

Highly efficient synthesis of 1-thioglycosides in solution and solid phase using iminophosphorane bases

Weizheng Xu, Shawn A. Springfield, John T. Koh *

The Department of Chemistry and Biochemistry, University of Delaware, Newark, DE 19716, USA

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Abstract

Disaccharides of 1-thioglycosides, an important class of glycomimics, can be synthesized by direct S-alkylation in exceptionally high yields when iminophosphorane bases are employed. The reaction conditions employed appear to be general and stereospecific. Axial and equatorial 4-triflates and primary tosylates of alkyl pyranosides provided excellent yields of thio-disaccharides without substantial elimination products. The iminophosphorane bases also proved to be useful in solid support-bound couplings of thioglycosides though with lower efficiency. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Glycomimics; Solid-phase synthesis; Thioglycosides

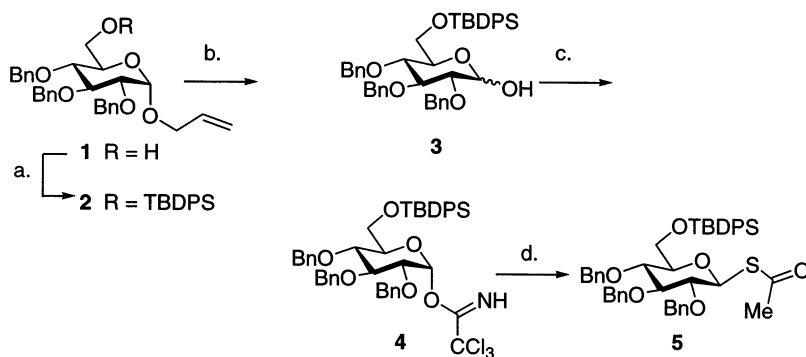
1. Introduction

Several recent reports have highlighted a renewed interest in the synthesis of 1-thioglycosides as glycomimics that have favorable chemical and biological stability [1–4]. The direct alkylation of glycosyl thiolates is a particularly attractive route to thio-oligosaccharide construction because it generally occurs with retention of anomeric configuration resulting from the observation that glycosyl thiolates do not mutarotate under basic conditions [2,5,6]. The straightforward, stereospecific construction of 1-thioglycosides from configurationally pure glycosyl thiolates, which is essentially independent of neighboring group effects, makes direct alkylation of glycosyl thiolates an attractive approach to the construction of libraries of glycomimics.

The attributes of the direct alkylation approach to thioglycoside synthesis are greatly overshadowed by the poor yields often associated with the reaction with secondary pyranoside electrophiles in solution. Relatively high yields (75%) have been obtained for the thiol-alkylation coupling of pyranosides in solution [6]. However, yields in the range of 30–60% are more common and have been shown to result from competing elimination reactions and the transesterification of *O*-acyl or *O*-benzoyl protecting groups to the anomeric thiolate [2,7–10]. One strategy has been to couple the furanose form of an electrophile, which is less likely to eliminate, and subsequently to convert it to the desired pyranoside [11]. More recently, it has been demonstrated that high yields of thio-oligosaccharides can be obtained using support-bound glycosyl thiolates where elimination products are not incorporated into the growing thio-oligosaccharide [12]. However, to obtain consistent high yields of solution-phase coupling of thioglycosides still

* Corresponding author. Tel.: +1-302-8311947.

E-mail address: johnkoh@udel.edu (J.T. Koh)



Scheme 1. (a) TBDPSCl, TEA, DMAP; (b) i. $(\text{PPh}_3)_3\text{RhCl}$, ii. $\text{I}_2/\text{pyridine}$; (c) CCl_3CN , DBU; (d) HSAc.

remains a significant challenge. This report illustrates the use of iminophosphorane bases to obtain thioglycosides by direct alkylation couplings in solution in unprecedented yields. In addition to demonstrating the efficiency of these reactions in solution, we have also demonstrated their utility in the synthesis of support-bound thioglycosides.

2. Results and discussion

Generic benzyl-protected model compounds **5** and **6** were synthesized (Scheme 1) and were used to survey a variety of commonly employed coupling conditions. Reaction of the thiolate generated from in situ deprotection of **5** with piperidine in the presence of potassium *tert*-butoxide or DBU in DMSO or HMPA afforded only low yields of the desired S-linked disaccharide **7** (Table 1, entries 1–3).

In these reactions elimination is the major competing reaction; however, the amount of elimination side products is notably less when DBU is employed as a base compared with *tert*-butoxide. These observations led us to consider the highly hindered iminophosphorane bases (Schwesinger bases) as suitable non-nucleophilic bases for this reaction [13].

The reaction yields are significantly increased when **8** is employed as a base instead of DBU or *tert*-butoxide. Our yields obtained for small-scale model reactions show excellent yields of compound **7** with almost no elimination side products, as demonstrated by high-performance liquid chromatography (HPLC) (Table 1, entry 5). This is perhaps the highest yield yet reported for the synthesis of a (1 →

4)-linked thiopyranoside by direct alkylation of glycosyl thiolates in solution. Importantly, none of the α -linked thiodisaccharide was observed in these reactions, demonstrating that these reactions are indeed stereospecific. The more basic (but less hindered) iminophosphorane bases **9** and **10** afforded only moderate to poor yields of **7** with significant elimination side products.

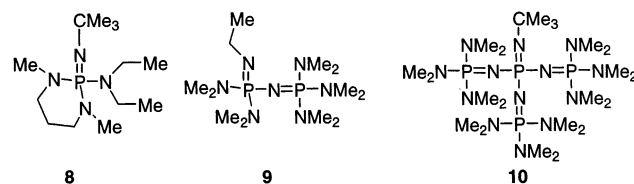
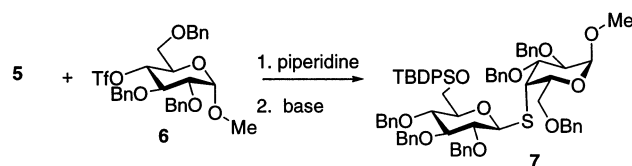
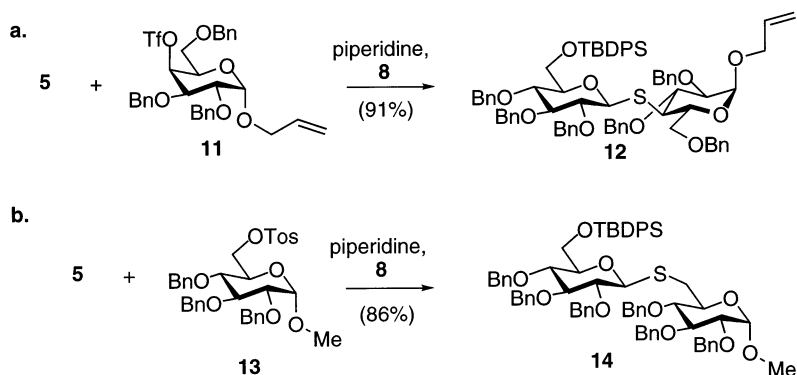


Table 1
Direct alkylation-coupling yields in solution using various bases^a

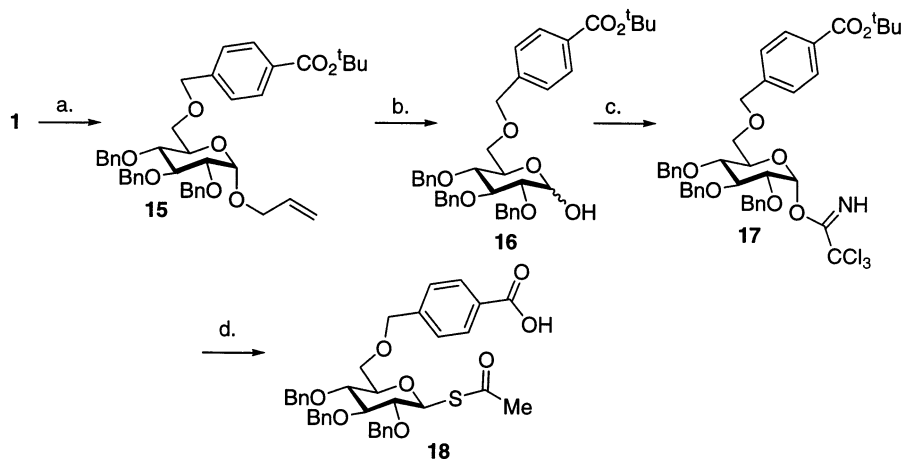


Entry	Bases	Solvent	Yield 7 (isolated) (%)
1	KO ^t Bu	Me ₂ SO	(33)
2	KO ^t Bu	HMPA	(29)
3	DBU	HMPA	(44)
4	8	Me ₂ SO	(86)
5	8	CH ₃ CN	92 (85)
6	9	CH ₃ CN	66
7	10	CH ₃ CN	44

^a Yields determined by HPLC or reported as isolated yields, (%), from 20-mg scale reactions.



Scheme 2.

Scheme 3. (a) NaH, *tert*-butyl-4-bromomethylbenzoate; (b) i. $(\text{PPh}_3)_3\text{RhCl}$, ii. $\text{I}_2/\text{pyridine}$; (c) CCl_3CN , DBU; (d) HSAc.

In addition to the equatorial triflate **6**, the axial triflate **11** and the primary tosylates **13** could also be coupled in high yield to the corresponding to (1→4)- and (1→6)-linked thiodisaccharides **12** and **14** (Scheme 2). These results illustrate that efficient thioglycoside coupling using **8** is indeed general and can potentially be used to assemble a range of thiodisaccharide structures.

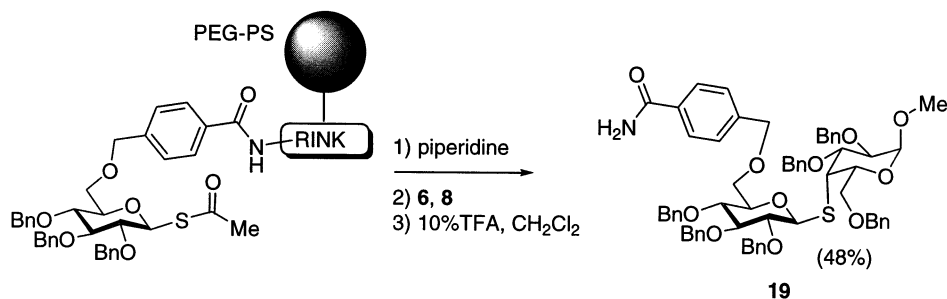
The efficiency of the iminophosphorane base-promoted alkylation in solution has led us to investigate glycosyl couplings of support-bound thiolates. The support-bound coupling of thiopyranosides by direct alkylation has recently been reported [12,14]. Compound **18** was synthesized as a model that would allow attachment of a range of standard amine-functionalized supports (Scheme 3). Compound **18** was attached to RINK-functionalized PEG-polystyrene resin (Novasyn TGR) using standard DCC coupling. The percentage loading was determined, using ninhy-

drin assay, to be greater than 97%. The support-bound thioacetate was deprotected by treatment with piperidine, washed and treated with a solution of compound **6** and **8**. The resulting product was cleaved from solid support with TFA to afford the thiodisaccharide **19** in an overall yield of 48% for the deprotection, alkylation and cleavage (Scheme 4).

The stability of **19** to the cleavage conditions of 10% TFA testifies to the unique stability of the thioglycosidic linkage. Although the overall yields are only modest, yields may be improved with the use of alternative supports. The use of iminophosphorane bases should be a notable improvement over existing methods for solution-phase couplings.

3. Experimental

General methods.—All synthetic compounds were purchased from Aldrich Chemi-



Scheme 4.

cal Company, unless otherwise noted. NMR spectra were recorded on Bruker DXR 400 and AM 250 spectrometers. Chromatography was performed using ICN SiliTech (60A) flash silica gel. HPLC analysis was performed on a Shimadzu LC-10AT with an SPD-10A UV–Vis detector using an Econosil C18/5 μ 250 \times 4.6 mm column (Alltech). Mass spectra were obtained by the University of Delaware Mass-Spect. Lab using a Micromass AutospecQ or Bruker BiflexIII MALDI-TOF spectrometer.

Allyl 2,3,4-tri-O-benzyl-6-O-tert-butylidiphenylsilyl- α -D-glucopyranoside (2).—To a solution of **1** (0.12 g, 0.24 mmol), triethylamine (30 mg, 0.30 mmol) and 4-dimethylaminopyridine (12 mg, 0.1 mmol) in 30 mL of dry CH_2Cl_2 , was added *tert*-butylchlorodiphenylsilyl (74 mg, 0.27 mmol). After 3 h at room temperature, the solution was diluted with 60 mL of CH_2Cl_2 and washed with water (60 mL), satd aq NH_4Cl (60 mL) and brine (60 mL). The organic fraction was dried over MgSO_4 and evaporated in vacuo. Flash chromatography (1:3 EtOAc–hexanes) afforded 0.17 g (0.23 mmol, 94%) of **2**. ^1H NMR (250 MHz, CDCl_3): δ 7.70–7.10 (m, 25 H), 5.93 (m, 1 H), 5.28 (dd, J 17.0, 1.6 Hz, 1 H), 5.18 (dd, J 10.0, 1.6 Hz, 1 H), 4.99 (d, J 10.7 Hz, 1 H), 4.83 (d, J 10.7 Hz, 1 H), 4.88 (d, J 10.7 Hz, 1 H), 4.85 (d, J 4.2 Hz, 1 H, H-1), 4.83 (d, J 12.0 Hz, 1 H), 4.79 (d, J 12.0 Hz, 1 H), 4.60 (d, J 10.7 Hz, 1 H), 4.15 (dd, J 13.2, 6.5 Hz, 1 H), 4.04 (dd, J 9.1, 9.2 Hz, 1 H), 3.96 (d, J 3.0 Hz, 1 H), 3.86 (m, 2 H), 3.74 (m, 1 H), 3.61 (dd, J 10.0, 10.0 Hz, 1 H), 3.57 (dd, J 9.5, 3.7 Hz, 1 H), 1.06 (s, 9 H). ^{13}C NMR (63 MHz, CDCl_3): δ 138.8, 138.3, 138.2, 135.8, 135.6, 133.8, 133.6, 133.3, 129.6, 129.0, 125.3, 118.2, 95.2, 82.2, 80.3, 75.2, 75.1, 73.1, 71.7, 67.8, 62.9, 26.8, 19.3. HRFABMS: m/z Calcd

for $\text{C}_{46}\text{H}_{52}\text{O}_6\text{Si} + \text{Na}$: 751.3431. Found: 751.3467.

2,3,4-Tri-O-benzyl-6-O-tert-butylidiphenylsilyl- α -D-glucopyranosyl trichloroacetimidate (4).—To a degassed solution of **2** (1.75 g, 2.40 mmol), DABCO (80 mg, 0.71 mmol) in 40 mL of 95% EtOH, was added $\text{RhCl}(\text{Ph}_3\text{P})_3$ (0.18 g, 0.19 mmol). The solution was heated to reflux for 6 h. After cooling, the solution was concentrated in vacuo and redissolved CH_2Cl_2 (50 mL). This solution was washed with water (50 mL), brine (50 mL) and then dried over MgSO_4 and concentrated in vacuo to afford a crude enol ether. To a solution of the crude enol ether in THF (23 mL), water (7 mL) and pyridine (0.79 mL) was added I_2 (1.22 g, 4.81 mmol). The solution was stirred for 10 min at ambient temperature, then cooled to 0 $^\circ\text{C}$ and treated with 10% aq Na_2SO_3 (50 mL). After 15 min at 0 $^\circ\text{C}$, the solution was extracted with EtOAc (3 \times 50 mL). The combined aqueous extracts were washed with 10% aq Na_2SO_3 (2 \times 50 mL) and water (50 mL), dried over MgSO_4 and concentrated in vacuo. Flash chromatography (1:9 EtOAc–toluene) afforded 1.40 g (1.96 mmol, 85%) of allyl 2,3,4-tri-O-benzyl-6-O-tert-butylidiphenylsilyl-D-glucopyranoside (**3**) as a mixture of anomers. FABMS: m/z Calcd for $\text{C}_{43}\text{H}_{48}\text{O}_6\text{Si} + \text{Na}$: 711.3. Found: 711.3. The mixture of anomers was used in subsequent reactions without further purification.

To a solution of **3** (0.40 g, 0.58 mmol) and DBU (0.097 mL, 0.70 mmol) in 5 mL of CH_2Cl_2 was added Cl_3CCN (0.58 mL, 5.8 mmol). After 4 h, the reaction mixture was directly applied to a column of silica and eluted with toluene to afford 0.39 g (0.46 mmol, 81%) of **4**. ^1H NMR (250 MHz, CDCl_3): δ 8.56 (s, 1 H), 7.68–7.18 (m, 25 H),

6.59 (d, J 3.5 Hz, 1 H, H-1), 4.95 (d, J 10.8 Hz, 1 H), 4.92 (d, J 10.6 Hz, 1 H), 4.83 (d, J 10.8 Hz, 1 H), 4.80 (d, J 11.6 Hz, 1 H), 4.70 (d, J 11.6 Hz, 1 H), 4.67 (d, J 10.6 Hz, 1 H), 4.08 (t, J 9.1 Hz, 1 H), 3.96–3.91 (m, 3 H), 3.87–3.73 (m, 2 H), 1.04 (s, 9 H). ^{13}C NMR (63 MHz, CDCl_3): δ 161.3, 138.6, 138.1, 138.0, 135.8, 135.6, 133.6, 133.1, 129.6, 129.0, 128.4, 128.3, 128.2, 128.0, 127.8, 127.7, 127.6, 127.5, 125.3, 94.3, 91.4, 81.5, 79.9, 76.9, 75.8, 75.4, 74.3, 72.9, 62.4, 26.8, 19.3.

1-S-Acetyl-2,3,4-tri-O-benzyl-6-O-tert-butylidiphenylsilyl-1-thio- β -D-glucopyranose (5).—To a solution of **4** (0.62 g, 0.74 mmol) in 10 mL of CH_2Cl_2 was added thiolacetic acid (0.80 mL, 11.2 mmol) under N_2 . After 12 h at ambient temperature, the solution was diluted with 50 mL of CH_2Cl_2 and washed with satd aq NaHCO_3 (2×50 mL), water (50 mL), and then brine (50 mL). The organic layer was dried over MgSO_4 and concentrated in vacuo. Flash chromatography with 3:97 EtOAc–toluene afforded 0.46 g (0.60 mmol, 82%) of compound **5**. ^1H NMR (400 MHz, CDCl_3): δ 7.75–7.66 (m, 4 H), 7.43–7.21 (m, 21 H), 5.19 (d, J 10.0 Hz, 1 H, H-1), 4.93–4.89 (m, 3 H), 4.82 (d, J 10.8 Hz, 1 H), 4.78 (d, J 10.7 Hz, 1 H), 4.77 (d, J 10.8 Hz, 1 H), 3.93 (m, 2 H), 3.86 (dd, J 9.4, 9.4 Hz, 1 H), 3.77 (dd, J 8.8, 9.1 Hz, 1 H), 3.55 (dd, J 8.8, 8.8 Hz, 1 H), 3.46 (dt, J 9.5, 2.2 Hz, 1 H), 2.57 (s, 3 H), 1.06 (s, 9 H). ^{13}C NMR (100 MHz, CDCl_3): δ 192.7, 138.3, 138.2, 137.9, 135.9, 135.6, 133.5, 133.0, 129.6, 129.5, 128.5, 128.4, 128.3, 128.0, 127.8, 127.7, 127.6, 127.4, 86.7, 81.5, 80.7, 80.0, 77.4, 75.9, 75.4, 75.1, 62.5, 30.8, 26.8, 19.3. HRFABMS: m/z Calcd for $\text{C}_{45}\text{H}_{50}\text{O}_6\text{SSi} + \text{Na}$: 769.2995. Found: 769.3033.

Methyl 2,3,6-tri-O-benzyl-4-O-trifluoromethylsulfonyl- α -D-glucopyranoside (6).—To a solution of methyl 2,3,6-tri-O-benzyl- α -D-glucopyranoside (0.41 g, 0.88 mmol) and 1.8 mL of pyridine in 15 mL of CH_2Cl_2 was added Tf_2O (1.5 mL, 8.8 mmol) at 0°C under N_2 . After 0.5 h at 0°C and 1 h at ambient temperature, the solution was concentrated in vacuo, redissolved in 20 mL of CH_2Cl_2 and washed with ice-cold 10% aq KHSO_4 (15 mL), satd aq NaHCO_3 (15 mL), water (15 mL) and brine (15 mL). The organic layer was then dried over MgSO_4 , concentrated in vacuo to

afford 0.50 g (0.84 mmol, 96%) of compound **6**. ^1H NMR (250 MHz, CDCl_3): δ 7.40–7.25 (m, 15 H), 5.02 (t, J 9.7 Hz, 1 H), 4.94 (d, J 10.3 Hz, 1 H), 4.83 (d, J 10.2 Hz, 1 H), 4.75 (d, J 10.3 Hz, 1 H), 4.60–4.45 (m, 4 H), 4.06 (t, J 9.4 Hz, 1 H), 3.98–3.96 (m, 1 H), 3.69–3.58 (m, 3 H), 3.38 (s, 3 H). ^{13}C NMR (63 MHz, CDCl_3): δ 149.8, 137.7, 137.5, 137.4, 135.0, 128.6, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 133.4, 97.9, 81.4, 80.1, 77.9, 75.5, 73.7, 73.6, 67.7, 67.5, 55.7.

Methyl 2,3,6-tri-O-benzyl-4-S-(2,3,4-tri-O-benzyl-6-O-tert-butylidiphenylsilyl- β -D-glucopyranosyl)-4-thio- α -D-glucopyranoside (7).—To a solution of **5** (17.8 mg, 2.33×10^{-2} mmol) in 0.8 mL of CH_3CN was added piperidine (5 μL , 5×10^{-2} mmol) under N_2 . After 15 min, BEMP **8** (10 μL , 3.4×10^{-2} mmol) was added. Then a solution of **6** (17.0 mg, 2.85×10^{-2} mmol) in 0.5 mL CH_3CN was added to the above reaction mixture. After stirring overnight at ambient temperature, the solution was diluted with 5 mL of EtOAc and washed with water (2×5 mL), and then brine (5 mL). The organic layer was dried over MgSO_4 and concentrated in vacuo. Flash chromatography with 3:7 EtOAc–hexanes afforded 23.3 mg (20.3×10^{-2} mmol, 85%) of compound **7**. ^1H NMR (400 MHz, CDCl_3): δ 7.69 (dd, J 7.9, 1.4 Hz, 2 H), 7.63 (dd, J 8.0, 1.3 Hz, 2 H), 7.46–7.08 (m, 36 H), 4.95 (d, J 10.7 Hz, 1 H), 4.93 (d, J 9.7 Hz, 1 H), 4.86 (d, J 10.9 Hz, 1 H), 4.82 (d, J 12.1 Hz, 1 H), 4.81 (d, J 10.8 Hz, 1 H), 4.77 (d, J 11.0 Hz, 1 H), 4.73 (d, J 10.7 Hz, 1 H), 4.65 (d, J 12.8 Hz, 1 H), 4.63 (obsc, 1 H), 4.61 (d, J 12.2 Hz, 1 H), 4.57 (d, J 10.9 Hz, 1 H), 4.44 (d, J 12.1 Hz, 1 H), 4.34 (d, J 12.1 Hz, 1 H), 4.24 (dm, J 7.6 Hz, 1 H), 4.06–4.09 (m, 2 H), 3.88 (dd, J 11.0, 1.7 Hz, 1 H), 3.85–3.71 (m, 3 H), 3.66–3.58 (m, 2 H), 3.54 (dd, J 8.8, 8.8 Hz, 1 H), 3.39 (s, 3 H), 3.38 (d, obsc, 1 H), 3.37 (dd, J 8.8 Hz, 1 H), 3.19–3.12 (m, 1 H), 1.05 (s, 9 H). ^{13}C NMR (100 MHz, CDCl_3): δ 138.6, 138.5, 138.1, 135.7, 135.5, 133.46, 133.15, 129.8, 129.7, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 98.8, 86.3, 83.8, 82.9, 79.8, 79.2, 77.7, 77.3, 75.7, 74.8, 74.7, 73.8, 73.1, 72.9, 72.8, 70.1, 63.2, 55.2, 46.9, 26.8, 19.4. HRFABMS: m/z Calcd for $\text{C}_{71}\text{H}_{78}\text{O}_{10}\text{SiS} + \text{Na}$: 1173.4981. Found: 1173.4981.

Allyl 2,3,6-tri-O-benzyl-4-S-(2,3,4-tri-O-benzyl-6-O-tert-butyl-diphenylsilyl- β -D-glucopyranosyl)-4-thio- α -D-galactopyranoside (12).—To a solution of allyl 2,3,6-tri-O-benzyl- α -D-galactopyranoside (0.26 g, 0.53 mmol) and 1.1 mL of pyridine in 10 mL of CH_2Cl_2 was added TiF_2O (0.89 mL, 5.3 mmol) at 0 °C under N_2 . After 0.5 h at 0 °C and 1 h at ambient temperature, the solution was concentrated in vacuo, then redissolved in 15 mL of CH_2Cl_2 and washed with ice-cold 10% aq KHSO_4 (10 mL), satd aq NaHCO_3 (10 mL), water (10 mL) and brine (10 mL). The organic layer was then dried over MgSO_4 and concentrated in vacuo to afford 0.32 g (0.51 mmol, 97%) of compound **11**. The product was immediately used without further purification. To a solution of **5** (14.0 mg, 1.88×10^{-2} mmol) in 0.8 mL of CH_3CN was added piperidine (4 μL , 4×10^{-2} mmol) under N_2 . After 15 min, BEMP **8** (8 μL , 2.8×10^{-2} mmol) was added. Then a solution of **11** (13.2 mg, 2.12×10^{-2} mmol) in 0.5 mL CH_3CN was added to the above reaction mixture. After stirring overnight at ambient temperature, the solution was diluted with 5 mL of EtOAc and washed with water (2×5 mL), and then brine (5 mL). The organic layer was dried over MgSO_4 and concentrated in vacuo. Flash chromatography with 3:7 EtOAc–hexanes afforded 17.9 mg (1.52×10^{-2} mmol, 81%) of compound **12**. ^1H NMR (400 MHz, CDCl_3): δ 7.68 (d, J 8.3 Hz, 2 H), 7.62 (d, J 8.2 Hz, 2 H), 7.40–7.10 (m, 36 H), 5.80 (m, 1 H), 5.18 (dd, J 17.2, 1.4 Hz, 1 H), 5.10 (dd, J 10.3, 1.0 Hz, 1 H), 4.97 (d, J 11.2 Hz, 1 H, H-1), 4.90 (d, J 10.8 Hz, 1 H), 4.86 (d, J 10.6 Hz, 1 H), 4.85 (d, J 10.9 Hz, 1 H), 4.83 (d, J 10.9 Hz, 1 H), 4.82 (d, J 4.0 Hz, 1 H, H-1), 4.79 (d, J 12.0 Hz, 1 H), 4.70 (d, J 11.8 Hz, 1 H), 4.69 (d, J 10.1 Hz, 1 H), 4.64 (d, J 10.0 Hz, 1 H), 4.56 (d, J 10.2 Hz, 1 H), 4.39 (m, 1 H), 4.02 (dd, J 10.6, 4.6 Hz, 1 H), 3.97–3.92 (m, 3 H), 3.87–3.73 (m, 4 H), 3.67 (t, J 8.9 Hz, 1 H), 3.57–3.54 (m, 2 H), 3.43 (t, J 9.4 Hz, 1 H), 3.26 (t, J 10.8 Hz, 1 H), 3.22 (d, J 9.5, 2.1 Hz, 1 H), 1.03 (s, 9 H). ^{13}C NMR (100 MHz, CDCl_3): δ 139.0, 138.4, 138.3, 138.2, 138.1, 135.8, 135.6, 133.7, 133.3, 133.1, 129.7, 128.4, 128.3, 128.2, 128.1, 128.0, 127.7, 127.6, 127.5, 127.4, 127.3,

127.2, 127.0, 95.7, 87.0, 83.4, 82.0, 81.1, 79.7, 77.4, 77.1, 75.9, 75.5, 75.3, 74.8, 73.3, 73.2, 70.9, 68.0, 63.1, 47.0, 26.9, 19.3. HRFABMS: m/z Calcd for $\text{C}_{73}\text{H}_{80}\text{O}_{10}\text{SSi} + \text{Na}$: 1199.5139. Found: 1199.5186.

Methyl 2,3,4-tri-O-benzyl-6-O-(4-methylbenzenesulfonyl)- α -D-glucopyranoside (13).—To a solution of methyl 2,3,4-tri-O-benzyl- α -D-glucopyranoside (0.35 g, 0.75 mmol) and pyridine (0.12 mL, 1.50 mmol) in 3 mL of CHCl_3 , was added a solution of TsCl (0.22 g, 1.16 mmol) in 5 mL of CHCl_3 at 0 °C under N_2 . After 6 h the solution was diluted to 25 mL with CHCl_3 and washed with water (2×15 mL) and brine (20 mL). The organic layer was dried over MgSO_4 and concentrated in vacuo. Flash chromatography with 1:9 EtOAc–toluene afforded 0.40 g (0.38 mmol, 86%) of compound **13**. ^1H NMR (250 MHz, CDCl_3): δ 7.75 (d, J 8.3 Hz, 2 H), 7.34–7.12 (m, 17 H), 4.97 (d, J 10.9 Hz, 1 H), 4.82 (d, J 10.7 Hz, 1 H), 4.77 (d, J 10.9 Hz, 1 H), 4.76 (d, J 12.1 Hz, 1 H), 4.56 (d, J 12.1 Hz, 1 H), 4.52 (d, J 3.5 Hz, 1 H, H-1), 4.42 (d, J 10.7 Hz, 1 H), 4.18 (m, 2 H), 3.95 (dd, J 9.2, 9.3 Hz, 1 H), 3.76 (m, 1 H), 3.46 (dd, J 9.6, 3.6 Hz, 1 H), 3.43 (dd, J 9.1, 9.3 Hz, 1 H), 3.31 (s, 3 H), 2.39 (s, 3 H). ^{13}C NMR (63 MHz, CDCl_3): δ 144.8, 138.5, 137.9, 137.7, 132.8, 129.8, 128.5, 128.4, 128.1, 127.9, 127.8, 127.6, 98.0, 81.8, 79.7, 76.9, 75.7, 74.9, 73.4, 68.6, 68.5, 55.3, 21.6. HRFABMS: m/z Calcd for $\text{C}_{35}\text{H}_{38}\text{O}_8\text{S} + \text{Na}$: 641.2185. Found: 641.2174.

Methyl 2,3,4-tri-O-benzyl-6-S-(2,3,4-tri-O-benzyl-6-O-tert-butyl-diphenylsilyl- β -D-glucopyranosyl)-6-thio- α -D-glucopyranoside (14).—To a solution of **5** (25.1 mg, 3.36×10^{-2} mmol) in 0.8 mL of CH_3CN was added piperidine (7 μL , 7×10^{-2} mmol) under N_2 . After 15 min, BEMP **8** (15 μL , 5.2×10^{-2} mmol) was added. Then a solution of **13** (24.9 mg, 4.03×10^{-2} mmol) in 0.5 mL of CH_3CN was added to the above reaction mixture. After stirring overnight at ambient temperature, the solution was diluted with 5 mL of EtOAc and washed with water (2×5 mL), and then brine (5 mL). The organic layer was dried over MgSO_4 and concentrated in vacuo. Flash chromatography with 1:3 EtOAc–hexanes afforded 32.0 mg (2.78×10^{-2} mmol, 83%) of compound **14**. ^1H NMR (400 MHz, CDCl_3): δ

7.75 (dd, J 5.9, 2.3 Hz, 2 H), 7.69 (dd, J 7.9, 1.4 Hz, 2 H), 7.46–7.14 (m, 36 H), 4.98, (d, J 10.8 Hz, 1 H), 4.90 (d, J 10.8 Hz, 1 H), 4.90 (d, J 8.9 Hz, 1 H), 4.88 (d, J 10.5 Hz, 1 H), 4.85 (d, J 10.7 Hz, 1 H), 4.80 (d, J 10.9 Hz, 1 H), 4.76 (d, J 12.2 Hz, 1 H), 4.75 (d, J 10.4 Hz, 1 H), 4.69 (d, J 10.7 Hz, 1 H), 4.66 (d, J 13.7 Hz, 1 H), 4.63 (d, J 12.2 Hz, 1 H), 4.58 (d, J 11.1 Hz, 1 H), 4.56 (d, J 10.4 Hz, 1 H), 4.55 (d, J 1.7 Hz, 1 H), 3.97 (t, J 9.3 Hz, 1 H), 3.93–3.85 (m, 3 H), 3.77 (t, J 9.3 Hz, 1 H), 3.65 (t, J 8.9 Hz, 1 H), 3.48 (dd, J 9.6, 3.9, Hz, 1 H), 3.42 (t, J 9.6 Hz, 1 H), 3.32 (s, 3 H), 3.33 (t, obsc, 1 H), 3.27 (d, J 9.6, 2.5 Hz, 1 H), 3.11 (dd, 13.6, 8.0 Hz, 1 H), 2.89 (dd, J 13.6, 8.0 Hz, 1 H), 1.03 (s, 9 H). ^{13}C NMR (100 MHz, CDCl_3): δ 138.7, 138.5, 138.2, 138.1, 135.9, 135.5, 133.7, 133.0, 129.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 97.8, 86.7, 85.0, 82.3, 81.9, 81.0, 79.9, 79.7, 77.6, 75.9, 75.7, 75.4, 75.2, 75.1, 73.3, 71.5, 62.7, 55.2, 31.2, 26.8, 19.3. HRFABMS: m/z Calcd for $\text{C}_{71}\text{H}_{78}\text{O}_{10}\text{SSi} + \text{Na}$: 1173.498104. Found: 1173.498104.

Allyl 2,3,4-tri-O-benzyl-6-O-[4-(tert-butoxycarbonyl)benzyl]- α -D-glucopyranoside (15).—To a solution of **1** (0.67 g, 1.37 mmol) in 20 mL of dry DMF was added NaH (66 mg, 1.65 mmol) under N_2 . After 20 min, a solution of *tert*-butyl 4-bromomethylbenzoate (0.37 g, 1.37 mmol) in 5 mL of anhyd DMF was added dropwise. The solution was heated to 85 °C for 12 h. After cooling, the solution was poured into 70 mL of water and extracted with EtOAc (3×50 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL) and dried over MgSO_4 . The solution was evaporated in vacuo, and the residue was chromatographed 1:19 EtOAc–toluene) to afford 0.80 g (1.14 mmol, 86%) of **15**. ^1H NMR (250 MHz, CDCl_3): δ 7.93 (d, J 8.2 Hz, 2 H), 7.37–7.14 (m, 17 H), 5.93 (m, 1 H), 5.30 (dd, J 17.2, 1.3, 1 H), 5.21 (dd, J 17.2, 1.3 Hz, 1 H), 5.00 (d, J 12.8 Hz, 1 H), 4.85 (d, J 10.6 Hz, 1 H), 4.82 (d, J 3.8 Hz, 1 H, H-1), 4.81 (d, J 12.8 Hz, 1 H), 4.77 (d, J 12.0 Hz, 1 H), 4.65 (d, J 12.1 Hz, 1 H), 4.62 (d, J 12.8 Hz, 1 H), 4.48 (d, J 12.8 Hz, 1 H), 4.47 (d, J 10.9 Hz, 1 H), 4.19–3.96 (m, 3 H), 3.83–3.54 (m, 5 H), 1.58 (s, 9 H). ^{13}C NMR (63 MHz, CDCl_3): δ 165.5,

142.6, 138.8, 138.2, 133.7, 131.3, 129.5, 128.4, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 127.2, 118.2, 95.7, 82.1, 80.9, 79.9, 77.7, 75.7, 75.1, 73.2, 72.8, 70.2, 68.8, 68.2, 28.2. HRFABMS: m/z Calcd for $\text{C}_{42}\text{H}_{48}\text{O}_8 + \text{Na}$: 703.3247. Found: 703.3231.

2,3,4-Tri-O-benzyl-6-O-[4-(tert-butoxycarbonyl)benzyl]- α -D-glucopyranosyl trichloroacetimidate (17).—To a degassed solution of **15** (0.50 g, 0.74 mmol) and DABCO (0.021 g, 0.019 mmol) in 15 mL of 95% EtOH was added $\text{RhCl}(\text{Ph}_3\text{P})_3$ (0.068 g, 0.073 mmol). The solution was heated to reflux for 6 h. After cooling, the solution was concentrated in vacuo and the residue was redissolved in CH_2Cl_2 (40 mL). This solution was washed with water (40 mL) followed by 40 mL of brine and then dried over MgSO_4 and concentrated in vacuo, to afford a crude enol ether. To a solution of the crude enol ether in THF (23 mL), water (7 mL) and pyridine (0.26 mL) was added I_2 (1.22 g, 4.81 mmol). The solution was stirred for 10 min at ambient temperature, then cooled to 0 °C and treated with 10% aq Na_2SO_3 (20 mL). After 15 min at 0 °C, the solution was extracted with ether (3×30 mL). The combined organic extracts were washed with 10% aq Na_2SO_3 (2×50 mL) and water (50 mL), dried over MgSO_4 and concentrated in vacuo. The residue was chromatographed (1:4 EtOAc–toluene) to afford 0.38 g of **16** (0.34 mmol, 81%) as a mixture of anomers. HRFABMS: m/z Calcd for $\text{C}_{39}\text{H}_{44}\text{Cl}_3\text{O}_8\text{N} + \text{Na}$: 663.2934. Found: 663.2966. The refined anomeric mixture was used in subsequent reactions without further purification.

To a solution of **16** (0.28 g, 0.44 mmol) and DBU (0.079 mL, 0.53 mmol) in 6 mL CH_2Cl_2 was added Cl_3CCN (0.44 mL, 4.4 mmol) under N_2 . After 4 h, the reaction mixture was directly applied to a silica gel column and eluted with toluene to afford 0.28 g (0.35 mmol, 82%) of the imidate **17**. ^1H NMR (250 MHz, CDCl_3): δ 8.58 (s, 1 H), 7.92 (d, J 8.3 Hz, 2 H), 7.35–7.12 (m, 17 H), 6.51 (d, J 3.5 Hz, 1 H, H-1), 4.99–4.46 (m, 8 H), 4.09–3.97 (m, 2 H), 3.79–3.67 (m, 4 H), 1.58 (s, 9 H). HRFABMS: m/z Calcd for $\text{C}_{41}\text{H}_{44}\text{Cl}_3\text{O}_8\text{N} + \text{Na}$: 806.2030. Found: 806.2041.

2,3,4-Tri-O-benzyl-6-O-[4-(tert-butoxycarbonyl)benzyl]-1-S-acetyl-1-thio- β -D-glucopyranose (18).—To a solution of **17** (0.28 g, 0.36 mmol) and HSAc (0.5 mL, 7.0 mmol) in 10 mL of CH_2Cl_2 was added $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.030 mL, 0.24 mmol) under N_2 . After 12 h at ambient temperature, the reaction was diluted with 50 mL of CH_2Cl_2 and washed with 50 mL of satd aq NaHCO_3 , 50 mL of water and 50 mL of brine. The organic layer was dried over MgSO_4 , concentrated in vacuo and chromatographed (1:3 EtOAc–toluene) to afford 0.19 g (0.30 mmol, 83%) of the thioacetate **18**. ^1H NMR (250 MHz, CDCl_3): δ 8.05 (d, J 8.1 Hz, 2 H), 7.43–7.14 (m, 17 H), 5.17 (d, J 10.1 Hz, 1 H, H-1), 4.88–4.50 (m, 8 H), 3.76–3.58 (m, 6 H), 2.37 (s, 3 H). ^{13}C NMR (63 MHz, CDCl_3): δ 192.8, 170.9, 144.4, 138.3, 138.0, 137.8, 130.3, 129.0, 128.4, 128.2, 128.0, 127.8, 127.7, 127.3, 86.8, 81.7, 80.3, 79.3, 77.0, 75.8, 75.4, 75.0, 72.7, 68.9, 30.9. HRMS (MALDI): m/z Calcd for $\text{C}_{37}\text{H}_{38}\text{O}_8\text{S} + \text{Na}$: 665.218. Found: 665.220.

Methyl 2,3,6-tri-O-benzyl-4-S-(2,3,4-tri-O-benzyl-6-O-(4-carboxamidobenzyl)- β -D-glucopyranosyl)-4-thio- α -D-glucopyranoside (19).—To a mixture of NovaSyn TGR Resin (112 mg, 0.022 mmol) and 0.5 mL of CH_2Cl_2 was added a premixed solution of compound **18** (60 mg, 0.093 mmol), DCC (18 mg, 0.087 mmol) and DMAP (1.5 mg, 0.012 mmol) in 1.5 mL of CH_2Cl_2 under N_2 . The reaction mixture was mixed for 36 h. After filtration, the resin was washed with CH_2Cl_2 (5 mL), MeOH (5 mL) and CH_2Cl_2 (5 mL). The resin was dried under vacuum. The amount of unreacted amine was quantified using standard ninhydrin assay (Perkin–Elmer/Applied Biosystems) to obtain a percentage loading of 98%. To 36 mg of the loaded resin (0.0072 mmol) was added 1 mL of 1:4 piperidine– CH_3CN . After 2 h, the resin was washed with CH_3CN (2×5 mL). To the support-bound thiol was added a solution of compound **6** (26 mg, 0.044 mmol) and BEMP **8** (13 μL , 0.045 mmol) in CH_3CN (0.6 mL). After shaking for 48 h, the resin was filtered and washed with CH_2Cl_2 (2×5 mL), MeOH (2×5 mL) and CH_3CN (2×5 mL) and dried under vacuum. To the dried resin was added 1 mL of 1:9

TFA– CH_2Cl_2 . After 10 min, the resin was washed with CH_2Cl_2 (3×3 mL). The collected washings were concentrated in vacuo to afford 4.2 mg (3.9 μmol , 50%) of compound **19**. The yield was confirmed by HPLC analysis to be 48%. ^1H NMR (250 MHz, CDCl_3): 7.70 (d, J 8.2 Hz, 2 H), 7.41–7.20 (m, 32 H), 4.88–4.47 (m, 14 H), 4.30–4.10 (m, 4 H), 3.76–3.50 (m, 9 H), 3.39 (s, 3 H), 3.34 (m, 1 H). HR-FABMS: m/z Calcd for $\text{C}_{63}\text{H}_{67}\text{N}_1\text{O}_{11}\text{S} + \text{Na}$: 1068.4333. Found: 1068.4358.

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