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An Approach to Acyclo-1-Deazathymidine C-Nucleosides via 3,5-Dichloro-6-Methyl-2*H*-1,4-Oxazin-2-one.

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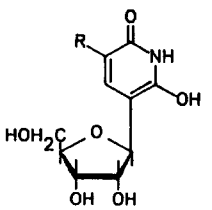
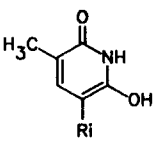
Abstract : An approach to the synthesis of acyclo-1-deazathymidine nucleosides is described. Diels-Alder reaction of 3,5-dichloro-6-methyl-2*H*-1,4-oxazin-2-one with acetylenic compounds **4** and **5** yielded the 3-[(tetrahydropyran-2-yl)oxy]-methyl- and 3-bromomethyl-5-methyl-2,6-dichloropyridine intermediates **7** and **8**. The bromomethyl group of compound **8** underwent easy substitution with the appropriate nucleophiles, permitting the introduction of acyclo sugar moieties. The resulting 3-substituted 2,6-dichloro-5-methyl pyridines **9a,b** - precursors for some acyclo pyridine-C-nucleosides - were treated with sodium phenylmethoxide to afford 2,6-dibenzyloxypyridines **10a,b**. Debenzylation using a palladium-strontium carbonate catalyst gave the unstable C-nucleosides **2a,b** of the 6-hydroxy-1*H*-pyridin-2-one type. A stable 6-hydroxy-1*H*-pyridin-2-one **2c**, exempt from benzylic oxygen, was obtained via cycloaddition of THP-protected 6-hydroxy-1-hexyne.

INTRODUCTION

Pyridine C-nucleosides are described scantily in the literature. Mertes et al[1] reported the synthesis of the 1-deazauridine **1a**, a 6-hydroxy-1*H*-pyridin-2-one-C-nucleoside which was found to be unstable and subject to oxidative degradation. Koomen et al[2] confirmed the unstable character of nucleoside **1a** which they prepared through oxidation of the corresponding glutarimide. Although they expected a higher stability for the 1-deazathymidine **1b**, this compound eluded their synthetic efforts.[3]



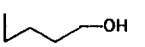


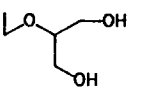
2a–c

1a : R = H

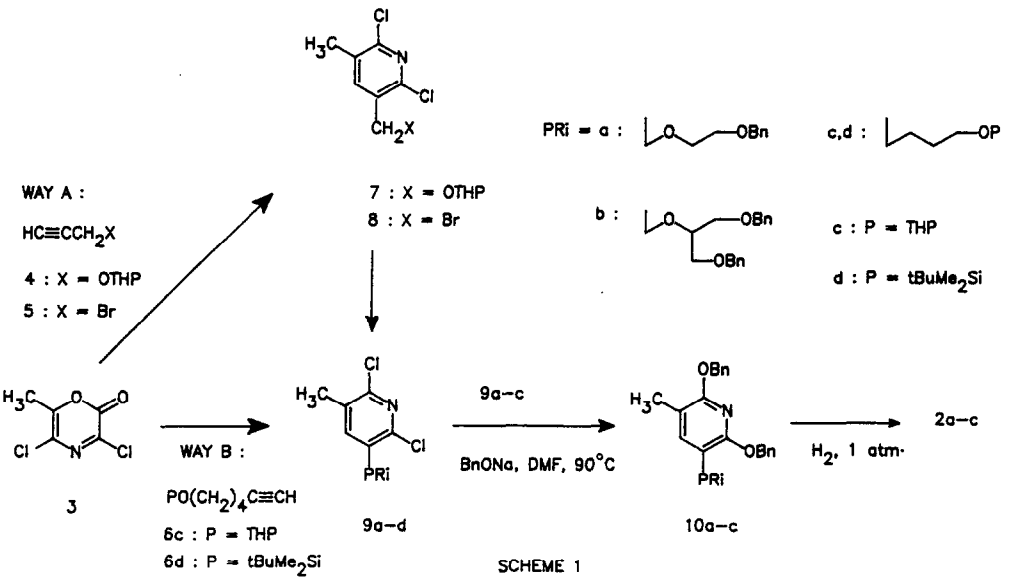
1b : R = CH_3

a : Ri = 

c : Ri = 

b : Ri = 

We tried an alternative approach to 1-deaza-thymidine compounds **2a-c** using the excellent Diels-Alder reactivity of the 2-azadiene system of 3,5-dichloro-6-methyl-2*H*-1,4-oxazin-2-one **3**,[4] prepared from 2-hydroxy-1-propanenitrile and oxalyl chloride.[5] Acyclo analogues of nucleosides, more easily accessible than those with cyclic carbohydrate structure, exhibit antiviral and antitumour activity [e.g. acyclovir and 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine].[6] The bioactivity observed for these acyclo analogues with structural features common to that of the ß-D-ribofuranosyl group, and the recent interest in carbocyclic[7-10] and carba acyclo[11-13] nucleoside analogues encouraged us to tackle the synthesis of acyclo and carba acyclo C-nucleosides of type **2a,b** and **2c**.

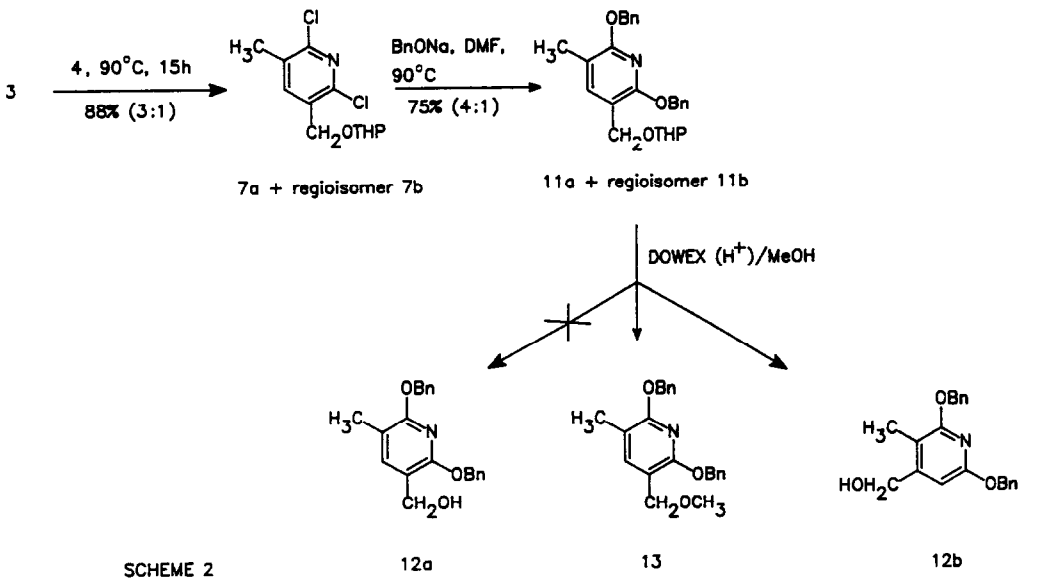


SCHEME 1

RESULTS AND DISCUSSION

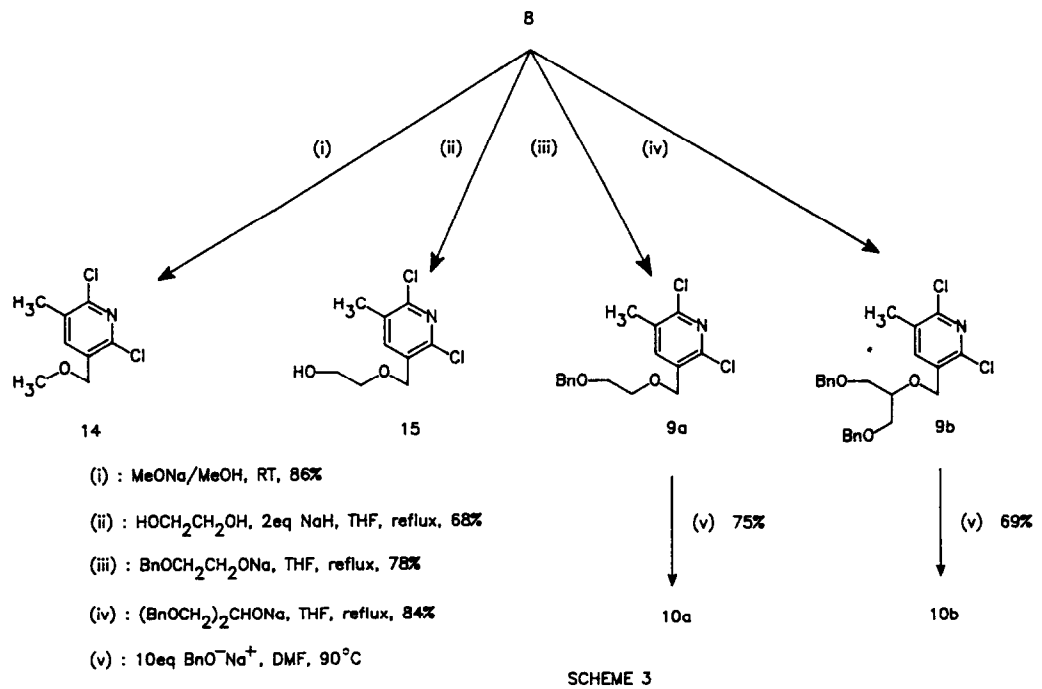
Two approaches (way A and B in Scheme 1) were considered for the synthesis of **2a-c**. The indirect way A used for compounds **2a,b** involves the Diels-Alder reaction of the acetylenes **4** and **5** and oxazinone **3** to generate precursors **7** and **8**. These could be elaborated further into compounds **10a,b** via intermediates **9a,b** . The more direct approach involving cycloaddition of the appropriate acetylene **6** to oxazinone **3** should produce precursors **9c,d**, ready for conversion into C-nucleoside **2c** via compounds of type **10**.

We first tested the Diels-Alder reaction of oxazinone **3** with THP-protected acetylene **4** (scheme 2). Heating at 90°C in toluene for several hours yielded the 2,6-dichloropyridine **7a** (66%) and the undesired regioisomer **7b** (22%) . To avoid a tedious chromatographic separation, the mixture of regioisomers was heated at 90°C with an excess of sodium phenylmethoxide in dimethylformamide to give the corresponding 2,6-dibenzyloxypyridines **11a,b**. Since separation of the isomers was difficult, acid deprotection of the tetrahydropyranyl group was tried out on the mixture. However, this acid treatment (Dowex 50W/H^+ in methanol) gave rise to another problem. Whereas **11b** gave the expected compound **12b**, regioisomer **11a** did not produce 3-hydroxymethylpyridine **12a**, but instead the 3-methoxymethyl derivative **13**. A similar observation with an analogous THP-protected hydroxymethyl pyridine has been reported.[14]



SCHEME 2

In view of the poor regioselectivity (**7a**/**7b**), the tedious chromatographic separation and the unsuccessful deprotection of compound **11a**, this approach had to be abandoned. The 3-bromomethyl derivative **8** proved to be a more suitable intermediate in the synthesis of compounds **2a,b**. It was formed regioselectively in the Diels-Alder reaction. Subsequent selective substitution of the bromine atom with methoxide afforded the model compound 3-methoxymethyl pyridine **14** (scheme 3).

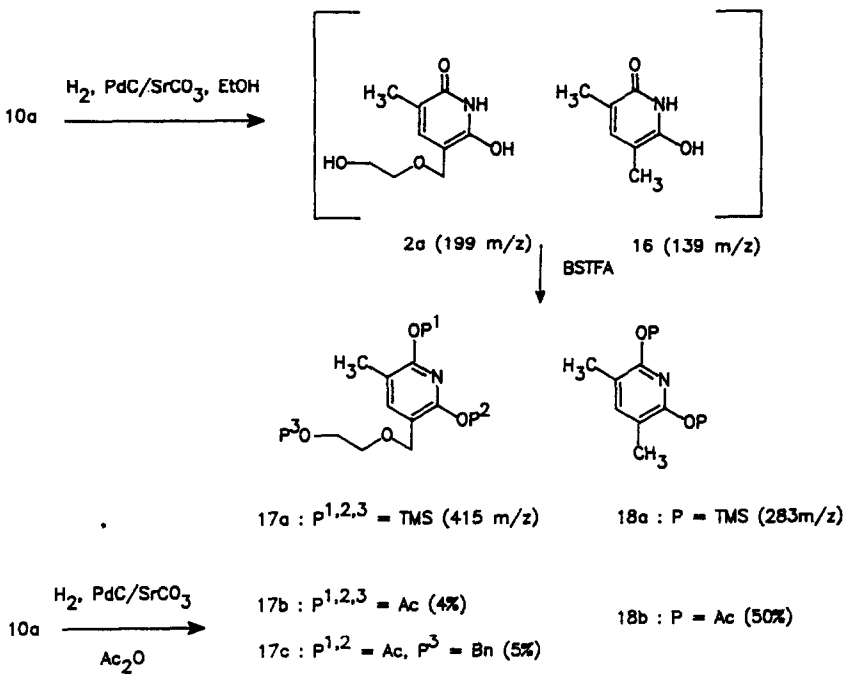


SCHEME 3

Selective substitution also was observed in the reaction of **8** with the anions of 1,2-ethanediol, 2-benzyloxyethanol and 1,3-dibenzyloxy-2-propanol yielding the respective pyridines **15** and **9a,b**. The selectivity of the substitution reaction was demonstrated by ^{13}C-NMR spectral data. The absorption of the bromomethyl carbon in compound **8** at 28.1 ppm was shifted to ca 68 ppm for pyridines **14-15** and **9a,b**. The absorptions for the carbons in positions 2 and 6 remained unchanged with respect to the values for compound **8**.

Pyridines **9a,b** were converted to the 2,6-dibenzyloxypyridines **10a,b** by heating at 90°C with an excess of sodium phenylmethoxide in dry dimethylformamide (scheme 3). The ^{13}C-NMR absorptions of carbon atoms 2 and 6 in the pyridine ring shifted from 144-148 ppm (**9a,b**) to 157-158 ppm (**10a,b**).

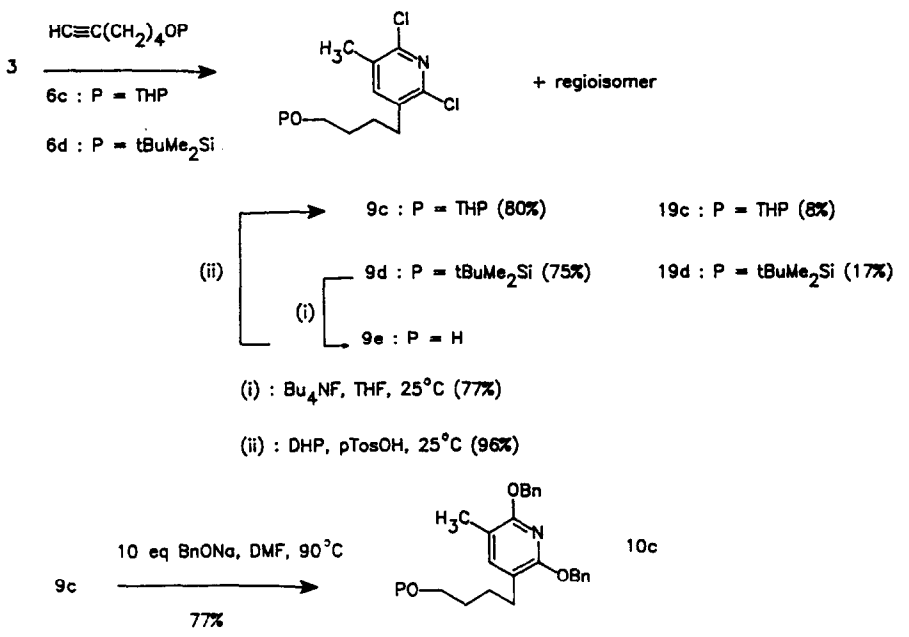
Removal of the benzyl groups was performed in ethanol with hydrogen at atmospheric pressure, using a gas buret for control of the hydrogen consumption. Palladium on carbon catalyst poisoned by strontium carbonate[15] was used to prevent overreduction to glutarimide.[1] Work-up of the reaction mixture by centrifugation, filtration and evaporation yielded a white powder which turned purple after a few minutes. Direct mass spectrometric analysis of the mixture from **10a** suggested the presence of mainly two 6-hydroxy-1H-pyridin-2-ones, **2a** and **16** (scheme 4). The molecular ion of the latter compound appeared at m/z 139, whereas only the ion $[M-17]^+$ (m/z 182) could be detected for **2a**. The reaction mixture was treated with BSFTA (bistrifluorotrimethylsilyl acetamide) to obtain the trimethylsilyl-protected derivatives **17a** and **18a**. The mass spectral analysis showed a peak at m/z 282 corresponding to loss of the 2-(trimethylsilyloxy)ethoxy group from the molecular ion of the silylated derivative **17a** (MW : 415). The ion at m/z 283 is in agreement with the molecular formula of **18a**.



SCHEME 4

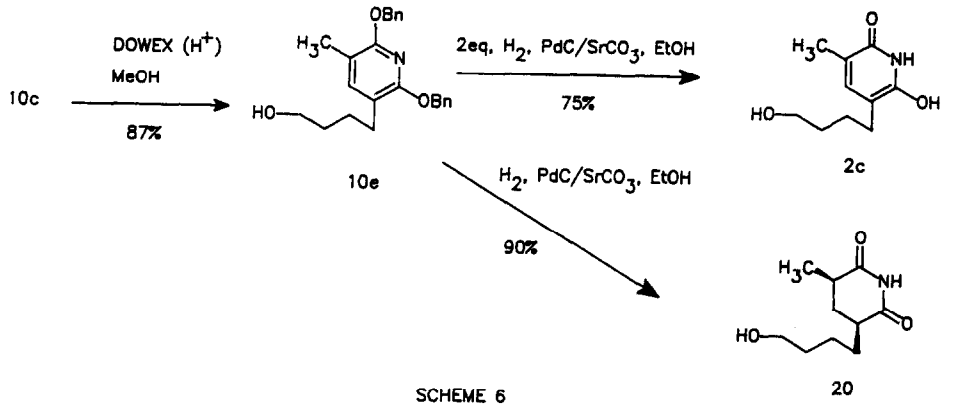
Further information regarding to the nature of hydrogenation products was obtained by a trapping experiment. Hydrogenation using acetic anhydride instead of ethanol, afforded a mixture of acetylated products which was separated by column chromatography. The stable acetylated derivatives **17b**(4%) and **18b**(50%) were isolated together with **17c**(5%). In accord with the proposed structure, the ^{13}C-NMR data of compound **17b** were found to be comparable to those for the benzyl protected derivative **10a**.

As the ether cleavage observed for **2a** is precluded for carba acyclo analogues, we next turned our attention to the synthesis of the C-nucleoside **2c**. This was accomplished via cycloaddition of the O-protected 6-hydroxy-1-hexyne **6** and oxazinone **3** yielding precursors **9c,d**, in addition to regioisomers **19c,d** (scheme 5). HPLC separation of the regioisomers succeeded only in the case of **9d**, **19d**. The pure pyridine **9d** then was treated with sodium phenylmethoxide in dry dimethylformamide at 90°C. However, under these conditions deprotection of the *t*-butyldimethylsilyl group occurred, giving rise to further decomposition products. Since the THP-group is more stable under basic conditions (see **7a** and sodium phenylmethoxide), the silyl derivative **9d** was deprotected to afford compound **9e** which then was converted into the THP-compound **9c** with dihydropyran. Treatment of **9c** with sodium phenylmethoxide gave compound **10c** in good yield (77%).



SCHEME 5

Deprotection of the THP-derivative **10c** to **10e** (scheme 6) was performed on a Dowex column with methanol as the eluent. Selective debenzylation of **10e** was carried out in a gas buret using a palladium-strontium carbonate catalyst to afford the 6-hydroxy-1H-pyridin-2-one C-nucleoside **2c** in good yield (75%) as a stable colourless oil. The spectral data were in agreement with structure **2c**. In the hydrogenation of **10e** consumption of hydrogen has to be controlled carefully. Otherwise overreduction leads to a quantitative yield of glutarimide **20** having an overall cis substitution pattern.



SCHEME 6

In summary, the Diels-Alder reaction of 3,5-dichloro-6-methyl-2*H*-1,4-oxazin-2-one with specific acetylenes provides a novel approach for the synthesis of precursors of some pyridine-C-nucleosides. A model synthesis of the carba acyclo-1-deazathymidine C-nucleoside **2c** was accomplished. Unfortunately, due to an ether cleavage the method is not valid for the preparation of acyclo C-nucleosides **2a,b** which are in addition subject to oxidative degradation.

EXPERIMENTAL SECTION

IR-Spectra were recorded as thin films between NaCl-plates or as solids in KBr-pellets on a Perkin Elmer 297 grating IR-spectrophotometer. ^{1}H-NMR spectra and ^{13}C-NMR spectra were recorded on a Bruker WM 250 instrument operating at 250 MHz for ^{1}H- and 63 MHz for ^{13}C-measurements. The ^{1}H- and ^{13}C-chemical shifts are reported in ppm relative to tetramethylsilane as an internal reference. Mass spectra were run by using a Kratos MS50 instrument and DS90 data system. Exact mass measurements were performed at a resolution of 10,000. Besides the spectral and analytical data mentioned below, the purity of all compounds was checked by TLC. Analytical TLC plates (Sil G/UV 254) and silica gel (70-230 mesh) were purchased from Macherey-Nagel. Melting points were taken using a Reichelt-Jung Thermovar apparatus and are uncorrected. Microanalyses were performed by Janssen Pharmaceutica on a Carlo Erba elemental analyser type 1106. HPLC was performed on a Li Chrosorb Si 60 (4x30 cm, 3/8") column with 5% EtOAc/$CHCl_3$ as eluent for componds **10a,b**, **12b** and **13**. Compound **9d** and **19d** were separated on a Sorbax Sil (25 cm, 1") HPLC column with 5% EtOAc/hexane (recycling n=8).

2,6-Dichloro-5-methyl-3-[((tetrahydropyran-2-yl)oxy)methyl] pyridine 7a and isomer 7b. A solution of 3[5] (5 g, 27.8 mmol) in neat acetylene 4[18] (11 g, 78 mmol) was stirred under nitrogen at 90°C for 15 h. Evaporation of the excess dienophile and chromatography of the residue on silica gel (gradient elution 0 to 5% EtOAc-$CHCl_3$) afforded the mixture **7a,b** (6.7 g, 88%) in a ratio of (3:1) as a colourless oil. IR (film) 3020, 1220, 910 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.50-1.95 (m, 6H, CH_2-3'-4'-5', **7a,b**), 2.26 (s, 3H, CH_3, **7b**), 2.37 (s, 3H, CH_3, **7a**), 3.56+ 3.85 (m, 2H, CH_2-6', **7a,b**), 4.48 (d, ^2J = 15 Hz, 1H, $PyCH_2$, **7b**), 4.5 (d, ^2J = 15 Hz, 1H, $PyCH_2$, **7a**), 4.74 (m, 1H, CH-2', **7a,b**), 4.80 (d, ^2J = 15 Hz, 2H, $PyCH_2$, **7a,b**), 7.43 (s, 1H, PyH, **7b**), 7.77 (s, 1H, PyH, **7a**); ^{13}C-NMR ($CDCl_3$) δ 14.1 (CH_3, **7b**), 18.5 (CH_3, **7a**), 19.1, 25.0, 30.0 (CH_2-4'-3'-5'-, **7a,b**), 62.1 (CH_2-6', **7a,b**), 64.4 ($PyCH_2$, **7a**), 65.1 ($PyCH_2$, **7b**), 98.3 (CH-2', **7b**), 98.5 (CH-2', **7a**), 120.6 (C-5, **7b**), 127.8 (C-3, **7b**), 131.2 (C-5, **7a**), 131.7 (C-3, **7a**), 140.1 (C-4, **7a**), 144.8 (C-Cl, **7a**), 147.2 (C-Cl, **7b**), 148.2 (C-Cl, **7a**), 149.8 (C-Cl, **7b**), 151.5 (C-4, **7b**); m/z 275 (2, M^+), 240(32), 194(17), 174(100), 85(54); exact mass calcd for $C_{12}H_{15}Cl_2NO_2$: 275.0474; found: 275.0470.

2,6-Dichloro-3-[2-(benzyloxy)ethoxy]methyl-5-methylpyridine 9a. A mixture of 2-benzyloxyethanol (1.08 g, 7 mmol) and NaH (210 mg, 7 mmol of a 80% dispersion in paraffin oil) in dry THF (45 ml) was refluxed for 30 min under nitrogen. To this was added dropwise a solution of pyridine **8**[4] (1.5 g, 5.9mmol) in dry THF (15 ml) and the mixture was refluxed for 12 h. The cold mixture then was poured into a 10% NH_4CL solution (100 ml), extracted with $CHCl_3$ (3x100 ml), dried ($MgSO_4$), and evaporated. Chromatography on a silica gel column using $CHCl_3$ as the eluent yielded pyridine **9a** (1.5 g, 78%) as a pale yellow oil. IR (film) 3080, 3060, 3020, 2860, 1590, 1550, 1090 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.3(s, 3H, CH_3), 3.73(m, 4H, CH_2CH_2), 4.56, 4.58(s, 4H, $PyCH_2$, $PhCH_2$), 7.32(m, 5H, Ph), 7.74(s, 1H, PyH); ^{13}C-NMR ($CDCl_3$) δ 18.6(CH_3), 68.3, 69.2, 70.4(CH_2-2'-3', $PhCH_2$), 73.1(CH_2-1'), 127.4, 128.1(m-,o-,p-Ph)131.3, 131.6(C-3, C-5), 137.9(ipso-Ph), 140.0(C-4), 144.5, 148.2(C-2, C-6); m/z : 325(0.5, M^+), 290(7), 234(40), 190(34), 174(30), 107(38), 91(100); exact mass calcd for $C_{16}H_{17}Cl_2NO_2$: 325.0636; found : 325.0641.

3-[(1,3-(Dibenzyloxy)-2-propoxy)methyl]-2,6-dichloro-5-methyl-pyridine 9b. Compound **9b** was obtained from **8** (1.5 g, 5.9 mmol) and 1,3-dibenzyloxy-2-propanol (1.94 g, 7.2 mmol) in the same way as described for **9a** (reflux in THF for 15 h). Chromatography using $CHCl_3$ as the eluent yielded **9b** (2.2 g, 84%) as a pale yellow oil. IR (film) 3080, 3060, 3030, 2860, 1590, 1550, 1100cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.28(s, 3H, CH_3), 3.7(d, ^{3}J=5 Hz, 4H, CH_2-3'), 3.9(quin., ^{3}J=5 Hz, 1H, CH-2'), 4.58(s, 4H, CH_2Ph), 4.78(s, 2H, CH_2-1'), 7.32 (m, 10H, Ph), 7.83(s, 1H, PyH); ^{13}C-NMR ($CDCl_3$) δ 18.6 (CH_3), 67.4(CH-1'), 70.2(CH_2-3'), 73.3($PhCH_2$), 78.4(CH_2-1'), 127.5, 128.3, 127.6(o-, m-, p-Ph), 131.3(C-3), 132.1(C-5), 137.9 (ipso-Ph), 140.3(C-4), 144.5(C-2), 148.2(C-6); m/z : 445(O.1, M+), 410(1.5), 354(14), 248(4), 174(52), 91(100); exact mass calcd for $C_{24}H_{25}Cl_2NO_3$: 445.1203; found : 445.1153.

2,6-Dichloro-5-methyl-3-[4-((tetrahydropyran-2-yl)oxy)butyl] pyridine 9c and isomer 19c. A solution of **3** (1.5 g, 8.3 mmol) and acetylene **6c**[19](1.7 g, 9.3 mmol) in dry toluene (5 ml) was heated at 95°C for 64 h under nitrogen. Evaporation followed by chromatography on a silica gel column (gradient elution 50% Hex/$CHCl_3$ to $CHCl_3$) yielded (2.6 g, 88%) of a mixture of isomers **9c** and **19c** (9:1), which were not further separated. IR (film) 2940, 2870, 1590, 1580, 1550cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.5-1.9(m, 10H, CH_2), 2.34(s, 3H, CH_3), 2.72(t, ^{3}J=7 Hz, 2H, $PyCH_2$), 3.47(m, 2H, CH_2O), 3.82(m, 2H, CH_2O), 4.59(m, 1H, OCHO), 7.16(s, 1H, PyH, **19c**), 7.42(s, 1H, PyH **9c**); ^{13}C-NMR ($CDCl_3$) δ 14.9, 18.6, 19.6, 25.3, 25.8, 29.1, 30.6, 31.9, 33.3, (CH_2, CH_3), 62.3, 66.9(CH_2O), 98.8(OCHO), 123.0(C-5, **19c**), 131.1(C-3), 135.0(C-5), 141.6(C-4, **9c**), 146.7(C-6), 147.1(C-2); m/z 317(1, M^+), 282(4), 133(33), 174(40), 85(100); exact mass calcd for $C_{15}H_{21}Cl_2NO_2$: 317.0942; found : 317.0933.

2,6-Dichloro-5-methyl-3-[4-[(*t*-butyldimethylsilyl)-oxy]butyl]pyridine 9d and isomer 19d. A solution of **3**(2 g, 11.1 mmol) in acetylene **6d**[20](3.5 g, 15 mmol) was heated at 80°C for 20 h under nitrogen. Work-up by evaporation and chromatography on a silica gel column (gradient elution hexane to 5% EtOAc/Hex) yielded (3.2 g, 92%) of a mixture of isomers **9d** and **19d** (5:1), which was separated further by HPLC (Silica, $CHCl_3$).

9d : IR (film) 2960, 2940, 2860, 1590, 1550, 1110 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.08(s, 6H, $SiCH_3$), 0.9(s, 9H, *t-Bu*), 1.65(m, 4H, CH_2CH_2), 2.35(s, 3H, CH_3), 2.69(t, ^{3}J= 7.5 Hz, 2H, $PyCH_2$), 3.66(t, ^{3}J=7.5 Hz, 2H, CH_2O), 7.4(s, 1H, PyH); m/z : 347(0, M^+), 332(2), 290(48), 248(100), 180 (41), 162(37); exact mass calcd for $C_{16}H_{27}Cl_2NOSi$ (M^+ -CH_3) : 332.0996; found : 332.0993.

19d : IR (film) 2960, 2940, 2860, 1580, 1545, 1110 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.1(s, 6H, $SiCH_3$), 0.91(s, 9H, *t*-Bu), 1.5-1.84(m, 4H, CH_2CH_2), 2.3(s, 3H, CH_3), 2.7(t, ^{3}J=7.5 Hz, 2H, $PyCH_2$), 3.7(t, ^{3}J=7.5 Hz, 2H, CH_2O), 7.09(s, 1H, PyH); exact mass calcd for $C_{16}H_{27}Cl_2NOSi$ (M^+ -CH_3) : 332.0996; found : 332.1000.

2,6-Dichloro-3-[4-(hydroxy)butyl]-5-methylpyridine 9e and protection into 9c. A solution of **9d**(3.2 g, 9 mmol) in dry THF (40 ml) was treated with $Bu_4NF.3H_2O$(3.46 g, 11 mmol) under nitrogen at room temperature for 30 min. Work-up by evaporation and flash chromatography (Silica gel, 5% EtOAc/$CHCl_3$) yielded **9e**(1.6 g, 77%) as white crystals. mp (EtOH) 54°C. A solution of **9e**(1.3 g, 5.6 mmol) and dihydropyran (0.65 g, 0.7 mL) in dry diethyl ether(15 ml) was treated with $TosOH.H_2O$ (86 mg) under nitrogen at 0°C. The solution was allowed to come to room temperature during 90 min, then washed with water (50 mL). The organic layer was dried ($MgSO_4$) and evaporated at room temperature. Chromatography on a silica gel column ($CHCl_3$) afforded **9c**(1.7 g, 96%) as a colourless oil with the spectral data described above. For **9e** : IR (KBr) 3370, 2940, 2870, 1590, 1550 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.4(s, 1H, OH), 1.55-1.75(m, 4H, CH_2CH_2), 2.36(s, 3H, CH_3), 2.73(t, ^3J=7.5 Hz, $PyCH_2$), 3.72 (t, ^3J=7.5 Hz, CH_2OH), 7.49(s, 1H, PyH), m/z 233(19, M^+), 200(11), 187(100), 180(35), 174(35); exact mass calcd for $C_{10}H_{13}Cl_2NO$: 233.0369, found : 233.0379. Anal. Calcd for $C_{10}H_{13}Cl_2NO$: C, 51.30; H, 2.59; N, 5.98. Found C, 51.50; H, 2.65; N, 5.87.

3-[(2-(Benzyloxy)ethoxy)methyl]-2,6-dibenzyloxy-5-methyl-pyridine 10a. A mixture of distilled benzyl alcohol (4.9 g, 46mmol) and NaH (1.4 g, 46mmol of a 80% dispersion in paraffin oil) in dry DMF (50ml) was stirred under nitrogen for 30 min. at 90°C. To this was added dropwise a solution of **9a** (1.5 g, 4.6 mmol) in dry DMF (20 ml). After stirring overnight at 90°C the solution was cooled and treated with a 10% NH_4Cl solution (200 ml). The mixture was extracted with $CHCl_3$ (3x200 ml) and the combined organic layers were dried ($MgSO_4$) and evaporated. Chromatography on a silica gel column ($CHCl_3$) yielded **10a** (1.56g, 75%) as a colourless oil. IR (film) 3090, 3060, 3030, 2920, 2850, 1120, 1020 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.1(s, 3H, CH_3), 3.6(m, 4H, CH_2-2'-3'), 4.5(s, 4H, CH_2-1', $PhCH_2$), 5.3(s, 4H, $PhCH_2$), 7.2-7.35(m, 16H, Ph, PyH); ^{13}C-NMR ($CDCl_3$) δ 14.5(CH_3), 66.9, 67.2(CH_2-2', -3', 69.4, 69.5 ($PhCH_2$), 73.0(CH_2-1'), 111.0, 111.1(C-3, C-5), 127.2, 127.2, 127.3, 127.5, 128.1(o-,m-,p-Ph), 138.0, 138.2(ipso-Ph), 141.7 (C-4), 157.2, 158.8(C-2, C-6); m/z 469(7, M^+), 378(4), 318 (4), 227(5), 91(100); exact mass calcd for $C_{30}H_{31}NO_4$: 469.2244, found 469.2251. Anal. Calcd for $C_{30}H_{31}NO_4$ C, 76.74; H, 6.65; N, 2.98. Found : C, 76.68; H, 6.67; N, 2.88.

2,6-Dibenzyloxy-3-[(1,3-(dibenzyloxy)-2-propoxy)methyl]-2,6-dichloro-5-methylpyridine 10b. Compound **10b** was prepared from **9b** (1.38 g, 3.1 mmol) in the same way as **10a** from **9a**. Chromatography was performed with gradient elution (0% to 2% EtOAc/ $CHCl_3$) yielding **10b** (1.23 g, 69%) as a colourless oil. IR (film) 3090, 3060, 3030, 2920, 2850, 1120, 1020 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.1(s, 3H, CH_3), 3.58(d, ^3J=6 Hz, 4H, CH_2-3'), 3.8(quin, ^3J=6 Hz, 1H, CH-2'), 4.46(s, 4H, $PhCH_2$), 4.65(s, 2H, CH_2-1'), 5.3(s, 4H, $PhCH_2$), 7.2-7.4(m, 20H, Ph), 7.48(s, 1H, PyH); ^{13}C-NMR ($CDCl_3$) δ 14.5(CH_3), 66.0, 67.3, 70.2, 73.2 ($PhCH_2$, CH_2-3'-1'), 76.5(CH-2'), 111.1, 111.5(C-3, C-5), 127.2, 127.3, 127.4, 127.7, 128.2(o-, m-, p-Ph), 138.1, 138.3 (ipso-Ph), 141.9(C-4), 157.2, 158.9(C-2, C-6); m/z : 589(3, M^+), 498(3), 421(9), 318(6), 227(3), 91(100); exact mass calcd for $C_{38}H_{39}NO_5$: 589.2841; found : 589.2828. Anal. Calcd for $C_{38}H_{39}NO_5$: C, 77.39; H, 6.67; N, 2.38. Found : C, 77.21; H, 6.60; N, 2.33.

2,6-Dibenzyloxy-5-methyl-3-[4-((tetrahydropyran-2-yl)oxy)-butyl]pyridine 10c. Compound **10c** was prepared from **9c** (1.71g, 5.4 mmol) in the same way as **10a** from **9a** : yielding a colourless oil (1.9g, 77%). IR (film) 3090, 3070, 3040, 2940, 2870, 1600 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.3-1.9(m, 10H, CH_2), 2.13 (s, 3H, CH_3), 2.58(m, 2H, $PyCH_2$), 3.3-3.57(m, 2H, CH_2O), 3.66-3.94(m, 2H, CH_2O), 4.55(m, 1H, CHO), 5.34(s, 4H, $PhCH_2$), 7.14 (s, 1H, PyH), 7.18-7.5(m, 10H, Ph); ^{13}C-NMR ($CDCl_3$) δ 14.5 (CH_3), 19.6, 25.5, 26.3, 28.6, 29.4, 30.7(CH_2), 62.2, 67.2, 67.5($PyCH_2$, $PhCH_2$), 98.8(OCHO), 110.7, 115.1(C-3,C-5), 127.3, 128.3(o-, m-, p-Ph), 138.5(ipsoPh), 141.9(C-4), 157.4(C-2,C-6); m/z 461(16, M^+), 376(14), 269(20), 91(100); exact mass calcd for $C_{29}H_{35}NO_4$: 461.2556; found : 461.2532.

2,6-Dibenzyloxy-3-(4-hydroxybutyl)-5-methylpyridine 10e. A solution of **10c** (0.67 g, 1.46 mmol) in methanol (25 ml) was applied to a column of freshly activated Dowex 50WX8(H^+). The column was eluted with methanol (250 ml) and the combined solutions were evaporated. Chromatography on silica gel (gradient elution 0% to 10% EtOAc-$CHCl_3$) afforded **10e** (478 mg, 87%) : mp (Hex/Et_2O) 48-49°C; IR (KBr) 3350, 3090, 3070, 3040, 2940, 2860, 1600, 1500 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.6(m, 4H, CH_2CH_2), 1.9(s, 1H, OH), 2.13(s, 3H, CH_3), 2.53(t, ^{3}J=7.5 Hz, $PyCH_2$), 3.57(t, ^{3}J=7.5 Hz, CH_2OH), 5.36(s, 4H, $PhCH_2$), 7.17(s, 1H, PyH), 7.18-7.49(m, 10H, Ph); ^{13}C-NMR ($CDCl_3$) δ 14.5(CH_3), 25.8, 28.4, 32.3(CH_2), 62.7(CH_2OH), 67.2($PhCH_2$), 110.7, 114.9 (C-3, C-5), 127.3, 128.3(o-, m-, p-Ph), 138.4(ipso-Ph), 141.9 (C-4), 157.3, 157.7(C-2, C-6); m/z 377(18, M^+), 286(2), 180 (10), 91(100); exact mass calcd for $C_{24}H_{27}NO_3$: 377.1983; found ; 377.1980. Anal. Calcd for $C_{24}H_{27}NO_3$: C, 76.37; H, 7.21; N, 3.71. Found C, 76.07; H, 7.12; N, 3.62.

2,6-Dibenzyloxy-5-methyl-3-[((tetrahydropyran-2-yl)oxy)methyl] pyridine 11a and isomer 11b. Sodium hydride (3 g of 80 W% dispersion in paraffin oil, 0.125 mol) was added under inert atmosphere to a stirred solution of distilled benzyl alcohol (10.8 g, 0.1 mol) in dry DMF (70 ml). The temperature was raised to 90°C and after 30 min a solution of **7a,b** (1.44g, 5 mmol, 3:1) in dry DMF (30 ml) was added dropwise. The mixture was stirred overnight at 90°C, cooled to room temperature and treated with 10%-NH_4Cl solution (200 ml). Extraction with $CHCl_3$ (3 x 200 ml), washing of the combined extracts with brine (2 x 100 ml), drying over $MgSO_4$, evaporation and chromatography on silica gel (gradient elution 0% to 5% EtOAc-$CHCl_3$) yielded **11a,b** (1.6 g, 75%) as an oil (ratio 4:1). IR (film) 3090, 3070, 3040, 2950, 2870, 1600 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.40-1.90 (m, 6H, CH_2-3'-4'-5', **11a,b**), 2.07 (s, 3H, CH_3, **11b**), 2.15 (s, 3H, CH_3, **11a**), 3.45 (m, 1H, CH_2-6', **11a,b**), 3.88 (m, 1H, CH_2-6', **11a,b**), 4.44 (d, ^{2}J = 12 Hz, 1H, $PyCH_2$, **11a,b**), 4.72 (d, ^{2}J = 12 Hz, 1H, $PyCH_2$, **11a,b**), 4.68 (dd, $^3J_{aa}$ = 8 Hz, $^3J_{ae}$ = 4 Hz, 1H, CH-2', **11a,b**), 5.32 (s, 4H, $PhCH_2$, **11a,b**), 6.55 (s, 1H, PyH, **11b**), 7.12 (s, 1H, PyH, **11a**), 7.2-7.4 (m, 10H, Ph, **11a,b**); ^{13}C-NMR ($CDCl_3$) δ 9.8 (CH_3, **11b**), 14.5 (CH_3, **11b**), 19.3, 25.4, 30.5 (CH_2-3'-4'-5', **11a,b**), 61.8, 63.3 ($PyCH_2$, CH_2-6', **11a**), 67.2 ($PhCH_2$, **11a,b**), 97.9(OCHO, **11a,b**), 100.0(C-5, **11b**) 110.9, 111.2 (C-3-5, **11a**), 127.2, 127.3, 128.2 (Ph, **11a**), 138.0 (ipso-Ph, **11a**), 141.8 (C-4, **11a**), 157.4, 158.9 (C-2-6, **11a**); m/z 419 (4, M^+), 318(6), 227(15), 91 (100); exact mass calcd for $C_{26}H_{29}N0_4$: 419.2088; found : 419.2119.

2,6-Dibenzyloxy-4-hydroxymethyl-3-methylpyridine 12b and 2,6-dibenzyloxy-5-methyl-3-methoxymethylpyridine 13. A solution of **11a,b** (11 g, 0.026 mol, 4:1) in methanol (110 ml) was eluted with methanol (1 l) over a freshly activated Dowex 50WX8(H^+) column. Evaporation of the combined solutions and chromatography on silica gel (gradient elution 0% to 10% EtOAc-$CHCl_3$) afforded **13** (4 g) as a colourless oil and **12b** (1.4 g) as a white solid.

12b : mp (Hex/Et_2O) 102-103°C; IR (KBr) 3450, 3100, 3080, 3040, 2950, 2880, 1600 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.85 (s, 1H, OH); 2.06 (s, 3H, CH_3); 4.59 (s, 2H, CH_2OH) 5.30 (s, 2H, $PhCH_2$), 5.34 (s, 2H, $PhCH_2$), 6.50 (s, 1H, PyH), 7.2-7.4(m, 10H, Ph); ^{13}C-NMR ($CDCl_3$) δ 9.8 (CH_3), 62.3 (CH_2OH), 67.5 ($PhCH_2$), 67.6 ($PhCH_2$), 99.5 (C-5), 108.1 (C-3), 127.4, 127.5, 127.6, 128.3 (o, p m, Ph), 137.8, 138.1 (ipso Ph), 152.5 (C-4), 159.6, 160.2 (C-2, C-6); m/z 335 (8, M^+), 244(5), 180(11), 91 (100); exact mass calcd for $C_{21}H_{21}NO_3$: 335.1515; found : 335.1481. Anal Calcd for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18. Found : C, 74.55; H, 6.22; N, 4.00.

13 : IR (film) 3080, 3060, 3020, 2920, 1600 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.14 (s, 3H, CH_3), 3.35 (s, 3H, CH_3O), 4.40 (s, 2H, CH_2O), 5.34 (s, 4H, $PhCH_2$), 7.13 (s, 1H, PyH), 7.2-7.4 (m, 10H, Ph); ^{13}C-NMR ($CDCl_3$) δ 314.1 (CH_3), 58.0 (CH_3O), 67.3 (CH_2Ph), 68.4 (CH_2O) 111.1 (C-3, C-5), 127.2, 127.3, 128.2 (o,p,m-Ph), 138.1 (ipso-Ph), 141.7 (C-4), 157.3, 159 (C-2, C-6); m/z 349 (15, M^+), 317(5), 258(3), 227(5), 91 (100); exact mass calcd for $C_{22}H_{23}NO_3$: 349.1678; found : 349.1684. Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N,4.01. Found : C, 75.77; H, 6.58; N, 3.90.

2,6-Dichloro-3-methoxymethyl-5-methylpyridine 14. A mixture of NaH (166 mg, 5.6 mmol; 80 w% dispersion in paraffin oil) and methanol (15 ml) was stirred at room temperature for 30 min under nitrogen. A solution of **8** (1 g, 4 mmol) in dry diethylether (5 ml) was added dropwise. The mixture was stirred for 4.5h, treated with a 10% NH_4Cl solution (50 ml) and extracted with $CHCl_3$ (3x100 ml). The organic layer was dried ($MgSO_4$) and evaporated. Chromatography of the residual oil on silica gel (20% Hex/$CHCl_3$) yielded 707 mg (86%) of pyridine **14** as a colourless oil. IR (film) 2920, 1590, 1550, 1400, 1365, 1100 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.36(s, 3H, CH_3), 3.50(s, 3H, CH_3O), 4.45(s, 2H, CH_2O), 7.66(s, 1H, PyH); ^{13}C-NMR ($CDCl_3$) δ 18.6 (CH_3), 58.7(CH_3O), 69.8(CH_2O), 131.4, 131.5(C-3, C-5), 139.9 (C-4), 144.7, 148.3(C-2, C-6); m/z 205(54, M^+), 190(33), 174(100), 170(93); exact mass calcd for $C_8H_9Cl_2NO$: 205.0057; found : 205.0070.

2,6-Dichloro-3-(2-hydroxyethoxy)methyl-5-methylpyridine 15. A mixture of 1,2-ethanediol (142.7 mg, 2.3mmol) and NaH (65 mg, 2.1 mmol of a 80% dispersion in paraffin oil) in dry THF (15 ml) was refluxed for 30 min under nitrogen. To this was added dropwise a solution of pyridine **8** (476 mg, 1.88 mmol) in dry THF (5 ml) and the mixture was refluxed for 7 h. The cold mixture then was poured into a 10% NH_4CL solution (50 ml), extracted with $CHCl_3$ (3x100 ml), dried ($MgSO_4$), and evaporated. Chromatography on a silica gel column (gradient elution 0% to 6% MeOH/$CHCl_3$) yielded pyridine **15** (300 mg, 68%) as white crystals : mp (Hex/$CHCl_3$ 1:2 mixture) 64-65°C. IR (KBr) 3080, 2920, 2860, 1590, 1555, 1100 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.37(s, 3H, CH_3), 2.77(s, 1H, OH), 3.72(dd, ^{2}J=3Hz, ^{3}J=5Hz, 2H, CH_2O), 3.84(dd, ^{2}J=3Hz, ^{3}J=5Hz, 2H, CH_2O), 4.58(s, 2H, $PyCH_2$), 7.74 (s, 1H, PyH); ^{13}C-NMR ($CDCl_3$) δ 18.6(CH_3), 61.4(CH_2-2'), 68.45 (CH_2-1'), 72.3(CH_2-3'), 131.2(C-3), 131.5(C-5), 140.2(C-4), 144.7(C-2), 148.4(C-6); m/z 235(10, M^+), 190(48), 174(100); exact mass calcd for $C_9H_{11}Cl_2NO_2$: 235.0171; found : 235.0168. Anal calcd for $C_9H_{11}Cl_2NO_2$: C, 45.79; H, 4.70; N, 5.93. Found : C, 45.64; H, 4.68; N, 5.84.

Attempt to synthesis of 6-hydroxy-5-[(2-hydroxyethoxy)methyl]-3-methyl-1H-pyridin-2-one 2a. A solution of **10a** (200 mg, 0.4 mmol) in ethanol (20 ml) admixed with 10% Pd on C/$SrCO_3$(75 mg, 1:1.7) was degassed three times, then hydrogenated at atmospheric pressure. The hydrogen consumption (ca. 30 ml) was controlled by using a gas buret. The solution was filtered and the catalyst washed with ethanol (ca. 200 ml). Evaporation at room temperature afforded a white solid (**2a, 16**) which within a few minutes changed into a blue oil. MS for **2a**, $C_9H_{13}NO_4$, MW 199, m/z 182(9); for **16**, $C_7H_9NO_2$ m/z 139(22, M^+), 107(11), 96(100). A fresh sample was heated with pyridine and BSFTA (bistri-fluorotrimethylsilyl acetamide) for 5 min : MS for **17a**, $C_{18}H_{37}NO_4Si_3$,MW 415 m/z 341(1), 282(21), 268(14), 207(13), 117(32); for **18a**, $C_{13}H_{25}NO_2Si_2$ m/z 283(9, M^+), 268 (14), 207(13).

5-(4-Hydroxybutyl)-6-hydroxy-3-methyl-1H-pyridin-2-one 2c. A solution of **10e**(190 mg, 0.5 mmol) in ethanol (13 ml), admixed with 10% Pd on C/$SrCO_3$(95 mg, 1:1), was degassed three times and then hydrogenated at atmospheric pressure. The hydrogen consumption (ca. 24 ml, ca. 1 h) was controlled by using a gas buret. The solution was filtered and the catalyst washed with ethanol (ca. 200 ml). The solution was evaporated at room temperature to afford **2c** as an oil (74 mg, 75%), which was shown to be pure on TLC (6% MeOH/$CHCl_3$) and stable at 0°C for several weeks. IR (film) 3400, 2940, 2860, 1695, 1650, 1240, 1060 cm^{-1}; ^{1}H-NMR (CD_3OD) δ 1.6(m, 4H, CH_2CH_2), 2.16(s, 3H, CH_3), 2.56(t, ^{3}J=7 Hz, $PyCH_2$), 3.62(t, ^{3}J=7 Hz,CH_2OH), 7.68(s, 1H, PyH); ^{13}C-NMR (CD_3OD) δ 14.4(CH_3), 27.2, 28.5, 32.5(CH_2), 62.7(CH_2OH), 111.9(, 115.8(C-3, C-5), 150.3(C-4), 156.1, 156.8(C-2, C-6); m/z 197(12, M^+), 179 (45), 164(45), 138(81), 125(100); exact mass calcd for $C_{10}H_{15}NO_3$: 197.1047, found 197.1043; UV in methanol : λ_{max} 316 nm (2425); in H_2O : λ_{max} 320 nm (2234); pH 1 : λ_{max} 309 nm (2672); pH 14 : λ_{max} 235 nm (4739),λ_{max} 338 nm (4102).

Deprotection of 10a in acetic anhydride as solvent : isolation of 17b, 17c and 18b. A solution of **10a**(1.78 g, 3.8 mmol) in freshly distilled acetic anhydride (25 ml) was admixed with 10% Pd on $C/SrCO_3$(676 mg, 1:1.7), degassed three times and then hydrogenated at atmospheric pressure for 5 h. The hydrogen consumption (ca. 273 ml) was controlled by using a gas buret. The solution was filtered and the catalyst washed with acetic anhydride (ca. 200 ml). The filtrate was refuxed for 30 min under nitrogen. The solution was evaporated in vacuo at room temperature. The residue was separated on a silica gel column (gradient elution $CHCl_3$ to 5% ETOAc/$CHCl_3$) into three fractions. The most polar fraction containing 17b (4 %) and 17c (5 %) was separated further by HPLC (Silica, 5% EtOAc/$CHCl_3$). The less polar fraction contained 2-(benzyloxy)ethylacetate and the other one compound **18b** (50 %).

17b (colourless oil) : IR (film) 2940, 2870, 1770, 1740, 1710, 1600, 1180 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.05(s, 3H, CH_3), 2.18(s, 3H, $CH_3C=O$), 2.31(s, 6H, $CH_3C=O$), 3.66, 4.23(2xt, ^3J=5 Hz, 4H, CH_2CH_2), 4.47(s, 2H, $PyCH_2$), 7.76(s, 1H, PyH); ^{13}C-NMR ($CDCl_3$) δ 15.0(CH_3), 20.8($\underline{C}H_3C=O$), 63.3, 66.9, 68.6(CH_2), 124.1(C-5), 127.7(C-3), 142.9(C-4), 154.0(C-2, C-6), 168.4(C=O); m/z 325(1, M^+), 283(19), 241(100), 199(23), 181(10), 139(30), 87 (79); exact mass calcd for $C_{15}H_{19}NO_7$: 325.1155; found : 325.1150.

17c (colourless oil : IR (film) 3090, 3060, 3040, 2930, 2870, 1770 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.17(s, 3H, CH_3), 2.28, 2.33(s, 6H, $CH_3C=O$), 3.66(s, 4H, CH_2CH_2), 4.50(s, 2H, $PyCH_2$), 4.58(s, 2H, $PhCH_2$), 7.33(m, 5H, Ph), 7.73(s, 1H, PyH); ^{13}C-NMR ($CDCl_3$) δ 15.2(CH_3), 20.7($\underline{C}H_3C=O$), 66.9, 69.4, 70.0, 73.3(CH_2), 124.0, 124.4(C-3, C-5), 127.6, 127.7, 128.3(o-, m-, p-Ph), 138 (ipsoPh), 142.9(C-4), 151.6, 153.2(C-2, C-6), 168.2(C=O); m/z 373(2, M^+), 331(24), 289(22), 198(9), 138(24), 91(100); exact mass calcd for $C_{20}H_{23}NO_6$: 373.1518; found : 373.1511.

18b (white crystals) mp (Et_2O/Hex) 56-57°C; IR (KBr) 2960, 2940, 2860, 1765, 1600 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.18 (s, 6H, CH_3), 2.31(s, 6H, $CH_3C=O$), 7.47(s, 1H, PyH); ^{13}C-NMR ($CDCl_3$) δ 14.9(CH_3), 20.6($\underline{C}H_3C=O$), 123.6(C-3, C-5), 144.5 (C-4), 152.5(C-2, C-6), 168.2(C=O); m/z 223(1, M^+), 181 (10), 139(100), 121(3), 111(6); exact mass calcd for $C_{11}H_{13}N0_4$: 223.0840; found 223.0847. Anal. Calcd for $C_{11}H_{13}N0_4$: C, 59.19; H, 5.87; N, 6.27. Found C, 59.15; H, 5.88; N, 6.25.

3-[4-(hydroxy)butyl]-5-methylglutarimide 20. Compound **20** was prepared by hydrogenation of **10e** for 6h, under the conditions described for **2c**. Crystallization from hexane/diethyl ether afforded **20** (85 mg, 85%) : mp 75-76°C. IR (KBr) 3400, 2940, 2880, 1710, 1220 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.25-1.68(m, 10H, CH_2-1', -2', -3', CH_3, H_{ax}-4), 1.30(d, ^3J=7 Hz, CH_3), 1.54(ddd, ^2J=13 Hz, $^3J_{aa}$=13 Hz, $^3J_{aa}$=13 Hz, H_{ax}-4), 2.08 (ddd, 1H, ^2J=13 Hz, $^3J_{ea}$=5 Hz, $^3J_{ea}$=5 Hz, H_{eq}-4), 2.43-2.64(m, 2H, ^3J=7 Hz, $^3J_{ae}$=5 Hz, $^3J_{aa}$=13 Hz, H_{ax}-3 and H_{ax}-5), 3.69(t, 2H, ^3J=6 Hz, CH_2OH), 8.27(s_{br}, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ 15.1 (CH_3), 22.8, 29.1, 32.4(CH_2), 37.2, 42.2(CH-3, -5), 62.3 (CH_2OH), 175.0, 175.2(C=O); m/z 199(1, M^+), 181(5), 140 (21), 127(100), 99(22); exact mass calcd for $C_{10}H_{17}NO_3$: 199.1204; found 199.1195. Anal calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found C, 59.86; H, 8.24; N, 6.71.

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