7.60 (m, 10H, 2 Ph); IR (KBr) ν_{max} 3384 (m), 1460 (m), 1391 (s), 1106 (s), 1069 (s), 999 (s), 759 (s) cm^{-1}; FAB-MS *m*/*z* 436 $(MH)^+$, 458 $(M + Na)^+$. Anal. ($C_{20}H_{21}NO_8S$) C, H, N, S.

2,3-*O*-(Isopropylidene)-4,5-*O*-dimethyl-β-D-fructopyranose Sulfamate (63). A mixture of NaH (60% oil dispersion, 1.28 g, 0.032 mol) in DMF (5 mL) was treated with a soultion of diol **40** (3.2 g, 0.01 mol) in 20 mL of DMF, and the reaction was stirred at 0 °C for 30 min. The reaction mixture was treated dropwise with methyl iodide (3.84 mL, 0.062 mol), stirred for 30 min, allowed to warm to 23 °C, stirred for 2 h, treated with cold water, and extracted with ethyl acetete three times. The combined extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to afford 1.80 g (53%) of the syrupy dimethoxy analogue, some of which (0.005 mol) was combined with 10% Pd/C (0.85 g) in anhydrous ethanol (30 mL), placed on a Parr apparatus with hydrogen (50 psig), shaken for 24 h, filtered through a Nylon-66 filter (0.45 μm), and concentrated in vacuo to afford 1.22 g (92%) of the alcohol as a syrup. This alcohol (1.15 g, 0.005 mol) in DMF (10 mL) was added to a mixture of NaH (60% oil dispersion, 0.24 g, 0.006 mol) in DMF (10 mL), and the reaction was stirred at 0 °C for 30 min. Sulfamoyl chloride (1.06 g, 0.009 mol) was added portionwise at 0−10 °C. After 1 h of stirring, the mixture was poured onto ice and extracted with ethyl acetate twice. The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to a syrup, which was purified by preparative HPLC (ethyl acetate/hexanes, 1:1) to give **63** (0.96 g, 58%) as a white solid: mp 135−138 °C; ^{1}H NMR (400 MHz) δ 1.44/1.57 (2 s, 6H, 2 Me), 3.45/3.58 (2 s, 6H, 2 OMe), 3.73 (ddd, 1H, J_{45} = 3.2 Hz, J_{56a} = 8.4 Hz, J_{56e} = 4.9 Hz, H_5), 3.81 (dd, 1H, J_{6a6e} = 11.3 Hz, J_{56a} = 8.4 Hz, H_{6a}), 3.88 (ddd, 1H, J_{6a6e} = 11.3 Hz, J_{56e} = 4.9 Hz, J_{46e} = 0.9 Hz, H_{6e}), 3.92 (ddd, 1H, J_{34} = 3.6 Hz, J_{45} = 3.2 Hz, J_{46e} = 0.9 Hz, H_4), 4.24 (d, 1H, J_{34} = 3.6 Hz, H_3), 4.34/4.45 (pair of d, 2H, J_{ab} = 11.5 Hz, H_1), 5.01 (br s, 2H, NH_2). Anal. ($C_{11}H_{21}NO_8S$) C, H, N.

4,5-*O*-Diethyl-2,3-*O*-(isopropylidene)-β-D-fructopyranose Sulfamate (64). A mixture of NaH (60% oil dispersion, 1.40 g, 0.036 mol) in DMF (10 mL) was treated with a mixture of diol **40** (3.5 g, 0.011 mol) in 20 mL of DMF, and the reaction

was stirred at 0 °C for 30 min. The mixture was treated dropwise with ethyl iodide (5.7 mL, 0.07 mol), stirred for 30 min, allowed to warm to 23 °C, stirred for 2 h, treated with cold water, and extracted with ethyl acetete three times. The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to afford 3.22 g (80%) of the syrupy diethoxy analogue, some of which (0.009 mol) was combined with 10% Pd/C (1.79 g) in anhydrous ethanol (60 mL), placed on a Parr apparatus under hydrogen (50 psig), shaken for 24 h, filtered through a Nylon-66 filter (0.45 μm), and concentrated in vacuo to afford 1.98 g (78%) of the alcohol as a syrup. Similar to **63**, reaction of this alcohol (1.96 g, 0.007 mol) with NaH (0.37 g, 0.009 mol) in DMF (20 mL) and sulfamoyl chloride (1.63 g, 0.014 mol) furnished a syrup, which was purified by preparative HPLC (ethyl acetate/hexane, 1:1) to give **64** (1.32 g, 54%) as a syrup: ^{1}H NMR (400 MHz) δ 1.22/1.24 (2 overlapping t, 6H, J = 7.1 Hz, 2 Me), 1.42/1.56 (2 s, 6H, 2 Me), 3.45−3.65 (m, 2H, OCH_2), 3.65−3.80 (m, 2H, OCH_2), 3.80−3.90 (m, 3H, H_5 and H_6), 3.99 (m, 1H, H_4, decoupled at H_5 and H_3: J_{34} = 3.6 Hz, J_{45} = 2.8 Hz), 4.19 (d, 1H, J_{34} = 3.6 Hz, H_3), 4.29/4.49 (pair of d, 2H, J_{ab} = 11.3 Hz, H_1), 5.22 (br s, 2H, NH_2). Anal. ($C_{13}H_{25}NO_8S\cdot 0.1H_2O$) C, H, N.

4,5-Dideoxy-2,3-*O*-(isopropylidene)-β-D-fructopyranose Sulfamate (65). Alkene **66**[29] (2.48 g, 9.4 mmol) was combined with PtO_2 (0.25 g) in anhydrous ethanol (40 mL) and placed in a Parr apparatus under hydrogen (50 psig) at 23 °C. After 1 h, the reaction was filtered through a Nylon-66 filter (0.45 μm) and concentrated in vacuo. The residue was recrystallized (benzene/hexanes, 1:1) to give 2.20 g (88%) of **65** a white solid: ^{1}H NMR (400 MHz) δ 1.40 (s, 3H, Me), 1.58 (s, 3H, Me), 1.59−1.90 (m, 3H), 2.05−2.20 (m, 1H), 3.60−3.75 (m, 1H, H_6), 3.90−4.05 (m, 1H, H_6), 4.20−4.30 (m, 1H, H_3), 4.25 (s, 2H, H_1), 5.21 (br s, 2H, NH_2); IR (KBr) ν_{max} 3362 (m), 3243 (m), 1563 (m), 1382 (s), 1184 (s), 1055 (s), 837 (s), 759 (s) cm^{-1}; FAB-MS m/z 268 $(MH)^+$, 290 $(M + Na)^+$. Anal. ($C_9H_{17}NO_6S$) C, H, N.

4,5-Dideoxy-2,3-*O*-(isopropylidene)-β-D-fructopyranose-7,7-dichlorocyclopropane 1-Sulfamic Acid Ester (76) from Diol 40. A mixture of diol **40** (10.0 g, 0.032 mol) and 1,1′-thiocarbonyldiimidazole (13.8 g, 0.08 mol) in THF (145 mL) was stirred at 23 °C for 24 h. The solvent was evaporated in vacuo, and the residue was dissolved in ethyl acetate, washed twice with water and once with 1 N HCl, dried (Na_2SO_4), and concentrated to afford 10.48 g (92%) of the crude thiocarbonate as a solid. A mixture of thiocarbonate (15.3 g, 0.04 mol) and trimethyl phosphite (92 mL) was refluxed for 3 h and concentrated in vacuo to a syrup, which was purified by preparative HPLC (hexane/ethyl acetate. 3:1) to afford the alkene (10.3 g, 86%) as a syrup. A mixture of alkene (5.76 g, 0.02 mol), benzyltriethylammonium chloride (0.29 g), 50% NaOH (180 mL), and chloroform (180 mL) was stirred at 23 °C for 24 h. The resultant semiemulsion was filtered through glass wool and separated. The organic solution was washed sequentially with water and brine, dried (Na_2SO_4), and concentrated in vacuo to afford 8.5 g of the crude bis-chloro adduct **74** (contaminated with solvent), as a brown syrup. A solution of this material (8.2 g) in methylene chloride (1 L) was treated with water (10 mL) and *N*-bromosuccinimide (6.0 g), and the solution was degassed with argon for 60 min by using a gas dispersion tube. More NBS (20.0 g; 0.15 mol total) was added portionwise followed by the addition of water (5 mL). The mixture was stirred for 10 min while being irradiated with a 150-W Phillips flood lamp. The mixture was treated with cyclohexene (5 mL) and triethylamine (5 mL), stirred for 5 min, and concentrated in vacuo to afford a gum, which was treated with ethyl acetate and filtered. The filtrate was concentrated to a syrup which was purified by preperative HPLC (hexanes/ethyl acetate, 4:1) to afford 1.35 g of **75** (18% based on pure **74**) as a syrup. A mixture triethylamine (0.96 g, 9.5 mmol) in DMF (10 mL) was treated with **75** (1.30 g, 4.8 mmol) in DMF (5 mL), the mixture was stirred at 0 °C for 30 min, and sulfamoyl chloride (1.13 g, 9.8 mmol) was added portionwise at 0−10 °C. After 1 h of stirring, the mixture was poured into water and extracted with ethyl acetate twice. The combined organic extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to a syrup, which was purified by preparative HPLC (ethyl acetate/hexanes, 1:1) to afford 0.84 g (50%) of **76** as a syrup: ^{1}H NMR (600 MHz) δ 1.45/1.55 (2 s, 6H, 2 Me), 1.85 (dd, 1H, J_{45} = 11.0 Hz, J_{56e} = 3.6 Hz, H_5), 2.15 (d, 1H, J_{45} = 11.0 Hz, H_4), 4.12/4.18 (pair of d, 2H, J_{ab} = 10.9 Hz, H_1), 4.20 (d, 1H, J_{6a6e} = 12.6 Hz, H_{6a}), 4.30 (s, 1H, H_3), 4.35 (dd, 1H, J_{6a6e} = 12.6 Hz, J_{56e} = 3.6 Hz, H_{6e}), 4.95 (br s, 2H, NH_2). Anal. ($C_{10}H_{15}Cl_2NO_6S$) H; C: calcd, 34.49; found, 34.05; N: calcd, 4.02; found, 3.55.

4,5-Anhydro-2,3-*O*-(isopropylidene)-β-D-fructopyranose Sulfamate (77). Sodium hydride (60% oil dispersion; 0.89 g, 22.3 mmol, washed with ether) was suspended in 15 mL of DMF, cooled to 5 °C with stirring, and treated with epoxide **79**[26] (3.00 g, 14.8 mmol). The mixture was stirred for 1.5 h, treated with sulfamoyl chloride (1.23 g, 10.6 mmol), and slowly warmed to 23 °C over 3 h. The reaction was diluted with cold water, and extracted three times with CH_2Cl_2. The combined extract was rinsed twice with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by preparative HPLC (CH_2Cl_2/ethyl acetate, 4:1) and recrystallized (2-propanol) to yield **77** (2.19 g, 53%) as a white solid: ^{1}H NMR (300 MHz) δ 1.46/1.53 (2 s, 6H, 2 Me), 3.28 (d, 1H, J_{45} = 3.8 Hz, H_5), 3.32 (d, 1H, J_{45} = 3.8 Hz, H_4), 4.08/4.32 (pair of d, 2H, J_{ab} = 11.6 Hz, H_1), 4.10 (d, 1H, J_{6a6e} = 13.5 Hz, H_{6a}), 4.22 (d, 1H, J_{6a6e} = 13.5 Hz, H_{6e}), 4.39 (s, 1H, H_3), 4.96 (br s, 2H, NH_2); IR (KBr) ν_{max} 3341 (s), 3239 (m), 1380 (s), 1187 (s), 1071 (s), 1010 (s), 817 (s) cm^{-1}; CI-MS m/z 282 $(MH)^+$, 299 $(M + NH_4)^+$. Anal. ($C_9H_{15}NO_7S$) C, H, N, S.

Synthesis of N-Substituted 2,3-*O*-(Isopropylidene)-4,5-*O*-sulfonyl-β-D-fructopyranose Sulfamate (83). A. General Procedure. A solution of alcohol **81**[26,76] and pyridine (10.0 g, 127 mmol) in toluene (420 mL) was added dropwise to a solution of sulfuryl chloride (17.1 g,127 mmol) in 100 mL of toluene over 45 min at −55 to −60 °C with vigorous stirring. After 2 h, the mixture was filtered through diatomaceous earth, and the filtrate was extracted sequentially with water, twice with 1 N H_2SO_4, twice with $NaHCO_3$ (saturated aqueous), twice with brine, then dried ($MgSO_4$), and concentrated in vacuo to afford a brown oil. This material was purified by preparative HPLC (CH_2Cl_2) to provide 28.9 g (72%) of **82** as a white solid. An analytical sample was recrystallized from absolute ethanol: mp 93−95 °C; $[\alpha]^{25}_D$ −35.4° (*c* 0.86, MeOH); ^{1}H NMR (400 MHz) δ 1.46/1.61 (2 s, 6H, 2 Me), 4.00−4.25 (m, 2H, H_6), 4.42/4.66 (pair of d, 2H, J_{ab} = 10.8 Hz, H_1), 4.53 (d, 1H, J_{34} = 2.7 Hz, H_3), 5.03 (d, 1H, J_{45} = 7.9 Hz, H_5), 4.94 (dd, 1H, J_{34} = 2.7 Hz, J_{45} = 7.9 Hz, H_4); ^{13}C NMR (100 MHz) δ 25.1 (Me), 26.4 (Me), 59.5 (CH_2), 68.7 (CH), 72.1 (CH), 72.3, (CH_2), 75.4 (CH), 100.0 (C), 111.6 (C); IR (KBr) ν_{max} 1409 (s), 1219 (s), 1089 (s), 990 (s), 834 (m) cm^{-1}; CI-MS m/z 398 $(M + NH_4)^+$. Anal. Calcd for $C_9H_{13}ClO_{10}S_2$: C, 28.39; H, 3.44; Cl, 9.31; S, 16.84. Found: C, 28.53; H, 3.46; Cl, 9.17; S, 16.98.

Sulfamates **83**[76] were prepared by treating this chlorosulfate with 2−4 equiv of the requisite anhydrous nucleophile in dry THF or acetonitrile with stirring at 0 °C. The reaction was warmed to 23 °C (if necessary) over 0.5−18 h, and the resulting white slurry was either quenched with water and concentrated in vacuo or filtered through diatomaceous earth and concentrated in vacuo. The resulting residue was dissolved in ethyl acetate and washed three times with 1 N H_2SO_4, twice with $NaHCO_3$ (saturated aqueous), twice with brine, then dried ($MgSO_4$), concentrated in vacuo, and purified by preparative HPLC.

B. 2,3-*O*-(Isopropylidene)-4,5-*O*-sulfonyl-β-D-fructopyranose Methylsulfamate (83a). A solution of the chlorosulfate (2.48 g, 6.5 mmol) in dry THF (33 mL) was cooled to 5 °C with stirring. Excess anhydrous methylamine was bubbled through the solution over 30 min at 5−10 °C. After 30 min, the reaction was filtered through diatomaceous earth and concentrated in vacuo. The residue was purified by preparative HPLC (hexanes/ethyl acetate, 6:1) to furnish 2.21 g (90%) of **83a** as a hard glass: ^{1}H NMR (400 MHz, $CD_3OD/CDCl_3$) δ 1.48/1.60 (2 s, 6H, 2 Me), 2.76 (s, 3H, NMe), 3.95−4.25 (m,

4H, 2 H_1 and 2 H_6), 4.63 (br s, 1H, H_3), 5.10−5.25 (m, 1H, H_5), 5.35−5.50 (m, 1H, H_4); IR ($CHCl_3$) ν_{max} 3402 (m), 1407 (s), 1182 (s), 1093 (s), 981 (s) 865 (s); CI-MS *m/z* 300 $(M + NH_4)^+$. Anal. ($C_{10}H_{17}NO_{10}S_2$) C, H, N.

C. 2,3-*O*-(Isopropylidene)-4,5-*O*-sulfonyl-*β*-D-fructopyranose Diethylsulfamate (83n). A solution of chlorosulfate (3.00 g, 7.9 mmol) in dry THF (40 mL) was cooled to 5 °C and treated with anhydrous diethylamine (1.73 g, 23.6 mmol). After 4 h, the reaction was quenched with water (5 mL), concentrated in vacuo, and dissolved in ethyl acetate. The ethyl acetate solution was washed three times with 1 N H_2SO_4, twice with $NaHCO_3$ (saturated aqueous), twice with brine, then dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by preparative HPLC (hexanes/ethyl acetate, 7:3) to give 1.55 g (44%) of **83n** as a white foam: ^{1}H NMR (400 MHz) δ 1.22 (t, 6H, J = 7.1 Hz, 2 Me), 1.45/1.58 (2 s, 6H, 2 Me), 3.25−3.45 (m, 4H, 2 CH_2), 3.95−4.25 (m, 4H, 2 H_1 and 2 H_6), 4.58 (d, 1H, J_{34} = 2.5 Hz, H_3), 4.98 (d, 1H, J_{45} = 7.9 Hz, H_5), 5.28 (dd, 1H, J_{34} = 2.5 Hz, J_{45} = 7.9 Hz, H_4); IR (KBr) ν_{max} 2990, 1395, 1364, 1213, 1167, 1090, 1053, 969, 796 cm^{-1}; CI-MS *m/z* 435 $(M + NH_4)^+$. Anal. ($C_{13}H_{23}NO_{10}S_2$) C, H, N, S.

D. 2,3-*O*-(Isopropylidene)-4,5-*O*-sulfonyl-*β*-D-fructopyranose Imidazole-1-sulfonate (83q). A solution of the chlorosulfate (2.00 g, 5.3 mmol) in dry THF (40 mL) was cooled to 5 °C with stirring, treated with imidazole (1.07 g, 15.8 mmol), and allowed to warm to 23 °C. After 6 h, the reaction was filtered through diatomaceous earth, and the filtrate was concentrated in vacuo. The residue was purified by preparative HPLC (hexanes/ethyl acetate, 3:2) to afford 1.75 (81%) as a hard white foam: ^{1}H NMR (400 MHz) δ 1.44/1.61 (2 s, 6H, 2 Me), 3.95−4.15 (m, 2H, H_6), 4.25/4.37 (pair of d, 2H, J_{ab} = 10.9 Hz, H_1), 4.46 (d, 1H, J_{34} = 2.7 Hz, H_3), 5.02 (d, 1H, J_{45} = 7.9 Hz, H_5), 5.32 (dd, 1H, J_{34} = 2.7 Hz, J_{45} = 7.9 Hz, H_4), 7.24 (s, 1H), 7.41, (s, 1H), 8.05 (s, 1H); IR (KBr) ν_{max} 1380 (m), 1210 (s), 1055 (m), 990 (m), 852 (m) cm^{-1}; CI-MS *m/z* 413 $(MH)^+$. Anal. ($C_{12}H_{16}N_2O_{10}S_2$) C, H, N, S.

2,3-*O*-(Isopropylidene)-4,5-*O*-sulfonyl-*β*-D-fructopyranose Azidosulfate (83r). The chlorosulfate (2.00 g, 5.3 mmol) was combined with pyridine (0.83 g, 1.05 mmol) in 26 mL of acetonitrile (26 mL) with stirring at 23 °C. Sodium azide (0.68 g, 0.0105 mol) was added, and the reaction was stirred for 18 h, filtered through diatomaceous earth, and concentrated in vacuo. The residue was purified by preparative HPLC (hexanes/ethyl acetate, 4:1) to provide 1.76 g (87%) of **83r** as a clear glass: ^{1}H NMR (400 MHz) δ 1.46/1.61 (2 s, 6H, 2 Me), 4.00−4.20 (m, 2H, H_6), 4.34/4.48 (pair of d, 2H, J_{ab} = 11.0 Hz, H_1), 4.52 (d, 1H, J_{34} = 2.6 Hz, H_3), 5.02 (d, 1H, J_{45} = 7.9 Hz, H_5), 5.33 (dd, 1H, J_{34} = 2.6 Hz, J_{45} = 7.9 Hz, H_4); IR (KBr) ν_{max} 2148 (s), 1410 (s), 1181 (m), 1093 (s), 1002 (s), 843 (m) cm^{-1}; CI-MS *m/z* 405 $(M + NH_4)^+$. Anal. ($C_9H_{13}N_3O_{10}S_2$) C, H, N; S: calcd, 16.30; found, 15.84.

2,3-*O*-(Isopropylidene)-4,5-*O*-sulfonyl-*β*-D-fructopyranose Carbamate (84). A solution of alcohol **81**[26,76] (3.75 g, 13.3 mmol) and pyridine (1.1 mL, 13.3 mmol) in THF (18 mL) was added dropwise over 15 min at 5 °C to a stirred solution of trichloromethyl chloroformate (1.60 mL, 13.3 mmol) in THF (18 mL). The reaction was slowly warmed to 23 °C over 2 h, filtered through diatomaceous earth, and concentrated in vacuo. The residue was dissolved in THF (36 mL), cooled to 5 °C, and treated with an excess of ammonia gas over 10 min with stirring. The reaction was filtered through diatomaceous earth and concentrated in vacuo. The residue in ethyl acetate was rinsed twice with $NaHCO_3$ and once with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by preparative HPLC (hexanes/ethyl acetate, 1:1) to give **84** (3.06 g, 71%) as a hard white foam: ^{1}H NMR (400 MHz) δ 1.41/1.57 (2 s, 6H, 2 Me), 4.00−4.15 (m, 2H, H_6), 4.17/4.35 (pair of d, 2H, J_{ab} = 11.7 Hz, H_1), 4.46 (d, 1H, J_{34} = 1.5 Hz, H_3), 4.90 (br s, 2H, NH_2), 5.02 (d, 1H, J_{45} = 8.0 Hz, H_5), 5.33 (dd, 1H, J_{34} = 1.5 Hz, J_{45} = 8.0 Hz, H_4); IR (KBr) ν_{max} 3494 (m), 3396 (m), 1733 (s), 1211 (s), 1094 (s), 983 (m), 851 (m) cm^{-1}; CI-MS *m/z* 326 $(MH)^+$, 343 $(M + NH_4)^+$. Anal. ($C_{10}H_{15}NO_9S$) C, H, N, S.

2,3-*O*-(Cyclohexylidene)-4,5-*O*-sulfonyl-*β*-D-fructopyranose Sulfamate (85). Compound **58** (20.4 g, 48.6 mmol) was dissolved in THF (408 mL), acidified with 204 mL of 6 N HCl, and heated at 47−50 °C for 5 h with vigorous stirring. The reaction was cooled to 5 °C, the pH was cautiously adjusted to pH 7 with Na_2CO_3, and the aqueous layer was saturated with NaCl. The aqueous layer was extracted three times with THF, and then the combined THF extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by preparative HPLC (ethyl acetate/CH_2Cl_2, 3:2) to give 2.85 g (17%) of 2,3-*O*-(cyclohexylidene)-*β*-D-fructopyranose 1-sulfamate as a white foam. This product (2.33 g, 6.9 mmol) was combined with pyridine (1.22 mL, 15.1 mmol), dissolved in ethyl acetate (69 mL), and reacted with sulfuryl chloride (1.33 mL, 16.5 mmol) as described above to provide the bis-chlorosulfate. Analogous dechlorosulfation of this bis-chlorosulfate with $NaHCO_3$ (3.76 g, 44.8 mmol) in methanol (70 mL), followed by purification by preparative HPLC (hexanes/ethyl acetate, 7:3), provided 1.42 g of solid, which was recrystallized from 20 mL of EtOH/water (1:1) to provide 1.21 g (44%) of **85** as a white solid: mp 139−141 °C; $[\alpha]^{25}_D$ −31.5° (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30−1.80 (m, 10H), 3.95−4.10 (m, 4H, 2 H_1 and 2 H_6), 4.58 (d, 1H, J_{34} = 2.5 Hz, H_3), 5.49 (d, 1H, J_{45} = 7.8 Hz, H_5), 5.70 (dd, 1H, J_{34} = 2.5 Hz, J_{45} = 7.8 Hz, H_4), 7.72 (s, 2H, NH_2); IR (KBr) ν_{max} 3390 (m), 3269 (m), 2957 (m), 1378 (s), 1214 (s), 1107 (s), 1051 (s), 818 (m) cm^{-1}; CI-MS *m/z* 419 $(M + NH_4)^+$. Anal. ($C_{12}H_{19}NO_{10}S_2$) C, H, N, S.

2,3-*O*-(Ethylpropylidene)-4,5-*O*-sulfonyl-*β*-D-fructopyranose Sulfamate (86). Compound **59** (14.56 g, 36.8 mol) was dissolved in THF (360 mL), heated to 43 °C, and acidified with 185 mL of 6 N HCl with vigorous stirring. After 1 h, the reaction was cooled to 5 °C, the pH was adjusted to pH 7 with Na_2CO_3, and the aqueous layer was saturated with NaCl. The aqueous layer was extracted twice with THF, and the combined extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by preparative HPLC (ethyl acetate/CH_2Cl_2, 3:2) to give 2.53 g (21%) of 2,3-*O*-(1-ethylpropylidene)-*β*-D-fructopyranose 1-sulfamate as a clear syrup: $[\alpha]^{25}_D$ +22.7° (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 0.85−1.00 (m, 6H, 2 Me), 1.67 (q, 2H, J = 7.5 Hz), 1.76 (q, 2H, J = 7.6 Hz), 3.53 (dd, J_{6a} = 4.9 Hz, J_{6a6e} = 11.0 Hz, 1H, H_{6a}), 3.65 (dd, J_{6e} = 5.5 Hz, J_{6a6e} = 11.0 Hz, 1H, H_{6e}), 3.90−3.95 (m, 1H, H_5), 4.00−4.10 (m, 2H, H_3 and H_4), 4.15/4.19 (pair of d, 2H, J_{ab} = 10.5 Hz, H_1); IR (KBr) ν_{max} 3408 (m), 2957 (m), 2914 (m), 1377 (s), 1214 (s), 994 (s) cm^{-1}; CI-MS *m/z* 345 $(M + NH_4)^+$. Anal. Calcd for $C_{11}H_{21}NO_8S$: C, 40.36; H, 6.47; N, 4.28; S, 9.79. Found: C, 40.46; H, 6.50; N, 4.12; S, 9.66. This product (1.82 g, 5.6 mol) and pyridine (1.06 mL, 13.4 mmol) were dissolved in ethyl acetate (55 mL) and reacted with sulfuryl chloride (1.65 g, 12.2 mmol) as described above to provide the bis-chlorosulfate. Treatment with $NaHCO_3$ (2.67 g, 31.8 mmol) in MeOH (16 mL), followed by preparative TLC purification (ether/hexanes, 7:3), provided 1.03 g (47%) of **86** as a white solid: mp 130−133 °C; $[\alpha]^{25}_D$ −23.1° (*c* 1.17, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.83 (t, 3H, Me), 0.91 (t, 3H, Me), 1.66 (q, 2H, J = 7.5 Hz), 1.77 (q, 2H, J = 7.6 Hz), 3.95−4.10 (m, 4H, H_1 and H_6), 4.56 (d, 1H, J_{34} = 2.6 Hz, H_3), 5.49 (d, 1H, J_{45} = 7.9 Hz, H_5), 5.70 (dd, 1H, J_{34} = 2.6 Hz, J_{45} = 7.9 Hz), 7.73 (br s, 2H, NH_2); IR (KBr) ν_{max} 3403 (m), 3299 (m), 2986 (m), 2914 (m), 1567 (m), 1380 (s), 1217 (s), 1178 (s), 979 (s), 930 (s) cm^{-1}; CI-MS *m/z* 407 $(M + NH_4)^+$. Anal. ($C_{11}H_{19}NO_{10}S_2$) C, H, N, S.

Isomeric Mixture (5.3:1) of 2,3-*O*-(Isopropylidene)-(*S*)- and 2,3-*O*-(Isopropylidene)-(*R*)-4,5-*O*-sulfinyl-*β*-D-fructopyranose Sulfamates (87a/b). Thionyl chloride (10 mL, 137 mmol) was added dropwise over 15 min (exothermic) to a solution of diol **40** (4.00 g, 13.4 mmol) in THF (40 mL) at 23 °C with stirring. After 1.5 h, the mixture was concentrated in vacuo, dissolved in ethyl acetate, washed twice with $NaHCO_3$ (saturated aqueous), dried ($MgSO_4$), and concentrated in vacuo. The residue was crystallized from absolute ethanol to give a 5.3:1 mixture of **87a** and **87b** (2.63 g, 57%) as an off-white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.37/1.51 (2

s, 6H, 2 Me), 3.75−4.25 (m, 4H, 2 H_1 and 2 H_6), 4.49 (d, 0.16 H, J_{34} = 2.6 Hz, H_{3R}), 4.54 (d, 0.84 H, J_{34} = 2.6 Hz, H_{3S}), 5.09 (d, 0.16H, J_{45} = 7.9 Hz, H_{5R}), 5.20 (dd, 0.16H, J_{34} = 2.6 Hz, J_{45} = 7.9 Hz, H_{4R}), 5.31 (d, 0.84H, J_{45} = 7.9 Hz, H_{5S}), 5.43 (dd, 0.84H, J_{34} = 2.6 Hz, J_{45} = 7.9 Hz, H_{4S}), 7.67 (s, 0.32H, NH_2-*R*), 7.68 (s, 1.68H, NH_2-*S*); IR (KBr) ν_{max} 3381 (s), 3286 (m), 1359 (s), 1208 (s), 1088 (s), 966 (m), 911 (m), 800 (m), 710 (m) cm^{-1}; FAB-MS *m*/*z* 346 $(MH)^+$, 363 $(M + H_2O)^+$, 368 $(M + Na)^+$. Anal. ($C_9H_{15}NO_9S_2$) C, H, N, S.

2,3-*O*-(Isopropylidene)-(*S*)- and 2,3-*O*-(Isopropylidene)-(*R*)-(4,5-*O*-sulfinyl)-*β*-D-fructopyranose Sulfamates (87a and 87b). Diol **40** (6.00 g, 19.3 mmol) was dissolved in 75 mL of anhydrous 1,4-dioxane and heated to reflux with stirring. Thionyl chloride (28 mL, 384 mmol) was added dropwise over 10 min to the refluxing solution. After 15 min, the mixture was cooled to 23 °C and concentrated in vacuo. The residue was dissolved in ethyl acetate, rinsed twice with $NaHCO_3$ (saturated aqueous) and twice with brine, then dried ($MgSO_4$), and concentrated in vacuo to yield a 2:1 mixture of the *S* and *R* isomers of 1-*O*-benzyl-2,3-*O*-(isopropylidene)-4,5-*O*-sulfinyl-*β*-D-fructopyranose (6.50 g, 95%). The diastereomers were separated by preparative HPLC (hexanes/ethyl acetate, 9:1). The fractions containing the faster-eluting isomer were combined and concentrated in vacuo to give the *S* isomer (4.05 g) as a white solid: mp 92−94 °C; ^{1}H NMR (400 MHz) *δ* 1.44/1.57 (2 s, 6H, 2 Me), 3.48/3.66 (pair of d, 2H, J_{ab} = 10.8 Hz, H_1), 3.85 (d, 1H, J_{6a6e} = 13.7 Hz, H_{6a}), 4.06 (dd, J_{56e} = 1.7 Hz, J_{6a6e}= 13.7 Hz, 1H, H_{6e}), 4.50−4.70 (m, 3H, H_3 and CH_2Ph), 5.04 (dd, 1H, J_{45} = 7.9 Hz, J_{56e} = 1.5 Hz, H_5), 5.33 (dd, 1H, J_{34} = 2.2 Hz, J_{45} = 7.9 Hz, H_4), 7.33 (s, 5H, Ph); CI-MS *m*/*z* 374 $(M + NH_4)^+$. Similarly, the fractions containing the slower-eluting isomer were combined and concentrated in vacuo to give the *R* isomer (1.93 g) as a clear oil: ^{1}H NMR (400 MHz) *δ* 1.46/1.57 (2 s, 6H, 2 Me), 3.48/3.69 (pair of d, 2H, J_{ab} = 10.9 Hz, H_1), 3.98 (d, 1H, J_{6a6e} = 13.9 Hz, H_{6a}), 4.11 (dd, J_{56e} = 2.3 Hz, J_{6a6e}= 13.9 Hz, 1H, H_{6e}), 4.50−4.70 (m, 3H, H_3 and CH_2Ph), 4.83 (dd, 1H, J_{45} = 8.6 Hz, J_{56e} = 2.3 Hz, H_5), 4.97 (dd, 1H, J_{34} = 2.3 Hz, J_{45} = 8.6 Hz, H_4) 7.34 (s, 5H, Ph); CI-MS *m*/*z* 374 $(M + NH_4)^+$.

The *S* isomer (3.99 g, 112 mmol) was dissolved in CH_2Cl_2 (560 mL) that had been saturated with water. *N*-Bromosuccinimide (1.99 g, 112 mmol) was added, and the solution was sparged with nitrogen for 60 min. The solution was cooled to 5 °C, irradiated with a 150-W incandescent floodlight for 15 min, quenched with excess cyclohexene (7 mL), basified with triethylamine (1.56 mL), and concentrated in vacuo. The residue was mixed with 200 mL of ethyl acetate and filtered through diatomaceous earth. The filtrate was concentrated in vacuo to provide a mixture of isomers (*S*/*R* = 17:1), which were separated by preparative HPLC (hexanes/ether, 3:2) to furnish (*S*)-2,3-*O*-(isopropylidene)-4,5-*O*-sulfinyl-*β*-D-fructopyranose (2.43 g, 81%) as a clear oil: ^{1}H NMR (400 MHz) *δ* 1.45/1.59 (2 s, 6H, 2 Me), 1.82 (dd, 1H, *J* = 5.3, 8.9 Hz, OH), 3.42−3.75 (m, 2H, H_1), 3.85−4.15 (m, 2H, H_6), 4.52 (d, 1H, J_{34} = 2.2 Hz, H_3), 5.06 (dd, 1H, J_{45} = 7.8 Hz, J_{56e} = 1.5 Hz, H_5), 5.36 (dd, 1H, J_{34} = 2.2 Hz, J_{45} = 7.9 Hz, H_4); CI-MS *m*/*z* 267 $(MH)^+$, 284 $(M + NH_4)^+$. This product (2.29 g, 8.6 mmol) and triethylamine (14 mL) were dissolved in ethyl acetate (86 mL) and cooled to −60 °C with stirring. Sulfamoyl chloride (6.45 g, 55.8 mmol) was added, and the reaction was slowly warmed to 23 °C over 18 h. The reaction was washed twice with 3 N HCl, twice with $NaHCO_3$ (saturated aqueous), and twice with brine, then dried ($MgSO_4$), and concentrated in vacuo. The crude product was crystallized from ethanol to provide **87a** (1.20 g, 40%) as a white solid: mp 151.5−153.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 1.38/1.52 (2 s, 6H, 2 Me), 3.75−4.05 (m, 4H, 2 H_1 and 2 H_6), 4.54 (d, 1H, J_{34} = 2.3 Hz, H_3), 5.31 (d, 1H, J_{45} = 8.0 Hz, H_5), 5.43 (dd, 1H, J_{34} = 2.3 Hz, J_{45} = 8.0 Hz, H_4), 7.67 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) *δ* 24.9 (Me), 25.9 (Me), 59.4 (CH_2), 68.2 (CH_2), 68.9 (CH), 72.3, (CH), 76.7 (CH), 100.6 (C), 109.4 (C). Anal. ($C_9H_{15}NO_9S_2$) C, H, N, S.

In the same manner, the *R* isomer (4.33 g, 12.2 mmol) was oxidatively debenzylated with *N*-bromosuccinimide (2.17 g, 12.2 mol) to provide a mixture of isomers (*R*/*S* = 2.4:1), which were separated by preparative HPLC (hexanes/ether, 3:2) to provide (*R*)-2,3-*O*-(isopropylidene)-4,5-*O*-sulfinyl-*β*-D-fructopyranose (1.09 g, 34%) as a clear oil: ^{1}H NMR (400 MHz) *δ* 1.41/1.56 (2 s, 6H, 2 Me), 2.60−2.75 (m, 1H, OH), 3.55−3.70 (m, 1H, H_{1a}), 3.85−4.15 (m, 3H, H_{1b} and 2 H_6), 4.64 (d, 1H, J_{34} = 2.2 Hz, H_3), 4.90 (dd, 1H, J_{45} = 8.8 Hz, J_{56e} = 2.3 Hz, H_5), 5.01 (dd, 1H, J_{34} = 2.1 Hz, J_{45} = 8.8 Hz, H_4); CI-MS *m*/*z* 267 $(MH)^+$, 284 $(M + NH_4)^+$. This material was reacted with sulfamoyl chloride (2.86 g, 24.8 mmol), and the crude product was recrystallized from ethanol to furnish **87b** (0.25 g, 18%) as a white solid: mp 197−199 °C; ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 1.37/1.51 (2 s, 6H, 2 Me), 3.82−3.97 (m, 2H, H_6), 3.98/4.22 (pair of d, 2H, J_{ab} = 10.5 Hz, H_1), 4.49 (d, 1H, J_{34} = 2.2 Hz, H_3), 5.10 (d, 1H, J_{45} = 8.7 Hz, H_5), 5.20 (dd, 1H, J_{34} = 2.2 Hz, J_{45} = 8.7 Hz, H_4), 7.67 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) *δ* 25.1 (Me), 26.0 (Me), 59.7 (CH_2), 67.8 (CH_2), 69.1 (CH), 75.5, (CH), 78.2 (CH), 100.7 (C), 108.8 (C). Anal. ($C_9H_{15}NO_9S_2$) C, H, N, S.

2,3-*O*-(Isopropylidene)-(*S*)-4,5-*O*-[*N*-(4-methylbenzenesulfonyl)imidosulfinyl]-*β*-D-fructopyranose Sulfamate (90a). A solution of *N*-(*p*-toluenesulfonyl)imidothionyl chloride[49] (34.1 g, 125 mmol; crude material) in benzene (120 mL) was added dropwise at 5 °C over 15 min with vigorous stirring to a solution diol **28** (10.0 g, 33.4 mmol) in THF (120 mL). The reaction was slowly warmed to 23 °C over 2 h and concentrated in vacuo. The residue was cautiously quenched with $NaHCO_3$ (saturated aqueous) and extracted three times with ethyl acetate. The combined extracts were rinsed with $NaHCO_3$ (saturated aqueous) and brine, then dried ($MgSO_4$), and concentrated in vacuo. The residue was dissolved in 200 mL of warm CH_2Cl_2/ethyl acetate (19:1) and the *p*-toluenesulfonamide precipitated on cooling to 23 °C. The solid was removed by filtration, and the filtrate was concentrated in vacuo. The residue was purified by preparative HPLC (CH_2Cl_2/ethyl acetate, 19:1) to provide **90a** (9.35 g, 56%) as a white foam, which was contaminated with 0.1 molar equiv of **87a/b**: ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 1.37/1.52 (2 s, 6H, 2 Me), 3.80−4.05 (m, 4H, 2 H_1 and 2 H_6), 4.60 (s, 1H, H_3), 5.52 (s, 2H, H_4 and H_5), 7.42 (d, 2H, *J* = 8.0 Hz), 7.70 (br s, 2H, NH_2), 7.77 (d, 2H, *J* = 8.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) *δ* 21.1 (Me), 24.9 (Me), 25.9 (Me), 59.5 (CH_2), 68.5 (CH_2), 69.2 (CH), 75.4, (CH), 80.0 (CH), 100.7 (C), 109.7 (C), 126.2 (CH), 129.8 (CH), 139.2 (C), 143.6 (C); IR (KBr) ν_{max} 3365 (m), 3275 (m), 1383 (s), 1159 (s), 1087 (s), 963 (m), 685 (m) cm^{-1}; CI-MS *m*/*z* 499 $(MH)^+$. Anal. ($C_{16}H_{22}N_2O_{10}S_3 \cdot 0.1C_9H_{15}NO_9S_2$) C, H, N, S.

2,3-*O*-(Isopropylidene)-4,5-*O*-[*N*-(4-methylbenzenesulfonyl)imidosulfonyl]-*β*-D-fructopyranose Sulfamate (91a). Compound **90a** (3.10 g, 6.2 mmol) was dissolved in acetonitrile (19 mL) and diluted with CCl_4 (19 mL) and water (28 mL). This mixture was cooled to 5 °C with vigorous mechanical stirring. Sodium periodate (2.92 g, 13.6 mmol) was added followed by a catalytic amount of $RuCl_3 \cdot H_2O$ (0.030 g, 0.15 mmol). The reaction was slowly warmed to 23 °C over 20 h. The mixture was extracted three times with ethyl acetate, and the combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by preparative HPLC (ether/hexanes, 4:1) to give a syrup, which was dissolved in CH_2Cl_2 and concentrated in vacuo to provide **91a** (0.72 g, 23%) as a white foam that was contaminated with 0.09 molar equiv of **2**: ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 1.39/1.54 (2 s, 6H, 2 Me), 2.41 (s, 3H, Me), 3.85−4.2 (m, 4H, 2 H_1 and 2 H_6), 4.68 (d, 1H, J_{34} = 2.4 Hz, H_3), 5.82 (d, 1H, J_{45} = 8.2 Hz, H_5), 5.88 (dd, 1H, J_{34} = 2.4 Hz, J_{45} = 8.2 Hz, H_4), 7.44 (d, 2H, *J* = 8.0 Hz), 7.75 (s, 2H, NH_2), 7.83 (d, 2H, *J* = 8.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) *δ* 21.0 (Me), 25.0 (Me), 25.8 (Me), 59.1 (CH_2), 67.5 (CH_2), 67.9 (CH), 76.7, (CH), 81.6 (CH), 100.7 (C), 110.2 (C), 126.5 (CH), 129.8 (CH), 138.1 (C), 144.0 (C); IR (KBr) ν_{max} 3395 (m), 3282 (m), 1385 (m), 1339 (s), 1164 (s), 1090 (s), 970 (m), 810 (m) cm^{-1}; CI-MS *m*/*z* 532 $(M + NH_4)^+$, 515 $(MH)^+$. Anal. ($C_{16}H_{22}N_2O_{11}S_3 \cdot 0.09C_9H_{15}NO_{10}S_2 \cdot 0.2CH_2Cl_2 \cdot 0.1C_6H_{14}$) C, H, N, S.

2,3-*O*-(Isopropylidene)-(*S*)-4,5-*O*-[*N*-(1,1-dimethylethoxycarbonyl)imidosulfinyl]-*β*-D-fructopyranose Sulfa-

mate (93a). *N*,*N*-Dichloro-*tert*-butylcarbamate (10.0 g, 53.7 mmol) was combined with elemental sulfur (1.72 g, 53.7 mmol) and tetrabutylammonium bromide (1.73 g, 5.4 mmol) in 50 mL of dry benzene. The suspension was heated at 40 °C for 2 h with vigorous stirring. After cooling to 23 °C, this solution of crude *N*-(*tert*-butoxycarbonyl)imidothionyl chloride was added dropwise at 5 °C over 15 min to a vigorously stirred solution of diol **28** (5.19 g, 17.3 mmol) and dry pyridine (4.60 mL, 56.8 mmol) in 173 mL of dry THF. The reaction was stirred at 5 °C for 3 h, filtered through diatomaceous earth, and concentrated in vacuo. The residue was dissolved in ethyl acetate and washed twice with $NaHCO_3$ (saturated aqueous) and twice with brine, then dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by preparative HPLC (hexanes/ethyl acetate, 7:3) and recrystallized from absolute ethanol to yield pure **93a** (2.11 g, 27%) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.36 (s, 3H, Me), 1.40 (s, 9H, *t*-Bu), 1.50 (s, 3H, Me), 3.80−3.95 (m, 2H, H_6), 3.99 (s, 2H, H_1), 4.53 (d,1H, J_{34} = 1.7 Hz, H_3), 5.30−5.40 (m, 2H, H_4 and H_5), 7.69 (s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.9 (Me), 26.0 (Me), 27.5 (Me), 59.9 (CH_2), 68.5 (CH_2), 69.3 (CH), 76.9 (CH), 80.7 (C), 80.8 (CH), 100.7 (C), 109.4 (C), 155.3 (C); IR (KBr) ν_{max} 3398 (m), 3288 (m), 1689 (m), 1650 (m), 1371 (s), 1277 (s), 1184 (s), 1155 (s), 1086 (m), 967 (m), 832 (m), 730 (m), 701 (m) cm^{-1}; CI-MS *m*/*z* 446 $(MH)^+$. Anal. ($C_{14}H_{24}N_2O_{10}S_2$) C, H, N, S.

[3aα,5a*β*,8a*β*,8bα](Octahydro-2,2-dimethyl-5a*H*-indeno-[4,5-*d*]-1,3-dioxol-5a-yl)methyl Sulfamic Acid Ester (95).[54] To a mixture of *N*-methylmorpholine *N*-oxide (2.0 g,17.3 mmol), water (9 mL), acetone (3.6 mL), *tert*-butyl alcohol (2.5 mL), and OsO_4 (12 mg, 0.05 mmol) was added **97**[76] (2.47 g, 16.3 mmol) at 0 °C. After gradual warming to 23 °C and stirring overnight, the mixture was treated with a slurry of $Na_2S_2O_4$ (0.16 g), Florisil (2 g), and water (13 mL) with stirring. The slurry was filtered through Dicalite, the filter cake was rinsed with acetone, and the filtrate was adjusted to pH 7 with 1 N H_2SO_4. The acetone was removed under reduced pressure; the aqueous residue was adjusted to pH 3 with 1 N H_2SO_4 and extracted four times with ethyl acetate. The combined extracts were rinsed with brine, dried (Na_2SO_4), and concentrated to afford 2.6 g (86%) of the corresponding triol as a semisolid that was used in the next step without further purification: ^{1}H NMR (90 MHz) δ 1.07−2.30 (m, 1H), 3.27−3.63 (m, 5H), 3.63−3.97 (m, 2H); CI-MS (CH_4) *m*/*z* 187 (MH^+). A solution of 4.7 g (25.3 mmol) of the triol in 54 mL of 2,2-dimethoxypropane was treated with 0.3 g of *p*-toluenesulfonic acid and stirred for 4h. The mixture was diluted with 250 mL of chloroform and washed with excess $NaHCO_3$ (saturated aqueous). The aqueous phase was washed with chloroform, and the combined extracts were dried (Na_2SO_4) and concentrated to give 3.41 g (60%) the corresponding acetonide, as a pale yellow oil that was used without further purification: ^{1}H NMR (90 MHz) δ 0.95−2.28 (overlapping m, 16H, contains *gem*-Me_2 at δ 1.32 and 1.48), 2.92 (br s, 1H, OH), 3.34 (br s, 2H), 4.27−4.51 (m, 2H). A solution of the acetonide (3.4 g, 15.0 mmol) in 35 mL of DMF was added to a suspension of NaH (0.5 g, 19.5 mmol, washed with hexanes) at 0 °C. After 1 h, 3.5 g (30 mmol) of sulfamoyl chloride was added in two portions, and the mixture was stirred at 0 °C for 2 h. After quenching at 0 °C with excess $NaHCO_3$ (saturated aqueous), the mixture was extracted four times with ethyl acetate, and the combined extracts were washed with water, dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography (CH_2Cl_2/ethyl acetate, 9:1) and recrystallized from ethyl acetate/hexanes to give 1.1 g (24%) of **95** as a white solid: mp 168−170 °C; ^{1}H NMR (400 MHz) δ 1.26−1.48 (m, 5H), 1.51−1.88 (m, 9H), 1.88−1.92 (m, 2H), 2.08−2.13 (m, 1H), 3.95/4.26 (pair of d, 2H, J = 9 Hz), 4.28−4.75 (m, 2H); ^{1}H NMR (360 MHz, C_6D_6) δ 0.82−0.87 (m, 1H), 0.94−1.00 (m, 1H), 1.18−1.35 (m, 4H), 1.22 (s, 3H), 1.46 (s, 3H), 1.51−1.73 (m, 4H), 1.89 (ddd, 1H, J = 12.0, 2.4, 7.8 Hz), 3.41 (br s, 2H), 3.81 (d, 1H, J = 9.1 Hz), 3.95−4.00 (m, 2H), 4.09 (d, 1H, J = 9.1 Hz); IR (KBr) ν_{max} 3327, 3217, 3111, 2941, 1456, 1353, 1186, 1028, 973, 938 cm^{-1}. Anal. ($C_{13}H_{23}NO_5S$) C, H, N.

[3aα,5a*β*,8a*β*,8bα](Octahydro-2,2,7,7-tetramethyl-5a*H*-indeno[4,5-*d*]-1,3-dioxol-5a-yl)methyl Sulfamic Acid Ester (96).[54] A solution of methyl 2-oxo-4,4-dimethylcyclopent-1-ylcarboxylate[76] (21.7 g, 0.13 mol) and methyl vinyl ketone (10.6 mL, 0.13 mol) in 100 mL of benzene was stirred for 4 d. The mixture was concentrated in vacuo, and the residue was distilled (95−98 °C at 0.015 Torr) to afford 17.1 g (54%) of methyl [3,3-dimethyl-2-oxo-1-(3-oxobutyl)-cyclopent]-1-ylcarboxylate as a pale yellow oil: ^{1}H NMR (90 MHz) δ 1.11 (s, 3H), 1.16 (s, 3H), 1.72−2.77 (overlapping m, 8H), 2.14 (s, 3H), 3.72 (s, 3H); FAB-MS *m*/*z* 241 (MH^+). The keto ester (1.0 g, 4.2 mmol) in 100 mL of benzene was treated with Al(*t*-BuO)$_3$[78] (1.5 g, 6.2 mmol) and refluxed for 60 h. The mixture was cooled to 23 °C, quenched with 3 N HCl (11 mL), and extracted twice with ether. The combined extracts were dried (Na_2SO_4) and concentrated, and the residue was dissolved in 10 mL of benzene and treated again with Al(*t*-BuO)$_3$ (0.75 g, 3.1 mmol). After 18 h of reflux, the mixture was cooled and worked up as described above. The residue was purified by flash column chromatography (hexanes/ethyl acetate, 3:1) to afford 0.24 g (28% based on consumed starting material) of methyl 2,2-dimethyl-1,2,3,4,5,6-hexahydro-6-oxo-3a*H*-inden-3a-ylcarboxylate as an oil: ^{1}H NMR (90 MHz) δ 0.9−2.95 (m, 8H, Me s at δ 1.02 and 1.15), 3.5 (s, 3H), 5.93 (m, 1H). A solution of enone (0.2 g, 0.90 mmol) in 95% ethanol was treated with *p*-toluenesulfonyl hydrazide (0.184 g, 1.0 mmol) and warmed on a steam bath. After 20 min of heating, the mixture was concentrated to afford 0.29 g of the corresponding tosylhydrazone: ^{1}H NMR (90 MHz) δ 0.63−1.8 (overlapping m, 10H, Me singlets at δ 0.93 and 1.08), 1.83−2.87 (overlapping m, 8H, Me s at δ 2.38) 3.62, (s, 3H), 5.90 (br s, 1H), 7.22−7.87 (m, 4H). The tosylhydrazone was dissolved in 2 mL of chloroform and cooled to 0 °C, and catecholborane (0.10 mL, 0.94 mmol) was added dropwise. After 3 h at 0 °C, the mixture was treated with NaOAc·3H_2O (0.35 g, 2.55 mmol) and refluxed for 4 h. The mixture was quenched with ice and extracted with chloroform; the extract was dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography (hexanes/ether, 3:1) to give 0.10 g (51% from enone) of methyl 2,2-dimethyl-1,2,3,4,5,7a-hexahydro-*cis*-3a*H*-inden-3a-ylcarboxylate as a clear viscous oil: ^{1}H NMR (90 MHz) δ 0.98 (s, 3H), 1.00 (s, 3H), 1.20−2.14 (m, 8H), 3.03−3.23 (m, 1H), 3.62 (s, 3H), 5.7 (m, 2H). A solution of olefin (1.13 g, 5.4 mmol) in THF (4 mL) was added dropwise to a suspension of $LiAlH_4$ (0.31 g, 8.1 mmol) in THF (4 mL) at 0 °C. After stirring for 0.5 h at 0 °C and 23 °C for 2.5 h, the reaction was quenched at 0 °C with moist Na_2SO_4 and filtered through Dicalite. Concentration of the filtrate gave 1.0 g of oily (2,2-dimethyl-1,2,3,4,5,7a-hexahydro-*cis*-3a*H*-inden-3a-yl)methanol: ^{1}H NMR (90 MHz) δ 1.00−2.36 (overlapping m, 9H, Me s at δ 1.00 and 1.07), 3.23−3.87 (overlapping m, 3H), 5.67 (br s, 2H). This product was added to a mixture of NMO (0.70 g, 5.94 mmol), water (5 mL), acetone (2.5 mL), *tert*-butyl alcohol (0.9 mL), and OsO_4 (4.3 mg, 0.017 mmol), and the reaction was stirred for 18 h at 23 °C, then treated with a slurry of Na_2SO_4 (42 mg, 0.24 mmol), 0.8 g of Florisil, and 5 mL of water. After 5 min of stirring, the mixture was filtered, and the filtrate was neutralized with 1 N H_2SO_4. The volatiles were removed in vacuo, and the aqueous residue was adjusted to pH 3 with 1 N H_2SO_4. The mixture was extracted three times with ethyl acetate, and the combined extracts were dried (Na_2SO_4) and concentrated to give 0.62 g of triol, as a yellow oil. The crude material was dissolved of 2,2-dimethoxypropane (8 mL), treated with catalytic amount of *p*-toluenesulfonic acid, and stirred for 18 h. The mixture was diluted with chloroform and water, the layers were separated, and the aqueous layer was extracted twice with chloroform. The combined extracts were washed with water, dried (Na_2SO_4), and concentrated to a residue that was purified by flash column chromatography (hexanes/ethyl acetate, 4:1) to furnish [3aα,5a*β*,8a*β*,8bα]-(octahydro-2,2-dimethyl-5a*H*-indeno[4,5-*d*]-1,3-dioxol-5a-yl)-

methanol (0.54 g, 39% from indene carboxylate) as a clear viscous oil: ^{1}H NMR (90 MHz) δ 0.57−2.13 (overlapping m, 20H, Me s at δ 1.00, 1.03, 1.23, and 1.48), 2.30−2.63 (m, 1H), 2.93−3.63 (overlapping m, 3H), 3.87 (m, 2H). A solution of the alcohol (0.53 g, 2.09 mmol) and triethylamine (0.44 mL, 3.13 mmol) in DMF (5 mL) was cooled to 0 °C and treated with sulfamoyl chloride in one portion. After 1.5 h at 0 °C, the mixture was quenched with ice and extracted three times with ethyl acetate. The combined extracts were washed with water, dried (Na_2SO_4), and concentrated. Purification by flash column chromatography (CH_2Cl_2/MeOH, 95:5) and recrystallization from ethyl acetate/hexanes afforded 0.28 g (40%) of **96** as a white solid, mp 152−154 °C. ^{1}H NMR δ (400 MHz, $CDCl_3$/DMSO-d_6) δ 1.07 (s, 3H, Me), 1.04 (s, 3H, Me), 1.30 (s, 3H, Me), 1.32−1.42 (m, 2H), 1.40 (d, 1H, J = 14.0 Hz), 1.47 (s, 3H, Me), 1.58−1.67 (m, 4H), 1.84 (d, 1H, J = 14.0 Hz), 2.31−2.36 (m, 1H), 3.97/4.20 (pair of d, 2H, J = 9.0 Hz), 4.25 (m, 2H), 6.54 (br s, 2H); IR (KBr) ν_{max} 3339, 3239, 3124, 2947, 2866, 1587, 1466, 1373, 1185, 1029, 975 cm^{-1}. Anal. ($C_{15}H_{27}NO_5S$) C, H, N.

[3aα,5aβ,8aβ,8bα](Octahydro-2,2-dioxo-5a*H*-indeno[4,5-*d*]-1,3-dioxol-2-thia-5a-yl)methyl Sulfamic Acid Ester (100).[54] To a solution of **98**[76] (0.23 g, 0.83 mmol) in 16 mL of THF was added NaH (61 mg, 2.5 mmol, washed with hexanes) at 0 °C, and the mixture was stirred for 0.5 h. A solution of sulfuryldiimidazole (0.19 g, 0.95 mmol) in 8 mL of THF was added dropwise at 0 °C, and the mixture was stirred for 3.5 h at 23 °C. The mixture was filtered through Dicalite, and the filter cake was washed with THF. The filtrate was concentrated, and the residue was purified by flash column chromatography (hexanes/ethyl acetate, 3:1) to afford 0.16 g (50%) of the 6,7-cyclic sulfate derivative as a clear oil: ^{1}H NMR (90 MHz) δ 0.9−2.1 (m, 10H), 2.21−2.57 (m, 1H), 3.20/3.40 (pair of d, 2H, J = 9.0 Hz), 4.48 (br s, 2H), 5.67−4.80 (m, 2H), 7.31 (s, 5H); FAB-MS m/z 339 (MH^+). A solution of this cyclic sulfate (3.1 g, 9.1 mmol) in 18 mL of 95% ethanol was added to 1.6 g of 10% Pd−C and hydrogenated at 50 psig on a Parr apparatus for 40 h. The mixture was filtered through Dicalite, and the filtrate was concentrated. The residue was purified by flash column chromatography (hexanes/ethyl acetate, 3:2) to afford 0.6 g of **99** (71%) as a white solid: mp 91−94 °C; ^{1}H NMR (400 MHz) δ 1.30−2.14 (m, 11H, contains OH), 2.35−2.41 (m, 1H), 3.40/3.71 (pair of d, 2H, J = 10.5 Hz), 5.01−5.07 (m, 2H); IR (KBr) ν_{max} 3234, 2945, 2876, 1456, 1374, 1208, 1040, 952, 842 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_5S$: C, 48.37; H, 6.50. Found: C, 48.71; H, 6.76. A solution of **99** (1.3 g, 5.2 mmol) and triethylamine (1.1 mL, 7.9 mmol) in 5 mL of DMF was cooled to 0 °C, and sulfamoyl chloride (0.9 g, 7.8 mmol) was added in one portion. The mixture gradually reached 23 °C and, after a total of 2 h, was quenched with ice and extracted four times with ethyl acetate. The combined extracts were dried (Na_2SO_4) and concentrated in vacuo at 23 °C (compound is heat sensitive!!). The residue was purified by flash column chromatography (hexanes/ethyl acetate, 1:1) to afford 0.94 g (55%) of **100** as a white solid: mp 70 °C (dec); ^{1}H NMR (400 MHz) δ 1.33−1.75 (m, 7H), 1.87−1.94 (m, 2H), 1.99−2.08 (m, 1H), 2.29−2.34 (m, 1H), 3.69/4.12 (pair of d, 2H, J = 9.4 Hz), 5.28−5.31 (m, 1H), 5.42−5.47 (m, 1H), 7.52 (br s, 2H, NH_2); IR (KBr) ν_{max} 3389, 3280, 2962, 2878, 1557, 1466, 1386, 1354, 1203, 1172 cm^{-1}. Anal. ($C_{10}H_{17}NO_7S_2$) C, H, N.

***cis*-1,2,3,4,5,7a-Hexahydro-3a*H*-indene-3a-methyl Sulfamic Acid Ester (101).** A solution of **97** (3.4 g, 22.3 mmol) in 33 mL of DMF was added dropwise to a suspension of 0.7 g (29 mmol) of NaH (washed with pentane) in 2.9 mL of DMF at 0 °C. After 45 min, 5.1 g (44.6 mmol) of sulfamoyl chloride was added in two portions at 0 °C, and the mixture was allowed to reach 23 °C gradually. After being stirred overnight, the mixture was cooled to 0 °C, quenched slowly with $NaHCO_3$ (saturated aqueous), and extracted four times with ethyl acetate. The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/ethyl acetate, 3:1) to afford 2.1 g (41%) of **101**, as a waxy solid: ^{1}H NMR δ 1.36−1.97 (m, 7H), 1.78−2.39 (m, 4H), 3.81/4.21 (pair of d, 2H, J = 9.0 Hz), 4.81 (s, 2H), 5.61−5.70 (m, 2H); IR ($CHCl_3$) ν_{max} 3282, 2950, 2872, 1556, 1456, 1361, 1182, 948 cm^{-1}. Anal. ($C_{10}H_{17}NO_3S$) C, H, N.

***cis*-1,2,3,4,5,6,7,7a-Octahydro-3a*H*-indene-3a-methyl Sulfamic Acid Ester (102).** A mixture of **97** (2.4 g, 15 mmol) in 20 mL of 95% ethanol was treated with 0.2 g of 10% Pd−C and hydrogenated at 50 psig for 2.5 h. The mixture was filtered and concentrated, and the residue was purified by flash column chromatography (ethyl acetate/hexanes, 1:1) to afford 2.3 g (94%) of the saturated alcohol: ^{1}H NMR (90 MHz) δ 0.97−1.75 (m, 16H), 3.00−3.95 (m, 2H). A solution of this alcohol (2.3 g, 15 mmol) in 35 mL of DMF was added to a suspension of 0.45 g (0.02 mmol) of NaH (washed with hexanes) in 35 mL of DMF at 0 °C. After 0.75 h, sulfamoyl chloride (3.45 g, 30 mmol) was added in one portion. After being warmed to 23 °C, the reaction was stirred for 2 h and then quenched with excess $NaHCO_3$ (saturated aqueous). The mixture was extracted five times with ethyl acetate, and the extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (hexanes/ethyl acetate, 4:1) to afford 2.37 g (68%) of **102** as an amorphous solid: ^{1}H NMR (400 MHz) δ 1.24−1.75 (m, 15H), 3.82/4.28 (pair of d, 2H, J = 9.3 Hz), 4.82 (br s, 2H); IR ($CHCl_3$) ν_{max} 3443, 3353, 3297, 2933, 2862, 1370, 1181 cm^{-1}. Anal. ($C_{10}H_{19}NO_3S$) C, H, N.

[3aα,5aβ,6aβ,6bα](1,2,3,4,5,5a,6,6a-Octahydrocycloprop-[*e*]inden-3a-yl)methyl Sulfamic Acid Ester (104). A solution of **97** (2.3 g, 15 mmol) in 23 mL of *tert*-butylmethyl ether was cooled to 0 °C and treated with 3.3 mL (32 mmol) of diethylzinc, followed by dropwise addition of 2.0 mL (25 mmol) of diiodomethane. The mixture was refluxed for 3.5 h, then cooled to 23 °C, and poured onto a mixture of ice and dilute HCl. It was extracted five times with ether, and the combined extracts were washed with water, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexanes/ethyl acetate, 4:1) to give 1.6 g (64%) of **103** as a clear oil: ^{1}H NMR (90 MHz) δ 0.17−0.27 (m, 1H), 0.29−0.35 (m, 1H), 0.59−0.67 (m, 1H), 0.94−0.98 (m, 1H), 1.14−2.01 (m, 12H), 3.19 (br s, 2H). A solution of **103** (1.5 g, 9.0 mmol) in 9.0 mL of DMF was added to a suspension of NaH (0.28 g, 11.7 mmol, washed with hexanes) in 5 mL of DMF at 0 °C, and the mixture was stirred for 45 min. Following treatment with sulfamoyl chloride (2.8 g, 24.6 mmol) at 0 °C in two portions, the mixture was allowed to warm to 23 °C. After being stirred overnight, it was quenched with ice, and the mixture was extracted five times with ethyl acetate. The combined extracts were washed with water, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexanes/ethyl acetate, 5:1) and recrystallized (hexanes/ether) to afford 1.6 g (72%) of **104** as a white solid: ^{1}H NMR (400 MHz,) δ 0.18−0.22 (m, 1H), 0.33−0.39 (m, 1H), 0.61−0.67 (m, 1H), 0.97−1.01 (m, 1H), 1.24−1.39 (m, 2H), 1.43−1.58 (m, 4H), 1.66−1.83 (m, 2H), 1.84−1.99 (m, 3H), 3.79 (s, 2H), 4.70 (br s, 2H); IR (KBr) ν_{max} 3364, 3272, 2955, 2902, 2866, 1569, 1359, 1181, 932 cm^{-1}. Anal. ($C_{11}H_{19}NO_3S$) C, H, N.

2,3:4,5-Bis-*O*-(isopropylidene)-β-L-fructopyranose Sulfamate (106). L-Fructose[59] (2.40 g, 13.3 mmol) was reacted with H_2SO_4 (2.33 mL, 8.3 mmol) in acetone (57 mL) according to the procedure for the preparation of **4**[6] to furnish 2,3:4,5-bis-*O*-(isopropylidene)-β-L-fructopyranose (1.93 g, 56%) as white needles, after recrystallization twice from ether/pentane (1:1), mp 94−96 °C. A portion of this material (1.71 g, 6.57 mmol) was combined with pyridine (0.64 mL g, 7.99 mmol) in toluene (8.8 mL) and added dropwise over 15 min at −15 °C to a vigorously stirred solution of sulfuryl chloride (0.63 mL, 7.88 mmol) in 8.8 mL of toluene. The reaction was slowly warmed to 23 °C over 3 h and diluted with water. The toluene layer was extracted three times with citric acid (10% aq), three times with $NaHCO_3$ (saturated aqueous), and twice with brine, then dried (Na_2SO_4), and concentrated in vacuo to afford crude 2,3:4,5-bis-*O*-(isopropylidene)-β-L-fructopyranose chlorosulfate as an amber oil. The crude material was dissolved in THF (150 mL) and placed in a vigorously stirred autoclave with

anhydrous ammonia (30 psig) over 48 h. After being filtered, the white precipitate was washed with hexanes and recrystallized from 20 mL of ethanol/water (1:1) to afford **106** (1.61 g, 72%) as a white crystalline solid: mp 125−126 °C; ^{1}H NMR (400 MHz) δ 1.35 (s, 3H, Me), 1.42 (s, 3H, Me), 1.49 (s, 3H, Me), 1.55 (s, 3H, Me), 3.70−3.95 (m, 2H, H_6), 4.15−4.40 (m, 4H, 2 H_1, H_3, and H_5), 4.62 (dd, 1H, J_{34} = 2.0 Hz, J_{45} = 7.8 Hz, H_4), 5.36 (br s, 2H, NH_2); ^{13}C NMR (100 MHz) δ 23.9 (Me), 25.0 (Me), 25.7 (Me), 26.3 (Me), 61.5 (CH_2), 69.7 (CH), 70.3 (CH), 70.7 (CH_2), 76.9 100.8 (C), 109.2 (C), 109.3 (C); IR (KBr) ν_{max} 3383 (s), 3245 (m), 3212 (m), 3113 (m), 2997 (m), 1579 (m), 1356 (s), 1211 (s), 1183 (s), 1072 (s), 958 (m), 882 (m), 791 (m) cm^{-1}; CI-MS *m/z* 340 $(MH)^+$, 357 $(M + NH_4)^+$. Anal. ($C_{12}H_{21}NO_8S$) C, H, N.

2,3-*O*-(Isopropylidene)-4,5-*O*-sulfonyl-β-L-fructopyranose Sulfamate (107). A solution of **106** (14.4 g, 42.4 mmol) in THF (70 mL) was diluted with 3 N HCl (70 mL) and heated at 40−45 °C with stirring. After 3 h, the mixture was cooled to 23 °C and adjusted to pH 7 with Na_2CO_3 (11.5 g) and saturated NaCl (17.5 g). The aqueous layer was extracted three times with THF, and the combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by preparative HPLC (ethyl acetate/dichloromethane, 7:3) to furnish 2,3-*O*-(isopropylidene)-β-L-fructopyranose sulfamate (4.75 g, 38%) as a white solid. A solution of this material (4.30 g, 14.4 mmol) and pyridine (2.74 g, 34.5 mmol) in ethyl acetate (143 mL) was reacted with sulfuryl chloride (2.54 mL, 31.6 mmol) and processed as described for **2** (D-isomer of **107**) to afford 4,5-bis-*O*-chlorosulfonyl-2,3-*O*-(isopropylidene)-β-L-fructopyranose sulfamate as a white solid (3.40 g, 48%). This material was dissolved in methanol (22 mL), treated with $NaHCO_3$ (3.75 g, 44.7 mmol), and processed as for **2**. The crude product was purified by preparative HPLC (dichloromethane/ethyl acetate, 9:1) and recrystallized from ethanol/water (1:1) to give **107** (1.25 g, 51%) as a white crystalline solid: mp 128−129 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.38 (s, 3H, Me), 1.53 (s, 3H, Me), 3.90−4.10 (m, 4H, 2 H_1 and 2 H_6), 4.59 (d, 1H, J_{34} = 2.7 Hz, H_3), 5.49 (d, 1H, J_{45} = 7.8 Hz, H_5), 5.70 (dd,1H, J_{34} = 2.7 Hz, J_{45} = 7.8 Hz, H_4), 7.75 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 25.0 (Me), 26.0 (Me), 59.2 (CH_2), 67.9 (CH_2), 68.1 (CH), 73.2, (CH), 77.6 (CH), 100.7 (C), 110.2 (C); IR (KBr) ν_{max} 3376 (s), 3267 (s), 1568 (m), 1377 (s), 1213 (s), 1189 (s), 1050 (s), 832 (m) cm^{-1}; FAB-MS *m/z* 362 $(MH)^+$, 379 $(M + H_2O)^+$, 384 $(M + Na)^+$. Anal. ($C_9H_{15}NO_{10}S_2$) C, H, N, S.

Single-Crystal X-ray Analysis of Topiramate (1).[75,76] The procedure used for **1** is representative of that used for **2**, **21a**, and **95**, experimental details and results for which are supplied in Supporting Information.[76] Crystals of $C_{12}H_{21}NO_8S$ (MW 339.36, colorless rectangular parallelpipeds from ethanol/water) are orthorhombic (space group $P2_12_12_1$) with a = 7.2432(9) Å, b = 11.004(1) Å, c = 19.636(2) Å, $\alpha = \beta = \gamma$ = 90.0°, V = 1565.1(3) Å^3, and d_{calcd} = 1.440 g/cm^3 for Z = 4. The intensity data were collected from a single crystal (0.40 × 0.50 × 0.55 mm) on a computer-controlled Four-Circle Nicolet autodiffractometer at 293 K by using $\theta-2\theta$ scans and nickel-filtered Cu $K\alpha$ radiation (λ = 1.541 84 Å). We used 1369 independent reflections having intensities greater than 2.0θ(Cu $K\alpha$) < 120.0° (equivalent of 0.65 limiting Cu $K\alpha$ spheres). The structure was solved by using Direct Methods with a modified Siemens SHELXTL-PC software package. The resulting structural parameters were refined to convergence [R_1(unweighted, based on F) = 0.042 for 1300 independent reflections with 2.0θ(Cu $K\alpha$) < 120.0° and $I > 3\sigma(I)$] by using counter-weighted, full-matrix least-squares methods and a structural model that incorporated anisotropic thermal parameters for all non-hydrogen atoms and isotropic thermal parameters for all hydrogen atoms. Hydrogen atoms on the NH_2 group, H_{1N1} and H_{1N2}, were located from a difference Fourier map and refined as independent isotropic atoms. The four methyl groups (C8, C9, C11, C12, and their hydrogen atoms) were included in the structural model as rigid rotors with sp^3 geometry and a C−H bond distance of 0.96 Å. The refined positions for the rigid rotor methyl groups gave C−C−H angles ranging from 100 to 116°. The remaining hydrogen atoms were included in the structure factor calculations as idealized atoms. The isotropic thermal parameters for H_{1N1} and H_{1N2} refined to a final value of 3(1) Å^2; the isotropic thermal parameter of each remaining hydrogen atom was set at 1.2 times the equivalent isotropic thermal parameter for its associated carbon atom. The molecular structure of **1** is depicted in Figure 2.

Single-Crystal X-ray Analysis of 2.[75,76] Crystals of $C_9H_{15}NO_{10}S_2$ (MW 361.3, colorless rectangular parallelpipeds) are hexagonal [space group $P6_1$; $a = b$ = 9.760(2) Å, c = 27.070(8) Å, V = 2235(1) Å^3, Z = 6]. The intensity data were collected from a single crystal by using full ω scans and graphite-monochromated Mo $K\alpha$ radiation (λ = 0.710 73 Å). A total of 2041 independent reflections having intensities 2.0θ(Mo $K\alpha$) < 55.0° were used, and the structure was solved by Direct Methods. The resulting structural parameters were refined to convergence [R_1(unweighted, based on F) = 0.039 for 1752 independent reflections]. The molecular structure of **2** is depicted in Figure 3.

Single-Crystal X-ray Analysis of 95.[75,76] Crystals of $C_{13}H_{23}NO_5S$ (MW 305.4, colorless rectangular parallelpipeds) are monoclinic [space group $P2_1/n$; a = 10.094(3) Å, b = 11.712(4) Å, c = 13.239(4) Å, β = 103.04(3)°, V = 1525(1) Å^3, Z = 4]. The intensity data were collected from a single crystal by using ω scans and graphite-monochromated Mo $K\alpha$ radiation. A total of 3493 independent reflections having intensities greater than 2.0θ(Mo $K\alpha$) < 55.0° were used, and the structure was solved by using Direct Methods. The resulting structural parameters were refined to convergence [R_1(unweighted, based on F) = 0.048 for 2689 independent reflections]. The molecular structure of **95** is depicted in Figure 4.

Maximal Electroshock Seizure (MES) Assay.[60] This anticonvulsant test was performed according to the procedure described previously.[2a] Our standard protocol was to evaluate each test compound in mice at 1 and 4 h by both intraperitoneal and oral administration, generally with 10 mice per group. The oral 4-h testing results are reported in Table 1.

Inhibition of Carbonic Anhydrase.[79] Details are provided in the Supporting Information.[76]

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Supporting Information Available: Experimental procedures for **81**, **97**, **98**, and methyl (4,4-dimethyl-2-oxo-cyclopent)-1-yl-carboxylate; ^{1}H NMR spectral data for **83b**−**m**, **83o**, and **83p**; detailed data for the X-ray analyses of **1**, **2**, and **95**, including tables of atomic coordinates, bond lengths, bond angles, and thermal parameters, as well as experimental details and results for **2** and **95**; procedure for carbonic anhydrase inhibition; 95% confidence limits for the ED_{50} values in Table 1 (34 pages). Ordering information is given on any current masthead page.

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(75) Details for the crystallography are given in the Supporting Information.

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