Stereoselective Synthesis of Protected Thymine Polyoxin C via [2,3]-Wittig−Still Rearrangement of Ribose-Derived Allylic Stannyl Ethers

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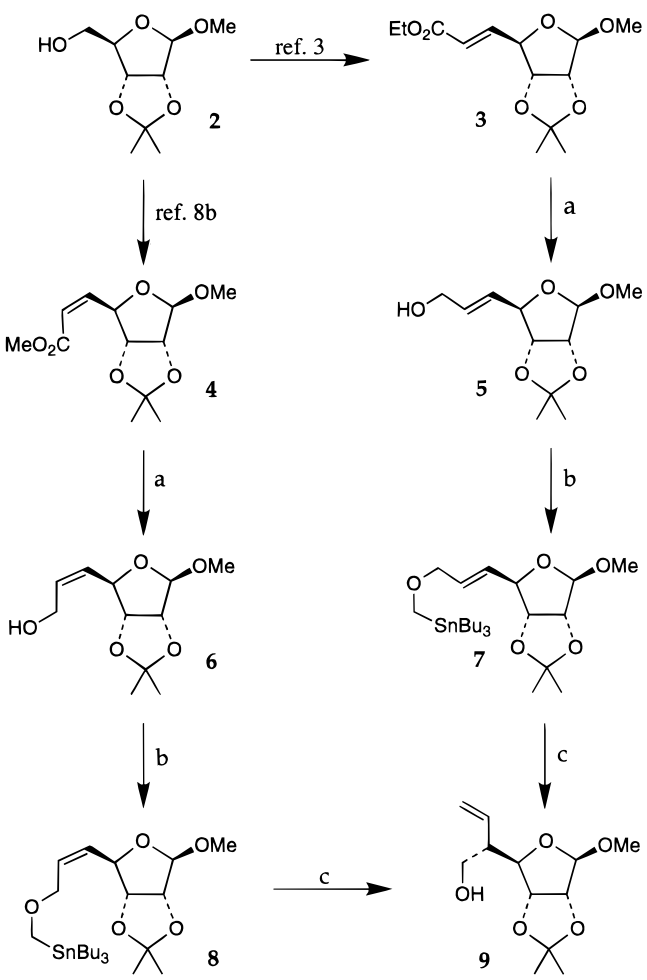
The [2,3]-Wittig rearrangement leading to stereocontrolled carbon−carbon bond formation has been increasingly utilized in organic synthesis.[1] The synthetic potential of this reaction is extended even further in Still's variant of the [2,3]-Wittig rearrangement (Wittig−Still rearrangement) where unstable oxymethyllithium is generated at low temperature by a tin−lithium exchange reaction.[2] Recently, we reported a stereoselective synthesis of an antifungal nucleoside, sinefungin.[3] In our continuing interest in the development of synthetic methodologies for bioactive amino acid nucleosides, we have investigated the [2,3]-Wittig rearrangement of *E*- and *Z*-allylic stannyl ethers derived from an isopropylidene D-ribose derivative. Herein we report that the [2,3]-rearrangement of *Z*-allylic stannyl ether proceeded with nearly complete syn selectivity and excellent isolated yield. The resulting [2,3]-rearranged product was converted to the protected thymine polyoxin C, which is a basic component of many bioactive polyoxins, including polyoxin J (**1**). Polyoxins are important antifungal agents with chitin synthetase inhibitory properties.[4] Synthesis and biological evaluation of polyoxins and their variants have been the subject of immense interest over the years.[5,6] Early syntheses of polyoxin nucleosides via cyanohydrin formation at the C-5′ aldehyde of uridine have been reported.[5g,h] A very useful strategy to polyoxin C and other glycosyl α-amino acids has been developed from D-serinal.[5c] Protected ribose-derived nitro olefin and nitrone-based strategies have also been utilized in the synthesis of polyoxin C.[5b,d] Thymine polyoxin has been synthesized from myoinositol and other noncarbohydrate precursors as well.[5a,e,6c] Our approach to polyoxin C synthesis is based upon the chain lengthening of sugars by a highly stereoselective [2,3]-Wittig rearrangement.

Scheme 1[a]



[a] Key: (a) DIBAL, CH_2Cl_2, −78 °C, 2−3 h (92−95%); (b) KH, $Bu_4N^+I^-$, Bu_3SnCH_2I, THF, 23 °C, 4 h; (c) ^{n}BuLi, THF, −78 °C, 2 h (74−84%).

The known[7] methyl glycoside **2** was readily converted to *trans*-α,*β*-unsaturated ester **3** by Swern oxidation followed by Horner−Emmons olefination with sodium hydride and triethyl phosphonoacetate as described previously.[3] The *cis*-α,*β*-unsaturated ester **4** was prepared selectively by Still's variant of Horner−Emmons olefination with bis(2,2,2-trifluoroethyl)methoxycarbonylmethyl phosphonate.[8] Reduction of these esters with DIBAL in CH_2Cl_2 at −78 °C for 2 h provided the respective *trans*- and *cis*-allylic alcohols **5** and **6** in excellent yields (Scheme 1). Etherification of alcohols **5** and **6** with potassium hydride and Bu_3SnCH_2I in the presence of catalytic amounts of $^nBu_4N^+I^-$ afforded the respective *E*- and *Z*-stannylated ethers **7** and **8**. Tin−

(1) (a) Nakai, T.; Mikami, K. *Org. React.* **1994**, *46*, 105. (b) Marshall, J. A. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, p 975 and references therein.

(2) (a) Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927. (b) Bruckner, R.; Priepke, H. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 278.

(3) Ghosh, A. K.; Liu, W. *J. Org. Chem.* **1996**, *61*, 6175.

(4) (a) Isono, K.; Suzuki, S. *Heterocycles* **1979**, *13*, 333. (b) Gooday, G. W. *Abh. Dtsch. Akad. Wiss. DDR, Abt. Math. Naturwiss.*; Tech., Issue 2N; 1979; p 159. (c) Mori, M.; Kakiki, K.; Misato, T. *Agric. Biol. Chem.* **1974**, *38*, 699.

(5) For synthesis of polyoxin nucleotides, see: (a) Dehoux, C.; Fontaine, E.; Escudier, J.-M.; Baltas, M.; Gorrichon, L. *J. Org. Chem.* **1998**, *63*, 2601. (b) Dondoni, A.; Junquera, F.; Merchan, F. L.; Merino, P.; Tejero, T. *Tetrahedron Lett.* **1994**, *35*, 9439. (c) Garner, P.; Park, J. M. *J. Org. Chem.* **1990**, *55*, 3772. (d) Barrett, A. G. M.; Lebold, S. A. *J. Org. Chem.* **1990**, *55*, 3853. (e) Auberson, Y.; Vogel, P. *Tetrahedron* **1990**, *46*, 7019. (f) Tabusa, F.; Yamada, T.; Suzuki, K.; Mukaiyama, T. *Chem. Lett.* **1984**, 405. (g) Damodaran, N. P.; Jones, G. H.; Moffatt, J. G. *J. Am. Chem. Soc.* **1971**, *93*, 3812. (h) Naka, T.; Hashizume, T.; Nishimura, M. *Tetrahedron Lett.* **1971**, 95.

(6) For the total synthesis of polyoxins, see: (a) Akita, H.; Uchida, K.; Kato, K. *Heterocycles* **1998**, *47*, 157. (b) Dondoni, A.; Junquera, F.; Merchan, F. L.; Merino, P.; Tejero, T. *J. Org. Chem.* **1997**, *62*, 5497. (c) Chida, N.; Koizumi, K.; Kitada, Y.; Yokoyama, C.; Ogawa, S. *J. Chem. Soc. Chem. Commun.* **1994**, 111. (d) Mukaiyama, T.; Suzuki, K.; Yamada, T.; Tabusa, F. *Tetrahedron* **1990**, *46*, 265. (e) Kazuhara, H.; Ohrui, H.; Emoto, S. *Tetrahedron Lett.* **1973**, 5055 and references therein.

(7) (a) Ghosh, A. K.; McKee, S. P.; Sanders, W. M.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Quintero, J. C.; Huff, J. R.; Anderson, P. S. *Drug Des. Discovery* **1993**, *10*, 77. (b) Levene, P. A.; Stiller, E. T. *J. Biol. Chem.* **1934**, 299.

(8) (a) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405. (b) Spada, M. R.; Ubukata, M.; Isono, K. *Heterocycles* **1992**, *34*, 1147.

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lithium exchange of *E*-stannyl ether **7** with ^{n}BuLi at −78 °C in THF resulted in a syn/anti mixture (4.4:1 by 400-MHz ^{1}H NMR) of rearranged product **9** and its epimer in 84% yield after silica gel chromatography. On the other hand, the reaction of *Z*-stannyl ether **8** with ^{n}BuLi provided exclusively the syn product **9** in 74% isolated yield. ^{1}H NMR (400 MHz) revealed the presence of a single isomer.

The initial stereochemical assignment of the [2,3]-rearranged syn product **9** has been made on the basis of previous stereochemical studies of [2,3]-Wittig−Still rearrangement by Brückner and co-workers.[9] Further evidence of this stereochemical assignment was provided after the syn-rearranged product **9** was converted to thymine polyoxin C. The stereochemical assignment is also consistent with "Houk-like" transition-state models as shown in Figure 1.[10] In these models, the allylic C−O bond is orthogonal to the plane of the allylic C═C and is antiperiplanar with respect to the impending carbanion. Consistent with these models, both compounds **7** (*E*-isomer) and **8** (*Z*-isomer) provided the same major rearranged product **9** through the more favorable transition states **A** and **C**, respectively. Between the corresponding diastereomeric transition states **B** (*E*-isomer) and **D** (*Z*-isomer), transition state **D** is highly disfavored because of severe developing allylic [1,3] strain. This may explain why compound **8** (*Z*-isomer) provided exclusively syn-rearranged product **9** compared to compound **7** (*E*-isomer), which has exhibited a syn/anti product ratio of 4.4:1.

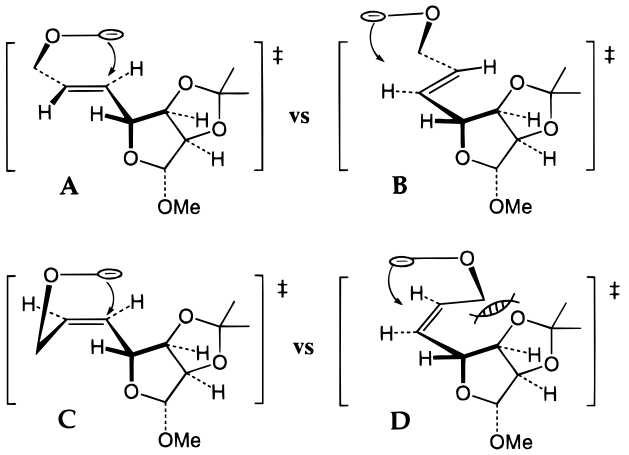
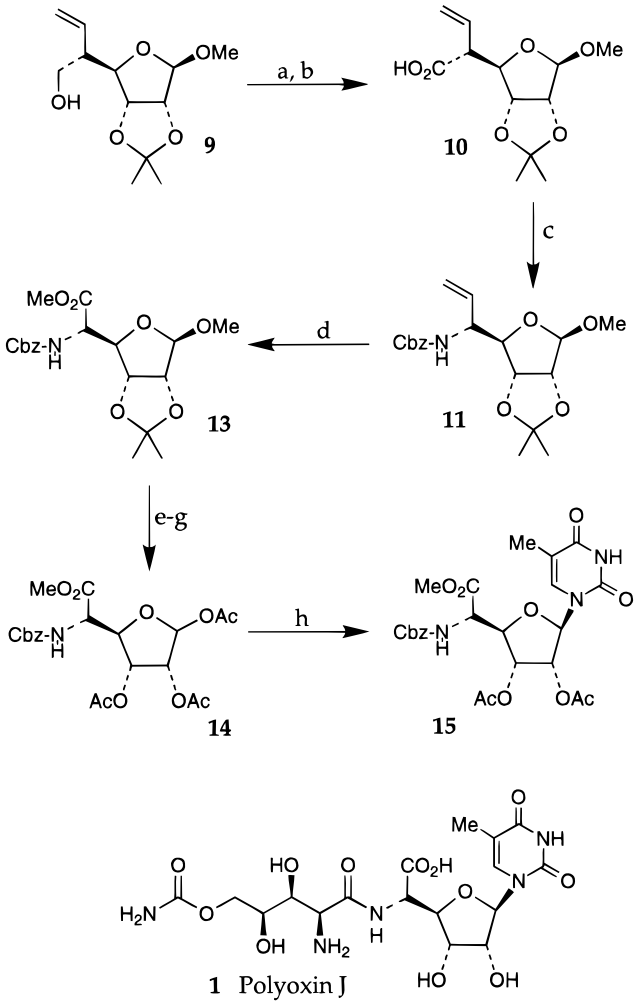


Figure 1.

As shown in Scheme 2, alcohol **9** was converted to Cbz-protected amine derivative **11** by oxidation followed by Curtius rearrangement of the resulting carboxylic acid. Thus, Swern oxidation of **9** provided the corresponding aldehyde which, upon exposure to sodium chlorite in *tert*-butyl alcohol, afforded the acid **10**. It is important to note that the use of triethylamine in the standard Swern oxidation protocol resulted in a substantial amount of epimerization of the resulting β,γ-unsaturated carboxaldehyde. This epimerization was circumvented by the use of diisopropylethylamine instead of triethylamine. The above acid **10** without further purification was exposed to diisopropylethylamine, methyl chloroformate, and sodium azide at 0 °C. The resulting acyl azide was dissolved in toluene and heated at 100 °C for 1 h. After this period, benzyl alcohol was added and the mixture was heated at reflux for 12 h to furnish the Cbz derivative **11** in 68% yield (from **9**) after silica gel chromatography. Since the Curtius rearrangement proceeds with retention of configuration of the migrating carbon atom, the stereochemistry of the urethane-bearing chiral center in **11** was assigned accordingly.[11] Of particular note, the attempted Curtius rearrangement of **10** with diphenylphosphoryl azide and triethylamine followed by treatment with benzyl alcohol and subsequent heating at reflux for 10 h resulted in α,β-unsaturated ester **12** as the major product, along with a small amount of Cbz derivative **11**.[12] For conversion of the vinyl group in **11**

Scheme 2[a]



[a] Key: (a) Swern oxidation; (b) $NaClO_2$, Me_2C═CHMe, ^{t}BuOH, 23 °C, 12 h; (c) MeOCOCl, ^{i}Pr$_2$NEt, NaN_3 then $PhCH_2OH$, PhMe, 100 °C, 12 h (68% from **9**); (d) O_3, NaOH, CH_2Cl_2, MeOH, −78 to 23 °C, 2 h (94%); (e) Dowex 50W, MeOH, 65 °C, 12 h; (f) Ac_2O, Py, 23 °C, 4 h; (g) Ac_2O, AcOH, CH_2Cl_2, cat. H_2SO_4, 23 °C, 2 h (70% from **13**); (h) Thymine-bis-TMS, Cl $(CH_2)_2$Cl, TMSOTf, 45 °C, 2 h (80%).

(9) (a) Priepke, H.; Brückner, R. *Chem. Ber.* **1990**, *123*, 153. (b) Priepke, H.; Brückner, R.; Harms, K. *Chem. Ber.* **1990**, *123*, 555. (c) Scheuplein, S. W.; Kusche, A.; Brückner, R.; Harms, K. *Chem. Ber.* **1990**, *123*, 917 and references therein.

(10) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108.

(11) (a) Ghosh, A. K.; Hussain, K. A.; Fidanze, S. *J. Org. Chem.* **1997**, *62*, 6080. (b) Grunewald, G. L.; Ye, Q. *J. Org. Chem.* **1988**, *53*, 4021. (c) Ninomiya, K.; Shiori, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151 and references therein.

to methyl ester **13**, ozonolytic cleavage was carried out in methanolic sodium hydroxide solution to afford **13** in 94% yield after chromatography.[13]

To install thymine at the anomeric center, the protecting group interconversion of **13** to triacetate **14** was carried out in a three-step sequence: (1) removal of the isopropylidene group with Dowex 50W H^+ in methanol, (2) acetylation of the resulting diol with acetic anhydride in pyridine, and (3) acetal exchange by treatment with acetic anhydride and a catalytic amount of concentrated sulfuric acid in a mixture of glacial acetic acid and CH_2Cl_2 at 23 °C for 2 h (70%, 2:1 mixture of anomers). Triacetate **14** was exposed to Vorbrüggen reaction conditions[14] with 5-methyl-2,4-bis(trimethylsilyloxy)pyrimidine in the presence of TMSOTf in dichloroethane at 45 °C for 2 h to afford the protected β-nucleoside **15** (mp 81−83 °C) in 80% yield after silica gel chromatography. The spectral properties (^{1}H and ^{13}C NMR) of **15** ($[\alpha]^{23}_D$ +17.1, *c* 0.45, $CHCl_3$; lit.[5a] $[\alpha]^{23}_D$ +19.8, *c* 0.56, $CHCl_3$) are in full agreement with the reported values.

In conclusion, a stereoselective synthesis of protected thymine polyoxin C has been accomplished starting from D-ribose. The key steps in the synthesis are a highly diastereoselective [2,3]-sigmatropic reaction of *Z*-allylic stannyl ethers, followed by conversion of the resulting hydroxymethyl group to the Cbz-protected amine derivative by a Curtius rearrangement. The stereoelectronic effects of the [2,3]-Wittig rearrangement of the ribose-derived *E*- and *Z*-stannyl ethers are noteworthy. Further application of this stereoselective [2,3]-Wittig−Still rearrangement in synthesis is in progress.

Experimental Section

All melting points were recorded and uncorrected. Anhydrous solvents were obtained as follows: 1,2-dichloroethane was first refluxed for 2 h over P_2O_5 and then distilled, tetrahydrofuran was distilled from sodium and benzophenone, methylene chloride was distilled from CaH_2 and trimethylchlorosilane and pyridine were distilled from CaH_2. All other solvents were HPLC grade. Column chromatography was performed with Whatman 240−400 mesh silica gel under a low pressure of 5−10 psi. Thin-layer chromatography (TLC) was carried out with Merck silica gel 60 F-254 plates.

Methyl (*E*)-5,6-Dideoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hept-5- enofuranoside (5). To a stirred solution of ester **3**[3] (1.7 g, 6.62 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added DIBAL (1 M in hexane, 19 mL, 19 mmol) solution, and the resulting mixture was stirred at −78 °C for 2 h. After this period, the reaction was carefully quenched with water (3 mL) and the mixture was allowed to warm to 23 °C. The mixture was filtered through a glass wool plug, and the solid was rinsed several times with CH_2Cl_2 and water. The combined filtrate was transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic layers were dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue which was purified on a silica gel column (50% ethyl acetate/hexane) to afford **5** as a colorless oil (1.335 g, 92%): $[\alpha]^{23}_D$ −42.2 (*c* 0.83, $CHCl_3$); IR (neat) 3423, 2950, 2930, 1630, 1374, 1088 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (m, 2H), 4.98 (s, 1H), 4.66 (d, 1H, *J* = 8.2 Hz), 4.61 (s, 2H), 4.15 (t, 1H, *J* = 5.4 Hz), 3.34 (s, 3H), 1.49 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 26.4, 54.7, 62.6, 84.5, 85.4, 87.4, 109.3, 112.3, 130.4, 132.4; MS (EI) *m*/*z* 230 (M^+), 215 (M^+ − Me), 198, 155. Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.22; H, 7.94.

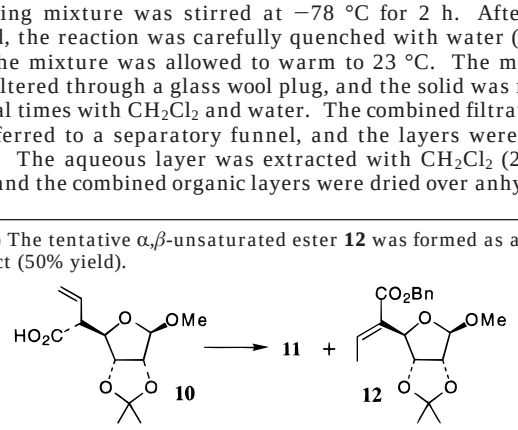
Methyl (*Z*)-5,6-Dideoxy-2,3-*O*-isopropylidene-β-D-ribo-hept-5-enofuranoside (6). To a stirred solution of ester **4**[8] (1.07 g, 4.15 mmol) in CH_2Cl_2 (15 mL) at −78 °C was added DIBAL (1.0 M in hexane, 12.4 mL, 12.4 mmol) solution, and the resulting mixture was stirred for 3 h at −78 °C. After this period, the reaction was worked up as described for **5** to furnish the allyl alcohol **6** as a colorless oil (930 mg, 95%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (m, 1H), 5.61 (m, 1H), 4.97 (s, 1H), 4.95 (d, 1H, *J* = 9.5 Hz), 4.62 (d, 1H, *J* = 5.9 Hz), 4.58 (d, 1H, *J* = 5.9 Hz),4.33 (m, 1H), 4.24 (m, 1H), 3.31 (s, 3H), 1.49 (s, 3H), 1.30 (s, 3H); MS (EI) *m*/*z* 230 (M^+), 215 (M^+ − Me), 198, 155.

Methyl 5-(*S*)-Deoxy-5-vinyl-2,3-*O*-isopropylidene-β-D-*ribo*-hexanofuranoside (9). To a suspension of KH (418 mg, 10.4 mmol, prewashed with hexane) and tetrabutylammonium iodide (25 mg) in dry THF (10 mL) at 0 °C was added dropwise a solution of alcohol **5** (1.2 g, 5.23 mmol) in THF (2 mL). The resulting red suspension was allowed to warm to 23 °C, and the mixture was stirred for 1 h. The reaction was cooled to 0 °C, and Bu_3SnCH_2I (2.1 g, 6.8 mmol) in THF (2 mL) was added dropwise over a period of 2 min. The mixture was stirred at 0−23 °C for 4 h. After this period, the reaction was quenched with a saturated NH_4Cl solution (10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4. Evaporation of the solvents provided the allyl stannylmethyl ether **7** as a colorless oil. This material was used for the next reaction without further purification. An analytical sample of **7** was obtained by flash chromatography over silica gel (5% ethyl acetate/hexane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71−5.74 (m, 2H), 4.98 (s, 1H), 4.65 (d, 1H, *J* = 10.9 Hz), 4.61 (s, 2H), 3.85 (d, 2H, *J* = 6.8 Hz), 3.69 (s, 2H), 3.32 (s, 3H), 1.49 (s, 3H), 1.35 (s, 3H), 1.20−1.62 (m, 12H), 0.85−0.94 (m, 15H).

To a stirred solution of above crude stannyl ether **7** in THF (10 mL) at −78 °C, was added ^{n}BuLi (2.5 M in hexane, 3.2 mL, 8 mmol) dropwise by a syringe pump over a period of 1 h. The resulting mixture was stirred for 2 h at −78 °C. After this period, the reaction was quenched with saturated NH_4Cl solution and the resulting mixture was warmed to 23 °C. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Evaporation of the solvents gave a residue which was chromatographed over silica gel (25% ethyl acetate/hexane) to furnish an inseparable mixture (4.4:1 by ^{1}H NMR) of **9** and its epimer (1.07 g, 84% from **5**) as a colorless oil. Major isomer **9**: IR (neat) 3454, 2988, 2936, 1643, 1374, 1090 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (m, 1H), 5.27 (dd, 1H, *J* = 1.1, 10 Hz), 5.21 (dd, 1H, *J* = 1.1, 18 Hz), 4.95 (s, 1H), 4.71 (dd, 1H, *J* = 1.5, 6.2 Hz), 4.53 (d, 1H, *J* = 6.2 Hz), 4.25 (dd, 1H, *J* = 1.5, 8 Hz), 3.72 (m, 1H), 3.59 (m, 1H), 3.35 (s, 3H), 2.46 (m, 1H), 1.49 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136, 135.4, 118.9, 112.6, 109.4, 87.3, 85.3, 82.2, 64.1, 63.2, 55.6; MS (EI) *m*/*z* 213 (M^+ − OMe), 197, 173, 59. Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.0; H, 8.25. Found: C, 58.90; H, 8.40. Minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (m, 1H), 5.29 (m, 2H), 4.99 (s, 1H), 4.68 (dd, 1H, *J* = 1, 5.9 Hz), 4.57 (d, 1H, *J* = 5.9 Hz), 4.14 (d, 1H, *J* = 11.2 Hz), 3.81 (m, 1H), 3.66 (m, 1H), 3.40 (s, 3H), 2.46 (m, 1H), 1.48 (s, 3H), 1.31 (s, 3H).

Methyl 5-(*S*)-Deoxy-5-vinyl-2,3-*O*-isopropylidene-β-D-*ribo*-hexanofuranoside (9). (prepared from *Z*-alcohol **6**). The *Z*-alcohol **6** (672.8 mg, 2.92 mmol) was converted to *Z*-stannyl ether **8** as a colorless oil by following the procedure described for *E*-stannyl ether **7**. This material was used for the next reaction without further purification. An analytical sample of **8** was obtained by flash chromatography over silica gel (5% ethyl acetate/hexane). ^{1}H NMR for **8**: (400 MHz, $CDCl_3$) δ 5.61 (dd, 2H, *J* = 4.2, 5 Hz), 4.96 (s, 1H), 4.92 (d, 1H, *J* = 6.7 Hz), 4.62 (d, 1H, *J* = 5.8 Hz), 4.56 (d, 1H, *J* = 5.6 Hz), 4.0 (d, 1H, *J* = 4.1

(12) The tentative α,β-unsaturated ester **12** was formed as a major product (50% yield).



Compound **11** was isolated in a small amount (<10% yield): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35 (m, 5H), 6.16 (q, 1H, *J* = 7.4 Hz), 5.23 (brs, 1H), 5.12 (d, 2H, *J* = 4.7 Hz), 5.03 (s, 1H), 4.65 (dd, 1H, *J* = 1.0, 6.0 Hz), 4.59 (d, 1H, *J* = 6.0 Hz), 3.43 (s, 3H), 1.77 (d, 3H, *J* = 7.4 Hz), 1.52 (s, 3H), 1.30 (s, 3 H).

(13) Marshall, J. A.; Garofalo, A. W.; Sedrani, R. *Synlett* **1992**, 643.
(14) Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234.

Hz), 3.72 (s, 2H), 3.31 (s, 3H), 1.43 (s, 3H), 1.29 (s, 3H), 1.24−1.63 (m, 12H), 0.86−0.98 (m, 15H). Wittig−Still rearrangement of *Z*-stannyl ether **8** as described above (for stannyl ether **7**) provided the alcohol **9** (528 mg, 74% from **6**) exclusively as a colorless oil: $[\alpha]^{23}_D$ −29 (*c* 0.13, $CHCl_3$).

Methyl 5-(*R*)-*N*-[(Phenylmethoxy)carbonyl]-5,6-dideoxy-2,3-*O*-isopropylidene-*β*-D-*ribo*-hept-6-enfuranoside (11). To a stirred solution of DMSO (0.18 mL, 2.54 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added dropwise oxalyl chloride (0.13 mL, 1.52 mmol). The resulting mixture was stirred for 2 min, and then a solution of alcohol **9** (248 mg, 1.02 mmol) in CH_2Cl_2 (2 mL) was added dropwise over a period of 1 min. The mixture was stirred at −78 °C for an additional hour. The reaction was quenched with diisopropylethylamine (0.9 mL, 5.08 mmol), and the mixture was allowed to warm to 0 °C for 30 min. Ethyl acetate (20 mL) was added to the reaction mixture, and the mixture was successively washed with a 1 M aqueous $NaHSO_4$ solution (20 mL) and pH 7 buffered solution (20 mL). The organic layer was dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude aldehyde, which was used for the next reaction immediately without further purification.

To a stirred solution of the above aldehyde in a mixture of *tert*-butyl alcohol (10 mL) and 2-methyl-2-butene (3 mL) at 23 °C were added sodium chlorite (900 mg, 10 mmol) in water (1 mL) and NaH_2PO_4 (1.38 g, 10 mmol) in water (1 mL) sequentially. The resulting mixture was stirred at 23 °C for 12 h. After this period, the reaction mixture was diluted with saturated NH_4Cl (10 mL) and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Evaporation of the solvent provided the acid, which was directly used for the next reaction.

To a stirred solution of the above acid in acetone (4 mL) was added diisopropylethylamine (0.21 mL, 1.22 mmol) at 0 °C. The resulting mixture was stirred for 10 min, and $ClCO_2Me$ (0.1 mL, 1.32 mmol) was added dropwise over a period of 1 min. The reaction mixture was stirred at 0 °C for 30 min, and then sodium azide (132 mg, 2.03 mmol) in water (2 mL) was added. The mixture was stirred for an additional 30 min at 0 °C. After this period, CH_2Cl_2 (20 mL) and water (20 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were successively washed with 1 M $NaHSO_4$ (20 mL) and pH 7 buffer (20 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave a colorless oil, which was dissolved in toluene (5 mL). The resulting mixture was heated at 100 °C for 1 h. After this period, benzyl alcohol (0.21 mL, 2 mmol) was added and the resulting mixture was refluxed for 12 h. The reaction was cooled to 23 °C, and the solvent was evaporated to give a yellow residue, which was chromatographed over silica gel (5% ethyl acetate/benzene) to furnish the Cbz derivative **11** (249 mg, 68% from **9**) as a white solid: mp 80−82 °C; $[\alpha]^{23}_D$ −11 (*c* 0.18, $CHCl_3$); IR (neat) 3447, 2925, 1643, 1239, 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26−7.37 (m, 5H), 5.95 (m, 1H), 5.28 (d, 1H, J = 11.4 Hz), 5.25 (dd, 1H, J = 1, 4.7 Hz) 5.12 (dd, 1H, J = 4.7, 17 Hz), 4.98 (s, 1H), 4.97 (br s, 1H), 4.74 (d, 1H, J = 4.9 Hz), 4.59 (d, 1H, J = 4.9 Hz), 4.29 (dd, 1H, J = 5.6, 9.9 Hz), 3.98 (dd, 1H, J = 1.1, 9.4 Hz), 3.34 (s, 3H), 1.46 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 26.5, 55.0, 55.5, 66.9, 88.9, 109.7, 112.5, 116.8, 126.9, 127.5, 128.0, 128.1, 128.4, 135.3, 136.2, 155.9; MS (EI) *m*/*z* 363 (M^+), 331, 173, 146, 115, 91. Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.80; H, 6.93; N, 3.86. Found: C, 62.19; H, 7.14; N, 3.58.

Methyl (Methyl-5-*N*-[(phenylmethoxy)carbonyl]-5-deoxy-2,3-*O*-isopropylidene-*β*-D-allofuranoside)uronate (13). To a stirred solution of **11** (36.5 mg, 0.1 mmol) in a mixture of CH_2Cl_2 (3 mL) and MeOH (1 mL) was added solid NaOH (20 mg), and a stream of ozonized oxygen was bubbled through this stirred mixture at −78 °C until the color of the solution changed from yellow to blue. The reaction mixture was diluted with water and allowed to warm to 23 °C. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was chromatographed over silica gel (15% ethyl acetate/hexane) to provide the methyl ester **13** (37.1 mg, 94%) as a white solid: mp 66−68 °C; $[\alpha]^{23}_D$ −14 (*c* 2.81, $CHCl_3$); IR (neat) 3428, 1720, 1643, 1109 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.41 (m, 5H), 5.52 (d, 1H, J = 8.3 Hz), 5.11 (brs, 2H), 4.96 (s, 1H), 4.93 (d, 1H, J = 5.8 Hz), 4.57 (d, 1H, J = 5.8 Hz), 4.49 (t, 1H, J = 8 Hz), 4.33 (d, 1H, J = 7.6 Hz), 3.75 (s, 3H), 3.32 (s, 3H), 1.51 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 26.4, 52.5, 55.8, 56.4, 67.3, 81.3, 85.0, 87.6, 110.1, 112.6, 128.2, 128.5, 135.9, 155.7, 170.5; MS (EI) *m*/*z* 396 (M^+ + H), 395 (M^+), 173, 91. Anal. Calcd for $C_{19}H_{25}NO_8$: C, 57.71; H, 6.31; N, 3.54. Found: C, 57.53; H, 6.36; N, 3.75.

Methyl 5-Deoxy-5-[(phenylmethoxy)carbonyl]amino]-*β*-D-allofuranuronate-1,2,3-triacetate (14). To a stirred solution of **13** (446.5 mg, 1.14 mmol) in MeOH (20 mL) was added Dowex 50W H^+ resin (600 mg), and the mixture was heated at 65 °C for 12 h. After this period, the resin was filtered off and the solvent was removed under reduced pressure. The residue was dissolved in pyridine (4 mL), Ac_2O (1 mL) was added, and the resulting mixture was stirred at 23 °C for 4 h. The reaction mixture was poured into ice, stirred for 30 min, and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were successively washed with saturated aqueous $CuSO_4$ solution and brine and then dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was dissolved in a mixture of CH_2Cl_2 (2 mL) and AcOH (2 mL). To this mixture at 0 °C was added Ac_2O (0.5 mL), followed by a drop of concentrated H_2SO_4. The resulting mixture was stirred at 0 °C for 1 h and then at 23 °C for 2 h. The reaction mixture was poured onto ice and stirred for 30 min. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layer was successively washed with saturated $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent provided a residue, which was chromatographed on silica gel (33% ethyl acetate/hexane) to furnish the triacetate **14** (373 mg, 70% from **13**) as a colorless oil: IR (neat) 3420, 1750, 1720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 5H), 6.36 (d, 0.33H, J = 8.9 Hz, α-anomer), 6.09 (s, 0.67H, *β*-anomer), 5.54 (m, 1H), 5.29 (d, 1H, J = 4.7 Hz), 5.11 (s, 2H), 4.67 (dd, 1H, J = 4.4, 8.7 Hz), 4.45 (dd, 1H, J = 4.4, 7.6 Hz), 3.76 (s, 3H), 2.10 (s, 3H), 2.01 (s, 6H).

Methyl 1,5-Dideoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2*H*)-pyrimidinyl)-5-[[(phenylmethoxy)carbonyl]amino]-*β*-D-allofuranuronate-2,3-diacetate (15). To a stirred suspension of thymine (17 mg, 0.13 mmol) in hexamethyl disilazane (2 mL) was added trimethylchlorosilane (0.1 mL), and the resulting mixture was heated at 120 °C for 5 h. The mixture was cooled to 23 °C, and the solvent was removed under reduced pressure to give the crude bis-silylated thymine. The residue was dissolved in dichloroethane (2 mL), and a solution of triacetate **14** (20 mg, 0.043 mmol) in dichloroethane (1 mL) followed by TMSOTf (46 μL, 0.126 mmol) was added at 23 °C. The resulting mixture was heated at 45 °C for 2 h, cooled to 23 °C, and quenched with saturated sodium bicarbonate solution. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvents were evaporated under reduced pressure. The resulting residue was chromatographed on silica gel (40% ethyl acetate/benzene) to give the title nucleoside **15** (18.4 mg, 80%) as a pale yellow solid: mp 81−83 °C; $[\alpha]^{23}_D$ +17.1 (*c* 0.45, $CHCl_3$); IR (neat), 3380, 1750, 1715 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.35 (s, 5H), 7.05 (d, 1H, J = 0.7 Hz), 5.93 (d, 1H, J = 5.6 Hz), 5.79 (d, 1H, J = 8.1 Hz), 5.51 (t, 1H, J = 5.9 Hz), 5.26 (t, 1H, J = 5.9 Hz), 5.14 (s, 2H), 4.81 (dd, 1H, J = 3.7, 8.5 Hz), 4.39 (dd, 1H, J = 3.7, 4.7 Hz), 3.81 (s, 3H), 2.09 (s, 6H), 1.87 (d, 3H, J = 0.7 Hz); ^{13}C NMR (100 MHz, CD_3COCD_3) δ 12.3, 20.3, 52.8, 56.1, 67.1, 70.6, 72.9, 81.8, 89.3, 111.6, 128.5, 128.6, 129.1, 137.3, 137.7, 151.4, 157.4, 164.0, 169.9, 170.0, 170.1; MS (EI) *m*/*z* 534 (M^+ + H), 408, 91.

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Supporting Information Available: ^1H NMR spectra for compounds **6**−**8**, **12**, and **14**−**15** and ^{13}C NMR spectra for **10** and **15** (8 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.

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