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Total syntheses of the *Strychnos* indole alkaloids (−)-tubifoline, (−)-tubifolidine, and (−)-19,20-dihydroakuammicine

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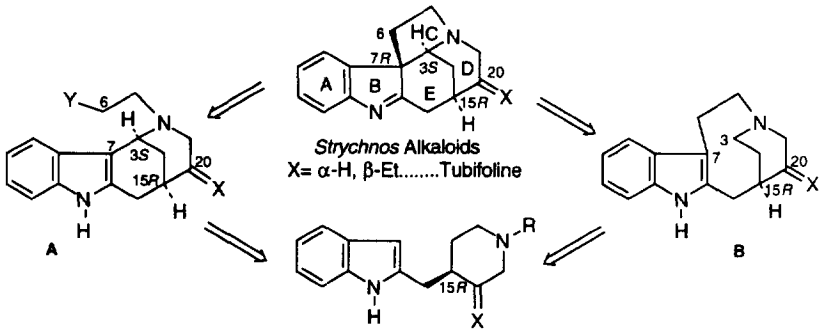
Abstract: Two different strategies for the synthesis of pentacyclic *Strychnos* alkaloids in enantiomerically pure form are explored. Both of them involve the use of enantiopure 2-(4-piperidylmethyl)indoles prepared by kinetic resolution of 1-(3-pyridyl)ethanol, followed by partial reduction of the pyridine ring to the tetrahydropyridine level, Claisen rearrangement of the resulting allylic alcohol, and finally Smith indolization. Whereas 2-(4-piperidylmethyl)indole **6** could not be converted to tetracyclic ABDE substructures of *Strychnos* alkaloids, photocyclization of chloroacetamide **14**, derived from (piperidylmethyl)indole **13**, satisfactorily afforded the stemmadenine-type tetracycle **15**, which was then converted to the alkaloids (−)-tubifoline, (−)-tubifolidine, and (−)-19,20-dihydroakuammicine.

In recent years there has been a considerable interest in the synthesis of *Strychnos* indole alkaloids, resulting in numerous total syntheses of alkaloids of this group in racemic form.[1] However, the enantioselective synthesis of *Strychnos* alkaloids has been little explored: apart from a few enantiopure intermediates[2] and models,[3] at the beginning of our studies[4] Wieland–Gumlich aldehyde, (−)-strychnine, *ent*-strychnine,[5] and *ent*-tubotaiwine[1a] were the only *Strychnos* alkaloids to have been synthesized in enantiomerically pure form.[6] Very recently, the synthesis of (−)-mossambine and *ent*-mossambine by resolution of an advanced racemic intermediate has been reported.[1f]

An inspection of the pentacyclic ABCDE structure of *Strychnos* alkaloids reveals that the stereogenic carbons common to two or more rings are configurationally correlated and that their relative configurations can be unambiguously attained starting from a suitable 2-(4-piperidylmethyl)indole, following the synthetic strategies outlined in Scheme 1.



Scheme 1.

In fact, as a consequence of the bridgehead character of C-3 and C-15[7] in the tetracyclic 6,7-seco intermediate **A**, the configuration of C-15 would determine that of C-3 and afterwards that of the quaternary C-7 centre in the closure of the five-membered C ring.[8] Similarly, the

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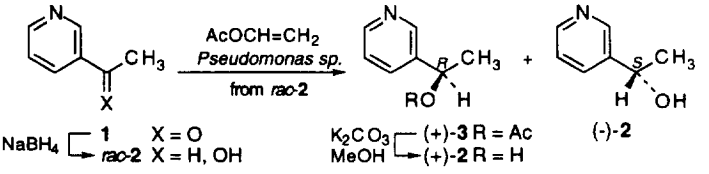
configuration of C-15 in the 3,7-seco intermediate **B** would determine those of C-3 and C-7 in the transannular cyclization leading to the pentacyclic *Strychnos* skeleton.[9] Consequently, enantiopure 2-(4-piperidylmethyl)indoles seem to be *a priori* promising intermediates for the enantioselective synthesis of *Strychnos* alkaloids.

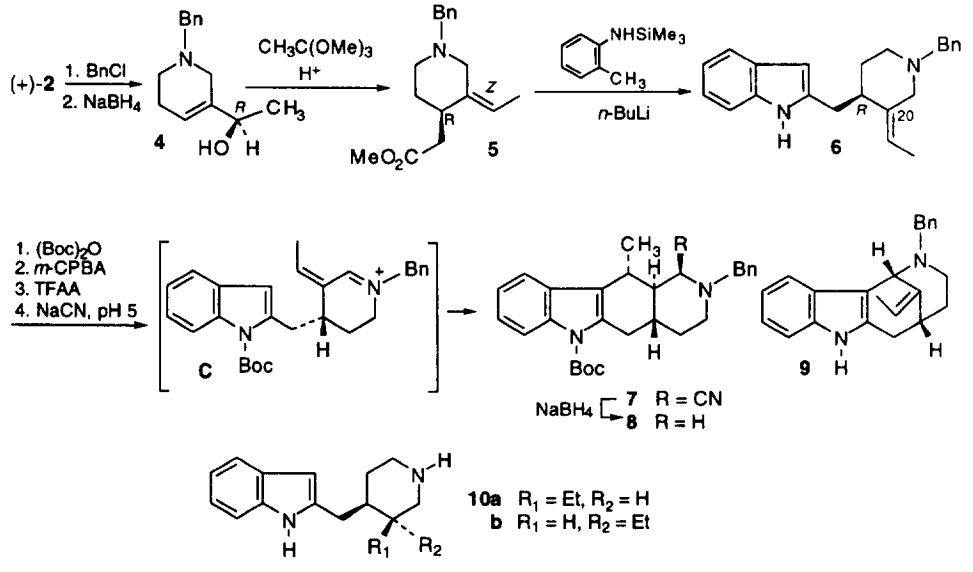
We present here our work in the above context. For the preparation of enantiopure 2-(4-piperidylmethyl)indoles we envisaged a route involving as the key steps i) the kinetic resolution of racemic 1-(3-pyridyl)ethanol (*rac*-**2**), ii) the orthoester Claisen rearrangement[10] of a homochiral tetrahydropyridine-derived allylic alcohol following the methodology developed by Uskokovic[11] to prepare enantiopure 3(*Z*)-ethylidene-4-piperidineacetates by transfer of chirality from the tetrahydropyridine side chain to the piperidine 4-position, and iii) a Smith indolization[12] taking advantage of the resulting ester function.

The required enantiopure (1*R*)-(3-pyridyl)ethanol (+)-**2** was prepared in 45% chemical yield and 96% e.e. by enzymatic esterification of the racemic alcohol *rac*-**2** with vinyl acetate promoted by lipase PS (Amano, *Pseudomonas sp.*), followed by methanolysis of the resulting acetate (+)-**3**[13] (Scheme 2).



Scheme 2.

The unreacted *S* alcohol (−)-**2** was recovered in 47% yield.[14] Treatment of the pyridine derivative (+)-**2** with benzyl chloride followed by $NaBH_4$ reduction afforded the allylic tetrahydropyridine alcohol **4**,[11] which was stereoselectively converted to the 3(*Z*)-ethylidene-4(*R*)-piperidineacetate **5** by refluxing in DME in the presence of methyl orthoacetate and a catalytic amount of pivalic acid[15] (Scheme 3). Both the *R* configuration at the piperidine 4-position, which is the same as at C-15 in *Strychnos* alkaloids, and the *Z* configuration of the ethylidene double bond[16] result from the most stable chair-like transition state in this sigmatropic rearrangement.



Scheme 3.

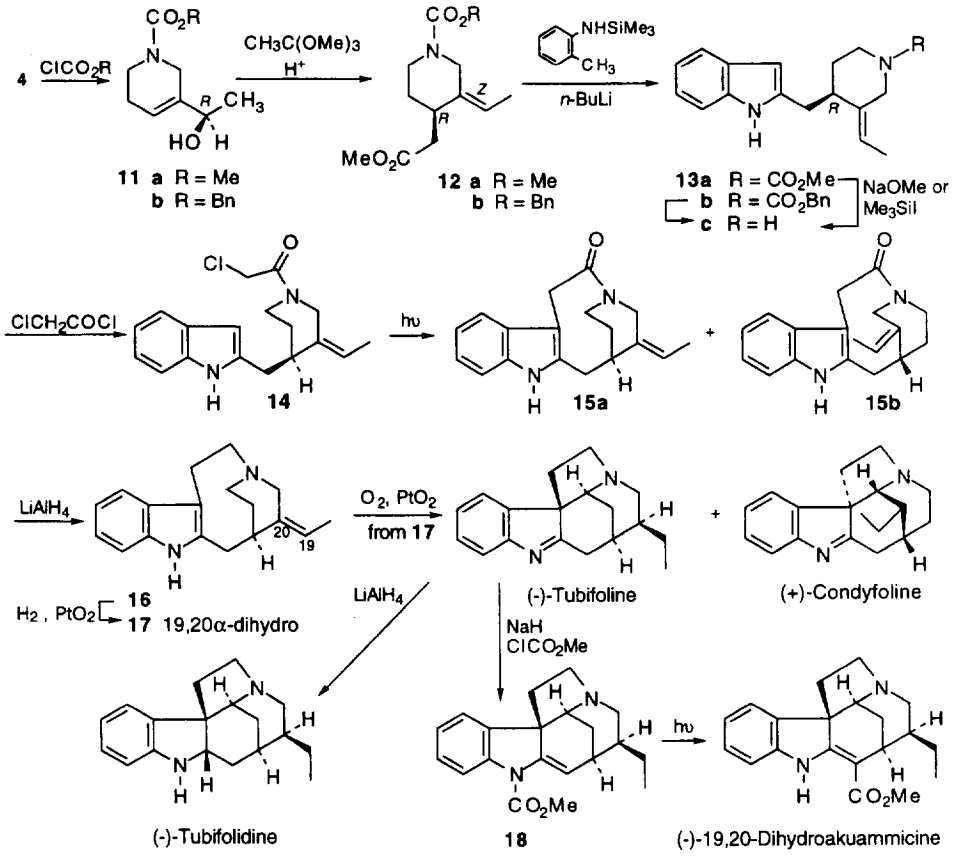
Indolization of ester **5** by treatment with the organodilithium reagent derived from *N*-trimethylsilyl-*o*-toluidine[12] led to (piperidylmethyl)indole **6** in 69% yield. For the closure of the carbocyclic E ring we had planned to follow the methodology we had successfully used in the racemic series from a dihydro derivative of **6**,[8] consisting in the cyclization of an iminium ion generated from a 2-cyanopiperidine, which in turn would be prepared by oxidative cyanation of the piperidine ring by way of the corresponding *N*-oxide.[17] For this purpose, the indole ring of **6** was first protected as a N_a-Boc derivative using the phase-transfer technique[18] and then sequentially treated with *m*-CPBA, TFAA, and NaCN. However, the tetracyclic α-amino nitrile **7** was obtained in 50% yield as the only isolable product. Neither the 2-cyanopiperidine resulting from the trapping of the intermediate iminium ion **C** by cyanide nor the Aspidospermatan-type tetracycle **9** that would derive from a 1,2-addition of the indole ring were detected. Formation of **7** can be rationalized by considering that the initially formed conjugated iminium ion **C** undergoes cyclization by 1,4-addition of the indole ring[19] to give an enamine in equilibrium with the corresponding iminium ion, which is then trapped by cyanide ions. The structure of **7** was confirmed by $NaBH_4$ reduction to the octahydropyridocarbazole **8**. To avoid the above undesirable cyclization it was therefore necessary to reduce the ethylidene double bond. However, as could be expected, the catalytic hydrogenation of **6**, using either $Pd(OH)_2$ or 10% Pd/C as the catalyst, was not stereoselective and took place with simultaneous debenzylation to give a mixture of secondary amines **10**. The *cis*-isomer **10a**, with the natural relative stereochemistry, was the minor product.[20]

The above unsuccessful result prompted us to develop the alternative strategy outlined in Scheme 1, *via* a tetracyclic 3,7-seco derivative **B**. For the closure of the nine-membered ring we selected the photocyclization of chloroacetamide **14**, a procedure that has been successfully used in related ring closures.[21]

The required enantiopure chloroacetamide was prepared from the allylic alcohol **4**, as depicted in Scheme 4.

The *N*-benzyl substituent was initially removed using methyl chloroformate.[22] Claisen rearrangement from the resulting carbamate **11a**[11] followed by elaboration of the indole ring, as in the above *N*-benzyl series, led to (piperidylmethyl)indole **13a** (40% yield from **11a**). A higher overall yield (~55%) in this two-step sequence was obtained from the *N*-benzyloxycarbonyl derivative **11b**. Deprotection of the piperidine nitrogen of either **13a** or **13b** with iodotrimethylsilane[23] (77% yield) followed by treatment of the resulting *N*-unsubstituted piperidine **13c** with chloroacetyl chloride in a CH_2Cl_2/aqueous NaOH two-phase system gave chloroacetamide **14** (90% yield) as a mixture of rotamers due to the restricted rotation of the amide group.[24] Photocyclization of **14** took place in 45% yield upon irradiation with a medium-pressure mercury lamp to give the expected tetracyclic lactam **15** along with variable amounts (approximate ratio 3:1) of the *E*-ethylidene isomer coming from the photoisomerization of the carbon–carbon double bond.[25] The NMR spectra of both **15** and its *E* isomer showed duplicate signals, thus indicating the existence of two rotamers (**a** and **b**) with a high energy barrier to interconversion as no coalescense into single peaks was observed on raising the temperature to 100°C. Although the major *Z*-ethylidene lactam **15a,b** could be obtained in pure form and then subjected to $LiAlH_4$ reduction to give pure tetracyclic amine **16**, from the synthetic standpoint it was more convenient to use the mixture of *Z/E* lactams and then to hydrogenate the resulting *Z/E* mixture of unsaturated tetracyclic amines.

As expected, catalytic hydrogenation of **16** (or a mixture of **16** and its *E* isomer) using either 10% Pd–C or PtO_2 as the catalyst took place stereoselectively, with uptake of hydrogen from the most accessible face of the exocyclic double bond, to give the known tetracyclic amine **17**,[26] bearing a β-ethyl substituent at C-20, *i.e.* possessing the natural configuration at this point. However, rather surprisingly, the alkaloid (−)-tubifoline was also isolated from the reaction mixture.[27] The ratio amine **17**/(−)-tubifoline was variable (54% and 20% yield, respectively, in the run reported in the Experimental section), although when operating on a lower scale (−)-tubifoline was formed as the



Scheme 4.

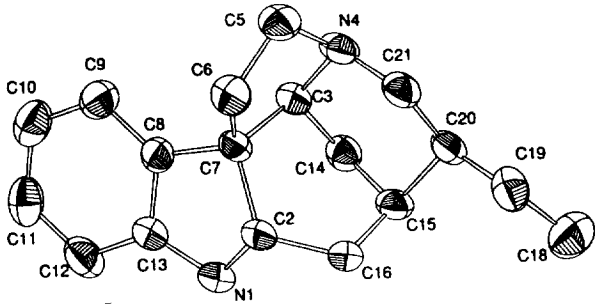


Figure 1.

major or even the exclusive product. (+)-Condyfoline was also isolated as a minor product in some runs.

Finally, treatment of the tetracyclic amine **17** with oxygen in the presence of platinum, following the procedure previously reported,[28] afforded (−)-tubifoline[29] in 55% yield. Minor amounts (<5%) of (+)-condyfoline[28] were also isolated. $LiAlH_4$ reduction[26c] of (−)-tubifoline gave (−)-tubifolidine,[29] whose crystal structure[30] determined by X-ray analysis is given in Figure 1.[31]

The synthesis of *Strychnos* alkaloids with the curan skeleton required the introduction of the oxidized one-carbon substituent at C-16. This was accomplished in two steps, by *N*-methoxycarbonylation of (−)-tubifoline followed by photochemical rearrangement of the resulting

N-(methoxycarbonyl)enamine **18**[32] to give (−)-19,20-dihydroakuammicine.[29,33] By virtue of a previous correlation,[34] the synthesis of this alkaloid also constitutes a formal total synthesis of (+)-geissoschizoline.

Experimental section

General

Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Gemini-200 instrument (200 and 50.3 MHz, respectively) or in a Varian Gemini-300 instrument (300 and 70.4 MHz, respectively). Chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. IR spectra were recorded on a Nicolet 205 FT-IR spectrophotometer. Mass spectra were determined on a Hewlett–Packard 5988A mass spectrometer or on a Autospec-VG (HRMS). Optical rotations were measured on a Perkin–Elmer 241 polarimeter using a 1 dm cell with a total volume of 1 ml. Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 0.040–0.060 mm). Chiral HPLC separations were done on a Kontron (detector 420) or Jasco 875-UV instrument. All reactions were carried out under nitrogen or argon atmosphere. Drying of organic extracts during the work-up of reactions was performed over anhydrous Na_2SO_4. Microanalyses were performed on a Carlo Erba 1106 analyzer by the Centro de Investigación y Desarrollo (CSIC), Barcelona.

(±)-1-(3-Pyridyl)ethanol rac-*2*

Sodium borohydride (3.78 g, 100 mmol) was slowly added to a solution of 3-acetylpyridine (10 g, 82 mmol) in MeOH (500 ml), and the resulting mixture was stirred at 25°C for 2 h. Then, NH_4Cl (1.1 g) was added, and the solvent was removed under reduced pressure. The residue was dissolved in AcOEt and washed with brine. The aqueous phase was extracted with AcOEt, and the combined organic extracts were dried and concentrated. The residue was chromatographed (95:5 AcOEt–EtOH) to give alcohol *rac*-**2** (9.8 g, 98%).

(1R)-1-(3-Pyridyl)ethyl acetate (+)-3

Vinyl acetate (2.8 ml, 30 mmol) and lipase PS (Amano, *Pseudomonas sp.*) (200 mg) were added to a solution of alcohol *rac*-**2** (1.23 g, 10 mmol) in *t*-butyl methyl ether (20 ml), and the mixture was stirred for 40 h. The suspension was filtered, the filtrate was concentrated, and the residue was chromatographed (AcOEt and 9:1 AcOEt–EtOH) to give acetate (+)-**3** (0.80 g, 48%) and (1*S*)-1-(3-pyridyl)ethanol (−)-**2** (0.58 g, 47%). (+)-**3**: $[\alpha]_D^{22}$+100.0 (*c* 0.96, $CHCl_3$) [lit.[13a] $[\alpha]_D^{22}$+99.6 (*c* 0.96, $CHCl_3$)]. The e.e. of (+)-**3** (≥96%) was determined by HPLC using a chiral column (Chiralcel OB, 9:1 hexane-*i*-PrOH). (−)-**2**: $[\alpha]_D^{22}$−43.3 (*c* 1.86, MeOH) [lit.[11] $[\alpha]_D^{25}$+47.2; lit[13a] $[\alpha]_D^{22}$−53.5 (*c* 1.09, $CHCl_3$)].

(1R)-1-(3-Pyridyl)ethanol (+)-2

A mixture of acetate (+)-**3** (6.65 g, 40 mmol) and K_2CO_3 (16.6 g, 120 mmol) in MeOH (40 ml) was stirred at 25°C for 1h. The solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 and washed with brine. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried, filtered, and concentrated. The residue was purified by column chromatography (AcOEt) to afford alcohol (+)-**2** (4.68 g, 95%): $[\alpha]_D^{22}$+52.8 (*c* 1.40, $CHCl_3$) [lit.[11] $[\alpha]_D^{25}$+46.7; lit.[13a] $[\alpha]_D^{22}$+52.4 (*c* 1.40, $CHCl_3$)]. The e.e. (96%) was determined by HPLC using a chiral column (Chiralcel OB, 9:1 hexane-*i*-PrOH).

(1R)-1-(1-Benzyl-1,2,5,6-tetrahydro-3-pyridyl)ethanol 4

Benzyl chloride (1.0 ml, 8.7 mmol) was added to a solution of pyridine (+)-**2** (1.0 g, 8.1 mmol) in anhydrous MeOH (0.5 ml), and the mixture was stirred at 80°C for 3 h. After cooling, the solvent was evaporated to give the *N*-benzyl pyridinium salt, which was dissolved in anhydrous MeOH (6 ml) and treated with $NaBH_4$ (0.61 g, 16.3 mmol) at 0°C. The resulting mixture was stirred at 25°C

for 12 h, then was concentrated, and the residue was dissolved in 1:1 Et_2O–H_2O (17 ml). Potassium carbonate (0.8 g) was added, and the mixture was stirred at 25°C for 1 h. The aqueous layer was separated and extracted with Et_2O. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed (Et_2O) to give tetrahydropyridine **4** (0.95 g, 54%) and 1-benzyl-3(Z)-ethylidene-1,2,3,6-tetrahydropyridine (0.2 g, 12%). **4**: $[\alpha]_D^{22}$+6.4 (*c* 0.53, MeOH); IR (film) 3360 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) 1.25 (d, *J*=6.5 Hz, 3H, CH_3), 2.15 (m, 3H, H-5 and OH), 2.46 and 2.57 (2dt, *J*=11.2, 5.8 Hz, 2H, H-6), 2.93 and 3.06 (2dm, *J*=15.8 Hz, 2H, H-2), 3.58 and 3.64 (2d, *J*=13.0 Hz, 2H, C$H_2C_6H_5$), 4.17 (q, *J*=6.5 Hz, 1H, C*H*OH), 5.67 (m, 1H, H-4), 7.26–7.35 (m, 5H, C_6H_5); ^{13}C-NMR ($CDCl_3$, 50.3 MHz) 21.8 (CH_3), 25.2 (C-5), 49.6 (C-6), 51.4 (C-2), 62.8 (*C*$H_2C_6H_5$), 69.5 (CHOH), 118.6 (C-4), 127.0 (C-*p*), 128.0 (C-*m*), 129.4 (C-*o*), 137.1 (C-*ipso*), 140.1 (C-3).

Methyl (3Z,4R)-1-benzyl-3-ethylidene-4-piperidineacetate **5**

Methyl orthoacetate (23 ml, 183 mmol) and pivalic acid (190 mg, 1.86 mmol) were added to a stirred solution of tetrahydropyridine **4** (4.0 g, 18.4 mmol) in anhydrous DME (105 ml), and the mixture was refluxed until no starting material was observed by TLC (about 48 h). The solvent was evaporated under reduced pressure, and the residue was taken up with CH_2Cl_2. The organic solution was washed with saturated aqueous $NaHCO_3$, dried, and concentrated. Column chromatography (2:3 Et_2O–hexane) gave pure ester **5** (3.1 g, 62%): $[\alpha]_D^{22}$+8.7 (*c* 1, MeOH); IR (film) 1739 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) 1.42 (m, 1H, H-5), 1.53 (d, *J*=6.6 Hz, 3H, CH_3), 1.79 (m, 1H, H-5), 2.31 (dd, *J*=17.0, 10.0 Hz, 1H, CH_2CO_2), 2.39 (m, 1H, H-6), 2.58 (masked, 1H, H-4), 2.59 (dd, *J*=17.0, 7.0 Hz, 1H, CH_2CO_2), 2.67 and 3.34 (2d, *J*=12.2 Hz, 2H, H-2), 2.74 (m, 1H, H-6), 3.54 and 3.58 (2d, *J*=13.0 Hz, 2H, C$H_2C_6H_5$), 3.66 (s, 3H, CH_3O), 5.20 (q, *J*=6.5 Hz, 1H, =CH), 7.26–7.33 (m, 5H, C_6H_5); ^{13}C-NMR ($CDCl_3$, 50.3 MHz) 12.5 (CH_3), 31.7 (C-5), 36.9 (*C*H_2CO_2), 38.3 (C-4), 51.2 (CH_3O), 52.0 (C-6), 52.2 (C-2), 62.6 (*C*$H_2C_6H_5$), 116.5 (=CH), 126.7 (C-*p*), 127.9 (C-*m*), 128.8 (C-*o*), 136.5 (C-3), 137.9 (C-*ipso*), 172.9 (C=O).

(3Z,4R)-1-Benzyl-3-ethylidene-4-(2-indolylmethyl)piperidine **6**

A solution of *n*-BuLi (7.6 ml of a 1.6 M solution in hexane, 12.1 mmol) was added dropwise to a stirred solution of *N*-trimethylsilyl-*o*-toluidine[12] (0.98 g, 5.5 mmol) in anhydrous hexane (36 ml), and the mixture was refluxed for 4 h. After cooling, the suspension was transferred via canula to a stirred solution of ester **5** (1.0 g, 3.66 mmol) in anhydrous THF (16 ml) at −78°C. The temperature was slowly raised to 25°C, and then the mixture was poured into brine. The aqueous layer was extracted with Et_2O, and the combined organic extracts were dried and concentrated. The resulting residue was chromatographed (from 3:7 AcOEt–hexane to AcOEt) to afford pure indole **6** (0.84 g, 69%): $[\alpha]_D^{22}$+7.6 (*c* 0.5, MeOH); ^{1}H-NMR ($CDCl_3$, 300 MHz) 1.43 (m, 1H, H-5), 1.56 (d, *J*=6.6 Hz, 3H, CH_3), 1.73 (m, 1H, H-5), 2.33 (ddd, *J*=12.0, 9.0, 3.3 Hz, 1H, H-6), 2.40 (m, 1H, H-4), 2.69–2.80 (m, 3H, H-6, H-2 and CH_2Ind), 3.06 (dd, *J*=14.5, 6.3 Hz, 1H, CH_2Ind), 3.40 (d, *J*=12.0 Hz, 1H, H-2), 3.55 and 3.61 (2d, *J*=13.0 Hz, 2H, C$H_2C_6H_5$), 5.34 (q, *J*=6.6 Hz, 1H, =CH), 6.22 (s, 1H, H-3′), 7.07 (m, 2H, H-5′ and H-6′), 7.20–7.37 (m, 6H, C_6H_5 and H-7′), 7.51 (dm, *J*=7.6 Hz, 1H, H-4′), 7.8 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$, 75 MHz) 12.8 (CH_3), 30.9 (C-5), 31.5 (CH_2Ind), 41.8 (C-4), 52.2 (C-6), 52.4 (C-2), 62.8 (*C*$H_2C_6H_5$), 100.5 (C-3′), 110.3 (C-7′), 117.3 (=CH), 119.5 (C-4′), 119.6 (C-5′), 120.8 (C-6′), 127.1 (C-*p*), 128.1 (C-*m*), 128.7 (C-3′a), 129.2 (C-*o*), 135.8 (C-2′), 137.4 (C-3), 137.9 (C-7′a), 138.1 (C-*ipso*). HRMS Calcd for $C_{23}H_{26}N_2$: 330.2096. Found: 330.2081.

*(1S,4aR,11R,11aS)-2-Benzyl-6-(*tert*-butoxycarbonyl)-1-cyano-11-methyl-1,2,3,4,4a,5,11,11a-octahydropyrido[4,3-b]carbazole* **7**

A mixture of **6** (250 mg, 0.75 mmol), tetrabutylammonium hydrogen sulfate (75 mg, 0.22 mmol) in toluene (3 ml), and 50% aqueous NaOH (1.8 ml) was stirred at 25°C for 15 min, and then a solution of di-*t*-butyl dicarbonate (331 mg, 1.5 mmol) in toluene (1.5 ml) was added dropwise. The stirring was continued for 10 min, the organic phase was separated, and the aqueous layer was extracted with

CH_2Cl_2. The combined organic extracts were dried and concentrated to give crude *N*-protected indole, which, without further purification, was dissolved in CH_2Cl_2 (2.5 ml). A solution of *m*-CPBA (95%, 157 mg, 0.86 mmol) in anhydrous CH_2Cl_2 (3.5 ml) was added at 0°C. The mixture was stirred for 1 h, the temperature was lowered to −15°C, and trifluoroacetic anhydride (0.37 ml, 2.66 mmol) was slowly added. After stirring at −15°C for 1 h and at 25°C for 15 min, a solution of NaCN (148 mg, 2.26 mmol) in H_2O (1.2 ml) was added, the pH was adjusted to 5 by addition of NaOAc, and the stirring was continued for 30 min. The mixture was basified with 10% aqueous Na_2CO_3, and the resulting solution was extracted with CH_2Cl_2. The combined organic extracts were washed with water, dried, and concentrated. Column chromatography (AcOEt–hexane–DEA 5:15:0.6) of the residue afforded tetracycle **7** (172 mg, 50%): $[\alpha]_D^{22}$ −93.8 (*c* 0.5, MeOH); IR 2200, 1729 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) 1.23 (d, *J*=6.5 Hz, 3H, CH_3), 1.46 (qd, *J*=12.5, 5.0 Hz, 1H, H-4), 1.58 (s, 9H, Me_3C), 1.60 (ddd, *J*=12.0, 10.0, 4.0 Hz, 1H, H-11a), 1.70 (m, 1H, H-4a), 1.82 (dm, *J*=12.5 Hz, 1H, H-4), 2.55 (td, *J*=12.5, 2.5 Hz, 1H, H-3), 2.58 (ddd, *J*=17.5, 10.5, 2.5 Hz, 1H, H-5), 2.88 (dm, *J*=12.5 Hz, 1H, H-3), 3.06 (m, 1H, H-11), 3.28 (ddd, *J*=17.5, 5.0, 1.0 Hz, 1H, H-5), 3.70 and 3.76 (2d, *J*=13.2 Hz, 2H, $CH_2C_6H_5$), 4.13 (d, *J*=4.0 Hz, 1H, H-1), 7.21 (m, 2H, H-8 and H-9), 7.28–7.39 (m, 5H, C_6H_5), 7.48 (dm, *J*=7.0 Hz, 1H, H-10), 8.09 (dm, *J*=8.0 Hz, 1H, H-7); ^{13}C-NMR ($CDCl_3$, 50.3 MHz) 19.1 (CH_3), 28.2 (Me_3), 30.1 (C-11), 32.0 (C-4), 32.3 (C-5), 32.9 (C-4a), 47.4 (C-11a), 48.5 (C-3), 56.2 (C-1), 60.5 ($CH_2C_6H_5$), 83.6 (CMe_3), 115.3 (C-10b), 115.4 (C-7), 119.0 (C-10), 119.1 (CN), 122.3 (C-9), 123.3 (C-8), 127.6 (C-*p*), 128.5 (C-*m*), 128.9 (C-*o*), 133.9 (C-5a), 136.0 (C-6a), 136.9 (C-*ipso*), 150.5 (C=O); mp 164°C (EtOH). Anal. Calcd for $C_{29}H_{33}N_3O_2$: C, 76.45; H, 7.30; N, 9.22. Found: C, 76.49; H, 7.32; N, 9.13.

*(4aR,11R,11aS)-2-Benzyl-6-(*tert*-butoxycarbonyl)-11-methyl-1,2,3,4,4a,5,11,11a-octahydropyrido-[4,3-*b*]carbazole* **8**

$NaBH_4$ (10 mg, 0.26 mmol) was added to a solution of aminonitrile **7** (50 mg, 0.11 mmol) in absolute MeOH (3 ml), and the resulting mixture was stirred at 40°C for 16 h. The solvent was removed under reduced pressure, and the residue was dissolved in AcOEt. The organic solution was washed with brine, dried, and concentrated. The residue was chromatographed (5:15:0.2 AcOEt–hexane–DEA) to give pure **8** (27 mg, 57%): $[\alpha]_D^{22}$ −106.8 (*c* 1.05, MeOH); IR (film) 1728 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) 1.35 (d, *J*=6.6 Hz, 3H, CH_3), 1.39–1.60 (complex signal, 3H, H-4, H-4a and H-11a), 1.66 (s, 9H, Me_3C), 1.78 (t, *J*=11.0 Hz, 1H, H-1), 1.82 (dm, *J*=13.0 Hz, 1H, H-4), 1.98 (td, *J*=11.3, 2.3 Hz, 1H, H-3), 2.50–2.62 (m, 2H, H-11 and H-5), 2.93 (dm, *J*=11.0 Hz, 1H, H-1), 3.15 (dm, *J*=16.2 Hz, 1H, H-5), 3.33 (dm, *J*=11.3 Hz, 1H, H-3), 3.52 and 3.65 (2d, *J*=13.2 Hz, 2H, $CH_2C_6H_5$), 7.15–7.37 (m, 7H, C_6H_5, H-8 and H-9), 7.50 (m, 1H, H-10), 8.10 (d, *J*=7.1 Hz, 1H, H-7); ^{13}C-NMR ($CDCl_3$, 75 MHz) 19.4 (CH_3), 28.3 (Me_3), 31.7 (C-11), 32.7 (C-5), 37.2 (C-4a), 45.3 (C-11a), 53.4 (C-3), 58.9 (C-1), 63.5 ($CH_2C_6H_5$), 83.4 (CMe_3), 115.4 (C-7), 119.0 (C-10), 120.3 (C-10b), 122.1 (C-9), 123.0 (C-8), 127.0 (C-*p*), 128.2 (C-*m*), 129.2 (C-*p*), 134.9 (C-5a), 136.0 (C-6a), 138.3 (C-*ipso*), 150.6 (C=O). HRMS Calcd for $C_{28}H_{34}N_2O_2$: 430.2620. Found: 430.2620.

(R)-1-[1-(Methoxycarbonyl)-1,2,5,6-tetrahydro-3-pyridyl]ethanol **11a**

The tetrahydropyridine **4** obtained operating as described above from pyridine (+)-**2** (2.0 g, 16.3 mmol) was dissolved without purification in anhydrous CH_2Cl_2 (40 ml), and methyl chloroformate (1.4 ml, 18.2 mmol) was added. The resulting mixture was stirred at 25°C for 3 h, and then CH_2Cl_2 and saturated aqueous $NaHCO_3$ were added. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried and concentrated. Purification of the residue by column chromatography (Et_2O) gave carbamate **11a** (1.5 g, 50%): $[\alpha]_D^{22}$ +3.4 (*c* 0.74, $CHCl_3$); IR (film) 3455, 1690 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) 1.31 (d, *J*=6.5 Hz, 3H, CH_3), 2.00 (br s, 1H, OH), 2.15 (m, 2H, H-5), 3.45 (dt, *J*=12.0, 6.2 Hz, 1H, H-6), 3.54 (br s, 1H, H-6), 3.71 (s, 3H, OCH_3), 3.93 and 4.02 (2dm, *J*=17.0 Hz, 2H, H-2), 4.26 (q, *J*=6.5 Hz, 1H, C*H*OH), 5.81 (m, 1H, H-4); ^{13}C-NMR

($CDCl_3$, 75 MHz) 21.6 (CH_3), 24.2 (C-5), 40.2 (C-6), 42.3 (C-2), 52.4 (OCH_3), 69.4 (CHOH), 119.0 and 119.6 (C-4), 138.6 and 139.2 (C-3), 156.0 (C=O).

(1R)-1-[1-(Benzyloxycarbonyl)-1,2,5,6-tetrahydro-3-pyridyl]ethanol ***11b***

Benzyl chloroformate (0.4 ml, 2.8 mmol) was slowly added to a solution of tetrahydropyridine **4** (500 mg, 2.3 mmol) in anhydrous CH_2Cl_2 (6 ml), and the mixture was refluxed for 8 h. Then, additional benzyl chloroformate (0.4 ml, 2.8 mmol) was added, and the reflux was continued for 1 h. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic extracts were dried, and the solvent was removed under vacuum. The residue was purified by column chromatography (Et_2O) to give carbamate **11b** (300 mg, 50%): $[\alpha]_D^{22}$+1.1 (*c* 1.0, $CHCl_3$); IR (film) 3400, 1690 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) 1.31 (d, *J*=6.4 Hz, 3H, CH_3), 1.63 (m, 1H, OH), 2.15 (br s, 2H, H-5), 3.49 (dt, *J*=12.0, 6.8 Hz, 1H, H-6), 3.58 (m, 1H, H-6), 3.97 and 4.06 (2dm, *J*=17.6 Hz, 2H, H-2), 4.26 (m, 1H, C*H*OH), 5.16 (s, 2H, C$H_2C_6H_5$), 5.82 (br s, 1H, H-4), 7.26–7.38 (m, 5H, C_6H_5); ^{13}C-NMR ($CDCl_3$, 50.3 MHz) 21.6 (CH_3), 24.1 and 24.4 (C-5), 40.2 and 40.3 (C-6), 42.3 and 42.4 (C-2), 66.8 (*C*$H_2C_6H_5$), 69.3 (CHOH), 118.9 and 119.4 (C-4), 127.6 (C-*p*), 127.7 (C-*o*), 128.2 (C-*m*), 136.4 (C-*ipso*), 138.5 and 139.0 (C-3), 155.3 (C=O); HRMS Calcd for $C_{15}H_{19}NO_3$: 261.1365. Found: 261.1366.

Methyl (3Z,4R)-1-(methoxycarbonyl)-3-ethylidene-4-piperidineacetate ***12a***

Operating as in the preparation of ester **5**, from tetrahydropyridine **11a** (3.6 g, 19.5 mmol), methyl orthoacetate (23 ml, 183 mmol), and pivalic acid (200 mg, 1.96 mmol) was obtained ester **12a** (4.0 g, 84%) after purification by column chromatography (3:7 AcOEt–hexane): $[\alpha]_D^{22}$+17.3 (*c* 0.8, MeOH) [lit.[11] $[\alpha]_D^{25}$+13.4]; IR (film) 1738, 1704 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) 1.38 (m, 1H, H-5), 1.71 (d, *J*=6.5 Hz, 3H, CH_3), 1.82 (m, 1H, H-5), 2.37 (dd, *J*=15.0, 7.6 Hz, 1H, CH_2CO_2), 2.62 (dd, *J*=15.0, 7.0 Hz, 1H, CH_2CO_2), 2.72 (m, 1H, H-4), 3.33 (ddd, *J*=13.5, 9.2, 4.0 Hz, 1H, H-6), 3.69 (masked, 1H, H-2), 3.70 and 3.72 (2s, 3H each, CO_2CH_3), 3.80 (m, 1H, H-6), 4.40 (d, *J*=14.4 Hz, 1H, H-2), 5.26 (q, *J*=6.5 Hz, 1H, =CH); ^{13}C-NMR ($CDCl_3$, 75 MHz) 12.7 (CH_3), 31.9 (C-5), 36.9 (*C*H_2CO_2), 38.1 (C-4), 42.6 (C-6), 43.1 (C-2), 51.4 (CH_3O), 52.3 (CH_3O), 117.9 (=CH), 135.0 (C-3), 155.6 (NCO), 172.6 (CO_2).

Methyl (3Z,4R)-1-(benzyloxycarbonyl)-3-ethylidene-4-piperidineacetate ***12b***

Operating as above, from tetrahydropyridine **11b** (558 mg, 2.14 mmol), methyl orthoacetate (2.6 ml, 21 mmol), and pivalic acid (22 mg, 0.21 mmol) was obtained ester **12b** (637 mg, 93%) after purification by column chromatography (2:3 AcOEt–hexane): $[\alpha]_D^{22}$+7.5 (*c* 0.5, MeOH); IR (film) 1736, 1700 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) 1.38 (m, 1H, H-5), 1.58–1.88 (m, 4H, H-5 and CH_3), 2.35 (dd, *J*=15.0, 7.7 Hz, 1H, CH_2CO_2), 2.60 (dd, *J*=15.0, 7.0 Hz, 1H, CH_2CO_2), 2.71 (m, 1H, H-4), 3.34 (ddd, *J*=13.0, 9.0, 3.5 Hz, 1H, H-6), 3.68 (s, 3H, CH_3O), 3.69 and 4.44 (2d, *J*=14.4 Hz, 2H, H-2), 3.82 (m, 1H, H-6), 5.14 (s, 2H, CH_2O), 5.24 (m, 1H, =CH), 7.35 (m, 5H, C_6H_5); ^{13}C-NMR ($CDCl_3$, 50.3 MHz) 12.9 (CH_3), 32.1 (C-5), 37.0 (*C*H_2CO_2), 38.3 (C-4), 42.8 (C-6), 43.3 (C-2), 51.5 (CH_3O), 67.0 (CH_2O), 118.0 (=CH), 127.7 (C-*p*), 127.8 (C-*o*), 128.4 (C-*m*), 135.1 (C-3), 136.7 (C-*ipso*), 155.0 (NCO_2), 172.8 (CO_2). HRMS Calcd for $C_{18}H_{23}NO_4$: 317.1627. Found: 317.1625.

(3Z,4R)-1-(Methoxycarbonyl)-3-ethylidene-4-(2-indolylmethyl)piperidine ***13a***

Operating as in the preparation of **6**, from *N*-trimethylsilyl-*o*-toluidine[12] (2.53 g, 14.13 mmol) and ester **12a** (2.27 g, 9.42 mmol) was obtained pure indole **13a** (1.23 g, 44%) after purification by column chromatography (CH_2Cl_2 and 9:1 CH_2Cl_2–AcOEt): $[\alpha]_D^{22}$+28.0 (*c* 0.5, MeOH); IR (film) 1684 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) 1.34 (m, 1H, H-5), 1.71 (d, *J*=6.6 Hz, 3H, CH_3), 1.72 (masked, 1H, H-5), 2.53 (m, 1H, H-4), 2.75 (dd, *J*=14.7, 9.0 Hz, 1H, CH_2Ind), 3.07 (dd, *J*=14.7, 5.8 Hz, 1H, CH_2Ind), 3.25 (ddd, *J*=13.2, 9.0, 3.8 Hz, 1H, H-6), 3.66 (masked, 1H, H-6), 3.70 (s, 3H, CH_3O), 3.73 (masked, 1H, H-2), 4.40 (m, 1H, H-2), 5.37 (q, *J*=6.6 Hz, 1H, =CH), 6.24 (s, 1H, H-3′), 7.09 (m, 2H, H-5′ and H-6′), 7.29 (dm, *J*=8.0 Hz, 1H, H-7′), 7.52 (d, *J*=7.6 Hz, 1H, H-4′), 8.00 (br

s, 1H, NH); ^{13}C-NMR ($CDCl_3$, 50.3 MHz) 12.7 (CH_3), 30.8 (C-5), 31.3 (CH_2Ind), 41.4 (C-4), 42.6 (C-6), 43.1 (C-2), 52.4 (CH_3O), 100.4 (C-3′), 110.2 (C-7′), 118.2 (=CH), 119.3 (C-4′), 119.5 (C-5′), 120.7 (C-6′), 128.4 (C-3′a), 135.7 (C-2′), 137.4 (C-3), 137.4 (C-7′a), 155.8 (C=O); mp 123–124°C (Et_2O). Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.45; H, 7.43; N, 9.38. Found: C, 72.42; H, 7.44; N, 9.32.

(3Z,4R)-1-(Benzyloxycarbonyl)-3-ethylidene-4-(2-indolylmethyl)piperidine ***13b***

Operating as in the preparation of **6**, from *N*-trimethylsilyl-*o*-toluidine[12] (507 mg, 2.83 mmol) and ester **12b** (600 mg, 1.89 mmol) was obtained pure indole **13b** (420 mg, 59%) after purification by column chromatography (increasing polarity from hexane to AcOEt): $[\alpha]_D^{22}$+30.0 (*c* 0.5, MeOH); IR (film) 1697 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) 1.38 (m, 1H, H-5), 1.60–1.73 (m, 4H, H-5 and CH_3), 2.53 (m, 1H, H-4), 2.75 (dd, *J*=14.7, 9.0 Hz, 1H, CH_2Ind), 3.06 (dd, *J*=14.7, 5.8 Hz, 1H, CH_2Ind), 3.28 (ddd, *J*=13.0, 9.0, 3.8 Hz, 1H, H-6), 3.75 (d, *J*=14.5 Hz, 1H, H-2), 3.78 (masked, 1H, H-6), 4.45 (d, *J*=14.5 Hz, 1H, H-2), 5.13 (s, 2H, CH_2O), 5.37 (m, 1H, =CH), 6.24 (s, 1H, H-3′), 7.09 (m, 2H, H-5′ and H-6′), 7.28–7.36 (m, 6H, H-7′ and C_6H_5), 7.52 (dm, *J*=7.5 Hz, 1H, H-4′), 7.90 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$, 50.3 MHz) 13.0 (CH_3), 31.0 (C-5), 31.5 (CH_2Ind), 41.6 (C-4), 42.8 (C-6), 43.3 (C-2), 67.1 (CH_2O), 100.6 (C-3′), 110.4 (C-7′), 118.4 (=CH), 119.6 (C-4′), 119.7 (C-5′), 121.0 (C-6′), 127.8 (C-*p*), 127.9 (C-*o*), 128.4 (C-*m*), 128.6 (C-3′a), 135.9 (C-2′), 136.7 (C-3), 137.5 (C-*ipso*), 137.5 (C-7′a), 155.5 (C=O). HRMS Calcd for $C_{24}H_{26}N_2O_2$: 374.1994. Found: 374.1994.

(3Z,4R)-3-Ethylidene-4-(2-indolylmethyl)piperidine ***13c***

From ***13a***

Method A. A solution of carbamate **13a** (100 mg, 0.33 mmol) in anhydrous MeOH (4 ml) was added to a solution of NaOMe (excess) in MeOH (7 ml), and the mixture was refluxed for 48 h. The solvent was removed under vacuum, and the residue was dissolved in CH_2Cl_2. The organic solution was washed with saturated aqueous $NaHCO_3$, dried, and concentrated. Column chromatography (90:5:5 Et_2O–EtOH–DEA) of the residue afforded pure secondary amine **13c** (50 mg, 62%): $[\alpha]_D^{22}$+3.0 (*c* 0.4, MeOH); ^{1}H-NMR ($CDCl_3$, 300 MHz) 1.38 (m, 1H, H-5), 1.66 (d, *J*=6.8 Hz, 3H, CH_3), 1.75 (m, 1H, H-5), 2.30 (br s, 1H, NH), 2.52 (m, 1H, H-4), 2.76 (dd, *J*=14.8, 9.0 Hz, 1H, CH_2Ind), 2.80 (masked, 1H, H-6), 3.08 (dd, *J*=14.8, 5.2 Hz, 1H, CH_2Ind), 3.10 (masked, 1H, H-6), 3.20 and 3.72 (2d, *J*=13.2 Hz, 2H, H-2), 5.32 (q, *J*=6.8 Hz, 1H, =CH), 7.09 (m, 2H, H-5′ and H-6′), 7.30 (dm, *J*=7.6 Hz, 1H, H-7′), 7.53 (dm, *J*=8.5 Hz, H-4′), 8.13 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$, 50.3 MHz) 12.7 (CH_3), 31.1 (C-5), 34.3 (CH_2Ind), 42.3 (C-4), 45.1 (C-6), 45.4 (C-2), 100.5 (C-3′), 110.3 (C-7′), 116.5 (=CH), 119.4 (C-4′), 119.6 (C-5′), 120.8 (C-6′), 128.7 (C-3′a), 135.8 (C-2′), 138.0 (C-3), 138.8 (C-7′a); HRMS Calcd for $C_{16}H_{20}N_2$: 240.1626. Found: 240.1628; Anal. Calcd for $C_{16}H_{20}N_2$: C, 79.95; H, 8.39; N, 11.65. Found: C, 79.82; H, 8.95; N, 11.57.

Method B. Trimethylsilyl iodide (1.7 ml, 12.4 mmol) was added dropwise to a solution of carbamate **13a** (900 mg, 3.02 mmol) in anhydrous acetonitrile (63 ml) at 0°C. The mixture was stirred at 0°C for 30 min and at 25°C for 1 h 30 min, and then MeOH (2 ml) was added. The solvent was removed under reduced pressure, and the residue was chromatographed to give pure **13c** (570 mg, 78%).

From ***13b***

Trimethylsilyl iodide (0.42 ml, 3.0 mmol) was slowly added to a solution of carbamate **13b** (278 mg, 0.74 mmol) in anhydrous acetonitrile (16 ml) at 0°C. The mixture was stirred for 30 min, and then MeOH (0.5 ml) was added. The solvent was removed under reduced pressure, and the residue was chromatographed to give pure **13c** (137 mg, 77%).

(3Z,4R)-1-(Chloroacetyl)-3-ethylidene-4-(2-indolylmethyl)piperidine ***14***

A solution of chloroacetyl chloride (0.77 ml, 9.67 mmol) in CH_2Cl_2 (24 ml) was added dropwise to a two-phase mixture of amine **13c** (1.16 g, 4.83 mmol) in CH_2Cl_2 (48 ml) and 2 N aqueous

NaOH (15 ml) at 0°C. The mixture was stirred at 25°C for 1 h and poured into brine. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried and concentrated. Flash chromatography of the residue (7:3 AcOEt–hexane) afforded chloroacetamide **14** (1.33 g, 87%): $[\alpha]_D^{22}$+37.2 (*c* 0.7, MeOH); IR (film) 1636 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz, major rotamer) 1.45 (m, 1H, H-5), 1.74 (d, *J*=6.8 Hz, 3H, CH_3), 1.83 (m, 1H, H-5), 2.61 (m, 1H, H-4), 2.79 (d, *J*=14.5 Hz, 1H, CH_2Ind), 3.10 (dd, *J*=14.5, 5.5 Hz, 1H, CH_2Ind), 3.37 (m, 1H, H-6), 3.70 (dt, *J*=13.5, 5.4 Hz, 1H, H-6), 3.83 and 4.66 (2d, *J*=14.4 Hz, 2H, H-2), 4.06 (s, 2H, CH_2Cl), 5.43 (q, *J*=6.8 Hz, 1H, =CH), 6.26 (s, 1H, H-3′), 7.11 (m, 2H, H-5′ and H-6′), 7.31 (dm, *J*=8.0 Hz, 1H, H-7′), 7.54 (dm, *J*=7.3 Hz, 1H, H-4′), 8.05 (br s, 1H, NH); (more significant signals of the minor rotamer) 2.80 (d, *J*=14.5 Hz, 1H, CH_2Ind), 3.09 (dd, *J*=14.5, 5.5 Hz, 1H, CH_2Ind), 3.90 and 4.33 (2d, *J*=14.4 Hz, 2H, H-2), 3.98 (m, 1H, H-6), 4.13 (s, 2H, CH_2Cl); ^{13}C-NMR ($CDCl_3$, 75 MHz, major rotamer) 13.0 (CH_3), 30.9 (C-5), 31.6 (CH_2Ind), 41.2 (CH_2Cl), 41.3 (C-4), 41.8 (C-6), 44.9 (C-2), 100.5 (C-3′), 110.4 (C-7′), 119.4 (=CH), 119.6 (C-4′), 119.7 (C-5′), 120.9 (C-6′), 128.5 (C-3′a), 134.8 (C-7′a), 135.9 (C-2′), 137.3 (C-3), 164.6 (C=O); (significant signals of the minor rotamer) 13.1 (CH_3), 30.5 (C-5), 31.0 (CH_2Ind), 41.2 (CH_2Cl and C-6), 41.3 (C-4), 45.1 (C-2), 137.2 (C-3), 164.7 (C=O). HRMS Calcd. for $C_{18}H_{21}ClN_2O$: 316.1342. Found: 316.1345.

*Photocyclization of chloroacetamide **14***

A solution of chloroacetamide **14** (125 mg, 0.39 mmol) and $NaHCO_3$ (240 mg) in 1:1 MeOH–H_2O (294 ml) was irradiated under a stream of argon with a 125 W medium-pressure mercury lamp in a quartz inmersion well reactor for 15 min at 25°C. The mixture was evaporated to dryness, and the residue was chromatographed (98:2 CH_2Cl_2–MeOH) to give a mixture (approximate ratio 3:1, 50 mg, 45%) of tetracycle **15** (mixture of amide rotamers **15a** and **15b**) and the *E* carbon–carbon double bond isomer (mixture of rotamers). After successive crystallizations (MeOH), pure *Z*-isomer **15** was isolated as a mixture of rotamers: IR (film) 1615 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz, major rotamer **15a**) 1.37 and 1.46 (2m, 2H, H-14), 1.59 (dt, *J*=6.8, 1.5 Hz, 3H, H-18), 2.62–3.00 (m, 3H, H-15 and H-16), 3.10 (m, 1H, H-3), 3.40 and 5.40 (2dm, *J*=17.0 Hz, 2H, H-21), 3.60 (m, 1H, H-3), 3.70 and 4.15 (2d, *J*=16.3 Hz, 2H, H-6), 5.29 (m, 1H, H-19), 7.05–7.50 (m, 4H, ArH), 8.00 (br s, 1H, NH); (more significant signals of minor rotamer **15b**) 1.08 (dt, *J*=6.8, 1.5 Hz, 3H, H-18), 1.87 and 2.18 (2m, 2H, H-14), 3.73 and 4.10 (2d, *J*=16.3 Hz, 2H, H-6), 4.19 (dm, *J*=17.3 Hz, 1H, H-21), 4.80 (m, 1H, H-3), 5.01 (m, 1H, H-19), 7.80 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$, 75 MHz, major rotamer **15a**) 12.5 (C-18), 25.5 (C-14), 30.3 (C-16), 33.1 (C-6), 37.3 (C-15), 43.3 (C-3), 43.9 (C-21), 105.3 (C-7), 110.6 (C-12), 117.6 (C-9), 117.8 (C-19), 119.3 (C-10), 121.6 (C-11), 128.1 (C-8), 133.6 (C-13), 134.8 (C-2), 139.1 (C-20), 172.7 (C-5); (minor rotamer **15b**) 12.4 (C-18), 29.7 (C-14), 31.3 (C-16), 33.3 (C-6), 38.2 (C-3), 38.4 (C-15), 49.1 (C-21), 104.8 (C-7), 110.3 (C-12), 117.4 (C-9), 119.0 (C-10), 118.5 (C-19), 121.3 (C-11), 127.8 (C-8), 133.9 (C-13), 134.7 (C-2), 136.9 (C-20), 173.3 (C-5); mp 230°C (MeOH). Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.08; H, 7.18; N, 10.02.

*16-(Dehydroxymethyl)-16-(demethoxycarbonyl)isostemmadenine **16***

$LiAlH_4$ (130 mg, 3.43 mmol) was added to a solution of amide **15** (425 mg, 1.52 mmol) in anhydrous THF (43 ml), and the mixture was refluxed for 2 h. The temperature was lowered to 0°C and the excess hydride was destroyed by dropwise addition of 15% aqueous NaOH (5 ml) and H_2O (5 ml). The resulting suspension was filtered through a Celite® pad, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (98:2 Et_2O–DEA) to afford amine **16** (340 mg, 84%): $[\alpha]_D^{22}$−6.64 (*c* 0.5, MeOH); ^{1}H-NMR ($CDCl_3$, 300 MHz) 1.58 (d, *J*=6.8 Hz, 3H, H-18), 1.67 and 1.89 (2m, 2H, H-14), 2.52 (m, 1H, H-3), 2.82 (m, 1H, H-6), 2.95–3.24 (complex signal, 7H), 3.32 and 3.60 (2d, *J*=17.0 Hz, 2H, H-21), 5.34 (m, 1H, H-19), 7.10 (m, 2H, H-10 and H-11), 7.28 (m, 1H, H-12), 7.47 (m, 1H, H-9), 7.78 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$, 75 MHz) 12.5 (C-18), 24.6 (C-6), 26.7 (C-14), 36.7 (C-16), 36.8 (C-15), 44.8 (C-3), 47.7 (C-21), 57.6 (C-5), 110.4 (C-12), 110.8 (C-7), 117.6 (C-9), 118.6 (C-19), 118.7 (C-10), 120.6 (C-11), 128.2 (C-8), 135.0

(C-13), 135.2 (C-2), 142.7 (C-20). HRMS Calcd for $C_{18}H_{22}N_2$: 266.1783. Found: 266.1787. When the reaction was carried out from the crude *Z* and *E* mixture of isomers obtained by photocyclization, small amounts of the *E* isomer of tetracycle **16** were isolated after successive purifications by column chromatography: ^{1}H-NMR ($CDCl_3$, 300 MHz) 1.58 (m, 1H, H-14), 1.72 (d, *J*=7.0 Hz, 3H, H-18), 1.83 (m, 1H, H-14), 2.28 (m, 1H, H-3), 2.49 (m, 1H, H-6), 2.76–3.36 (complex signal, 8H), 3.80 (dm, *J*=17.2 Hz, 1H, H-21), 5.50 (m, 1H, H-19), 7.11 (m, 2H, H-10 and H-11), 7.28 (dm, 1H, H-12), 7.50 (m, 1H, H-9), 7.90 (br s, 1H, NH).

*Catalytic hydrogenation of tetracycle **16***

A solution of compound **16** (370 mg, 1.39 mmol) in absolute EtOH (100 ml) containing PtO_2 (370 mg) was shaken under H_2 at 25°C for 12 h. The catalyst was removed by filtration through a Celite® pad, and the filtrate was concentrated under reduced pressure. The residue was chromatographed (97:3 Et_2O–DEA) to give pure **16-(dehydroxymethyl)-16-(demethoxycarbonyl)-19,20-dihydrostemmadenine 17** (200 mg, 54%) and (−)-tubifoline (74 mg, 20%). **17**: $[\alpha]_D^{22}$ −46.3 (*c* 0.38, AcOEt) [lit.[28] $[\alpha]_D^{22}$ −50±5 (*c* 0.351, AcOEt)]; IR (film) 3300 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) 0.94 (t, *J*=7.5 Hz, 3H, H-18), 1.31 (m, 2H, H-19), 1.66–1.84 (m, 2H, H-14), 2.42 (m, 1H, H-15), 2.56 (t, *J*=11.0 Hz, 1H, H-21), 2.74–3.20 (complex signal, 10 H), 7.12 (m, 2H, H-10 and H-11), 7.30 (m, 1H, H-12), 7.52 (m, 1H, H-9), 7.84 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$, 75 MHz) 12.0 (C-18), 24.1 (C-19), 24.8 (C-6), 28.0 (C-14), 30.3 (C-20), 30.4 (C-16), 38.5 (C-15), 45.2 (C-3), 48.5 (C-21), 55.9 (C-5), 110.3 (C-12), 110.7 (C-7), 117.4 (C-9), 118.7 (C-10), 120.5 (C-11), 128.5 (C-8), 134.8 (C-2), 136.1 (C-13).

(−)-Tubifoline

A suspension of PtO_2 (500 mg) in AcOEt (40 ml) was stirred under H_2 for 15 min and then a solution of tetracyclic amine **17** (224 mg, 0.83 mmol) in AcOEt (40 ml) was added. The resulting mixture was stirred under an oxygen atmosphere at 25°C for 2 h, the catalyst removed by filtration though a Celite® pad, and the filtrate concentrated under vacuum. The residue was chromatographed (97:3 Et_2O–DEA) affording (−)-tubifoline (124 mg, 55%) and a fraction consisting of a mixture of (−)-tubifoline and (+)-condyfoline, from which, after column chromatography (5:1 $CHCl_3$–MeOH), pure (+)-condyfoline (7 mg, 3%) was isolated. (−)-Tubifoline: $[\alpha]_D^{22}$ −303 (*c* 0.61, AcOEt) [lit.[28] $[\alpha]_D^{22}$ −356±15 (*c* 0.179, AcOEt); lit.[29] $[\alpha]_D^{23}$ −342±3 (*c* 0.549, $CHCl_3$)]. The e.e. (95%) was determined by HPLC using a chiral column (Chiralcel OD, 75:25:0.1 hexane–*i*-PrOH–DEA, 0.5 cm^3 min^{-1}, 254 nm) and racemic tubifoline[32] as reference. The ^{1}H- and ^{13}C-NMR spectra of (−)-tubifoline were identical to those of a racemic sample of the alkaloid.[32] (+)-Condyfoline: ^{1}H-NMR ($CDCl_3$, 300 MHz, most significant signals) 0.58 (m, 3H, H-18), 0.60 (m, 1H, H-19), 2.38 (m, 1H, H-15), 2.68 (dd, *J*=16.0, 1.5 Hz, 1H, H-16), 3.16 (dd, *J*=16.0, 10.5 Hz, 1H, H-16), 3.25 (td, *J*=12.0, 6.0 Hz, 1H, H-3), 3.86 (m, 1H, H-21), 7.19 (td, *J*=7.5, 1.2 Hz, 1H, H-10), 7.31 (td, *J*=7.5, 1.2 Hz, 1H, H-11), 7.34 (dm, *J*=7.5 Hz, 1H, H-9), 7.52 (dm, *J*=7.5 Hz, 1H, H-12).

(−)-Tubifolidine

A solution of (−)-tubifoline (100 mg, 0.37 mmol) in anhydrous THF (40 ml) was added dropwise to a suspension of $LiAlH_4$ (598 mg, 15.7 mmol) in anhydrous THF (28 ml), and the mixture was stirred at 30°C for 30 min. The temperature was lowered to 0°C, and the excess hydride was destroyed by slow addition of 10% NaOH (0.6 ml) and water (0.6 ml). The mixture was filtered through a Celite® pad, and the filtrate was dried and concentrated. Column chromatography (99:1 AcOEt–DEA) of the residue gave pure (−)-tubifolidine (30 mg, 30%) and tetracyclic amine **17** (24 mg). (−)-Tubifolidine: $[\alpha]_D^{22}$ −41.6 (*c* 0.61, $CHCl_3$) [lit.[29] $[\alpha]_D^{29}$ −67±3 (*c* 0.6144, $CHCl_3$)]. The e.e. (95.3%) was determined by HPLC using a chiral column (Chiralcel OD, 75:25:0.1 hexane–*i*-PrOH–DEA, 0.5 cm^3 min^{-1}, 254 nm) and racemic tubifolidine[32] as reference. The ^{1}H- and ^{13}C-NMR spectra of (−)-tubifolidine were identical to those of a racemic sample of the alkaloid.[32]

Methyl 2,16-didehydrotubifolidine-1-carboxylate **18**

NaH (25 mg, 0.57 mmol, 55% oil dispersion washed with hexane prior to use) was added to a solution of (−)-tubifoline (34 mg, 0.13 mmol) in anhydrous DME (2 ml), and the mixture was stirred for 15 min at 25°C. Then, methyl chloroformate (0.05 mL, 0.65 mmol) was added, and the stirring was continued at 60°C for 2 h. The reaction was quenched by addition of 10% aqueous Na_2CO_3 (10 ml) and AcOEt (10 ml). The aqueous layer was extracted with AcOEt, and the combined organic extracts were dried and concentrated. The resulting residue was chromatographed (97:2:1 Et_2O–DEA–EtOH) to give **18**[32] (13 mg, 32%): $[\alpha]_D^{22}-71$ (*c* 0.37, AcOEt); ^{13}C-NMR ($CDCl_3$, 75 MHz) 11.5 (C-19), 26.4 (C-18), 29.9 (C-14), 31.5 (C-15), 39.0 (C-20), 41.7 (C-6), 51.8 (C-21), 52.4 (C-7), 52.8 (CH_3), 53.7 (C-5), 61.1 (C-3), 111.8 (C-16), 114.9 (C-12), 119.3 (C-9), 123.7 (C-10), 127.1 (C-11), 136.7 (C-8), 140.9 (C-13), 148.2 (C-2), 153.0 (C=O).

(−)-19,20-Dihydroakuammicine

A solution of **18** (59 mg, 0.18 mmol) in MeOH (170 ml) was irradiated under a stream of argon with a 125 W medium-pressure mercury lamp in a quartz inmersion well reactor for 50 min at 25°C. The reaction mixture was concentrated, and the residue was chromatographed (97:3 $CHCl_3$–MeOH) to give (−)-tubifoline (16 mg, 33%) and (−)-19,20-dihydroakuammicine (14 mg, 24%): $[\alpha]_D^{22}-568$ (*c* 0.175, MeOH) [lit[35] $[\alpha]_D^{27}-636\pm4$ (*c* 0.736, MeOH)]. The ^{1}H- and ^{13}C-NMR spectra of (−)-19,20-dihydroakuammicine were identical to those of a racemic sample of the alkaloid.[32]

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