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Synthesis and Conformational Analysis of Bicyclic Sulfonium Salts. Structures Related to the Glycosidase Inhibitor Australine

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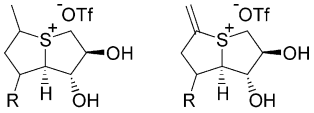

R = H or OH

The syntheses of eight sulfonium compounds with structures related to the naturally occurring pyrrolizidine alkaloid, australine, in which the bridgehead nitrogen atom is replaced by a sulfonium ion, are described. The synthetic strategy relies on the intramolecular attack of a cyclic thioether across a terminal double bond in the presence of a suitable electrophile. We postulate that these compounds, having a permanent positive charge on the sulfur atom, will mimic the highly unstable oxacarbenium ion transition state in a glycosidase-catalyzed hydrolysis reaction. The conformational preferences of these compounds, based on analysis of $^{1}H-^{1}H$ vicinal coupling constants and 1D-NOESY data, are attributed to both steric and electrostatic interactions. These compounds will be used in the study of structure−activity relationships with glycosidase enzymes.

Introduction

Cell surface carbohydrates play an essential role in biological communication, including fertilization, infection, the inflammatory response, cell adhesion, and cancer metastasis.[1−7] The maturation of these oligosaccharides involves the trimming of nascent glycoproteins by glucosidase and mannosidase enzymes to provide the core structure that is required to build a more complex glycoprotein by the action of glycosyltransferase enzymes. Inhibiting these glucosidase enzymes by natural or synthetic inhibitors provides a means of studying the structure−activity relationships of the enzyme-catalyzed reaction and may also provide chemotherapeutic agents for the treatment of viral infections, cancer, and other metabolic disorders such as diabetes.

The most important class of reversible glycosidase inhibitors is composed of naturally occurring polyhydroxylated pyrrolidine, piperidine, pyrrolizidine, and indolizidine alkaloids.[8−14] These are monocyclic and bicyclic amines such as (2*R*,5*R*,3*R*,4*R*)-2,5-bis(hydroxymethyl)-3,4-dihydroxypyrrolidine (DMDP, **1**), deoxynojirimycin (**2**), alexine (**3**), australine (**4**), castanospermine (**5**), and swainsonine (**6**). It is postulated that these compounds mimic the shape and charge of the oxacarbenium-like transition state for the enzyme-catalyzed hydrolysis reaction,

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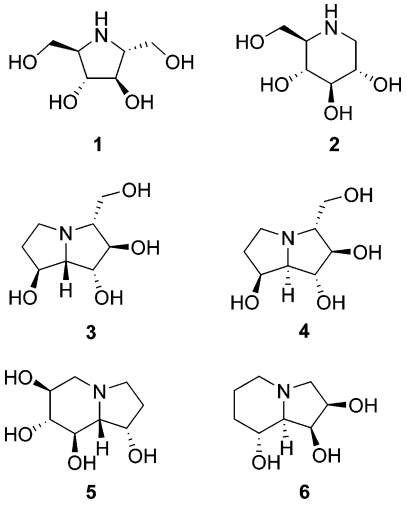
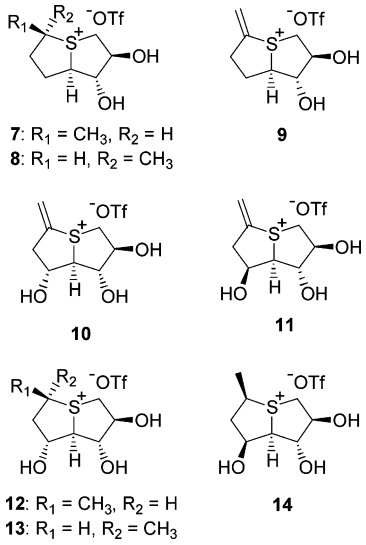
thus making them good glycosidase inhibitors.[15,16] The bridgehead nitrogen atoms in these compounds are protonated at physiological pH, and it is believed that this provides the stabilizing electrostatic interactions between the inhibitor and the carboxylate residues in the enzyme active site.



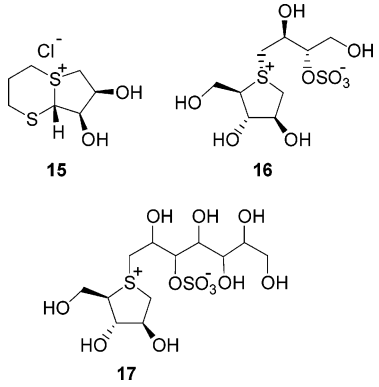
Preparation of structurally modified analogues of these naturally occurring compounds has generated much interest since the biological activity of these molecules varies substantially with the number, position, and the stereochemistry of the centers bearing hydroxyl groups, as well as the ring size.[17−22] We, therefore, designed the analogues (**7**−**14**) in which the bridgehead nitrogen atom is replaced by a sulfonium ion as candidate glycosidase inhibitors. We reasoned that the permanent positive charge on the sulfur atom would mimic the highly unstable oxacarbenium ion transition state and enhance the electrostatic interactions between the inhibitor and the enzyme. These compounds (**7**−**14**) can be considered to be either sulfonium analogues of alexine (**3**) and australine (**4**) or the ring-contracted analogues of swainsonine (**6**).

The synthesis of bicyclic sulfonium salts to serve as glycosidase inhibitors has precedent in the work of Siriwardena and co-workers.[23−25] Most recently, they have reported the synthesis of compound **15** and shown that it not only is a potent inhibitor of several mannosidases but also exhibits more selectivity than swainsonine.[25] In addition, the discovery of a new class of glycosidase inhibitor, salacinol (**16**) and kotalanol (**17**), with



intriguing innersalt sulfonium sulfate structures has led to significant synthetic efforts to derive sulfonium salts with potential glycosidase inhibitory activity.[26−34]

We report herein the synthesis of the sulfonium ions **7**−**14**, together with their conformational analysis, as inferred from ^{1}H−^{1}H vicinal coupling constants ($^3J_{H,H}$) of the ring protons and one-dimensional nuclear Overhauser enhancement spectroscopy (1D-NOESY) experiments. The effects of both electrostatic and steric interactions on the conformations of these compounds are described.



Results and Discussion

Synthesis. Retrosynthetic analysis of compounds **7**−**14** revealed that they could be synthesized from a common

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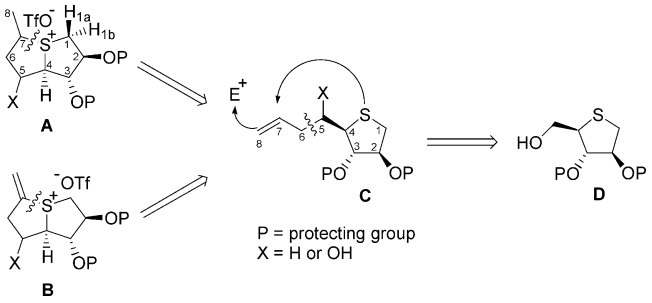
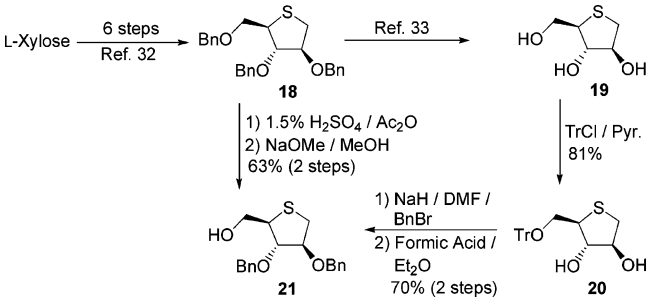
SCHEME 1



SCHEME 2



precursor **C** (Scheme 1). Compounds **A** and **B** could be synthesized by intramolecular addition of the cyclic thioether across the double bond in the presence of a suitable electrophile. Compound **C** could, in turn, be synthesized from **D**.

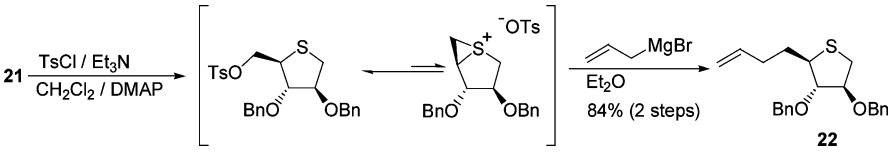
Scheme 2 outlines two methods for the synthesis of **21**, corresponding to **D**. Compound **18** was synthesized from commercially available L-xylose in six steps using the procedure of Satoh et al.[35] Compound **18** was initially debenzylated using standard Birch reduction to give compound **19**.[33] The primary hydroxyl group was then selectively protected using a trityl group to give **20**. The two secondary hydroxyl groups were protected as their benzyl ethers, and the trityl group was removed to give the desired precursor **21**. Alternatively, compound **21** was synthesized directly from **18** by selective removal of the primary benzyl ether using 1.5% H_2SO_4/Ac_2O to give the corresponding acetate, which was subsequently removed by methanolysis to give **21**. The second sequence was higher yielding and shorter than the first.

To synthesize compounds **7**−**9**, the primary hydroxyl group in **21** was converted to a tosylate that was treated, in turn, with allylmagnesium bromide to give compound **22** (Scheme 3). After tosylation, there was always a small amount of a more polar compound present, as indicated by TLC. We reasoned that this polar compound might be the bicyclic sulfonium salt formed from the thioether displacement of the tosylate. The polar compound was in equilibrium with the less polar tosylated compound and could not be isolated by column chromatography. This type of sulfur participation was reported earlier by Hughes et al.,[36,37] who applied the ring contraction of a 5-thiopyranoside to make a 4-thiofuranoside. We employed the same strategy to add an allyl group at C-5. Usually, the formation of a C−C bond by displacement of a tosylate group with a Grignard reagent is low yielding or is transition metal-catalyzed,[38−41] but in this case the reaction proceeded smoothly at ambient temperature. We believe that allylmagnesium bromide reacts with the intermediate strained bicyclic sulfonium salt to give compound **22**.

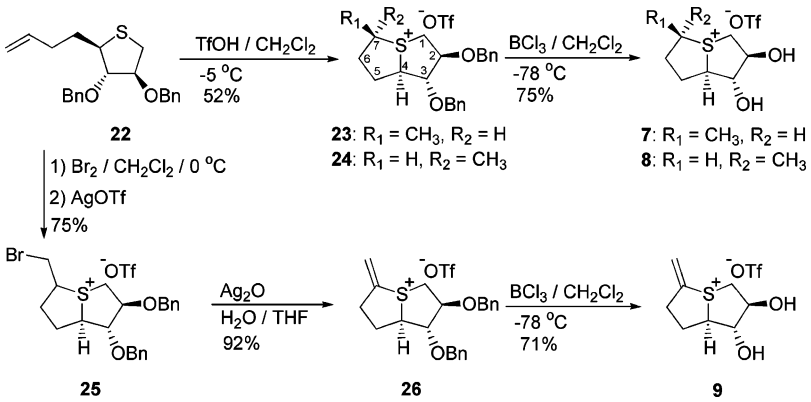
Compound **22** was treated with triflic acid at −5 °C to give spontaneously an inseparable 1:1 mixture of **23** and **24** (Scheme 4). At lower temperatures, the reaction was inconveniently slow and at higher temperatures, only decomposition of the starting material was observed. The ring junction of these bicyclic compounds (**23**, **24**) is *cis* as expected since the *trans* isomer would be strained and of higher energy, in agreement with the work of Cere and co-workers.[42,43] The stereochemistry at C-7 was assigned with the aid of a 1D-NOESY experiment which showed a correlation between H-1a and H-8 for compound **23** and a correlation between H-1a and H-7 for compound **24**. Debenzylation of compounds **23** and **24** gave the desired products **7** and **8**, respectively.

Compound **9** was also synthesized starting from the common intermediate **22**. Treatment of compound **22** with bromine at 0 °C afforded the bicyclic sulfonium salt as a 4:1 diastereomeric mixture, with a bromide counterion. The counterion was immediately exchanged to triflate, using silver triflate, to give compound **25** (Scheme 4), since our previous work had shown

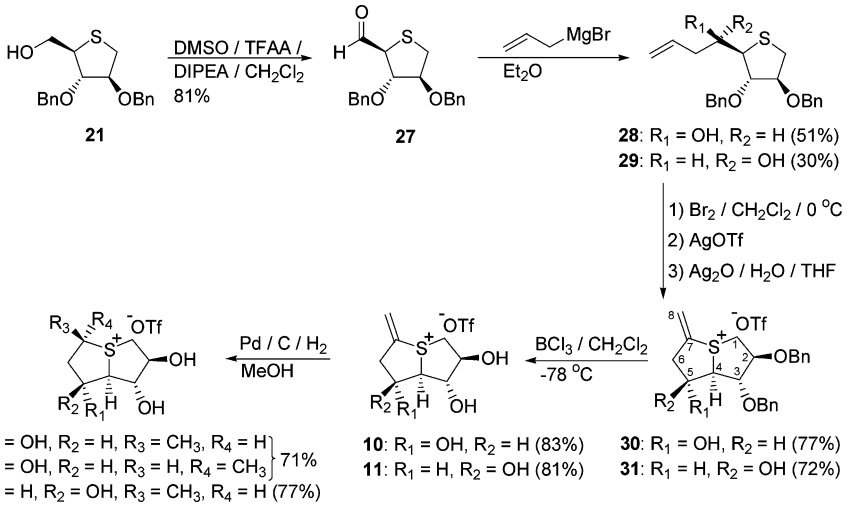
SCHEME 3



SCHEME 4



SCHEME 5



that the bromide counterion resulted in reversible ring opening in a related bicyclic sulfonium salt.[44] The diastereomeric mixture **25** was treated with silver oxide in aqueous THF under mild conditions to give the alkene **26**, the sulfonium center making the elimination reaction more facile because of the acidity of H-7. Even storing compound **25** for several months at room temperature, resulted in spontaneous elimination to give compound **26**. Finally, the benzyl groups were removed to give the desired product **9**.

Compounds **10**−**14** were synthesized from **21** as shown in Scheme 5. Swern oxidation of compound **21** using TFAA[45] afforded compound **27** which subsequently was treated with allylmagnesium bromide to give a 1:2 mixture of diastereomers **29** and **28**.

Compounds **11** and **14** were synthesized from compound **29** (Scheme 5). Treatment of compound **29** with bromine gave the bicyclic sulfonium salt whose bromide counterion was exchanged with triflate using silver triflate. The corresponding salt, when subjected to treatment with aqueous silver oxide, underwent elimination to give compound **31**. The stereochemistry at C-5 of compound **31** was suggested by the absence of a H_3/H_5 correlation in the 1D-NOESY spectrum; the stereochemistry of compound **29** was thus assigned by inference. Deprotection of the benzyl groups gave the target compound **11**. Reduction of the double bond using Pd/C gave a 4:1 diastereomeric mixture of which compound **14** was the major product. The stereochemistry at C-7 was assigned by means of a 1D-NOESY experiment which showed a correlation between H-1a and H-8. The diastereoselectivity can be explained by the fact that compound **11** has a concave structure and the addition of hydrogen takes place from the least hindered, convex face.

The same series of reactions was applied to compound **28** to synthesize compound **10**. Reduction of the double bond using Pd/C gave a 3:2 diastereomeric mixture of **12** and **13**. With the aid of 1D-NOESY experiments, the stereochemistry at C-7 was assigned such that the structure **13** was attributed to the isomer which showed a strong correlation between H-1a and H-7 whereas structure **12** was assigned to the isomer which showed no correlation between H-1a and H-7, but a correlation between H-1a and H-8. The reduction of the double bond in compound **10** was less diastereoselective, presumably because the hydroxyl group at C-5 blocks the convex face of compound **10**.

Conformational Analysis. Application of the Karplus relationship[46] to the observed vicinal $^1H-^1H$ coupling constants led to the proposed conformations of compounds **7**−**14** (Table 1). These conformations were further confirmed with the aid of one-dimensional nuclear Overhauser enhancement spectroscopy (1D-NOESY) experiments (Figure 1). We suggest that ring **A** of compounds **8**−**14** exists in a ^2E conformation since the vicinal coupling constant between H(1a)−H(2), H(2)−H(3), and H(3)−H(4) is small (0.0−2.4 Hz), whereas the coupling constant between H(1b)−H(2) is ∼4.0−4.8 Hz (Figure 2). This is in agreement with the 1D-NOESY experiments where compounds **8**−**14** do not show any H(1a)/H(3) NOE correlation since they adopt a ^2E conformation in which both H(1a) and H(3) are in pseudoequatorial orientations. This conformation would place the hydroxyl groups at C-2 and C-3 in pseudoaxial positions, a higher energy conformation than the E_2 conformation in which the hydroxyl groups occupy pseudoequatorial positions. Similar results were noted in our previous work in which the preferred conformation of the bicyclic sulfonium ion positioned the hydroxyl groups in axial orientations. The conformational preference was attributed to favorable electrostatic attraction between the hydroxyl groups with the sulfonium center which outweighed the steric effects.[34,44] On the other hand, ring **A** of compound **7** adopts an E_2 conformation since it exhibits an

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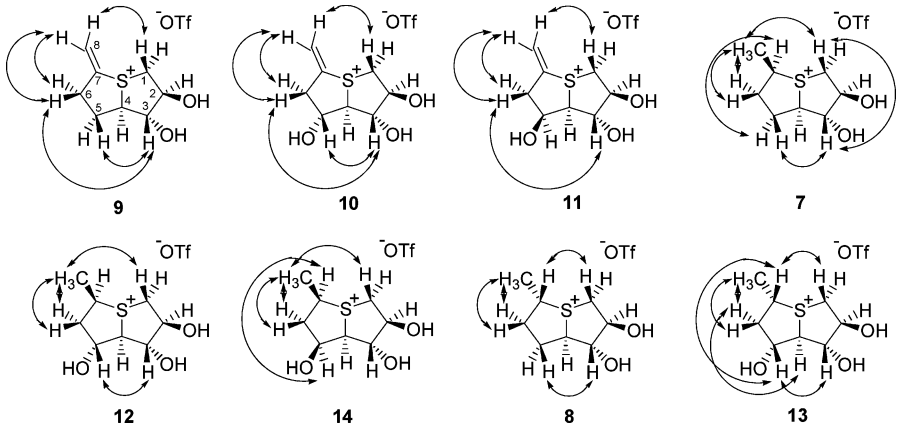

FIGURE 1. Observed NOE correlations for compounds **7**−**14**.

TABLE 1. Vicinal Coupling Constants for Compounds 7−14 and Their Proposed Conformations

vicinal coupling constant (Hz)	compounds							
	7	**8**	**9**	**10**	**11**	**12**	**13**	**14**
$J_{1a,2}$	4.8	2.0	0.0	2.1	0.0	2.4	0.0	2.2
$J_{1b,2}$	4.8	4.0	4.3	4.2	4.1	4.8	4.1	4.6
$J_{2,3}$	4.8	2.0	0.0	2.0	0.0	2.4	2.0	2.2
$J_{3,4}$	3.8	0.0	0.0	2.0	0.0	2.4	0.0	2.2
$J_{4,5a}$	3.8	8.0	4.3	0.0	na	1.5	5.2	na
$J_{4,5b}$	5.9	8.0	9.9	na	8.0	na	na	6.3
$J_{5a,6a}$	overlap	overlap	8.6	5.2	na	3.7	5.2	na
$J_{5a,6b}$	overlap	overlap	5.0	2.3	na	0	7.9	na
$J_{5b,6a}$	overlap	overlap	8.6	na	7.2	na	na	11.2
$J_{5b,6b}$	overlap	overlap	8.6	na	9.8	na	na	6.1
$J_{6a,7}$	6.0	6.9	na	na	na	11.3	6.8	6.7
$J_{6b,7}$	6.0	6.9	na	na	na	5.6	9.9	6.7
proposed conformation	^{6}E E_2	E_6 ^{2}E	$^4T_5$ ^{2}E	$^4T_5$ ^{2}E	$^4T_5$ ^{2}E	^{6}E ^{2}E	E_6 ^{2}E	^{6}E ^{2}E

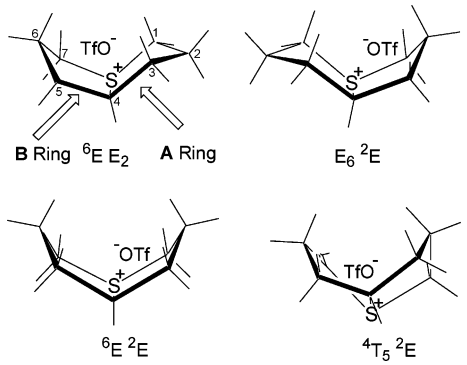

FIGURE 2. Schematic representations of ^{6}E E_2, E_6 ^{2}E, ^{6}E ^{2}E, and $^4T_5$ ^{2}E conformations.

H(1a)/H(3) correlation; hence, both H(1a) and H(3) are in pseudoaxial orientations. Based on analysis of vicinal coupling constants, we also propose that compounds **9**−**11** with a double bond at C-7 have ring **B** in a twist conformation; hence, compounds **9**−**11** have an overall conformation of $^4T_5$ ^{2}E. This conformation was further supported by 1D-NOESY experiments which showed H(1a)/H(8b), H(3)/H(5a), H(6a)/H(8a), H(6b)/H(8a), and H(3)/H(6a) correlations. From the analysis of vicinal coupling constants and 1D-NOESY data, we propose that the **B** ring of compounds **7**, **12**, and **14** has a ^{6}E conformation. There was a NOE correlation between H(5b)/H(7) for compounds **7** and **14** and there was no correlation between H(5a)/H(8) for compounds **7** and **12**; hence, they are present in a ^{6}E conformation. Based on analysis of vicinal coupling constants, we also propose that ring **B** of compounds **8** and **13** has an E_6 conformation, as corroborated by 1D-NOESY experiments which showed a NOE correlation between H(5b)/H(7) and H(4)/H(6b) for compound **13**. Both compounds **8** and **13** showed a NOE correlation between H(8)/H(6a) and also between H(8)/H(6b), which implies that the methyl group is in a pseudoequatorial orientation. In compounds **7**, **8**, **12**, **13**, and **14**, the methyl group has a significant effect on the conformation since it occupies a pseudoequatorial position. By changing the configuration at C-7 in compounds **7** and **12**, and hence the orientation of the methyl group, the conformation of ring **B** changes from ^{6}E to E_6. In compound **14**, the hydroxyl group at C-5 is in a pseudoaxial orientation, whereas the C-5 hydroxyl group of compound **12** is in a pseudoequatorial orientation; thus, the configuration of the carbon bearing the methyl group and hence the orientation of the methyl group plays a major role in determining the conformation of the **B** ring. Hence, compounds **7**, **8**, **12**, **13**, and **14** have overall conformations of ^{6}E E_2, E_6 ^{2}E, ^{6}E ^{2}E, E_6 ^{2}E, and ^{6}E ^{2}E, respectively. Both electrostatic and steric effects control the conformations of compounds **7**−**14**. Thus, changing the configuration at C-7 or changing the C-7 substituent from a methyl group to an *exo*-methylene group has a significant impact on the conformation of these compounds. The ability to tailor the preferred conformations of these compounds through the judicious choice of the type, location, and stereochemistry of pendant functional groups could be of significance in the design of molecules as candidate glycosidase inhibitors.

Experimental Section

General Methods. Optical rotations were measured at 23 °C. ^{1}H and ^{13}C NMR spectra were recorded with frequencies of 500 and 125 MHz, respectively. All assignments were confirmed with the aid of two-dimensional ^{1}H, ^{1}H (gCOSY) and ^{1}H, ^{13}C (gHMQC) experiments using standard Varian pulse programs. Processing of the spectra was performed with MestRec software. 1D-NOESY experiments were recorded at 295 K on a 500 MHz spectrometer. For each 1D-NOESY spectrum, 512 scans were acquired with Q3 Gaussian Cascade pulse. A mixing time of 500 or 800 ms was used in all the 1D-NOESY experiments. Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectra were obtained using 2,5-dihydroxybenzoic acid as a matrix. Analytical thin-layer chromatography (TLC) was performed on aluminum plates precoated with silica gel 60F-254 as the adsorbent. The developed plates were air-dried, exposed to UV light, and/or sprayed with a

solution containing 1% $Ce(SO_4)_2$ and 1.5% molybdic acid in 10% aqueous H_2SO_4, and heated. Column chromatography was performed with silica gel 60 (230−400 mesh).

1,4-Anhydro-5-*O*-trityl-4-thio-D-arabinitol (20). A mixture of compound **19** (4.10 g, 27.3 mmol) and trityl chloride (12.90 g, 1.7 equiv) in pyridine (200 mL) was stirred at room temperature under an N_2 atmosphere for 40 h. The reaction mixture was concentrated, and the crude product was purified by flash chromatography [CH_2Cl_2/MeOH, 1:0 → 20:1] to give compound **20** as white foam (8.70 g, 81%): $[\alpha]_D$ +6.15 (*c* 0.65, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.46−7.20 (m, 15H, Ar), 4.21 (ddd, 1H, $J_{1a,2} = 6.9$ Hz, $J_{1b,2} = J_{2,3} = 7.1$ Hz, H-2), 3.81 (dd, 1H, $J_{3,4} = 6.8$ Hz, H-3), 3.48−3.35 (m, 2H, H-4, H-5a), 3.30 (dd, 1H, $J_{4,5b} = J_{5a,5b} = 7.3$ Hz, H-5b), 3.04 (dd, 1H, $J_{1a,1b} = 10.6$ Hz, H-1a), 2.69 (dd, 1H, H-1b); ^{13}C NMR (CD_2Cl_2) δ 136.05 ($3C_{ipso}$), 128.8−127.4 ($15C_{Ar}$), 87.5 (Ph_3C), 81.7 (C-3), 78.1 (C-2), 67.1 (C-5), 48.2 (C-4), 33.0 (C-1); MALDI-TOF MS *m*/*e* 415.17 (M^+ + Na), 431.20 (M^+ + K). Anal. Calcd for $C_{24}H_{24}O_3S$: C, 73.44; H, 6.16. Found: C, 73.65; H, 6.30.

1,4-Anhydro-2,3-di-*O*-benzyl-4-thio-D-arabinitol (21). A mixture of compound **20** (8.00 g, 20.5 mmol) and 60% NaH (2.70 g, 2.5 equiv) in DMF (250 mL) was stirred in an ice bath for 10 min. A solution of benzyl bromide (7.0 mL, 2.2 equiv) in DMF (20 mL) was added, and the solution was stirred in an ice bath for 90 min. The reaction was quenched with ice−water (150 mL) and extracted with Et_2O (2 × 200 mL). The combined organic phase was washed with brine (100 mL), dried (Na_2SO_4), and concentrated. The residue was dissolved in 1:1 formic acid/Et_2O solution (300 mL), and the solution was stirred at room temperature for 90 min. The mixture was diluted with Et_2O (200 mL) and washed with H_2O (2 × 100 mL), saturated aqueous $NaHCO_3$ (2 × 100 mL), and brine (100 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography [hexanes/EtOAc, 4:1 → 3:1] to give compound **21** as a pale yellow oil (4.71 g, 70%).

Alternative Method for the Synthesis of 1,4-Anhydro-2,3-di-*O*-benzyl-4-thio-D-arabinitol (21). Compound **18** (6.01 g, 14.3 mmol) in 1.5% H_2SO_4/Ac_2O (30.0 mL) was stirred at room temperature for 16 h and then partitioned between EtOAc (200 mL) and H_2O (100 mL). The organic layer was washed with H_2O (100 mL) and saturated aqueous $NaHCO_3$ (3 × 100 mL), followed by brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product was diluted with MeOH (150 mL), and 1 M NaOMe/MeOH solution was added until the solution was basic. The mixture was stirred at room temperature for 1 h and then neutralized with AcOH. The mixture was concentrated and then partitioned between EtOAc (200 mL) and H_2O (100 mL). The organic phase was washed with H_2O (100 mL) and brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography [hexanes/EtOAc, 4:1 → 3:1] to give compound **21** as a colorless oil (2.97 g, 63%): $[\alpha]_D$ −9.67 (*c*, 1.14, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.39−7.24 (m, 10H, Ar), 4.69 and 4.63 (2d, each 1H, $J_{a,b} = 11.8$ Hz, CH_2Ph), 4.58 and 4.53 (2d, each 1H, $J_{a,b} = 11.8$ Hz, CH_2Ph), 4.19 (ddd, 1H, $J_{1a,2} = J_{1b,2} = J_{2,3} = 5.3$ Hz, H-2), 4.04 (dd, 1H, $J_{3,4} = 4.8$ Hz, H-3), 3.69 (dd, 1H, $J_{4,5a} = 5.3$ Hz, $J_{5a,5b} = 11.4$ Hz, H-5a), 3.66 (dd, 1H, $J_{4,5b} = 5.2$ Hz, H-5b), 3.48(ddd, 1H, H-4), 3.04 (dd, 1H, $J_{1a,1b} = 11.2$ Hz, H-1a), 2.86 (dd, 1H, H-1b); ^{13}C NMR ($CDCl_3$) δ 138.2, 137.9 ($2C_{ipso}$), 128.8−128.0 ($10C_{Ar}$), 85.3 (C-3), 85.0 (C-2), 72.7, 72.1 (2 *C*H_2Ph), 63.7 (C-5), 51.5 (C-4), 32.6 (C-1); MALDI-TOF MS *m*/*e* 331.20 (M^+ + H), 353.19 (M^+ + Na), 369.17 (M^+ + K). Anal. Calcd for $C_{19}H_{22}O_3S$: C, 69.06; H, 6.71. Found: C, 69.36; H, 6.65.

(2*S*,3*S*,4*R*)-2,3-Dibenzyloxy-4-(but-3-enyl)thiolane (22). Triethylamine (0.19 mL, 1.26 mmol), tosyl chloride (260 mg, 1.33 mmol), and 4-(dimethylamino)pyridine (20.0 mg, 0.13 mmol) were added to a stirred solution of **21** (370 mg, 1.12 mmol) in CH_2Cl_2 (10 mL) at 0 °C under N_2 atmosphere. The mixture was stirred at 0 °C for 2 h and then concentrated. The crude tosylated product was purified by flash chromatography [hexanes/EtOAc, 6:1], and the product was dissolved in Et_2O (20 mL). Allylmagnesium bromide (1 M in Et_2O, 2.5 mL, 2.5 mmol) was added dropwise, and the mixture was stirred at ambient temperature under an N_2 atmosphere for 16 h. The reaction was quenched with ice (5 mL), and the mixture was diluted with Et_2O (100 mL). The reaction mixture was washed with H_2O (2 × 50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography [hexanes/EtOAc, 1:0 → 10:1] to give compound **22** as a colorless oil (330 mg, 84%): $[\alpha]_D$ +9.80 (*c* 1.02, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.38−7.28 (m, 10H, Ar), 5.68 (dddd, 1H, $J_{6a,7} = J_{6b,7} = 6.6$ Hz, $J_{7,8b} = 17.0$ Hz, $J_{7,8a} = 10.2$ Hz, H-7), 5.02 (dddd, 1H, $J_{6a,8b} = J_{6b,8b} = J_{8a,8b} = 1.6$ Hz, H-8b), 4.96 (dd, 1H, H-8a), 4.68 and 4.60 (2d, each 1H, $J_{a,b} = 11.7$ Hz, CH_2Ph), 4.59 and 4.55 (2d, each 1H, $J_{a,b} = 11.9$ Hz, CH_2Ph), 4.08 (ddd, 1H, $J_{1a,2} = J_{1b,2} = J_{2,3} = 5.9$ Hz, H-2), 3.80 (dd, 1H, $J_{3,4} = 5.7$ Hz, H-3), 3.23(ddd, 1H, $J_{4,5a} = 5.1$ Hz, $J_{4,5b} = 9.9$ Hz, H-4), 3.17(dd, 1H, $J_{1a,1b} = 10.9$ Hz, H-1a), 2.85 (dd, 1H, H-1b), 2.10 (m, 1H, H-6b), 2.05 (ddddd, 1H, $J_{5b,6a} = J_{6a,6b} = 7.3$ Hz, $J_{5a,6a} = 14.2$ Hz, H-6a), 1.95 (dddd, 1H, $J_{5a,5b} = 6.5$ Hz, H-5b), 1.62 (dddd, 1H, H-5a); ^{13}C NMR ($CDCl_3$) δ 138.4, 138.2 ($2C_{ipso}$), 137.9 (C-7), 128.7−128.0 ($10C_{Ar}$), 115.5 (C-8), 88.7 (C-3), 85.1 (C-2), 72.8, 72.2 (2 *C*H_2Ph), 48.2 (C-4), 34.8 (C-5), 32.7 (C-6), 31.7 (C-1); MALDI-TOF MS *m*/*e* 355.30 (M^+ + H), 377.28 (M^+ + Na), 393.22 (M^+ + K). Anal. Calcd for $C_{22}H_{26}O_2S$: C, 74.54; H, 7.39. Found: C, 74.68; H, 7.38.

(2*S*,3*S*,4*R*,7*R*/*S*)-2,3-Dibenzyloxy-7-methyl-*cis*-1-thio-niabicyclo-[3.3.0]octane triflate (23/24). A solution of trifluoromethanesulfonic acid (0.05 mL, 0.57 mmol) in CH_2Cl_2 (2 mL) was added dropwise to a stirred solution of **22** (200 mg, 0.57 mmol) in CH_2Cl_2 (8 mL) at −5 °C under N_2 atmosphere. The mixture was stirred at −5 °C for 2 h and then concentrated. The crude product was purified by flash chromatography [CH_2Cl_2/MeOH, 1:0 → 20:1] to give a pale yellow oil (150 mg, 52%). Analysis by NMR showed that the product was a mixture of two isomers (∼1:1) at the stereogenic C-7 center. The stereochemistry was assigned with the aid of a 1D-NOESY spectrum which showed a strong correlation between H-1a and H-7 for compound **24** and no correlation for compound **23**.

Data for the (2*S*,3*S*,4*R*,7*R*)-2,3-dibenzyloxy-7-methyl-*cis*-1-thioniabicyclo[3.3.0]octane triflate (**23**): ^{1}H NMR (CD_3OD) δ 7.38−7.12 (m, 10H, Ar), 4.87 (dd, 1H, $J_{4,5a} = 2.6$ Hz, $J_{4,5b} = 7.7$ Hz, H-4), 4.60 and 4.48 (2d, each 1H, $J_{a,b} = 11.9$ Hz, CH_2Ph), 4.53 and 4.41 (2d, each 1H, $J_{a,b} = 12.2$ Hz, CH_2Ph), 4.32 (d, 1H, $J_{1b,2} = 5.0$ Hz, H-2), 4.19 (s, 1H, H-3), 4.15 (m, 1H, H-7), 3.60 (dd, 1H, $J_{1a,1b} = 15.3$ Hz, H-1b), 3.34 (d, 1H, H-1a), 2.46 (m, 1H, H-6a), 2.38 (m, 1H, H-5a), 2.21 (m, 1H, H-5b), 2.05 (m, 1H, H-6b), 1.48 (d, 3H, H-8); ^{13}C NMR (CD_3OD) δ 136.4−136.1 ($2C_{ipso}$), 129.1−128.3 ($10C_{Ar}$), 121.0 (q, 1C, $J_{C,F} = 318.6$ Hz, OTf), 87.2 (C-3), 83.5 (C-2), 72.2, 72.1 (2 *C*H_2Ph), 70.5 (C-4), 61.8 (C-7), 40.3 (C-1), 38.9 (C-6), 31.7 (C-5), 15.1 (C-8).

Data for the (2*S*,3*S*,4*R*,7*S*)-2,3-dibenzyloxy-7-methyl-*cis*-1-thioniabicyclo[3.3.0]octane triflate (**24**): ^{1}H NMR (CD_3OD) δ 7.38−7.12 (m, 10H, Ar), 4.83 (dd, 1H, $J_{4,5a} = J_{4,5b} = 8.8$ Hz, H-4), 4.56 and 4.51 (2d, each 1H, $J_{a,b} = 11.7$ Hz, CH_2Ph), 4.46 (d, 1H, $J_{1b,2} = 4.5$ Hz, H-2), 4.55 and 4.42 (2d, each 1H, $J_{a,b} = 11.9$ Hz, CH_2Ph), 4.30 (m, 1H, H-7), 4.25 (s, 1H, H-3), 3.66 (d, 1H, $J_{1a,1b} = 15.0$ Hz, H-1a), 3.60 (dd, 1H, H-1b), 2.50−2.39 (m, 2H, H-5a, H-5b), 2.27−2.15 (m, 2H, H-6a, H-6b), 1.60 (d, 3H, H-8); ^{13}C NMR (CD_3OD) δ 136.4−136.1 ($2C_{ipso}$), 129.1−128.3 ($10C_{Ar}$), 121.0 (q, 1C, $J_{C,F} = 318.6$ Hz, OTf), 86.2 (C-3), 84.9 (C-2), 72.7, 72.2 (2 *C*H_2Ph), 70.4 (C-4), 56.5 (C-7), 46.4 (C-1), 36.5 (C-6), 31.2 (C-5), 17.6 (C-8).

For the mixture of **23** and **24**: MALDI-TOF MS *m*/*e* 355.04 (M^+ − OTf). Anal. Calcd for $C_{23}H_{27}F_3O_5S_2$: C, 54.75; H, 5.39. Found: C, 54.38; H, 5.55.

(2*S*,3*S*,4*R*,7*R*/*S*)-2,3-Dihydroxy-7-methyl-*cis*-1-thionia-bicyclo-[3.3.0]octane Triflate (7/8). BCl_3 gas was bubbled vigorously through a solution of **23/24** (100 mg, 0.20 mmol) in CH_2Cl_2 (15 mL) at −78 °C under N_2 atmosphere for 5 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 (5 mL), and the solvent was removed. The residue was coevaporated with MeOH (2 × 5 mL), and the crude product was washed with CH_2Cl_2 (2 × 2 mL) to give a yellow oil (48.0 mg, 75%). Analysis by NMR showed that the product was a mixture of two isomers (∼1:1) at the stereogenic C-7 center. The stereochemistry was assigned with the aid of a 1D-NOESY spectrum which showed a strong correlation between H-1a and H-7 for compound **8**, whereas there was a correlation between H-1a and H-8 for compound **7**.

Data for (2*S*,3*S*,4*R*,7*R*)-2,3-Dihydroxy-7-methyl-*cis*-1-thioniabicyclo[3.3.0]octane triflate (**7**): ^{1}H NMR (CD_3OD) δ 4.41 (ddd, 1H, $J_{1a,2} = J_{1b,2} = J_{2,3} = 4.8$ Hz, H-2), 4.29 (ddd, 1H, $J_{3,4} = J_{4,5a} = 3.8$ Hz, $J_{4,5b} = 5.9$ Hz, H-4), 4.16 (dd, 1H, H-3), 4.01 (ddq, 1H, $J_{6a,7} = J_{6b,7} = 6.0$ Hz $J_{7,8} = 6.9$ Hz, H-7), 3.51 (dd, 1H, $J_{1a,1b} = 14.0$ Hz, H-1a), 3.18 (dd, 1H, H-1b), 2.46−1.88 (m, 4H, H-5a, H-5b, H-6a, H-6b), 1.41 (d, 3H, H-8); ^{13}C NMR (CD_3OD) δ 119.8 (q, 1C, $J_{C,F} = 315.4$ Hz, OTf), 81.6 (C-3), 81.0 (C-2), 68.9 (C-4), 56.6 (C-7), 38.2 (C-1), 35.2 (C-6), 31.1 (C-5), 13.3 (C-8).

Data for (2*S*,3*S*,4*R*,7*S*)-2,3-Dihydroxy-7-methyl-*cis*-1-thioniabicyclo[3.3.0]octane triflate (**8**): ^{1}H NMR (CD_3OD) δ 4.59 (ddd, 1H, $J_{1a,2} = J_{2,3} = 2.0$ Hz, $J_{1b,2} = 4.0$ Hz, H-2), 4.51 (dd, 1H, $J_{4,5a} = J_{4,5b} = 8.0$ Hz, H-4), 4.42 (d, 1H, H-3), 4.15 (ddq, 1H, $J_{6a,7} = J_{6b,7} = J_{7,8} = 6.9$ Hz, H-7), 3.68 (dd, 1H, $J_{1a,1b} = 14.5$ Hz, H-1a), 3.48 (dd, 1H, H-1b), 2.46−1.88 (m, 4H, H-5a, H-5b, H-6a, H-6b), 1.44 (d, 3H, H-8); ^{13}C NMR (CD_3OD) δ 119.8 (q, 1C, $J_{C,F} = 315.4$ Hz, OTf), 79.7 (C-2), 76.4 (C-3), 71.8 (C-4), 61.5 (C-7), 46.4 (C-1), 38.0 (C-5), 32.0 (C-6), 16.7 (C-8).

For the mixture of **7** and **8**: MALDI-TOF MS *m*/*e* 175.24 (M^+ − OTf). Anal. Calcd for $C_9H_{15}F_3O_5S_2$: C, 33.33; H, 4.66. Found: C, 33.01; H, 4.58.

(2*S*,3*S*,4*R*,7*R*)-2,3-Dibenzyloxy-7-bromomethyl-*cis*-1-thioniabicyclo[3.3.0]octane Triflate (25). Br_2 (61.0 μL, 1.20 mmol) was added dropwise to a stirred solution of **22** (420 mg, 1.19 mmol) in CH_2Cl_2 (10 mL) at 0 °C under N_2. The mixture was stirred at 0 °C for 2 h, and then silver triflate (310 mg, 1.20 mmol) was added. Stirring was continued at 0 °C for an additional 2 h, and the mixture was concentrated. The crude product was purified by flash chromatography [CH_2Cl_2/MeOH, 1:0 à 20:1] to give a colorless oil (520 mg, 75%) as a 4:1 mixture of diastereomers. The major component of the mixture was assigned to be the diastereomer with the *R* configuration at C-7 on the basis of analysis of a 1D-NOESY spectrum which showed a correlation between H-1a and H-8.

Data for the major isomer (**25**): ^{1}H NMR (CD_2Cl_2) δ 7.42−7.24 (m, 10H, Ar), 5.02 (dd, 1H, $J_{4,5a} = J_{4,5b} = 8.7$ Hz, H-4), 4.70 and 4.63 (2d, each 1H, $J_{a,b} = 11.9$ Hz, C*H*$_2$Ph), 4.64 (d, 1H, $J_{1b,2} = 4.3$ Hz, H-2), 4.62 and 4.56 (2d, each 1H, $J_{a,b} = 11.7$ Hz, C*H*$_2$-Ph), 4.59 (m, 1H, H-7), 4.42 (s, 1H, H-3), 4.08 (d, 1H, $J_{1a,1b} = 15.2$ Hz, H-1a), 4.04 (dd, 1H, $J_{8a,8b} = 11.5$ Hz, $J_{7,8a} = 4.9$ Hz, H-8a), 3.97 (dd, 1H, $J_{7,8b} = 7.8$ Hz, H-8b), 3.83 (dd, 1H, H-1b), 2.72 (m, 1H, H-5a), 2.61 (m, 1H, H-5b), 2.55 (m, 1H, H-6a), 2.43 (m, 1H, H-6b); ^{13}C NMR (CD_2Cl_2) δ 126.8, 126.6 ($2C_{ipso}$), 119.1−118.3 ($10C_{Ar}$), 111.1 (q, 1C, $J_{C,F} = 306.1$ Hz, OTf), 75.9 (C-3), 75.4 (C-2), 63.0, 62.3 (2 *C*H$_2$Ph), 61.3 (C-4), 58.4 (C-7), 37.7 (C-1), 26.3 (C-6), 21.8 (C-5), 20.5 (C-8).

For the mixture of diastereomers: MALDI-TOF MS *m*/*e* 435.13, 433.13 (M^+ − OTf), 353.22 (M^+ − (OTf, HBr)). Anal. Calcd for $C_{23}H_{26}Br_1F_3O_5S_2$: C, 47.34; H, 4.49. Found: C, 47.66; H, 4.36.

(2*S*,3*S*,4*R*)-2,3-Dibenzyloxy-7-methylene-*cis*-1-thionia-bicyclo-[3.3.0]octane Triflate (26). Silver oxide (126 mg, 0.61 mmol) was added to a stirred solution of **25** (320 mg, 0.55 mmol) in H_2O/THF (1:1, 10 mL). The mixture was stirred at ambient temperature for 20 h and concentrated. The crude product was purified by flash chromatography [CH_2Cl_2/MeOH, 1:0 → 20:1] to give compound **26** as a colorless oil (254 mg, 92%): $[\alpha]_D$ +50.2 (*c* 1.08, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.31−7.09 (m, 10H, Ar), 6.24 (ddd, 1H, $J_{6a,8a} = J_{6b,8a} = J_{8a,8b} = 1.9$ Hz, H-8a), 5.83 (ddd, 1H, $J_{6a,8b} = J_{6b,8b} = 1.9$ Hz, H-8b), 4.99 (dd, 1H, $J_{4,5a} = 4.6$ Hz, $J_{4,5b} = 10.1$ Hz, H-4), 4.58 and 4.48 (2d, each 1H, $J_{a,b} = 11.9$ Hz, C*H*$_2$Ph), 4.48 and 4.40 (2d, each 1H, $J_{a,b} = 11.6$ Hz, C*H*$_2$Ph), 4.42 (d, 1H, $J_{1b,2} = 4.0$ Hz, H-2), 4.33 (s, 1H, H-3), 3.95 (dd, 1H, $J_{1a,1b} = 14.8$ Hz, H-1b), 3.78 (d, 1H, H-1a), 3.01 (ddddd, 1H, $J_{5a,6a} = J_{5b,6a} = 8.0$ Hz, $J_{6a,6b} = 16.0$ Hz, H-6a), 2.82 (ddddd, 1H, $J_{5a,6b} = 5.6$ Hz, $J_{5b,6b} = 7.7$ Hz, H-6b), 2.64 (dddd, 1H, $J_{5a,5b} = 13.3$ Hz, H-5b), 2.30 (dddd, 1H, H-5a); ^{13}C NMR ($CDCl_3$) δ 142.8 (C-7), 136.1, 135.8 ($2C_{ipso}$), 128.8−128.0 ($10C_{Ar}$), 124.9 (C-8), 120.1 (q, 1C, $J_{C,F} = 306.5$ Hz, OTf), 87.8 (C-3), 83.7 (C-2), 72.2, 72.0 (2 *C*H$_2$Ph), 70.2 (C-4), 52.5 (C-1), 35.6 (C-6), 29.8 (C-5); MALDI-TOF MS *m*/*e* 353.06 (M^+ − OTf). Anal. Calcd for $C_{23}H_{25}F_3O_5S_2$: C, 54.97; H, 5.01. Found: C, 54.67; H, 5.29.

(2*S*,3*S*,4*R*)-2,3-Dihydroxy-7-methylene-*cis*-1-thionia-bicyclo-[3.3.0]octane Triflate (9). BCl_3 gas was bubbled vigorously through a solution of **26** (55.0 mg, 0.11 mmol) in CH_2Cl_2 (10 mL) at −78 °C under N_2 atmosphere for 5 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 (5 mL), and the solvent was removed. The residue was coevaporated with MeOH (2 × 5 mL), and the crude product was washed with CH_2Cl_2 (2 × 2 mL) to give compound **9** as an amorphous solid (25.0 mg, 71%): $[\alpha]_D$ +133.9 (*c* 0.91, MeOH); ^{1}H NMR (CD_3OD) 6.11 (ddd, 1H, $J_{6a,8a} = J_{6b,8a} = J_{8a,8b} = 1.7$ Hz, H-8a), 6.03 (ddd, 1H, $J_{6a,8b} = J_{6b,8b} = 1.9$ Hz, H-8b), 4.72 (dd, 1H, $J_{4,5a} = 4.3$ Hz, $J_{4,5b} = 9.9$ Hz, H-4), 4.59 (d, 1H, $J_{1b,2} = 4.3$ Hz, H-2), 4.52 (s, 1H, H-3), 4.08 (dd, 1H, $J_{1a,1b} = 14.1$ Hz, H-1b), 3.47 (d, 1H, H-1a), 3.38 (ddddd, 1H, $J_{5a,6a} = J_{5b,6a} = 8.6$ Hz, $J_{6a,6b} = 16.0$ Hz, H-6a), 2.89 (ddddd, 1H, $J_{5a,6b} = 5.0$ Hz, $J_{5b,6b} = 8.6$ Hz, H-6b), 2.55 (dddd, 1H, $J_{5a,5b} = 12.9$ Hz, H-5a), 2.42 (dddd, 1H, H-5b); ^{13}C NMR (CD_3OD) δ 144.6 (C-7), 123.4 (C-8), 120.6 (q, 1C, $J_{C,F} = 315.9$ Hz, OTf), 83.4 (C-3), 79.2 (C-2), 73.8 (C-4), 55.0 (C-1), 35.2 (C-6), 29.7 (C-5); MALDI-TOF MS *m*/*e* 173.24 (M^+ − OTf). Anal. Calcd for $C_9H_{13}F_3O_5S_2$: C, 33.54; H, 4.07. Found: C, 33.23; H, 4.21.

(2*S*,3*S*,4*R*)-2,3-Dibenzyloxy-4-formaldehydethiolane-(27). A solution of trifluoroacetic anhydride (0.7 mL, 9.3 mmol) in CH_2Cl_2 (5 mL) was added to a stirred solution of DMSO (1.2 mL, 17.2 mmol) in CH_2Cl_2 (12 mL) at −78 °C under N_2 atmosphere dropwise, and the mixture was stirred at −78 °C for 30 min. A solution of **21** (0.70 g, 2.12 mmol) in CH_2Cl_2 (12 mL) was added dropwise while maintaining the temperature below −78 °C, and stirring was continued for 1.5 h. A solution of diisopropylethylamine (2.0 mL, 11.0 mmol) in CH_2Cl_2 (12 mL) was added dropwise, and the stirring was continued at −78 °C for an additional 2 h. The reaction was quenched with aqueous HCl (0.5 M, 5 mL), and the mixture was partitioned between Et_2O (150 mL) and H_2O (50 mL). The Et_2O layer was washed with H_2O (50 mL) and brine (50 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography [hexanes/EtOAc, 6:1] to give compound **27** as a pale yellow oil (0.56 g, 81%): $[\alpha]_D$ −3.5 (*c* 1.15, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 9.44 (d, 1H, $J_{4,5} = 2.8$ Hz, H-5), 7.36−7.25 (m, 10H, Ar), 4.66 and 4.57 (2d, each 1H, $J_{a,b} = 11.9$ Hz, C*H*$_2$Ph), 4.49 (s, 2H, C*H*$_2$-Ph), 4.44 (dd, 1H, $J_{2,3} = J_{3,4} = 2.5$ Hz, H-3), 4.23 (ddd, 1H, $J_{1a,2} = J_{1b,2} = 3.2$ Hz, H-2), 3.80 (dd, 1H, H-4), 3.16 (dd, 1H, $J_{1a,1b} = 11.4$ Hz, H-1a), 3.00 (dd, 1H, H-1b); ^{13}C NMR ($CDCl_3$) δ 198.4 (C-5), 137.4, 137.4 ($2C_{ipso}$), 128.8−128.0 ($10C_{Ar}$), 85.6 (C-3), 83.4 (C-2), 72.3, 71.5 (2 *C*H$_2$Ph), 58.5 (C-4), 34.7 (C-1); MALDI-TOF MS *m*/*e* 329.15 (M^+ + H), 351.13 (M^+ + Na), 367.09 (M^+ + K). Anal. Calcd for $C_{19}H_{20}O_3S$: C, 69.48; H, 6.14. Found: C, 69.61; H, 6.26.

(2*S*,3*S*,4*R*,1′*S*/*R*)-2,3-Dibenzyloxy-4-(1′-hydroxybut-3′-enyl)-thiolane (28/29). Allylmagnesium bromide (1 M in Et_2O, 1.4 mL, 1.4 mmol) was added to a stirred solution of **27** (230 mg, 0.70 mmol) in anhydrous Et_2O (5 mL) under N_2 atmosphere at 0 °C dropwise, and the mixture was stirred at ambient temperature for 16 h. The reaction was quenched with ice (5 mL), and the mixture was diluted with Et_2O (100 mL). The reaction mixture was washed with H_2O (2 × 50 mL) and brine (50 mL). The organic layer was

dried over anhydrous Na_2SO_4, filtered, and concentrated. Analysis by NMR showed that the crude product was present as 1:2 mixture of diastereomers **28** and **29**, respectively. The crude product was purified by flash chromatography [CH_2Cl_2/MeOH, 1:0 → 49:1] to give **28** (133 mg, 51%) and **29** (78 mg, 30%).

Data for the major diastereomer (**28**): $[\alpha]_D$ −12.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.38−7.27 (m, 10H, Ar), 5.81 (dddd, 1H, $J_{6b,7}$ = 6.9 Hz, $J_{6a,7}$ = 7.3 Hz, $J_{7,8a}$ = 10.2 Hz, $J_{7,8b}$ = 17.0 Hz, H-7), 5.11 (dddd, 1H, $J_{6a,8b}$= $J_{6b,8b}$ = $J_{8a,8b}$ = 1.8 Hz, H-8b), 5.09 (dddd, 1H, $J_{6a,8a}$= $J_{6b,8a}$ = 1.1 Hz H-8a), 4.78 and 4.63 (2d, each 1H, $J_{a,b}$ = 11.6 Hz, C*H*$_2$Ph), 4.60 and 4.58 (2d, each 1H, $J_{a,b}$ = 11.8 Hz, C*H*$_2$Ph), 4.18 (ddd, 1H, $J_{1a,2}$ = $J_{1b,2}$ = $J_{2,3}$ = 5.6 Hz, H-2), 4.11 (dd, 1H, $J_{3,4}$ = 5.5 Hz, H-3), 3.83 (ddd, 1H, $J_{4,5}$ = 2.8 Hz, $J_{5,6b}$ = 5.9 Hz, $J_{5,6a}$ = 7.4 Hz, H-5), 3.49 (dd, 1H, H-4), 3.02 (dd, 1H, $J_{1a,1b}$ = 11.1 Hz, H-1a), 2.83 (dd, 1H, H-1b), 2.24 (ddddd, 1H, $J_{6a,6b}$ = 14.1 Hz, H-6a), 2.12 (ddddd, 1H, H-6a); ^{13}C NMR ($CDCl_3$) δ 138.2, 137.7 (2C_{ipso}), 134.5 (C-7), 128.8−128.0 (10C_{Ar}), 118.1 (C-8), 86.0 (C-3), 84.5 (C-2), 73.1, 72.2 (2 *C*H$_2$Ph), 70.2 (C-5), 54.9 (C-4), 41.6 (C-6), 31.9 (C-1); MALDI-TOF MS *m*/*e* 371.17 (M^+ + H), 393.19 (M^+ + Na), 409.16 (M^+ + K). Anal. Calcd for $C_{22}H_{26}O_3S$: C, 71.32; H, 7.07. Found: C, 71.59; H, 7.21.

Data for the minor diastereomer (**29**): $[\alpha]_D$ −25.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 7.39−7.28 (m, 10H, Ar), 5.83 (dddd, 1H, $J_{6b,7}$ = 6.8 Hz, $J_{6a,7}$ = 7.7 Hz, $J_{7,8a}$ = 9.6 Hz, $J_{7,8b}$ = 17.5 Hz, H-7), 5.13 (dddd, 1H, $J_{6a,8b}$= $J_{6b,8b}$ = $J_{8a,8b}$ = 1.5 Hz, H-8b), 5.11 (dddd, 1H, $J_{6a,8a}$= $J_{6b,8a}$ = 1.5 Hz H-8a), 4.71 and 4.65 (2d, each 1H, $J_{a,b}$ = 11.7 Hz, C*H*$_2$Ph), 4.59 and 4.56 (2d, each 1H, $J_{a,b}$ = 11.9 Hz, C*H*$_2$Ph), 4.30 (dd, 1H, $J_{2,3}$ = $J_{3,4}$ = 4.1 Hz, H-3), 4.22 (ddd, 1H, $J_{1a,2}$ = $J_{1b,2}$ = 4.7 Hz, H-2), 3.77 (ddd, 1H, $J_{4,5}$ = $J_{5,6b}$ = 7.6 Hz, $J_{5,6a}$ = 4.0 Hz, H-5), 3.36 (dd, 1H, H-4), 3.08 (dd, 1H, $J_{1a,1b}$ = 11.2 Hz, H-1a), 2.90 (dd, 1H, H-1b), 2.45 (m, 1H, H-6a), 2.19 (ddddd, 1H, H-6a); ^{13}C NMR ($CDCl_3$) δ 138.1, 134.6 (2C_{ipso}), 134.5 (C-7), 128.8−128.0 (10C_{Ar}), 118.6 (C-8), 85.0 (C-3), 84.9 (C-2), 73.0 (C-5), 72.2, 71.8 (2 *C*H$_2$Ph), 54.3 (C-4), 40.3 (C-6), 33.4 (C-1); MALDI-TOF MS *m*/*e* 371.12 (M^+ + H), 393.14 (M^+ + Na). Anal. Calcd for $C_{22}H_{26}O_3S$: C, 71.32; H, 7.07. Found: C, 71.57; H, 6.89.

(2*S*,3*S*,4*R*,5*S*)-2,3-Dibenzyloxy-5-hydroxy-7-methylene-*cis*-1-thioniabicyclo[3.3.0]octane Triflate (30). Br_2 (11.4 μL, 0.21 mmol) was added to a stirred solution of **28** (78 mg, 0.21 mmol) in CH_2Cl_2 (6 mL) at 0 °C under N_2. The mixture was stirred at 0 °C for 1.5 h, and then silver triflate (65 mg, 0.21 mmol) was added. Stirring was continued at 0 °C for an additional 2 h, and the mixture was filtered. The filtrate was concentrated and then dissolved in H_2O/THF (1:1, 5 mL). Silver oxide (48 mg, 0.25 mmol) was added, and the mixture was stirred at ambient temperature for 16 h and concentrated. The crude product was purified by flash chromatography [CH_2Cl_2/MeOH, 1:0 à 10:1] to give compound **30** as a pale yellow oil (81 mg, 77%). The stereochemistry at C-5 was assigned with the aid of a 1D-NOESY spectrum which showed no correlation between H-3 and H-5: $[\alpha]_D$ +47.0 (*c* 1.1, CH_2Cl_2); ^{1}H NMR (CD_2Cl_2): δ 7.38−7.21 (m, 10H, Ar), 6.14 (dd, 1H, $J_{6a,8a}$ = $J_{8a,8b}$ = 2.4 Hz, H-8a), 6.03 (dd, 1H, $J_{6a,8b}$ = 2.4 Hz, H-8b), 5.16 (s, 1H, H-3), 5.11 (d, 1H, $J_{5,OH}$ = 5.4 Hz, OH), 5.02 (d, 1H, $J_{4,5}$ = 8.5 Hz, H-4), 4.98 (m, 1H, H-5), 4.75 and 4.60 (2d, each 1H, $J_{a,b}$ = 11.6 Hz, C*H*$_2$Ph), 4.68 and 4.43 (2d, each 1H, $J_{a,b}$ = 11.3 Hz, C*H*$_2$Ph), 4.49 (d, 1H, $J_{1b,2}$ = 4.5 Hz, H-2), 4.08 (dd, 1H, $J_{1a,1b}$ = 14.5 Hz, H-1b), 3.70 (d, 1H, H-1a), 3.32 (dddd, 1H, $J_{6a,6b}$ = 16.1 Hz, H-6a), 3.04 (dd, 1H, H-6b); ^{13}C NMR (CD_2Cl_2) δ 136.8, 136.7 (2C_{ipso}), 135.9 (C-7), 128.9−128.6 (10C_{Ar}), 128.7 (C-8), 120.9 (q, 1C, $J_{C,F}$ = 318.1 Hz, OTf), 83.9 (C-3), 83.8 (C-2), 72.6, 72.5 (2 *C*H$_2$Ph), 72.2 (C-5), 71.0 (C-4), 54.4 (C-1), 40.0 (C-6); MALDI-TOF MS *m*/*e* 369.26 (M^+ − OTf). Anal. Calcd for $C_{23}H_{25}F_3O_6S_2$: C, 53.27; H, 4.86. Found: C, 53.19; H, 4.76.

(2*S*,3*S*,4*R*,5*R*)-2,3-Dibenzyloxy-5-hydroxy-7-methylene-*cis*-1-thioniabicyclo[3.3.0]octane Triflate (31). Br_2 (10.2 μL, 0.19 mmol) was added to a stirred solution of **29** (70 mg, 0.19 mmol) in CH_2Cl_2 (6 mL) at 0 °C under N_2. The mixture was stirred at 0 °C for 1.5 h, and then silver triflate (58 mg, 0.19 mmol) was added. Stirring was continued at 0 °C for an additional 2 h, and the mixture was filtered. The filtrate was concentrated, and the residue was dissolved in H_2O/THF (1:1, 5 mL). Silver oxide (43 mg, 0.22 mmol) was added, and the mixture was stirred at ambient temperature for 16 h and concentrated. The crude product was purified by flash chromatography [CH_2Cl_2/MeOH, 1:0 → 10:1] to give compound **31** as a pale yellow oil (68 mg, 72%). The stereochemistry at C-5 was assigned with the aid of a 1D-NOESY spectrum which showed a strong correlation between H-3 and H-5: $[\alpha]_D$ +101.3 (*c* 0.8, CH_2Cl_2); ^{1}H NMR (CD_2Cl_2): δ 7.31−7.14 (m, 10H, Ar), 6.15 (dd, 1H, $J_{6a,8a}$ = $J_{8a,8b}$ = 2.7 Hz, H-8a), 5.96 (dd, 1H, $J_{6a,8b}$ = 2.7 Hz, H-8b), 5.03 (d, 1H, $J_{5,OH}$ = 3.6 Hz, OH), 4.80 (bs, 2H, H-4, H-5), 4.63 and 4.49 (2d, each 1H, $J_{a,b}$ = 11.6 Hz, C*H*$_2$Ph), 4.56 (s, 1H, H-3), 4.41 (s, 2H, C*H*$_2$Ph), 4.38 (d, 1H, $J_{1b,2}$ = 4.7 Hz, H-2), 3.84 (dd, 1H, $J_{1a,1b}$ = 14.7 Hz, H-1b), 3.59 (d, 1H, H-1a), 3.33 (ddddd, 1H, $J_{6a,6b}$ = 16.0 Hz, H-6a), 2.79 (bd, 1H, H-6b); ^{13}C NMR (CD_2Cl_2) δ 141.5 (C-7), 136.5, 135.9 (2C_{ipso}), 129.0−128.4 (10C_{Ar}), 127.5 (C-8), 120.9 (q, 1C, $J_{C,F}$ = 318.4 Hz, OTf), 86.2 (C-3), 83.9 (C-2), 80.4 (C-4), 75.2 (C-5), 72.7, 72.6 (2 *C*H$_2$Ph), 52.5 (C-1), 43.1 (C-6); MALDI-TOF MS *m*/*e* 369.36 (M^+ − OTf). Anal. Calcd for $C_{23}H_{25}F_3O_6S_2$: C, 53.27; H, 4.86. Found: C, 53.31; H, 4.72.

(2*S*,3*S*,4*R*,5*R*)-2,3,5-Trihydroxy-7-methylene-*cis*-1-thioniabicyclo[3.3.0]octane Triflate (10). BCl_3 gas was bubbled vigorously through a solution of **30** (102 mg, 0.20 mmol) in CH_2Cl_2 (10 mL) at −78 °C under N_2 atmosphere for 4 min. The mixture was stirred at −78 °C for 1.5 h, and a stream of dry air was blown vigorously over the solution to remove excess BCl_3. The reaction was quenched with MeOH (5 mL), and the solvent was removed. The residue was coevaporated with MeOH (2 × 5 mL), and the crude product was washed with CH_2Cl_2 (2 × 2 mL) to give compound **10** as a colorless oil (55 mg, 83%): $[\alpha]_D$ +169.1 (*c* 0.9, MeOH); ^{1}H NMR (CD_3OD) δ 6.29 (dd, 1H, $J_{6b,8a}$ = 1.2 Hz, $J_{6a,8a}$ = 2.7 Hz, H-8a), 6.16 (dd, 1H, $J_{6b,8b}$ = 2.3 Hz, $J_{6a,8b}$ = 2.7 Hz, H-8b), 4.87 (dd, 1H, $J_{5,6b}$ = 2.3 Hz, $J_{5,6a}$ = 5.2 Hz, H-5), 4.60 (dd, 1H, $J_{2,3}$ = $J_{3,4}$ = 2.0 Hz, H-3), 4.56 (ddd, 1H, $J_{1a,2}$ = 2.1 Hz, $J_{1b,2}$ = 4.2 Hz, H-2), 4.13 (bs, 1H, H-4), 4.10 (dd, 1H, $J_{1a,1b}$ = 14.1 Hz, H-1b), 3.70 (dddd, 1H, $J_{6a,6b}$ = 16.2 Hz, H-6a), 3.55 (dd, 1H, H-1a), 2.87 (dddd, 1H, H-6b); ^{13}C NMR (CD_3OD) δ 142.2 (C-7), 125.9 (C-8), 120.6 (q, 1C, $J_{C,F}$ = 316.5 Hz, OTf), 81.4 (C-2), 81.0 (C-4), 78.8 (C-3), 74.2 (C-5), 54.2 (C-1), 42.9 (C-6); MALDI-TOF MS *m*/*e* 189.24 (M^+ − OTf). Anal. Calcd for $C_9H_{13}F_3O_6S_2$: C, 31.95; H, 3.87. Found: C, 31.75; H, 3.91.

(2*S*,3*S*,4*R*,5*S*)-2,3,5-Trihydroxy-7-methylene-*cis*-1-thioniabicyclo[3.3.0]octane Triflate (11). BCl_3 gas was bubbled vigorously through a solution of **31** (80 mg, 0.15 mmol) in CH_2Cl_2 (10 mL) at −78 °C under N_2 atmosphere for 4 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 (5 mL), and the solvent was removed. The residue was coevaporated with MeOH (2 × 5 mL), and the crude product was washed with CH_2Cl_2 (2 × 2 mL) to give compound **11** as a colorless oil (42 mg, 81%): $[\alpha]_D$ +203.8 (*c* 0.8, MeOH); ^{1}H NMR (CD_3OD) δ 6.18 (dd, 1H, $J_{6b,8a}$ = $J_{6a,8a}$ = 2.9 Hz, H-8a), 6.11 (bs, 1H, H-8b), 4.97 (s, 1H, H-3), 4.79 (ddd, 1H, $J_{5,6b}$ = 7.2 Hz, $J_{4,5}$ = 8.0 Hz, $J_{5,6a}$ = 9.8 Hz, H-5), 4.60 (d, 1H, $J_{1b,2}$ = 4.1 Hz, H-2), 4.58 (d, 1H, H-4), 4.14 (dd, 1H, $J_{1a,1b}$ = 14.1 Hz, H-1b), 3.59 (dd, 1H, H-1a), 3.47 (dddd, 1H, $J_{6a,6b}$ = 15.6 Hz, H-6a), 3.05 (dd, 1H, H-6b); ^{13}C NMR (CD_3OD) δ 138.4 (C-7), 125.9 (C-8), 120.6 (q, 1C, $J_{C,F}$ = 316.1 Hz, OTf), 79.4 (C-3), 79.1 (C-4), 73.2 (C-2), 71.4 (C-5), 55.2 (C-1), 40.3 (C-6); MALDI-TOF MS *m*/*e* 189.12 (M^+ − OTf). Anal. Calcd for $C_9H_{13}F_3O_6S_2$: C, 31.95; H, 3.87. Found: C, 31.66; H, 3.83.

(2*S*,3*S*,4*R*,5*R*,7*R*/*S*)-2,3,5-Trihydroxy-7-methyl-*cis*-1-thioniabicyclo[3.3.0]octane Triflate (12/13). Pd/C (10 mg) was added to a stirred solution of **10** (38 mg, 0.11 mmol) in MeOH (5 mL). The mixture was stirred under H_2 pressure (100 psi) for 5 h, filtered though Celite, and concentrated. The residue was washed with CH_2Cl_2 (2 × 2 mL) to give a pale yellow oil (27 mg, 71%). Analysis by NMR showed that the product was a mixture of two isomers

(~3:2) at the stereogenic C-7 center. The stereochemistry was assigned with the aid of NOESY spectrum which showed a strong correlation between H-1a and H-8 for compound **12**, whereas compound **13** showed a correlation between H-1a and H-7.

Data for the major diastereomer (**12**): ^{1}H NMR (CD_3OD) δ 4.99 (ddd, 1H, $J_{4,5} = J_{5,6a} = 5.2$ Hz, $J_{5,6b} = 7.9$ Hz, H-5), 4.66 (dd, 1H, $J_{2,3} = 2.0$ Hz, $J_{1b,2} = 4.1$ Hz, H-2), 4.62 (bs, 1H, H-3), 4.31 (d, 1H, H-4), 4.28 (m, 1H, H-7), 3.80 (dd, 1H, $J_{1a,1b} = 14.4$ Hz, H-1b), 3.68 (d, 1H, H-1a), 2.80 (ddd, 1H, $J_{6a,6b} = 13.8$ Hz, H-6a), 2.11 (ddd, 1H, H-6b), 1.68 (d, 3H, H-8); ^{13}C NMR (CD_3OD) δ 120.6 (q, 1C, $J_{C,F} = 253.0$ Hz, OTf), 81.0 (C-3), 80.4 (C-2), 79.9 (C-4), 75.4 (C-5), 57.6 (C-7), 48.6 (C-1), 44.4 (C-6), 17.6 (C-8).

Data for the minor diastereomer (**13**): ^{1}H NMR (CD_3OD) δ 4.77 (dd, 1H, $J_{4,5} = 1.5$ Hz, $J_{5,6b} = 3.7$ Hz, H-5), 4.51 (ddd, 1H, $J_{1a,2} = J_{2,3} = 2.4$ Hz, $J_{1b,2} = 4.8$ Hz, H-2), 4.46 (m, 1H, H-7), 4.40 (dd, 1H, $J_{3,4} = 4.8$ Hz, H-3), 4.28 (dd, 1H, H-4), 3.71 (dd, 1H, $J_{1a,1b} = 14.5$ Hz, H-1b), 3.44 (d, 1H, H-1a), 2.73 (ddd, 1H, $J_{6a,6b} = 14.2$ Hz, H-6a), 2.34 (dd, 1H, H-6b), 1.61 (d, 3H, H-8); ^{13}C NMR (CD_3OD) δ 120.6 (q, 1C, $J_{C,F} = 316.3$ Hz, OTf), 80.6 (C-3), 80.6 (C-4), 79.8 (C-2), 76.1 (C-5), 53.4 (C-7), 43.1 (C-6), 40.6 (C-1), 13.0 (C-8).

For the mixture of **12** and **13**: MALDI-TOF MS *m*/*e* 191.26 ($M^+ - OTf$). Anal. Calcd for $C_9H_{15}F_3O_6S_2$: C, 31.76; H, 4.44. Found: C, 31.69; H, 4.62.

(2*S*,3*S*,4*R*,5*S*,7*R*)-2,3,5-Trihydroxy-7-methyl-*cis*-1-thioniabicyclo[3.3.0]octane Triflate (14). Pd/C (12 mg) was added to a stirred solution of **11** (45 mg, 0.13 mmol) in MeOH (6 mL). The mixture was stirred under H_2 pressure (100 psi) for 4 h, filtered though Celite, and concentrated. The residue was washed with CH_2Cl_2 (2 × 2 mL) to give a pale yellow oil (35 mg, 77%). Analysis by NMR showed that the product was a mixture of two isomers (~4:1) at the stereogenic C-7 center. The major component of the mixture was assigned to be the diastereomer with the *R* configuration at C-7 on the basis of a 1D-NOESY spectrum, which showed a correlation between H-1a and H-8.

Data for the major diastereomer (**14**): ^{1}H NMR (CD_3OD) δ 4.78 (dd, 1H, $J_{2,3} = J_{3,4} = 2.2$ Hz, H-3), 4.70 (ddd, 1H, $J_{4,5} = 6.3$ Hz, $J_{5,6b} = 8.3$ Hz, $J_{5,6a} = 11.2$ Hz, H-5), 4.54 (ddd, 1H, $J_{1a,2} = 2.2$ Hz, $J_{1b,2} = 4.6$ Hz, H-2), 4.35 (dd, 1H, H-4), 4.08 (ddt, 1H, $J_{6b,7} = J_{7,8} = 6.7$ Hz, $J_{7,8} = 12.9$ Hz, H-3), 3.76 (dd, 1H, $J_{1a,1b} = 14.6$ Hz, H-1b), 3.51 (dd, 1H, H-1a), 2.61 (ddd, 1H, $J_{6a,6b} = 12.4$ Hz, H-6a), 2.43 (dd, 1H, H-6b), 1.56 (d, 3H, H-8); ^{13}C NMR (CD_3OD) δ 120.6 (q, 1C, $J_{C,F} = 316.3$ Hz, OTf), 79.0 (C-3), 77.9 (C-2), 73.2 (C-5), 71.2 (C-4), 48.8 (C-7), 41.5 (C-1), 40.0 (C-6), 13.2 (C-8); MALDI-TOF MS *m*/*e* 191.14 ($M^+ - OTf$). Anal. Calcd for $C_9H_{15}F_3O_6S_2$: C, 31.76; H, 4.44. Found: C, 31.43; H, 4.68.

Conclusions

The syntheses of the bicyclic sulfonium analogues (**7**−**14**) related to australine have been achieved starting from a common precursor **21**. The conformational preferences of these compounds based on vicinal proton coupling constants and NOE data have been proposed. We note that there is significant conformational change when changing an *exo*-methylene group to a methyl group. We also note that the hydroxyl groups at C-2 and C-3 prefer to occupy pseudoaxial positions. Both electrostatic effects and steric effects govern the conformational preferences of these compounds. The activities of these compounds as glycosidase inhibitors will be the subject of future investigations.

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