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MODIFIED SYNTHESIS OF 3′-OTBDPS-PROTECTED FURANOID GLYCAL

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Abstract

Thermolytic cleavage of 3′-OH protected thymidine is the most common method of preparing furanoid glycals. We have observed that glycosidic bond cleavage is more facile when the 5′-OH of thymidine was also protected with a silyl group. Addition of trimethylsilyl chloride facilitated cleavage of the glycosidic bond; thus, both modifications are required for the formation of the fura-noid glycal. Investigations into the selective deprotection of 5′-silyl versus 3′-silyl and subsequent glycosidic bond cleavage are reported herein.

Keywords

Furanoid glycal; *C*-nucleosides

INTRODUCTION

Furanoid glycals are important intermediates in the synthesis of *C*-nucleosides using Heck methodology.[1–3] The Heck coupling reaction is preferred over other methods due to the excellent regio- and stereoselectiv-ity it affords.[2,3] It has been shown that the presence of a bulky protecting group such as *t*-butyldiphenylsilyl (TBDPS) on the C-3′-OH directs the approach of the nucleobase from the *β*-face of the glycal giving the desired *β*-*C*-nucleoside.[1,3] Typically, the 3′-O-TBDPS- glycal (Figure 1) is made via thermolysis of 3′-O-TBDPS thymidine in refluxing HMDS in the presence of $(NH_4)_2SO_4$. However, in our hands inconsistent cleavage of the glycosidic bond was observed.[4–6] As a result, a more facile and higher yielding route was sought. Herein, we report the modified synthesis of the 3′-O-TBDPS-protected glycal using a more robust, high yielding, and reproducible procedure.

Several routes to the glycal have been reported by various research groups (Figures 2 and 3).[4–9] For example, Ireland and coworkers first reported a linear route to the glycal starting from D-ribonolactone in 1980.[9] The key step of this reaction was the reductive fragmentation of 2′,3′-O-isopropylidene-protected furanosyl chloride.

Their work was later modified by Daves and coworkers in the early 90s to give the 3′-O-TBDPS-protected glycal, which was subsequently used for Heck-like coupling.[8] Daves further suggested that the 5′-OH on the glycal should not be protected for successful coupling under Heck conditions.[1,3] In contrast to Daves' findings, Pedersen and coworkers subsequently reported that thermolytic cleavage of 5′-O-silyl protected thymidine actually

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improved the synthesis of the glycal (Figure 3).[6] In a similar fashion, McLaughlin utilized the 4,4′-dimethoxyltrityl (DMTr) protection of 5′-OH in an orthogonal protection scheme.[5] Thus, from the literature it was concluded that protection of both the 3′- and 5′-OH appeared important for successful synthesis of the glycal.

RESULTS AND DISCUSSION

Our initial approach began with the protection of the 5′-OH with DMTr.[5] However, DMTr is acid labile and is easily cleaved on a silica column, thereby lowering the yield significantly. Next, as shown in Scheme 1, the more stable silyl protecting groups were considered. Protection of thymi-dine (**1**) with *t*-butyldimethylsilyl (TBDMS) (series a) and TBDPS (series b) was then undertaken. Both groups are commonly used and methods for their protection and selective deprotection are well known.[4–7,10] Thymidine (**1**) was protected with TBDMS (**2a**) and TBDPS (**2b**), as shown in Scheme 1. Selective deprotection of 5′-OTBDMS and 5′-OTBDPS was attempted using one equivalent of tetra-*n*-butyl ammonium fluoride (TBAF). However, this resulted in deprotection of both of the silyl protecting groups. The same reaction was tried at lower temperatures with slow addition of TBAF, and shorter reaction times (15 minutes), to arrest the deprotection of the second silyl protecting group; however, no selectivity was achieved in any of our attempts.

Turning to a selective deprotection reported by Sekine et al. (Scheme 1) that used 1:1 and 1:2 mixtures of TBAF and boron trifluoride diethyletherate ($BF_3{\cdot}OEt_2$) was undertaken.[10] As per Sekine's report (Scheme 1), 5′-OTBDMS (**4**) was selectively cleaved over the 5′-OTBDPS (**5**) and 3′-OTBDMS (**2a**). Among the two TBDMS groups on **2a**, 5′-OTBDMS selectively cleaved over 3′-OTBDMS giving **3a** in 76% yield; however, this cleavage of the 5′-OTBDMS group occurs rapidly (in under 15 minutes). In our lab, it was observed that prolonged stirring of **2a** with 1:1 mixture of TBAF and $BF_3{\cdot}OEt_2$ progressively cleaved the 3′-OTBDMS giving thymidine (**1**), thus making the reaction sensitive and unsuitable for our purposes. In the case of 3′,5′bis-OTBDPS protected thymidine (**2b**), no cleavage of either silyl group was observed. Thus, it can be concluded that the mixture of TBAF and $BF_3{\cdot}OEt_2$ is not suitable for selective deprotection of a silyl group when both the silyl groups on 3′-OH and 5′-OH are identical.

Switching strategies, instead of obtaining a mono-silyl thymidine intermediate before thermolysis, the decision was made to reverse the sequence and obtain the glycal before selective removal of the 5′-OH protecting group (Scheme 2). Thus, the glycosidic bond of the bis-silyl thymidines **2a** and **2b** were subjected to thermolysis, and glycals **6a** and **6b** were obtained in yields of 69% and 79%, respectively.[4] In contrast to the previous literature reports, it appeared that glycosidic bond cleavage is more successful when the 5′-OH is silyl protected.

Next, to realize the glycals **7a** and **7b** needed for Heck coupling, selective cleavage of the 5′-O-silyl group using the above-mentioned methods (TBAF or TBAF/$BF_3{\cdot}OEt_2$ mixture) was tried. Unfortunately, both methods failed to provide the desired products. Use of one equivalent of TBAF did give **7a** but in low yields that were difficult to reproduce. Moreover, in most cases, cleavage of both silyl groups was observed. As a result, the use of two different protecting groups was considered as a way to potentially overcome this roadblock.

Sekine's results were revisited wherein it was reported that both 1:1 and 1:2 mixtures of TBAF and $BF_3{\cdot}OEt_2$ have the propensity to cleave 5′-O-TBDMS faster than 5′-O-TBDPS due to steric factors.[10] Based on Sekine's findings and our results from Scheme 1, two different silyl groups, TBDMS and TBDPS, were installed on thymidine (Scheme 3) to give **8**. As shown in Scheme 3, addition of thymidine to a stirred solution of TBDMSCl (1.2

equivalents) and imidazole (2 equivalents) gave **4**, which was treated with TBDPSCl using standard conditions to afford **8**. Selective deprotection of 5′-O-TBDMS over 3′-OTBDPS was then achieved using ten equivalents of a 1:1 $BF_3{\cdot}OEt_2$: TBAF mixture to provide **3b** in an 85% yield upon stirring overnight. This selectivity can be attributed to the steric bulk of the 3′-TBDPS group that prevents its cleavage compared to the 5′-TBDMS group that is smaller in size and is more rapidly cleaved to give **3b**. Interestingly, when more than 10 equivalents were used, the yields dropped to 60%; however, when less than nine equivalents were used, the reaction failed to go to completion. Clearly, this approach is more viable when compared to cleavage of 5′-O-TBDMS over 3′-O-TBDMS as shown in Scheme 1.

Reports of another procedure that involved selective deprotection of one silyl group in the presence of another utilized a trifluoroacetic acid (TFA) and water mixture to selectively cleave the 5′-O-TBDMS group, leaving the 3′-O-TBDMS intact.[11] This method seemed suitable, and upon stirring a solution of **8** in THF with a mixture of TFA:H_2O, **3b** was obtained in a 70% yield. Comparison of the two methods revealed that the TBAF:$BF_3{\cdot}OEt_2$ mixture is superior as it provided **3b** in 85% yield as compared to 70% using the TFA:H_2O mixture. Moreover, cleavage of both silyl groups was observed when the TFA:H_2O mixture was allowed to stir for longer periods, resulting in formation of thymidine (**1**), and requiring frequent monitoring by TLC. In contrast, the TBAF:$BF_3{\cdot}OEt_2$ method was stable upon stirring overnight at room temperature.

Turning our attention to the thermolysis reaction (Scheme 4), attempts to cleave **3b** in the presence of HMDS and $(NH_4)_2SO_4$ had previously proven unsuccessful. From the results shown in Scheme 2, it was evident that both the hydroxyls of thymidine needed to be silyl protected for successful cleavage of the glycosidic bond. As a result, reprotection of the 5′-OH group was achieved with one equivalent of trimethylsilyl chloride (TMSCl) followed immediately by the thermolysis reaction, giving **7b** in 80% yield, with an overall yield of 55% over four steps as compared to 44% of McLaughlin's process.

From the literature, it had also been observed that acidic catalysts like $(NH_4)_2SO_4$, TMSCl, and TMSOTf were typically added to refluxing HMDS mixtures when the rate of silylation proved low.[12] Upon addition of these catalysts however, ammonium salts would form in the reflux condenser and the reaction mixture would become turbid. Both observations were noted upon addition of TMSCl, indicating successful silylation of the protected thymidine. Notably, these observations were not seen when **3b** was stirred with $(NH_4)_2SO_4$ in boiling HMDS. As a result, it appears that the use of a catalytic amount of $(NH_4)_2SO_4$ is insufficient to help HMDS silylate the protected thymidine. In contrast, TMSCl appears to be important for successful silylation and glycosidic bond cleavage. It should also be noted that, along with the product, migration of the 3′-OTBDPS to 5′-OH was observed, as confirmed by NMR.[13]

In summary, we have reported herein an optimized approach to the synthesis of the furanoid glycal that overcomes some of the difficulties noted in previously reported methods. The approach is robust and high yielding and, given the importance of the furanoid glycal in Heck coupling, this methodology should prove advantageous in the pursuit of C-nucleosides.

EXPERIMENTAL

Materials and Methods

All chemicals and reagents listed in this section were purchased through commercially available sources unless otherwise noted. All reactions run in CH_2Cl_2, CH_3CN, and THF were obtained from a solvent purification system (SPS, Model: mBraun Labmaster 130). All

reactions run in anhydrous DMF, MeOH and pyridine were obtained from Sigma–Aldrich or Acros Organics. All ^{1}H and ^{13}C NMR spectra were obtained from a JEOL ECX 400 MHz NMR. All NMR solvents were obtained from Cambridge Isotope Laboratories. All reactions were monitored by thin layer chromatography (TLC) on 0.25 mm precoated glass plates. All column chromatography was run on 32–63 u silica gel obtained from Dynamic Adsorptions Inc. (Norcross, GA, USA) All mass spectra (MS) were recorded and obtained from the University of Maryland Baltimore County Mass Spectrometry Facility.

5′-O-(*tert*-Butyldimethylsilyl) Thymidine (4)

In a dry flask, DMF (15 mL) was added to a mixture of TBDMSCl (1.49 g, 9.91 mmol) and imidazole (1.12 g, 16.5 mmol) under nitrogen. The resulting clear solution was stirred for 15 minutes and thymidine **1** (2.0 g, 8.3 mmol) added. The mixture was stirred for 3 hours at rt, at which point TLC analysis indicated the absence of thymidine. Water (100 mL) was added to the reaction mixture, resulting in a white precipitate. The organic materials were extracted in CH_2Cl_2 (50 mL), and the aqueous layer washed with CH_2Cl_2 (50 mL). The organic layers were combined, washed with saturated $NaHCO_3$ solution (25 mL), and brine (50 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated. The resulting crude compound was purified using column chromatography eluting with 95:5 CH_2Cl_2:MeOH to give **4** as a white solid (2.64 g, 90%). R_f 0.45, 95:5 CH_2CL_2:MeOH. NMR spectra agree with literature values.[6]

5′-O-(*tert*-Butyldimethylsilyl)-3′-O-(*tert*-Butyldiphenylsilyl Thymidine (8)

In a dry flask, TBDPSCl (2.16 mL, 8.89 mmol), imidazole (1.01 g, 14.83 mmol), and **4** (2.64 g, 7.41 mmol) were combined and DMF (15 mL) added under nitrogen. The resulting clear solution was stirred for 15 minutes.

The reaction mixture was heated to 50°C and stirred under nitrogen with monitoring by TLC. The reaction was complete in 18 hours. The reaction mixture was cooled to rt and water (50 mL) added to result in a white precipitate. The organic materials were extracted in EtOAc (50 mL), and the aqueous layer washed with an additional portion of EtOAc (50 mL). The organic layers were combined and washed with a saturated solution of $NaHCO_3$ (25 mL), then with brine (50 mL). The organic layer was dried over $MgSO_4$, and purified by column chromatography eluting with hexanes: EtOAc 9:1 followed by hexanes: EtOAc 4:1 to provide **8** as a white foam (3.97 g, 90%). R_f 0.5 in 4:1 hexanes: EtOAC. NMR spectra agree with literature values.[14]

3′-O-(*tert*-Butyldiphenylsilyl) Thymidine (3b)

To a stirred 1M solution of TBAF in THF (60.05 mL, 60.05 mmol) under N_2, $BF_3{\cdot}OEt_2$ (48%, 15.7 mL, 60.05 mmol) was added dropwise. In a separate flask, **8** (3.97 g, 6.67 mmol) was dissolved in anhydrous CH_3CN. The solution of $BF_3{\cdot}OEt_2$/TBAF was added dropwise and the mixture stirred at rt overnight. The reaction mixture was concentrated and purified via column chromatography eluting with 9:1 hexanes:EtOAc, followed by 4:1 hexanes:EtOAc to provide **3b** as a white foam (2.7 g, 85%,). R_f 0.5 in 95:5 CH_2Cl_2: MeOH. NMR spectra agree with literature values.[4, 5]

1,4-Anhydro-3-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-D-*erythro*-pent-1enitol (7b)

In a dry flask, **3b** (1.3 g, 2.7 mmol) and $(NH_4)_2SO_4$ (89 mg, 0.68 mmol) were combined and HMDS (30 mL) added under a N_2 atmosphere. The suspension was stirred at 80°C until **3b** dissolved. The solution was cooled to 40°C, at which point TMSCl (0.34 mL, 2.7 mmol) was added to obtain a white precipitate. The white suspension was heated to reflux (125–130°C) for 4 hours. During the course of the reaction, the solution turned from yellow to

light brown solution. The HMDS was removed in vacuo and the residue dissolved in CH_2Cl_2 (50 mL). The organic layer was washed with water (25 mL), $NaHCO_3$ (25 mL), followed by brine (50 mL). The volatiles were removed and the residue dissolved in MeOH (50 mL). The residue was treated with aq. NH_3 and stirred overnight. The volatiles were removed in vacuo and the residue purified by column chromatography eluting with hexanes:EtOAc (9:1) to give **7b** as a colorless syrup (0.76 g, 80%). R_f 0.5 in 4:1 hexanes:EtOAc. NMR spectra agree with literature values.[4,5]

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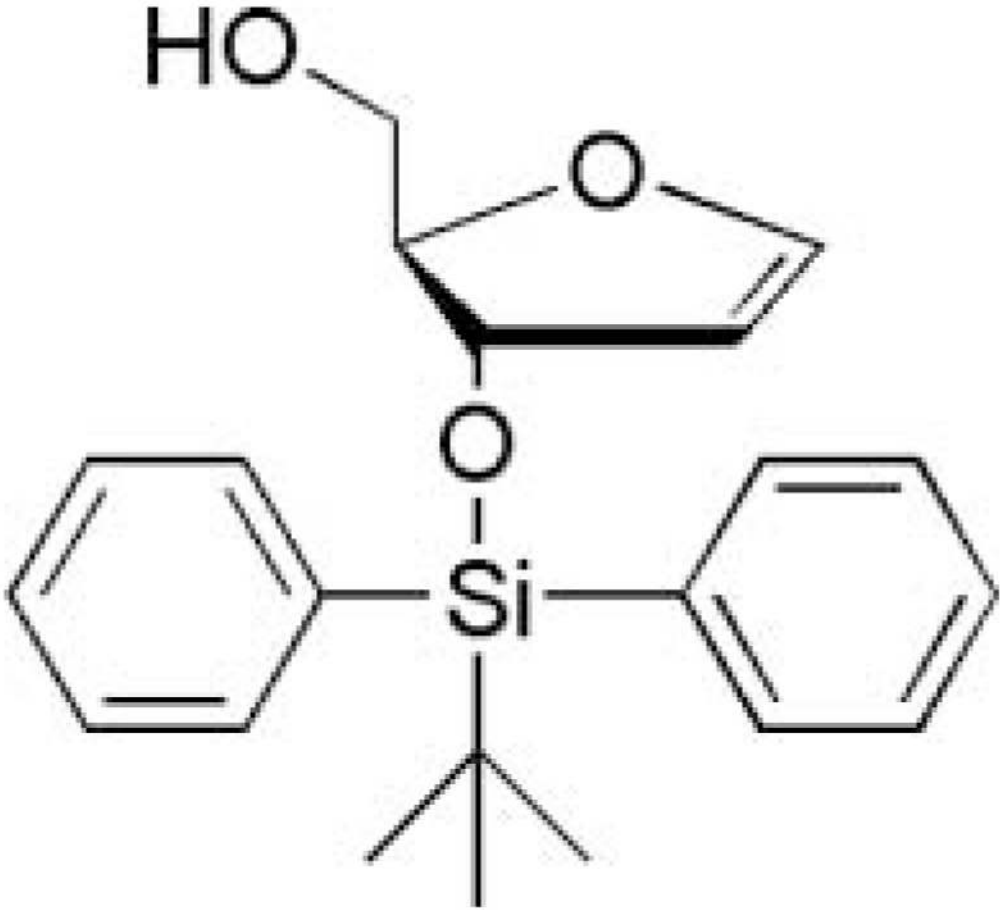


FIGURE 1.
Glycal intermediate for *C*-nucleoside synthesis by way of Heck coupling.

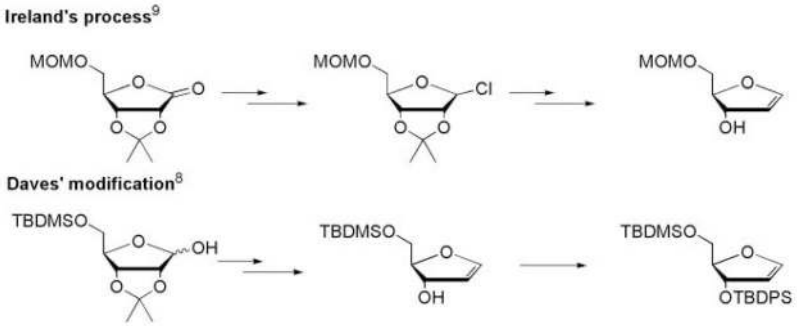


FIGURE 2.
Early reports of glycal preparation.

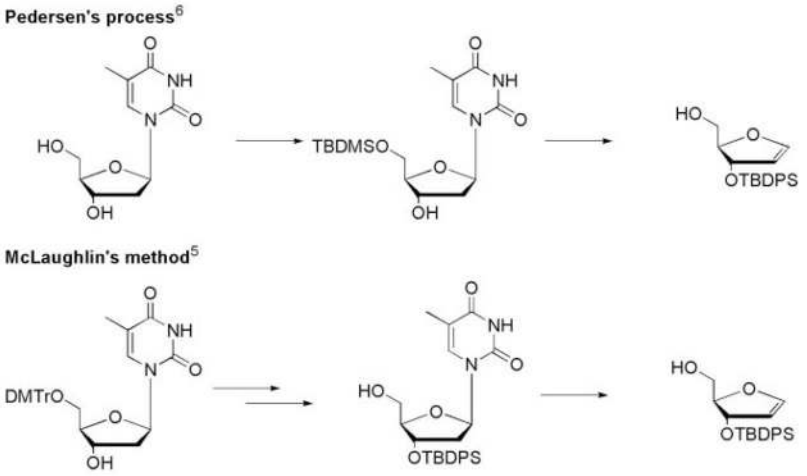
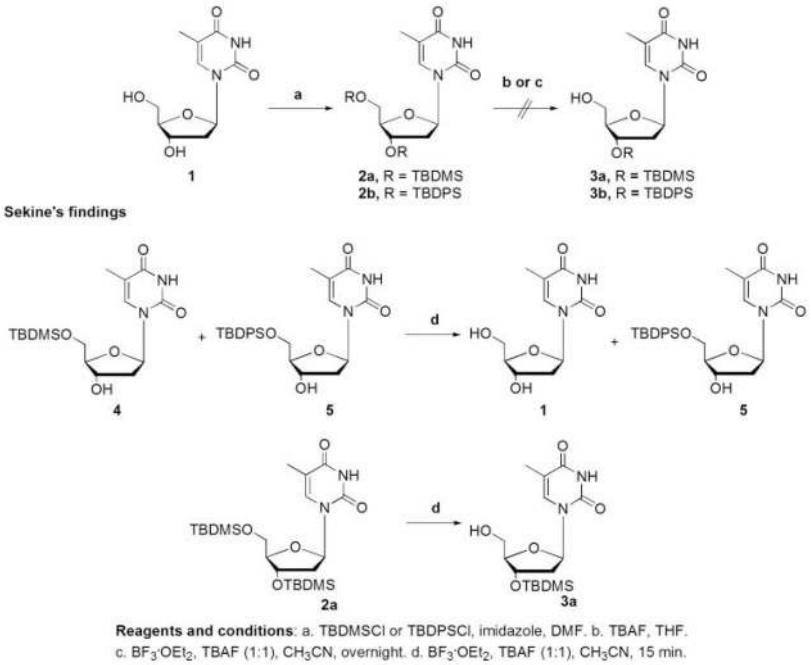
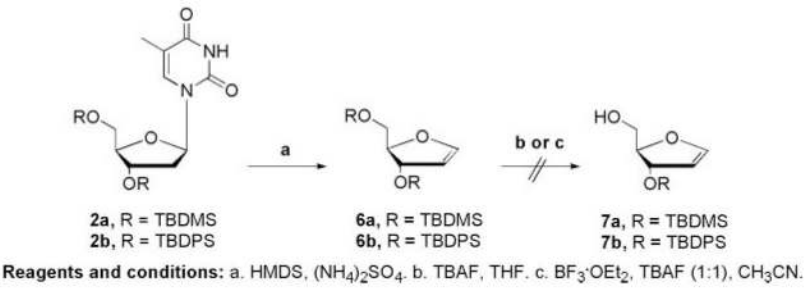


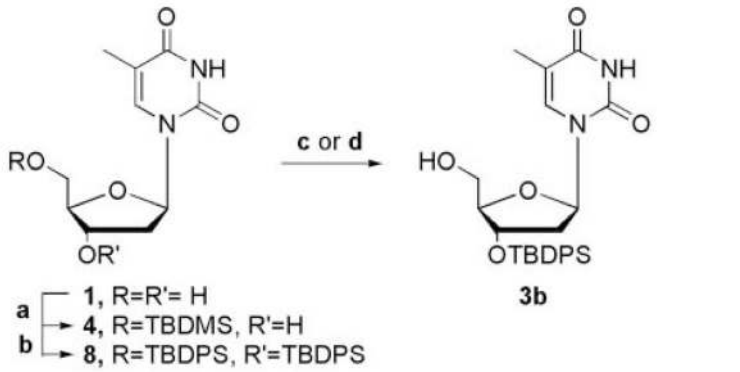
FIGURE 3.
Glycal preparation by thermolysis of the glycosidic bond.



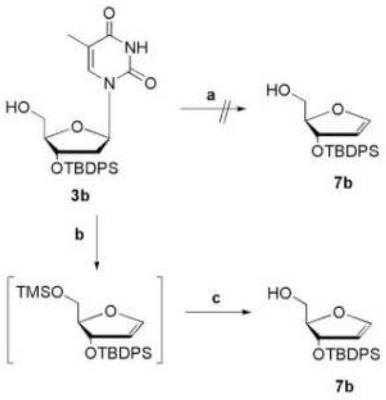
SCHEME 1.
Selective deprotection of silyl protecting groups.



SCHEME 2.
Cleavage of glycosidic bond.



SCHEME 3.
Selective cleavage of 5′-OTBDMS.



Reagents and conditions: a. HMDS, $(NH_4)_2SO_4$. b. HMDS, $(NH_4)_2SO_4$, TMSCl, reflux. c. NH_4OH, MeOH.

SCHEME 4.
Glycal preparation by glycosidic bond cleavage.