A Facile, Multigram Synthesis of Ribofuranoid Glycals

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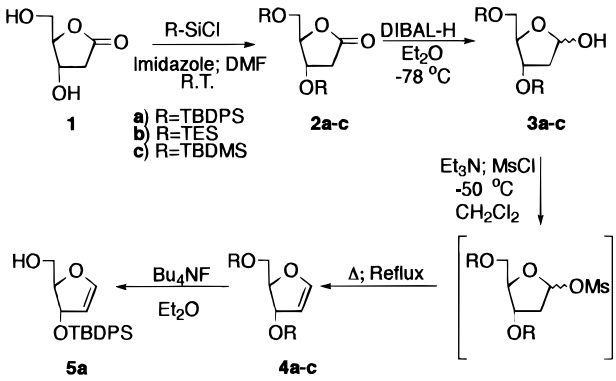
Introduction

Our research group has been interested in the synthesis of nucleoside analogs for a number of years. Recently, we have taken an interest in the preparation of various 2′-deoxy-*C*-nucleoside analogs.[1] The synthetic approaches to these compounds can be grouped into four categories. These categories are (1) total synthesis from noncarbohydrate and nonheterocyclic precursors, (2) chemical interconversion of preformed *C*-nucleosides, (3) introduction of a functional group at the anomeric position of a carbohydrate followed by a construction of the heterocyclic moiety, and (4) condensation of sugar derivatives with preformed heterocycles.[1a] Employing the fourth methodology, Daves and co-workers have developed the use of palladium-catalyzed cross-coupling reactions using iodoheterocycles and ribofuranoid glycals (2,3-dihydrofurans) to afford 2′-deoxy-*C*-nucleosides in a direct, two-step procedure.[2,3]

We envisaged this route as being synthetically compatible for our specific purposes and initiated research using this approach. In the course of our research, we developed a need for multigram quantities of various silylated glycals. Although the Ireland procedure,[4] used by Daves[5a] and Chmielewski,[5b] is an elegant method to provide ribofuranoid glycals, the scale-up of the reaction is limited due to a lithium/liquid ammonia-promoted fragmentation.[4] This prompted us to initiate studies designed to provide a route for the synthesis of ribofuranoid glycals from readily available starting materials that could easily be scaled-up to multigram quantities.

It is known that, under basic conditions, sulfonate esters undergo elimination reactions via an E2 process involving β-hydrogen extraction to give the unrearranged, unsaturated product.[6] As shown in Scheme 1, we predicted that an appropriately 3,5-bisprotected-2-deoxy-D-ribofuranose could be mesylated and then undergo the elimination process in a basic environment to give the desired glycal. We now report a procedure developed in our laboratories that is suitable for a multigram synthesis of bis-silylated ribofuranoid glycals from 2-deoxy-D-ribose.

Scheme 1



Results and Discussions

Protection of 2-deoxy-D-ribono-1,4-lactone (**1**, synthesized in 90−95% yields via bromine oxidation of 2-deoxy-D-ribose[7]) at the 3- and 5-positions with the appropriate silyl chloride in dimethylformamide in the presence of imidazole gave the 3,5-bis-*O*-silylated products **2a**−**c**. These compounds, after simple aqueous extractions, were very pure based on TLC and NMR analysis and were used without further purification. Also, while **2a** and **2b** were isolated as syrups, **2c** is a solid and thus easier to handle. Reduction of the lactones **2a**−**c** using diisobutylaluminum hydride at −78 °C gave the requisite 2-deoxy-D-*erythro*-pentofuranose derivatives **3a**−**c** as 1:1 mixtures of anomers. Again, these compounds were sufficiently pure, after 0.5 M disodium tartrate washes, to be used in the subsequent step.

At this point, the syrupy compounds **3a**−**c** were dissolved in dry dichloromethane and cooled to −50 °C. To this solution was added 4 equiv of triethylamine followed by methanesulfonyl chloride. The temperature of the reaction was maintained at −40 to −50 °C until TLC showed a complete consumption of **3a**−**c** (and presumed formation of the intermediate mesylate). The reactions were then warmed to reflux, and the elimination was allowed to occur at reflux temperature over a period of 15−18 h. After column chromatography, the title compounds **4a**−**c** were isolated in 53−86% yields on a multigram scale. We have found that chromatography of these compounds on silica gel using ethyl acetate/hexane as the eluent leads to the formation of the aromatic furans. However, a solvent system of diethyl ether/petroleum ether[5a,8] does not lead to aromatization. Finally, compound **4a** was selectively desilylated at the 5-position using tetrabutylammonium fluoride to give **5a**. This compound was spectrometrically identical to the compound as synthesized by Farr and Daves.[8]

We have found that **4c** is the easiest compound to work with due to its surprising stability. Whereas **4b** decomposes to the furan, as determined by ^{1}H NMR, in 24 h at

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room temperature and **4a** was stable under similar conditions for less than two days, **4c** was found to be stable for at least one week.[9] We have also found that,[10] as reported,[3] these bis-protected glycals still retain regio- and stereospecificity in the palladium-catalyzed cross-couplings.

In conclusion, we have developed a preparation of bis-protected ribofuranoid glycals that is not only high yielding(53−86%), but also very amenable to multigram scale-up. The glycals prepared in our laboratory have been successfully utilized for the synthesis of a novel class of 2′-deoxy-*β*-D-ribofuranos-1′-yl pyrazine *C*-nucleosides in high yields.[10]

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used as provided. Dimethylformamide (calcium oxide), dichloromethane (phosphorus pentoxide), and tetrahydrofuran (sodium/benzophenone) were distilled from the indicated drying agent and stored over activated 4 Å molecular sieves under a positive pressure of argon prior to use. 2-Deoxy-D-ribono-1,4-lactone was synthesized via the method of Deriaz *et al.*[7] The phrase "evaporated *in vacuo*" is meant to imply the use of a rotary evaporator with a bath temperature not exceeding 40 °C using a water aspirator. Thin-layer chromatography (TLC) was accomplished on Analtech 60F-254 silica gel plates, and the detection of components on TLC was made via a methanolic sulfuric acid spray followed by heat. Solvent systems are expressed as a percentage of the more polar component with respect to total volume (v/v%). Mallinckrodt SilicAR 230−400 mesh (40−63 μm) was used for chromatography, which was carried out by using the flash technique.[11] Melting points are uncorrected. Mass spectroscopy and elemental analyses were performed by the University of Michigan Chemistry Department. The presence of solvent as indicated by elemental analysis was verified by ^{1}H NMR spectroscopy.

Note: The reactions described below are general for all of the compounds in Scheme 1 and will be illustrated by the synthesis of **4a**.

1,4-Anhydro-3,5-*O*-bis[(1,1-dimethylethyl)diphenylsilyl]-2-deoxy-D-*erythro*-pent-1-enitol (4a). A flame-dried, evacuated 1000 mL round-bottom flask equipped with a Claisen arm and an addition funnel was charged with **1**[7] (9.53 g, 72.1 mmol) under argon. To this was added imidazole (24.54 g, 360 mmol), and the mixture was dissolved in 100 mL of dry DMF. The solution was cooled to 0 °C, and *tert*-butylchlorodiphenylsilane (39.4 mL, 151.4 mmol) was added dropwise over the course of 45 min while maintaining the temperature at 0 °C. The reaction was warmed to room temperature and then stirred under argon for 18 h. At this time, the reaction was poured into 1500 mL of ethyl acetate, and the precipitated imidazole hydrochloride was removed by filtration through a bed of Celite/silica gel/sand (90 × 120 mm; equal parts). The filtration bed was washed thoroughly with ethyl acetate. The ethyl acetate layer was extracted with 0.5 N HCl (400 mL), water (2 × 500 mL), and brine (150 mL), dried over magnesium sulfate, and filtered, and the filtrate was evaporated *in vacuo* to give crude **2a** as an off-white syrup: ^{1}H NMR (300 MHz; DMSO-d_6) δ 7.34−7.70 (m, 20), 4.49 (m, 1), 4.46 (m, 1), 3.54 (dd, 1, J = 2.9 Hz, 11.7 Hz), 3.26 (dd, 1, J = 2.9 Hz, 11.7 Hz), 2.40−2.80 (m, 2).

A flame-dried, evacuated 500 mL round-bottom flask equipped with a Claisen arm and an addition funnel was charged with a portion of **2a** (13.73 g, 22.5 mmol), as obtained above, under argon. Anhydrous diethyl ether (100 mL) was added and the resulting solution cooled to −78 °C. At this time, diisobutylaluminum hydride (1.5 M solution in toluene, 22.5 mL, 33.8 mmol) was added dropwise over the course of 10 min. The reaction was stirred at −78 °C for 5 h, and then methanol (20 mL) was added to quench the reaction. The solution was warmed to 0 °C and poured into 1000 mL of diethyl ether. At room temperature, the ethereal solution was washed with a 0.5 M disodium tartrate solution (2 × 500 mL) and water (500 mL), dried over magnesium sulfate, and evaporated *in vacuo* to give **3a** as a clear, colorless syrup which was not purified any further: ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.26 and 6.20 (d, 1, J = 5.4 Hz, 1-OH α and β).

A flame-dried, evacuated 200 mL round-bottom flask equipped with a reflux condenser was charged with a portion of **3a** (4.19 g, 6.85 mmol), as obtained above, under argon. Dry dichloromethane (50 mL) was added, and the resulting solution was cooled to −50 °C. To this solution was added triethylamine (3.62 mL, 26 mmol) followed by methanesulfonyl chloride (0.66 mL, 8.56 mmol). Stirring was continued, maintaining the temperature between −40 °C and −50 °C, for 2.5 h. At this time, **3a** had been entirely consumed as determined by tlc (5% diethyl ether/petroleum ether). The reaction was warmed to room temperature and then heated at reflux temperature for 15 h. The reaction was then cooled to room temperature and filtered through a short silica gel bed (90 × 100 mm). The filtrate was evaporated to afford a clear oil that was subjected to silica gel chromatography (40 × 150 mm, 5% diethyl ether/petroleum ether, R_f = 0.79) to give, after solvent evaporation, 3.54 g (86% from **1**) of **4a** as a clear, colorless syrup: $[\alpha]^{22}_D$ +119.5° (*c* 0.255, CH_2Cl_2) ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.60 (m, 10), 7.34 (m, 10), 6.41 (dd, 1, J = 0.8 Hz, 2.7 Hz), 4.90 (ddt, 1, J = 0.9 Hz, 2.7 Hz, 2.7 Hz), 4.82 (dd, 1, J = 2.6 Hz, 2.6 Hz), 4.46 (m, 1), 3.38 (m, 2), 1.04 (s, 9), 0.94 (s, 9). ^{13}C NMR (90 MHz, $CDCl_3$) δ 149.5, 136.0, 134.2, 133.5, 129.8, 127.8, 103.6, 89.4, 77.0, 64.0, 26.9, 19.4, 19.3. HRMS calcd for $C_{37}H_{44}Si_2O_3H$: 593.2907. Found 593.2851. Anal. Calcd for $C_{37}H_{44}Si_2O_3 \cdot 0.5\ H_2O$: C, 73.91; H, 7.54. Found: C, 73.95; H, 7.87.

1,4-Anhydro-3,5-*O*-bis(triethylsilyl)-2-deoxy-D-*erythro*-pent-1-enitol (4b): via **2b** [clear syrup. ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.48 (d, 1, J = 6.7 Hz), 4.32 (m, 1), 3.75 (m, 2), 2.80 (dd, 1, J = 6.6 Hz, 17.6 Hz), 2.36 (d, 1, J = 17.6 Hz), 0.91(m, 12), 0.53 (m, 15)].

Without purification, this was reduced to **3b** which subsequently gave, as described above, 7.73 g (53% from **1**) of **4b** as a clear syrup. R_f = 0.67 in 5% diethyl ether/petroleum ether. ^{1}H NMR (270 MHz; $CDCl_3$) δ 6.49 (dd, 1, J = 0.6 Hz, 2.6 Hz), 5.03 (t, 1, J = 2.6 Hz), 4.83 (m, 1), 4.32 (ddt, 1, J = 0.6 Hz, 2.5 Hz, 6.3 Hz), 3.69 (dd, 1, J = 6.1 Hz, 10.5 Hz), 3.46 (dd, 1, J = 6.1 Hz, 10.5 Hz). ^{13}C NMR (67.5 MHz; $CDCl_3$) δ 149.1, 103.6, 89.4, 76.1, 62.9, 6.6, 5.3, 4.7.

1,4-Anhydro-3,5-*O*-bis[(1,1-dimethylethyl)dimethylsilyl]-2-deoxy-D-*erythro*-pent-1-enitol (4c): via **2c** [white solid. Mp 72−74 °C. ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.44 (m, 1), 4.28 (m, 1), 3.73 (m, 2), 2.76 (dd, 1, J = 6.7 Hz, 17.6 Hz), 2.33 (dd, 1, J = 2.6 Hz, 17.6 Hz), 0.82(s, 18), 0.09 (s, 12). ^{13}C NMR (90 MHz, $CDCl_3$) δ 176.8, 88.3, 69.8, 62.6, 39.2, 26.0, 25.8, 18.4, 18.1, −4.5, −5.4].

Without purification, this was reduced to **3c** which subsequently gave, as described above, 11.26 g (66% from **1**) of **4c** as a clear syrup: R_f = 0.91 in 5% diethyl ether/petroleum ether. $[\alpha]^{22}_D$ +79.5° (*c* 0.247; CH_2Cl_2). ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.47 (dd, 1, J = 0.8 Hz, 2.6 Hz), 5.01 (t, 1, J = 2.6 Hz), 4.87 (m, 1), 4.29 (m, 1), 3.69 (dd, 1, J = 5.7 Hz, 10.7 Hz), 3.51 (dd, 1, J = 5.7 Hz, 10.7 Hz). ^{13}C NMR (90 MHz, $CDCl_3$) δ 149.2, 103.6, 89.1, 76.2, 63.0, 26.1, 18.6, 18.3, −4.1, −5.1. HRMS calcd for $C_{17}H_{36}Si_2O_3H$: 345.2275. Found 345.2281. Anal. Calcd for $C_{17}H_{36}Si_2O_3 \cdot 0.1CH_2Cl_2$: C, 57.89; H, 10.29. Found: C, 58.11; H, 10.20.

1,4-Anhydro-2-deoxy-3-*O*-[(1,1-dimethylethyl)diphenylsilyl]-D-*erythro*-pent-1-enitol (5a). A 200 mL round-bottom flask was charged with **4a** (3.50 g, 5.9 mmol). Diethyl ether (80 mL) was added, and to the resulting solution was added a 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran (5.9 mmol). The reaction was continued at room temperature until TLC showed the complete consumption of **4a** (approximately 90 min). The reaction was quenched with 1,2-dichloroethane, and the solvent was evaporated *in vacuo*. The resultant

(9) The decomposition of **4a-c** were followed by observing the ^{1}H NMR spectra of samples in $CDCl_3$ kept at room temperature. While **4a** and **4b** were fully decomposed after 48 h, **4c** showed no decomposition even after 150 h.

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oil was subjected to silica gel chromatography (45 × 200 mm, 50% diethyl ether/petroleum ether) to give, after solvent evaporation of the appropriate fractions, 502 mg of **5a** (24%) as a clear oil. The proton NMR was identical to the glycal as synthesized by Farr and Daves.[8]

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