A Synthetic Entry to Ervatamine Alkaloids − Synthesis of (±)-6-Oxo-16-episilicine and (±)-6-Oxosilicine

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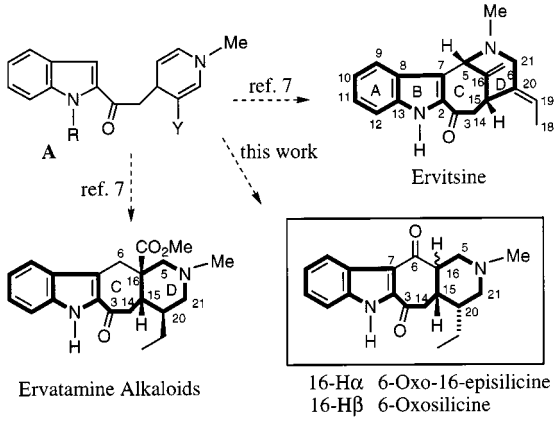
Catalytic hydrogenation of several 3-acyl-4-[2-(indolyl)carbonylmethyl]-5-(methoxycarbonyl)-1,4-dihydropyridines **4** gives chemoselectively the corresponding 1,2,3,4-tetrahydropyridyl esters **5**, which have been elaborated into the tetracyclic 2,3-diacylindole system **6** of oxosilicine alkaloids. Barton decarboxylation of the *N*-benzyl derivative **6e**, followed by debenzylation and subsequent stereoselective reduction of the 5,16-double bond gives (±)-6-oxo-16-episilicine. This compound is converted into (±)-6-oxosilicine by base-catalyzed epimerization.

Introduction

The ervatamine alkaloids[1] constitute a group of 2-acylindole alkaloids of the corynanthean[2] type, with an unusual skeleton in which the tryptamine atoms (C-5/C-6, biogenetic numbering)[3] are in a rearranged orientation with C-5/C-16 and C-6/C-16 bonds. These alkaloids are characterized by a seven-membered ring C in a fused bicyclic system (bridged in the unique alkaloid ervitsine) bearing an ethyl or (*E*)-ethylidene substituent at C-20 and a methoxycarbonyl group at C-16. The latter is not present in the silicine series. In spite of their apparent structural simplicity, these alkaloids have received little synthetic attention. When we started our studies, 6-oxosilicine, isolated from several *Hazunta* species,[4] was the only alkaloid of this group with a known total synthesis.[5,6]

We have recently reported[7] straightforward biomimetic syntheses of two alkaloids of the ervatamine group (19,20-didehydroervatamine, 20-epiervatamine) and the biogenetically related alkaloid ervitsine via 4-[(2-indolyl)carbonylmethyl]-1,4-dihydropyridines (**A**), either through the corresponding 3,5-diacyldihydropyridines or by electrophile-promoted cyclization via a dihydropyridinium cation, respectively. Here we wish to further illustrate the potential and synthetic flexibility of 3,5-diacyl-4-[(2-indolyl)carbonylmethyl]-1,4-dihydropyridines. They provide access to the tetracyclic system of the C-16 unsubstituted ervatamine alkaloids, and lead to the total synthesis of (±)-6-oxo-16-episilicine and (±)-6-oxosilicine[8] (Scheme 1).



Scheme 1

Results and Discussion

Our synthesis consists of three well-differentiated phases: i) chemoselective differentiation of the 3,5-diacyl-1,4-dihydropyridine double bonds by partial catalytic hydrogenation, ii) formation of the seven-membered ring C by electrophilic cyclization at the indole 3-position (bond formed C-6/C-7) taking advantage of the methoxycarbonyl substituent of the resulting tetrahydropyridine, and iii) elaboration of the C-20 ethyl appendage. The required 3,5-diacyl-1,4-dihydropyridines **4a−f** were easily accessible by reaction of the enolate derived from 2-acetylindoles **1** with pyridinium salts **2**, followed by acylation of the resulting 1,4-dihydropyridines with trichloroacetic anhydride (TCAA) and subsequent haloform-type reaction of the trichloroacetyl derivatives **3** with sodium methoxide in methanol (Scheme 2).[9] In series **e** the nucleophilic addition to the pyridinium ring was not regioselective, and a 1:1 mixture of the desired 1,4-dihydropyridine **3e** (30%) and its 1,2-regioisomer was obtained (see Experimental Section).

The partial reduction of the dihydropyridine ring was initially explored from the model symmetrical dihydropyridines **4a** and **4b**. Although the reduction of 1,4-dihydropyridines to the corresponding tetrahydropyridines is a known process,[10] there are few examples of the reduction of 1,4-dihydropyridines generated by addition of stabilized carbanions to pyridinium salts,[11] probably owing to the reversibility of the addition. In our case, the higher stability of the 3,5-diacyl-substituted dihydropyridines **4a** and **4b** made their catalytic hydrogenation possible. Hydrogenation of **4a** and **4b** in methanol using platinum as the catalyst led stere-

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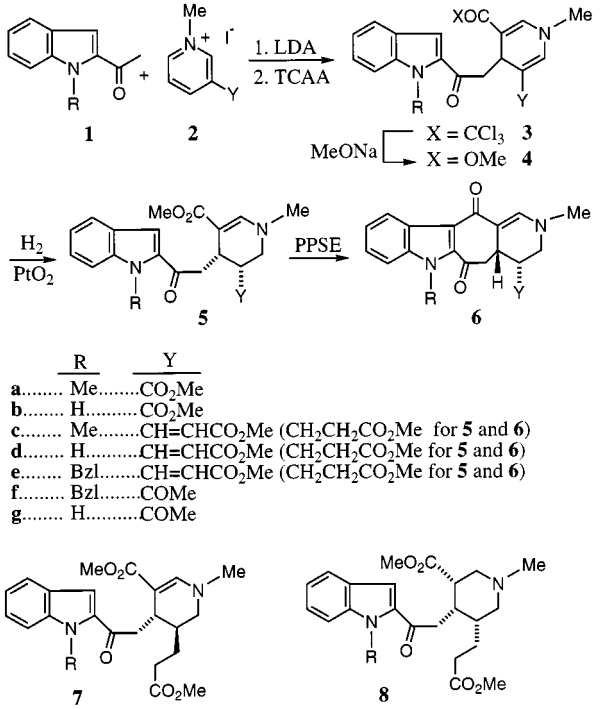


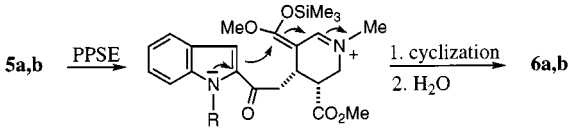
Scheme 2

oselectively to the corresponding *cis*-tetrahydropyridines **5a** (80%) and **5b** (60%). In contrast, fragmentation to the starting products was observed when **4a** was treated with several hydrides in acidic media (Et_3SiH/TFA, n-Bu_3SnH/TFA or $NaBH_3CN$/AcOH) under the conditions reported for the reduction of the carbon−carbon double bond in vinylogous urethanes.[12] The relative stereochemistry of the tetrahydropyridine substituents is assigned as *cis* as a result of the hydrogen uptake from the less hindered face of the dihydropyridine ring.

As was expected, reduction of the doubly vinylogous urethane moiety occurred with dihydropyridines **4c−e** to give the corresponding *cis*-tetrahydropyridines **5c−e** as the major products, although in lower yields (34%, 25% and 50%, respectively) than in the above 3,5-bis(methoxycarbonyl) series. With compounds **4c−e**, over-reduction to the corresponding piperidines **8c−e** was observed and the hydrogenation was less stereoselective since minor amounts of the corresponding *trans*-tetrahydropyridines **7c** and **7e** were also isolated.

The relative stereochemistry of tetrahydropyridines **5** and **7** and piperidines **8** was determined from their NMR spectra. In the case of **5** the *cis* relationship involves the equatorial disposition of the substituent at the 3-position and the pseudoaxial disposition of the (indolylcarbonyl)methyl group.

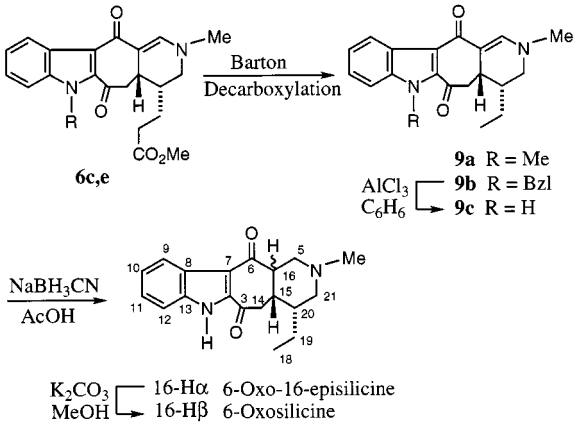
With a variety of functionalized tetrahydropyridyl esters **5** in hand, we set out to explore the feasibility of the formation of the carbon ring C of silicine alkaloids. Initial attempts [n-Bu_3SnH, AIBN, C_6H_6, reflux; $(CF_3SO_3Cu)_2 \cdot C_6H_6$, C_6H_6, room temp.] to promote this key cyclization via seleno ester **5** (R = Me; Y = COSeMe), prepared in 62% yield by treatment of **5a** with $Me_2AlSeMe$, resulted in failure. In fact it is known that the electrophilic acylation at the 3-position of 2-acetylindoles is a difficult process.[13] However, gratifyingly, treatment of 3,5-bis(methoxycarbonyl)tetrahydropyridines **5a** and **5b** with trimethylsilyl polyphosphate (PPSE) promoted the chemoselective cyclization on the α,β-unsaturated ester group to give the model silicine-type tetracycles **6a** and **6b** in 30 and 40% yield, respectively. To the best of our knowledge, these are the first examples of PPSE-promoted Friedel−Crafts cyclizations with indoles.[14] The observed chemoselectivity can be accounted for by the greater nucleophilic character of the carbonyl oxygen atom of the conjugate ester at C-5 compared with the isolated ester at C-3. Activation of the C-5 carbonyl group by PPSE would give rise to a reactive *O*-methyl *O*-silyl ketene ketal conjugated to an iminium ion. Cyclization as depicted in Scheme 3, followed by hydrolysis of the resulting ketal would lead to the tetracyclic enaminones **6a**,**b**.



Scheme 3

In a similar manner, tetrahydropyridyl esters **5c−e** underwent cyclization to the tetracyclic 2,3-diacylindoles **6c−e**. Tetrahydropyridyl esters **5f**,**g**, with a two-carbon substituent at C-20, had proved to be valuable synthetic intermediates in our synthesis of ervatamines.[7] However, **5f** and **g**, in oxosilicine synthesis were found to be less satisfactory because epimerization at C-20 occurred to some extent under the cyclization conditions, so further synthetic use of the resulting tetracycles **6f**,**g** was abandoned. Tetracycle **6g** was alternatively obtained by debenzylation of **6f** with $AlCl_3$ in C_6H_6.[15]

The final phase in the synthesis of 6-oxosilicines was the elaboration of the C-20 ethyl appendage from the propionate moiety of tetracycles **6c−e**. To this end, we turned our attention to the Barton decarboxylation,[16] a process that makes use of the easy homolytic decomposition of thiohydroxamic esters. Preliminary experimentation was carried out using the model N_{ind}-methyl tetracycle **6c**. Reaction of the corresponding acyl chloride with the sodium salt of 2-mercaptopyridine *N*-oxide, followed by reductive decarboxylation of the intermediate thiohydroxamate ester with n-Bu_3SnH/AIBN gave the 20-ethyl-substituted tetracycle **9a** in 40% yield (Scheme 4). Although a moderate yield (30%) of **9b** was also obtained when the same protocol was applied to the *N*-benzyl derivative **6e**, the use of the *N*-unsubstituted indole **6d** was unsuccessful due to its low solubility. An important improvement of this reaction was obtained when the acid derived from **6e** was treated with 2,2′-dithiobis(pyridine *N*-oxide) and tributylphosphane,[17] with subsequent photolysis in the presence of 2-methyl-2-propanethiol as the hydrogen donor. As a result 1-benzyl-5,16-didehydro-16-oxosilicine (**9b**) was obtained in 75% yield. Debenzylation of the indole ring of **9b** by treatment with $AlCl_3$ in C_6H_6 (86%), followed by stereoselective reduction of the



Scheme 4

5,16-double bond of the resulting enaminone **9c** with $NaCNBH_3$ (80%) completed the synthesis of (±)-6-oxo-16-episilicine.

The nature of the *trans* fusion of the C/D rings was established by a careful inspection of the ^1H and ^{13}C NMR spectroscopic data, hitherto unreported, with the aid of 2D NMR techniques. The synthesis described here constitutes the first total synthesis of (±)-6-oxo-16-episilicine, an alkaloid isolated from *Hazunta modesta*.[4d] On the other hand, base-catalyzed epimerization of (±)-6-oxo-16-episilicine afforded (±)-6-oxosilicine, with a *cis* C/D ring fusion. The NMR-spectroscopic data of this synthetic product are identical with those reported for the natural product.[4b]

Conclusion

The above results further illustrate the versatility and rich reactivity of 1,4-dihydropyridines formed by nucleophilic addition of indole-containing enolates to 3-acyl-*N*-alkylpyridinium salts, and broaden the synthetic possibilities of this powerful methodology for alkaloid synthesis.[18] After methoxycarbonylation of the initially formed 3-acyl-1,4-dihydropyridine, it is possible to take advantage of the functionality of the resulting 3-acyl-4-[(2-indolyl)carbonylmethyl]-5-(methoxycarbonyl)-1,4-dihydropyridines to ultimately assemble the tetracyclic 2,3-diacylindole system of oxosilicine alkaloids.

Experimental Section

General Remarks: All nonaqueous reactions were performed under argon. All solvents were dried by standard methods. Drying of organic extracts during the workup of reactions was performed with anhydrous Na_2SO_4. Evaporation of the solvents was accomplished under reduced pressure with a rotatory evaporator. − Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 0.04−0.06 mm). − Melting points were taken with a Büchi apparatus and are uncorrected. − Microanalyses (Carlo Erba 1106 analyzer) and HRMS (Autospec-EQ) were performed by Centro de Investigación y Desarrollo (CSIC), Barcelona. − Only noteworthy IR absorptions (cm^{-1}; Perkin−Elmer 1600) are listed. − NMR: Varian Gemini-300 (300 and 75.4 MHz, for ^1H and ^{13}C, respectively) or (when indicated) Varian VXR 500 (500 MHz). For ^1H NMR $CDCl_3$ was used as the solvent and TMS as an internal reference; for ^{13}C NMR $CDCl_3$ was used as the solvent, $\delta_C = 77.0$. The biogenetic numbering was used for the NMR description of all tetracyclic compounds.

4-[(1-Benzyl-2-indolyl)carbonylmethyl]-3-[(*E*)-2-(methoxycarbonyl)-vinyl]-1-methyl-5-(trichloroacetyl)-1,4-dihydropyridine (3e): 2-Acetyl-1-benzylindole (**1**, R = Bzl, 0.5 g, 2 mmol) in THF (35 mL) was allowed to react with LDA (2.2 mmol) at −70 °C for 30 min and then with pyridinium salt **2** (R = CH=CHCO$_2$Me, 0.61 g, 2 mmol) at −30 °C for 30 min. TCAA (1.1 mL, 6 mmol) was slowly added, and the mixture was stirred at 0 °C for 3 h, poured into saturated aqueous Na_2CO_3, and extracted with Et_2O. The organic extracts were dried and concentrated to give a nearly equimolar crude mixture of 1,4-dihydropyridine **3e** and the corresponding 1,2-dihydropyridine. Flash chromatography (hexanes/AcOEt, 7:3 and 6:4) allowed the isolation of both compounds. 1,4-Dihydropyridine **3e** (0.34 g, 30%). − M.p. 152−154 °C (Et_2O/acetone). − IR (KBr): $\tilde{\nu}$ = 1560, 1650, 1695. − ^1H NMR: δ = 2.96 (dd, *J* = 13.4, 5.1 Hz, 1 H, CH_2CO), 3.06 (s, 3 H, NMe), 3.10 (dd, *J* = 13.4, 5.6 Hz, 1 H, CH_2CO), 3.72 (s, 3 H, OMe), 4.37 (dd, *J* = 5.6, 5.1 Hz, 1 H, 4-H), 5.65 and 5.83 (2d, *J* = 16.2 Hz, 2 H, CH_2Ph), 5.95 (d, *J* = 15.5 Hz, 1 H, =CH), 6.24 (s, 1 H, 2-H), 7.04−7.30 (m, 9 H, Ar), 7.32 (d, *J* = 15.5 Hz, 1 H, =CH), 7.63 (s, 1 H, 6-H), 7.73 (d, *J* = 8 Hz, 1 H, indole 4-H). − ^{13}C NMR: δ = 30.9 (C-4), 42.1 (NMe), 43.9 (CH_2CO), 48.0 (CH_2Ph), 51.4 (OMe), 95.9 (CCl_3), 102.5 (C-3), 110.7 (indole C-7), 113.4, 114.2 (=CH, indole C-3), 117.6 (C-5), 120.9 (indole C-5), 123.2 (indole C-4), 125.9 (indole C-3a), 126.2 (indole C-6), 126.4, 126.8, 128.3 (Ph), 134.8 (indole C-2), 134.9 (C-2), 138.5 (indole C-7a), 140.2 (Ph), 142.3 (=CH), 145.5 (C-6), 167.6, 178.8, 191.3 (CO). − $C_{29}H_{25}Cl_3N_2O_4$ (571.5): calcd. C 60.91, H 4.41, N 4.90; found C 60.55, H 4.47, N 4.86.

2-[(1-Benzyl-2-indolyl)carbonylmethyl]-5-[(*E*)-2-(methoxycarbonyl)-vinyl]-1-methyl-3-(trichloroacetyl)-1,2-dihydropyridine: 0.34 g, 30%. − M.p. 140−142 °C (Et_2O/acetone). − IR (KBr): $\tilde{\nu}$ = 1597, 1669, 1702. − ^1H NMR: δ = 2.85 (dd, *J* = 16.1, 2.8 Hz, 1 H, CH_2CO), 2.95 (s, 3 H, NMe), 3.54 (dd, *J* = 16.1, 8.4 Hz, 1 H, CH_2CO), 3.74 (s, 3 H, OMe), 5.05 (dm, *J* = 8.4 Hz, 1 H, 2-H), 5.76 (d, *J* = 15.5 Hz, 1 H, =CH), 5.78 and 5.87 (2d, *J* = 16 Hz, 2 H, CH_2Ph), 7.05−7.40 (m, 12 H, 4-H, =CH, Ar), 7.85 (s, 1 H, 6-H). − ^{13}C NMR: δ = 43.5 (CH_2CO), 43.9 (NMe), 48.2 (CH_2Ph), 51.5 (OMe), 55.7 (C-2), 97.5 (CCl_3), 100.4 (C-5), 110.8 (indole C-7), 112.9 (=CH), 113.9 (indole C-3), 118.4 (C-3), 121.4 (indole C-5), 123.3 (indole C-4), 125.7 (indole C-3a), 125.8 (indole C-6), 126.2, 127.1, 128.5 (Ph), 131.8 (C-4), 133.7 (indole C-2), 138.0 (indole C-7a), 140.6 (Ph), 153.6 (C-6), 167.4, 176.0, 189.4 (CO). − $C_{29}H_{25}Cl_3N_2O_4$ (571.5): calcd. C 60.91, H 4.41, N 4.90; found C 60.93, H 4.46, N 4.88.

Methyl 4-[(1-Benzyl-2-indolyl)carbonylmethyl]-5-[(*E*)-2-(methoxycarbonyl)vinyl]-1-methyl-1,4-dihydropyridine-3-carboxylate (4e): (Trichloroacetyl)dihydropyridine **3e** (0.25 g, 0.43 mmol) in a solution of MeOH/THF (1:2; 30 mL) was slowly added to a solution of MeONa (1.3 mmol) in MeOH (40 mL), and the resulting mixture was stirred at room temperature for 3 min. The solvent was removed, and the residue was partitioned between H_2O and AcOEt and extracted with AcOEt. Concentration of the dried extracts gave a residue, which was chromatographed (flash, hexanes/AcOEt, 7:3) to give dihydropyridine **4e** (0.18 g, 85%). − M.p. 160−162 °C (Et_2O/acetone). − IR (KBr): $\tilde{\nu}$ = 1566, 1612, 1650, 1693. − ^1H NMR: δ = 2.95 (dd, *J* = 13.1, 5.5 Hz, 1 H, CH_2CO), 2.99 (s, 3 H, NMe), 3.05 (dd, *J* = 13.1, 5.2 Hz, 1 H, CH_2CO), 3.59 and 3.70 (2s,

3 H, OMe), 4.29 (dd, J = 5.5, 5.2 Hz, 1 H, 4-H), 5.70 and 5.84 (2d, J = 16.3 Hz, 2 H, CH_2Ph), 5.87 (d, J = 15.5 Hz, 1 H, =CH), 6.23 (s, 1 H, 6-H), 7.01 (s, 1 H, 2-H), 7.04−7.35 (m, 10 H, =CH, Ar), 7.73 (d, J = 8 Hz, 1 H, indole 4-H). − ^{13}C NMR: δ = 30.7 (C-4), 41.3 (NMe), 45.7 (CH_2CO), 48.0 (CH_2Ph), 51.2, 51.3 (OMe), 104.2 (C-5), 110.9 (indole C-7), 111.6, 113.0 (indole C-3, =CH), 114.6 (C-3), 120.8 (indole C-5), 123.1 (indole C-4), 125.9 (indole C-3a), 126.0 (indole C-6), 126.4, 126.8, 128.4 (Ph), 135.1 (indole C-2), 138.5 (indole C-7a), 140.0 (CHN), 140.1 (Ph), 143.6 (CHN), 167.3, 168.0, 191.8 (CO). − $C_{29}H_{28}N_2O_5$ (484): calcd. C 71.88, H 5.82, N 5.78; found C 72.20, H 5.93, N 5.78.

Dimethyl *cis*-1-Methyl-4-[(1-methyl-2-indolyl)carbonylmethyl]-1,2,3,4-tetrahydropyridine-3,5-dicarboxylate (5a): A solution of dihydropyridine **4a**[9] (0.1 g, 0.26 mmol) in MeOH (5 mL) was hydrogenated in the presence of PtO_2 (25 mg) at atmospheric pressure for 48 h. The catalyst was filtered off and the solution was concentrated. Flash chromatography (hexanes/AcOEt, 1:1) of the residue gave tetrahydropyridine **5a** (80 mg, foam, 80%). − IR (film): ṽ = 1622, 1663, 1730. − ^{1}H NMR (500 MHz): δ = 2.87 (masked, 1 H, 3-H), 2.88 (dd, J = 14.5, 5.5 Hz, 1 H, CH_2CO), 2.99 (dd, J = 14.5, 7.5 Hz, 1 H, CH_2CO), 3.01 (s, 3 H, NMe), 3.16 (ddd, J = 13, 4.5, 1.5 Hz, 1 H, 2-H_{eq}), 3.43 (t, J = 13 Hz, 1 H, 2-H_{ax}), 3.53 and 3.65 (2s, 3 H, OMe), 3.83 (m, 1 H, 4-H), 4.02 (s, 3 H, NMe), 7.10 (m, 1 H, indole 5-H), 7.35 (m, 4 H, indole, 6-H), 7.68 (d, J = 8 Hz, 1 H, indole 4-H). − ^{13}C NMR: δ = 29.7 (C-4), 32.0 (NMe), 41.2 (C-3), 42.7 (NMe), 44.2 (CH_2CO), 44.6 (C-6), 50.7, 51.8 (OMe), 97.0 (C-5), 110.2 (indole C-7), 111.2 (indole C-3), 120.4 (indole C-5), 122.8 (indole C-4), 125.5 (indole C-6), 125.8 (indole C-3a), 134.8 (indole C-2), 139.9 (indole C-7a), 145.9 (C-6), 167.7, 172.6, 192.8 (CO). − $C_{21}H_{24}N_2O_5$ (384): calcd. C 65.61, H 6.29, N 7.29; found C 65.60, H 6.41, N 7.12.

Dimethyl *cis*-4-[(2-Indolyl)carbonylmethyl]-1-methyl-1,2,3,4-tetrahydropyridine-3,5-dicarboxylate (5b): As above, tetrahydropyridine **5b** (60 mg, foam, 60%) was obtained from dihydropyridine **4b**[9] (0.1 g, 0.27 mmol) and PtO_2 (25 mg) after flash chromatography (hexanes/AcOEt, 3:2). − IR (KBr): ṽ = 1600, 1660, 1680, 1734, 3280. − ^{1}H NMR: δ = 2.83 (dd, J = 14.5, 8 Hz, 1 H, CH_2CO), 2.86 (masked, 1 H, 3-H), 2.99 (dd, J = 14.5, 4.5 Hz, 1 H, CH_2CO), 3.03 (s, 3 H, NMe), 3.23 (ddd, J = 13, 4.4, 1.3 Hz, 1 H, 2-H_{eq}), 3.46 (t, J = 13 Hz, 1 H, 2-H_{ax}), 3.59 and 3.60 (2s, 3 H, OMe), 3.87 (m, 1 H, 4-H), 7.12 (m, 1 H, indole 5-H), 7.31 (m, 4 H, indole, 6-H), 7.60 (d, J = 8 Hz, 1 H, indole 4-H), 9.90 (br. s, 1 H, NH). − ^{13}C NMR: δ = 30.0 (C-4), 41.0 (C-3), 42.7 (NMe), 43.6 (CH_2CO), 44.4 (C-2), 50.7, 51.6 (OMe), 96.9 (C-5), 108.9 (indole C-7), 112.3 (indole C-3), 120.6 (indole C-5), 122.9 (indole C-4), 125.8 (indole C-6), 127.5 (indole C-3a), 135.2 (indole C-2), 137.3 (indole C-7a), 146.3 (C-6), 168.1, 172.0, 191.0 (CO). − $C_{20}H_{22}N_2O_5$ (370): calcd. C 64.85, H 5.99, N 7.56; found C 64.71, H 6.09, N 7.48.

Catalytic Hydrogenation of Dihydropyridine 4c: A solution of dihydropyridine **4c**[9] (160 mg, 0.39 mmol) in AcOEt (25 mL) was hydrogenated in the presence of PtO_2 (40 mg) for 5 h. Workup as above gave a crude residue, which was chromatographed (hexanes/AcOEt, increasing polarity and AcOEt/Et_2NH, 95:5) to give the following compounds.

Methyl *trans*-3-[2-(Methoxycarbonyl)ethyl]-1-methyl-4-[(1-methyl-2-indolyl)carbonylmethyl]-1,2,3,4-tetrahydropyridine-5-carboxylate (7c): 24 mg, foam, 15%. − ^{1}H NMR: δ = 1.53 (m, 2 H, CH_2C), 1.86 (m, 1 H, 3-H), 2.31 (m, 2 H, CH_2CO_2Me), 2.56 (dd, J = 14.6, 10.8 Hz, 1 H, CH_2CO), 2.78 (br. d, J = 13 Hz, 1 H, 2-H), 3.00 (s, 3 H, NMe), 3.05 (m, 1 H, 4-H), 3.34 (dd, J = 13, 3.6 Hz, 1 H, 2-H), 3.45 (dd, J = 14.6, 3.3 Hz, 1 H, CH_2CO); 3.57 and 3.70 (2s, 3 H, OMe), 4.07 (s, 3 H, NMe), 7.15 (m, 1 H, indole 5-H), 7.37 (m, 3 H, indole, 6-H), 7.54 (s, 1 H, indole 3-H), 7.72 (d, J = 8 Hz, 1 H, indole 4-H). − ^{13}C NMR: δ = 27.2 (CH_2C), 32.1 (C-4, CH_2CO_2Me, NMe), 33.1 (C-3), 43.1 (NMe), 47.4 (C-2), 47.5 (CH_2CO), 50.6, 51.6 (OMe); 94.9 (C-5), 110.2 (indole C-7), 112.1 (indole C-3), 120.5 (indole C-5), 123.1 (indole C-4), 125.8 (indole C-6 and C-3a), 134.7 (indole C-2), 140.0 (indole C-7a), 146.1 (C-6), 168.8, 173.8, 193.5 (CO) − $C_{23}H_{28}N_2O_5$: calcd. for [M^+] 412.1988; found 412.1999.

Methyl *cis*-3-[2-(Methoxycarbonyl)ethyl]-1-methyl-4-[(1-methyl-2-indolyl)carbonylmethyl]-1,2,3,4-tetrahydropyridine-5-carboxylate (5c): 55 mg, foam, 34%. − IR (KBr): ṽ = 1620, 1660, 1734. − ^{1}H NMR: δ = 1.67 (m, 2 H, CH_2C), 1.93 (m, 1 H, 3-H), 2.45 (m, 2 H, CH_2CO_2Me), 2.74 (dd, J = 14.3, 6 Hz, 1 H, CH_2CO), 2.95 (m, 3 H, CH_2CO, 2-H), 3.40 (m, 1 H, 4-H), 3.00 (s, 3 H, NMe), 3.42 and 3.65 (2 s, 3 H, OMe), 4.05 (s, 3 H, NMe), 7.15 (m, 1 H, indole 5-H), 7.34 and 7.37 (2 s, 1 H, indole 3-H, 6-H), 7.35 (m, 2 H, indole 6-H and 7-H), 7.69 (dm, J = 8 Hz, 1 H, indole 4-H). − ^{13}C NMR: δ = 25.4 (CH_2C), 30.6 (C-4), 31.8 (CH_2CO_2Me), 32.1 (NMe), 35.9 (C-3), 42.7 (NMe), 43.1 (CH_2CO), 49.1 (C-2), 50.4, 51.6 (OMe), 98.0 (C-5), 110.3 (indole C-7), 111.9 (indole C-3), 120.4 (indole C-5), 122.9 (indole C-4), 125.6 (indole C-6), 125.8 (indole C-3a), 135.3 (indole C-2), 140.1 (indole C-7a), 146.1 (C-6), 168.3, 173.6, 193.4 (CO). − $C_{23}H_{28}N_2O_5$: calcd. for [M^+] 412.1988; found 412.2017.

Methyl *c*-5-(Methoxycarbonyl)-1-methyl-*c*-4-[(1-methyl-2-indolyl)-carbonylmethyl]-*r*-3-piperidinepropionate (8c): 25 mg, foam, 15%. − ^{1}H NMR: δ = 1.54 (m, 2 H, CH_2C), 1.90 (m, 2 H, CH_2CO_2Me), 2.36 (s, 3 H, NMe), 2.37 (m, 3 H), 2.65 (br. d, J = 9 Hz, 1 H), 2.90 (m, 4 H), 3.17 (m, 1 H), 3.51 and 3.62 (2 s, 3 H, OMe), 4.05 (s, 3 H, NMe), 7.15 (m, 1 H, indole 5-H), 7.31 (s, 1 H, indole 3-H), 7.37 (m, 2 H, indole), 7.70 (d, J = 8 Hz, 1 H, indole 4-H). − ^{13}C NMR: δ = 25.9 (CH_2C), 31.6 (C-4, CH_2CO_2Me), 32.1 (NMe), 39.7 (C-3), 45.9 (NMe), 46.1 (C-5), 51.6 (CH_2CO, CH_2N), 51.7, 52.0 (OMe), 56.1 (CH_2N), 110.3 (indole C-7), 110.9 (indole C-3), 120.7 (indole C-5), 122.8 (indole C-4), 125.7 (indole C-3a), 125.8 (indole C-6), 134.6 (indole C-2), 140.0 (indole C-7a), 173.4, 173.7, 191.8 (CO). − $C_{23}H_{30}N_2O_5$: calcd. for [M^+] 414.2154; found 414.2154.

Catalytic Hydrogenation of Dihydropyridine 4d: A solution of dihydropyridine **4d**[9] (0.1 g, 0.25 mmol) in MeOH (50 mL) was hydrogenated in the presence of PtO_2 (30 mg) for 5 h. Workup as above followed by flash chromatography (hexanes/AcOEt, increasing polarity and AcOEt/MeOH, 95:5) gave the following compounds.

Methyl *cis*-4-[(2-Indolyl)carbonylmethyl]-3-[2-(methoxycarbonyl)-ethyl]-1-methyl-1,2,3,4-tetrahydropyridine-5-carboxylate (5d): 25 mg, foam, 25%. − IR (KBr): ṽ = 1597, 1667, 1682, 1740. − ^{1}H NMR: δ = 1.68 (m, 2 H, CH_2C), 1.92 (m, 1 H, 3-H), 2.37 (m, 2 H, CH_2CO_2Me), 2.84 (d, J = 6 Hz, 2 H, CH_2CO), 2.98 (masked, 2 H, 2-H), 2.99 (s, 3 H, NMe), 3.40 (m, 1 H, 4-H), 3.53 and 3.62 (2 s, 3 H, OMe), 7.15 (t, J = 8 Hz, 1 H, indole 5-H), 7.26 and 7.36 (2 s, 1 H, indole 3-H, 6-H), 7.35 (t, J = 8 Hz, 1 H, indole 6-H), 7.44 (d, J = 8 Hz, 1 H, indole 7-H), 7.70 (d, J = 8 Hz, 1 H, indole 4-H), 9.90 (br. s, 1 H, NH). − ^{13}C NMR: δ = 25.2 (CH_2C), 30.7 (C-4), 31.5 (CH_2CO_2Me), 35.9 (C-3), 42.4 (CH_2CO), 42.7 (NMe), 48.8 (C-2), 50.5, 51.6 (OMe), 97.7 (C-5), 109.0 (indole C-7), 112.3 (indole C-3), 120.6 (indole C-5), 122.9 (indole C-4), 125.8 (indole C-6), 127.4 (indole C-3a), 135.5 (indole C-2), 137.4 (indole C-7a), 146.4 (C-6), 168.6, 173.5, 192.5 (CO). − $C_{22}H_{26}N_2O_5$: calcd. for [M^+] 398.1841; found 398.1838.

Methyl *c*-4-[(2-Indolyl)carbonylmethyl]-*c*-5-(methoxycarbonyl)-1-methyl-*r*-3-piperidinepropionate (8d): 15 mg, foam, 15%. − ^{1}H NMR (most significant signals): δ = 2.36 (s, 3 H, NMe), 3.46 and

3.61 (2s, 3 H, OMe), 7.15 (t, J = 8 Hz, 1 H, indole 5-H), 7.23 (br. s, 1 H, indole 3-H), 7.34 (t, J = 8 Hz, 1 H, indole 6-H), 7.44 (d, J = 8 Hz, 1 H, indole 7-H), 7.71 (d, J = 8 Hz, 1 H, indole 4-H). − ^{13}C NMR: δ = 25.8 (CH_2C), 31.4 (C-4), 31.7 (CH_2CO_2Me), 39.4 (C-3), 45.8 (NMe), 45.9 (C-5), 51.5, 51.8 (OMe), 51.7, 55.9, 56.8, (CH_2N, CH_2CO), 109.1 (indole C-7), 112.8 (indole C-3), 120.8 (indole C-5), 122.9 (indole C-4), 126.2 (indole C-6), 127.4 (indole C-3a), 134.8 (indole C-2), 137.4 (indole C-7a), 173.1, 173.7, 191.0 (CO). − $C_{22}H_{28}N_2O_5$: calcd. for [M^+] 400.1988; found 400.1986.

Catalytic Hydrogenation of the Dihydropyridine 4e: Dihydropyridine **4e** (0.4 g, 0.82 mmol) in AcOEt (120 mL) was hydrogenated as above in the presence of PtO_2 (0.1 g) for 2 h. The usual workup followed by flash chromatography (hexanes/AcOEt, 7:3 and AcOEt/Et_2NH, 95:5) gave the following compounds.

Methyl *trans*-4-[(1-Benzyl-2-indolyl)carbonylmethyl]-3-[2-(methoxycarbonyl)ethyl]-1-methyl-1,2,3,4-tetrahydropyridine-5-carboxylate (7e): 40 mg, foam, 10%. − IR (film): $\tilde{\nu}$ = 1622, 1660, 1735. − ^{1}H NMR: δ = 1.44 (m, 2 H, CH_2C), 1.61 (m, 1 H, 3-H), 2.13 (m, 2 H, CH_2CO_2Me), 2.45 (dd, J = 14.1, 11.2 Hz, 1 H, CH_2CO), 2.67 (br. d, J = 13.2 Hz, 1 H, 2-H), 2.96 (s, 3 H, NMe), 2.99 (m, 1 H, 4-H), 3.26 (dd, J = 13.1, 3.5 Hz, 1 H, 2-H), 3.50 (dd, J = 14.1, 3.3 Hz, 1 H, CH_2CO), 3.55 and 3.71 (2 s, 6 H, OMe), 5.80 and 5.90 (2 d, J = 16 Hz, 2 H, CH_2Ph), 6.99 (m, 1 H, Ar), 7.12−7.40 (m, 8 H, Ar), 7.69 (s, 1 H, 6-H), 7.77 (d, J = 8 Hz, 1 H, indole 4-H). − ^{13}C NMR: δ = 27.0 (CH_2C), 31.8 (CH_2CO_2Me), 32.6 (C-4), 32.8 (C-3), 43.0 (NMe), 47.2, 47.6, 47.9 (C-2, CH_2CO, CH_2Ph), 50.5, 51.4 (OMe), 94.8 (C-5), 110.7 (indole C-7), 113.4 (indole C-3), 120.0 (indole C-5), 123.2 (indole C-4), 125.8 (indole C-3a), 126.1(indole C-6), 126.3, 126.9, 128.4 (Ph), 134.1 (indole C-2), 138.5 (Ph), 140.0 (indole C-7a), 146.0 (C-6), 168.8, 173.7, 193.3 (CO). − $C_{29}H_{32}N_2O_5$ (488): calcd. C 71.29, H 6.60, N 5.73; found C 71.27, H 6.61, N 5.78.

Methyl *cis*-4-[(1-Benzyl-2-indolyl)carbonylmethyl]-3-[2-(methoxycarbonyl)ethyl]-1-methyl-1,2,3,4-tetrahydropyridine-5-carboxylate (5e): 200 mg, foam, 50%. − IR (film): $\tilde{\nu}$ = 1620, 1660, 1735. − ^{1}H NMR: δ = 1.57 (m, 2 H, CH_2C), 1.89 (m, 1 H, 3-H), 2.31 (m, 2 H, CH_2CO_2Me), 2.78 (dd, J = 14.6, 5.3 Hz, 1 H, 14-H), 2.94 (m, 3 H, 2-H, 14-H), 3.40 (m, 1 H, 4-H), 2.95 (s, 3 H, NMe), 3.48 and 3.62 (2 s, 3 H, OMe), 5.58 and 5.87 (2 d, J = 16 Hz, 2 H, CH_2Ph), 7.05 (m, 1 H, Ar), 7.10−7.35 (m, 8 H, Ar), 7.45 (s, 1 H, 6-H), 7.72 (d, J = 8 Hz, 1 Hz, indole 4-H). − ^{13}C NMR: δ = 25.3 (CH_2C), 30.4 (C-4), 31.5 (CH_2CO_2Me), 35.7 (C-3), 42.6 (NMe), 43.0 (CH_2CO), 48.2, 49.0 (C-2, CH_2Ph), 50.3, 51.6 (OMe), 97.9 (C-5), 110.8 (indole C-7), 112.3 (indole C-3), 120.8 (indole C-5), 123.0 (indole C-4), 125.8 (indole C-6 and C-3a), 126.4, 126.8, 128.4 (Ph), 134.8 (indole C-2), 138.5 (Ph), 140.0 (indole C-7a), 146.1 (C-6), 168.3, 173.6, 192.9 (CO). − $C_{29}H_{32}N_2O_5$ (488): calcd. C 71.29, H 6.60, N 5.73; found C 71.20, H 6.64, N 5.72.

Methyl 4-[(1-Benzyl-2-indolyl)carbonylmethyl]-5-(methoxycarbonyl)-1-methyl-3-piperidinepropionate (8e): 80 mg, mixture of stereoisomers, foam, 20%. − ^{1}H NMR (most significant signals): δ = 2.33 (s, 3 H, NMe), 3.32 and 3.60 (2 s, 3 H, OMe), 5.80 (m, 2 H, CH_2Ph), 6.90−7.40 (m, 9 H, Ar), 7.70 (dm, J = 8 Hz, 1 H, indole 4-H).

Methyl *cis*-2,7-Dimethyl-6,12-dioxo-3,4,4a,5,6,12-hexahydro-2*H*-pyrido[3′,4′:4,5]cyclohepta[1,2-*b*]indole-4-carboxylate (6a): A mixture of tetrahydropyridine **5a** (35 mg, 0.1 mmol) and trimethylsilyl polyphosphate (PPSE, 2 mL) was heated at 100 °C for 1 h. The cooled reaction mixture was partitioned between H_2O and Et_2O and extracted with Et_2O. Concentration of the dried extracts gave a residue, which was chromatographed (AcOEt and AcOEt/MeOH, 98:2) to give tetracycle **6a** (foam, 10 mg, 30%). − ^{1}H NMR: δ = 2.68 (m, 2 H, 14-H), 3.03 (m, 1 H, 20-H), 3.18 (s, 3 H, NMe), 3.36 (m, 2 H, 21-H), 3.56 (m, 1 H, 15-H), 3.75 (s, 3 H, OMe), 3.98 (s, 3 H, NMe), 7.26 (m, 1 H, 10-H), 7.41 (m, 2 H, 11-H, 12-H), 7.73 (s, 1 H, 5-H), 8.45 (d, J = 8 Hz, 1 H, 9-H). − ^{13}C NMR: δ = 28.9 (C-15), 32.6 (NMe), 41.4 (C-20), 43.3 (NMe), 45.3 (C-21), 48.0 (C-14), 52.3 (OMe), 107.8 (C-16), 110.1 (C-12), 113.4 (C-7), 122.8 (C-10), 124.8 (C-9), 125.9 (C-8), 126.5 (C-11), 135.0 (C-2), 139.3 (C-13), 147.1 (C-5), 171.5 (CO), 183.5 (C-6), 194.2 (C-3). − $C_{20}H_{20}N_2O_4 \cdot 1/2H_2O$ (361): calcd. C 66.47, H 5.85, N 7.75; found C 66.63, H 5.85, N 7.53.

Methyl *cis*-2-Methyl-6,12-dioxo-3,4,4a,5,6,12-hexahydro-2*H*-pyrido[3′,4′:4,5]cyclohepta[1,2-*b*]indole-4-carboxylate (6b): As above, tetracycle **6b** (30 mg, foam, 40%) was obtained from tetrahydropyridine **5b** (80 mg, 0.23 mmol) and PPSE (4 mL) after flash chromatography (AcOEt and AcOEt/MeOH, 97:3). − IR (film): $\tilde{\nu}$ = 1625, 1658, 1734. − ^{1}H NMR (500 MHz): δ = 2.64 (dd, J = 17.5, 1.5 Hz, 1 H, 14-H), 2.74 (dd, J = 17.5, 12.5 Hz, 1 H, 14-H), 3.05 (m, 1 H, 20-H), 3.16 (s, 3 H, NMe), 3.36 (m, 2 H, 21-H), 3.55 (dd, J = 12.5, 2.7 Hz, 1 H, 15-H), 3.75 (s, 3 H, OMe), 7.30 (m, 1 H, 10-H), 7.40 (m, 2 H, 11-H, 12-H), 7.74 (s, 1 H, 5-H), 8.55 (d, J = 8 Hz, 1 H, 9-H), 9.50 (br. s, 1 H, NH). − ^{13}C NMR: δ = 29.4 (C-15), 42.1 (C-20), 43.1 (NMe), 45.2 (C-21), 46.4 (C-14), 52.3 (OMe), 108.7 (C-16), 111.8 (C-12), 119.8 (C-7), 122.8 (C-10), 125.3 (C-9), 127.0 (C-11), 127.5 (C-8), 133.6 (C-2), 136.3 (C-13), 146.4 (C-5), 171.6 (CO), 183.8 (C-6), 192.8 (C-32). − $C_{19}H_{18}N_2O_4$ (338): calcd. C 67.45, H 5.36, N 8.28; found C 67.56, H 5.39, N 8.08.

Methyl *cis*-2,7-Dimethyl-6,12-dioxo-3,4,4a,5,6,12-hexahydro-2*H*-pyrido[3′,4′:4,5]cyclohepta[1,2-*b*]indole-4-propionate (6c): As above, tetracycle **6c** (40 mg, foam, 40%) was obtained from tetrahydropyridine **5c** (110 mg, 0.26 mmol) and PPSE (5 mL) (reaction time 1 h 45 min), after flash chromatography (AcOEt and AcOEt/MeOH, 95:5). − IR (KBr): $\tilde{\nu}$ = 1647, 1653, 1733. − ^{1}H NMR: δ = 1.74 (m, 2 H, 19-H), 2.04 (m, 1 H, 20-H), 2.36 (m, 2 H, 18-H), 2.55 (dd, J = 18, 12.7 Hz, 1 H, 14-H), 2.87 (dd, J = 18, 2.2 Hz, 1 H, 14-H), 3.02 (m, 3 H, 15-H, 21-H), 3.10 (s, 3 H, NMe), 3.65 (s, 3 H, OMe), 3.99 (s, 3 H, NMe), 7.28 (m, 1 H, 10-H), 7.41 (m, 2 H, 11-H, 12-H), 7.12 (s, 1 H, 5-H), 8.50 (d, J = 8 Hz, 1 H, 9-H). − ^{13}C NMR: δ = 24.6 (C-19), 29.7 (C-15), 31.7 (C-18), 32.5 (NMe), 35.0 (C-20), 43.0 (NMe), 46.0 (C-21), 49.6 (C-14), 51.8 (OMe), 108.9 (C-16), 110.0 (C-12), 121.3 (C-7), 122.6 (C-10), 124.9 (C-9), 126.0 (C-8), 126.4 (C-11), 134.9 (C-2), 139.3 (C-13), 146.5 (C-5), 173.2 (CO), 184.5 (C-6), 195.3 (C-3). − $C_{22}H_{24}N_2O_4$: calcd. for [M^+] 380.1736; found 380.1745.

Methyl *cis*-2-Methyl-6,12-dioxo-3,4,4a,5,6,12-hexahydro-2*H*-pyrido[3′,4′:4,5]cyclohepta[1,2-*b*]indole-4-propionate (6d): As above, tetracycle **6d** (10 mg, foam, 27%) was obtained from tetrahydropyridine **5d** (40 mg, 0.1 mmol) and PPSE (4 mL) (reaction time 20 min) after flash chromatography (AcOEt and AcOEt/MeOH, 95:5). − IR (KBr): $\tilde{\nu}$ = 1625, 1640, 1730. − ^{1}H NMR: δ = 1.62 (m, 2 H, 19-H), 1.89 (m, 1 H, 20-H), 2.38 (m, 2 H, 18-H), 2.63 (m, 2 H), 2.94 (m, 2 H), 3.07 (s, 3 H, NMe), 3.55 (s, 3 H, OMe), 7.15 (m, 1 H, 10-H), 7.30 (m, 1 H, 11-H), 7.46 (d, J = 8.2 Hz, 1 H, 12-H), 7.56 (s, 1 H, 5-H), 8.31 (d, J = 8.1 Hz, 1 H, 8-H). − ^{13}C NMR: δ = 24.7 (C-19), 30.5 (C-15), 31.6 (C-18), 35.5 (C-20), 43.0 (NMe), 43.9 (C-14), 49.7 (C-21), 51.8 (OMe), 109.8 (C-16), 111.6 (C-12), 122.8 (C-10), 123.0 (C-7), 125.4 (C-9), 126.9 (C-11), 127.6 (C-8), 133.5 (C-2), 136.2 (C-13), 146.7 (C-5), 173.1 (CO), 184.1 (C-6), 193.6 (C-3). − $C_{21}H_{22}N_2O_4$: calcd. for [M^+] 366.1579; found 366.1583.

Methyl *cis*-7-Benzyl-2-methyl-6,12-dioxo-3,4,4a,5,6,12-hexahydro-2*H*-pyrido[3′,4′:4,5]cyclohepta[1,2-*b*]indole-4-propionate (6e): As above, tetracycle **6e** (35 mg, foam, 35%) was obtained from tetrahydropyridine **5e** (110 mg, 0.22 mmol) and PPSE (5 mL) (reaction time 1 h 30 min) after flash chromatography (AcOEt and AcOEt/MeOH, 95:5). − IR (film): $\tilde{\nu}$ = 1547, 1630, 1660, 1735. − ^{1}H NMR: δ = 1.66 (m, 2 H, 19-H), 2.00 (m, 1 H, 20-H), 2.22 (t, *J* = 7.6 Hz, 2 H, 18-H), 2.47 (dd, *J* = 18.3, 12.6 Hz, 1 H, 14-H), 2.63 (dd, *J* = 18.3, 2.4 Hz, 1 H, 14-H), 2.96 (m, 3 H, 15-H, 21-H), 3.10 (s, 3 H, NMe), 3.65 (s, 3 H, OMe), 5.65 and 5.75 (2 d, *J* = 16.1 Hz, 2 H, CH_2Ph), 7.00 (m, 2 H, Ar), 7.18−7.30 (m, 4 H, Ar), 7.35 (m, 2 H, Ar), 7.71 (s, 1 H, 5-H), 8.48 (d, *J* = 8 Hz, 1 H, 9-H). − ^{13}C NMR: δ = − 24.3 (C-19), 29.4 (C-15), 31.3 (C-18), 34.7 (C-20), 43.0 (NMe), 45.8 (C-21), 48.2, 49.7 (C-14, CH_2Ph), 51.7 (OMe), 108.7 (C-16), 110.4 (C-12), 122.0 (C-7), 122.7 (C-10), 124.7 (C-9), 126.0 (C-8), 126.2 (C-11), 126.3, 127.3, 128.6 (Ph), 134.7 (C-2), 137.9, 139.2 (C-13, Ph), 146.5 (C-5), 173.0 (CO), 184.5 (C-6), 195.2 (C-3). − $C_{28}H_{28}N_2O_4$: calcd. for [M$^+$] 456.2049; found 456.2047.

4-Acetyl-7-benzyl-2-methyl-3,4,4a,5,6,12-hexahydro-2*H*-pyrido-[3′,4′:4,5]cyclohepta[1,2-*b*]indole-6,12-dione (6f): As above, tetracycle **6f** (30 mg, foam, mixture of stereoisomers, 40%) was obtained from tetrahydropyridine **5f**[7] (70 mg, 0.16 mmol) and PPSE (4 mL) after flash chromatography (AcOEt). − IR (KBr): $\tilde{\nu}$ = 1630, 1660. 1708. − ^{1}H NMR (major stereoisomer, most significant signals): δ = 2.17 (s, 3 H, MeCO), 3.17 (s, 3 H, NMe), 5.62 and 5.72 (2 d, *J* = 16 Hz, 2 H, CH_2Ph), 7.05 (m, 2 H, Ar), 7.20−7.50 (m, 6 H, Ar), 7.78 (s, 1 H, 5-H), 8.50 (d, *J* = 8 Hz, 1 H, 9-H). − ^{13}C NMR (major stereoisomer): δ = 28.5 (C-15), 29.1 (C-18), 43.3 (NMe), 45.7 (C-21), 48.6 (C-14), 51.0 (C-20), 52.1 (CH_2Ph), 106.5 (C-16), 110.6 (C-12), 120.2 (C-7), 122.8 (C-10), 125.1 (C-8, C-9), 126.5 (C-11), 137.7 (C-2), 139.4 (C-13), 146.7 (C-5), 183.9 (C-6), 193.7 (C-3), 206.1 (C-19). − $C_{26}H_{24}N_2O_3$·1/2H_2O (421): calcd. C 74.06, H 5.97, N 6.64; found C 74.07, H 5.99, N 6.50.

4-Acetyl-2-methyl-3,4,4a,5,6,12-hexahydro-2*H*-pyrido[3′,4′:4,5]-cyclohepta[1,2-*b*]indole-6,12-dione (6g). − Method A: As above, tetracycle **6g** (8 mg, mixture of stereoisomers, 40%) was obtained from tetrahydropyridine **5g**[7] (23 mg, 0.06 mmol) and PPSE (2 mL) (reaction time 45 min) after flash chromatography (AcOEt). − IR (KBr): $\tilde{\nu}$ = 1627, 1650, 1711. − ^{1}H NMR (major stereoisomer, most significant signals): δ = 2.19 (s, 3 H, MeCO), 3.18 (s, 3 H, NMe), 7.20−7.50 (m, 3 H, indole), 7.78 (s, 1 H, 5-H), 8.55 (d, *J* = 8 Hz, 1 H, 9-H), 9.30 (br. s, 1 H, NH). − $C_{19}H_{18}N_2O_3$ (322): calcd. C 70.78, H 5.62, N 8.69; found C 70.66, H 5.84, N 8.30. − **Method B:** Anhydrous $AlCl_3$ (80 mg, 0.59 mmol) was added to a solution of tetracycle **6f** (25 mg, 0.06 mmol) in anhydrous C_6H_6 (5 mL), and the resulting mixture was stirred at room temperature for 5 h. The mixture was poured into H_2O, basified with saturated aqueous $NaHCO_3$, and extracted with AcOEt. The organic extracts were dried and concentrated, and the residue was chromatographed (flash, AcOEt and AcOEt/MeOH, 99:1) to give tetracycle **6g** (18 mg, 93%).

1-Methyl-5,16-didehydro-6-oxosilicine (9a): A solution of tetracycle **6c** (30 mg, 0.08 mmol) and LiOH·H_2O (5 mg, 0.12 mmol) in MeOH/H_2O (5:1; 6 mL) was refluxed for 3 h. The solvent was evaporated, and the resulting residue was dissolved in H_2O. The aqueous solution was carefully acidified with 1 N HCl and extracted with AcOEt. The organic extracts were dried and concentrated to give a solid residue, which was dried under vacuum. A solution of the above residue in anhydrous CH_2Cl_2 (3 mL) was treated with oxalyl chloride (0.08 mL, excess) at 0 °C, and the resulting mixture was stirred at room temperature for 30 min. The solvent and excess oxalyl chloride were removed, and the resulting residue was dissolved in anhydrous C_6H_6 (5 mL). DMAP (catalytic amount) and the sodium salt of 2-mercaptopyridine *N*-oxide (15 mg, 0.1 mmol) were added to the above solution, and the mixture was refluxed for 30 min. AIBN (catalytic amount) and *n*Bu_3SnH (0.1 mL, 0.37 mmol) were then added, and the reflux was continued for an additional 5 h. The mixture was partitioned between H_2O and AcOEt, and extracted with AcOEt. The organic extracts were dried and concentrated, and the resulting residue was chromatographed (flash, AcOEt/Et_2NH, 97:3) to give tetracycle **9a** (10 mg, foam, 40%). − ^{1}H NMR: δ = 0.95 (t, *J* = 7.4 Hz, 3 H, 18-H), 1.42 (m, 2 H, 19-H), 1.94 (m, 1 H, 20-H), 2.52 (dd, *J* = 18.3, 12.9 Hz, 1 H, 14-H), 2.88 (dd, *J* = 18.3, 2.1 Hz, 1 H, 14-H), 2.92 (m, 3 H, 15-H, 21-H), 3.11 and 3.98 (2 s, 3 H, NMe), 7.29 (m, 1 H, 10-H), 7.40 (m, 2 H, 11-H, 12-H), 7.72 (s, 1 H, 5-H), 8.49 (d, *J* = 8.1 Hz, 1 H, 9-H). − ^{13}C NMR: δ = 11.9 (C-18), 22.4 (C-19), 29.6 (C-15), 32.4 (NMe), 37.2 (C-20), 43.0 (NMe), 46.1 (C-21), 49.8 (C-14), 109.0 (C-12), 109.2 (C-16), 121.4 (C-7), 122.5 (C-10), 124.9 (C-9), 126.0 (C-11), 126.3 (C-8), 135.0 (C-2), 139.1 (C-13), 146.6 (C-5), 184.0 (C-6), 195.8 (C-3). − $C_{20}H_{22}N_2O_2$: calcd. for [M$^+$] 322.1681; found 322.1695.

1-Benzyl-5,16-didehydro-6-oxosilicine (9b). − Method A: As above, tetracycle **9b** (8 mg, foam, 30%) was obtained from tetracycle **6e** (30 mg, 0.066 mol) after flash chromatography (hexanes/AcOEt/Et_2NH, 50:46:4). − IR (film): $\tilde{\nu}$ = 1629, 1655. − ^{1}H NMR: δ = 0.85 (t, *J* = 7.5 Hz, 3 H, 18-H), 1.33 (m, 2 H, 19-H), 1.90 (m, 1 H, 20-H), 2.43 (dd, *J* = 18.3, 12.8 Hz, 1 H, 14-H), 2.65 (dd, *J* = 18.3, 2.3 Hz, 1 H, 14-H), 2.96 (m, 3 H, 15-H, 21-H), 3.10 (s, 3 H, NMe), 5.64 and 5.77 (2 d, *J* = 16.2 Hz, 2 H, CH_2Ph), 7.00 (m, 2 H, Ar), 7.20−7.35 (m, 4 H, Ar), 7.37 (m, 2 H, Ar), 7.73 (s, 1 H, 5-H), 8.48 (d, *J* = 8 Hz, 1 H, 9-H). − ^{13}C NMR: δ = 11.6 (C-18), 22.3 (C-19), 29.2 (C-15), 36.9 (C-20), 43.0 (NMe), 45.9 (C-21), 48.2, 49.9 (C-14, CH_2Ph), 109.0 (C-16), 110.4 (C-12), 122.5 (C-7), 122.6 (C-10), 124.8 (C-9), 126.2 (C-8), 126.3 (C-11), 126.4, 127.3, 128.6 (Ph), 135.0 (C-2), 137.9, 138.9 (C-13, Ph), 146.7 (C-5), 184.2 (C-6), 195.9 (C-3). − $C_{26}H_{26}N_2O_2$: calcd. for [M$^+$] 398.1994; found 398.1992. − **Method B:** A solution of tetracycle **6e** (40 mg, 0.088 mmol) and LiOH·H_2O (11 mg, 0.26 mmol) in MeOH/THF (5:1; 12 mL), was refluxed for 1 h. Workup as above gave a crude acid, which was dried under vacuum. Tributylphosphane (26 mL, 0.1 mmol) was added to a solution of this acid and 2,2′-dithiobis(pyridine 1,1′-dioxide) (27 mg, 0.1 mmol) in anhydrous CH_2Cl_2 (5 mL) at 0 °C, and the mixture was stirred at room temperature for 45 min. 2-Methyl-2-propanethiol (0.14 mL, 0.56 mmol) was added, and the mixture was irradiated at 0 °C with a 300-W tungsten lamp for 2 h. The mixture was diluted with CH_2Cl_2 (10 mL) and washed with saturated aqueous $NaHCO_3$. The organic solution was dried and concentrated, and the residue was chromatographed (flash, hexanes/AcOEt, 1:1, and AcOEt) to give tetracycle **9b** (26 mg, 75%).

5,16-Didehydro-6-oxosilicine (9c): Anhydrous $AlCl_3$ (121 mg, 0.9 mmol) was added to a solution of tetracycle **9b** (30 mg, 0.075 mmol) in anhydrous C_6H_6 (6 mL), and the resulting mixture was stirred at room temperature for 1 h 30 min. The mixture was poured into H_2O, basified with saturated aqueous $NaHCO_3$, and extracted with AcOEt. The organic extracts were dried and concentrated, and the residue was chromatographed (flash, AcOEt and AcOEt/MeOH, 95:5) to give tetracycle **9c** (20 mg, 86%). − ^{1}H NMR: δ = 0.95 (t, *J* = 7.2 Hz, 3 H, 18-H), 1.44 (m, 2 H, 19-H), 1.94 (m, 1 H, 20-H), 2.55 (dd, *J* = 17.3, 12.6 Hz, 1 H, 14-H), 2.88 (d, *J* = 17.3 Hz, 1 H, 14-H), 3.00 (m, 3 H, 15-H, 21-H), 3.11 (s, 3 H, NMe), 7.25 (m, 1 H, 10-H), 7.38 (m, 2 H, 11-H, 12-H), 7.75 (s, 1 H, 5-H), 8.57 (d, *J* = 8.2 Hz, 1 H, 9-H), 9.40 (br. s, 1 H, NH).

(±)-6-Oxo-16-episilicine: Tetracycle **9c** (15 mg, 0.048 mmol) in anhydrous MeOH (3 mL) was treated with glacial AcOH (0.5 mL) and $NaCNBH_3$ (excess) at room temperature for 3 h. The reaction mixture was poured into H_2O, carefully basified with solid Na_2CO_3, and extracted with AcOEt. The organic extracts were dried and concentrated. Flash chromatography (AcOEt/Et_2NH, 99:1) of the residue gave 6-oxo-16-episilicine (12 mg, 80%). – ^1H NMR (500 MHz): δ = 0.96 (t, *J* = 7.5 Hz, 3 H, 18-H), 1.34 (m, 1 H, 19-H), 1.63 (m, 1 H, 20-H), 1.73 (m, 1 H, 19-H), 1.85 (t, *J* = 11.5 Hz, 1 H, 5-H_{ax}), 1.88 (br. d, *J* = 13 Hz, 1 H, 21-H_{ax}), 2.26 (td, *J* = 11 and 4 Hz, 1 H, 15-H_{ax}), 2.29 (s, 3 H, NMe), 2.78 (d, *J* = 16 Hz, 1 H, 14-H), 2.94 (dt, *J* = 13 and 1.7 Hz, 1 H, 21-H_{eq}), 2.97 (td, *J* = 11.5 and 4 Hz, 1 H, 16-H_{ax}), 2.99 (dd, *J* = 16 and 11 Hz, 1 H, 14-H), 3.55 (ddd, *J* = 11.5, 4 and 1.4 Hz, 1 H, 5-H_{eq}), 7.32 (m, 1 H, 10-H), 7.45 (m, 2 H, 11-H and 12-H), 8.37 (d, *J* = 8.1 Hz, 1 H, 9-H), 9.40 (s, 1 H, NH). – ^{13}C NMR: δ = 12.7 (C-18), 18.3 (C-19), 36.7 (C-15), 42.4 (C-20), 46.4 (NMe), 47.3 (C-14), 51.8 (C-16), 57.5 (C-21), 59.5 (C-5), 111.9 (C-12), 118.2 (C-7), 123.8 (C-10), 124.6 (C-9), 127.4 (C-11), 128.6 (C-8), 134.3 (C-2), 135.8 (C-13), 192.8, 197.7 (C-3, C-6). – $C_{19}H_{22}N_2O_2$: calcd. for [M^+] 310.1681; found 310.1667.

(±)-6-Oxosilicine: A solution of 6-oxo-16-episilicine (15 mg, 0.048 mmol) in a saturated MeOH solution of K_2CO_3 (10 mL) was stirred at room temperature for 6 d. The solvent was removed, and the residue was partitioned between H_2O and CH_2Cl_2 and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give a 1:4 mixture of 6-oxo-16-episilicine and 6-oxosilicine (14 mg, 94%). Flash chromatography (Et_2O/Et_2NH, 98:2) gave pure 6-oxosilicine (8 mg). – ^1H NMR: δ = 0.92 (t, *J* = 7.4 Hz, 3 H, 18-H), 1.40 (m, 2 H, 19-H), 1.77 (t, *J* = 11.5 Hz, 1 H, CHN_{ax}), 1.82 (m, 1 H, 20-H), 2.35 (masked, 1 H), 2.40 (s, 3 H, NMe), 2.70 (m, 3 H), 2.97 (dd, *J* = 15.7, 11.1 Hz, 1 H, 14-H), 3.17 (dm, *J* = 12.5 Hz, 1 H, CHN_{eq}), 3.48 (dm, *J* = 11.5 Hz, 1 H, CHN_{eq}), 7.28–7.50 (m, 3 H, indole), 8.40 (d, *J* = 8.1 Hz, 1 H, 9-H), 9.45 (br. s, 1 H, NH). – ^{13}C NMR: δ = 11.4 (C-18), 23.5 (C-19), 32.1 (C-15), 35.9 (C-14), 41.7 (C-20), 45.7 (NMe), 52.2. 56.2 (C-5, C-21), 53.8 (C-16), 112.0 (C-12), 118.7 (C-7), 124.0 (C-10), 124.6 (C-9), 127.4 (C-11), 128.6 (C-8), 134.3 (C-2), 135.7 (C-13), 192.6, 196.9 (C-3, C-6). – $C_{19}H_{22}N_2O_2$: calcd. for [M^+] 310.1681, found 310.1677.

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