Use of Acyclic Glycosyl Donors for Furanoside Synthesis

Joseph C. McAuliffe and Ole Hindsgaul*

Department of Chemistry, University of Alberta, Edmonton, Alberta T6G 2G2, Canada

Received October 1, 1996[⊗]

Treatment of the peracetylated ethyl dithioacetals of D-glucose, D-galactose, and D-mannose with acetyl chloride and boron trifluoride diethyl etherate at reflux yields the known acyclic 1-chloro-1-(ethylthio) derivatives. These compounds are shown to effectively glycosylate a variety of carbohydrate acceptors using silver trifluoromethanesulfonate as the promotor, affording stereospecifically the corresponding acyclic *O,S*-acetals in good to excellent yield. Furthermore, following deacetylation, treatment of these *O,S*-acetals with a mixture of mercuric salts in either methanol or dimethylformamide gives rise to disaccharides terminating in D-furanosyl residues.

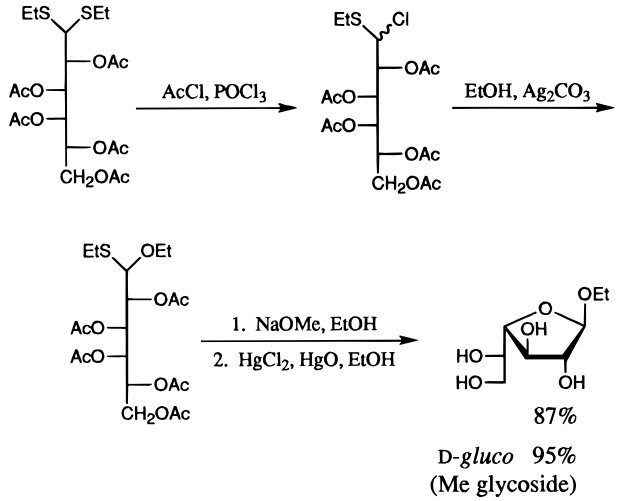
Introduction

Complex carbohydrates play a crucial role in many biochemical processes including the modulation of enzyme and hormone activity, adhesion to host cells by pathogens, and the response of tissues to wounding.[1,2] The physical properties and inherent structural diversity of carbohydrates enable this class of biomolecules to store and transmit cellular information through their recognition by carbohydrate-binding proteins.[3] A better understanding of this intercellular currency may allow the development of new strategies for the effective treatment of a variety of disorders. The efficient synthesis of putative carbohydrate ligands and their analogues is a prerequisite for understanding their roles in information transfer.

Despite the significant advances made in the last few decades, the chemical synthesis of carbohydrates remains a labor-intensive process, often involving tedious manipulations of protective groups and resulting in low overall yields.[4,5] Additional complications include the low reactivity of certain carbohydrate alcohols and poor stereoselectivity encountered in glycoside bond formation. While many strategies have evolved to address these problems with regard to pyranoside synthesis, methods for the construction of the furanosidic linkage have only recently begun to attract significant attention. This is due primarily to the current interest in the chemistry[6−12] and biology[13] of β-D-galactofuranosides owing to the widespread occurrence of this moiety in lower organisms.

Simple alkyl furanosides have been prepared from sugar dithioacetals by means of a process involving transformation into an *O,S*-acetal,[14,15] followed by cyclization upon treatment with a thiophilic promoter (Scheme 1).[16,17] There is considerable scope for the further extension of this type of methodology. For example, dithioacetals and their equivalents, in effect potential acyclic glycosyl donors, have not previously been used to glycosylate sugar alcohols and may offer advantages over cyclic donors. In addition, an *O,S*-acetal (Scheme 2) has the potential to form either a five-, six-, or seven-membered ring upon cyclization. Such a divergent glycosylation strategy would clearly complement the current "parallel" approach and warrants investigation. In this paper, we demonstrate the efficient glycosylation of carbohydrate acceptors by the known 1-chloro-1-(ethylthio)-2,3,4,5,6-penta-*O*-acetyl derivatives of D-glucose, D-galactose, and D-mannose.[14,15,18] The *O,S*-acetals so obtained are readily converted into D-furanosides by means of a convenient two-pot procedure.

Scheme 1



Results and Discussion

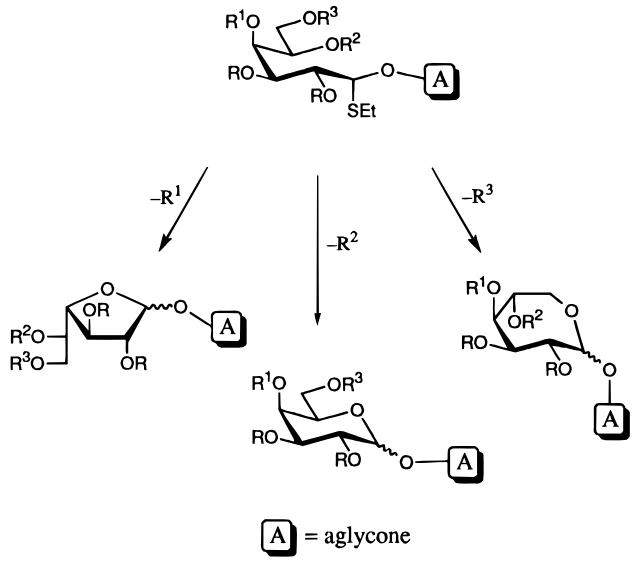
Sugar dithioacetals were first prepared by Emil Fischer last century, and as such, represent some of the oldest

[⊗] Abstract published in *Advance ACS Abstracts,* February 1, 1997.

(1) Varki, A. *Glycobiology* **1993**, *3*, 97.
(2) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683.
(3) Drickamer, K. In *Molecular Glycobiology*; Fukuda, M., Hindsgaul, O., Eds; IRL: Oxford, 1994; Chapter 2, pp 53−87.
(4) Toshima, K; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503.
(5) Boons, G.-J. *Tetrahedron* **1996**, *52*, 1095.
(6) van Heeswijk, W. A. R.; Visser, H. G. J.; Vliegenthart, J. F. G. *Carbohydr. Res.* **1977**, *59*, 81.
(7) Sugawara, F.; Nakayama, H.; Ogawa, T. *Agric. Biol. Chem.* **1986**, *50*, 1557.
(8) Veeneman, G. H.; Hoogerhout, P.; Westerduin, P.; Notermans, S.; van Boom, J. H. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 129.
(9) Zuurmond, H. M.; van der Klein, P. A. M.; Veeneman, G. H.; van Boom, J. H. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 437.
(10) Marino, C.; Varela, O.; de Lederkremer, R. M. *Carbohydr. Res.* **1989**, *190*, 65.
(11) Gallo-Rodriguez, C.; Varela, O.; de Lederkremer, R. M. *J. Org. Chem.* **1996**, *61*, 1886.
(12) Arasappan, A.; Fraser-Reid, B. *Tetrahedron Lett.* **1995**, *36*, 7967.
(13) de Lederkremer, R. M.; Colli, W. *Glycobiology* **1995**, *5*, 547.
(14) Wolfrom, M. L.; Weisblat, D. I. *J. Am. Chem. Soc.* **1940**, *62*, 878.
(15) Wolfrom, M. L.; Weisblat, D. I.; Hanze, A. R. *J. Am. Chem. Soc.* **1940**, *62*, 3246.
(16) Green, J. W. *Adv. Carbohydr. Chem. Biochem.* **1966**, *21*, 95.
(17) Wolfrom, M. L.; Weisblat, D. I.; Hanze, A. R. *J. Am. Chem. Soc.* **1944**, *66*, 2065.
(18) Farkas, I.; Menyhárt, M.; Bognár, R.; Gross, H. *Chem. Ber.* **1965**, *98*, 1419.

S0022-3263(96)01858-0 CCC: $14.00

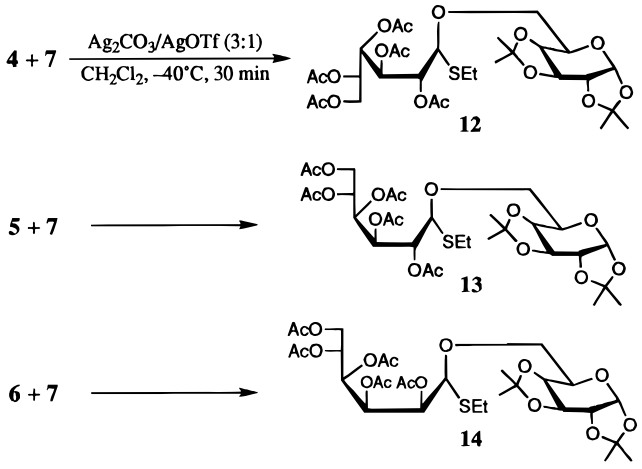
Scheme 2



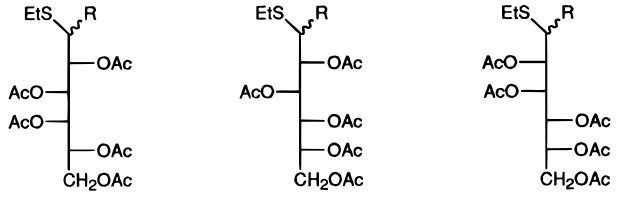
known carbohydrate derivatives.[19,20] Further studies were undertaken by Pascu and Green, who demonstrated the direct conversion of various sugar dithioacetals to furanosides upon treatment with $HgCl_2$ and HgO in various aliphatic alcohols.[16,21] These procedures were later refined by Wolfrom and co-workers, who prepared the 1-chloro-1-(ethylthio) derivatives of D-glucose and D-galactose from the corresponding dithioacetal pentaacetates and demonstrated their utility as acyclic glycosyl donors in conjunction with silver carbonate.[14,15] The *O,S*-acetals so formed were found to undergo a regio- and stereoselective cyclization following deacetylation and treatment with a mixture of HgO and $HgCl_2$ in either methanol or ethanol to give the corresponding β-D-furanosides in very high yield (Scheme 1).[17] Despite the elegance of this method no attempt has since been made to further its application.

As the first part of a program[22] designed to take advantage of the potential versatility of acyclic glycosyl donors, the suitability of the D-galactose derivative **4** for the synthesis of β-D-galactofuranose-containing disaccharides was examined. The targets chosen are representative of β-D-galactofuranosides found in various *Mycobacteria* species,[23–25] fungi including members of the genera *Aspergillus* and *Penicillium*,[26,27] and pathogenic protozoa such as *Trypanosoma cruzi* and certain *Leishmania* species.[13,28,29] The application of this methodology to D-glucose and D-mannose was also examined.

Scheme 3



Synthesis of the Glycosyl Donors. Several methods for the conversion of ethyl dithioacetal pentaacetates into the corresponding 1-chloro-1-(ethylthio) derivatives have been described, including treatment with a mixture of acetyl chloride and $POCl_3$[14,15] at reflux and dichloromethyl methyl ether at room temperature.[17] In the present study, it was found that a mixture of acetyl chloride and a catalytic amount of $BF_3 \cdot Et_2O$ at reflux resulted in a smooth conversion of the dithioacetal pentaacetates **1**–**3** into the 1-chloro derivatives **4**–**6** over several hours. Workup was effected simply by coevaporation twice with chloroform to give the essentially pure 1-chloro-1-(ethylthio) derivatives as 1:1 mixtures of diastereoisomers. The D-galactose derivative **4** was recrystallized before use, whereas compounds **5** and **6**, derived from D-glucose and D-mannose, respectively, were used as syrups.



1 R = SEt **2** R = SEt **3** R = SEt
4 R = Cl **5** R = Cl **6** R = Cl

Glycosylation of Carbohydrate Acceptors. Glycosylation of 1,2:3,4-di-*O*-isopropylidene-α-D-galactose **7** with a slight excess of the D-*galacto* donor **4** in the presence of a mixture of AgOTf and Ag_2CO_3 (1:3) in CH_2Cl_2 containing 4 Å molecular sieves at −40 °C, gave rise to the *O,S*-acetal **12** in 81% yield (Scheme 3). Workup involved the elution of the reaction mixture through a short plug of silica with EtOAc/hexanes and was followed by column chromatography. In a similar fashion, the D-*gluco* and D-*manno* derivatives, **5** and **6**, were treated with the acceptor **7** to afford compounds **13** and **14** in yields of 76% and 60%, respectively. The excellent stereoselectivity (ca. >20:1 as determined by ^1H NMR) of these glycosylations is likely the result of anchimeric assistance by the neighboring 2-*O*-acetyl group during the reaction, a process that would be expected to give rise to an absolute configuration about the anomeric carbon opposite to that at C2′ (Scheme 4).

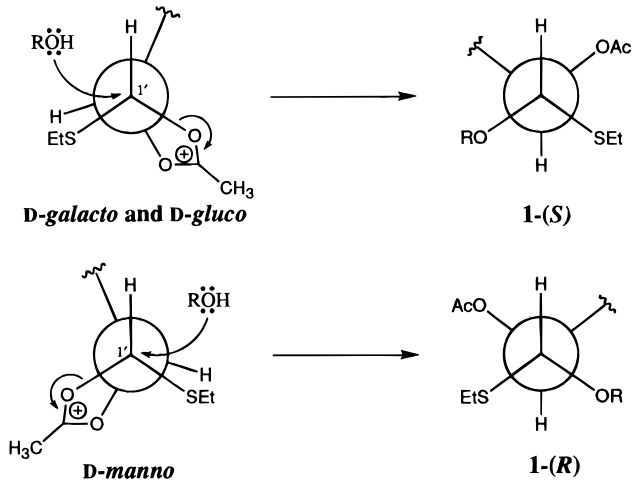
The behavior of the D-*galacto* donor **4** was examined with a variety of acceptors (**7**–**11**) (Table 1), and in all

(19) Fischer, E. *Ber.* **1894**, *27*, 673.
(20) Wander, J. D.; Horton, D. *Adv. Carbohydr. Chem. Biochem.* **1976**, *32*, 15.
(21) Pascu, E.; Green, J. W. *J. Am. Chem. Soc.* **1936**, *58*, 1823.
(22) McAuliffe, J. C.; Hindsgaul, O. *XVIIIth International Carbohydrate Symposium*, Milano, 1996; Abstracts of Papers, BP 169.
(23) Vilkas, E.; Amar, C.; Markovits, J.; Vliegenthart, J. F. G.; Kamerling, J. P. *Biochim. Biophys. Acta* **1973**, *297*, 423.
(24) McNeil, M.; Wallner, S. J.; Hunter, S. W.; Brennan, P. J. *Carbohydr. Res.* **1987**, *166*, 299.
(25) McNeil, M.; Daffe, M.; Brennan, P. J. *J. Biol. Chem.* **1990**, *265*, 18200.
(26) Gander, J. E.; Jentoft, N. H.; Drewes, L. R.; Rick, P. D. *J. Biol. Chem.* **1974**, *249*, 2063.
(27) Barreto-Bergter, E.; Gorin, P. A. J.; Travassos, L. R. *Carbohydr. Res.* **1981**, *95*, 205.
(28) de Lederkremer, R. M.; Lima, C.; Ramirez, M. I.; Ferguson, M. A. J.; Homans, S. W.; Thomas-Oates, J. *J. Biol. Chem.* **1991**, *266*, 23670.
(29) McConville, M. J.; Collidge, T. A. C.; Ferguson, M. A. J.; Schneider, P. *J. Biol. Chem.* **1993**, *268*, 15595.

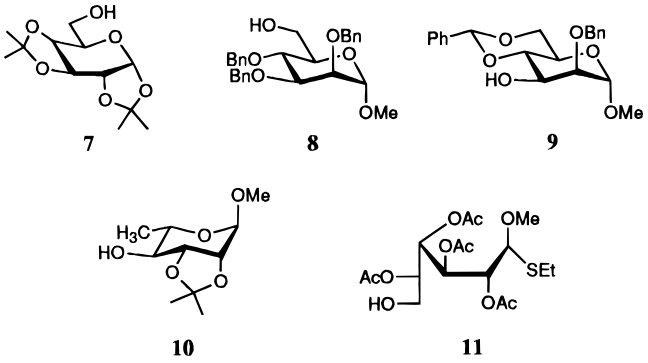
Table 1. Glycosylation with Acyclic Donors

entry	donor	acceptor	product	yield (%)
1	**4**	**7**	**12**	81
2	**5**	**7**	**13**	76
3	**6**	**7**	**14**	60
4	**4**	**8**	**15**	68
5	**4**	**9**	**16**	82
6	**4**	**10**	**17**	84
7	**4**	**11**	**18**	71

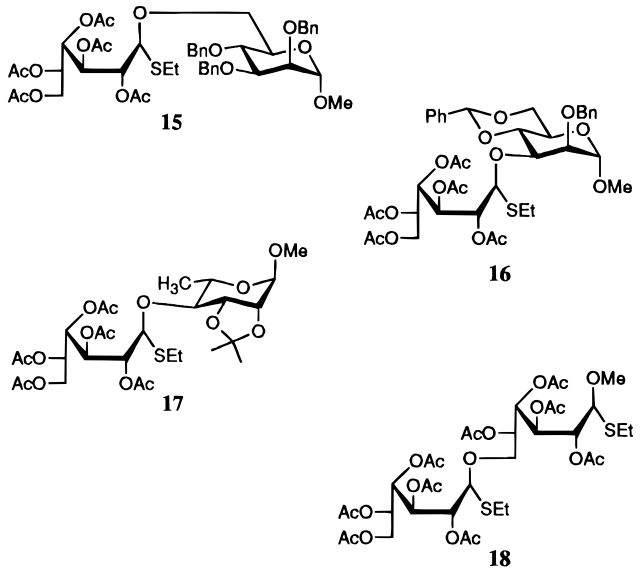
Scheme 4



cases, the corresponding *O,S*-acetals were formed in good to excellent yield. In a number of cases the donor **4** was added in one portion as a solid with little difference in the yields of product obtained.



Cyclization to *β*-D-galactofuranosides. The *β*-D-galactofuranoside **19** was prepared in 86% yield by *O*-deacetylation of compound **12** under Zémplen conditions, followed by addition of HgO and $HgCl_2$ to the methanolic solution. TLC analysis of the reaction mixture after a short time suggested the presence of a single compound. The residue remaining upon filtration and evaporation of the mixture was then acetylated (Ac_2O/pyridine) overnight (Scheme 5). The product obtained following workup contained only minor impurities that could be removed by either column chromatography or recrystallization. The assignment of the *β*-D-galactofuranosidic structure was made on the basis of the small coupling constant between H1′ and H2′ (<0.5 Hz) and the chemical shifts of H4′ (4.28 ppm) and C1′ (104.9 ppm).[10,30] Application of this method to D-galactosides **15**−**18** resulted in moderate to excellent yields of the *β*-D-furanosides **20**−**23** (Scheme 6, Table 2). To our knowledge, the syntheses of the *β*-D-gal*f*-(1→3)-D-Mann*p* (*T. cruzi, Leishmania* sp.),[13] *β*-D-gal*f*-(1→4)-L-Rham*p* (*Mycobacterium leprae, Mycobacterium tuberculosis*),[26] and *β*-D-gal*f*-(1→6)-D-Mann*p* (*Aspergillus* and *Penicillium* sp.)[27] linkages have not been previously reported.



Despite the fact that these reactions were performed in methanol, the production of mixed acetals with methanol was estimated by ^{1}H NMR to account for only a few percent of the crude products. Additional minor impurities, most likely either other ring sizes or α-D-furanosides, were also detected in the cases of compounds **21**−**23**. The remarkable regio- and stereoselectivity of the cyclizations can also be attributed to the highly favorable positioning of O4′ with respect to the anomeric carbon in the acyclic precursors. The cyclizations resulted predominantly in the inversion of configuration about C1′, implicating either an S_N2 or a tight ion-pair S_N1 mechanism. The formation of **23** in 70% yield is particularly noteworthy since it involved two simultaneous cyclizations to form a difuranoside.

Derivatives of D-Gluco- and D-Mannofuranose. Treatment of compound **13** in the same fashion as for the D-galacto analogue **12** gave the corresponding *β*-D-glucofuranoside **24** ($J_{H1',H2'}$ = 0 Hz; H4′, 4.51 ppm; C1′, 105.7 ppm)[30] in 83% yield (Scheme 7, Table 2). This method, however, was not applicable to the D-*manno* compound **14** as a mixture of products was formed. When the cyclization procedure was performed in DMF instead, the number of impurities was reduced and allowed the isolation of the α-D-mannofuranoside **25** ($J_{H1',H2'}$ = 2.8 Hz; H4′, 4.49 ppm; C1′, 105.5 ppm)[30] in a yield of 40% after recrystallization.

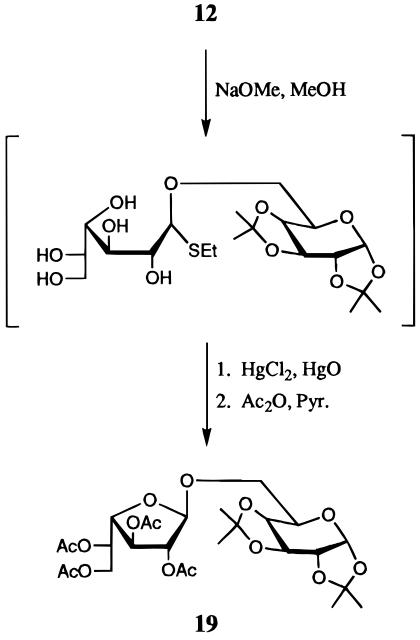
The synthesis of partially protected *O,S*-acetals may also allow access to six- and seven-membered sugars upon cyclization, and work toward this end is currently in progress. In addition, the application of acyclic glycosyl donors to the synthesis of carbohydrate analogues and novel macrocycles is envisioned.

Experimental Section

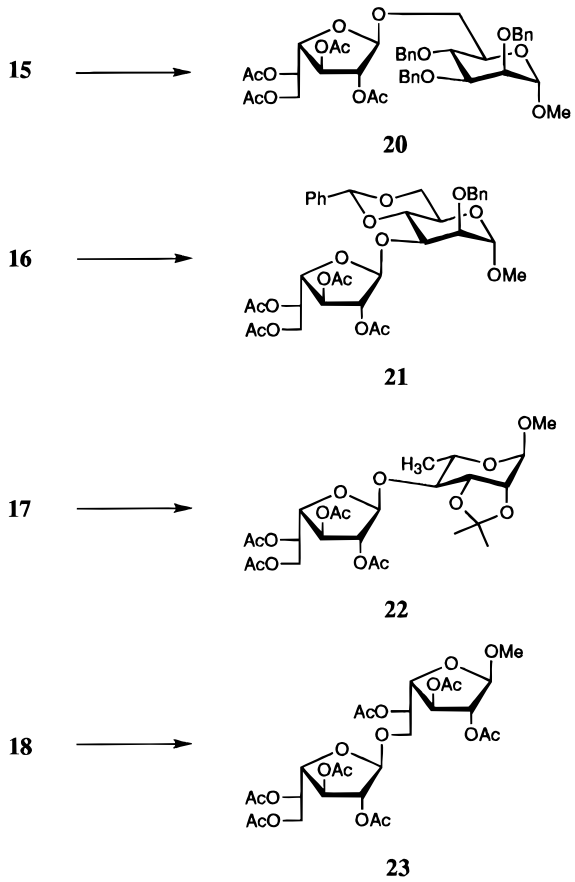
General Methods. TLC was performed on silica gel 60-F_{254} (Merck) with detection by charring with a 10% solution of H_2SO_4 in ethanol. Flash chromatography was performed on silica gel 60 (230−400 mesh, Merck). Optical rotations were measured at the sodium D line at 22 ± 2 °C in $CHCl_3$. ^{1}H NMR spectra were recorded at 360 MHz (Bruker WM 360) or 500

(30) Cyr, N.; Perlin, A. S. *Can. J. Chem.* **1979**, *57*, 2504.

Scheme 5



Scheme 6



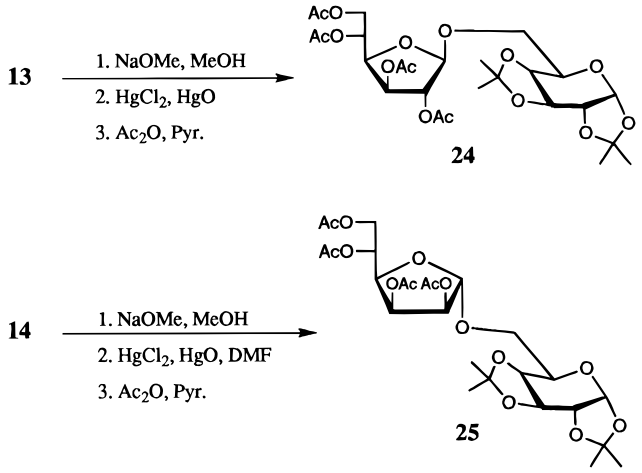
MHz (Varian Unity 500) as indicated and referenced to either internal $CHCl_3$ (δ = 7.24 ppm) or external acetone (δ = 2.225 ppm). ^{13}C NMR spectra were recorded at 75 MHz (Bruker AM 300) using $CDCl_3$ (δ = 77.1 ppm) as the reference.

General Method for the Synthesis of Donors 4−6. A solution of the dithioacetal pentaacetate (1.0 g, 2.0 mmol) in AcCl (4 mL) was treated with $BF_3{\cdot}Et_2O$ (50 μL) and held at reflux for 4 h. The reaction mixture was then diluted with $CHCl_3$ (20 mL) and concentrated to give the crude 1-chloro sulfides (**5** and **6**) or recrystallized (**4**). For **4**: $[\alpha]_D = -30°$ (*c* 0.95) [lit.[14,17] $[\alpha]_D = -27°$]; mp 110−112 °C (*i*-Pr_2O/CH_2Cl_2)

Table 2. Cyclization of *O,S*-Acetals to D-Furanosides

entry	*O,S*-acetal	furanoside	yield (%)
1	**12**	**19**	86
2	**15**	**20**	89
3	**16**	**21**	65
4	**17**	**22**	74
5	**18**	**23**	70
6	**13**	**24**	83
7	**14**	**25**	40

Scheme 7



[lit.[14,17] mp = 111−112 °C]; ^1H NMR (360 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.5 Hz, 3H), 1.99, 2.05, 2.06, 2.07, 2.10 (5s, 15H), 2.69−2.78 (m, 2H), 3.80 (dd, *J* = 7.2, 11.7 Hz, 1H), 4.25 (dd, *J* = 5.0 Hz, 1H), 5.00 (d, *J* = 7.0 Hz, 1H), 5.18 (ddd, *J* = 2.0 Hz, 1H), 5.20 (dd, *J* = 9.7 Hz, 1H), 5.36 (dd, *J* = 1.8 Hz, 1H), 5.67 (dd, 1H).

6-*O*-[1(*S*)-[2,3,4,5,6-Penta-*O*-acetyl-1-(ethylthio)-D-galactityl]]-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (12). AgOTf (150 mg, 0.58 mmol) and Ag_2CO_3 (450 mg, 1.63 mmol) were added with stirring to a cooled (−40 °C) mixture of the acceptor **7** (273 mg, 1.03 mmol) and powdered 4 Å molecular sieves (500 mg) in CH_2Cl_2 (5 mL). After 5 min, a solution of the donor **4** (653 mg, 1.39 mmol) in CH_2Cl_2 (3 mL) was added slowly dropwise, and stirring was continued for 30 min. The mixture was then eluted (EtOAc/hexanes, 3:2) through a short plug of silica gel to give a clear oil (740 mg) that was further purified by flash chromatography to give **12** as a solid (577 mg, 81%): $[\alpha]_D = +14°$ (*c* 0.75); mp 131−132 °C (*i*-Pr_2O); ^1H NMR (360 MHz, $CDCl_3$) δ 1.14 (t, *J* = 7.5 Hz, 3H), 1.30, 1.31, 1.40, 1.55 (4s, 12H), 1.98, 2.00, 2.04, 2.06, 2.08 (5s, 15H), 2.42−2.62 (m, 2H), 3.20−3.24 (m, 1H), 3.79 (dd, *J* = 7.3, 11.7 Hz, 1H), 3.95−4.02 (m, 2H), 4.18 (m, *J* = 7.9 Hz, 1H), 4.18 (d, *J* = 6.6 Hz, 1H), 4.24 (dd, *J* = 4.8 Hz, 1H), 4.28 (dd, *J* = 5.0, 2.5 Hz, 1H), 4.56 (dd, 1H), 5.14 (ddd, *J* = 2.0 Hz, 1H), 5.19 (dd, *J* = 2.0 Hz, 1H), 5.22 (dd, *J* = 9.9 Hz, 1H), 5.49 (d, 1H), 5.60 (dd, 1H); ^{13}C NMR (75 MHz) δ 14.3, 20.7, 20.9, 21.6, 24.6, 25.0, 26.0, 62.4, 66.8, 67.5, 67.9, 68.1, 68.3, 68.8, 70.4, 70.7, 71.6, 84.5, 96.4, 108.6, 109.4, 168.9, 169.9, 170.1, 170.2, 170.5. Anal. Calcd for $C_{30}H_{46}O_{16}S$: C, 51.86; H, 6.67; S, 4.61. Found: C, 51.78; H, 6.77; S, 4.35.

6-*O*-[1(*S*)-[2,3,4,5,6-Penta-*O*-acetyl-1-(ethylthio)-D-glucityl]]-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (13). A solution of the acceptor **7** (280 mg, 1.06 mmol) and 4 Å sieves (500 mg) in CH_2Cl_2 (5 mL, −30 °C) was treated with a mixture of AgOTf and Ag_2CO_3 (600 mg, 1:3) followed by a solution the crude donor **5** (690 mg, 1.4 mmol), prepared as described above, in CH_2Cl_2 (2 mL) in the same fashion as for compound **12**. Filtration through a plug of silica gel (EtOAc/hexanes, 1:1) was followed by flash chromatography to give **13** as an oil (565 mg, 76%): $[\alpha]_D = -9.6°$ (*c* 0.92); ^1H NMR (360 MHz, $CDCl_3$) δ 1.18 (t, *J* = 7.5 Hz, 3H), 1.28, 1.29, 1.39, 1.49 (4s, 12H), 1.98, 2.01, 2.04, 2.05, 2.12 (5s, 15H), 2.48−2.64 (m, 2H), 3.36−3.42 (m, 1H), 3.88−3.95 (m, 2H), 4.08 (dd, *J* = 5.4, 11.9 Hz, 1H), 4.16 (m, *J* = 7.9 Hz, 1H), 4.23 (dd, *J* = 5.2

Hz, 1H), 4.26 (dd, J = 5.0, 2.4 Hz, 1H), 4.37 (d, J = 7.6 Hz, 1H), 4.56 (dd, 1H), 5.06 (dt, J = 5.7 Hz, 1H), 5.29 (dd, J = 4.0 Hz, 1H), 5.38 (t, J = 6.2 Hz, 1H), 5.45 (d, 1H), 5.54 (dd, 1H); ^{13}C NMR (75 MHz) δ 14.5, 20.6, 20.7, 20.9, 21.9, 24.6, 25.0, 25.9, 26.0, 32.4, 61.3, 66.7, 68.1, 69.0, 69.5, 69.7, 70.2, 70.5, 70.7, 71.3, 84.5, 96.3, 108.6, 109.3, 169.4, 169.7, 169.8, 170.0, 170.5. Anal. Calcd for $C_{30}H_{46}O_{16}S$: C, 51.86; H, 6.67; S, 4.61. Found: C, 51.77; H, 6.40; S, 4.66.

6-*O*-[1(*R*)-[2,3,4,5,6-Penta-*O*-acetyl-1-(ethylthio)-D-mannityl]]-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (14). A solution of the acceptor **7** (464 mg, 1.76 mmol) and 4 Å sieves (800 mg) in CH_2Cl_2 (7 mL, −40 °C) was treated with a mixture of AgOTf and Ag_2CO_3 (1.0 g, 1:3) followed by a solution the crude donor **6** (1.1 g, 2.3 mmol), prepared as described above, in CH_2Cl_2 (3 mL) in the same fashion as for compound **12**. Filtration through a plug of silica gel (EtOAc/hexanes, 1:1) was followed by flash chromatography to give **14** as a solid (740 mg, 60%): $[\alpha]_D$ = −37° (*c* 0.95); mp 115−116 °C (Et_2O/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18 (t, J = 7.5 Hz, 3H), 1.28, 1.29, 1.40, 1.51 (4s, 12H), 2.02, 2.03, 2.04, 2.06 (5s, 15H), 2.51−2.63 (m, 2H), 3.53−3.58 (m, 1H), 3.93−3.98 (m, 2H), 4.07 (dd, J = 5.3, 12.5 Hz, 1H), 4.17 (dd, J = 2.7 Hz, 1H), 4.20 (m, J = 7.9 Hz, 1H), 4.27 (dd, J = 5.0, 2.3 Hz, 1H), 4.55 (dd, 1H), 4.59 (d, J = 6.4 Hz, 1H), 5.06 (ddd, J = 8.7 Hz, 1H), 5.28 (t, J = 6.4 Hz, 1H), 5.47 (dd, J = 2.0 Hz, 1H), 5.48 (d, 1H), 5.51 (dd, 1H); ^{13}C NMR (126 MHz) δ 14.6, 20.6, 20.7, 20.8, 20.9, 23.0, 24.4, 24.9, 26.0, 61.9, 66.7, 67.0, 67.6, 68.1, 68.8, 70.5, 70.6, 70.8, 70.9, 86.1, 96.2, 108.5, 109.2, 169.5, 169.7, 169.8, 169.9, 170.6. Anal. Calcd for $C_{30}H_{46}O_{16}S$: C, 51.86; H, 6.67; S, 4.61. Found: C, 51.81; H, 6.75; S, 4.44.

Methyl 6-*O*-[1(*S*)-[2,3,4,5,6-Penta-*O*-acetyl-1-(ethylthio)-D-galactityl]]-2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (15). A solution of the acceptor **8**[31] (327 mg, 0.70 mmol) and 4 Å sieves (800 mg) in CH_2Cl_2 (6 mL, −40 °C) was treated with a mixture of AgOTf and Ag_2CO_3 (600 mg, 1:3) followed by a solution of the donor **4** (452 mg, 0.96 mmol) in CH_2Cl_2 (3 mL) in the same fashion as for compound **12**. Filtration through a plug of silica gel (EtOAc/hexanes, 1:1) was followed by flash chromatography to give **15** as an oil (431 mg, 68%): $[\alpha]_D$ = +46° (*c* 0.82); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.16 (t, J = 7.5 Hz, 3H), 1.92, 1.99, 2.02, 2.06, 2.09 (5s, 15H), 2.46−2.63 (m, 2H), 3.32 (s, 3H), 3.53 (bd, J = 10.2 Hz, 1H), 3.68−3.78 (m, 2H), 3.74 (dd, J = 1.7, 3.1 Hz, 1H), 3.81 (dd, J = 7.2, 11.7 Hz, 1H), 3.88 (dd, J = 8.4 Hz, 1H), 3.93 (dd, J = 6.7 Hz, 1H), 4.25 (dd, J = 4.9 Hz, 1H), 4.35 (dd, J = 7.8 Hz, 1H), 4.64 (d, J = 1.7 Hz, 1H), 4.56−4.94 (m, 6H), 5.16 (ddd, J = 2.0 Hz, 1H), 5.19 (dd, J = 1.8 Hz, 1H), 5.22 (dd, J = 9.8 Hz, 1H), 5.64 (dd, 1H), 7.16−7.36 (m, 15H); ^{13}C NMR (75 MHz) δ 14.4, 20.5, 20.7, 20.8, 21.0, 22.6, 54.7, 62.4, 67.3, 67.9, 68.2, 68.8, 69.4, 71.0, 72.1, 72.7, 74.6, 74.8, 75.3, 80.2, 85.5, 98.8, 127.6, 127.7, 127.8, 127.9, 128.3, 128.4, 138.3, 138.5, 138.7, 169.1, 170.0, 170.3. Anal. Calcd for $C_{46}H_{58}O_{16}S$: C, 61.45; H, 6.50; S, 3.57. Found: C 61.40; H, 6.54; S, 3.73.

Methyl 3-*O*-[1(*S*)-[2,3,4,5,6-Penta-*O*-acetyl-1-(ethylthio)-D-galactityl]]-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (16). A solution of the acceptor **9**[32] (252 mg, 0.677 mmol) and 4 Å sieves (750 mg) in CH_2Cl_2 (6 mL, −40 °C) was treated with a mixture of AgOTf and Ag_2CO_3 (600 mg, 1:3) followed by the donor **4** (450 mg, 0.95 mmol) in CH_2Cl_2 (3 mL) in the same fashion as for compound **12**. Filtration through a plug of silica gel (EtOAc/hexanes, 1:2) was followed by flash chromatography to give **16** as an oil (496 mg, 82%): $[\alpha]_D$ = +55° (*c* 1.35); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.12 (t, J = 7.5 Hz, 3H), 1.54, 1.90, 1.97, 2.06, 2.07 (5s, 15H), 2.40−2.58 (m, 2H), 3.33 (s, 3H), 3.67 (dd, J = 1.4, 3.2 Hz, 1H), 3.77 (ddd, J = 9.5, 4.6, 7.3 Hz, 1H), 3.78 (dd, J = 4.8, 11.7 Hz, 1H), 3.89 (t, J = 10.0 Hz, 1H), 4.17 (dd, 1H), 4.25 (dd, J = 7.3 Hz, 1H), 4.26 (t, J = 9.9 Hz, 1H), 4.63 (dd, 1H), 4.67 (d, 1H), 4.72, 4.84 (2d, J = 12.2 Hz, 2H), 4.93 (d, J = 9.1 Hz, 1H), 5.10 (dd, J = 1.3 Hz, 1H), 5.10 (ddd, J = 1.9 Hz, 1H), 5.14 (dd, J = 9.7 Hz, 1H), 5.55 (s, 1H), 5.83 (dd, 1H), 7.24−7.42 (m, 10H); ^{13}C NMR (75 MHz) δ 15.0, 20.5, 20.7, 21.0, 23.5, 54.9, 62.4, 63.8, 67.2, 67.8, 68.4, 68.9, 69.6, 71.9, 73.7, 77.8, 79.7, 85.6, 100.6, 101.3, 126.1, 127.7, 127.9, 128.3, 128.4, 129.1, 137.7, 138.3, 168.9, 169.8, 170.0, 170.4, 170.5. Anal. Calcd for $C_{39}H_{50}O_{16}S$: C, 58.05; H, 6.24; S, 3.97. Found: C, 57.67; H, 6.26 ; S, 3.92.

Methyl 4-*O*-[1(*S*)-[2,3,4,5,6-Penta-*O*-acetyl-1-(ethylthio)-D-galactityl]]-2,3-*O*-isopropylidene-α-L-rhamnopyranoside (17). A solution of the acceptor **10**[33] (180 mg, 0.82 mmol) and 4 Å sieves (550 mg) in CH_2Cl_2 (8 mL, −30 °C) was treated with a mixture of AgOTf and Ag_2CO_3 (800 mg, 1:3) followed by the donor **4** (550 mg, 1.17 mmol) in a similar fashion as for compound **12**. Filtration through a plug of silica gel (EtOAc/hexanes, 1:2) was followed by recystallization to give **17** as white needles (449 mg, 84%): $[\alpha]_D$ = +8.5° (*c* 1.11); mp 125.5−126.5 °C (*i*-Pr_2O/hexanes); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.14 (t, J = 7.5 Hz, 3H), 1.24−1.26 (m, 3H), 1.30, 1.50 (2s, 6H), 1.97, 2.02, 2.03, 2.06 (4s, 15H), 2.51−2.68 (m, 2H), 3.31 (s, 3H), 3.49−3.58 (m, 2H), 3.79 (dd, J = 6.0, 12.0 Hz, 1H), 4.06 (d, J = 5.9 Hz, 1H), 4.22 (dd, J = 4.5 Hz, 1H), 4.27 (m, 1H), 4.78 (s, 1H), 4.83 (d, J = 6.1 Hz, 1H), 5.17 (m, J = 1.6 Hz, 1H), 5.18 (dd, J = 1.4 Hz, 1H), 5.22 (dd, J = 9.6 Hz, 1H), 5.52 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 18.1, 20.7, 20.8, 21.0, 23.2, 26.3, 27.9, 54.9, 62.4, 64.2, 67.6, 67.9, 68.2, 69.2, 75.9, 77.0, 80.0, 83.8, 98.0, 109.2, 169.5, 169.9, 170.2, 170.5. Anal. Calcd for $C_{28}H_{44}O_{15}S$: C, 51.52; H, 6.79; S, 4.91. Found: C, 51.49; H, 6.94; S, 4.69.

6-*O*-[1(*S*)-[2,3,4,5,6-Penta-*O*-acetyl-1-(ethylthio)-D-galactityl]]-2,3,4,5-tetra-*O*-acetyl-1(*S*)-(ethylthio)-1-*O*-methyl-D-galactitol (18). A solution of the acceptor **11**[34] (177 mg, 0.417 mmol) and 4 Å sieves (260 mg) in CH_2Cl_2 (5 mL, −30 °C) was treated with a mixture of AgOTf and Ag_2CO_3 (250 mg, 1:4) followed by a solution the donor **4** (253 mg, 0.538 mmol) in a similar fashion as for compound **12**. Filtration through a plug of silica gel (EtOAc/hexanes, 1:1) was followed by flash chromatography to give **18** as an oil (255 mg, 71%): $[\alpha]_D$ = +37° (*c* 1.58); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11, 1.14 (2t, J = 7.5 Hz, 6H), 1.97, 2.04, 2.05, 2.06, 2.08, 2.10 (6s, 27H), 2.37−2.51 (m, 4H), 3.17 (dd, J = 10.0, 4.9 Hz, 1H), 3.30 (s, 3H), 3.67 (dd, J = 7.0 Hz, 1H), 3.78 (dd, J = 11.7, 7.2 Hz, 1H), 4.04 (d, J = 8.8 Hz, 1H), 4.11 (d, J = 8.8 Hz, 1H), 4.23 (dd, J = 4.7 Hz, 1H), 5.05 (dd, J = 1.7 Hz, 1H), 5.11 (dd, J = 1.7 Hz, 1H), 5.13 (ddd, J = 2.0 Hz, 1H), 5.15 (dd, J = 9.9 Hz, 2H), 5.17 (ddd, J = 2.0 Hz, 1H), 5.56 (2dd, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 14.5, 20.6, 20.7, 20.8, 20.9, 21.5, 21.6, 56.0, 62.3, 67.3, 67.5, 67.6, 67.8, 68.0, 68.3, 68.6, 68.7, 84.2, 85.9. Anal. Calcd for $C_{35}H_{54}O_{20}S_2$: C, 48.94; H, 6.34; S, 7.46. Found: C, 48.99; H, 6.46; S, 7.45.

6-*O*-(2,3,5,6-Tetra-*O*-acetyl-β-D-galactofuranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (19). The *O,S*-acetal **12** (214 mg, 0.308 mmol) in methanol (3 mL) was deacetylated with a methanolic solution of NaOMe (150 μL of 1 M) over 2 h. The mixture was then cooled (5 °C), and HgO (150 mg, 0.69 mmol) and $HgCl_2$ (180 mg, 0.66 mmol) were added with rapid stirring. Following a period of stirring (30 min), the mixture was filtered, a small amount of pyridine added (150 μL), and the solvent removed to give a white residue. This residue was dissolved in pyridine (4 mL) and treated with Ac_2O (3 mL) in the presence of DMAP (50 mg) over 12 h. The mixture was then diluted with water and thoroughly extracted with EtOAc. The organic extract was washed sequentially with water, 10% aqueous $CuSO_4$ twice, water, and brine. Drying (Na_2SO_4) and concentration of this extract gave an oil that was purified by flash chromatography (EtOAc/hexanes, 1:1) to give compound **19** as a solid (156 mg, 86%): $[\alpha]_D$ = −79° (*c* 1.02); mp 123−4 °C (*i*-Pr_2O/hexanes); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.30, 1.31, 1.42, 1.51 (4s, 12H), 2.02, 2.04, 2.06, 2.10 (4s, 12H), 3.56 (dd, J = 6.5, 9.8 Hz, 1H), 3.83 (dd, J = 6.7 Hz, 1H), 3.95 (dt, J = 1.8 Hz, 1H), 4.16 (dd, J = 7.6, 12.0 Hz, 1H), 4.22 (dd, J = 8.0 Hz, 1H), 4.27 (dd, J = 5.8, 3.5 Hz, 1H), 4.28 (dd, J = 5.0, 2.4 Hz, 1H), 4.35 (dd, J = 2.3 Hz, 1H), 4.58 (dd, 1H), 4.94 (dd, J = 1.8, 5.8 Hz, 1H), 5.04 (d, J = 2.8 Hz, 1H), 5.07 (s, 1H), 5.38 (ddd, 1H), 5.48 (d, 1H); ^{13}C

(31) Contreras, R. R.; Kamerling, J. P.; Vliegenthart, J. F. G. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 85.

(32) Borén, H. B.; Garegg, P. J.; Wallin, N.-H. *Acta Chem. Scand.* **1972**, *26*, 1082.

(33) Bebault, G. M.; Dutton, G. G. S. *Can. J. Chem.* **1972**, *50*, 3373.

(34) McAuliffe, J. C.; Hindsgaul, O. Manuscript in preparation.

NMR (75 MHz, $CDCl_3$) δ 20.7, 20.8, 24.4, 24.9, 26.0, 26.1, 63.1, 65.0, 66.5, 69.4, 70.6, 70.9, 76.6, 80.2, 81.1, 96.3, 104.9, 108.6, 109.3, 169.5, 169.9, 170.1, 170.6. Anal. Calcd for $C_{26}H_{38}O_{15}$: C, 52.88; H, 6.48. Found: C, 53.03; H, 6.54.

Methyl 6-*O*-(2,3,5,6-Tetra-*O*-acetyl-*β*-D-galactofuranosyl)-2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (20). The *O,S*-acetal **15** (221 mg, 0.246 mmol) was treated in the same fashion as for compound **19** to give compound **20** (174 mg, 89%): $[\alpha]_D = -31°$ (*c* 0.48); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.99, 2.02, 2.06, 2.10 (4s, 12H), 3.29 (s, 3H), 3.67−3.70 (m, 1H), 3.74−3.78 (m, 2H), 3.84−3.90 (m, 3H), 4.08 (dd, J = 7.8, 11.9 Hz, 1H), 4.33 (dd, J = 3.8 Hz, 1H), 4.35 (dd, J = 5.8, 3.4 Hz, 1H), 4.70 (s, 1H), 4.58−4.92 (m, 6H), 4.94 (dd, J = 2.1 Hz, 1H), 5.09 (d, 1H), 5.11 (s, 1H), 5.38 (dt, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 20.7, 20.8, 54.7, 63.1, 66.8, 69.4, 71.5, 72.1, 72.7, 74.7, 74.8, 75.0, 80.0, 80.2, 81.1, 99.0, 105.6, 127.6, 127.7, 127.9, 128.4, 129.0, 129.7, 138.2, 138.5, 169.5, 170.1, 170.6. Anal. Calcd for $C_{42}H_{50}O_{15}$: C, 63.47; H, 6.34. Found: C, 63.17; H, 6.71.

Methyl 3-*O*-(2,3,5,6-Tetra-*O*-acetyl-*β*-D-galactofuranosyl)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (21). The *O,S*-acetal **16** (195 mg, 0.242 mmol) was treated in the same fashion as for compound **19** to give compound **21** (110 mg, 65%): $[\alpha]_D = -24°$ (*c* 1.02); mp 156−158 °C (*i*-Pr_2O/hexanes); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.89, 1.91, 2.06, 2.09 (4s, 12H), 3.32 (s, 3H), 3.76 (dt, J = 8.7, 4.2, 9.9 Hz, 1H), 3.78 (dd, J = 1.7, 4.1 Hz, 1H), 3.84 (t, J = 9.6 Hz, 1H), 3.90 (dd, J = 4.1, 11.9 Hz, 1H), 4.07 (dd, J = 7.6 Hz, 1H), 4.08 (dd, J = 10.2 Hz, 1H), 4.16 (dd, 1H), 4.23 (dd, 1H), 4.34 (dd, J = 5.9, 3.4 Hz, 1H), 4.68 (d, 1H), 4.70, 4.83 (2s, J = 12.2 Hz, 2H), 4.89 (bdd, J = 1.4 Hz, 1H), 5.03 (d, 1H), 5.05 (bs, 1H), 5.27 (dt, 1H), 5.57 (s, 1H), 7.24−7.45 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 20.6, 20.8, 54.9, 62.9, 64.2, 68.9, 69.3, 71.9, 73.9, 74.9, 76.8, 76.9, 80.1, 81.7, 100.5, 101.7, 102.3, 126.0, 127.8, 128.1, 128.2, 128.4, 129.0, 137.7, 138.1, 169.8, 170.0, 170.1, 170.4. Anal. Calcd for $C_{35}H_{42}O_{15}$: C, 59.82; H, 6.02. Found: C, 59.78; H, 6.00.

Methyl 4-*O*-(2,3,5,6-Tetra-*O*-acetyl-*β*-D-galactofuranosyl)-2,3-*O*-isopropylidene-α-L-rhamnopyranoside (22). The *O,S*-acetal **17** (230 mg, 0.351 mmol) was treated in the same fashion as for compound **19** to give compound **22** (142 mg, 74%): $[\alpha]_D = -53°$ (*c* 0.6); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.21 (d, J = 6.2 Hz, 3H), 1.28, 1.49 (2s, 6H), 2.01, 2.03, 2.07, 2.08 (4s, 12H), 3.32 (s, 3H), 3.48 (dd, J = 7.4, 10.0 Hz, 1H), 3.61 (dq, 1H), 4.04 (bd, J = 5.5 Hz, 1H), 4.15 (dd, 1H), 4.16 (dd, J = 7.2, 11.7 Hz, 1H), 4.18 (dd, J = 5.4, 4.0 Hz, 1H), 4.27 (dd, J = 4.9 Hz, 1H), 4.81 (bs, 1H), 4.95 (bdd, J = 1.7 Hz, 1H), 5.03 (d, 1H), 5.33 (dt, 1H), 5.51 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.7, 20.6, 20.7, 20.8, 26.4, 27.9, 32.1, 54.8, 62.4, 63.8, 67.5, 69.3, 76.0, 76.4, 76.7, 78.1, 80.6, 81.1, 98.0, 103.8, 109.5, 169.5, 169.9, 170.0, 170.4. Anal. Calcd for $C_{24}H_{36}O_{14}$: C, 52.55; H, 6.61. Found: C, 52.26; H, 6.55.

6-*O*-(2,3,5,6-Tetra-*O*-acetyl-*β*-D-galactofuranosyl)-2,3,5-tri-*O*-acetyl-*β*-D-galactofuranoside (23). The *O,S*-acetal **18** (143 mg, 0.166 mmol) was treated in the same fashion as for compound **19** to give compound **23** (75 mg, 70%): $[\alpha]_D = -37°$ (*c* 0.84); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.02, 2.06, 2.07, 2.10, 2.11 (6s, 18H), 3.63 (dd, J = 6.9, 10.2 Hz, 1H), 3.82 (dd, J = 6.1 Hz, 1H), 4.17 (dd, J = 7.3, 11.9 Hz, 1H), 4.26 (dd, J = 5.5, 4.0 Hz, 1H), 4.26 (dd, J = 5.7, 3.3 Hz, 1H), 4.32 (dd, J = 4.1 Hz, 1H), 4.90 (s, 1H), 4.95 (dd, J = 2.0 Hz, 1H), 4.98 (dd, J = 2.0 Hz, 1H), 5.00 (d, 1H), 5.00 (s, 1H), 5.01 (d, 1H), 5.30 (dt, 1H), 5.36 (dt, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 20.8, 20.9, 55.1, 62.7, 65.3, 69.3, 70.0, 76.5, 79.9, 80.4, 81.0, 81.4, 105.6, 106.7, 169.5, 169.7, 170.0, 170.1. Anal. Calcd for $C_{27}H_{38}O_{18}$: C, 49.85; H, 5.89. Found: C, 49.62; H, 5.52.

6-*O*-(2,3,5,6-Tetra-*O*-acetyl-*β*-D-glucofuranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (24). The *O,S*-acetal **13** (229 mg, 0.33 mmol) was treated in the same fashion as for compound **19** to give compound **24** (182 mg, 83%): $[\alpha]_D = -52°$ (*c* 1.27); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.28, 1.34, 1.40, 1.49 (4s, 12H), 1.92, 1.98, 2.03, 2.05 (4s, 12H), 3.45 (dd, J = 5.9, 8.7 Hz, 1H), 3.84 (t, J = 7.5 Hz, 1H), 3.91 (dt, J = 1.8 Hz, 1H), 4.16 (dd, J = 4.1, 12.4 Hz, 1H), 4.22 (dd, J = 8.0 Hz, 1H), 4.27 (dd, J = 5.0, 2.3 Hz, 1H), 4.51 (dd, J = 5.4, 9.8 Hz, 1H), 4.58 (dd, 1H), 4.58 (dd, J = 2.3 Hz, 1H), 4.99 (s, 1H), 5.00 (s, 1H), 5.26 (ddd, 1H), 5.35 (bd, 1H), 5.46 (d, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 20.7, 20.8, 24.2, 24.9, 25.9, 26.1, 63.2, 65.8, 66.3, 68.8, 70.5, 70.6, 70.7, 71.0, 73.3, 78.3, 80.2, 96.3, 105.7, 108.7, 109.3, 169.2, 169.4, 169.6, 170.6. Anal. Calcd for $C_{26}H_{38}O_{15}$: C, 52.88; H, 6.48. Found: C, 52.97; H, 6.54.

6-*O*-(2,3,5,6-Tetra-*O*-acetyl-α-D-mannofuranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (25). The *O,S*-acetal **14** (236 mg, 0.34 mmol) in methanol (6 mL) was treated with a methanolic solution of NaOMe (100 μL of 1 M) over 1 h. The solution was neutralized with Amberlite IRC-50 (H^+), filtered, and concentrated. The residue was dissolved in DMF (5 mL) and was cooled to −30 °C. A mixture of HgO (150 mg, 0.69 mmol) and $HgCl_2$ (180 mg, 0.66 mmol) was added with rapid stirring, and the mixture was allowed to warm to room temperature over 1 h. The mixture was filtered and treated with pyridine (4 mL) and Ac_2O (3 mL), and the resulting solution was stirred overnight. The solution was processed as described for the preparation of **19** to give compound **25** (80 mg, 40%): $[\alpha]_D = +30°$ (*c* 1.02); mp 164−165 °C (*i*-Pr_2O/hexanes); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.30, 1.31, 1.41, 1.51 (4s, 12H), 1.98, 2.02, 2.03, 2.04 (4s, 12H), 3.68 (dd, J = 7.0, 10.4 Hz, 1H), 3.75 (dd, J = 6.4 Hz, 1H), 3.95 (dt, J = 1.9 Hz, 1H), 4.09 (dd, J = 5.6, 12.3 Hz, 1H), 4.20 (dd, J = 7.9 Hz, 1H), 4.29 (dd, J = 5.0, 2.4 Hz, 1H), 4.39 (dd, J = 4.4, 8.7 Hz, 1H), 4.55 (dd, J = 2.3 Hz, 1H), 4.58 (dd, 1H), 5.13 (d, J = 2.8 Hz, 1H), 5.21 (dd, J = 5.1 Hz, 1H), 5.24 (ddd, 1H), 5.48 (d, 1H), 5.55 (t, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.3, 20.4, 20.7, 20.8, 24.5, 24.9, 26.0, 26.1, 62.9, 66.2, 67.3, 68.3, 70.6, 70.8, 75.8, 76.2, 96.3, 105.5, 108.6, 109.3, 169.3, 169.5, 169.7, 170.6. Anal. Calcd for $C_{26}H_{38}O_{15}$: C, 52.88; H, 6.48. Found: C, 52.77; H, 6.72.

Acknowledgment. This work was supported by the Natural Sciences and Engineering Research Council of Canada.

JO9618583