Dearomatization of *N*-Phenyl-2,6-dialkylpiperidines: Practical Synthesis of (±)-Solenopsin A and (±)-Dihydropinidine

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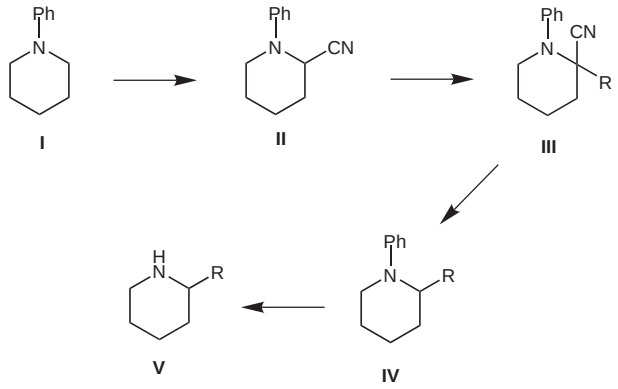
Abstract: The fire ant venom alkaloid (±)-solenopsin A was prepared in 4 steps (34%) starting from the *N*-phenyl-2-undecyl piperidine (**1c**). The key step in this synthesis involved the dearomatization of the phenyl group of *N*-phenyl-2-methyl-6-undecyl-piperidine (**9c**), which was carried out under Birch conditions.

Key words: alkaloids, carbanions, diastereoselectivity, lithium, piperidines

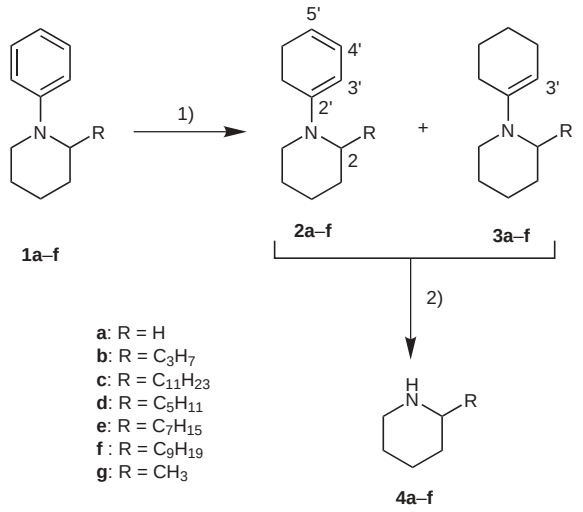
Due to their interesting biological properties,[1] piperidine alkaloids and related analogs have been the subject of numerous synthetic approaches.[2] These synthetic routes involve: i) alkylation of α-lithiated piperidine derivatives,[3] ii) reduction of imines or masked iminium ions,[4] iii) aza-Diels–Alder reactions with imines,[5] iv) alkylation of aminonitrile systems.[6] This latest approach is based on the utilization of cyano-stabilized carbanions which proved efficient intermediates for the elaboration of new carbon to carbon bonds. To this end, the development in our laboratory of a one step synthesis of new aminonitrile systems (**II**) starting from aromatic amines of the type of (**I**) seemed to us a promising possibility (Scheme 1).[7]



Scheme 1

Subsequent studies have shown that the sequence of lithiation (lithium diisopropylamide, tetrahydrofuran, –30 °C) of these aminonitriles, electrophilic substitution (R-Br), and reductive decyanation ($NaBH_4$, EtOH) of the intermediate bifunctional cyanoamine **III**, allowed the synthesis of several *N*-phenyl-2-alkylpiperidines **IV**.[8] It is worth noting that in this sequence, the phenyl group, easily added, should be considered as an effective activator for the elaboration of **I** to **IV**.[9] Moreover, since numerous methods are now available for the synthesis of aniline derivatives,[10] this approach makes **I** a useful building block for the construction of natural piperidine-type compounds. Thus, to synthesize **V**, conditions were needed for a clean removal of the phenyl group from **IV**. To this end, dearomatization[11] of **IV** via single electron transfer[12] seemed to us a valuable synthetic approach. In this paper, we report the synthesis of mono- and disubstituted piperidine derivatives, including three piperidine alkaloids, as well as the course of the reactions.

We set mono-substituted amines **4a**–**f** as initial synthetic targets of this study. With this aim in mind, it was felt that Birch reduction of the aromatic ring of amines **1a**–**f** could lead to the expected secondary amines **4a**–**f** after hydrolysis of the intermediate enamines **2** and **3**.



Scheme 2 Synthesis of 2-substituted piperidines **4a**–**f** from *N*-phenylpiperidines **1a**–**f**. *Conditions*: 1) Li, liq. NH_3–THF–EtOH or *t*-BuOH, –35 °C, 2) 10% HCl, EtOH, 60 °C, 10 min.

Model studies were carried out for screening the reduction conditions by using various *N*-phenylpiperidines substituted at C-2 by aliphatic side chains of an increasing length. As shown in Table 1, reduction of **1a** occurred in liquid ammonia in the presence of lithium and *t*-BuOH as

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proton donor to afford **2a** (90%), which was obtained as an oil without purification (entry 1). In the ^{1}H NMR spectrum (C_6D_6) of this oil, characteristic resonance multiplet signals attributed to H-3′, H-4′ and H-5′ were found at δ = 4.97, 6.13 and 5.43 ppm, respectively. In addition, spectroscopic features for this form include a set of four low-field ^{13}C resonance lines, two of these are due to the C-2′ and C-3′ carbon atoms found at δ = 148.8 and 97.8 ppm. Collectively, these results indicate that reduction of the phenyl group readily occurred to give the conjugated dienamine **2a**.

Table 1 Synthesis of 2-Substituted Piperidines **4a–f** According to Scheme 2

Entry	Products	Method	Time (h)	Yield[a,b] (%)
1	**4a**	A	1.5	80[c]
2	**4b**	A	3.0	70[c]
3	**4c**	A	8.0	≤5[d]
4	**4c**	B	2.0	44
5	**4c**	C	4.0	90
6	**4d**	B	2.0	84
7	**4e**	B	2.0	81
8	**4f**	B	2.0	77

Method A: Reduction with Li (5 equiv) at –35 °C in the mixture liq. NH_3–THF–*t*-BuOH (30:10:5). Method B: Li (10 equiv), liq. NH_3–THF–EtOH (20:10:4). Method C: Li (150 equiv), liq. NH_3–THF–EtOH (20:10:8). For a complete description see ref.[13]

[a] All products were isolated and characterized by IR, ^{1}H NMR, ^{13}C NMR and HRMS.

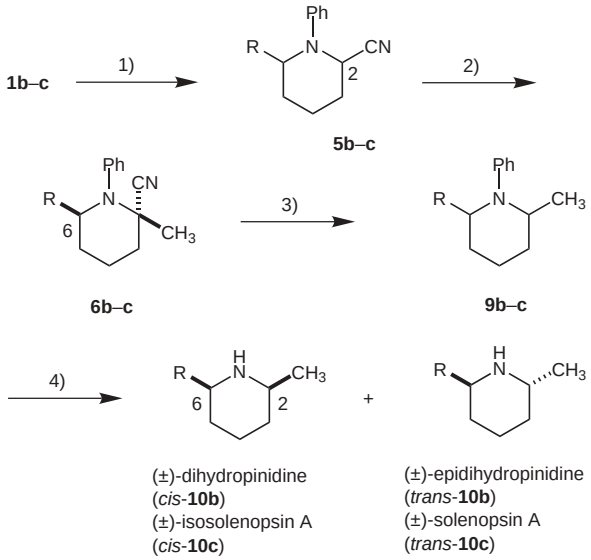
[b] Yields were determined after chromatography over silica (Et_2O saturated with gaseous NH_3).

[c] Amines **4a**,**b** were obtained as their Boc derivatives.

[d] Starting compound was recovered in 90% yield.

Under this methodology, (±)-coniine, the poisonous hemlock alkaloid, can be easily prepared. Conversion of the *N*-phenyl-2-propylpiperidine (**1b**) was made as described above to give **2b** in nearly quantitative yield. The resulting oil was then refluxed (10 min) in EtOH in the presence of 10% HCl to give (±)-coniine as its chlorohydride salt. The Boc group was then introduced under standard conditions to provide **4b** in an overall 70% yield from **2b**. Conversely, little conversion (≤5%) was determined when **1c** was reduced under similar reaction conditions. Moreover, in this experiment, starting material was recovered almost entirely (entry 3). This observation is consistent with the prediction that with substrates that bear hydrophobic side chains, the intermediate radical anions are formed in concentrations that are too low to allow protonation by the tertiary alcohol which itself has a low solubility in liquid ammonia. In contrast, primary alcohols (EtOH) dissolve readily in liquid ammonia and protonate the intermediate radical anion more rapidly. Indeed, when increasing amounts of EtOH were used, reduction of **1c** readily occurred (entry 4 and 5). Note that 150 equivalents of Li should be used for the reduction of **1c** to be complete (entry 5). Hydrolysis of the enamine moiety was made during acid workup, leading after column chromatography to 2-undecylpiperidine **4c** in 90% yield. We were pleased to find that this protocol could be done cleanly and reproducibly on anilines **1d**,**f** to yield the corresponding secondary amines **4d**,**f** (entries 6–8).[13] It should be noted that when ethanol was used as proton donor over-reduction occurred. A more detailed examination of the spectrum of **2d** revealed the presence of an additional triplet absorption (δ = 4.6 ppm), which was further attributed to the vinylic proton of **3d**. Interestingly, both enamines **2** and **3** were readily hydrolyzed into the corresponding amines **4**.

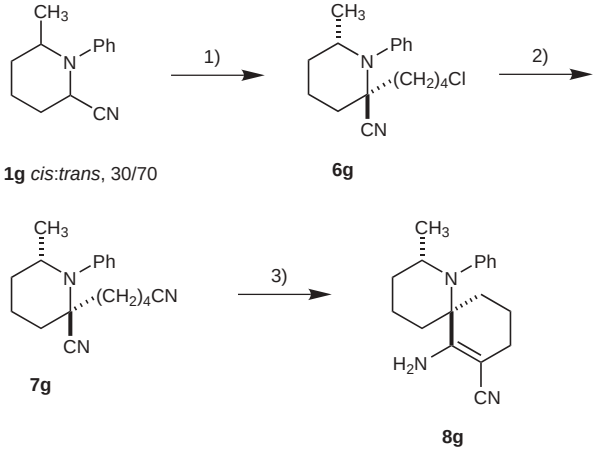
Having these data in hands, we envisaged that the present methodology could have applications for the preparation of the *trans*-alkaloid (±)-solenopsin A (**9c**), and the *cis*-alkaloid (±)-dihydropinidine (**9b**).[14,15]



Scheme 3 Synthesis of (±)-solenopsin A and (±)-dihydropinidine from anilines **1b**,**c**. *Conditions*: 1) –2e$^-$, –H$^+$, MeOH, NaCN, (**5b**, 77%, *c*:*t* = 37:63, **5c**, 78%, *c*:*t* = 40:60); 2) LDA (1 equiv), THF, CH_3I, –78 °C to r.t.; (**6b**, 88%, **6c**, 96%); 3) $NaBH_4$ (4 equiv), EtOH, r.t., (**9b**, 90%, *c*:*t* = 40:60, **9c**, 96%, *c*:*t* = 35:65); 4) Li (30 equiv), liq. NH_3–THF–EtOH (20:10:4), 10% HCl, EtOH, 60 °C, 15 min, (*cis*-**10b**, 24%, *trans*-**10b**, 32%, *cis*-**10c**, 25%, *trans*-**10c**, 47%).

Thus, the electrolysis of a methanolic solution of **1b** was performed (Ep = +0.75 V/ECS, NaCN, 2.2 F/mol) in a batch cell equipped with a glassy carbon electrode as anode to afford **5b** as a single regioisomer. It should be noted that the ^{1}H NMR spectrum of this aminonitrile revealed the presence of an inseparable mixture of epimers at C-6. The exposure of a THF solution of **5b** to a stoichiometric amount of LDA at –78 °C, followed by the introduction of CH_3I onto the resulting anion solution, led to the clean formation of **6b** in 88% yield (Scheme 3).[16] The ^{1}H NMR spectrum of **6b** revealed the presence of a single diastereomer (de 99%), and showed H-6 as a multiplet signal at δ = 3.3 ppm with a width at half-height of about 20 Hz, which is more consistent with an axial rather than an equatorial orientation. However, the relative

stereochemistry of **6b** could not be determined at this stage, but was presumed to be as drawn in Scheme 3. This stereochemical assignment was verified in the spiropiperidine derivative **8g**, which could be simply prepared from the *N*-phenyl-2-cyano-6-methylpiperidine (**1g**) according to a protocol reported in a former paper (Scheme 4).[8b] Fortunately, a slow crystallization of a solution of **8g** gave single crystals. A further X-ray study performed on these crystals indicated that both the alkyl chains were in a *cis* configuration (Figure 1).[17]



Scheme 4 Synthesis of spiropiperidine **8g**: 1) LDA (1 equiv), THF, $Br(CH_2)_4Cl$, –78 °C to r.t., 80%; 2) NaCN (4 equiv), DMSO, *n*-Bu_4NI (5 mol%), r.t., 100 h, 85%; 3) LDA, THF, –78 °C to r.t., 12 h, 88%.

For the preparation of (±)-dihydropinidine, conditions were needed to effect the reduction of aminonitrile **6b** while retaining the configuration at C-2. To this end, several reducing reagents including hydride anions and dissolving metals were used, and selected results are reported in Table 2. In all cases, the reductive decyanation afforded the expected piperidine **9b** with good to excellent yields but with little diastereoselectivity. It is noteworthy that when an excess of $NaBH_4$ was used (entries 1, 2), *trans*-**9b** predominated,[18] while reductions with solvated electrons[19] yielded *cis*-**9b** as the major product (entries 4, 5). These results were in keeping with previous observations, which clearly indicate that hydride reduction of aminonitriles of the type of **6b** proceeded with inversion of configuration, and that an intermediate iminium species with ring inversion is involved during the reductive process. We and others observed that this ring inversion was at the root of the lack of stereoselectivity during the reductive process.[20] Finally, we effected the deprotection of both isomers by reduction of **9b** with Li in a mixture of THF and liquid ammonia in the presence of ethanol (Scheme 3). Work up[13] gave an oily residue, which was purified over a silica column. The less polar (±)-dihydropinidine (*cis*-**10b**, 24%) eluted first, followed by the more polar (±)-epidihydropinidine (*trans*-**10**b, 32%). At this point, it was clear that this sequence was found more convenient for the preparation of *trans*-2,6-dialkylpiperidines rather than for their *cis* counterparts. Therefore, synthesis of (±)-solenopsin A, a representative example of the *trans* series was undertaken. As depicted beyond, the key intermediate **6c** was prepared with an overall 75% yield starting from **1c**. Next, treatment of **6c** with an excess of $NaBH_4$ yielded the *cis* and *trans* piperidines **9c** as an in-

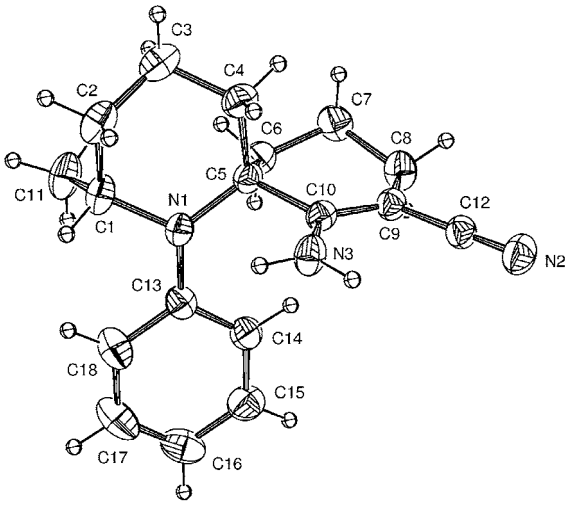


Figure 1 ORTEP drawing of spiropiperidine **8g** in the solid state.

Table 2 Synthesis of *N*-Phenylpiperidines **9b**,**c**

Entry	Products	Reducing agent (equiv)	Yield (%)[a]	dr[b], *c*:*t*	Conditions
1	**9b**	$NaBH_4$ (4.0)	70	30:70	EtOH, r.t., 5 h
2	**9b**	$NaBH_4$ (4.0)	90	40:60	EtOH, –90 °C to r.t., 12 h
3	**9b**	DIBALH (1.2)	46	50:50	CH_2Cl_2, –30 °C to r.t., 4 h
4	**9b**	Na (5.0)	80	65:35	NH_3–THF (20:5), –70 °C, 4 h[c]
5	**9b**	Na (5.0)	70	55:45	NH_3–THF–*t*-BuOH (50:25:3), –70 °C, 4 h
6	**9c**	$NaBH_4$ (4.0)	96	35:65	EtOH, r.t., 5 h

[a] Yields were determined after column chromatography over silica (Et_2O–petroleum ether = 5:95.
[b] Diastereomeric ratios were determined by ^1H NMR and GC.
[c] The solution was worked up after the slow addition of a THF solution of *t*-BuOH at –70 °C.

separable mixture (Table 2, entry 6). This product distribution and the identity of each isomer were confirmed after the removal of the phenyl group by the separation and characterization of pure (±)-solenopsin A (*trans*-**10c**, 48%).[21]

In summary, an effective and practical procedure that allows the preparation of 2,6-dialkylpiperidines has been developed. The advantages of the present synthesis lie in its simplicity and conciseness. Attempts to develop an enantioselective variant of this approach are currently under investigation in our laboratory and results will be reported in due course.

Acknowledgment

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References

(1) (a) Fodor, G. B.; Colasanti, B. In *Alkaloids: Chemical and Biological Perspectives*, Vol. 3; Pelletier, S. W., Ed.; John Wiley: New York, **1985**, 1. (b) Schneider, M. J. In *Alkaloids: Chemical and Biological Perspectives*, Vol. 10; Pelletier, S. W., Ed.; Pergamon: New York, **1996**, 155.

(2) (a) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781. (b) Jeyaraman, R.; Chandrasekaran, L. *Chem. Rev.* **1983**, *83*, 379.

(3) (a) Beak, P.; Zajdel, W. J. *Chem. Rev.* **1984**, *84*, 471. (b) Meyers, A. I.; Edwards, P. D.; Rieker, W. F.; Bailey, T. R. *J. Am. Chem. Soc.* **1984**, *106*, 3270. (c) Gawley, R. E.; Low, E.; Zhang, Q.; Harris, R. *J. Am. Chem. Soc.* **2000**, *122*, 3344.

(4) (a) Matsumura, Y.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1982**, *23*, 1929. (b) Dhavale, D. D.; Saha, N. N.; Desai, V. N. *J. Org. Chem.* **1997**, *62*, 7482. (c) Reding, M. T.; Buchwald, S. L. *J. Org. Chem.* **1998**, *63*, 6344. (d) Katritzky, A. R.; Qiu, G.; Yang, B.; Steel, P. J. *J. Org. Chem.* **1998**, *63*, 6699. (e) Bonin, M.; Romero, J. R.; Grierson, D. S.; Husson, H. P. *Tetrahedron Lett.* **1982**, *23*, 3369.

(5) (a) Grieco, P. A.; Kaufman, M. D. *J. Org. Chem.* **1999**, *64*, 6041. (b) Kranke, B.; Hebrault, D.; Schultz-Kukula, M.; Kunz, H. *Synlett* **2004**, 671.

(6) For a review on nitrile anions chemistry see: (a) Fleming, F. F.; Shook, B. C. *Tetrahedron* **2002**, *58*, 1. (b) Husson, H. P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383.

(7) Le Gall, E.; Hurvois, J. P.; Renaud, T.; Moinet, C.; Tallec, A.; Uriac, P.; Sinbandhit, S.; Toupet, L. *Liebigs Ann. Recl.* **1997**, 2089.

(8) (a) Malassene, R.; Toupet, L.; Hurvois, J. P.; Moinet, C. *Synlett* **2002**, 895. (b) Malassene, R.; Vanquelef, E.; Toupet, L.; Hurvois, J. P.; Moinet, C. *Org. Biomol. Chem.* **2003**, *1*, 547.

(9) (a) Caubère, P.; Derozier, N. *Bull. Soc. Chim. Fr.* **1969**, 1737. (b) Bhaskar Kanth, J. V.; Periasamy, M. *J. Org. Chem.* **1993**, *58*, 3156.

(10) (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (b) Ma, D.; Xia, C. *Org. Lett.* **2001**, *3*, 2583.

(11) (a) Kolis, S. P.; Gonzales, J.; Bright, L. M.; Harman, W. D. *Organometallics* **1996**, *15*, 245. (b) Pape, A. R.; Kaliappan, K. P.; Kündig, E. P. *Chem. Rev.* **2000**, *100*, 2917.

(12) (a) Birch, A. J.; Hutchinson, E. G.; Rao, G. S. *J. Chem. Soc., Chem. Commun.* **1970**, 657. (b) Leonard, N. J.; Steinhardt, C. K.; Lee, C. *J. Org. Chem.* **1962**, *27*, 4027. (c) Rabideau, P. W.; Marcinov, Z. In *Organic Reactions*, Vol. 42; Paquette, L. A., Ed.; John Wiley: New York, **1992**, 1; and references therein.

(13) **General Procedure (Method B) for the Preparation of Amines 4c–f:** To 20 mL of liquid NH_3 2 mL of anhyd. EtOH and 10 mL of THF containing 350 mg (1.35 mmol) of *N*-phenyl-2-heptylpiperidine (**1e**) were successively added. Under a stream of Ar, Li (0.1 g, 10 equiv) was added in small pieces, upon which the solution became blue. The resulting solution was stirred at –40 °C for 2 h. After the blue color had disappeared, the mixture was diluted with 10 mL of EtOH. To this mixture H_2O (100 mL) was added, and the aqueous phase was extracted with Et_2O. The combined organic phases were dried and concentrated in vacuo. The residue was dissolved in 10 mL of EtOH containing 1 mL of 37% HCl and refluxed for 10 min. EtOH was distilled, and the solid residue was stirred in a 20% KOH (5 mL) solution and extracted several times with Et_2O. The ethereal layers were combined and dried over $MgSO_4$. The crude product was chromatographed on silica column eluting with Et_2O saturated with gaseous NH_3 to give 200 mg (81%) of 2-heptylpiperidine(**4e**) as a slightly yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, 3 H, *J* = 6.4 Hz), 0.95–1.10 (m, 1 H), 1.20–1.65 (m, 17 H), 1.70–1.80 (m, 1 H), 2.23–2.42 (m, 1 H), 2.10 (td, 1 H, *J* = 11.70 Hz and 2.85 Hz), 3.05 (dm, 1 H, *J* = 10.50 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.06, 22.63, 24.94, 25.88, 26.69, 29.25, 29.78, 31.80, 33.04, 37.53, 47.27, 56.91. HRMS: *m/z* calcd for $C_{12}H_{25}N$ [M^+]: 183.1987; found: 183.1987.

(14) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109.

(15) For recent syntheses of (±)-dihydropinidine see: (a) Hong, S.; Kawaoka, A. M.; Marks, T. J. *J. Am. Chem. Soc.* **2002**, *125*, 7886. (b) Loh, T. P.; Lye, P. L.; Wang, R. B.; Sim, K. K. *Tetrahedron Lett.* **2000**, *41*, 7779.

(16) Enders, D.; Kirchhoff, J.; Gerdes, P.; Mannes, D.; Raabe, G.; Runsink, J.; Boche, G.; Marsch, M.; Ahlbrecht, H.; Sommer, H. *Eur. J. Org. Chem.* **1998**, 63; and references therein.

(17) Further details of the crystal structure analysis of compound **8g** are available on request from the Cambridge Crystallographic Data Centre as supplementary publication no: 237635. Copies of the data can be obtained free of charge on application to the director CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (1223)336033, e-mail: deposit@ccdc.cam.ac.uk].

(18) For hydride reduction of α-aminonitriles, see: (a) Ogura, K.; Shimamura, Y.; Fujita, M. *J. Org. Chem.* **1991**, *56*, 2920. (b) Sassaman, M. B. *Tetrahedron* **1996**, *52*, 10835.

(19) For dissolving metal reduction of α-aminonitriles see: (a) Fabre, C.; Welvart, Z. *C. R. Acad. Sci.* **1970**, 1887. (b) Bunnelle, W. H.; Shevlin, C. G. *Tetrahedron Lett.* **1989**, *30*, 4203.

(20) For relevant examples see: (a) Jefford, C. W.; Wang, J. B. *Tetrahedron Lett.* **1993**, *34*, 2911. (b) Comins, D. L.; Weglarz, M. *J. Org. Chem.* **1991**, *56*, 2506. (c) Ref.[4e]

(21) **Preparation of (±)-Solenopsin A:** To 20 mL of liquid NH_3 4 mL of anhyd EtOH and 10 mL of THF containing 250 mg (0.76 mmol) of *N*-phenyl-2-methyl-6-undecylpiperidine (**9c**, *c*:*t*, 35:65) were successively added. Under a stream of Ar, Li (60 mg, 30 equiv) was added in small pieces, upon which the solution became blue. The resulting solution was stirred at –40 °C for 2 h. Workup[13] gave an oily residue, which was chromatographed on silica (eluent: Et_2O saturated with gaseous NH_3) to afford *cis*-**10c** (48 mg, 25%) and *trans*-**10c** (90 mg, 47%). (±)-Solenopsin A: ^{1}H NMR (300 MHz,

$CDCl_3$): δ = 0.85 (t, 3 H, *J* = 6.30 Hz), 1.04 (d, 3 H, *J* = 6.60 Hz), 1.16–1.66 (m, 27 H), 2.80–2.88 (m, 1 H), 2.97–3.08 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.07 (CH_3-), 19.56, 21.24 (CH_3-), 22.63, 26.45, 29.33, 29.62, 29.64 (2 C), 29.78, 30.80, 31.89, 33.00, 34.07, 45.78 (CH-), 50.80 (CH-). HRMS: *m/z* calcd for $C_{17}H_{35}N$ [M^+]: 253.2769; found: 253.2760. (±)-Isosolenopsin A: ^1H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, 3 H, *J* = 6.04 Hz), 0.94–1.05 (m, 1 H), 1.05 (d, 3 H, *J* = 6.30 Hz), 1.20–1.65 (m, 25 H), 1.70–1.80 (m, 1 H), 2.42–2.50 (m, 1 H), 2.55–2.66 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.09, 22.67, 23.10, 24.88, 25.99, 29.34, 29.60, 29.62, 29.66, 29.84, 31.90, 32.28, 34.44, 37.47, 52.46, 57.13. HRMS: *m/z* calcd for $C_{17}H_{35}N$ [M^+]: 253.2769; found: 253.2767.