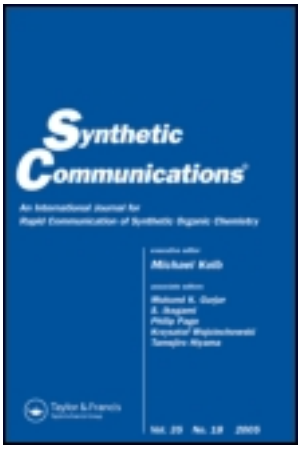

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Anodic Cyanation of (-)-N-Phenyl-2-Methylpiperidine: A Short Synthesis of (+)-Solenopsin A and (+)-Isosolenopsin A

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Anodic Cyanation of (−)-*N*-Phenyl-2-Methylpiperidine: A Short Synthesis of (+)-Solenopsin A and (+)-Isosolenopsin A

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Abstract: A convenient method for the preparation of (+)-Solenopsin A **1** (5 steps, 21%) involving regiospecific anodic cyanation of (−)-*N*-phenyl-2-methylpiperidine **4** is described.

Keywords: Solenopsin A, isosolenopsin A, electrolysis

INTRODUCTION

Solenopsin A **1** together with its *cis* isomer isosolenopsin A **2** (Fig. 1), are constituents of nonproteinaceous piperidine alkaloids secreted by the fire ant *Solenopsis invicta*.[1] Despite a limited systemic toxicity, these substances, which are injected by massive stings, have pronounced haemolytic, cytotoxic,

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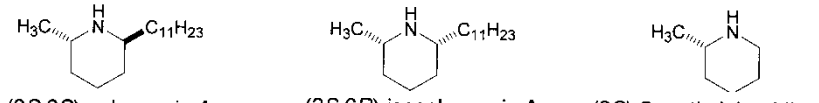


Figure 1. Chemical structures for (+)-solenopsin A and (+)-isosolenopsin A.

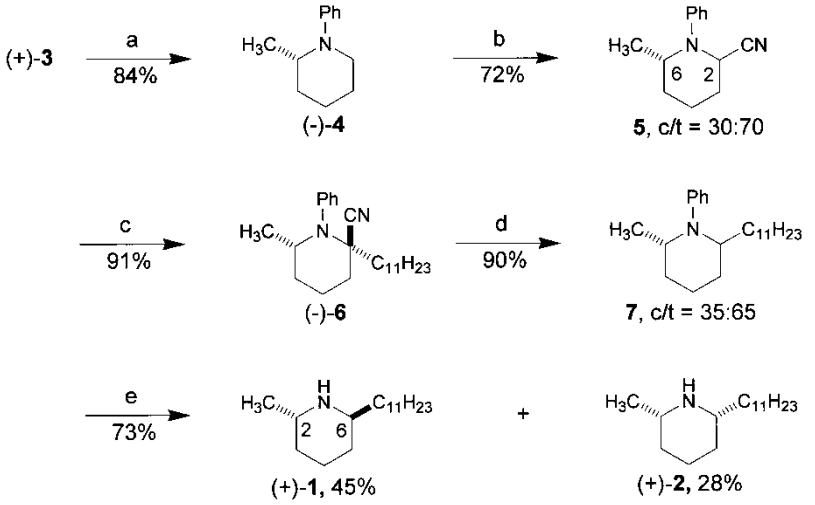
and histamine-releasing properties.[2] In addition a recent study showed that isosolenopsin A was a potent and a selective inhibitor of three neuronal nitric oxide synthase isoforms.[3] These interesting biological properties coupled with their *cis*/*trans* isomerism have made **1** and **2** popular synthetic targets on which to study new synthetic tools.

Therefore, during the last decade, several enantioselective syntheses of Solenopsin A were developed which include: ex-chiral pool syntheses, chiral auxilliary controlled methods, and asymmetric catalytic reactions.[4] In this context, chiral nonracemic aminonitrile systems were soon recognized as useful synthetic intermediates for the elaboration of piperidine alkaloids substituted at both the C-2 and C-6 carbon atoms.[5] A recent study performed in our laboratory shows clearly that any *N*-phenyl-2-cyano-6-alkylpiperidines could be prepared by anodic cyanation of the corresponding *N*-phenyl-2-alkylpiperidine.[6] In the continuation of these studies, we felt that our synthetic approach would be suitable to exploit the innate chirality of 2-methylpiperidine. Thus, for an efficient synthesis of (+)-**1**, the homochiral (*S*)-2-methylpiperidine **3** was an obvious starting material.[7] In the present paper we describe a concise synthesis of **1** and **2** that embodies Caubère *N*-aryl coupling,[8a] anodic cyanation, and Birch reductive dearomatization as key features.

RESULTS AND DISCUSSION

Our synthetic route (Scheme 1) began with the condensation of the commercially available (*S*)-(+)-2-methylpiperidine **3** with phenyl bromide (1.1 equiv.) in tetrahydrofuran (THF) (50°C, 16 h) in the presence of a *t*-BuONa/$NaNH_2$ mixture.[8a] Under these conditions, (*S*)-(−)-*N*-phenyl-2-methylpiperidine **4** was obtained in 84% yield {$[\alpha]_D$, −26.5°, (c = 0.30, $CHCl_3$)}.

Chiral capillary gas chromatography gave ee values up to 98%, and we were pleased to find that no racemization occurred during the coupling process.[9a] For the synthesis of aminonitrile **5**, a range of conditions was investigated. When the electrolysis [Ep = +0.75 V/SCE, MeOH, AcOLi (20 g/l), NaCN (6 equiv.)] was conducted in a divided cell and in connection with the amount of electricity (2.3–2.5 Faraday per mol) that was consumed during theses electrolyses, one can assume that a redox reaction between the nitrogen-centered cation radical and cyanide anions partially occurred.[10]



Scheme 1. *Reagents and conditions*: (a) $NaNH_2/t$-BuOH, C_6H_5Br, THF, 50°C, 16 h, 84%; (b) −2e, $-H^+$, MeOH, NaCN (6 equiv.), 72%; (c) LDA (1.1 equiv.), $C_{11}H_{23}Br$, THF, −78°C to rt, 91%; (d) $NaBH_4$ (4 equiv.), EtOH, 15 h, 90%; (e) Li (75 equiv.), NH_3/THF/EtOH (20:10:6), 10% HCl, EtOH, 60°C, 15 min, (+)-**1**, 45%, (+)-**2**, 28%.

When similar transformations were achieved in an undivided cell, the amount of electricity was close to the theoretical 2 Faraday per mol process. It seems likely that using this device, lithium hydroxide is produced at the cathode from the electrolyte and readily deprotonates the cation radical species. Thus, for sake of simplicity, the electrolysis of (−)-**4** was carried out in an undivided cell with a glassy carbon electrode as anode and a carbon rod as cathode. After work-up, the expected cyano adduct, **5**, was obtained as a single regioisomer (72%). On the other hand, the examination of the ^{1}H NMR spectrum of **5** revealed the presence of a mixture of epimers. In order to determine the structure of each isomer, separate experiments were undertaken in the racemic series. In one of these, we observed that treatment of a *cis*/*trans* mixture (30:70) of (±)-**5** with a stoichiometric amount of LDA (lithium diisopropylamide) at −20°C, followed by the subsequent addition of water onto the resulting anion solution, led to an unexpected *trans* to *cis* isomerization (>99% *de*). A further X-ray study performed on (±)-*cis*-**5** revealed that both the methyl and the cyano groups were axially oriented (Fig. 2).

The incorporation of the requisite *n*-undecyl side chain was made through the metallation of the aminonitrile function of **5**. The anion formation was made by treatment at −78°C of a THF solution of a *cis*/*trans* mixture (30:70) of **5** followed by the addition of *n*-undecylbromide. A 15 h stirring period at +5°C led to (−)-**6** [90%, {$[\alpha]_D$, −9.5°, (c = 1.80, $CHCl_3$)}]. It should be pointed out that no reaction took place when the condensation was

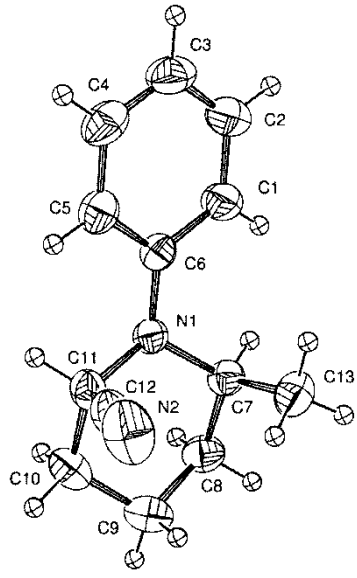


Figure 2. Oak Ridge Thermal Ellipsoid Plot (ORTEP) drawing of aminonitrile (±)-*cis*-**5**.

carried out at temperatures below −20°C. The ^{1}H NMR spectrum of (−)-**6** revealed the presence of a single adduct and showed H-6 as a multiplet signal at $\delta = 3.33$ with a width at half-height of ca. 20 Hz. Taken together, these results indicated that the alkylation procedure proceeded with a high degree of stereoselectivity (>99% *de*) placing both the alkyl chains in a *cis* diequatorial disposition.[6,11] The reductive decyanation of (−)-**6** remained a critical step. In analogy with former investigations, all attempts made to improve the diastereoselectivity of that transformation were unsuccessful.[6] However, best yields and reaction rates were obtained upon the exposure of (−)-**6** to $NaBH_4$ in ethanol. Compound **7** was obtained in 90% yield as an inseparable *cis*/*trans* mixture (35:65). The low stereocontrol of this last step was in agreement with a rapid equilibrium between the two half-chair conformations **A** and **B** (Fig. 3).

Delivery of hydride on **A** and **B** (under a stereoelectronically controlled mode)[12] produced *cis*- and *trans*-**7**, respectively. In contrast to *N*-Boc[13] or *N*-tosyl[14] iminium derivatives, the phenyl group in **A** does not interfere to a great extent with the equatorial methyl substituent. As a result, our model is not susceptible to $A^{1,2}$ strain and *trans*-**7** was obtained in a moderate 58% yield. Finally, the cleavage of the *N*-aryl bond in **7** was carried out through the reductive dearomatization of the phenyl substituent.[6] For this, **7** was reduced with Li (75 equiv.) in a NH_3/THF/EtOH (20:10:6) mixture. The unstable dienamine **C**[15] (Fig. 3) was obtained in nearly quantitative yield,

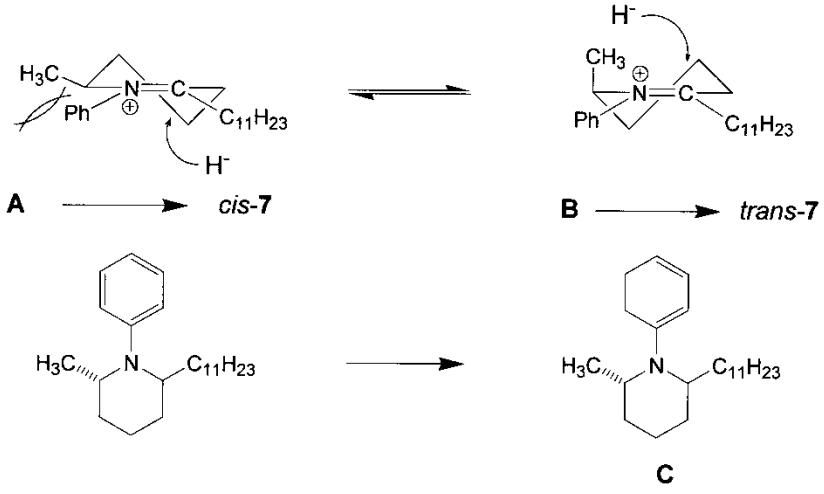


Figure 3. Stereochemistry for the hydride addition on minimum systems A and B.

and was subjected without purification to acid hydrolysis (10% HCl, 60°C, EtOH, 15 min). The oily residue was purified by column chromatography (silica gel, diethyl ether saturated with gaseous NH_3). The (2*S*,6*R*)-(+)-isosolenopsin A **2** {**2**·**HCl** mp 150°C; $[\alpha]_D$, −10.3° (c = 1.74, $CHCl_3$)}; lit. [4 h] mp 152–153°C; $[\alpha]_D$, −10.1°, (c = 1.0, $CHCl_3$)} eluted first, followed by the more polar *trans* isomer (2*S*,6*S*)-(+)-solenopsin A **1**, which was isolated in an overall 45% yield from **7**. The optical rotation of the hydrochloride salt of our synthetic solenopsin A was dextrorotatory and was consistent with that reported in the literature {**1**·**HCl** mp 148°C; $[\alpha]_D$, +7.4° (c = 1.97, $CHCl_3$)}; lit.[5] mp 146°C; $[\alpha]_D$, +7.5°, (c = 1.3, $CHCl_3$)}.

CONCLUSION

In summary, an efficient process (5 steps, 21%) to (2*S*,6*S*)-(+)-solenopsin A from the readily available enantiomerically pure (*S*)-(+)-2-methylpiperidine has been developed. Application of a similar strategy to the synthesis of more complex alkaloids is currently under investigations in our laboratory.

EXPERIMENTAL

General Information

All glassware was oven dried (120°C) over a 24 h period and cooled under an atmosphere of argon. Tetrahydrofuran (THF) was distilled before use from

sodium benzophenone ketyl. Lithium acetate dihydrate was purchased from Acros. Solution of *n*-butyllithium (1.6 M) was purchased from Acros. Diisopropylamine was distilled over KOH pellets and was stored under argon. Lithium diisopropylamide solutions were prepared prior to use by the addition of *n*-butyllithium (2.0 M in THF/heptane) on a THF solution containing 1.1 equivalent of diisopropylamine, or were purchased from Aldrich and used without titration. (*S*)-(+)-2-methylpiperidine (98% ee) was purchased from Aldrich and was used as supplied. *Tert*-butanol was distilled over CaH_2 and was stored under nitrogen. Air sensitive reagents were transferred by syringe or with a double-ended canula. Purification by column chromatography was performed using 70–230 Mesh silica gel (Merck). Thin layer chromatography (TLC) analyses were carried out on alumina sheets precoated with silica gel $60F_{254}$. R_f values are given for guidance. The NMR spectra were recorded on a Bruker AH 300 Ft spectrometer [300 MHz (^{1}H) and 75 MHz (^{13}C) or a Brucker DPI 200 FT [200 MHz (^{1}H) and 50 MHz (^{13}C)]. Chemical shifts are expressed in ppm downfield from TMS where s, d, dd, t, q, and m designate singlet, doublet, doublet of doublets, triplet, quartet, and multiplets, respectively, and coupling constants are expressed in Hz. High Resolution Mass Spectra (HRMS) were obtained with a MAT 311 double focusing instrument at the CRMPO (Centre Regional de Mesures Physiques de l'Ouest) with a source temperature of 170°C. An ion accelerating potential of 3 kV and ionizing electrons of 70 eV. were used. Analytical capillary gas chromatography was performed on a VARIAN CP 3380 gas chromatograph equipped with a programmable temperature control, a flame ionization detector and a CP-Chirasil-Dex CB column (25 m × 0.25 mm × 0.25 μm). Optical rotations ($[\alpha]_D$)were recorded on a PERKIN polarimeter and were all conducted at 20°C.

(2*S*)-(−)-1-Phenyl-2-methylpiperidine (4)

To a THF (30 mL) suspension of $NaNH_2$ (1.65 g, 42.30 mmol) was added dropwise (by syringe) 10 mL of THF containing 1.5 mL (1.16 g, 15.70 mmol) of *t*-BuOH. The resulting mixture was stirred at room temperature for 1 h under an atmosphere of argon. (*S*)-(+)-2-methylpiperidine **3** (1.40 g, 14.11 mmol in 5 mL of THF) and bromobenzene (2.46 g, 1.65 mL, 15.65 mmol) were successively added over a 15 min period. The resulting solution was stirred at 50°C for 16 h and the reaction mixture was quenched by the addition of an excess of water, and extracted with ether (50 mL × 3).

The combined organic layers were extracted by a 10% HCl solution (50 mL), which was made basic by the addition of NaOH pellets. The oily residue was extracted with ether (50 mL × 3) and dried over $MgSO_4$. The organic phases were concentrated in vacuo and the crude material was purified by column chromatography (diethyl ether/petroleum ether, 5:95, $R_f = 0.50$) to

afford **4** (2.07 g, 84%) as slightly yellow oil. $[\alpha]_D^{20}$, -26.5° (c = 0.30 $CHCl_3$). δ_H(200 MHz, $CDCl_3$) 1.01 (3 H, d, $J = 6.6$ Hz), 1.52–1.95 (6 H, m), 2.98 (1 H, td, $J = 11.0$ and 3.0 Hz), 3.21 (1 H, dm, $J = 11.0$ Hz), 3.90 (1 H, m), 6.82 (1 H, t, $J = 7.2$ Hz), 6.94 (2 H, m), 7.24 (2 H, m). δ_C(50 MHz, $CDCl_3$) 14.38 (CH_3), 20.31, 26.62, 32.30, 45.59, 51.92 (CH), 118.15, 119.70, 129.44, 151.90. HRMS calcd. for $C_{12}H_{17}N$ (M^+) 175.1361, found 175.1369. VPC: $t_R = 5.62$ min (150–200°C at 5°C/min, 98% ee).

(2*R*,6*S*)-6-Methyl-1-phenylpiperidine-2-carbonitrile (5)

Compound (−)-**4** (1 g, 5.70 mmol) was dissolved in 100 mL of methanol in the presence of 2 g of lithium acetate and 1.7 g (6 equiv.) of sodium cyanide. The resulting solution was oxidized at +0.80 V/SCE in an undivided cell fitted at a planar vitreous carbon electrode. After the consumption of 1140 coulomb the electrolysis was stopped. The solution was concentrated under reduced pressure and the crude material was taken up with water (20 mL) and extracted with CH_2Cl_2 (50 mL × 2). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude reaction mixture was purified by column chromatography (diethyl ether/petroleum ether, 1:2 to afford **5** (0.820 g, 72%) as a mixture (30:70) of *cis*/*trans* isomers. A further purification on a silica column using diethyl ether/petroleum ether, 10:90 as eluent ($R_f = 0.33$), allowed the partial separation of (2*R*,6*S*)-**5**. Capillary gas chromatography analysis indicated that our sample was contaminated (7%) by the *cis* derivative. δ_H(200 MHz, $CDCl_3$) 0.89 (3 H, d, $J = 5.90$ Hz), 1.23–1.38 (1 H, m), 1.71–2.01 (5 H, m), 3.29 (1 H, m), 4.12 (1 H, t, $J = 3.5$ Hz), 7.09–7.33 (5 H, m). δ_C(50 MHz, $CDCl_3$) 21.37 (CH_3), 21.49, 31.45, 34.70, 50.56 (CH), 57.63 (CH), 121.70 (CN), 126.08, 126.43, 129.91, 149.66. HRMS calcd. for $C_{13}H_{16}N_2$ (M^+) 200.1313, found 200.1316, VPC: $t_R = 8.21$ min (150–200°C at 5°C/min).

Cis-6-Methyl-1-phenylpiperidine-2-carbonitrile (5)

To a THF solution containing (±)-**5** (*cis*/*trans* = 30:70, 1.94 g, 9.70 mmol) at −78°C, were added 1.1 equiv. of LDA. The solution was allowed to warm up to −20°C and was stirred at that temperature for 2 h. An excess (10 mL) of water was poured onto the resulting solution, which was extracted with diethyl ether (100 mL × 2). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by column chromatography (diethyl ether/petroleum ether, 10:90, $R_f = 0.30$) to yield (±)-*cis*-**5** (1.90 g, 97%) as a slightly yellow viscous oil that solidifies upon cooling, m. p. = 78°C. δ_H(300 MHz, $CDCl_3$) 1.16 (3 H, d, $J = 6.80$ Hz), 1.65–1.73 (2 H, m), 1.81–2.02 (3 H, m), 2.05–2.14 (1 H, m), 3.96 (1 H, m),

4.34 (1 H, t, $J = 4.45$ Hz), 6.93–7.05 (3 H, m), 7.28–7.35 (2 H, m). δ_C(75 MHz, $CDCl_3$) 15.93 (CH_3), 17.33, 30.12, 31.10, 46.47 (CH), 51.32 (CH), 117.96, 120.70 (CN), 121.46, 129.46, 147.99. HRMS calcd. for $C_{13}H_{16}N_2$ (M^+) 200.1314, found 200.1316.

Crystal Data, X-ray Data Collection, and Refinement Results of (±)-*cis*-(5)

$C_{13}H_{16}N_2$, $M = 200.28$, monoclinic, space group $P2_1/n$, $a = 9.360(3)$, $b = 7.525(2)$, $c = 16.409(6)$ Å, $\beta = 104.24(1)^\circ$, $V = 1120.2(6)$ Å^{-3}, $Z = 4$, $D_x = 1.188$ Mg m^{-3}, λ (MoKα) = 0.71073 Å, $\mu = 0.71$ cm^{-1}, $F(000) = 432$, $T = 290$ K. The sample (plate: 0.40 × 0.35 × 0.35 mm) is studied on a NONIUS Kappa CCD with graphite monochromatized MoKα radiation. The cell parameters are obtained with Denzo and Scalepack[16] with 10 frames (psi rotation: 1° per frame). The data collection[17] ($2\theta_{max} = 54^\circ$, 129 frames via 2° omega rotation and 20 s per frame, range *HKL*: H 0,12 K 0,9 L–21,20) gives 7390 integrated reflections. The data reduction with Denzo and Scalepack[16] leads to 2527 independent reflections [1947 with $I > 2.0\sigma(I)$]. The structure was solved with SIR-97,[18] which reveals all the nonhydrogen atoms of the compound and the solvent. After anisotropic refinement, the hydrogen atoms are found with a Fourier difference. The whole structure was refined with SHELXL97[19] by the full matrix least-square techniques (use of F square magnitude; x, y, z, β_{ij} for C and N atoms and riding mode for H atoms; 137 variables and 2527 observations with $I > 2.0\sigma(I)$; calc $w = 1/[\sigma^2(Fo^2) + (0.176P)^2 + 0.176P]$ where $P = (Fo^2 + 2Fc^2)/3$ with the resulting R = 0.044, Rw = 0.116, and Sw = 1.05 (residual $\Delta\rho < 0.17$ eÅ^{-3}). Atomic scattering factors are available from International Tables for X-ray Crystallography.[20] The ORTEP views were realized with PLATON98.[21] All the calculations were performed on a Pentium NT Server computer. Further details of the crystal structure analysis are available on request from the Cambridge Crystallographic Data Center as supplementary publication no: 241073. 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.)

(2*R*,6*S*)-(−)-6-Methyl-2-undecyl-1-phenylpiperidine-2-carbonitrile (6)

To a THF solution (15 mL) containing 0.980 mL (0.707 g, 7.0 mmol) of diisopropylamine at −80°C were added (by syringe) 3.1 mL (6.2 mmol) of *n*-BuLi (2 M). The solution was stirred at that temperature for 15 min and was allowed to warmed to 0°C over a 30 min period. The resulting LDA solution was transferred (by syringe) to a THF solution (15 mL) cooled at −80°C containing the

aminonitrile **5** (0.82 g, 4.10 mmol, *cis*/*trans* mixture, 30 : 70). The solution was allowed to warm up to −30°C for 1 h and *n*-bromoundecane (1.64 g, 1.56 mL, 7 mmol) was added dropwise. The reaction mixture was stirred at +5°C for 12 h, diluted with water (100 mL), and extracted with diethyl ether (100 mL × 2). The oily residue was purified by rapid filtration over a silica column with diethyl ether/petroleum ether (5:95, $R_f = 0.63$) to yield (−)-**6** (1.32 g, 91%) as a viscous yellow oil. $[\alpha]_D^{20}$, −9.7° (c = 1.08 $CHCl_3$). δ_H(300 MHz, $CDCl_3$) 0.72 (3 H, $J = 6.10$ Hz), 0.74 (1 H, m), 0.89 (3 H, $J = 6.50$ Hz), 1.05–1.50 (21 H, m), 1.62 (1 H, m), 1.80–1.88 (2 H, m), 2.06 (1 H, dm, $J = 11.0$ Hz), 3.33 (1 H, m), 7.22–7.34 (5 H, m). δ_C(75 MHz, $CDCl_3$) 14.12, 21.67, 22.23 (CH_3), 22.68, 23.84, 29.32, 29.37, 29.42, 29.56, 29.61, 31.90, 34.77, 35.64, 39.42, 54.14 (CH), 62.35, 121.22 (CN), 126.85, 128.72, 129.35, 146.49. HRMS calcd. for $C_{24}H_{38}N_2$ (M^+) 354.3035, found 354.3060.

2-Methyl-1-phenyl-6-undecylpiperidine (7)

To an ethanol solution (15 mL) of (−)-**6** (1.27 g, 3.58 mmol) at room temperature, 0.545 g (14.40 mmol) of $NaBH_4$ was added. The solution was stirred at that temperature overnight and the solvent was evaporated. The crude material was taken-up with water (50 mL) and extracted with diethyl ether (100 mL × 2). The combined organic portions were dried over $MgSO_4$ and concentrated to give a crude mixture that was chromatographed on silica with diethyl ether/petroleum ether (5:95, $R_f = 0.4$) affording **7** (1.06 g, 90%) as a viscous colorless oil consisting of a mixture of diastereoisomers (*cis*/*trans* = 65:35), as determined by capillary gas chromatography analysis. δ_H(300 MHz, $CDCl_3$) 0.84 {3 H (*cis* isomer), d, $J = 6.4$ Hz}, 0.90 {6 H (*cis* and *trans* isomers), t, $J = 6.50$ Hz}, 0.97 {3 H (*trans* isomer), d, $J = 6.20$ Hz}, 1.07–1.91 {43 H (*cis* and *trans* isomers), m}, 2.93–3.03 {1 H (*cis* isomer), m}, 3.05–3.16 {1 H (*cis* isomer), m}, 3.24–3.31 {1 H (*trans* isomer), m}, 3.43–3.53 (1 H (*trans* isomer), m}, 6.85–7.06 (6 H, m), 7.18–7.26 (4 H, m). δ_C(75 MHz, $CDCl_3$) 14.14 (CH_3), 17.78 (CH_3), 18.37, 21.11, 21.79, 22.70, 26.28, 26.55, 28.44, 29.35, 29.56, 29.63, 29.65, 29.69, 29.78, 30.50, 31.93, 33.56, 33.95, 34.19, 50.56 (CH), 55.29 (CH), 57.03 (CH), 59.53 (CH), 121.51, 122.68, 123.54, 128.21, 128.76, 150.46, 150.82. HRMS calcd. for $C_{23}H_{39}N$ (M^+) 329.3082, found 329.3078. VPC: $t_R = 23.35$ min (*cis*), $t_R = 27.46$ min (*trans*) (200°C).

(2*S*,6*S*)-(+)-2-Methyl-6-undecylpiperidine (1) and (2*S*,6*R*)-(+)-2-Methyl-6-undecylpiperidine (2)

In a Schlenck tube containing 10 mL of THF at −40°C, 6 mL of absolute ethanol were added, 0.6 g (1.82 mmol) of **7** (*cis*/*trans* = 35:65), and 20 mL

of liquid ammonia in that order. Then, 0.830 g (120 mmol) of lithium wire was added in small pieces over a 2 h period, the solution then became blue. The solution was stirred for 1 h and quenched with an excess of water (100 mL). The ammonia was allowed to evaporate, and the resulting solution was extracted by diethyl ether (100 mL × 2). The organic layers were dried over $MgSO_4$ and concentrated to give a mixture of unstable dienamines as colorless oil. [*Selected data only*: δ_H (200 MHz, $CDCl_3$) = 4.81 (d, $J = 6$ Hz), 4.91 (d, $J = 5.60$ Hz), 5.26 (m), 5.34 (m), 5.90 (m)]. After being dissolved in an H_2SO_4/H_2O/EtOH (0.5:5:4.5) mixture, the crude material was heated at 60°C for 15 min. The solvents were evaporated and the resulting oily residue was dissolved in water (10 mL). The aqueous mixture was made basic by the addition of NaOH pellets and the aqueous layer was extracted with diethyl ether (20 mL × 2). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed at reduced pressure. The resulting crude oil was purified by column chromatography with diethyl ether saturated with gaseous ammonia to afford the *cis* isomer (+)-**2** ($R_f = 0.85$, 0.130 g, 28%) and the *trans* isomer (+)-**1** ($R_f = 0.35$, 0.210 g, 45%) as pale yellow oils. (2*S*,6*S*)-(+)-solenopsin A **1**: δ_H(300 MHz, $CDCl_3$) 0.85 (3 H, t, $J = 6.95$ Hz), 1.04 (3 H, d, $J = 6.50$ Hz), 1.11–1.66 (27 H, m), 2.81–2.88 (1 H, m), 2.98–3.08 (1 H, m). δ_C(75 MHz, $CDCl_3$) 14.07 (CH_3), 19.56, 21.24 (CH_3), 22.66, 26.45, 29.33, 29.61, 29.64, 29.77, 30.80, 31.89, 33.00, 34.07, 45.78 (CH), 50.80 (CH). HRMS calcd. for $C_{17}H_{35}N$ (M^+) 253.2769, found 253.2760. VPC: $t_R = 14.42$ min (150–200°C at 5°C/min). (2*S*,6*R*)-(+)-isosolenopsin A **2**: δ_H(300 MHz, $CDCl_3$) 0.87 (3 H, t, $J = 6.05$ Hz), 0.94–1.08 (1 H, m), 1.05 (3 H, d, $J = 7.0$ Hz), 1.12–1.68 (25 H, m), 1.70–1.79 (1 H, m), 2.41–2.51 (1 H, m), 2.55–2.66 (1 H, m). δ_C(75 MHz, $CDCl_3$) 14.09 (CH_3), 22.67, 23.10 (CH_3), 24.88, 25.99, 29.34, 29.60, 29.62, 29.66, 29.84, 31.90, 32.28, 34.44, 37.47, 52.46 (CH), 57.13 (CH). HRMS calcd. for $C_{17}H_{35}N$ (M^+) 253.2769, found 253.2767. VPC: $t_R = 13.55$ min (150–200°C at 5°C/min).

(2*S*,6*S*)-(+)-Solenopsin A Hydrochloride (1)·HCl

The amine **1** (0.210 g, 0.83 mmol) was dissolved in 10 mL of dry diethyl ether and dry gaseous HCl was bubbled through the solution to precipitate the hydrochloride salt (0.240 g, 100%). M. p. 148°C (diethyl ether); lit.[5] 146°C (CH_2Cl_2–diethyl ether). $[\alpha]_D^{20}$, +7,4° (c = 1.97 $CHCl_3$), lit.[5] $[\alpha]_D^{20}$, +7.5° (c = 1.30 $CHCl_3$). δ_H(300 MHz, $CDCl_3$) 0.83 (3 H, t, $J = 6.50$ Hz), 1.11–1.38 (21 H, m), 1.43 (3 H, d, $J = 6.60$ Hz), 1.50–1.78 (5 H, m), 1.82–20.5 (3 H, m), 3.16–3.31 (1 H, m), 3.41–3.57 (1 H, m), 9.19–9.43 (2 H, s, br). δ_C(75 MHz, $CDCl_3$) 14.05 (CH_3), 16.81 (CH_3), 17.32, 22.62, 25.80, 26.11, 28.85, 29.28, 29.29, 29.45, 29.51, 29.56, 30.67, 31.85, 47.86 (CH), 51.68 (CH).

(2*S*,6*R*)-(+)-Isosolenopsin A Hydrochloride (2)·HCl

The amine **2** (0.130 g, 0.51 mmol) was dissolved in 10 mL of dry diethyl ether and dry gaseous HCl was bubbled through the solution to precipitate the hydrochloride salt (0.130 g, 87%). M. p. 150°C (diethyl ether), lit.[4h] 152–153°C (CH_2Cl_2–diethyl ether). $[\alpha]_D^{20}$ −10.3° (c = 1.74 $CHCl_3$), lit.[4h] $[\alpha]_D^{20}$, −10.1° (c = 1.0 $CHCl_3$). δ_H(300 MHz, $CDCl_3$) 0.86 (3 H, t, J = 6.9 Hz), 1.10–1.50 (21 H, m), 1.56 (3 H, d, J = 6.40 Hz), 1.70–2.03 (5 H, m), 2.06–2.21 (1 H, m), 2.80–2.96 (1 H, m), 2.99–3.14 (1 H, m), 8.95–9.16 (1 H, br), 9.43–9.52 (1 H, br). δ_C(75 MHz, $CDCl_3$) 14.08 (CH_3), 19.45 (CH_3), 22.65, 22.90, 25.69, 27.46, 29.31, 29.36, 29.54, 29.61, 30.72, 31.88, 33.23, 54.50 (CH), 58.61 (CH).

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REFERENCES

1. (a) Absolute configuration of solenopsins: Leclercq, S.; Thirionet, I.; Broeders, F.; Daloze, D.; Vander Meer, R.; Braeckman, J. C. Absolute configuration of the solenopsins, venom alkaloids of the fire ants. *Tetrahedron* **1994**, *50*, 8465–8478. (b) For a review see: Leclercq, S.; Daloze, D.; Braekman, J. C. Synthesis of the fire ant alkaloids, solenopsins. A review. *Org. Prep. Proced. Int.* **1996**, *28*, 501–543.
2. Fodor, G. B.; Colasanti, B. The pyridine and piperidine alkaloids: chemistry and pharmacology. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; John Wiley: New York, 1985; Vol. 3, pp. 1–91.
3. Yi, G. B.; McClendon, D.; Desaiah, D.; Goddard, J.; Lister, A.; Moffitt, J.; Vander Meer, R. K.; deShazo, R.; Lee, K. S.; Rockhold, R. W. Fire ant venom alkaloid, isosolenopsin A, a potent and selective inhibitor of neuronal nitric oxide synthase. *Int. J. Toxicol.* **2003**, *22*, 81–86.
4. For recent enantioselective syntheses of Solenopsin A see: (a) Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. Enantioselective synthesis of piperidine, indolizidine, and quinolizidine alkaloids from a phenylglycinol-derived δ-lactam. *J. Org. Chem.* **2003**, *68*, 1919–1928; (b) Takahata, H.; Ouchi, H.; Ichinose, M.; Nemoto, H. A novel C_2-symmetric 2,6-diallypiperidine carboxylic acid methyl ester as a promising chiral building block for piperidine-related alkaloids. *Org. Lett.* **2002**, *4*, 3459–3462; (c) Kumareswaran, R.; Hassner, A. Asymmetric synthesis of *N*-acetyl-(*R*)-coniine and *N*-Boc-(2*R*,6*R*)-solenopsin A via ring-closing metathesis. *Tetrahedron: Asymmetry* **2001**, *12*, 2269–2276; (d) Wilkinson, T. J.; Stehle, N. W.; Beak, P. Enantioselective synthesis of 2-alkyl- and 2,6-dialkylpiperidine alkaloids: preparation of the hydrochlorides of (−)-coniine, (−)-solenopsin A, and (−)-dihydropinidine. *Org. Lett.* **2000**, *2*, 155–158; (e) Guilloteau-Bertin, B.; Compère, D.; Gil, L.; Marazano, C.;

Das, B. C. Stereocontrolled alkylation of chiral pyridinium salt toward a short enantioselective access to 2-alkyl and 2,6-dialkyl-1,2,5,6-tetrahydropyridines. *Eur. J. Org. Chem.* **2000**, 1391–1399; (f) Amat, M.; Hidalgo, J.; Llor, N.; Bosch, J. Enantioselective synthesis of the *trans*-2,6-dialkylpiperidine alkaloids (2*R*,6*R*)-lupetidine and (2*R*,6*R*)-solenopsin A. *Tetrahedron: Asymmetry* **1998**, *9*, 2419–2422; (g) Redding, M. T.; Buchwald, S. L. Short enantioselective total synthesis of the piperidine alkaloids (*S*)-coniine and (2*R*,6*R*)-*trans*-solenopsin A via catalytic asymmetric imine hydrosilylation. *J. Org. Chem.* **1998**, *63*, 6344–6347; (h) Poerwono, H.; Higashiyama, K.; Yamauchi, T.; Kubo, H.; Ohmiya, S.; Takahashi, H. Stereocontrolled preparation of *cis*- and *trans*-2,6-dialkylpiperidines via diastereoselective reaction of 1-aza-4-oxabicyclo[4.3.0]nonane derivatives with Grignard reagents. *Tetrahedron* **1998**, *54*, 13955–13970; (i) Comins, D. L.; Benjelloun, N. R. Enantiopure *N*-acyldihydropyridones as synthetic intermediates. An asymmetric synthesis of solenopsin A. *Tetrahedron Lett.* **1994**, *35*, 829–832; (j) Oppolzer, W.; Bochet, C. G.; Merifield, E. Diastereo- and enantioselective syntheses of (−)-coniine, (−)-solenopsin A, (−)solenopsis fugax venom and (−)-xenovenine via deoxygenative decarboxylation of 2-carbonylsultam-substituted *N*-hydroxy-piperidines and -pyrrolidines. *Tetrahedron Lett.* **1994**, *38*, 7015–7018.

5. Grierson, D. S.; Royer, J.; Guerrier, L.; Husson, H. P. Asymmetric synthesis. 6. Practical synthesis of (+)-solenopsin A. *J. Org. Chem.* **1986**, *51*, 4475–4477.
6. Girard, N.; Gauthier, C.; Malassene, R.; Hurvois, J. P.; Moinet, C.; Toupet, L. Dearomatization of *N*-phenyl-2,6-dialkylpiperidines: practical synthesis of (±)-solenopsin A and (±)-dihydropinidine. *Synlett* **2004**, 2005–2009.
7. Adamo, M. F. A.; Aggarwal, V. K.; Sage, M. A. An improved resolution of 2-methylpiperidine and its use in the synthesis of homochiral *trans*-2,6-dialkylpiperidines. *Synth. Commun.* **1999**, *29*, 1747–1756.
8. (a) Caubère, P.; Loubinoux, B. Réactivité des halobenzènes en milieu aprotique. Les mélanges de bases. *Bull. Soc. Chim. Fr.* **1968**, *9*, 3857–3861; (b) Bhaskar Kanth, J. V.; Periasamy, M. Convenient procedure for *N*-phenylation of amines. *J. Org. Chem.* **1993**, *58*, 3156–3157.
9. (a) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. Palladium-catalyzed coupling of optically active amines with arylbromides. *J. Am. Chem. Soc.* **1997**, *119*, 8451–8458; (b) For a review see: Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. L. Rational development of practical catalysts for aromatic carbon-nitrogen bond formation. *Acc. Chem. Res.* **1998**, *31*, 805–818.
10. Le Gall, E.; Hurvois, J. P.; Renaud, T.; Moinet, C.; Tallec, A.; Uriac, P.; Toupet, L. Electrosynthesis of α-aminonitriles: anodic cyanation of *N*-substituted tetrahydroquinolines and *N*-phenylpiperidines. *Liebigs Ann./Recueil* **1997**, 2089–2101.
11. For a review on the reactivity of cyano-stabilized carbanions see: Fleming, F. F.; Shook, B. C. Nitrile anion cyclizations. *Tetrahedron* **2002**, *58*, 1–23.
12. Deslonchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983, pp. 209–288.
13. Comins, D. L.; Weglarz, M. A. Stereocontrolled preparation of *cis*- and *trans*-2,6-dialkylpiperidines via 1-acyldihydropyridine intermediates. Synthesis of (±)-solenopsin A and (±)-dihydropinidine. *J. Org. Chem.* **1991**, *56*, 2506–2512.
14. Jefford, C. W.; Wang, J. B. An enantiospecific synthesis of solenopsin A. *Tetrahedron Lett.* **1993**, *34*, 2911–2914.
15. Leonard, N. J.; Musliner, W. J. The synthesis of substituted tricyclo[6.2.2.0]dodecanes from 2-cyclohexenones. *J. Org. Chem.* **1966**, *31*, 639–646.

16. Otwinowski, Z.; Minor, W. Processing of X-ray Data Collected in Oscillation Mode. In *Methods in Enzymology; Macromolecular Crystallography, Part A*; Carter, C. W., Sweet, R. M., Eds.; Academic Press: London, 1997; Vol. 276, pp. 307–326.
17. Nonius, *Kappa CCD Software*; Nonius, B. V. Delft, The Netherlands, 1999.
18. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G.; Giacovazzo, C.; Guargliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. J. *Appl. Crystall.* **1999**, *32*, 115–119.
19. Sheldrick, G. M. SHELX97, Program for the Refinement of Crystal Structures. Univ. of Göttingen: Germany, 1997.
20. *International Tables for X-ray Crystallography*; A. J. C., Ed.; Kluwer Academic Publishers: Dordrecht, 1992; Vol. C.
21. Spek, A. L. PLATON. A Multipurpose Crystallographic Tool. Utrech University: Utrech, The Netherlands, 1998.