JOC*Article*

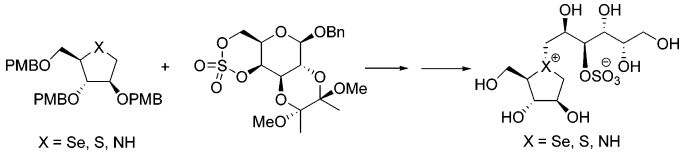
# New Synthetic Routes to Chain-Extended Selenium, Sulfur, and Nitrogen Analogues of the Naturally Occurring Glucosidase Inhibitor Salacinol and their Inhibitory Activities against Recombinant Human Maltase Glucoamylase

Hui Liu,[†] Ravindranath Nasi,[†] Kumarasamy Jayakanthan,[†] Lyann Sim,[‡] Heather Heipel,[‡] David R. Rose,[‡] and B. Mario Pinto*,[†]

*Department of Chemistry, Simon Fraser University, Burnaby, British Columbia, Canada V5A 1S6, and Department of Medical Biophysics, University of Toronto and Division of Cancer Genomics and Proteomics, Ontario Cancer Institute, Toronto, Canada M5G 1L7*

*bpinto@sfu.ca*

*Received May 17, 2007*




Six heteroanalogues (X = S, Se, NH) of the naturally occurring glucosidase inhibitor salacinol, containing polyhydroxylated, acyclic chains of 6-carbons, were synthesized for structure−activity studies with different glycosidase enzymes. The target zwitterionic compounds were synthesized by means of nucleophilic attack of the PMB-protected 1,4-anhydro-4-seleno-, 1,4-anhydro-4-thio-, and 1,4-anhydro-4-imino-D-arabinitols at the least hindered carbon atom of 1,3-cyclic sulfates. These 1,3-cyclic sulfates were derived from D-glucose and D-galactose, and significantly, they utilized butane diacetal as the protecting groups for the *trans* 2,3-diequatorial positions. Deprotection of the coupled products proceeded smoothly, unlike in previous attempts with different protecting groups, and afforded the target selenonium, sulfonium, and ammonium sulfates with different stereochemistry at the stereogenic centers. The four new heterosubstituted compounds (X = Se, NH) inhibited recombinant human maltase glucoamylase (MGA), one of the key intestinal enzymes involved in the breakdown of glucose oligosaccharides in the small intestine. The two selenium derivatives each had $K_i$ values of 0.10 $\mu$M, giving the most active compounds to date in this general series of zwitterionic glycosidase inhibitors. The two nitrogen compounds also inhibited MGA but were less active, with $K_i$ values of 0.8 and 35 $\mu$M. The compounds in which X = S showed $K_i$ values of 0.25 and 0.17 $\mu$M. Comparison of these data with those reported previously for related compounds reinforces the requirements for an effective inhibitor of MGA. With respect to chain extension, the configurations at C-2′ and C-4′ are critical for activity, the configuration at C-3′, bearing the sulfate moiety, being unimportant. It would also appear that the configuration at C-5′ is important but the relationship is dependent on the heteroatom.

## Introduction

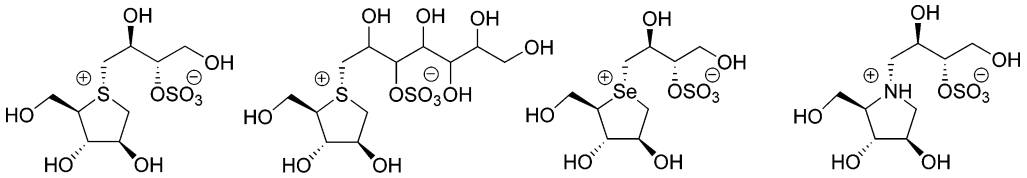
Recently, a new class of glycosidase inhibitor, namely salacinol (**1**)[1] and kotalanol (**2**)[2] (Chart 1), with an intriguing inner-salt sulfonium−sulfate structure, was isolated from the roots and stems of the plant *Salacia reticulata*. Salacinol has been shown to be an inhibitor of intestinal glucosidase enzymes[1−4] and, thus, capable of attenuating the spike in blood glucose levels that is experienced by diabetics after consuming a meal

* To whom correspondence should be addressed. Tel: (604) 291-4152. Fax: (604) 291-4860.
[†] Simon Fraser University.
[‡] University of Toronto and Ontario Cancer Institute.

(1) Yoshikawa, M.; Murakami, T.; Shimada, H.; Matsuda, H.; Yamahara, J.; Tanabe, G.; Muraoka, O. *Tetrahedron Lett.* **1997**, *38*, 8367−8370.
(2) Yoshikawa, M.; Murakami, T.; Yashiro, K.; Matsuda, H. *Chem. Pharm. Bull.* **1998**, *46*, 1339−1340.
(3) Yuasa, H.; Takada, J.; Hashimoto, H. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1137−1139.
(4) Yoshikawa, M.; Morikawa, T.; Matsuda, H.; Tanabe, G.; Muraoka, O. *Bioorg. Med. Chem.* **2002**, *10*, 1547−1554.

10.1021/jo071045m CCC: $37.00 
Published on Web 07/21/2007

**CHART 1**

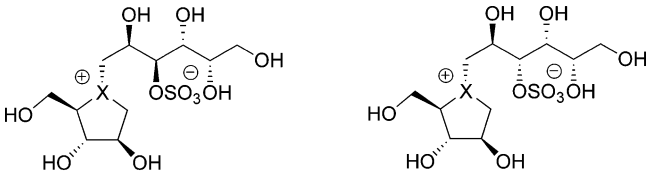


**1** **2** **3** **4**

rich in carbohydrates.[5] It is noteworthy that a double blind study of the effects of the extract from *Salacia reticulata* on human patients with type II diabetes mellitus has shown that the extract is an effective treatment of type 2 diabetes with side effects comparable to the placebo control group.[6] It is postulated that the inhibition of glucosidases by salacinol and kotalanol is due to their ability to mimic both the shape and charge of the oxacarbenium-ion-like transition state involved in the enzymatic reactions.[7] The structure of kotalanol is very similar to salacinol, with the alditol side chain being extended by three carbons. However, the absolute configuration of the stereogenic centers in the heptitol chain has not been determined. The 1,4-thioanhydropentitol portion of kotalanol has the identical D-arabinitol configuration as salacinol.

We and others have synthesized salacinol,[7,8] as well as its selenium (blintol, **3**)[9] and nitrogen (ghavamiol, **4**)[10] congeners (Chart 1). Other stereoisomers of salacinol,[11] analogues containing six-membered heterocyclic rings,[12,13] and some chain-extended analogues of salacinol have also been synthesized.[14−16] The selenium analogue of salacinol, blintol, has been shown to be very effective in controlling blood glucose levels in rats after a carbohydrate meal, thus providing a lead candidate for the treatment of type 2 diabetes.[9] Structure−activity studies revealed an interesting variation in the inhibitory power of these compounds against glycosidase enzymes of different origin.[9−12,14−17] The molecular basis for this selectivity is being investigated through structural studies of the enzyme-bound inhibitors using molecular modeling in conjunction with conformational analysis by STD-NMR techniques[18] and X-ray crystallography.[19]

**CHART 2**



**5**. X = Se
**6**. X = S
**7**. X = NH

**8**. X = Se
**9**. X = S
**10**. X = NH

Our previous studies had indicated that the stereochemistry at the stereogenic center at the 2′ position of the side chain, namely the *S*-configuration, might be critical for inhibitory activity. Thus, the chain-extended sulfonium ions **6** and **9** with the 2′-*S*-configuration were active against human maltase glucoamylase with $K_i$ values of similar magnitudes as those of salacinol.[15] However, the synthetic route that afforded compounds **6** and **9** was not readily applicable to the syntheses of the corresponding selenium analogues and did not afford these compounds. Since the selenium congener of salacinol, blintol, was shown to be a glucosidase inhibitor with a $K_i$ value in the same range as salacinol,[9] the synthesis of chain-extended selenium analogues of salacinol was of particular interest. Accordingly, we have designed an alternative synthetic route and report herein its application to the synthesis of the selenium, sulfur, and nitrogen analogues **5**−**10** (Chart 2).

## Results and Discussion

Our synthetic strategy was analogous to that used for the synthesis of the sulfonium analogues **6** and **9**[15] in that it involved the opening of a 1,3-cyclic sulfate ring by nucleophilic attack of a protected heteroether (Scheme 1). However, in the previous report of the synthesis of **6** and **9**, benzyl groups were used to protect both anhydroheteroalditols and cyclic sulfates, and hydrogenolysis was used to remove the benzyl protecting groups.[15] The corresponding synthesis of the selenium analogues using this strategy was unsuccessful owing to poisoning of the catalyst. Our new strategy is reliant on the protection of the *trans*-diequatorial 1,2-hydroxyl groups as a butane diacetal. *p*-Methoxybenzyl (PMB) groups were used to protect the 2-, 3-, and 5-positions in the heteroanhydroalditols. However, for the desired 1,3-cyclic sulfates derived from D-galactose and D-glucose, PMB groups were deemed to be unsuitable since they were susceptible to oxidation. Methods for selective

(5) Serasinghe, S.; Serasinghe, P.; Yamazaki, H.; Nishiguchi, K.; Hombhanje, F.; Nakanishi, S.; Sawa, K.; Hattori, M.; Namba, T. *Phytother. Res*. **1990**, *4*, 205−206.
(6) Jayawardena, M. H. S.; de Alwis, N. M. W.; Hettigoda, V.; Fernando, D. J. S. *J. Ethnopharmacol*. **2005**, *97*, 215−218.
(7) Ghavami, A.; Johnston, B. D.; Pinto, B. M. *J. Org. Chem*. **2001**, *66*, 2312−2317. Ghavami, A.; Sadalapure, K. S.; Johnston, B. D.; Lobera, M.; Snider, B. B.; Pinto, B. M. *Synlett* **2003**, 1259−1262.
(8) Yuasa, H.; Takada, J.; Hashimoto, H. *Tetrahedron Lett.* **2000**, *41*, 6615−6618.
(9) Johnston, B. D.; Ghavami, A.; Jensen, M. T.; Svensson, B.; Pinto, B. M. *J. Am. Chem. Soc*. **2002**, *124*, 8245−8250. Liu, H.; Pinto, B. M. *J. Org. Chem*. **2005**, *70*, 753−755. Pinto, B. M.; Johnston, B. D.; Ghavami, A.; Szczepina, M. G.; Liu, H.; Sadalapure, K. US Patent, Filed June 25, 2004.
(10) Ghavami, A.; Johnston, B. D.; Jensen, M. T.; Svensson, B.; Pinto, B. M. *J. Am. Chem. Soc*. **2001**, *123*, 6268−6271. Muraoka, O.; Ying, S.; Yoshikai, K.; Matsuura, Y.; Yamada, E.; Minematsu, T.; Tanabe, G.; Matsuda, H.; Yoshikawa, M. *Chem. Pharm. Bull*. **2001**, *49*, 1503−1505.
(11) Ghavami, A.; Johnston, B. D.; Maddess, M. D.; Chinapoo, S. M.; Jensen, M. T.; Svensson, B.; Pinto, B. M. *Can. J. Chem*. **2002**, *80*, 937−942. Kumar, N. S.; Pinto, B. M. *Carbohydr. Res*. **2005**, *340*, 2612−2619.
(12) Szczepina, M. G.; Johnston, B. D.; Yuan, Y.; Svensson, B.; Pinto, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 12458−12469.
(13) Gallienne, E.; Benazza, M.; Demailly, G.; Bolte, J.; Lemaire, M. *Tetrahedron* **2005**, *61*, 4557−4568.
(14) Liu, H.; Pinto, B. M. *Can. J. Chem.* **2006**, *84*, 497−505. Liu, H.; Sim, L.; Rose, D. R.; Pinto, B. M. *J. Org. Chem*. **2005**, *71*, 3007−3013.
(15) Johnston, B. D.; Hensen, H. H.; Pinto, B. M. *J. Org. Chem.* **2006**, *71*, 1111−1118.
(16) Nasi. R.; Sim, L.; Rose, D. R.; Pinto, B. M. *J. Org. Chem.* **2007**, *72*, 180−186.
(17) Li, Y.; Scott, C. R.; Chamoles, N. A.; Chavami, A.; Pinto, B. M.; Frantisek, T.; Gelb, M. H. *Clin. Chem.* **2004**, *50*, 1785−1790.
(18) Wen, X.; Yuan, Y.; Kuntz, D. A.; Rose, D. R.; Pinto, B. M. *Biochemistry* **2005**, *44*, 6729−6738.
(19) Kuntz, D.; Ghavami, A.; Johnston, B. D.; Pinto, B. M.; Rose, D. R. *Tetrahedron: Asymmetry* **2005**, *16*, 25−30.

**SCHEME 1**

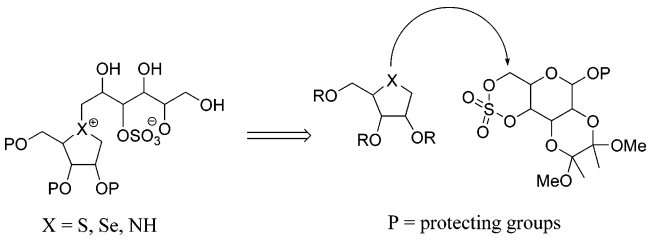
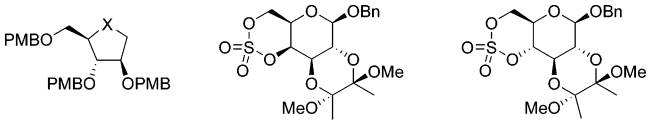



**CHART 3**



**11** X = Se
**12** X = S
**13** X = NH

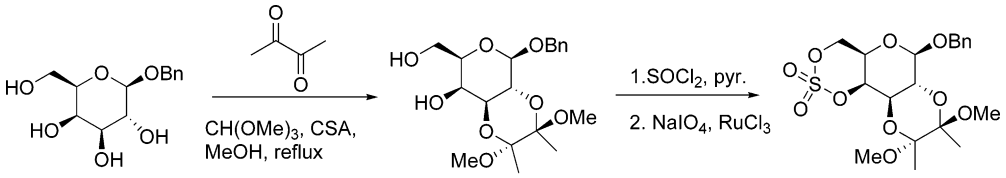
**14** **15**

protection of vicinal trans diequatorial diols are rare. In recent years, Ley and co-workers[20] have introduced dispiroketals as protecting groups for trans diequatorial 1,2-diols, the high selectivity in the protection of trans diequatorial 1,2-diols being attributed to the combination of two factors: the formation of the sterically less demanding trans ring junction and the control of configuration at the two acetal centers by the operation of anomeric effects.[20] Recently, Hense et al.[21] reported a convenient method to utilize butane diacetal (BDA) protecting groups for trans diequatorial 1,2-diols. We envisioned the use of butane diacetal (BDA) protecting groups for the cyclic sulfates **14** and **15** (Chart 3). Our previous work also suggested that the release of additional ring strain in the opening of a cyclic sulfate was beneficial.[7,9−11] The BDA at the 2,3-positions of the cyclic sulfates **14** and **15** would thus play a dual role as a protecting group and a reaction facilitator for the coupling reactions with the anhydro heteroalditols **11**−**13** (Chart 3). We reasoned that after the coupling reactions the BDA and PMB groups could be readily removed by treatment with trifluoroacetic acid.

The synthesis of the BDA-protected cyclic sulfate (**14**) started from benzyl $\beta$-D-galactopyranoside (**16**)[22] (Scheme 2). Following the procedure described by Hense et al. for the preparation of similar compounds,[21] compound **16** was refluxed with 2,3-butanedione, trimethyl orthoformate, and methanol, with CSA as a catalyst, for 12 h. The resulting benzyl 2,3-*O*-[(2*R*,3*R*)-2,3-dimethoxybutane-2,3-diyl]-$\beta$-D-galactopyranoside **17** was then reacted with thionyl chloride to afford the corresponding cyclic sulfites, which were subsequently oxidized with sodium periodate and $RuCl_3$ to afford the cyclic sulfate **14** in 60% yield (Scheme 2).

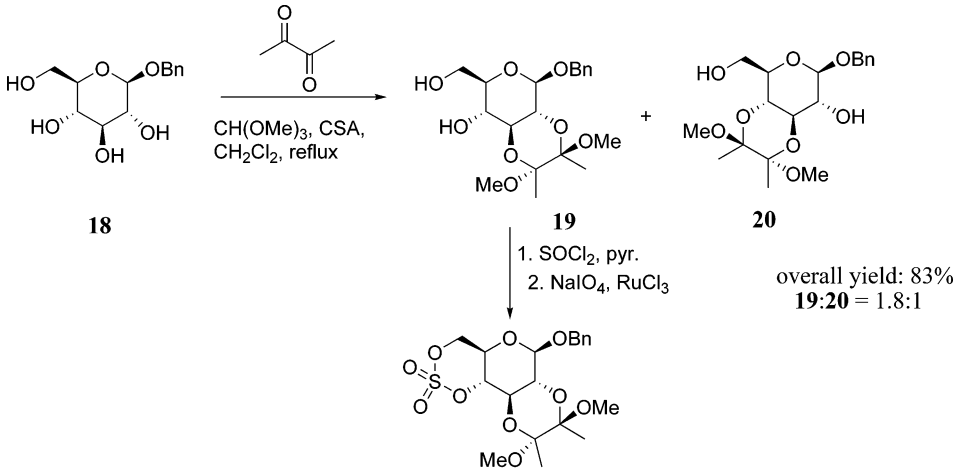
The synthesis of the BDA-protected cyclic sulfate (**15**) started from the benzyl $\beta$-D-glucopyranoside (**18**)[23] (Scheme 3). Compound **18** was refluxed with 2,3-butanedione, trimethyl orthoformate, and methanol, with CSA as a catalyst, for 12 h to give a mixture of the desired benzyl 2,3-*O*-[(2*R*,3*R*)-2,3-dimethoxybutane-2,3-diyl]-$\beta$-D-glucopyranoside (**19**) and benzyl 3,4-*O*-[(2*R*,3*R*)-2,3-dimethoxybutane-2,3-diyl]-$\beta$-D-glucopyranoside (**20**). The ratio of products **19**/**20** was 1.8:1, which suggested that the reaction had not proceeded with any significant regioselectivity.[21] Fortunately, compound **19** could be readily separated from the reaction mixture by column chromatography. The purified compound **19** was treated with thionyl chloride to afford the cyclic sulfites, which were

**SCHEME 2**




**16** **17** (72%) **14** (60% in two steps)

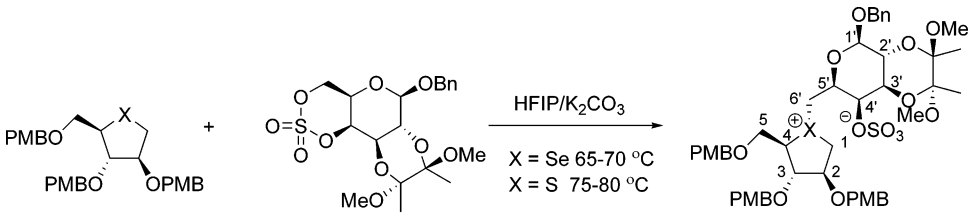
**SCHEME 3**




**18** **19** **20**

**15** (67% in two steps)

**SCHEME 4**

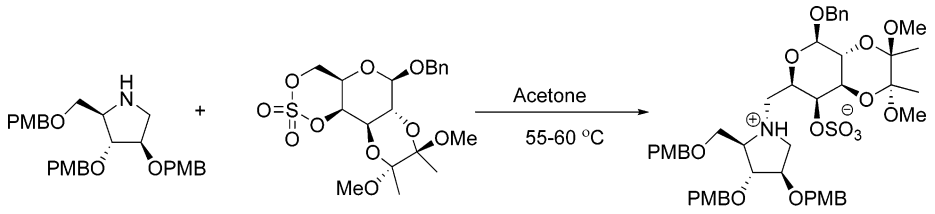



**11**. X = Se
**12**. X = S

**14**

**21**. X = Se (72%)
**22**. X = S (75%)

**SCHEME 5**

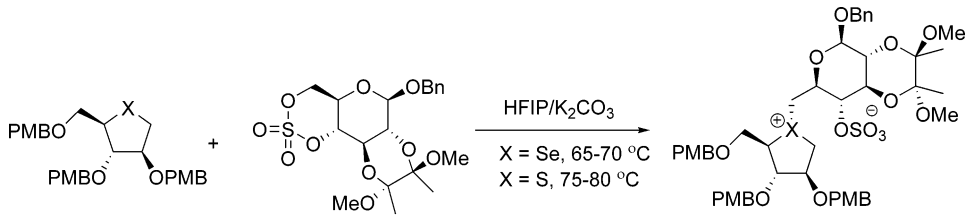



**13**

**14**

**23** (89%)

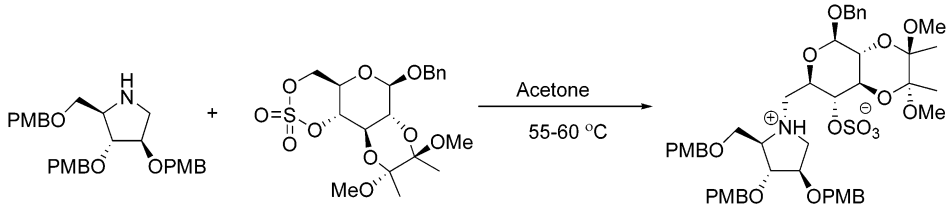
**SCHEME 6**




**11**. X = Se
**12**. X = S

**15**

**24**. X = Se (70%)
**25**. X = S (78%)




**13**

**15**

**26** (90%)

subsequently oxidized by sodium periodate and $RuCl_3$ to afford the corresponding cyclic sulfate **15** in 67% yield (Scheme 3).

The coupling reactions of the PMB-protected 1,4-anhydro-4-seleno-D-arabinitol (**11**) and 1,4-anhydro-4-thio-D-arabinitol (**12**) with the cyclic sulfate **14** were carried out in 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HFIP), which offers significant advantage compared with other solvents.[7,9,11,14] The cyclic sulfate **14** reacted with the PMB-protected 1,4-anhydro-4-seleno-D-arabinitol (**11**) and 1,4-anhydro-4-thio-D-arabinitol (**12**), to give the corresponding protected selenonium and sulfonium sulfates **21** and **22** in 72% and 75% yields, respectively (Scheme 4). Potassium carbonate was added to the reaction mixture to neutralize any acid generated by the possible decomposition of the cyclic sulfate **14** reacting with a trace amount of water. However, the presence of $K_2CO_3$ also led to a significant amount of byproduct from the reaction of the cyclic sulfate **14** with HFIP anion. Based on this observation, the amount of $K_2CO_3$ added was greatly reduced in later trials, and no byproduct was isolated. The presence of the cyclic sulfate **14** in slight excess over the seleno- and thioalditols **11** and **12** also resulted in improved yields. The coupling reactions of the PMB-protected 1,4-dideoxy-1,4-imino-D-arabinitol (**13**) with the cyclic sulfate **14** was carried out in dry acetone and proceeded smoothly to give the corresponding protected ammonium sulfate **23** in 89% yield (Scheme 5).

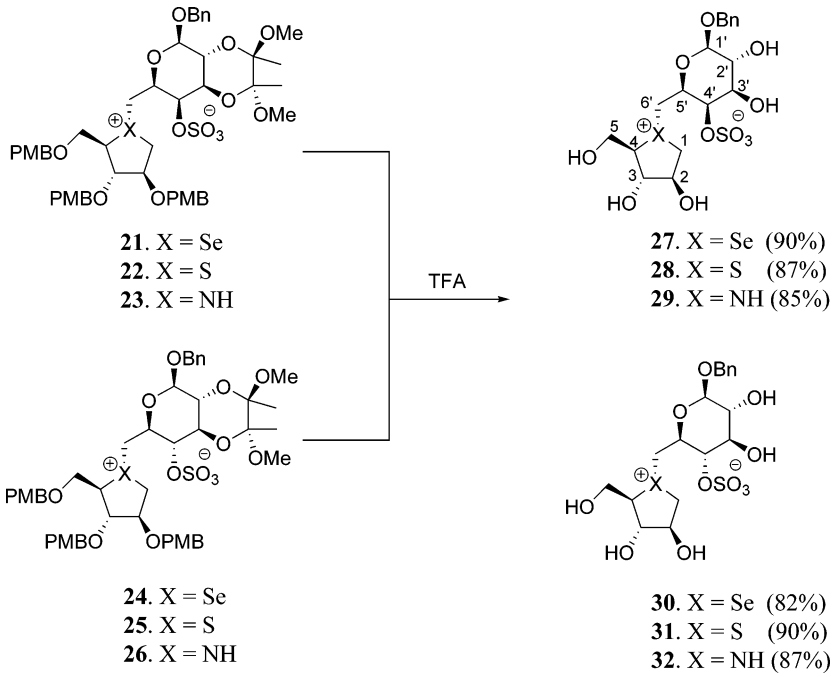
(20) Ley, S. V.; Baeschlin, D. K.; Dixon, D. J.; Foster, A. C.; Ince, S. J.; Priepke, H. W. M.; Reynolds, D. J. *Chem. Rev.* **2001**, *101*, 53−80 and the references within.

(21) Hense, A.; Ley, S. V.; Osborn, H. M. I.; Owen, D. R.; Poisson, J.-F.; Warriner, S. L.; Wesson, K. E. *J. Chem. Soc., Perkin Trans.* **1997**, *1*, 2023−2031.

(22) Xia, J.; Alderfer, J. L.; Piskorz, C. F.; Matta, K. L. *Chem. Eur. J.* **2001**, *7*, 356−367.

(23) Smits, E.; Engberts, J. B. F. N.; Kellogg, R. M.; van Doren, H. A. *J. Chem. Soc., Perkin Trans.* **1996**, *1*, 2873−2877.

**SCHEME 7**




**21**. X = Se
**22**. X = S
**23**. X = NH

**27**. X = Se (90%)
**28**. X = S (87%)
**29**. X = NH (85%)

**24**. X = Se
**25**. X = S
**26**. X = NH

**30**. X = Se (82%)
**31**. X = S (90%)
**32**. X = NH (87%)

The coupling reactions of the cyclic sulfate **15** with the PMB-protected 1,4-anhydro-4-seleno-D-arabinitol (**11**) and 1,4-anhydro-4-thio-D-arabinitol (**12**) were carried out in HFIP to give the corresponding protected selenonium and sulfonium sulfates **24** and **25** in 70% and 78% yields, respectively (Scheme 6). The PMB-protected 1,4-dideoxy-1,4-imino-D-arabinitol (**13**) also reacted with the cyclic sulfate **15** in dry acetone to afford the ammonium sulfate **26** in 90% yield (Scheme 6).

The reactivity of the PMB-protected 1,4-anhydroheteroalditols **11**−**13** with the cyclic sulfates **14** and **15** varied. The 1,4-dideoxy-1,4-iminoarabinitol **13** was the most reactive of the three and reacted with the cyclic sulfates **14** and **15** in good yields. The PMB-protected 1,4-anhydro-4-seleno- and -thio-D-arabinitols **11** and **12** were less reactive with the cyclic sulfates **14** and **15**, and the reactions proceeded very slowly in acetone. The polar solvent HFIP, which was believed to facilitate the reactions by stabilizing the transition states, had to be used instead. The PMB-protected 1,4-anhydro-4-seleno-D-arabinitol **11** was slightly more reactive than its sulfur counterpart **12**, as demonstrated by the different reaction temperatures required in the coupling reactions. The coupling reaction of compound **11** with **14** and **15** proceeded smoothly at 60−65 °C to give the desired products in moderate yields. However, attempts to improve the yields further by raising the reaction temperatures caused decomposition of the products. On the other hand, reaction of the PMB-protected 1,4-anhydro-4-thio-D-arabinitol **12** with the cyclic sulfates **14** and **15** proceeded slowly at 65−70 °C for 12 h, with about 30% of starting material **12** still remaining. Raising the temperature to 75−80 °C resulted in completion of the reactions in high yields.

The selectivity for attack at the primary center of the cyclic sulfates **14** and **15** over possible alternative attack of compounds **11**−**13** at the primary over the secondary cyclic sulfate center was invariably excellent, and in no case were isolable quantities of the regioisomers detected. In the case of the coupling reaction of the selenoarabinitol **11** with the cyclic sulfates **14** and **15**, there was a detectable amount (5−10%) of the stereoisomers that were diastereomeric at the selenonium center. However, due to the similarity in chromatographic mobilities, these minor products could not be isolated free from the major isomers. However, this type of minor product was not detected in the reactions of the corresponding thioarabinitol **12**.

Deprotection of the coupled products **21**−**26** was carried out by a three-step procedure. Since PMB and BDA groups were both sensitive to acidic conditions, they were readily cleaved by treatment with TFA (Scheme 7). After rinsing away the cleaved PMB and BDA groups, the residue was purified by column chromatography to afford the corresponding compounds **27**−**32** as amorphous, hygroscopic solids. The benzyl protecting groups at the anomeric positions in compounds **27**−**32** were not cleaved after prolonged treatment with TFA at elevated temperatures, only trace amounts of cleavage products being observed.

The absolute stereochemistry at the heteroatom center of compounds **27**−**32** was established by NOESY experiments. For example, the NOESY spectrum of compound **27** (Figure 1) clearly exhibited the H-4 to H-1′b correlation, implying that these two hydrogens are syn-facial. Therefore, C-1′ of the side chain must be anti to C-5 of the sulfonium salt ring.

Compounds **27**−**32** were subjected to hydrogenolysis in 90% acetic acid using $Pd(OH)_2/C$ as the catalyst. After 24 h, the anomeric benzyl groups of **27**−**32** were completely removed to yield the corresponding hemiacetals. The crude hemiacetals were subsequently reduced with $NaBH_4$ in water to provide the desired final products **5**−**10** (Scheme 8). The moderate yields

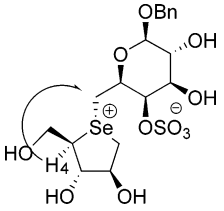
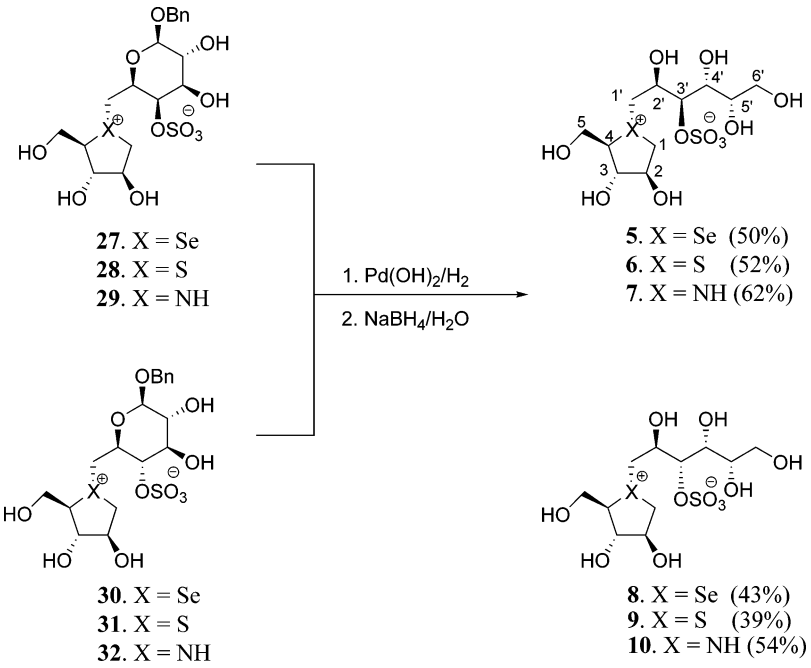



**FIGURE 1.** NOE correlations observed in the NOESY spectrum of **27**.

**SCHEME 8**




**27**. X = Se
**28**. X = S
**29**. X = NH

**5**. X = Se (50%)
**6**. X = S (52%)
**7**. X = NH (62%)

**30**. X = Se
**31**. X = S
**32**. X = NH

**8**. X = Se (43%)
**9**. X = S (39%)
**10**. X = NH (54%)

for the three-step deprotection sequence were due in part to the difficulty in separation of the final products from contaminating borate salts. Compounds **5**−**10** were obtained as hygroscopic gums that were unsuitable for combustion analysis but were characterized by spectroscopic methods. The $^1$H and $^{13}$C NMR spectra of compounds **6** and **9** matched the data in our previous publication.[15] MALDI mass spectrometry for compounds **5**−**10** in the positive-ion mode typically showed base peaks for masses attributable to sodium adduct ions (M + Na) and lower intensity peaks corresponding to M + H and M + H − $SO_3$ ions. The compounds were also characterized by $^1$H and $^{13}$C NMR spectroscopy and high-resolution mass spectrometry.

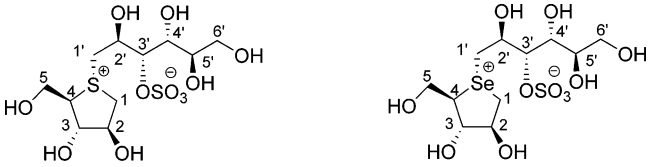
Finally, we comment on the inhibitory activities of the compounds synthesized in this and previous studies against recombinant human maltase glucoamylase (MGA), a critical intestinal glucosidase involved in the processing of oligosaccharides of glucose into glucose itself. The selenium derivatives, **5** and **8**, have $K_i$ values of 0.10 ± 0.03 and 0.10 ± 0.01 $\mu$M, respectively (Table 1). Both of the nitrogen analogues are less active, **10** with a $K_i$ value of 8 ± 1 $\mu$M and **7** with a $K_i$ value of 35 ± 2 $\mu$M. The sulfur analogues **6** and **9** were shown in a previous study[15] to be active, with $K_i$ values of 0.25 ± 0.02 and 0.17 ± 0.02 $\mu$M, respectively. Thus, the configuration at C-3′ does not appear to be critical for inhibitory activity since all pairs, i.e., **5** and **8**, **6** and **9**, **7** and **10**, show $K_i$ values in the same range as also recently deduced with other derivatives.[16] It is of interest that the sulfonium ion **33** with the enantiomeric configuration at C-5′ to **9** has a $K_i$ value of 0.65 ± 0.10 $\mu$M.[16] In contrast, the corresponding selenonium ion **34** with enantiomeric configuration at C-5′ to **8** is just as active, with a $K_i$ value of 0.14 ± 0.03 $\mu$M.[16] The $K_i$ values for the selenium derivatives **5** and **8** are lower than for their lower homologue blintol **3** ($K_i$ = 0.49 ± 0.05 $\mu$M),[24] indicating the importance of chain elongation relative to blintol **3**. The sulfur derivatives **6** and **9** synthesized in this study are in the same range as those for salacinol **1** ($K_i$ = 0.19 ± 0.02 $\mu$M) (Table 1). Further rationalization of these data will have to await details of contacts between the ligands and the active site of MGA from the X-ray crystal structures of MGA complexes (Chart 4).

**TABLE 1. Experimentally Determined $K_i$ Values**[a]

| inhibitor | $K_i$ ($\mu$M) |
|---|---|
| salacinol **(1)** | 0.19 ± 0.02[c] |
| blintol (**3**) | 0.49 ± 0.05[c] |
| ghavamiol (**4**) | NA[b,d] |
| **5** | 0.10 ± 0.03 |
| **6** | 0.25 ± 0.02[c] |
| **7** | 35 ± 2 |
| **8** | 0.10 ± 0.01 |
| **9** | 0.17 ± 0.02[c] |
| **10** | 8 ± 1 |
| **33** | 0.65 ± 0.1[e] |
| **34** | 0.14 ± 0.03[e] |

[a] Analysis of MGA inhibition was performed using p-nitrophenyl α-D-glucopyranoside as the substrate and measuring the release of glucose. Absorbance measurements were averaged to give a final result. [b] NA: not active. [c] Reference 24. [d] Reference 25. [e] Reference 16.

**CHART 4**



**33** **34**

## Conclusions

Four hitherto elusive heteroanalogues (X = Se, NH) of the naturally occurring glucosidase inhibitor salacinol, containing extended acyclic chains of six carbons, were synthesized. These syntheses utilized the 1,3-cyclic sulfates derived from commercially available D-glucose and D-galactose. The PMB and butanediacetal protecting groups on the coupled products

(24) Rossi, E. J; Sim, L.; Kuntz, D. A.; Hahn, D.; Johnston, B. D.; Ghavami, A.; Szczepina, M. D.; Kumar, N. S.; Sterchi, E. E.; Nichols, B. L.; Pinto, B. M.; Rose, D. R. *FEBS J.* **2006**, *273*, 2673−2683.
(25) Rose, D. R. Unpublished observations.

ensured facile deprotection with TFA. After hydrogenolysis to cleave the anomeric benzyl groups and subsequent $NaBH_4$ reduction of the resulting hemiacetals, the final compounds **5** to **10** were obtained. The four new target compounds inhibited human maltase glucoamylase, with *Ki* values ranging from 0.10 to 35 $\mu$M. The selenium derivatives **5** and **8** represent the most active compounds in this general series of compounds synthesized to date. The two compounds in which $X$ = S previously showed *Ki* values of 0.25 and 0.17 $\mu$M. These data, when compared to those reported previously for related compounds, reinforce the requirements for an effective inhibitor of MGA.

## Experimental Section

**Enzyme Kinetics.** Kinetic parameters of MGA with compounds **12** and **22** were determined using the pNP-glucose assay to follow the production of *p*-nitrophenol upon addition of enzyme (500 nM). The $K_i$ obtained for salacinol **2** in this assay was identical to that obtained using the glucose oxidase assay above. The assays were carried out in 96-well microtiter plates containing 100 mM MES buffer pH 6.5, inhibitor (at three different concentrations), and *p*-nitrophenyl-D-glucopyranoside (pNP-glucose) as substrate (2.5, 3.5, 5, 7.5, 15, and 30 mM) with a final volume of 50 $\mu$L. Reactions were incubated at 37 °C for 35 min and terminated by addition of 50 $\mu$L of 0.5 M sodium carbonate. The absorbance of the reaction product was measured at 405 nm in a microtiter plate reader. All reactions were performed in triplicate, and absorbance measurements were averaged to give a final result. Reactions were linear within this time frame. The program GraFit 4.0.14 was used to fit the data to the Michaelis−Menten equation and estimate the kinetic parameters, $K_m$, $K_{mobs}$ ($K_m$ in the presence of inhibitor), and $V_{max}$, of the enzyme. $K_i$ values for each inhibitor were determined by the equation $K_i = [I]/((K_{mobs}/K_m) \pm 1)$. The $K_i$ reported for each inhibitor was determined by averaging the $K_i$ values obtained from three different inhibitor concentrations.

**Benzyl 2,3-*O*-[(2*R*,3*R*)-2,3-Dimethoxybutane-2,3-diyl]-$\beta$-D-galactopyranoside (17).** To a solution of benzyl $\beta$-D-galactopyranoside (**16**)[21] (10.0 g, 37.0 mmol) in dry MeOH (200 mL) were added 2,3-butanedione (4.0 mL, 45.6 mmol), trimethyl orthoformate (25 mL, 0.23 mol). CSA (300 mg) was added as a catalyst at room temperature, and the reaction mixture was then refluxed for 24 h. When TLC analysis of aliquots (hexane/EtOAc, 1:1) showed total consumption of the starting material, the reaction was stopped by the addition of triethylamine (1 mL). Purification by column chromatography (hexane/EtOAc, 2:1) yielded compound **17** as a colorless solid (10.2 g, 72%): $[\alpha]^{22}_D$ −58.7 (*c* 1.0, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 7.40−7.24 (m, 5H, Ar), 4.90 and 4.74 (2 d, 2H, $J_{AB}$ = 12.3 Hz, C$H_2$Ph), 4.60 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 3.98 (dd, 1H, $J_{2,3}$ = 10.3 Hz, H-2), 3.95 (m, 1H, H-4), 3.94 (dd, 1H, $J_{5,6a}$ = 6.7 Hz, H-6a), 3.81 (dd, 1H, $J_{5,6b}$ = 4.6, $J_{6a,6b}$ = 11.7 Hz, H-6b), 3.74 (dd, 1H, $J_{3,4}$ = 3.0 Hz, H-3), 3.57 (m, 1H, H-5), 3.28 and 3.25 (2 s, 6H, 2 × OC$H_3$), 1.33 and 1.32 (2 s, 6H, 2 × C$H_3$); $^{13}$C NMR ($CDCl_3$) $\delta$ 138.0, 128.4, 127.7, 127.6 ($C_{Ar}$), 100.9 (C-1), 100.5, 100.0 (2 × C(OMe)(OR)), 75.2 (C-5), 71.3 (*C*$H_2$Ph), 70.4 (C-3), 68.4 (C-4), 67.1 (C-2), 62.7 (C-6), 48.3, 48.2 (2 × O*C*$H_3$), 17.9, 17.8 (2 × *C*$H_3$). Anal. Calcd for $C_{19}H_{28}O_8$: C, 59.36; H, 7.34. Found: C, 59.33; H, 7.30.

**Benzyl 2,3-*O*-[(2*R*,3*R*)-2,3-Dimethoxybutane-2,3-diyl]-$\beta$-D-glucopyranoside (19) and Benzyl 3,4-*O*-[(2*R*,3*R*)-2,3-Dimethoxybutane-2,3-diyl]-$\beta$-D-glucopyranoside (20).** To a solution of benzyl $\beta$-D-glucopyranoside (**18**)[22] (15.0 g, 55.5 mmol) in dry MeOH (200 mL) were added 2,3-butanedione (6.0 mL, 68.4 mmol) and methyl orthoformate (37.5 mL, 0.34 mol). CSA (300 mg) was added as a catalyst at room temperature, and the reaction mixture was then refluxed for 24 h. When TLC analysis of aliquots (hexane/EtOAc, 1:1) showed total consumption of the starting material and the formation of two main products **19** and **20**. The reaction was stopped by the addition of triethylamine (1 mL). Purification by column chromatography (hexane/EtOAc, 2:1) yielded compound **19** and **20** (**19**/**20** = 1.8:1) as colorless solids (11.4 g, 53% for **19**, 6.3 g, 30% for **20**, yields based on **18**).

For compound **19**: $[\alpha]^{22}_D$ −48.3 (*c* 1.0, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 7.41−7.20 (m, 5H, Ar), 4.86 and 4.67 (2 d, 2H, $J_{AB}$ = 12.3 Hz, C$H_2$Ph), 4.62 (d, 1H, $J_{1,2}$ = 7.9 Hz, H-1), 3.84 (dd, 1H, $J_{5,6a}$ = 3.0, $J_{6a,6b}$ = 12.0 Hz, H-6a), 3.79 (dd, 1H, $J_{5,6b}$ = 4.4 Hz, H-6b), 3.73 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.5 Hz, H-4), 3.67 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, H-3), 3.55 (dd, 1H, H-2), 3.34 (ddd, 1H, H-5), 3.26 and 3.25 (2 s, 6H, 2 × OC$H_3$), 1.31 and 1.30 (2 s, 6H, 2 × C$H_3$); $^{13}$C NMR ($CDCl_3$) $\delta$ 137.8, 128.5, 127.9, 127.6 ($C_{Ar}$), 100.7 (C-1), 99.8, 99.7 (2 × C(OMe)(OR)), 76.2 (C-5), 72.8 (C-3), 71.7 (*C*$H_2$Ph), 69.5 (C-2), 68.2 (C-4), 62.6 (C-6), 48.2, 48.1 (2 × O*C*$H_3$), 17.8 (2 × *C*$H_3$). Anal. Calcd for $C_{19}H_{28}O_8$: C, 59.36; H, 7.34. Found: C, 59.18; H, 7.22.

For compound **20**: $[\alpha]^{22}_D$ +8.2 (*c* 1.0, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 7.40−7.25 (m, 5H, Ar), 4.90 and 4.68 (2 d, 2H, $J_{AB}$ = 11.7 Hz, C$H_2$Ph), 4.47 (d, 1H, $J_{1,2}$ = 7.4 Hz, H-1), 3.88 (dd, 1H, $J_{5,6a}$ = 3.0, $J_{6a,6b}$ = 12.0 Hz, H-6a), 3.75 (dd, 1H, $J_{5,6b}$ = 4.8 Hz, H-6b), 3.74−3.68 (m, 2H, H-3, H-4), 3.62 (dd, 1H, $J_{2,3}$ = 8.6 Hz, H-2), 3.54 (ddd, 1H, H-5), 3.30 and 3.26 (2 s, 6H, 2 × OC$H_3$), 1.34 and 1.30 (2 s, 6H, 2 × C$H_3$); $^{13}$C NMR ($CDCl_3$) $\delta$ 137.1, 128.8, 128.4, 128.3 ($C_{Ar}$), 102.9 (C-1), 99.9, 99.8 (2 × C(OMe)(OR)), 74.3 (C-5), 72.0 (*C*$H_2$Ph), 71.9 (C-4), 71.5 (C-2), 66.0 (C-3), 61.6 (C-6), 48.3, 48.2 (2 × O*C*$H_3$), 17.9, 17.8 (2 × *C*$H_3$). Anal. Calcd for $C_{19}H_{28}O_8$: C, 59.36; H, 7.34. Found: C, 59.08; H, 7.26.

**Benzyl 2,3-*O*-[(2*R*,3*R*)-2,3-Dimethoxybutane-2,3-diyl]-$\beta$-D-galactopyranoside-4,6-cyclic Sulfate (14).** To a solution of benzyl 2,3-*O*-[(2*R*,3*R*)-2,3-dimethoxybutane-2,3-diyl]-$\beta$-D-galactopyranoside (**17**) (10.0 g, 26.0 mmol) in $CH_2Cl_2$ (50 mL) and pyridine (50 mL) cooled at 0 °C was added thionyl chloride (4.7 mL, 64.4 mmol) in $CH_2Cl_2$ (20 mL) dropwise. After the addition, the reaction mixture was warmed to room temperature and stirred for 2 h. The progress of the reaction was followed by TLC (hexane/EtOAc, 1:1). When the starting material **22** had been essentially consumed, the reaction mixture was poured into crushed ice (100 mL), extracted with $CH_2Cl_2$ (2 × 100 mL), washed with brine (50 mL), and dried over $Na_2SO_4$. After removal of the solvent and excess pyridine under reduced pressure, the crude product was passed through a short silica gel column. The cyclic sulfites were subsequently dissolved in $CH_3CN-CCl_4-H_2O$ mixture (10:10:1, 84 mL), and sodium periodiate (7.2 g, 33.8 mmol) was added. To this reaction mixture was added $RuCl_3 \cdot 3H_2O$ (100 mg) as a catalyst. The reaction mixture was stirred at room temperature for 3 h. The progress of the reaction was followed by TLC (hexane/EtOAc, 2:1). When the cyclic sulfites had been consumed, a single slightly less polar spot was observed. The reaction mixture was filtered through a short column of Celite, and the Celite was washed with $CH_2Cl_2$ (2 × 20 mL). The filtrate was combined, and the solvents were evaporated. The residue was redissolved in $CH_2Cl_2$ (200 mL), washed with $H_2O$ (2 × 20 mL) and brine (2 × 10 mL), and dried over $Na_2SO_4$. Purification by column chromatography (hexane/EtOAc, 1:1) gave compound **14** as a colorless solid (7.1 g, 60% for two steps): mp 123−125 °C dec; $[\alpha]^{22}_D$ −165.3 (*c* 1.0, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 7.40−7.22 (m, 5H, Ar), 5.08 (d, 1H, $J_{1,2}$ = 3.0 Hz, H-1), 4.95 and 4.70 (2 d, 2H, $J_{AB}$ = 12.1 Hz, C$H_2$Ph), 4.78 (dd, 1H, $J_{5,6a}$ = 1.7, $J_{6a,6b}$ = 12.3 Hz, H-6a), 4.68 (d, 1H, H-4), 4.63 (dd, 1H, $J_{5,6b}$ = 0.9 Hz, H-6b), 4.00 (dd, 1H, $J_{2,3}$ = 10.4, $J_{3,4}$ = 7. Hz, H-3), 3.92 (dd, 1H, H-2), 3.66 (br s, 1H, H-5), 3.30 and 3.26 (2 s, 6H, 2 × OC$H_3$), 1.34 and 1.31 (2 s, 6H, 2 × C$H_3$); $^{13}$C NMR ($CDCl_3$) $\delta$ 138.1, 128.6, 128.0, 127.6 ($C_{Ar}$), 100.9, 100.0 (2 × C(OMe)(OR)), 100.4 (C-4), 81.1 (C-1), 74.6 (C-6), 71.2 (*C*$H_2$Ph), 67.6 (C-2), 66.1 (C-3), 64.8 (C-5), 48.5, 48.3 (2 × O*C*$H_3$), 17.9, 17.6 (2 × *C*$H_3$). Anal. Calcd for $C_{19}H_{26}O_{10}S$: C, 51.11; H, 5.87. Found: C, 51.30; H, 5.79.

**Benzyl 2,3-*O*-[(2*R*,3*R*)-2,3-Dimethoxybutane-2,3-diyl]-$\beta$-D-glucopyranoside-4,6-cyclic Sulfate (15).** To a solution of benzyl 2,3-*O*-[(2*R*,3*R*)-2,3-dimethoxybutane-2,3-diyl]-$\beta$-D-glucopyranoside (**19**) (14.0 g, 36.4 mmol) in $CH_2Cl_2$ (50 mL) and pyridine (50 mL)

cooled to 0 °C was added thionyl chloride (6.6 mL, 90.4 mmol) dissolved in $CH_2Cl_2$ (20 mL) dropwise. After the addition, the reaction mixture was warmed to room temperature and stirred for 2 h. The progress of the reaction was followed by TLC (hexane/EtOAc, 1:1). When the starting material **19** had been essentially consumed, the reaction mixture was poured into crushed ice (100 mL), extracted with $CH_2Cl_2$ (2 × 100 mL), washed with brine (50 mL), and dried with $Na_2SO_4$. After removal of the solvent and excess pyridine under reduced pressure, the crude product was passed through a short silica gel column to give a mixture of cyclic sulfites. The cyclic sulfites were subsequently dissolved in a $CH_3CN-CCl_4-H_2O$ mixture (10:10:1, 105 mL), and sodium periodiate (9.3 g, 43.6 mmol) was added. To this reaction mixture was added $RuCl_3 \cdot 3H_2O$ (100 mg) as a catalyst, and the reaction mixture was stirred at room temperature for 3 h. The progress of the reaction was followed by TLC (hexane/EtOAc, 2:1). When the cyclic sulfite had been consumed, a single slightly less polar spot was observed. The reaction mixture was filtered through a short column of Celite, and the Celite was washed with $CH_2Cl_2$ (2 × 20 mL). The filtrates were combined and the solvents evaporated. The residue was dissolved in $CH_2Cl_2$ (200 mL), washed with $H_2O$ (2 × 50 mL) and brine (2 × 50 mL), and dried over $Na_2SO_4$. Purification by column chromatography (hexane/EtOAc, 1:1) gave compound **15** as a colorless solid (10.9 g, 67% for two steps): mp 132−135 °C; $[\alpha]^{22}_D$ −169.0 (*c* 1.0, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$) $\delta$ 7.40−7.23 (m, 5H, Ar), 4.90 and 4.71 (2 d, 2H, $J_{AB}$ = 12.1 Hz, C*H*$_2$Ph), 4.74 (d, 1H, H-1), 4.70−4.68 (d, 1H, H-4), 4.67 (dd, 1H, $J_{5,6a}$ = 10.4 Hz, H-6a), 4.53 (dd, 1H, $J_{5,6b}$ = 5.0, $J_{6a,6b}$ = 10.6 Hz, H-6b), 4.02 (dd, 1H, $J_{3,4}$ = 9.9 Hz, H-3), 3.80 (ddd, 1H, $J_{4,5}$ = 10.3 Hz, H-5), 3.70 (dd, 1H, $J_{2,3}$ = 9.2, $J_{1,2}$ = 8.5 Hz, H-2), 3.28 and 3.26 (2 s, 6H, 2 × OC*H*$_3$), 1.38 and 1.35 (2 s, 6H, 2 × C*H*$_3$). $^{13}$C NMR ($CDCl_3$) $\delta$ 138.3, 128.6, 128.2, 127.6 ($C_{Ar}$), 101.1 (C-1), 100.3, 100.2 (2 × C(OMe)(OR)), 80.7 (C-4), 72.0 (C-6), 71.8 (*C*H$_2$Ph), 69.7 (C-2), 68.5 (C-3), 65.8 (C-5), 48.5, 48.3 (2 × OC*H*$_3$), 17.7, 17.6 (2 × *C*H$_3$). Anal. Calcd for $C_{19}H_{26}O_{10}S$: C, 51.11; H, 5.87. Found: C, 51.15; H, 6.09.

**General Procedure for the Preparation of Selenonium, Sulfonium, and Ammonium Sulfates 21−26.** A mixture of the 1,4-anhydro-2,3,5-*O*-p-methoxybenzyl-4-seleno-D-arabinitol **11** or 1,4-anhydro-2,3,5-*O*-p-methoxybenzyl-4-thio-D-arabinitol **12** and the cyclic sulfate **14** or **15** in HFIP was placed in a sealed tube, and $K_2CO_3$ (10 mg) was added. In the case of the reaction of 1,4-dideoxy-1,4-imino-2,3,5-tri-*O*-*p*-methoxybenzyl-D-arabinitol **13** with the cyclic sulfates **14** and **15**, dry acetone was used instead of HFIP. The stirred reaction mixture was heated at the indicated temperature for the indicated time, as given below. The progress of the reaction was followed by TLC (EtOAc/MeOH, 10:1). When the limiting reagent had been essentially consumed, the mixture was cooled to room temperature, diluted with $CH_2Cl_2$, and then evaporated to give a syrupy residue. Purification by column chromatography (EtOAc to EtOAc/MeOH, 10:1) gave the purified selenonium, sulfonium, and ammonium salts **21**−**26**.

**Benzyl 2,3-*O*-[(2*R*,3*R*)-2,3-dimethoxybutane-2,3-diyl]-4-*O*-sulfoxy-6-deoxy-6-[1,4-dideoxy-2,3,5-tri-*O*-*p*-methoxybenzyl-1,4-episelenoniumylidene-D-arabinitol]-$\beta$-D-galactopyranoside Inner Salt (21).** Reaction of **11** (800 mg, 1.43 mmol) with the cyclic sulfate **14** (770 mg, 1.72 mmol) in HFIP (2.0 mL) for 12 h at 65−70 °C gave compound **21** as a colorless, amorphous foam (1.04 g, 72% based on **11**): $[\alpha]^{22}_D$ −48.4 (*c* 1.0, $CH_2Cl_2$); $^1$H NMR ($(CD_3)_2O$) $\delta$ 7.45−6.85 (m, 17H, Ar), 4.95 and 4.68 (2 d, 2H, $J_{AB}$ = 12.7 Hz, C*H*$_2$Ph), 4.76 (m, 1H, H-3′), 4.72 (ddd, 1H, H-2), 4.68 (d, 1H, $J_{1',2'}$ = 7.4 Hz, H-1′), 4.64 and 4.60 (2 d, 2H, $J_{AB}$ = 11.7 Hz, C*H*$_2$Ph), 4.58 (m, 1H, H-3), 4.50 and 4.42 (2d, 2H, $J_{AB}$ = 11.5 Hz, C*H*$_2$Ph), 4.42 (m, 1H, H-5′), 4.32 and 4.28 (2 d, 2H, $J_{AB}$ = 11.7 Hz, C*H*$_2$Ph), 4.20 (dd, 1H, $J_{5',6'a}$ = 6.2 Hz, H-6′a), 4.18 (m, 1H, H-4), 4.14 (dd, 1H, $J_{5',6'b}$ = 2.1, $J_{6'a,6'b}$ = 12.0 Hz, H-6′b), 3.96 (dd, 1H, $J_{1a,1b}$ = 12.4, $J_{1a,2}$ = 1.3 Hz, H-1a), 3.90−3.87 (m, 2H, H-2′, H-4′), 3.79, 3.78, 3.75 (3 s, 9H, 3 × OC*H*$_3$), 3.81−3.77 (m, 2H, H-5a, H-5b), 3.63 (dd, 1H, $J_{1b,2}$ = 3.2 Hz, H-1b), 3.23 and 3.20 (2 s, 6H, 2 × OC*H*$_3$), 1.24 (s, 6H, 2 × C*H*$_3$); $^{13}$C NMR ($(CD_3)_2CO$) $\delta$ 159.9, 159.8, 159.7, 138.6, 130.1, 130.0, 129.8, 129.7, 129.6, 129.5, 129.3, 128.4, 127.5, 127.0, 114.1, 114.0, and 113.9 ($C_{Ar}$), 101.3 (C-1′), 100.0, 99.4 (2 × *C*(OR)$_2$(OMe)$_2$), 83.8 (C-3), 82.9 (C-2), 74.4 (C-3′), 72.7, 71.6, 71.1, and 70.6 (4 × *C*H$_2$Ph), 70.7 (C-5′), 68.5 (C-4′), 67.0 (C-5), 66.9 (C-2′), 64.1 (C-4), 54.9, 54.8, and 54.7 (3 × OC*H*$_3$), 47.9 (C-6′), 47.4, 47.2 (2 × OC*H*$_3$), 44.7 (C-1), 17.45, 17.44 (2 × CH$_3$); MALDI MS *m*/*e* 1027.22 ($M^+$ + Na), 1005.34 ($M^+$ + H), 925.23 ($M^+$ + H − $SO_3$). Anal. Calcd for $C_{48}H_{60}O_{16}SSe$: C, 57.42; H, 6.02. Found: C, 57.11; H, 6.14.

**Benzyl 2,3-*O*-[(2*R*,3*R*)-2,3-Dimethoxybutane-2,3-diyl]-4-*O*-sulfoxy-6-deoxy-6-[1,4-dideoxy-2,3,5-tri-*O*-*p*-methoxybenzyl-1,4-episulfoniumylidene-D-arabinitol]-$\beta$-D-galactopyranoside Inner Salt (22).** Reaction of **12** (800 mg, 1.57 mmol) with the cyclic sulfate **14** (840 mg, 1.88 mmol) in HFIP (2.0 mL) for 12 h at 75−80 °C gave compound **22** as a colorless, amorphous foam (1.12 g, 75% based on **12**): $[\alpha]^{22}_D$ −47.2 (*c* 1.0, $CH_2Cl_2$); $^1$H NMR ($(CD_3)_2O$) $\delta$ 7.60−6.80 (m, 17H, Ar), 4.86 and 4.68 (2 d, 2H, $J_{AB}$ = 13.0 Hz, C*H*$_2$Ph), 4.67 and 4.59 (2 d, 2H, $J_{AB}$ = 13.0 Hz, C*H*$_2$-Ph), 4.62 (m, 1H, H-2), 4.50 and 4.44 (2 d, 2H, $J_{AB}$ = 11.4 Hz, C*H*$_2$Ph), 4.48−4.42 (m, 2H, = H-1′, H-3), 4.41 (s, 2H, C*H*$_2$Ph), 4.34 (ddd, 1H, H-5′), 4.29 (m, 1H, H-4′), 4.26 (dd, 1H, $J_{5',6'a}$ = 6.2, $J_{6'a,6'b}$ = 13.1 Hz, H-6′a), 4.14 (dd, 1H, $J_{5',6'b}$ = 4.3 Hz, H-6′b), 4.10 (m, 1H, H-4), 4.09 (dd, 1H, $J_{1a,1b}$ = 13.1 Hz, H-1a), 3.90 (dd, 1H, $J_{4,5a}$ = 3.4 Hz, $J_{5aa,5b}$ = 10.3 Hz, H-5a), 3.88 − 3.79 (m, 4H, H-5b, H-1b, H-2′, H-3′), 3.78, 3.76 (2 s, 9H, 3 × OC*H*$_3$), 3.26 and 3.19 (2 s, 6H, 2 × OC*H*$_3$), 1.25 and 1.24 (2 s, 6H, 2 × C*H*$_3$); $^{13}$C NMR ($(CD_3)_2CO$) $\delta$ 159.9, 159.8, 159.7, 138.6, 138.5, 132.8, 130.4, 130.1, 130.0, 129.8, 129.7, 129.6, 128.4, 127.5, 127.1, 112.6, 112.6, and 112.5 ($C_{Ar}$), 101.5 (C-1′), 100.0, 99.4 (2 × *C*(OR)$_2$(OMe)$_2$), 82.8 (C-3), 82.4 (C-2), 73.7, 72.9, 71.3, and 70.9 (4 × *C*H$_2$Ph), 71.9 (C-4), 71.6 (C-5′), 68.5 (C-3′), 67.1 (C-5), 67.0 (C-2′), 65.2 (C-4′), 54.9, 54.8 (3 × OC*H*$_3$), 49.0 (C-6′), 47.7, 47.4 (2 × OC*H*$_3$), 47.2 (C-1), 17.5, 17.4 (2 × CH$_3$); MALDI MS *m*/*e* 979.39 ($M^+$ + Na), 957.42 ($M^+$ + H), 877.43 ($M^+$ + H − $SO_3$); HRMS calcd for $C_{48}H_{60}O_{16}S_2Na$ 979.3215, found 979.3217.

**Benzyl 2,3-*O*-[(2*R*,3*R*)-2,3-Dimethoxybutane-2,3-diyl]-4-*O*-sulfoxy-6-deoxy-6-[1,4-dideoxy-2,3,5-tri-*O*-*p*-methoxybenzyl-1,4-iminonium-D-arabinitol]-$\beta$-D-galactopyranoside Inner Salt (23).** Reaction of **13** (1.0 g, 2.02 mmol) with the cyclic sulfate **14** (1.09 g, 2.43 mmol) in dry acetone (3.0 mL) for 12 h at 55−60 °C gave compound **23** as a colorless, amorphous foam (1.69 g, 89% based on **13**): $[\alpha]^{22}_D$ −38.5 (*c* 1.0, $CH_2Cl_2$); $^1$H NMR ($CD_2Cl_2$; pH = 8) $\delta$ 7.55−6.78 (m, 17H, Ar), 4.85 and 4.58 (2 d, 2H, $J_{AB}$ = 12.4 Hz, C*H*$_2$Ph), 4.73 (m, 1H, H-4′), 4.52 and 4.35 (2 d, 2H, $J_{AB}$ = 11.7 Hz, C*H*$_2$Ph), 4.45 (m, 1H, H-1′), 4.62 (m, 1H, H-2), 4.50 and 4.44 (2 d, 2H, $J_{AB}$ = 11.4 Hz, C*H*$_2$Ph), 4.48−4.42 (m, 2H, = H-3), 4.41 and 4.34 (2 d, 2H, $J_{AB}$ = 11.8 Hz, C*H*$_2$Ph), 4.31 and 4.27 (2d, 2H, $J_{AB}$ = 11.5 Hz, C*H*$_2$Ph), 3.88 − 3.70 (m, 5H, H-2, H-3, H-2′, H-3′, H-5′), 3.76, 3.75, and 3.73 (3s, 9H, 3 × OC*H*$_3$), 3.56 (dd, 1H, $J_{4,5a}$ = 5.1, $J_{5a,5b}$ = 9.9 Hz, H-5a), 3.44 (dd, 1H, $J_{4,5b}$ = 3.8 Hz, H-5b), 3.34−3.20 (m, 2H, H-6′b, H-1′b), 3.27 and 3.24 (2 s, 6H, 2 × OC*H*$_3$), 3.00−2.62 (m, 3H, H-6′a, H-1a, H-4), 1.32 and 1.23 (2 s, 6H, 2 × C*H*$_3$); $^{13}$C NMR ($CD_2Cl_2$) $\delta$ 159.5, 159.4, 159.3, 137.8, 130.4, 130.1, 129.9, 129.8, 129.4, 128.4, 127.8, 127.7, 127.6, 113.9, 113.8, 113.7 ($C_{Ar}$), 112.0 (C-1′), 100.5, 100.0 (2 × *C*(OR)$_2$-(OMe)$_2$), 84.2 (C-2), 81.1 (C-5′), 75.8 (C-4′), 74.7 (C-3), 72.7, 71.1, 71.0, and 70.6 (4 × *C*H$_2$Ph), 70.4 (C-4), 69.3 (C-3′), 68.6 (C-5), 67.5 (C-2′), 58.4 (C-1), 55.4, 55.3, and 55.2 (3 × OC*H*$_3$), 55.0 (C-6′), 48.5, 48.2 (2 × OC*H*$_3$), 17.6, 17.5 (2 × CH$_3$); MALDI MS *m*/*e* 962.66 ($M^+$ + Na), 939.63 ($M^+$ + H), 860.78 ($M^+$ + H − $SO_3$); HRMS calcd for $C_{48}H_{60}NO_{16}S$ 938.3640, found 938.3638.

**Benzyl 2,3-*O*-[(2*R*,3*R*)-2,3-Dimethoxybutane-2,3-diyl]-4-*O*-sulfoxy-6-deoxy-6-[1,4-dideoxy-2,3,5-tri-*O*-p-methoxybenzyl-1,4-episelenoniumylidene-D-arabinitol]-$\beta$-D-glucopyranoside Inner Salt (24).** Reaction of **11** (800 mg, 1.43 mmol) with the cyclic sulfate **15** (770 mg, 1.72 mmol) in HFIP (2.0 mL) for 12 h at 65−70 °C gave compound **24** as a colorless, amorphous foam (1.01 g, 70% based on **11**): $[\alpha]^{22}_D$ −47.5 (*c* 1.0, $CH_2Cl_2$); $^1$H NMR

($(CD_3)_2O$) $\delta$ 7.45−6.83 (m, 17H, Ar), 4.90 and 4.72 (2 d, 2H, $J_{AB}$ = 12.4 Hz, C$H_2$Ph), 4.84 (m, 1H, H-2), 4.73 (d, 1H, $J_{1',2'}$ = 8.3 Hz, H-1′), 4.65 and 4.53 (2 d, 2H, $J_{AB}$ = 11.3 Hz, C$H_2$Ph), 4.66−4.62 (m, 2H, C$H_2$Ph), 4.59 (m, 1H, H-3), 4.46 and 4.42 (2 d, 2H, $J_{AB}$ = 11.9 Hz, C$H_2$Ph), 4.36 (dd, 1H, $J_{5',6'a}$ = 3.1, $J_{6'a,6'b}$ = 12.1 Hz, H-6′a), 4.33 (m, 1H, H-4), 4.30 (t, 1H, $J_{3',4'} = J_{4',5'}$ = 9.5 Hz, H-4′), 4.16 (dd, 1H, $J_{5',6'b}$ = 3.3 Hz, H-6′b), 4.08 (dd, 1H, $J_{1a,1b}$ = 12.4 Hz, H-1a), 4.08−4.02 (m, 1H, H-5′), 3.86−3.76 (m, 3H, H-3′, H-5a, H-5b), 3.80, 3.79, 3.77 (3 s, 9H, 3 × OC$H_3$), 3.75 (dd, 1H, $J_{1b,2}$ = 3.2, H-1b), 3.62 (dd, 1H, $J_{2',3'}$ = 9.7, H-2′), 3.24 and 3.21 (2 s, 6H, 2 × OC$H_3$), 1.26 and 1.25 (2 s, 6H, 2 × C$H_3$); $^{13}$C NMR ($(CD_3)_2O$) $\delta$ 164.5, 164.4, 164.3, 143.0, 134.7, 134.4, 134.3, 134.2, 134.0, 133.9, 133.0, 132.2, 132.0, 118.6, 118.5, and 118.4($C_{Ar}$), 105.1 (C-1′), 104.1, 104.0 (2 × $C$(OR)$_2$(OMe)$_2$), 88.8 (C-3), 87.7 (C-2), 77.9 (C-4′), 77.2 (C-5′), 77.2, 76.3, 75.9, and 75.3 (4 × $C$H$_2$-Ph), 74.6 (C-2′), 74.5 (C-3′), 71.4 (C-5), 70.0 (C-4), 59.5, 59.4 (3 × OC$H_3$), 52.5 (C-6′), 51.8, 51.7 (2 × OC$H_3$), 50.0 (C-1), 21.9, 21.7 (2 × C$H_3$); MALDI MS *m*/*e* 1027.19 ($M^+$ + Na), 1005.13 ($M^+$ + H), 925.24 ($M^+$ + H − $SO_3$). Anal. Calcd for $C_{48}H_{60}O_{16}$-SSe: C, 57.42; H, 6.02. Found: C, 57.12; H, 6.09.

**Benzyl 2,3-*O*-[(2*R*,3*R*)-2,3-Dimethoxybutane-2,3-diyl]-4-*O*-sulfoxy-6-deoxy-6-[1,4-dideoxy-2,3,5-tri-*O*-*p*-methoxybenzyl-1,4-episulfoniumylidene-D-arabinitol]-β-D-glucopyranoside Inner Salt (25).** Reaction of **12** (800 mg, 1.57 mmol) with the cyclic sulfate **15** (840 mg, 1.88 mmol) in HFIP (2.0 mL) for 12 h at 75−80 °C gave compound **25** as a colorless, amorphous foam (1.17 g, 78% based on **12**): $[\alpha]^{22}_D$ −48.0 (*c* 1.0, $CH_2Cl_2$); $^1$H NMR ($(CD_3)_2$-CO) $\delta$ 7.45−6.85 (m, 17H, Ar), 4.89 and 4.70 (2 d, 2H, $J_{AB}$ = 12.5 Hz, C$H_2$Ph), 4.75 (m, 1H, H-2), 4.67 and 4.53 (2 d, 2H, $J_{AB}$ = 11.2 Hz, C$H_2$Ph), 4.66−4.60 (m, 3H, H-1′, C$H_2$Ph), 4.54 (m, 1H, H-3), 4.48 (m, 2H, C$H_2$Ph), 4.38 (dd, 1H, $J_{1a,2}$ = 3.4, $J_{1b,2}$ = 3.1 Hz, H-1b), 4.10 (m, 2H, H-5′, H-6′a), 3.94−3.83 (m, 3H, H-5a, H-5b, H-6′b), 3.82−3.79 (m, 1H, H-3′), 3.80, 3.79 and 3.78 (3 s, 9H, 3 × OC$H_3$), 3.62 (dd, 1H, $J_{1',2'}$ = 8.1, $J_{2',3'}$ = 9.8 Hz, H-2′), 3.25 and 3.22 (2 s, 6H, 2 × OC$H_3$), 1.25 and 1.24 (2 s, 6H, 2 × C$H_3$); $^{13}$C NMR ($(CD_3)_2CO$) $\delta$ 164.6, 164.5, 142.9, 134.8, 134.7, 134.5, 134.3, 133.0, 132.2, 131.9, 118.7, 118.6, 118.5 ($C_{Ar}$), 105.3 (C-1′), 104.0 (2 × $C$(OR)$_2$(OMe)$_2$), 88.1 (C-3), 87.0 (C-2), 77.4, 76.3, 76.1, and 75.5 (4 × $C$H$_2$Ph), 76.9 (C-4′), 76.8 (C-5′), 74.5 (C-3′), 74.4 (C-2′), 71.3 (C-5), 70.2 (C-4), 59.5, 59.4 (3 × OC$H_3$), 53.6 (C-1), 52.0 (C-6′), 51.9, 51.7 (2 × OC$H_3$), 21.9, 21.8 (2 × C$H_3$); MALDI MS *m*/*e* 979.47 ($M^+$ + Na), 957.46 ($M^+$ + H), 877.50 ($M^+$ + H − $SO_3$); HRMS calcd for $C_{48}H_{60}O_{16}S_2Na$ 979.3215, found 979.3215.

**Benzyl 2,3-*O*-[(2*R*,3*R*)-2,3-dimethoxybutane-2,3-diyl]-4-*O*-sulfoxy-6-deoxy-6-[1,4-dideoxy-2,3,5-tri-*O*-*p*-methoxybenzyl-1,4-iminonium-D-arabinitol]-β-D-glucopyranoside Inner Salt (26).** Reaction of **13** (1.0 g, 2.02 mmol) with the cyclic sulfate **15** (1.09 g, 2.43 mmol) in dry acetone (3.0 mL) for 12 h at 55−60 °C gave compound **26** as a colorless, amorphous foam (1.71 g, 90% based on **13**): $[\alpha]^{22}_D$ −39.1 (*c* 1.0, $CH_2Cl_2$); $^1$H NMR ($CD_2Cl_2$; pH = 8) $\delta$ 7.42−6.60 (m, 17H, Ar), 4.72 and 4.47 (2 d, 2H, $J_{AB}$ = 12.2 Hz, C$H_2$Ph), 4.55−4.49 (m, 1H, H-1′), 4.49 and 4.24 (2 d, 2H, $J_{AB}$ = 11.9 Hz, C$H_2$Ph), 4.36 and 4.34 (2 d, 2H, $J_{AB}$ = 12.0 Hz, C$H_2$Ph), 4.18−4.14 (m, 1H, H-4′), 4.14 and 4.08 (2 d, 2H, $J_{AB}$ = 11.3 Hz, C$H_2$Ph), 3.87 (t, 1H, $J_{2',3'} = J_{3',4'}$ = 9.8 Hz, H-3′), 3.80−3.60 (m, 3H, H-2, H-3, H-5′), 3.68, 3.67, and 3.66 (3 s, 9H, 3 × OC$H_3$), 3.53 (m, 1H, H-5a), 3.50 (dd, 1H, H-2′), 3.40−3.25 (m, 2H, H-6′a, H-5b), 3.23 (dd, 1H, H-1a), 3.16 and 3.13 (2 s, 6H, 2 × OC$H_3$), 2.72−2.55 (m, 3H, H-1b, H-4, H-6′b), 1.19 and 1.18 (2 s, 6H, 2 × C$H_3$); $^{13}$C NMR ($CD_2Cl_2$) $\delta$ 159.5, 159.4, 159.3, 137.9, 137.8, 130.2, 130.1, 130.0, 129.8, 129.4, 128.2, 127.7, 127.5, 127.4, 114.0, 113.9, and 112.1 ($C_{Ar}$), 100.0 (C-1′), 99.8, 99.7 (2 2 × $C$(OR)$_2$-(OMe)$_2$), 84.7 (C-2), 79.9 (C-5′), 75.5 (C-4′), 74.8 (C-3), 72.8, 71.2, 70.9, and 70.8 (4 × $C$H$_2$Ph), 70.8 (C-3′), 70.0 (C-4), 69.9 (C-2′), 67.6 (C-5), 58.4 (C-1), 55.4, 55.3, and 55.2 (3 × OC$H_3$), 52.1 (C-6′), 48.4, 48.0 (2 × OC$H_3$), 17.7, 17.6 (2 × C$H_3$); MALDI MS *m*/*e* 962.97 ($M^+$ + Na), 940.00 ($M^+$ + H), 860.13 ($M^+$ + H − $SO_3$). Anal. Calcd for $C_{48}H_{60}KNO_{16}S$: C, 58.94; H, 6.18; N, 1.43. Found: C, 58.65; H, 6.03; N, 1.45.

**General Procedure for the Preparation of the Sulfate Salts 27−32.** The protected coupled products **21**−**26** were dissolved in $CH_2Cl_2$ (2 mL), TFA (10 mL) was then added, and the mixture was stirred for 2 h at rt. The progress of the reaction was followed by TLC analysis of aliquots (EtOAc/MeOH/$H_2O$, 7:3:1). When the starting material had been consumed, TFA and $CH_2Cl_2$ were removed under reduced pressure. The residue was rinsed with $CH_2$-$Cl_2$ (4 × 2 mL), and the $CH_2Cl_2$ was decanted to remove the cleaved protecting groups. The remaining gum was dissolved in methanol and purified by column chromatography (EtOAc and EtOAc/MeOH, 2:1) to give the purified compounds **27**−**32** as colorless, amorphous, and hygroscopic solids.

**Benzyl 4-*O*-Sulfoxy-6-deoxy-6-[1,4-dideoxy-1,4-episelenoniumylidene-D-arabinitol]-β-D-galactopyranoside Inner Salt (27).** To a solution of **21** (900 mg, 0.90 mmol) in $CH_2Cl_2$ (2 mL) was added TFA (10 mL) to yield compound **27** as a colorless, amorphous, and hygroscopic solid (427 mg, 90%): $[\alpha]^{22}_D$ +11.6 (*c* 1.0, $H_2O$); $^1$H NMR ($CD_3OD$) $\delta$ 7.46−7.24 (m, 5H, Ar), 4.92 and 4.70 (2 d, 2H, $J_{AB}$ = 11.9 Hz, C$H_2$Ph), 4.73−4.70 (m, 1H, H-2), 4.67−4.65 (m, 1H, H-4′), 4.49−4.44 (m, 2H, H-1′, H-3), 4.24−4.20 (m, 1H, H-5′), 4.15−4.10 (m, 1H, H-4), 3.99 (dd, 1H, $J_{4,5a}$ = 5.7, $J_{5a,5b}$ = 11.7 Hz, H-5a), 3.94 (dd, 1H, $J_{5',6'a}$ = 5.3, $J_{6'a,6'b}$ = 11.5 Hz, H-6′a), 3.92 (dd, 1H, H-6′b), 3.91 (dd, 1H, $J_{4,5b}$ = 2.4 Hz, H-5b), 3.73 (dd, 1H, $J_{1a,2}$ = 2.0, $J_{1a,1b}$ = 11.9 Hz, H-1a), 3.70 (dd, 1H, $J_{1b,2}$ = 3.1 Hz, H-1b), 3.64 (dd, 1H, $J_{3',4'}$ = 3.1, $J_{2',3'}$ = 9.8 Hz, H-3′), 3.58 (dd, 1H, $J_{1',2'}$ = 7.7 Hz, H-2′); $^{13}$C NMR ($CD_3OD$) $\delta$ 137.9, 128.2, 128.0, 127.6 ($C_{Ar}$), 103.2 (C-1′), 79.3 (C-3), 78.7 (C-2), 77.2 (C-4′), 72.4 (C-4), 72.3 (C-3′), 71.5 (C$H_2$-Ph), 71.2 (C-2′), 69.6 (C-5′), 59.8 (C-6′), 47.3 (C-1), 44.5 (C-5); MALDI MS *m*/*e* 553.22 ($M^+$ + Na), 531.23 ($M^+$ + H), 451.33 ($M^+$ + H − $SO_3$); HRMS calcd for $C_{18}H_{26}O_{11}SSeNa$ 553.0253, found 553.0252.

**Benzyl 4-*O*-Sulfoxy-6-deoxy-6-[1,4-dideoxy-1,4-episulfoniumylidene-D-arabinitol]-β-D-galactopyranoside Inner Salt (28).** To a solution of **22** (900 mg, 0.94 mmol) in $CH_2Cl_2$ (2 mL) was added TFA (10 mL) to yield compound **28** as a colorless, amorphous, and hygroscopic solid (395 mg, 87%): $[\alpha]^{22}_D$ +21.3 (*c* 1.0, $H_2O$); $^1$H NMR ($CD_3OD$) $\delta$ 7.46−7.26 (m, 5H, Ar), 4.92 and 4.72 (2 d, 2H, $J_{AB}$ = 12.0 Hz, C$H_2$Ph), 4.73 (m, 1H, H-4′), 4.63 (m, 1H, H-2), 4.50 (d, 1H, $J_{1',2'}$ = 7.8 Hz, H-1′), 4.39 (m, 1H, H-3), 4.24 (m, 1H, H-5′), 4.14−4.06 (m, 2H, H-4, H-5a), 3.96 (dd, 1H, $J_{5',6'a}$ = 9.6, $J_{6'a,6'b}$ = 13.3 Hz, H-6′a), 3.91 (dd, 1H, $J_{4,5b}$ = 9.2, $J_{5a,5b}$ = 10.1 Hz, H-5b), 3.84 (dd, 1H, $J_{5',6'b}$ = 2.7 Hz, H-6′b), 3.80−3.73 (m, 2H, H-1a, H-1b), 3.73 (dd, 1H, $J_{3',4'}$ = 3.0 Hz, H-3′), 3.59 (dd, 1H, $J_{2',3'}$ = 9.7 Hz, H-2′); $^{13}$C NMR ($CD_3OD$) $\delta$ 137.9, 128.2, 127.9, 127.7 ($C_{Ar}$), 103.3 (C-1′), 78.4 (C-3), 78.0 (C-2), 76.6 (C-4′), 72.2 (C-3′), 72.1 (C-4), 71.6 (C$H_2$Ph), 71.1 (C-2′), 69.6 (C-5′), 59.6 (C-5), 49.7 (C-1), 47.3 (C-6′); MALDI MS *m*/*e* 505.19 ($M^+$ + Na), 483.16 ($M^+$ + H), 403.28 ($M^+$ + H − $SO_3$); HRMS calcd for $C_{18}H_{26}O_{11}S_2Na$ 505.0809, found 505.0807.

**Benzyl 4-*O*-Sulfoxy-6-deoxy-6-[1,4-dideoxy-1,4-iminonium-D-arabinitol]-β-D-galactopyranoside Inner Salt (29).** To a solution of **23** (1.2 g, 1.28 mmol) in $CH_2Cl_2$ (2 mL) was added TFA (10 mL) to yield compound **29** as a colorless, amorphous, and hygroscopic solid (505 mg, 85%): $[\alpha]^{22}_D$ −1.3 (*c* 1.0, $H_2O$); $^1$H NMR ($D_2O$; pH = 8) $\delta$ 7.34−7.22 (m, 5H, Ar), 4.76 and 4.60 (2 d, 2H, $J_{AB}$ = 11.7 Hz, C$H_2$Ph), 4.50 (m, 1H, H-4′), 4.37 (d, 1H, $J_{1',2'}$ = 7.9 Hz, H-1′), 3.95 (ddd, 1H, H-2), 3.79−3.72 (m, 2H, H-3, H-5′), 3.58 (dd, 1H, $J_{3',4'}$ = 3.2 Hz, H-3′), 3.58−3.55 (m, 2H, H-5a, H-5b), 3.40 (dd, 1H, $J_{2',3'}$ = 10.0 Hz, H-2′), 3.04 (dd, 1H, $J_{5',6'a}$ = 2.2, $J_{6'a,6'b}$ = 14.1 Hz, H-6′a), 2.91 (dd, 1H, $J_{1a,2}$ = 1.2, $J_{1a,1b}$ = 11.1 Hz, H-1a), 2.68 (dd, 1H, $J_{1b,2}$ = 5.8 Hz, H-1b), 2.59 (dd, 1H, $J_{5',6'b}$ = 8.4 Hz, H-6′b), 2.45 (ddd, 1H, H-4); $^{13}$C NMR ($D_2O$) $\delta$ 136.7, 128.8, 128.7, 128.6 ($C_{Ar}$), 101.8 (C-1′), 78.8 (C-4′), 78.7 (C-3), 75.7 (C-2), 73.5 (C-5′), 72.0 (C-4), 71.9 (C-3′), 71.8 (C$H_2$-Ph), 70.9 (C-2′), 60.6 (C-5), 59.9 (C-1), 55.3 (C-6′); MALDI MS

*m/e* 488.04 ($M^+ + Na$), 466.11 ($M^+ + H$), 386.19 ($M^+ + H - SO_3$); HRMS calcd for $C_{18}H_{26}NO_{11}S$ 464.1221, found 464.1224.

**Benzyl 4-*O*-Sulfoxy-6-deoxy-6-[1,4-dideoxy-1,4-episelenoniumylidene-D-arabinitol]-β-D-glucopyranoside Inner Salt (30).** To a solution of **24** (900 mg, 0.90 mmol) in $CH_2Cl_2$ (2 mL) was added TFA (10 mL) to yield compound **30** as a colorless, amorphous, and hygroscopic solid (389 mg, 82%): $[\alpha]^{22}_D$ −7.2 (*c* 1.0, $H_2O$); $^1$H NMR ($CD_3OD$) δ 7.46−7.24 (m, 5H, Ar), 4.90 and 4.72 (2 d, 2H, $J_{AB}$ = 12.1 Hz, C*H*$_2$Ph), 4.70−4.68 (m, 1H, H-2), 4.54 (d, 1H, $J_{1',2'}$ = 7.9 Hz, H-1′), 4.45 (m, 1H, H-3), 4.14 (t, 1H, $J_{3',4'} = J_{4',5'}$ = 8.9 Hz, H-4′), 4.14−4.10 (m, 1H, H-4), 4.08 (dd, 1H, $J_{4,5a}$ = 2.8 Hz, H-5a), 3.98 (dd, 1H, $J_{5',6'a}$ = 5.7, $J_{6'a,6'b}$ = 12.0 Hz, H-6′a), 3.97−3.92 (m, 1H, H-5′, H-6′b), 3.90 (dd, 1H, $J_{5a,5b}$ = 12.3 Hz, H-5b), 3.75−3.71 (m, 2H, H-1a, H-1b), 3.64 (dd, 1H, $J_{3',4'}$ = 8.9 Hz, H-3′), 3.40 (dd, 1H, $J_{1',2'}$ = 8.4 Hz, H-2′); $^{13}$C NMR ($CD_3OD$) δ 137.8, 128.3, 128.0, 127.7 ($C_{Ar}$), 102.7 (C-1′), 79.3 (C-3), 78.7 (C-2), 78.5 (C-4′), 74.4 (C-3′), 73.6 (C-2′), 73.0 (C-4), 71.7 (*C*H$_2$-Ph), 70.4 (C-5′), 59.7 (C-6′), 47.5 (C-1), 45.3 (C-5); MALDI MS *m/e* 553.25 ($M^+ + Na$), 531.28 ($M^+ + H$), 451.31 ($M^+ + H - SO_3$); HRMS calcd for $C_{18}H_{26}O_{11}SSeNa$ 553.0253, found 553.0251.

**Benzyl 4-*O*-Sulfoxy-6-deoxy-6-[1,4-dideoxy-1,4-episulfoniumylidene-D-arabinitol]-β-D-glucopyranoside Inner Salt (31).** To a solution of **25** (900 mg, 0.94 mmol) in $CH_2Cl_2$ (2 mL) was added TFA (10 mL) to yield compound **31** as a colorless, amorphous, and hygroscopic solid (408 mg, 90%): $[\alpha]^{22}_D$ −8.2 (*c* 1.0, $H_2O$); $^1$H NMR ($D_2O$) δ 7.36−7.26 (m, 5H, Ar), 4.72 (s, 2H, C*H*$_2$Ph), 4.55 (ddd, 1H, H-2), 4.52 (d, 1H, $J_{1',2'}$ = 8.1 Hz, H-1′), 4.28 (m, 1H, H-3), 4.07 (dd, 1H, $J_{4',5'}$ = 9.2 Hz, H-4′), 3.96−3.90 (m, 2H, H-5′, H-6′a), 3.86 (dd, 1H, $J_{4,5a}$ = 8.3, $J_{5a,5b}$ = 15.4 Hz, H-5a), 3.80−3.71 (m, 3H, H-4, H-5b, H-6′b), 3.62 (dd, 1H, $J_{1a,2}$ = 4.1, $J_{1a,1b}$ = 13.2 Hz, H-1a), 3.56 (t, 1H, $J_{2',3'} = J_{3',4'}$ = 9.4 Hz, H-3′), 3.53 (dd, 1H, $J_{1b,2}$ = 5.1 Hz, H-1b), 3.29 (dd, 1H, $J_{2',3'}$ = 9.4 Hz, H-2′); $^{13}$C NMR ($D_2O$) δ 136.9, 129.0, 128.8, 128.7 ($C_{Ar}$), 102.4 (C-1′), 77.8 (C-3), 77.5 (C-4′), 76.8 (C-2), 73.5 (C-3′), 73.0 (*C*H$_2$-Ph), 72.7 (C-2′), 70.2 (C-5′), 70.1 (C-4), 58.7 (C-5), 47.6 (C-6′), 47.4 (C-1); MALDI MS *m/e* 505.41 ($M^+ + Na$), 483.36 ($M^+ + H$), 403.44 ($M^+ + H - SO_3$); HRMS calcd for $C_{18}H_{26}O_{11}S_2Na$ 505.0809, found 505.0809.

**Benzyl 4-*O*-Sulfoxy-6-deoxy-6-[1,4-dideoxy-1,4-iminonium-D-arabinitol]-β-D-glucopyranoside Inner Salt (32).** To a solution of **26** (1.2 mg, 1.28 mmol) in $CH_2Cl_2$ (2 mL) was added TFA (10 mL) to yield compound **32** as a colorless, amorphous, and hygroscopic solid (517 mg, 87%): $[\alpha]^{22}_D$ −2.5 (c 1.0, $H_2O$); $^1$H NMR ($D_2O$; pH = 8) δ 7.34−7.23 (m, 5H, Ar), 4.74 and 4.62 (2 d, 2H, $J_{AB}$ = 11.7 Hz, C*H*$_2$Ph), 4.44 (d, 1H, $J_{1',2'}$ = 8.0 Hz, H-1′), 3.95 (ddd, 1H, H-2), 3.85 (dd, 1H, $J_{4',5'}$ = 9.5 Hz, H-4′), 3.77 (dd, 1H, $J_{2,3}$ = 2.9, $J_{3,4}$ = 5.2 Hz, H-3), 3.57 (d, 2H, H-5a, H-5b), 3.54 (m, 1H, H-5′), 3.53 (dd, 1H, $J_{3',4'}$ = 9.3 Hz, H-3′), 3.34 (dd, 1H, H-6′a), 3.24 (dd, 1H, $J_{2',3'}$ = 9.4 Hz, H-2′), 2.94 (dd, 1H, $J_{1a,2}$ = 1.2 Hz, H-1a), 2.68 (dd, 1H, $J_{1b,2}$ = 5.8, $J_{1a,1b}$ = 11.3 Hz, H-1b), 2.46 (ddd, 1H, $J_{4,5a} = J_{4,5b}$ = 10.1 Hz, H-4), 2.38 (dd, 1H, $J_{5',6'b}$ = 8.7, $J_{6'a,6'b}$ = 14.2 Hz, H-6′b); $^{13}$C NMR ($D_2O$) δ 136.7, 128.9, 128.6, 128.5 ($C_{Ar}$), 101.2 (C-1′), 78.8 (C-4′), 78.7 (C-3), 75.8 (C-2), 74.3 (C-3′), 74.2 (C-5′), 73.1 (C-2′), 72.1 (C-4), 72.0 (*C*H$_2$Ph), 60.5 (C-5), 60.2 (C-1), 54.8 (C-6′); MALDI MS *m/e* 488.05 ($M^+ + Na$), 466.12 ($M^+ + H$), 386.23 ($M^+ + H - SO_3$); HRMS calcd for $C_{18}H_{26}NO_{11}S$ 464.1221, found 464.1220.

**General Procedure for the Preparation of the Final Compounds 5−10.** The partially deprotected compounds **27**−**32** were dissolved in 90% AcOH (10 mL), $Pd(OH)_2$/C (20%, 300−500 mg, depending on the amount of starting material) was added, and the reaction mixture was subjected to hydrogenolysis for 24 h at rt. After the $Pd(OH)_2$/C was filtered, water (100 mL) was used to wash it repeatedly. The combined filtrate was then evaporated under reduced pressure. The remaining gum was dissolved in water (20 mL), and the pH of the solution was carefully adjusted to 8 by addition of 2 M NaOH solution. $NaBH_4$ (1.2 equiv of starting material) was slowly added to the reaction mixture. The progress of the reaction was followed by TLC (EtOAc/MeOH/$H_2O$, 7:3:1). When the starting material had been essentially consumed, the pH of the reaction mixture was carefully adjusted to 4 by the addition of a 2 M HCl solution. After removal of the solvents under reduced pressure, the residue was purified by column chromatography (EtOAc and EtOAc/MeOH/$H_2O$, 3:2:1) to give the purified compounds **5**−**10** as colorless, amorphous, hygroscopic solids.

**1,4-Dideoxy-1,4-[[(2*S*,3*R*,4*R*,5*S*)-2,4,5,6-tetrahydroxy-3-(sulfoxy)hexyl]episelenoniumylidene]-D-arabinitol (5).** Compound **27** (400 mg, 0.76 mmol) was dissolved in 90% AcOH (10 mL), $Pd(OH)_2$/C (20%, 400 mg) was added, and the reaction mixture was subjected to hydrogenolysis for 24 h at room temperature. The resulting hemiacetals were reduced with $NaBH_4$ (35 mg, 0.92 mmol) to give compound **5** (123 mg, 50%) as a colorless, amorphous, hygroscopic solid: $[\alpha]^{22}_D$ +43.3 (*c* 1.0, $H_2O$); $^1$H NMR ($D_2O$) δ 4.68 (dt, 1H, H-2), 4.51 (ddd, 1H, H-2′), 4.38 (dd, 1H, $J_{2,3}$ = 3.6, H-3), 4.30 (dd, 1H, $J_{2',3'}$ = 1.3, $J_{3',4'}$ = 9.1 Hz, H-3′), 4.05 (ddd, 1H, $J_{3,4}$ = 3.1, H-4), 3.97 (dd, 1H, $J_{4,5a}$ = 5.1, $J_{5a,5b}$ = 12.5 Hz, H-5a), 3.89 (dt, 1H, $J_{5',6'a} = J_{5',6'b}$ = 6.3 Hz, H-5′), 3.87−3.84 (m, 2H, H-1′a, H-1′b), 3.83 (dd, 1H, $J_{4,5b}$ = 3.8 Hz, H-5b), 3.72 (dd, 1H, $J_{4',5'}$ = 0.9 Hz, H-4′), 3.69−3.64 (2d, 2H, H-1a, H-1b), 3.54 (d, 2H, H-6′a, H-6′a); $^{13}$C NMR ($D_2O$) δ 78.8 (C-3′), 78.5 (C-3), 77.7 (C-2), 69.6 (C-4), 69.5 (C-5′), 68.7 (C-4′), 65.6 (C-2′), 62.8 (C-6′), 59.4 (C-5), 48.6 (C-1′), 44.8 (C-1); MALDI MS *m/e* 465.27 ($M^+ + Na$), 363.36 ($M^+ + H - SO_3$); HRMS calcd for $C_{11}H_{22}O_{11}SSeNa$ 464.9940, found 464.9943.

**1,4-Dideoxy-1,4-[[(2*S*,3*R*,4*R*,5*S*)-2,4,5,6-tetrahydroxy-3-(sulfoxy)hexyl]episulfoniumy lidene]-D-arabinitol (6).** Compound **28** (300 mg, 0.62 mmol) was dissolved in 90% AcOH (10 mL), $Pd(OH)_2$/C (20%, 300 mg) was added, and the reaction mixture was subjected to hydrogenolysis for 24 h at room temperature. The resulting hemiacetals were reduced with $NaBH_4$ (29 mg, 0.77 mmol) to give compound **6** (127 mg, 52%) as a colorless, amorphous, hygroscopic solid. The $^1$H NMR and $^{13}$C NMR data matched those reported in our previous publication.[14]

**1,4-Dideoxy-1,4-[[(2*S*,3*R*,4*R*,5*S*)-2,4,5,6-tetrahydroxy-3-(sulfoxy)hexyl]iminonium]-D-arabinitol (7).** Compound **29** (500 mg, 1.07 mmol) was dissolved in 90% AcOH (10 mL), $Pd(OH)_2$/C (20%, 500 mg) was added, and the reaction mixture was subjected to hydrogenolysis for 24 h at room temperature. The resulting hemiacetals were reduced with $NaBH_4$ (50 mg, 1.32 mmol) to give compound **7** (250 mg, 62%) as a colorless, amorphous, hygroscopic solid: $[\alpha]^{22}_D$ +44.5 (*c* 1.0, $H_2O$); $^1$H NMR ($D_2O + K_2CO_3$) δ 4.27 (dd, 1H, $J_{3',4'}$ = 8.6, $J_{3',2'}$ = 1.3 Hz, H-3′), 4.06 (ddd, 1H, $J_{2',1a'}$ = 4.8, $J_{2',1b'}$ = 8.0 Hz, H-2′), 3.95 (ddd, 1H, $J_{2,1a}$= 2.1, $J_{2,1b}$ = 5.8 Hz, H-2), 3.84 (dt, 1H, $J_{5',4'}$ = 1.5, $J_{5',6}$ = 5.5 Hz, H-5′), 3.78 (dd, 1H, $J_{3,2}$ = 2.8, $J_{3,4}$ = 5.2 Hz, H-3), 3.72 (dd, 1H, H-4′), 3.57 (dd, 1H, $J_{5a,5b}$ = 12.0, $J_{5a,4}$ = 5.2 Hz, H-5a), 3.56 (dd, 1H, $J_{5b,4}$ = 4.3 Hz, H-5b), 3.53 (d, 2H, $H_2$-6), 2.97 (dd, 1H, $J_{1a',1b'}$ = 13.2 Hz, H-1a′), 3.94 (dd, 1H, $J_{1a,1b}$ = 11.3, H-1a), 2.70 (dd, 1H, H-1b′), 2.50 (dd, 1H, H-1b′), 2.42 (ddd, 1H, H-4); $^{13}$C NMR ($D_2O$) δ 78.9 (C-3′), 78.8 (C-3), 75.8 (C-2), 72.4 (C-4), 70.0 (C-5′), 69.1 (C-4′), 68.6 (C-2′), 62.9 (C-6′), 60.6 (C-5), 59.8 (C-1), 58.0 (C-1′); MALDI MS *m/e* 400.09 ($M^+ + Na$), 298.35 ($M^+ + H - SO_3$); HRMS calcd for $C_{11}H_{22}NO_{11}S$ 376.0908, found 376.0912.

**1,4-Dideoxy-1,4-[[(2*S*,3*S*,4*R*,5*S*)-2,4,5,6-tetrahydroxy-3-(sulfoxy)hexyl]episelenonium ylidene]-D-arabinitol (8).** Compound **30** (400 mg, 0.76 mmol) was dissolved in 90% AcOH (10 mL), $Pd(OH)_2$/C (20%, 400 mg) was added, and the reaction mixture was subjected to hydrogenolysis for 24 h at room temperature. The resulting hemiacetals were reduced with $NaBH_4$ (35 mg, 0.92 mmol) to give compound **8** (108 mg, 43%) as a colorless, amorphous, hygroscopic solid: $[\alpha]^{22}_D$ +22.3 (*c* 1.0, $H_2O$); $^1$H NMR ($D_2O$) δ 4.66 (m, 1H, $J_{1a,2} = J_{1b,2}$ = 7.8 Hz, H-2), 4.36 (dd, 1H, $J_{2,3}$ = 3.5, $J_{3,4}$ = 3.0 Hz, H-3), 4.32 (ddd, 1H, H-2′), 4.26 (dd, 1H, $J_{2',3'}$ = 1.5, $J_{3',4'}$ = 7.3 Hz, H-3′), 4.04 (ddd, 1H, $J_{4,5a}$ = 5.1, $J_{4,5b}$ = 9.1 Hz, H-4), 3.94 (dd, 1H, $J_{5a,5b}$ = 12.5 Hz, H-5a), 3.94 (dd, 1H, $J_{1'a,2'}$ = 3.8, $J_{1'a,1'b}$ = 12.3 Hz, H-1′a), 3.82 (dd, 1H, $J_{1'b,2'}$ = 5.9 Hz, H-1′b), 3.78 (m, 3H, H-5b, H-4′, H-5′)), 3.67 (d, 2H, H-1a, H-1b), 3.62 (dd, 1H, $J_{5',6'a}$ = 3.4, $J_{6'a,6'b}$ = 8.5 Hz, H-6′a), 3.51 (dd, 1H,

$J_{5',6'b}$ = 5.8 Hz, H-6′b); $^{13}$C NMR ($D_2O$) $\delta$ 80.0 (C-3′), 78.5 (C-3), 77.6 (C-2), 71.6 (C-5′), 70.0 (C-4), 69.0 (C-4′), 66.5 (C-2′), 62.3 (C-6′), 59.4 (C-5), 48.5 (C-1′), 45.0 (C-1); MALDI MS *m*/*e* 465.13 ($M^+ + Na$), 363.23 ($M^+ + H - SO_3$); HRMS calcd for $C_{11}H_{22}O_{11}SSeNa$ 464.9940, found 464.9939.

**1,4-Dideoxy-1,4-[[(2*S*,3*S*,4*R*,5*S*)-2,4,5,6-tetrahydroxy-3-(sulfoxy)hexyl]episulfoniumylidene]-D-arabinitol (9).** Compound **31** (300 mg, 0.62 mmol) was dissolved in 90% AcOH (10 mL), $Pd(OH)_2$/C (20%, 300 mg) was added, and the reaction mixture was subjected to hydrogenolysis for 24 h at room temperature. The resulting hemiacetals were reduced with $NaBH_4$ (29 mg, 0.77 mmol) to give compound **9** (95 mg, 39%) as a colorless, amorphous, hygroscopic solid. The $^1$H NMR and $^{13}$C NMR data matched those reported in our previous publication.[14]

**1,4-Dideoxy-1,4-[[(2*S*,3*S*,4*R*,5*S*)-2,4,5,6-tetrahydroxy-3-(sulfoxy)hexyl]iminonium]-D-arabinitol (10).** Compound **32** (500 mg, 1.07 mmol) was dissolved in 90% AcOH (10 mL), $Pd(OH)_2$/C (20%, 500 mg) was added, and the reaction mixture was subjected to hydrogenolysis for 24 h at room temperature. The resulting hemiacetals were reduced with $NaBH_4$ (50 mg, 1.32 mmol) to give compound **10** (218 mg, 54%) as a colorless, amorphous, hygroscopic solid: $[\alpha]^{22}_D$ −2.7 (*c* 1.0, $H_2O$); $^1$H NMR ($D_2O$ + $K_2CO_3$) $\delta$ 4.26 (dd, 1H, $J_{2',3'}$ = 5.0, $J_{3',4'='}$ = 2.1 Hz, H-3′), 3.97 (m, 2H, H-2, H-2′), 3.80 (dd, 1H, $J_{4',5'}$ = 6.4 Hz, H-4′), 3.77 (dd, 1H, $J_{3,4}$ = 4.9, $J_{3,2}$ = 2.8 Hz, H-3), 3.73 (ddd, 1H, $J_{5',6a'}$ =3.6, $J_{5',6b'}$ = 6.3 Hz, H-5′), 3.61 (dd, 1H, $J_{6a',6b'}$ = 12.0 Hz, H-6a′), 3.57 (dd, 1H, $J_{5a,5b}$ = 9.8, $J_{5a,4}$ = 5.6 Hz, H-5a), 3.55 (dd, 1H, $J_{5b,4}$ = 5.3 Hz, H-5b), 3.50 (dd, 1H, H-6b′), 3.09 (dd, 1H, $J_{1a,2}$ = 5.1, $J_{1a,1b}$ = 13.3 Hz, H-1a), 2.98 (dd, 1H, $J_{1a',1b'}$ = 11.3, $J_{1a',2'}$ = 1.8 Hz, H-1a′), 2.71 (dd, 1H, $J_{1b',2'}$ = 5.7 Hz, H-1b′), 2.44 (ddd, 1H, H-4), 2.39 (dd, 1H, $J_{1a,2}$ = 7.6 Hz, H-1b); $^{13}$C NMR ($D_2O$) $\delta$ 80.4 (C-3′), 78.7 (C-3), 75.8 (C-2), 72.3 (C-4), 71.9 (C-5′), 70.6 (C-4′), 69.6 (C-2′), 62.4 (C-6′), 60.9 (C-1), 59.7 (C-5), 56.9 (C-1′); MALDI MS *m*/*e* 400.03 ($M^+ + Na$), 298.22 ($M^+ + H - SO_3$); HRMS calcd for $C_{11}H_{22}NO_{11}S$ 376.0908, found 376.0908.

**Acknowledgment.** We are grateful to the Canadian Institutes of Health Research for financial support and to B. D. Johnston for helpful discussions.

**Supporting Information Available:** General experimental procedures and copies of $^1$H and $^{13}$C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO071045M