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Dehydrative Glycosylation with the Hendrickson Reagent

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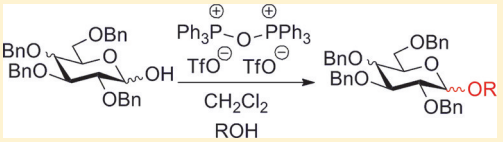
Supporting Information

ABSTRACT: The Hendrickson reagent is able to perform efficiently dehydrative glycosylation of 1-hydroxyglycosyl donors. The reaction occurs under mild conditions through an anomeric oxophosphonium intermediate detected by nuclear magnetic resonance. Further insight into the mechanism was gained by ^{18}O labeling of anomeric OH.



The importance of the glycosylation reaction is appreciated today because of the biological relevance of oligosaccharides and glycoconjugates.[1] On the other hand, despite the progresses made in developing new procedures for the synthesis of glycosides, such a reaction remains demanding and no universal method for the synthesis of any glycosidic linkage has emerged.

The common way to perform glycosylations involves the derivatization of the anomeric position of a sugar with a latent leaving group, which is then activated in the presence of a glycosyl acceptor to form the glycosidic bond.[2] Less attention has been paid to glycosidic bond formation through dehydrative glycosylation, where the hydroxyl group of a hemiacetal sugar can be converted into a leaving group in situ and exploited directly for glycosylation.

Various conditions have been used for dehydrative glycosylation, from the classical Fisher glycosylation protocol to the elegant works of Gin et al., which exploited anomeric oxosulfonium donors,[3] and Shingu et al., who developed the activation of 1-OH sugars by their in situ conversion to bromides under dehydrative conditions using the Appel reagent.[4]

Among different dehydrating agents, the so-called Hendrickson reagent (POP), triphenylphosphonium anhydride trifluoromethanesulfonate, was used for the synthesis of esters and amides through oxophosphonium species.[5−7]

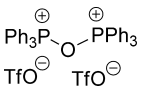


Figure 1. Hendrickson POP reagent.

In an interesting work,[8] it was also mechanistically studied in comparison with the Mitsunobu reaction for ester formation. As the Hendrickson reagent was quite rarely used, we thought to try such a reagent in dehydrative glycosylation. It is worth mentioning that Mukaiyama's group described the use of triphenylphosphine oxide to catalyze glycosylation reactions of glycosyl bromides and iodides through the postulated formation of a reactive intermediate anomeric oxophosphonium salt.[9]

Careful bibliographic examination revealed only a paper by Mukaiyama,[10] who tested the POP reagent just for the glycosylation of furanoses. In spite of the interest in the reaction, the investigation was not extended, especially in the case of more interesting pyranose hemiacetal donors, prompting us to pursue our study.

Although the Hendrickson reagent is commonly used in the presence of a base (see, e.g., ref 5), we initially considered the possibility of activating the hemiacetal donor without addition of a base as it is known that phosphine oxides are weak bases;[11] therefore, the phosphine oxide liberated from POP reagent upon activation of the hydroxyl group should buffer the formed triflic acid. The POP reagent (1.1 equiv) was generated according to a literature method[8] from 3.3 equiv of $Ph_3P{=}O$ and 1.1 equiv of Tf_2O at 0 °C in CH_2Cl_2; to the so formed reagent was added 1 equiv of 2,3,4,6-tetra-*O*-benzylgalactopyranose **1a**. The reaction took place immediately, giving rise to an almost quantitative yield of perbenzylated galacto trehaloses. This observation suggests that the self-condensation between the activated donor and the 1-OH sugar is faster than the reaction of 1-OH with the POP reagent. Therefore, we modified the order of addition of the donor and acceptor, adding the acceptor (2-propanol, 2 equiv) to the POP reagent before the donor. Under such conditions, the glycoside was formed in fair yield (58%) (Scheme 1).

The result prompted us to employ more complex acceptors. The use of cholesterol as an acceptor (2 equiv) gave an intriguing result. Besides the expected glycoside **4a** in 44% yield and an α:β ratio of 63:37, we observed the formation of an inseparable mixture of Δ3,5-cholestadiene[12] and cholesteryl ether[13] (Scheme 1). Further attempts to glycosylate protected sugar acceptors revealed that, despite the presence of phosphine oxide, the reaction conditions were too acidic and acid labile protecting groups, such as silyl ethers, did not survive.[14]

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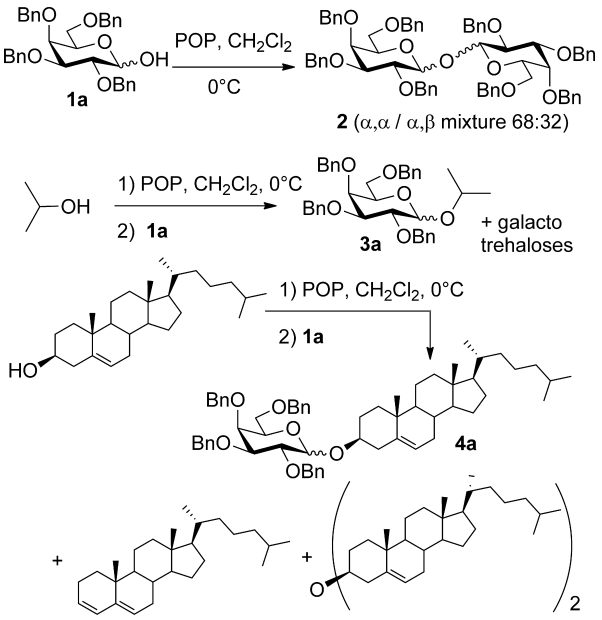
Scheme 1. Glycosylation under Acidic Conditions



We therefore moved toward the use of a stronger base and ran the reaction under slightly modified conditions with respect to those described previously (see Experimental Section), adding a mixture of DIPEA and compound **1a** to the Hendrickson reagent and then leaving the mixture for 2 h at 0 °C to allow its activation by conversion into the phosphonium salt. Under these conditions, formation of the galacto trehalose was almost completely suppressed, and upon addition of the acceptor, the expected glycosides were formed in good yields.

The glycosylation reaction was then extended using other acceptors, as shown in Table 1, in good yield.

It is worth noting that it was possible to satisfactorily glycosylate a poorly reactive 4-OH (entry 4, product **6a**); moreover, the method is compatible with the presence of a thioglycoside, therefore opening the possibility of orthogonal glycosylations.

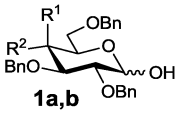
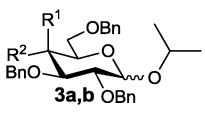
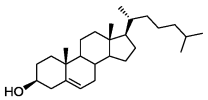
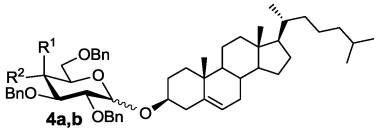
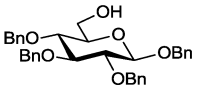
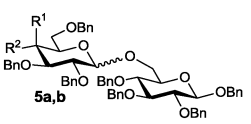
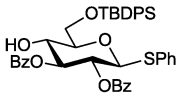
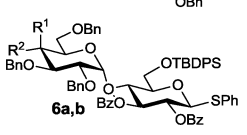
Then we moved to 2,3,4,6-tetra-*O*-benzylglucopyranose **1b** as a donor. The activation was performed under the same conditions previously described. Surprisingly, and in a manner different from that of galactose, after 2 h the formation of a relevant amount of trehalose was observed. This fact was quite unexpected as it is known that tetrabenzylglucosyl donors are less reactive than the corresponding galactosyl derivatives.[15] Monitoring the reaction provided evidence that the formation of trehalose was not immediate but its amount increased with reaction time. Decreasing the temperature to −20 °C resulted in an almost complete suppression of formation of the undesired trehaloses, and addition of 2-propanol afforded the desired glycoside **3b**.

The same acceptors previously glycosylated with **1a** as a donor were also used for reactions with **1b** at −20 °C, giving similar results.

Some experiments were performed with different solvents and additives to improve the α:β ratio. The use of diethyl ether and acetonitrile led to practical problems because of the low solubility of the POP reagent; the reaction performed in DMF gave a low yield, while the use of tetramethylurea instead of DIPEA gave a similar yield and did not improve the stereoselectivity. Finally, tetrabenzoylgalactose was used as a donor, but no product formation was observed even the reaction mixture was warmed, probably because it is too disarmed.

From the examination of the anomeric ratio of the products obtained in our set of experiments, and with the hypothesis that alkoxyphosphonium ions are the reactive intermediates, some information can be inferred. First, the different ratio between the anomeric alkoxyphosphonium ions (see below) and the related glycosides suggests that the α/β intermediate species are in fast equilibrium; moreover, the amount of α anomer in the glycoside mixture, which in some cases (Table 1, entry 4) is the only product, indicates that the reaction does not occur exclusively with direct displacement with inversion and that the β intermediate appears to be more reactive than the α anomer as can be deduced from the fact that less reactive nucleophiles gave higher α:β ratios.[16]

Table 1. Glycosylation of Tetrabenzyl Donors under Basic Conditions[a]

Entry	Donor	Acceptor	Product	Yield(%)[b] (α:β ratio)[c]
1	 **1a,b**	**a** R^1 = OBn, R^2 = H **b** R^1 = H, R^2 = OBn		 **3a,b**	**3a**: 98 (44:56) **3b**: 97 (25:75)
2	**1a,b**		 **4a,b**	**4a**: 95 (42:58) **4b**: 95 (27:73)
3	**1a,b**		 **5a,b**	**5a**: 98 (60:40) **5b**: 96 (37:63)
4	**1a,b**		 **6a,b**	**6a**: 75 (α only) **6b**: 72 (α only)

[a]See Experimental Section for reaction conditions. [b]Isolated yield. [c]Determined by ^{13}C NMR.

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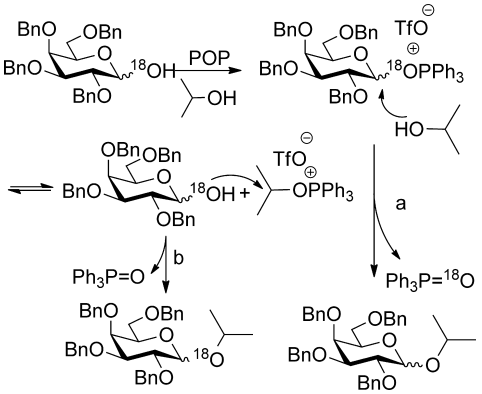
To improve our understanding of the mechanism either under acidic or under basic conditions, we performed the reaction under both conditions using C1-OH ^{18}O-labeled tetrabenzylgalactose (prepared from tetrabenzylgalactose, POP reagent, and 97% $H_2{}^{18}O$; 77 ± 5% sugar labeling) as a donor and 2-propanol as an acceptor.

Two possible patways can be envisaged for the glycosylation reaction: the anomeric alkoxyphosphonium ion can be attacked by the acceptor (Scheme 3, path a), or less probably, the alkoxyphosphonium ion derived from the acceptor can be substituted with the hemiacetal hydroxyl group (Scheme 3, path b). One mechanism or the other could be effective depending on the conditions, the order of addition of two reagents, and the rate of the equilibria between the different ions in solution.

Running the reaction under basic conditions led to the recovery of ^{18}O-labeled $Ph_3P{=}O$ (25 ± 5% ^{18}O incorporation); surprisingly, under acidic conditions, the ^{18}O was found neither on $Ph_3P{=}O$ nor on the glycoside.

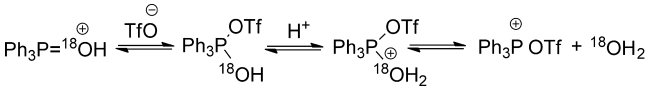
We could therefore conclude that the more likely pathway presumably followed by the reaction is path a (Scheme 2)

Scheme 2. Possible Mechanisms for the Glycosylation Reaction



under both acidic and basic conditions, but under acidic conditions, the ^{18}O may be scrambled, ending with the loss of labeling in water (see Scheme 3).

Scheme 3. Possible Loss of Labeling under Acidic Conditions



From a practical point of view, the basic conditions provided far better results; therefore, the mechanism of the reaction under acidic conditions was not further investigated.

On the other hand, to improve our understanding of the mechanism under basic conditions, the detection of reactive intermediates was attempted by NMR at low temperatures. In an NMR tube, tetrabenzylgalactose **1a** (50 mg) was added at −10 °C to a suspension of 2 equiv of POP reagent[17] in CD_2Cl_2 (giving a solution that was submitted to ^1H, ^{13}C, and ^{31}P NMR at the same temperature). The ^{31}P spectrum exhibited a main peak at 64.08 ppm compatible with the formation of a major intermediate alkoxyphosphonium ion together with a minor peak at 66.16 ppm in an 88:12 ratio.[18] A broad peak around 45.0 ppm was also present, probably because of the excess of POP reagent in fast equilibrium with $Ph_3P{=}O$ liberated during activation of the anomeric hydroxyl group. The ^{13}C NMR spectrum revealed a doublet for the anomeric carbon at 103.2 ppm with a $J_{C,P}$ of 9.17 Hz, while the minor isomer was not detectable. The ^1H NMR spectrum also exhibited the presence of a doublet of doublets (J = 3.1 and 6.7 Hz) because of an anomeric proton at 5.59 ppm. Unfortunately, again it was not possible to detect the signal for the other anomer as it was most likely hidden under the signal of $CDHCl_2$ around 5.3 ppm. The chemical shifts in the ^{31}P NMR spectrum and the coupling constant in the ^1H NMR spectrum strongly suggest that the major anomer is the α one.

Upon addition of the acceptor, the signal at 5.6 ppm in the ^1H NMR spectrum quickly almost disappeared as well as the signals at 66.1 and 64.0 ppm in the ^{31}P NMR spectrum, where a new signal at 59.6 ppm, which can be attributed to the phosphonium salt of the acceptor, became visible.

To detect the signal for the other anomeric proton, we repeated the experiment in $CDCl_3$. After activation for 30 min, the ^{31}P NMR spectrum showed again two peaks at 66.2 and 64.1 ppm in a 26:74 ratio. The proton spectrum revealed a situation more complex than the one that was expected, showing, apart from a doublet of doublets at 5.47 ppm (J = 3.1 and 6.7 Hz), other signals around 5.3 ppm that may due to the β anomer together with other unidentified signals that did not allow confident identification of the signal due to the β anomer.

Comparing the rate and stereoselection of our reactions, especially in the case of more reactive acceptors, with those described with Appel-Lee reagent in ref 4 suggests that in our case the reaction is much faster but much less stereoselective. The rate difference, together with the observation of the prevalence of the α anomer of the alkoxyphosphonium intermediate, can help to explain the difference in stereoselectivity. In fact, in both cases in situ anomerization probably takes place. However, in less reactive anomeric bromides, the difference in the activation energy for the attack on the more reactive β anomer with respect to the α one allows generation of mainly the α glycoside, while in more reactive anomeric alkoxyphosphonium, the activation energy difference is not enough to minimize the reactivity of the α-alkoxyphosphonium giving rise to an anomeric mixture of the glycosides.

In conclusion, an approach to dehydrative glycosylation with 1-hydroxyglycopyranosyl donors by means of the POP Hendrickson reagent has been established. The use of ^{18}O-labeled donors indicates that the activation occurs through the formation of an alkoxyphosphonium intermediate, further confirmed by NMR analysis of the dehydrative glycosylation process. The operative conditions are quite simple, avoiding exceedingly low temperatures and the unwanted formation of donor self-condensation products.

The obtained results open the possibility of improving the reaction by testing other phosphine oxides and modifying the conditions; moreover, the procedure will be applied to reactions with different donors and acceptors and to activate the anomeric position to promote the substitution reaction with nucleophiles other than oxygen.

EXPERIMENTAL SECTION

General Experimental Methods. Flash column chromatography was performed on Merck silica gel 60 (0.040−0.063 mm), following the procedure described in ref 19. Reactions were monitored by TLC on Merk silica gel 60 F_{254} plates, and the compounds were detected by

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examination under UV light and by charring with 10% sulfuric acid in methanol. Solvents were removed under reduced pressure below 40 °C. CH_2Cl_2 was dried and stored over 4 Å molecular sieves. All reactions (if not specifically including water as a reactant, solvent, or cosolvent) were performed under an Ar atmosphere, in oven-dried or microwave oven-dried glassware. Unless noted otherwise, ^{1}H NMR spectra were recorded in $CDCl_3$ at 300 MHz, ^{13}C NMR spectra at 75 MHz with chloroform (7.27 ppm for ^{1}H, 77.20 ppm for ^{13}C) as an internal reference, and ^{31}P NMR spectra in $CDCl_3$ at 121.5 MHz with H_3PO_4 as an external reference. Chemical shifts (δ) are given in parts per million; multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Coupling constants (J) are reported in hertz.

Glycosylation Reactions. *Method A. Typical Procedure from a Galactosyl Donor.* To a solution of triphenylphosphine oxide (175 mg, 6.75 equiv) in dry CH_2Cl_2 (3 mL) was added dropwise the trifluoromethanesulfonic anhydride (0.046 mL, 3 equiv) at 0 °C. After the mixture had been stirred for 30 min at the same temperature, a solution of 2,3,4,6-tetra-*O*-benzyl-D-galactopyranose (100 mg, 2 equiv) and diisopropylethylamine (0.054 mL, 3.3 equiv) in dry CH_2Cl_2 (2 mL) was added dropwise. Stirring was continued for 30 min at 0 °C, and then a solution of acceptor (1 equiv) and diisopropylethylamine (0.054 mL, 3.3 equiv) in dry CH_2Cl_2 (2 mL) was added dropwise, at the same temperature. After the reaction had reached completion (~15 min), the mixture was diluted with EtOAc and washed with a saturated $NaHCO_3$ solution, water, and brine; the organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (cyclohexane/ethyl acetate) to afford the desired compound (**3a**, **4a**, **5a**, or **6a**). All products were characterized as anomeric mixtures.

Method B. Typical Procedure from a Glucosyl Donor. To a solution of triphenylphosphine oxide (175 mg, 6.75 equiv) in dry CH_2Cl_2 (3 mL) was added dropwise the trifluoromethanesulfonic anhydride (0.046 mL, 3 equiv) at 0 °C. After the mixture had been stirred for 30 min at the same temperature, the reaction mixture was cooled to −20 °C and a solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (100 mg, 2 equiv) and diisopropylethylamine (0.054 mL, 3.3 equiv) in dry CH_2Cl_2 (2 mL) was added dropwise. Stirring was continued for 30 min at −20 °C, and then a solution of acceptor (1 equiv) and diisopropylethylamine (0.054 mL, 3.3 equiv) in dry CH_2Cl_2 (2 mL) was added dropwise, at the same temperature. After the reaction had reached completion (~15 min), the mixture was diluted with EtOAc and washed with a saturated $NaHCO_3$ solution, water, and brine; the organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (cyclohexane/ethyl acetate) to afford the desired compound (**3b**, **4b**, **5b**, or **6b**). All products were characterized as anomeric mixtures.

Isopropyl 2,3,4,6-tetra-*O*-benzylgalactopyranoside (3a).[20] was obtained by method A as a colorless syrup in 98% yield (44:56 α:β ratio): R_f = 0.55 [8:2 (v/v) cyclohexane/ethyl acetate]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45−7.20 (m, 20 H), 4.99 (d, 0.44 H, J = 3.5 Hz, H-1α), 4.98−4.39 (m, 8.56 H, 4 CH_2Ph and H-1β), 4.09−3.86 [m, 3.32 H, H-2α, H-3α, H-4α, H-5α, H-4β, CH(CH_3)$_2$], 3.82 (dd, 1 H, J = 7.6, 9.8 Hz, H-2β), 3.63−3.47 (m, 3.12 H, H-3β, H-5β, 2 H-6), 1.31−1.19 (m, 6 H, 2 CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.5−138.4 (cluster of s, Ar), 128.7−127.8 (cluster of d, CH Ar), 102.8 (d, C-1β), 95.8 (d, C-1α), 82.7 (d), 79.9 (d), 79.6 (d), 76.8 (d), 75.5 (d), 75.4 (t), 75.0 (t), 74.7 (t), 73.9 (d), 73.8 (t), 73.7 (t), 73.7 (d), 73.5 (t), 73.5 (t), 73.4 (t), 72.4 (d), 69.5 (d, 2 C), 69.4 (t, 2 C), 23.9 (q), 23.5 (q), 22.4 (q), 21.6 (q). Elemental anal. Calcd for $C_{37}H_{42}O_6$: C, 76.26%; H, 7.26%. Found: C, 76.31%; H, 7.41%.

Cholesteryl 2,3,4,6-tetra-*O*-benzylgalactopyranoside (4a).[21] was obtained by method A as a light yellow syrup in 95% yield (42:58 α:β ratio): R_f = 0.75 [8:2 (v/v) cyclohexane/ethyl acetate]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45−7.20 (m, 20 H), 5.34 (br d, 0.58 H, J = 4.6 Hz, H-6 chol. in β anomer), 5.28 (br d, 0.42 H, J = 4.3 Hz, H-6 chol. in α anomer), 5.01 (d, 0.42 H, J = 3.4 Hz, H-1α), 5.00−4.39 (m, 8.58 H, 4 CH_2Ph and H-1β), 4.12−3.87 (m, 2.68 H, H-2α, H-3α, H-4α, H-5α, H-3 chol.), 3.89 (d, 0.58 H, J = 2.4 Hz, H-4β), 3.83 (dd, 0.58 H, J = 7.6, 9.8 Hz, H-2β), 3.65−3.45 (m, 3.16 H, H-3β, H-5β, 2 H-6), 2.51−2.25 (m, 2 H), 2.08−1.79 (m, 5 H), 1.68−0.82 (m, 38 H), 0.70 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.2 (s, C-5 chol. of α anomer), 141.1 (s, C-5 chol. of β anomer), 139.5−138.4 (cluster of s, quaternary Ar), 128.7−127.5 (cluster of d, CH Ar), 122.0 (d, C-6 chol. of β anomer), 121.9 (d, C-6 chol. of α anomer), 102.8 (d, C-1β), 95.8 (d, C-1α), 82.7 (d), 80.0 (d), 79.8 (d), 79.6 (d), 77.1 (d), 76.9 (d), 75.6 (t), 75.5 (d), 75.1 (t), 74.8 (t), 73.9 (d), 73.8 (t), 73.7 (t), 73.7 (d), 73.5 (t), 73.5 (t), 73.4 (t), 69.6 (d), 69.5 (t), 69.4 (t), 57.1 (d), 57.1 (d), 56.5 (d), 50.5 (d), 50.5 (d), 42.7 (t, 2 C), 42.7 (s, 2 C), 40.1 (t), 40.0 (t), 39.8 (t), 39.3 (t), 37.6 (t), 37.5 (t), 37.1 (q), 36.5 (q), 36.1 (d), 32.3 (t, 2 C), 32.2 (d, 2 C), 28.6 (t, 2 C), 28.3 (d, 2 C), 24.6 (t, 2 C), 24.1 (t, 2 C), 23.1 (q, 2 C), 22.9 (q, 2 C), 21.4 (t, 2 C), 19.7 (q, 2 C), 19.0 (q, 2 C), 12.1 (q, 2 C). Elemental anal. Calcd for $C_{61}H_{80}O_6$: C, 80.57%; H, 8.87%. Found: C, 80.43%; H, 8.65%.

Benzyl 2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (5a).[22] was obtained by method A as a colorless syrup in 98% yield (60:40 α:β ratio): R_f = 0.5 [8:2 (v/v) cyclohexane/ethyl acetate]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.5−7.2 (m, 40 H), 5.12 (d, 0.6 H, J = 3.4 Hz, H-1′α), 5.05−4.38 [m, 17.4 H, 8 CH_2Ph, H-1′β, H-1(α1′→6), H-1(β1′→6)], 4.22 [br d, 0.4 H, J = 10.6 Hz, H-6(β1′→6)], 4.12−4.00 (m, 1.4 H), 4.0−3.8 (m, 3.2 H), 3.76−3.32 (m, 7 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.5−137.9 (cluster of s, Ar), 128.8−127.8 (cluster of d, CH Ar), 104.7 (d, C-1′β), 103.0 [d, C-1(β1′→6)], 102.9 [d, C-1(α1′→6)], 98.4 (d, C-1′α), 85.2 (d), 85.1 (d), 82.9 (d), 82.7 (d), 82.6 (d), 79.9 (d), 78.9 (d), 78.8 (d), 78.4 (d), 76.2 (t), 76.0 (t), 75.8 (d), 75.6 (t), 75.5 (t), 75.4 (t), 75.2 (t), 74.0 (d), 74.0 (t), 73.8 (t), 73.5 (t), 73.0 (d), 71.6 (t), 71.4 (t), 69.8 (d), 69.5 (t), 69.1 (t), 68.8 (t), 66.6 (t). Elemental anal. Calcd for $C_{68}H_{70}O_{11}$: C, 76.81%; H, 6.64%. Found: C, 76.73%; H, 6.55%.

Phenyl tetra-*O*-benzyl-α-D-galactopyranosyl-(1→4)-2,3-di-*O*-benzoyl-6-*O*-*tert*-butyldiphenylsilyl-1-thio-β-D-glucopyranoside (6a). was obtained by method A as a colorless syrup in 75% yield (α only): R_f = 0.59 [8:2 (v/v) cyclohexane/ethyl acetate]; $[\alpha]_D^{20}$ = +43.5° (c = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.97−7.90 (m, 4 H), 7.77 (q, 4 H, J = 6.1, 18.7 Hz), 7.55−7.05 (m, 37 H), 5.83 (t, 1 H, J = 9.5, H-3), 5.48 (t, 1 H, J = 9.5, H-2), 5.15 (d, 1 H, J = 3.1 Hz, H-1′α), 4.99 (d, 1 H, J = 9.8 Hz, H-1), 4.83 (d, 1 H, J = 11.0 Hz, CHPh), 4.57−4.45 (m, 3 H, CHPh, CH_2Ph), 4.35−4.16 (m, 6 H, H-4, H-4′, H-6a, CHPh, CH_2Ph), 3.95 (d, 1 H, J = 10.4, H-6b), 3.93 (d, 1 H, J = 12.5 Hz, CHPh), 3.84−3.63 (m, 4 H, H-5, H-2′, H-3′, H-5′), 3.33 (d, 2 H, J = 6.1 Hz, H-6′a,b), 1.07 (s, 9 H, 3 CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.6 (s, C═O), 164.2 (s, C═O), 137.8 (s), 137.5 (s), 137.2 (s), 136.8 (s), 134.8 (d), 134.6 (d), 132.6 (s), 132.2 (s), 131.9 (d), 131.8 (s), 131.6 (d), 130.4 (d), 128.2 (s), 128.6−126.2 (cluster of d, CH Ar), 97.9 (d, C-1′), 85.4 (C-1), 79.2 (d), 77.5 (d), 74.7 (d), 74.5 (d), 73.9 (d), 73.8 (d), 73.3 (t), 72.1 (t, 2 C), 71.4 (t), 69.8 (d), 69.3 (d), 67.9 (t), 62.1 (t), 25.8 (q, 3 CH_3), 18.1 [s, C(CH_3)$_3$]. Elemental anal. Calcd for $C_{76}H_{76}O_{12}SSi$: C, 73.52%; H, 6.17%. Found: C, 73.43%; H, 6.08%.

Isopropyl 2,3,4,6-tetra-*O*-benzylglucopyranoside (3b).[23] was obtained by method B as a white solid in 97% yield (25:75 α:β ratio): R_f = 0.59 [8:2 (v/v) cyclohexane/ethyl acetate]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45−7.13 (m, 20 H), 4.90 (d, 0.25 H, J = 3.6 Hz, H-1α), 5.05−4.43 (m, 8.75 H, 4 CH_2Ph and H-1β), 4.09−3.97 [m, 1 H, H-3α, CH(CH_3)$_2\beta$], 396−3.82 [m, 0.5 H, H-5α, CH(CH_3)$_2\alpha$], 3.80−3.41 (m, 5.5 H, H-2α, H-2β, H-3β, H-4, H-5β, 2 H-6), 1.33 (d, 2.25 H, J = 6.1 Hz, C$H_3\beta$), 1.30−1.22 (m, 3 H, C$H_3\beta$ and C$H_3\alpha$), 1.19 (d, 0.75 H, J = 6.1 Hz, C$H_3\alpha$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.2−138.5 (cluster of s, Ar), 129.0−127.0 (cluster of d, CH Ar), 102.7 (d, C-1β), 95.2 (d, C-1α), 85.3 (d), 82.7 (d), 82.6 (d), 80.4 (d), 78.5 (d), 78.4 (d), 76.1 (t, 2 C), 75.6 (t), 75.4 (t), 75.3 (t), 73.9 (d), 73.6 (t), 72.8 (d), 70.5 (d), 69.7 (t), 69.5 (d), 69.0 (t), 24.2 (q), 23.6 (q), 22.7 (q), 21.6 (q). Elemental anal. Calcd for $C_{37}H_{42}O_6$: C, 76.26%; H, 7.26%. Found: C, 76.48%; H, 7.36%.

Cholesteryl 2,3,4,6-tetra-*O*-benzylglucopyranoside (4b).[24] was obtained by method B as a colorless syrup in 95% yield (27:73 α:β ratio): R_f = 0.73 [8:2 (v/v) cyclohexane/ethyl acetate]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45−7.15 (m, 20 H), 5.37 (br d, 0.73 H, J = 4.9 Hz, H-6 chol. in β anomer), 5.31 (br d, 0.27 H, J = 4.9 Hz, H-6 chol. in

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α anomer), 5.06−4.43 (m, 9 H, 4 CH_2Ph, H-1α and H-1β), 4.03 (t, 0.27 H, J = 9.4 Hz, H-3α), 3.91 (br d, 0.27 H, H-5α), 3.81−3.42 (m, 6.46 H, H-2α, H-2β, H-3β, H-4α, H-4β, H-5β, 2 H-6, H-3 chol.), 2.51−2.25 (m, 2 H), 2.15−1.79 (m, 5 H), 1.68−0.82 (m, 38 H), 0.70 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.3 (s, C-5 chol. of α anomer), 141.1 (s, C-5 chol. of β anomer), 139.5−138.4 (cluster of s, quaternary Ar), 129.5−127.8 (cluster of d, CH Ar), 122.4 (d, C-6 chol. of β anomer), 122.2 (d, C-6 chol. of α anomer), 102.7 (d, C-1β), 95.1 (d, C-1α), 85.3 (d), 82.8 (d), 82.6 (d), 80.4 (d), 80.1 (d), 78.5 (d), 78.4 (d), 77.0 (d), 76.2 (t), 75.6 (t), 75.5 (t), 75.3 (d), 73.9 (t), 73.6 (t), 70.5 (d), 69.7 (t), 69.0 (t), 57.2 (d), 56.6 (d), 50.7 (d), 50.6 (d), 42.8 (t), 42.8 (s), 40.1 (t), 40.4 (t), 40.3 (t), 40.0 (t), 39.6 (t), 37.8 (t), 37.2 (q), 36.7 (q), 36.3 (d), 32.4 (t, 2 C), 32.3 (d, 2 C), 28.7 (t, 2 C), 28.5 (d, 2 C), 24.7 (t, 2 C), 24.3 (t, 2 C), 23.3 (q, 2 C), 23.1 (q, 2 C), 21.6 (t, 2 C), 19.9 (q, 2 C), 19.2 (q, 2 C), 12.3 (q, 2 C). Elemental anal. Calcd for $C_{61}H_{80}O_6$: C, 80.57%; H, 8.87%. Found: C, 80.29%; H, 8.94%.

Benzyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (5b).[25] was obtained by method B as a white solid in 96% yield (37:63 α:β ratio): R_f = 0.5 [8:2 (v/v) cyclohexane/ethyl acetate]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.5−7.2 (m, 40 H), 5.03 (d, 0.37 H, J = 3.7 Hz, H-1′α), 5.08−4.41 [m, 16.63 H, 8 CH_2Ph, H-1′β, H-1(α1′→6), H-1(β1′→6)], 4.24 [br d, 0.63 H, J = 10.5 Hz, H-6(β1′→6)], 4.28 (t, 0.37 H, J = 9.2 Hz, H-3′α), 3.93 (m, 0.37 H, H-5′α), 3.86−3.35 (m, 10.63 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.2−137.8 (cluster of s, Ar), 128.9−127.7 (cluster of d, CH Ar), 104.5 (d, C-1′β), 103.1 [d, C-1(β1′→6)], 102.7 [d, C-1(α1′→6)], 97.6 (d, C-1′α), 85.3 (d), 85.2 (d), 82.9 (d), 82.8 (d), 82.6 (d), 82.3 (d), 80.5 (d), 78.8 (d), 78.3 (d), 76.2 (t), 76.1 (t), 75.6 (d), 75.4 (t), 75.3 (t), 75.2 (t), 74.0 (t), 73.9 (t), 73.0 (t), 71.6 (t), 71.4 (t), 70.6 (d), 69.4 (t), 69.1 (t), 68.9 (t). Elemental anal. Calcd for $C_{68}H_{70}O_{11}$: C, 76.81%; H, 6.64%. Found: C, 76.89%; H, 6.77%.

Phenyl tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3-di-*O*-benzoyl-6-*O*-*tert*-butyldiphenylsilyl-1-thio-β-D-glucopyranoside (6b). was obtained by method B as a colorless syrup in 72% yield (α only): R_f = 0.6 [8:2 (v/v) cyclohexane/ethyl acetate]; $[\alpha]_D^{20}$ = +43.9° (c = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.99−7.93 (m, 4 H), 7.77 (q, 4 H, J = 6.1, 18.7 Hz), 7.55−7.05 (m, 37 H), 5.84 (t, 1 H, J = 9.1 Hz, H-3), 5.49 (t, 1 H, J = 9.5 Hz, H-2), 5.09 (d, 1 H, J = 3.1 Hz, H-1α), 5.00 (d, 1 H, J = 9.8 Hz, H-1), 4.77 (d, 1 H, J = 11.0 Hz, C*H*Ph), 4.65 (s, 2 H, CH_2Ph), 4.45 (d, 1 H, J = 11.9 Hz, C*H*Ph), 4.4 (d, 1 H, J = 11.0 Hz, C*H*Ph), 4.36−4.21 (m, 4 H, 2 C*H*Ph, H-4, H-6a), 4.04 (d, 1 H, J = 11.64 Hz, H-6b), 3.96−3.82 (m, 3 H, H-3′, CH_2Ph), 3.77 (br d, 1 H, H-5′), 3.67 (br d, 1 H, H-5), 3.58−3.45 (m, 2 H, H-4′, H-6′a), 3.41−3.25 (m, 2 H, H-2′, H-6′b), 1.08 (s, 9 H, 3 CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.6 (s, C═O), 164.3 (s, C═O), 137.8 (s), 137.4 (s), 137.1 (s), 136.9 (s), 134.9 (d), 134.6 (d), 132.7 (s), 132.6 (s), 132.1 (d), 131.9 (s), 131.7 (d), 130.5 (d), 128.8 (d), 128.5 (d), 128.4 (d), 128.3 (s), 127.9−126.2 (cluster of d, CH Ar), 97.9 (d, C-1′), 85.5 (C-1), 80.4 (d), 79.2 (d), 78.2 (d), 76.3 (d), 74.7 (d), 74.4 (d), 74.3 (t), 73.8 (t), 72.3 (t), 71.4 (t), 70.6 (d), 69.9 (t), 67.5 (t), 61.9 (t), 25.9 (q, 3 CH_3), 18.3 [s, C$(CH_3)_3$]. Elemental anal. Calcd for $C_{76}H_{76}O_{12}SSi$: C, 73.52%; H, 6.17%. Found: C, 73.73%; H, 6.25%.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of the products and ^{1}H, ^{13}C, and ^{31}P NMR spectra of the intermediate. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ DEDICATION

Dedicated to the memory of Prof. David Y. Gin.

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During the preparation of the manuscript the authors were not aware of the works of Prof. Chapleur's group on anomeric aminophosphonium salts, see: Chretien, F.; Chapleur, Y.; Castro, B.; Gross, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 381−384, and references cited therein. This paper published ASAP on October 11, 2011 and then reposted with this note October 14, 2011.