# Synthesis of the Shimofuridin Nucleoside Disaccharide

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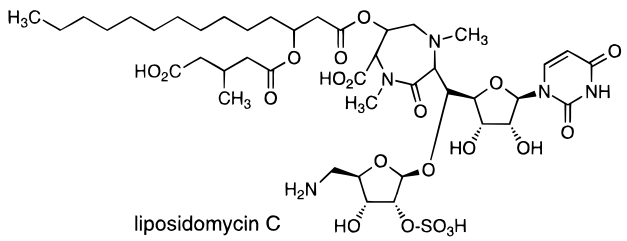
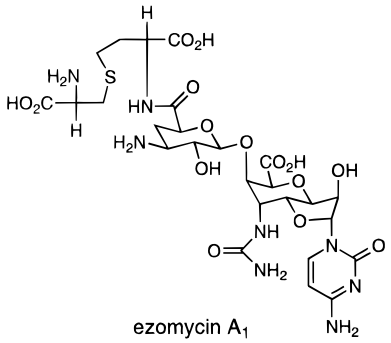
## Introduction

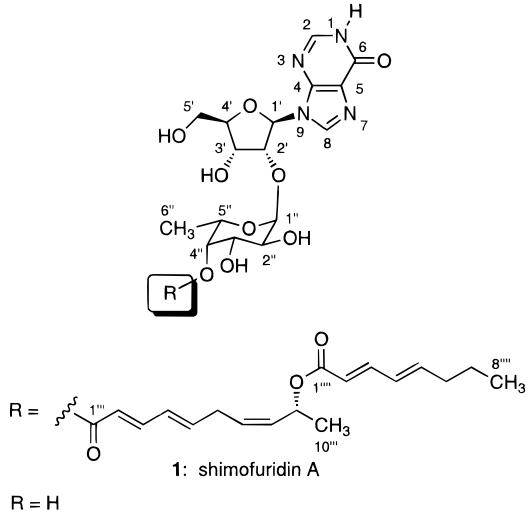
Many complex nucleoside antibiotics, such as ezomycin $A_1$ and liposidomycin C (shown below), contain O-glycosylated nucleoside substructures.[1−3] Synthetic approaches to these compounds must include an O-glycosylation step (to form the disaccharide), or an N-glycosylation step (to form the nucleoside), or both. While there are plenty of examples of efficient nucleoside formation from simple, elaborated, or disaccharidal glycosyl donors, there are fewer cases of successful O-glycosylation of a nucleoside.[1−3] In most of these reactions, the nucleoside pyrimidine or purine base is more reactive toward the glycosyl donor than the desired hydroxyl site, and, although base-glycosylation may be reversible, an excess of donor is usually required.[4,5] A base-glycosylated product that is formed initially may be less reactive toward further glycosylation and can hydrolyze back to the original nucleoside acceptor upon quench[4] or hydrolysis[5] or (in the case of purine nucleoside acceptors) may depurinate under the reaction conditions.[5,6] Frequently glycosylation yields are low, even with a primary hydroxyl acceptor site,[4,7] and successful nucleoside glycosylations at a hindered secondary hydroxyl site, mostly pyrimidine examples, can be counted on the fingers of one hand.[4,8−11]

In 1993, Kobayashi and co-workers reported the isolation of several milligrams of a complex nucleoside from the Okinawan marine tunicate *Aplidium multiplicatum*.[12] The compound, shimofuridin A, exhibited cytotoxic, antimicrobial, and protein kinase C inhibitory activities and was shown by degradation studies and by $^1$H NMR, $^{13}$C NMR, mass, infrared, and ultraviolet spectroscopy to possess the unusual fatty acyl−fucopyranosyl−inosine structure **1**. A small quantity of **1** was




hydrolyzed under basic conditions to give fatty acid components and the shimofuridin nucleoside disaccharide **2**, and further acidic degradation of **2** enabled assignment of the absolute configuration of the D-ribose and L-fucose subunits.




**2**: shimofuridin nucleoside disaccharide

We viewed the structure of shimofuridin in the context of complex nucleoside synthesis as a challenge for glycosylation chemistry: attachment of a fucopyranosyl subunit at O-2′ of inosine would represent a rare example of O-glycosylation of a purine nucleoside at a secondary hydroxyl[11] and would require surmounting the double obstacle of steric hindrance and competing depurination. In this Note we report the synthesis of the shimofuridin degradation product **2** by fucosylation of a suitably protected inosine derivative under mild conditions.

## Results and Discussion

Protection of the 2′ hydroxyl of 3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)inosine[13] (**3**, Scheme 1) as its acetate

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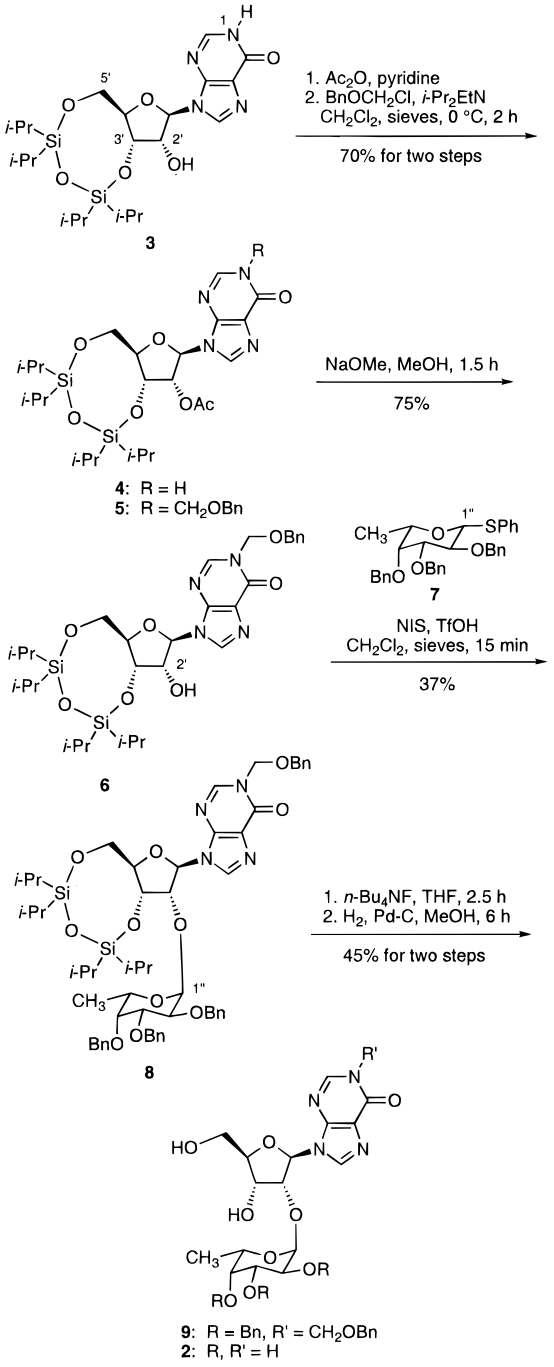
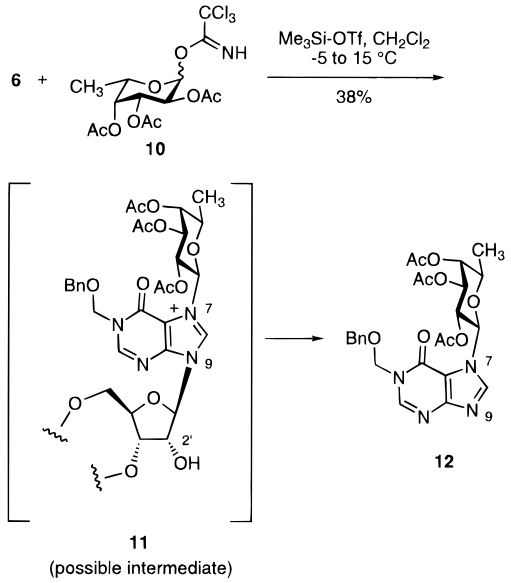
**Scheme 1. Synthesis of the Shimofuridin Nucleoside Disaccharide 2**




ester allowed N-1 alkylation with (benzyloxy)methyl chloromethyl ether, leading to inosine derivative **5**. Deacetylation at O-2′ gave the glycosylation acceptor **6**. The benzyl-protected fucopyranosyl donor **7** was prepared according to the literature procedure;[14] the nonparticipating benzyloxy group at C-2″ was expected to direct α-glycosylation.[15]

Activation of the donor **7** (5.75 equiv) with *N*-iodosuccinimide and triflic acid[16] at 23 °C in the presence of acceptor **6** (1 equiv) led to the consuption of both starting

**Scheme 2. Trans Purinylation by Schmidt Donor**




materials and formation of a glycosylated product that can be formulated as **8** on the basis of its $^1$H NMR, $^{13}$C NMR, exact mass, IR, and UV spectra. In particular, the fucopyranosyl anomeric H-1″ appears as a doublet with $J$ = 4.3, indicating the α-anomer. The use of fewer equivalents of fucopyranosyl donor or lower reaction temperature resulted in much less disaccharide product **8**, and attempted glycosylation of the (N-1)-*unprotected* acceptor **3** failed to produce any isolable disaccharide, perhaps because of preferential glycosylation at O-6.[5]

By comparison to the successful glycosylation by **7**, a *peracetylated* fucopyranosyl donor, 2,3,4-tri-*O*-acetyl-(α/β)-L-fucopyranosyl trichloroacetimidate[17] (**10**), reacted with **6** by the trans-purinylation pathway[6] to give a β-fucopyranosyl hypoxanthine product **12** in 38% yield (Scheme 2). The position of glycosylation in **12** was established unambiguously as N-7 by comparison of the hypoxanthine C-4 and C-5 chemical shifts in the $^{13}$C NMR spectrum (156.9 and 114.5 ppm, respectively) with those of N-7 (157.7 and 114.7 ppm) and N-9 (148.4 and 124.6 ppm) ribosylated hypoxanthine.[18] The peracetylated donor **10** may be more reactive for trans-purinylation vs O-glycosylation than the perbenzylated donor because it is more electron-withdrawing once attached to the hypoxanthine N-7, as in **11**.[5]

Stepwise removal of the disiloxan-1,3-diyl (with fluoride ion) and benzyl and BOM (by hydrogenolysis) protecting groups gave the desired shimofuridin nucleoside disccharide **2**. Its spectroscopic characteristics ($^1$H NMR, $^{13}$C NMR, HR-FAB-MS, IR, and UV) are fully consistent with the assigned structure. However, an authentic sample of the natural shimofuridin degradation product was unavailable, and no $^1$H or $^{13}$C NMR spectra had been taken due to the limited amount of material isolated in the degradation experiments.[12] Thus, synthetic **2** could only be compared with natural **1**.

Figure 1 displays graphically the Δδ values calculated as the $^{13}$C and $^1$H chemical shifts of synthetic **2** minus

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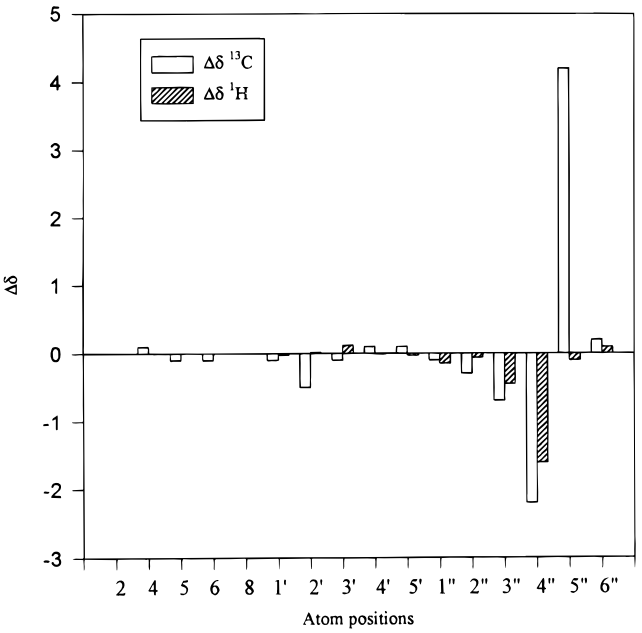


**Figure 1.** $^{13}C$ and $^{1}H$ chemical shift differences ($\Delta\delta$) between synthetic **2** and natural **1**.

the chemical shifts[12] of the corresponding atoms of **1** in DMSO-$d_6$ solution. A small positive or negative $\Delta\delta$ value corresponds to a close match in chemical shift. The carbons of synthetic **2** were assigned by a HETCOR-2D NMR experiment (see supporting information) and by comparison to the $^{13}C$ NMR spectrum of authentic methyl α-L-fucopyranoside.[19] Thus, **2** can be seen as a fucosylated inosine that closely matches **1** at all carbons ([$\Delta\delta$] < 1 ppm) except for C-5″ and the supposed point of acylation, C-4″. The upfield shift of C-5″ ($\Delta\delta = 4.2$ ppm) in response to acylation at C-4″ (as in **1**) finds precedent in a 4-O-benzoylated α-fucopyranoside described by Binkley.[19] The downfield shifts of C-4″ ($\Delta\delta = -2.2$ ppm) and H-4″ (−1.6 ppm) upon acylation at that site are reasonable values.[19] Therefore, based on the spectroscopic correlations and the method of synthesis, the structure of synthetic **2** corresponds to the nucleoside disaccharide core of shimofuridin **1**.

## Experimental Section

**2′-*O*-Acetyl-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)-inosine (4).** A solution of 250 mg (0.489 mmol) of 3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)inosine in 5 mL of pyridine was treated with 1 mL (10.6 mmol) of acetic anhydride. The reaction mixture was stirred at room temperature for 6 h, cooled to 0 °C, quenched with 5 mL of water, and stirred for another 0.5 h. Concentration under high vacuum gave a residue that was partitioned between 100 mL of ethyl acetate and 30 mL of water. The organic layer was separated and then extracted sequentially with 20% aqueous citric acid, water, and brine. The organic layer was dried over sodium sulfate, concentrated, and then chromatographed with 19:1 dichloromethane/methanol as the eluant to give 260 mg (96%) of the pure acetate **4**: $^{1}H$ NMR (400 MHz, $CDCl_3$) $\delta$ 13.18 (br s, N*H*), 8.14 (s, H-8), 8.10 (s, H-2), 6.08 (d, $J = 0.9$, H-1′), 5.75 (d, $J = 5.1$, H-2′), 4.97 (dd, $J = 5.6$, 5.13, H-3′), 4.08−4.26 (m, 2 H-5′, H-4′), 2.24 (s, $OCOCH_3$), 1.07−1.17 (m, 4 $CH(CH_3)_2$); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 169.2, 159.2, 148.1, 144.9, 138.7, 125.6, 87.6, 82.2, 75.7, 68.7, 60.3, 20.6, 17.4, 16.9, 13.3, 12.8; IR (film) 1751, 1699 $cm^{-1}$; HR-FAB-MS *m/z* 553.2513 (calculated for M + H 553.2514); UV (MeOH) $\lambda_{max}$ 246 nm.

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**2′-*O*-Acetyl-1-*N*-[(benzyloxy)methyl]-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)inosine (5)**. A solution of 125 mg (0.22 mmol) of the inosine acetate **4** in 5 mL of dichloromethane containing dry 4 Å sieves and 0.2 mL (1.15 mmol) of *N*,*N*-diisopropylethylamine was treated with 0.05 mL (0.29 mmol) of benzyl chloromethyl ether at 0 °C for 2.5 h. TLC analysis of the reaction mixture at this point indicated complete disappearance of the starting material and formation of a higher $R_f$ product. The reaction was quenched with 3 mL of water, stirred for 0.5 h, and then diluted with dichloromethane. The organic layer was washed with water and then brine, dried over sodium sulfate, and concentrated. Chromatography of the residue with 30:1 dichloromethane/methanol as the eluant gave 110 mg (73%) of the N-protected nucleoside **5** as a colorless oil: $^{1}H$ NMR $\delta$ 8.10 (s, H-8), 8.04 (s, H-2), 7.37−7.39 (m, 5 Ar-H), 6.03 (d, $J = 0.9$, H-1′), 5.72 (d, $J = 5.1$, H-2′), 5.66 and 5.62 (ABq, $J = 10.5$, $NCH_2O$), 4.91−4.95 (m, H-3′), 4.73 (s, $PhCH_2$), 4.07−4.26 (m, 2 H-5′, H-4′), 2.23 (s, $OCOCH_3$), 1.07−1.16 (m, 4 $CH(CH_3)_2$); $^{13}C$ NMR $\delta$ 169.2, 156.6, 147.4, 146.5, 138.5, 136.7, 128.5, 128.1, 127.9, 127.8, 125.1, 87.5, 82.1, 75.7, 74.3, 71.9, 68.6, 60.2, 20.6, 17.4, 16.8, 13.3, 12.8; IR (film) 1753, 1706 $cm^{-1}$; HR-FAB-MS *m/z* 673.3080 (calculated for M + H 673.3089); UV $\lambda_{max}$ 246 nm.

**1-*N*-[(Benzyloxy)methyl]-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)inosine (6).** A solution of 125 mg (0.186 mmol) of the $N^1$-[(benzyloxy)methyl]inosine **5** in 5 mL of methanol was treated with 8 mg (0.148 mmol) of sodium methoxide, and the reaction mixture was stirred at room temperature for 1.5 h. TLC analysis of the reaction mixture at this point indicated complete disappearance of the starting material, and a new spot with a slightly lower $R_f$ than the starting material was observed. The reaction mixture was neutralized with Amberlite IR-120 ($H^+$) resin, filtered, and then concentrated to give the crude product, which was chromatographed with 30:1 dichloromethane/methanol as the eluant to give 88 mg (75%) of **6** as a colorless oil: $^{1}H$ NMR $\delta$ 8.10 (s, H-8), 8.00 (s, H-2), 7.38−7.39 (m, 5 Ph-H), 6.00 (d, $J = 1.3$, H-1′), 5.66 and 5.63 (ABq, $J = 10.9$, $NCH_2O$), 4.94 (app t, $J = 5.6$, H-3′), 4.74 (s, $PhCH_2$), 4.51 (br d, $J = 5.6$, H-2′), 4.10−4.21 (m, 2 H-5′, H-4′), 3.15 (d, $J = 1.3$, O*H*), 1.07−1.16 (m, 4 $CH(CH_3)_2$); $^{13}C$ NMR $\delta$ 157.0, 147.2, 138.8, 136.7, 128.5, 128.1, 127.9, 125.3, 89.5, 82.1, 75.3, 74.3, 71.2, 70.4, 61.4, 17.3, 16.9, 13.3, 12.8; IR (film) 3418, 1706 $cm^{-1}$; HR-FAB-MS *m/z* 631.2988 (calculated for M + H 631.2983); UV $\lambda_{max}$ 248 nm.

**1-*N*-[(Benzyloxy)methyl]-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)-2′-*O*-(2″,3″,4″-tri-*O*-benzyl-α-L-fucopyranosyl)inosine (8).** A stirred solution of 96 mg (0.207 mmol) of phenyl 1,6-dideoxy-1-thio-2,3,4-tri-*O*-benzyl-β-L-fucopyranoside (**7**) and 23 mg (0.036 mmol) of nucleoside acceptor **6** in 4 mL of dichloromethane was treated sequentially with 75 mg of activated 3 Å sieves, 42 mg (0.187 mmol) of *N*-iodosuccinimide, and 0.30 mL (0.080 mmol) of a 4% dichloromethane solution of triflic acid. After 15 min the reaction was quenched by adding 10% aqueous sodium thiosulfate solution until the purple color was discharged. The reaction mixture was diluted with dichloromethane, washed sequentially with saturated aqueous sodium bicarbonate, water, and brine, dried over sodium sulfate, concentrated, and then chromatographed with 3:2 hexane/ethyl acetate as the eluant to give 14 mg (37%) of the protected nucleoside disaccharide **8**: $^{1}H$ NMR $\delta$ 8.24 (s, H-8), 7.99 (s, H-2), 7.26−7.41 (m, 20 PhH), 5.99 (s, H-1′), 5.69 (d, $J = 4.3$, H-1″), 5.61 and 5.55, (ABq, $J = 10.3$, $NCH_2O$), 4.63−5.01 (m, 8 $PhCH_2$), 4.56 (dd, $J = 3.4$, 4.3, H-3′), 4.46 (d, $J = 3.4$, H-2′), 4.20−4.35 (m, H-3″, H-4′), 4.14−4.19 (m, H-5″, H-5′), 4.00−4.07 (m, H-5′, H-2″), 3.78 (d, $J = 1.3$, H-4″), 0.96−1.11 [m, 3 H-6″, 4 $CH(CH_3)_2$]; $^{13}C$ NMR $\delta$ 156.7, 147.0, 146.1, 138.9, 138.6, 138.4, 137.8, 136.8, 128.8, 128.5, 128.3, 128.2, 128.1, 127.9, 127.7, 127.6, 127.4, 95.9, 88.9, 81.4, 79.0, 76.1, 75.5, 74.8, 74.3, 73.4, 72.0, 71.8, 69.5, 67.0, 59.3, 17.5, 17.3, 16.9, 16.8, 16.7, 13.4, 13.0, 12.9, 12.4; IR (film) 1708 $cm^{-1}$; HR-FAB-MS *m/z* 1047.4965 (calculated for M + H 1047.4971); UV $\lambda_{max}$ 246 nm.

**1-*N*-[(Benzyloxy)methyl]-2′-*O*-(2″,3″,4″-tri-*O*-benzyl-α-L-fucopyranosyl)inosine (9).** A solution of 28.5 mg (0.027 mmol) of the disaccharide **8** in 3 mL of dry THF was treated with 0.035 mL (0.035 mmol) of a 1 M solution of tetra-*n*-butylammonium fluoride in THF. The reaction mixture was stirred at room temperature for 2.5 h and then concentrated. The crude product was extracted into ethyl acetate, which was washed with water followed by brine, dried over sodium sulfate, and then concentrated to a residue, which was triturated with hexane (2 × 25

mL). Chromatography with 16:1 dichloromethane/methanol as the eluant gave 13.5 mg (62%) of **9**: $^1$H NMR $\delta$ 8.13 (s, H-8), 7.8 (s, H-2), 7.28−7.40 (m, 20 PhH), 5.87 (d, $J$ = 7.7, H-1′), 5.61 and 5.53 (ABq, $J$ = 10.7, NC$H_2$O), 5.14 (d, $J$ = 11.1, 5′-O$H$), 4.91 (t, $J$ = 11.2, PhC$H_2$), 4.80 (dd, $J$ = 7.7, 5.1, H-2′), 4.77 (s, PhC$H_2$), 4.71 (d, $J$ = 4.3, H-1″), 4.57 and 4.68 (ABq, $J$ = 12.0, PhC$H_2$), 4.67 (s, PhC$H_2$), 4.38 (d, $J$ = 5.1, H-3′), 4.35 (s, 3′-O$H$), 4.02 (dd, J = 10.2, 3.4, H-5′), 3.88−3.94 (m, H-2″, H-3″, H-4′), 3.74 (t, $J$ = 11.1, H-5′), 3.60 (s, H-4″), 3.39 (q, $J$ = 6.8, H-5″), 0.74 (d, $J$ = 6.8, 3 H-6″); IR (film) 3447, 1715 cm$^{-1}$; HR-FAB-MS $m/z$ 805.3446 (calculated for M + H 805.3448); UV $\lambda_{max}$ 248 nm.

**2′-*O*-(α-L-Fucopyranosyl)inosine (2).** A solution of 12 mg (0.015 mmol) of the nucleoside disaccharide **9** in 6 mL of methanol was stirred with 8 mg of 20% palladium hydroxide on carbon at room temperature under hydrogen atmosphere for 6 h. The catalyst was removed by filtration through a Celite pad, and the filter cake was washed twice with 20 mL of methanol. The combined filtrate was concentrated to give 4.5 mg (73%) of the pure nucleoside disaccharide **2**: $^1$H NMR (DMSO-$d_6$) $\delta$ 12.42 (br s, N$H$), 8.36 (s, H-8), 8.09 (s, H-2), 6.02 (d, $J$ = 6.8, H-1′), 5.14 (br t, $J$ = 5, 5′-OH), 5.01 (d, $J$ = 3.9, H-1″), 4.73 (dd, $J$ = 6.8, 4.9, H-2′), 4.72 (br d, $J$ = 11.7, 2 O$H$), 4.60 (br s, O$H$), 4.43 (d, $J$ = 4.9, H-3′), 4.29 (br d, O$H$), 3.99 (br d, $J$ = 2, H-4′), 3.63 (m, 2 H-5′), 3.50 (br m, H-2″, H-5″), 3.29−3.33 (m, H-3″, H-4″), 0.58 (d, $J$ = 5.9, 3 H-6″); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 146.0 (C-2), 148.2 (C-4), 124.4 (C-5), 156.4 (C-6), 138.8 (C-8), 85.5 (C-1′), 80.2 (C-2′), 69.6 (C-3′), 85.9 (C-4′), 61.3 (C-5′), 100.1 (C-1″), 67.9 (C-2″), 66.6 (C-3″), 71.4 (C-4″), 69.4 (C-5″), 15.7 (C-6″); IR (film) 3427 and 1600 cm$^{-1}$; HR-FAB-MS $m/z$ 415.1479 (calculated for M + 1 415.1465); UV $\lambda_{max}$ 246 nm (MeOH, pH 7), 250 nm (pH 2), 254 nm (pH 11).

**Trans-Purinylation with Schmidt Donor. 1-*N*-[(Benzyloxy)methyl]-7-(2,3,4-tri-*O*-acetyl-β-L-fucopyranosyl)hypoxanthine (12).** A solution of 17 mg (0.027 mmol) of the inosine acceptor **6** and 19 mg (0.044 mmol) of 2,3,4-tri-*O*-acetyl-L-fucopyranosyl trichloroacetimidate (**10**) in 3.0 mL of dichloromethane was cooled to 0 °C and then treated with 0.008 mL (0.044 mmol) of trimethylsilyl trifluoromethanesulfonate. The reaction mixture was stirred for 1 h, during which time the bath temperature rose to 15 °C. TLC analysis indicated complete consumption of the acceptor and the formation of a new product with lower $R_f$. The reaction was quenched with 2 mL of saturated aqueous sodium bicarbonate and extracted with 25 mL of dichloromethane. The organic layer was dried over sodium sulfate and then concentrated to a residue, which was chromatographed with 49:1 dichloromethane/methanol as the eluant to afford 8.6 mg (38%) of the fucosylated hypoxanthine **12**. $^1$H NMR ($CDCl_3$) $\delta$ 8.24 (s, H-8), 8.15 (s, H-2), 7.29−7.36 (m, 5 Ph-H), 6.29 (d, $J$ = 9.4, H-1′), 5.68 (t, $J$ = 9.7, H-2′), 5.68 (s, NC$H_2$O), 5.39 (d, $J$ = 3.3, H-4′), 5.27 (dd, $J$ = 10.0, 3.4, H-3′), 4.68 (s, OC$H_2$Ph), 4.16 (q, $J$ = 6.4, H-5′), 2.26, 2.01, and 1.85 (3 s, OCOC$H_3$), 1.26 (d, J = 6.4, three H-6′); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 170.4 , 169.8, 169.2 (3 OCOCH$_3$'s), 156.9 (C-4), 154.0 (C-6), 146.9 (C-2), 142.1 (C-8), 136.4 (ipso-Ph), 128.6, 128.3, 127.9 (*o*-, *m*-, *p*-Ph), 114.5 (C-5), 82.8 (C-1′), 74.1, 72.5, 71.8, 71.6, 70.0, 68.1, 20.7, 20.5, 20.3 (3 OCOC$H_3$), 16.1 (C-6′); HR-FAB-MS $m/z$ 529.1950 (calculated for M + 1 529.1934).

**Methyl (α and β)-L-Fucopyranoside.** A reference sample of the two fucopyranoside anomers was synthesized from L-fucose and methanol according to the literature procedure,[19] resulting in a 2:1 α/β mixture that could be analyzed as such by $^1$H and $^{13}$C NMR spectroscopy. α-Anomer $^1$H NMR (partial, DMSO-$d_6$) $\delta$ 4.48 (d, $J$ = 2.6, H-1); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 100.5 (C-1), 71.8 (C-4), 69.9 (C-5), 68.3 (C-2), 65.9 (C-3), 54.8 (OC$H_3$), 16.7 (C-6). β-Anomer $^1$H NMR (partial, DMSO-$d_6$) $\delta$ 4.00 (d, $J$ = 7.6, H-1); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 104.5 (C-1), 73.7 (C-4), 71.3 (C-5), 70.4 (C-2), 70.2 (C-3), 56.0 (OC$H_3$), 19.6 (C-6).

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**Supporting Information Available:** HETCOR-2D NMR spectrum of **2** (4 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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