A Unified Synthetic Strategy for the Indolopyridine Alkaloid Group[1]

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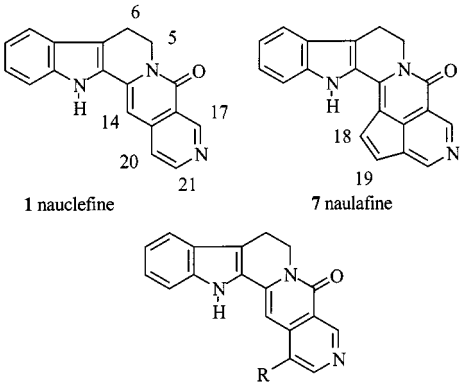
Thermal or acetyl chloride induced cyclization of bromoenamide **10** affords the pentacyclic derivative **12** with high yield and regioselectivity. From this common synthetic intermediate, palladium-catalyzed reactions allow the total synthesis of indolopyridine alkaloids **1**–**6**.

Introduction

The development of general methods in natural product synthesis constitutes a highly pursued goal that enables the preparation of different members of a biogenetic class (as well as non-natural analogues) by using the same methodology. This flexible approach is even more useful when it involves the manipulation of common synthetic intermediates.[2] With this perspective in mind, we envisaged the preparation of indolopyridine alkaloids, a group of natural products belonging to the Vallesiachotaman class of monoterpenoid indole alkaloids, some of them showing interesting biological activities.[3] Nauclefine (**1**),[4] angustine (**2**),[5] naucletine (**4**),[4] angustoline (**5**),[5,6] 19-*O*-methylangustoline (**6**),[7] and naulafine (**7**)[8] may be listed among the most representative alkaloids of this structural type. 18,19-Dihydroangustine (**3**), although it is also a natural product,[3c] was initially described as a synthetic compound prepared in the context of the structural elucidation of angustine[5,9] (Scheme 1).



Scheme 1. Indolopyridine alkaloids

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Extensive studies on the total synthesis of these alkaloids have been reported in the literature.[10] The most classical approaches involve photocyclization of enamides,[11] pyridone functionalizations,[12] naphthyridine formation,[13] nucleophilic additions upon *N*-alkylpyridinium salts,[14] and organometallic additions upon activated imines.[15][16] All the previous syntheses to date require the preparation of specifically substituted nicotinic acid derivatives as the starting materials. The common structural features of the pentacyclic system present in the indolopyridine alkaloids call for a flexible and unified synthetic route. It would be highly desirable to share the benefits of a single intermediate capable of an easy conversion (1−2 steps) into the final products.

Results and Discussion

Considering our recent findings on the nucleophilic addition upon *N*-acylpyridinium salts, in which deacylation and oxidation processes lead to γ-substituted pyridines,[17] and taking into account the feasibility of using 3,5-disubstituted pyridinium salts in irreversible nucleophilic additions,[18,19] we decided to test the intramolecular addition of an enamide upon an *N*-acetyl-3-halo-5-carbonylpyridinium salt to gain rapid access to the target pentacyclic ring system using the previously described condensation of harmalan with 5-halonicotinoyl chloride.[11b] Afterwards, through palladium-catalyzed transformations, the total synthesis of the alkaloids would be completed[20] (Scheme 2).

Commercially available 5-bromonicotinic acid (**8**) was chosen as the starting material; in the cases where more reactive halides were needed, the corresponding iodide **9** (62%)[21] was prepared through the low-temperature lithiation of **8**,[22] followed by iodine quenching. Treatment of the above nicotinic acids with oxalyl chloride afforded the corresponding acid chlorides hydrochlorides, which were condensed with harmalan in the presence of Et_3N to afford enamides **10**[11b] (84%) and **11** (75%), respectively. Acetyl chloride treatment of **10** in CH_2Cl_2 solution regioselectively afforded 20-bromonauclefine **12** (42%),[11b] through a sequence presumably involving the intramolecular nucleophilic addition of the enamide moiety upon the γ-position of the in situ formed *N*-acylpyridinium salt, followed by spontaneous oxidation and hydrolysis of the resulting *N*-

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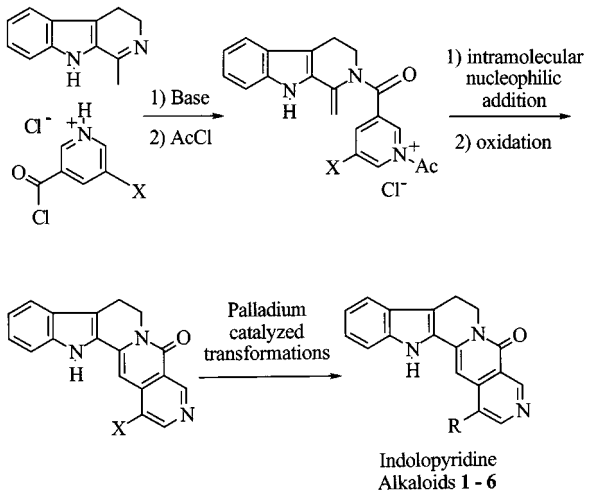
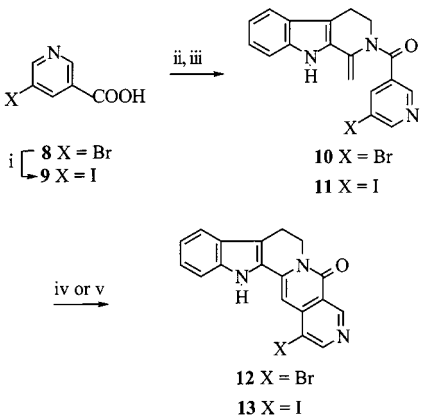


Scheme 2. Synthetic strategy

acetyl-1,4-dihydropyridine.[23] In sharp contrast with the described photocyclization of **10**[11b] (or related substrates), which afforded **12** together with significant amounts of the *wrong* (undesired) regioisomer (bond formation between the enamide terminal carbon atom and the pyridine α-position), this ionic process yields only the bromonauclefine **12**, probably reflecting the tendency of *N*-acylpyridinium salts to undergo mainly γ-addition. Although acid- or TFAA[16a]-promoted cyclizations of **10** failed, further improvement of the yield was achieved by heating this enamide at 180°C under reduced pressure. Under these conditions the process was again regioselective, giving exclusively **12** in 83% yield; in a similar manner, **11** was converted into 20-iodonauclefine (**13**, 20%). These transformations can be rationalized by considering a thermal electrocyclization followed by a 1,5-H shift and spontaneous oxidation of the resulting dihydropyridine derivative.[24] On the other hand, the halogen exchange from **12** to **13** (CuI, HMPA, or *n*BuLi and I_2) resulted in failure (Scheme 3).

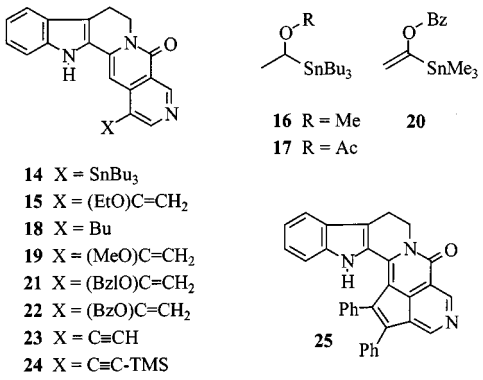


Scheme 3. Reagents, conditions, and yields: (i) *n*BuLi, THF, −100°C, then I_2 (62%); (ii) $(COCl)_2$, benzene, r.t.; (iii) harmalan, Et_3N, CH_2Cl_2, 40°C (**10**, 84%; **11**, 75%); (iv) AcCl, CH_2Cl_2, 40°C (**12**, 42%); (v) 180°C, 0.1 Torr (**12**, 83%; **13**, 20%)

Replacement of the bromine atom in **12** by hydrogen was initially attempted, although without success, by metallation and subsequent protic quenching, and by treatment with tributyltin hydride and AIBN. In sharp contrast, the use of sodium methoxide as a hydrogen donor in a palladium-catalyzed reaction (Helquist method)[25] resulted in the formation of nauclefine (**1**, 96%), identical to the natural product in all aspects.

The preparation of angustine from the common pentacyclic bromo derivative **12** required the introduction of a vinyl group; knowing the reduced reactivity of β-halopyridines (compared with their α- or γ-isomers) in palladium-mediated reactions,[26] we decided to test the transformation on a simplified model compound. The methyl ester of 5-bromonicotinic acid was prepared and, whereas the Heck reaction [ethylene, 200 psi, $Pd(OAc)_2$, Et_3N] proved to be a low-yielding process, the Stille coupling[27] with tributylvinyltin in the presence of palladium(0) was effective,[28] affording methyl 5-vinylnicotinate[29] in 90% yield. As expected, treatment of bromopyridine **12** in toluene − DMF solution with tributylvinyltin in the presence of $Pd(PPh_3)_4$ at 100°C gave angustine (**2**) in 95% yield. A similar process using tetraethyltin in HMPA solution afforded 18,19-dihydroangustine (**3**) in 87% yield.

The introduction of an acetyl group in **12** was planned through the CO insertion into the aryl−Pd intermediate, followed by tetramethyltin coupling.[30] The reaction failed under low pressures of CO, but at 80 psi in the presence of LiCl gave a modest yield of naucletine (**4**, 23%). Looking for a more efficient way to prepare this alkaloid, we studied the palladium-catalyzed coupling of the haloarene **12** to afford an enol ether, which, after hydrolysis, would furnish the methyl ketone **4**. After several attempts to carry out either Heck-type reactions with vinyl acetate and benzyl vinyl ether[31] [HMPA, $Pd(OAc)_2$, Et_3N][32,33] or the palladium-catalyzed coupling of acetyl chloride with stannane **14** (prepared by treatment of **12** with *n*Bu_3SnLi, 20% unoptimized yield),[34] again the Stille coupling of (α-ethoxyvinyl)trimethylstannane[35] with **12** in the presence of $Pd(PPh_3)_4$ was the most efficient method, and yielded the enol ether **15**. Subsequent acid hydrolysis (MeOH, HCl 2 N, room temp.) afforded the alkaloid **4** (48% overall yield) in a slightly improved procedure (Scheme 4).



Scheme 4

Next we attempted a *direct* synthesis of (±)-angustoline (**5**) and (±)-*O*-methylangustoline (**6**) by the coupling of a

properly α-susbstituted alkylstannane.[36] With this aim in mind we prepared the organometallic derivatives **16**[37] (through interaction of nBu$_3$SnLi with α-chloroethyl methyl ether) and **17**[38] (from the reaction of nBu$_3$SnLi with 1-bromoethyl acetate). However, interaction of these stannanes with bromoarene **12** [Pd(PPh$_3$)$_4$, HMPA] resulted in the recovery of the starting material or decomposition. In spite of some recent reports in which α-alkoxy- or α-acetoxy-branched alkyl groups were transferred in Stille or related couplings,[39] these results probably show the reluctance of sterically hindered substituents to undergo the selective group transfer; in fact, in some of these experiments 20-butylnauclefine (**18**, 10%)[40] was isolated. We then turned our attention to sp^2-linked stannanes, and coupling of (α-methoxyvinyl)tributylstannane[41] with **12** under the usual reaction conditions gave enol ether **19** in satisfactory yield (68%). Careful hydrogenation [H$_2$, Pd(OH)$_2$] of the olefin moiety afforded 19-*O*-methylangustoline (**6**, 80%). In contrast, the coupling of bromoarene **12** with the benzoyloxy derivative **20**, which was prepared (27%) by Pd-catalyzed stannylation[42] of the corresponding bromide[43] with hexamethylditin, gave a complex mixture, where small amounts of nauclefine (**1**) and naucletine (**4**) were detected, thus indicating the intermediacy of the expected product **22**. Other methods tested for the synthesis of angustoline (**5**) resulted in failure: Baker's yeast mediated reduction of naucletine (**4**) and metallation of **12** (**13** or **14**, in some cases) [Li or Ni^{II}/Cr^{II}] and acetaldehyde interaction. After these studies, the previously reported NaBH$_4$ reduction of naucletine (**4**) still remains the most convenient way to prepare (±)-angustoline (**5**).[11a]

The first approaches to naulafine (**7**) involved the functionalization of C-14 in bromoarene **12**. However, attempted formylation (DMF−POCl$_3$; dichlorocarbene addition followed by hydrolysis) or halogenation (NIS; LiI or HCl−CAN) resulted in the recovery of the starting material, showing the difficulty of introducing substituents at this sterically hindered position. On the other hand, Pd(OAc)$_2$ oxidation of angustine (**2**) did not afford **7** under any condition tested.[44] Palladium-catalyzed cascade processes involving the interaction of **12** or **13** with alkynes[45] were studied next; on reaction with **13**, bis(trimethylsilyl)acetylene [Pd(OAc)$_2$, PPh$_3$, DEA, HMPA afforded a small amount (26%) of ethynylnauclefine (**23**) or its protected derivative **24** (using DMF as the solvent; 21%); on the other hand DMAD gave complex mixtures. Finally, the expected annelation took place with diphenylacetylene in the presence of Pd(OAc)$_2$, PPh$_3$, and Tl(OAc),[46] to afford the desired hexacyclic compound **25** (16%).[47] The unusual structural features of **25** are reflected in the shielding of the 1- and 7-indole protons in the ^{1}H-NMR spectra (δ = 8.09 and 6.61, respectively), suggesting a close interaction with the nearby phenyl ring (assignments based on COSY and NOESY spectra). Although much work is needed to accomplish the total synthesis of naulafine, the preparation of the 18,19-diphenyl derivative (**25**) opens interesting perspectives in this respect.

In conclusion, a unified synthetic entry for the indolopyridine alkaloid group has been developed, allowing the total synthesis of the pentacyclic natural products to be carried out using the same intermediate. The key reactions are the intramolecular nucleophilic addition upon an *N*-acetyl-3,5-disubstituted pyridinium salt or the thermal cyclization of an enamide to furnish the bromonaphthyridine derivative **12**, and the subsequent transformation of this common intermediate into the alkaloids **1**−**6** by palladium-mediated processes.

Experimental Section

General: All solvents were dried by standard methods. All reagents were of commercial quality from freshly opened containers. All reactions were conducted under dry N_2. Prior to concentration under reduced pressure, all organic extracts were dried with anhydrous Na_2SO_4 powder. − Melting points were taken using a Büchi apparatus and are uncorrected. − Microanalyses were performed with a Carlo Erba 1106 analyzer by Centro de Investigación y Desarrollo (CSIC), Barcelona. − NMR: Varian Gemini-200 (200 and 50.3 MHz, for ^{1}H and ^{13}C, respectively), Varian Gemini-300 (300 and 75.4 MHz), Varian VXR 500 (500 and 125.6 MHz). For ^{1}H NMR, $CDCl_3$ as solvent, TMS as an internal reference, [D$_6$]DMSO as solvent, δ_H = 2.50; for ^{13}C, $CDCl_3$ as solvent, δ_C = 77:0, [D$_6$]DMSO as solvent, δ_C = 39.5. − IR: Perkin Elmer 1600 series FTIR. − UV: Hitachi U-2000 apparatus in MeOH solution. − MS: Hewlett-Packard 5989A (70 eV, low resolution) and Autospec-EQ (high resolution).

5-Iodonicotinic Acid (9): To a solution of 1.0 g (4.95 mmol) of 5-bromonicotinic acid (**8**) in 50 mL of THF, kept at −100°C, was added 6.4 mL (10.25 mmol) of butyllithium (1.6 M in hexanes), and the mixture was stirred for 15 min. A solution of iodine (2.70 g, 10.63 mmol) in 60 mL of THF was added, and the resulting mixture was stirred at room tempearture for 12 h. The solvent was removed under reduced pressure, and an aqueous solution of sodium thiosulfate (150 mL, 0.1 M) was added; to the resulting solution, aqueous HCl (2 M) was added until pH = 2, and the precipitate formed was filtered and dried in a dessicator to furnish carboxylic acid **9** (760 mg, 62%), which was used in the next step without further purification. − IR (KBr): $\tilde{\nu}$ = 1729 (C=O). − ^{1}H NMR ([D$_6$]DMSO): δ = 8.53 (t, J = 1.8 Hz, 1 H), 9.02 (m, 2 H), 15.5 (br. s, 1 H).

Bromoenamide 10: To a solution of 337 mg (1.67 mmol) of 5-bromonicotinic acid (**8**) in anhydrous CH_2Cl_2 (50 mL), kept at 0°C, 5 drops of DMF and 0.5 mL (5.73 mmol) of oxalyl chloride were added, and the resulting mixture was stirred for 1 h at this temperature and another 30 min at room temperature. The volatiles were removed under reduced pressure, the residue was taken up in CH_2Cl_2 (50 mL), Et_3N (15 mL) was added, and the mixture was stirred at room temperature for 1 h. A solution of harmalane (307 mg, 1.67 mmol) in CH_2Cl_2 (50 mL) was added, and the resulting mixture was heated under reflux for 2 h. The solvent was removed under reduced pressure, and the residue was chromatographed on neutral alumina (hexanes/ethyl acetate, 4:1) to afford enamide **10** (516 mg, 84%). M.p. 167−169°C (reported[11b] 158°C). The spectroscopic data found are in good agreement with the reported data.[11b]

Iodoenamide 11: Following the above procedure, from 5-iodonicotinic acid (**9**) (100 mg, 0.40 mmol) and harmalane (74 mg, 0.40 mmol), and after the same chromatographic purification, iodoena-

mide **11** (125 mg, 75%) was obtained. − IR (film): $\tilde{\nu}$ = 3200 (NH), 1630 (C=O). − UV (MeOH): λ_{max} (lg ε) = 305 nm (4.20). − ^{1}H NMR ($CDCl_3$): δ = 3.04 (t, *J* = 5.8 Hz, 2 H), 4, 25 (t, *J* = 5.8 Hz, 2 H), 4.38 (s, 1 H), 5.08 (s, 1 H), 7.15−7.35 (m, 3 H), 7.55 (d, *J* = 7.8 Hz, 1 H), 8.18 (t, *J* = 1.7 Hz, 1H), 8,56 (br. s, 2 H), 8.83 (d, *J* = 1.7 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 22.0 (t), 44.6 (t), 92.7 (s), 103.5 (t), 111.3 (d), 113.6 (s), 119.3 (d), 120.3 (d), 124.2 (d), 126.6 (s), 128.7 (s), 133.6 (s), 137.2 (s), 137.4 (s), 143.8 (d), 147.1 (d), 156.6 (d), 161.1 (s). − MS (70 eV); *m/z* (%): 415 (26) [M^+], 414 (25) [M^+ − H], 387 (68), 386 (100). − $C_{18}H_{14}IN_3O$: calcd. for [M^+] 415.0182; found 415.0186.

20-Bromonauclefine (12): a) To a solution of 100 mg (0.27 mmol) of bromoenamide **10** and 2 mL of Et_3N in CH_2Cl_2 (20 mL), kept at 0°C, 30 μL (0.41 mmol) of acetyl chloride was added, and the resulting mixture was stirred for 1 h at this temperature and 2 h at reflux temperature. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (hexanes/ethyl acetate, 7:3), to furnish bromonauclefine **12** (42 mg, 42%). − b) 100 mg (0.27 mmol) of bromoenamide **10** was heated at 190°C under a reduced pressure of 0.05 Torr for 20 min. After the purification, bromonauclefine **12** (83 mg, 83%) was isolated. The material isolated in both procedures showed the same physical and spectroscopic data as reported in the literature.[11b] − ^{13}C NMR ([D_6]DMSO): δ = 19.2 (t), 40.8 (t), 95.4 (d), 112.2 (d), 115.8 (s), 116.9 (s), 120.0 (d), 120.1 (d), 120.6 (s), 124.9 (d), 125.3 (s), 127.4 (s), 138.7 (s), 138.9 (s), 141.1 (s), 149.6 (d), 152.3 (d), 160.5 (s).

20-Iodonauclefine (13): Following the above procedure (b), from iodoenamide **11** (100 mg, 0.24 mmol), and after the same chromatographic purification, iodonauclefine **13** (20 mg, 20%) was isolated. M.p. > 350°C. − IR (KBr): $\tilde{\nu}$ = 3200 (NH), 1590 (C=O). UV (MeOH): λ_{max} (lg ε) = 384 nm (4.06), 402 nm (4.10). − ^{1}H NMR ([D_6]DMSO): δ = 3.12 (t, *J* = 6.2 Hz, 2 H), 4.39 (t, *J* = 6.2 Hz, 2 H), 6.99 (s, 1 H), 7.10 (t, *J* = 7. 3 Hz, 1 H), 7.28 (t, *J* = 7.3 Hz, 1 H), 7.47 (d, *J* = 7.3 Hz, 1 H), 7.63 (d, *J* = 7.3 Hz, 1 H), 9.02 (s, 1 H), 9.20 (s, 1 H), 12.11 (s, 1 H). − ^{13}C NMR ([D_6]DMSO): δ = 19.2 (t), 40.8 (t), 94.4 (s), 100.2 (d), 112.2 (d), 115.8 (s), 119.9 (d), 120.1 (d), 120.3 (s), 124.9 (d), 125.4 (s), 127.4 (s), 136.6 (s), 138.9 (s), 144.0 (s), 150.1 (d), 158.4 (d), 160.7 (s). − MS (70 eV); *m/z* (%): 413 (100) [M^+], 286 (20) [M^+ − I]. − $C_{18}H_{12}IN_3O$ (413.2): calcd. C 52.30, H 2.90, N 10.17; found C 52.12, H 3.01, N 9.95.

Nauclefine (1): To solution of sodium methoxide (10.5 mg, 0.19 mmol) and $(PPh_3)_4Pd$ (1.1 mg, 0.9 μmol) in DMF (5 mL), kept at room temperature, 5 mg (14 μmol) of bromonauclefine **12** was added, and the mixture was stirred at 100°C for 5 h. 1 mg of the palladium catalyst was added, and stirring was continued for 1 h; water (50 mL) was added, and the mixture was extracted with ethyl acetate (5 × 25 mL). The organic extracts were washed with water (25 mL) and brine (25 mL), dried, filtered, and concentrated under reduced pressure to give a residue wich was chromatographed on silica gel (ethyl acetate) to afford pure nauclefine (**1**, 3.8 mg, 96%) identical in all aspects (TLC and spectroscopical data) with an authentic sample.[3c,4a]

Angustine (2): To a suspension of bromonauclefine **12** (20 mg, 54 μmol) in a mixture of toluene (3 mL) and DMF (2 mL); tributyl(vinyl)tin (26 mg, 82 μmol) and $(PPh_3)_4Pd$ (3 mg, 2.6 μmol) were added, and the mixture was stirrred at 90°C for 7 h. Additional amounts of tributyl(vinyl)tin (17 mg, 54 μmol) and $(PPh_3)_4Pd$ (1.8 mg, 1.6 μmol) were added, and stirring at 90°C was continued for 12 h. The solution was cooled to room temperature and an aqueous saturated NH_4Cl solution (20 mL) was added. The mixture was extracted with ethyl acetate (5 × 20 mL), the organic phases were dried, filtered, and concentrated under reduced pressure to give a residue wich was chromatographed on silica gel (hexanes/ethyl acetate/triethylamine, 60:30:5) to afford pure angustine (**2**, 16 mg, 95%) identical in all aspects (TLC and spectroscopical data) with an authentic sample.[3c]

18,19-Dihydroangustine (3): To a solution of bromonauclefine **12** (15 mg, 41 μmol) in anhydrous HMPA (5 mL), tetraethyltin (150 mg, 640 μmol) and $(PPh_3)_4Pd$ (0.5 mg, 0.4 μmol) were added, and the mixture was stirrred at 65°C for 7 h. Additional amounts of tetraethyltin (75 mg, 320 μmol) and $(PPh_3)_4Pd$ (0.5 mg, 0.4 μmol) were added, and stirring at 65°C was continued for 12 h. The solution was cooled to room temperature and an aqueous saturated NH_4Cl solution (20 mL) was added. The mixture was extracted with ethyl acetate (5 × 20 mL), the organic phases were washed with water (5 × 10 mL), and with an aqueous saturated KF solution (30 mL), dried, filtered, and concentrated under reduced pressure to give a residue wich was chromatographed on silica gel (ethyl acetate) to afford pure 18,19-dihydroangustine **3** (11.2 mg, 87%) which showed the same spectroscopical data than the natural product.[3c]

Naucletine (4): a) A solution of bromonauclefine **12** (100 mg, 270 μmol), LiCl (200 mg, 4.7 mmol), tetramethyltin (250 mg, 1.4 mmol) and $(PPh_3)_4Pd$ (60 mg, 52 μmol) in anhydrous HMPA (15 mL) was placed in a stainless steel autoclave. Carbon monoxide was introduced at 80 psi, and the mixture was stirred at 80°C for 72 h. The solution was cooled to room temperature and an aqueous saturated NH_4Cl solution (50 mL) was added. The mixture was extracted with ethyl acetate (5 × 20 mL), the organic phases were washed with water (5 × 10 mL), dried, filtered, and concentrated under reduced pressure to give a residue wich was chromatographed on silica gel (hexanes/ethyl acetate/triethylamine, 38:60:2) to afford pure naucletine (**4**, 21 mg, 23%). − b) A solution of bromonauclefine **12** (115 mg, 310 μmol), tributyl(1-ethoxyvinyl)tin (360 mg, 1 mmol), and $(PPh_3)_4Pd$ (60 mg, 52 μmol) in anhydrous HMPA (15 mL) was stirred at 90°C for 36 h. The solution was cooled to room temperature and an aqueous saturated NH_4Cl solution (50 mL) was added. The mixture was extracted with ethyl acetate (5 × 20 mL), the organic phases were washed with water (5 × 10 mL), dried, filtered, and concentrated under reduced pressure to give a residue wich was disolved in a mixture of methanol (20 mL) and an aqueous solution of HCl (2 M, 75 mL). The resulting solution was stirred at room temperature for 36 h; basified with solid Na_2CO_3 and extracted with ethyl acetate (5 × 20 mL), the organic phases were washed with water (5 × 10 mL), dried, filtered, and concentrated under reduced pressure to give a residue, which was chromatographed on silica gel to afford pure naucletine (**4**, 49 mg, 48%). The isolated material shows spectroscopic properties in good agreement with the reported data[4] and was identical (TLC comparison) with an authentic sample.

(±)-19-*O*-Methylangustoline (6): A solution of bromonauclefine **12** (50 mg, 140 μmol), tributyl(1-methoxyvinyl)tin (190 mg, 550 μmol) and $(PPh_3)_4Pd$ (15mg, 13 μmol) in anhydrous HMPA (10 mL) was stirred at 70°C for 72 h. The solution was cooled to room temperature and water (50 mL) was added. The mixture was extracted with ethyl acetate (5 × 20 mL), the organic phases were washed with water (5 × 10 mL), dried, filtered and concentrated under reduced pressure to give a residue, which was chromatographed on neutral alumina (hexanes/ethyl acetate/triethylamine, 50:45:5) to afford the enol ether **19** (32 mg, 68%). − ^{1}H NMR ([D_6]DMSO): δ = 3.05 (t, *J* = 6.8 Hz, 2 H), 3.88 (s, 3 H), 4.40 (t, *J* = 6.8 Hz, 2 H), 4.44 (d, *J* = 1.2 Hz, 1 H), 4.70 (d, *J* = 1.2 Hz, 1 H), 7.12 (m, 2 H), 7.25 (t, *J* = 7.3 Hz, 1 H), 7.47 (d, *J* = 7.3 Hz, 1 H), 7.65 (d, *J* = 7.6 Hz, 1 H), 8.60 (s, 1 H), 9.25 (s, 1 H), 11.6 (s, 1 H). − A suspension

of enol ether **19** (30 mg, 87 μmol) and $Pd(OH)_2$ (36 mg, 257 μmol) in ethyl acetate (10 mL) was hydrogenated at atmospheric pressure for 9 h. After filtration of the catalyst, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel (hexanes/ethyl acetate/triethylamine, 70:25:5) to afford (±)-19-*O*-methylangustoline (**6**, 24 mg, 80%), whose spectroscopical properties were in good agreement with the data reported in the literature.[7b]

Stannane 14: Obtained in 20% yield by the interaction of bromonauclefine **12** with tributylstannyllithium in a mixture of THF/HMPA at room temperature for 12 h. − ^{1}H NMR ([D$_6$]DMSO): δ = 0.81 (t, *J* = 7.2 Hz, 9 H), 1.2−1.5 (m, 18 H), 3.06 (t, *J* = 6.4 Hz, 2 H), 4.40 (t, *J* = 6.4 Hz, 2 H), 6.60 (s, 1 H), 7.10 (t, *J* = 7.2 Hz, 1 H), 7.28 (t, *J* = 7.8 Hz, 1 H), 7.53 (d, *J* = 7.8 Hz, 1 H), 7.63 (d, *J* = 7.2 Hz, 1 H), 8.56 (s, 1 H), 9.26 (s, 1 H), 11.71 (s, 1 H). − MS (70 eV); *m/z* (%): 577 and 575 (2) [M^+], 520 (8) [M^+ − Bu], 406 (100) [M^+ − 3 Bu], 286 (52) [M^+ − Sn(Bu)$_3$].

20-Butylnauclefine (18): Isolated in 11% yield in the $(PPh_3)_4Pd$-catalyzed reaction of stannane **17** with bromonauclefine **12** in HMPA solution at 90°C. − ^{1}H NMR ([D$_6$]DMSO): δ = 0.94 (t, *J* = 7.0 Hz, 3 H), 1.40 (m, 2 H), 1.66 (m, 2 H), 2.93 (t, *J* = 7.3 Hz, 2 H), 3.12 (t, *J* = 6.5 Hz, 2 H), 4.40 (t, *J* = 6.5 Hz, 2 H), 7.08 (t, *J* = 7.2 Hz, 1 H), 7.18 (s, 1 H), 7.25 (t, *J* = 7.8 Hz, 1 H), 7.49 (d, *J* = 7.8 Hz, 1 H), 7.62 (d, *J* = 7.2 Hz, 1 H), 8.52 (s, 1 H), 9.20 (s, 1 H), 11.71 (s, 1 H). − MS (70 eV); *m/z* (%): 343 (100) [M^+], 328 (11) [M^+ − CH_3], 314 (12) [M^+ − C_2H_5], 300 (77) [M^+ − C_3H_7].

Stannane 20: Prepared (27%) by the interaction of 1-bromovinyl benzoate, hexamethylditin, PPh_3, and $Pd_2(dba)_3$ in DMF. − IR (NaCl): $\tilde{\nu}$ = 1711 cm^{-1} (C=O). − ^{1}H NMR ($CDCl_3$): δ = 0.26 (s, 9 H), 4.89 (d, *J* = 0.7 Hz, 1 H), 5.65 (d, *J* = 0.7 Hz, 1 H), 7.47 (m, *J* = 7.3 and 8.2 Hz, 2 H), 7.59 (t, *J* = 7.3 Hz, 1 H), 8.10 (d, *J* = 8.2 Hz, 2 H). − ^{13}C NMR ($CDCl_3$): δ = −6.8 (q), 111.4 (t), 128.4 (d), 129.3 (s), 129.8 (d), 133.3 (d), 163.4 (s), 165.9 (s).

19-Benzyloxyangustine (21): Obtained in 40% yield by reaction of iodonauclefine **13**, benzyl vinyl ether, Et_3N, and $Pd(OAc)_2$ in HMPA at 70°C for 12 h. − IR (NaCl): $\tilde{\nu}$ = 3400 (NH), 1695 cm^{-1} (C=O). − ^{1}H NMR ($CDCl_3$): δ = 3.07 (t, *J* = 6.7 Hz, 2 H), 4.48 (d, *J* = 6.7 Hz, 2 H), 4.63 (d, *J* = 0.7 Hz, 1 H), 4.71(d, *J* = 0.7 Hz, 1 H), 5.09 (s, 2 H), 6.90 (s, 1 H), 7.10−7.60 (m, 9 H), 7.90 (br. s, 1 H), 8.77 (s, 1 H), 9.57 (s, 1 H). − MS (70 eV); *m/z* (%): 421 (2) [M^+], 419 (8) [M^+ − H_2], 328 (44) [M^+ − C_7H_7].

20-Ethynylnauclefine (23): Obtained (13%) by reaction of iodonauclefine **13** and bis(trimethylsilyl)acetylene in the presence of PPh_3, Et_2NH, and $Pd(OAc)_2$, in HMPA solution at 70°C. − ^{1}H NMR ([D$_6$] DMSO): δ = 3.13 (t, *J* = 6.4 Hz, 2 H), 3.20 (s, 1 H), 4.39 (t, *J* = 6.4 Hz, 2 H), 7.09 (m, *J* = 6.9 Hz, 1 H), 7.21 (s, 1 H), 7.27 (m, *J* = 7.8 Hz, 1 H), 7.46 (d, *J* = 6.9 Hz, 1 H), 7.62 (d, *J* = 7.8 Hz, 1 H), 8.79 (s, 1 H), 9.25 (s, 1 H), 12.07 (s, 1 H).

20-Trimethylsilylethynylnauclefine (24): Operating as above, but in DMF solution, at 110°C, silyl derivative **24** (21%) was obtained. − ^{1}H NMR ([D$_6$]DMSO): δ = 0.14 (s, 9 H), 3.12 (t, *J* = 6.5 Hz, 2 H), 4.37 (t, *J* = 6.5 Hz, 2 H), 7.03 (s, 1 H), 7.10 (m, *J* = 7.3 Hz, 1 H), 7.21 (m, *J* = 7.7 Hz, 1 H), 7.40 (d, *J* = 7.3 Hz, 1 H), 7.59 (d, *J* = 7.9 Hz, 1 H), 8.65 (s, 1 H), 9.17 (s, 1 H), 11.60 (s, 1 H). − ^{13}C NMR ([D$_6$]DMSO): δ = 0.2 (q), 19.3 (t), 40.7 (t), 79.8 (s), 95.1 (d), 99.7 (q), 104.2 (s), 112.3 (d), 114.7 (s), 120.0 (d), 120.2 (d), 125.0 (d), 126.0 (s), 128.4 (s), 130.0 (s), 138.3 (s), 139.2 (s), 142.1 (s), 150.0 (d), 154.5 (d), 160.6 (s). − MS (70 eV); *m/z* (%): 383 (100) [M^+], 368 (38) [M^+ − CH_3], 310 (17) [M^+ − SiC_3H_9].

18,19-Diphenylnaulafine (25): A solution of iodonauclefine **13** (10 mg, 24 μmol), diphenylacetylene (4 mg, 24 μmol), PPh_3 (2.5mg, 9 μmol), $Pd(OAc)_2$ (1.5 mg, 7 μmol), and TlOAc (13 mg, 49 μmol) in anhydrous DMF (5 mL) was stirred at 90°C for 12 h and at 120°C for 4 h. The solution was cooled to room temperature and brine (25 mL) was added. The mixture was extracted with ethyl acetate (5 × 15 mL), the organic phases were washed with water (5 × 10 mL), dried, filtered and concentrated under reduced pressure to give a residue, which was chromatographed on neutral alumina (hexanes/ethyl acetate, 1:1) to afford diphenylnaulafine **25** (1.8 mg, 16%). − IR (KBr): $\tilde{\nu}$ = 3133 (NH), 1634 (C=O). − UV (MeOH): λ_{max} (lg ε) = 383 nm (4.59), 400 (4.62). − ^{1}H NMR ([D$_6$]DMSO + D_2O): δ = 3.17 (t, *J* = 6.2 Hz, 2 H), 4, 20 (t, *J* = 6.2 Hz, 2 H), 6.61 (d, *J* = 8.2 Hz, 1 H), 7.04 (m, *J* = 7.2 Hz and 8.2 Hz, 1 H), 7.16 (t, *J* = 8.2 Hz, 1 H), 7.34 (m, 10 H), 7.63 (d, *J* = 7.2 Hz, 1 H), 8.09 (s, 1 H), 8.82 (s, 1 H), 9.17 (s, 1 H). − MS (70 eV); *m/z* (%): 463 (100) [M^+], 386 (23) [M^+ − Ph]. − $C_{32}H_{21}N_3O$: calcd. for [M^+] 463.1685; found 463.1693.

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