First Enantioselective Synthesis of (−)-Akagerine by a Chemoenzymatic Approach

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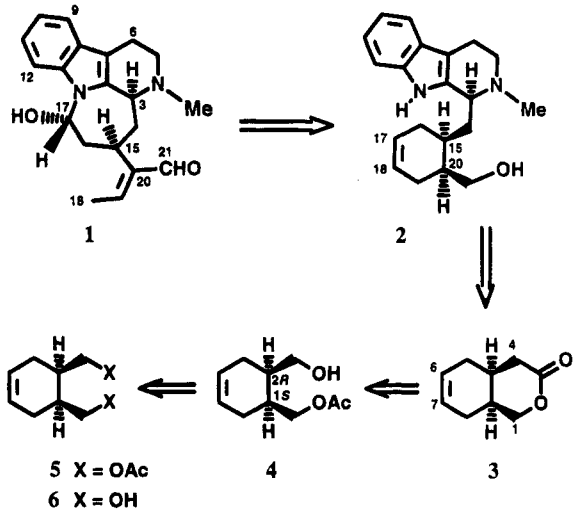
(−)-Akagerine (**1**) was synthesized in an efficient and stereocontrolled fashion from the readily available (1*S*,2*R*)-cyclohexenedimethanol monoacetate **4**. Key steps were the cleavage of the C(17)/C(18) bond of **14a** and the regio- and stereoselective cyclization of the dialdehyde **16** to give the tetracyclic skeleton of akagerine.

(−)-Akagerine (**1**), a tetracyclic indole alkaloid first isolated from *Strychnos usambarensis Gilg* (*Loganiaceae*)[1a] and later from several *Strychnos* species,[1b-i] has been shown to cause convulsive[1f] and antiprotozoal[2] activities in mice. Its unusual structure is characterized by a perhydroazepine ring coupled to the tetrahydro-β-carboline moiety by a N(1)/C(17) aminal bond. In spite of its significant activity and structural features, only one approach to racemic **1** has been described to date.[3] We report here the full details of our chemoenzymatic approach to (−)-akagerine **1**, its first enantioselective total synthesis.[4]

The synthetic strategy (Scheme 1) is based on the observation that the non-tryptamine portion of **1** may be derived from the C_1-symmetric (1*S*,2*R*)-cyclohex-4-enedimethanol monoacetate (**4**)[5] via the pivotal intermediate **2** and lactone **3**.[6] Thus the C(17) and C(18) of **1** can be considered as being derived from the dissection of the C(17)/C(18) double bond of **2**,[7] and C(15)-*R* of **1** will have an absolute configuration identical to C(2)-*R* of **4**. Moreover, it can be expected that controlling a suitable reaction sequence will lead to the creation of the stereogenic centers C(3)-*S* and C(17)-*S* in **1**, as well as the correct (*E*)-configuration of the C(20)-ethylidene residue.

Scheme 1



Access to **4** can be achieved by either enzyme-mediated hydrolysis[8] of σ-symmetrical cyclohex-4-ene 1,2-diacetate **5** or the acetylation[9] of the corresponding 1,2-dimethanol **6**. Hydrolysis of the *meso*-diacetate **5** in the presence of pig liver esterase (PLE) has been reported to give **4** in 78% yield and 96% ee.[8b] However in our hands, this procedure on a multigram scale gave **4** in good, but variable, ee (70–80%).[10] In order to find a reproducible methodology for the production of **4** and to improve the enantioselectivity of the process, we turned our attention to the enzyme-catalyzed monoacetylation of the corresponding *meso*-diol **6** in organic solvents.[11] This transformation was described by Schneider[9] who obtained **4** in 67% yield and 88% ee using lipase SAM-II in anhydrous MeO*t*-Bu at rt in the presence of vinyl acetate. We found that by using porcine pancreatic lipase (PPL)[12] in

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(1) (a) Angenot, L.; Dideberg, O.; Dupont, L. *Tetrahedron Lett.* **1975**, *16*, 1357–1358. (b) Verpoorte, R.; Svendsen, A. B.; Sandberg, F. *Acta Pharm. Suec.* **1975**, *12*, 455–460. (c) Oguakwa, J. U.; Galeffi, C.; Nicoletti, M.; Messana, I.; Patamia, M.; Marini-Bettolo, G. B. *Gazz. Chim. Ital.* **1980**, *110*, 97–100. (d) Rolfsen, W.; Bohlin, L.; Yeboah, S. K.; Geevaratne, M.; Verpoorte, R. *Planta Med.* **1978**, *34*, 264–273. (e) Oguakwa, J. U.; Nicoletti, M.; Messana, I.; Galeffi, C.; Marini-Bettolo, G. B. *Atti Accad. Naz. Lincei, Cl. Sci. Fis., Mat. Nat., Rend.* **1978**, *65*, 299–301 [C. A. **92** (1980) 160537h]. (f) Rolfsen, W.; Olaniyi, A. A.; Hylands, P. J. *J. Nat. Prod.* **1980**, *43*, 97–102. (g) Marini-Bettolo, G. B.; Messana, I.; Nicoletti, M.; Patamia, M.; Galeffi, C. *J. Nat. Prod.* **1980**, *43*, 717–720. (h) Verpoorte, R.; Joosse, F. T.; Groenink, H.; Svendsen, A. B. *Planta Med.* **1981**, *42*, 32–36. (i) Massiot, G.; Thepenier, P.; Jacquier, M.-J.; LeMen-Olivier, L.; Verpoorte, R.; Delaude, C. *Phytochemistry* **1987**, *26*, 2839–2846.

(2) Wright, C. W.; Bray, D. H.; O'Neill, M. J.; Warhurst, D. C.; Phillipson, J. D.; Quetin-Leclercq, J.; Angenot, L. *Planta Med.* **1991**, *57*, 337–340.

(3) Benson, W.; Winterfeldt, E. *Heterocycles* **1981**, *15*, 935–941.

(4) Our original research on this subject was briefly summarized in (a) Danieli, B.; Lesma, G.; Mauro, M.; Palmisano, G. in *Chemoenzymatic Approach to some Indole Alkaloids*: Heterocycles in Bioorganic Chemistry, Bergman, J., Van der Plas, H. C., Somonyi, M., Ed.; 1991; pp 28–53. (b) Danieli,B.; Lesma, G.; Passarella, D.; Riva, S. Chiral Synthons via Enzyme-Mediated Asymmetrization of Meso-Compounds. In *Advances in the Use of Synthons in Organic Chemistry*; Dondoni, A., Ed.; 1993; Vol. 1, pp 143–219.

(5) Enantiomeric (1*R*,2*S*)-cyclohex-4-enedimethanol monoacetate has long been used as versatile starting material for the enantioselective total synthesis of natural products. For a recent review see ref 4(b).

(6) Riva, R.; Banfi, L.; Danieli, B.; Guanti, G.; Lesma, G.; Palmisano, G. *J. Chem. Soc., Chem Commun.* **1987**, 299–300.

(7) We retained for **2** and related compounds the same numbering system as for **1**.

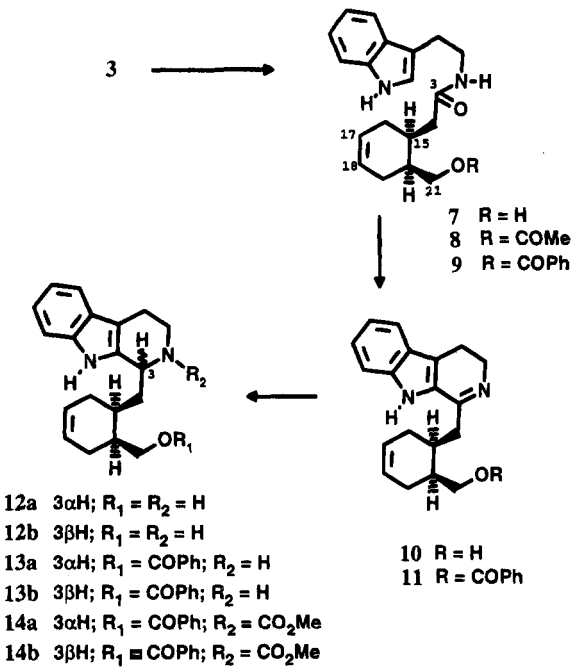
(8) (a) Laumen, K.; Schneider, M. *Tetrahedron Lett.* **1985**, *26*, 2073–2076. (b) Guanti, G.; Banfi, L.; Narisano, E.; Riva, R.; Thea, S. *Tetrahedron Lett.* **1986**, *27*, 4639–4642.

(9) Ader, U.; Breitgoff, D.; Klein, P.; Laumen, K. E.; Schneider, M. P. *Tetrahedron Lett.* **1989**, *30*, 1793–1796.

(10) These unsatisfactory results were consistent with a recent report of Jones which has shown that with different batches of the enzyme PLE, the same levels of enantiomeric excess could not be obtained, see: Lam, L. K. P.; Hui, R. A. H. F.; Jones, J. B. *J. Org. Chem.* **1986**, *51*, 2047–2050.

0022-3263/95/1960-2506$09.00/0

Scheme 2



anhydrous EtOAc, **6** was selectively monoacetylated to give **4**, in 88% yield and >99% ee,[13] according to NMR analysis of the corresponding Mosher's (+)-MTPA esters.[14]

The conversion of **4** into the lactone **3** proceeds uneventfully, as previously described by us,[15] by the sequential treatment of **4** with CBr_4/PPh_3 and KCN in DMSO, followed by reaction with alkaline H_2O_2 (66.5%, three steps).

The first step in our synthesis, the preparation of the β-carboline derivative **12a** with the proper absolute stereochemistry at the stereogenic center C(3), was done *via* the amide **8** in a Bischler–Napieralski cyclization–reduction two-step process (Scheme 2): lactone **3** was treated with tryptamine in *n*-BuOH at reflux. This afforded the amide **7** in 97% yield, which was then quantitatively converted to the C(21)-O-acetyl derivative **8**. The $POCl_3$-mediated cyclization of **8** gave the hydroxyimine **10** (92%) with the concomitant cleavage of the labile acetate group, most likely during the workup procedure.

The attempted reduction of the chiral imine **10** using $NaBH_4$ in MeOH failed to produce substantial diastereofacial selectivity, affording **12** in 94% isolated yield as a 1:1.2 ratio of diastereomers **12a** and **12b** (by 300 MHz ^1H NMR integration of the signals of H-3 protons). Careful TLC of the partially separable isomers was

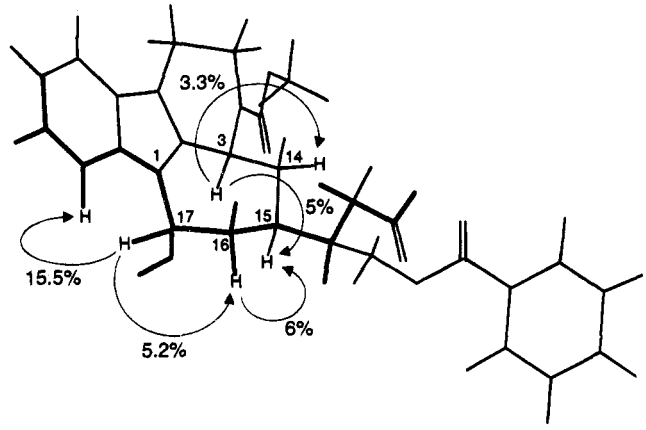


Figure 1. Fully optimized energy conformations of **10** and **11** as determined by molecular mechanics calculations (HyperChem output).

successful, although in a practical sense it could not be used to separate large quantities of material. Unfortunately the ^{13}C and ^1H chemical shifts and ^1H–^1H coupling constants of **12a** and **12b** were too close to allow a confident absolute configurational assignment at C(3) by application of the usual shielding/deshielding arguments and conformational analysis. Therefore, the absolute configuration at C(3) of **12a** and **12b** was determined as 3*S*(3α-H) and 3*R*(3β-H), respectively, by their circular dichroism spectra[16] which showed, as expected, identical strong Cotton effects at 268, 286, and 295 nm, but opposite in sign.

In contrast, reduction of **10** with $Zn(BH_4)_2$ in THF at 0 °C resulted in a complex reaction mixture from which **12** could be isolated in poor yield (<25%) as a 5:1 mixture of **12a** and **12b**. Also other methods of reduction [$NaBH_3CN$/MeOH; DIBAH/THF, −70 °C; DIBAH, $ZnCl_2$/THF, −70 °C; $Zn(BH_3CN)_2$/MeOH] were unsuccessful, the undesired **12b** with low diastereoselectivity prevailing (**12a**:**12b** 1:1.1–1.4).

In order to investigate whether increased π-facial stereoselectivity in the above hydride reduction might result from steric effects,[17] we performed at this stage, force field studies involving the imine **10** and its derivative **11** in which a large benzoyl residue was introduced at C(21)-O. Extensive molecular mechanics calculations[18] yielded the fully optimized conformations **10-I** and **10-II** for **10** and conformations **11-I**, **11-II** for **11** (Figure 1), **10-II** and **11-I**, respectively, being the global minima. A particularly pertinent finding, consistent with the above results, was the negligible energy difference between structures **10-I** and **10-II** ($\Delta E \approx 0.1$ kcal/mol), structures that can be expected to have opposite face selectivity.[19] On introducing the benzoyl group at C(21)-O the energy difference relative to the lower energy conformations of opposite face selectivity (**11-II** *vs* **11-I**, Figure 1) increased substantially, by over 1.8 kcal/mol. Thus, in the absence

(11) Recent reviews on enzymatic esterification in organic solvent: (a) Chen, C.-S.; Sih, C, J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 695–707. (b) Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 114–120. (c) Boland, W.; Frossl, C.; Lorenz, M. *Synthesis* **1991**, 1049–1072. (d) Xie, Z.-F.; *Tetrahedron: Asymm.* **1991**, 2, 733–750. (e) Faber, K.; Riva, S. *Synthesis* **1992**, 895–910. (f) ref 4(b).

(12) This enzyme is known to possess high stability and to give high reproducibility even if used as crude preparation (straight from the jar).

(13) During the drafting of this manuscript a further example was published of this transformation, in 76% yield and 93.6% ee, using crude PPL supported on Celite and vinyl acetate as both solvent and acylating agent: Guanti, G.; Banfi, L.; Riva, R. *Tetrahedron: Asymm.* **1994**, *5*, 9–12.

(14) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.

(15) Danieli, B.; Lesma, G.; Mauro, M.; Palmisano, G.; Passarella, D. *Tetrahedron* **1994**, *50*, 8837–8852.

(16) Klyne, W.; Swan, R. J.; Dastoor, N. J.; Gorman, A. A.; Schmid, H. *Helv. Chim. Acta* **1967**, *50*, 115–125.

(17) This follows the suggestion that the π-facial stereoselectivity in the reduction of sterically unbiased ketones reflects steric effects; for the case of the bulky solvated BH_4-moiety see for example: Williams, L.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1994**, 353–355, and references therein.

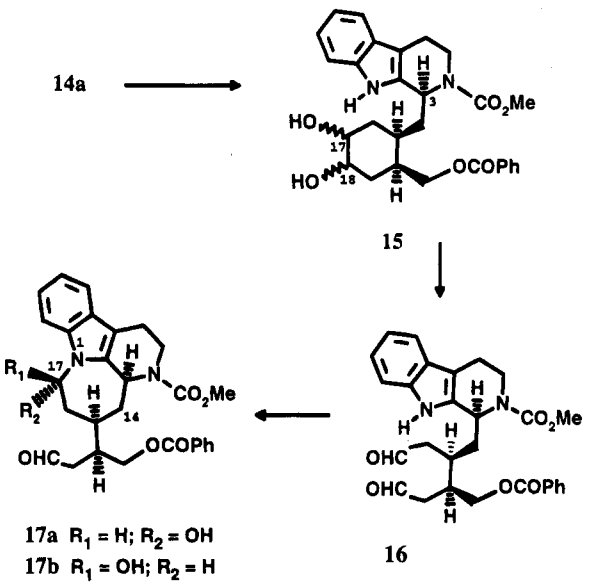
(18) All calculations were performed with HyperChem program (release 4.0, Autodesk, Inc.). Candidate conformations were generated by dihedral driving using constrained minimization. Once the alternative conformation was generated, constraints were removed and the structure was reminimized.

of any particular bias, the expectation was that the $NaBH_4$ reduction of **11** would give, preferentially, the kinetically more favored **13a** (α-attack) rather than **13b** (β-attack).[19]

In order to test the above predictions the imino ester **11**, prepared from **7** *via* **9**[20] as described for **10**, was reduced with $NaBH_4$ in MeOH. Indeed **13** was isolated in 88% yield as a 1.8:1 inseparable mixture of **13a** (3α-H, 3*S*) and **13b** (3β-H, 3*R*) epimers. The absolute configuration at the stereogenic center C(3) (and relative ratio) of the diastereomers **13a,b** was unambiguously determined by the removal of the benzoyl group (K_2CO_3/EtOH), affording a 1.8:1 mixture of the previously isolated **12a** and **12b** in nearly quantitative yield. The product ratio in the last reduction could be markedly improved by conducting the reaction according to a modification of the Kametani protocol.[21] In fact, when the imine **11** was first converted to its HCl salt and then added to $NaBH_4$ in EtOH at 0 °C, **13a** and **13b** were produced in high-yield (>95%) and in a ratio greater than 5:1. Treatment of this mixture with methyl chloroformate introduced the methoxycarbonyl protecting group at N(4)[22] in quantitative yield and allowed an easy, large scale, chromatographic separation of the isomers. The pure major urethane **14a** (3α-H, 3*S*) was thus obtained in 66% overall yield from **7**. The proof of the absolute stereochemistry at C(3) in **14a** (and **14b**) came from the conversion of **14a** to **12a** (and **14b** to **12b**)[23] by sequential hydrolysis of the benzoate and urethane functions.[24-25]

With the stereogenic centers C(3)-*S* and C(15)-*R* properly incorporated into **14a,** we turned our attention to explore the two key steps on which our approach was based, namely the oxidative cleavage of the C(17)/C(18) bond of **14a**, and the acid-catalyzed cyclization of the resulting dialdehyde **16** to give the tetracyclic skeleton of akagerine (Scheme 3). The reaction of **14a** with catalytic OsO_4 in THF/H_2O in the presence of *N*-methylmorpholine *N*-oxide[26] (NMO) gave, in 83% yield, the diastereomeric diols **15**.[27] Treatment of the unseparated mixture of **15** with sodium periodate in THF/H_2O, at 0 °C, proceeded cleanly to give the rather unstable dialdehyde **16,** which was used without purification[28] in

Scheme 3



the subsequent highly favored 7-*exo* trig[29] cyclization to **17**. Although this perhydroazepine-forming reaction involving a regioselective nucleophilic attack of N(1) at C(17) is predictable, there was some uncertainity with regard to the C(17) stereochemistry in the resultant product **17**.

In any event, the acid-promoted cyclization of **16** under kinetically controlled conditions (0.02 N HCl, THF, 25 °C, 30 min) proceeds smoothly with high levels of regio- and stereoselectivity to give the carbinolamine **17a** (17*S*) in 84% yield as a single isomer. This stereochemical assignment follows from the detection, in the ^1H NMR spectrum of **17a**, of the methine proton H-17 at δ 6.30 weakly coupled to the C(16) methylene protons (J = 4.5 and <0.5 Hz). These values indicate an equatorial arrangement for H-17, nearly coplanar with the aromatic ring. Furthermore, this assignment was confirmed conclusively by nuclear Overhauser effects difference spectroscopy (NOEDS) measurements (Figure 2).

With the efficient approach to **17a** realized, the stage was now set for the completion of the synthesis as shown in Scheme 4. Treatment of **17a** with $NaBH_4$ in MeOH at 0 °C gave, with high regiospecificity the alcohol **18** in virtually quantitative yield without any reduction of the hemiaminal function.[30]

In order to avoid the formation of side products in the subsequent elaboration of the vinyl appendage, **18** was stereoselectively converted to the aminal **19** (98% yield) by reaction with gaseous HCl in MeOH.[1d] Again the stereochemical assignment of **19** was made from its ^1H NMR spectrum and NOEDS measurements. Irradiation of the C(17) methine doublet (δ 5.95) resulted in enhancement of H-12 (δ 7.62, 20.1%) and H-16α (δ 2.39, 7.0%). Similarly irradiation of the C(17)-OCH_3 protons (δ 3.15) resulted in enhancement of the methine H-3 (δ 5.18, 3.1%).

Conversion of **19** to the vinyl derivative **21** was cleanly effected in 79% yield by the well-established Grieco method,[31] via the seleno derivative **20** which was im-

(19) We assumed that the relative energy differences of the lowest energy conformations will parallel the energy differences in the transition state of the reduction process.

(20) Holy, A.; Soucek, M. *Tetrahedron Lett.* **1971**, 185–188.

(21) Kametani, T.; Suzuki, T.; Unno, K. *Tetrahedron* **1981**, *37*, 3819–3823

(22) Protection of the N(4) was necessary to prevent its interaction in view of the strongly oxidative conditions in the next stages of the synthesis. Moreover the methoxycarbonyl protecting group appeared at the outset to be eminently suited as a precursor of the N(4)-Me function via LAH reduction. For a similar transformation, see: Sánchez, I. H.; Soria, J. J.; López, F. J.; Larraza, M. I.; Flores, H. J. *J. Org. Chem.* **1984**, *49*, 157–163.

(23) As in the case of **12a,b**, the close similarities of the ^1H and ^{13}C resonances in the nonrigid compounds **14a** and **14b** made it impossible to distinguish between the 3α-H and 3β-H isomers by NMR spectroscopy.

(24) Wenkert, E.; Hudlicky, T.; Showalter, H. D. H. *J. Am. Chem. Soc.* **1978**, *100*, 4893–4894.

(25) Since **14b** could be efficiently returned to **11** by acidic hydrolysis followed by mercuric acetate oxidation, the undesired isomer could be readily recycled. For similar oxidation see for example: Wenkert, E.; Roychaudhuri, D. K. *J. Org. Chem.* **1956**, *21*, 1315–1317.

(26) McCormick, J. P.; Shinmyozu, T.; Pachlatko, J. P.; Schafer, T. R.; Gardner, J. W.; Stipanovic, R. D. *J. Org. Chem.* **1984**, *49*, 34–40.

(27) Since the stereochemistry at C(17) and C(18) in **15** would be lost in the subsequent C(17)/C(18) bond cleavage, we did not separate these isomers, nor did we attempt to establish their stereochemistry.

(28) The crude product comprised approximately 95–96% of **15** and ca. 4–5% of unidentified materials. Attempts to purify this material led to vast decomposition.

(29) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736.

(30) For a similar example of a C(17) carbinolamine function surviving reduction with $NaBH_4$, see ref 1(i).

(31) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485–1486.

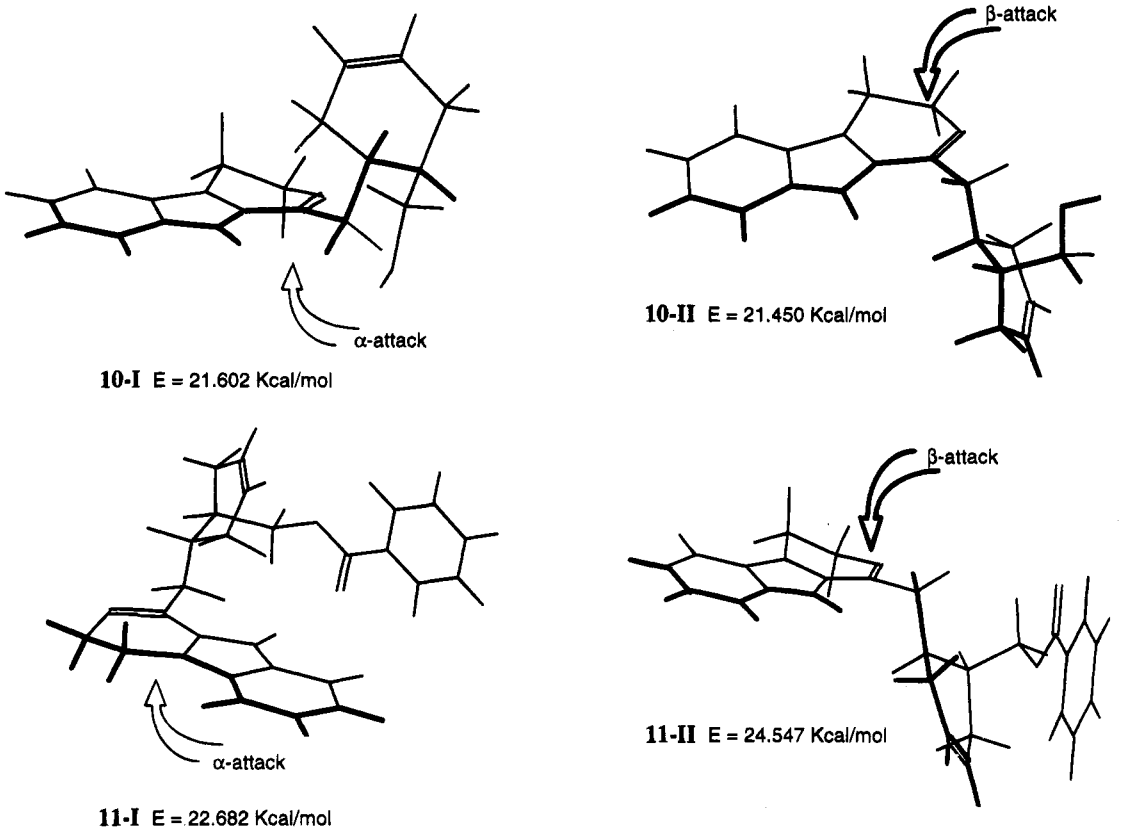
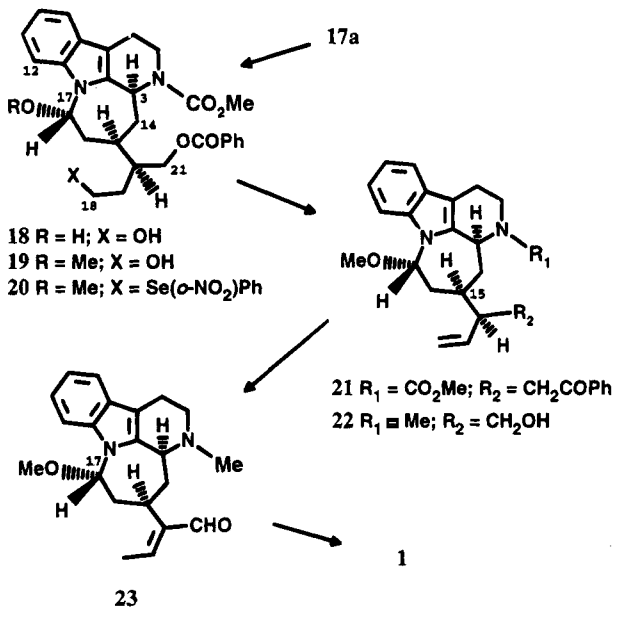


Figure 2. Nuclear Overhauser effects difference spectroscopy (NOEDS) data for **17a.**

Scheme 4



mediately oxidized with sodium periodate in aqueous MeOH at 0 °C. Subsequent treatment of **21** with LAH in THF at 80 °C removed the benzoyl residue at C(21)-O with concomitant reduction of the methoxycarbonyl protecting group to give, ultimately, the N(4)-methyl alcohol **22** in excellent yield.

Finally, we investigated the elaboration of the side chain at C(15) of **22** into the required α,β-unsaturated aldehyde function with the proper (*E*)-stereochemistry as in **1**. This result was achieved in a single step by treatment of **22** with a sulfur trioxide−pyridine complex in DMSO in the presence of triethylamine.[32] In fact, oxidation of the C(21) hydroxymethyl was accompanied by the concomitant migration of the terminal double bond to give 17-*O*-methylakagerine (**23**) in 93% yield as a single stereoisomer.

The final acidic hydrolysis of aminal **23** cleanly afforded (−)-akagerine (**1**) in 96% yield in pure form with no observable epimerization at C(17). The synthetic product had spectroscopic data, optical rotation, and TLC behavior identical with an authentic sample of (−)-akagerine.

In conclusion, the first enantioselective total synthesis of (−)-akagerine (**1**) has been achieved in seventeen steps and 19.3% yield from the enzymatically generated (1*S*,2*R*)-cyclohex-4-enedimethanol monoacetate (**4**). This result also demonstrates the potential of **4** as a synthon for the enantiosynthesis of indole alkaloids.[4]

Experimental Section[33]

Materials. Porcine pancreatic lipase Type II (EC 3.1.1.3) (PPL) was obtained from Sigma. Ethyl acetate for enzymatic esterification (analytical grade) was used without further purification, apart from drying, by shaking with 3-Å molecular sieves (Merck).

General Method. Enzymatic transesterification of compound **6** was followed by gas chromatography (GC) with a 2-m OVI-101 column at 170 °C (N_2 as carrier gas, detector and injector port at 300 °C). Unless otherwise indicated, all separations were carried out under flash chromatography (FC) conditions on silica gel 60 (230−400 mesh) using the indicated solvents. The organic extracts were dried over anhydrous Na_2SO_4 prior to solvent removal on a rotary evaporator.

PPL-Catalyzed Acetylation of 6 in EtOAc. A mixture of *meso*-cyclohex-4-ene-1,2-dimethanol (**6**) (1 g, 7.05 mmol) and

(32) Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.

(33) For typical experimental protocols see ref 15.

PPL (4.55 g) in EtOAc (100 mL) was stirred at 20 °C. After 14.5 h, GC analysis indicated that 90% of **6** was acetylated. After filtration, the solvent was removed *in vacuo* and the resulting residue purified by FC (Et_2O) to give (1*S*,2*R*)-cyclohex-4-enedimethanol monoacetate (**4**) (1.13 g, 88%) as a colorless oil: >99% ee [determined by ^{19}F NMR analysis (188.22 MHz) of the corresponding (+)-MTPA ester[14]; R_f (Et_2O) 0.15; $[\alpha]^{25}_D$ +19.0° (*c* 5.65, $CHCl_3$), [lit.[8a] $[\alpha]^{25}_D$ -19.4°($CHCl_3$), (maximum specific rotation given in literature for the 1*R*,2*S* enantiomer of **4** with >99% ee)]. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.76. Found: C, 64.89; H, 8.81.

(4a*S*,8a*S*)-1,4,4a,5,8,8a-Hexahydro-3*H*-2-benzopyran-3-one (3). Lactone **3** was prepared from the cyclohexene **4** according to the reported method:[15] yield 66.5%; $[\alpha]^{25}_D$ −5.44° (*c* 2.02, $CHCl_3$); HRMS calcd for $C_9H_{12}O_2$152.0837, found 152.0833.

(1*S*,2*S*)-*N*-[2-(1*H*-Indol-3-yl)ethyl]-1-(hydroxymethyl)-cyclohex-4-ene-2-acetamide (7). A mixture of lactone **3** (1.90 g, 12.5 mmol) and tryptamine (3.00 g, 18.75 mmol) in *n*-BuOH (6 mL) was stirred at reflux for 2 h. The solvent was removed *in vacuo*, and the residue was purified by FC with EtOAc to give 3.77 g (97%) of amide **7** as an oil which crystallized to a pale yellow solid of indefinite mp on standing: R (9:1 EtOAc:MeOH) 0.36; $[\alpha]^{25}_D$ −3.80° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3470, 1645 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.37 (br, s, 1H), 7.58 (br, d, *J* = 7.5 Hz, 1H), 7.36 (br, d, *J* = 7.5 Hz, 1H), 7.19 (br, t, *J* = 7.5 Hz, 1H), 7.11 (br, t, *J* = 7.5 Hz, 1H), 7.01 (d,*J* = 2.2 Hz, 1H), 5.98 (m, 1H), 5.64 (m, 2H), 3.68−3.51 (m, 2H), 3.41 (br, dd, *J* = 11.8, 5.0 Hz, 1H), 3.34 (br, dd, *J* = 11.8, 8.2 Hz, 1H), 2.95(t, *J* = 6.7 Hz, 2H), 2.48 (m, 1H), 2.22 (dd, *J* = 14.4, 6.4 Hz, 1H), 2.14 (m, 1H), 2.02−1.75 (m, 4H), 1.61 (m, 1H); ^{13}C NMR (75.4 MHz, APT, $CDCl_3$) δ 174.6, 137.0, 127.9, 126.2, 125.9, 122.8, 122.6, 119.9, 119.1, 113.1, 112.0, 64.0, 40.4, 38.9, 31.0, 30.4, 26.1, 25.8; EIMS *m*/*z* (relative intensity) 312 (6, M^+), 294(1), 282(1), 170(4), 143(100), 130(81). Anal. Calcd for $C_{19}H_{23}N_2O_2$: C, 73.04; H, 7.75; N, 8.97. Found: C, 72.90; H, 7.60; N, 8.84.

(1*S*,2*S*)-*N*-[2-(1*H*-Indol-3-yl)ethyl]-1-[(acetyloxy)methyl]cyclohex-4-ene-2-acetamide (8). To a stirred solution of the amide **7** (1.63 g, 5.22 mmol) in 20 mL of CH_2Cl_2 containing pyridine (1.7 mL, 20.9 mmol) was added dropwise acetic anhydride (639 mg, 6.26 mmol) at 0 °C under nitrogen. After being stirred at room temperature for 12 h, the reaction mixture was diluted with additional CH_2Cl_2 (50 mL), washed with 10% HCl, saturated $NaHCO_3$, and brine, and dried. The solvent was removed and the residue purified by FC (1:4 hexane:EtOAc) to give 1.81 g (98%) of the amide-acetate **8** as a clear, colorless syrup: R_f (9:1 EtOAc:MeOH) 0.48; $[\alpha]^{25}_D$ −5.1° (*c* 1.15, $CHCl_3$); IR ($CHCl_3$) 3480, 1730, 1660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 50 °C) δ 8.37 (br, s, 1H), 7.58 (br, d, *J* = 7.5 Hz, 1H), 7.36 (br, d, *J* = 7.5 Hz, 1H), 7.18(dt, *J* = 1.2, 7.5 Hz, 1H), 7.10(dt, *J* = 1.2, 7.5 Hz, 1H), 7.00(br d, *J* = 2.4 Hz, 1H), 5.77 (br, t, *J* = 6.5 Hz, 1H), 5.57 (br s, 2H), 4.08 (dd, *J* = 11.0, 6.4 Hz, 1H), 3.85 (dd, *J* = 11.0, 7.5 Hz, 1H), 3.59 (q, *J* = 6.5 Hz, 2H), 2.96 (t, *J* = 6.5 Hz, 1H), 2.35 (m, 1H), 2.25−2.00 (m, 5H), 1.98 (s, 3H) 1.82 (m, 2H); EIMS *m*/*z* (relative intensity) 354 (9, M^+), 294 (0.6), 212 (1.8), 143 (100), 130 (17); HRMS calcd for $C_{21}H_{26}N_2O_3$ 354.4656, found 354.4668. Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.40; N, 7.90. Found C, 71.55; H, 7.53; N, 7.72.

1-[(1*S*,2*S*)-[[1-(Hydroxymethyl)-cyclohex-4-en-2-yl]-methyl]-3,4-dihydro-9*H*-pyrido[3,4-*b*]indole (10). Freshly distilled $POCl_3$ (1.3 mL, 13.9 mmol) was cautiously added via a syringe to a refluxing solution of the-amide acetate **8** (700 mg, 1.98 mmol) in CH_2Cl_2 (43 mL) under nitrogen. The solution was stirred at reflux for 2 h, the solvent removed *in vacuo*, and the residue taken up in a mixture of EtOAc and saturated $NaHCO_3$ (1:1, 140 mL). The organic phase was washed with brine and dried, the solvent removed, and the residue purified by FC (9:1 EtOAc:MeOH) to afford 537 mg of imine **10** (92%) as a yellow crystalline solid: mp 65−67 °C; R_f (9:1 EtOAc:MeOH) 0.23; $[\alpha]^{25}_D$ +32.0° (*c* 0.4, $CHCl_3$); IR ($CHCl_3$) 3470, 3300 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.6−9.10 (br, m, 1H), 7.57 (br, d, *J* = 7.6 Hz, 1H), 7.39 (br, d, *J* = 7.6 Hz, 1H), 7.27 (br, t, *J* = 7.6 Hz, 1H), 7.13 (br, t, *J* = 7.6 Hz, 1H), 5.62 (m, 2H), 3.92(dt, *J* = 15.7, 8.4 Hz, 1H), 3.83(dt, *J* = 15.7, 8.4 Hz, 1H), 3.70(dd, *J* = 11.6, 4.7 Hz, 1H), 3.56(dd, *J* = 11.6, 10.0 Hz, 1H), 2.92(t, *J* = 8.4 Hz, 2H), 2.69 (m, 1H), 2.50 (m, 1H), 2.27−1.58 (m, 7H); ^{13}C NMR (75.4 MHz, APT, acetone-d_6) δ 164.0, 138.6, 129.3, 126.5, 126.2, 125.6, 120.8 (2C), 118.0, 113.4, 62.9, 47.6, 39.2, 32.0, 29.6, 26.4, 19.7; EIMS *m*/*z* (relative intensity) 294 (20, M^+), 276 (15), 263 (6), 240 (4), 221 (26), 184 (100). Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.53; N, 9.51. Found: C, 77.88; H, 7.53; N, 9.33.

(3*S*,3α)-1-[(1*S*,2*S*)-[[1-(Hydroxymethyl)cyclohex-4-en-2-yl]methyl]]-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (12a) and (3*R*,3β)-1-[(1*S*,2*S*)-[[1-(Hydroxymethyl)cyclohex-4-en-2-yl]methyl]]-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (12b). To a stirred solution of the imine **10** (56 mg, 0.19 mmol) in MeOH (2.5 mL) was added $NaBH_4$ (15 mg, 0.38 mmol). The reaction mixture was stirred for 2 h at room temperature, cooled to 0 °C and quenched with 1% HOAc. The mixture was poured into water (5 mL), made basic (pH 9) with 10% NaOH, and extracted with EtOAC. The combined organic layer was dried, the solvent removed, and the residue purified by TLC [47:3:1 EtOAC:*i*-PrOH:NH_3(*d* 0.88)] to give 29 mg (51%) of amino alcohol **12b** and 24 mg (43%) of amino alcohol **12a** as white foams which crystallize from EtOH/*i*-Pr_2O.

12b(3β-H,3*R*): mp 191−192 °C; R_f [47:3:1 EtOAc:*i*-PrOH:NH_3(*d* 0.88)] 0.20; $[\alpha]^{25}_D$ +59.9° (*c* 1.3, MeOH); IR ($CHCl_3$) 3470, 3320, 3240 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.40 (br, s, 1H), 7.42 (d,*J* = 7.5 Hz, 1H), 7.28 (d,*J* = 7.5 Hz, 1H), 7.09(t, *J* = 7.5 Hz, 1H), 7.02(t, *J* = 7.5 Hz, 1H), 5.62 (m, 2H), 4.16 (br, t, *J* = 5.7 Hz, 1H), 3.58 (m, 1H), 3.46 (t, *J* = 10.5 Hz, 1H), 3.33 (ddd, *J* = 12.2, 4.5, 2.1 Hz, 1H), 2.99 (ddd, *J* = 12.2, 9.0, 5.9 Hz, 1H), 2.82−2.62 (m, 2H), 2.30 (m, 1H), 2.20−2.08 (m, 1H), 2.08−1.82 (m, 4H), 1.72−1.60 (m, 1H), 1.45 (dt, *J* = 14.5, 6.5 Hz, 1H0; ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 136.1, 135.8, 127.3, 125.7 (2C), 121.5, 119.3, 118.0, 110.8, 108.7, 64.1, 52.2, 43.3, 38.6, 33.7, 31.9, 29.7, 25.0, 22.3; CD (MeOH) $[\Theta]_{295}$ −2929, $[\Theta]_{286}$ −2798, $[\Theta]_{268}$ -4766; EIMS *m*/*z* (relative intensity) 296 (13, M^+), 294 (10), 276 (8), 266 (4), 221 (10), 184 (38), 171 (100). Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.17; N, 9.45. Found: C, 77.35; H, 8.09; N, 9.32.

12a(3α-H,3*S*): mp 165−168 °C; R_f [47:3:1 EtOAc:*i*-PrOH:NH_3(*d* 0.88)] 0.17; $[\alpha]^{25}_D$ −19.9° (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) identical to **12b**; ^1H NMR (300 MHz, $CDCl_3$, 45 °C) δ 8.02 (br, s, 1H), 7.45 (br, d, *J* = 7.7 Hz, 1H), 7.28 (br, d, *J* = 7.7 Hz, 1H), 7.13 (br, t, *J* = 7.7 Hz, 1H), 7.06 (br, t, *J* = 7.7 Hz, 1H), 5.68 (m, 2H), 4.00 (br, d, *J* = 10.4 Hz, 1H), 3.57(dd, *J* = 11.6, 5.8 Hz, 1H), 3.45(dd, *J* = 11.5, 8.6 Hz, 1H) 3.21 (br, dt, *J* = 12.4, 6.0 Hz, 1H), 3.12(ddd, *J* = 12.4, 8.0, 4.6 Hz, 1H), 2.84 (br, s, 2H), 2.72 (m, 2H), 2.36−2.25 (m, 2H), 2.12−1.88 (m, 3H), 1.76−1.62 (m, 2H), 1.57(ddd, *J* = 14.3, 6.8, 3.7 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 136.3 (2C), 127.8, 127.1, 125.9, 122.3, 120.0, 118.6, 111.3, 109.3, 64.2, 52.2, 41.2, 39.2, 33.8, 30.2, 25.8, 23.1; CD (MeOH) $[\Theta]_{295}$ +2346, $[\Theta]_{286}$ +2151, $[\Theta]_{268}$ +3129; EIMS *m*/*z* (relative intensity) 296 (6, M^+), 294 (10), 221 (17), 184 (56), 171 (100). Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.17; N, 9.45. Found: C, 77.30; H, 8.02; N, 9.59.

(1*S*,2*S*)-*N*-[2-(1*H*-Indol-3-yl)ethyl]-1-[(benzoyloxy)-methyl]cyclohex-4-ene-2-acetamide (9). To a stirred solution of the amide **7** (5.08 g, 16.3 mmol) and *N*,*N*-diisopropylethylamine (Hünig base) (4.45 mL, 26.7 mmol) in CH_2Cl_2 (100 mL) was added benzoyl cyanide (2.8 g, 21.4 mmol) portionwise. After being stirred at room temperature for 2 h, saturated $NaHCO_3$ solution (50 mL) was added and the resulting mixture was stirred for an additional 30 min. The organic phase was washed successively with 3% aqueous H_3PO_4, water, saturated $NaHCO_3$(aq), and brine and dried. After removal of the solvent the residue was purified by FC (1:4 hexane:EtOAc) to give 6.32 g (93%) of amide-benzoate **9** as a pale yellow solid which did not crystallize: R_f (EtOAc) 0.54; $[\alpha]^{25}_D$ −6.5° (*c* 1.15, $CHCl_3$); IR ($CHCl_3$) 3470, 1720, 1660 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 60 °C) δ 10.64 (br, s, 1H), 8.00 (d,*J* = 7.8 Hz, 2H), 7.75 (br, t, *J* = 6.5 Hz, 1H), 7.67 (t, *J* = 7.8 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 2H), 7.54 (d,*J* = 7.4 Hz, 1H), 7.35 (d,*J* = 7.4 Hz, 1H), 7.13 (d,*J* = 2.4 Hz, 1H), 7.07(t, *J* = 7.4 Hz, 1H), 6.98(t, *J* = 7.4 Hz, 1H), 5.66 (br, s, 2H), 4.31(dd, *J* = 11.2, 5.1 Hz, 1H), 4.21(dd, *J* = 11.2, 7.8 Hz, 1H), 3.18 (br, q, *J* = 7.2 Hz, 2H), 2.84(t, *J* = 7.2 Hz, 2H), 2.40 (m, 1H), 2.23(dd, *J* = 14.4, 5.7 Hz, 1H), 2.10 (dd, *J* = 14.4, 8.9 Hz, 1H), 2.25−1.82 (m, 5H); ^{13}C NMR (20.1

MHz, $CDCl_3$) δ 172.6, 167.0, 136.7, 133.2, 131.4, 129.7 (2C), 128.6 (2C), 127.5, 125.8, 125.1, 122.4, 122.1, 119.4, 118.7, 112.8, 111.6, 65.5, 40.1, 37.7, 35.7, 31.8, 29.3, 26.9, 25.5; EIMS *m/z* (relative intensity) 416 (12, M^+), 294 (5), 143 (100), 130 (87), 105(81). Anal. Calcd for $C_{26}H_{28}N_2O_3$: C, 74.97; H, 6.78; N, 6.72. Found: C, 75.18, H, 6.54; N, 6.97.

1-[(1*S*,2*S*)-[[1-[(Benzoyloxy)methyl]-cyclohex-4-en-2-yl]-methyl]]-3,4-dihydro-9*H*-pyrido[3,4-*b*]indole (11). $POCl_3$ cyclization of the amide-benzoate **9** (2.4 g, 5.77 mmol) as described above for the preparation of **10** gave, after FC (24:1 EtOAc:MeOH), 2.09 g (91%) of imine-benzoate **11** as pale yellow crystalline solid which was recrystallized from hexane/Et_2O: mp 71−73 °C; R_f (EtOAc) 0.18; $[\alpha]^{25}_D$ −8.3° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3470, 1725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.89 (br, s, 1H), 8.07 (d,*J* = 7.7 Hz, 2H), 7.56(t, *J* = 7.7 Hz, 1H), 7.53 (br, d, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.28 (br, d, *J* = 7.5 Hz, 1H), 7.22 (br, t, *J* = 7.5 Hz, 1H), 7.10 (br, t, *J* = 7.5 Hz, 1H), 5.69 (m, 2H), 4.78 (dd, *J* = 10.8, 7.8 Hz, 1H), 4.22 (dd, *J* = 10.8, 6.0 Hz, 1H), 3.93 (dt, *J* = 15.4, 7.7 Hz, 1H), 3.81 (br, ddd, *J* = 15.4, 9.0, 7.0 Hz, 1H), 2.93 (br, dd, *J* = 13.0, 3.9 Hz, 1H), 2.88−2.80 (m, 2H), 2.61 (dd, *J* = 13.0, 10.4 Hz, 1H), 2.47 (m, 1H), 2.37 (m, 1H), 2.23−1.97 (m, 4H); ^{13}C NMR (75.4 MHz, APT, $CDCl_3$, 50 °C) δ 161.5, 137.4, 133.7, 130.6, 130.2 (2C), 129.0 (2C), 128.3, 126.3, 125.6, 125.2, 120.8, 120.4, 117.8, 112.8, 66.3, 48.4, 37.4, 34.9, 32.4, 29.4, 26.7, 19.9; EIMS *m/z* (relative intensity) 398 (2, M^+), 277 (75), 276 (69), 221(100), 122(65), 105(95). Anal. Calcd for $C_{26}H_{26}N_2O_2$: C, 78.36; H, 6.58; N, 7.03. Found: C, 77.97; H, 6.44; N, 7.22.

(3*S*,3α)-1-[(1*S*,2*S*)-[[1-[(Benzoyloxy)methyl]-cyclohex-4-en-2-yl]methyl]]-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (13a) and (3*R*,3β)-1-[(1*S*,2*S*)-[[1-[(Benzoyloxy)methyl]-cyclohex-4-en-2-yl]methyl]]-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (13b) (mixture of epimers). $NaBH_4$ reduction of the imine-benzoate **11** (398 mg, 1.0 mmol) as described above for **10** gave, after FC (EtOAc), 351 mg (88%) of amine-benzoate **13** as an inseparable mixture of two diastereomers **13a** and **13b** (1.8:1 ratio from 300 MHz ^1H NMR): white foam; R_f (EtOAc) 0.17; IR ($CHCl_3$) 3468, 3380, 1715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.53 (br, s), 8.06 (m, 2H), 7.73 (br, s), 7.61−7.51 (m, 1H), 7.49−7.39 (m, 4H), 7.26 (br, d, *J* = 7.5 Hz, 1H), 7.18−7.03 (m, 2H), 5.71 (m, 2H), 4.79 (dd, *J* = 10.4, 4.6 Hz), 4.41 (dd, *J* = 10.5, 6.4 Hz), 4.23 (dd, *J* = 10.5, 6.4 Hz), 4.18−4.08(m), 3.36−3.22 (m, 1H), 3.09−2.93 (m, 1H), 2.80−2.65 (m, 2H), 2.49−1.58 (m, 9H); ^{13}C NMR (75.4 MHz, acetone-d_6); **13a**: δ 166.9, 138.2, 136.9, 133.7, 131.5, 130.2 (2C), 129.3 (2C), 128.6, 126.8, 126.0, 121.4, 119.3, 118.3, 111.5, 108.8, 66.1, 50.8, 42.4, 37.4, 35.9, 30.8, 29.3, 27.4, 23.4; **13b**: δ 167.1, 138.1, 136.9, 133.8, 131.9, 130.2 (2C), 129.3 (2C), 128.6, 127.4, 125.7, 121.4, 119.3, 118.3, 111.5, 108.8, 65.3, 51.6, 42.6, 37.4, 35.9, 32.3, 31.1, 28.0, 23.4; EIMS *m/z* (relative intensity) 400(8, M^+), 278(36), 277(41), 221(4), 171(100), 122 (11). Anal. Calcd for $C_{26}H_{28}N_2O_2$: C, 77.96; H, 7.05; N, 6.99. Found: C, 77.61; H, 7.00; N, 7.15.

Hydrolysis of 13a and 13b to the Amino Alcohols 12a and 12b. To a solution of the above mixture of **13a** and **13b** (320 mg, 0.80 mmol) in EtOH (5 mL) was added potassium carbonate (12 mg, 0.08 mmol), and the reaction mixture was stirred at 45 °C for 22 h. After removal of the solvent the residue was diluted with EtOAc (50 mL) and the organic layer washed with brine and dried. Evaporation of the solvent and TLC of the residue [47:3:1 EtOAc:*i*-PrOH:NH_3(*d* 0.88)] gave 83 mg (35%) of **12b** and 147 mg (62%) of **12a** identical to those isolated from the $NaBH_4$ reduction of imine **10**.

Reduction of 11·HCl with $NaBH_4$. To a cooled (0 °C) solution of the imine-benzoate **11**(1.42 g, 3.56 mmol) in EtOH (25 mL) was added 1.3 mL of 2.74 N HCl/EtOH (3.56 mmol). After being stirred for 15 min at 0 °C, the resulting solution was slowly introduced *via* cannula (15 min) into an equally cold solution of $NaBH_4$ (676 mg, 17.8 mmol) in EtOH (60 mL). The reaction mixture was stirred at the same temperature for an additional 30 min and then worked up as described for the reduction of imine **10**. FC (EtOAc) of the residue gave 1.35 g (95%) of a 5.1:1 inseparable mixture of **13a** and **13b** (^1H NMR).

(3S,3α)-1-[(1*S*,2*S*)-[[1-[(Benzoyloxy)methyl]cyclohex-4-en-2-yl]methyl]]-2-(methoxycarbonyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (14a) and (3*R*,3β)-1-[(1*S*,2*S*)-[[1-[(Benzoyloxy)methyl]cyclohex-4-en-2-yl]methyl]]-2-(methoxycarbonyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (14b). To a cold (0 °C) and stirred solution of the above 5.1:1 mixture of diastereomers **13a/13b** (1.0 g, 2.5 mmol) and triethylamine (303 mg, 3.0 mmol) in dry CH_2Cl_2 (27 mL) was added dropwise a solution of methyl chloroformate (471 mg, 4.98 mmol) in CH_2Cl_2 (12 mL). After 30 min, the reaction mixture was diluted with water (12 mL) and saturated NH_4Cl solution (20 mL) and extracted with CH_2Cl_2. The extracts were washed with saturated $NaHCO_3$ (aq) and water and dried. The solvent was removed and the residue purified by FC (gradient, 0−50% EtOAc in CH_2Cl_2) to give 188 mg (16%) of urethane **14b** and 939 mg (82%) of urethane **14a**.

14b(3β-H, 3*R*): mp 122 °C (EtOAc); R_f (15.6:1 CH_2Cl_2: Et_2O) 0.47; $[\alpha]^{25}_D$ −188.4° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3460, 1710, 1690 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 70 °C) δ 10.71 (br, s, 1H), 8.01 (br, d, *J* = 7.8 Hz, 2H), 7.66(t, *J* = 7.8 Hz, 1H), 7.52(t, *J* = 7.8 Hz, 2H), 7.40 (br, d, *J* = 7.5 Hz, 1H), 7.33 (br, d, *J* = 7.5 Hz, 1H), 7.07 (br, t, *J* = 7.5 Hz, 1H), 6.98 (br, t, *J* = 7.5 Hz, 1H), 5.68 (m, 2H), 5.36 (br, dd, *J* = 8.0, 3.4 Hz, 1H), 4.49(dd, *J* = 10.4, 5.6 Hz, 1H), 4.32(dd, *J* = 10.4, 8.4 Hz, 1H), 4.27 (br, dd, *J* = 13.2, 4.0 Hz, 1H), 3.67(s, 3H), 3.24(ddd, *J* = 13.2, 10.4, 5.4 Hz, 1H), 2.80−2.63 (m, 2H), 2.44 (m, 1H), 2.24−2.04 (m, 5H), 2.00−1.85 (m, 1H), 1.79(ddd, *J* = 15.6, 9.2, 5.8 Hz, 1H); ^{13}C NMR (20.1 MHz, $CDCl_3$) δ 167.4, 156.8, 136.4, 135.1, 133.4, 130.4, 129.8 (2C), 128.7 (2C), 127.0 (2C), 125.4, 121.7, 119.4, 118.1, 111.2, 107.9, 64.9, 52.8, 50.0, 38.3, 37.0, 34.6, 32.5, 29.6, 28.6, 21.5; EIMS *m/z* (relative intensity) 458(27, M^+), 399(8), 230(68), 229(100). Anal. Calcd for $C_{28}H_{30}N_2O_4$: C, 73.34; H, 6.60; N, 6.11. Found: C, 72.06; H, 6.70; N, 6.12.

14a(3α-H, 3*S*): mp 158−160 °C (EtOAc); R_f (15.6:1 EtOAc: Et_2O) 0.35; $[\alpha]^{25}_D$ −10.2° (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) 3465, 1715, 1692 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 100 °C) δ 10.53 (br, s, 1H), 7.94 (d,*J* = 7.7 Hz, 2H), 7.63(t, *J* = 7.7 Hz, 1H), 7.49(t, *J* = 7.7 Hz, 2H), 7.38 (br, d, *J* = 7.4 Hz, 1H), 7.32 (br, d, *J* = 7.4 Hz, 1H), 7.06(t, *J* = 7.4 Hz, 1H), 6.98(t, *J* = 7.4 Hz, 1H), 5.82−5.68 (m, 2H), 5.34 (dd, *J* = 7.5, 6.5 Hz, 1H), 4.31 (dd, *J* = 10.4, 6.4 Hz, 1H), 4.26 (dd, *J* = 10.4, 6.4 Hz, 1H), 3.64 (s, 3H), 3.23 (ddd, *J* = 13.8, 10.4, 4.8 Hz, 1H), 2.74 (ddd, *J* = 15.2, 13.8, 6.4 Hz, 1H), 2.64 (ddd, *J* = 15.2, 4.8, 1.6 Hz, 1H), 2.33 (m, 1H), 2.30−1.95 (m, 5H), 1.92 (br, t, *J* = 7.0 Hz, 2H); ^{13}C NMR (20.1 MHz, $CDCl_3$) δ 166.9, 157.2, 136.2, 134.7, 133.1, 130.3, 129.6 (2C), 128.5 (2C), 127.0, 126.0, 123.1. 121.8, 119.5, 118.1, 111.0, 108.1, 65.6, 52.9, 49.7, 38.2, 36.4, 34.1, 29.8, 29.0, 26.2, 21.4; EIMS *m/z* (relative intensity) 458 (14, M^+), 399(5), 242(2), 230(45), 229(100), 169(14). Anal. Calcd for $C_{28}H_{30}N_2O_4$: C, 73.34; H, 6.60; N, 6.11. Found: C, 72.18; H, 6.68; N 6.20.

Conversion of Urethane 14a to Amino Alcohol 12a. A 92 mg (0.2 mmol) amount of the urethane **14a** and 64 mg (1.6 mmol) of NaOH were combined in 3 mL of ethylene glycol: H_2O (29:1) and heated to 130 °C. After 36 h the solution was chilled to 20 °C. Water and Et_2O (10 mL each) were added and stirred vigorously. The ether layer was dried and then concentrated *in vacuo*. The oil residue was purified by TLC [47:3:1 EtOAc:*i*-PrOH:NH_3(*d* 0.88)] to give 55 mg (93%) of amino alcohol **12a** identical in all respects to that isolated from the $NaBH_4$ reduction of imine **10**.

Conversion of Urethane 14b to Amino Alcohol 12b. The procedure described for the urethane **14a** was employed with 92 mg (0.2 mmol) of urethane **14b**. Purification of the residue as described above afforded 52 mg (88%) of amino alcohol **12b** identical in all respects to that isolated from the $NaBH_4$ reduction of imine **10**.

(3S,3α)-1-[(1S*,2R*,4S,5R)-[1,2-Dihydroxy-4-[(benzoyloxy)methyl]cyclohex-5-yl]methyl]]-2-(methoxycarbonyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (15) (mixture of diastereomers 1:1). Osmium tetraoxide, as a 0.039 M solution in t-BuOH (2.14 mL, 0.083 mmol), was added to a solution of the urethane **14a** (1.93 g, 4.21 mmol) and *N*-methylmorpholine *N*-oxide (610 mg, 5.92 mmol) in 9:1 THF/H_2O (50 mL) at 0 °C. After 12 h at room temperature, the mixture was treated with Florisil (1.9 g) and $NaHSO_3$ (600 mg), stirred for 1 h, filtered, and concentrated. The residue was diluted with EtOAc and the organic layer was washed sequentially with 5% H_3PO_4 and brine, dried, and concentrated

in vacuo to afford 1.71 g of diastereomeric diols **15** (1:1 ratio, 83%) as a colorless foam, used in the next step without further purification. **15**: R_f (47:3:1 EtOAc:*i*-PrOH:NH_3 (*d* 0.88)] 0.70 (minor) and 0.62 (major); IR ($CHCl_3$) 3470, 3300, 1710, 1690 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.06 (br, s), 8.80(m), 8.43 (br, s), 7.98 (br, d, J = 7.8 Hz, 2H), 7.59–7.00 (m, 7H), 5.63–5.22 (m, 1H), 4.45–3.70 (m, 5H), 3.64(s), 3.63(s), 3.30–1.40 (m, 13H); EIMS m/z (relative intensity) 492(80, M^+), 474(47), 456(18), 433(32), 370(8), 229(100); HRMS calcd for $C_{28}H_{32}N_2O_6$ 492.5912, found 492.5909.

(3*S*,3α)-1-[(3*S*,4*R*)-[4-[(Benzoyloxy)methyl]-2,3-bis-(formylmethyl)butyl]]-2-(methoxycarbonyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (16). A solution of the diols **15** (300 mg, 0.61 mmol) in 50 mL of THF/H_2O (1:2) at 0 °C was treated with a 0 °C solution of 138 mg (0.64 mmol) of sodium metaperiodate in 6 mL of water. After stirring for 1.5 h at 0 °C, the reaction mixture was diluted with water and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with brine, dried, and concentrated *in vacuo* to give 287 mg of crude dialdehyde **16**[28] which was not further purified but used directly in the next stage. **16**: pale yellow gum; R_f (1:3 EtOAc:CH_2Cl_2) 0.42; IR ($CHCl_3$) 3465, 2720, 1725,1690 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 9.80 (br, s, 1H), 9.74 (br, s, 1H), 8.95(m), 8.60 (br, s), 7.95 (m, 2H), 7.60–6.95 (m, 7H), 5.35 (m, 1H), 4.62–4.08 (m, 3H), 3.66(s, 3H), 3.30–2.40 (m, 7H), 2.05–1.45 (m, 4H); EIMS m/z (relative intensity) 490(18, M^+), 472(24), 350(22), 229(100); HRMS calcd for $C_{28}H_{30}N_2O_6$ 490.5740, found 490.5728.

[3a*S*-[3aα,5β(*S*),7α]]-β-(Formylmethyl)-1,2,3,3a,4,5,6,7-octahydro-7-hydroxy-3-(methoxycarbonyl)-3,7a-diazacyclohepta[*jk*]fluorene-5-ethanol Benzoate (17a). A solution of the crude dialdehyde **16**[28] (1.10 g, 2.13 mmol) in THF (99 mL) and 2 N aqueous HCl (1 mL) was stirred at room temperature. After 30 min the solution was cooled to 5 °C, neutralized with 5% $NaHCO_3$ (aq), and evaporated under reduced pressure. The residue was dissolved in EtOAc (100 mL) and the solution was washed with brine, dried, and concentrated *in vacuo*. FC (1:4 EtOAc:CH_2Cl_2) of the crude material afforded hemiaminal **17a** (877 mg, 84%) as a colorless solid which did not crystallize: mp 130 °C dec; R_f (1:3 EtOAc:CH_2Cl_2) 0.39; $[\alpha]^{25}_D$ +23.4° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3600, 3390, 2720, 1720, 1690 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 70 °C) δ 9.78 (br, s, 1H), 7.97 (d,J = 7.8 Hz, 2H), 7.67(t, J = 7.8 Hz, 1H), 7.54(t, J = 7.8 Hz, 2H), 7.50 (br, d, J = 7.5 Hz, 1H), 7.44 (br, d, J = 7.5 Hz, 1H), 7.14 (t, J = 7.5 Hz, 1H), 7.03 (t, J = 7.5 Hz, 1H), 6.30 (br, dd, J = 8.5, 4.5 Hz, 1H), 6.28 (m, 1H), 5.34 (br, d, J = 11.7 Hz, 1H), 4.42–4.22 (m, 3H), 3.67(s, 3H), 3.12(ddd, J = 12.3, 10.8, 3.9 Hz, 1H), 2.74 (br, t, J = 12.0, 1H), 2.72–2.51 (m, 5H), 2.27(ddd, J = 13.8, 4.5, 2.1 Hz, 1H), 2.01 (br, d, J = 11.7 Hz, 1H), 1.85(q, J = 11.7 Hz, 1H), 1.52 (br, t, J = 13.8 Hz, 1H); ^{13}C NMR (20.1 MHz, $CDCl_3$) δ 201.1, 166.5, 155.9, 135.8, 135.0, 133.2, 129.8, 129.6 (2C), 128.5 (2C), 126.3, 121.8, 119.6, 118.4, 109.2, 108.5, 75.0, 65.8, 52.8, 51.6, 44.1, 39.2, 38.2, 37.7 (2C), 32.3, 21.4; EIMS m/z (relative intensity) 490(14, M^+), 472(41), 413(13), 350(14), 229(100). Anal. Calcd for $C_{28}H_{30}N_2O_6$:C, 68.55; H, 6.17; N, 5.71. Found: C, 68.31; H 6.11; N, 5.83.

[3a*S*-[3aα,5β(*S*),7α]]-γ-[(Benzoyloxy)methyl]-1,2,3,3a,4,5,6,7-octahydro-7-hydroxy-3-(methoxycarbonyl)-3,7a-diazacyclohepta[*jk*]fluorene-5-propanol (18). To a solution of the hemiaminal **17a** (200 mg, 0.41 mmol) in MeOH (10 mL) at 0 °C was added $NaBH_4$ (24 mg, 0.63 mmol). After stirring at 0 °C for 1 h, the reaction mixture was poured into brine and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried and concentrated *in vacuo* to give 198 mg (98%) of hemiaminal-alcohol **18** which was recrystallized from EtOH/i-Pr_2O: mp 104 °C; R_f (2.3:1 EtOAc:hexane) 0.36; $[\alpha]^{25}_D$ +25.1° (*c* 0.6, $CHCl_3$); IR ($CHCl_3$) 3420, 1715, 1685 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 70 °C) δ 7.94 (d,J = 7.8 Hz, 2H), 7.63(t, J = 7.8 Hz, 1H), 7.50(t, J = 7.8 Hz, 2H), 7.44 (br, d, J = 7.5 Hz, 1H), 7.41 (br, d, J = 7.5 Hz, 1H), 7.12(t, J = 7.5 Hz, 1H), 7.01 (br, t, J = 7.5 Hz, 1H), 6.26 (br, s, 1H), 6.24 (br, d, J = 4.5 Hz, 1H), 4.30 (br, dd, J = 12.3, 3.6 Hz, 1H), 4.28 (d,J = 6.3 Hz, 2H), 4.24 (m, 1H), 3.62(s, 3H), 3.57–3.49 (m, 2H), 3.06(ddd, J = 12.3, 10.8, 3.9 Hz, 1H), 2.75–2.56 (m, 3H), 2.25 (br, dd, J = 13.8, 4.5 Hz, 1H), 2.01 (m, 1H), 1.96 (br, d, J = 11.9 Hz, 1H), 1.83(q, J = 11.9 Hz, 1H), 1.66- 1.46 (m, 2H), 1.47 (br, t, J = 13.8 Hz, 1H); ^{13}C NMR (75.4 MHz, APT, $CDCl_3$) δ 135.2, 133.7, 130.3 (2C), 129.1 (2C), 122.9, 121.0, 119.1, 111.5, 110.4, 82.8, 67.9, 64.7, 53.4, 51.5, 44.2, 40.6, 35.2, 35.1, 32.4, 31.5, 22.7; EIMS m/z (relative intensity) 474(78, $M^+ - H_2O$), 415(21), 352(41), 281(100), 229(99). Anal. Calcd for $C_{28}H_{32}N_2O_6$:C, 68.27; H, 6.55; N, 5.69. Found: C, 68.16; H, 6.54; N, 5.74.

[3a*S*-[3aα,5β(*S*),7α]]-γ-[(Benzoyloxy)methyl]-1,2,3,3a,4,5,6,7-octahydro-7-methoxy-3-(methoxycarbonyl)-3,7a-diazacyclohepta[*jk*]fluorene-5-propanol (19). To a solution of the hemiaminal alcohol **18** (300 mg, 0.61 mmol) in 40 mL of MeOH was added 2 mL of 17 M HCl/MeOH. The reaction mixture was stirred 20 min at room temperature, neutralized with saturated $NaHCO_3$ (aq), and concentrated *in vacuo*. The semisolid residue was taken up in 50 mL of water and 50 mL of CH_2Cl_2. The aqueous phase was extracted with another 20 mL of CH_2Cl_2, the combined organic extracts were dried, and the solvent was removed under reduced pressure. The residue was recrystallized from MeOH/i-Pr_2O to afford 302 mg of aminal **19** (98%): mp 91–92 °C; R_f (1:1 EtOAc:hexane) 0.31; $[\alpha]^{25}_D$ +24.7° (*c* 0.65, $CHCl_3$); IR ($CHCl_3$) 3380, 1710, 1685 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 70 °C) δ 7.96 (d,J = 7.8 Hz, 2H), 7.68(t, J = 7.8 Hz, 1H), 7.53(t, J = 7.8 Hz, 2H), 7.62 (d,J = 7.5 Hz, 1H), 7.46 (br, d, J = 7.5 Hz, 1H), 7.17(t, J = 7.5 Hz, 1H), 7.06(t, J = 7.5 Hz, 1H), 5.95 (br, d, J = 4.4 Hz, 1H), 5.18 (br, d, J = 11.7 Hz, 1H), 4.35 (br, dd, J = 12.3, 3.6 Hz, 1H), 4.32 (d, J = 6.3 Hz, 1H), 4.26(t, J = 5.4 Hz, 1H), 3.66(s, 3H), 3.63–3.47 (m, 2H), 3.15(s, 3H), 3.11(ddd, J = 12.3, 10.8, 4.0 Hz, 1H), 2.77–2.64 (m, 2H), 2.60 (br, t, J = 12.0 Hz, 1H), 2.39 (br, dd, J = 13.8, 4.4 Hz, 1H), 2.04 (m, 1H), 2.00 (br, d, J = 11.7 Hz, 1H), 1.89(q, J = 11.7 Hz, 1H), 1.66–1.51 (m, 3H); ^{13}C NMR (75.4 MHz, APT, $CDCl_3$, 40 °C) δ 156.7, 133.7, 130.3 (2C), 129.1 (2C), 122.9, 121.0, 119.1, 110.4, 82.8, 67.9, 64.7, 53.4, 51.5 (2C), 44.2, 40.6, 35.2, 35.1, 32.4, 31.6, 22.8; CD (MeOH) $[\Theta]_{296}$ +1437, $[\Theta]_{287}$ +3046, $[\Theta]_{269}$ +8793; EIMS m/z (relative intensity) 506 (23, M^+), 474 (94), 415 (25), 352 (51), 281 (100), 229 (50). Anal. Calcd for $C_{29}H_{34}N_2O_6$:C, 68.75; H, 6.77; N, 5.53. Found: C, 68.70; H, 6.73; N, 5.60.

[3a*S*-[3aα, 5β(*S*),7α]]-α-Ethenyl-1,2,3,3a,4,5,6,7-octahydro-7-methoxy-3-(methoxycarbonyl)-3,7a-diazacyclohepta[*jk*]fluorene-5-ethanol Benzoate (21). Tri-*n*-butylphosphine (487 mg, 2.4 mmol) was injected dropwise over 5 min into a stirred solution of the aminal **19** (860 mg, 1.7 mmol) and 2-nitrophenyl selenocyanate (565 mg, 2.4 mmol) in dry THF (68 mL) under nitrogen. After 30 min at room temperature, the solvent was removed *in vacuo*. FC (1:3 hexane:Et_2O) of the yellow residue yielded the selenide **20** (1.59 g, 96%) as yellow amorphous solid: R_f (1:3 hexane:Et_2O) 0.39; IR ($CHCl_3$) 1715, 1685, 1590 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 45 °C) δ 8.25 (br, d, J = 8.0 Hz, 1H), 7.98 (d,J = 7.8 Hz, 2H), 7.62–7.04 (m, 10 H), 5.72 (br, d, J = 4.6 Hz, 1H), 5.30 (m, 1H), 4.45 (m, 1H), 4.41(dd, J = 11.1, 5.4 Hz, 1H), 4.27 (br, dd, J = 11.1, 5.7 Hz, 1H), 3.74(s, 3H), 3.17(s, 3H), 3.18–2.96 (m, 3H), 2.90–2.70 (m, 3H), 2.42 (m, 1H), 2.18–1.79 (m, 5H), 1.55 (m, 1H); MS (FAB$^+$) 691 (MH^+).

To a cold (0 °C) solution of the above selenide **20** in MeOH/H_2O (4.5:1, 100 mL) was added portionwise a solution of sodium metaperiodate (400 mg, 1.87 mmol) in water (16 mL). After being stirred for 4 h at room temperature, *N*,*N*-diisopropylethylamine (Hünig base, 1 mL) was added and, after further 4 h at room temperature, the solvent was removed *in vacuo*. The residue was diluted with water and extracted with Et_2O. The residue thus obtained was purified by FC (1:1 hexane:Et_2O) to give the vinyl derivative **21** (655 mg, 79% yield from **19**), as a colourless foam: R_f (1:1 hexane:Et_2O) 0.37; $[\alpha]^{25}_D$ +4.3° (*c* 1.25, $CHCl_3$); IR ($CHCl_3$) 1710, 1690 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 70 °C) δ 7.99 (d,J = 7.8 Hz, 2H), 7.68(t, J = 7.8 Hz, 1H), 7.62 (d,J = 7.5 Hz, 1H), 7.55(t, J = 7.8 Hz, 2H), 7.47 (br, d, J = 7.5 Hz, 1H), 7.17 (br, t, J = 7.5 Hz, 1H), 7.07(t, J = 7.5 Hz, 1H), 5.94 (br, d, J = 4.4 Hz, 1H), 5.82(ddd, J = 18.0, 9.8, 7.8 Hz, 1H), 5.22–5.13 (m, 3H), 4.46–4.31 (m, 3H), 3.67(s, 3H), 3.13 (m, 1H), 3.12(s, 3H), 2.79–2.67 (m, 2H), 2.66–2.54 (m, 2H), 2.41 (br, dd, J = 13.8, 4.4 Hz, 1H), 2.04 (br, d, J = 12.0 Hz, 1H), 1.79(q, J = 12.0 Hz, 1H), 1.51 (br, t, J = 13.8 Hz, 1H); ^{13}C NMR (75.4 MHz, APT, DMSO-d_6, 50

°C) δ 165.4, 154.7, 136.9, 136.3, 134.8, 133.0, 129.7, 128.8 (2C), 128.5 (2C), 125.4, 121.3, 119.0, 117.8, 117.6, 108.9, 108.1, 82.0, 64.8, 54.7, 52.2, 50.9, 47.8, 38.5, 37.2, 35.9, 31.7, 20.9; EIMS *m/z* (relative intensity) 488(19, M^+), 456(81), 397(3), 335(28), 281(73), 229(100); HRMS calcd for $C_{29}H_{32}N_2O_5$ 488.6032, found 488.6023.

[3a*S*-[3aα, 5β(*S*),7α]]-α-Ethenyl-1,2,3,3a,4,5,6,7-octahydro-7-methoxy-3-methyl-3,7a-diazacyclohepta[*jk*]fluorene-5-ethanol (22). The vinyl derivative **21** (161 mg, 0.33 mmol) in anhydrous THF (5 mL) was added in portions to a stirring suspension of $LiAlH_4$ (63 mg, 1.66 mmol) in THF (7 mL) at 0 °C under nitrogen. The reaction mixture was allowed to come to room temperature and then boiled 1.5 h under reflux with stirring. It was cooled to 0 °C and then successively treated with water (10 mL), 15% aqueous NaOH (1 mL), and Et_2O (10 mL). The organic layer was filtered off, and the white residue was washed with Et_2O. The combined organic filtrates were dried and concentrated under reduced pressure and the residue thus obtained was purified by FC (1:9 MeOH:$CHCl_3$) to give 108 mg (96%) of the vinyl alcohol **22** as a colorless glass which did not crystallize: R_f (1:9 MeOH:$CHCl_3$) 0.44; $[\alpha]^{25}_D$ +7.8° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3670, 3400 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 45 °C) δ 7.49 (br, d, *J* = 7.5 Hz, 1H), 7.33 (br, d, *J* = 7.5 Hz, 1H), 7.17 (br, t, *J* = 7.5 Hz, 1H), 7.09 (br, t, *J* = 7.5 Hz, 1H), 5.69 (br, d, *J* = 4.0 Hz, 1H), 5.65(ddd, *J* = 19.0, 10.0, 8.5 Hz, 1H), 5.16 (dd, *J* = 10.8, 2.0 Hz, 1H), 5.13 (dd, *J* = 19.0, 2.0 Hz, 1H), 3.72 (dd, *J* = 10.4, 6.0 Hz, 1H), 3.62 (dd, *J* = 10.4, 7.8 Hz, 1H), 3.58 (br, d, *J* = 11.2 Hz, 1H), 3.10−3.04 (m, 1H), 3.03(s, 3H), 2.80−2.69 (m, 3H), 2.54(s, 3H), 2.45 (br,t, *J* = 12.0 Hz, 1H), 2.33−2.15 (m, 3H), 1.59 (br,t, *J* = 13.0 Hz, 1H), 1.52 (br, s, 1H), 1.36 (br, q, *J* = 12.5 Hz, 1H); ^{13}C NMR (75.4 MHz, APT, $CDCl_3$) δ 138.3, 137.8, 137.5, 127.2, 122.1, 120.1, 119.6, 119.0, 109.1, 108.0, 83.8, 64.3, 61.2, 55.8, 53.8, 51.6, 43.6, 39.6, 36.8, 33.4, 20.7; EIMS *m/z* (relative intensity) 340 (33, M^+), 309 (16), 269 (71), 185 (100). HRMS calcd for $C_{21}H_{28}N_2O_2$ 340.4838, found 340.4840.

[3a*S*-[3aα, 5β(*E*),7α]]-α-Ethylidene-1,2,3,3a,4,5,6,7-octahydro-7-methoxy-3-methyl-3,7a-diazacyclohepta[*jk*]-fluorene-5-acetaldehyde (23) [(−)-17-*O*-methylakagerine]. To a magnetically stirred solution of the vinyl alcohol **22** (136 mg, 0.4 mmol) in dry DMSO (2 mL) under nitrogen was added triethylamine (209 mg, 2.07 mmol) followed by dropwise addition of a solution of sulfur trioxide−pyridine complex (191 mg, 1.2 mmol) in dry DMSO (2 mL). After 1.5 h the reaction was quenched by addition of saturated $NaHCO_3$ (aq) and extracted with CH_2Cl_2. The combined organic extracts were washed with water, dried, and concentrated. FC (1:19 MeOH:$CHCl_3$) of the residue gave 126 mg (93%) of 17-*O*-methylakagerine (**23**) which was recrystallized from aqueous EtOH: mp 183−186 °C dec, (lit.[1d] 187−189 °C); R_f (1:9 MeOH:$CHCl_3$) 0.58; $[\alpha]^{25}_D$ −15.8° (*c* 1.0, MeOH); CD (MeOH) $[\Theta]_{296}$ +1974, $[\Theta]_{287}$ +4888, $[\Theta]_{269}$ +13775. Anal. Calcd for $C_{21}H_{26}N_2O_2$:C, 74.52; H, 7.75; N, 8.27. Found: C, 74.47; H 7.72; N, 8.33. The synthetic material had IR, ^1H NMR, ^{13}C NMR, and MS spectra identical with those reported for natural **23**.[1d,f]

[3a*S*-[3aα, 5β(*E*),7α]]-α-Ethylidene-1,2,3,3a,4,5,6,7-octahydro-7-hydroxy-3-methyl-3,7a-diazacyclohepta[*jk*]fluorene-5-acetaldehyde (1) [(−)-akagerine]. A solution of 17-*O*-methylakagerine (**23**) (118 mg, 0.35 mmol) and 1 N HCl (2.5 mL) in THF/H_2O (1:2, 5 mL) was stirred at room temperature for 4 h, basified with saturated $NaHCO_3$ (aq), and extracted with $CHCl_3$. The organic extract was dried and evaporated to leave a residue that was purified by FC (1:4:5 diethylamine: $CHCl_3$:cyclohexane) to give (−)-akagerine (**1**) (109 mg, 96%) as white crystals from EtOH/Et_2O: mp 180−184 °C, [lit.[1a] 188 °C, dec (hexane)]; R_f (1:3:6 diethylamine: $CHCl_3$:cyclohexane) 0.27; $[\alpha]^{25}_D$ −16.5° (*c* 1.0, MeOH), [lit.[1c] −16.6° (*c* 1.0, MeOH0]; CD (MeOH) $[\Theta]_{266}$ +13180 {lit.[1a] $[\Theta]_{265}$ +13200}. Anal. Calcd for $C_{20}H_{24}N_2O_2$:C, 74.04; H, 7.46; N, 8.63. Found: C, 74.11; H, 7.48; N, 8.59. The synthetic material had IR,[1a] ^1H NMR,[1d] ^{13}C NMR,[1d] and MS[1a] identical with an authentic sample of (−)-akagerine.

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Supplementary Material Available: ^1H NMR spectra of compounds **1**, **7**−**17a**, **18**−**23** and ^{13}C NMR spectra of compounds **1**, **7**, **9**−**14**, **17a**, **18**, **19**, **21**−**23**; global minimum energy conformations of **17a**, **17b**, **19**, (C-17)-*epi* **19**, akagerine (**1**) and its C-19/C-20 (*Z*) isomer (49 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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