A Synthesis of α-Substituted Amines

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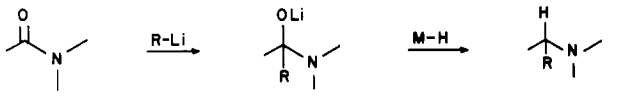
The reaction of amides with organolithium reagents followed by hydride reducing agents has been studied as a synthetic route to α-substituted amines. The stereochemistry of the amine has been observed to depend upon the nature of the reducing agent.

Introduction and Results

It is often a requirement for the synthesis of cyclic as well acyclic amines to form carbon–carbon bonds α to the nitrogen atom. There are strategies available for accomplishing this goal, common ones being the reaction of iminium ions with nucleophiles[1] or the reaction of dipole-stabilized anions with alkylating agents.[2] However, a very simple solution to this problem would be to use the reaction of the amide carbonyl group with an organometallic reagent. Amides are valuable reactants in a synthetic process. There are many methods known for their preparation, and they are relatively stable.

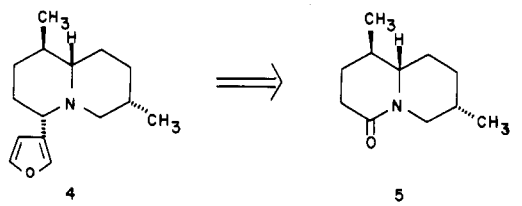
To contrast to the information available on the reaction of organometallic reagents with other carbonyl groups, such as aldehydes and ketones, there is little information available on their reaction with amides.[3] A reasonable scheme for the use of amides to prepare α-substituted amines would first involve the reaction of an amide **1** with an organometallic reagent followed by reduction of the intermediate carbinol amine **2**. Although there are ex-



1 2 3

amples reported in the literature[4] of the process shown below, the conditions necessary to bring about this transformation have not been extensively explored. Because of the importance of α-substituted amines as synthetic goal compounds,[5] we are reporting our experience using amides as precursors to α-substituted amines.

In connection with another problem, the total synthesis of deoxynupharidine **4**, it was necessary to introduce a furan substituent using the amide carbonyl of **5**. This



4 5

transformation has previously been accomplished[6] by first

Table I. Reactions of Amide 6

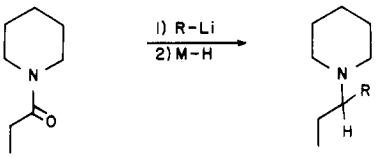
R	reducing agent	yield, %
CH_3–	$LiAlH_4$	85
Ph–	$LiAlH_4$	61
3-furyl	$LiAlH_4$	82
3-furyl	$BH_3{\cdot}SMe_2$	80

Table II. Reactions of Quinolizidinone 5 and Indolizidinone 9

reactant	reducing agent, M-H	product (ratio)	yield, %
5	$LiAlH_4$	**8** + **4** (3:1	84
5	$BH_3{\cdot}SMe_2$	**8** + **4** (1:18)	79
9	$LiAlH_4$	**10** + **11** (2:1)	68
9	$BH_3{\cdot}SMe_2$	**10** + **11** (1:1.6)	68
9	$NaBH_4$–TFA	**10** + **11** (1:2.2)	64

treatment of the amide **5** with 3-lithiofuran followed by conversion to the enamine. Stereoselective[7] reduction of the enamine using catalytic hydrogenation[6] has been reported to give deoxynupharidine (**4**).

In an effort to simplify and improve the yield of this process we explored the possibility of reducing directly the putative carbinol amine intermediate (i.e., **2**). For a model system we chose the tertiary amide **6**. The results of this



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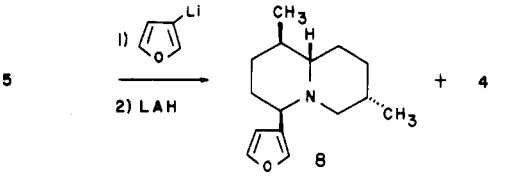
study are shown in Table I. The most convenient procedure for the conversion of amides to α-substituted amines proved to be addition of the organolithium reagent followed by the reduction with lithium aluminum hydride.

Application of this method to **5** gave, much to our surprise, the 4-*epi*-deoxynupharidine **8** possessing an axial



8

8/4 = 3

furan ring as the major product. If the reaction mechanism involves direct substitution of the carbinol amine derivative resulting in inversion of stereochemistry, then the observed result requires that lithiofuran would have to attack the amide carbonyl group from the α side. Alternatively, if the reaction mechanism involves conversion of the carbinolamine derivative to the iminium ion, then the reducing agent would have to approach the iminium ion from

(1) Bohme, H.; Viehe, H. G. "Iminium salts in Organic Chemistry"; Wiley: New York, 1979; Parts 1 and 2.
(2) For leading references see: (a) Meyers, A. I.; Fuentes, L. M.; Kubota, Y. *Tetrahedron* **1984**, *40*, 1361. (b) Beak, P.; Zajdel, W. J. *J. Am. Chem. Soc.* **1984**, *106*, 1010.
(3) For example, see the discussion by Challis: Challis, B. C.; Challis, J. A. in "Comprehensive Organic Chemistry"; Sutherland, I. O., Ed.; Pergamon Press: Oxford, 1979; Vol. 2, p 1010.
(4) (a) Craig, L. C. *J. Am. Chem. Soc.* **1933**, *55*, 295. (b) LaLonde, R. T.; Muhammad, N.; Wang, C. F.; Sturiale, E. R. *J. Org. Chem.*, **1980**, *45*, 3664. (c) Yamaguchi, M.; Hirao, *Tetrahedron Lett.* **1983**, 1719.
(5) Glasby, J. S. "Encyclopedia of the Alkaloids"; Plenum Press: New York, 1975; Vols. 1–3.
(6) Bohlmann, F.; Winterfeldt, E.; Studt, P.; Laurent, H.; Boroschewski, G.; Kleine, K-M. *Chem. Ber.* **1961**, *94*, 3151.
(7) Wrobel, J. T. In "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1967; Vol. 9, p 411 and 1977; Vol. 16, p 181.

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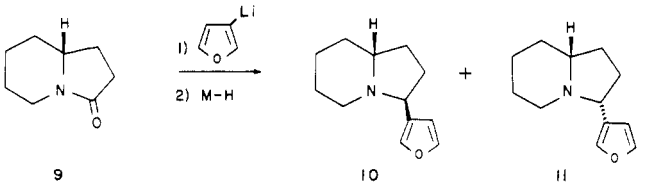
Table III. Reactions of Pyrrolidinone 12a

reducing agent	trans/cis (14a/13a)	yield, %
$LiAlH_4$	0.5:1	80
$NaBH_4$	3:1	60
DIBAH	3:1	70
DIBAH[a]	4:1	71
$BH_3{\cdot}SMe_2$	3:1	80
$LiAlH_4$–$AlMe_3$	0.8:1	60
$NaBEt_3H$	*b*	95
$LiAlH_4$–MeOH	*c*	75
$LiAlH_4$–$TiCl_4$	4:1	60

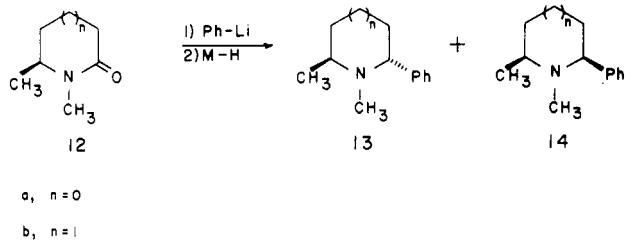
[a] Methylene chloride was added as a cosolvent. [b] The amino alcohol **16a** was the only product. [c] The enamine **15a** was the only product.

the α side to give the observed result. The approach of any reagent from the α direction at position 4 in the quinolizidine series is without precedent.[7] The desired deoxynupharidine **4** was obtained by using the borane–dimethyl sulfide complex as a reducing agent. Only a trace of the C-4 epimer could be detected. In order to explore further this interesting stereochemical control for the synthesis of α-substituted amines from amides we have extended these studies to other bicyclic as well monocyclic amides.

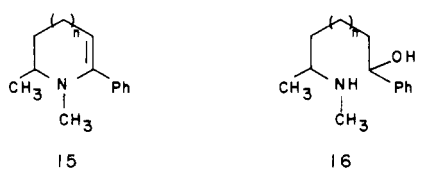
Although the effects were not as dramatic, the same trend was observed with the five-membered ring of the indolizidinone **9** (see Table II). Lithium aluminum hydride reduction gave **10** as the major product, whereas borane–dimethyl sulfide complex reduction gave its epimer **11** as the major product.



Simple five- and six-membered rings compounds, **12a** and **12b**, that could be used to investigate the stereochemistry of transformation are depicted below. We also used these compounds to explore a wider range of reducing agents (see Tables III and IV). The results are analogous to those observed for the bicyclic amides **5** and **9**. That is, lithium aluminum hydride gave predominantly the trans-substituted heterocycle, whereas other reducing agents gave predominantly the cis isomer. Also, there is greater stereoselectivity with the six-membered compared to the five-membered ring compounds.



In addition to the expected α-substituted amines **13** and **14**, two other type of products, **15** and **16**, were observed.



The first of these, the enamine **15**, most likely arises by dehydration of the intermediate carbinolamine.[8] The second, amino alcohol **16**, probably also arises from the carbinolamine by a ring-opening reaction to the amino ketone followed by a reduction of the carbonyl group.

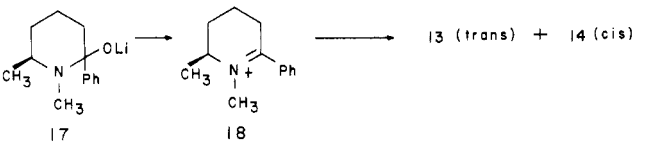
Table IV. Reactions of Piperidinone 12b

reducing agent	trans/cis (14b/13b)	yield, %
$LiAlH_4$	0.25:1	95
$NaBH_4$–TFA	1.8:1[a]	56
DIBAH	*b*	90
$BH_3{\cdot}SMe_2$	1.5:1	60
$LiAlH_4$–$AlMe_3$	0.25:1[b]	90
$NaBEt_3H$	*a*	80
$LiAlH_4$–TMEDA	8.5:1[b]	80
$LiAlH_4$–TMEDA[c]	20:1[a,b]	85

[a] The amino alcohol **16b** was present. [b] The enamine **15b** was present. [c] The reaction was carried out at 0 °C.

Discussion

If it is assumed that the reduction of the carbinol amine **17** to the amine involves the iminium ion **18**, then the data in Tables III and IV are analogous of recent results obtained by both Overman and Yamamoto and their associated co-workers.[9] These groups also observed, under certain circumstances, that lithium aluminum hydride reduction occurred predominantly from the sterically hindered face. It was postulated by both of these groups that $A^{1,2}$ strain[10] plays an important role in determining the overall stereochemical course of these reductions.



For an understanding of all of these results it is useful to recognize that additions to carbon–nitrogen double bonds require an anti periplanar arrangement between the developing lone pair and the attacking nucleophile.[11] If reaction pathways are further restricted to those that involve chair conformations,[11] then an understanding of these results reduces to an analysis of the relative energies of two transition states, such as **19** and **20**.

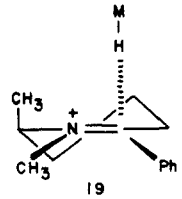
It is convenient to consider separately the nonbonded "intermolecular" forces operating between the reactants, the reducing agent M–H and the iminium ion, and the nonbonded "intramolecular" forces operating within the six-membered-ring iminium ion. Because of the "intermolecular" interaction between the pseudoaxial methyl group and the reducing agent in **19**, the energy of this transition state would be anticipated to increase in energy to a greater extent than **20** as the distance between the iminium ions and the reducing agent decreases. A consideration of this factor would predict that the cis

(8) This reaction has precedent; for example, the DIBAL reduction of amides presumably gives the carbinol amine which is dehydrated under the reaction conditions. For example, see: (a) Moos, W. H.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 226. (b) LaLonde, R. T.; Tsai, A. I-M.; Wang, C. J.; Wong, C.; Lee, G. *J. Med. Chem.* **1976**, *19*, 214. (c) Bohlmann, F.; Mueller, H. J.; Schumann, D. *Chem. Ber.* **1973**, *106*, 3026. (d) Stevens, R. V.; Mehra, R. K.; Zimmerman, R. L. *J. Chem. Soc., Chem. Commun.* **1969**, 877.

(9) (a) Overman, L. E.; Lesusse, D.; Hashimoto, M. *J. Am. Chem. Soc.* **1983**, *105*, 5373. (b) Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831. Similar results are also known for other reducing agents. For example see: Bonin, M.; Romero, J. R.; Grierson, D. S.; Husson, H-P. *Tetrahedron Lett.* **1982**, 3369.

(10) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.

(11) These ideas have been eloquently articulated by Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289.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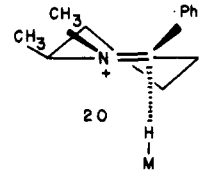
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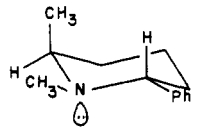
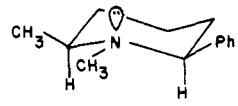
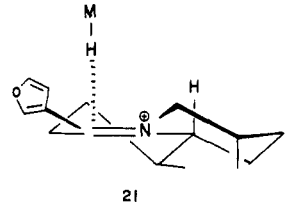

13b


14b

isomer (**14b**) would increase with the lateness of the transition state. These nonbonded repulsive forces are less important with early transition states, and intermolecular interactions of the iminium ion become more important in determining the relative energies of **19** and **20**. Earlier transition states would be anticipated with more reactive reducing agents.[12] These ideas form the basis of our approach as well as earlier approaches[9a] to understanding the reactions of these cyclic iminium ions.[13]

Previously,[9] it was postulated that in certain reactions of iminium ions $A^{1,2}$ strain[10] dominates and the more stable transition state has the nucleophile on the same face as the substituent α to the nitrogen atom (i.e., **19**). This explanation works well for our results on the five- as well as six-membered monocyclic rings but has difficulty with the bicyclic systems **5** and **9**. This is because studies in conformational analysis[14] suggest that the intramolecular forces present in the iminium ion will favor transition state **21** over **22**. The fusion of a six-membered ring to an unsaturated six-membered ring, using the vinyl and the pseudoaxial bond, introduces considerable angle strain. This angle strain overwhelms $A^{1,2}$ strain and the quasi-trans conformer is more stable.[14] Thus, the application

of conformational analysis to transition states would predict **21**, leading to product **4**, would be more stable in reactions involving early transition states. Since **21** should also be more stable in reactions involving late transition states, product **4** should dominate in all reductions. However, our observations were that the reductions of the bicyclic as well as the monocyclic systems were similar.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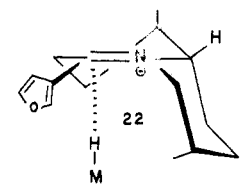
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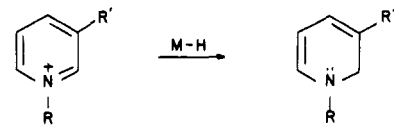
The lithium aluminium hydride reductions always proceeded to give predominantly the *trans*-piperidines.

In all of our reductions the most favorable pathway involves lithium aluminum hydride approaching the iminium ion from the more hindered direction. It is interesting to note that this type of reaction pathway is not rare in chemistry[15] and is not even rare in the reduction of cyclic iminium ions. For example, it is well-known[16] that reduction of 3-substituted pyridinium ions gives almost exclusively the 3-substituted dihydropyridine.



In this example, conformational arguments involving the six-membered rings are not relevant. In order to explain these and related results the dominance of attractive forces[17] with early transitions has been suggested.[15,16]

Whatever the mechanism for the stabilization of the more encumbered reaction pathway, it can be concluded from the above analysis that changes in the experimental parameters that enhance the reactivity of lithium aluminum hydride without changing its effective size should result in an earlier transition state and should enhance the proportion of the reaction proceeding through the sterically encumbered transition state. Because we specualted that lithium ion complexation might enhance the reactivity of lithium aluminum hydride with respect to iminium ions, we explored the use of tetramethylethylenediamine (TMEDA) to possibly accelerate the reduction. We were pleased to observed an increase in the ratio of **13** to **14** from 4:1 to 10:1, which further increased to 20:1 when the reaction was carried out in an ice bath. Unfortunately, the

(12) (a) Evans, M. G.; Polanyi, M. *Trans. Faraday Soc.* **1938**, *34*, 11. (b) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334. (c) Ingold, C. K.; "Structure and Mechanism in Organic Chemistry," 2nd. ed.; Cornell University Press: Ithaca, N.Y., 1969, 827.

(13) Undoubtedly the Curtin–Hammett principle would be applicable to this reaction, and the product ratio is a consequence of the relative energies of the two transition states: Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.

(14) (a) Bucourt, R.; Cohen, N. C.; Lemoine, G. *Bull. Chim. Soc. Fr.* **1975**, 903. (b) Bucourt, R. *Top. Stereochem.* **1974**, *8*, 159. (c) Another model for these iminium ions would be the 4-quinolizidinones which are also known to exist predominately in the quasi-trans conformation: Crabb, T. A.; Newton, R. F.; Jackson, D. *Chem. Rev.* **1971**, *71*, 109.

(15) The literature reveals there are many examples of transition states and ground states in which the encumbered situation is most stable. For example, see: (a) Schlosser, M. *Top. Stereochem.* **1970**, *5*, 1. (b) Liberles, A.; Greenberg, A.; Eilers, J. E. *J. Chem. Ed.* **1973**, *50*, 676. For a recent and leading reference see: Hirota, M.; Sekiya, T.; Kazuhisa, A.; Hiroshi, T.; Karatsu, M.; Nishio, M.; Osawa, E. *Tetrahedron* **1983**, *39*, 3091.

(16) The reduction of three substituted *N*-alkylpyridinium ions initially occurs on the carbon atom between the nitrogen atom and the substituent at position three (e.g., see: Raucher, S.; Lawrence, R. F. *Tetrahedron Lett.* **1983**, *2927*). Although these reactive dihydropyridines can be isolated (e.g.: Kutney, J. P. *Heterocycles*, **1977**, *7*, 593), they are usually further reduced to the tetrahydropyridines. If the pyridinium ion carries an acyl function on the nitrogen then the 1,2-dihydropyridines are readily isolated (Beeken, P.; Bonfiglio, J. N.; Hasan, I.; Piwinski, J. J.; Weinstein, B.; Zollo, K. A. *J. Am. Chem. Soc.* **1979**, *101*, 6677). Attractive forces have been used to rationalize this regiochemistry: (Abramovitch, R. A.; Saha, J. G. *Adv. Heterocyclic Chem.* **1976**, *6*, 229).

(17) Different theoretical approaches to describing attractive interactions have been taken. For leading references see: (a) Hoffmann, R.; Levin, C. C.; Moss, R. A. *J. Am. Chem. Soc.* **1973**, *95*, 629. (b) Eilers, J. E.; Liberles, A. *J. Am. Chem. Soc.* **1975**, *97*, 4183. (c) Carter, R. E.; Stilbs, P. *J. Am. Chem. Soc.* **1976**, *98*, 7515.

effect of TMEDA does not appear to be general. The use of methyllithium did not show a dramatic increase in stereoselectivity.

In summary, we have observed that the treatment of amides with organolithium reagents followed by a reducing agent is a relatively simple procedure for the synthesis of α-substituted amines. The stereochemistry of this overall process depends upon the nature of the reducing agent. Although our stereochemical observations are consistent with earlier studies,[9] they are not readily accommodated with the concept of A[1,2] strain playing a dominate role in determining the energy of the transition states leading to the *trans*-piperidines.

Experimental Section

General. Melting points were recorded on a Thomas-Hoover Unimelt melting point apparatus or on a Fisher-Johns melting point block and were uncorrected. Optical rotations were determined at 20 °C with a Perkin-Elmer Model 241 polarimeter equipped with a Haake D1 thermostat and are corrected with (+)-camphor: $[\alpha]^{25}_D$ +44.1° (*c* 10, EtOH). Infrared spectra were recorded on either a Perkin-Elmer 727 or a Perkin-Elmer 567 spectrometer as either thin films or KBr solid solutions. The absorption intensities are described as being either strong (s), medium (m), or weak (w) and were referenced to either the 1601.4- or the 1944-cm^{-1} absorption of polystyrene. Proton NMR spectra were recorded on either a Varian HFT-80 or a Nicolet NT-300 spectrometer. Carbon-13 NMR spectra were recorded on a Nicolet NT-300 spectrometer. All chemical shifts were reported in ppm (units) from tetramethylsilane as an internal standard and described as being either singlet (s), doublet (d), triplet (t), quartet (q), quintet (q'), or multiplet (m). Low-resolution mass spectra (MS) were recorded on a Hewlett-Packard 5980A spectrometer. High-resolution mass spectra (HRMS) were recorded on an AEI MS-30 spectrometer. Analytical gas chromatography (GC) was determined on a Hewlett-Packard 5830 chromatograph equipped with a flame ionization detector. Preparative gas chromatography was carried out on a Varian 920 chromatograph equipped with a hot wire detector. Thin-layer chromatography (TLC) was carried out on Anatech silica gel HLF precoated thin-layer chromatography plates. Flash column chromatography was carried out with 230–400 mesh silica gel 60 (E. Merck). Dry tetrahydrofuran (THF) and diethyl ether were freshly distilled over sodium benzophenone ketyl under a nitrogen atmosphere. Dry hexamethylphosphoramide (HMPA) was distilled over calcium hydride and stored over 4-Å molecular sieves under a nitrogen atmosphere.

Preparation of 1-(1-Oxopropyl)piperidine (6). To a cooled (ice bath) solution of piperidine (4.25 g, 50 mmol) and triethylamine (5.05 g, 50 mmol) in carbon tetrachloride (60 mL) was added dropwise a solution of propionyl chloride (4.85 g, 55 mmol) in carbon tetrachloride (40 mL). The resulting mixture was stirred at room temperature for 1.5 h and then washed with 5% sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate and sodium carbonate. After filtration, the filtrate was concentrated in vacuo and then distilled under reduced pressure to afford pure **6** (5.95 g, 85%) as a colorless liquid: bp 45–47 °C (0.05 torr) (lit.[18] 230 °C); ^{1}H NMR ($CDCl_3$) δ 1.14 (t, 3 H, *J* = 7 Hz, Me), 1.58 (br s, 6 H), 2.31 (q, 2 H, *J* = 7 Hz, CH_2CO), 3.43 (m, 4 H, CH_2NCH_2); IR (film) 2950 (s), 2870 (s), 1640 (s), 1440 (s), 1260 (s), 1230 (s), 1145 (m), 1080 (m), 1030 (m), 860 (m) cm^{-1}.

Preparation of (1*R*,7*S*,9a*S*)-1,7-Dimethyloctahydro-4*H*-quinolizin-4-one (5). This compound was prepared from (1*R*,9a*S*)-1,7-dimethyl-4*H*-quinolizin-4-one[19] by a catalytic hydrogenation: A 3:1 mixture of the above compound and its C-9a epimer (240 mg, 1.3 mmol) was hydrogenated (1 atm) in ethanol (10 mL) over 5% Pd–C (36.4 mg, 15 mmol) at room temperature for 24 h (approximately 30 mL of hydrogen was absorbed). The resulting mixture was passed through a short column of Celite and then concentrated in vacuo to afford crude product (238 mg, 98%) which consists of 74.4% of **5** and 24.6% of its 7-epi,9a-epi isomer. The crude mixture was chromatographically separated (silica gel, eluted with 4:5 ethyl acetate–hexanes) to afford pure **5** (174 mg, R_f 0.26; $[\alpha]^{20}$ +55.2° (*c* 5.0, MeOH) and its 7-epi,9a-epi isomer (56 mg, R_f 0.19) as colorless liquid (total yield 95%). Compound **5** had 100% of purity, according to GC (OV-1, 160 °C). The physical properties of **5** are also consistent with those previously reported:[6,7] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.96 (d, 3 H, *J* = 7.2 Hz, C_7Me), 1.06 (d, 3 H, *J* = 6.3 Hz, C_1Me), 1.4–1.80 (m, 7 H), 1.99 (m, 1 H, C_7H), 2.34 (ddd, 1 H, *J* = 17.0, 11.6, 5.4 Hz, C_3H_{ax}), 2.46 (ddd, 1 H, *J* = 17.0, 5.4, 4.0 Hz, C_3H_{eq}), 2.59 (dd, 1 H, *J* = 13.0, 3.0 Hz, C_6H_{ax}), 2.79 (ddd, 1 H, *J* = 11.0, 8.4, 2.7 Hz, C_{9a}H), 4.55 (td, 1 H, *J* = 13.0, 2.2 Hz, C_6H_{eq}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.8, 18.9, 27.2, 27.3, 27.7, 30.0, 31.9, 35.4, 47.2, 63.4, 169.8; IR (CH_2Cl_2) 2980 (m), 1625 (s), 1470 (m) cm^{-1}; MS, *m/z* (relative intensity) 181 (M^+, 58), 166 (93), 152 (32), 139 (38), 111 (100), 98 (36), 97 (53), 82 (22), 55 (25); HRMS, *m/e* 181.1460 ($C_{11}H_{19}NO$ requires 181.1466).

Preparation of Hexahydro-3(2*H*)-indolizinone (9). This amide was prepared by palladium-catalyzed hydrogenation of the enamide 1,7,8,8a-tetrahydro-3(2*H*)-indolizinone (prepared from *N*-allyl-O-acetylhydroxylamine and pent-4-enoyl chloride[20] in 55% yield) using the same procedure described for the preparation of compound **5**. Thus, 274 mg (2 mmol) of the enamide gave 278 mg of the amide **9** (100%) as a colorless liquid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.10–2.25 (m, 8 H), 2.36 (br t, 2 H, *J* = 7.5 Hz, C_2HH), 2.62 (dt, 1 H, *J* = 12.5, 4.0 Hz, C_5H_{ax}), 3.41 (m, 1 H, C_{8a}H), 4.12 (td, 1 H, *J* = 12.5, 2.2 Hz, C_5H_{eq}); IR (film) 3000 (s), 2950 (s), 1675 (s) cm^{-1}. The data for compound **9** are also consistent with those previously reported for this compound.[21]

Preparation of 1,6-Dimethyl-2-piperidone (12b). First, 1,6-dimethyl-5,6-dihydro-2-pyridone was made. The method of (1H) Fischer and Schlotterbeck[22] was slightly modified. A 40% aqueous methylamine solution (400 mL in large excess) was added to sorbic acid (Aldrich Chemical Co.) (20 g, 0.18 mol). The mixture was heated at 100–110 °C for 13 h. The solution was evaporated with heating under reduced pressure. Before a syrupy residue (70-mL solution) was obtained the solution was transfered to a 100-mL flask and heated to afford a brown syrupy residue. The residue was then dissolved in 20 drops of hot methanol and heated at 150 °C until no more methylamine was evolved (about 2 h). The residue was distilled under reduced pressure, and the fraction at 100–110 °C (7 mmHg) was collected as a yellow liquid (crude yield 95%). The crude product was washed with 20% NaOH and water, extracted with ether, then dried over magnesium sulfate, and concentrated in vacuo (85–90%). IR (film): 3200 (m), 2950 (s), 1620 (s), 1240 (s), 810 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.68–6.01 (m, 2 H, CH=C), 3.46–3.68 (m, 1 H, CHMe), 2.97 (s, 3 H, N-CH_3), 1.81–2.02 (m, 2 H, C=CCH_2), 1.22 (d, *J* = 6.4 Hz, 3 H, CCH_3). The other physical properties were identical with those previously reported.[26] The reduction procedure was modified from that described by Verbiscar and Campbell.[23] Reduction of 1,6-dimethyl-5,6-dihydro-2(1*H*)-pyridone (11 g, 0.09 mol) was carried out in 100 mL of absolute ethanol and an initial hydrogen pressure of 40 psi for 40 min. The mixture was filtered and evaporated in vacuo to get the crude product as a light yellow liquid (85%). The crude product was purified by column chromatography on silica gel (ether). To dry the compound, calcium hydride (0.2 g) was added, and the mixture was stirred for 1.5 h and then distilled under reduced pressure to afford the pure compound as a colorless liquid: TLC (ether), R_f 0.36; GLC (Silicone OV-17, 130–250 °C, 8 °C/min) 3.59 min; IR (film) 3460 (br, m), 2960 (m), 1620 (m), 1400 (m), 1340 (m), 1250 (m), 1060 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.25–3.61 (m, 1 H, NCHC), 2.92 (s, 3 H, NCH_3), 2.23–2.44 (m, 2 H, CH_2C=O), 1.35–1.94 (m, 4 H, CH_2CH_2), 1.23 (d, *J* = 6.4 Hz,

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3 H, CCH_3); MS, m/z (relative intensity) 127 (M^+, 36), 112 (100), 55 (14), 42 (9.3).

General Procedure for the Preparation of α-Substituted Amines from Amides. To an ethereal solution of organolithium compound (2–4 equiv) was added dropwise a solution of amide (1 equiv) in dry diethyl ether at 0 °C. The ice bath was removed and the mixture was stirred at room temperature for a period of 30 min to 1 h. To this resulting carbinol amine solution was added dropwise a solution of hydride reagent in solvent (excess). After the addition was complete, the reaction mixture was allowed to stir at room temperature for a period of 1 to 2 h. The crude product was obtained after a workup process. Several hydride reagents were used as reducing agents.

Method A: LAH Reduction. The reduction was completed in 20–30 min. The reaction mixture was worked up by careful addition of a 20% NaOH aqueous solution. The crude product was obtained after filtration and concentration of the filtrate in vacuo.

Method B: DIBAH Reduction. The reduction was completed within 30 min. The reaction mixture was worked up with 20% Na_2CO_3 aqueous solution. The crude product was obtained after filtration and concentration of the filtrate in vacuo.

Method C: $NaBH_4$–TFA Reduction. Trifluoroacetic acid (1 equiv) was mixed into a solution of sodium borohydride (1 equiv) in THF under the N_2 gas to make the $NaBH_4$–TFA complex. The reduction was completed in about 40–45 min. The reaction was worked up with 20% Na_2CO_3 aqueous solution. The crude product was obtained after filtration and concentration of the filtrate in vacuo.

Method D: BH_3–SMe_2 Reduction. The reduction was completed within 1 h. The reaction mixture was concentrated in vacuo, and then a large excess of 2 N HCl solution was added and the solution boiled at 100 °C for 30 min. After cooling to room temperature, the mixture was neutralized with 20% NaOH solution, then extracted, and washed with ether. The ethereal solution was dried with anhydrous $MgSO_4$ and concentrated in vacuo to afford the crude product.

Method E: $NaBEt_3H$ Reduction. The reduction was completed within 45 min. The reaction mixture was worked up with a 20% Na_2CO_3 solution, filtered, and concentrated in vacuo. The separate the product, acid–base extraction was done by 10% HCl and 20% NaOH solutions; the product was extracted and washed with ether. The ethereal solution was dried with anhydrous $MgSO_4$ and concentrated in vacuo to afford the crude product.

Method F: LAH–$AlMe_3$ Reduction. Trimethylaluminum (1 equiv) was added into a LAH solution (1 equiv) in ether under N_2 gas to afford LAH–$AlMe_3$ complex. The rest of the reduction procedure was followed by method A.

Method G. LAH–MeOH Reduction. Methanol (2 equiv) was added into the LAH solution (1 equiv) in ether under N_2 gas. The rest of reduction procedure was followed by method A.

Method H: LAH–$TiCl_4$ Reduction. Titanium tetrachloride (1 equiv) was mixed with a LAH solution (1 equiv) in ether under N_2 gas to afford the complex. The rest of procedure was followed by method A.

Method I: LAH–TMEDA Reduction. The various amounts of tetramethylethylenediamine (0.8–20 equiv) were mixed with a LAH solution (1 equiv) in ether under N_2 gas to afford the complex for the different runs. The rest of procedure was similar to method A.

1-(1-Methylpropyl)piperidine (7) (R = Me). This compound was obtained, from the amide **6** by method A, as a colorless liquid[24] upon distillation (85% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, 3 H, J = 7.2 Hz, $MeCH_2$), 0.96 (d, 3 H, J = 7 Hz, MeCH), 1.26 (m, 2 H, CH_2Me), 1.42 (m, 2 H, C_3H and C_5H), 1.56 (m, 4 H), 2.45 (m, 5 H, CH_2NCH_2 and CHN); IR (film) 2940 (s), 2870 (m), 2550 (s), 1460 (s), 1380 (m) cm^{-1}; MS, m/z (relative intensity) 141 (M^+, 4), 126 (14), 113 (8), 112 (100).

1-(1-Phenylpropyl)piperidine (7) (R = Ph). This compound was prepared from the amide **6** by method A in 61% yield after an acid–base extraction of the crude product: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.73 (t, 3 H, J = 7.2 Hz, Me), 1.35 (m, 2 H, CH_2Me), 1.54 (m, 4 H), 2.34 (m, 6 H), 3.19 (dd, 1 H, J = 9.3, 4.8 Hz, PhCHN), 7.27 (m, 5 H, Ph); IR (film) 3050 (w), 3040 (m), 3020 (m), 2950 (s), 2870 (s), 1645 (s), 1440 (s), 1380 (m), 1260 (s), 1230 (s), 1145 (m), 1080 (m), 1030 (m), 860 (m) cm^{-1}; MS, m/z (relative intensity) 203 (M^+, 2), 175 (13), 174 (100), 126 (3), 91 (15); HRMS, m/e 203.1667 ($C_{14}H_{21}N$ requires 203.1674).

1-(1-(3-Furyl)propyl)piperidine (7) (R = 3-Furyl). This compound was obtained, as a colorless liquid, from the amide **6** by method A (82% yield) and method D (80% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.83 (d, 3 H, J = 7.2 Hz, Me), 1.36 (m, 2 H, CH_2Me), 1.45–1.87 (m, 6 H), 2.23–2.50 (m, 4 H, CH_2NCH_2), 3.26 (dd, 1 H, J = 9.6, 4.8 Hz, CHN), 6.30 (s, 1 H, 4-furyl-H), 7.24 (s, 1 H, 2-furyl-H), 7.38 (s, 1 H, 5-furyl-H); IR (film) 2940 (s), 2810 (m), 1500 (m), 1450 (m), 1380 (m), 1170 (s), 1120 (m), 1030 (s), 880 (s), 800 (m), 780 (m), 730 (m) cm^{-1}; MS, m/z (relative intensity) 193 (M^+, 2), 165 (10), 164 (100), 81 (10), 79 (2); HRMS, m/e 193.1467 ($C_{12}H_{19}NO$ requires 193.1466).

Deoxynupharidine (4) and Its C-4 Epimer (8). Compounds **4** and **8** were prepared from the amide **5** (1 equiv) by the addition of 3-lithiofuran (3 equiv) followed either by the lithium aluminum hydride reduction (4 equiv, method A) in a ratio of 1:3, respectively, or by the borane–dimethyl sulfide complex reduction (4 equiv, method D) in a ratio of 18:1, respectively. The ratio of compounds **4** and **8** in the crude product was determined by GC (OV-1, 160 °C) and NMR (^{1}H and ^{13}C). Flash column chromatography (silica gel, eluted with 1:7 ethyl acetate–hexanes) of the crude mixture afforded pure **4** and pure **8** (method A, 84%; method D, 79% yield). Compound **4**: $[\alpha]^{20}$ −82.5° (c 1.94, MeOH) (lit.[25] −90° (c 1.0); lit.[26] −109.86° (c 1.16, EtOH); lit.[27] −105° (c 2.5, MeOH)); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (d, 3 H, J = 6.4 Hz, C_1Me), 0.99 (d, 3 H, J = 7.0 Hz, C_7Me), 1.12 (m, 1 H, C_8H_{ax}), 1.38–1.78 (m, 10 H), 1.81 (dd, 1 H, J = 11.5, 3.0 Hz, C_6H_{ax}), 2.65 (td, 1 H, J = 11.5, 2.0 Hz, C_6H_{eq}), 2.92 (dd, 1 H, J = 8.0, 6.0 Hz, C_4H_{ax}), 6.38 (m, 1 H, 4-furyl-H), 7.25 (m, 1 H, 2-furyl-H), 7.32 (m, 1 H, 5-furyl-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.6 (q), 19.1 (q), 25.7 (t), 28.6 (d), 30.5 (t), 33.9 (t), 34.9 (t), 35.7 (d), 58.1 (t), 60.1 (d), 69.5 (d), 109.6 (d), 129.9 (s), 139.2 (d), 142.7 (d); IR (film) 3140 (w), 2970 (s), 2940 (s), 2870 (s), 2805 (m), 2780 (m), 1600 (w), 1570 (w), 1500 (m), 1470 (m), 1450 (m), 1390 (s), 1380 (s), 1160 (s), 1035 (s), 880 (s), 790 (s), 770 (m), cm^{-1}; MS, m/z (relative intensity) 233 (M^+, 18), 232 (9), 204 (14), 190 (23), 162 (22), 148 (42), 136 (45), 98 (100), 94 (88), 55 (18); HRMS, m/e 233.1784 ($C_{15}H_{23}NO$ requires 233.1779). Compound **8**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.79 (d, 3 H, J = 7.0 Hz, C_1Me), 0.98 (d, 3 H, J = 7.2 Hz, C_7Me), 1.10–1.80 (m, 9 H), 2.13 (ddt, 1 H, J = 13, 6, 5 Hz, C_3H_{ax}), 2.32 (td, 1 H, J = 10, 5 Hz, $C_{9a}H$), 2.43 (dd, 1 H, J = 11, 4 Hz, C_6H_{ax}), 2.54 (dd, 1 H, J = 11, 7 Hz, C_6H_{eq}), 3.79 (br d, 1 H, J = 6 Hz, C_4H_{eq}), 6.36 (m, 1 H, 4-furyl-H), 7.31 (m, 1 H, 2-furyl-H), 7.36 (m, 1 H, 5-furyl-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.1, 19.2, 26.5, 26.7, 29.1, 30.1, 30.7, 33.9, 57.2, 57.6, 58.7, 111.5, 126.2, 139.8, 142.1; IR (film) 2940 (s), 2880 (s), 2820 (w), 2780 (w), 1500 (w), 1450 (m), 1370 (m), 1170 (s), 1035 (s), 880 (s), 770 (m) cm^{-1}; MS, m/z (relative intensity) 233 (M^+, 12), 204 (10), 190 (30), 162 (23), 148 (26), 136 (63), 98 (100), 94 (86); HRMS, m/e 233.1766.

Octahydro-3-(3-furyl)indolizine (10 and 11). Compounds **10** and **11** were prepared from the amide **9** (1 equiv) by the addition of the 3-lithiofuran (3 equiv) followed by (i) lithium aluminum hydride reduction (4 equiv, method A) in a ratio of 2:1, respectively; (ii) borane–dimethyl sulfide reduction (4 equiv, method D) in a ratio of 1:1.6, respectively; or (iii) sodium borohydride–TFA reduction (4 equiv, method C) in a ratio of 1:2.2, respectively, according to GC (OV-1, temperature program 120–180 °C) and ^{1}H, ^{13}C NMR. Flash column chromatography (silica gel, eluted with 1:1 diethyl ether–hexanes) of the crude product afforded pure **11** (R_f 0.4) and pure **10** (R_f 0.25) (method A, 68%; method D, 68%; method C, 64% yield). Compound **10**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.10–2.10 (m, 10 H), 2.30 (m, 1 H, $C_{8a}H$), 2.51 (m, 1 H, C_5H_{ax}), 2.81 (m of d, 1 H, J = 12.0 Hz, C_5H_{eq}), 4.22 (dd, 1 H, J = 8.3, 3.1 Hz, C_6H), 6.27 (m, 1 H, 4-furyl-H), 7.27 (m, 1 H, 2-furyl-H), 7.37 (m, 1 H, 5-furyl-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.9, 29.5, 30.1, 30.8, 47.8, 56.6, 59.8, 110.8, 124.2, 140.6, 143.1; IR (film) 2970 (s), 2940 (s), 2870 (s), 1500 (w), 1450 (m), 1265 (m), 1140 (m), 1040 (s), 880 (m), 800 (w) cm^{-1}; MS, m/z (relative intensity) 191 (M^+, 57), 190 (100), 163 (19), 162 (36), 134 (41), 120 (15); HRMS, m/e 191.1302 ($C_{12}H_{17}NO$ requires 191.1310). Compound **11**: ^{1}H NMR ($CDCl_3$, 300 MHz), δ 1.18–2.05 (m, 12 H), 2.93 (m of d, 1H, J = 11.5 Hz, C_5H_{eq}), 3.06 (t, 1 H, J = 8.0

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Hz, C_3H), 6.41 (m, 1 H, 4-furyl-H), 7.33 (m, 1 H, 2-furyl-H), 7.36 (m, 1 H, 5-furyl-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.5, 25.5, 29.4, 30.6, 31.3, 51.4, 61.0, 65.4, 109.8, 126.9, 140.0, 143.0; IR (film) 2950 (s), 2870 (m), 1500 (w), 1450 (m), 1270 (m), 1150 (m), 1050 (s), 880 (m), 800 (w) cm^{-1}; MS, m/z (relative intensity) 191 (M^+, 54), 190 (100), 163 (21), 162 (38), 134 (42), 120 (15); HRMS, m/e 191.1300.

1,5-Dimethyl-2-phenylpyrrolidine (13a and 14a). 1,5-Dimethyl-2-pyrrolidone (Aldrich Chemical Co.) was dried with calcium hydride, distilled in vacuo, and stored under a nitrogen atmosphere. The pyrrolidone (0.5 mmol) was added dropwise to a solution of phenyllithium (1 mmol) in dry ethyl ether (2 mL) and stirred under the nitrogen gas for 1 h from 0 °C to room temperature. The different reduction conditions are also summarized in Table III. A 0.5:1 ratio of **14a** and **13a** was obtained by method A (yield 80%); 3:1 by method B (yiled 70%); 3:1 by method C (yield 60%); 3:1 by method D (yield 80%); 0.8:1 by method F (yield 60%); 4:1 by method H (yield (60%). The crude product was purified and the isomers were separated column chromatography on silica gel ($CHCl_3$–MeOH 10:1). From the first elution, the cis isomer **14a** was obtained: TLC, R_f 0.41 ($CHCl_3$–MeOH 10:1); GLC (Silicon OV-1, 130 °C), t_R 4.65 min; IR (film) 3025 (m), 2910 (s), 2775 (s), 1600 (m), 1450 (s), 1210 (m) cm^{-1}, ^1H NMR ($CDCl_3$) δ 7.15–7.73 (m, 5H, aryl CH), 3.15 (t, J = 8.3 Hz, 1 H, NCHPh), 2.31–2.38 (m, 1 H, NCHMe), 209 (s, 3 H, NCH_3), 1.49–2.10 (m, 4 H, CH_2CH_2), 1.19 (d, J = 6.3 Hz, 3 H, CCH_3); MS, m/z (relative intensity) 175 (M^+, 8), 174 (9), 160 (100), 98 (13); HRMS, m/e 175.1352 ($C_{12}H_{17}N$ requires 175.1361). From the later elution, the trans isomer **13a** was collected: TLC, R_f 0.30 ($CHCl_3$–MeOH 10:1); GLC (Silicone OV-1, 130 °C), t_R 6.39 min; IR (film) 3030 (m), 2920 (s), 2771 (s), 1612 (m), 1455 (s), 1205 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20–7.70 (m, 5 H, aryl CH), 3.77 (t, J = 7.2 Hz, 1 H, NCHPh), 3.37–3.42 (m, 1 H, NCHMe), 2.15 (s, 3H, NCH_3), 1.53–2.40 (m, 4 H, CH_2CH_2), 1.08 (d, J = 6.3 Hz, 3 H, CCH_3); MS, m/z (relative intensity) 175 (M^+, 10), 174 (8), 160 (100), 98 (M – 77, 20.7); HRMS, m/e 175.1339 ($C_{12}H_{17}$ N requires 175.1361).

1,2-Dimethyl-5-phenyl-1,2-dihydropyrrole (15a). Compound **15a** was obtained by method G (yield 75%): GLC (Silicon OV-1, 130 °C) t_R = 8.77 min; IR (film): 3405 (w), 3040 (m), 1625 (s), 1430 (s), 1365 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20–7.47 (m, 5 H, aryl CH), 4.85 (t, J = 3.8 Hz, 1 H, C=CH), 295–3.15 (m, 1 H, CHMe), 2.48 (s, 3 H, NCH_3), 1.95–2.13 (m, 2 H, CH_2), 1.34 (d, J = 6.4 Hz, 3 H, CCH_3); MS, m/z (relative intensity) 173 (M^+, 34), 172 (16), 158 (100), 143 (26), 77 (5); HRMS, m/e 173.1198 ($C_{12}H_{15}N$ requires 173.1205).

1-Phenyl-4-(methylamino)-1-pentanol (16a). Compound **16a** was obtained by method E (yield 95%): GLC (Silicone OV-1, 130 °C) t_R 9.25 min; IR (film) 3250 (s, br.), 2910 (s), 2830 (s), 1650 (s), 1440 (s), 1360 (m), 7.35 (m), 700 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.22–7.50 (m, 5 H, aryl CH), 4.68 (t, J = 6.4 Hz, 1 H, OCHPh), 3.60 (br., 2 H, NH + OH), 2.50–2.75 (m, 1 H, NCHC), 2.39 (s, 3 H, NCH_3), 1.52–1.90 (m, 4 H, 2 CH_2), 1.12 (d, J = 5.6 Hz, 3 H, CCH_3); MS, m/z (relative intensity) 193 (M^+, 5), 178 (3), 160 (21), 77 (16), 58 (100); HRMS, m/e 193.1465 ($C_{12}H_{19}NO$ requires 193.1467).

1,6-Dimethyl-2-phenylpiperidine (14b and 13b). 1,6-Dimethyl-2-piperidone (0.5 mmol) was added dropwise to a phenyllithium solution in dry ether (2 mL) and stirred under nitrogen gas for 1 h from 0 °C to room temperature. The different reduction conditions are also summarized in Table IV. The ratio of **14b** and **13b** was obtained as following: 0.25:1 by method A (yield 95%); 1.8:1 by method C (yield 56%); 1.5:1 by method D (yield 60%); 0.25:1 by method F (yields 90%); 0.12 and 0.05:1 by method I (yield 80 and 85% for the LAH–TMEDA ratio 1:0.75 and 1:1.2 respectively). The crude product was purified and isomers were separated by preparative GLC (Carbowax 20%, 20 m, DMCS 45/60, 130 °C). From the first elution the cis isomer was collected, t_R 9.42 min; IR (film) 3400 (w), 3040 (m), 2945 (s), 1455 (s), 1205 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.22–7.35 (m, 5 H, aryl CH), 2.89 (dd, J = 10.5 Hz, J = 3.3 Hz, 1 H, CHPh), 2.02–2.12 (m, 1 H, CHMe), 1.97 (s, 3 H, NCH_3), 1.40–1.76 (m, 6 H, $3CH_2$), 1.16 (d, J = 6.4 Hz, 3 H, CCH_3); ^{13}C NMR ($CDCl_3$) δ 144.73, 128.30, 127.49, 126.73, 71.38, 60.48, 40.48, 36.37, 35.01, 25.00, 21.44, MS, m/z (relative intensity) 189 (M^+, 6), 174 (100), 117 (51), 112 (27); HRMS, m/e 189.1512 ($C_{13}H_{19}N$ requires 189.1518). From the later elution, the trans was obtained, t_R 12.65 min; IR (film) 3410 (w), 3040 (m), 2940 (s), 1450 (s), 1210 (m), 740 (s), 700 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.24–7.38 (m, 5 H, aryl CH), 3.40 (dd, J = 9.6 Hz, J = 3.2 Hz, 1 H, CHPh), 3.26–3.34 (m, 1 H, CHMe), 1.99 (s, 3 H, NCH_3), 1.57–1.73 (m, 6 H, 3 CH_2), 1.07 (d, J = 6.4 Hz, 3 H, CCH_3); ^{13}C NMR ($CDCl_3$) δ 145.03, 128.39, 127.28, 126.97, 62.24, 55.10, 40.94, 35.95, 32.28, 19.19, 9.15; MS, m/z (relative intensity) 189 (M^+, 8), 174 (100), 117 (49), 112 (22); HRMS, m/e 189.1521 ($C_{13}H_{19}N$ requires 189.1518).

1,2-Dimethyl-6-phenyl-1,2,3,4-tetrahydropyridine (15b). Compound **15b** was prepared by method B (yield 90%) and also presented by methods F and I in a small amount: GLC (Silicone OV-17, 130–250 °C 8 °C/min) t_R 4.68 min; IR (film) 3400 (w), 3050 (m), 2925 (s), 1620 (s), 1440 (s), 1370 (s), 750 (m), 700 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.21–7.45 (m, 5 H, aryl CH), 4.98 (t, J = 3.6 Hz, 1 H, C=CH), 3.10–3.20 (m, 1 H, CHMe), 2.42 (s, 3 H, NCH_3), 1.48–1.81 (m, 4 H, 2 CH_2), 1.15 (d, J = 5.6 Hz 3 H, CCH_3); MS, m/z (relative intensity): 187 (M^+, 58), 186 (59), 172 (100), 118 (35), 77 (13); HRMS, m/e 187.1355 ($C_{13}H_{17}N$ requires 187.1361).

1-Phenyl-5-(methylamino)-1-hexanol (16b). Compound **16b** was prepared by method E (yield 80%) and also presented by method C in a small amount: GLC (Silicone OV-17, 130–250 °C, 8 °C/min) t_R 9.79 min; IR (film) 3300 (s, br.), 2925 (s), 1660 (m), 1450 (s), 1380 (m), 740 (m), 700 (m) cm^{-1}; ^1H NMR (HFT-80) δ 7.21–7.43 (m, 5 H, aryl CH), 4.64 (t, J = 6.4 Hz, 1 H, OCHPh), 2.48–2.55 (m, 1 H, NCHMe), 2.32 (s, 3 H, NCH_3), 2.22 (br., 2 H, NH + OH), 1.63–1.82 (m, 2 H, CH_2COH), 1.28–1.50 (m, 4 H, $2CH_2$); MS, m/z (relative intensity) 207 (M^+, 5), 192 (4), 174 (10), 117 (24), 77 (16), 58 (100); HRMS, m/e 207.1631 ($C_{13}H_{21}NO$ requires 207.1623).

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