Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Displacement of Sugar Triflates with C-Nucleophiles: D-Glucopyranose and D-Ribofuranose Chain Extension and Functionalization

Quanrong Shen [a], Darby G. Sloss [a] & David B. Berkowitz [a]
[a] Department of Chemistry, University of Nebraska-Lincoln, Lincoln, NE, 68588
Version of record first published: 23 Sep 2006.

To cite this article: Quanrong Shen, Darby G. Sloss & David B. Berkowitz (1994): Displacement of Sugar Triflates with C-Nucleophiles: D-Glucopyranose and D-Ribofuranose Chain Extension and Functionalization, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 24:11, 1519-1530

To link to this article: http://dx.doi.org/10.1080/00397919408010152

SYNTHETIC COMMUNICATIONS, 24(11), 1519-1530 (1994)

DISPLACEMENT OF SUGAR TRIFLATES WITH C-NUCLEOPHILES: D-GLUCOPYRANOSE AND D-RIBOFURANOSE CHAIN EXTENSION AND FUNCTIONALIZATION

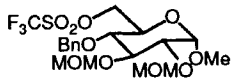
Quanrong Shen, Darby G. Sloss and David B. Berkowitz*

Department of Chemistry, University of Nebraska-Lincoln, Lincoln, NE 68588

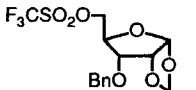
Abstract: Treatment of methyl 4-*O*-benzyl-2,3-di-*O*-methoxymethyl-6-*O*-trifluoromethanesulfonyl-α-D-glucopyranoside **1** or 3-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-trifluoromethenesulfonyl-α-D-ribofuranoside **2** with a variety of functionalized C-nucleophiles in THF/HMPA leads to the corresponding chain-extended sugars in very good to excellent yields.

Although primary sugar triflates have been known for some time,[1,2] there use has been largely restricted[3] to displacement reactions involving heteroatom-centered nucleophiles such as alkoxides,[4] carboxylates,[5,6] nitrite,[7] nitrate,[8] sulfate,[9] hydrogen sulfide,[10] amines[11] and halides.[1,2a,11] In connection with a project directed toward the synthesis of analogs of sugar phosphates, we required a convenient method for sugar chain homologation and terminal functionalization.[12] We have found that the primary triflates **1** and **2**, derived from α-D-glucopyranose and α-D-ribofuranose, respectively, are cleanly and rapidly displaced by a variety of functionalized C-nucleophiles. In this way, phosphonate, α-amino phosphonate, α-amino acid, sulfone, dithiane, nitrile or ester functionalities may be efficiently appended to the glucopyranose or ribofuranose nucleus.

The requisite triflates are easily synthesized from the corresponding alcohols using triflic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine[2] in methylene chloride at -40°C. To our knowledge, prior to this investigation, only two reports of primary triflates of D-ribofuranose had appeared.[13] In the first, the ribofuranose triflate eluded isolation,[13a] and in the second, the ribofuranose triflates apparently decomposed when isolated neat at room temperature.[13b] In contrast, we obtain pure ribofuranose triflate **2**, following an aqueous bicarbonate workup and chromatography. Furthermore, triflate **2** is completely stable, in neat form, for at least 20 h at room temperature, if kept under vacuum.



1



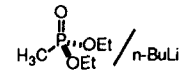
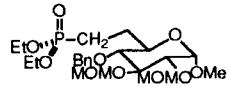
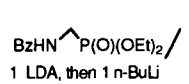
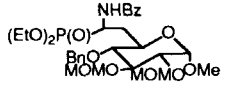
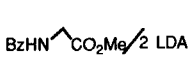
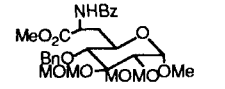
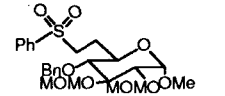
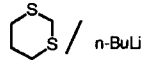
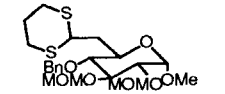
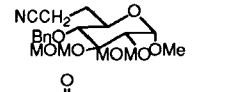
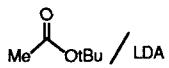
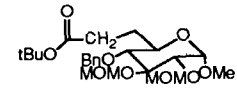
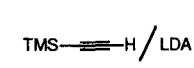
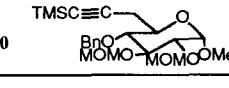
2

Most importantly, **1** and **2** react cleanly with a spectrum of carbon nucleophiles to provide very good yields of the direct displacement products (see Tables 1 and 2). We find it most convenient to use an excess of anion containing an equimolar amount of HMPA in THF as solvent. *Under these conditions, triflate displacement is usually complete in 10 minutes at -78°C.* Interestingly, despite the formidable basicity of several of these carbon nucleophiles (i.e entries 1-3 & 5), no competing triflate elimination was observed in any case.

Several entries are particularly worthy of note. Triflate displacement with diethyl lithiomethylphosphonate (entries 1) provides a convenient route to simple phosphonate analogs of sugar phosphates, such as glucose 6-phosphate and ribose 5-phosphate. This approach is clearly more direct than the stabilized Wittig olefination/hydrogenation sequence traditionally employed to generate such sugar phosphonates.[14]

In two instances, dianions were successfully employed as nucleophiles. In both cases, only C-alkylation was observed,[15] with diastereoselectivity ranging

Table 1: Displacements with D-Glucopyranose Triflate 1

	Nucleophile	Equiv.	Product	Yield[a]
(1)		2.8	 3	82%
(2)	 1 LDA, then 1 n-BuLi	1.5	 4 a, b	79% (2:1 diast. ratio)[b]
(3)		3.5	 5 a, b	86% (8:1 diast. ratio)[b]
(4)	$MeSO_2Ph$/LDA	3.5	 6	89%
(5)		3.5	 7	99%
(6)	H_3CCN/LDA	3.5	 8	78%
(7)		3.5	 9	96%
(8)		3.5	 10	89%

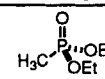
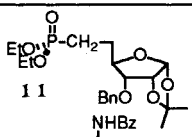
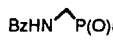
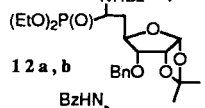
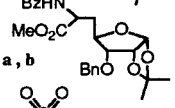
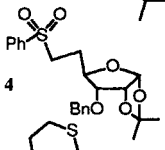
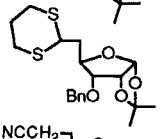
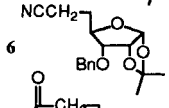
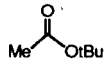
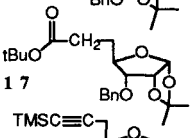
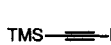
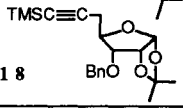
(a) All reactions were complete in 10 min at -78°C. Reactions were typically run on a 0.1-0.5 g scale and yields given are isolated yields.

(b) Ratio of diasteromers based on integration of the ^1H NMR. The absolute stereochemistry of the major diastereomer has not been determined.

from low (entries 2, α-benzamidophosphonate derived dianion) to very good (entries 3, methyl hippurate derived dianion).[16] This chemistry provides ready access to carbohydrate-derived α-amino acids and α-amino phosphonates, both of which are of considerable current interest.[17,18]

To our knowledge, entries 2 represent the first uses of a dianion derived from an α-benzamidophosphonate. The efficiency of this carbon-carbon bond-

Table 2: Displacements with D-Ribofuranose Triflate 2

	Nucleophile	Equiv.	Product	Yield[a]
(1)		2.3	 11	90%
(2)	 1 LDA, then 1 n-BuLi	3	 12a,b	84% (1.4:1 diast. ratio)[b]
(3)		3.5	 13a,b	85% (7:1 diast. ratio)[b]
(4)	$MeSO_2Ph$/LDA	3.5	 14	98%
(5)		3.2	 15	97%
(6)	H_3CCN/LDA	3.5	 16	83%
(7)		3.5	 17	97%
(8)		3.5	 18	72%

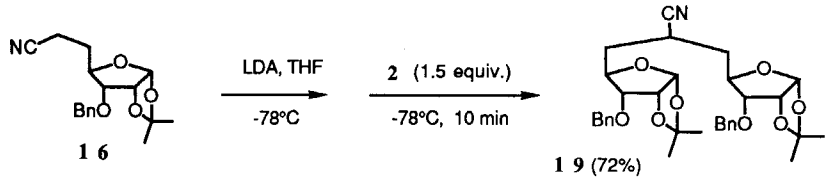
(a) All reactions were complete in 10 min at -78°C. Reactions were typically run on a 0.1-0.5 g scale and yields given are isolated yields.

(b) Ratio of diastereomers based on integration of the ^{1}H NMR. The absolute stereochemistry of the major diastereomer has not been determined.

forming reaction suggests that triflate displacement with this dianion may be a generally useful procedure for the construction of non-carbohydrate α-amino phosphonates. These compounds are of interest as amino acid mimics and as building blocks for potential protease inhibitors.[19]

The ease and efficiency of these triflate displacements suggested that such a strategy might also be employed to link two monosaccharides via C-C bonds and

thereby construct novel higher order sugars.[20] In fact, when displacement product **16** was deprotonated as before and subjected to a second round of alkylation with ribose triflate **2** (1.5 equiv.), dialkylation product **19** was obtained in very good yield (72%; 86% based upon recovered **16**):



1 6 **1 9** (72%)

In summary, primary sugar triflates are convenient vehicles for chain extension and functionalization of naturally occurring sugars. Specifically, we have found that the displacement of triflates **1** and **2** with a variety of C-nucleophiles provides rapid and direct access to a variety of novel, terminally functionalized derivatives of D-glucopyranose and D-ribofuranose.

Experimental

Triflate Synthesis

Methyl 4-*O*-Benzyl-2,3-di-*O*-methoxymethyl-6-*O*-trifluoromethanesulfonyl-α-D-glucopyranoside (1). To a solution of the corresponding alcohol[12] (149 mg, 0.40 mmol) and 2,6-di-tert-butyl-4-methylpyridine (103 mg, 0.50 mmol) in CH_2Cl_2 (4 mL) at -40°C was added triflic anhydride (74 μL, 0.44 mmol), dropwise, via syringe. The reaction was quenched by addition of $NaHCO_3$ (aq, 3 mL) and Et_2O (5 mL) upon completion (TLC). The aqueous layer was further extracted with Et_2O (2 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated. Purification by flash chromatography (25% Et_2O-hexane) afforded **1** (193 mg, 96%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.39 (s, 3 H), 3.40 (s, 3 H), 3.41 (s, 3 H), 3.41 (app t, J = 9.5 Hz, 1 H), 3.52 (dd, J = 3.5, 10 Hz, 1 H), 3.86 (ddd, J = 2, 5, 10 Hz, 1 H), 4.02 (app t, J = 9.5 Hz, 1 H), 4.44 (dd, J = 5, 11 Hz, 1 H), 4.55 (dd, J = 2, 11 Hz, 1 H), 4.57 (d, J = 11 Hz, 1 H), 4.72 (d, J = 7 Hz, 1 H), 4.79 (d, J = 7 Hz, 1 H), 4.84 (d, J = 3.5 Hz, 1 H), 4.86 (s, 2 H), 4.94 (d, J = 11 Hz, 1 H), 7.28-7.38 (m, 5 H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 55.35, 55.44, 56.3, 68.1, 74.8, 74.9, 76.7, 78.3, 78.7, 97.7, 98.3, 99.1, 114.7-122.3 (q, $J_{F,C}$

= 318 Hz), 128.0, 128.2, 128.6, 137.3; HRMS (FAB, 3-NOBA/NaI) calcd for $C_{19}H_{27}O_{10}F_3SNa$ (MNa^+) 527.1175, obsd 527.1162.

3-*O*-Benzyl-1,2-*O*-isopropylidene-5-*O*-trifluoromethanesulfonyl-α-D-ribofuranoside (2). Triflate **2** (137 mg, 79%) was synthesized from the corresponding alcohol[12] (118 mg, 0.42 mmol) plus 2,6-di-tert-butyl-4-methylpyridine (108 mg, 0.52 mmol) and triflic anhydride (78 μL, 0.46 mmol) in CH_2Cl_2 (4.2 mL) according to the procedure described for **1** and purified by flash chromatography (30% Et_2O-hexane) to afford a colorless oil: ^1H NMR (360 MHz, $CDCl_3$): δ 1.36 (s, 3 H), 1.58 (s, 3 H), 3.77 (dd, *J* = 4, 9 Hz, 1 H), 4.25 (ddd, *J* = 2, 3, 9 Hz, 1 H), 4.45 (dd, *J* = 3, 11 Hz, 1 H), 4.55 (d, *J* = 12 Hz, 1 H), 4.59 (app t, *J* = 4 Hz, 1 H), 4.71 (dd, *J* = 2, 11 Hz, 1 H), 4.79 (d, *J* = 12 Hz, 1 H), 5.74 (d, *J* = 4 Hz, 1 H), 7.33-7.38 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.4, 26.7, 72.4, 73.4, 75.7, 76.6, 76.8, 104.1, 113.5, 112.1-124.8 (q, $J_{F,C}$ = 320 Hz), 128.1, 128.4, 128.6, 136.8; HRMS (FAB, 3-NOBA/Na_2CO_3) calcd for $C_{16}H_{19}O_7F_3SNa$ (MNa^+) 435.0701, obsd 435.0700.

Typical Triflate Displacement Procedure

All solutions were deoxygenated by freezing (liquid nitrogen) and subjecting to five cycles of evacuation and purging with Ar. To a solution of diisopropylamine (216 μL, 1.55 mmol) and HMPA (268 μL, 1.55 mmol) in THF (2 mL) at -78°C was added n-butyllithium (97 μL of a 1.6 M solution in hexane, 1.55 mmol). The resulting solution was stirred for 30 min at 0°C, then cooled to -78°C. To this solution were added, via cannula, a cooled (-78°C) solution of dry acetonitrile (82 μL, 1.55 mmol) in THF (1 mL) and then, 2 min later, a cooled (-78°C) solution of triflate **2** (180 mg, 0.436 mmol) in THF (2 mL). After 10 min at -78°C, the reaction was quenched [NH_4Cl (aq, 3 mL)/Et_2O (3 mL)]. The aqueous layer was further extracted with EtOAc (2 x 15 mL) and the combined extracts dried ($MgSO_4$), filtered and evaporated. Flash chromatography (30% EtOAc-hexane) gave **16** (110 mg, 83%): ^1H NMR (360 MHz, $CDCl_3$): δ 1.35 (s, 3 H), 1.58 (s, 3 H), 1.71 (m, 1 H), 2.05 (m, 1 H), 2.38-2.43 (m, 2 H), 3.44 (dd, *J* = 4, 9 Hz, 1 H), 4.03 (app dt, *J* = 4, 9 Hz, 1 H), 4.52 (d, *J* = 12 Hz, 1 H), 4.59 (app t, *J* = 4 Hz, 1 H), 4.80 (d, *J* = 12 Hz, 1 H), 5.71 (d, *J* = 3.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.7, 26.5, 26.7, 28.1, 72.1, 76.0, 77.4, 80.9, 103.9, 113.2, 119.5 (CN), 128.2, 128.4, 128.7, 137.1; HRMS (FAB, 3-NOBA/Na_2CO_3) calcd for $C_{17}H_{21}NO_4Na$ (MNa^+) 326.1369, obsd 326.1366.

Spectral Data

3: ^1H NMR (360 MHz, $CDCl_3$): δ 1.29 (app t, *J* = 7 Hz, 6 H), 1.6-1.8 (m, 2 H), 1.95-2.2 (m, 2 H), 3.16 (app t, *J* = 9 Hz, 1 H), 3.36 (s, 3 H), 3.38 (s, 3 H), 3.39 (s, 3 H), 3.50 (dd, *J*

= 3.7, 10 Hz, 1 H), 3.57 (m, 1 H), 3.95 (app t, J = 9 Hz, 1 H), 4.02-4.11 (m, 4 H), 4.62 (d, J = 11 Hz, 1 H), 4.71 (d, J = 7 Hz, 1 H), 4.76 (d, J = 3.7 Hz, 1 H), 4.79 (d, J = 7 Hz, 1 H), 4.82 (d, J = 6 Hz, 1 H), 4.85 (d, J = 6 Hz, 1 H), 4.87 (d, J = 11 Hz, 1 H), 7.25-7.35 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.3, 16.4, 21.7 (d, J_{P-C}= 142 Hz), 24.6 (br), 55.0, 55.4, 56.1, 61.4 (br, 2 C), 69.7 (d, J_{P-C}= 17 Hz), 75.0, 78.2, 79.0, 81.6, 97.6, 98.2, 98.7, 127.7, 127.8, 128.3, 137.7; HRMS (FAB, 3-NOBA) calcd for $C_{23}H_{40}O_{10}P$ (MH^+) 507.2359, obsd 507.2349.

4a,b: (All data for the 2:1 mixture of diastereomers) ^{1}H NMR (300 MHz, $CDCl_3$) Diast. ratio determined from the baseline resolved NH protons: minor diast. (m): δ 6.57 (d, J = 10 Hz, 1 H); major diast. (M): δ 6.66 (d, J = 9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.1 (m) 16.2 (m), 16.26 (M), 16.33 (M), 31.7 (d, J_{P-C}= 4 Hz) (m), 32.1 (d, J_{P-C}= 4 Hz) (M), 41.7 (d, J_{P-C}= 157 Hz) (m), 44.0 (d, J_{P-C}= 157 Hz) (M), 55.3 (m + M), 55.40 (M), 55.45 (m); 56.1 (M), 62.3 (d, J_{P-C}= 6 Hz) (M), 62.5 (d, J_{P-C}= 7 Hz) (m), 62.7 (d, J_{P-C}= 6 Hz) (m), 62.9 (d, J_{P-C}= 6 Hz) (M), 66.1 (d, J_{P-C}= 13 Hz) (m), 69.5 (d, J_{P-C}= 13 Hz) (M), 74.6 (M), 74.9 (m), 77.9 (m), 78.1 (M), 78.8 (m + M), 81.8 (m), 81.9 (M), 97.4 (m + M), 98.2 (m + M), 98.9 (m), 99.0 (M), 126.9, 127.50, 127.55, 127.7, 127.9, 128.2, 128.3, 128.5, 131.5, 131.6, 133.9, 134.0, 137.7, 137.8, 166.4 (d, J_{P-C}= 4 Hz) (M), 167.0 (d, J_{P-C}= 3 Hz) (m); HRMS (FAB, 3-NOBA) calcd for $C_{30}H_{45}NO_{11}P$ (MH^+) 626.2730, obsd 626.2732.

5a,b: (8:1 mixture of diastereomers) ^{1}H NMR (300 MHz, $CDCl_3$) Diast. ratio determined from the baseline resolved $CO_2\underline{Me}$ protons: minor diast.: δ 3.74 (s, 3 H); major diast.: δ 3.76 (s, 3 H). For the diast. mixture: HRMS (FAB, 3-NOBA) calcd for $C_{28}H_{38}NO_{10}$ (MH^+) 548.2496, obsd 548.2502.

For the major diastereomer: ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.93 (ddd, J = 6, 10, 14 Hz, 1 H), 2.51 (ddd, J = 2, 6, 14 Hz, 1 H), 3.17 (app t, J = 9 Hz, 1 H), 3.37 (s, 6 H), 3.39 (s, 3 H), 3.49 (dd, J = 4, 10 Hz), 3.76 (s, 3 H), 3.81 (app dt, J = 2, 10 Hz, 1 H), 3.94 (app t, J = 9 Hz, 1 H), 4.63 (d, J = 11 Hz, 1 H), 4.71 (d, J = 11 Hz, 1 H), 4.71 (d, J = 3.7 Hz, 1 H), 4.75-4.81 (m, 1 H), 4.81 (d, J = 11 Hz, 1 H), 4.82 (s, 2 H), 4.84 (d, J = 11 Hz, 1 H), 6.94-7.00 (d, J = 6 Hz, 1 H), 7.28-7.34 (m, 5 H), 7.39-7.47 (m, 2 H), 7.48-7.54 (m, 1 H), 7.75-7.79 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 33.6, 41.7, 50.9, 52.5, 55.5, 55.8, 56.2, 67.5, 75.1, 77.8, 78.9, 81.4, 97.7, 98.2, 99.3, 127.9, 128.1, 128.4, 128.6, 131.8, 133.5, 137.4, 166.6, 172.7.

6: ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.74 (m, 1 H), 2.16 (m, 1 H), 3.08 (m, 1 H), 3.10 (app t, J = 9 Hz, 1 H), 3.27 (m, 1 H), 3.33 (s, 3 H), 3.37 (s, 6 H), 3.45 (dd, J = 3.7, 10 Hz, 1 H), 3.60 (app dt, J = 3, 10 Hz, 1 H), 3.91 (app t, J = 9 Hz, 1 H), 4.52 (d, J = 11 Hz, 1 H), 4.69 (d, J = 7 Hz, 1 H), 4.70 (d, J = 3.7 Hz, 1 H), 4.76 (d, J = 7 Hz, 1 H), 4.81 (s, 2 H), 4.83 (d, J = 11 Hz, 1 H), 7.21-7.34 (m, 5 H), 7.51 (m, 2 H), 7.63 (m, 2 H), 7.85 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.1, 52.5, 55.2, 55.4, 56.2, 68.0, 74.9, 78.1, 78.9, 81.1, 97.6, 98.2, 98.8,

127.9, 128.0, 128.4, 129.2, 133.6, 137.4, 138.6; HRMS (FAB, 3-NOBA/NaI) calcd for $C_{25}H_{34}O_9SNa$ (MNa^+) 533.1821, obsd 533.1839.

7: ^1H NMR (360 MHz, $CDCl_3$): δ 1.75 (ddd, J = 4, 10, 14 Hz, 1 H), 1.87 (m, 1 H), 2.07 (m, 1 H), 2.27 (ddd, J = 3, 11, 14 Hz, 1 H), 2.68-2.88 (m, 4 H), 3.17 (app t, J = 9 Hz, 1 H), 3.38 (s, 3 H), 3.39 (s, 3 H), 3.44 (s, 3 H), 3.51 (dd, J = 3.7, 10 Hz, 1 H), 3.97 (m, 1 H), 3.98 (app t, J = 9 Hz, 1 H), 4.19 (dd, J = 4, 11 Hz, 1 H), 4.63 (d, J = 11 Hz, 1 H), 4.71 (d, J = 7 Hz, 1 H), 4.76 (d, J = 3.7 Hz, 1 H), 4.79 (d, J = 7 Hz, 1 H), 4.83 (s, 2 H), 4.87 (d, J = 11 Hz, 1 H), 7.26-7.34 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.9, 29.1, 29.8, 37.7, 42.9, 55.35, 55.43, 56.2, 66.4, 74.8, 78.2, 79.0, 82.0, 97.6, 98.3, 98.7, 127.8, 127.9, 128.4, 137.8; HRMS (FAB, 3-NOBA/NaI) calcd for $C_{22}H_{34}O_7S_2Na$ (MNa^+) 497.1644, obsd 497.1644.

8: ^1H NMR (360 MHz, $CDCl_3$): δ 1.63 (m, 1 H), 2.10 (m, 1 H), 2.38 (m, 1 H), 2.32-2.43 (m, 2 H), 3.16 (app t, J = 9 Hz, 1 H), 3.39 (s, 3 H), 3.40 (s, 3 H), 3.41 (s, 3 H), 3.49 (dd, J = 3.7, 10 Hz, 1 H), 3.68 (app dt, J = 3, 10 Hz, 1 H), 3.98 (app t, J = 9 Hz, 1 H), 4.61 (d, J = 11 Hz, 1 H), 4.71 (d, J = 7 Hz, 1 H), 4.77 (d, J = 3.7 Hz, 1 H), 4.79 (d, J = 7 Hz, 1 H), 4.84 (s, 2 H), 4.90 (d, J = 11 Hz, 1 H), 7.30-7.40 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.3, 27.5, 55.4, 55.5, 56.3, 68.2, 74.9, 78.3, 79.1, 81.1, 97.7, 98.4, 99.0, 119.3, 128.0 (2 C), 128.5, 137.8; HRMS (FAB, 3-NOBA/NaI) calcd for $C_{20}H_{29}O_7NNa$ (MNa^+) 418.1841, obsd 418.1838.

9: ^1H NMR (360 MHz, $CDCl_3$): δ 1.42 (s, 9 H), 1.67 (m, 1 H), 2.11 (m, 1 H), 2.23-2.37 (m, 2 H), 3.17 (app t, J = 9 Hz, 1 H), 3.37 (s, 6 H), 3.39 (s, 3 H), 3.51 (dd, J = 3.7, 10 Hz, 1 H), 3.59 (app dt, J = 2, 10 Hz, 1 H), 3.94 (app t, J = 9 Hz, 1 H), 4.65 (d, J = 11 Hz, 1 H), 4.71 (d, J = 7 Hz, 1 H), 4.74 (d, J = 3.7 Hz, 1 H), 4.79 (d, J = 7 Hz, 1 H), 4.81 (d, J = 6 Hz, 1 H), 4.84 (d, J = 6 Hz, 1 H), 4.85 (d, J = 11 Hz, 1 H), 7.25-7.35 (m, 5 H); HRMS (FAB, 3-NOBA/NaI) calcd for $C_{24}H_{38}O_9Na$ (MNa^+) 493.2414, obsd 493.2407.

10: ^1H NMR (360 MHz, $CDCl_3$): δ 0.15 (s, 9 H), 2.53 (dd, J = 6.5, 17 Hz, 1 H), 2.65 (dd, J = 3, 17 Hz, 1 H), 3.39 (s, 3 H), 3.40 (s, 3 H), 3.41 (s, 3 H), 3.42 (app t, J = 9 Hz, 1 H), 3.55 (dd, J = 3.7, 10 Hz, 1 H), 3.72 (ddd, J = 3, 6.5, 9 Hz, 1 H), 3.97 (app t, J = 9 Hz, 1 H), 4.68 (d, J = 11 Hz, 1 H), 4.72 (d, J = 7 Hz, 1 H), 4.81 (d, J = 7 Hz, 1 H), 4.82 (d, J = 7 Hz, 1 H), 4.83 (d, J = 7 Hz, 1 H), 4.84 (d, J = 3.7 Hz, 1 H), 4.88 (d, J = 11 Hz, 1 H), 7.26-7.33 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.01, 22.7, 54.9, 55.4, 56.2, 68.5, 75.1, 78.3, 78.9, 80.5, 86.9, 97.6, 98.3, 99.0, 102.9, 127.8, 128.4 (2 C), 138.0; HRMS (FAB, 3-NOBA/NaI) calcd for $C_{23}H_{36}O_7SiNa$ (MNa^+) 475.2128, obsd 475.2134.

11: ^1H NMR (360 MHz, $CDCl_3$): δ 1.27 (t, J = 7 Hz, 6 H), 1.31 (s, 3 H), 1.55 (s , 3 H), 1.69-1.90 (m, 3 H), 1.96 (m, 1 H), 3.37 (dd, J = 4, 9 Hz, 1 H), 3.95-4.09 (m, 5 H), 4.52 (d, J = 12 Hz, 1 H), 4.53 (app t, J = 4 Hz, 1 H), 4.74 (d, J = 12 Hz, 1 H), 5.67 (d, J = 3.7 Hz, 1 H),

7.28-7.33 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.2, 16.3, 21.6 (d, J_{P-C}= 142 Hz), 25.1 (br), 26.3, 26.5, 61.3 (br, 2 C), 71.9, 77.1, 77.5, 81.1, 103.7, 112.6, 127.8, 127.9, 128.3, 137.2; HRMS (FAB, 3-NOBA) calcd for $C_{20}H_{32}O_7P$ (MH^+) 415.1886, obsd 415.1881.

12a,b: (All data for the 1.4:1 mixture of diastereomers) ^1H NMR (300 MHz, $CDCl_3$) Diast. ratio determined from the baseline resolved anomeric protons and NH protons: minor diast. (m): δ 5.63 (d, J = 3.7 Hz, 1 H); 6.93 (d, J = 10 Hz, 1 H); major diast. (M): δ 5.68 (d, J = 3.6 Hz, 1 H); 6.86 (d, J = 9.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.18 (M) 16.25 (m + M), 16.32 (m), 31.5 (d, J_{P-C}= 2 Hz) (M), 31.8 (d, J_{P-C}= 2 Hz) (m), 43.3 (d, J_{P-C}= 158 Hz) (m + M), 62.4 (d, J_{P-C}= 8 Hz) (m + M), 62.7 (d, J_{P-C}= 6 Hz) (m), 62.8 (d, J_{P-C}= 6 Hz) (M), 71.8 (M), 72.0 (m), 75.1 (d, J_{P-C}= 10 Hz) (m), 75.9 (d, J_{P-C}= 13 Hz) (M), 76.6 (M), 76.8 (m), 81.1 (M), 81.2 (m), 103.8 (m + M), 112.8 (M), 113.0 (m), 126.9, 127.1, 127.67, 127.75, 127.8, 127.9, 128.2, 128.3, 128.4, 128.5, 131.3, 131.4, 133.9, 134.1, 137.2, 137.3, 166.5 (d, J_{P-C}= 4 Hz) (m), 166.9 (d, J_{P-C}= 4 Hz) (M); HRMS (FAB, 3-NOBA) calcd for $C_{27}H_{37}NO_8P$ (MH^+) 534.2257, obsd 534.2263.

13a,b: (7:1 mixture of diastereomers) ^1H NMR (300 MHz, $CDCl_3$) Diast. ratio determined from the most downfield acetonide methyl signals which are baseline resolved: major diast.: δ 1.53 (s, 3 H); minor diast.: δ 1.55 (s, 3 H). For the diast. mixture: HRMS (FAB, 3-NOBA) calcd for $C_{25}H_{30}NO_7$ (MH^+) 456.2022, obsd 456.2016.

For the major diastereomer: ^1H NMR (360 MHz, $CDCl_3$): δ 1.34 (s, 3 H), 1.53 (s, 3 H), 1.97 (ddd, J = 8, 9, 14.5 Hz, 1 H), 2.37 (ddd, J = 3, 5, 14.5 Hz, 1 H), 3.44 (dd, J = 4, 9 Hz, 1 H), 3.74 (s, 3 H), 4.15 (app dt, J = 3, 9 Hz, 1 H), 4.52 (d, J = 12 Hz, 1 H), 4.54 (app t, J = 3 Hz, 1 H), 4.71-4.78 (m, 1 H), 4.77 (d, J = 12 Hz, 1 H), 5.72-5.73 (d, J = 3.4 Hz, 1 H), 7.16 (d, J = 6 Hz, 1 H), 7.30-7.36 (m, 8 H), 7.76-7.81 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.4, 26.5, 33.6, 51.4, 52.4, 72.0, 75.5, 76.6, 81.3, 104.0, 113.0, 127.1, 127.9, 128.4, 128.5, 129.8, 131.6, 133.4, 137.1, 167.1, 172.2.

14: ^1H NMR (360 MHz, $CDCl_3$): δ 1.32 (s , 3 H), 1.53 (s , 3 H), 1.88 (m, 1 H), 2.12 (m, 1 H), 3.08-3.24 (m, 2 H), 3.37 (dd, J = 4, 9 Hz, 1 H), 3.96 (app dt, J = 3, 9 Hz, 1 H), 4.50 (d, J = 12 Hz, 1 H), 4.54 (app t, J = 4 Hz, 1 H), 4.75 (d, J = 12 Hz, 1 H), 5.65 (d, J = 3.7 Hz, 1 H), 7.30-7.39 (m, 5 H), 7.52-7.59 (m, 3 H), 7.85-7.88 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.3, 26.4, 26.5, 52.7, 72.0, 75.9, 77.0, 81.2, 103.9, 112.9, 128.0, 128.1, 128.47, 128.53, 129.2, 133.6, 137.1, 139.1; HRMS (FAB, 3-NOBA/NaI) calcd for $C_{22}H_{26}O_6SNa$ (MNa^+) 441.1348, obsd 441.1341.

15: ^1H NMR (360 MHz, $CDCl_3$): δ 1.34 (s , 3 H), 1.59 (s , 3 H) 1.77-1.87 (m, 2 H), 2.02-2.12 (m, 2 H), 2.75-2.86 (m, 4 H), 3.41 (dd, J = 4, 9 Hz, 1 H), 4.19 (dd, J = 5, 9 Hz, 1 H), 4.31 (app dt, J = 3, 9 Hz, 1 H), 4.54 (d, J = 12 Hz, 1 H), 4.54 (app t, J = 4 Hz, 1 H), 4.78 (d, J =

12 Hz, 1 H), 5.70 (d, J = 3.7 Hz, 1 H), 7.29-7.36 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.9, 26.7, 26.8, 29.8, 30.2, 38.5, 43.3, 72.1, 74.6, 77.3, 81.9, 103.9, 113.0, 127.9, 128.0, 128.5, 137.5; HRMS (FAB, 3-NOBA/NaI) calcd for $C_{19}H_{26}O_4S_2Na$ (MNa^+) 405.1170, obsd 405.1178.

17: ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.42 (s, 9 H), 1.47 (s , 3 H), 1.57 (s , 3 H) 1.71 (m, 1 H), 2.02 (m, 1 H), 2.23-2.39 (m, 2 H), 3.40 (dd, J = 4, 9 Hz, 1 H), 4.00 (app dt, J = 4, 9 Hz, 1 H), 4.54 (d, J = 12 Hz, 1 H), 4.55 (app t, J = 4 Hz, 1 H), 4.77 (d, J = 12 Hz, 1 H), 5.69 (d, J = 3.7 Hz, 1 H), 7.30-7.40 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.5, 26.6, 27.4, 28.0, 31.6, 72.0, 77.1, 77.2, 80.0, 81.4, 103.8, 112.6, 127.9 (2 C), 128.4, 137.5, 172.4; HRMS (FAB, 3-NOBA/NaI) calcd for $C_{21}H_{30}O_6Na$ (MNa^+) 401.1940, obsd 401.1926.

18: ^{1}H NMR (360 MHz, $CDCl_3$): δ 0.11 (s, 9 H), 1.35 (s , 3 H), 1.59 (s , 3 H), 2.54 (dd, J = 5, 8 Hz, 1 H), 2.70 (dd, J = 4, 8 Hz, 1 H), 3.73 (dd, J = 4, 9 Hz, 1 H), 4.00 (m, 1 H), 4.53 (app t, J = 4 Hz, 1 H), 4.60 (d, J = 12 Hz, 1 H), 4.78 (d, J = 12 Hz, 1 H), 5.73 (d, J = 3.7 Hz, 1 H), 7.30-7.40 (m, 5 H); HRMS (FAB, 3-NOBA/Na_2CO_3) calcd for $C_{20}H_{28}O_4SiNa$ (MNa^+) 383.1655, obsd 383.1654.

19: ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.34 (s, 3 H), 1.35 (s, 3 H), 1.57 (m, 1 H), 1.56 (s, 3 H), 1.60 (s, 3 H), 1.87-2.02 (m, 3 H), 3.00 (m, 1 H), 3.39 (dd, J = 4, 9 Hz, 1 H), 3.49 (dd, J = 4, 9 Hz, 1 H), 4.10 (m, 1 H), 4.21 (app dt, J = 2, 10 Hz, 1 H), 4.52 (d, J = 12 Hz, 2 H), 4.77 (d, J = 12 Hz, 2 H), 5.69 (d, J = 3.7 Hz, 1 H), 5.70 (d, J = 3.7 Hz, 1 H), 7.28-7.38 (m, 10 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.8, 26.4, 26.56 (2 C), 26.62, 34.6, 34.8, 71.86, 71.90, 74.8, 75.3, 76.8, 77.1, 81.3, 81.5, 103.8, 103.9, 112.8, 113.0, 121.3, 127.85, 127.89, 127.92, 128.3 (2 C), 137.2, 137.3; HRMS (FAB, 3-NOBA/Na_2CO_3) calcd for $C_{32}H_{39}NO_8Na$ (MNa^+) 588.2573, obsd 588.2580.

Acknowledgment

We wish to thank the Elsa U. Pardee Foundation and the Donors of The Petroleum Research Fund, administered by the American Chemical Society, for financial support. High resolution mass spectra were obtained from the Midwest Center for Mass Spectrometry, supported by NSF DIR9017262. D.G.S. is the recipient of a GAANN Fellowship from the U.S. Department of Education (P200A100067).

References and Notes

1. Binkley, R. W.; Hehemann, D. G. *J. Org. Chem.* **1978**, *43*, 3244-3245 and references cited therein.
2. Pyridine is known to displace certain primary triflates: (a) Binkley, R. W.; Ambrose, M. G.; *J. Org. Chem.* **1983**, *48*, 674-677; (b) Hall, L.; Miller, D. C. *Carbohydr. Res.* **1976**, *47*, 299-305.

3. For a recent example of sugar triflate displacement with aceteylenic nucleophiles, see: (a) Kotsuki, H.; Kadota, I.; Ochi, M. *Tetrahedron Lett.* **1990**, *31*, 4609-4612.

4. (a) Vlahov, I. R.; Vlahova, P. I.; Schmidt, R. R. *Tetrahedron Lett.* **1992**, *33*, 7503-7506; (b) Esswein, A.; Rembold, H.; Schmidt, R. R. *Carbohydr. Res.* **1990**, *200*, 287-305; (c) Paulsen, H.; von Deyn, W. *Liebigs Ann. Chem.* **1987**, 141-152.

5. (a) Alais, J.; David, S. *Carbohydr. Res.* **1990**, *201*, 69-77; (b) Liav, A.; Goresh, M. B. *Chemistry and Physics of Lipids* **1989**, *51*, 9-13.

6. Binkley, R. W. *J. Org. Chem.* **1991**, *43*, 3244-3245 (demonstrated for secondary triflates only).

7. Latif, F.; Shekhani, M. S.; Voelter, W. *J. Chem. Soc. Perkin. Trans. I* **1990**, 1573-1575 (demonstrated for secondary triflates only).

8. Hoch, M.; Heinz, E.; Schmidt, R. *Carbohydr. Res.* **1989**, *191*, 21-28.

9. Kimmich, R.; Voelter, W. *Liebigs Ann. Chem.*. **1981**, 1100-1104 (demonstrated for secondary triflates only).

10. Fleet, G. W. J.; Gough, M. J.; Shing, T. K. M. *Tetrahedron Lett.* **1984**, *25*, 4029-4032; For related chemistry involving secondary triflates, see: (b) Kowollik, W.; Malik, A.; Afza, N.; Voelter, W. *J. Org. Chem.* **1985**, *50*, 3325-3330.

11. (a) Doboszewski, B.; Hay, G. W.; Szarek, W.A. *Can. J. Chem.* **1987**, *65*, 412-419; (b) Card, P.J.; Hitz, W. D. *J. Am. Chem. Soc.* **1984**, *106*, 5348-5350; (c) Albert, R.; Dax, K.; Stutz, A. E. *Tetrahedron Lett.* **1983**, *24*, 1763-1766.

12. For studies on the synthesis of (α,α-difluoroalkyl)phosphonates, see: Berkowitz, D. B.; Eggen, M.; Shen, Q.; Sloss, D. G.; *J. Org. Chem.* **1993**, *58*, 6174-6176.

13. (a) Binkley, R.W.; Ambrose, M.G.; Hehemann, D.G. *J. Org. Chem.* **1980**, *45*, 4387-4391; (b) Schmidt, R.R.; Moering, U.; Reichrath, M. *Chem. Ber.* **1982**, *115*, 39-49.

14. (a) Roach, D. J. W.; Harrison, R.; Hall, C. R.; Inch, T. D. *Biochem. J.* **1981**, *197*, 735-737; (b) Adams, P. R.; Harrison, R.; Inch, T. D.; Rich, P. *Biochem. J.* **1976**, *155*, 1-4.

15. (a) Pedersen, M. L.; Berkowitz, D. B. *J. Org. Chem.*, in press. (b) McIntosh, J.M.; Thangarasa, R.; Ager, D. J.; Zhi, B. *Tetrahedron*

1992, *48*, 6219-6224; (c) Krapcho, A. P.; Dundulis, E. A. *Tetrahedron Lett.* **1976**, *26*, 2205-2208.

16. For other examples of asymmetric induction from electophiles fixed to carbohydrate templates, see: Kunz, H.; Sager, W.; Schanzenbach, D.; Decker, M. *Liebigs Ann. Chem.* **1991**, 649-654.
17. For other approaches to sugar α-amino acids, see: (a) Bouifraden, S.; El Hadrami, M.; Ittobane, N.; Lavergne, J.-P.; Viallefont, P. *Synth. Commun.* **1993**, *23*, 2559-2562; (b) Columbo, L.; Casiraghi, G.; Pittalis, A.; Rassu, G. *J. Org. Chem.* **1991**, *56*, 3897-3900 & ref. 10b.
18. For another approach to (α-amino)phosphono-carbohydrates, see: Paulsen, H.; Kuhne, H. *Chem. Ber.* **1975**, *108*, 1239-1245.
19. Giannousis, P. P.; Bartlett, P. A. *J. Med. Chem.* **1987**, *30*, 1603-1609.
20. For related approaches to higher carbon sugars via the "tail to tail" coupling of two monosaccharides, see: Jarosz, S.; Fraser-Reid, B. *Tetrahedron Lett.* **1989**, *30*, 2359-2362.

(Received in the USA 01 November 1993)