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Enantioselective Synthesis of Piperidine, Indolizidine, and Quinolizidine Alkaloids from a Phenylglycinol-Derived δ-Lactam

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Received October 25, 2002

Starting from a common lactam, (3*R*,8a*S*)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (**1**), or its enantiomer, the enantioselective synthesis of 2-alkylpiperidines and *cis*- and *trans*-2,6-dialkylpiperidines is reported. The potential of this approach is illustrated by the synthesis of the piperidine alkaloids (*R*)-coniine, (2*R*,6*S*)-dihydropinidine, (2*R*,6*R*)-lupetidine, and (2*R*,6*R*)-solenopsin A, the indolizidine alkaloids (5*R*,8a*R*)-indolizidine 167B and (3*R*,5*S*,8a*S*)-monomorine I, and the nonnatural base (4*R*,9a*S*)-4-methylquinolizidine.

The piperidine ring is found in one of the simplest alkaloids, coniine, in other diversely substituted piperidine alkaloids, mainly *cis*- and *trans*-2,6-dialkyl substituted (e.g. pinidine, lupetidine, solenopsins),[1] in bicyclic indolizidine (e.g. monomorine I), perhydroquinoline (e.g. pumiliotoxin C), and quinolizidine (e.g. lupinine) alkaloids,[2] as well as in many of the most complex polycyclic alkaloids (e.g. morphine, strychnine).[3] These nitrogen derivatives occur not only in plants but also in insects[4] and amphibians.[2b−d] Most of these natural products exhibit notable biological activities, and many piperidine-containing entities are under pharmaceutical research.[5] For these reasons, and because the structural diversity of these alkaloids makes them a good vehicle for the testing of synthetic methodology, the synthesis of enantiopure piperidine derivatives has attracted considerable synthetic attention over the last years.[6] In this context, the development of chiral nonracemic piperidine building blocks, with the final aim of synthesizing diversely substituted enantiopure piperidine derivatives, constitutes an area of current interest.[7] In particular, chiral bicyclic lactams derived from *R*- or *S*-phenylglycinol have emerged as powerful tools as they allow the stereoselective incorporation of substituents at the different carbon atom positions of the piperidine ring.[8]

In this paper we report the enantioselective synthesis of 2-alkylpiperidines and stereocontrolled routes to enantiopure *cis*- and *trans*-2,6-dialkylpiperidines, the former also providing access to substituted indolizidines and quinolizidines, starting from a common bicyclic lactam **1**. The interest and usefulness of this approach

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(7) (a) Rubiralta, M.; Giralt, E.; Díez, A. *Piperidine. Structure, Preparation, Reactivity, and Synthetic Applications of Piperidine and its Derivatives*; Elsevier: Amsterdam, The Netherlands, 1991. (b) Oppolzer, W. *Pure Appl. Chem.* **1994**, *66*, 2127−2130. (c) Husson, H.-P.; Royer, *J. Chem. Soc. Rev.* **1999**, *28*, 383−394. (d) Comins, D. L. *J. Heterocycl. Chem.* **1999**, *36*, 1491−1500. (e) Guilloteau-Bertin, B.; Compère, D.; Gil, L.; Marazano, C.; Das, B. C. *Eur. J. Org. Chem.* **2000**, 1391−1399. For a chemoenzymatic approach to enantiopure piperidine derivatives, see: (f) Danieli, B.; Lesma, G.; Passarella, D.; Silvani, A. *Curr. Org. Chem.* **2000**, *4*, 231−261.

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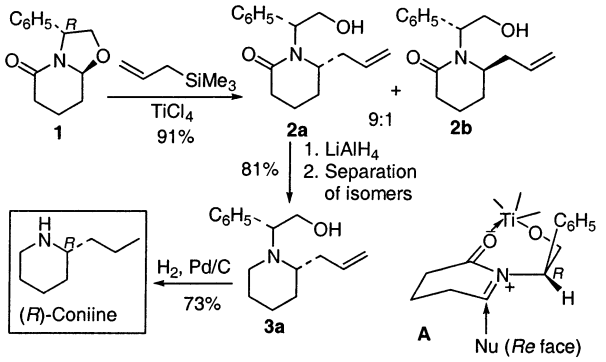
10.1021/jo0266083 CCC: $25.00
Published on Web 02/07/2003

SCHEME 1. Enantioselective Synthesis of (*R*)-Coniine



is illustrated by the synthesis of several alkaloids with the above-mentioned structural types.

Results and Discussion

The starting bicyclic lactam **1** was prepared in 74% overall yield by our previously reported procedure, by cyclocondensation of *R*-phenylglycinol with methyl 5-oxopentanoate in refluxing toluene, followed by equilibration of the initially formed cis/trans mixture of lactams with TFA/CH_2Cl_2 at room temperature.[9,10] The enantioselective synthesis of 2-alkylpiperidines required the stereocontrolled introduction of substituents at the piperidine α position by asymmetric α-amidoalkylation.[11] Interaction of **1** with a Lewis acid would generate an acyl iminium ion **A** (Scheme 1), which would undergo nucleophilic attack upon the less hindered *Re* face, thus producing a new stereocenter with a well-defined configuration. The application of this concept with $TiCl_4$ and allyltrimethylsilane as the nucleophile led to the allylated piperidones **2a** and **2b** in good yield and diastereoselectivity (9:1).[12] $LiAlH_4$ reduction of the lactam carbonyl, followed by separation of the resulting diastereomeric piperidines **3** and, finally, simultaneous hydrogenation of the carbon−carbon double bond and debenzylation from the major isomer **3a** completed the enantioselective synthesis of (*R*)-coniine.[13,14] The absolute configuration of the stereogenic center was confirmed to be *R* from the sign of the specific rotation of the hydrochloride.

SCHEME 2. Synthesis of Enantiopure 2-Alkylpiperidines

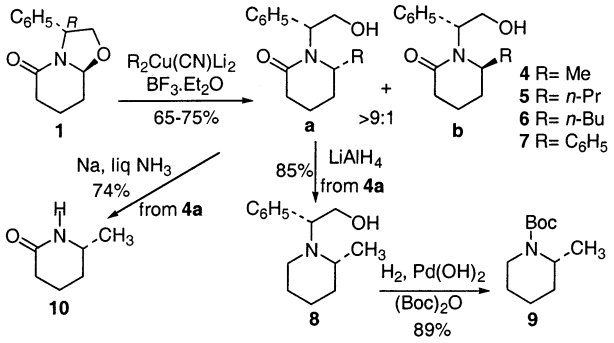


TABLE 1. Diagnostic NMR Chemical Shifts for 6-Substituted Lactams[a]

R	lactam	C-1′	C-6	H-1′
(*R*)-CH_3	**4a**[b]	64.6	52.8	4.60
(*S*)-CH_3	**4b**[c]	62.6	51.8	5.21
(*R*)-*n*-Pr	**5a**	66.1	57.7	4.54
(*S*)-*n*-Pr	**5b**[d]	63.4	56.4	5.24
(*R*)-*n*-Bu	**6a**	66.3	58.0	4.59
(*S*)-C_6H_5	**7a**	67.9	62.6	4.21
(*R*)-C_6H_5	**7b**	60.4	58.2	5.90
(*S*)-3-indolyl[e]		68.0	57.0	4.40
(*R*)-3-indolyl[e]		59.7	50.5	5.97

[a] δ values in ppm from TMS. [b] Data also reported in ref 16b. [c] Data from ref 16c. [d] Data from ref 10c. [e] Data from ref 12a.

Similarly, the addition of higher order cyanocuprates[15] to lactam **1** in the presence of $BF_3{\cdot}Et_2O$ took place to give the corresponding alkylated (**4**−**6**) or arylated (**7**) products (Scheme 2) in good yields and high diastereoselectivities (approximate **a**:**b** ratios: 95:5 for **4** and **5**; 9:1 for **6** and **7**). The absolute configuration of the new stereogenic center was assigned from the ^1H and ^{13}C NMR data (Table 1)[16] and by conversion of the allyl derivative **2a** into **5a** by catalytic hydrogenation. The procedure constitutes an alternative and general method for the synthesis of enantiopure 2-substituted piperidines.[17] Thus, $LiAlH_4$ reduction of **4a** followed by catalytic hy-

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(10) Lactam **1** (or its enantiomer) has also been prepared by alternative procedures: (a) Royer, J.; Husson, H.-P. *Heterocycles* **1993**, *36*, 1493−1496. (b) Micouin, L.; Quirion, J.-C.; Husson, H.-P. *Synth. Commun*. **1996**, *26*, 1605−1611. (c) Terán, J. L.; Gnecco, D.; Galindo, A.; Juárez, J.; Bernes, S.; Enríquez, R. G. *Tetrahedron*: *Asymmetry* **2001**, *12*, 357−360. However, in this article the authors misleadingly report that they have prepared the 8a-epimer of **1**.

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(12) (a) A similar stereoselectivity was observed in the reaction of **1** with indole in the presence of $TiCl_4$: Amat, M.; Llor, N.; Bosch, J.; Solans, X. *Tetrahedron* **1997**, *53*, 719−730. For a disscusion on the stereoselectivity of allyltrimethylsilane α-amidoalkylations to related (*R*)-phenylglycinol- or (*S*)-1-phenylethylamine-derived δ- and γ-lactams, see: (b) Polniaszek, R. P.; Belmont, S. E.; Alvarez, R. *J. Org. Chem*. **1990**, *55*, 215−223. (c) Kiguchi, T.; Nakazono, Y.; Kotera, S.; Ninomiya, I.; Naito, T. *Heterocycles* **1990**, *31*, 1525−1535. (d) Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc*. **1991**, *113*, 9858−9859. (e) Interestingly, the reaction of **1** with PrMgBr takes place with opposite diastereoselectivity to give piperidone **5b** as the major product: see ref 10c.

(13) For a preliminary account of this part of the work, see ref 9a.

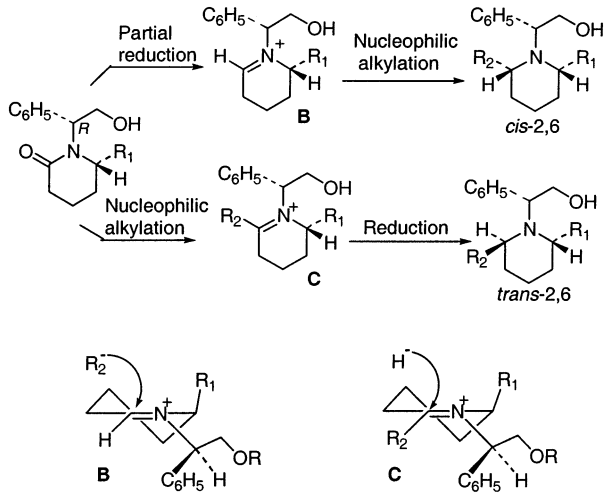
(14) For recent enantioselective syntheses, see: (a) Wilkinson, T. J.; Stehle, N. W.; Beak, P. *Org. Lett*. **2000**, *2*, 155−158. (b) Andrés, J. M.; Herráiz-Sierra, I.; Pedrosa, R.; Pérez-Encabo, A. *Eur. J. Org. Chem*. **2000**, 1719−1726. (c) Bois, F.; Gardette, D.; Gramain, J.-C. *Tetrahedron Lett*. **2000**, *41*, 8769−8772. (d) Hunt, J. C. A.; Laurent, P.; Moody, C. J. *Chem. Commun*. **2000**, 1771−1772. (e) Eskici, M.; Gallagher, T. *Synlett* **2000**, 1360−1362. (f) Charette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc*. **2001**, *123*, 11829−11830. (g) Pachamuthu, K.; Vankar, Y. D. *J. Organomet. Chem*. **2001**, *624*, 359−363.

(15) (a) Lipshutz, B. H. In *Organocopper Reagents. A Practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: New York, 1994; pp 105−128. (b) For the use of organocopper derivatives in intermolecular α-amidoalkylation reactions, see: Ludwig, C.; Wistrand, L.-G. *Acta Chem. Scand*. **1994**, *48*, 367−371.

(16) (a) In the major isomers **a** the methine benzylic proton appears more shielded, and both the benzylic and C-6 carbons more deshielded, than in the minor isomers **b**. (b) Fréville, S.; Bonin, M.; Célérier, J.-P.; Husson, H.-P.; Lhommet, G.; Quirion, J.-C.; Thuy, V. M. *Tetrahedron* **1997**, *53*, 8447−8456. (c) Lienard, P.; Varea, T.; Quirion, J.-C.; Husson, H.-P. *Synlett* **1994**, 143−144.

(17) For related approaches, involving the reductive ring-opening of phenylglycinol-derived 8a-substituted bicyclic δ-lactams, see: (a) Munchhof, M. J.; Meyers, A. I. *J. Org. Chem*. **1995**, *60*, 7084−7085. (b) Fréville, S.; Célérier, J. P.; Thuy, V. M.; Lhommet, G. *Tetrahedron*: *Asymmetry* **1995**, *6*, 2651−2654. See also ref 8e.

SCHEME 3. Synthesis of Enantiopure *cis*- and *trans*-2,6-Dialkylpiperidines

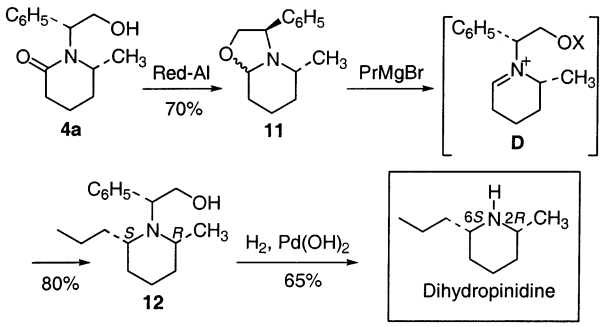


drogenolysis of the resulting 2-methylpiperidine **8** in the presence of $(Boc)_2O$ gave (*R*)-*N*-Boc-2-methylpiperidine (**9**).[18] Alternatively, debenzylation of **4a** with Na in liquid NH_3 gave enantiopure 6-methyl-2-piperidone (**10**).

The 6-alkyl-2-pyridones resulting from the alkylation of bicyclic lactam **1** were envisaged as synthetic precursors of both *cis*- and *trans*-2,6-dialkylpiperidines. Thus, partial reduction of the lactam carbonyl group followed by nucleophilic alkylation of the resulting iminium cation **B** with a Grignard reagent would lead to enantiopure *cis*-2,6-dialkylpiperidines (Scheme 3). Reversal of this sequence, i.e. nucleophilic alkylation with an organometallic reagent followed by hydride reduction of the resulting iminium species **C**, should afford enantiopure *trans*-2,6-dialkylpiperidines. In both cases, the stereoselectivity of the second step would be a consequence of the stereoelectronically preferred axial approach[19] of the nucleophile to the iminium intermediate, in a half-chair conformation with the 6-alkyl substituent in a pseudoaxial disposition to relieve the $A^{(1,2)}$ strain.[7c] The attack of either the organometal derivative R_2 on **B** or the hydride ion on **C** would occur cis with respect to the substituent R_1 via a chairlike transition state.

In accordance with these expectations, Red-Al reduction of piperidone **4a** gave oxazolopiperidone **11** (a 2:1 mixture of epimers at C-8a), which is, in fact, a single masked iminium ion **D** (Scheme 4).[20] A subsequent reaction with propylmagnesium bromide led to the enantiopure *cis*-dialkylpiperidine **12** as the only isomer detectable from the reaction mixture.[21] The cis relationship between the methyl and propyl substituents in **12** was deduced from the difference between the ^{13}C NMR chemical shifts corresponding to the methine and methylene carbons of the chiral auxiliary.[22] A catalytic de-

SCHEME 4. Synthesis of Enantiopure *cis*-2,6-Dialkylpiperidines: (−)-Dihydropinidine



benzylation completed the enantioselective synthesis of the piperidine alkaloid dihydropinidine,[23] which was isolated as the hydrochloride. Our dihydropinidine·HCl was dextrorotatory, thus indicating a natural 2*R*,6*S*[24] absolute configuration.[25]

The above methodology can be extended to the synthesis of bicyclic quinolizidine derivatives bearing a *cis*-2,6-dialkylpiperidine moiety. In this case, the alkylation of the masked iminium ion **11** had to be effected with a four-carbon Grignard reagent incorporating a protected aldehyde group (Scheme 5). Thus, reaction of oxazolopiperidine **11** with the Grignard reagent derived from 2-(3-bromopropyl)-1,3-dioxolane stereoselectively gave *cis*-2,6-disubstituted piperidine **13**. Catalytic hydrogenation of **13** under slightly acidic hydrolytic conditions brought about debenzylation, deprotection of the carbonyl group, and closure of the second piperidine ring by a reductive amination process to give enantiopure *cis*-4-methylquinolizidine **14**.

Operating in a similar manner, but using a three-carbon Grignard reagent bearing a protected aldehyde group, the above approach leads to enantiopure indolizidines embodying a *cis*-2,6-dialkylpiperidine moiety. Scheme 6 outlines the reaction sequences leading to

(18) For the preparation of both enantiomers of **9**, which are valuable synthetic intermediates, see: Doller, D.; Davies, R.; Chackalamannil, S. *Tetrahedron*: *Asymmetry* **1997**, *8*, 1275−1278.

(19) (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; Chapter 6. (b) For related highly stereoselective approaches to α- and *β*-*C*-glycopyranosides, see: Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976−4978.

(20) For a preliminary account of this part of the work, see: Amat, M.; Llor, N.; Hidalgo, J.; Hernández, A.; Bosch, J. *Tetrahedron*: *Asymmetry* **1996**, *7*, 977−980.

(21) For the opening of hexahydrooxazolo[3,2-*a*]pyridines with Grignard reagents, see: (a) Guerrier, L.; Royer, J.; Grierson, D. S.; Husson, H.-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754−7755. (b) Katritzky, A. R.; Qiu, G.; Yang, B.; Steel, P. J. *J. Org. Chem.* **1998**, *63*, 6699−6703. For a study on the stereoselectivity of the reaction, see: (c) Poerwono, H.; Higashiyama, K.; Yamauchi, T.; Kubo, H.; Ohmiya, S.; Takahashi, H. *Tetrahedron* **1998**, *54*, 13955−13970.

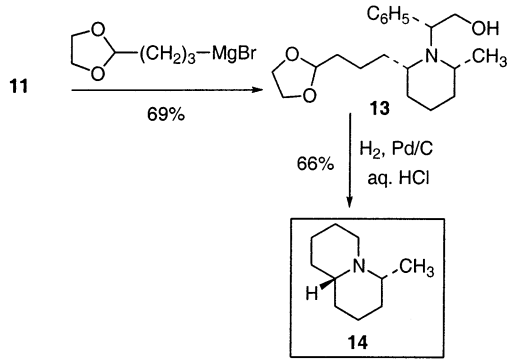
(22) A positive value of $\Delta(\delta CH - \delta CH_2)$ is indicative of a 2,6-cis relationship, whereas the trans isomers show a slightly negative value: Yue, C.; Nicolay, J.-F.; Royer, J.; Husson, H.-P. *Tetrahedron* **1994**, *50*, 3139−3148.

(23) Although dihydropinidine was first isolated as the hydrogenation product of the alkaloid pinidine,[23a−c] it has also been isolated from the Mexican Bean Beetle, *Epilachna varivestis*:[23d] (a) Tallent, W. H.; Stromberg, V. L.; Horning, E. C. *J. Am. Chem. Soc.* **1955**, *77*, 6361−6364. (b) Tallent, W. H.; Horning, E. C. *J. Am. Chem. Soc.* **1956**, *78*, 4467−4469. (c) Absolute configuration: Hill, R. K.; Chan, T. H.; Joule, J. A. *Tetrahedron* **1965**, *21*, 147−161. (d) Attygalle, A. B.; Xu, S.-C.; McCormick, K. D.; Meinwald, J.; Blankespoor, C. L.; Eisner, T. *Tetrahedron* **1993**, *49*, 9333−9342.

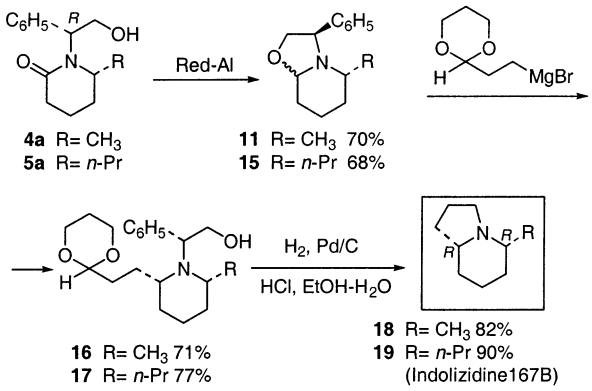
(24) (a) To avoid confusion with other reports, it must be noted that, according to the IUPAC recommendations, we assign the lower locant (i.e., 2) to the chain that should be cited first in the name (i.e., methyl). (b) It must also be noted that the $[\alpha]_D$ value for the base has been reported to be −1.2 (*c* 1.62, EtOH)[23a,b] and that, therefore, dihydropinidine is levorotatory. There is also a confusion in the literature in this respect.

(25) For recent enantioselective syntheses of dihydropinidine, see: (a) Ciblat, S.; Besse, P.; Papastergiou, V.; Veschambre, H.; Canet, J.-L.; Troin, Y. *Tetrahedron*: *Asymmetry* **2000**, *11*, 2221−2229. (b) Fréville, S.; Delbecq, P.; Thuy, V. M.; Petit, H.; Célérier, J. P.; Lhommet, G. *Tetrahedron Lett.* **2001**, *42*, 4609−4611. See also ref 14a and references cited therein.

SCHEME 5. Synthesis of Enantiopure 4-Substituted Quinolizidines



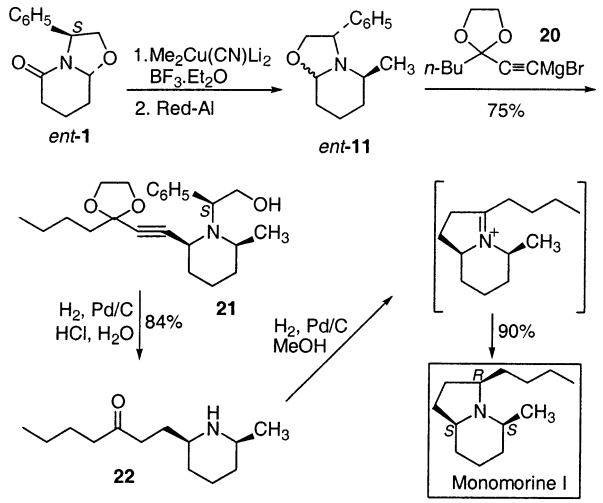
SCHEME 6. Synthesis of Enantiopure 5-Substituted Indolizidines: Indolizidine 167B



5-methyl- and 5-propylindolizidine (**18** and **19**, respectively), the latter being indolizidine 167B (gephyrotoxin 167B), a minor alkaloid isolated from the skin secretions of neotropical frogs.[26] The syntheses proceed via oxazolopiperidines **11** and **15** (a mixture of C-8a epimers), respectively, the latter prepared by Red-Al reduction of propyl lactam **5a**. In this case, minor amounts of the corresponding fully reduced piperidine (deoxo-**5a**) were isolated from the reaction mixture. Reaction of the masked iminium ions **11** and **15** with the Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxane gave the respective *cis*-2,6-disubstituted piperidines **16** and **17**. Finally, hydrogenation in the presence of Pd/C under acidic hydroalcoholic conditions led to the enantiopure *cis*-5-alkylindolizidines **18**[27] and **19**,[28] with an *R* configuration at both piperidine α-carbons.

As the *S* isomer of phenylglycinol is also commercially available, the enantiomer of lactam **1** is also easily accessible, thus expanding the potential of the methodology, as it provides access to *cis*-5-alkylindolizidine alkaloids with an *S* configuration at both piperidine α carbons, for instance monomorine I, the trail pheromone of the Pharaoh ant.[29] The synthesis proceeds via the

SCHEME 7. Synthesis of the Indolizidine Alkaloid Monomorine I

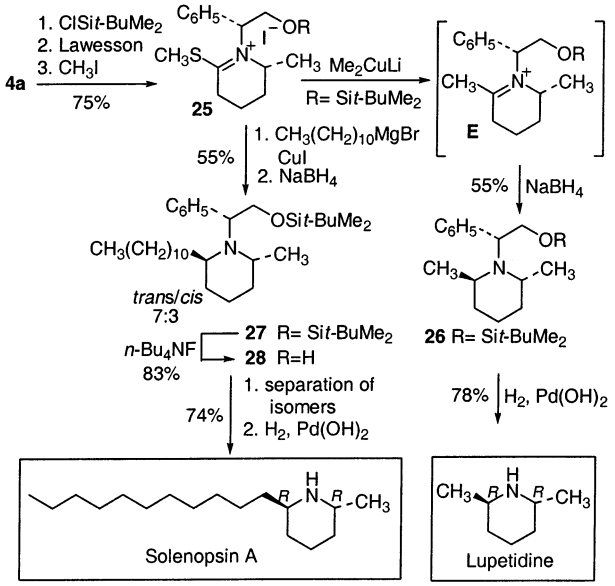


enantiomers of lactam **4a** and oxazolopiperidine **11** (Scheme 7). In this series, the introduction of the second chain on the piperidine ring of *ent*-**11** was effected by using the functionalized acetylide **20**, which already incorporates the four-carbon chain present at C-3 in monomorine I.[30] The reaction between *ent*-**11** and **20** furnished the *cis*-2,6-disubstituted piperidine **21** in 75% yield, again as a single stereoisomer. Catalytic hydrogenation of **21** under acidic conditions led to the *N*-unsubstituted piperidine ketone **22** in excellent yield, in a one-pot reaction involving hydrogenation of the triple bond, debenzylation, and hydrolysis of the acetal group. Closure of the pyrrolidine ring, with generation of the third stereogenic center, was accomplished in a subsequent step by reductive amination, using hydrogen in MeOH solution in the absence of acid.[31] Monomorine I was obtained as a single stereoisomer in 90% yield.[32]

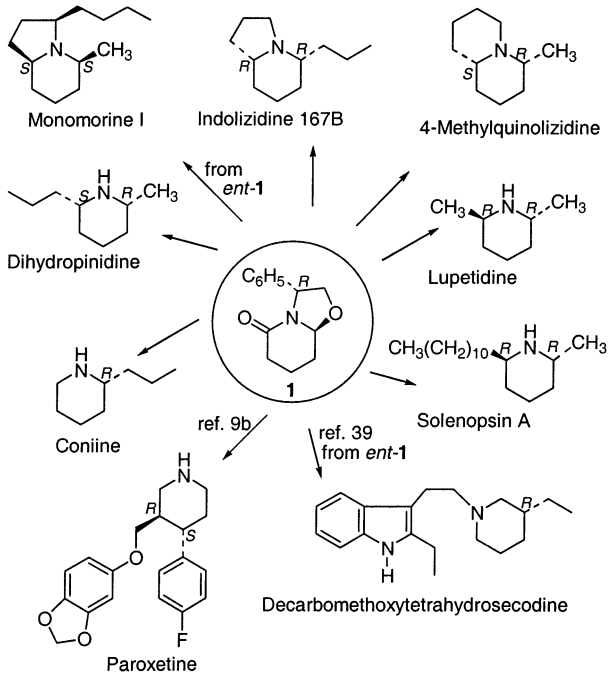
As we have depicted in Scheme 3, we expected that reversing the reduction and nucleophilic alkylation steps from the starting phenylglycinol-derived 6-alkyl-2-piperidones would result in the preparation of the trans-2,6 isomers. However, attempts to prepare *trans*-2,6-dialkylpiperidines by treating lactam **4a** with Grignard, organolithium, or organocerium reagents, followed by a hydride reduction, resulted in failure.[33] For this reason, we used the synthetically equivalent, but more reactive thioimidate salt **25**, which was prepared in 75% overall yield from **4a**, by silylation of the hydroxy group, followed by treatment with Lawesson's reagent and subsequent methylation of the resulting thioamide **24** (Scheme 8).

(26) Daly, J. W. *Prog. Chem. Nat. Prod.* **1982**, *41*, 205−340.
(27) Fora previous enantioselective synthesis, see: Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, *55*, 4688−4693.
(28) For recent enantioselective syntheses of indolizidine 167B, see: (a) Yamazaki, N.; Ito, T.; Kibayashi, C. *Org. Lett.* **2000**, *2*, 465−467. (b) Back, T. G.; Nakajima, K. *J. Org. Chem.* **2000**, *65*, 4543−4552. (c) Kim, G.; Lee, E. *Tetrahedron: Asymmetry* **2001**, *12*, 2073−2076. (d) Zaminer, J.; Stapper, C.; Blechert, S. *Tetrahedron Lett.* **2002**, *43*, 6739−6741.
(29) (a) Isolation: Ritter, F. J.; Rotgans, I. E. M.; Talman, E.; Verwiel, P. E. J.; Stein, F. *Experientia* **1973**, *29*, 530−531. (b) Absolute configuration: Royer, J.; Husson, H.-P. *J. Org. Chem.* **1985**, *50*, 670−673.
(30) Attempts to generate a Grignard reagent from several 1-halo-3-heptanone acetals were unsuccessful.
(31) This stereoselective cyclization has previously been reported: Yamaguchi, R.; Hata, E.; Matsuki, T.; Kawanisi, M. *J. Org. Chem.* **1987**, *52*, 2094−2096. See also ref 29b.
(32) For previous enantioselective syntheses of monomorine I, see: Riesinger, S. W.; Löfstedt, J.; Pettersson-Fasth, H.; Bäckvall, J.-E. *Eur. J. Org. Chem.* **1999**, 3277−3280 and references cited therein.
(33) It has been reported recently that the sodium salt of lactam **4a** satisfactorily reacts with CH_3MgCl to give, after hydride reduction, *trans*-2,6-dimethylpiperidine **26** (R = H): see ref 16b.

SCHEME 8. Synthesis of Enantiopure *trans*-2,6-Dialkylpiperidines: Lupetidine and Solenopsin A



SCHEME 9. Synthetic Applications of Chiral Nonracemic Bicyclic Lactam 1



We expected that the addition of an organometallic reagent to the iminium moiety of **25**, followed by elimination of the methylsulfanyl group, would lead to the required iminium cation, for instance **E**. However, sequential treatment of **25** with MeLi or MeMgBr, and then with $NaBH_4$, afforded the 2-substituted piperidine **8** (as *O*-TBDMS derivative) as the only identifiable product. This result was attributed to the basicity of the above organometallic reagents, which deprotonate the α position of thioimidate **25** yielding an enamine; the subsequent addition of a hydride ion under protic conditions (MeOH) affords the reduced product. In accordance with the above interpretation, the use of the less basic lithium dimethylcuprate, followed by $NaBH_4$ reduction of the resulting iminium species **E**, stereoselectively afforded the desired *trans*-2,6-dimethylpiperidine **26**.[34] Only trace amounts (<5%) of the cis isomer were detected by NMR. Piperidine **8** (as the *O*-TBDMS derivative) was also isolated in ∼15% yield. Finally, hydrogenolysis of the benzylic substituent of **26** gave *trans*-2*R*,6*R*-dimethylpiperidine, whose hydrochloride showed an [α] value (dextrorotatory) and spectroscopic data in agreement with those reported for the hydrochloride of the alkaloid lupetidine.[35] The above methodology provides a general synthetic entry to enantiopure *trans*-2,6-dialkylpiperidines. This was illustrated by the synthesis of solenopsin A, an alkaloid isolated from the venom secreted by fire ants.[36] Introduction of the undecyl chain via a copper reagent on the same thioimidate **25**, followed by reduction with $NaBH_4$, afforded *trans*-piperidine **27**, although in this case with moderate stereoselectivity (cis/trans ratio 3:7).[37] After desilylation, the resulting alcohols **28** were separated by column chromatography, and the major trans-isomer was debenzylated to give solenopsin A,[38] which was isolated as the hydrochloride. The NMR spectral data and [α] value of our synthetic material agreed with those reported for the natural product.

In conclusion, bicyclic lactam **1** (and its enantiomer) has proven to be a versatile chiral building block for the enantioselective synthesis of diversely substituted piperidine derivatives as it allows the stereocontrolled formation of C−C bonds at the different carbon atom positions of the nitrogen heterocycle. Scheme 8 outlines the most important synthetic goals achieved from **1**. In addition to the 2-alkyl- and *cis*- and *trans*-2,6-dialkylpiperidines reported here, alkylation at the α position of the carbonyl group of lactam **1** provides access to enantiopure 3-alkylpiperidines,[39] whereas conjugate addition to α,*β*-unsaturated lactams derived from **1** ultimately leads to enantiopure *trans*-3,4-disubstituted piperidines, such as the antidepressive drug paroxetine.[9b]

(34) For a preliminary account of this part of the work, see: Amat, M.; Hidalgo, J.; Llor, N.; Bosch, J. *Tetrahedron*: *Asymmetry* **1998**, *9*, 2419−2422.

(35) (a) Isolation: Kuzovkov, A. D.; Menshikov, G. P. *Zh. Obshch. Khim.* **1950**, *20*, 1524−1527; *Chem. Abstr.* **1951**, *45*, 2485g. (b) Absolute configuration: Hill, R. K.; Morgan, J. W. *J. Org. Chem.* **1966**, *31*, 3451−3452. (c) It must be noted that lupetidine base is levorotatory. (d) For previous enantioselective syntheses, see: Najdi, S.; Kurth, M. J. *Tetrahedron Lett.* **1990**, *31*, 3279−3282. See also ref 16b. (e) For the synthesis of *ent*-lupetidine (2*S*,6*S*), see: Adamo, M. F. A.; Aggarwal, V. K.; Sage, M. A. *Synth. Commun.* **1999**, *29*, 1747−1756. See also ref 7e.

(36) (a) Isolation: MacConnell, J. G.; Blum, M. S.; Fales, H. M. *Tetrahedron* **1971**, *26*, 1129−1139. (b) Absolute configuration: Leclercq, S.; Thirionet, I.; Broeders, F.; Daloze, D.; Vander Meer, R.; Braekman, J. C. *Tetrahedron* **1994**, *50*, 8465−8478.

(37) The lower stereoselectivity in the hydride reduction of the C=N bond in related 1-piperidinium salts when R is an alkyl group larger than methyl has previously been reported: (a) Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831−2843. (b) Ukaji, Y.; Watai, T.; Sumi, T.; Fujisawa, T. *Chem. Lett.* **1991**, 1555−1558.

(38) (a) For previous enantioselective syntheses, see ref 14a and references cited therein. See also: (b) Takahata, H.; Ouchi, H.; Ichinose, M.; Nemoto, H. *Org. Lett.* **2002**, *4*, 3459−3462. (c) For a review, see: Leclercq, S.; Daloze, D.; Braekman, J.-C. *Org. Prep. Proc. Int.* **1996**, *28*, 499−543. (d) For the synthesis of the 2*S*,6*S*-enantiomer, see: Grierson, D. S.; Royer, J.; Guerrier, L.; Husson, H.-P. *J. Org. Chem.* **1986**, *51*, 4475−4477.

(39) Amat, M.; Pshenichnyi, G.; Bosch, J.; Molins, E.; Miravitlles, C. *Tetrahedron*: *Asymmetry* **1996**, *7*, 3091−3094.

Experimental Section

General Procedures. Melting points were determined in a capillary tube and are uncorrected. Unless otherwise indicated, NMR spectra were recorded at 200 or 300 MHz (^{1}H) and 50.3 or 75 MHz (^{13}C) and are reported downfield from TMS. Only noteworthy IR absorptions are listed. Thin-layer chromatography was done on SiO_2 (silica gel 60 F_{254}), and the spots were located with aqueous potassium permanganate solution or with iodoplatinate reagent. All nonaqueous reactions were performed under an inert atmosphere. Solvents for chromatography and reactions were distilled at atmospheric pressure prior to use and dried using standard procedures. Drying of the organic extracts during the workup of reactions was performed over anhydrous Na_2SO_4 or $MgSO_4$. Evaporation of solvents was accomplished with a rotatory evaporator. Microanalyses and HRMS were performed by Centre d'Investigació i Desenvolupament (CSIC), Barcelona.

(6*S*)-6-Allyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-piperidone (2a). Allyltrimethylsilane (2.0 mL, 12.6 mmol) was added at room temperature to a solution of bicyclic lactam **1** (880 mg, 4.05 mmol) in anhydrous CH_2Cl_2 (15 mL). Then, a solution of $TiCl_4$ (0.45 mL, 4.1 mmol) in CH_2Cl_2 (15 mL) was added, and the dark mixture was stirred at room temperature for 4 h and poured into an aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2, and the combined organic solutions were dried, filtered, and concentrated to give compound **2** (956 mg, 91%) as a 9:1 mixture of C-6 isomers **2a** and **2b**, respectively. **2a**: IR (film) 3367, 1616 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.60−1.78 (m, 2 H), 1.80−1.90 (m, 2 H), 2.20−2.23 (m, 2 H), 2.40−2.55 (m, 2 H), 3.31 (dddd, J = 8.5, 5.5, 5.5, 3.0 Hz, 1 H), 4.00 (dd, J = 12.0, 3.5 Hz, 1 H), 4.23 (dd, J = 12.0, 7.5 Hz, 1 H), 4.67 (dd, J = 7.5, 3.5 Hz, 1 H), 4.95−5.03 (m, 2 H), 5.55 (m, 1H), 7.20−7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 15.6 (CH_2), 25.3 (CH_2), 31.7 (CH_2), 37.0 (CH_2), 57.3 (CH), 64.1 (CH_2), 65.9 (CH), 118.3 (CH_2), 127.6 (CH), 127.8 (CH), 128.7 (CH), 134.0 (CH), 137.3 (C), 172.3 (C).

(2*S*)-2-Allyl-[(1*R*)-2-hydroxy-1-phenylethyl]piperidine (3a). A solution of the above mixture of epimers **2a** and **2b** (900 mg, 3.46 mmol) in anhydrous Et_2O (10 mL) was slowly added to a suspension of $LiAlH_4$ (530 mg, 14.0 mmol) in anhydrous Et_2O (300 mL). The mixture was heated at reflux for 1 h and cooled to 0 °C. The excess of hydride was destroyed by successive dropwise addition of 15% aqueous NaOH (10 mL) and H_2O (10 mL). The suspension was filtered through a Celite pad and the aqueous layer was extracted with Et_2O. The combined organic layers were dried, filtered, and concentrated to give a yellow oil (635 mg). Flash chromatography (3:2 Et_2O−hexane) afforded isomers **3b** (77 mg, 9%) and **3a** (622 mg, 73%). **3a**: IR (film) 3390 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.00−1.70 (m, 6 H), 1.82 (td, J = 11.0, 2.6 Hz, 1 H), 2.42−2.53 (m, 3 H), 2.90 (ddd, J = 11.0, 3.5, 3.5 Hz, 1 H), 3.58 (dd, J = 10.3, 5.3 Hz, 1 H), 4.00 (t, J = 10.3 Hz, 1 H), 4.33 (dd, J = 10.3, 5.3 Hz, 1 H), 5.03−5.20 (m, 2 H), 5.76−5.98 (m, 1 H), 7.10−7.45 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 23.8 (CH_2), 26.1 (CH_2), 31.6 (CH_2), 37.0 (CH_2), 45.3 (CH_2), 56.7 (CH), 59.6 (CH_2), 60.8 (CH), 117.2 (CH_2), 127.5 (CH), 128.0 (CH), 128.8 (CH), 134.6 (CH), 135.8 (C); $[\alpha]^{22}_D$ −61 (*c* 1.0, EtOH). Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 77.95; H, 9.53; N, 5.67. **3b**: IR (film) 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.43−1.60 (m, 6 H), 2.14−2.38 (m, 1 H), 2.45−2.68 (m, 2 H), 2.97−3.05 (m, 1 H), 3.66−3.85 (m, 2 H), 3.76 (t, J = 10.0 Hz, 1 H), 4.93−5.03 (m, 2 H), 5.61−5.82 (m, 5 H), 7.10−7.50 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.4 (CH_2), 25.9 (CH_2), 28.0 (CH_2), 30.9 (CH_2), 43.1 (CH_2), 57.2 (CH), 61.8 (CH_2), 67.7 (CH), 116.1 (CH_2), 127.5 (CH), 128.3 (CH), 128.6 (CH), 136.6 (CH), 140.4 (C).

(*R*)-2-Propylpiperidine [(*R*)-Coniine]. Pd−C (10%, 68 mg) was added to a solution of piperidine **3a** (400 mg, 1.62 mmol) in MeOH (100 mL), and the resulting suspension was hydrogenated at atmospheric pressure for 24 h. The catalyst was removed by filtration, and the solution was acidified by addition of a few drops of methanolic HCl and concentrated. The residue was dissolved in water and washed with Et_2O, and the aqueous phase was evaporated. The resulting residue was purified by crystallization (Et_2O−EtOH) to give pure (*R*)-coniine hydrochloride (195 mg, 73%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.91 (t, J = 7.5 Hz, 3 H), 1.35−1.41 (m, 3 H), 1.57−1.63 (m, 1 H), 1.65−1.73 (m, 1 H), 1.76−1.80 (m, 1 H), 1.84−2.00 (m, 4 H), 2.75−2.82 (m, 1 H), 2.84−2.93 (m, 1 H), 3.41 (dm, J = 12.5 Hz, 1 H), 9.17 (br s, 1 H), 9.43 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 13.6 (CH_3), 18.4 (CH_2), 22.0 (CH_2), 22.2 (CH_2), 27.9 (CH_2), 35.2 (CH_2), 44.6 (CH_2), 56.9 (CH); $[\alpha]^{22}_D$ −7.1 (*c* 1.0, EtOH) {lit.[14b] $[\alpha]^{23}_D$ −7.3 (*c* 0.33, EtOH)}.

(6*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-6-methyl-2-piperidone (4a). MeLi (17.3 mL of a 1.5 M solution in Et_2O, 26.0 mmol) was added to a suspension of CuCN (1.16 g, 13.0 mmol) in anhydrous THF (40 mL) at −78 °C, and the mixture was stirred under nitrogen for 2 h. The resulting suspension was added via cannula to a solution of lactam **1** (945 mg, 4.35 mmol) and BF_3·Et_2O (1.65 mL, 13.0 mmol) in anhydrous THF (5 mL) at − 78 °C, and the stirring was continued for 2 h. The crude mixture was poured into saturated aqueous NH_4Cl, the organic layer was extracted with AcOEt, and the combined organic extracts were dried, filtered, and concentrated to give an oil (1.6 g). Flash chromatography (AcOEt) afforded compound **4** (710 mg, 70%) as a 97:3 mixture of epimers **4a** and **4b**, respectively. Pure **4a** was obtained by crystallization from Et_2O: IR (film) 3550, 1616 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.20 (d, J = 7.0 Hz, 3 H), 1.60−2.00 (m, 4 H), 2.48 (ddd, J = 17.0, 10.0, 7.5 Hz, 1 H), 2.54 (dddd, J = 17.0, 8.0, 3.5, 1.0 Hz, 1 H), 3.48−3.54 (m, 1 H), 4.04 (ddd, J = 12.0, 4.0, 3.5 Hz, 1 H), 4.28 (ddd, J = 12.0, 9.0, 7.0 Hz, 1H), 4.46 (dd, J = 9.0, 4.0 Hz, 1 H), 4.60 (dd, J = 7.0, 3.5 Hz, 1 H), 7.20−7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.0 (CH_2), 19.6 (CH_3), 29.3 (CH_2), 31.8 (CH_2), 52.8 (CH), 63.4 (CH_2), 64.5 (CH), 127.2 (CH), 127.3 (CH), 128.2 (CH), 137.4 (C), 171.6 (C); mp 81−83 °C (lit.[16b] mp 82 °C); $[\alpha]^{22}_D$ −19 (*c* 1.0, EtOH) {lit.[16b] $[\alpha]^{20}_D$ −12.2 (*c* 1.3, MeOH)}. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.20; N, 6.00. Found: C, 71.78; H, 8.27; N, 5.84.

(6*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-6-propyl-2-piperidone (5a). Operating as above, starting from lactam **1** (1.44 g, 6.63 mmol) and *n*-PrLi (49.5 mL of a 0.8 M solution in Et_2O, 39.6 mmol), compound **5** (1.1 g, 65%) was obtained as a 93:7 mixture of epimers **5a** and **5b**, respectively, after purification of the crude mixture by flash chromatography (AcOEt). Crystallization from Et_2O afforded pure **5a**: IR (film) 3403, 1645 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J = 7.0 Hz, 3 H), 1.00−2.00 (m, 8 H), 2.46−2.54 (m, 2 H), 3.20−3.26 (m, 1 H), 4.00 (dd, J = 11.8, 3.2 Hz, 1 H), 4.18−4.29 (m, 1 H), 4.54 (dd, J = 7.0, 3.2 Hz, 1 H), 4.67 (br s, 1 H), 7.27−7.34 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 13.7 (CH_3), 15.8 (CH_2), 19.5 (CH_2), 25.3 (CH_2), 31.7 (CH_2), 34.4 (CH_2), 57.7 (CH), 64.1 (CH_2), 66.1 (CH), 127.4 (CH), 127.5 (CH), 128.4 (CH), 137.3 (C), 171.8 (C); $[\alpha]^{22}_D$ −32 (*c* 2.0, MeOH). Anal. Calcd for $C_{16}H_{23}NO_2$·$^1/_3H_2O$: C, 71.87; H, 8.92; N, 5.24. Found: C, 71.73; H, 8.91; N, 5.24.

(6*R*)-6-Butyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-piperidone (6a). Operating as above, starting from lactam **1** (250 mg, 1.15 mmol) and *n*-BuLi (4.4 mL of a 1.6 M solution in hexane, 7.0 mmol), compound **6** (205 mg, 65%) was obtained as a 91:9 mixture of epimers **6a** and **6b**, respectively, after purification of the crude mixture by flash chromatography (Et_2O). **6a**: IR (film) 3480, 1593 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.86 (t, J = 7.5 Hz, 3 H), 1.00−1.15 (m, 1 H), 1.20−1.35 (m, 3 H), 1.45−1.60 (m, 2 H), 1.60−1.80 (m, 2 H), 1.82−1.90 (m, 2 H), 2.47−2.52 (m, 2 H), 3.18−3.22 (m, 1 H), 4.02 (ddd, J = 11.0, 3.0, 3.0 Hz, 1 H), 4.24−4.30 (m, 1 H), 4.53 (dd, J = 7.0, 3.5 Hz, 1 H), 4.59 (dd, J = 8.5, 3.0 Hz, 1 H), 7.20−7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.8 (CH_3), 16.0 (CH_2), 22.4 (CH_2), 25.4 (CH_2), 28.5 (CH_2), 31.9 (CH_2), 32.0 (CH_2), 58.0 (CH), 64.3 (CH_2), 66.3 (CH), 127.4 (CH), 127.5 (CH), 128.4 (CH), 137.4 (C), 171.8 (C); $[\alpha]^{22}_D$ −37 (*c* 1.0, EtOH). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.08. Found: C, 73.96; H, 9.14; N, 5.08.

(6*S*)-[(1*R*)-2-Hydroxy-1-phenylethyl]-6-phenyl-2-piperidone (7a). Operating as above, starting from lactam **1** (200 mg, 0.92 mmol) and PhLi (3.0 mL of a 1.8 M solution in 7:3 cyclohexanes−Et_2O, 5.5 mmol), epimeric compounds **7a** (182 mg, 67%) and **7b** (22 mg, 8%) were obtained after flash chromatography (99:1 $CHCl_3$−EtOH). **7a:** IR (KBr) 3500−3300, 1613 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.65−1.80 (m, 2 H), 1.82−1.92 (m, 1 H), 2.00−2.14 (m, 1 H), 2.62 (ddd, J = 17.0, 10.0, 7.0 Hz, 1 H), 2.73 (m, 1 H), 4.02 (dd, J = 12.4, 3.0 Hz, 1 H), 4.10 (dd, J = 12.4, 6.4 Hz, 1 H), 4.21 (dd, J = 6.4, 3.0 Hz, 1 H), 4.51 (dd, J = 5.3, 4.5 Hz, 1 H), 7.20−7.40 (m, 10 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.9 (CH_2), 31.5 (CH_2), 32.8 (CH_2), 62.6 (CH), 64.4 (CH_2), 67.9 (CH), 126.5 (CH), 127.4 (CH), 127.4 (CH), 127.6 (CH), 128.4 (CH), 128.7 (CH), 137.1 (C), 140.7 (C), 172.6 (C); mp 124−125 °C (Et_2O); $[\alpha]^{22}_D$ +10.8 (*c* 0.54, EtOH). Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.25; H, 7.16; N, 4.74. Found: C, 77.29; H, 7.20; N, 4.73. **7b:** IR (KBr) 3400−3200, 1612 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.60−1.90 (m, 4 H), 2.58 (ddd, J = 17.2, 9.7, 7.4 Hz, 1 H), 2.72 (dm, J = 17.2 Hz, 1 H), 3.73 (dd, J = 11.3, 8.5 Hz, 1 H), 3.79 (dd, J = 11.3, 6.0 Hz, 1 H), 4.36 (dd, J = 4.4, 3.6 Hz, 1 H), 5.90 (dd, J = 8.5, 6.0 Hz, 1 H), 7.11−7.30 (m, 10 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.0 (CH_2), 31.8 (CH_2), 32.0 (CH_2), 58.2 (CH), 60.4 (CH), 63.0 (CH_2), 126.7 (CH), 128.4 (CH), 128.6 (CH), 127.6 (CH), 128.0 (CH), 136.6 (C), 141.9 (C), 172.7 (C); mp 144−146 °C (Et_2O); $[\alpha]^{22}_D$ −26 (*c* 0.32, EtOH). Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.25; H, 7.16; N, 4.74. Found: C, 77.24; H, 7.20; N, 4.76.

(2*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-2-methylpiperidine (8). Piperidone **4a** (100 mg, 0.43 mmol) was added to a suspension of $LiAlH_4$ (82 mg, 2.2 mmol) in anhydrous THF (30 mL), and the resulting mixture was stirred for 1 h at 0 °C. Then, a 15% aqueous NaOH solution (15 mL) was slowly added, and the crude mixture was filtered through a Celite pad. The solution was washed with brine, and the aqueous layer was extracted with Et_2O. The organic extracts were dried, filtered, and concentrated to give a yellow oil (103 mg), which was purified by flash chromatography (AcOEt) affording compound **8** (80 mg, 85%) as an oil: IR (film) 3400−3200 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.08−1.20 (m, 1 H), 1.28 (d, J = 5.8 Hz, 3 H), 1.32−1.50 (m, 2 H), 1.57−1.62 (m, 3 H), 1.70 (td, J = 11.5, 2.5 Hz, 1 H), 2.42 (m, 1 H), 2.88 (dm, J = 11.5 Hz, 1 H), 3.54 (dd, J = 10.5, 5.2 Hz, 1 H), 3.98 (t, J = 10.5 Hz, 1 H), 4.31 (dd, J = 10.5, 5.2 Hz, 1 H), 7.16−7.34 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.1 (CH_3), 24.5 (CH_2), 26.5 (CH_2), 36.0 (CH_2), 45.5 (CH_2), 53.5 (CH), 59.0 (CH_2), 60.8 (CH), 127.6 (CH), 128.0 (CH), 128.2 (CH), 135.6 (C); $[\alpha]^{22}_D$ −59 (*c* 0.5, EtOH) {lit.[40] $[\alpha]^{20}_D$ − 83.3 (*c* 1.16, $CHCl_3$)}. Anal. Calcd for $C_{14}H_{21}NO$: C, 76.66; H, 9.65; N, 6.38. Found: C, 76.81; H, 9.74; N, 6.10.

(*R*)-*N*-(*tert*-Butoxycarbonyl)-2-methylpiperidine (9). A solution of compound **8** (273 mg, 1.24 mmol) and di-*tert*-butyl dicarbonate (470 mg, 2.15 mmol) in AcOEt (40 mL) containing 10% $Pd(OH)_2$−C (100 mg) was hydrogenated at 25 °C for 48 h. The catalyst was removed by filtration, and the solvent was evaporated to give an oil. Flash chromatography (9:1 hexanes−Et_2O) afforded carbamate **9** (220 mg, 89%): IR (film) 1693 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.12 (d, J = 7.0 Hz, 3 H), 1.20−1.70 (m, 6 H), 1.46 (s, 9 H), 2.81 (td, J = 12.7, 2.3 Hz, 1 H), 3.92 (dm, J = 13.4 Hz, 1 H), 4.38 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.6 (CH_3), 18.6 (CH_2), 25.6 (CH_2), 28.4 (CH_3), 30.0 (CH_2), 38.6 (CH_2), 45.9 (CH), 78.9 (C), 154.9 (C); $[\alpha]^{22}_D$ − 47 (*c* 1.5, $CHCl_3$) {lit.[18] $[\alpha]^{20}_D$ − 46.4 (*c* 0.83, $CHCl_3$)}.

(*R*)-6-Methyl-2-piperidone (10). A solution of lactam **4a** (300 mg, 1.29 mmol) in THF (15 mL) was cooled to − 78 °C and then ammonia was bubbled through the flask until approximately 40 mL was collected. The reaction mixture was allowed to warm to −33 °C, and small pieces of sodium were added until the blue color persisted. After 30 s of stirring, the mixture was quenched by slow addition of solid NH_4Cl. The ammonia was evaporated by allowing the reaction mixture to warm to room temperature, and the resulting mixture was poured into water and extracted with $CHCl_3$. The organic layer was dried, filtered, and concentrated to give a residue, which was chromatographed (AcOEt) affording piperidone **10** (108 mg, 74%): IR (KBr) 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20 (d, J = 6.6 Hz, 3 H), 1.21−1.40 (m, 1 H), 1.60−1.80 (m, 1 H), 1.87−1.91 (m, 2 H), 2.27−2.30 (m, 1 H), 2.37 (dm, J = 18.0 Hz, 1 H), 3.51 (m, 1 H), 6.45 (br s, 1 H);^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.8 (CH_2), 22.7 (CH_3), 30.4 (CH_2), 30.9 (CH_2), 48.7 (CH), 172.4 (C); $[\alpha]^{22}_D$ − 24 (*c* 2.5, CH_2Cl_2) {lit.[41] $[\alpha]^{22}_D$ − 21.9 (*c* 1.92, H_2O)}.

(2*R*,5*R*)-5-Methyl-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (11). A solution of lactam **4a** (1.69 g, 7.24 mmol) in anhydrous THF (100 mL) was cooled to − 78 °C, and then an excess of Red-Al (6.53 mL of a 65% solution in toluene 21.7 mmol) was added in three portions at intervals of 40 min. The resulting solution was stirred at − 78 °C for 24 h, and a 25% aqueous KOH solution (25 mL) was slowly added. The aqueous layer was extracted with AcOEt, and the combined organic extracts were dried, filtered, and concentrated to give an oil. Flash chromatography (7:2 AcOEt−hexane) afforded compound **11** (1.1 g, 70%) as a mixture of epimers, which could not be separated, and minor amounts of piperidine **8**. **11**: IR (film) 2934 cm^{-1}; MS *m*/*z* (rel intensity) 217 (M, 22), 216 (M − 1, 71), 202 (100). Major epimer: ^1H NMR ($CDCl_3$, 300 MHz) δ 0.90 (d, J = 7.0 Hz, 3 H), 1.20−1.80 (m, 5 H), 2.00−2.04 (m, 1 H), 3.14 (m, 1 H), 3.57 (t, J = 7.5 Hz, 1 H), 3.92 (t, J = 7.5 Hz, 1 H), 4.10 (t, J = 7.5 Hz, 1 H), 4.23 (dd, J = 9.5, 3.0 Hz, 1 H), 7.26−7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.6 (CH_3), 18.4 (CH_2), 31.3 (CH_2), 32.2 (CH_2), 47.7 (CH), 62.3 (CH), 73.7 (CH_2), 87.6 (CH), 128.7 (CH), 129.0 (CH), 129.5 (CH), 139.0 (C). Minor epimer: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.08 (d, J = 6.0 Hz, 3H), 1.20−1.80 (m, 5 H), 2.21−2.26 (m, 1 H), 3.10−3.20 (m, 1 H), 4.00 (dd, J = 8.0, 2.0 Hz, 1 H), 4.33 (dd, J = 9.5, 3.0 Hz, 1 H), 4.38 (dd, J = 8.0, 6.5 Hz, 1 H), 4.53 (dd, J = 6.5, 2.0 Hz, 1 H), 7.26−7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.9 (CH_3), 22.3 (CH_2), 31.3 (CH_2), 34.3 (CH_2), 50.8 (CH), 62.0 (CH), 73.0 (CH_2), 90.7 (CH), 127.8 (CH), 128.1 (CH), 128.4 (CH), 140.9 (C).

(2*R*,6*S*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-2-methyl-6-propylpiperidine (12). A solution of compound **11** (500 mg, 2.30 mmol) in anhydrous Et_2O (8 mL) was slowly added to a cooled (−60 °C) solution of propylmagnesium bromide [prepared from magnesium turnings (559 mg) and 1-bromopropane (2.1 mL, 23 mmol) in anhydrous THF (5 mL)], and the resulting mixture was stirred at −60 °C for 20 h and poured into brine. The aqueous layer was extracted with AcOEt, and the organic extracts were dried, filtered, and concentrated to give an oil, which was purified by flash chromatography (AcOEt) affording piperidine **12** (480 mg, 80%): IR (film) 3400−3200 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.91 (t, J = 7.2 Hz, 3 H), 1.06 (d, J = 6.6 Hz, 3 H), 1.10−1.65 (m, 10 H), 2.83−2.89 (m, 1 H), 2.88−3.20 (m, 1 H), 3.69 (dd, J = 10.3, 5.5 Hz, 1 H), 3.80 (dd, J = 10.3, 7.6 Hz, 1 H), 4.00 (dd, J = 7.6, 5.5 Hz, 1 H), 7.31−7.33 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.3 (CH_3), 15.5 (CH_2), 20.0 (CH_3), 21.1 (CH_2), 26.1 (CH_2), 31.1 (CH_2), 36.5 (CH_2), 50.4 (CH), 52.5 (CH), 61.7 (CH_2), 65.0 (CH), 127.4 (CH), 128.2 (CH), 128.3 (CH), 139.9 (C); $[\alpha]^{22}_D$ − 3.4 (*c* 1.0, CH_2Cl_2). Anal. Calcd for $C_{17}H_{27}NO$: C, 78.11; H, 10.41; N, 5.35. Found: C, 78.16; H, 10.50; N, 5.27.

(2*R*,6*S*)-2-Methyl-6-propylpiperidine [(2*R*,6*S*)-Dihydropinidine]. A solution of piperidine **12** (410 mg, 1.57 mmol) in MeOH (20 mL) containing 10% $Pd(OH)_2$−C (246 mg) was hydrogenated for 4 h at room temperature. The catalyst was removed by filtration, and the resulting solution was acidified by addition of methanolic HCl. The solvent was removed under reduced pressure, and the residue was dissolved in water. The aqueous solution was washed with Et_2O and concentrated, and

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the residue was purified by crystallization (2:1 EtOH−AcOEt) to give pure (2*R*,6*S*)-dihydropinidine hydrochloride (182 mg, 65%) as a white solid: IR (film) 2937 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.90 (t, J = 7.5 Hz, 3 H), 1.26−1.36 (m, 1 H), 1.38−1.50 (m, 2 H), 1.57 (d, J = 6.5 Hz, 3 H), 1.58−1.66 (m, 1 H), 1.70−1.84 (m, 3 H), 1.86−1.98 (m, 2 H), 2.08−2.18 (m, 1 H), 2.84−2.94 (m, 1 H), 3.02−3.12 (m, 1 H), 9.05 (br s, 1 H), 9.43 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.6 (CH_3), 18.6 (CH_2), 19.2 (CH_3), 22.7 (CH_2), 27.2 (CH_2), 30.4 (CH_2), 35.0 (CH_2), 54.2 (CH), 58.1 (CH); mp 247−249 °C (lit.[25a] mp 242−243 °C); $[\alpha]^{22}_D$ +12 (*c* 1.0, EtOH) {lit.[21a] $[\alpha]^{22}_D$ +12.5 (*c* 1.0, EtOH)}.

(2*R*,6*R*)-2-[3-(1,3-Dioxolan-2-yl)propyl]-1-[(1*R*)-2-hydroxy-1-phenylethyl]-6-methylpiperidine (13). A solution of 3-(ethylenedioxy)-1-propylmagnesium bromide [prepared from 2-(3-bromopropyl)-1,3-dioxane (2.24 g, 11.5 mmol) and magnesium turnings (280 mg) in anhydrous THF (9 mL)] was slowly added to a solution of compound **11** (634 mg, 2.92 mmol) in THF (48 mL) at 0 °C, and the resulting solution was stirred for 30 min. The ice bath was removed and the mixture was stirred at room temperature for 72 h. The crude mixture was poured into brine, the aqueous layer was extracted with Et_2O, and the combined organic extracts were dried, filtered, and concentrated. Flash chromatography (gradient from 1:1 hexane−AcOEt to AcOEt) of the residue afforded compound **13** (670 mg, 69%): IR (film) 3453 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.06 (d, J = 6.6 Hz, 3 H), 1.00−1.75 (m, 12 H), 2.84−2.89 (m, 1 H), 2.90−3.04 (m, 1 H), 3.69 (dd, J = 10.0, 5.5 Hz, 1 H), 3.80 (dd, J = 10.0, 8.0 Hz, 1 H), 3.84 (m, 1 H), 3.85 (dd, J = 5.0, 3.0 Hz, 1 H), 3.95 (dd, J = 5.0, 3.0 Hz, 1 H), 3.97 (m, 1 H), 4.00 (dd, J = 8.0, 5.5 Hz, 1 H), 4.84 (t, J = 4.7 Hz, 1 H), 7.25−7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.5 (CH_2), 20.2 (CH_3), 22.3 (CH_2), 25.9 (CH_2), 31.0 (CH_2), 33.9 (CH_2), 34.3 (CH_2), 50.3 (CH), 52.7 (CH), 61.6 (CH_2), 64.8 (CH_2), 65.0 (CH), 104.3 (CH), 127.4 (CH), 128.2 (CH), 128.3 (CH), 140.0 (C). Anal. Calcd for $C_{20}H_{32}ClNO_3$: C, 64.93; H, 8.72; N, 3.79. Found: C, 64.58; H, 8.73; N, 3.77.

(4*R*,9a*S*)-4-Methylquinolizidine (14). Piperidine **13** (150 mg, 0.45 mmol) was dissolved in a 0.06 M aqueous HCl solution (10 mL) and hydrogenated at atmospheric pressure and room temperature for 72 h in the presence of 10% Pd−C (35 mg). The mixture was filtered, washed with Et_2O, basified by addition of solid Na_2CO_3, and extracted with CH_2Cl_2. The organic solution was concentrated to give **14** as an oil, which was taken up with an ethereal HCl solution. Elimination of the solvent under reduced pressure afforded the hydrochloride of compound **14** (56 mg, 66%) as a white solid: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.56 (d, J = 6.3 Hz, 3 H), 1.40−1.68 (m, 8 H), 1.75−1.92 (m, 6 H), 2.06−2.60 (m, 5 H), 2.76 (m, 1 H), 2.88 (m, 1 H), 3.82 (dm, J = 11.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.5 (CH_3), 22.5 (CH_2), 22.7 (CH_2), 23.0 (CH_2), 30.3 (CH_2), 30.4 (CH_2), 31.7 (CH_2), 51.1 (CH_2), 62.2 (CH), 65.3 (CH); $[\alpha]^{22}_D$ − 23 (*c* 0.5, $CHCl_3$). Anal. Calcd for $C_{10}H_{20}ClN\cdot H_2O$: C, 61.01; H, 10.65; N, 7.11. Found: C, 61.01; H, 10.54; N, 7.14. For the base: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.09 (d, J = 6.0 Hz, 3 H), 1.15−2.00 (m, 15 H), 3.26 (dm, J = 10.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.7 (CH_3), 24.5 (CH_2), 24.6 (CH_2), 26.3 (CH_2), 33.8 (CH_2), 34.0 (CH_2), 35.3 (CH_2), 51.7 (CH_2), 59.0 (CH), 63.0 (CH).

(3*R*,5*R*)-3-Phenyl-5-propyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (15). Operating as described for **11**, starting from lactam **5a** (400 mg, 1.53 mmol), compound **15** (mixture of epimers, 255 mg, 68%) and (2*R*)-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-propylpiperidine (deoxo-**5a**; 61 mg, 16%) were obtained after purification of the crude mixture by flash chromatography (7:3 AcOEt−hexane). Major epimer: ^1H NMR ($CDCl_3$, 300 MHz) δ 0.81 (t, J = 7.2 Hz, 3 H), 0.88−2.10 (m, 10 H), 2.86 (m, 1 H), 3.58 (t, J = 7.2 Hz, 1 H), 4.02 (t, J = 7.2 Hz, 1 H), 4.10 (dd, J = 7.8, 6.9 Hz, 1 H), 4.23 (dd, J = 9.3, 3.3 Hz, 1 H), 7.20−7.45 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2 (CH_3), 17.9 (CH_2), 20.6 (CH_2), 24.7 (CH_2), 27.4 (CH_2), 31.6 (CH_2), 52.2 (CH), 61.3 (CH), 73.3 (CH_2), 87.7 (CH), 127.5 (CH), 127.9 (CH), 128.4 (CH), 139.5 (C). Minor epimer: ^1H NMR ($CDCl_3$, 300 MHz) δ 0.77 (t, J = 7.2 Hz, 3 H), 0.90−2.10 (m, 10 H), 2.14−2.25 (m, 1 H), 4.00 (dd, J = 8.1, 2.7 Hz, 1 H), 4.34 (dd, J = 9.6, 3.0 Hz, 1 H), 4.38 (dd, J = 8.1, 6.9 Hz, 1 H), 4.55 (dd, J = 6.9, 2.7 Hz, 1 H), 7.20−7.50 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2 (CH_3), 18.5 (CH_2), 21.7 (CH_2), 30.3 (CH_2), 30.7 (CH_2), 36.0 (CH_2), 54.8 (CH), 61.0 (CH), 72.6 (CH_2), 90.4 (CH), 127.3 (CH), 128.2 (CH), 128.9 (CH), 140.1 (C). Deoxo-**5a**: IR (film) 3595 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.85−1.80 (m, 10 H), 0.95 (t, J = 7.5 Hz, 3 H), 1.80 (td, J 11.3, 2.3 Hz, 1 H), 2.39 (m, 1 H), 2.89 (dm, J = 11.5 Hz, 1 H), 3.58 (dd, J = 10.4, 5.2 Hz, 1 H), 3.99 (t, J = 10.4 Hz, 1 H), 4.32 (dd, J = 10.4, 5.2 Hz, 1 H), 7.10−7.50 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.7 (CH_3), 17.7 (CH_2), 24.0 (CH_2), 26.2 (CH_2), 31.4 (CH_2), 34.8 (CH_2), 45.6 (CH_2), 57.3 (CH), 59.5 (CH_2), 60.5 (CH), 127.6 (CH), 128.5 (CH), 128.9 (CH), 135.8 (C); $[\alpha]^{22}_D$ −58.4 (c 0.83, EtOH). Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.67; H, 10.12; N, 5.74.

(2*R*,6*R*)-2-[2-(1,3-Dioxan-2-yl)ethyl]-1-[(1*R*)-2-hydroxy-1-phenylethyl-6-methylpiperidine (16). A solution of 2-[2-(bromomagnesio)ethyl]-1,3-dioxane [prepared from 2-(2-bromoethyl)-1,3-dioxane (0.35 mL, 3.0 mmol) and magnesium turnings (73 mg) in anhydrous THF (6 mL)] was slowly added at 0 °C to a solution of compound **11** (160 mg, 0.74 mmol) in THF (4 mL), and the resulting solution was stirred for 20 h. The crude mixture was poured into brine and extracted with AcOEt. The organic extracts were dried, filtered, and concentrated. Flash chromatography (gradient from hexane to AcOEt) of the residue afforded compound **16** (174 mg, 71%): IR (film) 3439 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.07 (d, J = 6.7 Hz, 3 H), 1.10−1.80 (m, 11 H), 2.00−2.20 (m, 1 H), 2.84−2.94 (m, 1 H), 2.96−3.10 (m, 1 H), 3.71 (dd, J = 10.5, 5.5 Hz, 1 H), 3.78 (t, J = 11.0 Hz, 1 H), 3.79 (m, 1 H), 3.82 (dd, J = 10.5, 7.5 Hz, 1 H), 4.02 (dd, J = 7.3, 5.3 Hz, 1 H), 4.13 (m, 2 H), 4.53 (t, J = 4.6 Hz, 1 H), 7.20−7.50 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.3 (CH_2), 20.1 (CH_3), 25.8 (CH_2), 28.3 (CH_2), 30.9 (CH_2), 33.4 (CH_2), 50.0 (CH), 52.4 (CH), 61.8 (CH_2), 65.1 (CH), 66.8 (2 CH_2), 102.3 (CH), 127.4 (CH), 128.2 (CH), 128.4 (CH), 140.0 (C). Anal. Calcd for $C_{20}H_{31}NO_3$: C, 72.04; H, 9.37; N, 4.20. Found: C, 72.12; H, 9.38; N, 4.17.

(2*R*,6*R*)-2-[2-(1,3-Dioxan-2-yl)ethyl]-1-[(1*R*)-2-hydroxy-1-phenylethyl]-6-propylpiperidine (17). Operating as above, starting from compound **15** (433 mg, 1.76 mmol) piperidine **17** (492 mg, 77%) was obtained after purification by flash chromatography (gradient from 1:1 hexane−AcOEt to AcOEt): IR (film) 3590 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.83 (t, J = 7.4 Hz, 3 H), 0.90−1.80 (m, 15 H), 2.08 (m, 1 H), 2.75−2.82 (m, 1 H), 2.91−3.01 (m, 1 H), 3.70 (dd, J = 10.5, 5.0, 1 H), 3.74−3.83 (m, 2 H), 3.84 (dd, J = 10.7, 7.5 Hz, 1 H), 3.98 (dd, J = 7.4, 5.2 Hz, 1 H), 4.10−4.15 (m, 2 H), 4.54 (t, J = 4.6 Hz, 1 H), 7.25−7.45 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2 (CH_3), 14.7 (CH_2), 20.8 (CH_2), 25.8 (2 CH_2), 27.2 (CH_2), 27.9 (CH_2), 33.5 (CH_2), 35.6 (CH_2), 52.3 (CH), 56.0 (CH), 62.0 (CH_2), 66.9 (2 CH_2), 67.2 (CH), 102.3 (CH), 127.6 (CH), 128.3 (CH), 128.6 (CH).

(5*R*,8a*R*)-5-Methylindolizine (18). A solution of compound **16** (200 mg, 0.60 mmol) in EtOH (10 mL) and 1.0 M aqueous HCl (1 mL) containing 10% Pd−C (30 mg) was hydrogenated under vigorous stirring at room temperature and atmospheric pressure for 18 h. The catalyst was removed by filtration, and the solution was concentrated under vacuum. The residue was taken-up with 1.0 N aqueous HCl (10 mL) and extracted with Et_2O. The aqueous layer was basified by addition of solid Na_2CO_3 and extracted with Et_2O. The ethereal solution was acidified by addition of a few drops of ethereal HCl and concentrated under vacuum to give the hydrochloride of **18** (86 mg, 82%) as a white solid: IR (film) 3398 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, assigned by $^1H-^1H$ correlation NMR experiments) δ 1.45 (qd, J = 13.5, 4.5 Hz, 1 H, H-7), 1.47 (d, J = 6.5 Hz, 3H, CH_3), 1.79 (dm, J = 14.5 Hz, 1 H, H-6), 1.87−2.00 (m, 4 H, H-1, H-2, H-6, H-8), 2.05−2.26 (m, 4 H, H-1, H-2, H-6, H-8), 2.65 (m, 1 H, H-3), 2.72−2.80 (m, 1 H, H-8a), 2.80−2.84 (m, 1 H, H-5), 3.78−3.82 (m, 1 H, H-3), 11.6 (br s, 1H, NH);

^{13}C NMR ($CDCl_3$, 75 MHz, assigned by ^{1}H−^{13}C NMR correlation experiments) δ 18.0 (CH_3), 19.1 (C-2), 23.0 (C-7), 27.0 (C-1), 28.4 (C-8), 30.8 (C-6), 50.2 (C-3), 61.0 (C-5), 67.6 (C-8a); $[\alpha]^{22}_D$ −96 (*c* 1.0, EtOH). Anal. Calcd for $C_9H_{18}ClN$: C, 61.52; H, 10.33; N, 7.97. Found: C, 61.29; H, 10.29; N, 7.76. For the base: IR (film) 2810 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.04 (d, J = 6.7 Hz, 3 H), 1.10−1.80 (m, 11 H), 1.91 (m, 1 H), 1.95 (m, 1 H), 3.13 (tm, J = 9.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.2 (CH_3), 21.0 (CH_2), 24.6 (CH_2), 29.9 (CH_2), 30.4 (CH_2),, 34.0 (CH_2), 51.5 (CH_2), 58.8 (CH), 64.6 (CH).

(5*R*,8a*R*)-5-Propylindolizidine (19) [Gephyrotoxin 167B]. Operating as described for **18**, starting from **17** (321 mg, 0.89 mmol), the hydrochloride of compound **19** (164 mg, 90%) was obtained as a white solid: IR (film) 3350 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.91 (t, J = 7.0 Hz, 3 H), 1.15−1.25 (m, 1 H), 1.26−1.45 (m, 2 H), 1.60.1.80 (m, 1 H), 1.85−2.05 (m, 6 H), 2.06−2.25 (m, 4 H), 2.50−2.65 (m, 2H), 2.66−2.68 (m, 1 H), 3.80−3.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7 (CH_3), 18.9 (CH_2), 19.4 (CH_2), 23.2 (CH_2), 27.1 (CH_2), 27.8 (CH_2), 28.5 (CH_2), 33.5 (CH_2), 50.4 (CH_2), 65.5 (CH), 68.3 (CH). For the base: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.94 (t, J = 6.9 Hz, 3 H), 1.21−2.10 (m, 17 H), 3.32 (td, J = 8.8, 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.5 (CH_3), 19.1 (CH_2), 20.3 (CH_2), 24.6 (CH_2), 30.4 (CH_2), 30.7 (CH_2), 30.8 (CH_2), 36.7 (CH_2), 51.5 (CH_2), 63.8 (CH), 65.1 (CH); $[\alpha]^{22}_D$ −109 (*c* 1.32, CH_2Cl_2) {lit.[28b] $[\alpha]^{20}_D$ −106.9 (*c* 1.1, CH_2Cl_2)}.

(2*S*,6*S*)-2[(2-Butyl-1,3-dioxolan-2-yl)ethynyl]-1-[(1*S*)-2-hydroxy-1-phenylethyl]-6-methylpiperidine (21). A 1.0 M solution of ethylmagnesium bromide (3.7 mL, 3.7 mmol) in THF was slowly added to a solution of 2-butyl-2-ethynyl-1,3-dioxolane (567 mg, 3.68 mmol) in anhydrous THF (15 mL) at 0 °C. After 30 min of stirring, the solution was added via cannula to a solution of ***ent*-11** (200 mg, 0.92 mmol) in anhydrous THF (2 mL) at 0 °C. The resulting mixture was warmed to room temperature, stirred for 14 h, poured into brine, and extracted with AcOEt. The organic extracts were dried, filtered, and concentrated to give a residue, which was purified by flash chromatography (98:2 hexanes−Et_2NH) affording piperidine **21** (256 mg, 75%): IR (film) 3460, 2222 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.96 (t, J = 7.3 Hz, 3 H), 1.12 (d, J = 6.8 Hz, 3 H), 1.35−1.45 (m, 4 H), 1.53−1.63 (m, 3 H), 1.80−1.94 (m, 5 H), 2.18 (m, 1 H), 2.86−2.91 (m, 1 H), 3.85−3.95 (m, 3 H), 4.00−4.13 (m, 5 H), 7.25−7.50 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0 (CH_3), 14.4 (CH_3), 16.6 (CH_2), 22.6 (CH_2), 26.2 (CH_2), 32.2 (2 CH_2), 38.8 (CH_2), 44.9 (CH), 49.7 (CH), 63.7 (CH_2), 64.5 (2 CH_2), 64.8 (CH), 82.5 (C), 85.7 (C), 103.4 (C), 127.5 (CH), 128.4 (CH), 128.5 (CH), 139.9 (C). Anal. Calcd for $C_{23}H_{33}NO_3$: C, 74.37; H, 8.95; N, 3.77. Found: C, 73.98; H, 9.11; N, 3.52.

(2*S*,6*S*)-2-Methyl-6-(3-oxoheptyl)piperidine (22). A solution of acetal **21** (256 mg, 0.69 mmol) in 0.2 N aqueous HCl (10 mL) containing 10% Pd−C (90 mg) was hydrogenated for 72 h at room temperature and atmospheric pressure. The catalyst was removed by filtration, and the solution was diluted with 2 N aqueous HCl (5 mL) and extracted with Et_2O. The aqueous layer was basified by addition of solid Na_2CO_3 and extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated to give ketone **22** (122 mg, 84%). For the hydrochloride: ^{1}H NMR ($CDCl_3$, 200 MHz, most significant signals) δ 0.87 (t, J = 7.5 Hz, 3 H), 1.54 (d, J = 4.6 Hz, 3 H), 3.00 (m, 1 H), 3.10 (m, 1 H), 9.00 (br s, 1 H), 9.15 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 13.7 (CH_3), 19.2 (CH_3), 22.1 (CH_2), 22.7 (CH_2), 25.6 (CH_2), 27.1 (CH_2), 27.7 (CH_2), 30.1 (CH_2), 38.3 (CH_2), 42.3 (CH_2), 54.0 (CH), 57.4 (CH) 209.3 (C).

(3*R*,5*S*,8a*S*)-3-Butyl-5-methylindolizidine (Monomorine I). A solution of ketone **22** (100 mg, 0.47 mmol) in MeOH (15 mL) containing 10% Pd−C was hydrogenated for 14 h at room temperature and atmospheric pressure. The suspension was filtered, and the solution was concentrated to give an oil (83 mg, 90%), which was identified as the alkaloid monomorine: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, J = 6.8 Hz, 3 H), 1.13 (d, J = 6.5 Hz, 3 H), 1.05−1.95 (m, 16 H), 2.02−2.09 (m, 1 H), 2.18−2.24 (m, 1 H), 2.42−2.50 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.2 (CH_3), 22.9 (CH_3), 22.9 (CH_2), 24.9 (CH_2), 29.4 (CH_2), 29.8 (CH_2), 30.3 (CH_2), 30.9 (CH_2), 35.8 (CH_2), 39.7 (CH_2), 60.3 (CH), 62.9 (CH), 67.1 (CH); $[\alpha]^{22}_D$ +33 (*c* 0.6, hexane) {lit.[32] $[\alpha]^{22}_D$ +34.7 (*c* 1.02, hexane)}.

(6*R*)-1-[(1*R*)-2-(*tert*-Butyldimethylsilyloxy)-1-phenylethyl]-6-methyl-2-piperidone (23). To a solution of alcohol **4a** (685 mg, 2.94 mmol) in anhydrous CH_2Cl_2 (11 mL) were added TBDMSCl (904 mg, 6.0 mmol), Et_3N (0.84 mL, 6.0 mmol), and imidazole (204 mg, 3.0 mmol), and the resulting mixture was stirred under argon at room temperature for 36 h. The crude reaction mixture was poured into saturated aqueous NH_4Cl, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated to give a yellow oil (1.9 g) which, after flash chromatography (1:1 AcOEt−hexane), afforded compound **23** (931 mg, 91%) as a transparent oil: IR (KBr) 1626 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.03 (s, 3 H), 0.04 (s, 3 H), 0.87 (s, 9 H), 0.96 (d, J = 6.5 Hz, 3 H), 1.58−1.64 (m, 1 H), 1.67−2.00 (m, 3 H), 2.33−2.51 (m, 2 H), 3.66−3.70 (m, 1 H), 4.22 (dd, J = 10.4, 6.5 Hz, 1 H), 4.27 (dd, J = 10.4, 6.5 Hz, 1 H), 5.06 (t, J = 6.5 Hz, 1 H), 7.20−7.45 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.6 (CH_3), −5.5 (CH_3), 16.2 (CH_3), 18.0 (C), 20.2 (CH_2), 25.7 (CH_3), 29.8 (CH_2), 31.8 (CH_2), 51.2 (CH), 61.6 (CH), 63.4 (CH_2), 127.2 (CH), 128.1 (CH), 128.2 (CH), 139.0 (C), 170.2 (C); mp 50−52 °C (Et_2O); $[\alpha]^{22}_D$ −19 (*c* 1.0, EtOH). Anal. Calcd for $C_{20}H_{33}NO_2Si$: C, 69.11; H, 9.57; N, 4.03. Found: C, 69.06; H, 9.67; N, 3.97.

(6*R*)-1-[(1*R*)-2-(*tert*-Butyldimethylsilyloxy)-1-phenylethyl]-6-methyl-2-piperidinethione (24). Lawesson's reagent (1.82 g, 4.50 mmol) was added to a solution of lactam **23** (2.60 g, 7.50 mmol) in anhydrous toluene (135 mL) heated at 75 °C, and the resulting solution was stirred for 40 min. The mixture was cooled to room temperature and concentrated under reduced pressure, and the resulting residue was purified by flash chromatography (4:1 hexanes−Et_2O) affording thiolactam **24** (2.24 g, 82%) as a brown solid: IR (film) 1470 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.11 (s, 3 H), 0.12 (s, 3 H), 0.60 (d, J = 6.8 Hz, 3 H), 0.90 (s, 9 H), 1.60−1.95 (m, 5 H), 3.04 (ddd, J = 18.2, 8.9, 5.5 Hz, 1 H), 3.33 (ddd, J = 18.2, 8.5, 5.4 Hz, 1 H), 4.06−4.10 (m, 1 H), 4.19 (dd, J = 10.7, 5.5 Hz, 1 H), 4.30 (dd, J = 10.7, 5.5 Hz, 1 H), 7.19 (t, J = 5.5 Hz, 1 H), 7.35 (m, 3 H), 7.57 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.7 (CH_3), −5.5 (CH_3), 16.2 (CH_2), 18.0 (C), 19.3 (CH_3), 25.7 (CH_3), 28.6 (CH_2), 39.9 (CH_2), 51.9 (CH), 61.4 (CH_2), 63.3 (CH), 127.9 (CH), 128.3 (CH), 129.2 (CH), 136.8 (C), 200.9 (C); mp 58−61 °C; $[\alpha]^{22}_D$ −169 (*c* 0.29, EtOH).

(2*R*,6*R*)-[(1*R*)-2-(*tert*-Butyldimethylsilyloxy)-1-phenylethyl]-2,6-dimethylpiperidine (26). Iodomethane (1.2 mL, 19 mmol) was added to a solution of thiolactam **24** (700 mg, 1.93 mmol) in anhydrous Et_2O (1 mL), and the mixture was stirred at room temperature for 14 h. Evaporation of the solvent and excess of iodomethane under nitrogen at reduced pressure afforded iminium salt **25** as an orange foam: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.02 (s, 6 H), 0.68 (d, J = 6.6 Hz, 3 H), 0.76 (s, 9 H), 1.65−2.15 (m, 4 H), 2.92 (s, 3 H), 3.11 (dt, J = 20.5, 7.5 Hz, 1 H), 3.90 (ddd, J = 20.5, 8.7, 1.3 Hz, 1 H), 4.18 (dd, J = 11.2, 5.0 Hz, 1 H), 4.33 (dd, J = 11.2, 8.0 Hz, 1 H), 5.78 (dd, J = 8.0, 5.0 Hz, 1 H), 7.25−7.48 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −4.0 (2 CH_3), 14.1 (CH_2), 18.0 (CH_3), 20.0 (CH_3), 25.5 (3 CH_3), 27.6 (CH_2), 32.8 (CH_2), 55.4 (CH), 61.0 (CH_2), 69.2 (CH), 129.0 (2 CH), 129.3 (2 CH), 130.0 (CH), 131.1 (C), 193.5 (C). Compound **25** was dissolved in anhydrous THF (7 mL), cooled to 0 °C, and added via cannula to a 0.2 M solution of Me_2CuLi·LiI (19 mL) in THF−Et_2O. The mixture was stirred at − 5 °C for 30 min and then $NaBH_4$ (154 mg, 4.07 mmol) was added. The resulting suspension was stirred at 0 °C for 10 min, glacial AcOH (3.5 mL) was slowly added, and the stirring was continued for 1 h at room temperature. The crude reaction mixture was poured into water (15 mL) and solid Na_2CO_3 was added till alkaline pH. The aqueous

layer was extracted with Et_2O, and the combined organic extracts were dried, filtered, and concentrated to give a yellow oil (632 mg) which, after flash chromatography (1:1 Et_2O−hexane), afforded compound **26** (368 mg, 55%) and **(2*R*)-1-[(1*R*)-2-(*tert*-butyldimethylsilyloxy)-1-phenylethyl]-2-methylpiperidine** (*O*-TBDMS-**8**, 96 mg, 15%). **26**: IR (film) 2928 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.03 (s, 3 H), 0.05 (s, 3 H), 0.85−0.87 (m, 15 H), 1.25−1.32 (m, 2 H), 1.50−1.60 (m, 4 H), 3.18 (m, 2 H), 3.97 (dd, J = 10.0, 6.0 Hz, 1 H), 4.03 (dd, J = 10.0, 7.0 Hz, 1 H), 4.14 (t, J = 6.3 Hz, 1 H), 7.10−7.50 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.3 (2 CH_3), 18.3 (2 CH_3), 18.6 (C), 19.8 (CH_2), 25.9 (3 CH_3), 34.0 (2 CH_2), 48.5 (2 CH), 61.9 (CH), 64.6 (CH_2), 125.9 (CH), 127.6 (2 CH), 128.2 (2 CH), 144.0 (C); $[\alpha]^{22}_D$ −40 (*c* 1.8, EtOH). Anal. Calcd for $C_{21}H_{37}NOSi$: C, 72.56; H, 10.73; N, 4.03. Found: C, 72.56; H, 10.71; N, 4.04. *O*-TBDMS-**8**: IR (film) 2954 cm^{-1}; ^1H MNR ($CDCl_3$, 300 MHz) δ −0.07 (s, 3 H), −0.04 (s, 3 H), 0.78 (s, 9 H), 1.13 (d, J = 6.2 Hz, 3 H), 1.05−1.19 (m, 1 H), 1.20−1.35 (m, 1 H), 1.47−1.59 (m, 4 H), 2.16−2.24 (m, 1 H), 2.37−2.42 (m, 1 H), 2.72−2.78 (m, 1 H), 3.85−4.03 (m, 3 H), 7.24−7.28 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.5 (CH_3), −5.4 (CH_3), 17.2 (CH_3), 22.8 (CH_2), 25.7 (CH_3), 26.5 (CH_2), 34.6 (CH_2), 46.6 (CH_2), 52.4 (CH), 64.6 (CH), 65.4 (CH_2), 126.6 (CH), 127.5 (CH), 129.1 (CH), 138.5 (C). Anal. Calcd for $C_{20}H_{35}NOSi$: C, 72.01; H, 10.57; N, 4.19. Found: C, 71.86; H, 10.50; N, 4.11.

(2*R*,6*R*)-2,6-Dimethylpiperidine (Lupetidine). Pd-$(OH)_2$−C (20%, 60 mg) was added to a solution of compound **26** (594 mg, 1.71 mmol) in a 0.5 M ethanolic HCl solution (5 mL), and the mixture was hydrogenated at 75 psi for 13 h. The catalyst was removed by filtration, and the solution was concentrated under vacuum to give a brown gum, which was taken up with water. The aqueous solution was washed with Et_2O and concentrated to dryness. The residue was crystallized from Et_2O−EtOH to give the hydrochloride of the alkaloid lupetidine (199 mg, 78%): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.48 (d, J = 6.8 Hz, 6 H), 1.58 (dd, J = 15.0, 6.0 Hz, 1 H), 1.62−1.71 (m, 3 H), 1.96−2.00 (m, 2 H), 3.53−3.56 (m, 2 H), 9.40 (br s, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.8 (2 CH_3), 17.2 (CH_2), 28.7 (2 CH_2), 47.3 (2 CH); mp 243−245 °C (lit.[35d] mp 247−249 °C); $[\alpha]^{22}_D$ +12.4 (*c* 3.04, EtOH) {lit.[35d] $[\alpha]_D$ +12.8 (*c* 3.06, EtOH)}.

(2*R*,6*R*)-1-[(1*R*)-2-(*tert*-Butyldimethylsilyloxy)-1-phenylethyl]-2-methyl-6-undecylpiperidine (27). To a cooled (0 °C) solution of undecylmagnesium bromide [prepared from undecyl bromide (1.75 mL, 7.86 mmol) and magnesium turnings (191 mg)] in anhydrous THF (15 mL) was added CuI (748 mg, 3.93 mmol), and the mixture was stirred at 0 °C for 10 min. Then, a solution of salt **25** [prepared from thioamide **24** (700 mg, 1.93 mmol) as described above] in anhydrous THF (7 mL) was added, and the mixture was stirred at 0 °C for 30 min. The temperature was lowered to −20 °C, $NaBH_4$ (154 mg, 4.07 mmol) was added, and the stirring was continued for 10 min. Then, glacial AcOH (2.1 mL) was added, the cooling bath was removed and, after 1 h of stirring, the solution was poured into water (15 mL), made alkaline by addition of solid Na_2CO_3, and extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated to give an oil (750 mg). Flash chromatography (9:1 hexanes−Et_2O) afforded compound **27** (516 mg, 55%) as a 7:3 mixture of trans−cis isomers, respectively. *trans*-**27**: ^1H NMR ($CDCl_3$, 300 MHz) δ 0.01 (s, 3 H), 0.03 (s, 3 H), 0.86 (s, 9 H), 0.88 (t, J = 7.0 Hz, 3 H), 0.98 (d, J = 6.7 Hz, 3 H), 1.00−1.70 (m, 26 H), 2.96 (m, 1 H), 3.15 (m, 1 H), 3.94−4.00 (m, 2 H), 4.15 (t, J = 6.5 Hz, 1 H), 7.10−7.50 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz, most significant signals) δ −5.3 (CH_3), 14.6 (CH_3), 20.3 (CH_3), 20.3 (CH_2), 25.9 (CH_3), 48.5 (CH), 52.9 (CH), 61.2 (CH), 64.9 (CH_2), 125.8 (CH), 127.4 (CH), 128.5 (CH), 144.4 (C).

(2*R*,6*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-2-methyl-6-undecylpiperidine (28). A 1.0 M solution of tetra-*n*-butylammonium fluoride (2.0 mL, 2.0 mmol) in THF was added to a solution of compound **27** (516 mg, 1.06 mmol, mixture of isomers) in anhydrous THF (5 mL), and the mixture was stirred at room temperature for 4 h. The mixture was poured into brine (10 mL), and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated to give an oil (560 mg), which, after flash chromatography (95:5 CH_2Cl_2−Et_2NH), afforded *trans*-**28** (229 mg, 58%) and *cis*-**28** (98 mg, 25%). *trans*-**28**: IR (film) 3425 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.53 (m, 1 H), 0.90 (t, J = 6.9 Hz, 3 H), 1.06 (d, J = 6.3 Hz, 3 H), 0.80−1.80 (m, 25 H), 2.93−2.98 (m, 1 H), 3.20−3.25 (m, 1 H), 3.57 (dd, J = 9.7, 4.7 Hz, 1 H), 4.02 (t, J = 10.4 Hz, 1 H), 4.35 (dd, J = 10.4, 5.1 Hz, 1 H), 7.20−7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1 (CH_3), 19.4 (CH_2), 20.0 (CH_3), 22.7 (CH_2), 27.1 (CH_2), 28.4 (CH_2), 29.3 (3 CH_2), 29.4 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 29.9 (CH_2), 30.2 (CH_2), 31.9 (CH_2), 36.4 (CH_2), 47.2 (CH), 51.4 (CH), 58.4 (CH), 58.6 (CH_2), 127.4 (CH), 127.9 (CH), 128.4 (CH), 140.5 (C); $[\alpha]^{22}_D$ −32 (*c* 1.1, MeOH). *cis*-**28**: IR (film) 3418 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, J = 6.9 Hz, 3 H), 1.13 (d, J = 6.5 Hz, 3 H), 1.17−1.80 (m, 26 H), 2.89−2.93 (m, 1 H), 3.08−3.11 (m, 1 H), 3.78 (dd, J = 10.9, 5.1 Hz, 1 H), 3.87−3.93 (m, 1 H), 4.07−4.11 (m, 1 H), 7.25−7.45 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz, most significant signals) δ 14.1 (CH_3), 15.7 (CH_2), 19.8 (CH_3), 22.7 (CH_2), 26.1 (CH_2), 28.1 (CH_2), 29.3 (CH_2), 29.8 (CH_2), 31.0 (CH_2), 32.0 (CH_2), 33.8 (CH_2), 51.3 (CH), 53.8 (CH), 61.8 (CH_2), 65.5 (CH), 127.7 (CH), 128.4 (CH), 128.6 (CH), 140.0 (C).

(2*R*,6*R*)-2-Methyl-6-undecylpiperidine (Solenopsin A). A solution of *trans*-**28** (151 mg, 0.40 mmol) in MeOH (20 mL) containing 20% Pd$(OH)_2$−C (15 mg) was hydrogenated at atmospheric pressure overnight under vigorous stirring. The suspension was filtered, and the solution was acidified by addition of a few drops of ethereal HCl and concentrated. The residue was dissolved in water, and the resulting aqueous solution was washed with Et_2O and then concentrated to dryness. Purification of the resulting residue by crystallization from EtOH−Et_2O afforded a white solid (87 mg, 74%), which was identified as the hydrochloride of the alkaloid solenopsin A: ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 6.5 Hz, 3 H), 1.16−1.40 (m, 18 H), 1.47 (d, J = 6.8 Hz, 3 H), 1.54−1.80 (m, 5 H), 1.86−2.08 (m, 3 H), 3.24−3.29 (m, 1 H), 3.50−3.55 (m, 1 H), 9.40 (br s, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1 (CH_3), 16.8 (CH_3), 17.3 (CH_2), 22.6 (CH_2), 25.8 (CH_2), 26.1 (CH_2), 29.0 (CH_2), 29.3 (2 CH_2), 29.4 (CH_2), 29.5 (3 CH_2), 30.7 (CH_2), 31.8 (CH_2), 47.9 (CH), 51.7 (CH); mp 143−144 °C (lit.[42] mp 141−142 °C); $[\alpha]^{22}_D$ −7.0 (*c* 1.3, $CHCl_3$) {lit.[42] $[\alpha]^{22}_D$ −7.6 (*c* 0.5, $CHCl_3$)}.

Acknowledgment. This work was supported by the DGICYT, Spain (BQU2000-0651). Thanks are also due to the DURSI, Generalitat de Catalunya, for Grant 2001SGR-0084, to the "Ministerio de Educación y Ciencia" for a fellowship to J.H., and to the SCT of the University of Barcelona. We thank DSM Deretil (Almería, Spain) for the generous gift of (*R*)-phenylglycine.

Supporting Information Available: NMR spectra of compounds **2a**−**7a**,**b**, **9**−**19**, **21**, **22**, **26**, *cis*-**28**, *trans*-**28**, coniine-HCl, dihydropinidine-HCl, monomorine I, lupetidine-HCl, and solenopsin A-HCl. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0266083

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