Unsaturated oxazolopiperidone lactams: an unexpected domino-type double conjugate addition–cyclization process

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Dedicated to Prof. Rosa Mª Claramunt on the occasion of her 65th birthday

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Abstract
Reactions of 2-acetylindole enolate with unsaturated oxazolopiperidones **3**, **4** and **10** unexpectedly gives pentacyclic dilactams **6**, **7** and **11**, respectively, resulting from a domino-type process involving two successive conjugate additions and a final cyclization.
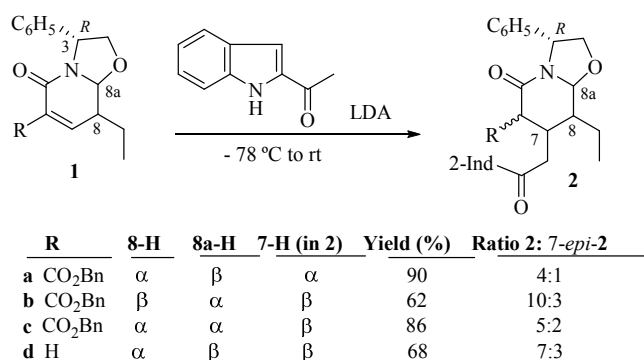
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Introduction

Conjugate addition reactions to phenylglycinol-derived unsaturated oxazolopiperidone lactams[1-3] have been satisfactorily used for the stereocontrolled introduction of substituents at the 4-position of the piperidine ring, providing access to diversely substituted enantiopure piperidine derivatives, in some cases *en route* to complex alkaloids.[4-7]

The addition of organocuprates requires the presence of an additional activating electron-withdrawing substituent,[8-11] usually an alkoxycarbonyl group, α to the lactam carbonyl, and takes place under stereoelectronic control[12,13] with high *exo* facial selectivity.[14] In contrast, the conjugate addition of stabilized anions does not require the presence of the activating ester substituent and can be a reversible process, depending on the nature of the nucleophile and lactam, as well as the reaction conditions.[15-18]

In recent work,[19] in the context of model studies on the enantioselective synthesis of the indole alkaloid ervitsine we studied the stereochemical outcome of the conjugate addition of 2-acetylindole enolates to a variety of stereochemically diverse phenylglycinol-derived unsaturated oxazolopiperidone lactams **1**, belonging to both the 3,8a-*cis* and -*trans* series (Scheme 1).

R	8-H	8a-H	7-H (in 2)	Yield (%)	Ratio 2: 7-*epi*-2
a CO_2Bn	α	β	α	90	4:1
b CO_2Bn	β	α	β	62	10:3
c CO_2Bn	α	α	β	86	5:2
d H	α	β	β	68	7:3

Scheme 1. Conjugate addition of 2-acetylindole enolate to unsaturated oxazolopiperidone lactams.

The kinetic adducts **2a-c** (7-H/8a-H *trans*) resulting from an *exo* attack were formed as the major products from the activated lactams **1a-c**, whereas the alternative *endo* attack (7-H/8a-H *cis*) predominantly occurred from the non-activated lactam **1d**, leading to the most stable 7-H/8-H *trans* isomer **2d**. The best results in terms of chemical yield were obtained using an excess (5 equiv.) of the nucleophile.

To gain further insight into the factors governing the stereoselectivity of these reactions, in this paper we report similar conjugate addition reactions using the simplest oxazolopiperidone lactams **3** and **4**, which lack both the benzyloxycarbonyl and ethyl substituents present in **1** and differ in the configuration of C-8a.
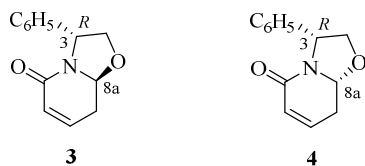

**Figure 1.** Simple phenylglycinol-derived unsaturated oxazolopiperidone lactams.

Results and Discussion

The reaction of 2-acetylindole with lactam **3** (3,8a-*trans* series) was carried out under the aforementioned conditions (LDA as the base, 5 equiv. of 2-acetylindole, –78 ℃ to rt).[19] Surprisingly, besides the expected addition product **5** (17%), an unexpected pentacyclic derivative **6** incorporating two oxazolopiperidone units was isolated in 30% yield (Scheme 2).
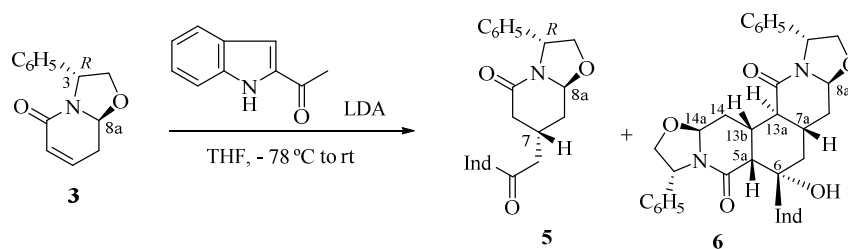
Scheme 2. Conjugate addition of 2-acetylindole enolate to unsaturated lactam **3**.

The formation of **6** can be rationalized as outlined in Scheme 3. The lactam enolate **i** resulting from the initial conjugate addition acts as a nucleophile in a second conjugate addition with another molecule of oxazolopiperidone **3** to give the 3,4-disubstituted 2-piperidone intermediate **ii**, with a *trans*-3,4 relative configuration. In fact, there are examples[6] in which the intermediate lactam enolate resulting from the conjugate addition to an unsaturated lactam is trapped *in situ* by an electrophile to give a *trans*-3,4-substituted 2-piperidone derivative. The same stereochemistry has been observed in the alkylation of a 4-substituted 2-piperidone enolate.[20] A final nucleophilic attack of the new lactam enolate intermediate on the acylindole carbonyl group generates the central six-membered carbocyclic ring leading to **6**. Interestingly, both conjugate addition reactions occurred in an *exo* manner, resulting in a product with a *trans*-relationship between the oxazolidine 2-H and the piperidone 4-H.
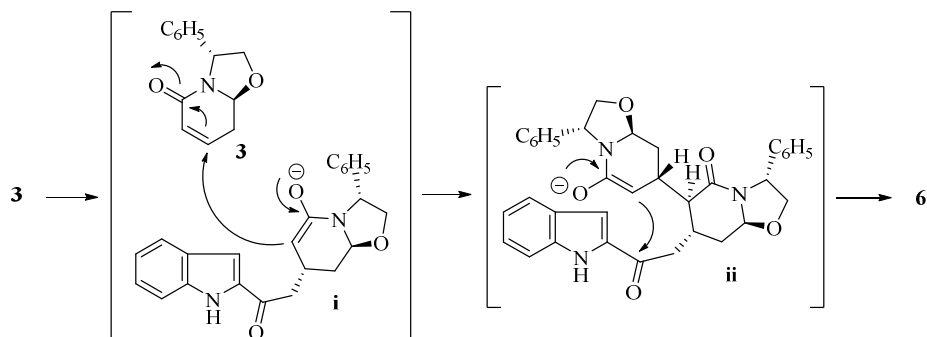
Scheme 3. Plausible mechanism for the formation of pentacyclic dilactam **6**.

The relative configuration of **6** was deduced from the ^{1}H- and ^{13}C-NMR data, with the aid of gCOSY, gHSQC (Figure 2) and NOESY experiments (Figure 3). Thus, the coupling constant (*J* 12 Hz) of the triplet at δ 2.05 attributable to 13a-H made evident the *trans* diaxial relationship of this proton with 7a-H and 13b-H. The axial disposition of 7a-H was confirmed from the multiplicity (quartet of triplets) of the signal at δ 2.20 attributable to this proton, which displays *trans* diaxial coupling constants (*J* 12 Hz) with 13a-H and the axial protons of the 7- and 8-positions. Finally, the small coupling constant (*J* 3.6 Hz) between 5a-H and 13b-H revealed a *cis* 5a-H/13b-H relationship. On the other hand, the positive NOE effects between 13a-H and 8a-H and 14a-H, as well as between the indole 3-proton and 5a-H and 7a-H are in good agreement with the stereochemical assignment depicted for **6**.
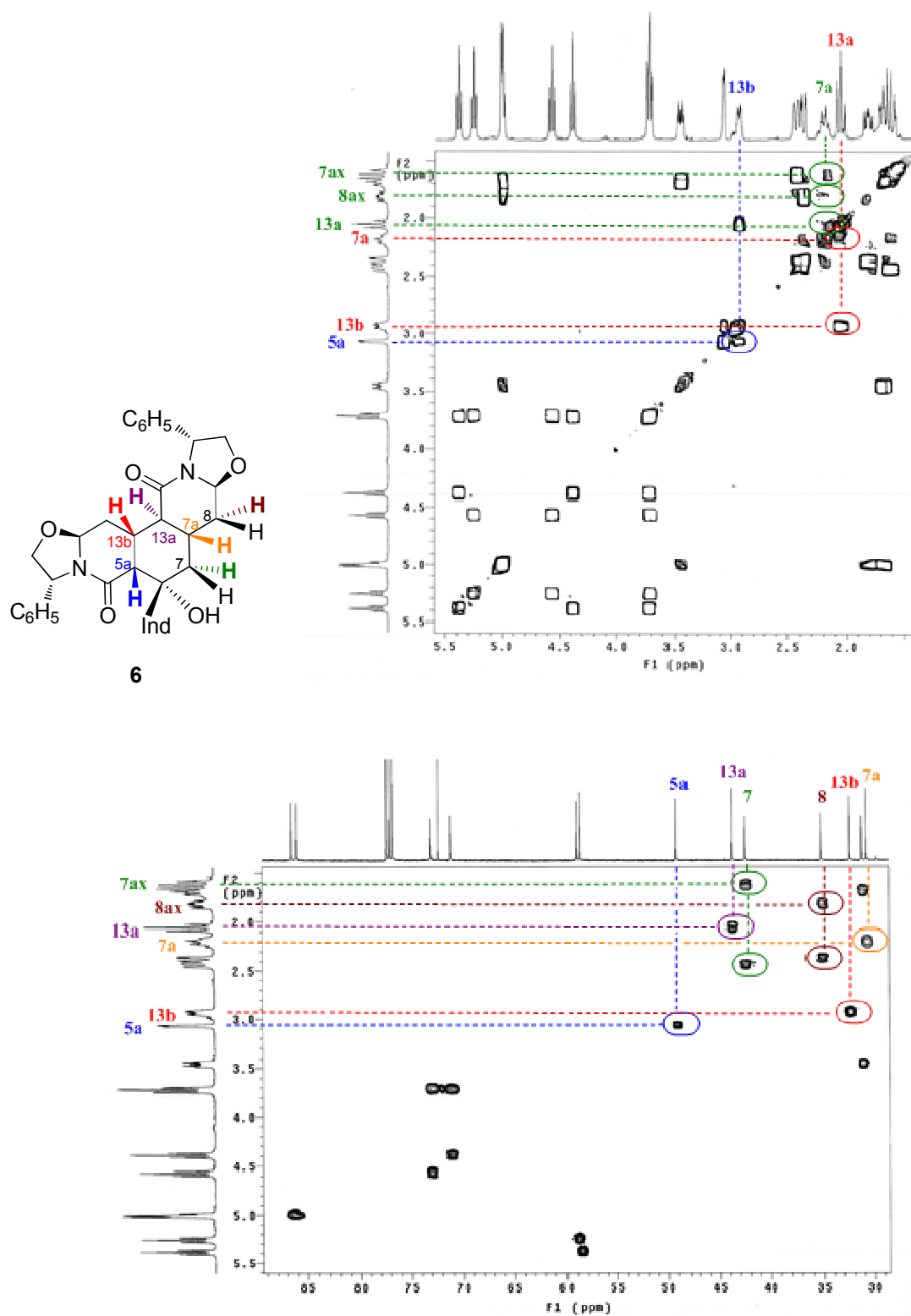
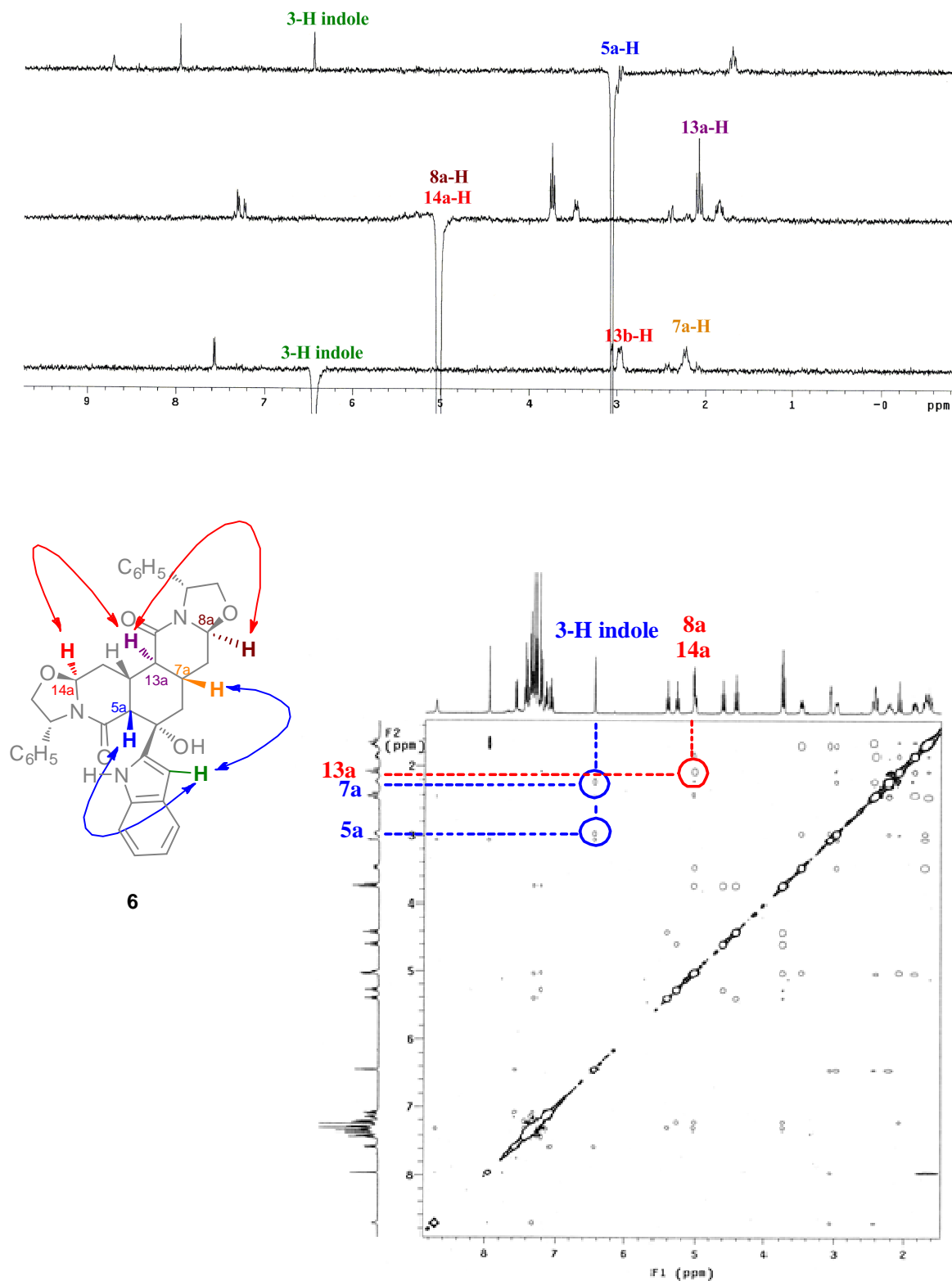**Figure 2.** gCOSY and gHSQC spectra of **6**.

Figure 3. NOESY(1D) and NOESY(2D) experiments with **6**.

A similar domino-type process, involving two successive *exo* conjugate additions followed by cyclization, was observed from oxazolopiperidone **4** (3,8a-*cis* series). The relative stereochemistry of the resulting pentacyclic dilactam **7** was established by NMR on the same grounds as in the above pentacycle **6**.
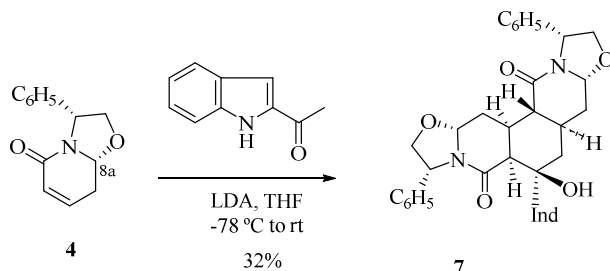

Scheme 4. Conjugate addition of 2-acetylindole enolate to unsaturated lactam **4**.

This stereochemical outcome of the above double conjugate additions is in sharp contrast with the *endo* facial selectivity observed in the conjugate addition of the 2-acetylindole enolate to the analogous ethyl-substituted lactam **1d**,[19] thus highlighting the dramatic influence exerted by the C-8 ethyl substituent on the stereoselectivity of the conjugate addition of stabilized anions to oxazolopiperidone lactams. Similar differences in stereoselectivity have been observed when lactams **1d** and **3** (or **4**)[16] undergo conjugate addition of 2-indoleacetate enolates: whereas the nucleophilic attack takes place on the *exo* face of **3** or **4**, leading to the kinetic products (Scheme 5), the conjugate addition to lactam **1d** occurs under thermodynamic control, with *endo* facial selectivity, to give the more stable *trans*-4,5-disubstituted 2-piperidone derivative.
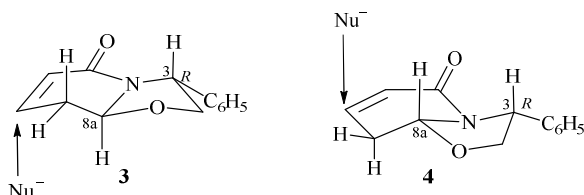
Scheme 5. Stereoelectronic control in the conjugate addition.

We then decided to study the conjugate addition to unsaturated lactam **10** (3,8a-*trans* series), which possesses the same configuration at C-8a as lactam **3** but incorporates a C-8 ethyl substituent. This new lactam was prepared in excellent yield from the known saturated lactam **8**,[21] by treatment with KH and methyl benzenesulfinate, followed by heating of the resulting sulfoxides **9** in toluene solution (Scheme 6).
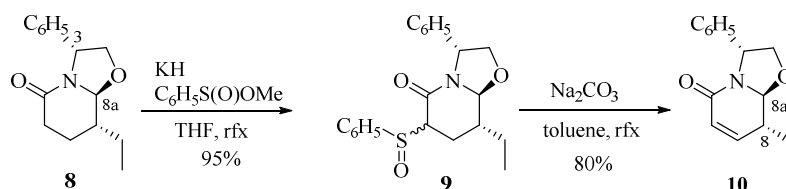
Scheme 6. Preparation of unsaturated oxazolopiperidone lactam **10**.

Rather surprisingly, in contrast with what was observed from 8-ethyl substituted lactam **1d** (3,8a-*cis* series), the double conjugate addition–cyclization cascade also occurred from lactam **10**, leading in excellent overall yield to two pentacyclic dilactams, alcohol **11a** (32%) and its dehydration product **11b** (48%) (Scheme 7).
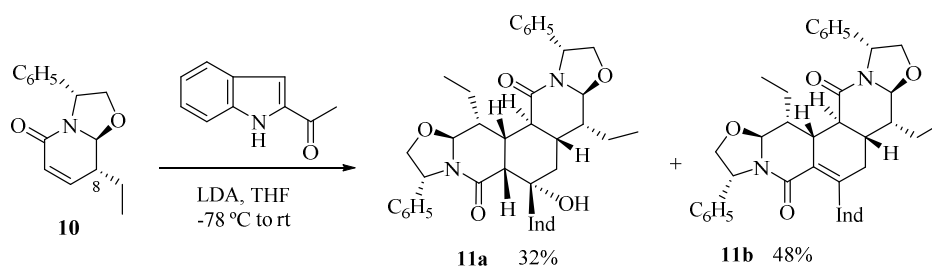
Scheme 7. Conjugate addition of 2-acetylindole enolate to unsaturated lactam **10**.

The results reported herein further illustrate how the outcome of conjugate addition reactions to phenylglycinol-derived unsaturated oxazolopiperidone lactams can be affected by a variety of factors, such as the nature of the nucleophile, the configuration of the stereocenter at the angular position (C-8a), the presence or absence of substituents on the piperidone ring, and the reaction conditions.[1]

Experimental Section

General. Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 35-70 µm). Melting points were taken with a Büchi apparatus. Optical rotations were measured on a 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}; Nicolet Avantar 320 FT-IR) are listed. NMR spectra were recorded with either a Varian Gemini-300 (300 and 75.4 MHz for ^{1}H and ^{13}C, respectively) or Mercury-400 (400 and 100.6 MHz for ^{1}H and ^{13}C, respectively) spectrometer.

Conjugate addition of 2-acetylindole to lactam 3. LDA (6.2 mL of a 1.5 M solution in cyclohexene, 9.3 mmol) was slowly added at –78 ºC to a solution of 2-acetylindole (740 mg, 4.65 mmol) in THF (28 mL), and the mixture was stirred at this temperature for 1 h. This solution was added via *cannula* to a solution of lactam **3**[22] (200 mg, 0.93 mmol) in THF (17 mL) at –78 ºC. The resulting mixture was stirred at room temperature for 20 h and poured into saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc, and the combined organic extracts were dried and concentrated. Flash chromatography (hexane to 4:1 hexane-EtOAc) of the resulting oil afforded **5** (64 mg, 17%) and **6** (86 mg, 30%).

(3*R*,7*R*,8a*S*)-7-[2-(2-Indolyl)-2-oxoethyl]-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (5). $[\alpha]^{25}_D$ –38.8 (*c* 0.18, $CHCl_3$). IR (film): 1649 (NCO) and 1734 (CO) cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz, gCOSY, gHSQC): δ_H 2.00-2.06 (m, 1H, H-8), 2.16-2.26 (m, 1H, H-8), 2.39 (dd, *J* 17.2, 6.4 Hz, 1H, H-6), 2.64 (dd, *J* 17.2, 4.8 Hz, 1H, H-6), 2.79-2.88 (m, 1H, H-7), 2.99-3.10 (m, 2H, C*H*₂CO), 3.77 (dd, *J* 8.4, 7.2 Hz, 1H, H-2), 4.48 (t, *J* 8.4 Hz, 1H, H-2), 5.08 (t, *J* 5.2 Hz, 1H, H-8a), 5.38 (t, *J* 7.2 Hz, 1H, H-3), 7.13-7.41 (m, 9H, ArH and H-ind), 7.69 (d, *J* 7.6 Hz, 1H, H-ind), 9.43 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ_C 26.5 (C-7), 32.0 (C-8), 37.8 (C-6), 42.1 (C-9), 58.1 (C-3), 71.9 (C-2), 86.1 (C-8a), 109.6 (C-3 ind), 112.3 (C-7 ind), 121.1 (C-5 ind), 123.1 (C-4 ind), 125.9 (C-*o*), 126.7 (C-6 ind), 127.4 (C-2 ind), 127.6 (C-*p*), 128.8 (C-*m*), 134.9 (C-*i*), 137.6 (C-3a ind), 139.7 (C-7a ind), 168.9 (NCO), 190.6 (CO). HMRS calcd for $[C_{23}H_{22}N_2O_3 + H]^+$: 375.1703, found: 375.1703.

(3*R*,5a*R*,6*S*,7a*S*,8a*S*,11*R*,13a*S*,13b*R*,14a*S*)-6-Hydroxy-6-(2-indolyl)-5,13-dioxo-3,11-diphenylperhydrodioxazolo[3,2-*b*][3',2'-*j*]-2,8-phenanthroline (6). $[\alpha]^{25}_D$ –48.2 (*c* 0.50, $CHCl_3$). IR (KBr): 1660 (NCO), 1735 (CO) and 2922 (OH) cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz, gCOSY, gHSQC): δ_H 1.62 (t, *J* 13.2 Hz, 1H, H-7), 1.68 (ddd, *J* 13.2, 10.0, 3.2 Hz, 1H, H-14), 1.82 (ddd, *J* 14.5, 12.0, 6.0 Hz, 1H, H-8), 2.05 (t, *J* 12.0 Hz, 1H, H-13a), 2.20 (qt, *J* 12.0, 12.0, 12.0, 3.6, 3.6 Hz, 1H, H-7a), 2.37 (dd, *J* 14.5, 3.6 Hz, 1H, H-8), 2.43 (dm, *J* 13.2 Hz, 1H, H-7), 2.93 (dm, *J* 11.6 Hz, 1H, H-13b), 3.06 (d, *J* 3.6 Hz, 1H, H-5a), 3.45 (td, *J* 13.2, 4.8, 4.8 Hz, 1H, H-14), 3.72 (2d, *J* 10.0 Hz, 2H, H-2 and H-10), 4.39 and 4.57 (t, *J* 8.4 Hz, 2H, H-2 and H-10), 4.98 and 5.01 (2d, *J* 7.2, 6.0 Hz, 2H, H-8a and H-14a), 5.26 and 5.39 (2t, *J* 8.0 Hz, 2H, H-3 and H-11), 6.43 (d, *J* 1.6 Hz, 1H, H-3 ind), 7.05-7.43 (m, 14H, ArH and H-ind), 7.98 (s, 1H, OH), 8.84 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ_C 30.7 (C-7a), 31.1 (C-14), 32.3 (C-13b), 35.0 (C-8), 42.3 (C-7), 43.6 (C-13a), 49.0 (C-5a), 58.6 and 58.9 (C-3 and C-11), 71.1 and 72.9 (C-2 and C-10), 72.2 (C-6), 85.9 and 86.4 (C-8a and C-14a), 100.5 (C-3 ind), 111.1 (C-7 ind), 119.8 (C-5 ind), 120.5 (C-4 ind), 122.2 (C-6 ind), 125.5 and 126.3 (C-*o*), 127.8 and 127.9 (C-*p*), 128.0 (C-3 ind), 128.8 and 129.1 (C-*m*), 135.4 (C-7a ind), 139.0 and 139.9 (C-*i*), 140.4 (C-2 ind), 170.6 and 171.8 (NCO). HMRS calcd for $[2C_{36}H_{35}N_3O_5 - 2H_2O + H]^+$: 1143.5015, found 1143.5029.

Conjugate addition of 2-acetylindole to lactam 4. Following the procedure described for the above conjugate addition, from a solution of 2-acetylindole (518 mg, 3.25 mmol) in THF (20 mL), LDA (4.33 mL of a 1.5 M solution in cyclohexene, 6.5 mmol) and lactam **4**[22] (140 mg,

0.65 mmol), pentacyclic lactam **7** (58 mg, 32%) was obtained after flash chromatography (4:1 hexane-EtOAc to EtOAc).

(3R,5aS,6R,7aR,8aR,11R,13aR,13bS,14aR)-6-Hydroxy-6-(2-indolyl)-5,13-dioxo-3,11-diphenylperhydrodioxazolo[3,2-b][3',2'-j]-2,8-phenanthroline (7). [α]$^{25}_D$ –3.9 (c 0.57, CHCl$_3$). IR (KBr): 1662 (NCO), 1727 (CO) and 2925 (NH) cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz, gCOSY, gHSQC): δ$_H$ 1.75-1.87 (m, 2H, H-14 and H-7), 1.98 (t, J 12.0 Hz, H-13a), 2.02-2.07 (m, 1H, H-8), 2.33-2.36 (m, 2H, H-7a and H-8), 2.43 (d, J 13.6 Hz, 1H, H-7), 2.80 (d, J 4.0 Hz, 1H, H-5a), 2.90 (ddd, J 12.0, 8.0, 3.6 Hz, 1H, H-13b), 3.53 (dt, J 13.2, 3.6 Hz, 1H, H-14), 4.03-4.25 (m, 4H, H-2 and H-10), 4.90 (d, J 6.4 Hz, 2H, H-3 and H-11), 4.97 (d, J 11.2, 4.0 Hz, 1H, H-8a), 5.12 (t, J 6.4 Hz, 1H, H-14a), 6.24 (s, 1H, H-3 ind), 6.98-7.47 (m, 14H, ArH and H-ind), 8.72 (s, 1H, OH), 9.26 (br s, 1H, NH). ^{13}C NMR (CDCl$_3$, 100.6 MHz): δ$_C$ 30.8 (C-14), 32.2 (C-7a), 32.5 (C-13b), 35.1 (C-8), 42.4 (C-13a), 43.4 (C-7), 49.8 (C-5a), 58.6 and 59.7 (C-3 and C-11), 72.3 (C-6), 74.2 and 74.3 (C-2 and C-10), 85.1 and 86.4 (C-8a and C-14a), 100.1 (C-3 ind), 110.9 (C-7 ind), 119.7 (C-5 ind), 120.4 (C-4 ind), 122.0 (C-6 ind), 126.1 and 126.2 (C-o), 128.0 (C-p), 128.1 (C-2 ind), 134.9 (C-7a ind), 140.7 (C-2 ind), 140.6 and 140.8 (C-i), 167.7 and 170.4 (NCO). HMRS calcd for [C$_{36}$H$_{35}$N$_3$O$_5$ – H$_2$O + H]$^+$: 572.2544, found 572.2537.

(3R,8R,8aS)-8-Ethyl-5-oxo-3-phenyl-2,3,8,8a-tetrahydro-5H-oxazolo[3,2-a]pyridine (10). Methyl benzenesulfinate (2.5 g, 16.02 mmol) and KH (2.0 g, 20-30 wt % dispersion in mineral oil) were added to a solution of lactam **8**^{21} (2.0 g, 8.16 mmol) in THF (80 mL). The suspension was heated at reflux for 3 h and concentrated. The resulting residue was taken up in 0.5 M aqueous H$_3$PO$_4$ and extracted with CH$_2$Cl$_2$. The combined organic extracts were dried and concentrated, and the resulting residue was washed with hexane and chromatographed (CH$_2$Cl$_2$) to give **(3R,8R,8aS)-8-ethyl-5-oxo-3-phenyl-6-(phenylsulfinyl)-2,3,6,7,8,8a-hexahydro-5H-oxazolo[3,2-a]pyridine** (**9**, 2.87 g, 95%) as a mixture of four isomers. IR (KBr, mixture of isomers): 1044 (SO) and 1652 (NCO) cm^{-1}. ^{1}H RMN (CDCl$_3$, 300 MHz, selected resonances): δ$_H$ 0.97 (t, J 7.5 Hz, 3H, CH$_3$ ethyl), 2.35 (ddd, J 13.8, 6.3, 2.7 Hz, 1H, H-6), 3.64 (dd, J 9.0, 7.8 Hz, 1H, H-2), 4.39 (dd, J 9.0, 7.8 Hz, 1H, H-2), 4.73 (d, J 8.7 Hz, 1H, H-8a), 5.14 (t, J 7.8 Hz, 1H, H-3). ^{13}C NMR (CDCl$_3$, 75.4 MHz, selected resonances): δ$_C$ 10.6 (CH$_3$ ethyl), 19.2 (CH$_2$ ethyl), 24.1 (C-7), 39.9 (C-8), 58.2 (C-3), 63.3 (C-6), 72.2 (C-2), 91.8 (C-8a), 138.3 and 141.2 (C-i), 163.4 (NCO). Na$_2$CO$_3$ (4.13 g, 39 mmol) was added to a solution of the above sulfoxide **9** (2.87 g, 7.77 mmol) in toluene (100 mL), and the mixture was heated at reflux for 10 h, filtered through Celite$^®$, and concentrated. The resulting oil was chromatographed (4:1 to 1:1 hexane-EtOAc) to afford lactam **10** (1.51 g, 80%): [α]$^{25}_D$ +4.9 (c 1.0, CHCl$_3$). IR (film): 1657 (NCO) cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz, gCOSY, HETCOR): δ$_H$ 1.08 (t, J 7.3 Hz, 3H, CH$_3$ ethyl), 1.52-1.64 (m, 1H, CH$_2$ ethyl), 1.77-1.86 (m, 1H, CH$_2$ ethyl), 2.47-2.53 (m, 1H, H-8), 3.88 (dd, J 8.7, 6.0 Hz, 1H, H-2), 4.47 (dd, J 8.7, 6.9 Hz, 1H, H-2), 5.08 (d, J 9.6 Hz 1H, H-8a), 5.24 (t, J 6.8 Hz, 1H, H-3), 5.97 (dd, J 10.0, 2.9 Hz, 1H, H-7), 6.35 (dd, J 10.0, 2.0 Hz, 1H, H-6), 7.26-7.34 (m, 5H, ArH). ^{13}C NMR (CDCl$_3$, 75.4 MHz): δ$_C$ 10.8 (CH$_3$ ethyl), 24.0 (CH$_2$ ethyl), 42.1 (C-8), 57.9 (C-3), 72.9 (C-2), 91.2 (C-8a), 124.8 (C-7), 125.9 (C-o), 127.5 (C-m), 128.6 (C-p),

139.1 (C-*i*), 139.9 (C-6), 160.6 (CO). Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76; O, 13.15. Found C, 73.95; H, 7.05; N, 5.69; O, 13.31.

Conjugate addition of 2-acetylindole to lactam 10. Following the procedure described in the above conjugate addition reactions, from a solution of 2-acetylindole (450 mg, 2.8 mmol) in THF (20 mL), LDA (3.7 mL of a 1.5 M solution in THF, 5.6 mmol) and lactam **10** (137 mg, 0.56 mmol) in THF (10 mL), compounds **11a** (59 mg, 32%) and **11b** (88 mg, 48%) were obtained after flash chromatography (9:1 to 4:1 hexane-EtOAc).

(3*R*,5a*R*,6*S*,7a*S*,8*R*,8a*S*,11*R*,13a*S*,13b*R*,14*R*,14a*S*)-8,14-Diethyl-6-hydroxy-6-(2-indolyl)-5,13 -dioxo-3,11-diphenylperhydrodioxazolo[3,2-*b*][3',2'-*j*]-2,8-phenanthroline (11a). $[\alpha]^{25}_D$ –28.6 (*c* 0.6, CHCl₃). IR (KBr): 1653 (NCO) and 2922 (OH) cm⁻¹. ¹H NMR (CDCl₃, 400 MHz, gCOSY, gHSQC): δ_H 0.72 and 0.92 (t, *J* 7.4 Hz, 6H, 2 CH₃ ethyl), 1.37-1.72 (m, 4H, 2CH₂ ethyl), 1.38 (m, 1H, H-8), 1.72 (m, 1H, H-7a), 1.94 (t, *J* 11.2 Hz, 1H, H-13a), 2.20 (t, *J* 12.0 Hz, 1H, H-7), 2.39 (dm, *J* 11.6 Hz, 1H, H-13b), 2.53 (br d, *J* 12.0 Hz, 1H, H-7), 3.16 (d, *J* 4.4 Hz, 1H, H-5a), 3.63 (m, 1H, H-14), 3.65 (t, *J* 8.8 Hz, 1H, H-2 or H-10), 3.90 (dd, *J* 9.0, 4.5 Hz, 1H, H-2 or H-10), 4.34 (t, *J* 8.8 Hz, 1H, H-2 or H-10), 4.39 (dd, *J* 9.0, 6.5 Hz, 1H, H-2 or H-10), 4.70 (d, *J* 8.4 Hz, 1H, H-8a or H-14a), 4.93 (d, *J* 6.0 Hz, 1H, H-8a or H-14a), 5.18 (t, *J* 8.0 Hz, 1H, H-3 or H-11), 5.21 (dd, *J* 6.5, 4.4 Hz, 1H, H-3 or H-11), 6.46 (d, *J* 1.6 Hz, 1H, H-3 ind), 7.09-7.37 (m, 13H, ArH and H-ind), 7.61 (d, *J* 8.0 Hz, 1H, H-ind), 8.71 (br s, 1H, NH). ¹³C NMR (CDCl₃, 100.6 MHz): δ_C 9.9 and 10.9 (2CH₃ ethyl), 20.4 and 26.3 (2CH₂ ethyl), 36.4 (C-7a), 38.6 (C-7), 39.6 (C-14), 41.5 (C-13b), 43.5 (C-8), 47.2 (C-13a), 48.0 (C-5a), 58.5 and 58.9 (C-3 and C-11), 71.8 and 72.3 (C-2 and C-10), 72.5 (C-6), 91.2 and 91.3 (C-8a and C-14a), 100.0 (C-3 ind), 111.3 (C-7 ind), 119.9 (C-5 ind), 120.4 (C-4 ind), 122.3 (C-6 ind), 126.1 and 126.2 (C-*o*), 127.6 and 127.8 (C-*p*), 127.9 (C-3a ind), 128.6 and 128.9 (C-*m*), 135.7 (C-2 ind), 138.9 and 139.1 (C-*i*), 140.9 (C-7a ind), 169.5 and 169.9 (NCO). HMRS calcd for $[C_{40}H_{43}N_3O_5 + H]^+$: 646.3275, found 646.3263.

(3*R*,7a*S*,8*R*,8a*S*,11*R*,13a*S*,13b*R*,14*R*,14a*S*)-8,14-Diethyl-6-(2-indolyl)-5,13-dioxo-3,11-diphenyl-2,3,5,7,7a,8,8a,10,11,13,13a,13b,14,14a-tetradecahydrodioxazolo[3,2-*b*][3',2'-*j*]-2,8-phenanthroline (11b). $[\alpha]^{25}_D$ –83.0 (*c* 0.3, CHCl₃). IR (KBr): 1662 (NCO) and 2922 (OH) cm⁻¹. ¹H NMR (CDCl₃, 400 MHz, gCOSY, gHSQC): δ_H 1.04 and 1.09 (2t, *J* 7.6 Hz, 6H, 2CH₃ ethyl), 1.58 (m, 1H, H-8), 1.62-1.81 (m, 2H, CH₂ ethyl), 1.90-2.03 (m, 2H, CH₂ ethyl), 1.87 (m, 1H, H-14), 2.39 (m, 1H, H-7), 2.44 (m, 1H, H-13a), 2.46 (dddd, *J* 12.0, 12.0, 7.2, 2.8 Hz, 1H, H-7a), 3.17 (dd, *J* 10.5, 7.0 Hz, 1H, H-13b), 3.31 (dd, *J* 16.0, 2.8 Hz, 1H, H-7), 3.74 (dd, *J* 8.0, 6.4 Hz, 1H, H-2 or H-10), 3.76 (dd, *J* 8.4, 6.0 Hz, 1H, H-2 or H-10), 4.55 (dd, *J* 8.0, 7.2 Hz, 1H, H-2 or H-10), 4.57 (dd, *J* 8.4, 6.8 Hz, 1H, H-2 or H-10), 4.81 (d, *J* 8.4 Hz, 1H, H-8a or H-14a), 4.82 (d, *J* 8.0 Hz, 1H, H-8a or H-14a), 5.26 (t, *J* 8.0 Hz, 1H, H-3 or H-11), 5.36 (t, *J* 8.0 Hz, 1H, H-3 or H-11), 6.75 (d, *J* 1.2 Hz, 1H, H-3 ind), 7.06-7.42 (m, 13H, ArH and H-ind), 7.59 (d, *J* 8.0 Hz, 1H, H-ind), 12.27 (br s, 1H, NH). ¹³C NMR (CDCl₃, 100.6 MHz): δ_C 10.6 and 13.4 (2CH₃ ethyl), 21.7 and 24.4 (2CH₂ ethyl), 33.2 (C-7), 35.2 (C-13a), 39.7 (C-13b), 44.7 (C-14), 45.3 (C-7a), 49.8 (C-8), 57.8 and 58.4 (C-3 and C-11), 73.1 and 73.2 (C-2 and C-10), 91.4 and 94.5 (C-

8a and C-14a), 104.4 (C-3 ind), 112.0 (C-7 ind), 119.7 (C-5 ind), 120.4 (C-4 ind), 123.3 (C-6 ind), 125.7 (C-*o*), 127.2 (C-2 ind), 127.4 (C-3a ind), 127.7 and 127.8 (C-*p*), 129.0 and 129.1 (C-*m*), 135.2 (C-7a ind), 136.0 (C-5a), 137.0 (C-6), 139.3 and 139.7 (C-*i*), 167.8 and 170.1 (NCO). HMRS calcd for $[C_{40}H_{41}N_3O_4 + H]^+$: 628.3170, found 628.3165.

Acknowledgements

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