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THE STEREOCONTROLLED SYNTHESIS OF 1,2-TRANS HEXOPYRANOSYL NUCLEOSIDES VIA A NOVEL ANOMERIC ACTIVATION

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Key words: nucleoside, anomeric activation

Abstract: The coupling of 2-(2',3',4',6'-tetra-O-benzyl-β-D-hexopyranosyloxy)-3-methoxypyridine as well as 2-(2',3',4',6'-tetra-O-benzyl-β-D-hexopyranosyl)-thiopyridylcarbonate, with silylated pyrimidine bases by activation with trimethylsilyl trifluoromethanesulfonate and silver triflate respectively afforded the corresponding 1,2-*trans* nucleosides with high selectivity. Copyright © 1996 Elsevier Science Ltd

The very first nucleoside ever synthesized, 9-β-D-glucopyranosyladenine, by Fischer and Helferich [1] was in the hexopyranose form. Since then, many purine and pyrimidine hexopyranosyl nucleosides have been prepared. Although a greater level of biological interest has been generated by pentofuranosyl nucleosides over the years, a number of naturally occurring[2] and synthetic[3] hexopyranosyl nucleosides are known. For example, 1-(2'-deoxy-β-D-*arabino*-hexopyranosyl)-thymine,[4] was recognized many years ago to be an inhibitor of a pyrimidine nucleoside phosphorylase from Ehrlich ascites tumor.[5] 9-β-D-Fucopyranosyladenine has been reported to be an inhibitor of the development of leukemia cells L 1210.[6] More recently, some hexopyranosyl nucleoside analogues were found as potential anti-HIV agents.[7]

The classical approach to the synthesis of 1,2-*trans* nucleosides relies on neighboring group participation of an appropriate ester group[8] which leads to a per-O-acetylated nucleoside. If an O-benzyl ether group was needed in such nucleosides for compatibility with subsequent transformations, it would have to be prepared indirectly by an ester assisted coupling step, deesterification, followed by benzylation. The direct method involving an O-benzylated glycosyl precursor will most probably lead to stereochemical uncertainty in the final nucleoside, in view of the absence of neighboring group participation in a hexopyranosyl system.

We have recently discovered that the 2-methoxypyridyloxy (MOP) and 2-thiopyridylcarbonate (TOPCAT) groups are excellent activators of O-benzylated hexopyranoses in O-glycoside synthesis based on the remote activation concept.[9] These anomeric activating groups have been successfully used for the highly stereoselective synthesis of 1,2-*cis* nucleosides in the D-*ribo* and D-*arabino* series.[10] We describe herein the adaptation of this method to the synthesis of 1,2-*trans* hexopyranosyl pyrimidine nucleosides with excellent stereochemical control.

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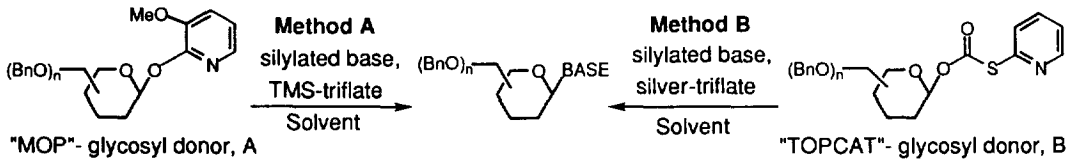
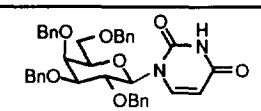
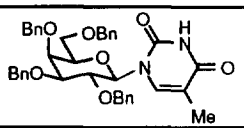
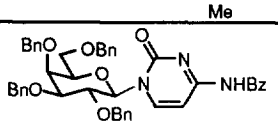
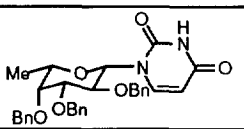
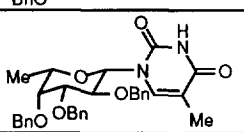
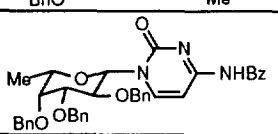
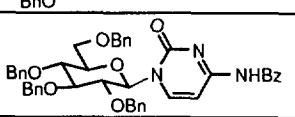
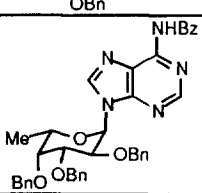
Table 1



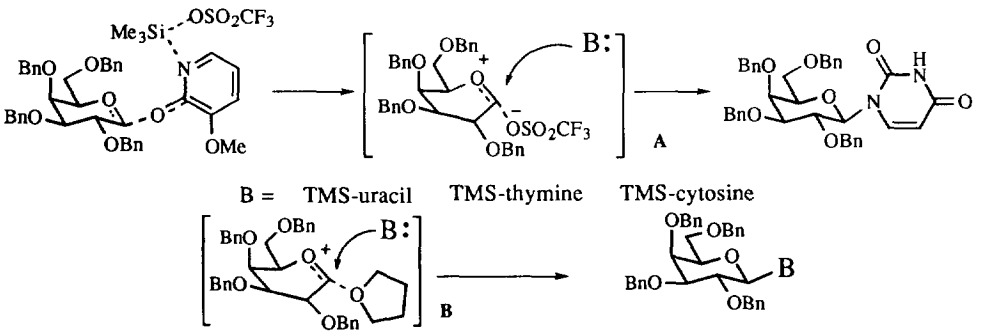
Entry	Product	Donor type	Yield [a]	α/β- Ratio [b]	Conditions, 25°C
1		A B	90% 76%	7:93 6:94	6 h, THF 32 h, Toluene
2		A	70%	4:96	12 h, THF
3		A	86%	8:92	18 h, Toluene
4		B B	60% 70%	3:97 2:98	5 h, THF 24 h, Toluene
5		B	80%	β	25 h, Toluene
6		B	60	β	5 h, THF
7		B B	76 80	20:80 83:17	12 h, THF 24 h, Toluene
8		B	80 [c]	90:10	12 h, DMF

a. Yield of isolated, chromatographically pure nucleoside. b. Ratio determined by ^{1}H NMR at 300 MHz, and confirmed by weights of isolated nucleosides whenever possible. c. Br_2 was used as promoter.

Thus treatment of 2,3,4,6-tetra-O-benzyl-β-D-galactopyranosyl and the 2,3,4-tri-O-benzyl-β-L-fucopyranosyl MOP and TOPCAT derivatives with a silylated[11] pyrimidine base in the presence of TMS triflate and silver triflate, gave the corresponding 1,2-*trans* nucleosides. Table 1 shows the results with D-*galacto*, L-*fuco* and D-*gluco* glycosyl donors utilizing silylated pyrimidine bases. However, the main product obtained from the reaction between the L-*fuco*-TOPCAT donor and N-benzoyladenine using bromine as a promoter[12] was the 1,2-*cis* isomer. No product could be obtained when Methods A or B were utilized. Also, preliminary studies showed that the reaction with *D-gluco* or *D-galacto* donors were not as promising as with the *L-fuco* case. Perhaps this is a reflection of an electronic effect which enhances reactivity in this case. The reversal in anomeric configuration may also depend on the nature of activated ion-pairs. Excellent 1,2-*trans* selectivity was observed using either THF or toluene as solvents with the exception of the D-*gluco* case (Table 1, entry 7). The benzyl ether protective groups were hydrogenolyzed to give the unprotected nucleosides. Both glycosyl donors were used as the β-anomers and no dramatic difference was noticed in their reactivity. The use of THF as solvent seemed to accelerate the reaction (Table 1, entries 1, 4, 7). In contrast to the results obtained in the furanose ring series,[10] the polarity of the solvent did not reverse the stereochemistry in the D-*galacto* and L-*fuco* derivatives. However, an important dependence on the nature of the solvent (5:1 in toluene vs 1:4 in THF), was seen in the D-*gluco* case (Table 1, entry 7).

The design of the MOP group was predicated upon its activation by the catalyst most likely at nitrogen which generates an oxonium ion pair species. Based on the observed stereochemistry, we could exclude an S_N2 like attack by the nucleophilic pyrimidine base. The 1,2-*trans* MOP donor most likely undergoes activation by TMS triflate, and the charged adduct leaves to generate a stereoelectronically favored *cis*-1,2-oxonium-triflate ion pair A which leads to the 1,2-*trans* nucleoside. Alternatively, solvent participation[13] may also generate a transient oxonium ion **B**, as shown in Scheme 1. In spite of the presence of a pseudo-axial benzyloxy group in the D-*galacto* and L-*fuco* systems, 1,2-*trans* attack predominates in both cases. The D-*gluco* system leads to the 1,2-*cis* product in toluene possibly due to a proportionately higher population of 1,2-*trans* oxonium-triflates in this solvent compared to THF. A direct S_N2-like attack of the pyrimidine base on the original TOPCAT activated oxonium intermediate is also possible.

Scheme 1



Although by design, the nature of the remote activation is different in the TOPCAT leaving group compared to MOP as we have reported previously [10] the final result is identical using either mode of activation (Table 1).

In conclusion, we have described an efficient and highly stereocontrolled synthesis of 1,2-*trans* pyrimidine D-galactopyranosyl and L-fucopyranosyl nucleosides in the absence of neighboring group participation.

EXPERIMENTAL

Melting points are uncorrected. Optical rotations were measured on a Perkin-Elmer polarimeter model 141 at 22-24°C. The ^1H and ^{13}C spectra were recorded on a Brucker WH90 instrument with trimethylsilane as internal standard in deuteriochloroform as solvent. IR spectra were recorded as thin films between NaCl plates or as solids in KBr pellets on a Unicam SP100 spectrophotometer.

General method for the preparation of MOP pyranosyl donor:

2-(2',3',4',6'-Tetra-O-benzyl-β-D-galactopyranosyloxy)-3-methoxypyridine (donor A).

To a solution of 2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl bromide (3.67g, 8.93 mmol) in toluene (40 mL) was added the silver salt of 3-methoxy-2-hydroxypyridine (3g, 12.9 mmol). The reaction mixture was stirred at 110° C for 30 min. After being cooled to r.t, the mixture was filtered over Celite and washed with CH_2Cl_2. Evaporation of the solvent and purification of the residue by flash chromatography (hexanes-EtOAc-CH_2Cl_2, 1:1:1) gave the corresponding 3-methoxypyridyl glycoside, mp 62-64°C; $[\alpha]_D$ +37.1° (c 1.26, $CHCl_3$). This was deacetylated (NaOMe, MeOH) in the usual way, and the product was benzylated (DMF, BnBr, NaH, 24h) to give the title compound after chromatography (70%); mp 66-68°C; $[\alpha]_D$ +11.48° (c 0.53, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.75 (dd, 1H, H-6'), 7.26-7.42 (m, 20H, benzyl), 7.12 (dd, 1H, H-4), 6.93 (dd, 1H, H-5), 6.10 (d, 1H, J=8.1 Hz, H-1'), 4.41-5.05 (m, 8H, 4xCH_2-Ph), 4.24 (dd, 1H, $J_{2'-1'}$=8.1 Hz, $J_{2'-3'}$=9.7 Hz, H-2'), 4.05 (d, 1H, J=3.6 Hz, H-4'), 3.86 (s, 4H, OCH_3, H-3'), 3.73 (m, 3H, H-5', H-6'a, H-6'b); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ (ppm) 152.3, 144.1, 138.6, 138.4, 137.8, 136.8, 126.8-126.4 (benzyl), 118.3, 96.51, 82.05, 78.78, 74.98, 74.52, 73.72, 73.64, 73.32, 72.82, 68.20, 55.51 (OCH_3); HRMS (FAB) calcd. for $C_{40}H_{42}NO_7$ 648.2961; found 648.2930.

General method for the preparation of pyranosyl thiocarbonates:

2-(2',3',4',6'-Tetra-O-benzyl-β-D-glucopyranosyl)-thiopyridylcarbonate (donor B).

To a solution of 2,3,4,6-tetra-O-benzyl-D-glucopyranose (330 mg; 0.6 mmol) in CH_2Cl_2 (6 mL) were added bis-2,2-thiopyridylcarbonate (410 mg; 1.6 mmol) and Et_3N (230 μL; 1.6 mmol) and the solution was stirred for 1 day. After concentration, the residue was purified by flash chromatography (hexanes-EtOAc, 1:2 to 1:1) to give the desired product as a pale yellow solid (393 mg, 95%); mp 71-73°C; $[\alpha]_D^{25}$ +15° (c 1.5, $CHCl_3$); IR: υ_{max} (KBr); 1750 (C=O): ^1H NMR (300 MHz, $CDCl_3$): δ 8.60 (m, 1H, H-6), 7.73 (m, 2H, H-3, H-4), 7.12-7.35 (m, 21H, benzyl, H-5), 5.64 (d, 1H, J=8.1 Hz, H-1'), 4.93 (d, 1H, J=11.7 Hz, CH_2-Ph), 4.78 (s, 2H, CH_2-Ph), 4.72 (s, 2H, CH_2-Ph), 4.60 (d, 1H, J=11.7 Hz), 4.44 (d, 1H, J=11.7 Hz), 4.40 (d, 1H, J=11.7 Hz), 3.96 (m, 2H), 3.55-3.71 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ (ppm) 167.5 (C=O), 96.61 (C-1'); HRMS calcd. for $C_{40}H_{39}NO_7SNa^+$ (M + Na^+), 700.2344; found 700.2306.

1-(2',3',4',6'-Tetra-O-benzyl-β-D-galactopyranosyl)-uracil .

(Method A). To a solution of 2-(2',3',4',6'-tetra-O-benzyl-β-D-galactopyranosyloxy)-3-methoxypyridine (47 mg, 0.07 mmol) in THF (1.2 mL) were added bis-O-trimethylsilyluracil (54 mg, 3 eq) and TMS triflate (27 μL, 2 eq). The solution was stirred under argon at r.t overnight, then quenched with sat. $NaHCO_3$. After extraction of the aqueous phase with CH_2Cl_2 and washing with brine, the solution was dried over anh. Na_2SO_4, filtered and concentrated under vacuum to give a residue which was purified by flash chromatography (hexanes-EtOAc, 2:1) yielding 45 mg (90%) of the desired product.

(Method B) To a solution of 2-(2',3',4',6'-tetra-O-benzyl-β-D-galactopyranosyl)-thiopyridylcarbonate (61 mg, 0.1 mmol) in THF (2.5 mL) were added bis-O-trimethylsilyluracil (76.5 mg, 3 eq) and silver triflate (23 mg, 2 eq). The solution was stirred under argon for 32 h, then quenched with sat. $NaHCO_3$. After extraction of the aqueous phase with CH_2Cl_2 and washing with brine, the solution was dried over anh. Na_2SO_4, filtered and concentrated under vacuum to give a residue which was purified by flash chromatography (hexanes-EtOAc, 2:1) yielding 43 mg (76%) of the desired product; $[\alpha]_D$ -24.5° (c 0.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.61 (1H, NH), 7.32 (m, 18H, benzyl), 6.94 (d, 1H, J=8.2Hz, H-6), 5.60 (d, 1H, J=9 Hz, H-1'), 5.36 (dd, 1H, H-5), 4.96 (d, 1H, CH_2-Ph), 4.80 (m, 3H, CH_2-Ph), 4.44-4.62 (m, 4H, CH_2-Ph), 4.00 (ld, 1H, H-4'), 3.85 (m, 1H, H-3'), 3.76 (m, 2H, H-2', H-5'), 3.53 (m, 2H, H-6'a, H-6'b); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ (ppm) 162 (C=O), 150.3 (C=O), 139.0, 138.3, 137.6, 137.3, 137.0, 128.4 (benzyl), 102.6, 83.24 (C-1'), 81.45, 75.46, 75.13, 74.57, 74.42, 73.15, 72.50, 67.82; HRMS (FAB) calcd. for $C_{40}H_{39}N_2O_7$, 657.2576; found 657.2587.

1-(2',3',4',6'-Tetra-O-benzyl-β-D-galactopyranosyl)-thymine.

(Method A). To a solution of 2-(2',3',4',6'-tetra-O-benzyl-β-D-galactopyranosyloxy)-3-methoxypyridine (52 mg, 0.08 mmol) in THF (1.5 mL) were added bis-O-trimethylsilylthymine (86 mg, 4 eq) and TMS triflate (31 μL, 2 eq). The solution was stirred under argon at r.t for 6 h, then quenched with sat. $NaHCO_3$. After extraction of the aqueous phase with CH_2Cl_2 and washing with brine, the solution was dried over anh. Na_2SO_4, filtered and concentrated under vacuum to give a residue which was purified by flash chromatography (hexanes-EtOAc, 2:1) yielding 36 mg (70%) of the expected product; $[\alpha]_D$ -50.3 (c 3.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.54 (1H, NH), 7.30 (m, 15 H, benzyl), 6.70 (d, 1H, J=1.2 Hz, H-6), 5.60 (d, 1H, J=8.8 Hz, H-1'), 5.0 (d, 1H, CH_2-Ph), 4.80 (m, 3H, CH_2-Ph), 4.41-4.64 (m, 4H, CH_2-Ph), 4.01 (d, 1H, H-4'), 3.76-4.0 (m, 3H, H-2', H-3', H-5'), 3.54 (m, 2H, H-6'a, H-6'b), 1.64 (d, 3H, CH_3-thymine); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ (ppm) 163.1 (C=O), 150.3 (C=O), 138.4, 137.7, 137.4, 137.1, 134.6, 128.4 (benzyl), 110.7, 83.50 (C-1'), 81.40, 75.47, 74.70, 74.26, 73.37, 72.54, 67.84, 12.37 (CH_3); HRMS (FAB) calcd. for $C_{39}H_{40}N_2O_7Na^+$ (M+ Na^+), 657.2913; found 657.2894.

1-(2',3',4',6'-Tetra-O-benzyl-β-D-galactopyranosyl)-N-benzoylcytosine.

(Method A). To a solution of 2-(2',3',4',6'-tetra-O-benzyl-β-D-galactopyranosyl)-3-methoxypyridine (50 mg, 0.07 mmol) in toluene (2.5 mL) were added N-benzoyl-O-trimethylsilylcytosine (60 mg, 2 eq) and TMS triflate (30 μL, 2 eq). The solution was stirred under argon at r.t for 18 h, then quenched with sat. $NaHCO_3$. After extraction of the aqueous phase with CH_2Cl_2 and washing with brine, the solution was dried over anh. Na_2SO_4, filtrated and concentrated under vacuum to give a residue which was purified by flash chromatography (hexanes-EtOAc, 2:1) yielding 53 mg (86%) of the desired product; $[\alpha]_D$ +4.4° (c 1.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.05 (1H, H-6), 7.96 (d, 2 H, benzoyl), 7.50-7.62 (m, 3H, benzoyl), 7.15-7.40 (m, 16H, benzyl, H-5), 5.90 (d, 1H, J=8.8 Hz, H-1'), 4.40-5.0 (m, 8H, 4xCH_2-Ph), 4.10 (d, 1H, J=1.9 Hz, H-4'), 3.92 (t, 1H, J=9 Hz, H-3'), 3.82 (m, 1H, H-2'), 3.55 (m, 3H, H-6'a, H-5', H-6'b); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ (ppm) 161.4 (C=O), 144.0 (C=O), 138.0, 137.3, 137.0, 136.6, 132.6, 128.0 (benzyl), 82.87 (C-1'), 81.95, 75.90, 75.44, 74.23, 73.97, 72.99, 72.96, 72.26, 67.43; HRMS (FAB) calcd. for $C_{45}H_{43}N_3O_7$, 738.3179; found 738.3239.

2-(2',3',4'-Tri-O-benzyl-β-L-fucopyranosyl)-thiopyridylcarbonate .

Preparation was done following the general method to give a syrup; IR υ_{max} ($CHCl_3$): 3020, 1740 (C=O), 1580, 1460, 1430, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.54 (m, 1H, H-6), 7.71 (m, 2 H, H-3, H-4), 7.21-7.37 (m, 16H, benzyl, H-5), 5.62 (d, 1H, J=7.92 Hz, H-1'), 4.66-5.0 (m, 6H, 3xCH_2-Ph), 3.97 (m, 1H, H-3'), 3.58 (m, 3H, H-2', H-4', H-5'), 1.19 (d, 3H, CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ (ppm) 167.8 (C=O), 151.6, 138.3, 138.2, 138.1, 137.2, 129.1, 127.6-128.4 (benzyl), 122.4, 97.01 (C-1'), 82.47, 76.63, 76.02, 75.33, 74.78, 73.18, 71.80, 16.65 (CH_3). Anal. calcd. for $C_{33}H_{33}O_6NS$: C, 69.35; H, 5.82; N, 2.45; S, 5.59. Found, C, 69.22; H, 5.77; N, 2.38; S, 5.51.

1-(2',3',4'-Tri-O-benzyl-β-L-fucopyranosyl)-uracil .

(**Method B**). To a solution of 2-(2',3',4'-tri-O-benzyl-β-L-fucopyranosyl)-thiopyridylcarbonate (50 mg, 0.08 mmol) in THF (1.5 mL) were added bis-O-trimethylsilyluracil (61 mg, 3 eq) and silver triflate (34 mg, 2 eq). The solution was stirred under argon at r.t for 5h, then quenched with sat. $NaHCO_3$. After extraction of the aqueous phase with CH_2Cl_2 and washing with brine, the solution was dried over anh. Na_2SO_4, filtered and concentrated under vacuum to give a residue which was purified by flash chromatography (hexanes-EtOAc, 2:1) yielding 27 mg (60%) of the expected product as a syrup; $[\alpha]_D$ +8.1° (c 2.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.55 (1H, NH), 7.17-7.41 (m, 15H, benzyl), 7.0 (d, 1H, J=8.2 Hz, H-6), 5.80 (d, 1H, J=9 Hz, H-1'), 5.40 (dd, 1H, H-5), 5.03 (m, 6H, 3xCH_2-Ph), 3.86 (t, 1H, J=9.1 Hz, H-3'), 3.75 (dd, 1H, J=9.5 Hz, H-2'), 3.65 (m, 2H, H-4', H-5'), 1.19 (d, 3H, CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ (ppm) 162.2 (C=O), 149.9, 138.7, 137.8, 137.3, 127.7 (benzyl), 102.1, 83.24 (C-1'), 81.10, 75.80, 74.71, 74.36, 74.07, 72.80, 72.34, 16.30 (CH_3); HRMS (FAB), calcd. for $C_{31}H_{32}N_2O_6$, 528.2317; found 528.2301.

1-(2',3',4'-Tri-O-benzyl-β-L-fucopyranosyl)-thymine .

(**Method B**). To a solution of 2-(2',3',4'-tri-O-benzyl-β-L-fucopyranosyl)-thiopyridylcarbonate (50 mg, 0.1 mmol) in toluene (2 mL) were added bis-O-trimethylsilylthymine (94 mg, 3.5 eq) and silver triflate (41 mg, 1.5 eq). The solution was stirred under argon at r.t for 25h, then quenched with sat. $NaHCO_3$. After extraction of the aqueous phase with CH_2Cl_2 and washing with brine, the solution was dried over anh. Na_2SO_4, filtered and concentrated under vacuum to give a residue which was purified by flash chromatography (hexanes-EtOAc, 2:1) yielding 41 mg (86%) of the desired product as a syrup; $[\alpha]_D$ +50.1° (c 2.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.50 (s, 1H, NH), 7.19-7.45 (m, 15H, benzyl), 6.73 (d, 1H, J=1.2 Hz, H-6), 5.85 (d, 1H, J=8.8 Hz, H-1'), 4.60-5.07 (m, 6H, 3xCH_2-Ph), 3.82 (t, 1H, J=9.1 Hz, H-2'), 3.80 (dd, 1H, $J_{3'-4'}$=2.5 Hz, $J_{3'-2'}$=9.4 Hz, H-3'), 3.70 (m, 2H, H-4', H-5'), 1.70 (d, 3H, CH_3), 1.21 (d, 3H, CH_3-fucose); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ (ppm) 163.2 (C=O), 150.5, 138.3, 137.8, 137.1, 134.8, 127.8 (benzyl), 110.7, 83.86 (C-1'), 81.35, 76.16, 74.62, 74.59, 74.23, 73.16, 72.74, 16.76 (CH_3), 12.38 (CH_3); HRMS (FAB), calcd. for $C_{32}H_{34}N_2O_6$, 543.2495; found 543.2472.

1-(β-L-Fucopyranosyl)-thymine.

To a solution of (2',3',4'-tri-O-benzyl-β-L-fucopyranosyl)-thymine (47.5 mg, 0.1 mmol) in MeOH (2 mL) was added $Pd(OH)_2/C$.[14] Hydrogen was passed through the reaction mixture for 24 h. The catalyst was then filtered and the solution was concentrated to give the desired product (16.8 mg, 95%) as a white solid, mp 241°C: $[\alpha]_D$ -27.1° (c 1.9, MeOH): $[\alpha]_D$ -26° (c 0.5, water); reported[15] mp 240-241 °C; $[\alpha]_D$ -25° (c 0.1, water): ^1H-NMR (300

MHz, D_2O): δ (ppm) 7.70 (d, 1H, J=1.1 Hz, H-6), 5.53 (d, 1H, J=8.6 Hz, H-1'), 3.82-3.98 (m, 4H, H-2', H-3', H-4', H-5'), 1.90 (s, 3H, CH_3), 1.25 (d, 3H, CH_3); ^{13}C NMR (75.4 MHz, D_2O): δ (ppm) 164.6 (C=O), 150.5, 135.7, 110.5, 81.22 (C-1'), 72.42, 69.61, 66.73, 13.86 (CH_3), 9.81 (CH_3).

1-(2',3'4'-Tri-O-benzyl-β-L-fucopyranosyl)-N-benzoylcytosine .

(Method B). To a solution of 2-(2',3',4'-tri-O-benzyl-β-L-fucopyranosyl)-thiopyridylcarbonate (50 mg, 0.1 mmol) in THF (1 mL) were added N-benzoyl-O-trimethylsilylcytosine (68 mg, 3 eq) and silver triflate (45 mg, 2 eq). The solution was stirred under argon at r.t for 5h, then quenched with sat. $NaHCO_3$. After extraction of the aqueous phase with CH_2Cl_2 and washing with brine, the solution was dried over anh. Na_2SO_4, filtered and concentrated under vacuum to give a residue which was purified by flash chromatography (hexanes-EtOAc, 2:1) yielding 30 mg (60%) of the expected product; $[\alpha]_D$ -16.4° (c 1.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.95 (d, 2H, benzoyl), 7.50-7.65 (m, 3H, benzoyl), 7.13-7.44 (m, 16H, benzyl, H-5), 5.86 (d, 1H, J=9 Hz, H-1'), 4.54-5.05 (m, 6H, 3xCH_2-Ph), 3.90 (t, 1H, J=9.3 Hz, H-2'), 3.80 (dd, 1H, $J_{3'-4'}$=2.6 Hz, $J_{3'-2'}$=9.5 Hz, H-3'), 3.67 (m, 2H, H-4', H-5'), 1.19 (d, 3H, CH_3-fucose); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ (ppm) 161.4 (C=O), 140.0, 137.9, 137.4, 136.7, 132.6, 132.5, 128.0 (benzyl), 83.22 (C-1'), 81.93, 75.78, 74.36, 73.93, 73.11, 72.44, 16.27 (CH_3), MS m/z 632 (M^+): 306, 216, 91; HRMS (M+H), calcd. for $C_{38}H_{37}N_3O_6$, 631.2748; found 631.2742.

1-(2',3',4',6'-Tetra-O-benzyl-α-glucopyranosyl)-N-benzoylcytosine and 1-(2',3',4',6'-tetra-O-benzyl-β-glucopyranosyl)-N-benzoylcytosine. **(Method B).** To a solution of 2-(2',3',4',6'-tetra-O-benzyl-β-D-glucopyranosyl)-thiopyridylcarbonate (40 mg, 0.06 mmol) in toluene (1.5 mL) were added N-benzoyl-O-trimethylsilylcytosine (78 mg, 5 eq) and silver triflate (46 mg, 3 eq). The solution was stirred under argon for 24 h., then quenched with sat. $NaHCO_3$. After extraction of the aqueous phase with CH_2Cl_2 and washing with brine, the solution was dried over anh. Na_2SO_4, filtered and concentrated under vacuum to give a residue which was purified by flash chromatography (hexanes-EtOAc, 2:1) yielding 38 mg (80%) of a 4:1 mixture of the the α- and β-products: **α-anomer:** $[\alpha]_D$ -47.4° (c 2.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.67 (1H, NH), 8.16 (d, 1H, H-6), 7.94 (d, 2H, benzoyl), 7.51-7.63 (m, 3H, benzoyl), 7.12-7.36 (m, 16H, benzyl, H-5), 6.20 (d, 1H, J=3.3 Hz, H-1'), 4.56-4.62 (m, 3H, CH_2-Ph), 4.31-4.44 (m, 7H, CH_2-Ph, H-4', H-3'), 3.80 (t, 1H, J=2.6 Hz, H-2'), 3.75 (dd, 1H, $J_{6'a-5'}$=2.8 Hz, $J_{6'a-6'b}$=10.4 Hz, H-6'a), 3.65 (m, 2H, H-5', H-6'b); HRMS (FAB) calcd. for $C_{45}H_{43}N_3O_7$ 738.3187; found 738.3244; **β-anomer** ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.67 (1H, NH), 8.20 (d, 1 H, H-6), 7.96 (d, 2H, benzoyl), 7.51-7.64 (m, 3H, benzoyl), 7.12-7.36 (m, 16H, benzyl, H-5), 5.92 (d, 1H, H-1'), 4.45-4.93 (m, 8H, 4xCH_2-Ph), 3.92 (t, 1H, J=9 Hz, H-4'), 3.80 (t, 1H, J=10 Hz, H-3'), 3.74 (m, 1H, H-2'), 3.53-3.70 (m, 3H, H-6'a, H-5', H-6'b); HRMS (M+H), calcd. for $C_{45}H_{43}N_3O_7$, 738.3187; found 738.3244.

9-(2',3'4'-Tri-O-benzyl-β-L-fucopyranosyl)-N-benzoyladenine .

(Method B). To a solution of 2-(2',3',4'-tri-O-benzyl-β-L-fucopyranosyl)-thiopyridylcarbonate (44 mg, 0.07 mmol) in DMF (1.5 mL) were added N-benzoyladenine (74 mg, 4 eq) and bromine (16 mL, 4 eq). The solution was stirred under argon for 12 h, then quenched with sat. $NaHCO_3$. After extraction of the aqueous phase with CH_2Cl_2 and washing with brine, the solution was dried over anh. Na_2SO_4, filtered and concentrated under vacuum to give a residue which was purified by flash chromatography (hexanes-EtOAc, 2:1) yielding 43 mg (80%) of the

expected product; $[\alpha]_D$ -8.7° (c 1.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.75 (s, 1H, H-8), 8.30 (d, 2H, H-2), 8.06 (d, 2H, benzoyl), 7.52-7.61 (m, 3H, benzoyl), 6.95-7.40 (m, 15H, benzyl), 6.40 (d, 1H, J=3.3 Hz, H-1'), 4.62-4.76 (m, 4H, 2xCH_2-Ph), 4.15-4.40 (m, 4H, CH_2-Ph, H-3', H-2'), 4.06 (m, 1H, H-5'), 4.0 (t, 1H, J=3.7 Hz, H-4'); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ (ppm) 164.3 (C=O), 151.7, 150.8, 148.6, 142.6, 137.5, 136, 133.1, 132.2, 129.2, 127.5, 121.6, 76.68 (C-1'), 75.01, 74.60, 73.61, 72.97, 72.75, 72.32, 71.10, 14.13 (CH_3); HRMS (FAB) calcd. for $C_{39}H_{40}N_2O_7$ 649.2913; found 649.2894.

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