Lipase-Catalyzed Acylation and Deacylation Reactions of Pyridoxine, a Member of Vitamin-B_6 Group

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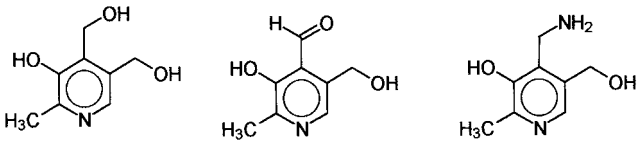
A series of acyloxy derivatives of pyridoxine (**1**) have been prepared by transesterification reactions of **1** and ethyl carboxylates, catalyzed by several lipases. Moreover, acetylated derivatives of **1** were selectively deacetylated by enzymatic catalysis in organic media.

Introduction. – Regioselective transformation of polyfunctional compounds is a challenging problem in organic synthesis, especially in case of a structure sensitive to acid, base, oxidation, or reduction, which limits the choice of reagents needed to accomplish a particular transformation. In recent years, lipases have become attractive as biocatalysts for regioselective reactions under mild conditions [1]. They can be used in a wide variety of organic solvents and do not require a coenzyme for activity. Although lipases are well-known as catalysts useful for transformations of natural products, such as carbohydrates [2], steroids [3], and terpenes [4], studies regarding their application on vitamin-B_6 compounds have not been reported. The vitamin-B_6 group consists of three phosphorylated and unphosphorylated vitamers: 5-hydroxy-6-methylpyridine-3,4-dimethanol named usually pyridoxine (**1**), 3-hydroxy-5-(hydroxymethyl)-2-methylpyridine-4-carbaldehyde, named pyridoxal (**2**), and 4-(aminomethyl)-5-hydroxy-6-methylpyridine-3-methanol, named pyridoxamine (**3**). They can be interconverted within the organism and show identical biological activity.



1 **2** **3**

The compounds **1**–**3** are essential cofactors to a large number of enzymes involved in the metabolism of amino acids [5]. Pyridoxine (**1**) is the main dietary and therapeutic form of the vitamin-B_6 group [6]. It can be used as antioxidant in cosmetic formulations [7] and food additives [8]. Less polar derivatives of the compounds **1**–**3**, such as esters, having better affinity for membrane lipids and increased skin penetration could be useful for the above mentioned purposes. These ester groups can be easily hydrolyzed *in vivo* providing the active molecule. Moreover, regioselective acylation products could be useful intermediates in synthetic pathway of vitamin-B_6 derivatives [9].

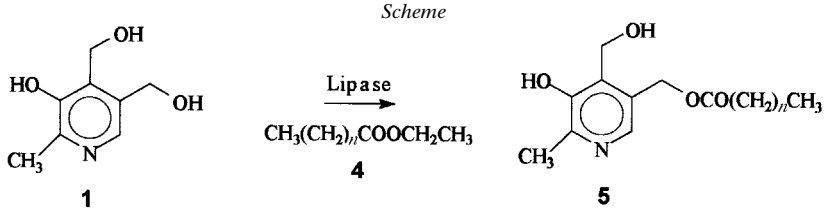
Selective esterification in a specific position of the pyridoxine (**1**) molecule is difficult because of three OH groups present. Attempts to acylate **1** under controlled conditions to furnish monoacylated compounds always resulted in a mixture of esters in which the desired compound could be isolated only after careful separation. Esterification in a specific position has been reported by chemical methods through several protection and deprotection steps [10], sometimes involving cyclic six- or seven-membered ketals as intermediates [11][12].

On the other hand, the application of the enzymatic approach to solve selectivity problems in acylation reactions by means of activated esters under the catalysis of enzymes in anhydrous organic solvents is well-known. Thus, in previous papers we have described this methodology for regio- and chemoselective acylation [13–18] and deacylation [19–21] of polyfunctional compounds using simple ethyl carboxylates, which are readily available and less expensive than the activated ones. In continuation of our work on application of lipases, we report in the present paper the results obtained in lipase-catalyzed acylation of pyridoxine (**1**) and alcoholysis of its acyl derivatives.

Results and Discussion. – We have prepared, under mild reaction conditions, mono- and diacylated derivatives of pyridoxine (**1**) in a regiospecific manner and in moderate-to-high yields. Different compounds have been obtained by acylation of the substrate or by alcoholysis of derivatives using lipases from several sources as catalysts: porcine pancreas lipase (PPL), lipozyme (LIP), *Candida rugosa* lipase (CRL), and *Candida antarctica* lipase (CAL).

1. *Enzymatic Acylation*. The enzyme-catalyzed acylation led, in a regiospecific way, to monoacylated derivatives with the acyl group exclusively suited in the 5-position of pyridine ring (see *Scheme 1* and *Table 1*).

Scheme



a $n=0$; **b** $n=4$; **c** $n=8$; **d** $n=12$

As in our previous work on enzymatic acylation [13–19], we carried out acylations using ethyl carboxylates as acylating agents. To improve yields, we tested activated esters such as vinyl or isopropenyl carboxylates; however, with unsuccessful results. In case of **5a**, AcOEt acted both as solvent and acylating agent. Although all four enzymes led to regiospecific results, CAL gave better yield in lower reaction time than the other three (*Table 1*). To optimize the reaction conditions, we performed several experiments, varying reaction parameters such as temperature, enzyme/substrate relation (E/S), and acylating agent/substrate ratio (A/S). Under standard conditions, reactions were conducted at 30° with an E/S ratio of 2.5 and with an A/S ratio of 3.0 with acyl derivatives other than acetate. The efficiency of the tested enzymes in acylation

Table 1. *Lipase-Catalyzed Acylation of Pyridoxine* (**1**)[a])

Enzyme	Acylating agent	Solvent	Time [h]	Product	Yield [%]
PPL	**4a**	AcOEt	144	**5a**	54
LIP	**4a**	AcOEt	96	**5a**	48
CRL	**4a**	AcOEt	96	**5a**	30
CAL	**4a**	AcOEt	3	**5a**	74
CAL	**4b**	MeCN	24	**5b**	55
CAL	**4b**	acetone	24	**5b**	69
CAL	**4c**	MeCN	24	**5c**	53
CAL	**4c**	acetone	48	**5c**	64
CAL	**4d**	acetone	72	**5d**	57

[a]) Reactions were performed under standard conditions.

reactions was variable and decreased with the increasing chain length of the acylating agent. Regioselectivity was retained in every case.

Solvent effects were also investigated. Due to its highly hydroxylated nature, pyridoxine (**1**) is only soluble in polar solvents. Nonpolar solvents such as hexane, toluene, and CH_2Cl_2 were not effective. MeCN and acetone turned out to be the best choice. Without enzymes, pyridoxine (**1**) did not react at all even using AcOEt, which afforded the best yield in the enzymatic reaction.

Monoacetyl derivative **5a** was characterized as 5-(acetoxymethyl)-3-hydroxy-4-(hydroxymethyl)-2-methylpyridine on the basis of its spectroscopic properties. EI-MS Analysis showed a M^+ ion at m/z 211 indicating the presence of one Ac group. The HR-MS result was in agreement with the calculated value. The position of the $AcOCH_2$ group is established by ^{1}H- and ^{13}C-NMR spectra and confirmed by analysis of a COLOC spectrum. Complete ^{13}C-NMR assignments were also performed by 2D-NMR experiments. HETCOR Spectra were used to assign unambiguously ^{13}C signals of $CH_2(8)$, $CH_2(9)$, and C(6)[1]).

^{1}H-NMR Spectra of compounds **5b**, **5c**, and **5d** were recorded in $CDCl_3$ instead of (D_6)DMSO for reasons of solubility. ^{1}H Chemical shifts of CH_2 groups of **5a** in both solvents are given in *Table 2*.

Table 2. *^{1}H-NMR Chemical Shifts of CH_2 Groups of Pyridoxine* (**1**) *and 5-(Acetoxymethyl)-3-hydroxy-4-(hydroxymethyl)-2-methylpyridine* (**5a**)[a])

Proton	**1** ((D_6)DMSO)	**5a** ($CDCl_3$)	**5a** ((D_6)DMSO)
$CH_2(8)$	4.76	4.99	4.70
$CH_2(9)$	4.49	5.01	5.11

[a]) Chemical shifts (δ) in ppm. Solvents are indicated in parentheses.

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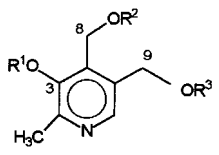
[1]) Arbitrary numbering used for NMR assignments:



5a $R^1 = R^2 = H$, $R^3 = Ac$
6 $R^1 = R^2 = R^3 = Ac$
7 $R^1 = R^2 = Ac$, $R^3 = H$
8 $R^1 = H$, $R^2 = R^3 = Ac$
9 $R^1 = H$, $R^2 = Ac$, $R^3 = H$

Table 3. *Lipase-Catalyzed Alcoholysis of the Acetyl Derivatives of Pyridoxine* (**1**)[a])

Substrate	Nucleophile	Solvent	Product	Yield [%]
5a	EtOH	EtOH	**1**	99
6	EtOH	EtOH	**7**	80
6	EtOH	MeCN	**7**	78
6	BuOH	MeCN	**7**	79
6	Octan-1-ol	MeCN	**7**	80
8	EtOH	EtOH	**9**	69
8	BuOH	MeCN	**9**	68

[a]) Reactions were carried out at 30°, 24 h, and with CAL as biocatalyst.

For **5a**, $\Delta\delta$ between both signals is 0.02 ppm in $CDCl_3$ and 0.41 in (D_6)DMSO. As this effect was retained in longer-chain monoacyl derivatives **5b**–**d**, it was possible to establish substitution position, which was additionally confirmed by COLOC spectrum.

2. *Enzymatic Alcoholysis.* The results of the alcoholysis of acetyl derivatives of pyridoxine (**1**) are presented in *Table 3*.

Lipase-catalyzed alcoholysis of triacetylated pyridoxine **6** gave, after 24 h, the 3,8-diacetylated derivative **7**. After longer reaction periods, a mixture of 8-monoacetylated compound **9** and pyridoxine (**1**) was obtained. Melting point of **7** is in agreement with that reported in [22], and spectroscopic data confirmed the identity.

Compound **9** was also obtained by enzymatic treatment of 8,9-diacetylated pyridoxine **8**. Data reported in [23] for **9** differ from that found in the present work. We determined a melting point of 104–105° for the 4-(acetoxymethyl) derivative of pyridoxine while *Korytnyk* and *Paul* reported 155–157°, a value similar to the melting point of our 5-(acetoxymethyl) derivative **5a**. There are also differences in the assignments of ^{1}H-NMR signals corresponding to $CH_2(8)$ and $CH_2(9)$. *Table 4* shows chemical-shift values for these protons of compounds **1**, **5a**, **8**, and **9**, and those reported by *Korytnyk* and *Paul* for *their* compound **9**.

Table 4. *^{1}H-NMR Chemical Shifts of CH_2 Groups of Compounds* **1**, **5a**, **8**, *and* **9**[a])

Compound	$CH_2(8)$	$CH_2(8)$[b])	$CH_2(9)$	$CH_2(9)$[b])
1	4.76	–	4.49	–
5a	4.70	–	5.11	–
9	5.15	5.15	4.51	4.78
8	5.13	–	5.10	–

[a]) Chemical shifts δ in ppm, solvent: (D_6)DMSO. [b]) Data reported in [23].

According to our data, $CH_2(8)$ and $CH_2(9)$ protons of pyridoxine (**1**) resonate at 4.76 and 4.49 ppm, respectively. The diacetyl derivative **8** showed in its ^{1}H-NMR spectrum corresponding signals at 5.13 and 5.10 ppm, respectively, while corresponding signals in the ^{1}H-NMR spectrum of **5a** were at 4.70 and 5.11 ppm, respectively, *Korytnyk* and *Paul* reported absorptions at 5.15 and 4.78 ppm, respectively, for the mentioned protons, indicating that, in their product, the AcO group should by located at C(9) instead of C(8). We concluded, therefore, that the described 4-(acetoxymeth-

yl)-3-hydroxy-5-(hydroxymethyl)-2-methylpyridine of *Korytnyk* and *Paul* is indeed 5-(acetoxymethyl)-3-hydroxy-4-(hydroxymethyl)-2-methylpyridine (**5a**).

Alcoholysis reaction was conducted with several alcohols are nucleophiles, leading to similar results with all of them. Remarkable is the good performance exhibited by CAL in EtOH, a reagent which is not considered an appropriate solvent for enzymatic reactions carried out in organic medium.

Conclusion. – This work describes application of enzymes for the preparation of specifically acylated derivatives of pyridoxine. Lipases from different sources exhibited good performance as catalysts both in alcoholysis and acylation reactions. *Candida antarctica* lipase gave the best results in both reactions. By enzymatic acylation at C(5) of the pyridine ring, various monoacylated derivatives **5a**–**d** of pyridoxine (**1**) have been regiospecifically obtained; these products have not been previously reported early in literature.

All enzymatic reactions were performed under mild conditions, and ethyl carboxylates, which are considered inert as acylating agents in traditional chemical methodology, were used as acylating agents. Regiospecifity cannot be attained by conventional acylating agents, and polyacylated compounds are usually obtained.

Alcoholysis reactions yielded good results even with the short-chain alcohols such as EtOH. Based on current results and the general behavior displayed by CAL, it can be assumed that the active site of the enzyme acts only at C(5) of the pyridine ring of pyridoxine both in acylation and alcoholysis reaction.

Experimental Part

General. Pyridoxine, lipase from *Candida cylindracea* (905 units/mg solid), and lipase (type II crude) from porcine pancreas (190 units/mg protein) were purchased from *Sigma Chemical Co*. Lipozyme (lipase *IM-60* from *Mucor miehei* in the immobilized form on a microporous anion exchange resin) and *Candida antarctica* lipase (Novozym 435 (7400 PLU/g) acrylic-resin-supported lipase produced by a host organism *Aspergillus oryzae*, after transfer of the genetic coding for lipase B from *Candida antarctica*) were generous gifts of *Novo Nordisk Bioindustrial Group*. All enzymes were used 'straight from the bottle'. M.p.: *Fisher-Johns* apparatus, uncorrected. TLC: *Merck* silica gel *60F-254* aluminum sheets (0.2 mm thickness). Column chromatography (CC): *Merck* silica gel *60* (0.040–0.063 mm). IR Spectra: *Nicolet-Magna-550-FT/IR* spectrophotometer; in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: at 200 and 50 MHz, respectively, using a *Bruker AC-200* spectrometer; chemical shifts (δ) relative to Me_4Si; (D_6)DMSO, $CDCl_3$, and CD_3OD as solvents, assignments[1]) based on COLOC and HETCOR spectra. EI-MS: at 70 eV using a *TRIO-2 VG Masslab* and *Shimadzu QP-5000* spectrometers, in *m/z* (%). HR-MS: *VG-ZAB BEQ* instrument.

[5-Hydroxy-4-(hydroxymethyl)-6-methylpyridin-3-yl]methyl Acetate (**5a**). To a soln. of **1** (200 mg, 1.2 mmol) in AcOEt (10 ml), 500 mg of CAL were added. The suspension was shaken (200 rpm) at 30°, and the progress of the reaction was monitored by TLC (AcOEt). After 3 h, the enzyme was filtered off, the solvent evaporated, and the crude residue purified by CC (AcOEt): 184 mg (74%) of **5a**. White solid. M.p. 152–153°. IR (KBr): 3437, 2924, 2360, 1740, 1384, 1248, 1035. ^1H-NMR ((D_6)DMSO[1]): 7.91 (*s*, H–C(6)); 5.11 (*s*, CH_2(9)); 4.70 (*s*, CH_2(8)); 2.36 (*s*, Me(7)); 2.03 (*s*, MeCO). ^{13}C-NMR ((D_6)DMSO[1]): 170.3 (C(14)); 149.7 (C(3)); 147.5 (C(2)); 140.4 (C(6)); 132.4 (C(4)); 128.0 (C(5)); 61.5 (C(9)); 56.3 (C(8)); 20.8 (C(15)); 19.6 (C(7)). EI-MS: 211 (15, M^+), 193 (22, $[M-18]^+$), 151(89), 123(49), 106(57), 94(36), 43(100). HR-MS: 211.0843 ($C_{10}H_{13}NO_3^+$; calc. 211.0845).

[5-Hydroxy-4-(hydroxymethyl)-6-methylpyridin-3-yl]methyl Hexanoate (**5b**). To a soln. of **1** (200 mg, 1.2 mmol) in acetone (10 ml) containing ethyl hexanoate (0.5 ml, 3 mol-equiv.), 500 mg of CAL were added. The suspension was stirred (200 rpm) for 24 h at 30°, and the progress of reaction was monitored by TLC (AcOEt). The enzyme was filtered off, the mixture was concentrated *in vacuo* and purified by chromatography (silica gel; AcOEt: hexane 1:3): 217 mg (69%) of **5b**. M.p. 78–79°. IR (KBr): 3450, 3197, 2952, 2874, 2646, 1747,

1391, 1255, 1163, 1042. ^{1}H-NMR ($CDCl_3$)[1]): 7.88 (*s*, H–C(6)); 5.03 (*s*, CH_2(9)); 4.99 (*s*,CH_2(8)); 2.44 (*s*, Me(7)); 2.28 (*t*, *J* = 7.8, CH_2(15)); 1.27 (*m*, CH_2(16), CH_2(17), CH_2(18)); 0.87 (*t*, *J* = 6.9, Me(19)). ^{13}C-NMR ($CDCl_3$/CD_3OD)[1]): 173.6 (C(14)); 151.6 (C(3)); 148.0 (C(2)); 139.2 (C(6)); 130.8 (C(4)); 126.2 (C(5)); 61.2 (C(9)); 59.6 (C(8)); 40.0 (C(15)); 31.0 (C(16)); 24.4 (C(17)); 22.0 (C(18)); 18.0 (C(7)); 13.6 (C(19)). EI-MS: 267 (3, M^+), 151(60), 123(28), 106(37), 94(22), 71(41), 60(27), 43(100). HR-MS: 267.1476 ($C_{14}H_{21}NO_4^+$; calc. 267.1471).

[5-Hydroxy-4-(hydroxymethyl)-6-methylpyridin-3-yl]methyl Decanoate (**5c**). As described for **5b**, but using ethyl decanoate (0.7 ml, 3 mol-equiv.) as acylating agent and stirring the suspension for 48 h: 272 mg (64%) of **5c**. M.p. 79–80°. IR (KBr): 3430, 3166, 2924, 2852, 2717, 1733, 1384, 1255, 1163, 1048. ^{1}H-NMR ($CDCl_3$)[1]): 7.88 (*s*, H–C(6)); 5.03 (*s*, CH_2(9)); 4.99 (*s*, CH_2(8)); 2.44 (*s*, Me(7)); 2.28 (*t*, *J* = 7.8, CH_2(15)); 1.25 (*m*, CH_2(16)–CH_2(22)); 0.87 (*t*, *J* = 6.9, Me(23)). ^{13}C-NMR ($CDCl_3$:CD_3OD)[1]): 173.4 (C(14)); 151.5 (C(3)); 147.6 (C(2)); 138.7 (C(6)); 131.2 (C(4)); 126.4 (C(5)); 61.0 (C(9)); 59.0 (C(8)); 33.7 (C(15)); 31.4 (C(16)); 28.9 (C(17)); 28.8 (C(18)); 28.6 (C(19)); 24.5 (C(20)); 24.4 (C(21)); 22.2 (C(22)); 17.5 (C(7)); 13.4 (C(23)). EI-MS: 323 (1, M^+), 151(77), 123(50), 106(43), 94(21), 71(30), 55(43), 43(100). HR-MS: 323.2097 ($C_{18}H_{29}NO_4^+$; calc. 323.2097).

[5-Hydroxy-4-(hydroxymethyl)-6-methylpyridin-3-yl]methyl Tetradecanoate (**5d**). As described for **5b**, but using ethyl tetradecanoate (0.9 ml, 3 mol-equiv.) as acylating agent and stirring the suspension for 72 h: 283 mg (57%) of **5d**. M.p. 93–94°. IR (KBr): 3435, 3183, 2924, 2859, 2695, 1747, 1427, 1241, 1170, 1042. ^{1}H-NMR ($CDCl_3$)[1]): 7.88 (*s*, H–C(6)); 5.03 (*s*, CH_2(9)); 4.99 (*s*, CH_2(8)); 2.44 (*s*, Me(7)); 2.28 (*t*, *J* = 7.8, CH_2(15)); 1.25 (*m*, CH_2(16)–CH_2(26)); 0.87 (*t*, *J* = 6.9, Me(27)). ^{13}C-NMR ($CDCl_3$:CD_3OD)[1]): 173.6 (C(14)); 151.6 (C(3)); 148.0 (C(2)); 139.2 (C(6)); 130.9 (C(4)); 126.3 (C(5)); 61.2 (C(9)); 59.6 (C(8)); 33.9 (C(15)); 31.7 (C(16)); 29.4, 29.2, 29.1, 29.0, 28.9 (C(17) to C(24)); 24.7 (C(22)); 22.5 (C(23)); 17.9 (C(7)); 13.8 (C(27)). EI-MS: 379 (1, M^+), 151(100), 123(55), 106(29), 94(13), 71(15), 57(41), 43(92). HR-MS: 379.2725 ($C_{22}H_{37}NO_4^+$; calc. 379.2723).

4,5-Bis(acetoxymethyl)-2-methylpyridin-3-yl Acetate (**6**). A mixture of pyridoxine hydrochloride (450 mg, 2.2 mol-equiv.) and excess Ac_2O in 1.5 ml of dry pyridine was kept overnight at r.t. The mixture was poured into ice-water to remove the excess reagents. The oily phase was separated and AcOEt (30 ml) was added. The resulting soln. was washed with aq. 1N NaOH soln. (5 × 20 ml) and H_2O (2 × 20 ml), dried (Na_2SO_4), and evaporated *in vacuo*: **6** (370 mg, 57%). Viscous oil [24]. IR (film): 2970, 2942, 1763, 1602, 1370, 1225, 1041. ^{1}H-NMR ($CDCl_3$)[1]): 8.37 (*s*, H–C(6)); 5.19 (*s*, CH_2(8)); 5.07 (*s*, CH_2(9)); 2.34 (*s*, Me(7)); 2.31 (*s*, Me(11)); 2.01 (*s*, Me(15)); 1.96 (*s*, Me(13)). ^{13}C-NMR ($CDCl_3$)[1]): 170.1 (C(12)); 170.0 (C(14)); 168.3 (C(10)); 153.0 (C(3)); 147.7 (C(6)); 144.5 (C(2)); 135.4 (C(4)); 129.3 (C(5)); 61.0 (C(9)); 56.7 (C(8)); 20.6 (C(13)); 20.3 (C(15), C(11)); 19.4 (C(7)). EI-MS: 295 (2, M^+), 253(35), 235(26), 193(66), 151(100), 123(62), 106(51), 94(19), 43(79).

4-(Acetoxymethyl)-5-(hydroxymethyl)-2-methylpyridin-3-yl Acetate (**7**). To a soln. of **6** (200 mg, 0.68 mmol) in abs. EtOH (10 ml), 800 mg of CAL were added. The suspension was shaken (200 rpm) at 30° and the progress of reaction monitored by TLC (AcOEt). After 24 h, the enzyme was filtered off, the solvent evaporated, and the crude residue purified by chromatography (silica gel; AcOEt): 136 mg (80%) of **7**. M.p. 88–89° ([22]: 90–92°). IR (KBr): 3450, 3197, 2919, 1773, 1736, 1240, 1205, 1035. ^{1}H-NMR ((D_6)DMSO)[1]): 8.37 (*s*, H–C(6)); 5.08 (*s*, CH_2(8)); 4.62 (*s*, CH_2(9)); 2.35 (*s*, Me(7)); 2.29 (*s*, Me(11)); 1.97 (*s*, Me(13)). ^{13}C-NMR ((D_6)DMSO)[1]): 170.0 (C(12)); 168.8 (C(10)); 150.8 (C(3)); 146.0 (C(6)); 144.3 (C(2)); 135.3 (C(4)); 134.6 (C(5)); 58.5 (C(9)); 56.8 (C(8)); 20.4 (C(13)); 19.2 (C(11)); 17.4 (C(7)). EI-MS: 253 (2, M^+), 211(4), 193(30), 151(54), 123(15), 94(46), 43(100).

3-Hydroxy-6-methylpyridine-3,4-dimethyl Diacetate (**8**). This compound was prepared according to [25] to give 4,5-bis(acetoxymethyl)-3-hydroxy-2-methylpyridine hydrochloride (1.69 g). The hydrochloride was dissolved in H_2O, and aq. NH_3 was added until precipitation of a white solid (pH 6.05). The white solid was filtered off and washed with H_2O to provide **8** (1.3 g, 70%). M.p. 97–98° ([26]: 99–100°). IR (KBr): 3458, 2945, 2375, 1755, 1740, 1384, 1234, 1042, 1027. ^{1}H-NMR ((D_6)DMSO)[1]): 7.99 (*s*, H–C(6)); 5.13 (*s*, CH_2(8)); 5.10 (*s*, CH_2(9)); 2.40 (*s*, Me(7)); 2.01 (*s*, Me(13), Me(15)). ^{13}C-NMR ((D_6)DMSO)[1]): 170.4 (C(12)); 170.2 (C(14)); 150.0 (C(3)); 148.3 (C(2)); 141.0 (C(6)); 129.3 (C(4)); 128.8 (C(5)); 61.5 (C(9)); 57.1 (C(8)); 20.7 (C(15), C(13)); 20.0 (C(7)). EI-MS: 253 (18, M^+), 193 (44, [M – AcOH]$^+$), 151(76), 123(61), 106(62), 94(32), 43(100).

[3-Hydroxy-5-(hydroxymethyl)-2-methylpyridin-4-yl]methyl Acetate (**9**). This compound was prepared as described for **7**, but using 200 mg (0.79 mmol) of **8** as substrate: 119 mg (69%) of **9**. M.p. 104–105° ([23]: 155–157°). IR (KBr): 3309, 2930, 2517, 2097, 1749, 1526, 1377, 1241, 1035. ^{1}H-NMR ((D_6)DMSO)[1]): 7.97 (*s*, H–C(6));

5.15 (*s*, CH_2(8)); 4.51 (*s*, CH_2(9)); 2.38 (*s*, Me(7)); 2.00 (*s*, Me(13)). ^{13}C-NMR ((D_6)DMSO)[1]): 170.6 (C(12)); 149.8 (C(3)); 146.7 (C(2)); 139.6 (C(6)); 134.9 (C(4)); 127.9 (C(5)); 58.9 (C(9)); 57.1 (C(8)); 20.8 (C(13)); 19.9 (C(7)). EI-MS: 211 (12, M^+), 193 (13, $[M - H_2O]^+$), 151 (89), 123 (30), 106 (49), 94 (48), 43 (100).

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