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Tetrahedron 62 (2006) 4784–4794
Tetrahedron

Unusual anomeric rearrangement of *para*-nitrobenzoylxanthate D-glycosides: a new direct stereoselective access to α-thioglycosides from pyranose sugars

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Received 19 January 2006; revised 2 March 2006; accepted 7 March 2006
Available online 31 March 2006

Abstract—A mild and general procedure for the synthesis of α-thioglycosides from glycopyranoses is described. The method involves the treatment of pyranose reductive sugar with sodium hydride, carbon disulfide, and *p*-nitrobenzoyl chloride, as a key step, to yield *p*-nitrobenzoyl-α-D-thioglycopyranose intermediates with high stereoselectivity, in a one-pot-two-step process. The interest of the strategy highlights a direct stereoselective access to ether-protected 1-thiol-α-D-glycopyranose derivatives (Gal, Glc, and Man) from pyranoses in the absence of anomeric 'Lewis acid' promoters.

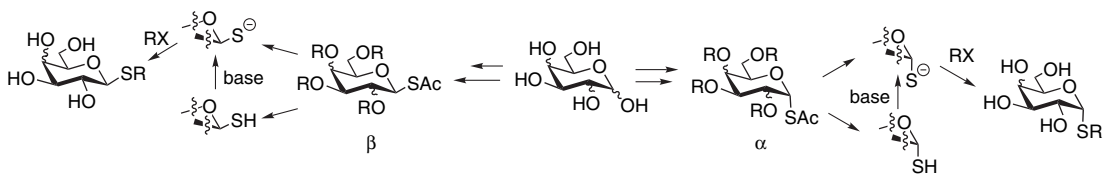
1. Introduction

The thiosaccharides, in which the oxygen of the glycosidic bond is replaced by a sulfur atom, are receiving considerable attention in glycobiology as potential enzyme substrates or inhibitors due to their resistance to acid/base or enzyme-mediated hydrolysis.[1–3] They have recently been highlighted as potent new therapeutic agents, for example, in anti-tumoral[4,5] or anti-HIV treatment.[6]

Within the range of general glycosylation methods, a number of glycosyl donors have been differentiated by the nature of the anomeric groups with a critical effect upon the activation step under acidic catalysis, neutral or basic conditons.[7–13] In the course of the stereoselective thioglycosylation process, halide, trichloroacetimidate, thio-alkyl or -aryl, and sulfoxide donors remain among efficient donors. The modulation of their reactivity with various promoters allows the anomeric substitution by nucleophilic partners including thiol-derivatives.[1,14]

However, base promoted S-alkylation of configurationally pure anomeric α and β-glycosyl thiol, xanthate or thiourea, by S_N2 displacement of alkylating agents has been found as one of the most elegant and powerful routes for the preparation of α and β-1-thioglycosides, respectively.[14,15] Indeed, it has been observed that the thioglycosyl anions do not mutarotate under basic conditions[1,16,17] and their anomerization is very slow[18] (Scheme 1).

The α and β-glycosyl thiolates are obtained from isolable α and β-anomeric thiols, respectively,[18–21] or by in situ



Scheme 1.

Keywords: Stereoselective α-thioglycosylation; α-Glycopyranoside thiols; α-Galactoside thiol; Thiolo-thiono rearrangement; α-Thiogalactolipids.
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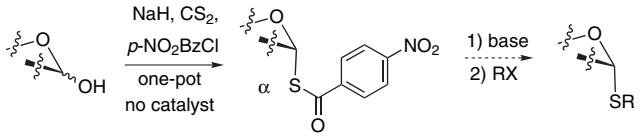
doi:10.1016/j.tet.2006.03.024

S-deacetylation of the corresponding anomeric thioacetates in the presence of bases (Et_2NH, MeONa,…).[1,17,22,23] The efficiency of the S-alkylation approach is overshadowed by the variable yields often associated with the generation of the anomeric thiolate and its subsequent reactivity with the electrophilic partner in solution. The use of costly hindered iminophosphorane bases has been recently proposed to minimize undesirable competing elimination and to avoid a trans-esterification side reaction when other sensitive *O*-ester protecting groups are present.[23] Furthermore, the access to configurationally pure α- and β-thioacetate (or xanthate and thiourea) anomers has been mainly performed by preliminary catalyzed S-glycosylation from suitable activated 2,3,4,6-ester-protected glycosyl halide, acetate and acetimidate donors in the presence of tetrabutylamonium salt of thioacetic acid and potassium thioacetate, respectively (or potassium ethyl xanthate and thiourea).[24–30] The attribute of the latter process, catalyzed by an ammonium salt or Lewis acid promoters, strongly depends on the nature of the activated donors and mostly affords high stereocontrol to produce 1,2-*trans*-thio-D-glycosides (β-gluco, β-galacto or α-manno) when a neighboring acyloxonium anomeric participation can be involved. Alternatively, Michael-addition of thionucleophiles to sugar enones has also been prone to achieve the access to thioglycosides.[5]

Due to the relative difficulty of conveniently achieving 1,2-*cis* glycosylation,[11] the introduction of a thioacetate group in a pure α-anomeric configuration in galacto or gluco series (or β-configuration for mannosides) and its subsequent in situ deacetylation for S-alkylation process has been promoted.[14] However, only a few syntheses of 1,2-*cis* thioglycosides have been reported.[14,24,31] Driguez and co-workers have used a fair combination of ester-protected α-1-thiolacetate glycosides,[31,32] derived from β-chloro and α-triphenylmetylthio-donors, to produce linear and branched α-thiooligosaccharides. In their convergent approaches, the authors performed the conversion of α-1-thiotrityl intermediates to α-1-thioacetate glycosides by subsequent $Hg(OAc)_2$, H_2S, and Ac_2O treatments. Alternatively, 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-glucopyranose can be also produced almost exclusively by fair photochemical addition of thioacetic acid, catalyzed by *tert*-butyl or cumene hydroperoxide, from tetra-*O*-acetyl-1,5-anhydro-D-arabino-hex-1-enitol.[33–35]

We describe here a mild and general procedure for the direct access to novel *S*-*p*-nitrobenzoyl-α-D-thioglycopyranose from ether-protected D-glycopyranose precursors, which can be regarded as new potent intermediates in the preparation of α-glycoside thiolates. The method involves the treatment of the reductive sugar with sodium hydride, carbon disulfide, and *p*-nitrobenzoyl chloride, as a key step, to yield in a one-pot-two step process the corresponding *S*-*p*-nitrobenzoyl-α-D-thioglycopyranose with high stereoselectivity (Scheme 2).

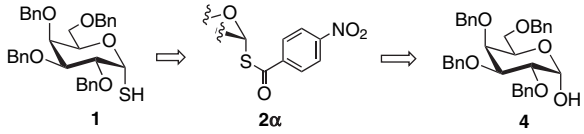


Scheme 2.

The results are discussed in terms of interpretation of an original mechanism and a first application to the preparation of α-thiogalactoconjugates following S-alkylation process.

2. Results and discussion

In our search for new thioglycosylation methods, we investigated a stereoselective access to 1-thiol-α-D-galactopyranose **1** (1,2-*cis*) derivatives from 2,3,4,6-tetra-*O*-benzyl-D-galactose **4**, via the 1-*S*-*p*-nitrobenzoyl-α-thiogalactopyranose **2α** (Scheme 3).

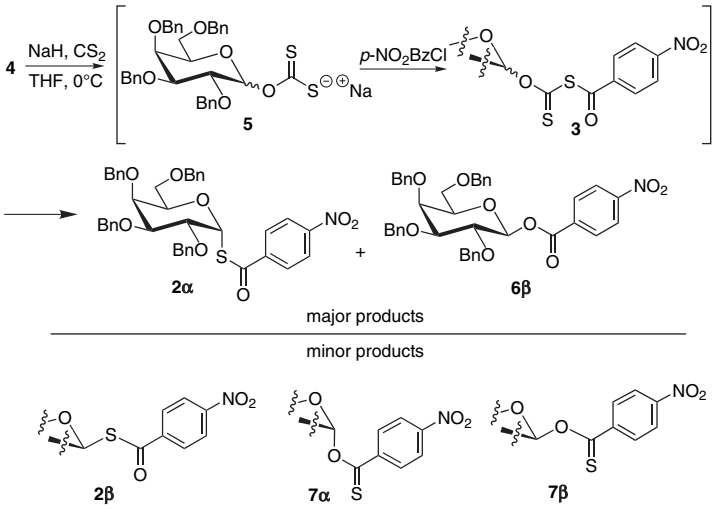


Scheme 3. Retrosynthesis of 1-thiol-α-D-galactopyranose **1**.

The 1-*S*-*p*-nitrobenzoyl-α-thiogalactopyranose **2α** resulted from an in situ rearrangement of the 1-*O*-(*S*-*p*-nitrobenzoyl)-dithiocarbonate-D-galactopyranose **3** formed by the treatment of tetrabenzyl-galactopyranose **4** with sodium hydride and carbon disulfide and subsequent addition of *p*-nitrobenzoyl chloride to the resulting xanthate salt (Scheme 4). When 1.1 equiv of each reagent were used, in THF, the 1-*S*-*p*-nitrobenzoyl-α-thiogalactopyranose **2α** and the 1-*O*-*p*-nitrobenzoyl-β-galactopyranose **6β** were identified as the major products formed in the reaction and were isolated in almost 50% yield. By-products, **2β**, **7α**, and **7β**, were also present in less than 10% overall yield and 25% of starting material **4** remained.

We attempted to improve the preparation of the thioester **2α** using the following optimized proportion of reagents: 1.2 equiv of NaH, 3 equiv of CS_2, and 1.2 equiv of *p*-NO_2BzCl in THF. The ratio between α-thioester **2α** and β-ester **6β** was evaluated and the most significant results are summarized in Table 1. When the reaction was run at 0 °C, the thioester **2α** and ester **6β** were formed in almost 60% yield (entry 1), with 20% of galactopyranose **4** remaining. After purification by chromatography on silica gel, compounds **2α** and **6β** were isolated in a 7/3 ratio. No decrease in the remaining initial pyranose **4** and no appearance of *O*-*p*-nitrobenzoyl anomer **6α** were observed when the reaction was continued for 6 h after the addition of *p*-NO_2BzCl, which indicates that sodium hydride and the acid chloride were consumed (entry 2). When the reaction was run entirely at rt, **2α** and **6β** were produced in the same proportion (5/5) in 67% yield (entry 3). The formation of the alkoxide at rt for 15 min prior to the addition of CS_2 and *p*-NO_2BzCl at 0 °C, increased the ratio in favor of **2α** (8/2, entry 4). Finally, the best selectivity leading to a **2α/6β** ratio of 9/1 (entry 5) was obtained when the alkoxide formation was carried out for 30 min. In these conditions, a **2α/6β** mixture was isolated in 78% yield and only 10% of galactopyranose **4** remained.

We then applied the latter procedure to manno- and gluco-pyranose rings. The results obtained in the manno series seemed to lend weight to this unusual anomeric phenomenon, which occurred in the absence of an activating catalyst.

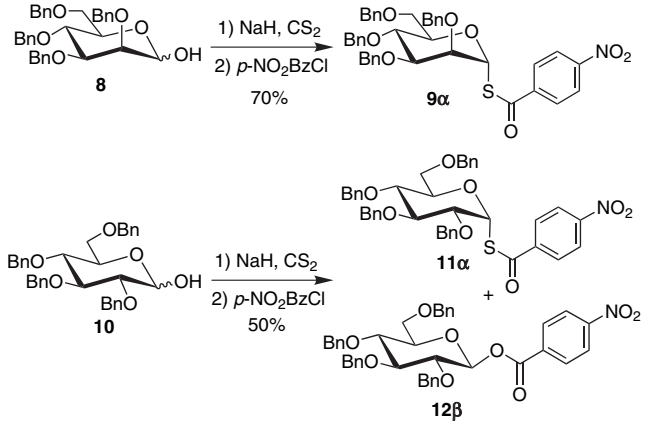


Scheme 4.

Table 1

Entry	NaH		CS_2	*p*-NO_2BzCl		Yield % of **2α+6β**	Ratio of **2α/6β**
	θ (°C)	*t* (min)	θ (°C)/60 min	θ (°C)	*t* (min)		
1	0	15	0	0	60	60	7/3
2	0	15	0	0	360	61	7/3
3	rt	15	rt	rt	60	67	5/5
4	rt	15	0	0	60	70	8/2
5	rt	30	0	0	60	78	9/1

Thus, by a similar one-pot rearrangement the targeted 1-*S*-*p*-nitrobenzoyl-α-thiomannopyranose ester **9α** was produced as the sole product of the reaction from the tetrabenzyl-mannopyranose **8** in 70% yield (Scheme 5).



Scheme 5.

When tetrabenzyl-glucopyranose **10** was subjected to the same reaction conditions, the results were confirmed but in a slightly lower yield and ratio (Scheme 5) as the mixture of α-thioester **11α** and β-ester **12β** was isolated in almost 50% yield, in a 6/4 ratio. The three homologue by-products, previously described in the galacto series, were also identified in the gluco series (<3% from ^{1}H NMR spectra of the crude reaction mixture) but were not isolated. The difference in the reactivity between the gluco and the galacto series is difficult to rationalize but can be correlated to results usually encountered in the literature for the preparation of α-glucoside derivatives, whereas galacto analogues are easier to prepare in good yields.

2.1. Mechanism interpretation

In a preliminary study on the galactose series, the formation of 1-*O*-(*S*-*p*-nitrobenzoyl)dithiocarbonate-D-galactopyranoses **3** was first suggested as key isolable intermediates in the transformation of tetrabenzyl-galactose **4** (1.1 equiv of NaH, 3 equiv of CS_2, and 1.1 equiv of *p*-NO_2BzCl).[36] However, recent advances in the elucidation of the mechanism have highlighted some misunderstanding of this hypothesis, mostly due to the spontaneous evolution of the reaction products even in mild storage conditions.[37] Therefore, the analysis of the crude reaction mixture and the characterization of the intermediates formed were not so straightforward.

Although the reaction should a priori take into account a rearrangement of intermediates **3α** and **3β** (Scheme 4), these latter appeared to be unstable and evolved differently in the medium to give the anomers **2**, **6**, and **7**, as shown by ^{1}H NMR (400 MHz) analysis (Fig. 1, Table 2). A reference experiment was initially recorded exposing galactose **4** to the conditions described in entry 5 (Table 1) but at a lower temperature (−20 °C) and concentrating the THF medium under vacuum only 20 min after the addition of the *p*-nitrobenzoyl chloride (instead of 60 min). Usual workup with dichloromethane/H_2O and the concentration of the dried organic layer were then achieved. The latter procedure revealed the appearance in the crude reaction mixture of all derivatives **2**, **3**, **6**, and **7**, which could be involved in the transformation of the pyranose **4** (Fig. 1A). The evolution of each derivative was then monitored using ^{1}H NMR analysis from the same sample kept for 60 min and 12 h, in $CDCl_3$ solution (Fig. 1B and C).

The presence of 1-*O*-(*S*-*p*-nitrobenzoyl)dithiocarbonate-α-D-galactopyranose **3α** (δH_1=7.00 ppm, d, $J_{1,2}$=3.3 Hz) and thus of 1-*S*-*p*-nitrobenzoyl-α-thiogalactopyranose **2α** (δH_1=6.50 ppm, d, $J_{1,2}$=5.3 Hz) was unambiguously

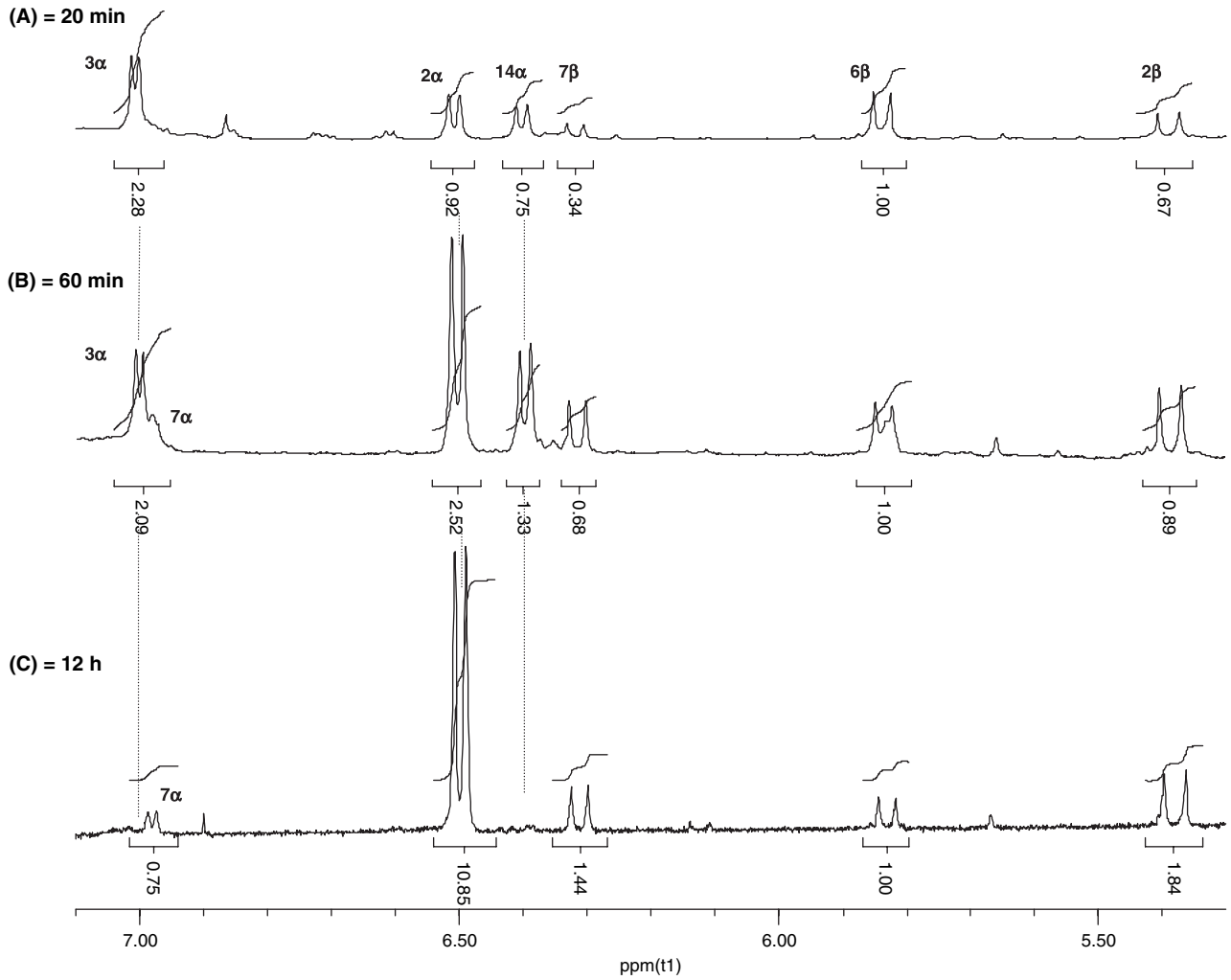
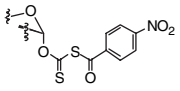
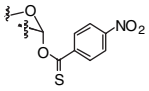
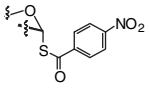
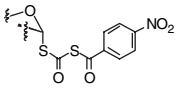
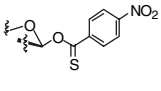
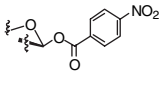
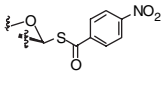


Figure 1. Zone of ^{1}H NMR spectra (5.3–7.1 ppm) showing the anomeric proton signals: evolution of the proportion of compounds **2**, **3**, **6**, **7**, and **14** with time: 20 min (A), 60 min (B), and 12 h (C).

Table 2

	 **3α**	 **7α**	 **2α**	 **14α**	 **7β**	 **6β**	 **2β**
H_1 (ppm)	7.00	6.91	6.50	6.38	6.30	5.84	5.37
J_{1-2} (Hz)	3.3	3.3	5.3	5.4	7.7	8.0	10.1

assigned (Fig. 1A–C). However, the appearance of a signal at 6.38 ppm (δH_1), which increased after 60 min (Fig. 1B) and disappeared after 12 h (Fig. 1C), revealed the existence of a novel intermediate **14α** (d, $J_{1,2}$=5.4 Hz) related to the rearrangement of **3α** into thioester **2α**. When repeating these NMR investigations in order to validate this observation, we have also observed, in some experiments, the total lack of the intermediate **3α** in favor of **14α** (Fig. 2A). Despite the difficulty in controlling the timing of the predominant formation of **14α**, this phenomenon was confirmed several times during ^{1}H NMR experiments, even when the same procedures leading to the data depicted in Fig. 1 were rigorously reproduced.[38] The identification of the 1-*S*-(*S*-*p*-nitrobenzoyl)dithiocarbonate-1-thio-α-D-galactopyranose **14α** (^{13}C NMR, δCO=183.8, 178.4 ppm for the two carbonyls), which is unstable on silica gel supports and in storage conditions, was confirmed by the analysis of its hydrolysis product, α-thiogalactopyranose **15α** (δH_1=5.82 ppm, t, $J_{1,2}$=$J_{1\text{-SH}}$=5.3 Hz). The formation of the latter was observed together with thioester **2α** (Fig. 2B) when silica gel was added to the crude mixture of a reaction in which **14α** was detected as the major α-anomer, whereas 1-*S*-*p*-nitrobenzoyl-α-thiogalactopyranose **2α** remained stable on silica gel.

This evidence led us to propose a revised mechanism for the stereoselective and concomitant formation of the α-thioester **2α** and β-ester **6β** from tetrabenzyl-galactopyranose **4** (Scheme 6). Our hypothesis is based on an original

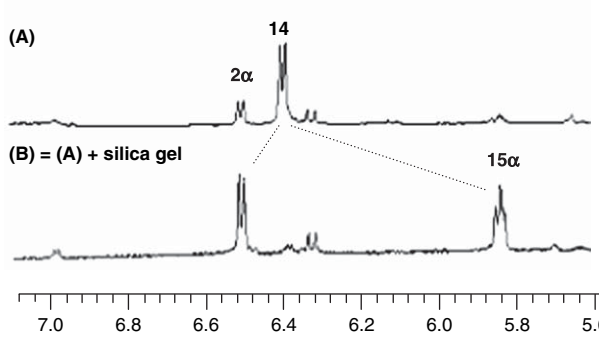
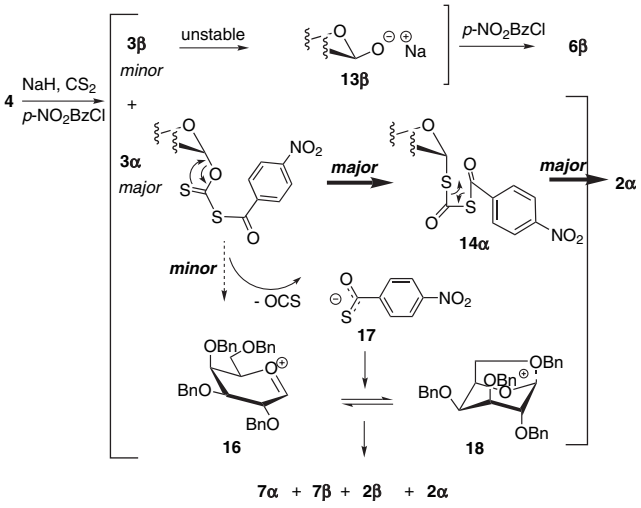


Figure 2. ^{1}H NMR spectra of crude reaction mixture after work-up: (A): reaction conditions: 1.2 equiv NaH, rt, 30 min, CS_2, 0 °C, 60 min, *p*-NO_2BzCl, 0 °C, 2 h; (B): (A)+silica gel.

and surprising one-pot-two-step stereospecific double rearrangement of 1-*O*-(*S*-*p*-nitrobenzoyl)dithiocarbonate-α-D-galactopyranose **3α** into 1-*S*-*p*-nitrobenzoyl-α-thiogalactopyranose **2α**, via the 1-*S*-(*S*-*p*-nitrobenzoyl)dithiocarbonate-1-thio-α-D-galactopyranose **14α**.



Scheme 6.

The anomer counterpart **3β** would not be able to achieve such transformations and the total absence of a signal related to the 1-*O*-(*S*-*p*-nitrobenzoyl)dithiocarbonate-β-D-galactopyranose anomer **3β** in ^{1}H NMR experiments (Figs. 1 and 2) prompted us to suspect its instability. In contrast, the remarkable conservation of the α-stereochemistry during a consecutive double rearrangement of **3α** can be highlighted. The mechanism could be envisaged as following a thiono/thiolo rearrangement of **3α** giving the intermediate **14α**, which could evolve through an anomeric pericyclic process to form **2α**.

Thiono/thiolo rearrangement, known as the Schrönberg rearrangement[39–41] in the case of thionocarbonates and as Newman–Karnes rearrangement[42–45] in the case of thiocarbamates, tends to usually occur at very high temperatures. Thus, to best of our knowledge, only two examples of such transformations have been previously mentioned on pyranose sugars, from a secondary C-4 carbamate[46] and an anomeric xanthate.[47] In both the cases, the process was initiated under acidic catalysis in refluxing solvent (THF or toluene) while, surprisingly, it occurred in situ between the glycosides **3α** and **14α** at 0 °C in the present case. Furthermore, it is interesting to note that the thionoester **7α** also spontaneously rearranged into the thioester **2α**, even when stored under argon at −10 °C.

Logically, the formation of by-products **2β**, **7α**, and **7β** should then involve the participation of an oxonium intermediate **16**, which could result from an inevitable partial degradation of dithiocarbonate **3α**. The addition of the released oxathiocarbonyl **17** to oxonium **16** would then also explain the presence of anomers **2** and **7**. This comment takes into account the significant increase in the H_1 signal of **2β** observed in the NMR experiments (Fig. 1A, B), while no trace of dithiocarbonate **3β** was detected. As the formation of the xanthate salt precursor (NaH, CS_2) cannot be considered as the determining step, if the dithiocarbonate **3β** is formed, it is too unstable to achieve its rearrangement into thioester **2β** and the appearance of the latter would then be understood as coming from the oxonium **16** in the presence of **17**.

In other end, according to Tsuboyama et al.,[48] who has described a one-step synthesis of *S*-1-(1′-phenyl-1*H*-tetrazolyl)-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose in the absence of catalytic activation by reacting *S*-*S*′-bis(1-phenyl-1*H*-tetrazol-5-yl)-dithiocarbonate with tetrabenzylglucopyranose, the predominant formation of **2α** from an oxonium ion **18** cannot be entirely ruled out.

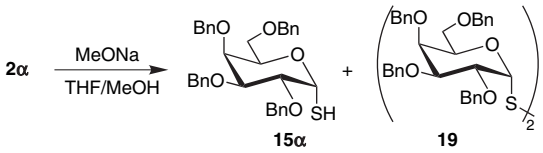
The formation of 1-*O*-*p*-nitrobenzoyl-β-D-galactopyranose **6β** should now be understood as a simple reaction of β-alcoholate anomer **13β** with the remaining *p*-nitrobenzoyl chloride reagent. Moreover, it should be noted that the protected 1-*O*-*p*-nitrobenzoyl anomer **6β** is also of interest as it has already been reported as an efficient glycoside donor in the usual stereoselective α-glycosylations.[49]

In conclusion to this mechanism study, it should be noted that the direct access to α-(*p*-nitrobenzoyl)-thioglycopyranose from pyranose sugars is quite remarkable and efficient particularly as it occurs in the absence of activating promoters with a high stereoselectivity.

2.2. Thioalkylation process

The study of the galacto series was then continued to evaluate the potential of the thioester **2α** for S-alkylation reactions. The de-esterification of **2α** was first attempted to obtain the corresponding α-thiol donor **15α**, anticipating that the corresponding thiolate anion could participate efficiently in the S_N2 displacement of electrophiles to generate a variety of α-thioglycoconjugates or α-thioglycosides. De-esterification of the thioester **2α** was first carried out at rt in THF with a catalytic amount of sodium methoxide (1 M solution in MeOH). In these conditions, the desired thiogalactopyranose **15α** was obtained with a concomitant formation of the disulfide **19** (Scheme 7).

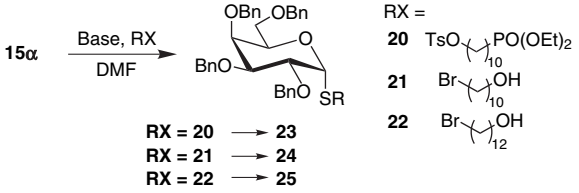
When the reaction was performed with an equimolar quantity of MeONa in a 1/1 THF/MeOH mixture at lower temperature[50] (−40, −15, and 0 °C), the thiol **15α** was formed quantitatively, as confirmed by ^{1}H NMR analysis of the



Scheme 7.

crude mixture of the reaction. Nevertheless, significant degradation occurred during flash chromatography on silica gel since the purified thiol compound was finally isolated with a maximum yield of 50%. This result suggested that thiol **15α** should be used in the next step without further purification. However, de-esterification of **2α** in the presence of NaH and imidazole (2 equiv) in acetonitrile, gave the disulfide **19** as the single product of the reaction (85% yield) and its subsequent reduction into the desired thiol **15α** was fully achieved by treatment with tributylphosphine (1 equiv) in wet THF.[51]

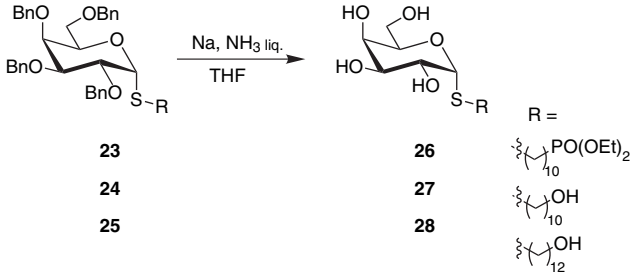
Alkylation of the thiogalactopyranose **15α** was then attempted in the presence of three electrophiles, 10-diethoxyphosphoryl-1-*O*-tosyldecanol **20**,[52] 1-bromodecanol **21**, and 1-bromododecanol **22** (Scheme 8). The results are summarized in Table 3.



Scheme 8.

The purified thiol **15α** treated with NaH (1 equiv), tosylate **20** (1.5 equiv), and crown-ether[53] (1 equiv) gave the desired alkylation product **23** as the major compound but the presence of the disulfide **19** and degradation products was also observed (entry 1). The thiol **15α**, generated in situ by reduction of the disulfide **19** (Fig. 3A) prior to the addition of Cs_2CO_3 (1 equiv) and tosyl **20** (1.2 equiv) in DMF,[54] gave quantitatively the 1-*S*-diethyldecanphosphonate-α-thiogalactoside **23** (entry 2). When electrophiles **21** and **22** were used, similar results were obtained to yield 1-(10-hydroxydecanyl)-α-thiogalactoside **24** and 1-(12-hydroxydodecanyl)-α-thiogalactoside **25**, respectively (entries 3 and 4). Although the ^{1}H NMR spectra of the crude products of the reactions showed a quantitative formation of the desired compounds (Fig. 3B), the thiogalactosides **23**, **24**, and **25** were recovered in moderate 25–30% yields after flash chromatography on silica gel. This inconvenience led us to attempt the following deprotection step without purification.

As predictable, attempts to achieve hydrogenolysis of the benzyl ether groups on thiogalactosides in the presence of Pd/C or $Pd(OH)_2$ failed while the debenzylation of **23**, **24**, and **25** by sodium in liquid ammonia[55,56] was successful, affording the targeted free α-thioglycosides **26**, **27**, and **28**, respectively (Scheme 9).



Scheme 9.

Thus, the reaction sequence: disulfide reduction, thiol-alkylation, and Birch reduction, was carried out without subsequent purification and, after final chromatography on silica gel, the free sugar analogues were obtained in almost 30% overall yields from 2,3,4,6-tetra-*O*-benzyl-α,β-D-galactopyranose.

3. Conclusion

We describe an original alternative for α-thioglycosylation, which compares well with results related in the literature following other methods starting from D-glycopyranose precursors.

The strategy involves, as a key step, the in situ double consecutive rearrangements of 2,3,4,6-tetra-*O*-benzyl-1-*O*-(*S*-*p*-nitrobenzoyl)dithiocarbonate-α-D-glycopyranoses into the corresponding 1-*S*-*p*-nitrobenzoyl-α-D-thioglycopyranoses. The latter rearrangement proceeds in the absence of anomeric activation with a high α-stereoselectivity from reductive sugars. As anticipated, the resulting α-glycoside 1-thioesters are expected to be involved as source of α-anomeric thiolate anions for *S*-alkylations with a total retention of the anomeric configuration. The study of the influence of the ether protecting groups on the efficiency of the methodology, in order to perform the access to branched thioglycosides by convergent approaches, is currently in progress by exchanging benzyloxy groups with *para*-methoxybenzyl, hydrolysis-sensitive substituents or mixed ester–ether groups.

Table 3

Entry	Starting material	Base	RX	Crown-ether	Product[a]	Isolated yield[b] (%)
1	**15α**	NaH	**20**	15-crown-5	**23** maj.[c]	25
2	**27** Reduction	Cs_2CO_3	**20**	None	**23** quant.	28
3	**27** Reduction	Cs_2CO_3	**21**	None	**24** quant.	25
4	**27** Reduction	Cs_2CO_3	**22**	None	**25** quant.	30

[a] Evaluated by ^{1}H NMR.
[b] After purification by flash chromotagraphy on silica gel.
[c] With traces of side products.

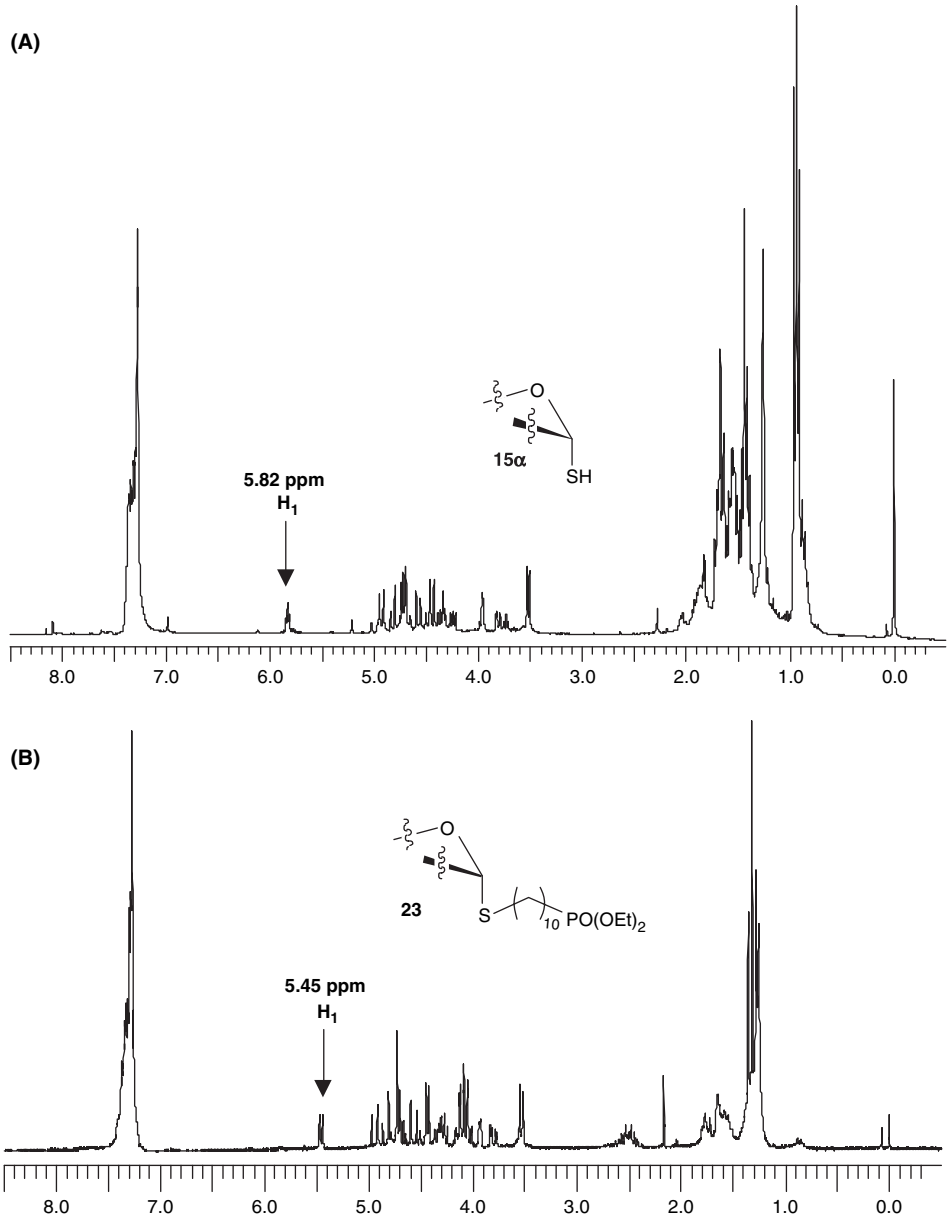


Figure 3. Crude NMR spectra of: (A) reduction of disulfide **19** into **15α** with tributylphosphine in wet THF; (B) alkylation of thiol **15α** into **23**.

The usefulness of this strategy has been illustrated by the first synthesis of three α-thiogalactoconjugates, which are of interest as potential glycomimics and an extension to the synthesis of thiofuranose analogues is underway. The thioglycosylation process is also now being exploited for the synthesis of thio-analogues of α-*O*-galactoceramides,[57] which express anti-cancer and anti-malaria potentials.

4. Experimental section

4.1. General methods

Solvents were purified and dried by standard methods prior to use.[58] All reactions were carried out under argon. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 400 at rt with TMS as internal standard for ^{1}H spectra. Coupling constants *J* are given in Hertz. All assignments were confirmed with the aid of two-dimensional ^{1}H, ^{1}H (COSYDFTP) or ^{1}H, ^{13}C (INVBTP) experiments using standard Bruker pulse programs. All reactions were monitored by TLC on commercially available pre-coated plates (Kieselgel 60 F_{254}) and the products were visualized with mostaïne solution (250 mL H_2O, 10.5 g of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, 0.5 g of $Ce(SO_4)_2$, and 15 mL of H_2SO_4). Kieselgel 60, 230–400 mesh (Merck) was used for column chromatography. Optical rotations were measured at 20±1 °C on Perkin Elmer 341 in the indicated solutions whose concentrations are expressed in grams per 100 mL. Mass spectra were measured by CI with NH_3 on a quad. Hewlett Packard 5989A. HRMS were measured on an LCT spectrometer from Micromass (Lokspray, channel 2795 from Waters, flow: MeOH/H_2O 50/50: 0.2 mL/min) and were performed at the Institut de Chimie des Substances Naturelles, CNRS, Gif-sur-Yvette, France. FTIR spectra were obtained in the 500–4000 cm^{-1} range on a Bruker Vector 22 FT-IR spectrometer using NaCl pellets.

4.2. General procedure for the preparation of 1-*S*-*p*-nitrobenzoyl-2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-glycopyranose

To a stirred suspension of sodium hydride (0.14 g, 3.43 mmol) in 10 mL of THF was added a solution of 2,3,4,6-tetra-*O*-benzyl-α,β-D-glycopyranose (1.57 g, 2.86 mmol) in 10 mL of dry THF at rt under argon. After 30 min, carbon disulfide (0.52 mL, 8.60 mmol) was added dropwise to the reaction mixture at 0 °C and stirring was continued for 1 h at the same temperature. The reaction mixture was then treated with *p*-nitrobenzoyl chloride (0.64 g, 3.43 mmol) and was stirred for another 1 h at 0 °C. The solvent was removed under vacuum and the residue was dissolved in CH_2Cl_2. The resulted solution was washed with brine, dried over $MgSO_4$, concentrated, and purified by flash chromatography.

4.2.1. 1-*S*-*p*-Nitrobenzoyl-2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-galactopyranose (2α). Synthesized following the general procedure from 2,3,4,6-tetra-*O*-benzyl-α,β-D-galactopyranose **4** in 63% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.53 (m, 1H, H_{6a}), 3.61 (m, 1H, H_{6b}), 3.64 (dd, 1H, H_3, $^3J_{3-4}$=2.8, $^3J_{3-2}$=10.0), 3.97 (m, 1H, H_5), 4.03 (m, 1H, H_4), 4.37 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.7), 4.43 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.7), 4.48 (dd, 1H, H_2, $^3J_{2-3}$=10.0, $^3J_{2-1}$=5.3), 4.59 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.3), 4.71 (s, 2H, CH_2(OBn)), 4.74 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.7), 4.84 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.7), 4.96 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.3), 6.50 (d, 1H, H_1, $^3J_{1-2}$=5.3), 7.22–7.36 (m, 20H, CH(OBn)), 8.12 (d, 1H, CH_{ar}, ^3J=9.0), 8.28 (d, 1H, CH_{ar}, ^3J=9.0); ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.3 (C_6), 73.3, 73.6 ($2CH_2$(OBn)), 74.0 (C_5), 74.5 (C_4), 75.1 ($2CH_2$(OBn)), 75.4 (C_2), 80.6 (C_3), 84.1 (C_1), 123.9 (CH_{ar}), 127.5–128.7 (CH(OBn)), 137.7–138.5 (Cq(OBn)), 141.7, 150.7 (Cq_{ar}), 188.3 (CO); IR ν (cm^{-1}) 1671 (C=O); $[\alpha]_D^{20}$ +141.1 (*c* 1.0, CH_2Cl_2); HRMS *m*/*z* calcd for $C_{41}H_{39}NO_8SNa$ 728.2294, found 728.2303.

4.2.2. 1-*S*-*p*-Nitrobenzoyl-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-galactopyranose (2β). Isolated in less than 3% yield during synthesis of thioester **2α**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.59 (m, 2H, $2H_6$), 3.72 (dd, 1H, H_3, $^3J_{3-2}$=9.1, $^3J_{3-4}$=2.4), 3.80 (m, 1H, H_5), 4.04 (m, 2H, H_2, H_4), 4.40 (d, 1H, CH_2(OBn), $^3J_{gem}$=11.7), 4.46 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.7), 4.63 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.5), 4.75 (m, 3H, CH_2(OBn)), 4.89 (d, 1H, CH_2(OBn), $^2J_{gem}$=10.8), 4.94 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.5), 5.37 (d, 1H, H_1, $^3J_{1-2}$=10.1), 7.24–7.35 (m, 20H, CH(OBn)), 8.04 (d, 2H, CH_{ar}, ^3J=8.8), 8.28 (d, 2H, CH_{ar}, ^3J=8.8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.2 (C_6), 72.9 (CH_2(OBn)), 73.7 (C_2 or C_4, CH_2(OBn)), 74.9, 75.9 ($2CH_2$(OBn)), 77.2 (C_2 or C_4), 78.0 (C_5), 82.4 (C_1), 84.4 (C_3), 124.1 (CH_{ar}), 127.8–128.6 (CH(OBn), CH_{ar}), 137.9, 138.0, 138.2, 138.6 (Cq(OBn)), 141.4, 150.8 (Cq_{ar}), 188.1 (CO); HRMS *m*/*z* calcd for $C_{41}H_{39}NO_8SNa$ 728.2294, found 728.2289.

4.2.3. 1-*O*-*p*-Nitrobenzoyl-2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranose (6β). Formed along with **2α** in 7% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (m, 2H, $2H_6$), 3.71 (dd, 1H, H_3, $^3J_{3-4}$=2.7, $^3J_{3-2}$=9.6), 3.79 (m, 1H, H_5), 4.03 (d, 1H, H_4, $^3J_{4-3}$=2.7), 4.12 (dd, 1H, H_2, $^3J_{2-3}$=9.6, $^3J_{2-1}$=8.0), 4.41 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.6), 4.46 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.6), 4.65 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.6), 4.72–4.76 (m, 3H, CH_2(OBn)), 4.87 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.2), 4.96 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.6), 5.84 (d, 1H, H_1, $^3J_{1-2}$=8.0), 7.13–7.36 (m, 20H, CH(OBn)), 8.10 (d, 2H, CH_{ar}, ^3J=7.0), 8.21 (d, 2H, CH_{ar}, ^3J=7.0); ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.1 (C_6), 73.0 (CH_2(OBn)), 73.2 (C_4), 73.7, 74.6 ($2CH_2$(OBn)), 75.0 (C_5), 75.4 (CH_2(OBn)), 77.8 (C_2), 82.7 (C_3), 95.5 (C_1), 123.6 (CH_{ar}), 127.8–128.6 (CH(OBn)), 131.3 (CH_{ar}), 134.8 (Cq_{ar}), 137.8–138.5 (Cq(OBn)), 150.9 (Cq_{ar}), 163.3 (CO); IR ν (cm^{-1}) 1732 (C=O), 1266 (O–CO); $[\alpha]_D^{20}$ –8.2 (*c* 1.1, CH_2Cl_2); HRMS *m*/*z* calcd for $C_{41}H_{39}NO_9Na$ 712.2523, found 712.2547.

4.2.4. 1-*O*-*p*-Nitrothiobenzoyl-2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranose (7α). Isolated in less than 3% yield during synthesis of thioester **2α**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.45 (m, 1H, H_{6a}), 3.55 (m, 1H, H_{6b}), 3.94 (m, 2H, H_3, H_5), 4.05 (m, 1H, H_4), 4.29 (m, 2H, H_2, CH_2(OBn)), 4.36 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.6), 4.55 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.6), 4.63 (d, 1H, CH_2(OBn), $^2J_{gem}$=12.7), 4.71 (d, 1H, CH_2(OBn), $^2J_{gem}$=12.7), 4.76 (s, 2H, CH_2(OBn)), 4.93 (d, 1H, CH_2(OBn), $^2J_{gem}$=12.1), 6.91 (d, 1H, H_1, $^3J_{1-2}$=3.3), 7.15–7.32 (m, 20H, CH(OBn)), 8.11 (m, 4H, CH_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.3 (C_6), 72.8 (CH_2(OBn)), 73.0 (C_5), 73.8 (CH_2(OBn)), 74.3 (C_4), 75.1, 75.8 ($2CH_2$(OBn)), 78.3 (C_3), 97.7 (C_1), 123.5 (CH_{ar}), 128.0–128.6 (CH(OBn)), 129.9 (CH_{ar}).

4.2.5. 1-*O*-*p*-Nitrothiobenzoyl-2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranose (7β). Isolated in less than 3% yield during synthesis of thioester **2α**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (m, 2H, $2H_6$), 3.74 (dd, 1H, H_3, $^3J_{3-2}$=9.7, $^3J_{3-4}$=2.3), 3.81 (m, 1H, H_5), 4.05 (m, 1H, H_4), 4.29 (m, 1H, H_2), 4.40 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.5), 4.48 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.5), 4.60–4.79 (m, 4H, $2CH_2$(OBn)), 4.87 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.4), 4.96 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.3), 6.30 (d, 1H, H_1, $^3J_{1-2}$=7.7), 7.20–7.36 (m, 20H, CH(OBn)), 8.17 (m, 4H, CH_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.3 (C_6), 73.1 (CH_2(OBn)), 73.4 (C_4), 73.7 (CH_2(OBn)), 74.7 (C_5), 74.9, 75.4 ($2CH_2$(OBn)), 78.1 (C_2), 82.6 (C_3), 99.6 (C_1), 123.3 (CH_{ar}), 127.9–128.5 (CH(OBn)), 130.1 (CH_{ar}), 138.0, 138.4 (Cq(OBn)), 142.1, 150.2 (Cq_{ar}), 206.5 (CS).

4.2.6. 1-*S*-*p*-Nitrobenzoyl-2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-mannopyranose (9α). Obtained in 60% yield as the only product of the reaction following the general procedure from 2,3,4,6-tetra-*O*-benzyl-α,β-D-mannopyranose **8**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (m, 2H, H_{6a}, H_5), 3.81 (m, 2H, H_{6b}, H_3), 3.87 (m, 1H, H_2), 4.12 (m, 1H, H_4), 4.53 (m, 4H, $2CH_2$(OBn)), 4.65 (d, 1H, CH_2(OBn), $^2J_{gem}$=12.1), 4.76 (d, 1H, CH_2(OBn), $^2J_{gem}$=12.4), 4.91 (d, 2H, CH_2(OBn), $^2J_{gem}$=11.0), 6.41 (d, 1H, H_1, $^3J_{1-2}$=1.7), 7.17–7.19, 7.25–7.34, 7.44–7.46 (m, 20H, CH(OBn)), 8.08 (d, 2H, CH_{ar}, ^3J=8.8), 8.31 (d, 2H, CH_{ar}, ^3J=8.8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 69.0 (C_6), 71.9, 72.0, 73.6 ($3CH_2$(OBn)), 74.3 (C_4), 75.4 (CH_2(OBn)), 76.6 (C_2), 77.2 (C_5), 80.2 (C_3), 80.9 (C_1), 124.0 (CH_{ar}), 127.6–128.7 (CH(OBn)), 137.8–138.3 (Cq(OBn)), 141.2, 150.8 (Cq_{ar}), 187.5 (CO); IR ν (cm^{-1}) 1675 (C=O); MS (IC^+, NH_3) 723 (M+18); $[\alpha]_D^{20}$ +72.1 (*c* 1.0; CH_2Cl_2).

4.2.7. 1-*S*-*p*-Nitrobenzoyl-2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-glucopyranose (11α). Obtained following the general procedure from 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranose **10** in 36% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62–3.83 (m, 5H, H_3, H_4, H_5, $2H_6$), 4.01 (dd, 1H, H_2, $^3J_{2-1}$=5.2, $^3J_{2-3}$=9.0), 4.44–4.99 (m, 8H, $4CH_2$(OBn)), 6.49 (d, 1H, H_1, $^3J_{1-2}$=5.2), 7.13–7.14 (m, 2H, CH(OBn)), 7.24–7.32 (m, 18H, CH(OBn)), 8.15 (d, 2H, CH_{ar}, ^3J=8.0), 8.31 (d, 2H, CH_{ar}, ^3J=8.0); ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.1 (C_6), 73.2, 73.7 ($2CH_2$(OBn)), 75.2 (C_3 or C_4 or C_5), 75.4, 75.9 ($2CH_2$(OBn)), 77.2 (C_3 or C_4 or C_5), 78.7 (C_2), 83.1 (C_1), 83.7 (C_3 or C_4 or C_5), 123.8–124.0 (CH_{ar}), 127.9–128.8 (CH(OBn), CH_{ar}), 137.4, 137.9, 138.1, 138.6 (Cq(OBn)), 141.5, 150.8 (Cq_{ar}), 188.0 (CO); IR ν (cm^{-1}) 1672 (C=O); HRMS *m/z* calcd for $C_{41}H_{39}NO_8SNa$ 728.2294, found 728.2307.

4.2.8. 1-*O*-*p*-Nitrobenzoyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranose (12β). Formed along with **11α** in 24% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68–3.84 (m, 6H, H_2, H_3, H_4, H_5, $2H_6$), 4.46–4.91 (m, 8H, $4CH_2$(OBn)), 5.87–5.91 (m, 1H, H_1), 7.16–7.32 (m, 20H, CH(OBn)), 8.12 (m, 2H, CH_{ar}), 8.25 (m, 2H, CH_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.1 (C_6), 73.6, 75.0 ($2CH_2$(OBn)), 75.7 (C_2 or C_3 or C_4 or C_5, $2CH_2$(OBn)), 77.2, 80.7, 85.0 (C_2 or C_3 or C_4 or C_5), 95.1 (C_1), 123.5 (CH_{ar}), 127.9–128.5 (CH(OBn)), 131.1 (CH_{ar}), 134.6 (Cq_{ar}), 137.8–138.3 (Cq(OBn)), 150.8 (Cq_{ar}), 163.1 (CO); IR ν (cm^{-1}) 1739 (C=O), 1268 (O–CO); MS (IC^-, NH_3) 689 [M]; $[\alpha]_D^{20}$ –34.2 (*c* 1.0, CH_2Cl_2); mp 74–76 °C; HRMS *m/z* calcd for $C_{41}H_{39}NO_9Na$ 712.2523, found 712.2531.

4.2.9. 2,3,4,6-Tetra-*O*-benzyl-1-*S*-(S-*p*-nitrobenzoyl)-dithiocarbonate-1-thio-α-D-galactopyranose (14α). ^{1}H NMR (400 MHz, $CDCl_3$) δ (analysis of the crude product) 6.38 (d, 1H, H_1, $^3J_{1-2}$=5.4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.8, 178.4 (CO).

4.2.10. 2,3,4,6-Tetra-*O*-benzyl-1-thio-α-D-galactopyranose (15α). *Procedure A*: To a solution of thioester **2α** (0.845 g, 1.20 mmol) in 8 mL of a mixture of dry THF/MeOH (1/1) was added a solution of sodium methoxide (1 M in MeOH, 1.12 mL, 1.12 mmol). The reaction was stirred for 1 h and neutralized with Dowex acidic resin. The resin was filtered off and the filtrate was concentrated under reduced pressure to give the thiogalactopyranose **15α** (100% on NMR spectrum of the crude product). This was used immediately for the next step.

Procedure B: A solution of disulfide **19** (0.250 g, 0.22 mmol) in 3 mL of wet THF was treated with tributylphosphine (0.055 mL, 0.22 mmol). After 3 h at rt, the solvent was removed under vacuum and the residue was dissolved in EtOAc, washed with brine, dried over $MgSO_4$ then concentrated under reduced pressure to afford the thiogalactopyranose **15α** (100% on NMR spectrum of the crude product). This was used immediately for the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81 (d, 1H, SH, $^3J_{SH-1}$=3.9), 3.52 (d, 2H, $2H_6$, $^3J_{6-5}$=6.4), 3.80 (dd, 1H, H_3, $^3J_{3-4}$=2.7, $^3J_{3-2}$=9.8), 3.95 (d, 1H, H_4, $^3J_{4-3}$=2.7), 4.24 (dd, 1H, H_2, $^3J_{2-3}$=9.8, $^3J_{2-1}$=5.3), 4.38 (m, 1H, H_5), 4.43 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.9), 4.47 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.9), 4.57 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.4), 4.66 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.5), 4.71 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.7), 4.72 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.5), 4.81 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.7), 4.92 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.4), 5.82 (dd, 1H, H_1, $^3J_{1-SH}$=3.9, $^3J_{1-2}$=5.3), 7.22–7.37 (m, 20H, CH(OBn)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.7 (C_6), 70.5 (C_5), 72.7–73.6 ($4CH_2$(OBn)), 74.9 (C_4), 76.0 (C_2), 78.8 (C_3), 79.8 (C_1), 127.6–128.5 (CH(OBn)), 138.0, 138.1, 138.6, 138.7 (Cq(OBn)); MS (IC^+, NH_3) 574 (M+18); $[\alpha]_D^{20}$ +125.3 (*c* 1.0, CH_2Cl_2); HRMS *m/z* calcd for $C_{34}H_{36}O_5SNa$ 579.2181, found 579.2194.

4.2.11. Bis[2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl]disulfide (19). To a solution of thioester **2α** (1.29 g, 1.83 mmol) in 20 mL of dry CH_3CN was added imidazole (0.25 g, 3.67 mmol) followed by sodium hydride (0.15 g, 3.67 mmol). The reaction mixture was stirred for 2 h and the solvent was removed. The crude product was diluted in EtOAc, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. It was then purified by flash chromatography (15% EtOAc/petroleum ether) to afford 1.73 g of disulfide **19** as a white solid (85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.57 (dd, 1H, H_{6a}, $^2J_{6a-6b}$=9.0, $^3J_{6a-5}$=5.2), 3.67 (t, 1H, H_{6b}, $^2J_{6b-6a}$=$^3J_{6b-5}$=9.0), 3.79 (dd, 1H, H_3, $^3J_{3-2}$=9.9, $^3J_{3-4}$=2.3), 4.02 (d, 1H, H_4, $^3J_{4-3}$=2.3), 4.17 (dd, 1H, H_5, $^3J_{5-6a}$=5.2, $^3J_{5-6b}$=9.0), 4.29 (dd, 1H, H_2, $^3J_{2-1}$=5.3, $^3J_{2-3}$=9.9), 4.35 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.6), 4.46 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.6), 4.57 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.2), 4.60 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.6), 4.68 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.6), 4.79 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.6), 4.93 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.2), 5.40 (d, 1H, H_1, $^3J_{1-2}$=5.3), 7.24–7.35 (m, 20H, CH(OBn)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.2 (C_6), 70.6 (C_5), 72.6, 73.4, 73.6, 75.1 ($4CH_2$(OBn)), 74.9 (C_4), 76.7 (C_2), 79.4 (C_3), 87.1 (C_1), 127.6–128.4 (CH(OBn)), 138.1–138.8 (Cq(OBn)); MS (ES^+) 1133.5 (M+Na); $[\alpha]_D^{20}$ +270.5 (*c* 1.0, CH_2Cl_2).

4.3. General procedure for the preparation of thiogalactopyranosides (23), (24), and (25)

A solution of the thiogalactopyranose **15α** (0.70 g, 1.26 mmol), from the crude product of the disulfide reduction, in 10 mL of DMF was treated with cesium carbonate (0.41 g, 1.26 mmol). After 10 min at rt, the electrophile was added to the reaction mixture (10-diethoxyphosphoryl-1-*O*-tosyldecanol **20** (0.68 g, 1.5 mmol) for the preparation of **23**, 10-bromodecan-1-ol **21** (0.36 g, 1.5 mmol) for the preparation of **24**, and 10-bromododecan-1-ol **22** (0.40 g, 1.5 mmol) for the preparation of **25**). The solution was stirred at rt for 3 h then the reaction mixture was diluted with Et_2O and washed with brine. The organic layer was dried over $MgSO_4$ and then concentrated under vacuum. The crude product can be purified by flash chromatography at this step (15% EtOAc/petroleum ether) to afford 0.29 g of **23** (28%) or 0.22 g of **24** (25%). In the case of **25**, crude product was directly run in the next step.

4.3.1. 2,3,4,6-Tetra-*O*-benzyl-1-*S*-diethyldecanphosphonate-1-thio-α-D-galactopyranoside (23). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17–1.75 (m, 24H, $9CH_2$, $2CH_3$(OEt)), 2.45–2.54 (m, 2H, CH_2S), 3.53 (m, 2H, $2H_6$), 3.81 (dd, 1H, H_3, $^3J_{3-4}$=2.4, $^3J_{3-2}$=9.9), 3.92 (d, 1H, H_4,

$^3J_{4-3}$=2.4), 4.06–4.11 (m, 4H, 2CH_2(OEt)), 4.26–4.31 (m, 2H, H_2, H_5), 4.40 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.8), 4.47 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.8), 4.57 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.5), 4.68 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.7), 4.70 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.8), 4.74 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.7), 4.83 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.8), 4.94 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.5), 5.45 (d, 1H, H_1, $^3J_{1-2}$= 5.5), 7.21–7.39 (m, 20H, CH(OBn)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7, 16.8 (2CH_3(OEt)), 22.5, 22.6, 25.2, 26.6, 29.1, 29.3, 29.4, 29.6, 30.7, 30.9 (10CH_2), 61.5, 61.6 (2CH_2(OEt)), 69.2 (C_6), 69.8 (C_5), 72.6, 73.5, 73.5, 74.9 (4CH_2(OBn)), 75.3 (C_4), 76.4 (C_2), 79.7 (C_3), 83.8 (C_1), 127.6–128.5 (CH(OBn)), 138.2, 138.4, 138.8, 139.0 (Cq(OBn)); ^{31}P NMR (80 MHz, $CDCl_3$) δ 32.61; $[\alpha]_D^{20}$ +79.3 (*c* 1.0, CH_2Cl_2).

4.3.2. 2,3,4,6-Tetra-*O*-benzyl-(10-hydroxydecanyl)-1-thio-α-D-galactopyranoside (24). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16–1.60 (m, 16H, 8CH_2), 2.44–2.57 (m, 2H, CH_2S), 3.53 (m, 2H, 2H_6), 3.62 (t, 2H, CH_2OH, ^3J=6.6), 3.81 (dd, 1H, H_3, $^3J_{3-4}$=2.8, $^3J_{3-2}$=9.9), 3.92 (d, 1H, H_4, $^3J_{4-3}$=2.8), 4.28 (m, 2H, H_5, H_2), 4.40 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.8), 4.47 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.8), 4.57 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.5), 4.68 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.7), 4.70 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.8), 4.74 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.7), 4.83 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.8), 4.94 (d, 1H, CH_2(OBn), $^2J_{gem}$=11.5), 5.45 (d, 1H, H_1, $^3J_{1-2}$=5.5), 7.22–7.40 (m, 20H, CH(OBn)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 29.0–29.5, 23.9 (9CH_2), 63.1 (CH_2OH), 69.2 (C_6), 69.8 (C_5), 72.6, 73.5, 74.9 (4CH_2(OBn)), 75.3 (C_4), 76.4 (C_2), 79.7 (C_3), 83.7 (C_1), 127.7–128.4 (CH(OBn)), 138.2, 138.4, 138.7, 138.9 (Cq(OBn)); IR ν (cm−1) 3420 (OH), 2925 (CH_2), 2854 (CH_2); $[\alpha]_D^{20}$ +109.8 (*c* 1.0, CH_2Cl_2); HRMS *m/z* calcd for $C_{44}H_{56}O_6SNa$ 735.3695, found 735.3735.

4.4. General procedure for the debenzylation of thioglycosides

A solution of liquid ammonia was treated with sodium (0.057 mg, 2.40 mmol) at −78 °C. The thiogalactopyranoside **23**, **24** or **25** (crude product of the thioalkylation step) in 2 mL of THF was added to the reaction mixture. After 1 h 30 at −78 °C, the reaction mixture was neutralized with NH_4Cl (0.128 g, 2.40 mmol) before evaporation of the solvent. The crude product was purified by flash chromatography to afford the deprotected thioglycosides **26**, **27**, and **28** in 55% yield from disulfide **19** (i.e., over three steps).

4.4.1. 1-*S*-Diethyldecanphosphonate-1-thio-α-D-galactopyranoside (26). ^{1}H NMR (400 MHz, CD_3OD) δ 1.30–1.41, 1.52–1.63, 1.73–1.82 (m, 24H, 2CH_3(OEt), 9CH_2), 2.50–2.67 (m, 2H, CH_2S), 3.60 (dd, 1H, H_3, $^3J_{3-2}$=9.8, $^3J_{3-4}$=2.4), 3.71 (m, 2H, 2H_6), 3.89 (d, 1H, H_4, $^3J_{4-3}$= 2.4), 4.05–4.12 (m, 6H, H_2, 2CH_2(OEt)), 4.18 (m, 1H, H_5), 5.36 (d, 1H, H_1, $^3J_{1-2}$=5.3); ^{13}C NMR (100 MHz, CD_3OD) δ 16.7, 16.8 (2CH_3(OEt)), 30.0–31.5 (10CH_2), 62.6 (C_6), 63.0, 63.1 (2CH_2(OEt)), 69.8 (C_2), 70.9 (C_4), 72.2 (C_3), 72.6 (C_5), 87.4 (C_1); ^{31}P NMR (80 MHz, CD_3OD) δ 34.34; $[\alpha]_D^{20}$ +174,0 (*c* 0.3, MeOH).

4.4.2. (10-Hydroxydecanyl)-1-thio-α-D-galactopyranoside (27). ^{1}H NMR (300 MHz, CD_3OD) δ 1.39–1.66 (m, 14H, 7CH_2), 1.87 (m, 2H, CH_2), 2.51–2.68 (m, 2H, CH_2S), 3.54 (t, 2H, CH_2OH, ^3J=7.7), 3.61 (dd, 1H, H_3, $^3J_{3-2}$=10.1, $^3J_{3-4}$=3.3), 3.73 (m, 2H, H_6), 3.92 (m, 1H, H_4), 4.07 (dd, 1H, H_2, $^3J_{2-1}$=5.6, $^3J_{2-3}$=10.1), 4.18 (m, 1H, H_5), 5.37 (d, 1H, H_1, $^3J_{1-2}$=5.6); ^{13}C NMR (75 MHz, CD_3OD) δ 26.5, 26.9, 30.0, 30.3, 30.5, 30.6, 30.7, 30.8, 33.6 (9CH_2), 62.6 (C_6), 63.0 (CH_2OH), 69.7 (C_2), 71.0 (C_4), 72.2 (C_3), 72.5 (C_5), 87.5 (C_1).

4.4.3. (12-Hydroxydodecanyl)-1-thio-α-D-galactopyranoside (28). ^{1}H NMR (400 MHz, CD_3OD) δ 1.30–1.35 (m, 16H, 8CH_2), 1.41 (m, 2H, CH_2), 1.63 (m, 2H, CH_2), 2.51–2.65 (m, 2H, CH_2S), 3.54 (t, 2H, CH_2OH, ^3J=6.3), 3.60 (dd, 1H, H_3, $^3J_{3-2}$=9.9, $^3J_{3-4}$=3.5), 3.71 (m, 2H, H_6), 3.88 (m, 1H, H_4), 4.07 (dd, 1H, H_2, $^3J_{2-1}$=5.3, $^3J_{2-3}$=9.9), 4.18 (m, 1H, H_5), 5.37 (d, 1H, H_1, $^3J_{1-2}$=5.3).

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