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Cyclocondensation Reactions of 2-Acyl-3-indoleacetic Acid Derivatives with Phenylglycinol. Enantioselective Synthesis of 1-Substituted Tetrahydro-β-carboline Alkaloids

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Cyclocondensation reactions of a variety of 2-acyl-3-indoleacetic acid derivatives with (*R*)-phenylglycinol are 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.

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Introduction

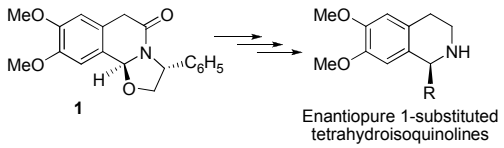
The tetrahydro-β-carboline ring system is present in many naturally occurring compounds, either simple tetrahydro-β-carboline alkaloids[1] or more complex natural products bearing additional fused rings,[2] most of them displaying significant biological and pharmacological activities.[3] This heterocyclic 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 susbstituted piperidines and complex piperidine-containing natural products,[10] we present here a practical synthetic route to enantiopure 1-substituted tetrahydro-β-carbolines.

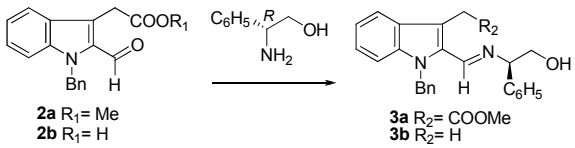
Results and Discussion

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



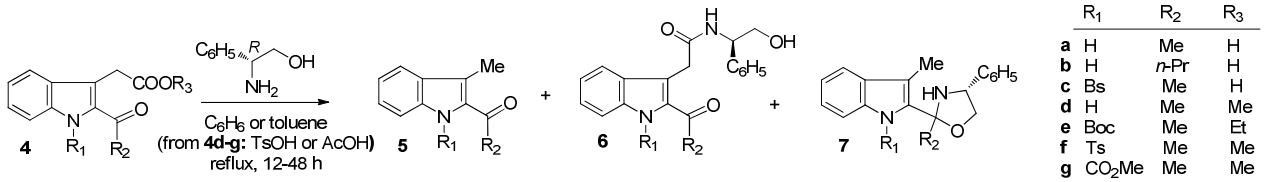
Scheme 1. Enantioselective access to 1-substituted tetrahydroisoquinolines.

Apparently, the extension of the above methodology to the enantioselective synthesis of 1-substituted tetrahydro-β-carbolines simply required using a 2-formyl-3-indoleacetic acid derivative in the generation of the starting lactam. However, attempts at cyclocondensation reactions of aldehydes **2a**[12] and **2b**[13] (C_6H_6, reflux, 48 h) with (*R*)-phenylglycinol resulted in failure, aldimines **3a** and **3b**, respectively, being quantitatively formed instead (Scheme 2). Decarboxylation of the labile 3-indoleacetic acid moiety occurred from **2b** (a vinylogous β-keto acid).



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

As an alternative but related approach to the target tetrahydro-β-carbolines we focused our attention on cyclocondensation reactions from keto acids, which would directly afford 1-substituted derivatives, thus avoiding the need of a subsequent α-amidoalkylation reaction. However, also unsuccessful were the cyclocondensation reactions from the *N*-unsubstituted 2-acyl-3-indoleacetic acids **4a** and **4b**.[14] Decarboxylation was the only process observed under the usual reaction conditions[15] (see



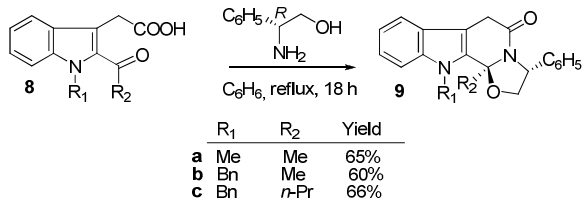
Scheme 3. Attempted cyclocondensation reactions of *N*-unsubstituted and *N*-EWG protected 2-acyl-3-indoleacetic acids with (*R*)-phenylglycinol.

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

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



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

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 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.

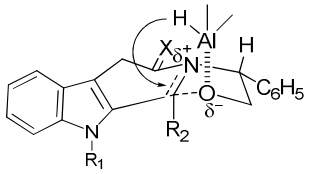
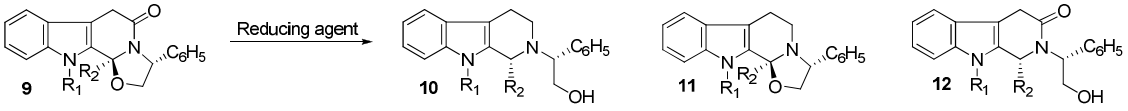


Figure 1. Retention of configuration in the reductive cleavage of the oxazolidine ring.

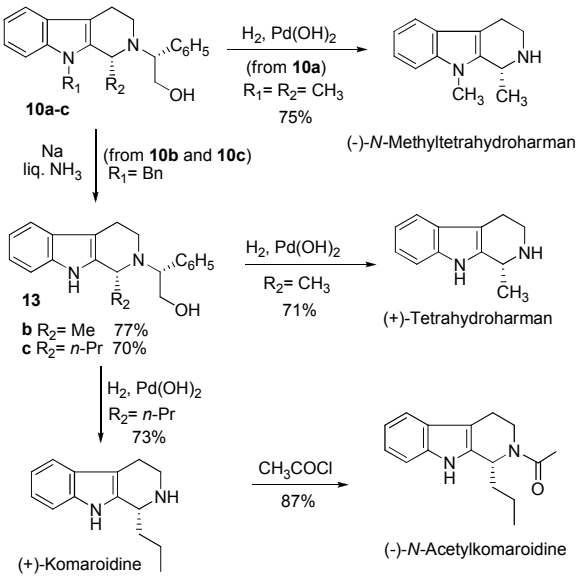
Table 1. Reduction of tetracyclic lactams **9**.



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 ºC, 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 ºC, 3 h (**9a**), 1h (**9b**). [f] THF, reflux, 4 h.

Finally, removal of the phenylethanol moiety from **10a** by debenzylation with hydrogen in the presence of $Pd(OH)_2$ led to (–)-*N*-methyltetrahydroharman[27] (Scheme 5). On the other hand, debenzylation of the indole nitrogen of **10b** and **10c** with Na in liq. 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 to 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] the cyclocondensation reaction fails from 2-formyl-3-indoleacetic acid derivatives **2** and from *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 to the corresponding tetracyclic lactams **9**, thus providing easy access to enantiopure 1-substituted tetrahydro-β-carbolines. Starting from indoles bearing an 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 on Perkin-Elmer 241 polarimeter. High resolution mass spectra (HMRS; LC/MSD TOF Agilent Technologies) were performed by Centres Científics i Tecnològics de la Universitat de Barcelona. Microanalyses (Carlo Erba 1106 analyzer) were performed by Centre d'Investigació i Desenvolupament (CSIC), Barcelona. Only noteworthy IR absorptions (cm^{-1}; Perkin-Elmer 1600) are listed. NMR spectra were recorded with either a Varian Gemini-300 (300 and 75.4, MHz for ^1H and ^{13}C, respectively) or Mercury-400 (400 and 100.6, MHz for ^1H and ^{13}C, respectively) spectrometer.

Data for new 2-acyl-3-indoleacetic acid derivatives 2, 4, 8 and indoles 3, 5-7:

1-Benzyl-2-formyl-3-indoleacetic acid (2b): ^1H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 4.12 (s, 2H, CH_2), 5.76 (s, 2H, NCH_2), 7.04 (d, *J* = 7.2 Hz, 2H, H-o), 7.18-7.23 (m, 4H, H-5, H-6 and H-*m*), 7.33-7.37 (m, 2H, H-7 and H-*p*), 7.73 (d, *J* = 7.6 Hz, 1H, H-4), 10.1 (s, 1H, CHO) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): 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): IR (KBr): υ = 1454, 1493, 1534, 1664, 1736, 2924 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 3.63 (dd, *J* = 11.2, 8.8 Hz, 1H, CH_2OH), 3.66 (s, 3H, CH_3), 3.71 (dd, *J* = 11.2, 4.4 Hz, 1H, CH_2OH), 3.99 (d, *J* = 16.0 Hz, 1H, C$H_2CO_2CH_3$), 4.10 (d, *J* = 16.0 Hz, 1H, C$H_2CO_2CH_3$), 4.32 (dd, *J* = 8.8, 4.4 Hz, 1H, CHAr), 5.82 (d, *J* = 16.8 Hz, 1H, NCH_2), 5.95 (d, *J* = 16.8 Hz, 1H, NCH_2), 6.96 (d, *J* = 7.2 Hz, 2H, ArH), 7.15-7.34 (m, 11H, H-4, H-6, H-7 and ArH), 7.69 (d, *J* = 7.6 Hz, 1H, H-5), 8.59 (s, 1H, CHN) ppm. ^{13}C NMR (100.6 MHz, CDCl3, 25ºC): δ = 30.3 ($CH_2CO_2CH_3$), 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. 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, $CDCl_3$, 25ºC): δ = 2.47 (s, 3H CH_3), 3.59 (dd, *J* = 11.2, 8.8 Hz, 1H, CH_2OH), 3.66 (dd, *J* = 11.2, 4.0 Hz, 1H, CH_2OH), 4.26 (dd, *J* = 8.8, 4.0 Hz, 1H, CHAr), 5.88 (d, *J* = 16.4 Hz, 1H, NCH_2), 6.06 (d, *J* = 16.4 Hz, 1H, NCH_2), 6.94 (d, *J* = 8.4 Hz, 2H, ArH), 7.08-7.33 (m, 11H, H-4, H-6, H-7 and ArH), 7.63 (d, *J* = 8.0 Hz, 1H, H-5), 8.65 (s, 1H, CHN) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): 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-(benzenesulfonyl)-3-indoleacetic acid (4c): ^1H NMR (400 MHz, CD_3Cl_3, 25ºC): δ = 2.79 (s, 3H, CH_3), 3.71 (s, 2H, CH_2), 7.24-7.30 (m, 3H, H-6 and ArH), 7.38-7.48 (m, 3H, H-Ind and ArH), 7.51 (d, *J* = 7.6 Hz, 2H, ArH), 8.07 (d, *J* = 8.4 Hz, 1H, H-7) ppm. ^{13}C NMR (400 MHz, CD_3Cl_3, 25ºC): 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 (Cp), 134.5 (C-2), 137.8 (C-*i*), 138.3 (C-7a), 172.1 (COOH), 197.1 (C=O). 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): IR (KBr): υ = 1453, 1565, 1693, 1735, 2933, 2980 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 1.23 (t, *J* = 6.8 Hz, 3H, CH_3CH$_2$), 1.65 [s, 9H, C(CH_3)$_3$], 2.51 (s, 3H, $COCH_3$), 3.79 (s, 2H, CH_2), 4.12 (q, *J* = 6.8 Hz, 2H, $CO_2CH_2CH_3$), 7.29 (m, 1H, H-5), 7.41 (ddd, *J* = 8.5, 6.8, 1.2 Hz, 1H, H-6), 7.58 (d, *J* = 8.5 Hz, 1H, H-7), 8.09 (d, *J* = 8.5 Hz, 1H, H-4) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): δ = 14.1 (CH_3CH_2), 27.9 ($COCH_3$), 29.7 (CH_2), 31.2 [C(CH_3)$_3$], 61.1 ($CO_2CH_2CH_3$), 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 ($CO_2CH_2CH_3$), 194.9 ($COCH_3$) ppm. HRMS calcd for $C_{19}H_{23}NO_5$ [M + H]$^+$: 346.1648; found 346.1648.

Methyl 2-acetyl-1-tosyl-3-indoleacetate (4f): IR (KBr): υ = 1364, 1595, 1684, 1743 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 2.25 (s, 3H, $COCH_3$), 2.72 (s, 3H, CH_3Ar), 3.61 (s, 3H, CO_2CH_3), 3.72 (s, 2H, CH_2), 7.05 (d, *J* = 8.4 Hz, 1H, H-7), 7.22 (t, *J* = 8,0 Hz, 1H, H-5), 7.38 (d, *J* = 7.6 Hz, 1H, H-6), 7.46 (s, 2H, ArH), 7.48 (s, 2H, ArH), 8.02 (d, *J* = 8.4 Hz, 1H, H-4) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25ºC): δ = 21.4 ($COCH_3$), 29.6 (CH_2), 32.1 (CH_3Ar), 52.1 (CO_2CH_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 (CO_2CH_3), 195.8 ($COCH_3$) ppm. HRMS calcd for $C_{20}H_{19}NO_5S$ $[M + H]^+$: 386.1056; found: 386.1051.

Methyl 2-acetyl-1-(methoxycarbonyl)-3-indoleacetate (4g): ^1H NMR (300 MHz, $CDCl_3$, 25ºC): δ = 2.48 (s, 3H, $COCH_3$), 3.68 (s, 3H, CO_2CH_3), 3.83 (s, 2H, CH_2), 4.04 (s, 3H, NCO_2CH_3), 7.31 (t, *J* = 7.2 Hz, 1H, H-5), 7.44 (t, *J* = 7.2 Hz, 1H, H-6), 7.57 (d, *J* = 7.5 Hz, 1H, H-7), 8.07 (d, *J* = 7.5 Hz, 1H, H-4) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25ºC): δ = 29.5 (CH_2), 30.6 ($COCH_3$), 52.2 (NCO_2CH_3), 54.2 (CO_2CH_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 (CO_2CH_3), 194.4 ($COCH_3$) ppm.

2-Butanoyl-3-methylindole (5b): ^1H NMR (300 MHz, $CDCl_3$, 25ºC): δ = 0.98 (t, *J* = 7.5 Hz, 3H, CH_2CH_3), 1.75 (m, 2H, CH_2CH_3), 2.57 (s, 3H, CH_3), 2.85 (t, *J* = 7.2 Hz, 2H, $CH_2CH_2CH_3$), 7.05 (ddd, *J* = 8.0, 6.0, 1.2 Hz, 1H, H-5), 7.25-7.31 (m, 2H, H-6, H-7), 7.61 (d, *J* = 8.0 Hz, 1H, H-4), 9.00 (s, 1H, NH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25ºC): δ = 11.3 (CH_2CH_3), 14.1 (CH_3), 17.7 (CH_2CH_3), 43.0 ($CH_2CH_2CH_3$), 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): IR (KBr): υ = 1531, 1649, 2933, 3013, 3308 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25ºC): δ = 2.35 (s, 3H, $COCH_3$), 3.72 (dd, *J* = 11.5, 6.6 Hz, 1H, CH_2OH), 3.80 (dd, *J* = 11.5, 4.2 Hz, 1H, CH_2OH), 4.06 (s, 2H, CH_2CONH), 5.06 (m, 1H, CHAr), 7.10-7.29 (m, 8H, H-5, H-6, H-7, ArH), 7.69 (d, *J* = 8.4 Hz, 1H, H-4), 9.40 (s, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): 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 ($COCH_3$) ppm. 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): ^1H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 1.81 (s, 3H, $OCCH_3$), 2.39 (s, 3H, CH_3), 4.28 (dd, *J* = 8.5, 6.8 Hz, 1H, CH_2), 4.75 (t, *J* = 8.5 Hz, 1H, CH_2), 5.28 (t, *J* = 7.2 Hz, 1H, CHAr), 7.30-7.44 (m, 7H, H-5, H-6, ArH), 7.54 (d, *J* = 8.0 Hz, 1H, H-7), 7.93 (d, *J* = 7.6 Hz, 1H, H-4) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): δ = 8.4 (CH_3), 22.5 ($OCCH_3$), 59.8 (CHAr), 74.3 (CH_2), 95.3 ($OCCH_3$), 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 (%): (M^+ + 27) 319 (100); 320 (28); 318 (9).

1-(Benzenesulfonyl)-3-methyl-2-[(*R*)-2-methyl-4-phenyl-1,3-oxazolidin-2-yl]indole (7c): ^1H NMR (300 MHz, $CDCl_3$, 25ºC): δ = 2.14 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.99 (m, 2H, CH_2), 5.04 (m, 1H, *CH*Ar), 7.20-7.56 (m, 11H, ArH), 7.80 (d, *J* = 7.2 Hz, 2H, ArH), 8.02 (d, *J* = 8.1 Hz, 1H, H-7) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): 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): IR (KBr): υ = 1611, 1732, 3440 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25ºC): δ = 2.54 (s, 3H, $COCH_3$), 4.07 (s, 2H, CH_2), 5.63 (s, 2H, NCH_2), 6.96 (d, *J* = 7.5 Hz, 2H, H-*o*), 7.14-7.34 (m, 6H, H-5, H-6, H-7, H-*m*, H-*p*), 7.69 (d, *J* = 7.8 Hz, 1H, H-4), 12.23 (COOH) ppm. ^{13}C-NMR (75.4 MHz, $CDCl_3$, 25ºC): 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_2H), 192.7 ($COCH_3$) ppm. HRMS calcd for $C_{19}H_{17}NO_3$ $[M + Na]^+$: 330.1101; found 330.1093.

1-Benzyl-2-butanoyl-3-indoleacetic acid (8c): IR (KBr): υ = 1652, 3436 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 0.83 (t, *J* = 7.6 Hz, 3H, CH_3CH_2), 1.64 (sext, 2H, *J* = 7.6 Hz, CH_3CH_2), 2.83 (t, *J* = 7.6 Hz, 2H, $CH_2CH_2CH_3$), 4.07 (s, 2H, CH_2), 5.62 (s, 2H, NCH_2), 6.97 (d, *J* = 6.8 Hz, 2H, H-*o*), 7.18-7.34 (m, 6H, H-5, H-6, H-7, H-*m*, H-*p*), 7.73 (d, *J* = 8.0 Hz, 1H, H-4) ppm. ^{13}C-NMR (75.4 MHz, $CDCl_3$, 25ºC): δ = 13.6 (CH_3CH_2), 17.9 (CH_3CH_2), 32.0 (CH_2), 44.5 ($CH_2CH_2CH_3$), 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_2H), 196.7 ($COCH_3$) ppm. 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 produced by a Dean-Stark apparatus. The resulting suspension was cooled and concentrated. Flash chromatography (8:2 hexane–EtOAc) afforded lactam **9a** (475 mg, 65%) as a white solid; m. p. 166–168ºC (hexane-EtOAc). $[\alpha]^{22}_D$ = – 62.9 (*c* = 1.0, $CHCl_3$). IR (KBr): υ = 1382, 1470, 1661, 2927 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 1.70 (s, 3H, CH_3), 3.82 (s, 2H, H-6), 3.88 (s, 3H, NCH_3), 4.19 (dd, *J* = 8.4, 6.8 Hz, 1H, H-2), 4.65 (t, *J* = 8.4 Hz, 1H, H-2), 5.49 (t, *J* = 8.0 Hz, 1H, H-3), 7.16 (t, *J* = 8.0 Hz, 1H, H-9), 7.26-7.40 (m, 7H, H-8, H-10, ArH), 7.52 (d, *J* = 8.0 Hz, 1H, H-7) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): 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. 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): Operating 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), lactam **9b** (121 mg, 60%) was obtained after flash chromatography (9:1 to 8:2 hexane–EtOAc). $[\alpha]^{22}_D$ = – 96.6 (*c* = 1.0, $CHCl_3$). IR (KBr): υ = 1382, 1454, 1495, 2924 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 1.60 (s, 3H, CH_3), 3.85 (d, *J* = 20.1 Hz, 1H, H-6), 3.90 (d, *J* = 20.1 Hz, 1H, H-6), 4.14 (dd, *J* = 9.0, 6.6 Hz, 1H, H-2), 4.53 (dd, *J* = 9.0, 8.4 Hz, 1H, H-2), 5.50 (t, *J* = 7.5 Hz, 1H, H-3), 5.55 (d, *J* = 16.8 Hz, 1H, NCH_2), 5.65 (d, *J* = 16.8 Hz, 1H, NCH_2), 7.05 (d, *J* = 7.2 Hz, 2H, H-*m*), 7.14-7.38 (m, 11H, H-8, H-9, H-10, ArH), 7.56 (d, *J* = 6.4 Hz, 1H, H-7) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): 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. 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): Operating 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), lactam **9c** (156 mg, 66%) was obtained as a yellow oil after flash chromatography (95:5

hexane–EtOAc). [α] $^{22}_{D}$ = – 96.4 (*c* = 1.01, $CHCl_3$). IR (KBr): υ = 1453, 1663, 2927, 2960 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 0.55 (t, *J* = 7.2 Hz, 3H, CH_3), 0.84-0.91 (m, 1H, CH_2CH$_3$), 1.25-1.37 (m, 1H, *CH*$_2$CH$_3$), 1.60 (td, *J* = 13.4, 4.8 Hz, 1H, CH_2CH$_2$CH$_3$), 1.80 (td, *J* = 13.4, 4.0 Hz, 1H, C*H*$_2$CH$_2$CH$_3$), 3.87 (s, 2H, H-6), 4.19 (dd, *J* = 8.8, 7.2 Hz, 1H, H-2), 4.59 (t, *J* = 8.8 Hz, 1H, H-2), 5.51 (d, *J* = 17.2 Hz, 1H, NCH_2), 5.57 (t, *J* = 7.6 Hz, 1H, H-3), 5.68 (d, *J* = 17.2 Hz, 1H, NCH_2), 7.03 (d, *J* = 7.6 Hz, 2H, H-*m*), 7.15-7.40 (m, 11H, H-8, H-9, H-10, ArH), 7.54 (m, 1H, H-7) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): δ = 13.1 (CH_3), 17.2 (*C*H$_2$CH$_3$), 30.8 (C-6), 40.9 (*C*H$_2$CH$_2$CH$_3$), 48.0 (*C*H$_2$C$_6$H$_5$), 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. 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 to a suspension of $AlCl_3$ (173 mg, 1.3 mmol) in THF (12 mL) at 0 °C and the mixture was stirred for 3.5 h. After cooling 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 cooling to 0°C, the reaction 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 7:3 hexane–EtOAc) of the residue afforded compound **10a** as a pale yellow oil (181.5 mg, 94%). [α]$^{22}_{D}$ = – 36.8 (*c* = 1.0, $CHCl_3$). IR (KBr): υ = 1469, 2930, 3408 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 1.50 (d, *J* = 6.8 Hz, 3H, CH_3), 2.51 (dt, *J* = 15.2, 4.0 Hz, 1H, H-4), 2.70 (dddd, *J* = 15.2, 5.2, 4.8, 0.8 Hz, 1H, H-4), 2.83 (ddd, *J* = 13.2, 4.8, 4.0 Hz, 1H, H-3), 3.18 (ddd, *J* = 13.2, 9.2, 5.2 Hz, 1H, H-3), 3.60 (s, 3H, NCH_3), 3.84 (dd, *J* = 8.0, 2.4 Hz, 1H, C*H*$_2$OH), 3.89 (dd, *J* = 8.0, 6.8 Hz, 1H, C*H*$_2$OH), 3.91 (q, *J* = 6.8 Hz, 1H, CHAr), 4.30 (q, *J* = 6.8 Hz, 1H, H-1), 7.08 (ddd, *J* = 8.2, 6.8, 1.0 Hz, 1H, H-6), 7.18 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H, H-7), 7.25-7.38 (m, 6H, H-8, ArH), 7.45 (dt, *J* = 7.2, 1.0 Hz, 1H, H-5) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): 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. 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): Operating as in the above reduction of **9a**, starting 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), tetrahydro-β-carboline **10b** (95 mg, 60%) was obtained after flash chromatography (7:3 hexane–EtOAc). [α] $^{22}_{D}$ = – 80.1 (*c* 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 1.42 (d, *J* = 6.8 Hz, 3H, CH_3), 2.51 (ddd, *J* = 16.0, 4.4, 2.8 Hz, 1H, H-4), 2.70 (ddd, *J* = 16.0, 10.4, 6.0 Hz, 1H, H-4), 2.84 (m, 1H, H-3), 3.19 (ddd, *J* = 14.0, 10.4, 5.2 Hz, 1H, H-3), 3.63 (m, 1H, C*H*$_2$OH), 3.76 (t, *J* = 4.8 Hz, 1H, C*H*$_2$OH), 4.15 (m, 1H, H-1), 5.14 (d, *J* = 16.8 Hz, 1H, NCH_2), 5.34 (d, *J* = 16.8 Hz, 1H, NCH_2), 6.93 (d, *J* = 7.6 Hz, 1H, H-5), 7.06-7.29 (m, 12H, H-6, H-8, ArH), 7.49 (m, 1H, H-7) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): δ = 19.2 (C-4), 20.3 (CH_3), 40.0 (C-3), 46.5 (*C*H$_2$C$_6$H$_5$), 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): Operating 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), tetrahydro-β-carboline **10c** (68 mg, 70%) was obtained after flash chromatography (95:5 hexane–EtOAc). [α] $^{22}_{D}$ = – 82.5 (c 1.0, $CHCl_3$). IR (KBr): υ = 1453, 1647, 2955 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 0.91 (t, *J* = 7.2 Hz, 3H, CH_3), 1.50-1.63 (m, 4H, C*H*$_2$C*H*$_2$CH$_3$), 2.38 (ddd, *J* = 15.0, 4.0, 2.0 Hz, 1H, H-4), 2.66 (ddd, *J* = 15.0, 10.8, 5.6 Hz, 1H, H-4), 2.78 (dd, *J* = 14.0, 4.0 Hz, 1H, H-3), 3.18 (ddd, *J* = 14.0, 10.8, 5.2 Hz, 1H, H-3), 3.49 (dd, *J* = 12.4, 4.8 Hz, 2H, C*H*$_2$OH), 3.68 (t, *J* = 4.8 Hz, 1H, H-1), 4.04 (d, *J* = 9.2 Hz, 1H, CHAr), 5.17 (d, *J* = 17.0 Hz, 1H, NCH_2), 5.40 (d, *J* = 17.0 Hz, 1H, NCH_2), 6.98 (d, *J* = 6.8 Hz, 2H, ArH), 7.10-7.14 (m, 2H, H-6, H-7), 7.23-7.30 (m, 9H, H-8, ArH), 7.48 (d, *J* = 7.2 Hz, 1H, H-5) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): δ = 13.9 (CH_3), 17.7 (C-4), 19.7 (*C*H$_2$CH$_3$), 36.9 (*C*H$_2$CH$_2$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. 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, 12:

(*S*)-2-[(*R*)-2-Hydroxy-1-phenylethyl]-1,9-dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]indole (1-*epi*-10a): ^{1}H NMR (300 MHz, $CDCl_3$, 25ºC, from a mixture **10a**:*epi*-**10a**): δ = 1.36 (d, *J* = 6.9 Hz, 3H, CH_3), 2.40-2.48 (m, 2H, H-4), 2.90-3.02 (m, 1H, H-3), 3.31 (m, 1H, H-3), 3.40 (s, 3H, NCH_3), 3.79 (dd, *J* = 6.0, 4.5 Hz, 1H, C*H*$_2$OH), 4.30 (m, 1H, H-1), 7.05-7.48 (m, 9H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25ºC): δ = 18.4 (C-4), 19.2 (CH_3), 29.1 (NCH_3), 39.7 (C-3), 49.1 (C-1), 63.9 (C*H*$_2$OH), 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): [α] $^{22}_{D}$ = – 75.8 (*c* 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 0.68 (t, *J* = 7.5 Hz, 3H, CH_3), 1.15-1.30 (m, 2H, C*H*$_2$C*H*$_2$CH$_3$), 1.54-1.61 (m, 1H, CH$_2$C*H*$_2$CH$_3$), 1.73-1.79 (m, 1H, C*H*$_2$CH$_2$CH$_3$), 2.64 (dm, 1H, *J* = 16.0 Hz, H-4), 3.07 (ddd, *J* = 16.0, 10.4, 7.2 Hz, 1H, H-4), 3.41 (m, 2H, H-3), 3.47 (t, *J* = 9.2 Hz, 1H, H-1), 3.74 (dd, *J* = 6.0, 3.2 Hz, 1H, CHAr), 3.84 (dd, *J* = 11.0, 3.2 Hz, 1H, C*H*$_2$OH), 4.03 (dd, *J* = 11.0 , 6.0 Hz, 1H, C*H*$_2$OH), 4.91 (d, *J* = 16.8 Hz, 1H, NCH_2), 4.96 (d, *J* = 16.8 Hz, 1H, NCH_2), 6.79 (m, 2H, ArH), 7.10-7.20 (m, 11H, ArH, H-Ind), 7.53 (m, 1H, H-8) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): 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 (C*H*$_2$OH), 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): [α]$^{22}_{D}$ = – 96.6 (*c* = 1.0, $CHCl_3$). IR (KBr): υ = 1382, 1470, 2927, 2934 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 1.78 (s, 3H, CH_3), 2.44 (dd, *J* = 16.0, 4.8 Hz, 1H, H-6), 2.91 (ddd, *J* = 16.0, 12.0, 5.6 Hz, 1H, H-6), 3.09 (dd, *J* = 14.4, 5.6 Hz, 1H, H-5), 3.17 (ddd, *J* = 14.4, 12.0, 5.2 Hz, 1H, H-5), 3.70 (t, *J* = 7.6 Hz, 1H, H-2), 3.80 (s, 3H, NCH_3), 3.97 (t, *J* = 7.6 Hz, 1H, H-2), 4.17 (t, *J* = 7.6 Hz, 1H, H-3), 7.04 (ddd, *J* = 14.4, 7.2, 0.8 Hz, 1H, H-9), 7.16 (ddd, *J* = 14.4, 7.5, 1.2 Hz, 1H, H-8), 7.23-7.28 (m, 5H, ArH), 7.43 (d, *J* = 7.5 Hz, 1H, H-7) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): 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. 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): $[\alpha]^{22}_D$ = + 70.8 (*c* = 0.5, $CHCl_3$). IR (KBr): υ = 1469, 1621, 2929, 3382 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 1.38 (d, *J* = 6.4 Hz, 3H, CH_3), 3.51 (s, 3H, NCH_3), 3.70 (d, *J* = 19.2 Hz, 1H, H-4), 3.82 (d, *J* = 19.2 Hz, 1H, H-4), 4.11 (dd, *J* = 12.0, 3.5 Hz, 1H, C*H*$_2$OH), 4.37 (dd, *J* = 12.0, 7.2 Hz, 1H, C*H*$_2$OH), 4.83 (dd, *J* = 7.2, 3.5 Hz, 1H, CHAr), 7.07-7.09 (m, 1H, H-6), 7.15-7.38 (m, 6H, H-7, H-8, ArH), 7.43 (d, *J* = 8.0 Hz, 1H, H-5) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): 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_2OH), 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. 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): $[\alpha]^{22}_D$ = + 18.25 (*c* = 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 1.29 (d, *J* = 6.4 Hz, 3H, CH_3), 3.68-3.79 (m, 2H, H-4, OH), 3.92 (m, 1H, H-4), 4.03 (dt, *J* = 12.0, 4.3 Hz, 1H, C*H*$_2$OH), 4.26 (dt, *J* = 12.0, 7.4 Hz, 1H, C*H*$_2$OH), 4.46 (q, *J* = 6.4 Hz, 1H, H-1), 4.88 (dd, *J* = 7.4, 4.3 Hz, 1H, CHAr), 5.09 (d, *J* = 16.8 Hz, 1H, NCH_2), 5.29 (d, *J* = 16.8 Hz, 1H, NCH_2), 6.85-6.88 (m, 1H, H-5), 7.14-7.28 (m, 12H, H-6, H-7, ArH), 7.53-7.56 (m, 1H, H-8) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): 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_2OH), 65.5 (*CH*CH$_2$), 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):** Into a three–necked round–bottomed equipped with a coldfinger condenser charged with dry ice-acetone was condensed 30 mL of NH_3 at – 78°C. The temperature was raised to – 33 °C, and a solution of amine **10b** (90 mg, 0.23 mmol) in THF (2 mL) was added. Then, sodium metal was 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 rt for 4h. The resulting residue was digested at rt with CH_2Cl_2, poured into water, and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated. Flash chromatography (8:2 hexane–EtOAc) of the residue afforded **13b** (54 mg, 77%) as a white solid. $[\alpha]^{22}_D$ = + 21.2 (*c* = 0.99, $CHCl_3$). IR (KBr): υ = 1454, 1644, 3440 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 1.59 (d, *J* = 6.6 Hz, 3H, CH_3), 2.40 (ddd, *J* = 12.3, 8.4, 5.1 Hz, 1H, H-3), 2.67 (m, 2H, H-4), 3.25 (dt, *J* = 12.3, 4.2 Hz, 1H, H-3), 3.77 (dd, *J* = 10.5, 4.8 Hz, 1H, C*H*$_2$OH), 4.10 (dd, *J* = 10.5, 9.0 Hz, 1H, C*H*$_2$OH), 4.11 (q, *J* = 6.6 Hz, 1H, H-1), 4.25 (dd, *J* = 9.0, 4.8 Hz, 1H, CHAr), 7.06-7.15 (m, 2H, H-6, H-7), 7.24-7.35 (m, 6H, H-8, ArH), 7.43 (m, 1H, H-5), 7.65 (brs, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): δ = 19.7 (CH_3), 21.4 (C-4), 42.2 (C-3), 50.5 (C-1), 60.9 (CH_2OH), 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. 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): Operating 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), compound **13c** (105 mg, 70%) was obtained as a white solid after flash chromatography (95:5 hexane–EtOAc). $[\alpha]^{22}_D$ = + 2.1 (*c* = 1.0, $CHCl_3$). IR (KBr): υ = 1454, 1626, 2957, 3406 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 0.95 (t, *J* = 7.6 Hz, 3H, CH_3), 1.30 (m, 1H, C*H*$_2$CH$_3$), 1.53 (m, 1H, C*H*$_2$CH$_3$), 1.72 (m, 1H, C*H*$_2$CH$_2$CH$_3$), 2.07 (m, 1H, C*H*$_2$CH$_2$CH$_3$), 2.50-2.68 (m, 2H, H-4), 2.65 (m, 1H, H-3), 3.25 (m, 1H, H-3), 3.80 (dd, *J* = 11.3, 5.2 Hz, 1H, C*H*$_2$OH), 4.01 (t, *J* = 11.3 Hz, 1H, C*H*$_2$OH), 4.10 (m, 1H, CHAr), 7.03 (ddd, *J* = 7.2, 7.2 ,1.2 Hz, 1H, H-6), 7.07 (ddd, *J* = 8.0, 8.0, 1.6 Hz, 1H, H-7), 7.32 (m, 6H, H-8, ArH), 7.42 (d, *J* = 7.6 Hz, 1H, H-5), 7.71 (s, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): 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_2OH), 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. 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 by hot MeOH. The solvent was evaporated, and the residue was purified by preparative TLC (SiO_2 deactivated with TEA, 95:5 CH_2Cl_2–MeOH) to obtain *N*-methyltetrahydroharman as an amorphous yellow solid (76 mg, 75%). $[\alpha]^{22}_D$ = –28.6 (*c* 1.0, $CHCl_3$). IR (KBr): υ = 1468, 1712, 2925; 2961, 2460 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ = 1.42 (d, *J* = 6.5 Hz, 3H, CH_3), 2.03 (brs, 1H, NH), 2.65 (t, *J* = 5.2 Hz, 2H, H-4), 3.07 (dt, *J* = 13.0, 4.4 Hz, 1H, H-3), 3.15 (ddd, *J* = 13.0, 13.0, 6.4 Hz, 1H, H-3), 3.55 (s, 3H, NCH_3), 4.15 (q, *J* = 6.5 Hz, 1H, H-1), 7.01 (ddd, *J* = 8.0, 8.0, 1.2 Hz, 1H, H-5), 7.11 (ddd, *J* = 7.2, 7.2, 1.2 Hz, 1H, H-7), 7.19 (d, *J* = 8.0 Hz, 1H, H-6), 7.41 (d, *J* = 7.6 Hz, 1H, H-8) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25ºC): 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. HRMS calcd for $C_{13}H_{16}N_2$ [M + H]$^+$: 201.1386; found 201.1385.

(+)-(*R*)-Tetrahydroharman: Operating 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), (*R*)-tetrahydroharman was obtained (28 mg, 71%) as an amorphous yellow solid after purification with preparative TLC (SiO_2 deactivated with TEA, 90:10 CH_2Cl_2–MeOH). $[\alpha]^{22}_D$ = + 49.6 (*c* 0.5, EtOH). IR (KBr): υ = 1453, 1725, 2853, 2925 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD, 25ºC): δ = 1.50 (d, *J* = 6.8 Hz, 3H, CH_3), 2.66-2.86 (m, 2H, H-4), 3.02 (ddd, *J* = 14.8, 9.6, 5.2 Hz, 1H, H-3), 3.32 (m, 1H, H-3), 4.20 (q, *J* = 6.8 Hz, 1H, H-1), 6.97 (t, *J* = 8.0 Hz, 1H, H-5), 7.05 (d, *J* = 8.0 Hz, 1H, H-8), 7.29 (d, *J* = 8.0 Hz, 1H, H-7), 7.38 (d, *J* = 8.0 Hz, 1H, H-6) ppm. ^{13}C NMR (100.6 MHz, CD_3OD, 25ºC): 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. HRMS calcd for $C_{12}H_{14}N_2$ [M + H]$^+$: 187.1230; found 187.1228.

(+)-(*R*)-Komaroidine: Operating as in the preparation of *N*-methyltetrahydroharman, from **13c** (80 mg, 0.24 mmol) and $Pd(OH)_2$ (20 mg) in MeOH (4 mL), (+)-*(R)*-komaroidine was obtained (37 mg, 73%) as an amorphous pale yellow solid after preparative TLC (SiO_2 deactivated with TEA, 98:2 CH_2Cl_2–MeOH). $[\alpha]^{22}_D$ = + 83.6 (*c* = 0.91, EtOH). IR (KBr): υ = 1454, 1622, 2927, 3282, 3410 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD, 25ºC): δ = 0.99 (t, *J* = 7.2 Hz, 3H, CH_3), 1.46-1.60 (m, 2H, C*H*$_2$CH$_3$), 1.62-1.71 (m, 1H, C*H*$_2$CH$_2$CH$_3$), 1.80-1.88 (m, 1H, C*H*$_2$CH$_2$CH$_3$), 2.74 (m, 2H, H-4), 3.02 (ddd, *J* = 13.0, 8.0, 5.6 Hz, 1H, H-3), 3.35 (dt, *J* = 13.0, 4.0 Hz, 1H, H-3), 4.07 (ddd, *J* = 6.4, 4.0, 2.0 Hz, 1H, H-1), 7.08 (ddd, *J* = 7.6, 7.6, 0.8 Hz, 1H, H-6), 7.14 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H, H-7), 7.29 (t, *J* = 1.2 Hz, 1H, H-8), 7.31 (t, *J* = 0.8 Hz, 1H, H-5) ppm. ^{13}C NMR (100.6 MHz, CD_3OD, 25ºC): δ = 14.2 (CH_3), 19.1 (*C*H$_2$CH$_3$), 22.7 (C-4), 37.2 (*C*H$_2$CH$_2$CH$_3$), 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. 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 (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 2h. 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, 7:3 hexane–EtOAc) gave acetylkomaroidine (31 mg, 87%) as a pale yellow oil. $[\alpha]^{22}_D = -93.4$ (*c* 1.0, $CHCl_3$). IR (KBr): υ = 1449, 1618, 2957, 3272 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD, 25ºC, two rotamers): major rotamer: δ = 0.96 (t, *J* = 7.6 Hz, CH_3), 1.43-1.56 (m, C*H*$_2$CH$_3$), 1.75-1.87 (m, C*H*$_2$CH$_2$CH$_3$), 2.24 (s, *CH*$_3$CO), 2.77-2.82 (m, H-4), 3.50 (ddd, *J* = 13.6, 11.2, 4.8 Hz, H-3), 3.99 (ddd, *J* = 13.6, 4.8, 1.2 Hz, H-3), 5.79 (dd, *J* = 8.4, 5.2 Hz, H-1), 7.07 (td, *J* = 8.0, 1.2 Hz, H-7), 7.13 (td, *J* = 7.2, 1.2 Hz, H-6), 7.30 (d, *J* = 7.6 Hz, H-8), 7.43 (d, *J* = 7.2 Hz, H-5), 8.35 (brs, NH) ppm; minor rotamer: δ = 0.98 (t, *J* = 7.6 Hz, CH_3), 1.43-1.56 (m, C*H*$_2$CH$_3$), 1.75-1.87 (m, C*H*$_2$CH$_2$CH$_3$), 2.17 (s, *CH*$_3$CO), 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 (brs, NH) ppm. ^{13}C NMR (100.6 MHz, CD_3OD, 25ºC): major rotamer: δ = 14.1 (CH_3), 19.6 (*C*H$_2$CH$_3$), 21.9 (*C*H$_3$CO), 22.0 (C-4), 36.8 (*C*H$_2$CH$_2$CH$_3$), 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 (*C*H$_2$CH$_3$), 21.0 (*C*H$_3$CO), 21.9 (C-4), 35.9 (*C*H$_2$CH$_2$CH$_3$), 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. HRMS calcd for $C_{16}H_{20}N_2O$ [M + H]$^+$: 257.1648; found 257.1646.

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[21] Keto esters **4f** and **4g** were prepared by *N*-protection (LiHMDS, TsCl, THF, -20 ºC, 24 h, or $MeCO_2CN$, C_6H_5Br, 160 ºC, 18 h, 97%) of 1-methylpyrano[3,4-*b*]indol-3(9*H*)-one (see ref [14]), followed by reaction 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 ºC, 22h, 51%) and alkaline hydrolysis (10% aqueous NaOH, EtOH, reflux, 0.5 h, then 2N HCl, 95%); 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 2N 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 ºC, 22h, 64%) and alkaline hydrolysis (10% aqueous NaOH, EtOH, reflux, 0.5 h, then 2N HCl, 99%).

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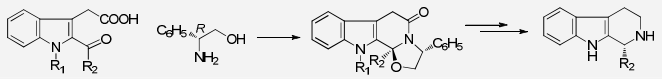

A short synthetic route to enantiopure 1-substituted tetrahydro-β-carbolines is reported. The key step is a stereoselective cyclocondensation reaction between an *N*-alkyl-2-acyl-3-indoleacetic acid and (*R*)-phenylglycinol. Subsequent reductive processes and debenzylation of the indole nitrogen provide access to N_a-unsubstituted alkaloids, such as tetrahydroharman and komaroidine.

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Cyclocondensation Reactions of 2-Acyl-3-indoleacetic Acid Derivatives with Phenylglycinol. Enantioselective Synthesis of 1-Substituted Tetrahydro-β-carboline Alkaloids

Keywords: Alkaloids / Tetrahydroisoquinolines / Lactams / Phenylglycinol / α-Amidoalkylation