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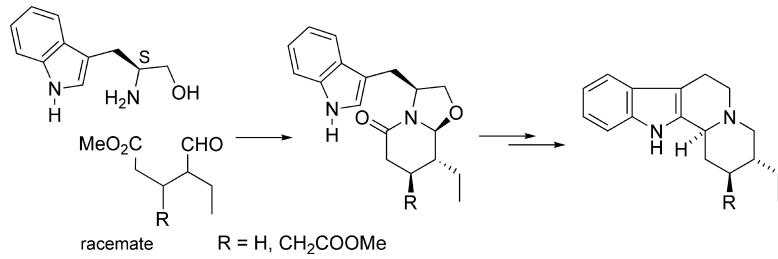

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Enantioselective Formal Synthesis of (+)-Dihydrocorynantheine and (−)-Dihydrocorynantheol†

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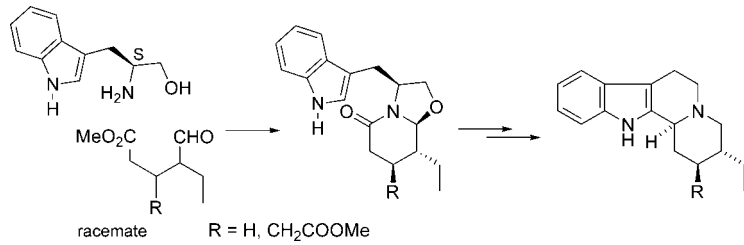

The enantioselective construction of the 3-ethylindolo[2,3-*a*]quinolizidine moiety present in numerous indole alkaloids is reported, the key steps being a stereoselective cyclocondensation of (*S*)-tryptophanol with an appropriate racemic δ-oxoester and a regio- and stereoselective cyclization of the resulting oxazolopiperidones on the lactam carbonyl group. A new procedure for the removal of the hydroxymethyl auxiliary group, involving oxidation to an aldehyde, dehydration of the corresponding oxime, and reductive decyanation of the resulting α-aminonitrile, has been developed. The preparation of indoloquinolizidine **27** represents a formal total synthesis of (+)-dihydrocorynantheine, (−)-dihydrocorynantheol, and other indolo[2,3-*a*]quinolizidine and oxindole alkaloids bearing the same substitution pattern.

Introduction

Although indolo[2,3-*a*]quinolizidine alkaloids are an abundant group of monoterpenoid-derived indole alkaloids that have received considerable synthetic attention,[1] their enantioselective synthesis has been little explored (Figure 1). For instance, the synthesis of (+)-dihydrocorynantheine was not reported until 1999,[2] and no additional enantioselective syntheses of this alkaloid have been described since then. The control of the relative and absolute stereochemistry of the three stereocenters on the piperidine ring of dihydrocorynantheine and related alkaloids represents a major challenge that makes these natural products attractive synthetic targets to evaluate the potential of synthetic methodology.

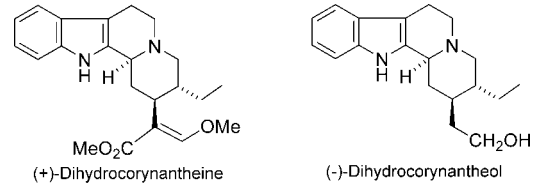

FIGURE 1. Representative indolo[2,3-*a*]quinolizidine alkaloids.

Previous work has demonstrated that aminoalcohol-derived oxazolopiperidone lactams are versatile building blocks that allow the enantioselective construction of structurally diverse piperidine-containing natural products and bioactive compounds.[3] These lactams are formed by a stereoselective cyclocondensation reaction between the chiral nonracemic aminoalcohol and a δ-oxoacid derivative. More recently, the scope and potential of the methodology was significantly expanded by using (*S*)-tryptophanol as the aminoalcohol partner. (*S*)-Tryptophanol not only constitutes the source of chirality but can also be used to assemble the target indoloquinolizidine system by

† Dedicated to Professor Josep Font on the occasion of his 70th birthday.
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§ Institut de Ciència de Materials.

(1) (a) Brown, R. T. 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, Chapter 3. (b) Szántay, C.; Blaskó, G.; Honty, K.; Dörnyei, G. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: London, UK, 1986; Vol. 27, Chapter 2. (c) Lounasmaa, M.; Tolvanen, A. In *Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed. In *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Ed.; Wiley: Chichester, UK, 1994; Vol. 25, Part 4, Chapter 3.

(2) Tietze, L. F.; Zhou, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 2045.

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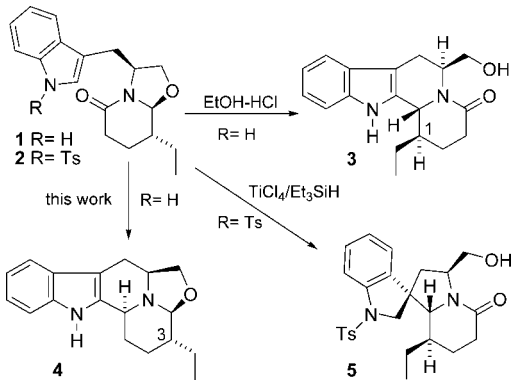
SCHEME 1. Tryptophanol-Derived Oxazolopiperidone Lactams, Versatile Intermediates in Indole Alkaloid Synthesis



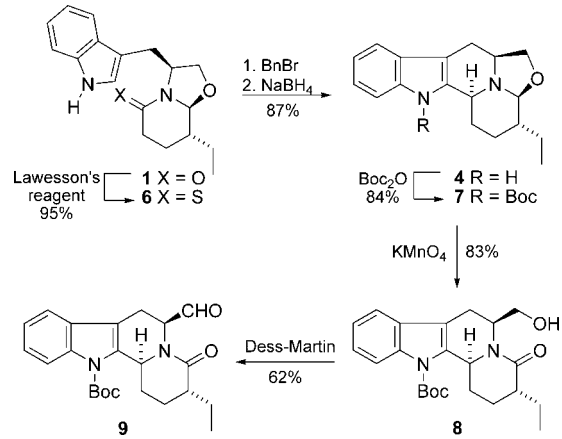
cyclization on the indole ring.[4] However, in all examples reported to date this cyclization occurs on the 6-position of the lactam ring by intramolecular α-amidoalkylation via an *N*-acyliminium cation.[5] For instance, under acidic conditions[4d] lactam **1** leads to the indoloquinolizidine derivative **3**, with the ethyl substituent at the C-1 position (Scheme 1).

The tendency of tryptophanol-derived oxazolopiperidone lactams to undergo acid-promoted intramolecular α-amidoalkylation reactions became evident in our initial attempts to assemble the 3-ethyl-substituted indolo[2,3-*a*]quinolizidine derivative **4** by cyclization on the lactam carbonyl group of **1** under classical Bischler−Napieralski conditions ($POCl_3$, toluene; then $NaBH_4$). Similarly, attempts to reductively open ($TiCl_4$−Et_3SiH) the oxazolidine ring of lactam **1** resulted in cyclization to **3**, thus pointing out that the α-amidoalkylation process is faster than the reduction of the initially formed *N*-acyliminium cation intermediate. Under the latter conditions, the deactivated *N*-tosyl lactam **2** also underwent α-amidoalkylation, but now on the indole 3-position, leading to the spiro indoline derivative **5**.[4c]

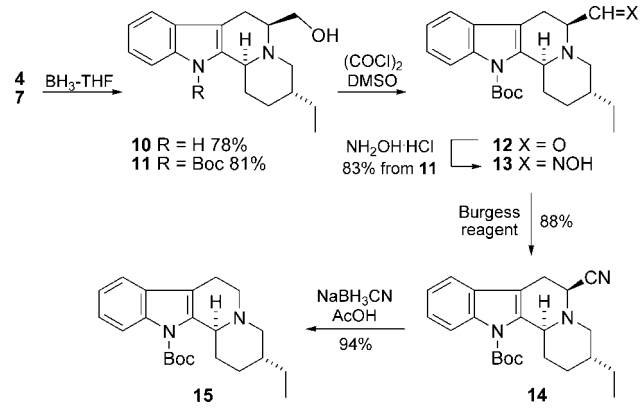
Results and Discussion

We present herein an unprecedented type of cyclization from tryptophanol-derived lactams that takes advantage of the lactam carbonyl group, leading in a regio- and stereoselective manner to the natural 3-ethylindolo[2,3-*a*]quinolizidine framework present in numerous indole alkaloids. Starting from an appropriately substituted lactam, this key cyclization opens enantioselective routes to (+)-dihydrocorynantheine, (−)-dihydrocorynantheol, and other indolo[2,3-*a*]quinolizidine and oxindole alkaloids with the same substitution pattern.

SCHEME 2. Cyclization under Modified Bischler−Napieralski Conditions



SCHEME 3. Removal of the Hydroxymethyl Appendage: Access to Enantiopure Indolo[2,3-*a*]quinolizidines



The regioselective cyclization on the lactam carbonyl was satisfactorily accomplished under nonacidic conditions via a (benzylthio)iminium salt intermediate, which was generated by treatment of lactam **1**[4d] with Lawesson's reagent followed by alkylation of the resulting thiolactam **6** with benzyl bromide. A subsequent $NaBH_4$ reduction of the resulting pentacyclic iminium species **A** stereoselectively led to a single indoloquinolizidine derivative **4**[6] (Scheme 2). The absolute configuration of the stereogenic center generated in this step was unambiguously established by X-ray crystallographic analysis of alcohol **10** (Scheme 3), which was obtained by borane reduction of **4**.

The observed stereoselectivity can be explained by considering a stereoelectronically controlled[7] axial attack of the hydride on the electrophilic carbon center of the iminium cation **A** in the more stable conformation depicted in Figure 2.

A limiting point in the use of tryptophanol-derived oxazolopiperidone lactams as chiral building blocks in indole alkaloid

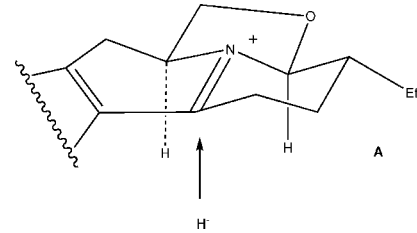


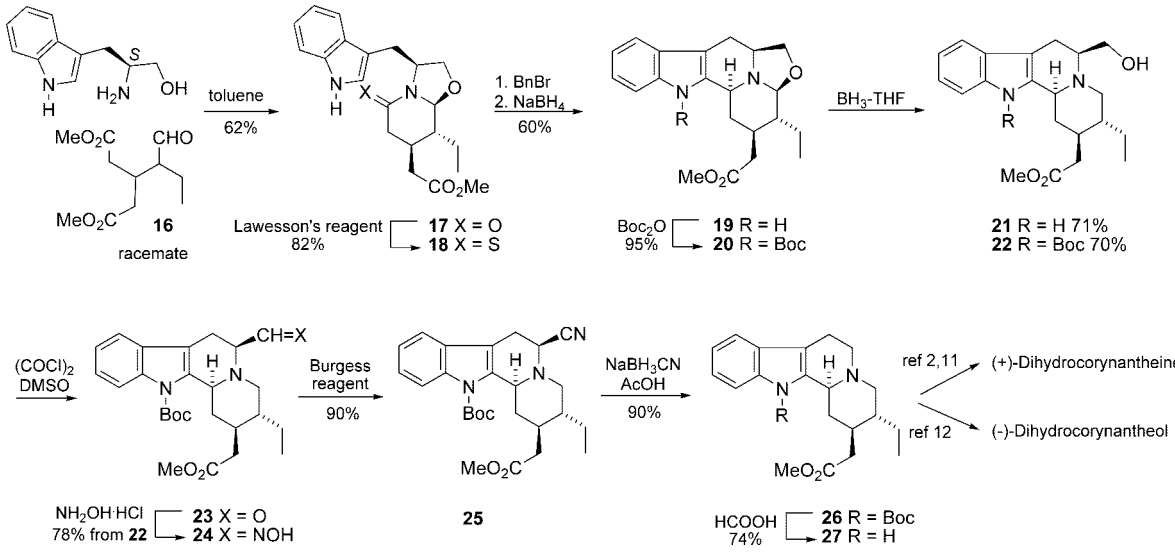
FIGURE 2. Stereoelectronic control.

(3) 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. For more recent work, see: (e) Amat, M.; Escolano, C.; Lozano, O.; Gómez-Esqué, A.; Griera, R.; Molins, E.; Bosch, J. *J. Org. Chem.* **2006**, *71*, 3804. (f) Amat, M.; Bassas, O.; Llor, N.; Cantó, M.; Pérez, M.; Molins, E.; Bosch, J. *Chem. Eur. J.* **2006**, *12*, 7872. (g) Amat, M.; Lozano, O.; Escolano, C.; Molins, E.; Bosch, J. *J. Org. Chem.* **2007**, *72*, 4431. (h) Amat, M.; Griera, R.; Fabregat, R.; Molins, E.; Bosch, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 3348. (i) Amat, M.; Pérez, M.; Minaglia, A. T.; Bosch, J. *J. Org. Chem.* **2008**, *73*, 6920.

(4) (a) Allin, S. M.; Thomas, C. I.; Doyle, K.; Elsegood, M. R. J. *J. Org. Chem.* **2005**, *70*, 357. (b) Allin, S. M.; Duffy, L. J.; Page, P. C. B.; McKee, V.; McKenzie, M. J. *Tetrahedron Lett.* **2007**, *48*, 4711. (c) Amat, M.; Santos, M. M. M.; Gómez, A. M.; Jokic, D.; Molins, E.; Bosch, J. *Org. Lett.* **2007**, *9*, 2907. (d) 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.

(5) For recent reviews on the chemistry of *N*-acyliminium ions, see: (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (b) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431.

SCHEME 4. Enantioselective Formal Synthesis of (+)-Dihydrocorynantheine and (−)-Dihydrocorynantheol



synthesis has been the removal of the hydroxymethyl auxiliary group due to the unreliability of the various methods reported for this purpose so far.[8] To perform this transformation we initially planned to use the procedure recently developed by Allin,[4a,8b] and successfully used from related substrates in the 1-ethyl series,[4d] which involves the oxidation of the hydroxymethyl group to a carboxylic acid and a subsequent radical reductive decarbonylation of the corresponding seleno ester. Thus, the indole nucleus of pentacycle **4** was protected as an *N*-Boc derivative, and the resulting pentacyclic aminal **7** was oxidized to hydroxy lactam **8** and then to aldehyde **9**. However, attempts to further oxidize either **8** [PDC in DMF or $Pb(OAc)_4$] or **9** ($NaClO_2$) to the corresponding carboxylic acid were unsuccessful. Similarly, decarbonylation of aldehyde **9** with $Rh(PPh_3)_2(CO)Cl$[8a] resulted in failure. These unsatisfactory results prompted us to develop an alternative procedure for the removal of the hydroxymethyl group. Thus, reductive cleavage with borane of the oxazolidine ring present in pentacyclic aminal **7**, followed by oxidation of the resulting alcohol **11** under Swern conditions led to aldehyde **12** (Scheme 3). A subsequent dehydration of the corresponding oxime **13** with Burgess reagent afforded α-amino nitrile **14**, which was then subjected to reductive decyanation to give the target indoloquinolizidine **15**.[9] This new, high-yielding procedure increases the potential and synthetic utility of tryptophanol-derived lactams in indole alkaloid synthesis.

Starting from an appropriately substituted tryptophanol-derived lactam bearing an additional acetate chain at the piperidine 4-position, the above sequence provides enantioselective access to indolo[2,3-*a*]quinolizidine alkaloids. Thus, lactam **17**, with the required *trans-R,R* configuration at the stereogenic centers of the piperidine 3- and 4-position, was envisaged as a synthetic precursor of (+)-dihydrocorynantheine and related indoloquinolizidine and oxindole alkaloids. This lactam was prepared[4d] in 62% yield by cyclocondensation of (*S*)-tryptophanol with racemic δ-oxo diester **16** in a process that involves a dynamic kinetic resolution and the differentiation of diastereotopic ester chains, with generation of three stereogenic centers with a well-defined configuration in a single synthetic step (Scheme 4).

The regio- and stereoselective cyclization on the lactam carbonyl group, leading to an indolo[2,3-*a*]quinolizidine derivative bearing the ethyl substituent at the β-outside position of the piperidine ring, took place under modified Bischler−Napieralski conditions as in the above model series, by alkylation of thiolactam **18** with benzyl bromide followed by $NaBH_4$ reduction. The absolute configuration of the resulting pentacycle **19** was unambiguously established by X-ray crystallographic analysis of alcohol **21**, which was obtained by borane reduction of **19**.

To complete the synthesis of the target alkaloids we only needed to remove the hydroxymethyl appendage, which was satisfactorily accomplished by the method previously developed in the model series. Thus, borane reduction of **20** followed by Swern oxidation of the resulting alcohol **22** gave aldehyde **23**, which was then converted to oxime **24**. A subsequent dehydration of **24** followed by $NaBH_4$ reductive decyanation of the resulting α-aminonitrile **25** gave indoloquinolizidine **26**.[10]

Finally, deprotection of the indole nitrogen led to the tetracyclic ester **27**,[10] a known synthetic precursor of the alkaloids (+)-dihydrocorynantheine[2,11] and (−)-dihydrocorynantheol,[12] so the above sequence represents a formal total synthesis of these alkaloids.[13]

(6) For the use of this procedure in the synthesis of tetrahydro-β-carbolines, see: Ishida, A.; Nakamura, T.; Irie, K.; Oh-Ishi, T. *Chem. Pharm. Bull.* **1985**, *33*, 3237.

(7) Deslongchamps P. In *Stereoelectronic Effects in Organic Chemistry*; Baldwin, J. E., Ed.; Pergamon: Oxford, UK, 1983.

(8) (a) Allin, S. M.; James, S. L.; Martin, W. P.; Smith, T. A. D.; Elsegood, M. R. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3029. (b) Allin, S. M.; Thomas, C. I.; Allard, J. E.; Doyle, K.; Elsegood, M. R. J. *Tetrahedron Lett.* **2004**, *45*, 7103. (c) Allin, S. M.; Gaskell, S. N.; Towler, J. M. R.; Page, P. C. B.; Saha, B.; McKenzie, M. J.; Martin, W. P. *J. Org. Chem.* **2007**, *72*, 8972. For the removal of an alcoxycarbonyl substituent from related tryptophan-derived substrates, see: (d) Akimoto, H.; Okamura, K.; Yui, M.; Shioiri, T.; Kuramoto, M.; Kikugawa, Y.; Yamada, S. *Chem. Pharm. Bull.* **1974**, *22*, 2614. (e) Johansen, J. E.; Christie, B. D.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 4914. (f) Yu, S.; Berner, O. M.; Cook, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 7827. (g) Deiters, A.; Chen, K.; Eary, C. T.; Martin, S. F. *J. Am. Chem. Soc.* **2003**, *125*, 4541.

(9) No previous enantioselective syntheses of **15** or the corresponding NH derivative have been reported so far. The ^1H and ^{13}C NMR data of **15** were identical with those reported in the racemic series: Tamminen, T.; Jokela, R.; Tirkkonen, B.; Lounasmaa, M. *Tetrahedron* **1999**, *45*, 2692.

(10) The ^1H and ^{13}C NMR data of **26**[10a] and **27**[10b] were identical with those reported in the racemic series: (a) Lounasmaa, M.; Hanhinen, P. *Tetrahedron* **1996**, *52*, 15225. (b) Lounasmaa, M.; Jokela, R.; Tirkkonen, B.; Miettinen, J.; Halonen, M. *Heterocycles* **1992**, *34*, 321.

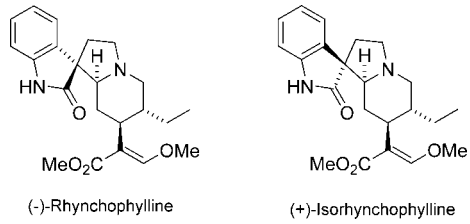


FIGURE 3. Oxindole alkaloids.

Taking into account previous correlations,[14] the synthesis of **27** also constitutes a formal synthesis of the oxindole alkaloids (−)-rhynchophylline and (+)-isorhynchophylline (Figure 3).[15]

Conclusion

In summary, we have accomplished for the first time cyclizations involving the lactam carbonyl group of tryptophanol-derived oxazolopiperidone lactams, thus enabling the enantioselective construction of the 3-ethylindolo[2,3-*a*]quinolizidine framework present in numerous indole alkaloids. To illustrate the synthetic usefulness of the methodology we have developed a short enantioselective synthetic route to (+)-dihydrocorynantheine and related indoloquinolizidine and oxindole alkaloids, involving as the key steps (i) a stereoselective cyclocondensation of (*S*)-tryptophanol with racemic *δ*-oxo diester **16**, (ii) a regio- and stereoselective cyclization of the resulting lactam on the indole ring, and (iii) a new procedure to remove the hydroxymethyl auxiliary.

The above results open new perspectives on the use of tryptophanol-derived lactams as versatile starting materials for the enantioselective synthesis of indole alkaloids. These lactams are not only easily accessible in enantiopure form in a single synthetic step but can undergo three complementary types of cyclization on the indole ring, depending on the substituent on the indole nitrogen (H or tosyl) and the reaction conditions, thus providing access to a wide variety of skeletal types as outlined in Figure 4.

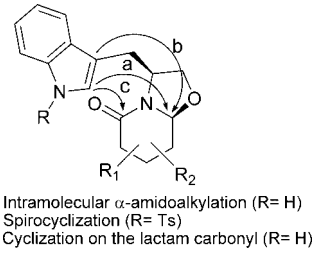


FIGURE 4. Complementary types of cyclization from tryptophanol-derived oxazolopiperidone lactams.

Experimental Section

(3*S*,8*R*,8a*S*)-8-Ethyl-3-(3-indolylmethyl)-5-thio-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (6). Lawesson's reagent (1.55 g, 3.82 mmol) was added to a stirred solution of lactam **1**[4d] (1.90 g, 8.64 mmol) in DME (30 mL), and the resulting mixture was heated at reflux for 4 h. The solvent was removed under reduced pressure, and the residue was dissolved in EtOAc. The organic solution was washed with saturated aqueous $NaHCO_3$, dried, and concentrated. The resulting residue was chromatographed (1:1 EtOAc−hexane to EtOAc) to afford **6** (1.9 g, 95%): IR (film) 1164, 1497, 3200−3400 cm^{-1}; ^1H NMR (400 MHz) δ 0.99 (t, J = 7.5 Hz, 3H, CH_3), 1.18−1.48 (m, 2H, CH_3CH_2, H-7), 1.63−1.80 (m, 2H, H-8, CH_3CH_2) 1.92−2.01 (m, 1H, H-7), 2.64 (dd, J = 13.5, 10.5 Hz, 1H, CH_2-ind), 2.87−3.08 (m, 2H, H-6), 3.73 (ddd, J = 9.5, 5.5, 1.5 Hz, 1H, H-2), 4.09−4.18 (m, 2H, H-2, CH_2-ind), 7.08 (d, J = 1.5 Hz, 1H, H-2 ind), 7.15 (td, J = 7.5, 1.5 Hz, 1H, H-5 ind), 7.21 (td, J = 7.0, 1.5 Hz, 1H, H-6 ind), 7.35 (d, J = 7.5 Hz, 1H, H-7 ind), 8.06 (d, J = 7.5 Hz, 1H, H-4 ind), 8.08 (s, 1H, NH); ^{13}C NMR (100.6 MHz) δ 10.7 (CH_3), 24.1 (C-7), 24.7 (CH_3CH_2), 25.4 (CH_2-ind), 40.4 (C-8), 40.7 (C-6), 61.0 (C-3), 69.5 (C-2), 94.4 (C-8a), 111.0 (C-7 ind), 112.3 (C-3 ind), 119.7 (C-4 ind), 120.0 (C-5 ind), 122.3 (C-6 ind), 122.6 (C-2 ind), 127.5 (C-3a ind), 136.2 (C-7a ind), 196.1 (NCS); mp 164−166 °C (EtOAc−hexane); $[\alpha]^{22}_D$ −367.0 (*c*1.0, $CHCl_3$); MS-EI *m*/*z* 314 (M^+, 100), 281 (21), 172 (34), 156 (26), 130 (71), 114 (81); HMRS (M^+ + 1) calcd for $C_{18}H_{22}N_2OS$ 315.1525, found 315.1536. Anal. Calcd for $C_{18}H_{22}N_2OS \cdot {}^1/_3H_2O$: C, 67.48; H, 7.13; N, 8.74; S, 10.01. Found: C, 67.59; H, 7.06; N, 8.64; S, 9.75.

(3*R*,4*S*,6*S*,12b*S*)-4,6-(Epoxymethano)-3-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (4). Benzyl bromide (1.51 mL, 12.7 mmol) was added to a solution, kept in the dark, of **6** (1.93 g, 6.37 mmol) in CH_3CN (50 mL), and the resulting mixture was heated at reflux for 44 h. The solvent was removed under reduced pressure, and the residue was dissolved in MeOH (200 mL). Then, $NaBH_4$ (723 mg, 19.1 mmol) was added to the cooled suspension (−78 °C) and the mixture was stirred at −78 °C for 5 h. Acetone (7 mL) was added, and the solvent was evaporated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 and washed with brine. The organic phase was dried and concentrated, and the residue was chromatographed (1:9 EtOAc−hexane to EtOAc) to afford **4** (1.50 g, 87%): IR (film) 1452, 1641, 2934, 3290 cm^{-1}; ^1H NMR (400 MHz) δ 0.97 (t, J = 7.5 Hz, 3H, CH_3), 1.14 (m, 1H, H-2), 1.22 (m, 1H, CH_2CH_3), 1.51−1.64 (m, 2H, H-1, H-3), 1.76 (m, 1H, CH_2CH_3), 2.04−2.11 (m, 2H, H-2, H-1), 2.65 (ddd, J = 14.5, 10.0, 2.5 Hz, 1H, H-7), 2.98 (ddd, J = 14.5, 5.0, 2.5 Hz, 1H, H-7), 3.05 (m, 1H, H-6), 3.53 (d, J = 11.5 Hz, 1H, H-12b), 3.58 (d, J = 8.5 Hz, 1H, H-4), 3.77 (t, J = 7.5 Hz, 1H, CH_2O), 4.25 (t, J = 7.5 Hz, 1H, CH_2O), 7.09 (td, J = 7.5, 0.8 Hz, 1H, H-9), 7.14 (td, J = 7.5, 1.0 Hz, 1H, H-10), 7.32 (d, J = 7.5 Hz, 1H, H-11), 7.46 (d, J = 7.5 Hz, 1H, H-8), 7.87 (s, 1H, NH); ^{13}C NMR (100.6 MHz) δ 11.2 (CH_3), 24.6 (CH_3CH_2), 25.2 (C-7), 28.0 (C-2), 29.3 (C-1), 42.8 (C-3), 55.3 (C-12b), 55.7 (C-6), 71.4 (CH_2O), 96.3 (C-4), 108.1 (C-7a), 110.9 (C-11), 118.1 (C-8), 119.6 (C-9), 121.5 (C-10), 127.2 (C-7b), 134.7 and 136.3 (C-11a, C-12a); $[\alpha]^{22}_D$ −67.6 (*c* 0.49, MeOH); MS-EI *m*/*z* 282 (M^+, 100), 251 (14), 198 (49), 170 (22), 156 (80); HMRS (M^+ + 1) calcd for $C_{18}H_{22}N_2O$ 283.1404, found 283.1807.

(3*R*,4*S*,6*S*,12b*S*)-12-(*tert*-Butoxycarbonyl)-4,6-(epoxymethano)-3-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (7). NEt_3 (1.28 mL, 9.2 mmol), *N*,*N*-dimethylaminopyridine (169 mg, 1.38 mmol), and di-*tert*-butyl dicarbonate (1.81 g, 8.28 mmol) were added to a solution of **4** (1.3 g, 4.6 mmol) in THF (57 mL), and the mixture was stirred at rt for 7 h. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2 and washed with 2 N aqueous HCl. The organic phase was dried and concentrated, and the resulting residue was chromatographed (Florisil, 5:95 EtOAc−hexane to EtOAc) to afford **7** (1.48 g, 84%): IR (film) 1728 cm^{-1}; ^1H NMR

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(14) Deiters, A.; Pettersson, M.; Martin, S. F. *J. Org. Chem.* **2006**, *71*, 6547.

(15) For the conversion of (−)-dihydrocorynantheine to (−)-rhynchophylline and (+)-isorhynchophylline, see: Finch, N.; Taylor, W. I. *J. Am. Chem. Soc.* **1962**, *84*, 3871.

(400 MHz) δ 0.97 (t, J = 7.5 Hz, 3H, CH_3CH$_2$), 1.19−1.28 (m, 2H, CH_2CH$_3$, H-2), 1.46 (m, 1H, H-7), 1.49 (m, 1H, H-3), 1.67 [s, 9H, C(CH$_3$)$_3$], 1.73 (m, 1H, CH_2CH$_3$), 2.02 (ddd, J = 13.0, 7.0, 4.0 Hz, 1H, H-2), 2.42 (ddd, J = 9.0, 5.5, 3.0 Hz, 1H, H-7), 2.61 (ddd, J = 15.0, 10.0, 2.5 Hz, 1H, H-1), 2.90 (ddd, J = 15.0, 4.0, 2.5 Hz, 1H, H-1), 3.09 (m, 1H, H-12b), 3.72 (t, J = 8.5 Hz, 1H, H-4), 3.74 (t, J = 7.5 Hz, 1H, CH$_2$O), 3.86 (d, J = 11.0 Hz, 1H, H-6), 4.24 (t, J = 7.5 Hz, 1H, CH$_2$O), 7.22 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H, H-9), 7.27 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H, H-10), 7.39 (d, J = 7.5 Hz, 1H, H-8), 8.05 (d, J = 7.6 Hz, 1H, H-11); ^{13}C NMR (100.6 MHz) δ 11.2 (CH$_3$), 24.7 (CH$_3$CH$_2$), 26.4 (C-1), 27.7 (C-2), 28.2 [C(*C*H$_3$)$_3$], 30.5 (C-7), 43.3 (C-3), 55.9 (C-12b), 57.2 (C-6), 71.2 (CH$_2$O), 83.8 [*C*(CH$_3$)$_3$], 96.3 (C-4), 115.2 (C-11), 116.7 (C-7a), 117.9 (C-8), 122.7 (C-9), 124.1 (C-10), 129.0 (C-7b), 136.6 and 137.0 (C-11a, C-12a), 150.4 (NCOO); mp 158−160 °C (EtOAc−hexane); $[\alpha]^{22}_D$ −204.0 (*c* 0.32, MeOH); MS-EI *m*/*z* 282 (M$^+$ − 100, 100), 251 (19), 198 (47), 156 (79). Anal. Calcd for $C_{23}H_{30}N_2O_3 \cdot {}^1/_3H_2O$; C, 71.12; H, 7.96; N, 7.21. Found: C, 71.19; H, 7.70; N, 7.24.

(3*R*,6*S*,12b*S*)-12-(*tert*-Butoxycarbonyl)-3-ethyl-6-(hydroxymethyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (11). BH$_3$·THF (1 M in THF, 3.93 mL, 3.93 mmol) was added to a cooled (0 °C) solution of **7** (500 mg, 1.31 mmol) in THF (8 mL), and the mixture was stirred at 0 °C for 7 h. Cold 2 N aqueous NaOH was added slowly until the mixture was basified. The resulting mixture was extracted with EtOAc and CH$_2$Cl$_2$, and the combined organic extracts were dried and concentrated. The crude residue was chromatographed (4:1 EtOAc−hexane to 9:1 EtOAc−MeOH) to afford **11** (408 mg, 81% yield): IR (film) 1724, 3211 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.93 (t, J = 7.5 Hz, 3H, CH$_3$), 1.14−1.37 (m, 3H, CH_2CH$_3$, H-2), 1.41 (dt, J = 12.5, 3.0, 1H, H-1), 1.58 (m, 1H, H-3), 1.65 [s, 9H, C(CH$_3$)$_3$], 1.91 (m. 1H, H-2), 2.00 (t, J = 10.5 Hz, 1H, H-4), 2.31 (d, J = 12.5 Hz, 1H, H-1), 2.63 (dt, J = 15.5, 2.5 Hz, 1H, H-7), 2.73 (dd, J = 10.0, 3.0 Hz, 1H, H-6), 2.91 (t, J = 12.0 Hz, 1H, H-7), 3.34 (dd, J = 11.0, 4.0 Hz, 1H, H-4), 3.68 (d, J = 9.5 Hz, 1H, H-12b), 3.75 (dd, J = 11.5, 3.0 Hz, 1H, CH_2OH), 4.00 (d, J = 11.0 Hz, 1H, CH_2OH), 7.20 (t, J = 7.5 Hz, 1H, H-9), 7.31 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H, H-10), 7.38 (d, J = 7.0 Hz, 1H, H-8), 8.03 (d, J = 7.5 Hz, 1H, H-11); ^{13}C NMR (100.6 MHz) δ 11.4 (CH$_3$), 25.8 (C-7), 27.3 (CH$_3$*C*H$_2$), 28.2 [C(*C*H$_3$)$_3$], 30.8 (C-2), 32.2 (C-1), 38.6 (C-3), 55.8 (C-4), 58.5 (C-6), 62.3 (C-12b), 63.3 (CH$_2$OH), 83.6 [*C*(CH$_3$)$_3$], 115.1 (C-11), 116.3 (C-7a), 117.9 (C-8), 122.6 (C-9), 123.9 (C-10), 129.0 (C-7b), 136.2 and 137.2 (C-11a, C-12a), 150.5 (NCOO); mp 166−167 °C (EtOAc); MS-EI *m*/*z* 384 (M$^+$, 1), 353 (32), 327 (12), 297 (100), 253 (16), 168 (10); HMRS calcd for $C_{23}H_{32}N_2O_3$ 385.2485, found 385.2475.

(3*R*,6*S*,12b*S*)-12-(*tert*-Butoxycarbonyl)-3-ethyl-6-formyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (12). A solution of DMSO (0.1 mL, 1.30 mmol) in CH$_2$Cl$_2$ (0.45 mL) was added to a cooled (−50 °C) solution of oxalyl chloride (57 μL, 0.68 mmol) in CH$_2$Cl$_2$ (2 mL), and the mixture was stirred for 15 min. Then, a solution of **11** (100 mg, 0.26 mmol) in CH$_2$Cl$_2$ (1.2 mL) was slowly added, and the mixture was stirred at −50 °C for 20 h. Et$_3$N (192 μL, 1.38 mmol) was added and, after 15 min, the mixture was allowed to warm to rt. CH$_2$Cl$_2$ was added and the solution was washed with H$_2$O. The organic layer was dried and concentrated to give **12** (100 mg), which was used without further purification in the next reaction: IR (film) 1729 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.91 (t, J = 7.5 Hz, 3H, CH_3CH$_2$), 1.25 (m, 3H, CH_2CH$_3$, H-2), 1.46 (m, 1H, H-1), 1.68 [br s, 10H, C(CH$_3$)$_3$, H-3], 1.99 (dd, J = 3.0, 13.0 Hz, 1H, H-2), 2.20 (t, J = 11.5 Hz, H-4), 2.36 (d, J = 13.0 Hz, 1H, H-1), 2.63 (ddd, J = 15.5, 4.0, 2.5 Hz, 1H, H-7), 2.88 (ddd, J = 15.5, 10.5, 2.5 Hz, 1H, H-7), 2.97 (dd, J = 11.5, 4.0 Hz, 1H, H-4), 3.23 (dt, J = 10.5, 4.5 Hz, 1H, H-6), 3.68 (dd, J = 10.0, 1.6 Hz, 1H, H-12b), 7.22 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H, H-9), 7.31 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H, H-10), 7.38 (d, J = 7.5 Hz, 1H, H-8), 8.04 (d, J = 8.0 Hz, 1H, H-11), 9.68 (d, J = 5.0 Hz, 1H, CHO); ^{13}C NMR (100.6 MHz) δ 11.3 (CH$_3$), 23.2 (C-7), 27.1 (CH$_3$*C*H$_2$), 28.2 [C(*C*H$_3$)$_3$], 31.3 (C-2), 32.1 (C-1), 38.5 (C-3), 59.9 (C-4), 61.3 (C-12b), 67.3 (C-6), 83.9 [*C*(CH$_3$)$_3$], 113.4 (C-7a), 115.2 (C-11), 117.8 (C-8), 122.8 (C-9), 124.3 (C-10), 128.6 (C-7b), 136.1 and 137.1 (C-11a, C-12a), 150.5 (NCOO), 202.6 (CHO); MS-EI *m*/*z* 382 (M$^+$, 1), 353 (29), 297 (100), 253 (11), 168 (9).

(3*R*,6*S*,12b*S*)-12-(*tert*-Butoxycarbonyl)-3-ethyl-6-(hydroxyiminomethyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (13). NH$_2$OH·HCl (346 mg, 4.99 mmol) was added to a solution of **12** (346 mg, 0.90 mmol) in pyridine (4 mL) and absolute EtOH (4 mL), and the mixture was heated at reflux for 3 h. The solvent was evaporated at reduced pressure, and 0.2 M aqueous H$_2$SO$_4$ (20 mL) was added. The resulting mixture was stirred for 10 min. After extraction with EtOAc, the organic layer was washed with 2 M aqueous NaOH, dried, and concentrated to a give 2:1 (^{1}H NMR) mixture of *E*/*Z* oximes (300 mg, 83% from **11**). **13** (*E* isomer): ^{1}H NMR (400 MHz) δ 0.90 (t, J = 7.5 Hz, 3H, CH$_3$), 1.16−1.28 (m, 3H, CH_2CH$_3$, H-2), 1.38−1.49 (m, 1H, H-1), 1.65 [br s, 9H, C(CH$_3$)$_3$], 1.65 (m, 1H, H-3), 1.95 (m, 1H, H-2), 2.05 (m, 1H, H-4), 2.33 (d, J = 12.5 Hz, 1H, H-1), 2.68 (ddd, J = 16.0, 10.5, 3.0 Hz, 1H, H-7), 2.88 (ddd, J = 16.0, 6.0, 6.0 Hz, 1H, H-7), 3.08 (dd, J = 11.0, 3.5 Hz, 1H, H-4), 3.38 (ddd, J = 12.5, 8.5, 3.5 Hz, 1H, H-6), 3.68 (t, J = 11.0 Hz, 1H, H-12b), 7.20 (m, 1H, H-9), 7.31 (m, 1H, H-10), 7.35 (t, J = 7.0 Hz, 1H, H-8), 7.52 (d, J = 8.5 Hz, 1H, CH=N), 8.03 (d, J = 8.0 Hz, 1H, H-11); ^{13}C NMR (100.6 MHz) δ 11.3 (CH$_3$), 27.3 (CH$_3$*C*H$_2$), 27.8 (C-7), 28.2 [C(*C*H$_3$)$_3$], 31.0 (C-2), 32.0 (C-1), 38.1 (C-3), 58.7 (C-6), 58.9 (C-4), 62.4 (C-12b), 83.8 [*C*(CH$_3$)$_3$], 115.0 (C-7a), 115.1 (C-11), 117.9 (C-8), 122.7 (C-9), 124.0 (C-10), 128.7 (C-7b), 136.2 and 137.2 (C-11a, C-12a), 150.5 (NCOO), 153.6 (CH=N). **13** (*Z* isomer): ^{1}H NMR (400 MHz, most significant peaks) δ 0.91 (t, J = 7.5 Hz, 3H, CH$_3$), 2.77 (m, 1H, H-7), 3.20 (dd, J = 11.6, 3.6 Hz, 1H, H-4), 3.31 (m, 1H, H-4), 4.14 (m, 1H, H-6), 6.95 (d, J = 7.6 Hz, 1H, CH=N), 8.03 (d, J = 8.0 Hz, 1H, H ind); ^{13}C NMR (100.6 MHz, most significant peaks) δ 25.6 (C-7), 53.2 (C-6), 58.9 (C-4), 152.8 (CH=N).

(3*R*,6*S*,12b*S*)-12-(*tert*-Butoxycarbonyl)-6-cyano-3-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (14). Burgess reagent (90 mg, 0.38 mmol) was added in three portions of 30 mg each at rt during 2 h to a solution of the crude oximes **13** (50 mg, 0.13 mmol) in CH$_2$Cl$_2$ (1 mL). The resulting mixture was stirred at rt for an additional 2 h, washed with H$_2$O, and extracted with CH$_2$Cl$_2$. The organic extracts were dried and concentrated to afford **14** (42 mg, 88%), which was used without further purification in the next reaction: IR (film) 1156, 1316, 1366, 1427, 1731, 2927 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.93 (t, J = 7.2 Hz, 3H, CH$_3$), 1.16−1.46 (m, 4H, CH_2CH$_3$, H-2, H-1), 1.54 [br s, 9H, C(CH$_3$)$_3$], 1.54 (br s, H-3), 1.96 (dm, J = 13.0 Hz, 1H, H-2), 2.40 (dm, J = 12.0 Hz, 1H, H-1), 2.45 (*t*, J = 11.1 Hz, 1H, H-4), 2.91−2.99 (m, 2H, H-4, H-7), 3.23 (ddd, J = 16.0, 5.5, 2.5 Hz, 1H, H-7), 3.83 (dd, J = 5.4, 1.5 Hz, 1H, H-12b), 4.03 (dd, J = 10.0, 2.0 Hz, 1H, H-6), 7.23 (ddd, J = 4.5, 4.5, 1.0 Hz, 1H, H-9), 7.31 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H, H-10), 7.38 (dm, J = 7.5 Hz, 1H, H-8), 8.08 (d, J = 7.5 Hz, 1H, H-11); ^{13}C NMR (100.6 MHz) δ 11.3 (CH$_3$), 26.6 (C-7), 27.0 (CH$_3$*C*H$_2$), 28.2 [C(*C*H$_3$)$_3$], 31.2 (C-2), 31.5 (C-1), 38.1 (C-3), 51.9 (C-6), 58.1 (C-12b), 60.2 (C-4), 84.1 [*C*(CH$_3$)$_3$], 112.7 (CN), 115.4 (C-11), 116.8 (C-7a), 117.8 (C-8), 122.8 (C-9), 124.4 (C-10), 128.5 (C-7b), 135.8 and 137.2 (C-11a, C-12a), 150.5 (NCOO); $[\alpha]^{22}_D$ −74.8 (*c* 0.7, MeOH); MS-EI *m*/*z* 397 (M$^+$ + 1, 1), 340 (40), 322 (55), 295 (100), 267 (53), 251 (79), 212 (58), 168 (53), 57 (44); HMRS (M$^+$ + 1) calcd for $C_{23}H_{29}N_3O_2$ 380.2332, found 380.2319.

(3*R*,12b*S*)-12-(*tert*-Butoxycarbonyl)-3-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (15). AcOH (30 μL, 3.12 mmol) was added to a solution of NaBH$_3$CN (50 mg, 0.79 mmol) in CH$_3$CN, (0.25 mL), and the mixture was stirred at rt for 30 min. Then, a solution of **14** (50 mg, 0.13 mmol) in CH$_3$CN (0.2 mL) was added, and the mixture was stirred at rt for 9 h, diluted with CH$_2$Cl$_2$, and extracted with 4 N aqueous NaOH. The organic phase was separated, washed with brine, dried, and concentrated to yield

15 (44 mg, 94%): ^{1}H NMR (400 MHz) δ 0.85 (t, J = 7.2 Hz, 3H, CH_3), 1.10−1.18 (m, 3H, CH_2CH$_3$, H-2), 1.42−1.51 (m, 2H, H-3, H-1), 1.59 [s, 9H, C(CH$_3$)$_3$], 1.87 (dm, J = 13.0 Hz, 1H, H-2), 2.07 (dm, J = 13.0 Hz, 1H, H-1), 2.42 (t, J = 12.0 Hz, 1H, H-4), 2.64−2.79 (m, 3H, H-7, H-6), 3.00−3.12 (m, 2H, H-4, H-6), 3.92 (d, J = 10.5 Hz, 1H, H-12b), 7.14 (m, 1H, H-9), 7.18 (m, 1H, H-10), 7.32 (dd, J = 7.0, 1.0 Hz, 1H, H-8), 8.01 (d, J = 7.5 Hz, 1H, H-11); ^{13}C NMR (100.6 MHz) δ 11.3 (CH_3), 22.3 (C-7), 27.3 (CH_3CH_2), 28.2 [C(CH_3)$_3$], 28.5 (C-1), 31.5 (C-2), 34.5 (C-3), 47.6 (C-6), 59.2 (C-12b), 61.6 (C-4), 83.5 [C(CH$_3$)$_3$], 115.4 (C-11), 115.6 (C-7a), 117.9 (C-8), 122.5 (C-9), 123.8 (C-10), 129.3 (C-7b), 136.3 and 137.2 (C-11a, C-12a), 150.5 (NCOO).

(3*S*,7*R*,8*R*,8a*S*)-8-Ethyl-3-(3-indolylmethyl)-7-(methoxycarbonylmethyl)-5-thio-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (18). Following the procedure described for **6**, from Lawesson's reagent (2.82 g, 6.98 mol) and lactam **17**[4d] (4.31 g, 11.64 mol) in DME (70 mL) at reflux for 4 h 30 min, thiolactam **18** (3.69 g, 82%) was obtained after column chromatography (1:4 EtOAc−hexane to EtOAc): IR (film) 1725, 2959, 3229 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.01 (t, J = 7.2 Hz, 3H, CH_3), 1.51−1.70 (m, 3H, CH$_3$CH_2, H-8), 2.28 (m, 1H, H-7), 2.40 (s, 1H, CH$_2$CO), 2.41 (d, J = 2.5 Hz, 1H, CH$_2$CO), 2.67 (dd, J = 13.5, 11.0 Hz, 1H, CH$_2$-ind), 2.83 (dd, J = 16.5, 11.0 Hz, 1H, H-6), 3.01 (dd, J = 16.5, 3.0 Hz, 1H, H-6), 3.71 (s, 3H, CH$_3$O), 3.79 (ddd, J = 9.0, 5.5, 1.5 Hz, 1H, H-8a), 4.05 (d, J = 13.5 Hz, 1H, CH$_2$-ind), 4.14 (d, J = 9.5 Hz, 1H, H-2), 4.56 (d, J = 9.0 Hz, 1H, H-2), 4.77 (ddd, J = 11.0, 5.5, 2.5 Hz, 1H, H-3), 7.10 (d, J = 2.0 Hz, 1H, H-2 ind), 7.15 (ddd, J = 7.0, 7.0, 1.0, 1H, H-6 ind), 7.21 (ddd, J = 8.0, 8.0, 1.0, 1H, H-5 ind), 7.36 (d, J = 7.5 Hz, 1H, H-4 ind), 8.04−8.06 (d, J = 7.5 Hz, 1H, H-7 ind); ^{13}C NMR (75.4 MHz) δ 10.5 (CH_3), 24.7 and 25.4 (CH$_2$-ind and CH$_3$$CH_2$), 32.8 (C-7), 39.4 ($CH_2$CO), 45.8 (C-8), 45.9 (C-6), 51.8 (CH$_3$O), 60.4 (C-3), 69.9 (C-2), 93.2 (C-8a), 110.9 (C-4 ind), 112.2 (C-3 ind), 119.8 (C-6 ind), 120.0 (C-7 ind), 122.4 (C-5 ind), 122.6 (C-2 ind), 127.5 (C-3a ind), 136.3 (C-7a ind), 172.2 (COO), 194.3 (NCS); mp 160−161 °C (EtOAc−hexane); MS-EI m/z 386 (M$^+$, 23), 353 (7), 214 (17), 181 (31), 156 (59), 129 (100), 107 (61); HMRS (M$^+$ + 1) calcd for $C_{21}H_{27}N_2O_3S$ 387.1737, found 387.1731. Anal. Calcd for $C_{21}H_{26}N_2O_3S\cdot{}^3/_4H_2O$: C, 63.16; H, 6.61; N, 6.95. Found: C, 63.05; H, 6.93; N, 7.00.

(2*R*,3*R*,4*S*,6*S*,12b*S*)-4,6-(Epoxymethano)-3-ethyl-2-(methoxycarbonylmethyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (19). Following the procedure described for the preparation of **4**, from thiolactam **18** (2.61 g, 6.76 mmol) and benzyl bromide (1.61 mL, 13.5 mmol) in CH$_3$CN (51 mL) and then NaBH$_4$ (767 mg, 20.3 mmol) in MeOH (200 mL), pentacycle **19** was obtained (1.43 g, 60%) after column chromatography (1:9 EtOAc−hexane to EtOAc): IR (film) 1731 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.00 (t, J = 7.5 Hz, 3H, CH_3), 1.39−1.49 (m, 2H, H-3, H-1), 1.55 (m, 1H, CH_2CH$_3$), 1.72 (m, 1H, CH_2CH$_3$), 2.03 (tdd, J = 11.0, 3.0, 3.0 Hz, H-2), 2.17 (dd, J = 15.5, 10.5 Hz, 1H, CH$_2$CO), 2.27 (ddd, J = 12.0, 3.0, 3.0 Hz, 1H, H-1), 2.63 (ddd, J = 14.5, 10.5, 2.5 Hz, H-7), 2.70 (dd, J = 15.5, 3.0 Hz, 1H, CH$_2$CO), 2.99 (ddd, J = 14.5, 4.5, 1.5 Hz, 1H, H-7), 3.05 (m, 1H, H-6), 3.58 (d, J = 10.5 Hz, 1H, H-12b), 3.71 (m, 1H, H-4), 3.72 (s, 3H, CH$_3$O), 3.80 (t, J = 7.0 Hz, 1H, CH$_2$O), 4.25 (t, J = 7.0 Hz, 1H, CH$_2$O), 7.09 (dt, J = 7.5, 1.0 Hz, H-9), 7.14 (dt, J = 7.5, 1.0 Hz, 1H, H-10), 7.29 (d, J = 7.5 Hz, 1H, H-8), 7.45 (d, J = 7.5 Hz, 1H, H-11), 7.97 (s, 1H, NH); ^{13}C NMR (100.6 MHz) δ 10.2 (CH_3), 20.5 (CH_3CH_2), 25.1 (C-7), 34.5 (C-2), 35.4 (C-1), 37.2 (CH_2CO), 45.7 (C-3), 51.7 (CH$_3$O), 53.9 (C-12b), 57.6 (C-6), 71.5 (CH$_2$O), 94.1 (C-4), 108.1 (C-7a), 110.9 (C-11), 118.0 (C-8), 119.5 (C-9), 121.5 (C-10), 127.1 (C-7b), 134.1 and 136.3 (C-11a, C-12a), 173.5 (COO); [α]$^{22}_D$ −23.4 (c 0.58, MeOH); MS-EI m/z 354 (M$^+$, 97), 323 (58), 270 (74), 207 (48), 156 (100); HMRS (M$^+$ + 1) calcd for $C_{21}H_{26}N_2O_3$ 355.2016, found 355.2015.

(2*R*,3*R*,4*S*,6*S*,12b*S*)-12-(*tert*-Butoxycarbonyl)-4,6-(epoxymethano)-3-ethyl-2-(methoxycarbonylmethyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (20). Following the procedure described for **7**, from pentacycle **19** (1.05 g, 2.97 mmol), NEt$_3$ (0.82 mL, 5.94 mmol), *N*,*N*-dimethylaminopyridine (109 mg, 0.89 mmol), and di-*tert*-butyl dicarbonate (1.16 g, 5.31 mmol) in THF (35 mL), the protected derivative **20** (1.28 g, 95%) was obtained after column chromatography (Florisil, 5:95 EtOAc−hexane to EtOAc): IR (film) 1733, 2974 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.01 (t, J = 7.5 Hz, 3H, CH_3), 1.26 (d, J = 9.0 Hz, 1H, H-1), 1.36 (m, 1H, H-3), 1.54 (m, 1H, CH_2CH$_3$), 1.68 [s, 9H, C(CH$_3$)$_3$], 1.74 (m, 1H, CH_2CH$_3$), 2.04 (m, 1H, H-2), 2.14 (m, 1H, CH$_2$CO), 2.51 (ddd, J = 11.5, 3.0, 3.0 Hz, 1H, H-1), 2.52 (dt, J = 2.5, 11.5 Hz, 1H, H-1), 2.58 (ddd, J = 15.0, 10.0, 3.0 Hz, 1H, H-7), 2.66 (dd, J = 13.5, 2.0 Hz, 1H, CH$_2$CO), 2.90 (ddd, J = 15.0, 4.0, 2.5 Hz, 1H, H-7), 3.11 (m, 1H, H-6), 3.68 (s, 3H, CH$_3$O), 3.75 (t, J = 7.5 Hz, 1H, CH$_2$O), 3.91 (m, 1H, H-12b), 3.92 (d, J = 8.5 Hz, 1H, H-4), 4.25 (t, J = 7.0 Hz, 1H, CH$_2$O), 7.22 (dt, J = 7.0, 1.0 Hz, 1H, H-9), 7.28 (dt, J = 9.0, 1.0 Hz, 1H, H-10), 7.39 (d, J = 7.0 Hz, 1H, H-8), 8.06 (dd, J = 8.5, 1.0 Hz, 1H, H-11); ^{13}C NMR (100.6 MHz) δ 10.3 (CH_3), 20.9 (CH_3CH_2), 26.2 (C-7), 27.9 [C(CH_3)$_3$], 34.8 (C-2), 36.6 (C-1), 37.8 (CH_2CO), 46.4 (C-3), 51.5 (CH$_3$O), 55.7 and 55.8 (C-12b, C-6), 71.4 (CH$_2$O), 84.0 [C(CH$_3$)$_3$], 94.2 (C-4), 115.2 (C-11), 116.8 (C-7a), 117.9 (C-8), 122.7 (C-9), 124.2 (C-10), 128.9 (C-7b), 135.9 and 137.1 (C-11a, C-12a), 150.3 (NCOO), 173.2 (COO); [α]$^{22}_D$ −109.2 (c 0.13, MeOH); MS-EI m/z 454 (M$^+$, 13), 397 (100), 358 (34), 57 (52); HMRS, (M$^+$ + 1) $C_{26}H_{34}N_2O_5$ 455.2540, found 455.2540.

(2*R*,3*R*,6*S*,12b*S*)-12-(*tert*-Butoxycarbonyl)-3-ethyl-6-(hydroxymethyl)-2-(methoxycarbonylmethyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (22). Following the procedure described for the preparation of **11**, from pentacycle **20** (735 mg, 1.62 mmol) and BH$_3$·THF (1 M in THF, 6.0 mL, 6.0 mmol) in THF (13.5 mL) at −78 °C for 6 h 30 min, alcohol **22** (515 mg, 70% yield) was obtained after column chromatography (1:1 EtOAc−hexane to EtOAc): IR (NaCl) 1156, 1368, 1730, 2930, 2965, 3432 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.94 (t, J = 7.0 Hz, 3H, CH_3), 1.20−1.28 (m, 2H, CH_2CH$_3$, H-1), 1.37 (m, 1H, H-3), 1.60 (m, 1H, CH_2CH$_3$), 1.67 [s, 9H, C(CH$_3$)$_3$], 1.93 (m, 1H, H-2), 2.03 (dd, J = 14.0, 1.0 Hz, 1H, CH$_2$CO), 2.11 (t, J = 11.0 Hz, 1H, H-4), 2.40 (dq, J = 12.5, 2.0 Hz, 1H, H-1), 2.60 (dd, J = 15.0, 3.5 Hz, CH$_2$CO), 2.65 (m, 1H, H-7), 2.75 (dq, J = 10.5, 3.2 Hz, 1H, H-6), 2.89 (ddd, J = 15.5, 13.5, 3.0 Hz, 1H, H-7), 3.42 (dd, J = 11.0, 4.5 Hz, 1H, H-4), 3.65 (s, 3H, CH$_3$O), 3.75−3.80 (m, 2H, H-12b, CH_2OH), 4.02 (dd, J = 11.0, 4.0 Hz, 1H, CH_2OH), 7.21 (ddd, J = 7.0, 7.0, 1.0 Hz, 1H, H-9), 7.25 (ddd, J = 7.0, 7.0, 1.0 Hz, 1H, H-10), 7.38 (d, J = 8.0 Hz, 1H, H-8), 8.03 (d, J = 7.5 Hz, 1H, H-11); ^{13}C NMR (100.6 MHz) δ 11.0 (CH_3), 23.8 (CH_3CH_2), 25.7 (C-7), 28.1 [C(CH_3)$_3$], 37.3 (C-2), 38.2 (C-1), 38.5 (CH_2CO), 42.6 (C-3), 51.4 (CH$_3$O), 53.8 (C-4), 58.4 (C-6), 61.5 (C-12b), 63.4 (CH$_2$OH), 83.9 [C(CH$_3$)$_3$], 115.2 (C-11), 116.5 (C-7a), 117.9 (C-8), 122.7 (C-9), 124.0 (C-10), 129.0 (C-7b), 135.8 and 137.2 (C-11a, C-12a), 150.5 (NCOO), 173.3 (COO); MS-EI m/z 353 (M$^+$ − CH$_2$OH, 32), 327 (12), 297 (100), 253 (16), 168 (10), 57 (13); [α]$^{22}_D$ −121.8 (c 0.62, MeOH); HMRS calcd for $C_{26}H_{36}N_2O_5$ 457.2696, found 457.2687. Anal. Calcd for $C_{26}H_{36}N_2O_5$: C, 68.40; H, 7.95; N, 6.14. Found: C, 68.07; H, 7.85; N, 6.06.

(2*R*,3*R*,6*S*,12b*S*)-12-(*tert*-Butoxycarbonyl)-3-ethyl-6-formyl-2-(methoxycarbonylmethyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (23). Following the procedure described for the preparation of **12**, from alcohol **22** (353 mg, 0.77 mmol) in CH$_2$Cl$_2$ (3.7 mL), DMSO (275 μL, 3.88 mmol), oxalyl chloride (170 μL, 2.02 mmol) in CH$_2$Cl$_2$ (10.4 mL), and then Et$_3$N (570 μL, 5.3 mmol), aldehyde **23** (350 mg) was obtained, which was used without further purification in the next reaction: IR (film) 1731, 2965 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.90 (t, J = 7.5 Hz, 3H, CH_3), 1.16−1.40 (m, 2H, CH_2CH$_3$, H-1), 1.51 (m, 1H, H-3), 1.60 (m, 1H, CH_2CH$_3$), 1.67 [s, 9H, C(CH$_3$)$_3$], 1.96 (m, 1H, H-2), 2.08 (dd, J = 15.0, 9.5 Hz, 1H, CH$_2$CO), 2.30 (t, J = 11.5 Hz, 1H, H-4), 2.44 (ddd, J = 13.5, 4.0, 1.6 Hz, H-1), 2.62 (dd, J = 15.0, 3.5 Hz, 1H, CH$_2$CO), 2.65 (ddd, J = 15.5, 4.5, 2.5 Hz, 1H, H-7), 2.88 (ddd, J = 15.5, 10.5, 3.0 Hz, 1H, H-7), 3.04 (dd, J = 11.5, 4.5 Hz,

1H, H-4), 3.25 (dt, J = 10.5, 4.5 Hz, 1H, H-6), 3.66 (s, 3H, CH_3O), 3.77 (dm, J = 10.5 Hz, 1H, H-12b), 7.23 (ddd, J = 7.0, 7.0, 1.0 Hz, 1H, H-9), 7.28 (ddd, J = 7.0, 7.0, 1.0 Hz, 1H, H-10), 7.38 (d, J = 7.0 Hz, 1H, H-8), 8.04 (d, J = 8.0 Hz, 1H, H-11), 9.68 (d, J = 4.5 Hz, 1H, CHO); ^{13}C NMR (100.6 MHz) δ 10.8 (CH_3), 23.1 (C-7), 23.5 (CH_3CH_2), 28.0 [$C(CH_3)_3$], 37.6 (C-2), 37.9 (C-1), 38.4 (CH_2CO), 42.3 (C-3), 51.4 (CH_3O), 57.8 (C-4), 60.4 (C-6), 66.9 (C-12b), 84.1 [$C(CH_3)_3$], 113.6 (C-7a), 115.3 (C-11), 117.8 (C-8), 122.8 (C-9), 124.3 (C-10), 128.5 (C-7b), 135.5 and 137.1 (C-11a, C-12a), 150.3 (NCOO), 173.3 (COO), 202.2 (CHO); MS-EI m/z 425 (M^+ − CHO, 32), 369 (100), 325 (18), 168 (10), 57 (8).

(2*R*,3*R*,6*S*,12b*S*)-12-(*tert*-Butoxycarbonyl)-3-ethyl-6-(hydroxyiminomethyl)-2-(methoxycarbonylmethyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (24). Following the procedure described for the preparation of **13**, from aldehyde **23** (350 mg, 0.77 mmol) and $NH_2OH.HCl$ (295 mg, 4.24 mmol) in pyridine (4.6 mL) and absolute EtOH (4.6 mL), a 2:1 (^{1}H NMR) mixture of *E*/*Z* oximes (282 mg, 78% from **22**) was obtained. Flash chromatography (1:4 Et_2O−hexane to Et_2O) gave pure *E* and *Z* oximes **24**. *E* isomer: IR (film) 1731, 2967 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.90 (t, J = 7.5 Hz, 3H, CH_3), 1.18−1.24 (m, 2H, CH_2CH_3, H-1), 1.41 (m, 1H, H-3), 1.59 (m, 1H, CH_2CH_3), 1.67 [s, 9H, $C(CH_3)_3$], 1.92 (m, 1H, H-2), 2.05 (dd, J = 14.5, 9.0 Hz, 1H, CH_2CO), 2.17 (t, J = 11.5 Hz, 1H, H-4), 2.42 (dm, J = 13.0 Hz, 1H, H-1), 2.61 (dd, J = 14.5, 3.5 Hz, 1H, CH_2CO), 2.70 (ddd, J = 15.5, 4.0, 2.0 Hz, 1H, H-7), 2.85 (ddd, J = 15.5, 10.0, 2.5 Hz, 1H, H-7), 3.14 (dd, J = 11.5, 4.5 Hz, 1H, H-4), 3.41 (ddd, J = 9.5, 9.5, 3.5 Hz, 1H, H-6), 3.65 (s, 3H, CH_3O), 3.76 (d, J = 10.5 Hz, 1H, H-12b), 7.21 (ddd, J = 7.0, 7.0, 1.0 Hz, 1H, H-9), 7.27 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H, H-10), 7.36 (d, J = 7.0 Hz, 1H, H-8), 7.50 (d, J = 8.5 Hz, 1H, CH═N), 8.04 (d, J = 8.5 Hz, 1H, H-11); ^{13}C NMR (100.6 MHz) δ 10.9 (CH_3), 23.6 (CH_3CH_2), 27.7 (C-7), 28.1 [$C(CH_3)_3$], 37.4 (C-2), 37.9 (C-1), 38.4 (CH_2CO), 41.9 (C-3), 51.5 (CH_3O), 57.0 (C-4), 58.5 (C-6), 61.6 (C-12b), 84.0 [$C(CH_3)_3$], 115.2 (C-7a), 115.3 (C-11), 117.9 (C-8), 122.7 (C-9), 124.2 (C-10), 128.7 (C-7b), 135.6 and 137.2 (C-11a, C12a), 150.4 (NCOO), 153.1 (CH═N), 173.3 (COO); $[\alpha]^{22}_D$ −97.0 (c 1.0, MeOH); MS-EI m/z 470 (M^+ + 1, 1), 452 (36), 412 (100), 368 (50), 323 (73), 168 (33); HMRS (M^+ + 1) calcd for $C_{26}H_{35}N_3O_5$ 470.2649, found 470.2667. **24**, *Z* isomer: IR (film) 1731, 2967 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.91 (t, J = 7.5 Hz, 3H, CH_3), 1.18 (m, 1H, CH_2CH_3), 1.26 (m, 1H, H-1), 1.45 (m, 1H, H-3), 1.60 (ddd, J = 13.5, 7.5, 2.5 Hz, 1H, CH_2CH_3), 1.67 [s, 9H, $C(CH_3)_3$], 1.94 (m, 1H, H-2), 2.05 (dd, J = 15.0, 9.5 Hz, 1H, CH_2CO), 2.19 (t, J = 11.0 Hz, 1H, H-4), 2.42 (dm, J = 13.0 Hz, 1H, H-1), 2.61 (dd, J = 15.0, 3.5 Hz, 1H, CH_2CO), 2.72 (ddd, J = 16.0, 4.0, 2.0 Hz, 1H, H-7), 2.81 (ddd, J = 16.0, 4.4, 2.5 Hz, 1H, H-7), 3.25 (dd, J = 11.0, 4.0 Hz, 1H, H-4), 3.65 (s, 3H, CH_3O), 3.79 (d, J = 9.5 Hz, 1H, H-12b), 4.16 (m, 1H, H-6), 6.91 (d, J = 7.0 Hz, 1H, CH═N), 7.21 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H, H-9), 7.27 (ddd, J = 7.0, 7.0, 1.0 Hz, 1H, H-10), 7.36 (d, J = 7.0 Hz, 1H, H-8), 8.04 (d, J = 8.5 Hz, 1H, H-11); ^{13}C NMR (100.6 MHz) δ 11.0 (CH_3), 23.6 (CH_3CH_2), 25.7 (C-7), 28.1 [$C(CH_3)_3$], 37.7 (C-2), 38.1 (C-1), 38.5 (CH_2COO), 42.3 (C-3), 51.5 (CH_3O), 52.8 (C-6), 56.9 (C-4), 61.5 (C-12b), 84.1 [$C(CH_3)_3$], 115.2 (C-7a), 115.3 (C-11), 117.9 (C-8), 122.8 (C-9), 124.2 (C-10), 128.7 (C-7b), 135.6 and 137.2 (C-11a, C-12a), 150.4 (NCOO), 152.8 (CH═N), 173.3 (COO); $[\alpha]^{22}_D$ −116.9 (c 0.9, MeOH); MS-EI m/z 469 (M^+, 10), 412 (100), 369 (38), 323 (47), 168 (20); HMRS (M^+ + 1) calcd for $C_{26}H_{35}N_3O_5$ 470.2649, found 470.2658.

(2*R*,3*R*,6*S*,12b*S*)-12-(*tert*-Butoxycarbonyl)-6-cyano-3-ethyl-2-(methoxycarbonylmethyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (25). Following the procedure described for the preparation of **14**, from oximes **24** (67 mg, 0.14 mmol) and Burgess reagent (100 mg, 0.42 mmol) in CH_2Cl_2 (1 mL), nitrile **25** (57 mg, 90%) was obtained, which was used without further purification in the next reaction: ^{1}H NMR (400 MHz) δ 0.94 (t, J = 7.0 Hz, 3H, CH_3), 1.19 (m, 1H, H-1), 1.48 (m, 1H, H-3), 1.58−1.65 (m, 2H, CH_2CH_3), 1.68 [s, 9H, $C(CH_3)_3$], 1.91 (m, 1H, H-2), 2.07 (dd, J = 15.0, 9.0 Hz, 1H, CH_2CO), 2.46 (ddd, J = 13.0, 4.0, 2.0 Hz, 1H, H-1), 2.53 (t, J = 11.0, 1H, H-4), 2.61 (dd, J = 15.0, 3.5 Hz, 1H, CH_2CO), 2.96 (dt, J = 16.0, 2.0 Hz, 1H, H-7), 3.03 (dd, J = 11.0, 4.5 Hz, 1H, H-4), 3.22 (ddd, J = 16.0, 6.0, 3.0, 1H, H-7), 3.67 (s, 3H, CH_3O), 3.92 (m, 1H, H-12b), 4.06 (dd, J = 6.0, 1.5 Hz, 1H, H-6), 7.23 (t, J = 7.0 Hz, 1H, H-9), 7.30 (t, J = 7.0 Hz, 1H, H-10), 7.37 (d, J = 8.0 Hz, 1H, H-8), 8.09 (d, J = 8.5 Hz, 1H, H-11); ^{13}C NMR (100.6 MHz) δ 10.9 (CH_3), 23.5 (CH_3CH_2), 26.6 (C-7), 28.1 [$C(CH_3)_3$], 37.5 (C-1), 37.7 (C-2), 38.3 (CH_2CO), 41.9 (C-3), 51.4 (C-6), 51.5 (CH_3O), 57.3 (C-12b), 58.4 (C-4), 84.4 [$C(CH_3)_3$], 112.9 (CN), 115.5 (C-11), 116.7 (C-7a), 117.8 (C-8), 122.9 (C-9), 124.5 (C-10), 128.4 (C-7b), 135.3 and 137.3 (C-11a, C-12a), 150.1 (NCOO), 173.0 (COO); HMRS (M^+ + 1) calcd for $C_{26}H_{34}N_3O_4$ 452.2543, found 452.2544.

(2*R*,3*R*,12b*S*)-12-(*tert*-Butoxycarbonyl)-3-ethyl-2-(methoxycarbonylmethyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (26). Following the procedure described for the preparation of **15**, from nitrile **25** (40 mg, 0.09 mmol) and $NaBH_3CN$ (33 mg, 0.52 mmol) in AcOH (20 μL, 1.08 mmol) and CH_3CN (0.45 mL), the derivative **26** (34 mg, 90%) was obtained and used without further purification in the next reaction: ^{1}H NMR (300 MHz) δ 0.92 (t, J = 7.0 Hz, 3H, CH_3), 1.31 (m, 1H, H-1), 1.57−1.71 (m, 2H, CH_2CH_3), 1.67 [s, 9H, $C(CH_3)_3$], 1.88 (m, 1H, H-2), 2.07 (dd, J = 14.5, 9.5 Hz, 1H, CH_2CO), 2.20 (ddd, J = 12.5, 4.0, 2.5 Hz, 1H, H-1), 2.53 (t, J = 12.5 Hz, 1H, H-4), 2.62 (dd, J = 14.5, 3.5, 1H, CH_2CO), 2.70−2.85 (m, 3H, H-6, H-7), 3.10 (m, 1H, H-6), 3.20 (dd, J = 12.5, 4.0 Hz, 1H, H-4), 3.65 (s, 3H, CH_3O), 4.02 (d, J = 11.0 Hz, 1H, H-12b), 7.19−7.30 (m, 2H, H-9, H-10), 7.39 (d, J = 7.5 Hz, 1H, H-8), 8.10 (d, J = 7.5 Hz, 1H, H-11); ^{13}C NMR (100.6 MHz) δ 10.9 (CH_3), 22.3 (C-7), 23.4 (CH_3CH_2), 28.1 [$C(CH_3)_3$], 34.5 (C-1), 38.1 (C-2), 38.5 (CH_2CO), 38.6 (C-3), 47.6 (C-6), 51.4 (CH_3O), 58.8 (C-12b), 59.8 (C-4), 83.3 [$C(CH_3)_3$], 115.4 (C-11), 115.9 (C-7a), 117.9 (C-8), 122.6 (C-9), 123.9 (C-10), 129.2 (C-7b), 136.8 and 136.9 (C-11a, C-12a), 150.3 (NCOO). 173.3 (COO); $[\alpha]^{22}_D$ −87.0 (c 0.9, $CHCl_3$).

(2*R*,3*R*,12b*S*)-3-Ethyl-2-(methoxycarbonylmethyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (27). A solution of **26** (12.5 mg, 0.03 mmol) in HCOOH (0.1 mL) was stirred at rt for 40 h. The mixture was concentrated, and the resulting residue was dissolved in EtOAc. The solution was washed with brine, dried, and concentrated to furnish **27** (7 mg, 74%): ^{1}H NMR (400 MHz) δ 0.93 (t, J = 7.5 Hz, 3H, CH_3), 1.37 (m, 1H, H-1), 1.52 (m, 1H, H-3), 1.60−1.70 (m, 2H, CH_3CH_2), 1.82 (m, 1H, H-2), 2.10 (dd, J = 15.5, 9.5 Hz, 1H, CH_2CO), 2.14 (m, 1H, H-4), 2.23 (ddd, J = 12.5, 3.5, 3.0 Hz, 1H, H-1), 2.61 (ddd, J = 11.0, 11.0, 5.0 Hz, 1H, H-6), 2.69 (dd, J = 15.5, 4.0 Hz, 1H, CH_2CO), 2.72 (m, 1H, H-7), 2. 96 (m, 1H, H-7), 3.10 (m, 2H, H-4, H-6), 3.65 (dm, J = 11.5 Hz, 1H, H-12b), 3.72 (s, 3H, CH_3O), 7.07 (ddd, J = 7.0, 1.0 Hz, 1H, H-9), 7.12 (ddd, J = 7.0, 1.0 Hz, 1H, H-10), 7.29 (d, J = 7.5 Hz, 1H, H-11), 7.46 (d, J = 7.0 Hz, 1H, H-8), 7.82 (br s, 1H, NH); ^{13}C NMR (100.6 MHz) δ 10.9 (CH_3), 21.7 (C-7), 23.5 (CH_3CH_2), 36.0 (C-1), 37.3 (C-2), 38.0 (CH_2COO), 41.6 (C-3), 51.6 (CH_3O), 53.1 (C-6), 59.4 (C-12b), 60.1 (C-4), 108.1 (C-7a), 110.7 (C-11), 118.1 (C-8), 119.3 (C-9), 121.3 (C-10), 127.3 (C-7b), 134.5 (C-12a), 136.0 (C-11a), 173.6 (COO); $[\alpha]^{22}_D$ −5.0 (c 0.5, $CHCl_3$) {lit.^{13}C for the ethyl ester: $[\alpha]^{24}_D$ −4.6 (c 0.521, EtOH)}.

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Supporting Information Available: Experimental procedures for **8**, **9**, **10**, and **21**, copies of the ^{1}H and ^{13}C NMR spectra of all new compounds, and X-ray crystallographic data for compounds **10** and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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