

PII: S0957-4166(97)00071-2

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

Mercedes Amat,^{a,*} M.-Dolors Coll,^a Joan Bosch,^a Enric Espinosa^b and Elies Molins^b ^aLaboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, 08028 Barcelona, Spain ^bInstitut de Ciència de Materials (CSIC), Campus UAB, 08193 Cerdanyola, Spain

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. © 1997 Elsevier Science Ltd. All rights reserved.

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 intermediates² and models,³ at the beginning of our studies⁴ 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.





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

^{*} Corresponding author. Email: amat@farmacia.far.ub.es

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-(4piperidylmethyl)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 rearrangement¹⁰ of a homochiral tetrahydropyridine-derived allylic alcohol following the methodology developed by Uskokovic¹¹ 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 indolization¹² taking advantage of the resulting ester function.

The required enantiopure (1R)-(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 (+)-3¹³ (Scheme 2).







Scheme 3.

Indolization of ester 5 by treatment with the organodilithium reagent derived from N-trimethylsilylo-toluidine¹² 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 2cyanopiperidine, 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 technique¹⁸ 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 ring¹⁹ 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 NaBH₄ 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 11a¹¹ 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 ($\sim 55\%$) in this two-step sequence was obtained from the N-benzyloxycarbonyl derivative 11b. Deprotection of the piperidine nitrogen of either 13a or 13b with iodotrimethylsilane²³ (77% yield) followed by treatment of the resulting N-unsubstituted piperidine 13c with chloroacetyl chloride in a CH₂Cl₂/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 LiAlH₄ 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 PtO₂ 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





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 (-)-tubifoline²⁹ in 55% yield. Minor amounts (<5%) of (+)-condyfoline²⁸ were also isolated. LiAlH₄ reduction^{26c} of (-)-tubifoline gave (-)-tubifolidine,²⁹ whose crystal structure³⁰ 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. ¹H- and ¹³C-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 Me₄Si. 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 SiO₂ (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 Na₂SO₄. Microanalyses were performed on a Carlo Erba 1106 analyzer by the Centro de Investigación y Desarrollo (CSIC), Barcelona.

(\pm) -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, NH₄Cl (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%).

(IR)-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, CHCl₃) [lit.^{13a} $[\alpha]_D^{22}$ +99.6 (*c* 0.96, CHCl₃)]. 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, CHCl₃)].

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

A mixture of acetate (+)-3 (6.65 g, 40 mmol) and K₂CO₃ (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 CH₂Cl₂ and washed with brine. The aqueous layer was extracted with CH₂Cl₂, 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, CHCl₃) [lit.¹¹ $[\alpha]_D^{25}$ +46.7; lit.^{13a} $[\alpha]_D^{22}$ +52.4 (*c* 1.40, CHCl₃)]. 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 NaBH₄ (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 Et₂O–H₂O (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 Et₂O. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed (Et₂O) 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; ¹H-NMR (CDCl₃, 300 MHz) 1.25 (d, *J*=6.5 Hz, 3H, CH₃), 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, CH₂C₆H₅), 4.17 (q, *J*=6.5 Hz, 1H, CHOH), 5.67 (m, 1H, H-4), 7.26–7.35 (m, 5H, C₆H₅); ¹³C-NMR (CDCl₃, 50.3 MHz) 21.8 (CH₃), 25.2 (C-5), 49.6 (C-6), 51.4 (C-2), 62.8 (CH₂C₆H₅), 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 CH₂Cl₂. The organic solution was washed with saturated aqueous NaHCO₃, dried, and concentrated. Column chromatography (2:3 Et₂O–hexane) gave pure ester **5** (3.1 g, 62%): $[\alpha]_D^{22}$ +8.7 (*c* 1, MeOH); IR (film) 1739 cm⁻¹; ¹H-NMR (CDCl₃, 300 MHz) 1.42 (m, 1H, H-5), 1.53 (d, J=6.6 Hz, 3H, CH₃), 1.79 (m, 1H, H-5), 2.31 (dd, J=17.0, 10.0 Hz, 1H, CH₂CO₂), 2.39 (m, 1H, H-6), 2.58 (masked, 1H, H-4), 2.59 (dd, J=17.0, 7.0 Hz, 1H, CH₂CO₂), 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, CH₂C₆H₅), 3.66 (s, 3H, CH₃O), 5.20 (q, J=6.5 Hz, 1H, =CH), 7.26–7.33 (m, 5H, C₆H₅); ¹³C-NMR (CDCl₃, 50.3 MHz) 12.5 (CH₃), 31.7 (C-5), 36.9 (CH₂CO₂), 38.3 (C-4), 51.2 (CH₃O), 52.0 (C-6), 52.2 (C-2), 62.6 (CH₂C₆H₅), 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-toluidine¹² (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 Et₂O, 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); ¹H-NMR (CDCl₃, 300 MHz) 1.43 (m, 1H, H-5), 1.56 (d, J=6.6 Hz, 3H, CH₃), 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 CH₂Ind), 3.06 (dd, J=14.5, 6.3 Hz, 1H, CH₂Ind), 3.40 (d, J=12.0 Hz, 1H, H-2), 3.55 and 3.61 (2d, J=13.0 Hz, 2H, CH₂C₆H₅), 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, C₆H₅ and H-7'), 7.51 (dm, J=7.6 Hz, 1H, H-4'), 7.8 (br s, 1H, NH); ¹³C-NMR (CDCl₃, 75 MHz) 12.8 (CH₃), 30.9 (C-5), 31.5 (CH₂Ind), 41.8 (C-4), 52.2 (C-6), 52.4 (C-2), 62.8 (CH₂C₆H₅), 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 C₂₃H₂₆N₂: 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

CH₂Cl₂. 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 CH₂Cl₂ (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 H₂O (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 Na₂CO₃, and the resulting solution was extracted with CH₂Cl₂. 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; ¹H-NMR (CDCl₃, 500 MHz) 1.23 (d, J=6.5 Hz, 3H, CH3), 1.46 (qd, J=12.5, 5.0 Hz, 1H, H-4), 1.58 (s, 9H, Me₃C), 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, CH₂C₆H₅), 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, C₆H₅), 7.48 (dm, J=7.0 Hz, 1H, H-10), 8.09 (dm, J=8.0 Hz, 1H, H-7); ¹³C-NMR (CDCl₃, 50.3 MHz) 19.1 (CH₃), 28.2 (Me₃), 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 (CH₂C₆H₅), 83.6 (CMe₃), 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 C₂₉H₃₃N₃O₂: 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

NaBH₄ (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; ¹H-NMR (CDCl₃, 300 MHz) 1.35 (d, *J*=6.6 Hz, 3H, CH₃), 1.39–1.60 (complex signal, 3H, H-4, H-4a and H-11a), 1.66 (s, 9H, Me₃C), 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, CH₂C₆H₅), 7.15–7.37 (m, 7H, C₆H₅, H-8 and H-9), 7.50 (m, 1H, H-10), 8.10 (d, *J*=7.1 Hz, 1H, H-7); ¹³C-NMR (CDCl₃, 75 MHz) 19.4 (CH₃), 28.3 (Me₃), 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 (CH₂C₆H₅), 83.4 (CMe₃), 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 C₂₈H₃₄N₂O₂: 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 CH₂Cl₂ (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 CH₂Cl₂ and saturated aqueous NaHCO₃ were added. The aqueous layer was extracted with CH₂Cl₂, and the combined organic extracts were dried and concentrated. Purification of the residue by column chromatography (Et₂O) gave carbamate **11a** (1.5 g, 50%): $[\alpha]_D^{22}$ +3.4 (*c* 0.74, CHCl₃); IR (film) 3455, 1690 cm⁻¹; ¹H-NMR (CDCl₃, 300 MHz) 1.31 (d, *J*=6.5 Hz, 3H, CH₃), 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, OCH₃), 3.93 and 4.02 (2dm, *J*=17.0 Hz, 2H, H-2), 4.26 (q, *J*=6.5 Hz, 1H, CHOH), 5.81 (m, 1H, H-4); ¹³C-NMR

(CDCl₃, 75 MHz) 21.6 (CH₃), 24.2 (C-5), 40.2 (C-6), 42.3 (C-2), 52.4 (OCH₃), 69.4 (CHOH), 119.0 and 119.6 (C-4), 138.6 and 139.2 (C-3), 156.0 (C=O).

(IR)-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 CH₂Cl₂ (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 NaHCO₃ and extracted with CH₂Cl₂. The organic extracts were dried, and the solvent was removed under vacuum. The residue was purified by column chromatography (Et₂O) to give carbamate **11b** (300 mg, 50%): $[\alpha]_D^{22}$ +1.1 (*c* 1.0, CHCl₃); IR (film) 3400, 1690 cm⁻¹; ¹H-NMR (CDCl₃, 300 MHz) 1.31 (d, *J*=6.4 Hz, 3H, CH₃), 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, CHOH), 5.16 (s, 2H, CH₂C₆H₅), 5.82 (br s, 1H, H-4), 7.26–7.38 (m, 5H, C₆H₅); ¹³C-NMR (CDCl₃, 50.3 MHz) 21.6 (CH₃), 24.1 and 24.4 (C-5), 40.2 and 40.3 (C-6), 42.3 and 42.4 (C-2), 66.8 (*C*H₂C₆H₅), 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 C₁₅H₁₉NO₃: 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; ¹H-NMR (CDCl₃, 300 MHz) 1.38 (m, 1H, H-5), 1.71 (d, *J*=6.5 Hz, 3H, CH₃), 1.82 (m, 1H, H-5), 2.37 (dd, *J*=15.0, 7.6 Hz, 1H, CH₂CO₂), 2.62 (dd, *J*=15.0, 7.0 Hz, 1H, CH₂CO₂), 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, CO₂CH₃), 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); ¹³C-NMR (CDCl₃, 75 MHz) 12.7 (CH₃), 31.9 (C-5), 36.9 (CH₂CO₂), 38.1 (C-4), 42.6 (C-6), 43.1 (C-2), 51.4 (CH₃O), 52.3 (CH₃O), 117.9 (=CH), 135.0 (C-3), 155.6 (NCO), 172.6 (CO₂).

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; ¹H-NMR (CDCl₃, 300 MHz) 1.38 (m, 1H, H-5), 1.58–1.88 (m, 4H, H-5 and CH₃), 2.35 (dd, *J*=15.0, 7.7 Hz, 1H, CH₂CO₂), 2.60 (dd, *J*=15.0, 7.0 Hz, 1H, CH₂CO₂), 2.71 (m, 1H, H-4), 3.34 (ddd, *J*=13.0, 9.0, 3.5 Hz, 1H, H-6), 3.68 (s, 3H, CH₃O), 3.69 and 4.44 (2d, *J*=14.4 Hz, 2H, H-2), 3.82 (m, 1H, H-6), 5.14 (s, 2H, CH₂O), 5.24 (m, 1H, =CH), 7.35 (m, 5H, C₆H₅); ¹³C-NMR (CDCl₃, 50.3 MHz) 12.9 (CH₃), 32.1 (C-5), 37.0 (*C*H₂CO₂), 38.3 (C-4), 42.8 (C-6), 43.3 (C-2), 51.5 (CH₃O), 67.0 (CH₂O), 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 (NCO₂), 172.8 (CO₂). HRMS Calcd for C₁₈H₂₃NO₄: 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*-toluidine¹² (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 (CH₂Cl₂ and 9:1 CH₂Cl₂-AcOEt): $[\alpha]_D^{22}+28.0$ (*c* 0.5, MeOH); IR (film) 1684 cm⁻¹; ¹H-NMR (CDCl₃, 300 MHz) 1.34 (m, 1H, H-5), 1.71 (d, J=6.6 Hz, 3H, CH₃), 1.72 (masked, 1H, H-5), 2.53 (m, 1H, H-4), 2.75 (dd, J=14.7, 9.0 Hz, 1H, CH₂Ind), 3.07 (dd, J=14.7, 5.8 Hz, 1H, CH₂Ind), 3.25 (ddd, J=13.2, 9.0, 3.8 Hz, 1H, H-6), 3.66 (masked, 1H, H-6), 3.70 (s, 3H, CH₃O), 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); ¹³C-NMR (CDCl₃, 50.3 MHz) 12.7 (CH₃), 30.8 (C-5), 31.3 (CH₂Ind), 41.4 (C-4), 42.6 (C-6), 43.1 (C-2), 52.4 (CH₃O), 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 (Et₂O). Anal. Calcd for C₁₈H₂₂N₂O₂: 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*-toluidine¹² (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; ¹H-NMR (CDCl₃, 300 MHz) 1.38 (m, 1H, H-5), 1.60–1.73 (m, 4H, H-5 and CH₃), 2.53 (m, 1H, H-4), 2.75 (dd, *J*=14.7, 9.0 Hz, 1H, CH₂Ind), 3.06 (dd, *J*=14.7, 5.8 Hz, 1H, CH₂Ind), 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, CH₂O), 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 C₆H₅), 7.52 (dm, *J*=7.5 Hz, 1H, H-4'), 7.90 (br s, 1H, NH); ¹³C-NMR (CDCl₃, 50.3 MHz) 13.0 (CH₃), 31.0 (C-5), 31.5 (CH₂Ind), 41.6 (C-4), 42.8 (C-6), 43.3 (C-2), 67.1 (CH₂O), 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 C₂₄H₂₆N₂O₂: 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 CH₂Cl₂. The organic solution was washed with saturated aqueous NaHCO₃, dried, and concentrated. Column chromatography (90:5:5 Et₂O–EtOH–DEA) of the residue afforded pure secondary amine **13c** (50 mg, 62%): $[\alpha]_D^{22}$ +3.0 (*c* 0.4, MeOH); ¹H-NMR (CDCl₃, 300 MHz) 1.38 (m, 1H, H-5), 1.66 (d, *J*=6.8 Hz, 3H, CH₃), 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, CH₂Ind), 2.80 (masked, 1H, H-6), 3.08 (dd, *J*=14.8, 5.2 Hz, 1H, CH₂Ind), 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); ¹³C-NMR (CDCl₃, 50.3 MHz) 12.7 (CH₃), 31.1 (C-5), 34.3 (CH₂Ind), 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 C₁₆H₂₀N₂: 240.1626. Found: 240.1628; Anal. Calcd for C₁₆H₂₀N₂: 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 CH₂Cl₂, 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; ¹H-NMR (CDCl₃, 300 MHz, major rotamer) 1.45 (m, 1H, H-5), 1.74 (d, J=6.8 Hz, 3H, CH₃), 1.83 (m, 1H, H-5), 2.61 (m, 1H, H-4), 2.79 (d, J=14.5 Hz, 1H, CH₂Ind), 3.10 (dd, J=14.5, 5.5 Hz, 1H, CH₂Ind), 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, CH₂Cl), 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, CH₂Ind), 3.09 (dd, J=14.5, 5.5 Hz, 1H, CH₂Ind), 3.90 and 4.33 (2d, J=14.4 Hz, 2H, H-2), 3.98 (m, 1H, H-6), 4.13 (s, 2H, CH₂Cl); ¹³C-NMR (CDCl₃, 75 MHz, major rotamer) 13.0 (CH₃), 30.9 (C-5), 31.6 (CH₂Ind), 41.2 (CH₂Cl), 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 (CH₃), 30.5 (C-5), 31.0 (CH2Ind), 41.2 (CH2Cl and C-6), 41.3 (C-4), 45.1 (C-2), 137.2 (C-3), 164.7 (C=O). HRMS Calcd. for C₁₈H₂₁ClN₂O: 316.1342. Found: 316.1345.

Photocyclization of chloroacetamide 14

A solution of chloroacetamide 14 (125 mg, 0.39 mmol) and NaHCO₃ (240 mg) in 1:1 MeOH-H₂O (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_2CI_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; ¹H-NMR (CDCl₃, 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); ¹³C-NMR (CDCl₃, 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-16), 33.4 (C-16), 33. 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 C₁₈H₂₀N₂O: 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

LiAlH₄ (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 H₂O (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 Et₂O–DEA) to afford amine **16** (340 mg, 84%): $[\alpha]_D^{22}$ -6.64 (*c* 0.5, MeOH); ¹H-NMR (CDCl₃, 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); ¹³C-NMR (CDCl₃, 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: ¹H-NMR (CDCl₃, 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 PtO₂ (370 mg) was shaken under H₂ 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 Et₂O–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; ¹H-NMR (CDCl₃, 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); ¹³C-NMR (CDCl₃, 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 PtO₂ (500 mg) in AcOEt (40 ml) was stirred under H₂ 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 Et₂O–DEA) affording (–)-tubifoline (124 mg, 55%) and a fraction consisting of a mixture of (–)-tubifoline and (+)-condyfoline, from which, after column chromatography (5:1 CHCl₃-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, CHCl₃)]. The e.e. (95%) was determined by HPLC using a chiral column (Chiralcel OD, 75:25:0.1 hexane–*i*-PrOH–DEA, 0.5 cm³ min⁻¹, 254 nm) and racemic tubifoline³² as reference. The ¹H- and ¹³C-NMR spectra of (–)-tubifoline were identical to those of a racemic sample of the alkaloid.³² (+)-Condyfoline: ¹H-NMR (CDCl₃, 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 LiAlH₄ (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: $[\alpha]_D^{22}-41.6 (c 0.61, CHCl_3) [lit.²⁹ <math>[\alpha]_D^{29}-67\pm3 (c 0.6144, CHCl_3)]$. 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 cm³ min⁻¹, 254 nm) and racemic tubifolidine³² as reference. The ¹H- and ¹³C-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 Na₂CO₃ (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 Et₂O–DEA–EtOH) to give 18^{32} (13 mg, 32%): [α]_D²²-71 (*c* 0.37, AcOEt); ¹³C-NMR (CDCl₃, 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 (CH₃), 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 CHCl₃–MeOH) to give (–)-tubifoline (16 mg, 33%) and (–)-19,20-dihydroakuammicine (14 mg, 24%): $[\alpha]_D^{22}$ –568 (*c* 0.175, MeOH) [lit³⁵ $[\alpha]_D^{27}$ –636±4 (*c* 0.736, MeOH)]. The ¹H- and ¹³C-NMR spectra of (–)-19,20-dihydroakuammicine were identical to those of a racemic sample of the alkaloid.³²

Acknowledgements

Financial support from the DGICYT, Spain (project PB94-0214) is gratefully acknowledged. Thanks are also due to the 'Comissionat per a Universitats i Recerca' (Generalitat de Catalunya) for Grant SGR95-00428 and for a fellowship to M.-D. C.

References

- For reviews, see: (a) Sapi, J.; Massiot, G. Monoterpenoid Indole Alkaloids Saxton, J. E., Ed., In The Chemistry of Heterocyclic Compounds, Taylor, E. C., Ed., Wiley, New York, 1994, Supplement to Vol. 25, Part 4, pp. 279–355. (b) Bosch, J.; Bonjoch, J.; Amat, M. In The Alkaloids, Cordell, G. A., Ed., Academic Press, New York, 1996, Vol. 48, pp 75–189. For more recent total syntheses, see: (c) Bonjoch, J.; Solé, D.; Bosch, J. J. Am. Chem. Soc. 1995, 117, 11017. (d) Solé, D.; Bonjoch, J.; Bosch, J. J. Org. Chem. 1996, 61, 4194. (e) Solé, D.; Bonjoch, J.; García-Rubio, S.; Suriol, R.; Bosch, J. Tetrahedron Lett. 1996, 37, 5213. (f) Kuehne, M. E.; Wang, T.; Seraphin, D. J. Org. Chem. 1996, 61, 7873. (g) Martin, S. F.; Clark, C. W.; Ito, M.; Mortimore, M. J. Am. Chem. Soc. 1996, 118, 9804.
- (a) Magnus, P.; Giles, M.; Bonnert, R.; Johnson, G.; McQuire, L.; Deluca, M.; Merritt, A.; Kim, C. S.; Vicker, N. J. Am. Chem. Soc. 1993, 115, 8116. (b) Amat, M.; Coll, M.-D.; Bosch, J. Tetrahedron 1995, 51, 10759.
- Micouin, L.; Diez, A.; Castells, J.; López, D.; Rubiralta, M.; Quirion, J.-C.; Husson, H.-P. Tetrahedron Lett. 1995, 36, 1693.
- For a preliminary report of part of this work, see: Amat, M.; Coll, M.-D.; Passarella, D.; Bosch, J. Tetrahedron: Asymmetry 1996, 7, 2775.
- 5. Knight, S. D.; Overman, L. E.; Pairaudeau, G. J. Am. Chem. Soc. 1995, 117, 5776.
- 6. The synthesis of (-)-tubifolidine following the methodology reported in ref 1e has recently been completed in our laboratory: Bonjoch, J.; Solé, D.; García-Rubio, S.; Bosch, J., unpublished.
- 7. The biogenetic numbering and ring labeling is used throughout this paper: Le Men, J.; Taylor, W. I. *Experientia* 1965, 21, 508.
- 8. For the use of this strategy from 2-(4-piperidylmethyl)indoles in the synthesis of *Strychnos* alkaloids in the racemic series, see: Gràcia, J.; Casamitjana, N.; Bonjoch, J.; Bosch, J. J. Org. Chem. **1994**, 14, 3939.

- 9. For related transannular cyclizations in the synthesis of *Strychnos* alkaloids in the racemic series, see: Harley-Mason, J. Pure Appl. Chem. 1975, 41, 167. See also ref 2a.
- For reviews, see: (a) Rhoads, S. J.; Raulins, N. R. Org. React. 1975, 22, 1. (b) Wipf, P. In Comprehensive Organic Synthesis Trost, B. M., Ed., Pergamon Press, Oxford, 1991, Vol. 5, Chapter 7.2.
- 11. Uskokovic, M. R.; Lewis, R. L.; Partridge, J. J.; Despreaux, C. W.; Pruess, D. L. J. Am. Chem. Soc. 1979, 101, 6742.
- 12. Smith III, A. B.; Visnick, M.; Haseltine, J. N.; Sprengeler, P. A. Tetrahedron 1986, 42, 2957.
- For the preparation of optically pure 1-(pyridyl)ethanols by lipase-catalyzed transesterification, see: (a) Seemayer, R.; Schneider, M. P. Tetrahedron: Asymmetry 1992, 3, 827. (b) Orrenius, C.; Mattson, A.; Norin, T.; Öhrner, N.; Hult, K. Tetrahedron: Asymmetry 1994, 5, 1363. For other reports on the preparation of enantiopure 1-(3-pyridyl)ethanols, see: (c) Imuta, M.; Ziffer, H. J. Org. Chem. 1978, 43, 3530. (d) Ziffer, H.; Kawai, K.; Kasai, M.; Imuta, M.; Froussios, C. J. Org. Chem. 1983, 48, 3017. (e) Soai, K.; Niwa, S.; Kobayashi, T. J. Chem. Soc., Chem. Commun. 1987, 801. (f) Brown, H. C.; Park, W. S.; Cho, B. T.; Ramachandran, P. V. J. Org. Chem. 1987, 52, 5406. (g) Takeshita, M.; Terada, K.; Akutsu, N.; Yoshida, S.; Sato, T. Heterocycles 1987, 26, 3051. (h) Brown, H. C.; Srebnik, M.; Ramachandran, P. V. J. Org. Chem. 1989, 54, 1577. (i) Berenguer, R.; Garcia, J.; Vilarrasa, J. Tetrahedron: Asymmetry 1994, 5, 165. (j) Akakabe, Y.; Takahashi, M.; Kamezawa, M.; Kikuchi, K.; Tachibana, H.; Ohtani, T.; Naoshima, Y. J. Chem. Soc., Perkin Trans. 1 1995, 1295. See also ref cited therein.
- 14. For the inversion of this unreacted S alcohol to the R enantiomer, see ref 11.
- For examples of the Claisen rearrangement from 3-(1-hydroxyethyl)tetrahydropyridine derivatives, see: (a) Ziegler, F. E.; Sweeny, J. G. Tetrahedron Lett. 1969, 1097. (b) Langlois, Y.; Langlois, N.; Potier, P. Tetrahedron Lett. 1975, 955. (c) Langlois, Y.; Potier, P. Tetrahedron 1975, 31, 419. (d) Rackur, G.; Stahl, M.; Walkowiak, M.; Winterfeldt, E. Chem. Ber. 1976, 109, 3817. (e) Bosch, J.; Rubiralta, M.; Bolós, J. Tetrahedron, 1987, 43, 391. (f) Tirkkonen, B.; Miettinen, J.; Salo, J.; Jokela, R.; Lounasmaa, M. Tetrahedron 1994, 50, 3537. (g) Takayama, H.; Maeda, M.; Ohbayashi, S.; Kitajima, M.; Sakai, S.; Aimi, N. Tetrahedron Lett. 1995, 36, 9337. See also ref 11.
- 16. For a review on the elaboration of the ethylidene substituent in the synthesis of indole alkaloids, see: Bosch, J.; Bennasar, M.-L. *Heterocycles* 1983, 20, 2471.
- 17. For a review on the Polonovski reaction, see: Grierson, D. Org. React. 1990, 39, 85.
- 18. Illi, V. O. Synthesis 1979, 136.
- For related cyclizations, see: (a) Besselièvre, R.; Thal, C.; Husson, H.-P.; Potier, P. J. Chem. Soc., Chem. Comm. 1975, 90. (b) Chevolot, L.; Husson, A.; Kan-Fan, C.; Husson, H.-P.; Potier, P. Bull. Soc. Chim. France 1976, 1222. See also ref 15b.
- 20. For the stereoselective preparation and spectroscopic data of racemic 10a, see: Bonjoch, J.; Quirante, J.; Linares, A.; Bosch, J. *Heterocycles* 1988, 27, 2883.
- 21. (a) Wu, A.; Snieckus, V. Tetrahedron Lett. 1975, 2057. (b) For a review, see: Sundberg, R. J. Organic Photochemistry Padwa, A., Ed., Marcel Dekker, New York, 1983, Vol. 6, pp 121–176.
- 22. For a review on the dealkylation of amines with acyl chlorides, see: Cooley, J. H.; Evain, E. J. Synthesis 1989, 1.
- 23. For a review, see: Olah, G. A.; Narang, S. C. Tetrahedron 1982, 38, 2225.
- 24. Stewart, W. E.; Siddall, T. H. Chem. Rev. 1970, 70, 517.
- 25. For related photoisomerizations, see: Kuehne, M. E.; Xu, F. J. Org. Chem. 1993, 58, 7490. See also ref 2a.
- 26. (a) Amine 17 was first prepared by degradation of akuammicine: Smith, G. F.; Wróbel, J. T. J. Chem. Soc. 1960, 792. For syntheses of rac-17, see: (b) Dadson, B. A.; Harley-Mason, J.; Foster, G. H. Chem. Commun. 1968, 1233. (c) Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T.; Takeda, E. Tetrahedron 1983, 39, 3657. See also ref 21a.

- 27. For a similar 'spontaneous' transannular oxidative cyclization in a tetracyclic stemmademine-type system, see ref 2a.
- 28. Schumann, D.; Schmid, H. Helv. Chim. Acta 1963, 46, 1996. This platinum-mediated oxidative cyclization also constitutes the last step of two different syntheses of (±)-tubifoline: see ref 26b,c.
- 29. For the isolation and structural elucidation of this alkaloid, see: Kump, W. G.; Patel, M. B.; Rowson, J. M.; Schmid, H. Helv. Chim. Acta 1964, 47, 1497.
- 30. Crystal data: $C_{18}H_{24}N_2$, monoclinic, space group P2₁, *a*=7.901(4), *b*=7.222(3), *c*=12.935(5) Å, β =97.46(4)°, V=731.8(6) Å³, Z=2, μ (MoK α)=0.07 mm⁻¹, D_c=1.22 g cm⁻³. The experiment was done on an Enraf-Nonius CAD4 diffractometer using graphite monochromated MoK α radiation. The crystal had approximate dimensions of 0.72×0.58×0.31 mm. Data collection was up to a resolution of 20=60° producing 2515 reflections. The structure was solved by direct methods (SHELXS 86) after applying Lorentz, polarization and absorption (empirical psi scan method) corrections to the 2367 independent reflections. Full matrix least-squares refinement (SHELXL 93) using anisotropic thermal parametres for non-H atoms and a global isotropic temperature factor for the H-atoms (introduced at calculated positions) converged to a R factor of 0.195 (0.069 for reflections with I>2 σ (I)). Maximum and minimum heights at the final difference Fourier synthesis were 0.33 and -0.27 e Å⁻³. Complete data have been deposited at the Cambridge Crystallographic Data Centre.
- For X-ray crystallographic analysis of pentacyclic Strychnos alkaloids, see: (a) Zeches, M.; Ravao, T.; Richard, B.; Massiot, G.; Le Men-Olivier, L.; Guilhem, J.; Pascard, C. Tetrahedron Lett. 1984, 25, 659. (b) Hu, W.-L.; Zhu, J.-P.; Prewo, R.; Hesse, M. Phytochemistry 1989, 28, 1963. (c) For a detailed structural study of strychnine by X-ray crystallographic methods, see: Mostad, A. Acta Chem. Scand. 1985, B39, 705.
- 32. Amat, M.; Linares, A.; Bosch, J. J. Org. Chem. 1990, 55, 6299.
- 33. (a) For previous total syntheses of racemic tubifoline and tubifolidine, see ref 26b,c and 32. The synthesis of (±)-tubifolidine has also been reported in ref 1e and in: Bonjoch, J.; Solé, D.; Bosch, J. J. Am. Chem. Soc. 1993, 115, 2064. (b) For previous total syntheses of (±)-19,20-dihydroakuammicine, see ref 1e and 32. See also: Kuehne, M. E.; Frasier, D. A.; Spitzer, T. D. J. Org. Chem. 1991, 56, 2696. The syntheses of (±)-akuammicine constitute formal total syntheses of racemic 19,20-dihydroakuammicine: (c) Angle, S. R.; Fevig, J. M.; Knight, S. D.; Marquis, Jr., R. W.; Overman, L. E. J. Am. Chem. Soc. 1993, 115, 3966. (d) Kuehne, M. E.; Xu, F.; Brook, C. S. J. Org. Chem. 1994, 59, 7803. See also ref 1d.
- 34. Edwards, P. N.; Smith, G. F. J. Chem. Soc. 1961, 152.
- 35. Weissmann, Ch.; Schmid, H.; Karrer, P. Helv. Chim. Acta 1961, 44, 1877.

(Received in UK 20 January 1997)