Synthesis of a Potential Bifunctional Mimic of Transaminases

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As a potential bifunctional mimic of transaminases 3,7-dimethyl-10-[3-(4-aminomethyl-5-hydroxy-6-methyl-3-pyridyl)propyl]-3,7,10-triazatricyclo[3.3.3.$0^{1,5}$]undecane (**I**) has been synthesized by attaching 3,7-dimethyl-3,7,10-triazatricyclo[3.3.3.$0^{1,5}$]undecane (**II**) to a pyridoxamine nucleus via an all-carbon chain. The chain length between the pyridine ring and **II** is restricted to three atom units so that the possibility for **II** to act bifunctionally during the transamination is maximized. In its protonated form, the nitrogen closest to the pyridine ring cannot deliver the proton intramolecularly to the α-carbon of the developing amino acid. To make the synthetic route generally applicable, introduction of the side-arm base is arranged at a later stage of the synthesis so that different di- or poly-amines can easily be used in place of **II** to prepare other target molecules that might possess bifunctional catalytic activity. This arrangement also greatly reduces the polarity and water-solubility of the intermediates and the purification of these compounds thus becomes much easier. The method of introducing the amino functionality at the C-4 methylene group described herein provides an alternative to that currently in use (reduction of oximes).

Pyridoxamine is one of the B6 group of vitamins that plays an essential role in growth and maintenance of many life processes. As a model for the transaminase systems, pyridoxamine has been the subject of intensive studies[1] of various kinds since the 1950s. Recent efforts in this field have been directed towards making model compounds which have the potential to reproduce certain features of natural transaminases. For instance, to accelerate the reaction several monoamines have been attached to the pyridoxamine nucleus via side-chains of different length.[2] A still better mimic[3] contains both a catalytic group (ethylenediamine) and a binding group (β-cyclodextrin).

The key step (the rate-limiting step under most circumstances) in the transamination is a 1,3-proton transfer process, with deprotonation taking place at one end of the aza-allyl system while reprotonation occurs at the other end (Fig. 1). If a polyamine of appropriate three-dimensional structure is present in the intermediate ketimine it might catalyze the 1,3-proton transfer process in a bifunctional way; while one nitrogen in the polyamine abstracts the proton from the C-4 methylene group (pyridoxamine numbering), the other nitrogen (in protonated form) delivers another proton to the α-carbon of the developing amino acid (Fig. 2).

Bifunctional catalysis in other 1,3-proton transfer reactions has been a research topic in our group for several years.[4] According to a computer-assisted molecular-modeling study,[5] mono-and di-protonated **1** possess great potential to catalyze 1,3-proton transfer in allyl systems in a bifunctional way (Fig. 3). To explore bifunctional catalysis

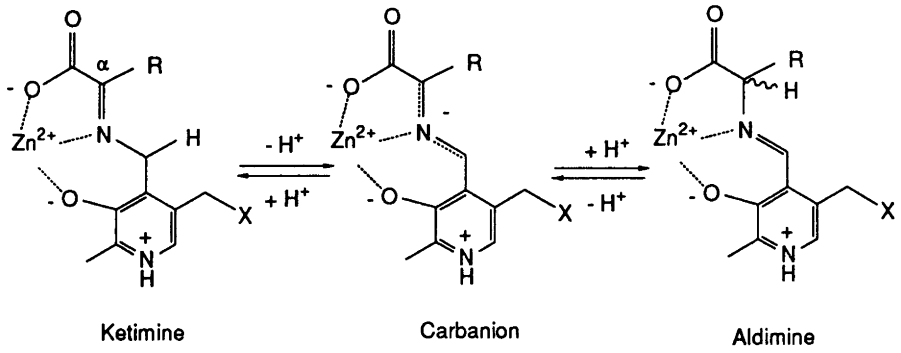

Fig. 1. The ketimine–aldimine tautomerization in the presence of Zn^{2+}. X represents the remainder of the model compound.

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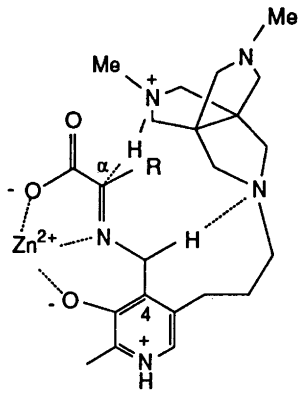


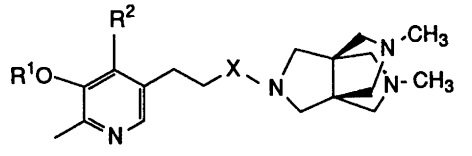
Fig. 2. A polyamine of appropriate three-dimensional structure in the ketimine-Zn^{2+} complex might catalyze the 1,3-proton transfer in a bifunctional way; while one N abstracts a proton from C-4 methylene group, the other protonated N delivers a proton to the α-carbon of the developing amino acid.

in the new context of imitating enzymes, we hoped that attachment of such a polyamine to the pyridoxamine nucleus would produce a new and efficient mimic of transaminases featuring bifunctional catalysis. In order to maximize the possibility for the base to act bifunctionally, the length of the chain between the pyridoxamine nucleus and **2** is restricted to three carbon units, so that the nitrogen atom abstracting the proton from the methylene group at C-4 cannot reach the α-carbon of the developing amino acid.

Results and discussion

Because of the concatenation of the two moieties, pyridoxamine and **2**, the target molecule **3** is expected to be a very polar, water-soluble, and air-sensitive substance. The choice of the precursor leading directly to the target molecule **3** is therefore of critical importance. An ideal precursor should be reasonably stable in air, have relatively low polarity and low solubility in water, while its conversion into **3** should not lead to extensive formation of side-products. Fig. 4 shows some of the compounds which are likely to meet these requirements. They all contain fewer basic nitrogen atoms than **3**. The acidic phenolic hydroxy group is also masked.

The first precursor chosen in this work was compound **4**. The corresponding synthetic route is shown in Scheme 1. Incorporation of the amine **2** is arranged at the final stage of the synthesis so that the polarity of all intermediates can



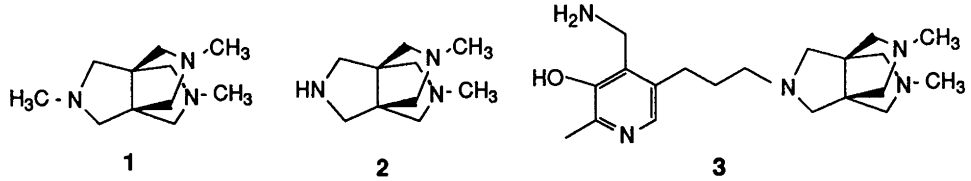
Compound	R^1	R^2	X
4	Ac	CN	C=O
5	Bn	CN	C=O
6	Bn	CN	CH_2
7	Bn	$AcNHCH_2$	CH_2

Fig. 4. Some of the compounds which are likely to meet the requirements for the precursor leading directly to **3**.

be kept within the limits convenient for chromatography on silica gel. An additional advantage gained in doing this is that the same sequence may easily be adapted for the preparation of other target molecules by using other polyamines in place of the amine **2**. The terminal vinyl group in the side arm serves as a protective group which is stable enough to withstand all the reaction conditions in the early stages of the sequence.

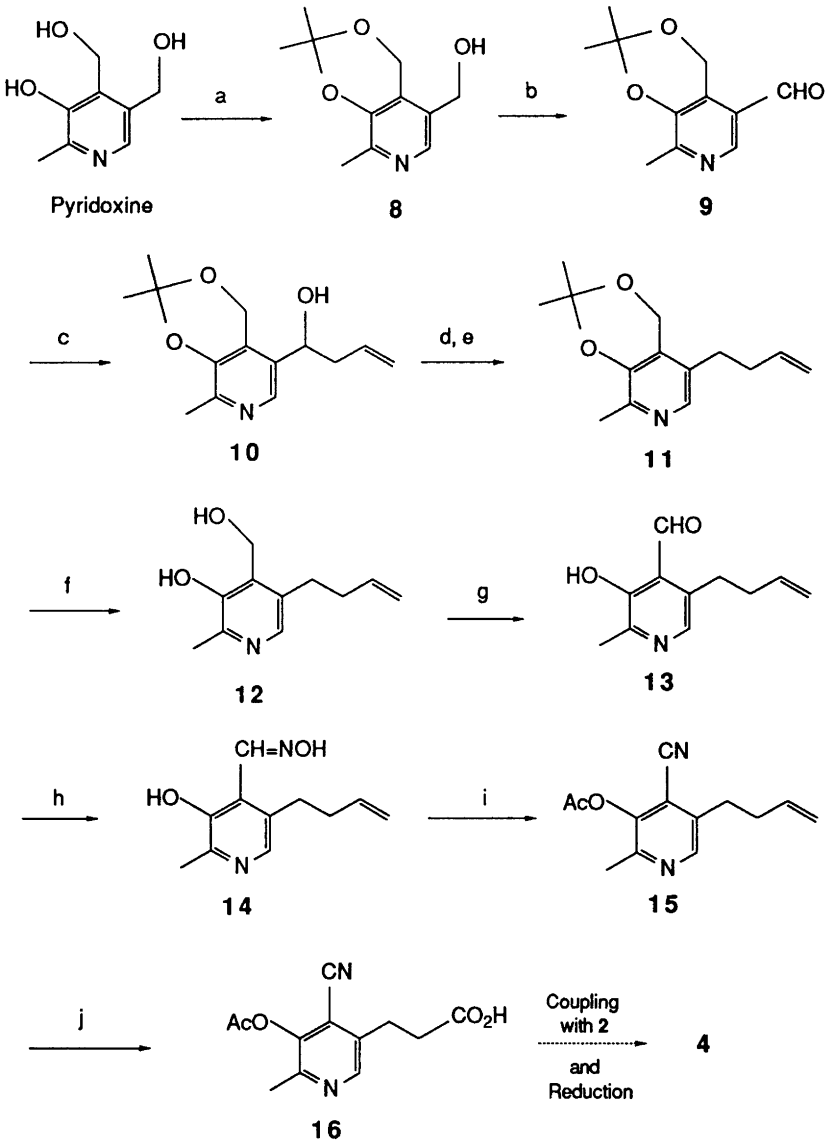
Protection of pyridoxine as acetonide (**8**) was performed as described previously.[6] Subsequent oxidation with activated MnO_2 led to the aldehyde **9**.[7] Treatment of the aldehyde **9** with a slight excess of allyl Grignard reagent at −70 °C gave the alcohol **10** in 86 % yield after chromatography, together with a small amount of the starting aldehyde. Deoxidation of the mesylate made *in situ* from **10** with lithium triethylborohydride provided **11** as a thick oil or a wax in ca. 90 % yield.

Cleavage of the ketal **11** in aqueous MeOH yielded a highly water-soluble diol (**12**). Owing to the presence of the basic nitrogen atom in the pyridine ring, more than 1 equivalent of acid was necessary to ensure a practical reaction rate. Sulfuric acid was used here because it could easily be removed by reaction with an excess of calcium carbonate followed by filtration (the high solubility of **12** in water made it impossible to remove acid by washing the organic solution with an aqueous basic solution). After removal of water by repeated co-evaporation with ethanol, **12** was



1 **2** **3**

Fig. 3. A modeling study indicates that mono- and di-protonated **1** have great potential to catalyze 1,3-proton transfer processes bifunctionally. Its nor-methyl analogue (**2**) was therefore chosen as the catalytic part of the target molecule (**3**) of this work.



Scheme 1. a, $Me_2C(OMe)_2/H_2SO_4/CH_2Cl_2$; b, MnO_2/CH_2Cl_2; c, allyl Grignard reagent/THF; d, MeLi/THF/−70 °C/MsCl; e, $LiBEt_3H$/−40 °C; f, 0.5 M H_2SO_4/50–100 °C; g, MnO_2/CH_2Cl_2; h, $NH_2OH \cdot HCl/NaOAc/H_2O$; i, Ac_2O/reflux; j, $KMnO_4$/Adogen 464/H_2O/CH_2Cl_2/HOAc/H_2SO_4.

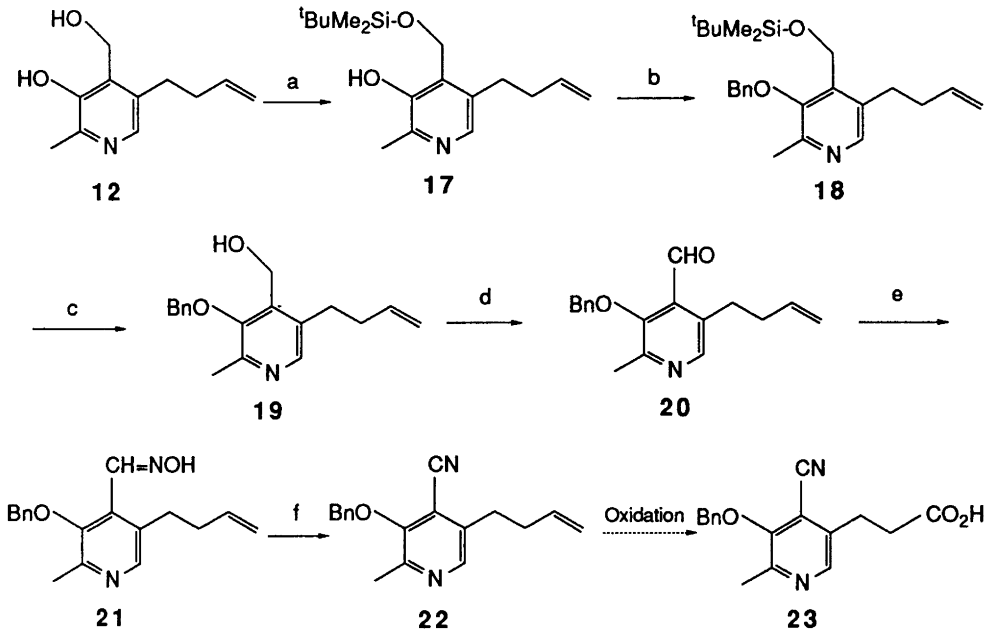
obtained as a yellowish solid which could be used directly in the following step.

Oxidation of the diol **12** with activated MnO_2 followed by condensation with hydroxylamine gave the oxime **14**. Treatment of the crude oxime in refluxing acetic anhydride afforded the nitrile **15**. Oxidative cleavage of the carbon–carbon double bond with $KMnO_4$ proceeded smoothly under the phase-transfer conditions described by Lee *et al.*[8] to afford the acid **16** in ca. 75 % yield. The subsequent coupling with **2**,[9] however, failed to give any satisfactory results; the acetyl group was far too reactive under the reaction conditions.

A straightforward solution to the problem was to use a more stable protective group. A benzyl group was thus chosen as the substitute. This alternative corresponded to adopting the precursor **5** instead of **4**. An additional modification made in this partially renewed route (Scheme 2) was that the benzyl group was introduced at an earlier stage instead of continuing from the acetate **15**, as this would lead to more stable intermediates and thus facilitate the purification.

The silylation catalyzed by 4-dimethylaminopyridine (DMAP) gave exclusively the mono silyl ether **17**. As the effort to purify this compound only led to unnecessary loss of the material, the crude product was directly used in the subsequent step. Benzylation of **17** in DMSO at room temperature gave compound **18** (in 48 % overall yield from **11**). Removal of the silyl protective group in **18** with tetrabutylammonium fluoride ($Bu_4N^+F^-$) proceeded rapidly at room temperature, to give the alcohol **19** as a white, crystalline substance in 95 % yield after chromatography.

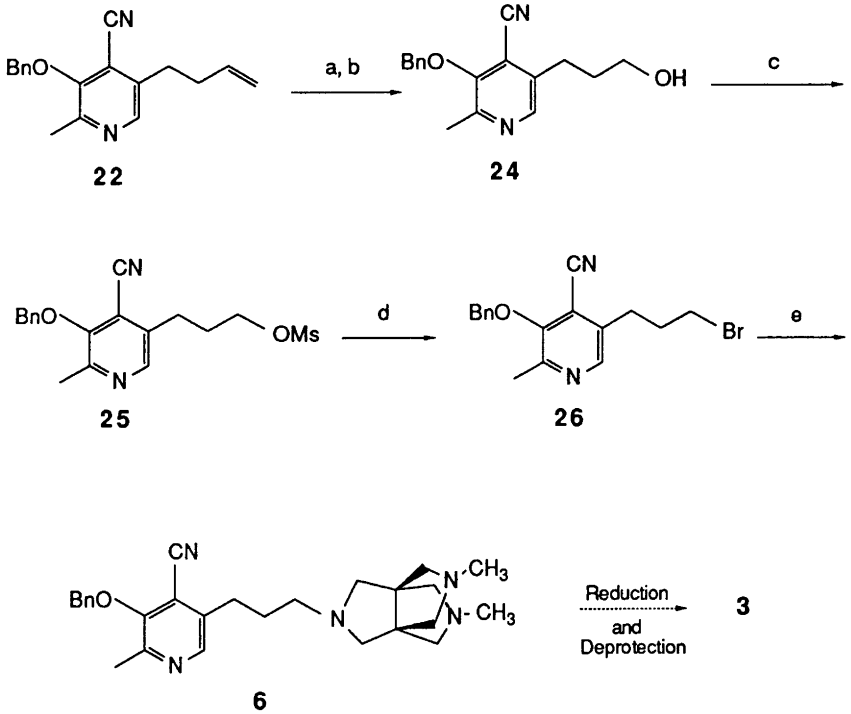
Modification of the C-4 methylene group was effected by



Scheme 2. a, TBDMS-Cl/DMAP/NEt_3/CH_2Cl_2; b, BnCl/NaH/DMSO; c, Bu_4NF/THF; d, PCC/NaOAc/CH_2Cl_2; e, $NH_2OH \cdot HCl$/NaOAc/H_2O/MeOH; f, Ac_2O/reflux.

a sequence similar to that used in the first route. Oxidation of the alcohol **19** with pyridium chlorochromate (PCC) yielded the aldehyde **20** in 91 % yield. Treatment of **19** with activated MnO_2 in refluxing CH_2Cl_2 also gave **20**. Condensation of the aldehyde **20** with hydroxylamine in the presence of sodium acetate provided the aldoxime **21** which in turn was converted into the corresponding nitrile by being refluxed in acetic anhydride. In preparative runs, the crude aldehyde (**20**, obtained from PCC oxidation) and the crude oxime were directly used in the subsequent reaction without any purification. the overall yield from **19** to **22** was 83 %.

In sharp contrast with the smooth reaction of **15** to **16**, oxidative cleavage of the carbon–carbon double bond in **22** under the same conditions led to extensive formation of side-products. The original route was therefore modified



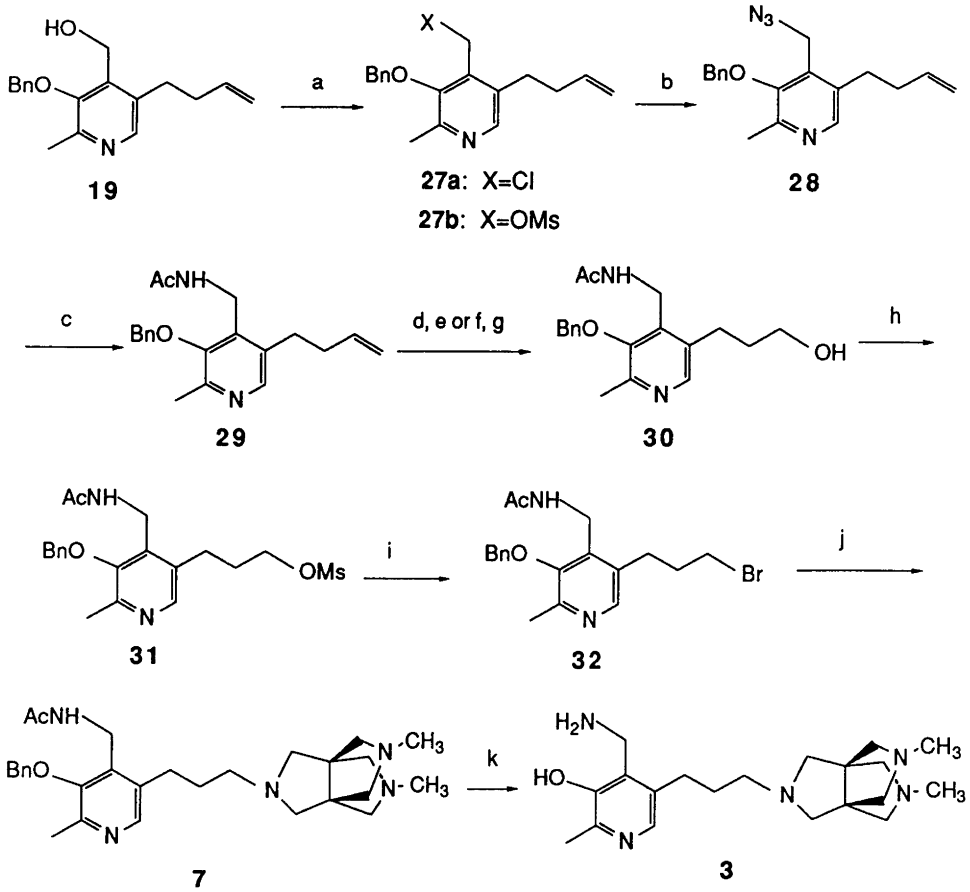
Scheme 3. a, OsO_4/$NaIO_4$/THF/H_2O; b, $NaBH_4$/MeOH; c, MsCl/NEt_3/DMAP/CH_2Cl_2; d, LiBr/acetone; e, $NaHCO_3$/**2**/MeCN.

once more (Scheme 3). A Lemieux–Johnson oxidation[10] ($OsO_4/NaIO_4$) was performed to remove one carbon from **22** thus yielding the corresponding aldehyde, which was immediately reduced with $NaBH_4$ without any purification. By this procedure the dark osmates from the Lemieux–Johnson oxidation could easily be removed with no significant loss of material. Crude **24**, after simple work-up, was practically pure as seen in the ^1H and ^{13}C NMR spectra and could be used directly in the subsequent step.

Conversion of **24** into the corresponding mesylate **25** with MsCl proceeded smoothly at room temperature. The mesylate was in turn transformed into the bromide **26** by being refluxed with LiBr in dry acetone. Coupling of the bromide **26** with the amine **2** in refluxing acetonitrile produced the expected compound **6** as an oil in 70 % yield after chromatography, with higher than 99.5 % purity as determined by HPLC. Direct coupling of **25** with the amine **2** also afforded **6**, but the reaction was much slower.

Reduction of **6** with $LiAlH_4$ was much more complex than we had expected. All the products were highly polar compounds that could not satisfactorily be isolated and purified by column chromatography. To investigate the problem we used **22**, a less polar and much more easily accessible compound, as a model compound to examine the reduction. It was then found that substantial amounts of side-products formed well before the starting nitrile was fully consumed, whereas prolonged reaction led to over-reduced products without the pyridine chromophore. We also tried several other reducing agents (e.g., BH_3,[11] $NaBH_4/CoCl_2$[12]) but none of them gave satisfactory results. Although we did manage to obtain compound **29** by quenching the reduction at an early stage followed by acetylation with acetic anhydride, the low yield would make it extremely difficult to continue further if we applied the same procedure to the conversion of **6** into **3**.

Rosen *et al.*[13] recently reported a procedure which converted azides into acetamides under very mild conditions. Application of this method in the present case would result in an acetamido group at the C-4 methylene group. The reduction problem mentioned above could thus be avoided altogether (Scheme 4). The azide (**28**) was first prepared by treating **19** with methanesulfonyl chloride at room temperature followed by NaN_3. Without using an excess of MsCl the first step (the reaction of **19** with MsCl) was rather



Scheme 4. a, $MsCl/NEt_3/DMAP/CH_2Cl_2$/r.t. or MeLi/MsCl/THF/−70 °C; b, NaN_3/DMF; c, MeCOSH; d, O_3/MeOH/r.t.; e, $NaBH_4$/MeOH; f, $OsO_4/NaIO_4$/THF/H_2O; g, $NaBH_4$/MeOH/0 °C; h, $MsCl/NEt_3/DMAP/CH_2Cl_2$; i, LiBr/acetone/reflux; j, $NaHCO_3$/**2**/MeCN; k, 48 % HBr/reflux.

sluggish. The yield (crude mass of the intermediate) could vary considerably from run to run simply because of some minor difference in e.g., work-up, and was often much lower than the theoretical yeild. Larger amounts of MsCl did not significantly improve the yield (in such cases, the intermediate isolated was identified as the chloride **27a**). By using a smaller amount of MsCl and quenching the reaction at an early stage followed by flash column chromatography on silica gel, it was possible to obtain **27b** as an unstable oil. This oil rapidly yielded a pink substance of very high polarity as shown by TLC. When allowed to stand at room temperature, it became a solid insoluble in common organic solvents.

The instability of the mesylate **27b** convinced us of that the yield of **28** could be improved if the mesylate **27b** was generated at a much lower temperature and treated directly with NaN_3 without a preceding work-up. Indeed, treatment of **19** in THF with 1 equiv. of MeLi followed by 1 equiv. of MsCl at −70 °C resulted in a yellowish clear solution, in contrast with the dark-red mixture obtained in previous runs. Addition of NaN_3 and DMF (to increase the solubility of NaN_3) to the reaction system led to a yellowish suspension after a few minutes of stirring at room temperature and complete conversion into **28** was realized within two hours in 77 % overall yield (from **19**).

Subsequent transformation of the azide **28** into the acetamide **29** by thioacetic acid proceeded very smoothly at room temperature. The reaction solution solidified near the end of the reaction. After removal of the excess of thioacetic acid, the crude product was chromatographed on silica gel to afford the pure acetamide **29** in 77 % yield.

It is noteworthy that in the ^1H NMR spectrum of **29** (as well as all the other intermediates with the same C-4 CH_2 acetamido partial structure) the C-4 CH_2 appeared as a sharp two-line signal which could easily be mistaken as the two inner lines of an AB system with two outer lines buried in the noise. The other possibility that the line splitting was caused by coupling with the amide NH did not seem to be likely since the amide NH signal was very broad, with no recognizable splitting. When this broad NH peak was irradiated, however, the CH_2 doublet collapsed into a sharp singlet. Irradiation at the doublet, moreover, led to recognizable sharpening of the NH signal. Such a coupling relation was also unequivocally confirmed by a very strong cross peak in the COSY spectrum (2D NMR).

Up to this point the modification of the C-4 CH_2 position was complete. A free amino group could be easily generated without involvement of a redox reaction. Before connecting the pyridoxamine moiety with the amine **2**, the only remaining task was to activate the side chain by converting the terminal vinyl group into a bromide. Unexpectedly, the previous easy and clean conversion (OsO_4/$NaIO_4$ oxidative cleavage followed by $NaBH_4$ reduction) turned out to be troublesome in this case; the intermediate aldehyde was highly polar and water-soluble. Neither aqueous work-up nor column chromatography could separate the intermediate aldehyde from the inorganic salts and osmates in acceptable yields. In the presence of these iodine-containing inorganic salts and osmates, reduction of the aldehyde with $NaBH_4$ led to complex products.

In the hope of finding a better method of preparing **30** we also attempted to modify the side chain before conversion of the azido group into the acetamido group. With an azido instead of an acetamido group at the C-4 CH_2 position, the aldehyde produced by OsO_4/$NaIO_4$ was indeed less water-soluble. Subsequent reduction with $NaBH_4$ followed by conversion of the azido group into an acetamido group with thioacetic acid gave **30** in improved yields. An even better yield was later obtained by ozonolysis of **29** followed by reductive work-up. Thus, treatment of a methanolic solution of **29** with ozone at room temperature (at low temperature **29** simply precipitated and no reaction with ozone took place) followed by reduction with $NaBH_4$ gave **30** as the only product.

Further transformation of **30** into the bromide **32** was accomplished in the same way, as for **24**, except that aqueous work-up was avoided. Coupling of **32** with the amine **2** under the same conditions used for the preparation of **6** furnished the expected precursor **7** in 78 % yield after column chromatography. Finally, the acetyl and the benzyl protective groups were removed by heating in 48 % HBr to afford the final product **3** as a white, air-sensitive powder.

The ^1H NMR spectrum of **3** was strongly pH-dependent. At near neutral pH the spectrum was rather complicated, indicating that **3** existed in several forms (with different numbers of deuterons attached at the nitrogens). Simplification of the spectrum was achieved at either strongly basic or strongly acidic pH.

The transamination activity of **3** was examined under the conditions described by Martell *et al.*[14] and Breslow *et al.*[2] Surprisingly, at pH 4 the reaction was so slow that even after 24 h very little of the aldimine was produced in this reaction system. At higher pH (near pH 7), however, the transamination could be followed by UV-VIS spectrophotometry. The spectra were similar to those of the compounds with only one amine group in the side arm, except that the maximum absorption for the aldimine–Zn^{2+} appeared at 395 nm instead of 385 nm. The rate was still lower than that with pyridoxamine. The reasons for this behavior are under investigation.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Varian XL-400 NMR spectrometer (operating at 400 MHz for ^1H) with Me_4Si as an internal standard and $CDCl_3$ as the solvent unless otherwise specified. The figures in the parentheses following carbon chemical shifts are chemical shifts of the protons to which the carbons are directly bonded as seen in HETCOR spectra (2D-NMR). IR spectra were collected on a Perkin-Elmer 1600 FT infrared spectrometer. The letters in parentheses after wavenumber values refer to the relative intensity (s = strong, m = medium and w = weak).

Mass spectra (GC/MS) were obtained on a modified Finnigan Mat 1020B instrument (electron impact mode, 70 eV). The relative intensity of the peaks is given in parentheses after the corresponding *m/z* value. High resolution mass spectra (HRMS) were recorded at room temperature on a ZAB-HF machine operating in FAB mode (fast atom bombardment) with 3-nitrobenzyl alcohol as the solvent, Xe as the fast atom and polyethylene glycol as the reference for exact mass measurement. Melting points were determined on a Reichert KIFA micromelting point apparatus and are uncorrected. Elemental analyses were performed by Mikro Kemi AB, Uppsala, Sweden. Pyridoxine hydrochloride (98 %), *tert*-butyldimethylsilyl chloride (TBDMS-Cl, 97 %), $LiBEe_3H$ (Superhydride, 1.0 M in THF), allylmagnesium chloride (2.0 M in THF), $Bu_4N^+F^-$ (1.0 M in THF), and Adogen 464 were purchased from Aldrich. Pyridium chlorochromate (98 %), MeLi (1.6 M in ether), activated MnO_2 (95 %), and NaH (55–60 % suspension in mineral oil) were purchased from Fluka AG. Silica gel for column chromatography (Kieselgel S, 230–400 mesh) was purchased from Riedel-de Haën AG. Dry solvents and reagents were obtained in the following manner. THF was refluxed over Na/benzophenone and distilled under a nitrogen atmosphere prior to use. CH_2Cl_2 and NEt_3 were refluxed over CaH_2 and distilled under nitrogen prior to use. Dimethyl sulfoxide (DMSO) was refluxed over Na and distilled under a nitrogen atmosphere and stored over 4 Å molecular sieves. *N,N*-Dimethylformamide (DMF) was dried over 4 Å molecular sieves. Diethyl ether was dired over Na wire and the supernatant was used directly in the work-up of **20**. Acetone was kept over anhydrous K_2CO_3. LiBr was dired at 120 °C/0.5 mmHg for 72 h. Aqueous NH_3 refers to 25 % ammonia solution in water. Aqueous NH_3-saturated diethyl ether for column chromatography was prepared by shaking 25 % aqueous NH_3 with diethyl ether and separating the ethereal phase.

2,2,8-Trimethyl-5-(1-hydroxy-3-butenyl)-4H-1,3-dioxino-[4,5-c]pyridine (**10**). Allylmagnesium chloride (about 2.3 M, 8.5 ml) was added dropwise via a syringe to a stirred solution of the aldehyde **9**[7] (4.00 g, 19.3 mmol) in dry THF (40 ml) at −70 °C (bath temperature) under N_2. After a further 20 min of stirring, the bath temperature was allowed to rise to room temperature and the reaction was quenched with aq. NH_4Cl. The reaction mixture was diluted with ether, washed once with brine and dried over $MgSO_4$. Filtration and evaporation left a white solid (4.69 g), which was chromatographed on silica gel (aq. NH_3-saturated diethyl ether) to afford 4.16 g (86 %) of pure **10**; m.p. 80–81 °C. ^1H NMR: δ 7.98 (1 H, s), 5.80 (1 H, m), 5.20–5.15 (2 H, m), 4.93 (2 H, s), 4.66 (1 H, m), 2.69 (1 H, br s, OH), 2.52 (2 H, m), 2.38 (3 H, s), 1.55 (3 H, s), 1.53 (3 H, s). ^{13}C NMR: δ 147.36, 145.80, 137.68 (7.98), 133.78 (5.80), 131.90, 124.43, 119.16 (5.20–5.15), 99.42, 69.26 (4.66), 58.72 (4.93), 42.13 (2.52), 24.95 (1.55), 24.55 (1.53), 18.50 (2.34). IR(KBr): 3166 (s), 1643 (w), 1602 (w), 1567 (w), 1402 (s), 1137 (s), 1055 (s), 850 (m) cm^{-1}. MS *m/z*: 249 (M^+, 28), 208 (32), 191 (17), 173 (36), 162 (71), 150 (83), 122 (100). Anal. $C_{14}H_{19}NO_3$: C, H, N.

2,2,8-Trimethyl-5-(3-butenyl)-4H-1,3-dioxino[4,5-c]pyridine (**11**). To a stirred solution of the alcohol **10** (2.52 g, 10.1 mmol) in dry THF (30 ml) at −75 °C under N_2, was added (via a syringe) MeLi (6.6 ml, over about 10 min) followed by MsCl (0.90 ml). Stirring was continued for another 30 min at −75 °C before the reaction mixture was allowed to warm gradually to −30 °C. $LiBEt_3H$ (23 ml) was then introduced via a syringe and the mixture was further warmed slowly to −20 °C. When TLC showed the demesylation to be complete, water was carefully added to destroy the excess hydride. The reaction mixture was partitioned between diethyl ether and water. The ethereal phase was washed with 25 % aqueous ammonia and brine, and dried over Na_2SO_4. After filtration and evaporation the crude residue was chromatographed on silica gel (aq. NH_3-saturated diethyl ether) to afford 2.09 g (88 %) of **11** as a yellowish oil (usually containing a trace amount of water) which became a wax after evacuation with an oil pump for 10 h at 40 °C followed by cooling at −20 °C overnight; ^1H NMR: δ 7.87 (s, 1 H), 5.82 (m, 1 H), 5.06 to 4.98 (2 H, m), 4.79 (2 H, s), 2.51 (2 H, br t, *J* 7.4 Hz), 2.37 (3 H, s), 2.31 (2 H, m), 1.54 (6 H, s). ^{13}C NMR: δ 145.69, 145.52, 140.06 (7.87), 137.07 (5.82), 129.91, 124.78, 115.81 (5.06 to 4.98), 99.39, 58.84 (4.79), 34.02 (2.31), 28.17 (2.51), 24.71 (1.54), 18.35 (2.37). IR (KBr): 2980 (w), 2850 (w), 1638 (w), 1600 (w), 1562 (w), 1404 (s), 1246 (s), 1060 (s), 853 (m) cm^{-1}; MS *m/z*: 233 (M^+, 40), 175 (92), 160 (100), 146 (50), 132 (53), 106 (100), 91 (47). HRMS: Found, 234.148. Calc. for $C_{14}H_{20}NO_2$ (M+1), 234.149.

3-Acetoxy-5-(3-butenyl)-2-methyl-4-pyridinecarbonitrile (**15**). A mixture of **11** (1.36 g, 5.8 mmol) and aqueous H_2SO_4 (1.0 N, 7.0 ml) was heated with stirring at 50 °C for 4 h before being neutralized with an excess of $CaCO_3$ and diluted with MeOH. The mixture was filtered and the filter cake was washed thoroughly with more MeOH. The filtrate and washings were evaporated to minimum volume on a rotary evaporator. The residue was diluted with CH_2Cl_2 and dried over Na_2SO_4. Filtration and evaporation left a yellowish solid (**12**, 1.09 g), which was dissolved in CH_2Cl_2 (35 ml) and refluxed with activated MnO_2 (2.05 g, 22.4 mmol) for 18 h. Filtration and evaporation afforded a brown oil (crude **13**, 922 mg, 85 %. Chromatography of this crude aldehyde led to a complex mixture) which solidified on prolonged standing at 0 °C; m.p. 49–51 °C. ^1H NMR: δ 11.40 (1 H, br s, OH), 10.36 (1 H, s), 7.99 (1 H, s), 5.82 (1 H, m), 5.08–4.99 (2 H, m), 3.01 (2 H, br t, *J* 7.7 Hz), 2.51 (3 H, s), 2.40 (2 H, m). IR (KBr): ca. 3000 (br), 1670 cm^{-1}. MS *m/z*: 191 (M^+, 25), 173 (34), 162 (8), 150 (55), 144 (23), 122 (64), 104 (22), 67 (100). To this crude aldehyde were added MeOH (8 ml), H_2O (15 ml), NaOAc (1.21 g, 14.7 mmol), and $NH_2OH \cdot HCl$ (800 mg, 11.5 mmol). The mixture was stirred for 10 min at room temper-

ature then for 35 min at 50 °C, and finally cooled at 0 °C, to yield a beige powder which was collected by suction filtration, washed with cold water, and dried at 50 °C. The resulting crude **14** (720 mg, 71 %) was then refluxed in acetic anhydride (15 ml) under N_2 for 1.5 h. The excess acetic anhydride was removed *in vacuo* and the residue was chromatographed on silica gel (1.5:1 hexane–ethyl acetate), giving a white solid (**15**, 694 mg, 52 % from **11**); m.p. 58–60 °C. ^{1}H NMR: δ 8.42 (1 H, s), 5.82 (1 H, m), 5.07–5.01 (2 H, m), 2.91 (2 H, t, *J* 7.6 Hz), 2.49–2.41 (8 H, m, including a singlet at 2.45, 2 × CH_3 and 1 × CH_2). ^{13}C NMR: δ 167.71, 150.81, 147.52 (8.42), 145.69, 137.67, 135.82 (5.82), 116.78 (5.07–5.01), 115.56, 112.63, 34.34 (2.49–2.41), 30.91 (2.91), 20.50 (2.49–2.41), 19.21 (2.49–2.41). IR (KBr): 2226 (w), 1766 (s), 1637 (w), 1590 (w), 1379 (m), 1167 (s), 914 (m) cm^{-1}. MS *m/z*: 230 (M^+, 4), 188 (17), 147 (12), 119 (6), 43 (100). Anal. $C_{13}H_{14}N_2O_2$: C, H, N.

An analytical sample of **12** was obtained by column chromatography on silica gel (100:10:1 ethyl acetate–MeOH–aq. NH_3); m.p. 100–100.5 °C. ^{1}H NMR: δ 7.85 (1 H, br s, OH), 7.62 (1 H, s), 5.75 (1 H, m), 5.05 to 4.95 (5 H, m, including 4.97 s and an OH), 2.54 (2 H, br t, *J* 8.0 Hz), 2.38 (3 H, s), 2.18 (2 H, m). ^{13}C NMR: δ 152.42, 144.75, 138.05 (7.62), 136.81 (5.75), 132.12, 130.74, 115.75 (5.05 to 4.95), 60.21 (4.97), 34.51 (2.18), 29.05 (2.54), 17.69 (2.38). IR (KBr): 3061 (s, br), 2602 (s, br), 1637 (w), 1555 (w), 1414 (s), 1285 (s), 909 (s), 750 (m) cm^{-1}. MS *m/z*: 193 (M^+, 91), 175 (36), 160 (66), 152 (47), 106 (100). Anal. $C_{11}H_{15}NO_2$: C, H, N.

Similarly, an analytical sample of **14** was obtained by column chromatography on silica gel (aq. NH_3-saturated diethyl ether); m.p. 183–184 °C. ^{1}H NMR: δ 10.35 (1 H, br s, OH), 9.74 (1 H, br s, OH), 8.51 (1 H, s), 7.89 (1 H, s), 5.84 (1 H, m), 5.10–5.01 (2 H, m), 2.79 (2 H, br t, *J* 7.8 Hz), 2.51 (3 H, s), 2.33 (2 H, m). ^{13}C NMR (CD_3OD): δ 152.21, 148.34 (8.51), 146.67, 140.27 (7.89), 138.08 (5.84), 134.61, 121.77, 116.30 (5.10–5.01), 36.74 (2.33), 29.93 (2.79), 18.22 (2.51). IR (KBr): 3400–2026 (m, br), 1766 (m, br), 1637 (m), 1484 (s), 1396 (s), 1238 (s), 1038 (m), 914 (m), 726 (m) cm^{-1}. MS *m/z*: 206 (M^+, 12), 189 (11), 188 (13), 178 (13), 165 (18), 148 (100), 119 (70), 92 (28). Anal. $C_{11}H_{14}N_2O_2$: C, H, N.

3-(5-Acetoxy-4-cyano-6-methyl-3-pyridyl)propionic acid (**16**). Solid $KMnO_4$ (507 mg, 3.2 mmol) was added (in small portions over 20 min) to a stirred two-phase mixture of Adogen 464 (22 mg), glacial acetic acid (130 µl, 2.3 mmol), **15** (1.13 mmol), aq. H_2SO_4 (0.96 M, 17.1 ml) and CH_2Cl_2 (6.5 ml) at 0 °C. Stirring was then continued at room temperature for a further 100 min before the reaction mixture was suction-filtered. The filter cake was washed with CH_2Cl_2 and H_2O. The brown filtrate and washings were extracted three times with CH_2Cl_2 and all CH_2Cl_2 phases were combined and dried over Na_2SO_4. Filtration and concentration *in vacuo* left ca. 4 ml of residue which crystallized when allowed to stand at room temperature to afford 105 mg of brownish needles. A second crop crystallized from the mother liquor after a further 2 days at room temperature, to afford another 131 mg of brownish needles which raised the total yield to 236 mg; m.p. 142–144 °C. ^{1}H NMR: δ 8.53 (1 H, s), 3.17 (2 H, t, *J* 7.1 Hz), 2.79 (2 H, t, *J* 7.1 Hz), 2.45 (6 H, s). ^{13}C NMR: δ 175.37, 167.63, 151.40, 147.27 (8.53), 145.97, 136.51, 116.02, 112.29, 33.74 (2.79), 26.29 (3.17), 20.48 (2.45), 18.97 (2.45). IR (KBr): 3630–2350 (m, br), 2243 (w), 1770 (s), 1722 (s), 1599 (w), 1410 (w), 1203 (s), 1163 (s) cm^{-1}. MS *m/z*: 248 (M^+, 2.3), 206 (55.6), 160 (100), 147 (33.7). Anal. $C_{12}H_{12}N_2O_4$: C, H, N.

*3-Benzyloxy-5-(3-butenyl)-4-*tert*-butyldimethylsilyloxymethyl-2-methylpyridine* (**18**). A mixture of the ketal **11** (955 mg, 4.09 mmol), MeOH (1.5 ml), and aq. H_2SO_4 (1.0 N, 8 ml) was stirred at 100 °C (hot-plate temperature) under N_2 for 2.5 h. The mixture was then diluted with MeOH and neutralized with an excess of $CaCO_3$. Solids were removed by filtration and the filtrate was evaporated to the minimum volume on a rotary evaporator (55 °C bath). EtOH was added to the residue and the resulting mixture was evaporated again to dryness. The residue was dissolved in CH_2Cl_2 and dried over Na_2SO_4. Filtration and evaporation left **12** as a yellowish solid (754 mg, 3.90 mmol). To this solid were added dry CH_2Cl_2 (15 ml), dry NEt_3 (1.1 ml), 4-dimethylaminopyridine (DMAP, about 20 mg) and finally *tert*-butyldimethylsilyl chloride (TBDMS-Cl, 612 mg, 3.94 mmol, added in portions). Stirring was continued at room temperature for 1.5 h before the reaction mixture was diluted with CH_2Cl_2, washed with water and brine (once each), and dried over $MgSO_4$. Filtration and evaporation afforded **17** as a yellowish solid (1.37 g). This was directly dissolved in dry DMSO (15 ml) treated with NaH (170 mg, 55–60 % suspension in mineral oil) and benzyl chloride (480 µl, 4.15 mmol). After being stirred for 20 h at room temperature under N_2, the brownish reaction mixture was diluted with diethyl ether, washed with water and brine (twice each) and dried over $MgSO_4$. The oily residue (259 mg) after filtration and evaporation was chromatographed on silica gel (1:3 ethyl acetate–hexane) to afford **18** as a yellowish oil (860 mg, 2.16 mmol, 52 % from **11**); ^{1}H NMR: δ 8.16 (1 H, s), 7.47–7.33 (5 H, m), 5.87 (1 H, m), 5.10–4.99 (2 H, m), 4.91 (2 H, s), 4.70 (2 H, s), 2.81 (2 H, br t, *J* 8.0 Hz), 2.50 (3 H, s), 2.39 (2 H, m), 0.88 (9 H, s), 0.08 (6 H, s). ^{13}C NMR: δ 151.34, 150.46, 145.61 (8.16), 139.31, 137.52 (5.87), 136.84, 135.57, 128.46 (7.47–7.33), 128.05 (7.47–7.33), 127.55 (7.47–7.33), 115.15 (5.10–4.99), 76.29 (4.91), 56.07 (4.70), 35.24 (2.39), 28.96 (2.81), 25.83 (0.88), 19.49 (2.50), 18.19, −5.47 (0.08). IR (neat): 2952 (m), 2931 (m), 2858 (m), 1638 (w), 1586 (w), 1465 (m), 1403 (m), 1366 (m), 1251 (m), 1214 (m), 1067 (s), 832 (s) cm^{-1}. MS *m/z*: 341 (*M*−*tert*-butyl, 52), 250 (5), 208 (4), 91 (100). HRMS: Found, 398.247. Calc. for $C_{24}H_{35}NO_2Si$ (*M*+1), 398.252.

From a small sample of purified **17** (silica gel, 100:4:1 ethyl acetate–MeOH–aq. NH_3) were obtained the following data: m.p. 71–71.5 °C. ^{1}H NMR: δ 8.82 (1 H, s, OH), 7.82 (1 H, s), 5.82 (1 H, m), 5.08–4.99 (2 H, m), 4.97 (2 H, s), 2.56 (2 H, br t, *J* 7.8 Hz), 2.44 (3 H, s), 2.25 (2 H, m), 0.96 (9 H, s), 0.19 (6 H, s). ^{13}C NMR: δ 150.88, 145.67, 140.24 (7.82), 136.93 (5.82), 130.70, 127.61, 115.60 (5.08–4.99), 62.12 (4.97), 34.85 (2.25), 29.14 (2.56), 25.66 (0.96), 18.74 (2.44), 18.11, −5.59 (0.19). IR (KBr): 3676–2000 (m, v br), 2552 (m, br), 1642 (w), 1560 (w), 1414 (m), 1223 (s), 1070 (s), 840 (s), 776 (s) cm^{-1}. MS *m/z*: 307 (M^+, 11), 250 (100), 232 (52), 176 (32), 160 (14), 75 (87). Anal. $C_{17}H_{29}NO_2Si$: C, H, N.

3-Benzyloxy-5-(3-butenyl)-2-methyl-4-pyridylmethanol (**19**). A mixture of **18** (149 mg, 0.38 mmol) and $Bu_4N^+F^-$ (1.0 M solution in THF, 1.5 ml) was stirred at room temperature for 30 min before being diluted with diethyl ether, washed twice with water and once with brine, and dried over $MgSO_4$. Filtration and evaporation left a brownish oil, which gave white needles (**19**, 101 mg, 95 %) after chromatography on silica gel (3:1 ethyl acetate–hexane); m.p. 87–88 °C. ^{1}H NMR: δ 8.15 (1 H, s), 7.44–7.37 (5 H, m), 5.82 (1 H, m), 5.06–4.97 (2 H, m), 4.93 (2 H, s), 4.60 (2 H, d, *J* 6.0 Hz), 2.76 (2 H, br t, *J* 7.8 Hz), 2.55 (3 H, s), 2.32 (2 H, m), 2.00 (1 H, br t, *J* 6.0 Hz, OH). ^{13}C NMR: δ 151.77, 150.50, 145.85 (8.15), 139.88, 137.26 (5.82), 136.46, 134.66, 128.75 (7.44–7.37), 128.58 (7.44–7.37), 128.17 (7.44–7.37), 115.64 (5.06–4.97), 76.11 (4.93), 56.50 (4.60), 35.45 (2.32), 29.21 (2.76), 19.48 (2.55). IR (KBr): 3050 (s, br), 1641 (w), 1596 (w), 1448 (m), 1372 (m), 1224 (s), 904 (s), 737 (s) cm^{-1}. MS *m/z*: 283 (M^+, 8), 175 (6), 160 (5), 91 (100). Anal. $C_{18}H_{21}NO_2$: C, H, N.

3-Benzyloxy-5-(3-butenyl)-2-methyl-4-pyridinecarboxaldehyde (**20**). To a stirred mixture of alcohol **19** (501 mg, 1.77 mmol) and anhydrous NaOAc (440 mg) in dry CH_2Cl_2 (13 ml) under nitrogen was added pyridium chlorochromate (776 mg, 3.53 mmol). Stirring was continued at room temperature for 3 h before the reaction mixture was filtered through a short pad of silica gel (eluted with dry ether) to remove the colored chromium species. The filtrate was concentrated to minimum volume and chromatographed on silica gel (3:1 hexane–ethyl acetate) to afford a yellowish oil, which solidified with time (**20**, 457 mg, 92 %; m.p. 31–31.5 °C. ^{1}H NMR: δ 10.39 (1 H, s), 8.26 (1 H, s), 7.43–7.34 (5 H, m), 5.83 (1 H, m), 5.04–4.96 (4 H, m, containing 4.97 s), 2.95 (2 H, t, *J* 7.6 Hz), 2.59 (3 H, s), 2.29 (2 H, m). ^{13}C NMR: δ 192.12 (10.39), 154.57, 152.73, 147.37 (8.26), 137.39 (5.83), 135.31, 134.71, 133.14, 128.97 (7.43–7.34), 128.87 (7.43–7.34), 128.55 (7.43–7.34), 115.61 (5.04–4.96), 77.92 (4.97), 35.24 (2.29), 29.50 (2.95), 19.23 (2.59). IR (KBr): 1692 (s), 1637 (w), 1540 (w), 1447 (m), 1355 (s), 1240 (s), 1186 (s), 908 (s), 690 (s) cm^{-1}. MS *m/z*: 281 (M^+, 5), 263 (2), 189 (2), 162 (3), 91 (100). Anal. $C_{18}H_{19}NO_2$: C, H, N.

3-Benzyloxy-5-(3-butenyl)-2-methyl-4-pyridinecarbonitrile (**22**). A mixture of NaOAc (630 mg), $NH_2OH \cdot HCl$ (317 mg), and the crude aldehyde (**20**, prepared from 612 mg of **19** by PCC oxidation) in aq. MeOH (1 ml of MeOH plus 3 ml of water) was stirred at room temperature for 10 min, at 50 °C for another 10 min, and finally cooled to 0 °C for 10 min. The yellowish solid was collected by suction filtration, washed with cold water, and dried under an IR heating lamp. The off-white powder (crude **21**, 570 mg, 1.92 mmol) was stirred in acetic anhydride (4 ml) and heated under reflux for 1.5 h. The excess acetic anhydride was removed *in vacuo*. MeOH was added to the residue and the resultant solution was evaporated to the minimum volume on a rotary evaporator. Chromatography of the residue on silica gel (3:1 hexane–ethyl acetate) gave a white solid (**22**, 498 mg, 1.79 mmol, 83 % from **19**); m.p. 54.5–55 °C. ^{1}H NMR: δ 8.25 (1 H, s), 7.50–7.37 (5 H, m), 5.83 (1 H, m), 5.17 (2 H, s), 5.06–5.00 (2 H, m), 2.90 (2 H, t, *J* 7.5 Hz), 2.48 (3 H, s), 2.44 (2 H, m). ^{13}C NMR: δ 153.64, 151.98, 144.82 (8.25), 137.69, 136.16 (5.83), 135.40, 128.91 (7.50–7.37), 128.75 (7.50–7.37), 128.73 (7.50–7.37), 116.61 (5.06–5.00), 114.19, 114.05, 76.59 (5.17), 34.49 (2.44), 30.93 (2.90), 19.45 (2.48). IR (KBr): 2231 (w), 1644 (w), 1583 (w), 1545 (w), 1473 (m), 1410 (m), 1364 (s), 1194 (s), 914 (m), 746 (s) cm^{-1}. MS *m/z*: 278 (M^+, 7), 91 (100). Anal. $C_{18}H_{18}N_2O$: C, H, N.

An analytical sample of **21** was obtained by recrystallization from methanol; m.p. 171–172 °C. ^{1}H NMR: δ 8.39 (1 H, s), 8.23 (1 H, br s, OH), 8.17 (1 H, s), 7.43–7.33 (5 H, m), 5.81 (1 H, m), 5.03–4.94 (2 H, m), 4.83 (2 H, s), 2.89 (2 H, t, *J* 7.7 Hz), 2.50 (3 H, s), 2.30 (2 H, m). ^{13}C NMR: (5:2 of CD_3OD–DMSO-d_6) δ 152.42, 151.51, 146.34 (8.17), 144.82 (8.39), 138.59 (5.81), 137.47, 135.40, 133.78, 129.31 (7.43–7.33), 129.25 (7.43–7.33), 129.17 (7.43–7.33), 115.56 (5.03–4.94), 76.88 (4.83), 35.44 (2.30), 31.08 (2.89), 18.99 (2.50). IR (KBr): 2721 (m, v br), 1638 (w), 1586 (m), 1492 (m), 1361 (s), 994 (s), 900 (s), 743 (s) cm^{-1}; MS *m/z*: 296 (M^+, 34), 278 (5), 205 (8), 191 (8), 147 (9), 91 (100). Anal. $C_{18}H_{20}N_2O_2$: C, H, N.

3-(5-Benzyloxy-4-cyano-6-methyl-3-pyridyl)propanol (**24**). To a stirred mixture of **22** (263 mg, 0.94 mmol), OsO_4 (6.4 mg), THF (15 ml), and water (5 ml) was added solid $NaIO_4$ (1.4 g, 6.5 mmol, in portions over 80 min). Stirring was continued for another 2 h before the reaction mixture was suction-filtered. The filtrate was diluted with diethyl ether, washed once with water, twice with aq. $NaHSO_3$, and once with brine. The combined aqueous phases were back-extracted once more with diethyl ether and washed as before. The ethereal phases were combined and dried over Na_2SO_4. After removal of solvent, the residue [the intermediate aldehyde; ^{1}H NMR: δ 9.82 (1 H, s), 8.30 (1 H, s), 7.48–7.37 (5 H, m), 5.16 (2 H, s), 3.10 (2 H, t, *J* 7.4 Hz), 2.89 (2 H, t, *J* 7.4 Hz), 2.48 (3 H, s)] was dissolved in MeOH (10 ml) and treated with an excess of $NaBH_4$ at 0 °C. The reaction was quenched with water and the product was taken up into diethyl ether. The ethereal phase

was washed twice with water and dried over $MgSO_4$. The reddish residue obtained after removal of solvent was redissolved in diethyl ether and another portion of $MgSO_4$ was added to remove the colored species. Filtration and evaporation left a yellowish oil, which solidified with time (**24**, 217 mg); m.p. 80.5–82 °C. This crude product contained only negligible amounts of impurities (as shown by both ^1H and ^{13}C NMR spectroscopy) and could be used directly for the following step. The overall yield was 82 % (from **22**).

Chromatography on silica gel (100:20:1 ethyl acetate–MeOH–aq. NH_3) gave an analytical sample; m.p. 81.5–82 °C. ^1H NMR: δ 8.28 (1 H, s), 7.50–7.38 (5 H, m), 5.16 (2 H, s), 3.70 (2 H, t, *J* 5.9 Hz), 2.90 (2 H, t, *J* 7.8 Hz), 2.47 (3 H, s), 1.93 (2 H, m), 1.82 (1 H, br s, OH). ^{13}C NMR: δ 154.31, 152.59, 145.27 (8.28), 138.65, 135.94, 129.49 (7.50–7.38), 129.33 (7.50–7.38), 129.28 (7.50–7.38), 114.64, 77.16 (5.16), 62.04 (3.70), 33.70 (1.93), 28.35 (2.90), 19.96 (2.47). IR (KBr): 3297 (s, br), 2229 (w), 1581 (w), 1542 (w), 1497 (w), 1450 (m), 1408 (s), 1361 (s), 1214 (s), 1057 (s), 936 (m), 889 (m), 743 (s), 690 (s) cm^{-1}. MS *m/z*: 282 (M^+, 7.9), 91 (100). Anal. $C_{17}H_{18}N_2O_2$: C, H, N.

3-(5-Benzyloxy-4-cyano-6-methyl-3-pyridyl)propyl methanesulphonate (**25**). A solution of **24** (217 mg, 0.77 mmol), NEt_3 (0.8 ml), DMAP (8 mg), and MsCl (65 µl) in CH_2Cl_2 (10 ml) was stirred at room temperature for 50 min before a further 15 µl of MsCl was introduced. Stirring was continued for another hour. The mixture was diluted with diethyl ether, washed twice with water and once with brine and dried over $MgSO_4$. Filtration and evaporation left a yellowish oil, which solidified when allowed to stand overnight at room temperature (276 mg, 0.76 mmol, 99 %, m.p. 61–62.5 °C). An analytical sample was obtained by chromatography on silica gel (100:4:1 ethyl acetate–MeOH–aq. NH_3); m.p. 63–64 °C. ^1H NMR: δ 8.29 (1 H, s), 7.50–7.38 (5 H, m), 5.19 (2 H, s), 4.28 (2 H, t, *J* 6.1 Hz), 3.06 (3 H, s), 2.95 (2 H, t, *J* 7.7 Hz), 2.49 (3 H, s), 2.15 (2 H, m). ^{13}C NMR: δ 153.75, 152.64, 144.44 (8.29), 136.27, 135.21, 128.88 (7.50–7.38), 128.70 (7.50–7.38), 128.63 (7.50–7.38), 113.93, 113.85, 76.62 (5.19), 67.92 (4.28), 37.58 (3.06), 29.77 (2.15), 27.49 (2.95), 19.54 (2.49). IR (KBr): 2224 (w), 1464 (w), 1404 (w), 1338 (s), 1164 (s), 979 (s), 815 (m), 701 (m) cm^{-1}. MS *m/z*: 360 (M^+, 1), 149 (2), 91 (100). Anal. $C_{18}H_{20}N_2O_4S$: C, H, N.

3-(5-Benzyloxy-4-cyano-6-methyl-3-pyridyl)propyl bromide (**26**). A mixture of **25** (276 mg, 0.76 mmol) and dry LiBr (410 mg, 4.7 mmol) in dry acetone (10 ml) was refluxed under N_2 with stirring for 5 h before being diluted with diethyl ether, washed once with water and twice with brine, and dried over $MgSO_4$. Filtration and evaporation left a yellow oil, which solidified after two days at 0 °C. Further removal of the volatile impurities from this solid under oil pump vacuum afforded **26** as a white solid (255 mg, 0.74 mmol, 97 %, m.p. 65–67 °C), which could be used directly in the following step. An analytical sample was obtained by chromatography on silica gel (1:1 ethyl acetate–hexane); m.p. 72–72.5 °C. ^1H NMR: δ 8.30 (1 H, s), 7.49–7.38 (5 H, m), 5.18 (2 H, s), 3.42 (2 H, t, *J* 6.5 Hz), 2.97 (2 H, t, *J* 7.6 Hz), 2.50 (3 H, s), 2.24 (2 H, m). ^{13}C NMR: δ 153.80, 152.56, 144.62 (8.30), 136.50, 135.24, 128.93 (7.49–7.38), 128.74 (7.49–7.38), 128.69 (7.49–7.38), 113.97, 113.87, 76.59 (5.18), 32.85 (2.24), 31.92 (3.42), 29.80 (2.97), 19.52 (2.50). IR (KBr): 2230 (w), 1588 (w), 1543 (w), 1497 (w), 1476 (m), 1454 (m), 1412 (s), 1368 (s), 1189 (s), 745 (s), 698 (s) cm^{-1}. MS *m/z*: 346 (M^+, 2), 344 (M^+, 2), 256 (1), 254 (1), 186 (1), 184 (1), 167 (2), 149 (5), 147 (5), 119 (5), 118 (3), 104 (7), 92 (100). Anal. $C_{17}H_{17}BrN_2O$: C, H, N.

3,7-Dimethyl-10-[3-(5-benzyloxy-4-cyano-6-methyl-3-pyridyl)propyl]-3,7,10-triazatricyclo[3.3.3.0^{1,5}]undecane (**6**). A mixture of **26** (155 mg, 0.45 mmol), **2** (81 mg, 0.45 mmol), and $NaHCO_3$ (270 mg, 3.2 mmol) in dry acetonitrile (6.5 ml) was refluxed under N_2 with stirring for 20 h. The mixture was then filtered, concentrated to the minimum volume, and chromatographed on silica gel (100:20:2 of ethyl acetate–MeOH–aq. NH_3) to afford **6** as a brownish oil (139 mg, 70 %) with purity higher than 99.5 % as determined by HPLC; ^1H NMR: δ 8.28 (1 H, s, pyridine H), 7.51–7.37 (5 H, m, Ph H), 5.16 (2 H, s, $PhCH_2$), 2.86 (2 H, t, *J* 7.3 Hz, the CH_2 adjacent to pyridine), 2.57–2.43 (17 H) including: 2.52 [s, chain-$N(CH_2)_2$ in amine **2** moiety], 2.54 and 2.50 AB system (*J* 9.0 Hz, 4 × CH_2 adjacent to NMe), 2.48 (s, pyridine CH_3) and 2.46 (t, *J* 7.1 Hz, the chain CH_2 adjacent to amine **2** moiety), 2.32 (6 H, s, 2×NCH_3), 1.83 (2 H, br quintet, the middle CH_2 in the side chain). ^{13}C NMR: δ 153.63, 151.64, 144.97 (8.28), 138.53, 135.40, 128.82 (7.51–7.37), 128.70 (7.51–7.37), 128.62 (7.51–7.37), 114.05, 114.03, 76.55 (5.16), 66.41 (2.54 and 2.50), 63.79 (2.52), 61.77, 53.08 (2.46), 41.44 (2.32), 29.13 (2.86), 29.09 (1.83), 19.38 (2.48). IR (neat): 2921 (s), 2790 (s), 2224 (w), 1578 (w), 1545 (w), 1496 (w), 1469 (s), 1409 (m), 1365 (m), 1213 (s), 1137 (s), 880 (m), 695 (m) cm^{-1}. HRMS: Found, 446.295. Calc. for $C_{27}H_{36}N_5O$ (M+1), 446.292.

4-Azidomethyl-3-benzyloxy-5-(3-butenyl)-2-methylpyridine (**28**): *two-step procedure.* An excess of MsCl (ca. 5 equivs., at ca. 2 h intervals, monitored by TLC) was added in portions via a syringe to a stirred mixture of **19** (440 mg, 1.55 mmol), DMAP (11 mg, 0.09 mmol), NEt_3 (9.5 ml, 68 mmol) in dry CH_2Cl_2 (40 ml) at room temperature under N_2. When TLC showed a complete conversion, the reaction mixture was diluted with diethyl ether, washed with water and brine, and dried over Na_2SO_4. Filtration and evaporation gave crude **27** as a brown oil. To this oily residual were added NaN_3 (550 mg, 8.5 mmol) and dry DMF (5 ml). After being stirred for 15 min at 70 °C (hot-plate temperature) and 1 h at room temperature, the reaction mixture was diluted with ether, washed with water (3×4 ml) and brine (2×2 ml), and dried over Na_2SO_4. Filtration and evaporatioan left crude **28** as a brown oil, which was chromatographed on silica gel (2.5:1 ethyl acetate–hexane) to furnish pure **28** (320 mg) as a yellowish oil with an overall

(two-step) yield of 67%; ^{1}H NMR: δ 8.19 (1 H, s), 7.45–7.39 (5 H, m), 5.81 (1 H, m), 5.05–4.98 (2 H, m), 4.89 (2 H, s), 4.33 (2 H, s), 2.72 (2 H, t, *J* 7.8 Hz), 2.55 (3 H, s), 2.33 (2 H, m). ^{13}C NMR: δ 151.66, 150.69, 145.72 (8.19), 136.75 (5.81), 136.21, 134.71, 134.69, 128.55 (7.45–7.39), 128.29 (7.45–7.39), 127.72 (7.45–7.39), 115.73 (5.05–4.98), 75.95 (4.89), 44.91 (4.33), 34.99 (2.33), 29.20 (2.72), 19.72 (2.55). IR (neat): 2096 (s), 1640 (w), 1588 (w), 1454 (m), 1407 (s), 1369 (s), 1213 (s), 916 (m), 699 (m) cm^{-1}. MS *m/z*: 308 (M^+, less than 1% but at least more than ten times as intense as the background noise), 280 (2), 239 (7), 189 (7), 175 (6), 174 (6), 162 (5), 161 (5), 160 (15), 148 (8), 147 (9), 146 (8), 132 (11), 120 (6), 119 (7), 118 (6), 117 (5), 106 (60), 93 (100). HRMS: Found, 309.1715. Calc. for $C_{18}H_{21}N_4O$ (M+1): 309.1715.

Chromatography on silica gel (3:1 ethyl acetate–hexane) gave pure **27a** as a yellowish oil, which solidified when allowed to stand at −20°C overnight; m.p. 46–46.5°C. ^{1}H NMR: δ 8.19 (1 H, s), 7.52–7.35 (5 H, m), 5.83 (1 H, m), 5.10–5.00 (2 H, m), 4.98 (2 H, s), 4.62 (2 H, s), 2.81 (2 H, br t, *J* 7.9 Hz), 2.55 (3 H, s), 2.41 (2 H, m). ^{13}C NMR: δ 151.28, 150.93, 145.82 (8.19), 137.19, 137.00 (5.83), 136.49, 134.67, 128.68 (7.52–7.35), 128.45 (7.52–7.35), 128.02 (7.52–7.35), 115.86 (5.10–5.00), 75.83 (4.98), 35.99 (4.62), 34.87 (2.41), 28.79 (2.81), 19.63 (2.55). IR (neat): 1638 (w), 1583 (w), 1556 (w), 1404 (m), 1355 (m), 1256 (m), 1197 (s), 984 (m), 908 (m), 690 (s) cm^{-1}. MS *m/z*: 301 (M^+, 1), 266 (2), 175 (3), 160 (3), 106 (4), 105 (3), 91 (100). The presence of Cl was clearly shown by the characteristic ratio of the isotope peaks. Anal. $C_{18}H_{20}ClNO$: C, H, N.

By using a smaller amount of MsCl and quenching the reaction at an earlier stage followed by column chromatography on silica gel (3:1 ethyl acetate–hexane) the mesylate **27b** was obtained as an unstable oil; ^{1}H NMR: δ 8.23 (1 H, s), 7.47–7.35 (5 H, m), 5.82 (1 H, m), 5.20 (2 H, s), 5.07–4.99 (2 H, m), 4.91 (2 H, s), 2.90 (3 H, s), 2.78 (2 H, t, *J* 7.8 Hz), 2.57 (3 H, s), 2.35 (2 H, m).

4-Azidomethyl-3-benzyloxy-5-(3-butenyl)-2-methylpyridine (**28**): *one-pot procedure.* MeLi (1.6 M, 240 µl, 0.38 mmol) was added dropwise via a syringe to a solution of **19** (100 mg, 0.35 mmol) in dry THF (5 ml) stirred at −70°C under N_2. After 5 min, MsCl (29 µl, 0.37 mmol) introduced via a syringe. Stirring was continued for 30 min during which the bath temperature was allowed to rise to −30°C. To the reaction mixture was then added NaN_3 (222 mg, 3.4 mmol), followed by dry DMF (5 ml). Stirring was continued for another 2 h. The reaction mixture was diluted with diethyl ether, washed with water and brine (twice each) and dried over Na_2SO_4. The crude oil after removal of solvent was chromatographed on silica gel (3:1 ethyl acetate–hexane) to afford pure **28** as an almost colorless oil (82 mg, 77% from **19**).

4-Acetamidomethyl-3-benzyloxy-5-(3-butenyl)-2-methylpyridine (**29**). A mixture of **28** (227 mg, 0.74 mmol) in thioacetic acid (500 µl) was stirred at room temperature under N_2 for 2.5 h. The excess thioacetic acid was removed *in vacuo* with occasional slight heating (50°C hotplate). The residual yellowish solid was then chromatographed twice on silica gel (5:1:5 CH_2Cl_2–MeOH–hexane and 100:4 ethyl acetate–MeOH) to afford 184 mg of **29** (77%) as a white solid; m.p. 127–128°C, ^{1}H NMR: δ 8.14 (1 H, s), 7.43–7.39 (5 H, m), 5.80 (1 H, m), 5.62 (1 H, br s, NH), 5.40–4.96 (2 H, m), 4.89 (1 H, s), 4.35 (2 H, d, *J* 5.7 Hz), 2.76 (2 H, t, *J* 7.7 Hz), 2.57 (3 H, s), 2.28 (2 H, m), 1.84 (3 H, s). ^{13}C NMR: δ 169.45, 152.09, 150.29, 146.05 (8.14), 137.77, 137.07 (5.80), 136.30, 134.79, 128.89 (7.43–7.39), 128.79 (7.43–7.39), 128.39 (7.43–7.39), 115.84 (5.40–4.96), 75.63 (4.89), 35.32 (2.28), 34.87 (4.35), 29.24 (2.76), 23.04 (1.84), 19.66 (2.57). IR (KBr): 3284 (s), 1637 (s), 1537 (s), 1367 (m), 1214 (m), 691 (m) cm^{-1}. MS *m/z*: 324 (M^+, 0.8), 281 (0.7), 251 (0.4), 252 (0.3), 233 (0.6), 174 (0.6), 106 (6.4), 91 (100). Anal. $C_{20}H_{24}N_2O_2$: C, H, N.

3-[4-Acetamidomethyl-5-benzyloxy-6-methyl-3-pyridyl]-propanol (**30**) *from* **29** *by ozonolysis.* Ozone-containing air was bubbled into a methanolic solution of **29** (90 mg, 0.28 mmol, in 2 ml) at room temperature until TLC showed complete consumption of the starting material. After expulsion of the excess ozone in the solution with N_2, $NaBH_4$ (34 mg, 0.9 mmol) was added with cooling (ice–water bath) and stirring to the reaction mixture in small portions over 20 min. Stirring was continued for 30 min at room temperature before solid NH_4Cl (104 mg) was introduced. After the addition, stirring was continued for another hour. The reaction mixture was evaporated to dryness on a rotary evaporator and then further evacuated with an oil pump. The white solid residue was triturated with CH_2Cl_2, filtered, and washed with more CH_2Cl_2. The combined CH_2Cl_2 filtrate and washings were evaporated to dryness to afford 86 mg of crude product. Chromatography on silica gel (10:3:0.5 ethyl acetate–MeOH–aq. NH_3) gave pure **30** as a white solid (62 mg, 68%); m.p. 142–143°C. ^{1}H NMR: δ 8.18 (1 H, s), 7.48–7.40 (5 H, m), 4.92 (2 H, s), 4.41 (2 H, d, *J* 5.9 Hz), 3.67 (2 H, t, *J* 5.8 Hz), 2.80 (2 H, t, *J* 7.9 Hz), 2.59 (3 H, s), 1.87 (3 H, s), 1.79 (2 H, m). ^{13}C NMR: δ 169.73, 152.24, 150.29, 146.15 (8.18), 137.83, 136.32, 135.11, 128.99 (7.48–7.40), 128.91 (7.48–7.40), 128.48 (7.48–7.40), 75.67 (4.92), 61.53 (3.67), 34.78 (4.41), 34.49 (1.79), 25.86 (2.80), 23.23 (1.87), 19.75 (2.59). IR (KBr): 3272 (s), 1643 (s), 1555 (m), 1437 (m), 1361 (m), 1208 (m), 1067 (m), 744 (m) cm^{-1}. MS *m/z*: 328 (M^+, 3), 285 (3), 207 (3), 178 (8), 163 (3), 160 (3), 149 (3), 148 (4), 137 (3), 136 (2), 106 (4), 92 (100). Anal. $C_{19}H_{24}N_2O_3$: C, H, N.

3-[4-Acetamidomethyl-5-benzyloxy-6-methyl-3-pyridyl]-propanol (**30**) *from* **28** *by Lemieux–Johnson oxidation.* Solid $NaIO_4$ (1.2 g, 5.6 mmol) was added over 1.5 h to a stirred mixture of **28** (320 mg, 1.04 mmol), OsO_4 (ca. 10 mg) in THF (9 ml) and water (3 ml). Stirring was continued overnight. The white solids were removed by suction filtration and washed with CH_2Cl_2. The filtrate and washings

were combined, diluted with CH_2Cl_2, washed with brine and aq. $NaHSO_3$ (once each) and dried over Na_2SO_4/$MgSO_4$. The crude oil after removal of solvent was immediately dissolved in MeOH (4 ml) and treated with an excess of $NaBH_4$ (112 mg, added in portions) at 0 °C for 45 min before being diluted with CH_2Cl_2, washed with aqueous NH_4Cl, and dried over Na_2SO_4/$MgSO_4$. Filtration and evaporation left a red-brown oil (327 mg), which was immediately treated with thioacetic acid (2 ml) as described for the preparation of **29**. The excess thioacetic acid was removed *in vacuo* and the dark oily residue was chromatographed on silica gel (4.5:1:4.5, then 10:3:10, CH_2Cl_2–MeOH–hexane) to give 163 mg of **30**.

3-[4-Acetamidomethyl-5-benzyloxy-6-methyl-3-pyridyl]propyl methanesulfonate (**31**). The reaction conditions were the same as for the preparation of **25** from **24**. When TLC showed complete conversion, the reaction mixture was concentrated to ca. half volume on a rotary evaporator and then chromatographed on silica gel (eluting with 5:3:5 CH_2Cl_2–MeOH–hexane) to furnish **31** as a white solid (93 %); m.p. 128–128.5 °C. ^{1}H NMR δ 8.14 (1 H, s), 7.46–7.40 (5 H, m), 5.78 (1 H, br s, NH), 4.91 (2 H, s), 4.36 (2 H, d, *J* 5.8 Hz), 4.25 (2 H, t, *J* 6.2 Hz), 3.05 (3 H, s), 2.80 (2 H, t, *J* 7.7 Hz), 2.57 (3 H, s), 1.99 (2 H, m), 1.83 (3 H, s). ^{13}C NMR: δ 169.59, 152.35, 150.92, 145.83 (8.14), 138.12, 136.27, 133.64, 128.99 (7.46–7.40), 128.93 (7.46–7.40), 128.46 (7.46–7.40), 75.71 (4.91), 68.83 (4.25), 37.45 (3.05), 34.70 (4.36), 30.59 (1.99), 25.77 (2.80), 23.09 (1.83), 19.75 (2.57). IR (KBr): 3292 (m), 1643 (m), 1349 (s), 1175 (m), 984 (m), 842 (m) cm^{-1}. MS *m/z*: (M^+, 0.4), 363 (1), 311 (1), 273 (2), 177 (2), 160 (3), 91 (100). Anal. $C_{20}H_{26}N_2O_5S$: C, H, N.

3-[4-Acetamidomethyl-5-benzyloxy-6-methyl-3-pyridyl]propyl bromide (**32**). A mixture of **31** (111 mg, 0.27 mmol) and dry LiBr (235 mg, 2.7 mmol) in dry acetone (5 ml) under N_2 was heated to reflux with stirring for 25 min. After cooling to room temperature, the solids were removed by filtration. The greenish filtrate was concentrated *in vacuo* and chromatographed on silica gel (5:1 ethyl acetate–MeOH) to afford **32** as a white solid, which gave the following after being washed with hexane (to remove aldol products from acetone) and drying (75 mg, 70 %); m.p. 127–127.5 °C. ^{1}H NMR: δ 8.17 (1 H, s), 7.46–7.38 (5 H, m), 5.66 (1 H, br s, NH), 4.91 (2 H, s), 4.35 (2 H, d, *J* 5.6 Hz), 3.42 (2 H, t, *J* 6.6 Hz), 2.83 (2 H, t, *J* 7.7 Hz), 2.58 (3 H, s), 2.09 (2 H, m), 1.85 (3 H, s). ^{13}C NMR: δ 169.39, 152.20, 150.75, 146.02 (8.17), 137.92, 136.18, 133.62, 128.92 (7.46–7.38), 128.87 (7.46–7.38), 128.41 (7.46–7.38), 75.62 (4.91), 34.80 (4.35), 34.05 (2.09), 32.62 (3.42), 28.25 (2.83), 23.13 (1.85), 19.79 (2.58); IR (KBr) 3292 (s), 1649 (s), 1567 (m), 1371 (m), 1213 (m), 1066 (w), 755 (m), 706 (m) cm^{-1}. MS *m/z*: 392 (M^+, 1), 390 (M^+, 1), 349 (1), 347 (1), 311 (2), 259 (2), 257 (2), 243 (1), 241 (1), 177 (1), 160 (4), 148 (2), 132 (2), 121 (2), 106 (6), 92 (100). Anal. $C_{19}H_{23}BrN_2O_2$: C, H, N.

3,7-Dimethyl-10-[3-(4-acetamidomethyl-5-benzyloxy-6-methyl-3-pyridyl)propyl]-3,7,10-triazatricyclo[3.3.3.0^{1,5}]undecane (**7**). A mixture of **32** (86 mg, 0.22 mmol), **2** (40 mg, 0.22 mmol) and $NaHCO_3$ (220 mg, 22 mmol) in dry acetonitrile (6 ml) under N_2 was heated to reflux with stirring for 14 h. The solids were filtered off and washed with MeOH. The yellowish filtrate and washings (ca. 8 ml) were concentrated on a rotary evaporator and applied to a silica gel column which had already been pre-eluted with MeOH–aq. NH_3 (80:1) until the effluent was clear. Elution with the same solvents (80:1, then 40:1) under slightly positive pressure gave **7** as a clear oil (84 mg, 78 %); ^{1}H NMR: δ 8.12 (1 H, s, pyridine H), 7.42–7.40 (5 H, m, Ph H), 5.93 (1 H, br s, NH), 4.88 (2 H, s, $PhCH_2$), 4.38 (2 H, d, *J* 5.2 Hz, $AcNCH_2$), 2.71 (2 H, t, *J* 7.3 Hz, the CH_2 adjacent to pyridine), 2.54 (3 H, s, pyridine CH_3), 2.53–2.46 (12 H) including 2.50 and 2.48 AB system (*J* 9.0 Hz, 4×CH_2 adjacent to NMe) and 2.48 [s, chain-N(CH_2)$_2$ in amine **2** moiety], 2.40 (t, *J* 7.1 Hz, 2 H, the CH_2 adjacent to amine **2** moiety), 2.31 (6 H, s, 2×NCH_3), 1.85 (3 H, s, CH_3CO), 1.68 (2 H, br quintet, the middle CH_2 in the side chain). ^{13}C NMR δ 169.79, 152.56, 150.52, 146.78 (8.12), 138.16, 136.75, 135.81, 129.32 (7.42–7.40), 129.20 (7.42–7.40), 128.77 (7.42–7.40), 76.07 (4.88), 66.98 (2.50 and 2.48), 64.37 (2.48), 62.24, 53.72 (2.40), 41.97 (2.31), 35.40 (4.38), 30.44 (1.68), 27.74 (2.71), 23.61 (1.85), 20.15 (2.54). IR (neat): 3270 (m), 2932 (s), 2790 (s), 1654 (s), 1540 (s), 1469 (s), 1365 (s), 1267 (s), 1112 (s), 733 (s) cm^{-1}. HRMS: Found, 492.337. Calc. for $C_{29}H_{42}N_5O_2$ (M+1), 492.334.

3,7-Dimethyl-10-[3-(4-aminomethyl-5-hydroxy-6-methyl-3-pyridyl)propyl]-3,7,10-triazatricyclo[3.3.3.0^{1,5}]undecane (**3**). A mixture of **7** (26 mg, 0.053 mmol) in 48 % HBr (0.3 ml) under N_2 was heated at 150 °C (hot-plate temperature) with stirring for 5.5 h. The reddish reaction mixture was made alkaline with NH_4HCO_3 and then chromatographed on Sephadex C-25 ion-exchange resin (eluting with 0.01–0.5 M aqueous NH_4HCO_3) to afford **3** (14.3 mg, 75 %) as an off-white, air-sensitive powder after removal of H_2O and NH_4HCO_3 by lyophilization; ^{1}H NMR (CD_3OD–D_2O–conc. H_2SO_4): δ 8.25 (1 H, s, pyridine H), 4.45 (2 H, s, the C-4 CH_2), 4.23 and 3.25 (12 H, br m, 6×CH_2 in amine **2** moiety), 3.54 (2 H, br t, *J* 8.0 Hz, the chain CH_2 adjacent to amine **2** moiety), 3.15 (6 H, s, 2× NCH_3), 3.02 (2 H, br t, *J* 7.4 Hz, the chain CH_2 adjacent to pyridine), 2.73 (3 H, s, pyridine CH_3), 2.20 (2 H, br m, the CH_2 in the middle of the chain). IR (KBr): 3425 (s), 2932 (w), 2802 (w), 1620 (m), 1449 (m), 1396 (m), 1337 (m), 1132 (w), 703 (w) cm^{-1}.

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