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Catalyst-free regioselective acetylation of primary hydroxy groups in partially protected and unprotected thioglycosides with acetic acid†

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Highly regioselective acetylation of primary hydroxy groups in thioglycoside derivatives with *gluco*- and *galacto*-configurations was achieved by treatment with aqueous or anhydrous acetic acid (60–100% AcOH) at elevated temperatures (80–118 °C), avoiding complex, costly and time-consuming manipulations with protective groups. Acetylation of both 4,6-*O*-benzylidene acetals and the corresponding diols as well as the unprotected tetraol with AcOH was shown to lead selectively to formation of 6-*O*-acetyl derivatives. For example, the treatment of phenyl 1-thio-β-D-glucopyranoside with anhydrous AcOH at 80 °C for 24 h gave the corresponding 6-*O*-acetylated derivative in 47% yield (71% based on the reacted starting material) and unreacted starting tetraol in 34% yield, which can easily be recovered by silica gel chromatography and reused in further acetylation.

Introduction

Regioselective synthesis is a prominent challenge in organic chemistry and especially in carbohydrate chemistry since carbohydrates contain several hydroxyl groups of similar reactivity.[1–5] Although primary hydroxy groups are generally considered more reactive in esterification reaction,[6,7] regioselective acetylation of primary hydroxy groups in carbohydrates is surprisingly complicated[4] and is usually conducted using specific catalysts and conditions.[8,9] Disadvantages of many known acetylation methods are related to the use of environmentally toxic and expensive reagents.

Typical examples of selective 6-*O*-acetylation in monosaccharides include the use of EtOAc in combination with acidic[10,11] or basic[12,13] catalysis, vinyl acetate and germanium compounds as catalysts,[14] acetic acid (AcOH) and uronium-based coupling agents,[15] 1-acetyloxybenzotriazole[16,17] as well as acetyl chloride or acetic anhydride in the presence of bases,[18–22] iodine,[23] Al_2O_3 (ref. 24) or 4 Å molecular sieves.[25] Reactions employing organotin[4,26] and organosilicon[27] derivatives were used for regioselective acetylation of carbohydrates. It was noted that the selectivity of acetylation is dramatically influenced by the nature of counter-ion of acetylating agent and reaction conditions.[28] Based on these findings, regioselective acetylation of diols and polyols using catalytic amounts of acetate ion has been developed.[29] Lewis acid catalysed removal of 6-*O*-protective group in per-*O*-trimethylsilylated[30,31] or benzylated[32,33] compounds with subsequent one-pot acetylation of monosaccharides affording 6-*O*-acetylated fully protected sugars has been described. A method involving *N*-acetylthiazolidine-2-thione[34] as acetylation agent has also been developed. 1-Acetylimidazole was used for selective acetylation of the primary hydroxy groups in derivatives of methyl glycosides in 1,2-dichloroethane at 80 °C (ref. 35) or, more recently, in water in the presence of tetramethylammonium hydroxide (TMAH).[36] Highly selective but less accessible chiral organocatalysts[37,38] for direct acetylation have also been proposed. Recently, 6-*O*-acetylation by migration of acetyl group from *O*-2 has been developed.[39] Enzymatic acetylation[40–42] has also been applied for the selective introduction of acetyl groups at primary hydroxy groups of sugars.

Acetylation at O-6 is common for carbohydrate low-molecular weight metabolites in plants.[43–47] Bacterial polysaccharides often contain 6-*O*-acetyl groups, which play a complex role in the functional immune response.[48–51] Hence, the development of ways for selective acetylation of unprotected and partially protected carbohydrates would contribute greatly to the study of naturally occurring carbohydrate molecules.

The non-catalysed (auto-catalysed) acetylation of simple alcohols is well-known.[52–59] It has been extensively studied for industrial purposes like reactive distillation,[60,61] which is used for esterification or for recovery of dilute acetic acid from wastewater.[62–65] However, only few examples of the use of this

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Table 1 Acidic conditions used for removal of benzylidene acetal and acetylation of thioglycoside diols and tetraol[a]

Method	Concentration of AcOH (%, v/v)	Temperature[b] (°C)	Time (h)
A	60	80	24
B	80	80	24
C	100	80	24
D	100	100	24
E	100	130[c,d]	24
F	100	130[c,d]	2.5
G	100	130[c,d]	2
H	60	117[c,e]	24
I	80	117[c,f]	24

[a] Aqueous or anhydrous AcOH, heating at indicated temperature. [b] Bath temperature. [c] Reflux. [d] Bp 118 °C. [e] Bp 102 °C. [f] Bp 105 °C.

reaction for acetylation of carbohydrates are known. The primary hydroxy group of several carbohydrates was selectively esterified by treatment with 50% AcOH at 100 °C for 24 h. For example, after removal of excess of AcOH *in vacuo* the syrup containing unchanged D-glucose, 6-*O*-acetyl-D-glucose, and a di-*O*-acetyl-D-glucose was obtained.[66] The preparation of 6-*O*-acetyl-D-glucose by esterification of D-glucose was also performed by treatment with 75% AcOH at 100 °C for 8 h.[67] Preparative yields of 6-*O*-acetylated products were moderate (10–30%).

Herein, we describe a method for regioselective acetylation of primary hydroxyl group in glycosides using acetic acid as single reagent in the absence of added catalyst. We focused on regioselective acetylation of thioglycoside diols and tetraol with 60–100% (v/v) AcOH using Methods **A–I** (Table 1).

Results and discussion

Cleavage of 4,6-*O*-benzylidene group by aqueous AcOH with concomitant acetylation

Selective cleavage of 4,6-*O*-benzylidene group[68,69] in various carbohydrate derivatives is commonly achieved by acidic hydrolysis[70] (heating with aq AcOH,[71] treatment with trifluoroacetic acid (TFA) in CH_2Cl_2–ethylene glycol[72] or aq TFA in CH_2Cl_2 (ref. 73 and 74)), which leads to formation of the corresponding 4,6-diol. This procedure is considered to be robust and efficient and is widely used in protective group strategies.[1,75]

We have recently reported that the cleavage of 4,6-*O*-benzylidene group in derivatives of β-configured ethyl 1-thio-β-D-galactopyranoside with silyl (TIPS or TBDPS) groups at O-2 and O-3 with 80% aq AcOH (80 °C, 1 h) gave the expected 4,6-diols in 68–75% yields, while treatment with aq TFA in CH_2Cl_2 led to pyranose ring contraction.[76] To study the effect of anomeric configuration on the result of treatment of benzylidene acetals with acids, we synthesised ethyl 4,6-*O*-benzylidene-1-thio-α-D-galactopyranoside (**1**) and the corresponding 2,3-*O*-TIPS (**2**) and TBDPS (**3**) derivatives, starting from the known[77] ethyl 1-thio-α-D-galactopyranoside.

Surprisingly, the reaction of α-configured ethyl 4,6-*O*-benzylidene-2,3-bis-*O*-triisopropylsilyl-1-thio-α-D-galactopyranoside (**2**) with 80% aq AcOH under similar conditions was not complete in 1–2 h. After 24 h of treatment with 80% aq AcOH at 80 °C (method **B**, Table 1, Fig. 1) the formation of the expected diol **4** (19%) was accompanied by considerable amounts (22%) of 6-*O*-acetylated product **5**. Besides, the minor 4-*O*-acetylated product **7** and 6-*O*-acetylated thioglycoside **6** with a single TIPS group at O-2 were also obtained.

Unlike the cleavage of 4,6-*O*-benzylidene group in TIPS-containing derivative **2**, the treatment of thiogalactopyranoside

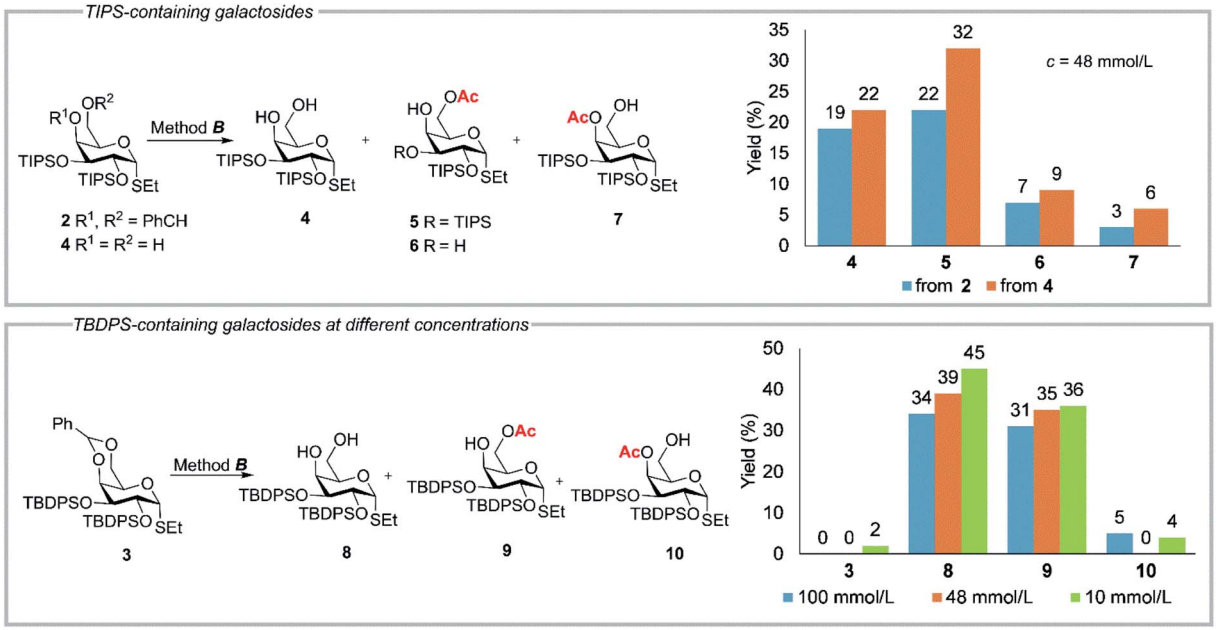

Fig. 1 Results of acetylation of TIPS-containing compounds **2**, **4** and TBDPS-containing compound **3** according to method **B**. TIPS = $(i\text{-Pr})_3Si$. TBDPS = $t\text{-BuPh}_2Si$. See also Tables 1S and 2S in ESI.†

3 with TBDPS groups at O-2 and O-3 under identical conditions (according to method **B**) (Fig. 1) at the same concentration (c = 48 mmol L^{-1}) gave diol **8** and 6-*O*-acetylated product **9** in 39 and 35% yields, respectively (Fig. 1). Apparently, the TBDPS groups are more stable under acidic conditions than the TIPS groups. A study of influence of the concentration on the outcome of acetylation revealed an additional formation of a minor amount of 4-*O*-acetylated product **10** at higher and lower concentrations (Fig. 1).

To check if the preferential formation of the product of *O*-acetylation of primary hydroxy group is related to limited solubility of extremely hydrophobic silyl-containing ethyl thio-α-D-galactopyranosides **2–4** we tested the known ethyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-galactopyranoside (**11**)[71] with less hydrophobic benzyl groups at O-2 and O-3 in the reaction with acetic acid according to method **B** (Table 1) at two similar yet different concentrations (c = 58 and 68 mmol L^{-1}) (Fig. 2). The yield of 6-*O*-acetylated thiogalactoside **14** was 41 and 43%, respectively. Diol **12** (ref. 71) was isolated in 36 and 30% yields, when the reaction was performed at 58 and 68 mmol L^{-1} of **11**, respectively (Fig. 2). Besides, 4-*O*-acetylated thiogalactoside **13** was also obtained.

Similar results were obtained in *gluco*-series. Thus, the cleavage of benzylidene group in phenyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside (**15**) with 80% aq AcOH at 80 °C under conditions of method **B** (Table 1) gave diol **16** and 6-*O*-acetylated product **17** in 43 and 45% yields, respectively (Fig. 3). 4-*O*-Acetylated thiogalactoside **18** was also isolated in 6% yield. A decrease in AcOH concentration to 60% led to the expected decrease in the proportion of 6-*O*-acetylated product **17**, which was obtained in 27% yield (Fig. 3) under conditions of method **A** (Table 1).

Acetylation of 4,6-diols with aqueous AcOH

Recently, the transformation of mono- and oligosaccharide 4,6-*O*-benzylidene acetals to the corresponding 6-*O*-acetyl derivatives with free 4-hydroxy group by treatment with 60% aq AcOH at 80 °C has been reported.[78] The authors emphasise that the presence of 4,6-*O*-benzylidene acetal is critical for the success of the transformation; no acetylation occurs with the corresponding 4,6-diols under identical conditions. In particular, according to the authors,[78] when diol **16** was treated with 60% aq AcOH "no primary *O*-acetylation product could be identified even after 24 h" at 80 °C (these conditions mirror conditions of method **A**, Table 1). Our data do not support these findings. In our hands, after the treatment of diol **16** with 60% aq AcOH at 80 °C according to method **A** (Fig. 3) 6-*O*-acetylated product **17** was isolated in 28% yield. Unreacted diol **16** was recovered in 51% yield. Besides, the minor amount of 4-*O*-acetylated thioglucoside **18** was isolated in 2% yield.

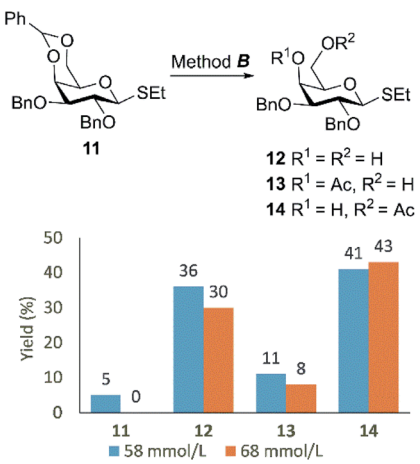

Fig. 2 The yields of products **11–14** after acetylation of compound **11** according to method **B** at different concentrations of substrate **11**. See also Table 3S in ESI.†

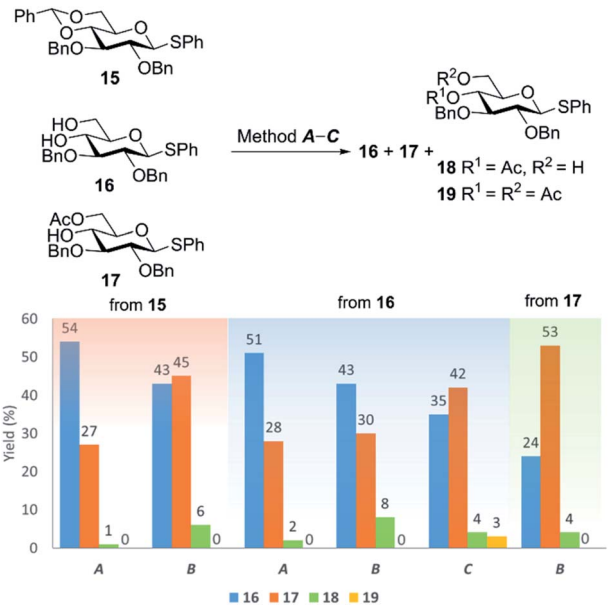

Fig. 3 The yields of products **16–19** obtained from compounds **15–17** under acetylation conditions according to methods **A–C**. Concentration of substrate (**15**, **16** or **17**) c = 20 mmol L^{-1}. See also Table 4S in ESI.†

Note that the increase in concentration of AcOH to 80% while keeping the temperature at 80 °C (method **B**) for acetylation of diol **16** with *gluco*-configuration led to comparable yield (30%) of 6-*O*-acetylated product **17** (Fig. 3). Similar results were obtained in acetylation of diol **4** with *galacto*-configuration under identical conditions (80% aq AcOH 80 °C, method **B**), which gave 6-*O*-acetylated thioglycoside **5** (32%) as well as the product with acetyl group at O-4 (**7**, 6%) and 6-*O*-acetylated thioglycoside **6** (9%) with a single TIPS group at O-2 (Fig. 1).

Esterification of alcohols with AcOH is known to be a reversible process that occurs under thermodynamic control.[52–59] Indeed, when 6-*O*-acetylated product **17** was treated under the reaction conditions (80% aq AcOH, 80 °C, 24 h; method **B**) the parent diol **16** (24%) and 4-acetate **18** (4%) were isolated from the reaction mixture in addition to the starting 6-acetate **17** (53%) (Fig. 3).

Acetylation of 4,6-diols with anhydrous AcOH

In accordance with this view on the mechanism of esterification of alcohols with aqueous AcOH,[52–59] the use of anhydrous AcOH

shifted the esterification equilibrium towards the formation of acetylated products. Thus, the treatment of *gluco*-diol **16** with anhydrous AcOH at 80 °C according to method **C** (Fig. 3) increased the yield of 6-*O*-acetylated product **17** (42%). Small amounts of 4-*O*-acetylated (**18**, 4%) and 4,6-di-*O*-acetylated (**19** (ref. 79), 3%) derivatives were also isolated. It should be noted that unreacted diol **16** (35%) can be easily recovered by silica gel chromatography and reused in further acetylation.

Thus, we demonstrated that not only 4,6-*O*-benzylidene acetals (as claimed in ref. 78) but also the corresponding 4,6-diols can form 6-*O*-acetylated thioglycosides by treatment with aqueous or anhydrous AcOH. Importantly, the regioselectivity of acetylation does not depend on configuration of monosaccharide: thioglycosides with both *gluco*- and *galacto*-configurations (with equatorial and axial 4-OH, respectively) perform equally well in the acetylation reactions.

Acetylation of tetraol with aqueous or anhydrous AcOH

The next step was to study if the found conditions for acetylation of carbohydrate diols with AcOH would be applicable for carbohydrate derivatives with larger number of hydroxyl groups.

Treatment of unprotected phenyl 1-thio-β-D-glucopyranoside (**20**)[80] with anhydrous AcOH at 80 °C for 24 h according to method **C** (Fig. 4, 5) gave the corresponding 6-*O*-acetylated derivative **21** in 47% yield and unreacted tetraol **20** in 34% yield along with minor amounts of mono- (**26**) and diacetylated derivatives **27** as well as 3,6-di-*O*-acetylated thioglycoside **22** (Fig. 4 and 5). This result is remarkable considering that the unreacted starting tetraol **20** can easily be recovered by silica gel chromatography and reused in further acetylation (thus making the yield of **21** fairly practical – 71% based on the reacted starting material). The only, although minor, drawback of this method for selective acetylation is the incomplete conversion of the starting tetraol **20** even after the long reaction time.

Increasing the reaction temperature to 100 °C (24 h, method **D**) resulted in almost complete conversion of **20** (95%) and a decrease in the yield of 6-*O*-acetylated derivative **21** to 34%. Substantial amounts of di- and triacetylated products **27** and **28** in addition to minor amounts of monoacetylated derivative **26** were formed after 24 h at 100 °C (Fig. 4 and 5).

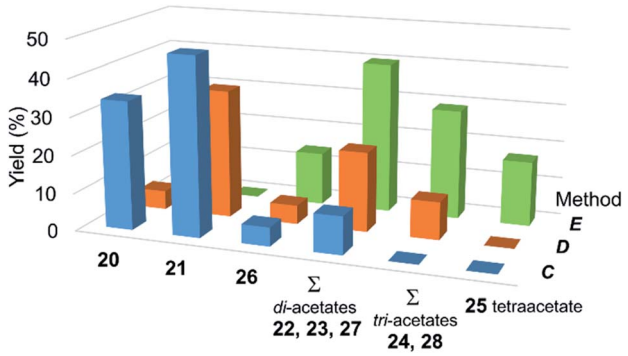

Fig. 5 The effect of temperature on selectivity of acetylation. The yields of acetylated derivatives **20**–**28** isolated after acetylation of compound **20** with anhydrous AcOH at 80, 100 and 118 °C according to methods **C**, **D**, **E**, respectively. Concentration of **20** c = 20 mmol L^{-1}. See also Table 5S in ESI.†

Reflux of tetraol **20** in more dilute AcOH solutions at *ca.* 100 °C for 24 h was not very effective either (Fig. 4). The conversion of tetraol **20** dropped to 50% in 60% AcOH (bp 102 °C, method **H**) as did the yield of 6-*O*-acetylated derivative **21** (33%). Although the yield of 6-*O*-acetylated derivative **21** somewhat increased to 42% in 80% AcOH (bp 105 °C, method **I**), the amount of recovered tetraol **20** decreased to 19%.

Further increase in reaction temperature resulted in preferential formation of di-, tri- and tetraacetylated products **22**–**28** when tetraol **20** was treated with anhydrous AcOH at reflux (bp 118 °C) for 24 h according to method **E** (Fig. 4 and 5). Importantly, neither tetraol **20** nor monoacetate **21** were detected under these conditions.

Variation of the reaction time (methods **F** and **G**) revealed that the treatment of tetraol **20** with anhydrous AcOH at reflux according to method **F** allows the preparation of the 6-*O*-acetylated derivative **21** in 49% yield, virtually identical to that achieved (47%) under conditions of method **C**, but in much shorter time (2.5 h *vs.* 24 h), albeit accompanied by a decrease in the yield of unreacted starting tetraol **20** (20%).

Our data are in qualitative agreement with the known results for the preparation of 6-*O*-acetyl-D-glucose by esterification of D-

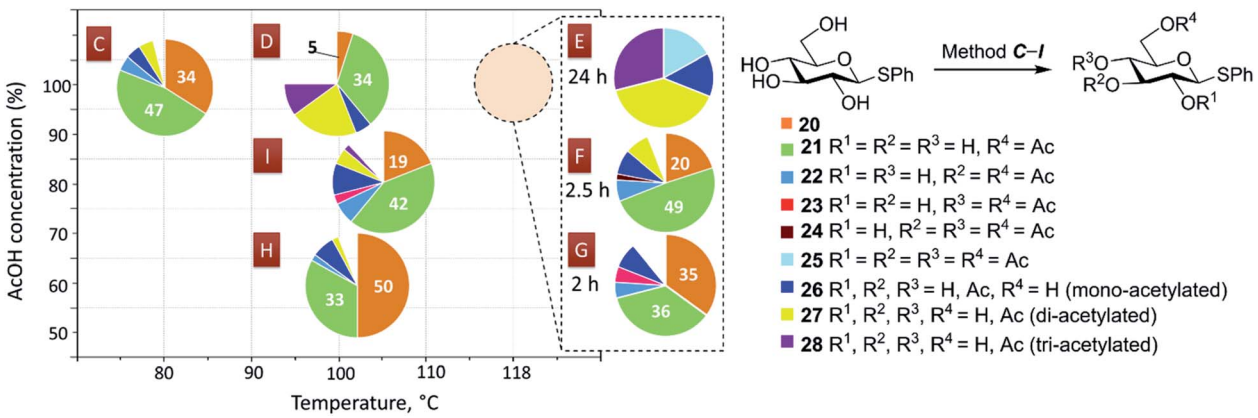

Fig. 4 The results of acetylation of compound **20** according to methods **C**–**I**. Concentration of **20** c = 20 mmol L^{-1}. See also Table 5S in ESI.†

glucose with 50–75% AcOH at 100 °C,[66,67] although the yields achieved in our work are considerably higher.

Note that the highest yields of 6-*O*-acetylated derivatives achieved by esterification of tetraol (49%), 4,6-diols (42%) or 4,6-*O*-benzylidene derivatives (45%) by aqueous or anhydrous AcOH are similar.

A possibility of esterification of carbohydrate alcohols by aqueous or anhydrous AcOH should be considered seriously as this reaction may constitute an important side process considerably diminishing the yield of the target transformation performed in the presence of AcOH.

Conclusions

We have developed an efficient and green procedure for the highly regioselective acetylation of primary hydroxy groups in thioglycosides, which was achieved by treatment with aqueous or anhydrous AcOH, avoiding complex, costly and time-consuming manipulations with protective groups. To this end, acetylation of thioglycoside derivatives with *gluco*- and *galacto*-configurations at various temperatures (80–118 °C) and concentrations of AcOH (60–100%) was studied. Acetylation of both 4,6-*O*-benzylidene acetals and the corresponding diols as well as the unprotected tetraol with AcOH was shown to lead selectively to formation of 6-*O*-acetyl derivatives. Unreacted starting polyol can easily be recovered by silica gel chromatography and reused in further acetylation, which is important from the preparative point of view.

Experimental

General procedure for deprotection of benzylidene acetals 2, 3, 11, 15 and acetylation of alcohols 4, 16, 17

To thioglycosides **2**, **3**, **4**, **11**, **15–17** (0.1–0.5 mmol) 60–100% (v/v) AcOH was added and the reaction mixture (c = 10–100 mmol L^{-1}) was stirred at T °C according to methods **A–C** (Table 1). Then the reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with satd aq $NaHCO_3$ (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL) and the combined organic extracts were filtered through a cotton wool plug, concentrated, and dried *in vacuo.* The products were purified by silica gel column chromatography in gradient of EtOAc in light petroleum (1 → 20%) for isolating of silyl (TBDPS or TIPS)-containing thioglycosides **4–10** and in gradient of EtOAc in light petroleum (5 → 60%) for isolating of benzyl-containing thioglycosides **16–19**. The yields of purified products are shown in Fig. 1–3 (see also Tables 1S–4S in ESI†). See ESI† for the characterisation data and copies of NMR spectra.

General procedure for acetylation of thioglycoside 20

To thioglycoside **20** (150 mg, 0.55 mmol) 60–100% (v/v) AcOH (27.5 mL) was added and the reaction mixture (c = 20 mmol L^{-1}) was stirred at T °C according to methods **C–I** (Table 1). Then the reaction mixture was concentrated under reduced pressure and dried *in vacuo.* The products were purified by silica gel column chromatography in gradient of EtOAc in light petroleum (5 → 60%) to afford acetylated products **21–28**. The yields of purified products are shown in Fig. 4 and 5 (see also Table 5S in ESI†). See ESI† for the characterisation data and copies of NMR spectra.

Phenyl 6-*O*-acetyl-1-thio-β-D-glucopyranoside (21)

Method **C**. Yield 47% (71% based on the reacted starting material). R_f = 0.30 (light petroleum–EtOAc 1 : 9). $[\alpha]_D^{23}$ −61.7 (c 2.0 in $CHCl_3$). ^{1}H NMR (300 MHz; CD_3OD): δ = 2.04 (s, 3H, CH_3CO), 3.22 (dd, $J_{2,3}$ = 8.5 Hz, $J_{2,1}$ = 9.7 Hz, 1H, H-2), 3.24–3.33 (m, 1H, H-4), 3.40 (dd ∼ t, J_{app} = 8.8 Hz, 1H, H-3), 3.50 (ddd, $J_{5,6b}$ = 2.2 Hz, $J_{5,6a}$ = 6.6 Hz, $J_{5,4}$ = 9.8 Hz, 1H, H-5), 4.19 (dd, $J_{6a,5}$ = 6.6 Hz, $J_{6a,6b}$ = 11.9 Hz, 1H, H-6a), 4.40 (dd, $J_{6b,5}$ = 2.2 Hz, $J_{6b,6a}$ = 11.9 Hz, 1H, H-6b), 4.59 (d, $J_{1,2}$ = 9.7 Hz, 1H, H-1), 7.19–7.38 (m, 3H, PhS (H-3, H-4, H-5)), 7.45–7.61 (m, 2H, PhS (H-2, H-6)); ^{13}C NMR (75 MHz, MeOD): δ = 20.8 ($\underline{C}H_3CO$), 64.9 (C-6), 71.4 (C-4), 73.7 (C-2), 79.0 (C-5), 79.4 (C-3), 89.0 (C-1), 128.5 (PhS (C-4)), 129.8 (PhS (C-3, C-5)), 133.0 (PhS (C-2, C-6)), 134.8 (PhS (C-1)), 172.7 (CO). HRMS (ESI): m/z calcd for $C_{14}H_{18}O_6S$ + Na^+: 337.0716 $[M + Na]^+$; found: 337.0715.

Conflicts of interest

There are no conflicts to declare.

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