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Enantioselective Synthesis of 3,3-Disubstituted Piperidine Derivatives by Enolate Dialkylation of Phenylglycinol-Derived Oxazolopiperidone Lactams

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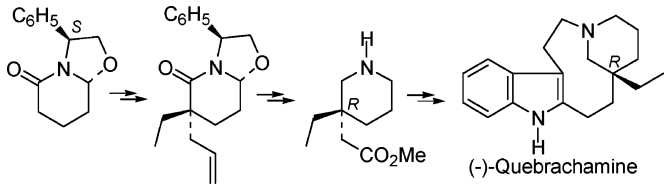


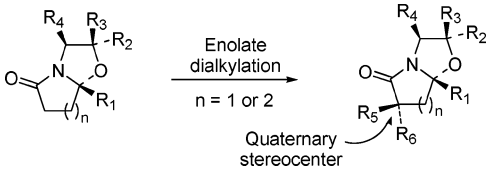
The stereochemical outcome of the enolate dialkylation of simple phenylglycinol-derived oxazolopiperidone lactams is studied. High stereoselectivities in the generation of the quaternary stereocenter are obtained by the appropriate choice of both the configuration of the starting lactam and the order of introduction of the substituents. The usefulness of the methodology is illustrated by the conversion of some of the dialkylated lactams into known synthetic precursors of alkaloids and by the total synthesis of (−)-quebrachamine.

Introduction

Chiral nonracemic bicyclic lactams have proven to be extremely useful and versatile building blocks for the enantioselective preparation of a wide variety of natural and unnatural products. The first studies in this field were reported by A. I. Meyers, who described highly diastereoselective dialkylation reactions of chiral lactam enolates and demonstrated the synthetic utility of this transformation with the asymmetric construction of a variety of cyclopentenones, cyclohexenones, and carboxylic acids containing quaternary carbon centers.[1] More recent work on the use of chiral bicyclic lactams in asymmetric synthesis has shown that they are also excellent precursors for the synthesis of optically active pyrrolidine and piperidine derivatives.[2]

The numerous examples described by Meyers of the dialkylation of enolates generated from a wide structural variety of chiral oxazolopyrrolidone lactams (Scheme 1, $n = 1$) make evident that the second alkylation step almost invariably takes place endo with respect to the substituent R_1 at the angular position, although when this substituent is hydrogen the stereoselectivities are poor.[3] The presence of an alkyl or aryl substituent on the 2 position oriented toward the endo concave face ($R_2 \neq H$) provokes a reversal in the facial stereoselectivity, resulting in an exclusive alkylation on the exo face.[3c] On the other hand, although there are no systematic studies about the influence of the aminoalcohol moiety substituents on the stereoselectivity of enolate dialkylations of chiral oxazolopiperidone lactams (Scheme 1, $n = 2$), in the reported examples of such dialkylations, all of them from lactams bearing an alkyl or aryl substituent at the angular position, the reaction always takes place with endo selectivity, even when $R_2 = C_6H_5$.[4] No

SCHEME 1. Enolate Dialkylations of Bicyclic Lactams



† University of Barcelona.

‡ Institut de Ciència de Materials.

(1) For reviews, see: (a) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503. (b) Meyers, A. I. In *Stereocontrolled Organic Synthesis*; Trost, B. M., Ed.; Blackwell Scientific Publications: Oxford, 1994; pp 145−175.

(2) For reviews, see: (a) Meyers, A. I.; Brengel, G. P. *Chem. Commun.* **1997**, 1. (b) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843. (c) Escolano, C.; Amat, M.; Bosch, J. *Chem. Eur. J.* **2006**, *12*, 8198.

(3) (a) Meyers, A. I.; Seefeld, M. A.; Lefker, B. A. *J. Org. Chem.* **1996**, *61*, 5712. (b) Meyers, A. I.; Seefeld, M. A.; Lefker, B. A.; Blake, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 4565. (c) Meyers, A. I.; Seefeld, M. A.; Lefker, B. A.; Blake, J. F.; Williard, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 7429.

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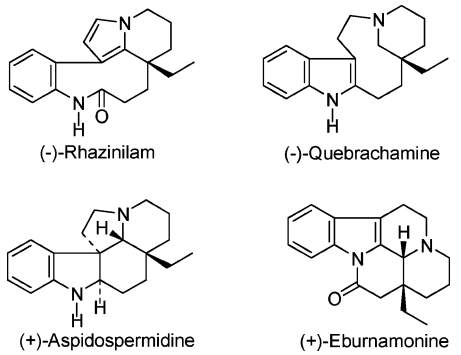
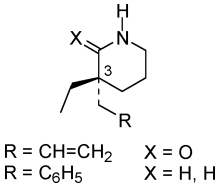


FIGURE 1. Alkaloids embodying a 3,3-disubstituted piperidine moiety.

dialkylation reactions of oxazolopiperidone lactams unsubstituted at the angular position have been described so far.

In a previous paper we reported the enolate monoalkylation of a variety of phenylglycinol-derived oxazolopiperidone lactams[5] and discussed the influence of the configuration at C-8a and the effect of substituents at the C-8 and C-8a positions on the stereoselectivity of the reaction.[6] Herein, we report our results on the sequential dialkylation of the enolate of simple phenylglycinol-derived oxazolopiperidone lactams **1a** and **1b**,

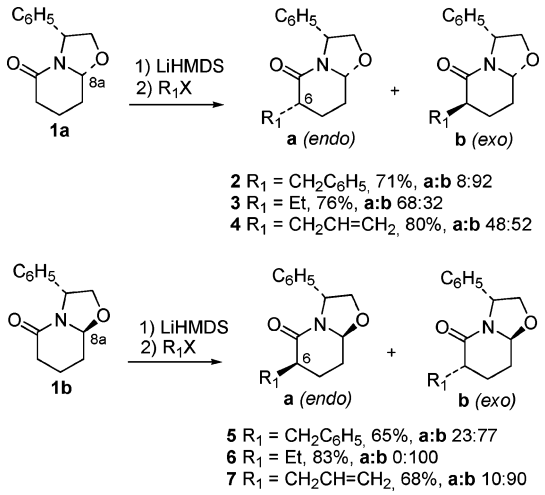


unsubstituted at the angular position, and the subsequent elaboration of the resulting dialkylated lactams into enantiopure piperidine derivatives with two different substituents at the 3-position. As target compounds we selected piperidines bearing an ethyl and either a benzyl or an allyl substituent at the quaternary stereocenter. The ethyl substituent is a common structural unit present in many alkaloids, whereas the allyl substituent can be further elaborated by known oxidative procedures to give synthetic precursors of complex natural products such as (−)-rhazinilam, (+)-eburnamonine, (+)-aspidospermidine, or (−)-quebrachamine (Figure 1).

Results and Discussion

To establish the most convenient protocol for the stereoselective generation of a quaternary stereocenter at the 3 position of the piperidine ring by dialkylation of oxazolopiperidone lactams we investigated the influence on the stereoselectivity of (i) the order of incorporation of the substituents and (ii) the configuration of the C-8a stereocenter. Three monoalkylated

SCHEME 2. Monoalkylation of Oxazolopiperidone Lactams



lactams, bearing a benzyl, ethyl, or allyl substituent, were initially prepared from each of the C-8a isomeric lactams **1a** and **1b** following our previously described procedure.[5] Thus, treatment of a THF solution of lactams **1a** and **1b** with LiHMDS at −78 °C, followed by addition of benzyl bromide, ethyl iodide, or allyl bromide at the same temperature, afforded the corresponding alkylated products **2**−**4** and **5**−**7**, respectively, as epimeric mixtures at the new stereogenic center (Scheme 2). In all cases the exo isomer was predominant except in the alkylation of lactam **1a** with ethyl iodide. The stereoselectivity of these reactions ranged from excellent (**6b** was isolated as a single isomer) to very low (as in **4**). However, this was not a drawback since the C-6 isomeric mixtures of lactams **2**−**7** could be used in the subsequent alkylation as the stereochemical outcome of this process is irrespective of the configuration of the C-6 stereocenter in the starting material.

The introduction of the second substituent from the above monoalkylated lactams was initially attempted under the reaction conditions we had successfully used to perform monoalkylation reactions from **1a** and **1b**. Surprisingly, all attempts to alkylate the 6-benzyl-substituted lactam **2** at −78 °C by treatment of a THF solution of the lactam with LiHMDS (3 equiv) for 2 h, followed by addition of an excess (3 equiv) of ethyl iodide were unfruitful. A similar result was observed when the reaction was carried out at 0 °C, whereas treatment of **2** with LiHMDS at room temperature for 2 h, followed by addition of ethyl iodide at this temperature afforded an equimolecular mixture of isomers **8a** and **8b** (see Scheme 3). An increase of the stereoselectivity was observed upon cooling the enolate solution to −78 °C before the addition of an excess of ethyl iodide: under these conditions a 33:67 isomeric mixture of the endo and exo alkylation products (**8a** and **8b**, respectively) was obtained in 76% yield. More satisfactorily, alkylation of the enolate (generated at 25 °C) of the 6-ethyl-substituted lactam **3** with benzyl bromide at −78 °C afforded with very high stereoselectivity the disubstituted lactam **8a**, resulting from an exo diastereofacial alkylation of the enolate. This result makes evident that the order in which the substituents are incorporated dramatically affects the stereochemical outcome of the dialkylation.

In contrast with what we had observed from the above cis H-3/H-8a lactams **2** and **3**, the enolate of the C-8a epimeric lactam **5** (H-3/H-8a trans) could be efficiently generated at −78 °C by using LiHMDS as the base (Scheme 4). A

(4) (a) Meyers, A. I.; Hanreich, R.; Wanner, K. T. *J. Am. Chem. Soc.* **1985**, *107*, 7776. (b) Meyers, A. I.; Lefker, B. A.; Wanner, K. T.; Aitken, R. A. *J. Org. Chem.* **1986**, *51*, 1936. (c) Meyers, A. I.; Lefker, B. A. *Tetrahedron* **1987**, *43*, 5663. (d) Meyers, A. I.; Berney, D. *J. Org. Chem.* **1989**, *54*, 4673. (e) Resek, J. E.; Meyers, A. I. *Synlett* **1995**, 145. (f) Reeder, M. R.; Meyers, A. I. *Tetrahedron Lett.* **1999**, *40*, 3115. (g) Watson, D. J.; Meyers, A. I. *Tetrahedron Lett.* **2000**, *41* 1519. (h) Hughes, R. C.; Dvorak, C. A.; Meyers, A. I. *J. Org. Chem.* **2001**, *66*, 5545. See also, (i) Schwarz, J. B.; Meyers, A. I. *J. Org. Chem.* **1998**, *63*, 1619.

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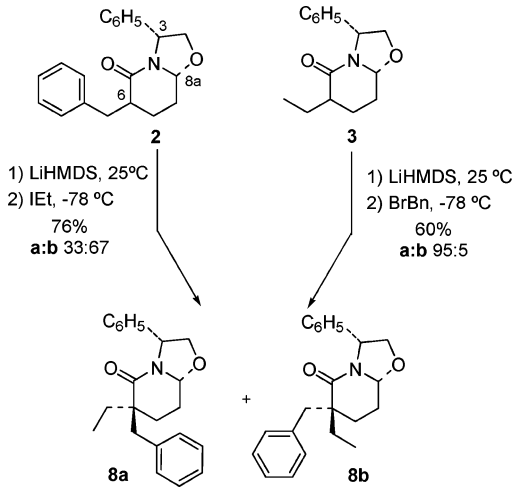
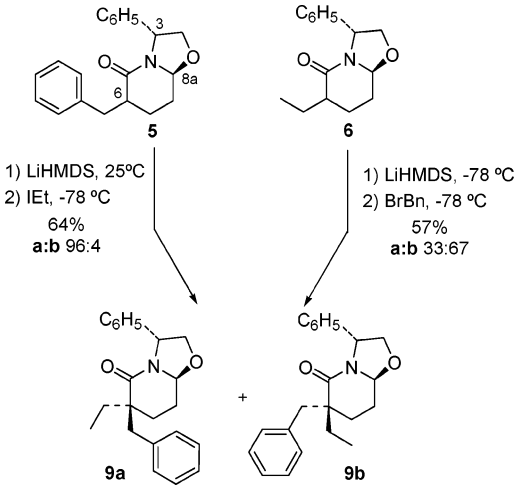
(6) Soteras, I.; Lozano, O.; Gómez-Esqué, A.; Escolano, C.; Orozco, M.; Amat, M.; Bosch, J.; Luque, F. J. *J. Am. Chem. Soc.* **2006**, *128*, 6581.

SCHEME 3. Alkylation of 6-Substituted Cis H-3/H-8a Oxazolopiperidone Lactams: Benzyl and Ethyl Substituents



SCHEME 4. Alkylation of 6-Substituted Trans H-3/H-8a Oxazolopiperidone Lactams: Benzyl and Ethyl Substituents

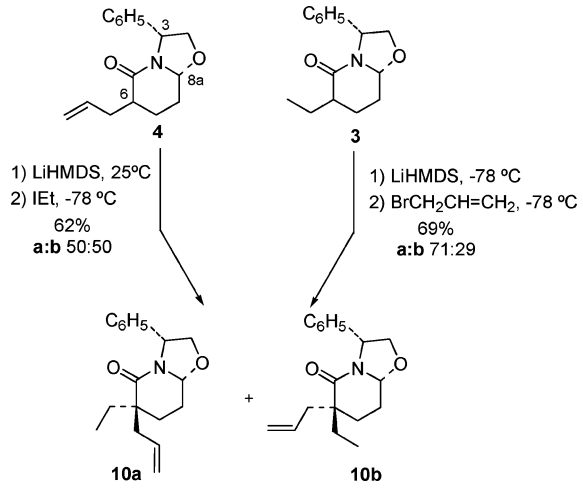


subsequent addition of ethyl iodide afforded the corresponding exo isomer **9a**[7] with excellent stereoselectivity (**9a:9b** 96:4). A higher temperature (25 °C) in the enolate ethylation resulted in a poorer stereoselectivity (**9a:9b** 60:40). In this trans H-3/H-8a series, the ethyl-substituted lactam **6** underwent enolate alkylation with benzyl bromide in poor stereoselectivity, even at −78 °C, leading to a 33:67 mixture of isomers **9a** and **9b**. Again, the order of introduction of the substituents has a crucial influence on the stereoselectivity of the dialkylation.

We next investigated the preparation of lactams bearing an allyl and ethyl substituent at the 3 position of the piperidine ring. As already observed when operating from lactams **2** and **3**, generation of the enolate of the cis H-3/H-8a configurated lactam **4** (LiHMDS, THF) required working at room temperature. A subsequent addition of ethyl iodide at −78 °C yielded an equimolecular mixture of dialkylated compounds **10a**[7] and **10b** (Scheme 5). Alternatively, addition of allyl bromide to the enolate of ethyl-substituted lactam **3** occurred with only moderate stereoselectivity, leading to a mixture of isomers **10a** and **10b**, in which the exo-allylated product predominated (71:29).

(7) The absolute configuration of the dialkylated lactams **9a** and **10a** was unambiguously confirmed by X-ray crystallographic analysis.

SCHEME 5. Alkylation of 6-Substituted Cis H-3/H-8a Oxazolopiperidone Lactams: Allyl and Ethyl Substituents



SCHEME 6. Alkylation of 6-Substituted Trans H-3/H-8a Oxazolopiperidone Lactams: Allyl and Ethyl Substituents

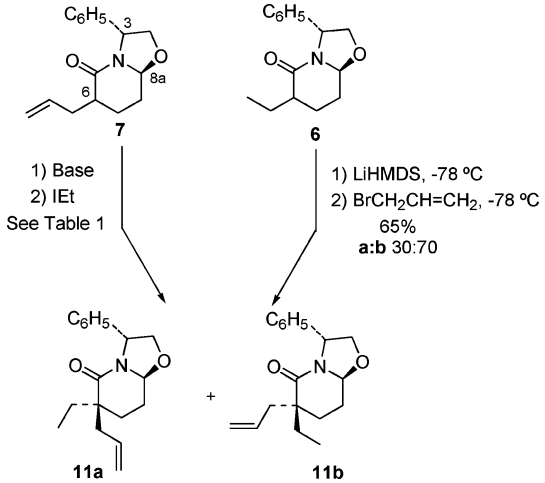


TABLE 1. Alkylation of Oxazolopiperidone 7

entry	base	solvent	*T*, °C enolate formation	*T*, °C alkylation	yield, %	**11a**:**11b**
1	LiHMDS	THF	−78	−78	71	91:9
2	LiHMDS	THF	25	−78	72	91:9
3	LiHMDS	THF	25	25	67	77:23
4	NaHMDS	THF	−78	−78	50	93:7
5	KHMDS	THF	−78	−78	62	95:5
6	KHMDS	toluene	−78	−78	56	98:2

Better stereochemical results in the preparation of allyl-ethyl-substituted lactams were obtained from the trans H-3/H-8a 6-allyl lactam **7**. Thus, treatment of the lithium enolate of **7** with ethyl iodide at −78 °C afforded isomer **11a**, resulting from alkylation on the exo face of the enolate, with good stereoselectivity (Scheme 6 and Table 1, entries 1 and 2; **11a**:**11b** 91:9). As expected, the stereoselectivity decreased when the temperature of the alkylation step was raised to 25 °C (entry 3). The use of NaHMDS or KHMDS as the base, instead of LiHMDS (entries 4 and 5), resulted in a slight increase in stereoselectivity. Finally, changing the solvent from THF to toluene (entry 6), when using KHMDS, resulted in the stereoselective formation of lactam **11a**. The order in which the

alkylating agents are added again modifies the stereochemical outcome of the dialkylation since allylation of the ethyl-substituted lactam **6** with allyl bromide at −78 °C took place with only a modest exo facial selectivity to give a 30:70 mixture of isomers **11a** and **11b**, respectively.

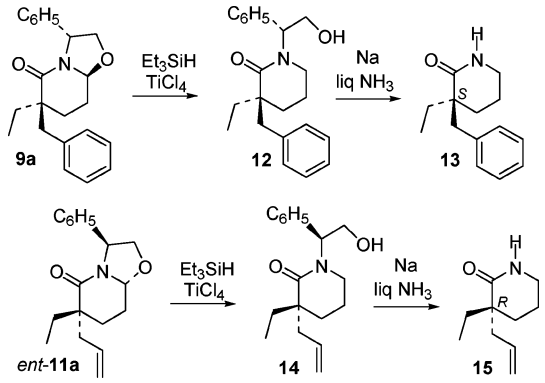
The above results deserve some comments. In contrast with the endo diastereofacial selectivity observed by Meyers for the enolate dialkylation of oxazolopiperidone lactams bearing a substitutent at the C-8a angular position, C-8a unsubstituted lactams **2**−**7** preferently undergo the second alkylation on the exo face of the enolate. On the other hand, for a given cis or trans H-3/H-8a relationship, the best stereoselectivities in the introduction of the second substituent parallel those observed in the monoalkylation reactions from lactams **1a** (cis) and **1b** (trans) when the same alkylating reagent is used. Thus, in the cis H-3/H-8a series, starting from unsubstituted lactam **1a** the best stereoselectivity was observed in the benzylation reaction leading to the exo isomer **2b**.[5] Similarly, only the exo benzylation of the ethyl-substituted cis H-3/H-8a lactam **3** was highly stereoselective, whereas the ethylation of **2** and **4** or the allylation of **3** were not. In turn, in the trans H-3/H-8a series the best stereoselectivity from the unsubstituted lactam **1b** was observed in the ethylation reaction leading to the exo isomer **6b**.[5] Again, the exo ethylation of the benzyl- and allyl-substituted trans H-3/H-8a lactams **5** and **7**, respectively, was highly stereoselective, whereas the benzylation or the allylation of **6** took place with moderate stereoselectivity.

Thus, from a stereochemical point of view, the best sequences for the preparation of lactams with benzyl and ethyl substituents at the quaternary stereocenter involve either the ethylation of **1a** followed by benzylation of the resulting monoalkylated lactam **3** to give **8a** or the benzylation of lactam **1b** followed by ethylation of the resulting lactam **5** to give **9a**. Since in both cases the second alkylation step takes place with exo diastereofacial selectivity, the two sequences afford dialkylated lactams with the same absolute configuration at the quaternary stereocenter. On the other hand, the best sequence for the stereoselective preparation of a bicyclic lactam bearing allyl and ethyl substituents involves the allylation of the enolate of **1b** followed by stereoselective exo ethylation of the monoalkylated lactam **7** to give **11a**.

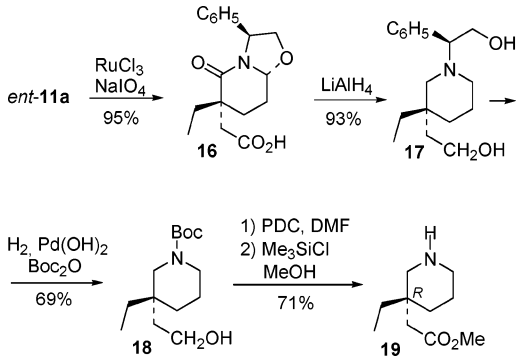
The conversion of the dialkylated lactams into 3,3-disubstituted piperidine derivatives simply requires the removal of the phenylethanol moiety of the chiral inductor by reductive cleavage of the C_{8a}−O and benzylic C_3−N bonds of the oxazolidine ring. Starting from lactam **9a** this was accomplished by treatment with Et_3SiH and $TiCl_4$ followed by removal of the benzylic substituent from the resulting piperidone **12** with sodium in liquid ammonia (Scheme 7). In this way, (*S*)-3-benzyl-3-ethyl-2-piperidone (**13**) was obtained in 80% overall yield.

By selection of the appropriate *R* or *S* enantiomer of phenylglycinol, both commercially available, both enantiomers of a target 3,3-substituted-2-piperidone are accessible through the above methodology. This was illustrated with the synthesis of (*R*)-3-allyl-3-ethyl-2-piperidone (**15**),[8] which possesses the absolute configuration required for the synthesis of the indole alkaloids depicted in Figure 1. Thus, sequential enolate dialkylation of (*S*)-phenylglycinol-derived lactam *ent*-**1b** with allyl bromide and ethyl iodide, as described above for its enantiomer,

SCHEME 7. Synthesis of Enantiopure 3,3-Disubstituted Piperidine Derivatives



SCHEME 8. Synthesis of Methyl (*R*)-3-Ethyl-3-piperidineacetate



afforded disubstituted lactam *ent*-**11a**, which was converted as in the above benzyl-ethyl series to piperidone **15** in 65% overall yield. In both series, the configuration of the quaternary stereogenic center was unequivocally established by X-ray crystallographic analysis of the intermediate phenylglycinol-derived piperidones **12** and **14**. Taking into account that racemic **15** has previously been used in the synthesis of rhazinilam[9] (see Figure 1), chiral piperidone **15** can be considered a precursor for the enantioselective synthesis of this natural product.

To further illustrate the usefulness of the above 3,3-disubstituted piperidines for the enantioselective synthesis of natural products, bicyclic lactam *ent*-**11a** was converted to methyl (*R*)-3-ethyl-3-piperidineacetate (**19**). This was accomplished in good overall yield by ruthenium oxidation of the carbon−carbon double bond of *ent*-**11a**, followed by $LiAlH_4$ reduction of the resulting acid **16**, hydrogenolysis, and subsequent conventional functional group interconversions, as outlined in Scheme 8. In the racemic series, amino ester **19** has been used as a platform for the synthesis of several indole alkaloids such as (±)-eburnamonine, (±)-aspidospermidine, or (±)-quebrachamine.[10]

The synthesis of the *Aspidosperma* indole alkaloid (−)-quebrachamine from **19** requires the introduction of the 2-(3-indolyl)ethyl chain on the piperidine nitrogen, the closure of the nine-membered ring by electrophilic cyclization on the indole 2-position, and finally, the adjustment of the oxidation level in the resulting tetracyclic keto lactam. Following a route

(8) For the synthesis of enantioenriched (ee = 42%) lactam **15** by asymmetric dialkylation of a chiral *N*-(dialkylamino)lactam, see: Enders, D.; Teschner, P.; Raabe, G.; Runsink, J. *Eur. J. Org. Chem*. 2001, 4463.

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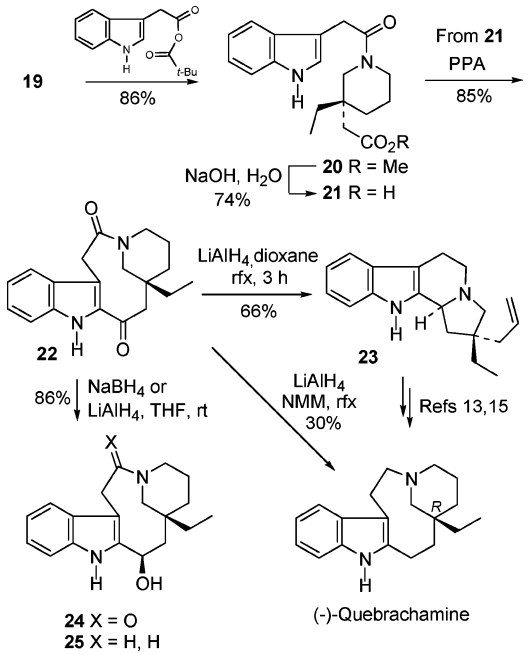
SCHEME 9. Enantioselective Synthesis of (−)-Quebrachamine



that parallels the one used in our previous synthesis of (20*R*)- and (20*S*)-dihydrocleavamine,[5] piperidine **19** was acylated with the mixed anhydride of indole-3-acetic acid and pivalic acid[11] to give amido ester **20**, which was converted to the corresponding carboxylic acid **21** and then cyclized[10a] by treatment with polyphosphoric acid to give the desired tetracyclic keto lactam **22** in good overall yield (Scheme 9). Although **22** could be partially reduced in excellent yield to alcohols **24** and **25** by treatment with $NaBH_4$ (MeOH, rt) and $LiAlH_4$ (THF, rt), respectively, the complete reduction of **22** to (−)-quebrachamine proved to be more difficult. This conversion was accomplished in only moderate yield (30%) with $LiAlH_4$ in refluxing *N*-methylmorpholine (NMM),[12] which nevertheless represents a significant improvement of the reported yield (6%) for this reduction (from *rac*-**22**) in refluxing dioxane.[10a] Under the latter conditions, reduction of **22** led to the known indoloindolizidine **23**,[13,14] which, taking into account previous correlations,[13,15] constitutes an alternative formal synthesis of (−)-quebrachamine.[16] The NMR data[15e] and $[\alpha]_D$ value[17] of our synthetic quebrachamine were coincident with those reported in the literature for the natural product.

Conclusion. By the appropriate choice of both the configuration of the starting lactam (H-3/H-8a, either cis or trans) and the order of introduction of the substituents, the enolate dialkylation of phenylglycinol-derived oxazolopiperidone lactams allows the stereoselective introduction of substituents at the β-position of the piperidine ring, with generation of a quaternary sterocenter, to ultimately lead to enantiopure 3,3-disubstituted piperidine derivatives. Taking into account that both enantiomers of phenylglycinol are commercially available, the procedure provides access to 3,3-disubstituted piperidines in both enantiomeric series.

Experimental Section

General Procedure for the Alkylation of Lactams 2−6. A solution of the lactam (1 mmol) in THF was added to a solution of LiHMDS (1 M in THF, 1.5 or 3.0 mmol) in THF at 25 °C for lactams **2**−**4** and at −78 °C for lactams **5**−**7**. After the solution was stirred at the same temperature for 2 h, the alkylating reagent (2.6 mmol) was added at −78 °C, and stirring was continued at this temperature for an additional 3 h. The reaction was quenched by the addition of saturated aqueous NaCl, and the resulting mixture was extracted with EtOAc and CH_2Cl_2. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed.

[3*R*,6*S*(and 6*R*),8a*R*]-6-Benzyl-6-ethyl-5-oxo-3-phenyl-2,3,6,7,8,-8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (8a and 8b). From lactam 2: Following the general procedure, lactam **2** (200 mg, 0.65 mmol) in THF (8 mL), LiHMDS (1.95 mL, 1.95 mmol) in THF (2 mL), and ethyl iodide (0.14 mL, 1.69 mmol) afforded a 33:67 (calculated by GC/MS) mixture of epimers **8a** and **8b** (168 mg, 76%), which were separated by flash chromatography (7:3 hexane−Et_2O). **From lactam 3:** Following the general procedure, lactam **3** (372 mg, 1.52 mmol) in THF (15 mL), LiHMDS (4.6 mL, 4.6 mmol) in THF (5 mL), and benzyl bromide (0.50 mL, 4.00 mmol) afforded a 95:5 (calculated by GC/MS) mixture of epimers **8a** and **8b** (290 mg, 60%), which were separated by flash chromatography (7:3 hexane−Et_2O). **8a**: IR (film) 1650 cm^{-1}; ^1H NMR (400 MHz) δ 0.77 (t, J = 7.5 Hz, 3H, CH_3CH_2), 1.47 (m, 1H, CH_3CH_2), 1.72−1.85 (m, 4H, H-7, H-8, CH_3CH_2), 2.13 (m, 1H, H-8), 2.41 and 3.19 (2d, J = 13.2 Hz, 2H, CH_2Ph), 3.92 (dd, J = 9.0, 2.0 Hz, 1H, H-2), 3.96 (dd, J = 9.0, 6.5 Hz, 1H, H-2), 4.10 (m, 1H, H-8a), 4.80 (dd, J = 6.5, 2.0 Hz, 1H, H-3), 7.18−7.34 (m, 10H, ArH); ^{13}C NMR (100 MHz) δ 9.1 (CH_3CH_2), 25.9 (C-7), 26.8 (C-8), 33.6 (CH_3CH_2), 44.2 (CH_2Ph), 46.8 (C-6), 59.2 (C-3), 73.9 (C-2), 88.3 (C-8a), 126.4 (CH), 126.6 (2CH), 127.4 (CH), 128.0 (2CH), 128.4 (2CH), 130.7 (2CH), 138.2 (C *i*), 142.1 (C *i*), 171.2 (NCO); MS-EI *m*/*z* 335 (M^+, 13), 91 (80), 104 (100), 243 (36); HRMS calcd for $C_{22}H_{25}NO_2$, 335.1885; found, 335.1897. **8b**: IR (film) 1647 cm^{-1}; ^1H NMR (400 MHz) δ 0.88 (t, J = 7.5 Hz, 3H, CH_3CH_2), 1.13 (dddd, J = 14.0, 12.0, 10.0, 4.0 Hz, 1H, H-8), 1.28 (m, 1H CH_3CH_2), 1.69 (ddd, J = 14.4, 14.0, 4.0 Hz, 1H, H-7), 1.80−1.89 (m, 2H, CH_3CH_2, H-7), 2.01 (ddd, J = 12.0, 6.8, 4.0 Hz, 1H, H-8), 2.40 and 3.11 (2d, J = 13.5 Hz, 2H, CH_2Ph), 4.03 (dd, J = 9.0, 1.2 Hz, 1H, H-2), 4.12 (dd, J = 9.0, 6.8 Hz, 1H, H-2), 4.72 (dd, J = 10.0, 4.0 Hz, 1H, H-8a), 4.87 (dd, J = 6.8, 1.2 Hz, 1H, H-3),

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6.83−6.85 (m, 2H, ArH), 7.11−7.37 (m, 8H, ArH); ^{13}C NMR (100 MHz) δ 8.8 (*C*H$_3$CH$_2$), 25.8 (C-7), 26.3 (C-8), 32.7 (CH$_3$*C*H$_2$), 45.3 (*C*H$_2$Ph), 46.5 (C-6), 59.3 (C-3), 74.1 (C-2), 88.8 (C-8a), 126.3 (CH), 127.4 (2CH), 127.5 (CH), 128.1 (2CH), 128.3 (2CH), 130.4 (2CH), 137.7 (C *i*), 141.7 (C *i*), 171.6 (NCO); MS-EI *m*/*z* 335 (M$^+$, 5), 91 (58), 104 (32), 232 (100); HRMS calcd for $C_{22}H_{25}NO_2$, 335.1885; found, 335.1895.

[3*R*,6*S*(and 6*R*),8a*S*]-6-Benzyl-6-ethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (9a and 9b). From lactam 5: Following the general procedure, lactam **5** (330 mg, 1.07 mmol) in THF (8 mL), LiHMDS (3.2 mL, 3.20 mmol) in THF (10 mL), and ethyl iodide (0.2 mL, 2.78 mmol) afforded an 96:4 (calculated by GC/MS) mixture of epimers **9a** and **9b** (231 mg, 64%), which were separated by flash chromatography (1:4 Et$_2$−hexane). **From lactam 6:** Following the general procedure, lactam **6** (150 mg, 0.61 mmol) in THF (6 mL), LiHMDS (1.83 mL, 1.83 mmol) in THF (2 mL), and benzyl bromide (0.2 mL, 1.6 mmol) afforded an 33:67 (calculated by GC/MS) mixture of epimers **9a** and **9b** (124 mg, 57%), which were separated by flash chromatography (1:4 Et$_2$O−hexane). **9a**: IR (film) 1647 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.78 (t, J = 7.5 Hz, 3H, C*H*$_3$CH$_2$), 0.98 (m, 1H, H-8), 1.30 (m, 1H, CH$_3$C*H*$_2$), 1.71 (dd, J = 6.0, 4.0 Hz, 1H, H-7), 1.74 (d, J = 4.0 Hz, 1H, H-7), 1.86 (m, 1H, CH$_3$C*H*$_2$), 1.98 (ddd, J = 12.6, 7.8, 4.3 Hz, 1H, H-8), 2.65 and 3.23 (2d, J = 13.2 Hz, 2H, CH$_2$Ph), 3.70 (dd, J = 8.7, 8.1 Hz, 1H, H-2), 4.39 (dd, J = 8.7, 8.1 Hz, 1H, H-2), 4.95 (dd, J = 9.3, 4.3 Hz, 1H, H-8a), 5.22 (t, J = 8.1 Hz, 1H, H-3), 7.10−7.33 (m, 10H, ArH); ^{13}C NMR (75.4 MHz) δ 8.6 (*C*H$_3$CH$_2$), 24.2 (C-7), 25.7 (C-8), 32.9 (CH$_3$*C*H$_2$), 44.4 (*C*H$_2$Ph), 46.6 (C-6), 58.9 (C-3), 72.8 (C-2), 88.9 (C-8a), 126.0 (2CH), 126.4 (CH), 127.3 (CH), 128.0 (2CH), 128.5 (2CH), 130.1 (2CH), 138.0 (C *i*), 139.6 (C *i*), 173.0 (NCO); mp 111−113 °C (Et$_2$O−EtOAc); $[\alpha]_D^{22}$ −208 (*c* 1.0, MeOH); MS-EI *m*/*z* 335 (M$^+$, 31), 91 (100), 306 (93). Anal. calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 78.55; H, 7.46; N, 4.15. **9b**: IR (film) 1648 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.00 (t, J = 7.2 Hz, 3H, C*H*$_3$CH$_2$), 1.62 (m, 1H, H-8), 1.70−1.74 (m, 2H, H-7), 1.81 (m, 2H, C*H*$_2$CH$_3$), 2.10 (dddd, J = 11.6, 4.4, 4.4, 3.2 Hz, 1H, H-8), 2.45 and 3.22 (2d, J = 13.2 Hz, 2H, CH$_2$Ph), 3.62 (dd, J = 8.8, 8.0 Hz, 1H, H-2), 4.39 (dd, J = 8.8, 8.0 Hz, 1H, H-2), 4.60 (dd, J = 8.8, 4.8 Hz, 1H, H-8a), 5.18 (t, J = 8.8 Hz, 1H, H-3), 6.94 (dd, J = 8.5, 6.8 Hz, 2H, ArH), 7.05 (dd, J = 8.0, 1.6 Hz, 2H, ArH), 7.11 (tm, J = 7.0 Hz, 2H, ArH), 7.17 (m, 1H, ArH), 7.25−7.33 (m, 3H, ArH); ^{13}C NMR (75.4 MHz) δ 8.9 (*C*H$_3$CH$_2$), 23.6 (C-7), 25.4 (C-8), 31.5 (CH$_3$*C*H$_2$), 43.2 (*C*H$_2$Ph), 46.5 (C-6), 58.7 (C-3), 72.9 (C-2), 88.5 (C-8a), 126.1 (CH, Ar), 126.6 (2CH), 127.5 (CH), 128.0 (2CH), 128.5 (2CH), 130.7 (2CH), 137.7 (C *i*), 139.5 (C *i*), 172.8 (NCO); MS-EI *m*/*z* 335 (M$^+$, 25), 104 (100), 91 (90).

[3*R*,6*S*(and 6*R*),8a*R*]-6-Allyl-6-ethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3, 2-*a*]pyridine (10a and 10b). From lactam 4: Following the general procedure, lactam **4** (200 mg, 0.78 mmol) in THF (8 mL), LiHMDS (2.3 mL, 2.3 mmol) in THF (2 mL), and ethyl iodide (0.16 mL, 2.00 mmol) afforded an 50:50 (calculated by GC/MS) mixture of epimers **10a** and **10b** (137 mg, 62%), which were separated by flash chromatography (1:1 Et$_2$O−hexane). **From lactam 3:** Following the general procedure, lactam **3** (200 mg, 0.82 mmol) in THF (8 mL), LiHMDS (2.5 mL, 2.5 mmol) in THF (2 mL), and allyl bromide (0.18 mL, 2.12 mmol) afforded an 71:29 (calculated by GC/MS) mixture of epimers **10a** and **10b** (160 mg, 69%), which were separated by flash chromatography (1:1 Et$_2$O−hexane). **10a**: IR (film) 1647 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.71 (t, J = 7.5 Hz, 3H, C*H*$_3$CH$_2$), 1.42 (m, 1H, CH$_3$C*H*$_2$), 1.64 (m, 1H, CH$_3$C*H*$_2$), 1.70−1.92 (m, 3H, H-7, H-8), 1.99 (dd, J = 13.2, 8.7 Hz, 1H, C*H*$_2$CH═), 2.26 (m, 1H, H-8), 2.45 (dddd, J = 13.2, 6.0, 1.5, 1.5 Hz, 1H, C*H*$_2$CH═), 4.00 (dd, J = 9.0, 1.2 Hz, 1H, H-2), 4.14 (dd, J = 9.0, 6.6 Hz, 1H, H-2), 4.76 (dd, J = 9.3, 3.6 Hz, 1H, H-8a), 4.87 (dd, J = 6.6, 1.2 Hz, 1H, H-3), 5.04 (dm, J = 7.8 Hz, 1H, C*H*$_2$═), 5.08 (m, 1H, C*H*$_2$═), 5.72 (m, 1H, CH$_2$C*H*═), 7.20−7.35 (m, 5H, ArH); ^{13}C NMR (75.4 MHz) δ 8.8 (*C*H$_3$CH$_2$), 26.4 (C-7 and C-8), 32.3 (CH$_3$*C*H$_2$), 42.6 (*C*H$_2$CH═), 44.5 (C-6), 59.0 (C-3), 73.8 (C-2), 88.5 (C-8a), 118.2 (*C*H$_2$═), 126.4 (2CH), 127.2 (CH), 128.2 (2CH), 134.4 (CH$_2$*C*H═), 141.8 (C i), 171.3 (NCO); mp 132−134 °C (Et$_2$O−hexane); $[\alpha]_D^{22}$ −158 (*c* 0.5, MeOH); MS-EI *m*/*z* 285 (M$^+$, 3), 104 (100), 243 (56), 257 (53). Anal. calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.69; H, 8.19; N, 5.12. **10b**: IR (film) 1646 cm^{-1}: ^{1}H NMR (300 MHz) δ 0.86 (t, J = 7.5 Hz, 3H, C*H*$_3$CH$_2$), 1.33 (m, 1H, CH$_3$C*H*$_2$), 1.72 (m, 1H, CH$_3$C*H*$_2$), 1.75−1.80 (m, 2H, H-7), 1.87−2.00 (m, 1H, H-8), 2.05 (dd, J = 13.5, 7.5 Hz, 1H, C*H*$_2$CH═), 2.24 (ddd, J = 12.0, 7.0, 3.3 Hz, 1H, H-8), 2.34 (dd, J = 13.5, 7.2 Hz, 1H, C*H*$_2$CH═), 4.03 (dd, J = 9.0, 0.9 Hz, 1H, H-2), 4.16 (dd, J = 9.0, 6.6 Hz, 1H, H-2), 4.81 (dd, J = 9.9, 3.3 Hz, 1H, H-8a), 4.87 (dm, J = 6.6 Hz, 1H, H-3), 4.93 (m, 1H, C*H*$_2$═), 4.97 (m, 1H, C*H*$_2$═), 5.53 (m, 1H, CH$_2$C*H*═), 7.23−7.36 (m, 5H, ArH); ^{13}C NMR (75.4 MHz) δ 8.7 (*C*H$_3$CH$_2$), 26.2 and 26.3 (C-7 and C-8), 31.0 (CH$_3$*C*H$_2$), 44.1 *C*H$_2$CH═), 45.1 (C-6), 59.0 (C-3), 73.8 (C-2), 88.6 (C-8a), 117.6 (*C*H$_2$═), 126.5 (2CH), 127.2 (CH), 128.2 (2CH), 134.1 (CH$_2$*C*H═), 141.7 (C *i*), 171.7 (NCO); mp 131−133 °C (Et$_2$O−hexane); $[\alpha]_D^{22}$ −45 (*c* 0.5, MeOH); MS-EI *m*/*z* 285 (M$^+$, 5), 104 (100), 243 (42). Anal. calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.67; H, 8.21; N, 4.94.

[3*R*,6*S*(and 6*R*),8a*S*]-6-Allyl-6-ethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3, 2-*a*]pyridine (11a and 11b). From lactam 7: Following the general procedure, lactam **7** (970 mg, 3.77 mmol) in THF (10 mL), LiHMDS (11.0 mL, 11.0 mmol) in THF (42 mL), and ethyl iodide (0.8 mL, 9.81 mmol) afforded a 91:9 (calculated by GC/MS) mixture of epimers **11a** and **11b** (768 mg, 71%), which were separated by flash chromatography (1:4 Et$_2$O−hexane). **From lactam 6:** Following the general procedure, lactam **6** (250 mg, 1.02 mmol) in THF (10 mL), LiHMDS (3.1 mL, 3.1 mmol) in THF (3 mL), and allyl bromide (0.23 mL, 2.65 mmol) afforded a 30:70 (calculated by GC/MS) mixture of epimers **11a** and **11b** (188 mg, 65%), which were separated by flash chromatography (1:4 Et$_2$O−hexane). **11a**: IR (film) 1640 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.78 (t, J = 7.5 Hz, 3H, CH$_2$C*H*$_3$), 1.40 (m, 1H, C*H*$_2$CH$_3$), 1.59−1.78 (m, 4H, H-7, H-8, C*H*$_2$CH$_3$), 2.20 (m, 1H, H-8), 2.29 (dd, J = 14.0, 7.0 Hz, 1H, C*H*$_2$CH═), 2.47 (dd, J = 14.0, 7.0 Hz, 1H, C*H*$_2$CH═), 3.73 (dd, J = 9.0, 8.1 Hz, 1H, H-2), 4.47 (dd, J = 9.0, 8.1 Hz, 1H, H-2), 5.01 (t, J = 4.5 Hz, 1H, H-8a), 5.05 (m, 1H, C*H*$_2$═), 5.09 (dm, J = 6.6 Hz, 1H, C*H*$_2$═), 5.20 (t, J = 8.1 Hz, 1H, H-3), 5.80 (m, 1H, CH$_2$═C*H*), 7.24−7.34 (m, 5H, ArH); ^{13}C NMR (75.4 MHz) δ 8.6 (CH$_2$*C*H$_3$), 24.8 (C-7), 26.0 (C-8), 32.0 (*C*H$_2$CH$_3$), 42.8 (*C*H$_2$CH═), 45.3 (C-6), 58.8 (C-3), 73.0 (C-2), 89.1 (C-8a), 117.9 (*C*H$_2$═), 126.1 (2CH), 127.4 (CH), 128.6 (2CH), 134.4 (CH$_2$═*C*H), 139.7 (C *i*), 170.1 (NCO); mp 90−96 °C (Et$_2$O−hexane); MS-EI *m*/*z* 285 (M$^+$, 8), 104 (100), 243 (71), 257 (66). Anal. calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.45; H, 8.45; N, 4.99. **11b**: IR (film) 1643 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.92 (t, J = 7.5 Hz, 3H, CH$_2$C*H*$_3$), 1.55−1.88 (m, 5H, H-7, H-8, C*H*$_2$CH$_3$), 2.03 (dd, J = 13.5, 8.7 Hz, 1H, C*H*$_2$CH═), 2.21 (dddd, J = 16.6, 4.5, 4.5, 3.0 Hz, 1H, H-8), 2.43 (dddd, J = 13.5, 6.0, 1.5, 1.5 Hz, 1H, C*H*$_2$CH═), 3.72 (dd, J = 9.0, 8.0 Hz, 1H, H-2), 4.47 (dd, J = 9.0, 8.0 Hz, 1H, H-2), 4.97 (dd, J = 9.0, 4.5 Hz, 1H, H-8a), 5.03−5.07 (m, 2H, C*H*$_2$═), 5.20 (t, J = 8.0 Hz, 1H, H-3), 5.52−5.66 (m, 1H, CH$_2$═C*H*), 7.15−7.35 (m, 5H, ArH); ^{13}C NMR (75.4 MHz) δ 8.9 (CH$_2$*C*H$_3$), 24.6 (C-7), 26.0 (C-8), 30.8 (*C*H$_2$CH$_3$), 43.2 (*C*H$_2$–CH═), 44.8 (C-6), 58.6 (C-3), 72.9 (C-2), 88.7 (C-8a), 118.3 (CH$_2$═), 126.0 (2CH), 127.2 (CH), 128.4 (2CH), 134.0 (CH$_2$═*C*H), 139.6 (C *i*), 173.0 (NCO); mp 71−75 °C (Et$_2$O−hexane); MS-EI *m*/*z* 285 (M$^+$, 5), 104 (92), 244 (47), 257 (100); HRMS calcd for $C_{18}H_{23}NO_2$, 285.1728; found, 285.1721.

Following the general procedure, from lactam *ent*-**7** were obtained lactams *ent*-**11a** ($[\alpha]_D^{22}$ −154 (*c* 0.5, MeOH)) and *ent*-**11b** ($[\alpha]_D^{22}$ +61 (*c* 1.1, MeOH)).

(3*S*)-3-Benzyl-3-ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-piperidone (12). Triethylsilane (0.08 mL, 0.48 mmol) and TiCl$_4$

(0.10 mL, 0.72 mmol) were added to a cooled (−78 °C) solution of lactam **9a** (160 mg, 0.48 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature for 6 h, quenched by the addition of saturated aqueous NH_4Cl, and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed (1:1 EtOAc−hexane) to afford piperidone **12** (145 mg, 90%): IR (film) 1606, 3401 cm^{-1}; ^1H NMR (300 MHz) δ 0.92 (t, J = 7.5 Hz, 3H, CH_3CH$_2$), 1.22−1.34 (m, 2H, H-5), 1.48 (m, 1H, CH$_3$CH_2), 1.56 (m, 1H, H-4), 1.63 (dd, J = 9.6, 4.0 Hz, 1H, H-5) 1.73 (m, 1H, H-4), 1.97 (m, 1H, CH$_3$CH_2), 2.59 and 3.34 (2d, J = 13.0 Hz, 2H, CH_2Ph), 2.73 (ddd, J = 12.6, 8.5, 4.0 Hz, 1H, H-6), 2.85 (m, 1H, H-6), 4.00 (dd, J = 11.5, 8.5 Hz, 1H, H-2′), 4.07 (dd, J = 11.5, 5.4 Hz, 1H, H-2′), 5.85 (dd, J = 8.5, 5.4 Hz, 1H, H-1′), 7.21−7.32 (m, 10H, ArH); ^{13}C NMR (75.4 MHz) δ 8.9 (*C*H$_3$CH$_2$), 20.2 (C-5), 28.2 (C-4), 33.3 (CH$_3$*C*H$_2$), 44.3 (C-6), 45.2 (*C*H$_2$Ph), 47.6 (C-3), 58.9 (C-1′), 61.6 (C-2′), 126.3 (CH), 127.5 (CH), 127.8 (2CH), 127.9 (2CH), 128.5 (2CH), 130.4 (2CH), 136.9 (C *i*), 138.3 (C *i*), 175.8 (NCO); mp 115−116 °C (EtOAc); $[\alpha]_D^{22}$ −107 (*c* 0.5, MeOH); MS-EI *m*/*z* 338 [(M^+ + 1), 2), 91 (100), 228 (52), 278 (30), 306 (72). Anal. calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15. Found: C, 77.95; H, 7.99; N, 4.02.

(*S*)-3-Benzyl-3-ethyl-2-piperidone (13). Into a three-necked, 100 mL round-bottomed flask equipped with a coldfinger condenser charged with dry ice-acetone was condensed NH_3 (15 mL) at −78 °C. The temperature was raised to −33 °C, and a solution of lactam **12** (68 mg, 0.20 mmol) in THF (2 mL) was added. Then sodium metal was added in small portions until a blue color persisted, and the reaction was stirred at the same temperature for 90 s. The reaction was quenched by addition of solid NH_4Cl until the blue color disappeared, and the mixture was stirred at room temperature for an additional 4 h. The resulting residue was diluted with water and extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated, and the crude residue was chromatographed (1:1 EtOAc−hexane) to afford piperidone **13** (39 mg, 89%): IR (film) 1656 cm^{-1}; ^1H NMR (300 MHz) δ 0.93 (t, J = 7.5 Hz, 3H, CH_3CH$_2$), 1.45 (m, 1H, CH$_3$CH_2), 1.60−1.70 (m, 4H, H-4, H-5), 1.89 (m, 1H, CH$_3$CH_2), 2.25 and 2.58 (2d, J = 13.2 Hz, 2H, CH_2Ph), 3.04 (m. 1H, H-6), 3.15 (m, 1H, H-6), 5.18 (br s, 1H, NH), 7.19−7.26 (m, 5H, ArH); ^{13}C NMR (75.4 MHz) δ 8.7 (*C*H$_3$CH$_2$), 19.8 (C-5), 28.0 (C-4), 29.7 (C-3), 32.1 (CH$_3$*C*H$_2$), 42.6 (C-6), 44.2 (*C*H$_2$Ph), 46.7 (C-3), 126.3 (CH), 128.0 (2CH), 130.5 (2CH), 138.2 (C *i*), 176.5 (NCO); $[\alpha]_D^{22}$ −23 (*c* 0.67, MeOH); MS-EI *m*/*z* 217 (M^+, 18), 55 (34), 91 (73), 188 (100); HRMS calcd for $C_{14}H_{19}NO$, 217.1466; found, 217.1467. Anal. calcd for $C_{14}H_{19}NO \cdot {}^1/_4H_2O$: C, 75.81; H, 8.86; N, 6.31. Found: C, 75.87; H, 8.63; N, 6.21.

(3*R*)-3-Allyl-3-ethyl-1-[(1*S*)-2-hydroxy-1-phenylethyl]-2-piperidone (14). Following the procedure described for the preparation of **12**, triethylsilane (0.17 mL, 1.05 mmol), $TiCl_4$ (0.22 mL, 1.58 mmol), and a solution of lactam *ent*-**11a** (300 mg, 1.05 mmol) in CH_2Cl_2 (18 mL) afforded piperidone **14** (259 mg, 86%) after column chromatography (1:1 EtOAc−hexane): IR (film) 1608 cm^{-1}; ^1H NMR (300 MHz) δ 0.90 (t, J = 7.5 Hz, 3H, CH_3CH$_2$), 1.47 (m, 1H, CH$_3$CH_2), 1.63−1.73 (m, 4H, H-4, H-5), 1.86 (m, 1H, CH$_3$CH_2), 2.19 (dd, J = 13.5, 8.0 Hz, 1H, CH_2CH═), 2.55 (ddt, J = 13.5, 8.0, 1.2 Hz, 1H, CH_2CH═), 2.90 (m, 1H, H-6), 3.15 (m, 1H, H-6), 3.59 (br s, 1H, OH), 4.03 (m, 1H, H-2′), 4.14 (m, 1H, H-2′), 5.04−5.10 (m, 2H, CH_2═), 5.76 (m, 1H, CH$_2$C*H*═), 5.91 (dd, J = 9.5, 5.0 Hz, 1H, H-1′), 7.21−7.34 (m, 5H, ArH); ^{13}C NMR (75.4 MHz) δ 8.9 (*C*H$_3$CH$_2$), 20.3 (C-5), 28.7 (C-4), 32.0 (CH$_3$*C*H$_2$), 43.9 (C-6), 44.1 (*C*H$_2$CH═), 46.0 (C-3), 58.4 (C-1′), 61.5 (C-2′), 117.8 (*C*H$_2$═), 127.4 (CH), 127.6 (2CH), 128.4 (2CH), 134.6 (CH$_2$*C*H═), 137.2 (C *i*), 176.0 (NCO); mp 79−80 °C (Et_2O−hexane); $[\alpha]_D^{22}$ +148 (*c* 0.5, MeOH); MS-EI *m*/*z* 287 (M^+, 3), 91 (82), 256 (100). Anal. calcd for $C_{18}H_{25}NO_2$: C, 75.23; H, 8.77; N, 4.87. Found: C, 74.99; H, 8.89; N, 4.89.

(*R*)-3-Allyl-3-ethyl-2-piperidone (15). Following the procedure described for the preparation of **13**, lactam **14** (100 mg, 0.35 mmol) in NH_3 (15 mL) gave piperidone **15** (51 mg, 88%) after flash chromatography (1:1 EtOAc−hexane): IR (film) 1658 cm^{-1}; ^1H NMR (300 MHz) δ 0.89 (t, J = 7.5 Hz, 3H, CH_3CH$_2$), 1.51 (m, 1H, CH$_3$CH_2), 1.67−1.83 (m, 5H, H-4, H-5, CH$_3$CH_2), 2.18 (dd, J = 13.5, 7.8 Hz, 1H, CH_2CH═), 2.49 (dddd, J = 13.5, 6.6, 1.2, 1.2 Hz, 1H, CH_2CH═), 3.23−3.28 (m, 2H, H-6), 5.05 and 5.10 (2 m, 2H, CH_2═), 5.79 (m, 1H, CH$_2$C*H*═), 6.35 (br s, 1H, NH); ^{13}C NMR (75.4 MHz) δ 8.6 (*C*H$_3$CH$_2$), 19.6 (C-5), 28.5 (C-5), 31.0 (CH$_3$*C*H$_2$), 42.4 (C-6), 42.7 (*C*H$_2$CH═), 44.6 (C-3), 117.5 (*C*H$_2$═), 134.5 (CH$_2$*C*H═), 176.8 (NCO); $[\alpha]_D^{22}$ + 11 (*c* 0.5, MeOH); MS-EI *m*/*z* 167 (M^+, 5), 55 (100), 138 (95); HRMS calcd for $C_{10}H_{17}NO$, 167.1310; found, 167.1312.

[(3*S*,6*R*,8a*R*)-6-Ethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3, 2-*a*]pyridine-6-acetic Acid (16). A suspension of the lactam *ent*-**11a** (4.28 g, 15.02 mmol), $NaIO_4$ (12.8 g, 60.0 mmol), and $RuCl_3$ (150 mg, 0.72 mmol) in a mixture of CCl_4 (64 mL), acetonitrile (64 mL), and water (93 mL) was vigorously stirred at room temperature for 24 h. The mixture was extracted with CH_2Cl_2, and the combined organic extracts were dried and concentrated. The resulting dark residue was digested with Et_2O. The solution was filtered through Celite and concentrated to yield **16** (4.27 g, 94%): IR (film) 1650, 1730 cm^{-1}; ^1H NMR (300 MHz) δ 0.86 (t, J = 7.5 Hz, 3H, CH_3CH$_2$), 1.65−1.82 (m, 4H, CH$_3$CH_2, H-8, H-7), 1.90 (dd, J = 10.5, 3.6 Hz, 1H, H-7), 2.30 (m, 1H, H-8), 2.65 (d, J = 15.6 Hz, 1H, CH_2COO), 2.75 (d, J = 15.6 Hz, 1H, CH_2COO), 3.76 (t, J = 8.1 Hz, 1H, H-2), 4.51 (dd, J = 9.3, 8.4 Hz, 1H, H-2), 5.06 (dd, J = 8.4, 4.5 Hz, 1H, H-8a), 5.22 (t, J = 8.1 Hz, 1H, H-3), 7.23−7.38 (m, 5H, ArH); ^{13}C NMR (75.4 MHz) δ 8.3 (*C*H$_3$CH$_2$), 25.6 (C-8), 26.7 (C-7), 31.5 (CH$_3$*C*H$_2$), 42.7 (*C*H$_2$COO), 43.7 (C-6), 59.0 (C-3), 72.7 (C-2), 88.8 (C-8a), 126.0 (2CH), 127.6 (CH), 128.6 (2CH), 138.7 (C *i*), 173.7 (NCO), 174.4 (COO); mp 94−100 °C (CH_2Cl_2); $[\alpha]_D^{22}$ +95 (*c* 0.87, MeOH); MS-EI *m*/*z* 303 (M^+, 46), 104 (100), 120 (61). Anal. calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.16; H, 6.98; N, 4.49.

(3*R*)-3-Ethyl-3-(2-hydroxyethyl)-1-[(1*S*)-2-hydroxy-1-phenylethyl]piperidine (17). $LiAlH_4$ (3.0 g, 80.86 mmol) was added to a solution of **16** (2.45 g, 8.09 mmol) in THF (150 mL), and the mixture was stirred at room temperature for 28 h. The reaction was quenched by the addition of cool brine, and the resulting extracts were dried and concentrated to give **17** (1.95 g, 88%): IR (film) 2932, 3376 cm^{-1}; ^1H NMR (300 MHz) δ 0.81 (t, J = 7.5 Hz, 3H, CH_3CH$_2$), 1.36 (m, 1H, CH$_3$CH_2), 1.24−1.40 (m, 3H, CH$_3$CH_2, H-4), 1.52−1.78 (m, 4H, CH_2CH$_2$OH, H-5), 2.02 (dddm, J = 9.5, 9.5, 2.0 Hz, 1H, H-6), 2.10 (d, J = 11.0 Hz, 1H, CH_2-OH), 2.41 (d, J = 11.0 Hz, 1H, CH_2OH), 2.66 (ddd, J = 9.5, 4.5, 4.5 Hz, 1H, H-6), 3.02 (br s, 1H, OH), 3.55 (dd, J = 8.5, 5.0 Hz, 1H, H-1′), 3.68 (ddd ap, J = 7.0, 7.0, 1.2 Hz, 2H, H-2), 3.74 (dd, J = 11.0, 5.0 Hz, 1H, H-2′), 3.97 (dd, J = 11.0, 8.5 Hz, 1H, H-2′), 7.17−7.30 (m, 2H, ArH), 7.31−7.35 (m, 3H, ArH); ^{13}C NMR (75.4 MHz) δ 7.3 (*C*H$_3$CH$_2$), 22.2 (C-5), 31.1 (C-4), 33.7 (CH$_3$*C*H$_2$), 35.6 (C-3), 38.3 (*C*H$_2$CH$_2$OH), 50.0 (C-6), 58.7 (C-2), 60.1 (CH$_2$-OH), 61.2 (C-2′), 70.8 (C-1′), 127.5 (CH), 128.0 (2CH), 128.7 (2CH), 136.3 (C *i*); $[\alpha]_D^{22}$ +18 (*c* 1.15, MeOH); MS-EI *m*/*z* 278 [(M^+ + 1), 100], 246 (47), 260 (34); HRMS calcd for $C_{17}H_{27}NO_2$, 277.2041; found, 277.2032. Anal. calcd for $C_{17}H_{27}NO_2 \cdot {}^1/_3H_2O$: C, 72.06; H, 9.81; N, 4.94. Found: C, 71.75; H, 9.64; N, 4.81.

(*R*)-1-(*tert*-Butoxycarbonyl)-3-ethyl-3-(2-hydroxyethyl)piperidine (18). A solution of **17** (2.75 g, 9.93 mmol) and di-*tert*-butyldicarbonate (4.3 g, 19.86 mmol) in EtOH (400 mL) containing 10% $Pd(OH)_2$/C was hydrogenated at room temperature and atmospheric pressure for 65 h. The catalyst was removed by filtration, the solvent was evaporated, and the resulting residue was chromatographed (1:4 EtOAc−hexane) to give **18** (1.75 g, 69%): IR (film) 1692, 3444 cm^{-1}; ^1H NMR (300 MHz) δ 0.84 (t, J = 7.5 Hz, 3H, CH$_2$CH_3), 1.25 (m, 1H), 1.30−1.66 (m, 13H), 3.65

(m, 2H, CH_2OH); ^{13}C NMR (75.4 MHz) δ 7.2 (CH_2CH_3), 21.0 (CH_2), 27.1 (CH_2), 28.2 [C(CH_3)$_3$], 34.2 (CH_2), 35.1 (C-3), 36.4 (CH_2), 44.1 (CH_2), 52.3 (C-2), 58.0 (CH_2OH), 79.1 [C(CH$_3$)$_3$], 154.8 (NCO); $[\alpha]_D^{22}$ +73 (c 1.07, MeOH); MS-EI *m*/*z* 257 (M, 1), 57 (100), 113 (14), 156 (15); HRMS calcd for $C_{14}H_{27}NO_3$, 257.1991; found, 257.1979. Anal. calcd for $C_{14}H_{27}NO_3 \cdot {}^1/_4H_2O$: C, 64.21 H, 10.58; N, 5.35. Found: C, 64.48; H, 10.36; N, 5.25.

Methyl (*R*)-3-Ethylpiperidine-3-acetate (19). Piridinium dichromate (2.60 g, 7.00 mmol) was added to a solution of **18** (300 mg, 1.17 mmol) in DMF (12 mL), and the mixture was stirred at room temperature for 24 h. Cooled 1 N aqueous HCl was added, and the mixture was extracted with Et_2O. The combined organic extracts were washed with saturated aqueous NaCl, dried, and concentrated to give crude (3*R*)-1-(*tert*-butoxycarbonyl)-3-ethylpiperidine-3-acetic acid (289 mg, 92%), which was used in the next reaction without further purification: ^{1}H NMR (300 MHz) δ 0.86 (t, J = 7.5 Hz, 3H), 1.42−1.51 (m, 5H), 1.47 (br s, 9H), 2.07 (d ap, J = 10.5 Hz, 2H), 3.11−3.55 (m, 2H), 4.09 (t, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz) δ 7.4 (CH_3), 20.1 (CH_2), 27.6 (C), 28.2 (CH_3), 33.7 (CH_2), 36.1 (CH_2), 38.5 (CH_2), 43.6 (CH_2), 52.1 (CH_2), 79.5 (C), 155.1 (C), 177.0 (C). A solution of the above acid (134 mg, 0.49 mmol) and chlorotrimethylsilane (0.14 mL, 1.09 mmol) in MeOH (2 mL) was stirred at room temperature for 24 h. The solvent was evaporated, and the residue was dissolved in Et_2O and washed with 5% aqueous $NaHCO_3$ and brine. The combined organic extracts were dried and concentrated to afford **19** (70 mg, 77%): IR (film) 1734, 2929 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.94 (t, J = 7.5 Hz, 3H), 1.49 (q, J = 7.5 Hz, 2H), 1.49 (m, 1H), 1.58−1.65 (m, 3H), 2.02 (br s, 1H), 2.43 and 2.50 (2d, J = 14.0 Hz, 2H), 2.60 and 2.82 (2d, J = 13.0 Hz, 2H), 2.77 (m, 1H), 2.92 (m, 1H), 3.73 (s, 3H); ^{13}C H NMR (100 MHz) δ 7.1 (CH_3), 22.2 (CH_2), 28.7 (CH_2), 33.9 (CH_2), 35.4 (C), 38.8 (CH_2), 46.7 (CH_2), 51.0 (CH_3), 55.0 (CH_2), 172.6 (C); $[\alpha]_D^{22}$ −37 (*c* 1.0 MeOH); MS-EI *m*/*z* 184 [(M$^+$ − 1), 9], 58 (8), 111 (100), 154 (60); HRMS calcd for $C_{10}H_{19}NO_2$, 185.1416; found, 185.1411.

Methyl (*R*)-3-Ethyl-1-(3-indolylacetyl)piperidine-3-acetate (20). The mixed anhydride of pivalic acid and indole-3-acetic acid[11] (4.30 g, 24.5 mmol) was added to a suspension of piperidine **19** (1.26 g, 6.84 mmol) in THF (10 mL), and the mixture was stirred at room temperature for 3 days. The solvent was evaporated, and the resulting residue was chromatographed (3:7 EtOAc−hexane to EtOAc) to give **20** (2.02 g, 86%): IR (film) 1625, 1729, 3406 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.97 and 1.02 (t, J = 7.5 Hz, 3H), 1.45−1.56 (m, 4H), 1.68−1.72 (m, 2H), 2.35−2.45 (m, 2H), 3.30 and 3.52 (2d, J = 13.0 Hz, 2H), 3.50 (m, 1H), 3.74 (dd, J = 12.6, 10.2 Hz, 1H), 3.78 and 3.79 (s, 3H, OCH_3), 3.85−4.13 (m, 2H), 7.08 (d, J = 15.3 Hz, 1H), 7.23−7.34 (m, 2H), 7.44 (d, J = 8.1 Hz, 1H), 7.80 (t, J = 7.5 Hz, 1H), 9.11 (br s, 1H); ^{13}C NMR (75.4 MHz) δ Minor rotamer 7.3 (CH_3), 20.6 (C-5), 27.6 (CH_2), 30.7 (CH_2), 33.1 (CH_2), 36.4 (C-3), 38.0 (CH_2), 42.2 (C-6), 50.0 (C-2), 51.2 (CH_3), 108.5 (CH), 111.2 (C), 118.4 (CH), 119.0 (CH), 121.5 (CH), 122.6 (CH), 126.7 (C), 136.1 (C), 170.5 (C), 172.0 (C); Major rotamer:7.5 (CH_3), 21.4 (C-5), 28.0 (CH_2), 31.5 (CH_2), 33.5 (CH_2), 36.5 (C-3), 38.5 (CH_2), 46.7 (C-6), 51.1 (CH_3), 54.3 (C-2), 108.6 (CH), 111.2 (C), 118.5 (CH), 119.0 (CH), 121.6 (CH), 122.8 (CH), 126.9 (C), 136.1 (C), 171.1 (C), 172.1 (C); MS-EI *m*/*z* 342 [(M$^+$ −23), 6], 130 (100), 212 (1); HRMS calcd for $C_{20}H_{26}N_2NaO_3$, 365.1841; found, 365.1836.

(*R*)-3-Ethyl-1-(3-indolylacetyl)piperidine-3-acetic Acid (21). A solution of **20** (150 mg, 0.44 mmol) in MeOH (4 mL) and 5% aqueous NaOH (4.8 mL) was heated at reflux temperature for 2.5 h. The solvent was evaporated, and the resulting residue was dissolved in 2 N aqueous HCl and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated to give **21** (106 mg, 74%): IR (film) 1624, 1702, 3410 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.73 and 1.13 (t, J = 7.5 Hz, 3H), 1.22−1.53 (m, 6H), 2.08 and 2.21 (2d, J = 13.6 Hz, 2H), [2.93 (d, J = 13.6 Hz), 3.11 (ddd, J = 13.2, 10.0, 3.2 Hz), 3.20 (d, J = 13.6 Hz), 3.55 (m), 3.50 (d, J = 13.6 Hz), 3.66 (m), 3.80 (d, J = 17.2 Hz), 3.86−3.93 (m)] (6H), 6.93−7.31 (m, 4H), 7.60 (d, J = 8 Hz), [8.35 (d, J = 17.6 Hz) and 8.46 (br s)] (1H); ^{13}C NMR (75.4 MHz) δ Minor rotamer 7.3 (CH_3), 20.6 (CH_2), 27.2 (CH_2), 30.8 (CH_2), 33.4 (CH_2), 36.3 (C), 38.2 (CH_2), 42.5 (CH_2), 50.8 (CH_2), 108.0 (C), 111.3 (CH), 118.3 (CH), 119.2 (CH), 121.7 (CH), 122.8 (CH), 126.6 (C), 136.1 (C), 171.8 (C), 174.0 (C); Major rotamer 7.3 (CH_3), 21.7 (CH_2), 29.6 (CH_2), 31.2 (CH_2), 33.6 (CH_2), 36.6 (C), 38.9 (CH_2), 47.3 (CH_2), 54.4 (CH_2), 108.4 (C), 111.4 (CH), 118.6 (CH), 119.3 (CH), 122.0 (CH), 123.2 (CH), 127.0 (C), 136.1 (C), 172.0 (C), 176.0 (C); MS-EI *m*/*z* 328 [(M$^+$, −23), 7], 77 (1), 130 (100); HRMS calcd for $C_{19}H_{24}N_2NaO_3$, 351.1685; found, 351.1679.

(−)-5,16-Dioxoquebrachamine (22). A stirred suspension of **21** (301 mg, 0.92 mmol) in PPA (30 g) was heated at 90 °C for 30 min. The mixture was poured into ice and extracted with CH_2Cl_2. The dried combined organic extracts were concentrated to afford **22** (243 mg, 85%): IR (KBr) 1633, 3440 cm^{-1}; ^{1}H NMR (300 MHz) δ: 1.00 (t, J = 7.5 Hz, 3H, H-18), 1.20 (m, 1H, H-19), 1.33 (m, 1H, H-19), 1.46 (dd, J = 13.0, 8.4 Hz, 1H, H-15), 1.55 (m, 1H, H-14), 1.73−1.85 (m, 2H, H-14 and H-15), 2.34 (dd, J = 12.6, 1.5 Hz, 1H, H-17), 2.61 (ddd, J = 13.0, 13.0, 3.8 Hz, 1H, H-3), 2.98 (dd, J = 13.5, 1.2 Hz, 1H, H-21), 3.30 (d, J = 12.6 Hz, 1H, H-17), 3.89 (d, J = 13.5 Hz, 1H, H-21), 4.04 (d, J = 16.8 Hz, 1H, H-6), 4.30 (d, J = 16.8 Hz, 1H, H-6), 4.69 (ddd, J = 13.0, 3.0, 1.5 Hz, 1H, H-3), 7.13 (m, 1H, H-10), 7.34 (dd, J = 3.0, 0.9 Hz, 2H, H-9, H-11), 7.35 (d, J = 0.9 Hz, 1H, H-12), 7.63 (d, J = 8.0 Hz, H-9), 9.33 (br s, 1H, NH); ^{13}C NMR (75.4 MHz) δ 7.1 (C-18), 19.6 (C-14), 30.4 (C-19), 34.9 (C-6), 35.4 (C-15), 40.3 (C-20), 44.1 (C-3), 44.3 (C-17), 55.2 (C-21), 111.7 (C-12), 115.2 (C-7), 120.5 (C-10), 121.0 (C-9), 126.8 (C-11), 128.7 (C-8), 132.4 (C-13), 135.4 (C-2), 170.1 (NCO), 192.8 (CO); mp 140−144 °C (CH_2Cl_2); $[\alpha]_D^{22}$ −365 (c 0.55, MeOH); MS-EI *m*/*z* 310 (M$^+$, 100), 129 (91), 143 (91), 226 (36); HRMS calcd for $C_{19}H_{22}N_2O_2$, 310.1681; found, 310.1676. Anal. calcd for $C_{19}H_{22}N_2O_2 \cdot {}^1/_3H_2O$: C, 72.14; H, 7.22; N, 8.86. Found: C, 71.88; H, 7.12; N, 8.37.

(2*R*,11b*S*)-2-Allyl-2-ethyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole (23). A solution of **22** (100 mg, 0.32 mmol) in dioxane (10 mL) was added to a suspension of $LiAlH_4$ (159 mg, 4.20 mmol) in dioxane (20 mL), and the mixture was heated at reflux for 3 h. The mixture was cooled (0 °C), and water was added until the suspension turned colorless. The mixture was filtered, the filtrate was concentrated, and the resulting residue was chromatographed (1:4 EtOAc−hexane to 9:1 EtOAc−hexane) to give **23** (59 mg, 66%): ^{1}H NMR (400 MHz) δ 0.74 (t, J = 7.5 Hz, 3H, CH_3CH$_2$), 1.22−1.28 (m, 2H, CH$_3$CH_2), 1.61 (dd, J = 12.8, 5.6 Hz, 1H, H-1), 2.11 (dd, J = 12.8, 8.0 Hz, 1H, H-1), 2.23−2.30 (m, 2H, H-1′), 2.60 (m, 1H, H-5), 2.64 (d, J = 9.2 Hz, 1H, H-3), 2.73 (d, J = 9.2 Hz, 1H, H-3), 2.90 (m, 1H, H-6), 2.97 (ddd, J = 11.2, 11.2, 4.0 Hz, 1H, H-5), 3.25 (m, 1H, H-6), 4.21 (t ap, 1H, H-11), 5.07−5.13 (m, 2H, CH_2=), 5.80 (m, 1H, CH$_2$=CH), 7.05−7.12 (m, 2H, H-7 and H-8), 7.28 (d, J = 7.2 Hz, 1H, H-10), 7.46 (d, J = 7.6 Hz, 1H, H-9), 8.0 (br s, 1H, NH); ^{13}C NMR (100.6 MHz) δ 8.9 (CH$_3$CH$_2$), 17.6 (C-5), 31.6 (CH$_3$$CH_2$), 41.2 (C-1), 42.1 ($CH_2$CH=), 44.6 (C-2), 46.0 (C-6), 56.9 (C-11), 60.0 (C-3), 107.3 (C-6a), 110.7 (C-10), 117.2 (CH$_2$=), 118.0 (C-9), 119.2 (C-7), 121.2 (C-8), 127.4 (C-6b), 135.4 (CH$_2$$C$H=), 135.7 (C), 136.0 (C); MS-EI *m*/*z* 279 [(M$^+$ − 1), 74], 156 (32), 184 (30), 208 (36), 237 (100); $[\alpha]_D^{22}$ −14 (*c* 1.05, CHCl$_3$); HRMS calcd for $C_{19}H_{24}N_2$, (M$^+$ + 1) 281.1939; found, 281.2012.

(−)-16-Hydroxy-5-oxoquebrachamine (24). $NaBH_4$ (183 mg, 4.84 mmol) was added to a solution of **22** (150 mg, 0.48 mmol) in MeOH (5 mL), and the suspension was stirred at room temperature for 1.5 h. The solvent was evaporated, water was added to the resulting residue, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated to yield **24** (130 mg, 86%): IR (film) 1654, 3207 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.60 (t, J = 7.5 Hz, 3H, H-18), 0.93−1.02 (m, 2H, H-19), 1.31 (m, 1H, H-15), 1.53 (m, 1H, H-14), 1.64 (m, 1H, H-15),

1.73 (m, 1H, H-14), 1.80 (d, J = 14.0 Hz, 1H, H-17), 1.88 (dd, J = 14.0, 10.0 Hz, 1H, H-17), 2.52 (td, J = 12.6, 3.2 Hz, 1H, H-3), 2.60 (d, J = 13.6 Hz, 1H, H-21), 3.54 (d, J = 16.0 Hz, 1H, H-6), 3.68 (d, J = 16.0 Hz, 1H, H-6), 3.77 (d, J = 13.6 Hz, 1H, H-21), 4.62 (dm, J = 12.6 Hz, 1H, H-3), 5.33 (d, J = 10.0 Hz, 1H, H-16), 6.98 (t, J = 7.2 Hz, 1H, H-10), 7.05−7.16 (m, 2H, H-9, H-11), 7.23 (d, J = 8.0 Hz, 1H, H-12), 8.90 (s, 1H, NH); ^{13}C NMR (100.6 MHz) δ 7.0 (C-18), 20.5 (C-14), 33.2 (C-6), 34.7 (C-20), 35.6 (C-19), 38.5 (C-15), 42.5 (C-3), 47.2 (C-17), 51.9 (C-21), 63.9 (C-16), 103.0 (C-7), 110.8 (C-12), 117.8 (C-9), 119.2 (C-10), 121.8 (C-11), 127.8 (C-8), 134.8 (C-13), 138.2 (C-2), 169.9 (NCO); MS-EI m/z 312 (M^+, 100), 130 (69), 156 (47), 296 (37); HRMS calcd for $C_{19}H_{24}N_2O_2$, ($M^+ + 1$) 313.1910; found, 313.1910.

(−)-16-Hydroxyquebrachamine (25). A solution of **22** (80 mg, 0.26 mmol) in THF (3 mL) was added to a suspension of $LiAlH_4$ (137 mg, 3.61 mmol) in THF (5 mL), and the mixture was stirred at room temperature for 5 h. After the mixture was cooled (0 °C), and water was added until the suspension turned colorless. After filtration of the mixture, the filtrate was concentrated to give **25** (67 mg, 87%): ^{1}H NMR (400 MHz) δ 0.66 (t, J = 7.5 Hz, 3H, H-18), 0.77−0.85 (m, 2H, H-19), 0.96 (m, 1H, H-15), 1.52 (m, 1H, H-14), 1.61 (m, 1H, H-15), 1.70−1.93 (2d, J = 12 Hz, H-21), 1.81−1.98 (m, 2H, H-14, H-17), 2.14 (ddd, J = 13.0, 13.0, 1.2 Hz, 1H, H-5), 2.65 (m, 1H, H-17), 2.41 (m, 1H, H-3), 2.56 (dm, J = 13.0 Hz, 1H, H-5), 2.65 (ddd, J = 13.0, 13.0, 4.0 Hz, 1H, H-6), 2.80 (dm, J = 13.0 Hz, 1H, H-6), 2.91 (m, 1H, H-3), 4.10 (br s, 1H, OH), 6.23 (dd, J = 11.2, 2.4 Hz, 1H, H-16), 7.02−7.15 (m, 2H, H-9, H-10), 7.31 (d, J = 8.0 Hz, 1H, H-12), 7.48 (d, J = 8.0 Hz, 1H, H-11), 9.10 (br s 1H, NH); ^{13}C NMR (100.6 MHz) δ 7.4 (C-18), 24.0 (C-14), 26.1 (C-6), 35.7 (C-20), 35.8 (CH_3CH_2), 38.2 (C-15), 47.2 (C-17), 54.0 (C-3 and C-5), 66.1 (C-16), 109.6 (C-7), 110.8 (C-12), 118.2 (C-11), 118.6 (C-9), 121.2 (C-10), 127.7 (C-8), 135.7 (C-13), 140 (C-2).

(−)-Quebrachamine. $LiAlH_4$ (627 mg, 16.5 mmol) was added to a solution of **22** (170 mg, 0.55 mmol) in *N*-methylmorpholine (NMM) (40 mL), and the mixture was heated at reflux for 7 h. After the mixture (0 °C) cooled, water was added until the suspension turned colorless. Then, the mixture was filtrated through Celite, the filtrate was evaporated, and the resulting residue was chromatographed (1:4 EtOAc−hexane to EtOAc) to give (−)-quebrachamine (44 mg, 30%) and indoloindolizidine **23** (79 mg, 52%). (−)-Quebrachamine: ^{1}H NMR (500 MHz) δ 0.84 (t, J = 7.5 Hz, 3H, H-18), 1.01−1.11 (m, 2H, H-17, H-19), 1.13−1.26 (m, 3H, H-14, H-17, H-19), 1.48 (d, J = 12.0 Hz, 1H, H-21), 1.50−1.60 (m, 2H, H-14, H-15), 1.90 (ddd, J = 14.0, 7.0, 1.5 Hz, 1H, H-15), 2.21 (td, J = 11.5, 3.5 Hz, 1H, H-3), 2.30 (td, J = 11.5, 4.5 Hz, 1H, H-5), 2.40 (ddd, J = 11.5, 4.5, 3.0 Hz, 1H, H-5), 2.43 (m, 1H, H-3), 2.63 (ddd, J = 15.0, 7.5, 1.5 Hz, 1H, H-6), 2.70 (ddd, J = 15.0, 10.0, 1.5 Hz, 1H, H-6), 2.80 (ddd, J = 14.5, 4.5, 3.0 Hz, 1H, H-16), 2.90 (ddd, J = 14.5, 12.0, 5.0 Hz, 1H, H-16), 3.25 (dm, J = 12.0 Hz, 1H, H-21), 7.05 (m, 2H, H-10, H-11), 7.25 (m, 1H, H-12), 7.43 (m, 1H, H-9), 7.68 (br s, 1H, NH); ^{13}C NMR (100 MHz) δ 7.8 (C-18), 22.0 (C-6), 22.4 (C-16), 22.7 (C-14), 32.0 (C-19), 33.4 (C-15), 34.7 (C-17), 37.0 (C-20), 53.2 (C-5), 55.0 (C-3), 56.6 (C-21), 108.7 (C-7), 110.0 (C-12), 117.4 (C-9), 118.6 (C-10), 120.2 (C-11), 129.0 (C-8), 134.8 (C-13), 140.0 (C-2); $[\alpha]_D^{22}$ −99 (c 0.27, $CHCl_3$) (lit.[17] $[\alpha]_D$ −100 ($CHCl_3$)).

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Supporting Information Available: Table with ^{13}C NMR assignments for lactams **8**−**11**, copies of the ^{1}H and ^{13}C NMR spectra of compounds **8**−**25** and (−)-quebrachamine, and X-ray crystallographic data for compounds **9a**, **10a**, **12**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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