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Enantiopure Intermediates for the Synthesis of *Strychnos* Alkaloids

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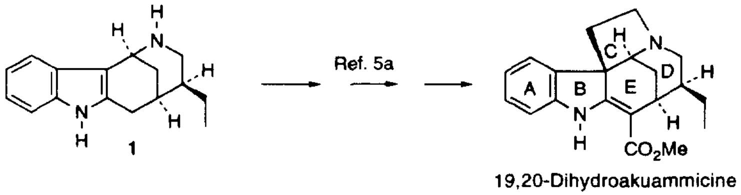
Abstract: The addition of 2-(lithiomethyl)indole **2** to the enantiopure oxazolinylpyridine **18** followed by acidic treatment afforded a mixture of tetracyclic compounds **21a** and **21b** in a 3:2 ratio. The major epimer **21a** was converted to tetracycle **25a**, a tetracyclic ABDE substructure of *Strychnos* alkaloids

The synthesis of *Strychnos* indole alkaloids has received considerable attention during the last few years. The activity in this field has culminated in the total synthesis of numerous pentacyclic *Strychnos* alkaloids and in several total syntheses of strychnine, the most complex alkaloid of this group.[1] However, the enantioselective synthesis of *Strychnos* alkaloids has been little explored. Only the enantioselective synthesis of (-)- and (+)-strychnine[2] and (-)-tubotaiwine,[1] the unnatural enantiomer of the alkaloid, and the preparation of a few enantiopure intermediates[3] and models[4] have been reported.

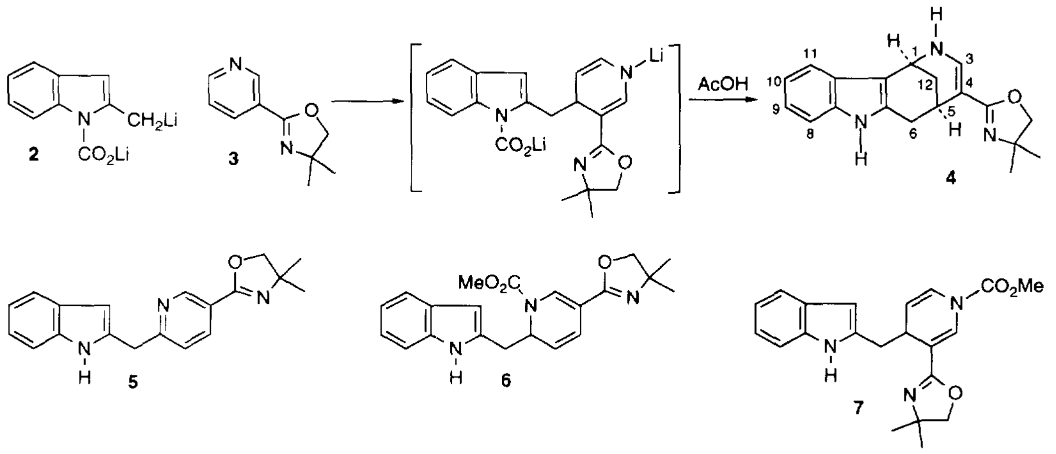
In previous papers we reported[5] a new synthetic entry to pentacyclic *Strychnos* alkaloids based on the closure of the pyrrolidine C ring by cyclization upon the indole 3-position of an appropriate hexahydro-1,5-methanoazocino[4,3-*b*]indole (tetracyclic ABDE substructure of *Strychnos* alkaloids). Following this methodology, the racemic tetracycle **1** was converted to (±)-tubifoline, (±)-tubifolidine, and (±)-dihydroakuammicine (Scheme 1).[5a]



Scheme 1

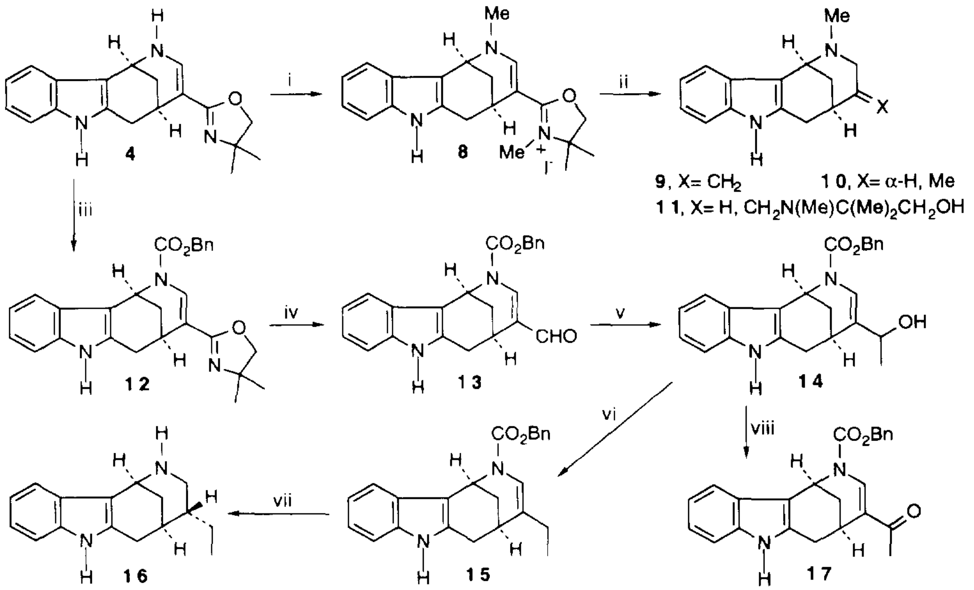
With the final aim of applying this methodology to the asymmetric synthesis of *Strychnos* alkaloids, we present here our studies on the synthesis of enantiopure hexahydro-1,5-methanoazocino[4,3-*b*]indoles. The route selected for the construction of this tetracyclic system involves the nucleophilic attack of an appropriately activated 2-methylindole derivative upon the 4-position of a pyridine bearing a chiral auxiliary at the 3-position,[6,7] followed by acid cyclization of the resulting 4-(2-indolylmethyl)-1,4-dihydropyridine.[8] For this purpose we chose the chiral oxazolinylpyridine **18** previously used by Meyers for the regio-[9] and stereoselective[7] addition of organolithium reagents to the pyridine nucleus.[10]

To test the feasibility of this strategy, a model study was carried out using the achiral oxazolinylpyridine **3**. As Scheme 2 illustrates, addition of the lithium derivative **2**[11] to pyridine **3**,[9] followed by acid treatment, led to the expected tetracyclic derivative **4** in 25% yield. This yield can be considered as fairly satisfactory taking into account that tetracycle **4** is formed in a one-pot process from easily accessible starting materials. The addition also occurred to some extent at the pyridine α-position: 2-(pyridylmethyl)indole **5**, arising from aromatization of the initially formed 1,2-dihydropyridine, was also isolated. The lack of regioselectivity in the nucleophilic attack of **2** on the pyridine ring of **3**, in contrast with the regioselectivity usually shown in the addition of alkyl- or aryl-lithium derivatives to oxazolinylpyridines,[9] was more evident when the intermediate dihydropyridines were trapped with methyl chloroformate to provide a nearly equimolecular mixture of *N*-methoxycarbonyl-1,2- and 1,4-dihydropyridines, **6** and **7** respectively.



Scheme 2

Attempts to reduce the vinylogous amidine carbon-carbon double bond present in **4** under several reaction conditions resulted in failure. Reductive cleavage of the oxazoline ring of **4** by way of the corresponding metho salt **8** was not satisfactory from the synthetic standpoint because a mixture of tetracycles **9** (27%), **10** (<5%), and **11** (<5%) was obtained (Scheme 3). The formation of these over-reduced products can be rationalized by considering the participation of the piperidine nitrogen lone pair.[12] For this reason, the reductive cleavage was effected after protecting the piperidine nitrogen as a benzyloxycarbonyl derivative. In this manner, the tetracyclic formyl derivative **13** was obtained in 64% overall yield from **4**, and then elaborated, via the unstable alcohol **14**, to tetracycles **15-17**, which incorporate the C-20 two-carbon appendage present in *Strychnos* alkaloids.



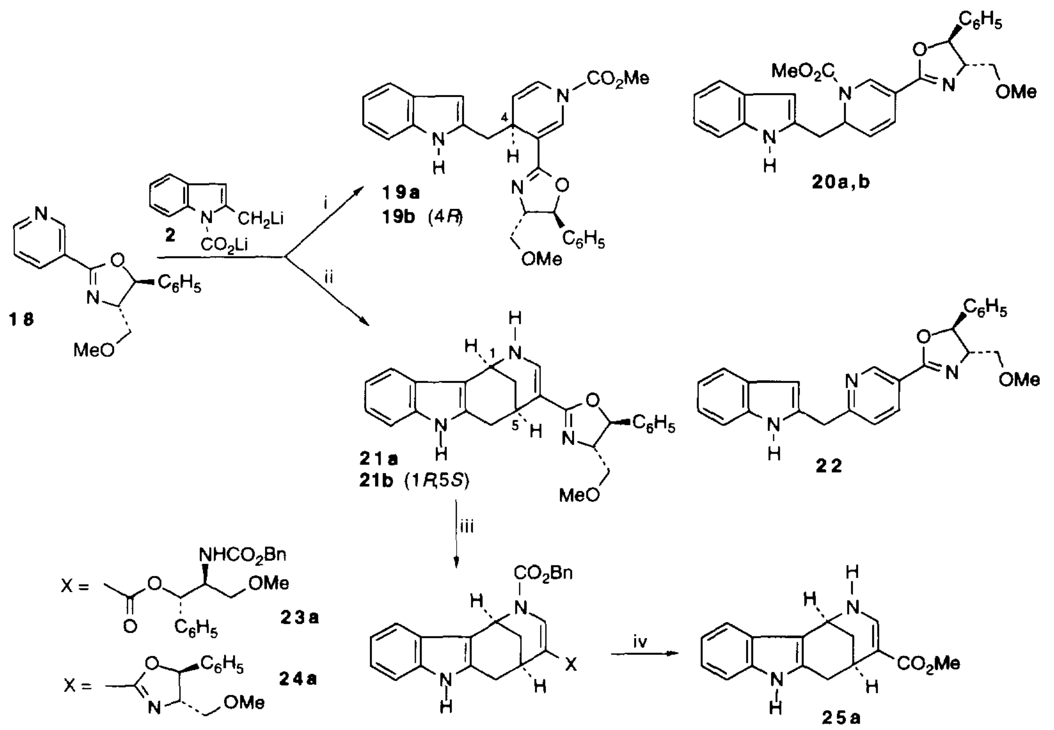
Reagents and conditions: i) MeI, acetone, reflux; ii) $NaBH_4$, MeOH, reflux; iii) NaH, $ClCO_2Bn$, THF; iv) MeOTf, CH_2Cl_2 followed by $NaBH_4$, THF-MeOH, then oxalic acid, THF-H_2O; v) MeLi, THF; vi) Et_3SiH, $TiCl_4$, CH_2Cl_2; vii) H_2, 10% Pd-C, MeOH; viii) PDC, CH_2Cl_2.

Scheme 3

The above methodology was then applied to the enantiopure oxazolinylpyridine **18**.[7d] Nucleophilic addition of the lithium derivative **2** to the pyridine ring of **18**, followed by trapping of the initially formed dihydropyridines with methyl chloroformate, led to a 9:4 mixture of *N*-protected 1,4- and 1,2-dihydropyridines (**19a,b** and **20a,b**, respectively) in satisfactory chemical yield (62%) (Scheme 4). Although the regioselectivity of the nucleophilic attack was higher than that observed from the above achiral oxazolinylpyridine **3**, probably due to the presence of the methoxy group, unfortunately, only a 3:2 ratio of diastereomeric 1,4-dihydropyridines **19a** and **19b** was formed. The configuration at the pyridine C-4 position in the major isomer **19a** was assigned as *S* by analogy with the results obtained in the addition of other organolithium derivatives to the same oxazolinylpyridine **18**. It is worth mentioning that this configuration corresponds to the absolute configuration at C-15 in *Strychnos* alkaloids. As could be expected, 1,2-dihydropyridines **20** were formed as a nearly equimolecular mixture of diastereomers (54:46 ratio).

Acid cyclization of the initially formed mixture of *N*-unsubstituted dihydropyridines led to a 3:2 diastereomeric mixture of tetracycles **21a** and **21b** in 30% yield. Minor amounts (~5%) of the 2-substituted pyridine derivative **22** were also isolated. The lower chemical yields for **21** and **22**, as compared with the yields for dihydropyridines **19** and **20**, can be explained by considering that the intermediate (2-indolylmethyl)dihydropyridines undergo a fragmentation promoted by the initial protonation at the indole 3-position. Finally, removal of the auxiliary oxazolinyl group from the major diastereomer **21a** was effected by treatment with NaH and excess of benzyl chloroformate, followed by methanolysis of the resulting tetracyclic ester **23a**. The enantiopure tetracycle **25a** was obtained. Minor amounts of the *N*-benzyloxycarbonyl derivative **24a**, in which the oxazoline group was not cleaved, were also isolated after the former step.

The low regio- and stereoselectivity observed in the addition of 2-(lithiomethyl)indole **2** to the enantiopure oxazolinylpyridine **18** can be attributed to an inefficient coordination of the complex lithium species **2** with the methoxy group and the nitrogen atom of the oxazoline moiety, which seems to be a critical factor for the success of this type of stereoselective additions.[13]



Reagents and conditions: i) $ClCO_2Me$, THF; ii) 2:1:1 AcOH-dioxane-H_2O; iii) NaH, $ClCO_2Bn$, THF; iv) NaOMe, MeOH.

Scheme 4

EXPERIMENTAL SECTION

General. Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. ^1H and ^{13}C-NMR spectra were recorded on a Varian Gemini-200 instrument (200 and 50.3 MHz, respectively). Chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. IR spectra were recorded on a Nicolet 205 FT-IR spectrophotometer. Mass spectra were determined on a Hewlett-Packard 5988A mass spectrometer or on a Autospec-VG (HRMS). Optical rotations were measured on a Perkin-Elmer 241 polarimeter using a 1 dm cell with a total volume of 1 ml. Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 0.040-0.060 mm). Drying of organic extracts during the work-up of reactions was performed over anhydrous Na_2CO_3. Microanalyses were performed on a Carlo Erba 1106 analyzer by the Centro de Investigación y Desarrollo (CSIC), Barcelona.

4-(4,4-Dimethyl-2-oxazolinyl)-1,2,5,6-tetrahydro-1,5-methanoazocino[4,3-*b*]indole (4). A solution of 2-(lithiomethyl)indole **2** in anhydrous THF (80 ml, 3:1 THF-pentane), prepared as described[11] from 2-methylindole (4.5 g, 34 mmol), was added *via* cannula to a solution of oxazolinylpyridine **3**[9] (5 g, 28.4

mmol) in anhydrous THF (300 ml) at -78°C. The reaction mixture was stirred at -78°C for 3 h and then the solvent was removed under reduced pressure. The resulting residue was dissolved in a freshly degassed 2:1:1 mixture of AcOH-dioxane-water (450 ml). After 16 h of stirring at room temperature, the solution was poured into crushed ice, neutralized with concentrated aqueous NaOH, and extracted with AcOEt. The extracts were dried over Na_2SO_4 and concentrated under vacuum to give a residue which, after purification by flash chromatography (93:2:5 AcOEt-EtOH-Et_2NH), yielded the title compound **4** (2.2 g, 25%): IR (KBr) 3386, 3175, 1621 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.28 and 1.33 (2s, 6H, 2CH_3), 1.80-2.05 (m, 2H, H-12), 2.78 (dd, *J* = 16.5 and 4.5 Hz, 1H, H-6), 2.91 (d, *J* = 16.5 Hz, 1H, H-6), 3.23 (m, 1H, H-5), 3.84 (s, 2H, CH_2O), 4.60 (m, 1H, H-1), 5.03 (br s, 1H, NH), 6.98 (d, *J* = 5.6 Hz, 1H, H-3), 7.07 (m, 2H, H-9 and H-10), 7.25 (m, 1H, H-8), 7.48 (m, 1H, H-11), 8.80 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$) 27.0 (C-5), 28.7 and 28.8 (2CH_3), 29.2 (C-12), 31.1 (C-6), 42.3 (C-1), 66.3 (*C*Me$_2$), 78.4 (CH_2O), 97.9 (C-4), 111.4 (C-8), 111.9 (C-11b), 117.2 (C-11), 119.5 (C-10), 121.1 (C-9), 126.2 (C-11a), 136.1 (C-6a), 136.7 (C-7a), 138.9 (C-3), 164.6 (C=N); MS, m/e 307 (M^+, 34), 306 (27), 140 (100), 125 (37), 124 (14), 57 (13), 54 (15), 42 (26), 41 (41); mp 233-235°C (EtOH). Anal. Calcd for $C_{19}H_{21}N_3O.1/4\ C_2H_6O$: C, 73.44; H, 7.11; N, 13.17. Found: C, 73.40; H, 7.00; N, 13.20. On continuous elution with the same solvent system, 5-(4,4-dimethyl-2-oxazolinyl)-2-(2-indolylmethyl)pyridine (**5**) was obtained: IR (KBr) 3185, 1656 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.39 (s, 6H, 2CH_3), 4.13 (s, 2H, CH_2O), 4.31 (s, 2H, CH_2), 6.37 (s, 1H, H-3 ind), 7.10 (m, 2H, H-5 ind and H-6 ind), 7.27 (d, *J* = 8.0 Hz, 1H, H-3), 7.30 (d, *J*= 8.0 Hz, 1H, H-7 ind), 7.55 (d, *J* = 8.2 Hz, 1H, H-4 ind), 8.12 (dd, *J* = 8.0 and 2.0 Hz, 1H, H-4), 8.80 (br s, 1H, NH), 9.10 (d, *J* = 2.0 Hz, 1H, H-6); ^{13}C-NMR ($CDCl_3$) 27.8 (2CH_3), 36.7 (CH_2), 67.4 (*C*Me$_2$), 79.1 (CH_2O), 100.6 (C-3 ind), 110.7 (C-7 ind), 119.3 (C-4 ind), 119.8 (C-5 ind), 121.2 (C-6 ind), 122.0 (C-5), 122.9 (C-3), 128.4 (C-3a ind), 135.3 (C-2 ind), 136.6 (C-7a ind), 136.7 (C-4), 148.6 (C-6), 160.5 (C-2), 161.9 (C=N); mp 154-157°C (AcOEt-hexane). Anal. Calcd for $C_{19}H_{19}N_3O$: C, 74.73; H, 6.27; N, 13.76. Found: C, 74.68; H, 6.27; N, 13.39.

When the reaction mixture obtained after the reaction of oxazolinylpyridine **3** with 2-(lithiomethyl)indole **2** was treated with methyl chloroformate (2 equiv) and then stirred for 30 min at -30°C, a mixture of 3-(4,4-dimethyl-2-oxazolinyl)-4-(2-indolylmethyl)-1-(methoxycarbonyl)-1,4-dihydropyridine (**7**) and 5-(4,4-dimethyl-2-oxazolinyl)-2-(2-indolylmethyl)-1-(methoxycarbonyl)-1,2-dihydropyridine (**6**) was obtained. Flash column chromatography (95:3:2 ether-acetone-Et_2NH and then 97:3 $CHCl_3$-MeOH) afforded pure **7** (26% yield) and **6** (24% yield). **7**: IR (KBr) 3390, 1730, 1680, 1630 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.35 (s, 6H, 2CH_3), 2.78 (dd, *J*= 14.2 and 8.0 Hz, 1H, CH_2), 3.20 (dd, *J*= 14.2 and 3.0 Hz, 1H, CH_2), 3.70 (m, 1H, H-4), 3.82 (s, 3H, CH_3O), 3.97 and 4.00 (2d, *J*= 8.0 Hz, 2H, CH_2O), 5.1 (br s, 1H, H-5), 6.20 (s, 1H, H-3 ind), 6.80 (br s, 1H, H-6), 7.00-7.15 (m, 2H, H-5 ind and H-6 ind), 7.25 (m, 1H, H-7 ind), 7.50 (m, 1H, H-4 ind), 7.70 (br s, 1H, H-2), 9.95 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$) 28.0 and 28.1 (2CH_3), 33.4 (C-4), 37.4 (CH_2), 53.8 (CH_3O), 67.2 (*C*Me$_2$), 78.4 (CH_2O), 100.5 (C-3 ind), 109.0 (C-3), 110.6 (C-7 ind), 111.2 (C-5), 119.1 (C-5 ind), 119.7 (C-4 ind), 120.8 (C-6 ind), 121.1 (C-6), 128.5 (C-2), 129.1 (C-3a ind), 136.4 (C-2 ind), 137.3 (C-7a ind), 152.0 (C=O), 162.2 (C=N); MS, m/e 365 (M^+, 6), 235 (100), 130 (60), 106 (12), 105 (14), 103 (13), 93 (10), 78 (14), 77 (21), 59 (66), 57 (16), 55 (25). **6**: IR (KBr) 3390, 1730, 1655, 1620 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.32 and 1.35 (2s, 6H, 2CH_3), 2.95 (m, 2H, CH_2), 3.70 (s, 3H, CH_3O), 3.95 and 4.00 (2d, *J*= 8.0 Hz, 2H, CH_2O), 5.00 (m, 1H, H-2), 5.62 (dd, *J*= 9.8 and 5.7 Hz, 1H, H-3), 6.28 (s, 1H, H-3 ind), 6.54 (d, *J*= 9.8 Hz, 1H, H-4), 7.00-7.15 (m, 2H, H-5 ind and H-6 ind), 7.32 (m, 1H, H-7 ind), 7.52 (m, 1H, H-4 ind), 7.55 (br s, 1H, H-6), 8.35 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$) 28.9 and 30.0 (2CH_3), 34.4 (CH_2), 53.5 (C-2), 54.5

(CH_3O), 67.7 (*C*Me_2), 79.4 (CH_2O), 102.5 (C-3 ind), 108.0 (C-5), 111.2 (C-7 ind), 111.3 (C-3), 120.2 (C-4 ind), 120.4 (C-5 ind), 121.5 (C-6 ind), 122.0 (C-4), 129.5 (C-3a ind), 130.1 (C-6), 134.3 (C-2 ind), 136.8 (C-7a ind), 152.0 (C=O), 161.0 (C=N); MS, m/e 365 (M^+, 5), 235 (100), 130 (41), 59 (31), 41 (11).

Treatment of 4 with Methyl Iodide. Salt 8. A solution of compound **4** (200 mg, 0.65 mmol) and methyl iodide (1.6 ml, 26 mmol) in anhydrous acetone containing K_2CO_3 (90 mg, 0.65 mmol) was refluxed for 15 h with continuous stirring. The solvent was removed under reduced pressure and the residue was taken up with $CHCl_3$. The organic solution was washed with water, dried, and concentrated to give salt **8** (250 mg, 83%): IR (KBr) 3376, 1557 cm^{-1}; ^1H-NMR ($CDCl_3$) 1.33 and 1.36 (2s, 6H, $2CH_3$), 2.07 (m, 2H, H-12), 3.12 (m, 2H, H-6), 3.25 and 3.53 (2s, 6H, $2CH_3$), 3.40 (m, 1H, H-5), 4.23 and 4.33 (2d, J = 8.8 Hz, 2H, CH_2O), 4.67 (m, 1H, H-1), 7.08 (m, 2H, H-9 and H-10), 7.43 (m, 1H, H-8), 7.52 (m, 1H, H-11), 7.85 (s, 1H, H-3), 9.62 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$-CD_3OD) 23.3 and 23.6 ($2CH_3$), 24.3 (C-5), 28.1 (C-12), 30.0 and 44.2 ($2CH_3$), 31.7 (C-6), 50.1 (C-1), 65.6 (*C*Me_2), 78.1 (CH_2O), 90.3 (C-4), 108.5 (C-11b), 111.4 (C-8), 116.7 (C-11), 119.7 (C-10), 121.3 (C-9), 125.4 (C-11a), 135.0 (C-6a), 136.1 (C-7a), 152.6 (C-3), 165.6 (C=N); mp 177-179°C (AcOEt-EtOH). Anal. Calcd for $C_{21}H_{26}N_3OI.H_2O$: C, 52.34; H, 5.86; N, 8.73; I, 26.36. Found: C, 52.36; H, 5.85; N, 8.73; I, 26.42.

Reduction of Salt 8 with $NaBH_4$. $NaBH_4$ (69.6 mg, 1.84 mmol) was added to a solution of salt **8** (213 mg, 0.46 mmol) in anhydrous methanol (2 ml) and the resulting mixture was refluxed for 4 h. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2. The solution was washed with brine, dried, and evaporated to give a solid which, after flash column chromatography (95:5 to 80:20 ether-Et_2NH), afforded 2-methyl-4-methylene-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (**9**) (29 mg, 27%): IR (film) 3400, 1461 cm^{-1}; ^1H-NMR ($CDCl_3$) 1.96 (dt, J = 12.3 and 2.8 Hz, 1H, H-12), 2.22 (dm, J =12.3 Hz, 1H, H-12), 2.35 (s, 3H, CH_3), 2.65 (d, J = 17.0 Hz, 1H, H-6), 2.69 (d, J = 12.8 Hz, 1H, H-3), 2.95 (br s, 1H, H-5), 3.00 (d, J = 12.8 Hz, 1H, H-3), 3.15 (dd, J = 17.0 and 6.4 Hz, 1H, H-6), 4.20 (t, 1H, H-1), 4.80 and 4.85 (2m, 2H, =CH_2), 7.12 (m, 2H, H-9 and H-10), 7.32 (m, 1H, H-8), 7.55 (m, 1H, H-11), 8.15 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$) 30.0 (C-12), 32.8 (C-6), 34.4 (C-5), 43.4 (CH_3), 51.9 (C-1), 53.8 (C-3), 104.7 (C-11b), 110.5 (=CH_2), 110.8 (C-8), 118.1 (C-11), 119.9 (C-10), 121.3 (C-9), 128.1 (C-11a), 135.8 (C-6a), 136.7 (C-7a), 146.7 (C-4). Further elution gave compounds **10** and **11** in less than 5% yield. **10**: IR ($CHCl_3$) 3470 cm^{-1}; ^1H-NMR ($CDCl_3$) 0.96 (d, J = 7.0 Hz, 3H, CH_3), 1.71 (t, J = 11.5 Hz, 1H, H-3), 1.97 (dm, J = 12.0 Hz, 1H, H-12), 2.05-2.45 (m, 4H, H-3, H-4, H-5 and H-12), 2.30 (s, 3H, CH_3), 2.80 (br s, 2H, H-6), 4.15 (br s, 1H, H-1), 7.11 (m, 2H, H-9 and H-10), 7.30 (m, 1H, H-8), 7.53 (m, 1H, H-11), 7.21 (br s, 1H, NH); MS, m/e 240 (M^+, 26), 197 (9), 182 (27), 180 (11), 170 (14), 169 (100), 168 (50), 167 (46). **11**: IR ($CHCl_3$) 3470 cm^{-1}; ^1H-NMR ($CDCl_3$) 0.97 and 1.12 (2s, 6H, $2CH_3$), 1.70 (m, 1H, H-12), 2.00-2.40 (m, 4H, H-3, H-5, H-12 and CHN), 2.18 and 2.24 (2s, 6H, $2CH_3$), 2.65 (d, J = 17.5 Hz, 1H, H-6), 2.68 (1H, H-3), 3.03 (dd, J = 13.0 and 9.4 Hz, 1H, CHN), 3.20 (dd, J = 17.5 and 7.0 Hz, 1H, H-6), 3.33 and 3.61 (2d, J = 11.5 Hz, 2H, CH_2O), 4.13 (br s, 1H, H-1), 7.11 (m, 2H, H-9 and H-10), 7.33 (m, 1H, H-8), 7.50 (m, 1H, H-11), 8.11 (br s, 1H, N-H).

2-(Benzyloxycarbonyl)-4-(4,4-dimethyl-2-oxazolinyl)-1,2,5,6-tetrahydro-1,5-methanoazocino[4,3-*b*]indole (12). NaH (65.2 mg of a 60% oil dispersion, 1.63 mmol) was added to a solution of tetracycle **4** (250 mg, 0.81 mmol) in anhydrous THF (2 ml). The resulting mixture was stirred for 1 h at room temperature and then benzyl chloroformate (0.6 ml, 4.07 mmol) was added. After 20 h of stirring at room temperature, the solvent was eliminated under vacuum and the mixture was dissolved in $CHCl_3$. The solution was washed with saturated aqueous $NaHCO_3$, dried, and concentrated. The residue was chromatographed (94:6 ether-Et_2NH) to give pure compound **12** (318 mg, 88%): IR (KBr) 3400, 1706, 1637 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.29 and 1.34 (2s, 6H, $2CH_3$), 2.03 (m, 2H, H-12), 3.03 (br s, 2H, H-6), 3.34 (br s, 1H, H-5), 3.90 (br s, 2H, CH_2O), [5.14 and 5.30 (2d, *J* = 12.5 Hz) and 5.38 (s), 2H, CO_2CH_2], 5.68 and 5.84 (2br s, 1H, H-1), 6.90-7.50 (m, 8H, ArH), 7.59 and 7.74 (2s, 1H, H-3), 7.90 (m, 1H, H-11), 8.08 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$) 26.4 and 26.8 (C-5), 28.2 and 28.4 ($2CH_3$), 29.5 (C-6), 29.5 (C-12), 43.7 and 44.0 (C-1), 66.8 ($\mathit{C}Me_2$), 68.0 and 68.5 ($CO_2\mathit{C}H_2$), 78.2 (CH_2O), 108.4 (C-4), 109.5 (C-11b), 110.3 (C-8), 118.4 and 119.3 (C-11), 119.5 (C-10), 121.1 (C-9), 125.6 and 125.8 (C-11a), 128.0, 128.4 and 128.6 (*o*, *m* and *p*), 130.2 and 130.8 (C-3), 135.3 (C-6a), 135.5 (*ipso*), 135.9 (C-7a), 152.2 and 152.5 (C=O), 161.8 and 162.0 (C=N); mp 205-207°C (EtOH). Anal. Calcd for $C_{27}H_{27}O_3N_3$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.32; H, 6.24; N, 9.58.

2-(Benzyloxycarbonyl)-4-formyl-1,2,5,6-tetrahydro-1,5-methanoazocino[4,3-*b*]indole (13). A solution of oxazoline **12** (100 mg, 0.23 mmol) and methyl triflate (50 ml, 0.46 mmol) in CH_2Cl_2 (3 ml) was stirred at room temperature for 90 min, and then a solution of $NaBH_4$ (26 mg, 0.69 mmol) in THF-MeOH (4:1, 5 ml) was added. The stirring was continued for 2.5 h, the solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2. The solution was washed with saturated aqueous NH_4Cl, dried, and evaporated to give a residue which was dissolved in THF-H_2O (4:1, 5 ml). Oxalic acid dihydrate (43 mg, 1.15 mmol) was added to the above solution and the resulting mixture was stirred at room temperature for 20 h. The solution was concentrated, the residue was dissolved in CH_2Cl_2, and the organic solution was washed with saturated aqueous $NaHCO_3$ and dried. The CH_2Cl_2 was evaporated and the resulting mixture was purified by flash chromatography (97:3 AcOEt-EtOH) affording aldehyde **13** (69 mg, 73%): IR (KBr) 3400, 1724, 1653, 1609 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.93 (dt, *J* = 12.8 and 3.5 Hz, 1H, H-12), 2.15 (dm, *J* = 12.8 Hz, 1H, H-12), 2.85 (dd, *J* = 16.6 and 1.5 Hz, 1H, H-6), 3.05 (dd, *J* = 16.6 and 5.0 Hz, 1H, H-6), 3.36 (br s, 1H, H-5), 5.10-5.45 (m, 2H, OCH_2), 5.73 and 5.90 (2s, 1H, H-1), 6.80-7.45 (m, 8H, ArH), 7.59 and 7.75 (2s, 1H, H-3), 7.92 (m, 1H, H-11), 8.02 (br s, 1H, NH), 9.19 (br s, 1H, CHO); ^{13}C-NMR ($CDCl_3$-CD_3OD) 23.7 (C-5), 28.1 (C-12), 28.8-29.5 (C-6), 45.4 (C-1), 69.0 (OCH_2), 109.0 (C-11b), 110.6 (C-8), 118.6 and 118.8 (C-11), 119.4 (C-10), 121.1 (C-9), 124.0 (C-4), 125.5 (C-11a), 128.6 (*o*, *m*, and *p*), 135.0 (*ipso*), 135.3 (C-6a), 135.9 (C-7a), 145.0 (C-3), 152.0 (NCO_2), 190.9 (CHO); mp 204-206°C (acetone). Anal. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 74.32; H, 5.54; N, 7.42. Minor amounts (<10% yield) of 2-(benzyloxycarbonyl)-4-[(2-hydroxy-1,1-dimethylethyl)methylaminomethyl]-1,2,5,6-tetrahydro-1,5-methanoazocino[4,3-*b*]indole were also separated: IR ($CHCl_3$) 3469, 3325, 1695 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.04 and 1.05 (2s, 3H, CH_3), 1.06 and 1.08 (2s, 3H, CH_3), 2.02 (m, 2H, H-12), 2.04 and 2.07 (2s, 3H, CH_3), 2.68 and 2.73 (2d, *J* = 13.0 Hz, 1H, CH_2N), 2.80-2.90 (m, 2H, H-5 and H-6), 2.98 and 3.00 (2dd, *J* = 16.5 and 5.5 Hz, 1H, H-6), 3.18 and 3.24 (2d, *J* = 13.0 Hz, 1H, CH_2N), 3.36 and 3.44 (2d, *J* = 10.5 Hz, 2H, CH_2O), [5.10 and 5.25 (2d, *J* = 12.5 Hz) and 5.35 (s), 2H, CO_2CH_2], 5.65 and 5.81 (2 br s, 1H, H-1), 6.62 and 6.76 (2s, 1H, H-3), 6.80-7.60 (m, 8H, ArH), 7.95 (m, 1H, H-11), 8.19 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$) 19.8 and 21.3 ($2CH_3$), 26.9 and 27.3 (C-5), 28.2 (C-12), 29.4 and 29.7 (C-6), 33.1 (CH_3), 43.4 and 43.8 (C-1), 52.6 and 52.7 (CH_2N), 57.3 ($\mathit{C}Me_2$), 67.5 and 68.0 ($CO_2\mathit{C}H_2$), 68.1 (CH_2O), 109.4 and 110.0 (C-11b), 110.4 (C-8), 117.9 and 118.7 (C-4), 118.8 and 119.3 (C-11), 119.5 (C-10), 121.0 and 121.2 (C-9), 121.8 and 122.5 (C-3), 126.0 and 126.3 (C-11a), 128.1, 128.4, 128.6, and 129.0 (*o*, *m*, and *p*), 134.7 (C-6a), 135.8 (C-7a), 136.0 (*ipso*), 152.2 and 152.7 (C=O); mp 200-201°C (EtOH). Anal. Calcd for $C_{28}H_{33}N_3O_3$: C, 73.17; H, 7.23; N, 9.14. Found: C, 73.01; H, 7.19; N, 9.17.

2-(Benzyloxycarbonyl)-4-ethyl-1,2,5,6-tetrahydro-1,5-methanoazocino[4,3-*b*]indole (15). A solution of methyl-lithium (0.74 ml, 1.6 M in Et_2O, 1.2 mmol) was added to a solution of aldehyde **13** (200 mg, 0.54 mmol) in anhydrous THF (6 ml) and the resulting mixture was stirred at 0 °C for 30 min. The solution was poured into saturated aqueous NH_4Cl and the organic layer was extracted with AcOEt. The combined organic extracts were dried and evaporated to give alcohol **14** [^{1}H-NMR ($CDCl_3$) 1.29 and 2.33 (2d, *J* = 6.3 Hz, 3H, CH_3), 1.90 (m, 2H, H-12), 2.75-3.10 (m, 3H, H-5 and H-6), 4.28 (m, 1H, *CH*OH), [5.11 and 5.25 (2d, *J* = 12.5 Hz) and 5.36 (s), 2H, CO_2CH_2], 5.60 and 5.78 (2 br s, 1H, H-1), 6.72 and 6.83 (2s, 1H, H-3), 6.80-7.60 (m, 8H, ArH), 7.95 (m, 1H, H-11), 8.12 (br s, 1H, NH)], which underwent easy dehydration and was used in the next reaction without further purification. The above crude alcohol was dissolved in anhydrous CH_2Cl_2 (4 ml) and the solution was cooled to -78°C. After addition of $TiCl_4$ (0.07 ml, 0.64 mmol) and triethylsilane (0.35 ml, 2.15 mmol), the resulting mixture was stirred at -78°C for 90 min, poured into saturated aqueous Na_2CO_3, and extracted with CH_2Cl_2. The combined extracts were dried and evaporated to give a residue which, after flash column chromatography (1:4 AcOEt-hexane), afforded compound **15** (100 mg, 50%): IR (KBr) 3400, 3376, 1672 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.03 and 1.06 (2t, *J* = 7.5 Hz, 3H, CH_3), 1.92-2.15 (m, 4H, $\mathit{CH_2}CH_3$ and H-12), 2.65 (br s, 1H, H-5), 2.77 and 2.78 (2d, *J* = 16.5 Hz, 1H, H-6), 2.94 and 2.96 (2dd, *J* = 16.5 and 5.5 Hz, 1H, H-6), [5.10 and 5.26 (2d, *J* = 12.5 Hz) and 5.34 (s), 2H, CO_2CH_2], 5.63 and 5.79 (2t, *J* = 3.0 Hz, 1H, H-1), 6.47 and 6.52 (2s, 1H, H-3), 6.80-7.60 (m, 8H, ArH), 7.80 (br s, 1H, NH), 7.95 (m, 1H, H-11); ^{13}C-NMR ($CDCl_3$) 13.2 and 13.4 (CH_3), 26.7 ($\mathit{C}H_2CH_3$), 29.0 (C-12), 29.7 and 29.8 (C-5), 29.9 and 30.2 (C-6), 43.5 and 44.0 (C-1), 67.9 and 68.4 ($CO_2\mathit{C}H_2$), 110.4 and 110.7 (C-11b), 110.8 and 111.0 (C-8), 118.6 and 119.0 (C-11), 119.5 and 120.0 (C-10), 120.2 and 120.3 (C-9), 121.6 and 121.8 (C-3), 122.7 and 123.6 (C-4), 126.6 and 126.8 (C-11a), 128.4 and 128.5, 128.9, and 129.2 and 129.5 (*o*, *m* and *p*), 135.3 and 135.4 (C-6a), 136.4 (C-7a), 136.6 and 136.9 (*ipso*), 153.0 and 153.4 (C=O). HRMS Calcd for $C_{24}H_{24}N_2O_2$: 372.1837. Found 372.1839.

4α-Ethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (16). A solution of enecarbamate **15** (85 mg, 0.23 mmol) in anhydrous MeOH (5 ml) containing 10% Pd-C (10 mg) was hydrogenated at room temperature for 30 h. The catalyst was removed by filtration and the solution was concentrated under vacuum. The residue was taken up with CH_2Cl_2, and the resulting solution was washed with saturated aqueous $NaHCO_3$. The organic layer was dried and evaporated to give a solid which, after flash chromatography (70:30:5 ether-acetone-Et_2NH), afforded compound **16** (20 mg, 35%). Compound **16** was identified by comparison of its physical data with those of an authentic sample previously prepared in our laboratory.[5a] Minor amounts of the 4β-ethyl epimer were detected by TLC.

4-Acetyl-2-(benzyloxycarbonyl)-1,2,5,6-tetrahydro-1,5-methanoazocino[4,3-*b*]indole (17). Pyridinium dichromate (872 mg, 2.32 mmol) and molecular sieves were added to a solution of alcohol **14**, prepared as described above from aldehyde **13** (575 mg, 1.54 mmol), in CH_2Cl_2 (17 ml). The mixture was stirred at room temperature for 2 h and then diluted with ether and filtered through a Celite pad. The resulting solution was evaporated under vacuum and the residue was purified by flash column chromatography (1:1 AcOEt-hexane) affording ketone **17** (143 mg, 24%): IR (KBr) 3341, 1714, 1616 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.90 (dt, *J* = 12.8 and 3.5 Hz, 1H, H-12), 2.00-2.35 (m, 4H, H-12 and CH_3), 2.82 (dd, *J* = 16.8 and 1.4 Hz, 1H, H-6), 3.02 (dd, *J* = 16.8 and 4.7 Hz, 1H, H-6), 3.41 (m, 1H, H-5), 5.15-5.50 (m, 2H, CH_2O), 5.71 and 5.87 (2br s, 1H, H-1), 6.80-8.10 (m, 10H, ArH and H-3), 8.28 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$) 24.7 (CH_3), 26.2 and 26.3 (C-5), 28.3 (C-12), 28.9 and 29.3 (C-6), 44.2 and 44.7 (C-1), 68.5 and 69.1 (CH_2O), 108.5 and 109.0 (C-11b), 110.5 (C-8), 118.4 and 119.1 (C-11), 119.3 and 119.5 (C-10), 121.1 (C-9), 122.0 and 122.5 (C-4), 125.6 (C-11a), 128.1, 128.6, and 129.1 (*o*, *m*, and *p*), 134.8 and 135.1 (C-6a and C-7a), 135.6 and 135.8 (*ipso*), 137.0 and 137.6 (C-3), 151.9 and 152.4 (NCO_2), 196.4 and 196.7 (CO); mp 137-140°C (acetone). Anal. Calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.73; N, 7.25. Found: C, 74.32; H, 5.83; N, 6.98.

3-[4(*S*)-Methoxymethyl-5(*S*)-phenyl-2-oxazolinyl]-4-(2-indolylmethyl)-1-(methoxycarbonyl)-1,4-dihydropyridines 19a,b and 5-[4(*S*)-Methoxymethyl-5(*S*)-phenyl-2-oxazolinyl]-2-(2-indolylmethyl)-1-(methoxycarbonyl)-1,2-dihydropyridines 20a,b. Operating as described in the preparation of dihydropyridines **6** and **7**, starting from 2-methylindole (0.73 g, 5.57 mmol) and oxazolinylpyridine **18**[7d] (1.0 g, 3.73 mmol), a mixture of **19a,b** and **20a,b** was obtained. The C-4 epimeric mixture **19a,b** was separated from the C-2 epimers **20a,b** by column chromatography (95:3:2 ether-acetone-Et_2NH). The epimers **19a** (429 mg, 25%) and **19b** (310 mg, 18%) were separated by a further column chromatography (ether). The epimers **20a** (176 mg, 10%) and **20b** (152 mg, 9%) were also separated by column chromatography (95:5 AcOEt-hexane). **19a**: $[\alpha]^{22}_D$ +91 (*c* 0.2, EtOH); IR (KBr) 3400, 1735, 1686, 1633 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 2.92 (dd, *J* = 14.3 and 8.0 Hz, 1H, CH_2), 3.23 (dd, *J* = 14.3 and 3.0 Hz, 1H, CH_2), 3.47 (s, 3H, CH_3O), 3.58 (dd, *J* = 9.7 and 6.0 Hz, 1H, CH_2O), 3.67 (dd, *J* = 9.7 and 5.0 Hz, 1H, CH_2O), 3.73 (m, 1H, H-4), 3.83 (s, 3H, CO_2CH_3), 4.31 (q, *J* = 6.0 Hz, 1H, NCH), 5.12 (br s, 1H, H-5), 5.33 (d, *J* = 6.3 Hz, 1H, OCH), 6.23 (s, 1H, H-3 ind), 6.82 (br s, 1H, H-6), 7.07 (m, 2H, H-5 ind and H-6 ind), 7.20-7.42 (m, 6H, ArH), 7.52 (dm, *J* = 7.5 Hz, 1H, H-4 ind), 7.75 (br s, 1H, H-2), 9.52 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$) 33.6 (C-4), 37.1 (CH_2), 53.9 (CO_2CH_3), 59.3 (CH_3O), 74.3 (CH_2O), 74.3 (NCH), 82.8 (OCH), 100.8 (C-3 ind), 108.3 (C-3), 110.6 (C-7 ind), 111.2 (C-5), 119.1 (C-4 ind), 119.6 (C-5 ind), 120.7 (C-6 ind), 121.2 (C-6), 125.4 (*m*), 128.2 (*p*), 128.4 (C-3a ind), 128.8 (*o*), 129.7 (C-2), 136.3 (C-2 ind), 136.8 (C-7a ind), 140.5 (*ipso*), 151.4 (C=O), 163.7 (C=N). HRMS Calcd for $C_{27}H_{27}N_3O_4$: 457.2001. Found 457.2001. **19b**: $[\alpha]^{22}_D$ -95 (*c* 0.2, EtOH); IR (film) 3300, 1736, 1686, 1634 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 3.00 (dm, *J* = 14.5 Hz, 1H, CH_2), 3.30 (m, 1H, CH_2), 3.53 (s, 3H, CH_3O), 3.60-3.90 (m, 6H, CH_2O, H-4 and CO_2CH_3), 4.25 (dt, *J* = 6.6 and 4.2 Hz, 1H, NCH), 5.12 (br s, 1H, H-5), 5.40 (d, *J* = 6.6 Hz, 1H, OCH), 6.23 (s, 1H, H-3 ind), 6.85 (br s, 1H, H-6), 7.08 (m, 2H, H-5 ind and H-6 ind), 7.25-7.45 (m, 6H, ArH), 7.53 (dm, *J* = 7.5 Hz, 1H, H-4 ind), 7.70 (br s, 1H, H-2), 9.50 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$) 33.8 (C-4), 35.9 (CH_2), 53.8 (CO_2CH_3), 59.2 (CH_3O), 74.2 (CH_2O), 74.6 (NCH), 82.2 (OCH), 100.5 (C-3 ind), 107.5 (C-3), 110.4 (C-7 ind), 111.3 (C-5), 118.9 (C-4 ind), 119.6 (C-5 ind), 120.5 (C-6 ind), 121.4 (C-6), 125.5 (*m*), 128.2 (*p*), 128.6 (C-3a ind), 128.8 (*o*), 129.9 (C-2), 136.2 (C-2 ind), 136.7 (C-7a ind), 140.6 (*ipso*), 151.2 (C=O), 163.7 (C=N). HRMS Calcd for $C_{27}H_{27}N_3O_4$: 457.2001. Found 457.1981. **20a**: $[\alpha]^{22}_D$ +88 (*c* 0.2, EtOH); IR (film) 3400, 1725, 1655 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 3.02 (m, 2H, CH_2), 3.43 (s, 3H, CH_3O), 3.56 (dd, *J* = 9.8 and 6.3 Hz, 1H, CH_2O), 3.65 (dd, *J* = 9.8 and 4.7 Hz, 1H, CH_2O), 3.70-3.90 (m, 3H, CO_2CH_3), 4.21 (m, 1H, NCH), 5.05 (br s, 1H, H-2), 5.32 (d, *J* = 7.0 Hz, 1H, OCH), 5.63 (dd, *J* = 10.0 and 5.1 Hz, 1H, H-3), 6.30 (s, 1H, H-3 ind), 6.58 (d, *J* = 10.0 Hz, 1H, H-4), 7.10 (m, 2H, H-5 ind and H-6 ind), 7.20-7.45 (m, 6H, ArH), 7.54 (dm, *J* = 7.5 Hz, H-4 ind), 7.62 (br s, 1H, H-6), 8.30 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$) 33.8 (CH_2), 52.9 (C-2), 53.8 (CO_2CH_3), 59.2 (CH_3O), 74.1 (CH_2O), 74.4 (NCH), 83.2 (OCH), 101.7 (C-3 ind), 106.4 (C-5), 110.6 (C-7 ind), 119.5 (C-4 ind), 119.8 (C-5 ind), 120.5 (C-3), 121.2 (C-6 ind), 121.6 (C-4), 125.6 (*m*), 128.2 (*p*), 128.5 (C-3a ind), 128.7 (*o*), 130.2 (C-6), 133.6 (C-2 ind), 136.1 (C-7a ind), 140.6 (*ipso*), 153.5 (C=O), 162.4 (C=N). HRMS Calcd for $C_{27}H_{27}N_3O_4$: 457.2001. Found 457.2000. **20b**: $[\alpha]^{22}_D$ -57 (*c* 0.2, EtOH); IR (KBr) 3400, 1727, 1654 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 3.00 (m, 2H, CH_2), 3.11 (s, 3H, CH_3O), 3.54 (dd, *J* = 9.8 and 6.2 Hz, 1H, CH_2O), 3.64 (dd, *J* = 9.8 and 4.6 Hz, 1H, CH_2O), 3.70-3.95 (m, 3H, CO_2CH_3), 4.18 (m, 1H, NCH), 5.06 (br s, 1H, H-2), 5.32 (d, *J* = 7.0 Hz, 1H, OCH), 5.63 (dd, *J* =10.0 and 5.5 Hz, 1H, H-3), 6.30 (s, 1H, H-3 ind), 6.56 (d, *J* =10.0 Hz, 1H, H-4), 7.10 (m, 2H, H-5 ind and H-6 ind), 7.15-7.40 (m, 6H, ArH), 7.52 (dm, *J* = 7.5 Hz, H-4 ind), 7.60 (br s, 1H, H-6), 8.33 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$) 33.9 (CH_2), 52.9 (C-2), 53.8 (CO_2CH_3), 59.3 (CH_3O), 74.2 (CH_2O), 74.5 (NCH), 83.3 (OCH), 101.9 (C-3 ind), 106.3 (C-5), 110.6 (C-7 ind), 119.6 (C-4 ind), 119.9 (C-5 ind), 120.5 (C-3), 121.3 (C-6 ind), 121.7 (C-4), 125.6 (*m*), 128.2 (*p*), 128.5 (C-3a ind), 128.7 (*o*), 130.3 (C-6), 133.6 (C-2 ind), 136.1 (C-7a ind), 140.5 (*ipso*), 153.6 (C=O), 162.4 (C=N). HRMS Calcd for $C_{27}H_{27}N_3O_4$: 457.2001. Found 457.1973.

4-[4(*S*)-Methoxymethyl-5(*S*)-phenyl-2-oxazolinyl]-1,2,5,6-tetrahydro-1,5-methanoazocino[4,3-*b*]indoles 21a,b. Operating as described in the preparation of **4**, starting from 2-methylindole (0.73 g, 5.57 mmol) and oxazolinylpyridine **18**^{7d} (1.0 g, 3.73 mmol), a mixture of tetracyclic diastereomers **21a,b** and indolylmethylpyridine **22** was obtained. Flash column chromatography (97:3 ether-Et_2NH) allowed the separation of **21a** (268 mg, 18%), **21b** (178 mg, 12%), and **22** (74 mg, 5%). **21a**: $[\alpha]^{22}_D$ + 489 (*c* 0.5, CH_2Cl_2); IR (KBr) 3405, 3100, 1622 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 2.10 (br s, 2H, H-12), 3.08 (br s, 2H, H-6), 3.40 (m, 1H, H-5), 3.45 (s, 3H, CH_3O), 3.54 (dd, *J* = 10.0 and 7.0 Hz, 1H, CH_2O), 3.72 (dd, *J* = 10.0 and 4.4 Hz, 1H, CH_2O), 4.14 (m, 1H, NCH), 4.74 (br s, 1H, H-1), 4.88 (br s, 1H, NH), 5.26 (d, *J* = 6.0 Hz, 1H, OCH), 7.10-7.40 (m, 9H, H-3, H-8, H-9, H-10, and C_6H_5), 7.52 (m, 1H, H-11), 8.02 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$) 26.7 (C-5), 28.5 (C-12), 30.9 (C-6), 42.0 (C-1), 59.2 (CH_3O), 74.1 (NCH), 74.9 (CH_2O), 82.2 (OCH), 98.0 (C- 4), 110.8 (C-8), 111.8 (C-11b), 116.8 (C-11), 119.3 (C-10), 121.0 (C-9), 125.2 (*m*), 125.8 (C-11a), 127.6 (*p*), 128.4 (*o*), 135.6 (C-6a), 136.1 (C-7a), 138.2 (C-3), 141,6 (*ipso*), 165.3 (C=N). Anal. Calcd for $C_{25}H_{25}N_3O_2$: C, 75.16; H, 6.31; N, 10.51. Found: C, 75.13; H, 6.38; N, 10.34. **21b**: $[\alpha]^{22}_D$ -193 (*c* 0.5, CH_2Cl_2); IR (KBr) 3409, 1620 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 2.10 (br s, 2H, H-12), 3.06 (m, 2H, H-6), 3.37 (m, 1H, H-5), 3.42 (s, 3H, CH_3O), 3.45 (dd, *J* = 9.8 and 7.3 Hz, 1H, CH_2O), 3.68 (dd, *J* = 9.8 and 4.4 Hz, 1H, CH_2O), 4.16 (m, 1H, NCH), 4.72 (m, 1H, H-1), 4.86 (br s, 1H, NH), 5.20 (d, *J* = 6.0 Hz, 1H, OCH), 7.14 (s, 1H, H-3), 7.05-7.40 (m, 8H, H-8, H-9, H-10, and C_6H_5), 7.52 (m, 1H, H-11), 7.95 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$) 26.8 (C-5), 28.6 (C-12), 30.7 (C-6), 42.0 (C-1), 59.1 (CH_3O), 74.0 (NCH), 75.0 (CH_2O), 82.1 (OCH), 98.0 (C-4), 110.8 (C-8), 111.6 (C-11b), 116.8 (C-11), 119.2 (C-10), 120.8 (C-9), 125.4 (*m*), 125.7 (C-11a), 127.7 (*p*), 128.5 (*o*), 135.5 (C-6a), 136.1 (C-7a), 138.2 (C-3), 141.7 (*ipso*), 165.3 (C=N). Anal. Calcd for $C_{25}H_{25}N_3O_2 \cdot 1/2H_2O$: C, 73.1; H, 6.42; N, 10.28. Found: C, 73.90; H, 6.43; N, 10.28. **22**: $[\alpha]^{22}_D$ +73 (*c* 0.5, CH_2Cl_2); IR (KBr) 3405, 1658 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 3.44 (s, 3H, CH_3O), 3.63 (dd, *J* = 10.0 and 6.0 Hz, 1H, CH_2O), 3.71 (dd, *J* = 10.0 and 4.5 Hz, 1H, CH_2O), 4.30 (m, 1H, NCH), 4.32 (s, 2H, CH_2), 5.50 (d, *J* = 7.0 Hz, 1H, OCH), 6.36 (s, 1H, H-3 ind), 7.08 (m, 2H, H-5 ind and H-6 ind), 7.25-7.40 (m, 7H, H-3, H-7 ind, and C_6H_5), 7.53 (dm, *J* = 7.5 Hz, 1H, H-4 ind), 8.22 (dd, *J* = 8.0 and 2.2 Hz, 1H, H-4), 8.83 (br s, 1H, NH), 9.20 (d, *J* = 2.2 Hz, 1H, H-6); ^{13}C-NMR ($CDCl_3$) 37.0 (CH_2), 59.3 (CH_3O), 73.9 (CH_2O), 74.8 (NCH), 83.6 (OCH), 100.8 (C-3 ind), 110.7 (C-7 ind), 119.5 (C-4 ind), 119.9 (C-5 ind), 121.2 (C-6 ind), 121.6 (C-5), 122.6 (C-3), 125.5 (*m*), 128.3 (*p*), 128.5 (C-3a ind), 128.7 (*o*), 135.4 (C-2 ind), 136.4 (C-7a ind), 136.7 (C-4), 140.2 (*ipso*), 149.1 (C-6), 161.8 (C=N), 161.9 (C-2). Anal. Calcd for $C_{25}H_{23}N_3O_2.1/2H_2O$: C, 73.87; H, 5.95; N, 10.34. Found: C, 73.87; H, 5.98; N, 9.98.

2(*S*)-[(Benzyloxycarbonyl)amino]-3-methoxy-1(*S*)-phenylpropyl (1*S*,5*R*)-2-(Benzyloxycarbonyl)-1,2,5,6-tetrahydro-1,5-methanoazocino[4,3-*b*]indole-4-carboxylate (23a). NaH (40 mg of a 60% oil dispersion, 1.0 mmol) was added to a solution of tetracycle **21a** (200 mg, 0.50 mmol) in anhydrous THF (2 ml). The resulting mixture was stirred at room temperature for 1 h and then benzyl chloroformate (0.5 ml, 3.0 mmol) was added. After 20 h of stirring at room temperature, the reaction mixture was concentrated and then dissolved in $CHCl_3$. The solution was washed with saturated aqueous $NaHCO_3$, dried, and concentrated to give a residue which, after purification by column chromatography (AcOEt to 95:5 AcOEt-Et_2NH), gave ester **23a** (211 mg, 61%) and oxazoline **24a** (18 mg, 7%). **23a**: IR (KBr) 3424, 1721, 1698, 1621 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.75 (dm, *J* = 12.2 Hz, 1H, H-12), 2.05 (dm, *J* = 12.2 Hz, 1H, H-12), 2.83 (d, *J* = 16.5 Hz, 1H, H-6), 2.90-3.45 (m, 4H, H-5, H-6 and CH_2O), 3.24 (s, 3H, CH_3O), 4.16 (m, 1H, H-2'), 4.91 (m, 2H, CO_2CH_2), 5.15-5.45 (m, 2H, CO_2CH_2), 5.65 and 5.79 (2br s, 1H, H-1), 6.02 (d, *J* = 9.2 Hz, 1H, H-1'), 7.00-7.60 (m, 14H, ArH and H-3), 7.89 (m, 1H, H-11), 8.15 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$) 25.9 (C-5), 28.2 (C-6), 29.4 (C-12), 43.8 (C-1), 55.2 (C-2'), 58.7 (CH_3O), 66.1 (CO_2CH_2), 68.2 and 68.7 (CO_2CH_2), 71.0 (C-3'), 74.6 (C-1'), 109.4 (C-11b), 110.4 (C-8), 119.2 (C-11), 119.6 (C-10), 121.2 (C-9), 125.7 (C-4), 125.8 (C-11a), 135.0 (C-6a), 135.5 (C-3), 135.7 (C-7a), 152.2 (NC=O), 156.0 (NC=O), 166.3 (C=O). **24a**: $[\alpha]^{22}_D$ +237 (*c* 0.5, EtOH); IR (KBr) 3400, 1716 , 1637 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 2.03 (m, 2H, H-12), 3.02 (br s, 2H, H-6), 3.40 (br s, 1H, H-5), 3.42 (s, 3H, CH_3O), 3.54 (dd, *J* = 10.0 and 6.6 Hz, 1H, CH_2O), 3.66 (dd, *J* = 10.0 and 4.4 Hz, 1H, CH_2O), 4.15 (m, 1H, NCH), [5.07 and 5.33 (2d, *J* = 12.4 Hz) and 5.29 (s), 2H, CO_2CH_2], 5.31 (m, 1H, OCH), 5.67 and 5.85 (2br s, 1H, H-1), 6.75-7.45 (m, 13H, ArH), 7.55 and 7.72 (2s, 1H, H-3), 7.90 (m, 1H, H-11), 8.10 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$) 26.5 and 26.9 (C-5), 28.5 and 28.8 (C-6), 29.7 (C-12), 43.8 and 44.4 (C-1), 59.3 (CH_3O), 68.12 and 68.8 (CO_2CH_2), 74.6 (CH_2O), 74.6 (NCH), 82.6 (OCH), 108.5 and 109.2 (C-4), 109.4 and 109.9 (C-11b), 110.3 (C-8), 118.8 and 119.5 (C-11), 119.8 (C-10), 121.4 (C-9), 125.2 (*m*), 127.8 (C-11a), 128.2 (*p*), 128.6 (*o*), 130.9 and 131.6 (C-3), 135.3 (C-6a), 135.9 (C-7a), 141.0 (*ipso*), 152.3 and 152.5 (C=O), 164.0 (C=N). HRMS Calcd for $C_{33}H_{31}N_3O_4$: 533.2314. Found 533.2349.

Methyl (1*S*,5*R*)-1,2,5,6-Tetrahydro-1,5-methanoazocino[4,3-*b*]indole-4-carboxylate (25a). A solution of ester **23a** (200 mg, 0.29 mmol) and NaOMe (3.7 mmol) in anhydrous MeOH (7 ml) was refluxed for 7 h. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2. The resulting solution was washed with saturated aqueous $NaHCO_3$ and concentrated to give a residue which, after flash column chromatography (98:2 ether-Et_2NH), afforded pure ester **25a** (40 mg, 51%): $[\alpha]^{22}_D$ +489 (*c* 0.2, EtOH); **IR** (KBr) 3400, 3250, 1661, 1604 cm^{-1}; ^{1}H-NMR ($CDCl_3$-CD_3OD) 1.91 (dt, *J* = 12.2 and 3.4 Hz, 1H, H-12), 2.06 (dt, *J* = 12.2 and 2.6 Hz, 1H, H-12), 2.85 (dd, *J* = 16.5 and 1.8 Hz, 1H, H-6), 3.03 (dd, *J* = 16.5 and 4.8 Hz, 1H, H-6), 3.26 (br s, 1H, H-5), 3.65 (s, 3H, CH_3O), 4.72 (br s, 1H, H-1), 7.06 (m, 2H, H-9 **and** H-10), 7.30 (m, 1H, H-8), 7.44 (s, 1H, H-3), 7.53 (m, 1H, H-11), 9.65 (br s, 1H, NH); ^{13}C-NMR (**$CDCl_3$-CD_3OD**)

25.9 (C-5), 28.4 (C-12), 30.7 (C-6), 41.6 (C-1), 50.1 (CH_3O), 98.2 (C-4), 110.5 (C-8), 111.1 (C-11b), 116.4 (C-11), 118.6 (C-10), 120.3 (C-9), 125.4 (C-11a), 135.2 (C-6a), 136.0 (C-7a), 143.1 (C-3), 169.5 (C=O). HRMS Calcd for $C_{16}H_{16}N_2O_2$: 268.1211. Found 268.1224.

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