Nucleosides Having Quinolone Derivatives as Nitrogenated Base: Regiospecific and Stereospecific Ribosylation of 3-Carbethoxy-1,4-dihydro-4-oxoquinolines

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NUCLEOSIDES HAVING QUINOLONE DERIVATIVES AS NITROGENATED BASE : REGIOSPECIFIC AND STEREOSPECIFIC RIBOSYLATION OF 3-CARBETHOXY-1,4-DIHYDRO-4-OXOQUINOLINES

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ABSTRACT. Ribosylation reactions of previously silylated 3-carbethoxy-8-methyl-1,4-dihydro-4-oxoquinoline (6a) and 3-carbethoxy-6-methyl-1,4-dihydro-4-oxoquinoline (6b) with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (7), under Lewis acid catalysis, were studied. The method using hexamethyldisilazane (HMDS)/trimethylchlorosilane (TMCS) mixture for silylation and anhydrous stannic chloride as catalyst for ribosylation failed to give any nucleoside product. On the other hand, the protected nucleoside 3-carbethoxy-6-methyl-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-1,4-dihydro-4-oxoquinoline (8b) was obtained in good yields using bis(trimethylsilyl)trifluoroacetamide (BSTFA) containing 1% of TMCS and the same catalyst. Compound 8b was more easily isolated in higher yields with an improvement of the later method by replacing stannic chloride with trimethylsilyl trifluoromethanesulfonate (TMSOTf).

De-O-benzoylation of 8b with methanolic sodium hydroxide solution afforded the free riboside 3-carbomethoxy-6-methyl-1-β-D-ribofuranosyl-1,4-dihydro-4-oxoquinoline (9b). The structures of the obtained products were confirmed by their UV, MS, IR, ^{1}H and ^{13}C-NMR data.

Quinolones are well known antibacterial substances with great therapeutic importance.[1] Nalidixic acid (1), active against gram negative bacteria, was the first quinolone used in clinical practice for treatment of urinary infections. Ever since, more potent quinolones, with broad spectrum activity, such as norfloxacin (2) and ciprofloxacin (3), have been developed for pharmaceutical use.[1-3]
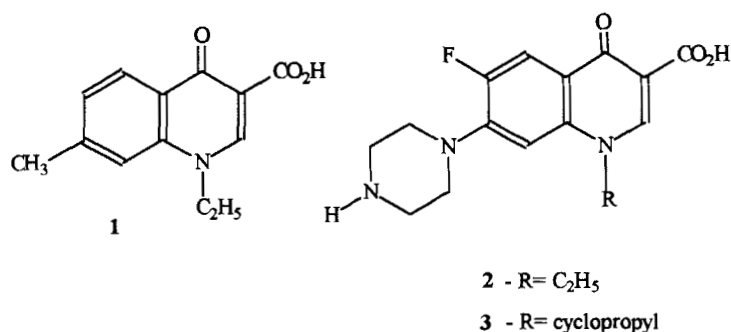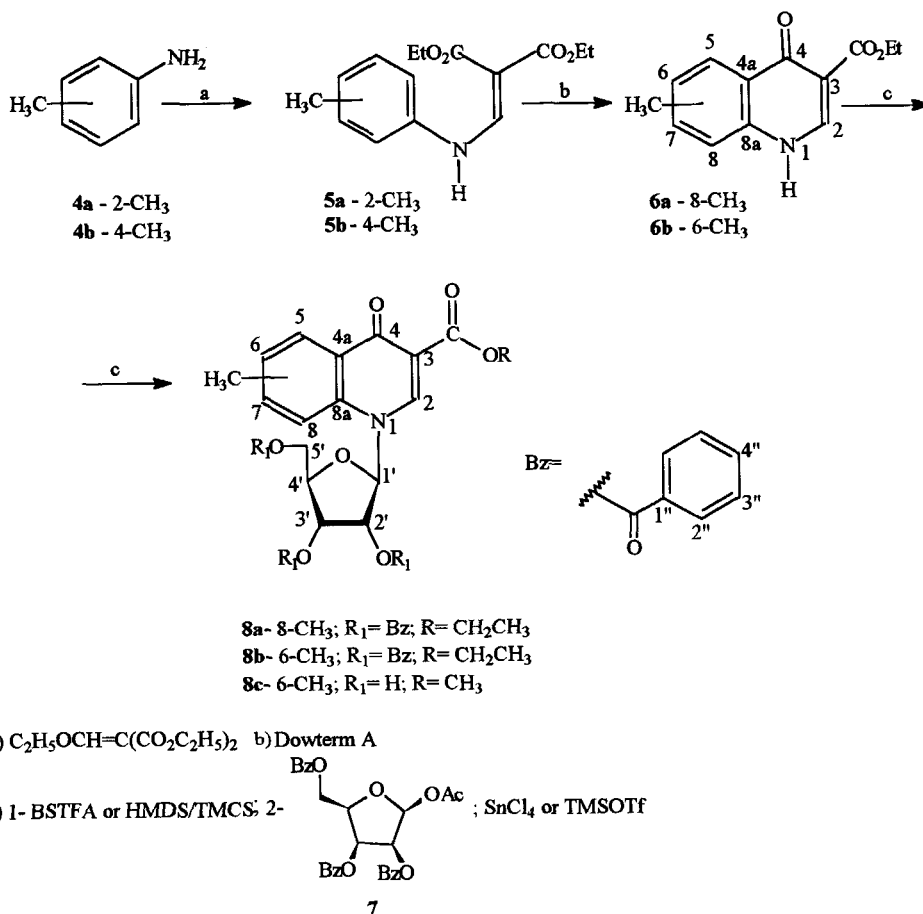
The synthesis of natural nucleosides analogues has been also intensively investigated during the past years for antiviral and anticancer therapy.[4]

Owing to the important pharmacological effects of both classes of compounds, we decided to synthesize new ribonucleosides having quinolones as nitrogenated base. In this report we will show our results on the regio and stereospecific ribosylation of 3-carbethoxy-8-methyl-1,4-dihydro-4-oxoquinoline **(6a)** and 3-carbethoxy-6-methyl-1,4-dihydro-4-oxoquinoline **(6b)**.

The quinolone derivatives were synthesized by treatment of *ortho* and *para*-toluidines **(4a** and **4b**, respectively) with diethyl ethoxymethylenemalonate[5] to obtain the enamine type derivatives diethyl methylanilinomethylenemalonates **5a** and **5b** in 90 % and 87 % yield, respectively, which were then cyclized in refluxing Dowtherm A[6] affording 3-carbethoxy-8-methyl-1,4-dihydro-4-oxoquinoline **(6a)** and 3-carbethoxy-6-methyl-1,4-dihydro-4-oxoquinoline[5] **(6b)** in 80 % and 75 % yield, respectively (Scheme I).

Among the various synthetic methods used for nucleoside synthesis the reaction of silylated heterocyclic bases with peracylated sugars, in the presence of a Lewis acid, has become the one most utilized by chemists. Thus, the ribosylation of **6a** and **6b** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**7**) was investigated using the silylated heterocyclic base method.[7,8]

However, attempts of silylation of **6a** or **6b** in a refluxing mixture of HMDS and TMCS followed by removing the reagents excess, and subsequent addition of **7**, under anhydrous stannic chloride catalysis, produced only an intractable mixture of products. When the later procedure was modified by replacing hexamethyldisilazane with bis(trimethylsilyl)trifluoroacetamide (BSTFA), at 70°, the protected ribonucleosides 3-carbethoxy-8-methyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,4-

4a - 2-CH$_3$
4b - 4-CH$_3$

5a - 2-CH$_3$
5b - 4-CH$_3$

6a - 8-CH$_3$
6b - 6-CH$_3$

8a- 8-CH$_3$; R$_1$= Bz; R= CH$_2$CH$_3$
8b- 6-CH$_3$; R$_1$= Bz; R= CH$_2$CH$_3$
8c- 6-CH$_3$; R$_1$= H; R= CH$_3$

a) C$_2$H$_5$OCH=C(CO$_2$C$_2$H$_5$)$_2$ b) Dowterm A

c) 1- BSTFA or HMDS/TMCS; 2- ; SnCl$_4$ or TMSOTf

7

SCHEME I

dihydro-4-oxoquinoline (8a) and 3-carbethoxy-6-methyl-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-1,4-dihydro-4-oxoquinoline (8b) were obtained in 5% and 74% yield from 6a and 6b, respectively (method A). The low yield obtained for 8a was probably due to steric hindrance effect from the 8-methyl substituent. Another procedure comprised the use of this same silylation reagent followed by TMSOTf catalysed ribosylation without removing the excess of BSTFA (method B). By method B, the protected ribonucleoside 8b was more easily obtained in a higher yield (81%). Despite this good result, this method also failed to afford 8a from 6a.

De-*O*-benzoylation was performed by treating **8b** with 0.5 N methanolic sodium hydroxide solution for two hours, at room temperature, and then filtering the resulting solution through Dowex 50 H⁺ column[9] to afford pure 3-carbomethoxy-6-methyl-1-β-D-ribofuranosyl-1,4-dihydro-4-oxoquinoline (**8c**) in 58 % yield. During this reaction the carbethoxy was transesterified to a carbomethoxy ester group.

The structures of the nucleosides were elucidated by ^{1}H and ^{13}C NMR experiments (^{1}H, PND, DEPT, ^{1}H x ^{1}H-COSY, HMBC, HMQC) and by FAB-HR analysis.

The ribosylation was regiospecific and no trace of reaction at the oxygen site was observed. The anomeric carbon stereochemistry of the nucleoside **8b** was assigned by one-dimensional nuclear Overhauser effect difference spectroscopy (nOeds). Upon irradiation of H1' (riboside) H4' increased by 3.2%, establishing β-configuration[10] and confirming the stereoselectivity of the reaction. In addition, H2 signal also increased by 7.1%, establishing the position of ribosylation as N1. These findings can be transferred to **8c**.

Carbon chemical shifts for C2 and C4 and for the anomeric carbon (C1') of **8a** and **8b** were very similar. Furthermore, **8a** and **8b** afforded UV curves pratically identical, clearly indicating that the ribosylation of **8a** also occurred at N1.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 1420 spectrometer as potassium bromide pellets and frequencies are expressed in cm^{-1}. Mass spectra were obtained using VG Autospec and VG-ZAB-E spectrometers. UV spectra were recorded on a UV 160A Shimadzu spectrophotometer. ^{1}H and ^{13}C NMR spectra were acquired on Bruker AC-300, Varian Unity Plus-300 and Varian VXR-500 instruments, in solvents specified. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane as an internal standard.

Proton and carbon spectra were typically obtained at room temperature. The two dimensional experiments were acquired using standard Varian Associates automated programs for data acquisition and processing. Nuclear Overhauser experiments were carried out at 299.94 MHz with a spectral window of 4000 Hz with a pulse flip of 45°,

acquisition time of 3.744 seconds and 5.0 seconds relaxation delay using gated decoupling.

General Procedure for diethyl methylanilinomethylenemalonates (**5a** and **5b**)

A solution of *ortho* or *para*-toluidine (10.7 g, 100 mmoles), and 20.4 ml (100 mmoles) of diethyl ethoxymethylenemalonate was heated under reflux for 3 hours. The mixture was allowed to cool, then poured into ice-cold water (100 g). The precipitate was collected by filtration and recrystallized from hexane to give:

5a: 24.93 g (90 %) as white crystals, mp 63 °C (lit.[5] mp 63 °C ; IR 1675 and 1635 (C=O), 1240 (C-O); MS: m/z (relative intensity) 277 (M$^+$, 100), 231 (85), 175 (30), 130 (48), 91 (29); ^{1}H-NMR (CDCl$_3$, 200.13 MHz) δ 11.12 (d, 1H, J= 12.9 Hz, NH), 8.55 (d, 1H, J= 13.5 Hz, Hβ), 7.26-7.18 (m, 1H, H6), 7.10-7.06 (m, 3H, H3-H5), 4.38-4.19 (m, 4H, (O-C$\underline{H}_2$), 2.37 (s, 3H, methyl), 1.42-1.28 (m, 6H, CH$_2$C$\underline{H}_3$); ^{13}C-NMR (CDCl$_3$, 50.0 MHz) δ 166.7 (C=O), 165.2 (C=O), 151.6 (Cβ), 137.4 (C1), 126.7 (C2), 130.7, 126.9, 126.7, 124.3 and 114.7 (C3-C6), 93.2 (Cα), 59.8 (OC̲H$_2$), 59.5 (OC̲H$_2$), 16.9 (C̲H$_3$-C2), 14.0 (CH$_2$C̲H$_3$), 13.9 (CH$_2$C̲H$_3$).

5b: 24.10 g (87 %) as white crystals, mp 46-48 °C (lit.[5] mp 48 °C); IR 1715 and 1685 (C=O), 1250 (C-O); MS: m/z (relative intensity) 277 (M$^+$, 87), 231 (100), 175 (56), 130 (30), 91 (24); ^{1}H-NMR (CDCl$_3$, 200.13 MHz) δ 10.96 (d, 1H, J= 13.1 Hz, NH), 8.48 (d, 1H, J= 13.9 Hz, Hβ), 7.15 (d, 2H, J= 8.2 Hz, H2,6 or H3,5), 7.01 (d, 2H, J= 8.2 Hz, H2,6 or H3,5), 4.33-4.16 (m, 4H, O-C$\underline{H}_2$), 2.31 (s, 3H, methyl), 1.39-1.26 (m, 6H, CH$_2$C$\underline{H}_3$); ^{13}C-NMR (CDCl$_3$, 50.0 MHz) 168.8 (C=O), 165.4 (C=O), 151.7 (Cβ), 136.5 (C1), 134.4 (C4), 130.0 (C3,5), 116.8 (C2,6), 92.6 (Cα), 59.9 (O-C̲H$_2$), 59.7 (O-C̲H$_2$), 20.4 (C̲H$_3$-C4), 14.1 (CH$_2$C̲H$_3$), 14.0 (CH$_2$C̲H$_3$).

General Procedure for 3-carbethoxy-8-methyl-1,4-dihydro-4-oxoquinoline (**6a**) and 3-carbethoxy-6-methyl-1,4-dihydro-4-oxoquinoline (**6b**)

To 10 ml of refluxing Dowtherm A, 3g (10.83 mmoles) of diethyl methylanilinomethylenemalonate (**5a** or **5b**) was added. The resulting mixture was heated

at reflux under nitrogen for 1.15 h. After the mixture had cooled the precipitate was collected by filtration, washed with petroleum ether and methylene chloride and recrystallized from glacial acetic acid to give:

6a: 2.00 g (80 %) as white crystals, mp 258 °C (lit.[5] mp 259 °C); IR   3300-2800 (OH/NH), 1690 (C=O), 1285 (C-O); MS: m/z (relative intensity) 231 (M^+, 42), 185 (100), 129 (41); ^{1}H-NMR [(CD$_3$)$_2$SO, 300.13 MHz] δ 11.62 (s, 1H, NH), 8.40 (s, 1H, H2), 8.10 (d, 1H, J= 7.2 Hz, H5), 7.55 (d, 1H, J= 7.0 Hz, H7), 7.25 (t, 1H, J= 7.2 Hz, H6), 4.22 (q, 2H, J= 7.1 Hz, O-C$\underline{H}_2$), 2.50 (s, 3H, methyl), 1.25 (t, 3H, J= 7.1 Hz, CH$_2$C$\underline{H}_3$); ^{13}C-NMR [(CD$_3$)$_2$SO, 75.0 MHz] 174.5 (C4), 165.7 (O=$\underline{C}$-O), 145.4, 138.4, 134.1, 128.4, 127.9, 125.2, 124.5, 110.6 (C2, C3, C5-C8, C4a, C8a), 60.5 (O-$\underline{C}$H$_2$), 17.9 ($\underline{C}$H$_3$-C8), 15.2 (CH$_2$$\underline{C}H_3$).

6b: 1.88 g (75 %) as white crystals, mp 267-268 °C (lit.[5] mp 268 °C); IR 3300-2800 (OH/NH), 1695 (C=O), 1290 (C-O); ^{1}H-NMR [(CD$_3$)$_2$SO, 300.13 MHz] 11.9 (bs, 1H, NH), 8.40 (s, 1H, H2), 7.95 (s, 1H, H5), 7.50 (s, 2H, H7 and H8), 4.30 (q, 2H, J= 7.2 Hz, O-C$\underline{H}_2$), 2.40 (s, 3H, methyl) 1.30 (t, 3H, J= 7.2 Hz, CH$_2$C$\underline{H}_3$); ^{13}C-NMR [(CD$_3$)$_2$SO, 75.0 MHz] 172.7 (C4), 164.4 (O=$\underline{C}$-O), 143.5 (C2), 136.6 (C8a), 126.9 (C5), 124.5 (C3), 118.1 (C7 or C8), 133.5, 132.9, 109.6 (C6, C4a, C7 or C8), 58.9 (O-$\underline{C}$H$_2$), 20.2 ($\underline{C}$H$_3$C6) , 13.8 (CH$_2$$\underline{C}H_3$).

3-Carbethoxy-8-methyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,4-dihydro-4-oxo-quinoline (**8a**)

Method A: Using BSTFA/TMCS, and anhydrous SNCl$_4$ catalysis

A stirred solution of 3-carbethoxy-dihydro-8-methyl-1,4-dihydro-4-oxoquinoline (**6a**) (0.100 g, 0.43 mmol), BSTFA (0.23 ml, 0.86 mmol) containing 1% TMCS was heated at 70 °C, under nitrogen, for 4 h. Excess was removed under reduced pressure. To the resulting product was added a solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**7**)   (0.159 g, 0.31 mmol) in 50 ml of 1,2-dichloroethane, followed by dropwise addition of anhydrous stannic chloride (a solution of 0.046 ml, 0.39 mmol in 2

ml of 1,2-dichloroethane). After the mixture had been stirred for 4 h at room temperature, 1,2-dichloroethane (10 ml) was added. The resulting mixture was filtered and washed with saturated sodium bicarbonate solution (3 x 20 ml). After drying over anhydrous magnesium sulfate, the solvent was removed under reduced pressure giving an oil which was purified by preparative cromatography on silica gel plates (20 x 20 cm), eluted with methylene chloride:ethyl acetate (6:4), to give 10.65 mg (5 %) of **8a** as a white viscous oil; UV λ_{max} (CH_3OH) 316 nm (ϵ 12875), 228 (ϵ 63061); IR (neat) 1720 (C=O), 1270 (C-O); ^{1}H-NMR ($CDCl_3$, 300.13 MHz) δ 8.82 (s, 1H, H2), 8.34 (d, 1H, J= 8.0 Hz, H5), 8.20 (d, 2H, J= 8.0 Hz, H2"), 7.95 (d, 2H, J= 7.8 Hz, H2"), 7.75 (d, 2H, J= 8.0 Hz, H2"), 7.65-7.25 (m, 11H, H6, H7, H3", H4"), 6.65 (d, 1H, J= 6.0 Hz, H1'), 5.95-5.82 (m, 2H, H2', H3'), 4.85-4.70 (m, 3H, H4', H5'), 4.25-4.00 (m, 2H, O-C$\underline{H}_2$), 2.80 (s, 3H, methyl), 1.30-1.20 (m, 3H, CH$_2$C$\underline{H}_3$); ^{13}C-NMR ($CDCl_3$, 75.0 MHz) δ 174.9 (C4), 164.8 (O=$\underline{C}$-C3), 166.0 (C2'-O-$\underline{C}$=O), 164.5 (C3'-O-$\underline{C}$=O), 164.0 (C5'-O-$\underline{C}$=O), 145.4 (C2), 140.0, 137.0, 133.7, 133.4, 130.3, 129.6, 129.5, 128.9, 128.6, 128.4, 128.3, 127.8, 125.9, 125.4, 125.1, 113.6 (aromatic carbons), 90.3 (C1'), 80.0 (C4'), 74.4 (C2'), 71.0 (C3'), 63.8 (C5'), 60.6 (O-$\underline{C}H_2$), 22.0 ($\underline{C}H_3$-C8), 14.1 (CH$_2$$\underline{C}H_3$).

3-Carbethoxy-6-methyl-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-1,4-dihydro-4-oxoquinoline (**8b**)

Method A: Using BSTFA/TMCS and anhydrous SnCl$_4$ catalysis

Compound **8b** was obtained as described for **8a**, using 0.720g (3.11 mmoles) of 3-carbethoxy-6-methyl-1,4-dihydro-4-oxoquinoline (**6b**), 2 ml (7.39 mmoles) of BSTFA containing 1% of TMCS, a solution of 1.27 g (2.5 mmoles) of **7** in 26 ml of 1,2-dichloroethane, and a solution of 0.36 ml (3.1 mmoles) of anhydrous stannic chloride in 7 ml of 1,2-dichloroethane. The nucleoside **8b** was isolated as a white solid which was recrystallized from ethanol to give 1.26 g (74%) of white crystals, mp 186 °C; UV λ_{max} (CH_3OH) 319 nm (ϵ 11356), 229 (ϵ 56204); IR 1720 (C=O), 1260 (C-O); high resolution MS (FAB) m/z: calcd for $C_{39}H_{34}NO_{10}$ (M+H)$^+$ 676.2183. Found 676.2173; ^{1}H-NMR ($CDCl_3$, 300.13 MHz) δ 8.89 (s, 1H, H2), 8.26 (s, 1H, H5), 8.10 (d, 2H, J= 8.5 Hz, H2"),

7.96 (d, 2H, J= 8.5 Hz, H2"), 7.93 (d, 2H, J= 8.5 Hz, H2"), 7.65-7.33 (m, 11H, H7, H8, H3", H4"), 6.51 (d, 1H, J= 5.0 Hz, H1'), 6.01 (t, 1H, J= 5.0 Hz, H2'), 5.91 (t, 1H, J= 5.0 Hz, H3'), 4.96-4.80 (m, 3H, H4', H5'), 4.28-4.02 (m, 2H, O-CH$_2$), 2.42 (s, 3H, methyl), 1.30-1.20 (m, 3H, CH$_2$CH$_3$); ^{13}C-NMR (CDCl$_3$, 75.0 MHz) δ 174.4 (C4), 165.1 (O=C-C3), 166.1 (C2'-O-C=O), 164.8 (C3'-O-C=O), 164.7 (C5'-O-C=O), 142.6 (C2), 127.9 (C5), 114.6 (C7 or C8), 136.4, 135.5, 134.1, 133.9, 133.8, 133.6, 129.9, 129.8, 129.7, 128.7, 128.6, 128.4, 128.2 and 111.8 (aromatic carbons), 90.4 (C1'), 80.9 (C4'), 74.4 (C2'), 70.8 (C3'), 63.4 (C5'), 60.7 (O-CH$_2$), 20.9 (CH$_3$-C6), 14.3 (CH$_2$CH$_3$).

Method B: Using BSTFA/TMCS and trimethylsilyl trifluoromethanesulfonate (TMSOTf) catalysis

A stirred solution of 3-carbethoxy-6-methyl-1,4-dihydro-4-oxoquinoline (**6b**) (0.400 g, 1.73 mmoles in 6.0 ml of acetonitrile) and BSTFA (2.0 ml, 7.39 mmoles) containing 1% of TMCS was heated at 70 °C, under nitrogen, for 2 h. The resulting mixture was allowed to cool and a solution of compound **7** in 6.0 ml of acetonitrile was added, followed by dropwise addition of TMSOTf (0.42 ml, 2.20 mmoles, in 1.0 ml of acetonitrile). Stirring was continued for an additional 3 h, at room temperature, and then the solution was poured into ice-cold water (15 g). The resulting mixture was extracted with methylene chloride (3 x 20 ml) and the combined organic phases were washed with a saturated sodium bicarbonate solution (3 x 20 ml) and water (3 x 20 ml). After drying over anydrous magnesium sulfate, the solvent was removed under reduced pressure to leave the product as white crystals which were recrystallized from ethanol to give pure **8b** (0.950 g, 81%).

3-Carbomethoxy-6-methyl-1-β-D-ribofuranosyl-1,4-dihydro-4-oxoquinoline (**8c**)

A mixture of **8b** (0.400 g, 0.59 mmol) in 0.5 N methanolic sodium hydroxide (30 ml) was stirred for 2 h at room temperature, under nitrogen. The resulting solution was passed through a column of Dowex 50 H$^+$ (20 ml) previously washed with methanol:water mixture (3:1). The filtrate was evaporated furnishing a solid which was partitioned between water and ethyl ether. The aqueous solution was evaporated under

reduced pressure to give 0.120 g of **8c** (58 %), as white crystals, mp 218 °C; IR 3650-3000 (OH), 1690 (C=O), 1200 (C-O); high resolution MS (FAB) m/z: calcd for $C_{17}H_{20}NO_7$ (M+H)$^+$ 350.1240. Found 350.1233; ^{1}H-NMR (CD$_3$OD, 300.13 MHz) δ 9.40 (s, 1H, H2), 8.20 (d, 1H, J= 1.5 Hz, H5), 7.73 (d, 1H, J= 8.5 Hz, H8), 7.65 (dd, 1H, J= 8.5 and 1.5 Hz, H7), 6.15 (d, 1H, J= 5.0 Hz, H1'), 4.25-4.20 (m, 3H, H2', H3', H4'), 4.05 (d, 1H, J= 7.0 Hz, H5'), 3.85 (d, 1H, J= 7.0 Hz, H5', 3.80 (s, 3H, O-CH$_3$), 2.45 (s, 3H, methyl); ^{13}C-NMR (CD$_3$OD, 75.0 MHz) δ 176.8 (C4), 167.0 (O=C-C3), 145.2, 138.2, 137.1, 135.6, 129.1, 127.4, 117.5, 110.7 (aromatic carbons) 94.2 (C1'), 86.1 (C4'), 76.8 (C2'), 70.6 (C3'), 61.4 (C5'), 52.0 (O-CH$_3$), 21.0 (CH$_3$-C6).

Acknowledgements

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