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Nucleosides and Nucleotides

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Intramolecular Glycosylation to Form 4-Methoxy-2,6-Dioxopyrimidine

Nucleosides via O^6 , 5'-Cyclonucleosides

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INTRAMOLECULAR GLYCOSYLATION TO FORM 4-METHOXY-2,6-DIOXOPYRIMIDINE NUCLEOSIDES VIA 0⁶,5'-CYCLONUCLEOSIDES

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ABSTRACT: Lewis-acid promoted intramolecular N1 glycosylation to form the novel O^6 ,5'-cyclonucleoside **1a** occurs in high yield from the corresponding acyclic thiophenylglycoside **12**. The relative stability of the O^6 ,5' tether compared with O^2 ,5' and O^2 ,3' tethers is reported. Cleavage of the anhydro bond was effected with aqueous base to yield the 4-methoxybarbituric acid nucleoside analogue **14**.

One of the major problems in the synthesis of modified nucleosides is the coupling of the purine or pyrimidine base to the modified sugar to give the desired β -anomer of This is especially true for 2'-deoxy analogues where the normal the nucleoside. anchimeric directing effect of the 2'- α -acyloxy group is absent. Recently, we¹ and others² have reported the use of intramolecular N-glycosylation reactions to synthesize important modified β -nucleosides. This approach, using an oxygen tether to deliver the base to the anomeric center, has yielded several biologically active ß-nucleosides,^{2b,2d} all limited however to the 2,4-dioxopyrimidine derivatives.³ We now report the application of this methodology to the synthesis of 2'-deoxy-4-methoxy-3'-O-methyl-O⁶,5'-Cyclonucleosides like 1 are potentially versatile cyclouridine (1) (Scheme 1). compounds since they might be useful precursors for not only the traditional 2,4dioxopyrimidine β -nucleosides 2, but also the novel 6-hydroxyuridines 3.⁴ Moreover, displacement of the pyrimidyl methoxy group in 1 by hydroxide or ammonia would permit access to anti-restricted nucleosides, namely 3'-O-alkyl-2'-deoxy-4-hydroxy- O^{6} ,5'-cyclouridine (4) and its cytidine analogue 5, which are useful conformational probes.4,5

2415



Scheme 1

As shown in Scheme 2, our initial O^{6} ,5'-bridged cyclization precursor 8, easily prepared from commercially available 6-chloro-2,4-dimethoxypyrimidine (7) and the methyl ribosides 6,⁶ did not produce the desired cyclonucleoside 1a upon treatment with several Lewis acids (TMSOTf, TBSOTf, SnCl₄, TiCl₄, Et₂AlCl). Prolonged exposure to these reagents either hydrolyzed the methyl acetal of 8 or decomposed the starting material by cleaving the O^{6} ,5'-tether to yield the free base and the carbohydrate. However, treatment of 8 with boron trichloride yielded the unexpected adduct 9 in 40% yield (80% based on recovered starting material).⁶ As we reported previously, the formation of 9 is reasonable based on intramolecular glycosylation occurring after pyrimidyl base transfer from C5 to O3.⁶

In order to circumvent the formation of this novel anhydro adduct, other modes of activating the anomeric center to nucleophilic attack by N1 of the pyrimidine base were considered. Since thiophenyl glycosides have been used extensively in glycosylation reactions, we hoped to convert **8** into its corresponding thioglycoside using trimethylsilyl triflate (TMSOTf) and trimethyl(thiophenyl)silane (TMSSPh).⁷ This approach would require fewer steps than the alternative of initial preparation of the



Scheme 2

thiophenyl glycoside and its subsequent coupling with the chloropyrimidine 7. Of concern, however, was that the conditions used to install the thiophenyl group might cleave the tether, since previous work in our laboratories had shown that systems with an O^2 ,5' linkage are very sensitive to nuc-leophilic attack.⁸ For example, compound 10 was rapidly converted to the corresponding 5-deoxy-5-phenylthioriboside 11 and free uracil upon exposure to TMSSPh and TMSOTf (Scheme 3).

Fortunately, the O^{6} ,5' tether proved to be more stable than the O^{2} ,5' linkage, and an anomeric mixture of thiophenyl glycoside 12 was prepared from 8 in good yield (Scheme 3). It would appear that the greater stability of this type of linkage makes compounds such as 8 easier to manipulate than the corresponding O^{2} ,5' systems. However, if the aqueous basic work-up step is omitted in the formation of 12, only the thioketal 13 is isolated. This is unexpected since bis(thiophenyl) acetals of carbohydrates are rare, although the corresponding bis(thioalkyl) compounds are common.⁹

The critical cyclization step (Scheme 4) was successfully accomplished using dimethyl(methylthio)sulfonium tetrafluoroborate as the activating agent, the Lewis acid used extensively by Sugimura's group in their intramolecular glycosylation reactions.^{2a,b} The cyclized adduct **1a** formed in good yield with dichloromethane as the solvent; the only other product isolated (10-15%) was starting material hydrolyzed at the anomeric center. This cyclization reaction proved to be very sensitive to the solvent used. In



Scheme 3

acetonitrile, only trace amounts of the desired product were identified by TLC, a result which differs from those of the Sugimura group since in their systems cyclization was much more effective in acetonitrile. In addition, Sugimura has suggested that the amount of hydrolyzed starting material recovered is minimized when a 3'-substituent is present.^{2b} The appearance of hydrolyzed adduct in our case seems to suggest that the role of the 3'-substituent is not as significant as the role of the solvent. To return to the synthesis of the nucleosides, removal of the pyrimidyl methoxy group was accomplished with aqueous base under rather vigorous conditions (1M sodium hydroxide in refluxing acetonitrile)¹⁰ to give the desired O⁶,5'-cyclouridine **4a** in 60-64% yield along with the 2'-deoxy-4-methoxy-2,6-dioxopyrimidine **14** in 30-34% yield.





That N1 cyclization had occurred was evident from the large downfield shift of H1' from the acyclic precursor 12 (5.6-5.8 ppm, α or β anomer) to the cyclic product 1 (7.1 ppm). Moreover, the two H5' protons showed the characteristic shifts and splitting pattern typical of O⁶,5'-cyclopyrimidine nucleosides (two doublets of doublets with one large and one small coupling constant: J = 12.5 and 1 Hz at δ 4.43 and J = 12.5 and 1.2 Hz at δ 3.97 ppm).¹¹ Finally, the high resolution mass spectrometry for both 1a and 4a showed a cleavage pattern similar to those reported for other O⁶,5'-cyclonucleosides.¹² The isolation and characterization of 1a is especially noteworthy because it represents the first synthesis of an anhydronucleoside *via* this route in high yield. While the Lipshutz group has studied O⁶,5'-tethers to a 5,6-dihydro-5-bromopyrimidine, ring closures have been problematic with yields less than 50%.^{2c} Reports using O²,3' or O²,5' tethers to deliver the aglycone propose the existence of a cycloadduct based on the isolation of the β -nucleoside after aqueous work-up.^{2a,b,d} In our earlier work, the anhydro adduct was isolated but only in modest yield (<20%).¹

In conclusion, O^6 ,5'-cyclonucleosides and β -barbituric acid nucleosides should be readily accessible using the intramolecular glycosylation approach. We have shown that this method can be used to synthesize both the 2'-deoxy- O^6 ,5'-cyclouridines 1a and 4a and 2'-deoxy-4-methoxy-2,6-dioxopyrimidine nucleoside 14. Furthermore, we believe that the greater stability of the O^{6} ,5' tether makes these sugar-base hybrid compounds much more useful than systems having an O^{2} ,5' bridge.

Experimental

General: ¹H (at 400MHz) and ¹³C NMR (at 100 MHz) were recorded on a Bruker DPX-400 spectrometer (δ in ppm, *J* in Hz). Infrared spectra were obtained using a 6020 Galaxy FT-IR or MIDAC Corporation Prospect-IR spectrometer. High resolution mass spectra were obtained from the Mass Spectrometry Facility at the University of California, San Francisco. Samples were analyzed by electron impact (EI) using a VG 7OSE mass spectrometer. Melting points were obtained using a Mel-Temp apparatus and are uncorrected. TLC was carried out on Baker Si250F TLC precoated glass plate silica gel, 0.25mm layer thickness. Acetonitrile and dichloromethane were distilled over calcium hydride. Tetrahydrofuran (THF) was distilled from Na/benzophenone ketyl prior to use. Other solvents were used without further purification. Flash column chromatography with silica gel was carried out according to the method of Still.¹³ All reactions were carried out under an inert nitrogen or argon atmosphere.

Phenyl 2-deoxy-5-O-(2,6-dimethoxypyrimidin-4-yl)-3-O-methyl-1-thio-α,β-Derythro-pentofuranoside (12). (Phenylthio)trimethylsilane (0.39 mL, 2.1 mmol) and trimethylsilyl trifluoromethanesulfonate (TMSOTf, 0.32 mL, 1.6 mmol) were added slowly via syringe to a solution of 8 (0.41 g, 1.4 mmol) in dichloromethane (60 mL) at 0° C. After stirring for 5 h, the reaction mixture washed twice with saturated NaHCO3 solution and once with saturated NaCl solution. The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The resulting residue was purified by flash chromatography (2:1 hexane/EtOAc) to yield an anomeric mixture of 12 (0.34 g, 82%) as an oil; Rf 0.6 (2:1 hexane/EtOAc). ¹H NMR (CDCl₃): δ 7.51 (m, 2H, H-Ph), 7.27 (m, 3H, H-Ph), 5.76 (s, 0.55 H, 5-H), 5.75 (s, 0.45 H, 5-H). 5.74 (m, 0.55H, 1'-H), 5.61 (dd, J =8.1, 6.2, 0.45 H, 1'-H), 4.53-4.36 (m, 4 H, 3'-H, 4'-H, 2 x 5'-H), 3.97 (s, 3 H, OCH₃), 3.94 (s, 3 H, OCH₃), 3.39 (s, 1.6 H, OCH₃), 3.33 (s, 1.4 H, OCH₃), 2.69 (ddd, J = 13.8, 7.4, 7.4, 0.55 H, 2'-H), 2.45 (ddd, J = 13.8, 6.2, 2.7, 0.45 H, 2'-H), 2.17 (m, 1 H, 2'-H). ¹³C NMR (CDCl₃): δ 172.77, 171.94, 171.79, 164.66, 135.76, 134.10, 131.62, 130.76, 128.72, 127.17, 126.78, 87.15, 85.94, 83.73, 82.80, 82.07, 80.95, 80.88, 66.56, 65.89, 58.21, 57.46, 54.61, 53.98, 38.59, 37.82 (several lines unresolved). IR (neat): 3055, 2988, 2939, 2901, 1598, 1465, 1396, 1267, 1204, 1170, 1106, 1059 cm⁻¹. HRMS: calcd for C₁₈H₂₃N₂O₅S (MH⁺) 379.1328, found 379.1329,

2-Deoxy-5-O-(2,6-dimethoxypyrimidin-4-yl)-3-O-methyl-D-erythro-pentose diphenyl dithioacetal (13). The same procedure described above for the preparation of 12 was used to prepare the thioacetal 13 with one variation, namely, the aqueous workup steps were omitted. Instead, the reaction mixture was concentrated *in vacuo* and purified *via* flash chromatography (2:1 hexane:EtOAc) to yield a pale yellow syrup (87%); R_f 0.5 (2:1 hexane/EtOAc). ¹H NMR (CDCl₃): δ 7.49 (m, 4H, H-Ph), 7.23 (m, 6H, H-Ph), 5.76 (s, 1H, 5-H), 4.72 (dd, J = 9.7, 4.6, 1H, 1'-H), 4.37 (dd, J = 11.4, 4.0, 1H, 5'-H), 4.33 (dd, J = 11.4, 6.2, 1H, 5'-H), 4.07 (ddd, J = 6.2, 4.5, 4.0, 1H, 4'-H), 3.96 (s, 3H, OCH₃), 3.95 (s, 3H, OCH₃), 3.77 (ddd, J = 8.6, 4.6, 4.6, 1H, 3'-H), 3.40 (s, 3H, OCH₃), 3.10 (br s, 1H, OH), 2.27 (ddd, J = 13.6, 9.1, 4.6, 1H, 2'-H), 1.99 (ddd, J = 13.6, 9.7, 3.4, 1H, 2'-H). ¹³C NMR (CDCl₃): δ 173.36, 172.43, 165.13, 135.18, 134.03, 133.36, 132.80, 129.35, 129.32, 128.24, 128.03, 84.33, 79.21, 71.22, 68.33, 58.73, 55.19, 54.81, 54.57, 37.19. IR (neat): 3421, 2947, 1594, 1461, 1363, 1169, 1108 cm⁻¹. HRMS: calcd for C₂₄H₂₈N₂O₅S₂ 488.1440, found 488.1442.

3,4,5,6-Tetrahydro-4,10-dimethoxy-3,6-epoxy-2H,8H-pyrimido[6,1-b][1,3]oxazocin-8-one (1a). A solution of the thiosugar 12 (0.12 g, 0.31 mmol) in dichloromethane (70 mL) was added to activated molecular sieves (4Å, 5 g) at 25 °C. The reaction mixture was cooled to -20 °C and stirred for 20 min, after which dimethyl-(methylthio)sulfonium tetrafluoroborate (0.075 g, 0.38 mmol) was introduced. After further stirring for 1 h and 40 min, the reaction was guenched with 1M NaOH (4 mL). The organic layer was washed with saturated NaHCO₃, saturated NaCl, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash chromatography (2:1 hexane/EtOAc-EtOAc, gradient elution). 1a was isolated as a white solid (0.057 g, 70%); Rf 0.5 (EtOAc), mp 142-143 °C. ¹H NMR (CDCl₃): δ 7.08 (dd, J = 8.4, 1.8,1H, 1'-H), 5.46 (s, 1H, 5-H), 4.44 (s, 1H, 4'-H), 4.43 (dd, J = 12.5, 1, 1H, 5'-H), 4.16 $(dd, J = 6.8, 0.7, 1H, 3'-H), 3.97 (dd, J = 12.5, 1.2, 1H, 5'-H), 3.86 (s, 3H, 4-OCH_3),$ 3.28 (s, 3H, 3'-OCH₃), 2.46 (dd, J = 14.7, 8.4, 1H, 2'-H), 2.26 (ddd, J = 14.7, 6.8, 1.8, 1H, 2'-H). ¹³C NMR (CDCl₃): δ 172.56, 163.83, 155.97, 85.58, 85.15 (2C), 82.39, 77.52, 56.46, 54.47, 39.51. IR: 2953, 1674, 1622, 1537, 1387, 1194, 1182, 1135 cm⁻¹. HRMS: calcd for C₁₁H₁₄N₂O₅ 254.0902, found 254.0897.

3,4,5,6-Tetrahydro-4-methoxy-3,6-epoxy-2H,8H-pyrimido[6,1-*b*][1,3]oxazocin-8,10(9H)-dione (4a) and 2'-deoxy-4-methoxy-3-O-methyl-2,6-dioxouridine (14). To a solution of 1a (0.015 g, 0.059 mmol) in acetonitrile (2 mL) at 25 °C was added 1M NaOH (0.35 mL). After refluxing for 72 h, the solution was subjected to flash chromatography (ethyl acetate) to yield both 4a (0.009 g, 64%, mp 180-185 °C) and 14 (0.005 g, 32%, mp 110-114 °C) as white solids . Compound 4a: ¹H NMR (CDCl₃): δ 8.20 (br s, 1H, NH), 6.94 (dd, J = 8.4, 2, 1H, 1'-H), 5.40 (s, 1H, 5-H), 4.52 (app s, 1H, 4'-H), 4.50 (dd, J = 13.2, 1.4, 1H, 5'-H), 4.24 (dd, J = 6.6, 1, 1H, 3'-H), 4.05 (dd, J = 13.2, 1.6, 1H, 5'-H), 3.37 (s, 3H, OCH₃), 2.55 (ddd, J = 14.9, 8.4, 1, 1H, 2'-H), 2.41 (ddd, J = 14.9, 6.7, 2, 1H, 2'-H). ¹³C NMR (CDCl₃): δ 162.09, 149.47, 149.40, 90.78, 84.68, 82.44, 82.38, 77.92, 56.58, 39.46. IR: 3185, 3071, 2944, 2827, 1728, 1682, 1624, 1537, 1461, 1387, 1183, 1088 cm⁻¹. HRMS: calcd for C₁₀H₁₂N₂O₅ 240.0746, found 240.0745. Compound 14: ¹H NMR (acetone-d₆): δ 6.64 (dd, J = 8.2, 7.2, 1H, 1'-H), 6.11 (br s, 1H, NH), 5.09 (s, 1H, 5-H), 4.14 (ddd, J = 6.6, 2.6, 2.6, 1H, 3'-H), 3.98 (app q, J = 2.9, 1H, 4'-H), 3.93 (s, 3H, 4-OCH₃), 3.73 (dd, J = 11.9, 3, 1H, 5'-H), 3.59 (dd, J = 11.9, 3, 1H, 5'-H), 3.33 (s, 3H, 3'-OCH₃), 2.87 (br s, 1H, OH), 2.85 (ddd, J = 13.1, 8.3, 6.7, 1H, 2'-H), 2.10 (m, 1H, 2'-H). ¹³C NMR (CDCl₃): δ 164.37, 162.40, 150.75, 85.86, 82.77, 82.49, 77.52, 63.47, 56.72, 56.35, 33.91. IR (KBr): 3469, 3118, 2947, 2865, 1728, 1634, 1520, 1429, 1250, 1097, 1066 cm⁻¹.

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