C-NUCLEOSIDES. 21.[1] SYNTHESIS OF ISOXAZOLE C-NUCLEOSIDE FROM FURANONE GLYCOSIDE VIA ENAMINONE GLYCOSIDE

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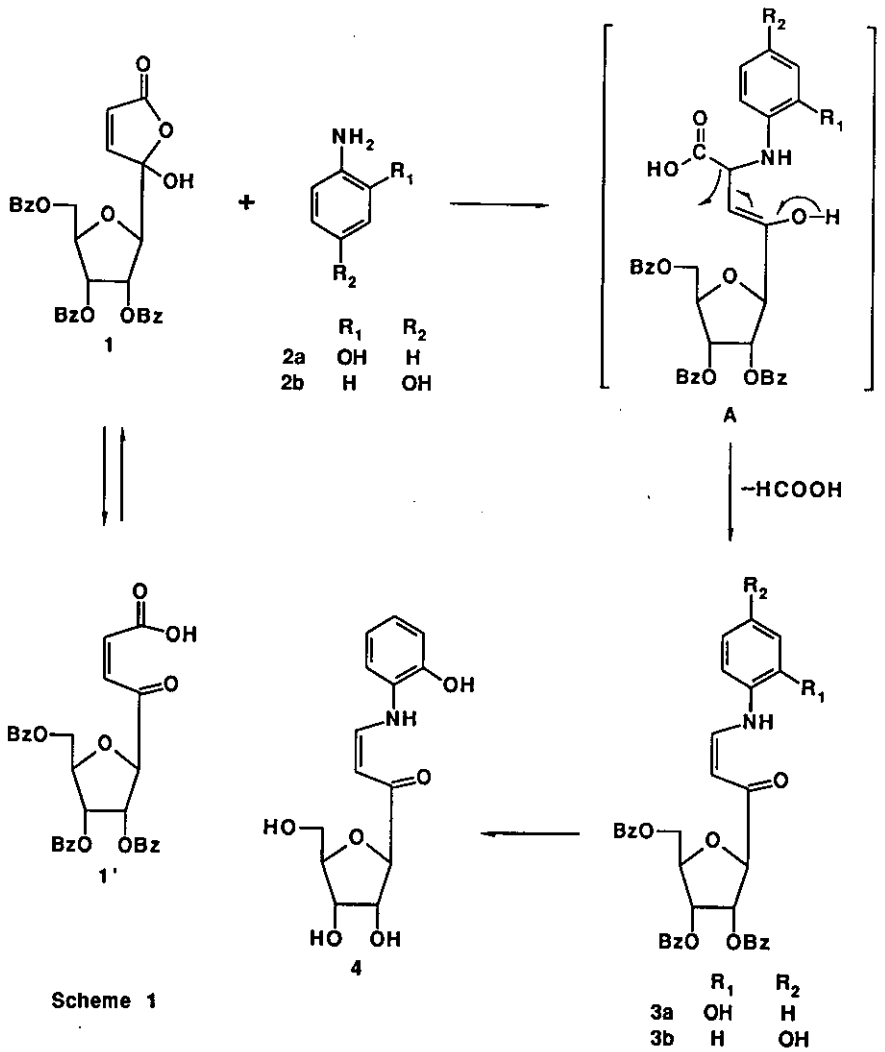
Abstract ---- Synthesis of the versatile and stable C-nucleoside precursor enaminone glycosides (**3a,b**) was achieved by reaction of furanone glycoside (**1**) with 2- and 4-aminophenols. Treatment of enaminone (**3b**) with hydroxylamine hydrochloride yielded 5-hydroxy-4,5-dihydroisoxazole(**5**), which on dehydration with toluene-p-sulfonic acid in benzene gave 5-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)isoxazole (**6**). Deblocking of compound (**6**) with sodium carbonate gave 5-(β-D-ribofuranosyl)isoxazole (**7**).

Recent reports[2] from our laboratory have described the synthesis of 1,5-benzodiazepin-2-one and 1,5-benzothiazepin-4-one homo-C-nucleosides through condensation of 1,2-diaminobenzenes and 2-aminothiophenol with furanone glycoside, 5-hydroxy-5-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)furan-2(5H)-one (**1**),[3] which can be obtained from glycosylfuran by oxidation of its furan ring. We now describe the synthesis of unsubstituted isoxazole C-nucleoside from furanone (**1**) via enaminone intermediates, (**3a**) and (**3b**). Common methods of preparation of enaminones include condensation of a 1,3-dicarbonyl compound with an amine,[4] Michael addition of an amine to an acetylenic ester or ketone,[5] and substitution of a vinylogous acid chloride or ester with an amine.[6] We found a new method for synthesizing enaminone from furanone by reaction with aminophenols.

The furanone (**1**) reacted with 2-aminophenol (**2a**) in chloroform under reflux for 3 h. Purification of the crude product by preparative thin layer chromatography (plc) using chloroform-hexane (4:1) gave 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-3-(2-hydroxy)anilino-2-propen-1-one (**3a**) in 26% yield, while yields in other solvents such as benzene, methanol and

tetrahydrofuran were lower. In the ^{1}H nmr spectrum of enaminone (3a) the signals for olefinic proton appeared at δ 5.75 and 7.29-8.08 as a complex multiplet within the signals for 3'-H and the aromatic proton of protecting groups. The pesence of an intramolecular NH chelated proton is clearly observed in the ^{1}H nmr spectrum at δ 11.95.[7] In order to clarify the olefinic proton signals, the enaminone (3a) was treated with aqueous sodium carbonate in methanol at room temperature to give deprotected compound (4) in 31% yield. Its ^{1}H nmr spectrum showed an AMX pattern at δ 5.67 (d, J=7.7), 7.75 (dd, J=7.7 and 13.1) and 11.68 (d, J=13.1). The signal of the NH proton (δ 11.68) disappeared with the addition of deuterium oxide. This coupling constant indicated that the product exists exclusively as a Z form of the enaminone structure depicted in Scheme 1.



Scheme 1

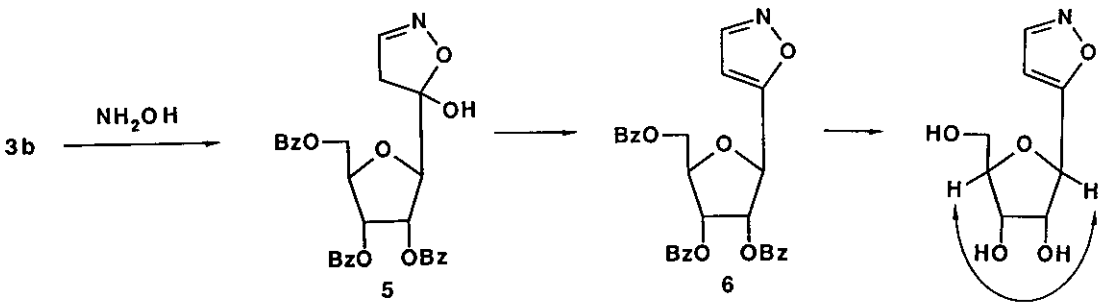
Furthermore, ^{13}C nmr spectrum of compound (4) exhibited the signals of two olefinic carbons at δ 94.8 and 147.1, and of a carbonyl carbon at δ 199.8. The mass spectral data also agreed with the structure of compound (4).

A plausible explanation for the formation of enaminone (3a) involves Michael addition of the amino group of 2-aminophenol to ring opening tautomer (1') and subsequent formation of A. Elimination of a formic acid molecule from A would give the enaminone glycoside (3a) (Scheme 1). The ^1H nmr spectrum of the reaction mixture indicates the presence of a formic acid (δ 8.2, singlet) as sodium salt. The use of β-keto aldehydes, with a variety of masking agents, as a starting material for pyrazoles, isoxazoles and pyrimidines is well known in the literature.[8] The enaminone (3a) is considered a masked 3-keto aldehyde glycoside and may be regarded as a versatile, anomerically functionalized intermediate for the synthesis of glycosylated heterocycles. To obtain this versatile enaminone glycoside at a satisfactory yield, we attempted to react the furanone (1) with 3- and 4-aminophenol. The reaction of furanone (1) with 3-aminophenol produced side products which were observed by thin layer chromatography, but could not be identified due to their instability and small amounts. However, reaction of furanone (1) with 4-aminophenol (2b) produced 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-3-(4-hydroxy)anilino-2-propen-1-one (3b) in 54% yield.

Reaction of enaminone 3b with hydroxylamine hydrochloride in methanol under reflux for 3 h gave (5R)- and (5S)-5-hydroxy-5-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-4,5-dihydroisoxazoles (5) in 90% yield as a 1:1 inseparable mixture of two diastereoisomers by ^1H nmr spectroscopy. The 1'-H signal of compound (5) was observed at δ 4.48, higher than that of 5'-H at δ 4.57-4.80. The difference may be attributed to the shielding effect of the hydroxy group adjacent to the anomeric proton.[9] The similar chemical shift of the anomeric protons in the nmr spectrum of the isomers indicated that both had the β-configuration and thus were diastereomeric only at the carbon bearing the hydroxy group. Dehydration was conducted by treating compound (5) with toluene-p-sulfonic acid (PTSA) in benzene at 60°C for 2 h to give 5-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)isoxazole (6) in 96% yield after chromatographic purification. The removal of the sugar protecting groups in compound (6) was readily accomplished with aqueous sodium carbonate to produce 5-(β-D-ribofuranosyl)isoxazole (7) in 65% yield.

The stereochemistry of compound (7) was determined by a nuclear Overhauser effect experiment. Irradiation of the 1'-H signal (δ 4.93) in isoxazole (7) gave a 2% enhancement of the signal at δ 3.99 assignable to the 4'-H. This data indicate that the β-ribofuranoside configuration had been

preserved during the reaction sequence. To the best of our knowledge, the result represents the first example of the use of furanone in isoxazole synthesis. The biological activities of compound (7) is currently being investigated.



Scheme 2

EXPERIMENTAL

Mass spectra were taken on a Hitachi M-80 instrument by direct insertion at 70 ev; fast-atom bombardment (fab) mass spectra were run on a JMS-HX 110 spectrometer. ^{1}H And ^{13}C nmr spectra were measured with a JNM-GX-270 and a GX-400 (JEOL) spectrometers, with tetramethylsilane as internal standard. J-Values are given in Hz. Analytical tlc was performed on glass plates coated with a 0.5 mm layer of silica gel GF_{254} (Merck). The compounds were detected by uv light (254 nm).

Z-1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-3-(2-hydroxy)anilino-2-propen-1-one (3a). A solution of compound (1) (102.3 mg, 0.19 mmol) and 2-aminophenol (2a) (29.7 mg, 0.27 mmol) in chloroform (4 ml) was heated under reflux for 3 h. Chloroform was removed under reduced pressure and the residue was chromatographed over a column of silica gel with chloroform-hexane (4:1) as eluent. This afforded 29.4 mg (25.8%) of compound (3a) as a yellow foam: $[\alpha]^{24.5}_{D}$ -107.03° (c 0.68, methanol); ^{1}H nmr ($CDCl_3$) δ 4.61 (1H, dd, J=4.0, 11.3, 5'-Ha), 4.72 (1H, m, 4'-H), 4.83 (1H, m, 5'-Hb), 4.86 (1H, d, J=3.4, 1'-H), 5.75 (2H, m, 2-, 3'-H), 5.97 (1H, dd, J=3.4, 5.1, 2'-H), 6.87 (3H, m, ArH), 7.02 (1H, m, ArH), 7.29-8.08 (16H, m, ArH and 3-H), 11.95 (1H, br d, J=12.3, NH, exchanges with D_2O); ^{13}C nmr ($CDCl_3$) δ 63.9 (C-5'), 72.1, 75.2, 79.5, 85.1 (C-1', -2', -3', -4'), 92.4 (C-2), 114.1, 116.2, 120.6, 124.6 and 127.9-133.5 (Ar-C), 145.7 (C-3), 145.9 (Ar-C), 165.2, 165.3, 166.4 (C=O), 194.2 (C-1). Fabms (nitrobenzyl alcohol as matrix) Found: $[M+H]^+$ m/z 608.1951. Calcd for $C_{35}H_{30}NO_9$; [M+H], 608.1921.

Z-1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-3-(4-hydroxy)anilino-2-propen-1-one (3b). A solution of compound (1) (117.0 mg, 0.22 mmol) and 4-aminophenol (**2b**) (46.8 mg, 0.43 mmol) in chloroform (4 ml) was heated at 40°C for 7 h. Chloroform was removed under reduced pressure and the residue was chromatographed over a column of silica gel with chloroform-hexane (5:1) as eluent. This afforded 70.6 mg (54.1%) of compound **3b** as a yellow foam: $[\alpha]^{24.5}_{D}$ -118.54° (c 0.32, methanol); ^{1}H nmr ($CDCl_3$) δ 4.62 (1H, dd, J=4.7, 12.1, 5'-Ha), 4.73 (1H, m, 4'-H), 4.79 (1H, d, J=3.7, 1'-H), 4.85 (1H, dd, J=3.7, 12.1, 5'-Hb), 5.67 (1H, d, J=7.4, 2-H), 5.73 (1H, dd, J=5.4, 6.7, 3'-H), 5.93 (1H, dd, J=3.7, 5.4, 2'-H), 6.81 and 6.87 (2H each, each d, J=9.4, ArH), 7.17 (1H, dd, J=7.4, 12.5, 3-H), 7.30-8.09 (15H, m, ArH), 11.80 (1H, br d, J=12.5, NH, exchanges with D_2O); ^{13}C nmr ($CDCl_3$) δ 64.0 (C-5'), 72.3, 75.0, 79.4, 84.9 (C-1', -2', -3', -4'), 91.7 (C-2), 116.5, 118.4, 128.4-133.4 (Ar-C), 147.5 (C-3), 153.5 (Ar-C), 165.4, 165.5, 166.4 (C=O), 194.1 (C-1). Fabms (nitrobenzyl alcohol as matrix) Found: $[M+H]^+$ m/z 608.1954. Calcd for $C_{35}H_{30}NO_9$; [M+H], 608.1921.

Z-1-(β-D-Ribofuranosyl)-3-(2-hydroxy)anilino-2-propen-1-one (4). To a solution of compound (**3a**) (22.4 mg, 0.04 mmol) in methanol (2 ml) was added 0.3 N sodium carbonate (0.5 ml, 0.11 mmol) at room temperature for 1.5 h, and then the reaction mixture was rendered neutral with acetic acid and evaporated. The residue was purified by plc with chloroform-methanol (9:1) as the eluent. This afforded 3.4 mg of compound (**4**) (31%) as yellow oil: $[\alpha]^{24.5}_{D}$ -76.81° (c 0.21, methanol); ^{1}H nmr (DMSO-d_6) δ 3.48 (1H, br d, J=12.1, 5'-Ha), 3.60 (1H, br d, J=12.1, 5'-Hb), 3.78 (2H, m, 3'-, 4'-H), 3.93 (1H, br s, 2'-H), 4.08 (1H, d, J=4.0, 1'-H), 4.80, 4.87, 5.16 (3H, each br s, OH, exchanges with D_2O), 5.67 (1H, d, J=7.7, 2-H), 6.77-6.90 (3H, m, ArH), 7.36 (1H, d, J=7.7, ArH), 7.75 (1H, dd, J=7.7, 13.1, 3-H), 10.25 (1H, br, OH, exchanges with D_2O), 11.68 (1H, d, J=13.1, NH, exchanges with D_2O); ^{13}C nmr (CD_3OD) δ 64.0 (C-5'), 73.3, 77.5, 86.5, 88.7 (C-1', -2', -3', -4'), 94.8 (C-2), 115.7, 117.2, 122.1, 126.1, 130.2 (Ar-C), 147.1 (C-3), 148.3 (Ar-C), 199.8 (C-1). Fabms (glycerol as matrix) Found: $[M+H]^+$ m/z 296.1151. Calcd for $C_{14}H_{18}NO_6$; [M+H], 296.1134.

(5R)- and (5S)-5-Hydroxy-5-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-4,5-dihydroisoxazole (5). To a solution of compound (**3b**) (32.8 mg, 0.05 mmol) in methanol (2 ml) was added hydroxylamine hydrochloride (8.2 mg, 0.12 mmol). The mixture was heated under reflux for 3 h, then evaporated under reduced pressure. The residue was purified by plc with chloroform-methanol (49:1) as the eluent. This afforded 25.8 mg of compound (**5**)

(90%) as syrup: ^{1}H Nmr ($CDCl_3$) δ 2.95, 3.06 (each 0.5H, each dd, J=1.7, 18.2, 4-Ha), 3.35, 3.53 (each 0.5H, each dd, J=1.7, 18.2, 4-Hb), 4.48 (1H, d, J=3.7, 1'-H), 4.57-4.80 (3.5H, m, 4'-, 5'-H, OH, exchanges with D_2O), 5.06 (0.5H, br s, OH, exchanges with D_2O), 5.60 (1H, m, 3'-H), 5.84 (1H, m, 2'-H), 7.19 (0.5H, t, J=1.7, 3-H), 7.27-8.14 (15.5H, m, ArH and 3-H); ^{13}C nmr ($CDCl_3$) δ 42.7, 43.4 (C-4), 63.4, 64.0 (C-5'), 72.2, 72.5, 72.7, 72.9, 79.3, 79.6, 85.0, 85.3 (C-1', -2', -3', -4'), 104.0, 104.3 (C-5), 128.5-133.9 (Ar-C), 146.8, 146.9 (C-3), 165.2, 165.7, 166.4, 166.5 (C=O). Fabms (thioglycerol as matrix) Found: $[M+Na]^+$ m/z 554.1453. Calcd for $C_{29}H_{25}NO_9Na$; [M+Na], 554.1427.

5-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)isoxazole (6). A solution of compound (5) (25.8 mg, 0.05 mmol) in benzene (2 ml) containing a trace of PTSA was heated at 60°C for 2 h. The reaction mixture was neutralized with aq. sodium hydrogen carbonate and extracted with chloroform. The extracts were combined, washed with water, dried over magnesium sulfate, and evaporated under reduced pressure to afford a syrup. The residue was purified by plc with chloroform as eluent. This afforded 23.8 mg of compound (6) (95.5%) as syrup: $[\alpha]^{24.5}_D$ -33.05° (c 0.23, methanol); ^{1}H nmr ($CDCl_3$) δ 4.61 (1H, dd, J=3.7, 11.4, 5'-Ha), 4.78 (2H, m, 4'-H, 5'-Hb), 5.49 (1H, d, J=4.7, 1'-H), 5.87 (2H, m, 2'-, 3'-H), 6.37 (1H, d, J=1.7, 4-H), 7.34-8.09 (15H, m, ArH), 8.20 (1H, d, J=1.7, 3-H); ^{13}C nmr ($CDCl_3$) δ 63.7 (C-5'), 72.3, 74.8, 75.7, 80.4 (C-1', -2', -3', -4'), 102.1 (C-4), 128.5-133.6 (Ar-C), 150.1 (C-3), 165.1, 165.2, 166.1, (C=O), 167.8 (C-5). Fabms (nitrobenzyl alcohol as matrix) Found: $[M+H]^+$ m/z 514.1530. Calcd for $C_{29}H_{24}NO_8$; [M+H], 514.1502.

5-(β-D-Ribofuranosyl)isoxazole (7). The same procedure was used as for the deprotection of compound (3a) with 0.3 N sodium carbonate solution: yield 65.4%; $[\alpha]^{24.5}_D$ -13.2° (c 0.34, methanol); ^{1}H nmr (CD_3OD) δ 3.64 (1H, dd, J=4.7, 12.1, 5'-Ha), 3.75 (1H, dd, J=3.7, 12.1, 5'-Hb), 3.99 (1H, q, J=3.7, 4.7, 4'-H), 4.07 (1H, t, J=5.0, 3'-H), 4.19 (1H, t, J=5.0, 2'-H), 4.93 (1H, d, J=5.0, 1'-H), 6.50 (1H, d, J=1.7, 4-H), 8.34 (1H, d, J=1.7, 3-H); ^{13}C nmr (CD_3OD) δ 64.1 (C-5'), 73.6, 77.4, 79.3, 87.2 (C-1', -2', -3', -4'), 103.5 (C-4), 152.2 (C-3), 172.8 (C-5). Fabms (glycerol as matrix) Found: $[M+H]^+$ m/z 202.0724. Calcd for $C_8H_{12}NO_5$; [M+H], 202.0716.

ACKNOWLEDGEMENT

We thank Mr. K. Masuda, Analytical Center on our University, for measurement of some fabms spectra.

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Received, 9th February, 1993