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Efficient Routes to Ethyl-2-Deoxy-2-phthalimido-1-β-D-thio-galactosamine Derivatives via Epimerization of the Corresponding Glucosamine Compounds

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Short synthetic routes to protected ethyl 2-deoxy-2-phthalimido-1-*β*-D-thio-galactosamine derivatives via epimerization of the corresponding glucosamine compounds are described. Starting from D-glucosamine hydrochloride, the epimerizations were performed by displacement of presynthesized triflates with nitrite anions and by an oxidation/reduction route. The latter method involved Moffatt oxidation to the corresponding 4-ketohexoses and subsequent reduction using sodium borohydride/tetrabutylammonium borohydride, zinc borohydride, or lithium tri-*sec*-butyl borohydride in THF. The displacement route was found to be the preferred method for epimerization of 3-*O*-acyl (benzoyl) derivatives. For glucosamine compounds with 3-*O*-etheral- (allyl or benzyl) and 6-*O*-benzyl protecting groups, the oxidation/reduction route was the most convenient procedure to achieve corresponding galactosamine compounds. The produced galactosamine derivatives will be useful building blocks in the synthesis of antifreeze glycoproteins substances and analogues thereof.

Keywords Galactosamine, Epimerization, Oligosaccharides, Glycosyl donors, Antifreeze glycoproteins

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INTRODUCTION

2-*N*-Acetamido-2-deoxy-D-galactopyranosides are building units found in, for example, the mucin class of glycopeptides, human blood specific glycoproteins, and the oligosaccharide portion of glycosphingolipids.[1] Moreover, α-glycosidic bonds of 2-*N*-acetamido-2-deoxy-D-galactopyranosides to threonine are present in antifreeze glycoproteins.[2,3] In 1978 Lemieux presented the azidonitration of 3,4,6-tri-acetyl-D-galactal as a most convenient method to achieve multigrams of D-galactosamine and 2-deoxy-2-azido-D-galactosyl donors/acceptors, which is a well-known problem in the synthesis of 2-*N*-acetamido/2-amino-2-deoxy-D-galactopyranoside containing compounds.[4] The use of the azido group as a masked amine is well known and was introduced in the carbohydrate field by Paulsen and co-workers in 1978.[5–7] During glycosylation with this nonparticipating azido group at position 2, the α-*O*-linked glycoside is obtained as the major product. To form 1,2-trans glycosidic bonds, the use of a participating neighboring group is necessary. The *N*-phthalimido group fulfills this requirement and has been used widely after its introduction in carbohydrate chemistry in the mid-70s.[8]

Antifreeze glycoproteins (AFGPs) are found in the bloodstream of some fish species living in subzero environments and inhibit, in a noncolligative manner, the growth of ice crystals in the blood and thereby allow these organisms to survive. A typical AFGP consists of a repeating tripeptide (Thr-Ala-Ala), in which every hydroxyl of the threonine residue is glycosylated with a β-D-Gal-(1 $\rightarrow$ 3)-α-D-GalNAc disaccharide. We are interested in ethyl-2-deoxy-2-phthalimido-thiogalactosyl donors/acceptors to be used in the synthesis of AFGPs and analogues thereof. The aim of this project was to find (a) satisfying method(s) for the epimerization of C-4 in ethyl-2-deoxy-2-phthalimido-thioglucosamine compounds, with acyl- or alkyl-protecting groups at C-3 and C-6, respectively, to their axial analogues. Thioglycosides are easily prepared, show stability in a variety of conditions, and can be selectively activated with several thiophilic promoters.[9] Further, for synthetic flexibility in future and ongoing projects, C-3 was protected with a benzoyl, a benzyl, or an allylic group, whereas C-6 was protected either with a benzoyl or a benzyl group. With respect to these protecting groups, we focused on two different methods for the epimerization, a substitution with inversion (S_N2-type) and an oxidation/reduction route.

In 1974 Lattrell and Lohaus found that when a chiral secondary sulfonate was treated with sodium nitrite in DMSO, the corresponding alcohol with inverted stereochemistry was isolated.[10] This was further developed by Albert et al., showing promising results in carbohydrate chemistry by substitution of trifluoromethanesulfonate (triflate) glucosides with sodium- or tetrabutylammonium nitrite in DMF or acetonitrile to provide the corresponding inverted hydroxyl compounds.[11] As a consequence, there are several reports

using this epimerization method in carbohydrate synthesis.[12–19] To our knowledge, there is only one example using this method for employing an ethyl-*N*-phthalimido thiogalactosamine compound.[12] Since they only investigated the epimerization with benzoyl-protecting groups, we decided to examine this procedure further with our series of *N*-phthalimido glucosamine derivatives.

The second method was an oxidation/reduction route where the alcohols were converted to their ketoform via Moffatt oxidation,[20,21] followed by reduction of the crude ketosugars with sodium borohydride ($NaBH_4$) and a catalytic amount of tetrabutylammonium borohydride (Bu_4NBH_4), zinc borohydride ($Zn(BH_4)_2$), or lithium tri-*sec*-butyl borohydride (L-selectride®) in THF. The factors in controlling the stereoselective reduction of 4-ketohexoses with $NaBH_4$ were recently summarized in a publication pointing at the characteristic of the vicinal-protecting group as a criterion to predict the formation of an axial or equatorial hydroxyl group.[22] It was suggested that the presence of a *vicinal equatorial alkoxyl* group will favor the formation of an axial hydroxyl group. Moreover, the protecting groups at C-6 of the 4-keto sugars were stated to have a minor effect in controlling the stereoselectivity in the reductions. However, these conclusions were drawn from compounds with rather large structural differences compared to the 2-deoxy-2-phthalimido-glucosamine compounds we have synthesized and compared. The only relevant example we found in the literature is in a paper from Vliegenthart and co-workers, where the reduction of ethyl 3-*O*-benzyl-2-deoxy-2-phthalimido-6-*O*-trityl-β-D-xylo-thiohexa-pyranoside-4-ulose with Bu_4NBH_4 formed the *galacto* and *gluco* epimers in a 10:1 ratio.[23] $Zn(BH_4)_2$ was chosen as a reagent to investigate the ability of controlling the stereoselectivity in the reductions by chelation of the zinc cation between the carbonyl oxygen and the vicinal donor substituents. Reduction of α-hydroxy ketones and α-alkoxy ketones have shown, through chelated transition states, to give the *anti* products in preference where the hydride is delivered from the least sterically hindered face.[24–26] On the other hand, L-selectride® is a sterically demanding borohydride and has been used earlier in carbohydrate chemistry with the purpose of stereoselective reduction of 4-ketohexoses forming the axial alcohol as major product.[27–29]

RESULTS AND DISCUSSION

Bearing the cost aspect of galactosamine in mind, our starting point was thioglycoside **1** (Sch. 2), which can be prepared in multigram scale from D-glucosamine hydrochloride using standard synthetic methods.[30,31] With conventional methods, C-3 was protected either with a benzoyl, benzyl, or an allylic group, whereas C-6 was protected either with a benzoyl or benzyl group, leading to a series of six ethyl-2-deoxy-2-phtalimido-thioglucosides available for epimerization (Fig. 1).

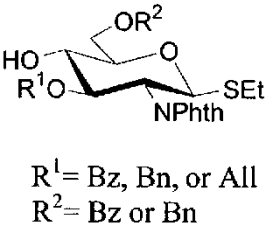
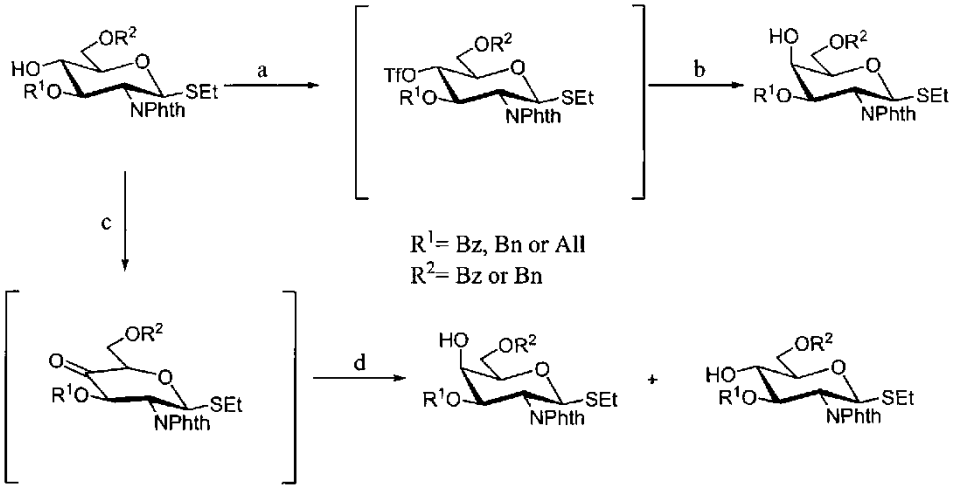


Figure 1: The C-3 and C-6 protecting groups used on the ethyl 2-deoxy-2-phthalimido-1-β-D-thio-glucosamine compounds subjected to epimerization.

Conversion of the secondary alcohols to triflates, treating them with nitrite anion, gave alcohols with inverted stereochemistry as the main products. Furthermore, all alcohols were oxidized to their corresponding ketoform following the procedure described by Moffatt using DCC, pyridine, and trifluoroacetic acid in DMSO and CH_2Cl_2. Reduction of the crude ketohexoses were performed using $NaBH_4/Bu_4BH_4$, $Zn(BH_4)_2$ and L-selectride® for comparison of the stereoselectivity (Sch. 1).

For the synthesis of the 4-OH derivatives **3** and **4** prepared for epimerization, **1** was treated with benzoyl chloride in pyridine to give crystalline **2** in nearly quantitative yield (99%). Removal of the benzylidene acetal with ethylene glycol in CH_2Cl_2/TFA (4:1) and subsequent benzoylation of the primary alcohol with benzoyl chloride in pyridine afforded compound **3**[12] in



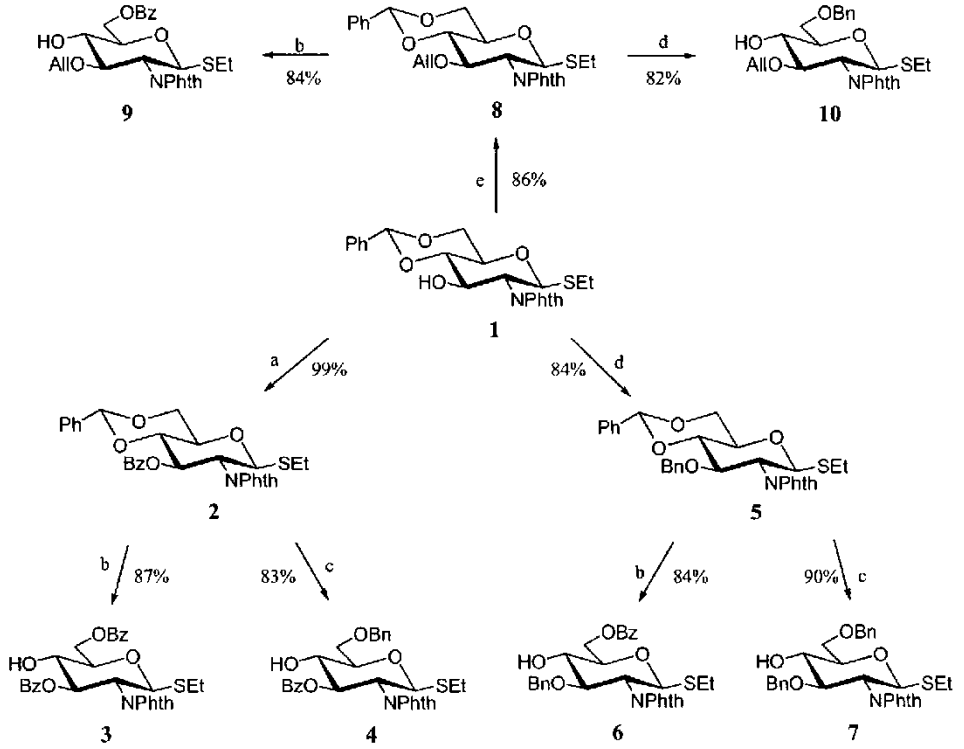
Scheme 1: The displacement and the oxidation/reduction route, respectively, used for the epimerization of the glucosamine compounds: **(a)** Tf_2O, pyridine, CH_2Cl_2; **(b)** $NaNO_2$/DMF or Bu_4NNO_2/toluene; **(c)** DCC, TFA, pyridine, DMSO/CH_2Cl_2 (l:1); **(d)** $NaBH_4/Bu_4NBH_4$, $Zn(BH_4)_2$, or L-selectride in THF.

87% yield for the two steps. Reductive opening of the benzylidene acetal in **2** with sodium cyanoborohydride and HCl saturated diethyl ether in THF gave compound **4** in good yield (83%).

The 3-*O*-benzylated compound **5**[32] was produced in 84% yield from **1** using benzyl bromide and sodium hydride in DMF, and treated in a similar fashion as in the preparation of **3** and **4** to give derivatives **6** and **7**[32] in 84% and 90% yield, respectively. Analogically, the two allylic compounds **9** and **10** were synthesized. The 3-OH position in **1** was treated with allylic bromide and sodium hydride in DMF to give compound **8**[33] in 86% yield, and was used to produce the two derivatives **9** (84%) and **10**[33] (82%) following the same protocols as described above (Sch. 2).

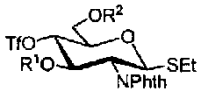
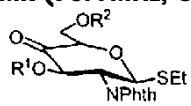
For all the glucosamine compounds, (**3**, **4**, **6**, **7**, **9**, and **10**), the conversions to the corresponding triflates were followed with TLC and proved by the typical downfield shift of H-4 in ^{1}H NMR (Table 1). The triflates were used directly in the displacement reactions without further characterization.

The results of the epimerization of the 4-OH derivatives using the displacement route are presented in Table 2. The 3-*O*-benzoylated derivatives



Scheme 2: (a) BzCl, pyridine; (b) 1. ethylene glycol, TFA/CH_2Cl_2 (5:1); 2. BzCl, pyridine; (c) $NaCNBH_3$, Et_2O/HCl, THF; (d) BnBr, NaH, DMF; (e) AllBr, NaH, DMF.

Table 1: Selected NMR data for the crude triflates and ketohexoses.

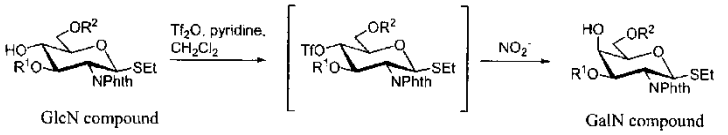
R^1	R^2	^{1}H NMR (300 MHz, $CDCl_3$) 	^{13}C NMR (75.4 MHz, $CDCl_3$) 
Bz	Bz	δ 5.38 (dd, 1H, J = 9.6, 9.6 Hz, H-4), 5.67 (d, 1H, J = 10.8 Hz, H-1)	δ 194.1 (C-4), 81.7 (C-1)
Bz	Bn	δ 5.43 (dd, 1H, J = 9.6, 9.6 Hz, H-4), 5.57 (d, 1H, J = 10.8 Hz, H-1)	δ 194.7 (C-4), 81.4 (C-1)
Bn	Bz	δ 5.15 (dd, 1H, J = 9.3, 9.3 Hz, H-4), 5.30 (d, 1H, J = 10.5 Hz, H-1)	δ 199.6 (C-4), 81.5 (C-1)
Bn	Bn	δ 5.10 (dd, 1H, J = 9.3, 9.3 Hz, H-4), 5.23 (d, 1H, J = 10.4 Hz, H-1)	δ 200.2 (C-4), 81.3 (C-1)
All	Bz	δ 5.07 (dd, 1H, J = 9.3, 9.3 Hz, H-4), 5.35 (d, 1H, J = 10.5 Hz, H-1)	δ 199.3 (C-4), 81.7 (C-1)
All	Bn	δ 5.02 (dd, 1H, J = 9.6, 9.6 Hz, H-4), 5.28 (d, 1H, J = 10.5 Hz, H-1)	δ 200.5 (C-4), 81.5 (C-1)

3 and **4** (entries i and ii) were successfully epimerized to their *galacto* epimers **11**[12] and **12** in good yields, 88% and 82%, respectively, using 10 molar eq. of $NaNO_2$ in DMF at rt. The triflates of **3** and **4** were both totally consumed during 3 hr at rt. In the former reaction, no byproduct was observed, but in the latter one, the slightly lower yield of the desired product could be explained by the observation of the 4-*O*-benzoylated-3-OH *galacto* epimer in 5% yield.

On the other hand, the reaction of triflates of the 3-*O*-benzylated derivatives **6** and **7** (entries iii and v) with $NaNO_2$ in DMF was slower. To obtain complete consumption of the triflates, the reaction mixture was heated to 35°C for 12 hr. Raising the temperature additionally gave lower yields of products. *Galacto* epimers **13** and **14** were obtained in 74% and 71% yield, respectively. The significantly lower yield of the benzylated compounds compared to their benzoylated analogues encouraged us to optimize the conditions in the displacement route. Using tetrabutylammonium nitrite (Bu_4NNO_2) in toluene was found to increase the yield of **13** (82%) and **14** (78%) (entries iv and vi). Still, the reaction rates were similar to the displacement reactions using $NaNO_2$ in DMF.

The 3-*O*-allylic compounds **9** and **10** showed the same behavior as their benzylated analogues and needed longer reaction times than the corresponding benzoylated compounds to achieve complete consumed triflate. The *galacto* epimers **15** and **16**[33] were produced in 68% and 63% yields, respectively, using $NaNO_2$ in DMF for 12 hr at 35°C (entries vii and ix). Also here, changing to Bu_4NNO_2 in toluene increased the yield of the desired products **15** (73%) and **16** (68%) (entries viii and x).

Table 2: Epimerization using displacement of presynthesized triflates by nitrite anions



GlcN compound GalN compound

Entry	GlcN compound	R^1	R^2	Conditions[a]	Results: Product	Results: Yield (%)
i	**3**	Bz	Bz	$NaNO_2$ DMF, rt, 2 hr	**11**	88
ii	**4**	Bz	Bn	$NaNO_2$ DMF, rt, 3 hr	**12**	82
iii	**6**	Bn	Bz	$NaNO_2$ DMF, 35°C, 12 hr	**13**	74
iv	**6**	Bn	Bz	$(Bu)_4NNO_2$ toluene, 35°C, 12 hr	**13**	82
v	**7**	Bn	Bn	$NaNO_2$ DMF, 35°C, 12 hr	**14**	71
vi	**7**	Bn	Bn	$(Bu)_4NNO_2$ toluene, 35°C, 12 hr	**14**	78
vii	**9**	All	Bz	$NaNO_2$ DMF, 35°C, 12 hr	**15**	68
viii	**9**	All	Bz	$(Bu)_4NNO_2$ toluene, 35°C, 12 hr	**15**	73
ix	**10**	All	Bn	$NaNO_2$ DMF, 35°C, 12 hr	**16**	63
x	**10**	All	Bn	$(Bu)_4NNO_2$ toluene, 35°C, 12 hr	**16**	68

[a]All triflates were treated with 7–10 molar eq. of $NaNO_2$.

To our knowledge there is a limited number of reports in the literature thoroughly discussing mechanistic aspects of the inversion with nitrite anions. Binkley has proposed a nitrous acid ester as an intermediate that, after attack from a second nitrite anion, collapses to the alcohol and N_2O_3.[15] To investigate if a nitrous acid ester intermediate could be identified, we followed the substitution of presynthesized triflate of **3** with $NaNO_2$ in DMF-d_7 in the NMR-tube (see Fig. 2). Interestingly, directly after addition of $NaNO_2$, a doublet appeared at 6.1 ppm ($J = 3.6$ Hz) from a new compound. Moreover, both a doublet and a double doublet at 5.5 ppm ($J = 10.2$ Hz) and 6.0 ppm ($J = 3.6$, 11.0 Hz), respectively, were seen and most likely belong to H-1 and H-3 in this compound. This observation could be the intermediate nitrous acid ester with respect to the chemical shift and coupling pattern of the proton at 6.1 ppm. After stirring for 1 hr at 25°C, both signals from the triflate and the intermediate compound had disappeared and the only observed compound was the *galacto* epimer (H-3, 5.50 ppm ($J = 3.0$, 11.1 Hz); H-1, 5.26 ppm ($J = 10.5$ Hz)). Whether this is a general reaction pathway for all the triflates synthesized has not been investigated.

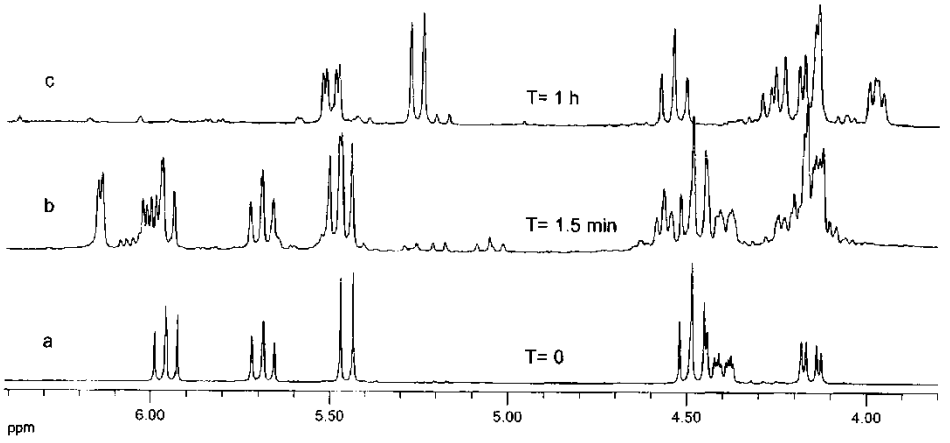


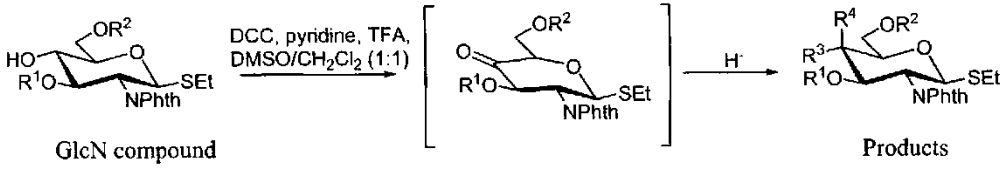
Figure 2: ^{1}H NMR spectra from the substitution of presynthesized triflate of **3** using $NaNO_2$ in DMF-d7. (a) T = 0, synthesized triflate of compound **3**; (b) T = 1.5 min, mixture of starting compound and the suggested intermediate nitrous acid ester; (c) *T* = 1 hr, only *galacto* epimer **11** is observed after collapse of the intermediate compound. For further information see text.

To summarize the epimerization via the displacement route there is a correlation between the yield/reaction rates and the choice of protecting group in position 3. The 3-*O*-benzoylated- and the 3-*O*-allyl derivatives gave the highest and lowest yield, respectively, of their inverted analogues. These results indicate the displacement route to be better for glucosamine compounds with electron-withdrawing acyl protecting groups at position 3. Moreover as a "trend," a benzoyl group is better in position 6 than the benzyl group.

As the alternative route, the 4-OH position was subjected to an oxidation/reduction inversion. The glucosamine compounds were oxidized using DCC, pyridine, and TFA in CH_2Cl_2 and DMSO (1:1) and used directly in the reduction step. We found the ketosugars forming the corresponding *gem*-diols to a varied extent when purified on silica gel column, which has been reported earlier in the oxidation of similar structures.[34,35] Therefore, the crude ketohexoses were subjected to reduction immediately after identification by ^{1}H and ^{13}C NMR (Table 1). Fortunately, the oxidation was complete using 1.5 eq. of DCC, and after workup, the insoluble impurities as dicyclohexylurea could be filtered off following the original procedure with minor modifications.[20,21] Due to the poor solubility of $NaBH_4$ in THF, a catalytic amount of Bu_4NBH_4 was used in the reductions. The results from the reduction of the 4-ketohexoses are summarized in Table 3.

In the reduction of the ketohexose formed from 3,6-di-*O*-benzoylated **3** (entry i, Table 3) with $NaBH_4/Bu_4NBH_4$, the *galacto*/*gluco* epimers **11** and **3** were formed in a 1:2 ratio in 81% total yield. There were no problems in separating galactosamine derivative **11** from the corresponding glucosamine

Table 3: Epimerization of the glucosamine compounds via the oxidation/reduction route.



GlcN compound

Entry	GlcN Compound	R^1	R^2	Reducing agent[a]	Products	Results[b] R^1	Results[b] R^2	Results[b] R^3	Results[b] R^4	Yield (%)
i	**3**	Bz	Bz	$NaBH_4/(Bu)_4NBH_4$	**11**			H	OH	27
					3			OH	H	54
ii	**3**	Bz	Bz	L-selectride®	**11**			H	OH	20
					17	H	Bz	H	OBz	49
iii	**3**	Bz	Bz	$Zn(BH_4)_2$	**11**			H	OH	11
					3			OH	H	71
iv	**4**	Bz	Bn	$NaBH_4/(Bu)_4NBH_4$	**12**			H	OH	11
					4			OH	H	67
v	**4**	Bz	Bn	L-selectride®	**12**			H	OH	39
					18	H	Bn	H	OBz	43
vi	**4**	Bz	Bn	$Zn(BH_4)_2$	**12**			H	OH	4
					4			OH	H	76
vii	**6**	Bn	Bz	$NaBH_4/(Bu)_4NBH_4$	**13**			H	OH	62[c]
					6			OH	H	15[c]
viii	**6**	Bn	Bz	L-selectride®	**13**			H	OH	58
					19	Bn	OH	H	OBz	20
ix	**6**	Bn	Bz	$Zn(BH_4)_2$	**13**			H	OH	37[c]
					6			OH	H	44[c]

(*continued*)

Table 3: Continued.

Entry	GlcN Compound	R^1	R^2	Reducing agent[a]	Products	Results[b] R^1	R^2	R^3	R^4	Yield (%)
x	**7**	Bn	Bn	$NaBH_4/(Bu)_4NBH_4$	**14**			H	OH	66[c]
					7			OH	H	11[c]
xi	**7**	Bn	Bn	L-selectride®	**14**			H	OH	80[c]
xii	**7**	Bn	Bn	$Zn(BH_4)_2$	**14**			H	OH	50[c]
					7			OH	H	33[c]
xiii	**9**	All	Bz	$NaBH_4/(Bu)_4NBH_4$	**15**			H	OH	61[c]
					9			OH	H	12[c]
xiv	**9**	All	Bz	L-selectride®	**15**			H	OH	50
					20	All	OH	H	OBz	20
xv	**9**	All	Bz	$Zn(BH_4)_2$	**15**			H	OH	53[c]
					9			OH	H	26[c]
xvi	**10**	All	Bn	$NaBH_4/(Bu)_4NBH_4$	**16**			H	OH	66[c]
					10			OH	H	9[c]
xvii	**10**	All	Bn	L-selectride®	**16**			H	OH	83
xviii	**10**	All	Bn	$Zn(BH_4)_2$	**16**			H	OH	60[c]
					10			OH	H	15[c]

[a] The reductions were performed at −10°C for $NaBH_4/(Bu)_4NBH_4$ and L-selectride® and at 0°C for $Zn(BH_4)_2$, all in THF.
[b] Unless otherwise stated, R^1 and R^2 are identical to the groups presented in corresponding row.
[c] The epimers were not separated; the ratio was determined from ^1H NMR (300 MHz).

compound **3**. Reduction with L-selectride® produced only the *galacto* isomer, but unfortunately, the benzoyl group at C-3 partly migrated to the axial hydroxyl, leading to the formation of **11** (20%) and the 4-*O*-benzoylated analogue **17** in 49% yield (entry ii). Using $Zn(BH_4)_2$ as the reducing agent obstructed the desired stereoselectivity leading to *galacto*/*gluco* epimers **11** and **3** being formed in a 1:6.5 relationship (entry iii).

In the reduction of oxidized **4** with $NaBH_4/Bu_4NBH_4$, the *galacto* epimer **12** was observed in 11% yield together with regenerated starting compound **4** (67%) (entry iv). When reduction was performed with L-selectride® (entry v), the benzoyl-migrated compound **18** (43%) was found as the major product, together with the compound **12** in 39% yield. $Zn(BH_4)_2$ reduction of 3-*O*-benzoyl-6-*O*-benzylated ketohexose gave almost *gluco* epimer **4** (76%) (entry vi). It should be noted, that, no *gluco* epimer was observed using L-selectride® for either of the oxidized 3-*O*-benzoylated compounds **3** and **4**.

For the 3-*O*-benzylated ketohexoses formed from compounds **6** and **7**, the stereoselectivity in the reduction with $NaBH_4/Bu_4NBH_4$ favored the formation of **13** and **14** with axial hydroxyl groups (entries vii and x). The best ratio of *galacto*/*gluco* epimer was observed for the 6-*O*-benzylated derivative **7** (6:1, 77%) (entry x). Unfortunately, it was impossible to separate the product from the starting material in both reductions using silica gel chromatography. The ratio between the isomers was determined from ^1H NMR experiments. Changing to L-selectride® gave only the *galacto* epimer, but as described above, the reaction conditions enabled the 6-*O*-benzoyl group to migrate to the axial hydroxyl group on C-4. Derivative **13** was isolated in 58% yield together with the migrated analogue **19** in 20% yield (entry viii). On the other hand, when oxidized compound **7** was treated with L-selectride®, the only product was the corresponding galactosamine compound **14** in 80% yield (entry xi). The reductions with $Zn(BH_4)_2$ gave remarkable changes in stereoselectivity compared to using $NaBH_4/Bu_4NBH_4$. For 3-*O*-benzyl-6-*O*-benzoyl ketohexose produced from **6**, the ratio of *galacto*/*gluco* epimer changed from 4:1 to 0.8:1 (entries vii and ix). The stereoselectivity of the corresponding reaction of 3,6-di-*O*-benzyl derivative **7** with $Zn(BH_4)_2$ was nearly leveled out (entry xii).

Further, the oxidized 3-*O*-allyl protected derivatives **9** and **10** showed favored formation of their axial analogues **15** and **16**, respectively, when treated with $NaBH_4/Bu_4NBH_4$. Also here the 6-*O*-benzylated derivative **10** gave the highest ratio (7.3:1) of axial alcohol compared to the 6-*O*-benzoyl compound **9** (5:1), and likewise, the separation between the two sets of epimers failed (entries xvi and xiii). Reduction of ketohexose of **9** with L-selectride® gave the desired galactosamine derivative **15** in 50% yield together with the 4-*O*-benzoylated compound **20** in 20% yield (entry xiv). In the reduction of oxidized **10** with L-selectride®, the result was satisfying; the epimer **16** with an axial hydroxyl group was found in 83% total yield for

the oxidation/reduction route (entry xvii). As in all former reactions with $Zn(BH_4)_2$, the selectivity for formation of *galacto* epimer were turned to preferred formation of *gluco* isomer compared to the reductions using $NaBH_4/Bu_4NBH_4$. For the 3-*O*-allylic-6-*O*-benzoyl compound, the ratio of *galacto*/*gluco* epimer was changed from 5:1 to 2:1 (entries xiii and xv), whereas the corresponding 6-*O*-benzylated derivative changed from 7.3:1 to 4:1 (entries xvi and xviii).

In conclusion, the oxidation/reduction route is a most convenient epimerization method with L-selectride® as a reducing agent, when no benzoyl-protecting groups are used, due to their migratory aptitude during these conditions. No glucosamine derivatives were obtained in the reductions using L-selectride®. The stereoselectivity in the reductions with $NaBH_4/Bu_4NBH_4$ gave a favored *galacto*/*gluco* epimer ratio for the 3-*O*-etheral (allyl or benzyl) derivatives compared to the 3-*O*-benzoylated compounds. Interestingly, for the 3-*O*-etheral compounds, a 6-*O*-benzylic group enhanced the formation of the *galacto* epimer, whereas for the 3-*O*-benzoylic derivatives, a 6-*O*-benzoyl-protecting group favored the formation of axial alcohol.

CONCLUSIONS

The displacement route via the triflate using $NaNO_2$ in DMF was most convenient for the 3-*O*-benzoylated species **3** and **4** with respect to yield and reaction times. Using alkoxy groups in position 3 gave both acceptable and similar yields of inverted epimers **13**–**16** (74–63%). Improvements were found using Bu_4NNO_2 in toluene (82–68%), but still the epimerizations required longer reaction times and higher temperatures than the 3-*O*-benzoylated derivatives. The influence of the chemical character of the C-6 protecting group is risky to state as the differences in yield are small.

The stereoselectivity in the reductions of oxidized acylated compounds **3** and **4** with $NaBH_4/Bu_4NBH_4$ were not satisfying and, using L-selectride®, gave partial acyl migrations to the formed axial hydroxyl. Thus, to obtain derivatives **11** and **12**, the preferred method is the displacement route. For the benzylated compounds **6** and **7**, the stereoselectivity using $NaBH_4/Bu_4NBH_4$ was much better, but unfortunately, the *galacto*/*gluco* epimers could not easily be separated. For 3,6-di-*O*-benzylated **7**, this would not be a problem as changing the reducing agent to L-selectride® produced the *galacto* epimer **14** in good yield (80%). On the other hand, the best way to epimerize C-4 in **6** → **13** would be to use the displacement route. Of note is that a benzylated C-6 gave higher stereoselectivity to produce axial hydroxyl (ratio 6:1 for **14**/**7** compared to 4:1 for **13**/**6**; see Table 2 entries ix and vii). This relationship was also found for the two 3-*O*-allylic species **9** and **10** (ratio 7.3:1 for **16**/**10** compared to 5:1 for **15**/**9**, entries xvi and xiii). The diastereocourse of the reduction of oxidized 3-*O*-benzoyl derivatives was shown

to be the opposite. Here, the benzylated C-6 compound **4** gave a diminished stereoselectivity toward axial *galacto* epimer (ratio 1:2 for **11**/**3** compared to 1:6 for **12**/**4**, entries i and iv). As mentioned above, the epimers were not possible to separate. Naturally, choosing between the epimerization methods, the displacement route is preferred for **9** → **15** and the oxidation/reduction using L-selectride® for the conversion of **10** → **16**. To summarize the reductions of synthesized 4-ketohexoses with $Zn(BH_4)_2$, the *galacto*/*gluco* ratio was in all cases disfavored compared with the reductions using $NaBH_4/Bu_4NBH_4$, revealing $Zn(BH_4)_2$ not to be a good choice as a reducing agent in the oxidation/reduction route.

Efficient synthetic protocols for ethyl-2-deoxy-2-phtalimido-thiogalactosyl acceptors/donors have been worked out using the ability to prepare crystalline thioglycoside **1** in a large amount from D-glucosamine hydrochloride. These results will be undertaken in future projects involving oligosaccharide synthesis, for example, the synthesis of antifreeze glycoprotein derivatives.

EXPERIMENTAL

General Methods

Organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* below 40°C. NMR spectra were recorded on a Varian Mercury 300 (^{1}H 300 MHz and ^{13}C 75.4 MHz) instrument at 25°C in $CDCl_3$/MeOH 99:1 (^{1}H, for deuteration of alcohol protons) or in 100% $CDCl_3$ (^{13}C). Chemical shifts are given in ppm relative to TMS ($\delta = 0.00$) for ^{1}H and to $CDCl_3$ ($\delta = 77.0$), for ^{13}C, respectively. Signals were assigned by using DEPT, 2D (COSY and HMQC), and homonuclear decoupled experiments. TLC was performed on silica gel F_{254} (E. Merck) with detection by UV light (254 nm) and/or by charring with ethanol/sulfuric acid/*p*-anisaldehyde/acetic acid (90:3:2:1) followed by heating at 250°C. Silica gel MERCK 60(0.040–0.063 mm) was used for flash chromatography (FC). Optical measurements were recorded at rt with a Perkin-Elmer 241 polarimeter. Melting points were recorded with an uncorrected Gallenkamp melting point apparatus. MALDI-TOF mass spectra were recorded with a Voyager-DE STR Biospectrometry Workstation, in positive mode, using a α-cyano-4-hydroxycinnamic acid matrix and the dimer (m/z 379.0930) as internal standard. IR spectra were recorded (KBr pellets) on a Perkin-Elmer SPECTRUM 1000 FT-IR Spectrometer.

Triflate Formation

To a solution of alcohol (0.70 mmol) and pyridine (1.40 mmol) in dry CH_2Cl_2 (5 mL) was added Tf_2O (0.90 mmol) at −5°C. The solution was allowed to reach rt during 1 hr, diluted with CH_2Cl_2, and washed sequentially with 0.1 M aq.

hydrochloric acid and aq. $NaHCO_3$ (sat.). The organic phase was dried, filtered, and concentrated to give the crude triflate.

Displacement of Triflates with Nitrite Anions

A. $NaNO_2$/DMF

To a solution of triflate (0.70 mmol) in DMF (4 mL), $NaNO_2$ (7 mmol) was added. When the triflate was consumed according to TLC, the mixture was diluted with CH_2Cl_2, washed with water, dried, filtered, and concentrated followed by purification with FC.

B. Bu_4NNO_2/toluene

To a solution of triflate (0.70 mmol) in toluene (4 mL), Bu_4NNO_2 (4.9 mmol) was added. When the triflate was consumed according to TLC, the mixture was concentrated followed by purification with FC.

Oxidation to 4-Ketohexose

DCC (1.05 mmol) was added to a solution of alcohol (0.70 mmol), pyridine (0.74 mmol), and TFA (0.39 mmol) in CH_2Cl_2/DMSO (4 mL, 1:1). The mixture was stirred overnight and diluted with CH_2Cl_2, filtered through zelite, and washed twice with water. The organic phase was dried, filtered, and concentrated. The crude ketosugar was dissolved in Et_2O (15 mL), insoluble materials were filtered off, and concentration of the filtrate gave crude ketohexose.

Reduction of 4-ketohexoses with Hydrides

A. $NaBH_4$/Bu_4NBH_4

To a solution of the obtained ketosugar (0.70 mmol) in THF (6 mL) was added $NaBH_4$ (0.70 mmol) and *n*-Bu_4NBH_4 (0.14 mmol) at $-10^{\circ}C$. After 10 min the solution was diluted with CH_2Cl_2, washed twice with aq. $NaHCO_3$ (sat.), dried, filtered, and concentrated, and the obtained residue was subjected to FC.

B. L-selectride®

To the crude ketohexose (0.70 mmol) dissolved in THF (6 mL) at $-10^{\circ}C$, L-selectride® (0.80 mmol, 1 M in THF) was added. The solution was stirred for 10 min, diluted with CH_2Cl_2, poured into a separatory funnel, and washed sequentially with 0.1 M aq. hydrochloric acid and aq. $NaHCO_3$ (sat.). The organic phase was dried, filtered, and concentrated, and the obtained residue was subjected to FC.

C. $Zn(BH_4)_2$

To the crude ketohexose (0.70 mmol) dissolved in THF (6 mL) at $0^{\circ}C$, $Zn(BH_4)_2$[26] (1.40 mmol, 0.35 M in Et_2O) was added. The solution was stirred for 30 min, diluted with CH_2Cl_2, poured into a separatory funnel, and washed sequential with aq. $NaHCO_3$ (sat.). The organic phase was dried, filtered, and concentrated, and the obtained residue was purified by silica FC.

Ethyl-4,6-*O*-benzylidene-3-*O*-benzoyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (2). To an ice-cold solution of thioglucoside **1**[30] (5.00 g, 11.30 mmol) in pyridine (25 mL), benzoylchloride (1.90 mL, 16.35 mmol) was added dropwise. After 1 hr the solution was diluted with CH_2Cl_2, washed with water, and concentrated. The crude product was dissolved in CH_2Cl_2 and washed with 1 M aq. hydrochloride acid, aq. $NaHCO_3$ (sat.), dried, filtered, and concentrated. FC (toluene/EtOAc 10:1 → 4:1) gave **2** (6.120 g, 11.23 mmol, 99%) as a white foam. R_f 0.56 (toluene/EtOAc 6:1); $[\alpha]_D = +48$ (*c* 1.0, $CHCl_3$); m.p. 102°C (from MeOH); IR $\nu_{max}\,cm^{-1}$ 530, 646, 701, 712, 762, 874, 994, 1069, 1097, 1261, 1385, 1451, 1468, 1601, 1717, 1777, 2870, 1929, 1973, 3034, 3063; ^1H NMR δ 1.22 (3H, t, $J = 7.4$ Hz, CH_3CH_2), 2.62–2.81 (2H, m, CH_3CH_2), 3.83–3.97 (3H, m, H-4,5,6a), 4.46 (1H, dd, $J = 9.1$, 10.2, Hz, H-6b), 4.56 (1H, t, $J = 10.1$ Hz, H-2), 5.57 (1H, s, PhCH-), 5.65 (1H, d, $J = 10.1$ Hz, H-1) 6.22 (1H, t, $J = 10.1$ Hz, H-3), 7.26–7.88 (14H, Ph); ^{13}C NMR δ 14.9 (CH_3CH_2), 24.5 (CH_3CH_2), 54.2 (C-2), 68.7 (C-6), 70.7 (C-5), 70.9 (C-4), 79.7 (C-1), 81.9 (C-3), 101.6 (PhCH), 123.7 (Ph), 126.2 (Ph), 128.2–129.8 (Ph), 130.1 (Ph), 130.5 (Ph), 131.2 (Ph), 131.6 (Ph), 133.1 (Ph), 133.6 (Ph), 134.1 (Ph), 134.3 (Ph), 134.5 (Ph), 136.8 (Ph), 165.6 (PhCOO), 167.3 (PhCON), 167.8 (PhCON); Anal. Calcd for $C_{30}H_{27}NO_7S$: C, 66.04; H, 4.99. Found: C, 66.27; H, 5.04. MALDI-TOF calcd for $C_{30}H_{27}NO_7S$: $[M + Na]^+$ 568.1. Found: $[M + Na]^+$ 568.1.

Ethyl-3,6-di-*O*-benzoyl-2-deoxy-2-phtalimido-1-thio-β-D-glucopyranoside (3). Compound **2** (1.24 g, 2.28 mmol) and ethylene glycol (3.5 mL) were stirred in CH_2Cl_2/TFA (5:1, 24 mL). After 1 hr, the mixture was diluted with CH_2Cl_2, washed with aq. $NaHCO_3$ (sat.), dried, filtered, and concentrated. The residue was dissolved in pyridine (10 mL) and cooled to 0°C, whereupon benzoyl chloride (0.41 mL, 3.53 mmol) was added. After 2 hr the mixture was diluted with toluene and washed with 1 M aq. H_2SO_4 and aq. $NaHCO_3$ (sat.), dried, filtered, and concentrated. FC (toluene/EtOAc 10:1 → 3:1) gave **3** (1.10 g, 1.98 mmol, 87%) as a white solid. R_f 0.36 (toluene/EtOAc 4:1); IR $\nu_{max}\,cm^{-1}$ 531, 650, 713, 872, 968, 1027, 1085, 1118, 1180, 1271, 1285, 1321, 1375, 1390, 1450, 1601, 1698, 1722, 1780, 2870, 2885, 2930, 2948, 2964, 2976, 3064; ^1H spectrum was identical to that previously published.[12] ^{13}C NMR δ 14.9 (CH_3CH_2), 24.3 (CH_3CH_2), 53.7 (C-2), 64.0 (C-6), 69.9 (C-4), 74.7 (C-3), 78.2 (C-5), 81.0 (C-1), 123.4 (Ph), 128.0–129.6 (Ph), 131.0–134.2 (Ph), 166.6 (PhCOO), 166.7(PhCOO), 167.3 (PhCON), 167.9 (PhCON); MALDI-TOF calcd for $C_{30}H_{27}NO_8S$: $[M + Na]^+$ 584.1. Found: $[M + Na]^+$ 584.1.

Ethyl-3-*O*-benzoyl-6-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (4). Sodium cyanoborohydride ($NaCNBH_3$) (4.15 g, 65.99 mmol) was added at rt to a solution of **2** (4.00 g, 7.33 mmol) and 3 Å molecular sieves

in dry THF (50 mL). Under vigorous stirring the mixture was treated with HCl in diethyl ether until gas evolution ceased. The mixture was stirred for 2 hr, filtered through a pad of celite, and concentrated. FC (toluene/EtOAc 10:1 → 4:1) gave **4** (3.33 g, 6.08 mmol, 83%) as a white amorphous solid. R_f 0.39 (toluene/EtOAc 4:1); $[\alpha]_D + 91$ (*c* 1.1, $CHCl_3$); IR $\nu_{max}\,cm^{-1}$ 3087, 3030, 2966, 2927, 2869, 1776, 1717, 1601, 1496, 1451, 1386, 1270, 1199, 1178, 1070, 1026, 968, 875, 713, 650, 530; ^{1}H NMR δ 1.23 (t, 3H, $J = 7.5$ Hz, CH_3CH$_2$), 2.60–2.77 (m, 2H, CH$_3$CH_2), 3.82 (ddd, 1H, $J = 3.3$, 4.5, 8.1, Hz, H-5), 3.87–3.89 (m, 2H, H-6ab), 3.93 (dd, 1H, $J = 8.1$, 8.7 Hz, H-4), 4.52 (dd, 1H, $J =$ 10.2, 10.5 Hz, H-2), 4.61 (d, 1H, $J = 12.0$ Hz, CH_2Ph), 4.66 (d, 1H, $J = 12.0$ Hz, CH_2Ph), 5.53 (d, 1H, $J = 10.5$ Hz, H-1), 5.93 (dd, 1H, $J = 8.7$, 10.2 Hz, H-3), 7.29–7.86 (m, 14H, Ph); ^{13}C NMR δ 14.8 (*C*H$_3$CH$_2$), 24.1 (CH$_3$*C*H$_2$), 53.6 (C-2), 69.8 (C-6), 70.6 (C-4), 73.5 (*C*H$_2$Ph), 74.8 (C-3), 79.0 (C-5), 80.8 (C-1), 123.4 (Ph), 127.5 (Ph), 128.2 (Ph), 128.8 (Ph), 129.6 (Ph), 130.9 (Ph), 131.3 (Ph), 133.2 (Ph), 134.0 (Ph), 134.1 (Ph), 137.8 (Ph), 166.5 (Ph*C*OO), 167.3 (Ph*C*ON), 167.8 (Ph*C*ON). Anal. Calcd for $C_{30}H_{29}NO_7S$: C, 65.80; H, 5.34. Found: C, 65.67; H, 5.42. MALDI-TOF calcd for $C_{30}H_{29}NO_7S$: $[M + Na]^+$ 570.2. Found: $[M + Na]^+$ 570.2.

Ethyl-6-*O*-benzoyl-3-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (6). Compound **6** (2.615 g, 4.78 mmol, 84%) was synthesized following the same procedure as for **3**, using **5** (3.00 g, 5.69 mmol), ethylene glycol (4.0 mL), CH_2Cl_2/TFA (5:1, 30 mL), benzoyl chloride (0.92 mL, 7.97 mmol), and pyridine (10 mL). FC (toluene/EtOAc 6:1 → 3:1) gave **6** as a white solid. R_f 0.32 (toluene/EtOAc 4:1) $[\alpha]_D + 26$ (*c* 2.0, $CHCl_3$); IR $\nu_{max}\,cm^{-1}$ 3087, 3064, 3028, 2958, 2940, 2924, 2882, 1782, 1716, 1602, 1583, 1495, 1452, 1386, 1319, 1288, 1180, 1119, 1086, 1061, 976, 965, 873, 751, 719, 651, 532; ^{1}H NMR δ 1.17 (t, 3H, $J = 7.4$ Hz, CH_3CH$_2$), 2.53–2.74 (m, 2H, CH$_3$CH_2), 3.69 (dd, 1H, $J = 8.0$, 9.9 Hz, H-4), 3.78 (ddd, 1H, $J = 2.1$, 4.0, 9.9 Hz, H-5), 4.23 (dd, 1H, $J = 9.9$, 10.2 Hz, H-2), 4.31 (dd, 1H, $J = 8.0$, 10.2 Hz, H-3), 4.55 (d, 1H, $J = 12.1$ Hz, CH_2Ph), 4.59 (dd, 1H, $J = 2.1$ 12.2 Hz, H-6a), 4.75 (d, 1H, $J = 12.1$ Hz, CH_2Ph), 4.78 (dd, 1H, $J = 4.0$, 12.2 Hz, H-6b), 5.32 (d, 1H, $J = 9.9$ Hz, H-1) 6.95–8.10 (m, 14H, Ph); ^{13}C NMR δ 14.9 (*C*H$_3$CH$_2$), 24.0 (CH$_3$*C*H$_2$), 54.5 (C-2), 63.8 (C-6), 71.8 (C-4), 74.6 (*C*H$_2$Ph), 78.1 (C-5), 79.5 (C-3), 81.2 (C-1), 123.2 (Ph), 123.4 (Ph), 127.4 (Ph), 127.8–129.7 (Ph), 131.4 (Ph), 133.2 (Ph), 133.8 (Ph), 137.8 (Ph), 167.1 (Ph*C*OO), 167.4 (Ph*C*ON), 168.0 (Ph*C*ON); Anal. Calcd for $C_{30}H_{29}NO_7S$: C, 65.80; H, 5.34. Found: C, 65.76; H, 5.44. MALDI-TOF calcd for $C_{30}H_{29}NO_7S$: $[M + Na]^+$ 570.2. Found: $[M + Na]^+$ 570.2.

Ethyl-3-*O*-allyl-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (8). A solution of **1**[30] (3.00 g, 6.80 mmol) and allylbromide (1.20 mL, 13.60 mmol) in DMF (25 mL) was added dropwise to NaH (544 mg,

13.60 mmol, 60% dispersion in oil) at 0°C and stirred for 2 hr. Ac_2O (5 mL) was added and the mixture was stirred for an additional 2 hr, quenched with MeOH, and diluted with toluene. The organic phase was washed with water, dried, filtered, and concentrated. FC (toluene/EtOAc 8:1) gave **8** (2.81 g, 5.84 mmol, 86%) as a white solid. R_f 0.63 (toluene/EtOAc 4:1); IR ν_{max} cm^{-1} 3083, 3068, 3055, 3035, 3007, 2978, 2964, 2938, 2924, 2871, 2853, 1774, 1717, 1610, 1468, 1455, 1392, 1293, 1258, 1106, 1060, 1012, 982, 961, 917, 877, 770, 722, 701, 647, 541, 531; ^1H spectrum was identical to that previously published.[33] ^{13}C NMR δ 14.8 (CH_3CH_2), 24.0 (CH_3CH_2), 54.8 (C-2), 68.6 (C-6), 70.5 (C-5), 73.2 ($CHCH_2O$), 76.0 (C-3), 81.9 (C-1), 82.6 (C-4), 101.2 (PhCH), 117.0 (CH_2=CH), 123.2 (Ph), 123.7 (Ph) 126.0 (Ph), 128.2 (Ph), 128.9 (Ph), 131.5 (Ph), 131.6 (Ph), 134.2 (Ph), 134.3 (Ph), 137.2 (CH_2=CH), 167.4 (PhCON), 168.2 (PhCON); MALDI-TOF calcd far $C_{26}H_{27}NO_6S$: $[M + Na]^+$ 504.2. Found: $[M + Na]^+$ 504.2.

Ethyl-3-*O*-allyl-6-*O*-benzoyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (9). Compound **9** (1.68 g, 4.73 mmol, 84%) was synthesized according to the method of **6**, using **8** (2.00 g, 4.02 mmol), ethylene glycol (4.0 mL), CH_2Cl_2/TFA (5:1, 30 mL), benzoyl chloride (0.65 mL, 5.63 mmol), and pyridine (12 mL). FC (toluene/EtOAc 10:1 → 4:1) gave **9** as a white solid. R_f 0.29 (toluene/EtOAc 4:1) $[\alpha]_D + 2$ (*c* 2.0, $CHCl_3$); IR ν_{max} cm^{-1} 3063, 2963, 2927, 2871, 1776, 1714, 1601, 1468, 1452, 1388, 1315, 1275, 1197, 1177, 1070, 1026, 873, 718, 650, 530; ^1H NMR δ 1.18 (t, 3H, $J = 7.5$ Hz, CH_3CH_2), 2.54–2.75 (m, 2H, CH_3CH_2), 3.64 (dd, 1H, $J = 8.4$, 9.9 Hz, H-4), 3.78 (ddd, 1H, $J = 2.1$, 4.5, 9.9 Hz, H-5), 3.98 (dddd, 1H, $J = 1.5$, 1.5, 6.0, 12.6 Hz, $CHCH_2O$), 4.16–4.25 (m, 3H, H-2,3, $CHCH_2O$), 4.60 (dd, 1H, $J = 2.1$, 12.0 Hz, H-6a), 4.73 (dd, 1H, $J = 4.5$, 12.0 Hz, H-6b), 4.85–5.07 (m, 2H, CH_2=CH), 5.35 (d, 1H, $J = 9.9$ Hz, H-1), 5.54–5.67 (m, 1H, $CH_2 = CH$), 7.43–8.08 (m, 9H, Ph); ^{13}C NMR δ 14.9 (CH_3CH_2), 24.0 (CH_3CH_2), 54.6 (C-2), 63.8 (C-6), 71.3 (C-4), 73.5 ($CHCH_2O$), 78.2 (C-5), 79.9 (C-3), 81.3 (C-1), 117.3 (CH_2=CH), 123.2 (Ph), 123.7 (Ph), 128.3 (Ph), 129.8 (Ph), 131.5 (Ph), 133.2 (Ph), 134.2 (Ph and CH_2=CH), 134.3 (Ph), 167.1 (PhCOO), 167.5 (PhCON), 168.4 (PhCON); Anal. Calcd for $C_{26}H_{27}NO_7S$: C, 62.76; H, 5.47. Found: C, 62.55; H, 5.35. MALDI-TOF calcd for $C_{26}H_{27}NO_7S$: $[M + Na]^+$ 520.1. Found: $[M + Na]^+$ 520.1.

Ethyl-3-*O*-allyl-6-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (10). Compound **10** (1.56 g, 3.24 mmol, 82%) was synthesized following the same procedure as for **4**, using **8** (1.90 g, 3.95 mmol), $NaCNBH_3$ (2.48 g, 39.5 mmol), 3 Å molecular sieves, and HCl/Et_2O in dry THF (25 mL) at 0°C. FC (toluene/EtOAc 6:1 → 1:1) gave **10** as a colorless syrup. R_f 0.30 (toluene/EtOAc 4:1); IR ν_{max} cm^{-1} 3086, 3064, 3028, 2926, 2870, 1775, 1716, 1612, 1468, 1453, 1389, 1292, 1266, 1197, 1088, 968, 874, 721, 699, 651, 531;

^{1}H spectrum was identical to that previously published.[33] ^{13}C NMR δ 14.8 (*C*H$_3$CH$_2$), 23.9 (CH$_3$*C*H$_2$), 54.5 (C-2), 70.1 (C-6), 72.4 (C-4), 73.2 (O*C*H$_2$CH), 73.6 (*C*H$_2$Ph), 78.7 (C-5), 79.9 (C-3), 81.0 (C-1), 117.0 (*C*H$_2$=CH), 123.1 (Ph), 123.6 (Ph), 127.6 (Ph), 128.3 (Ph), 131.4 (Ph), 131.5 (Ph), 134.1 (Ph), 134.3 (Ph), 137.7 (CH$_2$=*C*H), 167.6 (Ph*C*ON), 168.4 (Ph*C*ON). MALDI-TOF calcd for $C_{26}H_{29}NO_6S$: $[M + Na]^+$ 506.2. Found: $[M + Na]^+$ 506.2.

Ethyl-3,6-di-*O*-benzoyl-2-deoxy-2-phthalimido-1-thio-β-D-galactopyranoside (11). 11: R_f 0.44 (toluene/EtOAc 4:1); IR ν_{max} cm^{-1} 3089, 3032, 2971, 2960, 2922, 2910, 1765, 1720, 1600, 1467, 1452, 1390, 1344, 1316, 1265, 1157, 1114, 1071, 1025, 989, 924, 721, 709, 623, 531; ^{1}H spectrum was identical to that previously published.[12] ^{13}C NMR δ 14.9 (*C*H$_3$CH$_2$), 24.2 (CH$_3$*C*H$_2$), 50.0 (C-2), 63.3 (C-6), 66.8 (C-4), 71.8 (C-3), 76.1 (C-5), 81.3 (C-1), 123.4 (Ph), 123.5 (Ph), 125.2 (Ph), 128.1–129.7 (Ph), 131.1 (Ph), 131.5 (Ph), 133.1 (Ph), 133.3 (Ph), 134.1 (Ph), 135.0 (Ph), 135.1 (Ph), 137.7 (Ph), 165.3 (Ph*C*OO), 166.4 (Ph*C*OO), 167.5 (Ph*C*ON), 168.1 (Ph*C*ON). MALDI-TOF calcd for $C_{30}H_{27}NO_8S$: $[M + Na]^+$ 584.1. Found: $[M + Na]^+$ 584.1.

Ethyl-3-*O*-benzoyl-6-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-galactopyranoside (12). 12: R_f 0.49 (toluene/EtOAc 4:1) $[\alpha]_D + 82$ (*c* 1.1, $CHCl_3$); IR ν_{max} cm^{-1} 3087, 3062, 3030, 2961, 2927, 2869, 1774, 1716, 1601, 1496, 1468, 1452, 1386, 1315, 1269, 1152, 1111, 1070, 1026, 993, 876, 714, 699, 625, 530; ^{1}H NMR δ 1.24 (t, 3H, $J = 7.5$ Hz, C*H*$_3$CH$_2$), 2.64–2.85 (m, 2H, CH$_3$C*H*$_2$), 3.82 (dd, 1H, $J = 5.1$, 10.2 Hz, H-6a), 3.87 (dd, 1H, $J = 5.1$, 10.2 Hz, H-6b), 3.99 (ddd, 1H, $J = 0.9$, 5.1, 5.1 Hz, H-5), 4.45 (dd, 1H, $J = 0.9$, 3.0 Hz, H-4), 4.59 (d, 1H, $J = 12.0$ Hz, C*H*$_2$Ph), 4.63 (d, 1H, $J = 12.0$ Hz, C*H*$_2$Ph), 4.95 (dd, 1H, $J = 10.5$, 10.5 Hz, H-2), 5.52 (d, 1H, $J = 10.5$ Hz, H-1), 5.88 (dd, 1H, $J = 3.0$, 10.5 Hz, H-3), 7.16–8.18 (m, 14H, Ph); ^{13}C NMR δ 14.8 (*C*H$_3$CH$_2$ 23.7 (CH$_3$*C*H$_2$), 49.8 (C-2), 67.4 (C-4), 69.5 (C-6), 72.0 (C-3), 73.4 (*C*H$_2$Ph), 76.8 (C-5), 80.9 (C-1), 123.2 (Ph), 123.3 (Ph), 127.5–130.2 (Ph), 131.0 (Ph), 131.3 (Ph), 133.0 (Ph), 133.9 (Ph), 134.0 (Ph), 134.4 (Ph), 137.5 (Ph), 165.2 (Ph*C*OO), 167.4 (Ph*C*ON), 168.0 (Ph*C*ON); Anal. Calcd for $C_{30}H_{29}NO_7S$: C, 65.80; H, 5.34. Found: C, 65.87; H, 5.46. MALDI-TOF calcd for $C_{30}H_{29}NO_7S$: $[M + Na]^+$ 570.2. Found: $[M + Na]^+$ 570.2.

Ethyl-6-*O*-benzoyl-3-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-galactopyranoside (13). 13: R_f 0.33 (toluene/EtOAc 4:1) $[\alpha]_D + 80$ (*c* 1.0, $CHCl_3$); IR ν_{max} cm^{-1} 3087, 3062, 3030, 2963, 2927, 2871, 1772, 1713, 1602, 1496, 1468, 1452, 1388, 1315, 1278, 1154, 1117, 1067, 1027, 899, 751, 718, 701, 631, 530; ^{1}H NMR δ 1.17 (t, 3H, $J = 7.6$ Hz, C*H*$_3$CH$_2$), 2.54–2.76 (m, 2H, CH$_3$C*H*$_2$), 4.00 (ddd, 1H, $J = 0.9$, 5.4, 5.4 Hz, H-5), 4.18 (dd, 1H, $J = 0.9$, 3.3 Hz, H-4), 4.34 (dd, 1H, $J = 3.3$, 10.4 Hz, H-3), 4.38 (dd, 1H, $J = 10.4$, 10.4 Hz, H-2), 4.53–4.70 (m, 4H, H-6ab, C*H*$_2$Ph), 5.27 (d, 1H, $J = 10.4$ Hz,

H-1), 6.96–8.08 (m, 14H, Ph); ^{13}C NMR δ 14.9 (CH$_3$CH$_2$), 24.0 (CH$_3$$CH_2$), 50.9 (C-2), 63.8 (C-6), 65.7 (C-4), 71.4 (CH$_2$Ph), 75.5 (C-5), 76.0 (C-3), 81.2 (C-1), 123.2 (Ph), 123.5 (Ph), 127.8–129.9 (Ph), 131.5 (Ph), 133.1 (Ph), 133.8 (Ph), 133.9 (Ph), 137.0 (Ph), 166.3 (PhCOO), 167.6 (PhCON), 168.1 (PhCON); Anal. Calcd for $C_{30}H_{29}NO_7S$: C, 65.80; H, 5.34. Found: C, 65.66; H, 5.61. MALDI-TOF calcd for $C_{30}H_{29}NO_7S$: $[M + Na]^+$ 570.2. Found: $[M + Na]^+$ 570.2.

Ethyl-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-galactopyranoside (14). 14: R_f 0.33 (toluene/EtOAc 4:1) $[\alpha]_D + 62$ (c 1.0, CHCl$_3$); m.p. 117°C (from EtOH); IR ν_{max} cm^{-1} 3085, 3063, 3028, 2971, 2917, 2869, 1771, 1709, 1616, 1495, 1453, 1387, 1366, 1264, 1201, 1154, 1088, 1063, 993, 895, 875, 832, 749, 720, 700, 630, 529; ^{1}H NMR δ 1.17 (t, 3H, $J = 7.4$ Hz, CH_3CH$_2$), 2.55–2.77 (m, 2H, CH$_3$CH_2), 3.76–3.86 (m, 3H, H-5,6ab), 4.21 (d, 1H, $J =$ 3.3 Hz, H-4), 4.27 (dd, 1H, $J = 3.3$, 10.4 Hz, H-3), 4.31 (dd, 1H, $J = 10.4$, 10.4 Hz, H-2), 4.54 (d, 1H, $J = 10.7$ Hz, CH_2Ph), 4.59–4.65 (m, 3H, CH_2Ph), 5.23 (d, 1H, $J = 10.4$ Hz, H-1), 6.92–7.86 (m, 14H, Ph); ^{13}C NMR δ 14.8 (CH$_3$CH$_2$), 23.6 (CH$_3$$CH_2$), 50.9 (C-2), 65.7 (C-4), 69.1 (C-6), 71.1 (CH$_2$Ph), 73.6 (CH$_2$Ph), 75.6 (C-3), 77.1 (C-5), 81.0 (C-1), 123.1 (Ph), 123.4 (Ph), 127.6–128.3 (Ph), 131.5 (Ph), 131.6 (Ph), 133.7 (Ph), 133.9 (Ph), 137.1 (Ph), 137.9 (Ph), 167.6 (PhCON), 168.1 (PhCON); Anal. Calcd for $C_{30}H_{31}NO_6S$: C, 67.52; H, 5.86. Found: C, 67.31; H, 5.74. MALDI-TOF calcd for $C_{30}H_{31}NO_6S$: $[M + Na]^+$ 556.2. Found: $[M + Na]^+$ 556.2.

Ethyl-3-*O*-allyl-6-*O*-benzoyl-2-deoxy-2-phthalimido-1-thio-β-D-galactopyranoside (15). 15: R_f 0.27 (toluene/EtOAc 4:1); $[\alpha]_D + 51$ (c 0.7, CHCl$_3$); IR ν_{max} cm^{-1} 3063, 2965, 2927, 2871, 1773, 1712, 1602, 1468, 1451, 1388, 1315, 1277, 1194, 1175, 1118, 1087, 1068, 1027, 990, 774, 715, 621, 530; ^{1}H NMR δ 1.18 (t, 3H, $J = 7.5$ Hz, CH_3CH$_2$), 2.57–2.77 (m, 2H, CH$_3$CH_2), 3.89 (dddd, 1H, $J = 1.5$, 1.5, 6.0, 12.9 Hz, CHCH_2O), 4.00–4.11 (m, 2H, H-5, CHCH_2O), 4.19 (d, 1H, $J = 3.3$ Hz, H-4), 4.31 (dd, 1H, $J = 3.3$, 10.4 Hz, H-3), 4.58 (dd, 1H, $J = 10.4$, 10.4 Hz, H-2), 4.61 (dd, 1H, $J = 6.1$, 11.5 Hz, H-6a), 4.69 (dd, 1H, $J = 5.2$, 11.5 Hz, H-6b), 4.96–5.14 (m, 2H, CH_2 = CH), 5.30 (d, 1H, $J = 10.4$ Hz, H-1), 5.57–5.70 (m, 1H, CH$_2$ = CH), 7.14–8.08 (m, 9H, Ph); ^{13}C NMR δ 14.9 (CH$_3$CH$_2$), 24.1 (CH$_3$$CH_2$), 51.0 (C-2), 63.9 (C-6), 66.0 (C-4), 70.5 (CHCH$_2$O), 75.7 (C-3), 76.1 (C-5), 81.3 (C-1), 118.1 (CH$_2$=CH), 123.2 (Ph), 123.7 (Ph), 128.3 (Ph), 129.7 (Ph) 129.9 (Ph), 131.6 (Ph), 131.7 (Ph), 133.1 (Ph), 133.6 (CH = CH$_2$), 134.1 (Ph), 166.4 (PhCOO), 167.6 (PhCON), 168.6 (PhCON); Anal. Calcd for $C_{26}H_{27}NO_7S$: C, 62.76; H, 5.47. Found: C, 62.51; H, 5.32. MALDI-TOF calcd for $C_{26}H_{27}NO_7S$: $[M + Na]^+$ 520.1. Found: $[M + Na]^+$ 520.1.

Ethyl-3-*O*-allyl-6-*O*-benzyl-2-deoxy-2-phtalimido-1-thio-β-D-galactopyranoside (16). 16: R_f 0.31 (toluene/EtOAc 4:1); IR ν_{max} cm^{-1} 3074, 3062,

3049, 2956, 2926, 2869, 1773, 1712, 1613, 1468, 1453, 1387, 1265, 1146, 1097, 1061, 991, 924, 721, 700, 621, 530; ^{1}H spectrum was identical to that previously published.[33] ^{13}C NMR δ 14.8 (*C*H_3CH$_2$), 23.7 (CH$_3$*C*H$_2$), 51.0 (C-2), 65.9 (C-4), 69.2 (C-6), 70.3 (CH*C*H$_2$O), 73.6 (*C*H$_2$Ph), 75.8 (C-3), 77.2 (C-5), 81.2 (C-1), 117.9 (*C*H$_2$=CH), 123.1 (Ph), 123.7 (Ph), 127.7–129.0 (Ph), 131.6 (Ph), 131.7 (Ph), 133.8 (*C*H=CH$_2$), 134.0 (Ph), 134.1 (Ph), 138.0 (Ph), 167.7 (Ph*C*ON), 168.6 (Ph*C*ON). MALDI-TOF calcd for $C_{26}H_{29}NO_6S$: $[M + Na]^+$ 506.2. Found: $[M + Na]^+$ 506.2.

Ethyl-4,6-di-*O*-benzoyl-2-deoxy-2-phthalimido-l-thio-β-D-galactopyranoside (17). 17: R_f 0.28 (toluene/EtOAc 4:1); $[\alpha]_D$ +50 (*c* 1.0, $CHCl_3$); IR ν_{max} cm^{-1} 3063, 3033, 2966, 2929, 2872, 1774, 1715, 1602, 1584, 1492, 1469, 1452, 1389, 1316, 1273, 1195, 1177, 1115, 1070, 1051, 1026, 907, 869, 803, 758, 711, 622, 579, 531; ^{1}H NMR δ 1.23 (t, 3H, $J = 7.5$ Hz, C*H*$_3$CH$_2$), 2.62–2.82 (m, 2H, CH$_3$C*H*$_2$), 4.28 (dd, 1H, $J = 6.0$, 7.2 Hz, H-5), 4.40 (dd, 1H, $J = 6.0$, 11.4 Hz, H-6a), 4.57 (dd, 1H, $J = 7.2$, 11.4 Hz, H-6b), 4.58 (dd, 1H, $J = 10.5$, 10.5 Hz, H-2), 4.81 (dd, 1H, $J = 3.6$, 10.5 Hz, H-3), 5.48 (d, 1H, $J = 10.5$ Hz, H-1), 5.77 (d, 1H, $J = 3.6$ Hz, H-4), 7.39–7.63 (m, 6H, Ph), 7.66–7.72 (m, 2H, Ph), 7.78–7.83 (m, 2H, Ph), 7.99–8.03 (m, 2H, Ph), 8.11–8.16 (m, 2H, Ph); ^{3}C NMR δ 15.0 (*C*H$_3$CH$_2$), 24.5 (CH$_3$*C*H2), 53.3 (C-2), 62.8 (C-6), 68.6 (C-3), 70.8 (C-4), 75.3 (C-5), 81.9 (C-1), 123.3 (Ph), 123.7 (Ph), 128.3–130.1 (Ph), 131.6 (Ph), 131.7 (Ph), 133.2 (Ph), 133.6 (Ph), 134.1 (Ph), 166.1 77 (Ph*C*OO), 166.7 (Ph*C*OO), 168.0 (PhCON), 168.4 (PhCON); Anal. Calcd for $C_{30}H_{27}NO_8S$: C, 64.16; H, 4.85. Found: C, 63.97; H, 4.84. MALDI-TOF calcd for $C_{30}H_{27}NO_8S$: $[M + Na]^+$ 584.1. Found: $[M + Na]^+$ 584.1.

Ethyl-4-*O*-benzoyl-6-*O*-benzyl-2-deoxy-2-phthalimido-l-thio-β-D-galactopyranoside (18). 18: R_f 0.28 (toluene/EtOAc 4:1); $[\alpha]_D + 49$ (*c* 1.0, $CHCl_3$); IR ν_{max} cm^{-1} 3063, 3031, 2966, 2927, 2870, 1772, 1714, 1602, 1584, 1496, 1468, 1452, 1389, 1314, 1272, 1196, 1177, 1110, 1070, 1049, 1026, 907, 869, 794, 718, 700, 668, 623, 578, 531; ^{1}H NMR δ 1.23 (t, 3H, $J = 7.4$ Hz, C*H*$_3$CH$_2$), 2.63–2.83 (m, 2H, CH$_3$C*H*$_2$), 3.60 (dd, 1H, $J = 6.7$, 9.8 Hz, H-6a), 3.67 (dd, 1H, $J = 6.2$, 9.8 Hz, H-6b), 4.10 (dd, 1H, $J = 6.2$, 6.7 Hz, H-5), 4.42 (d, 1H, $J = 11.8$ Hz, C*H*$_2$Ph), 4.52 (d, 1H, $J = 11.8$ Hz, C*H*$_2$Ph), 4.53 (dd, 1H, $J = 10.7$, 10.7 Hz, H-2), 4.78 (dd, 1H, $J = 3.6$, 10.7 Hz, H-3), 5.42 (d, 1H, $J = 10.7$ Hz, H-1), 5.71 (d, 1H, $J = 3.6$ Hz, H-4), 7.18–7.27 (m, 5H, Ph), 7.44–7.49 (m, 2H, Ph), 7.57–7.62 (m, 1H, Ph), 7.67–7.71 (m, 2H, Ph), 7.78–7.84 (m, 2H, Ph), 8.0–8.12 (m, 2H, Ph); ^{13}C NMR δ 14.9 (CH$_3$CH$_2$), 24.2 (CH$_3$*C*H$_2$), 53.3 (C-2), 68.3 (C-6), 68.5 (C-3), 71.1 (C-4), 73.5 (CH$_2$Ph), 76.6 (C-5), 81.6 (C-1), 123.2 (Ph), 123.6 (Ph), 127.6–130.0 (Ph), 131.6 (Ph), 131.7 (Ph), 133.4 (Ph), 134.1 (Ph), 137.6 (Ph), 166.8 (Ph*C*OO), 168.1 (Ph*C*ON), 168.4 (Ph*C*ON); Anal. Calcd for $C_{30}H_{29}NO_7S$: C, 65.80; H,

5.34. Found: C, 65.62; H, 5.28. MALDI-TOF calcd for $C_{30}H_{29}NO_7S$: $[M + Na]^+$ 570.2. Found: $[M + Na]^+$ 570.2.

Ethyl-4-*O*-benzoyl-3-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-galacto-pyranoside (19). 19: R_f 0.18 (toluene/EtOAc 4:1); $[\alpha]_D + 109$ (*c* 1.0, $CHCl_3$); IR ν_{max} cm^{-1}, 3063, 3031, 2965, 2929, 2873, 1773, 1714, 1602, 1496, 1468, 1453, 1389, 1273, 1314, 1273, 1177, 1113, 1088, 1068, 1026, 908, 870, 720, 629, 530; ^{1}H NMR δ 1.22 (t, 3H, $J = 7.4$ Hz, CH_3CH$_2$), 2.63–2.82 (m, 2H, CH$_3$CH_2), 3.61 (m, 1H, H-6a), 3.82 (m, 1H, H-6b), 3.95 (dd, 1 H, $J = 6.9$, 6.9 Hz, H-5), 4.33 (d, 1 H, $J = 12.4$ Hz, CH_2Ph), 4.50 (dd, I H, $J = 3.3$, 10.4 Hz, H-3), 4.71 (t, 1H, $J = 10.4$ Hz, H-2), 5.37 (d, 1H, $J = 10.4$ Hz, H-1), 5.79 (d, 1H, J = 3.3 Hz, H-4), 6.91–7.06 (m, 5H, Ph), 7.49–7.86 (m, 7H, Ph), 8.14–8.16 (m, 2H, Ph); ^{13}C NMR δ 14.9 (CH$_3$CH$_2$), 24.0 (CH$_3$*C*H$_2$), 51.8 (C-2), 61.0 (C-6), 67.2 (C-4), 71.0 (CH$_2$Ph), 74.0 (C-3), 77.9 (C-5), 81.7 (C-1), 123.3 (Ph), 123.6 (Ph), 127.7–130.1 (Ph), 131.7 (2C, Ph), 133.6 (Ph), 133.9 (Ph), 134.0 (Ph), 137.2 (Ph), 167.1 (Ph*C*OO), 167.6 (Ph*C*ON), 168.0 (Ph*C*ON); Anal. Calcd for $C_{30}H_{29}NO_7S$: C, 65.80; H, 5.34. Found: C, 65.90; H, 5.39. MALDI-TOF calcd for $C_{30}H_{29}NO_7S$: $[M + Na]^+$ 570.2. Found: $[M + Na]^+$ 570.2.

Ethyl-4-*O*-benzoyl-3-*O*-allyl-2-deoxy-2-phthalimido-l-thio-β-D-galacto-pyranoside (20). 20: R_f 0.17 (toluene/EtOAc 4:1); $[\alpha]_D + 108$ (*c* 1.0, $CHCl_3$); IR ν_{max} cm^{-1} 3068, 2972, 2934, 2879, 1769, 1714, 1601, 1468, 1454, 1393, 1350, 1316, 1273, 1194, 1179, 1109, 1089, 1063, 1028, 933, 917, 870, 796, 759, 724, 715, 668, 619, 530; ^{1}H NMR δ 1.24 (t, 1H, $J = 7.4$ Hz, CH_3CH$_2$), 2.62–2.84 (m, 2H, CH$_3$CH_2), 3.59–3.64 (m, 1H, H-6a), 3.76–3.92 (m, 2H, H-6b, CHCH_2O), 3.95–4.06 (m, 2H, H-5, CHCH_2O), 4.55 (dd, 1H, $J = 3.0$, 10.4 Hz, H-3), 4.73 (dd, 1H, $J = 10.4$, 10.4 Hz, H-2), 4.91–5.08 (m, 2H, CH_2=CH), 5.41 (d, 1H, $J = 10.4$ Hz, H-1), 5.48–5.61 (m, 1H, CH$_2$=C*H*), 5.74 (d, 1H, $J = 3.0$ Hz, H-4), 7.47–8.15 (m, 14H, Ph); ^{13}C NMR δ 14.9 (*C*H$_3$CH$_2$), 24.0 (CH$_3$CH$_2$), 51.8 (C-2), 61.0 (C-6), 67.4 (C-4), 70.2 (CH*C*H$_2$O), 74.2 (C-3), 77.9 (C-5), 81.8 (C-1), 117.8 (*C*H$_2$=CH), 123.2 (Ph), 123.7 (Ph), 128.6 (Ph), 130.1 (Ph), 131.7 (2C, Ph), 133.6 (Ph), 133.7 (*C*H=CH$_2$), 134.2 (Ph), 168.5 (Ph*C*OO), 167.6 (Ph*C*ON), 168.5 (Ph*C*ON); Anal. Calcd for $C_{26}H_{27}NO_7S$: C, 62.76; H, 5.47. Found: C, 62.60; H, 5.41. MALDI-TOF calcd for $C_{26}H_{27}NO_7S$: $[M + Na]^+$ 520.1. Found: $[M + Na]^+$ 520.1.

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