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This paper presents the synthesis of some novel acyclonucleosides containing 2-pyridinones and 2-hydroxyethoxymethyl, 2,3-dihydroxy-propyl side chain. The tosylate of these nucleosides analogues could be modified to azido derivatives. Also, acyclonucleosides with 1-ethoxymethyl, 1-benzyloxymethyl, 1-methylthiomethyl and 2-hydroxyethyl side chains have been investigated. The *O*-alkylated pyridine derivatives were obtained during most reactions.

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Reverse transcriptase (RT), being the pivot in the human immunodeficiency virus (HIV) replication [1], is still one of the most attractive targets for the development of new antiviral agents [2]. Among these compounds, 2-pyridinones (A) have been described as HIV-1 specific reverse transcriptase inhibitors [3]. The synthesis of acyclonucleosides such as 9-(2-hydroxyethoxymethyl)guanine (acyclovir) [4], 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEBT) [5], 6-benzyl-1-ethoxymethy-5-isopropyluracil (MKC-442) [6] and (*S*)-9-(2,3-dihydroxypropyl)adenine, ((*S*)-DHPA) [7] has been also intensively investigated during the past years for antiviral and anticancer therapy (Figure 1).

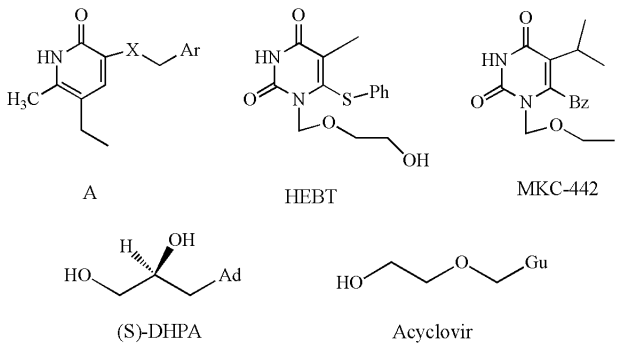
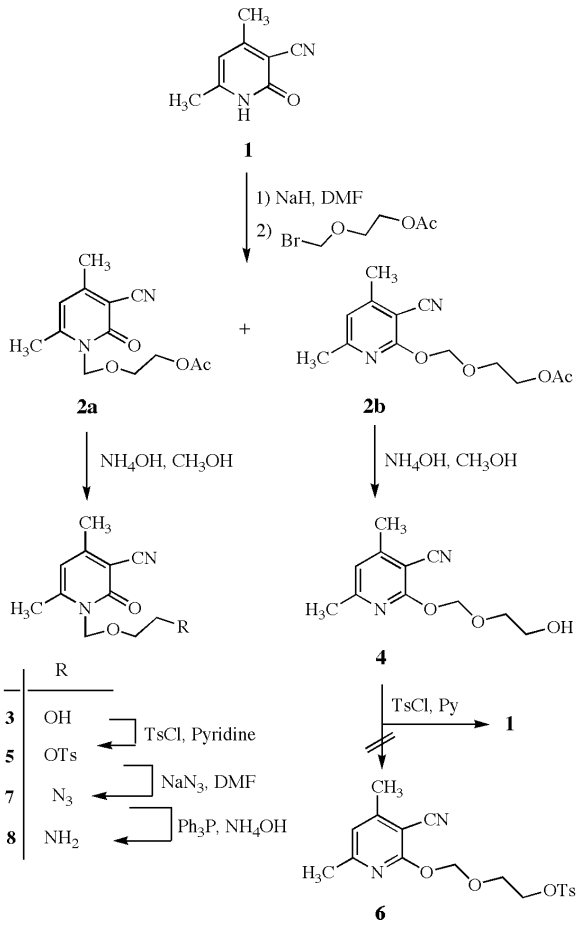


Figure 1

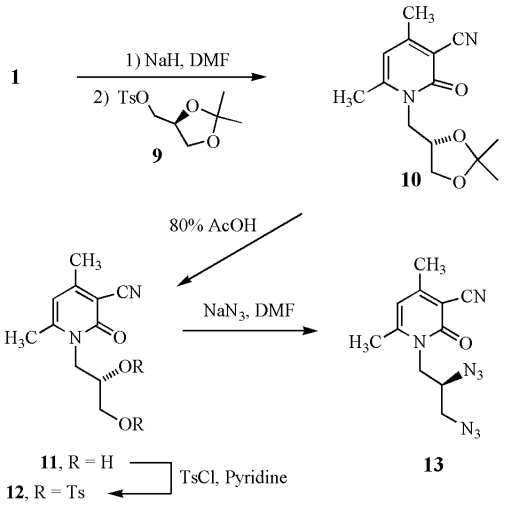
Owing to the important pharmacological effects of both classes of compounds and as a continuation of our interest in the synthesis of nucleosides [8], we decided to synthesize new acyclo-*N*-nucleosides having 2-pyridinones as nitrogen base. A literature search revealed that such type compounds are completely unknown, exception made for the recently synthesized 1-hydroxyalkylpyrid-4-ones [9] starting from the maltol or ethylmaltol. Furthermore, synthesis of *N*-glycosylated pyridines by the condensation of acetobromosuger with 3-cyanopyridones in the presence of potassium hydroxide or their chloromercuric salt in anhydrous xylene has been described [10]. The pyridinone derivative **1** was synthesized by treatment of acetylacetone with cyanoacetamide in presence of base [11]. Following the reported method [12], compound **1** was alkylated, after its treatment with 60% sodium hydride in anhydrous *N,N*-dimethylformamide, with 2-acetoxyethoxy methyl bromide [13] to give two alkylated derivatives **2a** and **2b** which were separated by column chromatography with ethyl acetate in chloroform (0-10%) to give **2a** and **2b** in 49% and 34% yield, respectively. The ^{1}H nmr spectra of **2a,b** showed that the acetoxyethoxymethyl moiety of the *O*-alkylated product **2b** is shifted downfield compared with that of *N*-alkylated product **2a**. The methylene singlet signal appeared at δ 5.70 ppm for *O*-alkylated product **2b** compared to δ 5.57 ppm for the *N*-alkylated product **2a**. In addition, the infrared spectrum confirmed the absence of the carbonyl functional group in the *O*-alkylated product **2b**, which is present in the *N*-alkylated product **2a**. Also, the ^{13}C nmr spectrum showed the chemical shift at C-1 of a cyclic part of **2a** at δ 73.04 ppm while that of compound **2b** at δ 90.86 ppm. This indicated that the alkylation of **1** occurred on the nitrogen atom to give **2a** and on the oxygen atom to give **2b**, respectively. The mass spectra of **2a** and **2b** showed the same molecular ion peak at m/z 264. Treatment of these compounds with ammonia in methanol at room temperature for 24 h resulted in complete deprotection of the hydroxy group and the corresponding compounds **3** and **4** were obtained, respectively, in good yield. Tosylation of **3** was easily performed in anhydrous pyridine with *p*-toluenesulfonyl chloride, and the product identified, besides nmr, mass spectra and elemental analysis, by a characteristic peak at 1199 cm^{-1} in the infrared spectrum. However, tosylation of the acetal **4**, under the same condition, afforded the starting material **1** and not tosyl derivative **6**. The intermediate tosylate **5** could then be converted to 2-azido derivative **7** with sodium azide. Ir, nmr and elemental analysis established the structure of **7**. The infrared spectrum showed the absorption band of the N_3 group at 2095 cm^{-1}. Following the reported method [14], we reduced the azido group of compound **7** using triphenylphosphine in pyridine and obtained the 2-amino analogue **8** in 45% yield (Scheme 1).

(*R*)-2,2-Dimethyl-1,3-dioxolan-4-ylmethyl *p*-toluenesulfonate (**9**) was prepared by treating (*S*)-2,2-dimethyl-1,3-dioxolane-4-methanol with 1 equivalent *p*-toluenesulfonyl chloride in anhydrous pyridine [15]. For the synthesis of dioxalane derivative **10**, compound **1** was likewise treated with 1 equiv. sodium hydride in anhydrous *N,N*-dimethylformamide followed by 1 equiv. of **9**. Treatment of **10**, after its chromatographic purification, with 80% acetic acid at room temperature afforded the corresponding dihydroxy

Scheme 1



Scheme 2

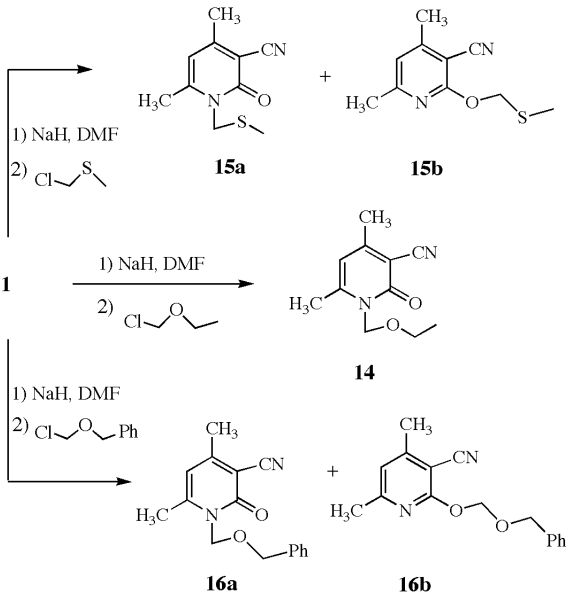


compound **11**, which was purified by column chromatography with methanol in chloroform (0-10%) to give the product **11** in 88% yield. Tosylation of **11** with 2 equiv. of tosyl chloride in anhydrous pyridine, the ditosylate derivative **12** was obtained in 37% yield. Azidation of **12** was performed in anhydrous *N,N*-dimethylformamide at 80 °C with sodium azide. The product **13** was identified by nmr, mass spectroscopy, elemental analysis and by characteristic peaks at 2092 and 2127 cm^{-1} in the infrared spectrum (Scheme 2).

We have also investigated the preparation of 1-(ethoxymethyl) pyridinone derivative **14**, which was obtained as a sole product, by alkylation of compound **1**, after its treatment with 60% sodium hydride in anhydrous *N,N*-dimethylformamide, with chloromethyl ethyl ether at room temperature followed by chromatographic purification. The structure of **14** was assigned on the basis of data of similar compounds [16]. Its ^1H nmr showed a singlet at δ 5.53 ppm corresponding to N-CH_2-O group and ^{13}C nmr showed a chemical shift of C-1 of the a cyclic part at δ 72.57 ppm. Similarly, treatment of **1** with sodium hydride in anhydrous *N,N*-dimethylformamide, followed by reaction with, either chloromethyl methyl sulfide, or benzyl chloromethyl ether gave a mixture of *N*- and *O*-alkylated products, **15a**, **16a** and **15b**, **16b**, respectively (Scheme 3). These product mixtures were separated by column chromatography with ethyl acetate in chloroform (0-10%); nmr, mass spectra and elemental analysis established their structures.

Finally, we investigated the preparation of the 1-(hydroxyethyl)pyridine derivative **18a**. The compound **1** was alkylated with 2-bromoethyl acetate by the method of Sasaki *et al* [12]. Alkylation at nitrogen and oxygen atoms took place to

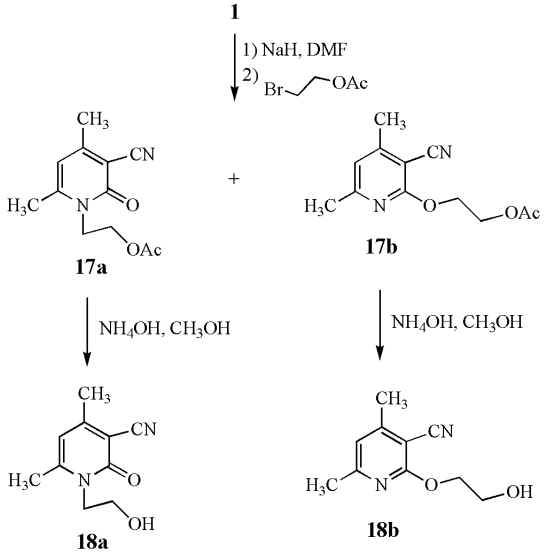
Scheme 3



afford two alkylated derivatives **17a** and **17b**, which could be separated by column chromatography with ethyl acetate in chloroform (0-10%). In the H^1 nmr spectra of **17a,b**, the triplet signals of the methylene protons appear at about δ 4.28-4.37 ppm for *N*-alkylated product **17a** and at δ 4.42-

4.62 ppm of *O*-alkylated product **17b**. In addition, ^{13}C nmr spectra showed the chemical shift of C-1 of the a cyclic part of **17a** at δ 43.94 ppm, while that of compound **17b** at δ 62.29 ppm. This indicated that the alkylation occurred on the nitrogen atom to give **17a** and on the oxygen atom to give **17b** in 54 and 29% yield, respectively. The subsequent ammonolysis of **17a,b**, with 1:1 mixture of methanol and concentrated ammonia at room temperature, afforded the corresponding hydroxy compounds **18a,b** in good yields (Scheme 4).

Scheme 4



EXPERIMENTAL

Melting points were determined on a Boetius melting point apparatus, and are uncorrected. Optical rotations were measured on Optical activity LTD, USA Patent NO. 4118125 at the Arab Drug Company, Cairo, Egypt. NMR were recorded at 300 MHz for ^1H nmr, 75.5 MHz for ^{13}C nmr on a Varian Gemini 2000 300 spectrometer; δ-values are in ppm relative to tetramethylsilane as internal standard. Mass spectra (EI, 70 eV) were obtained on a Varian Mat CH-6 spectrometer, and FAB spectra on a Kratos MS 50 RF spectrometer. The ir-spectra were recorded on a Nicolet 250 FT-IR spectrophotometer as potassium bromide pellets. Analytical silica gel (tlc) was performed on Merck precoated 60 F254 plates. The silica gel (0.040-0.063 mm) used for column chromatography was purchased from Merck. Elemental analyses were performed at the Chemistry Institute, Copenhagen University, Denmark and at the Micro Analytical Center, Faculty of Science, Cairo University.

General Procedure for the Preparation of Compounds **2a,b**, **14**, **15a,b 16a,b** and **17a,b**.

A mixture of **1** (2.0 g, 14 mmol) and 60% oil-immersed sodium hydride (560 mg, 14 mmol) in anhydrous *N,N*-dimethylformamide (20 ml) was stirred at room temperature for 2 h. Then, the appropriate 2-(acetoxyethoxy)methyl bromide or chloromethyl ethyl ether or chloromethyl methylsulfide or benzyl chloromethyl ether and/or bromo ethylacetate (14.1 mmol) was added dropwise at 0 °C. After completion of the addition, the reaction mixture was stirred for an additional 12 h at room temperature. The solvent was removed by evaporation in *vacuo* and the resulting residue was co-evaporated with anhydrous toluene (3x10 ml). The compounds were purified by silica gel column chromatography with ethyl acetate in chloroform: (0-10%). Fractions with *O*-alkylated derivatives **2b**, **15b, 16b** and **17b** were eluted faster than their *N*-alkylated counterparts **2a**, **15a**, **16a** and **17a**. While, *N*-alkylated product **14** was obtained as a sole product.

1-(2-Acetoxyethoxymethyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**2a**).

This compound was obtained as colorless prisms, yield 1.7 g (49%); mp 74-76 °C (diisopropyl ether); ir (potassium bromide): CN 2219, CO 1745. CO 1650 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.05 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 3.83 (t, J = 4.6 Hz, 2H, CH_2), 4.18 (t, J = 4.6 Hz, 2H, CH_2), 5.57 (s, 2H, NCH_2O), 6.06 (s, 1H, C_5-H); ^{13}C nmr (deuteriochloroform): δ 20.01, 20.89, 21.15 (3 x CH_3), 63.10, 68.06 (2 x CH_2), 73.04 (NCH_2O), 102.01 (C-3), 109.91 (CN), 115.18 (C-4), 151.28 (C-5), 159.80 (C-6), 161.63 (C-2), 170.83 (CO); EI ms: m/z 264 (30%, M^+), 149 (15), 148 (17), 43 (100).

Anal. Calcd. for $C_{13}H_{16}N_2O_4$ (264.28): C, 59.08; H, 6.10; N, 10.60. Found: C, 59.29; H, 6.16; N, 10.51.

2-[(2-Acetoxyethoxymethoxy)]-4,6-dimethylpyridine-3-carbonitrile (**2b**).

This compound was obtained as colorless prisms, yield 1.2 g (34%); mp 49-51 °C (petroleum ether); ir (potassium bromide): CN 2222, CO 1741 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.06 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 3.99 (t, J = 4.7 Hz, 2H, CH_2), 4,26 (t, J = 4.7 Hz, 2H, CH_2), 5.70 (s, 2H, OCH_2O), 6.76 (s, 1H, C_5-H); ^{13}C nmr (deuteriochloroform): δ 20.00, 20.78, 24.46 (3 x CH_3), 63.18, 67.06 (2 x CH_2), 90.86 (OCH_2O), 94.46 (C-3), 114.55 (CN), 118.44 (C-4), 154.53 (C-5), 160.69 (C-6), 162.61 (C-2), 170.24 (CO); EI ms: m/z 264 (4%, M^+), 148 (5), 87 (20), 43 (100).

Anal. Calcd. for $C_{13}H_{16}N_2O_4$ (264.28): C, 59.08; H, 6.10; N, 10.60. Found: C, 58.73; H, 6.19; N, 10.47.

4,6-Dimethyl-1-ethoxymethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**14**).

This compound was obtained as colorless prisms, yield 1.7 g (59%); mp 94 – 96 °C (diisopropyl ether); ^1H nmr (deuteriochloroform): δ 1.18 (t, J = 6.5 Hz, 3H, CH_3) 2.39 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 3.64 (q, J = 7.0 Hz, 2H, CH_2), 5.53 (s, 2H, CH_2), 6.05 (s, 1H, C_5-H); ^{13}C nmr (deuteriochloroform): δ 14.94, 19.84, 20.92 (3 x CH_3), 65.43 (CH_2) 72.57 (NCH_2O), 101.65 (C-3), 109.64 (CN), 115.17 (C-4), 151.29 (C-5), 159.37 (C-6), 161.41 (C-2), EI ms: m/z 206 (30%, M^+), 177 (20), 162 (90), 149 (100).

Anal. Calcd. for $C_{11}H_{14}N_2O_2$ (206.24): C, 64.06; H, 6.84; N, 13.58. Found: C, 64.00; H, 6.97; N, 13.42.

4,6-Dimethyl-1-(methylthiomethyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (**15a**).

This compound was obtained as yellow crystals, yield 0.9 g (32%); mp 92-94 °C (diisopropyl ether); ^1H nmr (deuteriochloroform): δ 2.30 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 5.17 (s, 2H, CH_2), 6.08 (s, 1H, C_5-H); ^{13}C nmr (deuteriochloro-

form): δ 15.93, 20.70, 20.86 (3 x CH_3), 46.69 (CH_2), 101.24 (C-3), 109.97 (CN), 115.22 (C-4), 150.42 (C-5), 158.45 (C-6), 161.12 (C-2), EI ms: m/z 208 (50%, M^+), 162 (55), 149 (40), 61 (100).

Anal. Calcd. for $C_{10}H_{12}N_2O_S$ (208.24): C, 57.67; H, 5.81; N, 13.45. Found: C, 57.45; H, 5.83; N, 13.30.

4,6-Dimethyl-2-(methylthiomethoxy)pyridine-3-carbonitrile (**15b**).

This compound was obtained as yellow crystals, yield 1.3 g (46%); mp 61-62 ˚C (petroleum ether); ^{1}H nmr (deuteriochloroform): δ 2.32 (s, 3H, CH_3), 2.46 (s, 6H, 2 x CH_3), 5.56 (s, 2H, CH_2), 6.74 (s, 1H, C_5-H); ^{13}C nmr (deuteriochloroform): δ 15.16, 19.97, 24.43 (3 x CH_3), 70.68 (CH_2), 94.84 (C-3), 114.62 (CN), 118.10 (C-4), 154.49 (C-5), 160.45 (C-6), 162.70 (C-2); EI ms: m/z 208 (10%, M^+), 162 (50), 149 (30), 61 (100).

Anal. Calcd. for $C_{10}H_{12}N_2OS$ (208.24): C, 57.67; H, 5.81; N, 13.45. Found: C, 57.96; H, 5.64; N, 13.63.

1-Benzyloxymethyl-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**16a**).

This compound was obtained as colorless crystals, yield 1.9 g (53%); mp 127-129 ˚C (diisopropyl ether); ^{1}H nmr (deuteriochloroform): δ 2.36 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 4.66 (s, 2H, CH_2), 5.60 (s, 2H, CH_2), 6.00 (s, 1H, C_5-H), 7.30-7.33 (m, 5H, phenyl); ^{13}C nmr (deuteriochloroform): δ 19.93, 20.94, (2 x CH_3), 72.08, 72.58 (2 x CH_2), 102.02 (C-3), 109.70 (CN), 115.15 (C-4), 127.62, 127.69, 127.87, 128.34, 137.00 (Phenyl), 151.14 (C-5), 159.48 (C-6), 161.45 (C-2); ms: m/z 268 (1%, M^+), 238 (5), 162 (30), 91 (100).

Anal. Calcd. for $C_{16}H_{16}N_2O_2$ (268.31): C, 71.62; H, 6.01; N, 10.44. Found: C, 71.55; H, 5.80; N, 10.21.

2-Benzyloxymethyloxy-4,6-dimethylpyridine-3-carbonitrile (**16b**).

This compound was obtained as colorless crystals, yield 1.0 g (28%); mp 39-42 ˚C (petroleum ether); ^{1}H nmr (deuteriochloroform): δ 2.45 (s, 6H,2 x CH_3), 4.85 (s, 2H, CH_2), 5.68 (s, 2H, CH_2), 6.66 (s, 1H, C_5-H), 7.25-7.41 (m, 5H, Phenyl); ^{13}C nmr (deuteriochloroform): δ 19.81, 23.97, (2 x CH_3), 71.24, 89.77 (2 x CH_2), 99.13 (C-3), 109.16 (CN), 118.34 (C-4), 127.66, 127.77, 127.88, 128.06, 137.78 (Phenyl), 154.55 (C-5), 160.82 (C-6), 162.13 (C-2); HRms (MALADI): m/z 291 (M+Na^+): *Anal*. Calcd. For $C_{16}H_{16}N_2O_2Na$: 291.1104. Found: 291.1102.

Anal. Calcd. for $C_{16}H_{16}N_2O_2$ (268.31): C, 71.62; H, 6.01; N, 10.44. Found: C, 71.34; H, 6.10; N, 10.00.

1-(2-Acetoxyethyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**17a**).

This compound was obtained as colorless prisms, yield 1.9 g (54%); mp 119-121 ˚C (diisopropyl ether); ^{1}H nmr (deuteriochloroform): δ 2.05 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 4.28 (t, J = 5.3 Hz, 2H, CH_2), 4.37 (t, J = 5.3 Hz, 2H, CH_2), 6.08 (s, 1H, C_5-H); ^{13}C nmr (deuteriochloroform): δ 20.67, 20.80, 21.07 (3 x CH_3), 43.94, 61.18 (2 x CH_2), 101.51 (C-3), 109.60 (CN), 115.18 (C-4), 150.83 (C-5), 158.45 (C-6), 160.77 (C-2), 170.33 (CO); EI ms: m/z 234 (10%, M^+), 173 (20), 149 (70), 43 (100).

Anal. Calcd. for $C_{12}H_{14}N_2O_3$ (234.25): C, 61.53; H, 6.02; N, 12.01. Found: C, 61.63; H, 6.13; N, 11.96.

2-(2-Acetoxyethoxy)-4,6-dimethylpyridine-3-carbonitrile (**17b**).

This compound was obtained as colorless prisms, yield 1.0 g (29%); mp 74-76 ˚C (petroleum ether); ^{1}H nmr (deuteriochloroform): δ 2.09 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 4.42 (t, J = 4.8 Hz, 2H, CH_2), 4.62 (t, J = 4.8 Hz, 2H, CH_2), 6.72 (s, 1H, C_5-H); ^{13}C nmr (deuteriochloroform): δ 19.98, 20.78, 24.42 (3 x CH_3), 62.29, 64.43 (2 x CH_2), 94.05 (C-3), 114.67 (CN), 117.79 (C-4), 154.49 (C-5), 162.44 (C-6), 163.32 (C-2), 170.93 (CO); EI ms: m/z 234 (2%, M^+), 148 (10), 87 (50), 43 (100).

Anal. Calcd. for $C_{12}H_{14}N_2O_3$ (234.25): C, 61.53; H, 6.02; N, 12.01. Found: C, 61.58; H, 6.14; N, 11.95.

[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl 4-methylbenzenesulfonate (**9**) [15].

p-Toluenesulfonyl chloride (8.57 g, 50 mmol) was added to an ice-cooled solution of (*S*)-2,2-dimethyl-1,3-dioxolane-4-methanol (6.6 g, 50 mmol) in anhydrous pyridine (100 ml) and left to stand for 24 h at 4 ˚C, then 4 h at room temperature. The pyridine was removed by evaporation *in vacuo*, co-evaporated with toluene (3x10 ml) and the residue purified by silica gel column chromatography with diethyl ether:petroleum ether (5:95, v/v) to give **9** (12.3 g. 97%) as a colorless viscous oil; $[\alpha]_D^{20}$ +110° (c 0.113, MeOH); ^{1}H nmr (deuteriochloroform): δ 1.16 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.62 (q, J = 4.9 Hz, 1H, Ha of CH_2), 3.82-3.90 (m, 3H, Hb of CH_2 and CH_2), 4.12 (t, J = 5.7 Hz, 1H, CH), 7.20 (d, J = 8.2 Hz, 2H, Ar-H), 7.64 (d, J = 8.2, 2H, Ar-H); ^{13}C nmr (deuteriochloroform): δ 21.59, 25.09, 26.58 (3 x CH_3), 66.12, 69.44 (2 x CH_2), 72.85 (CH), 109.99 (CMe_2), 127.93, 129.86, 132.59, 145.02 (Ar).

1-{[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl}-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**10**).

To a stirred solution of **1** (2.0 g, 14 mmol) in anhydrous *N,N*-dimethylformamide (20 ml) was added sodium hydride (560 mg of 60% dispersion in mineral oil, 14 mmol), and after complete evolving of hydrogen (2 h), then compound **9** (3.56 g, 14 mmol) was added, the reaction mixture stirred for additional 12 h at 90 ˚C, cooled to room temperature and filtered through Celite. The filtrate was evaporated till dryness at reduced pressure, co-evaporated with toluene (3x10 ml) and the residue was purified by silica gel column chromatography with ethyl acetate:chloroform (10:90, v/v) to give **10** (1.5 g, 43%) as a white solid mp 142-144˚C; $[\alpha]_D^{20}$ -121° (c 1.10, MeOH); ^{1}H nmr (deuteriochloroform): δ 1.30 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 3.67-3.72 (m, 1H, CH_2), 3.89-3.96 (m, 1H, CH_2), 4.16-4.21 (m, 1H, CH) 4.37-4.52 (m, 2H, CH_2), 6.07 (s, 1H, H-5); ^{13}C nmr (deuteriochloroform): δ 20.81, 21.59, 24.91, 26.35 (4 x CH_3), 47.86 (CH_2), 67.11 (CH_2), 73.66 (CH), 109.69 (CN), 109.73 (C(CH_3)2), 101.15 (C-3), 115.28 (C-4), 151.71 (C-5), 158.34 (C-6), 161.07 (C-2); EI ms: m/z 262 (5%, M^+), 247 (20), 148 (20), 43 (100).

Anal. Calcd. for $C_{14}H_{18}N_2O_3$ (262.31): C, 64.11; H, 6.92; N, 10.68. Found: C, 63.88; H, 7.04; N, 10.45.

General Procedure for the Deprotection of Compounds **2a,b** and **17a,b**.

A mixture of **2a** or **2b** or **17a** and/or **17b** (4 mmol), methanol (30 ml), and concentrated aqueous ammonia (25%, 30 ml) was stirred at room temperature for 24 h. The solvent was evaporated in *vacuo* and the residue was triturated with a small volume of ethanol. A white precipitate was collected by filtration, dried and recrystallized from methanol to give **3, 4, 18a** and **18b,**respectively.

4,6-Dimethyl-1-(2-hydroxyethoxymethyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (**3**).

This compound was obtained as colorless prisms, yield 0.9 g (89%); mp 91-93 °C; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.32 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 3.46-3.52 (m, 4H, 2 x CH_2), 4.64 (br s, 1H, OH), 5.49 (s, 2H, NCH_2O), 6.32 (s, 1H, C_5-H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 18.85, 20.03 (2 x CH_3), 59.41, 70.42(2 x CH_2), 72.09(NCH_2O) 99.18 (C-3), 108.99 (CN), 115.29 (C-4), 152.17 (C-5), 159.43 (C-6), 160.32 (C-2); EI ms: m/z 222 (3%, M^+), 161 (40), 148 (100).

Anal. Calcd. for $C_{11}H_{14}N_2O_3$ (222.24): C, 59.45; H, 6.35; N, 12.60. Found: C, 59.21; H, 6.37; N, 12.61.

4,6-Dimethyl-2-(2-hydroxyethoxymethoxy)pyridine-3-carbonitrile (**4**).

This compound was obtained as colorless prisms, yield 0.5 g (63%); mp 36-38 °C; ^{1}H nmr (deuteriochloroform): δ 2.46 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 3.80 (t, J = 4.4 Hz, 2H, CH_2), 3.91 (t, J = 4.4 Hz, 2H, CH_2), 4.78 (br s, 1H, OH), 5.71 (s, 2H, OCH_2O), 6.78 (s, 1H, C_5-H); ^{13}C nmr (deuteriochloroform): δ 19.95, 24.39 (2 x CH_3), 60.50, 71.45 (2 x CH_2), 91.24 (OCH_2O), 94.32 (C-3), 114.57 (CN), 118.45 (C-4), 154.58 (C-5), 160.70 (C-6), 162.63 (C-2); EI ms: m/z 222 (5%, M^+), 148 (100), 119 (70).

Anal. Calcd. for $C_{11}H_{14}N_2O_3$ (222.24): C, 59.45; H, 6.35; N, 12.60. Found: C, 59.62; H, 6.37; N, 12.63.

4,6-Dimethyl-1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (**18a**).

This compound was obtained as colorless prisms, yield 0.7 g (95%); mp 139-141 °C; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.30 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 3.62 (q, J = 5.6 Hz, 2H, CH_2), 4.03 (t, J = 5.6 Hz, 2H, CH_2), 4.96 (t, J = 5.5 Hz, 1H, OH), 6.29 (s, 1H, C_5-H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 19.76, 20.50 (2 x CH_3), 46.61, 57.53 (2 x CH_2), 98.47 (C-3), 108.57 (CN), 115.64 (C-4), 153.04 (C-5), 157.62 (C-6), 159.88 (C-2); EI ms: m/z 192 (15%, M^+), 149 (100), 133 (40), 119 (50).

Anal. Calcd. for $C_{10}H_{12}N_2O_2$ (192.22): C, 62.49; H, 6.29; N, 14.57. Found: C, 62.54; H, 6.35; N, 14.56.

4,6-Dimethyl-2-(2-hydroxyethoxy)pyridine-3-carbonitrile (**18b**).

This compound was obtained as colorless prisms, yield 0.5 g (65%); mp 43-45 °C; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.40 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.72 (t, J = 5.1 Hz, 2H, CH_2), 4.39 (t, J = 5.1 Hz, 2H, CH_2), 4.88 (br s, 1H, OH), 6.95 (s, 1H, C_5-H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 19.05, 23.68 (2 x CH_3), 58.54, 67.74 (2 x CH_2), 92.43 (C-3), 114.33 (CN), 117.22 (C-4), 154.23 (C-5), 159.95 (C-6), 162.81 (C-2); EI ms: m/z 192 (5%, M^+), 149 (40), 119 (60), 31 (100).

Anal. Calcd. for $C_{10}H_{12}N_2O_2$ (192.22): C, 62.49; H, 6.29; N, 14.57. Found: C, 62.17; H, 6.02; N, 14.88.

1-[(2*S*)-2,3-dihydroxypropyl]-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**11**).

Compound **10** (400 mg) was stirred in 80% aqueous acetic acid (10 ml) for 24 h at room temperature. The solvent was removed by evaporation in *vacuo* and the resulting residue co-evaporated with water (10 ml), and finally ethanol (3x5ml). The residue was purified by silica gel column chromatography with methanol:chloroform (10:90, v/v) to give **11** (300 mg, 88%) as a white prisms, mp 201-203 °C (methanol); $[\alpha]_D^{20}$ -275° (c 0.100, MeOH); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.30 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 3.75-3.84 (m, 3H, CH, CH_2), 4.15-4.19 (m, 2H, CH_2), 4.81 (br s, 1H, OH), 5.09 (br s, 1H, OH), 6.28 (s, 1H, H-5); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 19.75, 20.71 (2 x CH_3), 47.66 (CH_2), 63.58 (CH_2), 67.99 (CH), 98.36 (C-3), 108.60 (CN), 115.71 (C-4), 153.48 (C-5), 157.49 (C-6), 160.09 (C-2).

Anal. Calcd. for $C_{11}H_{14}N_2O_3$•0.5H_2O (231.25): C, 57.13; H, 6.10; N, 12.11. Found: C, 56.75; H, 6.39; N, 11.72.

4,6-Dimethyl-1-(2-O-*p*-Tolylsulfonylethoxymethyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (**5**).

p-Toluenesulfonyl chloride (760 mg, 4 mmol) was added to an ice-cooled stirred solution of **3** (890 mg, 4 mmol) in anhydrous pyridine (15 ml) and left to stand overnight at 4 °C. Pyridine was removed by evaporation under reduced pressure and the resulting gum was triturated with ice water. The product solidified as a white precipitate and was collected by filtration, washed with water, dried and recrystallized from diethyl ether to afford **5** (0.9 g, 60%) as a colorless crystals mp 76-78 °C; ir (potassium bromide): CN 2221, CO 1653, O-SO_2 1199 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.39 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 3.82 (t, J = 1.3 Hz, 2H, CH_2), 4.09 (t, J = 1.3 Hz, 2H, CH_2), 5.49 (s, 2H, NCH_2O), 6.04 (s, 1H, C_5-H), 7.34 (d, J = 8.7 Hz, 2H, Ar-H), 7.76 (d, J = 8.7 Hz, 2H, Ar-H); ^{13}C nmr (deuteriochloroform): δ 19.88, 21.05, 21.60 (3 x CH_3), 67.57, 68.70 (2 x CH_2), 72.78 (NCH_2O) 102.21 (C-3), 109.95 (CN), 115.06 (C-4), 127.81, 129.86, 132.67, 144.99 (Ar), 151.10 (C-5), 159.84 (C-6), 161.58 (C-2); EI ms: m/z 376 (10%, M^+), 229 (30), 155 (75), 91 (100).

Anal. Calcd. for $C_{18}H_{20}N_2O_5S$ (376.42): C, 57.43; H, 5.36; N, 7.44 Found: C, 57.08; H, 5.45; N, 7.59.

3-Cyano-4,6-dimethyl-2(1*H*)pyridone (**1**).

This compound was prepared from **4** (890 mg, 4 mmol) and *p*-toluenesulfonyl chloride (760 mg, 4 mmol) by the method described for the preparation of **5** to afford a product, which was spectroscopically equivalent with the starting material **1**, and the melting point of the two mixed materials was undepressed; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.23 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 6.16 (s, 1H, C_5-H), 12.30 (br s, 1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 18.37, 20.10 (2 x CH_3), 98.58 (C-3), 106.91(CN), 115.54 (C-4), 150.69 (C-5), 159.89 (C-6), 160.44 (C-2).

(1*R*)-2-(3-Cyano-4,6-dimethyl-2-oxopyridin-1(2*H*)-yl)-1-{[(4-methylbenzenesulfonyl)oxy]methyl}ethyl 4-methylbenzenesulfonate (**12**).

This compound was prepared from **11** (800 mg, 3.2 mmol) and *p*-toluenesulfonyl chloride (1.2 g, 6.4 mmol) by the method described for the preparation of **5**. The crude product was recrystallized from diethyl ether to give **12** (700 mg, 37%) as a colorless crystals, mp 147-149 °C; $[\alpha]_D^{20}$ +135° (c 0.052, MeOH); ^{1}H nmr (deuteriochloroform): δ 2.35 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 4.03-4.36 (m, 4H, 2 CH_2), 4.95-4.99 (dd, J_1 = 2.7, J_2 = 9.6, 1H, CH), 5.94 (s, 1H, H-5), 7.22 (d, J = 8.1 Hz, 2H, Ar-H), 7.39 (d, J = 8.0, 2H, Ar-H), 7.49 (d, J = 8.1, 2H, Ar-H), 7.80 (d, J = 8.0 Hz, 2H, Ar-H); ^{13}C nmr (deuteriochloroform): δ 20.80, 21.25, 21.71, 21.85 (4 x CH_3), 45.75 (CH_2), 68.77 (CH_2), 74.46 (CH), 101.48 (C-3), 109.68 (CN), 114.65 (C-4), 127.69, 128.05, 129.93, 130.15, 131.11, 131.49, 145.58, 145.72 (Ar-C), 151.00 (C-5), 158.50 (C-6), 160.39 (C-2).

Anal. Calcd. for $C_{25}H_{26}N_2O_7S_2$ (530.61): C, 56.59; H, 4.94; N, 5.28 Found: C, 56.36; H, 4.78; N, 5.11.

1-(2-Azidoethoxymethyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**7**).

A mixture of **5**, (750 mg, 2 mmol) and sodium azide (130 mg, 2 mmol) in anhydrous *N,N*-dimethylformamide (10 ml) was heated for 2 h at 80 °C. The solvent was removed by evaporation under reduced pressure and the remaining syrup triturated with ice water. A white precipitate was collected by filtration, washed with ice-water. The product was recrystallized from diethyl ether to give **7** as colorless crystals, 340 mg (75%); mp 87-89 °C; ir (potassium bromide): CN 2218, N_3 2095, CO 1651 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.40 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 3.37 (t, J = 4.6 Hz, 2H, CH_2), 3.83 (t, J = 4.6 Hz, 2H, CH_2), 5.58 (s, 2H, NCH_2O), 6.07 (s, 1H, C_5-H); ^{13}C nmr (deuteriochloroform): δ 19.84, 21.02 (2 x CH_3), 50.47, 69.01 (2 x CH_2), 72.81 (NCH_2O), 101.84 (C-3), 109.87 (CN), 115.02 (C-4), 151.07 (C-5), 159.75 (C-6), 161.51 (C-2).

Anal. Calcd. for $C_{11}H_{13}N_5O_2$ (247.25): C, 53.43; H, 5.30; N, 28.32 Found: C, 53.32; H, 5.31; N, 27.40.

1-(2-Aminoethoxymethyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**8**).

The azido compound **7** (250 mg, 1 mmol) and triphenylphosphine (263 mg, 1 mmol) were dissolved in 15 ml of pyridine and stirred at room temperature for 1 h. Concentrated aqueous ammonia (25%, 5 ml) was then added and the solution was stirred for 2 h. The solvent was removed by evaporation in *vacuo* and the resulting residue was co-evaporated with anhydrous toluene (2x10 ml). The product was purified by silica gel column chromatography in methanol:chloroform (0-30%) to give **8** (100 mg, 45%) as a colorless crystals, mp 57-59 °C (methanol); ir (potassium bromide): NH_2 3400-3500, CN 2219, CO 1653 cm^{-1}; ^1H nmr (deuteriumoxide): δ 2.40 (br s, 3H, CH_3), 2.52 (br s, 3H, CH_3), 2.80 (dd, J = 5.2 Hz, 2H, CH_2), 3.66 (dd, J = 5.2 Hz, 2H, CH_2), 4.76 (d, J = 5.2 Hz, 2H, NH_2), 5.55 (d, J = 5.5 Hz, 2H, CH_2), 6.44 (d, J = 5.4 Hz, 1H, C_5-H); HRms (MALADI): m/z 244 ($M+Na^+$): *Anal*. Calcd. for $C_{11}H_{15}N_3O_2Na$: 244.1057. Found: 244.1053.

1-[(2*S*)-2,3-diazidopropyl]-4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-carbonitrile (**13**).

This compound was prepared from **12** (530 mg, 1 mmol) and sodium azide (130 mg, 2 mmol) by the method described for the preparation of **7**. The product was recrystallized from diethyl ether as colorless crystals, 0.12 g (60%); mp 83-86 °C; $[\alpha]_D^{20}$ -336° (c 0.052, MeOH); ir (potassium bromide): CN 2217, N_3 2127, N_3 2092, CO 1646 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.41 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 3.46-3.52 (m, 1H, CH_2), 3.69-3.83 (m, 3H, CH and CH_2), 4.22-4.32 (m, 2H, CH_2), 6.11 (s, 1H, C_5-H); ^{13}C nmr (deuteriochloroform): δ 20.91, 21.54 (2 x CH_3), 46.67 (CH_2), 52.70 (CH_2), 59.10 (CH), 101.55 (C-3), 110.06 (CN), 115.02 (C-4), 151.16 (C-5), 158.95 (C-6), 161.00 (C-2); HRms (MALDI): m/z 295 ($M+Na^+$): *Anal*. Calcd. for $C_{11}H_{12}N_8ONa$: 295.1026, $C_{11}H_{12}N_4ONa$ (MNa^+-N_4): 239.0903, Found 295.1030, 239.0898.

Anal. Calcd. for $C_{11}H_{12}N_8O$ (272.28): C, 48.52; H, 4.44; N, 41.16 Found: C, 48.16; H, 4.36; N, 40.86.

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