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Conjugate Addition of 2-Acetylindole Enolates to Unsaturated Oxazolopiperidone Lactams. Enantioselective Access to the Tetracyclic Ring System of Ervitsine

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Dedicated to Prof. Carmen Nájera on the occasion of her 60th birthday

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The stereochemical outcome of the conjugate addition reactions of 2-acetylindole enolates to unsaturated phenylglycinol-derived oxazolopiperidone lactams **1a-f** is studied. After reduction of the 2-acylindole carbonyl group, the Michael adduct *cis*-**6** underwent a Lewis acid-promoted intramolecular α-amidoalkylation, enantioselectively leading to the tetracyclic ring system of the indole alkaloid ervitsine.

Introduction

Phenylglycinol-derived oxazolopiperidone lactams have proven to be versatile scaffolds that allow the regio- and stereocontrolled introduction of substituents at the different positions of the piperidine ring, thus providing access to enantiopure piperidines bearing virtually any type of substitution pattern and also to more complex piperidine-containing alkaloids, including indole alkaloids.[1] In particular, the stereoselective introduction of carbon appendages at the piperidine 4-position by conjugate addition reactions requires the activation of this position, which can be accomplished by generation of a conjugated carbon-carbon double bond taking advantage of the lactam carbonyl group.

In previous work we have exploited the conjugate addition of lower order alkyl- and arylcyanocuprates to unsaturated oxazolopiperidone lactams for the enantioselective synthesis of *cis*-2,4-[2] and *cis*-3,4-disubstituted piperidines,[3] as well as 2,4-bridged[2] and *cis*-3,4-fused piperidine[4] derivatives, including the antidepressant drug (–)-paroxetine[5] and synthetic intermediates en route to the indole alkaloid (–)-16-episilicine[6] and alkaloids of the madangamine group.[7]

Similarly, stereocontrolled conjugate addition reactions of sulfur-stabilized nucleophiles and indoleacetic ester enolates have been successfully employed as the key steps in enantioselective formal syntheses of uleine[8] and *Strychnos* alkaloids.[9,10]

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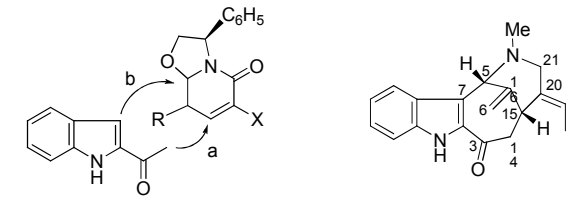
Results and Discussion

We report herein the conjugate addition of 2-acetylindole enolates to unsaturated phenylglycinol-derived oxazolopiperidone lactams and the subsequent construction of the tetracyclic framework of the indole alkaloid ervitsine by closure of the seven-membered ring by intramolecular α-amidoalkylation on the indole 3-position (Scheme 1).

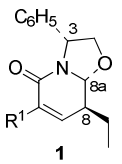


a) Stereoselective conjugate addition (bond formed: C^{14}–C^{15})
b) Intramolecular α-amidoalkylation (bond formed: C^{5}– C^{7})

Ervitsine (biogenetic numbering)

Scheme 1. Synthetic strategy.

As the starting unsaturated lactams we selected lactams **1a-f** (Figure 1 and Scheme 2), all of them bearing an ethyl substitutent at the 8-position of the oxazolopiperidone system. The preparation of 3,8a-*cis* lactams **1a-d**[3,6,8] has previously been reported. The new 3,8a-*trans* lactams **1e** and **1f** were prepared from the known lactams **2a**[11] and **2b**[11], via the respective seleno derivatives **3a** and **3b**, as outlined in Scheme 2.

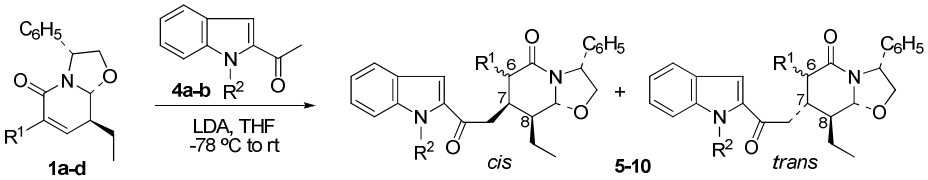


1

a R^1 = H
b R^1 = CO_2Bn
c R^1 = CO_2Me
d R^1 = CO_2tBu

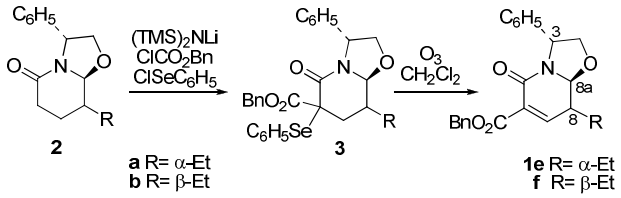
Figure 1. Unsaturated oxazolopiperidone lactams.

Table 1. Conjugate addition reactions of 2-acetylindoles to unsaturated lactams **1a-d**.



Entry	Lactam	Indole (equiv.)	Time	R^1	R^2	Product	H^7–H^8 *cis/trans* ratio	Yield (%)[a]
1	**1a**	**4a** (1.2)	16 h	H	Me	**5**	1:2	24
2	**1a**	**4b** (1.2)	10 h	H	H	**6**	1:3	30
3	**1a**	**4b** (2.5)	12 h	H	H	**6**	1:2.3	56
4	**1a**	**4b** (5.0)	24 h	H	H	**6**	1:2.3	68
5	**1a**	**4b** (5.0)	3 h	H	H	**6**	1:1.3	73
6	**1b**	**4a** (1.2)	23 h	CO_2Bn	Me	**7**	3:1	42
7	**1c**	**4b** (1.2)	16 h	CO_2Me	H	**8**	3:1	38
8	**1b**	**4b** (1.2)	16 h	CO_2Bn	H	**9**	4:1	46
9	**1b**	**4b** (5.0)	5h	CO_2Bn	H	**9**	4:1	90
10	**1d**	**4b** (5.0)	4 h	CO_2tBu	H	**10**	5:1	87

[a] For the relative configuration of the epimerizable C-6 stereocenter, see the Experimental Section



Scheme 2. Preparation of unsaturated lactams **1e** and **1f**.

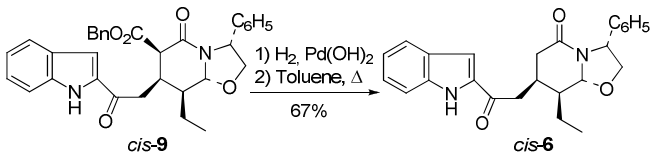
Table 1 summarizes the results obtained in the conjugate addition reactions of 2-acetylindole enolates **4a** and **4b** to unsaturated lactams **1a-d**. The initial experiments were carried out using the enolate of 2-acetyl-1-methylindole (**4a**). Starting from unsaturated lactam **1a**, which lacks the activating electron-withdrawing benzyloxycarbonyl group, the use of a slight excess (1.2 equiv.) of the nucleophile (entry 1) led to the expected adducts **5** in low yield (24%) as a 1:2 epimeric mixture of C-7/C-8 *cis/trans* isomers. A similar result was observed using the enolate of 2-acetylindole (**4b**): compound **6** was obtained in 30% yield as a C-7/C-8 *cis/trans* epimeric mixture in a 1:3 ratio (entry 2). The yield grew progressively higher as the excess of the nucleophile was increased (entries 3 and 4), reaching 68% when using 5 equiv. of enolate.

The relative configuration of the *cis* and *trans* isomers was evident from the shielding of the oxazolopiperidone 6-carbon in the ^{13}C NMR spectrum of *cis*-**6** (δ 37.9 ppm; compare with δ 42.0 ppm in *trans*-**6**) exerted by the axial ethyl substituent at C-8.

The facial selectivity of the conjugate addition reactions to lactam **1a** (R^1 = H) can be accounted for by considering that the addition of stabilized anions to α,β-unsaturated carbonyl compounds is a reversible process that in the case of 5-substituted 5,6-dihydro-2-pyridones leads to the thermodynamically more stable *trans*-4,5-disubstituted derivative.[12] Accordingly, in the reaction of lactam **1a** with acetylindole **4b** an increase of the ratio of the isomer *cis*-**6** was observed when the reaction was quenched after a short reaction time (Table 1, entry 5).

In clear contrast from the stereochemical standpoint, similar conjugate addition reactions from the activated lactams **1b-d**, which bear an additional activating alcoxycarbonyl substituent, led to the respective adducts **7**-**10** as diastereoisomeric mixtures in which the C-7/C-8 *cis* isomers predominated (entries 6-10).[13] As in the above lactam **1a**, the use of a 5 equiv. excess of nucleophile in these reactions resulted in higher yields, lactams **9** and **10** being formed in 90% (compare entries 8 and 9) and 87% yield (entry 10), respectively, even after shorter reaction times.

The C-7/C-8 *cis* relative configuration in the major isomer *cis*-**9** was confirmed by its conversion [H_2, $Pd(OH)_2$; then toluene at reflux] to *cis*-**6**, the minor isomer obtained from lactam **1a** (Scheme 3).



Scheme 3. Removal of the benzyloxycarbonyl substituent.

On the other hand, the predominance of the *cis* isomer in the conjugate addition to lactams **1b-d** (R^1 = CO_2R) can be rationalized by considering that in these cases the equilibration

takes place to a lesser extent as a consequence of the higher stability of the initially formed adduct (a 1,3-dicarbonyl enolate). The process would then occur mainly under stereoelectronic control,[14] which involves an axial approach of the nucleophile to the electrophilic carbon of the conjugate double bond from the *exo* face of the bicyclic system as depicted in Figure 2. In fact, irreversible conjugate additions (for instance, of organocuprates) to unsaturated oxazolopiperidone lactams (**1a-f** or related lactams) have been reported to occur under stereoelectronic control with complete *exo* facial selectivity. [15]

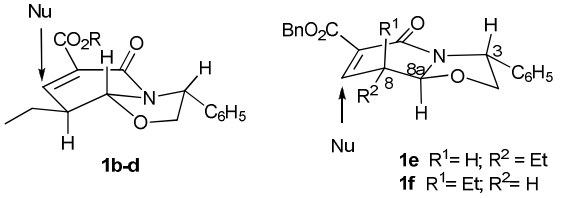
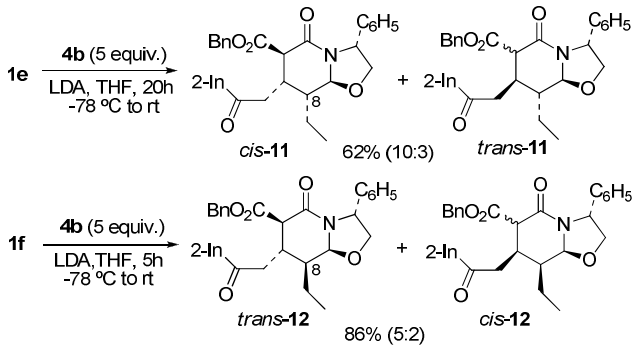


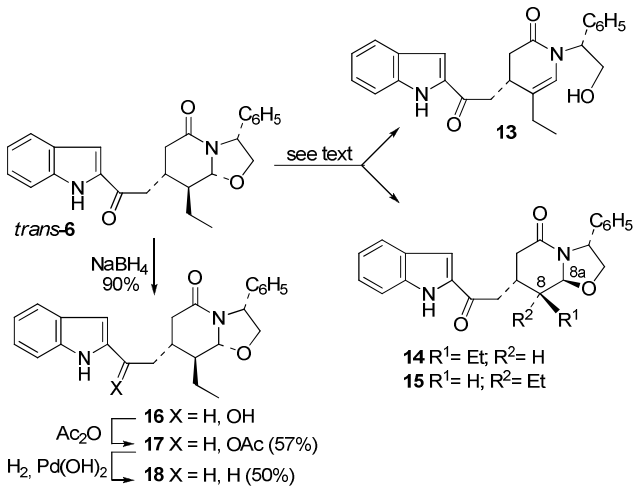
Figure 2. Stereoelectronic control in the conjugate addition.

A similar stereoelectronically controlled facial stereoselectivity was observed in the conjugate addition of the enolate of **4b** to the C-8 epimeric 3,8a-*trans* lactams **1e** and **1f** (Figure 2), the respective *exo* adducts *cis*-**11** and *trans*-**12** being formed as the major isomers (Scheme 4).



Scheme 4. Conjugate addition reactions of 2-acetylindole to unsaturated lactams **1e** and **1f**; In= indolyl.

To study the closure of the seven-membered ring characteristic of ervitsine, we initially selected lactam *trans*-**6**. However, all attempts to promote the cyclization under a variety of acidic conditions ($TiCl_4$, CH_2Cl_2, reflux; $BF_3{\cdot}Et_2O$, CH_2Cl_2, reflux; HCl, MeOH or C_6H_6) resulted in failure. Enamide **13**[16] and the 8a-epimer (**14**) and the 8,8a-diastereoisomer (**15**) of *trans*-**6** were the only isolable products (Scheme 5).[17] The stereochemistry of **14** and **15** was confirmed when these compounds were unambiguously prepared from *trans*-**12** and *cis*-**11**, respectively, by debenzylation [H_2, $Pd(OH)_2$] followed by decarboxylation.



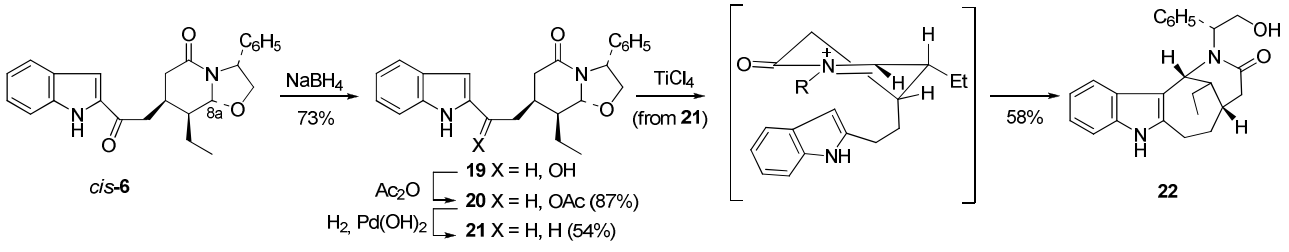
Scheme 5.

Taking into account that the isolation of compounds **13**-**15** clearly indicated that the *N*-acyl iminium cation[18] had been formed, the failure of the cyclization was attributed to the deactivating effect of the carbonyl group conjugated with the indole ring. For this reason, acylindole *trans*-**6** was converted to alcohol **16** and then to the indolylethyl derivative **18** by hydrogenolysis of the corresponding acetate **17**.

The desired cyclization upon the indole 3-position did not occur from **16** or **18** either, under a variety of acidic conditions, only extensive decomposition being observed.

Bearing in mind that the closure of the seven-membered ring of ervitsine and analogs has been successfully achieved by a related intramolecular iminium ion cyclization,[19] at this point we reasoned that conformational factors could be responsible for the reluctance of the above C-7/C-8 *trans* derivatives to undergo intramolecular α-amidoalkylation: cyclization would involve an encumbered conformation in which both C-7 and C-8 substituents should be axial. To confirm this hypothesis, we decided to study related α-amidoalylation reactions from C-7/C-8 *cis* lactams.

However, no cyclized products were detected upon treatment of *cis*-**6** with $TiCl_4$, the 8a-epimer of *cis*-**6** being the only isolable product.[20] As in the above C-7/C-8 *trans* series, 2-acylindole *cis*-**6** was reduced to alcohol **19**, and then converted to indolylethyl derivative **21** via the corresponding acetate **20** (Scheme 6).



Scheme 6. Access to the tetracyclic ring system of ervitsine.

Although alcohol **19** underwent extensive decomposition upon acidic treatment, to our delight, when the reduced derivative **21** was treated with $TiCl_4$ in refluxing CH_2Cl_2, tetracycle **22** was isolated in 58% yield.

Conclusions

In conclusion, conjugate addition reactions of 2-acetylindole enolates to phenylglycinol-derived unsaturated δ-lactams allow the stereocontrolled formation of C–C bonds at the piperidine 4-position. Depending on the absence or presence of an additional electron-withdrawing substituent conjugated with the C–C double bond, the reaction predominantly leads to either *trans*- or *cis*-4,5-disubtituted enantiopure 2-piperidone derivatives, respectively.

The synthetic potential of the resulting Michael adducts has been demonstrated with the enantioselective construction of the tetracyclic ring system of ervitsine, a minor indole alkaloid isolated from *Pandaca boiteaui*[21] that lacks the characteristic tryptamine moiety present in most monoterpenoid indole alkaloids. Starting from an appropriate lactam bearing a C-8 substituent precursor of the exocyclic methylene group, the strategy developed here, involving a stereoselective conjugate addition and an intramolecular α-amidoalkylation as the key steps (see Scheme 1), may be applied to the enantioselective synthesis of ervitsine.[22]

Experimental Section

General: Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 0.04-0.06 mm) or (when indicated) using a cartridge containing amine functionalized silica. Optical rotations were measured on Perkin-Elmer 241 polarimeter. High resolution mass spectra (HMRS; LC/MSD TOF Agilent Technologies) were performed by *Serveis Científico-Tècnics*, 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 at 200, 300, 400 or 500 MHz (^1H) and 75.4, 100.6 or 125.9 MHz (^{13}C).

(3*R*,8*R*,8a*S*)-6-(Benzyloxycarbonyl)-8-ethyl-5-oxo-3-phenyl-6-(phenylselenyl)-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (3a): Lithium bis(trimethylsilyl)amide (9.4 mL of a 1.0 M solution in THF, 9.4 mmol) was slowly added at −78 ºC to a solution of lactam **2a**[11] (1.08 g, 4.24 mmol) in anhydrous THF (50 mL), and the resulting mixture was stirred for 90 min. Then, benzyl chloroformate (710 μL, 4.24 mmol) and, after 2 h of continuous stirring at −78 ºC, a solution of C_6H_5SeCl (1.14 g, 5.09 mmol) in anhydrous THF (5 mL) were added. The mixture was stirred for 2 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 the corresponding selenides **3a** as a mixture of C-6 epimers (1.40 g, 62%). Data for **3a**: Orange oil. ^1H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 0.74 (t, *J* = 7.5 Hz, 3H, CH_3 ethyl), 0.80 (t, *J* = 7.3 Hz, 3H, CH_3 ethyl), 1.12-1.18 (m, 1H, CH_2 ethyl), 1.12-1.22 (m, 1H, CH_2 ethyl), 1.57-1.95 (m, 3H, CH_2 ethyl, H-7, H-8), 1.61-1.72 (m, 2H, CH_2 ethyl, H-8), 1.83-2.00 (m, 2H, H-7), 2.33 (dd, *J* = 13.8, 2.1 Hz, 1H, H-7), 3.71 (dd, *J* = 9.0, 7.8 Hz, 1H, H-2), 3.78 (dd, *J* = 9.0, 7.5 Hz, 1H, H-2), 4.34 (d, *J* = 8.1 Hz, 1H, H-8a), 4.37 (dd, *J* = 9.0, 7.5 Hz, 1H, H-2), 4.46 (dd, *J* = 9.0, 7.8 Hz, 1H, H-2), 4.67 (d, *J* = 7.8 Hz, 1H, H-8a), 5.20 (d, *J* = 6.9 Hz, 1H, C*H*$_2$C$_6$H$_5$), 5.20 (s, 2H, C*H*$_2$C$_6$H$_5$), 5.24 (d, *J* = 6.9 Hz, 1H, C*H*$_2$C$_6$H$_5$), 5.25 (d, *J* = 7.8 Hz, 1H, H-3), 5.30 (t, *J* = 7.5 Hz, 1H, H-3), 7.18-7.70 (m, 30H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 10.5, 10.7 (CH_3 ethyl), 23.7, 24.0 (CH_2 ethyl), 32.5, 35.2 (C-7), 37.8, 39.3 (C-8), 54.2, 55.6 (C-6), 58.8 (C-3), 67.7, 67.8 (*C*H$_2$C$_6$H$_5$), 72.1, 72.3 (C-2), 92.0, 92.3 (C-8a), 125.7, 126.1 (C-*o*), 126.6, 126.7 (C-*m*), 127.3, 127.5 (C-*p*), 127.9, 128.0 (C-*o*), 128.0, 128.1 (C-*p*), 128.3, 128.4 (C-*m*), 128.5, 128.6 (C-*o*), 128.7, 128.8 (C-*m*), 129.3, 129.5 (C-*i*), 135.0, 135.1 (C-*i*), 138.0 (C-*p*), 138.5, 138.7 (C-*i*), 164.5, 164.9 (NCO), 169.9, 170.9 (COO) ppm.

(3*R*,8*S*,8a*S*)-6-(Benzyloxycarbonyl)-8-ethyl-5-oxo-3-phenyl-6-(phenylselenyl)-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (3b): Operating as in the above preparation of **3a**, from lactam **2b**[11] (2 g, 7.90 mmol) in THF (100 mL), LiHMDS (17.3 mL of a 1.0 M solution in THF), benzyl chloroformate (1.2 mL, 8.6 mmol), and C_6H_5SeCl (1.70 g, 8.80 mmol) in THF (20 mL), a mixture of C-6 epimeric selenides (3.46 g, 82%) was obtained. Pure isomers were isolated after a subsequent flash chromatography (hexane to 9:1 hexane–EtOAc). Data for **3b** (higher R_f epimer): Orange oil; $[\alpha]^{22}_D$ = – 84.0 (*c* = 0.5, $CHCl_3$). IR (film): ν = 1664, 1724 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 0.82 (t, *J* = 7.5 Hz, 3H, CH_3 ethyl), 1.29-1.38 (m, 1H, CH_2 ethyl), 1.53-1.63 (m, 1H, CH_2 ethyl), 1.72-1.81 (m, 1H, H-8), 1.88-2.02 (m, 1H, H-7), 1.99 (dd, *J* = 12.9, 5.1 Hz, 1H, H-7), 3.73 (dd, *J* = 8.7, 6.9 Hz, 1H, H-2), 4.45 (t, *J* = 8.7 Hz, 1H, H-2), 4.60 (d, *J* = 5.4 Hz, 1H, H-8a), 5.09 (d, *J* = 12.3 Hz, 1H, C*H*$_2$C$_6$H$_5$), 5.32 (d, *J* = 12.3 Hz, 1H, C*H*$_2$C$_6$H$_5$), 5.56 (t, *J* = 8.1 Hz, 1H, H-3), 7.13-7.55 (m, 15H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 ºC): δ = 11.4 (CH_3 ethyl), 23.3 (CH_2 ethyl), 33.6 (C-7), 35.9 (C-8), 54.2 (C-6), 58.1 (C-3), 67.4 (*C*H$_2$C$_6$H$_5$), 70.8 (C-2), 87.8 (C-8a), 125.6 (C-*o*), 126.7 (C-*m*), 127.3 (C-*p*), 128.1 (C-*o*), 128.2 (C-*m*), 128.4 (C-*p*), 128.6 (C-*o*), 129.5 (C-*m*), 135.2 (C-*p*), 138.5 (C-*i*), 139.5 (C-*i*), 167.1 (NCO), 169.4 (COO) ppm. $C_{29}H_{29}NO_4Se$ (534.51): calcd. C 65.17, H 5.47, N 2.62; found C 65.19, H 5.58, N 2.54. Data for **3b** (lower R_f epimer): Orange oil; $[\alpha]^{22}_D$ = – 22.0 (*c* = 0.5, $CHCl_3$). IR (film): ν = 1661, 1732 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 0.81 (t, *J* = 7.5 Hz, 3H, CH_3 ethyl), 1.12-1.23 (m, 1H, CH_2 ethyl), 1.55-1.67 (m, 1H, CH_2 ethyl), 2.04 (dd, *J* = 15.0, 4.2 Hz, 1H, H-7), 2.22-2.28 (m, 1H, H-8), 2.56 (dd, *J* = 15.0, 6.6 Hz, 1H, H-7), 3.84 (dd, *J* = 8.7, 6.3 Hz, 1H, H-2), 4.34 (dd, *J* = 8.7, 7.5 Hz, 1H, H-2), 4.85 (d, *J* = 4.8 Hz, 1H, H-8a), 5.18 (s, 2H, C*H*$_2$C$_6$H$_5$), 5.35 (t, *J* = 6.8 Hz, 1H, H-3), 7.06-7.47 (m, 15H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 ºC): δ = 11.6 (CH_3 ethyl), 18.7 (CH_2 ethyl), 32.5 (C-7), 37.2 (C-8), 52.7 (C-6), 58.6 (C-3), 67.9 (*C*H$_2$C$_6$H$_5$), 71.6 (C-2), 89.0 (C-8a), 126.5 (C-*o*), 126.7 (C-*m*), 127.6 (C-*p*), 128.1 (C-*o*), 128.4 (CHAr), 128.7 (CHAr), 129.4 (CHAr), 135.2 (C-*i*), 137.7 (C-*i*), 139.2 (C-*i*), 165.1 (NCO), 170.2 (COO) ppm. $C_{29}H_{29}NO_4Se$ (534.51): calcd. C 65.17, H 5.47, N 2.62; found C 64.81, H 5.64, N 2.64.

(3*R*,8*R*,8a*S*)-6-(Benzyloxycarbonyl)-8-ethyl-5-oxo-3-phenyl-3,5,8,8a-tetrahydro-5*H*-oxazolo[3,2-*a*]pyridine (1e): A stream of ozone gas was bubbled through a cooled (−78 ºC) solution of the selenides **3a** (161 mg, 0.30 mmol) in anhydrous CH_2Cl_2 (50 mL) until it turned pale blue (5 min). Then, the solution was purged with O_2, and the temperature was slowly raised to 25 ºC. After 30

min of stirring, the mixture was poured intro brine, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated to give unsaturated lactam **1e**, which due to its instability was used in the next reaction without further purification. Data for **1e**: Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 1.10 (t, *J* = 7.5 Hz, 3H, CH_3 ethyl), 1.57-1.66 (m, 1H, CH_2 ethyl), 1.81-1.90 (m, 1H, CH_2 ethyl), 2.53-2.61 (m, 1H, H-8), 3.94 (dd, *J* = 9.0, 6.0 Hz, 1H, H-2), 4.44 (dd, *J* = 9.0, 6.9 Hz, 1H, H-2), 5.10 (d, *J* = 9.3 Hz, 1H, H-8a), 5.26 (d, *J* = 5.3 Hz, 1H, C*H*$_2$C$_6$H$_5$), 5.29 (m, 1H, H-3), 5.30 (d, *J* = 5.3 Hz, 1H, C*H*$_2$C$_6$H$_5$), 7.19-7.40 (m, 11H, H-7, ArH) ppm.

(3*R*,8*S*,8a*S*)-6-(Benzyloxycarbonyl)-8-ethyl-5-oxo-3-phenyl-3,5,8,8a-tetrahydro-5*H*-oxazolo[3,2-*a*]pyridine (1f): Operating as in the above preparation of **1e**, from a mixture of selenides **3b** (246 mg, 0.46 mmol) in CH_2Cl_2 (15 mL), unsaturated lactam **1f** (173 mg, 0.46 mmol) was obtained, which due to instability was used in the next reaction without further purification. Data for **1f**: Orange oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 0.99 (t, *J* = 7.5 Hz, 3H, CH_3 ethyl), 1.38-1.48 (m, 1H, CH_2 ethyl), 1.83-1.92 (m, 1H, CH_2 ethyl), 2.76-2.81 (m, 1H, H-8), 4.00 (dd, *J* = 8.4, 5.7 Hz, 1H, H-2), 4.47 (dd, *J* = 8.4, 6.9 Hz, 1H, H-2), 5.22-5.26 (m, 3H, C*H*$_2$C$_6$H$_5$, H-3), 5.50 (d, *J* = 5.4 Hz, 1H, H-8a), 7.24-7.62 (m, 11H, H-7, ArH) ppm.

General Procedure for the Conjugate Addition Reactions: LDA was added to a cooled (–78 ºC) solution of 2-acetylindole (**4a** or **4b**) in THF, and the mixture was stirred at this temperature for 1 h. Then, a solution of unsaturated lactam **1** in THF was added to the solution (–78 ºC). The resulting mixture was stirred at room temperature until the disappearance of the starting material was observed by TLC. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and the mixture was extracted with EtOAc. The combined extracts were dried and concentrated to give a residue, which was purified by chromatography.

(3*R*,7*R*,8*S*,8a*R*)-8-Ethyl-7-[2-(1-methyl-2-indolyl)-2-oxoethyl]-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (*trans*-5) and its 7*S* epimer (*cis*-5): Operating as described in the general procedure, from lactam **1a**[3b,8] (200 mg, 0.82 mmol) in THF (30 mL), LDA (0.65 mL of a solution 1.5 M in cyclohexane, 0.98 mmol), and a solution of indole **4a** (170 mg, 0.98 mmol) in 30 mL of THF for 16 h, compound **5** was obtained as a mixture of C-7 epimers. Flash chromatography (from 1:1 to 3:7 hexane–EtOAc) afforded *trans*-**5** (53 mg, 16%) and *cis*-**5** (27 mg, 8%). Data for *trans*-**5:** Yellow foam; $[\alpha]^{22}_D$ = − 13.0 (*c* = 0.5, $CHCl_3$). IR (film): ν = 1644, 1661 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 1.07 (t, *J* = 7.4 Hz, 3H, CH_3 ethyl), 1.65-1.89 (m, 3H, CH_2 ethyl, H-8), 2.16 (dd, *J* = 18.2, 9.2 Hz, 1H, H-6), 2.50-2.60 (m, 2H, H-6, H-7), 2.87 (dd, *J* = 16.2, 7.6 Hz, 1H, CH_2CO), 3.10 (dd, *J* = 16.2, 5.2 Hz, 1H, CH_2CO), 4.05 (s, 3H, NCH_3), 4.09 (d, *J* = 9.0 Hz, 1H, H-2), 4.18 (dd, *J* = 9.0, 6.8 Hz, 1H, H-2), 4.73 (d, *J* = 7.6 Hz, 1H, H-8a), 4.96 (dd, *J* = 6.8, 1.2 Hz, 1H, H-3), 7.11 (s, 1H, H-3 ind), 7.13-7.20 (m, 1H, H-7 ind), 7.26-7.40 (m, 7H, H-5, H-6 ind, ArH), 7.67 (dd, *J* = 8.2, 1.2 Hz, 1H, H-4 ind) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 10.2 (CH_3 ethyl), 22.7 (CH_2 ethyl), 32.2 (C-7), 37.5 (C-6), 43.7 (*C*H$_2$CO), 44.8 (C-8), 58.4 (C-3), 73.9 (C-2), 91.1 (C-8a), 110.3 (C-3 ind), 111.8 (C-7 ind), 120.7 (C-4 ind), 122.9 (C-6 ind), 125.6 (C-5 ind), 126.2 (C-2 ind), 126.7 (C-*o*), 128.6 (C-*m*), 127.6 (C-*p*), 134.7 (C-*i*), 140.2 (C-3a ind), 141.2 (C-7a ind), 166.7 (NCO), 192.0 (CO) ppm. HRMS calcd. for $C_{26}H_{29}N_2O_3$ [M+ H]$^+$: 417.2178; found 417.2172. Data for *cis*-**5**: Yellow foam. ^{1}H NMR (200 MHz, $CDCl_3$, 25 ºC): δ = 1.11 (t, *J* = 7.4 Hz, 3H, CH_3 ethyl), 1.38-1.63 (m, 1H, CH_2 ethyl), 1.87-2.06 (m, 2H, CH_2 ethyl, H-8), 2.33-2.48 (m, 2H, H-6, H-7), 2.94-3.03 (m, 3H, 2CH_2CO, H-6), 4.06-4.22 (m, 2H, H-2), 4.08 (s, 3H, NCH_3), 4.68 (d, *J* = 9.6 Hz, 1H, H-8a), 4.94 (d, *J* = 5.8 Hz, 1H, H-3), 7.12-7.43 (m, 9H, ArH, H-ind), 7.69 (d, *J* = 8.0 Hz, 1H, H-4 ind) ppm.

(3*R*,7*R*,8*S*,8a*R*)-8-Ethyl-7-[2-(2-indolyl)-2-oxoethyl]-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (*trans*-6) and its 7*S* epimer (*cis*-6): Table 1, entry 4: Operating as described in the general procedure, from unsaturated lactam **1a**[3b,8] (400 mg, 1.64 mmol) in THF (30 mL), LDA (11 mL of a solution 1.5 M in cyclohexane, 16.5 mmol), a solution of 2-acetylindole **4b** (1.3 g, 8.2 mmol) in 50 mL of THF for 24 h, compound **6** was obtained as a mixture of C-7 epimers. Flash chromatography (from 1:1 to 3:7 hexane–EtOAc) afforded *trans*-**6** (316 mg, 48%) and *cis*-**6** (132 mg, 20%). Table 1, entry 5: Operating as above, from lactam **1a** (296 mg, 1.21 mmol) and acetylindole **4b** (970 mg, 6.12 mmol) for 3 h, pure lactams *trans*-**6** (201 mg, 42 %) and *cis*-**6** (150 mg, 31 %) were obtained after flash chromatography. Data for *trans*-**6**: Yellow foam. $[\alpha]^{22}_D$ = − 7.0 (*c* =0.5, $CHCl_3$). IR (film): ν = 1657, 1735, 3312 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 1.04 (t, *J* = 7.2 Hz, 3H, CH_3 ethyl), 1.64-1.88 (m, 3H, CH_2 ethyl, H-8), 2.16 (dd, *J* = 16.5, 7.6 Hz, 1H, CH_2CO), 2.57 (m, 1H, H-7), 2.68 (dd, *J* = 16.5, 6.0 Hz, 1H, H-6), 2.79 (dd, *J* = 16.5, 9.2 Hz, 1H, CH_2CO), 3.00 (dd, *J* = 16.5, 4.5 Hz, 1H, H-6), 4.10 (dd, *J* = 9.0, 1.2 Hz, 1H, H-2), 4.18 (dd, *J* = 9.0, 6.6 Hz, 1H, H-2), 4.71 (d, *J* = 8.1 Hz, 1H, H-3), 4.98 (d, *J* = 5.7 Hz, 1H, H-8a), 6.87 (d, *J* = 1.5 Hz, 1H, H-3 ind), 7.04-7.08 (m, 1H, H-6 ind), 7.18-7.25 (m, 1H, H-5 ind), 7.28-7.41 (m, 7H, ArH, H-4 ind), 10.05 (s, 1H, NH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 ºC): δ = 10.1 (CH_3 ethyl), 22.4 (CH_2 ethyl), 30.8 (C-7), 37.2 (*C*H$_2$CO), 42.0 (C-6), 44.6 (C-8), 58.3 (C-3), 73.8 (C-2), 90.7 (C-8a), 109.3 (C-3 ind), 112.5 (C-7 ind), 120.3 (C-4 ind), 122.6 (C-6 ind), 125.8 (C-5 ind), 126.7 (C-*o*), 127.0 (C-3a ind), 127.5 (C-*m*), 128.5 (C-*p*), 135.0 (C-7a ind), 137.7 (C-*i*), 141.3 (C-2 ind), 167.2 (NCO), 190.4 (CO) ppm. $C_{25}H_{26}N_2O_3$·1/4 EtOAc (424.52): calcd. C 73.56, H 6.65, N 6.60; found C 73.77, H 6.63, N 6.47. Data for *cis*-**6**: Yellow foam. $[\alpha]^{22}_D$ = − 70.4 (*c* = 0.5, $CHCl_3$). IR (film): ν = 1657, 1735, 3325 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 1.10 (t, *J* = 7.3 Hz, 3H, CH_3 ethyl), 1.45-1.54 (m, 1H, CH_2 ethyl), 1.89-2.03 (m, 2H, CH_2 ethyl, H-8), 2.45 (m, 2H, CH_2CO), 3.00 (m, 3H, 2H-6, H-7), 4.04 (dd, *J* = 9.3, 4.3 Hz, 1H, H-2), 4.18 (dd, *J* = 9.3, 6.9 Hz, 1H, H-2), 4.68 (d, *J* = 9.3 Hz, 1H, H-3), 4.94 (d, *J* = 5.7 Hz, 1H, H-8a), 6.87 (d, *J* = 1.5 Hz, 1H, H-3 ind), 7.11-7.36 (m, 9H, ArH, H ind), 7.68 (dd, *J* = 8.1, 0.9 Hz, 1H, H-4 ind), 9.50 (s, 1H, NH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 ºC): δ = 11.3 (CH_3 ethyl), 21.2 (CH_2 ethyl), 29.0 (C-7), 36.5 (*C*H$_2$CO), 37.9 (C-6), 43.6 (C-8), 59.4 (C-3), 73.8 (C-2), 90.2 (C-8a), 109.4 (C-3 ind), 112.4 (C-7 ind), 120.8 (C-4 ind), 122.8 (C-6 ind), 126.2 (C-5 ind), 126.3 (C-*o*), 127.2 (C-3a ind), 127.4 (C-*m*), 128.4 (C-*p*), 135.0 (C-7a ind), 137.6 (C-*i*), 141.3 (C-2 ind), 166.8 (NCO), 190.7 (CO) ppm. $C_{25}H_{26}N_2O_3$·1/2 H_2O (411.19): calcd. C 73.78, H 6.56, N 6.88; found C 73.40, H 6.27, N 6.98.

(3*R*,6*R*,7*R*,8*S*,8a*R*)-6-(Benzyloxycarbonyl)-8-ethyl-7-[2-(1-methyl-2-indolyl)-2-oxoethyl]-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (*cis*-7): Operating as

described in the general procedure**,** from the crude of unsaturated lactam **1b**[3a] (500 mg, 1.32 mmol) in THF (10 mL), LDA (0.8 mL of a solution 2.0 M in THF–ether, 1.6 mmol), and a solution of indole **4a** (274 mg, 1.58 mmol) in 20 mL of THF for 23 h, compound **7** was obtained as a mixture of diastereoisomers. Flash chromatography (from 9:1 to 1:1 hexane–EtOAc) afforded *cis*-**7** (228 mg, 32%) and *trans*-**7** (mixture of C-6 epimers; 76 mg, 10%). Data for *cis*-**7**: Yellow foam. $[\alpha]^{22}_D$ = − 69.8 (*c* = 1.0, $CHCl_3$). IR (film): ν = 1660, 1735 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 1.02 (t, *J* = 7.5 Hz, 3H, CH_3 ethyl), 1.40-1.50 (m, 1H, CH_2 ethyl), 1.85-1.94 (m, 1H, CH_2 ethyl), 2.42-2.51 (m, 1H, H-8), 2.95 (dd, *J* = 16.2, 11.1 Hz, 1H, CH_2CO), 3.13 (dd, *J* = 16.2, 2.4 Hz, 1H, CH_2CO), 3.15-3.19 (m, 1H, H-7), 3.45 (d, *J* = 0.3 Hz, 1H, H-6), 4.01-4.12 (m, 1H, H-2), 4.05 (s, 3H, NCH_3), 4.18 (dd, *J* = 9.0, 6.9 Hz, 1H, H-2), 4.67 (d, *J* = 9.6 Hz, 1H, H-8a), 4.95 (t, *J* = 5.7 Hz, 1H, H-3), 5.06 (d, *J* = 12.3 Hz, 1H, C*H*$_2C_6H_5$), 5.13 (d, *J* = 12.3 Hz, 1H, C*H*$_2C_6H_5$), 7.15-7.40 (m, 14H, ArH, H-ind), 7.68 (dd, *J* = 7.8 Hz, 1H, H-ind) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 ºC): δ = 11.1 (CH_3 ethyl), 20.8 (CH_2 ethyl), 32.2 (NCH_3), 33.1 (C-7), 37.4 (*C*H_2CO), 40.2 (C-8), 53.4 (C-6), 59.7 (C-3), 66.9 (*C*$H_2C_6H_5$), 74.0 (C-2), 90.3 (C-8a), 110.5 (C-3 ind), 114.4 (C-7 ind), 120.9 (C-5 ind), 122.9 (C-4 ind), 125.6 (CAr), 126.3 (CHAr), 126.4 (CHAr), 127.5 (CAr), 127.8 (CHAr), 128.0 (CAr), 128.4 (CHAr), 128.5 (CHAr), 134.5 (C-*i*), 135.6 (C-2 ind), 140.3 (C-3a ind), 140.6 (C-7a ind), 162.1 (NCO), 169.5 (COO), 190.8 (CO) ppm. $C_{34}H_{34}N_2O_5 \cdot 1/3$ EtOAc (579.73): calcd. C 73.18, H 6.37, N 4.83; found C 72.97, H 6.24, N 5.06.

(3*R*,6*S*,7*R*,8*S*,8a*R*)-8-Ethyl-7-[2-(2-indolyl)-2-oxoethyl]-6-(metoxycarbonyl)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (*cis*-8) and its 6*R*,7*S* diastereoisomer (*trans*-8): Operating as described in the general procedure, from the crude of unsaturated lactam **1c**[3a] (657 mg, 2.18 mmol) in THF (10 mL), LDA (3.84 mL of a solution 1.5 M in THF, 5.76 mmol), and a solution of 2-acetylindole **4b** (417 mg, 2.61 mmol) in 30 mL of THF for 16 h, compound **8** was obtained as a mixture of diastereoisomers. Flash chromatography (hexane to 9:1 hexane–EtOAc) afforded *cis*-**8** (290 mg, 29%) and *trans*-**8** (90 mg, 9%). Data for *cis*-**8**: Yellow foam. $[\alpha]^{22}_D$ = − 65.3 (*c* = 1.0, $CHCl_3$). IR (film): ν = 1655, 1736, 3324 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 1.11 (t, *J* = 7.6 Hz, 3H, CH_3 ethyl), 1.44-1.54 (m, 1H, CH_2 ethyl), 1.89-1.99 (m, 1H, CH_2 ethyl), 2.46-2.55 (m, 1H, H-8), 2.93 (dd, *J* = 16.2, 11.1 Hz, 1H, CH_2CO), 3.12 (dd, *J* = 16.2, 2.7 Hz, 1H, CH_2CO), 3.17-3.21 (m, 1H, H-7), 3.41 (d, *J* = 10.5 Hz, 1H, H-6), 3.60 (s, 3H, OCH_3), 4.06 (dd, *J* = 9.0, 1.5 Hz, 1H, H-2), 4.20 (dd, *J* = 9.0, 7.2 Hz, 1H, H-2), 4.68 (d, *J* = 9.9 Hz, 1H, H-8a), 4.97 (dd, *J* = 7.2, 1.5 Hz, 1H, H-3), 7.13-7.40 (m, 9H, ArH, H-ind), 7.68 (dd, *J* = 8.1, 0.9 Hz, 1H, H-4 ind), 9.27 (s, 1H, NH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 ºC): δ = 11.2 (CH_3 ethyl), 20.0 (CH_2 ethyl), 33.4 (C-7), 35.8 (*C*H_2CO), 40.1 (C-8), 52.4 (C-6), 53.1 (OCH_3), 59.7 (C-3), 74.0 (C-2), 90.3 (C-8a), 109.6 (C-3 ind), 112.5 (C-7 ind), 121.0 (C-4 ind), 122.9 (C-5 ind), 126.5 (C-6 ind), 126.6 (C-*o*), 127.3 (C-2 ind), 127.5 (C-*m*), 128.3 (C-*p*), 134.8 (C-*i*), 137.7 (C-3a ind), 140.6 (C-7a ind), 162.4 (NCO), 170.2 (COO), 190.1 (CO) ppm. $C_{27}H_{28}N_2O_5 \cdot 1/2$ EtOAc (504.58): calcd. C 69.03, H 6.39, N 5.55; found C 68.99, H 6.16, N 5.59. Data for *trans*-**8**: Yellow foam. $[\alpha]^{22}_D$ = + 3.6 (*c* = 1.0, $CHCl_3$). IR (film): ν = 1656, 1737, 3310 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 1.11 (t, *J* = 7.5 Hz, 3H, CH_3 ethyl), 1.63-1.75 (m, 1H, CH_2 ethyl), 1.75-1.87 (m, 1H, CH_2 ethyl), 1.96-2.01 (m, 1H, H-8), 2.89-2.98 (m, 1H, H-7), 3.02-3.06 (m, 2H, CH_2CO), 3.52 (d, *J* = 7.2 Hz, 1H, H-6), 3.69 (s, 3H, OCH_3), 4.12 (dd, *J* = 9.3, 1.2 Hz, 1H, H-2), 4.21 (dd, *J* = 9.3, 6.6 Hz, 1H, H-2), 4.83 (d, *J* = 8.4 Hz, 1H, H-8a), 4.98-5.00 (m, 1H, H-3), 7.01 (d, *J* = 1.8 Hz, 1H, H-3 ind), 7.11-7.45 (m, 8H, ArH, H-ind), 7.66 (d, *J* = 8.1 Hz, 1H, H-4 ind), 9.32 (s, 1H, NH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 ºC): δ = 10.3 (CH_3 ethyl), 23.1 (CH_2 ethyl), 33.7 (C-7), 41.1 (*C*H_2CO), 44.7 (C-8), 52.6 (OCH_3), 54.9 (C-6), 59.0 (C-3), 73.8 (C-2), 90.4 (C-8a), 109.6 (C-3 ind), 112.3 (C-7 ind), 120.9 (C-4 ind), 122.9 (C-5 ind), 126.8 (C-6 ind), 126.6 (C-*o*), 127.3 (C-2 ind), 127.5 (C-*p*), 128.5 (C-*m*), 134.8 (C-*i*), 137.6 (C-3a ind), 140.8 (C-7a ind), 162.7 (NCO), 170.0 (COO), 190.1 (CO) ppm. $C_{27}H_{28}N_2O_5 \cdot 3/4$ H_2O (474.04): calcd. C 68.41, H 6.27, N 5.91; found C 68.12, H 6.10, N 5.64.

(3*R*,6*R*,7*R*,8*S*,8a*R*)-6-(Benzyloxycarbonyl)-8-ethyl-7-[2-(2-indolyl)-2-oxoethyl]-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (*cis*-9) and its 6*S*,7*S* diastereoisomer (*trans*-9): Operating as described in the general procedure**,** from the crude of unsaturated lactam **1b**[3a] (1.55 g, 4.11 mmol) in THF (50 mL), LDA (27.4 mL of a solution 1.5 M in THF, 41.1 mmol), and a solution of 2-acetylindole **4b** (3.27 g, 20.5 mmol) in 100 mL of THF for 5 h, compound **9** was obtained as a mixture of diastereoisomers. Flash chromatography (hexane to 1:1 hexane–EtOAc) afforded *cis*-**9** (accompanied by trace amounts of the C-6 epimer; 1.53 g, 69%) and *trans*-**9** (457 mg, 21%). Data for *cis*-**9**: Yellow foam. $[\alpha]^{22}_D$ = − 87.0 (*c* = 0.2, $CHCl_3$). IR (film): ν = 1655, 1735, 3320 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 1.02 (t, *J* = 7.6 Hz, 3H, CH_3 ethyl), 1.40-1.50 (m, 1H, CH_2 ethyl), 1.83-1.94 (m, 1H, CH_2 ethyl), 2.42-2.51 (m, 1H, H-8), 2.92 (dd, *J* = 16.2, 11.1 Hz, 1H, CH_2CO), 3.10 (dd, *J* = 16.2, 2.7 Hz, 1H, CH_2CO), 3.16 (m, 1H, H-7), 3.47 (d, *J* = 1.2 Hz, 1H, H-6), 4.03 (dd, *J* = 9.0, 1.5 Hz, 1H, H-2), 4.19 (dd, *J* = 9.0, 7.2 Hz, 1H, H-2), 4.67 (d, *J* = 9.6 Hz, 1H, H-8a), 4.97 (dd, *J* = 7.2, 1.5 Hz, 1H, H-3), 5.03 (d, *J* = 16.8 Hz, 1H, C*H*$_2C_6H_5$), 5.08 (d, *J* = 16.8 Hz, 1H, C*H*$_2C_6H_5$), 7.12-7.41 (m, 14H, ArH), 7.69 (dd, *J* = 8.4, 1.2 Hz, 1H, H-4 ind), 9.22 (s, 1H, NH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 ºC): δ = 11.1 (CH_3 ethyl), 20.7 (CH_2 ethyl), 33.4 (C-7), 35.8 (*C*H_2CO), 40.1 (C-8), 53.1 (C-6), 59.5 (C-3), 66.7 (*C*$H_2C_6H_5$), 73.8 (C-2), 90.0 (C-8a), 109.3 (C-3 ind), 112.6 (C-7 ind), 120.6 (C-2 ind), 122.5 (C-6 ind), 126.1 (C-5 ind), 126.2 (C-4 ind), 126.9, 127.2, 127.5, 127.7, 127.9, 128.1 (C-*o*, *m*, *p*), 134.6 (C-3a ind), 135.2 (C-7a ind), 140.5 (C-*i*), 137.7 (C-*i*), 162.2 (COO), 169.2 (NCO), 189.9 (CO) ppm. $C_{33}H_{32}N_2O_5 \cdot 1/4$ EtOAc (558.65): calcd. C 73.10, H 6.13, N 5.01; found C 73.08, H 6.00, N 4.99. Data for *trans*-**9**: Yellow foam. ^1H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 0.99 (t, *J* = 7.6 Hz, 3H, CH_3 ethyl), 1.71-2.04 (m, 3H, CH_2 ethyl, H-8), 2.87-3.18 (m, 3H, 2CH_2CO, H-7), 3.56 (d, *J* = 5.6 Hz, 1H, H-6), 4.01-4.20 (m, 2H, H-2), 4.71 (d, *J* = 8.4 Hz, 1H, H-8a), 4.97 (d, *J* = 6.0 Hz, 1H, H-3), 5.09 (d, *J* = 11.6 Hz, 1H, C*H*$_2C_6H_5$), 5.14 (d, *J* = 11.6 Hz, 1H, C*H*$_2C_6H_5$), 6.95 (d, *J* = 1.6 Hz, 1H, H-3 ind), 7.12-7.41 (m, 13H, ArH), 7.65 (d, *J* = 7.6 Hz, 1H, H-4 ind), 9.09 (bs, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 10.4 (CH_3 ethyl), 23.1 (CH_2 ethyl), 34.9 (C-7), 41.1 (*C*H_2CO), 44.7 (C-8), 55.0 (C-6), 58.9 (C-3), 67.3 (*C*$H_2C_6H_5$), 73.8 (C-2), 90.4 (C-8a), 109.7 (C-3 ind), 112.3 (C-7 ind), 120.9 (C-2 ind), 123.0 (C-6 ind), 126.4 (C-5 ind), 126.5 (C-4 ind), 126.9-128.6 (C-*o*, *m*, *p*), 134.8 (C-3a ind), 137.5 (C-7a ind), 140.6 (C-*i*), 140.8 (C-*i*), 162.7 (COO), 169.9 (NCO), 190.0 (CO) ppm.

(3*R*,6*R*,7*R*,8*S*,8a*R*)-6-(*tert*-Butoxycarbonyl)-8-ethyl-7-[2-(2-indolyl)-2-oxoethyl]-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (*cis*-10): Operating as described in the general procedure**,** from crude unsaturated lactam **1d**[6] (1.0 g, 2.90 mmol) in THF (50 mL), LDA (19.5 mL of a solution 1.5 M in cyclohexane, 29 mmol), and a solution of 2-acetylindole **4b** (2.3 g, 14.5 mmol) in 100 mL of THF for 4 h, compound **10** was obtained as a mixture of diastereoisomers. Flash chromatography (hexane to 1:1 hexane–EtOAc) afforded *cis*-**10** (1.17 g, 80%) and *trans*-**10** (mixture of C-6 epimers; 230 mg, 7%). Data for *cis*-**10**: Yellow foam. $[\alpha]^{22}_{D} = -21.5$ (*c* = 0.2, $CHCl_3$). IR (KBr): ν = 1662, 1728, 2958 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 1.11 (t, *J* = 7.6 Hz, 3H, CH_3 ethyl), 1.34 [s, 9H, $(CH_3)_3C$], 1.43-1.52 (m, 1H, CH_2 ethyl), 1.88-1.96 (m, 1H, CH_2 ethyl), 2.56 (ddd, *J* = 13.6, 9.2, 4.8 Hz, 1H, H-8), 2.91 (dd, *J* = 16.0, 10.8 Hz, 1H, CH_2CO), 3.08 (dd, *J* = 16.0, 2.4 Hz, 1H, CH_2CO), 3.20 (m, 1H, H-7), 3.30 (s, 1H, H-6), 4.04 (d, *J* = 8.4 Hz, 1H, H-2), 4.19 (dd, *J* = 8.4, 7.2 Hz, 1H, H-2), 4.66 (d, *J* = 9.6 Hz, 1H, H-8a), 4.97 (d, *J* = 6.4 Hz, 1H, H-3), 7.12-7.40 (m, 9H, ArH), 7.68 (d, *J* = 8.4 Hz, 1H, H-4 ind), 9.36 (bs, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 11.2 (CH_3 ethyl), 20.8 (CH_2 ethyl), 27.8 [C(*C*H_3)$_3$], 32.9 (C-7), 36.0 (*C*H_2CO), 40.3 (C-8), 54.4 (C-6), 59.6 (C-3), 74.1 (C-2), 81.9 [*C*$(CH_3)_3$], 90.3 (C-8a), 109.5 (C-3 ind), 112.3 (C-7 ind), 121.0 (C-5 ind), 123.0 (C-6 ind), 126.5 (C-*o*), 126.6 (C-2 ind), 127.4 (C-*m*), 128.4 (C-*p*), 134.9 (C-3a ind), 137.5 (C-7a ind), 140.8 (C-*i*), 162.5 (NCO), 168.3 (COO), 190.1 (CO) ppm. HRMS calcd. for $C_{30}H_{35}N_2O_5$ [M + H]$^+$: 503.2540; found 503.2541.

(3*R*,6*R*,7*S*,8*R*,8a*S*)-6-(Benzyloxycarbonyl)-8-ethyl-7-[2-(2-indolyl)-2-oxoethyl]-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (*cis*-11): Operating as described in the general procedure**,** from crude unsaturated lactam **1e** (161 mg, 0.43 mmol) in THF (10 mL), LDA (2.86 mL of a solution 1.5 M in THF, 4.3 mmol), and a solution of 2-acetylindole **4b** (342 mg, 2.15 mmol) in 15 mL of THF for 20 h, compound **11** was obtained as a mixture of diastereoisomers. Flash chromatography (9:1 hexane–EtOAc to EtOAc) afforded *cis*-**11** (110 mg, 48%) and *trans*-**11** (1:1 mixture of C-6 epimers; 32 mg, 14%). Data for *cis*-**11**: Yellow foam. $[\alpha]^{22}_{D} = -101.1$ (*c* = 1.2, $CHCl_3$). IR (KBr): ν = 1656, 1735 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 0.98 (t, *J* = 7.5 Hz, 3H, CH_3 ethyl), 1.61 (m, 1H, CH_2 ethyl), 1.76 (m, 1H, CH_2 ethyl), 1.91 (m, 1H, H-8), 2.91 (m, 1H, H-7), 3.12 (dd, *J* = 5.4, 2.4 Hz, 2H, CH_2CO), 3.67 (d, *J* = 9.3 Hz, 1H, H-6), 3.73 (dd, *J* = 9.0, 7.8 Hz, 1H, H-2), 4.49 (dd, *J* = 9.0, 7.8 Hz, 1H, H-2), 4.93 (d, *J* = 8.4 Hz, 1H, H-8a), 5.04 (d, *J* = 12.3 Hz, 1H, C*H*$_2$C$_6$H$_5$), 5.13 (d, *J* = 12.3 Hz, 1H, C*H*$_2$C$_6$H$_5$), 5.29 (t, *J* = 7.8 Hz, 1H, H-3), 7.12-7.37 (m, 14H, ArH, H-ind), 7.67 (d, *J* = 8.1 Hz, 1H, H-4 ind), 9.21 (bs, 1H, NH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 ºC): δ = 9.9 (CH_3 ethyl), 21.5 (CH_2 ethyl), 33.4 (C-7), 38.6 (*C*H_2CO), 40.3 (C-8), 55.4 (C-6), 58.7 (C-3), 67.4 (*C*$H_2C_6H_5$), 72.6 (C-2), 90.6 (C-8a), 109.4 (C-3 ind), 112.3 (CHind), 121.0 (CHind), 123.1 (CHind), 125.7 (CHAr), 126.5 (CHAr), 127.4 (C-*i*), 127.6 (CHAr), 128.0 (CHAr), 128.2 (CHAr), 128.4 (CHAr), 128.8 (CHAr), 134.8 (C-*i*), 135.2 (C-2 ind), 137.4 (C-3a ind), 138.6 (C-7a), 164.1 (NCO), 170.1 (COO), 190.0 (CO) ppm. $C_{33}H_{32}N_2O_5$ (536.62): calcd. C 73.86, H 6.01, N 5.22; found C 73.46, H 6.08, N 5.34.

[3*R*,6*R*(and 6*S*),7*S*,8*S*,8a*S*]-6-(Benzyloxycarbonyl)-8-ethyl-7-[2-(2-indolyl)-2-oxoethyl]-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (*trans*-12): Operating as described in the general procedure**,** from the crude of unsaturated lactam **1f** (1 g, 2.65 mmol) in THF (50 mL), LDA (26.5 mL of a solution 1 M in THF, 26.5 mmol), and a solution of 2-acetylindole **4b** (2.11 g, 13.25 mmol) in 100 mL of THF for 5 h, compound **12** was obtained as a mixture of diastereoisomers. Flash chromatography (9:1 hexane–EtOAc to EtOAc) afforded *trans*-**12** (9:1 mixture of C-6 epimers; 1.02 g, 72%) and *cis*-**12** (mixture of C-6 epimers; 211 mg, 14%). Data for *trans*-**12** (major 6*S*-epimer): Yellow foam. IR (film): ν = 1655, 1736, 3324 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 0.95 (t, *J* = 7.2 Hz, 3H, CH_3 ethyl), 1.26-1.41 (m, 1H, CH_2 ethyl), 1.64-1.71 (m, 1H, CH_2 ethyl), 2.23-2.31 (m, 1H, H-8), 2.98-3.04 (m, 1H, H-7), 3.09 (dd, *J* = 12.4, 6.0 Hz, 1H, CH_2CO), 3.13 (dd, *J* = 12.4, 6.4 Hz, 1H, CH_2CO), 3.66 (d, *J* = 8.8 Hz, 1H, H-6), 3.86 (dd, *J* = 8.8, 6.8 Hz, 1H, H-2), 4.45 (dd, *J* = 8.8, 8.0 Hz, 1H, H-2), 5.09 (d, *J* = 9.2 Hz, 1H, H-8a), 5.16 (d, *J* = 12.5 Hz, 1H, C*H*$_2$C$_6$H$_5$), 5.19 (d, *J* = 12.5 Hz, 1H, C*H*$_2$C$_6$H$_5$), 5.33 (t, *J* = 7.6 Hz, 1H, H-3), 7.10 (d, *J* = 1.4 Hz, 1H, H-3 ind), 7.15-7.42 (m, 13H, ArH, H-ind), 7.69 (t, *J* = 8.0 Hz, 1H, H-ind), 9.09 (bs, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 11.3 (CH_3 ethyl), 19.9 (CH_2 ethyl), 33.1 (C-7), 40.5 (*C*H_2CO), 42.1 (C-8), 53.8 (C-6), 58.8 (C-3), 67.2 (*C*$H_2C_6H_5$), 72.3 (C-2), 88.0 (C-8a), 109.5 (C-3 ind), 112.2 (C-7 ind), 121.1 (C-4 ind), 123.2 (C-5 ind), 125.6 (C-6 ind), 126.3, 126.7, 127.8, 128.1, 128.3, 128.4, 128.8, (C-*o*, C-*m*, C-*p*, C-3a ind), 134.7 (C-2 ind), 135.5 (C-7a ind), 139.1 (C-*i*), 166.0 (NCO), 169.6 (COO), 190.3 (CO) ppm. HRMS calcd. for $C_{33}H_{32}N_2NaO_5$ [M + Na]$^+$: 559.2203; found 559.2207. Data for *trans*-**12** (minor 6*R*-epimer): ^1H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 1.00 (t, *J* = 7.4 Hz, 3H, CH_3 ethyl), 1.30-1.42 (m, 2H, CH_2 ethyl), 3.15-3.20 (m, 2H, H-7, H-8), 3.25 (dd, *J* = 16.0, 7.2 Hz, 1H, CH_2CO), 3.30 (dd, *J* = 16.0, 5.6 Hz, 1H, CH_2CO), 3.74 (dd, *J* = 8.7, 7.6 Hz, 1H, H-2), 3.78 (d, *J* = 5.6 Hz, 1H, H-6), 4.52 (t, *J* = 8.4 Hz, 1H, H-2), 5.07 (d, *J* = 12.4 Hz, 1H, C*H*$_2$C$_6$H$_5$), 5.13 (d, *J* = 12.4 Hz, 1H, C*H*$_2$C$_6$H$_5$), 5.16 (masked, 1H, H-8a), 5.38 (t, *J* = 7.6 Hz, 1H, H-3), 7.00 (d, *J* = 1.4 Hz, 1H, H-3 ind), 7.10-7.42 (m, 13H, ArH, H-ind), 7.68 (t, *J* = 8.6 Hz, 1H, H-ind), 9.07 (bs, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 11.6 (CH_3 ethyl), 19.5 (CH_2 ethyl), 32.0 (C-7), 38.4 (*C*H_2CO), 39.6 (C-8), 50.5 (C-6), 58.1 (C-3), 67.3 (*C*$H_2C_6H_5$), 71.9 (C-2), 87.6 (C-8a), 109.5 (C-3 ind), 112.2 (C-7 ind), 121.1 (C-4 ind), 123.2 (C-5 ind), 125.6 (C-6 ind), 126.6, 127.5, 128.4, 128.5, 128.6, 128.8, 128.9 (C-*o*, C-*m*, C-*p*, C-3a ind), 135.1 (C-2 ind), 134.8 (C-7a ind), 137.3 (C-*i*), 164.8, (NCO), 169.2 (COO), 190.1.

Conversion of *cis*-9 to *cis*-6: A solution of *cis*-**9** (200 mg, 0.43 mmol) in EtOAc (10 mL) containing $Pd(OH)_2$ (20 mg) was hydrogenated with vigorous stirring at room temperature and atmospheric pressure for 24 h. The catalyst was removed by filtration, and the solvent was evaporated to give an oil, which was dissolved in toluene (30 mL). The resulting solution was heated at reflux for 16 h and concentrated to dryness. The residue was chromatographed (4:1 hexane–EtOAc to EtOAc) to give *cis*-**6** (97 mg, 65%).

(3*R*,7*R*,8*S*,8a*S*)-8-Ethyl-7-[2-(2-indolyl)-2-oxoethyl]-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (14): Operating as above, from *trans*-**12** (900 mg, 1.68 mmol), 30% $Pd(OH)_2$ (270 mg) in EtOAc (50 mL), and then refluxing in toluene (100 mL), compound **14** was obtained (452 mg, 67%) after column chromatography (hexane to 1:1 hexane–EtOAc). Data for **14**: Yellow foam. $[\alpha]^{22}_{D} = -21.6$ (*c* = 0.5, $CHCl_3$). IR (KBr): 1649,

3312 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 1.01 (t, *J* = 7.4 Hz, 3H, CH_3 ethyl), 1.21-1.28 (m, 1H, CH_2 ethyl), 1.71-1.79 (m, 1H, CH_2 ethyl), 2.18 (ddd, *J* = 14.0, 6.0, 4.8 Hz, 1H, H-8), 2.36 (dd, *J* = 18.4, 3.2 Hz, 1H, CH_2CO), 2.63 (dd, *J* = 18.4, 6.4 Hz, 1H, CH_2CO), 2.84 (m, 1H, H-7), 3.09-3.11 (m, 2H, H-6), 3.79 (dd, *J* = 8.8, 7.6 Hz, 1H, H-2), 4.48 (t, *J* = 8.8 Hz, 1H, H-2), 5.23 (d, *J* = 4.4 Hz, 1H, H-8a), 5.30 (t, *J* = 7.6 Hz, 1H, H-3), 7.14-7.41 (m, 9H, ArH), 7.69 (d, *J* = 8.0 Hz, 1H, H-4 ind), 9.35 (bs, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 11.6 (CH_3 ethyl), 18.7 (CH_2 ethyl), 29.6 (C-7), 33.7 (*C*H_2CO), 40.7 (C-8), 41.9 (C-6), 58.3 (C-3), 72.2 (C-2), 88.0 (C-8a), 109.5 (C-3 ind), 112.3 (C-7 ind), 121.1 (C-5 ind), 123.1 (C-6 ind), 126.0 (C-*o*), 126.7 (C-2 ind), 127.7 (C-*m*), 128.9 (C-*p*), 134.9 (C-3a ind), 137.5 (C-7a ind), 139.6 (C-*i*), 168.1 (NCO), 190.7 (CO) ppm. HRMS cald. for $C_{25}H_{27}N_2O_3$ $[M + H]^+$: 403.2016; found: 403.2014.

(3*R*,7*R*,8*R*,8a*S*)-8-Ethyl-7-[2-(2-indolyl)-2-oxoethyl)]-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (15): Operating as above, from *cis*-**11** (620 mg**,** 1.15 mmol), 20% $Pd(OH)_2$ (124 mg) in MeOH (40 mL), and then refluxing in toluene (70 mL), compound **15** was obtained (288 mg, 62%) after column chromatography (hexane to 1:1 hexane–EtOAc). Data for **15**: Yellow foam. $[\alpha]^{22}_D = -74.7$ (*c* = 0.67, $CHCl_3$). IR (KBr): ν = 1648 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 1.08 (t, *J* = 7.6 Hz, 3H, CH_3 ethyl), 1.45-1.54 (m, 1H, CH_2 ethyl), 1.75-1.90 (m, 2H, CH_2 ethyl, H-8), 2.54-2.66 (m, 2H, H-6, H-7), 2.90 (m, 1H, H-6), 2.97 (d, *J* = 11.8 Hz, 1H, CH_2CO), 3.08 (d, *J* = 11.8 Hz, 1H, CH_2CO), 3.80 (t, *J* = 8.4 Hz, 1H, H-2), 4.56 (t, *J* = 8.4 Hz, 1H, H-2), 4.78 (d, *J* = 9.2 Hz, 1H, H-8a), 5.35 (t, *J* = 8.0 Hz, 1H, H-3), 7.12-7.41 (m, 9H, ArH, H ind), 7.66 (d, *J* = 8.4 Hz, 1H, H-ind), 9.26 (bs, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 11.5 (CH_3 ethyl), 22.1 (CH_2 ethyl), 29.0 (C-7), 36.1 (*C*H_2CO), 37.4 (C-6), 44.0 (C-8), 58.3 (C-3), 72.4 (C-2), 90.9 (C-8a), 109.4 (C-3 ind), 112.3 (C-7 ind), 121.1 (C-4 ind), 123.0 (C-5 ind), 125.9 (C-*o*), 126.7 (C-6 ind), 127.4 (C-2 ind), 127.8 (C-*m*), 129.0 (C-*p*), 135.0 (C-*i*), 137.5 (C-3a), 139.7 (C-7a), 168.3 (NCO), 190.9 (CO) ppm. HRMS calcd. for $C_{25}H_{27}N_2O_3$ $[M + H]^+$: 403.2016; found: 403.2018. $C_{25}H_{26}N_2O_3 \cdot 1/2\ H_2O$ (411.50): calcd. C 72.97, H 6.61, N 6.81; found C 72.94, H 6.61, N 6.45.

(3*R*,7*R*,8*S*,8a*R*)-8-Ethyl-7-[2-hydroxy-2-(2-indolyl)ethyl]-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (**16**): $NaBH_4$ (117 mg, 3.11 mmol) was slowly added to a solution of *trans*-**6** (128 mg, 0.31 mmol) in MeOH (11 mL) at 0 ºC. The mixture was stirred at 0 ºC for 1 h and the temperature was slowly raised to 25 ºC. The mixture was concentrated, water was added, and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried and concentrated to give a foam, which was chromatographed (1:1 hexane–EtOAc to EtOAc) to afford alcohol **16** as a mixture of epimers (115 mg, 90%). Data for **16** (higher R_f epimer): Yellow foam. ^1H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 0.80 (t, *J* = 7.4 Hz, 3H, CH_3 ethyl), 1.37-1.62 (m, 5H, CH_2 ethyl, C*H*$_2$CHOH, H-7, H-8), 1.88 (dd, *J* = 16.8, 7.2 Hz, 1H, H-6), 1.97 (dd, *J* = 10.4, 8.0 Hz, 1H, C*H*$_2$CHOH), 2.22 (bs, 1H, OH), 2.43 (dd, *J* = 16.8, 4.4 Hz, 1H, H-6), 3.92 (dd, *J* = 8.8, 1.6 Hz, 1H, H-2), 3.96 (dd, *J* = 8.8, 6.0 Hz, 1H, H-2), 4.20 (d, *J* = 7.6 Hz, 1H, H-8a), 4.59 (m, 1H, C*H*OH), 4.77 (d, *J* = 5.2 Hz, 1H, H-3), 6.20 (s, 1H, H-3 ind), 7.02-7.27 (m, 8H, ArH, H-ind), 7.50 (d, *J* = 7.2 Hz, 1H, H-4 ind), 9.16 (bs, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 9.5 (CH_3 ethyl), 21.2 (CH_2 ethyl), 31.2 (C-7), 37.4 (C-6), 40.5 (*C*H_2CHOH), 44.4 (C-8), 58.7 (C-3), 66.6 (CHOH), 73.7 (C-2), 90.5 (C-8a), 98.9 (C-3 ind), 111.3 (C-7 ind), 119.6 (C-5 ind), 120.3 (C-4 ind), 121.7 (C-6 ind), 126.5 (C-*o*), 127.6 (C-*p*), 128.0 (C-2 ind), 128.5 (C-*m*), 136.0 (C-3a ind), 140.8 (C-7a ind), 141.2 (C-*i*), 167.6 (NCO) ppm. Data for **16** (lower R_f epimer): Yellow foam. ^1H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 0.91 (t, *J* = 7.3 Hz, 3H, CH_3 ethyl), 1.19-1.26 (m, 1H, C*H*$_2$CHOH), 1.41-1.45 (m, 1H, H-8), 1.49-1.59 (m, 1H, CH_2 ethyl), 1.68 (ddd, *J* = 14.4, 7.2, 4.0 Hz, 1H, CH_2 ethyl), 1.88-1.92 (m, 1H, H-6), 1.95-2.04 (m, 2H, C*H*$_2$CHOH, H-7), 2.21 (bs, 1H, OH), 2.55 (dd, *J* = 16.4, 4.8 Hz, 1H, H-6), 3.91-3.97 (m, 2H, H-2), 4.29 (d, *J* = 9.2 Hz, 1H, H-8a), 4.73 (d, *J* = 9.2 Hz, 1H, C*H*OH), 4.78 (d, *J* = 4.8 Hz, 1H, H-3), 6.18 (s, 1H, H-3 ind), 7.04 (dd, *J* = 6.4, 1.2 Hz, 1H, H-7 ind), 7.08 (dd, *J* = 7.6, 1.6 Hz, 1H, H-5 ind), 7.09-7.24 (m, 6H, ArH, H-6 ind), 7.53 (d, *J* = 8.0 Hz, 1H, H-4 ind), 9.24 (bs, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 9.3 (CH_3 ethyl), 20.5 (CH_2 ethyl), 29.2 (C-7), 36.5 (C-6), 39.7 (*C*H_2CHOH), 44.2 (C-8), 59.0 (C-3), 64.4 (CHOH), 73.7 (C-2), 90.6 (C-8a), 97.5 (C-3 ind), 111.1 (C-7 ind), 119.4 (C-5 ind), 120.2 (C-4 ind), 121.3 (C-6 ind), 126.4 (C-*o*), 127.6 (C-*p*), 128.2 (C-2 ind), 128.6 (C-*m*), 135.8 (C-3a ind), 141.2 (C-7a ind), 142.4 (C-*i*), 167.7 (NCO) ppm.

(3*R*,7*R*,8*S*,8a*R*)-7-[2-Acetyl-2-(2-indolyl)ethyl]-8-ethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (**17**): DMAP (8 mg, 0.06 mmol) and Ac_2O (140 µL, 1.48 mmol) were added to a cooled (0 ºC) solution of alcohols **16** (135 mg, 0.34 mmol) in CH_2Cl_2 and pyridine (2 mL, 4:1). The mixture was stirred at rt for 4h, diluted with $CHCl_3$, and successively washed with 1 N aqueous HCl and saturated aqueous $NaHCO_3$. The organic solution was dried and concentrated to afford an epimeric mixture of acetates **17** (86 mg, 57%), which was used in the next reaction without further purification. Data for **17**: Yellow foam. ^1H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 0.87 (t, *J* = 7.2 Hz, 3H, CH_3 ethyl), 1.04 (t, *J* = 7.4 Hz, 3H, CH_3 ethyl), 1.12-1.17 (m, 2H, H-7), 1.23-2.21 (m, 8H, CH_2 ethyl, C*H*$_2$CHO, H-8), 2.20 (s, 3H, CH_3CO), 2.25 (s, 3H, CH_3CO), 2.55-2.63 (m, 2H, C*H*$_2$CHO), 2.34 (dd, *J* = 14.0, 6.8 Hz, 1H, H-6), 3.32-3.49 (m, 3H, H-6), 4.01 (d, *J* = 9.0 Hz, 1H, H-2), 4.05 (d, *J* = 8.8 Hz, 1H, H-2), 4.07 (d, *J* = 8.8 Hz, 1H, H-2), 4.17 (dd, *J* = 9.0, 6.8 Hz, 1H, H-2), 4.47-4.54 (m, 3H, CH_2CHO, H-8a), 4.70 (d, *J* = 8.4 Hz, 1H, H-8a), 4.90 (d, *J* = 6.4 Hz, 1H, H-3), 4.95 (d, *J* = 6.0 Hz, 1H, H-3), 6.33 (s, 1H, H-3 ind), 6.44 (s, 1H, H-3 ind), 7.10 (dd, *J* = 14.8, 7.2 Hz, 1H, H-ind), 7.17 (dd, *J* = 14.8, 7.2 Hz, 1H, H-ind), 7.07-7.59 (m, 18H, ArH, H-ind), 8.30 (bs, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 9.6, 9.9 (CH_3 ethyl), 15.2, 15.3 (CH_2 ethyl), 21.5, 21.6 (CO*C*H_3), 30.3, 30.9 (C-7), 36.9, 37.4 (C-6), 44.8, 44.9 (*C*H_2CO), 58.7, 58.7 (C-3), 64.3, 64.5 (CHOAc), 73.9, 74.0 (C-2), 90.7, 91.1 (C-8a), 100.4, 102.1 (C-3 ind), 110.9, 111.0 (C-7 ind), 119.8, 119.9 (C-5 ind), 120.4, 120.5 (C-4 ind), 121.8, 122.1 (C-6 ind), 126.4, 126.5 (C-*o*), 127.5 (C-*p*), 128.0, 128.2 (C-2 ind), 128.6 (C-*m*), 135.9, 136.2 (C-3a ind), 137.7, 139.4 (C-3a ind), 141.2, 141.3 (C-*i*), 166.6 (NCO), 166.8 (COO) ppm.

(3*R*,7*R*,8*S*,8a*R*)-8-Ethyl-7-[(2-indolyl)ethyl]-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (**18**): A solution of acetates **17** (160 mg, 0.36 mmol) in EtOAc (25 mL) containing 20% Pd-C (17 mg) was hydrogenated at rt for 4 days at atmospheric pressure. The catalyst was removed by filtration, and the solvent was evaporated to give an oil. Flash chromatography (from 9:1 to 4:1 hexane–EtOAc) afforded **18** (70 mg, 50%). Data

for **18**: Yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 0.99 (t, *J* = 7.6 Hz, 3H, CH_3 ethyl), 1.63-2.18 (m, 7H, CH_2 ethyl, H-7, H-8, indCH_2CH_2, indCH_2CH_2), 2.49-2.64 (m, 1H, indCH_2CH_2), 2.53 (dd, *J* = 15.0, 6.0 Hz, 1H, H-6), 2.77 (ddd, *J* = 15.0, 9.6, 4.8 Hz, 1H, H-6), 4.06 (dd, *J* = 9.2, 1.2 Hz, 1H, H-2), 4.16 (dd, *J* = 9.2, 6.8 Hz, 1H, H-2), 4.63 (d, *J* = 8.4 Hz, 1H, H-8a), 4.94 (d, *J* = 5.6 Hz, 1H, H-3), 6.20 (s, 1H, H-3 ind), 7.03-7.57 (m, 9H, ArH, H-ind), 8.22 (bs, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 10.0 (CH_3 ethyl), 22.0 (CH_2 ethyl), 24.9 (C-6), 33.2 (C-7, indCH_2CH_2), 36.8 (indCH_2), 45.1 (C-8), 58.7 (C-3), 74.0 (C-2), 91.0 (C-8a), 99.5 (C-3 ind), 110.4 (C-7 ind), 119.5 (C-5 ind), 119.7 (C-4 ind), 121.0 (C-6 ind), 126.4, 126.6 (C-*o*), 127.6 (C-*p*), 128.6 (C-*m*), 128.7 (C-2 ind), 135.9 (C-3a ind), 138.6 (C-7a ind), 141.2 (C-*i*), 167.0 (NCO) ppm.

(3*R*,7*S*,8*S*,8a*R*)-8-Ethyl-7-[2-hydroxy-2-(2-indolyl)ethyl]-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (**19**): Operating as in the above reduction of *trans*-**6**, from a solution of *cis*-**6** (1.05 mg, 2.60 mmol) in THF (50 mL) and $NaBH_4$ (148 mg, 3.91 mmol) for 3 h, a foam was obtained. Flash chromatography (1:1 hexane–EtOAc to EtOAc) gave two epimeric alcohols **19** (higher R_f epimer: 462 mg, 44%; lower R_f epimer: 308 mg, 29%). Data for **19** (higher R_f epimer): Yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 1.03 (t, *J* = 7.4 Hz, 3H, CH_3 ethyl), 1.38-2.49 (m, 8H, CH_2 ethyl, CH_2CHOH, H-6, H-7, H-8), 3.14 (bs, 1H, OH), 3.94-4.04 (m, 2H, H-2), 4.50 (d, *J* = 8.4 Hz, 1H, H-8a), 4.81 (m, 2H, C*H*OH, H-3), 6.29 (s, 1H, H-3 ind), 7.07 (t, *J* = 7.4 Hz, 1H, H-ind), 7.13 (t, *J* = 7.4 Hz, 1H, H-ind), 7.21-7.31 (m, 6H, ArH, H-ind), 7.54 (d, *J* = 7.6 Hz, 1H, H-4 ind), 8.78 (bs, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 11.2 (CH_3 ethyl), 20.7 (CH_2 ethyl), 28.6 (C-7), 35.4 (C-6), 36.9 (*C*H_2CHOH), 43.8 (C-8), 59.3 (*C*HOH), 65.3 (C-3), 73.8 (C-2), 90.3 (C-8a), 98.1 (C-3 ind), 111.0 (C-7 ind), 119.7 (C-5 ind), 120.4 (C-4 ind), 121.7 (C-6 ind), 126.3 (C-*o*), 127.6 (C-*p*), 128.2 (C-2 ind), 128.6 (C-*m*), 135.7 (C-3a ind), 141.4 (C-7a ind), 141.6 (C-*i*), 167.7 (NCO) ppm. Data for **19** (lower R_f epimer): Yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 0.83 (t, *J* = 7.4 Hz, 3H, CH_3 ethyl), 1.34-2.72 (m, 8H, CH_2 ethyl, CH_2CHOH, H-6, H-7, H-8), 3.87-4.00 (m, 2H, H-2), 4.51 (d, *J* = 6.8 Hz, 1H, H-8a), 4.62-4.78 (m, 2H, C*H*OH, H-3), 6.27 (s, 1H, H-3 ind), 7.66-7.28 (m, 8H, ArH, H-ind), 7.54 (d, *J* = 7.6 Hz, 1H, H-4 ind), 9.20 (bs, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 11.2 (CH_3 ethyl), 20.8 (CH_2 ethyl), 29.7 (C-7), 30.8 (C-6), 38.0 (*C*H_2CHOH), 44.2 (C-8), 59.3 (*C*HOH), 68.2 (C-3), 73.8 (C-2), 90.3 (C-8a), 99.2 (C-3 ind), 111.3 (C-7 ind), 119.6 (C-5 ind), 120.3 (C-4 ind), 121.8 (C-6 ind), 126.3 (C-*o*), 127.6 (C-*p*), 127.9 (C-2 ind), 128.6 (C-*m*), 136.2 (C-3a ind), 141.0 (C-7a ind), 141.4 (C-*i*), 170.2 (NCO) ppm.

(3*R*,7*S*,8*S*,8a*R*)-7-[2-Acetyl-2-(2-indolyl)ethyl]-8-ethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (**20**): Operating as in the above preparation of **17** (reaction time 14 h), from alcohols **19** (770 mg, 1.90 mmol), DMAP (8 mg, 0.06 mmol), and Ac_2O (0.8 mL, 7.61 mmol) in CH_2Cl_2 and pyridine (12.5 mL, 4:1), two epimeric acetates **20** (higher R_f epimer: 440 mg, 52%; lower R_f epimer: 300 mg, 35%) were obtained after column chromatography (hexane to 9:1 hexane-EtOAc). Data for **20** (higher R_f epimer): Yellow foam. $[\alpha]^{22}_D$ = + 47.5 (*c* = 1.0, $CHCl_3$). IR (KBr): ν = 1641, 1739, 3267 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 1.11 (t, *J* = 7.3 Hz, 3H, CH_3 ethyl), 1.54-1.63 (m, 1H, CH_2 ethyl), 1.79 (dd, *J* = 11.2, 2.8 Hz, 1H, H-6), 1.92-1.99 (m, 2H, CH_2 ethyl, H-8), 2.10 (s, 3H, CH_3CO), 2.26-2.31 (m, 1H, H-7), 2.35-2.45 (m, 3H, CH_2CHO, H-6), 2.54 (d, *J* = 17.6 Hz, 1H, CH_2CHO), 3.99 (dd, *J* = 9.2, 1.2 Hz, 1H, H-2), 4.12 (dd, *J* = 9.2, 6.8 Hz, 1H, H-2), 4.62 (d, *J* = 9.2 Hz, 1H, H-8a), 4.89 (d, *J* = 6.8 Hz, 1H, H-3), 6.03 (dd, *J* = 10.8, 2.4 Hz, 1H, CH_2CHO), 6.49 (d, *J* = 2.4 Hz, 1H, H-3 ind), 7.08-7.32 (m, 8H, ArH, H-ind), 7.58 (d, *J* = 7.2 Hz, 1H, H-ind), 9.18 (bs, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 11.0 (CH_3 ethyl), 20.6 (CH_2 ethyl), 21.1 (OCH_3), 28.9 (C-7), 32.3 (C-6), 37.1 (*C*H_2CHO), 43.7 (C-8), 59.4 (C-3), 67.5 (CH_2*C*HO), 73.9 (C-2), 90.1 (C-8a), 100.2 (C-3 ind), 111.4 (C-4 ind), 119.8 (C-5 ind), 120.6 (C-4 ind), 122.3 (C-6 ind), 126.3 (C-*o*); 127.5, 127.6 (C-*p*, C-2 ind), 128.6 (C-*m*), 136.0 (C-3a ind), 137.0 (C-3a ind), 141.5 (C-*i*), 166.8 (NCO), 171.2 (COO) ppm. HRMS calcd. for $C_{27}H_{31}N_2O_4$ $[M + H]^+$: 447.2278; found: 447.2300. Data for **20** (lower R_f epimer): Yellow foam. $[\alpha]^{22}_D$ = + 4.6 (*c* = 1.0, $CHCl_3$). IR (KBr): ν = 1645, 1732, 3261 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 0.95 (t, *J* = 7.3 Hz, 3H, CH_3 ethyl), 1.48-1.52 (m, 1H, CH_2 ethyl), 1.83-1.95 (m, 3H, CH_2 ethyl, H-6, H-8), 2.05 (s, 3H, CH_3CO), 2.05-2.11 (m, 1H, H-7), 2.31-2.38 (m, 1H, H-6), 2.35 (d, *J* = 17.6, 5.6 Hz, 1H, CH_2CHO), 2.59 (d, *J* = 17.6 Hz, 1H, CH_2CHO), 3.40 (dd, *J* = 8.8, 1.2 Hz, 1H, H-2), 4.13 (dd, *J* = 9.2, 8.8 Hz, 1H, H-2), 4.65 (d, *J* = 9.2 Hz, 1H, H-8a), 4.92 (d, *J* = 6.8 Hz, 1H, H-3), 5.96 (dd, *J* = 9.2, 6.0 Hz, 1H, CH_2CHO), 6.52 (d, *J* = 2.0 Hz, 1H, H-3 ind), 7.11 (td, *J* = 7.6, 0.8 Hz, 1H, H-ind), 7.17-7.32 (m, 7H, ArH, H-ind), 7.59 (d, *J* = 8.4 Hz, 1H, H-ind), 8.98 (bs, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 11.4 (CH_3 ethyl), 20.9 (CH_2 ethyl), 21.2 (OCH_3), 30.2 (C-7), 31.8 (C-6), 37.5 (*C*H_2CHO), 44.2 (C-8), 59.4 (C-3), 69.2 (CH_2*C*HO), 73.9 (C-2), 90.1 (C-8a), 101.0 (C-3 ind), 111.4 (C-4 ind), 120.0 (C-5 ind), 120.8 (C-4 ind), 122.6 (C-6 ind), 126.3 (C-*o*), 127.5, 127.6 (C-*p*, C-2 ind), 128.6 (C-*m*), 135.8 (C-3a ind), 135.9 (C-3a ind), 141.4 (C-*i*), 166.7 (NCO), 171.0 (COO) ppm. HRMS calcd. for $C_{27}H_{30}N_2NaO_4$ $[M + Na]^+$: 469.2098; found: 469.2113.

(3*R*,7*S*,8*S*,8a*R*)-8-Ethyl-7-[(2-indolyl)ethyl]-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (**21**): A solution of acetates **20** (150 mg, 0.34 mmol) in EtOAc (20 mL) containing 20% $Pd(OH)_2$ (30 mg) was hydrogenated at rt under 400 psi of pressure for 2 days. The catalyst was removed by filtration, and the solvent was evaporated to give a foam. Flash chromatography (from 9:1 to 1:1 hexane–EtOAc) afforded **21** (71 mg, 54%). Data for **21**: Yellow foam. $[\alpha]^{22}_D$ = − 42.5 (*c* = 0.2, $CHCl_3$). IR (KBr): ν = 1642 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 0.98 (t, *J* = 7.6 Hz, 3H, CH_3 ethyl), 1.45-1.56 (m, 2H, CH_2 ethyl, indCH_2CH_2), 1.82-1.93 (m, 2H, CH_2 ethyl, indCH_2CH_2), 1.95-2.02 (m, 1H, H-8), 2.09-2.14 (m, 1H, H-7), 2.40 (dd, *J* = 18.0, 5.2 Hz, 1H, indCH_2), 2.52 (dd, *J* = 18.0, 2.0 Hz, 1H, indCH_2), 2.66 (ddd, *J* = 14.8, 10.0, 7.2 Hz, 1H, H-6), 2.95 (ddd, *J* = 14.8, 10.0, 4.8 Hz, 1H, H-6), 3.99 (dd, *J* = 9.2, 1.2 Hz, 1H, H-2), 4.11 (dd, *J* = 9.2, 7.2 Hz, 1H, H-2), 4.61 (d, 1H, *J* = 9.6 Hz, 1H, H-8a), 4.89 (d, *J* = 6.0 Hz, 1H, H-3), 6.24 (d, *J* = 1.2 Hz, 1H, H-3 ind), 7.05-7.53 (m, 9H, ArH, H-ind), 8.07 (bs, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 11.3 (CH_3 ethyl), 20.9 (CH_2 ethyl), 26.5 (C-6), 27.5 (indCH_2*C*H_2), 32.4 (C-7), 36.8 (ind*C*H_2), 44.1 (C-8), 59.3 (C-3), 73.8 (C-2), 90.3 (C-8a), 99.9 (C-3 ind), 110.4 (C-7 ind), 119.7 (C-5 ind), 119.8 (C-4 ind), 121.2 (C-6 ind), 126.3 (C-*o*), 127.5 (C-*p*), 128.6 (C-*m*), 128.7 (C-2 ind), 135.9 (C-3a ind), 138.3 (C-7a ind), 141.5 (C-*i*), 171.5 (NCO) ppm. HRMS calcd. for $C_{25}H_{29}N_2O_2$ $[M + H]^+$: 389.2224; found: 389.2224.

(1*R*,5*S*,13*S*)-2-[(1*R*)-2-Hydroxy-1-phenylethyl]-13-ethyl-3-oxo-2,3,4,5,6,7-hexahydro-3*H*-1,5-methanoazocine[4,3-*b*]indole (**22**): $TiCl_4$ (1 mL of a 1.0 M solution in CH_2Cl_2, 1.0 mmol) was added to a solution of **21** (38 mg, 0.10 mmol) in CH_2Cl_2 (2 mL) at rt, and the resulting mixture was heated at reflux for 24 h. $TiCl_4$ (1 mL of a 1.0 M solution in CH_2Cl_2, 1.0 mmol) was then added and once again after a further 24 h, and the mixture was maintained at reflux for an additional 48 h. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed using a cartridge containing amine functionalized silica (1:1 hexane-EtOAc to 1:1 EtOAc-MeOH) to give **22** (22 mg, 58%). Data for **22**: Yellow foam. $[\alpha]^{22}_D$ = − 88.2 (*c* = 0.5, $CHCl_3$). IR (KBr): ν = 1608, 2926 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 25 ºC): δ = 0.72 (t, *J* = 7.5 Hz, 3H, CH_3 ethyl), 1.11 (td, *J* = 7.5, 7.5, 2.0 Hz, 2H, CH_2 ethyl), 1.73 (ddd, *J* = 14.0, 7.0, 5.0 Hz, 1H, H-6), 1.95 (dt, *J* = 14.0, 2.5 Hz, 1H, H-6), 2.05-2.10 (m, 1H, H-13), 2.42-2.50 (m, 1H, H-5), 2.55 (ddd, *J* = 16.0, 5.0, 3.0 Hz, 1H, H-7), 2.75 (d, *J* = 18.5 Hz, 1H, H-4), 3.00 (dd, *J* = 18.5, 8.5 Hz, 1H, H-4), 3.12 (m, 1H, H-7), 3.54 (m, 1H, $C_6H_5CHCH_2$), 3.80-3.83 (m, 1H, $C_6H_5CHCH_2$), 4.51 (d, *J* = 5.0 Hz, 1H, H-1), 5.74 (m, 1H, $C_6H_5CHCH_2$), 6.98-7.31 (m, 9H, ArH, H-ind), 8.03 (bs, 1H, NH) ppm. ^{13}C NMR (125.9 MHz, $CDCl_3$, 25 ºC): δ = 11.7 (CH_3 ethyl), 23.0 (CH_2 ethyl), 23.4 (C-6), 26.9 (C-7), 33.8 (C-5), 38.4 (C-4), 41.7 (C-13), 53.0 (C-1), 60.5 ($C_6H_5CHCH_2$), 63.2 ($C_6H_5CHCH_2$), 110.6 (C-12b), 110.8 (C-9), 117.4 (C-12), 119.6 (C-11), 121.0 (C-10), 127.6 (C-*m*), 128.1 (C-*o*), 128.2 (C-7a), 128.3 (C-*p*), 133.9 (C-12a), 136.9 (C-8a), 138.5 (C-*i*), 172.1 (NCO) ppm. HRMS calcd. for $C_{25}H_{29}N_2O_2$ $[M + H]^+$: 389.2224; found: 389.2222.

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[16] Data for **13**: Yellow foam. $[\alpha]^{22}_D$ = − 14.4 (*c* = 0.35, $CHCl_3$). IR (KBr): ν = 1635 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 0.95 (t, *J* = 7.6 Hz, 3H, CH_3 ethyl), 1.94-1.99 (m, 2H, CH_2 ethyl), 2.62 (dd, *J* = 16.0, 2.2 Hz, 1H, CH_2CO), 2.76 (dd, *J* = 16.0, 6.0 Hz, 1H, CH_2CO), 2.76-2.82 (m, 2H, H-3), 2.89-2.95 (m, 1H, H-4), 4.11-4.17 (m, 2H, H-2'), 5.85 (t, *J* = 7.2 Hz, 1H, H-1'), 5.94 (s, 1H, H-6), 6.75 (d, *J* = 1.6 Hz, 1H, H-3 ind), 7.25-7.42 (m, 8H, ArH, H ind), 7.58 (d, *J* = 8.4 Hz, 1H, H-4 ind), 9.53 (bs, 1H, NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ = 12.6 (CH_3 ethyl), 25.5 (CH_2 ethyl), 31.2 (C-4), 37.3 (CH_2CO), 39.5 (C-3), 57.9 (C-1'), 62.1 (C-2'), 110.0 (C-3 ind), 112.2 (C-7 ind), 120.5 (C-6), 120.8 (C-4 ind), 123.0 (C-5 ind), 125.9 (C-5), 126.4 (C-6 ind), 127.3 (C-3a ind), 127.6 (C-*o*), 127.9 (C-*p*), 128.8 (C-*m*), 135.2 (C-*i*), 137.6 (C-2 ind), 137.7 (C-7a ind), 169.5 (NCO), 191.2 (CO) ppm. HRMS calcd. for $C_{25}H_{27}N_2O_3$ $[M+ H]^+$: 403.2016; found: 403.2016.

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(CO) ppm. HRMS calcd. for $C_{25}H_{27}N_2O_3$ [M+ H]$^+$: 403.2016; found: 403.2014.

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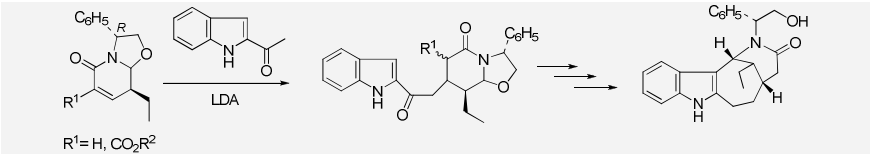

The stereochemical outcome of the conjugate addition reactions of 2-acetylindole enolates to phenylglycinol-derived unsaturated lactams is studied. A subsequent Lewis acid-promoted intramolecular α-amidoalkylation reaction leads to the tetracyclic ring system of ervitsine.

M. Amat,* B. Checa, N. Llor, M. Pérez, J. Bosch ……..... Page No. – Page No.

Conjugate Addition of 2-Acetylindoles to Unsaturated Oxazolopiperidone Lactams. Enantioselective Access to the Tetracyclic Ring System of Ervitsine.

Keywords: Lactams / Asymmetric synthesis / Cyclization / Michael addition / Heterocycles