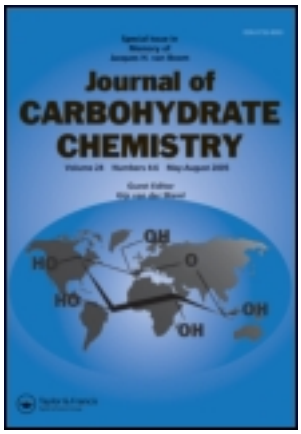

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Silver Triflate. A Mild Alternative Catalyst for Glycosylation Conditions Using Trichloroacetimidates as Glycosyl Donors

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Silver Triflate. A Mild Alternative Catalyst for Glycosylation Conditions Using Trichloroacetimidates as Glycosyl Donors

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ABSTRACT

Although trimethylsilyl triflate (TMSOTf) has been widely used to promote glycosyl trichloroacetimidates in oligosaccharide synthesis, silver triflate (AgOTf) was proved to be a mild and in some cases more efficient catalyst in TMSOTf-sensitive glycosylations. Migration and degradation in some specific coupling reactions can be reduced significantly under this alternative glycosylation condition.

INTRODUCTION

In synthetic carbohydrate chemistry, trichloroacetimidates have become the most widely used glycosyl donors.[1] They can be easily prepared by a base-catalyzed reaction of a lactol with trichloroacetonitrile. The standard glycosylation step corresponding to this kind of donor is usually activated by a catalytic amount of Lewis acid, with trimethylsilyl triflate (TMSOTf) and boron trifluoride etherate ($BF_3 \cdot Et_2O$) being the reagents most commonly used.[2–4] *O*-Trichloroacetimidates

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exhibit outstanding donor properties in terms of easy formation, stability, reactivity, and applicability, and generally give high yields of the products. In addition to TMSOTf and $BF_3 \cdot Et_2O$, TsOH, TfOH, $Sn(OTf)_2$ and $ZnCl_2$ have been occasionally applied to activate trichloroacetimidates.[5–8]

In our efforts to synthesize active avermectin B_{1a} analogues, we need to couple a monosaccharide to the avermectin macrolactone. To this end, glucopyranosyl trichloroacetimdate **1**[9] was selected to couple with a modified avermectin lactone **2**[10] with reaction promotion with TMSOTf in anhydrous methylene chloride. To our surprise, sluggish glycosylation results were obtained although solvents and reaction temperatures were considered seriously.[a] Further investigation found that the macrolactone alone is highly unstable and decomposed quickly in the presence of TMSOTf. However, when AgOTf, first introduced by Krepinsky and co-workers,[11] was used to catalyze the glycosylation between imidate **1** and aglycone **2**, a very clean reaction was observed and a 91% yield of desired compound **3** was isolated (see Scheme 1). Attracted by this result, we studied the AgOTf catalyzed glycosylation carefully using trichloroacetimidates as donors.[b] Here, we wish to report more examples of using silver triflate as a mild alternative catalyst for glycosylation conditions using trichloroacetimidates as glycosyl donors.

RESULTS AND DISCUSSION

Glycosylation of 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl trichloroacetimdate (**1**, Scheme 1) and avermectin derivative **2** in dry CH_2Cl_2 at – 42°C with AgOTf as promoter afforded avermectin derivative **3** in a yield of 91%. Attempted preparation of **3** using TMSOTf, $BF_3 \cdot Et_2O$, TfOH and $ZnCl_2$ in CH_2Cl_2 as catalysts gave no desired product at all. We thus explored more examples to see the scope and limitation of this method. In our previous research project, we found that the condensation of trichloroacetimidate **4** (Scheme 2) and 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**5**) gave the desired disaccharide **6** in 56% yield.[15] The by-product was proved to be the 3,5-*O*-isopropylidenated product, presumably due to migration of the 5,6-*O*-isopropylidene group of **5**. We reinvestigated this glycosylation using AgOTf (0.5 equiv) in CH_2Cl_2 at – 42°C and found that the yield was significantly improved (88%). The efficacy of this method was further demonstrated by the high yield reaction of trisaccharide imidate **7**[15] and furanosyl acceptor **5** using 0.5 equiv of AgOTf to give schizophyllan tetrasacharide derivative **8** (85%). Doublets at δ 5.64, 4.97, 5.10 and 5.16 ppm from ^{1}H NMR spectra corresponding to H-1^{I} (J 3.6 Hz), H-1^{II} (J 9.5 Hz), H-1^{III} (J 8.0 Hz) and H-1^{IV} (J 8.4 Hz), respectively, confirming the structural assignment of **8**. Partially acetylated glycosyl imidate **9**[16] was reacted with 1,6-hexanediol in CH_2Cl_2 in the presence of TMSOTf and gave an acceptable yield of dimer **10** by consuming more equiv of donor **9** (up to 4 equiv). The same reaction processed well using 1 equiv of AgOTf and 2.2 equiv of **9**, thus giving at 0°C a 69% yield of **10**. When cholesterol **11** was glycosylated with **1** using 0.3 equiv of AgOTf, an orthoester intermediate was

[a]We have tried to apply CH_2Cl_2, ether, toluene, acetonitrile, nitromethane, hexane and THF as glycosylation solvents under temperatures from – 42°C to rt.
[b]Examples using AgOTf in glycosylation reactions: Refs. [12–14].

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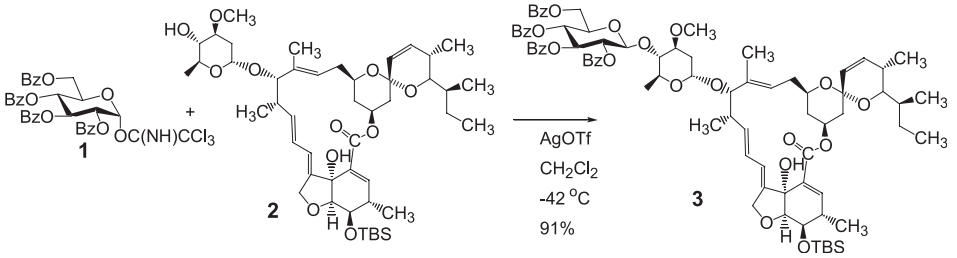
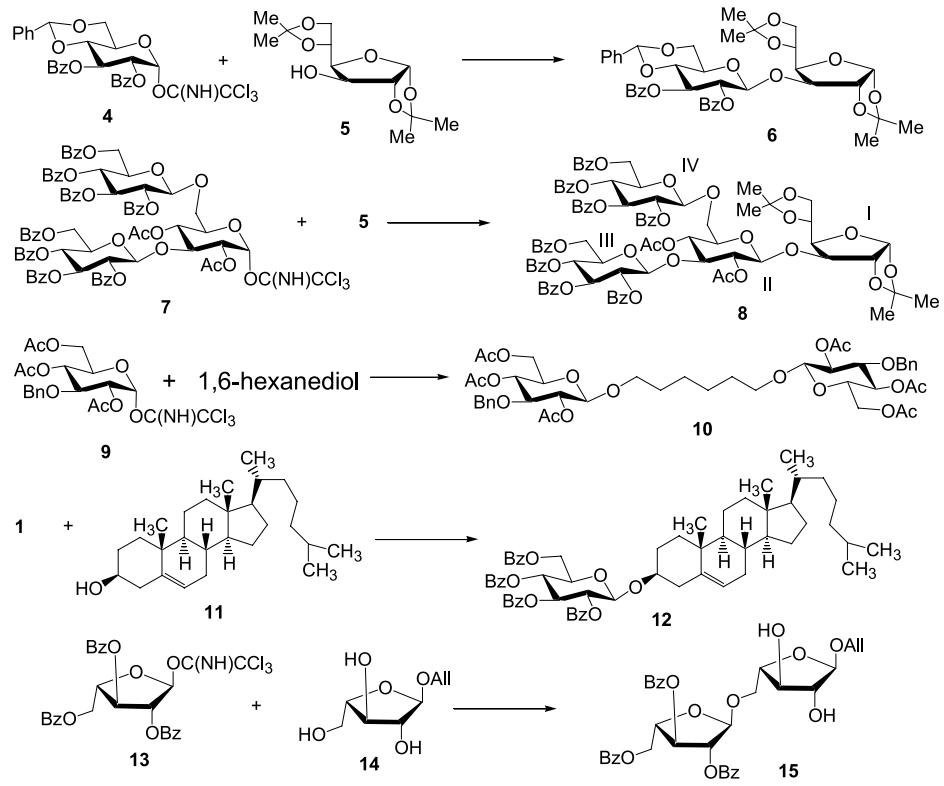


Scheme 1.

observed based on TLC and in situ transformation to the expected compound **12** (90%) was carried out smoothly by adding more AgOTf (additional 0.7 equiv) into the mixture. Silver triflate catalyzed regioselective glycosylation of furanosyl trichloroacetimidate **13** with triol **14** at 0°C gave desired (1 → 5)-linked disaccharide **13** in 78% yield, comparable to that of TMSOTf catalyzed regioselective glycosylation.[17] It is noteworthy that the above AgOTf catalyzed reactions did not occur in THF or CH_3CN under similar glycosylation conditions (Scheme 3).



Scheme 2. Reaction conditions: AgOTf, CH_2Cl_2, − 42°C – 0°C; 88% for **6**; 85% for **8**; 69% for **10**; 90% for **12**; 78% for **15**.

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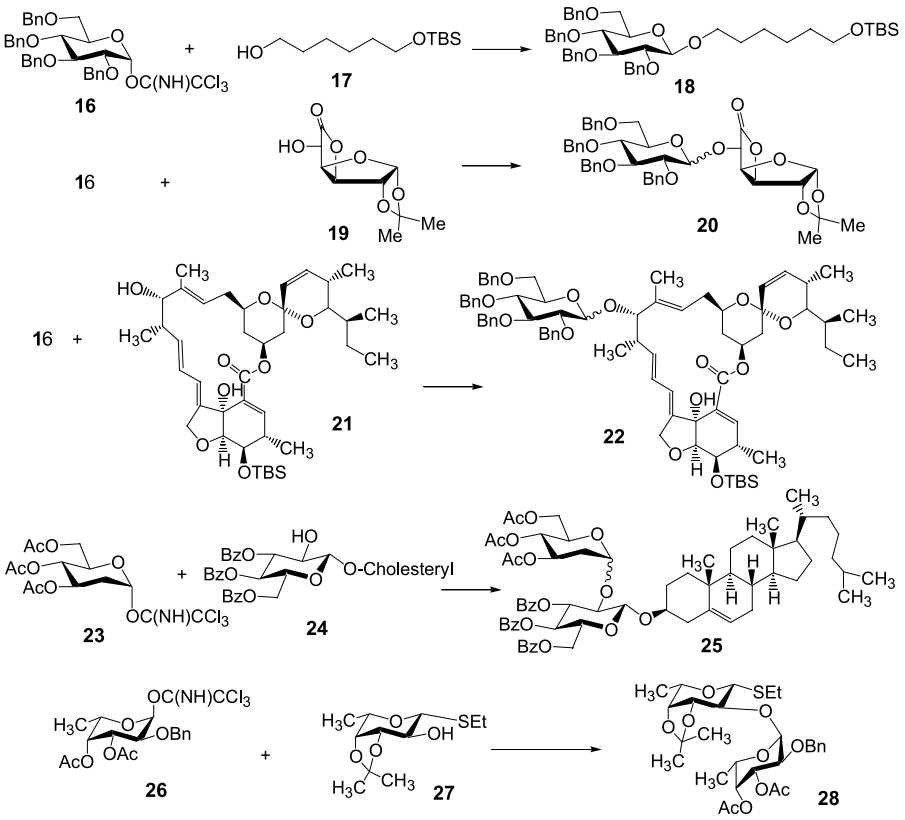

Scheme 3. Reaction conditions: AgOTf, CH_2Cl_2, − 42°C − 0°C; 95% for **18** (α:β = 1:9); 85% for **20** (α:β = 7:10); 80% for **22** (α:β = 2:5); 73% for **25** (α:β = 6:1); 83% for **28**.

To further investigate the scope and the limitation of this reaction, more examples were subjected to the AgOTf-imidate glycosylation system. When fully benzylated α-trichloroacetimidate **16**,[18] without a C-2 neighboring participation group, was coupled with hexanediol derivative **17**[19] in the presence of 0.3 equiv of AgOTf in anhydrous CH_2Cl_2 at − 42°C, β product **18** was formed predominantly (β:α > 9:1 based on NMR spectra) in 95% isolated yield. However the same donor, in parallel reactions, gave inseparable α,β mixtures when employing acceptors as glucuronate lactone **19** (→ inseparable **20**, 85%, α:β = 7:10) and macrolactone **21** (→ inseparable **22**, 80%, α:β = 2:5).[c] The reactions gave generally better total yields in CH_2Cl_2 (>80%) than in THF and toluene (< 30%) for benzylated imidate **16**. Condensation of acetylated

[c]For inseparable mixture of **20**, MALDITOF-MS Calcd for $C_{43}H_{46}O_{11}$: 738.30; Found 761 (M + Na). Selected ^{1}H NMR ($CDCl_3$): β isomer, δ 4.51 (d, 1 H, *J* 8.1 Hz, H-1′), 6.13 (d, 1 H, *J* 1.7 Hz, H-1); α isomer, δ 4.92 (d, 1 H, *J* 3.5 Hz, H-1′), 6.05 (d, 1 H, *J* 1.2 Hz, H-1). Inseparable mixture of **22** gave highly overlapped ^{1}H NMR spectra. MALDITOF-MS Calcd for $C_{74}H_{96}O_{13}Si$: 1220.66; Found 1243.6 (M + Na).

2-deoxy-α-D-glucopyranosyl imidate **23**[20] with saponin derivative **24**[21] under the same reaction conditions gave **25** as a mixture in favor of α product (6:1, 73% of total yield). More impressively, when fucosyl imidate **26**[22] was reacted with fucosyl thioglycoside **27** in the presence of TMSOTf, only a 50% yield of the disaccharide **28** was isolated. The major side reaction was the formation of the thioglycoside of the donor, i.e., ethyl 3,4-di-*O*-acetyl-2-*O*-benzyl-1-thio-L-fucopyranoside.[23] When the above reaction was catalyzed with 0.1 equiv of AgOTf in CH_2Cl_2 at −42°C, α-L-disaccharide **28** was afforded in an excellent yield (83%) with no detectable thio-migration product. This advantage may be applicable to the one-pot sequential synthesis of fucosyl oligosaccharides.[24]

In summary, we have demonstrated that the silver triflate promoted glycosylation reactions of various trichloroacetimidate donors are highly efficient. The stereochemical outcome of C-2 benzoylated imidates gave exclusively 1,2-trans linked products but differed case by case in C-2 benzylated counterparts. Side reactions such as migration and degradation in coupling reactions could be reduced significantly under this mild glycosylation condition.

EXPERIMENTAL

General methods. Optical rotations were determined at 20°C with a Perkin–Elmer Model 241-Mc automatic polarimeter. ^{1}H NMR, ^{13}C NMR, ^{1}H–^{1}H COSY and HMQC spectra were recorded with ARX 400 spectrometers for solutions in $CDCl_3$. Chemical shifts are given in ppm downfield from internal Me_4Si. Mass spectra were measured using MALDI-TOF-MS with α-cyano-4-hydroxycinnamic acid (CCA) as matrix. Thin-layer chromatography (TLC) was performed on silica gel HF_{254} with detection by charring with 30% (v/v) H_2SO_4 in MeOH or in some cases by a UV detector. Column chromatography was conducted by elution of a column (10 × 250 mm, 18 × 300 mm, 35 × 400 mm) of silica gel (100–200 mesh) with EtOAc–petroleum ether (bp 60–90°C) as the eluent. Solutions were concentrated at < 60°C under diminished pressure.

Typical procedure for AgOTf catalyzed glycosylation: To a solution of imidate donor (1.05 mmol) and alcohol acceptor (1 mmol) in dry CH_2Cl_2 (5–8 mL) was added 4Å molecular sieves. The mixture was stirred at rt for about 15 min under an N_2 atmosphere, then cooled down to − 42°C. AgOTf (0.1–1.0 equiv) was then added avoiding light. The mixture was stirred under these conditions for 30 to 60 min, then neutralized with triethylamine, diluted with CH_2Cl_2 (20 mL) and washed with water (2 × 10 mL). The organic phase was dried over $MgSO_4$, concentrated and purified on a silica gel column using EtOAc-petroleum ether as the eluent to give the desired compound.

Avermectin B_{1a} derivative 3. $[\alpha]_D^{20}$ + 15 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.12–0.13 (m, 6 H), 0.80–0.92 (m, 19 H), 1.11 (d, 3 H), 1.23–1.25 (m, 3 H), 1.45–1.60 (m, 6 H), 1.70–1.79 (m, 4 H), 2.0–2.05 (m, 4 H), 2.13–2.27 (m, 5 H), 2.47–2.51 (m, 1 H), 3.31–3.46 (m, 4 H), 3.76–3.87 (m, 4 H), 4.10–4.14 (m, 3 H), 4.43–4.50 (m, 2 H), 4.59 (dd, 1 H), 4.62–4.67 (m, 2 H), 4.72 (d, 1 H, *J* 3.7 Hz, H-1′), 4.97 (br t, 1 H),

5.25 (d, 1 H, *J* 8.0 Hz, H-1″), 5.31–5.36 (m, 2 H), 5.50 (dd, 1 H, H-2″), 5.54 (dd, 1 H), 5.62-5.68 (m, 2 H), 5.70–5.75 (m, 2 H), 5.80–5.86 (m, 1 H, H-9), 5.93 (t, 1 H, H-3″), 7.15–7.35 (m, 20 H). MALDITOF-MS Calcd for $C_{81}H_{100}O_{20}Si$: 1420.66; Found 1443.6 (M + Na).

Anal. Calcd for $C_{81}H_{100}O_{20}Si$: C, 68.43; H, 7.09. Found: C, 68.18; H, 7.23.

2,3-Di-*O*-benzoyl-4,6-*O*-benzylidene-β-D-(1 → 3)-1,2:5,6-di-*O*-isopyopylidene-α-D-glucopyranose (6). $[\alpha]_D^{20}$ − 29 (*c* 2.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.17, 1.24, 1.26, 1.38 (4 s, 12 H, CH_3), 3.70 − 3.74 (m, 1 H, H-5′), 3.87–3.91 (m, 2 H, H-3, H-4), 3.96 (t, 1 H, *J* 9.6 Hz, H-4′), 4.04 (d, 1 H, *J* 1.8 Hz, H-6a), 4.35 (br s, 1 H, H-5), 4.40–4.46 (m, 2 H, 2 H-6′), 4.52 (d, 1 H, *J* 1.8 Hz, H-6b), 4.55 (d, 1 H, *J* 3.6 Hz, H-2), 4.83 (d, 1 H, *J* 7.9 Hz, H-1′), 5.54 (s, 1 H, PhCH), 4.56 (dd, 1 H, *J* 7.9, 9.6 Hz, H-2′), 5.81 (t, 1 H, *J* 9.6 Hz, H-3′), 5.95 (d, 1 H, *J* 3.6 Hz, H-1), 7.31–8.00 (m, 10 H, Ph). MALDITOF-MS Calcd for $C_{39}H_{42}O_{13}$: 718; Found 741.15 (M + Na).

2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl-(1 → 3)-[2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1 → 6)]-2,4-di-*O*-acetyl-β-D-glucopyranosyl-(1 → 3)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (8). $[\alpha]_D^{20}$ − 53 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.27, 1.43, 1.45, 1.50 (4 s, 12 H), 1.60, 1.73 (2 s, 6 H, Ac), 3.55 (dd, 1 H), 3.65 (t, 1 H), 3.74–3.76 (m, 2 H), 3.82–3.86 (m, 2 H), 3.91–3.96 (m, 2 H), 4.06–4.08 (m, 2 H), 4.11–4.28 (m, 2 H), 4.36–4.39 (m, 2 H), 4.55–4.64 (m, 4 H), 4.97 (d, 1 H, *J* 9.5 Hz, H-1^{II}), 5.10 (d, 1 H, *J* 8.0 Hz, H-1^{III}), 5.16 (d, 1 H, *J* 8.4 Hz, H-1^{IV}), 5.43–5.54 (m, 3 H), 5.64 (d, 1 H, *J* 3.6 Hz, H-1^{I}), 5.72 (t, 1 H), 5.84 (t, 1 H), 5.92 (t, 1 H), 7.30–8.0 (m, 40 H). MALDITOF-MS Calcd for $C_{90}H_{86}O_{31}$: 1662.53; Found 1685.3 (M + Na).

Anal. Calcd for $C_{90}H_{86}O_{31}$: C, 64.98; H, 5.21. Found: C, 64.72; H, 5.25.

1,6-Di-*O*-(2,4,6-tri-*O*-acetyl-3-*O*-benzyl-β-D-glucopyranosyl)hexane (10). $[\alpha]_D^{20}$ + 22 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.24–1.32 (m, 4 H), 1.50–1.60 (m, 6 H), 1.97, 2.00, 2.08 (3 s, 18 H, 6 Ac), 3.43, 3.84 (2 dt, 4 H, *J* 6.6, 9.5 Hz, 2 OCH_2), 3.57 (ddd, 2 H, 2 H-5), 3.69 (t, 2 H, *J* 9.4 Hz, 2 H-3), 4.10 (dd, 2 H, *J* 2.5, 12.0 Hz, 2 H-6a), 4.20 (dd, 2 H, *J* 6.0, 12.0 Hz, 2 H-6b), 4.39 (d, 2 H, *J* 8.0 Hz, 2 H-1), 4.57, 4.61 (2 d, 4 H, *J* 12.0 Hz, 2 $PhCH_2$), 5.03 (dd, 2 H, *J* 8.0, 9.6 Hz, 2 H-2), 5.12 (t, 2 H, *J* 9.6 Hz, 2 H-4), 7.21–7.35 (m, 10 H, Ph).

Anal. Calcd for $C_{44}H_{58}O_{18}$: C, 60.40; H, 6.68. Found: C, 60.23; H, 6.80.

Cholest-5-en-3β-yl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside (12). $[\alpha]_D^{20}$ + 41 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.64 (s, 3 H), 0.80–0.90 (m, 14 H), 0.95–1.0 (m, 3 H), 1.05–1.13 (m, 6 H), 1.24–1.41 (m, 8 H), 1.48–1.57 (m, 3 H), 1.68–1.72 (m, 2 H), 1.73–1.86 (m, 1 H), 1.88–1.92 (m, 2 H), 1.97–2.00 (m, 1 H), 2.12–2.16 (m, 2 H), 3.47–3.54 (m, 1 H), 4.11–4.16 (m, 1 H, H-5), 4.80–4.53 (dd, 1 H, $J_{5,6a}$ 6.0, $J_{6a,6b}$ 12.0 Hz, H-6a), 4.57–4.61 (dd, 1 H, $J_{5,6b}$ 3.4, $J_{6a,6b}$ 12.0 Hz, H-6b), 4.92 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 5.21 (br d, 1 H), 5.46–5.50 (dd, 1 H, $J_{2,3}$ 9.7, $J_{1,2}$ 7.8 Hz, H-2), 5.58–5.64 (dd, 1 H, $J_{3,4}$ 9.3, $J_{4,5}$ 9.7 Hz, H-4), 5.86–5.90 (dd, 1 H, $J_{2,3}$ 9.7, $J_{4,3}$ 9.3 Hz, H-3), 7.24–8.0 (m, 20 H).

Anal. Calcd for $C_{61}H_{72}O_{10}$: C, 75.91; H, 7.52. Found: C, 76.26; H, 7.69.

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Allyl 2,3,5-tri-*O*-benzoyl-α-L-arabinofuranosyl-(1 → 5)-α-L-arabinofuranoside (15). $[\alpha]_D^{20}$ + 105 (*c* 1, $CHCl_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.9, 63.5, 67.0, 68.0, 77.5, 78.1, 79.5, 81.8, 82.0, 85.6, 106.1, 109.9, 117.0, 128.3, 128.5, 128.6, 128.7, 129.6, 129.8, 129.9, 130.1, 133.1, 133.5, 133.6, 165.2, 165.9, 166.0.

Anal. Calcd for $C_{34}H_{34}O_{12}$: C, 64.35; H, 5.36. Found: C, 64.11; H, 5.45.

6-*Tert*-butyldimethylsilyloxyhexyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside (18). $[\alpha]_D^{20}$ + 5 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ − 0.01 (s, 6 H, CH_3), 0.89 (m, 9 H, $(CH_3)_3C$), 1.26–1.43 (m, 5 H), 1.47–1.57 (m, 3 H), 1.63–1.69 (m, 2 H), 3.42–3.47 (m, 2 H, H-2, H-5), 3.50–3.54 (m, 1 H, one proton of $O(CH)_2$), 3.56–3.73 (m, 3 H, H-6a, H-3, H-4), 3.75 (dd, 1 H, *J* 1.8, 10.8 Hz, H-6b), 3.93–3.99 (m, 1 H, one proton of $O(CH)_2$), 4.38 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 4.51, 4.54, 4.63, 4.72, 4.78, 4.83, 4.92, 4.95 (8 d, 8 H, 4 $PhCH_2$), 7.15–7.35 (m, 20 H, Ph).

Anal. Calcd for $C_{46}H_{62}O_7Si$: C, 73.17; H, 8.28. Found: C, 73.40; H, 8.31.

Cholest-5-en-3β-yl 2-deoxy-3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl-(1 → 2)-3,4,6-tri-*O*-benzoyl-β-D-glucopyranoside (25). $[\alpha]_D^{20}$ + 18 (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.67 (s, 3 H), 0.83–0.95 (m, 14 H), 1.00–1.03 (m, 1 H), 1.08–1.14 (m, 6 H), 1.24–1.40 (m, 8 H), 1.43–1.62 (m, 9 H), 1.75 (s, 3 H), 1.77 (s, 3 H), 1.97–2.02 (m, 5 H), 2.25–2.30 (m, 2 H), 3.47–3.62 (m, 4 H, 2 H-6′, H-5′, H-3 of cholesterol), 3.90 (dd, 1 H, *J* 7.8, 9.7 Hz, H-2), 4.01–4.06 (m, 1 H, *J* 6.2, 3.7, 9.6 Hz, H-5), 4.47–4.54 (m, 2 H, 2 H-6), 4.74 (d, 1 H, *J* 7.8 Hz, H-1), 4.83 (t, 1 H, *J* 9.8 Hz, H-4′), 5.01–5.05 (m, 1 H, H-3′), 5.35 (br d, 1 H, *J* 5.2 Hz), 5.50 (dd, 1 H, *J* 9.7, 9.3 Hz, H-4), 5.56 (d, 1 H, $J_{1,2a}$ 3.2 Hz, H-1′), 5.70–5.75 (dd, 1 H, *J* 9.3, 9.7 Hz, H-3), 7.24–8.0 (m, 15 H).

Anal. Calcd for $C_{66}H_{84}O_{16}$: C, 69.94; H, 7.47. Found: C, 70.29; H, 7.51.

Ethyl 3,4-di-*O*-acetyl-2-*O*-benzyl-α-L-fucopyranosyl-(1 → 2)-3,4-*O*-isopropylidene-1-thio-β-L-fucopyranoside (28). $[\alpha]_D^{20}$ − 63 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.10 (d, 3 H), 1.23 (t, 3 H), 1.35 (s, 3 H), 1.39 (d, 3 H), 1.52 (s, 3 H), 1.99, 2.11 (2 s, 6 H, Ac), 2.70–2.74 (m, 2 H), 3.69 (dd, 1 H), 3.80–3.87 (m, 2 H), 4.05 (dd, 1 H), 4.18 (t, 1 H), 4.43 (d, 1 H, *J* 10.3 Hz, H-1), 4.53 (q, 1 H), 4.55, 4.88 (2 d, 2 H), 5.28–5.34 (m, 2 H), 5.52 (d, 1 H, *J* 3.6 Hz, H-1′), 7.25–7.36 (m, 5 H). MALDITOF-MS Calcd for $C_{28}H_{40}O_{10}S$: 568.23; Found 581.1 (M + Na).

Anal. Calcd for $C_{28}H_{40}O_{10}S$: C, 59.14; H, 7.09. Found: C, 58.91; H, 6.94.

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