Synthesis of the Unusual Octahydropyrano[2,3-*b*]pyridine Ring System of ′Upenamide

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We describe for the first time the preparation of a model octahydropyrano[2,3-*b*]pyridine **23** bearing substituents at positions 2 and 8, as in the natural alkaloid ′upenamide. The four inseparable diastereoisomers of **23**, present in an 81:3:16:trace ratio, were analyzed by NMR spectroscopy experiments to fully determine their relative configurations and conformations. The major diastereoisomer of this non-macrocyclic analog has the same configuration as in natural ′upenamide.

Introduction

′Upenamide is a macrocyclic alkaloid that was isolated recently from the Indonesian sponge *Echinochalina* sp.[1] Its structure consists of an unusual octahydropyrano[2,3-*b*]pyridine (DE) linked, through a 20-membered macrocycle, to an unprecedented spirooxaquinolizidinone (ABC) ring system (Figure 1). Because of our longstanding interest in the chemistry of sponge alkaloids,[2] we recently started model studies for the synthesis of ′upenamide. In this paper, we present the first results concerning our strategy, depicted in Figure 1, for accessing the DE hemiaminal ring system of ′upenamide. Although a few methods are available to build this octahydropyrano[2,3-*b*]pyridine ring system, the nature and position of the substituents attainable by these methods do not meet our requirements.[3,4]

We assumed that the target bicyclic hemiaminal **1**, which is a model for the DE part of ′upenamide, is in thermodynamic equilibrium via the open iminium ion **2** and the corresponding enamine **3**. As a consequence, we expected to obtain model compounds **1** as an inseparable thermodynamic mixture of four diastereoisomers.[5] The question arose as to whether there would be a single or major isomer that adopts the same configuration as in the natural macrocycle. We thought that the most efficient way to achieve this synthesis was to prepare the iminium ion **2** from the dihydropyridinium salt **4**, which is itself derived from the corresponding pyridine. These kinds of transformations are well documented[6] and have been used successfully in our group.[7–9] In the particular case of **4**, however, care must be taken to protect the hydroxy group to prevent its cyclization onto position 4 of the eniminium moiety, which would probably be the preferred site of attack.[10] By contrast, cyanide ions are known to add selectively to position 2 of

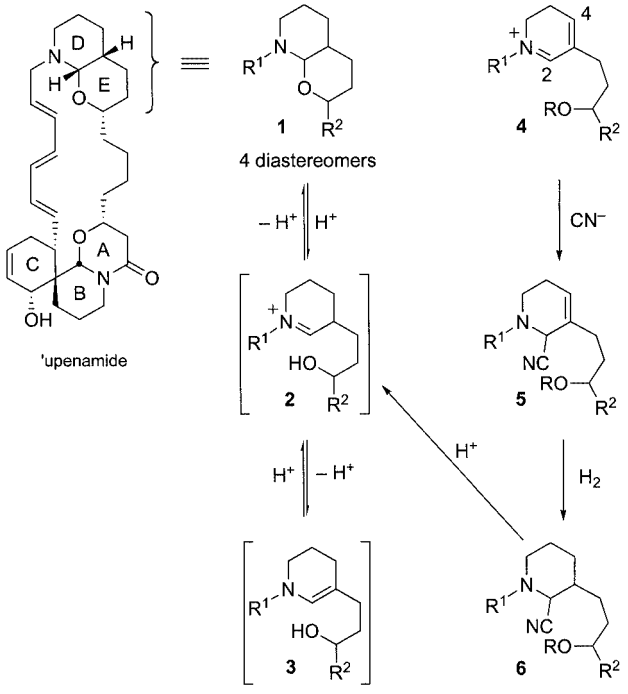

Figure 1. Structure of ′upenamide and a retrosynthetic analysis of its northern part

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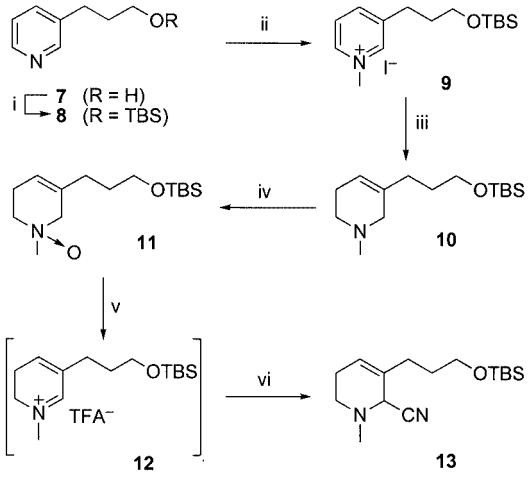
substrates such as **4**,[6] and this preference would allow us to prepare the unsaturated aminonitrile **5** that we could hydrogenate to **6** before regenerating the iminium moiety in **2**.

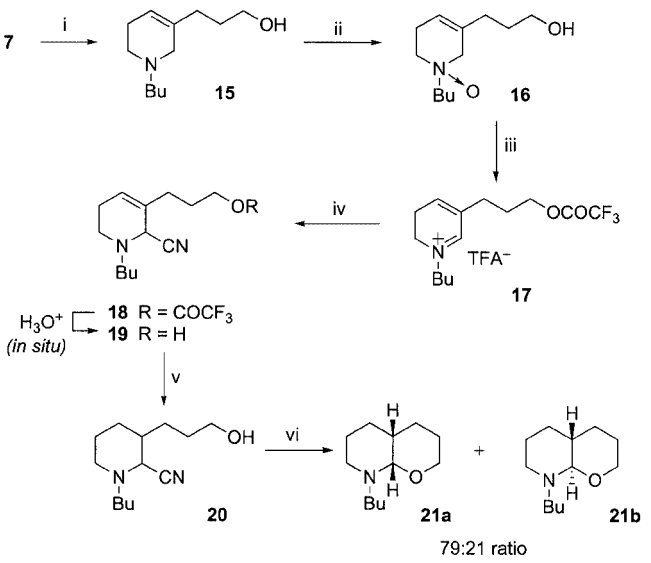
Results and Discussion

At first we attempted to use a *tert*-butyldimethylsilyl ether as a protecting group for the hydroxy moiety (Scheme 1). Thus, the starting 3-(3-pyridyl)propanol (**7**) was protected under standard conditions and alkylated with methyl iodide in quantitative yield to give the pyridinium salt **9**. This salt was then reduced to the tetrahydropyridine **10**, which was contaminated by 10−15% of its $\Delta^{4,5}$ isomer.[11] Oxidation of the tetrahydro derivative **10** with *m*-chloroperbenzoic acid afforded the corresponding *N*-oxide **11** in 66% yield over two steps. Transformation of **11** into the aminonitrile **13** was achieved by a Polonovsky−Potier reaction, followed by trapping of the intermediate dihydropyridinium salt **12** with potassium cyanide, but we obtained only a disappointing 27% yield over the two steps. Conducting the Polonovsky−Potier reaction in an NMR tube showed that the conversion of **11** into the dihydropyridinium salt **12** is fast and quantitative, but that the product readily decomposes (only 40% remaining after 40 minutes). This instability, along with a possible partial deprotection of the silyl ether in the acidic reaction medium, must account for this low yield.



Scheme 1. Reaction conditions: (i) TBDMSCl, TEA, DMAP (cat.), THF; (ii) neat MeI; (iii) $NaBH_4$, MeOH/H_2O; (iv) *m*CPBA, DCM; (v) TFAA, DCM; (vi) KCN, H_2O/DCM, pH 3

Earlier observations from our laboratory have suggested that the Polonovsky−Potier reaction can be carried out directly starting from a molecule bearing a free alcoholic function if two or more equivalents of TFAA are used. In such a case, the hydroxy group is protected in situ as a trifluoroacetate that is hydrolyzed during the extraction procedure. Thus, we examined first the reaction of the *N*-oxide

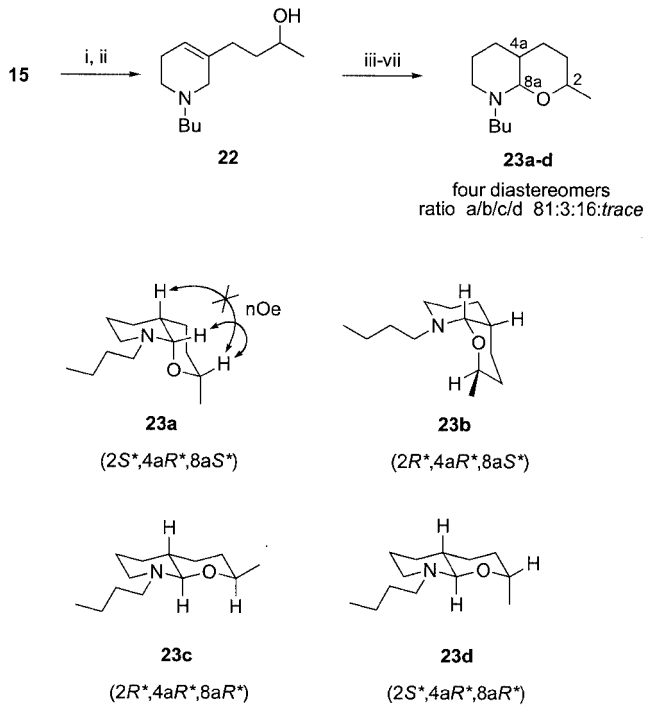


Scheme 2. Reaction conditions: (i) neat BuBr, 80 °C then $NaBH_4$, MeOH/H_2O; (ii) *m*CPBA, DCM; (iii) TFAA, DCM; (iv) KCN, DCM/H_2O, pH 1; (v) H_2, 5% Pd/C, MeOH; (vi) $AgBF_4$, THF

16, obtained from **7**, using the procedure above (Scheme 2). A Polonovsky−Potier reaction afforded the iminium ion **17**, which was not isolated but instead rapidly treated with potassium cyanide at pH 1 in water/dichloromethane to give a mixture of trifluoroacetate **18** and alcohol **19**. It is worth noting that, in contrast to the formation of aminonitrile **13**, acidic conditions (pH = 1) proved necessary for the reaction to take place (see cautionary note in Exp. Sect.). In addition, the ratio of **18**/**19** depends greatly on the amount of water used in the reaction. The mixture was then hydrogenated over 5% Pd/C to lead exclusively to the deprotected aminonitrile **20** in 90% yield. Regeneration of the iminium ion from crude **20** and spontaneous cyclization using silver tetrafluoroborate gave 82% of the expected product as an inseparable mixture of diastereoisomers **21a**/**21b** in a 79:21 ratio, as determined by high-field NMR spectroscopy experiments. Accordingly, the major diastereoisomer corresponds to the configuration of natural ′upenamide.

Finally, having validated our strategy, we introduced a methyl group in position 2 of the pyran ring to act as a model for the alkyl chain of ′upenamide. The presence of this substituent should allow us to further study the conformation of the octahydropyrano[2,3-*b*]pyridine ring. The alcohol **22** was prepared from **15** by Swern oxidation and then addition of methylmagnesium chloride in 40% over the two steps (Scheme 3). Following the same procedure as for **15**, the target hemiaminal **23** was obtained from **22** in 29% yield over five steps.

NMR spectroscopy experiments revealed that **23** was unexpectedly contaminated by 10% of its non-methylated analogue, **21**,[12] but its presence does not impair the clear identification of the four diastereoisomers of **23**, whose ratio we estimated, by integration of their hemiaminal proton



Scheme 3. Reaction conditions: (i) Swern oxidation; (ii) MeMgCl, THF; (iii) *m*CPBA, DCM; (iv) TFAA, DCM; (v) KCN, DCM/H_2O, pH 1; (vi) H_2, 5% Pd/C, MeOH; (vii) $AgBF_4$, THF

signal, to 81:3:16:trace (Scheme 3). The major diastereoisomer, **23a**, represents 81% of the total and has the relative configuration (2*S**,4a*R**,8a*S**), i.e. the same as natural ′upenamide. The *cis* ring junction of isomers **23a** and **23b** is characterized by a small coupling constant between protons 4a-H and 8a-H, typically 2 Hz, and a chemical shift above δ = 4 ppm for the hemiaminal proton. By contrast, the *trans* isomer **23c** exhibits a strong 4a-H/8a-H coupling (J = 7.8 Hz) and a chemical shift below δ = 3 ppm for proton 8a-H.[3] The relative configuration at the C-2 center was determined by the chemical shift of proton 2-H, which is, as expected, ca. 0.5 ppm higher when 2-H is equatorial, as is seen in the spectrum of **21**. This assumption was further confirmed by a NOESY experiment using **23**: diastereoisomer **23a** shows a strong NOE between 2-H and 8a-H, which means that both of these protons are axial relative to the pyran ring. The spectra of diastereoisomers **23b** and **23c** also show the signal of the 2-H protons at below δ = 3.5 ppm, which indicates that the methyl group at the C-2 center always assumes an equatorial position, even for **23b** in which the large conformational changes induce a loss of the stabilizing *exo*-anomeric effect, present in **23a**, of the equatorial nitrogen atom ($n_N-\sigma^*_{C-O}$).[13,14] The only diastereoisomer bearing an axial methyl group at the C-2 position is the conformationally restricted **23d**, which was identified by a $^1H,^1H$-COSY experiment ($\delta_{2\text{-Heq.}}$ = 3.9 ppm).

Conclusion

We have described a practical approach to the octahydropyrano[2,3-*b*]pyridine system, which corresponds to the DE ring system of ′upenamide. NMR spectroscopy studies showed that the major diastereoisomer (81%) possesses the same relative configuration (2*S**,4a*R**,8a*S**) as the alkaloid, and that it adopts a chair−chair conformation where the nitrogen atom is equatorial to the pyran ring. Our current work on the preparation of the ABC spirooxaquinolizidinone system will be reported in due course.

Experimental Section

General Procedures

A. Reduction of Pyridinium Salts using Sodium Borohydride: Sodium borohydride (2 equiv.) was added slowly to a solution of the pyridinium salt (10 g) in methanol/water (9:1, 200 mL) and then the mixture was stirred at room temperature for 24 h. After evaporation to dryness, CH_2Cl_2 was added to the residue and the organic layer was washed with water and dried ($MgSO_4$) and then the solvents were evaporated.

B. Formation of *N*-Oxides: A solution of *m*-chloroperbenzoic acid (3 equiv., tech. 70%) in CH_2Cl_2 was dried with $MgSO_4$ and then the supernatant was added to a solution of the tetrahydropyridine (1 g) in CH_2Cl_2 (50 mL) at 0 °C. After 30 min at this temperature, solid sodium sulfite was added and the mixture was stirred for 30 min; solid sodium carbonate was then added and the suspension was stirred for another 30 min. The solids were filtered out and the filtrate was evaporated to dryness. The crude *N*-oxide was purified by filtration through a short pad of neutral alumina (CH_2Cl_2/MeOH, 99:1 to 96:4).

C. Polonovsky−Potier Reaction and Trapping the Iminium Ion as an Aminonitrile: Trifluoroacetic anhydride (3 equiv.) was added to a solution of the *N*-oxide (1 g) in dry CH_2Cl_2 (50 mL) at room temperature. After 15 min, water (5 mL) was added to the reaction medium. When necessary, the pH of the water layer was adjusted with solid NaOAc. CH_2Cl_2 (20 mL) was added, followed by KCN (5 equiv.) dissolved in water (10 mL). After 3 h, the aqueous layer was neutralized to pH 8−9 with a saturated solution of $NaHCO_3$. The mixture was extracted with CH_2Cl_2, the organic phases were dried with $MgSO_4$, and then the solvents were evaporated under reduced pressure. The residue was purified by filtration through a short pad of neutral alumina (CH_2Cl_2/MeOH, 100:0 to 98:2). ***CAUTION:*** Extremely toxic hydrogen cyanide is likely to evolve when potassium cyanide is added to an acidic solution, and the reaction must be carried out under a very well-ventilated hood. If the reaction is to be performed using a significant amount of material, the hydrogen cyanide that evolves should be bubbled through a sodium hydroxide solution (pH > 10). The resulting solution should be treated with excess sodium hypochlorite at pH > 10 for at least 3 h before being disposed.

D. Hydrogenation of Aminonitriles: 5% Palladium on charcoal (300 mg) was added to a solution of the aminonitrile (1 g) in dry MeOH (25 mL). The mixture was degassed, placed under an atmosphere of hydrogen (20 psi) and shaken on a Parr apparatus for 6 h. The saturated aminonitrile was obtained after filtration through a pad of celite and evaporation under reduced pressure, and was used without further purification.

E. Cyclization of Aminonitriles: A solution of silver tetrafluoroborate (1 equiv.) in dry THF (10 mL) was added at room temperature to a solution of the aminonitrile (300 mg) in dry THF (10 mL). After 3 h, the black suspension was treated with 1 M ammonia liquor until complete discoloration occurred. The reaction medium was extracted with CH_2Cl_2, the combined organic layers were washed with water and dried ($MgSO_4$), and then the solvents were evaporated under reduced pressure. The crude material was purified by column chromatography over neutral alumina (heptanes/EtOAc, 9:1).

3-[3-(*tert*-Butyldimethylsilyloxy)propyl]pyridine (8): Triethylamine (1.0 mL, 7.3 mmol), *tert*-butyldimethylsilyl chloride (1.1 g, 7.3 mmol), and a catalytic amount of 4-(dimethylamino)pyridine (DMAP, 0.09 g, 0.73 mmol) were added to a solution of 3-(3-pyridyl)propanol (**7**, 1.0 g, 7.3 mmol) in dry THF (30 mL). The mixture was stirred at room temperature for 24 h before being extracted with water and CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and the solvents were then evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel (heptanes/EtOAc, 80:20) afforded the title compound in quantitative yield (1.80 g). This compound has been described by Sih, but most of its analytical data were not.[15] ^{1}H NMR ($CDCl_3$, 300 MHz): δ = −0.04 (s, 6 H), 0.81 (s, 15 H), 1.77−1.86 (m, 2 H), 2.68 (t, *J* = 7.9 Hz, 2 H), 3.62 (t, *J* = 6.1 Hz, 2 H), 7.20 (dd, *J* = 4.8, 7.7 Hz, 1 H), 7.50 (m, 1 H), 8.45 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = −5.3, 18.3, 25.9, 34.0, 61.8, 123.2, 135.9, 147.2, 150.0, 137.4 ppm. HRMS (ESI$^+$, MeOH): *m*/*z* = 252.1759 [M + H]$^+$ (calcd. for $C_{14}H_{26}NOSi$ *m*/*z* = 252.1784). $C_{14}H_{25}NOSi$: calcd. C 66.87, H 10.02, N 5.57; found C 66.83, H 10.24, N 5.49.

3-[3-(*tert*-Butyldimethylsilyloxy)propyl]-1-methylpyridinium Iodide (9): Neat methyl iodide (3.4 mL, 55 mmol) was added to 3-(3-pyridyl)propanol (**7**, 5.0 g, 36 mmol) under argon. The mixture was stirred at room temperature for 3 h, diluted with CH_2Cl_2, and then the solvents were evaporated in vacuo to afford the oily pyridinium salt in quantitative yield (12.8 g). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = −0.01 (s, 6 H), 0.84 (s, 9 H), 1.88−1.97 (m, 2 H), 2.95 (t, *J* = 7.8 Hz, 2 H), 3.62 (t, *J* = 6.0 Hz, 2 H), 4.63 (s, 3 H), 8.01 (dd, *J* = 5.4, 7.2 Hz, 1 H), 8.24 (d, *J* = 8.1 Hz, 1 H), 9.12 (s, 1 H), 9.16 (d, *J* = 6.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = −5.4, 18.1, 25.8, 29.1, 32.8, 49.2, 61.3, 127.7, 143.0, 143.7, 144.8, 145.0 ppm. HRMS (ESI$^+$, MeOH): *m*/*z* = 266.1910 [pyridinium]$^+$ (calcd. for $C_{15}H_{28}NOSi$: *m*/*z* = 266.1940). $C_{15}H_{28}INOSi$: calcd. C 45.80, H 7.17, N 3.56; found C 45.39, H 7.19, N 3.35.

3-[3-(*tert*-Butyldimethylsilyloxy)propyl]-1-methyl-1,2,5,6-tetrahydropyridine (10): Following the general procedure A, the pyridinium salt **9** (3.3 g, 8.4 mmol) was converted into the title compound. Yield: 1.85 g (6.9 mmol containing 10% of the $\Delta^{4,5}$ isomer, 74%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = −0.01 (s, 6 H), 0.70 (s, 9 H), 1.55−1.67 (m, 2 H), 1.94 (br. t, 2 H, *J* = 7.8 Hz), 2.11 (br. s, 2 H), 2.29 (s, 3 H), 2.39 (t, *J* = 6.0 Hz, 2 H), 2.75 (s, 2 H), 3.55 (t, *J* = 6.5 Hz, 2 H), 5.39 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = −5.3, 18.3, 26.0, 30.8, 31.3, 45.9, 52.0, 57.5, 62.7, 118.6, 135.7 ppm. MS (ESI$^+$, MeOH): *m*/*z* = 270 [M + H]$^+$. An analytically pure sample of the contaminant, the $\Delta^{4,5}$ isomer, was isolated by column chromatography over neutral alumina. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.04 (s, 6 H), 0.89 (s, 9 H), 1.32−1.45 (m, 2 H), 1.53−1.62 (m, 2 H), 2.14 (dd, *J* = 8.7, 12 Hz, 1 H), 2.44 (s, 3 H), 2.84−2.92 (m, 2 H), 3.16−3.23 (m, 1 H), 3.61 (t, *J* = 6.0 Hz, 2 H), 5.62−5.76 (m, 2 H, CH=CH) ppm. HRMS (ESI$^+$, MeOH): *m*/*z* = 270.2268 [M + H]$^+$ (calcd. for $C_{15}H_{32}NOSi^+$: *m*/*z* = 270.2248).

3-[3-(*tert*-Butyldimethylsilyloxy)propyl]-1-methyl-1,2,5,6-tetrahydropyridine *N*-Oxide (11): Following the general procedure B, using the tetrahydropyridine **10** (2.50 g, 9.3 mmol), the corresponding *N*-oxide was obtained (2.11 g, 80%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = −0.03 (s, 6 H), 0.85 (s, 9 H), 1.52−1.63 (m, 2 H), 2.03 (br. t, *J* = 7.8 Hz, 2 H), 2.24−2.32 (m, 1 H), 2.54−2.63 (m, 1 H), 3.14 (s, 3 H), 3.29−3.36 (m, 2 H), 3.57 (t, *J* = 6.0 Hz, 2 H), 3.65−3.84 (m, 2 H), 5.55 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = −5.3, 18.4, 23.9, 26.0, 30.4, 30.9, 56.5, 62.3, 64.2, 70.5, 117.5, 132.8 ppm. HRMS (ESI$^+$, MeOH): *m*/*z* = 286.2194 [M + H]$^+$ (calcd. for $C_{15}H_{32}NO_2Si^+$: *m*/*z* = 286.2197).

3-[3-(*tert*-Butyldimethylsilyloxy)propyl]-1-methyl-5,6-dihydropyridinium Trifluoroacetate (12): For identification purposes, TFAA (0.042 mL, 0.30 mmol) was added rapidly to a solution of *N*-oxide **11** (45.8 mg, 0.16 mmol) in $CDCl_3$ (0.5 mL) in an NMR tube and the ^{1}H NMR spectrum was recorded immediately. Because the *N*-oxide was contaminated with 15% of its $\Delta^{4,5}$ isomer, the 2,3-dihydro- and 5,6-dihydropyridinium salts were obtained in an 85:15 ratio. ^{1}H NMR (characteristic signals; $CDCl_3$, 400 MHz): δ = 8.41 (m, 0.15 H), 8.30 (s, 0.85 H), 7.08 (m, 0.15 H), 6.75 (br. s, 0.85 H), 6.45 (m, 0.15 H) ppm.

3-[3-(*tert*-Butyldimethylsilyloxy)propyl]-1-methyl-1,2,5,6-tetrahydropyridine-2-carbonitrile (13): The *N*-oxide **11** (250 mg, 0.88 mmol) was reacted as described in general procedure C, except that the Polonovsky−Potier reaction time was limited to 2 min. The title compound was obtained as an oil (70 mg, 0.24 mmol, 27% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.05 (s, 6 H), 0.90 (s, 9 H), 1.56−1.82 (m, 2 H), 2.00−2.41 (m, 4 H), 2.41−2.59 (m, 5 H), 2.67−2.77 (dd, *J* = 6.0, 11.7 Hz, 1 H), 3.63 (t, *J* = 6.0 Hz, 2 H), 3.93 (s, 1 H), 5.58−5.78 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = −5.3, 18.2, 25.3, 25.9, 30.0, 30.5, 43.3, 47.1, 56.4, 62.2, 116.0, 123.5, 131.4 ppm. HRMS (ESI$^+$, MeOH): *m*/*z* = 268.2010 [M − CN]$^+$ (calcd. for $C_{15}H_{30}NOSi^+$: *m*/*z* = 268.2091), 300.2299 [M − CN + MeOH]$^+$ (calcd. for $C_{16}H_{34}NO_2Si^+$: *m*/*z* = 300.2353), 562.4213 [2^m − CN]$^+$ (calcd. for $C_{31}H_{60}N_3O_2Si_2^+$: *m*/*z* = 562.4224).

1-Butyl-3-(3-hydroxypropyl)-1,2,5,6-tetrahydropyridine (15): Neat 1-bromobutane (7.80 mL, 72.8 mmol) was added to 3-(3-pyridyl)propanol (**7**, 5.0 g, 36 mmol) under argon. The mixture was heated at 80 °C for 3 h before being cooled to room temperature. The solid pyridinium salt was washed with heptane. Yield: 9.80 g (98%). ^{1}H NMR (CD_3OD, 300 MHz): δ = 1.00 (t, *J* = 6.0 Hz, 3 H), 1.36−1.49 (m, 2 H), 1.90−2.06 (m, 4 H), 2.98 (t, *J* = 7.5 Hz, 2 H), 3.62 (t, *J* = 6.0 Hz, 2 H), 4.64 (t, *J* = 7.5 Hz, 2 H), 8.03 (dd, *J* = 3.0, 6.0 Hz, 1 H), 8.49 (d, *J* = 3.0 Hz, 1 H), 8.87 (d, *J* = 6.0 Hz, 1 H), 9.98 (s, 2 H) ppm.

Following the general procedure A, the pyridinium salt (9.80 g, 36 mmol) was reduced to the title tetrahydropyridine, which was purified by chromatography on neutral alumina (CH_2Cl_2/MeOH, 98:2). Yield: 4.93 g (25 mmol, 69%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.93 (t, *J* = 7.4 Hz, 3 H), 1.21−1.40 (m, 2 H), 1.45−1.72 (m, 4 H), 2.02 (br. t, *J* = 7.6 Hz, 2 H), 2.11−2.20 (m, 2 H), 2.33−2.44 (m, 2 H), 2.50 (t, *J* = 5.8 Hz, 2 H), 2.81−2.86 (m, 2 H), 3.61 (t, *J* = 6.6 Hz, 2 H), 5.45 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.1, 20.9, 25.8, 29.1, 30.6, 31.5, 50.0, 55.7, 58.4, 62.3, 119.2, 135.5 ppm.

1-Butyl-3-(3-hydroxypropyl)piperidine-2-carbonitrile (20): Procedures B, C, and then D were applied to **15** (1.0 g, 5.1 mmol) to afford **20** (426 mg, 1.9 mmol, 37% overall yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.92 (t, *J* = 7.6 Hz, 3 H), 1.17−1.27 (m, 2 H), 1.28−1.37 (m, 2 H), 1.39−1.51 (m, 4 H), 1.53−1.62 (m, 2 H),

1.69−1.81 (m, 1 H), 1.84−1.98 (m, 2 H), 2.24 (dt, J = 3.1 Hz, 12.4 Hz, 1 H), 2.42−2.51 (m, 2 H), 2.77−2.81 (m, 1 H), 3.66 (br. t, J = 6.2 Hz, 2 H), 3.85 (d, J = 4.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.0, 20.0, 25.0, 27.1, 29.0, 29.1, 29.4, 38.3, 49.0, 56.0, 58.5, 62.5 ppm. IR (NaCl): $\tilde{\nu}$ = 3406 (ν_{OH}), 2172 (ν_{CN}) cm^{-1}.

8-Butyloctahydropyrano[2,3-*b*]pyridine (21): Following the general procedure E, the aminonitrile **20** (300 mg, 1.34 mmol) was converted into the heminaminal **21** in 82% yield (216 mg, 1.10 mmol). Diastereoisomers **21a** and **21b**, bearing a *cis* and *trans* ring junctions, respectively, were present in a 79:21 ratio. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 0.56 (t, J = 7.5 Hz, 1 H, 4'-H **21b**), 0.86 (t, J = 7.5 Hz, 3 H, 4'-H **21a**), 0.92−1.02 (m, 0.3 H, 5-H **21b**), 1.15−1.78 (m, 17.8 H), 1.92−1.97 (m, 0.6 H, 7-H$^{ax.}$ and 9-H **21b**), 2.43−2.50 (m, 2 H, 7-H and 9-H **21a**), 2.54 (ddd, J = 3.2, 11.1, 12.1 Hz, 1 H, 7-H **21a**), 2.58−2.63 (m, 1 H, 9-H **21a**), 2.93 (d, 0.3 H, J = 7.8 Hz, 8a-H **21b**), 2.98−3.03 (m, 0.6 H, 7-H$^{eq.}$ and 9-H **21b**), 3.32 (dt, J = 2.9, 12.0 Hz, 1 H, 2-H$^{ax.}$ **21a**), 3.41 (ddd, 0.3 H, J = 2.4, 11.4, 12.1 Hz, 2-H$^{ax.}$ **21b**), 3.89−3.92 (m, 1 H, 2-H$^{eq.}$ **21a**], 3.96−3.98 (m, 0.3 H, 2-H$^{eq.}$ **21b**], 4.03 (d, J = 2.0 Hz, 1 H, 8a-H **21a**) ppm. ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 14.0 (C-4′ **21a**), 14.1 (C-4′ **21b**), 20.7 (C-3′ **21a**), 21.0 (C-3′ **21b**), 21.4 (C-3 **21a**), 23.5 (C-5 **21a**), 25.0 (C-6 **21b**), 25.4 (C-6 **21a**), 26.3 (C-3 **21b**), 28.7 (C-2′ **21b**), 29.2 (C-4 **21a**), 29.9 (C-2′ **21a**, C-4 **21b**), 30.2 (C-5 **21b**), 35.5 (C-4a **21a**), 40.4 (C-4a **21b**), 45.7 (C-7 **21a**), 51.7 (C-7 **21b**), 52.3 (C-1′ **21b**), 53.9 (C-1′ **21a**), 67.2 (C-2 **21b**), 67.3 (C-2 **21a**), 89.9 (C-8a **21a**), 97.3 (C-8a **21b**) ppm. HRMS (ESI$^+$, MeOH): m/z = 198.1858 [M + H]$^+$ (calcd. for $C_{12}H_{24}NO^+$: m/z = 198.1852).

1-Butyl-3-(3-hydroxybutyl)-1,2,5,6-tetrahydropyridine (22): Oxalyl chloride (0.88 mL, 10 mmol) was added to a solution of DMSO (1.43 mL, 20 mmol) in dry CH_2Cl_2 (20 mL) at −60 °C. After 15 min, a solution of **15** (1 g, 5.1 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise and the mixture was stirred at −60 °C for 30 min. Triethylamine (7 mL, 50 mmol) was added and the reaction medium was warmed to room temperature. After 20 min, the crude reaction mixture was extracted with water/CH_2Cl_2, the combined organic layers were dried ($MgSO_4$), and the solvents were evaporated to dryness. Yield: 1.23 g. This aldehyde was used without purification as it readily decomposes during column chromatography. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.93 (t, J = 7.5 Hz, 3 H), 1.28−1.37 (m, 2 H), 1.47−1.57 (m, 2 H), 2.11−2.20 (m, 2 H), 2.24−2.34 (m, 2 H), 2.36−2.45 (m, 2 H), 2.46−2.52 (m, 2 H), 2.53−2.60 (m, 2 H), 2.82−2.90 (m, 2 H), 5.57 (br. s, 1 H), 9.76 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.2, 20.9, 26.1, 27.4, 29.4, 41.8, 50.0, 56.0, 58.5, 120.1, 134.4, 202.3 ppm.

Methylmagnesium chloride in THF (3 M, 2.1 mL, 6.3 mmol) was added slowly to a solution of the aldehyde (600 mg, 3.1 mmol) in dry THF (20 mL) at 0 °C. The solution was stirred at 0 °C for 15 min before being warmed to room temperature and stirred for another 30 min. Et_2O (5 mL) and a saturated solution of NH_4Cl (5 mL) were added and the mixture was extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and evaporated to dryness in vacuo and then the residue was purified by column chromatography on neutral alumina (heptanes/EtOAc, 90:10 to 50:50) to afford the title compound (428 mg, 40% overall yield from **15**). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.92 (t, J = 7.3 Hz, 3 H), 1.18 (d, J = 6.6 Hz, 3 H), 1.27−1.39 (m, 2 H), 1.45−1.61 (m, 4 H), 1.98−2.22 (m, 4 H), 2.35−2.44 (m, 2 H), 2.49 (t, J = 6.0 Hz, 2 H), 2.83−2.87 (m, 2 H), 3.72−3.84 (m, 1 H), 5.49 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.2, 21.0, 23.6, 26.0, 29.3, 31.7, 37.2, 50.2, 55.9, 58.5, 67.9, 119.3, 135.9 ppm.

8-Butyl-2-methyloctahydropyrano[2,3-*b*]pyridine (23): Following the general procedures B, C, D, and E, the alcohol **22** (400 mg, 1.9 mmol) was converted into the heminaminal **23** in 29% overall yield (127 mg, 0.6 mmol, contaminated by 10 mol% of **21**). Diastereoisomers **23a**−**d** are depicted in Scheme 3. Integrals are uncorrected. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 0.81−0.87 (m, 5.47 H, CH_2CH_3 **23a**−**d**), 1.07 (d, J = 6.6 Hz, 0.18 H, CH_3 **23d**), 1.09 (d, J = 6.6 Hz, 3.40 H, CH_3 **23a**), 1.12 (d, J = 6.3 Hz, 1.04 H, CH_3 **23c**), 1.15 (d, J = 6.3 Hz, 0.41 H, CH_3 **23b**), 1.17−1.30 (m, 8.99 H), 1.33−1.42 (m, 4.15 H), 1.46−1.57 (m, 3.82 H), 1.57−1.75 (m, 5.97 H), 1.82−2.04 (m, 1.69 H, 7-H$^{ax.}$ and 9-H **23c**), 2.41−2.51 (m, 2.52 H, 7-H and 9-H **23a**), 2.51−2.57 (m, 1.28 H, 7-H **23a**), 2.58−2.64 (m, 1.30 H, 9-H **23a**), 2.91 (d, J = 8.2 Hz, 0.02 H, 8a-H **21b**), 2.94 (d, J = 8.2 Hz, 0.20 H, 8a-H **23c**), 2.96−3.07 (m, 0.62 H, 7-H$^{eq.}$ and 9-H **23c**), 3.25−3.35 (m, 1.26 H, 2-H$^{ax.}$ **23a**), 3.40−3.47 (m, 0.27 H, 2-H$^{ax.}$ **23c**), 3.48−3.52 (m, 0.05 H, 2-H$^{ax.}$ **23b**), 3.85−3.97 [m, 0.13 H, 2-H$^{eq.}$ **21a** + **21b**, 2-H$^{eq.}$ **23d**], 4.01 (d, J = 2.0 Hz, 0.10 H, 8a-H **21a**), 4.06 (d, J = 2.2 Hz, 1 H, 8a-H **23a**), 4.28 (s, 0.03 H, 8a-H **23b**) ppm. ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 14.1 (CH_2CH_3 **23a**−**c** and **21a**−**b**), 20.7, 20.8, 21.0, 21.1 (CH_3 **23d**), 21.4 (CH_3 **23b**), 21.7 (CH_3 **23c**), 21.9 (CH_3 **23a**), 23.4, 23.5, 24.1, 24.4, 25.2, 25.4, 25.6, 26.4, 28.6, 29.2, 29.3, 29.7, 29.9, 30.0, 31.6, 32.2, 33.6, 34.7 (C-4a **23a**), 34.9, 35.5, 39.9 (C-4a **23c**), 40.1, 45.7 (C-7 **23a**), 45.8, 51.7 (C-7 **23c**), 52.0, 52.3 (C-9 **23c**), 53.5, 53.8 (C-9 **23a**), 53.9, 58.3, 67.4 (C-2 **21a**,**b**), 71.5 (C-2 **23b**), 72.7 (C-2 **23a** and **23c**), 88.2 (C-8a **23b**), 89.4 (C-8a **23a**), 90.0 (C-8a **21a**), 96.8 (C-8a **23c**) ppm. HRMS (ESI$^+$, MeOH): m/z = 212.2027 [M + H]$^+$ (calcd. for $C_{13}H_{26}NO^+$: m/z = 212.2009).

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