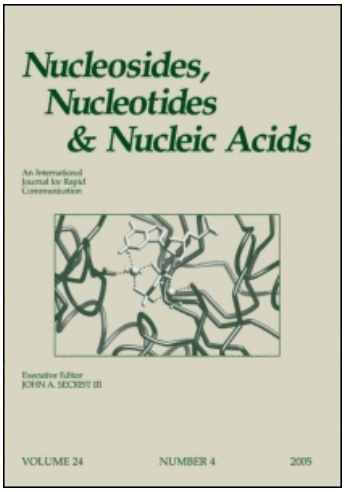


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# Stereoselective Synthesis and X-Ray Structure of 1-(4-O-Benzyl-1,5-anhydro-2,3-dideoxy-D-arabino-hex-1-enitol-3-yl)-4-methoxy-1H-pyrimidin-2-one

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NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, 19(3), 629–635 (2000)

# STEREOSELECTIVE SYNTHESIS AND X-RAY STRUCTURE OF 1-(4-*O*-BENZYL-1,5-ANHYDRO-2,3-DIDEOXY-D-*arabino*-HEX-1-ENITOL-3-YL)-4-METHOXY-1*H*-PYRIMIDIN-2-ONE

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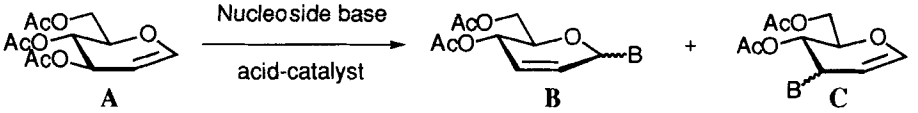
**ABSTRACT**: The intramolecular glycosylation of a 6-*O*-(4-methoxypyrimidin-2-yl) derivative of phenyl 2,3-didehydrohex-2-eno-1-thiopyranoside afforded 3-deoxy-3-(4-methoxypyrimidin-2-on-1-yl)glycal as the major product in a stereoselective manner. The isolated 3'-deoxyglycal nucleoside was characterized by X-ray and NMR spectral analyses.



The acid-catalyzed reaction of pyranosyl glycals (**A**) with nucleoside bases generally provides 2',3'-unsaturated pyranosyl nucleosides (**B**) (Ferrier rearrangement products) as major products,[1-6] which are often accompanied by small amounts of 3-deoxyglycals (**C**) with the bases attached at C-3. These side-products, however, are of interest due to their potent biological properties as well as their usefulness as synthetic intermediates for other nucleoside analogs.[7] Although a few reports have described for the preparation of the 3'-deoxyglycal purine nucleosides,[2,7] the results are unsatisfactory in both the chemical yields and the selectivity regarding stereochemistry at the 3' position. Therefore, an efficient and stereocontrolled method for the preparation of 3'-deoxyglycal nucleosides is still desirable.




A B C

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As part of our study on the stereoselective synthesis of various nucleoside derivatives employing an intramolecular glycosylation approach,[8] we have explored the reaction using 2,3-unsaturated pentofuranoside as a substrate and found that the 1',2'-unsaturated 3'-deoxypentofuranosyl nucleoside is produced with complete stereoselectivity.[9] We now report that the 3'-deoxypyranosylglycal nucleoside can be formed in a stereoselective manner *via* this intramolecular glycosylation and characterized by X-ray and NMR spectral analyses.

## RESULTS AND DISCUSSION

The substrate **1**, required for the intramolecular glycosylation, was prepared by the usual protection-deprotection sequence, followed by introduction of a pyrimidine derivative[10] (*t*-$BuPh_2SiCl$, DMAP, Pyr; NaH, BnBr, DMF; $Bu_4NF$, THF; NaH, 2-chloro-4-methoxypyrimidine, DMF), starting with the known phenyl 2,3-dideoxy-1-thio-D-*erythro*-2-enopyranoside[11] derived from tri-*O*-acetyl-D-glucal.

Treatment of **1** with 1.1 equimolar amounts of $Me_2S(SMe)BF_4$ in MeCN under our standard glycosylating conditions[8] (–20 °C for 4 h), followed by hydrolysis with an aqueous solution of NaOH (0 °C, 1 h), gave three major products — 2',3'-unsaturated nucleoside **2**, C-1 hydrolyzed product **3**, and 3'-deoxyglycal nucleoside **4** in 13%, 29% and 41% yields, respectively (run 1 in Table 1). When the same reaction was carried out at higher temperature (0 °C for 5 h), improvement in the yield of **4** was observed (run 2). However, prolonging the reaction time at this temperature did not lead to any changes in the products' ratio, but lowered the total yields due to slight decomposition of the cationic intermediates in the reaction mixture.

Based on these findings, it is proposed that the formation of these products occurred *via* the mechanism outlined in Scheme 1. Compound **2** resulted from attack of the hydroxide at C-6 of the intermediate **6**. Similarly, compound **3** could be formed by direct hydrolysis of **5** and/or the attack of the hydroxide at C-1 of **6**. In contrast, compound **4** would be produced *via* bond-cleavage at C-6 of the intermediate **7**. Since the intermediate **6** is the unstable α-oxo allylic pyridinium ion, it might be gradually converted into the more stable intermediate **7** through an equilibrium with the α-oxo allylic cation **5**. Hence, under thermodynamically controlled conditions, intermediate **7** is considered to exist as a major component in the reaction mixture, affording a good yield of the 3'-deoxyglycal nucleoside **4** after the basic hydrolysis.

The β-configuration of the 2',3'-unsaturated nucleoside **2** was assigned by the $^1H$ NMR chemical shifts analogous to similar unsaturated nucleosides.[6] The structure and stereochemistry of compound **4** were unequivocally determined by X-ray crystallography. Figure 1 shows the molecular structure and the atomic numbering

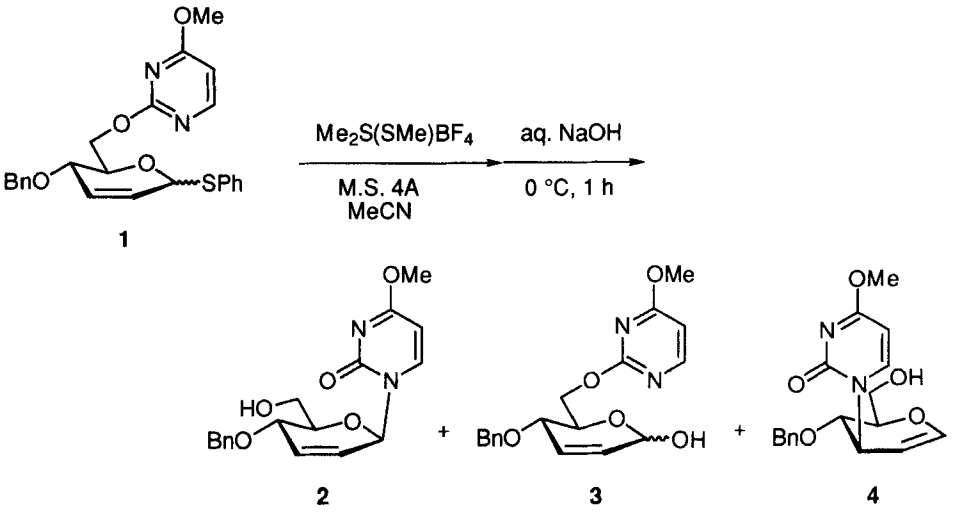
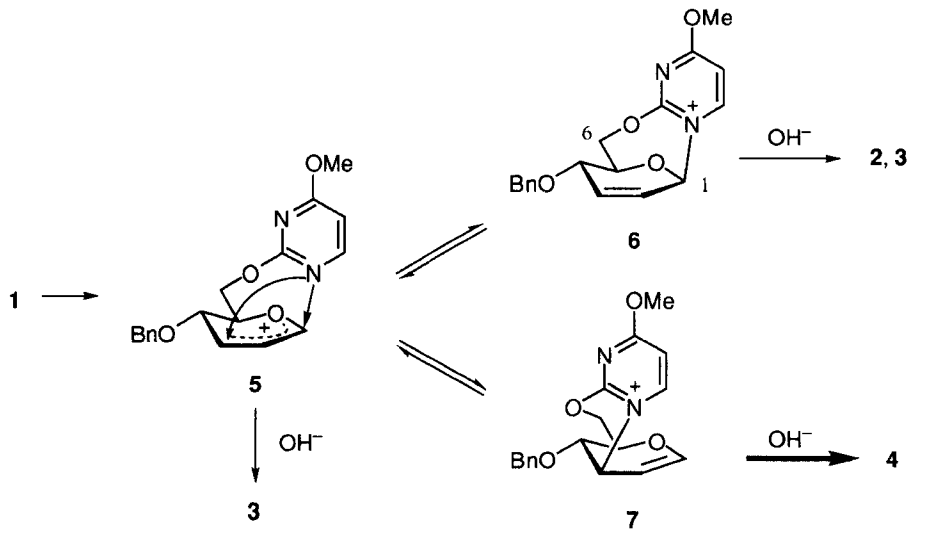



**TABLE 1**

| Run | Conditions for activation | | Isolated yields/% | | |
|---|---|---|---|---|---|
| | Temp./°C | Time/h | **2** | **3** | **4** |
| 1 | −20 | 4 | 13 | 29 | 41 |
| 2 | 0 | 5 | 10 | 10 | 73 |
| 3 | 0 | 16 | 8 | 8 | 59 |






**SCHEME 1**

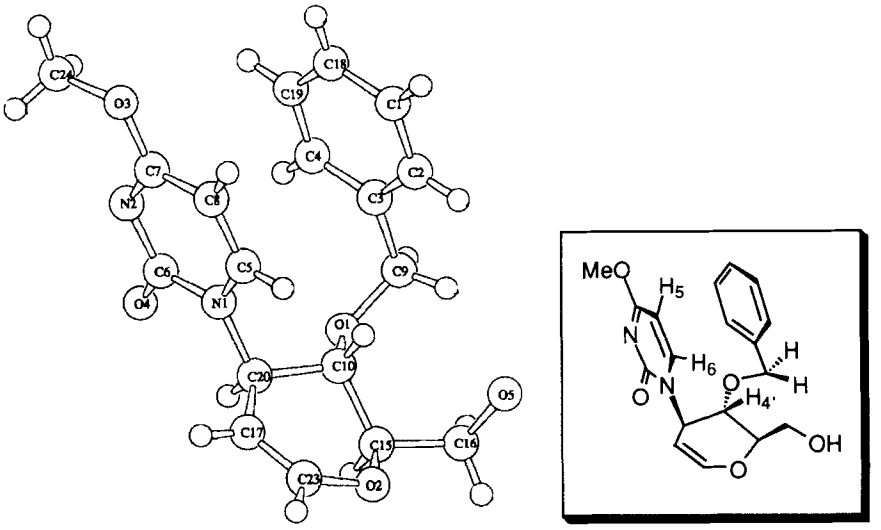



**FIG 1.** ORTEP drawing of **4** showing crystallographic numbering scheme.

**TABLE 2.** Crystal data for **4**.

| | |
|---|---|
| Empirical Formula | $C_{18}H_{20}O_5N_2$ |
| Formula Weight | 344.37 |
| Crystal Dimensions | 0.15 × 0.20 × 0.45 mm |
| Crystal System | triclinic |
| No. of Reflections Used for Unit Cell Determination ($2\theta$ range) | 25 ( 33.5-38.4° ) |
| Omega Scan Peak Width at Half-height | 0.40° |
| Lattice Parameters | a = 7.518(1) Å<br>b = 9.7057(8) Å<br>c = 6.5460(8) Å<br>α = 101.556(8)°<br>β = 111.624(10)°<br>γ = 100.296(9)°<br>V = 417.96(10) Å$^3$ |
| Space Group | P1 (#1) |
| Z value | 1 |
| $D_{calc}$ | 1.368 g/cm$^3$ |
| $F_{000}$ | 182.00 |
| μ(MoKα) | 1.01 cm$^{-1}$ |

**TABLE 3.** Bond lengths (Å) and angles (°) for **4**.

| | | | | | |
|---|---|---|---|---|---|
| O(1)-C(9) | 1.442(4) | O(2)-C(15) | 1.440(4) | O(3)-C(7) | 1.341(3) |
| O(4)-C(6) | 1.236(3) | N(1)-C(5) | 1.364(3) | N(1)-C(20) | 1.484(3) |
| N(2)-C(7) | 1.301(3) | C(1)-C(18) | 1.363(6) | C(2)-C(3) | 1.382(4) |
| C(3)-C(4) | 1.378(4) | C(4)-C(19) | 1.370(5) | C(5)-C(8) | 1.339(4) |
| C(7)-C(8) | 1.413(4) | C(10)-C(15) | 1.527(3) | C(17)-C(23) | 1.311(5) |
| C(18)-C(19) | 1.359(6) | O(1)-C(10) | 1.421(3) | O(2)-C(23) | 1.355(4) |
| O(3)-C(24) | 1.444(4) | O(5)-C(16) | 1.411(4) | N(1)-C(6) | 1.396(3) |
| N(2)-C(6) | 1.368(3) | C(1)-C(2) | 1.385(5) | C(3)-C(9) | 1.502(4) |
| C(10)-C(20) | 1.523(4) | C(15)-C(16) | 1.500(4) | C(17)-C(20) | 1.498(4) |

| | | | |
|---|---|---|---|
| C(9)-O(1)-C(10) | 114.8(2) | C(7)-O(3)-C(24) | 117.4(2) |
| C(5)-N(1)-C(20) | 118.8(2) | C(6)-N(2)-C(7) | 118.9(2) |
| C(1)-C(2)-C(3) | 120.4(3) | C(2)-C(3)-C(9) | 121.4(3) |
| C(3)-C(4)-C(19) | 120.9(3) | O(4)-C(6)-N(1) | 120.1(2) |
| N(1)-C(6)-N(2) | 118.4(2) | O(3)-C(7)-C(8) | 115.5(2) |
| C(5)-C(8)-C(7) | 116.1(2) | O(1)-C(10)-C(20) | 108.7(2) |
| C(15)-C(10)-C(20) | 108.9(2) | O(2)-C(15)-C(16) | 105.0(2) |
| C(10)-C(15)-C(16) | 114.6(3) | C(15)-O(2)-C(23) | 115.0(2) |
| C(5)-N(1)-C(6) | 120.9(2) | C(6)-N(1)-C(20) | 120.3(2) |
| C(2)-C(1)-C(18) | 120.4(4) | C(2)-C(3)-C(4) | 118.0(3) |
| C(4)-C(3)-C(9) | 120.5(3) | N(1)-C(5)-C(8) | 120.9(3) |
| O(4)-C(6)-N(2) | 121.4(2) | O(3)-C(7)-N(2) | 119.7(2) |
| N(2)-C(7)-C(8) | 124.8(2) | O(1)-C(9)-C(3) | 113.0(2) |
| O(1)-C(10)-C(15) | 108.8(2) | O(2)-C(15)-C(10) | 111.1(2) |
| C(1)-C(18)-C(19) | 119.5(4) | N(1)-C(20)-C(10) | 111.2(2) |
| O(2)-C(23)-C(17) | 126.1(3) | O(5)-C(16)-C(15) | 114.0(2) |
| C(20)-C(17)-C(23) | 121.7(3) | C(4)-C(19)-C(18) | 120.7(4) |
| N(1) -C(20)-C(17) | 110.4(2) | C(10)-C(20)-C(17) | 109.7(2) |



scheme. The crystal data are listed in Table 2. The list of bond distances and angles is given in Table 3. The ORTEP drawing revealed that the presence of the π stacking interaction between the pyrimidinone ring and the benzene ring of the 3-*O*-benzyl protecting group, despite the 1,2-*trans* relationship of these two substituents on the pyranose ring. This unexpected stacking interaction was observed not only in the solid state but in a solution of $CDCl_3$. The $^1H$ NMR spectrum of compound **4** showed the large upfield shifts of the protons at positions 5 and 6 on the pyrimidinone ring (i.e., 0.3 ppm and 0.5 ppm upfield shifts of the H-5 and H-6 signals compared to the corresponding protons of compound **2**; see the experimental section), indicating the shielding effect of the benzene ring. NOE experiments provided further evidence for the stacking structure in the solution. For instance, NOE enhancements were observed between the H-4' and H-6 protons and also between H-4' and one of the benzylic protons.

In conclusion, the 3'-deoxyglycal nucleoside derivative **4** was prepared in a good yield with complete stereoselectivity in favor of the β-form *via* the intramolecular glycosylation method. The stereochemistry of the newly formed carbon center as well as unexpected stacking conformation was disclosed by X-ray and NMR spectral analyses.

## EXPERIMENTAL

All melting points are uncorrected. The $^1H$ and $^{13}C$ NMR spectra were obtained using a JEOL JNM-EX400 spectrometer in $CDCl_3$ with $Me_4Si$ as the internal standard. The IR spectrum was recorded using a Perkin-Elmer Spectrum BX spectrophotometer. TLC was performed on plates coated with silica gel 60 $F_{254}$ (Merck). For column chromatography, Wakogel C-300 (Wako Chemicals) was used. X-Ray measurements were made on a Rigaku AFC7R diffractometer with graphite monochromated Mo-Kα radiation and a 12kW rotating anode generator. The structure was solved by direct method (SIR88) and expanded using Fourier techniques (DIRDIF92).



**General Procedure for Intramolecular Glycosylation** To a solution of **1** (0.2 mmol) in MeCN (50 mL) under Ar, powdered molecular sieves 4A (1 g) were added. After 30 min, the solution was cooled to –20 °C, and $Me_2S(SMe)BF_4$ (0.22 mmol) was then added. After 5 h, aqueous NaOH (1M, 30 mL) was added to the reaction mixture, and the mixture was warmed to 0 °C for over 1 h. After saturated aqueous $NH_4Cl$ was added, the solution was stirred at room temperature for 30 min, then filtered through Celite and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by a silica gel TLC plate with hexane:AcOEt (1:2). The elution of the fastest band afforded **4-*O*-benzyl-2,3-dehydro-2,3-dideoxy-6-O-(4-methoxypyrimidin-2-yl)-α,β-D-*erythro*-hexopyranose (3)** as a syrup; $^1H$ NMR δ: 1.79 (br, 1H), 3.93 & 3.97 (s×2, 3H), 4.06–4.35 (m, 2H), 4.46–4.73 (m, 4H), 5.43–5.52 (m, 1H), 5.83–5.95 (m, 1H), 6.05–6.18 (m, 1H), 6.34–6.40 (m, 1H), 7.22–7.40 (m, 5H), 8.14–8.23 (m, 1H). The second band gave **1-(4-*O*-benzyl-2,3-dehydro-2,3-dideoxy-β-D-*erythro*-hexopyranosyl)-4-methoxy-1*H*-pyrimidin-2-one (2)** as a syrup; $^1H$ NMR δ: 3.74–3.93 (m, 3H), 3.97 (s, 3H), 4.13–4.23 (m, 1H), 4.60 (d, *J*=11.6 Hz, 1H), 4.70 (d, *J*=11.6 Hz, 1H), 5.72 (d, *J*=10.2 Hz, 1H), 5.91 (d, *J*=7.3 Hz, 1H, *H-5*), 6.31 (d, *J*=10.2 Hz, 1H), 6.70 (s, 1H), 7.36 (s, 5H), 7.42 (d, *J*=7.3 Hz, 1H, *H-6*). The slowest band gave **1-(4-*O*-benzyl-1,5-anhydro-2,3-dideoxy-D-*arabino*-hex-1-enitol-3-yl)-4-methoxy-1*H*-pyrimidin-2-one (4)**, which was crystallized from AcOEt as colorless needles; mp 172.0–173.0 °C; $[\alpha]_D^{25}$ +73.1° (*c* 0.674, $CHCl_3$); $^1H$ NMR δ: 2.45 (br, 1H), 3.85 (t, *J*=9 Hz, 1H), 3.90-4.05 (m, 2H), 3.96 (s, 3H), 4.46 (d, *J*=11.7 Hz, 1H), 4.49 (dd, *J*=2.0, 5.9 Hz, 1H), 4.63 (d, *J*=11.7 Hz, 1H), 5.62 (d, *J*=7.3 Hz,

1H, *H-5*), 5.66 (d, *J*=7.8 Hz, 1H), 6.54 (dd, *J*=2.0, 5.9 Hz, 1H), 7.14 (d, *J*=7.3 Hz, 1H, *H-6*), 7.22 (s, 5H); $^{13}$C NMR δ: 54.3, 55.8, 60.7, 72.3, 73.1, 79.0, 96.1, 100.4, 127.9, 128.4, 128.5, 128.7, 136.9, 142.8, 147.0, 156.7, 170.9; IR (KBr) 3430, 1657, 1651, 1634, 1545, 1482, 1363, 1312, 1203, 1097, 1059 cm$^{-1}$; .Anal. Calcd for $C_{18}H_{20}N_2O_5$: C, 62.78; H, 5.85; N, 8.13. Found: C, 62.60; H, 5.91; N, 8.06.

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