JOC*Article*

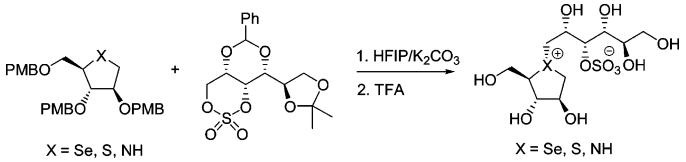
A New Class of Glucosidase Inhibitor: Analogues of the Naturally Occurring Glucosidase Inhibitor Salacinol with Different Ring Heteroatom Substituents and Acyclic Chain Extension

Hui Liu,[†] Lyann Sim,[‡] David R. Rose,[‡] and B. Mario Pinto*,[†]

Department of Chemistry, Simon Fraser University, Burnaby, B.C., Canada V5A 1S6, and Department of Medical Biophysics, University of Toronto and Division of Molecular and Structural Biology, Ontario Cancer Institute, Toronto, ON, Canada M5G 2M9

bpinto@sfu.ca

Received December 11, 2005



Six chain-extended analogues of the naturally occurring glycosidase inhibitor salacinol, with ring-heteroatom variation, were synthesized for structure−activity studies with different glycosidase enzymes. The syntheses involved the reaction of PMB-protected D- and L- seleno-, thio-, and iminoarabinitol with a benzylidene- and isopropylidene-protected 1,3-cyclic sulfate, derived from commercially available D-sorbitol, in 1,1,1,3,3,3-hexafluoro-2-propanol containing potassium carbonate. Deprotection of the products afforded the novel selenonium, sulfonium, and iminium analogues of salacinol containing polyhydroxylated, monosulfated, extended acyclic chains of 6-carbons, differing in stereochemistry at the stereogenic centers and ring-heteroatom constitution. Four of these compounds inhibit recombinant human maltase glucoamylase, one of the key intestinal enzymes involved in the breakdown of glucose oligosaccharides in the small intestine, with K_i values in the micromolar range, thus providing lead candidates for the treatment of Type 2 diabetes.

Introduction

The controlled inhibition of glycosidase enzymes plays important roles in the biochemical processing of biopolymers containing carbohydrates.[1,2] For patients suffering from Type 2 diabetes, insulin secretion may be normal but the entry into cells of glucose (normally mediated by insulin) is compromised. Hence, the management of blood glucose levels for these patients is crucial.[3] One strategy to achieve this goal is to administer drugs that can inhibit the activity of pancreatic α-amylase and intestinal glucosidases that break down oligosaccharides to glucose. This enzyme inhibition delays glucose absorption into the blood and results in a lowering or smoothing of blood glucose levels.[4]

It is of interest that Nature seems to have selected non-carbohydrate mimics as natural inhibitors of glycosidase enzymes, likely due to the intrinsic low affinities of carbohydrate−protein interactions. Some naturally occurring compounds, such as acarbose (**1**) and swainsonine (**2**), are potent glycosidase

* 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) For example: Garcia-Olmeda, F.; Salcedo, G.; Sanchez-Monge, R.; Gomez, L.; Royo, L.; Carbonero, P. *Oxford Surveys of Plant Molecular and Cell Biology*; Clarendon Press: Oxford, 1987; Vol. 4, pp 275−334. Bompard-Gilles, C.; Rousseau, P.; Rouge, P.; Payan, F. *Structure* **1996**, *4*, 1441−1452. Vallee, F.; Kadziola, A.; Bourne, Y.; Juy, M.; Rodenburg, K. W.; Svensson, B.; Haser, R. *Structure* **1998**, *6*, 649−659. Strobl, S.; Maskos, K.; Wiegand, G.; Huber, R.; GomisRuth, F.-X.; Glockshuber, R. *Structure* **1998**, *6*, 911−921.

(2) For leading references: *Essentials of Glycobiology*; Varki, A., Cummings, R., Esko, J., Freeze, H., Hart, G., Marth, J., Eds.; Cold Spring Harbor Laboratory Press: Cold Spring Harbor, New York, 1999. Elbein, A. D.; Molyneux, R. J. In *Comprehensive Natural Products Chemistry*; Pinto, B. M., Ed.; Barton, D. H. R., Nakanishi, K., Meth-Cohn, O., Ser. Eds.; Elsevier: UK, 1999; Vol. 3, Chapter 7. Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645−1680. McCarter, J. D.; Withers, S. G. *Curr. Opin. Struct. Biol.* **1994**, *4*, 885−892. Ly, H. D.; Withers, S. G. *Annu. Rev. Biochem.* **1999**, *68*, 487−522.

(3) Crivello, J. V. *Adv. Polym. Sci.* **1984**, *62*, 1−48. Sherwood, L. *Fundamentals of Physiology*, 2nd ed.; West: New York, 1995; Chapter 17, p 517.

(4) Holman, R. R.; Cull, C. A.; Turner, R. C. *Diabetes Care* **1999**, *22*, 960−964. Jacob, G. S. *Curr. Opin. Struct. Biol.* **1995**, *5*, 605−611.

10.1021/jo052539r CCC: $33.50
Published on Web 03/21/2006

CHART 1

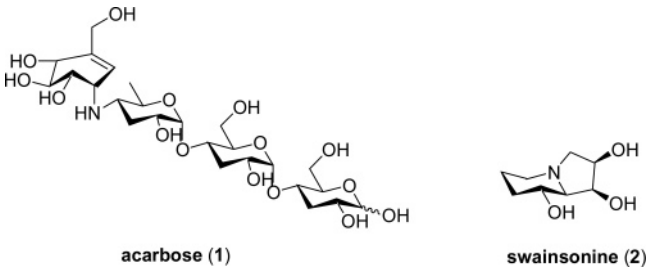
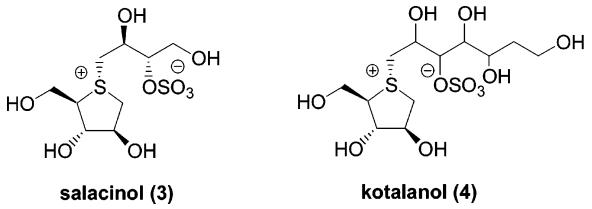


CHART 2



inhibitors (Chart 1).[5] Acarbose is currently used for the oral treatment of diabetes.[4]

Recently, a new class of glycosidase inhibitors, namely salacinol (**3**) and kotalanol (**4**), with an intriguing inner-salt sulfonium−sulfate structure was isolated from the roots and stems of the plant *Salacia reticulata* (Chart 2).[6−8] These compounds have been found to be potent inhibitors of intestinal glucosidase enzymes[6−8] and thus should attenuate the undesirable spike in blood glucose that is experienced by diabetics after consuming a meal rich in carbohydrates. The structural similarities of **3** and **4** are obvious, with both possessing the same 1,4-anhydrothio-D-arabinitol ring, the alditol chain of kotalanol **4** being extended by three carbons (Chart 2). It is believed that the inhibition of glucosidases by salacinol and kotalanol is in fact due to their ability to mimic both the shape and charge of the oxacarbenium-ion-like transition state involved in the enzymatic reactions.[9−11]

The syntheses of salacinol (**1**),[10,11] its stereoisomers,[12,13] the selenium congener blintol (**5**),[14,15] and the nitrogen congener ghavamiol (**6**)[16] have been reported (Chart 3). Blintol exhibited

CHART 3

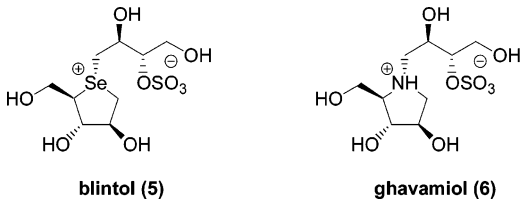
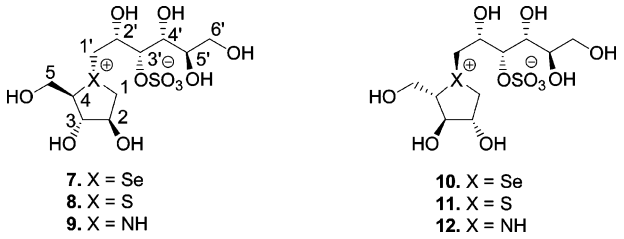
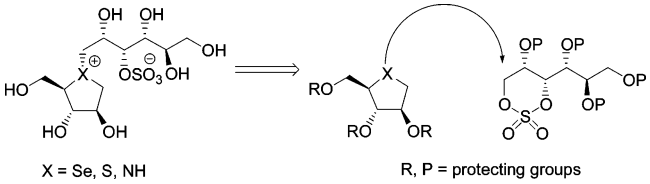


CHART 4



SCHEME 1



stronger inhibitory activities than salacinol, and in addition, we found that analogues **5** and **6** and salacinol **3** showed discrimination on selectivity for certain glycosidase enzymes.[14−17] These studies have revealed interesting differences in the inhibitory activities of these compounds for glycosidase enzymes of different origin.

Interestingly, kotalanol **4** was claimed to have even greater inhibitory power than salacinol for certain glycosidase enzymes.[7] It was therefore of interest to examine homologues of salacinol containing polyhydroxylated, sulfated chains. We have recently reported the synthesis of such homologues containing five- and six-carbon chains.[18] We now report simpler synthetic routes to six-carbon chain homologues, their selenium and nitrogen congeners, and the corresponding diastereomers resulting from changes in stereochemistry at the stereogenic centers in the heterocyclic ring (**7**−**12**, Chart 4).

Results and Discussion

Retrosynthetic analysis indicated that the analogues **7**−**12** could be synthesized by alkylation of a protected anhydroalditol at the ring heteroatom with a terminal 1,3-cyclic sulfate derived from D-sorbitol (Scheme 1).

However, the choice of protecting groups for the cyclic sulfate merited careful consideration, especially in the case of the selenonium analogues. Our previous studies[14,15] had suggested that the *p*-methoxybenzyl ether was the most appropriate protecting group for the anhydroalditol moiety. Our previous work also suggested that the release of ring strain in the opening of a cyclic sulfate was beneficial. Accordingly, we envisioned that the cyclic sulfate **13** (Chart 5), in which the 2,4-positions were protected by a benzylidene acetal, would serve this

(5) Bock, K.; Sigurskjold, B. *Struct. Nat. Prod. Chem*. **1990**, *7*, 29−86. Stutz, A. E. *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*; Wiley-VCH: New York, 1999.

(6) Yoshikawa, M.; Murakami, T.; Shimada, H.; Matsuda, H.; Yamahara, J.; Tanabe, G.; Muraoka, O. *Tetrahedron Lett*. **1997**, *38*, 8367−8370.

(7) Yoshikawa, M.; Murakami, T.; Yashiro, K.; Matsuda, H. *Chem. Pharm. Bull*. **1998**, *46*, 1339−1340.

(8) Yoshikawa, M.; Murikawa, T.; Matsuda, H.; Tanabe, G.; Muraoka, O. *Bioorg. Med. Chem*. **2002**, *10*, 1547−1550.

(9) Svansson, L.; Johnston, B. D.; Gu, J. H.; Patrick, B.; Pinto, B. M. *J. Am. Chem. Soc*. **2000**, *122*, 10769−10775.

(10) Yuasa, H.; Takada, J.; Hashimoto, H. *Tetrahedron Lett*. **2000**, *41*, 6615.

(11) Ghavami, A. Johnston, B. D.; Pinto, B. M. *J. Org. Chem*. **2001**, *66*, 2312.

(12) Ghavami, A.; Sadalapure, K. S.; Johnston, B. D.; Lobera, M.; Snider, B. B.; Pinto, B. M. *Synlett* **2003**, 1259−1262.

(13) 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.

(14) Johnston, B. D.; Ghavami, A.; Jensen, M. T.; Svensson, B.; Pinto, B. M. *J. Am. Chem. Soc*. **2002**, *124*, 8245−8250.

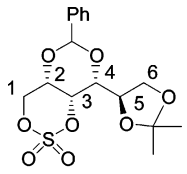
(15) Liu, H.; Pinto, B. M. *J. Org. Chem*. **2005**, *70*, 753−755. Pinto, B. M.; Johnston, B. D.; Ghavami, A.; Szczepina, M. G.; Liu, H.; Sadalapure, K. US Patent, Filed June 25, 2004.

(16) Ghavami, A.; Johnston, B. D.; Jensen, M. T.; Svensson, B.; Pinto, B. M. *J. Am. Chem. Soc*. **2001**, *123*, 6268−6271.

(17) Li, Y.; Scott, C. R.; Chamoles, N. A.; Ghavami, A.; Pinto, B. M.; Turecek, F.; Gelb, M. H. *Clin. Chem*. **2004**, *50*, 1785−1796.

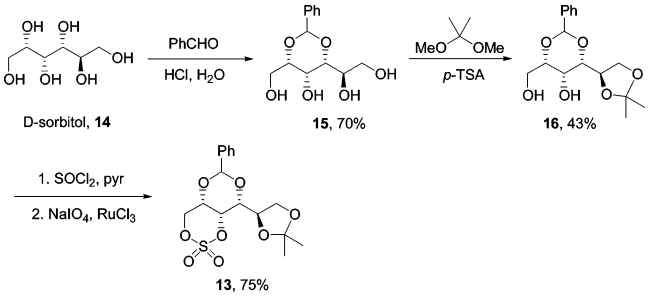
(18) Johnston, B. D.; Hensen, H. J.; Pinto, B. M. *J. Org. Chem.* **2006**, ASAP.

CHART 5

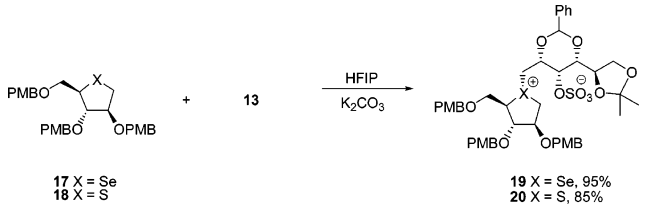


13

SCHEME 2



SCHEME 3



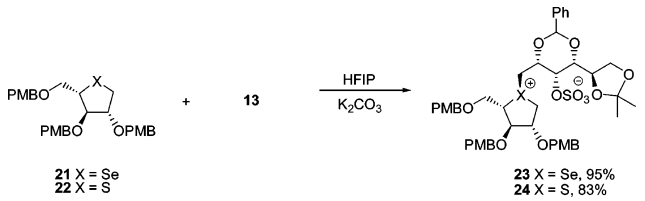
function. The 5,6-positions could be protected with an isopropylidene acetal. After the coupling reactions, the products could then be readily deprotected by simple treatment with trifluoroacetic acid.

The synthesis of the cyclic sulfate **13**, as depicted in Scheme 2, started from the commercially available D-sorbitol (**14**). Following the reported method by Kuszmann et al.,[19] D-sorbitol was first treated with benzaldehyde in hydrochloric acid and water to give 2,4-*O*-benzylidene-D-glucitol (**15**). Compound **15** was then reacted with 2,2-dimethoxypropane to afford the 2,4-*O*-benzylidene-5,6-*O*-isopropylidene-D-glucitol (**16**).[19] The glucitol derivative **16** was then converted to the cyclic sulfite by treatment with thionyl chloride and pyridine, and the sulfite was then oxidized with sodium periodate and ruthenium(III) chloride as a catalyst to yield the desired cyclic sulfate **13**, as a crystalline solid in 75% yield.

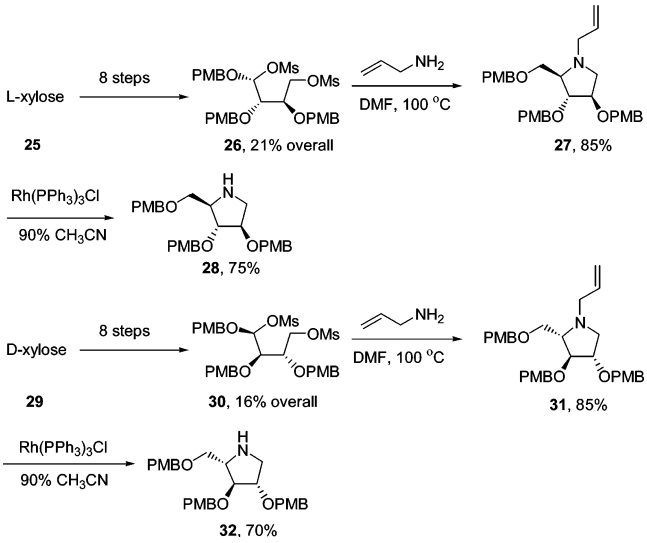
The coupling reactions of the cyclic sulfate **13** with the protected selenoarabinitols and thioarabinitols were investigated first. The PMB-protected D-selenoarabinitol **17** and D-thioarabinitol **18** were prepared by methods described in our earlier work.[12,15] The cyclic sulfate **13** was reacted with D-selenoarabinitol **17**[15] and D-thioarabinitol **18**[12] to give the protected selenonium and sulfonium compounds **19** and **20**, respectively (Scheme 3). The solvent 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) offered significant advantage, as observed in our previous work.[12,14,15] For example, while the coupling reaction of **17** with the cyclic sulfate **13** did not proceed in acetone at 100 °C, it proceeded in HFIP at 65 °C within 12 h to give **19** in 95% yield.

The PMB-protected L-selenoarabinitol **21** and L-thioarabinitol **22** were prepared as described for the corresponding D-isomers **17** and **18**, respectively.[15] The cyclic sulfate **13** was reacted with

SCHEME 4



SCHEME 5



L-selenoarabinitol **21** and L-thioarabinitol **22** in HFIP to give the corresponding protected selenonium and sulfonium compounds **23** and **24**, respectively (Scheme 4).

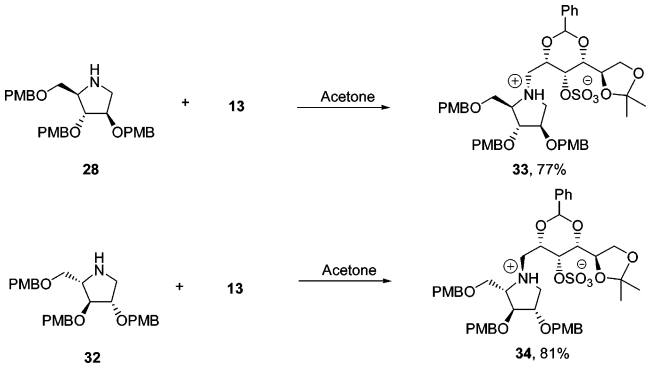
We turned next to the synthesis of the corresponding chain-extended nitrogen analogues. The synthesis of the PMB protected D- and L-iminoarabinitols **28** and **32** took advantage of our established method for the synthesis of blintol (Scheme 5). Starting from L-xylose and D-xylose, respectively, the corresponding dimesylates **26** and **30**[15] were prepared in overall yields of 21% and 16%, respectively. The dimesylates **26** and **30** were subsequently treated with allylamine and heated to 90 °C in DMF for 12 h to yield the allylimino compounds **27** and **31**, respectively. Compounds **27** and **31** were refluxed in 90% aqueous acetonitrile with Wilkinson's catalyst for 4 h to afford the desired D-iminoarabinitol **28** and L-iminoarabinitol **32**, respectively.

The coupling reactions of **28** and **32** with the cyclic sulfate **13** were then carried out in acetone, as described previously for the synthesis of ghavamiol **6**.[16] The reactions proceeded smoothly at 55 °C to give the corresponding coupling products **33** and **35**, respectively (Scheme 6).

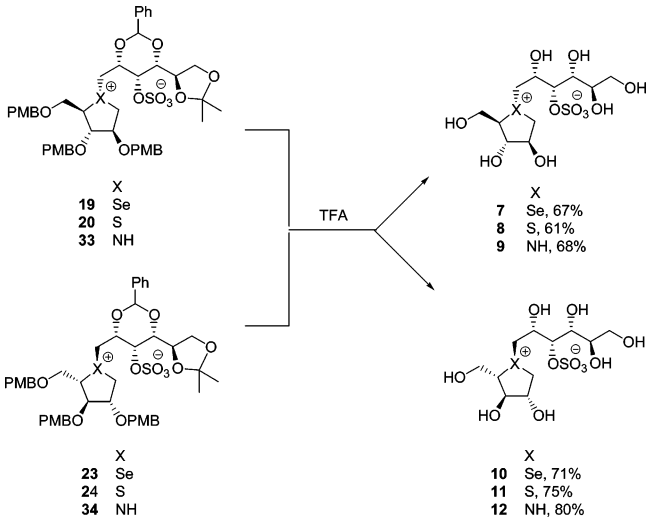
The reactivities of the seleno-, thio-, and iminoarabinitols with the cyclic sulfate **13** varied slightly. The iminoarabinitols were the most reactive, while the thioarabinitols were the least reactive of the three. Selectivity for attack of the seleno-, thio-, and iminoarabinitol derivatives at the primary carbon of the cyclic sulfate over possible alternative attack at the secondary carbon was invariably excellent, and in no case were isolable quantities of the regioisomers detected. Of note, in the case of the coupling reactions of selenoarabinitols **17** and **21** with the cyclic sulfate **13**, there was a small amount (less than 10%) of the stereo-

(19) Kuszmann, J.; Medgyes, G.; Boros, S. *Carbohydr. Res.* **2004**, *339*, 2407−2414.

SCHEME 6



SCHEME 7



isomers formed through electrophilic attack on the β-face of the D-selenoarabinitol **17** and the α-face of the L-selenoarabinitol **21** to give products that were diastereomeric at the selenonium center.

The deprotection of the coupled products **19**, **20**, **23**, **24**, **33**, and **34** was carried out by treatment with trifluoroacetic acid (Scheme 7). The resulting residues were purified by flash chromatography to yield compounds **7** to **12** as amorphous, hygroscopic solids.

The absolute stereochemistry at the heteroatom center of compounds **7**−**12** was established by NOESY NMR spectroscopy (Figure 1). For example, in the NOESY spectrum of compound **8**, the H-4 to H-1′b correlation was clearly exhibited, implying that they are syn-facial. Therefore, C-1′ of the side chain must be anti to C-5 of the sulfonium salt ring (Figure 1). However, the correlation of H-1′a or H-1′b with H-1a,1b could not be clearly established owing to overlap of signals.

As a final point of interest, we comment on the inhibitory activities of the compounds synthesized in this study against recombinant human maltase glucoamylase (MGA), a critical intestinal glucosidase involved in the processing of oligosaccharides of glucose into glucose itself. Compounds **7** and **9**, with the D-arabinitol configuration in the heterocyclic ring displayed by salacinol, have K_i values of 41 ± 7 and 26 ± 9 μM, respectively. In contrast, the sulfur analogue **8** is not active. Of compounds **10**−**12**, with the unnatural L-arabinitol configuration in the heterocyclic ring, the sulfur and nitrogen congeners **11** and **12** are active, with K_i values of 25 ± 5 and 5 ± 1 μM, respectively.

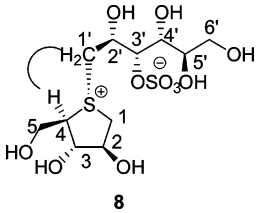


FIGURE 1. NOE correlations observed in the NOESY spectrum of **8**.

Conclusions

Three series of chain-extended analogues of the naturally occurring glucosidase inhibitor salacinol were synthesized. The analogues contained extended acyclic chains of six carbons, as well as ring-heteroatom substitution (N, Se, S) and changes of stereochemistry in the five-membered ring. These syntheses utilized the 1,3-cyclic sulfate derived from commercially available D-sorbitol in four steps. The PMB, isopropylidene acetal, and benzylidene acetal protecting groups on the coupling products ensured facile deprotection with TFA to yield the final compounds **7** to **12**. Compounds **7**, **9**, **11**, and **12** show inhibition of recombinant human maltase glucoamylase, a critical intestinal glucosidase, in the micromolar range.

Experimental Section

Enzyme Activity Assay. Analysis of MGA inhibition was performed using maltose as the substrate and measuring the release of glucose. Reactions were carried out in 100 mM MES buffer pH 6.5 at 37 °C for 15 min. The reaction was stopped by boiling for 3 min. Twenty microliter aliquots were taken and added to 100 μL of glucose oxidase assay reagent (Sigma) in a 96-well plate. Reactions were developed for 1 h, and absorbance was measured at 450 nm to determine the amount of glucose produced by MGA activity in the reaction. One unit of activity is defined as the hydrolysis of one mole of maltose per minute. All reactions were performed in triplicate, and absorbance measurements were averaged to give a final result.

Enzyme Kinetics. Kinetic parameters of recombinant MGA were determined using the glucose oxidase assay to follow the production of glucose upon addition of enzyme (15 nM) at increasing maltose concentrations (from 1 mM to 3.5 mM) with a reaction time of 15 min. The program GraFit 4.0.14 was used to fit the data to the Michaelis−Menten equation and estimate the kinetic parameters, K_m and V_{max}, of the enzyme. K_i values for each inhibitor were determined by measuring the rate of maltose hydrolysis by MGA at varying inhibitor concentrations. Data were plotted in Lineweaver−Burk plots (1/rate vs 1/[substrate]), and K_i values were determined by the equation $K_i = K_m[I]/(V_{max})m - K_m$, where m is the slope of the line. The K_i reported for each inhibitor was estimated by averaging the K_i values obtained from each of the different inhibitor concentrations.

2,4-*O*-Benzylidene-5,6-*O*-isopropylidene-D-glucitol 1,3-Cyclic Sulfate (13). The 2,4-*O*-benzylidene-5,6-*O*-isopropylidene-D-glucitol (**16**) was prepared by the literature method.[17] To a solution of **16** (4.7 g, 15 mmol) in CH_2Cl_2 (80 mL)was added pyridine (10 mL) at room temperature. Thionyl chloride (1.65 mL, 22 mmol) dissolved in CH_2Cl_2 (20 mL) was then added, and the mixture was heated at 40−50 °C for 4 h. The progress of the reaction was followed by TLC analysis of aliquots (developing solvent hexane/EtOAc, 2:1). When starting material **16** had been essentially consumed, the reaction mixture was cooled, poured into ice−water, extracted with CH_2Cl_2 (100 mL), washed with brine (20 mL), and dried over Na_2SO_4. After evaporation of the solvent, the crude sulfite was passed through a short silica gel column. The resulting sulfite

was redissolved in a mixture of CH_3CN, CCl_4, and water ($CH_3CN/CCl_4/H_2O$, 3:3:0.5, 65 mL). Ruthenium(III) chloride (50 mg) was then added to the solution. At room temperature, $NaIO_4$ (4.26 g, 20 mmol) was added to the mixture, and the mixture was stirred for 2 h. When TLC analysis of aliquots (developing solvent hexane/EtOAc, 1:1) showed total consumption of the starting material, the reaction mixture was filtered through a short column of silica gel and the silica gel was washed with CH_2Cl_2 (100 mL). The filtrate was combined and evaporated to dryness. It was then redissolved in EtOAc (100 mL), washed with water (50 mL), and dried over Na_2SO_4. Purification by column chromatography (hexane/EtOAc, 1:1), followed by recrystallization with Hexane/EtOAc yielded **13** as a colorless, crystalline solid (3.9 g, 70%). Mp: 126−128 °C dec. $[\alpha]_D = +12.3$ (*c* 1.1, CH_2Cl_2). ^{1}H NMR (CD_2Cl_2) δ: 7.50−7.30 (m, 5H, Ar), 5.73 (s, 1H, C*H*Ph), 5.07 (br t, 1H, $J_{3,4} = 1.4$, H-4), 4.98 (dd, 1H, $J_{5,6b} = 1.8$, $J_{6a,6b} = 12.6$, H-6b), 4.72 (dd, 1H, $J_{5,6a} = 1.3$, H-6a), 4.36 (ddd, 1H, $J_{1a,2} = 3.6$, $J_{1b,2} = 6.0$, $J_{2,3} = 8.9$, H-2), 4.13 (dd, 1H, $J_{1a,1b} = 9.0$, H-1b), 4.09 (m, 1H, H-5), 4.08 (dd, 1H, H-1a), 3.94 (dd, 1H, H-3). ^{13}C NMR (CD_2Cl_2) δ: 136.7, 129.8, 128.6, and 126.4 (4C, Ar), 110.2 ($(CH_3)_2C$), 101.0 (*C*HPh), 78.0 (C-3), 77.2 (C-4), 75.4 (C-6), 71.7 (C-2), 67.9 (C-5), 66.7 (C-1), 27.1, and 24.8 (2 *C*H$_3$). Anal. Calcd for $C_{16}H_{20}O_8S$: C, 51.60; H, 5.41. Found: C, 51.56; H, 5.41.

***N*-Allyl-2,3,5-*O*-*p*-methoxybenzyl-1,4-dideoxy-1,4 -imino-D-arabinitol (27).** The dimesylate (**26**) was prepared by a literature method.[15] To a solution of the dimesylate **26** (8.0 g, 12.0 mmol) in DMF (30 mL) was added allylamine (10 mL, 0.13 mol), and the reaction mixture was heated at 90 °C for 12 h. The reaction mixture was poured into water (100 mL), extracted with Et_2O (4 × 50 mL), washed with water (10 × 20 mL), and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by column chromatography (hexane/EtOAc, 1:1) to give **27** as a colorless oil (5.4 g, 85%). $[\alpha]_D$: −8.6 (*c* 2.2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ: 7.20−6.70 (m, 12H, Ar), 5.85 (dddd, 1H, $J_{1a',2'} = 7.4$, $J_{1b',2'} = 5.8$, $J_{2',3a'} = 9.9$, $J_{2',3b'} = 17.1$, H-2′), 5.10 (d, 1H, H-3b′), 5.02 (d, 1H, H-3a′), 4.34 (s, 2H, CH_2Ph), 4.38 and 4.28 (two d, 2H, $J_{AB} = 12.0$, CH_2Ph), 3.82 (m, 2H, CH_2Ph), 3.80 (dd, 1H, $J_{2,3} = 4.0$, $J_{1a,2} = 4.8$, H-2), 3.76 (dd, 1H, $J_{3,4} = 5.1$, H-3), 3.72, 3.71, and 3.70 (three s, 9H, 3 OCH$_3$), 3.48 (dd, 1H, $J_{4,5b} = 5.2$, $J_{5a,5b} = 9.8$, H-5b), 3.44 (dd, 1H, H-1b′), 3.40 (dd, 1H, $J_{4,5a} = 6.6$, H-5a), 3.05 (d, 1H, $J_{1a,1b} = 10.4$, H-1b), 2.92 (dd, 1H, $J_{1a'2'} = 7.4$, $J_{1a',1b'} = 12.8$, H-1a′), 2.64 (m, 1H, H-4), 2.50 (dd, 1H, H-1a). ^{13}C NMR (CD_2Cl_2) δ: 159.4, 159.3, 159.2, 133.2, 133.1, 132.9, 130.8, 130.7, 130.6, 128.3, 112.0, and 111.9 (12 C, Ar), 135.9 (C-2′), 114.0 (C-3′), 85.5 (C-3), 81.2 (C-2), 73.0, 71.2 (2 *C*H$_2$Ph), 70.8 (C-5), 68.6 (C-4), 58.3 (C-1′), 57.3 (C-1), 56.5 (*C*H$_2$Ph), 55.5 (3 O*C*H$_3$). Anal. Calcd for $C_{32}H_{39}NO_6$: C, 72.02; H, 7.37; N, 2.62. Found: C, 71.74; H, 7.16; N, 2.84.

***N*-Allyl-2,3,5-*O*-*p*-methoxybenzyl-1,4-dideoxy-1,4-imino-L-arabinitol (31).** The dimesylate (**30**) was prepared by a literature method.[15] To a solution of the dimesylate **30** (3.6 g, 5.4 mmol) in DMF (30 mL) was added allylamine (10 mL, 0.13 mol), and the reaction mixture was heated at 90 °C for 12 h. The reaction mixture was poured into water (100 mL), extracted with Et_2O (4 × 50 mL), washed with water (10 × 20 mL), and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by column chromatography (hexane/EtOAc, 1:1) to give **31** as a colorless oil (2.5 g, 85%). $[\alpha]_D$: +15.7 (*c* 3.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ: 7.30−6.80 (m, 12H, Ar), 5.93 (dddd, 1H, $J_{1a',2'} = 7.3$, $J_{1b',2'} = 5.6$, $J_{2',3a'} = 9.9$, $J_{2',3b'} = 17.1$, H-2′), 5.18 (d, 1H, H-3b′), 5.10 (d, 1H, H-3a′), 4.46 and 4.43 (two d, 2H, $J_{AB} = 12.1$, CH_2Ph), 4.41 (s, 2H, CH_2Ph), 4.41 and 4.36 (two d, 2H, $J_{AB} = 11.9$, CH_2Ph), 3.85 (m, 1H, H-2), 3.83 (m, 1H, H-3), 3.80, 3.79, and 3.78 (three s, 9H, 3 OCH$_3$), 3.56 (dd, 1H, $J_{4,5b} = 5.5$, $J_{5a,5b} = 10.9$, H-5b), 3.52 (m, 1H, H-1b′), 3.48 (dd, 1H, $J_{4,5a} = 6.3$, H-5a), 3.12 (d, 1H, H-1b), 3.00 (dd, 1H, $J_{1a',1b'} = 12.9$, H-1a′), 2.72 (m, 1H, H-4), 2.56 (dd, 1H, $J_{1a,2} = 4.8$, H-1a). ^{13}C NMR (CD_2Cl_2) δ: 159.4, 159.3, 159.2, 130.9, 130.8, 130.7, 130.6, 130.5, 129.6, 129.5, 112.0, and 111.9 (12C, Ar), 135.9 (C-2′), 114.0 (C-3′), 85.5 (C-3), 81.2 (C-2), 73.0, 71.2 (2 *C*H$_2$Ph), 70.8 (C-5), 68.6 (C-4), 58.4 (C-1′), 57.4 (C-1), 55.5 (*C*H$_2$Ph), 55.4 (3 O*C*H$_3$). Anal. Calcd for $C_{32}H_{39}NO_6$: C, 72.02; H, 7.37; N, 2.62. Found: C, 71.89; H, 7.04; N, 2.63.

2,3,5-*O*-*p*-Methoxybenzyl-1,4-dideoxy-1,4-imino-D-arabinitol (28). To a solution of the *N*-allyl compound **27** (5.0 g, 9.3 mmol) in 90% CH_3CN (50 mL) was added Wilkinson's catalyst ($Rh(PPh)_3Cl$, 100 mg), and the reaction mixture was refluxed for 4 h. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (hexane/EtOAc, 1:1) to afford **28** as a colorless oil (3.5 g, 75%). $[\alpha]_D$: +0.8 (*c* 4.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ: 7.50−6.80 (m, 12H, Ar), 4.46 (m, 2H, CH_2Ph), 4.47 and 4.43 (two d, 2H, $J_{AB} = 10.9$, CH_2Ph), 4.49 and 4.41 (two d, 2H, $J_{AB} = 11.4$, CH_2Ph), 3.97 (m, 1H, H-2), 3.82 (dd, 1H, $J_{2,3} = 4.3$, $J_{3,4} = 3.0$, H-3), 3.81, 3.80, 3.79 (three s, 3 OCH$_3$), 3.58 (dd, 1H, $J_{4,5b} = 5.0$, $J_{5a,5b} = 9.5$, H-5b), 3.53 (dd, 1H, $J_{4,5a} = 3.6$, H-5a), 3.25 (dd, 1H, H-4), 3.09 (d, 2H, H-1a, H-1b). ^{13}C NMR (CD_2Cl_2) δ: 159.5, 159.4, 159.3, 133.2, 133.1, 133.0, 130.5, 130.4, 130.3, 130.2, 114.0, and 111.9 (12C, Ar), 85.3 (C-3), 84.1 (C-2), 73.1, 71.8, 70.9 (3 *C*H$_2$Ph), 70.1 (C-5), 64.2 (C-4), 55.5, 55.4, and 55.3 (3 O*C*H$_3$), 51.1 (C-1). Anal. Calcd for $C_{29}H_{35}NO_6$: C, 70.57; H, 7.15; N, 2.84. Found: C, 70.90; H, 7.21; N, 2.99.

2,3,5-*O*-*p*-Methoxybenzyl-1,4-dideoxy-1,4-imino-L-arabinitol (32). To a solution of the *N*-allyl compound **31** (3.0 g, 5.6 mmol) in 90% CH_3CN (50 mL) was added Wilkinson's catalyst ($Rh(PPh)_3Cl$, 100 mg), and the reaction mixture was refluxed for 4 h. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (hexane/EtOAc, 1:1) to give **32** as a colorless oil (1.9 g, 70%). $[\alpha]_D$: −0.34 (*c* 0.6, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ: 7.24−6.84 (m, 12H, Ar), 4.46 (m, 2H, CH_2Ph), 4.48 and 4.45 (two d, 2H, $J_{AB} = 11.5$, CH_2Ph), 4.44 and 4.40 (two d, 2H, $J_{AB} = 11.5$, CH_2Ph), 3.98 (m, 1H, H-2), 3.84 (dd, 1H, $J_{2,3} = 4.6$, $J_{3,4} = 1.6$, H-3), 3.82, 3.81, 3.80 (three s, 3 OCH$_3$), 3.58 (dd, 1H, $J_{4,5b} = 5.1$, $J_{5a,5b} = 10.2$, H-5b), 3.52 (dd, 1H, $J_{4,5a} = 5.7$, H-5a), 3.20 (ddd, 1H, H-4), 3.06 (dd, 1H, $J_{1b,2} = 4.6$, $J_{1a,1b} = 12.3$, H-1b), 3.05 (dd, 1H, $J_{1a,2} = 3.0$, H-1a). ^{13}C NMR (CD_2Cl_2) δ: 159.5, 159.4, 159.3, 130.6, 130.5, 130.4, 129.6, 129.5, 129.4, 114.1, 114.0, and 113.9 (12C, Ar), 85.5 (C-3), 84.4 (C-2), 73.1, 71.7, 70.9 (3 *C*H$_2$Ph), 70.2 (C-5), 64.3 (C-4), 55.5, 55.4, and 55.3 (3 O*C*H$_3$), 51.2 (C-1). Anal. Calcd for $C_{29}H_{35}NO_6$: C, 70.57; H, 7.15; N, 2.84. Found: C, 70.70; H, 6.95; N, 3.02.

General Procedure for the Preparation of Selenium and Sulfonium Sulfates 19, 23, 20, and 24. A mixture of the selenoarabinitol **17** or **21** or the thioarabinitol **18** or **22** and the cyclic sulfate **13** in HFIP (1,1,1,3,3,3-hexafluoro-2-propanol) was placed in a reaction vessel, and K_2CO_3 (20 mg) was added. The stirred reaction mixture was heated in a sealed tube at the indicated temperature for the indicated time, as given below. The progress of the reaction was followed by TLC analysis of aliquots (developing solvent EtOAc/MeOH, 10:1). When the limiting reagent had been essentially consumed, the mixture was cooled, diluted with CH_2Cl_2, and evaporated to give a syrupy residue. Purification by column chromatography (EtOAc to EtOAc/MeOH, 10:1) gave the purified selenonium salts **19**, **23** and sulfonium salts **20**, **24**.

2,3,5-Tri-*O*-*p*-methoxybenzyl-1,4-dideoxy-1,4-[[(2*R*,3*S*,4*R*,5*R*)-2,4-benzylidenedioxy-5,6-isopropylidenedioxy-3-(sulfooxy)hexyl]-episelenoniumylidene]-D-arabinitol Inner Salt (19). Reaction of the selenoarabinitol **17** (500 mg, 0.89 mmol) with the cyclic sulfate **13** (430 mg, 1.1 mmol) in HFIP (2 mL) for 12 h at 65 °C gave compound **19** as a colorless, amorphous solid (790 mg, 95% based on **17**). $[\alpha]_D$: −39 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (CD_2Cl_2) δ: 7.50−6.80 (m, 17H, Ar), 5.70 (s, 1H, C*H*Ph), 4.60 (m, 1H, H-4′), 4.55-(dd, 1H, $J_{2',3'} = 8.2$, H-2′), 4.53−4.48 (m, 5H, H-3′, 2CH_2Ph), 4.44 (m, 1H, H-2), 4.43 and 4.38 (two d, 2H, $J_{AB} = 11.4$, CH_2Ph), 4.28 (m, 2H, H-3, H-6′a), 4.25 (dd, 1H, $J_{1'a,1'b} = 11.8$, $J_{1'b,2'} = 1.9$, H-1′b), 4.23−4.17 (m, 3H, H-5′, H-4, H-6′b), 4.00 (dd, 1H, $J_{4,5a} = 5.9$, $J_{5a,5b} = 9.8$, H-5a), 3.92 (dd, 1H, $J_{1'a,2'} = 5.9$, $J_{1'a,1'b} = 11.8$, H-1′a), 3.80 (m, 1H, H-5b), 3.81, 3.80, and 3.79 (three s, 9H, 3 OCH$_3$),

3.52 (dd, 1H, $J_{1b,2}$ = 1.1, $J_{1a,1b}$ = 12.3, H-1b), 3.30 (dd, $J_{1a,2}$ = 3.3, 1H, H-1a), 1.36 and 1.38 (two s, 6H, 2 CH_3). ^{13}C NMR (CD_2Cl_2) δ: 160.0, 159.9, 159.7, 137.4, 130.2, 129.8, 129.7, 129.6, 129.5, 128.6, 128.5, 128.3, 114.3, 114.2, 114.1, 114.0 (16C, Ar), 108.3 ($(CH_3)_2C$), 101.0 (*C*HPh), 84.5 (C-2), 82.2 (C-3′), 79.3 (C-5′), 75.8 (CH_2Ph), 74.0 (C-2′), 73.3 and 71.8 (2 *C*H_2Ph), 71.6 (C-3), 70.8 (C-4′), 67.0 (C-5), 65.0 (C-6′), 64.2 (C-4), 55.5, 55.4, and 55.3 (3 O*C*H_3), 48.6 (C-1′), 47.4 (C-1), 26.4, 25.5 (2 *C*H_3). HRMS: calcd for $C_{45}H_{55}O_{14}SSe$ 931.2477. found 931.2471.

2,3,5-Tri-*O*-*p*-methoxybenzyl-1,4-dideoxy-1,4-[[(2*R*,3*S*,4*R*,5*R*)-2,4-benzylidenedioxy-5,6-isopropylidenedioxy-3-(sulfooxy)hexyl]-episelenoniumylidene]-L-arabinitol Inner Salt (23). Reaction of the selenoarabinitol **21** (400 mg, 0.72 mmol) with the cyclic sulfate 13 (350 mg, 0.93 mmol) in HFIP (2 mL) for 12 h at 65 °C gave compound **23** as a colorless, amorphous solid (630 mg, 95% based on **21**). $[\alpha]_D$: −14 (*c* 2.8, CH_2Cl_2). ^1H NMR (CD_2Cl_2) δ: 7.50−6.80 (m, 17H, Ar), 5.73 (s, 1H, C*H*Ph), 4.69 (br s, 1H, H-4′), 4.64 (dd, 1H, $J_{1'a,\ 2'}$ = 6.9, $J_{1'b,2'}$ = 5.5, H-2′), 4.54 (ddd, 1H, $J_{5',6'a}$ = 9.9, $J_{5',6b'}$ = 3.5, $J_{4',5'}$ = 6.5, H-5′), 4.48 (d, 2H, CH_2Ph), 4.44 (m, 1H, H-2), 4.37 (m, 1H, H-3), 4.32−4.24 (m, 3H, H-3′, H-6′a, H-6′b), 4.32 and 4.25 (two d, 2H, J_{AB} = 11.5, CH_2Ph), 4.16 (br d, 1H, $J_{1'a,1'b}$ = 11.9, H-1′b), 4.03 (dd, 1H, $J_{1'a,2'}$ = 6.9, H-1′a), 4.00 (m, 1H, H-1b), 4.10 and 3.95 (two d, 2H, J_{AB} = 11.6, CH_2Ph), 3.88 (m, 1H, H-4), 3.81, 3.80, and 3.79 (three s, 9H, 3 OCH_3), 3.56 (dd, 1H, $J_{1a,2}$ = 2.7, $J_{1a,1b}$ = 12.2, H-1a), 3.44 (dd, 1H, $J_{4,5b}$ = 9.6, $J_{5a,5b}$ = 9.7, H-5b), 3.24 (dd, 1H, $J_{4,5a}$ = 6.7, H-5a), 1.38 and 1.42 (two s, 6H, 2 CH_3). ^{13}C NMR (CD_2Cl_2) δ: 160.0, 159.9, 159.7, 137.6, 130.1, 130.0, 129.8, 129.7, 129.6, 129.5, 128.8, 128.7, 128.5, 114.2, 114.1, 113.9 (16C, Ar), 108.5 ($(CH_3)_2C$), 101.2 (*C*HPh), 83.1 (C-3′), 82.9 (C-2), 79.1 (C-5′), 75.8 (C-2′), 73.9 72.8, and 71.9 (3 *C*H2Ph), 71.4 (C-3), 71.3 (C-4′), 66.7 (C-5), 65.3 (C-4), 65.0 (C-6′), 55.5, 55.4, and 55.3 (3 O*C*H_3), 47.4 (C-1′), 45.2 (C-1), 26.5, 25.6 (2 *C*H_3). HRMS: calcd for $C_{45}H_{55}O_{14}SSe$ 931.2477, found 931.2479.

2,3,5-Tri-*O*-*p*-methoxybenzyl-1,4-dideoxy-1,4-[[(2*R*,3*S*,4*R*,5*R*)-2,4-benzylidenedioxy-5,6-isopropylidenedioxy-3-(sulfooxy)hexyl]-episulfoniumylidene]-D-arabinitol Inner Salt (20). Reaction of the thioarabinitol **18** (500 mg, 0.98 mmol) with the cyclic sulfate **13** (470 mg, 1.27 mmol) in HFIP (1.5 mL) for 12 h at 75 °C gave compound **20** as a colorless, amorphous solid (731 mg, 85% based on **18**). $[\alpha]_D$: −26 (*c* 1.0, CH_2Cl_2). ^1H NMR (CD_2Cl_2) δ: 7.50−6.82 (m, 17H, Ar), 5.56 (s, 1H, C*H*Ph), 4.53−4.50 (m, 2H, H-4′, H-5′), 4.49 and 4.41 (two d, 2H, J_{AB} = 11.7, CH_2Ph), 4.42 (m, 1H, H-2′), 4.42 and 4.32 (two d, 2H, J_{AB} = 11.2, CH_2Ph), 4.36 and 4.32 (two d, 2H, J_{AB} = 11.5, CH_2Ph), 4.34−4.28 (m, 2H, H-2, H-3), 4.26 (dd, 1H, $J_{5',6'b}$ = 6.4, $J_{6'a,6'b}$ = 8.6, H-6′b), 4.20 (dd, 1H, $J_{5',6'a}$ = 6.6, H-6′a), 4.09 (dd, 1H, $J_{1'b,2'}$ = 7.1, $J_{1'a,1'b}$ = 13.3, H-1′b), 4.08−4.04 (m, 2H, H-3′, H-4), 4.04 (dd, 1H, $J_{1'a,2'}$ = 4.0, H-1′a), 3.86−3.81 (m, 2H, H-1b, H-5b), 3.81, 3.80, 3.79 (3s, 9H, 3 OCH_3), 3.76 (dd, 1H, $J_{5a,5b}$ = 9.4, $J_{4,5a}$ = 8.8, H-5a), 3.58(dd, 1H, $J_{1a,2}$ = 3.5, $J_{1a,1b}$ = 13.2, H-1a), 1.37 (s, 6H, two CH_3). ^{13}C NMR (CD_2Cl_2) δ: 160.1, 160.0, 159.8, 137.5, 133.4, 133.2, 133.1, 130.2, 129.9, 129.8, 129.5, 128.5, 126.3, 114.3, 114.2, and 114.1 (16C, Ar), 108.3 (*C*HPh), 101.3 ($(CH_3)_2C$), 82.7 (C-2), 82.1 (C-3), 79.3 (C-3′), 75.9 (C-5′), 74.6 (C-2′), 73.5, 72.0, 71.8 (3 *C*H_2Ph), 69.5 (C-4′), 67.0 (C-5), 66.0 (C-4), 64.8 (C-6′), 55.4, 55.3, and 55.2 (3 O*C*H_3), 49.2 (C-1′), 48.9 (C-1), 26.4, and 25.6 (2 *C*H_3). HRMS: calcd for $C_{45}H_{55}O_{14}S_2$ 883.3033, found 883.3031.

2,3,5-Tri-*O*-*p*-methoxybenzyl-1,4-dideoxy-1,4-[[(2*R*,3*S*,4*R*,5*R*)-2,4-benzylidenedioxy-5,6-isopropylidenedioxy-3-(sulfooxy)hexyl]-episulfoniumylidene]-L-arabinitol Inner Salt (24). Reaction of the thioarabinitol **22** (400 mg, 0.78 mmol) with the cyclic sulfate **13** (372 mg, 1.0 mmol) in HFIP (1.5 mL) for 12 h at 75 °C gave compound **24** as a colorless, amorphous solid (570 mg, 83% based on **22**). $[\alpha]_D$: +21 (*c* 4.4, CH_2Cl_2). ^1H NMR (CD_2Cl_2) δ: 7.50−6.70 (m, 17H, Ar), 5.58 (s, 1H, C*H*Ph), 4.50−4.46 (m, 2H, H-4′, H-5′), 4.42 (ddd, 1H, $J_{1'a,2'}$ = 5.7, $J_{1'b,2'}$ = 3.2, $J_{2',3'}$ = 9.8, H-2′), 4.37 (s, 2H, CH_2Ph), 4.22−4.10 (m, 8H, H-6′b, H-1′b, H-2, H-3, H-3′, CH_2Ph), 3.87 (dd, 1H, $J_{1b,2}$ = 1, H-1b), 3.85 (dd, 1H, $J_{1'a,2'}$ = 5.7, $J_{1'a,1'b}$ = 12.5, H-1′a), 3.96 and 3.83 (two d, 2H, J_{AB} = 11.3, CH_2Ph), 3.74 (dd, 1H, $J_{3,4}$ = 7.9, H-4), 3.72, 3.70, 3.68 (three s, 9H, three OCH_3), 3.49 (dd, 1H, $J_{1a,1b}$ = 13.1, $J_{1a,2}$ = 3.2, H-1a), 3.40 (dd, 1H, $J_{4,\ 5b}$ = 9.4, H-5b), 3.20 (dd, 1H, $J_{4,5a}$ = 6.7, $J_{5a,5b}$ = 9.5, H-5a), 1.27 and 1.29 (two s, 6H, two CH_3). ^{13}C NMR (CD_2Cl_2) δ: 160.1, 160.0, 159.7, 137.5, 130.2, 129.8, 129.7, 129.6, 129.5, 128.6, 128.5, 128.2, 126.5, 114.2, 114.1, and 113.9 (16C, Ar), 108.3 (*C*HPh), 101.1 ($(CH_3)_2C$), 82.5 (C-2), 82.1 (C-3′), 79.2 (C-3), 75.9 (C-5′), 73.8 (C-2′), 72.9, 72.0, 71.6 (3 *C*H_2Ph), 70.6 (C-4′), 66.6 (C-5), 66.4 (C-4), 64.9 (C-6′), 55.5, 55.4, and 55.3 (3 O*C*H_3), 49.7 (C-1′), 48.2 (C-1), 26.4 and 25.6 (2 *C*H_3). Anal. Calcd for $C_{45}H_{54}O_{14}S_2$: C, 61.21; H, 6.16. Found: C, 61.25; H, 6.13.

2,3,5-Tri-*O*-*p*-methoxybenzyl-1,4-dideoxy-1,4-[[(2*R*,3*S*,4*R*,5*R*)-2,4-benzylidenedioxy-5,6-isopropylidenedioxy-3-(sulfooxy)hexyl]-iminoniumlidene]-D-arabinitol Inner Salt (33). A mixture of the iminoarabinitol **28** (450 mg, 0.9 mmol) and the cyclic sulfate **13** (470 mg, 1.2 mmol) in acetone (2 mL) containing K_2CO_3 (20 mg) was warmed at 55 °C in a sealed reaction vessel with stirring for 12 h. The progress of the reaction was followed by TLC analysis of the aliquots (developing solvent EtOAc/MeOH, 10:1). When the iminoarabinitol **28** had been completely consumed, the mixture was cooled, diluted with CH_2Cl_2, and evaporated to give a syrupy residue. Purification by column chromatography (EtOAc to EtOAc/MeOH, 10:1) gave the iminium salt **33** as an amorphous solid (600 mg, 77% based on **28**). $[\alpha]_D$: +10 (*c* 0.5, CH_2Cl_2). ^1H NMR (CD_2Cl_2) δ: 7.50−6.73 (m, 17H, Ar), 5.54 (s, 1H, C*H*Ph), 4.56−4.53 (m, 2H, H-3′, H-5′), 4.52 and 4.38 (two d, 2H, J_{AB} = 12.4, CH_2Ph), 4.46 and 4.36 (two d, 2H, J_{AB} = 12.0, CH_2Ph), 4.20 and 4.14 (two d, 2H, J_{AB} = 11.5, CH_2Ph), 4.15 (m, 1H, H-2′), 4.11 (dd, 1H, $J_{5',6'b}$ = 4.2, $J_{6'a,6'b}$ = 8.6, H-6′b), 4.09 (dd, 1H, $J_{5',6'a}$ = 6.1, H-6′a), 3.89 (br d, 1H, $J_{3',4'}$ = 6.7, H-4′), 3.74 (m, 1H, H-3), 3.77, 3.75, 3.73 (three s, 9H, 3 OCH_3), 3.65 (d, 1H, $J_{1b,2}$ = 3.5, H-2), 3.58 (dd, 1H, $J_{4,5b}$ = 4.1, $J_{5a,5b}$ = 10.0, H-5b), 3.43 (dd, 1H, $J_{4,5a}$ <1, H-5a), 3.30 (m, 2H, H-1′b, H-1b), 3.14 (dd, 1H, $J_{1'a,1'b}$ = 12.1, $J_{1'a,2'}$ = 6.1, H-1′a), 2.96 (dd, 1H, $J_{1a,2}$ <1, $J_{1a,1b}$ = 10.1, H-1a), 2.80 (m, 1H, H-4), 1.18 and 1.21 (two s, 6H, 2 CH_3). ^{13}C NMR (CD_2Cl_2) δ: 159.6, 159.5, 159.4, 138.1, 130.3, 130.2, 130.1, 129.9, 129.8, 129.4, 128.9, 128.3, 126.3, 113.9, 113.8, 113.7 (16C, Ar), 109.2 (*C*HPh), 100.8 ($(CH_3)_2C$), 79.8 (C-2), 79.7 (C-3), 77.1 (C-4′), 74.6 (C-3′), 73.0 (C-2′), 71.6, 71.1, 71.0 (3 *C*H_2Ph, C-5′), 68.4 (C-4), 65.6 (C-5), 59.2 (C-6′), 56.4 (C-1), 55.4, 55.3, 55.2 (3 O*C*H_3), 55.2 (C-1′), 27.0 and 25.6 (2 *C*H_3). Anal. Calcd for $C_{45}H_{54}KNO_{14}S$: C, 59.78; H, 6.02; N, 1.55. Found: C, 60.01; H, 6.07; N, 1.55.

2,3,5-Tri-*O*-*p*-methoxybenzyl-1,4-dideoxy-1,4-[[(2*R*,3*S*,4*R*,5*R*)-2,4-benzylidenedioxy-5,6-isopropylidenedioxy-3-(sulfooxy)hexyl]-iminoniumlidene]-L-arabinitol Inner Salt (34). A mixture of the iminoarabinitol **32** (450 mg, 0.9 mmol) and the cyclic sulfate **13** (470 mg, 1.2 mmol) in acetone (2 mL) containing K_2CO_3 (20 mg) was warmed at 55 °C in a sealed reaction vessel with stirring for 12 h. The progress of the reaction was followed by TLC analysis of the aliquots (developing solvent EtOAc/MeOH, 10:1). When the iminoarabinitol **32** had been completely consumed, the mixture was cooled, diluted with CH_2Cl_2, and evaporated to give a syrupy residue. Purification by column chromatography (EtOAc to EtOAc/MeOH, 10:1) gave the iminium salt **34** as an amorphous solid (620 mg, 81% based on **32**). $[\alpha]_D$: +15 (*c* 1.0, CH_2Cl_2); ^1H NMR (CD_2Cl_2) δ: 7.38−6.68 (m, 17H, Ar), 5.57 (s, 1H, C*H*Ph), 4.51−4.47 (m, 2H, H-3′, H-5′), 4.36 and 4.31 (two d, 2H, J_{AB} = 11.8, CH_2Ph), 4.54 and 4.17 (two d, 2H, J_{AB} = 11.8, CH_2Ph), 4.15 and 4.06 (two d, 2H, J_{AB} = 11.6, CH_2Ph), 4.04−4.01 (m, 3H, H-6′a, H-6′b, H-2′), 3.86 (dd, 1H, $J_{3',4'}$ = 6.3, H-4′), 3.69 (m, 2H, H-2, H-3), 3.68, 3.66, and 3.65 (three s, 9H, 3 OCH_3), 3.57 (dd, 1H, $J_{4,5b}$ = 3.3, $J_{5a,5b}$ = 10.0, H-5b), 3.38 (dd, 1H, $J_{1'a,1'b}$ = 13.3, $J_{1'b,2'}$ = 5.6, H-1′b), 3.28 (dd, 1H, $J_{4,5a}$ = 2.9, H-5a), 3.16 (dd, 1H, $J_{1a,1b}$ = 10.3, H-1b), 2.58 (m, 2H, H-4, H-1′a), 2.53 (dd, 1H, $J_{1a,2}$ = 3.9, H-1a), 1.27 and 1.34 (two s, 6H, 2 CH_3). ^{13}C NMR (CD_2Cl_2) δ: 159.7, 159.5, 159.4, 138.1, 130.2, 130.1, 130.0, 129.9, 129.7, 129.4, 128.9, 128.3, 126.2, 114.0, 113.9, and 113.8 (16C, Ar), 109.3 (*C*HPh),

100.9 ($(CH_3)_2C$), 83.5 (C-2), 80.4 (C-3), 79.6 (C-4′), 77.6 (C-2′), 74.7 (C-3′), 72.7 (CH_2Ph), 71.2 (two CH_2Ph, C-5′, C-4), 66.9 (C-5), 65.6 (C-6′), 58.1 (C-1), 55.4 (3 OCH_3, C-1′), 26.9, and 25.7 (two CH_3). Anal. Calcd for $C_{45}H_{54}KNO_{14}S$: C, 59.78; H, 6.02; N, 1.55. Found: C, 60.12; H, 6.17; N, 1.60.

General Procedure for the Deprotection of the Coupling Products To Yield the Final Compounds 7−12. The protected coupling products **19**, **20**, **23**, **24**, **33**, or **34** were dissolved in CH_2Cl_2 (2 mL), TFA (10 mL) was then added, and the mixture was stirred for 6−8 h at room temperature. The progress of the reaction was followed by TLC analysis of aliquots (developing solvent EtOAc/MeOH/H_2O, 7:3:1). When the starting material had been consumed, the TFA and CH_2Cl_2 were removed under reduced pressure. The residue was rinsed with CH_2Cl_2 (4 × 2 mL), and the CH_2Cl_2 was decanted to remove the cleaved protecting groups. The remaining gum was dissolved in MeOH and purified by column chromatography (EtOAc and EtOAc/MeOH, 2:1) to give the purified compounds **7**−**12** as colorless, amorphous, and hygroscopic solids.

1,4-Dideoxy-1,4-[[(2*R*,3*S*,4*R*,5*R*)-2,4,5,6-tetrahydroxy-3-(sulfooxy)hexyl]episelenoniumylidene]-D-arabinitol Inner Salt (7). To a solution of **19** (500 mg) in CH_2Cl_2 (2 mL) was added TFA (10 mL) to yield the compound **7** as a colorless, amorphous, and hygroscopic solid (160 mg, 67%). $[\alpha]_D$: −21 (*c* 0.1, H_2O). ^1H NMR (D_2O) δ: 4.70 (m, 1H, H-2), 4.55 (dd, 1H, $J_{2',3'} = 4.9$, $J_{3',4'} = 1.3$, H-3′), 4.49 (ddd, 1H, $J_{1'b,2'} = 9.7$, $J_{1'a,2'} = 3.9$, H-2′), 4.39 (dd, 1H, $J_{3,4} = 3.1$, $J_{2,3} = 3.7$, H-3), 4.14 (ddd, 1H, $J_{4,5a} = 8.3$, $J_{4,5b} = 5.2$, $J_{3,4} = 3.1$, H-4), 3.96 (dd, 1H, $J_{5a,5b} = 12.6$, H-5b), 3.91 (dd, 1H, $J_{1'a,1'b} = 12.1$, H-1′b), 3.87 (dd, 1H, H-5a), 3.81 (dd, 1H, H-1′a), 3.78 (dd, 1H, $J_{4',5'} = 9.2$, H-4′), 3.71 (dd, 1H, $J_{5',6'b} = 2.8$, $J_{6'a,6'b} = 11.6$, H-6′b), 3.69 (m, 1H, H-5′), 3.67 (br d, 2H, H-1a, H-1b), 3.54 (dd, 1H, $J_{5',6'a} = 5.6$, H-6′a). ^{13}C NMR (D_2O) δ: 78.6 (C-3), 78.2 (C-3′), 77.8 (C-2), 70.5 (C-5′), 70.1 (C-4), 69.2 (C-4′), 67.7 (C-2′), 62.7 (C-6′), 59.4 (C-5), 46.5 (C-1′), 44.4 (C-1). HRMS: calcd for $C_{11}H_{22}O_{11}SSeNa$ (M + Na) 464.9946, found 464.9945.

1,4-Dideoxy-1,4-[[(2*R*,3*S*,4*R*,5*R*)-2,4,5,6-tetrahydroxy-3-(sulfooxy)hexyl]episelenoniumylidene]-L-arabinitol Inner Salt (10). To a solution of **23** (500 mg) in CH_2Cl_2 (2 mL) was added TFA (10 mL) to yield the compound **10** as a colorless, amorphous, and hygroscopic solid (210 mg, 71%). $[\alpha]_D$: −45 (*c* 0.1, H_2O). ^1H NMR (D_2O) δ: 4.69 (m, 1H, H-2), 4.57 (dd, $J_{3',4'} = 1.3$, $J_{2',3'} = 4.9$, 1H, H-3′), 4.48 (ddd, 1H, $J_{1'a,2'} = 9.2$, $J_{1'b,2'} = 4.6$, H-2′), 4.37 (t, $J_{2,3} = J_{3,4} = 3.2$, 1H, H-3), 4.05 (ddd, 1H, $J_{4,5a} = 8.6$, $J_{3,4} = 3.2$, $J_{4,5b} = 5.1$, H-4), 3.98 (dd, 1H, $J_{5a,5b} = 12.5$, $J_{4,5b} = 5.1$, H-5b), 3.86 (dd, 1H, H-5a), 3.85 (dd, 1H, H-1′b), 3.82 (dd, 1H, $J_{1'a,1'b} = 12.3$, H-1′a), 3.77 (dd, 1H, $J_{4',5'} = 4.9$, H-4′), 3.72 (dd, 1H, $J_{5',6'a} = 5.3$, $J_{5',6'b} = 1.8$, H-5′), 3.68 (br d, 2H, H-1a, H-1b), 3.67 (dd, 1H, $J_{6'a,6'b} = 11.2$, H-6′b), 3.53 (dd, 1H, H-6′a). ^{13}C NMR (D_2O) δ: 78.4 (C-3), 78.1 (C-3′), 77.8 (C-2), 70.5 (C-5′), 69.7 (C-4), 69.2 (C-4′), 67.2 (C-2′), 62.7 (C-6′), 59.4 (C-5), 46.4 (C-1′), 44.9 (C-1). HRMS: calcd for $C_{11}H_{22}O_{11}SSeNa$ (M + Na) 464.9946, found 464.9944.

1,4-Dideoxy-1,4-[[(2*R*,3*S*,4*R*,5*R*)-2,4,5,6-tetrahydroxy-3-(sulfooxy)hexyl]episulfoniumylidene]-D-arabinitol Inner Salt (8). To a solution of **20** (500 mg) in CH_2Cl_2 (2 mL) was added TFA (10 mL) to yield the compound **8** as a colorless, amorphous, and hygroscopic solid (136 mg, 61%). $[\alpha]_D$: −19 (*c* 0.2, MeOH). ^1H NMR (D_2O) δ: 4.62 (ddd, 1H, $J_{2,3} = 3.4$, $J_{1a,2} = 3.4$, $J_{1b,2} = 6.7$, H-2), 4.57 (dd, 1H, $J_{3',4'} = 1.4$, $J_{2',3'} = 5.0$, H-3′), 4.49 (ddd, 1H, $J_{1'a,2'} = 3.9$, $J_{1'b,2'} = 8.9$, $J_{2',3'} = 5.0$, H-2′), 4.35 (dd, 1H, $J_{3,4} = 2.7$, H-3), 4.06 (ddd, 1H, $J_{4,5a} = 8.4$, $J_{4,5b} = 4.8$, H-4), 3.99 (dd, 1H, $J_{5a,5b} = 12.4$, H-5b), 3.87 (dd, 1H, H-5a), 3.85 (dd, 1H, $J_{1'b,2'} = 8.9$, $J_{1'a,1'b} = 13.5$, H-1′b), 3.83 (dd, 1H, H-1′a), 3.80 (dd, 1H, $J_{4',5'} = 8.8$, H-4′), 3.75 (m, 2H, H-1a, H-1b), 3.71 (dd, 1H, $J_{5',6'b} = 2.6$, $J_{6'a,6'b} = 11.6$, H-6′b), 3.68 (ddd, 1H, $J_{5',6'a} = 5.7$, H-5′), 3.54 (dd, 1H, H-6′a). ^{13}C NMR (D_2O) δ: 78.0 (C-3), 77.6 (C-3′), 76.9 (C-2), 70.4 (C-5′), 69.9 (C-4), 68.9 (C-4′), 67.6 (C-2′), 62.7 (C-6′), 59.3 (C-5), 48.6 (C-1′), 46.9 (C-1). HRMS: calcd for $C_{11}H_{22}O_{11}S_2Na$ (M + Na) 417.0501, found 417.0500.

1,4-Dideoxy-1,4-[[(2*R*,3*S*,4*R*,5*R*)-2,4,5,6-tetrahydroxy-3-(sulfooxy)hexyl]episulfoniumylidene]-L-arabinitol Inner Salt (11). To a solution of **24** (400 mg) in CH_2Cl_2 (2 mL) was added TFA (10 mL) to yield the compound **11** as a colorless, amorphous, and hygroscopic solid (165 mg, 75%). $[\alpha]_D$: −9.6 (*c* 0.5, MeOH). ^1H NMR (D_2O) δ: 4.63 (ddd, 1H, $J_{1a,2} = 4.0$, $J_{1b,2} = 4.0$, $J_{2,3} = 3.3$, H-2), 4.57 (dd, 1H, $J_{2',3'} = 5.0$, $J_{3',4'} = 1.2$, H-3′), 4.50 (ddd, $J_{2',3'} = 5.0$, H-2′), 4.35 (br t, 1H, $J_{2,3} = 3.3$, H-3), 4.07 (ddd, 1H, $J_{3,4} = 2.7$, $J_{4,5a} = 1.9$, $J_{4,5b} = 5.1$, H-4), 3.99 (dd, 1H, $J_{5a,5b} = 12.4$, H-5b), 3.87 (dd, 1H, H-5a), 3.85 (dd, 1H, $J_{1'b,2'} = 4.0$, $J_{1'a,1'b} = 9.6$, H-1′b), 3.83 (dd, 1H, $J_{1'a,2'} = 3.9$, H-1′a), 3.80 (dd, 1H, $J_{4',5'} = 8.8$, H-4′), 3.75 (m, 2H, H-1a, H-1b), 3.71 (dd, 1H, $J_{5',6'b} = 2.7$, $J_{6'a,6'b} = 11.6$, H-6′b), 3.68 (ddd, 1H, $J_{5',6'a} = 5.6$, H-5′), 3.54 (1H, dd, H-6′a). ^{13}C NMR (D_2O) δ: 77.9 (C-3), 77.6 (C-3′), 76.9 (C-2), 70.4 (C-5′), 69.9 (C-4), 68.9 (C-4′), 67.5 (C-2′), 62.7 (C-6′), 59.3 (C-5), 48.6 (C-1′), 46.9 (C-1). HRMS: calcd for $C_{11}H_{22}O_{11}S_2Na$ (M + Na) 417.0501, found 417.0501.

1,4-Dideoxy-1,4-[[(2*R*,3*S*,4*R*,5*R*)-2,4,5,6-tetrahydroxy-3-(sulfooxy)hexyl]iminoniumylidene]-D-arabinitol Inner Salt (9). To a solution of **33** (800 mg) in CH_2Cl_2 (2 mL) was added TFA (10 mL) to yield the compound **9** as a colorless, amorphous, and hygroscopic solid (236 mg, 68%). $[\alpha]_D$: −11 (*c* 0.5, MeOH). ^1H NMR (D_2O) δ: 4.56 (dd, 1H, $J_{2',3'} = 5.3$, $J_{3',4'} = 1.2$, H-3′), 4.40 (ddd, 1H, $J_{1'a,2'}$, = 7.0, $J_{1'b,2'} = 1.8$, $J_{2',3'} = 5.3$, H-2′), 4.27 (ddd, 1H, $J_{1a,2} = 5.1$, $J_{1b,2} = 2.5$, $J_{2,3} = 2.9$, H-2), 4.01 (dd, 1H, $J_{3,4} = 3.6$, H-3), 3.90 (dd, 1H, $J_{5a,5b} = 12.7$, $J_{4,5b} = 4.6$, H-5b), 3.87 (dd, 1H, $J_{4,5a} = 6.7$, H-5a), 3.77 (dd, 1H, $J_{4',5'}$ =9.1, $J_{3',4'} = 1.2$, H-4′), 3.71 (dd, 1H, $J_{1'a,1'b} = 11.8$, H-1′b), 3.68 (dd, 1H, $J_{1a,1b} = 12.8$, H-1b), 3.67 (m, 1H, H-5′), 3.64 (d, $J_{6'a,6'b} = 13.2$, H-6′b), 3.53 (dd, 1H, H-1′a), 3.52 (m, 2H, H-1a, H-4), 3.45 (d, 1H, H-6′a). ^{13}C NMR (D_2O) δ: 77.1 (C-3′), 75.8 (C-3), 75.1 (C-4), 73.6 (C-2), 70.4 (C-5′), 68.5 (C-4′), 66.2 (C-2′), 62.7(C-1), 58.6 (C-1′), 58.1 (C-6′), 57.9 (C-5). HRMS: calcd for $C_{11}H_{23}NO_{11}SNa$ (M + Na) 400.0889, found 400.0887.

1,4-Dideoxy-1,4-[[(2*R*,3*S*,4*R*,5*R*)-2,4,5,6-tetrahydroxy-3-(sulfooxy)hexyl]iminoniumylidene]-L-arabinitol Inner Salt (12). To a solution of **34** (600 mg) in CH_2Cl_2 (2 mL) was added TFA (10 mL) to yield the compound **12** as a colorless, amorphous, and hygroscopic solid (265 mg, 80%). $[\alpha]_D$: −35 (c 0.1, MeOH). ^1H NMR (D_2O) δ: 4.53 (dd, $J_{3',4'} = 1.2$, $J_{2',3'} = 5.2$, 1H, H-3′), 4.49 (m, 1H, H-2′), 4.24 (m, 1H, H-2), 4.00 (m, 1H, H-3), 3.88 (dd, 1H, $J_{5a,5b} = 12.5$, $J_{4,5b} = 4.9$, H-5b), 3.85 (dd, 1H, $J_{4,5a} = 7.3$, H-5a), 3.77 (dd, 1H, $J_{4',5'} = 9.0$, $J_{3',4'} = 1.2$, H-4′), 3.73 (dd, 1H, $J_{1'a,1'b} = 11.8$, H-1′b), 3.71 (dd, 1H, H-1′a), 3.66 (dd, 1H, $J_{1a,1b} = 12.8$, H-1b), 3.65 (m, 1H, H-5′), 3.54−3.49 (m, 4H, H-1a, H-4, H-6′a, H-6′b). ^{13}C NMR (D_2O) δ: 77.2 (C-3′), 75.9 (C-3), 75.8 (C-4), 74.1 (C-2), 70.4 (C-5′), 68.5 (C-4′), 66.9 (C-2′), 62.8(C-1), 60.9 (C-1′), 58.8 (C-6′), 58.6 (C-5). HRMS: calcd for $C_{11}H_{23}NO_{11}SNa$ (M + Na) 400.0889, found 400.0887.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada for financial support and to B. D. Johnston for helpful discussions.

Supporting Information Available: General experimental procedures and copies of ^1H and ^{13}C NMR spectra for compounds **19**, **23**, **20**, and **7**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO052539R