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Synthesis of 6-Methoxy- and 6-Chloro-2(1*H*)-Pyridinone Acyclo-C-Nucleosides from 2*H*-1,4-Oxazin-2-ones.

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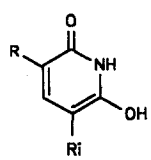
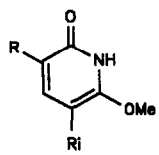
***Abstract** : Starting from 6-variated 3-methoxy- and 3-chloro-2H-1,4-oxazin-2-ones **4a-e** the synthesis of a series of 6-methoxy- and 6-chloro-2(1H)-pyridinone acyclo-C-nucleosides **2a-d** and **3a-d** was accomplished. Diels-Alder reaction of the oxazinones **4a-e** with propargyl bromide yielded the corresponding 3-bromomethylpyridines **5a-e**, which underwent easy substitution of the bromine atom with the appropriate nucleophiles, permitting the introduction of acyclo sugar moieties. Further treatment with sodium phenylmethoxide in dry dimethyl formamide afforded the benzyl protected C-nucleosides **8a-d** and **9a-d**. Debenzylation of **8a-d** in ethanol using a palladium-carbon catalyst poisoned with strontium carbonate and deprotection of **9a-d** with boron trichloride at -78°C provided stable 6-methoxy- and 6-chloro-2(1H)-pyridinone acyclo-C-nucleosides **2a-d** and **3a-d** respectively.*

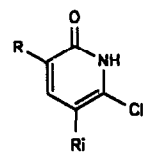
In contrast to 3-deazapyrimidine nucleosides,[1a-c] 1-deazapyrimidine C-nucleosides are described scantily in the literature.[2a,b] Variably substituted 2(1*H*)-pyridinone C-nucleosides are unknown and especially 6-hydroxy-2(1*H*)-pyridinone C-nucleosides **1a,b** are subject to oxidative degradation,[2a-c] exception made for the recently synthesized[2c] 6-hydroxy-2(1*H*)-pyridinone **1c**, a model compound for carbocyclic 6-hydroxy-2(1*H*)-pyridinone C-nucleosides.



1 a: R=H, Ri=β-D-ribofuranosyl
b: R=Me, Ri=(i) or (ii)
c: R=Me, Ri=(iii)

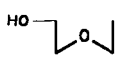


2 a: R=Me, Ri=(i)
b: R=Et, R=(i)
c: R=Me, Ri=(ii)
d: R=Et, Ri=(ii)
e: R=Me, Ri=$MeOCH_2$

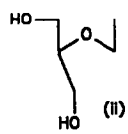


3 a: R=Me, Ri=(i)
b: R=H, Ri=(ii)
c: R=Me, Ri=(ii)
d: R=Et, Ri=(ii)
e: R=Me, Ri=$MeOCH_2$

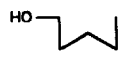
Ri=



(i)



(ii)



(iii)

Pyridine C-nucleosides with modified heterocyclic base and/or sugar moiety being of interest for biological evaluation,[3a,b] we tried the synthesis of 3,6-disubstituted 2(1*H*)-pyridinone acyclo-C-nucleosides of type **2a-d** and **3a-d** starting from 6-alkyl substituted 3-methoxy- and 3-chloro-2*H*-1,4-oxazin-2-ones **4a-e**.[4a,b] Acyclo analogues of nucleosides, more easily accessible than those with a cyclic carbohydrate structure, exhibit antiviral and antitumour activity (e.g. acyclovir and 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine).[5]

RESULTS AND DISCUSSION

In order to improve the stability of C-nucleosides of type **1b**, we tried to replace the 6-hydroxy group by a 6-methoxy or a 6-chloro substituent as in compounds **2a-d** and **3a-d**. A direct regioselective methylation or chlorination of **1b** being very difficult,[6] the appropriated 2*H*-1,4-oxazin-2-ones **4a-e** were used as starting materials (scheme 1). Oxazinones **4a-c** were synthesized from the corresponding cyanohydrines and oxalyl chloride,[4a] whereas the 3-methoxy derivatives **4d** and **4e** were obtained from compounds **4b** and **4c** after trituration with a saturated solution of hydrochloric acid in dry methanol.[4b]

The oxazinones **4a-e** underwent a regioselective cycloaddition reaction with propargyl bromide affording 3-bromomethylpyridines **5a-e** in very high yield (>80%).[7] Easy substitution of the bromine atom in **5a-e** by the sodium salts of the appropriate benzyl protected polyalcohols (glycol, 1,3-diprotected glycerol) or sodium methoxide in refluxing tetrahydrofuran afforded compounds **6a-e** and **7a-e** (scheme 1). Compound **6e** and a minor amount (<10%) of its regio isomer was obtained by regioselective Diels-Alder reaction of **4d** with methyl propargyl ether at 90°C.

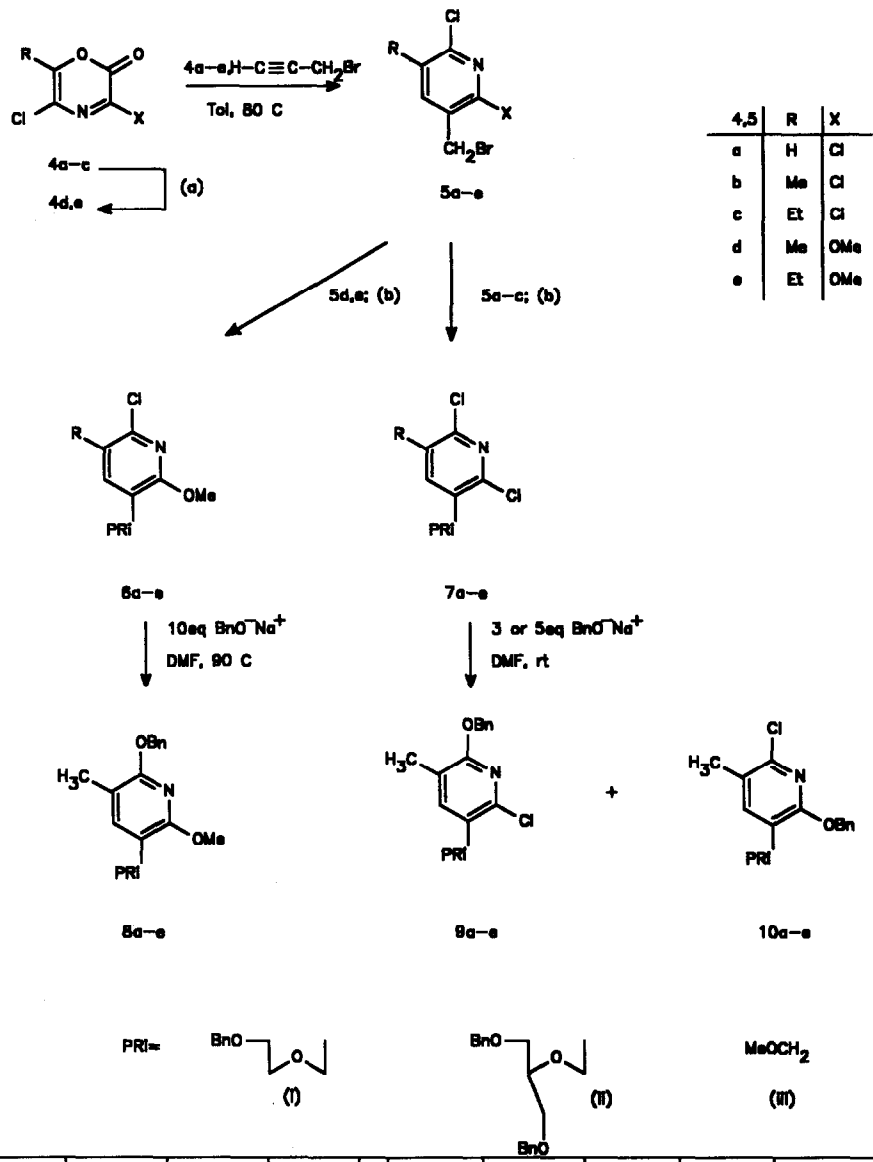
First the synthesis of the model compounds **2e** and **3e**, proceeding via pyridines **6e** and **7e** respectively, served to assess the accessibility and stability of the target C-nucleosides **2a-d** and **3a-d**.

Several attempts to hydrolize the 6-chloropyridine **6e** into the model compound **2e** using an aqueous solution of sodium hydroxide in dioxane were unsuccessful. Instead, we applied a technique described in a previous paper:[2c] substitution of the chlorine atom in **6e** by sodium phenylmethoxide in dry dimethyl formamide at 90°C yielding compound **8e** (79%). The pyridines **6a-d** were treated in the same way with sodium phenylmethoxide affording 6-benzyloxypyridines **8a-d** in good yields (75-89%) (scheme 1).

The selective substitution of the 6-chlorine atom in model compound **7e** and in the required pyridines **7a-d** needed milder reaction conditions. Performing the reaction at room temperature with three (for compounds **7a** and **7e**) or five equivalents of sodium phenylmethoxide (for compounds **7b-d**) appeared to be the most suitable method. The resulting isomeric mixtures of pyridines **9a-e** and **10a-e** were separated via HPLC (silica gel; $CHCl_3$) affording the 6-benzyloxypyridines **9a-e** in smooth excess with regard to the isomers **10a-e** (scheme 1). This isomeric excess can be explained by the bulkyness of the acyclo sugar moiety, although the influence of the substituent in the 5-position can not be denied.

The spectral data are all consistent with the proposed structures (see Experimental Section). The NMR data for the 6-benzyloxy-2-methoxypyridines **8a-e** are comparable with those obtained for the earlier synthesized 2,6-dibenzyloxypyridines.[2c] Both isomers **9a-e** and **10a-e** can be identified by means of their ^1H and ^{13}C NMR spectra since both the R-substituent in the 5-position of compounds **9a-e** and the 3-methylene group in pyridines **10a-e** are shielded due to the neighbouring benzyloxy group.

Deprotection of model compound **8e** in ethanol using a palladium-carbon catalyst poisoned by strontium carbonate gave a nearly quantitatively yield (>95%) of a stable crystalline 6-methoxy-2(1*H*)-pyridinone **2e** (scheme 2). Ether cleavage and generation of a product of type **11**- as observed in the hydrogenation of 2,6-dibenzyloxypyridines[2c] - could not be detected in the crude reaction mixture. However, problems were encountered on hydrogenation of pyridines **8a-d**. Debenzylation of **8a** and **8b** gave a good yield of target C-nucleosides **2a** (76%) and **2b** (79%), although the partially deprotected compounds **12a** and **12b** (ca. 10%) were also observed. This partial deprotection was even more pronounced for the



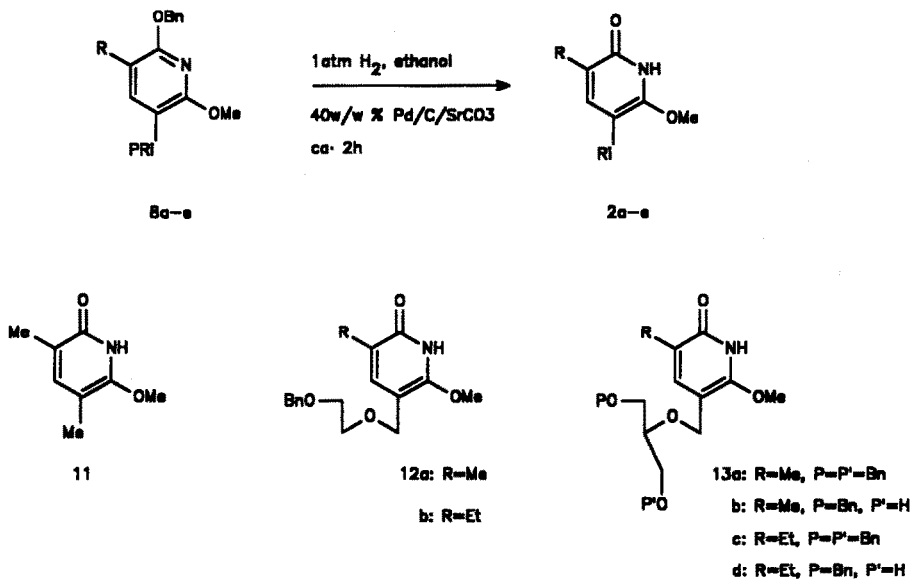
	R	PRi	6 (%)	8 (%)		R	PRi	7 (%)	9 (%)	10 (%)	9 : 10 [c]
a	Me	(i)	86	89		Me	(i)	78	42	25	1.7 : 1
b	Et	(i)	79	84		H	(ii)	72	54	21	2.6 : 1
c	Me	(ii)	76	86		Me	(ii)	84	50	33	1.5 : 1
d	Et	(ii)	72	75		Et	(ii)	71	47	28	1.7 : 1
e	Me	$MeOCH_2$	89 [d]	79		Me	$MeOCH_2$	86	59	27	2.2 : 1

(a) MeOH/HCl, 0°C; (b) $BnOCH_2CH_2ONa$, $(BnOCH_2)_2CHONa$ or CH_3ONa, THF, 3h reflux; (c) yields and ratio of compounds **9a-e** and **10a-e** were calculated after HPLC separation (d) compound **6e** was obtained directly from the Diels-Alder reaction of **4d** with methyl propargyl ether at 90°C for 2.5 days.

Scheme 1

hydrogenation of **8c** and **8d**: up to 50% yield of mixtures of **13a,b** and **13c,d** were detected. The yield for C-nucleosides **2c** and **2d** never surpassed 30% even when changing the reaction conditions for the hydrogenation of **8c** : *solvent*: ethanol, acetic acid or tetrahydrofuran; *catalyst*: 10 %wt, 20 %wt or 40 %wt of a 1:1 mixture of $PdC/SrCO_3$; *hydrogen pressure*: 15 or 40 psi. Using a pure palladium-carbon catalyst, applying hydrogen pressure up to 40 psi or prolonged hydrogenation at atmospheric pressure led to ether cleavage yielding a compound of type **11**.

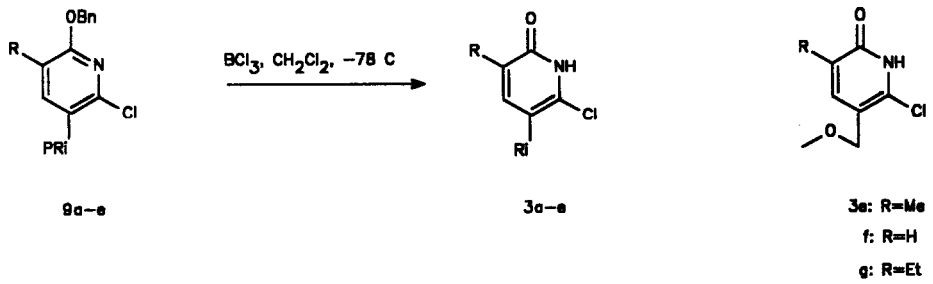
When the chlorine atom of compounds **9a-e** had to be maintained, an alternative debenzylation method with boron trichloride at -78°C followed by work-up in methanol was used.[8a,b] This afforded the model compound **3e** in good yield (93%) from **9e**. Application of this debenzylation method to compounds **9a-d** afforded the stable target C-nucleosides **3a-d** in low to moderate yield (scheme 3). Ether cleavage followed by reaction with methanol on work-up explains the isolation of side products of type **3e-g**, which are less abundant for a more bulky Ri-substituent.



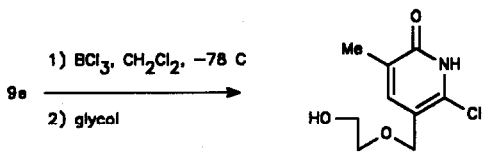
2	R	Ri	yield (%)	side products
a	Me	(i)	76	**12a** (10%)
b	Et	(i)	79	**12b** (<10%)
c	Me	(ii)	30	**13a** + **13b** (ca. 50%)
d	Et	(ii)	24	**13c** + **13d** (ca. 50%)
e	Me	$MeOCH_2$	95	

Scheme 2

The yield of **3a** could be improved by using the BCl_3 promoted cleavage and work-up with ethylene glycol at -78°C, thus avoiding formation of **3e**. After evaporation in vacuo followed by chromatographic purification on a silica gel column (gradient elution: chloroform to 30% $MeOH/CHCl_3$) we isolated C-nucleoside **3a** in 89% yield (scheme 3).



9a–e 3a–e 3a: R=Me f: R=H g: R=Et



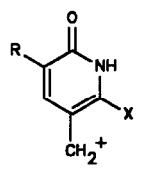
3a (89%)

3	R	Ri	yield (%)	side products
a	Me	(i)	7	3e (68%)
b	H	(ii)	37	3f [a]
c	Me	(ii)	50	3e (45%)
d	Et	(ii)	45	3g (50%)
e	Me	$MeOCH_2$	93	

(a) was only detected in the mass spectrum of the crude reaction mixture

Scheme 3

All spectral data are in agreement with the assigned C-nucleoside structures **2a-e** and **3a-e**. The IR spectra of compounds **2a-e** and **3a-e** show an amide stretching at ca. 1640 cm^{-1} and ca. 1660 cm^{-1}, respectively. The molecular ion signal for the proposed structures are clearly present in their mass spectra; moreover, the fragment ion with a relative abundance of 100% could be assigned to structures **14a** and **14b** proceeding from a loss of the sugar moiety.



14a: X=OMe b: X=Cl

In summary, stable 3-alkyl substituted 6-methoxy- and 6-chloro-2(1*H*)-pyridinone acyclo-C-nucleosides **2a-d** and **3a-d** can be elaborated in a four step synthesis from 6-alkyl substituted 3-methoxy-5-chloro- and 3,5-dichloro-2*H*-1,4-oxazin-2-ones **4a-e**. The key process - a regioselective Diels-Alder reaction of propargyl bromide with the appropriate 2*H*-1,4-oxazin-2-ones **4a-e** - provides the functionality for the introduction of the acyclo sugar moieties, whereas the pyridinone system is generated by substitution of the 5-chloro substituent from the original oxazinone.

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. UV-spectra were recorded on a Perkin-Elmer Lambda 6 UV/Vis spectrometer. ^{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. HPLC separations of compounds **9a-e/10a-e** were performed on a Lichrosorb 10 μm silica gel column (length : 50 cm). 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. The catalyst used for hydrogenation was a mixture of 10% palladium on carbon admixed with strontium carbonate in a ratio of (1:1). Oxazinones **4a-c**[4a], 2,6-dichloropyridines **5a-c**[7] and pyridines **7a,c,e**[2c] were prepared according to methods described in previous papers.

Synthesis of the 6-methoxypyridinones 2a-e. General procedure.
A solution of 1.00 mmol of the pyridines **8a-e** in ethanol (100 mL) admixed with 10% Pd on $C/SrCO_3$ (150 mg) was degassed three times, then hydrogenated at atmospheric pressure. Hydrogen consumption was controlled by a gas buret. The solution was filtered and the catalyst was washed with ethanol (ca. 150 mL). Evaporation at room temperature followed by chromatography on a silica gel column (gradient elution 0% to 10% MeOH/$CHCl_3$) yielded compounds **2a-e**. Products of type **12** and **13** were also generated and isolated in the case of **12a**.

5-[(2-Hydroxyethoxy)methyl]-6-methoxy-3-methyl-2(1*H*)-pyridinone 2a.
Compound **2a** (162 mg; 76%) was isolated as well as compound **12a** (30 mg; 10%). Both compounds obtained from the reaction of **8a** were recrystallized from an ethanol/water mixture yielding white crystals.
2a : mp = >215°C$_{dec}$; IR (KBr) cm^{-1}: 3300, 1610; UV (EtOH) λ_{max} nm: 289(2683), 227(2850); ^{1}H-NMR (CD_3OD) δ: 2.13(s, 3H, CH_3), 3.58(t, ^{3}J=6Hz, 2H, CH_2-2'), 3.71(t, ^{3}J=6Hz, 2H, CH_2-3'), 3.90(s, 3H, OCH_3), 4.48(s, 2H, $PyCH_2$), 7.42(s, 1H, PyH); ^{13}C-NMR (CD_3OD) δ: 14.8(qxd, ^{1}J=128, ^{3}J=5, CH_3), 54.0(q, ^{1}J=146, OCH_3), 62.1(t_{br}, ^{1}J=142, CH_2OH), 68.1(txq, ^{1}J=142, ^{3}J=5, $PyCH_2$), 72.4(t_{br}, ^{1}J=142, OCH_2), 110.3(q, ^{2}J=6, C-3), 111.1(t, ^{2}J=4, C-5), 143.6(dxsext., ^{1}J=156, ^{3}J=5, C-4), 159.7(m, C-6), 161.3(m, C-2); MS m/z : 213(33, M^+), 168(9), 152(100), 120(25); exact mass calcd for $C_{10}H_{15}NO_4$: 213.0996; found: 213.0957; anal calcd for $C_{10}H_{15}NO_4$: C 56.33, H 7.09, N 6.57; found: C 55.82, H 7.13, N 6.63
12a : mp = 232-233°C; IR (KBr) cm^{-1}: 3225, 1620; UV (EtOH) λ_{max} nm: 288, 226; ^{1}H-NMR ($CDCl_3$) δ: 2.08(s, 3H, CH_3), 3.60(s, 4H, CH_2), 3.85(s, 3H, OCH_3), 4.40(s, 2H, $PhCH_2$), 4.50(s, 2H, $PyCH_2$), 7.28(m, 6H, PyH+Ph); ^{13}C-NMR ($CDCl_3$) δ: 14.9(CH_3), 54.1(OCH_3), 68.1($PyCH_2$), 70.4, 70.6(CH_2), 74.1($PhCH_2$), 110.4, 111.4(C-3, C-5), 128.7, 128.9, 129.4(o-, p-, m-Ph), 139.6(ipso-Ph), 143.7(C-4), 159.8(C-6), 161.3(C-2); MS m/z : 303(22, M^+), 212(36), 168(38), 152(100), 120(20), 91(51); exact mass calcd for $C_{17}H_{21}NO_4$: 303.1464; found: 303.1467

5-[(2-Hydroxyethoxy)methyl]-3-ethyl-6-methoxy-2(1*H*)-pyridinone 2b.
Compound **2b** (179 mg; 79%) was obtained as a white amorphous powder.
IR (KBr) cm^{-1}: 3415, 1640; UV (MeOH) λ_{max} nm: 288(7870), 222(14953); ^{1}H-NMR (CD_3OD) δ: 1.17(t, 3H, CH_3), 2.49(q, 2H, CH_2), 3.55(t, ^{3}J=6Hz, 2H, CH_2-2'), 3.68(t, ^{3}J=6Hz, 2H, CH_2-3'), 3.87(s, 3H, OCH_3), 4.43(s, 2H, $PyCH_2$), 7.38(s, 1H, PyH); ^{13}C-NMR (CD_3OD) δ: 14.4(CH_3), 23.1(CH_2), 54.0(OCH_3), 62.1(CH_2-3'), 68.2($PyCH_2$), 72.5(CH_2-2'), 111.1(C-3), 116.7(C-5), 142.2(C-4), 159.7(C-6),

161.1(C-2); MS m/z : 227(16, M^+), 182(10), 166(100), 106(27); exact mass calcd for $C_{11}H_{17}NO_4$: 359.1152; found: 359.1147

5-[(1,3-Dihydroxy-2-propoxy)methyl]-6-methoxy-3-methyl-2(1*H*)-pyridinone 2c.

Compound **2c** (73 mg; 30%) was isolated as a gum.

IR (KBr) cm^{-1}: 3380, 1650, 1610; UV (MeOH) λ_{max}: 291(8149), 221(17521); ^{1}H-NMR (CD_3OD) δ: 2.07(s, 3H, CH_3), 3.50-3.72(m, 5H, CH_2-3', CH-2'), 3.86(s, 3H, OCH_3), 4.53(s, 2H, $PyCH_2$), 7.40(s, 1H, PyH); ^{13}C-NMR (CD_3OD) δ: 14.7(qxd, ^1J=128/^3J=5Hz, CH_3), 54.1(q, ^1J=147Hz, OCH_3), 62.4(txm, ^1J=142Hz, CH_2-3'), 67.2(txt, ^1J=144/^3J=5Hz, $PyCH_2$), 81.3(dxm, ^1J=142Hz, CH_2-2'), 110.4(q, ^2J=6.5Hz, C-3), 111.5(t, ^2J=4.5Hz, C-5), 143.7(dxsext, ^1J=159/^3J=5Hz, C-4), 159.6(m, C-6), 161.2(m, C-2); MS m/z : 243(14, M^+), 168(19), 152(100); exact mass calcd for $C_{11}H_{17}NO_5$: 243.1101; found: 243.1110

5-[(1,3-Dihydroxy-2-propoxy)methyl]-3-ethyl-6-methoxy-2(1*H*)-pyridinone 2d.

Compound **2d** (62 mg; 24%) was obtained as white crystals after recrystallization from a CH_2Cl_2/EtOH mixture.

mp = 138-139°C; IR (KBr) cm^{-1}: 3400, 1640; UV (MeOH) λ_{max} nm: 291(1786), 224(4536); ^{1}H-NMR ($CDCl_3$) δ: 1.16(t, 3H, CH_3), 2.50(q, 2H, CH_2), 3.60-3.86(m, 7H, CH_2-3', CH-2', OH), 3.88(s, 3H, OCH_3), 4.53(s, 2H, $PyCH_2$), 7.34(s, 1H, PyH); ^{13}C-NMR ($CDCl_3$) δ: 13.7(CH_3), 21.9(CH_2), 54.1(OCH_3), 62.1(CH_2-3'), 67.1($PyCH_2$), 79.6(CH_2-2'), 110.0(C-3), 116.6(C-5), 142.1(C-4), 158.7 (C-6), 159.5(C-2); MS m/z : 257(10, M^+), 182(18), 166(100); exact mass calcd for $C_{12}H_{19}NO_5$: 257.1257; found: 257.1251.

6-Methoxy-5-methoxymethyl-3-methyl-2(1*H*)-pyridin-2-one 2e.

Compound **2e** (174 mg; 95%) was obtained as white crystals after recrystallization from a CH_2Cl_2/hexane mixture.

mp = 63-64°C. IR (KBr) cm^{-1}: 3240, 1650, 1600, 1580; ^{1}H-NMR ($CDCl_3$) δ: 2.15(s, 3H, CH_3), 3.40(s, 3H, OCH_3), 3.90(s, 3H, $PyOCH_3$), 4.38(s, 2H, CH_2O), 7.39(s, 1H, PyH), 8.53(s_{br}, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ: 14.5(CH_3), 54.5($PyOCH_3$), 57.9(OCH_3), 68.4(CH_2O), 110.5(C-3, C-5), 142.9(C-4), 157.4 (C-6), 159.7(C-2); MS m/z : 183(28, M^+), 168(3), 152(100), 120(19), 92(13); exact mass calcd for $C_9H_{13}NO_3$: 183.0891; found: 183.0895; anal calcd for $C_9H_{13}NO_3$: C 59.00, H 7.15, N 7.65; found: C 59.41, H 6.89, N 7.71

Synthesis of the 5-substituted 3-alkyl-6-chloropyridinones 3a-g. General procedure.

A 1M solution of BCl_3 (7.0 mL) in CH_2Cl_2 under nitrogen atmosphere was added dropwise to a solution of **9a-e** (1.00 mmol) in dry CH_2Cl_2 (20 mL) at -78°C. After stirring for two hours at -78°C methanol was added dropwise. The solution was allowed to warm up to room temperature, evaporated and co-evaporated with methanol (3 times). The residue was admixed with methanol and silica gel (2.5 g) and, after evaporation, the mixture was applied to a silica gel column. Gradient elution (0% to 30% MeOH/$CHCl_3$) yielded compounds **3a-g** as pale yellow oils.

6-Chloro-5-[(2-hydroxyethoxy)methyl]-3-methyl-2(1*H*)-pyridin-2-one 3a.

Compound **3a** (15 mg; 7%) was obtained as a minor product and recrystallized from an ethanol/water mixture as white crystals; compound **3e** (127 mg; 68%), recrystallized from an ethanol/diethylether mixture, was the major product.

In an alternative method for the synthesis of **3a**, a 1M solution of BCl_3 (7.0 mL) in dry CH_2Cl_2 under nitrogen atmosphere was added dropwise to a solution of **9a** (385 mg; 1.00 mmol) in CH_2Cl_2 (20 mL) at -78°C. After 2h stirring at -78°C dry 1,2-ethanediol (6 mL) was added dropwise. The solution was allowed to warm to room temperature. Evaporation of the solvent under vacuum followed by 2 times coevaporation with 1,2-ethanediol and chromatography as described above afforded **3a** as a crystalline product (131 mg; 89%).

3a : mp=124-126°C; IR (KBr) cm^{-1}: 3480, 1650, 1615; UV (MeOH) λ_{max} nm: 288(7870), 222(14953); ^{1}H-NMR (DMSO-d^6) δ: 2.08(s, 3H, CH_3), 3.48(t, ^{3}J=5Hz, 2H, CH_2-2'), 3.53(q, ^{3}J=5Hz, 2H, CH_2-3'), 4.40(s, 2H, $PyCH_2$), 4.64(t, ^{3}J=5Hz, 1H, OH), 7.60(s, 1H, PyH), 11.51(s_{br}, 1H, NH); ^{13}C-NMR (DMSO-d^6) δ: 14.8(CH_3), 60.2(CH_2OH), 68.2($PyCH_2$), 71.8(OCH_2), 118.2(C-3), 122.2(C-5), 141.6 (C-4), 141.9(C-6), 161.3(C-2); MS m/z : 217(18, M^+), 172(35), 156(100), 120(35), 92(24); exact mass calcd for $C_9H_{12}ClNO_3$: 217.0503; found: 217.0504, anal calcd for $C_9H_{12}ClNO_3$: C 49.67, H 5.56, N 6.44; found: C 49.56, H 5.48, N 6.30

6-Chloro-5-[(1,3-dihydroxy-2-propoxy)methyl]-2(1*H*)-pyridin-2-one 3b.

Compound **3b** (86 mg; 37%) was recrystallized from an ethanol/diethylether mixture; compound **3f**, detected in the mass spectrum of the crude reaction mixture, was lost during work-up.

3b : mp = 134-135°C; IR (KBr) cm^{-1}: 3360, 1740, 1660, 1610; UV (MeOH) λ_{max} nm: 283(6195), 226(9064); ^{1}H-NMR (CD_3OD) δ: 3.65(m, 5H, $(CH_2)_2CH$), 4.63(s, 2H, $PyCH_2$); 6.6(d, ^{3}J=8.5Hz, 1H, H-5), 7.82(d, ^{3}J=8.5Hz, 1H, H-4); ^{13}C-NMR (CD_3OD) δ: 62.5(txq, ^{1}J=140/^{3}J=3Hz, CH_2), 68.7(txt, ^{1}J=144/^{3}J=4Hz, $PyCH_2$), 82.2(dxm, ^{1}J=140Hz, CH), 111.3(dxs_{br}, ^{1}J=168Hz, C-3), 123.2(m, C-5), 143.6(dxt, ^{1}J=163Hz/^{3}J=4Hz, C-4), 144.9(t, ^{3}J=8Hz, C-6), 164.5(m, C-2); MS m/z : 233(2, M^+), 158(27), 142(100), 106(35); exact mass calcd for $C_9H_{12}ClNO_4$: 233.0450; found: 233.0461

3f : MS (m/z): 173(55, M^+), 158(15), 142(100)

6-Chloro-5-[(1,3-dihydroxy-2-propoxy)methyl]-3-methyl-2(1*H*)-pyridin-2-one 3c.

Compound **3c** (123 mg; 50%) was obtained as a gum; compound **3e** (84 mg; 45%) was also isolated.

3c : IR (KBr) cm^{-1}: 3400, 1725, 1670, 1610; UV (MeOH) λ_{max} nm: 287(5313), 225(7649); ^{1}H-NMR (CD_3OD) δ: 2.12(s, 3H, CH_3), 3.5-3.75(m, 5H, $(CH_2)_2CH$)), 4.60(s, 2H, $PyCH_2$); 7.5(s, 1H, H-4); ^{13}C-NMR (CD_3OD) δ: 15.6(CH_3), 62.5(CH_2), 68.6($PyCH_2$), 82.0(CH), 120.7(C-3), 123.5(C-5), 139.0(C-6), 142.7(C-4), 164.0(C-2); MS m/z : 247(8, M^+), 172(20), 156(100), 120(28); exact mass calcd for $C_{10}H_{14}ClNO_4$: 247.0608; found: 247.0621

6-Chloro-5-[(1,3-dihydroxy-2-propoxy)methyl]-3-ethyl-2(1*H*)-pyridin-2-one 3d and compound 3g.

Compound **3d** (119 mg; 45%) was recrystallized from an ethanol/dichloromethane mixture; compound **3g** (123 mg; 50%) was also obtained after recrystallization from hexane.

3d : mp = 138-139°C; IR (KBr) cm^{-1}: 3330, 1650, 1610; UV (MeOH) λ_{max} nm: 287(5648), 230(6667); ^{1}H-NMR (CD_3OD) δ: 1.19(t, 3H, CH_3), 2.54(q, 2H, CH_2), 3.52, 3.68(m, 5H, $(CH_2)_2CH$)), 4.60(s, 2H, $PyCH_2$); 7.61(s, 1H, H-4); ^{13}C-NMR (CD_3OD) δ: 13.4(CH_3), 23.6(CH_2), 62.5(CH_2), 68.6($PyCH_2$), 82.0(CH), 120.8(C-3), 129.4(C-5), 138.8(C-6), 141.2(C-4), 163.4(C-2); MS m/z : 261(8, M^+), 186(24), 170(100), 106(20); exact mass calcd for $C_{11}H_{16}ClNO_4$: 261.0762; found: 261.0766; anal calcd for $C_{11}H_{16}ClNO_4$: C 50.48, H 6.16, N 5.35; found: C 50.05, H 5.91, N 5.01

3g : mp (hexane) = 89-90°C; IR (KBr) cm^{-1}: 3380, 1650, 1610; UV (MeOH) λ_{max} nm: 286(9208), 230(7095); ^{1}H-NMR ($CDCl_3$) δ: 1.24(t, 3H, CH_3), 2.61(q, 2H, CH_2), 3.41(s, 3H, CH_3O), 4.40(s, 2H, CH_2O), 7.50(s, H-4), 9.5(s_{br}, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ: 12.9(CH_3), 22.5(CH_2), 58.2(CH_3O), 70.0(CH_2O), 120.0(C-3), 128.3(C-5), 138.2(C-6), 139.7(C-4), 162.9(C-2); MS m/z : 201(70, M^+), 170(100), 106(8); exact mass calcd for $C_9H_{12}ClNO_2$: 201.0552; found: 201.0563

6-Chloro-5-methoxymethyl-3-methyl-2(1*H*)-pyridin-2-one 3e

Compound **3e** (159 mg; 93%) was obtained from **9e** and recrystallized from an ethanol/diethylether mixture.

3e : mp = 115-116°C; IR (KBr) cm^{-1}: 3440, 1730, 1655, 1610; UV (MeOH) λ_{max} nm: 287(3606), 229(4502)nm. ^{1}H-NMR ($CDCl_3$) δ: 2.12(s, 3H, CH_3), 3.32(s, 3H, OCH_3), 4.30(s, 2H, $PyCH_2$), 7.42(s, 1H, PyH), 11.3(s_{br}, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ: 15.4(CH_3), 58.1(OCH_3), 69.9($PyCH_2$), 120.3(C-3), 122.2(C-5), 138.6(C-6), 141.3(C-4), 163.1(C-2); MS m/z : 187(60, M^+), 156(100), 120(37), 92(23); exact mass calcd for $C_8H_{10}ClNO_2$: 187.0398; found: 187.0400

Synthesis of the 5-Chloro-3-methoxy-2*H*-1,4-oxazin-2-ones 4d and 4e.

To an icecold saturated solution of dry hydrochloric acid in methanol (100 mL) was added the corresponding 3,5-dichloro-6-alkyl-2*H*-1,4-oxazin-2-one **4b** or **4c** [4a] (30.0 mmol). After 15 min stirring the solution was

evaporated at room temperature. Flash column chromatography on silica gel ($CHCl_3$) afforded oxazinones **4d** and **4e**.

5-Chloro-3-methoxy-6-methyl-2*H*-1,4-oxazin-2-one 4d.
Compound **4d** (4.78 g; 91%) was obtained after recrystallization from a 1:1 mixture of pentane/ether.
mp = 82°C; IR (KBr) cm^{-1}: 1760, 1620; ^{1}H-NMR ($CDCl_3$) δ: 2.29(s, 3H, Me), 4.00(s, 3H, OMe); ^{13}C-NMR ($CDCl_3$) δ: 16.1(CH_3), 55.6(OCH_3), 121.5(C-5), 142.0(C-6), 149.7(C-3), 150.2(C-2); MS, m/z 175(61, M^+), 147(40), 132(100); exact mass calcd for $C_6H_6ClNO_3$: 175.0036; found: 175.0038
5-Chloro-6-ethyl-3-methoxy-2*H*-1,4-oxazin-2-one 4e.
Compound **4e** (3.57 g; 63%) was obtained as an oil.
IR (film) cm^{-1}: 1765, 1625, 1580; ^{1}H-NMR ($CDCl_3$) δ: 1.19(t, ^{3}J=7Hz, 3H, CH_3), 2.57(q, ^{3}J=7Hz, CH_2), 3.76(s, 3H, OCH_3); ^{13}C-NMR ($CDCl_3$) δ: 10.7(CH_3), 23.4(CH_2), 55.6(OCH_3), 120.8(C-5), 146.3(C-6), 149.6(C-3), 150.3(C-2); MS m/z : 189(19,M^+), 161(6), 146(50), 101(12), 57(100); exact mass calcd for $C_7H_8ClNO_3$: 189.0189; found: 189.0178

Synthesis of the 3-Bromomethyl-6-chloro-2-methoxypyridines 5d and 5e.
A solution of **4d** or **4e** (30.0 mmol) in propargyl bromide (26 g of a 80%wt solution in toluene; 180.0 mmol) was stirred overnight 90°C under nitrogen. Evaporation folowed by flash chromatography on silica gel ($CHCl_3$) and recrystallization (hexane) yielded **5d** (7.45 g; 95%) and **5e** (6.56 g; 82%) as white crystals.

3-Bromomethyl-6-chloro-2-methoxy-5-methylpyridine 5d.
mp = 86°C. IR (KBr) cm^{-1}: 1610, 1570; ^{1}H-NMR ($CDCl_3$) δ: 2.3(s, 3H, CH_3), 4.0(s, 3H, OCH_3), 4.55(s, 2H, CH_2Br), 7.50(s, 1H, PyH); ^{13}C-NMR ($CDCl_3$) δ: 18.2(CH_3), 40.0(CH_2), 54.2(CH_3O), 118.5(C-5), 124.1(C-3), 141.8(C-4), 147.5(C-2), 158.9(C-6); MS m/z : 249(6, M^+), 170(100), 140(38); exact mass calcd for $C_8H_9BrClNO$: 248.9552; found: 248.9549; anal calcd for $C_8H_9BrClNO$: C 38.36, H 3.62, N 5.59; found: C 38.31, H 3.48, N 5.54
3-Bromomethyl-6-chloro-5-ethyl-2-methoxypyridine 5e.
Compound **5e** was obtained as a colourless oil.
IR (film) cm^{-1}: 1610, 1570; ^{1}H-NMR ($CDCl_3$) δ: 1.20(t, 3H, CH_3), 2.64(q, 2H, CH_2), 3.96(s, 3H, OCH_3), 4.43(s, 2H, CH_2Br), 7.45(s, 1H, PyH); ^{13}C-NMR ($CDCl_3$) δ: 13.7(CH_3), 25.2(CH_2), 26.9(CH_2Br), 54.3(CH_3O), 119.1(C-5), 129.9(C-3), 141.0(C-4), 147.3(C-2), 158.9(C-6); MS m/z : 263(5, M^+), 184(100), 154(28); exact mass calcd for $C_9H_{11}BrClNO$: 262.9711; found: 262.9713

Synthesis of the 3-[(2-(Benzyloxy)ethoxy)methyl]-6-chloro-2-methoxypyridines 6a-b and of the 3-[(1,3-(Dibenzyloxy-2-propoxy)methyl]-6-chloro-2-methoxypyridines 6c-d. General procedure.
A solution of 2-benzyloxyethanol (182 mg; 1.2 mmol) or 1,3-dibenzyloxy-2-propanol (326 mg; 1.2 mmol) and NaH (39 mg; 1.2 mmol of a 80% dispersion in paraffin oil) in dry THF (15 mL) was refluxed for 30 min under nitrogen. Then a solution of pyridine **5d** or **5e** (1.0 mmol) in dry THF (10 mL) was added dropwise and the mixture was refluxed for 7h. The cold mixture then was poured into a 10% NH_4Cl solution (50 mL), extracted with $CHCl_3$ (3x 80 mL), dried ($MgSO_4$), and evaporated. Chromatography on a silica gel column ($CHCl_3$) yielded pyridines **6a** (276 mg; 86%) and **6b** (265 mg; 79%) as colourless oils, and pyridines **6c** (315mg; 76%) and **6d** (327mg; 72%) as pale yellow oils.

3-[(2-(Benzyloxy)ethoxy)methyl]-6-chloro-2-methoxy-5-methylpyridine 6a.
IR (film) cm^{-1}: 3090, 3060, 3030, 1610; ^{1}H-NMR ($CDCl_3$) δ: 2.24(s, 3H, CH_3), 3.68(m, 4H, CH_2CH_2), 3.80(s, 3H, OCH_3), 4.50(s, 2H, $PyCH_2$), 4.58(s, 2H, $PhCH_2$), 7.31(m, 5H, Ph), 7.53(s, 1H, PyH); MS m/z : 321(1, M^+), 230(24), 186(48), 151(40), 107(30), 91(100); exact mass calcd for $C_{17}H_{18}ClNO_3$: 321.1125; found: 321.1122

3-[(2-(Benzyloxy)ethoxy)methyl]-6-chloro-2-methoxy-5-ethylpyridine 6b.
IR (film) cm^{-1}: 3100, 3080, 3040, 1610; ^{1}H-NMR ($CDCl_3$) δ: 1.18(t, 3H, CH_3), 2.65(q, 2H, CH_2), 3.71(m, 4H, CH_2CH_2), 3.96(s, 3H, OCH_3), 4.50(s, 2H, $PyCH_2$), 4.57(s, 2H, $PhCH_2$), 7.34(m, 5H, Ph), 7.59(s, 1H, PyH); ^{13}C-NMR ($CDCl_3$) δ: 13.9(CH_3), 25.3(CH_2), 53.9(OCH_3), 66.9($PyCH_2$), 69.5, 70.3(CH_2CH_2), 73.3($PhCH_2$), 119.9(C-3), 127.6, 127.7, 128.4(o-, m-, p-Ph), 129.5(C-5), 138.3(ipso-Ph), 139.1(C-4), 145.5(C-6), 1587(C-2); MS m/z : 335(1, M^+), 244(39), 200(56), 151(62), 107(38), 91(100); exact mass calcd for $C_{18}H_{22}ClNO_3$: 335.1283; found: 335.1286

3-[(1,3-(Dibenzyloxy-2-propoxy)methyl]-6-chloro-2-methoxy-5-methylpyridine 6c.
IR (film) cm^{-1}: 3090, 3060, 3040, 1620; ^{1}H-NMR ($CDCl_3$) δ: 2.20(s, 3H, CH_3), 3.63(m, 4H, CH_2), 3.82(m, 1H, CH), 3.91(s, 3H, OCH_3), 4.55(s, 2H, $PhCH_2$), 4.61(s, 2H, $PyCH_2$), 7.29(m, 10H, Ph), 7.61(s, 1H, PyH); ^{13}C-NMR ($CDCl_3$) δ: 18.2(CH_3), 53.8(CH_3O), 70.2($PyCH_2$), 73.5(CH_2), 78.1(CH), 120(C-3), 123.6(C-5), 127.6, 128.3, 128.2(o-, m-, p-Ph), 138.2(ipso-Ph), 140.2(C-4), 145.2(C-6), 158.5(C-2); MS m/z : 441(1, M^+), 350(21), 406(2), 91(100); exact mass calcd for $C_{25}H_{28}ClNO_4$: 441.1698; found: 441.1692

3-[(1,3-(Dibenzyloxy-2-propoxy)methyl]-6-chloro-2-methoxy-5-ethylpyridine 6d.
IR (film) cm^{-1}: 3090, 3060, 3030, 1605; ^{1}H-NMR ($CDCl_3$) δ: 1.13(t, 3H, CH_3), 2.63(q, 2H, CH_2), 3.68(m, 4H, CH_2), 3.80(m, 1H, CH), 3.95(s, 3H, OCH_3), 4.62(s, 4H, $PhCH_2$), 4.70(s, 2H, $PyCH_2$), 7.37(m, 10H, Ph), 7.7(s, 1H, PyH); MS m/z : 455(0.1, M^+), 378(0.1), 364(12), 271(19), 184(52), 91(100); exact mass calcd for $C_{23}H_{30}ClNO_4$: 455.1863; found: 455.1845

6-Chloro-2-methoxy-3-methoxymethyl-5-methylpyridine 6e.
A solution of oxazinone **4d** (176 mg; 1.00 mmol) in neat methyl propargyl ether (2 mL) was heated in a sealed tube at 90°C for 2.5 days. Evaporation of the solvent and chromatography (silica gel; $CHCl_3$) yielded **6e** (179 mg; 89%) as a colourless oil. The crude reaction mixture contained a small amount of the isomer 2-chloro-6-methoxy-4-methoxymethyl-3-methylpyridine (< 10%).
IR (film) cm^{-1}: 1615, 1575; ^{1}H-NMR ($CDCl_3$) δ: 2.28(s, 3H, CH_3), 3.43(s, 3H, CH_3O), 3.97(s, 3H, CH_3OPy), 4.39(s, 2H, OCH_2), 7.49(s, 1H, PyH); ^{13}C-NMR ($CDCl_3$) δ: 18.1(CH_3), 53.8(CH_3O), 58.4(CH_3OPy), 68.1(CH_2O), 119.3(C-3), 123.5(C-5), 140.1(C-4), 145.9(C-2), 158.6(C-6); MS m/z: 201(65, M^+)186(81), 170(100), 155(49); exact mass calcd for $C_9H_{12}O_2NCl$: 201.0552; found: 201.0551; anal calcd for $C_9H_{12}O_2NCl$: C 53.61, H 6.00, N 6.95; found: C 53.24, H 5.72, N 7.03; ^{1}H-NMR ($CDCl_3$) of the isomer δ: 2.2, 3.43, 3.90, 4.05, 7.34

Synthesis of the 3-[(1,3-Dibenzyloxy-2-propoxy)methyl]-2,6-dichloropyridines 7b and 7d.
A solution of 1,3-dibenzyloxy-2-propanol (324mg; 1.2 mmol) and NaH (36 mg, 1.2 mmol of a 80% dispersion in paraffin oil) in dry THF (55 mL) was refluxed for 30 min under nitrogen. A solution of pyridines **5a** or **5c** (1.0 mmol) in dry THF (15 mL) was added dropwise and the mixture was refluxed for 3h. The cold mixture then was poured into a 10% NH_4Cl solution (25 mL), extracted with $CHCl_3$ (3x 30 mL), dried ($MgSO_4$), and evaporated. Chromatography on a silica gel column ($CHCl_3$) yielded pyridines **7b** (540mg; 72%) and **7d** (400mg; 71%) as colourless oils.

3-[(1,3-Dibenzyloxy-2-propoxy)methyl]-2,6-dichloropyridine 7b.
IR (film) cm^{-1}: 3090, 3070, 3035, 1580, 1555; ^{1}H-NMR ($CDCl_3$) δ: 3.62(m, 4H, CH_2), 3.82(m, 1H, CH), 4.52(s, 4H, $PhCH_2$), 4.70(s, 2H, $PyCH_2$), 7.15(d, ^{3}J=9Hz, 1H, PyH-5), 7.3(m, 10H, Ph), 7.90(d, ^{3}J=9Hz, 1H, PyH-4); ^{13}C-NMR ($CDCl_3$) δ: 67.7($PyCH_2$), 70.5(CH_2), 73.5($PhCH_2$), 78.7(CH), 120.6(C-3), 122.9(C-5), 127.6, 127.7, 128.4(o-, m-, p-Ph), 132.5, 138.0(ipso-Ph), 139.7(C-4), 147.7, 148.6(C-2, C-6); MS m/z : 431(0.3, M^+), 396(1.7), 340(12), 234(31), 160(20), 91(100); exact mass calcd for $C_{23}H_{23}Cl_2NO_3$: 431.1047; found: 431.1058

3-[(1,3-Dibenzyloxy-2-propoxy)methyl]-2,6-dichloro-5-ethylpyridine 7d.
IR (film) cm^{-1}: 3090, 3060, 3030, 1595, 1550; ^{1}H-NMR ($CDCl_3$) δ: 1.19(t, 3H, CH_3), 2.67(q, 2H, CH_2), 3.67(m, 4H, CH_2), 3.87(m, 1H, CH), 4.58(s, 4H, $PhCH_2$), 4.74(s, 2H, $PyCH_2$), 7.40(m, 10H, Ph), 7.80(s, 1H, PyH); ^{13}C-NMR ($CDCl_3$) δ: 13.4(CH_3), 25.6(CH_2), 67.7($PyCH_2$), 70.4(CH_2), 73.5($PhCH_2$), 78.6(CH), 127.6, 127.7, 128.4(o-, m-, p-Ph), 132.4(ipso-Ph), 136.9, 138.0(C-3, C-5), 139.2(C-4), 144.7, 147.9(C-2, C-6); MS m/z : 459(0.1, M^+), 424(2), 368(13), 278(4), 188(32), 91(100); exact mass calcd for $C_{25}H_{27}Cl_2NO_3$: 459.1359; found: 459.1364

Synthesis of the 3-substituted 5-alkyl-6-Benzyloxy-2-methoxypyridines 8a-e. General procedure.
A mixture of freshly distilled benzyl alcohol (1.35 g; 12.5 mmol) and NaH (375 mg; 12.5 mmol of a 80% dispersion in paraffin oil) in dry DMF (15 mL) was stirred under nitrogen for 30 min at 90°C. Then a solution of the 6-chloro-2-methoxypyridines **6a-e** (1.25 mmol) in dry DMF (5 mL) was added dropwise. After stirring for the indicated reaction time (see below) at 90°C, the solution was cooled, treated with a 10% NH_4Cl solution (50 mL) and extracted with $CHCl_3$ (3x 50 mL). The combined extracts were dried ($MgSO_4$) and evaporated. Chromatography on a silica gel column with the indicated eluents yielded **8a-e** as oils.

6-Benzyloxy-3-[(2-benzyloxyethoxy)methyl]-2-methoxy-5-methylpyridine 8a.
Compound **8a** was obtained from **6a** after stirring for 3 hours at 90°C. Chromatography performed with gradient elution (0% to 2% EtOAc/Tol) yielded compound **8a** (437 mg; 89%) as a pale yellow oil.
IR (film) cm^{-1}: 3090, 3060, 3030, 1600; ^{1}H-NMR ($CDCl_3$) δ: 2.14(s, 3H, CH_3), 3.65(m, 4H, CH_2CH_2), 3.86(s, 3H, OCH_3), 4.46(s, 2H, $PhCH_2$), 4.56(s 2H, $PyCH_2$), 5.42(s, 2H, $PhCH_2$), 7.30(m, 10H, Ph), 7.42(s, 1H, PyH); ^{13}C-NMR ($CDCl_3$) δ: 14.5(CH_3), 53.3(OCH_3), 65.2($PyCH_2$), 67.1, 67.2(CH_2CH_2), 69.5($PhCH_2$), 73.2($PhCH_2$), 110.7, 110.8(C-3, -5), 126.8, 127.3, 127.4, 127.6, 128.2, 128.4(o-, m-, p-Ph), 138.2, 138.3(ipso-Ph), 141.8(C-4), 158.1, 159.1(C-2, -6); MS m/z : 393(33, M^+), 302(9), 242(19), 91(100); exact mass calcd for $C_{24}H_{27}NO_4$: 393.1932; found: 393.1935
6-Benzyloxy-3-[(2-benzyloxyethoxy)methyl]-5-ethyl-2-methoxypyridine 8b.
Compound **8b** was obtained from **6b** after stirring for 4 hours at 90°C. Chromatography performed with $CHCl_3$ as eluent yielded compound **8b** (408 mg; 84%) as a pale yellow oil.
IR (film) cm^{-1}: 3100, 3070, 3040, 1600; ^{1}H-NMR ($CDCl_3$) δ: 1.17(t, 3H, CH_3), 2.58(q, 2H, CH_2), 3.58(m, 4H, CH_2CH_2), 3.90(s, 3H, OCH_3), 4.48(s, 2H, $PhCH_2$), 4.59(s 2H, $PyCH_2$), 5.42(s, 2H, $PhCH_2$), 7.35(m, 10H, Ph), 7.44(s, 1H, PyH); ^{13}C-NMR ($CDCl_3$) δ: 14.0(CH_3), 22.0(CH_2), 53.3(OCH_3), 67.3($PyCH_2$, $PhCH_2$), 69.6 (CH_2CH_2), 73.2($PhCH_2$), 111.0, 116.9(C-3, -5), 127.4, 127.5, 127.7, 128.3(o-, m-, p-Ph), 138.3, 138.4(ipso-Ph), 140.4(C-4), 158.1, 158.8(C-2, -6); MS m/z : 407(21, M^+), 256(32), 91(100); exact mass calcd for $C_{25}H_{29}NO_4$: 407.2088; found: 407.2082
3-[(1,3-Dibenzyloxy-2-propoxy)methyl]-6-benzyloxy-2-methoxy-5-methylpyridine 8c.
Compound **8c** was obtained from **6c** after stirring for 8 hours at 90°C. Chromatography performed with gradient elution (50% to 0% hexane/$CHCl_3$) yielded **8c** (552 mg; 86%) as a pale yellow oil.
IR (film) cm^{-1}: 3090, 3060, 3030, 1600; ^{1}H-NMR ($CDCl_3$) δ: 2.11(s, 3H, CH_3), 3.63(m, 4H, CH_2), 3.79(m, 1H, CH), 3.86(s, 3H, OCH_3), 4.53(s, 2H, $PhCH_2$), 4.58(s, 2H, $PyCH_2$), 5.39(s, 2H $PhCH_2$), 7.30(m, 15H, Ph), 7.44(s, 1H, PyH); ^{13}C-NMR ($CDCl_3$) δ: 14.5(CH_3), 53.3(CH_3O), 66.2(PyCH2), 67.2(CH_2), 70.3($PhCH_2$), 73.3($PhCH_2$), 77.3(CH), 110.7(C-3), 111.3(C-5), 127.3, 127.4, 127.5, 128.2 (o-, m-, p-Ph), 138.3, 138.4 (ipso-Ph), 141.8(C-4), 158.0, 159.0(C-6, C-2); MS m/z : 513(7, M^+), 422(2), 242(20), 151(1), 120(1), 91(100); exact mass calcd for $C_{32}H_{35}NO_5$: 513.2505; found: 513.2519
6-Benzyloxy-3-[(1,3-dibenzyloxy-2-propoxy)methyl]-5-ethyl-2-methoxypyridine 8d.
Compound **8d** was obtained from **6d** after stirring for 6 hours at 90°C. Chromatography performed with gradient elution (0% to 10%EtOAc/Hex) yielded **8d** (494 mg; 75%) as a pale yellow oil.
IR (film) cm^{-1}: 3090, 3060, 3040, 1600; ^{1}H-NMR ($CDCl_3$) δ: 1.15(t, 3H, CH_3), 2.56(q, 2H, CH_2), 3.52(m, 4H, CH_2), 3.80(m, 1H, CH), 3.88(s, 3H, OCH_3), 4.54(s, 4H, $PhCH_2$), 4.61(s, 2H, $PyCH_2$),

5.41(s, 2H, $PhCH_2$); 7.30(m, 15H, Ph), 7.44(s, 1H, PyH); ^{13}C-NMR ($CDCl_3$) δ: 14.0(CH_3), 21.9(CH_2), 53.2(CH_3O), 66.3($PyCH_2$), 67.2, 67.3(CH_2), 70.3, 73.3($PhCH_2$), 77.4(CH), 111.4(C-5), 116.8(C-3), 127.3, 127.4, 127.5, 128.3(o-, p-,m-Ph), 140.4(C-4), 158.0, 158.7(C-2, C-6); MS m/z : 527(11, M^+), 436(2), 360(1), 91(100); exact mass calcd for $C_{33}H_{37}NO_5$: 527.2661; found: 527.2668

6-Benzyloxy-2-methoxy-3-methoxymethyl-5-methylpyridine 8e.

Compound **8e** was obtained from **6e** after stirring for 4 hours at 90°C. Chromatography performed with gradient elution (0% to 10% EtOAc/Tol) yielded **8e** (270 mg; 79%) as a colourless oil.

IR (film) cm^{-1}: 3090, 3070, 3090, 1600; ^{1}H-NMR ($CDCl_3$) δ: 2.13(s, 3H, CH_3), 3.34(s, 3H, OCH_3), 3.86(s, 2H, CH_2O), 3.88(s, 3H, $PyOCH_3$), 5.42(s, 2H, $PhCH_2$), 7.36(m, 6H, Ph+PyH); MS m/z : 273(33, M^+), 242(71), 197(10), 91(100); exact mass calcd for $C_{16}H_{19}NO_3$: 273.1359; found: 273.1368

Synthesis of the 6-Benzyloxy-2-chloropyridines 9a-e and 10a-e. General procedure.

A mixture of distilled benzyl alcohol (973 mg; 9.0 mmol for **7a,e** - 1.62 g; 15.0 mmol for **7b-d**) and NaH (270 mg; 9.0 mmol of a 80% dispersion in paraffin oil for **7a,e** - 450 mg; 15.0 mmol for **7b-d**) in dry DMF (30 mL) was stirred under nitrogen for 30 min at ambient temperature. To this was added dropwise a solution of **7a-e** (3.0 mmol) in dry DMF (25 mL). After stirring at room temperature for 4 hours a 10% NH_4Cl solution (100 mL) was added. The mixture was extracted with $CHCl_3$ (3x 150 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated. Chromatography on a silica gel column yielded a mixture of the compounds **9a-e** and **10a-e** which were separated further by HPLC to afford both regio isomers as colourless oils.

6-Benzyloxy-3-[(2-benzyloxyethoxy)methyl]-2-chloro-5-methylpyridine 9a and its regio isomer 10a.

Chromatography (gradient elution 0% to 2% EtOAc/$CHCl_3$) yielded a mixture of the regio isomers **9a** and **10a**, which were separated further by HPLC to afford compounds **9a** (500 mg; 42%) and **10a** (298 mg; 25%) as colourless oils.

9a : IR (film) cm^{-1}: 3100, 3080, 3040, 1610 1570; ^{1}H-NMR ($CDCl_3$) δ: 2.18(s, 3H, CH_3), 3.70(m, 4H, CH_2CH_2), 4.56,4.58(2x s, 4H, OCH_2Ph, $PyCH_2$), 5.38(s 2H, $PhCH_2$), 7.35(m, 10H, Ph), 7.54(s, 1H, PyH); ^{13}C-NMR ($CDCl_3$) δ: 15.1(CH_3), 68.1($PyCH_2$), 69.1, 69.4 (CH_2CH_2), 70.0($PhCH_2$), 73.2($PhCH_2$), 119.6(C-5), 124.2(C-3), 127.5, 127.6, 128.3(o-, m-, p-Ph), 137.1, 138.2(ipso-Ph), 140.1(C-4), 143.1(C-2), 160.3(C-6); MS m/z : 397(0.1, M^+), 306(16), 151(26), 91(100); exact mass calcd for $C_{23}H_{24}ClNO_3$: 397.1439; found: 397.1435

10a : ^{1}H-NMR ($CDCl_3$) δ: 2.25(s, 3H, CH_3), 3.68(m, 4H, CH_2CH_2), 4.52,4.56(2x s, 4H, OCH_2Ph, $PyCH_2$), 5.36(s 2H, $PhCH_2$), 7.35(m, 10H, Ph), 7.60(s, 1H, PyH); ^{13}C-NMR ($CDCl_3$) δ: 18.3(CH_3), 66.7($PyCH_2$), 68.0, 69.4, 70.3($PhCH_2$, CH_2CH_2), 73.2($PhCH_2$), 119.9(C-3), 124.1(C-5), 127.6, 127.8, 128.3(o-, m-, p-Ph), 137.1, 138.2(ipso-Ph), 140.4(C-4), 145.8(C-6), 158.0(C-2)

6-Benzyloxy-2-chloro-3-[(1,3-dibenzyloxy-2-2-propoxy)methyl]-pyridine 9b and its regio isomer 10b.

Chromatography ($CHCl_3$) yielded a mixture of the regio isomers **9b** and **10b**, which were separated further by HPLC to afford compounds **9b** (816 mg; 54%) and **10b** (317 mg; 21%) as colourless oils.

9b : IR (film) cm^{-1}: 3090, 3060, 3030, 1610, 1550; ^{1}H-NMR ($CDCl_3$) δ: 3.54(m, 4H, CH_2), 3.82(m, 1H, CH), 4.53(s, 4H, $PhCH_2$), 4.70(s, 2H, $PyCH_2$), 5.37(s, 2H, $PhCH_2$), 6.68(d, ^{3}J=8.5Hz, 1H, PyH-5), 7.3(m, 15H, Ph), 7.79(d, ^{3}J=8.5Hz, 1H, PyH-4); ^{13}C-NMR ($CDCl_3$) δ: 68.1($PyCH_2$), 68.3, 70.2($PhCH_2$+CH_2), 73.3($PhCH_2$), 78.0(CH), 109.5(C-5), 125.0(C-3), 127.5, 127.9, 128.1, 128.3, 128.4(o-, m-, p-Ph), 136.6, 138.1(ipso-Ph), 140.7(C-4), 146.0(C-2), 162.1(C-6); MS m/z: 503(0.2, M^+), 468(0.1), 412(7), 271(11), 91(100); exact mass calcd for $C_{30}H_{30}ClNO_4$: 503.1854; found: 503.1883

10b : ^{1}H-NMR ($CDCl_3$) δ: 3.60(m, 4H, CH_2), 3.8(m, 1H, CH), 4.51(s, 4H, $PhCH_2$), 4.68(s, 2H, $PyCH_2$), 5.38(s, 2H, $PhCH_2$), 6.88(d, ^{3}J=8.5Hz, 1H, PyH-5), 7.3(m, 15H, Ph), 7.75(d, ^{3}J=8.5Hz, PyH-4); ^{13}C-NMR ($CDCl_3$) δ: 65.9(PyCH2), 116.4(C-5), 120.4(C-3), 139.2(C-4), 146.5(C-6), 160.0(C-2)

6-Benzyloxy-2-chloro-3-[(1,3-dibenzyloxy-2-propoxy)methyl]-5-methylpyridine 9c and its regio isomer 10c.

Chromatography ($CHCl_3$) yielded a mixture of the regio isomers **9c** and **10c**, which were separated further by HPLC to afford compounds **9c** (777 mg; 50%) and **10c** (585 mg; 33%) as colourless oils.

9c : IR (film) cm^{-1}: 3090, 3060, 3040, 1610, 1580; ^{1}H-NMR ($CDCl_3$) δ: 2.14(s, 3H, CH_3), 3.65(m, 4H, CH_2), 3.84(m, 1H, CH), 4.53(s, 4H, $PhCH_2$), 4.67(s, 2H, $PyCH_2$), 5.37(s, 2H, $PhCH_2$), 7.32(m, 15H, Ph), 7.58(s, 1H, PyH); ^{13}C-NMR ($CDCl_3$) δ: 15.0(CH_3), 68.1($PyCH_2$), 68.2, 70.3($PhCH_2$ +CH_2), 73.4($PhCH_2$), 77.9(CH), 119.6(C-3), 124.6(C-5), 127.7, 127.8, 128.4(o-, m-, p-Ph), 137.3, 138.2 (ipso-Ph), 141.0(C-4), 143.1(C-2), 160.4(C-6); MS m/z : 517(0.2, M^+), 426(2.5), 336(2), 271(7), 246(7), 181(5), 91(100); exact mass calcd for $C_{31}H_{32}ClNO_4$: 517.2010; found: 517.1998

10c : ^{1}H-NMR ($CDCl_3$) δ: 2.21(s, 3H, CH_3), 3.60(m, 4H, CH_2), 3.79(m, 1H, CH), 4.49(s, 4H, $PhCH_2$), 4.65(s, 2H, $PyCH_2$), 5.35(s, 2H, $PhCH_2$), 7.28(m, 1H, Ph), 7.63(s, 1H, PyH); ^{13}C-NMR ($CDCl_3$) δ: 18.3(CH_3), 65.8($PyCH_2$), 120.3(C-3), 124.1(C-5), 140.6(C-4), 145.8(C-6), 158.0(C-2)

6-Benzyloxy-2-chloro-3-[(1,3-dibenzyloxy-2-propoxy)methyl]-5-ethylpyridine 9d and its regio isomer 10d.

Chromatography ($CHCl_3$) yielded a mixture of the regio isomers **9d** and **10d**, which were separated further by HPLC to afford compounds **9d** (749 mg; 47%) and **10d** (446 mg; 28%) as colourless oils.

9d : IR (film) cm^{-1}: 3090, 3060, 3030, 1600, 1560; ^{1}H-NMR ($CDCl_3$) δ: 1.16(t, 3H, CH_3), 2.58(q, 2H, CH_2), 3.68(m, 4H, CH_2), 3.86(m, 1H, CH), 4.54(s, 4H, $PhCH_2$), 4.70(s, 2H, $PyCH_2$), 5.40(s, 2H, $PhCH_2$), 7.30(m, 15H, Ph), 7.52(s, 1H, PyH); ^{13}C-NMR ($CDCl_3$) δ: 13.3(CH_3), 22.3(CH_2), 68.0($PyCH_2$), 68.3, 70.3($PhCH_2$+CH_2), 73.4($PhCH_2$), 77.9(CH), 124.7(C-3), 125.3(C-5), 127.6, 127.7, 127.8, 128.3(o-, m-, p-Ph), 137.2, 138.2(ipso-Ph), 139.4(C-4), 143.1(C-2), 159.9(C-6); MS m/z: 531(0.2, M^+), 440(9), 260(9), 91(100); exact mass calcd for $C_{32}H_{34}ClNO_4$: 531.2166; found: 531.2164

10d : ^{1}H-NMR ($CDCl_3$) δ: 1.15(t, 3H, CH_3), 2.61(q, 2H, CH_2), 3.61(m, 4H, CH_2), 3.80(m, 1H, CH), 4.50(s, 4H, $PhCH_2$), 4.67(s, 2H, $PyCH_2$), 5.35(s, 2H, $PhCH_2$), 7.30(m, 15H, Ph), 7.65(s, 1H, PyH); ^{13}C-NMR ($CDCl_3$) δ: 13.9(CH_3), 25.3(CH_2), 65.8($PyCH_2$), 120.4(C-5), 127.7(C-3), 139.3(C-4), 145.2(C-6), 157.8(C-2)

6-Benzyloxy-2-chloro-3-methoxymethyl-5-methylpyridine 9e and its regio isomer 10e.

Chromatography ($CHCl_3$) yielded a mixture of the regio isomers **9e** and **10e**, which were separated further by HPLC to afford compounds **9e** and **10e** as colourless oils. Recrystallization of **9e** (490 mg; 59%) from hexane and of **10e** (219 mg; 27%) from an ethanol/water mixture afforded white crystals.

9e : mp = 26-27°C; IR (film) cm^{-1}: 2930, 1610, 1575; ^{1}H-NMR ($CDCl_3$) δ: 2.21(s, 3H, CH_3), 3.43(s, 3H, OCH_3), 4.46(s, 2H, $PhCH_2$), 5.39(s, 2H, $PyCH_2$), 7.38(m, 5H, Ph), 7.50(s, 1H, PyH); ^{13}C-NMR ($CDCl_3$) δ: 15.2(CH_3), 58.5(OCH_3), 68.2($PyCH_2$), 70.6($PhCH_2$), 119.7(C-5), 124.1(C-3), 127.8, 127.9, 128.4(o-,m-,p-Ph), 137.2(i-Ph), 140.7(C-4), 143.4(C-2), 160.4(C-6); MS m/z : 277(4, M^+), 245(20), 186(28), 91(100); exact mass calcd for $C_{15}H_{16}ClNO_2$: 277.0870; found: 277.0863

10e : mp = 45-46°C; ^{1}H-NMR ($CDCl_3$) δ: 2.30(s, 3H, CH_3), 3.43(s, 3H, OCH_3), 4.44(s, 2H, $PhCH_2$), 5.39(s, 2H, $PyCH_2$), 7.38(m, 5H, Ph), 7.53(s, 1H, PyH); ^{13}C-NMR ($CDCl_3$) δ: 18.4(CH_3), 58.8 (OCH_3), 68.1 ($PyCH_2$ and $PhCH_2$), 119.8(C-5), 127.8, 127.9, 128.4(o-,m-,p-Ph), 137.1(i-Ph), 140.3(C-4), 145.9(C-6), 158.1 (C-2)

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