A Practical Route to Multifunctional 2-Azido-2-deoxy-D-glucopyranosyl Donors

Vince Pozsgay†

National Institute of Child Health and Human Development, National Institutes of Health, 6 Center Drive, MSC 2720, Bethesda, Maryland 20892-2720

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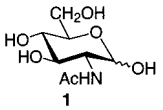
N-Acyl derivatives of 2-amino-2-deoxy-D-glucopyranose (**1**) are frequent components of naturally occurring glycoconjugates[1] including N- and O-linked glycoproteins, glycosaminoglycans (e.g., hyaluronic acid, heparin, keratan sulfate), proteoglycans, glycolipids, bacterial capsular polysaccharides,[2,3] lipopolysaccharides,[4] teichuronic acids,[5] antibiotics,[6,7] and other materials. As a consequence of this biological rationale, development of synthetic schemes for elaborating glycosides of **1** has been targeted



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by many investigators. In these endeavors the presence of an (acyl)amino functionality at the C-2 carbon atom next to the anomeric center introduces a major challenge. Numerous "participating" N-protecting groups have been proposed for the synthesis of 1,2-*trans* (*β*) glycosides of **1**.[8] In contrast, syntheses of 1,2-*cis*-linked (α) 2-amino-2-deoxy-D-glucopyranosides almost always rely on 2-azido-2-deoxyglucopyranose-derived donors.[8] The crucial step in the synthesis of such derivatives is the introduction of the azido functionality at C-2 in a diastereoselective process. Available methods include azidonitration,[9] azidochlorination,[10] and azidoselenation[11,12] of glycals, azide-opening of 2,3-mannoepoxides,[13,14] azide-displacement of O-2 triflate derivatives of *β*-mannosides[15,16] and 1,6-anhydro-*β*-mannopyranoses,[17−19] azide-displacement in 2-deoxy-2-iodo-1,6-anhydroglucopyranose,[20] and conversion of glucosamine derivatives in one step by diazo-transfer[21−24] using TfN_3, or through 2-deoxy-2-hydrazinoglucopyranose.[25] Despite many attempts, a high-yielding protocol that can be used safely to afford differentially protected azidoglucose derivatives on the multigram scale is still missing.

Our program[26,27] aimed at synthetic oligosaccharide-based glycoconjugate vaccines[28] against the Gram-negative pathogen *Shigella dysenteriae* type 1 requires relatively large amounts of 2-azido-2-deoxy-D-glucopyranosyl blocks as glycosyl donors for fashioning an α-linked *N*-acetyl-D-glucosamine residue that is part of the O-specific polysaccharide of this bacterium. Ideally, such donors are equipped with protecting group(s) that permit regioselective deprotection in a single step for extension of the existing oligosaccharide chain. Here we describe a practical route to 2-azido-2-deoxyglucopyranosyl building blocks that feature diverse protecting group patterns from an easily available starting material.

Our approach capitalizes on the observation of van Boom, who found that azide substitution of a triflyloxy group at C-2 of *β*-linked mannopyranose derivatives affords 2-azido-*gluco* compounds, whereas the corresponding α-diastereomers are unreactive.[15] Previous examples for employing this principle for the preparation of 2-azidoglucose derivatives[15,16,29] used either *β*-linked O-mannosides that are difficult to synthesize and to convert into glycosyl donors or 1,3,4,6-tetra-*O*-acetyl-*β*-D-mannopyranose, for which no efficient synthetic approach is available. In our logic the synthetic target is approached from a manno precursor that *already* contains a good leaving group at the anomeric position that (1) by its proper configuration does not interfere with the nucleophilic introduction of the azido group and (2) can be exploited for anomeric activation. In putting this concept into practice we capitalized on the easy availability of phenyl 1-thio-*β*-D-mannopyranoside (**2**) in large quantities.[30] Next we describe how this concept was realized.

† Tel: 301-402-0036. Email: vipo@helix.nih.gov.

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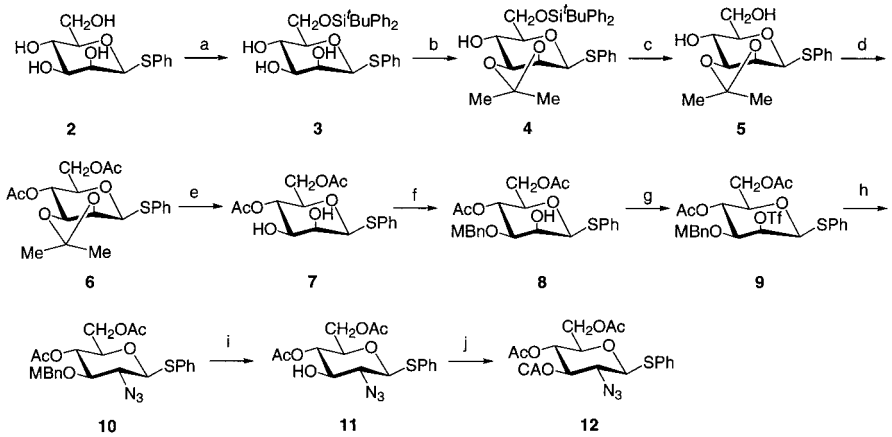
Scheme 1[a]



[a] Reagents and conditions: (a) 2 equiv of TBDPSiCl, C_5H_5N, 25 °C, 24 h, 86%; (b) DMP, CSA, 25 °C, 10 min, 96%; (c) Bu_4NF, THF, 25 °C, 24; (d) Ac_2O, C_5H_5N, 25 °C, 2 h; (e) TFA/MeOH, 25 °C, 2 h, 74% for three steps; (f) 1.2 equiv of Bu_2SnO, C_6H_6, reflux, 2 h, then MBnBr, Bu_4NI, 65−70 °C, 90 min, 66%; (g) Tf_2O, C_5H_5N, −15 °C, 20 min, (h) NaN_3, DMF, 25 °C, 84% for two steps; (i) 2.6 equiv of $Ce(NH_4)_2(NO_3)_6$, MeCN, H_2O, 25 °C, 2 h; (j) 1.4 equiv of $(CA)_2O$, C_5H_5N, 25 °C, 1 h, 94% for two steps. Abbreviations: CA, monochloroacetyl; MBn, 4-methoxybenzyl; Tf, trifluoromethanesulfonyl.

Our method is depicted in Scheme 1. The goal in the initial phase was to introduce protecting groups at O-3,4, and 6, leaving the hydroxyl group at C-2 unprotected. Thus, compound[30] **2** was treated with *tert*-butyldiphenylsilyl chloride to afford the silylated intermediate **3**, which was converted into the acetal **4** by treatment with dimethoxypropane in the presence of CSA. Next, the silyl group was removed by exposure of crude **4** to Bu_4NF to afford the diol **5**, which was acetylated in situ with acetic anhydride and pyridine. The diacetate **6** so obtained could be isolated in sufficient purity by crystallization without the need of chromatography. Subsequently, the acetal protection was removed by acid hydrolysis to provide the diol **7** in an analytically pure form after crystallization (71% for five steps without isolating the intermediates). Next, compound **7** was treated with dibutyltin oxide, followed by treatment of the intermediate stannylidene acetal with 4-methoxybenzyl bromide[31] under standard conditions[32] to yield the benzyl ether **8**. With the preparation of the partially protected derivative **8** that contains only HO-2 free, the stage was set for introduction of the azide group at C-2 using van Boom's protocol.[15] Thus, reaction of **8** with triflic anhydride/pyridine afforded the sulfonate **9**. This was treated in situ with NaN_3 to provide the targeted 2-azido-2-deoxy-thioglucoside derivative **10** in pure form in 84% yield after column chromatographic purification. To demonstrate the flexibility of our approach, **10** was converted to the fully acylated glucosamine donor **12** in a two-step sequence involving oxidative removal of the methoxybenzyl group to afford the alcohol **11**, which upon treatment with monochloroacetic anhydride provided the fully acylated glucosamine donor **12**.

In summary, we developed a practical approach to the azidoglucose donors **10** and **12** that are versatile building blocks for fashioning α-linked 2-amino-2-deoxyglucopyranose residues in complex molecules. The phenylthio group at their anomeric position may be used for direct anomeric activation by thiophilic reagents[33,34] or can be replaced by other leaving groups if so required, e.g., by halogens in one step[35] or by the powerful trichloroacetimidoyl group[36] after hydrolytic removal of the phenylthio moiety. The protecting groups in **10** and **12** are stable under a variety of glycosylation conditions and allow orthogonal deprotection at either O-3 or O-4 and O-6 for glycosylation or to introduce other protecting groups. The starting material is easily available, and the protocol can be performed at the multigram scale. Therefore, our method is likely to complement the already established protocols for the synthesis of azidoglucopyranose donors.

Experimental Section

General Methods. Optical rotations were measured at room temperature with an automatic polarimeter in $CHCl_3$. Melting points are uncorrected. TLC was performed on Kieselgel 60 F_{254} (Merck) with detection by charring with sulfuric acid. Column chromatography was performed on silica gel 60 (Merck 0.063−0.200 mm). The ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz nominal frequencies, respectively, in $CDCl_3$ solutions. Internal references were TMS (0.000 ppm for ^1H) and $CDCl_3$ (77.00 ppm for ^{13}C). The mass spectra were recorded in the chemical ionization mode using NH_3 as the ionizing gas. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

Phenyl 6-*O*-*tert*-Butyldiphenylsilyl-1-thio-β-D-mannopyranoside (3). To a solution of **2** (52 g, 191 mmol) in C_5H_5N (200 mL) was added *tert*-butyldiphenylsilyl chloride (100 mL, 385 mmol) at 25 °C. After 24 h the solution was concentrated. Toluene was added to and evaporated from the residue several times followed by extractive workup ($CHCl_3/H_2O$). Column chromatographic purification of the residue using 19:1 EtOAc−MeOH as the eluant afforded crystalline **3** (83.5 g, 86%): mp 129−131 °C, $[\alpha]_D$ −84° (*c* 1.0); NMR ^1H δ 7.69−7.22 (m, 15 H), 4.86 (br s, 1 H), 4.16 (br s, 1 H), 4.02−3.9 (m, 2 H), 3.83 (dt, 1 H), 3.58 (m, 1 H), 2.41 (m, 1 H), 2.65 (br s, 3 H), 1.05 (s, 9 H);

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^{13}C δ 135.6, 130.9, 129.9, 129.0, 127.8, 127.4, 87.0, 78.9, 75.0, 72.1, 70.0, 64.9, 26.8; CI−MS *m*/*z* 528 (M + NH_4^+). Anal. Calcd for $C_{28}H_{34}O_5SSi$: C, 65.85, H, 6.71. Found: C, 65.06; H, 6.71.

Phenyl 6-*O*-*tert*-Butyldiphenylsilyl-2,3-*O*-isopropylidene-1-thio-*β*-D-mannopyranoside (4). To a solution of **3** (50 g) in acetone (100 mL) were added 2,2-dimethoxypropane (200 mL) and CSA (approximately 2 g). After 10 min at 25 °C TLC (3:1 hexane−EtOAc) indicated the disappearance of **3**. The solution was treated with TEA, and then the volatiles were removed by distillation. The residue was equilibrated between $CHCl_3$ and H_2O. The organic layer was dried (Na_2SO_4) and concentrated to afford **4** (51.5 g, 96%) as a thick syrup: $[\alpha]_D$ −126° (*c* 1.2); NMR ^{1}H δ 7.75−7.20 (m, 15 H), 5.07 (d, 1 H, *J* = 1.8 Hz), 4.42 (dd, 1 H, *J* = 1.8 Hz, *J* = 5.4 Hz), 4.09 (t, 1 H, *J* = 6.3 Hz), 3.95 (m, 2 H), 3.88 (m, 1 H), 3.38 (m, 1 H), 2.77 (br s, 1 H), 1.58 and 1.42 (2 s, 2 × 3 H), 1.06 (s, 9 H); ^{13}C δ 135.6, 135.5, 130.4, 129.8, 128.9, 127.8, 127.1, 111.3, 84.1, 80.0, 78.0, 75.9, 71.2, 64.9, 28.1, 26.8, 26.4; CI−MS *m*/*z* 568 (M + NH_4^+). Anal. Calcd for $C_{31}H_{38}O_5SSi$: C, 67.48, H, 7.12. Found: C, 67.16; H, 6.89.

Phenyl 4,6-Di-*O*-acetyl-1-thio-*β*-D-mannopyranoside (7). (a) To a solution of **4** (48.5 g, 88 mmol) in THF (100 mL) was added Bu_4NF (30 mL of a 1 M solution in THF) at 25 °C. After 24 h, the solution containing **5** was treated with C_5H_5N (20 mL) and Ac_2O (20 mL). After 2 h, the volatiles were removed by distillation. Toluene was added to and removed by distillation from the residue several times. The crystalline residue was triturated with ether and hexane. Filtration afforded a solid (**6**) that was dissolved in CH_2Cl_2 (150 mL). To this solution were added TFA (50 mL) and MeOH (30 mL) at 25 °C. After 2 h, the solution was concentrated, and the residue was triturated with ether and diisopropyl ether to afford **7** (23.2 g, 74% for three steps): mp 149−150 °C, $[\alpha]_D$ −122° (*c* 0.8) NMR ^{1}H δ 7.9−7.3 (m, 5 H), 5.05 (t, 1 H, *J* = 9.8 Hz), 4.85 (s, 1 H), 4.28 (dd, 1 H, *J* = 6.1 Hz, *J* = 12.1 Hz), 4.19 (dd, 1 H, *J* = 2.2 Hz, 12.1 Hz), 3.69 (dd, 1 H, *J* = 4.8 Hz), 3.62 (1 H, ddd), 3.02 (br d, 1 H), 2.72 (br d, 1 H), 2.13, 2.08 (2 s, 2 × 3 H); ^{13}C δ 131.0, 129.0, 127.8, 87.2, 76.0, 73.5, 72.1, 69.7, 62.8, 21.0, 20.8; CI−MS *m*/*z* 374 (M + NH_4^+). Anal. Calcd for $C_{16}H_{20}O_7S$: C, 53.95, H, 5.66. Found: C, 53.66; H, 5.64.

(b) A solution of **2** (48.5 g, 178 mmol), *tert*-butyldiphenylsilyl chloride (53 mL, 203 mmol), and imidazole (13.5 g) in C_5H_5N (250 mL) was kept at 25 °C for 24 h. TLC (9:1 EtOAc−MeOH) indicated completed disappearance of **2**. The volatiles were removed by distillation. Toluene was added to and evaporated from the residue several times to afford a syrupy material (**3**) that was dissolved in acetone (75 mL). To this solution were added 2,2-dimethoxypropane (300 mL) and CSA (approximately 2 g). After 10 min at 25 °C TLC (1:1 hexane−EtOAc) indicated the disappearance of **3**. The solution was treated with aqueous $NaHCO_3$, and then the volatiles were removed by distillation. The residue was equilibrated between $CHCl_3$ and H_2O. The organic layer was dried (Na_2SO_4) and concentrated to a thick syrup (**4**). A solution of crude **4** in anhydrous THF (300 mL) was treated with Bu_4NF in THF (100 mL of a 1 M solution in THF). After 24 h at 25 °C TLC (1:1 hexane−EtOAc) showed complete disappearance of **4** and the formation of a product (**5**). Approximately half of the volatiles were removed by distillation. The solution was treated with pyridine (125 mL), Ac_2O (125 mL), and 4-(dimethylamino)pyridine (0.5 g). After 2 h the volatiles were removed by distillation. Toluene was added to and removed by distillation from the residue several times. The crystalline residue was triturated with ether and hexane. Filtration afforded impure **6**. [An analytical sample was obtained by column chromatographic purification of a previous batch using 2:1 hexane−EtOAc as the eluant. Pure **6**: mp 128−130 °C, $[\alpha]_D$ −120° (*c* 1.0); NMR ^{1}H δ 7.56−7.22 (m, 5 H), 5.08 (t, 1 H, *J* ≈ 8 Hz), 5.00 (br s, 1 H), 4.45 (br d, 1 H), 4.28−4.12 (m, 3 H), 3.61 (m, 1 H), 2.07, 2.05, 1.60, 1.38 (4 s, 4 × 3 H); ^{13}C δ 130.9, 128.9, 127.5, 84.4, 76.8, 75.7, 75.6, 69.0, 63.3, 27.4, 26.2, 20.9, 20.8; CI−MS *m*/*z* 414 (M + NH_4^+). Anal. Calcd for $C_{19}H_{24}O_7S$: C, 57.56, H, 6.10. Found: C, 57.38; H, 6.09.] A solution of the intermediate **6** in CH_2Cl_2 (300 mL) was treated with MeOH (50 mL) and TFA (150 mL) at 25 °C. After 15 min, the solution was concentrated. Toluene was added to and removed by distillation from the residue several times. The residue was triturated in ether and diisopropyl ether to afford **7** (45.5 g, 71% for five steps) that had physical properties identical to those of the preparation obtained in (a).

Phenyl 4,6-Di-*O*-acetyl-3-*O*-(4-methoxybenzyl)-1-thio-*β*-D-mannopyranoside (8). A mixture of **7** (10.0 g, 28.1 mmol), Bu_2SnO (8.4 g, 33.7 mmol), and benzene (200 mL) was stirred under reflux for 2 h using a Dean−Stark adapter to remove water. Approximately 50 mL of benzene was removed by distillation. The solution was cooled to 65−70 °C and was treated with 4-methoxybenzyl bromide (20 mL of an approximately 30% solution in benzene) followed by Bu_4NI (2.5 g). After 90 min, TLC (3:1 hexane−EtOAc) indicated the disappearance of **7**. The solution was cooled to 0 °C and then was treated with aqueous solutions of $NaHCO_3$ and $NaHSO_3$. Most of the benzene was removed by distillation. The residue was equilibrated between $CHCl_3$ and H_2O. The organic layer was concentrated, and the residue was partially dissolved in EtOAc and hexane. The slurry so obtained was applied to a column of silica gel (4 cm high) made in a fritted-glass funnel (14 cm in diameter) in 4:1 hexane−EtOAc. Elution by a gradient of hexane−EtOAc (4:1 to 1:1) afforded crystalline **8** (8.9 g, 66%): mp 124−126 °C, $[\alpha]_D$ −83° (*c* 1.2); NMR ^{1}H δ 5.25 (t, 1 H, *J* = 9.7 Hz), 4.77 (br s, 1 H), 4.62 and 4.48 (2 d, 2 H, *J* ≈ 12 Hz), 4.27 (m, 1 H), 4.22 (dd, 1 H, *J* = 6.3 Hz, *J* = 12.1 Hz), 4.12 (dd, 1 H, *J* = 2.6 Hz, *J* = 12.1 Hz), 3.80 (s, 3 H), 3.56 (ddd, 1 H), 3.53 (dd, 1 H, *J* = 3.5 Hz, *J* = 9.4 Hz), 2.87 (br s, 1 H), 2.05 and 2.03 (2 s, 2 × 3 H); ^{13}C δ 170.6, 169.6, 159.5, 134.6, 131.0, 129.4, 128.8, 113.9, 86.7, 78.6, 76.1, 71.2, 69.5, 67.3, 62.9, 55.2, 20.8, 20.7; CI−MS *m*/*z* 494 (M + NH_4^+). Anal. Calcd for $C_{24}H_{28}O_8S$: C, 60.49, H, 5.92. Found: C, 60.23; H, 5.90.

Phenyl 4,6-Di-*O*-acetyl-2-azido-2-deoxy-3-*O*-(4-methoxybenzyl)-1-thio-*β*-D-glucopyranoside (10). To a stirred mixture of **8** (11.0 g, 23 mmol), dry CH_2Cl_2 (100 mL), and C_5H_5N (11 mL) at −15 °C was added trifluoromethanesulfonic anhydride (5.5 mL, 32.7 mmol). After 20 min, the reaction mixture was treated with ice-cold aqueous $NaHCO_3$ solution. The mixture was concentrated under vacuum. Toluene was added to and evaporated from the residue several times to afford **9** as a syrup: NMR ^{1}H δ 7.56 (m, 2 H), 7.33 (m, 3 H), 7.20 (d, 2 H), 6.97 (d, 2 H), 5.39 (d, 1 H, *J* = 2.8 Hz), 5.14 (t, 1 H, *J* = 10.8 Hz), 4.85 (br s, 1 H), 4.74 and 4.41 (2 d, 2 × 1 H, *J* ≈ 12 Hz), 4.16 (d, 2 H, *J* = 4.6 Hz); 3.80 (s, 3 H), 3.65 (dd, 1 H, *J* = 3.1 Hz, 9.8 Hz), 3.59 (ddd, 1 H, *J* = 3.1 Hz), 2.06, 1.97 (2 s, 2 × 3 H); ^{13}C δ 170.6, 169.2, 132.0, 130.0, 129.2, 128.4, 113.9, 84.5, 83.8, 76.8, 76.0, 72.1, 66.8, 62.8, 55.2, 20.7. To a stirred solution of this residue in DMF (80 mL) was added NaN_3 (4.0 g, 59.7 mmol). After the disappearance of **9** as checked by TLC (2:1 hexane−EtOAc) the reaction mixture was concentrated under vacuum. Extractive workup ($CHCl_3$/H_2O) followed by chromatographic purification using 2:1 hexane−EtOAc as the eluant afforded **10** (9.7 g, 84% for two steps) as a syrup that crystallized upon standing: $[\alpha]_D$ −74° (*c* 0.8); NMR ^{1}H δ 4.86 (t, 1 H, *J* = 10.0 Hz), 4.49 (d, 1 H, *J* = 9.9 Hz), 4.22 (dd, 1 H, *J* = 12 Hz), 4.17 (dd, 1 H), 3.84 (s, 3 H), 3.72−3.50 (m, 2 H), 3.30 (t, 1 H, *J* ≈ 10 Hz), 2.11, 2.00 (2 s, 2 × 3 H); ^{13}C δ 171.0, 169.5, 134.0−128.5, 113.5, 86.2, 78.3, 76.2, 71.8, 69.1, 67.2, 62.8, 55.1, 20.8, 20.6; CI−MS *m*/*z* 519 (M + NH_4^+). Anal. Calcd for $C_{24}H_{27}N_3O_7S$: C, 57.47, H, 5.43. Found: C, 57.45; H, 5.43.

Phenyl 4,6-Di-*O*-acetyl-2-azido-3-*O*-chloroacetyl-2-deoxy-1-thio-*β*-D-glucopyranoside (12). To a stirred solution of **10** (16.9 mmol) in a 10:1 mixture of MeCN and H_2O was added $Ce(NH_4)_2(NO_3)_6$ (24.0 g, 43.8 mmol) at 25 °C. After 2 h TLC indicated disappearance of **10** and the formation of a single product [**11**: NMR ^{1}H δ 4.83 (dd, 1 H, *J* = 10.1 Hz, *J* = 9.6 Hz); 4.44 (s, 1 H, *J* = 10.1 Hz), 4.26 (dd, 1 H, *J* = 12.0 Hz, *J* = 5.0 Hz), 4.19 (dd, 1 Hz), 3.90 (s, 3 H), 3.623 (dd, 1 H), 3.618 (ddd, 1 H), 3.33 (t, 1 H, *J* = 9.8 Hz), 2.72 (d, 1 H, *J* = 4.5 Hz), 2.12, 2.09 (2 s, 2 × 3 H)]. The reaction mixture was treated with aqueous solutions of $NaHSO_3$ and $NaHCO_3$, followed by removal of MeCN under vacuum. The residue was equilibrated between $CHCl_3$ and H_2O. The organic layer was dried (Na_2SO_4) and concentrated to a volume of approximately 50 mL. To this solution were added C_5H_5N (3 mL) and monochloroacetic anhydride (4 g, 23.0 mmol) at 25 °C. After 1 h the reaction mixture was treated with aqueous $NaHCO_3$ solution. Extractive workup ($CHCl_3$/H_2O) followed by column chromatographic purification using 2:1 hexane−EtOAc as the eluant afforded **12** (6.6 g, 94% for two

steps) as a syrup: $[\alpha]_D$ −62° (*c* 1.1); NMR ^{1}H δ 7.6−7.3 (m, 5 H), 5.10 (t, 1 H, J = 9.6 Hz); 4.95 (t, 1 H, J = 9.8 Hz), 4.52 (d, 1 H, J = 10.0 Hz), 4.23 (dd, 1 H, J = 4.7 Hz, J = 12.1 Hz), 4.17 (dd, 1 H, J = 2.5 Hz, J = 12.1 Hz), 4.03 (dd, 2 H, J = 14.6 Hz), 3.71 (ddd, 1 H), 3.43 (t, 1 H, J = 10.0 Hz), 2.08, 2.01 (2 s, 2 × 3 H); ^{13}C δ 170.5, 169.7, 166.5, 134.1, 130.0, 129.1, 129.0, 85.9, 75.7, 67.8, 67.1, 62.4, 61.9, 40.3, 20.7, 20.5; CI−MS *m*/*z* 475 (M + NH_4^+). Anal. Calcd for $C_{18}H_{20}ClN_3O_7S$: C, 47.22, H, 4.40. Found: C, 47.48; H, 4.52.

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Additions and Corrections

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Ana M. Gomez,* Gerardo O. Danelón, Serafín Valverde, and J. Cristóbal López. Regio- and Stereocontrolled 6-*Endo-Trig* Radical Cyclization of Vinyl Radicals: A Novel Entry to Carbasugars from Carbohydrates.

Page 9626, reference 6. We inadvertantly overlooked the following reports of 6-*exo-trig* cyclizations to form carbasugars: (a) Schmid, W.; Whitesides, G. M. *J. Am. Chem. Soc.* **1990**, *112*, 9670. (b) Andersson, F. O.; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1990**, *55*, 4999. (c) Marco-Contelles, J.; Pozuelo, C.; Jimeno, M. L.; Martínez, L.; Martínez-Gran, A. *J. Org. Chem.* **1992**, *57*, 2625 and references cited to previous work. We thank Dr. Marco-Contelles for calling our attention to ref c above.

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