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Alkylation of Phenylglycinol-Derived Oxazolopiperidone Lactams. Enantioselective Synthesis of β-Substituted Piperidines

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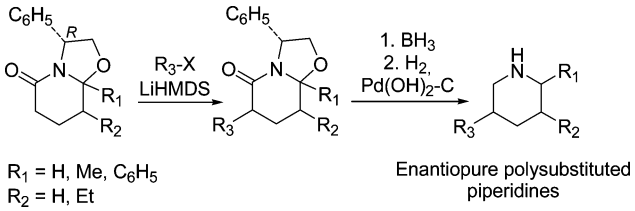

The stereochemical outcome of the alkylation of a variety of phenylglycinol-derived oxazolopiperidone lactams is studied. The influence of the configuration of the C-8a stereocenter and the effect of the substituents at the C-8 and C-8a positions on the stereoselectivity of the reaction are discussed. The synthetic utility of these alkylation reactions is illustrated with the synthesis of cis and trans 3,5-disubstituted, 2,5-disubstituted, and 2,3,5-trisubstituted enantiopure piperidines, and the indole alkaloids 20*R*- and 20*S*-dihydrocleavamine.

Introduction

Natural and synthetic piperidine derivatives display a broad range of important biological activities.[1] As a consequence, the development of general methods for their enantioselective synthesis continues to be the focus of considerable attention.[2] Over the last few years we have explored the synthetic utility of chiral bicyclic δ-lactams derived from (*R*)- or (*S*)-phenylglycinol for the enantioselective synthesis of natural products and pharmaceuticals bearing a piperidine unit as a central structural feature. With this purpose, we have prepared simple oxazolopiperidone lactams by cyclocondensation of phenylglycinol with methyl 5-oxopentanoate. We have also prepared substituted lactams by stereoselective cyclocondensation reactions of chiral amino alcohols with racemic or prochiral δ-oxoesters in processes involving a dynamic kinetic resolution of the racemic substrate or the desymmetrization of diastereotopic or enantiotopic ester chains.[3] These lactams can be subsequently elaborated by the introduction of further substituents on the piperidine ring, taking advantage of the functionalization present in the bicyclic system. Thus, they can undergo stereocontrolled amidoalkylation reactions[4] involving the cleavage of the C−O

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bond of the oxazolidine ring, nucleophilic alkylation of the lactam carbonyl group,[4b] as well as stereoselective conjugate addition,[5] Diels−Alder,[6] and dihydroxylation[7] reactions on their unsaturated derivatives. A subsequent reductive removal of the chiral auxiliary provides easy access to diversely substituted enantiopure piperidine derivatives.

In this paper we report the enolate alkylation of a variety of phenylglycinol-derived oxazolopiperidone lactams (**1**−**9**) and examine the influence of the configuration of the C-8a stereogenic center and the effect of the substituents at the C-8 and C-8a positions on the stereoselectivity of the reaction. Moreover, we illustrate the synthetic utility of these alkylation reactions with the synthesis of cis and trans 3,5-disubstituted, 2,5-disubstituted, and 2,3,5-trisubstituted enantiopure piperidines and the alkaloids 20*R*- and 20*S*-dihydrocleavamine.

The stereoselective double alkylation of chiral bicyclic lactams has been extensively studied by Meyers, who has demonstrated that this methodology constitutes a powerful tool to generate quaternary stereocenters with excellent control over the absolute stereochemistry.[8] The dialkylated lactams provide access to cyclopentenone, cyclohexenone, and hexahydroindenone systems, as well as to carboxylic acids bearing a quaternary stereocenter, which have been used for the synthesis of numerous natural and unnatural products in high enantiomeric purity. The dialkylation of enolates generated from a wide variety of chiral [3.3.0] bicyclic lactams (oxazolopyrrolidone lactams) affords products resulting from the endo facial attack of the electrophile in the second alkylation step with excellent stereoselectivity (endo/exo ratio, 10−50:1).[8] However, slight structural modifications in the oxazolidine ring (oxygen atom at the 3-position instead of the 2-position,[9] replacement of the oxygen by a methylene, or introduction of *gem*-dialkyl substituents at the 2-position[8c]) have been show to have a dramatic effect on the endo/exo selectivity. These intriguing results have stimulated Meyers et al.[10] and other authors[11] to find a rationale that explains the origin of the facial stereoselectivity of lactam enolate alkylations. Thus, steric considerations related to the concave−convex faces of the enolate, the anti-stereoelectronic

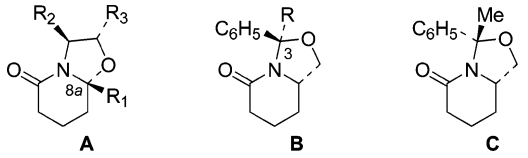

FIGURE 1. [4.3.0] Bicyclic lactams.

directing effect of the nitrogen lone pair, and the torsional strain in the transition state have been invoked to account for the observed stereoselectivities.

The alkylation of enolates derived from [4.3.0] bicyclic lactams (oxazolopiperidone lactams) has received less attention than that of their pyrrolidone homologues. Thus, the dialkylation of C-8a substituted lactams **A** (R_1 = Me, Et; Figure 1), derived from (*S*)-valinol (R_2 = *i*-Pr; R_3 = H) or (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol (R_2 = CH_2OH; R_3 = C_6H_5), was reported by Meyers et al.[12] to give the corresponding endo products in the second alkylation step in good to excellent stereoselectivities (endo/exo ratio, 3−50:1). On the other hand, Moloney et al.[13] described that the monoalkylation of the enolate of the C-3 isomeric [4.3.0] lactams **B** (R = H or Me) and **C**, derived from 6-oxopipecolic acid, predominantly affords the exo products with moderate stereoselectivity (exo/endo ratio, 2−10:1), although the efficiency of the process depends on the substitution at the hemiaminal system.

Results and Discussion

Lactams **1**−**3**, **5**−**7**, and **9** (Figure 2) were prepared as previously described, by a cyclocondensation reaction of (*R*)-phenylglycinol with the appropriate δ-oxoacid derivative (see Experimental Section). Treatment of lactam **2** under acidic conditions caused the isomerization of the C-8 and C-8a stereocenters, affording **4**. Lactam **8** was obtained from the known *O*-benzyl analogue[14] by hydrogenolysis, followed by silylation of the resulting alcohol.

The formation of the enolates of lactams **1**−**9** and subsequent alkylations were carried out under the same reaction conditions in all cases to allow a better comparison of the stereochemical

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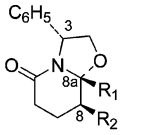
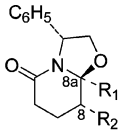


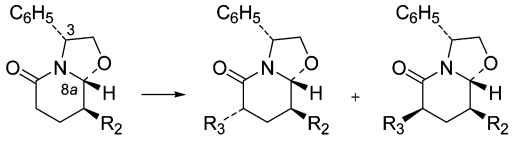
1 $R_1 = R_2 = H$
2 $R_1 = H$; $R_2 = Et$



3 $R_1 = R_2 = H$
4 $R_1 = H$; $R_2 = Et$
5 $R_1 = C_6H_5$; $R_2 = H$
6 $R_1 = C_6H_5$; $R_2 = Et$
7 $R_1 = Me$; $R_2 = H$
8 $R_1 = CH_2CH_2CH_2OTBDMS$; $R_2 = H$
9 $R_1 = Me$; $R_2 = Et$

FIGURE 2. Phenylglycinol-derived oxazolopiperidone lactams.

TABLE 1. Alkylation of cis H-3/H-8a Oxazolopiperidone Lactams



1 $R_2 = H$
2 $R_2 = Et$

a (*endo*) **b** (*exo*)

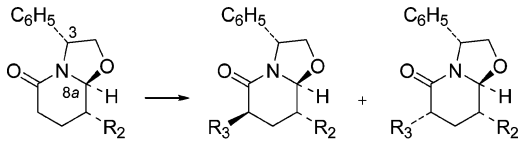
entry	lactam	R_3	product	endo/exo	yield (%)
1	**1**	Me	**10**	76:24	68
2	**1**	Et	**11**	68:32	76
3	**1**	CH_2CO_2t-Bu	**12**	88:12	75
4	**1**	$CH_2CH{=}CH_2$	**13**	48:52	80[a]
5	**1**	$CH_2CH{=}CMe_2$	**14**	45:55	49
6	**1**	$CH_2C_6H_5$	**15**	8:92	71
7	**2**	Me	**16**	71:29	94
8	**2**	CH_2CO_2t-Bu	**17**	83:17	85
9	**2**	$CH_2CH{=}CH_2$	**18**	48:52	82[a]
10	**2**	$CH_2C_6H_5$	**19**	10:90	93

[a] Variable amounts of the dialkylated product were isolated (see Experimental Section).

results. The enolates were generated by the treatment of lactams **1**−**9** with LiHMDS[15] (1.5 equiv) at −78 °C for 1 h, and then an excess (2.5 equiv) of the alkylating reagent was added to ensure a high yield of the alkylation product.[16] As can be observed in Table 1, the alkylation of lactams **1** and **2**, both with an H-3/H-8a cis relationship, with methyl iodide, ethyl iodide, or *tert*-butyl bromoacetate (entries 1−3 and 7−8) afforded the corresponding C-6-substituted lactams **10**−**12**, **16**, and **17** in good chemical yields as mixtures of diastereomers, with preferential formation of the endo products. However, the enolates of lactams **1** and **2** when treated with allyl bromide or prenyl bromide (entries 4, 5, and 9) afforded nearly equimolecular mixtures of the endo and exo isomers, **13**, **14**, and **18**, respectively, whereas with benzyl bromide (entries 6 and 10) the corresponding exo isomers **15b** and **19b** were formed in good stereoselectivity. Thus, diastereoselection in the alkylation of lactams **1** and **2** was found to be dependent on the nature of the alkylating reagent.[17]

The alkylation of the lithium enolates of lactam **3** and the 8-ethyl-substituted lactam **4**, both with an H-3/H-8a trans relationship, with methyl iodide, ethyl iodide, *tert*-butyl bromoacetate, allyl bromide, and benzyl bromide, in all cases preferentially afforded the corresponding exo isomers of lactams

TABLE 2. Alkylation of trans H-3/H-8a Oxazolopiperidone Lactams



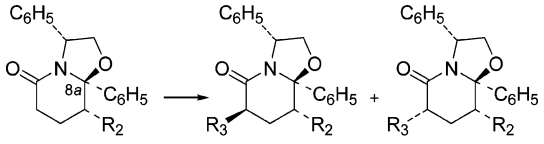
3 $R_2 = H$
4 $R_2 = Et$

a (*endo*) **b** (*exo*)

entry	lactam	R_3	product	endo/exo	yield (%)
1	**3**	Me	**20**	15:85	89
2	**3**	Et	**21**	0:100	83
3	**3**	CH_2CO_2t-Bu	**22**	32:68	45
4	**3**	$CH_2CH{=}CH_2$	**23**	10:90	65[a]
5	**3**	$CH_2C_6H_5$	**24**	23:77	65[a]
6	**4**	Me	**25**	5:95	85
7	**4**	CH_2CO_2t-Bu	**26**	23:77	77
8	**4**	$CH_2CH{=}CH_2$	**27**	17:83	78[a]
9	**4**	$CH_2C_6H_5$	**28**	31:69	72[a]

[a] Variable amounts of the dialkylated product were isolated (see Experimental Section).

TABLE 3. Alkylation of 8a-Phenyl-Substituted Oxazolopiperidone Lactams



5 $R_2 = H$
6 $R_2 = Et$

a (*endo*) **b** (*exo*)

entry	lactam	R_3	product	endo/exo	yield (%)
1	**5**	Et	**29**	59:41	69[a]
2	**5**	CH_2CO_2t-Bu	**30**	80:20	69
3	**5**	$CH_2CH{=}CH_2$	**31**	86:14	53[a]
4	**5**	$CH_2C_6H_5$	**32**	82:18	53[a]
5	**6**	Et	**33**	75:25	73
6	**6**	CH_2CO_2t-Bu	**34**	64:36	71
7	**6**	$CH_2CH{=}CH_2$	**35**	100:0	48[a]
8	**6**	$CH_2C_6H_5$	**36**	100:0	55[a]

[a] Variable amounts of the dialkylated product were isolated (see Experimental Section).

20−**28** (Table 2). In some cases (entries 2, 4, and 6), excellent stereoselectivities were observed, especially with ethyl iodide, which led to a single isomer, **21b**,[18] in good chemical yield.[19]

To gain further insight into the factors that influence the stereochemical course of the reaction, we carried out similar alkylation reactions from the lithium enolates of 8a-phenyl-substituted lactams **5** and **6** and 8a-alkyl-substituted lactams **7**, **8**, and **9**. As can be observed in Table 3, the alkylation of

(15) The alkylation of lactam **2** using LDA as the base gave poor or negligible chemical yields: (a) Micouin, L.; Varea, T.; Riche, C.; Chiaroni, A.; Quirion, J. C.; Husson, H. P. *Tetrahedron Lett*. **1994**, *35*, 2529. (b) Amat, M.; Llor, N.; Hidalgo, J.; Hernández, A.; Bosch, J. *Tetrahedron: Asymmetry* **1996**, *7*, 977. (c) For some preliminary results of the alkylations leading to **11**, **20b**, and **24b**, see: Amat, M.; Escolano, C.; Llor, N.; Lozano, O.; Gómez-Esqué, A.; Griera, R.; Bosch, J. *Arkivoc* **2005**, *9*, 115.

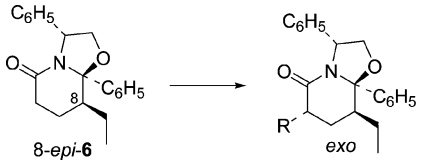
(16) Although epimerization at the C-6 stereocenter may occur to some extent as a result of the excess of base (1.5 equiv), these reaction conditions ensure an optimum balance between high chemical yield and stereoselection. Thus, when only one equivalent of base was used, substantial amounts of starting material were recovered.

(17) Differences in the stereoselectivity of enolate alkylation reactions with benzyl halides as compared with other alkylating reagents have been observed. In some cases, steric reasons have been invoked to explain these differences: Schwarz, J. B.; Meyers, A. I. *J. Org. Chem.* **1998**, *63*, 1619. See also refs 9b and 9c.

(18) For a preliminary report of this alkylation and the conversion of **21b** to (−)-*S*-decarbomethoxytetrahydrosecodine, see: Amat, M.; Pshenichnyi, G.; Bosch, J.; Molins, E.; Miravitlles, C. *Tetrahedron: Asymmetry* **1996**, *7*, 3091.

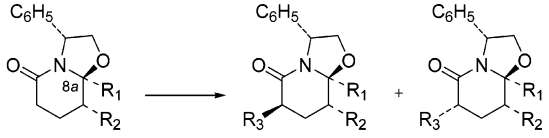
(19) Lactams **3** and **4** showed a higher tendency to undergo dialkylation than their respective isomers **1** and **2**, in particular, with the more reactive allyl and benzyl bromide alkylating reagents.

SCHEME 1. Alkylation of Lactam 8-*epi*-6



37 R = CH_2CO_2t-Bu
38 R = $CH_2CH{=}CH_2$
39 R = $CH_2C_6H_5$

TABLE 4. Alkylation of 8a-Alkyl-Substituted Oxazolopiperidone Lactams



7 R_1 = Me; R_2 = H
8 R_1 = $(CH_2)_3$OTBDMS; R_2 = H
9 R_1 = Me; R_2 = Et

entry	lactam	R_3	product	endo/exo	yield (%)
1	**7**	Et	**40**	5:95	77
2	**7**	$CH_2C_6H_5$	**41**	42:58	69[a]
3	**8**	Et	**42**	5:95	81
4	**9**	Et	**43**	5:95	66[a]
5	**9**	CH_2CO_2t-Bu	**44**	17:83	66
6	**9**	$CH_2CH{=}CH_2$	**45**	15:85	56[a]
7	**9**	$CH_2C_6H_5$	**46**	67:33	57[a]

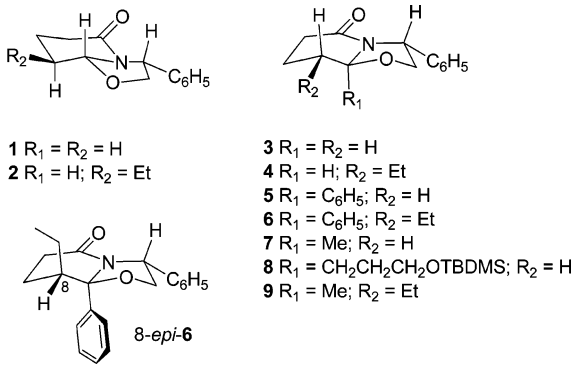
[a] Variable amounts of the dialkylated product were isolated (see Experimental Section).

lactams **5** and **6** afforded the corresponding endo isomers **29a**−**36a** as the major products, in constrast with the preferential exo facial selectivity observed in the related alkylations from the 8a-unsubstituted lactams **3** and **4**. Excellent stereoselectivities were observed in the alkylation with allyl and benzyl bromide (entries 3, 4, 7, and 8).

Interestingly, the lithium enolate of the 8-epimer of lactam **6** (8-*epi*-**6**) underwent alkylation with *tert*-butyl bromoacetate, allyl bromide, and benzyl bromide to give only the corresponding exo isomers **37**−**39** (Scheme 1), although in low yield (<40%). Thus, a change in the spatial disposition of the 8-ethyl substituent induces an opposite facial selectivity in the alkylation reaction, particularly in the reactions with allyl and benzyl bromide.

Finally, alkylation of the enolates derived from the 8a-alkyl-substituted lactams **7**−**9** take place with good to excellent stereoselectivy when using ethyl iodide, *tert*-butyl bromoacetate, and allyl bromide to give the corresponding exo products **40b** and **42b**−**45b** (Table 4), but with benzyl bromide (entries 2 and 7) the stereoselectivity was poor.

From the above results, it can be concluded that the 8-ethyl substituent in lactams **2**, **4**, **6**, and **9** does not have a significant influence on the stereoselectivity of the reaction, because the endo/exo ratios were similar to those obtained in the alkylation of the respective 8-deethyl lactams **1**, **3**, **5**, and **7**. In contrast, the presence of a phenyl substituent at the angular 8a-position in lactams **5** and **6** exerts a dramatic influence on the stereoselectivity of the alkylation, reversing the facial selectivity observed in the alkylation of the 8a-unsubstituted lactams **3** and **4**. This effect is not observed when the 8a-substituent is alkyl (lactams **7**, **8**, and **9**), except in the alkylations using the bulkier benzyl bromide.



1 R_1 = R_2 = H
2 R_1 = H; R_2 = Et

3 R_1 = R_2 = H
4 R_1 = H; R_2 = Et
5 R_1 = C_6H_5; R_2 = H
6 R_1 = C_6H_5; R_2 = Et
7 R_1 = Me; R_2 = H
8 R_1 = $CH_2CH_2CH_2$OTBDMS; R_2 = H
9 R_1 = Me; R_2 = Et

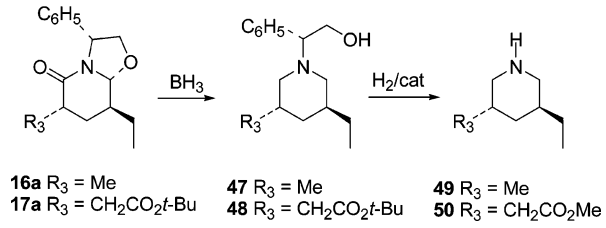
FIGURE 3. Spatial disposition of oxazolopiperone lactams **1**−**9**.

These results could be accounted for by assuming that in the enolates derived from lactams **2**, **4**, **6**, and **9** the ethyl substituent is in a pseudoequatorial position, far away from the nucleophilic carbon, while the 8a-substituent is pseudoaxially oriented (Figure 3). Consequently, steric factors associated with the size of this substituent may bias the facial approach of the electrophile. When R_1 is a methyl substituent, the alkylation takes place with the same level of exo selectivity as in C-8a unsubstituted lactams (R_1=H), except when using the sterically more demanding benzyl bromide (Table 4, entries 2 and 7). However, when a bulkier substituent, such as phenyl, occupies the 8a-position, the exo face is more shielded and the approach of the electrophile takes place preferentially by the endo face, especially with bulky alkylating reagents (Table 3). These results are also in agreement with the exo stereoselectivity observed in the alkylation of lactam 8-*epi*-**6**. In this case, both the 8-ethyl and 8a-phenyl substituents are pseudoaxially oriented in the corresponding enolate, thus shielding both the endo face and the exo face (see the X-ray of compound **39**). However, the closer spatial proximity of the ethyl group to the nucleophilic carbon of the enolate (in a 1,3-relative position) determines the facial exo selectivity.

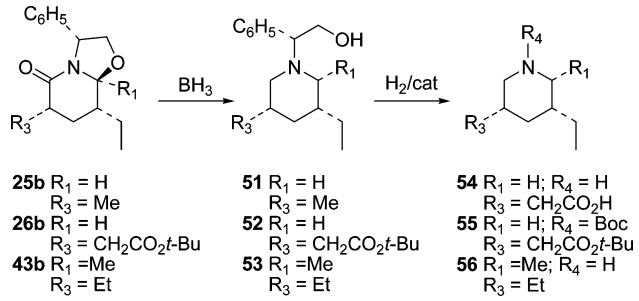
For compounds **15b**, **20b**, **21b**,[18] **32a**, **39**, and **40b**, the configuration of the stereogenic center generated in the alkylation reaction was unequivocally established by single-crystal X-ray crystallographic analysis (see Supporting Information). On the other hand, the stereochemical identity of lactams **17** and **26** was confirmed by their conversion into compounds of known configuration, as will be discussed later. The stereochemistry of the other alkylation products was indirectly assigned by the correlation of the spectroscopic data, especially from the ^{13}C NMR chemical shift of carbons C-6 and C-8. Thus, in the alkylated lactams **10**−**36** and **40**−**46**, the signals corresponding to C-6 and C-8 are more shielded (1.5−3.5 ppm) in the endo than the exo isomers (see Tables 5−8 in the Supporting Information).

The opposite endo/exo facial selectivity observed in the alkylation of the diasteromeric lactams **2** and **4** with alkyl halides and *tert*-butyl bromoacetate allows the preparation of either cis or trans enantiopure 3,5-disubstituted piperidines. Thus, borane reduction of lactams **16a** and **17a** brought about both the reduction of the carbonyl lactam and the reductive opening of the oxazolidine ring to give the corresponding piperidines **47** and **48** (Scheme 2). Hydrogenolysis of the benzylic substituent in HCl−MeOH solution gave rise to the *trans*-3,5-disubstituted piperidines **49** and **50**, which were isolated as hydrochlorides. Similarly, lactams **25b** and **26b** were reduced with borane to the corresponding *cis*-3,5-disubstituted piperidines **51** and **52**

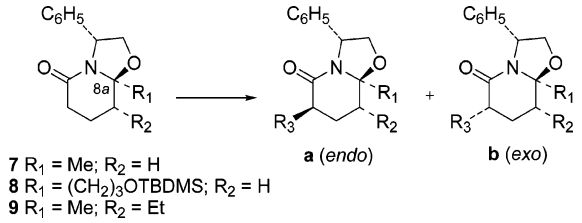
SCHEME 2. Synthesis of Enantiopure trans 3,5-Disubstituted Piperidines



SCHEME 3. Synthesis of Enantiopure cis 3,5-Disubstituted and All-cis 2,3,5-Trisubstituted Piperidines



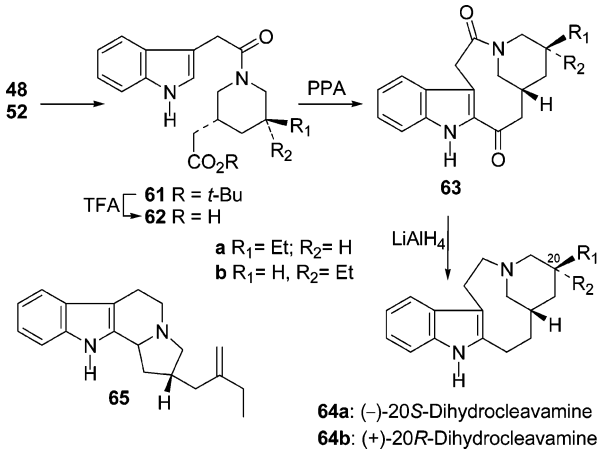
SCHEME 4. Synthesis of Enantiopure trans 2,5-Disubstituted and 2,3,5-Trisubstituted Piperidines



(Scheme 3). Debenzylation of the latter either directly under acidic conditions or via the *N*-Boc derivative **55** gave the *N*-unsubstituted piperidine **54**.

Following a similar reaction sequence, compounds resulting from the alkylation of 8a-substituted lactams **5**, **6**, and **9** were converted into enantiopure 2,5- and 2,3,5-substituted piperidines. In these series, the reductive opening of the oxazolidine ring involves the stereogenic center at the 2-position of the piperidine ring. As expected, borane reduction of the 8a-methyl substituted lactam **43b** (Scheme 3) took place with retention of the configuration[20] to give the all-cis 2-methyl-3,5-diethylpiperidine **53**, which was then debenzylated to the *N*-unsubstituted piperidine **56**. On the other hand, in accordance with previous observations on the reduction 8a-phenyl-substituted lactams,[21] borane reduction of **32a** (Scheme 4) took place with low stereoselectivity, affording a 67:33 mixture of **57a** and its 2-epimer **57b**. However, when $LiAlH_4$ or Red-Al were used in the reduction of **32a**, the *trans*-5-benzyl-2-phenylpiperidine **57a** was obtained in high stereoselectivity (the **57a**:**57b** ratio was 93:7 with $LiAlH_4$ and 95:5 with Red-Al). The major isomer **57a** was converted into the corresponding *N*-Boc derivative **59** following a conventional method. Similarly, $LiAlH_4$ reduction

SCHEME 5. Synthesis of 20*S*- and 20*R*-Dihydrocleavamine



of **33a** took place with retention of the configuration to give **58**, which was transformed as above into the enantiopure 2,3,5-trisubstituted piperidine **60**.

In summary, starting from racemic δ-ketoacid derivatives, in four synthetic steps involving cyclocondensation with (*R*)-phenylglycinol, alkylation of the resulting bicyclic lactam, hydride reduction, and catalytic hydrogenation, a variety of diversely cis and trans 3,5-disubstituted, 2,5-disubstituted, and 2,3,5-trisubstituted enantiopure piperidines can be obtained. As both enantiomers of phenylglycinol are commercially available, the above methodology provides easy access to enantiopure polysubstituted piperidines in both enantiomeric series.

Finally, to illustrate the usefulness of the methodology for the enantioselective synthesis of natural products, we have synthesized the tetracyclic indole alkaloids 20*R*- and 20*S*-dihydrocleavamine,[22] which embody a 3,5-disubstituted piperidine moiety but differ in the configuration of the piperidine carbon bearing the ethyl substituent.[23] The assembling of the skeletal framework of dihydrocleavamines from *cis*- and *trans*-5-ethyl-3-piperidineacetate derivatives required the introduction of the 2-(3-indolyl)ethyl chain on the piperidine nitrogen and the closure of the nine-membered ring by electrophilic cyclization of the carboxylate moiety on the indole 2-position. Subsequent adjustment of the oxidation level of the resulting tetracyclic keto lactams would render the target alkaloids.

Removal of the phenylethanol moiety present in the *trans*- and *cis*-5-ethyl-3-piperidineacetates **48** and **52** by hydrogenolysis using $Pd(OH)_2$ as the catalyst, in the presence of the mixed anhydride of indole-3-acetic acid and pivalic acid,[24] afforded 1-(3-indolylacetyl)piperidines **61a** and **61b**, respectively, which were converted in good chemical yields to the corresponding carboxylic acids **62a** and **62b** by treatment with TFA (Scheme 5).

Closure of the nine-membered ring from the trans isomer **62a** was carried out by heating with polyphosphoric acid (PPA) for 30 min at 90 °C to give the desired tetracyclic keto lactam **63a** in fairly good yield (64%).[25] Reduction of keto lactam **63a** with $LiAlH_4$ afforded the alkaloid (−)-20*S*-dihydrocleavamine, thus

(20) (a) Fréville, S.; Célérier, J. P.; Thuy, V. M.; Lhommet, G. *Tetrahedron: Asymmetry* **1995**, *6*, 2651. (b) Meyers, A. I.; Andres, C. J.; Resek, J. E.; Woodall, C. C.; McLaughlin, M. A.; Lee, P. H.; Price, D. A. *Tetrahedron* **1999**, *55*, 8931. (c) Agami, C.; Dechoux, L.; Hebbe, S.; Ménard, C. *Tetrahedron* **2004**, *60*, 5433.

(21) Amat, M.; Cantó, M.; Llor, N.; Bosch, J. *Chem. Commun*. **2002**, 526.

(22) For a preliminary account of this part of the work, see: Amat, M.; Escolano, C.; Lozano, O.; Llor, N.; Bosch, J. *Org. Lett*. **2003**, *5*, 3139.

(23) (a) Quirin, F.; Debray, M.-M.; Sigaut, C.; Thepenier, P.; Le Men-Olivier, L.; Le Men, J. *Phytochemistry* **1975**, *14*, 812. (b) van Beek, T. A.; Verpoorte, R.; Svendsen, A. B. *Tetrahedron* **1984**, *40*, 737.

(24) Szántay, C.; Bölcskei, H.; Gács-Baitz, E.; Keve, T. *Tetrahedron* **1990**, *46*, 1687.

completing the first enantioselective synthesis of this natural product. Indoloindolizidine **65** was isolated as a byproduct.[26] Taking into account that *cis*-5-ethyl-3-piperidineacetate **62b** has been previously converted into (+)-20*R*-dihydrocleavamine,[27] the above synthesis of this enantiopure piperidine constitutes an enantioselective formal total synthesis of this alkaloid.[28]

In conclusion, the enolate alkylation of the phenylglycinol-derived oxazolopiperidone lactams allows the stereoselective introduction of a variety of alkyl, benzyl, and functionalized (allyl, *tert*-butoxycarbonylmethyl) substituents at the β-position of the piperidine ring to ultimately lead to diversely substituted enantiopure piperidines. For C-8a unsubstituted lactams, the stereochemical outcome of the alkylation depends on the relative configuration of the C-8a methine carbon. The presence of an 8a-methyl group has a negligible stereochemical effect, but a bulky 8a-phenyl substituent exerts a dramatic influence on the stereoselectivity. Finally, the stereoselectivity is not affected by the presence or absence of an alkyl group at C-8.

Experimental Section

General Procedure for the Alkylation of Lactams 1−9. A solution of the lactam (1 mmol) in THF was added to a cooled (−78 °C) solution of LiHMDS (1 M in THF, 1.5 mmol) in THF. After stirring the solution at −78 °C for 1 h, the alkylating reagent (2.5−2.7 mmol) was added, and stirring was continued for an additional 2 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.

***tert*-Butyl [3*R*,6*R*(and 6*S*),8a*R*]-5-Oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine-6-acetate (12a and 12b).** Following the general procedure, lactam **1**[5a] (400 mg, 1.84 mmol) in THF (4 mL), LiHMDS (2.76 mL, 2.76 mmol) in THF (18 mL), and *tert*-butyl bromoacetate (0.67 mL, 4.53 mmol) afforded an 88:12 (calculated by ^{1}H NMR) mixture of epimers **12a** and **12b** (430 mg, 75%), which were separated by flash chromatography (1:1 EtOAc−hexane to EtOAc). **12a:** IR (film) 1666, 1720 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.42 [s, 9H, $(CH_3)_3$], 1.73 (m, 1H, H-7), 1.87−2.07 (m, 2H, H-7, H-8), 2.20 (dd, *J* = 17.7, 10.0 Hz, 1H, CH_2COO), 2.35 (m, 1H, H-8), 2.69−2.76 (m, 2H, H-6, CH_2COO), 4.04 (dd, *J* = 9.0, 0.9 Hz, 1H, H-2), 4.19 (dd, *J* = 9.0, 6.6 Hz, 1H, H-2), 4.84 (d_{ap}, *J* = 7.0 Hz, 1H, H-3), 4.96 (dd, *J* = 8.7, 4.5 Hz, 1H, H-8a), 7.21−7.33 (m, 5H, ArH); ^{13}C NMR (75.4 MHz) δ 22.6 (C-7), 25.9 (C-8), 28.0 [$(CH_3)_3$], 36.6 (CH_2COO), 36.7 (C-6), 58.4 (C-3), 74.2 (C-2), 80.5 [$C(CH_3)_3$], 87.5 (C-8a), 126.1 (2CH), 127.3 (CH), 128.4 (2CH), 141.1 (C *i*), 168.8 (NCO), 171.3 (COO); mp 69−70 °C (EtOAc); $[\alpha]^{22}_D$ −8.0 (*c* 0.1, MeOH). Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.63; H, 7.75; N, 4.15. **12b:** IR (film) 1659, 1727; ^{1}H NMR (400 MHz) δ 1.40 [s, 9H, $(CH_3)_3$], 1.69 (m, 1H, H-7), 1.85 (dddd, *J* = 14.0, 13.0, 10.0, 3.2 Hz, 1H, H-8a), 2.11 (m, 1H, H-7), 2.41 (ddd, *J* = 12.0, 6.5, 3.2 Hz, 1H, H-8eq), 2.46−2.53 (m, 1H, H-6), 2.61 (dd, *J* = 17.0, 7.0 Hz, 1H, CH_2COO), 2.67 (dd, *J* = 17.0, 4.0 Hz, CH_2COO), 4.03 (dd, *J* = 9.2, 0.8 Hz, 1H, H-2), 4.19 (dd, *J* = 9.2, 6.8 Hz, 1H, H-2), 4.91 (d_{ap}, *J* = 6.8 Hz, 1H, H-3), 4.93 (dd, *J* = 8.8, 3.2 Hz, 1H, H-8a), 7.21−7.32 (m, 5H, ArH); ^{13}C NMR (100.6 MHz) δ 24.3 (C-7), 28.3 [$(CH_3)_3$], 28.6 (C-8),36.8 (CH_2COO), 38.5 (C-6), 59.2 (C-3), 74.2 (C-2), 80.9 [$C(CH_3)_3$], 89.0 (C-8a), 126.7 (2CH), 127.7 (CH), 128.7 (2CH), 141.8 (C *i*), 168.6 (NCO), 171.5 (COO). Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.49; H, 7.71; N, 4.12.

[3*R*,6*R*(and 6*S*),8a*R*]-6-Benzyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (15a and 15b). Following the general procedure, lactam **1**[5a] (400 mg, 1.84 mmol) in THF (4 mL), LiHMDS (2.76 mL, 2.76 mmol) in THF (18 mL), and benzyl bromide (0.54 mL, 4.53 mmol) afforded an 8:92 (calculated by ^{1}H NMR) mixture of epimers **15a** and **15b** (402 mg, 71%), which were separated by flash chromatography (1:1 EtOAc−hexane). **15a:** IR (film) 1655 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.69−1.86 (m, 3H, 1H-7, H-8), 2.16−2.23 (m, 1H, H-8), 2.48−2.53 (m, 1H, H-6), 2.60 (dd, *J* = 12.5, 10.0 Hz, 1H, CH_2Ph), 3.12 (dd, *J* = 12.5, 3.0 Hz, 1H, CH_2Ph), 4.04 (dd, *J* = 9.0, 1.0 Hz, 1H, H-2), 4.17 (dd, *J* = 9.0, 6.6 Hz, 1H, H-2), 4.86 (dd, *J* = 9.0, 4.0 Hz, 1H, H-8a), 4.93 (dd, *J* = 6.6, 1.0 Hz, 1H, H-3), 7.10−7.37 (m, 10H, ArH); ^{13}C NMR (75.4 MHz) δ 21.3 (C-7), 25.3 (C-8), 37.4 (CH_2Ph), 41.8 (C-6), 58.7 (C-3), 74.1 (C-2), 88.4 (C-8a), 126.2 (CH), 126.4 (2CH), 127.5 (CH), 128.4 (2CH), 128.5 (2CH), 129.0 (2CH), 139.5 (C *i* Bn), 141.4 (C *i* Ph), 169.6 (NCO); $[\alpha]^{22}_D$ −65.0 (*c* 0.5, MeOH). Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.30; H, 6.92; N, 4.56. **15b:** IR (film) 1654 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.47 (dddd, *J* = 14.0, 14.0, 11.5, 3.0 Hz, 1H, H-7ax), 1.73 (dddd, *J* = 13.1, 13.1, 10.0, 3.0 Hz, 1H, H-8ax), 1.83−1.92 (m, 1H, H-7eq), 2.32 (ddd, *J* = 12.0, 6.8, 3.5 Hz, 1H, H-8eq), 2.47 (m, 1H, H-6), 2.64 (dd, *J* = 13.6, 10.0 Hz, 1H, CH_2Ph), 3.35 (dd, *J* = 13.6, 4.0 Hz, 1H, CH_2Ph), 4.01 (dd, *J* = 9.0, 0.8 Hz, 1H, H-2), 4.14 (dd, *J* = 9.0, 6.5 Hz, 1H, H-2), 4.75 (dd, *J* = 10.0, 3.5 Hz, 1H, H-8a), 4.90 (d, *J* = 6.5 Hz, 1H, H-3), 7.15−7.32 (m, 10H, ArH); ^{13}C NMR (75.4 MHz) δ 23.6 (C-7), 28.1 (C-8), 37.7 (CH_2Ph), 43.3 (C-6), 59.1 (C-3), 73.9 (C-2), 88.7 (C-8a), 126.1 (CH), 126.3 (2CH), 127.4 (CH), 128.3 (2CH), 128.4 (2CH), 129.1 (2CH), 139.5 (C *i* Bn), 141.5 (C *i* Ph), 168.6 (NCO). Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.31; H, 7.06; N, 4.56.

[3*R*,6*S*(and 6*R*),8*S*,8a*R*)]-8-Ethyl-6-methyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (16a and 16b). Following the general procedure, lactam **2**[29] (210 mg, 0.85 mmol) in THF (2 mL), LiHMDS (1.30 mL, 1.30 mmol) in THF (9 mL), and methyl iodide (132 μL, 2.12 mmol) afforded a 71:29 (calculated by ^{1}H NMR) mixture of epimers **16a** and **16b** (210 mg, 94%), which were separated by flash chromatography (1:4 EtOAc−hexane). **16a:** IR (film) 1666 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.04 (t, *J* = 7.5 Hz, 3H, C*H*$_3$CH$_2$), 1.15 (d, *J* = 7.2 Hz, 3H, C*H*$_3$), 1.37 (m, 1H, CH$_3$C*H*$_2$), 1.64 (ddd, *J* = 14.0, 10.0, 6.5 Hz, 1H, H-7), 1.70−1.86 (m, 2H, H-7, CH$_3$C*H*$_2$), 1.88−1.98 (m, 1H, H-8), 2.44 (qd, *J* = 7.2, 4.5 Hz, 1H, H-6), 4.00 (dd, *J* = 9.0, 1.0 Hz, 1H, H-2), 4.14 (dd, *J* = 9.0, 7.0 Hz, 1H, H-2), 4.54 (d, *J* = 8.7 Hz, 1H, H-8a), 4.90 (dd, *J* = 7.0, 1.0 Hz, 1H, H-3), 7.20−7.35 (m, 5H, ArH); ^{13}C NMR (75.4 MHz) δ 11.0 (*C*H$_3$CH$_2$), 18.2 (CH$_3$), 24.6 (CH$_3$*C*H$_2$), 31.7 (C-7), 34.9 (C-6), 37.6 (C-8), 58.4 (C-3), 73.9 (C-2), 92.3 (C-8a), 125.9 (C-*o*), 127.1 (C-*p*), 128.3 (C-*m*), 141.5 (C *i*), 170.6 (NCO); $[\alpha]^{22}_D$ −28.1 (*c* 0.5, MeOH); MS-EI *m*/*z* 259 (M$^+$, 76), 104 (76), 148 (100); HMRS calcd for $C_{16}H_{21}NO_2$, 259.1572; found, 259.1573. **16b:** IR (film) 1662 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.05 (t, *J* = 7.5 Hz, 3H, C*H*$_3$CH$_2$), 1.18 (d, *J* = 7.2 Hz, 3H, CH$_3$), 1.20 (m, 1H, H-7), 1.36 (m, 1H, CH$_3$C*H*$_2$), 1.76−1.92 (m, 2H, CH$_3$C*H*$_2$, H-8), 2.11 (ddd, *J* = 13.8, 6.6, 3.0 Hz, 1H, H-7), 2.32 (m, 1H, H-6), 4.01 (dd, *J* = 9.3, 1.2 Hz, 1H, H-2), 4.13 (dd, *J* = 9.3, 6.9 Hz, 1H, H-2), 4.52 (d, *J* = 8.7 Hz, 1H, H-8a), 4.86 (dd, *J* = 6.9, 1.2 Hz, 1H, H-3), 7.23−7.30 (m, 5H, ArH); ^{13}C NMR (75.4 MHz) δ 10.9 (*C*H$_3$CH$_2$), 17.0 (CH$_3$), 24.0 (CH$_3$*C*H$_2$), 32.9 (C-7), 36.8

(25) For a discussion of the mechanism and yield of related cyclizations, see: (a) Ziegler, F. E.; Kloek, J. A.; Zoretic, P. A. *J. Am. Chem. Soc*. **1969**, *91*, 2342. (b) See also: Imanishi, T.; Nakai, A.; Yagi, N.; Hanaoka, M. *Chem. Pharm. Bull*. **1981**, *29*, 901.

(26) For the mechanism and formation of similar allylindoloindolizidines in the $LiAlH_4$ reduction of related tetracyclic nine-membered 16-oxolactams, see ref 22.

(27) Danieli, B.; Lesma, G.; Passarella, D.; Silvani, A. *Tetrahedron Lett*. **2000**, *41*, 3489.

(28) For another enantioselective synthesis, see: Kanada, R. M.; Ogasawara, K. *Tetrahedron Lett*. **2001**, *42*, 7311.

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(C-6), 40.8 (C-8), 59.0 (C-3), 73.8 (C-2), 92.6 (C-8a), 126.3 (C-*o*), 127.2 (C-*p*), 128.3 (C-*m*), 141.6 (C *i*), 169.9 (NCO); $[\alpha]^{22}_D$ −21.7 (*c* 0.5, MeOH); MS-EI *m*/*z* 259 (M^+, 65), 104 (81), 148 (100); HMRS calcd for $C_{16}H_{21}NO_2$, 259.1572; found, 259.1560.

***tert*-Butyl [3*R*,6*R*(and 6*S*),8*S*,8a*R*]-8-Ethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine-6-acetate (17a and 17b).** Following the general procedure, lactam **2**[29] (200 mg, 0.82 mmol) in THF (2 mL), LiHMDS (1.23 mL, 1.23 mmol) in THF (9 mL), and *tert*-butyl bromoacetate (0.29 mL, 2.09 mmol) afforded an 83:17 (calculated by ^{1}H NMR) mixture of epimers **17a** and **17b** (248 mg, 85%), which were separated by flash chromatography (1:4 to 3:2 EtOAc−hexane). **17a:** IR (film) 1666, 1728 cm^{-1}; ^{1}H NMR (600 MHz) δ 1.02 (t, J = 7.2 Hz, 3H, CH_3CH$_2$), 1.40 (m, 1H, CH$_3$CH_2), 1.41 [s, 9H, (CH$_3$)$_3$], 1.64 (ddd, J = 14.0, 8.4, 6.8 Hz, 1H, H-7), 1.78 (m, 1H, CH$_3$CH_2), 1.82 (ddd, J = 14.0, 7.0, 7.0 Hz, 1H, H-7), 1.94 (m, 1H, H-8), 2.18 (dd, J = 16.2, 9.0 Hz, 1H, CH$_2$COO), 2.70 (dd, J = 16.2, 5.0 Hz, 1H, CH$_2$COO), 2.77 (m, 1H, H-6), 4.02 (dd, J = 9.0, 1.0 Hz, 1H, H-2), 4.15 (dd, J = 9.0, 6.7 Hz, 1H, H-2), 4.60 (d, J = 8.4 Hz, 1H, H-8a), 4.91 (d, J = 6.7 Hz, 1H, H-3), 7.25−7.35 (m, 5H, ArH); ^{13}C NMR (75.4 MHz) δ 11.1 (*C*H$_3$CH$_2$), 25.0 (CH$_3$*C*H$_2$), 28.0 [(CH$_3$)$_3$], 29.3 (C-7), 36.6 (C-6), 37.0 (*C*H$_2$COO), 38.7 (C-8), 58.5 (C-3), 74.1 (C-2), 80.5 [*C*(CH$_3$)$_3$], 91.8 (C-8a), 126.0 (2CH), 127.2 (C-*p*), 128.3 (2CH), 141.2 (C *i*), 168.7 (NCO), 171.2 (COO); $[\alpha]^{22}_D$ −7.7 (*c* 0.5, MeOH); MS-EI *m*/*z* 303 [(M^+ − [C(CH$_3$)$_3$]), 12], 104 (84), 148 (100); HMRS calcd for $C_{21}H_{29}NO_4$, 359.2097; found, 359.2092. Anal. Calcd for $C_{21}H_{29}NO_4 \cdot {}^1/_4H_2O$: C, 69.30; H, 8.17; N, 3.85. Found: C, 69.59; H, 8.31; N, 3.85. **17b:** IR (film) 1651, 1731 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.05 (t, J = 7.6 Hz, 3H, CH_3CH$_2$), 1.37−1.43 [m, 11H, H-7, CH$_3$CH_2, (CH$_3$)$_3$], 1.81−1.90 (m, 2H, H-8, CH$_3$CH_2), 2.11 (ddd, J = 13.6, 6.0, 2.8 Hz, 1H, H-7ax), 2.53 (m, 1H, H-6), 2.60 (dd, J = 16.4, 7.2 Hz, 1H, CH$_2$COO), 2.68 (dd, J = 16.4, 3.6 Hz, 1H, CH$_2$COO), 4.02 (dd, J = 9.0, 1.2 Hz, 1H, H-2), 4.16 (dd, J = 9.0, 7.0 Hz, 1H, H-2), 4.50 (d, J = 8.8 Hz, 1H, H-8a), 4.90 (d, J = 6.5 Hz, 1H, H-3), 7.10−7.30 (m, 5H, ArH); ^{13}C NMR (75.4 MHz) δ 11.1 (*C*H$_3$CH$_2$), 24.3 (CH$_3$*C*H$_2$), 28.3 [(CH$_3$)$_3$], 30.1 (C-7), 36.9 (*C*H$_2$COO), 38.9 (C-6), 41.1 (C-8), 59.4 (C-3), 74.1 (C-2), 80.9 [*C*(CH$_3$)$_3$], 92.6 (C-8a), 126.7 (2CH), 127.6 (C-*p*), 128.7 (2CH), 141.9 (C *i*), 168.6 (NCO), 171.5 (COO); $[\alpha]^{22}_D$ −14.2 (*c* 0.5, CH$_2$Cl$_2$); MS-EI *m*/*z* 303 [(M^+ − [C(CH$_3$)$_3$]), 62], 104 (99), 148 (100); HMRS calcd for $C_{21}H_{29}NO_4$, 359.2097; found, 359.2084.

[3*R*,6*R*(and 6*S*),8*S*,8a*R*)]-6-Benzyl-8-ethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (19a and 19b). Following the general procedure, lactam **2**[29] (200 mg, 0.82 mmol) in THF (2 mL), LiHMDS (1.23 mL, 1.23 mmol) in THF (9 mL), and benzyl bromide (250 μL, 2.10 mmol) afforded a 1:9 (calculated by HPLC) mixture of epimers **19a** and **19b** (254 mg, 93%), which were separated by flash chromatography (1:4 EtOAc−hexane). **19a**: IR (film) 1651 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.95 (t, J = 7.5 Hz, 3H, CH_3CH$_2$), 1.23 (m, 1H, CH$_3$CH_2), 1.40 (m, 1H, H-7), 1.64−1.80 (m, 2H, CH$_3$CH_2, H-8), 1.82 (m, 1H, H-7), 2.54−2.68 (m, 2H, CH$_2$Ph, H-6), 3.05 (dd, J = 12.0, 3.0 Hz, 1H, CH$_2$Ph), 4.02 (dd, J = 9.0, 1.5 Hz, 1H, H-2), 4.13 (dd, J = 9.0, 6.9 Hz, 1H, H-2), 4.50 (d, J = 8.4 Hz, 1H, H-8a), 4.92 (dd, J = 6.9, 1.5 Hz, 1H, H-3), 7.10−7.32 (m, 10H, ArH); ^{13}C NMR (75.4 MHz) δ 11.0 (*C*H$_3$CH$_2$), 24.2 (CH$_3$*C*H$_2$), 27.4 (C-7), 37.7 (C-8), 38.0 (CH$_2$Ph), 42.0 (C-6), 58.9 (C-3), 74.0 (C-2), 92.5 (C-8a), 126.2 (CH), 126.4 (2CH), 217.4 (CH), 128.3 (2CH), 128.4 (2CH), 129.3 (2CH), 138.4 (C *i* Bn), 141.5 (C *i* Ph), 169.6 (NCO); $[\alpha]^{22}_D$ +58.9 (*c* 1.0, MeOH); MS-EI *m*/*z* 325 (M^+, 36), 104 (88), 148 (100); HMRS calcd for $C_{22}H_{25}NO_2$, 335.1885; found, 335.1894. **19b:** IR (film) 1651 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.94 (t, J = 7.5 Hz, 3H, CH_3CH$_2$), 1.16 (ddd, J = 13.8, 12.3, 12.3 Hz, 1H, H-7ax), 1.26 (m, 1H, CH$_3$CH_2), 1.69−1.79 (m, 2H, H-8, CH$_3$CH_2), 1.84 (ddd, J = 13.8, 6.0, 2.7 Hz, 1H, H-7eq), 2.51 (m, 1H, H-6), 2.66 (dd, J = 13.5, 9.6 Hz, 1H, CH$_2$Ph), 3.32 (dd, J = 13.5, 3.6 Hz, 1H, CH$_2$ Ph), 3.95 (dd, J = 9.0, 1.2 Hz, 1H, H-2), 4.06 (dd, J = 9.0, 7.0 Hz, 1H, H-2), 4.39 (d, J = 8.7 Hz, 1H, H-8a), 4.86 (d, J = 7.0 Hz, 1H, H-3), 7.14−7.32 (m, 10H, ArH); ^{13}C NMR (75.4 MHz) δ 10.8 (*C*H$_3$CH$_2$), 24.0 (CH$_3$*C*H$_2$), 29.4 (C-7), 37.3 (CH$_2$ Ph), 40.5 (C-8), 43.4 (C-6), 59.1 (C-3), 73.6 (C-2), 92.2 (C-8a), 126.0 (CH), 126.1 (2CH), 127.2 (CH), 128.0 (2CH), 128.2 (2CH), 129.9 (2CH), 139.3 (C *i* Bn), 141.4 (C *i* Ph), 168.4 (NCO); $[\alpha]^{22}_D$ −49.0 (*c* 1.0, MeOH); MS-EI *m*/*z* 335 (M^+, 35), 104 (100), 148 (76); HMRS calcd for $C_{22}H_{25}NO_2$, 335.1885; found, 335.1884. Anal. Calcd for $C_{22}H_{25}NO_2 \cdot {}^2/_3H_2O$: C, 76.04; H, 7.64; N, 4.03. Found: C, 76.08; H, 7.30; N, 4.11.

[3*R*,6*S*(and 6*R*),8a*S*]-6-Allyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (23a and 23b) and (3*R*,8a*S*)-6,6-Diallyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (23c). Following the general procedure, lactam **3**[5a] (680 mg, 3.13 mmol) in THF (8 mL), LiHMDS (4.69 mL, 4.69 mmol) in THF (26 mL), and allyl bromide (0.70 mL, 8.08 mmol) afforded a 1:9 (calculated by ^{1}H NMR) mixture of epimers **23a** and **23b** (520 mg, 65%) and the diallyl derivative **23c** (150 mg, 16%), which were separated by flash chromatography (3:7 EtOAc−hexane). **23a:** IR (film) 1647 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.70 (m, 1H, H-8), 1.80−1.86 (m, 2H, H-7), 2.15−2.25 (m, 2H, H-8, CH_2-CH=), 2.45 (m, 1H, H-6), 2.69 (m, 1H, CH_2CH=), 3.77 (dd, J = 9.0, 7.8 Hz, 1H, H-2), 4.47 (dd, J = 9.0, 7.8 Hz, 1H, H-2), 5.01 (dd, J = 7.8, 4.5 Hz, 1H, H-8a), 5.04−5.14 (m, 2H, CH$_2$=), 5.25 (t, J = 7.8 Hz, 1H, H-3), 5.79 (dddd, J = 16.8, 10.8, 8.4, 6.0 Hz, 1H, CH$_2$=C*H*), 7.20−7.36 (m, 5H, ArH); ^{13}C NMR (CDCl$_3$, 100.6 MHz) δ 20.6 (C-7), 25.3 (C-8), 35.6 (*C*H$_2$CH=), 39.4 (C-6), 58.2 (C-3), 72.3 (C-2), 88.3 (C-8a), 117.0 (CH$_2$=), 126.1 (2CH), 127.4 (CH), 128.6 (2CH), 136.4 (CH$_2$=*C*H), 139.5 (C *i*), 171.0 (NCO); $[\alpha]^{22}_D$ −138.8 (*c* 0.5, MeOH), MS-EI *m*/*z* 257 (M^+, 100), 104 (88), 216 (61); HMRS calcd for $C_{16}H_{19}NO_2$, 257.1416; found, 257.1414. **23b:** IR (film) 1650 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.46−1.64 (m, 2H, H-7, H-8), 1.97 (m, 1H, H-7), 2.31−2.47 (m, 3H, H-6, H-8, CH_2CH=), 2.60 (m, 1H, CH_2CH=), 3.70 (dd, J = 9.0, 8.1 Hz, 1H, H-2), 4.49 (dd, J = 9.0, 8.1 Hz, 1H, H-2), 4.98 (dd, J = 8.8, 4.5 Hz, 1H, H-8a), 5.03−5.12 (m, 2H, CH$_2$=), 5.25 (t, J = 8.1 Hz, 1H, H-3), 5.72 (m, 1H, CH$_2$=C*H*), 7.21−7.30 (m, 5H, ArH); ^{13}C NMR (CDCl$_3$, 75.4 MHz) δ 22.4 (C-7), 28.0 (C-8), 36.7 (*C*H$_2$CH=), 41.3 (C-6), 58.2 (C-3), 72.7 (C-2), 88.8 (C-8a), 117.4 (CH$_2$=), 125.7 (2CH), 127.3 (CH), 128.6 (2CH), 135.0 (CH$_2$=*C*H), 139.4 (C *i*), 170.8 (NCO); $[\alpha]^{22}_D$ −55.3 (*c* 0.5, MeOH); MS-EI *m*/*z* 257 (M^+, 98), 104 (100), 216 (71); HMRS calcd for $C_{16}H_{19}NO_2$, 257.1416; found, 257.1428. **23c:** IR (film) 1643 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.58−1.78 (m, 2H, H-7, H-8), 1.83 (td, J = 14.0, 2.7 Hz, 1H, H-7), 2.03 (dd, J = 13.5, 8.5 Hz, 1H, CH_2CH=), 2.18 (dddd, J = 12.6, 4.5, 4.5, 3.0 Hz, 1H, H-8), 2.32 (dd, J = 13.8, 7.5 Hz, 1H, CH_2CH=), 2.47 (dm, J = 13.5 Hz, 1H, CH_2CH=), 2.52 (dm, J = 13.8 Hz, 1H, CH_2CH=), 3.71 (dd, J = 9.0, 8.4 Hz, 1H, H-2), 4.47 (dd, J = 9.0, 7.8 Hz, 1H, H-2), 4.87 (dd, J = 9.0, 4.2 Hz, 1H, H-8a), 5.04−5.13 (m, 4H, 2CH$_2$=), 5.19 (t_{ap}, J = 8.1 Hz, 1H, H-3), 5.58 (dddd, J = 17.0, 10.2, 9.0, 6.0 Hz, 1H, CH$_2$=C*H*), 5.80 (dddd, J = 17.0, 9.0, 8.0, 8.0 Hz, 1H, CH$_2$=C*H*), 7.24−7.32 (m, 5H, ArH); ^{13}C NMR (CDCl$_3$, 75.4 MHz) δ 24.9 (C-7), 25.8 (C-8), 42.7 (*C*H$_2$CH=), 43.6 (*C*H$_2$CH=), 44.8 (C-6), 58.7 (C-3), 73.0 (C-2), 89.0 (C-8a), 118.2 (CH$_2$=), 118.7 (CH$_2$=), 126.1 (CH), 127.4 (C H), 128.6 (2CH), 133.7 (CH$_2$=*C*H), 134.0 (CH$_2$=*C*H), 139.6 (C *i*), 172.5 (NCO); mp 88−90 °C (Et$_2$O); $[\alpha]^{22}_D$ −14.5 (*c* 0.5, MeOH); MS-EI *m*/*z* 297 (M^+, 15), 91 (56), 104 (100); HMRS calcd for $C_{19}H_{23}NO_2$, 297.1729; found, 297.1729. Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.79; N, 4.71. Found: C, 76.62; H, 8.08; N, 4.54.

[3*R*,6*R*(and 6*S*),8*R*,8a*S*]-8-Ethyl-6-methyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (25b). Following the general procedure, lactam **4** (200 mg, 0.82 mmol) in THF (2 mL), LiHMDS (1.23 mL, 1.23 mmol) in THF (9 mL), and methyl iodide (131 μL, 2.10 mmol) afforded a 5:95 (calculated by ^{1}H NMR) mixture of epimers **25a** and **25b** (179 mg, 85%). The major isomer **25b** was separated by flash chromatography (3:7 EtOAc−hexane). **25b:** IR (film) 1651; ^{1}H NMR (300 MHz) δ 1.02 (t, J = 7.5 Hz, 3H, CH_3CH$_2$), 1.25 (d, J = 7.2 Hz, 3H, CH$_3$), 1.20−

1.25 (m, 1H, H-7), 1.34 (m, 1H, CH_3CH_2), 1.55 (m, 1H, H-8), 1.76 (m, 1H, CH_3CH_2), 2.01 (ddd, J = 13.5, 5.7, 2.7 Hz, 1H, H-7), 2.41 (m, 1H, H-6), 3.72 (dd, J = 9.0, 8.1 Hz, 1H, H-2), 4.47 (dd, J = 9.0, 8.1 Hz, 1H, H-2), 4.67 (d, J = 8.4 Hz, 1H, H-8a), 5.23 (t_{ap}, J = 7.8 Hz, 1H, H-3), 7.20−7.40 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 11.1 (CH_3CH_2), 18.4 (CH_3), 24.7 (CH_3CH_2), 31.9 (C-7), 37.2 (C-6), 41.0 (C-8), 58.3 (C-3), 72.7 (C-2), 92.9 (C-8a), 125.8 (2CH), 127.3 (CH), 128.6 (2CH), 139.6 (C *i*), 172.2 (NCO); $[\alpha]^{22}_D$ −128.7 (c 0.5, MeOH); MS-EI *m*/*z* 259 (M^+, 54), 104 (86), 148 (100); HMRS calcd for $C_{16}H_{21}NO_2$, 259.1572; found, 259.1562.

***tert*-Butyl [3*R*,6*S*(and 6*R*),8*R*,8a*S*]-8-Ethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine-6-acetate (26a and 26b).** Following the general procedure, lactam **4** (200 mg, 0.82 mmol) in THF (2 mL), LiHMDS (1.23 mL, 1.23 mmol) in THF (9 mL), and *tert*-butyl bromoacetate (0.31 mL, 2.10 mmol) afforded a 23:77 (calculated by ^{1}H NMR) mixture of epimers **26a** and **26b** (226 mg, 77%), which were separated by flash chromatography (1:4 to 3:2 EtOAc−hexane). **26a:** IR (film) 1659, 1727; ^{1}H NMR (400 MHz) δ 1.01 (t, J = 7.5 Hz, 3H, CH_3CH_2), 1.38 (m, 1H, CH_3CH_2), 1.45 [s, 9H, $(CH_3)_3$], 1.60 (m, 1H, H-8), 1.71 (td, J = 14.0, 6.8 Hz, 1H, H-7), 1.76−1.83 (m, 2H, CH_3CH_2, H-7), 2.34 (dd, J = 16.0, 11.0 Hz, 1H, CH_2COO), 2.86 (dd, J = 16.0, 3.6 Hz, 1H, CH_2COO), 2.95 (m, 1H, H-6), 3.76 (dd, J = 8.8, 8.0 Hz, 1H, H-2), 4.45 (dd, J = 8.8, 8.0 Hz, 1H, H-2), 4.69 (d, J = 8.0 Hz, 1H, H-8a), 5.20 (t, J = 8.0 Hz, 1H, H-3), 7.25−7.33 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 11.3 (CH_3CH_2), 24.7 (CH_3CH_2), 27.9 (C-7), 28.3 ([$(CH_3)_3$]), 36.9 (C-6), 38.0 (CH_2COO), 38.3 (C-8), 58.8 (C-3), 72.7 (C-2), 81.0 [$C(CH_3)_3$], 92.9 (C-8a), 126.5 (2CH), 127.8 (CH), 129.0 (2CH), 139.6 (C *i*), 170.5 (NCO), 171.7 (COO); $[\alpha]^{22}_D$ −116.9 (*c* 0.5, MeOH); MS-EI *m*/*z* 303 [(M^+ − [$C(CH_3)_3$]), 25], 104 (63), 148 (100); HMRS calcd for $C_{21}H_{29}NO_4$, 359.2097; found, 359.2106. **26b:** IR (film) 1650, 1727 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.04 (t, J = 7.5 Hz, 3H, CH_3CH_2), 1.40 (m, 1H, CH_3CH_2), 1.45 [s, 9H, $(CH_3)_3$], 1.52−1.62 (m, 2H, H-8, H-7), 1.79 (m, 1H, CH_3CH_2), 2.03 (dd, J = 10.5, 5.5 Hz, 1H, H-7), 2.60 (dd, J = 15.0, 7.0 Hz, 1H, CH_2COO), 2.65 (m, 1H, H-6), 2.75 (dd, J = 15.0, 2.4 Hz, 1H, CH_2COO), 3.71 (dd, J = 9.0, 7.8 Hz, 1H, H-2), 4.49 (dd, J = 9.0, 8.0 Hz, 1H, H-2), 4.71 (d, J = 7.8 Hz, 1H, H-8a), 5.23 (t, J = 7.8 Hz, 1H, H-3), 7.25−7.32 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 11.0 (CH_3CH_2), 24.5 (CH_3CH_2), 28.0 [$(CH_3)_3$], 28.8 (C-7), 37.4 (CH_2COO), 38.8 (C-6), 40.9 (C-8), 58.4 (C-3), 72.7 (C-2), 80.5 [$C(CH_3)_3$], 92.4 (C-8a), 125.7 (2CH), 127.2 (CH), 128.5 (2CH), 139.3 (C *i*), 169.9 (NCO), 171.0 (COO); $[\alpha]^{22}_D$ −125.9 (*c* 0.5, MeOH); MS-EI *m*/*z* 303 [(M^+ − [$C(CH_3)_3$]), 33], 104 (94), 148 (100); HMRS calcd for $C_{21}H_{29}NO_4$, 359.2097; found, 360.2162.

[3*R*,6*S*(and 6*R*),8a*R*]-6-Benzyl-5-oxo-3,8*a*-diphenyl-2,3,6,7,8,-8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (32a and 32b) and (3*R*,8a*R*)-6,6-Dibenzyl-5-oxo-3,8a-diphenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (32c). Following the general procedure, lactam **5**[21] (2.01 g, 6.86 mmol) in THF (20 mL), LiHMDS (10.30 mL, 10.30 mmol) in THF (80 mL), and benzyl bromide (2.12 mL, 17.84 mmol) afforded an 82:18 (calculated by GC/MS) mixture of epimers **32a** and **32b** (1.40 g, 53%) and the dibenzyl derivative **32c** (257 mg, 8%), which were separated by flash chromatography (1:9 EtOAc−hexane to EtOAc). **32a:** IR (film) 1651 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.55−1.62 (m, 2H, H-7), 1.92 (m, 1H, H-8), 2.06 (ddd, J = 12.9, 4.2, 4.2 Hz, 1H, H-8), 2.72 (dd, J = 12.9, 10.5 Hz, 1H, CH_2Ph), 2.81 (m, 1H, H-6), 3.44 (dd, J = 13.2, 3.0 Hz, 1H, CH_2Ph), 3.68 (t, J = 9.3 Hz, 1H, H-2), 4.39 (dd, J = 9.3, 8.0 Hz, 1H, H-2), 5.31 (t, J = 8.4 Hz, 1H, H-3), 7.13−7.47 (m, 15H, ArH); ^{13}C NMR (75.4 MHz) δ 19.6 (C-7), 34.7 (C-8), 37.5 (CH_2Ph), 41.2 (C-6), 61.0 (C-3), 69.5 (C-2), 97.4 (C-8a), 126.2 (CH), 126.7 (2CH), 127.5 (CH), 128.0 (2CH), 128.2 (2CH), 128.3 (2CH), 128.4 (3CH), 129.2 (2CH), 137.9 (C *i*), 139.8 (C *i*), 141.4 (C *i*), 173.4 (NCO); mp 98−100 °C (Et_2O); $[\alpha]^{22}_D$ −38.9 (*c* 0.37, MeOH); MS-EI *m*/*z* 383 (M^+, 100), 306 (55), 263 (51), 224 (93). Anal. Calcd for $C_{26}H_{25}NO_2$: C, 81.43; H, 6.57; N, 3.65. Found: C, 81.52; H, 6.62; N, 3.65. **32b:** IR (film) 1654 cm^{-1}; ^{1}H NMR (300 MHz, representative peaks) δ 1.56−1.64 (m, 2H, H-7), 1.95 (ddd, J = 13.2, 13.2, 4.2 Hz, 1H, H-8), 2.14 (m, 1H, H-8), 2.79 (m, 1H, H-6), 3.00 (dd, J = 13.2, 3.8 Hz, 1H, CH_2Ph), 3.30 (dd, J = 13.6, 7.4 Hz, 1H, CH_2Ph), 3.50 (t, J = 9.4 Hz, 1H, H-2), 4.37 (dd, J = 9.2, 8.0 Hz, 1H, H-2), 5.32 (ddt, J = 9.4, 8.2 Hz, 1H, H-3), 6.83−7.40 (m, 15H, ArH); ^{13}C NMR (75.4 MHz) δ 20.4 (C-7), 36.6 (C-8), 38.1 (CH_2Ph), 44.0 (C-6), 60.7 (C-3), 69.5 (C-2), 97.3 (C-8a), 126.4 (CH), 126.9 (2CH), 127.2 (CH), 127.5 (CH), 128.0 (CH), 128.3 (CH), 130.2 (CH), 137.9 (C *i*), 138.4 (C *i*), 141.4 (C *i*), 172.7 (NCO); MS-EI *m*/*z* 383 (M^+, 58), 306 (31), 263 (30), 224 (60), 120 (52); HMRS calcd for $C_{26}H_{25}NO_2$, 383.1885; found, 383.1874. **32c:** IR (film) 2929, 1652 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.50 (ddd, J = 14.4, 3.5, 3.5 Hz, 1H, H-7), 1.68 (ddd, J = 12.4, 12.4, 5.2 Hz, 1H, H-7), 1.80 (ddd, J = 12.4, 12.4, 2.8 Hz, 1H, H-8), 1.90 (m, 1H, H-8), 2.40, 3.45 (2d, J = 12.8 Hz, 2H, CH_2Ph), 3.04, 3.42 (2d, J = 12.4 Hz, 2H, CH_2Ph), 3.44 (t, J = 9.2 Hz, 1H, H-2), 4.27 (t, J = 9.2, 8.0 Hz, 1H, H-2), 5.32 (dd, J = 9.6, 8.4 Hz, 1H, H-3), 6.38 (d, J = 6.8 Hz, 1H, ArH), 6.93−7.33 (m, 19H, ArH); ^{13}C NMR (75.4 MHz) δ 21.2 (C-7), 33.6 (C-8), 44.4 (CH_2-Ph), 44.8 (CH_2Ph), 48.5 (C-6), 60.9 (C-3), 69.1 (C-2), 97.2 (C-8a), 126.6 (CH), 126.8 (CH), 126.9 (CH), 127.3 (CH), 127.7 (CH), 127.8 (2CH), 128.0 (2CH), 128.1 (2CH), 128.3 (2CH), 128.4 (2CH), 131.0 (2CH), 131.5 (3CH), 137.2 (C *i*), 137.5 (C *i*), 137.7 (C *i*), 141.3 (C *i*), 175.2 (NCO); mp 119−122 °C (Et_2O); $[\alpha]^{22}_D$ +54.3 (*c* 1.33, CH_2Cl_2). Anal. Calcd for $C_{33}H_{21}NO_2 \cdot {}^1/_4H_2O$: C, 82.90; H, 6.64; N, 2.93. Found: C, 82.93; H, 6.60; N, 2.90.

[3*R*,6*R*(and 6*S*),8*R*,8a*R*]-6,8-Diethyl-5-oxo-3,8*a*-diphenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (33a and 33b) and (3*R*,8*R*,8a*R*)-6,6,8-Triethyl-5-oxo-3,8a-diphenyl-2,3,6,7,8,-8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (33c). Following the general procedure, lactam **6**[21] (1.95 g, 6.07 mmol) in THF (18 mL), LiHMDS (9.1 mL, 9.1 mmol) in THF (80 mL), and ethyl iodide (1.27 mL, 15.8 mmol) afforded a 75:25 (calculated by GC/MS) mixture of epimers **33a** and **33b** (1.54 g, 73%), traces of **33c**, and recovered lactam **6** (461 mg), which were separated by flash chromatography (1:9 EtOAc−hexane to EtOAc). **33a:** IR (film) 1651 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.62 (m, 1H, CH_3CH_2), 0.94 (t, J = 7.5 Hz, 3H, CH_3CH_2), 1.00 (t, J = 7.6 Hz, 1H, CH_3CH_2), 1.53 (d_{ap}, J = 13.5, 13.5, 8.5 Hz, 1H, H-7), 1.64−1.85 (m, 4H, H-7, H-8, $2CH_3CH_2$), 1.98 (m, 1H, CH_3CH_2), 2.59 (ddd, J = 8.7, 8.7, 3.9 Hz, 1H, H-6), 3.65 (t, J = 9.3 Hz, 1H, H-2), 4.40 (dd, J = 9.3, 8.1 Hz, 1H, H-2), 5.23 (t, J = 8.7 Hz, 1H, H-3), 6.94−6.99 (m, 2H, ArH), 7.10−7.15 (m, 3H, ArH), 7.36−7.44 (m, 5H, ArH); ^{13}C NMR (75.4 MHz) δ 11.6 ($2CH_3CH_2$), 23.0 (CH_3CH_2), 25.4, 25.7 (CH_3CH_2, C-7), 40.7 (C-6), 45.6 (C-8), 61.3 (C-3), 70.3 (C-2), 99.2 (C-8a), 127.3 (CH), 127.7 (2CH), 127.8 (2CH), 128.0 (2CH), 128.1 (2CH), 128.4 (CH), 138.0 (C *i*), 138.2 (C *i*), 173.2 (NCO); mp 72−74 °C (EtOAc−hexane); MS-EI *m*/*z* 349 (M^+, 10), 293 (30), 224 (100). Anal. Calcd for $C_{23}H_{27}NO_2$: C, 79.05; H, 7.79; N, 4.01. Found: C, 79.01; H, 7.78; N, 3.79. **33b:** IR (film) 1652 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.60 (m, 1H, H-7), 0.93 (t, J = 7.6 Hz, 3H, CH_3CH_2), 1.03 (t, J = 7.6 Hz, 1H, CH_3CH_2), 1.20 (m, 1H, CH_3CH_2), 1.64 (m, 1H, CH_3CH_2), 1.75 (m, 1H, H-7), 1.83 (m, 1H, H-8), 1.91 (m, 1H, CH_3CH_2), 2.15 (m, 1H, CH_3CH_2), 2.41 (m, 1H, H-6), 3.65 (t, J = 9.2 Hz, 1H, H-2), 4.42 (dd, J = 9.2, 8.4 Hz, 1H, H-2), 5.29 (dd, J = 9.2, 8.8 Hz, 1H, H-3), 6.90−6.93 (m, 2H, ArH), 7.11−7.13 (m, 3H, ArH), 7.34−7.43 (m, 5H, ArH); ^{13}C NMR (100.6 MHz) δ 11.5 (CH_3CH_2), 11.8 (CH_3CH_2), 23.1 (C-7), 26.3 (CH_3CH_2), 26.5 (CH_3CH_2), 44.1 (C-6), 46.6 (C-8), 61.0 (C-3), 70.2 (C-2), 99.1 (C-8a), 127.2 (CH), 127.5 (2CH), 127.7 (2CH), 128.1 (2CH), 128.4 (CH), 128.5 (2CH), 138.0 (C *i*), 138.5 (C *i*), 173.5 (NCO); $[\alpha]^{22}_D$ +44.6 (*c* 0.13, MeOH); MS-EI *m*/*z* 349 (M^+, 7.5), 293 (23), 224 (73), 105 (100). Anal. Calcd for $C_{23}H_{27}NO_2 \cdot {}^2/_3H_2O$: C, 76.41; H, 7.90; N, 3.87. Found: C, 76.29; H, 7.84; N, 3.56. **33c:** ^{1}H NMR (200 MHz) δ 0.54 (m, 1H), 0.93 (t, J = 7.5 Hz, 3H, CH_3CH_2), 0.95 (t, J = 7.5 Hz, 1H, CH_3CH_2), 0.98 (t, J = 7.5 Hz, 1H, CH_3CH_2), 1.45−1.85 (m, 7H), 2.01 (dddd, J = 10.0, 10.0, 3.4, 3.4 Hz, 1H), 3.66 (t, J = 9.2 Hz, 1H, H-2), 4.41 (dd, J

= 8.8, 8.2 Hz, 1H, H-2), 5.30 (t, J = 9.2 Hz, 1H, H-3), 6.91−6.96 (m, 2H, ArH), 7.09−7.13 (m, 3H, ArH), 7.33−7.38 (m, 3H, ArH), 7.46−7.51 (m, 2H, ArH); ^{13}C NMR (50.4 MHz) δ 9.2 (CH_3), 9.3 (CH_3), 11.6 (CH_3), 23.3 (CH_2), 29.4 (CH_2), 30.6 (CH_2), 31.7 (CH_2), 44.0 (CH), 45.7 (C), 61.0 (CH), 70.0 (CH_2), 99.3 (C), 127.0 (CH), 127.6 (CH), 128.0 (CH), 128.2 (CH), 128.5 (CH), 138.0 (C), 138.6 (C), 176.4 (C); MS-EI m/z 377 (M^+, 13), 349 (13), 292 (13), 224 (100); HMRS calcd for $C_{25}H_{31}NO_2$, 377.2354; found, 377.2350.

[3*R*,6*R*(and 6*S*),8a*S*]-6-Ethyl-8a-methyl-5-oxo-3-phenyl-2,3,6,-7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (40a and 40b). Following the general procedure, lactam **7**[30] (300 mg, 1.30 mmol) in THF (5 mL), LiHMDS (1.95 mL, 1.95 mmol) in THF (10 mL), and ethyl iodide (0.27 mL, 3.38 mmol) afforded a 5:95 (calculated by ^{1}H NMR) mixture of epimers **40a** and **40b** (259 mg, 77%), which were separated by flash chromatography (1:1 EtOAc−hexane). **40a:** ^{1}H NMR (300 MHz, representative peaks) δ 0.99 (t, J = 7.5 Hz, 3H), 3.96 (dd, J = 9.0, 7.5 Hz, 1H), 4.44 (t, J = 8.4 Hz, 1H), 5.33 (t, J = 6.9 Hz, 1H), 7.15−7.34 (m, 5H, ArH); ^{13}C NMR (75.4 MHz) δ 11.9 (CH_3), 21.7 (CH_2), 24.0 (CH_3), 24.3 (CH_3), 33.5 (CH_2), 40.4 (CH), 59.0 (CH), 69.9 (CH_2), 93.9 (C), 125.6 (CH), 127.1 (CH), 128.5 (2CH), 140.0 (C *i*), 172.3 (NCO). **40b:** IR (film) 2960, 2876, 1646 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.99 (t, J = 7.5 Hz, 3H), 1.45 (s, 3H), 1.65−1.79 (m, 3H), 1.96 (m, 1H), 2.07 (m, 1H), 2.21 (m, 1H), 2.38 (m, 1H), 3.93 (t, J = 8.7 Hz, 1H), 4.52 (t, J = 8.7 Hz, 1H), 5.39 (t, J = 8.7 Hz, 1H), 7.14−7.36 (m, 5H, ArH); ^{13}C NMR (75.4 MHz) δ 10.7 (CH_3), 22.7 (CH_2), 23.5 (CH_3), 25.9 (CH_2), 34.8 (CH_2), 42.7 (CH), 58.4 (CH), 69.6 (CH_2), 93.7 (C), 125.0 (CH), 126.9 (CH), 128.4 (2CH), 140.0 (C *i*), 172.1 (NCO); $[\alpha]^{22}_D$ −117.5 (*c* 0.69, MeOH).

[3*R*,6*R*(and 6*S*),8a*R*]-8a-[3-(*tert*-Butyldimethylsilyl)propyl]-6-ethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (42a and 42b) and (3*R*,8a*R*)-8a-[3-(*tert*-Butyldimethylsilyl)propyl]-6,6-diethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (42c). Following the general procedure, lactam **8** (200 mg, 0.52 mmol) in THF (3 mL), LiHMDS (0.78 mL, 0.78 mmol) in THF (8 mL), and ethyl iodide (0.11 mL, 1.35 mmol) afforded a 5:95 (calculated by GC/MS) mixture of epimers **42a** and **42b** (175 mg, 81%) and recovered lactam **8** (26 mg), which were separated by flash chromatography (1:4 EtOAc−hexane). **42a:** ^{1}H NMR (300 MHz) δ −0.03 (s, 3H, $SiCH_3$), −0.01 (s, 3H, $SiCH_3$), 0.82 [s, 9H, $SiC(CH_2)_3$], 0.98 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.44−2.02 (m, 9H, CCH_2, $CH_2CH_2CH_2OSi$, H-7, H-8, CH_2CH_3), 2.22 (m, 1H, CCH_2), 2.31 (m, 1H, H-6), 3.54 (t, J = 6.3 Hz, 2H, CH_2OSi), 3.88 (dd, J = 9.0, 7.8 Hz, 1H, H-2), 4.42 (t, J = 8.4, 1H, H-2), 5.32 (t, J = 8.1 Hz, 1H, H-3), 7.18−7.33 (m, 5H, ArH); ^{13}C NMR (75.4 MHz) δ −5.3 ($SiCH_3$), 11.8 (CH_3CH_2), 18.2 [$C(CH_3)_3$], 21.6 (CH_3CH_2), 24.2 (C-7), 25.8 [$C(CH_3)_3$], 27.4 (CH_2CH_2OSi), 31.7 (C-8), 30.0 (CCH_2), 40.6 (C-6), 59.0 (C-3), 62.4 (CH_2OSi), 69.4 (C-2), 95.8 (C-8a), 125.6 (2CH), 127.0 (CH), 128.4 (2CH), 140.0 (C), 172.6 (NCO). **42b:** IR (film) 2954, 2858, 1651 cm^{-1}; ^{1}H NMR (300 MHz) δ −0.04 (s, 6H, $SiCH_3$), 0.80 [s, 9H, $C(CH_3)_3$], 0.99 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.47−1.61 (m, 4H, CH_2CH_2OSi, CCH_2, H-7), 1.71 (m, 1H, CH_2CH_3), 1.76−1.82 (m, 2H, H-8), 1.91 (m, 1H, CH_2CH_3), 1.97 (m, 1H, H-7), 2.34 (m, 2H, $CH_2CH_2CH_2OSi$, H-6), 3.54 (ddd, J = 5.7, 5.7, 3.5 Hz, 2H, CH_2OSi), 3.82 (t, J = 8.5 Hz, 1H, H-2), 4.50 (t, J = 8.5, 1H, H-2), 5.37 (t, J = 8.4 Hz, 1H, H-3), 7.12 (d, J = 7.5 Hz, 2H, ArH), 7.22 (d, J = 7.2 Hz, 1H, ArH), 7.26−7.33 (m, 2H, ArH); ^{13}C NMR (75.4 MHz) δ −5.45 and −5.43 ($SiCH_3$), 10.8 (CH_3CH_2), 18.0 [$C(CH_3)_3$], 22.3 (CH_3CH_2), 25.7 [$C(CH_3)_3$], 26.1 (C-7), 27.1 (CH_2CH_2OSi), 30.4 (C-8), 30.7 (CCH_2), 42.9 (C-6), 58.5 (C-3), 62.2 (CH_2OSi), 69.6 (C-2), 95.6 (C-8a), 125.1 (2CH), 126.9 (CH), 128.4 (2CH), 140.0 (C), 172.3 (NCO); $[\alpha]^{22}_D$ −70 (*c* 0.84, MeOH); MS-EI m/z 360 [(M^{+-} − C_4H_9), 2], 282 (2), 244 (100), 224 (19). In some experiments, traces of the dialkylated product **42c** were isolated: IR (film) 2956, 1649 cm^{-1}; ^{1}H NMR (300 MHz) δ −0.0 (s, 6H), 0.85 (s, 9H), 0.92 (t, J = 7.2 Hz, 3H), 0.96 (t, J = 7.2 Hz, 3H), 1.45−1.91 (m, 11H), 2.27 (ddd, J = 12.6, 3.3, 3.3 Hz, 1H), 3.59 (m, 2H), 3.83 (t, J = 8.7 Hz, 1H), 4.49 (t, J = 9.0 Hz, 1H), 5.36 (t, J = 8.7, 1H), 7.18−7.34 (m, 5H, ArH); ^{13}C NMR (75.4 MHz) δ 9.17 and 9.09 (CH_3), 18.1 (C), 25.1 (CH_2), 25.8 (CH_3), 27.3 (CH_2), 29.0 (CH_2), 30.7 (CH_2), 31.4 (CH_2), 32.0 (CH_2), 45.7 (C), 59.1 (CH), 62.3 (CH_2), 69.7 (CH_2), 95.7 (C), 125.3 (2CH), 126.9 (CH), 128.5 (2CH), 140.2 (C), 174.8 (C); MS-EI m/z 417 [(M^{+-} − C_2H_4), 1], 388 (3), 310 (2), 272 (100), 252 (6).

[3*R*,6*R*(and 6*S*),8*R*,8a*S*]-6,8-Diethyl-8a-methyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (43b) and (3*R*,8*R*,8a*S*)-6,6,8-Triethyl-8a-methyl-5-oxo-3-phenyl-2,3,6,7,8,-8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (43c). Following the general procedure, lactam **9**[3a] (270 mg, 1.04 mmol) in THF (3 mL), LiHMDS (1.56 mL, 1.56 mmol) in THF (10 mL), and ethyl iodide (0.17 mL, 2.12 mmol) afforded a 5:95 (calculated by GC/MS) mixture of epimers **43a** and **43b** (197 mg, 66%) and the dialkylated product **43c** (19 mg, 6%), which were separated by flash chromatography (3:7 EtOAc−hexane to EtOAc). **43a:** IR (film) 1654 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.98 (t, J = 7.2 Hz, 3H, CH_3CH_2), 1.01 (t, J = 7.2 Hz, 3H, CH_3CH_2), 1.15−1.33 (m, 4H, CH_3CH_2, CH_3), 1.45−1.70 (m, 3H, H-7, H-8, CH_3CH_2), 1.73−1.84 (m, 2H, H-7, CH_3CH_2), 1.96 (m, 1H, CH_3CH_2), 2.39 (m, 1H, H-6), 3.96 (dd, J = 8.4, 7.2 Hz, 1H, H-2), 4.38 (d, J = 8.4 Hz, 1H, H-2), 5.29 (t, J = 7.6 Hz, 1H, H-3), 7.20−7.40 (m, 5H, ArH); ^{13}C NMR (100.6 MHz) δ 11.7 (CH_3CH_2), 12.0 (CH_3CH_2), 18.7 (CH_3), 23.6 (CH_3CH_2), 24.8 (CH_3CH_2), 27.6 (C-7), 40.1 (C-6), 45.0 (C-8), 59.4 (C-3), 70.0 (C-2), 96.3 (C-8a), 125.9 (2CH), 127.4 (CH), 128.6 (2CH), 140.0 (C *i*), 172.1 (NCO); $[\alpha]^{22}_D$ −79.5 (*c* 0.43, MeOH); MS-EI m/z 287 (M^+, 6), 272 (9), 231 (27), 162 (100); HMRS calcd for $C_{18}H_{25}NO_2$, 287.1885; found, 287.1887. **43b:** IR (film) 1651 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.99 (t, J = 7.5 Hz, 3H, CH_3CH_2), 1.02 (t, J = 7.5 Hz, 3H, CH_3CH_2), 1.19−1.28 (m, 1H, CH_3CH_2), 1.34 (dd, J = 13.5, 10.5 Hz, 1H, H-7), 1.30 (s, 3H, CCH_3), 1.58 (ddd, J = 9.3, 3.5, 3.5 Hz, 1H, H-8), 1.79 (m, 2H, CH_3CH_2), 1.92 (m, 1H, CH_3CH_2), 2.04 (ddd, J = 14.0, 7.8, 3.3 Hz, 1H, H-7), 2.42 (m, 1H, H-6), 3.89 (dd, J = 9.0, 8.1 Hz, 1H, H-2), 4.49 (t, J = 9.0 Hz, 1H, H-2), 5.37 (t, J = 8.4 Hz, 1H, H-3), 7.15−7.35 (m, 5H, ArH); ^{13}C NMR (75.4 MHz) δ 10.9 (CH_3CH_2), 12.1 (CH_3CH_2), 18.8 (CH_3), 23.2 (CH_3CH_2), 26.3 (CH_3CH_2), 27.9 (C-7), 43.2 (C-6), 46.2 (C-8), 58.9 (C-3), 69.7 (C-2), 96.1 (C-8a), 125.1 (2CH), 126.9 (CH), 128.5 (2CH), 140.0 (C *i*), 172.1 (NCO); mp 76−79 °C (EtOAc−hexane); $[\alpha]^{22}_D$ −133.3 (*c* 0.52, MeOH). Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.24; H, 8.74; N, 4.73. **43c:** IR (film) 1650 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.89 (t, J = 7.5 Hz, 3H, CH_2CH_3), 0.92 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.03 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.36 (s, 3H, CH_3), 1.43−1.85 (m, 9H), 3.88 (t, J = 9.0 Hz, 1H, H-2), 4.45 (t, J = 9.0 Hz, 1H, H-2), 5.33 (t, J = 8.5 Hz, 1H, H-3), 7.19−7.34 (m, 5H, ArH); ^{13}C NMR (50.3 MHz) δ 9.2 (CH_3CH_2), 9.4 (CH_3CH_2), 12.1 (CH_3CH_2), 18.8 (CH_3), 23.4 (CH_3CH_2), 31.0, 32.0, 32.6 ($2CH_3CH_2$, C-7), 44.7 (C-8), 46.2 (C-6), 59.6 (C-3), 70.0 (C-2), 96.2 (C-8a), 125.3 (2CH), 127.0 (CH), 128.5 (2CH), 140.1 (C *i*), 174.6 (NCO); MS-EI m/z 315 (M^+, 8), 300 (17), 287 (14), 162 (100); HMRS calcd for $C_{20}H_{29}NO_2$, 315.2198; found, 315.2192.

General Procedure for BH_3−THF Reduction. BH_3−THF (1 M solution in THF, 3−6 mmol) was added to a cooled (−78 °C) solution of the bicyclic lactam (1 mmol) in THF. The mixture was stirred, basified with 2 N aqueous NaOH, and extracted with EtOAc and CH_2Cl_2. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed.

(3*S*,5*S*)-3-Ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-5-methylpiperidine (47). Following the general procedure, a mixture of BH_3−THF (3.3 mL, 3.3 mmol) and lactam **16a** (287 mg, 1.10 mmol) in THF (5 mL) was stirred at −78 °C for 2 h and at 0 °C for 4 h to give piperidine **47** (179 mg, 65%) after flash chromatography (1:4 EtOAc−hexane): IR (film) 3444 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.89 (t, J = 7.5 Hz, 3H, CH_3CH_2), 0.93 (d, J = 7.0 Hz, 3H, CH_3), 1.23 (m, 2H, H-4), 1.34 (m, 2H, CH_3CH_2), 1.62 (m, 1H, H-5), 1.90

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(m, 1H, H-3), 2.15−2.23 (m, 2H, H-2, H-6), 2.30−2.34 (m, 2H, H-2, H-6), 3.16 (br s, 1H, OH), 3.59 (dd, J = 10.5, 5.0 Hz, 1H, H-2′), 3.69 (dd, J = 10.2, 5.0 Hz, 1H, H-1′), 3.97 (t, J = 10.2 Hz, 1H, H-2′), 7.14−7.17 (m, 2H, ArH), 7.25−7.37 (m, 3H, ArH); ^{13}C NMR (75.4 MHz) δ 12.0 (CH_3), 19.1 (CH_3CH_2), 25.9 (CH_3CH_2), 27.5 (C-3), 34.9 (C-5), 37.0 (C-4), 54.4 (C-2), 57.5 (C-6), 60.3 (C-2′), 70.3 (C-1′), 127.6 (CH), 128.0 (2CH), 128.8 (2CH), 136.0 (C *i*); $[\alpha]^{22}_D$ −41.1 (*c* 1.0, MeOH); MS-EI *m*/*z* 246 [(M^+ − 1), 1], 91 (20), 216 (100); HMRS calcd for $C_{16}H_{25}NO$, 247.1936; found, 247.1584.

***tert*-Butyl (3*R*,5*S*)-5-Ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-piperidine-3-acetate (48).** Following the general procedure, a mixture of BH_3−THF (42.0 mL, 42.0 mmol) and lactam **17a** (5.0 g, 14.0 mol) in THF (82 mL) was stirred at −78 °C for 15 min and at 0 °C for 5 h to give piperidine **48** (3.68 g, 76%) after flash chromatography (1:1 EtOAc−hexane): IR (film) 1726 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.88 (t, J = 7.5 Hz, 3H, CH_3CH_2), 1.19−1.44 (m, 4H, CH_3CH_2, H-4), 1.46 (s, 9H, [$(CH_3)_3$]), 1.64 (m, 1H, H-5), 2.14−2.27 (m, 3H, H-2, H-3, H-6), 2.22 (dd, J = 16.5, 6.4 Hz, 1H, CH_2COO), 2.41 (dd, J = 16.5, 10.0 Hz, 1H, CH_2COO), 2.44−2.52 (m, 2H, H-2, H-6), 2.80 (br s, 1H, OH), 3.59 (dd, J = 10.8, 4.8 Hz, 1H, H-2′), 3.68 (dd, J = 10.4, 5.0 Hz, 1H, H-1′), 3.97 (t, J = 10.4 Hz, 1H, H-2′), 7.13−7.15 (m, 2H, ArH), 7.29−7.34 (m, 3H, ArH); ^{13}C NMR (100.6 MHz) δ 12.0 (CH_3CH_2), 26.5 (CH_3CH_2), 28.3 [$(CH_3)_3$], 30.7 (C-3), 34.5 (C-5), 35.1 (C-4), 39.2 (CH_2COO), 53.2 (C-6), 56.6 (C-2), 60.4 (C-2′), 70.5 (C-1′), 80.5 [$C(CH_3)_3$], 128.0 (CH), 128.3 (2CH), 129.1 (2CH), 135.6 (C *i*), 172.8 (COO); $[\alpha]^{22}_D$ −18.5 (*c* 0.5, MeOH); MS-EI *m*/*z* 348 [(M^+ + 1), 1], 260 (100), 316 (45); HMRS calcd for $C_{21}H_{33}NO_3$, 347.2460; found, 347.2462.

***tert*-Butyl (3*R*,5*R*)-5-Ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-piperidine-3-acetate (52).** Following the general procedure, a mixture of BH_3−THF (27.3 mL, 27.3 mmol) and lactam **26b** (1.63 g, 4.55 mol) in THF (27 mL) was stirred at −78 °C for 15 min and at room temperature for 7 h to give piperidine **52** (894 mg, 57%) after flash chromatography (4:1 EtOAc−hexane): IR (film) 1724 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.43 (q_{ap}, J = 12.0 Hz, 1H, H-4ax), 0.85 (t, J = 7.5 Hz, 3H, CH_3CH_2), 1.12 (m, 2H, CH_3CH_2), 1.23 (t, J = 11.0 Hz, 1H, H-6), 1.42−1.47 (m, 10H, H-5, [$(CH_3)_3$]), 1.80 (br d, J = 12.0 Hz, 1H, H-4), 1.90 (t, J = 10.5 Hz, 1H, H-2), 2.04−2.08 (m, 3H, H-3, CH_2COO), 2.84−2.91 (m, 2H, H-2, H-6), 3.02 (br s, 1H, OH), 3.61 (dd, J = 10.5, 5.1 Hz, 1H, H-2′), 3.73 (dd, J = 10.5, 5.1 Hz, 1H, H-1′), 4.01 (t, J = 10.5 Hz, 1H, H-2′), 7.15−7.18 (m, 2H, ArH), 7.30−7.34 (m, 3H, ArH); ^{13}C NMR (75.4 MHz) δ 11.4 (CH_3CH_2), 27.1 (CH_3CH_2), 28.1 [$(CH_3)_3$], 34.1 (C-3), 37.3 (C-4), 38.0 (C-5), 40.6 (CH_2COO), 51.5 (C-6), 58.8 (C-2), 59.8 (C-2′), 69.8 (C-1′), 80.2 [$C(CH_3)_3$], 127.7 (CH), 128.0 (2CH), 128.8 (2CH), 135.1 (C *i*), 171.7 (COO); mp 59−61 °C (EtOAc−hexane); $[\alpha]^{22}_D$ −25.0 (*c* 0.5, MeOH). Anal. Calcd for $C_{21}H_{33}NO_3$: C, 72.58; H, 9.57; N, 4.03. Found: C, 72.24; H, 9.62; N, 3.96.

(2*R*,3*R*,5*S*)-3,5-Diethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-methylpiperidine (53). Following the general procedure, a mixture of BH_3−THF (8.4 mL, 8.4 mmol) and lactam **43b** (400 mg, 1.39 mol) in THF (8 mL) was stirred at −78 °C for 15 min and at 0 °C for 6 h to give piperidine **53** (244 mg, 64%) and recovered lactam **43b** (28 mg), which were separated by flash chromatography (1:4 EtOAc−hexane): IR (film) 3444 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.61 (d, J = 6.8 Hz, 3H, CH_3), 0.77 (t, J = 7.2 Hz, 3H, CH_3CH_2), 0.77 (m, 1H, H-4), 0.89 (t, J = 7.6 Hz, 3H, CH_3CH_2), 1.04 (m, 2H, CH_3CH_2), 1.22 (m, 2H, CH_3CH_2), 1.48−1.61 (m, 3H, H-3, H-4, H-5), 2.25 (t, J = 11.6 Hz, 1H, H-6), 2.82−2.89 (m, 2H, H-2, H-6), 3.64 (m, 1H, H-1′), 3.70 (m, 1H, H-2′), 3.90 (dd, J = 10.8, 5.2 Hz, 1H, H-2′), 7.26−7.36 (m, 5H, ArH); ^{13}C NMR (100.6 MHz) δ 5.3 (CH_3C), 11.4 (CH_3CH_2), 11.6 (CH_3CH_2), 26.3 (CH_3CH_2), 27.4 (CH_3CH_2), 31.2 (C-4), 38.2 (C-5), 41.8 (C-3), 48.9 (C-6), 51.9 (C-2), 63.0 (C-2′), 67.1 (C-1′), 127.5 (CH), 128.3 (2CH), 128.4 (2CH), 140.5 (C *i*); $[\alpha]^{22}_D$ −1.2 (*c* 0.17, MeOH), MS-EI *m*/*z* 276 [(M^+ + 1), 1], 244 (100), 140 (4), 91 (12).

(2*S*,5*S*)-5-Benzyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-phenylpiperidine (57a). $LiAlH_4$ (1.39 g, 36.5 mmol) was added to a solution of lactam **32a** (1.40 g, 3.65 mmol) in THF (64 mL), and the mixture was stirred at room temperature for 15 h. The reaction was quenched by the addition of cool saturated aqueous NaCl, and the resulting mixture was extracted with EtOAc. The combined extracts were dried and concentrated, and the residue was chromatographed (EtOAc) to afford a 93:7 (calculated by GC/MS) mixture of epimers **57a** and **57b** (903 mg, 67%). Flash chromatography (1:9 EtOAc−hexane) gave the major isomer **57a:** IR (film) 3460 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.88 (m, 1H, H-4), 1.51−1.78 (m, 4H, H-3, H-6, H-4), 1.93 (m, 1H, H-5), 2.38 (dd, J = 13.5, 8.0 Hz, 1H, CH_2Ph), 2.60 (dd, J = 13.5, 6.0 Hz, 1H, CH_2Ph), 3.10 (dm, J = 11.0 Hz, 1H, H-6), 3.23 (dd, J = 11.0, 3.0 Hz, 1H, H-2), 3.35 (t, J = 2.5 Hz, 1H, H-2′), 3.97 (t_{ap}, J = 2.5 Hz, 2H, H-2′, H-1′), 6.98−7.42 (m, 15H, ArH); ^{13}C NMR (75.4 MHz) δ 30.9 (C-4), 37.2 (C-3), 38.5 (C-5), 41.1 (CH_2Ph), 51.6 (C-6), 59.3 (C-2′), 61.8 (C-1′), 65.1 (C-2), 125.9 (CH), 127.2 (CH), 127.7 (CH), 127.8 (2CH), 127.9 (2CH), 128.2 (2CH), 128.7 (2CH), 128.9 (2CH), 129.3 (2CH), 134.2 (C *i*), 139.9 (C *i*), 143.7 (C *i*); $[\alpha]^{22}_D$ −55.6 (*c* 0.41, MeOH); MS-EI *m*/*z* 372 [(M + 1), 1], 340 (100), 120 (30), 91 (70); HMRS calcd for $C_{26}H_{29}NO$, 371.2249; found, 371.2257.

(2*S*,3*R*,5*R*)-3,5-Diethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-phenylpiperidine (58). $LiAlH_4$ (910 mg, 24 mmol) was added to a solution of lactam **33a** (835 mg, 2.40 mmol) in THF (42 mL), and the mixture was stirred at room temperature for 15 h. The reaction was quenched by the addition of cool saturated aqueous NaCl, and the resulting mixture was extracted with EtOAc. The combined extracts were dried and concentrated, and the residue was chromatographed (5:95 EtOAc−hexane to EtOAc) to afford **58** (539 mg, 67%): IR (film) 3451 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.64 (t, J = 7.2 Hz, 3H, CH_3CH_2), 0.91 (t, J = 7.6 Hz, 3H, CH_3CH_2), 0.93 (m, 1H, H-4), 1.10 (m, 1H, CH_3CH_2), 1.23 (m, 1H, CH_3CH_2), 1.30 (m, 1H, CH_3CH_2), 1.51 (t, J = 11.2, 1H, H-6ax), 1.49−1.56 (m, 3H, H-3, H-6, CH_3CH_2), 1.63 (m, 1H, H-6), 1.91 (ddm, J = 12.8, 1.6 Hz, 1H, H-4), 3.05 (d, J = 9.6 Hz, 1H, H-6eq), 3.49 (dd, J = 10.4 and 5.6 Hz, 1H, H-2′), 3.53 (d, J = 2.4 Hz, 1H, H-2), 3.70 (br s, 1H, OH), 4.14 (t, J = 10.8 Hz, 1H, H-2′), 4.34 (dd, J = 11.2, 5.6 Hz, 1H, H-2′), 6.86−6.88 (m, 2H, ArH), 7.25−7.42 (m, 8H, ArH); ^{13}C NMR (100.6 MHz) δ 11.4 (CH_3CH_2), 12.0 (CH_3CH_2), 19.0 (CH_3CH_2), 27.4 (CH_3CH_2), 32.0 (C-5), 33.3 (C-4), 42.3 (C-3), 51.9 (C-6), 59.5 (C-2′), 61.0 (C-1′), 69.2 (C-2), 126.7 (CH), 127.7 (CH), 127.9 (2CH), 128.1 (2CH), 129.4 (2CH), 129.6 (2CH), 134.3 (C *i*), 141.0 (C *i*); $[\alpha]^{22}_D$ −85.0 (*c* 0.10, MeOH); MS-EI *m*/*z* 338 [(M^+ + 1), 1], 306 (100), and 91 (62); HMRS calcd for $C_{23}H_{31}NO$, 337.2406; found, 337.2401.

General Procedure for Debenzylation Reactions. A solution of the *N*-substituted piperidine in MeOH−HCl was concentrated, and the residue was dissolved in MeOH. A mixture of the resulting solution and 10% $Pd(OH)_2$/C was hydrogenated at room temperature and atmospheric pressure for 24 h. The catalyst was removed by filtration, the solvent was evaporated, and the resulting residue was washed with ether to afford the *N*-unsubstituted piperidine as the hydrochloride.

(3*S*,5*S*)-3-Ethyl-5-methylpiperidine (49). Following the general procedure, piperidine **47** (91 mg, 0.37 mmol) in MeOH (5 mL) and 10% $Pd(OH)_2$−C (25 mg) afforded **49** hydrochloride (40 mg, 66%): IR (film) 3388 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.92 (t, J = 7.5 Hz, 3H, CH_3CH_2), 1.07 (d, J = 7.0 Hz, 3H, CH_3), 1.44 and 1.51 (2m, 4H, H-4, CH_3CH_2), 1.88 (m, 1H, H-5), 2.14 (m, 1H, H-3), 2.72 (dd, J = 12.5, 7.5 Hz, 1H, H-2), 2.83 (dd, J = 12.0, 7.0 Hz, 1H, H-6), 3.10 (dd, J = 12.5, 4.0 Hz, 1H, H-2), 3.13 (dd, J = 12.0, 4.0 Hz, 1H, H-6), 9.40 (br s, 2H, NH_2); ^{13}C NMR (100.6 MHz) δ 11.4 (CH_3CH_2), 18.4 (CH_3), 24.6 (C-3), 25.0 (CH_3CH_2), 31.4 (C-5), 34.6 (C-4), 47.6 (C-6), 49.4 (C-2); $[\alpha]^{22}_D$ − 0.7 (*c* 4.0, CH_2Cl_2).

(2*R*,3*R*,5*S*)-3,5-Diethyl-2-methylpiperidine (56). Following the general procedure, piperidine **53** (40 mg, 0.14 mmol) in MeOH (5 mL) and 10% $Pd(OH)_2$−C (16 mg) afforded **56** hydrochloride (16

mg, 58%): IR (film) 1728 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.94 (t, J = 7.2 Hz, 3H, CH_3CH$_2$), 0.95 (t, J = 7.2 Hz, 3H, CH_3CH$_2$), 1.03 (m, 1H), 1.21 (d, J = 7.2 Hz, 3H, CH$_3$), 1.25−1.43 (m, 4H), 1.56−1.84 (m, 3H), 2.72 (t, J = 13.0 Hz, 1H), 3.10 (ddd, J = 13.0, 4.2, 1.8 Hz, 1H), 3.65 (m, 1H); ^{13}C NMR (75.4 MHz) δ 9.4 (CH$_3$), 11.2 (*C*H$_3$CH$_2$), 11.5 (*C*H$_3$CH$_2$), 26.2 (CH$_2$), 27.4 (CH$_2$), 30.3 (CH$_2$), 36.8 (C-6), 40.0 (C-5), 43.6 (C-3), 52.3 (C-2); [α]$^{22}_D$ +117.5 (*c* 0.04, MeOH); MS-EI *m*/*z* 155 (M$^+$, 10), 140 (100), 126 (41), 84 (31); HMRS calcd for $C_{10}H_{21}N$, 155.1674; found, 155.1676.

General Procedure for Debenzylation with Introduction of a Boc Protecting Group. A solution of the *N*-substituted piperidine (1 mmol) and di-*tert*-butyl dicarbonate (1.8 mmol) in EtOAc containing 10% Pd(OH)$_2$−C was hydrogenated at room temperature and atmospheric pressure for 48−72 h. The catalyst was removed by filtration, the solvent was evaporated, and the resulting residue was chromatographed.

(2*S*,5*S*)-5-Benzyl-1-(*tert*-butoxycarbonyl)piperidine (59). Following the general procedure, piperidine **57a** (650 mg, 1.74 mmol), di-*tert*-butyl dicarbonate (685 mg, 3.14 mmol) in EtOAc (110 mL), and 10% Pd(OH)$_2$−C (284 mg) gave the *N*-Boc derivative **59** (460 mg, 75%) after flash chromatography (1:4 EtOAc−hexane): IR (film) 3026, 1801, 1685 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.39 (m, 1H, H-3), 1.47 [s, 9H, (CH$_3$)$_3$], 1.65 (m, 1H, H-4), 1.90 (m, 1H, H-5), 2.06 (ddd, J = 12.4, 8.4, 4.0 Hz, 1H, H-3), 2.17 (m, 1H, H-4), 2.66 (dd, J = 13.6, 7.6 Hz, 1H, CH$_2$Ph), 2.81 (dd, J = 13.6, 8.0 Hz, 1H, CH$_2$Ph), 2.97 (dd, J = 13.6, 4.0 Hz, 1H, H-6), 3.90 (d, J = 13.6 Hz, 1H, H-6), 5.40 (t, J = 4.4 Hz, 1H, H-2), 7.17−7.35 (m, 10H, ArH);^{13}C NMR (100.6 MHz) δ 23.7−23.8 (C-3, C-4), 28.4 [(CH$_3$)$_3$], 35.5 (C-5), 37.5 (CH$_2$Ph), 42.9 (C-6), 53.5 (C-2), 79.7 [*C*(CH$_3$)$_3$], 125.9 (CH), 126.3 (2CH), 126.4 (CH), 128.2 (2CH), 128.5 (2CH), 129.1 (2CH), 140.6 (C *i*), 140.9 (C *i*), 156.1 (NCO*)*.

(2*S*,3*R*,5*R*)-1-(*tert*-Butoxycarbonyl)-3,5-diethyl-2-phenylpiperidine (60). Following the general procedure, piperidine **58** (375 mg, 1.11 mmol), di-*tert*-butyl dicarbonate (434 mg, 2.0 mmol) in EtOAc (70 mL), and 10% Pd(OH)$_2$−C (180 mg) gave the *N*-Boc derivative **60** (257 mg, 73%) after flash chromatography (1:4 EtOAc−hexane): IR (film) 1689 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.86 (t, J = 7.6 Hz, 3H, CH_3CH$_2$), 0.96 (t, J = 7.6 Hz, 3H, CH_3-CH$_2$), 1.01 (m, 1H, CH$_3$CH_2), 1.23 (m, 1H, CH$_3$CH_2), 1.35 [s, 9H, (CH$_3$)$_3$], 1.36 (m, 1H, CH_3CH$_2$), 1.49−1.57 (m, 2H, CH$_3$CH_2, H-4), 1.70 (m, 1H, H-4), 1.81 (m, 1H, H-5), 2.01 (m, 1H, H-3), 3.39 (d$_{ap}$, J = 12.0 Hz, 1H, H-6), 3.63 (d$_{ap}$, J = 10.4 Hz, 1H, H-6), 5.14 (br s, 1H, H-2), 7.20−7.30 (m, 3H, ArH), 7.39 (d$_{ap}$, 2H, ArH); ^{13}C NMR (100.6 MHz) δ 11.8 (CH$_3$), 12.1 (CH$_3$), 25.0 (CH$_3$*C*H$_2$), 26.0 (CH$_3$*C*H$_2$), 28.3 [(CH$_3$)$_3$], 30.0 (C-4), 35.0 (C-5), 36.0 (C-3), 42.5 (C-6), 58.3 (C-2), 79.2 [*C*(CH$_3$)$_3$], 126.7 (2CH), 127.8 (2CH), 129.0 (CH), 140.2 (C *i*), 155.4 (NCO); [α]$^{22}_D$ −4.3 (*c* 0.31, MeOH); MS-EI *m*/*z* 317 (M$^+$, 1), 261 (100), 232 (16), 216 (60), 188 (41), 164 (38); HMRS calcd for $C_{20}H_{31}NO_2$, 317.2355; found, 317.2370.

***tert*-Butyl (3*R*,5*S*)-5-Ethyl-1-(3-indolylacetyl)piperidine-3-acetate (61a).** A suspension of lactam **48** (1.50 g, 4.35 mmol) in MeOH (20 mL) and 10% Pd(OH)$_2$/C (500 mg) was hydrogenated at room temperature and atmospheric pressure for 48 h. Then, the mixed anhydride of pivalic acid and indole-3-acetic acid[24] (1.17 g, 4.51 mmol) was added, and the mixture was shaken under a hydrogen atmosphere at room temperature for 3 days. The catalyst was removed by filtration, the solvent was evaporated, and the resulting residue was chromatographed (1:4 to 4:1 EtOAc−hexane) to afford **61a** (1.51 g, 91%): IR (film) 1623, 1724 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.70 (t, J = 7.5 Hz, 1.5H, CH_3CH$_2$), 0.89 (t, J = 7.5 Hz, 1.5H, CH_3CH$_2$), 1.10 (m, 1H, CH$_3$CH_2), 1.28 (m, 1H, CH$_3$CH_2), 1.43 and 1.45 (s, 9H, [(CH$_3$)$_3$]), 1.14−1.54 (m, 3H, H-5, CH$_2$CNO), 1.98−2.29 (m, 3H, H-3, CH$_2$COO), 2.91 (dd, J = 13.0, 8.0 Hz, 0.5H, H-2), 3.04 (m, 0.5H, H-6), 3.35−3.40 (m, 1.5H, 1H-2, 0.5H-6), 3.56 (dd, J = 13.0, 7.6 Hz, 0.5H, H-2), 3.67 (dd, J = 13.8, 5.4 Hz, 0.5H, H-6), 3.84 (m, 3H, H-4, H-6), 6.99 (br s, 1H, ArH), 7.13 (m, 3H, ArH), 7.30 (m, 1H, ArH), 7.62 (m, 1H, ArH), 8.47 (br s, 1H, NH); ^{13}C NMR (75.4 MHz, Rotamer A) δ 11.3 (*C*H$_3$-CH$_2$), 25.1 (CH$_3$*C*H$_2$), 28.0 [(CH$_3$)$_3$], 29.7 (C-3), 31.0 (C-4), 33.6 (C-5), 34.4 (*C*H$_2$CNO), 37.6 (*C*H$_2$COO), 46.5 (C-6), 50.4 (C-2), 80.3 ([*C*(CH$_3$)$_3$]), 108.5 (C-2a), 111.2 (CH), 118.4 (CH), 119.1 (CH), 121.6 (CH), 122.6 (CH), 126.7 (C-2b), 136.1 (C-6a), 170.7 (CNO), 171.7 (COO); ^{13}C NMR (75.4 MHz, Rotamer B) δ 11.5 (*C*H$_3$CH$_2$), 25.4 (CH$_3$*C*H$_2$), 28.0 [(CH$_3$)$_3$], 30.1 (C-3), 31.3 (C-4), 34.0 (C-5), 35.2 (*C*H$_2$CNO), 38.0 (*C*H$_2$COO), 46.7 (C-6), 51.3 (C-2), 80.5 [*C*(CH$_3$)$_3$], 108.5 (C-2a), 111.2 (CH), 118.5 (CH), 119.1 (CH), 121.7 (CH), 122.7 (CH), 127.0 (C-2b), 136.1 (C-6a), 170.7 (NCO), 171.7 (COO); [α]$^{22}_D$ −27.4 (*c* 0.5, MeOH); MS-EI *m*/*z* 384 (M$^+$, 98), 130 (100), 328 (43); HMRS calcd for $C_{18}H_{33}NO_2$, 384.2412; found, 384.2423.

(3*R*,5*S*)-5-Ethyl-1-(3-indolylacetyl)piperidine-3-acetic Acid (62a). TFA (8 mL, 106.6 mmol) was added to a solution of **61a** (630 mg, 1.64 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred for 15 min and evaporated to afford **62a** (511 mg, 95%), which was used in the next step without ulterior purification: IR (film) 3259, 1712, 1615 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.61 (t, J = 7.5 Hz, 1.5H, CH_3-CH$_2$), 0.86 (t, J = 7.5 Hz, 1.5H, CH_3CH$_2$), 1.00−1.55 (m, 5H), 1.95−2.40 (m, 3H), 2.81 (m, 0.5H), 3.14 (br d, 0.5H), 3.19−3.28 (m, 1H), 3.50 (m, 0.5H), 3.70 (m, 1H), 3.71−3.95 (m, 2H), 4.06 (m, 0.5H), 6.92−7.33 (m, 5H, ArH, NH), 7.57 (d, J = 7.8 Hz, 1H), 8.41 (s, 0.5H, COOH), 8.66 (s, 0.5H, COOH); ^{13}C NMR (75.4 MHz) δ 11.0 (CH$_3$), 11.5 (CH$_3$), 25.0 and 25.5 (CH$_2$), 29.6 and 29.9 (CH), 30.9 and 31.3 (CH$_2$), 33.9 and 34.0 (CH), 35.0 and 35.3 (CH$_2$), 36.6 (2CH$_2$), 46.5 and 46.8 (CH$_2$), 50.5 and 51.9 (CH$_2$), 107.8 and 108.0 (C), 111.3 and 111.4 (CH), 118.0 and 118.5 (CH), 119.2 and 119.4 (CH), 121.7 and 122.0 (CH), 122.8 and 123.2 (CH), 126.5 and 126.7 (C), 136.0 and 136.1 (C), 172.3 (NCO), 176.7 (COO); MS-EI *m*/*z* 328 (M$^+$, 12), 130 (100), 151 (13); HMRS calcd for $C_{19}H_{22}N_2O_2$, 328.1787; found, 328.1786.

20*S*-5,16-Dioxodihydrocleavamine (63a). A suspension of **62a** (780 mg, 3.18 mmol) in PPA (48 g) was heated at 90 °C for 30 min. The mixture was poured into ice and basified with saturated NH_4OH solution and extracted with CH_2Cl_2. The dried combined organic extracts were concentrated, and the resulting residue was chromatographed (3:7 EtOAc−hexane to EtOAc) to afford **63a** (471 mg, 64%): IR (film) 1634 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.91 (t, J = 8.0 Hz, 3H, CH_3CH$_2$), 1.78 (m, 1H, CH$_3$CH_2), 1.29 (m, 1H, CH$_3$CH_2), 1.41 (ddd, J = 13.0, 13.0, 4.0 Hz, 1H, H-11ax), 1.75 (m, 1H, H-10), 1.89 (dm, J = 13.0 Hz, 1H, H-11eq), 2.23 (t, J = 12.0 Hz, 1H, H-9), 2.33 (dm, J = 12.5 Hz, 1H, H-12), 2.38 (dm, J = 12.5 Hz, 1H, H-13), 3.20 (dm, J = 14.0 Hz, 1H, H-15), 3.26 (t, J = 12.0 Hz, 1H, H-13), 4.02 (dm, J = 14.0 Hz, 1H, H-15), 4.02 and 4.32 (2d, J = 17.0 Hz, 2H, H-6), 4.63 (dm, J = 13.0 Hz, 1H, H-9), 7.13 (m, 1H, ArH), 7.33 (m, 2H, ArH), 7.64 (dd, J = 8.0, 0.5 Hz, 1H, ArH), 9.11 (br s, 1H, NH); ^{13}C NMR (75.4 MHz) δ 11.1 (*C*H$_3$CH$_2$), 27.1 (CH$_3$*C*H$_2$), 30.8 (C-10), 35.0 (C-6), 35.7 (C-12), 37.6 (C-11), 42.4 (C-13), 49.8 and 50.0 (C-9 and C-15), 111.8 (CH), 115.6 (CH), 120.6 (CH), 121.0 (C-5b), 126.9 (CH), 128.7 (CH), 133.0 (CH), 135.4 (CH), 170.4 (NCO), 194.3 (COO); [α]$^{22}_D$ −287.3 (*c* 0.5, MeOH); MS-EI *m*/*z* 310 (M$^+$, 100), 143 (83), 198 (67); HMRS calcd for $C_{19}H_{22}N_2O_2$, 310.1681; found, 310.1681. Anal. Calcd for $C_{19}H_{22}N_2O_2 \cdot {}^1/_2H_2O$: C, 71.45; H, 7.26; N, 8.77. Found: C, 71.16; H, 7.03, N, 8.66.

(−)-20*S*-Dihydrocleavamine. A solution of **63a** (131 mg, 0.42 mmol) in dioxane (10 mL) was added to a suspension of $LiAlH_4$ (224 mg, 5.88 mmol) in dioxane (20 mL), and the mixture was heated at reflux for 24 h. Then, the mixture was cooled to 0 °C, H_2O was added until the suspension turned colorless, and it was filtered. Evaporation of the filtrate gave a residue, which was chromatographed (1:4 EtOAc−hexane to 9:1 EtOAc-MeOH) to afford (−)-20*S*-dihydrocleavamine (40 mg, 34%) and **(2*R*)-2-(2-ethyl-2-propenyl)-2,3,5,6,11,11*b*-hexahydro-1*H*-indolizino[8,7-*b*]indole** (**65**; 20 mg, 17%). The spectral data and optical rotation ×ed[α]$^{22}_D$ −97.0 (*c* 0.9 CHCl$_3$); [α] −87.0 (CHCl$_3$)[23a]×fd of our synthetic (−)-20*S*-dihydrocleavamine were coincident with those previously reported.[31] **65:** IR (film) 3281, 2927 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.83 (m, 2H), 1.00 (t, J = 7.5 Hz, 3H), 1.83−2.11 (m, 4H), 2.17 (d, J = 7.5 Hz, 1H), 2.36 (m, 1H), 2.67−2.51 (m,

2H), 3.15−2.90 (m, 2H), 3.25 (m, 1H), 4.24 (m, 1H), 4.72 (dm, J = 7.0 Hz, 1H), 7.04−7.50 (m, 5H, ArH), 7.90 (br s, 1H); ^{13}C NMR (50.3 MHz) δ 11.3 (CH_3), 16.6 (CH_2), 27.6 (CH_2), 33.4 (CH), 35.0 (CH_2), 41.3 (CH_2), 45.0 (CH_2), 54.1 (CH_2), 56.4 (CH), 107.1 (C), 107.7 (CH_2), 109.6 (CH), 116.9 (CH), 118.2 (CH), 120.3 (2CH), 126.2 (C), 133.6 (C), 134.7 (C), 148.8 (C); MS-EI m/z 280 (M^+, 28), 156 (13), 209 (100); HMRS calcd for $C_{19}H_{24}N_2$, 280.1939; found, 280.1944.

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Supporting Information Available: Experimental details and characterization data for all compounds reported in this manuscript not included in the Experimental Section, tables with ^{13}C NMR assignments for lactams **10**−**46**, and X-ray crystallographic data for compounds **15b**, **20b**, **32a**, **39**, and **40b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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