A General and Diastereoselective Synthesis of 1,2-*cis*-Hexofuranosides from 1,2-*trans*-Thiofuranosyl Donors

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Dedicated to Professor Dr. Pierre Sinaÿ on the occasion of his 62nd birthday

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The general formation of 1,2-*trans*-thioglycofuranosides derived from D-galactose, D-glucose and D-mannose was readily accomplished starting from the corresponding alkyl glycofuranosides via per-*O*-acetyl-hexofuranoses as key synthons. Glycosidation of ethyl or phenyl perbenzylated 1,2-*trans*-thiofuranosides afforded disaccharides containing a nonreducing 1,2-*cis*-hexofuranosyl unit, i.e. α-D-galactosyl, α-D-glucosyl or β-D-mannosyl, with interesting diastereoselectivities. Activation of the thiofuranosyl donors was performed by *N*-iodosuccinimide and a catalytic amount of tin(II) trifluoromethanesulfonate.

Introduction

The glycobiology of hexoses in their furanoid form is becoming a topic of increasing interest since the striking presence of D-galactofuranosyl (D-Gal*f*) residues in glycoconjugates found in archaebacteriae,[1,2] classical prokaryotes,[3] protozoae[4–6] or fungi[7] is now well established. These microorganisms are able to elaborate polysaccharides containing furanosides, for instance the backbone of the arabinogalactan of *Mycobacterium tuberculosis*,[8,9] but the galactofuranosyl moieties can also coexist with hexopyranosides either as terminal nonreducing units[4,7] or as part of the core of oligosaccharides.[4–6] In *Trypanosoma cruzi* glycoproteins,[4] the β-D-Gal*f* unit is the epitope involved in recognition phenomena.[4,10] Moreover, recent NMR studies showed the presence of galactofuranosyl residues with the opposite α-configuration, in *Leishmania*,[6] *Penicillium*[11] or *Clostridium*[12] species. In contrast to the *galacto*-conjugates, the nucleotide-sugar Agrocine 84,[13,14] a natural antibiotic that controls the plant cancer crown disease,[13] is notably characterized by a glucofuranose moiety whose anomeric configuration has not yet been clearly determined. Since the biosynthesis of glycoconjugates containing hexofuranosides seems to be restricted to lower organisms, it is assumed that compounds bearing such units could be strongly antigenic[4] and may be useful targets for therapy in fungal and parasitic diseases.

Despite significant advances in the synthesis of complex oligosaccharides, construction of *O*-furanosidic linkages from hexoses remains a challenging task. Various approaches were recently proposed as alternatives to the Koenigs-Knorr method.[15] Thus, 1-*O*-acylfuranoses,[16,17] 1,2-orthoesters,[18,19] 1,2-cyclic sulfites,[20] furanoid glycals,[21,22] phenyl 1-seleno glycosides[23] or ethyl 1-thioglycosides,[24–27] furanosyl trichloroacetimidates[28–30] and *n*-pentenyl furanosides[31,32] were proposed regarding their ability to yield target saccharides. Owing to the presence of participating protecting groups at the 2-position of the donor, 1,2-*trans*-furanosides were generally obtained with complete diastereoselectivity. Similar results were published by Hindsgaul et al.[33] by cyclization of unprotected *O*,*S*-acetals[34] promoted by mercuric salts.

As part of our program dealing with the synthesis of di- and oligosaccharides containing 1,2-*cis*-hexofuranosyl entities,[29] we needed a general route to stable hexofuranosyl donors bearing nonparticipating protecting groups. However, furanosides are generally characterized by lower anomeric effects,[35] thus rendering preparation of α-D-*glucofurano*-type derivatives more difficult than their pyranosidic counterparts. On the other hand, access to β-D-*mannofurano*-type isomers is obviously hindered by high steric effects. Nevertheless, we assumed that 1,2-*trans*-furanosyl donors may lead to the corresponding 1,2-*cis*-furanosides provided that the latter: (i) are formed under kinetically controlled conditions, and (ii) do not anomerize in situ into the thermodynamically more stable 1,2-*trans*-furanosides. In this context, and owing to the versatility of thioglycosides as "universal building blocks" and glycosyl donors,[36] we describe herein: (i) a quite general entry into perbenzylated aryl or alkyl 1,2-*trans*-thiofuranosides derived from D-galactose, D-glucose and D-mannose, and (ii) their behavior in glycosylation reactions for stereoselectively synthesizing disaccharides containing an α-D-galacto-, α-D-gluco- or β-D-mannofuranoside as the nonreducing unit.

Results and Discussion

Preparation of Perbenzylated 1,2-*trans*-Thiofuranosides

We recently demonstrated the versatile utility of alkyl hexofuranosides[37] as efficient starting materials for glycofuranosyl donors.[29] Octyl β-D-galactofuranoside **(1)**, read-

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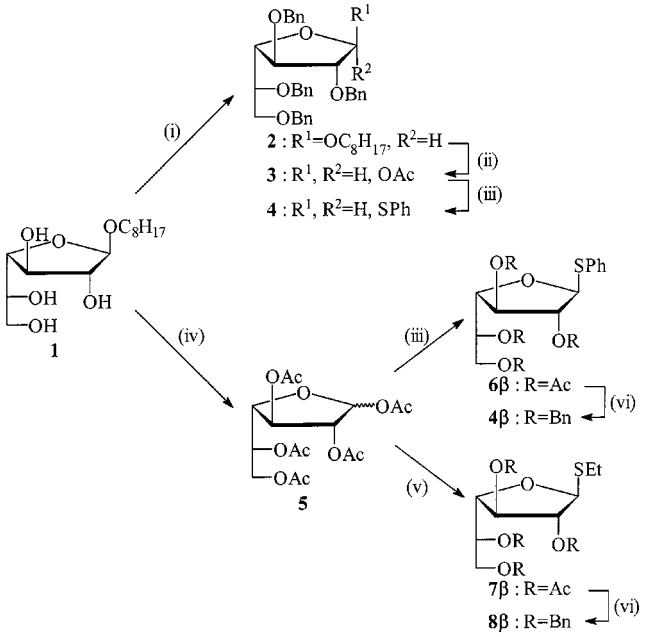
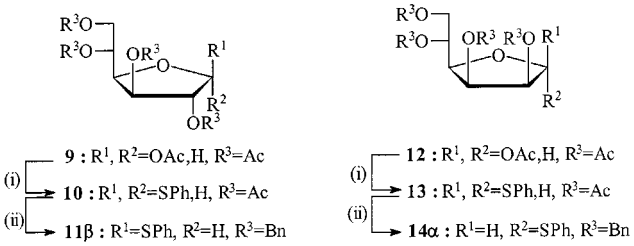
ily obtained in a one-step procedure from D-galactose[37] was benzylated under standard conditions and the resulting derivative **2** submitted to mild acetolysis in order to avoid either debenzylation or ring expansion of the five-membered ring to pyranoid compounds (Scheme 1). According to the procedure of Ferrier,[38] the thiogalactofuranoside **4** was obtained in a disappointing 40% yield, probably because of the lability of benzyl groups in the presence of the boron trifluoride diethyl ether complex ($BF_3{\cdot}OEt_2$). Moreover, the absence of participating group at the 2-position warranted the formation of a mixture of both anomers in nearly equal amounts. Although each anomer was chromatographically isolated, perbenzylated phenyl **(4β)** and ethyl 1-thiogalactofuranosides (**8β**), were better synthesized from the penta-*O*-acetyl-galactofuranose **(5)**[39] as precursor. Reaction of **5** with thiophenol or ethanethiol and $BF_3{\cdot}OEt_2$ as promoter afforded exclusively the β-thiogalactofuranosides **6β** and **7β** in 81% and 55% yields, respectively. Methanolysis under Zemplen conditions followed by standard benzylation gave the required products **4β** and **8β** in high yields.



Scheme 1. Synthesis of galactofuranosyl donors **4** and **8** from octyl β-D-galactofuranoside **1**: (i) BnBr, NaH, DMF (82%); (ii) Ac_2O, H_2SO_4, CH_2Cl_2 (81%); (iii) PhSH, $BF_3.OEt_2$, CH_2Cl_2, **4**: 40% (α/β = 1:1); **6β**: 81%; (iv) see ref.[39]; (v) EtSH, $BF_3{\cdot}OEt_2$, CH_2Cl_2 (55%); (vi) a. NaOMe, MeOH; b. BnBr, NaH, DMF, **4β**: 80%; **8β**: 74%

The same strategy was further spread out for the preparation of the *gluco*- and *manno*-derivatives **11β** and **14α** (Scheme 2). Thioglycosidation reactions of peracetylated furanoses[39] **9** and **12** yielded anomeric mixtures of **10** and **13** (1,2-*trans*/1,2-*cis* ≈ 9–15:1). However, subsequent protecting group manipulation allowed simple purification by column chromatography on silica gel of the desired tetra-*O*-benzylated 1,2-*trans* phenyl thiofuranosides **11β** and **14α**.

Anomeric configurations were determined by ^1H NMR spectroscopy and corroborated by optical rotation measurements. Thus, β-galacto- and β-glucothiofuranosides are



Scheme 2. Preparation of gluco- and mannofuranosyl donors **11β** and **14α**, respectively: (i) PhSH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, **10**: 70% (α/β = 1:9); **13**: 90% (α/β = 15.7:1); (ii) a. NaOMe, MeOH; b. BnBr, NaH, DMF, **11β**: 81%; **14α**: 73%

characterized by a small coupling constant between H-1 and H-2. In *O*-furanosides, this value is generally lower than 1 Hz[40] but the presence of a sulfur atom at the anomeric position substantially increases $J_{1,2}$ to almost 2 Hz. A similar difference is also observed between *O*- and *S*-pyranosides.[41] Nevertheless, as in the case of *O*-furanosides,[40] compounds **4β**, **8β** and **11β** are all levorotatory. The *manno*-isomer **14α** exhibits an exceptionally high value for $J_{1,2}$, i.e. 7.2 Hz, but the 1,2-*trans* configuration was strengthened by the positive value of optical rotation according to Hudson's rules.[40]

As expected, alkyl hexofuranosides are interesting starting materials for the stereospecific synthesis of novel perbenzylated 1,2-*trans*-thiohexofuranosides. Moreover, while the preparation of phenyl 1-thio-α-D-galactofuranoside according to the procedure of Wolfrom et al.[42] did not succeed, or afforded the expected product in yields lower than 30%,[43] the present methodology was efficiently applied to the synthesis of the corresponding β-anomer and was extended to other hexose derivatives and to alkyl or aryl thiol acceptors.

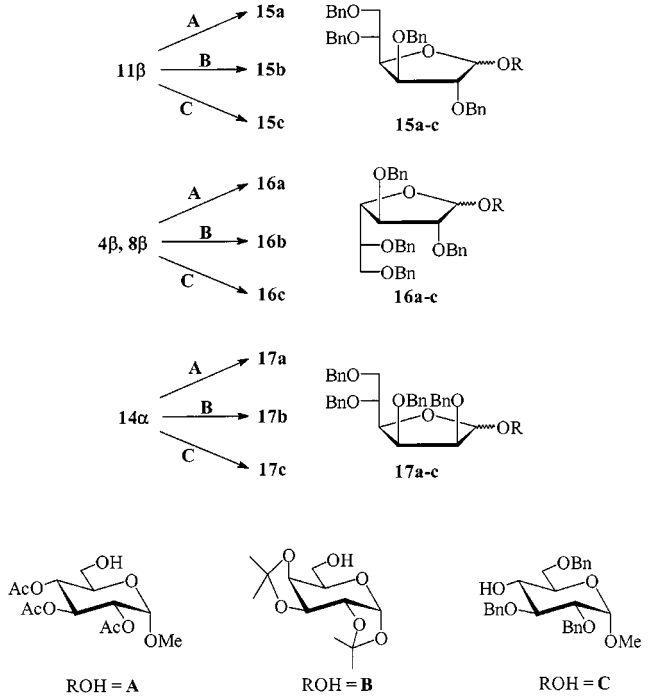
Glycosylation Reactions

With the thioglycosides **4β**, **8β**, **11β** and **14α** in hand, we then performed the glycosylation of the partially protected monosaccharides **A**, **B** and **C** as representative glycosyl acceptors (Scheme 3). The behavior of perbenzylated phenyl 1-thio-β-D-glucofuranoside (**11β**) towards acceptor **A** in dichloromethane was examined with a variety of promoters. Simple electrophilic sources such as iodine and *N*-iodosuccinimide (NIS) afforded disaccharide **15a** in moderate yields and selectivities. The reaction time significantly decreased when activation of the thiofuranoside was achieved by NIS and a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf) at 0 °C but in a disappointing yield (Table 1, entry 1). Both yield and stereoselectivity were significantly improved in the presence of NIS and the mild stannous trifluoromethanesulfonate [$Sn(OTf)_2$], in a typical ratio **11β/A**/NIS/$Sn(OTf)_2$ 1.2:1:1.2:0.1 (entry 2), and in the presence of molecular sieves (entry 3). These results show that the efficiency and diastereocontrol of the glycosylation reactions are highly sensitive to acidic conditions and that controlling this parameter allowed the selective synthesis of the target 1,2-*cis*-furanoside. From this favorable data, we attempted glycosylation of the more hindered acceptors **B**

Table 1. Reaction conditions for the selective synthesis of disaccharides containing 1,2-*cis*-hexofuranosyl units

Entry	Donor	ROH	Solvent	Promoter (1.2:0.1)	4Å, MS[a]	Time (min)	Product	Yield (%)	α/β
1	**11β**	**A**	CH_2Cl_2	NIS/TMSOTf	–	5	**15a**	14	3.8:1
2	**11β**	**A**	CH_2Cl_2	NIS/$Sn(OTf)_2$	–	15	**15a**	59	4.9:1
3	**11β**	**A**	CH_2Cl_2	NIS/$Sn(OTf)_2$	+	10	**15a**	84	5.7:1
4	**11β**	**B**	CH_2Cl_2	NIS/$Sn(OTf)_2$	+	10	**15b**	87	4.6:1
5	**11β**	**C**	CH_2Cl_2	NIS/$Sn(OTf)_2$	+	10	**15c**	68	2.1:1
6	**4β**	**A**	CH_2Cl_2	NIS/TMSOTf	–	5	**16a**	89	1:19
7	**4β**	**A**	CH_2Cl_2	NIS/$Sn(OTf)_2$	+	10	**16a**	84	5.3:1
8	**4β**	**B**	CH_2Cl_2	NIS/$Sn(OTf)_2$	+	20	**16b**	81	3.3:1
9	**4β**	**C**	CH_2Cl_2	NIS/$Sn(OTf)_2$	+	12	**16c**	83	1.7:1
10	8β	**B**	CH_2Cl_2	NIS/$Sn(OTf)_2$	+	20	**16b**	82	3.0:1
11	**8β**	**C**	CH_2Cl_2	NIS/$Sn(OTf)_2$	+	12	**16c**	70	1.5:1
12	**4β**	**A**	Et_2O	NIS/$Sn(OTf)_2$	+	1260	**16a**	60	1:1
13	**4β**	**A**	CH_3CN	NIS/$Sn(OTf)_2$	+	10	**16a**	54	1:4
14	**14α**	**A**	CH_2Cl_2	NIS/$Sn(OTf)_2$	–	10	**17a**	74	6.7:1
15	**14α**	**A**	CH_2Cl_2	NIS/$Sn(OTf)_2$	+	10	**17a**	90	1:3.3
16	**14α**	**B**	CH_2Cl_2	NIS/$Sn(OTf)_2$	+	12	**17b**	87	1:2.3
17	**14α**	**C**	CH_2Cl_2	NIS/$Sn(OTf)_2$	+	11	**17c**	92	1:1.9

[a] MS: molecular sieves.



Scheme 3. Stereoselective synthesis of 1,2-*cis*-glycofuranosides at 0 °C; for reagents and conditions, see Table 1

and **C**. Although steric effects lowered the α/β ratio, the disaccharides **15b** and **15c** were obtained within only a few minutes at 0 °C in good yields and interesting diastereoselectivities towards the α-anomers (entries 4 and 5).

The compounds **15a–c** were purified by flash-chromatography and **15bα** was isolated as a pure anomer. The latter was then easily characterized on the grounds of signals identified by COSY and heteronuclear ^1H-^{13}C 2D experiments (Table 2, Table 3 and Table 4). This analysis was the starting point to unequivocally assign signals for other disaccharides **15a,c**.

The relative relationship between H-1′ and H-2′ is based on the assumption of a large coupling constant between these two nuclei ($J_{1',2'}$ = 4.0–4.3 Hz) and a chemical shift for C-1′ at δ = 100.5–103.0 for the α-glucofuranosyl derivatives, while smaller values of $J_{1',2'}$ (< 1 Hz) and lower-field signals ($\delta_{C-1'}$ = 107.3–108.7) are characteristic of minor β-products.

Similar results were also obtained when optimized conditions were applied to the galactofuranosyl donors **4β** and **8β**. As previously observed when activation of the thiofuranoside was performed by NIS/TMSOTf in the absence of molecular sieves, the β-D-galactofuranoside corresponding to **16a** was selectively synthesized (Table 1, entry 6).

On the other hand, activation of the furanosyl donors under milder conditions afforded the desired disaccharides **16a–c** in near 80% yields and with acceptor-dependant diastereoselectivities, but still in favor of the more hindered 1,2-*cis*-furanosides (entries 7–11). It is also noteworthy that, while phenyl thiopyranosides are generally less reactive than ethyl thiopyranosides,[44] the phenyl (**4β**) and ethyl thioglycofuranosides (**8β**) reacted quite similarly and gave the disaccharides **16b** and **16c** in good yields and selectivities (entries 8,10 and 9,11). Moreover, we also studied glycosidation of donor **4β** in participating solvents[45,46] with **A** as the model acceptor. As expected, marked effects on the α/β ratio were observed since the disaccharide **16a** was obtained without any selectivity in diethyl ether (entry 12) while **16aβ** was predominant in the anomeric mixture when the reaction was performed in acetonitrile (entry 13). The data shows that optimized yields and α-stereocontrol still required nonparticipating solvents, e.g. dichloromethane. Finally, the relative stereocontrol assignment of the galactofuranosides was made by ^1H and ^{13}C NMR spectroscopy (Table 2, Table 3 and Table 4) starting from disaccharides **16cα** and **16cβ,** which were separated by column chromatography. The former is characterized by a large H-1′–H-2′ coupling constant ($J_{1',2'}$ = 4.5 Hz) and by a chemical shift

Table 2. ^{1}H NMR spectroscopic data (δ, ppm; nd: not determined) for disaccharides **15**–**17**

Product	δ (ppm)													
	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	H-1′	H-2′	H-3′	H-4′	H-5′	H-6′a	H-6′b
15aα[a]	4.91	4.83	5.46	5.13	3.93	3.81	3.52	5.03	3.97	4.27	4.33	3.92	3.83	3.68
15aβ[a]	4.90	4.86	5.47	5.01	3.92	3.77	3.50	5.03	4.01–4.09	4.01–4.09	4.35	4.01–4.09	3.88	3.65
15bα[b]	5.52	4.30	4.53	4.27	4.06	3.86	3.70	5.12	3.98	4.24	4.35	4.01	3.83	3.67
15bβ[b]	5.54	4.29	4.51	4.15	3.96	3.90	3.56	5.11	4.07–4.09	4.07–4.09	4.35	4.10	3.88	3.70
15cα[c]	4.62	3.55	3.98	3.73–3.76	3.84–3.90	3.76	3.63	5.57	3.81	4.08	4.19	3.84–3.90	3.73–3.76	3.57
15cβ[c]	4.57	3.44–3.49	3.91–4.00	3.75–3.82	3.63–3.67	3.75–3.82	3.63–3.67	5.34	3.91–4.00	4.21–4.25	3.98	3.91–4.00	3.67	3.52
16aα[a]	4.87	4.77	5.44	5.03	3.92	3.73	3.48	4.95	4.04	4.24	3.97	3.68	3.62	3.56
16aβ[a]	4.96	4.89	5.48	5.05	3.92	3.76	3.47	5.06	4.04	4.01	4.15	3.76	3.71	3.66
16bα[b]	5.52	4.30	4.55–4.58	4.29–4.33	4.03	3.86	3.63	5.05	4.06	4.29–4.33	3.96	3.71	3.64	3.58
16bβ[b]	5.54	nd	nd	4.18	nd	nd	nd	5.20	nd	nd	4.13	3.78	nd	nd
16cα[c]	4.61	3.56	4.01	3.79–3.82	3.79–3.82	3.79–3.82	3.79–3.82	5.51	3.84	4.14	3.79–3.82	3.71	3.62	3.58
16cβ[c]	4.58	3.54	3.89	3.83	3.74	3.61–3.63	3.61–3.63	5.29	3.95	3.99	4.25	3.67	3.56	3.44
17aα[a]	4.93	4.87	5.45	5.10	3.91	3.77	3.51	5.15	4.02	4.25	4.16	4.07	3.87	3.65
17aβ[a]	4.85	4.84	5.47	4.95	3.99	3.79	3.54	5.08	3.92	4.21	4.10	4.04	3.86	3.67
17bα[b]	5.53	4.31	4.58	4.27	4.03–4.08	3.78	3.74	5.22	4.03–4.08	4.22	4.23	4.03–4.08	3.86	3.64
17bβ[b]	5.52	4.27	4.44	4.23	4.03–4.12	3.93	3.56	5.11	3.88	4.20	4.15	4.03–4.12	3.86	3.73
17cα[c]	4.60	3.51	3.94	3.62	3.75–3.79	3.74	3.49–3.54	5.66	3.91	4.17	4.07	4.00	3.77	3.49–3.54
17cβ[c]	4.59	3.52	3.98	3.75	3.86	3.46–3.48	3.46–3.48	5.21	3.68	4.11	3.98	3.77	3.80	3.70

[a] δ = 7.19–7.38 (C_6H_5), δ = 4.27–5.00 (CH_2Ph), δ = 3.17–3.37 (OCH_3), δ = 1.94–2.08 (CH_3CO). – [b] δ = 7.18–7.39 (C_6H_5), δ = 4.39–4.92(CH_2Ph), δ = 1.16–1.52 [$C(CH_3)_2$]. – [c] δ = 7.13–7.36 (C_6H_5), δ = 4.23–5.08 (CH_2Ph), δ = 3.35–3.41 (OCH_3).

Table 3. ^{1}H NMR spectroscopic data (*J*, Hz, nd: not determined) for disaccharides **15**–**17**

Product	*J* (Hz)													
	1,2	2,3	3,4	4,5	5,6a	5,6b	6a,6b	1′,2′	2′,3′	3′,4′	4′,5′	5′,6′a	5′,6′b	6′a,6′b
15aα	3.6	10.2	9.6	10.1	4.4	2.4	11.3	4.1	4.1	6.0	6.4	2.0	6.4	10.5
15aβ	3.7	10.2	9.5	9.6	1.9	6.3	11.3	< 1	nd	4.4	8.8	1.8	5.4	10.5
15bα	5.0	2.4	8.0	1.9	6.0	1.8	9.8	4.3	3.7	5.9	7.5	2.2	6.5	10.5
15bβ	5.0	2.4	7.9	1.8	1.9	6.7	10.0	< 1	nd	4.8	9.2	2.0	5.5	10.6
15cα	3.9	9.5	9.2	nd	2.0	6.4	10.7	4.0	3.5	5.0	7.7	nd	6.2	10.2
15cβ	3.2	nd	nd	nd	nd	nd	nd	< 1	nd	5.4	9.4	1.9	4.5	10.5
16aα	3.6	10.2	9.4	10.1	5.4	2.8	11.4	4.2	7.5	7.3	6.7	4.0	6.3	10.4
16aβ	3.8	9.5	9.6	1.03	2.3	5.8	11.4	< 1	3.3	7.0	3.2	6.6	5.4	10.4
16bα	5.0	2.4	nd	nd	6.2	2.1	10.0	4.3	7.6	7.1	6.1	4.1	6.3	10.3
16bβ	5.0	nd	7.9	1.9	nd	nd	nd	< 1	nd	6.5	3.3	nd	nd	nd
16cα	3.9	9.6	8.3	nd	nd	nd	nd	4.5	6.0	6.8	4.5	4.6	6.5	10.0
16cβ	3.6	9.2	9.2	9.2	nd	nd	nd	< 1	2.0	5.6	3.9	7.5	3.1	10.5
17aα	3.6	10.2	9.8	9.7	4.6	2.0	11.3	3.6	3.9	3.8	8.2	1.7	5.9	10.7
17aβ	3.6	9.0	9.5	10.1	1.4	7.2	11.3	4.8	4.7	4.2	9.0	< 1	4.4	10.7
17bα	5.0	2.4	7.9	1.8	6.5	7.7	10.6	4.2	4.3	2.8	6.8	1.8	6.0	10.6
17bβ	5.0	2.0	8.0	1.4	6.8	6.2	9.7	4.5	4.6	4.6	8.8	1.1	4.2	10.5
17cα	4.1	9.6	8.9	10.0	nd	6.3	10.8	4.1	4.0	3.9	8.6	1.7	5.7	10.5
17cβ	3.6	9.6	9.5	9.5	2.1	4.8	nd	5.2	4.3	3.8	9.5	1.9	nd	10.7

for the anomeric center of the nonreducing moiety at δ = 101.9, while the corresponding NMR values for the β-anomer ($J_{1',2'} < 1$ Hz, $\delta_{C\text{-}1'} = 105.9$) are indicative of the *trans* relationship between H-1′ and H-2′. Compounds **16a** and **16b** were then fully analyzed by comparison with **16c**.

To demonstrate the scope of this methodology, we next attempted the preparation of disaccharides containing a β-D-mannofuranosyl unit which are more difficult to synthesize. Preliminary work from our laboratory[29] showed that glycosylation of **A**, with 2,3,5,6-tetra-*O*-benzyl-α-D-mannofuranosyl trichloroacetimidate as donor and $Sn(OTf)_2$ as catalyst, was specifically achieved with retention of configuration on the mannosyl moiety. This data was partly corroborated in the present study since the perbenzylated phenyl α-thiomannofuranoside **14α** reacted with acceptor **A**, with NIS/$Sn(OTf)_2$ as promoter but in the absence of molecular sieves (Table 1, entry 14), to yield selectively the less hindered disaccharide **17aα**. Nevertheless, all other reactions carried out in the presence of an acid scavenger afforded diastereoselectively the desired 1,2-*cis* compounds

Table 4. ^{13}C NMR spectroscopic data (δ, ppm) for disaccharides **15**–**17**

Product	δ (ppm)											
	C-1	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′
15aα	96.5	70.9	70.4	68.9	68.1	65.8	100.5	83.5	82.0	77.1	76.7	71.6
15aβ	96.4	70.9	70.3	69.1	68.4	66.8	108.0	85.2	80.7	80.3	76.4	70.8
15bα	96.3	70.6	70.7	70.7	65.5	66.3	100.9	83.5	82.1	77.0	76.5	71.6
15bβ	96.3	70.6	70.6	71.0	67.4	66.9	107.3	85.0	80.9	80.2	76.5	71.1
15cα	97.6	80.1	81.8	75.8	69.5	69.4	103.0	81.3	81.9	77.5	76.7	71.6
15cβ	98.1	79.6	80.6	75.7	68.9	69.9	108.7	85.6	80.0	80.0	75.8	70.1
16aα	96.3	71.0	70.3	69.4	68.1	65.8	100.1	84.1	80.8[a]	80.7[a]	79.6	70.3
16aβ	96.5	70.8	70.2	69.1	68.4	65.9	106.7	88.1	82.8	81.1	76.3	70.9
16bα	96.3	70.7[a]	70.7[a]	70.6[a]	65.4	65.9	100.3	83.9	80.8	80.6	79.4	70.5
16bβ	96.3	71.2[a]	71.3[a]	71.7	67.7	66.1	106.1	87.8	82.8	80.9	76.4	70.5
16cα	97.5	80.2	81.6	76.2	69.3	69.6	101.9	82.2	80.0	79.3	77.3	70.6
16cβ	98.1	79.9	80.1	74.1	70.0	68.7	105.9	87.9	82.8	82.9	77.1	71.6
17aα	96.7	70.9	70.4	68.7	68.1	65.9	105.9	84.4	78.2	78.5	76.3	71.0
17aβ	96.2	71.1	70.3	69.4	68.7	67.1	100.9	80.5	75.8	78.2	76.7	69.7
17bα	96.4	70.6	70.6	70.8	65.7	67.4	107.2	85.2	78.3[a]	78.2[a]	76.1	70.2
17bβ	96.3	70.7	70.4	70.8	67.2	65.4	99.7	80.2	75.8	78.4	76.7	69.7
17cα	97.8	79.9	81.7	75.3	69.8[a]	69.6[a]	106.4	84.7	77.8	78.2	76.2	70.6[a]
17cβ	98.0	79.6	80.6	76.7	70.0	68.0	100.9	80.6	75.2	77.7	76.2	69.0

[a] Signals may be interchanged.

17a–**17c** in almost quantitative yields and with interesting β/α ratios from 1.9:1 to 3.3:1 (entries 15–17). Molecular sieves hence appeared to be essential for limiting in situ anomerization of **17β** to the more stable anomers **17α**. These results therefore complement those obtained through 1-*O*-alkylation of 2,3:5,6-di-*O*-isopropylidene-D-mannose.[47] The β-configuration of the mannosyl moieties was ascertained by NMR spectroscopy (Table 2, Table 3 and Table 4) from compounds **17bβ** and **17cβ**, which were isolated by column chromatography. Although the coupling constants between H-1′ and H-2′ did not allow us to differentiate the α- from the β-mannofuranoside, the values observed for signals corresponding to the anomeric center of the nonreducing end were representative of the postulated configuration. Indeed, C-1′ of the 1,2-*trans* isomers resonates at δ = 105.9–107.2 while C-1′ of the target 1,2-*cis* compounds **17aβ**, **17bβ** and **17cβ** is shifted by approximately 5–6 ppm to higher field.

In conclusion, we have developed an efficient route to 1,2-*trans*-thiohexofuranosides which may be applied to the preparation of a wide range of alkyl or aryl thiofuranosyl donors. These latter were activated under very mild conditions using NIS/$Sn(OTf)_2$ as a new promoter of thioglycosides. Glycosidation reactions of these donors interestingly yielded 1,2-*cis*-hexofuranosides with good to high diastereoselectivities, even for the synthesis of β-D-mannofuranosides. Mechanistic studies for a better understanding of the progress of glycosylation reactions from thiofuranosides and the synthesis of analogues of natural glycoconjugates are currently under investigation.

Experimental Section

General: Dichloromethane, *N*,*N*-dimethylformamide (DMF) and acetonitrile were dried over phosphorus pentoxide and distilled, while diethyl ether was dried over sodium/benzophenone before distilling. All other chemicals were commercially available and used as received. Octyl β-D-galactofuranoside **(1)** was prepared according to ref.[37c] and compounds **5**, **9** and **12** according to ref.[39] All reactions were performed under nitrogen. – TLC analyses were carried out on precoated nonactivated plates (E. Merck 60 F_{254}) with detection by UV absorption (254 nm), when applicable, and charring with 5% H_2SO_4 in EtOH. – For column chromatography, E. Merck 60H (5–40 μm) Silica Gel was used. – Optical rotations were determined with a Perkin–Elmer 341 polarimeter at 20 °C using a 1 dm cell. – ^1H and ^{13}C NMR spectra were recorded on a Bruker ARX 400 spectrometer at 400 and 100 MHz, respectively. Chemical shifts are given in ppm (δ). $CDCl_3$ and TMS were used as solvent and internal standard, respectively. – Microanalyses were performed by the Service de Microanalyses de l′ICSN (Gif sur Yvette, France).

Octyl 2,3,5,6-Tetra-*O*-benzyl-β-D-galactofuranoside (2): To a cooled (0 °C) solution of octyl β-D-galactofuranoside **(1)**[37] (7.34 g, 25.1 mmol) in DMF were successively added a 60% dispersion of sodium hydride in mineral oil (4.82 g, 120.5 mmol) and, after 30 min, benzyl bromide (14.3 mL, 120.3 mmol). After stirring overnight at room temp., the reaction was quenched by adding methanol. The solvent was then removed under reduced pressure and the resulting crude oil partitioned between ethyl acetate (150 mL) and water (20 mL). The organic layer was washed with sat. aq. NaCl, dried ($MgSO_4$), concentrated and purification by flash-chromatography (light petroleum/diethyl ether, 9:1) gave **2** (13.39 g, 82%) as a colorless oil. – TLC (light petroleum/ethyl acetate, 4:1): R_f = 0.44. – $[\alpha]_D$ = –48.1 (c = 1.06, CH_2Cl_2). – ^1H NMR: δ = 0.87 (br. t, J = 6.9 Hz, 3 H, CH_3), 1.23–1.33 (m, 10 H, CH_2), 1.53–1.60 (m, 2 H, OCH_2CH_2), 3.37 (dt, ^2J = 9.7 Hz, ^3J = 6.7 Hz, 1 H, OCH_2CH_2), 3.66 (dt, ^3J = 6.8 Hz, 1 H, OCH_2CH_2), 3.68 (dd, $J_{6a,6b}$ = 9.9 Hz, $J_{6a,5}$ = 5.0 Hz, 1 H, H-6a), 3.72 (dd, $J_{6b,5}$ = 6.3 Hz, H-6b), 3.76–3.80 (m, 1 H, H-5), 3.98 (dd, $J_{2,3}$ = 3.4 Hz, $J_{1,2}$ = 1.4 Hz, 1 H, H-2), 4.01 (dd, $J_{3,4}$ = 7.2 Hz, 1 H, H-3), 4.12 (dd, $J_{4,5}$ = 3.1 Hz, 1 H, H-4), 4.27–4.74 (m, 8 H, CH_2Ph), 5.04 (br. s, 1 H, H-1), 7.28–7.40 (m, 20 H, C_6H_5). – ^{13}C NMR: δ = 14.1 (CH_3), 22.7, 26.2, 29.3, 29.4, 29.5 (CH_2), 31.8 (OCH_2CH_2), 67.6 (C-6), 71.0, 71.8, 72.0, 72.9, 73.3, 73.4 (OCH_2CH_2, CH_2Ph), 76.3 (C-5), 80.6 (C-4), 82.7 (C-3), 88.6 (C-2), 105.9 (C-1), 126.2–127.6 (C_6H_5), 137.7, 137.9, 138.3, 138.4 (C_{ipso}). – $C_{42}H_{52}O_6$ (652.87): calcd. C 77.27, H 8.03; found C 77.09, H 7.92.

1-*O*-Acetyl 2,3,5,6-Tetra-*O*-benzyl-D-galactofuranose (3): To a solution of **2** (2.00 g, 3.1 mmol) in dichloromethane (30 mL) were successively added at room temp. acetic anhydride (1.15 mL, 12.4 mmol) and sulfuric acid (66 μL, 1.2 mmol). After stirring for 24 h, the reaction medium was neutralized with $NaHCO_3$, filtered and concentrated under reduced pressure. Purification by flash chromatography (light petroleum/ethyl acetate, 87:13) yielded **3** (1.46 g, 81%, α/β = 1:4.9) as a colorless oil. – TLC (light petroleum/ethyl acetate, 4:1): R_f = 0.37. – $C_{36}H_{38}O_7$ (582.70): calcd. C 74.21, H 6.57; found C 74.31, H 6.62.

3α: ^{1}H NMR: δ = 2.07 (s, 3 H, CH_3CO), 3.61–3.65 (m, 2 H, H-6), 4.18 (dd, $J_{3,4}$ = 7.7 Hz, $J_{4,5}$ = 4.2 Hz, 1 H, H-4), 4.30–4.74 (m, 8 H, CH_2Ph), 6.22 (d, $J_{1,2}$ = 4.2 Hz, 1 H, H-1), 7.18–7.37 (m, 20 H, C_6H_5). – ^{13}C NMR: δ = 21.2 (*C*H_3CO), 70.2 (C-6), 72.4, 73.0, 73.1, 73.4 (*C*H_2Ph), 77.6 (C-5), 79.5 (C-4), 81.3 (C-3), 83.6 (C-2), 93.7 (C-1), 127.5–128.5 (C_6H_5), 137.2–138.5 (C_{ipso}), 170.2 (CO).

3β: ^{1}H NMR: δ = 2.07 (s, 3 H, CH_3CO), 3.67 (d, $J_{5,6}$ = 5.5 Hz, 2 H, H-6), 3.79 (dd, 1 H, $J_{4,5}$ = 4.4 Hz, 1 H, H-5), 4.02 (d, $J_{2,3}$ = 1.8 Hz, 1 H, H-2), 4.05 (dd, $J_{3,4}$ = 6.1 Hz, 1 H, H-3), 4.29 (dd, 1 H, H-4), 4.30–4.74 (m, 8 H, CH_2Ph), 6.25 (s, 1 H, H-1), 7.18–7.37 (m, 20 H, C_6H_5). – ^{13}C NMR: δ = 21.3 (*C*H_3CO), 70.6 (C-6), 71.8, 72.1, 73.2, 73.4 (*C*H_2Ph), 76.5 (C-5), 83.0 (C-4), 84.0 (C-3), 87.1 (C-2), 100.4 (C-1), 127.5–128.2 (C_6H_5), 137.2–138.5 (C_{ipso}), 170.0 (CO).

Phenyl 2,3,5,6-Tetra-*O*-benzyl-1-thio-D-galactofuranoside (4): To a cooled (0 °C) solution of **3** (1.50 g, 2.6 mmol) in dry dichloromethane (15 mL) were successively added thiophenol (0.32 mL, 3.1 mmol) and $BF_3{\cdot}OEt_2$ (0.65 mL, 5.1 mmol). After stirring at 0 °C for 1 h, the reaction medium was diluted with dichloromethane (40 mL), washed with 5% aq. $NaHCO_3$ (4 × 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by flash-chromatography (light petroleum/diethyl ether, 9:1) gave an anomeric mixture of **4** (0.65 g, 40%, α/β = 1:1). – TLC (light petroleum/ethyl acetate, 9:1): R_f = 0.3. – For characterization of **4β**, see above. – Selected data for the α anomer: ^{1}H NMR: δ = 3.55 (dd, $J_{6a,6b}$ = 10.6 Hz, $J_{5,6a}$ = 6.1 Hz, 1 H, H-6a), 3.65 (dd, $J_{5,6b}$ = 4.6 Hz, 1 H, H-6b), 3.95 (ddd, $J_{4,5}$ = 7.1 Hz, 1 H, H-5), 4.13 (dd, $J_{3,4}$ = 4.6 Hz, 1 H, H-4), 4.22 (t, $J_{2,3}$ = 4.6 Hz, 1 H, H-3), 4.26 (t, $J_{1,2}$ = 4.6 Hz, 1 H, H-2), 4.41–4.76 (m, 8 H, CH_2Ph), 5.69 (d, 1 H, H-1), 7.19–7.55 (m, 20 H, C_6H_5). – ^{13}C NMR: δ = 70.7 (C-6), 71.8, 72.4, 73.3, 73.4 (*C*H_2Ph), 78.5 (C-5), 81.9 (C-3), 84.1 (C-4), 84.3 (C-2), 89.4 (C-1), 126.6–130.6 (C_6H_5), 135.6, 137.3, 137.7, 138.2, 138.8 (C_{ipso}).

General Procedure for the Synthesis of Per-*O*-acetylated Thioglycofuranosides (6β, 7β, 10, 13): To a cooled (0 °C) solution of the appropriate penta-*O*-acetyl-hexofuranose[39] (1.00 g, 2.6 mmol) in dry dichloromethane (30 mL) were successively added at 0 °C the thiol (3.1 mmol) and $BF_3{\cdot}OEt_2$ (0.98 mL, 7.8 mmol). After stirring at 0 °C for 1.5–5 h, workup and purification [flash-chromatography (light petroleum/ethyl acetate, 3:1)] were then similar to that described for compound **4**.

Phenyl 2,3,5,6-Tetra-*O*-acetyl-1-thio-β-D-galactofuranoside (6β): Synthesis of **6β** was performed according to the previous procedure starting from **5**[39] and thiophenol (0.32 mL) within 3 h. Purification yielded 0.93 g (81%) of **6β** as a colorless oil. – TLC (light petroleum/ethyl acetate, 7:3): R_f = 0.3. – $[\alpha]_D$ = –105.9 (*c* = 1.01, CH_2Cl_2). – ^{1}H NMR: δ = 2.04, 2.09, 2.11, 2.13 (4 s, 12 H, CH_3CO), 4.18 (dd, $J_{6a,6b}$ = 11.8 Hz, $J_{5,6a}$ = 7.1 Hz, 1 H, H-6a), 4.33 (dd, $J_{5,6b}$ = 4.6 Hz, 1 H, H-6b), 4.48 (dd, $J_{3,4}$ = 6.0 Hz, $J_{4,5}$ = 3.8 Hz, 1 H, H-4), 5.08 (dd, $J_{2,3}$ = 2.6 Hz, 1 H, H-3), 5.23 (t, $J_{1,2} \approx J_{2,3}$ = 2.5 Hz, 1 H, H-2), 5.40 (dt, *J* = 4.2 Hz, 1 H, H-5), 5.51 (d, 1 H, H-1), 7.27–7.50 (m, 5 H, C_6H_5). – ^{13}C NMR: δ = 20.7, 20.8, 21.0 (*C*H_3CO), 62.5 (C-6), 69.0 (C-5), 76.5 (C-3), 79.6 (C-4), 81.2 (C-2), 90.4 (C-1), 127.9, 129.0, 132.2 (C_6H_5), 133.1 (C_{ipso}), 169.6, 169.9, 170.0, 170.5 (CO). – $C_{20}H_{24}O_9S$ (440.47): calcd. C 54.55, H 5.47; found C 54.49, H 5.53.

Ethyl 2,3,5,6-Tetra-*O*-acetyl-1-thio-β-D-galactofuranoside (7β): Synthesis of **7β** was performed according to the previous procedure starting from **5**[39] and ethanethiol (0.23 mL) within 1.5 h. Purification yielded 0.56 g (55%) of **7β** as a colorless oil. – TLC (light petroleum/ethyl acetate, 7:3): R_f = 0.4. – $[\alpha]_D$ = –98.4 (*c* = 1.01, CH_2Cl_2). – ^{1}H NMR: δ = 1.28 (t, ^3J = 7.1 Hz, 3 H, CH_3CH$_2$), 2.04, 2.08, 2.09, 2.11 (4 s, 12 H, CH_3CO), 2.62 (dq, ^2J = 12.7 Hz, 1 H, CH_3CH_2), 2.69 (dq, ^2J = 12.7 Hz, 1 H, CH_3CH_2), 4.18 (dd, $J_{6a,6b}$ = 11.8 Hz, $J_{5,6a}$ = 7.2 Hz, 1 H, H-6a), 4.31 (dd, $J_{5,6b}$ = 4.6 Hz, 1 H, H-6b), 4.38 (dd, $J_{3,4}$ = 6.1 Hz, $J_{4,5}$ = 3.6 Hz, 1 H, H-4), 5.02 (dd, $J_{2,3}$ = 2.0 Hz, 1 H, H-3), 5.06 (br. t, *J* = 2.4 Hz, 1 H, H-2), 5.32 (d, $J_{1,2}$ = 2.0 Hz, 1 H, H-1), 5.39 (ddd, 1 H, H-5). – ^{13}C NMR: δ = 14.8 (*C*H_3CH$_2$), 20.6, 20.7, 20.8, 20.9 (*C*H_3CO), 25.3 (CH_3CH_2), 62.5 (C-6), 69.0 (C-5), 76.7 (C-3), 79.2 (C-4), 81.7 (C-2), 87.6 (C-1), 169.7, 169.9, 170.0, 170.4 (CO). – $C_{16}H_{24}O_9S$ (392.43): calcd. C 48.97, H 6.16; found C 48.92, H 6.14.

Phenyl 2,3,5,6-Tetra-*O*-acetyl-1-thio-D-glucofuranoside (10): Synthesis of **10** was performed according to the previous procedure starting from **9**[39] and thiophenol (0.32 mL) within 5 h. Purification yielded 0.80 g (70%) of an anomeric mixture of **10** (α/β = 1:9). – TLC (light petroleum/ethyl acetate, 3:2): R_f = 0.45. – $C_{20}H_{24}O_9S$ (440.47): calcd. C 54.55, H 5.47; found C 54.72, H 5.51.

10β: ^{1}H NMR: δ = 2.01, 2.06, 2.09, 2.12 (4 s, 12 H, CH_3CO), 4.18 (dd, $J_{6a,6b}$ = 12.3 Hz, $J_{5,6a}$ = 4.8 Hz, 1 H, H-6a), 4.41 (dd, $J_{3,4}$ = 4.2 Hz, $J_{4,5}$ = 9.3 Hz, 1 H, H-4), 4.63 (dd, $J_{5,6b}$ = 2.4 Hz, 1 H, H-6b), 5.19 (dd, $J_{1,2}$ = 2.0 Hz, $J_{2,3}$ = 1.0 Hz, 1 H, H-2), 5.32 (d, 1 H, H-1), 5.35 (ddd, 1 H, H-5), 5.37 (d, 1 H, H-3), 7.27–7.53 (m, 5 H, C_6H_5). – ^{13}C NMR: δ = 20.7, 20.8 (*C*H_3CO), 63.1 (C-6), 68.1 (C-5), 74.0 (C-3), 78.9 (C-4), 81.2 (C-2), 91.1 (C-1), 127.9, 129.1 (C_6H_5), 132.3 (C_{ipso}), 169.1 169.3, 169.6, 170.6 (CO).

10α: selected data ^{1}H NMR: δ = 2.02–2.11 (4 s, 12 H, CH_3CO), 4.17 (dd, $J_{6a,6b}$ = 12.3 Hz, $J_{5,6a}$ = 5.2 Hz, 1 H, H-6a), 4.55 (dd, $J_{5,6b}$ = 2.4 Hz, 1 H, H-6b), 4.59 (dd, $J_{4,5}$ = 9.4 Hz, $J_{3,4}$ = 3.9 Hz, 1 H, H-4), 5.24 (ddd, 1 H, H-5), 5.43 (dd, $J_{1,2}$ = 5.2 Hz, $J_{2,3}$ = 1.5 Hz, 1 H, H-2), 5.47 (dd, 1 H, H-3), 5.80 (d, 1 H, H-1), 7.27–7.53 (m, 5 H, C_6H_5). – ^{13}C NMR: δ = 20.0–20.6 (*C*H_3CO), 63.1 (C-6), 67.5 (C-5), 74.7 (C-4), 75.9 (C-3), 77.7 (C-2), 90.3 (C-1), 132.0, 128.8 (C_6H_5), 133.6 (C_{ipso}), 169.1–170.6 (CO).

Phenyl 2,3,5,6-Tetra-*O*-acetyl-1-thio-D-mannofuranoside (13): Synthesis of **13** was performed according to the previous procedure starting from **12**[39] and thiophenol (0.32 mL) within 4.25 h. Purification yielded 1.03 g (90%) of an anomeric mixture of **13** (α/β = 15.7:1). – TLC (light petroleum/ethyl acetate, 3:2): R_f = 0.44. – $C_{20}H_{24}O_9S$ (440.47): calcd. C 54.55, H 5.47; found C 54.58, H 5.49.

13α: ^{1}H NMR: δ = 1.99, 2.07, 2.08 (4 s, 12 H, CH_3CO), 4,15 (dd, $J_{6a,6b}$ = 12.3 Hz, $J_{5,6a}$ = 5.1 Hz, 1 H, H-6a), 4.33 (dd, $J_{5,4}$ = 9.3 Hz, $J_{3,4}$ = 3.2 Hz, 1 H, H-4), 4.55 (dd, $J_{5,6b}$ = 2.3 Hz, 1 H, H-6b), 5.25 (dd, $J_{1,2}$ = 7.1 Hz, $J_{2,3}$ = 4.6 Hz, 1 H, H-2), 5.28 (ddd, 1 H, H-5), 5.40 (d, 1 H, H-1), 5.48 (dd, 1 H, H-3), 7.32–7.52 (m, 5 H, C_6H_5). – ^{13}C NMR: δ = 20.4, 20.7 (*C*H_3CO), 62.7 (C-6), 67.6 (C-5), 70.2 (C-3), 74.6 (C-2), 76.3 (C-4), 87.5 (C-1), 128.3, 129.0 (C_6H_5), 133.0 (C_{ipso}), 169.3, 169.6, 170.6 (CO).

13β: selected data ^{1}H NMR: δ = 2.02, 2.15 (4 s, 12 H, CH_3CO), 4.20 (dd, $J_{6a,6b}$ = 12.4 Hz, $J_{5,6a}$ = 4.6 Hz, 1 H, H-6a), 4.36 (dd,

$J_{4,5}$ = 9.5 Hz, $J_{3,4}$ = 4.4 Hz, 1 H, H-4), 4.63 (dd, $J_{5,6b}$ = 2.4 Hz, 1 H, H-6b), 5.41 (dd, $J_{1,2}$ = 6.8 Hz, $J_{2,3}$ = 4.8 Hz, 1 H, H-2), 5.46–5.49 (m, 1 H, H-5), 5.65 (br. t, J = 4.6 Hz,1 H, H-3), 5.79 (d, 1 H, H-1), 7.23–7.48 (m, 5 H, C_6H_5). – ^{13}C NMR: δ = 20.5, 20.6, 20.8 (CH_3CO), 62.7 (C-6), 68.5 (C-5), 69.5 (C-3), 72.1 (C-2), 76.0 (C-4), 89.9 (C-1), 127.5, 131.7 (C_6H_5), 132.0 (C_{ipso}), 169.5, 169.6, 169.7, 170.6 (CO).

General Procedure for the Synthesis of Per-*O*-benzylated Thioglycofuranosides (4β, 8β, 11β, 14α): To a solution of the appropriate tetra-*O*-acetyl-1-thio-D-hexofuranoside (1.1 mmol) in methanol (5 mL) was added a 0.1 M solution of sodium methylate in methanol (9 mL, 0.9 mmol). After stirring at room temp. for 10 min, the reaction was neutralized with IR-120 H^+-form resin, filtered and concentrated under reduced pressure. The resulting residue was then diluted with DMF (12 mL). To this solution cooled at 0 °C were successively added a 60% dispersion of sodium hydride in mineral oil (0.22 g, 5.4 mmol) and benzyl bromide (0.65 mL, 5.4 mmol). The reaction was allowed to stir at room temp. for 2 h, methanol added (10 mL) and concentrated under reduced pressure at 50 °C. Flash chromatography (light petroleum/ethyl acetate, 9:1) yielded the required 1,2-*trans* thioglycofuranoside.

Phenyl 2,3,5,6-Tetra-*O*-benzyl-1-thio-β-D-galactofuranoside (4β): Compound **4β** was obtained from **6β** (0.50 g) according to the previous procedure as a colorless oil in 80% yield (0.56 g). – TLC (light petroleum/ethyl acetate, 9:1): R_f = 0.3. – $[\alpha]_D$ = –121.4 (c = 1.54, CH_2Cl_2). – ^{1}H NMR: δ = 3.65 (dd, $J_{6a,6b}$ = 10.0 Hz, $J_{5,6a}$ = 5.4 Hz, 1 H, H-6a), 3.71 (dd, $J_{5,6b}$ = 6.4 Hz, 1 H, H-6b), 3.82 (ddd, $J_{4,5}$ = 3.2 Hz, 1 H, H-5), 4.08 (dd, $J_{2,3}$ = 3.0 Hz, $J_{1,2}$ = 2.4 Hz, 1 H, H-2), 4.09 (dd, $J_{3,4}$ = 6.7 Hz, 1 H, H-3), 4.28–4.71 (m, 8 H, CH_2Ph), 4.36 (dd, 1 H, H-4), 5.61 (d, 1 H, H-1), 7.20–7.48 (m, 25 H, C_6H_5). – ^{13}C NMR: δ = 70.6 (C-6), 72.0, 72.1, 73.2, 73.4 (CH_2Ph), 76.1 (C-5), 80.5 (C-4), 82.7 (C-3), 88.6 (C-2), 89.9 (C-1), 127.0–131.2 (C_6H_5), 134.7, 137.3, 137.6, 138.2, 138.3 (C_{ipso}). – $C_{40}H_{40}O_5S$ (632.82): calcd. C 75.94, H 6.34; found C 75.69, H 6.51.

Ethyl 2,3,5,6-Tetra-*O*-benzyl-1-thio-β-D-galactofuranoside (8β): Compound **8β** was obtained from **7β** (0.45 g) according to the previous procedure as a colorless oil in 74% yield (0.48 g). – TLC (light petroleum/ethyl acetate, 9:1): R_f = 0.52. – $[\alpha]_D$ = –99.5 (c = 1.0, CH_2Cl_2). – ^{1}H NMR: δ = 1.27 (t, ^3J = 7.4 Hz, 3 H, CH_2CH_3), 2.58 (dq, ^2J = 13.0 Hz, 1 H, CH_2CH_3), 2.68 (dq, 1 H, CH_2CH_3), 3.66 (dd, $J_{6a,6b}$ = 9.9 Hz, $J_{5,6a}$ = 5.1 Hz, 1 H, H-6a), 3.72 (dd, $J_{5,6b}$ = 6.5 Hz, 1 H, H-6b), 3.81 (ddd, $J_{4,5}$ = 3.1 Hz, 1 H, H-5), 3.93 (br. t, J = 2.9 Hz, 1 H, H-2), 4.04 (dd, $J_{3,4}$ = 7.4 Hz, $J_{2,3}$ = 3.2 Hz, 1 H, H-3), 4.25 (dd, 1 H, H-4), 4.26–4.73 (m, 8 H, CH_2Ph), 5.40 (d, $J_{1,2}$ = 2.7 Hz, 1 H, H-1), 7.19–7.34 (m, 25 H, C_6H_5). – ^{13}C NMR: δ = 15.0 (CH_2CH_3), 25.2 (CH_2CH_3), 71.0 (C-6), 71.8, 72.1, 73.3, 73.4 (CH_2Ph), 76.1 (C-5), 80.2 (C-4), 82.9 (C-3), 87.0 (C-2), 88.9 (C-1), 127.5–128.4 (C_6H_5), 137.5, 137.7, 138.2, 138.3 (C_{ipso}). – $C_{36}H_{40}O_5S$ (584.78): C 73.97, H 6.86; found C 73.98, H 6.89.

Phenyl 2,3,5,6-Tetra-*O*-benzyl-1-thio-β-D-glucofuranoside (11β): Compound **11β** was obtained from **6** (0.50 g) according to the previous procedure as a colorless oil in 81% yield (0.56 g). – TLC (light petroleum/ethyl acetate, 9:1): R_f = 0.33. – $[\alpha]_D$ = –92.5 (c = 0.94, CH_2Cl_2). – ^{1}H NMR: δ = 3.71 (dd, $J_{6a,6b}$ = 10.7 Hz, $J_{5,6a}$ = 5.1 Hz, 1 H, H-6a), 3.89 (dd, $J_{5,6b}$ = 2.0 Hz, 1 H, H-6b), 4.12–4.14 (m, 2 H, H-2, H-3), 4.16 (ddd, $J_{4,5}$ = 9.2 Hz, 1 H, H-5), 4.34 (dd, $J_{3,4}$ = 3.8 Hz, 1 H, H-4), 4.42–4.77 (m, 8 H, CH_2Ph), 5.39 (d, $J_{1,2}$ = 1.9 Hz, 1 H, H-1), 7.19–7.45 (m, 25 H, C_6H_5). – ^{13}C NMR: δ = 70.6 (C-6), 71.8, 71.9, 72.4, 73.3 (CH_2Ph), 76.1 (C-5), 81.2 (C-3), 81.3 (C-4), 86.4 (C-2), 90.5 (C-1), 126.7–130.6 (C_6H_5), 135.8, 137.2, 137.6, 138.6, 138.8 (C_{ipso}). – $C_{40}H_{40}O_5S$ (632.82): calcd. C 75.94, H 6.34; found C 75.85, H 6.33.

Phenyl 2,3,5,6-Tetra-*O*-benzyl-1-thio-α-D-mannofuranoside (14α): Compound **14α** was obtained from **7** (0.50 g) according to the previous procedure as a colorless solid in 73% yield (0.51 g) which was recrystallized from light petroleum/diethyl ether. – TLC (light petroleum/ethyl acetate, 9:1): R_f = 0.33. – m.p. 84–86 °C. – $[\alpha]_D$ = +64.0 (c = 1.00, CH_2Cl_2). – ^{1}H NMR: δ = 3.64 (dd, $J_{6a,6b}$ = 10.7 Hz, $J_{5,6a}$ = 4.7 Hz, 1 H, H-6a), 3.86 (dd, $J_{5,6b}$ = 1.8 Hz, 1 H, H-6b), 3.97 (dd, $J_{1,2}$ = 7.2 Hz, $J_{2,3}$ = 4.1 Hz, 1 H, H-2), 4.05 (ddd, $J_{4,5}$ = 8.8 Hz, 1 H, H-5), 4.11 (dd, $J_{3,4}$ = 2.6 Hz, 1 H, H-4), 4.13 (dd, 1 H, H-3), 4.42–4.91 (m, 8 H, CH_2Ph), 5.49 (d, 1 H, H-1), 7.20–7.45 (m, 25 H, C_6H_5). – ^{13}C NMR: δ = 70.0 (C-6), 72.2, 73.1, 73.6, 73.9 (CH_2Ph), 75.9 (C-5), 77.5 (C-3), 78.7 (C-4), 84.1 (C-2), 88.5 (C-1), 127.5–132.3 (C_6H_5), 134.0, 137.6, 138.5, 138.6, 138.8 (C_{ipso}). – $C_{40}H_{40}O_5S$ (632.82): calcd. C 75.94, H 6.34; found C 75.91, H 6.31.

General Procedure for the Synthesis of 1,2-*cis*-Hexofuranosides: A solution of hexofuranosyl donor (0.10 g, 0.16 mmol) and glycosyl acceptor (0.13 mmol) in dichloromethane (1 mL) was stirred together with 4 Å molecular sieves (100 mg) at room temp. for 10 min. To the solution placed in the dark and cooled at 0 °C were successively added *N*-iodosuccinimide (0.036 g, 0.16 mmol) and tin(II) triflate (5.0 mg, 0.01 mmol). The reaction was monitored by TLC and quenched with triethylamine after total disappearance of the acceptor. The resulting solution was filtered over a bed of celite, concentrated and purified by flash-chromatography.

Methyl 2,3,5,6-Tetra-*O*-benzyl-D-glucofuranosyl-(1→6)-2,3,4-tri-*O*-acetyl-α-D-glucopyranoside (15a): The synthesis of **15a** was performed starting from **11β** and acceptor **A** (0.042 g) for 10 min. Chromatographic purification (light petroleum/ethyl acetate, 3:1) gave an anomeric mixture of the desired disaccharide (0.093 g, α/β = 5.7:1) in 84% yield. – TLC (light petroleum/ethyl acetate, 7:3): R_f = 0.23. – $C_{47}H_{54}O_{14}$ (842.94): calcd. C 66.97, H 6.46; found C 66.69, H 6.56.

2,3,5,6-Tetra-*O*-benzyl-D-glucofuranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (15b): The synthesis of **15b** was performed starting from **11β** and acceptor **B** (0.034 g) for 10 min and yielded 0.082 g (87%, α/β = 4.6:1) of the required disaccharide. The major anomer could be chromatographically isolated (light petroleum/ethyl acetate, 17:3) as a colorless oil. – **15bα**: TLC (light petroleum/ethyl acetate, 7:3): R_f = 0.56. – $[\alpha]_D$ = +14.5 (c = 0.88, CH_2Cl_2). – $C_{46}H_{54}O_{11}$ (782.93): calcd. C 70.57, H 6.95; found C 70.35, H 6.91.

Methyl 2,3,5,6-Tetra-*O*-benzyl-D-glucofuranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (15c): The synthesis of **15c** was performed starting from **11β** and acceptor **C** (0.061 g) for 7 min and yielded 0.088 g (68% α/β = 2.1:1) of the required disaccharide after chromatographic purification (light petroleum/ethyl acetate, 17:3). – TLC (light petroleum/ethyl acetate, 7:3): R_f = 0.55. – $C_{62}H_{66}O_{11}$ (987.21): calcd. C 75.43, H 6.74; found C 75.46, H 6.78.

Methyl 2,3,5,6-Tetra-*O*-benzyl-D-galactofuranosyl-(1→6)-2,3,4-tri-*O*-acetyl-α-D-glucopyranoside (16a): The synthesis of **16a** was performed starting from **4β** and acceptor **A** (0.048 g) for 10 min. Chromatographic purification gave an anomeric mixture of the desired disaccharide (0.090 g, 84%, α/β = 5.3:1). – TLC (light petroleum/ethyl acetate, 3:2): R_f = 0.53. – $C_{47}H_{54}O_{14}$ (842.94): calcd. C 66.97, H 6.46; found C 67.01, H 6.57.

2,3,5,6-Tetra-*O*-benzyl-D-galactofuranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (16b): The synthesis of **16b** was performed starting from **4β** and acceptor **B** (0.034 g) for 20 min. Purification gave an anomeric mixture of the desired disaccharide

(0.082 g, 81%, α/β = 3.3:1). – TLC (light petroleum/ethyl acetate, 7:3): R_f = 0.57. – $C_{46}H_{54}O_{11}$ (782.93): calcd. C 70.57, H 6.95; found C 70.19, H 7.08.

Methyl 2,3,5,6-Tetra-*O*-benzyl-D-galactofuranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (16c): The synthesis of **16c** was performed starting from **4β** and acceptor **C** (0.061 g) for 12 min and yielded 0.108 g (83%, α/β = 1.7:1) of the required disaccharide. The major anomer could be chromatographically isolated (light petroleum/ethyl acetate, 7:3) as a colorless oil.

16cα: TLC (light petroleum/ethyl acetate, 7:3): R_f = 0.65. – $[\alpha]_D$ = +51.0 (c = 0.87, CH_2Cl_2). – $C_{62}H_{66}O_{11}$ (987.21): calcd. C 75.43, H 6.74; found C 75.66, H 6.71.

16cβ: TLC (light petroleum/ethyl acetate, 7:3): R_f = 0.60. – $[\alpha]_D$ = +18.2 (c = 1.00, CH_2Cl_2). – $C_{62}H_{66}O_{11}$ (987.21): calcd. C 75.43, H 6.74; found C 75.56, H 6.79.

Methyl 2,3,5,6-Tetra-*O*-benzyl-D-mannofuranosyl-(1→6)-2,3,4-tri-*O*-acetyl-α-D-glucopyranoside (17a): The synthesis of **17a** was performed starting from **14α** and acceptor **A** (0.042 g) for 10 min. Chromatographic purification (light petroleum/ethyl acetate, 7:3) gave an anomeric mixture of the required disaccharide (0.099 g, 90%, α/β = 1:3.3) as a colorless oil. – TLC (light petroleum/ethyl acetate, 7:3): R_f = 0.28. – $C_{47}H_{54}O_{14}$ (842.94): calcd. C 66.97, H 6.46; found C 66.71, H 6.60.

2,3,5,6-Tetra-*O*-benzyl-D-mannofuranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (17b): The synthesis of **17b** was performed starting from **14α** and acceptor **B** (0.034 g) for 12 min and yielded 0.088 g (87%, α/β = 1:2.3) of the desired disaccharide. Chromatographic purification (light petroleum/ethyl acetate, 17:3) gave the major β-anomer as a colorless oil. – **17bα**: TLC (light petroleum/ethyl acetate, 7:3): R_f = 0.64. – **17bβ**: TLC (light petroleum/ethyl acetate, 7:3): R_f = 0.58. – $[\alpha]_D$ = –88 (c = 0.47, CH_2Cl_2). – $C_{46}H_{54}O_{11}$ (782.93): calcd. C 70.57, H 6.95; found C 70.32, H 6.95.

Methyl 2,3,5,6-Tetra-*O*-benzyl-D-mannofuranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (17c): The synthesis of **17c** was performed starting from **14α** and acceptor **C** (0.061 g) for 11 min and yielded 0.118 g (92%, α/β = 1:1.9) of the required disaccharide. The major β-mannofuranoside could be chromatographically isolated (light petroleum/ethyl acetate, 17:3) as a colorless oil. – **17cα**: TLC (light petroleum/ethyl acetate, 7:3): R_f = 0.61. – **17cβ**: TLC (light petroleum/ethyl acetate, 7:3): R_f = 0.58. – $C_{62}H_{66}O_{11}$, H_2O (1005.23): calcd. C 74.08, H 6.82; found C 74.48, H 6.76.

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[1] G. D. Sprott, *J. Bioenerg. Biomembr.* **1992**, *24*, 555–566.
[2] Y. Koga, M. Nishihara, H. Morii, M. Akagawa-Matsushita, *Microbiol. Rev.* **1993**, *57*, 164–182.
[3] M. Nagaoka, S. Hashimoto, H. Shibata, I. Kimura, K. Kimura, H. Sawada, T. Yokokura, *Carbohydr. Res.* **1996**, *281*, 285–291.
[4] R. M. de Lederkremer, W. Colli, *Glycobiology* **1995**, *5*, 547–552.
[5] S. Merello, M. T. Xavier, A. J. Parodi, *Molec. Biochem. Parasitol.* **1990**, *69*, 73–79.
[6] [6a] M. J. McConville, A. Bacic, *Molec. Biochem. Parasitol.* **1990**, *38*, 57–68. – [6b] M. J. McConville, S. W. Homans, J. E. Thomas-Oates, A. Dell, A. Bacic, *J. Biol. Chem.* **1990**, *265*, 7385–7394.
[7] [7a] P. A. J. Gorin, J. F. T. Spencer, *Can. J. Chem*. **1959**, *37*, 499–502. – [7b] W. A. Ayer, N. Kawahara, *Tetrahedron Lett.* **1995**, *36*, 7953–7956.
[8] R. E. Hueber, K. G. Castro, *Annu. Rev. Med.* **1995**, *46*, 47–55.
[9] P. J. Brennan, H. Nikaido, *Annu. Rev. Biochem.* **1995**, *64*, 29–63.
[10] M. V. de Arruda, W. Colli, B. Zingales, *Eur. J. Biochem.* **1989**, *182*, 413–421.
[11] P. E. Jansson, B. Lindberg, *Carbohydr. Res.* **1980**, *82*, 97–102.
[12] G. J. Gerwig, J. P. Kamerling, J. F. G. Vliegenthart, E. Morag-Morgenstern, R. Lamed, E. A. Bayer, *Eur. J. Biochem.* **1991**, *196*, 115–122.
[13] R. J. Thompson, R. H. Hamilton, C. F. Pootjes, *Antimicrob. Agents Chemother.* **1979**, *16*, 293–296.
[14] T. Moriguchi, T. Wada, M. Sekine, *J. Org. Chem.* **1996**, *61*, 9223–9228.
[15] J. W. Green, *Adv. Carbohydr. Chem.* **1966**, *21*, 95–142.
[16] [16a] C. Gallo-Rodriguez, O. Varela, R. M. de Lederkremer, *J. Org. Chem.* **1996**, *61*, 1886–1889. – [16b] C. Gallo-Rodriguez, O. Varela, R. M. de Lederkremer, *Carbohydr. Res.* **1998**, *305*, 163–170.
[17] A. K. Pathak, Y. A. El-Kattan, N. Bansal, J. A. Maddry, R. C. Reynolds, *Tetrahedron Lett.* **1998**, *39*, 1497–1500.
[18] [18a] N. K. Kochetkov, A. J. Khorlin, A. F. Bochkov, *Tetrahedron* **1967**, *23*, 693–707. – [18b] N. K. Kochetkov, S. A. Nepogod'ev, L. V. Backinowsky, *Tetrahedron* **1990**, *46*, 139–150.
[19] J. C. Jacquinet, P. Sinaÿ, *Carbohydr. Res.* **1974**, *34*, 343–349.
[20] M. El Arabi Aouad, A. El Meslouti, R. Uzan, D. Beaupère, *Tetrahedron Lett.* **1994**, *35*, 6279–6282.
[21] K. Bischofberger, S. J. Eitelman, A. Jordaan, *Carbohydr. Res.* **1979**, *74*, 145–156.
[22] C. M. Timmers, J. C. Verheijen, G. A. van der Marel, J. H. van Boom, *Synlett* **1997**, 851–853.
[23] B. D. Johnston, B. M. Pinto, *Carbohydr. Res.* **1998**, *305*, 289–292.
[24] P. J. Garegg, *Adv. Carbohydr. Chem. Biochem*. **1997**, *52*, 179–205.
[25] H. M. Zuurmond, P. A. M. van der Klein, G. H. Veeneman, J. H. van Boom, *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 437–441.
[26] K. Osumi, M. Enomoto, H. Sugimura, *Carbohydr. Lett.* **1996**, *2*, 35–38.
[27] A. K. Choudhury, N. Roy, *Synlett* **1997**, 105–106.
[28] P. Fügedi, A. Lipták, P. Nánási, *Carbohydr. Res.* **1982**, *107*, C5–C8.
[29] M. Gelin, V. Ferrières, D. Plusquellec, *Carbohydr. Lett.* **1997**, *2*, 381–388.
[30] A. K. Choudhury, N. Roy, *Carbohydr. Res.* **1998**, *308*, 207–211.
[31] A. Arasappan, B. Fraser-Reid, *Tetrahedron Lett.* **1995**, *36*, 7967–7970.
[32] [32a] R. Velty, T. Benvegnu, D. Plusquellec, *Synlett* **1996**, 817–819. – [32b] R. Velty, T. Benvegnu, M. Gelin, E. Privat, D. Plusquellec, *Carbohydr. Res.* **1997**, *299*, 7–14.
[33] J. C. McAuliffe, O. Hindsgaul, *J. Org. Chem.* **1997**, *62*, 1234–1239.
[34] Even if these compounds have the potential to form five-, six- or seven-membered cyclized products, it appears very surprising and disconcerting that all D-galactosyl precursors led to improbable L-altrosides.
[35] A. J. Kirby, *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer-Verlag, Berlin Heidelberg New-York, **1983**, p. 61–62.
[36] Z. Zhang, I. R. Ollmann, X. S. Ye, R. Wischat, T. Baasov, C. H. Wong, *J. Am. Chem. Soc*. **1999**, *121*, 735–753.
[37] [37a] V. Ferrières, J. N. Bertho, D. Plusquellec, *Tetrahedron Lett*. **1995**, *36*, 2749–2752. – [37b] J. N. Bertho, V. Ferrières, D. Plusquellec, *J. Chem. Soc., Chem. Commun.* **1995**, 1391–1393. – [37c] V. Ferrières, J. N. Bertho, D. Plusquellec, *Carbohydr. Res.* **1998**, *311*, 25–35.
[38] R. Ferrier, R. H. Furneaux, *Carbohydr. Res.* **1976**, *52*, 63–68.
[39] V. Ferrières, M. Gelin, R. Boulch, L. Toupet, D. Plusquellec, *Carbohydr. Res.* **1999**, *314*, 79–83.
[40] S. J. Angyal, *Carbohydr. Res.* **1979**, *77*, 37–50.
[41] See for example: S. Hanessian, Y. Guindon, *Carbohydr. Res.* **1980**, *86*, C3–C6.

[42] M. L. Wolfrom, Z. Yosizawa, B. O. Juliano, *J. Org. Chem.* **1954**, *24*, 1529–1530.
[43] R. J. Ferrier, S. R. Haines, *Carbohydr. Res.* **1984**, *127*, 157–161.
[44] G. J. Boons, *Tetrahedron* **1996**, *52*, 1095–1121.
[45] A. Marra, J. Esnault, A. Veyrières, P. Sinaÿ, *J. Am. Chem. Soc*. **1992**, *114*, 6354–6360.
[46] R. R. Schmidt in *Comprehensive Organic Synthesis*, Pergamon Press, **1991**, volume 6, p. 33–64.
[47] R. R. Schmidt, M. Reichrat, U. Moering, *Tetrahedron Lett.* **1980**, *21*, 3561–3564.

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