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A Synthetic Approach to Ervatamine-Silicine Alkaloids. Enantioselective Total Synthesis of (−)-16-Episilicine†

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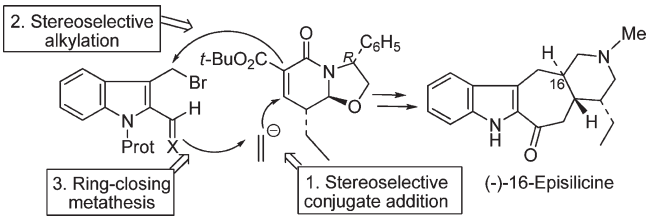

Starting from an appropriate unsaturated phenylglycinol-derived oxazolopiperidone lactam, the synthesis of (−)-16-episilicine is reported, the key steps being a stereoselective conjugate addition, a stereoselective alkylation, and a ring-closing metathesis reaction. This represents the first enantioselective total synthesis of an alkaloid of the silicine group.

Introduction

The ervatamine-silicine alkaloids[1] constitute a relatively numerous group of Corynanthean-type[2] 2-acylindole alkaloids with a rearranged skeleton that lacks the characteristic tryptamine moiety (Ind-C_6-C_5-N)[3] present in most indole alkaloids, having an unusual Ind-C_6-C_{16}-C_5-N connectivity instead (Figure 1).

Biogenetically, these alkaloids derive from secologanin via a vobasine *N*-oxide equivalent,[2] which undergoes a fragmentation reaction and then a cyclization to form the central carbocyclic seven-membered ring characteristic of these natural products (Scheme 1). As a consequence of their biogenetic origin, the configuration of the C-15 stereocenter in these alkaloids is usually *S* (H-15β),[4] the same configuration as for C-15 in secologanin. However, they differ in the relative stereochemistry of C-16 (*cis* or *trans* C/D ring fusion) and C-20 (there are also C-20 *E*-ethylidene derivatives), the oxidation level at C-6 (some are 6-oxo derivatives), and the presence or absence of a C-16 methoxycarbonyl group.

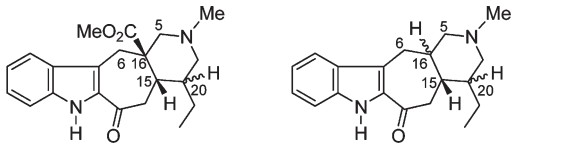

FIGURE 1. Representative alkaloids of the ervatamine-silicine group.

The alkaloids of the ervatamine-silicine group have received scarce attention from the synthetic standpoint,[5]

† Dedicated to Professor Pelayo Camps, University of Barcelona, on the occasion of his 65th birthday.

(1) (a) Joule, J. A. Indoles. The Monoterpenoid Indole Alkaloids; Saxton, J. E., Ed. In *The Chemistry of Heterocyclic Compounds*; Weissberger, A.;, Taylor, E. C., Eds.; Wiley: New York, 1983; Vol. 25, part 4, pp 232−239. (b) Danieli, B.; Palmisano, G. in *The Alkaloids*, ed. Brossi, A.; Academic Press, Orlando, vol. 27, 1986, pp 1−130. For more recent isolations, see: (c) Zhang, H.; Yue, J.-M. *Helv. Chim. Acta* **2005**, *88*, 2537.

(2) Kisakürek, M. V.; Leeuwenberg, A. J. M.; Hesse, M. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1983; Chapter 5.

(3) Biogenetic numbering is used throughout this paper for all tetracyclic and pentacyclic compounds: Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508.

(4) In a few cases (e.g., C-20 ethylidene derivatives), although the C-15 configuration is the same as in secologanin, it is specified as *R* as a consequence of the application of the sequence rule procedure.

(5) (a) Husson, H.-P.; Bannai, K.; Freire, R.; Mompon, B.; Reis, F. A. M. *Tetrahedron* **1978**, *34*, 1363. (b) Bennasar, M.-L.; Vidal, B.; Bosch, J. *J. Org. Chem.* **1997**, *62*, 3597. (c) Bennasar, M.-L.; Vidal, B.; Kumar, R.; Lázaro, A.; Bosch, J. *Eur. J. Org. Chem.* **2000**, 3919. For the synthesis of tetracyclic structures related to ervatamine-silicine alkaloids, see: (d) Langlois, Y.; Potier, P. *Tetrahedron* **1975**, *31*, 423. (e) Grierson, D. S.; Bettiol, J.-L.; Buck, I.; Husson, H.-P.; Rubiralta, M.; Diez, A. *J. Org. Chem.* **1992**, *57*, 6414.

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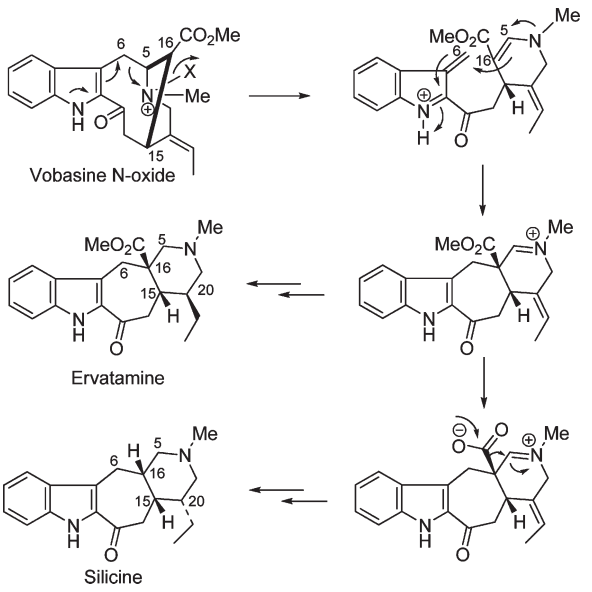
SCHEME 1. Biosynthetic Pathway to Ervatamine-Silicine Alkaloids. Absolute Configuration of C-15

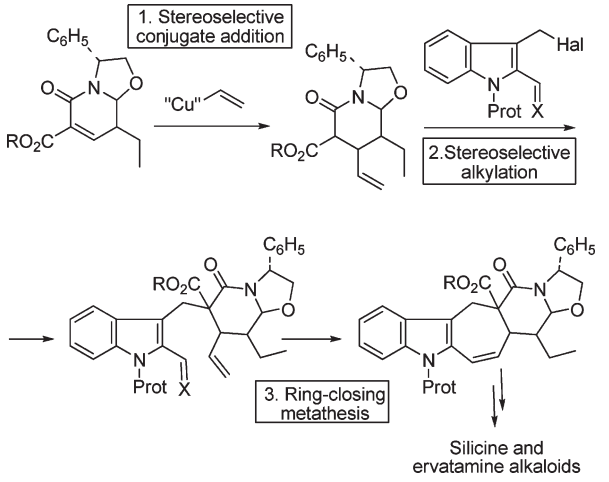


and with the exception of our preliminary report[6] on the synthesis of (−)-16-episilicine, no enantioselective total syntheses for these alkaloids have been reported so far.

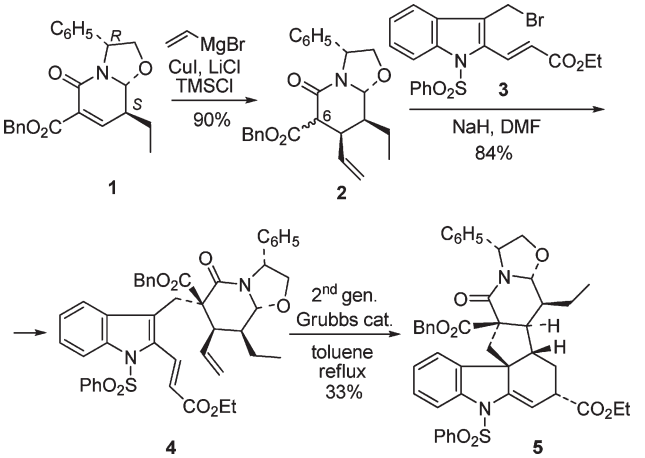
Ervatamines and silicines can be envisaged as enantiopure 3,4,5-trisubstituted piperidines (the former with an additional methoxycarbonyl substituent) that embody an ethyl substituent and a seven-membered carbocyclic ring fused on the *c* side of the heterocycle.

Bearing in mind the versatility of aminoalcohol-derived oxazolopiperidone lactams as chiral building blocks for the enantioselective construction of complex piperidine-containing derivatives,[7] the above structural features prompted us to explore the utility of these lactams as starting scaffolds for the synthesis of ervatamine-silicine alkaloids. Scheme 2 outlines our synthetic strategy, whose key steps would be (i) the stereoselective conjugate addition of a vinyl residue to an unsaturated lactam already incorporating the ethyl substituent present in the natural targets, (ii) a stereoselective alkylation to introduce a 2-vinyl-3-indolylmethyl fragment, and (iii) a ring-closing olefin metathesis (RCM) reaction[8] to construct the carbocyclic seven-membered C ring. Subsequent oxidation−reduction and protecting−deprotecting steps would complete the synthesis of ervatamines. The alkoxycarbonyl substituent in the starting lactam not only

SCHEME 2. Synthetic Strategy



SCHEME 3. First Synthetic Approach. Unexpected Diels−Alder Reaction



would facilitate the subsequent conjugate addition[9] and alkylation steps but could also be removed in advanced stages of the synthesis to provide access to the silicine series.

Results and Discussion

The known[10] lactam **1** was selected to carry out our initial studies. The conjugate addition of the vinyl group was accomplished in excellent chemical yield and complete *exo*-facial selectivity, *cis* with respect to the ethyl substituent. The subsequent alkylation of the resulting mixture of C-6 epimeric lactams **2**[11] with 3-(bromomethyl)indole **3**[12] took place stereoselectively on the most accessible face of the piperidine ring, providing derivative **4** in excellent yield (84%) as a single stereoisomer (Scheme 3). Surprisingly, treatment of **4**

(6) Amat, M.; Checa, B.; Llor, N.; Molins, E.; Bosch, J. *Chem. Commun.* **2009**, 2935.

(7) For reviews, see: (a) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503. (b) Meyers, A. I.; Brengel, G. P. *Chem. Commun.* **1997**, 1. (c) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843. (d) Escolano, C.; Amat, M.; Bosch, J. *Chem.—Eur. J.* **2006**, *12*, 8198. (e) Couty, F.; Evano, G. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J., Eds; Elsevier: Oxford, 2008; Vol 11, pp 409−499. For more recent work, see: (f) Amat, M.; Santos, M. M. M.; Bassas, O.; Llor, N.; Escolano, C.; Gómez-Esqué, A.; Molins, E.; Allin, S. M.; Mckee, V.; Bosch, J. *J. Org. Chem.* **2007**, *72*, 5193. (g) Amat, M.; Griera, R.; Fabregat, R.; Molins, E.; Bosch, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 3348. (h) Amat, M.; Gómez-Esqué, A.; Escolano, C.; Santos, M. M. M.; Molins, E.; Bosch, J. *J. Org. Chem.* **2009**, *74*, 1205. (i) Amat, M.; Fabregat, R.; Griera, R.; Bosch, J. *J. Org. Chem.* **2009**, *74*, 1794 and references therein.

(8) (a) *Handbook of Metathesis*; Grubbs, R. H., Ed; Wiley-VCH: Weinheim, 2003; Vols. 1−3. (b) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693. (c) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199.

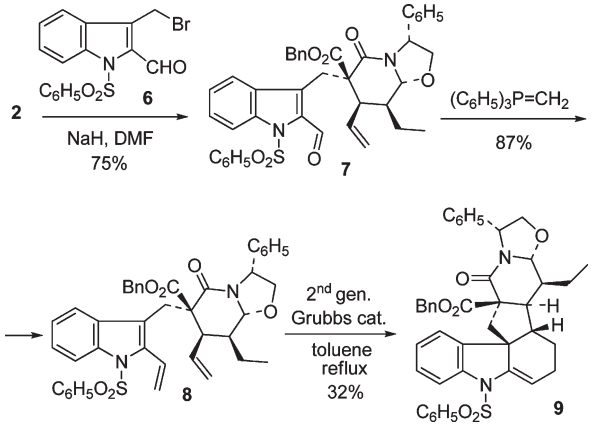
(9) (a) Overman, L. E.; Robichaud, A. J. *J. Am. Chem. Soc.* **1989**, *111*, 300. (b) Cossy, J.; Mirguet, O.; Gómez Pardo, D.; Desmurs, J.-R. *New J. Chem.* **2003**, *27*, 475. (c) Deiters, A.; Pettersson, M.; Martin, S. F. *J. Org. Chem.* **2006**, *71*, 6547 and references therein.

(10) Amat, M.; Pérez, M.; Llor, N.; Bosch, J.; Lago, E.; Molins, E. *Org. Lett.* **2001**, *3*, 611.

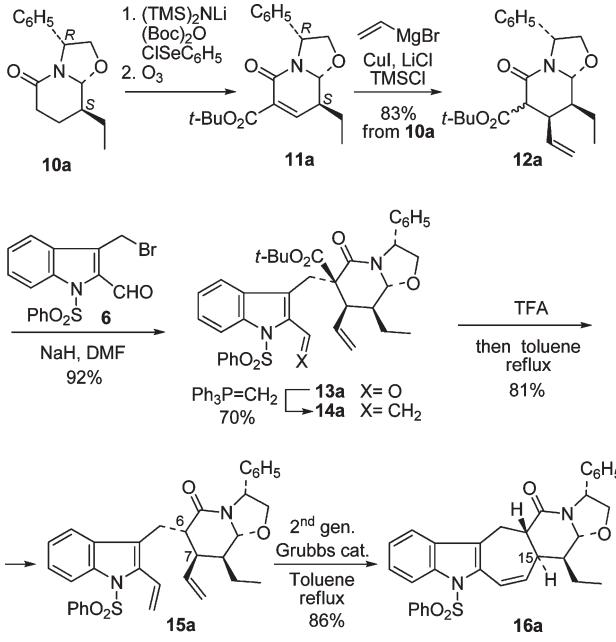
(11) For a preliminary communication reporting lactams **2** and **12a**, see: Amat, M.; Brunaccini, E.; Checa, B.; Pérez, M.; Llor, N.; Bosch, J. *Org. Lett.* **2009**, *11*, 4370.

(12) Mohanakrishnan, P. C.; Srinivasan, P. C. *J. Org. Chem.* **1995**, *60*, 1939.

SCHEME 4. Second Synthetic Approach



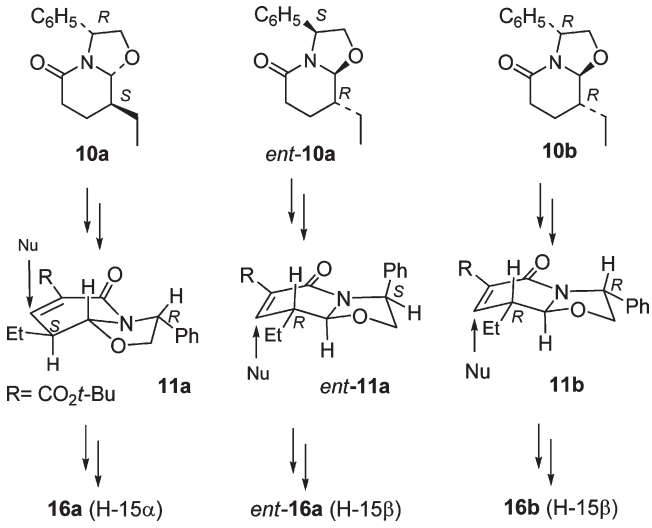
SCHEME 5. Third Synthetic Approach



with the second-generation Grubbs catalyst in refluxing toluene led to hexacycle **5** (33% yield), resulting from an intramolecular Diels–Alder process,[13] instead of the expected ring-closing metathesis product. A similar result was obtained using the Hoveyda–Grubbs catalyst. As might be expected, hexacycle **5** was also obtained (60% yield) when a solution of **4** in toluene was heated at reflux in the absence of a RCM catalyst.

To evaluate if the failure of the ring-closing metathesis reaction could be attributed to the deactivating effect of the ethoxycarbonyl substituent on the vinylindole moiety, we turned our attention to diene **8**, which bears an unsubstituted vinyl substituent on the indole ring. This diene was prepared in excellent overall yield by alkylation of the 1,3-dicarbonyl

SCHEME 6. Control of C-15 Configuration



derivative **2** with 3-(bromomethyl)indole **6**, followed by Wittig methylenation of the resulting 2-formylindole **7** (Scheme 4). However, heating a toluene solution of **8** in the presence of the second-generation Grubbs catalyst did not lead to the expected ring-closing metathesis product either, giving the Diels–Alder adduct **9** instead.

At this point, we reasoned that the failure in the closure of the seven-membered ring of the target alkaloids by a RCM reaction could have a conformational origin due to the steric crowding caused by the benzyloxycarbonyl substituent on the quaternary carbon. For this reason, we decided to prepare diene **14a**, i.e., the *tert*-butyl ester analogue of **8**, from which the *tert*-butoxycarbonyl group could be easily removed under nonreductive conditions without affecting the carbon–carbon double bonds. The synthesis of **14a** was performed as outlined in Scheme 5, following a synthetic route similar to that previously developed in the above benzyloxycarbonyl series but starting from the unsaturated lactam **11a**. This was readily accessible by sequential treatment of lactam **10a**[14] with $(TMS)_2NLi$, di-*tert*-butyl dicarbonate, and PhSeCl, followed by oxidation of the resulting mixture of selenides. Both the conjugate addition of the vinyl residue and the alkylation of the resulting lactam **12a**[11] (mixture of C-6 epimers) took place in excellent chemical yield and complete stereoselectivity. A subsequent Wittig methylenation of 2-formylindole **13a** led to the new key intermediate **14a**.

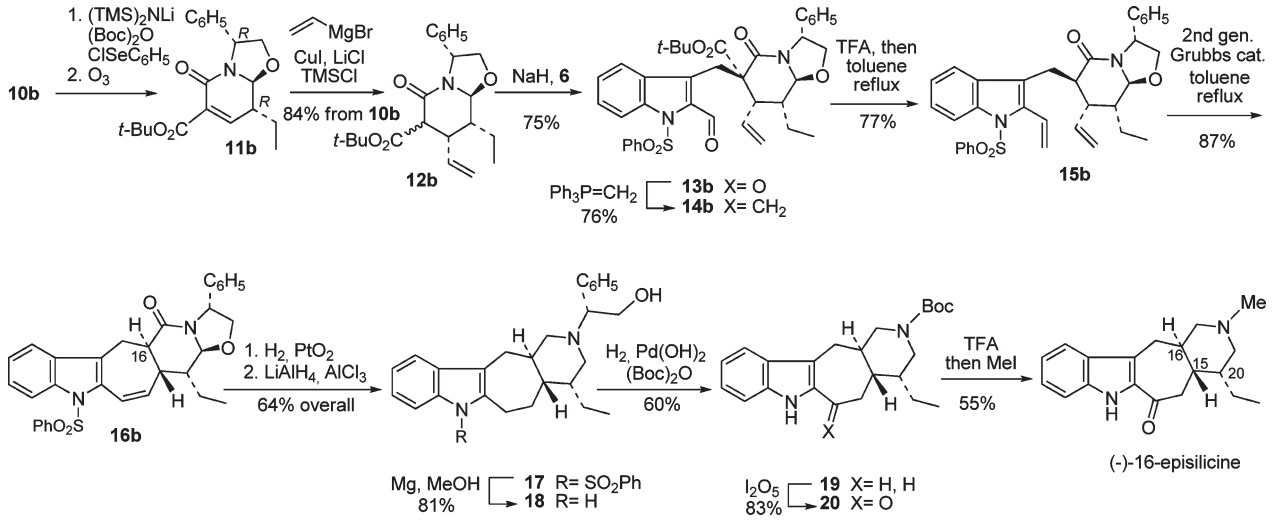
Removal of the C-6 *tert*-butoxycarbonyl group from **14a** was accomplished by treatment with TFA followed by heating of the resulting keto acid in refluxing toluene to give 6,7-*trans* oxazolopiperidone **15a** in 81% yield. Only trace amounts of the corresponding 6-epimer were detected.

Gratifyingly, as we had assumed, diene **15a** underwent a ring-closing metathesis reaction on treatment with the second-generation Grubbs catalyst in refluxing toluene, leading to the desired pentacycle **16a** in 86% yield. The absolute configuration of **16a** was unambiguously established by X-ray crystallographic analysis, thus confirming both the stereochemical outcome of the conjugate addition reaction,

(13) For related intramolecular Diels–Alder reactions, in which a 2-vinylindole moiety acts as the diene, see: (a) Kuehne, M. E.; Bornmann, W. G.; Earley, W. G.; Marko, I. *J. Org. Chem.* **1986**, *51*, 2913. (b) Kuehne, M. E.; Podhorez, D. E.; Mulamba, T.; Bornmann, W. G. *J. Org. Chem.* **1987**, *52*, 347. (c) Pindur, U. *Heterocycles* **1988**, *27*, 1253. (d) Lévy, J.; Sapi, J.; Laronze, J.-L.; Royer, D.; Toupet, L. *Synlett* **1992**, 601. (e) Abbiati, G.; Canevari, V.; Facoetti, D.; Rossi, E. *Eur. J. Org. Chem.* **2007**, 517.

(14) Amat, M.; Llor, N.; Hidalgo, J.; Bosch, J. *Tetrahedron: Asymmetry* **1997**, *8*, 2237.

SCHEME 7. Enantioselective Total Synthesis of (−)-16-Episilicine

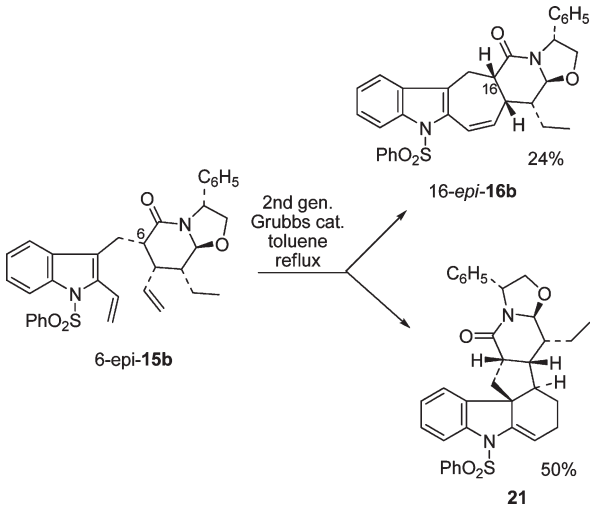


which leads to the unnatural configuration at C-15 (H-15α), and the *trans*-C/D ring fusion.

In fact, the conjugate addition of organocuprates to unsaturated oxazolopiperidone lactams is highly stereoselective[15] as a consequence of the conformational rigidity of the bicyclic system, occurring under stereoelectronic control,[16] axial to the electrophilic carbon of the conjugate double bond and, consequently, *cis* with respect to the adjacent pseudoequatorial ethyl substituent (see **11a** in Scheme 6). To obtain the natural (H-15*β*) absolute configuration at C-15, an obvious solution was to start from the enantiomeric lactam *ent*-**11a**, which would be accessible from the *S*-phenylglycinol-derived lactam *ent*-**10a**. However, taking into account the availability of lactam **10b**,[17] to access the natural C-15 absolute configuration we decided to use the unsaturated lactam **11b**, which presumably would also undergo a stereoselective conjugate addition ultimately leading to H-15*β* isomers. This lactam incorporates a C-8 ethyl substituent with the absolute configuration required for the synthesis of 16-episilicine, an alkaloid isolated in 1975 from *Pandaca caducifolia*.[18]

The synthetic sequence for the preparation of the key intermediate **16b** starting from lactam **10b** is outlined in Scheme 7 and parallels that previously developed starting from the diastereoisomeric lactam **10a**. As expected, the conjugate addition of the vinyl group to the unsaturated lactam **11b** took place stereoselectively leading to the *exo* isomer **12b** (mixture of C-6 epimers). A subsequent alkylation with the *N*-protected indole derivative **6** afforded **13b** in 75% yield as a single stereoisomer, thus confirming the facial stereoselectivity of the conjugate addition reaction.

SCHEME 8. RCM Reaction from Diene 6-*epi*-15b



Wittig methylenation of **13b** followed by removal of the *tert*-butoxycarbonyl group gave diene **15b** in 58% overall yield. Minor amounts (10%) of the C-6 epimer (6-*epi*-**15b**) were also isolated. The crucial ring-closing metathesis of **15b** was efficiently performed using the second-generation Grubbs catalyst under refluxing toluene to give the *trans*-fused pentacycle **16b** in 87% yield. Quite unexpectedly, a similar treatment from 6-*epi*-**15b** led to the anticipated *cis*-fused pentacycle 16-*epi*-**16b** in only 24% yield, the main product (50%) being the Diels−Alder adduct **21** (Scheme 8). As in the failure of the RCM reactions from dienes **4** and **8**, the different behavior of **15b** and 6-*epi*-**15b** under RCM reaction conditions can most probably be explained on conformational grounds. The absolute configuration of **16b**, coinciding at C-15 with the natural configuration (15*β*-H), and **21** were unambiguously established by X-ray crystallographic analysis.

Once the tetracyclic ring system of the target alkaloid, with the required *trans*-C_{15}−C_{16} and *cis*-C_{15}−C_{20} configuration, was assembled, to complete the synthesis from **16b** we only needed to remove the chiral auxiliary and the indole protecting group and to adjust the oxidation level. Catalytic hydrogenation of the

(15) (a) Amat, M.; Bosch, J.; Hidalgo, J.; Cantó, M.; Pérez, M.; Llor, N.; Molins, E.; Miravitlles, C.; Orozco, M.; Luque, J. *J. Org. Chem.* **2000**, *65*, 3074. (b) Amat, M.; Pérez, M.; Llor, N.; Escolano, C.; Luque, F. J.; Molins, E.; Bosch, J. *J. Org. Chem.* **2004**, *69*, 8681.

(16) (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; p 221. (b) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992; p 25.

(17) Amat, M.; Escolano, C.; Gómez-Esqué, A.; Lozano, O.; Llor, N.; Griera, R.; Molins, E.; Bosch, J. *Tetrahedron: Asymmetry* **2006**, *17*, 1581.

(18) (a) Zeches, M.; Debray, M. M.; Ledouble, G.; Le Men-Olivier, L.; Le Men, J. *Phytochemistry* **1975**, *14*, 1122. (b) Structural elucidation: Clivio, P.; Richard, B.; Nuzillard, J.-M.; Zèches-Hanrot, M. *Phytochemistry* **1995**, *40*, 987.

carbon−carbon double bond of **16b** followed by treatment with $LiAlH_4$−$AlCl_3$, which brought about both the reduction of the lactam carbonyl group and the reductive opening of the oxazolidine ring, gave tetracycle **17** in 64% overall yield. Deprotection of the indole nitrogen under smooth conditions, followed by a catalytic debenzylation in the presence of $(Boc)_2O$ led to the *N*-Boc protected piperidine derivative **19**. A chemoselective oxidation with I_2O_5[19] installed the 2-acylindole carbonyl group. Finally, removal of the Boc protecting group followed by methylation furnished (−)-16-episilicine, thus completing the first synthesis of this natural product.

The ^1H and ^{13}C NMR data of our synthetic 16-episilicine were in complete agreement with those previously reported[18b] for the alkaloid. However, the specific rotation of our synthetic material {$[\alpha]^{22}_D$ −20, *c* 1.0, $CHCl_3$)}, although coinciding in its absolute value with that reported for 16-episilicine {$[\alpha]^{22}_D$ +20, *c* 1.0, $CHCl_3$)},[18] had the opposite sign.[20] Taking into account that the C-15 configuration (*S*, 15*β*-H) of our synthetic 16-episilicine stems from the X-ray crystallographic analysis of the advanced intermediate **16b**, the discrepancy in the sign of the $[\alpha]_D$ values is striking since it might point to an uncommon 15α-H absolute configuration for the alkaloid 16-episilicine, which would be the enantiomer of the structure depicted in Figure 1. Hovewer, this would need to be confirmed with new material isolated from natural sources.

Conclusion

In summary, we have accomplished for the first time the enantioselective total synthesis of an alkaloid of the silicine group, thus further illustrating the potential and versatility of phenylglycinol-derived oxazolopiperidone lactams in the synthesis of enantiopure piperidine-containing complex natural products. The unexpected behavior of dienes **4** and **8** under RCM reaction conditions represents a serious drawback that precludes the application of the developed strategy to the synthesis of ervatamine alkaloids.

Experimental Section

(3*R*,7*R*,8*S*,8a*R*)-6-(Benzyloxycarbonyl)-8-ethyl-5-oxo-3-phenyl-7-vinyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (2). LiCl (906 mg, 21.3 mmol) was heated at 80 °C for 3 h under vacuum (10−15 mmHg) in a three-necked 500 mL round-bottomed flask. Then, CuI (5.6 g, 29.1 mmol) and THF (40 mL) were added at room temperature, and the mixture was stirred at rt for 5 min. The suspension was cooled at −78 °C, and vinylmagnesium bromide (1 M in THF, 29 mL), TMSCl (3.7 mL, 29.1 mmol), and a solution of the crude unsaturated lactam **1**[10] (2.88 g) in THF (100 mL) were successively added. The resulting mixture was stirred at −78 °C for 23 h. The reaction was quenched with saturated aqueous NH_4Cl, and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried and concentrated. Flash chromatography (4:1 hexane−EtOAc to 1:1 hexane−EtOAc) gave lactams **2** and 6-*epi*-**2** as a 4:1 mixture (2.80 g, 90% yield from the crude unsaturated lactam **1**). **2** (major epimer): IR (NaCl) 1664, 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR) *δ* 0.99 (t, *J* = 7.3 Hz, 3H, CH_3 ethyl), 1.36−1.46 (m, 1H, CH_2 ethyl), 1.74−1.87 (m, 1H, CH_2 ethyl), 2.24−2.31 (m, 1H, H-8), 3.02 (dd, *J* = 7.6, 3.6 Hz, 1H, H-7), 3.50 (d, *J* = 1.2 Hz, 1H, H-6), 3.99 (dd, *J* = 9.2, 1.2 Hz, 1H, H-2), 4.12 (dd, *J* = 9.2, 7.2 Hz, 1H, H-2), 4.55 (d, *J* = 10.0 Hz, 1H, H-8a), 4.91−4.95 (m, 1H, H-3), 5.02−5.26 (m, 4H, $CH_2C_6H_5$, CH_2=), 5.83 (ddd, *J* = 17.2, 10.4, 7.6 Hz, 1H, CH=), 7.19−7.35 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) *δ* 10.9 (CH_3 ethyl), 20.5 (CH_2 ethyl), 40.4 (C-7), 41.0 (C-8), 52.5 (C-6), 59.4 (C-3), 67.0 ($CH_2C_6H_5$), 73.9 (C-2), 90.1 (C-8a), 118.2 (CH=), 126.4 (C-*o*), 127.4 (C-*m*), 128.0 (C-*p*), 128.2 (C-*o*), 128.4 (C-*m*), 128.5 (C-*p*), 134.1 (CH_2=), 140.6 (C-*i*), 162.0 (NCO), 169.7 (CO). 6-*epi*-**2** (minor epimer): IR (NaCl) 1664, 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ* 1.04 (t, *J* = 7.4 Hz, 3H, CH_3 ethyl), 1.36−1.46 (m, 1H, CH_2 ethyl), 1.74−1.87 (m, 1H, CH_2 ethyl), 2.24−2.31 (m, 1H, H-8), 3.11 (ddd, *J* = 10.4, 6.4, 4.0 Hz, 1H, H-7), 3.56 (d, *J* = 6.4 Hz, 1H, H-6), 4.05 (dd, *J* = 9.2, 1.2 Hz, 1H, H-2), 4.13 (dd, *J* = 9.2, 7.2 Hz, 1H, H-2), 4.67 (d, *J* = 9.6 Hz, 1H, H-8a), 4.91−4.95 (m, 1H, H-3), 5.02−5.26 (m, 4H, $CH_2C_6H_5$, CH_2=), 5.73 (dt, *J* = 16.4, 10.8 Hz, 1H, CH=), 7.19−7.35 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) *δ* 10.9 (CH_3 ethyl), 20.9 (CH_2 ethyl), 42.6 (C-7), 44.4 (C-8), 53.9 (C-6), 59.7 (C-3), 66.8 ($CH_2C_6H_5$), 73.7 (C-2), 89.5 (C-8a), 120.1 (CH_2=), 126.4 (C-*o*), 127.4 (C-*m*), 128.0 (C-*p*), 128.2 (C-*o*), 128.4 (C-*m*), 128.5 (C-*p*), 132.4 (CH=), 135.4 (C-*i*), 162.3 (NCO), 168.4 (COO); HRMS calcd for [$C_{25}H_{27}NO_4$ + Na] 428.1832, found 428.1837.

(3*R*,6*R*,7*R*,8*S*,8a*R*)-6-[(1-Benzenesulfonyl-2-(*E*-ethoxycarbonyl)-vinyl-3-indolyl)methyl]-6-(benzyloxycarbonyl)-8-ethyl-5-oxo-3-phenyl-7-vinyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (4). NaH (60% dispersion in mineral oil, 60 mg, 1.51 mmol) was slowly added at 0 °C to a solution of lactams **2** (513 mg, 1.26 mmol) in dry DMF (18 mL), and the mixture was stirred at 0 °C for 1 h. Then, a solution of bromomethylindole **3**[12] (850 mg, 1.9 mmol) in DMF (6 mL) was added at 0 °C, and the resulting mixture was stirred at room temperature for 24 h. The mixture was poured into water, the aqueous layer was extracted with Et_2O, and the combined organic extracts were dried and concentrated. Flash chromatography of the resulting oil (9:1 hexane−EtOAc to 1:1 hexane−EtOAc) afforded pure compound **4** (820 mg, 84% yield): IR (film) 1659, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) *δ* 0.72 (t, *J* = 7.2 Hz, 3H, CH_3 ethyl), 1.12−1.18 (m, 2H, CH_2 ethyl, H-8), 1.37 (t, *J* = 7.2 Hz, 3H, CH_3CH_2CO), 1.48−1.54 (m, 1H, CH_2 ethyl), 2.94 (dd, *J* = 10.8, 4.4 Hz, 1H, H-7), 3.56 (d, *J* = 14.8 Hz, 1H, CH_2-ind), 3.66 (d, *J* = 14.8 Hz, 1H, CH_2-ind), 3.92 (dd, *J* = 9.0, 1.2 Hz, 1H, H-2), 4.00 (dd, *J* = 9.0, 6.5 Hz, 1H, H-2), 4.28−4.36 (m, 2H, CH_3CH_2CO), 4.62 (d, *J* = 9.2 Hz, 1H, H-8a), 4.82 (d, *J* = 6.5 Hz, 1H, H-3), 4.92−5.03 (m, 4H, $CH_2C_6H_5$, HC=CH_2), 5.57−5.67 (m, 1H, HC=CH_2), 6.26 (d, *J* = 16.4 Hz, 1 H, CH=CHCO), 6.69 (m, 1H, H-6 ind), 7.06−7.46 (m, 11H, ArH, H-5 ind), 7.65 (dd, *J* = 8.4, 1.2 Hz, 1H, H-7 ind), 8.05 (d, *J* = 16.4 Hz, 1H, CH=CHCO), 8.11 (d, *J* = 8.4 Hz, 1H, H-4 ind); ^{13}C NMR ($CDCl_3$, 100.6 MHz) *δ* 10.5 (CH_3 ethyl), 14.3 (CH_3CH_2CO), 20.1 (CH_2 ethyl), 29.7 (CH_2-ind), 43.4 (C-8), 46.0 (C-7), 59.9 (C-6), 60.2 (C-3), 60.8 (CH_3CH_2CO), 67.1 ($CH_2C_6H_5$), 74.2 (C-2), 88.7 (C-8a), 114.2 (CH=CHCO), 120.1 (HC=CH_2), 121.4 (C-7 ind), 121.7 (C-4 ind), 124.6 (C-3 ind), 124.9 (CH=CHCO), 126.0 (C-2 ind), 126.7 (C-6 ind), 126.9 (C-5 ind), 127.5 (C-*o*), 128.1 (C-*m*), 128.2 (C-*p*), 128.5 (C-*o*), 128.6 (C-*m*), 129.0 (C-*p*), 130.4 (C-*i*), 132.9 (HC=CH_2), 133.9 (C-*i*), 135.0 (C-*i*), 135.2 (C-*o*), 136.3 (C-*m*), 137.9 (C-3a ind), 140.9 (C-7a ind), 165.8 (COO), 165.9 (COO), 170.4 (NCO); $[\alpha]^{22}_D$ −58.3 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{45}H_{44}N_2O_8S$: C, 69.93; H, 5.74; N, 3.62; S, 4.15. Found: C, 69.93; H, 5.69; N, 3.55; S, 4.05.

Attempted RCM Reaction from 4. Second-generation Grubbs catalyst (2 mg) was added to a solution of compound **4** (60 mg, 0.08 mmol) in toluene (20 mL), and the resulting mixture was heated at reflux for 16 days, with an additional 2 mg of catalyst

(19) Yoshida, K.; Goto, J.; Ban, Y. *Chem. Pharm. Bull.* **1987**, *35*, 4700.

(20) We acknowledge Dr. J. M. Nuzillard (University of Reims) for providing us with a recently measured $[\alpha]_D$ value (+19.6, *c* 1.0, $CHCl_3$) of the isolated 16-episilicine.

being added each 24 h. The solvent was evaporated, and the resulting residue was chromatographed (99:1 CH_2Cl_2−EtOAc) to yield hexacycle **5** (20 mg, 33% yield): IR (film) 1678, 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR; see Supporting Information for the numbering system) δ 0.99 (t, J = 7.4 Hz, 3H, CH_3 ethyl), 1.31 (t, J = 7.1 Hz, 3H, CH_3CH_2CO), 1.36 (d, J = 15.6 Hz, 1H, H-15), 1.65 (d, J = 15.6 Hz, 1H, H-15), 1.79−1.87 (m, 1H, H-8), 1.89−1.99 (m, 2H, CH_2 ethyl), 2.13−2.19 (m, 1H, H-10), 2.46−2.53 (m, 2H, H-8a, H-9), 2.96−3.01 (m, 1H, H-7), 3.08 (dd, J = 9.6, 4.8 Hz, 1H, H-8b), 4.07 (d, J = 4.0 Hz, 2H, H-11), 4.17 (d, J = 6.4 Hz, 1H, CH_3CH_2CO), 4.21 (d, J = 6.4 Hz, 1H, CH_3CH_2CO), 4.77 (t, J = 4.0 Hz, 1H, H-12), 4.88 (d, J = 6.0 Hz, 1H, H-9a), 5.06 (d, J = 12.0 Hz, 1H, CH_2C$_6$H$_5$), 5.16 (d, J = 12.0 Hz, 1H, CH_2-C$_6$H$_5$), 6.38 (d, J = 3.6 Hz, 1H, H-6), 6.56 (d, J = 7.6 Hz, 1H, H-1), 6.75 (ddd, J = 8.8, 7.6, 1.2 Hz, 1H, H-2), 7.11 (dd, J = 8.4, 1.2 Hz, 1H, ArH), 7.16 (dd, J = 8.4, 1.2 Hz, 1H, ArH), 7.32−7.44 (m, 13H, ArH), 7.50 (dd, J = 8.8, 1.2 Hz, 1H, H-4), 7.77 (dd, J = 8.8, 0.8 Hz, 1H, H-3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 12.9 (CH_3 ethyl), 14.2 (CH_3CH$_2$CO), 24.3 (CH_2 ethyl), 25.2 (C-8), 39.7 (C-7), 43.0 (C-9), 43.8 (C-8a), 44.0 (C-15), 49.7 (C-8b), 53.2 (C-15a), 58.1 (C-12), 60.3 (C-14a), 61.1 (CH_3CH_2CO), 67.7 (CH_2C$_6$H$_5$), 74.1 (C-11), 93.5 (C-9a), 110.0 (C-6), 113.0 (C-4), 116.9 (C-2), 121.8 (C-3), 125.5 (C-1), 126.4 (C-*o*), 126.9 (C-*m*), 127.8 (C-*p*), 128.0 (C-*o*), 128.6 (C-*m*), 128.7 (C-*p*), 128.8 (C-*o*), 128.9 (C-*m*), 133.6 (C-*i*), 134.9 (C-*i*), 137.0 (C-*i*), 138.8 (C-15b), 140.2 (C-4a), 141.6 (C-5a), 144.4 (C-6), 166.0 (NCO), 170.8 (COO), 173.2 (COO); $[\alpha]^{22}_D$ −56.1 (*c* 0.5, $CHCl_3$). Anal. Calcd for $C_{45}H_{44}N_2O_8S$: C, 69.93; H, 5.74; N, 3.62; S, 4.15. Found: C, 69.81; H, 5.76; N, 3.29; S, 3.89.

1-(Benzenesulfonyl)-3-(bromomethyl)indole-2-carbaldehyde (6). Benzoyl peroxide (2 mg, 0.008 mmol) was added at rt to a solution of 1-(benzenesulfonyl)-3-methylindole-2-carbaldehyde[21] (250 mg, 0.84 mmol) and NBS (155 mg, 0.87 mmol) in anhydrous CCl_4 (20 mL). The mixture was heated at reflux for 4 h, cooled at rt, and filtered. The solution was concentrated, and the resulting residue was chromatographed (hexane to 9:1 hexane−EtOAc) to give formylindole **6** (188 mg, 60% yield): IR (film) 1678 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.91 (s, 2H, CH_2), 7.39−7.74 (m, 8H, ArH), 8.22 (d, J = 8.7 Hz, 1H, H-4), 10.66 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 20.6 (CH_2), 115.6 (C-7), 121.6 (C-4), 125.1 (C-6), 126.6 (C-5), 128.1 (C-3), 129.4 (C-*o*), 129.5 (C-*m*), 129.7 (C-*p*), 132.3 (C-2), 134.5 (C-3a), 137.1 (C-7a), 137.2 (C-*i*), 184.8 (CHO); HRMS calcd for [$C_{16}H_{12}NO_3SBr$ + H] 377.9794, found 377.9781.

(3*R*,6*R*,7*R*,8*S*,8a*R*)-6-[(1-Benzenesulfonyl-2-formyl-3-indolyl)-methyl]-6-(benzyloxycarbonyl)-8-ethyl-5-oxo-3-phenyl-7-vinyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (7). Operating as in the above preparation of **4**, from lactam **2** (39 mg, 0.1 mmol), NaH (60% dispersion in mineral oil, 4.8 mg, 0.12 mmol), and bromomethylindole **6** (63 mg, 0.16 mmol) in DMF (2 mL), compound **7** (51 mg, 75% yield) was obtained after column chromatography (9:1 hexane−EtOAc to 1:1 hexane−EtOAc) as a yellow foam: IR (film) 1661, 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 0.88 (t, J = 7.6 Hz, 3H, CH_3 ethyl), 1.26−1.31 (m, 1H, CH_2 ethyl), 1.61−1.69 (m, 2H, CH_2 ethyl, H-8), 3.62 (dd, J = 10.8, 4.4 Hz, 1H, H-7), 3.74 (d, J = 14.0 Hz, 1H, CH_2-ind), 3.78 (d, J = 14.0 Hz, 1H, CH_2-ind), 3.87 (d, J = 9.2 Hz, 1H, H-2), 4.03 (dd, J = 9.2, 7.2 Hz, 1H, H-2), 4.67 (d, J = 9.2 Hz, 1H, H-8a), 4.81 (d, J = 6.0 Hz, 1H, H-3), 4.95 (d, J = 12.4 Hz, 1H, CH_2C$_6$H$_5$), 5.00 (d, J = 12.4 Hz, 1H, CH_2C$_6$H$_5$), 5.04 (dd, J = 10.0, 1.6 Hz, 1H, HC=CH_2), 5.27 (dd, J = 16.0, 1.6 Hz, 1H, HC=CH_2), 5.68 (dt, J = 16.0, 10.0 Hz, 1H, *H*C=CH$_2$), 6.73 (t, J = 8.0 Hz, 1 H, H-5 ind), 6.87 (d, J = 4.4 Hz, 1 H, ArH), 7.05−7.08 (m, 1H, H-6 ind), 7.24−7.52 (m, 14H, ArH), 7.73 (dd, J = 8.0, 1.6 Hz, 1H, H-7 ind), 7.98 (d, J = 8.0 Hz, 1H, H-4 ind), 10.29 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 10.6 (CH_3 ethyl), 20.6 (CH_2 ethyl), 31.3 (CH_2-ind), 42.2 (C-8), 46.1 (C-7), 60.2 (C-6), 60.3 (C-3), 67.1 (CH_2C$_6$H$_5$), 74.3 (C-2), 89.1 (C-8a), 114.3 (C-7 ind), 120.0 (HC=CH_2), 120.3 (C-6 ind), 123.9 (C-5 ind), 128.4 (C-4 ind), 126.6 (C-3 ind), 126.7 (C-*o*), 127.4 (C-*m*), 128.1 (C-*p*), 128.2 (C-*o*), 128.4 (C-*m*), 128.8 (C-*p*), 129.4 (*H*C=CH$_2$), 130.8 (C-*o*), 133.2 (C-*m*), 134.1 (C-3a ind), 135.0 (C-*i*), 135.3 (C-*i*), 137.1 (C-*i*), 137.8 (C-2 ind), 140.1 (C-7a ind), 165.5 (COO), 170.6 (NCO), 183.9 (CHO); $[\alpha]^{22}_D$ −27.7 (*c* 0.3, $CHCl_3$). Anal. Calcd for $C_{41}H_{38}N_2O_7S\cdot 1/2CH_2Cl_2$: C, 66.88; H, 5.27; N, 3.76; S, 4.30. Found: C, 66.88; H, 5.29; N, 3.85; S, 4.31.

(3*R*,6*R*,7*R*,8*S*,8a*R*)-6-[(1-Benzenesulfonyl-2-vinyl-3-indolyl)-methyl]-6-(benzyloxycarbonyl)-8-ethyl-5-oxo-3-phenyl-7-vinyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (8). KHMDS (0.5 M in toluene, 2.16 mL, 1.08 mmol) was added to a solution of methyltriphenylphosphonium bromide (387 mg, 1.08 mmol) in anhydrous THF, and the mixture was stirred at rt for 30 min. This solution was slowy transferred to a solution of formylindole **7** (370 mg, 0.53 mmol) in anhydrous THF (20 mL), and the mixture was heated at reflux for 4 h. The reaction was quenched by addition of water, and the mixture was extracted with Et_2O. The combined organic extracts were dried and concentrated. Flash chromatography (9:1 hexane−CH_2Cl_2 to 1:1 hexane−CH_2Cl_2) gave **8** (323 mg, 87% yield): IR (film) 1658, 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 0.56 (t, J = 7.2 Hz, 3H, CH_3 ethyl), 1.08−1.20 (m, 2H, CH_2 ethyl, H-8), 1.47−1.55 (m, 1H, CH_2 ethyl), 2.98 (dd, J = 10.8, 4.4 Hz, 1H, H-7), 3.55 (d, J = 15.2 Hz, 1H, CH_2-ind), 3.71 (d, J = 15.2 Hz, 1H, CH_2-ind), 3.97 (dd, J = 9.2, 1.6 Hz, 1H, H-2), 4.01 (dd, J = 9.2, 6.4 Hz, 1H, H-2), 4.61 (d, J = 9.6 Hz, 1H, H-8a), 4.84 (dd, J = 6.4, 1.6 Hz, 1H, H-3), 4.94 (d, J = 12.4 Hz, 1H, CH_2C$_6$H$_5$), 4.95 (dt, J = 8.0, 1.6 Hz, 1H, CH=CH_2), 5.00 (d, J = 1.6 Hz, 1H, CH=CH_2), 5.05 (d, J = 12.4 Hz, 1H, CH_2C$_6$H$_5$), 5.37 (dd, J = 17.0, 1.6 Hz, 1H, ind-HC=CH_2), 5.51 (dd, J = 11.0, 1.6 Hz, 1H, ind-HC=CH_2), 5.63 (dd, J = 17.0, 11.0 Hz, 1H, ind-*H*C=CH$_2$), 6.80 (td, J = 8.0, 0.8 Hz, 1 H, C*H*=CH$_2$), 6.80 (td, J = 7.6, 0.8 Hz, 1H, H-5 ind), 6.85 (d, J = 11.6 Hz, 1 H, ArH), 6.88 (d, J = 11.6 Hz, 1 H, ArH), 7.16−7.38 (m, 13H, ArH), 7.45 (tt, J = 7.6, 1.2 Hz, 1H, H-6 ind), 7.70−7.73 (m, 1H, H-7 ind), 8.11 (dd, J = 7.6, 0.4 Hz, 1H, H-4 ind); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 10.3 (CH_3 ethyl), 20.0 (CH_2 ethyl), 28.9 (CH_2-ind), 43.2 (C-8), 45.1 (C-7), 60.1 (C-3), 60.2 (C-6), 67.0 (CH_2C$_6$H$_5$), 74.2 (C-2), 88.7 (C-8a), 114.0 (C-7 ind), 117.2 (C-5 ind), 119.7 (CH=*C*H$_2$), 120.9 (C-6 ind), 122.7 (ind-CH=*C*H$_2$), 124.1 (ind-*C*H=CH$_2$), 124.9 (C-3 ind), 126.8 (C-4 ind), 127.2 (*C*H=CH$_2$), 127.5 (C-*o*), 128.0 (C-*m*), 128.1 (C-*p*), 128.2 (C-*o*), 128.5 (C-*m*), 128.6 (C-*p*), 128.9 (C-*o*), 130.8 (C-3a ind), 133.3 (C-*m*), 133.6 (C-*p*), 135.3 (C-*i*), 135.4 (C-2 ind), 137.1 (C-*i*), 138.4 (C-*i*), 140.9 (C-7a ind), 166.3 (COO), 170.9 (NCO); $[\alpha]^{22}_D$ −21.5 (*c* 0.4, $CHCl_3$). Anal. Calcd for $C_{42}H_{40}N_2O_6S\cdot 1/2H_2O$: C, 67.63; H, 6.08; N, 3.76. Found C, 67.40; H, 5.68; N, 3.56.

Attempted RCM Reaction from 8. Operating as in the preparation of compound **5**, hexacycle **9** was obtained (8 mg, 32% yield) from lactam **8** (25 mg, 0.04 mmol) and the second−generation Grubbs catalyst (8 mg; 0.5 mg/day, 16 days) in toluene (10 mL) after flash chromatography (9:1 CH_2Cl_2−EtOAc). **9**: IR (film) 1661, 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR; see Supporting Information for the numbering system) δ 0.84 (t, J = 7.3 Hz, 3H, CH_3 ethyl), 1.42−1.78 (m, 6H, CH_2 ethyl, H-7, H-8), 2.20−2.25 (m, 1H, H-9), 2.55 (d, J = 16.0 Hz, 1H, H-15), 2.75 (d, J = 16.0 Hz, 1H, H-15), 2.97 (dd, J = 8.8, 4.8 Hz, 1H, H-8b), 3.06 (m, 1H, H-8a), 4.07 (d, J = 4.0 Hz, 2H, H-11), 4.88 (t, J = 4.0 Hz, 1H, H-12), 4.93 (d, J = 5.6 Hz, 1H, H-9a), 5.18 (d, J = 12.0 Hz,

(21) Benzies, D. W. M.; Martinez-Fresneda, P.; Jones, R. A. *Synth. Commun.* **1986**, *16*, 1799.

1H, $CH_2C_6H_5$), 5.23 (d, J = 12.0 Hz, 1H, $CH_2C_6H_5$), 6.27 (d, J = 7.6 Hz, 1H, H-6), 6.56 (td, J = 8.0, 0.8 Hz, 1H, H-1), 7.11 (td, J = 8.0, 1.2 Hz, 1H, H-2), 7.36−7.45 (m, 15H, ArH), 7.56 (d, J = 7.6 Hz, 1H, H-4), 8.00 (dd, J = 8.0, 1.6 Hz, 1H, H-3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 12.5 (CH_3 ethyl), 24.7 (CH_2 ethyl), 21.6 (C-8), 23.6 (C-7), 32.8 (C-15), 42.1 (C-9), 47.6 (C-8a), 49.9 (C-8b), 58.1 (C-12), 59.3 (C-15a), 60.2 (C-14a), 67.9 ($CH_2C_6H_5$), 74.0 (C-11), 93.7 (C-9a), 101.8 (C-6), 114.5 (C-4), 117.0 (C-2), 123.1 (C-3), 124.7 (C-1), 126.7 (C-*o*), 127.1 (C-*m*), 127.7 (C-*p*), 128.0 (C-*o*), 128.2 (C-*m*), 128.7 (C-*p*), 134.7 (C-*i*), 137.1 (C-*i*), 139.2 (C-15b), 140.2 (C-4b), 141.8 (C-5a), 167.7 (COO), 172.2 (NCO); $[\alpha]^{22}_D$ +14.6 (*c* 0.5, $CHCl_3$); HRMS calcd for [$C_{42}H_{40}N_2O_6S$ + H] 701.8509, found, 701.8504.

(3*R*,8*S*,8a*R*)-6-(*tert*-Butoxycarbonyl)-8-ethyl-5-oxo-3-phenyl-2,3,8,8a-tetrahydro-5*H*-oxazolo[3,2-*a*]pyridine (11a). Lithium bis(trimethylsilyl)amide (17.4 mL of a 1.0 M solution in THF) was slowly added at −78 °C to a solution of lactam **10a**[14] (2 g, 8.1 mmol) in anhydrous THF (100 mL), and the resulting mixture was stirred for 90 min. Then, $(Boc)_2O$ (1.90 g, 8.71 mmol) and, after 2 h of continuous stirring at −78 °C, a solution of PhSeCl (2.12 g, 11.05 mmol) in anhydrous THF (10 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 (1:9 hexane−EtOAc) of the resulting oil afforded the corresponding selenides as a mixture of C-6 epimers (3.64 g, 89% yield). Pure isomers were isolated after a subsequent chromatography. Higher R_f epimer: IR (NaCl) 1665, 1726 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR) δ 0.91 (t, J = 7.2 Hz, 3H, CH_3), 1.18 (m, 1H, CH_2 ethyl), 1.29 [s, 9H, (CH_3)$_3$C], 1.66 (m, 1H, CH_2 ethyl), 1.76 (t, J = 12.4 Hz, 1H, H-7), 1.81 (m, 1H, H-8), 2.36 (dd, J = 12.4, 1.2 Hz, 1H, H-7), 3.88 (d, J = 8.8 Hz, 1H, H-8a), 3.95 (dd, J = 9.2, 6.8 Hz, 1H, H-2), 3.98 (dd, J = 9.2, 2.4 Hz, 1H, H-2), 4.81 (dd, J = 6.8, 2.4 Hz, 1H, H-3), 7.20−7.55 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 10.6 (CH_3), 23.4 (CH_2 ethyl), 27.5 [(CH_3)$_3$C], 36.8 (C-7), 39.8 (C-8), 55.7 (C-6), 59.2 (C-3), 74.0 (C-2), 82.7 [(CH_3)$_3C$], 92.2 (C-8a), 126.9−129.5 (C-*o*, *m*, *p*), 138.3 (C-*i*), 140.8 (C-*i*), 163.6 (NCO), 168.9 (COO); HRMS calcd for [$C_{26}H_{31}NO_4Se$ + H] 502.1484, found 502.1491. Lower R_f epimer: IR (NaCl) 1668, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR) δ 0.91 (t, J = 7.2 Hz, 3H, CH_3), 1.18 (m, 1H, CH_2 ethyl), 1.45 [s, 9H, (CH_3)$_3$C)], 1.66 (m, 1H, CH_2 ethyl), 1.96 (dd, J = 14.0, 11.2 Hz, 1H, H-7), 2.04 (m, 1H, H-8), 2.13 (dd, J = 14.0, 3.6 Hz, 1H, H-7), 4.06 (dd, J = 9.2, 1.2 Hz, 1H, H-2), 4.16 (dd, J = 9.2, 6.8 Hz, 1H, H-2), 4.57 (d, J = 8.4 Hz, 1H, H-8a), 4.95 (dd, J = 6.8, 1.2 Hz, 1H, H-3), 7.20−7.55 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 10.8 (CH_3), 23.9 (CH_2 ethyl), 27.8 [(CH_3)$_3$C], 34.3 (C-7), 38.5 (C-8), 56.7 (C-6), 59.3 (C-3), 73.9 (C-2), 82.8 [(CH_3)$_3C$], 92.1 (C-8a), 126.7−129.5 (C-*o*, *m*, *p*), 138.1 (C-*i*), 140.7 (C-*i*), 163.5 (NCO), 168.6 (COO); HRMS calcd for [$C_{52}H_{62}N_2O_8Se_2$ + Na] 1025.2728, found 1025.2732. A stream of ozone gas was bubbled through a cooled (−78 °C) solution of the above selenides (3.64 g, 7.26 mmol) in anhydrous CH_2Cl_2 (215 mL) until it turned pale blue (5 min). Then, the solution was purged with O_2, and the temperature was slowly raised to 25 °C. 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 **11a** (2.5 g) as an oil, which due to its unstability was used in the next reaction without further purification: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.14 (t, J = 7.5 Hz, 3H, CH_3), 1.50 [s, 9H, C(CH_3)$_3$], 1.64 (m, 1H, CH_2 ethyl), 1.88 (m, 1H, CH_2 ethyl), 2.72 (m, 1H, H-8), 4.14 (dd, J = 8.7, 1.5 Hz, 1H, H-2), 4.21 (dd, J = 8.7, 6.3 Hz, 1H, H-2), 4.85 (d, J = 10.5 Hz, 1H, H-8a), 5.05 (dd, J = 6.3, 1.5 Hz, 1H, H-3), 7.03 (d, J = 1.4 Hz, 1H, H-7), 7.10−7.20 (m, 5H, ArH).

(3*R*,8*R*,8a*S*)-6-(*tert*-Butoxycarbonyl)-8-ethyl-5-oxo-3-phenyl-2,3,8,8a-tetrahydro-5*H*-oxazolo[3,2-*a*]pyridine (11b). Operating as in the above preparation of **11a**, from lactam **10b**[17] (1.56 g, 6.36 mmol) in THF (100 mL), LiHMDS (13.5 mL of a 1.0 M solution in THF), $(Boc)_2O$ (1.47 g, 6.74 mmol) in THF (20 mL), and PhSeCl (1.64 g, 8.54 mmol) in THF (10 mL), a 7:3 mixture of C-6 epimeric selenides (2.6 g, 82% yield) was obtained. Pure isomers were isolated after a subsequent flash chromatography (9:1 hexane−EtOAc to 4:1 hexane−EtOAc). Higher R_f epimer: IR (NaCl) 1658, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR) δ 0.73 (t, J = 7.3 Hz, 3H, CH_3 ethyl), 1.12−1.20 (m, 1H, CH_2 ethyl), 1.44 [s, 9H, C(CH_3)$_3$], 1.64−1.71 (m, 1H, CH_2 ethyl), 1.83−1.92 (m, 2H, H-7, H-8), 2.03 (dd, J = 11.2, 2.0 Hz, 1H, H-7), 3.73 (dd, J = 8.8, 0.4 Hz, 1H, H-2), 4.44 (dd, J = 8.8, 7.6 Hz, 1H, H-2), 4.67 (d, J = 8.0 Hz, 1H, H-8a), 5.25 (t, J = 7.6 Hz, 1H, H-3), 7.24−7.40 (m, 8H, ArH), 7.80 (m, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 10.8 (CH_3 ethyl), 24.0 (CH_2 ethyl), 27.7 [CH_3)$_3$C], 33.3 (C-7), 38.2 (C-8), 57.4 (C-6), 58.6 (C-3), 72.3 (C-2), 82.8 [(CH_3)$_3C$], 92.3 (C-8a), 125.8 (C-*o*), 127.2 (C-*m*), 127.4 (C-*p*), 128.6 (C-*o*), 128.8 (C-*m*), 129.4 (C-*p*), 138.1 (C-*i*), 138.9 (C-*i*), 165.0 (NCO), 170.0 (CO); $[\alpha]^{22}_D$ − 169.5 (*c* 1.0, $CHCl_3$); HRMS calcd for [$C_{26}H_{31}NO_4Se$ + Na] 524.1310, found 524.1312. Lower R_f epimer: IR (NaCl) 1662, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR) δ 0.93 (t, J = 7.3 Hz, 3H, CH_3 ethyl), 1.15−1.22 (m, 1H, CH_2 ethyl), 1.47 [s, 9H, C(CH_3)$_3$], 1.62−1.83 (m, 2H, CH_2 ethyl, H-8), 1.79 (d, J = 12.0 Hz, 1H, H-7), 2.39 (d, J = 12.0 Hz, 1H, H-7), 3.78 (dd, J = 8.8, 6.8 Hz, 1H, H-2), 4.28 (d, J = 8.0 Hz, 1H, H-8a), 4.37 (dd, J = 8.8, 7.6 Hz, 1H, H-2), 5.31 (t, J = 7.3 Hz, 1H, H-3), 7.11−7.37 (m, 9H, ArH), 7.50 (dd, J = 8.0, 1.2 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 10.8 (CH_3 ethyl), 23.9 (CH_2 ethyl), 27.7 [CH_3)$_3$C], 35.3 (C-7), 39.4 (C-8), 55.8 (C-6), 59.0 (C-3), 72.1 (C-2), 83.2 [(CH_3)$_3C$], 92.0 (C-8a), 126.5 (C-*o*), 126.8 (C-*m*), 127.5 (C-*p*), 128.6 (C-*o*), 128.7 (C-*m*), 129.1 (C-*p*), 138.0 (C-*i*), 138.9 (C-*i*), 165.5 (NCO), 169.1 (CO); $[\alpha]^{22}_D$ −13.1 (*c* 0.5, $CHCl_3$). Operating as described above for the preparation of compound **11a**, unstable lactam **11b** (1,78 g) was obtained from the corresponding selenides (2.6 g, 5.2 mmol) in CH_2Cl_2 (100 mL): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.11 (t, J = 7.3 Hz, 3H, CH_3 ethyl), 1.50 [s, 9H, C(CH_3)$_3$], 1.56−1.65 (m, 1H, CH_2 ethyl), 1.82−1.89 (m, 1H, CH_2 ethyl), 2.53 (dddd, J = 9.6, 8.0, 5.2, 2.0 Hz, 1H, H-8), 3.93 (dd, J = 9.2, 6.0 Hz, 1H, H-2), 4.43 (dd, J = 9.2, 7.2 Hz, 1H, H-2), 5.10 (d, J = 9.6 Hz, 1H, H-8a), 5.27 (t, J = 6.3 Hz, 1H, H-3), 6.98 (d, J = 2.0 Hz, 1H, H-7), 7.24−7.91 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 11.0 (CH_3 ethyl), 23.5 (CH_2 ethyl), 28.0 [C(CH_3)$_3$], 42.4 (C-8), 58.3 (C-3), 73.1 (C-2), 82.0 [C(CH_3)$_3$], 90.7 (C-8a), 126.3 (C-*o*), 127.7 (C-*p*), 128.7 (C-*m*), 131.5 (C-6), 138.9 (C-*i*), 144.7 (C-7), 157.8 (NCO), 162.5 (CO).

(3*R*,7*R*,8*S*,8a*R*)-6-(*tert*-Butoxycarbonyl)-8-ethyl-5-oxo-3-phenyl-7-vinyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (12a). Operating as in the above preparation of **2**, from LiCl (1.23 g, 29.29 mmol), CuI (5.54 g, 29.08 mmol), vinylmagnesium bromide (1 M in THF, 29.08 mL), TMSCl (3.7 mL, 29.1 mmol), and a solution of the crude unsaturated lactam **11a** (2.5 g, 7.27 mmol) in THF (100 mL), lactam **12a** was obtained as a mixture of C-6 epimers (ratio 77:23, 2.51 g, 83% overall yield from **10a**) after flash chromatography (9:1 hexane−EtOAc to 4:1 hexane−EtOAc). Higher R_f epimer: IR (NaCl) 1666, 1731 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR) δ 1.07 (t, J = 7.2 Hz, 3H, CH_3 ethyl), 1.37 [s, 9H, C(CH_3)$_3$], 1.45 (m, 1H, CH_2 ethyl), 1.83 (m, 1H, CH_2 ethyl), 2.36 (m, 1H, H-8), 3.05 (dd, J = 8.0, 3.6 Hz, 1H, H-7), 3.32 (d, J = 0.8 Hz, 1H, H-6), 3.98 (dd, J = 9.2, 1.2 Hz, 1H, H-2), 4.11 (dd, J = 9.2, 7.2 Hz, 1H, H-2), 4.52 (d, J = 10.0 Hz, 1H, H-8a), 4.90 (dd, J = 7.2, 1.2 Hz, 1H, H-3), 5.16 (d, J = 17.2 Hz, 1H, HC=CH_2), 5.23

(d, J = 10.8 Hz, 1H, HC═CH_2), 5.82 (ddd, J = 17.2, 10.8, 8.0 Hz, 1H, HC═CH$_2$), 7.20−7.35 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 11.0 (CH_3 ethyl), 20.5 (CH_2 ethyl), 27.8 [C(CH_3)$_3$], 40.6 (C-8), 40.8 (C-7), 53.6 (C-6), 59.4 (C-3), 74.0 (C-2), 81.9 [C(CH$_3$)$_3$], 90.1 (C-8a), 118.0 (HC═CH$_2$), 126.4, 128.3 (C-o, m), 127.3 (C-p), 134.6 (HC═CH$_2$), 140.9 (C-i), 162.4 (NCO), 168.6 (COO). Lower R_f epimer: ^{1}H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR) δ 1.04 (t, J = 7.6 Hz, 3H, CH_3 ethyl), 1.38 [s, 9H, C(CH_3)$_3$], 1.45 (bs, 1H, CH_2 ethyl), 1.83 (bs, 2H, CH_2 ethyl, H-8), 3.08 (dd, J = 6.0, 3.2 Hz, 1H, H-7), 3.36 (d, J = 6.0 Hz, 1H, H-6), 4.02 (dd, J = 9.2, 0.8 Hz, 1H, H-2), 4.13 (dd, J = 9.2, 8.8 Hz, 1H, H-2), 4.66 (d, J = 9.2 Hz, 1H, H-8a), 4.92 (bs, 1H, H-3), 5.21 (bs, 2H, HC═CH_2), 5.76 (dt, J = 16.8, 10.8 Hz, 1H; HC═CH$_2$), 7.20−7.35 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 10.9 (CH_3 ethyl), 20.9 (CH_2 ethyl), 28.0 [C(CH_3)$_3$], 42.4 (C-7), 44.6 (C-8), 54.6 (C-6), 59.7 (C-3), 73.7 (C-2), 81.5 [C(CH$_3$)$_3$], 89.6 (C-8a), 119.6 (HC═CH$_2$), 126.5 (C-o), 127.4 (C-m), 127.5 (C-p), 132.9 (HC═CH$_2$), 141.2 (C-i), 162.9 (COO), 167.7 (NCO). Anal. Calcd for $C_{22}H_{29}NO_4\cdot 1/2H_2O$: C, 69.45; H, 7.95; N, 3.68. Found C, 69.35; H, 7.93; N, 3.73.

(3*R*,7*S*,8*R*,8a*S*)-6-(*tert*-Butoxycarbonyl)-8-ethyl-5-oxo-3-phenyl-7-vinyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (12b). Operating as in the above preparation of **12a**, from LiCl (0.88 g, 20.8 mmol), CuI (3.95 g, 20.8 mmol), vinylmagnesium bromide (1 M in THF, 20.8 mL), TMSCl (2.7 mL, 20.8 mmol), and a solution of the crude unsaturated lactam **11b** (1.78 g, 5.2 mmol) in THF (100 mL), lactam **12b** was obtained as a mixture of C-6 epimers (ratio 4:1, 1.98 g, 84% overall yield from **10b**) after flash chromatography (hexane to 1:9 hexane−EtOAc). Pure isomers were isolated after a subsequent chromatography. Higher R_f epimer: ^{1}H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR) δ 1.01 (t, J = 7.3 Hz, 3H, CH_3 ethyl), 1.36−1.64 (m, 1H, CH_2 ethyl), 1.47 [s, 9H, (CH$_3$)$_3$C], 1.70−1.80 (m, 1H, CH_2 ethyl), 2.02−2.09 (m, 1H, H-8), 2.97 (ddd, J = 8.0, 3.6, 1.2 Hz, 1H, H-7), 3.45 (d, J = 1.2 Hz, 1H, H-6), 3.70 (dd, J = 13.6, 9.0 Hz, 1H, H-2), 4.51 (dd, J = 13.6, 8.4 Hz, 1H, H-2), 4.63 (d, J = 8.8 Hz, 1H, H-8a), 5.20−5.30 (m, 3H, H-3, HC═CH_2), 5.79−5.90 (m, 1H, HC═CH$_2$), 7.20−7.35 (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 11.1 (CH_3 ethyl), 21.2 (CH_2 ethyl), 27.8 [(CH$_3$)$_3$C], 40.8 (C-8), 41.0 (C-7), 53.4 (C-6), 58.7 (C-3), 72.5 (C-2), 82.0 [(CH$_3$)$_3$$C$], 90.5 (C-8a), 118.1 (HC═CH$_2$), 125.8 (C-o), 127.4 (C-m), 128.7 (C-p), 134.3 (HC═CH$_2$), 139.4 (C- i), 164.2 (NCO), 169.2 (CO); HRMS calcd for [$C_{22}H_{29}NO_4$ + H] 372.2169, found 372.2166. Lower R_f epimer: ^{1}H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR) δ 1.03 (t, J = 7.4 Hz, 3H, CH_3 ethyl), 1.36−1.64 (m, 1H, CH_2 ethyl), 1.42 [s, 9H, (CH$_3$)$_3$C], 1.70−1.80 (m, 1H, CH_2 ethyl), 2.02−2.09 (m, 1H, H-8), 3.06 (ddd, J = 10.8, 6.0, 3.2 Hz, 1H, H-7), 3.48 (d, J = 6.0 Hz, 1H, H-6), 3.69 (t, J = 8.5 Hz, 1H, H-2), 4.53 (dd, J = 8.5, 4.8 Hz, 1H, H-2), 4.66 (d, J = 9.2 Hz, 1H, H-8a), 5.19 (t, J = 1.2 Hz, 1H, H-3), 5.20−5.37 (m, 2H, HC═C H_2), 5.79−5.90 (m, 1H, HC═CH$_2$), 7.20−7.35 (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 11.0 (CH_3 ethyl), 21.6 (CH_2 ethyl), 27.9 [(CH $_3$)$_3$C], 42.2 (C-8), 44.4 (C-7), 54.6 (C-6), 58.1 (C-3), 72.2 (C-2), 81.7 [(CH$_3$)$_3$$C$], 90.4 (C-8a), 120.2 (HC═CH$_2$), 125.4 (C-o), 127.3 (C-m), 128.7 (C-p), 132.4 (HC═CH$_2$), 139.0 (C-i), 164.9 (NCO), 167.7 (CO); HRMS calcd for [$C_{44}H_{58}N_2O_8$ + Na] 765.4085, found 765.4080.

(3*R*,6*R*,7*R*,8*S*,8a*R*)-6-[(1-Benzenesulfonyl-2-formyl-3-indolyl)-methyl]-6-(*tert*-butoxycarbonyl)-8-ethyl-5-oxo-3-phenyl-7-vinyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (13a). Operating as described above for the preparation of **4**, from lactam **12a** (500 mg, 1.35 mmol), NaH (60% dispersion in mineral oil, 65 mg, 1.62 mmol), and formylindole **6** (2.55 mg, 6.76 mmol) in DMF (60 mL), compound **13a** (827 mg, 92% yield) was obtained after flash chromatography (9:1 hexane−EtOAc): IR (film) 1658, 1736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 0.85 (t, J = 7.4 Hz, 3H, CH_3 ethyl), 1.26−1.47 (m, 2H, CH_2 ethyl, H-8), 1.38 [s, 9H, C(CH_3)$_3$], 1.62−1.69 (m, 1H, CH_2 ethyl), 3.65−3.74 (m, 3H, CH_2-ind, H-7), 3.85 (d, J = 8.8 Hz, 1H, H-2), 4.04 (dd, J = 8.8, 6.4 Hz, 1H, H-2), 4.69 (d, J = 9.6 Hz, 1H, H-8a), 4.79 (d, J = 6.4 Hz, 1H, H-3), 5.20 (dd, J = 10.4, 1.6 Hz, 1H, HC═CH_2), 5.44 (dd, J = 16.8, 1.6 Hz, 1H, HC═CH_2), 5.83 (dt, J = 16.8, 10.4 Hz, 1H, HC═CH$_2$), 6.69 (t, J = 7.6 Hz, 1 H, H-5 ind), 6.78−6.83 (m, 3H, ArH, H-7 ind), 7.05 (ddd, J = 8.8, 6.0, 2.4 Hz, 1H, H-6 ind), 7.26−7.82 (m, 7H, ArH), 8.01 (d, J = 8.4 Hz, 1H, H-4 ind), 10.32 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 10.5 (CH_3 ethyl), 20.3 (CH_2 ethyl), 27.9 [(CH_3)$_3$C], 31.1 (CH_2-ind), 43.0 (C-8), 44.8 (C-7), 60.0 (C-6), 60.2 (C-3), 74.2 (C-2), 82.4 [(CH$_3$)$_3$$C$], 88.9 (C-8a), 114.2 (C-7 ind), 120.3 (HC═CH$_2$), 124.2 (C-6 ind), 124.8 (C-5 ind), 126.4 (C-o), 126.7 (C-m), 127.2 (C-p), 128.2 (C-o), 128.8 (C-p), 129.4 (C-m), 130.0 (C-3 ind), 131.2 (C-2 ind), 133.5 (HC═CH$_2$), 134.2 (C-4 ind), 135.0 (C-3a ind), 137.1 (C-*ipso*), 137.9 (C-7a ind), 141.2 (C-*ipso*), 166.3 (COO), 169.6 (NCO), 183.7 (CHO); [α]^{22} +19.2 (c 1.0, $CHCl_3$). Anal. Calcd for $C_{38}H_{40}N_2O_7S$: C, 68.24; H, 6.03; N, 4.19. Found: C, 67.85; H, 5.97; N, 3.76.

(3*R*,6*S*,7*S*,8*R*,8a*S*)-6-[(1-Benzenosulfonyl-2-formyl-3-indolyl)-methyl]-6-(*tert*-butoxycarbonyl)-8-ethyl-5-oxo-3-phenyl-7-vinyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (13b). Operating as described for the preparation of **13a**, pure compound **13b** (680 g, 75% yield) was obtained from the mixture of lactams **12b** and 6-*epi*-**12b** (500 mg, 1.35 mmol), NaH (65 mg, 1.62 mmol), and formylindole **6** (1.02 g, 2.70 mmol) in DMF (45 mL) after flash chromatography (9:1 hexane−EtOAc to 1:1 hexane−EtOAc). **13b**: IR (KBr) 1671, 1727 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 0.87 (t, J = 7.3 Hz, 3H, CH_3 ethyl), 1.22 [s, 9H, (CH$_3$)$_3$C], 1.27−1.37 (m, 1H, CH_2 ethyl), 1.68−1.74 (m, 1H, CH_2 ethyl), 2.00 (ddd, J = 13.2, 9.0, 3.6 Hz, 1H, H-8), 2.86 (dd, J = 10.0, 3.6 Hz, 1H H-7), 3.66 (t, J = 8.4 Hz, 1H, H-2), 3.70 (d, J = 13.2 Hz, 1H, CH_2-ind), 3.85 (d, J = 13.2 Hz, 1H, CH_2-ind), 4.49 (t, J = 8.4 Hz, 1H, H-2), 4.68 (d, J = 9.0 Hz, 1H, H-8a), 5.04 (t, J = 8.4 Hz, 1H, H-3), 5.22 (dd, J = 10.0, 1.6 Hz, 1H, HC═CH_2), 5.25 (dd, J = 17.6, 1.6 Hz, 1H, HC═CH_2), 5.81 (dt, J = 17.6, 10.0 Hz, 1 H, HC═CH$_2$), 7.20−7.30 (m, 7H, ArH, H-7 ind), 7.39 (dd, J = 8.0, 1.2 Hz, 2H, ArH), 7.43 (dd, J = 8.0, 1.2 Hz, 1H, H-5 ind), 7.74−7.76 (m, 2H, ArH), 8.00 (d, J = 8.0 Hz, 1H, H-6 ind), 8.09 (d, J = 8.8 Hz, 1H, H-4 ind), 10.52 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 10.8 (CH_3 ethyl), 21.4 (CH_2 ethyl), 27.8 [CH_3)$_3$C], 31.5 (CH$_2$-ind), 40.5 (C-8), 48.9 (C-7), 59.1 (C-3), 59.7 (C-6), 72.1 (C-2), 82.5 [(CH$_3$)$_3$$C$], 90.4 (C-8a), 115.0 (C-7 ind), 120.6 (HC═CH$_2$), 123.9 (C-6 ind), 124.1 (C-5 ind), 125.7 (C-4 ind), 126.8 (C-o), 127.2 (C-m), 128.4 (C-p), 128.7 (C-o), 129.0 (C-m), 129.9 (C-3 ind), 132.0 (C-2 ind), 132.7 (HC═CH$_2$), 133.8 (C-p), 134.8 (C-3a ind), 137.3 (C-i), 137.6 (C-7a ind), 139.4 (C-i), 166.0 (NCO), 170.3 (CO), 184.8 (CHO); [α]$^{22}_D$ −137.7 (*c* 0.5, $CHCl_3$); HRMS calcd for [$C_{38}H_{40}N_2O_7S$ + Na] 691.2447, found 691.2448.

(3*R*,6*R*,7*R*,8*S*,8a*R*)-6-[1-(1-Benzenosulfonyl-2-vinyl-3-indolyl)-methyl]-6-(*tert*-butoxycarbonyl)-8-ethyl-5-oxo-3-phenyl-7-vinyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (14a). Operating as described for the preparation of **8**, vinylindole **14a** was obtained (181 mg, 70% yield) from methyltriphenylphosphonium bromide (542 mg, 1.52 mmol), KHMDS (0.5 M in toluene, 3.0 mL, 1.52 mmol), and lactam **13a** (259 mg, 0.38 mmol) in THF (30 mL) after column chromatography (9:1 hexane−CH_2Cl_2 to 1:1 hexane−CH_2Cl_2). **14a**: IR (film) 1658, 1736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 0.57 (t, J = 7.2 Hz, 3H, CH_3 ethyl), 1.01−1.16 (m, 2H, CH_2 etthyl, H-8), 1.41 (s, 9H, (CH_3)$_3$C), 1.49−1.55 (m, 1H, CH_2 ethyl), 2.99 (dd, J = 10.8, 4.8 Hz, 1H, H-7), 3.51 (d, J = 14.8 Hz, 1H, CH_2-ind), 3.63 (d, J = 14.8 Hz, 1H, CH_2-ind), 3.97 (dd, J = 9.1, 1.2 Hz, 1H, H-2), 4.05 (dd, J = 9.1, 6.6 Hz, 1H, H-2), 4.66 (d, J = 9.6 Hz, 1H, H-8a), 4.83 (dd, J = 6.6, 1.2 Hz, 1H, H-3), 5.09 (dd, J = 6.7, 1.6 Hz, 1H, CH−CH═CH_2), 5.12 (m, 1H, CH−CH═CH_2), 5.39 (dd, J = 18.0,

1.6 Hz, 1H, ind-CH=CH_2), 5.53 (dd, J = 11.2, 1.6 Hz, 1H, ind-CH=CH_2), 5.75−5.85 (m, 1H, CH−CH=CH_2), 6.73 (dd, J = 7.2, 0.8 Hz, 1 H, H-5 ind), 6.92 (dd, J = 18.0, 11.2 Hz, 1H, ind-CH=CH $_2$), 7.12−7.35 (m, 9 H, ArH, H-ind), 7.44−7.73 (m, 2H, ArH, H-ind), 8.12 (d, J = 8.4 Hz, 1H, H-4 ind); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 10.2 (CH_3 ethyl), 19.6 (CH_2 ethyl), 27.9 [(CH_3)$_3$C], 28.6 (CH_2-ind), 43.9 (C-8), 44.4 (C-7), 60.0 (C-6), 60.3 (C-3), 74.3 (C-2), 82.2 [(CH_3)$_3C$], 88.5 (C-8a), 113.9 (C-7 ind), 117.5 (C-5 ind), 119.5 (CH−CH=CH_2), 121.2 (C-4 ind), 122.7 (ind-CH=CH_2), 124.1 (C-6 ind), 124.8 (C-3 ind), 126.7 (C-*o*), 127.1 (C-*m*), 127.4 (C-*p*), 128.1 (ind-CH=CH$_2$), 128.5 (C-*o*), 128.9 (C-*m*), 130.8 (C-2 ind), 133.6 (C-*p*), 133.8 (CH-CH=CH$_2$), 135.4 (C-3a ind), 136.9 (C-7a ind), 138.4 (C-*i*), 141.0 (C-*i*), 166.9 (NCO), 169.9 (CO); $[\alpha]^{22}_D$ −41.8 (*c* 0.5, $CHCl_3$); HRMS calcd for [$C_{39}H_{42}N_2O_6S$ + Na] 689.2662, found 689.2662.

(3*R*,6*S*,7*S*,8*R*,8*aS*)-6-[(1-Benzenesulfonyl-2-vinyl-3-indolyl)-methyl]-6-(*tert*-butoxycarbonyl)-8-ethyl-5-oxo-3-phenyl-7-vinyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (14b). Operating as in the above preparation of **14a**, vinylindole **14b** was obtained (1.1 g, 76% yield) from methyltriphenylphosphonium bromide (1.52 g, 4.27 mmol), KHMDS (0.5 M in toluene, 8.48 mL, 4.24 mmol) in THF (20 mL), and lactam **13b** (1.45 g, 2.17 mmol) in THF (20 mL) after flash chromatography (9:1 hexane−EtOAc to 1:1 hexane−EtOAc). **14b**: IR (film) 1655, 1729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 0.56 (t, J = 7.4 Hz, 3H, CH_3 ethyl), 0.97−1.09 (m, 1H, CH_2 ethyl), 1.26−1.38 (m, 2H, CH_2 ethyl, H-8), 1.36 [s, 9H, (CH_3)$_3$C], 2.73 (dd, J = 11.2, 4.0 Hz, 1H, H-7), 3.58 (dd, J = 8.4, 7.6 Hz, 1H, H-2), 3.64 (d, J = 14.8 Hz, 1H, CH_2-ind), 3.97 (d, J = 14.8 Hz, 1H, CH_2-ind), 4.08 (t, J = 8.4 Hz, 1H, H-2), 4.54 (d, J = 9.2 Hz, 1H, H-8a), 5.09−5.14 (m, 2H, HC=CH_2), 5.19 (t, J = 7.6 Hz, 1H, H-3), 5.58 (dd, J = 18.0, 1.2 Hz, 1H, ind-HC=CH_2), 5.69−5.78 (m, 1H, HC=CH$_2$), 5.77 (dd, J = 11.6, 1.2 Hz, 1H, ind-HC=CH_2), 7.12 (dd, J = 18.0, 11.6 Hz, 1H, ind-HC=CH$_2$), 7.22−7.38 (m, 10H, ArH), 7.48 (t, J = 7.6 Hz, 1 H, H-7 ind), 7.70 (d, J = 8.0 Hz, 1H, H-5 ind), 7.75 (d, J = 7.6 Hz, 1H, H-6 ind), 8.21 (d, J = 8.4 Hz, 1H, H-4 ind); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 10.3 (CH_3 ethyl), 20.9 (CH_2 ethyl), 28.0 [C(CH_3)$_3$], 30.4 (CH_2-ind), 41.6 (C-8), 46.1 (C-7), 59.0 (C-3), 59.3 (C-6), 71.7 (C-2), 82.6 [C(CH_3)$_3$], 89.4 (C-8a), 114.8 (C-7 ind), 118.4 (C-3 ind), 119.7 (HC=CH_2), 121.2 (C-4 ind), 122.6 (ind-HC=CH$_2$), 123.5 (C-5 ind), 125.4 (C-6 ind), 125.9 (C-*o*), 126.8 (C-*m*), 127.4 (C-*p*), 127.6 (C-*o*), 128.6 (C-*m*), 131.1 (C-2 ind), 133.2 (C-*p*), 133.7 (ind-HC=CH$_2$), 135.7 (C-*i*), 136.9 (C-3a ind), 138.3 (C-7a ind), 139.0 (HC=CH$_2$), 168.2 (NCO), 170.3 (CO); $[\alpha]^{22}_D$ +18.6 (*c* 0.5, $CHCl_3$); HRMS calcd for [$C_{39}H_{42}N_2O_6S$ + Na] 689.2662, found 689.2655.

(3*R*,6*S*,7*R*,8*S*,8a*R*)-6-[(1-Benzenesulfonyl-2-vinyl-3-indolyl)-methyl]-8-ethyl-5-oxo-3-phenyl-7-vinyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (15a). TFA (100 μL, 1.58 mmol) was added to a solution of **14a** (260 mg, 0.39 mmol) in CH_2Cl_2 (50 mL), and the mixture was stirred at room temperature for 2 h. Saturated aqueous Na_2CO_3 was added to the reaction to reach pH 6−7, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated to give an oil, which was dissolved in toluene (30 mL). The resulting solution was heated at reflux for 6 h and concentrated to dryness. The residue was chromatographed (1:1 hexane−CH_2Cl_2 to CH_2Cl_2) to afford lactam **15a** (178 mg, 81% yield): IR (film) 1655 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 0.93 (t, J = 7.2 Hz, 3H, CH_3 ethyl), 1.22−1.41 (m, 1H, CH_2 ethyl), 1.72−1.86 (m, 1H, CH_2 ethyl), 1.94−2.03 (m, 1H, H-8), 2.26 (dd, J = 8.1, 3.6 Hz, 1H, H-7), 2.75 (dd, J = 10.9, 4.2 Hz, 1H, H-6), 2.95 (dd, J = 14.5, 10.9 Hz, 1H, CH_2-ind), 3.01 (dd, J = 14.5, 4.2 Hz, 1H, CH_2-ind), 4.00 (dd, J = 9.2, 1.4 Hz, 1H, H-2), 4.11 (dd, J = 9.2, 6.9 Hz, 1H, H-2), 4.52 (d, J = 9.6 Hz, 1H, H-8a), 4.66 (dt, J = 17.2, 1.2 Hz, 1H, CHHC=CH_2), 4.88 (dd, J = 6.9, 1.4 Hz, 1H, H-3), 4.95 (d, J = 10.5 Hz, 1H, CHHC=CH_2), 5.47 (dd, J = 17.8, 1.7 Hz, 1H, ind-CH=CH_2), 5.64 (ddd, J = 17.2, 10.4, 8.1 Hz, 1H, CHHC=CH$_2$), 5.69 (dd, J = 11.4, 1.7 Hz, 1H, ind-CH=CH_2), 7.13 (dd, J = 17.8, 11.4 Hz, 1H, ind-CH=CH$_2$), 7.18−7.55 (m, 12H, ArH, H-ind), 7.69 (dd, J = 8.4, 1.2 Hz, 1 H, H-6 ind), 8.19 (d, J = 8.4 Hz, 1H, H-4 ind); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 11.2 (CH_3 ethyl), 20.9 (CH_2 ethyl), 26.9 (CH_2-ind), 39.5 (C-7 and C-8), 46.0 (C-6), 59.3 (C-3), 73.8 (C-2), 90.3 (C-8a), 115.1 (C-7 ind), 117.4 (CHHC=CH_2), 119.8 (C-5 ind), 120.4 (ind-CH=CH$_2$), 121.0 (C-4 ind), 123.9 (C-6 ind), 125.4 (C-3 ind), 126.2 (C-*o*), 126.6 (C-*m*), 127.5 (C-*p*), 127.9 (ind-CH=CH$_2$), 128.6 (C-*o*), 128.9 (C-*m*), 130.3 (C-2 ind), 133.6 (C-*p*), 135.6 (CHHC=CH $_2$), 135.7 (C-3a ind), 136.2 (C-7a ind), 138.1 (C-*i*), 141.9 (C-*i*), 168.9 (NCO); $[\alpha]^{22}_D$ +145.3 (*c* 0.3, $CHCl_3$); HRMS calcd for [$C_{34}H_{34}N_2O_4S$ + H] 567.2312, found 567.2316.

(3*R*,6*R*,7*S*,8*R*,8*aS*)-6-[(1-Benzenesulfonyl-2-vinyl-3-indolyl)-methyl]-8-ethyl-5-oxo-3-phenyl-7-vinyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (15b). Operating as above, compounds **15b** (756 mg, 77% yield) and 6-*epi*-**15b** (136 mg, 14% yield) were obtained from lactam **14b** (1.15 g, 1.73 mmol) in CH_2Cl_2 (150 mL) and TFA (5 mL, 0.06 mol) in toluene (250 mL) after flash chromatography (hexane to 9:1 hexane−EtOAc). **15b** (6*R*, major): IR (KBr) 1653 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 1.12 (t, J = 7.2 Hz, 3H, CH_3 ethyl), 1.46−1.56 (m, 1H, CH_2 ethyl), 1.87−1.95 (m, 2H, CH_2 ethyl, H-8), 2.45 (dd, J = 8.0, 2.4 Hz, 1H, H-7), 3.06 (dd, J = 12.0, 3.2 Hz, 1H, H-6), 3.23 (dd, J = 14.0, 12.0 Hz, 1H, CH_2-ind), 3.55 (dd, J = 14.0, 3.2 Hz, 1H, CH_2-ind), 3.86 (t, J = 8.5 Hz, 1H, H-2), 4.69 (t, J = 8.5 Hz, 1H, H-2), 4.81 (d, J = 8.8 Hz, 1H, H-8a), 4.87 (d, J = 16.8 Hz, 1H, HC=CH_2), 5.15 (d, J = 10.4 Hz, 1H, HC=CH_2), 5.41 (d, J = 8.5 Hz, 1H, H-3), 5.67 (dd, J = 17.6, 1.5 Hz, 1H, ind-HC=CH_2), 5.84 (dd, J = 11.2, 1.5 Hz, 1H, ind-HC=CH_2), 5.82−5.92 (m, 1H, HC=CH$_2$), 7.31 (dd, J = 17.6, 11.2 Hz, 1H, ind-HC=CH$_2$), 7.38−7.54 (m, 9H, ArH, H-7 ind), 7.63−7.67 (m, 2H, ArH), 7.79 (d, J = 8.0 Hz, 1H, H-5 ind), 7.90 (dd, J = 8.0, 1.2 Hz, 1H, H-6 ind), 8.40 (d, J = 8.4 Hz, 1H, H-4 ind); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 11.4 (CH_3 ethyl), 21.7 (CH_2 ethyl), 26.1 (CH$_2$-ind), 39.3 (C-7), 40.0 (C-8), 45.7 (C-6), 58.9 (C-3), 72.8 (C-2), 90.9 (C-8a), 115.1 (C-7 ind), 117.5 (HC=CH$_2$), 119.8 (C-6 ind), 120.6 (C-2 ind), 121.2 (ind-HC=CH$_2$), 123.9 (C-4 ind), 125.4 (C-5 ind), 126.0 (C-*o*), 126.6 (C-*m*), 127.6 (ind-HC=CH$_2$), 127.8 (C-*p*), 128.9 (C-*o*), 128.9 (C-*m*), 130.3 (C-3 ind), 133.6 (C-*p*), 135.5 (HC=CH$_2$), 135.8 (C-3a ind), 136.2 (C-7a ind), 138.1 (C-*i*), 139.6 (C-*i*), 170.2 (NCO); $[\alpha]^{22}_D$ −96.0 (*c* 0.5, $CHCl_3$); HRMS calcd for [$C_{34}H_{34}N_2O_4S$ + H] 567.2312, found 567.2316. 6-*epi*-**15b** (6*S*, minor): IR (KBr) 1656 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 0.85 (t, J = 7.3 Hz, 3H, CH_3 ethyl), 1.24−1.36 (m, 1H, CH_2 ethyl), 1.48−1.64 (m, 2H, CH_2 ethyl, H-8), 2.30 (dt, J = 6.4, 3.6 Hz, 1H, H-7), 2.83 (m, 1H, CH_2-ind), 2.90 (dd, J = 12.4, 4.4 Hz, 1H, H-6), 3.59 (d, J = 13.2 Hz, 1H, CH_2-ind), 3.71 (t, J = 8.5 Hz, 1H, H-2), 4.52 (t, J = 8.5 Hz, 1H, H-2), 4.62 (d, J = 8.8 Hz, 1H, H-8a), 4.98 (dd, J = 17.0, 1.4 Hz, 1H, HC=CH_2), 5.26 (t, J = 8.5 Hz, 1H, H-3), 5.32 (dd, J = 10.0, 1.4 Hz, 1H, HC=CH_2), 5.39 (dd, J = 17.8, 1.6 Hz, 1H, ind-CH=CH_2), 5.55 (dd, J = 11.4, 1.6 Hz, 1H, ind-CH=CH_2), 5.62 (dt, J = 17.0, 10.0 Hz, 1H, HC=CH$_2$), 7.04 (dd, J = 17.8, 11.4 Hz, 1H, ind-CH=CH$_2$), 7.22 (dt, J = 8.0, 1.2 Hz, 1H, H-7 ind), 7.25−7.39 (m, 9H, ArH), 7.47 (dt, J = 7.2, 1.2 Hz, 1H, H-5 ind), 7.57 (d, J = 8.0 Hz, 2H, ArH), 7.72 (dd, J = 8.0, 1.2 Hz, 1H, H-6 ind), 8.21 (d, J = 8.4 Hz, 1H, H-6 ind); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 11.4 (CH_3 ethyl), 22.7 (CH_2 ethyl), 23.0 (CH$_2$-ind), 42.1 (C-7), 44.9 (C-8), 47.1 (C-6), 58.9 (C-3), 73.0 (C-2), 91.6 (C-8a), 115.0 (C-7 ind), 119.9 (C-4 ind), 120.8 (C-3 ind), 121.4 (CH$_2$=CH), 122.0 (ind-CH=CH$_2$), 123.6 (C-5 ind), 125.1 (C-6 ind), 126.0 (C-*o*), 126.7 (C-*m*), 127.6 (C-*p*), 127.7 (C-*p*), 128.8 (C-*o*), 128.9 (C-*m*), 130.6 (C-2 ind), 132.9 (HC=CH$_2$), 133.5 (ind-CH=CH$_2$), 135.6 (C-*i*), 136.2 (C-*i*), 138.2 (C-3a ind), 140.0 (C-7a ind), 167.0 (NCO); $[\alpha]^{22}_D$ −16.0 (*c* 0.2, $CHCl_3$); HRMS calcd for [$C_{34}H_{34}N_2O_4S$ + Na] 589.2131, found 589.2132.

(1*R*,3a*R*,4*S*,4a*R*,12a*S*)-7-(Benzenesulfonyl)-4-ethyl-13-oxo-1-phenyl-1,2,3a,4,4a,12,12a,13-octahydrooxazolo[2″,3″:6′,1′]-pyrido[3′,4′:4,5]cyclohepta[1,2-*b*]indole (16a). Operating as described for the preparation of **5**, pentacycle **16a** was obtained (31 mg, 86% yield) from compound **15a** (38 mg, 0.07 mmol) and the second−generation Grubbs catalyst (12 mg; 1.7 mg/day, 7 days) in toluene (25 mL) after column chromatography (CH_2Cl_2): IR (KBr) 1655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 0.99 (t, J = 7.2 Hz, 3H, CH_3 ethyl), 1.62−1.76 (m, 2H, CH_2 ethyl), 2.12 (q, J = 8.0 Hz, 1H, H-4), 2.50 (ddd, J = 12.4, 8.4, 4.0 Hz, 1H, H-12a), 2.78 (dd, J = 17.6, 12.0 Hz, 1H, H-12), 2.79−2.85 (m, 1H, H-4a), 3.45 (dd, J = 17.6, 4.0 Hz, 1H, H-12), 4.15 (dd, J = 9.2, 1.2 Hz, 1H, H-2), 4.24 (dd, J = 9.2, 6.4 Hz, 1H, H-2), 4.78 (d, J = 8.0 Hz, 1H, H-3a), 4.93 (d, J = 6.1 Hz, 1H, H-1), 6.18 (dd, J = 12.0, 6.0 Hz, 1H, H-5), 7.19−7.41 (m, 12H, ArH, H-6, H-10), 7.46 (tt, J = 7.5, 1.2 Hz, 1H, H-9), 7.66 (dd, J = 8.4, 1.2 Hz, 1H, H-8), 8.24 (d, J = 8.4 Hz, 1H, H-11); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 11.5 (CH_3 ethyl), 20.5 (CH_2 ethyl), 25.2 (C-12), 40.2 (C-4), 44.9 (C-4a), 45.2 (C-12a), 58.9 (C-1), 74.4 (C-2), 90.3 (C-3a), 115.6 (C-8), 118.8 (C-9), 120.3 (C-11), 123.6 (C-6a), 124.2 (C-10), 125.6 (C-11a), 126.2 (C-11b), 126.5 (C-*o*), 126.8 (C-*m*), 127.7 (C-*p*), 128.6 (C-*o*), 128.8 (C-*m*), 131.0 (C-11a), 132.5 (C-5), 133.5 (C-*p*), 136.8 (C-7a), 138.1 (C-*i*), 141.0 (C-*i*), 168.5 (NCO); mp 195−144 °C (CH_3Cl, hexane); $[\alpha]^{22}_D$ +73.4 (*c* 0.2, $CHCl_3$). Anal. Calcd for $C_{32}H_{30}N_2O_4S \cdot 1/4CHCl_3$: C, 68.14; H, 5.36; N, 4.93. Found C, 67.88; H, 5.60; N, 4.59.

(1*R*,3a*S*,4*R*,4a*S*,12a*R*)-7-Benzenesulfonyl-4-ethyl-13-oxo-1-phenyl-1,2,3a,4,4a,12,12a,13-octahydrooxazolo[2″,3″:6′,1′]-pyrido[3′,4′:4,5]cyclohepta[1,2-*b*]indole (16b). Operating as described in the above preparation of **16a**, pentacycle **16b** was obtained (1.09 g, 87% yield) from lactam **15b** (1.31 g, 2.32 mmol) and the second−generation Grubbs catalyst (265 mg; 53 mg/day, 5 days) in toluene (300 mL) after flash chromatography (hexane to 1:1 hexane−EtOAc): IR (KBr) 1656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 0.99 (t, J = 7.4 Hz, 3H, CH_3 ethyl), 1.53−1.64 (m, 2H, CH_2 ethyl), 1.89−1.95 (m, 1H, H-4), 2.62 (dt, J = 10.0, 3.6 Hz, 1H, H-12a), 2.77 (ddd, J = 10.0, 5.4, 2.1 Hz, 1H, H-4a), 2.87 (dd, J = 16.8, 10.0 Hz, 1H, H-12), 3.46 (dd, J = 16.8, 3.6 Hz, 1H, H-12), 3.84 (dd, J = 9.0, 6.6 Hz, 1H, H-2), 4.40 (dd, J = 9.0, 7.8 Hz, 1H, H-2), 4.92 (d, J = 4.8 Hz, 1H, H-3a), 5.31 (t, J = 6.9 Hz, 1H, H-1), 6.10 (dd, J = 11.7, 5.1 Hz, 1H, H-5), 7.23−7.50 (m, 13H, ArH, H-6, H-9, H-10), 7.66 (dd, J = 8.4, 1.2 Hz, 1H, H-8), 8.24 (d, J = 8.1 Hz, 1H, H-11); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 12.1 (CH_3 ethyl), 19.9 (CH_2 ethyl), 24.3 (C-12), 39.8 (C-4a), 43.8 (C-4), 44.3 (C-12a), 58.6 (C-1), 71.8 (C-2), 90.2 (C-3a), 115.5 (C-8), 118.9 (C-9), 121.1 (C-6a), 123.8 (C-11), 124.1 (C-10), 125.5 (C-11a), 126.1 (C-11b), 126.4 (C-*o*), 127.6 (C-*m*), 128.7 (C-*p*), 128.8 (C-*o*), 130.8 (C-6), 132.6 (C-5), 132.8 (C-*m*), 133.5 (C-*p*), 136.7 (C-*i*), 137.9 (C-7a), 139.4 (C-*i*), 170.8 (NCO); mp 161−163 °C (MeOH); $[\alpha]^{22}_D$ −244.0 (*c* 0.3, $CHCl_3$). Anal. Calcd for $C_{32}H_{30}N_2O_4S \cdot 1/2H_2O$: C, 70.57; H, 5.67; N, 5.14; S, 5.89. Found C, 70.53; H, 5.74; N, 5.09; S, 5.89.

RCM Reaction from 6-*epi*-15b. Operating as in the preparation of compound **5**, pentacycle 6-*epi*-**16b** (240 mg, 24% yield) and hexacycle **21** (540 mg, 50% yield) were obtained from diene 6-*epi*-**15b** (1.08 g, 1.91 mmol) and the second−generation Grubbs catalyst (480 mg; 30 mg/day, 16 days) in toluene (500 mL) after flash chromatography (9:1 hexane−EtOAc to 4:1 hexane−EtOAc). 16-*epi*-**16b**: IR (film) 1655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 0.97 (t, J = 7.4 Hz, 3H, CH_3 ethyl), 1.46−1.73 (m, 2H, CH_2 ethyl), 1.89 (ddd, J = 14.0, 7.6, 5.2 Hz, 1H, H-4), 2.89−2.95 (m, 1H, H-4a), 2.92 (dd, J = 14.4, 10.4 Hz, 1H, H-12), 3.18 (dd, J = 14.4, 5.2 Hz, 1H, H-12), 3.31 (dt, J = 7.2, 5.2 Hz, 1H, H-12a), 3.63 (dd, J = 8.8, 8.4 Hz, 1H, H-2), 4.50 (dd, J = 8.8, 8.4 Hz, 1H, H-2), 4.78 (d, J = 9.2 Hz, 1H, H-3a), 5.20 (t, J = 8.0 Hz, 1H, H-1), 6.21 (dd, J = 11.6, 5.2 Hz, 1H, H-5), 6.88−7.79 (m, 14H, ArH, H-6, H-8, H-9, H-10), 8.20 (d, J = 8.4 Hz, 1H, H-11); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 11.4 (CH_3 ethyl), 22.1 (CH_2 ethyl), 25.4 (C-12), 38.6 (C-4a), 43.6 (C-4), 54.2 (C-12a), 58.3 (C-1), 72.6 (C-2), 90.7 (C-3a), 114.6 (C-8), 119.1 (C-9), 123.0 (C-6a), 124.0 (C-11), 124.2 (C-10), 125.2 (C-*o*), 125.3 (C-*p*), 126.5 (C-*m*), 127.0 (C-11a), 127.3 (C-11b), 128.7 (C-*o*), 129.2 (C-*m*), 130.1 (C-*p*), 130.6 (C-6), 133.6 (C-5), 136.2 (C-7a ind), 138.7 (C-*i*), 138.8 (C-*i*), 169.9 (NCO); $[\alpha]^{22}_D$ −252.0 (*c* 0.3, $CHCl_3$); HRMS calcd for $[C_{32}H_{30}N_2O_4S + H]$ 539.1999, found 539.1997. **21**: IR (film) 1655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR; see Supporting Information for the numbering system) δ 1.02 (dd, J = 13.2, 8.4 Hz, 1H, H-15), 1.10 (t, J = 7.4 Hz, 3H, CH_3 ethyl), 1.25−1.33 (m, 1H, H-15), 1.30 (d, J = 13.2 Hz, 1H, H-8), 1.56−1.69 (m, 1H, CH_2 ethyl), 1.71 (d, J = 13.2 Hz, 1H, H-8), 1.84 (ddd, J = 13.2, 9.2, 4.0 Hz, 1H, H-9), 1.99 (ddd, J = 13.6, 8.4, 2.4 Hz, 1H, CH_2 ethyl), 2.04 (dt, J = 13.2, 2.8 Hz, 1H, H-7), 2.17 (dt, J = 12.4, 2.8 Hz, 1H, H-7), 2.39 (t, J = 8.4 Hz, 1H, H-14a), 2.50 (ddd, J = 10.4, 6.0, 3.6 Hz, 1H, H-8b), 2.57 (dd, J = 10.4, 6.0 Hz, 1H, H-8a), 4.14 (dd, J = 9.2, 6.8 Hz, 1H, H-11), 4.44 (dd, J = 9.2, 8.0 Hz, 1H, H-11), 5.18 (d, J = 8.4 Hz, 1H, H-9a), 5.27 (t, J = 7.4 Hz, 1H, H-12), 6.03 (dt, J = 7.2, 0.8 Hz, 1H, H-1), 6.30 (dd, J = 8.0, 0.8 Hz, 1H, H-2), 6.35 (dd, J = 8.4, 2.8 Hz, 1H, H-6), 6.95 (dt, J = 8.0, 1.2 Hz, 1H, H-3), 7.35−7.70 (m, 11H, ArH, H-4); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 11.7 (CH_3 ethyl), 19.0 (C-7), 22.9 (CH_2 ethyl), 28.3 (C-8), 41.0 (C-8b), 41.5 (C-8a), 42.7 (C-9), 45.7 (C-14a), 47.1 (C-15), 59.5 (C-12), 71.8 (C-11), 90.3 (C-9a), 114.6 (C-6), 115.3 (C-4), 121.8 (C-2), 124.5 (C-1), 127.0 (C-*o*), 127.4 (C-*p*), 128.2 (C-*p*), 128.6 (C-*m*), 128.8 (C-15b), 128.9 (C-*o*), 129.1 (C-*m*), 133.4 (C-3), 138.1 (C-4a), 138.4 (C-5a), 139.0 (C-15a), 139.3 (C-*i*), 146.7 (C-*i*), 169.9 (NCO); mp 193−195 °C (MeOH); $[\alpha]^{22}_D$ −85.5 (*c* 0.6, $CHCl_3$); HRMS calcd for $[C_{34}H_{34}N_2O_4S + H]$ 567.2312, found 567.2310.

(1*R*,3a*S*,4*R*,4a*S*,12a*R*)-7-Benzenesulfonyl-4-ethyl-13-oxo-1-phenyl-1,2,3a,4,4a,5,6,12,12a,13-decahydrooxazolo[2″,3″:6′,1′]-pyrido[3′,4′:4,5]cyclohepta[1,2-*b*]indole (Dihydro-16b). A solution of lactam **16b** (500 mg, 0.93 mmol) in EtOAc (15 mL) containing 20% PtO_2 (100 mg) was hydrogenated at room temperature for 24 h. The catalyst was removed by filtration and washed with hot MeOH. The combined solution was concentrated, and the residue was chromatographed (9:1 hexane−EtOAc) to give dihydro-**16b** (360 mg, 72% yield): IR (KBr) 1662 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 1.00 (t, J = 7.6 Hz, 3H, CH_3 ethyl), 1.43−1.62 (m, 2H, CH_2 ethyl), 1.75 (ddd, J = 18.0, 9.2, 3.6 Hz, 1H, H-5), 1.87−1.95 (m, 2H, H-4, H-5), 2.08−2.16 (m, 1H, H-4a), 2.57 (ddd, J = 11.2, 8.4, 4.0 Hz, 1H, H-12a), 2.87 (dd, J = 16.0, 8.4 Hz, 1H, H-12), 3.21 (ddd, J = 17.2, 9.2, 4.4 Hz, 1H, H-6), 3.41−3.50 (m, 1H, H-6), 3.43 (dd, J = 16.0, 4.0 Hz, 1H, H-12), 3.78 (dd, J = 9.2, 7.2 Hz, 1H, H-2), 4.38 (t, J = 8.4 Hz, 1H, H-2), 4.74 (d, J = 2.8 Hz, 1H, H-3a), 5.36 (t, J = 7.4 Hz, 1H, H-1), 7.23−7.55 (m, 11H, ArH, H-8, H-9, H-10), 7.70 (dd, J = 8.8, 1.2 Hz, 2H, ArH), 8.19 (dd, J = 6.4, 1.6 Hz, 1H, H-11); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 12.6 (CH_3 ethyl), 19.6 (CH_2 ethyl), 22.2 (C-12), 25.3 (C-6), 28.1 (C-5), 37.6 (C-4a), 41.2 (C-12a), 44.6 (C-4), 58.5 (C-1), 71.4 (C-2), 89.8 (C-3a), 114.8 (C-8), 118.5 (C-9), 119.5 (C-6a), 123.6 (C-10), 124.2 (C-11), 126.0 (C-*o*), 126.2 (C-*m*), 127.6 (C-*p*), 128.8 (C-*o*), 129.2 (C-*m*), 130.7 (C-11b), 133.5 (C-*p*), 136.4 (C-11a), 136.6 (C-7a), 139.2 (C-*i*), 139.9 (C-*i*), 172.1 (NCO); $[\alpha]^{22}_D$ −22.5 (*c* 1.0, $CHCl_3$); HRMS calcd for $[C_{32}H_{32}N_2O_4S + H]$ 541.2155, found 541.2160. Anal. Calcd for $C_{32}H_{32}N_2O_4S \cdot 1/3CHCl_3$: C, 66.94; H, 5.62; N, 4.83; S, 5.53. Found C, 66.57; H, 5.81; N, 4.58; S, 5.13.

(4*R*,4a*S*,12a*R*)-7-Benzenesulfonyl-4-ethyl-2-[(1*R*)-2-hydroxy-1-phenylethyl]-1,3,4,4a,5,6,12,12a-octahydropyrido[3′,4′:4,5]-cyclohepta[1,2-*b*]indole (17). $LiAlH_4$ (436 mg, 11.5 mmol) was slowly added to a suspension of $AlCl_3$ (498 mg, 3.73 mmol) in THF (50 mL) at 0 °C. After the mixture was stirred at 25 °C for 30 min and cooled to −78 °C, a solution of dihydro-**16b** (940 mg, 1.74 mmol) in anhydrous THF (10 mL) was slowly added. The stirring was continued at −78 °C for 10 min and at 0 °C for 1 h 30 min. The reaction was quenched with water. The aqueous layer was extracted with EtOAc, and the combined organic extracts were dried and concentrated to give a foam, which was chromatographed (9:1 hexane−EtOAc to 4:1 hexane−EtOAc) to afford compound **17** (805 mg, 88% yield): IR (KBr) 3441 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 0.90 (t, J = 7.2 Hz, 3H, CH_3 ethyl), 1.17−1.54 (m, 7H, CH_2 ethyl, H-4, H-4a, H-5, H-12a), 2.10 (dd, J = 15.2, 10.8 Hz, 1H, H-3), 2.28 (d, J = 11.6 Hz, H-12), 2.57 (dd, J = 15.2, 1.6 Hz, 1H, H-3), 2.66 (dd, J = 15.2, 10.8 Hz, 1H, H-6), 2.85 (d, J = 8.8 Hz, 1H, H-1), 2.95 (d, J = 11.6 Hz, 1H, H-12), 3.62−3.77 (m, 3H, H-6, NCH, CH_2O), 4.01−4.09 (m, 1H, CH_2O), 7.19−7.51 (m, 11H, ArH, H-8, H-9, H-10), 7.66 (dd, J = 8.4, 0.8 Hz, 2H, ArH), 8.20−8.23 (m, 1H, H-11); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 12.7 (CH_3 ethyl), 18.8 (CH_2 ethyl), 25.4 (C-12), 28.8 (C-6), 31.5 (C-5), 35.3 (C-4a), 43.7 (C-12a), 49.7 (C-4), 53.4 (C-3), 55.6 (C-1), 60.2 (CH_2O), 70.0 (NCH), 115.3 (C-8), 117.7 (C-9), 121.1 (C-6a), 123.4 (C-10), 123.9 (C-11), 126.2 (C-*o*), 127.9 (C-*p*), 128.2 (C-*m*), 128.9 (C-*o*), 129.1 (C-*m*), 130.4 (C-11b), 133.5 (C-*p*), 135.2 (C-11a), 136.3 (C-7a), 139.3 (C-*i*), 139.6 (C-*i*); $[\alpha]^{22}_D$ +73.2 (*c* 0.37, $CHCl_3$); HRMS calcd for $[C_{32}H_{36}N_2O_3S + H]$ 529.2519, found 529.2526. Anal. Calcd for $C_{32}H_{36}N_2O_3S$: C, 72.70; H, 6.86; N, 5.30. Found C, 72.62; H, 7.12; N, 5.01.

(4*R*,4a*S*,12a*R*)-4-Ethyl-2-[(1*R*)-2-hydroxy-1-phenylethyl]-1,3,4,4a,5,6,12,12a-octahydropyrido[3′,4′:4,5]cyclohepta[1,2-*b*]-indole (18). Mg turnings (207 mg, 8.50 mmol) were added to a solution of compound **17** (805 mg, 1.53 mmol) in anhydrous MeOH (60 mL) at 0 °C. The resulting mixture was warmed to room temperature and vigorously stirred for 4 h. The reaction was quenched with water, and the resulting solution was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous NaCl, dried, and concentrated. The resulting residue was chromatographed (hexane to 4:1 hexane−EtOAc) to give the *N*-unsubstituted indole **18** (480 mg, 81% yield): IR (KBr) 3411, 2925 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 0.94 (t, J = 7.2 Hz, 3H, CH_3 ethyl), 1.21−1.74 (m, 7H, CH_2 ethyl, H-4, H-4a, H-5, H-12a), 2.22 (dd, J = 14.8, 11.2 Hz, 1H, H-12), 2.32 (d, J = 12.4 Hz, 1H, H-3), 2.72−2.84 (m, 3H, H-1, H-12), 2.94−3.01 (m, 2H, H-3, H-6), 2.65−3.75 (m, 2H, NCH, CH_2O), 4.07−4.16 (m, 1H, CH_2O), 7.08−7.46 (m, 9H, ArH, H-8, H-9, H-10, H-11), 7.75 (sa, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 12.8 (CH_3 ethyl), 18.8 (CH_2 ethyl), 27.9 (C-12), 29.4 (C-6), 32.5 (C-5), 36.5 (C-4a), 44.2 (C-12a), 49.4 (C-4), 53.6 (C-3), 55.6 (C-1), 60.3 (CH_2O), 70.1 (NCH), 110.3 (C-8), 110.9 (C-6a), 117.4 (C-9), 119.2 (C-10), 120.6 (C-11), 127.9 (C-11b), 128.2 (C-*o*), 128.8 (C-*p*), 129.0 (C-*m*), 134.1 (C-11a), 135.3 (C-7a), 138.0 (C-*i*); $[\alpha]^{22}_D$ +8.3 (*c* 0.29, $CHCl_3$); HRMS calcd for $[C_{26}H_{32}N_2O + H]$ 389.2594, found 389.2599. Anal. Calcd for $C_{26}H_{32}N_2O \cdot 1/4EtOAc$: C, 78.99; H, 8.35; N, 6.82. Found: C, 79.03; H, 8.41; N, 6.67.

(4*R*,4a*S*,12a*R*)-2-(*tert*-Butoxycarbonyl)-4-ethyl-1,3,4,4a,5,6,12,12a-octahydropyrido[3′,4′:4,5]cyclohepta[1,2-*b*]indole (19). A solution of indole **18** (160 mg, 0.41 mmol) and di-*tert*-butyl dicarbonate (94 mg, 0.43 mmol) in EtOAc (25 mL) containing 30% $Pd(OH)_2$-C (48 mg) was hydrogenated at rt for 16 h at atmospheric pressure. The catalyst was removed by filtration, and the solvent was evaporated to give an oil. Flash chromatography (hexane to 4:1 hexane−EtOAc) afforded **19** (91 mg, 60% yield): IR (KBr) 1667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 0.94 (t, J = 7.2 Hz, 3H, CH_3 ethyl), 1.12−1.45 (m, 3H, CH_2 ethyl, H-4), 1.47 [s, 3H, $C(CH_3)_3$], 1.60−1.74 (m, 4H, H-4a, H-5, H-12a), 2.29 (dd, J = 15.2, 10.0 Hz, 1H, H-6), 2.43−2.46 (m, 1H, H-1), 2.70−2.92 (m, 4H, H-3, H-6, H-12), 4.16 (d, J = 12.4 Hz, 1H, H-3), 4.30 (d, J = 12.0 Hz, 1H, H-1), 7.07−7.09 (m, 2H, H-9, H-10), 7.24−7.25 (m, 1H, H-8), 7.40−7.47 (m, 1H, H-11), 7.82 (sa, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 12.7 (CH_3 ethyl), 17.2 (CH_2 ethyl), 27.9 (C-3), 28.4 [$C(CH_3)_3$], 29.7 (C-5), 32.8 (C-6), 35.8 (C-4a), 44.2 (C-12a), 46.7 (C-3), 49.7 (C-1), 49.9 (C-3), 79.2 [$C(CH_3)_3$], 110.3 (C-8), 110.6 (C-6a), 117.4 (C-9), 119.2 (C-10), 120.6 (C-11), 128.8 (C-11b), 134.2 (C-11a), 138.0 (C-7a), 155.1 (NCO); $[\alpha]^{22}_D$ −0.4 (*c* 0.7, $CHCl_3$); HRMS calcd for $[C_{46}H_{64}N_4O_4 + H]$ 737.4844, found 737.4835.

(4*R*,4a*S*,12a*R*)-2-(*tert*-Butoxycarbonyl)-4-ethyl-6-oxo-1,3,4,4a,5,6,12,12a-octahydropyrido[3′,4′:4,5]cyclohepta[1,2-*b*]indole (20). I_2O_5 (84 mg, 0.25 mmol) was added to a solution of compound **19** (78 mg, 0.21 mmol) in THF−H_2O (9:1, 10 mL) at 0 °C, and the mixture was stirred at room temperature for 5 h 30 min. The mixture was poured into saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with 20% aqueous $Na_2S_2O_3$ and brine, dried, filtered, and concentrated. The resulting oil was chromatographed (CH_2Cl_2) affording compound **20** (67 mg, 83% yield): IR (KBr) 1692, 1729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 1.00 (t, J = 7.2 Hz, 3H, CH_3 ethyl), 1.24−1.34 (m, 2H, CH_2 ethyl), 1.46 [s, 3H, $C(CH_3)_3$], 1.60 (m, 1H, H-4), 1.91−2.00 (m, 1H, H-4a), 2.02−2.11 (m, 1H, H-12a), 2.47−2.53 (m, 1H, H-1), 2.72−2.87 (m, 2H, H-5), 2.77 (dd, J = 15.6, 7.2 Hz, 1H, H-3), 2.84 (dd, J = 16.4, 4.8 Hz, 1H, H-12), 3.16 (dd, J = 16.4, 6.0 Hz, 1H, H-12), 4.10 (dd, J = 10.4, 2.8 Hz, 1H, H-3), 4.31 (d, J = 12.0 Hz, 1H, H-1), 7.16 (ddd, J = 8.0, 6.0, 1.2 Hz, 1H, H-11), 7.33−7.39 (m, 2H, H-9, H-10), 7.64 (d, J = 8.0 Hz, 1H, H-8), 8.86 (sa, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 12.8 (CH_3 ethyl), 17.9 (CH_2 ethyl), 26.7 (C-12), 29.1 [$C(CH_3)_3$], 36.2 (C-12a), 42.6 (C-4a), 43.2 (C-4), 46.3 (C-5), 46.8 (C-1), 49.8 (C-3), 79.6 [$C(CH_3)_3$], 112.0 (C-8), 120.4 (C-10), 120.8 (C-11), 123.0 (C-11b), 126.6 (C-9), 127.6 (C-11a), 132.6 (C-6a), 136.4 (C-7a), 155.5 (NCO), 193.9 (CO); $[\alpha]^{22}_D$ −22.9 (*c* 0.24, $CHCl_3$); HRMS calcd for $[C_{23}H_{30}N_2O_3 + H]$ 383.2329, found 383.2329.

(−)-16-Episilicine. TFA (50 μL, 0.79 mmol) was added to a solution of indole **20** (67 mg, 0.18 mmol) in anhydrous CH_2Cl_2 (10 mL). The mixture was stirred at room temperature for 5 h and brought to pH 7 by addition of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried and concentrated to give the corresponding amine, which was used in the next reaction without further purification. The residue was dissolved in anhydrous CH_3CN (5 mL), MeI (18 μL, 0.29 mmol) was added, and the mixture was stirred at room temperature for 3 h. The solution was washed with saturated aqueous $NaHCO_3$, and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography using a cartridge containing amine functionalized silica (EtOAc to EtOAc−MeOH 4:1) afforded pure (−)-16-episilicine (30 mg, 55% yield): ^1H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 0.97 (t, J = 7.2 Hz, 3H, CH_3 ethyl), 1.34−1.46 (m, 2H, CH_2 ethyl), 1.56−2.02 (m, 5H, H-15, H-20, H-21, H-5), 2.20−2.40 (m, 1H, H-16), 2.29 (sa, 3H, NCH_3), 2.81 (d, J = 6.4 Hz, 2H, H-14), 2.84 (dd, J = 17.2, 4.8 Hz, H-21), 2.90−3.09 (m, 2H, H-5, H-6), 3.18 (dd, J = 16.4, 6.4 Hz, 1H, H-6), 7.14 (ddd, J = 8.0, 6.8, 1.0 Hz, 1H, H-10), 7.33 (ddd, J = 8.0, 6.4, 1.0 Hz, 1H, H-11), 7.37 (d, J = 8.0 Hz, 1H, H-12), 7.65 (d, J = 8.4 Hz, 1H, H-9), 8.79 (sa, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 12.9 (C-18), 18.9 (C-19), 27.1 (C-6), 35.7

(C-16), 41.9 (C-15), 43.0 (C-20), 46.2 (NCH_3), 46.8 (C-14), 57.8 (C-21), 63.4 (C-5), 112.1 (C-12), 120.3 (C-10), 120.7 (C-9), 123.1 (C-7), 126.5 (C-11), 127.7 (C-8), 132.6 (C-2), 136.4 (C-13), 194.3 (CO); $[\alpha]^{22}_{D}$ −20.0 (*c* 1.0, $CHCl_3$).

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Supporting Information Available: Copies of the ^{1}H and ^{13}C NMR spectra of all compounds and X-ray crystallographic data for compounds **16a**, **16b**, and **21**. This material is available free or charge via the Internet at http://pubs.acs.org.