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In(III) triflate-mediated solvent-free synthesis and activation of thioglycosides by ball milling and structural analysis of long chain alkyl thioglycosides by TEM and quantum chemical methods

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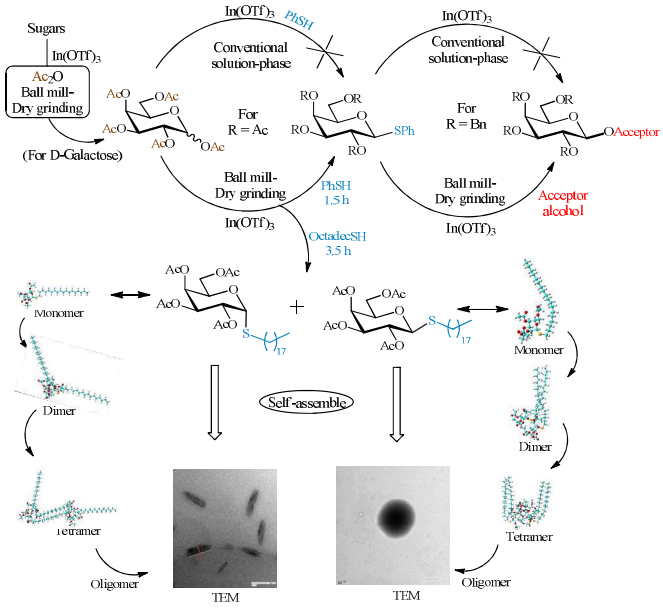
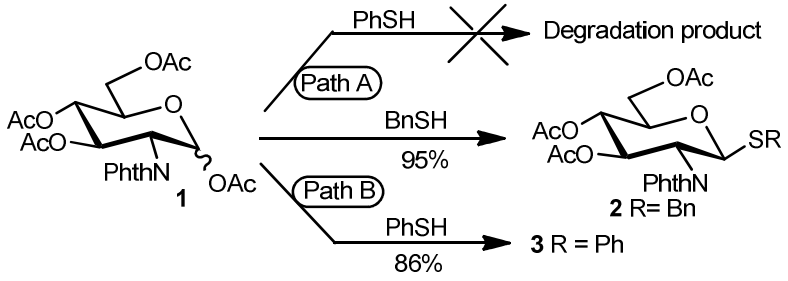


ABSTRACT: Conventional solution-phase synthesis of thioglycosides from glycosyl acetates and thiols in the presence of In(III) triflate as reported for benzyl thioglucoside failed when applied to the synthesis of phenolic and alkyl thioglycosides, But, it was achieved in high efficiency and diastereospecificity with ease by solvent-free grinding in a ball mill. The acetates in turn were also obtained by the homogenization of free sugars with stoichiometric amounts of acetic anhydride and catalytic $In(OTf)_3$ in the mill as neat products. Per-*O*-benzylated

thioglycosides on grinding with an acceptor sugar in the presence of $In(OTf)_3$ yield the corresponding *O*-glycosides efficiently. The latter in the case of a difficult secondary alcohol was nearly exclusive (>98%) in 1,2-*cis*-selectivity. In contrast, the conventional methods for this purpose require use of a co-reagent such as NIS along with the Lewis acid to help generate the electrophilic species that actually is responsible for the activation of the thioglycoside donor *in situ*. The distinctly different self-assembling features of the peracetylated octadecyl 1-thio-α- and β-D-galactopyranosides observed by TEM could be rationalized by molecular modelling.

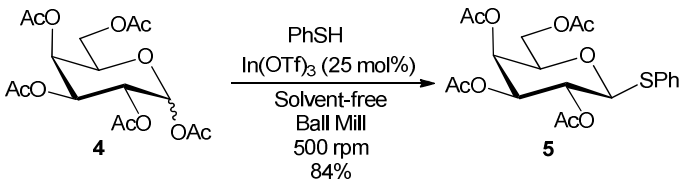
INTRODUCTION

The excellent potential that In(III) triflate holds for promoting various carbohydrate reactions became evident from the highly efficient acyl transfer reactions as well as the formation and hydrolysis of cyclic acetals of various carbohydrates reported some time ago.[1] A case of thioglycosylation reaction noted involved treatment of the glycosyl acetate **1** with benzyl mercaptan at 50 °C in dichloroethane to form the desired 1,2-*trans*-linked benzyl 1-thio-glycoside **2** in 2 h in virtually quantitative yield (Scheme 1, Path A). On the basis of the latter observation and from a need for synthesizing multi-gram quantities of the phenyl thio-β-D-galactoside derivative **5** in the context of an ongoing work, we recently tried to extend the above reaction to thiophenol as an acceptor for reaction with per-*O*-acetylated β-D-galactose **4** (For structures see Scheme 2 to follow later). It was disappointing to see that while at room



Scheme 1. Comparison of $In(OTf)_3$–mediated reaction of a glycosyl acetate with BnSH/PhSH under conventional and mechanochemical conditions.

temperature virtually no reaction took place, it was found to be accompanied by degradation products at 50 °C in dichloroethane as a result of which the yields were drastically affected unlike in the preparation of **2**. The latter reaction, when repeated using acetate **1** in place of **4** was also proved unsuccessful (Scheme 1, Path A). This led us to think of the reaction in solid state instead. Our own observations in this regard as well as those in the literature showed that the chemical reactivity and selectivity exhibited by many solid state reactions are often better than their corresponding solution-phase counterpart.[2] As an alternative therefore, the reaction was held under solvent-free conditions mechanochemically using a planetary ball mill (Scheme 2) and the results were indeed very interesting. Under the optimized conditions the acetate **4**



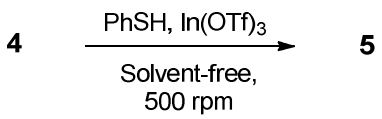
Scheme 2. $In(OTf)_3$–Mediated mechanochemical activation of galactosyl acetate for thioglycosylation.

reacted with thiophenol effectively, giving the desired phenyl thioglycoside **5** in 84% yield in 90 min. The details on the optimization of the reaction conditions as well as a comparison of the current method with that of a set of important conventional thioglycosylation methods are as under.

RESULTS AND DISCUSSION

Homogenization of galactosyl acetate **4** with mercaptophenol in the presence of $In(OTf)_3$ (25 mol%) for 1.5 h in the ball mill resulted in the complete disappearance of **4** from the reaction mixture as ascertained by TLC (EtOAc-Hexanes, 1:1, entry 1, Table 1). A new compound with R_f value marginally higher than that of the acetate **4**, and unlike **4** detectable under the UV detection lamp, had been formed instead. The solids were therefore subjected to an aqueous workup and the crude product so obtained was purified on a short column of silica (eluent, EtOAc-Hexanes, 2:8). Spectroscopic analysis showed the crystalline product obtained to be the desired phenyl thiogalactoside **5**.[3,4] The requirement of $In(OTf)_3$ was subsequently optimized by experiments as tabulated in Table 1. It was found that performing the reaction using 25 mol% of

Table 1. Optimization of reaction conditions for the $In(OTf)_3$-mediated solvent-free mechanochemical thiogalactosylation.[a]



Entry No	$In(OTf)_3$ (mol equiv)	Time (h)	Yield of **5**	Remarks
1	0.25	1.5	84	Complete consumption of **4**; only the β-glycoside (**5**) was formed
2	0.25	2.5	78	Some α-glycoside was also formed along with **5** but separated efficiently on silica gel chromatographically
3	0.15	2.0	45	50% of **4** had been consumed; only the β-glycoside (**5**) was formed
4	0.15	10.0	65	70% of **4** had been consumed; only the β-glycoside (**5**) was formed
5	0.10	10.0	--	Only 20% of **4** had been consumed (TLC); attempt to isolate **5** was not made
6	0.05	10.0	--	No reaction was observed

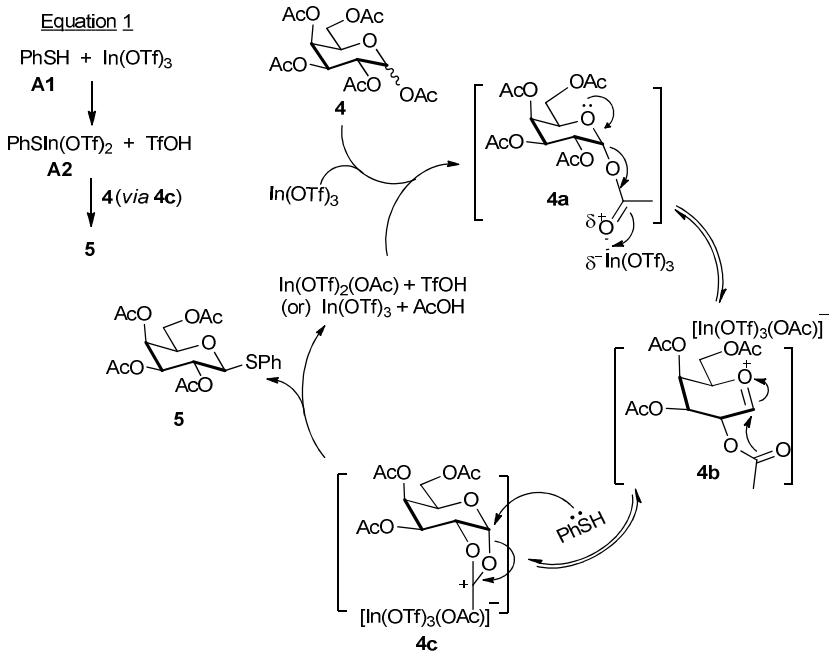
a 1 mmol (390.5 mg) of **4** was ground in an SS bowl containing SS balls along with thiophenol (3 mmol) and $In(OTf)_3$.[3,4]

the metal triflate was sufficient for satisfactory results. At lower levels of the metal triflate and at shorter reaction times, it was found that the 1,2-*trans*-linked thioglycoside was the only product formed. Longer periods of grinding beyond the completion of reaction led essentially to the anomerization product (1,2-*cis*-linked glycoside corresponding to **5**).

In accordance with a general Lewis acid-catalyzed reaction, $In(OTf)_3$ can be considered to activate the glycosyl acetate **4** as shown in Scheme 3. Coordination of the metal center in the catalyst with the carbonyl oxygen of the anomeric acetyl group can render the acyl group departure possible, with the assistance of the lone pair of electrons on ring oxygen (O-5) as

represented in the structure **4a**. This must lead to the successive formation of ion pairs **4b** and **4c**. Nucleophilic attack of the thiol can then result in the formation of the desired thioglycoside **5** stereospecifically. The formation of the thioglycoside (**5**) must also lead to the release of the metal salt suggesting that, in principle, the reaction must be catalytic in In(III) although in practice it was observed (see above) that 0.25 mol equiv of the salt was needed for the reaction to proceed in a reasonably short period of grinding.

Alternatively, the thiol activation by the metal triflate as represented in equation 1 (Scheme 3) if considered shall also culminate in the satisfactory formation of **5** upon reaction of the metallated thiol derivative **A2**, formed as an activated intermediate, on the cyclic oxocarbonium ion **4c** described earlier. However, circumstantial evidence suggests that the former mechanism is operative. It was observed that on terminating the reaction upon complete consumption of the glycosyl acetate leaves the thioglycoside formed stereospecifically. But on continued grinding for long periods beyond the completion of the reaction, acid-catalyzed anomerization product could also be obtained.

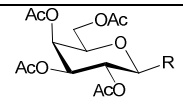
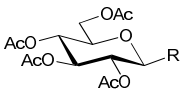
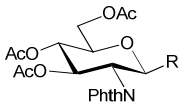
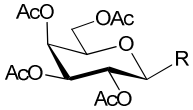


Scheme 3. Indium triflate-assisted thioglycosylation of galactose pentaacetate **4**.

A comparison of the current method for the preparation of 1,2-*trans*-linked 1-thioglycosides with the classical method that makes use of the more reactive glycosyl β-acetate

preferably has been presented in Table 2 below. Thus, while the $BF_3{\cdot}Et_2O$-promoted thioglycoside preparation reported by Ferrier and Furneaux, which is still used quite extensively, typically takes nearly 1.5 to 2 days for completion of the reaction (entries 1, 3 and 4, Table 2), the current method allows it in 1.5 h with better efficiency (entry 9, Table 2; see also later). The current method is also more effective than the well-accepted modified method later introduced by Pozsgay and Jennings (entries 2 and 5, Table 2). Again, while the current procedure is solvent-free, the iodine-promoted reactions (entries 6 – 8, Table 2), though are faster, of wide acceptance and of equal efficiency (product yield) as the current method, require use of the poisonous solvent, MeCN to be best successful. Clearly, the method reported herein is thus superior in many respects.

Table 2. A comparison of the reported thioglycosylation methods with the current method.

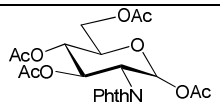
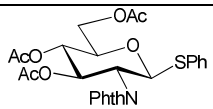
Entry	Transformation	Method					Lit ref[a]
		Thiol reagent	Promoter (mol%)	Solvent	Time (h)	Yield (%)	
							
1	R = OAc → R = SPh	PhSH	$BF_3{\cdot}Et_2O$ (300)	$CHCl_3$	43	69	5(a)
2	R = OAc → R = SMe	TMS-SMe	$BF_3{\cdot}Et_2O$ (60)	CH_2Cl_2	5	84	5(b)
							
3	R = OAc → R = SEt	EtSH	$BF_3{\cdot}Et_2O$ (22)	$CHCl_3$	35	83	5(a)
4	R = OAc → R = SBn	BnSH	$BF_3{\cdot}Et_2O$ (20)	$CHCl_3$	46	70	5(a)
							
5	R = OAc → R = SMe	TMS-SMe	TMSOTf (60)	CH_2Cl_2	48	93	5(b)
							

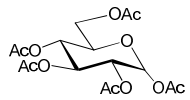
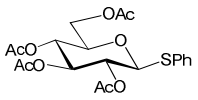
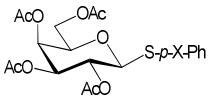
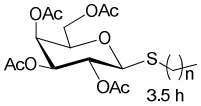
6	R = OAc → R = SPh	TMS-SPh	I_2 (120)	MeCN	2 min	80	5(c)
7	R = OAc → R = SEt	TMS-SEt	I_2 (120)	MeCN	2 min	85	5(c)
8	R = OAc → R = SEt	EtSH	I_2 (120)	MeCN	5 min	80	5(c)
9	R = OAc → R = SPh	PhSH	$In(OTf)_3$ (25)	None	1.5	86	-

a A 3-50% (w/v, based on the sugar substrate) solution in the desired solvent is employed for the reaction

Under the conditions optimized for **4** when the glucosamine derivative **1** was allowed to react with thiophenol the reaction took place effectively and the corresponding β-thioglycoside **3**[6] was obtained in 86% yield as colorless solid by crystallization (entry 1, Table 3; Scheme 1, Path B). Extending the reaction to α-D-glucose pentaacetate (**6**) also gave the desired 1,2-*trans*-linked thioglycoside **7** in good yield (entry 2, Table 3).[3,7] *p*-Nitrothiophenol (phenyl ring bearing an electron withdrawing substituent) and *p*-thiocresol (phenyl ring bearing an electron donating substituent) were also evaluated as acceptors for the thioglycosylation reaction. The desired respective thioglycosides **8**[3] and **9**[3] were also obtained stereospecifically in excellent yields on 60-90 min of grinding (entries 3-4, Table 3). The solution-phase method employing the relatively more toxic MoO_2Cl_2 is not only comparatively more sluggish but also requires the more reactive glycosyl β-acetate for the above reactions.[10b] In the context of another ongoing work in our laboratory, we needed 1-thio-β-D-galactopyranosides having long chain alkyl residues on the sulfur. Therefore the preparation of the desired galactosides **10**[8] and **11**[9] was also attempted under the above optimized reaction condition to successful completion (entries 5-6, Table 3).

Table 3. Indium triflate-mediated mechanochemical thioglycosylation of glycosyl acetates.[a]

Entry	Substrate	Product	Time (h)	Yield (%)
1	 **1**	 **3**	1.5	86

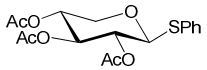
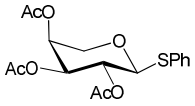
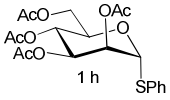
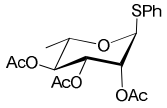
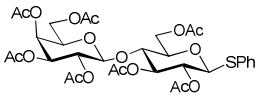
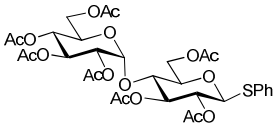
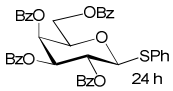
2	 **6**	 7	1.5	79
3	**3**	 **8** X = NO_2	1.5	90
4		**9** X = Me	1.0	84
5	Compound **3**		3.5	70-80[b]
6			3.5	
		10 n = 17		
		11 n = 13		

a A mixture of the per-*O*-acetylated monosaccharides (1 mmol), thiophenol (2.2 mmol) and $In(OTf)_3$ (0.25 mmol) was ground in an SS bowl containing SS balls using a planetary ball mill; b 7–8% of the α-anomer corresponding to **10**/**11** were also isolated.

As the preparation of the per-*O*-acetylated monosaccharides can also be carried out in quantitative yields in the presence of indium triflate,[1] the acetylation step was also carried out in the ball mill. Thus, anhydrous D-galactose (**12**) was mixed in an SS bowl with acetic anhydride in the ball mill for about half an hour in the presence of $In(OTf)_3$ (2-5 mg/g sugar, that is, ≤0.16 mol%) and the clear acetylation product was subjected to an alkaline aqueous workup. The solids obtained were dried and after putting back into the milling bowl were ground with thiophenol and the catalyst as described above (entry 1a, Table 4). The product was then obtained in a yield of 78% after a quick column chromatographic purification.[3,4,10] The reaction was then repeated on a preparative scale with 5 g of the hexose (**12**) as the starting material and the glycoside **4** was obtained in 85% yield as crystals on crystallization of the crude product obtained after the aqueous workup (entry 1b, Table 4). It has been consistently observed that solvent-free reactions in the ball mill work with higher efficiency when conducted on multi-gram quantities as better/more effective mixing can be achieved in such cases.[3] With this successful reaction, the method was extended to a range of other sugars (pentoses, entries 2-3, Table 4; hexoses, entries 4-5, Table 4; deoxyhexose, entry 6, Table 4; and disaccharides, entries 7-8, Table 4) to evaluate

the general applicability of the reaction. It was found that the respective phenylthioglycosides were obtained efficiently in all the cases (Table 4). As must be expected,

Table 4. Indium triflate-mediated mechanochemical thioglycosylation of sugars[a]

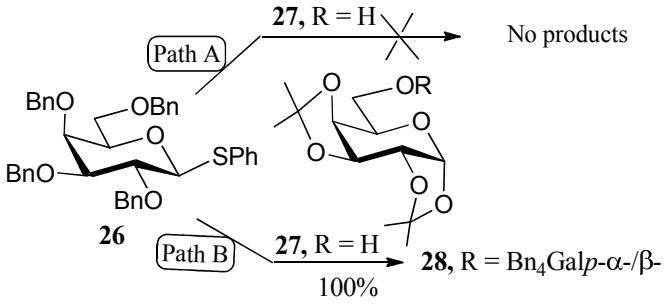
Entry	Substrate	Product (Lit reference)	Yield (%)
1a	D-Galactose (**12**) on 1 g scale	**5**	78
1b	D-Galactose (**12**) on 5 g scale	**5**	85
2	D-Xylose (**13**)	 **14**	74
3	L-Arabinose (**15**)	 **16**	68
4	D-Glucose (**17**)	**7**	77
5	D-Mannose (**18**)	 **19**	88
6	L-Rhamnose (**20**)	 **21**	74
7	D-Lactose (**22**)	 **23**	64
8	D-Maltose (**24**)	 **25**	65
9[b]	D-Galactose (**12**)	 **4B**	67

a A mixture of the monosaccharides/disaccharides (1 mmol), Ac_2O (1.1 mol equiv per OH group) and $In(OTf)_3$ (2-5 mg/g sugar) was ground in an SS bowl containing SS balls using a planetary ball mill for 30 min and the product after aqueous workup was directly subjected to the thioglycosylation as in Table 3; [b] The sugar was subjected to per-*O*-benzoylation by treatment with Bz_2O (instead of Ac_2O) before subjecting to thioglycosylation as in other cases.

the per-*O*-benzoylated D-galactose (structure not shown), prepared from D-galactose (**12**) by dry-grinding with benzoic anhydride in the presence of $In(OTf)_3$, also underwent facile solvent-free

thioglycosylation upon grinding with thiophenol in the presence of the metal triflate to afford the respective thioglycoside **4B** in good yield (entry 9, Table 4).

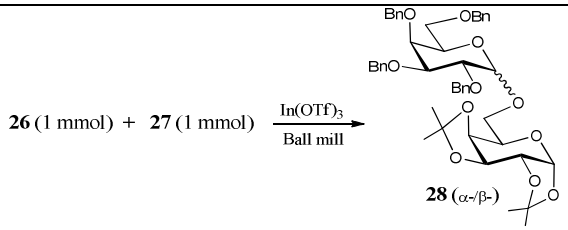
Based on the above results and the proven catalytic efficiency (as a Lewis acid) of $In(OTf)_3$, including its ability to cause anomerization of thioglycosides as has been observed above, the *O*-glycosylation using an "armed" thioglycoside (**26**) was performed in the absence of a co-promoter such as NIS which was proven impossible by the conventional procedure (Path A, Scheme 4). Thus, when the benzylated thiogalactoside **26** and the acetonide **27** were ground at 500 rpm in the presence of $In(OTf)_3$, complete consumption of the acceptor **27** occurred in a relatively short period of 1.5 h (Scheme 4, Path B) and the desired disaccharide product **27** was formed in excellent yield. As could be expected from the non-participatory group located on O-2 of the donor substrate, the product was a mixture of 1,2-*cis*-/*trans*-linked glycosides (**28 α/β**, as typical of these reactions)[17,18] obtained in a ratio of 1:9. During the process of monitoring the progress of the above reactions in the ball mill, it was noted that the initial chromatograms (TLC) showed the near-exclusive presence of the β-glycoside (**28β**) in the reaction mixture, although at the end of the 1.5 h reaction the ratio of **28α**: **28β** was 1:9. Most interestingly the α/β ratio for **28** could be altered effectively by controlling the conditions of grinding (for details see Table 5).



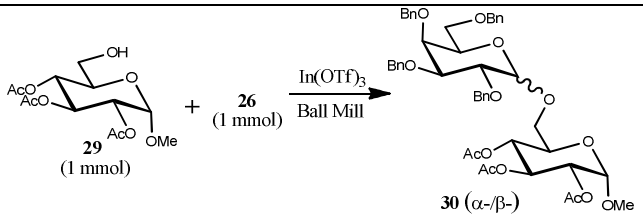
Path A: Conventional - $In(OTf)_3$ (up to 100 mol%), Et_2O, 25 °C, up to 48 h
Path B: Mechanochemical - $In(OTf)_3$ (25 mol%), Ball mill, 500 rpm, 1.5 h

Scheme 4. In(III) triflate-mediated disaccharide synthesis.

Table 5. In(III) triflate-promoted solvent-free *armed* thioglycoside-activation.



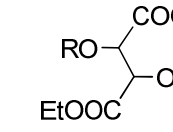
Entry	$In(OTf)_3$ (mmol)	Grinding speed (rpm)	Time (h)	Consumption of **26** (%)	Combined yield (%)	α:β
1	0.25	450	1	60	51	neat β-
2	0.25	450	1.5	65	55	β-, ≥95
3	0.25	500	1.5	100	61	1 : 9
4	0.25	550	0.75	100	66	1 : 9
5	0.25	550	1.0	100	40-45	2 : 3
6	0.25	550	1.25	100	40-45	5 : 3
7	0.25	500	1	50	40	1 : 4
8	0.25	500	2	100	64	1 : 1.2



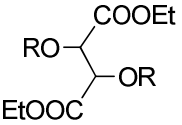
The $In(OTf)_3$-mediated glycosylation therefore was also tried at lower speeds of mixing in the ball mill. Thus, at 450 rpm at the end of a 1 h mixing period in the planetary ball mill the only glycoside product detected by TLC was **28β**, though 40% of the starting materials were still left (entry 1, Table 5). Continuing grinding for another 30 min could bring only marginal improvement in the consumption of the donor (entry 2, Table 5). However, by then the formation of **28α** had been started. In another experiment when mixing was allowed for 30 min at 500 rpm, following an initial 1.5 h at 450 rpm, complete consumption of the thioglycoside occurred (entry

not shown in the Table). Therefore another reaction at 500 rpm was carried out with 1.5 h as the mixing period. Again, the reaction was found to be complete but 10% of **28α** was also obtained along with the major β-product (**28β**, entry 3, Table 5) which at 550 rpm (entry 4, Table 5) was found obtainable in a shorter time of 0.75 h of grinding. Under the latter conditions while with a grinding time of 1 h the ratio of **28α**:**28β** isolated was found to be 2:3 (entry 5, Table 5), it was found to be 5:3 (entry 6, Table 5) for a grinding period of 1.25 h. Thus, a clear qualitative difference in the onset as well as rate of anomerization was visible as a function of grinding speed. Considering the significance of this observation, a detailed investigation on these factors is currently being pursued in our laboratory.

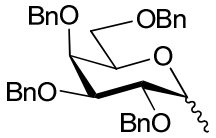
The partially acetylated glucose derivative **29**,[19] in which a possibility for acyl migration existed, was also examined as a typical acceptor for the above glycosylation. At 500 rpm when the glycosylation was allowed to take place in the ball mill for 1 h, at which time approximately 50% of the starting materials had been consumed, the disaccharide **30** was obtained in 40% yield with α:β = 1:4. No acetyl migration was observed. And at the end of a 2 h reaction, during which the complete consumption of the starting materials had taken place, the disaccharides **30α** and **30β** were obtained in a ratio of 1:1.2. The combined yield of the disaccharide was 64%. A small amount of 2,3,4,6-tetra-*O*-benzyl galactopyranose was also obtained as a by-product. The reaction was subsequently extended to a difficult secondary alcohol case, the diol substrate **31** to obtain the mono- and di-*O*-glycosylated products **32** and **33** in excellent yields (80-83%) in which the α-linked disaccharide was present in excess of 98%. On purification, **32α** and **33α** (required in connection with our work on synthetic polyvalent protein inhibitors) were obtained pure.



31 R = H
32 R = Bn_4Gal*p*-α-/β-



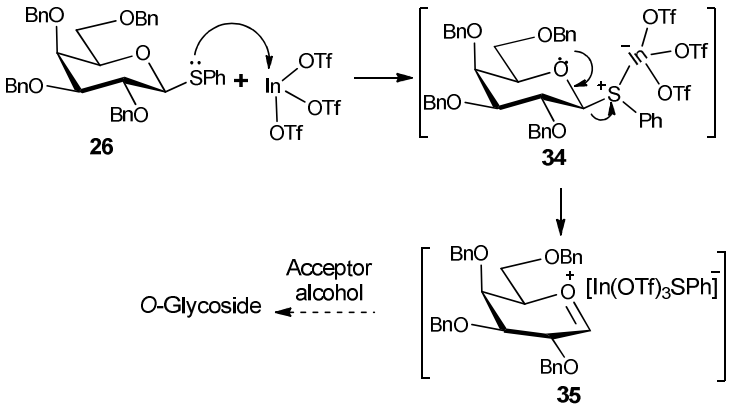
33 R = Bn_4Gal*p*-α-/β-



Bn_4Gal*p*-α-/β-
α-, >98%

In the case of *armed* thioglycosides, for example **26**, it would seem possible that the nucleophilicity of sulfur is sufficient enough to allow the lone pair of electrons on the atom to complex with the metal center in In(III) triflate to give rise to an activated intermediate **34** which

after the departure of the modified aglycone moiety, a process that can be reasoned possible by the assistance of the O-5-lone pair of electrons, forms the oxocarbenium ion intermediate **35** that upon further reaction with an acceptor alcohol yields the desired glycosides in the conventional manner (Scheme 5). The fact that *disarmed* thioglycosides, example **4**, does not smoothly react in the same manner lends support to this hypothesis as does the lower reactivity of the *p*-nitrophenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-galactcoside towards the same reaction. A clear



Scheme 5. Possible mechanism of activation of an *armed* thioglycoside by In(III) triflate.

advantage of the indium triflate-promoted solvent-free method of thioglycosylation was thus evident from a comparison of the observations noted in Schemes 1 & 4 and Table 1 (Entry 1).

However, as a comparison of the current method with the conventional solution-phase protocol must also be worthwhile and in context, the preparation of the disaccharide **28** from compounds **26** and **27** described above (see Scheme 4) was also performed in the conventional manner in solution-phase (Table 6). In the absence of a co-promoter (NIS) in anhydrous ether no disaccharide formation was observed even on continuing the reaction up to 2 days at room temperature (entries 1-3, Table 6) and in spite of using the metal triflate up to a level of 1 mol equiv. However, when the same reaction was carried out in the presence of added NIS it proceeded almost instantly giving rise to the expected disaccharide **28** in less than 2 min at rt. Although the reaction was neat, chromatographic isolation led to pure **28** in a yield of 68% (probably losing some product on the surface of silica) with the anomeric ratio of α:β = 3:2 (Entry 4, Table 6). Under the same conditions, the reaction carried out in acetonitrile or

dichloromethane led to poorer yields of the product (Entries 5 and 6, Table 6). In ether, the glycosylation was effective with the use of the metal triflate catalyst up to a level of 5 mol% (Entries 7-10, Table 6). The results thus, amply demonstrate that In(III) triflate can indeed serve

Table 6. Conventional In(III) triflate-promoted solution-phase synthesis of disaccharide **28**.[a]

Entry	$In(OTf)_3$ (mol equiv)	NIS (mol equiv)	Solvent	Time (min)	Yield, (%)	α : β
1	0.25	--	Et_2O	2 d	Nil	--
2	0.5	--	Et_2O	2 d	Nil	--
3	1.0	--	Et_2O	2 d	Nil	--
4	0.25	1	Et_2O	2	68	3 : 2
5	0.25	1	CH_3CN	5-10	48	1 : 1
6	0.25	1	CH_2Cl_2	30	33	3 : 2
7	0.20	1	Et_2O	2-5	65-75	7 : 3
8	0.15	1	Et_2O	2-5	65-75	7 : 3
9	0.10	1	Et_2O	10-15	65-75	7 : 3
10	0.05	1	Et_2O	20-25	65-75	7 : 3

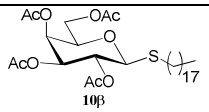
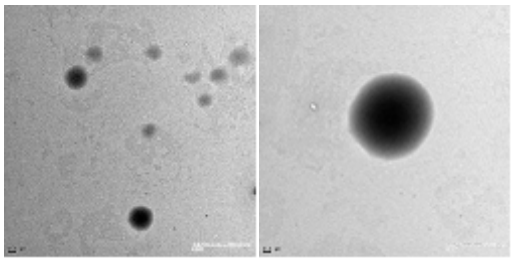
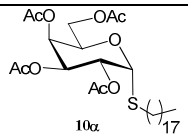
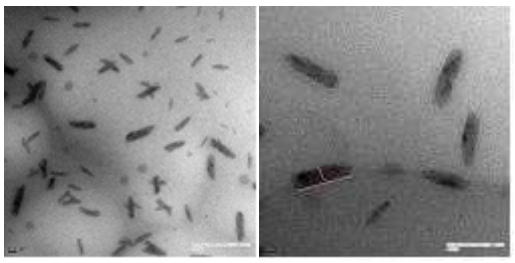
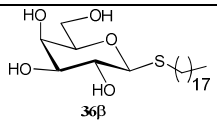
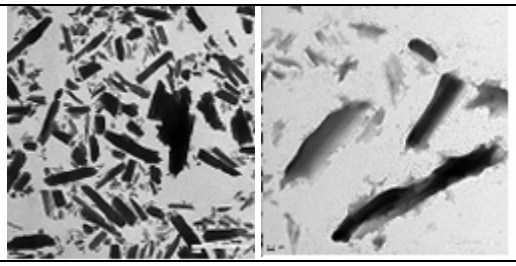
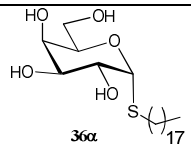
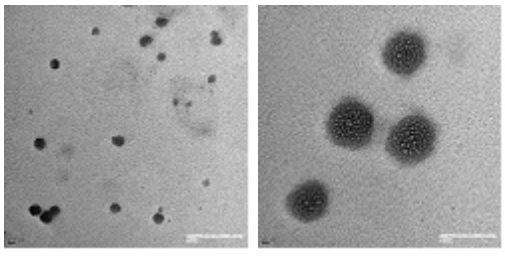
a The reaction was carried out by treating compounds **26** (1 mmol) and **27** (1 mmol) in the solvent (1 ml/100 mg sugar derivative) specified in the Table 5.

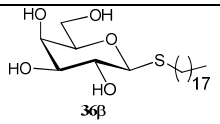
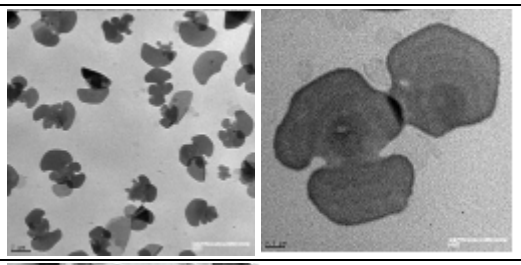
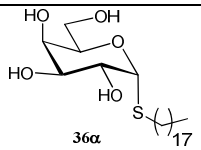
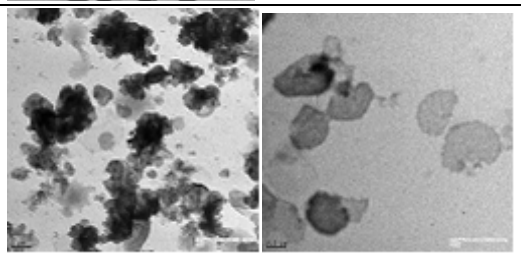
as an efficient Lewis acid catalyst in generating the activating species[20] (the iodonium species) when used with NIS in order to activate thioglycosides for *O*-glycosylation reactions. Compared to many of the other catalysts of this class such as AgOTf,[21] TfOH/TMSOTf,[22] etc., $In(OTf)_3$ holds distinct practical advantages in terms of its sensitivity to light, air, moisture, etc. and/or greenness and therefore, must find wide acceptance in future.

Further, in the course of the preparation of the alkyl thioglycosides **10** and **11**, we noticed that considerable degree of foaming occurred during the aqueous workup particularly when the organic solvent for extraction was shaken vigorously, as a consequence of which back extraction proved essential for securing complete recovery of the product present. Also, the foaming was considerably more prominent when dichloromethane was used in place of EtOAc for extraction. While the above observations were not surprising given the known surfactant-like properties of long chain alkyl glycosides as well as the poorer solubility of methylene chloride (compared to that of EtOAc) in water, it was certainly surprising that a qualitative difference in the foaming

characteristic was observed during the processing of the α- and β-thioglycosides. Intrigued by this, the above glycosides were subjected to analysis by TEM as well as quantum chemical studies and the results are summarized below.

Table 7. Transmission electron microscopic analysis of octadecyl 1-thiogalactopyranosides **10** (α & β) and **36** (α & β).

Entry	Compound structure	TEM images
1	 **10β** A solution of **10β** in hexane containing traces of CH_2Cl_2 was used for TEM. Magnification: X1700. Particle diameter: 325 nm to 650 nm.	
2	 **10α** A solution of **10α** in hexane containing traces of CH_2Cl_2 was used for TEM. Magnification: X7800 (Left), X19000 (Right). Particle length: 500 nm to 1500 nm.	
3	 **36β** A solution of **36β** in hexane containing traces of H_2O was used for TEM. Magnification: X330 (Left), X1700 (Right). Particle length: 335 nm to 1 μ	
4	 **36α** A solution of **36α** in hexane containing traces of H_2O was used for TEM. Magnification: X9600 (Left), X29000 (Right). Particle diameter: 96 nm to 258 nm	

5	 **36β** A solution of **36β** in MeOH containing traces of H_2O was used for TEM. Magnification: X420 (Left), X1700 (Right).	
6	 **36α** A solution of **36α** in MeOH containing traces of H_2O was used for TEM. Magnification: X420 (Left), X1700 (Right).	

Study of the literature shows that carbohydrate-based surfactants have been studied widely with respect to their surface active properties and liquid crystalline behavior.[23] In the former, the glycosides used for the studies have been otherwise unprotected. Also, till now the aggregation behaviour of these surfactants has been investigated as a function of the alkyl chain length, nature of the head group and its geometry.[24] Observations we made during the preparation of the α- and β- anomers of **10** and **11** seemed to suggest that it could also be dependent upon the stereochemistry at the anomeric center. TEM imaging showed that the self-assembly of octadecyl 2,3,4,6-tetraacetyl-α- and β-thiogalactosides (**10α** and **10β**) possessed distinct organizational patterns. Not unexpectedly though, it was also dependent upon the nature of the solvent used for the study (Table 7). Thus when a solution of the anomers **10α** and **10β** in hexane containing traces of methylene chloride was used for loading the sample onto the copper grid for TEM, while the β-anomer assembled into spherical particles the α-anomer organized to give ellipsoid particles (entries 1 and 2, Table 7). Most interestingly, upon deprotection of the acetyl groups on **10 α/β** (to give **36α/β**) a reversal of the organizational patterns obtained was observed (entries 3 and 4, Table 7). Thus, while **36β** gave rise to longitudinal pattern, spherical particles were produced in the case of the corresponding α-anomer. Further, upon changing the solvent system for the sample preparation from hexane to MeOH, the former organized into particles possessing morphological features akin to polygons whereas the α-anomer seemed to retain the spherical pattern, though it was rather irregular in nature. Therefore, in an attempt to

rationalize these behavioral differences obtained above, semi-empirical calculations on these molecules were carried out.

Electronic structure, interaction analysis and rationalization of the TEM morphological features.[25]

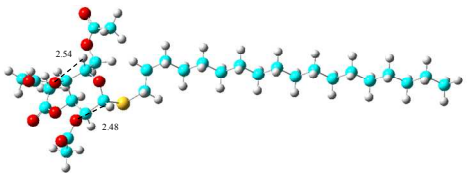
In order to understand the structural details of the protected α- and β-thiogalactosides (**10α** and **10β**) and to determine the distinct intermolecular and intramolecular interactions present in them, their structures were optimized employing the dispersion-corrected semi-empirical quantum chemical method, PM3-D using Gaussian09 package. The optimized 3D structures of the monomers of these thioglycosides obtained are shown in Fig. 1 (for the details of the methodology, see supporting information, S1). Two predominant intramolecular hydrogen bonding interactions (Fig. 1) were observed in **10α** as compared to one (only) intramolecular hydrogen bonding interaction observed in the β-anomer (**10β**). Several intramolecular van der Waals contacts are noticeable in the β-anomer (**10β**) giving rise to the 'δ-shaped' geometry, which are absent in the **α**-anomer. The monomeric structure **10β** was observed to be comparatively more stable than **10α** by 2.42 kcal/mol (Table 8). To confirm this fact, B3LYP/3-21G single point energy calculations were carried out, which showed that **10β** is more stable than **10α** by ~7 kcal/mol. To examine the self-assembling character of these molecules, dimeric structures were constructed from the optimized geometries of the monomers and were optimized using the PM3-D method. The optimized 3D geometries of the dimers are also shown in Fig. 1. It is clear from Fig. 1 that **10α** and **10β** exhibit distinct intermolecular interactions; **10α** is driven by the hydrogen bonding forces arising from the galactose moiety, while **10β** is driven by the hydrophobic interactions.

Table 8. The relative and stabilization energies of thiogalactosides, **10α** and **10β** and their dimers and tetramers, calculated using PM3-D method.

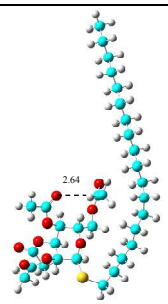
Thioglycoside	Relative Energy (kcal/mol)	Formulae	Dimerization Energy[a] (kcal/mol)
10α	2.42	-	-
10β	0.00	-	-
D-10α	45.82	$E_{D\text{-}10\alpha}$-2$E_{10\alpha}$	-28.75

D-10β	0.00	$E_{D\text{-}10\beta} - 2E_{10\beta}$	-69.73
T-10α	81.02	$E_{T\text{-}10\alpha} - 2E_{D\text{-}10\alpha}$	-81.18
T-10β	0.00	$E_{T\text{-}10\beta} - 2E_{D\text{-}10\beta}$	-70.55

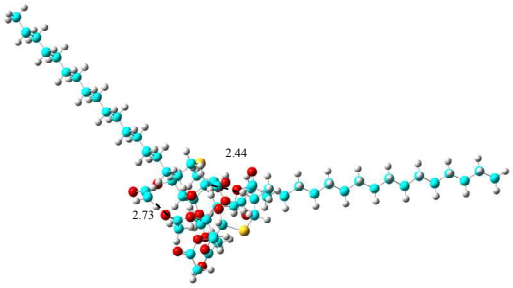
[a] Dimerization energies were calculated by subtracting the summation of energies of monomers and dimers from the energies of the dimers and tetramers respectively, as given in the formulae.



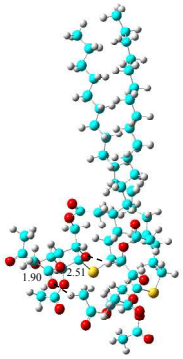
10α



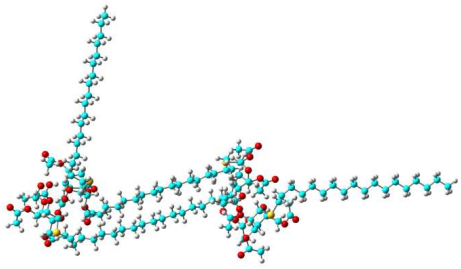
10β



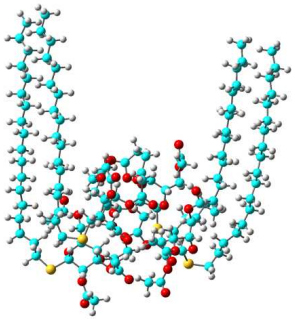
D-10α



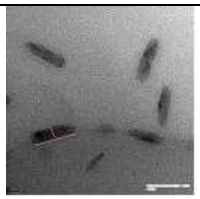
D-10β



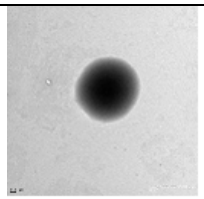
T-10α



T-10β



TEM-**10α**



TEM-**10β**

Figure 1. Optimized geometries of **10α** and **10β** in their monomeric, dimeric and tetrameric arrangements by PM3-D method. The self-assembly of the thioglycosides are shown in the form of dimer and tetramer structures showing distinct interactions and arrangement. The corresponding TEM images of the respective thioglycosides are also shown. All the distances indicating intermolecular and intramolecular interactions are given in Å. Colour code: carbon, sky blue; oxygen, red; hydrogen, grey; sulfur, yellow.

There are two different intermolecular interactions in the structure **D-10α**, namely H-bond interaction between the anomeric hydrogen of one monomer and the ester oxygen atom of the other [(C1)H---O(CO)-C6] and the acetyl (methyl) hydrogen atom of one monomer and the carbonyl oxygen atom of the other [C6-O-C(O)-CH---O=C-O-C4]. The H-bond distances were observed to be 2.44 Å and 2.73 Å respectively for these interactions. These intermolecular interactions provide a twisted L-shaped geometry to **D-10α**. On the other hand, the dimeric structure of **10β**, represented as **D-10β** ('δ-shaped') in Fig. 1, is observed to possess a head group containing the sugar portions and the tail containing side chains. This orientation of **D-10β** is due to two important intermolecular H-bonding interactions and hydrophobic interactions. The H-bonding interactions are (i) [C4-O-C=O---H-CH_2-C(O)-O-C3, 1.90 Å], and (ii) [C6-O-C(O)-CH---O (sugar ring), 2.51 Å], as shown in Fig. 1. The strong hydrophobic interactions observed due to dispersion effects result in the spiral-shaped orientation of the side chains in **D-10β**. These interactions stabilize the dimeric structure **D-10α** and **D-10β** in which **D-10β** was observed to be more stable (by ~46 kcal/mol) than **D-10α**. The higher stability of **D-10β** can be inferred owing to the presence of many intramolecular and intermolecular hydrophobic interactions. However, the hydrophobic interactions are less pronounced in **D-10α**. Also, the energy gain due to the dimer formation in **D-10α** and **D-10β** respectively is 28.75 kcal/mol and 69.73 kcal/mol respectively (Table 8). This indicates a higher stability of dimer **D-10β** as compared to **D-10α**. The stabilization energies of both the dimers, **D-10α** and **D-10β** suggest the clear possibility of self-assembling character in them.

The optimized geometries of the dimeric structures were further utilized to construct the tetrameric structures, **T-10α** and **T-10β**. **T-10α** was found to adopt an irregular linear arrangement, showing the side-chains in parallel orientation with each other, controlled mostly by van der Waals contacts. This indicated the presence of predominant hydrophobic interactions, contributing substantially to the stability of the tetrameric structure **T-10α** and hence, to the self-assembling property. This arrangement could also be considered to corroborate the TEM image

of **10α** showing an organized pattern of rectangular/ellipsoidal sheets (Fig. 1 and supporting information Figure S1). **T-10β** on the other hand adopts a spherical (globular) pattern, where the sugar portion of the dimers are oriented inwards (forming the head), while the long alkyl side chains are oriented outwardly (forming the tail). These tetramers can be extended further to the octameric structures where a more precise spherical arrangement, like a micelle, can be observed (as shown in supporting information Figure S2). This also is in line with the spherical pattern observed in the TEM images of **10β**.

Hence, the relative stabilization energies, different intramolecular, intermolecular interactions, hydrophobic, van der Waals interactions and different arrangements of the geometries arising from these interactions confirm the self-assembling property and the relative stabilities of these thiogalactosides. Thus, a relation between the polymeric arrangement of these thiogalactosides and their TEM analytical data could be identified using the dispersion-corrected semi-empirical quantum chemical methods. The self-assembling nature of these molecules could be judged to be due to the energy gain on thermodynamic grounds, along with the electrostatic factors, as well as hydrophobic forces.

CONCLUSION

In conclusion, we have demonstrated that $In(OTf)_3$ can be profitably employed in the formation and activation of thioglycosides under solvent-free conditions and without the aid of an additional co-promoter as in the conventional methods. The $In(OTf)_3$-promoted *O*-glycosylation in solution-phase was, however, ineffective in the absence of added NIS. Using NIS as a co-reagent the *O*-glycosylation was also facile and effective in ether although the desired stereoselectivity was poorer compared to the solvent-free reaction. Further work exploring wider applications of the solvent-free methodology is in progress in our laboratory. The distinct morphological features observed in the transmission electron micrographs of thiogalactosides **10α** and **10β** clearly suggest their self-assembly properties that must be distinctly different from each other. Optimization of their structures by semi-empirical quantum chemical methods has revealed the clearly distinguishing features of their association up to the size of tetrameric units and are thus supportive of the differently organized structures obtained on TEM imaging.

GENERAL EXPERIMENTAL METHODS

All the reagents used were as purchased without further purification. Solvents used for reactions were dried according to standard methods. Reactions were monitored by TLC, which was performed with 0.2 mm pre-coated silica gel 60 F254 aluminum sheets. Compounds were detected by dipping the TLC plates in an ethanolic solution of sulphuric acid (5%, v/v) and heating them. Melting points were determined on a melting point apparatus. Specific rotations were recorded on a digital Polarimeter at room temperature (approximately 20-25 °C). NMR spectra were recorded on 400 MHz spectrometer. ^{1}H NMR and ^{13}C NMR spectra were referenced using either residual solvent signals, or tetramethylsilane in the respective deuterated solvents. Wherever necessary ^{1}H-^{1}H COSY and ^{1}H-^{13}C HMQC spectra were used additionally to confirm the NMR peak assignments. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), and broad (br); the value of chemical shifts (δ) are given in ppm and coupling constants (J) are reported in Hertz (Hz). Mass spectra were recorded on a MALDI TOF/TOF or HRMS (TOF) spectrometer.

General procedure for the thioglycosylation of per-*O*-acylated monosaccharides by planetary ball mill

The glycosyl acetate (**1**/**3**/**6**, 0.391 g, 1 mmol), thiophenol (0.250 g, 2.2 mmol) and $In(OTf)_3$ (0.141g, 0.25 mmol) were allowed to mix in a stainless steel (SS) jar (capacity, 50 mL) containing SS balls (10 numbers, 10 mm o.d.) for 1.5 h (or until the reaction was complete: TLC, EtOAc:Hexanes, 1:1) in a planetary ball mill (Retsch PM-100, Retsch GmbH & Co. KG, Germany) at 550 rpm. [For reactions on a scale of 15 g or more of the glycosyl acetate, 2.0 mol equiv of the thiol were mixed in the SS jar (125 ml capacity) using SS balls (6 numbers, 20 mm o.d.) for about 80-90 min]. EtOAc followed by water were then added to the mixture, the organic layer was separated and washed successively with aq Na_2CO_3 solution (10%, w/v) and water, dried (Na_2SO_4), and concentrated under reduced pressure to afford the respective crude thioglycoside that was purified by column chromatography on silica using EtOAc-Hexanes (2:3) as eluent. In the case of preparations on multi-gram scale the products where they are crystalline could be isolated by crystallization from diethyl ether-*n*-Hex to obtain analytically pure product. The spectral data were in accordance with the expected structure and in agreement with the literature values (**3**,[6] **7**,[3,7] **8**, **9**[3], **10**[8] and **11**[9]).

General procedure for the thioglycosylation starting from free sugars by planetary ball mill

The desired free sugar, **12**/**13**/**15**/**17**/18/**20**/**22**/**24** (1 g), acetic anhydride (1.1 mol equiv per –OH group; typically 2.9 ml/g of hexose or 2.2 ml/g of a disaccharide made of hexose units) and $In(OTf)_3$ (catalytic, 0.1-0.2 mol%; typically 5 mg/g sugar)[26] were allowed to mix in a stainless steel (SS) jar (capacity, 50 mL) containing SS balls (10 numbers, 10 mm o.d.) for 30 min (or until the reaction was complete: TLC, EtOAc:Hexanes, 1:1) at 550 rpm as described above. The mixture was added to crushed ice and after stirring well the precipitated per-*O*-acetylated sugar was separated by filtration at the pump and was washed successively with cold aq Na_2CO_3 solution (10%, w/v) and water and was dried. The dried product was transferred back to the milling bowl and after adding thiophenol (typically, 1.35 g in the case of a hexose) and $In(OTf)_3$ (typically, 0.78 g, 25 mol% in the case of a hexose) was milled for 1.5 h. The product (**5**/[3,4,10] **14**/[11] **16**/[12] **7**/[3,6,7] **19**/[6] **21**/[13] **23**/[14] **25**/[15] **4B**,[16] respectively) was isolated and purified as described above. The details are given in Table 4.

Phenyl 3,4,6-tetra-*O*-acetyl-2-deoxy 2-phthaliimido-1-thio-β-D-galactopyranoside (3):

Yield 86% (0.45 g); White solid; mp 136.1 °C; $[\alpha]_D^{25}$ +61.4 (*c* 1.0 in $CHCl_3$), (lit +70.5 *c* 1.5 in $CHCl_3$); IR ν_{max} (KBr, cm^{-1}): 2929, 1750, 1427, 1369, 1222, 1082, 1054, 917, 749; ^1H NMR (400MHz, $CDCl_3$): δ 7.88-7.86 (m, 2H, 1&4Ph-H thali) 7.79-7.76 (m, 2H, 2&3Ph-H thali), 7.43-7.41 (m, 2H, 2&6 Ph-H), 7.31-7.25 (m, 3H, 3,4&5 Ph-H), 5.80 (t, *J* = 9.4 Hz, 1H, H-3), 5.73 (d, *J* = 10.6 Hz, 1H, H-1), 5.15 (t, *J* = 9.8 Hz, 1H, H-4), 4.37 (d, *J* = 10.4 Hz, 1H, H-2), 4.30 (dd, 1H, H-6_a), 4.21 (dd, 1H, H-6_b), 3.93-3.89 (m, 1H, H-5), 2.11, 2.03, 1.85 (3s, 9H, 3x$COCH_3$); $^{13}C\{^1H\}$ NMR (100MHz, $CDCl_3$): δ 170.7-169.4 (4C), 134.5, 134.4, 133.3, 128.9, 128.5, 83.1, 75.8, 71.7, 68.7, 62.2, 53.5, 29.7, 20.8, 20.6, 20.4; MS (MALDI-TOF) for $C_6H_{25}NO_9S$, calculated *m/z* 527.125, found 550.126 $[M+Na]^+$.

Phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (5):

Yield 84% (0.37 g); White solid; mp 64-65 °C; $[\alpha]_D^{25}$ +4.8 (*c* 1 in $CHCl_3$), (lit +4.2 *c* 1 in $CHCl_3$); IR ν_{max} (KBr, cm^{-1}): 2929, 1750, 1369, 1222, 1082, 1054, 917, 749; ^1H NMR (400MHz, $CDCl_3$): δ 7.54-7.51 (m, 2H, 2&6 Ph-H), 7.33-7.28 (m, 3H, 3,4&5 Ph-H), 5.42 (d, *J* = 2.4 Hz, 1H, H-4), 5.25 (t, *J* = 9.9 Hz, 1H, H-2), 5.06 (dd, J_1 = 3.3 Hz, J_2 = 9.9 Hz, 1H, H-3), 4.73 (d, *J*= 9.9 Hz, 1H, H-1), 4.23-4.10 (m, 2H, H-6_a, H-6_b), 3.95 (t, *J* = 8.4 Hz, 1H, H-5), 2.13, 2.12, 2.05, 1.98 (4s, 12H, 4x$COCH_3$); $^{13}C\{^1H\}$ NMR (100MHz, $CDCl_3$): δ 170.4-169.5 (4C), 132.5, 129.1,

128.2, 127.9, 90.5, 74.4, 72.0, 69.1, 61.6, 20.8, 20.7, 20.6, 20.5; MS (MALDI-TOF) for $C_{20}H_{24}O_9S$, calculated *m/z* 440.114, found 463.586 $[M+Na]^+$, 479.590 $[M+K]^+$.

Phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (7):

Yield 84% (0.35 g); White solid; mp 120-121 °C; $[\alpha]_D^{25}$ -19.2 (*c* 1 in $CHCl_3$); IR ν_{max} (KBr, cm^{-1}): 2949, 2891, 1744, 1372, 1255, 1226, 1089, 1043; ^1H NMR (400MHz, $CDCl_3$): δ 7.52-7.48 (m, 2H, 2,6-Ph-H), 7.33-7.29 (m, 3H, 3,4,5-Ph-H), 5.22 (t, *J* = 9.6 Hz, 1H, H-3), 5.04 (t, *J* = 10.0 Hz, 1H, H-2), 4.97 (t, *J* = 9.1 Hz, 1H, H-4), 4.70 (d, *J* = 10.1 Hz, 1H, H-1), 4.24-4.16 (m, 2H, H-6_a, H-6_b), 3.75-3.70 (m, 1H, H-5), 2.09, 2.08, 2.02, 1.99 (3s, 12H, 4x$COCH_3$); ^{13}C NMR (100MHz, $CDCl_3$): δ 170.7, 169.9, 169.8, 133.6, 128.9, 128.4, 85.7, 76.0, 74.0, 69.9, 68.3, 62.2, 20.8, 20.6; MS (MALDI-TOF) for $C_{20}H_{24}O_9S$, calculated *m/z* 440.114, found 463.470 $[M+Na]^+$, 479.460 $[M+K]^+$.

4-Nitrophenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (8):

Yield 90% (0.44 g); White solid; mp 145-146 °C; $[\alpha]_D^{25}$ -6.3 (*c* 1 in $CHCl_3$); IR ν_{max} (KBr, cm^{-1}): 2928, 1750, 1368, 1340, 1223, 1083, 1057; ^1H NMR (400 MHz, $CDCl_3$): δ 8.20-8.15 (m, 2H, 3,5-Ph-H), 7.63-7.59 (m, 2H, 2,6-Ph-H), 5.48 (d, *J* = 3.2 Hz, 1H, H-4), 5.30 (t, *J* = 9.9 Hz, 1H, H-2), 5.10 (dd, J_1 = 3.2, J_2 = 9.9, 1H, H-3), 4.88 (d, *J* = 9.9 Hz, 1H, H-1), 4.23-4.11 (m, 2H, H-6_a, H-6_b), 4.05 (bt, *J* = 6.2 Hz, 1H, H-5), 2.16, 2.08, 2.07, 1.98 (4s, 12H, 4x$COCH_3$); $^{13}C\{^1H\}$ NMR (100MHz, $CDCl_3$): δ 170.3, 170.0, 169.9, 169.4, 146.9, 144.1, 130.4, 126.4, 124.5, 124.0, 84.8, 74.8, 71.7, 67.1, 66.7, 61.7, 20.7, 20.6, 20.6, 20.5; MS (MALDI-TOF) for $C_{20}H_{23}NO_{11}S$, calculated *m/z* 485.102, found 508.112 $[M+Na]^+$, 524.013 $[M+K]^+$.

4-Methylphenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (9):

Yield 84% (0.38 g); White solid; mp 111-112 °C; $[\alpha]_D^{25}$ +4.8 (*c* 1 in $CHCl_3$), (lit.+4.2 *c*1 in $CHCl_3$); IR ν_{max} (KBr, cm^{-1}): 2971, 2938, 1750, 1369, 1224, 1083, 1055; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.1 Hz, 2H, 2,6-Ph-H), 7.15 (d, *J* = 7.9 Hz, 2H, 3,5-Ph-H), 5.42 (d, *J* = 3.3 Hz, 1H, H-4), 5.22 (t, *J* = 9.9 Hz, 1H, H-2), 5.04 (dd, J_1 = 3.2 Hz, J_2 = 9.9 Hz, 1H, H-3), 4.67 (d, *J* = 9.8 Hz, 1H, H-1), 4.22-4.07 (m, 2H, H-6_a, H-6_b), 3.93 (t, *J* = 6.4 Hz, 1H, H-5), 2.34 (s, 3H, CH_3), 2.11, 2.10, 2.04, 1.97 (4s, 12H, 4x$COCH_3$); $^{13}C\{^1H\}$ NMR (100MHz, $CDCl_3$): δ 170.4, 170.2, 170.1, 169.5, 138.5, 133.1, 129.7, 128.6, 87.0, 74.4, 72.1, 67.3, 67.2, 61.6, 21.2, 20.9, 20.7, 20.6; MS (MALDI-TOF) for $C_{21}H_{26}O_9S$, calculated *m/z* 454.130, found 477.119 $[M+Na]^+$, 493.096 $[M+K]^+$.

Octadecyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-galactopyranoside (10α):

Yield 7-8% (0.034 g); White amorphous solid; mp 52.7 °C; $[\alpha]_D^{25}$ +115.9 (*c* 1 in $CHCl_3$); IR ν_{max} (KBr, cm^{-1}): 2944, 2834, 1748, 1369, 1225, 1020; ^1H NMR (400 MHz, $CDCl_3$): δ 5.72 (d, *J* = 5.2 Hz, 1H, H-1), 5.45 (bd *J* = 2.3 Hz, 1H, H-4), 5.26-5.22 (m, J_1 = 5.2 Hz, J_2 = 3.0 Hz, 2H, H-2, H-3), 4.59 (bt, *J* = 7.1Hz, 1H, H-6), 4.11-4.09 (m, 2H, H-6, H-5), 2.70-2.67 (m, 2H, CH_2),

2.14, 2.07, 2.04, 1.99 (4s, 12H, 4x$COCH_3$), 1.60-1.58 (m, 2H, CH_2), 1.41-1.19 (m, 28H, 14xCH_2), 0.89 (m, 2H, CH_2); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.3-169.9 (4C), 82.1, 68.2, 68.0, 66.4, 61.8, 31.9, 29.8, 29.7, 29.6, 29.4, 29.3 28.9, 22.7, 20.8, 20.7, 14.1; MS (ESI HRMS) for $C_{32}H_{56}O_9SNa$, calculated *m/z* 639.3543, found 639.3546 $[M+Na]^+$.

Octadecyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (10β):

Yield 66% (0.46 g); White amorphous solid; mp 58 °C; $[\alpha]_D^{25}$ -15.29 (*c* 1 in $CHCl_3$); IR ν_{max} (KBr, cm^{-1}): 2944, 2834, 1748, 1369, 1225, 1020; ^1H NMR (400 MHz, $CDCl_3$): δ 5.43 (d, *J* = 3.1 Hz, 1H, H-4), 5.23 (t, *J* = 9.9 Hz, 1H, H-2), 5.06 (dd, J_1 = 3.3Hz, J_2 = 9.9Hz, 1H, H-3), 4.47 (d, *J* = 9.9Hz, 1H, H-1), 4.16-4.11 (m, 2H, H-6_a, H-6_b), 3.92 (bt, 1H, H-5), 2.70-2.67 (m, 2H, CH_2), 2.15, 2.07, 2.04, 1.98 (4s, 12H, 4x$COCH_3$), 1.60-1.58 (m, 2H, CH_2), 1.39-1.18 (m, 28H, 14xCH_2), 0.89 (m, 2H, CH_2); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.4-169.6 (4C), 84.2, 74.3, 71.9, 67.3, 61.5, 31.9, 29.7, 29.7, 29.6, 29.2, 28.8, 22.7, 20.6, 14.1; MS (ESI HRMS-TOF) for $C_{32}H_{56}O_9SNa$, calculated *m/z* 639.3543, found 639.3544 $[M+Na]^+$.

Tetradecyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-galactopyranoside (11α):

Yield 7-8% (0.030 g); Oil; $[\alpha]_D^{25}$ +52.0 (*c* 1 in $CHCl_3$); IR ν_{max} (KBr, cm^{-1}): 2943, 2827, 1737, 1366, 1225, 1010; ^1H NMR (400 MHz, $CDCl_3$): δ 5.73 (d, *J* = 5.2 Hz, 1H, H-1), 5.46 (bd *J* = 2.3 Hz, 1H, H-4), 5.27-5.23 (m, J_1 = 5.2 Hz, J_2 = 3.0 Hz, 2H, H-2, H-3), 4.60 (t, *J* = 7.1Hz, 1H, H-6), 4.12-4.10 (m, 2H, H-6, H-5), 2.59-2.46 (m, 2H, CH_2), 2.15, 2.08, 2.05, 2.00 (4s, 12H, 4x$COCH_3$), 1.59-1.57 (m, 2H, CH_2), 1.34-1.23 (m, 24H, 12xCH_2), 0.90 (m, 2H, CH_2); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.4-169.9 (4C), 82.2, 68.2, 68.0, 66.4, 61.9, 31.9, 29.8, 29.7, 29.6, 29.5, 28.9, 22.7, 20.8, 20.7, 14.1; MS (ESI HRMS-TOF) for $C_{28}H_{48}O_9SNa$, calculated *m/z* 583.2917, found 583.2917 $[M+Na]^+$.

Tetradecyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (11β):

Yield 65% (0.37 g); Oil; $[\alpha]_D^{25}$ -11.9 (*c* 1 in $CHCl_3$); IR ν_{max} (KBr, cm^{-1}): 2966, 2834, 1749, 1366, 1220, 1025; ^1H NMR (400 MHz, $CDCl_3$): δ 5.42 (d, *J* = 2.9 Hz, 1H, H-4), 5.22 (t, *J* = 9.9 Hz, 1H, H-2), 5.03 (dd, J_1 = 3.3 Hz, J_2 = 9.9Hz, 1H, H-3), 4.46 (d, *J* = 9.9 Hz, 1H, H-1), 4.14-4.10 (m, 2H, H-6_a, H-6_b), 3.93 (bt, 1H, H-5), 2.69-2.66 (m, 2H, CH_2), 2.15, 2.07, 2.04, 1.98 (4s, 12H, 4x$COCH_3$), 1.59-1.57 (m, 2H, CH_2), 1.37-1.24 (m, 24H, 12xCH_2), 0.86 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 170.2, 170.1, 169.9 (4C), 84.2, 74.3, 71.9, 67.3, 61.4, 31.9, 29.7, 29.6, 29.5, 29.3, 28.9, 22.6, 20.8, 14.1; MS (ESI HRMS-TOF) for $C_{28}H_{48}O_9SNa$, calculated *m/z* 583.2917, found 583.2917 $[M+Na]^+$.

Phenyl 2,3,4-tri-*O*-acetyl-1-thio-β-D-xylopyranoside (14):

Yield 74% (0.24 g); White solid; mp 76-77 °C; $[\alpha]_D^{25}$ -55.6 (*c* 1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.51-7.48 (m, 2H), 7.34-7.31 (m, 3H), 5.19 (t, J_1 = 8.2 Hz, 1H), 4.98-4.82 (m, 2H), 4.83 (d, *J* = 8.3 Hz, 1H, H-1), 4.29 (dd, J_1 = 11.8 Hz, J_2 = 4.9 Hz, 1H), 3.45 (dd, J_1 = 12.0 Hz, J_2

= 8.8 Hz, 1H), 2.19 2.11, 2.07 (3s, 9H, 3xCOCH$_3$); ^{13}C{^{1}H} NMR (100MHz, CDCl$_3$): δ 169.9, 169.8, 169.3, 132.7, 132.2, 129.0, 128.2, 86.3, 72.0, 69.8, 68.4, 65.2, 20.8, 20.7; M.W. ($C_{17}H_{20}O_7S$) 368.04; ESI-MS *m*/*z* 391.09 [M+Na]$^+$.

Phenyl 2,3,4-tri-*O*-acetyl-1-thio-β-L-arabinopyranoside (16):

Yield 68% (0.22 g); Oil, $[\alpha]_D^{25}$ -59.7 (*c* 1 in CH_2Cl_2); ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.49-7.46 (m, 2 H) 7.34-7.27 (m, 3H), 5.30-5.20 (m, 2H), 5.10 (dd, J_1 = 8.4 Hz, J_2 = 3.4 Hz, 1H), 4.82 (d, *J* = 7.8 Hz, 1H), 4.17 (dd, J_1 = 12.7 Hz, J_2 = 4.2 Hz, 1H), 3.68 (dd, J_1 = 12.7 Hz, J_2 = 2.0 Hz, 1H), 2.13 (s, 6H, 2xCOCH$_3$), 2.06 (s, 3H, COCH$_3$); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 170.3, 169.9, 169.5, 133.3, 132.2, 129.1, 128.6, 86.9, 70.9, 68.5, 67.5, 65.3, 20.9, 20.8, 20.7; M.W. ($C_{17}H_{20}O_7S$) 368.03; ESI-MS *m*/*z* 391.07 [M+Na]$^+$.

Phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranoside (19):

Yield 88% (0.38 g); Oily liquid, $[\alpha]_D^{25}$ = +84.9 (*c* 2 in CH_2Cl_2); ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.51-7.49 (m, 2H), 7.36-7.31 (m, 3H), 5.53-5.51 (m, 2H), 5.38-5.32 (m, 2H), 4.58-4.55 (m, 1H), 4.33 (dd, J_1 = 12.24 Hz, J_2 = 6.0 Hz, 1H), 4.10 (dd, J_1 = 12.4 Hz, J_2 = 2.3 Hz, 1H), 2.17-2.04 (4s, 12H, 4xCOCH$_3$); 13C{^{1}H} NMR (100MHz, CDCl$_3$): δ 170.5, 169.9, 169.8, 169.7, 132.6, 132.1, 129.2, 128.1, 85.7, 70.9, 69.5, 69.4, 66.4, 62.4, 20.9, 20.7, 20.7, 20.6; M.W. ($C_{20}H_{24}O_9S$) 440.11; ESI-MS *m*/*z* 463 [M+Na]$^+$.

Phenyl 2,3,4-tri-*O*-acetyl-1-thio-α-L-rhamnopyranoside (21):

Yield 74% (0.28 g); Colorless solid; mp 116-118 °C; $[\alpha]_D^{25}$ -105.8 (*c* 1 in $CHCl_3$); ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.49-7.46 (m, 2H, Ph-H) 7.34-7.27 (m, 3H, Ph-H), 5.50 (dd, 1H, J_1 = 1.6 Hz, J_2 = 3.3 Hz, H-2), 5.41 (d, J_1 = 1.6 Hz ,1H, H-l), 5.29 (dd, 1H, J_1 = 10.0 Hz, J_2 = 3.3 Hz, H-3), 5.17 (t, 1H, J_1 = 9.8 Hz, H-4), 4.39-4.32 (m, 1H, H-5), 2.20, 2.09, 2.01 (3s, 9H,COCH$_3$), 1.25 (d, 3H, J_1 = 6.2 Hz, CH$_3$); ^{13}C{^{1}H} NMR (100MHz, CDC1$_3$): δ 170.1 (2xCOCH$_3$), 169.9 (COCH$_3$), 133.3, 131.8, 129.2, 127.9, 85.7, 71.3, 71.1, 69.4, 67.8, 20.9, 20.9, 20.7 (CHSCO), 17.3 (C-6); M.W. ($C_{18}H_{22}O_7S$) 383.45, ESI-MS *m*/*z* 405.10 [M+Na]$^+$.

Phenyl 2,3,6-tri-*O*-acetyl-4-*O*-(2',3',4',6'-tetra-*O*-acetyl-β-D-galactopyranosyl)-1-thio-β-D-glucopyranoside (23):

Yield 64% (0.47 g); White solid; mp 89-90 °C; $[\alpha]_D^{25}$ -21.7 (*c* 1 in $CHCl_3$); ^{1}H NMR (400MHz, CDCl$_3$): δ 7.49-7.46 (m, 2H), 7.34-7.27 (m, 3H), 5.35 (d, J_1 = 3.2 Hz, 1H, H-4'), 5.22 (t, *J* = 9.1 Hz, 1H, H-3), 5.11 (dd, J_1 = 10.4 Hz, J_2 = 7.8 Hz, 1H, H-2'), 4.95 (dd, J_1 = 10.4 Hz, J_2 = 3.1 Hz, H-3'), 4.90 (t, J_1 = 9.5 Hz, 1H, H-2), 4.68 (d, J_1 = 10.1 Hz, 1H, H-1), 4.54 (dd, 1H, J_1 = 1.8 Hz, J_2 = 11.9 Hz, H-6), 4.47 (d, 1H, J_1 = 7.8, H-1'), 4.15-4.05 (m, 3H, 2xH-6', H-6), 3.88-3.85 (m, 1H, H-5'), 3.78-3.73 (m, 1H, H-4), 3.67-3.63 (m, 1H, H-5), 2.17, 2.15, 2.13,2.10, 2.09,1.98, 1.97 (7s, 21H, COCH$_3$); ^{13}C{^{1}H} NMR (100MHz, CDCl$_3$): δ 170.3, 170.3, 170.1, 170.1, 169.7, 169.1, 169.0, 133.1, 131.8, 128.9, 128.3, 101.0, 85.5, 76.7, 76.1, 73.8, 71.0, 70.7, 69.1, 66.6, 62.1, 60.8,

20.8, 20.8, 20.6, 20.5; M.W. ($C_{32}H_{40}O_{17}S$) 728.19; ESI-MS *m/z* 751.20 $[M+Na]^+$.

Phenyl 2,3,6-tri-*O*-acetyl-4-*O*-(2',3',4',6'-tetra-*O*-acetyl-α-D-glucopyranosyl)-1-thio-β-D-glucopyranoside (25):

Yield 65% (0.48 g); White solid; mp 89-90 °C; $[\alpha]_D^{25}$ +42.2 (*c* 1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.50-7.48 (m, 2H), 7.35-7.31 (m, 3H), 5.41 (d, J = 4.0 Hz, 1H), 5.36 (t, J = 9.8 Hz, 1H), 5.30 (t, J = 7.0 Hz, 1H), 5.06 (t, J = 9.9 Hz, 1H), 4.86 (dd, J_1 = 4.0 Hz, J_2 = 10.5 Hz, H-1), 4.84 (t, J = 8.9 Hz, 1H), 4.75 (d, J = 10.1, 1H), 4.55 (dd, J_1 = 2.4 Hz, J_2 = 12.1 Hz, 1H), 4.27-4.21 (m, 2H), 4.06 (dd, J_1 = 12.4 Hz, J_2 = 2.2 Hz, 1H), 3.98-3.93 (m, 2H), 3.76-3.71 (m, 1H), 2.14 (s, 3H, $COCH_3$), 2.12, 2.08, 2.06, 2.05, 2.01, 1.99 (7s, 21H, $COCH_3$); $^{13}C\{^1H\}$ NMR (100MHz, $CDCl_3$): δ 170.6, 170.4, 170.2, 170.0, 169.6, 169.5, 133.4, 131.3, 129.2, 128.9, 128.5, 95.6, 85.1, 76.5, 76.1, 72.4, 70.7, 70.0, 69.3, 68.5, 68.0, 62.8, 61.9, 20.9, 20.8, 20.7, 20.6, 20.5; M.W. ($C_{32}H_{40}O_{17}S$) 728.19; ESI-MS *m/z* 751.21 $[M+Na]^+$.

Phenyl 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranoside (4B):

Yield 67% (0.43 g); White solid; mp 81.3 °C; $[\alpha]_D^{25}$ +81.7 (*c* 1 in $CHCl_3$), (lit. +81.5 *c* 1 in $CHCl_3$); IR ν_{max} (neat, cm^{-1}): 2926, 1728, 1601, 1266, 1094, 1069, 1026, 749, 707; ^1H NMR (400 MHz, $CDCl_3$): δ 8.05-7.22 (m, 25H, Ph-H), 6.02 (bd, J = 2.9 Hz, 1H, H-4), 5.77 (t, J = 9.9 Hz, 1H, H-2), 5.61 (dd, J_1 = 3.2 Hz, J_2 = 9.9 Hz, 1H, H-3), 5.05 (d, J = 9.9 Hz, 1H, H-1), 4.69-4.64 (m, 1H, H-5), 4.48-4.39 (m, 2H, H-6); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 166.1, 165.5, 165.4, 165.2, 134.0, 133.6, 133.4, 133.3, 131.2, 130.0, 129.8, 129.8, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 85.9, 76.7, 75.1, 73.0, 68.3, 67.8, 62.5; MS (MALDI-TOF) for $C_{40}H_{32}O_{10}S$, calculated *m/z* 688.05, found *m/z* 726.987 $[M+K]^+$, 711.013 $[M+Na]^+$.

General procedure for the activation of thioglycosides under solvent-free conditions

A mixture of the desired benzylated phenyl thioglycoside (for **26**, 0.632 g, 1 mmol), the acceptor alcohol (for **27**, 0.310 g, 1.2 mmol) and $In(OTf)_3$ (0.141 g, 0.25 mmol) were allowed to mix in a stainless steel (SS) jar (capacity, 50 mL) containing SS balls (10 numbers, 10 mm o.d.) for 90 min (or until the reaction was complete: TLC, EtOAc:Hexanes, 1:1) at 500 rpm. The mixture was taken up in EtOAc and was transferred to a separatory funnel containing crushed ice. The organic layer was washed successively with cold aq Na_2CO_3 solution (10%, w/v) and water and after drying (Na_2SO_4) was concentrated to dryness under reduced pressure to afford the respective crude disaccharide that was purified by column chromatography on silica using EtOAc-Hexanes (1:4) as eluent.

General procedure for the activation of thioglycosides in solution-phase

To a solution of the desired benzylated phenyl thioglycoside (for **26**, 0.632 g, 1 mmol) and the acceptor alcohol **27**, (0.260 g, 1 mmol) was added NIS (0.225 g, 1 mmol) followed by $In(OTf)_3$ (0.030 g, 0.05 mmol) and the mixture was allowed to stir at rt for 5-10 min (or until the reaction was complete: TLC, EtOAc:Hexanes, 1:1). The mixture was diluted with EtOAc and was transferred to a separatory funnel containing crushed ice. The organic layer was washed successively with cold aq Na_2CO_3 solution (10%, w/v) and water and after drying (Na_2SO_4) was concentrated to dryness under reduced pressure to afford the respective crude disaccharide that was purified by column chromatography on silica using EtOAc-Hexanes (1:4) as eluent.

1:2,3:4-Di-*O*-isopropylidene-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-α-D-galactopyranose (28α):

Yield 7% (0.045 g); Oil; $[\alpha]_D^{25}$ +51.0 (*c* 2 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.4-7.2 (m, 20H), 5.51 (d, *J* = 5.0 Hz, 1H, H-1'), 5.00 (d, *J* = 3.6 Hz, 1H, H-1), 4.92 (d, *J* = 11.4 Hz, 1H, CH_2Ph), 4.82 (d, *J* = 11.7 Hz, 1H, CH_2Ph), 4.74-4.71 (m, 3H, CH_2Ph), 4.58-4.55 (m, 2H, Ph-H, H-3), 4.48-4.38 (q, *J* = 11.8 Hz, 2H, CH_2Ph), 4.32-4.28 (m, 2H, H-4 and H-2) 4.06-3.93 (m, 5H, H-2, H-3, H-4, H-5, H-5'), 3.80-3.70 (m, 2H, H-6'), 3.58-3.49 (m, 2H, H-6); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 139.3, 139.0, 138.8, 128.3, 128.3, 128.2, 127.6, 109.2, 108.6, 97.6, 96.4, 92.0, 79.0, 76.8, 74.8, 73.4, 73.1, 72.7, 70.9, 70.7, 70.6, 69.2, 68.7, 66.4, 30.2, 29.7, 29.6, 29.4; MS (MALDI-TOF) for $C_{46}H_{54}O_{11}Na$, calculated *m/z* 782.366, found 821.330 $[M+K]^+$, 805.356 $[M+Na]^+$.

1:2,3:4-Di-*O*-isopropylidene-6-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl)-α-D-galactopyranose (28β):

Yield 54% (0.42 g); Oil; $[\alpha]_D^{25}$ -107.4 (c 1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.5-7.2 (m, 20H), 5.58 (d, 1H, H-1'), 5.06 (d, 1H, CH_2Ph), 4.94 (d, 1H, CH_2Ph), 4.81-4.70 (m, 3H, CH_2Ph), 4.62 (d, 1H, CH_2Ph), 4.58 (d, 1H, H-3'), 4.46-4.39 (m, 3H, CH_2Ph, H-1), 4.33 (dd, 1H, H-2'), 4.23 (dd, 1H, H-4'), 4.14 (dd, 1H, H-6a'), 4.10-4.08 (m, 1H, H-5'), 3.90-3.89 (m, 1H, H-4), 3.85 (dd, 1H, H-2), 3.72 (dd, 1H, H-6b'), 3.62-3.57 (m, 2H, H-5, H-3), 3.54-3.50 (m, 2H, H-6a, H-6b), 1.50 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.32 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 139.2, 138.6, 139.9, 128.6, 128.4, 128.3, 128.1, 127.9, 127.8, 127.5, 109.3, 108.6, 104.7, 96.4, 81.9, 79.1, 76.7, 74.7, 74.5, 73.5, 73.3, 73.1, 71.5, 70.8, 70.5, 69.6, 68.6, 67.4, 29.7, 29.4, 26.0, 25.9, 25.1, 24.4. MS (MALDI-TOF) for $C_{46}H_{54}O_{11}Na$, calculated *m/z* 782.366, found 805.356 $[M+Na]^+$, 821.330 $[M+K]^+$.

Methyl 2,3,4-tri-*O*-acetyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-galactopyranosyl)-α-D-gluco-pyranoside (30α/β):

Yield 64% (0.54 g); Oil; ^{1}H NMR (400 MHz, $CDCl_3$, for **30β**): δ 7.41-7.27 (m, 20H, Ph-H of benzyl), 5.48 (t, 1H, H-3), 5.07 (t, 1H, H-4), 4.97-4.85 (m, 3H, CH_2Ph, H-1), 4.84-4.79 (m, 3H, CH_2Ph, H-1',H-2), 4.77 (d, 1H, CH_2Ph), 4.70 (d, 1H, CH_2Ph), 4.59 (d, 1H, CH_2Ph), 4.45 (d, 1H, CH_2Ph), 4.40 (d, 1H, CH_2Ph), 4.07 (bdd, 1H, H-6a), 4.01-3.90 (m, 4H, H-5, H-6b, H-2', H-4'), 3.77-3.73 (q, 1H, H-3), 3.51-3.47 (m, 3H, H-5', H-6a', H-6b'), 3.31 (s, 3H, OCH_3), 2.06, 2.05, 2.03 (s, 9H, 3x$COCH_3$); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.1, 169.8, 138.8, 138.7, 138.0, 128.5, 128.4, 128.3, 128.3, 128.2, 128.1, 127.9, 127.7, 127.6, 127.6, 127.5, 127.4, 97.7 (C-1β), 96.5, 78.6, 75.1, 75.0, 74.7, 73.4, 73.1, 72.9, 71.0, 70.4, 69.6, 69.2, 69.1, 67.9, 66.2, 55.2, 20.8, 20.7, 20.7; MS (MALDI-TOF) for $C_{48}H_{58}O_{11}Na$, calculated *m/z* 842.351, found 881.315 $[M+K]^+$, 865.346 $[M+Na]^+$.

2-*O*-(2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl) diethyl tartrate (32):

Yield 36% (0.26 g); Oil; racemate; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44-7.22 (m, 20H, Ph-H), 5.35 (d, J_1 = 3.6 Hz, 1H, H-1), 4.93 (d, 2H, CH_2Ph), 4.84 (d, 1H, CH_2Ph), 4.73-4.65 (m, 4H, CH_2Ph, C-H of diethyl tartrate), 4.55 (d, 2H, CH_2Ph), 4.45 (d, 2H, CH_2Ph), 4.38 (d, 2H, CH_2Ph), 4.25-4.21 (m, 3H, $COOCH_2$), 4.10 (dd, J_1 = 3.6 Hz, J_1 = 10.1 Hz, 1H, H-2), 4.02-3.94 (m, 1H, $COOCH_2$), 3.89 (m, 1H, H-4), 3.84 (dd, J_1 = 2.7 Hz, J_1 = 10.1 Hz, 1H, H-3), 3.68 (bt, 1H, H-5), 3.53 (t, 1H, H-6_a), 3.46 (t, 1H, H-6_b), 1.29 (t, 3H, CH_3), 1.18 (t, 3H, CH_3); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.1, 168.4, 138.8, 138.6, 138.2, 137.9, 128.4, 128.3, 128.2, 128.2, 127.9, 127.8, 127.7, 127.6, 127.60, 127.5, 95.3, 78.0, 77.4, 77.3, 77.1, 76.8, 75.9, 74.9, 74.8, 74.2, 73.5, 73.4, 72.5, 72.4, 70.1, 68.4, 61.9, 61.6, 14.2, 14.1; MS (ESI HRMS-TOF) $C_{42}H_{48}O_{11}Na$, calculated m/z 751.3094 $[M+Na]^+$, found m/z 751.3094 $[M+Na]^+$.

2,3-Di-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl) diethyl tartrate (33):

Yield 47% (0.57 g); Oil; racemate; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49-7.23 (m, 20H), 5.31 (d, J_1 = 3.4 Hz, 1H, H-1), 4.98 (t, 2H, CH_2Ph), 4.86-4.80 (m, 3H, CH_2Ph, C-H of diethyl tartrate), 4.72 (d, 1H, CH_2Ph), 4.59 (d, 1H, CH_2Ph), 4.49 (d, 1H, CH_2Ph), 4.43 (d, 1H, CH_2Ph), 4.28-4.23 (dd, 1H, $COOCH_2$), 4.19 (dd, J_1 = 3.4 Hz, J_2 = 10.1 Hz, 1H, H-2), 4.13-4.08 (m, 1H, $COOCH_3$), 4.04-4.01 (m, 2H, H-3, H-4), 3.97-3.92 (bm, 1H, H-5), 3.61-3.54 (m, 2H, H-6_a, H-6_b), 1.23 (t, 3H, CH_3); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.4, 139.2, 138.8, 138.7, 138.5, 138.1, 138.0, 128.5, 128.4, 128.3, 128.22, 128.21, 128.2, 128.1, 128.1, 127.9, 127.8, 127.6, 127.5, 127.4, 127.3, 127.3, 96.3, 78.8, 75.8, 75.2, 74.8, 74.6, 74.0, 73.7, 73.6, 73.4 73.1, 71.8, 70.1, 68.5, 61.6, 61.3, 14.2; MS (ESI HRMS-TOF) $C_{76}H_{82}O_{16}Na$, calculated m/z 1273.5501 $[M+Na]^+$, found m/z 1273.5500 $[M+Na]^+$.

Computational Details: The monomeric geometries were optimized using the dispersion-corrected semi-empirical PM3-D method,[27] using the G09 package.[28] All the other geometries were optimized using PM3-D method. This method has been reported to be helpful, reliable and applicable in the optimization studies of large molecules, and save considerable computing time.

PM3-D method incorporates dispersion effects, used to model hydrophobic and dispersion interactions, at reduced computational expense. The detailed studies using PM3-D method provides insights into the structural details of dimers, polymeric structures and supramolecular systems. Initially, the geometry optimizations of monomers, **10α** and **10β**, were computed. These optimized geometries were employed for the dimer-construction and thereafter, the dimers were optimized. The dimerization energies were also calculated for both the anomers. The optimized geometries of dimers were utilized for the construction of the tetramers, and further optimized. The optimized tetrameric geometries of **10α** and **10β** provide a clear depiction of the arrangement, which was correlated with TEM analysis. The energy and geometric parameters used in the discussion are based on PM3-D method unless otherwise specifically mentioned. Single point calculations were carried out on the two monomers of **10α** and **10β** using B3LYP/3-21G method.[29]

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SUPPORTING INFORMATION AVAILABLE: Experimental procedures, compound characterization data, and computational details are available free of charge via the Internet at http://pubs.acs.org.

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