Anionic Additions to Glycosyl Iodides: Highly Stereoselective Syntheses of *β C*-, *N*-, and *O*-Glycosides[1]

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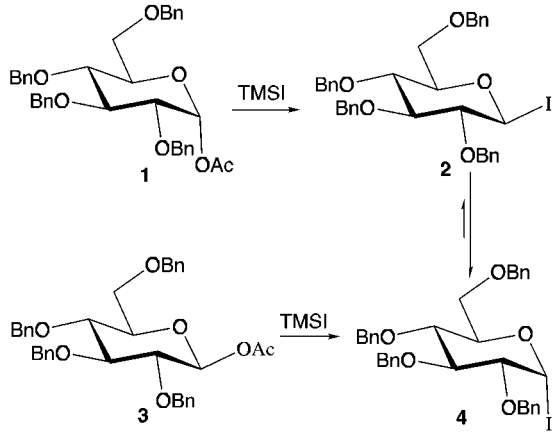
Classically, glycosyl halides are activated as glycosyl donors by metal chelation under Koenigs−Knorr or Helferich conditions. These reactions often proceed through oxonium formation, and the stereochemical outcome is dictated by the anomeric effect and/or the nature of the protecting group on the C2 hydroxyl. Alternatively, glycosyl halides may undergo direct displacement of the halide by an incoming nucleophile in an S_N2 mechanism. The latter reaction is far less common, and before this study it was primarily performed with glycosyl bromides. Having recently shown that both α and *β* glycosyl iodides could be efficiently generated, we embarked upon an investigation of nucleophilic additions to glycosyl iodides. The studies reported herein show that additions of stabilized anions to α-glycosyl iodides proceed with inversion of stereochemistry to give *β*-glycosides, even in the absence of a C2 participatory group. Glucosyl, galactosyl, and mannosyl iodides were studied, and the combined results indicate that the reactivity of 2,3,4,6-tetra-*O*-benzyl-α-D-galactosyl iodide > 2,3,4,6-tetra-*O*-benzyl-α-D-glucosyl iodide > 2,3,4,6-tetra-*O*-benzyl-α-D-mannosyl iodide. Both the glucosyl and galactosyl iodides are susceptible to E-2 elimination when treated with highly basic anions. In contrast, the mannosyl iodide undergoes substitution to give the 1,2 *cis* configuration. The overall sequence involves reaction of an anomeric acetate with trimethylsilyl iodide with *in vacuo* removal of the resulting trimethylsilyl acetate. The iodide is then treated with a nucleophile without further characterization. A variety of nucleophiles were stereoselectively added to the glycosyl halides providing *β*-, *C*-, *N*-, and *O*-glycosides.

Introduction

Glycosyl halides are most commonly employed in glycosylation methods involving activation of the halide through metal chelation.[2] The stereochemical outcome of the glycosylation may be dictated by a combination of factors including neighboring group participation,[3] solvent participation,[4] and the metal catalyst.[5] An alternative glycosylation strategy involves reaction of glycosyl halides under basic conditions. These reactions typically proceed through nucleophilic displacement of the anomeric halide in an S_N2 fashion, or by generation of an oxonium ion that is subsequently trapped by the nucleophile.[6]

One advantage of S_N2 displacement reactions is their potential for stereospecificity. In the absence of neighboring group participation, the α-glycosyl halide would be expected to give the *β*-glycoside and vice versa. Furthermore, the reactions often proceed under relatively neutral conditions. For example, treatment of a glycosyl bromide with an alcohol in the presence of 2,6-lutidine results in glycoside formation, albeit in low to moderate yields.[7] The yields and reaction rates can be increased by *in situ* generation of the more reactive *β*-glycosyl halide, with subsequent formation of the α-glycoside.

Scheme 1



Glycosyl iodides have also been generated from other glycosyl donors *in situ*, and they show greater reactivity toward nucleophilic displacement under neutral conditions.[8] *β*-Glycosides generally result from anionic additions to α-glycosyl bromides, but the yields are variable and often elimination of HBr and formation of the glycal is observed.[9]

Recently we reported on the stereoselective generation of glycosyl iodides from anomeric acetates.[10] In the course of those investigations we discovered that reaction of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl acetate **1** with trimethylsilyl iodide results in the initial formation of the *β*-glycosyl iodide **2**, whereas the *β*-anomeric acetate **3** is converted into the α-iodide **4** (Scheme 1). These

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(2) Helferich, B.; Gootz, R. *Ber.* **1929**, *62*, 2791. Déjter-Juszynski, M.; Flowers, H. M. *Carbohydr. Res.* **1971,** *18*, 219 and references cited therein.

(3) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212. Paulsen, H. *Chem. Soc. Rev.* **1984**, *13*, 15.

(4) Schmidt, R. R.; Rucker, E. *Tetrahedron Lett.* **1980**, *21*, 1421. Schmidt, R. R.; Behrendt, M.; Toepfer, A. *Synlett* **1990**, 694.

(5) For a recent example see: Lichtenthaler, F. W.; Kohler, B. *Carbohydr. Res.* **1994**, *258*, 77.

(6) Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056.

(7) Kronzer, F. J.; Schuerch, C. *Carbohydr. Res.* **1974**, *34*, 71.

(8) Schmid, U.; Waldemann, H. *Tetrahedron Lett.* **1996**, 3837. Hashimoto, S.-i; Honda, T. Ikegami, S. *Tetrahedron Lett.* **1990**, 4769.

(9) Somsák, L.; Papp, E.; Batta, Gy.; Farkas, I. *Carbohydr. Res.* **1991**, *211*, 173.

(10) Gervay, J.; Nguyen, T. N.; Hadd, M. J. *Carbohydr. Res.* **1997**, *300*, 119.

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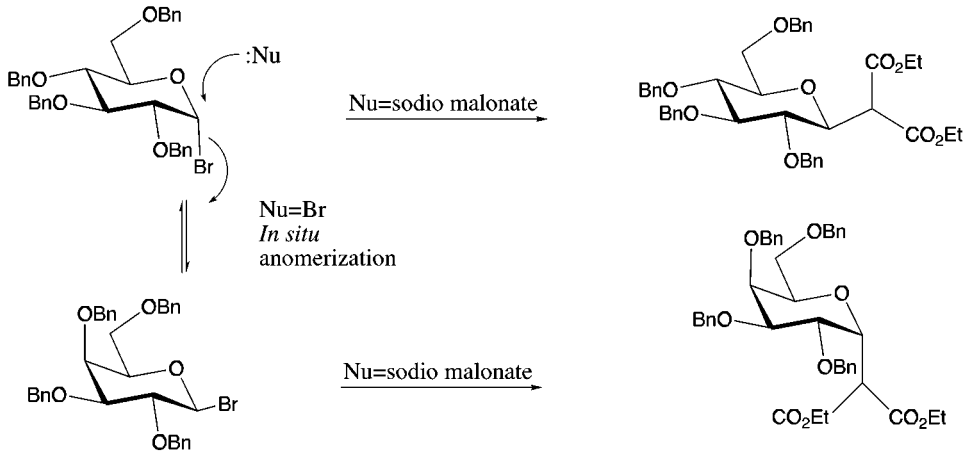
Scheme 2



reactions proceed in quantitative yield with the only byproduct being trimethylsilyl acetate which can be removed *in vacuo*. Although the intermediacy of **2** and **4** had been reported,[7,8] prior to our work these glycosyl iodides had not been isolated and/or characterized.

In view of the often less than satisfactory reactivity of glycosyl bromides in S_N2 reactions, we decided to investigate anionic additions to anomeric iodides. All prior reactions, wherein the glycosyl iodide was generated *in situ*, resulted in preferential α-glycoside formation, presumably through nucleophilic displacement of the *β*-iodide or an S_N1 mechanism. At the outset we were most interested in being able to achieve *β*-glycoside formation, since it is most difficult to achieve in the absence of neighboring group participation. Reported herein is the stereoselective addition of C-, N-, and O-based anions to α-glycosyl iodides.

Results and Discussion

In 1974 Hanessian reported that glycosyl bromides undergo reaction with sodio diethylmalonate to give a 3:1 *β*:α ratio of the *C*-glycoside.[11] The reaction was performed at room temperature for 40 h in diethyl malonate as a solvent, and 10 equiv of base was added. Upon addition of 10 equiv of tetrabutylammonium bromide, the α-selectivity increased to give a 1:3 *β*:α ratio. One possible mechanism that explains these results suggests that the α-anomeric bromide initially undergoes S_N2 attack by the malonate to give the *β*-*C*-glycoside. As the concentration of bromide ion increases so does the possibility of *in situ* anomerization to the *β*-anomeric bromide which is subsequently displaced by the malonate to give the α-*C*-glycoside. Addition of tetrabutylammonium bromide increases the rate of *in situ* anomerization relative to direct displacement of the α bromide by malonate thereby increasing the yield of the α-glycoside (Scheme 2). However it is possible that substitution via an S_N1 mechanism is a competing process.

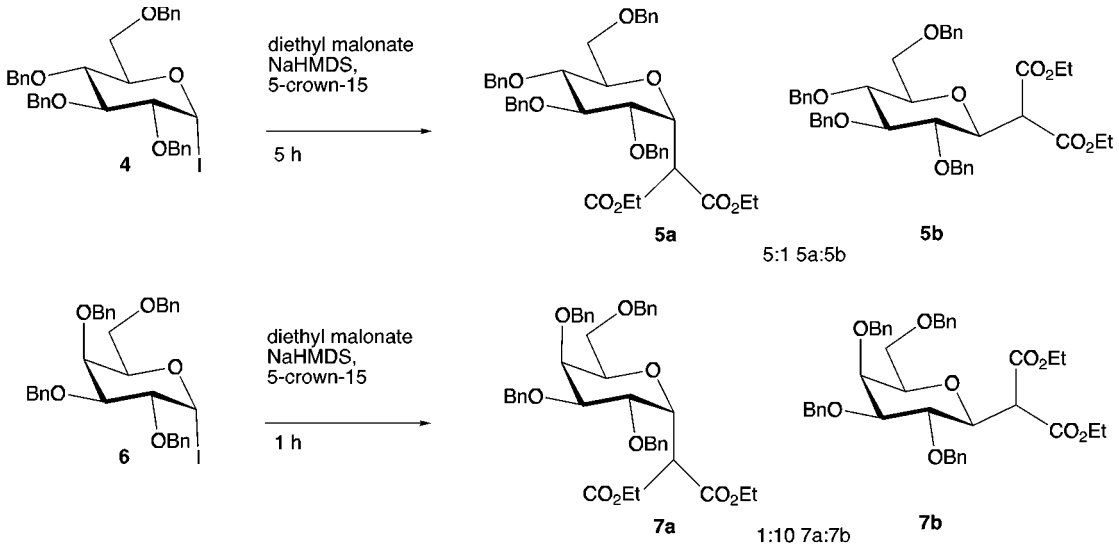
Reaction of **4** and 1.3 equiv of diethyl malonate that had previously been treated with sodium hexamethyldisilazane (NaHMDS) in the presence 15-crown-5 resulted in the preferential formation of the α-*C*-glycoside **5a** (5:1 α:*β*). The reaction was complete after 5 h at room temperature in THF. This is a relatively slow reaction (*vide infra*), suggesting that the α-iodide is not particularly susceptible to attack by the malonate anion. Rather, it appears that *in situ* anomerization is occurring and the *β*-iodide is preferentially undergoing attack, although here again an S_N1 mechanism cannot be ruled out. Interesting the galactosyl iodide **6** is much more reactive toward malonate displacement. The analogous reaction was complete within 1 h at room temperature, and a 1:10 α:*β* ratio of *C*-glycosides **7ab** was obtained, suggesting that *in situ* anomerization and/or oxonium formation do not effectively compete in this reaction (Scheme 3). We considered the possibility that the *C*-glycosides themselves could be undergoing anomerization via *β*-elimination followed by conjugate addition (Scheme 4). In order to rule this mechanism out, **7a** and **7b** were separated and resubjected to the reaction conditions and no erosion of stereochemistry was observed.

The addition of TMSCN to anomeric acetates to give pyranosyl cyanides has been reported,[12] but to our knowledge S_N2 displacement of anomeric halides by cyanide has not. In our investigations we first treated **4** with 5 equiv of tetrabutylammonium cyanide in THF at room temperature (Scheme 5). After 10 min TLC showed complete disappearance of starting material and the formation of two products. Isolation of the products revealed that the major product resulted from E-2 elimination of the glycosyl iodide to give the glycal **8**, in addition to a 32% yield of the *β*-glucosyl cyanide **9**. A number of different conditions were tried in order to minimize elimination, including lower reaction temperatures and utilizing fewer equivalents of tetrabutylammonium cyanide, but the glycal was consistently the major product obtained. We reasoned that the mannosyl iodide should not be susceptible to E-2 elimination. Therefore we prepared the α-mannosyl iodide **11** by reaction of α-2,3,4,6-tetra-*O*-benzylmannosyl acetate **10** with TMSI in CH_2Cl_2 at 0 °C for 40 min. The solvent was evaporated, and the mannosyl iodide was diluted in THF before adding 5 equiv of tetrabutylammonium cyanide. After 2 h the iodide was no longer present and a single product was observed on TLC. The crude NMR showed mainly one product, but the presence of other minor products could not be ruled out since the benzylic protons obscured the region where their resonances would appear. Column chromatography afforded a 55% yield of 1-deoxy-2,3,4,6-tetra-*O*-benzyl-*β*-D-mannosyl cyanide (**12**). This is a particularly important result since

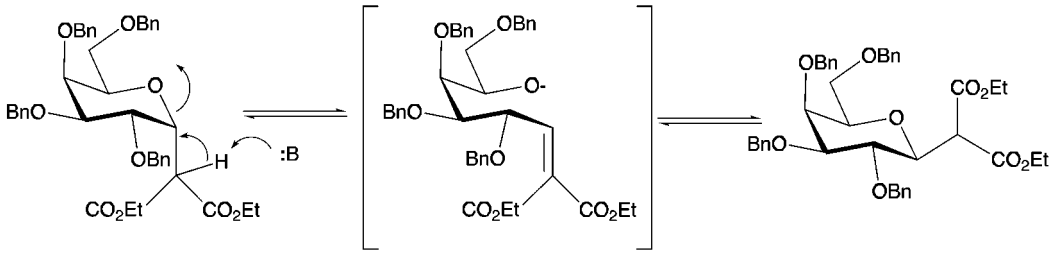
(11) Hanessian, S.; Pernet, A. G. *Can. J. Chem.* **1974**, *52*, 1266.

(12) López, M.-T. G.; De Las Heras, F. G.; Félix, A. S. *J. Carbohydr. Chem.* **1987**, *6*, 273. de las Heras, F. G.; Fernández-Reza, P. *J. Chem. Soc., Perkin Trans. 1* **1982**, 903.

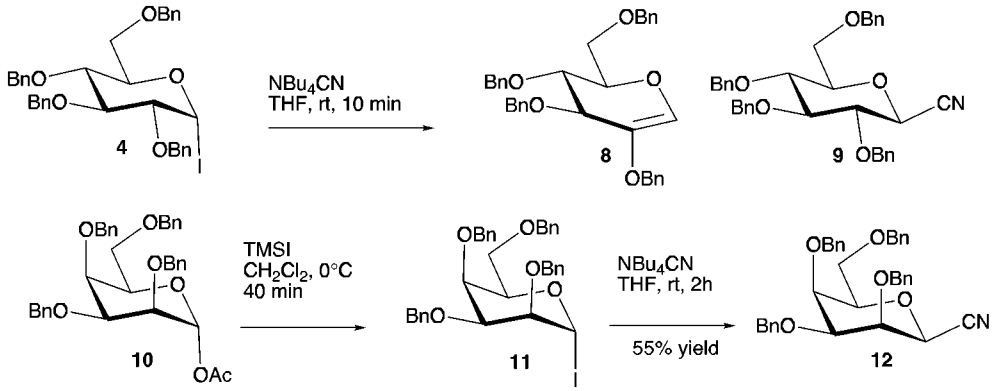
Scheme 3



Scheme 4



Scheme 5

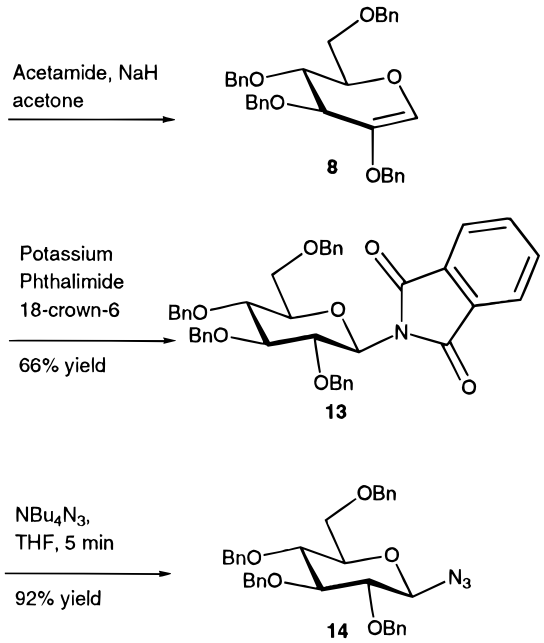


the *cis* 1,2 linkage in mannose is among the most difficult to achieve.[13] Furthermore, it indicates that the mannosyl iodide is less reactive than the glucosyl iodide since reaction of **4** was complete in 10 min rather than 2 h. The combined malonate and cyanide data suggest that galactosyl iodide is more reactive than glucosyl iodide, which is more reactive than mannosyl iodide.

We next looked at the possibility of addition of nitrogen-based nucleophiles. *N*-Glycosides are important natural products most commonly found as asparagine conjugates.[14] As a model for asparagine addition, acetamide was deprotonated with sodium hydride in acetone and added to **4** (Scheme 6). Unfortunately **8** was the only detectable product, presumably resulting from E-2 elimination. The more stabilized potassium phthalimide in the presence of 18-crown-6 did displace the iodide with inversion to give **13** in 66% yield. Similarly, addition of tetrabutylammonium azide to **4** gave the β-glucosyl azide (**14**) in 92% yield within 5 min at room temperature. Inspection of the crude NMR spectra from these reactions showed no detectable α-products, however the β-phthalimido derivative does undergo anomerization upon standing. S_N2 reactions of glycosyl chlorides and bromides with azide anion are known to occur even in the presence of a participatory group at C2.[15] For example, reaction of peracetylated mannosyl bromide with sodium azide in HMPA at 90 °C for 1 h gave a quantitative yield of the 1,2 *cis* glycosyl azide. Inversion of stereochemistry is also observed in the addition of NaN_3 to 1-bromoglucopyranosyl cyanides.[16] The earlier studies combined with our results demonstrate that glycosyl halides are useful

(13) Hodosi, G.; Kovác, P. *J. Am. Chem. Soc.* **1997**, *119*, 2335. Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 4506 and references cited therein.
(14) Montreuil, J. *Adv. Carbohydr. Chem. Biochem.* **1980**, *37*, 157. Paulsen, H. *Angew. Chem.* **1990**, *102*, 851.
(15) Gyorgydeák, Z.; Paulsen, H. *Liebigs Ann. Chem.* **1977**, 1987.
(16) Praly, J.-F.; Di Stefano, C.; Descotes, G.; Faure, R.; Somsák, L.; Eperjesi, I. *Tetrahedron Lett.* **1995**, 3329.

Scheme 6

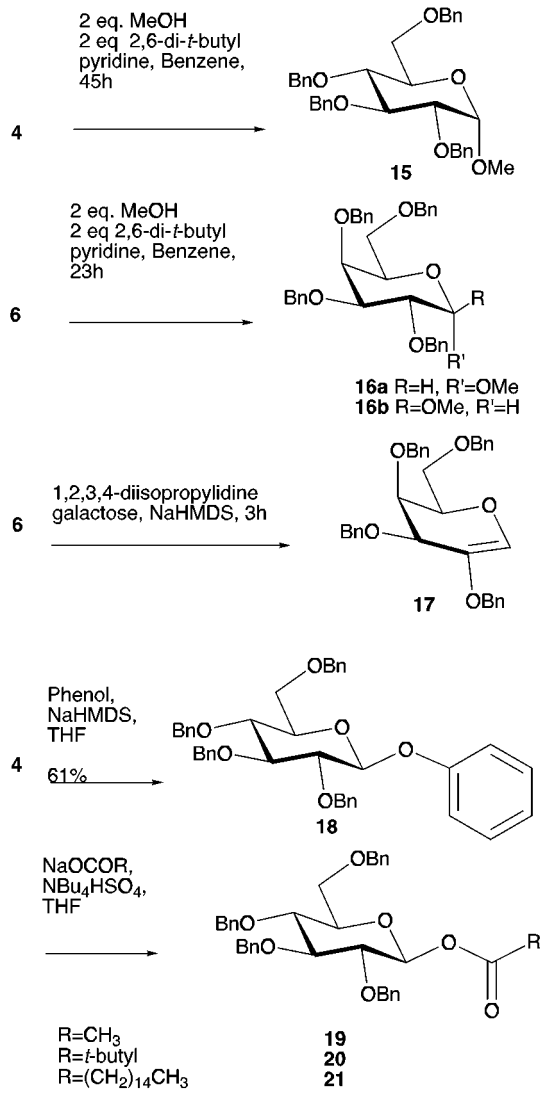


precursors to glycosyl azides and that the glycosyl iodides are more reactive than the corresponding bromides. Furthemore, within the detectable limits of NMR, these reactions are stereospecific. Glycosyl azides are important intermediates in route to N-linked glycopeptides[17] and peptidosaccharides.[18]

Glycosyl iodides are known to undergo *O*-glycosylation under neutral conditions to give the α-glycoside as the major product, but this was only reported with *in situ* generation of the iodide.[7] If S_N2 displacement is the mechanism of reaction, then it can be concluded that the *β*-iodide underwent attack in these reactions, and one would expect the α-iodide to give the *β*-glycoside. Interestingly when **4** was treated with 2 equiv of methanol in benzene at room temperature, the reaction proceeded slowly, giving the α-methyl glycoside (**15**) in 70% yield after 45 h (Scheme 7). Similar to the reaction of **4** with sodio diethyl malonate, the glucosyl iodide showed relatively low reactivity, and the formation of the α-glucoside is consistent with the *in situ* anomerization or S_N1 mechanisms invoked in the *C*-glycosylation experiment (Scheme 1). The reactivity of the galactosyl iodide toward neutral displacement was also studied. Consistent with earlier studies, it reacted faster than the glucosyl iodide (after 23 h TLC showed no further conversion of the iodide). Both anomers of the methyl galactoside were formed (**16ab**) in a 1.2:1 α:*β* ratio.

We next explored the possibility of effecting displacement by the reaction of an alkoxide anion. In the event 1,2:3,4-diisopropylidenegalactose was treated with NaHMDS in THF and added to **6** at room temperature. After 3 h the iodide was no longer present on TLC, and the only product obtained was the glycal **17**, an unpleasant reminder that E-2 elimination occurs with highly basic nucleophiles. However, the more stabilized phenoxide anion did undergo reaction with **4** to give the *β*-phenyl glycoside (**18**) in 61% yield. Carboxylate anions also add to the iodides in a highly efficient manner. Acetate anion, pivalate anion, and stearate anion[19] all undergo reaction

Scheme 7



with **4** in the presence of tetrabutylmmonium hydrogen sulfate in less than 5 min at room temperature to give virtually quantitative yields of the *β*-glycosides **19**, **20**, and **21**, respectively. *β*-D-Stearyl glucopyranoside is a member of a group of naturally occurring plant hormones called Brassins.[20] Inspection of the crude NMR spectra from these reactions showed no evidence of α-product formation supporting the contention that addition is stereospecific.

The combined *O*-glycosylation results suggest that neither neutral alcoholic additions nor basic alkoxide additions to benzyl protected glucosyl and galactosyl iodides are likely to lead to efficient syntheses of *β*-*O*-alkyl glycosides. However *β*-*O*-aryl and *β*-*O*-acyl glycosides are formed in a high-yielding and highly stereoselective process.

Conclusions

Reported herein are the first studies of anion additions to α-glycosyl iodides. The results of our studies are

(17) Gyorgydeák, Z.; Szilágy, L.; Paulsen, H. *J. Carbohydr. Chem.* **1993**, *12*, 139.

(18) Sabesan, S. *Tetrahedron Lett.* **1997**, *38*, 3127.

(19) For leading references, see: Mandava, N.; Mitchell, J. W. *Chem. Ind. (London)* **1972**, *23*, 930. Pfander, H.; Laderach, M. *Carbohydr. Res.* **1982**, *99*, 175. Pfeffer, P. E.; Rothman, E. S.; Moore, G. G. *J. Org. Chem.* **1976**, *41*, 2925.

(20) In the course of these experiments we observed that after complete conversion of the iodide the acetate began to reappear on TLC, suggesting that a nucleophilic acetate species was displacing the iodide. This problem was alleviated by removing trimethylsilyl acetate from the reaction by azeotrope with toluene.

Table 1. Compiled Results from Nucleophilic Additions to Glycosyl Iodides

glycosyl iodide	nucleophile	% yield[a]	α:β ratio
4	sodio diethyl malonate	66	5:1
5	sodio diethyl malonate	58	1:10
4	NBu_4CN	32[b]	only β observed
10	NBu_4CN	55	only β observed
4	sodium acetamide	0	only glycal observed
4	potassium phthalimide	66	only β observed
4	NBu_4N_3	92	only β observed
4	MeOH	70	only α observed
6	MeOH	41[c]	1.2:1
6	sodium 1,2,3,4-diisopropylidine galactosyl alkoxide	0	only glycal observed
4	sodium phenoxide	61	only β observed
4	sodium acetate	90	1:7
4	sodium pivalate	90	only β observed
4	sodium stearate	quantitative	>5:95

[a] In all reactions (except where noted) crude NMR and TLC indicated clean conversion of starting material, the isolated yields may reflect error in weighing out the oily starting material and unavoidable loss during purification. [b] The glycal resulting from E-2 elimination was the major product. [c] Unoptimized yield.

compiled in Table 1. Glucosyl, galactosyl, and mannosyl iodides were studied, and *C*-, *N*-, and *O*-glycosides were formed. The reactions proceed most efficiently with the additions of stabilized anions, and the mechanism of reaction is believed to be S_N2 displacement of the α-iodide to give the β-glycoside. Treatment of the iodides with highly basic anions results in elimination to give the corresponding glycal, with the exception of mannosyl iodide which is not susceptible to E-2 elimination. The iodides are displaced by neutral alcohols, but there is erosion of β-selectivity, presumably due to *in situ* anomerization to the more reactive β-glycosyl iodide which undergoes S_N2 reaction to give the α-glycoside.

Overall these studies offer highly efficient and stereoselective syntheses of β-*C*-, *N*-, and *O*-glycosides from precursors that do not require a C2 participatory group. Furthermore the starting acetates are readily available, and the iodide is quantitatively generated with *in vacuo* removal of the resulting trimethylsilyl acetate. The glycosyl iodides are used without further purification in subsequent nucleophilic addition reactions. Therefore these methods provide a one-pot procedure for transforming anomeric acetates into a variety of important precursors to both natural and unnatural products.

Experimental Section

Starting materials and reagents purchased from suppliers were used without further purification. Chemicals were obtained from the following suppliers: trimethylsilyl iodide and tetra-*O*-benzylglucopyranose, Fluka; tetrabutylammonium cyanide, tetrabutylammonium azide,[21] and sodium hexamethyldisilazane, Aldrich. Solvents were dried by distillation prior to use. Dichloromethane and toluene were dried over calcium hydride, and tetrahydrofuran was dried over sodium/benzophenone. Chromatography was performed using silica gel 60 (230−400 mesh ASTM). Mass spectrometry was preformed by the University of Minnesota Mass Spectrometry Service and the University of Arizona Mass Spectrometry Facility.

Dimethyl 2-(2,3,4,6-Tetra-*O*-benzyl-α,β-D-glucopyranosyl)malonates (5a/b). To a solution of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (344 mg, 0.59 mmol) in 3 mL of CH_2Cl_2 cooled to 0 °C was added 93 μL (0.65 mmol) of trimethylsilyl iodide and the reaction mixture let sit for 30 min. The solvent was then removed *in vacuo*, and 2 mL of toluene was added and again removed *in vacuo*. The resulting oil was diluted in 3 mL of THF and added to a previously stirring solution of dimethyl malonate (88 μL, 0.77 mmol), sodium hexamethyldisilazane (650 μL of a 1 M in THF, 0.65 mmol), and 15-crown-5 (129 μL, 0.65 mmol) in 5 mL of THF. The reaction mixture was let stir for 5 h, after which the solvent was removed *in vacuo* and the resulting oil chromatographed using 3:1 hexanes:ethyl acetate to yield 257 mg (66%) of a 5.1:1 (α:β) mixture of anomers. β-anomer: ^{1}H NMR (250 MHz, C_6D_6) δ 3.23 (s, 3H), 3.29 (s, 3H), 3.39−3.43 (m, 1H), 3.63−3.70 (m, 3H), 3.78 (t, 1H, J = 9.3 Hz), 3.93 (t, 1H, J = 9.5 Hz), 4.01 (d, 1H, J = 5.4 Hz, *CH*), 4.23 (dd, 1H, J = 5.3, 9.8 Hz, H-1), 4.38 (d, 1H, J = 12.3 Hz), 4.54 (d, 1H, J = 12.0 Hz), 4.60 (d, 1H, J = 11.4 Hz), 4.72−4.82 (m, 3H), 4.87 (d, 1H, J = 11.3 Hz), 5.07 (d,1H, J = 11.1 Hz), 7.04−7.36 (m, 20H); ^{13}C NMR (250 MHz, C_6D_6) δ 51.9, 54.4, 68.9, 73.4, 74.7, 74.8, 75.5, 77.6, 78.7, 79.8, 80.2, 87.7, 127.6, 127.8, 128, 128.4, 139.0, 165.4; HRFABMS calc for $C_{39}H_{42}O_9$ 654.2829, found 655.2903 for $(M + H)^+$. α-Anomer: ^{1}H NMR (250 MHz, C_6D_6) δ 3.10 (s, 3H), 3.39 (s, 3H), 3.65−3.85 (m, 6H), 4.0−4.10 (m, 1H), 4.31−4.55 (m, 7H), 4.67 (d, 1H, J = 11.4 Hz), 4.76−4.83 (m, 2H), 5.30 (dd, 1H, J = 5.2, 10.5 Hz, H-1), 7.05−7.32 (m, 20H); ^{13}C NMR (250 MHz, C_6D_6) δ 51.9, 52.2, 52.3, 69.7,73.3, 73.5, 73.8, 74.5, 74.7, 75.1, 78.0, 79.8, 82.0, 127.6, 128, 128.2, 128.4, 128.5, 166.6; HRFABMS calc for $C_{39}H_{42}O_9$ 654.2829, found 655.2928 $(M + H)^+$.

Dimethyl 2-(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl)malonate (7a/b). To a solution of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-galactopyranoside (170 mg, 0.29 mmol) in 3 mL of CH_2Cl_2 cooled to 0 °C was added 45 μL (0.32 mmol) of iodotrimethylsilane and the solution let sit for 30 min. The solvent was then removed *in vacuo*, and then 2 mL of THF was added and the resulting solution was transferred to an already stirring solution of dimethyl malonate (71 μL, 0.44 mmol), sodium hexamethyldisilazane (380 μL, 1 M solution in THF, 0.38 mmol), and 15-crown-5 (75 μL, 0.38 mmol) in 5 mL of THF. The reaction mixture was stirred for 1 h at room temperature and then concentrated. The residue was diluted in a small amount of methylene chloride, loaded onto a silica gel column, and subsequently eluted with 3:1 hexanes:ethyl acetate to yield 110 mg (58%) of a 10:1 (β:α) mixture: β-Anomer: ^{1}H NMR (250 MHz, C_6D_6) δ 3.16 (s, 3H), 3.30 (s, 3H), 3.43 (dd, 1H, J = 8.7, 2.6 Hz), 3.54−3.72 (m, 3H), 3.83 (d, 1H, J = 2.6 Hz), 4.02 (d, 1H, J = 5.7 Hz), 4.20 (d, 1H, J = 11.8 Hz), 4.23−4.48 (m, 6H), 4.53 (d, 1H, J = 11.5 Hz), 4.62 (d, 1H, J = 11.3 Hz), 4.92 (d, 1H, J = 11.5 Hz), 5.09 (d, 1H, J = 11.3 Hz), 7.0−7.39 (m, 20H); ^{13}C NMR (250 MHz, C_6D_6) δ 51.9, 55.2, 69.0, 72.0, 73.5, 74.3, 74.8, 74.9, 77.0, 77.8, 78.0, 85.5, 127.4, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.4, 128.5, 128.6, 138.7, 138.8, 139.5, 167.3; HRFABMS calc for $C_{39}H_{42}O_9$ 654.2829, found 655.2899 $(M + H)^+$.

1-Deoxy-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl Cyanide (9). To a solution of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (53.9 mg, 0.093 mmol) in 1 mL of CH_2Cl_2 cooled to 0 °C was added 14.5 μL (0.10 mmol) of trimethylsilyl iodide and the reaction mixture let sit for 30 min. The solvent was then removed *in vacuo*, and 1 mL of toluene was added and again removed *in vacuo*. The resulting oil was diluted in 2 mL of THF and added to a previously stirring solution of

(21) Brandstrom, A.; Lamm, B.; Palmertz, I. *Acta Chem. Scand. B* **1974**, *6*, 28.

tetrabutylammonium cyanide (124 mg, 0.46 mmol) containing 3 Å molecular sieves. After 10 min, the solvent was removed *in vacuo*, and the resulting material was chromatographed using 3:1 hexanes:ethyl acetate as eluent to yield 16.5 mg (32%) of the *C*-glycoside. ^{1}H spectra matched that of the previously reported compound.[12]

General Procedure for Acetylation of the 2,3,4,6-Tetra-*O*-benzylpyranosides (10). First, 3.0 g (5.55 mmol) of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose was dissolved in 10 mL of CH_2Cl_2 and cooled to 0 °C; 2.24 mL (27.7 mmol) of pyridine was then added followed by 1.57 mL (22.2 mmol) of acetyl chloride. The solution was stirred for 4 h, then diluted in CH_2Cl_2, extracted twice with 2 M H_2SO_4 followed by brine, and dried over sodium sulfate. The crude oil was subjected to flash column chromatography using hexanes:ethyl acetate as eluent to yield 2.9 g (89%) as a clear oil, with the α-anomer always as the major product (5−10:1, α:*β*). Characterization of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl acetate,[10] 2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl acetate,[12] and 2,3,4,6-tetra-*O*-benzyl-D-mannopyranosyl acetate is as follows. α-Anomer: ^{1}H NMR (250 MHz, C_6D_6) δ 1.54 (s, 3H), 3.68−3.76 (m, 2H), 3.83 (dd, 1H, J = 11.1, 4.3 Hz), 3.93−3.98 (dd, 1H, J = 9.5 , 3.0 Hz), 4.03−4.09 (m, 1H), 4.37−4.45 (m, 4H), 4.51−4.61 (m, 4H), 4.96 (d, 1H, J = 11.3 Hz), 6.59 (d, 1H, H-1, J = 1.9 Hz), 7.03 (m, 20H). *β*-Anomer: ^{1}H NMR (250 MHz, C_6D_6) δ 1.62 (s, 3H), 3.48 (dd, 1H, J = 9.3, 2.8 Hz), 3.50 (dq, 1H, J = 9.5, 2.1 Hz), 3.66−3.80 (m, 3H), 4.25 (t, 1H, J = 9.5 Hz), 4.32−4.41(m, 3H), 4.53 (apparent d, 1H, J = 11.4 Hz), 4.55 (apparent d, 1H, J = 12.0 Hz), 4.74−4.89 (m, 3H), 5.63 (s, 1H, H-1) 6.99−7.48 (m, 20H).

1-Deoxy-2,3,4,6-tetra-*O*-benzyl-*β*-D-mannopyranosyl Cyanide (12). To a solution of acetyl 2,3,4,6-tetra-*O*-benzyl-D-mannopyranoside (88 mg, 0.15 mmol) in 2 mL of CH_2Cl_2 cooled to 0 °C was added 24 μL (0.17 mmol) of trimethylsilyl iodide and the reaction mixture let sit for 40 min. The solvent was then removed *in vacuo*, and 1 mL of toluene was added and again removed *in vacuo*. The resulting oil was diluted in 2 mL of THF and added to a previously stirring solution of tetrabutylammonium cyanide (202 mg, 0.76 mmol) in 5 mL of THF. After 2 h the solvent was removed *in vacuo*, and the residue was chromatographed using 3:1 hexanes:ethyl acetate as eluent to yield 46 mg (55%) of the *C*-glycoside: $[\alpha]^{25}_D$ −51.2° (6.6, $CDCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.31−3.37 (m, 1H), 3.45 (dd, 1H, J = 9.3, 2.3 Hz, H-3), 3.61−3.63 (m, 2H), 3.83 (t, 1H, J = 9.3 Hz, H-4), 3.92 (d, 1H, J = 2.3 Hz, H-2), 4.12 (s, 1H, H-1), 4.43−4.60 (m, 6H), 4.76 (d, 1H, J = 10.8 Hz), 4.83 (d, 1H, J = 11.5 Hz), 4.90 (d, 1H, J = 11.5 Hz), 7.13−7.48 (m, 20H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 67.4, 68.8, 72.6, 73.6, 73.9, 74.1, 74.6, 75.3, 80.5, 82.3, 127.6, 127.8, 127.9, 128.0, 128.3, 128.4, 128.5, 137.3, 137.6, 137.8; HRFABMS calc for $C_{35}H_{35}O_5N$ 549.2515, found 550.2614 $(M + H)^+$.

Phthalimido 1-Deoxy-2,3,4,6-tetra-*O*-benzyl-*β*-D-glucopyranoside (13). To a solution of acetyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (332 mg, 0.57 mmol) in 3 mL of CH_2Cl_2 cooled to 0 °C was added 89 μL of trimethylsilyl iodide and the reaction mixture let sit for 30 min. The solvent was then removed *in vacuo*, and 2 mL of toluene was added and removed *in vacuo*. The compound was diluted in 2 mL of THF and added to an already stirring solution of potassium phthalimide (159 mg, 0.86 mmol) and 18-crown-6 (226 mg, 0.86 mmol) in 7 mL of THF at room temperature. The reaction was complete after 15 min, at which time the product was diluted in methylene chloride and washed twice with 1 M KOH and once with brine and then dried over sodium sulfate to yield a yellow oil. The resulting oil was subjected to flash column chromatography using 4:1 hexanes:ethyl acetate as eluent to yield 252 mg (66%) of the title compound: ^{1}H NMR (250 MHz, C_6D_6) δ 3.41−3.50 (m, 1H), 3.56 (d, 1H, J = 10.8 Hz), 3.63−3.75 (m, 2H), 3.90 (t, 1H, J = 9.5 Hz), 4.32 (d, 1H, J = 12.0 Hz), 4.50−4.67 (m, 3H), 4.80−4.90 (m, 4H), 5.03 (t, 1H, J = 9.2Hz), 5.64 (d, 1H, J = 9.4 Hz, H-1), 6.76 (m, 4H), 7.08 (m, 20H); ^{13}C NMR (250 MHz, C_6D_6) δ 69.1, 73.7, 74.9, 75.0, 75.5, 78.1, 78.3, 79.8, 87.0, 123.3, 127.3, 127.4, 127.6, 127.8, 127.9, 128.0, 128.2, 128.4, 128.5, 133.6, 138.9, 139.3, 167.3; HR-FABMS calcd for $C_{42}H_{39}O_7N$ 669.2726, found 670.2808 $(M + H)^+$.

Azido 1-Deoxy-2,3,4,6-tetra-*O*-benzyl-*β*-D-glucopyranoside (14). To a solution of acetyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (179 mg, 0.31 mmol) in 3 mL of CH_2Cl_2 cooled to 0 °C was added 48 μL (0.39 mmol) of trimethylsilyl iodide and the reaction mixture let sit for 30 min. The solvent was removed *in vacuo*, and 2 mL of toluene was added and again removed *in vacuo*. The resulting oil was diluted in 2 mL of THF and transferred to a previously stirring solution of tetrabutylammonium azide (437 mg, 1.53 mmol) in 3 mL of THF containing 3 Å molecular sieves. After 5 min TLC (3:1 hexanes:ethyl acetate) showed complete disappearance of the iodide, the solvent was removed under vacuum, and the resulting oil was subjected to flash column chromatography using 6:1 hexanes:ethyl acetate as the eluent to yield 160 mg (92%) of the *β*-azide: $[\alpha]^{25}_D$ +28.4° (19.0, $CDCl_3$); ^{1}H NMR (250 MHz, C_6D_6) δ 3.16−3.25 (m, 1H), 3.30 (t, 1H, J = 8.7 Hz), 3.48 (t, 1H, J = 9.0 Hz), 3.55−3.61 (m, 2H), 3.68 (t, 1 H, J = 9.2 Hz), 4.24 (d, 1H, J = 8.5 Hz, H-1), 4.32 (d, 1H, J = 12.2 Hz), 4.42 (d, 1H, J = 8.5 Hz), 4.55 (d, 1H, J = 11.2 Hz), 4.61 (d, 1H, J = 11.1 Hz), 4.75 (d, 2H, J = 11.4Hz), 4.81−4.90 (m, 2H), 7.0−7.40 (m, 20H); ^{13}C NMR (250 MHz, C_6D_6) δ 68.8, 73.7, 75.1, 75.6, 77.7, 82.1, 85.2, 90.3, 127.7, 127.8, 128.0, 128.1, 128.4, 128.5, 128.6, 128.7, 138.7, 138.8, 139.1, 139.3; HR-FABMS calcd for $C_{34}H_{35}O_5N_3$ 565.2576, found 564.2539 $(M - H)^+$.

Methyl 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranoside (15). To a solution of 2,3,4,6-tetra-*O*-benzyl glucosyl acetate (206 mg, 0.35 mmol) in 3 mL of methylene chloride was added 55 μL (0.39 mmol) of trimethylsilyl iodide and the reaction mixture let sit for 30 min at 0 °C. The solvent was removed *in vacuo*, and 2 mL of benzene was added and the resulting solution added to an already stirring solution of methanol (29 μL, 0.70 mmol) and 2,6 di-*tert*-butylpyridine (172 μL, 0.87 mmol) in 5 mL of benzene and let sit for 45 h. The solvent was removed *in vacuo* and the resulting oil put down a 6:1 column (hexanes:ethyl acetate) to yield 138 mg (70%) of the α-anomer.[6]

Methyl 2,3,4,6-Tetra-*O*-benzyl-α,*β*-D-galactopyranosides (16a/b). To a solution of 2,3,4,6-tetra-*O*-benzylgalactosyl acetate 158 mg (0.27 mmol) in 2 mL of methylene chloride was added 43 μL (0.30 mmol) of trimethylsilyl iodide and the reaction mixture let sit for 30 min at 0 °C. The solvent was removed *in vacuo*, and 2 mL of benzene was added and again removed *in vacuo*. An additional 2 mL of benzene was added and the resulting solution added to an already stirring solution of methanol (22 μL, 0.54 mmol) and 2,6 di-*tert*-butylpyridine (132 μL, 0.58 mmol) in 2 mL of benzene and let sit for 42 h. The solvent was removed *in vacuo* and the resulting oil put down a 6:1 column (hexanes:ethyl acetate) to yield 61.5 mg (41% unoptimized yield) of a 1.2:1 α:*β* mixture.[6]

Phenyl 2,3,4,6-Tetra-*O*-benzyl-*β*-D-glucopyranoside (18). To a solution of acetyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (303 mg, 0.52 mmol) in 4 mL of CH_2Cl_2 cooled to 0 °C was added 81 μL (0.57 mmol) of trimethylsilyl iodide and the reaction mixture let sit for 30 min. The solvent was removed *in vacuo*, and 2 mL of toluene was added and again removed *in vacuo*. The resulting oil was diluted in 3 mL of THF and transferred into a previously stirring solution of phenol (74 mg, 0.78 mmol), sodium hexamethyldisilazane (624 μL of a 1 M solution in THF, 0.63 mmol), and 15-crown-5 (124 μL, 0.63 mmol) in 5 mL of THF. After 15 min TLC (3:1 hexanes:ethyl acetate) showed complete disappearance of the iodide. The solution was diluted in ether and washed twice with 1 M NaOH and once with saturated brine and then dried over sodium sulfate. The resulting oil was purified on a column of silica gel using 6:1 hexanes:ethyl acetate as the eluent to yield 196 mg (61%) of the glycoside: $[\alpha]^{25}_D$ +42.3° (2.6, $CDCl_3$); ^{1}H NMR (250 MHz, C_6D_6) δ 3.32−3.4 (m, 1H), 3.59−3.75 (m, 4H), 3.82 (dd, 1H, J = 7.9, 8.8 Hz, H-2), 4.31 (d, 1H, J = 12.3 Hz), 4.40 (d, 1H, J = 12.1 Hz), 4.55 (d, 1H, J = 11.3 Hz), 4.77−4.88 (m, 3H), 4.96 (d, 1H, J = 7.7 Hz, H-1), 5.00 (d, 1H, J = 11.4 Hz), 5.09 (d, 1H, J = 11.3 Hz), 6.85−7.37 (m, 25H); ^{13}C NMR (250 MHz, C_6D_6) δ 69.2, 73.4, 74.9, 75.0, 75.5, 75.54, 82.4, 84.9, 102.1, 117.4, 122.8, 127.6, 127.7, 127.8, 127.9, 128.0, 128.4, 128.5, 128.8, 129.6, 138.8, 139.1, 139.4, 158.1; HR-FABMS calc for $C_{40}H_{40}O_6$ 616.2825, found 639.2693 $(M + Na)^+$.

Acetyl 2,3,4,6-Tetra-*O*-benzyl-*β*-D-glucopyranoside (19). To a solution of acetyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (207 mg, 0.36 mmol) in 3 mL of CH_2Cl_2 cooled to 0 °C was added 56 μL (0.39 mmol) of trimethylsilyl iodide and the reaction mixture let sit for 35 min. The solvent was removed *in vacuo*, and 2 mL of THF was added and the resulting solution transferred into an already stirring solution of anhydrous sodium acetate (88 mg, 1.07 mmol) and tetrabutylammonium hydrogen sulfate (133 mg, 0.39 mmol) in 5 mL of THF. The reaction mixture was stirred at room temperature for 1.5 h, at which point the solvent was removed *in vacuo* and the resulting oil chromatographed using 6:1 hexanes:ethyl acetate as eluent to yield 187 mg (90%) of a 7:1 mixture of β:α anomers.[12]

Pivaloyl 2,3,4,6-Tetra-*O*-benzyl-*β*-D-glucopyranoside (20). Method A. To a solution of acetyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (126 mg, 0.22 mmol) in 3 mL of CH_2Cl_2 cooled to 0 °C was added 34 μL (0.24 mmol) of trimethylsilyl iodide and the reaction mixture let sit for 30 min. The solvent was removed *in vacuo* , and 2 mL of THF was added and the resulting solution transferred into an already stirring solution of pivalic acid (45mg, 0.43 mmol), tetrabutylammonium trifluoromethanesulfonate (127 mg, 0.32 mmol), and sodium hexamethyldisilazane (324 μL pf a 1 M solution in THF, 0.32 mmol) in 5 mL of THF. The reaction mixture was stirred for 2 h at which point 15-crown-5 (43 μL, 0.22 mmol) was added and the reaction mixture let stir for 19 h. The solvent was removed *in vacuo* and the resulting oil chromatographed using 6:1 hexanes:ethyl acetate as eluent to yield 60 mg (45%) of the glycoside.

Method B. To a solution of acetyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (263 mg, 0.45 mmol) in 3 mL of CH_2Cl_2 cooled to 0 °C was added 71 μL (0.497 mmol) of trimethylsilyl iodide and the reaction mixture let sit for 30 min. The solvent was then removed *in vacuo* followed by the addition of 2 mL of toluene which again was removed *in vacuo*. Next, 2 mL of THF was added, and the resulting solution was pipeted into an already stirring solution of pivalic acid (230 mg, 2.3 mmol), tetrabutylammonium hydrogen sulfate (306 mg, 0.90 mmol), and sodium hexamethyldisilazane (1.80 μL of a 1 M solution in THF, 1.80 mmol) in 5 mL of THF. The reaction mixture was stirred for 20 min, at which point ethyl acetate was added and the reaction mixture was washed with sodium bicarbonate (twice) and brine. The ethyl acetate layer was dried over sodium sulfate and removed *in vacuo*. The resulting oil was chromatographed using 8:1 hexanes:ethyl acetate as eluent to yield 256 mg (90%) of the β-glycoside with no detectable α-product: $[\alpha]^{25}_D$ +98.9 (7.3, $CDCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.20 (s, 9H), 3.51−3.73 (m, 6H), 4.46 (d, 1H, J = 12.3 Hz), 4.52 (d, 1H, J = 11.0 Hz), 4.58 (d, 1H, J = 12.3 Hz), 4.68−4.86 (m, 5H), 5.57 (d, 1H, J = 7.9 Hz, H-1); ^{13}C NMR (250 MHz, C_6D_6) δ 27.0, 38.7, 68.6, 73.4, 74.7, 74.9, 75.4, 76.0, 77.7, 81.5, 85.1, 94.8, 127.6, 127.7, 127.9, 128.0, 128.4, 128.5, 128.6, 138.9, 139.2; HRFABMS calc for $C_{39}H_{44}O_7$ 624.3068, found 623.3013 $(M - H)^+$.

Stearyl 2,3,4,6-Tetra-*O*-benzyl-*β*-D-glucopyranoside (21). To a solution of 2,3,4,6-tetra-*O*-benzylglucosyl acetate (273 mg, 0.46 mmol) in 3 mL of methylene chloride was added 73 μL (0.51 mmol) of trimethylsilyl iodide and the mixture let sit for 30 min at 0 °C. The solvent was removed *in vacuo*, and 2 mL of toluene was added and again removed *in vacuo* followed by the addition of 2 mL of THF. This solution was added to an already stirring solution of sodium stearate (a mixture with sodium palmitate) (430 mg, 1.41 mmol) and tetrabutylammonium hydrogen sulfate (397 mg, 1.17 mmol) in 5 mL of THF. Immediately upon addition, TLC analysis (6:1 hexanes:ethyl acetate) showed complete disappearance of the iodide. The solvent was removed *in vacuo* after 10 min and the resulting oil purified using a 9:1 hexanes:ethyl acetate column to give a quantative yield of a >95:5 mixture of β:α-glycosides, as a mixture of lipids: ^{1}H NMR ($CDCl_3$) δ 1.23−1.31 (m), 1.63 (m), 1.90−1.96 (m), 2.55−2.63 (t, J = 7.5 Hz), 3.87−4.13 (m), 4.75 (d, J = 12 Hz), 4.86−4.94 (m), 5.10−5.32 (m), 6.06 (d, 1H, H-1, J = 7.9 Hz), 7.47−7.62 (m, 20H); HRFABMS for the stearate derivative calc for $C_{52}H_{70}O_7$ 806.5121, found 829.5035 $(M + Na)^+$; HRFABMS for the palmitate derivative calc for $C_{50}H_{66}O_7$ 778.4808, found 801.4694 $(M + Na)^+$. No mass peaks for the corresponding acids were identified, but ^{1}H NMR integration proved difficult with the varying lipid components.

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Supporting Information Available: ^{1}H NMR spectra for compounds lacking combustion analyses (**5a**/**b**, **7a**/**b**, **12**, **13**, **14**, **18**, **20**, **21**) (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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