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Cyclocondensation Reactions between 2-Acyl-3-indoleacetic Acid Derivatives and Phenylglycinol: Enantioselective Synthesis of 1-Substituted Tetrahydro-β-carboline Alkaloids

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Cyclocondensation reactions between a variety of 2-acyl-3-indoleacetic acid derivatives and (*R*)-phenylglycinol were studied. Successful results were obtained from *N*-alkyl keto acid derivatives. The resulting tetracyclic lactams provide straightforward access to enantiopure 1-substituted tetrahydro-β-carboline alkaloids.

Introduction

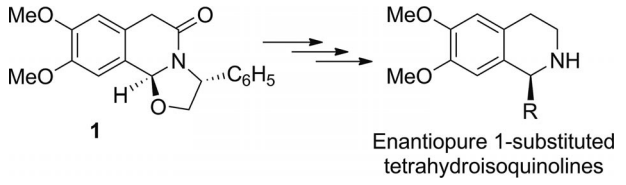
The tetrahydro-β-carboline ring system is present in many naturally occurring compounds, either simple tetrahydro-β-carboline alkaloids[1] or more complex natural products bearing additional fused rings,[2] most of them displaying significant biological and pharmacological activities.[3] This heterocyclic ring system is also present in numerous bioactive alkaloid-related synthetic compounds, some of which have emerged as important targets for pharmaceutical research.[4]

A common structural feature of the alkaloids and bioactive synthetic analogues containing the tetrahydro-β-carboline nucleus is the presence of a stereogenic center at the C–1 position. This has stimulated the development of a variety of enantioselective methods for the synthesis of 1-substituted tetrahydro-β-carbolines.[5–9]

In the context of our studies on the use of phenylglycinol-derived lactams as building blocks for the enantioselective synthesis of substituted piperidines and complex piperidine-containing natural products,[10] here we present a practical synthetic route to enantiopure 1-substituted tetrahydro-β-carbolines.

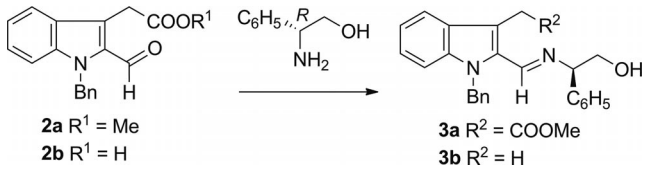
Results and Discussion

In previous work we have demonstrated that lactam **1** (Scheme 1), easily accessible through a cyclocondensation reaction between methyl 2-formyl-3,4-dimethoxyphenylacetate and (*R*)-phenylglycinol, provides general access to enantiopure 1-substituted tetrahydroisoquinoline alkaloids.[11] The key step in the synthetic sequence is a stereoselective α-amidoalkylation reaction promoted by a Grignard reagent for the introduction of the substituent at the hydroisoquinoline C-1 position.



Scheme 1. Enantioselective access to 1-substituted tetrahydroisoquinolines.

In theory, the extension of the above methodology to the enantioselective synthesis of 1-substituted tetrahydro-β-carbolines should simply require the use of a 2-formyl-3-indoleacetic acid derivative in the generation of the starting lactam. However, attempted cyclocondensation reactions between aldehydes **2a**[12] or **2b**[13] (Scheme 2, C_6H_6, reflux, 48 h) and (*R*)-phenylglycinol resulted in failure, with aldimines **3a** and **3b**, respectively, being quantitatively formed instead. In the case of **2b** (a vinylogous β-keto acid), decarboxylation of the labile 3-indoleacetic acid moiety occurred.



Scheme 2. Attempted cyclocondensation reactions between 2-formyl-3-indoleacetic acid derivatives and (*R*)-phenylglycinol.

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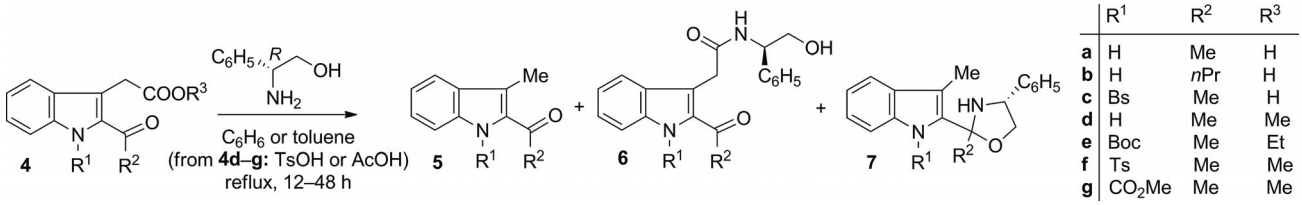
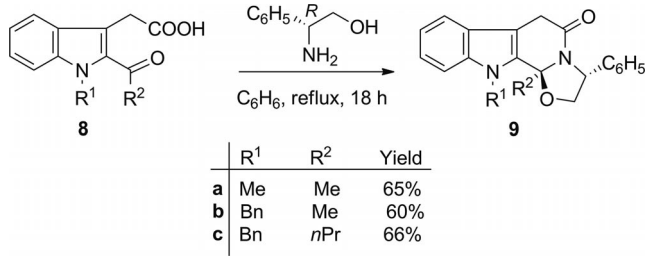


Scheme 3. Attempted cyclocondensation reactions between *N*-unsubstituted or *N*-EWG-protected 2-acyl-3-indoleacetic acids and (*R*)-phenylglycinol.

As an alternative but related approach to the target tetrahydro-β-carbolines we focused our attention on cyclocondensation reactions with keto acids, which should directly afford 1-substituted derivatives, thus avoiding the need for subsequent α-amidoalkylation. Attempted cyclocondensation reactions with the *N*-unsubstituted 2-acyl-3-indoleacetic acids **4a** and **4b** (Scheme 3), however, were also unsuccessful.[14] Under the usual reaction conditions[15] (see Scheme 3) the only process observed was decarboxylation, giving the corresponding ketones **5a**[16] (60%) and **5b** (90%), whereas amide **6a** (43%) was generated when the cyclocondensation reaction from **4a** was attempted at a lower temperature in the presence of Mukaiyama's reagent[17] (2-chloro-1-methylpyridinium iodide, CH_2Cl_2, Et_3N, reflux, 16 h). Decarboxylation also occurred in the case of the *N*-phenylsulfonyl derivative **4c**,[18] giving a mixture of 2-acetylindole **5c**[19] (15%) and oxazolidine **7c** (25%).

To avoid the undesirable decarboxylation, we also tried cyclocondensation reactions starting from δ-keto esters instead of δ-keto acids, either *N*-unsubstituted (**4d**)[14] or *N*-protected with an electron-withdrawing group (**4e**,[20] **4f**,[21] and **4g**[22]). Unfortunately, under the usual reaction conditions most of the starting materials were recovered.

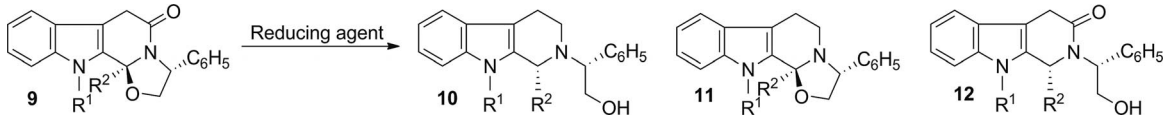
In contrast, the cyclocondensation reaction between 2-acetyl-1-methyl-3-indoleacetic acid (**8a**,[22] Scheme 4) and (*R*)-phenylglycinol led satisfactorily (65% yield) to a single tetracyclic lactam **9a**, the configuration of which was unambiguously established by X-ray crystallographic analysis[23]. Similar results were obtained from indoleacetic acids **8b**[24] and **8c**,[25] each bearing an easily removable benzyl substituent on the indole nitrogen. The resulting lactams **9b** and **9c** (configurations of the latter confirmed by X-ray crystallographic analysis[23]) were envisaged as synthetic precursors of the tetrahydro-β-carboline alkaloids tetrahydroharman and komaroidine.



Scheme 4. Cyclocondensation reactions between *N*-alkyl-2-acyl-3-indoleacetic acids and (*R*)-phenylglycinol.

For this purpose three synthetic steps were required: simultaneous reduction of the lactam carbonyl and reductive opening of the oxazolidine ring, removal of the benzylic substituent on the piperidine nitrogen, and debenzylation of the indole nitrogen. The best conditions for the first step were provided by alane, generated from $LiAlH_4$ and $AlCl_3$, at low temperature. Under these conditions, tetracyclic lactams **9a**–**c** were stereoselectively reduced, with retention of

Table 1. Reduction of tetracyclic lactams **9**.



Starting lactam	R^1	R^2	Reducing agent	Product (yield)
9a	Me	Me	$AlCl_3/LiAlH_4$[a]	**10a** (94%)
			$LiAlH_4$ [b]	**10a** (80%)
			$NaBH_4/I_2$[c]	**10a** (55%), 1-*epi*-**10a** (28%)[d]
			RedAl[e]	**10a** (16%), **11a** (58%), **12a** (18%)
9b	Bn	Me	$AlCl_3/LiAlH_4$[a]	**10b** (60%)
			$LiAlH_4$[b]	**10b** (41%)
			RedAl[e]	**10b** (<5%), **11b** (<5%), **12b** (10%)
			9-BBN[f]	**10b** (24%)
9c	Bn	*n*Pr	$AlCl_3/LiAlH_4$[a]	**10c** (70%)
			$LiAlH_4$[b]	**10c** (73%), 1-*epi*-**10c** (<5%)
			$NaBH_4/I_2$[c]	**10c** (76%), 1-*epi*-**10c** (9%)

[a] THF, –33 °C, 2 h; r.t., 2 h. [b] THF, r.t., 16 h (**9a**), 2 h (**9b**), 48 h (**9c**). [c] THF, reflux, 16 h. [d] Calculated by GC–MS analysis of a purified mixture. [e] CH_2Cl_2, 0 °C, 3 h (**9a**), 1 h (**9b**). [f] THF, reflux, 4 h.

configuration[26] (see Figure 1), to 1-substituted tetrahydro-β-carbolines **10a**–**c** in good yield (Table 1). Other reducing agents ($LiAlH_4$, $NaBH_4/I_2$, RedAl, or 9-BBN) gave less satisfactory results in terms of chemical yield and/or stereoselectivity (formation of minor amounts of the C–1 epimer). In some cases, partially reduced products (i.e., oxazolidines **11** and tricyclic lactams **12**) were isolated as byproducts.

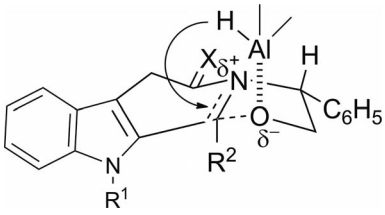
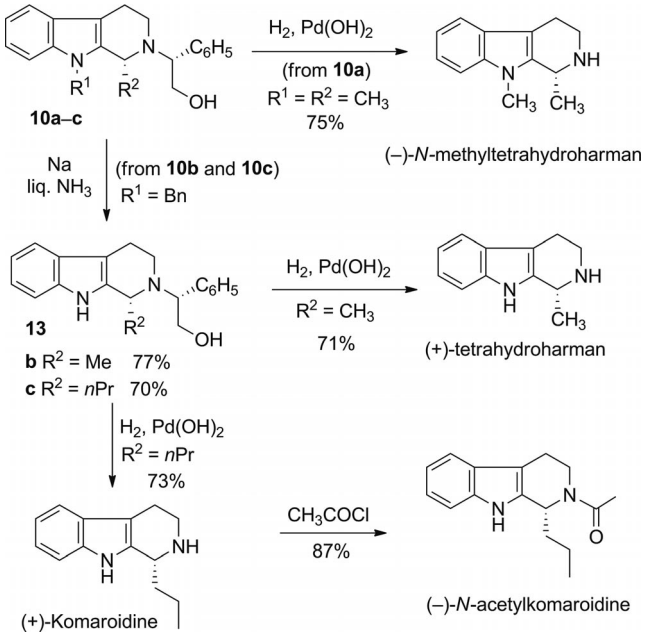


Figure 1. Retention of configuration in the reductive cleavage of the oxazolidine ring.

Finally, removal of the phenylethanol moiety from **10a** by debenzylation (hydrogen in the presence of $Pd(OH)_2$) led to (–)-*N*-methyltetrahydroharman[27] (Scheme 5). On the other hand, debenzylation of the indole nitrogen atoms of **10b** and **10c** with Na in liquid NH_3, followed by hydrogenolysis of the resulting *N*-unsubstituted indoles **13**, led to the alkaloids (+)-tetrahydroharman[28] and (+)-komaroidine.[29] The latter was converted into the alkaloid (–)-*N*-acetylkomaroidine[29a] by acetylation with acetyl chloride.



Scheme 5. Synthesis of 1-substituted tetrahydro-β-carboline alkaloids.

Conclusions

In contrast with many other cyclocondensation reactions between δ-oxoacid derivatives and (*R*)-phenylglycinol leading to oxazolopiperidone lactams,[10] cyclocondensation failed in the cases of the 2-formyl-3-indoleacetic acid derivatives **2** and the *N*-unsubstituted or *N*-EWG-protected 2-acyl-3-indoleacetic acid derivatives **4**. However, *N*-alkyl-substituted 2-acyl-3-indoleacetic acids **8** can be satisfactorily converted into the corresponding tetracyclic lactams **9**, thus providing easy access to enantiopure 1-substituted tetrahydro-β-carbolines. By starting from indoles bearing the easily removable *N*-benzyl group, the strategy developed here can be applied to the enantioselective synthesis of *N*-unsubstituted tetrahydro-β-carboline alkaloids.

Experimental Section

General: 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. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. High-resolution mass spectra (HMRS; LC/MSD TOF Agilent Technologies) were performed by the Centres Científics i Tecnològics de la Universitat de Barcelona. Microanalyses (Carlo–Erba 1106 analyzer) were performed by the Centre d'Investigació i Desenvolupament (CSIC), Barcelona. Only noteworthy IR absorptions (cm^{-1}; Perkin–Elmer 1600) are listed. NMR spectra were recorded either with a Varian Gemini 300 spectrometer (300 and 75.4, MHz for ^1H and ^{13}C, respectively) or with a Mercury 400 instrument (400 and 100.6 MHz for ^1H and ^{13}C, respectively).

Data for New 2-Acyl-3-indoleacetic Acid Derivatives 2, 4, and 8 and for Indoles 3 and 5–7

1-Benzyl-2-formyl-3-indoleacetic Acid (2b): ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.12 (s, 2 H, CH_2), 5.76 (s, 2 H, NCH_2), 7.04 (d, J = 7.2 Hz, 2 H, *o*-H), 7.18–7.23 (m, 4 H, 5-H, 6-H, *m*-H), 7.33–7.37 (m, 2 H, 7-H, *p*-H), 7.73 (d, J = 7.6 Hz, 1 H, 4-H), 10.1 (s, 1 H, CHO) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 29.8 (CH_2), 47.8 (NCH_2), 111.0 (C-7), 120.9 (C-3), 121.2 (C-6), 121.3 (C-4), 126.4 (C-*o*), 126.5 (C-3a), 127.4 (C-5), 127.7 (C-*p*), 128.6 (C-*m*), 131.2 (C-2), 137.5 (C-*i*), 139.2 (C-7a), 176.0 (CO_2H), 181.6 (CHO) ppm. HRMS calcd. for $C_{18}H_{15}NO_3$ $[M + H]^+$: 294.1124; found 294.1128.

Methyl 1-Benzyl-2-{*N*-[(*R*)-2-hydroxy-1-phenylethyl]iminomethyl}-3-indoleacetate (3a): ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.63 (dd, J = 11.2, 8.8 Hz, 1 H, CH_2OH), 3.66 (s, 3 H, CH_3), 3.71 (dd, J = 11.2, 4.4 Hz, 1 H, CH_2OH), 3.99 (d, J = 16.0 Hz, 1 H ppm. C$H_2CO_2CH_3$), 4.10 (d, J = 16.0 Hz, 1 H, C$H_2CO_2CH_3$), 4.32 (dd, J = 8.8, 4.4 Hz, 1 H, CHAr), 5.82 (d, J = 16.8 Hz, 1 H, NCH_2), 5.95 (d, J = 16.8 Hz, 1 H, NCH_2), 6.96 (d, J = 7.2 Hz, 2 H, ArH), 7.15–7.34 (m, 11 H, H-4, H-6, H-7, ArH), 7.69 (d, J = 7.6 Hz, 1 H, H-5), 8.59 (s, 1 H, CHN) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 30.3 (C$H_2CO_2CH_3$), 47.9 (NCH_2), 52.1 (CH_3), 68.0 (CH_2OH), 77.5 (CHAr), 110.0 (C-7), 114.2 (C-3), 119.5 (C-5), 120.4 (C-6), 124.8 (C-4), 125.8 (C-*o*), 127.0 (C-3a), 127.1 (C-*p*), 127.2 (C-*o*), 127.3 (C-*p*), 128.4 (C-*m*), 128.6 (C-*m*), 131.0 (C-2), 138.5 (C-*i*), 138.6 (C-7a), 140.4 (C-*i*), 152.7 (CHN), 171.8 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 1454, 1493, 1534, 1664, 1736, 2924 cm^{-1}. HRMS calcd. for $C_{27}H_{26}N_2O_3$ $[M + H]^+$: 427.2016; found 427.2010.

1-Benzyl-2-{*N*-[(*R*)-2-hydroxy-1-phenylethyl]iminomethyl}-3-methylindole (3b): ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.47 (s, 3 H, CH_3), 3.59 (dd, J = 11.2, 8.8 Hz, 1 H, CH_2OH), 3.66 (dd, J = 11.2, 4.0 Hz, 1 H, CH_2OH), 4.26 (dd, J = 8.8, 4.0 Hz, 1 H, CHAr), 5.88 (d, J = 16.4 Hz, 1 H, NCH_2), 6.06 (d, J = 16.4 Hz, 1 H, NCH_2), 6.94 (d, J = 8.4 Hz, 2 H, ArH), 7.08–7.33 (m, 11 H, 4-H, 6-H, 7-

H, ArH), 7.63 (d, J = 8.0 Hz, 1 H, 5-H), 8.65 (s, 1 H, CHN) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 8.7 (CH_3), 48.1 (NCH_2), 68.0 (CH_2OH), 77.5 (CHAr), 109.6 (C-7), 119.3 (C-3), 119.6 (C-5), 119.9 (C-6), 124.8 (C-4), 125.7 (C-*o*), 126.8 (C-*p*), 127.0 (C-*o*), 127.2 (C-*p*), 127.5 (C-3a), 128.3 (C-*m*), 128.4 (C-*m*), 129.8 (C-2), 139.0 (C-*i*), 139.4 (C-7a), 140.8 (C-*i*), 152.9 (CHN) ppm. HRMS calcd. for $C_{25}H_{24}N_2O$ [M + H]$^+$: 369.1961; found 369.1955.

2-Acetyl-1-(phenylsulfonyl)-3-indoleacetic Acid (4c): ^{1}H NMR (400 MHz, CD_3Cl_3, 25 °C): δ = 2.79 (s, 3 H, CH_3), 3.71 (s, 2 H, CH_2), 7.24–7.30 (m, 3 H, 6-H, ArH), 7.38–7.48 (m, 3 H, Ind-H, ArH), 7.51 (d, J = 7.6 Hz, 2 H, ArH), 8.07 (d, J = 8.4 Hz, 1 H, 7-H) ppm. ^{13}C NMR (400 MHz, CD_3Cl_3, 25 °C): δ = 31.3 (CH_2), 31.9 (CH_3), 116.5 (C-7), 121.1 (C-4), 125.6 (C-6), 126.9 (C-*o*), 128.5 (C-5), 128.8 (C-*m*), 130.3 (C-3a), 134.3 (C-*p*), 134.5 (C-2), 137.8 (C-*i*), 138.3 (C-7a), 172.1 (COOH), 197.1 (C=O) ppm. HRMS calcd. for $C_{18}H_{15}NO_5S$ [M + H]$^+$: 358.0744; found 358.0746.

Ethyl 2-Acetyl-1-(*tert*-butoxycarbonyl)-3-indoleacetate (4e): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.23 (t, J = 6.8 Hz, 3 H, CH_3CH$_2$), 1.65 [s, 9 H, C(CH$_3$)$_3$], 2.51 (s, 3 H, COCH$_3$), 3.79 (s, 2 H, CH$_2$), 4.12 (q, J = 6.8 Hz, 2 H, CO$_2$CH_2CH$_3$), 7.29 (m, 1 H, 5-H), 7.41 (ddd, J = 8.5, 6.8, 1.2 Hz, 1 H, 6-H), 7.58 (d, J = 8.5 Hz, 1 H, 7-H), 8.09 (d, J = 8.5 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 14.1 (*C*H$_3$CH$_2$), 27.9 (CO*C*H$_3$), 29.7 (CH$_2$), 31.2 [C(*C*H$_3$)$_3$], 61.1 (CO$_2$*C*H$_2$CH$_3$), 85.4 [*C*(CH$_3$)$_3$], 115.4 (C-7), 116.6 (C-3), 120.3 (C-6), 123.5 (C-4), 126.8 (C-5), 128.3 (C-3a), 136.0 (C-2), 136.4 (C-7a), 150.0 (NCO), 170.2 (*C*O$_2$CH$_2$CH$_3$), 194.9 (*C*OCH$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 1453, 1565, 1693, 1735, 2933, 2980 cm^{-1}. HRMS calcd. for $C_{19}H_{23}NO_5$ [M + H]$^+$: 346.1648; found 346.1648.

Methyl 2-Acetyl-1-tosyl-3-indoleacetate (4f): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.25 (s, 3 H, COCH$_3$), 2.72 (s, 3 H, CH$_3$Ar), 3.61 (s, 3 H, CO$_2$CH$_3$), 3.72 (s, 2 H, CH$_2$), 7.05 (d, J = 8.4 Hz, 1 H, 7-H), 7.22 (t, J = 8.0 Hz, 1 H, 5-H), 7.38 (d, J = 7.6 Hz, 1 H, 6-H), 7.46 (s, 2 H, ArH), 7.48 (s, 2 H, ArH), 8.02 (d, J = 8.4 Hz, 1 H, 4-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 21.4 (CO*C*H$_3$), 29.6 (CH$_2$), 32.1 (CH$_3$Ar), 52.1 (CO$_2$*C*H$_3$), 115.9 (C-7), 120.6 (C-6), 121.9 (C-3), 124.9 (C-4), 127.0 (C-*o*), 127.3 (C-5), 129.3 (C-*m*), 130.4 (C-2), 132.3 (C-3a), 136.9 (C-*i*), 138.0 (C-*i*), 145.0 (C-7a), 169.8 (*C*O$_2$CH$_3$), 195.8 (*C*OCH$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 1364, 1595, 1684, 1743 cm^{-1}. HRMS calcd. for $C_{20}H_{19}NO_5S$ [M + H]$^+$: 386.1056; found: 386.1051.

Methyl 2-Acetyl-1-(methoxycarbonyl)-3-indoleacetate (4g): ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.48 (s, 3 H, COCH$_3$), 3.68 (s, 3 H, CO$_2$CH$_3$), 3.83 (s, 2 H, CH$_2$), 4.04 (s, 3 H, NCO$_2$CH$_3$), 7.31 (t, J = 7.2 Hz, 1 H, 5-H), 7.44 (t, J = 7.2 Hz, 1 H, 6-H), 7.57 (d, J = 7.5 Hz, 1 H, 7-H), 8.07 (d, J = 7.5 Hz, 1 H, 4-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 29.5 (CH_2), 30.6 (CO*C*H$_3$), 52.2 (NCO$_2$*C*H$_3$), 54.2 (CO$_2$*C*H$_3$), 115.4 (C-7), 117.8 (C-3), 120.3 (C-4), 123.8 (C-5), 127.1 (C-6), 128.8 (C-3a), 135.6 (C-2), 136.4 (C-7a), 151.4 (NCO$_2$), 170.5 (*C*O$_2$CH$_3$), 194.4 (*C*OCH$_3$) ppm.

2-Butanoyl-3-methylindole (5b): ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.98 (t, J = 7.5 Hz, 3 H, CH$_2$CH_3), 1.75 (m, 2 H, CH_2CH$_3$), 2.57 (s, 3 H, CH$_3$), 2.85 (t, J = 7.2 Hz, 2 H, CH_2CH$_2$CH$_3$), 7.05 (ddd, J = 8.0, 6.0, 1.2 Hz, 1 H, H-5), 7.25–7.31 (m, 2 H, H-6, H-7), 7.61 (d, J = 8.0 Hz, 1 H, H-4), 9.00 (s, 1 H, NH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 11.3 (CH$_2$*C*H$_3$), 14.1 (CH$_3$), 17.7 (*C*H$_2$CH$_3$), 43.0 (*C*H$_2$CH$_2$CH$_3$), 112.0 (C-7), 118.0 (C-3), 120.0 (C-4), 121.2 (C-6), 126.3 (C-5), 129.0 (C-3a), 132.6 (C-2), 136.1 (C-7a), 193.5 (CO) ppm.

2-Acetyl-*N*-[(*R*)-2-hydroxy-1-phenylethyl]-3-indoleacetamide (6a): ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.35 (s, 3 H, COCH$_3$), 3.72 (dd, J = 11.5, 6.6 Hz, 1 H, CH_2OH), 3.80 (dd, J = 11.5, 4.2 Hz, 1 H, CH_2OH), 4.06 (s, 2 H, CH_2CONH), 5.06 (m, 1 H, CHAr), 7.10–7.29 (m, 8 H, 5-H, 6-H, 7-H, ArH), 7.69 (d, J = 8.4 Hz, 1 H, 4-H), 9.40 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 27.9 (CH_3), 33.6 (CH_2), 55.9 (CHAr), 66.4 (CH_2OH), 112.4 (C-7), 120.8 (C-4), 121.0 (C-6), 121.1 (C-5), 122.0 (C-3), 126.7 (C-*o*), 127.8 (C-*m*), 128.7 (C-*p*), 132.0 (C-3a), 132.3 (C-2), 136.1 (C-*i*), 138.7 (C-7a), 171.3 (CONH), 191.3 (*C*OCH$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 1531, 1649, 2933, 3013, 3308 cm^{-1}. EM (IQ$^+$): *m*/*z* (%): 336 (1), 305 (32), 200 (37), 172 (100), 158 (23), 144 (12), 130 (61), 104 (42), 77 (37), 51 (7).

3-Methyl-2-[(*R*)-2-methyl-4-phenyl-1,3-oxazolidin-2-yl]indole (7a): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.81 (s, 3 H, OCCH$_3$), 2.39 (s, 3 H, CH$_3$), 4.28 (dd, J = 8.5, 6.8 Hz, 1 H, CH$_2$), 4.75 (t, J = 8.5 Hz, 1 H, CH$_2$), 5.28 (t, J = 7.2 Hz, 1 H, CHAr), 7.30–7.44 (m, 7 H, 5-H, 6-H, ArH), 7.54 (d, J = 8.0 Hz, 1 H, 7-H), 7.93 (d, J = 7.6 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 8.4 (CH$_3$), 22.5 (OC*C*H$_3$), 59.8 (CHAr), 74.3 (CH$_2$), 95.3 (O*C*CH$_3$), 110.3 (C-3), 112.9 (C-7), 119.8 (C-6), 122.9 (C-4), 124.7 (C-5), 125.7 (C-*m*), 127.6 (C-*p*), 128.7 (C-*o*), 130.1 (C-3a), 134.9 (C-*i*), 139.8 (C-2), 155.4 (C-7a) ppm. EM (IQ$^+$): *m*/*z* (%):319 (100) [M + 27]$^+$, 320 (28), 318 (9).

1-(Benzenesulfonyl)-3-methyl-2-[(*R*)-2-methyl-4-phenyl-1,3-oxazolidin-2-yl]indole (7c): ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.14 (s, 3 H, CH$_3$), 2.39 (s, 3 H, CH$_3$), 3.99 (m, 2 H, CH$_2$), 5.04 (m, 1 H, *CH*Ar), 7.20–7.56 (m, 11 H, ArH), 7.80 (d, J = 7.2 Hz, 2 H, ArH), 8.02 (d, J = 8.1 Hz, 1 H, 7-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 9.16 (CH$_3$), 21.8 (CH$_3$), 67.3 (CHAr), 68.9 (CH$_2$), 115.4 (C-7), 119.8 (C-6), 124.3 (C-4), 127.1 (C-*o*), 127.6 (C-*m*), 128.5 (C-5), 128.7 (C-*p*), 132.0 (C-3a), 133.8 (C-2) ppm.

2-Acetyl-1-benzyl-3-indoleacetic Acid (8b): ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.54 (s, 3 H, COCH$_3$), 4.07 (s, 2 H, CH$_2$), 5.63 (s, 2 H, NCH$_2$), 6.96 (d, J = 7.5 Hz, 2 H, H-*o*), 7.14–7.34 (m, 6 H, H-5, H-6, H-7, H-*m*, H-*p*), 7.69 (d, J = 7.8 Hz, 1 H, H-4), 12.23 (COOH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 30.7 (COCH$_3$), 31.7 (CH$_2$), 48.5 (NCH$_2$), 110.8 (C-7), 115.1 (C-3), 120.7 (C-4), 121.1 (C-6), 126.0 (C-*o*), 126.4 (C-5), 126.8 (C-3a), 127.1 (C-*p*), 128.5 (C-*m*), 134.3 (C-2), 137.9 (C-*i*), 138.6 (C-7a), 176.0 (CO$_2$H), 192.7 (*C*OCH$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 1611, 1732, 3440 cm^{-1}. HRMS calcd. for $C_{19}H_{17}NO_3$ [M + Na]$^+$: 330.1101; found 330.1093.

1-Benzyl-2-butanoyl-3-indoleacetic Acid (8c): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.83 (t, J = 7.6 Hz, 3 H, CH_3CH$_2$), 1.64 (sext, J = 7.6 Hz, 2 H, CH$_3$CH_2), 2.83 (t, J = 7.6 Hz, 2 H, CH_2CH$_2$CH$_3$), 4.07 (s, 2 H, CH$_2$), 5.62 (s, 2 H, NCH$_2$), 6.97 (d, J = 6.8 Hz, 2 H, *o*-H), 7.18–7.34 (m, 6 H, 5-H, 6-H, 7-H, *m*-H, *p*-H), 7.73 (d, J = 8.0 Hz, 1 H, 4-H) ppm. ^{13}CNMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 13.6 (*C*H$_3$CH$_2$), 17.9 (CH$_3$*C*H$_2$), 32.0 (CH$_2$), 44.5 (*C*H$_2$CH$_2$CH$_3$), 48.7 (NCH$_2$), 110.8 (C-7), 114.4 (C-3), 120.7 (C-4), 121.2 (C-6), 126.0 (C-*o*), 126.3 (C-5), 126.8 (C-3a), 127.3 (C-*p*), 128.6 (C-*m*), 135.2 (C-2), 137.7 (C-*i*), 138.7 (C-7a), 175.2 (CO$_2$H), 196.7 (*C*OCH$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 1652, 3436 cm^{-1}. HRMS calcd. for $C_{21}H_{21}NO_3$ [M + Na]$^+$: 358.1417; found 358.1414.

(3*R*,11b*S*)-11,11b-Dimethyl-5-oxo-3-phenyl-3,5,6,11b-tetrahydro-2*H*-oxazolo[3′,2′:1,2]pyrido[3,4-*b*]indole (9a): (*R*)-Phenylglycinol (355 mg, 2.6 mmol) was added to a solution of keto acid **8a** (500 mg, 2.2 mmol) in benzene (35 mL). The mixture was heated at reflux for 18 h with azeotropic elimination of water through the use of a Dean–Stark apparatus. The resulting suspension was cooled and concentrated. Flash chromatography (hexane/EtOAc 8:2) afforded lactam **9a** (475 mg, 65%) as a white solid; m.p. 166–168 °C (hexane/EtOAc). $[\alpha]_D^{22}$ = –62.9 (c = 1.0, $CHCl_3$). ^{1}H NMR

(400 MHz, $CDCl_3$, 25 °C): δ = 1.70 (s, 3 H, CH_3), 3.82 (s, 2 H, 6-H), 3.88 (s, 3 H, NCH_3), 4.19 (dd, J = 8.4, 6.8 Hz, 1 H, 2-H), 4.65 (t, J = 8.4 Hz, 1 H, 2-H), 5.49 (t, J = 8.0 Hz, 1 H, 3-H), 7.16 (t, J = 8.0 Hz, 1 H, 9-H), 7.26–7.40 (m, 7 H, 8-H, 10-H, ArH), 7.52 (d, J = 8.0 Hz, 1 H, 7-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 26.8 (CH_3), 30.4 (C-6), 30.8 (NCH_3), 58.5 (C-3), 70.7 (C-2), 91.9 (C-11b), 104.6 (C-6a), 109.5 (C-10), 118.9 (C-7), 119.8 (C-9), 122.7 (C-8), 125.6 (C-*m*), 127.3 (C-*p*), 128.7 (C-*o*), 130.5 (C-6b), 133.5 (C-11a), 138.4 (C-*i*), 139.7 (C-10a), 168.3 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 1382, 1470, 1661, 2927 cm^{-1}. HRMS calcd. for $C_{21}H_{20}N_2O_2$ [M + H]$^+$: 333.1597; found 333.1592. $C_{21}H_{20}N_2O_2$ (332.15): calcd. C 75.88, H 6.06, N 8.43; found C 75.96, H 6.13, N 8.37.

(3*R*,11b*S*)-11-Benzyl-11b-methyl-5-oxo-3-phenyl-3,5,6,11b-tetrahydro-2*H*-oxazolo[3′,2′:1,2]pyrido[3,4-*b*]indole (9b): Lactam **9b** (121 mg, 60%) was obtained as in the above preparation of **9a**, from keto acid **8b** (150 mg, 0.5 mmol) and (*R*)-phenylglycinol (87 mg, 0.6 mmol) in benzene (8 mL), after flash chromatography (hexane/EtOAc 9:1 to 8:2). $[\alpha]_D^{22}$ = –96.6 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.60 (s, 3 H, CH_3), 3.85 (d, J = 20.1 Hz, 1 H, 6-H), 3.90 (d, J = 20.1 Hz, 1 H, 6-H), 4.14 (dd, J = 9.0, 6.6 Hz, 1 H, 2-H), 4.53 (dd, J = 9.0, 8.4 Hz, 1 H, 2-H), 5.50 (t, J = 7.5 Hz, 1 H, 3-H), 5.55 (d, J = 16.8 Hz, 1 H, NCH_2), 5.65 (d, J = 16.8 Hz, 1 H, NCH_2), 7.05 (d, J = 7.2 Hz, 2 H, *m*-H), 7.14–7.38 (m, 11 H, 8-H, 9-H, 10-H, ArH), 7.56 (d, J = 6.4 Hz, 1 H, 7-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 27.5 (CH_3), 30.5 (C-6), 48.0 (NCH_2), 58.4 (C-3), 70.7 (C-2), 92.1 (C-11b), 105.3 (C-6a), 110.6 (C-10), 118.9 (C-7), 120.1 (C-8), 123.0 (C-9), 125.1 (C-6b), 125.6 (C-*o*), 126.1 (C-*m*), 127.1 (C-*p*), 127.3 (C-*p*), 128.5 (C-*o*), 128.6 (C-*m*), 133.9 (C-*i*), 137.8 (C-10a), 138.0 (C-*i*), 139.6 (C-11a), 168.3 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 1382, 1454, 1495, 2924 cm^{-1}. HRMS calcd. for $C_{27}H_{24}N_2O_2$ [M + H]$^+$ 409.1911; found 409.1905.

(3*R*,11b*S*)-11-Benzyl-5-oxo-3-phenyl-11b-propyl-3,5,6,11b-tetrahydro-2*H*-oxazolo[3′,2′:1,2]pyrido[3,4-*b*]indole (9c): Lactam **9c** (156 mg, 66%) was obtained as a yellow oil as in the preparation of **9a**, from keto acid **8c** (180 mg, 0.54 mmol) and (*R*)-phenylglycinol (93 mg, 0.64 mmol) in benzene (10 mL), after flash chromatography (hexane/EtOAc 95:5). $[\alpha]_D^{22}$ = –96.4 (c = 1.01, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.55 (t, J = 7.2 Hz, 3 H, CH_3), 0.84–0.91 (m, 1 H, CH_2CH$_3$), 1.25–1.37 (m, 1 H, CH_2CH$_3$), 1.60 (td, J = 13.4, 4.8 Hz, 1 H, CH_2CH$_2$CH$_3$), 1.80 (td, J = 13.4, 4.0 Hz, 1 H, CH_2CH$_2$CH$_3$), 3.87 (s, 2 H, 6-H), 4.19 (dd, J = 8.8, 7.2 Hz, 1 H, 2-H), 4.59 (t, J = 8.8 Hz, 1 H, 2-H), 5.51 (d, J = 17.2 Hz, 1 H, NCH_2), 5.57 (t, J = 7.6 Hz, 1 H, 3-H), 5.68 (d, J = 17.2 Hz, 1 H, NCH_2), 7.03 (d, J = 7.6 Hz, 2 H, *m*-H), 7.15–7.40 (m, 11 H, 8-H, 9-H, 10-H, ArH), 7.54 (m, 1 H, 7-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 13.1 (CH_3), 17.2 (CH_2CH$_3$), 30.8 (C-6), 40.9 (CH_2CH$_2$CH$_3$), 48.0 ($CH_2C_6H_5$), 58.4 (C-3), 70.5 (C-2), 94.9 (C-11b), 106.9 (C-6a), 110.6 (C-10), 119.0 (C-7), 120.1 (C-9), 123.1 (C-8), 124.9 (C-6b), 125.3 (C-*m*), 125.8 (C-*o*), 127.1 (C-*p*), 127.3 (C-*p*), 128.5 (C-*o*), 128.6 (C-*m*), 131.5 (C-*i*), 137.9 (C-*i*), 138.2 (C-11a), 140.1 (C-10a), 169.1 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 1453, 1663, 2927, 2960 cm^{-1}. HRMS calcd. for $C_{29}H_{28}N_2O_2$ [M + H]$^+$: 437.2224; found 437.2213.

(*R*)-2-[(*R*)-2-Hydroxy-1-phenylethyl]-1,9-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]indole (10a): $LiAlH_4$ (151 mg, 4 mmol) was slowly added at 0 °C to a suspension of $AlCl_3$ (173 mg, 1.3 mmol) in THF (12 mL) and the mixture was stirred for 3.5 h. After the system had been further cooled to –33 °C, a solution of lactam **9a** (202 mg, 0.6 mmol) in THF (17 mL) was slowly added. The stirring was continued at –33 °C for 2 h and at room temperature for 2 h. After having been cooled to 0 °C, the reaction mixture was quenched with MeOH (2 mL) and water (2 mL). The aqueous layer was extracted with EtOAc, and the combined organic extracts were dried and concentrated. Flash chromatography (hexane to hexane/EtOAc 7:3) of the residue afforded compound **10a** as a pale yellow oil (181.5 mg, 94%). $[\alpha]_D^{22}$ = –36.8 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.50 (d, J = 6.8 Hz, 3 H, CH_3), 2.51 (dt, J = 15.2, 4.0 Hz, 1 H, 4-H), 2.70 (dddd, J = 15.2, 5.2, 4.8, 0.8 Hz, 1 H, 4-H), 2.83 (ddd, J = 13.2, 4.8, 4.0 Hz, 1 H, 3-H), 3.18 (ddd, J = 13.2, 9.2, 5.2 Hz, 1 H, 3-H), 3.60 (s, 3 H, NCH_3), 3.84 (dd, J = 8.0, 2.4 Hz, 1 H, CH_2OH), 3.89 (dd, J = 8.0, 6.8 Hz, 1 H, CH_2OH), 3.91 (q, J = 6.8 Hz, 1 H, CHAr), 4.30 (q, J = 6.8 Hz, 1 H, 1-H), 7.08 (ddd, J = 8.2, 6.8, 1.0 Hz, 1 H, 6-H), 7.18 (ddd, J = 8.2, 7.0, 1.2 Hz, 1 H, 7-H), 7.25–7.38 (m, 6 H, 8-H, ArH), 7.45 (dt, J = 7.2, 1.0 Hz, 1 H, 5-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 19.5 (C-4), 19.9 (CH_3), 29.6 (NCH_3), 40.4 (C-3), 48.4 (C-1), 63.4 (CH_2OH), 64.6 (CHAr), 106.8 (C-4a), 108.6 (C-8), 117.9 (C-5), 118.8 (C-6), 120.9 (C-7), 126.6 (C-4b), 127.6 (C-*p*), 128.3 (C-*m*), 128.5 (C-*o*), 137.1 (C-9a), 137.5 (C-*i*), 139.4 (C-8a) ppm. IR (KBr): $\tilde{\nu}$ = 1469, 2930, 3408 cm^{-1}. HRMS calcd. for $C_{21}H_{24}N_2O$ [M + H]$^+$: 321.1961; found 321.1954.

(*R*)-9-Benzyl-2-[(*R*)-2-hydroxy-1-phenylethyl]-1-methyl-1,2,3,4-tetrahydropyrido[3,4-*b*]indole (10b): Tetrahydro-β-carboline **10b** (95 mg, 60%) was obtained in the same way as in the above reduction of **9a**, from a solution of lactam **9b** (165 mg, 0.4 mmol) in THF (11 mL), $LiAlH_4$ (100 mg, 2.6 mmol), and $AlCl_3$ (117 mg, 0.88 mmol) in THF (8 mL), after flash chromatography (hexane/EtOAc 7:3). $[\alpha]_D^{22}$ = –80.1 (c = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.42 (d, J = 6.8 Hz, 3 H, CH_3), 2.51 (ddd, J = 16.0, 4.4, 2.8 Hz, 1 H, 4-H), 2.70 (ddd, J = 16.0, 10.4, 6.0 Hz, 1 H, 4-H), 2.84 (m, 1 H, 3-H), 3.19 (ddd, J = 14.0, 10.4, 5.2 Hz, 1 H, 3-H), 3.63 (m, 1 H, CH_2OH), 3.76 (t, J = 4.8 Hz, 1 H, CH_2OH), 4.15 (m, 1 H, 1-H), 5.14 (d, J = 16.8 Hz, 1 H, NCH_2), 5.34 (d, J = 16.8 Hz, 1 H, NCH_2), 6.93 (d, J = 7.6 Hz, 1 H, 5-H), 7.06–7.29 (m, 12 H, 6-H, 8-H, ArH), 7.49 (m, 1 H, 7-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 19.2 (C-4), 20.3 (CH_3), 40.0 (C-3), 46.5 ($CH_2C_6H_5$), 48.4 (C-1), 63.3 (CH_2OH), 64.7 (CHAr), 107.6 (C-4a), 109.4 (C-8), 118.1 (C-5), 119.3 (C-6), 121.3 (C-7), 125.9 (C-*o*), 126.9 (C-4b), 127.3 (C-*p*), 127.6 (C-*p*), 128.3 (C-*m*), 128.4 (C-*m*), 128.7 (C-*o*), 137.1 (C-8a), 137.4 (C-*i*), 137.6 (C-9a), 139.3 (C-*i*) ppm. EM (IQ$^+$): *m*/*z* (%): 397 (9), 277 (12), 121 (13), 105 (33), 91 (20), 57 (100).

(*R*)-9-Benzyl-2-[(*R*)-2-hydroxy-1-phenylethyl]-1-propyl-1,2,3,4-tetrahydropyrido[3,4-*b*]indole (10c): Tetrahydro-β-carboline **10c** (68 mg, 70%) was obtained in the same way as in the preparation of **10a**, from a solution of lactam **9c** (100 mg, 0.23 mmol) in THF (5 mL), $LiAlH_4$ (57 mg, 1.5 mmol), and $AlCl_3$ (67 mg, 0.5 mmol) in THF (6.5 mL), after flash chromatography (hexane/EtOAc 95:5). $[\alpha]_D^{22}$ = –82.5 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.91 (t, J = 7.2 Hz, 3 H, CH_3), 1.50–1.63 (m, 4 H, CH_2CH_2CH$_3$), 2.38 (ddd, J = 15.0, 4.0, 2.0 Hz, 1 H, 4-H), 2.66 (ddd, J = 15.0, 10.8, 5.6 Hz, 1 H, 4-H), 2.78 (dd, J = 14.0, 4.0 Hz, 1 H, 3-H), 3.18 (ddd, J = 14.0, 10.8, 5.2 Hz, 1 H, 3-H), 3.49 (dd, J = 12.4, 4.8 Hz, 2 H, CH_2OH), 3.68 (t, J = 4.8 Hz, 1 H, 1-H), 4.04 (d, J = 9.2 Hz, 1 H, CHAr), 5.17 (d, J = 17.0 Hz, 1 H, NCH_2), 5.40 (d, J = 17.0 Hz, 1 H, NCH_2), 6.98 (d, J = 6.8 Hz, 2 H, ArH), 7.10–7.14 (m, 2 H, 6-H, 7-H), 7.23–7.30 (m, 9 H, 8-H, ArH), 7.48 (d, J = 7.2 Hz, 1 H, 5-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 13.9 (CH_3), 17.7 (C-4), 19.7 (CH_2CH$_3$), 36.9 (CH_2CH$_2$CH$_3$), 39.6 (C-3), 46.7 (NCH_2), 52.5 (C-1), 63.8 (CH_2OH), 64.6 (CHAr), 107.9 (C-4a), 109.4 (C-8), 118.1 (C-5), 119.1 (C-6), 121.3 (C-7), 126.0 (C-*o*), 127.5 (C-*p*), 128.3 (C-*m*), 128.5 (C-4b), 128.8 (C-*m*), 136.6 (C-*i*), 137.1 (C-8a), 137.9 (C-*i*), 140.5 (C-9a) ppm. IR (KBr): $\tilde{\nu}$ = 1453,

1647, 2955 cm^{-1}. HRMS calcd. for $C_{29}H_{32}N_2O$ $[M + H]^+$: 425.2587; found 425.2583.

Data for 1-*epi* Derivatives and Partially Reduced Compounds 11 and 12

(*S*)-2-[(*R*)-2-Hydroxy-1-phenylethyl]-1,9-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]indole (1-*epi*-10a): ^1H NMR (300 MHz, $CDCl_3$, 25 °C, from a **10a**/*epi*-**10a** mixture): δ = 1.36 (d, J = 6.9 Hz, 3 H, CH_3), 2.40–2.48 (m, 2 H, 4-H), 2.90–3.02 (m, 1 H, 3-H), 3.31 (m, 1 H, 3-H), 3.40 (s, 3 H, NCH_3), 3.79 (dd, J = 6.0, 4.5 Hz, 1 H, CH_2OH), 4.30 (m, 1 H, 1-H), 7.05–7.48 (m, 9 H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 18.4 (C-4), 19.2 (CH_3), 29.1 (NCH_3), 39.7 (C-3), 49.1 (C-1), 63.9 (CH_2OH), 65.3 (CHAr), 106.2 (C-4a), 108.6 (C-8), 117.9 (C-5), 118.7 (C-6), 120.8 (C-7), 126.5 (C-4b), 127.5 (C-*p*), 128.2 (C-*m*), 128.3 (C-*o*), 137.1 (C-9a), 137.5 (C-*i*), 141.2 (C-8a) ppm.

(*S*)-9-Benzyl-2-[(*R*)-2-hydroxy-1-phenylethyl]-1-propyl-1,2,3,4-tetrahydropyrido[3,4-*b*]indole (1-*epi*-10c): $[\alpha]_D^{22}$ = –75.8 (c = 0.9, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.68 (t, J = 7.5 Hz, 3 H, CH_3), 1.15–1.30 (m, 2 H, CH_2CH_2CH$_3$), 1.54–1.61 (m, 1 H, CH$_2$CH_2CH$_3$), 1.73–1.79 (m, 1 H, CH_2CH$_2$CH$_3$), 2.64 (dm, J = 16.0 Hz, 1 H, H-4), 3.07 (ddd, J = 16.0, 10.4, 7.2 Hz, 1 H, H-4), 3.41 (m, 2 H, H-3), 3.47 (t, J = 9.2 Hz, 1 H, H-1), 3.74 (dd, J = 6.0, 3.2 Hz, 1 H, CHAr), 3.84 (dd, J = 11.0, 3.2 Hz, 1 H, CH_2OH), 4.03 (dd, J = 11.0, 6.0 Hz, 1 H, CH_2OH), 4.91 (d, J = 16.8 Hz, 1 H, NCH_2), 4.96 (d, J = 16.8 Hz, 1 H, NCH_2), 6.79 (m, 2 H, ArH), 7.10–7.20 (m, 11 H, ArH, H-Ind), 7.53 (m, 1 H, H-8) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 13.9 (CH_3), 17.4 (C-4), 19.8 (*C*H$_2$CH$_3$), 36.9 (*C*H$_2$CH$_2$CH$_3$), 39.6 (C-3), 46.4 (NCH_2), 53.2 (C-1), 64.4 (CH_2OH), 64.7 (CHAr), 107.0 (C-4a), 109.6 (C-8), 118.0 (C-5), 119.2 (C-6), 121.3 (C-7), 126.1 (C-*o*), 127.2 (C-*p*), 127.6 (C-4b), 128.8 (C-*p*), 128.6 (C-*m*), 128.7 (C-*m*), 136.9 (C-*i*), 137.0 (C-8a), 137.6 (C-*i*), 140.9 (C-9a) ppm. EM (IQ^+): m/z %: 424 (1), 393 (10), 381 (100), 288 (16), 261 (39), 169 (20), 103 (16), 91 (95).

(3*R*,11b*S*)-11,11b-Dimethyl-3-phenyl-3,5,6,11b-tetrahydro-2*H*-oxazolo[3′,2′:1,2]pyrido[3,4-*b*]indole (11a): $[\alpha]_D^{22}$ = –96.6 (c = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.78 (s, 3 H, CH_3), 2.44 (dd, J = 16.0, 4.8 Hz, 1 H, 6-H), 2.91 (ddd, J = 16.0, 12.0, 5.6 Hz, 1 H, 6-H), 3.09 (dd, J = 14.4, 5.6 Hz, 1 H, 5-H), 3.17 (ddd, J = 14.4, 12.0, 5.2 Hz, 1 H, 5-H), 3.70 (t, J = 7.6 Hz, 1 H, 2-H), 3.80 (s, 3 H, NCH_3), 3.97 (t, J = 7.6 Hz, 1 H, 2-H), 4.17 (t, J = 7.6 Hz, 1 H, 3-H), 7.04 (ddd, J = 14.4, 7.2, 0.8 Hz, 1 H, 9-H), 7.16 (ddd, J = 14.4, 7.5, 1.2 Hz, 1 H, 8-H), 7.23–7.28 (m, 5 H, ArH), 7.43 (d, J = 7.5 Hz, 1 H, 7-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 16.2 (C-6), 26.7 (CH_3), 30.8 (NCH_3), 40.9 (C-5), 61.3 (C-3), 72.8 (C-2), 92.1 (C-11b), 107.2 (C-6a), 109.0 (C-10), 118.7 (C-7), 119.0 (C-9), 121.9 (C-8), 126.0 (C-6b), 127.7 (C-*p*), 127.5 (C-*o*), 127.8 (C-*p*), 136.0 (C-*i*), 137.4 (C-11a), 140.1 (C-10a) ppm. IR (KBr): $\tilde{\nu}$ = 1382, 1470, 2927, 2934 cm^{-1}. HRMS calcd. for $C_{21}H_{22}N_2O$ $[M + H]^+$: 319.1810; found 319.1817.

(*R*)-2-[(*R*)-2-Hydroxy-1-phenylethyl]-1,9-dimethyl-3-oxo-1,2,3,4-tetrahydropyrido[3,4-*b*]indole (12a): $[\alpha]_D^{22}$ = +70.8 (c = 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.38 (d, J = 6.4 Hz, 3 H, CH_3), 3.51 (s, 3 H, NCH_3), 3.70 (d, J = 19.2 Hz, 1 H, 4-H), 3.82 (d, J = 19.2 Hz, 1 H, 4-H), 4.11 (dd, J = 12.0, 3.5 Hz, 1 H, CH_2OH), 4.37 (dd, J = 12.0, 7.2 Hz, 1 H, CH_2OH), 4.83 (dd, J = 7.2, 3.5 Hz, 1 H, CHAr), 7.07–7.09 (m, 1 H, 6-H), 7.15–7.38 (m, 6 H, 7-H, 8-H, ArH), 7.43 (d, J = 8.0 Hz, 1 H, 5-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 22.3 (CH_3), 29.6 (C-4), 30.8 (NCH_3), 53.0 (C-1), 64.3 (*C*HCH$_2$), 66.1 (CH$_2$OH), 103.9 (C-4a), 109.2 (C-8), 118.3 (C-5), 119.7 (C-6), 122.0 (C-7), 125.0 (C-4b), 127.3 (C-*p*), 128.2 (C-*m*), 128.7 (C-*o*), 134.0 (C-9a), 136.7 (C-8a), 137.9 (C-*i*), 171.6 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 1469, 1621, 2929, 3382 cm^{-1}. HRMS calcd. for $C_{21}H_{22}N_2O_2$ $[M + H]^+$: 335.1759; found 335.1749.

(*R*)-9-Benzyl-2-[(*R*)-2-hydroxy-1-phenylethyl]-1-methyl-3-oxo-1,2,3,4-tetrahydropyrido[3,4-*b*]indole (12b): $[\alpha]_D^{22}$ = +18.25 (c = 1.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.29 (d, J = 6.4 Hz, 3 H, CH_3), 3.68–3.79 (m, 2 H, 4-H, OH), 3.92 (m, 1 H, 4-H), 4.03 (dt, J = 12.0, 4.3 Hz, 1 H, CH_2OH), 4.26 (dt, J = 12.0, 7.4 Hz, 1 H, CH_2OH), 4.46 (q, J = 6.4 Hz, 1 H, 1-H), 4.88 (dd, J = 7.4, 4.3 Hz, 1 H, CHAr), 5.09 (d, J = 16.8 Hz, 1 H, NCH_2), 5.29 (d, J = 16.8 Hz, 1 H, NCH_2), 6.85–6.88 (m, 1 H, 5-H), 7.14–7.28 (m, 12 H, 6-H, 7-H, ArH), 7.53–7.56 (m, 1 H, 8-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 22.4 (CH_3), 31.1 (C-4), 46.9 (*C*H$_2$C$_6$H$_5$), 52.6 (C-1), 64.0 (CH$_2$OH), 65.5 (*C*HCH$_2$), 105.2 (C-4a), 109.8 (C-8), 118.4 (C-5), 120.0 (C-6), 122.3 (C-7), 125.4 (C-4b), 125.8 (C-*o*), 127.5 (C-*o*), 127.5 (C-*p*), 127.8 (C-*p*), 128.7 (C-*m*), 128.9 (C-*m*), 134.5 (C-8a), 136.6 (C-*i*), 136.9 (C-9a), 139.3 (C-*i*), 171.4 (CO) ppm. HRMS calcd. for $C_{27}H_{26}N_2O_2$ $[M + H]^+$: 411.2067; found 411.2071.

(*R*)-2-[(*R*)-2-Hydroxy-1-phenylethyl]-1-methyl-1,2,3,4-tetrahydropyrido[3,4-*b*]indole (13b): NH_3 (30 mL) was condensed at –78 °C into a three-necked round-bottomed condenser fitted with a cold finger charged with dry ice/acetone. The temperature was raised to –33 °C, and a solution of amine **10b** (90 mg, 0.23 mmol) in THF (2 mL) was added. Sodium metal was then added in small portions until the blue color persisted. The mixture was stirred at –33 °C for 1 min. The reaction was quenched by addition of solid NH_4Cl until the blue color disappeared. The mixture was stirred at room temp. for 4 h. The resulting residue was digested at room temp. with CH_2Cl_2, poured into water, and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated. Flash chromatography (hexane/EtOAc 8:2) of the residue afforded **13b** (54 mg, 77%) as a white solid. $[\alpha]_D^{22}$ = +21.2 (c = 0.99, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.59 (d, J = 6.6 Hz, 3 H, CH_3), 2.40 (ddd, J = 12.3, 8.4, 5.1 Hz, 1 H, 3-H), 2.67 (m, 2 H, 4-H), 3.25 (dt, J = 12.3, 4.2 Hz, 1 H, 3-H), 3.77 (dd, J = 10.5, 4.8 Hz, 1 H, CH_2OH), 4.10 (dd, J = 10.5, 9.0 Hz, 1 H, CH_2OH), 4.11 (q, J = 6.6 Hz, 1 H, 1-H), 4.25 (dd, J = 9.0, 4.8 Hz, 1 H, CHAr), 7.06–7.15 (m, 2 H, 6-H, 7-H), 7.24–7.35 (m, 6 H, 8-H, ArH), 7.43 (m, 1 H, 5-H), 7.65 (br. s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 19.7 (CH_3), 21.4 (C-4), 42.2 (C-3), 50.5 (C-1), 60.9 (CH$_2$OH), 62.8 (CHAr), 108.3 (C-4a), 110.7 (C-8), 118.1 (C-5), 119.4 (C-7), 121.5 (C-6), 127.0 (C-4b), 128.0 (C-*p*), 128.4 (C-*o*), 129.0 (C-*m*), 136.0 (C-*i*), 136.1 (C-8a), 136.2 (C-9a) ppm. IR (KBr): $\tilde{\nu}$ = 1454, 1644, 3440 cm^{-1}. HRMS calcd. for $C_{20}H_{22}N_2O$ $[M + H]^+$: 307.1805; found 307.1790.

(*R*)-2-[(*R*)-2-Hydroxy-1-phenylethyl]-1-propyl-1,2,3,4-tetrahydropyrido[3,4-*b*]indole (13c): Compound **13c** (105 mg, 70%) was obtained in the same way as in the above preparation of **13b** (reaction time 10 min), from **10c** (190 mg, 0.45 mmol) in THF (2 mL), sodium, and liquid NH_3 (30 mL), as a white solid after flash chromatography (hexane/EtOAc 95:5). $[\alpha]_D^{22}$ = +2.1 (c = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.95 (t, J = 7.6 Hz, 3 H, CH_3), 1.30 (m, 1 H, CH_2CH$_3$), 1.53 (m, 1 H, CH_2CH$_3$), 1.72 (m, 1 H, CH_2CH$_2$CH$_3$), 2.07 (m, 1 H, CH_2CH$_2$CH$_3$), 2.50–2.68 (m, 2 H, 4-H), 2.65 (m, 1 H, 3-H), 3.25 (m, 1 H, 3-H), 3.80 (dd, J = 11.3, 5.2 Hz, 1 H, CH_2OH), 4.01 (t, J = 11.3 Hz, 1 H, CH_2OH), 4.10 (m, 1 H, CHAr), 7.03 (ddd, J = 7.2, 7.2,1.2 Hz, 1 H, 6-H), 7.07 (ddd, J = 8.0, 8.0, 1.6 Hz, 1 H, 7-H), 7.32 (m, 6 H, 8-H, ArH), 7.42 (d, J = 7.6 Hz, 1 H, 5-H), 7.71 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 14.4 (CH_3), 18.1 (*C*H$_2$CH$_3$), 35.5 (*C*H$_2$CH$_2$CH$_3$), 41.5 (C-3), 54.6 (C-1), 62.1 (CH$_2$OH), 63.4 (CHAr), 109.1 (C-4a), 110.6 (C-8), 117.3 (C-5), 119.3 (C-7), 121.4

(C-6), 127.1 (C-4b), 128.0 (C-*p*), 128.4 (C-*o*), 128.9 (C-*m*), 135 (C-*i*), 135.9 (C-8a), 137.3 (C-9a) ppm. IR (KBr): $\tilde{\nu}$ = 1454, 1626, 2957, 3406 cm^{-1}. HRMS calcd. for $C_{22}H_{26}N_2O$ [M + H]$^+$: 335.2118; found 335.2121.

(–)-(*R*)-*N*-Methyltetrahydroharman: A solution of **10a** (164 mg, 0.51 mmol) in MeOH (7.5 mL) containing $Pd(OH)_2$ (16.4 mg) was hydrogenated at room temperature for 40 h. The catalyst was removed by filtration and washed with hot MeOH. The solvent was evaporated, and the residue was purified by preparative TLC (SiO_2 deactivated with TEA, CH_2Cl_2/MeOH 95:5) to afford *N*-methyltetrahydroharman as an amorphous yellow solid (76 mg, 75%). $[\alpha]_D^{22}$ = –28.6 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.42 (d, *J* = 6.5 Hz, 3 H, CH_3), 2.03 (br. s, 1 H, NH), 2.65 (t, *J* = 5.2 Hz, 2 H, 4-H), 3.07 (dt, *J* = 13.0, 4.4 Hz, 1 H, 3-H), 3.15 (ddd, *J* = 13.0, 13.0, 6.4 Hz, 1 H, 3-H), 3.55 (s, 3 H, NCH_3), 4.15 (q, *J* = 6.5 Hz, 1 H, 1-H), 7.01 (ddd, *J* = 8.0, 8.0, 1.2 Hz, 1 H, 5-H), 7.11 (ddd, *J* = 7.2, 7.2, 1.2 Hz, 1 H, 7-H), 7.19 (d, *J* = 8.0 Hz, 1 H, 6-H), 7.41 (d, *J* = 7.6 Hz, 1 H, 8-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 20.9 (CH_3), 22.8 (C-4), 29.8 (NCH_3), 39.2 (C-3), 46.3 (C-1), 107.2 (C-4a), 108.6 (C-8), 118 (C-7), 118.9 (C-5), 121.1 (C-6), 126.9 (C-4b), 136.9 (C-8a), 138.5 (C-9a) ppm. IR (KBr): $\tilde{\nu}$ = 1468, 1712, 2925, 2961, 2460 cm^{-1}. HRMS calcd. for $C_{13}H_{16}N_2$ [M + H]$^+$: 201.1386; found 201.1385.

(+)-(*R*)-Tetrahydroharman: (*R*)-Tetrahydroharman was obtained in the same way as in the above preparation of *N*-methyltetrahydroharman, from compound **13b** (66 mg, 0.21 mmol) and $Pd(OH)_2$ (6.6 mg) in MeOH (3 mL), as an amorphous yellow solid (28 mg, 71%) after purification with preparative TLC (SiO_2 deactivated with TEA, CH_2Cl_2/MeOH 90:10). $[\alpha]_D^{22}$ = +49.6 (*c* = 0.5, EtOH). ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 1.50 (d, *J* = 6.8 Hz, 3 H, CH_3), 2.66–2.86 (m, 2 H, 4-H), 3.02 (ddd, *J* = 14.8, 9.6, 5.2 Hz, 1 H, 3-H), 3.32 (m, 1 H, 3-H), 4.20 (q, *J* = 6.8 Hz, 1 H, 1-H), 6.97 (t, *J* = 8.0 Hz, 1 H, 5-H), 7.05 (d, *J* = 8.0 Hz, 1 H, 8-H), 7.29 (d, *J* = 8.0 Hz, 1 H, 7-H), 7.38 (d, *J* = 8.0 Hz, 1 H, 6-H) ppm. ^{13}C NMR (100.6 MHz, CD_3OD, 25 °C): δ = 19.8 (CH_3), 22.3 (C-4), 43.4 (C-3), 49.7 (C-1), 107.8 (C-4a), 111.9 (C-8), 118.6 (C-5), 119.8 (C-7), 122.2 (C-6), 128.4 (C-4b), 136.6 (C-8a), 137.8 (C-9a) ppm. IR (KBr): $\tilde{\nu}$ = 1453, 1725, 2853, 2925 cm^{-1}. HRMS calcd. for $C_{12}H_{14}N_2$ [M + H]$^+$: 187.1230; found 187.1228.

(+)-(*R*)-Komaroidine: (+)-(*R*)-Komaroidine was obtained in the same way as in the preparation of *N*-methyltetrahydroharman, from **13c** (80 mg, 0.24 mmol) and $Pd(OH)_2$ (20 mg) in MeOH (4 mL), as an amorphous pale yellow solid (37 mg, 73%) after preparative TLC (SiO_2 deactivated with TEA, CH_2Cl_2/MeOH 98:2). $[\alpha]_D^{22}$ = +83.6 (*c* = 0.91, EtOH). ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 0.99 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.46–1.60 (m, 2 H, CH_2CH_3), 1.62–1.71 (m, 1 H, $CH_2CH_2CH_3$), 1.80–1.88 (m, 1 H, $CH_2CH_2CH_3$), 2.74 (m, 2 H, 4-H), 3.02 (ddd, *J* = 13.0, 8.0, 5.6 Hz, 1 H, 3-H), 3.35 (dt, *J* = 13.0, 4.0 Hz, 1 H, 3-H), 4.07 (ddd, *J* = 6.4, 4.0, 2.0 Hz, 1 H, 1-H), 7.08 (ddd, *J* = 7.6, 7.6, 0.8 Hz, 1 H, 6-H), 7.14 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1 H, 7-H), 7.29 (t, *J* = 1.2 Hz, 1 H, 8-H), 7.31 (t, *J* = 0.8 Hz, 1 H, 5-H) ppm. ^{13}C NMR (100.6 MHz, CD_3OD, 25 °C): δ = 14.2 (CH_3), 19.1 (CH_2CH_3), 22.7 (C-4), 37.2 ($CH_2CH_2CH_3$), 42.6 (C-3), 52.4 (C-1), 108.9 (C-4a), 110.6 (C-8), 118.0 (C-5), 119.3 (C-6), 121.4 (C-7), 127.5 (C-4b), 135.6 (C-8a), 136.4 (C-9a) ppm. IR (KBr): $\tilde{\nu}$ = 1454, 1622, 2927, 3282, 3410 cm^{-1}. HRMS calcd. for $C_{14}H_{18}N_2$ [M + H]$^+$: 215.1543; found 215.1542.

(–)-(*R*)-Acetylkomaroidine: Acetyl chloride (20 μL, 0.28 mmol) was slowly added at 0 °C to a solution of (+)-(*R*)-komaroidine (30 mg, 0.14 mmol) and TEA (59 μL, 0.42 mmol) in CH_2Cl_2 (1 mL), and the mixture was stirred at room temperature for 2 h. Saturated aqueous $NaHCO_3$ solution was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated. Purification of the resulting oil by preparative TLC (SiO_2 deactivated with DEA, hexane/EtOAc 7:3) gave acetylkomaroidine (31 mg, 87%) as a pale yellow oil. $[\alpha]_D^{22}$ = –93.4 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, CD_3OD, 25 °C, two rotamers): major rotamer: δ = 0.96 (t, *J* = 7.6 Hz, CH_3), 1.43–1.56 (m, CH_2CH_3), 1.75–1.87 (m, $CH_2CH_2CH_3$), 2.24 (s, CH_3CO), 2.77–2.82 (m, 4-H), 3.50 (ddd, *J* = 13.6, 11.2, 4.8 Hz, 3-H), 3.99 (ddd, *J* = 13.6, 4.8, 1.2 Hz, 3-H), 5.79 (dd, *J* = 8.4, 5.2 Hz, 1-H), 7.07 (td, *J* = 8.0, 1.2 Hz, 7-H), 7.13 (td, *J* = 7.2, 1.2 Hz, 6-H), 7.30 (d, *J* = 7.6 Hz, 8-H), 7.43 (d, *J* = 7.2 Hz, 5-H), 8.35 (br. s, NH) ppm; minor rotamer: δ = 0.98 (t, *J* = 7.6 Hz, CH_3), 1.43–1.56 (m, CH_2CH_3), 1.75–1.87 (m, $CH_2CH_2CH_3$), 2.17 (s, CH_3CO), 2.65–2.75 (m, H-4), 2.98 (ddd, *J* = 12.0, 12.0, 5.2 Hz, H-4), 4.86 (t, *J* = 7.6 Hz, H-1), 4.94 (dd, *J* = 12.8, 5.6 Hz, H-3), 5.79 (dd, *J* = 8.4, 5.2 Hz, H-1), 7.05–7.15 (m, ArH), 7.48 (d, *J* = 7.6 Hz, H-5), 8.15 (br. s, NH) ppm. ^{13}C NMR (100.6 MHz, CD_3OD, 25 °C): major rotamer: δ = 14.1 (CH_3), 19.6 (CH_2CH_3), 21.9 (CH_3CO), 22.0 (C-4), 36.8 ($CH_2CH_2CH_3$), 41.0 (C-3), 48.9 (C-1), 107.2 (C-4a), 110.9 (C-8), 117.8 (C-5), 119.4 (C-7), 121.6 (C-6), 126.6 (C-4b), 134.8 (C-8a), 136.0 (C-9a), 169.7 (CO) ppm; minor rotamer: δ = 14.2 (CH_3), 19.5 (CH_2CH_3), 21.0 (CH_3CO), 21.9 (C-4), 35.9 ($CH_2CH_2CH_3$), 37.7 (C-3), 52.0 (C-1), 109.3 (C-4a), 110.8 (C-8), 118.3 (C-5), 119.7 (C-7), 122.0 (C-6), 126.7 (C-4b), 133.6 (C-8a), 136.1 (C-9a), 169.7 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 1449, 1618, 2957, 3272 cm^{-1}. HRMS calcd. for $C_{16}H_{20}N_2O$ [M + H]$^+$: 257.1648; found 257.1646.

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[18] Keto ester **4c** was prepared in four steps from 3-allyl-1-(phenylsulfonyl)indole: i) *s*BuLi, Ac_2O, THF, –70 °C, 20 h, 50%; ii) NMO, acetone/H_2O 4:1, OsO_4 (2.5% in *t*BuOH), 18 h; and iii) *t*BuOH/THF 2:1, $NaH_2PO_4 \cdot H_2O$, $NaClO_2$, H_2O/2-methylbut-2-ene, 0 °C, 1.5 h, 26% two steps.

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[21] Keto esters **4f** and **4g** were prepared by *N*-protection (LiHMDS, TsCl, THF, –20 °C, 24 h, or $MeCO_2CN$, C_6H_5Br, 160 °C, 18 h, 97%) of 1-methylpyrano[3,4-*b*]indol-3(9*H*)-one (see ref.[14]), followed by treatment with trimethylsilyl chloride (93% and 44%, respectively).

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[24] Keto acid **8b** was prepared by two alternative procedures: i) esterification of keto acid **4a** (see ref.[20]), followed by *N*-protection (K_2CO_3, BnBr, CH_3CN, 80 °C, 22 h, 51%) and alkaline hydrolysis (10% aqueous NaOH, EtOH, reflux, 0.5 h, then 2 N HCl, 95%), or ii) Friedel–Crafts reaction of methyl 1-benzyl-3-indoleacetate (acetyl chloride, $ZnCl_2$, 5 min, room temperature, 45%) followed by alkaline hydrolysis (10% aqueous NaOH, EtOH, reflux, 0.5 h, then 2 N HCl, 95%).

[25] Keto acid **8c** was prepared by esterification of keto acid **4b** (see ref[14]), followed by *N*-protection (K_2CO_3, BnBr, CH_3CN, 80 °C, 22 h, 64%) and alkaline hydrolysis (10% aqueous NaOH, EtOH, reflux, 0.5 h, then 2 N HCl, 99%).

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