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Straightforward Methodology for the Enantioselective Synthesis of Benzo[*a*]- and Indolo[2,3-*a*]quinolizidines

Mercedes Amat,*,† Maria M. M. Santos,† Oriol Bassas,† Núria Llor,† Carmen Escolano,† Arantxa Gómez-Esqué,† Elies Molins,‡ Steven M. Allin,§ Vickie McKee,§ and Joan Bosch*,†

Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, 08028-Barcelona, Spain, Institut de Ciència de Materials de Barcelona (CSIC), Campus UAB, 08193-Cerdanyola, Spain, and Department of Chemistry, Loughborough University, Loughborough, Leicestershire LE11 3TU, U.K.

amat@ub.edu; joanbosch@ub.edu

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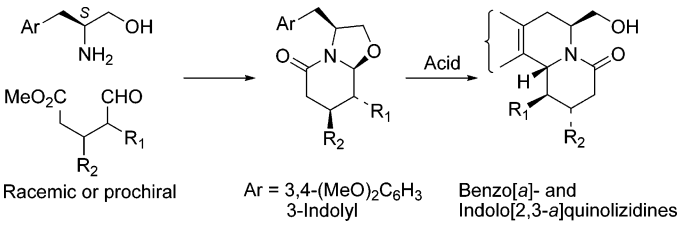

An enantioselective two-step route to substituted benzo[*a*]- and indolo[2,3-*a*]quinolizidines has been developed. It consists of (i) a stereoselective cyclocondensation of a racemic or prochiral δ-oxo(di)ester with either (*S*)-(3,4-dimethoxyphenyl)alaninol or (*S*)-tryptophanol in a process involving a dynamic kinetic resolution and/or the differentiation of enantiotopic or diastereotopic ester groups, and (ii) a subsequent stereocontrolled cyclization on the aromatic ring taking advantage of the masked *N*-acyl iminium ion present in the resulting oxazolopiperidone lactams.

Introduction

Aminoalcohol-derived oxazolopiperidone lactams have proven to be exceptionally versatile building blocks for the enantioselective construction of structurally diverse piperidine-containing natural products and bioactive compounds.[1] These lactams are easily accessible by the cyclocondensation reaction of δ-oxoacid derivatives with chiral nonracemic aminoalcohols, generally phenylglycinol, and allow the substituents to be introduced at the different ring positions in a regio- and stereocontrolled manner, providing access to enantiopure polysubstituted piperidines bearing virtually any type of substitution pattern and also to quinolizidines, indolizidines, perhydroquinolines, hydroisoquinolines, as well as indole alkaloids.[2] Particularly interesting are cyclocondensation reactions of phenylglycinol with racemic or prochiral δ-oxo(di)acid derivatives in processes involving dynamic kinetic resolution and/or differentiation of enantiotopic or diastereotopic ester groups, as they lead directly to lactams that already incorporate the carbon substitutents on the heterocyclic ring (Scheme 1).[3] In the above cyclocondensations, the chiral aminoalcohol constitutes a chiral latent form of ammonia, and a later debenzylation is needed to remove the phenylethanol appendage.

Results and Discussion

We present here an enantioselective two-step route to substituted benzo[*a*]- and indolo[2,3-*a*]quinolizidines, two het-

† University of Barcelona.
‡ Institut de Ciència de Materials.
§ Loughborough University.

(1) 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.

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(3) (a) Amat, M.; Cantó, M.; Llor, N.; Ponzo, V.; Pérez, M.; Bosch, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 335. (b) Amat, M.; Cantó, M.; Llor, N.; Escolano, C.; Molins, E.; Espinosa, E.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 5343. (c) Amat, M.; Pérez, M.; Llor, N.; Escolano, C.; Luque, F. J.; Molins, E.; Bosch, J. *J. Org. Chem.* **2004**, *69*, 8681. (d) Amat, M.; Escolano, C.; Lozano, O.; Gómez-Esqué, A.; Griera, R.; Molins, E.; Bosch, J. *J. Org. Chem*. **2006**, *71*, 3804. (e) Amat, M.; Bassas, O.; Llor, N.; Cantó, M.; Pérez, M.; Molins, E.; Bosch, J. *Chem. Eur. J.* **2006**, *12*, 7872. (f) Amat, M.; Escolano, C.; Gómez-Esqué, A.; Lozano, O.; Llor, N.; Griera, R.; Molins, E.; Bosch, J. *Tetrahedron: Asymmetry* **2006**, *17*, 1581.

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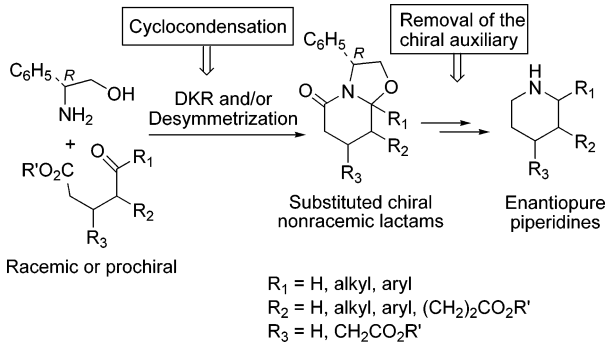
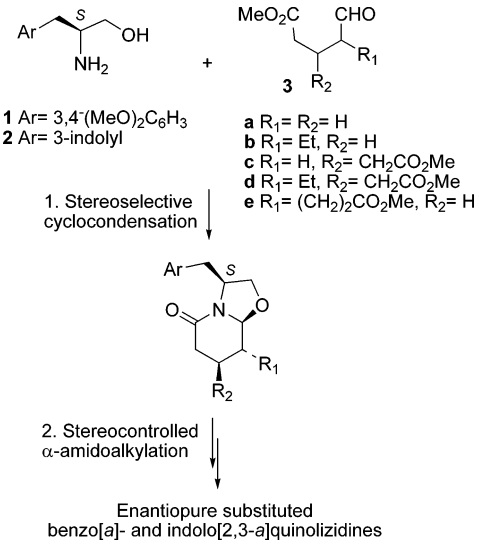
SCHEME 1. Enantioselective Synthesis of Polysubstituted Piperidines



SCHEME 2. Synthetic Strategy



erocyclic systems present in numerous monoterpenoid-derived alkaloids (Figure 1),[4] many of which possess considerable pharmacological and therapeutic interest.[5]

Our approach involves (i) the stereoselective cyclocondensation of a racemic or prochiral δ-oxo(di)ester with either (3,4-dimethoxyphenyl)alaninol (**1**) or tryptophanol (**2**) and (ii) a subsequent stereocontrolled cyclization on the aromatic ring taking advantage of the masked *N*-acyl iminium ion present in the resulting bicyclic lactams (Scheme 2).[6] As δ-oxoester partners we selected the racemic derivative **3b**, prochiral δ-oxodiesters **3c** and **3e** bearing two enantiotopic ester chains, and racemic δ-oxodiester **3d** bearing two diastereotopic ester chains. The aminoalcohol used as the chiral inductor in the cyclocondensation reaction not only constitutes the source of chirality but is also used to assemble the final target polycyclic products.[7]

Cyclocondensation of the L-DOPA-derived aminoalcohol **1** with racemic γ-alkyl δ-oxoester **3b**, which incorporates a

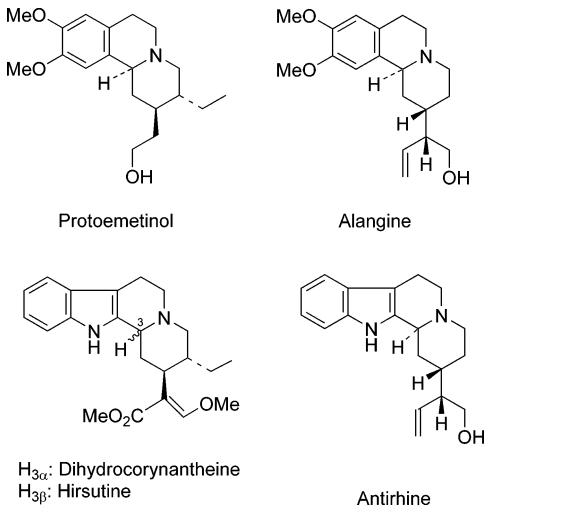


FIGURE 1. Benzo[*a*]- and indolo[2,3-*a*]quinolizidine alkaloids.

chirally labile stereocenter capable of undergoing in situ epimerization during the reaction, took place in good chemical yield and excellent stereoselectivity (dr $\sim$ 5:1), leading to one of the four possible enantiopure stereoisomeric lactams as the major product (**4b**, isolated in 77% yield) in a process involving a dynamic kinetic resolution (DKR)[8] of the racemic substrate (Scheme 3). Minor amounts of the diastereoisomer at the 8 and 8a positions (**4b′**) were also formed. Although such DKR processes represent a useful tool for preparing enantiopure chiral compounds, they have been rarely used in synthetic sequences due to the structural restrictions imposed by the substrate.

A stereoselective cyclocondensation also occurred from oxodiester **3c** in a process involving the desymmetrization[9,10] of two enantiotopic acetate chains. Enantiopure lactam **4c** was isolated in 67% yield along with minor amounts of the diastereoisomer at the 7 and 8a positions (**4c′**).[11] Even more interestingly, treatment of racemic δ-oxodiester **3d** with aminoalcohol **1** took place stereoselectively, with generation of three stereogenic centers in a single synthetic step, to lead to one of

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(5) (a) Neuss, N. *In Indole and Biogenetically Related Alkaloids*; Philipson, J. D., Zenk, M. H., Eds.; Academic Press: London, 1980; Chapter 17. (b) Dewick, P. *Medicinal Natural Products. A Biosynthetic Approach*; Wiley: Chichester, 2002.

(6) For preliminary accounts of part of this work, see: (a) Bassas, O.; Llor, N.; Santos, M. M. M.; Griera, R.; Molins, E.; Amat, M.; Bosch, J. *Org. Lett.* **2005**, *7*, 2817. (b) Allin, S. M.; Duffy, L. J.; McKee, V.; Edgar, M.; Amat, M.; Bassas, O.; Santos, M. M. M.; Bosch, J. *Tetrahedron Lett.* **2006**, *47*, 5713.

(7) For a related approach using unbranched oxoester **3a**, ultimately leading to unsubstituted benzo[*a*]- and indolo[2,3-*a*]quinolizidines, see: (a) Allin, S. M.; Vaidya, D. G.; James, S. L.; Allard, J. E.; Smith, T. A. D.; Mckee, V.; Martin, W. P. *Tetrahedron Lett.* **2002**, *43*, 3661. (b) Allin, S. M.; Thomas, C. I.; Allard, J. E.; Doyle, K.; Elsegood, M. R. J. *Tetrahedron Lett.* **2004**, *45*, 7103. (c) For an asymmetric synthesis of both enantiomers of the indole alkaloid deplancheine, see: Allin, S. M.; Thomas, C. I.; Doyle, K.; Elsegood, M. R. J. *J. Org. Chem.* **2005**, *70*, 357.

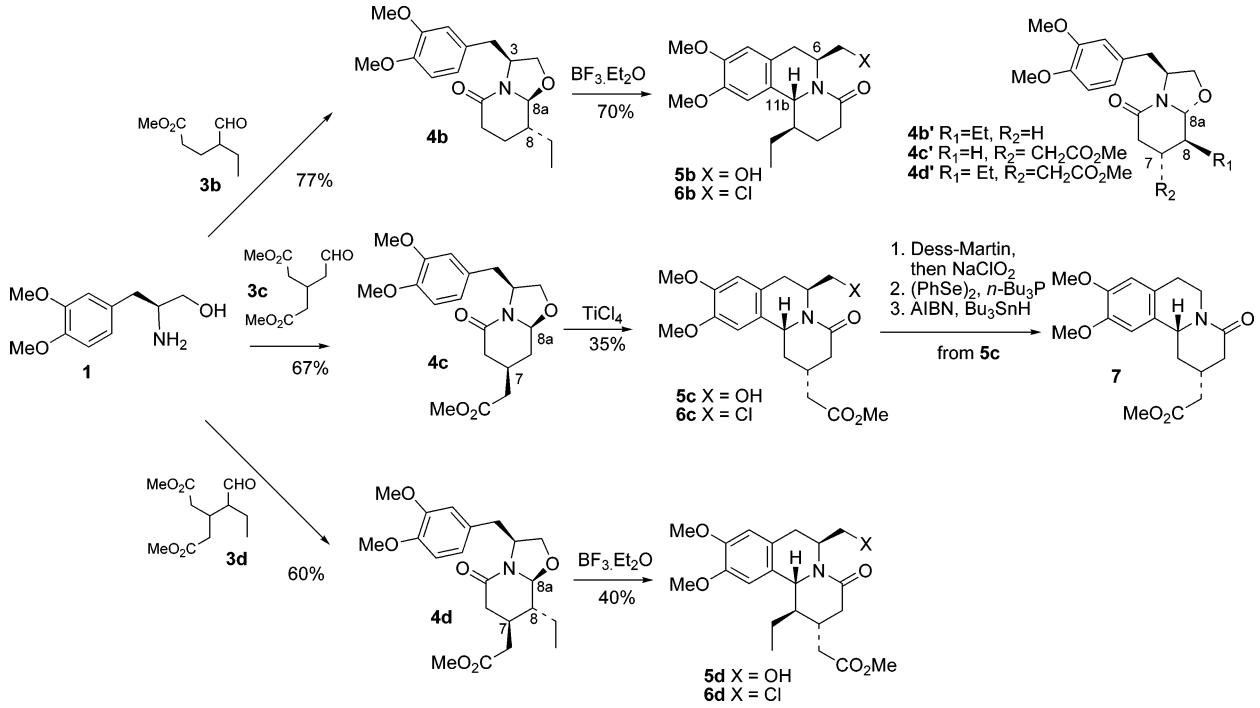
(8) For reviews, see: (a) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36. (b). Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475.4. (c) Caddick, S.; Jenkins, K. *Chem. Soc. Rev.* **1996**, *25*, 447. (d) Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J.-E. *Chem. Soc. Rev.* **2001**, *30*, 321. (e) Pellissier, H. *Tetrahedron* **2003**, *59*, 8291.

(9) For reviews, see: (a) Ward, R. S. *Chem. Soc. Rev.* **1990**, *19*, 1. (b) Danieli, B.; Lesma, G.; Passarella, D.; Riva, S. In *Advances in the Use of Synthons in Organic Chemistry, Vol. 1*; Dondoni, A., Eds.; JAI Press: London, 1993, pp 143. (c) Schoffers, E.; Golebiowski, A.; Johnson, C. R. *Tetrahedron* **1996**, *52*, 3769. (d) Willis, M. C. *J. Chem. Soc. Perkin Trans. 1* **1999**, 1765. (e) Danieli, B.; Lesma, G.; Passarella, D.; Silvani, A. *Curr. Org. Chem.* **2000**, *4*, 231. (f) García- Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2005**, *105*, 313.

(10) For the use of tryptophanol in the desymmetrization of *meso*-trihydroxylated glutaraldehyde, see: Tite, T.; Lallemand, M.-C.; Poupon, E.; Kunesch, N.; Tillequin, F.; Gravier-Pelletier, C.; Le Merrer, Y.; Husson H.-P. *Biorg. Med. Chem.* **2004**, *12*, 5091.

(11) The absolute configuration of lactams **4c**, **4c′**, and **8e**, benzo[*a*]-quinolizidines **5b**−**d**, and indolo[2,3-*a*]quinolizidines **9b′**, 1-*epi*-**9b**, 1-*epi*-**9b′**, and **9d** was unambiguously confirmed by X-ray crystallographic analysis (see supporting information; for X-ray data of **5c**, see reference 6b and CCDC code 297432).

SCHEME 3. Cyclocondensation Reactions from (*S*)-3,4-Dimethoxyphenylalaninol: Enantioselective Synthesis of Substituted Benzo[*a*]quinolizidines



the eight possible stereoisomeric lactams (**4d**) in 60% yield. Notably, this reaction involves a dynamic kinetic resolution of the racemic substrate, with subsequent preferential cyclization of one of the two diastereotopic acetate chains. Minor amounts of the diastereoisomer at the 7, 8, and 8a positions (**4d′**) were also isolated.

The high stereoselectivities observed in the above cyclocondensation reactions can be accounted for by considering that (i) the initially formed mixtures of oxazolidines are in equilibrium via the corresponding imines/enamines and (ii) the final irreversible lactamization occurs faster from a *cis*-oxazolidine intermediate via a transition state in which all the substituents in the incipient chairlike six-membered lactams are equatorial.[3e]

Intramolecular α-amidoalkylation of the above L-DOPA-derived[12] oxazolopiperidone lactams **4b**−**d** took place stereoselectively by treatment with BF_3•Et_2O or $TiCl_4$ to give the respective enantiopure benzo[*a*]quinolizidines **5b**−**d**[11,13] as single stereoisomers detectable by NMR. Taking into account that *N*-acyliminium ion cyclizations[14] upon the 3,4-dimethoxybenzene ring are known to occur under kinetic control and are devoid of stereochemical equilibration,[14c,15] the 6,11b-*trans* relationship resulting from the above cyclizations can be rationalized on the basis of a stereoelectronically controlled axial approach[16] of the aromatic ring to the electrophilic carbon center in the conformation **A** depicted in Figure 2. The alternative cyclization via the chairlike conformation **B** would be disfavored because of severe $A^{(1,3)}$ strain between the pseudoequatorial hydroxymethyl substituent (complexed with the Lewis acid) and the lactam carbonyl group in the transition state. It should be noted that the hydroxymethyl substituent plays a decisive role as a stereocontrol element in determining the relative stereochemistry of the C-11b stereocenter generated in the cyclization step.[17] The $A^{(1,3)}$ strain between the CH_2OH/C═O (and R_1/═CH when R_1 is ethyl) groups in the transition state derived from **B** is higher than the *syn*-axial 1,3-interactions of the substituents R_1 (ethyl) and/or R_2 (acetate chain) in the transition state coming from **A**. In accordance with this interpretation, (i) a 6,11b-*trans* benzoquinolizidine was also obtained as a single stereoisomer in the cyclization ($TiCl_4$) of the deethyl analogue of **4b**;[7a] (ii) there is no stereocontrol in related kinetically controlled cyclizations of six-membered *N*-acyliminium ions lacking the hydroxymethyl substituent but bearing an ethyl substituent at the carbon adjacent (α) to the electrophilic center[18] (both type-**A** and -**B** conformations are similarly favored); and (iii) a stereoselectivity opposite to that observed in the cyclization of **4c** was found in cyclizations from substrates bearing only a *β*

(12) For diastereoselective intramolecular α-amidoalkylation reactions of L-DOPA-derived five-membered *N*-acyliminium ions, see: García, E.; Arrasate, S.; Lete, E.; Sotomayor, N. *J. Org. Chem.* **2005**, *70*, 10368 and references therein.

(13) For a recent review on the asymmetric synthesis of isoquinoline alkaloids, see: Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341.

(14) For a review on the Pictet−Spengler condensation, including mechanisms for cyclization and isomerization, see: (a) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797. For recent reviews on the chemistry and cyclizations of *N*-acyliminium ions, see: (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (c) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431.

(15) Maryanoff, B. E.; McComsey, D. F.; Duhl-Emswiler, B. A. *J. Org. Chem.* **1983**, *48*, 5062.

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

(17) For related cyclizations where a substituent α to the amide nitrogen acts as an element of stereocontrol, see: (a) Maryanoff, B. E.; McComsey, D. F.; Almond, H. R., Jr.; Mutter, M. S.; Bemis, G. W.; Whittle, R. R.; Olofson, R. A. *J. Org. Chem.* **1986**, *51*, 1341. (b) Huizenga, R. H.; Pandit, U. K. *Tetrahedron* **1992**, *48*, 6521. (c) Allin, S. M.; Northfield, C. J.; Page, M. I.; Slawin, A. M. Z. *Tetrahedron Lett.* **1998**, *39*, 4905. (d) Heaney, H.; Taha, M. O. *Tetrahedron Lett.* **2000**, *41*, 1993. (e) Bahajaj, A. A.; Vernon, J. M.; Wilson, G. D. *J. Chem. Soc. Perkin Trans. 1* **2001**, 1446. (f) Nielsen, T. E.; Meldal, M. *J. Org. Chem.* **2004**, *69*, 3765. See also refs 7 and 15.

(18) Kalaus, G.; György, P.; Kajtár-Peredy, M.; Radics, L.; Szabó, L.; Szántay, C. *Chem. Ber.* **1981**, *114*, 1476.

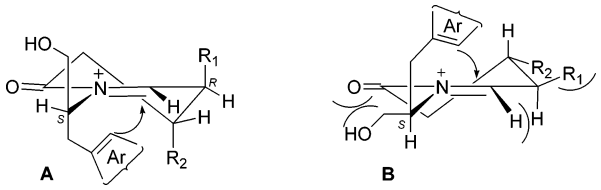


FIGURE 2. Stereochemical outcome of *N*-acyliminium cyclization reaction.

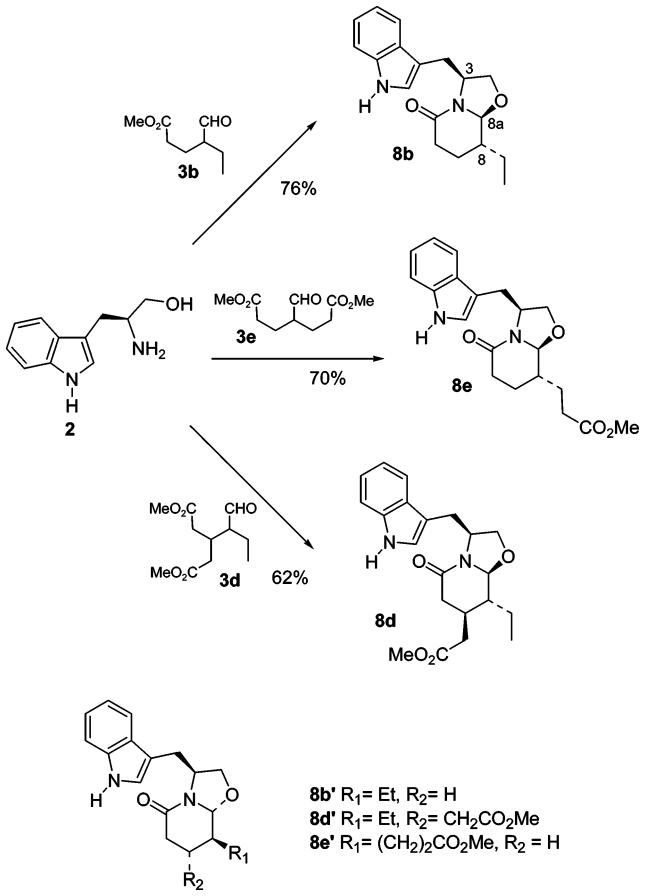
stereogenic center[19] (a type-**B** conformation operates, in which the substituent R_2 is equatorial).

The use of HCl (6 M in methanol, 50 °C, 24 h) in the above cyclizations was less satisfactory from the synthetic standpoint. Although these cyclizations took place in high overall yield (~80%) and complete stereoselectivity, mixtures of the expected 6,11b-*trans* benzoquinolizidines **5b**−**d** and the corresponding chlorides **6b**−**d** were formed (1−2:1 ratio). Interestingly, when the cyclization of **4b** using HCl was carried out at room temperature, a mixture of diastereoisomeric lactams **4b** and **4b′** (approximate 1:3 ratio) and minor amounts of the cyclized product **5b** were formed. This result indicates that under these conditions the equilibration[20] of the 3,8a-*cis* lactam **4b** to the most stable all-*trans* isomer **4b′** is faster than cyclization upon the benzene ring and that cyclization occurs exclusively from the *N*-acyliminium ion derived from **4b** (**A**; R_1 = Et, R_2H in Figure 2). The cyclization of the *N*-acyliminium ion derived from **4b′** should overcome the A(1,3) strain between the equatorial ethyl group and the hydrogen atom of the iminium cation. In agreement with this interpretation, cyclization (6.5 M HCl in methanol, 50 °C, 24 h) of pure lactam **4b′** (the minor stereoisomer in the cyclocondensation of **3b**) occurred with inversion of the configuration of the stereocenter adjacent to the iminium cation, leading to a mixture (71% overall yield) of the same benzoquinolizidine alcohol (**5b**) and chloride (**6b**) previously obtained from **4b**.

The removal of the hydroxymethyl appendage of **5c** to give the enantiopure *cis*-benzo[*a*]quinolizidine-2-acetate **7** was accomplished following the procedure recently developed by Allin:[7b,c] by oxidation to a carboxylic acid followed by a radical reductive decarbonylation of the corresponding seleno ester.

Highly stereoselective cyclocondensations also occurred from tryptophanol (**2**). Thus, reaction with racemic oxoester **3b** afforded enantiopure lactam **8b** in 76% yield, along with minor amounts (11%) of the 8,8a-diastereoisomer **8b′**, in a process again involving a dynamic kinetic resolution with epimerization of the stereogenic center α to the aldehyde carbonyl group (Scheme 4). Prochiral diester **3e**, in turn, reacted with tryptophanol to give the enantiopure lactam **8e** (70% yield), whereas racemic diester **3d** led to substituted lactam **8d** (62% yield) in cyclocondensations involving the desymmetrization of two enantiotopic propionate chains and a dynamic kinetic resolution

SCHEME 4. Cyclocondensation Reactions from (*S*)-Tryptophanol



with differentiation of diastereotopic acetate chains,[21] respectively. In these cases, minor amounts of the respective diastereoisomers at the 8,8a and 7,8,8a positions (**8e′** and **8d′**, respectively) were also isolated. As in the above L-DOPA-derived lactams, the relative stereochemistry of the oxazolidine moiety in the major lactams **8b**, **8d**, and **8e**[11] was *cis*.

Cyclization of **8b** by intramolecular α-amidoalkylation on the indole 2-position occurred smoothly, under kinetic control, by treatment with HCl (1.2 M in EtOH, rt, 24 h) to give the 6,12b-*trans* indoloquinolizidine **9b** in 80% yield (Scheme 5). Minor amounts (13% yield) of the epimeric 6,12b-*cis* indoloquinolizidine **9b′** were also isolated.[11] This result is consistent with that reported for the cyclization of the deethyl analogue of **8b**: a single 6,12b-*trans* indoloquinolizidine was obtained with 2 M HCl, whereas a 5:2 diastereoisomeric mixture of *trans*/*cis* isomers was formed using $TiCl_4$.[7b] In the indole series, the removal of the hydroxymethyl substituent required the protection of the indole nitrogen as a Boc derivative. In this way, following the protocol reported by Allin,[7b,c] **9b** was satisfactorily converted to indoloquinolizidine **10** as shown in Scheme 5.

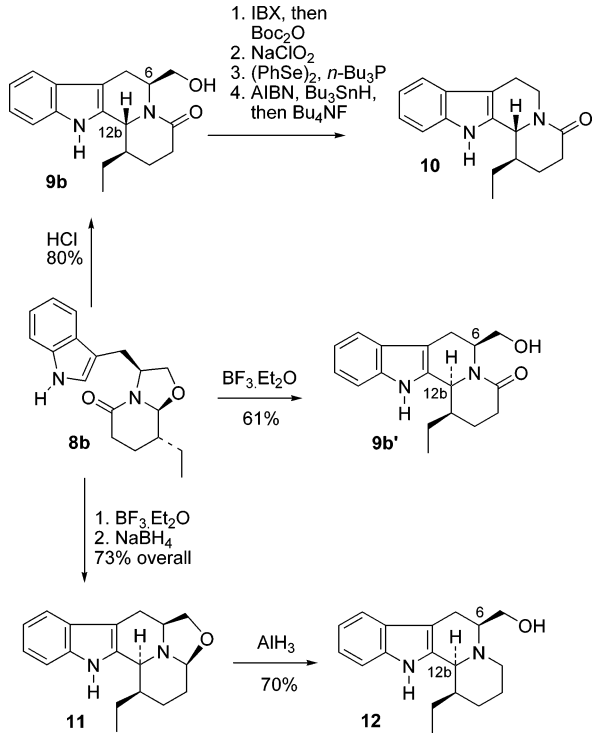
Remarkably, the use of BF_3·Et_2O (CH_2Cl_2, reflux, 24 h) in the cyclization of **8b** resulted in a dramatic change in the stereoselectivity as the 6,12b-*cis* indoloquinolizidine **9b′** was obtained as the major product (61% yield). Minor amounts

(19) (a) Takano, S.; Takahashi, M.; Ogasawara, K. *J. Am. Chem. Soc.* **1980**, *102*, 4282. (b) Pancrazi, A.; Kervagoret, J.; Khuong-Huu, Q. *Tetrahedron Lett.* **1991**, *32*, 4483. (c) Danieli, B.; Lesma, G.; Mauro, M.; Palmisano, G.; Passarella, D. *Tetrahedron* **1994**, *50*, 8837.

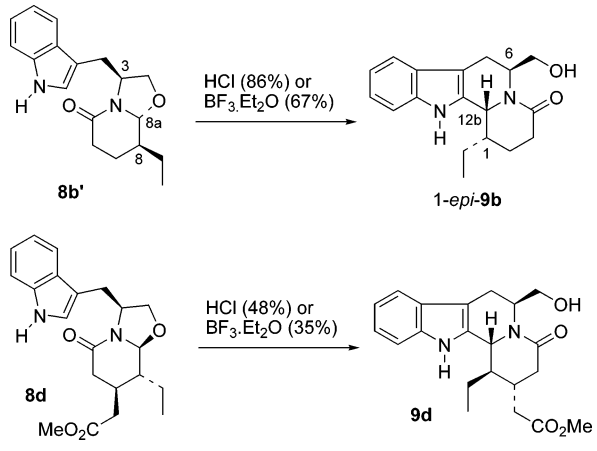
(20) For similar epimerizations of phenylglycinol-derived *cis*-oxazolopiperidone lactams to the *trans*-isomers, see: Amat, M.; Escolano, C.; Gómez-Esqué, A.; Lozano, O.; Llor, N.; Griera, R.; Molins, E.; Bosch, J. *Tetrahedron: Asymmetry* **2006**, *17*, 1581. See also ref 2a.

(21) For early precedents of the discrimination of diastereotopic acetaldehyde chains in the context of the synthesis of indole alkaloids, see: (a) Masamune, S.; Ang, S. K.; Egli, C.; Nakatsuka, N.; Sarkar, S. K.; Yasunari, Y. *J. Am. Chem. Soc.* **1967**, *89*, 2506. (b) van Tamelen, E. E.; Oliver, L. K. *J. Am. Chem. Soc.* **1970**, *92*, 2136.

SCHEME 5. Stereocontrolled Synthesis of 1-Ethylindolo[2,3-*a*]quinolizidines



SCHEME 6. Enantioselective Synthesis of Substituted Indolo[2,3-*a*]quinolizidines



(13%) of the *trans* epimer **9b** and, in some experiments conducted on a larger scale, trace amounts of a third indoloquinolizidine 1-*epi*-**9b′** were also isolated.[11] Interestingly, two C-12b epimeric indoloquinolizidines can be accessed from a single tryptophanol-derived lactam **8b** by an appropriate choice of acid for the cyclization. Even more satisfactorily in terms of chemical yield, lactam **8b** was converted to pentacyclic oxazolidine **11** in 73% overall yield by sequential treatment with BF_3•Et_2O and $NaBH_4$ in methanol. Under these conditions, indoloquinolizidine **9b** was isolated (13% yield) as a byproduct, showing that only the major isomer **9b′** in the initially formed **9b** + **9b′** mixture undergoes partial reduction of the lactam carbonyl group to give an iminium species, which is intramolecularly trapped by the hydroxy group. A subsequent reductive cleavage with alane of the oxazolidone ring present in **11** gave the enantiopure 6,12b-*cis* indoloquinolizidine **12** in 70% yield.

In contrast to the above cyclizations from **8b**, cyclization of the minor lactam **8b′** took place with the same stereoselectivity whether using BF_3•Et_2O (CH_2Cl_2, reflux, 24 h) or HCl (2 M in ethanol, rt, 3 days) to give a single 6,12b-*trans* indoloquinolizidine 1-*epi*-**9b**[11] (67 and 86% yields, respectively) (Scheme 6). A similar stereoselectivity was observed in the acid-promoted cyclization of lactam **8d**: the 6,12b-*trans* indoloquinolizidine **9d**[11] was the only isolable product, although in moderate yield (35%), when using BF_3•Et_2O (CH_2Cl_2, reflux, 14 h) and the major isomer (48%) with HCl (6.5 M in MeOH, rt, 25 h). Under the latter conditions, a minor (29%) C-1 isomeric indoloquinolizidine **9d′** was also isolated.

Conclusion

Oxazolopiperidone lactams derived from (3,4-dimethoxyphenyl)alaninol or tryptophanol significantly expand the potential and scope of chiral bicyclic lactams for the enantioselective synthesis of piperidine-containing derivatives, providing a two-step route to substituted enantiopure benzo[*a*]- and indolo[2,3-*a*]quinolizidines. (3,4-Dimethoxyphenyl)alaninol and tryptophanol not only constitute the source of chirality, acting as chiral inductors in highly stereoselective cyclocondensation reactions involving dynamic kinetic resolution and/or differentiation of enantiotopic or diastereotopic ester chains, but are also used to assemble the final polycyclic targets via an intramolecular α-amidoalkylation reaction in which the temporary hydroxymethyl appendage acts as an efficient element of stereocontrol.

Experimental Section

General Procedure for Cyclocondensation Reactions. (*S*)-3-(3,4-Dimethoxyphenyl)alaninol **1** or (*S*)-tryptophanol **2** (1.1 equiv) was added to a stirred solution of δ-oxo(di)ester **3b**−**e** (1 equiv) in anhydrous toluene. The mixture was heated at reflux under Dean−Stark conditions. Then, the solvent was removed under reduced pressure to yield a residue, which was chromatographed.

[(3*S*,8*R*,8a*S*) and (3*S*,8*S*,8a*R*)]-3-(3,4-Dimethoxybenzyl)-8-ethyl-5-oxo-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (4b) and (4b′). Following the general procedure, aminoalcohol (**1**; 1.47 g, 6.96 mmol) and methyl 4-formylhexanoate (**3b**; 1 g, 6.32 mmol) in toluene (25 mL) for 18 h afforded a mixture of lactams **4b** (1.55 g, 77%) and **4b′** (0.30 g, 15%), which were separated by flash chromatography (1:1 hexane−EtOAc to EtOAc). **4b**: IR (film) 1649 cm^{-1}; ^1H NMR (400 MHz) δ 0.98 (t, J = 7.8 Hz, 3H, CH_3), 1.20−1.47 (m, 3H, H-7, CH_2CH$_3$, H-8), 1.65−1.80 (m, 1H, CH_2-CH$_3$), 1.96−2.08 (m, 1H, H-7), 2.38−2.47 (m, 3H, CH_2Ar, H-6), 3.55 (dd, J = 13.2, 2.4 Hz, 1H, CH_2Ar), 3.67 (ddd, J = 9.0, 8.0, 1.2 Hz, 1H, H-2), 3.86 (s, 3H, CH_3O), 3.88 (s, 3H, CH_3O), 4.01 (dd, J = 9.0, 0.6 Hz, 1H, H-2), 4.13−4.20 (m, 1H, H-3), 4.34 (d, J = 9.0 Hz, 1H, H-8a), 6.75.4−6.82 (m, 3H, ArH); ^{13}C NMR (100.6 MHz) δ 10.8 (CH_3), 23.4 (C-7), 23.9 (CH_2CH$_3$), 31.3 (C-6), 36.4 (CH_2Ar), 40.9 (C-8), 55.7 and 55.8 (CH_3O), 57.0 (C-3), 69.0 (C-2), 92.5 (C-8a), 111.1 (CH), 112.5 (CH), 121.4 (CH), 130.6, 147.5 and 148.8 (C), 167.6 (NCO); MS-EI m/z 319 (M^+, 15), 178 (15), 168 (100), 151 (20), 126 (26); HMRS $C_{18}H_{25}NO_4$, 319.1784; found, 319.1783. **4b′**: IR (film) 1650 cm^{-1}; ^1H NMR (400 MHz) δ 0.96 (t, J = 7.6 Hz, 3H, CH_3), 1.23−1.42 (m, 3H, H-7, CH_2CH$_3$, H-8), 1.65−1.74 (m, 1H, CH_2CH$_3$), 1.88−1.92 (m, 1H, H-7), 2.30−2.39 (m, 1H, H-6), 2.55 (dd, J = 18.2, 5.0 Hz, 1H, H-6), 2.73 (dd, J = 18.2, 9.6 Hz, 1H, CH_2Ar), 3.20 (dd, J = 13.6, 3.6 Hz, 1H, CH_2-Ar), 3.62 (dd, J = 9.2, 7.6 Hz, 1H, H-2), 3.86 (s, 6H, CH_3O), 4.01 (dd, J = 8.8, 7.6 Hz, 1H, H-2), 4.20 (d, J = 7.6 Hz, 1H, H-8a), 4.45 (ddd, J = 16.4, 7.6, 3.6 Hz, 1H, H-3), 6.71−6.80 (m, 3H, ArH); ^{13}C NMR (100.6 MHz) δ 10.9 (CH_3), 22.8 (C-7), 24.4 (CH_2-CH$_3$), 31.5 (C-6), 37.1 (CH_2Ar), 40.9 (C-8), 55.3 (C-3), 55.7 and

55.8 (CH_3O), 69.1 (C-2), 91.3 (C-8a), 111.1 (CH), 112.5 (CH), 121.4 (CH), 129.3, 147.7 and 148.9 (C), 168.6 (NCO); $[\alpha]_D^{22}$ +33.5 (*c* 1.0, $CHCl_3$); MS-EI *m*/*z* 319 (M^+, 12), 178 (13), 168 (100), 151 (23), 126 (25); HMRS $C_{18}H_{25}NO_4$, 319.1784; found, 319.1783.

[(3*S*,7*R*,8a*S*) and (3*S*,7*S*,8a*R*)]-3-(3,4-Dimethoxybenzyl)-7-(methoxycarbonylmethyl)-5-oxo-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (4c) and (4c′). Following the general procedure, (*S*)-3-(3,4-dimethoxyphenyl)alaninol (**1**; 1.94 g, 9.2 mmol) and dimethyl 3-(2-oxoethyl)glutarate (**3c**; 1.86 g, 9.2 mmol) in toluene (4 mL) for 24 h afforded a mixture of lactams **4c** (2.23 g, 67%) and **4c′** (0.43 g, 13%), which were separated by flash chromatography (19:1 Et_2O−EtOH). **4c**: IR (film) 1644, 1734 cm^{-1}; ^1H NMR (400 MHz) δ 1.27 (m, 1H, H-8), 2.09 (dd, *J* = 17.6, 10.4 Hz, 1H, H-6), 2.34−2.41 (m, 3H, H-7, CH_2CO), 2.47 (dd, *J* = 13.2, 10.0 Hz, 1H, CH_2Ar), 2.60 (dd, *J* = 17.6, 4.8 Hz, 1H, H-6), 3.54 (dd, *J* = 13.2, 2.6 Hz, 1H, CH_2Ar), 3.70 (s, 3H, $COOCH_3$), 3.73 (ddd, *J* = 9.6, 6.4, 1.2 Hz, 1H, H-2), 3.86 (s, 3H, CH_3O), 3.87 (s, 3H, CH_3O), 4.03 (d, *J* = 9.2 Hz, 1H, H-2), 4.14−4.19 (m, 1H, H-3), 4.72 (dd, *J* = 16.4, 3.2 Hz, 1H, H-8a), 6.74−6.81 (m, 3H, ArH); ^{13}C NMR (100.6 MHz) δ 21.7 (C-7), 34.4 (C-8), 36.4 (CH_2Ar), 37.6 (C.6), 40.0 (CH_2CO), 51.7 ($COOCH_3$), 55.8 and 55.9 (CH_3O), 56.7 (C-3), 69.4 (C-2), 88.3 (C-8a), 111.1 (CH), 112.5 (CH), 121.5 (CH), 130.5 (C), 147.7 and 148.9 (C), 166.5 (NCO), 171.7 (COO); mp 108−109 °C (Et_2O); $[\alpha]_D^{22}$ +4.7 (*c* 0.81, $CHCl_3$). Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.80; H, 6.93; N, 3.85. Found: C, 62.70; H, 6.85; N, 3.88. **4c′**: IR (film) 1644, 1735 cm^{-1}; ^1H NMR (400 MHz) δ 1.25 (td, *J* = 12.4, 10.0 Hz, 1H, H-8), 2.03 (dd, *J* = 18.0, 11.2 Hz, 1H, H-6), 2.24−2.38 (m, 4H, H-7, H-8 and CH_2CO), 2.67 (dd, *J* = 18.0, 4.8, 1.6 Hz, 1H, H-6), 2.74 (dd, *J* = 13.6, 9.0 Hz, 1H, CH_2Ar), 3.19 (dd, *J* = 13.6, 3.6 Hz, 1H, CH_2Ar), 3.65 (dd, *J* = 8.8, 7.6 Hz, 1H, H-2), 3.70 (s, 3H, CH_3-OCO), 3.86 (s, 3H, CH_3O), 3.87 (s, 3H, CH_3O), 4.04 (d, *J* = 8.8, 7.6 Hz, 1H, H-2), 4.45 (m, 1H, H-3), 4.57 (dd, *J* = 9.2, 4.4 Hz, 1H, H-8a), 6.70−6.80 (m, 3H, ArH); ^{13}C NMR (100.6 MHz) δ 26.6 (C-7), 34.1 (C-8), 37.2 (CH_2Ar), 37.6 (C-6), 39.6 (CH_2CO), 51.8 (CH_3O_2C), 55.0 (C-3), 55.8 (CH_3O), 69.5 (C-2), 86.7 (C-8a), 111.1 (CH), 112.5 (CH), 121.4 (CH), 129.1, 147.8 and 148.9 (C), 167.4 (NCO), 171.7 (COO); mp 88−90 °C (Et_2O−EtOAc); $[\alpha]_D^{22}$ +41.9 (*c* 0.41, $CHCl_3$). Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.80; H, 6.93; N, 3.85. Found: C, 62.55; H, 6.85; N, 3.76.

[(3*S*,7*R*,8*R*,8a*S*) and (3*S*,7*S*,8*S*,8a*R*)]-3-(3,4-Dimethoxybenzyl)-8-ethyl-7-(methoxycarbonylmethyl)-5-oxo-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (4d) and (4d′). Following the general procedure, (*S*)-3-(3,4-dimethoxyphenyl)alaninol (**1**; 353 mg, 1.67 mmol) and dimethyl 3-(1-formylpropyl)glutarate (**3d**; 350 mg, 1.52 mmol) in toluene (5 mL) for 24 h afforded a mixture of lactams **4d** (353 mg, 59%) and **4d′** (100.6 mg, 17%), which were separated by flash chromatography (1:1 hexane−EtOAc to EtOAc). **4d**: IR (film) 1651, 1735 cm^{-1}; ^1H NMR (400 MHz) δ 0.97 (t, *J* = 7.2 Hz, 3H, CH_3), 1.41−1.47 (m, 1H, H-8), 1.56−1.71 (m, 2H, C*H*$_2$-CH_3), 2.21−2.28 (m, 3H, H-6, H-7, CH_2CO), 2.44 (dd, *J* = 13.2, 10.8 Hz, 1H, CH_2Ar), 2.50−2.59 (m, 2H, H-6, CH_2CO), 3.49 (dd, *J* = 13.2, 2.4 Hz, 1H, CH_2Ar), 3.70 (s, 3H, $COOCH_3$), 3.70−3.74 (m, 1H, H-2), 3.86 (s, 3H, CH_3O), 3.88 (s, 3H, CH_3O), 4.01 (d, *J* = 9.2 Hz, 1H, H-2), 4.15−4.20 (m, 1H, H-3), 4.53 (d, *J* = 8.8 Hz, 1H, H-8a), 6.76−6.85 (m, 3H, ArH); ^{13}C NMR (100.6 MHz) δ 9.9 (CH_3), 22.0 (*C*H_2CH_3), 31.1 (C-7), 36.9 (CH_2Ar), 37.4 and 38.4 (C-6 and CH_2CO), 44.8 (C-8), 51.8 ($COOCH_3$), 55.8 and 55.9 (CH_3O), 56.8 (C-3), 69.5 (C-2), 90.8 (C-8a), 111.2 (CH), 112.5 (CH), 121.5 (CH), 130.5, 147.7 and 149.0 (C), 166.7 (NCO), 172.2 (COO); $[\alpha]_D^{22}$ −13.2 (*c* 0.54, $CHCl_3$); MS-EI *m*/*z* 391 (M^+, 11), 360 (2), 240 (49), 178 (22), 166 (100), 151 (30); HMRS $C_{21}H_{29}NO_6$, 391.1995; found, 391.1998. **4d′**: IR (film) 1652, 1735 cm^{-1}; ^1H NMR (400 MHz) δ 0.93 (t, *J* = 7.6 Hz, 3H, CH_3), 1.40−1.46 (m, 1H, H-8), 1.49−1.56 (m, 1H, C*H*$_2CH_3$), 1.64−1.74 (m, 1H, C*H*$_2CH_3$), 2.10−2.18 (m, 2H, H-7, H-6), 2.30−2.61 (m, 3H, CH_2-CO, H-6), 2.71 (dd, *J* = 13.6, 9.2 Hz, 1H, CH_2Ar), 3.20 (dd, *J* = 13.6, 3.6 Hz, 1H, CH_2Ar), 3.63 (dd, *J* = 8.4, 7.6 Hz, 1H, H-2), 3.70 (s, 3H, $COOCH_3$), 3.86 (s, 3H, CH_3O), 3.87 (s, 3H, CH_3O), 4.01 (dd, *J* = 8.4, 8.0 Hz, 1H, H-2), 4.37 (d, *J* = 8.4 Hz, 1H, H-8a), 4.42−4.49 (m, 1H, H-3), 6.67−6.85 (m, 3H, ArH); ^{13}C NMR (100.6 MHz) δ 9.6 (CH_3), 20.7 (*C*H_2CH_3), 29.9 (C-7), 36.8 and 37.6 (C-6, CH_2CO), 37.3 (CH_2Ar), 43.4 (C-8), 51.8 ($COOCH_3$), 55.3 (C-3), 55.8 and 55.9 (CH_3O), 69.3 (C-2), 89.5 (C-8a), 111.2 (CH), 112.5 (CH), 121.4 (CH), 129.2 (C), 147.8 and 149.0 (C), 167.4 (C-5), 172.2 (COO); $[\alpha]_D^{22}$ +11.8 (*c* 0.52, $CHCl_3$); MS-EI *m*/*z* 391 (M^+, 5), 240 (46), 208 (7), 178 (45), 166 (100), 151 (41); HMRS $C_{21}H_{29}NO_6$, 391.1995; found, 391.1995.

[(3*S*,8*R*,8a*S*) and (3*S*,8*S*,8a*R*)]-8-Ethyl-3-(3-indolylmethyl)-5-oxo-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (8b) and (8b′). Following the general procedure, (*S*)-tryptophanol (**2**; 530 mg, 2.78 mmol) and methyl 4-formylhexanoate (**3b**; 440 mg, 2.78 mmol) in toluene (6 mL) for 23 h afforded a mixture of lactams **8b** (629 mg, 76%) and **8b′** (99 mg, 11%), which were separated by flash chromatography (1:4 hexane−EtOAc to 1:9 hexane−EtOAc). **8b**: IR (film) 1628 cm^{-1}; ^1H NMR (300 MHz) δ 1.00 (t, *J* = 7.2 Hz, 3H, CH_3), 1.28 (m, 1H, C*H*$_2CH_3$), 1.38 (m, 1H, H-8), 1.79 (m, 1H, C*H*$_2CH_3$), 2.02 (m, 1H, H-7), 2.47 (m, 2H, H-6), 2.62 (dd, *J* = 14.1, 10.5 Hz, 1H, CH_2 ind), 3.66 (ddd, *J* = 7.5, 6.0, 1.5 Hz, 1H, H-2), 3.76 (dt, *J* = 14.1, 1.5 Hz, 1H, CH_2 ind), 4.02 (d, *J* = 11.7 Hz, 1H, H-2), 4.30 (ddd, *J* = 9.6, 6.0, 3.0 Hz, 1H, H-3), 4.36 (d, *J* = 8.7 Hz, 1H, H-8a), 7.05 (s, 1H, ArH), 7.14 (ddd, *J* = 7.2, 7.2, 1.2 Hz, 1H, ArH), 7.20 (ddd, *J* = 7.2, 7.2, 1.2 Hz, ArH), 7.35 (d, *J* = 7.2 Hz, 1H, ArH), 7.85 (d, *J* = 7.2 Hz, 1H, ArH), 8.11 (br s, 1H, NH); ^{13}C NMR (75.4 MHz) δ 10.9 (CH_3), 23.5 (C-7), 24.0 (*C*H_2CH_3), 26.9 (CH_2 ind), 31.4 (C-6), 41.0 (C-8), 56.3 (C-3), 69.8 (C-2), 92.6 (C-8a), 111.0 (CH), 112.3 (C), 119.2 (CH), 119.3 (CH), 121.9 (CH), 122.3 (CH), 127.5 and 136.1 (C), 167.9 (C-5); mp 170−172 °C (Et_2O−hexane); $[\alpha]_D^{22}$ −82.3 (*c* 1.2, $CHCl_3$). Anal. Calcd for $C_{18}H_{22}N_2O_2 \cdot {}^1/_4H_2O$: C, 71.38; H, 7.49; N, 9.25. Found: C, 71.51; H, 7.69; N, 8.88. **8b′**: IR (film) 1632 cm^{-1}; ^1H NMR (300 MHz) δ 0.91 (t, *J* = 7.2 Hz, 3H, CH_3), 1.27 (m, 3H, H-7, H-8 and C*H*$_2CH_3$), 1.64 (m, 1H, C*H*$_2CH_3$), 1.83 (m, 1H, H-7), 2.34 (ddd, *J* = 18.0, 12.0, 6.6 Hz, 1H, H-6), 2.56 (dd, *J* = 18.0, 5.1 Hz, 1H, H-6), 3.00 (dd, *J* = 14.4, 9.0 Hz, 1H, CH_2 ind), 3.33 (dd, *J* = 14.4, 3.0 Hz, 1H, CH_2 ind), 3.65 (dd, *J* = 9.0, 7.5 Hz, 1H, H-2), 4.02 (dd, *J* = 7.5, 1.2 Hz, 1H, H-2), 4.13 (d, *J* = 8.1 Hz, 1H, H-8a), 4.60 (m, 1H, H-3), 6.96 (d, *J* = 2.1 Hz, 1H, H-2 ind), 7.09 (ddd, *J* = 7.5, 7.5, 1.2 Hz, 1H, H-5 ind), 7.16 (ddd, *J* = 7.5, 7.5, 1.2 Hz, 1H, H-6 ind), 7.33 (d, *J* = 7.5 Hz, 1H, H-7 ind), 7.69 (d, *J* = 7,5 Hz, 1H, H-4 ind), 8.74 (b s, 1H, NH); ^{13}C NMR (75.4 MHz) δ 10.9 (CH_3), 22.6 (C-7), 24.4 (*C*H_2CH_3), 27.4 (CH_2 ind), 31.5 (C-6), 40.8 (C-8), 54.6 (C-3), 69.6 (C-2), 91.1 (C-8a), 110.7 (C-3 ind), 111.1 (C-7 ind), 118.9 (C-4 ind), 119.2 (C-5 ind), 121.8 (C-6 ind), 122.6 (C-2 ind), 127.5 (C3a ind), 136.1 (C7a ind), 168.7 (NCO); mp 120−122 °C (Et_2O−hexane); $[\alpha]_D^{22}$ +17.0 (*c* 0.2, $CHCl_3$). Anal. Calcd for $C_{18}H_{22}N_2O_2 \cdot {}^3/_4H_2O$: C, 69.32; H, 7.59; N, 8.98. Found: C, 69.14; H, 7.47; N, 8.76.

[(3*S*,8*S*,8a*S*) and (3*S*,8*R*,8a*R*)]-3-(3-Indolylmethyl)-8-[2-(methoxycarbonyl)ethyl]-5-oxo-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo-[3,2-*a*]pyridine (8e) and (8e′). Following the general procedure, (*S*)-tryptophanol (**2**; 111 mg, 0.59 mmol) and dimethyl 4-formylpimelate (**3e**; 125 mg, 0.58 mmol) in toluene (5 mL) for 24 h afforded a mixture of lactams **8e** (145 mg, 70%) and **8e′** (10 mg, 5%), which were separated by flash chromatography (1:9 hexane−EtOAc to 9:1 EtOAc−EtOH). **8e**: IR (film) 1627, 1734 cm^{-1}; ^1H NMR (300 MHz) δ 1.43 (m, 1H, H-1′), 1.62 (m, 2H, H-7 and H-8), 1.94 (m, 2H, H-7 and H-1′), 2.45 (m, 4H, H-6 and H-2′), 2.62 (dd, *J* = 13.8, 10.2 Hz, 1H, CH_2 ind), 3.65 (m, 2H, H-2 and CH_2 ind), 3.68 (s, 3H, CH_3O), 4.00 (dd, *J* = 9.0, 3.6 Hz, 1H, H-2), 4.27 (m, 1H, H-3), 4.37 (d, *J* = 8.1 Hz, 1H, H-8a), 7.01 (s, 1H, H-2 ind), 7.12 (td, *J* = 7.5, 1.2 Hz, 1H, H-5 ind), 7.18 (td, *J* = 7.5, 1.2 Hz, 1H, H-6 ind), 7.34 (d, *J* = 7.5 Hz, 1H, H-7 ind), 7.81 (d, *J* = 7.5 Hz, 1H, H-4 ind), 8.41 (br s, 1H, NH); ^{13}C NMR (75.4 MHz) δ 24.2 (C-1′), 26.8 (C-7), 26.8 (CH_2 ind), 31.1 and 31.3 (C-6 and C-2′),

38.8 (C-8), 51.6 (CH_3O), 56.1 (C-3), 69.8 (C-2), 92.6 (C-8a), 111.0 (C-7 ind), 111.9 (C-3 ind), 119.0 (C-4 ind), 119.2 (C-5 ind), 121.8 (C-6 ind), 122.4 (C-2 ind), 127.4 (C-3a ind), 136.1 (C-7a ind), 167.7 (NCO), 173.6 (COO); mp 132−134 °C (Et_2O−hexane); $[\alpha]_D^{22}$ −50.0 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{20}H_{24}N_2O_4$: C, 67.40; H, 6.79; N, 7.86. Found: C, 67.33; H, 6.89; N, 7.92. **8e′**: IR (film) 1627, 1734 cm^{-1}; ^1H NMR (300 MHz) δ 1.33 (m, 1H, H-1′), 1.47 (m, 1H, H-8), 1.60 (m, 1H, H-7), 1.85 (m, 2H, H-7 and H-1′), 2.29−2.67 (m, 4H, H-6 and H-2′), 3.02 (dd, J = 14.0, 8.4 Hz, 1H, CH_2 ind), 3.30 (dd, J = 14.0, 3.3 Hz, 1H, CH_2 ind), 3.65 (s, 3H, CH_3O), 3.66 (m, 1H, H-2), 4.03 (dd, J = 9.0, 7.8 Hz, 1H, H-2), 4.11 (d, J = 8.1 Hz, 1H, H-8a), 4.58 (m, 1H, H-3), 6.99 (d, J = 2.1 Hz, 1H, H-2 ind), 7.10 (td, J = 7.5, 1.2 Hz, 1H, H-5 ind), 7.15 (td, J = 7.5, 1.2 Hz, 1H, H-6 ind), 7.34 (d, J = 7.5 Hz, 1H, H-7 ind), 7.68 (d, J = 7.5 Hz, 1H, H-4 ind), 8.38 (br s, 1H, NH); ^{13}C NMR (75.4 MHz) δ 23.7 (C-1′), 27.0 (C-7), 27.4 (CH_2 ind), 31.4 (C-6 and C-2′), 38.9 (C-8), 51.6 (CH_3O), 54.5 (C-3), 69.6 (C-2), 91.4 (C-8a), 110.9 (C-3 ind), 111.0 (C-7 ind), 119.0 (C-4 ind), 119.4 (C-5 ind), 122.0 (C-6 ind), 122.5 (C-2 ind), 127.6 (C-3a ind), 136.1 (C-7a ind), 168.3 (C-5), 173.6 (NCO).

[(3*S*,7*R*,8*R*,8a*S*) and (3*S*,7*S*,8*S*,8a*R*)]-8-Ethyl-3-(3-indolylmethyl)-7-(methoxycarbonylmethyl)-5-oxo-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (8d) and (8d′). Following the general procedure, (*S*)-tryptophanol (**2**; 350 mg, 1.84 mmol) and dimethyl 3-(1-formylpropyl)glutarate (**3d**; 385 mg, 1.67 mmol) in toluene (5 mL) for 9 h afforded lactams **8d** (383 mg, 62%) and **8d′** (80 mg, 13%), which were separated by flash chromatography (1:5 hexane−EtOAc to EtOAc). **8d**: IR (film) 1634, 1732 cm^{-1}; ^1H NMR (400 MHz) δ 0.97 (t, J = 7.6 Hz, 3H, CH_3), 1.48 (m, 1H, H-8), 1.56−1.72 (m, 2H, C*H*$_2$CH$_3$), 2.24−2.31 (m, 3H, H-7, H-6 and CH_2CO), 2.52−2.60 (m, 2H, H-6 and CH_2CO), 2.67 (dd, J = 13.6, 10.4 Hz, 1H, CH_2 ind), 3.66 (m, 2H, H-2 and CH_2 ind), 3.70 (s, 3H, CH_3O), 4.03 (d, J = 9.2 Hz, 1H, H-2), 4.30 (m, 1H, H-3), 4.52 (d, J = 8.4 Hz, 1H, H-8a), 7.03 (d, J = 2.0 Hz, 1H, H-2 ind), 7.13 (td, J = 7.6, 0.8 Hz, 1H, H-5 ind), 7.19 (td, J = 7.6, 0.8 Hz, 1H, H-6 ind), 7.35 (d, J = 7.6 Hz, 1H, H-7 ind), 7.81 (d, J = 7.6 Hz, 1H, H-4 ind), 8.25 (b s, 1H, NH); ^{13}C NMR (100.6 MHz) δ 9.9 (CH_3), 22.0 (*C*H$_2$CH$_3$), 27.2 (CH_2 ind), 31.2 (C-7), 37.3 and 38.5 (C-6 and CH_2CO), 44.8 (C-8), 51.7 (CH_3O), 55.9 (C-3), 70.2 (C-2), 90.8 (C-8a), 111.0 (C-7 ind), 112.4 (C-3 ind), 119.3 (C-4 ind), 119.5 (C-5 ind), 122.1 (C-6 ind), 122.3 (C-2 ind), 127.6 (C-3a ind), 136.2 (C-7a ind), 166.8 (NCO), 172.2 (COO); $[\alpha]_D^{22}$ −43.7 (*c* 0.65, $CHCl_3$); HMRS $C_{21}H_{26}N_2O_4$, 370.1893; found, 370.1892. **8d′**: IR (film) 1634, 1737 cm^{-1}; ^1H NMR (400 MHz) δ 0.86 (t, J = 7.6 Hz, 3H, CH_3), 1.40 (m, 1H, H-8), 1.48 (m, 1H, C*H*$_2$CH$_3$), 1.63 (m, 1H, C*H*$_2$CH$_3$), 2.13 (m, 3H, H-7, H-6 and CH_2CO), 2.55 and 2.70 (2m, 1H, H-6 or CH_2CO), 3.01 (dd, J = 14.4, 8.8 Hz, 1H, CH_2 ind), 3.33 (ddd, J = 14.4, 3.2, 0.4 Hz, 1H, CH_2 ind), 3.37 (dd, J = 9.2, 7.2 Hz, 1H, H-2), 3.70 (s, 3H, CH_3O), 4.03 (dd, J = 9.2, 7.6 Hz, 1H, H-2), 4.31 (d, J = 8.0 Hz, 1H, H-8a), 4.62 (m, 1H, H-3), 7.02 (d, J = 2.0 Hz, 1H, H-2 ind), 7.13 (td, J = 7.2, 1.2 Hz, 1H, H-5 ind), 7.18 (td, J = 7.2, 1.2 Hz, 1H, H-6 ind), 7.36 (d, J = 7.2 Hz, 1H, H-4 ind), 7.70 (d, J = 7.2 Hz, 1H, H-7 ind), 8.21 (br s, 1H, NH); ^{13}C NMR (100.6 MHz) δ 9.5 (CH_3), 20.6 (*C*H$_2$CH$_3$), 27.5 (CH_2 ind), 29.8 (C-7), 36.8 and 37.6 (C-6 and CH_2CO), 43.3 (C-8), 51.8 (CH_3O), 54.6 (C-3), 69.7 (C-2), 89.3 (C-8a), 111.1 (C-3 ind), 111.2 (C-7 ind), 119.1 (C-4 ind), 119.6 (C-5 ind), 122.2 (C-6 ind), 122.5 (C-2 ind), 127.7 (C-3a ind), 136.2 (C-7a ind), 167.5 (NCO), 172.2 (COO); $[\alpha]_D^{22}$ −31.0 (*c* 2.27, $CHCl_3$); HMRS $C_{21}H_{26}N_2O_4$, 370.1893; found, 370.1892.

(1*R*,6*S*,11b*R*)-1-Ethyl-6-(hydroxymethyl)-9,10-dimethoxy-4-oxo-1,2,3,6,7,11b-hexahydrobenzo[*a*]quinolizine (5b). $BF_3{\cdot}OEt_2$ (0.16 mL, 1.25 mmol) was added dropwise via syringe to a solution of lactam **4b** (99 mg, 0.31 mmol) in CH_2Cl_2 (3 mL), and the resulting mixture was heated at reflux for 18 h. The solvent was removed under reduced pressure, and the residue was dissolved in EtOAc. The organic solution was washed with saturated aqueous NaCl solution, the aqueous layer was extracted with EtOAc, and the combined organic extracts were dried and concentrated. The resulting residue was chromatographed (Et_2O−MeOH) to afford **5b** (69.5 mg, 70%): IR (film) 3100−3600, 1596 cm^{-1}; ^1H NMR (400 MHz) δ 1.05 (t, J = 7.2 Hz, 3H, CH_3), 1.50−1.61 (m, 1H, C*H*$_2$CH$_3$), 1.61−1.70 (m, 1H, C*H*$_2$CH$_3$), 1.72−1.80 (m, 1H, H-2), 2.01−2.09 (m, 1H, H-2), 2.20−2.27 (m, 1H, H-1), 2.33 (ddd, J = 17.6, 5.6, 4.4 Hz, 1H, H-3), 2.52 (ddd, J = 17.6, 10.8, 6.4 Hz, 1H, H-3), 2.61 (dd, J = 15.2, 9.6 Hz, 1H, H-7), 2.96 (dd, J = 15.2, 6.8 Hz, 1H, H-7), 3.61 (br s, 1H, OH), 3.66 (dd, J = 11.2, 7.6 Hz, CH_2OH), 3.73 (dd, J = 11.2, 3.6 Hz, CH_2OH), 4.16 (dd, J = 4.8 Hz, 1H, H-11b), 4.53−4.60 (m, 1H, H-6), 6.71 (s, 1H, ArH), 6.75.4 (s, 1H, ArH); ^{13}C NMR (100.6 MHz) δ 11.6 (CH_3), 21.4 (C-2), 25.0 (*C*H$_2$CH$_3$), 29.2 (C-3), 29.9 (C-7), 35.6 (C-1), 53.2 (C-6), 56.0 and 56.3 (CH_3O), 57.1 (C-11b), 66.1 (CH_2OH), 107.8 and 111.6 (C-8 and C-11), 128.0 and 129.4 (C-7a and C-11a), 147.4 and 148.4 (C-9 and C-10), 172.5 (C-4); mp 125−127 °C (Et_2O−EtOAc); $[\alpha]_D^{22}$ −36.7 (*c* 0.54, $CHCl_3$). Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.45; H, 7.80; N, 4.36.

(2*R*,6*S*,11b*R*)-6-(Hydroxymethyl)-9,10-dimethoxy-2-(methoxycarbonylmethyl)-4-oxo-1,2,3,6,7,11b-hexahydrobenzo[*a*]quinolizine (5c). $TiCl_4$ (3.3 mL, 30.3 mmol) was added dropwise to a cooled (−78 °C) solution of lactam **4c** (1.83 g, 5.04 mmol) in CH_2Cl_2 (100 mL), and the mixture was warmed at rt and stirred for 3.5 days. Saturated aqueous NH_4Cl solution was added, and the mixture was extracted with CH_2Cl_2. The dried combined organic extracts were concentrated, and the resulting residue was chromatographed (24:1 EtOAc−MeOH) to afford **5c** (0.64 g, 35%): IR (film) 1615, 1732, 3000−3500 cm^{-1}; ^1H NMR (400 MHz) δ 1.45 (ddd, J = 12.8, 12.4, 12.0 Hz, 1H, H-1), 2.16 (dd, J = 17.2, 11.2 Hz, 1H, H-3), 2.37−2.39 (m, 2H, CH_2CO), 2.55−2.58 (m, 2H, H-1 and H-2), 2.63 (d, J = 16.4 Hz, 1H, H-7), 2.73 (d, J = 17.2 Hz, 1H, H-3), 3.01 (dd, J = 16.4, 5.2 Hz, 1H, H-7), 3.53−3.64 (m, 2H, CH_2OH), 3.71 (s, 3H, $COOCH_3$), 3.86 (s, 3H, CH_3O), 3.87 (s, 3H, CH_3O), 4.65 (d, J = 10.0 Hz, 1H, H-11b), 5.28−5.29 (m, 1H, H-6), 6.58 (s, 1H, ArH), 6.64 (s, 1H, ArH); ^{13}C NMR (100.6 MHz) δ 28.5 (C-2), 29.0 (C-7), 37.5 (C-1), 38.2 (C-3), 40.2 (CH_2CO), 48.4 (C-6), 51.7 (CH_3O_2C), 52.9 (C-11b), 55.8 and 56.2 (CH_3O), 62.1 (CH_2OH), 108.3 and 111.8 (C-8 and C-11), 124.1 and 127.0 (C-7a and C-11a), 147.8 and 148.1 (C-9 and C-10), 172.0 (COO); mp 148−151 °C (EtOAc−$CHCl_3$); $[\alpha]_D^{22}$ +113.2 (*c* 0.34, $CHCl_3$); HMRS $C_{19}H_{25}NO_6$, 363.1682; found, 363.1678.

(1*R*,2*R*,6*S*,11b*R*)-1-Ethyl-6-(hydroxymethyl)-9,10-dimethoxy-2-(methoxycarbonylmethyl)-4-oxo-1,2,3,6,7,11b-hexahydrobenzo[*a*]quinolizine (5d). Operating as in the above preparation of **5b**, a solution of lactam **4d** (163 mg, 0.42 mmol) and $BF_3{\cdot}OEt_2$ (0.21 mL, 1.67 mmol) in CH_2Cl_2 (5 mL) was refluxed for 21 h. Flash chromatography (9:1 EtOAc−MeOH) afforded **5d** (66 mg, 40%): IR (film) 1637, 1733, 3000−3500 cm^{-1}; ^1H NMR (500 MHz) δ 0.92 (t, J = 7.5 Hz, 3H, CH_3), 1.40−1.47 (m, 1H, C*H*$_2$CH$_3$), 1.49−1.54 (m, 1H, H-1), 1.59−1.66 (m, 1H, C*H*$_2$CH$_3$), 2.28−2.29 (m, 2H, CH_2CO or H-3), 2.35 (dd, J = 15.5, 3.0 Hz, 1H, CH_2CO or H-3), 2.44−2.49 (m, 1H, H-2), 2.67 (dd, J = 15.5, 6.0 Hz, 1H, H-3), 2.70 (dd, J = 15.5, 5.0 Hz, 1H, H-7), 2.76 (sa, 1H, OH), 2.95 (dd, J = 15.5, 5.5 Hz, 1H, H-7), 3.30−3.35 (m, 1H, CH_2OH), 3.45−3.48 (m, 1H, CH_2OH), 3.63 (s, 3H, $COOCH_3$), 3.84 (s, 3H, CH_3O), 3.86 (s, 3H, CH_3O), 4.22 (d, J = 9,0 Hz, 1H, H-11b), 4.76−4.80 (m, 1H, H-6), 6.61 (s, 1H, ArH), 6.65 (s, 1H, ArH); ^{13}C NMR (100.6 MHz) δ 10.7 (CH_3), 24.7 (*C*H$_2$CH$_3$), 29.6 (C-7), 32.1 (C-2), 36.1 and 40.0 (C-3 and CH_2CO), 46.0 (C-1), 51.6 ($COOCH_3$), 51.7 (C-6), 55.9 and 56.2 (CH_3O), 57.5 (C-11b), 64.7 (CH_2OH), 111.0 and 112.0 (C-8 and C-11), 125.9 and 126.1 (C-7a and C-11a), 147.2 and 148.5 (C-9 and C-10), 172.2 (C-4), 173.0 (COO); mp 116−118 °C (Et_2O−acetone); $[\alpha]_D^{22}$ +53.3 (*c* 0.84, $CHCl_3$). Anal. Calcd for $C_{21}H_{29}NO_6$: C, 64.43; H, 7.47; N, 3.58. Found: C, 64.07; H, 7.86; N, 3.65.

(1*R*,6*S*,12b*R*)-1-Ethyl-6-(hydroxymethyl)-4-oxo-1,2,3,4,6,7,12,-12b-octahydroindolo[2,3-*a*]quinolizine (9b). HCl (1.2 M) in EtOH (4.1 mL) was added to a solution of lactam **8b** (306 mg, 1.03 mmol)

in EtOH (4.5 mL). The mixture was stirred at rt for 48 h. The solvent was removed, and the resulting solid was diluted with EtOAc and washed with saturated aqueous Na_2CO_3. After extraction with EtOAc, the combined organic extracts were washed with H_2O, dried, and concentrated to give a residue, which was chromatographed (1:1 EtOAc−hexane to EtOAc) to afford **9b** (245 mg, 80%) and its 12*b*-epimer **9b′** (40 mg, 13%). **9b**: IR (film) 1614, 3000−3500 cm^{-1}; ^1H NMR (400 MHz) δ 1.11 (t, $J = 7.2$ Hz, 3H, CH_3), 1.62−1.70 (m, 2H, CH_2CH$_3$, H-2), 1.85−1.92 (m, 2H, CH_2CH$_3$, H-2), 2.01−2.06 (m, 1H, H-1), 2.35 (ddd, $J = 17.6$, 6.5, 6.5 Hz, 1H, H-3), 2.52 (ddd, $J = 17.6$, 6.5, 6.5 Hz, 1H, H-3), 2.63 (d, $J = 16.0$ Hz, 1H, H-7), 3.04 (ddd, $J = 16.0$, 6.8, 2.4 Hz, 1H, H-7), 3.64−3.66 (m, 2H, CH_2OH), 4.54 (d, $J = 6.4$ Hz, 1H, H-12b), 5.45 (m, 1H, H-6), 7.10 (td, $J = 7.6$, 0.8 Hz, 1H, ArH), 7.18 (td, $J = 7.2$, 0.8 Hz, 1H, ArH), 7.35 (d, $J = 8.0$ Hz, 1H, ArH), 7.46 (d, $J = 8.0$ Hz, 1H, ArH), 8.13 (b s, 1H, NH); ^{13}C NMR (100.6 MHz) δ 11.5 (CH_3), 21.4 (C-7), 22.8 and 26.1 (*C*H_2CH$_3$ and C-2), 30.4 (C-3), 38.9 (C-1), 49.7 (C-6), 54.2 (C-12b), 61.8 (CH_2OH), 108.5 (C-7a), 111.0 (CH), 118.1 (CH), 119.8 (CH), 122.3 (CH), 127.1 (C-7b), 132.2 (C-12a), 136.0 (C-11a), 172.0 (C-4); mp 105 °C dec (hexane−EtOAc); $[\alpha]_D^{22}$ +67.3 (*c* 0.5, $CHCl_3$). Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.19; H, 7.39; N, 9.24. **9b′**: IR (film) 1616, 3000−3500 cm^{-1}; ^1H NMR (DMSO, 400 MHz) δ 0.85 (m, 4H, CH_2CH_3), 1.15 (m, 1H, CH_2CH$_3$), 1.41 (m, 1H, H-2), 2.12 (m, 1H, H-2), 2.25 (m, 1H, H-3), 2.41−2.62 (m, 3H, H-1, H-3, H-7), 2.90 (m, 1H, CH_2OH), 3.14−3.23 (m, 2H, H-7, CH_2OH), 4.62 (m, 1H, H-6), 4.84 (br s, 1H, OH), 4.87 (br s, 1H, H-12b), 6.97 (t, 1H, $J = 7.2$ Hz, H-9), 7.05 (t, 1H, $J = 7.2$ Hz, H-10), 7.34 (d, 1H, $J = 7.6$ Hz, H-11), 7.42 (d, 1H, $J = 7.2$ Hz, H-8), 10.92 (br s, 1H, NH); ^{13}C NMR (DMSO, 100.6 MHz) δ 11.6 (CH_3), 19.8 (C-7), 22.7 (C-2), 23.3 (*C*H_2CH$_3$), 30.6 (C-3), 36.8 (C-1), 49.5 (C-6), 54.3 (C-12b), 61.5 (CH_2OH), 106.2 (C-7a), 111.4 (C-11), 118.0 (C-8), 118.7 (C-9), 121.0 (C-10), 127.1 (C-7b), 131.5 (C-12a), 136.8 (C-11a), 171.7 (C-4); mp 250−252 °C (MeOH); $[\alpha]_D^{22}$ +81.7 (*c* 0.4, CH_3OH). Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.27; H, 7.47; N, 9.18.

(1*R*,6*S*,12b*S*)-1-Ethyl-6-(hydroxymethyl)-4-oxo-1,2,3,4,6,7,12,-12b-octahydroindolo[2,3-*a*]quinolizine (9b′). BF_3·OEt_2 (2.7 mL, 10.3 mmol) was added to a solution of lactam **8b** (1.02 g, 3.42 mmol) in CH_2Cl_2 (38 mL), and the resulting mixture was heated at reflux for 24 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in EtOAc. The organic solution was washed with saturated aqueous NaCl, the aqueous layer was extracted with EtOAc, and the combined organic extracts were dried and concentrated. The resulting residue was dissolved in CH_2Cl_2 and stirred for 18 h in the presence of KOH (710 mg). H_2O was added to the mixture, the organic phase was separated, and the aqueous phase was extrated with EtOAc. The combined organic extracts were dried and concentrated, and the resulting residue was digested with CH_2Cl_2 to yield a precipitate, which was filtered and recrystallized in EtOH to afford **9b′** (0.62 g, 61%). The previous filtrate was concentrated, and the resulting residue was chromatographed (hexane−EtOAc 1:4 to EtOAc−MeOH 9:1) to afford **9b** (0.13 mg, 13%). Ocasionally, minor amounts of 1-*epi*-**9b′** were isolated in the chromatography: IR (film) 1621, 3000−3500 cm^{-1}; ^1H NMR (DMSO, 400 MHz) δ 1.04 (t, 3H, $J = 7.2$ Hz, CH_3CH$_2$), 1.48−1.65 (m, 3H, CH$_3$CH_2, H-2), 1.75.4 (m, 1H, CH$_3$CH_2), 1.95 (m, 1H, H-3), 2.30−2.39 (m, 2H, H-1, H-3), 2.71 (1H, ddd, $J = 15.2$, 3.6, 1.2 Hz, H-7), 2.96 (ddd, 1H, $J = 15.2$, 11.2, 2.0 Hz, H-7), 3.45 (m, 1H, H-6), 3.84 (ddd, 1H, $J = 10.8$, 6.4, 4.0 Hz, CH_2OH), 4.00 (ddd, 1H, $J = 10.8$, 6.0, 6.0 Hz, CH_2OH), 4.69 (br s, 1H, H-12b), 4.98 (m, 1H, OH), 6.96 (td, 1H, $J = 7.2$, 0.8 Hz, H-9), 7.04 (td, 1H, $J = 7.2$, 1.2 Hz, H-10), 7.32 (d, 1H, $J = 8.0$ Hz, H-11), 7.37 (d, 1H, $J = 7.6$ Hz, H-8), 10.82 (s, 1H, NH); ^{13}C NMR (DMSO, 100.6 MHz) δ 12.0 (CH_3), 21.8 (C-2), 22.8 (C-7), 23.8 (CH_2CH_3), 29.5 (C-3), 35.8 (C-1), 62.0 (C-12b), 63.3 (C-6), 63.4 (CH_2OH), 109.5 (C-7a), 111.5 (C-11), 117.7 (C-8), 118.8 (C-9), 121.1 (C-10), 127.0 (C-7b), 135.8 (C-12a), 136.2 (C-11a), 172.1 (C-4); mp 203−204 °C; $[\alpha]_D^{22}$ −113.9 (*c* 0. 5, CH_3OH). Anal. Cald for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.34; H, 7.40; N, 9.29.

(1*R*,4*S*,6*S*,12b*S*)-4,6-(Epoxymethano)-1-ethyl-1,2,3,4,6,7,12,-12b-octahydroindolo[2,3-*a*]quinolizine (11). BF_3·OEt_2 (1.31 mL, 5 mmol) was added to a solution of lactam **8b** (494 mg, 1.66 mmol) in CH_2Cl_2 (19 mL), and the resulting mixture was heated at reflux for 24 h. The solvent was evaporated under reduced pressure, the residue (75.40 mg) was dissolved in MeOH (60 mL), $NaBH_4$ (141 mg, 3.71 mmol) was added to the solution, and the mixture was stirred for 40 min. The solvent was evaporated, and the resulting residue was dissolved in EtOAc. The organic phase was washed with H_2O, dried, and concentrated, and the resulting residue was chromatographed (EtOAc to EtOAc−MeOH 9:1) to afford **9b** (65 mg, 13%) and **11** (338 mg, 73%). **11**: IR (NaCl) 3313 cm^{-1}; ^1H NMR (300 MHz) δ 0.82 (t, $J = 7.5$ Hz, 3H, CH_3), 1.15 (m, 1H, CH_2CH$_3$), 1.52−1.68 (m, 3H, CH_2CH$_3$, H-2, H-1), 1.86−1.98 (m, 2H, H-1, H-3), 2.05 (m, 1H, H-2), 2.60 (ddd, $J = 15.3$, 10.8, 2.4 Hz, 1H, H-6), 2.92−3.02 (m, 2H, H-5a, H-6), 3.72−3.77 (m, 2H, H-5, H-3a), 3.88 (dd, $J = 9.0$, 3.0 Hz, 1H, H-11b), 4.20 (t, $J = 7.2$ Hz, 1H, H-5), 7.10 (td, $J = 7.2$, 1.2 Hz, ArH), 7.15 (td, $J = 7.2$, 1.2 Hz, 1H, ArH), 7.33 (dm, $J = 7.6$ Hz, 1H, ArH), 7.47 (dd, $J = 7.2$, 1.5 Hz, 1H, ArH), 7.84 (br s, 1H, NH); ^{13}C NMR (75.4.4 MHz) δ 12.3 (CH_3), 19.1 (CH_2CH$_3$), 24.3 (C-2), 25.0 (C-6), 26.1 (C-1), 37.9 (C-3), 57.5 (C-5a), 59.3 (C-11b), 71.2 (C-5), 92.6 (C-11b), 109.6 (C), 110.8 (CH), 117.9 (CH), 119.4 (CH), 121.4 (CH), 127.2 (C), 133.7 (C), 136.4 (C); MS-EI *m*/*z* 282 (M^+, 35), 265 (18), 253 (20), 240 (51), 184 (46), 169 (78).

(1*R*,6*S*,12b*S*)-1-Ethyl-6-(hydroxymethyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (12). $LiAlH_4$ (171 mg, 4.51 mmol) was added to a cooled (0 °C) solution of $AlCl_3$ (182 mg, 1.37 mmol) in THF (14 mL), and the mixture was stirred at room temperature for 30 min. The suspension was cooled (−78 °C), and a solution of oxazolidine **11** (189 mg, 0.67 mmol) in THF was added. The mixture was stirred at −78 °C for 90 min, warmed to room temperature, and stirred for additional 2 h. Cold H_2O was added, and the mixture was extrated with CH_2Cl_2. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed to furnish **12** (127 mg, 69%): ^1H NMR (DMSO, 300 MHz) δ 0.75.4 (t, 3H, $J = 10.0$ Hz, CH_3), 0.81−0.96 (m, 1H, CH_2CH$_3$), 1.38−1.52 (m, 3H, H-2, H-3, CH_2-CH$_3$), 1.59−1.80 (m, 2H, H-2, H-3), 2.06−2.13 (m, 2H, H-1, H-4), 2.30−2.38 (m, 1H, H-6), 2.43 (dd, 1H, $J = 14.7$, 2.1 Hz, H-7), 2.65 (dd, 1H, $J = 14.7$, 1.5 Hz, H-7), 3.20−3.42 (m, 2H, H-4, H-12b), 3.54 (dd, 1H, $J = 15.2$, 6.4 Hz, CH_2OH), 3.68 (dd, 1H, $J = 15.2$, 6.4 Hz, CH_2OH), 4.52 (br s, 1H, OH), 6.91 (td, 1H, $J = 6.9$, 1.2 Hz, H-9), 6.98 (td, 1H, $J = 6.9$, 1.2 Hz, H-10), 7.26 (d, 1H, $J = 10.4$ Hz, H-11), 7.31 (d, 1H, $J = 10.0$ Hz, H-8), 10.54 (s, 1H, NH); ^{13}C NMR (DMSO, 75.4.4 MHz) δ 12.3 (CH_3), 19.2 (CH_2-CH_3), 21.1 (C-2), 25.8 (C-7), 26.0 (C-3), 38.3 (C-1), 51.0 (C-4), 62.1 (C-6), 63.7 (CH_2OH), 64.7 (C-12b), 107.6 (C-7a), 111.0 (C-11), 117.3 (C-8), 118.2 (C-9), 120.2 (C-10), 126.8 (C-7b), 134.9 (C-12a), 136.3 (C-11a).

(1*R*,2*R*,6*S*,12b*R*)-1-Ethyl-6-(hydroxymethyl)-2-(methoxycarbonylmethyl)-4 -oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]-quinolizine (9d). HCl (6.5 M) in MeOH (1 mL) was added to a solution of lactam **8d** (133 mg, 0.36 mmol) in MeOH (3 mL). The mixture was stirred at room temperature for 25 h. The solvent was removed, and the resulting solid was diluted with EtOAc and washed with saturated aqueous Na_2CO_3. After extraction with EtOAc, the combined organic extracts were washed with H_2O, dried, and concentrated to give a residue, which was chromatographed (Et_2O) to afford 9d (64 mg, 48%) and its C-1 epimer **9d′** (39 mg, 29%). **9d**: IR (KBr) 1619, 1733, 3000−3500 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.12 (t, $J = 7.5$ Hz, 3H, CH_3), 1.67−1.74 (m, 1H, CH_2CH$_3$), 1.80 (m, 1H, CH_2CH$_3$), 1.91 (br s, 1H, OH), 2.12 (m, 1H, H-1), 2.21 (d, $J = 7.5$ Hz, 2H, $COOCH_2$), 2.33 (ddd, $J = 17.0$, 3.5, 1.0 Hz, 1H, H-3), 2.45 (m, 1H, H-2), 2.69 (dd,

J = 16.0, 2.5 Hz, 1H, H-7), 2.70 (dd, J = 17.0, 6.0 Hz, 1H, H-3), 3.01 (ddd, J = 16.0, 6.5, 2.5 Hz, 1H, H-7), 3.52 (s, 3H, CH_3O), 3.57 (t, J = 11.5 Hz, 1H, CH_2OH), 3.67 (dd, J = 11.5, 6.0 Hz, 1H, CH_2OH), 4.59 (m, 1H, H-12b), 5.41 (ddd, J = 10.0, 6.0, 6.0 Hz, 1H, H-6), 7.11 (td, J = 7.5, 1.0 Hz, 1H, ArH), 7.17 (td, J = 7.5, 1.0 Hz, 1H, ArH), 7.32 (d, J = 7.5 Hz, 1H, ArH), 7.46 (d, J = 7.5 Hz, 1H, ArH), 7.95 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 11.6 (CH_3), 21.4 (CH_2CH_3), 26.6 (CH_2CH_3), 31.3 (C-2), 34.8 (C-3), 38.1 (CH_2COO), 42.3 (C-1), 49.6 (C-6), 51.6 (CH_3O), 52.6 (C-12b), 62.5 (CH_2OH), 107.5 (C-7a), 111.0 (C-11), 118.3 (C-8), 120.0 (C-9), 122.4 (C-10), 127.3 (C-7b), 132.1 (C-12a), 136.1 (C-11a), 170.8 (C-4), 172.6 (COO); mp 203−204 °C; $[\alpha]_D^{22}$ +32.1 (*c* 0.32, $CHCl_3$). Anal. Calcd for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07; N, 7.56. Found: C, 68.24, H, 7.32, N, 7.56. **9d′**: IR (KBr) 1618, 1731, 3000−3500 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.13 (t, J = 7.6 Hz, 3H, CH_3CH_2), 1.55−1.62 (m, 2H, CH_3CH_2), 2.30−2.43 (m, 6H, H-1, H-2, H-3, CH_2COO), 2.52 (d, J = 16.0 Hz, 1H, H-7), 3.14 (ddd, J = 16.0, 7.2, 2.0 Hz, 1H, H-7), 3.70 (s, 3H, CH_3O), 3.73 (dd, J = 8.0, 1.6 Hz, 1H, CH_2OH), 3.78 (d, J = 8.0 Hz, 1H, CH_2OH), 4.78 (br s, 1H, H-12b), 5.40 (m, 1H, H-6), 7.11 (t, J = 7.2 Hz, 1H, H-9), 7.18 (t, J = 7.6 Hz, 1H, H-10), 7.39 (d, J = 8.0 Hz, 1H, H-11), 7.44 (d, J = 8.0 Hz, 1H, H-8), 8.38 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 12.7 (CH_3CH_2), 18.3 (CH_3CH_2), 21.5 (C-7), 29.2 (C-2), 34.9 and 35.0 (C-3, CH_2COO), 38.7 (C-1), 50.0 (C-6), 51.5 (C-12b), 51.8 (CH_3O), 61.6 (CH_2OH), 109.4 (C-7a), 111.4 (C-11), 118.0 (C-8), 119.8 (C-9), 122.2 (C-10), 127.6 (C-7b), 132.6 (C-12a), 136.0 (C-11a), 172.8 (COO); MS-EI *m*/*z* 370 (M^+, 10), 339 (42), 242 (27), 169 (65).

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Supporting Information Available: Experimental procedures for the HCl-promoted cyclization of lactams **4b**−**d** and for the conversions **5c** → **7**, **9b** → **10**, and **8b′** → 1-*epi*-**9b**, copies of the ^{1}H and ^{13}C NMR spectra of all new compounds, and X-ray crystallographic data for compounds **4c**, **4c′**, **5b**, **5d**, **8e**, **9b′**, 1-*epi*-**9b**, 1-*epi*-**9b′**, and **9d**. This material is available free or charge via the Internet at http://pubs.acs.org.

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