Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 12, pp. 2459-2473, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $7.00+0.00

0957-4166(94)00324-6

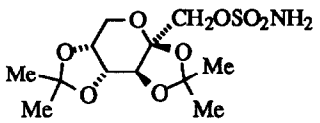
Non-Chair Six-Membered-Ring Conformations. Preference for a Twist-Boat (or Skew) Structure in α-L-Sorbopyranose Derivatives

Michael J. Costanzo, Harold R. Almond, Jr., A. Diane Gauthier, and Bruce E. Maryanoff*

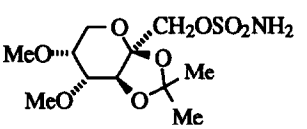
Drug Discovery, The R. W. Johnson Pharmaceutical Research Institute
Spring House, Pennsylvania 19477 USA

Abstract: The conformational preferences for 2,3-*O*-isopropylidene-α-L-sorbopyranose derivatives **3-6** were determined by using ^{1}H NMR data and empirical force field calculations. Proton NMR studies of **3-6** indicate that a twist-boat (or skew) conformation ($^3S_0$) prevails over possible chair forms for each compound. Force-field calculations (MM2, MNDO, AM1) on a model 2,3-*O*-isopropylidene-α-L-sorbopyranose system (**18**) indicate that the $^3S_0$ conformation is among the low-energy structures. X-Ray crystallographic analysis of α-L-sorbopyranose sulfamate **3**, a compound with potent anticonvulsant activity, demonstrates that the $^3S_0$ skew conformation is manifested in the solid state, as well.

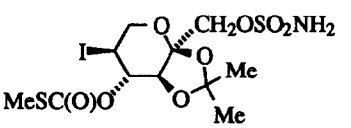
Molecules with saturated six-membered rings that exist primarily in a twist-boat (or skew) conformation, as opposed to a chair conformation, are rare. In the absence of rigid constraints, such as covalent bonds in twistane, twist-boat conformations prevail only when certain steric and/or electronic factors combine to tip the balance of energetics away from chair forms. The factors most commonly encountered have been: torsional strain induced by ring fusion(s),[1] unfavorable 1,3-diaxial interactions,[2] intramolecular hydrogen bonding,[3] the presence of second-row heteroatoms,[4] and the anomeric effect.[5] In this context, we have found an unusually strong preference for a skew ($^3S_0$) conformation in L-sorbopyranose sugar derivatives.



1



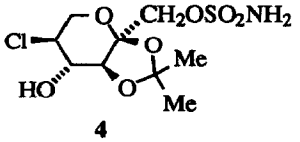
2



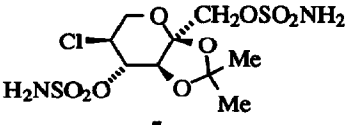
3

Topiramate (**1**), an important antiepileptic drug that was discovered in our laboratory, adopts a skew conformation ($^3S_0$) for the tetrahydropyran ring in solution and in the solid state.[6] 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.[6a] We have also suggested that such a skew conformation may be critical for the potent anticonvulsant activity of topiramate.[6a] In further studies with topiramate analogues, we had occasion to synthesize and biologically test some compounds with the 4,5-isopropylidene ring missing, such as **2**[7] and **3**. Although **2** is virtually devoid of anticonvulsant activity, **3** and related sorbopyranoses (**4-6**)

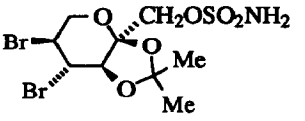
are about equipotent with topiramate.[8] This surprising observation appeared to be inexplicable at first, until we considered the conformations of these molecules. Indeed, **2** favors a chair conformation ($^5C_2$),[9] whereas **3** favors a skew conformation ($^3S_0$), which is heretofore unknown for the sorbopyranose system, albeit nicely consistent with our structural hypothesis for topiramate's bioactivity. In this paper, we report on our investigation into the conformational properties of 2,3-*O*-isopropylidene-α-L-sorbopyranoses **3-6**.



4



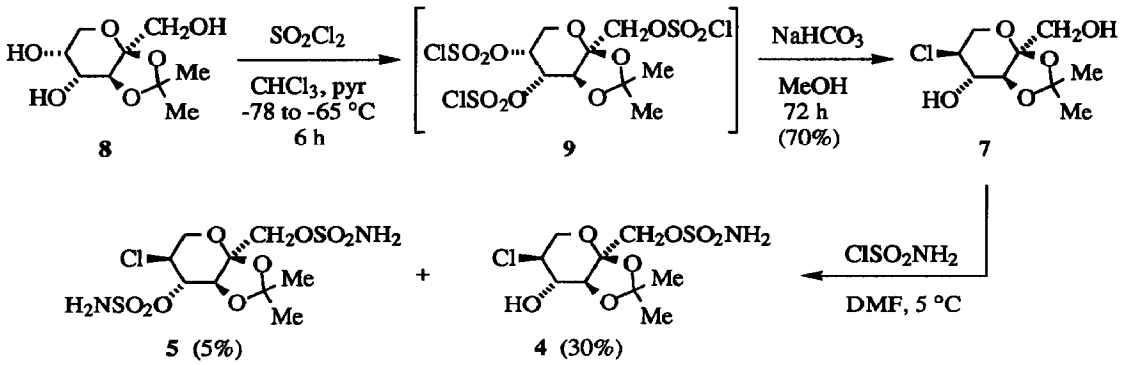
5



6

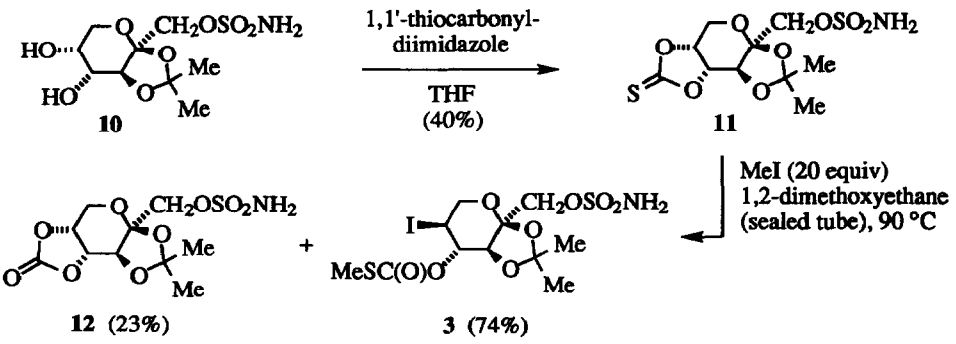
RESULTS AND DISCUSSION

Synthetic Chemistry. No 2,3-*O*-alkylidenesorbopyranose derivatives have yet been isolated from the direct ketalization of L-sorbose; only 1,2- and 1,3-*O*-isopropylidene-α-L-sorbopyranoses were obtained along with assorted sorbofuranoses.[3,10] In sharp contrast, closely related 2,3-*O*-isopropylidene-β-D-*fructo*pyranose derivatives, which only differ from the α-L-sorbopyranose system by stereoinversion at C_5, are easily prepared.[10] To date, there has been only one report of an α-L-sorbopyranose system with a cis 2,3-*O*-alkylidene ring fusion, namely compound **7**, which was first prepared by Martin et al.[11] Accordingly, low temperature reaction of α-D-fructopyranose[12] **8** with sulfuryl chloride afforded intermediate *tris*-chlorosulfate **9**, which was subsequently reacted with methanolic sodium bicarbonate to yield **7** (Scheme 1). We reacted **7** with sulfamoyl chloride to provide novel sulfamate **4** along with a small amount of *bis*-sulfamate **5**, which was inseparable from **4**. A sample enriched in *bis*-sulfamate **5** was obtained by using a large excess of sulfamoyl chloride.



Scheme 1

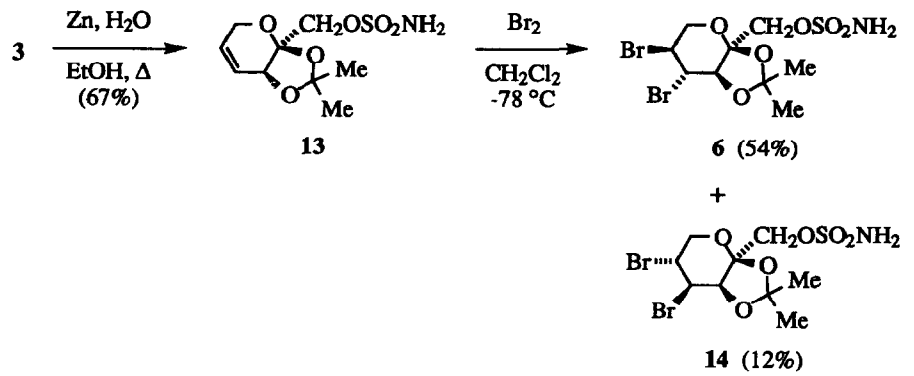
Iodo thiocarbonate **3** was synthesized from diol **10**[6a] (Scheme 2). Thus, reaction of **10** with 1,1'-thiocarbonyldiimidazole[13] furnished cyclic thiocarbonate **11**, which was reacted with methyl iodide[14] to provide **3** and carbonate **12**. Carbonate **12** presumably resulted from the reaction of the intermediate *S*-methylthiocarbonate salt (not shown) with adventitious water. The identity of **12** was confirmed through independent synthesis by the reaction of diol **10** with 1,1'-carbonyldiimidazole.



10 **11** **12** (23%) **3** (74%)

Scheme 2

Dibromo derivative **6** was synthesized from iodo thiocarbonate **3** (Scheme 3). Thus, reduction of **3** with zinc dust furnished intermediate alkene **13**, which was reacted with bromine to afford **6**, along with a small amount of the related β-D-tagatopyranose, **14** (**6**/**14** = 4.4:1). Attempts to prepare alkene **13** by heating cyclic thiocarbonate **11** in $(MeO)_3P$ or $(EtO)_3P$ were unsuccessful, although $(i\text{-}PrO)_3P$ gave a trace amount of **13**.[15]

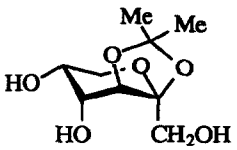


13 **6** (54%) + **14** (12%)

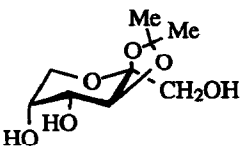
Scheme 3

Conformational Studies. The 2,3-*O*-isopropylidene-β-D-fructopyranose system is known to prefer the unusual $^5C_2$ chair conformation, **15**,[16] rather than the more commonly preferred $^2C_5$ conformation, **16**, which is stabilized by the anomeric effect.[9b] Presumably, the torsional strain introduced by a 2,3-*O*-isopropylidene

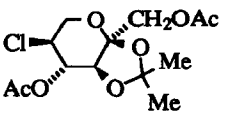
ring that is cis-fused overrides the stabilization afforded through the anomeric effect. By analogy, it is not unreasonable to expect the closely related 2,3-*O*-isopropylidene-α-L-sorbopyranose system to prefer the $^5C_2$ conformation. However, it became apparent from ^{1}H NMR vicinal coupling constants that the tetrahydropyran ring of **7** does not exist predominantly in either possible chair conformation, nor in a mixture thereof. By contrast, from a small proton-proton coupling constant in **17** (J_{34} = 2.9 Hz), a diacetylated derivative of **7**, Martin et al.[11] inferred a preference for the chair conformation: "these compounds adopt the unusual $^5C_2$ conformation; however, according to the other coupling-constant values, the true conformation probably deviates from the ideal chair to a flattened chair, as in the case of 2,3-*O*-isopropylidene-β-D-fructopyranose" (viz. **15**). Given the conflicting interpretations, we sought to explore this carbohydrate system in more detail.



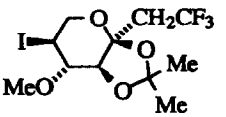
15 ($^5C_2$)



16 ($^2C_5$)

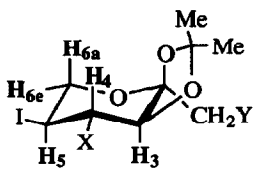


17

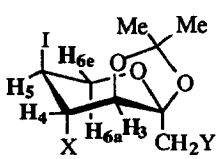


18

As a prelude to interpreting vicinal proton-proton coupling constants for the 2,3-*O*-isopropylidene-α-L-sorbopyranose system, we performed a molecular modeling study to determine the probable low-energy conformers, as well as their corresponding coupling constants. One would like to examine all possible conformations, within reason, and obtain relative energies. Since the current molecular mechanics force fields are limited in their application to carbohydrates when comparing relative conformational energies,[17] we took a conservative approach by employing three different force fields.

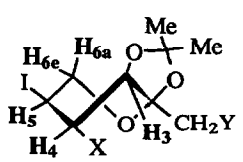


19 ($^2C_5$)

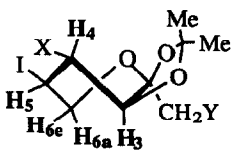


20 ($^5C_2$)

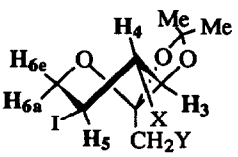
a: X = OMe; Y = CF_3
b: X = MeSC(O)O; Y = OSO_2NH_2



21 ($^3S_0$)



22 ($^0S_3$)



23 ($^4S_2$)

Figure 1. Low energy conformations of 2,3-*O*-isopropylidene-α-L-sorbopyranose derivatives.

In theory, the total number of possible distinct pyranose ring conformations for this system is 26: 2 chairs, 6 skews, 6 boats, and 12 half-chairs.[16] To facilitate energy minimization, structure **18** was chosen as a simplified approximation of iodo derivative **3**, wherein the sulfamate moiety is transformed to a trifluoromethyl group and the thiocarbonate ester is represented by a methoxy group. These changes eliminated four rotatable bonds from inconsequential substitutents and were more compatible with the force fields in use.[18] A total of 252 starting conformations for **18** were generated using the systematic SEARCH routine in SYBYL,[19] each of which were minimized with MAXIMIN2.[20] Since MAXIMIN2 is not parametrized for the anomeric effect, which typically is worth 1-2 kcal/mol,[21] we selected structures that covered a broad energy range to insure that conformations were not dropped from consideration because of this limitation. Therefore, those structures within 12 kcal/mol of the minimum energy conformation were selected and sorted into five distinct families (out of a possible 26). These families included the $^{2}C_{5}$ (**19a**) and $^{5}C_{2}$ (**20a**) chair conformers, as well as the $^{3}S_{0}$ (**21a**), $^{0}S_{3}$ (**22a**), and $^{4}S_{2}$ (**23a**) skew forms (Figure 1). The lowest energy forms of **19a-23a** were re-minimized separately with MM2,[22] MNDO,[23] and AM1[23] to incorporate the anomeric effect and to obtain independent results (Table 1).

Comparison of the relative energies for conformations **19a-23a** (Table 1) leads to several important observations. (1) All three force fields rank the $^{0}S_{3}$ conformer (**22a**) as among the least stable and therefore it may be eliminated from further consideration as a possible low energy form. Vicinal proton-proton coupling values (*vide infra*) safely remove this conformer from consideration, as well. (2) There is enough variability in the relative rankings between the force fields to justify consideration of all the remaining conformers (i.e., **19a-21a** and **23a**) as possible low energy forms. For example, MM2 ranked the $^{5}C_{2}$ conformation (**20a**) as the most stable conformer, whereas AM1 ranked it fifth. (3) Although these empirical force fields are limited for comparing low energy conformations of carbohydrates, they are useful for eliminating higher energy structures from consideration. In the present example, a total of 26 possible pyranose starting conformations was trimmed to four. (4) Each force field ranked the $^{3}S_{0}$ conformer (**21a**) as the second most stable one and, significantly, as the most stable skew conformation.

Conformation	MM2[a]	MNDO[a]	AM1[a]
$^{2}C_{5}$ (**19a**)	2.5 (42.1)	0.0 (-298.1)	0.0 (-320.8)
$^{5}C_{2}$ (**20a**)	0.0 (39.6)	1.1 (-297.0)	3.9 (-316.9)
$^{3}S_{0}$ (**21a**)	0.7 (40.3)	0.3 (-297.8)	0.2 (-320.6)
$^{0}S_{3}$ (**22a**)	5.2 (44.8)	2.9 (-295.2)	3.6 (-317.2)
$^{4}S_{2}$ (**23a**)	3.8 (43.4)	1.3 (-296.8)	1.9 (-318.9)

(a) Actual calculated value is in parentheses.

Table 1. Relative energies for conformations of **18** (kcal/mol).

The conformations of the model system **18** (**19a-23a**) were converted into low energy conformers of **3** (**19b-23b**) by replacement of the sulfamate and thiocarbonate moieties, followed by re-minimization with just

MNDO, since the MM2 and AM1 programs were not parameterized for these groups. Vicinal proton-proton coupling constants for conformations **19b-23b** were then calculated by using the Altona modification[24] of the Karplus equation (Table 2). It is apparent from these data that neither chair conformer alone, **19b** or **20b**, reasonably satisfies the observed couplings for **3** (^{1}H NMR data discussed below). In addition, an equilibrium mixture of chair conformers is unable to produce the observed couplings, primarily because the values for J_{45} and J_{56e} would be much too divergent.[25] In comparing the other structures, **21b-23b**, the coupling values for the $^3S_0$ conformer (**21b**) are closest to the observed values for **3**, indicating that **21b** is a principal contributor. Coupling constant values for **21b** calculated from the $^3S_0$ geometry of **3** in the solid state (vide infra) were employed in preference to those from the MNDO-derived geometry of **21b** for conformer mixing. Thus, a 4:1 mixture of the $^3S_0$ and $^2C_5$ conformers (**21b/19b**) provides a good fit of the calculated and observed coupling values, with the least accurate correlation occurring for J_{56e} (J_{calc} of 6.6 Hz vs. J_{obs} of 5.5 Hz). Although mixtures of the $^3S_0$ conformer (**21b**) with either **22b** or **23b** could reproduce the observed couplings, the latter conformers were discounted because of the high relative energies for **22a** and **23a** (Table 1).

Conformation[a]	J_{34}	J_{45}	J_{56a}	J_{56e}
$^2C_5$ (**19b**)	5.3	11.4	11.6	4.4
$^5C_2$ (**20b**)	0.7	0.6	4.3	1.0
$^3S_0$ (**21b**)	1.2	1.4	8.9	8.7
$^3S_0$ (**21b**)[b]	2.1	1.2	11.1	7.2
$^0S_3$ (**22b**)	6.0	7.5	8.5	2.4
$^4S_2$ (**23b**)	8.3	11.7	8.7	9.1
$^3S_0$ (**21b**)/$^2C_5$ (**19b**) = 4:1[c]	2.7	3.2	11.2	6.6
Observed for **3**[d]	3.1	2.9	10.3	5.5

(a) Minimum energy conformers calculated with MNDO, unless noted otherwise. (b) Couplings calculated from the X-ray crystal structure of **3**. (c) Averaged by using the data for **21b** from the X-ray structure of **3**. (d) From 400-MHz ^{1}H NMR spectrum recorded in $CDCl_3$ at 24 °C (± 0.2 Hz).

Table 2. Calculated and observed vicinal proton-proton coupling constants (Hz) for **3**.

The ^{1}H NMR spectrum of compound **3** is shown in Figure 2. One of the most diagnostic couplings in support of the predominance of the $^3S_0$ conformer (**21b**) is the long-range "W" coupling[26] observed between H_3 and H_5 ($^4J_{35}$ = 0.9 Hz). Of the five structures depicted in Figure 1, only the $^5C_2$ and $^3S_0$ conformations can manifest this long-range coupling. Further support for the predominance of the $^3S_0$ conformation is provided by the NOE observed between the isopropylidene methyl group at 1.6 ppm and H_{6a} (Figure 2), which would not exist in either of the chair forms (**19b** or **20b**).

We examined the ^{1}H NMR spectrum of **3** in several different solvent systems to see if there was any influence on conformer distribution (Table 3). The most striking feature of the data is *how little the coupling constants change* despite the diversity of solvents, which indicates that the $^3S_0$ conformation, (**21b**) or a fairly

constant equilibrium mixture (i.e., ca. 4:1) of the $^3S_0/^2C_5$ conformations (**21b/19b**), prevails. Moreover, in a variable temperature study in CD_3OD (24 to -60 °C) the coupling constants again changed only slightly, providing support for this viewpoint (Table 3). Given the unlikelihood that the skew/chair ratio for a mixture would remain invariant over such drastic changes in conditions, we suggest that skew conformer **21b** strongly predominates.

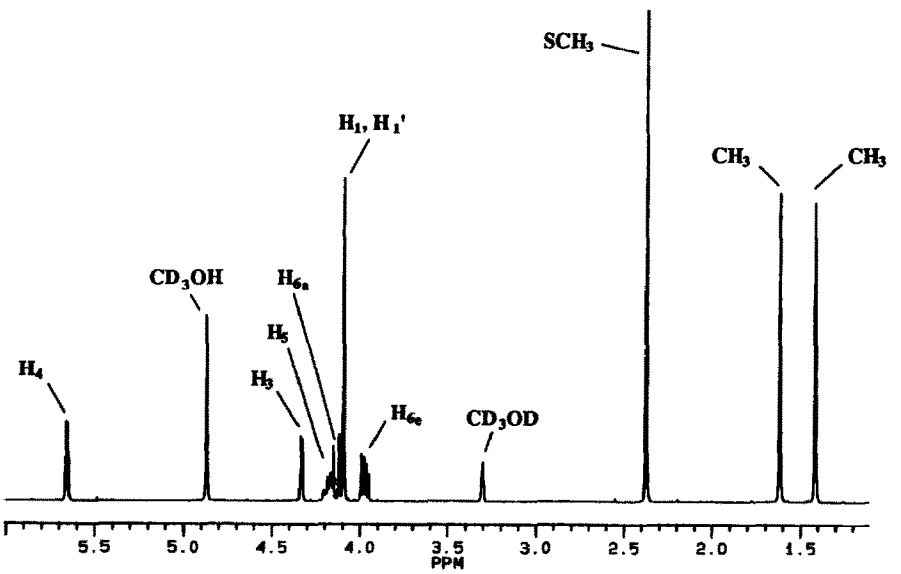


Figure 2. 400-MHz ^1H NMR spectrum of **3** recorded in CD_3OD at 24 °C.

Solvent[a]	J_{34}	J_{45}	J_{56a}	J_{56e}	J_{35}
$CDCl_3$	3.1	2.9	10.3	5.5	0.9
acetone-d_6	3.4	2.8	10.5	6.7	0.9
DMSO-d_6	3.1	3.1	10.3	6.8	0.7
CD_3OD	3.2	3.3	11.3	6.4	0.8
CD_3OD[b]	3.1	2.4	10.6	7.3	- - -

(a) Recorded at 24 °C unless noted otherwise. (b) Recorded at -60 °C; the long range J_{35} coupling was unresolved at this temperature.

Table 3. Observed vicinal proton-proton coupling constants (± 0.2 Hz) for **3** in various solvents (400 MHz).

The vicinal proton-proton couplings of 2,3-*O*-isopropylidene-α-L-sorbopyranose derivatives **3-7** are collected in Table 4 for comparison. The couplings observed for these compounds, including the diagnostic long range J_{35} coupling, correlate well with the observed values for **3**, indicating that the $^3S_0$ conformation is the prevalent conformer for this class of sorbose derivatives.

Cmpd	Solvent[a]	J_{34}	J_{45}	J_{56a}	J_{56e}	J_{35}
3	acetone-d_6	2.7	2.4	11.0	5.9	0.7
4	CD_3OD	2.5	1.9	9.3	7.0	0.8
5	CD_3OD	3.2	3.3	11.3	6.4	0.8
6	$CDCl_3$	2.7	1.0	8.3	6.1	0.6
7	CD_3OD	2.6	3.0	9.2	4.6	0.8

a) Recorded at 24 °C.

Table 4. Observed 400-MHz vicinal proton-proton coupling constants for **3-7** (± 0.2 Hz).

X-Ray Crystal Structure of 3. An orthorhombic crystal of **3** was subjected to an X-ray diffraction study, which corroborated its composition and stereochemistry. Additionally, we found that **3** adopts an $^3S_0$ skew conformation (**21b**) in the solid state (Figure 3). The similar carbon-oxygen bond lengths at C_2 indicate that the anomeric effect is indeed manifested in this structure,[27] which may partially explain the remarkable stability of the $^3S_0$ conformation. The solid-state structure was used to derive vicinal coupling constants for the $^3S_0$ structure **21b** (Table 2).

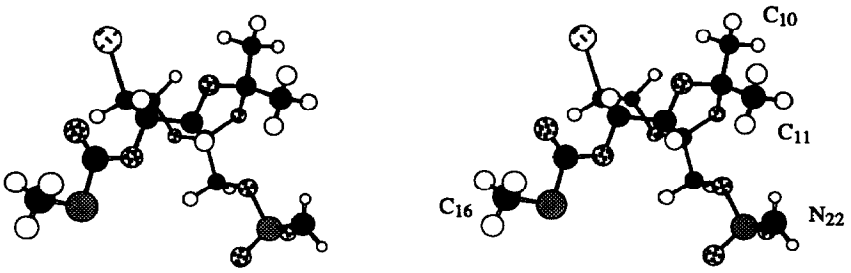
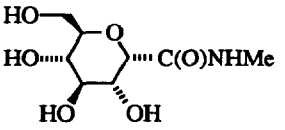


Figure 3. Stereoview of a ball-and-stick model of the X-ray crystal structure of **3** (●, carbon; ○, hydrogen; ⊙, iodine; ●, nitrogen; ⊗, oxygen; ●, sulfur).

CONCLUSION

Bis-acetals of β-D-fructopyranoses[3,6a,10] and α-D-galactopyranoses[28] adopt a skew conformation, presumably because the usually more stable chair conformations are disfavored by the "cis-anti-cis" arrangement for the 5-6-5 ring system.[6a] Although removal of one of the acetal rings (4,5 ring) in the case of the β-D-fructopyranose system (e.g., **8**) results in a preference for the $^5C_2$ chair conformation (**15**), this is not true for α-L-sorbopyranose derivatives. Through a combination of computational, NMR, and X-ray techniques, we found that certain L-sorbopyranose derivatives (**3-6**) exhibit a strong preference for the $^3S_0$ skew conformation in solution, and that this conformation is also manifested in the solid-state for **3**. Perhaps, the axial substituent at C_5 in the α-L-sorbopyranose system destabilizes the $^5C_2$ chair form (**20**), thereby favoring the $^3S_0$ skew conformation (**21**), which is stabilized by the anomeric effect. Presumably, the same torsional and steric factors that disfavor the $^2C_5$ chair conformation (**16**) in 2,3-*O*-isopropylidene-β-D-fructopyranoses also disfavor this conformation (**19**) in 2,3-*O*-isopropylidene-α-L-sorbopyranoses.

The high level of anticonvulsant activity elicited by derivatives **3-6** is significant and may be related to the prevalence of the $^3S_0$ skew structure, by analogy with topiramate (**1**). In addition to the findings of our research,[6] the biological relevance of pyranose skew conformations was recently implicated for an inhibitor of the regulatory enzyme glycogen phosphorylase, 2,6-anhydro-*N*-methyl-D-*glycero*-D-*ido*-heptonamide (**24**), a glucopyranose analogue that binds to glycogen phosphorylase in a skew conformation.[29]



24

EXPERIMENTAL SECTION

General Methods. The X-ray crystallography work on **3** was conducted by Crystalytics Co., Lincoln, NE. Elemental analysis was performed by Atlantic Microlab, Inc., Norcross, GA. TLC separations were conducted on 250-μm silica plates with visualization by iodine staining and by charring with $EtOH/H_2SO_4$ (95:5). Chromatographic separations were carried out on a Waters Prep-500 HPLC equipped with two PrepPak® cartridges (column: 47 x 300 mm; silica gel: 55-105 μm, 125 Å) connected in series by using refractive index detection. 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. Infrared spectra were recorded on a Nicolet SX 60 spectrometer (s = strong, m = medium). NMR spectra were acquired on a Bruker AM-400 instrument. ^1H NMR spectra were obtained at 400.13 MHz (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad; dist = distorted). ^{13}C NMR spectra were obtained at 100.61 MHz; distortionless enhancement by polarization transfer experiments with an editing pulse at 135° (DEPT-135) were

used to assign the carbon multiplicities. Chemical-ionization mass spectra (CI-MS) were recorded on a Finnigan 3300 mass spectrometer with ammonia as the reagent gas. 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.

5-Deoxy-5-iodo-2,3-*O*-(1-methylethylidene)-4-(methylthiocarbonyl)-α-L-sorbopyranose Sulfamate (3). Compound **11** (14.0 g, 0.041 mol), methyl iodide (51.0 mL, 0.820 mol) and 1,2-dimethoxyethane (51 mL) were combined in a pressure vessel and heated at 90 °C while stirring for 2.5 h. The reaction was filtered, the solvent was removed, and the residue was purified by chromatography (CH_2Cl_2/EtOAc, 9:1) to give **3** (14.59 g, 74%) and **12** (3.01 g, 23%). A sample of **3** was recrystallized from CH_2Cl_2/EtOAc to give a white crystalline solid; m.p. 135-136 °C; $[\alpha]_D^{25}$ +39.4 (*c* 1.00, MeOH). IR (KBr) ν_{max} 3396 (m), 3265 (m) 1714 (s), 1371 (s), 1191 (s), 1124 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (s, 3H, Me), 1.68 (s, 3H, Me), 2.40 (s, 3H, SMe), 3.99 (dd, 1H, J_{56e} = 5.5 Hz, J_{6a6e} = 10.4 Hz, H_{6e}), 4.08 (dist dddd, 1H, J_{35} = 0.9 Hz, J_{45} = 2.9 Hz, J_{56a} = 10.3 Hz, J_{56e} = 5.5 Hz, H_5), 4.16 (dd, 1H, J_{56a} = 10.3 Hz, J_{6a6e} = 10.4 Hz, H_{6a}), 4.25 (s, 2H, H_1 and $H_{1'}$), 4.30 (dd, 1H, J_{34} = 3.1 Hz, J_{35} = 0.9 Hz, H_3), 4.99 (br s, 2H, NH_2), 5.72 (dd, 1H, J_{34} = 3.1 Hz, J_{45} = 2.9 Hz, H_4); ^{13}C NMR ($CDCl_3$) δ 13.7 (Me), 15.6 (CHI), 25.6 (Me), 26.6 (Me), 64.3 (CH_2), 70.1 (CH_2), 74.0 (CH), 75.6 (CH), 101.3 (C), 111.1 (C), 170.6 (C=O); FAB-MS: *m/z*: 484 $(MH)^+$, 506 $(M+Na)^+$. Anal. Calcd for $C_{11}H_{18}INO_8S_2$: C, 27.34; H, 3.75; N, 2.90; S, 13.27. Found: C, 27.49; H, 3.52; N, 2.84; S, 13.90.

5-Chloro-5-deoxy-2,3-*O*-(1-methylethylidene)-α-L-sorbopyranose Sulfamate (4). A solution of **7**[9] (3.00 g, 0.013 mol) in dry DMF (25 mL) was cooled to 5 °C while stirring under argon. Sulfamoyl chloride (2.33 g, 0.020 mol) was added and the reaction was stirred at 5 °C for 2.5 h, diluted with 100 mL of satd. NaCl, and extracted with three portions of ethyl acetate. The combined extracts were washed twice with satd. $NaHCO_3$, dried ($MgSO_4$), filtered through diatomaceous earth, and concentrated at 40 °C. The residue was chromatographed (CH_2Cl_2/EtOAc, 4:1) and recrystallized from CH_2Cl_2/hexane (2:3) to give 1.38 g (35%) of white crystals, as a mixture of **4** (0.84 equiv) and **5** (0.16 equiv): mp 94-100 °C; $[\alpha]_D^{25}$ +7.7 (*c* 1.00, MeOH); IR (KBr) ν_{max} 3476 (s), 3357 (s), 3253 (s), 1553 (m), 1461 (m), 1362 (s), 1208 (s) cm^{-1}. Data for **4** in mixture: ^1H NMR (CD_3OD) δ 1.40 (s, 3H, Me), 1.55 (s, 3H, Me), 3.87 (dd, 1H, J_{56a} = 11.0 Hz, $J_{6a'}$ = 11.4 Hz, H_{6a}), 3.87-3.95 (m, 1H, H_5), 4.02 (dd, 1H, J_{6a6e} = 11.4 Hz, J_{56e} = 7.0 Hz, H_{6e}), 4.13 (ab q, 2H, $J_{11'}$ = 10.3 Hz, H_1 and H_1'), 4.18-4.25 (m, 2H, H_3 and H_4); ^{13}C NMR (CD_3OD) 26.2 (Me), 27.3 (Me), 56.3 (CH), 63.9 (CH_2), 69.4 (CH_2), 72.7 (CH), 77.7 (CH), 102.8 (C), 111.2 (C); CI-MS *m/z* 335 $(M+NH_4)^+$. Anal. Calcd for $C_9H_{16}ClNO_7S \cdot 0.16\ C_9H_{17}ClN_2O_9S_2$: C, 33.01; H, 4.96; N, 4.80; S, 10.99. Found: C, 33.15; H, 5.01; N, 4.88; S, 10.94.

5-Chloro-5-deoxy-2,3-*O*-(1-methylethylidene)-4-sulfamoyl-α-L-sorbopyranose Sulfamate (5). A solution of compound **7**[9] (2.09 g, 0.0088 mol) in dry DMF (17 mL) was cooled to 5 °C while stirring under argon. Sulfamoyl chloride (4.05 g, 0.035 mol) was added and the reaction was stirred at 5 °C for 18 h. The DMF was removed at 45 °C and the residue was dissolved in 200 mL of ethyl acetate. The solution was washed three times with satd. NaCl, twice with satd. $NaHCO_3$, dried ($MgSO_4$), filtered through diatomaceous earth, and concentrated at 40 °C. The residue was purified by chromatography (CH_2Cl_2/EtOAc, 4:1) to yield 1.20 g (36%) of white foam, as a mixture of **5** (0.67 equiv) and **4** (0.33 equiv): $[\alpha]_D^{20}$ +20.4 (*c* 1.00, MeOH); IR (neat) ν_{max} 3510 (m), 3370 (s), 3283 (s), 2994 (m), 1552 (m), 1459 (m), 1377 (s), 1185 (s) cm^{-1}. Data for **5** in mixture: ^1H NMR (CD_3OD) δ 1.41(s, 3H, Me), 1.59 (s, 3H, Me), 3.86 (dd, 1H, J_{56a} = 7.0 Hz, J_{6a6e} = 9.3

Hz, H_{6a}), 3.90-3.98 (dd, 1H, J_{56a} = 7.0 Hz, J_{6a6e} = 9.3 Hz, H_{6e}), 4.12 (ab q, 2H, $J_{11'}$ = 11.3 Hz, H_1 and $H_{1'}$), 4.16-4.35 (m, 1H, H_5), 4.45 (dd, 1H, J_{34} = 2.5 Hz, J_{35} = 0.8 Hz, H_3), 5.02 (dd, 1 H, J_{34} = 2.5 Hz, J_{45} = 1.9 Hz, H_4); ^{13}C NMR (CD_3OD) δ 25.8 (Me), 26.9 (Me), 52.9 (CH), 63.1 (CH_2), 69.1 (CH_2), 75.1 (CH), 78.4 (CH), 102.6 (C), 112.1 (C); CI-MS *m/z* 414 $(M+NH_4)^+$. Anal. Calcd for $C_9H_{17}ClN_2O_9S_2 \cdot 0.67\ C_9H_{16}ClNO_7S$: C, 29.60; H, 4.58; N, 6.14; S, 14.05. Found: C, 29.71; H, 4.74; N, 6.22; S, 14.21.

4,5-Dibromo-4,5-dideoxy-2,3-*O*-(1-methylethylidene)-α-L-sorbopyranose Sulfamate (6). A solution of **13** (1.04 g, 0.0039 mol) in 12 mL of dry dichloromethane was cooled to -78 °C while stirring under an argon atmosphere. Bromine (0.51 mL, 0.0098 mol) was added dropwise over 10 min and the reaction was stirred at -78 °C for 1 h, quenched by the addition of cyclohexene (1 mL, 0.0098 mol), basified with pyridine (0.8 mL, 0.0098 mol), warmed to 23 °C, and purified by chromatography (CH_2Cl_2/EtOAc, 19:1) to give 1.10 g (67%) of a clear glass, as a mixture of **6** (0.81 equiv) and **14** (0.19 equiv) by ^1H NMR: $[\alpha]_D^{25}$ +20.1 (*c* 1.00, MeOH); IR ($CHCl_3$) ν_{max} 1383 (s), 1185 (m), 1071 (s) cm^{-1}. Data for **6** in mixture: ^1H NMR ($CDCl_3$) δ 1.44 (s, 3H, Me), 1.66 (s, 3H, Me), 4.11 (dd, 1H, J_{56a} = 8.3 Hz, J_{6a6e} = 12.6 Hz, H_6), 4.20 (dd, 1H J_{56e} = 6.1 Hz, J_{6a6e} = 12.6 Hz, H_{6e}), 4.30-4.50 (m, 3H, H_1, $H_{1'}$, and H_5), 4.54 (dd, 1H, J_{34} = 2.7 Hz, J_{45} = 1.0 Hz, H_4), 4.72 (dd, 1H, J_{34} = 2.7 Hz, J_{35} = 0.63 Hz); most of the resonances of presumed **14** were obscured, except for a methyl group at 1.61 (s); ^{13}C NMR (CD_3OD) δ 26.0 (Me), 26.9 (Me), 42.9 (CH), 45.6 (CH), 63.2 (CH_2), 70.0 (CH_2), 76.1 (CH), 101.0 (C), 111.0 (C); presumed tagato isomer **14**: δ 25.4 (Me), 26.8 (Me), 48.3 (CH), 49.9 (CH), 67.4 (CH_2), 67.4 (CH_2), 78.2 (CH), 101.6 (C), 111.1 (C). Anal. Calcd for $C_9H_{15}Br_2NO_6S$: C, 25.43; H, 3.56; Br, 37.59; N, 3.29; S, 7.54. Found: C, 25.71; H, 3.61; Br, 37.49; N, 3.24; S, 7.61.

2,3-*O*-(1-Methylethylidene)-4,5-*O*-thiocarbonyl-β-D-fructopyranose Sulfamate (11). Compound **10** (32.5 g, 0.109 mol) was combined with 1,1'-thiocarbonyldiimidazole (47.3 g, 0.239 mol), dissolved in 500 mL of THF, and stirred at 23 °C for 6 h. The solvent was removed at 40 °C and the residue was dissolved in ethyl acetate. The solution was washed twice with 1 N HCl, three times with satd. $NaHCO_3$, once with satd. NaCl, dried ($MgSO_4$), filtered through diatomaceous earth, and concentrated at 40 °C to furnish 36.7 g of crude **11** as a brown oil. This material was purified by chromatography (CH_2Cl_2/EtOAc, 4:1) to provide 15.0 g (40%) of **11** as a white solid. A sample was recrystallized from anhydrous ethanol, m.p. 205-206 °C; $[\alpha]_D^{20}$ -75.1 (*c* 1.75, MeOH); IR (KBr) ν_{max} 3351(m), 3244 (m), 1352 (s), 1274 (s), 1168 (s), 1070 (s) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.38 (s, 3H, Me), 1.52 (s, 3H, Me), 3.88 (d, 1H, $J_{66'}$ = 10.3 Hz, H_6), 3.95 (ab q, 2H, $J_{11'}$ = 14.3 Hz, H_1 and $H_{1'}$), 4.02 (d, 1H, $J_{66'}$ = 10.3 Hz, $H_{6'}$), 4.54 (d, 1H, J_{34} = 2.7 Hz, H_3), 5.35 (d, 1H, J_{45} = 9.2 Hz, H_5), 5.55 (dd, 1H, J_{34} = 2.7 Hz, J_{45} = 9.2 Hz, H_4), 7.3 (br s, 2H, NH_2); CI-MS *m/z* 342 $(MH)^+$, 359 $(M+NH_4)^+$. Anal. Calcd for $C_{10}H_{15}NO_8S_2$: C, 35.19; H, 4.43; N, 4.10; S, 18.78. Found: C, 35.40; H, 4.46; N, 4.06; S, 18.84.

2,3-*O*-(1-Methylethylidene)-4,5-*O*-carbonyl-β-D-fructopyranose Sulfamate (12). Compound **10**[6a] (4.02 g, 0.0134 mol) was combined with 1,1'-carbonyldiimidazole (4.76 g, 0.0294 mol), dissolved in 60 mL of THF, and stirred at 23 °C for 18 h. The solvent was removed at 40 °C and the residue was purified by chromatography (CH_2Cl_2/EtOAc, 19:1). The white foam was recrystallized from anhydrous ethanol to afford 1.03 g (27%) of **12** as white crystals, m.p. 189-190 °C; $[\alpha]_D^{20}$ -45.5 (*c* 0.48, MeOH); IR (KBr) ν_{max} 3362 (m), 3270 (m), 1796 (s), 1374 (s), 1193, (s) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.37 (s, 3H, Me), 1.52 (s, 3H, Me), 3.89 (ab q, 2H, $J_{11'}$ = 14.5 Hz, H_1 and $H_{1'}$), 3.93 (ab q, 2H, $J_{66'}$ = 10.6 Hz, H_6 and $H_{6'}$), 4.49 (d, 1H, J_{34} = 2.7 Hz, H_3), 5.01 (d, 1H, J_{45} = 8.9 Hz, H_5), 5.26 (dd, 1H, J_{34} = 2.7 Hz, J_{45} = 8.9 Hz, H_4), 6.14 (br s, 2H, NH_2);

^{13}C NMR (DMSO-d_6) δ 24.9 (Me), 25.9 (Me), 59.4 (CH_2), 68.3 (CH_2), 68.5 (CH), 69.5 (CH), 71.6 (CH), 100.7 (C), 109.7 (C), 153.3 (C=O); CI-MS *m/z* 326 $(MH)^+$, 343 $(M+NH_4)^+$. Anal. Calcd for $C_{10}H_{15}NO_9S$: C, 36.92; H, 4.65; N, 4.31; S, 9.86. Found: C, 37.06; H, 4.64; N, 4.23; S, 9.92.

4,5-Dideoxy-2,3-*O*-(1-methylethylidene)-β-D-fruct-4-enopyranose Sulfamate (13). Compound **3** (14.09 g, 0.029 mol), zinc dust (11.45 g, 0.175 mol), H_2O (14 mL) and 95% ethanol (140 mL) were combined and heated at reflux with vigorous stirring for 2 h. After cooling to 23 °C, the reaction was filtered through diatomaceous earth and concentrated to give 15.5 g of a brown oil, which was purified via chromatography (CH_2Cl_2/EtOAc, 9:1) to provide **13** (solvate with ethyl acetate). This material was dissolved in chloroform, washed twice with satd. NaCl, dried ($MgSO_4$), filtered through diatomaceous earth, and concentrated to yield 5.43 g (67%) of **13** (solvate with chloroform), as a golden oil; $[\alpha]_D^{25}$ -0.9 (*c* 1.13, MeOH); IR (neat) ν_{max} 3362 (s), 3272 (s), 1376 (s), 1184 (s) cm^{-1}; ^1H NMR (C_6D_6) δ 1.33 (s, 3H, Me), 1.42 (s, 3H, Me), 3.72 (dd, 1H, J_{56} = 1.8 Hz, $J_{66'}$ = 16.7 Hz, H_6), 4.02 (d, 1H, $J_{66'}$ = 16.7 Hz, $H_{6'}$), 4.10 (ab q, 2H, $J_{11'}$ = 10.8 Hz, H_1 and $H_{1'}$), 4.25 (d, 1H, J_{34} = 3.7 Hz, H_3), 4.36 (br s, 2H, NH_2), 5.36-5.48 (m, 1H), 5.56-5.66 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 27.7 (Me), 27.8 (Me), 61.0 (CH_2), 69.0 (CH), 70.2 (CH_2), 101.4 (C), 110.7 (C), 123.3 (CH), 130.4 (CH); FAB-MS: *m/z*: 266 $(MH)^+$, 288 $(M+Na)^+$. Anal. Calcd for $C_9H_{15}NO_6S \cdot 0.1\ CHCl_3$: C, 39.11; H, 5.44; N, 5.00. Found: C, 39.25; H, 5.31; N, 4.86.

Computational Studies. The bicyclo[4.3.0]nonane ring skeleton of **18**, devoid of heteroatoms and substituents, was searched for possible conformations with the systematic SEARCH module in SYBYL.[19] The ring fusion bond was replaced by a constraint of 1.35-1.75 Å and a ring search with 10-degree increments on the resulting structures generated 252 initial conformations. These were reconstituted with the appropriate heteroatoms and substituents and minimized with MAXIMIN2.[20] The height from the plane of the six pyranose atoms provided measurements which were used in hierarchical analysis to separate the conformers of **18** into five families (**19a-23a**) that were within 12 kcal/mol of the minimum energy conformation.

^1H NMR Studies. Samples were dissolved in deuterated chloroform, methanol, dimethysulfoxide, benzene, or acetone at 2 mM. The deuterated solvent provided the field frequency lock and also served as an internal reference for the chemical shift scale, relative to tetramethylsilane. Spectra were acquired at 400.13 MHz with a 5-mm broad band inverse probe at 24 °C by using a 90-degree pulse-width of 8.8 μs and a 2-s recycling delay with 16 transients. The spectra were subsequently processed on an ASPECT 3000 computer by using an exponential weighting function of 0.1 Hz and a sweep width of 3000 Hz over 32K data points, giving a resolution of 0.2 Hz. Homodecoupling experiments were applied when the coupling constants could not be extracted directly from the spectrum. Temperatures in the variable temperature experiment were calibrated by using 100% methanol. Nuclear Overhauser experiments (NOE) were used to determine the stereochemistry or confirm any ambiguous proton assignments and were acquired by using an irradiation time of 1.8 s with 40 transients and processed by using the standard Bruker NMR software.

X-Ray Crystallography of 3.[30] Crystals of **3** ($C_{11}H_{18}INO_8S_2$, mw 483.3, colorless rectangular parallelpipeds from CH_2Cl_2/hexane; mp 137-139 °C) are orthorhombic (space group $P2_12_12_1$ with a = 6.682(2) Å, b = 10.802(3) Å, c = 24.817(5) Å, $\alpha = \beta = \gamma = 90.0°$, V = 1791(1) $Å^3$, and d_{calcd} = 1.792 g cm^{-3} for Z = 4. The intensity data were collected from a single crystal on a computer-controlled Four-Circle Nicolet Autodiffractometer with the θ-2θ scan technique at 293 K in two shells with scattering angles ranging from $3.0° < 2\theta < 55.0°$ by using Mo Kα radiation (λ = 0.71073 Å; graphite monochromator). Of a total of 2385

independent reflections collected, 2050 intensities greater than $3.0\sigma(I)$ were used. The structure was solved by heavy-atom Patterson techniques, locating the nonhydrogen atoms. Standard Lorentz and polarization corrections were applied to the data; the hydrogen atom positions were located. Structural refinement was accomplished by full-matrix least-squares methods with an anomalous dispersion correction for the iodine and sulfur atoms. Hydrogen atoms H_{22a} and H_{22b} were located from a difference Fourier synthesis and refined as independent isotropic atoms (Figure 3). The three methyl groups C_{10}, C_{11}, and C_{16}, and their hydrogens, were refined as rigid rotors with sp^3-hybridized geometry and a C-H bond length of 0.96 Å. The remaining hydrogen atoms were included in the structure factor calculations fixed at 1.2 times the equivalent isotropic thermal parameter of the carbon to which it was bonded. The final discrepancy factors, after four refinement cycles, were $R_1 = 0.025$ and $R_2 = 0.034$. The correctness of the enantiomeric description was verified in cycles of least-squares refinement in which the multiplier of $\Delta F''$ was varied.

Acknowledgment. We thank Samuel O. Nortey for the preparation of **2**, Marta E. Ortegon for biological testing, and Dr. Gregory Leo for technical assistance and helpful discussions.

REFERENCES AND NOTES

1. (a) Watkins, S. F.; Kim, S. J.; Fronczek, F. R.; Voll, R. J.; Younathan, E. S. *Carbohydr. Res.* **1990**, *197*, 33. (b) Lee, C.-K. *Ibid.* **1987**, *170*, 255. (c) Lis, T.; Weichsel, A. *Acta Crystallogr.* **1987**, *C43*, 1954. (d) Panagiotopoulos, N. C. *Ibid.* **1974**, *B30*, 1402. (e) Coxon, B. *Carbohydr. Res.* **1970**, *13*, 321.
2. Lin, G. H.-Y.; Sundaralingam, M.; Jackobs, J. *Carbohydr. Res.* **1973**, *29*, 439.
3. Maeda, T.; Tori, K.; Satoh, S.; Tokuyama, K. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2635.
4. (a) Maryanoff, B. E.; Hutchins, R. O.; Maryanoff, C. A. *Top. Stereochem.* **1979**, *11*, 187. (b) Maryanoff, B. E.; McPhail, A. T.; Hutchins, R. O. *J. Am. Chem. Soc.* **1981**, *103*, 4432.
5. (a) Grenier-Loustalot, M. F.; Metras, F.; Cottier, L.; Descotes, G. *Spectroscopy Lett.* **1982**, *15*, 963. (b) Luger, P.; Kothe, G.; Paulsen, H. *Chem. Ber.* **1976**, *109*, 1850.
6. (a) Maryanoff, B. E.; Nortey, S. O.; Gardocki, J. F.; Shank, R. P.; Dodgson, S. P. *J. Med. Chem.* **1987**, *30*, 880. (b) Maryanoff, B. E.; Costanzo, M. J.; Shank, R. P.; Schupsky, J. J.; Ortegon, M. E.; Vaught, J. L. *Bioorg. Med. Chem. Lett.* **1993**, *13*, 2653. (c) Greco, M. N.; Maryanoff, B. E. *Tetrahedron Lett.* **1992**, *33*, 5009. (d) Shank, R. P.; Gardocki, J. F.; Vaught, J. L.; Davis, C. B.; Schupsky, J. J.; Raffa, R. B.; Dodgson, S. J.; Nortey, S. O.; Maryanoff, B. E. *Epilepsia* **1994**, *35*, 450. (e) Maryanoff, B. E.; Margul, B. L. *Drugs Future* **1989**, *14*, 342. (f) Anon. *Ibid.* **1993**, *18*, 397.
7. Compound **2** was prepared by reacting 2,3-*O*-(1-methylethylidene)-1-*O*-(phenylmethyl)-β-D-fructopyranose with NaH and MeI followed by debenzylation and reaction with sulfamoyl chloride; details will appear in a future publication.
8. Compound **2** was inactive in the mouse maximal electroshock seizure test: 0% block of tonic extensor (TE) response, after 4 h at 75 mg/kg (p.o.). However, **3** gave a 90% block of TE (ED_{50} = 30.1 mg/kg at

4 h) and topiramate (**1**) elicited a 60% block of TE (ED_{50} = 53.5 mg/kg at 4 h).[6a,d] The ED_{50} values at 4 h for **4/5** (6:1) and **6/4** (4.4:1) were 23.7 mg/kg and 21.3 mg/kg, respectively.

9. (a) The 400-MHz vicinal proton-proton coupling constants J_{56a} = 8.6 Hz and J_{56e} = 4.9 Hz indicate that **2** 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, J_{46} = 0.9 Hz). (b) For a detailed conformational analysis of an analogous system, see: Köll, P.; Kopf, J. *Chem. Ber.* **1976**, *109*, 3346.
10. Brady, R. F., Jr. *Adv. Carbohydr. Chem. Biochem.* **1971**, *26*, 197.
11. (a) Martin, O. R.; Korppi-Tommola, S.-L.; Szarek, W. A. *Can. J. Chem.* **1982**, *60*, 1857. (b) Complete ^1H NMR spectrum for **7** (400 MHz, CD_3OD): δ 1.38 (s, 3H, Me), 1.54 (s, 3H, Me), 3.86 (dd, 1H, J_{56a} = 9.2 Hz, J_{6a6e} = 9.2 Hz, H_{6a}), 3.89-3.94 (m, 1H, H_5), 3.97 (dd, 1H, J_{56e} = 4.6 Hz, J_{6a6e} = 9.2 Hz, H_{6e}), 4.17 (dd, 1H, J_{34} = 2.6 Hz, J_{45} = 3.0 Hz, H_4), 4.21 (dd, 1H, J_{34} = 2.6 Hz, J_{35} = 0.8 Hz, H_3).
12. (a) Wolfrom, M. L.; Shilling, W. L.; Binkley, W. W. *J. Am. Chem. Soc.* **1950**, *72*, 4544. (b) Heyns, K.; Soldat, W.-D.; Köll, P. *Chem. Ber.* **1975**, *108*, 3619.
13. (a) Dudycz, L. W. *Nucleosides Nucleotides* **1989**, *8*, 35. (b) Chu, C. K.; Bhadti, V. S.; Doboszewski, B.; Gu, Z. P.; Kosugi, Y.; Pullaiah, K. C.; Van Roey, P. *J. Org. Chem.* **1989**, *54*, 2217. (c) Rosowsky, A.; Solan, V. C.; Sodroski, J. G.; Ruprecht, R. M. *J. Med. Chem.* **1989**, *32*, 1135.
14. (a) Vedejs, E.; Wu, E. S. C. *J. Org. Chem.* **1974**, *39*, 3641. (b) Barton, D. H. R.; Stick, R. V. *J. Chem. Soc., Perkin Trans. I* **1975**, 1773.
15. Corey, E. J.; Winter, R. A. *J. Am. Chem. Soc.* **1963**, *85*, 2677.
16. For the nomenclature of pyranose ring conformations, see: Schwartz, J. C. P. *J. Chem. Soc., Chem. Commun.* **1973**, 505.
17. (a) Rychnovsky, S. D.; Yang, G.; Powers, J. P. *J. Org. Chem.* **1993**, *58*, 5251. (b) Woods, R. J.; Szarek, W. A.; Smith, V. H., Jr. *J. Chem. Soc., Chem. Commun.* **1991**, 334.
18. The simplifications surmounted parametrization problems and reduced conformational heterogeneity from the side chains.
19. SYBYL Molecular Modeling Software, Version 5.3 (1989), Tripos Assoc., Inc. 1699 S. Hanley Rd., Suite 303, St. Louis, MO 63144.
20. MAXIMIN2 is the energy minimization force field of SYBYL.
21. Kirby, A. J. *Reactivity and Structure Concepts in Organic Chemistry Volume 15; The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: New York, 1983; pp 4-15.
22. Allinger, N. L., MM2/MMP2, Version 7.0 (1991). Distributed by Molecular Design, Ltd., 2132 Farallon Dr., San Leandro, CA 94577. For MM2/MMP2 studies of carbohydrates and related structures, see: (a) ref 17. (b) Gung, B. W.; Zhu, Z.; Mareska, D. A. *J. Org. Chem.*. **1993**, *58*, 1367. (c) Straathof, A. J. J.; van Estrik, A.; Kieboom, A. P. G.; Baas, J. M. A.; van de Graaf, B. *Carbohydr. Res.* **1989**, *194*, 296.
23. J. J. P. Stewart, MOPAC: A Semiempirical Molecular Orbital Program, QCPE #455 (1983), Version 5.0.; MOPAC contains both MNDO and AM1. For MNDO and AM1 studies involving carbohydrates or related structures, see: (a) ref 17. (b) Woods, R. J.; Szarek, W. A.; Smith, V. H., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 4732.
24. Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.

25. The observed coupling (J_{obs}) is define as $J_{obs} = x_1J_1 + x_2J_2$, where x_1 and x_2 are defined as the mole fraction of coupling constants J_1 and J_2 respectively.[9b]
26. Bhacca, N. S.; Williams, D. H. *Applications of NMR Spectroscopy in Organic Chemistry*, Holden-Day, Inc.: San Francisco, 1964, pp 115-121.
27. The C-O bond lengths from the anomeric carbon (C2) to the pyran ring oxygen and to the C2 oxygen are 1.399 Å and 1.415 Å, respectively. For diagnostic structural criteria for the anomeric effect, see: Schleifer, L.; Senderowitz, H.; Aped, P.; Tartakovsky, E.; Fuchs, B. *Carbohydr. Res.* **1990**, *206*, 1990.
28. (a) Midland, M. M.; Asirwatham, G.; Cheng, J.. C.; Miller, J. A.; Morell, L. A. *J. Org. Chem.* **1994**, *59*, 4438. (b) Cone, C.; Hough, L. *Carbohydr. Res.* **1965**, *1*, 1.
29. Watson, K. A.; Mitchell, E. P.; Johnson, L. N.; Son, J. C.; Bichard, C. J. F.; Fleet, G. W. J.; Ford, P.; Watkin, D. J.; Oikonomakos, N. G. *J. Chem. Soc., Chem. Commun.* **1993**, 654.
30. Tables of bond distances, bond angles, and positional and thermal parameters are available on request to the correspondence author.

(*Received* 29 *September* 1994)