Studies Directed toward the Synthesis of Polysialogangliosides: The Regio- and Stereocontrolled Synthesis of Rationally Designed Fragments of the Tetrasialoganglioside GQ_{1b}†

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The synthesis of suitably protected fragments of the tetrasialoganglioside GQ_{1b} (I), i.e., 1 (αNeuAc2→8αNeuAc2→3βGal1→4Glc), 2 (αNeuAc2→8αNeuAc2→3Gal), 3 (GalNAc), 4 (αNeuAc2→8NeuAc), 5 (βGal1→3GalNAc), and 42 [βGal1→3βGalNAc1→4(αNeuAc2→3)βGal→4Glc], is described. All are rationally designed so that the protecting groups can be regioselectively introduced and removed, as needed, before or after the stereoselective coupling of an appropriate pair of fragments. The syntheses of 1, 2, and 4 all feature stereoselective glycosylations by glycosyl donors that bear a C-3 thiophenoxy stereocontrolling auxiliary. Compound 3 was prepared from the D-glucosamine derivative 17 by way of a novel intramolecular nucleophilic displacement with inversion of configuration. Furthermore, model glycosylations of 4-hydroxygalactose derivatives, in which the thioglycoside 3 and the fluoride 40 served as glycosyl donors, were performed. The reaction of 3 with the glycosyl acceptor 30 gave the disaccharide 31 (GalNAcβ1→4Gal), whereas that of 40 with 41 afforded the pentasaccharide 42.

Introduction

Gangliosides, which are glycosphingolipids that incorporate sialic acid (*N*-acetylneuraminic acid, NeuAc), have attracted a great deal of attention because of their biochemical significance and potential medical applicability.[2] These compounds have fascinated carbohydrate chemists because of their structural complexity and diversity.[3] Furthermore, within the last few years astonishing progress has been made toward understanding the roles played in vivo by polysialogangliosides. For examples, the structure and the unique physiological activity of the tetrasialoganglioside GQ_{1b} (I) have only recently been described.[4] Until recently, synthesizing such complex molecules was a formidable undertaking, due to the lack of a reliable method for stereoselectively introducing a sialic acid residue into the nonreducing end of the glycan chains.[5-7] However, our recent efforts, which were inspired by reports[8] of the stereoselective synthesis of 2-deoxyglycosides through the use of glycosyl donors that bear a C-2 stereocontrolling substituent, led to the development of just such a method. Our method[9] features the use, as glycosyl donors, of 2-halo derivatives of *N*-acetylneuraminic acid which bear a 3β-phenylthio stereocontroller. With such a powerful tool now at our disposal, we focused our attention on how to apply it to the stereoselective synthesis of gangliosides. Thus, we have reported an improved synthesis of GM_3 (II)[10,11] and the first synthesis of GD_3 (III)[12] (see Table I). The latter achievement represents, so far, the only synthesis of a disialoganglioside which incorporates consecutive NeuAc residues joined by a α2→8 linkage and thus clearly demonstrates the versatility of our methodology.

Because the regio- and stereocontrolled attachment of the disialo residue (the monosaccharide units g and h) to the lactose portion (units a and b) could thus be achieved, what remained to be done in order to synthesize more complex members of the ganglioside family (Table I) was to construct fragments which corresponded to the units c–f of these molecules and to introduce them at the 4-hydroxy group of the galactose residue (b). Synthesizing the tetrasialoganglioside GQ_{1b} was our ultimate goal. Our investigation began by evaluating two synthetic strategies, A and B, which were suggested by the results of a retrosynthetic analysis that is summarized in Scheme I.

Table I. Structure of Polysialogangliosides[a]

	sugar residues present in addition to a, b, g [GM_3(II)]
GD_3 (III)	h
GD_2	c, h
GD_{1a} (IV)	c, d, e
GD_{1b}	c, d, h
GT_{1a} (V)	c, d, e, f
GT_{1b}	c, d, e, h
GQ_{1b} (I)	c, d, e, f, h

[a] For the numbering of the sugar residues, see GQ_{1b}(I) in Scheme I.

Here we describe the preparation of the potentially useful building-blocks 1–5 and also the results of model

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† Synthetic Studies on Cell Surface Glycans. 82. For part 81, see ref 1.

(1) Nukada, T.; Kitajima, T.; Nakahara, Y.; Ogawa, T.; *Carbohydr. Res.*, submitted for publication.

(2) *Structure and Function of Gangliosides*; Svennerholm, L., Mandel, P., Dreyfus, H., Urbun, P.-F., Eds.; Plenum Publishing: New York, 1980. *Ganglioside Structure, Function and Biomedical Potential*; Ledeen, R. W., Yu, R. K., Rapport, M. M., Suzuki, K., Eds.; Plenum Publishing: New York, 1984. *New Trends in Ganglioside Research*; Ledeen, R. W., Hogan, E. L., Tettamanti, G., Yates, A. J., Yu, R. K., Eds.; Liviana Press: Padova, 1988.

(3) For general reviews of sialic acid chemistry and biochemistry, see: Schauer, R. *Adv. Carbohydr. Chem. Biochem.* **1982**, *40*, 131; *Sialic Acids Chemistry, Metabolism and Function*; Schauer, R., Ed.; Springer-Verlag Wien.: New York, 1982.

(4) Tsuji, S.; Arita, M.; Nagai, Y. *J. Biochem.* **1983**, *94*, 303.

(5) For a recent review of this topic, see: Okamoto, K.; Goto, T. *Tetrahedron* **1990**, *46*, 5835.

(6) For earlier syntheses of gangliosides that use classical methodology, see: (a) Sugimoto, M.; Ogawa, T. *Glycoconjugate J.* **1985**, *2*, 5. (b) Sugimoto, M.; Numata, M.; Koike, K.; Nakahara, Y.; Ogawa, T. *Carbohydr. Res.* **1986**, *156*, C1. (c) Numata, M.; Sugimoto, M.; Koike, K.; Ogawa, T. *Carbohydr. Res.* **1987**, *163*, 209. (d) Numata, M.; Sugimoto, M.; Shibayama, S.; Ogawa, T. *Carbohydr. Res.* **1988**, *174*, 73. (e) Sugimoto, M.; Fujikura, K.; Nunomura, S.; Horisaki, T.; Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1990**, *31*, 385.

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(8) (a) Thiem, J.; Gerken, M. *J. Carbohydr. Chem.* **1982**, *1*, 229. (b) Jaurand, G.; Beau, J.-M.; Sinaÿ, P. *J. Chem. Soc., Chem. Commun.* **1981**, 572. (c) Nicolaou, K. C.; Ladduwahetty, T.; Randall, J. L.; Chucholouski, A. *J. Am. Chem. Soc.* **1986**, *108*, 2466.

(9) Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1988**, *29*, 3987. Ito, Y.; Ogawa, T. *Tetrahedron* **1990**, *46*, 89. See also: Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1987**, *28*, 6221.

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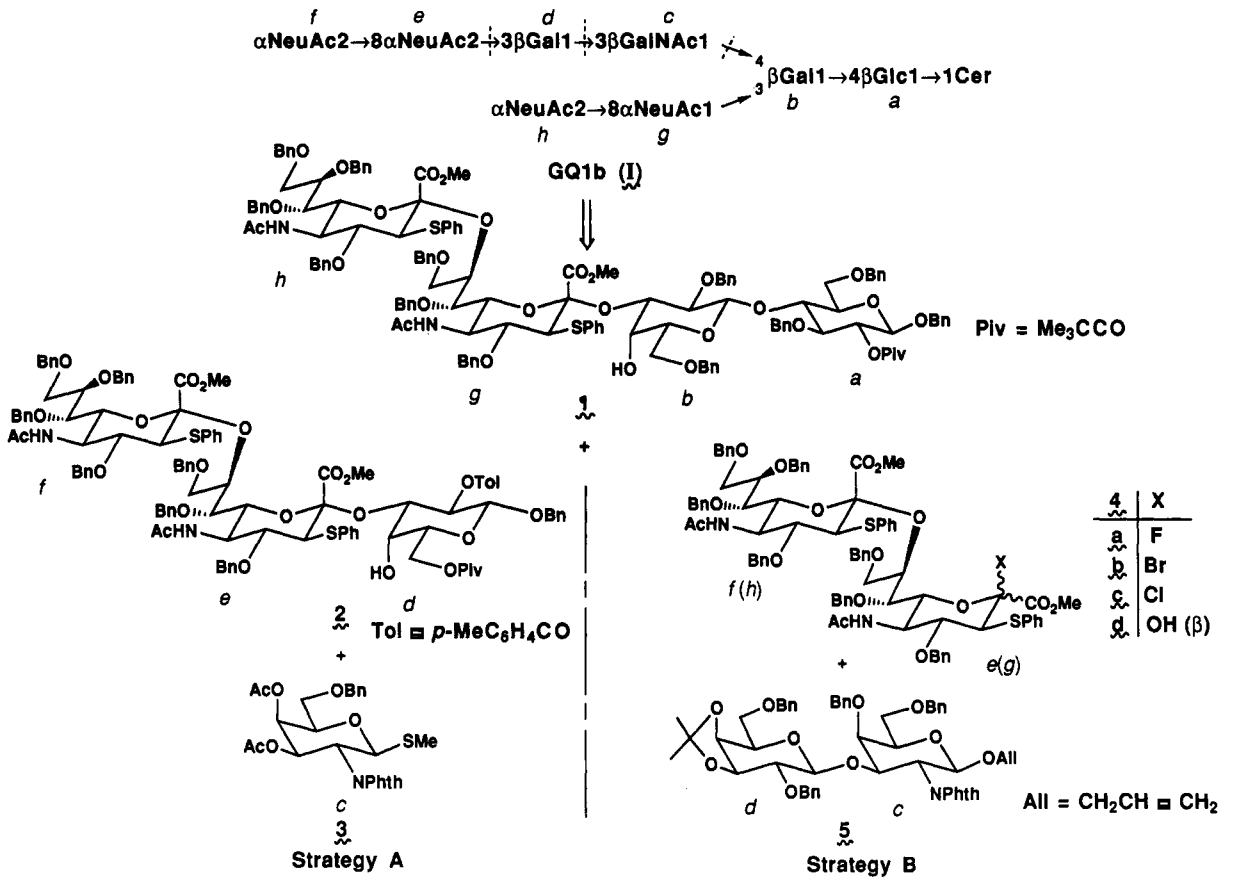
Scheme I



studies directed toward extending the glycan chain by attaching appropriate fragments at the sterically congested 4-hydroxy group of the galactose residue.

Results and Discussion

Synthesis of Disialyl Lactose Fragment 1. It was decided to prepare the tetrasaccharide fragment **1** by coupling one of the halides **4a–c** with the diol **13**. A preliminary report[12] of the preparation of **1**, a key intermediate in the synthesis of the ganglioside GD_3, has already appeared. Here the prepatation of **1** is described in detail.

It was assumed that the hemiketal **4d**, the common precursor of the disialo donors **4a**, **b**, and **c**, could be prepared from the 2,3-dehydro derivative **6** (Scheme II). An obvious way to prepare **6** was to couple **8** and **12**, a NeuAc donor and acceptor, respectively. The bromide **8** was prepared as described previously.[9] On the other hand, the 8-hydroxy derivative **12** was synthesized as follows: The known tetrol **9**[13] was acetalized [$PhCH(OMe)_2$, (±-10-camphorsulfonic acid (CSA)/MeCN] to afford the cyclic acetal **10** (85% yield), as a mixture of diastereomers (a new chiral center is generated at the acetal carbon). Benzylation of the remaining hydroxy groups was found, after considerable experimentation, to be best achieved under somewhat unusual conditions. Thus, treatment of **10** with BnBr, Bu_4NI, CaH_2,[14] and KOH in DMSO afforded **11** in 70% yield, after reesterification (CH_2N_2) of the carboxylic acid group that was unmasked during benzylation. Reductive opening of the ring of the cyclic acetal (BH_3·NMe_3, $AlCl_3$/THF[15]) occurred regioselectively to give **12** in 83% yield.[16]

Table II. Synthesis of Tetrasaccharide 1 by the Coupling of 4 and 13[a]

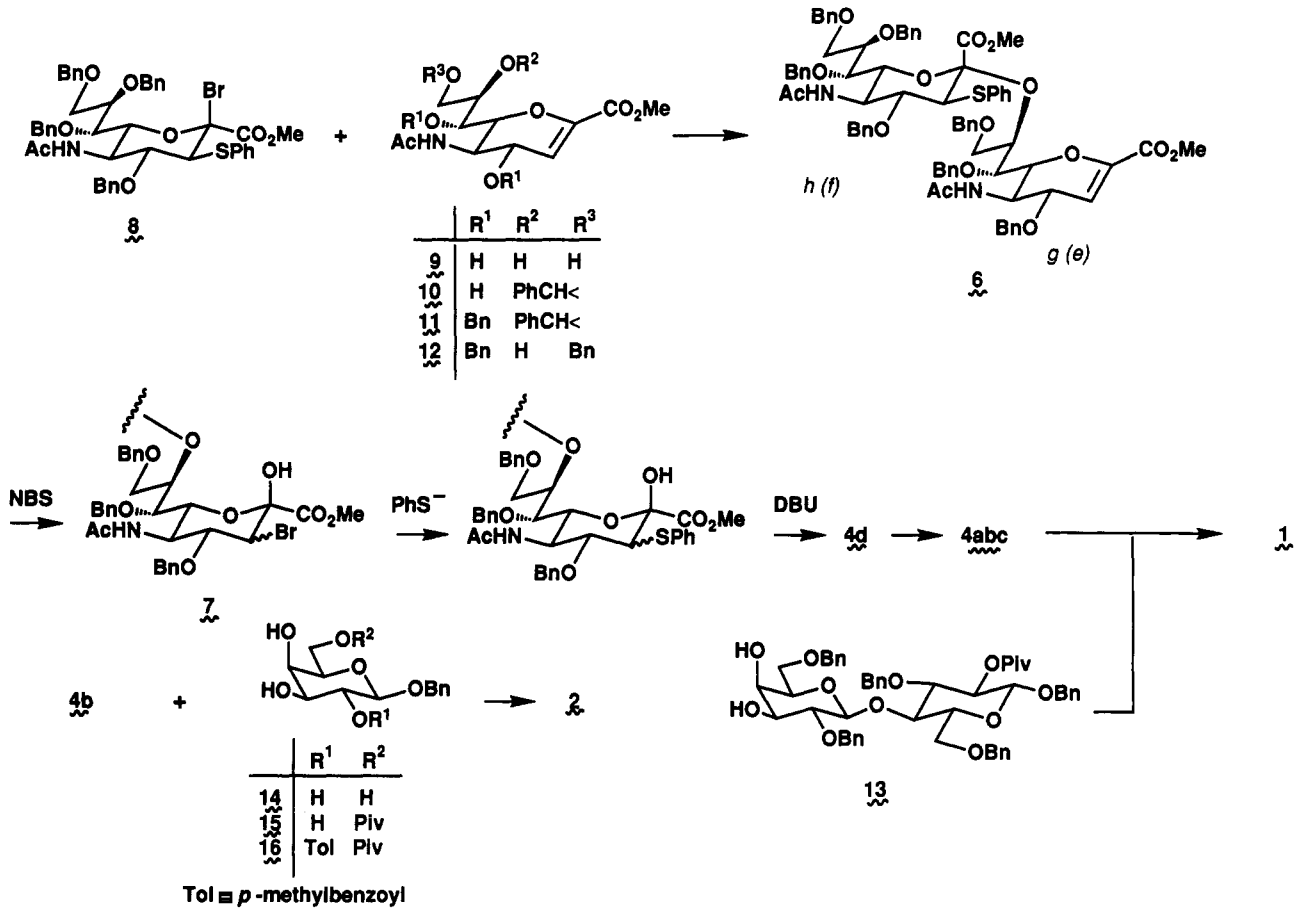
entry	donor	4:13[b]	promoter[c]	T (°C)	yield[d] (%)	α:β
1	**4a** (α)	1:1.1	A	rt	37	8:1
2	**4a** (β)	1:1.1	A	50	33	1:2
3	**4a** (α,β)[e]	1:1.2	A	rt	38	2:1
4	**4a** (α,β)[e]	1:1	B	rt	10	1:1
5	**4b**	1:1.1	C	0 rt	49[f]	60:1
6	**4c**	1:1.2	C	40	31	20:1

[a] In CCl_4 solution, 18 h. [b] Mole ratio. [c] A: Cp_2ZrCl_2/$AgOSO_2CF_3$.[21] B: $SnCl_2$/$AgOSO_2CF_3$.[22] C: $Hg(CN)_2$/$HgBr_2$. [d] Combined yield of **1** and its β-isomer, based on **4a** or **4c**. [e] α:β = 1:1.2. [f] Based on **4d**.

The coupling of **8** and **12** in CCl_4 solution in the presence of $Hg(CN)_2$ and $HgBr_2$ gave a single isomer of the expected product, **6**, in 64% yield. *The yield reported here for a product that incorporates a α2→8 link between two NeuAc residues is much higher than those that have been obtained by other methods.*[7c,d] The first step in the conversion of **6** into **4** was the functionalization of C-2 and C-3. Thus, **6** was treated with NBS in aqueous MeCN[13b] to afford a mixture of diastereomeric bromohydrins **7**. Without extensive purification, the mixture was treated with potassium thiophenoxide (generated in situ from

(10) Numata, M.; Sugimoto, M.; Ito, Y.; Ogawa, T. *Carbohydr. Res.* **1990**, *203*, 205. For the first reported synthesis, see ref 6a.
(11) For details of another efficient synthesis of GM_3, see: Murase, T.; Ishida, H.; Kiso, M.; Hasegawa, A. *Carbohydr. Res.* **1989**, *188*, 71.
(12) Ito, Y.; Numata, M.; Sugimoto, M.; Ogawa, T. *J. Am. Chem. Soc.*, **1989**, *111*, 8508.
(13) (a) Meindl, P.; Tuppy, H. *Monatsh. Chem.* **1969**, *100*, 1295. (b) Okamoto, K.; Kondo, T.; Goto, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 631.
(14) CaH_2 was added as a drying agent. The progress of the reaction can be followed by monitoring the rate of evolution of hydrogen.
(15) Ek, M.; Garegg, P. J.; Hultberg, H.; Oscarson, S. *J. Carbohydr. Chem.* **1983**, *2*, 305.
(16) The regiochemistry of **12** was inferred from the ^1H NMR spectrum of its 8-*O*-acetyl derivative (see Experimental Section).

Scheme II



thiophenol and potassium *tert*-butoxide) in THF/*t*-BuOH to yield the corresponding phenyl sulfides. Brief treatment of that mixture with DBU in toluene gave **4d** in 80% overall yield. The conversion of **4d** into the fluoride **4a**, the bromide **4b**,[17] and the chloride **4c** was cleanly effected by treatment with DAST ((diethylamino)sulfur trifluoride),[18] $CBr_4/(Me_2N)_3P$,[19] and $CCl_4/(Me_2N)_3P$,[19] respectively.

The disialo donors **4a**, **4b**, and **4c** were allowed to react individually with the previously described lactose derivative **13**,[10,12] which carries at C-2 a pivaloyloxy group that serves as a stereocontrolling auxilliary.[20] The results are summarized in Table II. The reaction of the bromide **4b** gave the highest yield of 1 and was also the most stereoselective: tetrasaccharide 1 was obtained in 48% yield (overall from **4d**) along with a small amount (0.8%) of its β-isomer. The reaction of the fluoride **4a** afforded rather unsatisfactory results in terms of both yield and stereoselectivity. However, it should be noted that, in this case, the stereoselectivity of the coupling depended on which fluoride anomer[23] was used. Thus, the β-fluoride showed a slight tendency to react to yield β-**1** (entry 2), whereas the reaction of the α-fluoride yielded α-**1** predominantly (entry 1). That the products are stereoisomers rather than regioisomers was confirmed by converting them into the corresponding acetates, the ^1H NMR spectra of which both show a downfield shift of the H-4b signals (see Experimental Section). Because of interference from the signals due to the benzyl group protons, the signals in the ^1H NMR spectra of the sialyl α-glycosides described in this section are only tentatively assigned. However, the presence of doublets (J = 9–11 Hz) at δ 3.1–3.5 assignable to H-3g,h is in accord with the results of earlier work.[9] That the stereochemistry of the glycosidic linkages was as depicted was eventually confirmed by converting 1 into the natural ganglioside GD_3.

Synthesis of the Disialyl Galactose Fragment 2. The nonreducing end-trisaccharide fragment **2**, which corresponds to αNeuAc2→8αNeuAc2→3Gal, was synthesized from **4b** and diol **16**. The first step in preparing diol **16** from benzyl β-D-galactopyranoside (**14**) was to selectively protect (pivaloyl chloride/pyridine) the primary hydroxy group, thus forming **15**. Subsequent isopropylidenation, protection of the remaining hydroxy group by *p*-methylbenzoylation, and unmasking of the 3- and 4-hydroxy groups afforded **16** in 49% yield overall from **14**.

The coupling of **16** with the bromide **4b** took place in the presence of $Hg(CN)_2$ and $HgBr_2$ to give the trisaccharide **2** (33% yield overall from **4d**). That the yield

(17) The bromide **4b** provided to be considerably less stable than its monosialo counterpart **8**. Attempts to purify **4b** by column chromatography on silica gel led to substantial decomposition.

(18) Rosenbrook, Wm., Jr.; Riley, D. A.; Lartey, P. A. *Tetrahedron Lett.* **1985**, *26*, 3. Posner, G. H.; Haines, S. R. *Tetrahedron Lett.* **1985**, *26*, 5.

(19) Castro, B.; Chapleur, Y.; Gross, B.; Selve, C. *Tetrahedron Lett.* **1972**, 5001. Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48.

(20) Sato, S.; Nunomura, S.; Nakano, T.; Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1988**, *29*, 4097. For the use of the pivaloyl group in glycosylations, see also: Kunz, H.; Harrews, A. *Liebigs Ann. Chem.* **1982**, 41. Vlahov, J.; Snatzke, G. *ibid.* **1983**, 570. Schmidt, R. R.; Zimmerman, P. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 725. Nicolaou, K. C.; Caulfield, T.; Kataoka, H.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 7910.

(21) Matsumoto, T.; Maeta, H.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1988**, *29*, 3567.

(22) Mukaiyama, T.; Murai, Y.; Shoda, S. *Chem. Lett.* **1981**, 431.

(23) The configurations of the anomers were established by ^{19}F NMR analysis (see Experimental Section).

Scheme III

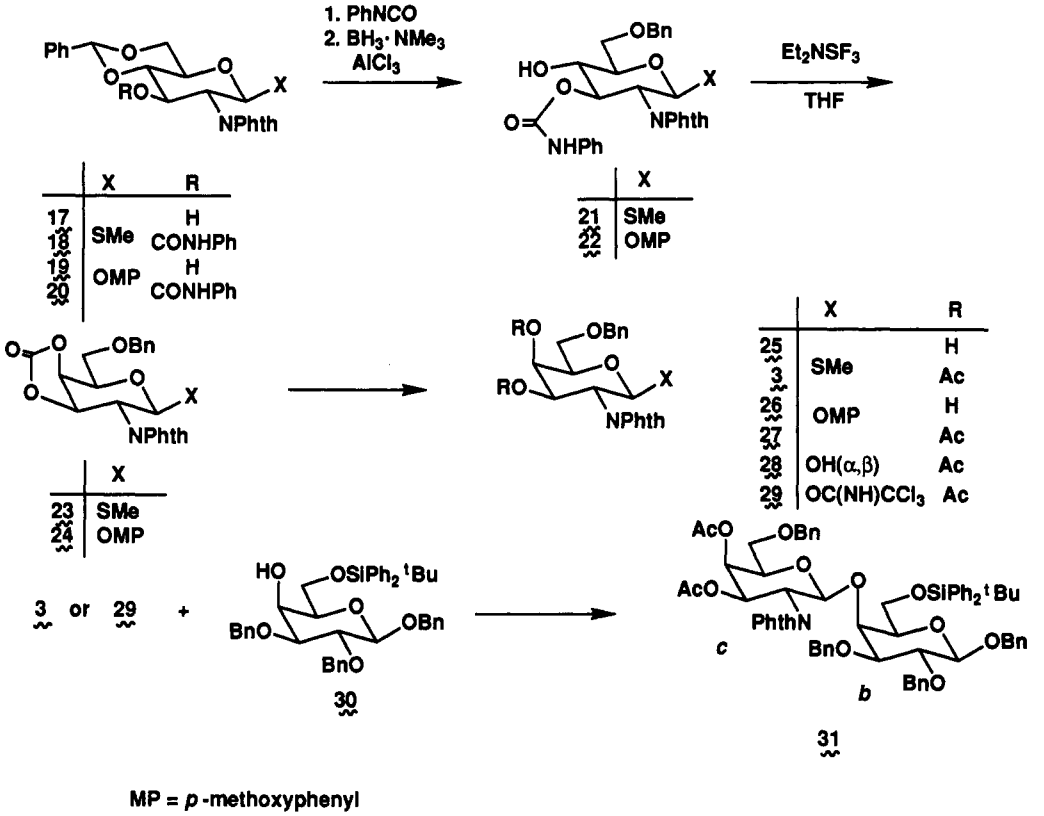


Table III. Synthesis of Disaccharide 31 by the Coupling of 3 (or 29) and 30

entry	donor	mole ratio[a]	promoter[b]	solvent	T (°C)	time (h)	yield (%)	β:α[c]
1	3	1.5:1	A	toluene	−40	0.5	37	3:1
2	3	1.5:1	B	$MeNO_2$	rt	18	38	4:1
3	3	1.5:1	C	toluene	−40 to −10	1.5	99	*d*
4	3	1.2:1	D	benzene	50	18	38	*d*
5	29	1.6:1	E	toluene	−23	0.5	95	*d*

[a] 3 (or 29):30. [b] A: $PhSeOSO_2CF_3$. B: $CuBr_2/Bu_4NBr/AgOSO_2CF_3$. C: NIS/CF_3SO_3H. D: $MeOSO_2CF_3$. E: $Me_3SiOSO_2CF_3$. [c] Determined by 500-MHz ^1H NMR analysis. [d] Only the β-isomer was detected.

of **2** was considerably lower than that of **1**, which was prepared in the same manner, may reflect the lower electron density at the 3-hydroxy group caused by the presence of the electron-withdrawing acyloxy groups.[24] Although the structure of **2** is yet to be rigorously established, that the regiochemistry of the coupling was as depicted was confirmed by converting **2** into the corresponding acetate, the ^1H NMR spectrum of which showed a downfield shift of the H-4d signal to δ 5.311 (d, J = 3.4 Hz). Also, that the stereochemistry of the compound **15** as depicted is strongly supported by the results of earlier work[9,10,12] and also by the presence in the compound's ^1H NMR spectrum of two doublets (J = 9.9 and 8.8 Hz, respectively), due to H-3e and 3f, at δ 3.435 and 3.205, respectively.[9]

Synthesis of the *N*-Acetylgalactosamine (GalNAc) Fragment 3 and Model Glycosylation Studies. The methyl thioglycoside **3**, which carries a phthalimido group at C-2, was designed to serve as a GalNAc fragment, for the reasons that follow. First, the presence of the phthalimido group should ensure that the stereochemical outcome of glycosylation will be what is desired.[25] Second, because glycosylations that use thioglycosides as glycosyl donors can now be achieved under a variety of conditions,[26] it should be possible to bring about the reaction of **3** with even a sterically hindered hydroxy group of a glycosyl acceptor. Finally, after glycosylation and replacement of the phthalimido group by a less bulky acetamido group, unmasking of the 3- and 4-hydroxy groups would generate reactive sites from which the glycan chain could subsequently be extended, by way of preferential reaction of the 3-hydroxy group.[27]

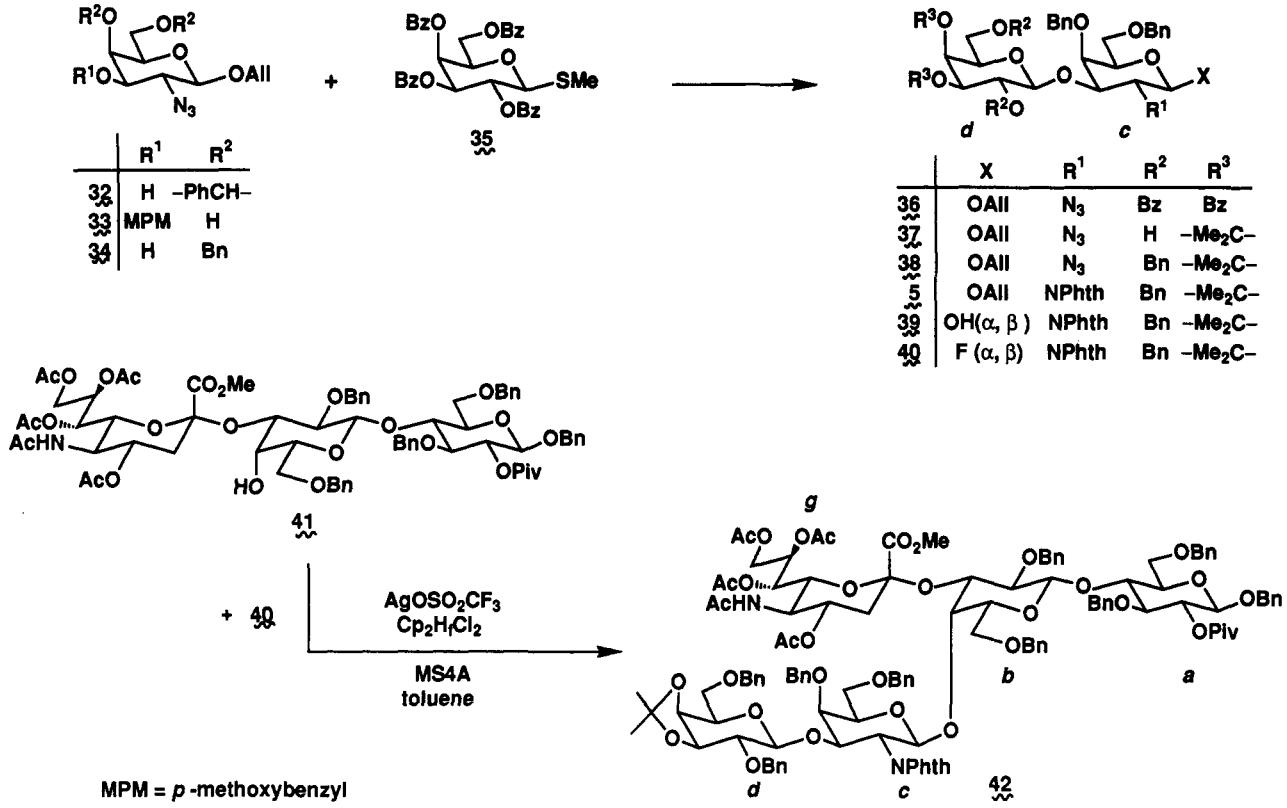
(24) For a discussion of this phenomenon, see: Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155.

(25) Lemieux, R. U.; Takeda, T.; Chung, B. Y. *ACS Symp. Ser.* **1976**, *39*, 90.

(26) For recent examples of the use of various reagents, see: (a) PhHgOTf: Garegg, P. J.; Henrichson, C.; Norberg, T. *Carbohydr. Res.* **1983**, *116*, 162. (b) NBS: Nicolaou, K. C.; Seitz, S. P.; Papahatjis, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 2430. (c) MeOTf: Lönn, H. *Carbohydr. Res.* **1985**, *139*, 105, 115. Lönn, H. *J. Carbohydr. Chem.* **1987**, *6*, 301. (d) $CuBr_2$–Bu_4NBr–Ag(I) or -Hg(II): Sato, S.; Mori, M.; Ito, Y.; Ogawa, T. *Carbohydr. Res.* **1986**, *155*, C6. (e) DMTST: Fügedi, P.; Garegg, P. J. *Carbohydr. Res.* **1986**, *149*, C9. Andersson, F.; Fügedi, P.; Garegg, P. J.; Nashed, M. *Tetrahedron Lett.* **1986**, *27*, 3919. (f) $NOBF_4$: Pozsgay, V.; Jennings, H. J. *J. Org. Chem.* **1987**, *52*, 4635. (g) Sulfenate ester–Me_3SiOTf: Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1987**, *28*, 4701. (h) SO_2Cl_2–TfOH: Lönn, H. *Glycoconjugate J.* **1987**, *4*, 117. (i) PhSeOTf: Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1988**, *29*, 1061. Ito, Y.; Numata, M.; Sugimoto, M.; Ogawa, T. *Carbohydr. Res.* **1990**, *202*, 165. (j) MeSOTf: Dasgupta, F.; Garegg, P. J. *Carbohydr. Res.* **1988**, *177*, C13. (k) IDCP: Veeneman, G. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 275. (l) NIS-TfOH: Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331. Konradsson, P.; Udodong, U. E.; Fraser-Reid, B. *Tetrahedron Lett.* **1990**, *31*, 4313. (m) In situ generation of bromide: Kihlberg, J. O.; Leigh, D. A.; Bundle, D. R. *J. Org. Chem.* **1990**, *55*, 2860.

(27) For example, see ref 6e.

Scheme IV



	R¹	R²
32	H	-PhCH-
33	MPM	H
34	H	Bn

	X	R¹	R²	R³
36	OAll	N_3	Bz	Bz
37	OAll	N_3	H	$-Me_2C-$
38	OAll	N_3	Bn	$-Me_2C-$
5	OAll	NPhth	Bn	$-Me_2C-$
39	OH(α, β)	NPhth	Bn	$-Me_2C-$
40	F (α, β)	NPhth	Bn	$-Me_2C-$

GalNAc derivatives are prepared most conveniently, by Lemieux's azidonitration method, from tri-*O*-acetyl-D-galactal.[28,29] The method is reasonably practical, but several derivatization steps are required to prepare suitable advanced intermediates. This being the case, it was decided to determine if a suitable GalNAc fragment could be prepared from a readily available glucosamine derivative, by way of intramolecular nucleophilic substitution with inversion of configuration.[30] What was done is summarized in Scheme III. Thus, the 4,6-*O*-benzylidene derivative **17**,[31] easily obtained from the corresponding triacetate, was allowed to react with phenyl isocyanate to afford the carbamate **18** nearly quantitatively. Reductive opening of the benzylidene ring of **18** by treatment with $BH_3 \cdot NMe_3/AlCl_3$ in THF[15] afforded the 6-*O*-benzyl derivative **21**. The subsequent intramolecular nucleophilic substitution with inversion of configuration at C-4, effected by employing a modification of Kunz's method,[30] *gave the cyclic carbonate 23 in a single step*. Thus, treatment of **21** with DAST ((diethylamino)sulfur trifluoride) in THF at 50 °C, followed by acidic workup,[32] afforded **23** in 81% yield. The carbonate ester protecting group was then removed without disturbing the phthalimido group, and the product, diol **25**, was converted into the diacetate **3**.

To determine how reactive the axial hydroxy group of the galactose residue would be, the glycosylation of the model compound **30**[33] was attempted. Methods which employ such reagents as MeOTf,[26c] PhSeOTf,[26i] $CuBr_2/Bu_4NBr/AgOTf$,[26d] and NIS/TfOH[26l] were evaluated (Table III). Of these, the method of van Boom and Fraser-Reid[26l] proved to be highly effective in this particular case and an almost quantitative yield of essentially one isomer of disaccharide **31** was obtained (entry 3). The assignment of stereochemistry to **31** was based on the compound's ^1H NMR spectrum, which showed a signal for H-1c at δ 5.273 (d, J = 8.5 Hz).

The *p*-methoxyphenyl glycoside **27** was synthesized in a similar manner, via **20**, **22**, **24**, and **26**. It was then converted into the trichloroacetimidate[35] **29**, via the hemiacetal **28**. Compound **29** also proved to be a quite satisfactory glycosyl donor (entry 5).

Synthesis of the Disaccharide Segment 5 and Model Glycosylation. So far have been described the results of an investigation of strategy A, in which the galactosamine derivative **3** and the disialyl galactose derivative **2** served as synthetic building blocks. The alternative strategy, Strategy B, requires a suitably protected βGal1→3GalNAc fragment which must meet following requirements: (1) It must be possible to specifically protect and deprotect the hydroxy group at the reducing end of the fragment and also those at C-3 and C-4 of the galactose residue without affecting the status of the other hydroxy and amino groups of the fragment. (2) The latent acetamido group of the galactosamine residue must, for stereochemical reasons, be a phthalimido group. The allyl glycoside **5**, which carries an isopropylidene group to temporarily protect the 3,4-diol functionality, met these requirements. A compound in which steric hindrance to approach to the 3-hydroxyl group is minimized, the 2-

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(29) See also: Bovin, N. V.; Zurabyan, S. É.; Ya Kholin, A. *Carbohydr. Res.* **1981**, *98*, 25. Kinzy, W.; Schmidt, R. R. *Liebigs Ann. Chem.* **1985**, 1537.
(30) Kunz, H.; Günther, W. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1086. Günther, W.; Kunz, H. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1050. For similar transformations of *O*-(*N*-benzoyl)carbamates, see: Knapp, S.; Kukkola, P. J.; Sharma, S.; Murali Dhar, T. G.; Naughton, A. B. J. *J. Org. Chem.* **1990**, *55*, 5700.
(31) Sato, S.; Ito, Y.; Ogawa, T. *Carbohydr. Res.* **1986**, *155*, C1.
(32) The yield of cyclic carbonate is critically dependent upon the manner of workup.
(33) Compound **30** was synthesized from benzyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside[34] (see Experimental Section).
(34) Turvey, J. R.; Williams, T. P.; *J. Chem. Soc.* **1962**, 2119.
(35) For a review of the excellent methodology, see: Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212.

azido-2-deoxy derivative **34**, was chosen to be the source of the galactosamine residue. It was prepared from the known cyclic acetal **32**.[36] Thus, **32** was first *p*-methoxybenzylated. The product was subjected to acid-catalyzed deacetalization to yield **33**. Diol **33** was then successively benzylated and treated with DDQ[37] to afford **34** in 75% yield overall from **32**. The thioglycosides **35**[38] was chosen to serve as the source of the galactose residue.

The glycosylation of **34** by **35** in the presence of MeOTf and molecular sieve 4A in toluene at 50 °C gave the desired β-glycoside **36** in excellent yield. A series of straightforward deprotection–protection steps [1. NaOMe/MeOH/CH_2Cl_2; 2. *t*-$BuPh_2SiCl$, imidazole/DMF; 3. $Me_2C(OMe)_2$, CSA/MeCN; 4. Bu_4NF/THF; 5. $PhCH_2Cl$, NaH/DMF] afforded the isopropylidene derivative **38**. The azido group was then reduced by treatment with $LiAlH_4$ in Et_2O. The amine that resulted was then *N*-phthaloylated by a standard method[28] to give **5** in 84% yield overall from **38**. In order to functionalize the reducing end of **5**, the allyl group was removed by successive treatment with Ir(I)[40] and iodine.[41] The hemiacetal **39** so obtained was then converted into the fluoride **40** by treatment with DAST. Compound **40** was obtained as a 2:3 mixture of its α- and β-anomers.

In a model glycosylation, the reaction of the trisaccharide **41**[7f] (the glycosyl acceptor) with **40** in the presence of Cp_2HfCl_2, AgOTf, and molecular sieve 4A[42] afforded the pentasaccharide **42** (56%), together with a small amount (14%) of its α-isomer.

Fluoride was chosen as the leaving group solely to avoid any complications that might arise if a strong acid (e.g., HBr, HCl) were liberated in the presence of an acid-labile acetonide group. It is possible that the efficiency of the glycosidic bond-forming reaction can be improved by using a glycosyl donor that bears a different leaving group. Methyl thioglycoside analogous to **40**, which should be obtainable by slightly modifying the method used to prepare **40**, would appear to be a suitable compound with which to test that possibility.

In any event, **42** represents the fully protected glycan fragment of GM_1. It should prove to be of value in studies directed toward the synthesis of GD_{1a} (IV) and GT_{1a} (V).

Conclusion

Described here are reasonably practical and rational routes to appropriately protected synthetic building blocks which should prove to be valuable in our ongoing project directed toward the synthesis of gangliosides. By applying the techniques described here and the technology developed earlier,[6,9,10,12,20] the synthesis of essentially all members of the ganglioside family now appears to be possible. Although problems, which are by no means trivial, still remain, including purely tactical ones which involve the order in which the sugar residues should be assembled and precisely which protecting groups should be employed in the advanced stages of a synthesis, all major regio- and stereochemical problems that could arise in a synthesis of even an especially complex molecule like GQ_{1b} have been solved in principle. Therefore, we conclude that the stage is now set to begin systematic investigations directed toward the synthesis of polysialogangliosides.

Experimental Section

General. Melting points were determined with a Büchi 510 melting point apparatus and are uncorrected. Optical rotations of $CHCl_3$ solutions were measured at 20 ± 3 °C with either a Perkin-Elmer Model 241 MC or a JASCO DIP 310 polarimator. The wavelength of the light used was that of the D line of sodium. Unless otherwise noted, ^1H NMR spectra of $CDCl_3$ solutions were recorded with either a JEOL GX500 (500-MHz) or a FX 90Q (90-MHz) spectrometer. Chemical shifts are expressed in ppm downfield (δ) from the signal for internal Me_4Si. ^{19}F NMR spectra of $CDCl_3$ solutions were recorded with a JEOL FX-100 spectrometer. Chemical shifts are expressed in ppm upfield (δ) from external CCl_3F and are referred indirectly to an internal standard of C_6F_6 (δ = 162.9). IR spectra of Nujol mulls were recorded with a Shimadzu IR-430. Unless noted otherwise, Merck silica gel (70–230 mesh) was used for column chromatography. Wakogel C-300 (200–300 mesh) was used for flash chromatography. Analytical TLC was performed with glass plates coated with silica gel 60 F_{254} (Merck). Unless indicated otherwise, a compound's retardation factor (R_f) is that observed upon development of the plate with the same solvent that was used as the eluant in the purification of the compound by column or flash chromatography. Preparative TLC was performed with 20-cm × 20-cm glass plates coated with a 0.5-mm thick layer of silica gel (Merck). Reaction solvents were distilled under N_2 from various drying agents: 1,2-dichloroethane, CCl_4, *t*-BuOH, pyridine, MeCN, $MeNO_2$, and benzene from CaH_2; toluene from Na, Et_2O from $LiAlH_4$, and THF from sodium benzophenone ketyl. DMF, DMSO, and $(Me_2N)_3P$ were distilled under reduced pressure from CaH_2. Powdered molecular sieve was activated by heating in vacuo at 180–200 °C prior to use. All reactions were performed under an atmosphere of dry N_2. Reaction mixtures were usually processed by washing with water, back-extracting the water layer with the organic solvent specified, washing the combined organic layers with saturated brine, drying ($MgSO_4$), and then concentrating the combined organic layers in vacuo, in that order.

Methyl 5-Acetamido-8,9-*O*-benzylidene-2,3-didehydro-3,5-dideoxy-D-*glycero*-D-*galacto*-2-nonulopyranosonate (10). A solution of **9** (2.239 g, 7.33 mmol), benzaldehyde dimethyl acetal (1.3 mL, 8.7 mmol), (±)-10-camphorsulfonic acid (CAS, 50 mg, 0.22 mmol), and DMF (20 mL) was stirred at rt. After 3 h, the mixture was made slightly basic (phenolphthalein indicator) by adding 1 M methanolic NaOMe (ca. 0.25 mL). The now alkaline mixture was immediately neutralized by adding a drop of HOAc and was then concentrated in vacuo. The residue was purified by column chromatography on silica gel (toluene/acetone (2:1)) to afford 2.452 g (85%) of **10**: R_f = 0.31; ^1H NMR (90 MHz; $CDCl_3/CD_3OD$ (5:1)) δ 5.97 (d, *J* = 2.4 Hz, H-3), 5.91 and 5.80 (s, PhC*H*), 3.79 (s, CO_2Me), 2.08 and 2.05 (s, NAc); IR 3600, 3330, 1720, 1650 cm^{-1}. Anal. Calcd for $C_{19}H_{23}NO_8$: C, 58.01; H, 5.89; N, 3.45. Found: C, 57.85; H, 5.96; N, 3.50.

Methyl 5-Acetamido-4,7-di-*O*-benzyl-8,9-*O*-benzylidene-2,3-didehydro-3,5-dideoxy-D-*glycero*-D-*galacto*-2-nonulopyranosonate (11). To a cold (0 °C) stirred solution of **10** (1.404 g, 3.569 mmol), BnBr (1.5 mL, 13 mmol), and 10:1 THF/DMSO (33 mL) under N_2 were successively added CaH_2 (0.82 g, 20 mmol), Bu_4NI (65 mg, 0.18 mmol), and powdered KOH (1.00 g, 17.8 mmol). The mixture was stirred at 0 °C for 4 h and then was allowed to warm to rt. After 16 h at rt, the mixture was diluted with EtOAc and was again cooled to 0 °C. With stirring, water was then carefully added. The two liquid layers were separated. The aqueous layer was acidified by adding 2 N aqueous HCl and then was extracted twice with EtOAc. The combined organic layers were processed as usual. The residue was suspended in MeOH (20 mL), and the suspension was treated with excess ethereal CH_2N_2. The mixture was then concentrated in vacuo. The residue was purified by silica gel column chromatography (toluene/acetone (86:14)) to afford 1.433 g (70%) of **11**: R_f = 0.42

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(toluene/acetone (3:1)); ^{1}H NMR (500 MHz) δ 6.094 and 6.079 (d, J = 3.1, 2.8 Hz, respectively, H-3), 5.947 and 5.741 (s, PhC*H*), 3.785 and 3.782 (s, CO_2Me), 1.639 and 1.601 (s, NAc). Anal. Calcd for $C_{33}H_{35}NO_8$: C, 69.10; H, 6.15; N, 2.44. Found: C, 69.08; H, 6.19; N, 2.41.

Methyl 5-Acetamido-4,7,9-tri-*O*-benzyl-2,3-didehydro-3,5-dideoxy-D-*glycero*-D-*galacto*-2-nonulopyranosonate (12). To an ice-cold mixture of **11** (1.408 g, 2.454 mmol), molecular sieve 4A (8.0 g), and THF (25 mL) under N_2 were added successively BH_3·NMe_3 (1.10 g, 15.1 mmol) and freshly pulverized $AlCl_3$ (1.98 g, 14.9 mmol). The mixture was stirred at 0 °C for 0.5 h and then at rt for 2 h. It was then diluted with Et_2O. Ice/water and 2 N aqueous HCl (10 mL) were added, and the mixture was filtered through Celite. The filtrate was extracted twice with Et_2O, and the combined extracts were processed as usual. MeOH was added to the residue, and the mixture was exposed to high vacuum. This treatment was repeated three times. Silica gel column chromatography (toluene/acetone (4:1)) of the residue afforded 1.175 g (83%) of **12**: R_f = 0.35 (toluene/acetone (2:1)); $[\alpha]_D$ +6.7° (*c* 0.9); ^{1}H NMR (500 MHz) δ 6.118 (d, J = 3.4 Hz, H-3), 5.094 (d, J = 7.0 Hz, N*H*Ac), 4.699 (dd, J = 7.3, 4.6 Hz, H-6), 4.366 (dd, J = 6.1, 3.4 Hz, H-4), 4.148 (m, H-8), 4.026 (q, J = 7 Hz, H-5), 3.907 (dd, J = 5.2, 4.6 Hz, H-7), 3.749 (s, CO_2Me), 3.744 (dd, J = 9.5, 4.9 Hz, H-9), 3.684 (dd, J = 9.5, 5.5 Hz, H-9′), 2.731 (d, J = 6.7 Hz, OH), 1.679 (s, NAc); IR 3300, 1730, 1660 cm^{-1}. Anal. Calcd for $C_{33}H_{37}NO_8$: C, 68.85; H, 6.48; N, 2.43. Found: C, 68.68; H, 6.49; N, 2.42.

Compound **12** was converted into the corresponding 8-*O*-OAc derivative (Ac_2O/pyridine): R_f = 0.40 (EtOAc/*n*-hexane (2:1)); ^{1}H NMR (500 MHz) δ 6.109 (d, J = 4.3 Hz, H-3), 5.397 (m, H-8), 5.160 (d, J = 7.6 Hz, N*H*Ac), 4.617 (dd, J = 8.5, 3.4 Hz, H-6), 4.190 (m, H-5), 3.925 (dd, J = 10.1, 6.1 Hz, H-9), 3.770 (s, CO_2Me), 3.670 (dd, J = 10.1, 5.2 Hz, H-9′), 1.991 (s, OAc), 1.710 (s, NAc). Anal. Calcd for $C_{35}H_{40}NO_9$: C, 68.06; H, 6.36; N, 2.27. Found: C, 67.80; H, 6.34; N, 2.18.

Methyl *O*-[Methyl (5-acetamido-4,7,8,9-tetra-*O*-benzyl-3,5-dideoxy-3-(phenylthio)-D-*erythro*-α-L-*gluco*-2-nonulopyranosid)onate]-(2→8)-5-acetamido-4,7,9-tri-*O*-benzyl-2,3-didehydro-3,5-dideoxy-D-*glycero*-D-*galacto*-2-nonulopyranosonate (6). A solution of **8** (1.477 g, 1.728 mmol), **12** (1.484 g, 2.578 mmol), and CCl_4 (30 mL) was dropped drop-by-drop to a cold (−20 °C) stirred suspension of $Hg(CN)_2$ (700 mg, 2.77 mmol), $HgBr_2$ (320 mg, 0.51 mmol), molecular sieve 4A (4 g), and CCl_4 (10 mL). The mixture was stirred at −20 °C for 0.5 h, at 0 °C for 1 h, and at rt for 18 h, and then it was diluted with $CHCl_3$ and was filtered through Celite. The filtrate was washed with 10% aqueous KI (100 mL). Back-extraction, the usual processing of the combined organic layers, and chromatographic purification of the residue on silica gel (toluene/EtOAc (3:1); then *n*-hexane/acetone (4:1); then *n*-hexane/acetone (2:1)) afforded 1.488 g (64%) of **6** together with recovered **12** (810 mg).

Compound 6: R_f = 0.30 (*n*-hexane/acetone (2:1)); $[\alpha]_D$ +12.0° (*c* 0.6); ^{1}H NMR (500 MHz) δ 5.973 (d, J = 2.8 Hz, H-3g), 3.643 and 3.599 (s, 2 CO_2Me), 3.480 (d, J = 10.4 Hz, H-3h), 1.777 and 1.693 (s, 2 NAc); IR 1730, 1660 cm^{-1}. Anal. Calcd for $C_{79}H_{84}N_2O_{16}S$: C, 70.31; H, 6.27; N, 2.08. Found: C, 70.02; H, 6.28; N, 2.00.

Methyl *O*-[Methyl (5-acetamido-4,7,8,9-tetra-*O*-benzyl-3,5-dideoxy-3-(phenylthio)-D-*erythro*-α-L-*gluco*-2-nonulopyranosid)onate]-(2→8)-5-acetamido-4,7,9-tri-*O*-benzyl-3,5-dideoxy-3-(phenylthio)-D-*erythro*-β-L-*gluco*-2-nonulopyranosonate (4d). To an ice-cold solution of **6** (1.197 g, 0.887 mmol) and 8:1 MeCN/water (27 mL) was added *N*-bromosuccinimide (116 mg, 0.933 mmol). The mixture was stirred at 0 °C for 1 h and at rt for 30 min, and then it was concentrated in vacuo. The residue was passed through a short column of silica gel (*n*-hexane/acetone (2:1)) to afford crude **7** (ca. 1.40 g; two diastereomers, R_f = 0.28 and 0.23). To a cold (0 °C) stirred solution of PhSK [generated from thiophenol (185 μL, 1.80 mmol) and *t*-BuOK (1.30 mmol)] in 1:1 THF/*t*-BuOH (10 mL) was added a solution of the crude **7** described above in THF. The mixture was stirred at 0 °C for 2 h, and then it was diluted with Et_2O and was washed with water. The aqueous wash was back-extracted with Et_2O. The combined organic layers were then washed with cold 0.2 N aqueous NaOH (50 mL) and were processed as usual. Toluene was added to the residue, and the mixture was exposed to high vacuum. The residue was again dissolved in toluene (20 mL). To the cold (0 °C) solution was added a solution of DBU (14 mg, 0.09 mmol) in toluene (0.9 mL). The mixture was stirred at 0 °C for 2 h and at rt for 0.5 h. Then it was diluted with EtOAc and was washed with 0.1 N aqueous HCl. Processing of the organic layers as usual and purification of the residue by column chromatography on silica gel (*n*-hexane/EtOAc (1:1)) afforded 1.050 g (80%) of **4d**, an oil which crystallized on standing at −40 °C: mp 74–76 °C; R_f = 0.30; $[\alpha]_D$ +29.7° (*c* 1.0); ^{1}H NMR (500 MHz) δ 3.568 and 3.486 (s, 2 CO_2Me), 3.521 (d, J = 10.4 Hz, H-3h), 1.672 and 1.538 (s, 2 NAc); IR 1750, 1670 cm^{-1}. Anal. Calcd for $C_{85}H_{90}N_2O_{17}S_2$: C, 69.18; H, 6.15; N, 1.90. Found: C, 68.85; H, 6.12; N, 1.87.

Methyl *O*-[Methyl (5-acetamido-4,7,8,9-tetra-*O*-benzyl-3,5-dideoxy-3-(phenylthio)-D-*erythro*-α-L-*gluco*-2-nonulopyranosid)onate]-(2→8)-5-acetamido-4,7,9-tri-*O*-benzyl-2,3,5-trideoxy-2-fluoro-3-(phenylthio)-D-*erythro*-α- and -β-L-*gluco*-2-nonulopyranosonate (4a). To a cold (−40 °C) stirred solution of **4d** (109 mg, 73.5 μmol) in toluene was added (diethylamino)sulfur trifluoride (DAST; 50 μL, 0.38 mmol). The mixture was allowed to gradually warm to rt over 2 h, and then it was diluted with EtOAc. The reaction was quenched by carefully adding aqueous $NaHCO_3$. Then the mixture was processed as usual. The residue was purified by preparative TLC (*n*-hexane/EtOAc (3:2)) to afford 57.6 mg (53%) of β-**4a** and 46.3 mg (43%) of α-**4a**. β-**4a**: R_f = 0.35 (*n*-hexane/EtOAc (1:1)); ^{1}H NMR (500 MHz) δ 3.689 and 3.492 (s, 2 CO_2Me), 1.690 and 1.643 (s, 2 NAc); ^{19}F NMR δ 127.4 (d, J = 27.4 Hz). α-**4a**: R_f = 0.31; ^{1}H NMR (500 MHz) 3.883 and 3.597 (s, 2 CO_2Me), 3.469 (d, J = 9.8 Hz, H-3h), 3.329 (dd, J = 13.6, 9.0 Hz, H-3g), 1.674 and 1.492 (s, 2 NAc); ^{19}F NMR δ 108.5 (d, J = 13.6 Hz).

Methyl *O*-[Methyl (5-acetamido-4,7,8,9-tetra-*O*-benzyl-3,5-dideoxy-3-(phenylthio)-D-*erythro*-α-L-*gluco*-2-nonulopyranosid)onate]-(2→8)-5-acetamido-4,7,9-tri-*O*-benzyl-2-chloro-2,3,5-trideoxy-3-(phenylthio)-D-*erythro*-β-L-*gluco*-2-nonulopyranosonate (4c). To a cold (−78 °C) solution of **4d** (51.6 mg, 35 μmol), CCl_4 (28 μL, 0.29 mmol), and THF (2 mL) was added $(Me_2N)_3P$ (50 μL, 0.28 mmol). The stirred mixture was allowed to gradually warm to rt (the mixture became turbid at ca. −30 °C) and was kept there for 18 h. The suspension that resulted was diluted with Et_2O, and then it was washed with ice-cold aqueous $NaHCO_3$ and processed as usual. Purification of the residue by flash chromatography (toluene/EtOAc (3:1)) afforded 43.6 mg (84%) of **4c**: R_f = 0.40 (toluene/EtOAc (2:1)); ^{1}H NMR (500 MHz) δ 4.914 (d, J = 11.0 Hz, N*H*Ac), 3.640 and 3.500 (s, 2 CO_2Me), 2.662 (d, J = 11.3 Hz, H-3g or -3h), 1.679 and 1.555 (s, 2 NAc).

Benzyl *O*-[Methyl (5-acetamido-4,7,8,9-tetra-*O*-benzyl-3,5-dideoxy-3-(phenylthio)-D-*erythro*-α-L-*gluco*-2-nonulopyranosid)onate]-(2→8)-*O*-[methyl (5-acetamido-4,7,9-tri-*O*-benzyl-3,5-dideoxy-3-(phenylthio)-D-*erythro*-α-L-*gluco*-2-nonulopyranosid)onate]-(2→3)-*O*-(2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranoside (1). Method A (from **4d** via bromide **4b**). To a cold (−78 °C) stirred solution of **4d** (427 mg, 0.289 mmol), CBr_4 (480 mg, 1.45 mmol), and THF (3 mL) was added, drop-by-drop, freshly distilled $(Me_2N)_3P$ (210 μL, 1.16 mmol). The lemon-yellow suspension that resulted was allowed to warm to rt over 3 h and was kept there for 1 h. The now milky white suspension was worked up in the manner described in the preparation of **4c** to afford crude **4b**, R_f = 0.36 (*n*-hexane/EtOAc (1:1)).

To a cold (0 °C) stirred mixture of $Hg(CN)_2$ (220 mg, 0.871 mmol), $HgBr_2$ (105 mg, 0.291 mmol), molecular sieve 4A (1.0 g), and CCl_4 (5 mL) was added, drop-by-drop, a solution of the crude **4b** described above, **13** (254 mg, 0.290 mmol), and CCl_4 (5 mL). The mixture was stirred at 0 °C for 1 h and then at rt for 18 h. Processing in the manner described in the preparation of **6**, followed by column chromatography of the residue, first on Bio Beads S-X3 (toluene) and then on silica gel (*n*-hexane/EtOAc (3:2)), afforded 321 mg (48%) of **1** and 5.5 mg (0.8%) of its β-isomer.

Compound **1**: R_f = 0.28; $[\alpha]_D$ +14.9° (*c* 1.0); ^{1}H NMR (500 MHz) δ 5.059 (dd, J = 9.2, 8.0 Hz, H-2a), 4.399 (d, J = 7.9 Hz, H-1b or -1a), 3.757 and 3.609 (s, 2 CO_2Me), 3.466 and 3.268 (d, J = 9.8, 10.1 Hz, respectively, H-3g,3h), 1.652 and 1.530 (s, 2 NAc), 1.099 (s, Me_3C); IR 1710, 1680 cm^{-1}. Anal. Calcd for

$C_{136}H_{148}N_2O_{28}S_2$: C, 70.48; H, 6.39; N, 1.21. Found: C, 70.59; H, 6.44; N, 1.22.

β-Isomer of 1: R_f = 0.51; $[\alpha]_D$ −12.0° (c 0.6); ^1H NMR (500 MHz) δ 5.077 (dd, J = 9.2, 7.9 Hz, H-2a), 4.392 (d, J = 7.6 Hz, H-1b or -1a), 3.568 and 3.381 (s, 2 CO_2Me), 1.747 and 1.413 (s, 2 NAc). Anal. Calcd for $C_{136}H_{148}N_2O_{28}S_2 \cdot H_2O$: C, 69.78; H, 6.46; N, 1.20. Found: C, 69.70; H, 6.57; N, 1.10.

Method B (from **4c**). A mixture of **4c** (40.0 mg, 26.8 μmol), **13** (28 mg, 32 μmol), $Hg(CN)_2$ (22 mg, 87 μmol), $HgBr_2$ (10 mg, 28 μmol), molecular sieve 4A (0.15 g), and CCl_4 (2.5 mL) was stirred at 40 °C for 18 h. Processing and chromatographic purification of the residue in the manner described in method A afforded 18.5 mg (29%) of **1** and 0.9 mg (1.4%) of its β-isomer.

Method C (from **4a**). To a cold (0 °C) stirred mixture of **13** (26 mg, 30 μmol), $AgOSO_2CF_3$ (20 mg, 79 μmol), Cp_2ZrCl_2 (23 mg, 79 μmol), molecular sieve 4A (0.15 g), and CCl_4 (0.5 mL) was added a solution of fluoride **4a** (α-isomer; 38.8 mg, 26.3 μmol) in CCl_4 (1.5 mL). The mixture was stirred at 0 °C for 0.5 h and at rt for 18 h. It was then diluted with EtOAc. Ice and aqueous $NaHCO_3$ were added. After 10 min of stirring, the mixture was filtered through Celite. The filtrate was processed as usual. Column chromatography of the residue afforded 20.1 mg (33%) of **1** and 2.6 mg (4%) of its β-isomer.

Compound **1** was converted into the corresponding *O*-acetyl derivatives (Ac_2O, 4-(dimethylamino)pyridine(DMAP)/pyridine; rt, 18 h): ^1H NMR (500 MHz) δ 5.392 (d, J = 3.5 Hz, H-4b), 5.047 (dd, J = 9.0, 8.5 Hz, H-2a), 3.881 and 3.533 (s, 2 CO_2Me), 3.122 (d, J = 10.7 Hz, H-3g or -3h), 1.884 (s, OAc). The spectrum of the acetate derived from the β-isomer showed characteristic signals at δ 5.330 (d, J = 3.5 Hz, H-4b), 5.090 (dd, J = 9.3, 8.1 Hz, H-2a), 3.538 and 3.367 (s, 2 CO_2Me), 1.863 (s, OAc).

Benzyl 6-*O*-Pivaloyl-β-D-galactopyranoside (15). To a cold (0 °C) stirred solution of **14** (666 mg, 2.47 mmol) in 7:1 THF/pyridine (8 mL) was added pivaloyl chloride (350 μL, 2.84 mmol). The mixture was stirred at 0 °C for 4 h and at rt for 0.5 h, and then it was diluted with EtOAc and water. The mixture was extracted three times with EtOAc. The usual processing of the combined extracts and purification of the residue by silica gel column chromatography (CH_2Cl_2/acetone (3:2)) afforded 449 mg (51%) of **15**: R_f = 0.39 (CH_2Cl_2/acetone (1:1)); $[\alpha]_D$ −31.3° (c 0.7); ^1H NMR (500 MHz, 20:1 $CDCl_3$–D_2O) δ 4.314 (m, H-6,6′), 4.267 (d, J = 7.6 Hz, H-1), 3.797 (dd, J = 3.4, 0.9 Hz, H-4), 3.684 (dd, J = 9.8, 7.6 Hz, H-2), 3.594 (td, J = 6.7, 0.9 Hz, H-5), 3.514 (dd, J = 9.8, 3.4 Hz, H-3), 1.220 (s, Me_3C); IR 3450, 1730 cm^{-1}.

Benzyl 2-*O*-(*p*-Methylbenzoyl)-6-*O*-pivaloyl-β-D-galactopyranoside (16). A mixture of **15** (426 mg, 1.20 mmol), 2,2-dimethoxypropane (240 μL, 1.95 mmol), (±)-10-camphorsulfonic acid (CSA, 5 mg, 0.02 mmol), and MeCN (10 mL) was stirred at rt for 18 h. The mixture was then diluted with EtOAc and was washed with aqueous $NaHCO_3$. Back-extraction of the aqueous layer with EtOAc followed by the usual processing of the combined organic layers afforded the crude acetonide. This was dissolved in pyridine (5 mL). To the stirred solution were added DMAP (10 mg, 0.08 mmol) and *p*-methylbenzoyl chloride (0.25 mL, 1.9 mmol). The mixture was stirred at rt for 3 h, and then MeOH (0.5 mL) was added. The mixture was stirred for 0.5 h and then was diluted with Et_2O. Toluene was added to the residue that was obtained by the usual processing, and the mixture was exposed to high vacuum. The oily residue that resulted was dissolved in 1:1 CH_2Cl_2/MeOH (12 mL) that contained (±)-10-camphorsulfonic acid (30 mg, 0.13 mmol). The solution was gently refluxed for 10 h, and then it was diluted with EtOAc and aqueous $NaHCO_3$ and was processed as usual. Purification of the residue by column chromatography on silica gel (toluene/EtOAc (2:1)) afforded 552 mg (97%) of **16**: mp 145–147 °C (hexane/Et_2O); R_f = 0.26; $[\alpha]_D$ −43.6° (c 1.0); ^1H NMR ($CDCl_3$/D_2O (20:1)) δ 5.214 (dd, J = 9.5, 8.1 Hz, H-2), 4.567 (d, J = 8.1 Hz, H-1), 4.444 (dd, J = 11.5, 6.0 Hz, H-6), 4.361 (dd, J = 11.5, 6.8 Hz, H-6′), 3.897 (d, J = 3.5 Hz, H-4), 3.739 (dd, J = 9.5, 3.5 Hz, H-3), 3.703 (dd, J = 6.8, 6.0 Hz, H-5), 2.430 (s, MeC_6H_4), 1.243 (s, Me_3C); IR 3500, 1730, 1705 cm^{-1}. Anal. Calcd for $C_{26}H_{32}O_8$: C, 66.09; H, 6.82. Found: C, 66.12; H, 6.83.

Benzyl *O*-[Methyl (5-acetamido-4,7,8,9-tetra-*O*-benzyl-3,5-dideoxy-3-(phenylthio)-D-*erythro*-α-L-*gluco*-2-nonulopyranosid)onate]-(2→8)-*O*-[methyl (5-acetamido-4,7,9-tri-*O*-benzyl-3,5-dideoxy-3-(phenylthio)-D-*erythro*-α-L-*gluco*-2-nonulopyranosid)onate]-(2→3)-2-*O*-(*p*-methylbenzoyl)-6-*O*-pivaloyl-β-D-galactopyranoside (2). The bromide **4b** (generated from 46.6 mg, 31.6 μmol of **4d**) was allowed to react with **16** (22.8 mg, 48.2 μmol) in the presence of $Hg(CN)_2$ (26 mg, 100 μmol) and $HgBr_2$ (12 mg, 33 μmol) in the manner described in the preparation of **1** (method A). Workup and purification of the residue, first by column chromatography on Bio Beads S-X3 (toluene) and then by preparative TLC (toluene/EtOAc (2:1)), afforded 20.1 mg (33%) of **2**: R_f = 0.41; $[\alpha]_D$ +12.3° (c 0.7); ^1H NMR (500 MHz) δ 5.339 (dd, J = 9.5, 8.1 Hz, H-2d), 3.657 and 3.629 (s, 2 CO_2Me), 3.435 and 3.205 (d, J = 9.9, 8.8 Hz, respectively, H-3e, -3f), 2.359 (s, MeC_6H_4), 1.664 and 1.600 (s, 2 NAc), 1.217 (s, Me_3C); IR 1730, 1680 cm^{-1}. Anal. Calcd for $C_{111}H_{120}N_2O_{24}S_2$: C, 69.07; H, 6.27; N, 1.45. Found: C, 68.97; H, 6.36; N, 1.49.

Compound **2** was converted, in the same manner as was **1**, into its *O*-acetyl derivative: ^1H NMR (500 MHz) δ 5.433 (dd, J = 9.9, 8.4 Hz, H-2d), 5.311 (d, J = 3.4 Hz, H-4d), 3.824 and 3.456 (s, 2 CO_2Me), 3.421 and 2.963 (d, J = 10.3, 10.6 Hz, respectively, H-3e, -3f), 2.356 (s, MeC_6H_4), 1.781, 1.601, and 1.587 (s, 3 Ac), 1.242 (s, Me_3C).

Methyl 4,6-*O*-Benzylidene-2-deoxy-3-*O*-(phenylcarbamoyl)-2-phthalimido-1-thio-β-D-glucopyranoside (18). A solution of **17** (2.958 g, 6.920 mmol), phenyl isocyanate (1.1 mL, 10 mmol), pyridine (0.80 mL, 9.9 mmol), DMAP (ca. 10 mg), and 1,2-dichloroethane (30 mL) was stirred at 50 °C for 4 h. The mixture was then concentrated in vacuo. The residue was purified by silica gel column chromatography (toluene/EtOAc (9:1)) to afford 3.763 g (99%) of **18**: mp 189–190 °C (Et_2O); R_f = 0.51 (toluene/EtOAc (4:1)); $[\alpha]_D$ −18.0° (c 0.8); ^1H NMR (500 MHz) δ 5.915 (t, J = 9.5 Hz, H-3), 5.565 (s, PhC*H*), 5.525 (d, J = 10.7 Hz, H-1), 4.454 (dd, J = 10.7, 9.5 Hz, H-2), 2.190 (s, SMe); IR 1780, 1740, 1715 cm^{-1}. Anal. Calcd for $C_{29}H_{26}N_2O_7S$: C, 63.73; H, 4.80; N, 5.12. Found: C, 63.55; H, 4.82; N, 5.10.

Methyl 6-*O*-Benzyl-2-deoxy-3-*O*-(phenylcarbamoyl)-2-phthalimido-1-thio-β-D-glucopyranoside (21). Compound **18** (3.583 g, 6.556 mmol) was treated with $BH_3 \cdot NMe_3$ (3.80 g, 52 mmol) and $AlCl_3$ (7.00 g, 52 mmol) in the manner described in the preparation of compound **12** (rt, 18 h). Workup and column chromatography of the residue on silica gel (toluene/EtOAc (3:1)) afforded 2.580 g (72%) of **21**: mp 148–150 °C (Et_2O); R_f = 0.29; $[\alpha]_D$ +19.4° (c 0.8); ^1H NMR (500 MHz) δ 5.669 (d, J = 10.4, 8.5 Hz, H-3), 5.399 (d, J = 10.4 Hz, H-1), 4.385 (t, J = 10.4 Hz, H-2), 3.386 (bs, OH), 2.158 (s, SMe); IR 1780, 1740, 1710 cm^{-1}. Anal. Calcd for $C_{29}H_{28}N_2O_7S \cdot 0.5H_2O$: C, 62.47; H, 5.24; N, 5.02. Found: C, 62.21; H, 5.36; N, 5.30.

Methyl 6-*O*-Benzyl-3,4-*O*-carbonyl-2-deoxy-2-phthalimido-1-thio-β-D-galactopyranoside (23). A solution of **21** (282 mg, 0.514 mmol), DAST (110 μL, 0.90 mmol), and THF (8 mL) was stirred at 50 °C for 5 h. It was then cooled to 0 °C and 2 N aqueous HCl (2 mL) was added. The stirred mixture was allowed to warm to rt over 0.5 h. It was then diluted with EtOAc and was processed in the usual manner. Column chromatography of the residue on silica gel (toluene/EtOAc (4:1, then 2:1)) afforded 192 mg (82%) of **23**: mp 154–155 °C (Et_2O); R_f = 0.40 (toluene/EtOAc (3:1)); $[\alpha]_D$ +43.3° (c 0.8); ^1H NMR (500 MHz) δ 5.414 (dd, J = 7.9, 6.7 Hz, H-3), 5.001 (d, J = 10.7 Hz, H-1), 4.936 (dd, J = 6.7, 2.1 Hz, H-4), 4.410 (dd, J = 10.7, 7.9 Hz, H-2), 4.185 (m, H-5), 3.851 (dd, J = 9.8, 6.1 Hz, H-6), 3.802 (dd, J = 9.8, 7.0 Hz, H-6′), 2.142 (s, SMe); IR 1800, 1780, 1715 cm^{-1}. Anal. Calcd for $C_{23}H_{21}NO_7S$: C, 60.66; H, 4.65; N, 3.08. Found: C, 60.46; H, 4.71; N, 3.16.

Methyl 6-*O*-Benzyl-2-deoxy-2-phthalimido-1-thio-β-D-galactopyranoside (25). To a cold (0 °C) stirred solution of **23** (953 mg, 2.09 mmol) in 3:1 MeOH/CH_2Cl_2 (20 mL) was added 1 M methanolic NaOMe (0.1 mL). The mixture was allowed to stand at 0 °C for 1 h, and then it was neutralized by adding Amberlyst 15 resin. The resin was removed by filtration. The filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (toluene/EtOAc (1:1)) to afford 846 mg (94%) of **25**: R_f = (0.33); ^1H NMR (500 MHz) δ 5.210 (d, J = 10.1 Hz, H-1), 4.501 (t, J = 10.0 Hz, H-2), 4.431 (dd, J = 10.4, 3.1 Hz, H-3), 4.193 (d, J = 3.1 Hz, H-4), 2.174 (s, SMe); IR 3500, 1775, 1710 cm^{-1}. Anal. Calcd for $C_{22}H_{23}NO_6S$: C, 61.52; H, 5.40; N, 3.26. Found: C, 61.72; H, 5.48; N, 3.15.

Methyl 3,4-Di-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-galactopyranoside (3). A solution of diol **25**

(535 mg, 1.25 mmol), Ac_2O (1 mL), pyridine (1 mL), DMAP (5 mg), and CH_2Cl_2 (10 mL) was stirred at rt for 18 h. The mixture was then concentrated in vacuo. Xylene was added to the residue, and the mixture was exposed to high vacuum. The residue was passed through a short column of silica gel (*n*-hexane/EtOAc (2:1)) to afford 634 mg (99%) of the diacetate **3**: R_f = 0.45; $[\alpha]_D$ +3.5° (*c* 1.0); ^1H NMR (90 MHz) δ 5.87 (dd, *J* = 11.0, 3.4 Hz, H-3), 5.60 (d, *J* = 3.4 Hz, H-4), 5.36 (d, *J* = 10.6 Hz, H-1), 4.61 (t, *J* = 11 Hz, H-2), 2.18, 2.10, and 1.84 (s, 2 OAc and SMe); IR 1780, 1730, 1700 cm^{-1}. Anal. Calcd for $C_{26}H_{27}NO_8S$: C, 60.81; H, 5.30; N, 2.73. Found: C, 61.20; H, 5.44; N, 2.61.

***p*-Methoxyphenyl 4,6-*O*-Benzylidene-2-deoxy-3-*O*-(phenylcarbamoyl)-2-phthalimido-β-D-glucopyranoside (20).** A solution of **19** (10.82 g, 21.62 mmol), phenyl isocyanate (2.8 mL, 26 mmol), Et_3N (6.0 mL, 43 mmol), and 1,2-dichloroethane (40 mL) was stirred at rt for 5 h. The mixture was then concentrated in vacuo. The residue was purified in the manner described in the preparation of **18**. Subsequent recrystallization (Et_2O) afforded 11.95 g (89%) of **20**: white needles; mp 195–196 °C; R_f = 0.54 (toluene/EtOAc (83:17)); $[\alpha]_D$ +29.1° (*c* 1.1); ^1H NMR (500 MHz) δ 6.011 (d, *J* = 8.5 Hz, H-1), 5.926 (dd, *J* = 10.4, 8.9 Hz, H-3), 5.577 (s, PhC*H*), 4.606 (dd, *J* = 10.4, 8.5 Hz, H-2), 3.725 (s, OMe), IR 3330, 1780, 1715, 1600 cm^{-1}. Anal. Calcd for $C_{35}H_{30}N_2O_9$: C, 67.52; H, 4.86; N, 4.50. Found: C, 67.52; H, 4.88; N, 4.47.

***p*-Methoxyphenyl 6-*O*-Benzyl-2-deoxy-3-*O*-(phenylcarbamoyl)-2-phthalimido-β-D-glucopyranoside (22).** Compound **20** (5.940 g, 9.59 mmol) was converted into **22** (4.690 g, 78%) in the manner described in the preparation of **21**. **22**: R_f = 0.40 (toluene/EtOAc (3:1)); $[\alpha]_D$ + 49.6° (*c* 1.0); ^1H NMR (500 MHz) δ 5.889 (d, *J* = 8.5 Hz, H-1), 5.671 (dd, *J* = 10.7, 8.6 Hz, H-3), 4.552 (dd, *J* = 10.7, 8.5 Hz, H-2), 3.718 (s, OMe); IR 1780, 1715, 1600 cm^{-1}. Anal. Calcd for $C_{35}H_{32}N_2O_9$: C, 67.30; H, 5.16; N, 4.48. Found: C, 67.23; H, 5.16; N, 4.33.

***p*-Methoxyphenyl 6-*O*-Benzyl-3,4-*O*-carbonyl-2-deoxy-2-phthalimido-β-D-galactopyranoside (24).** Compound **22** (3.824 g, 6.151 mmol) was converted into **24** (2.640 g, 81%) in the manner described in the preparation of **23**. **24**: mp 132–133 °C (Et_2O); R_f = 0.33 (toluene/EtOAc (4:1)); $[\alpha]_D$ +7.4° (*c* 0.7); ^1H NMR (500 MHz) δ 5.471 (d, *J* = 8.2 Hz, H-1), 5.404 (t, *J* = 7 Hz, H-3), 4.945 (dd, *J* = 7.0, 2.1 Hz, H-4), 4.626 (dd, *J* = 8.2, 7.3 Hz, H-2), 4.261 (td, *J* = 6.5, 2.1 Hz, H-5), 3.885 (dd, *J* = 9.8, 6.4 Hz, H-6), 3.853 (dd, *J* = 9.8, 6.7 Hz, H-6′), 3.715 (s, OMe); IR 3550, 3400, 1775, 1710 cm^{-1}. Anal. Calcd for $C_{29}H_{25}NO_9$: C, 65.53; H, 4.74; N, 2.64. Found: C, 65.65; H, 4.75; N, 2.51.

***p*-Methoxyphenyl 6-*O*-Benzyl-2-deoxy-2-phthalimido-β-D-galactopyranoside (26).** Compound **24** (2.831 g, 5.357 mmol) was deacylated in the manner described in the preparation of **25** to yield **26** (2.560 g, 95%): mp 165–167 °C; R_f = 0.25 (toluene/acetone (4:1)); $[\alpha]_D$ +27.1° (*c* 0.6); ^1H NMR (500 MHz) δ 5.705 (d, *J* = 8.6 Hz, H-1), 4.595 (dd, *J* = 11.0, 8.6 Hz, H-2), 4.416 (dd, *J* = 11.0, 3.4 Hz, H-3), 4.159 (d, *J* = 3.4 Hz, H-4), 3.716 (s, OMe); IR 3400, 1780, 1710 cm^{-1}.

3,4-Di-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-phthalimido-D-galactopyranoside (28). Compound **26** (403 mg, 0.802 mmol) was acetylated to yield **27**, in the manner described in the preparation of **3**. The reaction mixture was then concentrated in vacuo. EtOH was added to the residue, and the mixture was exposed to high vacuum. This treatment was repeated twice. Then toluene was added, and the mixture was again exposed to high vacuum. The crude **27** so obtained was dissolved in 3:4:3 toluene/MeCN/water (40 mL). Ceric ammonium nitrate (2.50 g, 4.6 mmol) was added, and the two-phase mixture was stirred at rt for 1 h. The mixture was then diluted with water and was extracted twice with Et_2O. The combined organic extracts were processed as usual. Column chromatography of the residue on silica gel (*n*-hexane/EtOAc (1:1)) afforded 336 mg (86%) of **28**: R_f = 0.40; ^1H NMR (500 MHz, 20:1 $CDCl_3/D_2O$) δ 6.372 (dd, *J* = 11.9, 3.4 Hz, H-3α), 5.866 (dd, *J* = 11.3, 3.4 Hz, H-3β), 5.645 (d, *J* = 3.4 Hz, H-4α), 5.539 (d, *J* = 3.4 Hz, H-4β), 5.492 (d, *J* = 8.6 Hz, H-1β), 5.448 (d, *J* = 3.4 Hz, H-1a), 2.115 and 1.854 (s, 2 Acβ), 2.092 and 1.847 (s, 2 Acα); IR 1750, 1710 cm^{-1}.

3,4-Di-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-phthalimido-β-D-galactopyranosyl Trichloroacetimidate (29). To a cold (0 °C) solution of **28** (296 mg, 0.613 mmol), trichloroacetonitrile (0.6 mL, 6 mmol), and toluene (6 mL) was added DBU (0.6 mL of a 1 M solution in toluene, 0.06 mmol). The stirred mixture was allowed to warm to rt over 2 h, and then it was diluted with EtOAc and was washed with aqueous NH_4Cl. The organic layer was processed as usual. Purification of the residue by column chromatography on silica gel (*n*-hexane/EtOAc (2:1)) afforded 347 mg (90%) of **29**: R_f = 0.42 (*n*-hexane/EtOAc (3:2)); ^1H NMR (500 MHz) δ 8.619 (s, NH), 6.573 (d, *J* = 8.9 Hz, H-1), 5.939 (dd, *J* = 11.3, 3.4 Hz, H-3), 5.634 (d, *J* = 3.4 Hz, H-4), 4.800 (dd, *J* = 11.3, 8.9 Hz, H-3), 4.249 (t, *J* = 6.5 Hz, H-5), 3.660 (dd, *J* = 9.8, 5.8 Hz, H-6), 3.571 (dd, *J* = 9.8, 7.3 Hz, H-6′), 2.126 and 1.875 (s, 2 Ac).

Benzyl 2,3-Di-*O*-benzyl-6-*O*-(*tert*-butyldiphenylsilyl)-β-D-galactopyranoside (30). A solution of benzyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside (1.054 g, 1.957 mmol), (±)-10-camphorsulfonic acid (45 mg, 0.19 mmol), and MeOH (20 mL) was stirred at 50 °C for 2 h. The mixture was worked up in the manner described in the preparation of **10**. Toluene was added to the crude product, and the mixture was exposed to high vacuum. The residue was then dissolved in DMF (20 mL). Imidazole (200 mg, 2.94 mmol) and *t*-$BuPh_2SiCl$ chloride (0.55 mL; 2.4 mmol) were added to the cold (0 °C) solution. The mixture was stirred at 0 °C for 5 h, and then it was diluted with water and extracted twice with Et_2O. The combined extracts were processed as usual. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc (86:14)) to afford 1.147 g (85%) of **30**: R_f = 0.52 (*n*-hexane/EtOAc (3:1)); $[\alpha]_D$ −24.7° (*c* 1.4); ^1H NMR (500 MHz) δ 4.418 (d, *J* = 7.6 Hz, H-1), 4.021 (dd, *J* = 3.1, 1.8 Hz, H-4), 3.976 (dd, *J* = 10.4, 6.1 Hz, H-6), 3.921 (dd, *J* = 10.4, 5.8 Hz, H-6′), 3.726 (dd, *J* = 9.5, 7.6 Hz, H-2), 3.453 (dd, *J* = 9.5, 3.1 Hz, H-3), 3.416 (t, *J* = 6 Hz, H-5), 2.500 (d, *J* = 1.8 Hz, OH), 1.068 (s, Me_3C). Anal. Calcd for $C_{43}H_{48}O_6Si$: C, 74.97; H, 7.02. Found: C, 74.57; H, 6.98.

Benzyl *O*-(3,4-Di-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-phthalimido-β-D-galactopyranosyl)-(1→4)-2,3-di-*O*-benzyl-6-*O*-(*tert*-butyldiphenylsilyl)-β-D-galactopyranoside (31). Method A. To a cold (−40 °C) stirred mixture of *N*-iodosuccinimide (41 mg, 0.18 mmol), molecular sieve 5A (0.4 g), and toluene (1 mL) was added a solution of **3** (71.3 mg, 139 μmol), **30** (63.0 mg, 91.4 μmol), and toluene (2 mL). Then CF_3SO_3H (10 μmol, 50 μL of a saturated (ca. 2 M) solution in CCl_4) was added. The stirred mixture was allowed to gradually warm to −10 °C over 1.5 h. Then it was diluted with EtOAc, and the reaction was quenched by adding aqueous $NaHCO_3$. The mixture was filtered through Celite. The two liquid layers were separated. The organic layer was washed with aqueous $Na_2S_2O_3$. The wash was back-extracted with EtOAc. The combined organic layers were then processed as usual. Column chromatography of the residue on silica gel (*n*-hexane/EtOAc (2:1)) afforded 105.0 mg (99%) of anomerically pure **31**: R_f = 0.43 (*n*-hexane/EtOAc (3:2)); $[\alpha]_D$ −52.4° (*c* 1.4); ^1H NMR (500 MHz) δ 6.044 (dd, *J* = 11.6, 3.4 Hz, H-3c), 5.541 (d, *J* = 3.4 Hz, H-4c), 5.273 (d, *J* = 8.5 Hz, H-2c), 2.062 and 1.862 (s, 2 Ac), 1.018 (s, Me_3C); IR 1750, 1720 cm^{-1}. Anal. Calcd for $C_{68}H_{71}NO_{14}Si$: C, 70.75; H, 6.20; N, 1.21. Found: C, 70.60; H, 6.20; N, 1.12.

Method B. Thioglycoside **3** (38.1 mg, 74.2 μmol) was allowed to react with **30** (34.9 mg, 50.7 μmol) in toluene in the presence of $PhSeOSO_2CF_3$ in the manner described in ref 25i. The product (21.5 mg, 37%) was a 3:1 mixture of β- and α-anomers. The ^1H NMR spectrum of the mixture showed minor peaks attributable to the α-anomer at δ 6.773 (dd, *J* = 11.5, 3.5 Hz, H-3c), 5.762 (d, *J* = 3.5 Hz, H-4c), 5.465 (d, *J* = 3.7 Hz, H-1c), 2.071 and 1.898 (s, 2 Ac).

Method C. Compounds **3** (45.9 mg, 89.4 μmol) and **30** (40.6 mg, 58.9 μmol) were allowed to react in $MeNO_2$ in the presence of $CuBr_2$–Bu_4NBr–$AgOSO_2CF_3$ in the manner described in ref 25d. The product (25.9 mg, 38%) was a 4:1 mixture of β- and α-anomers.

Method D. A mixture of **3** (13.2 mg, 25.7 μmol), **30** (15.0 mg, 21.8 μmol), $MeOSO_2CF_3$ (95 μmol), molecular sieve 4A (0.1 g), and benzene (1 mL) was stirred at 50 °C for 18 h. The reaction was then quenched by adding Et_3N (20 μL). The mixture was diluted with EtOAc and was filtered through Celite. The filtrate was concentrated in vacuo. The residue was purified by preparative TLC (*n*-hexane/EtOAc (3:2)) to afford 9.4 mg (37%) of a single isomer of **31**.

Method E. To a cold (−23 °C) stirred mixture of imidate **29** (74.1 mg, 118 μmol), **30** (51.9 mg, 75.3 μmol), molecular sieve 4A

(0.3 g), and toluene (5 mL) was added $Me_3SiOSO_2CF_3$ (17 μmol, 20 μL of a 0.84 M solution in 1,2-dichloroethane. The mixture was stirred at −23 °C for 0.5 h, and then the reaction was quenched by adding aqueous $NaHCO_3$. The mixture was diluted with EtOAc and was filtered through Celite. The usual processing of the filtrate and chromatographic purification of the residue afforded 82.3 mg (95%) of **31**.

Allyl 2-Azido-2-deoxy-3-*O*-(*p*-methoxybenzyl)-β-D-galactopyranoside (33). To a cold (0 °C) stirred solution of **32** (1.413 g, 4.239 mmol), *p*-methoxybenzyl chloride (0.8 mL, 5.9 mmol), and DMF (14 mL) was added, in small portions, NaH (7.5 mmol, 300 mg of a 60% mineral oil dispersion). The mixture was stirred at 0 °C for 0.5 h and then at rt for 1 h. It was again cooled to 0 °C, and MeOH (ca. 1 mL) was carefully added. After for 0.5 h, the mixture was diluted with water and was extracted with Et_2O. The extract was processed as usual. The residual oil was dissolved in 1:3 toluene/MeOH (40 mL) which contained (±)-10-camphorsulfonic acid (100 mg, 0.43 mmol). The solution was stirred at rt for 18 h, and then it was worked up in the manner described in the preparation of **10**. Column chromatography of the residue on silica gel (toluene/acetone (4:1 then 2:1)) afforded 1.191 g (77%) of **33**: mp 107–108 °C (Et_2O); R_f = 0.44 (toluene/acetone, (1:1)); $[\alpha]_D$ −35.4° (*c* 0.6); ^1H NMR (500 MHz) δ 4.273 (d, *J* = 8.2 Hz, H-1), 3.815 (s, OMe), 3.655 (dd, *J* = 10.1, 8.2 Hz, H-2), 3.306 (dd, *J* = 10.1, 3.4 Hz, H-3). Anal. Calcd for $C_{17}H_{23}N_3O_6$: C, 55.88; H, 6.34; N, 11.50. Found: C, 55.98; H, 6.32; N, 11.38.

Allyl 2-Azido-4,6-di-*O*-benzyl-2-deoxy-β-D-galactopyranoside (34). To an ice-cold solution of **33** (1.131 g, 3.095 mmol) in DMF (10 mL) was added, in small portions, NaH (9.5 mmol, 380 mg of a 60% mineral oil dispersion). Then a solution of BnBr (1.0 mL, 8.4 mmol) in DMF (15 mL) was added drop-by-drop over 20 min. The mixture was stirred at 0 °C for 1 h and at rt for 2 h. The reaction was then quenched by adding MeOH. The mixture was diluted with Et_2O and washed with water. The organic layer was processed as usual. The residue was dissolved in CH_2Cl_2 (20 mL) which also contained water (1 mL). To the cold (0 °C) mixture was added DDQ (910 mg, 4.01 mmol). The mixture was stirred in the dark at 0 °C for 0.5 h and at rt for 2 h. The suspension that resulted was diluted with EtOAc and was filtered through Celite. The filtrate was processed as usual. The residue was purified by column chromatography on silica gel (toluene, then toluene/EtOAc (4:1)) to afford 1.234 g (94%) of **34**: R_f = 0.29 (toluene/EtOAc (4:1)); $[\alpha]_D$ −9.4° (*c* 0.7); ^1H NMR (500 MHz) δ 4.278 (d, *J* = 8.1 Hz, H-1), 3.844 (d, *J* = 3.3 Hz, H-4), 3.560 (dd, *J* = 10.3, 8.1 Hz, H-2), 3.436 (ddd, *J* = 10.3, 7.8, 3.3 Hz, H-3), 2.192 (d, *J* = 7.8 Hz, OH); IR 3400, 2140 cm^{-1}. Anal. Calcd for $C_{23}H_{27}N_3O_5$: C, 64.93; H, 6.39; N, 9.88. Found: C, 64.72; H, 6.46; N, 9.33.

Methyl 2,3,4,6-Tetra-*O*-benzoyl-1-thio-β-D-galactopyranoside (35). A solution of methyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (1.241 g, 3.28 mmol), 1 M methanolic NaOMe (100 μL, 0.10 mmol), and MeOH (20 mL) was stirred at rt for 5 h. The mixture was then neutralized by adding Amberlyst 15 resin. The resin was removed by filtration, and the filtrate was concentrated in vacuo. The residue was thoroughly dried by exposure to high vacuum at 70 °C for 3 h, and then it was dissolved in pyridine (20 mL). To the cold (0 °C) stirred solution was added benzoyl chloride (2.5 mL, 22 mmol). The mixture was stirred at rt for 3 h, and then the reaction was quenched by adding MeOH (ca. 1 mL). The mixture was diluted with Et_2O and was processed as usual. Column chromatography of the residue on silica gel (toluene/EtOAc (95:5)) afforded 2.054 g (100%) of **35**: R_f = 0.65 (toluene/EtOAc (86:14)); $[\alpha]_D$ +113.0° (*c* 0.88); ^1H NMR (90 MHz) δ 6.04 (dd, *J* = 3.1, 0.5 Hz, H-4), 5.90 (t, *J* = 9.5 Hz, H-2), 5.65 (dd, *J* = 9.7, 3.1 Hz, H-3), 4.77 (d, *J* = 9.5 Hz, H-1), 2.34 (s, SMe). Anal. Calcd for $C_{35}H_{30}O_8S \cdot H_2O$: C, 66.86; H, 5.13. Found: C, 66.97; H, 4.82.

Allyl *O*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-galactopyranosyl)-(1→3)-2-azido-4,6-di-*O*-benzyl-2-deoxy-β-D-galactopyranoside (36). $MeOSO_2CF_3$ (4.4 mmol, 4.7 mL of a 0.95 M solution in CCl_4) was added to a mixture of **34** (685 mg, 1.61 mmol), **35** (1.376 g, 2.20 mmol), molecular sieve 4A (6 g), and toluene (20 mL). The mixture was stirred at 50 °C for 8 h, and then the reaction was quenched by adding Et_3N (ca. 1 mL). The mixture was diluted with EtOAc and was filtered through Celite. The filtrate was processed as usual. The residue was purified by column chromatography on silica gel (toluene/EtOAc (92:8)) to afford 1.480 g (91%) of **36**: R_f = 0.39 (toluene/EtOAc, 86:14); $[\alpha]_D$ +34.9° (*c* 1.2); ^1H NMR (90 MHz) δ 6.02 (d, *J* = 3.3 Hz, H-4d), 5.93 (dd, *J* = 10.3, 7.9 Hz, H-2d), 5.62 (dd, *J* = 10.3, 3.3 Hz, H-3d), 5.13 (d, *J* = 7.9 Hz, H-1d), 4.24 (d, *J* = 7.5 Hz, H-1c), 3.58 (dd, *J* = 10.8, 7.5 Hz, H-2c); IR 2130, 1730 cm^{-1}. Anal. Calcd for $C_{57}H_{53}N_3O_{14}$: C, 68.19; H, 5.32; N, 4.19. Found: C, 67.96; H, 5.31; N, 3.87.

Allyl *O*-(3,4-*O*-Isopropylidene-β-D-galactopyranosyl)-(1→3)-2-azido-4,6-di-*O*-benzyl-2-deoxy-β-D-galactopyranoside (37). A solution of **36** (1.619 g, 1.612 mmol), 1 M methanolic NaOMe (80 μL, 0.08 mmol) and 1:1 CH_2Cl_2/MeOH (30 mL) was refluxed for 3 h. The cooled solution was then neutralized by adding Amberlyst 15 resin. The mixture was filtrated, and the filtrate was concentrated in vacuo. The residue was thoroughly dried by exposure to high vacuum and was then dissolved in DMF (10 mL). To the cold (0 °C) solution were successively added imidazole (220 mg, 3.23 mmol) and *tert*-$BuPh_2SiCl$ (300 μL, 2.4 mmol). The mixture was stirred at 0 °C for 1.5 h and at rt for 0.5 h. It was then worked up in the manner described in the preparation of **30**. The residue was dissolved in MeCN (15 mL) which contained 2,2-dimethoxypropane (300 μL, 2.4 mmol) and (±)-10-camphorsulfonic acid (20 mg, 0.09 mmol). The solution was stirred at rt for 18 h, and then it was diluted with Et_2O and was washed with aqueous $NaHCO_3$. The organic layer was processed as usual. The residue was dissolved in THF (20 mL). To the cold (0 °C) solution was added Bu_4NF (2.5 mmol, 2.5 mL of a 1 M solution in THF). The mixture was stirred at 0 °C for 1.5 h and at rt for 1 h, and then it was diluted with Et_2O and was processed in the usual manner. The residue was purified by column chromatography on silica gel (toluene/acetone (3:1)) affording 716 mg (71%) of **37**: mp 119–120 °C (Et_2O); R_f = 0.55 (toluene/acetone (3:2)); $[\alpha]_D$ −1.5° (*c* 1.0); ^1H NMR (500 MHz) δ 4.414 (d, *J* = 8.6 Hz, H-1d), 4.309 (d, *J* = 7.9 Hz, H-1c), 1.531 and 1.361 (s, Me_2C); IR 3450, 2120 cm^{-1}. Anal. Calcd for $C_{32}H_{41}N_3O_{10}$: C, 61.23; H, 6.58; N, 6.69. Found: C, 60.99; H, 6.58; N, 6.40.

Allyl *O*-(2,6-Di-*O*-benzyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-(1→3)-2-azido-4,6-di-*O*-benzyl-2-deoxy-β-D-galactopyranoside (38). NaH (4.5 mmol, 180 mg of a 60% dispersion in mineral oil) and BnCl (390 μL, 3.4 mmol) were successively added to a cold (0 °C) stirred solution of compound **37** (704 mg, 1.12 mmol) in DMF (10 mL). The mixture was stirred at 0 °C for 1 h and at rt for 2 h, and then the reaction was quenched by adding MeOH. The mixture was diluted with Et_2O and was processed as usual. Purification of the residue by column chromatography on silica gel (*n*-hexane/EtOAc/Et_3N (73:25:2)) afforded 879 mg (97%) of **38**: R_f = 0.48 (*n*-hexane/EtOAc (2:1)); $[\alpha]_D$ +11.2° (*c* 0.7); ^1H NMR (500 MHz) δ 4.609 (d, *J* = 7.6 Hz, H-1d), 4.297 (d, *J* = 7.9 Hz, H-1c), 4.202 (t, *J* = 6 Hz, H-3d), 4.144 (dd, *J* = 5.8, 2.1 Hz, H-4d), 3.953 (d, *J* = 2.4 Hz, H-4c), 3.840 (dd, *J* = 10.4, 7.9 Hz, H-2c), 3.413 (dd, *J* = 7.6, 6.4 Hz, H-2d), 1.325 and 1.313 (s, Me_2C); IR 2100 cm^{-1}. Anal. Calcd for $C_{46}H_{53}N_3O_{10}$: C, 68.39; H, 6.61; N, 5.20. Found: C, 68.49; H, 6.67; N, 4.93.

Allyl *O*-(2,6-Di-*O*-benzyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-(1→3)-4,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-galactopyranoside (5). A solution of azide **38** (857 mg, 1.06 mmol) in Et_2O (7 mL) was added to a cold (−40 °C) stirred slurry of $LiAlH_4$ (200 mg) in Et_2O (3 mL). The stirred mixture was allowed to warm to rt over 2 h, and then the reaction was quenched by successively adding water (0.2 mL), 15% aqueous NaOH (0.2 mL), and water (0.6 mL). The mixture was stirred vigorously for 10 min, and then anhydrous Na_2SO_4 was added. The mixture was diluted with Et_2O and filtered through Celite. The two liquid layers were separated. The organic layer was concentrated in vacuo to afford the crude amine. This was dried by exposure to high vacuum and then was dissolved in 1,2-dichloroethane (20 mL). To the solution was added phthalic anhydride (230 mg, 1.55 mmol) and Et_3N (0.30 mL, 2.1 mmol). The mixture was stirred at 50 °C for 18 h, and then it was concentrated in vacuo. The residue was dissolved in 1:1 pyridine/Ac_2O (5 mL). The mixture was stirred at 50 °C for 18 h, and then it was concentrated in vacuo. Purification of the residue by column chromatography on silica gel (*n*-hexane/EtOAc (3:1)) afforded 813 mg (84%) of **5**: R_f = 0.43; $[\alpha]_D$ +32.5° (*c* 1.0); ^1H NMR (500

MHz) δ 5.083 (d, J = 8.5 Hz, H-1c), 4.858 (dd, J = 11.3, 8.5 Hz, H-2c), 4.475 (d, J = 7.9 Hz, H-1d), 4.179 (d, J = 2.1 Hz, H-4c), 4.040 (dd, J = 5.5, 2.1 Hz, H-4d), 3.914 (dd, J = 7.0, 5.5 Hz, H-3d), 3.200 (dd, J = 7.9, 7.0 Hz, H-2d), 1.231 and 1.129 (s, Me_2C); IR 1780; 1720 cm^{-1}. Anal. Calcd for $C_{54}H_{57}NO_{12}·0.5H_2O$: C, 70.41; H, 6.34; N, 1.52. Found: C, 70.55; H, 6.32; N, 1.47.

O-(2,6-Di-O-benzyl-3,4-O-isopropylidene-β-D-galactopyranosyl)-(1→3)-4,6-di-O-benzyl-2-deoxy-2-phthalimido-D-galactopyranose (39). Dry H_2 was passed through a stirred solution of $[Ir(COD)(PMePh_2)_2]PF_6$ (3 mg, 4 μmol) in THF (5 mL) until the faintly red solution became colorless. The flask was repeatedly evacuated and refilled with nitrogen in order to purge all of dissolved hydrogen. Then a solution of **5** (312 mg, 0.342 mmol) in THF was added. The mixture was stirred at rt for 1 h. Then were successively added water (1 mL), $NaHCO_3$ (0.5 g) and iodine (120 mg, 0.52 mmol). The mixture was stirred at rt for 1 h, and, then it was diluted with EtOAc and was washed with aqueous $Na_2S_2O_3$. The organic layer was processed as usual. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc (1:1)) to afford 223 mg (75%) of **39**: R_f = 0.39 (*n*-hexane/EtOAc (1:1)); ^1H NMR (500 MHz, 20:1 $CDCl_3/D_2O$) δ 5.370 (d, J = 3.5 Hz, H-1cα), 5.234 (dd, J = 11.9, 2.5 Hz, H-3cα), 5.156 (d, J = 8.2 Hz, H-1cβ), 5.072 (dd, J = 11.6, 3.5 Hz, H-2cα), 4.790 (dd, J = 11.3, 2.8 Hz, H-3cα), 4.715 (dd, J = 11.3, 8.2 Hz, H-2cβ), 1.244 and 1.141 (s, $Me_2Cα$), 1.229 and 1.131 (s, $Me_2Cβ$); IR 1675, 1710 cm^{-1}. Anal. Calcd for $C_{51}H_{53}NO_{12}$: C, 70.25; H, 6.13; N, 1.61. Found: C, 69.86; H, 6.18; N, 1.55.

O-(2,6-Di-O-benzyl-3,4-O-isopropylidene-β-D-galactopyranosyl)-(1→3)-4,6-di-O-benzyl-2-deoxy-2-phthalimido-α- and -β-D-galactopyranosyl Fluoride (40). Compound **39** (159 mg, 0.183 mmol) was treated with DAST (100 μL, 0.76 mmol) in toluene in the manner described in the preparation of **4a** to afford 147 mg (92%) of a 2:3 mixture of the α- and β-anomers of **40**. Compounds **40**: R_f = 0.37 and 0.32 (*n*-hexane/EtOAc (2:1)); ^1H NMR (500 MHz) δ 5.736 (dd, J = 53.9 and 8.1 Hz, H-1cβ), 5.678 (dd, J = 54.2, 2.5 Hz, H-1cα), 5.380 (dd, J = 11.7, 2.4 Hz, H-3cα), 5.047 (ddd, J = 30.4, 11.7, 2.5 Hz, H-2cα), 4.925 (td, J = 11.7, 8.1 Hz, H-2cβ), 4.719 (dd, J = 11.7, 2.4 Hz, H-3cβ), 4.247 (d, J = 2.9 Hz, H-4c), 4.095 and 4.046 (dd, J = 5.5, 1.8 Hz, H-4d), 4.054 and 3.933 (dd, J = 9.5, 6.6 Hz, H-3d), 1.258, 1.234, 1.174, and 1.140 (s, Me_2C). Anal. Calcd for $C_{51}H_{52}NO_{11}F$: C, 70.09; H, 6.00; N, 1.60. Found: C, 70.38; H, 6.06; N, 1.54.

Benzyl O-(2,6-Di-O-benzyl-3,4-O-isopropylidene-β-D-galactopyranosyl)-(1→3)-O-(4,6-di-O-benzyl-2-deoxy-2-phthalimido-β-D-galactopyranosyl)-(1→4)-O-[methyl (5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosid)onate-(2→3)]-O-(2,6-di-O-benzyl-β-D-galactopyranosyl)-(1→4)-3,6-di-O-benzyl-2-O-pivaloyl-β-D-glucopyranoside (42). To a cold (−20 °C) stirred mixture of $AgOSO_2CF_3$ (22 mg, 86 μmol), Cp_2HfCl_2 (32 mg, 84 μmol), molecular sieve 4A (0.2 g), and toluene (0.5 mL) was added a solution of **40** (56.4 mg, 64.5 μmol), **41** (57.0 mg, 42.2 μmol), and toluene (1.5 mL). The stirred mixture was gradually warmed to rt and was kept there for 3 h. After workup in the manner described in the preparation of **1** (method C), the residue was purified by column chromatography on silica gel (toluene/acetone/Et_3N (79:20:1 then 59:40:1)) to afford 52.1 mg (56%) of **42** and 12.0 mg (13%) of its α-isomer. Compound **42**: R_f = 0.16 (toluene/acetone (3:1)); $[α]_D$ +22.0° (*c* 1.3); ^1H NMR (500 MHz) δ 5.421 (m, H-8g), 5.261 (dd, J = 8.6, 2.8 Hz, H-7g), 5.177 (d, J = 8.2 Hz, H-1c), 5.137 (d, J = 10.4 Hz, N*H*Ac), 4.934 (dd, J = 11.8, 2.8 Hz, H-3c), 4.871 (dd, J = 11.3, 8.2 Hz, H-2c), 4.077 (dd, J = 9.8, 2.5 Hz, H-3b), 4.050 (dd, J = 5.0, 2.0 Hz, H-4d), 3.680 (s, OMe), 3.226 (t, J = 7 Hz, H-2d), 2.884 (dd, J = 12.8, 4.0 Hz, H-3geq), 2.831 (dd, J = 9.8, 7.3 Hz, H-2b), 2.089, 2.014, 1.890, 1.838, and 1.668 (s, 5 Ac), 1.234 and 1.142 (s, Me_2C), 1.189 (s, Me_3C); IR 1745, 1720 cm^{-1}. Anal. Calcd for $C_{123}H_{138}N_2O_{35}$: C, 67.02; H, 6.31; N, 1.27. Found: C, 66.99; H, 6.36; N, 1.24.

α-Isomer of **42**: R_f = 0.24; $[α]_D$ +48.4° (*c* 1.1); ^1H NMR (500 MHz) δ 5.627 (m, H-8g), 5.490 (dd, J = 11.4, 3.0 Hz, H-3c), 5.250 (dd, J = 8.5, 2.5 Hz, H-7g), 5.115 (d, J = 4.0 Hz, H-1c), 5.033 (dd, J = 8.8, 8.1 Hz, H-2a), 4.948 (dd, J = 11.4, 4.0 Hz, H-2c), 3.487 (s, OMe), 3.317 (dd, J = 8.8, 8.1 Hz, H-2b), 3.178 (dd, J = 8.1, 7.0 Hz, H-2d), 2.701 (dd, J = 12.5, 4.5 Hz, H-3geq), 2.072, 1.966, 1.815, 1.676, and 1.617 (s, 5 Ac), 1.230 and 1.096 (s, Me_2C), 1.096 (s, Me_3C). Anal. Found: C, 66.93; H, 6.36; N, 1.17.

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Application of the Ring–Chain-Transfer Concept to the Synthesis of 4-(ω-Aminoalkyl)imidazole Analogues of Histamine[1]

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Reaction of semicyclic 2-aza-3-(methylthio)-3-propeniminium iodides **1** with CH-acidic methylamines **2** gives rise to the formation of 4-(ω-aminoalkyl)imidazole **5** or corresponding hydroiodides. In this ring-transformation reaction the imidazole ring as well as the aminoalkyl substituent are formed within one procedure. The compounds obtained represent novel analogues of histamine.

Naturally occurring histamine (4-(2-aminoethyl)-imidazole) has important functions in biochemical processes. Analogues of histamine such as isohistamine (4-(3-aminopropyl)imidazole) or corresponding derivatives have gained practical interest because of their antihistamine activity in order to treat certain diseases, i.e., ulceral diseases in men. Such compounds are usually synthesized starting from a 1-functionalized ω-aminoalkane with the heterocyclic ring being formed in the final step. We became interested in applying a novel type of ring transformation by ring–chain-transfer[2,3] in order to provide

(1) Part VII on ring–chain-transfer reactions; for part VI see ref 2.

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