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The presence of water improves reductive openings of benzylidene acetals with trimethylaminoborane and aluminium chloride

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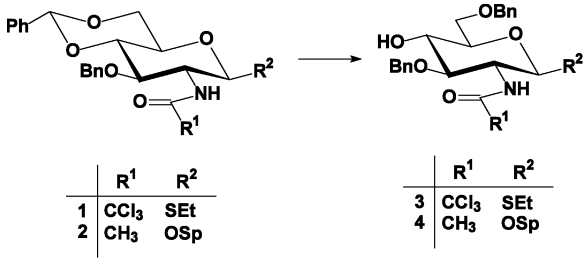
Abstract

The acidic reagent formed in situ from anhydrous $AlCl_3$ and H_2O in 3:1 ratio is much more efficient for the reductive openings of the cyclic benzylidene acetals with $Me_3N{\cdot}BH_3$ in tetrahydrofurane than the $AlCl_3$ alone. Under proposed conditions, the dioxane-type 4,6-*O*-bezylidene acetals of hexopyranosides give regioselectively the corresponding 4-hydroxy,6-*O*-benzyl derivatives in excellent yields. Reductive openings of the dioxolane-type 3,4-*O*-benzylidene acetals of galactopyranoside are also very efficient and regioselective and give either 3-*O*-benzyl derivative (from 3,4-*O*-*exo*-benzylidene acetal) or 4-*O*-benzyl derivative (from 3,4-*O*-*endo*-benzylidene acetal) depending on the configuration of the acetal carbon atom.

Keywords: Protecting group; Benzylidene acetal; Reductive opening; Hexopyranosides; Water

1. Introduction

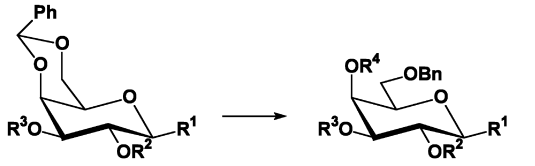
The cyclic benzylidene acetals can be transformed into the monobenzyl ethers of the corresponding diols by a number of reagents[1] including $NaBH_3CN–HCl$,[2] $Et_3SiH–CF_3CO_2H$,[3] Cl_2AlH,[4] i-Bu_2AlH.[5] Reductive opening of the dioxane ring of 4,6-*O*-benzylidenated hexopyranosides with equatorial phenyl group can be performed regioselectively to give either 4-*O*- or 6-*O*-benzyl derivatives depending on the reaction conditions. For the dioxolane ring of both 3,4-*O*- and 2,3-*O*-benzylidene acetals the direction of cleavage is determined not by the nature of reagent, but by the configuration of the acetal carbon atom.[6,7] Reductive benzylidene acetal opening was shown to be a useful technique for the protecting group manipulations and has found wide application.[1]



	R^1	R^2
1	CCl_3	SEt
2	CH_3	OSp

	R^1	R^2
3	CCl_3	SEt
4	CH_3	OSp

One of the most convenient procedures for reductive benzylidene acetal opening employs $Me_3N{\cdot}BH_3$ and $AlCl_3$ in THF.[8] Such treatment of 4,6-*O*-benzylidenated derivatives of D-glucose and D-galactose have been described[8] to give 4-hydroxy,6-*O*-benzyl ethers in 62–86% yields. Under the same conditions, methyl 4-*O*-benzyl-*exo*-2,3-*O*-benzylidene-α-L-rhamnopyranoside gave the 3,4-di-*O*-benzyl ether with the 2-OH free in 85% yield.



	R^1	R^2	R^3
5	SEt	Bz	Bz
6	OAll	Ac	Ac
7	SEt	H	Bz
8	SEt	H	H

	R^1	R^2	R^3	R^4
9	SEt	Bz	Bz	H
10	OAll	Ac	Ac	H
11	SEt	H	Bz	H
12	SEt	H	H	Bz
13	SEt	H	H	H

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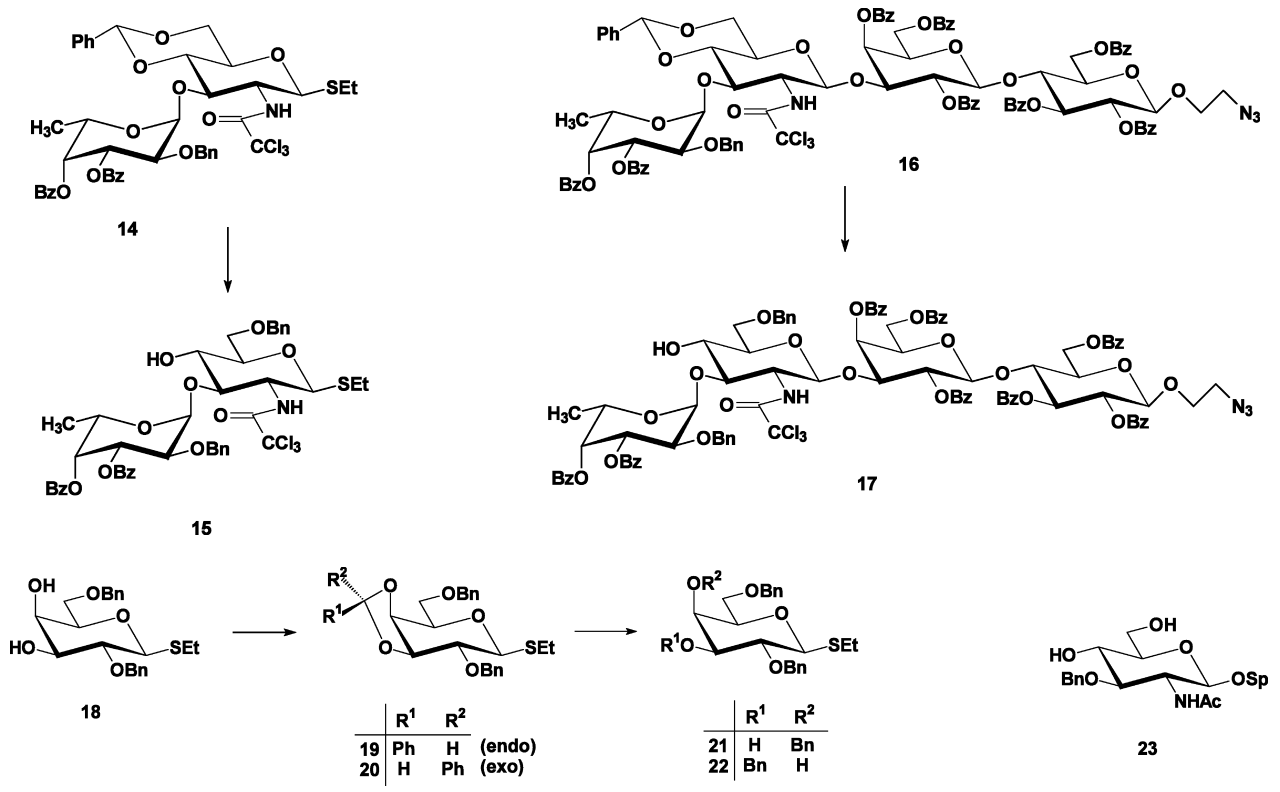

However, as we have described,[9] [10] when we attempted reductive opening of 4,6-*O*-benzylidene acetals in fully substituted compounds **1**[9] and **2**[10] with $Me_3N{\cdot}BH_3$ (6 equiv) and $AlCl_3$ (6 equiv) in THF, the reactions stopped after 10–15% of conversion into the desired products **3** and **4**, respectively, and even after 2 days at rt the unreactive starting materials were the main components of the reaction mixtures (Table 1, Entries 1, 3). The use of large (~ 20-fold) excess of the reagents did not improve the yields, while heating of

Table 1
Reductive openings of the benzylidene acetals rings in compounds **1**, **2**, **5**, **6**, **7**, **8**, **14**, **16**, **19**, **20**

Entry	Acetal	Procedure [a]	Time (h)	Product	Isolated yield (%)
1	**1**	A	72	**3**	10
2	**1**	B	6	**3**	89
3	**2**	A	48	**4**	12
4	**2**	B	6	**4**	87
5	**5**	A	48	**9**	13
6	**5**	B	5	**9**	91
7	**6**	A	48	**10**	15
8	**6**	B	8	**10**	82
9	**7**	A	18	**12** [b]	28
10	**7**	B	5	**11**	87
11	**8**	A	8	**13**	66
12	**8**	B	5	**13**	77
13	**14**	B	7	**15**	82
14	**16**	B	7	**17**	62
15	**19**	B	5	**21**	92
16	**20**	B	5	**22**	88
17	**20**	A	7	**22**	85

[a] Procedure A: $Me_3N{\cdot}BH_3$ (4 equiv), $AlCl_3$ (6 equiv) in THF at rt. Procedure B: $Me_3N{\cdot}BH_3$ (4 equiv), $AlCl_3$ (6 equiv), and H_2O (2 equiv) in THF at rt.

[b] In addition to **12**, the product of its O-debenzoylation **13** was also obtained in 31% yield.

the reaction mixtures lead to degradation. The same treatment of fully benzoylated or acetylated galactosides **5**[11] and **6**[12] gave also mainly recovered starting materials and the products **9** and **10**, respectively, were obtained in low yields (Entries 5, 7). In this communication we describe our investigation of the reductive opening of benzylidene acetals with $Me_3N{\cdot}BH_3$ and $AlCl_3$ in THF.

2. Results and discussion

Our study of the reaction revealed that addition of water to the reaction mixture favored dramatically the efficiency of benzylidene opening. After some experimentation, 2 equiv of water proved to be the optimal amount. Thus treatment of the acetals **1**, **2**, **5**, **6** with $Me_3N{\cdot}BH_3$ (4 equiv), anhydrous $AlCl_3$ (6 equiv), and H_2O (2 equiv) in THF (freshly distilled from Na–Ph_2CO) for 6–8 h at rt afforded 4-hydroxy,6-*O*-Bn derivatives **3**, **4**, **9**, **10** in 82–91% yields (Entries 2, 4, 6, 8) without formation of the isomeric 4-*O*-benzyl derivatives. No 3-*O*- → 4-*O*-acyl migration in the galactose derivatives **9** and in particular **10** was observed. More complex di- and tetrasaccharide substrates **14** and **16** (their preparation will be reported elsewhere) gave also regioselectively 4-hydroxy derivatives **15** and **17** in good yields (Entries 13 and 14), and no cleavage of the acid-labile α-L-fucose linkage occurred. Thus the reaction conditions tolerate the typical set of glycosidic bonds and carbohydrate protecting groups, including acyl, allyl (as in **6**), and azido (as in **16**) ones.

We also studied the reductive opening of mono- and dihydroxylated compounds in order to investigate whether substrate's free hydroxy groups may favor benzylidene opening by serving as proton donors necessary to catalyze the reaction. The reaction of monohydroxy substrate **7**[13] in the presence of 2 equiv of H_2O afforded rapidly a single product **11** in 87% yield (Entry 10). On the contrary, in the absence of H_2O the substrate **7** reacted slowly (Entry 9) and only traces of **11** were obtained. Instead, the major compounds formed after 18 h were the benzoyl group migration product **12** (28%) and debenzoylated derivative **13** (31%). Other components of the reaction mixture were unidentified degradation products of very low chromatographic mobility. Hence, the presence of only 1 equiv of protons in the reaction media is not enough for the efficient reductive opening.

The reactions of dihydroxylated benzylidene derivative **8**[11 14] in the presence and absence of water showed small difference in results (Entries 11 and 12) of reductive opening into 6-*O*-benzyl derivative **13**.[14] Although in the presence of water the reaction was faster and the yield of **13** was higher, its influence was not so crucial, because the acetal **8** contains the requisite amount of protons in itself.

Thus, catalysis of the reductive opening of the dioxane-type 4,6-*O*-benzylidene acetals of hexapyranosides by the acidic species formed from $AlCl_3$ and H_2O in 3:1 ratio is much more efficient than that by anhydrous $AlCl_3$.

The investigation of reductive openings of the dioxolane-type benzylidene acetals was performed with the use of 3,4-*O*-benzylidenated substrates **19** and **20**. The *endo*-acetal **19** (δ_{PhCH} 5.98 ppm) was obtained in 80% yield, together with 8% of its exo isomer **20** (δ_{PhCH} 6.07 ppm), by benzylidenation of diol **18**[15] with Ph-$CH(OMe)_2$ and TsOH in THF as described for its lactose analogue.[16]

In contrast to the dioxanes **1**, **2**, **5**, **6**, the completely substituted dioxolanes **19** and **20** underwent reductive opening into **21** and **22**, respectively, both with and without water (Entries 15–17). Although in the presence of water the reactions were faster, the result of the anhydrous experiment (Entry 17) shows that the acidity of $AlCl_3$ alone is sufficient in the case of more reactive[5] 2-phenyl-1,3-dioxolanes as compared to 2-phenyl-1,3-dioxanes. Similar conditions have already been recommended[8] for the reduction of methyl 4-*O*-benzyl-*exo*-2,3-*O*-benzylidene-α-L-rhamnopyranoside into methyl 3,4-di-*O*-benzyl-α-L-rhamnopyranoside. Compound **21** was successfully applied for the synthesis of aminoethyl glycosides of the carbohydrate chains of glycolipides Gb3, Gb4 and Gb5.[17]

As expected,[18] the openings of dioxolane rings proceeded regioselectively: the endo isomer **19** afforded the 3-OH derivative **21** ($\delta_{C\text{-}3}$ 75.6, $\delta_{C\text{-}4}$ 76.2 ppm) solely, while the 4-hydroxy derivative **22** ($\delta_{C\text{-}3}$ 82.5, $\delta_{C\text{-}4}$ 66.9 ppm) was obtained as the only product from the exo isomer **20**. Furthermore, both yield and regiochemical outcome of the reduction of **20** under anhydrous conditions (Entry 17) were the same as those in the presence of water (Entry 16). Thus, the direction of cleavage is determined by configuration of the acetal carbon atom solely, and independent on the nature of the acidic catalyst. The same independence can be concluded from the comparison between the dioxolane openings with $NaBH_3CN$–HCl and those with $LiAlH_4$–$AlCl_3$, both of which give the same regioselectivity.[18]

The regioselectivity of the dioxolane reductions supports the previous assumption[1] that the formation of the oxo-carbenium ion from the initial acetal is a slow rate-determining process, while further reduction of the cation with $Me_3N{\cdot}BH_3$ occurs very rapidly. Otherwise, racemization of the acetal carbon atom leading to the mixture of 3-*O*- and 4-*O*-benzyl ether products could be expected,[19] which actually is not observed.

In none of the water-assisted reactions investigated the products of benzylidene acetal hydrolysis were formed in appreciable amounts. Furthermore, when the

acetal **2** was treated with 4 equiv of $Me_3N{\cdot}BH_3$, 6 equiv of $AlCl_3$, and 20 equiv of H_2O (in THF for 24 h at rt), the reduced derivative **4** was still the major product (43% yield), but the corresponding 4,6-diol **23** was also obtained in 20% yield. Hence, the reaction of oxo-carbenium ion with the hydride donor is likely to occur faster then that with water.

In conclusion, further investigation of the known protocol[8] for the reductive openings of the cyclic benzylidene acetals with $Me_3N{\cdot}BH_3$ and anhydrous $AlCl_3$ in THF have shown that the scope of the method can be greatly broadened by changing the acidic catalyst to that formed in situ from anhydrous $AlCl_3$ and H_2O in 3:1 ratio.

3. Experimental

3.1. General methods

Trimethylaminoborane and anhyd $AlCl_3$ were purchased from Fluka. THF was always freshly distilled from dark-blue Na–Ph_2CO. Column chromatography was performed on silica gel 60 (Fluka, 70–230 mesh), and TLC was performed on silica gel 60 F_{254} (E. Merck, Darmstadt, Germany). Optical rotations were measured with JASCO DIP-360 digital polarimeter at 26–30 °C. NMR spectra were recorded at 27 °C with Bruker DRX-500 instrument (500 MHz for ^1H and 125 MHz for ^{13}C) using Me_4Si as internal standard, assignments were aided by APT, $^1H-^1H$, and $^1H-^{13}C$ correlation spectroscopies. Melting points were determined with a Kofler apparatus and are uncorrected.

3.2. Procedure A

$Me_3N{\cdot}BH_3$ (292 mg, 4 mmol) is added with stirring under Ar to a solution of benzylidene acetal (1 mmol) in abs THF (20 mL), followed by anhyd $AlCl_3$ (800 mg, 6 mmol) and the reaction mixture is stirred at rt for the time period shown in the Table 1. The reaction is terminated by addition of water (10 mL) followed by 1 M aq HCl (10 mL) and the mixture is extracted with EtOAc (3 × 20 mL), the extracts are washed with brine, dried, and concentrated. Chromatography of the residue on a column of silica gel (50 g) by gradient elution with the solvent system in which the R_f value is specified gives the product(s) in the yield(s) shown in the Table 1.

3.3. Procedure B

$Me_3N{\cdot}BH_3$ (292 mg, 4 mmol) is added with stirring under Ar to a solution of benzylidene acetal (1 mmol) in abs THF (20 mL), followed by anhyd $AlCl_3$ (800 mg, 6 mmol). After the dissolution of the reagents, H_2O (0.036 mL, 2 mmol) is added dropwise and stirring is continued at rt for the time period shown in the Table 1 until the complete consumption of the starting acetal (TLC control). Workup of the reaction mixture as in Section 3.2 gives the product(s) in the yield(s) shown in the Table 1.

3.4. Ethyl 3,6-di-*O*-benzyl-2-deoxy-1-thio-2-trichloroacetamido-β-D-glucopyranoside (3)

R_f 0.33 (4:1 toluene–EtOAc); $[\alpha]_D$ −9° (*c* 1, $CHCl_3$); NMR ($CDCl_3$): ^1H, see Table 2 for carbohydrate ring protons; δ 7.42–7.31 (m, 10 H, Ph), 6.82 (d, 1 H, $J_{N-H,2}$ 8 Hz, N–H), 4.79 (s, 2 H, $PhCH_2$), 4.62 (d, 1 H, *J* 12.1 Hz, $PhCH_2$), 4.55 (d, 1 H, $PhCH_2$), 2.89 (broad s, 1 H, OH), 2.71 (m, 2 H, S–CH_2), 1.37 (t, 3 H, *J* 7.5 Hz, S–CH_2CH_3); ^{13}C, see Table 2 for carbohydrate ring carbons; δ 161.8 (N–*C*(O)CCl_3), 137.8, 137.4 (2 *ipso* Ph), 128.6–127.8 (Ph), 92.4 (CCl_3), 74.8 ($PhCH_2$), 73.8 ($PhCH_2$), 24.4 (S–CH_2), 15.1 (S–CH_2CH_3). Anal. Calcd for $C_{24}H_{28}Cl_3NO_6S$: C, 52.52; H, 5.14; Cl, 19.38; N, 2.55; S, 5.84. Found: C, 52.49; H, 5.03; Cl, 18.99; N, 2.64; S, 5.71.

3.5. 3-Trifluoroacetamidopropyl 2-acetamido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (4)

R_f 0.3 (3:2 toluene–acetone); $[\alpha]_D$ −12° (*c* 1, acetone); NMR (acetone-d_6): ^1H, see Table 2 for carbohydrate ring protons; δ 7.35–7.18 (m, 10 H, Ph), 4.83 (d, 1 H, *J* 11.6 Hz, $PhCH_2$), 4.72 (d, 1 H, $PhCH_2$), 4.59 (m, 4 H, H-1, 2 $PhCH_2$, HNC(O)CF_3), 3.87 (m, 2 H, OCH_2-$(CH_2)_2$NHC(O)CF_3, H-6a), 3.58 (m, 2 H, H-4, OCH_2-$(CH_2)_2$NHC(O)CF_3,), 3.48 (m, 2 H, H-5, O$(CH_2)_2CH_2$-NHC(O)CF_3), 3.32 (m, 1 H, O$(CH_2)_2CH_2$NHC-(O)CF_3), 1.89 (s, 3 H, N–Ac), 1.81 (m, 2 H, OCH_2CH_2-CH_2); ^{13}C, see Table 2 for carbohydrate ring carbons; δ 170.8 (N–*C*(O)CH_3), 140.5, 140.0 (2 *ipso* Bn), 129.2–128.1 (Ph), 74.9, 73.9 (2 $PhCH_2$), 66.9 (O*C*$H_2(CH_2)_2$-NHC(O)CF_3), 37.9 (*C*H_2NHC(O)CF_3), 29.6 (OCH_2-*C*H_2CH_2), 23.5 (N–C(O)*C*H_3); Anal. Calcd for $C_{27}H_{33}F_3N_2O_7$: C, 58.48; H, 6.00; N, 5.05. Found: C, 58.33; H, 5.92; N, 4.88.

3.6. Ethyl 2,3-di-*O*-benzoyl-6-*O*-benzyl-1-thio-β-D-galactopyranoside (9)

R_f 0.48 (6:1 toluene–EtOAc); $[\alpha]_D$ 58° (*c* 1, EtOAc); mp 97–99 °C (from Et_2O–petroleum ether); lit.[11] $[\alpha]_D$ 69° (*c* 0.5, $CHCl_3$); mp 98–99 °C; NMR ($CDCl_3$): ^1H, see Table 2 for carbohydrate ring protons; δ 7.98 (d, 4 H, *J* 7.5 Hz, 4 ortho protons of 2 Bz), 7.55–7.31 (m, 11 H, Ph), 4.61 (s, 2 H, $PhCH_2$), 2.73 (m, 3 H, S–CH_2, OH), 1.31 (t, 3 H, *J* 7 Hz, S–CH_2CH_3). Anal. Calcd for $C_{29}H_{30}O_7S$: C, 66.65; H, 5.79. Found: C, 66.78; H, 5.87.

Table 2
Chemical shifts (δ, ppm) and coupling constants (J, Hz) for the carbohydrate ring protons and carbons in the ^{1}H and ^{13}C NMR spectra of compounds **3**, **4**, **9–13**, **15**, **17**, **19–22** in the solvent specified

Compound (solvent)		Unit	H-1 ($J_{1,2}$)	C-1	H-2 ($J_{2,3}$)	C-2	H-3 ($J_{3,4}$)	C-3	H-4 ($J_{4,5}$)	C-4	H-5 ($J_{5,6a}$)	C-5	H-6a ($J_{6a,6b}$)	H-6b ($J_{6b,5}$)	C-6
3	($CDCl_3$)		4.92 (10)	82.7	3.67 (8.8)	56.9	3.90 (9.4)	81.2	3.76	73.5	3.56	77.7	3.69–3.82		70.7
4	(acetone-d_6)		4.59 (8.9)	102.4	3.79 (10.2)	55.8	3.66 (10.2)	83.8	3.58	72.2	3.49 (1.6)	76.8	3.85 (10.8)	3.70 (5.8)	70.9
9	($CDCl_3$)		4.71 (10)		5.85 (9.9)		5.35 (3)		4.45 (0)		3.85		3.89	3.84	
10	($CDCl_3$)		4.50 (8)	100.1	5.31 (10.5)	69.4	4.94 (3.2)	73.5	4.14 (0)	68.0	3.69	73.1	3.79–3.81		69.1
11	($CDCl_3$)		4.43 (9.7)	86.5	4.07 (9.4)	67.5	5.09 (2.9)	76.9	4.27 (0)	68.1	3.75	76.8	3.79–3.71		69.4
12	($CDCl_3$)		4.31 (9.6)	86.3	3.66 (9.5)	70.5	3.78 (3)	73.9	5.57 (0)	70.8	3.80 (6.2)	76.5	3.51 (9.4)	3.48 (6.6)	68.4
13	($CDCl_3$)		4.23 (9.6)	86.1	3.65	70.3	3.49 (1)	74.9	3.92 (0)	69.5	3.54	77.5	3.68–3.59		69.6
15	($CDCl_3$)	GlcN	5.04 (10)	82.6	3.72 (9.4)	56.4	4.22 (9.4)	82.6	3.70	70.5	3.63 (2.7)	78.7	3.85 (10.7)	3.80 (5.09)	69.8
		Fuc	5.26 (3.5)	97.5	4.18 (10.5)	72.7	5.74 (3)	70.5	5.66 (0)	72.1	4.64 (6.5)	66.4	1.21		16.0
17	($CDCl_3$)	Glc	4.73 (7.8)	101.0	5.48 (9)	71.6	5.75 (7.4)	72.6	4.16 (8)	75.4	3.77 (5)	73.2	4.49	4.47 (5)	62.4
		Gal	4.65 (7.9)	100.9	5.55	72.0	4.15 (3.5)	76.0	5.64 (0)	69.7	3.71	72.0	3.93	3.24	62.1
		GlcN	5.16 (7.9)	98.2	3.24 (9)	58.1	4.14 (9)	80.8	3.49	70.1	3.47	74.4	3.67–3.73		69.6
		Fuc	5.02 (3.5)	97.4	4.04 (8)	72.5	5.59	70.5	5.58	71.7	4.42 (6.4)	66.3	1.09		16.0
19	(endo) ($CDCl_3$)		4.57 (9.6)	83.9	3.59 (6.4)	79.3	4.43 (6.1)	79.2	4.35 (1)	76.3	4.05 (5.4)	75.6	3.93 (10.2)	3.89 (6.9)	69.5
20	(exo) ($CDCl_3$)		4.58 (9.3)	83.7	3.66 (6.5)	76.4	4.60 (5.6)	80.3	4.31 (1)	74.1	3.96 (5.9)	76.0	3.87 (0)	3.87 (5.8)	69.8
21	($CDCl_3$)		4.45 (9.5)	85.1	3.61 (9.3)	79.3	3.71 (3)	75.6	3.93 (0)	76.2	3.67	77.3	3.70–3.65		68.7
22	($CDCl_3$)		4.47 (9.7)	85.1	3.72 (9.3)	77.0	3.58 (3)	82.5	4.13 (0)	66.9	3.60 (6.8)	77.9	3.82 (9.6)	3.78 (6.8)	69.4

3.7. Allyl 2,3-di-*O*-acetyl-6-*O*-benzyl-β-D-galactopyranoside (10)

R_f 0.28 (3:1 toluene–EtOAc); $[\alpha]_D$ −1° (*c* 1, EtOAc); NMR ($CDCl_3$): ^1H, see Table 2 for carbohydrate ring protons; δ 7.37–7.29 (m, 5 H, Ph), 5.86 (m, 1 H, $OCH_2CH{=}CH_2$), 5.26 (dd, 1 H, J_{trans} 17.1 Hz, J_{gem} 1 Hz, $OCH_2CH{=}CH_2$), 5.17 (dd, 1 H, J_{cis} 10.6 Hz, $OCH_2CH{=}CH_2$), 4.36 (dd, 1 H, J_{gem} 13.3 Hz, J_{vic} 4.9 Hz, $OCH_2CH{=}CH_2$), 4.10 (dd, 1 H, J_{vic} 6.2 Hz, $OCH_2CH{=}CH_2$), 2.69 (broad s, OH), 2.11, 2.06 (2 s, 3 H each, 2 $OC(O)CH_3$); ^{13}C, see Table 2 for carbohydrate ring carbons; δ 170.3, 169.6 (2 $OC(O)CH_3$), 137.6 (*ipso* Ph), 133.6 ($OCH_2CH{=}CH_2$), 128.5–127.7 (Ph), 117.3 ($OCH_2CH{=}CH_2$), 73.7 ($PhCH_2$), 69.7 ($OCH_2CH{=}CH_2$), 20.9, 20.8 (2 $OC(O)CH_3$). Anal. Calcd for $C_{20}H_{26}O_8$: C, 60.90; H, 6.64. Found: C, 60.89; H, 7.18.

3.8. Ethyl 3-*O*-benzoyl-6-*O*-benzyl-1-thio-β-D-galactopyranoside (11)

R_f 0.42 (4:1 toluene–acetone); $[\alpha]_D$ 9° (*c* 1, EtOAc); NMR ($CDCl_3$): ^1H, see Table 2 for carbohydrate ring protons; δ 8.09 (d, 2 H, *J* 7.2 Hz, ortho protons of Bz), 7.59–7.22 (m, 8 H, Ph),4.57 (s, 2 H, $PhCH_2$), 2.95 (broad s, 2 H, 2 OH), 2.74 (m, 2 H, $S–CH_2$), 1.31 (t, 3 H, *J* 7.4 Hz, $S–CH_2CH_3$); ^{13}C, see Table 2 for carbohydrate ring carbons; δ 166.3 (PhC(O)O), 137.7 (*ipso* Ph), 133.3, 129.9–127.8 (Ph), 73.4 ($PhCH_2$), 24.3 ($S–CH_2$), 15.2 ($S–CH_2CH_3$). Anal. Calcd for $C_{22}H_{26}O_6S$: C, 63.14; H, 6.26. Found: C, 63.11; H, 6.28.

3.9. Ethyl 4-*O*-benzoyl-6-*O*-benzyl-1-thio-β-D-galactopyranoside (12)

R_f 0.63 (1:1 toluene–acetone); $[\alpha]_D$ 7° (*c* 1, EtOAc); NMR ($CDCl_3$): ^1H, see Table 2 for carbohydrate ring protons; δ 8.07 (d, 2 H, *J* 7.4 Hz, ortho protons of Bz), 7.56 (t, 1 H, *J* 7.3 Hz, para proton of Bz), 7.43 (t, 1 H, *J* 7.7 Hz, meta protons of Bz), 7.29–7.15 (m, 5 H, Bn), 4.41 and 4.30 (2 d, 1 H each, *J* 11.8 Hz, $PhCH_2$), 3.18 (s, 1 H, 3-OH), 2.91 (s, 1 H, 2-OH), 2.67 (m, 2 H, $S–CH_2$), 1.23 (t, 3 H, *J* 7.4 Hz, $S–CH_2CH_3$); ^{13}C, see Table 2 for carbohydrate ring carbons; δ 166.6 (PhC(O)O), 137.7 (*ipso* Ph), 133.4, 130.2–127.8 (Ph), 73.6 ($PhCH_2$), 24.7 ($S–CH_2$), 15.4 ($S–CH_2CH_3$). Anal. Calcd for $C_{22}H_{26}O_6S$: C, 63.14; H, 6.26. Found: C, 63.15; H, 6.27.

3.10. Ethyl 6-*O*-benzyl-1-thio-β-D-galactopyranoside (13)

R_f 0.31 (1:1 toluene–acetone); $[\alpha]_D$ −25° (*c* 1, EtOAc); NMR ($CDCl_3$): ^1H, see Table 2 for carbohydrate ring protons; δ 7.37–7.22 (m, 5 H, Ph), 4.46 (s, 2 H, $PhCH_2$), 4.32 (s, 1 H, 3-OH), 3.83 (s, 1 H, 2-OH), 3.61 (s, 1 H, 4-OH), 2.62 (m, 2 H, $S–CH_2$), 1.15 (t, 3 H, *J* 7.1 Hz, $S–CH_2CH_3$); ^{13}C, see Table 2 for carbohydrate ring carbons; δ 138.0 (*ipso* Ph), 128.5 and 127.8 (Ph), 73.5 ($PhCH_2$), 24.7 ($S–CH_2$), 15.3 ($S–CH_2CH_3$). Anal. Calcd for $C_{15}H_{22}O_5S$: C, 57.30; H, 7.05. Found: C, 57.24; H, 7.09.

3.11. Ethyl *O*-(3,4-di-*O*-benzoyl-2-*O*-benzyl-α-L-fucopyranosyl)-(1→3)-6-*O*-benzyl-2-deoxy-1-thio-2-trichloroacetamido-β-D-glucopyranoside (15)

R_f 0.28 (4:1 toluene–EtOAc); $[\alpha]_D$ −118° (*c* 1, EtOAc); NMR ($CDCl_3$): ^1H, see Table 2 for carbohydrate ring protons; δ 7.93, 7.78 (2 d, 2 H each, *J* 7.7 Hz, ortho protons of 2 Bz), 7.65–7. 18 (m, 16 H, Ph), 7.30 (d, 1 H, $J_{N–H,2}$ 9 Hz, N–H), 4.61–4.70 (m, 5 H, 2 $PhCH_2$, H-5Fuc), 4.10 (broad s, 1 H, OH), 2.77 (m, 2 H, $S–CH_2$), 1.30 (t, 3 H, *J* 7.4 Hz, $S–CH_2CH_3$); ^{13}C, see Table 2 for carbohydrate ring carbons; δ 73.6 ($PhCH_2$), 73.2 ($PhCH_2$), 24.6 ($S–CH_2$), 15.1 ($S–CH_2CH_3$). Anal. Calcd for $C_{44}H_{46}Cl_3NO_{11}S$: C, 58.50; H, 5.13; N, 1.55. Found: C, 58.39; H, 5.08; N, 1.75.

3.12. 2-Azidoethyl *O*-(3,4-di-*O*-benzoyl-2-*O*-benzyl-α-L-fucopyranosyl)-(1→3)-*O*-(6-*O*-benzyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranosyl)-(1→3)-*O*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (17)

R_f 0.45 (5:1 toluene–EtOAc); $[\alpha]_D$ −45° (c 1, EtOAc); NMR ($CDCl_3$): ^1H, see Table 2 for carbohydrate ring protons; δ 8.21–7.70 (8 d, 2 H each, *J* 7.6 Hz, ortho protons of 8 Bz), 7.60–6.88 (m, 35 H, Ph, N–H), 4.50–4.46 (m, 4 H, 2 $PhCH_2$), 3.94, 3.63 (2 m, 1 H each, $OCH_2CH_2N_3$), 3.37 (m, 1 H, CH_2N_3), 3.24 (m, 2 H, H-6b^{Gal}, CH_2N_3), 1.91 (s, 1 H, OH); ^{13}C, see Table 2 for carbohydrate ring carbons; δ 165.8–164.6 (PhCO), 161.6 (Cl_3CCO), 138.4 (*ipso* Bn), 137.8 (*ipso* Bn), 133.3–127.5 (Ph), 73.4 ($PhCH_2$), 73.1 ($PhCH_2$), 68.3 ($OCH_2CH_2N_3$), 50.5 (CH_2N_3). Anal. Calcd for $C_{98}H_{89}Cl_3N_4O_{28}$: C, 62.71; H, 4.78; N, 2.98. Found: C, 62.95; H, 4.92; N, 2.76.

3.13. Ethyl 2,6-di-*O*-benzyl-3,4-*O*-*endo*-benzylidene-1-thio-β-D-galactopyranoside (19) and ethyl 2,6-di-*O*-benzyl-3,4-*O*-*exo*-benzylidene-1-thio-β-D-galactopyranoside (20)

A solution of **18** [15] (1.43 g, 3.54 mmol), *p*-TsOH monohydrate (215 mg, 1.13 mmol), and $PhCH(OMe)_2$ (2.6 mL, 17.1 mmol) in abs THF (37 mL) was stirred for 12 h at rt, Et_3N (0.2 mL) was added, and the reaction mixture was concentrated. Chromatography (petroleum ether → 3:2 petroleum ether–Et_2O) of the residue on a column of silica gel afforded *endo*-acetal **19** (1.4 g, 80%) and *exo*-acetal **20** (140 mg, 8%).

Compound **19**: R_f 0.37 (3:2 petroleum ether–Et_2O); $[\alpha]_D$ −20° (*c* 1, EtOAc); NMR ($CDCl_3$): ^1H, see Table 2 for carbohydrate ring protons; δ 7.45–7.28 (m, 15 H, Ph), 5.98 (s, 1 H, PhCH), 4.82 and 4.74 (2 d, 1 H each, *J* 11.4 Hz, $PhCH_2$), 4.68 and 4.62 (2 d, 1 H each, *J* 11.9 Hz, $PhCH_2$), 2.71 (m, 2 H, S–CH_2), 1.37 (t, 3 H, *J* 6.5 Hz, S–CH_2CH_3); ^{13}C, see Table 2 for carbohydrate ring carbons; δ 138.2, 137.7, 137.3 (3 *ipso* Ph), 129.0–128.0 (Ph), 104.7 (PhCH), 73.6, 73.3 (2 $PhCH_2$), 24.6 (S–CH_2), 15.0 (S–CH_2CH_3); Anal. Calcd for $C_{29}H_{32}O_5S$: C, 70.71; H, 6.55. Found: C, 70.89; H, 6.58.

Compound **20**: R_f 0.39 (3:2 petroleum ether–Et_2O); $[\alpha]_D$ −5° (*c* 1, EtOAc); NMR ($CDCl_3$): ^1H, see Table 2 for carbohydrate ring protons; δ 7.51–7.30 (m, 15 H, Ph), 6.07 (s, 1 H, PhCH), 4.96 and 4.90 (2 d, 1 H each, *J* 11.5 Hz, $PhCH_2$), 4.67 and 4.59 (2 d, 1 H each, *J* 11.9 Hz, $PhCH_2$), 2.72 (m, 2 H, S–CH_2), 1.40 (t, 3 H, *J* 6.8 Hz, S–CH_2CH_3); ^{13}C, see Table 2 for carbohydrate ring carbons; δ 138.6, 138.2, 137.6 (3 *ipso* Ph), 129.2–126.9 (Ph), 103.5 (PhCH), 73.6, 73.5 (2 $PhCH_2$), 24.8 (S–CH_2), 15.0 (S–CH_2CH_3); Anal. Calcd for $C_{29}H_{32}O_5S$: C, 70.71; H, 6.55. Found: C, 70.83; H, 6.49.

3.14. Ethyl 2,4,6-tri-*O*-benzyl-1-thio-β-D-galactopyranoside (21)

R_f 0.38 (1:1 petroleum ether–Et_2O); $[\alpha]_D$ −9° (*c* 1, EtOAc); NMR ($CDCl_3$): ^1H, see Table 2 for carbohydrate ring protons; δ 7.49–7.31 (m, 15 H, Ph), 4.98 and 4.73 (2 d, 1 H each, *J* 10.9 Hz, $PhCH_2$), 4.78 and 4.70 (2 d, 1 H each, *J* 12.1 Hz, $PhCH_2$), 4.56 and 4.49 (2 d, 1 H each, *J* 11.8 Hz, $PhCH_2$), 2.70 (m, 2 H, S–CH_2), 2.33 (broad s, 1 H, OH), 1.35 (t, 3 H, *J* 7 Hz, S–CH_2CH_3); ^{13}C, see Table 2 for carbohydrate ring carbons; δ 138.2, 137.8, 137.7 (3 *ipso* Ph), 128.5–127.7 (Ph), 75.3, 75.0, 73.5 (3 $PhCH_2$), 24.9 (S–CH_2), 15.1 (S–CH_2CH_3). Anal. Calcd for $C_{29}H_{34}O_5S$: C, 70.42; H, 6.93. Found: C, 70.47; H, 6.99.

3.15. Ethyl 2,3,6-tri-*O*-benzyl-1-thio-β-D-galactopyranoside (22)

R_f 0.38 (1:1 petroleum ether–Et_2O); $[\alpha]_D$ 2° (*c* 1, EtOAc); NMR ($CDCl_3$): ^1H, see Table 2 for carbohydrate ring protons; δ 7.49–7.29 (m, 15 H, Ph), 4.92 and 4.81 (2 d, 1 H each, *J* 10.3 Hz, $PhCH_2$), 4.77 and 4.72 (2 d, 1 H each, *J* 11.6 Hz, $PhCH_2$), 4.61 (s, 2 H, $PhCH_2$), 2.70 (m, 2 H, S–CH_2), 2.61 (broad s, 1 H, OH), 1.35 (t, 3 H, *J* 7 Hz, S–CH_2CH_3); ^{13}C, see Table 2 for carbohydrate ring carbons; δ 138.2, 137.9, 137.8 (3 *ipso* Ph), 128.5–127.8 (Ph), 75.9, 73.8, 72.1 (3 $PhCH_2$), 24.8 (S–CH_2), 15.2 (S–CH_2CH_3). Anal. Calcd for $C_{29}H_{34}O_5S$: C, 70.42; H, 6.93. Found: C, 70.54; H, 7.05.

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