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Synthesis of a Sulfonium Ion Analogue of the Glycosidase Inhibitor Swainsonine

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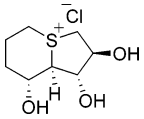
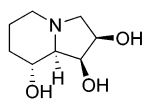


The synthesis of a bicyclic sulfonium ion analogue of a naturally occurring indolizidine alkaloid, swainsonine, in which the bridgehead nitrogen atom is replaced by a sulfonium ion, has been achieved by a multistep synthesis starting from (2*S*,3*S*,4*R*)-2,3-dibenzyloxy-4-formaldehyde-thiolane. The synthetic strategy relies on the intramolecular displacement of a leaving group on a pendant acyclic chain by a cyclic thioether. This bicyclic sulfonium salt provides a candidate with which to further probe the hypothesis that a sulfonium salt carrying a permanent positive charge would be an effective glycosidase inhibitor.

Cell surface oligosaccharides play an important role in intercellular recognition processes, and their modification has been implicated in disease states such as cancer.[1−7] Inhibition of the glycosidase enzymes involved in oligosaccharide processing of glycoproteins by natural or synthetic inhibitors might lead to therapeutic strategies for the treatment of viral infections, cancer, and other disorders.[3,4] For instance, swainsonine (**1**), a plant-derived indolizidine alkaloid, is an inhibitor of Golgi α-mannosidase II (GMII), a key enzyme in the N-glycosylation pathway, has been shown to reduce tumor mass in human patients with advanced malignancies, and is a potential drug therapy for patients suffering from breast, liver, and lung cancer and other malignancies.[8−10] Naturally occurring glycosidase inhibitors of the indolizidine alkaloid class, such as swainsonine (**1**) and castanospermine (**2**), are postulated to mimic the shape and charge of the oxacarbenium-like transition state for the enzyme-catalyzed hydrolysis reaction, thus making them good glycosidase inhibitors.[11,12] It is proposed that such inhibitors carry a positive charge at physiological pH, thus providing the stabilizing electrostatic interactions between the inhibitor and the carboxylate residues in the enzyme active site.[13]

An alternative means of achieving the required charge state to provide such electrostatic interactions would be with compounds that bear a permanent positive charge at a suitable position, for example, with compounds that bear a positively charged sulfur atom. Thus, we have described the synthesis, free and enzyme-bound conformations, and glycosidase inhibitory activity (albeit weak) of a sulfonium ion analogue (**3**) of castanospermine (**2**).[14,15] This concept was also exploited by Siriwardena and co-workers,[16−18] who have recently reported the synthesis of the sulfonium salt **4**, a potent inhibitor of several mannosidases with selectivity greater than that of swainsonine (**1**).[18]



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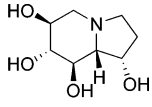

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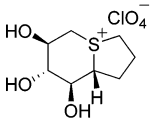

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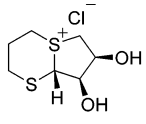

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In addition, the discovery of a new class of glycosidase inhibitors, namely, salacinol (**5**) and kotalanol (**6**) from *Salacia reticulata*, with intriguing inner-salt sulfonium sulfate structures[19−21] has led to significant synthetic efforts to derive

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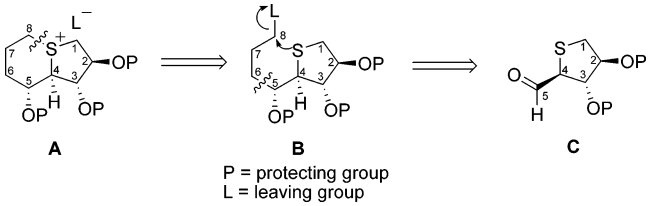
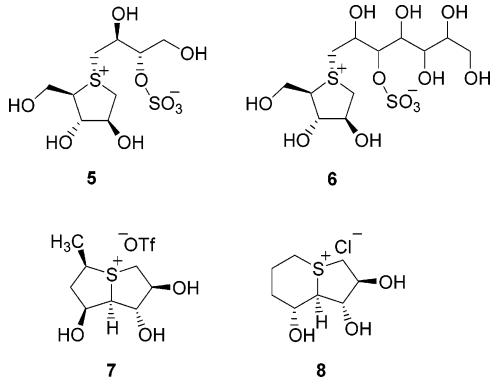
SCHEME 1



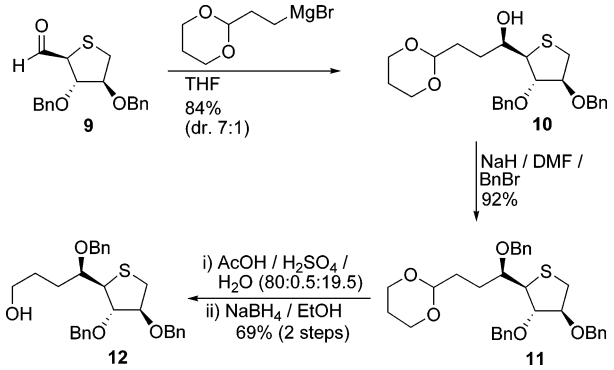
sulfonium salts with potential glycosidase inhibitory activities.[22−29] The 1,4-anhydro-4-thio-D-arabinitol moiety with the positive charge at the sulfur atom is postulated to bind to glycosidase enzymes by mimicry of the shape and charge of the oxacarbenium ion transition state in the glycosidase-mediated hydrolysis reaction.[30] It thus appears that even Nature has exploited sulfonium ions for glycosidase inhibition, and it is therefore of interest to examine sulfonium ion analogues of the known nitrogen-based glycosidase inhibitors as candidates with increased potency and selectivity. Accordingly, we have recently reported the synthesis of a sulfonium ion analogue (**7**)[31] of australine, and we report herein the synthesis of the sulfonium ion analogue (**8**) of swainsonine (**1**) as a potential glycosidase inhibitor. We note that compound **8** also differs from swainsonine (**1**) in the stereochemistry at C-3.



Retrosynthetic analysis of the bicyclic sulfonium salt **A** indicates that it could be synthesized by an intramolecular displacement of a suitable leaving group on a pendant side chain by a cyclic thioether (Scheme 1). The key intermediate **B** could, in turn, be synthesized from **C**.

Scheme 2 outlines the synthesis of the alcohol **12**, corresponding to **B**, which was synthesized, in turn, from the

SCHEME 2



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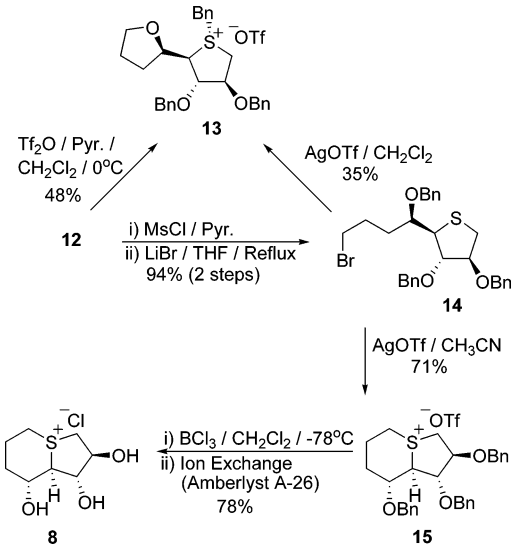

aldehyde **9**[31] (corresponding to **C**). Treatment of **9** with a freshly prepared Grignard reagent from the reaction of 2-(2-bromoethyl)-1,3-dioxane and magnesium furnished compound **10** as a 7:1 mixture of diastereomers. Compound **10** was isolated by crystallization, and after cyclization, it was deduced that compound **10** had the *R* configuration at C-5. The secondary hydroxyl group at C-5 was protected as a benzyl ether to give compound **11**. Finally, the 1,3-dioxane protecting group was hydrolyzed to give the corresponding aldehyde that was subsequently reduced using $NaBH_4$ to give **12**.

Initially, we anticipated that compound **15** could be synthesized directly from **12** by converting the hydroxyl group at C-8 to a triflate moiety, which could be displaced by the cyclic thioether. The reaction did not proceed as planned, and compound **13** was the only sulfonium salt that was isolated (Scheme 3). Presumably, the primary hydroxyl group at C-8 of compound **12** was converted to the corresponding triflate and then the oxygen atom at C-5 attacked C-8 faster than the thioether. Subsequent attack by the thioether on the benzyl group at C-5 would then yield **13**. The stereochemistry at the sulfonium ion center of compound **13** was assigned with the aid of 1D-NOESY experiments, which showed a correlation between H-4 and $^{+}SCH_2Ph$, suggesting that the benzyl group at the S^{+} center and the C-4 substituent were *trans* to each other. Treatment of **12** with methanesulfonyl chloride furnished the corresponding sulfonate ester, which was subsequently treated with LiBr to

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give the bromide **14**. In contrast to the tosylate analogue,[32] compound **14** did not undergo spontaneous cyclization to form the desired bicyclic sulfonium salt. Treatment of compound **14** with AgOTf in CH_2Cl_2 to promote cyclization gave the undesired product **13** once again. However, when the same reaction was carried out using CH_3CN as solvent, the reaction proceeded smoothly to give the desired sulfonium salt **15** as a stable, colorless oil. Compound **15** was remarkably stable even after long-term storage at room temperature. The ring junction of this bicyclic compound **15** was *cis* as expected because of the strain in the *trans* isomer, in agreement with the work of Izquierdo and co-workers.[32] The stereochemistry was further confirmed with the aid of 1D-NOESY experiments, which showed a correlation between H-3 and H-8ax, and the configuration at C-5 of compound **15** was also assigned by means of a 1D-NOESY experiment, which showed a correlation between H-3 and H-5; the stereochemistry of compound **10** was thus assigned by inference. The benzyl protecting groups were removed with boron trichloride at −78 °C to give the desired bicyclic sulfonium salt **8**. During the course of deprotection, some of the triflate counterion was exchanged with the chloride ion. Hence, the deprotected bicyclic sulfonium salt was treated with Amberlyst A-26 (chloride form) to completely exchange the triflate counterion with chloride ion.

In conclusion, the preparation of **8**, a bicyclic sulfonium ion analogue of the glycosidase inhibitor swainsonine (**1**), has been achieved.

Experimental Section

Procedure for the Synthesis of (2*S*,3*S*,4*R*,5*R*)-2,3,5-Tribenzyloxy-*cis*-1-thioniabicyclo[4.3.0]nonane Triflate (15). A solution of compound **14** (110 mg, 0.20 mmol) in CH_3CN (4 mL) was treated with AgOTf (104 mg, 2 equiv) for 20 h at ambient temperature. The solvent was removed and the crude product was purified by flash chromatography [CH_2Cl_2/MeOH, 1:0 to 20:1] to give compound **15** as a colorless oil (88 mg, 71%): $[\alpha]_D$ −14.40° (*c* 0.75, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 7.29−7.03 (m, 15H, Ar), 4.53 and 4.34 (2d, each 1H, $J_{a,b}$ = 11.5 Hz, C*H*$_2$Ph), 4.51 and 4.35 (2d, each 1H, $J_{a,b}$ = 12.1 Hz, C*H*$_2$Ph), 4.49 (m, 1H, H-2), 4.47 and 4.43 (2d, each 1H, $J_{a,b}$ = 12.0 Hz, C*H*$_2$Ph), 4.25 (dd, 1H, $J_{2,3}$ = 3.8 Hz, $J_{3,4}$ = 7.8 Hz, H-3), 4.04 (dd, 1H, $J_{4,5}$ = 4.4 Hz, H-4), 3.89 (dd, 1H, $J_{1a,1b}$ =14.8 Hz, $J_{1a,2}$ = 6.6 Hz, H-1a), 3.76 (ddd, 1H, $J_{5,6eq}$ = 4.9 Hz, $J_{5,6ax}$ = 1.9 Hz, H-5), 3.66 (dd, 1H, $J_{1b,2}$ = 3.0 Hz, H-1b), 3.61 (m, 1H, H-8eq), 3.29 (ddd, 1H, $J_{7ax,8ax} = J_{8ax,8eq}$ = 12.8 Hz, $J_{7eq,8ax}$ = 3.6 Hz, H-8ax), 1.92 (m, 1H, H-7ax), 1.74 (ddddd, 1H, J_{7ax7eq} = 15.3 Hz, $J_{6eq,7eq} = J_{6ax,7eq} = J_{7eq,8eq}$ = 4.1 Hz, H-7eq), 1.60 (dddd, 1H, $J_{6ax,6eq}$ = 13.9 Hz, $J_{6eq,7ax}$ = 4.4 Hz, H-6eq), 1.34 (dddd, 1H, $J_{6ax,7ax}$ = 11.7 Hz, H-6ax). ^{13}C NMR ($CDCl_3$): δ 137.0, 136.6, 136.4 (3C$_{ipso}$), 130.0−128.2 (15C$_{Ar}$), 120.9 (q, 1C, $J_{C,F}$ = 318.8 Hz, OTf), 84.8 (C-3), 83.6 (C-2), 72.9, 72.7, 71.0 (3*C*H$_2$Ph), 69.0 (C-5), 55.4 (C-4), 43.9 (C-1), 35.4 (C-8), 23.3 (C-6), 16.7 (C-7). MALDI-TOF MS: *m*/*e* 460.99 (M^+ − OTf). Anal. Calcd for $C_{30}H_{33}F_3O_6S_2$: C, 59.00; H, 5.45. Found: C, 58.92; H, 5.49.

Procedure for the Synthesis of (2*S*,3*S*,4*R*,5*R*)-2,3,5-Trihydroxy-*cis*-1-thioniabicyclo[4.3.0]nonane Triflate (8). BCl_3 gas was bubbled vigorously through a solution of **15** (100 mg, 0.16 mmol) in CH_2Cl_2 (6 mL) at −78 °C under N_2 atmosphere for 10 min. The mixture was stirred at −78 °C for 2 h and a stream of dry air was blown vigorously over the solution to remove excess BCl_3. The reaction was quenched with MeOH (2 mL) and the solvent was removed. The residue was coevaporated with MeOH (2 × 2 mL) and then washed with CH_2Cl_2 (2 × 2 mL) to give a white solid. The solid was dissolved in MeOH (5 mL) and a freshly washed ion-exchange resin (Amberlyst A-26 (chloride form), 100 mg) was added. The mixture was stirred at room temperature for 1 h and filtered. The filtrate was concentrated and recrystallized from MeOH:CH_2Cl_2 to give compound **8** as white crystals (29 mg, 78%): mp 195−197 °C; $[\alpha]_D$ − 38.00° (*c* 0.45, CH_3OH). ^{1}H NMR (CD_3OD): δ 4.49 (dd, 1H, $J_{2,3}$ = 6.0 Hz, $J_{3,4}$ = 8.6 Hz, H-3), 4.42 (m, 1H, H-5), 4.37 (ddd, 1H, $J_{1a,2}$ = 7.4 Hz, $J_{1b,2}$ = 5.9 Hz H-2), 3.86 (dd, 1H, $J_{1a,1b}$ = 13.8 Hz, H-1a), 3.69 (dd, 1H, $J_{4,5}$ = 4.3 Hz, H-4), 3.58 (ddd, 1H, $J_{8ax,8eq}$ = 12.3 Hz, $J_{7ax,8eq} = J_{7eq,8ax}$ = 4.0 Hz, H-8eq), 3.52, (ddd, 1H, $J_{7eq,8ax}$ = 3.6 Hz, $J_{7ax,8ax}$ = 12.1 Hz, H-8ax), 3.18 (dd, 1H, H-1b), 2.19 (ddddd, 1H, $J_{6ax,7ax}$ = 11.9 Hz, $J_{7ax,7eq}$ = 15.4 Hz, $J_{6eq,7ax}$ = 3.6 Hz, H-7ax), 2.06−1.81 (m, 3H, H-6ax, H-6eq, H-7eq). ^{13}C NMR (CD_3OD): δ 78.0 (C-3), 77.2 (C-2), 62.4 (C-5), 59.3 (C-4), 44.1 (C-1), 36.7 (C-8), 25.7 (C-6), 16.2 (C-7). MALDI-TOF MS: *m*/*e* 191.22 (M^+ − Cl). Anal. Calcd for $C_8H_{15}ClO_3S$: C, 42.38; H, 6.67. Found: C, 42.31; H, 6.72.

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Supporting Information Available: Experimental procedures and characterization data for compounds **10**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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