C-NUCLEOSIDES. 23.[1] SYNTHESIS OF ENAMINONE GLYCOSIDE AND 4-(β-D-RIBOFURANOSYL)QUINOLINE-2-CARBOXAMIDE FROM FURANONE GLYCOSIDE

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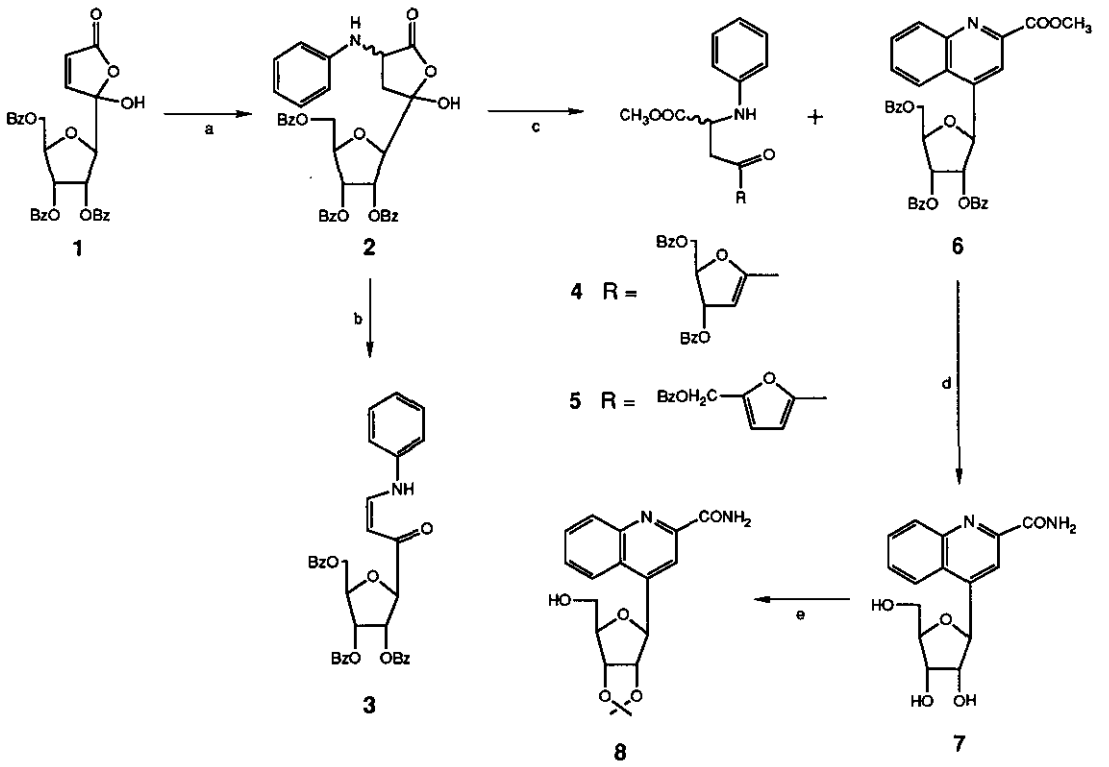
Abstract --- Furanone glycoside (1) was treated with aniline to yield 3-anilino-5-hydroxy-5-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)furan-2(5H)-one (2). Reaction of 2 with trifluoroacetic acid afforded enaminone glycoside (3), whereas treatment of 2 with hydrochloric acid in methanol brought about the ring formation to furnish methyl 4-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)quinoline-2-carboxylate (6) together with methyl 2-anilino-4-(3,5-di-O-benzoyl-1,4-anhydro-2-deoxy-D-erythropent-1-enofuranosyl)-4-oxobutanoate (4) and methyl 2-anilino-4-(5-benzoyloxymethylfuran-2-yl)-4-oxobutanoate (5) in yields of 12%, 12%, and 7%, respectively. The quinoline ester (6) reacted with aq. ammonia in methanol to produce quinolinecarboxamide C-nucleoside (7).

In pursuit of a general synthetic route to C-nucleosides, we synthesized furanone glycoside, 5-hydroxy-5-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-furan-2(5H)-one (1), and found it to be an important synthetic intermediate for C-nucleosides.[2] The present report describes the synthesis of enaminone glycoside (3) and 4-(β-D-ribofuranosyl)quinoline-2-carboxamide (7) from furanone glycoside (1).

Treatment of furanone glycoside (1) with aniline in N,N-dimethylformamide at room temperature for 24 h yielded 3-anilino-5-hydroxy-5-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)furan-2(5H)-one (2) at a yield of 92%.

Compound (2) reacted with trifluoroacetic acid in chloroform slowly at room temperature over 2 days, giving a 62% yield of Z-3-anilino-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2-propen-1-one (3) by the elimination of a formic acid molecule from compound (2).[3] The enaminone glycoside (3) is considered to be a masked 3-keto aldehyde glycoside, and may be regarded as a versatile, anomerically functionalized intermediate for the synthesis of glycosylated heterocycles.[3]



Reagents: (a) MeOH, Aniline; (b) $CHCl_3$, CF_3COOH; (c) CH_3OH, HCl; (d) CH_3OH, aq. NH_3; (e) Acetone, PTSA

Treatment of compound (2) with hydrochloric acid in methanol at room temperature for 2 days yielded afforded three products, methyl 2-anilino-4-(3,5-di-O-benzoyl-1,4-anhydro-2-deoxy-D-erythropent-1-enofuranosyl)-4-oxobutanoate (4), methyl 2-anilino-4-(5-benzoyloxymethylfuran-2-yl)-4-oxobutanoate (5), and methyl 4-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-quinoline-2-carboxylate (6) at yields of 12%, 7%, and 12%, respectively. The structure of 4 and 5 was established by ^{1}H and ^{13}C nmr spectra and mass spectrometry. The ^{1}H nmr spectrum of compound (6) included signals that is characteristic of a quinoline hydrogen atom (δ 8.53, 3-H) as a singlet. It is likely that quinoline formation proceeds by a similar mechanism involving Skraup's reaction.[4] There are several reports of C-glycosyl compounds containing a dihydrofuran moiety in which side reactions yielded a furan derivative.[5] The quinoline ester (6) reacted with aq. ammonia in methanol at room temperature for 8 days to produce quinolinecarboxamide C-nucleoside (7), at a yield of 53%. We assigned the anomeric configuration of compound (7) based on the difference in the chemical shifts of the two methyl signals of the corresponding 2,3-O-isopropylidene derivative (8). The ^{1}H nmr chemical-shift differential value (Δδ) of the methyl groups in the isopropylidene derivative is indicative of β stereochemistry in accordance with Imbach's rule[6] (<0.15 and >0.15 ppm for the α and β anomers, respectively) (see Experimental). This indicates that the β-ribofuranoside configuration had been preserved during the reaction sequence.

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 or a GX-400 (JEOL) spectrometer, with tetramethylsilane as an 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).

3-Anilino-5-hydroxy-5-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)furan-2(5H)-one (2). A solution of compound (1) (304.2 mg, 0.56 mmol) and aniline (78.1 mg, 0.84 mmol) in DMF (6 ml) was stirred at room temperature for 24 h. Water was added and the mixture was extracted with ethyl acetate (3X10 ml). The extracts were combined, washed with water, dried over magnesium sulfate, and evaporated to give a syrup. This syrup was

chromatographed over a column of silica gel with chloroform-methanol (99:1) as the eluent. This afforded 326.8 mg (92%) of compound (2) as pale yellow foam, ^{1}H nmr (DMSO-d_6) δ 4.45-4.79 (5H, m, 3-, 1'-, 4'-, 5'-H), 5.60 and 5.88 (each 1H, each m, 2'-, 3'-H), 6.56 (3H, m, ArH), 7.06 (2H, m, ArH), 7.36-7.95 (16H, m, NH, ArH). FABms (nitrobenzyl alcohol as matrix) Found: $[M+H]^+$ m/z 638.2004. Calcd for $C_{36}H_{32}NO_{10}$; [M+H], 638.2026.

Z-3-Anilino-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2-propen-1-one (3). To a solution of compound (2) (22.4 mg, 0.04 mmol) in chloform (2 ml) was added trifluoroacetic acid (4 mg) at room temperature for 2 days, and then the reaction mixture was rendered neutral with triethylamine and evaporated. The residue was purified by plc with chloroform as the eluent. This afforded 12.8 mg (62%) of compound (3) as syrup: $[\alpha]^{24}_D$ -104.2° (c 0.45, chloroform); ^{1}H nmr ($CDCl_3$) δ 4.61 (1H, dd, J=4.4, 11.8, 5'-Ha), 4.73 (1H, m, 4'-H), 4.81 (1H, d, J=3.7, 1'-H), 4.86 (1H, dd, J=3.4, 11.8, 5'-Hb), 5.74 (1H, dd, J=5.0, 6.7, 3'-H), 5.74 (1H, d, J=7.4, 2-H), 5.93 (1H, dd, J=3.7, 5.0, 2'-H), 7.00-8.10 (21H, m, ArH, 3-H), 11.77 (1H, d, J=12.8, NH, exchangeable with D_2O); ^{13}C nmr ($CDCl_3$) δ 64.0 (C-5'), 72.3, 74.9, 79.5, 85.1 (C-1', -2', -3', -4'), 92.8 (C-2), 116.6, 124.2, 128.4-133.4, 139.7 (Ar-C), 146.0 (C-3), 165.3, 166.3 (C=O), 195.1 (C-1). HRms Found: m/z 591.1873. Calcd for $C_{35}H_{29}NO_8$; M^+ 591.1890.

Methyl 2-Anilino-4-(3,5-di-O-benzoyl-1,4-anhydro-2-deoxy-D-erythropent-1-enofuranosyl)-4-oxobutanoate (4), Methyl 2-Anilino-4-(5-benzoyloxymethyl-furan-2-yl)-4-oxobutanoate (5), and Methyl 4-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)quinoline-2-carboxylate (6). To a solution of compound (2) (326.8 mg, 0.51 mmol) in methanol (4 ml) was added 1 ml of conc. hydrochloric acid at room temperature and the mixture was kept for 2 days. The reaction mixture was neutralized with saturated sodium bicarbonate solution and then extracted with chloroform (3X10 ml). After this time, three new compounds were detected (tlc) in the extracts which had Rf values of 0.22, 0.21, and 0.19 (chloroform), respectively. The extracts were combined, washed with water, dried over magnesium sulfate, and evaporated in vacuo to give a syrup. The residue was separated by plc with chloroform as the eluent after three elutions.

Compound (4): Rf 0.22; 32.5 mg (12%); ^{1}H nmr ($CDCl_3$) δ 3.27 (2H, m, 3-CH_2), 3.70 and 3.71 (each 1.5H, each s, CH_3), 4.50 (1H, br, NH, exchangeable with D_2O), 4.55 (1H, m, 4'-H), 4.63 (2H, m, 5'-H), 5.04 (1H, m, 2-CH), 6.08 (2H, m, 2'-, 3'-H), 6.63 (2H, dd, J=1.0, 7.7, ArH), 6.75 (1H, td, J=1.0, 7.7, ArH), 7.16-8.07 (12H, m, ArH); ^{13}C nmr ($CDCl_3$) δ 41.7, 41.8 (CH_2), 52.48,

52.52, 52.55 (C-4', CH_3), 63.8 (C-5'), 78.58, 78.64 (C-3'), 84.78, 84.87 (C-2'), 106.2-157-8 (C-1', Ar-C), 165.99, 166.06, 172.8, 190.36, 190.43 (C=O). FABms (nitrobenzyl alchol as matrix) Found: $[M+H]^+$ m/z 530.1829. Calcd for $C_{30}H_{28}NO_8$; [M+H], 530.1815.

Compound (5): Rf 0.21; 12.7 mg (7%); ^1H nmr ($CDCl_3$) δ 3.41 (2H, d, J=5.4, 3-CH_2), 3.73 (3H, s, CH_3), 4.50 (1H, br, NH, exchangeable with D_2O), 4.62 (1H, t, J=5.4, 2-CH), 5.34 (2H, s, 5'-CH_2), 6.61 (1H, d, J=3.7, furan 4'-H), 6.67 (2H, d, J=7.4, ArH), 6.74 (1H, t, J=7.4, ArH), 7.17-8.07 (8H, m, furan 3'-H, ArH); ^{13}C nmr ($CDCl_3$) δ 40.8 (CH_2), 52.5, 52.8 (CH, CH_3), 58.3 (CH_2), 112.8, 113.7, 118.4, 118.8, 128.5, 129.4, 129.8, 133.4, 146.2, 152.3, 154.1 (Ar-C), 165.9, 173.1, 186.0 (C=O). HRms Found: m/z 407.1340. Calcd for $C_{23}H_{21}NO_6$; M^+ 407.1366.

Compound (6): Rf 0.19; 36.8 mg (12%); $[\alpha]^{24}_D$ -53.3° (c 1.5, chloroform); ^1H nmr ($CDCl_3$) δ 3.92 (3H, s, CH_3), 4.81 (1H, dd, J=3.7, 11.8, 5'-Ha), 4.88 (1H, m, 4'-H), 4.97 (1H, dd, J=2.7, 11.8, 5'-Hb), 5.81 (1H, t, J=5.4, 3'-H), 5.88 (1H, t, J=5.4, 2'-H), 6.10 (1H, d, J=5.4, 1'-H), 7.31-8.38 (19H, m, ArH), 8.53 (1H, s, 3-H); ^{13}C nmr ($CDCl_3$) δ 53.1 (CH_3), 63.8 (C-5'), 72.1, 76.7, 79.2, 80.3 (C-1', -2', -3', -4'), 117.9, 122.9, 126.7, 128.4-133.6 (Ar-C), 145.1, 147.9, 148.1 (C-2, -4, -8a), 165.0, 165.3, 165.4, 166.3 (C=O). HRms Found: m/z 631.1847. Calcd for $C_{37}H_{29}NO_9$; M^+ 631.1840.

4-(β-D-Ribofuranosyl)quinoline-2-carboxamide (7). To a solution of compound (6) (30.2 mg, 0.05 mmol) in methanol (3 ml) was added 1 ml of 25% aq. ammonia at room temperature and the mixture was kept for 8 days, then the solvent was evaporated. The residue was purified by plc with chloroform as eluent to give compound (7) (7.8 mg, 53%) as syrup: $[\alpha]^{24}_D$ +33.6° (c 0.4, methanol); ^1H nmr (CD_3OD) δ 3.64-4.14 (5H, m, 2'-, 3'-, 4'-, 5'-H), 5.59 (1H, d, J=4.0, 1'-H), 7.70 and 7.83 (each 1H, each t, J=7.7, 6-, 7-H), 8.19 and 8.35 (each 1H, each d, J=7.7, 5-, 8-H), 8.47 (1H, s, 3-H); ^{13}C nmr (CD_3OD) δ 64.1 (C-5'), 73.4, 79.7, 83.3, 86.4 (C-1', -2', -3', -4'), 116.6 (C-4a), 126.1, 129.2, 130.0, 131.9, 132.3 (C-5, -6, -7, -8), 149.0, 151.0, 151.6 (C-2, -4, -8a), 170.5 (C=O). Hrms Found: m/z 304.1058. Calcd for $C_{15}H_{16}N_2O_5$; M^+ 304.1059.

4-(2,3-O-Isopropylidene-β-D-ribofuranosyl)quinoline-2-carboxamide (8). To a solution of compound (7) (5.8 mg, 0.02 mmol) in acetone (2 ml) was added PTSA (5 mg), and the mixture was stirred at room temperature for 5 h. The reaction mixture was neutralized with saturated sodium bicarbonate solution, and the solvent was evaporated. The residue was purified by plc with chloroform-methanol (19:1) as the eluent to give compound (8) (2.8 mg,

43%). ^{1}H Nmr ($CDCl_3$) δ 1.37 and 1.73 (each 3H, each s, isopropylidene Me), 3.90 (1H, dd, J=4.4, 12.4, 5'-Ha), 4.19 (1H, dd, J=3.0, 12.4, 5'-Hb), 4.32 (1H, m, 4'-H), 4.58 (1H, dd, J=5.0, 7.1, 2'-H), 4.84 (1H, dd, J=4.4, 7.1, 3'-H), 5.62 (1H, d, J=5.0, 1'-H), 5.89 (1H, br s, NH, exchangeable with D_2O), 7.69 and 7.79 (each 1H, each t, J=7.3, 6-, 7-H), 8.15 and 8.23 (each 1H, each d, J=7.3, 5-, 8-H), 8.15 (1H, s, NH, exchangeable with D_2O), 8.53 (1H, s, 3-H). HRms Found: m/z 344.1360. Calcd for $C_{18}H_{20}N_2O_5$; M^+ 344.1370.

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