Facile Preparation of Protected Furanoid Glycals from Thymidine

Melissa A. Cameron, Sarah B. Cush, and Robert P. Hammer*

Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803

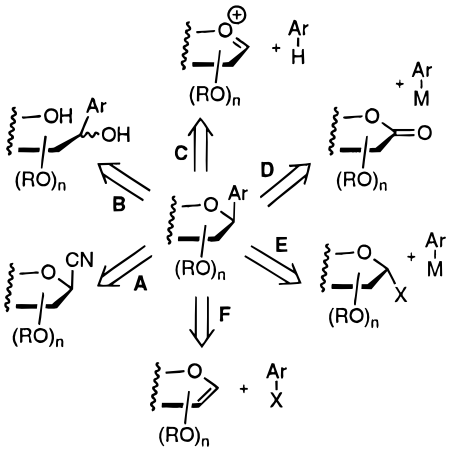
Received May 29, 1997[⊗]

The synthesis of *O*-silyl- and *O*-acyl-protected furanose glycals from free thymidine was investigated. The method of glycal formation reported by Pedersen *et al.* was successfully expanded to include 5-ester (toluoyl) protected glycals as well as various combinations of 5′-ester and 3- and 5-*tert*-butyldimethylsilyl and *tert*-butyldiphenylsilyl protection. Gram quantities of furanoid glycals can be prepared in a few days in two−four synthetic steps in overall yields ranging from 17 to 80%.

The preparation of aryl *C*-glycosides and *C*-nucleosides is of intense interest because of their potential antiviral and antitumor activity[1] and their use as novel base-pairing moieties in oligonucleotides.[2] Several approaches have been developed for the preparation of *C*-glycosides and *C*-nucleosides including multistep assembly of the aryl unit *de novo* on the sugar moiety (Scheme 1, path A),[3] multistep assembly of the sugar *de novo* on the aromatic aglycon (Scheme 1, path B),[4] electrophilic aromatic substitution with a glycosyl cation (Scheme 1, path C),[5] and nucleophilic attack of aryl organometallics directly onto lactones (Scheme 1, path D)[2e,6] or glycosyl halides (Scheme 1, path E).[2a−d] An alternative strategy for preparation of *C*-nucleosides has been developed by Daves *et al.*[7,8] which utilizes a Pd-catalyzed Heck-type coupling of aryl halides to cyclic enol ethers, either pyranoid or furanoid glycals (Scheme 1, path F).

A limitation of this latter approach has been poor accessibility of the furanoid glycals, which in contrast to pyranose glycals are highly acid labile. For example, reduction of pyranosyl halides by elemental zinc in acetic acid produces good yields of pyranose glycals;[9] this method fails for furanosyl glycals.[10] Ireland *et al.*[11] demonstrated a synthesis of 5-*O*-protected glycals in four

Scheme 1



steps from 2,3-isopropylidene-protected ribonolactone. The overall yield was 60%, but the 5-*O*-protection possibilities were limited and scale-up was difficult because of the aluminum hydride reduction, chlorination, and dissolving metal reduction required in this route. A modified approach was developed by Daves *et al.*[12] to allow for differential protection of the 3- and 5-hydroxyl groups. The method required six steps with an overall yield of 25%. The protecting group choices were increased to include silyl-protecting groups, but the chemistry was still limited because of the need for DIBAl-H reduction, chlorination, and Na/NH_3 reduction. More recently, two groups have developed methods to prepare glycals from 2-deoxyribose. Kassou and Castillón[13] have used a selenoxide elimination approach to access glycals (three−five steps, ≤ 40−65% yield) that is compatible with 3- and 5-acyl protection. Townsend and co-workers[14] utilized the elimination of a 1-*O*-mesylate on a protected 2-deoxyribose to prepare mono- or bis-silyl-protected glycals (four−five steps, 20−82% yields).

Pedersen *et al.*[15] reported that furanose *erythro*-glycals can be produced easily from free thymidine or 5′-*O*-(*tert*-butyldiphenylsilyl)thymidine (**1c**) by using typical base silylation conditions: refluxing 1,1,1,3,3,3-hexamethyldisilazane (HMDS) and $(NH_4)_2SO_4$ (eq 1). This approach

* Dr. Robert P. Hammer, Department of Chemistry, 232 Choppin Hall, Louisiana State University, Baton Rouge, LA 70803, Telephone: (504) 388-4025, Facsimile: (504) 388-3458, Internet: chammer@chrs1.chem.lsu.edu

⊗ Abstract published in *Advance ACS Abstracts,* December 1, 1997.

(1) (a) Daves, G. D., Jr.; Cheng, C. C. *Prog. Med. Chem.* **1976**, *13*, 303−349. (b) Hacksell, U.; Daves, G. D., Jr. *Prog. Med. Chem.* **1985**, *22*, 1−65.

(2) (a) Schweitzer, B. A.; Kool, E. T. *J. Org. Chem.* **1994**, *59*, 7238−7242. (b) Schweitzer, B. A.; Kool, E. T. *J. Am. Chem. Soc.* **1995**, *117*, 1863−1872. (c) Ren, R. X.-F.; Chaudhuri, N. C.; Paris, P. L.; Rumney, S.; Kool, E. T. *J. Am. Chem. Soc.* **1996**, *118*, 7671−7678. (d) Moran, S.; Ren, R. X.-F.; Rumney, S.; Kool, E. T. *J. Am. Chem. Soc.* **1997**, *119*, 2056−2057. (e) Hildbrand, S.; Leumann, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1968−1970.

(3) Watanabe, K. A. *Chemistry of Nucleosides and Nucleotides*, Vol. 3, Plenum Press: New York, 1994; pp 438−477.

(4) Solomon, M. S.; Hopkins, P. B. *Tetrahedron Lett.* **1991**, *32*, 3297−3300.

(5) Jaramillo, C.; Knapp, S. *Synthesis* **1994**, 1−20.

(6) Kraus, G. A.; Molina, M. T. *J. Org. Chem.* **1988**, *53*, 752−753.

(7) (a) Arai, I.; Daves, G. D., Jr. *J. Org. Chem.* **1978**, *43*, 4110−4112. (b) Arai, I.; Daves, G. D., Jr. *J. Org. Chem.* **1979**, *44*, 21−22. (c) Daves, G. D., Jr. *Acc. Chem. Res* **1990**, *23*, 201−206. (d) Kwok, D.-I.; Farr, R. N.; Daves, G. D., Jr. *J. Org. Chem.* **1991**, *56*, 3711−3713. (e) Zhang, H.; Brakta, M.; Daves, G. D., Jr. *Nucleosides Nucleotides* **1995**, *14*, 105−116.

(8) For more recent examples by other groups, see: (a) Chen, J. J.; Walker, J. A.; Liu, W.; Wise, D. S.; Townsend, L. B. *Tetrahedron Lett.* **1995**, *36*, 8363−8366. (b) Erion, M. D.; Rydzewski, R. M. *Nucleosides Nucleotides* **1997**, *16*, 315−337.

(9) Sharma, M.; Brown, R. K. *Can. J. Chem.* **1966**, *44*, 2825−2835.

(10) Ferrier, R. J. *Adv. Carbohydr. Chem.* **1969**, *24*, 199−266.

(11) Ireland, R. E.; Thairisvongs, S., Vanier, D.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48−61.

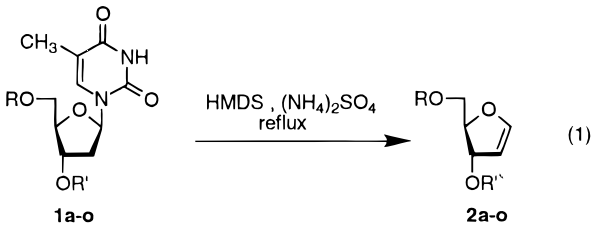
(12) Cheng, J. C.; Hacksell, U.; Daves, G. D., Jr. *J. Org. Chem.* **1985**, *50*, 2778−2780.

(13) Kassou, M.; Castillón, S. *Tetrahedron Lett.* **1994**, *35*, 5513−5516.

(14) Walker, J. A.; Chen, J. J.; Wise, D. S.; Townsend, L. B. *J. Org. Chem.* **1996**, *61*, 2219−2221.

(15) Larsen, E.; Jorgensen, P. T.; Sofan, M. A.; Pedersen, E. B. *Synthesis* **1994**, 1037−1038.

S0022-3263(97)00947-X CCC: $14.00



has the advantage of readily available starting materials, potential compatibility with a wide range of protecting groups, and very straightforward experimental procedures. Thus, we envisioned this as an ideal method for making up to gram amounts of glycals *rapidly* and *efficiently*, as it avoids the experimental diffculties of previous glycal preparations (e.g., large scale dissolving metal reductions,[11,12] large scale aluminum hydride reductions[11−13]). Herein we show that this method works very well for preparation of furanose glycals with a wide range of *O*-silyl protection. Additionally, 5-*O*-acyl-protected glycals, previously only accessible by a selenoxide elimination method,[13] can also be prepared in good to excellent yields with this straighforward chemistry.

Protected thymidines **1a**−**o** were prepared according to known procedures in one (**1b**−**g**), two (**1h**−**m**), or at most three (**1n**−**o**) steps (see Scheme 2, Experimental Section, and Supporting Information). The protection groups on the thymidines were introduced by silylation with either *tert*-butyldimethylsilyl chloride (TBDMSCl) or *tert*-butyldiphenylsilyl chloride (TBDPSCl) and imidazole in DMF or by toluoylation with *p*-toluoyl chloride in pyridine. Where 5′-toluoyl groups were used as temporary protection, they were removed by treatment with ammonia in methanol.

On ∼0.2−3 mmol scales, the thymidines were treated under Pedersen's conditons (excess HMDS, $(NH_4)_2SO_4$, reflux) and all, except for the 3′-*O*-toluoyl-protected thymidines (**1g**, **1i**, **1k**), were converted to the corresponding protected glycals (Table 1). In the cases where a free hydroxyl group was present (**2b**−**d**, **2n**, **2o**), the initial product formed was the *O*-trimethylsilyl (TMS) derivative, but under the workup conditions the TMS group was cleaved and the free hydroxyl compound was isolated. For optimal glycal yields, heating should be discontinued as soon as all the nucleoside is consumed (TLC). In general, the crude products from extraction are pure enough for further reactions, though we report here yields after flash chromatographic purification (Table 1).

Yields of glycal products with *O*-TBDMS protection were always lower than analogous TBDPS derivatives [e.g., **2b** (74%) vs **2c** (91%); **2e** (69%), **2j** (59%) vs **2f** (80%); **2l** (74%) vs **2m** (94%); **2n** (36%) vs **2o** (79%)]. This suggests some cleavage of TBDMS ethers under the slightly acidic conditions of the reaction or overall lower stability of the TBDMS glycals. As previously noted by Pedersen,[15] thymidines in which a 3′-ester group was included (**1g**, **1i**, **1k**) produced no isolable glycal products though starting material was consumed slowly[16] to form furfuryl alcohol derivatives.[17] The 5′-*O*-toluoylthymidines (**1d**, **1l**, **1m**) were successfully converted to the corresponding glycals and were found to be much more stable to storage than those with only silyl protection (Table 1, footnote c).

(16) Free thymidine (**1a**) and toluoyl-protected thymidines (**1d**, **1g**, **1i**, **1k**−**m**) are much less soluble in HMDS and dissolve slowly in the refluxing HMDS.

Table 1. Product Yields for Glycals

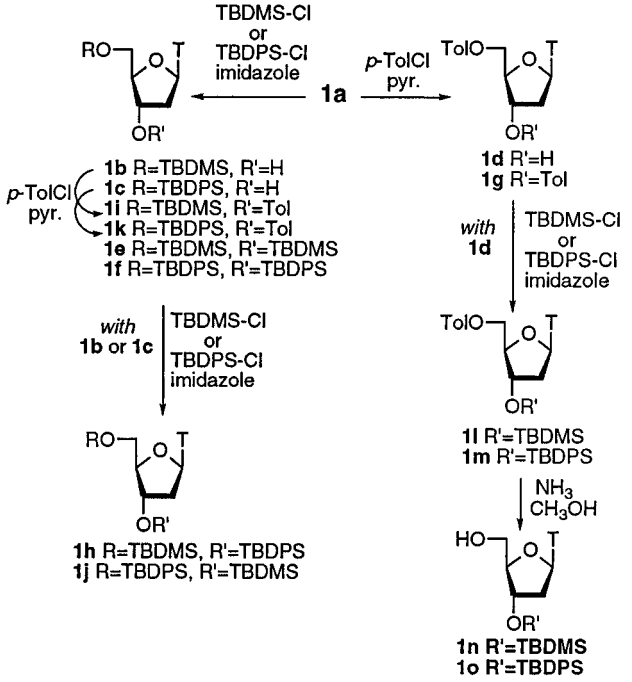
thymidine	glycal	R	R′	yield (%)[b,c]	yield (%) from **1a**[d]
1a	**2a**[e]	H	H	80	80 (1)
1b	**2b**[e]	TBDMS	H	74	53 (2)
1c	**2c**[e]	TBDPS	H	91	70 (2)
1d	**2d**	Tol	H	52	38 (2)
1e	**2e**[e]	TBDMS	TBDMS	69	47 (2)
1f	**2f**[e]	TBDPS	TBDPS	80	76 (2)
1g	**2g**	Tol	Tol	*a*	*a*
1h	**2h**	TBDMS	TBDPS	79	55 (3)
1i	**2i**	TBDMS	Tol	*a*	*a*
1j	**2j**	TBDPS	TBDMS	59	40 (3)
1k	**2k**	TBDPS	Tol	*a*	*a*
1l	**2l**	Tol	TBDMS	74	39 (3)
1m	**2m**	Tol	TBDPS	94	64 (3)
1n	**2n**	H	TBDMS	36	18 (4)
1o	**2o**	H	TBDPS	79	53 (4)

[a] No glycal product obtained. [b] Isolated yield after chromatography. [c] Purified silyl-protected glycals decompose readily at room temperature, though they may be stored in the freezer up to several weeks. In contrast, the 5-*O*-toluoylglycals (**2d**, **2l**, **2m**) are stable at room temperature for several days and appear to be indefinetely stable in the freezer. [d] The number in parentheses indicates the number of steps required to prepare the glycal from commercially available free thymidine **1a**. [e] A separate time course experiment was run to determine the rate of glycal formation for several of the protected thymidines: Thymidine (**1a-c**, **1e**, **1f**; 0.1 mmol), $(NH_4)_2SO_4$ (0.5 g, 3.8 mmol) in HMDS (5 mL). Reaction mixtures were lowered simultaneously into preheated oil baths and all started refluxing within 30 s. Disappearance of starting material (TLC, GC) was considered as the end of the reaction. Reaction times: **2a**, 170 min; **2b**, 125 min; **2c**, 145 min; **2e**, 180 min; **2f**, 180 min.

Using Pedersen's method, we have prepared furanoid glycals having both *O*-silyl and, for the first time, 5-*O*-acyl protection. The advantages of this method are the greater generality of protecting groups that can be used and the speed and experimental ease with which glycals can be made. Previous methods for preparing furanose glycals starting from ribonolactone[11,12] require at least six steps and are difficult to scale-up because of the required sequential DIBAl-H reduction, low-temperature chlorination, and Na/NH_3 reduction. The more recent approaches to glycals from 2-deoxyribose[13,14] are much improved, but still have some disadvantages relative to the Pedersen route from thymidine. The Castillón method requires use of the toxic, pungent, and expensive reagent benzeneselenol. Townsend's approach requires a low-temperature reduction step that is incompatible with 5-*O*-ester protection (e.g., **2d**, **2j**, **2l**, **2m**). Yields of glycals made herein under Pedersen conditions, including the four previously unknown glycals **2d**, **2j**, **2l**, **2m**, are comparable to those acheived by Townsend. Also, production of glycals by the Pedersen method is always one less step from commercially available material than the Townsend Route: bis-*O*-TBDMS glycal **2e**, two steps from thymidine (**1a**), 47% yield, or three steps from 2-deoxyribose, 63% yield; bis-*O*-TBDPS glycal **2f**, two steps from **1a**, 76% yield, or three steps from 2-deoxyribose, 80% yield; 3-*O*-TBDPS glycal **2o**, four steps from **1a**, 53% yield, or five steps from 2-deoxyribose, 20% yield. Gram quantities of furanoid glycals can now be prepared in a few days using standard nucleoside protection chemistry and typical HMDS silylation conditions. Im-

(17) For example, attempted preparation of **2k** by method D resulted in formation of the TBDPS ether of furfuryl alcohol: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.65−7.61 (m, 4H, *Ar*), 7.38−7.26 (m, 6H, *Ar*), 6.21 (m, 1H, *H2*), 6.06 (d, 1H, *H3*), 2.18 (s, 2H, *H5*), 0.99 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.1 (C1), 110.2 (C2), 107.4 (C3), 58.9 (C5), 26.8 ($C(CH_3)_3$), 14.2 ($C(CH_3)_3$).

Scheme 2



proved access to differentially protected five-member glycals should greatly increase their potential as intermediates in organic synthesis, especially for preparation of aryl- and heteroaryl-2-deoxy-*C*-furanosides.[8]

Experimental Section

General methods of synthesis, purification, and characterization have been described previously.[18] The protected thymidine derivatives **1a-o** were prepared according to Scheme 2 and methods A, B, and C below. Glycal formation from thymidines **1** was accomplished using method D with variations detailed for each specific compound.

Method A. General Conditions for Silylation. 5′-*O*-(*tert*-Butyldimethyl)-3′-*O*-(*tert*-butyldiphenylsilyl)thymidine (1h).[19] 5′-*O*-(*tert*-Butyldimethylsilyl)thymidine (**1b**) (3.37 g, 9.46 mmol) was introduced to a dried flask under Ar. DMF (40 mL) was added, and the solution was stirred until **1b** dissolved. Imidazole (2.07 g, 30.40 mmol) was added followed by TBDPSCl (3.17 g, 11.54 mmol). The solution was stirred for 24 h. It was poured into water (500 mL) and extracted with ether (3 × 250 mL). The ether layer was then washed with aqueous $NaHCO_3$ (200 mL) followed by distilled water (200 mL). It was dried with Na_2SO_4 and evaporated under reduced pressure to give a clear oil. This was purified by flash chromatography (hexanes and then ether) to yield a white solid (5.5 g, 98%): TLC R_f 0.91 (9:1 $CHCl_3$−CH_3OH); mp 56 °C; FABMS (MNBA) 596.5 $(M + H)^+$; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.62 (s, 1H, *H3*), 7.67−7.63 (m, 4H, *Ar and H6*), 7.47−7.37 (m, 7H, *Ar*), 6.53 (dd, $J_{H2'} = 5.5$, $J_{H2'} = 8.9$ Hz, 1H, *H1′*), 4.34 (d, $J = 5.2$ Hz, 1H, *H3′*), 4.00 (s, 1H, *H4′*), 3.63 (dd, $J_{H4'} = 1.3$, $J_{H5'} = 11.0$ Hz, 1H, *H5′*), 3.14 (dd, $J_{H4'} = 1.8$, $J_{H5'} = 10.9$ Hz, 1H, *H5′*), 2.34 (dd, $J = 5.3$, 13.0 Hz, 1H, *H2′*), 1.87 (s, 3H, *C5-CH3*) 1.85−1.82 (m, 1H, *H2′*), 1.09 (s, 9H, $C(CH_3)_3$), 0.78 (s, 9H, $C(CH_3)_3$), −0.07 (s, 3H, *Si-CH3*), −0.11 (s, 3H, *Si-CH3*); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 164.0 (C4), 150.5 (C2), 135.6 (C6), 135.4, 133.3, 133.0, 129.9, 127.8 (Ar), 110.7 (C5), 88.0 (C4′), 85.0 (C1′), 74.2 (C3′), 63.1 (C5′), 41.3 (C2′), 26.8 ($C(CH_3)_3$), 25.7 ($C(CH_3)_3$), 18.9 ($C(CH_3)_3$), 18.1 ($C(CH_3)_3$), 12.3 (CH_3), −5.6 (Si-*CH3*), −5.8 (Si-*CH3*).

Method B. General Conditions for Toluoylation. 5′-*O*-(*tert*-Butyldimethylsilyl)-3′-*O*-(*p*-toluoyl)thymidine (1i). 5′-*O*-(*tert*-Butyldimethylsilyl)thymidine (**1b**) (0.207 g, 0.58 mmol) was introduced to a dried flask under Ar. Pyridine (5 mL) was added, and the solution was cooled to 0 °C. The *p*-toluoyl chloride (0.15 mL, 1.13 mmol) was added slowly over 15 min. The solution was allowed to warm to room temperature followed by heating to 50−55 °C for 4 h. Then, it was cooled to room temperature and poured onto ice followed by an extraction with CH_2Cl_2. The organic layer was washed with aqueous $NaHCO_3$ and then distilled water. The washed layer was dried with Na_2SO_4 and concentrated under reduced pressure. It was recrystallized from CH_2Cl_2 to yield a white solid (0.219 g, 80%): TLC R_f 0.84 (1:2 CH_2Cl_2−EtOAc); mp 173 °C; FABMS (MNBA) 475.2 $(M + H)^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.84 (s, 1H, *H3*), 7.95−7.92 (m, 2H, *Ar*), 7.61 (app d, $J_{Me} = 1.2$ Hz, 1H, *H6*), 7.28−7.25 (m, 2H, *Ar*), 6.48 (dd, $J_{H2'} = 5.3$, $J_{H2'} = 9.3$ Hz, 1H, *H1′*), 5.49 (d, $J = 6.1$ Hz, 1H, *H3′*), 4.25 (s, 1H, *H4′*), 4.04 (dd, $J_{H4'} = 2.0$, $J_{H5'} = 11.3$ Hz, 1H, *H5′*), 3.97 (dd, $J_{H4'} = 1.9$, $J_{H5'} = 11.3$ Hz, 1H, *H5′*), 2.58 (dd, $J_{H1'} = 5.3$, $J_{H2'} = 13.8$ Hz, 1H, *H2′*), 2.42 (s, 3H, *C5-CH3*), 2.27−2.19 (m, 1H, *H2′*), 1.95 (d, $J_{H6} = 1.0$ Hz, 3H, *Ar-CH3*), 0.96 (s, 9H, $C(CH_3)_3$), 0.17 (s, 6H, *Si-CH3*); ^{13}C NMR (75 MHz,$CDCl_3$) δ 166.3 (*C*(O)-Ar), 163.6 (C4), 150.4 (C2), 144.4 (C(O)-*Ar*), 135.1 (C6), 129.8, 129.3 (Ar), 126.6 (*Ar*-CH_3), 111.3 (C5), 85.7 (C4′), 84.9 (C1′), 75.8 (C3′), 63.7 (C5′), 38.2 (C2′), 25.9 ($C(CH_3)_3$), 21.7 (Ar-*CH3*), 18.4 ($C(CH_3)_3$), 12.5 (C5-*CH3*), −5.3, −5.4 (Si-*CH3*). Anal. Calcd for $C_{24}H_{34}N_2O_6Si\cdot H_2O$: C, 58.51; H, 7.37; N, 5.69. Found: C, 58.38; H, 6.72; N, 5.78.

Method C. General Conditions for Detoluoylation. 3′-*O*-(*tert*-Butyldimethylsilyl)thymidine (1n).[20] 3′-*O*-(*tert*-Butyldimethylsilyl)-5′-*O*-(*p*-toluoyl)thymidine (**1l**) (0.062 g, 0.13 mmol) was introduced into a dried flask under N_2. NH_3-saturated CH_3OH (10 mL) was added. Additional NH_3(g) was bubbled through the solution for 5 min, and the reaction was left to stir for 24 h. It was evaporated under reduced pressure to an oil that was purified by flash chromatography (EtOAc) to yield a white solid (0.044 g, 95%): TLC R_f 0.72 (EtOAc); mp 90 °C (lit. mp 83−84 °C);[20] FABMS (glycerol) 357.2 $(M + H)^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.88 (br, 1H, *H3′*), 7.37 (app d, J_{Me} =1.1 Hz, 1H, *H6′*), 6.14 (t, $J = 6.7$, 1H, *H1′*), 4.49 (m, 1H, *H3′*), 3.96−3.89 (m, 2H, *H4′* and H5′), 3.76 (m, 1H, *H5′*), 2.72 (br, *OH*), 2.43−2.15 (m, 2H, *H2′*), 1.91 (d, $J_{H6} = 0.9$ Hz, 3H, *C5-CH3*), 0.89 (s, 9H, *C(CH3)3*), 0.09 (s, 6H, *Si-CH3*); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 163.7 (C4), 150.3 (C2), 137.0 (C6), 111.0 (C5), 87.6 (C4′), 86.9 (C1′), 71.6 (C3′), 62.0 (C5′), 40.5 (C2′) 25.7 ($C(CH_3)_3$), 17.9 ($C(CH_3)_3$), 12.5 (C5-*CH3*), −4.7, −4.9 (Si-*CH3*).

Method D. General Conditions for Glycal Formation.[21] **1,4-Anhydro-3,5-bis-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-D-*erythro*-pent-1-enitol (2f).**[14] 3′,5′-Bis-*O*-(*tert*-butyldiphenylsilyl)thymidine (**1f**) (0.99 g, 1.38 mmol) was introduced to a dried flask under Ar. HMDS (10.0 mL, 47.3 mmol) was added, and the solution was stirred until dissolved. After the addition of the $(NH_4)_2SO_4$ (0.29 g, 2.19 mmol), the solution was refluxed for 4 h. The HMDS was evaporated under reduced pressure and the residue was partitioned between water and cyclohexane. The organic layer was washed with aqueous $NaHCO_3$ and then distilled water. It was dried with Na_2SO_4 and evaporated under reduced pressure to give a yellow oil that was purified by alumina flash chromatography (1:2 ether−hexanes) (0.648 g, 79%): TLC R_f 0.65 (1:2 ether−hexanes); FABMS (MNBA) 591.3 $(M - H)^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.79−7.62 (m, 9H, *Ar*), 7.48−7.36 (m, 11H, *Ar*), 6.51 (d, $J_{H2} = 2.3$ Hz, 1H, *H1*), 4.99 (t, $J = 2.0$ Hz, 1H, *H2*), 4.92 (m, 1H, *H3*), 4.59−4.53 (m, 1H, *H4*), 3.49−3.45 (m, 2H, *H5*), 1.12, 1.03 (2s, 18H, $C(CH_3)_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.3 (C1), 135.8, 135.6, 135.0, 134.9, 134.2, 134.0, 129.7, 129.3, 127.7, 127.5 (Ar), 103.4 (C2), 89.2 (C3), 77.0 (C4), 63.8 (C5), 26.9, 26.8 ($C(CH_3)_3$), 19.2, 19.1 ($C(CH_3)_3$).

(18) (a) Fernandez, M. d. F.; Vlaar, C. P.; Fan, H.; Hammer, R. P. *J. Org. Chem.* **1995**, *60*, 7390−7391. (b) Flanagan, J. H., Jr.; Khan, S. H.; Menchen, S.; Soper, S. A.; Hammer, R. P. *Bioconjugate Chem.* **1997**, *8*, 751−756.

(19) Perbost, M.; Hoshiko, T.; Morvan, F.; Swayze, E.; Griffey, R. H.; Sanghvi, Y. S. *J. Org. Chem.* **1995**, *60*, 5150−5156.

(20) Ogilvie, K. K. *Can. J. Chem.* **1973**, *51*, 3799−3807.

(21) Reaction times vary with starting glycal and with the scale; larger scales require longer times. Molar amount of $(NH_4)_2SO_4$ does not appear to be critical to success of the reaction, though more than 1 equiv is preferred to get reasonable reaction rates.

1,4-Anhydro-2-deoxy-D-*erythro*-pent-1-enitol (2a)[15] was prepared according to method D from **1a** (96 mg, 0.40 mmol) and $(NH_4)_2SO_4$ (0.157 g, 1.19 mmol) in 5 mL of HMDS. No extraction was performed, and the product was isolated by alumina flash chromatography (1:2 ether−hexanes) to yield a yellow oil (0.0367 g, 80%): TLC R_f 0.24 (1:2 ether−hexanes); CIMS (isobutane) 117.1 $(M + H)^+$; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.49 (d, $J_{H2} = 2.3$ Hz, 1H, *H1*), 5.02 (t, $J = 2.4$ Hz, 1H, *H2*), 4.81 (m, 1H, *H3*), 4.31 (dt, $J = 2.5$, 6.5 Hz, 1H, *H4*), 3.65 (dd, $J = 5.9$, 10.7 Hz, 1H, *H5*), 3.43 (dd, $J = 6.8$, 10.7 Hz, 1H, *H5*); ^{13}C NMR (50 MHz, CD_3OD) δ 150.6 (C1), 104.3 (C2), 90.6 (C3), 76.1 (C4), 63.3 (C5).

1,4-Anhydro-5-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-D-*erythro*-pent-1-enitol (2b)[12] was prepared according to method D from **1b** (0.502 g, 1.41 mmol), HMDS (7 mL, 33.2 mmol), and $(NH_4)_2SO_4$ (0.196 g, 1.48 mmol). The product was purified by alumina flash chromatography (1:2 ether−hexanes) to yield a yellow oil (0.24 g, 74%): TLC R_f 0.98 (9:1 CH_2Cl_2−EtOAc); CIMS (NH_3) 230.2 $(M + H)^+$, 247.2 $(M + NH_4)^+$; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.53 (d, $J_{H2} = 2.4$ Hz, 1H, *H1*), 5.14 (t, $J = 2.9$ Hz, 1H, *H2*), 4.78 (br, 1H, *H3*), 4.33 (dt, $J_{H5} = 5.8$, $J_{H3} = 2.9$ Hz, 1H, *H4*), 3.71 (dd, $J_{H5} = 10.7$, $J_{H4} = 5.8$ Hz, 1H, *H5*), 3.51 (m, 1H, *H5*), 1.60 (br, 1H, *OH*), 0.89 (s, 9H, *C*)*C*H_3)$_3$), 0.07, 0.06 (2s, 6H, *Si*-*CH*$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 150.1 (C1), 103.1 (C2), 89.3 (C3), 75.7 (C4), 62.9 (C5), 25.8 (C(*C*H_3)$_3$), 18.3 (*C*(CH$_3$)$_3$), −5.4 (Si-*CH*$_3$).

1,4-Anhydro-5-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-D-*erythro*-pent-1-enitol (2c)[14] was prepared according to method D from **1c** (0.302 g, 0.63 mmol), HMDS (1 mL, 4.74 mmol), and $(NH_4)_2SO_4$ (0.350 g, 2.65 mmol). The product was purified by alumina flash chromatography (1:2 ether−hexanes) to yield a yellow oil (0.204 g, 91%): TLC R_f 0.79 (1:2 ether−hexanes); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.77−7.74 (m, 4H, *Ar*), 7.51−7.40 (m, 7H, *Ar*), 6.56 (d, $J_{H2} = 2.6$ Hz, 1H, *H1*), 5.10 (t, $J = 2.8$ Hz, 1H, *H2*), 5.04 (m, 1H, *H3*), 4.45 (dt, $J_{H3} = 2.4$, $J_{H5} = 5.2$ Hz, 1H, *H4*), 3.80 (dd, $J_{H4} = 5.0$, $J_{H5} = 10.8$ Hz, 1H, *H5*), 3.70 (dd, $J_{H4} = 5.8$, $J_{H5} = 10.7$ Hz, 1H, *H5*), 1.11 (s, 9H, *C*-(*CH*$_3$)$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 149.4 (C1), 135.6, 134.0, 133.3, 129.7, 127.7 (Ar), 103.3 (C2), 88.8 (C3), 75.7 (C4), 63.7 (C5), 26.8 (C(*C*H_3)$_3$), 19.3 (*C*(CH$_3$)$_3$).

1,4-Anhydro-5-*O*-(*p*-toluoyl)-2-deoxy-D-*erythro*-pent-1-enitol (2d) was prepared according to method D from **1d** (0.0369 g, 0.102 mmol), HMDS (1 mL, 4.74 mmol), and $(NH_4)_2SO_4$ (0.3 g, 2.3 mmol). The product was purified by alumina flash chromatography (1:2 ether−hexanes) to yield a clear oil (0.012 g, 52%): TLC R_f 0.67 (1:2 ether−hexanes); HR−FABMS (MNBA) theoretical $(M + H)^+$ 235.0970, found 234.0948; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.96, (d, $J_{Ar} = 8.5$ Hz, 2H, *Ar*), 7.20 (d, $J_{Ar} = 8.2$ Hz, 2H, *Ar*), 6.49 (d, $J_{H2} = 2.0$ Hz, 1H, *H1*), 4.95 (t, $J = 2.7$ Hz, 1H, *H2*), 4.87 (m, 1H, *H3*), 4.70 (m, 1H, *H4*), 3.99 (m, 2H, *H5*), 2.41 (s, 3H, *Ar*-*CH*$_3$); ^{13}C NMR (50 MHz $CDCl_3$) δ 165.9 (*C*(O)-Ar), 149.1 (C1), 143.3 (C(O)-*Ar*), 129.4, 128.7 (Ar), 127.4 (*Ar*-CH$_3$), 103.1 (C2), 86.0 (C3), 76.8 (C4), 63.7 (C5), 21.3 (tol-*CH*$_3$). Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.58, H, 6.05.

1,4-Anhydro-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-D-*erythro*-pent-1-enitol (2e)[14] was prepared according to method D from **1e** (1.055 g, 2.24 mmol) and $(NH_4)_2SO_4$ (0.61 g, 4.62 mmol) in 10 mL of HMDS and yielded a yellow oil (0.534 g, 69%) after purification by alumina flash chromatography (1:2 ether−hexanes): TLC R_f 0.86 (1:2 CH_2Cl_2−EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.45 (d, $J_{H2} = 2.6$ Hz, 1H, *H1*), 5.00 (t, $J = 2.50$ Hz, 1H, *H2*), 4.87 (br, 1H, *H3*), 4.28 (dt, $J_{H3} = 2.7$, $J_{H5} = 5.9$ Hz, 1H, *H4*), 3.69 (dd, $J_{H4} = 5.6$, $J_{H5} = 10.6$ Hz, 1H, *H5*), 3.50 (dd, $J_{H4} = 6.4$, $J_{H5} = 10.6$ Hz, 1H, *H5*), 0.90, 0.89 (2s, 18H, *C*(*CH*$_3$)$_3$), 0.08, 0.06 (2s, 12H, *Si*-*CH*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.2 (C1), 103.6 (C2), 89.1 (C3), 76.2 (C4), 63.0 (C5), 26.1, 25.9 (C(*CH*$_3$)$_3$), 18.6, 18.3 (*C*(CH$_3$)$_3$), −4.1 (Si-*CH*$_3$), −4.2 (Si-*CH*$_3$), −5.1 (Si-*CH*$_3$).

1,4-Anhydro-5-*O*-(*tert*-butyldimethylsilyl)-3-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-D-*erythro*-pent-1-enitol (2h)[22] was prepared according to method D from **1h** (1.80 g, 3.03 mmol) and $(NH_4)_2SO_4$ (0.55 g, 4.16 mmol). The product was purified by alumina flash chromatography (1:1 ether−hexanes) to yield a yellow oil (1.12 g, 79%): TLC R_f 0.72 (1:2 ether−hexanes); CIMS (NH_3) 469.3 $(M + H)^+$, 486.3 $(M + NH_4)^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.57−7.49 (m, 4H, *Ar*), 7.23−7.19 (m, 6H, *Ar*), 6.30 (br, 1H, *H1*), 4.86 (m, 2H, *H2 and H3*), 4.23 (br, 1H, *H4*), 3.61 (dd, $J_{H4} = 5.2$, $J_{H5} = 10.9$ Hz, 1H, *H5*), 3.51 (dd, $J_{H4} = 5.2$, $J_{H5} = 10.9$ Hz, 1H, *H5*), 0.94, 0.76 (2s, 18H, *C*(*CH*$_3$)$_3$), −0.07 (s, 6H, Si-*CH*$_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.2 (C1), 135.6, 135.0, 133.3, 129.8, 127.8, 127.5 (Ar), 103.5 (C2), 89.0 (C3), 76.1 (C4), 63.7 (C5), 26.9, 26.0 (C(*CH*$_3$)$_3$), 19.3, 18.1 (*C*(CH$_3$)$_3$), −4.1 (Si-*CH*$_3$), −4.3 (Si-*CH*$_3$).

1,4-Anhydro-3-*O*-(*tert*-butyldimethylsilyl)-5-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-D-*erythro*-pent-1-enitol (2j) was prepared according to method D from **1j** (0.72 g, 1.21 mmol) and $(NH_4)_2SO_4$ (0.60 g, 4.54 mmol). The product was purified by alumina flash chromatography to yield a yellow oil (0.337 g, 59%): TLC R_f 0.79 (1:2 EtOAc−hexanes); HR-FABMS (MNBA) theoretical $(M - H)^+$ 467.2438, found 467.2430; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.72−7.66 (m, 4H, *Ar*), 7.46−7.37 (m, 6H, *Ar*), 6.52 (d, $J_{H2} = 2.6$ Hz, 1H, *H1*), 5.06 (m, 1H, *H2*), 4.99 (m, 1H, *H3*), 4.38 (dt, $J_{H3} = 3.1$, $J_{H5} = 5.1$ Hz, 1H, *H4*), 3.74 (dd, $J_{H4} = 5.5$, $J_{H5} = 10.9$ Hz, 1H, *H5*), 3.67 (dd, $J_{H4} = 5.2$, $J_{H5} = 10.8$ Hz, 1H, *H5*), 1.09, 0.91 (2s, 18H, *C*(*CH*$_3$)$_3$), 0.01 (s, 6H, *Si*-*CH*$_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.1 (C1), 135.6, 129.66, 127.65 (Ar), 103.5 (C2), 89.0 (C3), 76.0 (C4), 63.7 (C5), 25.8, 25.7 (C(*CH*$_3$)$_3$), 19.2 (*C*(CH$_3$)$_3$), −4.2, −4.4 (Si-*CH*$_3$). Anal. Calcd for $C_{27}H_{40}O_3Si_2$: C, 69.18; H, 8.60. Found: C 68.91; H, 8.77.

1,4-Anhydro-3-*O*-(*tert*-butyldimethylsilyl)-5-*O*-(*p*-toluoyl)-2-deoxy-D-*erythro*-pent-1-enitol (2l) was prepared according to method D from **1l** (0.114 g, 0.24 mmol) and $(NH_4)_2SO_4$ (0.210 g, 1.59 mmol). A yellow oil (0.062 g, 74%) was obtained after purification by alumina flash chromatography: TLC R_f 0.87 (1:2 EtOAc−hexanes); HR-FABMS (MNBA) theoretical $(M + H)^+$ 349.1835, found 349.1830; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.97, (d, $J_{Ar} = 8.1$ Hz, 2H, *Ar*), 7.28 (d, $J_{Ar} = 9.6$ Hz, 2H, *Ar*), 6.58 (d, $J_{H2} = 2.6$ Hz, 1H, *H1*), 5.25 (t, $J = 2.5$ Hz, 1H, *H2*), 5.05 (m, 1H, *H3*), 4.74 (dt, $J = 2.9$, 5.9 Hz, 1H, *H4*), 4.48 (d, $J_{H4} = 5.9$ Hz, 2H, *H5*), 2.44 (s, 3H, *Ar*-*CH*$_3$), 0.92 (s, 9H, *C*(*CH*$_3$)$_3$), 0.08 (s, 6H, *Si*-*CH*$_3$); ^{13}C NMR (50 MHz $CDCl_3$) δ 166.4 (*C*(O)-Ar), 149.1 (C1), 143.8 (C(O)-*Ar*), 129.7, 129.0 (Ar), 127.0 (*Ar*-CH$_3$), 103.6 (C2), 86.3 (C3), 76.4 (C4), 64.1 (C5), 25.8 (C(*CH*$_3$)$_3$), 21.6 (tol-*CH*$_3$), 18.0 (*C*(CH$_3$)$_3$), −4.3, −4.5 (Si-*CH*$_3$). Anal. Calcd for $C_{19}H_{28}O_4Si$: C, 65.48; H, 8.10. Found: C, 65.63; H, 8.23.

1,4-Anhydro-2-deoxy-3′-*O*-(*tert*-butyldiphenylsilyl)-5′-*O*-(*p*-toluoyl)-D-*erythro*-pent-1-enitol (2m) was prepared according to method D from **1m** (1.26 g, 2.10 mmol) and $(NH_4)_2SO_4$ (0.708 g, 5.36 mmol). A yellow oil (0.93 g, 94%) was obtained after purification by alumina flash chromatography (EtOAc): TLC R_f 0.88 (1:2 EtOAc−hexanes); HR-FABMS (MNBA) theoretical $(M + H)^+$ 473.2148, found: 473.2148; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.83 (d, $J_{Ar} = 7.9$ Hz, 2H, *Ar*), 7.68−7.65 (m, 4H, *Ar*), 7.41−7.34 (m, 6H, *Ar*), (7.20 (d, $J_{Ar} = 7.9$, 2H, *Ar*), 6.46 (d, $J_{H2} = 2.9$ Hz, 1H, *H1*), 4.93 (t, $J = 2.6$ Hz, 1H, *H2*), 4.85 (br, 1H, *H3*), 4.68 (br, 1H, *H4*), 3.99−3.94 (m, 2H, *H5*), 2.40 (s, 3H, *Ar*-*CH*$_3$), 1.05 (s, 9H, *C*(*CH*$_3$)$_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.3 (*C*(O)-Ar), 149.1 (C1), 143.7 (C(O)-*Ar*), 135.7, 134.9, 129.9, 129.8, 129.3, 129.0, 127.8, 127.7 (Ar), 127.0 (*Ar*-CH$_3$), 103.5 (C2), 86.4 (C3) 77.2 (C4), 64.1 (C5), 26.9 (C(*CH*$_3$)$_3$), 19.0 (*C*(CH$_3$)$_3$). Anal. Calcd for $C_{29}H_{32}O_4Si$: C, 73.70; H, 6.83. Found: C, 73.82, H, 6.63.

1,4-Anhydro-3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-D-*erythro*-pent-1-enitol (2n)[23] was repared according to method D from **1n** (0.1607 g, 0.45 mmol) and $(NH_4)_2SO_4$ (0.304 g, 2.30 mmol). Alumina flash chromatography yielded a yellow oil (0.0375 g, 36%): TLC R_f 0.76 (1:2 EtOAc−hexanes); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.47 (dd, $J_{H2} = 2.5$ Hz, 1H, *H1*), 5.01 (t, $J = 2.5$ Hz, 1H, *H2*), 4.81 (t, $J = 2.3$, 1H, *H3*), 4.30 (dt, $J = 2.7$, 9.1 Hz, 1H, *H4*), 3.65 (dd, $J_{H4} = 6.3$, $J_{H5} = 10.7$ Hz, 1H, *H5*), 3.44 (dd, $J_{H4} = 6.6$, $J_{H5} = 10.7$ Hz, 1H, *H5*), 0.89 (s, 9H, *C*(*CH*$_3$)$_3$), 0.13 (s, 6H, *Si*-*CH*$_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ

(22) Farr, R. N.; Daves, G. D. *J. Carbohydr. Chem.* **1990**, *9*, 653−660.

(23) Gold, B. I. PCT Int. Appl. WO9623777 Aug 8, 1996; *Chem. Abstr.* **1996**, *125*, 248328.

148.9 (C1), 103.4 (C2), 88.8 (C3), 76.1 (C4), 62.2 (C5), 25.9 ($C(CH_3)_3$), 18.1 ($C(CH_3)_3$), −4.3 (Si-CH_3).

1,4-Anhydro-3-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-D-*erythro*-pent-1-enitol (2o)[14,22] was prepared according to method D from **1o** (0.180 g, 0.37 mmol) and $(NH_4)_2SO_4$ (0.245 g, 1.86 mmol). The product was purified using alumina flash chromatography to yield a yellow oil (0.105 g, 79%): TLC R_f 0.90 (1:2 EtOAc−hexanes); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.76−7.66 (m, 4H, *Ar*), 7.46−7.38 (m, 6H, *Ar*), 6.45 (d, $J_{H2} = 2.5$ Hz, 1H, *H1*), 4.87 (t, $J = 2.7$ Hz, 1H, *H2*), 4.78 (t, $J = 2.5$, 1H, *H3*), 4.53−4.47 (m, 1H, *H4*), 3.41 (dd, $J_{H4} = 7.0$, $J_{H5} = 10.8$ Hz, 1H, *H5*), 3.26 (dd, $J_{H4} = 5.1$, $J_{H5} = 10.8$ Hz, 1H, *H5*), 1.10 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.0 (C1), 135.8, 135.2, 134.2, 129.6, 127.7 (Ar), 103.3 (C2), 89.1 (C3), 76.4 (C4), 62.4 (C5), 26.6 ($C(CH_3)_3$), 19.0 ($C(CH_3)_3$).

Acknowledgment. We thank the Petroleum Research Fund of the American Chemical Society and the National Cancer Institute of the National Institutes of Health (CA65930) for support of this research. We are also grateful to the Louisiana Educational Quality Support Fund (LEQSF) for a Board of Regents Fellowship to M.A.C. Grants to LSU from the NSF REU program (CHE-9424021) and the Howard Hughes Medical Institute (HHMI 71195-520302) provided stipends to S.B.C. We give special thanks to Dr. Tracy McCarley at Louisiana State University and Dr. Edward Larka at the University of Minnesota for expert assistance with mass spectrometric measurements.

Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR spectra of compounds **1b-g, 1j-m,** and **1o** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO970947S