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Synthesis of hydroxylated derivatives of topiramate, a novel antiepileptic drug based on D-fructose: Investigation of oxidative metabolites [1]

Samuel O. Nortey, Wu-Nan Wu, Bruce E. Maryanoff *

The R.W. Johnson Pharmaceutical Research Institute, Spring House, PA 19477, USA

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Abstract

To corroborate the structures of two monohydroxylated metabolites of topiramate (**1**), we synthesized four monosaccharide derivatives from D-fructose: 4,5-*O*-[(1*R**)- and 4,5-*O*-[(1*S**)-1-hydroxymethylethylidene]-2,3-*O*-isopropylidene-β-D-fructopyranose sulfamates (**2a** and **2b**); 2,3-*O*-[(1*R**)- and 2,3-*O*-[(1*R**)-1-hydroxymethylethylidene]-4,5-*O*-isopropylidene-β-D-fructopyranose sulfamates (**3a** and **3b**). The route to **2a** and **2b** was brief and straightforward, while that to **3a** and **3b** was more involved. In the latter case, the D-fructose bis-acetal **10** was benzylated and converted to a monoacetal dibenzoate (**14**) (50% yield), which was then transacetalized to give a mixture of 4,5-dibenzoyl-2,3-*O*-[(1*R**)- and 4,5-dibenzoyl-2,3-*O*-[(1*S**)-1-benzyloxymethylethylidene]-β-D-fructopyranose (**16a** and **16b**) (22%). The individual diastereomers were separated and processed via ester saponification, acetonation, sulfamoylation, and hydrogenolysis into **3a** (36%) and **3b** (27%). Structure **2b** was confirmed for one oxidative metabolite, but the other metabolite was found not to correspond with either **2a**, **3a**, or **3b**. On the basis of CI-MS and ^{1}H NMR data, a (2-hydroxy-1,4-dioxano)pyran structure, **4**, is proposed for this unidentified metabolite. © 1997 Published by Elsevier Science Ltd.

Keywords: Topiramate; Fructose derivatives; Metabolites

1. Introduction

Given the multiple etiologies of epilepsy, and our limited understanding about the mechanisms behind this disorder, the discovery of novel antiepileptic drugs is often an empirical exercise. We were fortunate to discover topiramate (**1**; Topamax®) [1–3], a novel sugar sulfamate derivative, and to demonstrate its antiepileptic efficacy through extensive clinical

Abbreviations: Bn, benzyl; Bz, benzoyl; TFA, trifluoroacetic acid

* Corresponding author. Fax: +1 215-628-4985.

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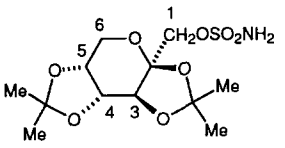
trials [4,5]. Topiramate is now available for therapeutic use in several worldwide markets. [2]

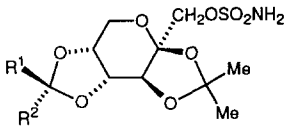
Metabolism studies of new drug substances are a necessary part of the drug development process. Oral administration of a drug to assorted species generally results in diverse metabolites, many of which are present at low levels in plasma, urine, and/or feces. After oral administration in several animal species, including humans, topiramate is excreted largely unchanged; however, some meaningful biotransformation of the original drug substance does occur. Metabolism studies were conducted to achieve an understanding of the route of excretion of topiramate and its metabolites, as well as to isolate, identify, and quantitate the metabolites [6]. According to mass spectral and proton NMR data, two of the metabolites resulted from monohydroxylation of the drug and were initially assigned structures **2** and **3**. However, this preliminary structural assignment required confirmation, particularly with respect to stereochemistry of the new stereocenter generated by metabolic hydroxylation, which was not evident from the analytical data. We report herein our synthetic work directed toward the stereoisomers of **2** and **3**, starting from natural D-fructose, which led to the assignment of **2b** to one metabolite and the rejection of **3a/3b** as possible structures for the other metabolite. We rationalize our data for the second metabolite in terms of unusual structure **4**, which could be derived via a molecular rearrangement of **3b** either in vivo or during isolation.

2. Results and discussion

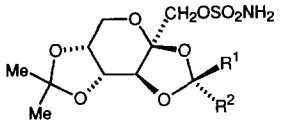
As many as six metabolic products from topiramate have been isolated from the plasma, urine, bile, and/or feces of various mammalian species (e.g., mice, rats, rabbits, dogs, and humans) [6]. In the case of canine and rat urine/fecal samples, we obtained three significant metabolites, **2**, **3**, and **5**, and one minor one, **6**, the structures of which had been assigned preliminarily on the basis of mass spectral and ^{1}H NMR data [6]. After administration of ^{14}C-topiramate, metabolites **2**, **3**, and **5** accounted for 10, 12, and 18% of the radioactive dose in the fecal extract from male rats and 12, 14, and 20% of the radioactive dose in the urine extract from dogs, respectively.



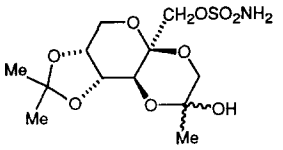
1 topiramate



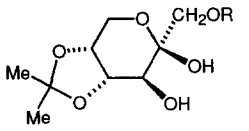
2a R^1 = Me, R^2 = CH_2OH
2b R^1 = CH_2OH, R^2 = Me



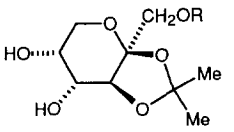
3a R^1 = Me, R^2 = CH_2OH
3b R^1 = CH_2OH, R^2 = Me



4



5 R = SO_2NH_2
7 R = H

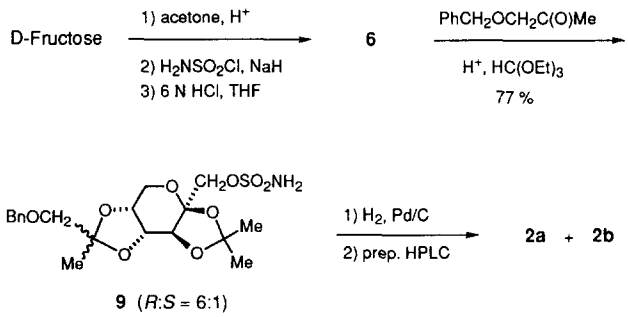


6 R = SO_2NH_2
8 R = H

Some of the metabolites were readily identified, such as **5** and **6**, which have lost an isopropylidene unit. In the case of **6**, the structure was confirmed by comparison with an authentic sample that we had prepared earlier [1,7], leaving the structure assignment for **5** quite apparent. However, it was not straightforward to establish the structures of the two oxidative metabolites, monohydroxylated on the methyl groups, because of the stereochemical issues involved. These compounds were tentatively assigned as **2** and **3**, without defining the stereochemistry, on the basis of the spectral data. We had to resort to independent chemical synthesis to verify the composition and establish the stereochemistry.

Synthesis of **2a** *and* **2b**.—The synthesis of **2a** and **2b** was fairly straightforward. The early stage involved protection of D-fructose with acetone under acidic conditions, sulfamoylation of the primary alcohol to give **1**, and selective deacetalization of the dioxolane ring at the 4,5-position to give **6** (Scheme 1). Reaction of **6** with benzyloxyacetone in the presence of triethyl orthoformate led to key intermediate **9**, as a mixture of *R* and *S* acetals in a 6:1 ratio.

[2] Topiramate was first approved for antiepileptic therapy in the United Kingdom in 1995, and is now approved for marketing in several other countries, including the United States of America.

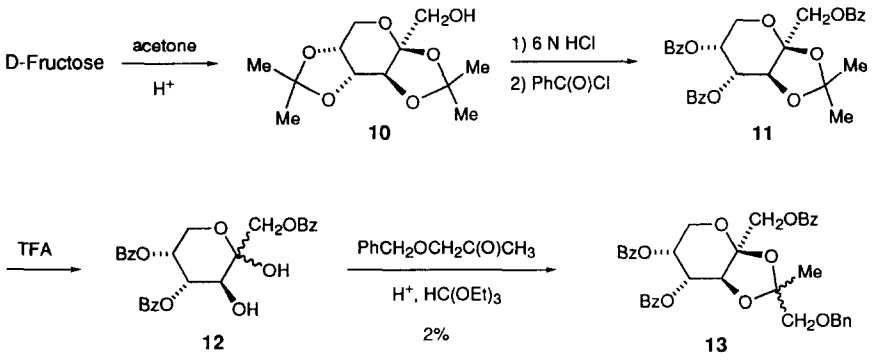


Scheme 1.

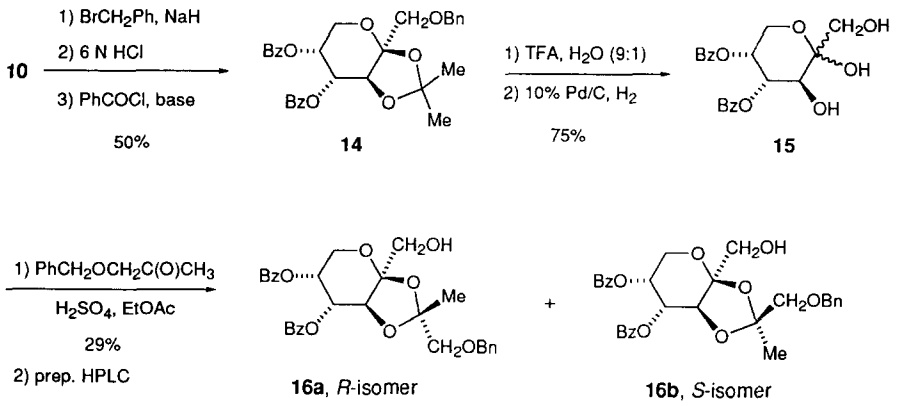
Debenzylation by hydrogenolysis and purification by HPLC afforded **2a** and **2b**, which were readily distinguished by their MS and ^{1}H NMR data. A salient NMR feature for making the stereochemical assignment was the observed nuclear Overhauser effect (NOE) on irradiation of the singular methyl group: for **2a** there was a pronounced NOE for Me-H-4–H-5, whereas for **2b** there was a NOE for Me-H-3–H-1. Compound **2b** was identical to the isolated metabolite on the basis of a chemical-ionization mass spectra (CI-MS) and ^{1}H NMR comparison, and **2a** did not correspond to the other monohydroxylated metabolite. Reference to a molecular model of topiramate [1] suggests that the biotransformed pro-*S* methyl group should be more sterically accessible to oxidative enzymes. While topiramate is orally effective in the maximal electroshock seizure (MES) test in rats and mice, with ED_{50} values of 12.8 and 40.9 mg/kg, respectively, 4 h after dosing [1–3], **2a** was just weakly active and **2b** was virtually inactive.

Synthesis of **3a** *and* **3b**.—The synthesis of **3a** and **3b** was much more elaborate, involving a total of 15 steps. For the purpose of synthetic feasibility, we chose to synthesize tribenzoate **11** from D-fructose, which would allow us to obtain **12** from D-fructose in only five steps. However, condensation of **12** with benzyloxyacetone was inauspicious, with only 2% of key intermediate **13** being isolated after a tedious purification process (Scheme 2). It appeared from several reactions that the C-1 benzoate group was sterically hindering a smooth transformation of **12** into **13**.

To circumvent this problem, fructose bis-acetal **10** was first benzylated at C-1 and then hydrolyzed selectively at the 4,5 dioxolane ring; the resulting diol was protected as dibenzoate **14** (Scheme 3). It is important to note that when **10** was subjected to acid hydrolysis the 4,5-isopropylidene protecting group was lost first; only at longer reaction times did complete hydrolysis to D-fructose occur. Since a bulky group at C-1 impeded condensation of the diol with benzyloxyacetone, we decided to treat **14** with a catalyst under a hydrogen atmosphere to yield the corresponding primary alcohol. However, to our amazement no reaction occurred even after 14 days. Ultimately, **15** was obtained by first hydrolyzing the 2,3-isopropylidene group and then conducting the hydrogenolysis. This outcome further supported our supposition that the protecting group on the C-1 primary alcohol interfered with 2,3-acetal formation. Reaction of **15** with benzyloxyacetone gave an isomeric mixture of **16** in 29% yield, which was subjected to preparative HPLC to give **16a** and **16b**. Each isomer was debenzoylated with base, protected at the 4,5-positions with 2,2-dimethoxypropane under acidic conditions, sulfamoylated, and debenzylated to afford **3a** and **3b** (Scheme 4). These two isomers were readily distinguished by their MS and ^{1}H NMR data. A salient feature for making the assignment was an NOE observed on irradiating the singular methyl



Scheme 2.

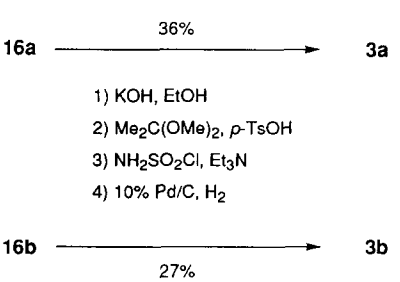


Scheme 3.

group: for **3a** there was a NOE for Me-H-6, whereas for **3b** there was a NOE for Me-H-1 (weak to H-3). Unfortunately, neither compound corresponded to the isolated metabolite (CI-MS and ^{1}H NMR comparison).

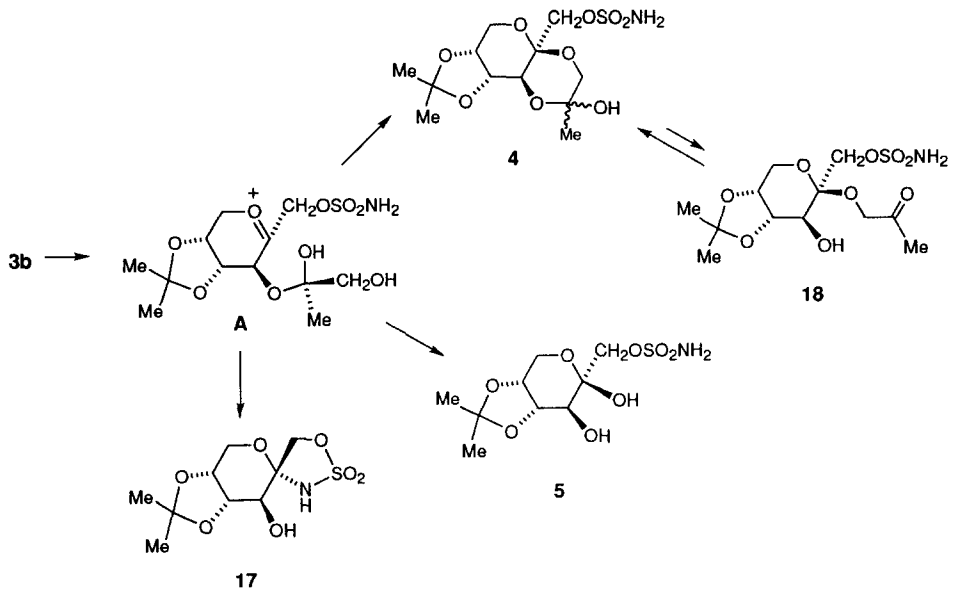
Structure of the unusual metabolite.—Chemical-ionization mass spectra (CI-MS) and fast-atom-bombardment mass spectra (FAB-MS) analyses of various metabolites of topiramate, isolated by column chromatography, HPLC, or TLC, have shown intense ammonium-adduct and sodium-adduct molecular ions, respectively, as well as informative fragment ions for elucidating structure [6] [3]. This is well exemplified for topiramate (**1**): CI-MS (NH_3) *m/z* (ion) 357 (MH_4^+), 340 (MH^+), 299 (MH_4^+–acetone, 100%), 282 (MH^+–acetone), 243 (MH^+–OSO_2NH_2), 241 (MH_4^+–2 acetone), 224 (MH^+–2 acetone), 185 (MH^+–acetone–OSO_2NH_2), 127 (MH^+–2 acetone–OSO_2NH_2), 113 (MH^+–2 acetone–$CH_2OSO_2NH_2$); FAB-MS (thioglycerol) *m/z* (ion, rel abund) 362 (MNa^+, 100%), 340 (MH^+, 70%), 324 (M^+–Me), 282 (MH^+–acetone), 264 (MH^+–acetone–H_2O), 217, 185 (MH^+–acetone–OSO_2NH_2), 127 (MH^+–2 acetone–OSO_2NH_2, 80%), 109. For isolated metabolite **2b**, the CI-MS showed an ammonium-adduct molecular ion (*m/z* 373) and FAB-MS showed a sodium-adduct molecular ion (*m/z* 378); characteristic fragment ions were also found: CI-MS *m/z* (ion, rel abund) 373 (MNH_4^+, 80%), 315 (MNH_4^+–acetone, 55%), 297 (MNH_4^+–acetone–H_2O, 30%), 238 (35%), 218 (MNH_4^+–acetone–H_2O–SO_2NH, 100%), 201 (MH^+–acetone–H_2O–SO_2NH, 90%), 183 (30%), 173 (35%), 127 (MH^+–2 ketones–OSO_2NH_2, 70%); FAB-MS *m/z* (ion, rel abund) 378 (MNa^+, 50%), 356 (MH^+, 25%), 324 (M^+–Me, 35%), 311 (50%), 224 (MH^+–2 ketones, 100%) [8].

For the unidentified metabolite, CI-MS and FAB-MS data were analogous for adduct molecular ions, but not for fragmentation patterns: CI-MS *m/z* (ion, rel abund) 373 (MNH_4^+, 35%), 356 (MH^+, 4%), 355 (MNH_4^+–H_2O, 5%), 338 (MH^+–H_2O, 10%), 299 (MNH_4^+–$C_3H_6O_2$, 45%), 282 (MH^+–$C_3H_6O_2$, 25%), 259 (MH^+–$HOSO_2NH_2$, 30%), 241 (MNH_4^+–2 ketones, 35%), 224 (MH^+–2 ketones, 35%), 220 (MNH_4^+–$\cdot O_2CCH_2OSO_2NH_2$, 55%), 203 (MH^+–$\cdot O_2CCH_2OSO_2NH_2$, 100%), 185 (MH^+–hydroxyacetone–OSO_2NH_2, 45%), 127 (MH^+–2 ketones–OSO_2NH_2, 80%); FAB-MS *m/z* (ion, rel abund) 378 (MNa^+, 90%), 356 (MH^+, 15%), 338 (MH^+–H_2O, 20%), 282 (60%), 239 (30%), 237 (40%), 217 (100%), 181 (30%) [8]. It is noteworthy that the CI-MS for **5** also showed strong peaks at 259 (45%), 224 (35%), 220 (60%), 203 (100%), and 127 (50%), which is consistent with a structure for the unidentified metabolite that can fragment similarly to **5**, such as **4**, or especially its tautomeric form, **18**. The ^{1}H NMR spectrum (CD_3OD) of the unusual metabolite has three methyl singlets at δ 1.32 (4,5 dioxolane ring), 1.42 (4,5 dioxolane ring), and 1.48 (dioxane ring), while that for topiramate has four singlets at δ 1.31



Scheme 4.

[3] EI-MS data for **1** and its analogues: see ref. [8].

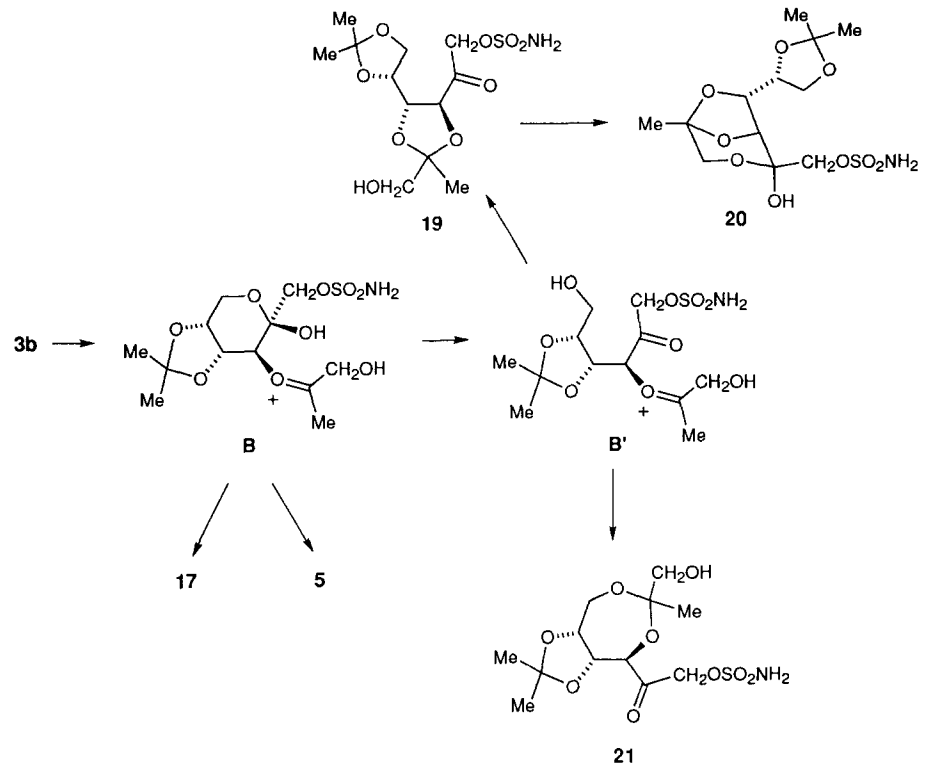


Scheme 5.

(4,5 fused dioxolane ring), 1.38 (4,5 dioxolane ring), 1.42 (2,3 dioxolane ring), and 1.50 (2,3 dioxolane ring), and that for **2b** has three singlets at δ 1.37, 1.41, and 1.51. [4] Clearly, it is the methyl group in topiramate that resonates at δ 1.31, the pro-*S* one on the 4,5 dioxolane ring, that is hydroxylated to give **2b**. For the unusual metabolite, the MS and NMR data indicate a hydroxyl group attached to one of the two isopropylidene units of topiramate, the one at the 2,3-position; however, since this metabolite is neither **2a**, **2b**, **3a**, nor **3b**, a different, less straightforward constitution must be considered. In canine and rat species, we suggest that hydroxylation of topiramate occurs at the more accessible methyl group of the 2,3-isopropylidene unit to furnish **3b**, but that this compound subsequently rearranges to furnish **4**.

Since the MS and ^{1}H NMR data for the unusual metabolite indicated a monohydroxylated monosaccharide sulfamate, we entertained diverse structural possibilities. Since a molecular model of topiramate [1] indicates that the two methyl groups on the 2,3-ring are similarly accessible to an enzyme (for addition of oxygen), one can presume that hydroxylation would occur on the pro-*S* methyl group of the 2,3-ring by analogy to the biotransformation of topiramate to **2b**. Assuming that **3b** might actually have formed in this manner, we analyzed potential acid-catalyzed rearrangement pathways (Schemes 5–7). One can envision **3b** generating three possible oxonium species **A**–**C**, two of which, **B** and **C**, might be prone to rearrange to species **B′** and **C′** by acetal interchange. Oxonium ion **A** could degrade to **17** or **5**, but more likely cyclize to **4**, which would be in equilibrium with its chain tautomer **18** (Scheme 5). Oxonium ion **B** could degrade to **17** [1] or **5**; however, if it converts to **B′**, then **19**, **20**, which seems to be strained, or dioxepane **21** could form (Scheme 6). Oxonium ion **C** could give **22** [1] or highly strained **23**; however, if it converts to **C′**, then **24** could be formed (Scheme 7). Of the reasonable options (**20** and **23** being excluded), **17** and **5** are definitely not consistent with the MS and NMR data, **19**, **21**, **22**, and **24** are probably inconsistent with the MS fragmentation data, which leaves **4**/**18** as the candidate structure. A reported example of a stable 2-methoxy-1-hydroxy-1,4-dioxane lends credence to this point of view [9]. As mentioned above, this formulation of the metabolite is also supported by the presence of key CI-MS fragments that correspond to those in 2,3-diol **5**. Our attempts to effect rearrangement of authentic **3b** to **4** under mild acid catalysis were unsuccessful. When **3b** was exposed to dilute HCl, a syrup was obtained that lost an isopropylidene group according to ^{1}H NMR data. Treatment of the syrup with dimethoxypropane under acidic conditions regenerated **3b**, and there was no evidence for the presence of **4**.

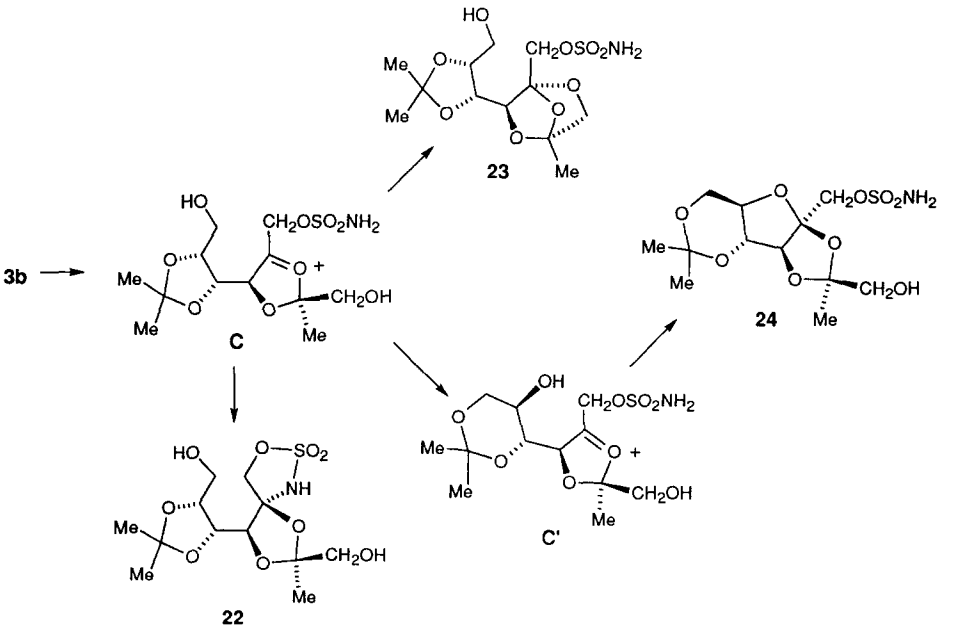
[4] Other ^{1}H NMR signals for **4** are consistent with this assignment: δ 3.43–3.57 (dd, 2, *J* 12 Hz, dioxane–CH_2), 3.70–3.95 (dd, 2, *J* 13 Hz, H-6), 4.10–4.16 (dd, 2, *J* 10 Hz, H-1), 4.25 (d, 1, *J* 7.6 Hz, H-5), 4.36 (d, 1, *J* 2.5 Hz, H-3), 4.65 (dd, 1, *J* 7.6 Hz, H-4).



Scheme 6.

3. Conclusion

We have synthesized compounds **2a**, **2b**, **3a**, and **3b**, in stereoisomerically pure form, to address a structural assignment problem with respect to the monohydroxylated metabolites of topiramate (**1**). Thus, we found that synthetic **2b** is identical with one of these metabolites; however, neither **2a**, **3a**, nor **3b**



Scheme 7.

is identical with the other monohydroxylated metabolite. Although a structure has yet to be precisely established, we tentatively propose structure **4** for this substance on the basis of spectroscopic data.

4. Experimental section

General procedures.—Chromatographic separations were carried out on a Waters Prep-500 HPLC equipped with two PrepPak cartridges (column: 47 × 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 determined on a Perkin–Elmer 241 polarimeter. TLC separations were conducted on 250-μm silica gel plates with visualization by iodine staining and by charring with 19:1 EtOH–H_2SO_4. ^1H NMR spectra, referenced to Me_4Si, were obtained at 400.13 MHz on a Bruker DMX-400 instrument or at 300 MHz on a Bruker AC-300 instrument (s = singlet; d = doublet; m = multiplet; br = broad). Fast-atom-bombardment mass spectra (FAB-MS) were recorded on a VG 7070E high-resolution mass spectrometer by using an argon beam at 7 kV and 2 mA of current in a thioglycerol matrix. Chemical-ionization mass spectra (CI-MS) were recorded by using a Hewlett–Packard 5989A single quadrupole mass spectrometer system with either NH_3 or CH_4 as a reagent gas. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

4,5-O-(1-Benzyloxymethylethylidene)-2,3-O-isopropylidene-β-D-fructopyranose sulfamate (R:S = 6:1) (**9**).—A mixture of benzyloxyacetone (15 g, 0.091 mol), concentrated H_2SO_4 (0.5 mL), triethyl orthoformate (10.7 g, 0.07 mol), and EtOH (10 mL) was stirred for 3 h, and then treated with a mixture of the fructopyranose sulfamate **6** (10 g, 0.03 mol) in 20 mL of THF. After stirring for 24 h, the mixture was neutralized with Na_2CO_3 (to pH 7), filtered, and concentrated under reduced pressure to a light-yellow syrup, which was purified by preparative HPLC (2:1 hexane–EtOAc) to give **9** (10.31 g, 77%) as a pale-yellow syrup: $[\alpha]_D^{25}$ −28.4° (*c* 1.00, MeOH); ^1H NMR ($CDCl_3$, 400 MHz): δ 1.35, 1.41, 1.54 (3 s, 9, Me), 3.41–3.47 (dd, 1, *J* 11 Hz, *S*-CHO), 3.52–3.59 (dd, 1, *J* 11 Hz, *R*-CHO), 3.81–3.93 (dd, 2, *J* 13 Hz, H-6), 4.23–4.28 (m, 2, H-1), 4.30–4.32 (d, 1, *J* 7.9 Hz, H-5), 4.35–4.37 (d, 1, *J* 2 Hz, H-3), 4.57–4.68 (dd, 1, *J* 7.6 Hz, H-4), 4.62–4.65 (d, 2, *J* 13 Hz, CH_2Ph), 5.05 (br s, 2, NH_2), 7.26–7.36 (m, 5, aromatic). Anal. Calcd for $C_{19}H_{27}NO_9S$: C, 51.23; H, 6.11; N, 3.14. Found: C, 51.28; H, 6.22; N, 3.26. ^1H NMR analysis indicated an *R*:*S* ratio of 5.6:1.

4,5-O-[(1R)-1-Hydroxymethylethylidene]-2,3-O-isopropylidene-β-D-fructopyranose sulfamate* (**2a**) *and 4,5-O-[(1S*)-1-hydroxymethylethylidene]-2,3-O-isopropylidene-β-D-fructopyranose sulfamate* (**2b**).—A mixture of **9** (6.7 g, 0.015 mol) and 10% Pd/C (5.3 g) in EtOH (70 mL) was shaken on a Parr apparatus under a hydrogen atmosphere for 24 h. After filtration, the solvent was removed in vacuo to give a thick colorless syrup (5.40 g), which was purified and separated by preparative HPLC (1:1 EtOAc–hexane) to give diastereomers **2a** (2.67 g), *R*-isomer, and **2b** (0.51 g), *S*-isomer, as solids: mp (**2a**) 106–108 °C; $[\alpha]_D^{25}$ −28.0° (*c* 1.00, MeOH); CI-MS *m/z* (ion, rel abund) 373 (MNH_4^+, 100%), 356 (MH^+, 7%), 324 (13%), 315 (27%), 297 (8%), 280 (8%), 218 (30%), 201 (45%), 200, (18%), 183 (13%), 173 (25%), 140 (18%), 127 (25%), 113 (17%), 97 (13%), 81 (21%), 74 (16%); ^1H NMR (Me_2SO-d_6, 400 MHz): δ 1.32, 1.42, 1.53 (3 s, 9, Me), 3.50–3.59 (pair of d, 2, *J* 12 Hz, CH_2OH), 3.73–3.76 (d, 1, *J* 13 Hz, H-6), 3.88–3.91 (d, 1, *J* 13 Hz, H-6), 4.10–4.22 (dd, 2, *J* 10 Hz, H-1), 4.31 (d, 1, *J* 7.6 Hz, H-5), 4.40 (d, 1, *J* 2.3 Hz, H-3), 4.65 (dd, 1, *J* 7.6 Hz, H-4), 7.20 (br s, 2, NH_2); NOE: Me-H-4–H-5 (none to H-3–H-1). Anal. Calcd for $C_{12}H_{21}NO_9S$: C, 40.56; H, 5.96; N, 3.94. Found: C, 40.61; H, 6.11; N, 3.83. Mp (**2b**) 136–140 °C; $[\alpha]_D^{25}$ −28.4° (*c* 0.78, MeOH); CI-MS *m/z* (ion, rel abund) 373 (MNH_4^+, 50%), 356 (MH^+, 65%), 324 (24%), 315 (43%), 297 (25%), 218 (64%), 201 (100%), 200 (36%), 173 (48%), 140 (25%), 127 (43%), 113 (26%), 97 (26%), 81 (39%), 74 (30%); ^1H NMR (Me_2SO-d_6, 400 MHz): δ 1.37, 1.41, 1.52 (3 s, 9, Me), 3.45 (m, 2, CH_2OH), 3.69–3.72 (d, 1, *J* 13 Hz, H-6), 3.85–3.88 (d, 1, *J* 13 Hz, H-6), 4.07–4.10 (d, 1, *J* 10 Hz, H-1), 4.15–4.18 (d, 1, *J* 10 Hz, H-1), 4.34–4.36 (m, 1, H-5), 4.37 (d, 1, *J* 2.5 Hz, H-3), 4.61 (m 1, OH), 4.76–4.78 (dd, 1, *J* 7.8 Hz, H-4), 7.25 (br s, 2, NH_2); NOE: Me-H-3–H-1 (none to H-4–H-5). Anal. Calcd for $C_{12}H_{21}NO_9S$: C, 40.56; H, 5.96; N, 3.94. Found: C 40.70; H, 6.05; N, 3.88.

1,4,5-Tri-O-benzoyl-2,3-O-isopropylidene-β-D-fructopyranose (**11**).—A mixture of 2,3-*O*-isopropylidene-β-D-fructopyranose (4.0 g, 18 mmol), **8** [10], obtained from fructose diacetal **10** [11], in CH_2Cl_2 (40 mL) was treated with pyridine (15 mL), and cooled to 0 °C. Benzoyl chloride (8.06 g, 57 mmol) was cautiously added. The mixture was allowed to warm to room temperature and then stirred for 18 h. It was poured into water and extracted with an addi-

tional amount of CH_2Cl_2. The combined extracts were washed twice with 1N HCl, dried (Na_2SO_4), and concentrated to a light-brown syrup (9.27 g), which was purified by preparative HPLC (2:1 hexane–EtOAc) to give an off-white solid (7.51 g). Recrystallization from ethanol gave the tribenzoate **11** as a white crystalline solid (5.10 g, 50%): mp 100–103 °C; $[\alpha]_D^{25}$ −2.2° (*c* 0.50, MeOH); CI-MS *m/z* 535 (MH^+).

1,4,5-Tri-O-benzoyl-α,β-D-fructopyranose (**12**).—A solution of **11** (1.0 g, 1.8 mmol) in 90% TFA (v/v, 10 mL) was stirred at room temperature for 30 min, and then concentrated in vacuo to give **12** as a solid (0.8 g, 90%): $[\alpha]_D^{25}$ −100.8° (*c* 1.00, MeOH); CI-MS *m/z* 476 (MH^+–OH).

1,4,5-Tri-O-benzoyl-2,3-O-(1-benzyloxymethylethylidene)-β-D-fructopyranose (**13**).—A mixture of benzyloxyacetone (0.6 g, 3.6 mmol), concentrated H_2SO_4 (0.11 g), and triethyl orthoformate (0.27 g, 1.8 mmol) in EtOH (0.25 mL) was stirred for 2 h at 50 °C, and then treated with the above solid **12** (0.25 g, 3.6 mmol). The reaction mixture was stirred at 50 °C for 6 h, cooled, and neutralized with anhydrous K_2CO_3. Solids were filtered and the filtrate was concentrated to a light-brown syrup of crude **13** (0.05 g), which was purified by preparative TLC (9:1 chloroform–EtOAc) to give a semi-pure syrup (8.0 mg, 2.5%; mixture of diastereomers).

4,5-Di-O-benzoyl-1-O-benzyl-2,3-O-isopropylidene-β-D-fructopyranose (**14**).—Sodium hydride (8.4 g, 0.21 mol, 60% oil dispersion) was added to a cold solution (−4 °C) of **10** (50 g, 0.19 mol) in dry DMF (200 mL). The solution was stirred for 30 min, and a mixture of benzyl bromide (32.9 g, 0.19 mol) in DMF (25 mL) was added dropwise. The mixture was allowed to warm to room temperature, stirred for 18 h, poured over ice, and extracted twice with EtOAc. The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated to a light-brown syrup (58.0 g, 89%). To a solution of this syrup (10 g, 0.29 mol) in THF (180 mL) was added 6N HCl (90 mL) and the mixture was stirred at 45 °C for 7 h. It was then cooled (5 °C), neutralized with Na_2CO_3 (pH 8), and filtered. Filtrate was treated with brine and the organic phase separated, dried over Na_2SO_4, and concentrated to a colorless syrup (7.18 g), which was purified by preparative HPLC (1:1 hexane–EtOAc) to give the 4,5-diol as a white solid (2.34 g, 26%). To a cold solution of this solid (20 g, 65 mmol) in pyridine (60 mL) and CH_2Cl_2 (106 mL) was added BzCl (22.8 g, 0.16 mol). The mixture was allowed to warm to room temperature, stirred for 24 h, washed (sequence: water, 1N NaOH, 1N HCl, and brine), and dried (Na_2SO_4). The solvent was removed under diminished pressure to give a syrup (31.1 g, 95%) that crystallized immediately. Recrystallization of 3.1 g of material from 95% EtOH gave **14** (1.7 g, 51%) as a light-yellow solid: mp 110–111 °C; $[\alpha]_D^{25}$ −11.0° (*c* 0.50, MeOH); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.45, 1.68 (2 s, 6, Me), 3.70–3.82 (dd, 2, *J* 9.5 Hz, H-1), 3.95–4.04 (dd, 1, *J* 13.0, 2.5 Hz, H-6), 4.22–4.32 (dd, 1, *J* 13.2, 2.5 Hz, H-6), 4.50–4.66 (pair of d, 2, *J* 12.0 Hz, CH_2Ph), 4.56 (m, 1, H-3), 5.5–5.62 (m, 1, H-5), 6.0 (m, 1, H-4), 7.3–8.0 (m, 15, aromatic); CI-MS *m/z* 519 (MH^+). Anal. Calcd for $C_{30}H_{30}O_8$: C, 69.49; H, 5.83. Found: C, 69.63; H, 5.71.

4,5-Di-O-benzoyl-α,β-D-fructopyranose (**15**).—A solution of **14** (1.0 g, 1.93 mmol) in 90% TFA (2 mL) was stirred at room temperature for 24 h, and solvents were then removed under diminished pressure to give a syrup (0.90 g, 97%), which was immediately dissolved in EtOH (20 mL), treated with 10% Pd/C (0.22 g), and shaken on a Parr apparatus under a hydrogen atmosphere for 3 h. The catalyst was filtered and the solvent removed under diminished pressure to give **15** as a syrup (0.69 g, 75%), which was unstable at room temperature and thus was used immediately in the next step.

4,5-Di-O-benzoyl-2,3-O-[(1R)-1-benzyloxymethylethylidene]-β-D-fructopyranose* (**16a**) *and 4,5-di-O-benzoyl-2,3-O-[(1S*)-1-benzyloxymethylethylidene]-β-D-fructopyranose* (**16b**).—A mixture of **15** (10.26 g, 0.026 mol) and benzyloxyacetone (22.54 g, 0.14 mol) was stirred until it was homogeneous, and concentrated H_2SO_4 (3.5 g) was added. The reaction was stirred at 35 °C for 24 h, cooled, treated with EtOAc, washed (water, then dilute $NaHCO_3$), dried (Na_2SO_4), and concentrated under diminished pressure to give a thin syrup (25.4 g), which was purified and separated by preparative HPLC (6:3:1 CH_2Cl_2–hexane–EtOAc) to give diastereomers **16a** and **16b** as syrups (10.6 g total; 29% yield; 4.2 g of *R*-isomer **16a** and 6.4 g of *S*-isomer **16b**). For **16a**: $[\alpha]_D^{25}$ −107.7° (*c* 0.50, MeOH); CI-MS *m/z* 535 (MH^+). For **16b**: $[\alpha]_D^{25}$ −41.8° (*c* 0.77, MeOH); CI-MS *m/z* 535 (MH^+). Anal. Calcd for $C_{30}H_{30}O_9$: C, 67.41; H, 5.66. Found (**16a**): C, 67.96; H, 5.70. Found (**16b**): C, 67.89; H, 6.46.

2,3-O-[(1R)-1-Hydroxymethylethylidene]-4,5-O-isopropylidene-β-D-fructopyranose sulfamate* (**3a**).—A mixture of **16a** (4.2 g, 7.8 mmol) and KOH (2 g, 36 mmol) in EtOH (40 mL) was refluxed for 2 h, cooled, and treated cautiously with 6N ethanolic HCl

(pH 7). The salts were filtered and the filtrate was concentrated under diminished pressure to give a syrup, which was purified by preparative HPLC (6:3:1 CH_2Cl_2–hexane–EtOAc) to give the triol as a light-yellow wax (1.23 g). To a mixture of this wax (0.80 g, 2.4 mmol) in 2,2-dimethoxypropane (10 mL) was added *p*-toluenesulfonic acid (0.11 g). The mixture was stirred for 24 h, neutralized with Na_2CO_3 (to pH 8), and filtered. The filtrate was concentrated in vacuo to give the 4,5-protected adduct as a light-yellow syrup (0.94 g). A cold solution of this syrup (0.73 g, 2.0 mmol) in dry DMF (10.0 mL) was treated with Et_3N (0.54 g, 5.0 mmol), stirred for 20 min, and treated with sulfamoyl chloride (0.63 g, 5.0 mmol). The mixture was stirred at room temperature for 2.5 h, poured over ice, and extracted with EtOAc. The organic extract was washed with dilute $NaHCO_3$, brine, and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the sulfamate as a colorless syrup (0.62 g, 89%). A mixture of this syrup (0.42 g, 0.94 mmol) in EtOH (30 mL) was treated with 10% Pd/C (0.40 g) and hydrogenated with a Parr apparatus for 18 h. The catalyst was filtered and the solvent evaporated under diminished pressure to give a pale-yellow syrup (0.26 g), which was purified by preparative TLC (2:1 EtOAc–hexane) to give **3a** as a hydrated white foam (82 mg, 24.5%): $[\alpha]_D^{25}$ −64.6° (*c* 0.33, MeOH); CI-MS *m/z* (ion, rel abund) 373 (MNH_4^+, 100%), 356 (MH^+, 2%), 299 (50%), 282 (14%), 259 (11%), 241 (12%), 220 (17%), 203 (10%), 202 (17%), 185 (6%), 160 (6%), 144 (21%), 127 (19%), 74 (12%); ^1H NMR ($CDCl_3$, 400 MHz): δ 1.27, 1.36, 1.43 (3 s, 9, Me), 3.35–3.45 (pair of d, 2, *J* 12 Hz, CH_2OH), 3.84–3.87 (d, 1, *J* 9.0 Hz, H-1), 3.89–3.93 (d, 1, *J* 13.5 Hz, H-6), 4.13–4.15 (d, 1, *J* 13.3 Hz, H-6), 4.23–4.25 (d, 1, *J* 9.0 Hz, H-1), 4.31–4.32 (dd, 1, *J* 5.4, 2.5 Hz, H-5), 4.40 (dd, 1, *J* 7.6 Hz, H-4), 4.45 (d, 1, *J* 7.6 Hz, H-3), 5.30 (br s, 2, NH_2); NOE: Me-H-6 (none to H-3). Anal. Calcd for $C_{12}H_{21}NO_9S \cdot 0.5\ H_2O$: C, 39.56; H, 6.08; N, 3.84; H_2O, 2.47. Found: C, 39.69; H, 6.02; N, 3.84; H_2O, 2.60.

2,3-O-[(1S)-1-Hydroxymethylethylidene]-4,5-O-isopropylidene-β-D-fructopyranose sulfamate* (**3b**).—A mixture of **16b** (6.4 g, 11.9 mmol) and KOH (3.25 g, 58 mmol) in ethanol (70 mL) was refluxed for 2 h, cooled, treated with 6N ethanolic HCl (to pH 7), and filtered. The filtrate was concentrated under diminished pressure to give a syrup, which was purified by preparative HPLC (10:1 EtOAc–MeOH) to give the triol as a thick colorless syrup (0.69 g). By the method discussed for the synthesis of **3a**, a mixture of this triol (0.65 g, 2.0 mmol), 2,2-dimethoxypropane (8.0 mL), and *p*-toluenesulfonic acid (0.16 g) was reacted to give the 4,5-protected sugar as a brown syrup (0.58 g). To a cold solution of this syrup 0.20 g (0.50 mmol), in DMF (3.0 mL), was added Et_3N (0.15 g,1.4 mmol) and sulfamoyl chloride (0.18 g, 1.4 mmol) to give 0.17 g (70%) of the title sulfamate, a waxy solid. A mixture of this sulfamate (0.11 g, 0.25 mmol) and 10% Pd/C (0.15 g) in EtOH (10 mL) was hydrogenated in a Parr apparatus for 24 h and filtered. The solvent was evaporated under diminished pressure to give a light-yellow syrup (31.0 mg), which was purified by preparative TLC (2:1 EtOAc–hexane) to give **3b** as a colorless syrup (14 mg, 17%): $[\alpha]_D^{25}$ −27.4° (*c* 1.00, MeOH); CI-MS *m/z* (ion, rel abund) 373 (MNH_4^+, 85%), 356 (MH^+, 2%), 356 (3%), 338 (105), 299 (45%), 282 (45%), 276 (8%), 258 (27%), 241 (36%), 224 (8%), 203 (10%), 202 (41%), 185 (20%), 169 (29%), 160 (38%), 144 (63%), 143 (50%), 127 (100%), 109 (62%), 81 (29%), 74 (88%); ^1H NMR ($CDCl_3$, 400 MHz): δ 1.36, 1.38, 1.55 (3 s, 9, Me), 3.46–3.55 (pair of d, 2, *J* 12 Hz, CH_2OH), 3.85 (d, 1, *J* 9.0 Hz, H-1), 3.95 (d, 1, *J* 13.5 Hz, H-6), 4.20 (dd, 1, *J* 13.5, 2.5 Hz, H-6), 4.25 (d, 1, *J* 9.0 Hz, H-1), 4.34 (dd, 1, *J* 5.4, 2.5 Hz, H-5), 4.38 (dd, 1, *J* 7.6 Hz, H-4), 4.50 (d, 1, *J* 7.6 Hz, H-3), 5.20 (br s, 2, NH_2); NOE: Me-H-1 (weak to H-3; none to H-6). Anal. Calcd for $C_{12}H_{21}NO_9S$: C, 40.56; H, 5.96; N, 3.94. Found: C, 39.92; H, 5,75; N, 3.70.

Procedure used for the isolation of metabolites of topiramate (**1**).—The following description of the isolation of two topiramate metabolites, **2b** and **4**, is representative of the standard conditions employed. Urine samples (0–24 h) from Sprague–Dawley rats (90 mg/kg oral dose) or beagle dogs (40 mg/kg oral dose) were extracted with EtOAc and each extract was evaporated to dryness in vacuo. The residue was dissolved in MeOH and separated either by column chromatography (neutral alumina) with hexane, CH_2Cl_2, and CH_2Cl_2–MeOH mixtures as eluents or by HPLC (C18 column) with MeOH and water containing 0.2% NH_4OAc as eluents. Fractions were further separated by TLC (silica gel) with 2:5 hexane–EtOAc to obtain metabolites **2b** and **4** (extracted from the plate with 9:1 CH_2Cl_2–MeOH–EtOAc.

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