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SYNTHESIS OF NAUCLÉFINE, ANGUSTIDINE, ANGUSTINE, (±)-13b,14-DIHYDRO-ANGUSTINE AND NAULAFINE

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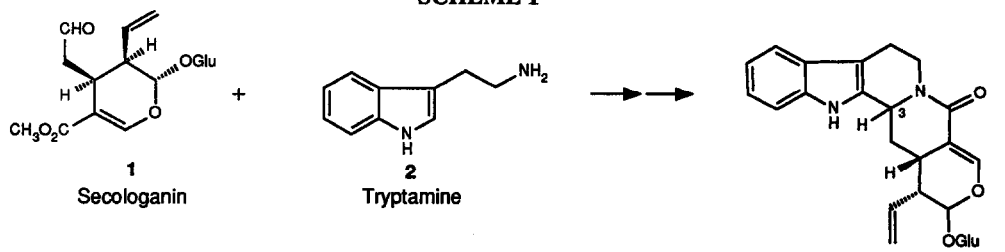
ABSTRACT: *The lithio derivatives of 3-cyano-4-methylpyridines and 6,7-dihydro-5H-2-pyrindine-4-carbonitrile react with 2,9-bis-(trimethylsilyl)-3,4-dihydropyrido[3,4-b]indolium trifluoromethanesulfonate to form cyclic amidines which, upon hydrolysis and oxidation, produce the title alkaloids.*

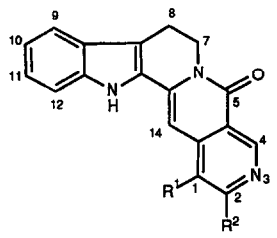
Alkaloids of the indolo[2′:3′, 3:4]pyrido[1,2-*b*] [2,7]naphthyridine system have been found to occur in a number of genera including *Nauclea* L., *Mitragyna* Korth., *Strychnos* L., *Uncaria* Schreb. and *Anthocephalus* A. Rich.[2-6]

The biogenesis of these molecules has been postulated[3] to occur through the intermediacy of strictosamide **3** or its C-3 epimer vincoside lactam **4**, the latter materials being derived from secologanin **1** and tryptamine **2** (Scheme 1). The isolation[7] of strictosamide **3** from N*auclea latifolia* Smith and the incorporation[8] of radiolabelled loganin in the biosynthesis of strictosidine (the immediate precursor of strictosamide) in cultivated *Vinca rosea* L. would lend support to the proposed pathway. It has been suggested[3] that alkaloids such as angustine **5b** might arise only as artifacts of extraction processes in which ammonium hydroxide is used. It has further been suggested that "...subsequent modification can then be rationalized in simple combinations of oxidation, addition of water, β-dicarbonyl or *retro*-aldol cleavages, all of which can occur spontaneously..."[9] However, our attempts to convert angustine **5b** into either angustoline **5d** or nauclétine **5e** by oxidative means have been unsuccessful. Using a variety of agents such as *m*-chloroperbenzoic acid, hydrogen peroxide, and thallium trinitrate, the unexpectedly unreactive vinyl side chain remained intact.[10] Thus it is unlikely that alkaloids such as nauclétine **5e** or the hexacyclic naulafine **7** could arise as mere artifacts of an extraction process. In addition, angustine and related alkaloids have been isolated from natural sources even when ammonium hydroxide was not used in the extraction process.[3]

SCHEME 1

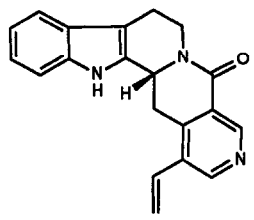


1 Secologanin + **2** Tryptamine →→ **3** H-3α Strictosamide, **4** H-3β Vincoside Lactam

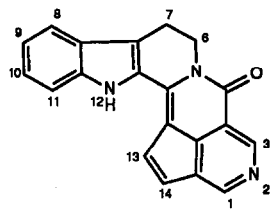


5

	R^1	R^2	
a	H	H	Naucléfine
b	CH_2=CH	H	Augustine
c	H	CH_3	Augustidine
d	$CH(OH)CH_3$	H	Angustoline
e	$COCH_3$	H	Naucléfine



12b
13b,14-Dihydroaugustine



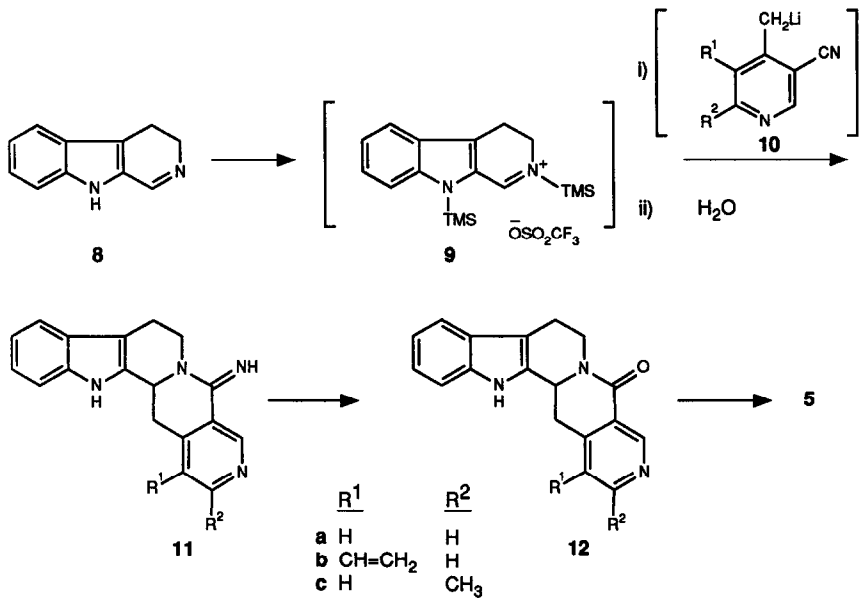
7
Naulafine

Herein we report the syntheses of five of these substances of which we have given preliminary accounts.[11-13] Previous strategies for the preparation of members of this structural family have been briefly reviewed.[11] Most of these methods suffer from a number of disadvantages, including low overall yields, lack of regiospecificity with regard to the pyridine nitrogen, and lack of generality.

Our approach to these alkaloids has been based upon two observations: 1) the reaction of lithiated toluamides[14,15] or lithiated cyanopicolines[16,17] with cyclic imines to produce 8-oxoberbines and 10-azaberbines, respectively, and 2) the use of trimethylsilyl trifluoromethanesulfonate (TMS-triflate) to activate imines to nucleophilic attack by lithium carbanions.[16,18] Thus, while neither 3,4-dihydro-9*H*-pyrido-[3,4-*b*]indole **8** nor its 9-lithio-(or 9-benzyl-) derivative would undergo condensation with lithiated 3-cyano-4-methylpyridine **10a** or lithiated 3-cyano-4-methyl-5-vinylpyridine, **10b**, both picolyl anions reacted smoothly with TMS triflate-activated 9-benzyl-3,4-dihydro-β-carboline.[11] However, the benzyl-protecting group could not be removed in a way that would leave the pentacyclic ring system intact. This last difficulty was overcome by using the bis-trimethylsilyl species, **9** (Scheme 2).

Treatment of 3,4-dihydro-β-carboline **8** at -70 °C with one equivalent of n-BuLi and then with two equivalents of trimethylsilyl trifluoromethane sulfonate generated the TMS-protected, TMS triflate-activated imine

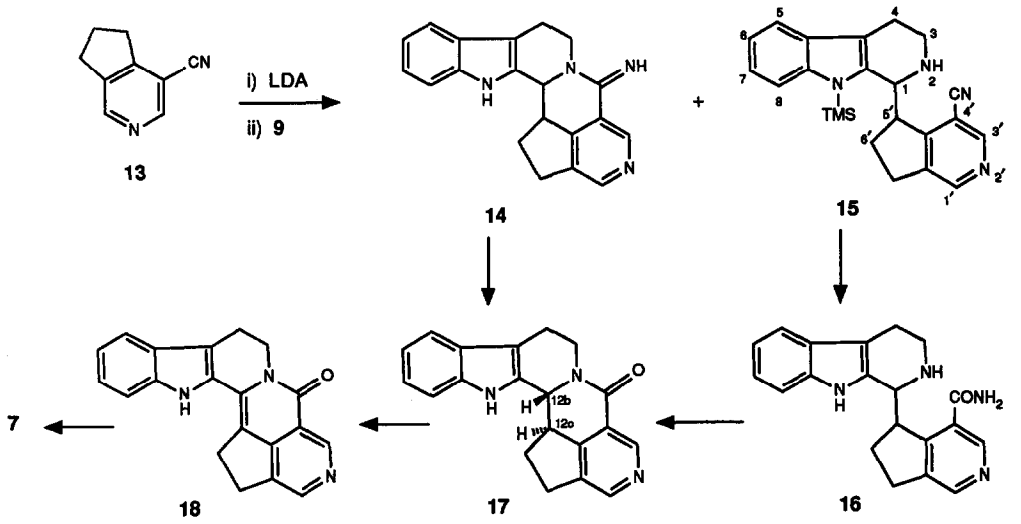
SCHEME 2



9. Reaction of **9** with the highly colored LDA-generated anion solutions of 3-cyano-4-methylpyridine **10a**[19], 3-cyano-4-methyl-5-vinylpyridine **10b**[20], or 3-cyano-4,6-dimethylpyridine **10c**[21] at -70 °C followed by aqueous workup afforded the de-protected pentacyclic amidines **11a-11c**. The amidine **11c** was obtained in only 11% yield. This can probably be explained by the facile abstraction of a proton by lithium from the 6-methyl group of **10c** as well as from the 4-methyl group. This type of behavior has been previously noted with metalation of 2,4-lutidine and its derivatives.[22-24] Hydrolysis of **11a-11c** with potassium hydroxide in aqueous dioxane under reflux provided the lactams **12a-12c**. Compound **12b** is the natural product (±)-13b,14-dihydroangustine.[25] Oxidation of the lactams with iodine in methanol or ethanol under reflux produced the alkaloids naucléfine **5a**, angustine **5b**, and angustidine **5c**.

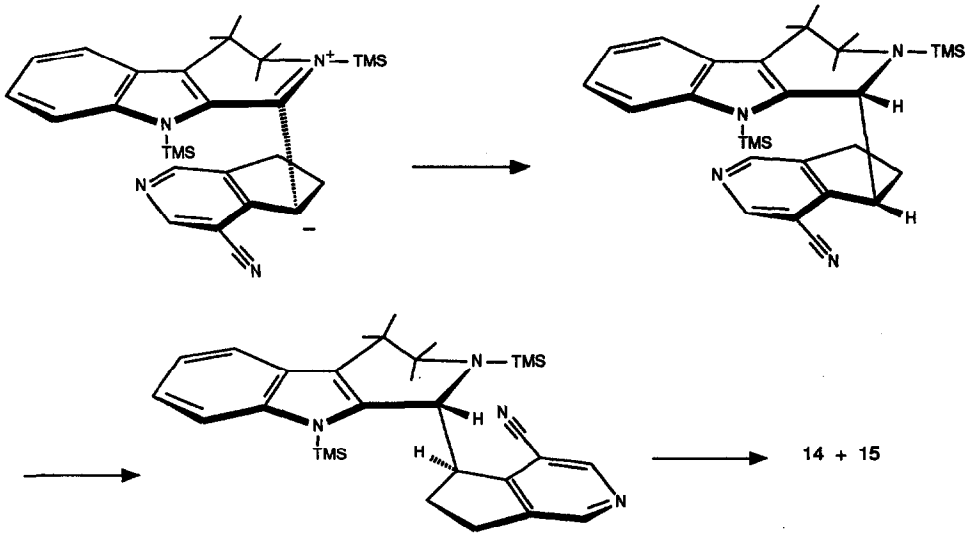
The synthesis of naulafine **7** (Scheme 3), a compound unique among the *Nauclea* alkaloids by virtue of its sixth fused ring, was conducted in a similar manner. Reaction of **9** with the lithium anion of 6,7-dihydro-5*H*-2-pyrindine-4-carbonitrile[26,27] **13** gave the expected amidine **14**. The yield of **14** was only 19%. Examination of the reaction mixture revealed that the major product was the "open" aminonitrile **15**. The structure of **15** was confirmed by spectroscopic analyses. Compound **15** exhibited an infrared band at 2182 cm^{-1} (nitrile), a singlet for the indole-TMS group at 0.7 ppm in its ^1H nmr spectrum, and a lack of a signal for the indole N-H proton which reappeared as a D_2O-exchangable singlet at 11.32 ppm upon treatment with acid. Either **14** or **15** or a mixture thereof could be converted to tetrahydronaulafine **17** by treatment with potassium hydroxide. When applied only to **15**, the appearance of the transient amide **16** was initially observed. That **17** is the only diastereomer formed is demonstrated by ^1H NMR spectroscopy. The proton at C-12b appears as a doublet at 4.86 ppm with $J_{12b,12c}$ = 11.29 Hz indicating a trans relationship to the proton at C-12c.[28] We envision this to reflect a

SCHEME 3



preferred endo interaction for the reactants (as depicted in Figure 1) possibly stabilized by a favorable coordination of lithium. In the addition of lithiated pathalides to dihydroisoquinolines a similar argument in favor of the endo case has been postulated.[29]

FIGURE 1. Postulated endo-interaction between picolyl anion and iminium salt.



The conversion of **17** to dihydronaulafine **18** proceeded smoothly with iodine in ethanol at reflux. Under these conditions there was no evidence of further oxidation to naulafine **7**. Compound **18** was remarkably resistant to the introduction of further unsaturation. The use of DDQ in benzene, selenium dioxide in glacial acetic acid, molten sulfur, manganese dioxide in dioxane, *n*-butyl lithium/TMEDA in cyclohexane, or platinum oxide in hot

TABLE 1

^1H and ^{13}C NMR Data in $DMSOd_6$ for Naulafine 7

Position	^1H Chem. Shift (multiplicity)	Coupling Constants	^{13}C Chem. Shift (multiplicity)	Position	^1H Chem. Shift (multiplicity)	Coupling Constants	^{13}C Chem. Shift (multiplicity)
1	9.07 (s)		144.27 (d)	11	7.60 (d)	J = 8.0 Hz	112.75 (d)
3	8.89 (s)		143.47 (d)	11a	---		137.43 (s)
3a	---		116.07 (d)	12	11.51 (nm)		--------
4	---		161.16 (s)	12a	---		140.26 (s)
6	4.45 (t)	J = 6.6 Hz	40.66 (t)	12b	---		139.76 (s)
7	3.19 (t)	J = 6.6 Hz	19.51 (t)	12c	---		120.45 (s)
7a	---		110.20 (s)	13	7.16 (d)	J = 5.0 Hz	124.05 (d)
7b	---		126.76 (s)	14	7.82 (d)	J = 5.0 Hz	127.28 (d)
8	7.71 (d)	J = 7.9 Hz	120.19 (d)	14a	---		124.57 (s)
9	7.15 (dd)	J = 7.9, 8.0 Hz	120.36 (d)	14b	---		131.88 (s)
10	7.35 (dd)	J = 8.0, 8.0 Hz	125.76 (d)				

J = coupling constant
s = singlet, d = doublet, t = triplet, nm = narrow multiplet, dd = doublet of doublets

The ^1H NMR spectrum (500 MHz) was recorded with a 6 kHz sweep width using a pulse width of 2μsec (9.5 μsec = 90°flip angle), 32 K data points and an acquisition time of 2.72 sec. The ^{13}C NMR spectrum (125.8 MHz) was recorded using a 29.4 kHz sweep width, a pulse width of 2.5 μsec (6.0 μsec = 90° flip angle), 32 K data points and an aquisition time of 0.56 sec. The 2D NMR spectra were acquired using the standard Bruker microprograms COSYLR, XHCORR, and GATEDEC.

xylene proved unsuccessful.[30] A 40% yield of naulafine **7** was obtained when **18** was heated at reflux in *p*-cymene or, better, in 1,2,4,-trichlorobenzene in the presence of 20% palladium-on-carbon (reduced Pearlman's catalyst). The ^1H and ^{13}C NMR assignments for naulafine **7** are summarized in Table I. Proton assignments were confirmed by a long range ^1H-^1H homonuclear shift-correlation (COSY) experiment. ^1H-^{13}C heteronuclear shift-correlation (HETCOR) was used to assign the protonated carbons in the ^{13}C NMR spectrum. A heteronuclear gated decoupling experiment was used to assign the singlet carbons based on the expected ^1H-^{13}C coupling constants. The assignments of the H-1 and H-3 resonances in the ^1H NMR spectrum have been reversed from those reported by Hotellier, et. al[31] due to the observation of two strong cross peaks for H-1, H-14 and H-1, H-13 in the long range COSY spectrum.

The cyclocondensation methodology used in the syntheses of these indolopyrido alkaloids provides regiochemical control with respect to the position of the pyridine nitrogen and offers flexibility in the substituents on the indole and pyridine nucleus. This methodology also demonstrates the synthetic utility of trimethylsilyl triflate in the activation of imines for carbon-carbon bond formation as well as for the *in situ* protection of the indole nitrogen with the removable trimethylsilyl group.

EXPERIMENTAL

^1H and ^{13}C magnetic resonance spectra were recorded on either Bruker WM 300 or Bruker AM 500 instruments and are reported in ppm (δ) downfield from an internal standard of tetramethylsilane. EI mass spectra were recorded with an Atlaswerke CH-7 and high resolution mass spectra (hrms) were obtained with either a Finnigan MAT 311A or a VG Analytical ZAB E equipped with a VG 11-250 data system. Infrared spectra were recorded with an IBM IR/44. Melting points are uncorrected. Elemental analyses were obtained from the Syntex Analytical department. Column chromatography was carried out with silica gel 60A, 70-230 mesh. Preparative thick layer chromatography was performed with 20 x 20 cm glass plates coated with 2000μ layers of silica gel GF (Analtech, Newark, Delaware). THF was dried by distillation from sodium prior to use.

2,9-Bis-(trimethylsilyl)-3,4-dihydropyrido[3,4-*b*]-indolium trifluoromethanesulfonate. **9**.

To a stirred solution of 3,4-dihydropyrido[3,4-b]indole[32] **8** (629 mg, 3.70 mmol) in 7.0 mL freshly distilled THF at -70 °C under a nitrogen atmosphere was added 2.3 mL (3.7 mmol) of a solution of *n*-BuLi (1.6 M) in hexane. The heavy precipitate which appeared after 30 min. was treated with TMS-triflate (1.43 mL, 7.40 mmol). The resulting reaction mixture was stirred for 15 min. at -70 °C and then at -5 °C for 90 min. The heterogeneous mixture containing **9** was then cooled to -70 °C and treated with various picolyl lithiums as follows.

(±)-Dihydronaucléfine. ((±)-8,13,13b,14-Tetrahydroindolo[2′,3′:3,4]pyrido[1,2-*b*][2,7]-naphthyridin-5[7*H*]-one) **12a**.

To a stirred solution of LDA (prepared from 0.62 mL (4.44 mmol) of diisopropylamine and 2.8 mL (4.44 mmol) of 1.6 M *n*-BuLi/hexane) in 25 mL of THF at -70 °C under N_2 was added dropwise a solution of 3-cyano-4-methyl pyridine[19] (524 mg, 4.44 mmol) in THF (10 mL). The resulting yellow solution was transferred via cannula to a suspension of **9** (prepared as above).

After the addition was complete, the reaction mixture was stirred for 10 min. at -70 °C and then it was added to 200 mL of saturated aqueous NaCl. The resulting mixture was extracted with CH_2Cl_2 (200 mL) and the organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was stirred for 10 min. in ethyl acetate (10 mL) and the solid that separated was collected by filtration and dried *in vacuo* to give **11a**, 700 mg (49%) which was used without further purification. The amidine **11a** (700 mg, 2.43 mmol) was heated under reflux in a mixture of 60 mL dioxane and 20 mL 20% aqueous KOH for 24 h. The solvent was then removed under reduced pressure at 50 °C and the residue was partitioned between CH_2Cl_2 (200 mL) and H_2O (50 mL). The organic layer was separated and dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate to give **12a**, 447 mg (89%), m.p. 266-268 °C; ^1H nmr (500 MHz) $CDCl_3$, δ: 2.90-3.00 (complex multiplet, 2H), 3.02-3.09 (complex multiplet, 2H), 3.45 (dd, *J*=16.3, 3.4 Hz, 1H), 5.19 (m, 1H), 5.22 (m, 1H), 7.14 (m, Hz, 1H), 7.21 (m, 1H), 7.25 (dd, *J*=5.0, 1.1Hz, 1H), 7.38 (dd, *J*=8.0, 0.9Hz, 1H), 7.56 (d, *J*=7.8 Hz, 1H), 8.62 (d, *J*=5.0 Hz, 1H), 9.24 (s, 1H); ms (EI), m/z (%): 289 (100) M^+, 288 (43), 274 (29), 260 (13), 231 (13), 169 (46), 143 (13), 119 (17); Exact mass (hrms): Calcd. for $C_{18}H_{15}N_3O$: 289.1215, Found: 289.1225; Analysis: Calcd.: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.31; H, 5.28; N, 14.48.

(±)-Dihydroangustine. ((±)-1-Ethenyl-8,13,13b,14-tetrahydroindolo[2′,3′:3,4]pyrido[1,2-*b*][2,7]-naphthyridin-5[7*H*]-one. **12b**.

The compound **12b** was prepared in the same manner as described for **12a** using 3-cyano-4-methyl-5-vinyl

pyridine. **12b**: (93%); m.p. 305-306 °C (EtOAc); ^{1}H nmr (300 MHz) $CDCl_3$, δ: 2.73-3.04 (complex m, 4H), 3.95 (dd, *J*=16.5, 4.2 Hz, 1H), 4.98-5.09 (complex m, 2H), 5.61 (dd, *J*=11.2, 1.0 Hz, 1H), 5.98 (dd, *J*=17.7, 1.0 Hz, 1H), 6.96-7.13 (complex m, 3H), 7.36 (apparent d, *J*=8.0 Hz, 1H), 7.48 (apparent d, *J*=7.6 Hz, 1H), 8.87 (s, 1H), 8.98 (s, 1H), 11.14 (br s, 1H, exchanges with D_2O); ms (EI), m/z (%): 315 (100) M^+, 314 (43), 300 (26), 257 (10), 169 (34), 143 (10), 117 (26); Exact mass (hrms): Calcd. for $C_{20}H_{17}N_3O$: 315.1372, Found: 315.1370; Analysis: Calcd. for $C_{20}H_{17}N_3O$•0.5 H_2O: C, 74.05; H, 5.59; N, 12.95. Found: C, 74.04; H, 5.25; N, 13.14.

(±)-Dihydroangustidine. ((±)-2-Methyl-8,13,13b,14-tetrahydroindolo[2′,3′:3,4]pyrido[1,2-*b*] [2,]-naphthyridin-5[7*H*]-one. **12c**.

This compound was prepared using 3-cyano-4,6-dimethylpyridine following the same procedure as that described for **12a**. **12c**: (10%); m.p. 288-289 °C (EtOAc/hexane); ^{1}H nmr (300 MHz) $CDCl_3$, δ: 2.60 (s, 3H), 2.93-3.04 (complex m, 4H), 3.42 (dd, *J*=16.2, 4.0 Hz, 1H), 5.03 (m, 1H), 5.17 (m, 1H), 7.12 (s, 1H), 7.09-7.22 (complex m, 2H), 7.38 (apparent d, *J*=8.0 Hz, 1H), 7.55 (apparent d, *J*=7.6 Hz, 1H), 9.09 (s, 1H); ms (EI), m/z (%): 303 (100) M^+, 302 (43), 288 (30), 245 (13), 207 (9), 169 (38), 133 (27), 115 (14); Exact mass (hrms): Calcd. for $C_{19}H_{17}N_3O$: 303.1372, Found: 303.1375; Analysis: Calcd. for $C_{19}H_{17}N_3O$•0.25 H_2O: C, 74.13; H, 5.73; N, 13.65. Found: C, 74.23; H, 5.68; N, 13.66.

(±)-Tetrahydronaulafine. ((±)-7,12,12b,12c,13,14-hexahydrocyclopent[*de*]indolo[2′,3′:3,4]pyrido-[1,2-*b*][2,7]naphthyridin-4[6*H*]-one. **17**.

A solution of LDA was prepared at -70 °C under a nitrogen atmosphere from diisopropylamine (0.77 mL, 5.5 mmol) and 1.6 M *n*-BuLi in hexane (3.44 mL, 5.5 mmol) in 40 mL of THF. A solution of 6,7-dihydro-5*H*-2-pyridine-4-carbonitrile **13**[26,27] (792 mg, 5.5 mmol) in 40 mL of THF was added rapidly to the above LDA solution. The deep purple solution was then transferred via cannula to a previously prepared suspension of **9** (5.0 mmol) in 15 mL THF at -70 °C. After the addition was complete the reaction mixture was stirred at -70 °C for 20 min. and then it was poured into 200 mL of saturated aqueous sodium chloride. The resulting mixture was extracted with 400 mL of CH_2Cl_2 and the organic phase was separated, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was recrystallized from EtOAc to give **15**, 750 mg (39%); m.p. 224-226 °C; IR, 2182 cm^{-1}, nitrile; ^{1}H nmr (300 MHz) $CDCl_3$, δ: 0.7 (s, 9H), 1.55-1.74 (complex m, 1H), 1.76-1.84 (complex m, 1H), 2.72-2.81 (m, 3H), 2.95-3.07 (m, 3H), 4.04 (m, 1H), 5.41 (m, 1H), 7.2 (m, 2H), 7.51 (m, 2H), 8.60 (s, 1H), 8.71 (s, 1H); ^{13}C nmr (125.76 MHz), $CDCl_3$, δ: 2.42 ($SiCH_3$), 23.25 (C-7′ or C-8), 24.96 (C-6), 28.82 (C-4 or C-7′), 41.80 (C-3), 51.83 (C-5′), 52.13 (C-1), 106.07 (C-3′), 113.96 (C-8), 116.58 (C≡N), 116.63 (C-7′a), 118.10 (C-7), 119.73 (C-5), 121.30 (C-6), 130.35 (C-4b), 139.10 (C-8a), 142.08 (4′a or 4a), 142.6 (4a or 4′a) 149.51 (C-2′), 150.83 (C-9′), 156.08 (C-9a), ms (EI), m/z (%): 386 (<5) (M^+), 243 (100), 241 (64), 143 (55), 73 (84); Analysis: Calcd. for $C_{23}H_{26}N_4Si$: C, 71.46; H, 6.78; N, 14.49. Found: C, 71.05; H, 6.82; N, 14.42.

Concentration of the mother liquor from the recrystallization of **15** afforded the crude amidine **14**. In practice, it was found to be expedient to treat the crude mixture of **14** and **15** under the conditions described for the preparation of **12a** in order to obtain **17** in 61% yield. **17**: m.p. 310-312 °C (EtOAc); ^{1}H nmr (500 MHz), DMSO-d_6, δ: 2.28 (m, 1H), 2.73 (m, 2H), 2.88 (m, 2H), 3.07 (m, 2H), 3.26 (m, 1H), 4.86 (d, *J*=11.3 Hz, 1H), 5.05 (m, 1H), 7.00 (dd, *J*=7.8. 0.7 Hz, 1H), 7.09 (dd, *J*=8.1, 1.0 Hz, 1H), 7.42 (apparent d, *J*=8.1 Hz, 1H), 7.44 (apparent d, *J*=7.8 Hz, 1H), 8.61 (s, 1H), 8.73 (s, 1H), 10.54 (s, exchanges with D_2O, 1H); ^{13}C nmr (125.76 MHz), δ: 20.8 (C-7), 29.8 (C-14), 31.7 (C-13), 39.2 (C-6), 44.6 (C-12c), 58.6 (C-12b), 108.0 (C-7a), 111.4 (C-11), 117.6 (C-8), 118.6 (C-9), 121.1 (C-10), 121.2 (C-3a), 125.7 (C-7b), 132.7 (C-12a), 136.6 (C-11a), 137.5 (C-14a), 144.1 (C-3),

147.4 (C-1), 153.6 (C-3b), 162.4 (>C=O); ms (EI), m/z (%): 315 (96) M^+, 314 (24), 286 (9), 169 (73), 145 (100), 117 (31), 90 (24); Exact mass (hrms): Calcd. for $C_{20}H_{17}N_3O$: 315.1373; Found: 315.1372; Anal. Calcd. for $C_{20}H_{17}N_3O \cdot 0.25\ H_2O$: C, 75.10; H, 5.51; N, 13.14; Found: C, 75.30; H, 5.46; N, 13.19.

(±)-1-[5′-(4′-Carboxamido-6,7-dihydro-5*H*-2-pyrindine)]-1,2,3,4-tetrahydropyrido[3,4-*b*]indole. **16**.

A solution of the TMS-nitrile **15** (1.0 g, 2.58 mmol) in dioxane (50 mL) and 20% aqueous KOH (30 mL) was heated under reflux for 24 h. The mixture was cooled to 40 °C and the solvent was removed under reduced pressure. The residue was partitioned between 100 mL of H_2O and 200 mL of CH_2Cl_2. The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was dissolved in 30 mL of hot EtOAc. After standing at room temperature for 1 h the crystals were collected and dried to give 460 mg (61%) of **17**. The mother liquor was concentrated under reduced pressure and subjected to column chromatography on silica gel. Elution with 5% MeOH in CH_2Cl_2 containing 1% NH_4OH gave **16** (140 mg, 16%) which was recrystallized from EtOAc; m.p. 167-168 °C; ir (KBr): 1670 cm^{-1}; ^1H nmr (500 MHz), DMSO-d_6, δ: 1.85 (m, 2H), 2.51 (m, 1H), 2.70 (m, 2H), 2.80 (m, 1H), 3.01 (m, 1H), 3.09 (m, 1H), 4.50 (m, 1H), 4.69 (s, 1H), 6.94 (t, *J*=7.4 Hz, 1H), 7.01 (m, 1H), 7.30 (apparent d, *J*=8.0 Hz, 1H), 7.35 (apparent d, *J*=7.8 Hz, 1H), 7.55 (s, exchanges with D_2O, 1H), 8.01 (s, exchanges with D_2O, 1H), 8.49 (s, 1H), 8.58 (s, 1H), 10.83 (s, exchanges with D_2O, 1H); ms (EI), m/z (%): 332 (<5) M^+; 171 (100), 162 (18), 144 (14).

Oxidation of lactams **12a,12b,12c,17** to dehydrolactams **5a,5b,5c** and **7**.

Naucléfine. (8,13-Dihydroindolo[2′3′:3,4]pyrido[1,2-*b*][2,7]naphthyridin-5[7*H*]-one **5a**.

A solution of lactam **12a** (200 mg, 0.69 mmol) and iodine (400 mg) in MeOH (50 mL) was gently heated under reflux for 12 h. The solvent was removed *in vacuo* and the residue was treated with 10% $Na_2S_2O_3$ solution to decompose excess iodine. The resulting mixture was basefied with saturated Na_2CO_3 solution and the product was thoroughly extracted into 10% MeOH in CH_2Cl_2. The combined organic extracts were washed successively with 10% $Na_2S_2O_3$ solution and brine, and dried over Na_2SO_4.

Removal of the solvent *in vacuo* gave naucléfine **5a** (181 mg, 91%) which was crystallized from MeOH. m.p. 288-292 °C (lit.[33] m.p. 285-290 °C); ^1H nmr (300 MHz) DMSO-d_6, δ: 3.13 (t, *J*=6.7 Hz, 2H), 4.41 (t, *J*=6.7 Hz, 2H), 7.02 (s, 1H), 7.09 (m, 1H), 7.26 (m, 1H), 7.45 (apparent d, *J*=8.2 Hz, 1H), 7.51 (d, *J*=5.5 Hz, 1H), 7.62 (d, *J*=7.9 Hz, 1H), 8.65 (d, *J*=5.4 Hz, 1H), 9.32 (s, 1H), 11.81 (s, exchanges with D_2O, 1H); ms (EI), m/z (%): 287 (100) M^+, 286 (91), 285 (26) 272 (18), 257 (11), 144 (20), 129 (15), 115 (20); Exact mass (hrms): Calcd. for $C_{18}H_{13}N_3O$: 287.1059; Found: 287.1059.

Angustine. (1-Ethenyl-8,13-dihydroindolo[2′,3′:3,4]pyrido[1,2-*b*][2,7]naphthyridin-5[7*H*]-one) **5b**.

The oxidation of the lactam **12b** (500 mg) with iodine (500 mg) in MeOH (150 mL) was carried out in a similar manner as described above yielding angustine **5b** (469 mg, 94%) crystallized from $CHCl_2$/MeOH; softens at 209 °C, m.p. >350 °C (lit.[33] m.p. >300 °C, lit.[2] m.p. 283-284 °C, lit.[3] >340 °C); ^1H nmr (300 MHz), DMSO-d_6, δ: 3.11 (t, *J*=6.7 Hz, 2H), 4.39 (t, *J*=6.7 Hz, 2H), 5.62 (d, *J*=11.2 Hz, 1H), 6.04 (d, *J*=17.5 Hz, 1H), 7.08 (m, *J*=7.8 Hz, 1H), 7.22 (dd, *J*=17.5, 11.2 Hz, 1H), 7.29 (m, 2H), 7.45 (apparent d, *J*=8.1 Hz, 1H), 7.59 (apparent d, *J*=8.0 Hz, 1H), 8.82 (s, 1H), 9.20 (s, 1H), 11.83 (s, exchanges with D_2O, 1H); ms (EI), m/z (%): 313 (100) M^+, 312 (59), 298 (16), 255 (7), 156 (11), 128 (13); Exact mass (hrms): Calcd. for $C_{20}H_{15}N_3O$: 313.1215; Found: 313.1215.

Angustidine. (8,13-Dihydro-2-methylindolo[2′,3′:3,4]pyrido[1,2-*b*][2,7]naphthyridin-5[7*H*]-one). **5c**.

Oxidation of the lactam **12c** (50 mg) with iodine (100 mg) in MeOH (20 mL) by the method described above for the oxidation of **12a** to **5a** gave angustidine **5c** (47 mg, 95%) which was crystallized from MeOH, m.p.

>350 °C (lit.[3] m.p. 309-311 °C, lit.[34] m.p. 300 °C): ^{1}H nmr (300 MHz), DMSO-d_6, δ: 2.70 (s, 3H), 3.19 (t, *J*=6.7 Hz, 2H), 4.43 (t, *J*=6.7 Hz, 2H), 7.12 (m, 2H), 7.32 (m, 1H), 7.48 (apparent d, *J*=8.3 Hz, 1H), 7.67 (apparent d, *J*=8.1 Hz, 1H), 7.74 (s, 1H), 9.27 (s, 1H), 12.13 (s, exchanges with D_2O, 1H); ms (EI), m/z (%): 301 (100) M^+; 300 (100), 299 (42), 285 (20), 269 (6), 230 (8) 151 (11), 115 (12); Exact mass (hrms): Calcd. for $C_{19}H_{15}N_3O$: 301.1216; Found: 301.1218.

(±)-Dihydronaulafine. ((±)-7,12,13,14-Tetrahydrocyclopent[*de*]indolo[2′,3′:3,4]prido-[1,2-*b*][2,7]naphthyridin-4[6*H*]-one). **18**.

The oxidation of the lactam **17** (500 mg, 1.6 mmol) was carried out with iodine (1.0 g, 3.94 mmol) in EtOH (250 mL) by heating under reflux for 48 h. Workup as described previously gave dehydrolactam **18** (448 mg, 89%) which was crystallized from MeOH, m.p. >300 °C; ^{1}H nmr (500 MHz), DMSO-d_6, δ: 3.05 (t, *J*=6.4 Hz, 2H), 3.37 (d, *J*=4.2 Hz, 2H), 3.49 (d, *J*=4.2 Hz, 2H), 4.38 (t, *J*=6.4 Hz, 2H), 7.08 (t, *J*=7.2 Hz, 1H), 7.22 (t, *J*=7.2 Hz, 1H), 7.55 (d, *J*=7.9 Hz, 1H), 7.59 (d, *J*=7.9 Hz, 1H), 8.54 (s, 1H), 8.97 (s, 1H), 10.82 (s, exchanges with D_2O, 1H); ms (EI), m/z (%): 313 (100) M^+, 312 (38), 298 (34); Exact mass (hrms): Calcd. for $C_{20}H_{15}N_3O$: 313.1215; Found: 313.1209; Anal. Calcd. for $C_{20}H_{15}N_3O{\cdot}0.75\ H_2O$: C, 73.49; H, 5.08; N, 12.86; Found: C, 73.47; H, 5.03; N, 12.62.

Naulafine. (7,12-Dihydrocyclopent[*de*]indolo[2′,3′:3,4]pyrido[1,2-*b*][2,7]naphthyridine-4[6*H*]-one.) **7**.

A mixture of dihydronaulafine **18** (50 mg, 0.16 mmol) and 50 mg 20% Pd-C in 5 mL of 1,2,4,-trichlorobenzene was stirred and heated at 200 °C for 15 h. The warm reaction mixture was filtered through Whatman No. 1 filter paper and the residue remaining on the paper was washed with 100 mL of hot 10% MeOH/$CHCl_3$. The combined filtrate and washings were concentrated under reduced pressure and the residue was filtered through a short column of silica gel using 2% MeOH/CH_2Cl_2 as eluant. The residue from the concentrated eluate was subjected to preparative thick layer chromatography. The plates were developed twice, first in 2% MeOH in $CHCl_3$ and then in 3% MeOH in $CHCl_3$. The product band was eluted with hot 10% MeOH/$CHCl_3$. The eluate was concentrated under reduced pressure to give naulafine **7** as a red solid, 20 mg (40%). Dihydronaulafine **18** (20 mg, 40%) was also recovered.

7: m.p. >350 °C (lit.[28] >300 °C); ms (EI), m/z (%): 311 (100) M^+, 310 (85), 296 (11) 281 (9), 280 (9).

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