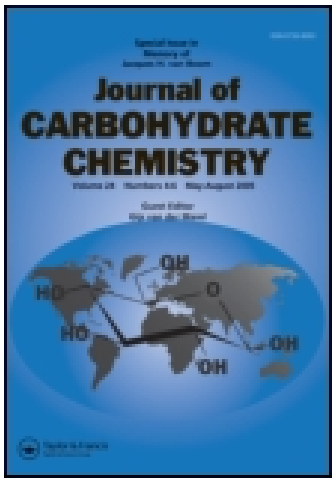

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LARGE SCALE SYNTHESIS OF 2-AZIDODEOXY GLUCOSYL DONORS

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Dedicated to Professor Joachim Thiem on the occasion of his 60th birthday.

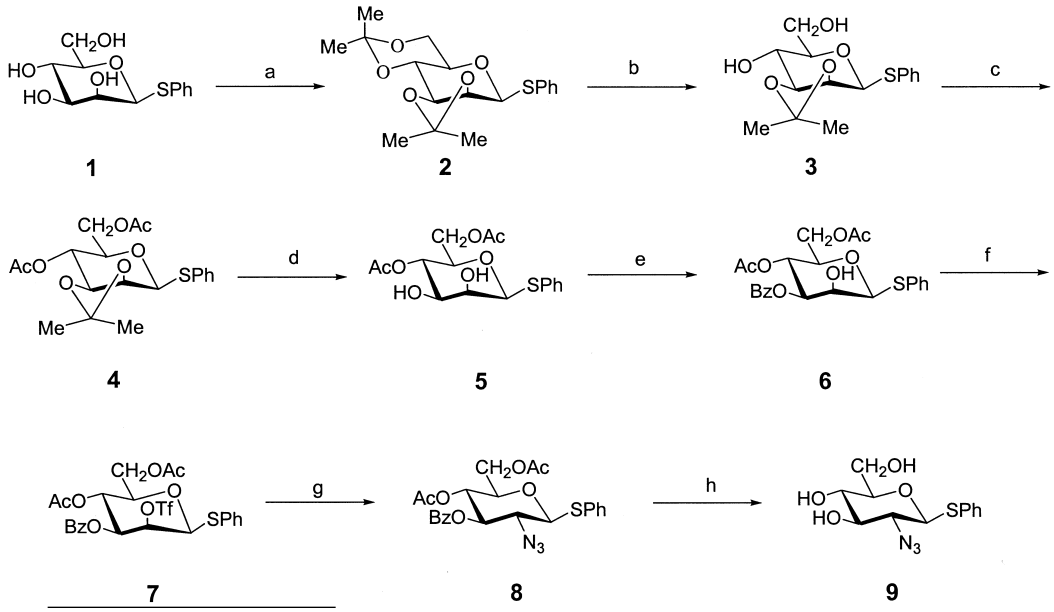
ABSTRACT

Starting from readily available phenyl 1-thio-β-D-mannopyranoside, phenyl 2-azido-2-deoxy-1-thio-β-D-glucopyranoside (**9**) was synthesized on multigram scale using inexpensive reagents.

INTRODUCTION

The success of oligosaccharide synthesis by chemical methods critically depends on efficient glycosyl donors that should be easily accessible. An often encountered problem lies in the synthesis of 2-(acyl)amino-2-deoxyglycosides, that frequently occur in complex carbohydrates, e.g. bacterial polysaccharides, lipopolysaccharides, teichuronic acids, aminocyclitol-type antibiotics, blood-group substances, glycosaminoglycans and membrane-bound glycoproteins.[1] The numerous donors developed for the construction of β-linked 2-aminoglycosides usually contain an amino function that is masked by various acyl or urethane-type protecting groups. On the other hand, most synthetic approaches towards the corresponding α-linked 2-aminoglycosides almost always employ 2-azido-2-deoxy glycosyl donors as halides,[2] trichloroacetimidates,[3] thioglycosides,[4] and *n*-pentenyl glycosides.[5] In these donors the azido function allows the formation of the α glycosidic linkage by its non-participating nature. In addition to *O*-acyl and *O*-alkyl protecting groups, the 4,6-*O*-benzylidene acetal protecting group has also

been used in an attempt to improve α-selectivity by conformational constraint.[6,7] While such donors have been accessible on a small scale since the development of Lemieux's azidonitration procedure,[8] access to large quantities of 2-azido-2-deoxy glucosyl donors is time consuming and often includes several chromatographic steps requiring further improvements to the original protocol.[9] Vasella's method of direct replacement of an acetamido group by an azido functionality using trimethylsilyl azide stands out as a very successful, direct route to 2-azidoglucosides.[10] Yet, in spite of many attempts by a number of groups,[11] 2-azidosugars "are not readily available" as stated by Schmidt in his recent review.[12] Cost efficiency is an added requirement which becomes accentuated in large-scale work. An ingenious approach to the introduction of an azido function at C-2 in the *gluco* configuration was reported through azide substitution of a triflyloxy group in β-mannosides.[13] The corresponding α-mannosides were unreactive. Previously, we have capitalized on this approach to synthesize multigram quantities of 2-azido-2-deoxy glucosyl donors as β-phenylthioglycosides.[1] Starting from phenylthiomannoside **1** (Scheme 1), the diol **3** was prepared in a series of protecting group changes employing *inter alia* the *tert*-butyldiphenylsilyl group. After conversion to the di-*O*-acetyl derivative **5**, a 4-methoxybenzyl group was regioselectively introduced at *O*-



[a]Reagents and conditions: (a) $Me_2C(Me0)_2$, Me_2CO, $Sc(OTf)_3$, 23 °C, 2 h, 93%; (b) CH_2Cl_2, MeOH, AcOH, reflux, 4 h; (c) C_5H_5N, Ac_2O, DMP, 23 °C, 4 h, 68% for two steps; (d) AcOH, H_2O, reflux, 15–20 min, 90%; (e) 1.5 equiv of BzCl, CH_2Cl_2, C_5H_5N, −45 to −30 °C, 20 min, 86%; (f) 1.4 equiv of Tf_2O, C_5H_5N, CH_2Cl_2, −20 to −10 °C; (g) NaN_3, DMF, 23 °C, 3 h, 85% for two steps; (h) NaOMe, MeOH, 23 °C, 12 h, 97%.

Scheme 1[a].

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3 using a dibutyltin activation procedure, followed by triflylation at *O*-2 and configuration inversion at C-2 by an azido group. The reported approach necessitated at least two chromatographic steps, needed large quantities of *tert*-butyldiphenylsilyl chloride and dibutyltin oxide as auxiliary reagents, and suffered from a less then optimum yield in the methoxybenzylation step. Here we report an improved procedure to 2-azido-2-deoxy glucosyl donors as thioglycosides using inexpensive chemicals. In this protocol all intermediates are crystalline and only the final step requires chromatographic purification.

RESULTS AND DISCUSSION

Our improved procedure is summarized in Scheme 1. Phenylthiomannoside **1** was prepared as described by Sinaÿ's group[14] and was now obtained in a crystalline form. Routine acetalization[15] with 2,2-dimethoxypropane under catalysis by $Sc(OTf)_3$ afforded the diacetal **2** as a crystalline material. While selective acetalization of mannosides is a low-yielding procedure (see e.g., ref. 14), acidolytic cleavage of α-mannoside diacetals has been reported to proceed in a high regioselectivity leading to the 2,3-*O*-acetal derivatives.[16] We found that the di-*O*-isopropylidene derivative of β-phenylthiomannoside **2** behaves similarly: its treatment with AcOH in CH_2Cl_2 and MeOH afforded the 2,3-*O*-acetal (**3**) predominantly. The only side product was the tetraol **1**, whereas no isomeric acetal was seen in the reaction mixture. We note that careful monitoring of this reaction (e. g., by thin-layer chromatography) is important to prevent excessive cleavage of the dioxolane ring. The unpurified diol **3** was acetylated to afford crystalline **4** in 68% yield for two steps. Subsequent removal of the remaining acetal protecting group by aqueous AcOH furnished compound **5**. Crucial to the success of this protocol was the recognition that the diol **5** can be benzoylated (benzoyl chloride, C_5H_5N) regioselectively at *O*-3 without any site directing reagent and that crystallization of the crude product from isopropyl ether affords the monobenzoate **6** in 86% yield in at least 95% purity (NMR). As an important practical point we note that up to this stage all mother liquors were collected, combined, and recycled to give pure **1** in a two-step sequence (1. AcOH, 2. NaOMe). In the final stage of the protocol, the axial hydroxyl group in **6** was triflylated (→ **7**) followed by treatment with sodium azide in DMF to afford the equatorial azide **8** in 85% combined yield. Finally, routine deacylation afforded the triol **9** previously reported by Garegg's group[17] which can serve as a precursor to a number of variously functionalized 2-azido-2-deoxyglucosyl donors.

In summary, a high-yielding and inexpensive procedure is described for the large-scale preparation of 2-azido-2-deoxyglucosyl donors from an easily available thiomannoside. Because the anomeric position is blocked by the phenylthio moiety that is resistant to numerous reaction conditions, a variety of *O*-protecting group schemes may be realized. Additionally, the phenylthio moiety can be exploited for either direct activation or after routine conversion to other activator types.

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EXPERIMENTAL

General Methods. All chemicals were commercial grade and were used without purification. Anhydrous solvents were obtained from Aldrich. Column chromatography was performed on silica gel 60 (0.040–0.063 mm). Melting points were taken on a Meltemp capillary melting point apparatus and are uncorrected. Optical rotations were measured at 23 °C with a Perkin-Elmer Type 341 polarimeter in $CHCl_3$ unless stated otherwise. The ^1H and ^{13}C NMR spectra were recorded at 500 and 125 MHz nominal frequencies, respectively. Internal references: TMS (0.00 ppm) for ^1H for solutions in $CDCl_3$ and $CDCl_3$ (77.00 ppm) for ^{13}C for solutions in $CDCl_3$. Coupling constants are given in Hz. The mass spectra were recorded at the Laboratory of Bioorganic Chemistry, NIDDK, NIH, Bethesda, MD. Ammonia was used as the ionizing gas for the chemical ionization (CI) mass spectra. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

Phenyl 1-thio-β-D-mannopyranoside (**1**) was obtained from acetobromomannose and thiophenol essentially as described in ref. 14. The following modifications were made. Phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-mannopyranoside was purified by filtration through a silica gel column. Removal of the *O*-acetyl groups (Zemplén) followed by stirring the solid residue in ethyl acetate for several hours afforded crystalline **1**: mp sintering above 180 °C, $[\alpha]_D$ −76° (*c* 1.1, MeOH). For NMR data, see ref. 14.

Phenyl 2,3:4,6-di-*O*-isopropylidene-1-thio-β-D-mannopyranoside (2). To a stirred mixture of phenyl 1-thio-β-D-mannopyranoside (**1**) (54.0 g, 198 mmol), acetone (250 mL), and 2,2-dimethoxypropane (800 mL) was added $Sc(OTf)_3$ (500 mg). After dissolution (*ca.* 20 min) approx. 600 mL of the volatiles were removed by distillation. Acetone (500 mL) was added to the crystalline mixture. After dissolution, the solution was concentrated to approx. 500 mL by distillation followed by addition of Et_3N (3 mL) and removal of the volatiles under diminished pressure. To the residue was added CH_2Cl_2 followed by concentration. The crystalline residue was dissolved in CH_2Cl_2 (300 mL). The solution was extracted with water twice (150 mL each). The combined organic layer was concentrated to afford **2** (68 g, 93%) as a crystalline material: mp 140–142 °C, $[\alpha]_D$ −145° (*c* 0.7); NMR ^1H δ 7.53−7.39 (m, 2 H), 7.34−7.26 (m, 3 H), 5.10 (d, 1 H, $J = 2.3$), 4.46 (dd, 1 H, $J = 2.3$, $J = 5.3$), 4.08 (dd, 1 H, $J = 5.3$, $J \sim 8$), 3.92 (dd, 1 H, $J = 5.8$, $J = 11.0$), 3.87 (dd, 1 H, $J \sim 8$, $J = 9.8$), 3.85 (t, 1 H, $J = 11.0$), 3.18 (m, 1 H), 1.62 and 1.52 (2 s, 2 × 3 H), 1.42 (s, 6 H); ^{13}C, δ 131.2, 129.0, 127.7, 110.6, 99.7, 84.7, 76.6, 76.2, 72.4, 69.8, 61.8, 29.0, 28.3, 26.3, 18.8; CI-MS *m/z* 370 ($M+NH_4^+$).

Anal. Calcd for $C_{18}H_{24}O_5S$ (352.45): C, 61.34; H, 6.86. Found: C, 61.53; H, 6.71.

Phenyl 4,6-di-*O*-acetyl-2,3-*O*-isopropylidene-1-thio-β-D-mannopyranoside (4). A stirred mixture of **2** (32.0 g) in CH_2Cl_2 (30 mL), MeOH (80 mL), and acetic acid (40 mL) was boiled under reflux for 4–5 h. Boiling was discontin-

ued when TLC (2:1 hexane—EtOAc) indicated the formation of a major product (**3**) together with approximately equal amounts of unreacted **2** and tetraol **1**. The solution was concentrated. Toluene was added to and evaporated from the residue thrice followed by addition of C_5H_5N (50 mL), acetic anhydride (50 mL), and a catalytic amount of 4-dimethylaminopyridine at 20 °C. After 4 h, the volatiles were removed under reduced pressure. The residue was stirred in ether (400 mL) for 12 h followed by filtration to afford **4** (24.5 g, 68%): mp 126–128 °C, lit.[1] mp 128–130 °C, $[\alpha]_D$ −121° (*c* 1.4), lit.[1] $[\alpha]_D$ −120° (*c* 1.0).

Phenyl 4,6-di-*O*-acetyl-1-thio-β-D-mannopyranoside (5). A stirred solution of **4** (43.4 g) in AcOH (140 mL) and water (20 mL) was warmed quickly to boiling. After 15 min TLC (2:1 EtOAc—hexane) indicated complete disappearance of the starting material. The solution was concentrated under reduced pressure at 30 °C. Toluene was added to and evaporated from the residue twice. Extractive work-up of the residue ($CHCl_3/H_2O$) afforded a solid that was treated with ether (250 mL). Filtration afforded **4** (34.0 g, 90%): mp 147–149 °C, lit.[1] mp 149–150; $[\alpha]_D$ −125° (*c* 1.4), lit.[1] $[\alpha]_D$ −122° (*c* 0.8).

Phenyl 4,6-di-*O*-acetyl-3-*O*-benzoyl-1-thio-β-D-mannopyranoside (6). To a stirred solution of the diol **5** (40.0 g, 112 mmol) in dry CH_2Cl_2 (250 mL) and C_5H_5N (40 mL) was added at −45 °C benzoyl chloride (20 mL, 172 mmol) dropwise. After 20 min, at *ca.* −30 °C the mixture was successively extracted with 5% aq ice cold 5% hydrochloric acid (200 mL) and water (twice). The organic layer was dried (Na_2SO_4) and concentrated. To the crystalline residue was added isopropyl ether. The mixture was stirred overnight. Filtration afforded **6** (44.0g, 86%) as a white crystalline material whose purity was >95% as judged by NMR data: NMR ($CDCl_3$) ^{1}H δ 8.05−7.30 (m, 10 H), 5.59 (t, 1 H, J = 10.0), 5.16 (dd, 1 H, J = 10.0, J = 3.2), 4.98 (br s, 1 H), 4.51 (m, 1 H), 4.32 (dd, 1 H, J = 12.1, J = 6.0), 4.19 (dd, 1 H, J = 12.1, J = 2.2), 3.76 (ddd, 1 H), 2.55 (d, 1 H, J = 5.6 Hz), 2.10 (s, 3 H), 1.96 (s, 3 H); ^{13}C δ 170.7, 169.6, 165.7, 133.6−127.9, 87.3, 76.4, 75.0, 70.6, 65.6, 62.7, 20.7, 20.6; CI-MS *m/z* 478 ($M+NH_4^+$).

Anal. Calcd for $C_{23}H_{24}O_8S$ (460.50): C, 59.99; H, 5.25. Found: C, 60.09; H, 5.12.

Phenyl 4,6-di-*O*-acetyl-2-azido-3-*O*-benzoyl-2-deoxy-1-thio-β-D-glucopyranoside (8). To a stirred solution of alcohol **6** (109 g, 237 mmol) in dry CH_2Cl_2 (600 mL) and C_5H_5N (140 mL) was added trifluoromethanesulfonic anhydride (57 mL, 338 mmol) at −20 °C over 15 min. The solution was allowed to reach −10 °C. TLC (2:1 hexane—EtOAc) indicated that a slightly faster moving product (**7**) was formed. The mixture was treated with ice-cold aqueous $NaHCO_3$. The organic layer was separated. The aqueous layer was extracted thrice with $CHCl_3$ (50 mL each). The combined organic layer was concentrated. To a stirred solution of the residue in DMF was added NaN_3 (50 g) at 23 °C. After 3 h TLC (2:1 hexane—EtOAc) indicated the disappearance of the starting material and the formation of a faster moving product together with a minor product that is only

slightly faster moving than the triflate **7.** Concentration of the mixture below 30 °C followed by extractive work-up ($CHCl_3/H_2O$) afforded a crude product that was purified by column chromatography using *ca*. 2 L of silica gel to give azide **8** (98 g, 85%) as a syrup that crystallized spontaneously. Recrystallization of a sample from ether afforded **8** in analytically pure form: mp 93–94 °C, $[\alpha]_D$ −32° (*c* 0.7); NMR ($CDCl_3$) ^{1}H δ 8.02−7.35 (m, 10 H), 5.35 (t, 1 H, J = 9.7), 5.13 (t, 1 H, J = 9.7), 4.60 (d, 1 H, J = 10), 4.27 (dd, 1 H, J = 12.3, J = 5.0), 4.20 (dd, 1 H, J = 12.3, J = 1.9), (4.78 (ddd, 1 H), 3.54 (t, 1 H), 2.10 (s, 3 H), 1.90 (s, 3 H); ^{13}C δ 170.5, 169.5, 165.5, 134.0−128.5, 86.2, 75.9, 74.6, 68.0, 63.0, 62.1, 20.7, 20.4; CI-MS *m/z* 503 ($M+NH_4^+$).

Anal. Calcd for $C_{23}H_{23}N_3O_7S$ (485.51): C, 56.90; H, 4.77. Found: C, 56.78; H, 4.70.

Phenyl 2-azido-2-deoxy-1-thio-β-D-glucopyranoside (9). To a solution of **8** (95 g) in MeOH (500 mL) was added a 25% solution of NaOMe in MeOH (2 mL) at 23 °C. After 12 h, the solution was treated with Dowex 50WX8-100 (H^+) followed by filtration and concentration. The crystalline residue was stirred in diisopropyl ether 3 h. Filtration afforded the azide **9** (56.4g, 97%): mp 109–110 °C, lit.[17] mp 112–114 °C; $[\alpha]_D$ −28° (*c* 0.7, MeOH), lit.[17] $[\alpha]_D$ −29° (*c* 1.0, MeOH).

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