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HIGHLY STEREOSELECTIVE SYNTHESIS OF SUBSTITUTED HYDRINDANES RELATED TO THE ANTIEPILEPTIC DRUG TOPIRAMATE

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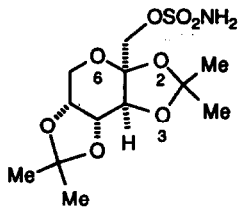
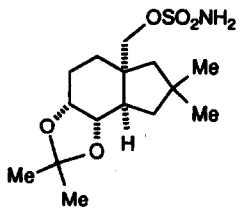
Summary: Multistep syntheses of two "carbocyclic" analogues **2** and **3** of topiramate (**1**) were effected with excellent stereocontrol. Two key reactions employed were: deoxygenation-rearrangement of an enone with *p*-tosylhydrazine and catecholborane (**14** --> **15** and **5** --> **7**) and face-selective vicinal dihydroxylation with OsO_4 (viz. **15** --> **16** and **8** --> **9**).

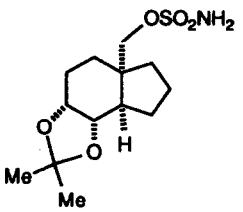
Topiramate is a promising antiepileptic drug with a novel sugar sulfamate structure.[1] The sugar unit comprises a D-fructopyranose system, the pyran ring of which adopts a skew (twist-boat) conformation in solution and the solid state.[1a] In our structure-function studies with this series, we were intent on evaluating the significance of the various "sugar-associated" oxygen atoms on C_1 through C_6. Thus, one of our objectives became replacement of oxygen atoms O_2, O_3, and O_6 with methylene groups, as depicted in structure **2**. We report in this Letter a highly stereoselective synthesis of hydrindane derivatives **2** and **3**.[2]



1 (topiramate)



2

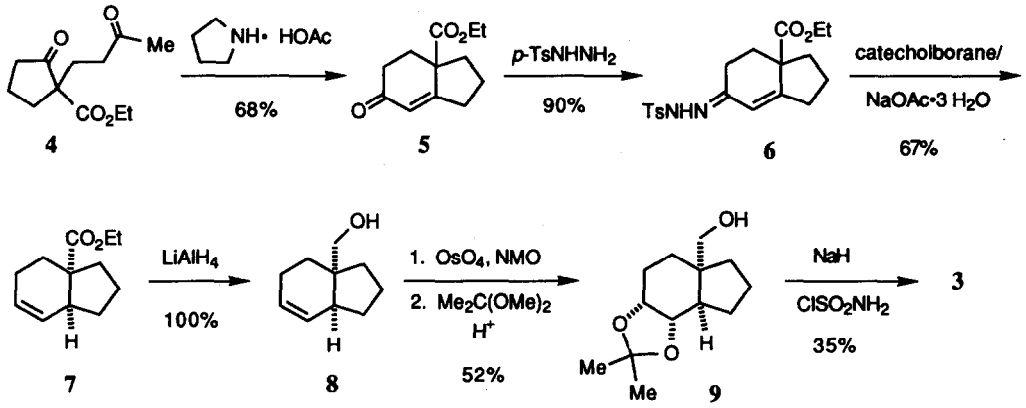


3

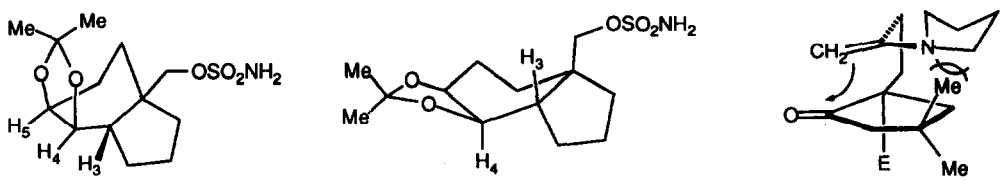
For the purpose of synthetic simplicity, we first elected to study a model system devoid of one set of gem-dimethyl groups. We envisioned construction of the requisite hydrindane skeleton with an angular carbalkoxy group by aldol cyclization/dehydration (viz. **4** --> **5**),[3] according to known procedures for preparing related enones bearing an angular methyl group.[4a,b] Enone **5** was formed conveniently and in good yield by using a variant of existing methodology.[4b,5] Thus, treatment of **4**[3] with pyrrolidinium acetate in ethyl ether followed by acidic workup afforded **5**.

A key transformation in our synthetic strategy was the deoxygenation-rearrangement of **5** to **7** with control of stereochemistry at the ring juncture.[6a,b] Although initial experiments with $NaBH_3CN$ as the reducing agent resulted in low yields,[6a,b] the use of catecholborane proved rewarding.[7] This procedure furnished the desired cis-fused hydrindane stereochemistry exclusively because the hydride was selectively delivered to the beta face of

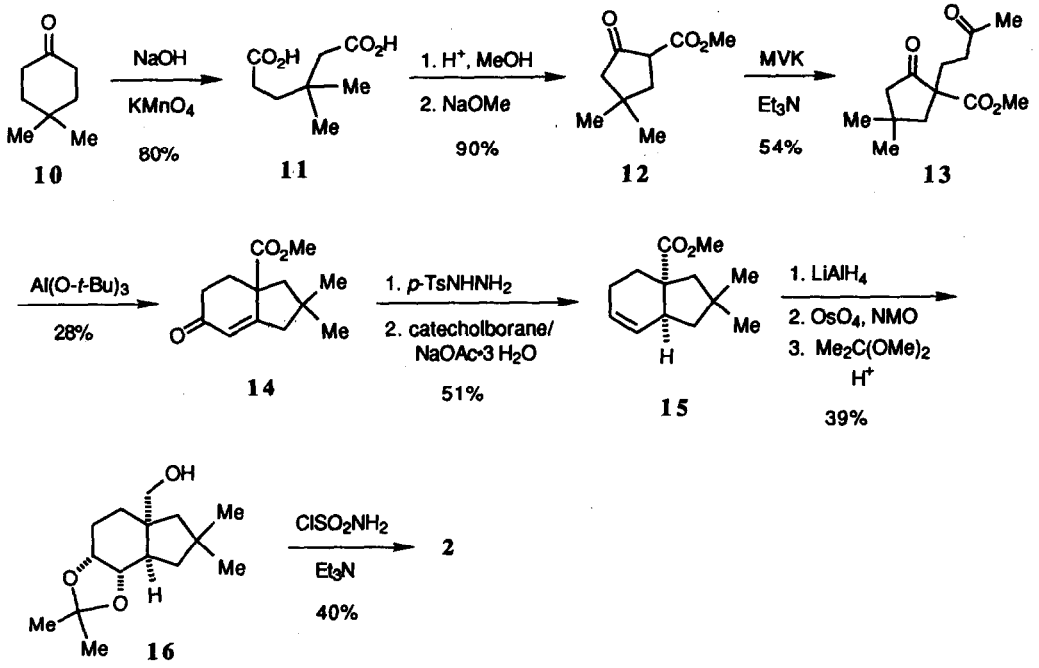
the C=N group in **6**, and the intermediate α-diazene decomposed with intramolecular, suprafacial transfer of hydrogen to the alpha face, as expected.[8] Although ^{1}H NMR analysis supported structure **7**, the ring juncture stereochemistry could not be assigned definitively. Therefore, we opted to complete the synthesis and carry out an X-ray analysis on the final product (vide infra). Stereoselective vicinal dihydroxylation of **7** with osmium tetroxide and *N*-methylmorpholine *N*-oxide (NMO)[9] was successful, but the product mixture contained an inseparable by-product. Consequently, we reduced ester **7** to alcohol **8** for subsequent osmylation. Osmylation and acetonide formation afforded **9** with high stereoselectivity (>95%). Sulfamoylation of **9** then produced model target **3**, which was chromatographed (flash column, silica gel: CH_2Cl_2-AcOEt, 9:1) and recrystallized from ethyl acetate to give analytically pure material in 35% yield (mp 168-170°C).[10]



Target **3** was closely examined by 360-MHz 2D COSY ^{1}H NMR to establish its relative stereochemistry and its conformation in C_6D_6 solution. Thus, we derived the following parameters: δ 0.82-0.87 (m, 1H), 0.94-1.00 (m, 1H), 1.18-1.35 (overlapping 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 (1/2 of AB q, 1H, J = 9.1 Hz), 3.95-4.00 (m, 2H), 4.09 (1/2 of AB q, 1H, J = 9.1 Hz). Analysis of the observed coupling between H_3 and H_4 served to distinguish between the chair and skew conformers **I** and **II**, respectively. In conformer **I**, the dihedral angle between H_3 and H_4 is approximately 50°, while the angle in **II** is approximately 180°. Since the observed vicinal coupling of 2.4 Hz is more consistent with the smaller dihedral angle, we have assigned the skew (or twist boat) conformer **I**. A single-crystal X-ray analysis (Figure 1) confirmed the stereochemistry and also illustrated the skew conformation in the solid state, similar to that reported for **1**.[1a]



With **3** in hand, we sought to apply this reaction sequence to obtain **2**. Cyclohexanone **10**[11] was oxidized (via the enol form) to diacid derivative **11**,[12] which was esterified and cyclized to the requisite cyclopentanone ester **12**.[13] Reaction of **12** with methyl vinyl ketone afforded **13**; however, attempted cyclization with pyrrolidinium acetate (as above) failed to provide enone **14**. The reluctance of **13** to undergo cyclization under these conditions is curious in light of the comparative ease with which **5** was formed from **4** under identical conditions. Apparently, the gem-dimethyl grouping causes an unfavorable steric interaction in the transition state involving alignment of the enamine side chain and the carbonyl of the cyclopentane, as depicted in structure **III**. Fortunately, use of Al(O-*t*-Bu)$_3$ furnished **14**, albeit in moderate yield.[3] In any event, **14** was converted by the developed methodology to target **2**, which was chromatographed (flash column, silica gel: CH_2Cl_2-CH_3OH, 95:5) and recrystallized from ethyl acetate to give analytically pure material (mp 152-154°C).[10] ^{1}H NMR data supported the stereochemical assignment and skew conformation here, as well. ^{1}H NMR ($CDCl_3$/DMSO-d_6, 400 MHz): δ 1.07 (s, 3H), 1.04 (s, 3H), 1.30 (s, 3H), 1.32-1.42 (m, 2H), 1.40 (1/2 of AB q, 1H, J = 14.0 Hz), 1.47 (s, 3H), 1.58-1.67 (m, 4H), 1.84 (1/2 of AB q, 1H, J = 14.0 Hz), 2.31-2.36 (m, 1H), 3.97/4.20 (AB q, 2H, J = 9.0 Hz), 4.25 (m, 2H), 6.54 (br s, 2H).[14]



The hydrindane nucleus is contained in many important classes of natural products, such as terpenes and steroids. Consequently, there has been a long-standing interest in the stereocontrolled synthesis of various hydrindane skeletons.[15] The route described herein is a useful addition to existing methodology for the construction of cis-hydrindanes. In particular, our method affords stereoselective positioning of a functionalized

angular substituent such as a carbalkoxy group, which is rarely addressed in the numerous methods available.[2,3,16] Furthermore, the stereofacial bias inherent in **7** and **15** should allow further elaboration of the hydrindane skeleton with a high degree of stereoselectivity.

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References and Notes

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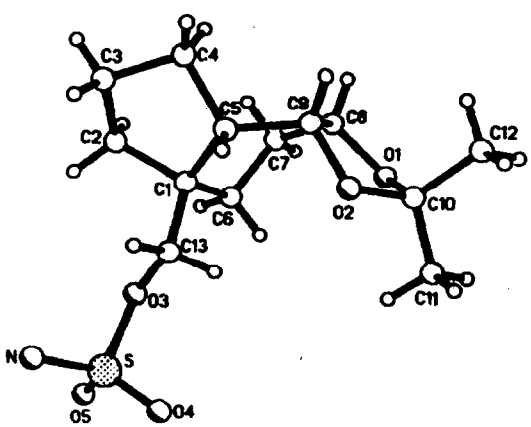

Figure 1.

Molecular structure of **3** from X-ray analysis.

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