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An Enantioselective Route to *trans*-2,6-Disubstituted Piperidines†

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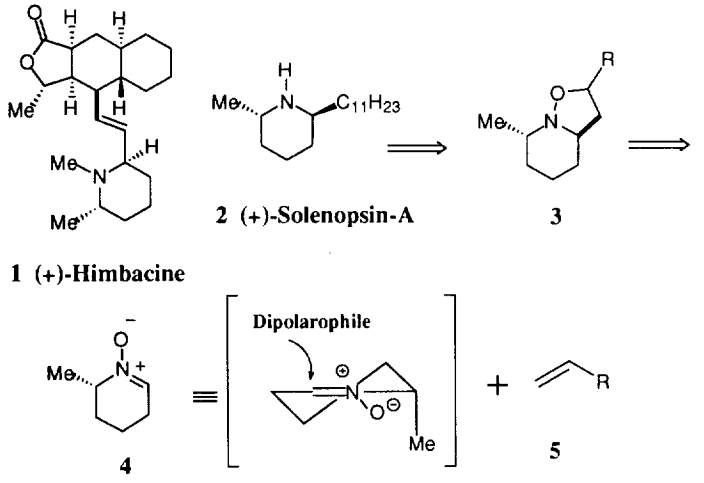
Abstract: The synthesis of (*S*)-2-methyl tetrahydropyridine-N-oxide (**4**), a key intermediate for the enantioselective construction of *trans*-2,6-disubstituted piperidines *via* [3+2] nitrone cycloaddition reaction, is described. Nitrone **4** was elaborated to the fire ant venom alkaloid (+)-solenopsin-A (**2**) *via* intermediate **14**.

Piperidine ring systems bearing a *trans*-2,6-disubstitution pattern are found in several natural products such as himbacine (**1**) and solenopsin-A (**2**).[1-4] There are several diastereoselective syntheses of *cis*-2,6-disubstituted[5-10] as well as *trans*-2,6-disubstituted[11-17] piperidines. However, enantioselective syntheses of *trans*-2,6-disubstituted piperidines are rather limited. In the context of our studies directed towards the total synthesis

Scheme 1



1 (+)-Himbacine

2 (+)-Solenopsin-A

3

4

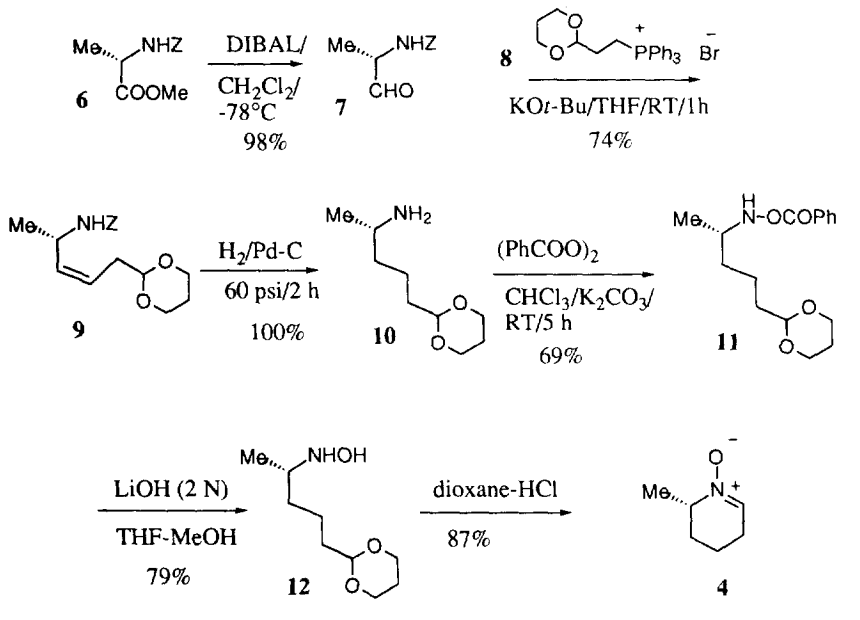
5

† This paper is dedicated to Professor Samuel J. Danishefsky in appreciation of his outstanding service to synthetic and bioorganic chemistry.

of (+)-himbacine, a piperidine alkaloid with potential therapeutic application in Alzheimer's disease,[18,19] we needed an enantioselective method for appending a *trans*-2,6-disubstituted piperidine to a suitable chiral alkene derivative. Carruthers has reported that 1,3-dipolar cycloaddition between the racemic version of nitrone **4** and a monosubstituted alkene (**5**) would produce the perhydroisoxazolopyridine derivative **3** in which the incoming dipolarophile assumes a *trans* relationship to the preexisting substitutent α to the nitrogen (Scheme 1).[20] A plausible mechanistic explanation for this remarkable stereoselectivity is that, in order to relieve $A^{1,2}$ strain, the substituent α to the nitrone assumes a preferred axial disposition in the transition state. This conformation dictates the approach of the dipolarophile from the face opposite to the α-substitituent. Reductive ring opening of isoxazolidine **3** produces *trans*-2,6-disubstituted piperidine (Scheme 1). When alkene **5** has a chiral substituent, the use of racemic nitrone **4** would give rise to a mixture of diastereomers. We addressed this issue by the enantiospecific synthesis of nitrone **4**. In this report we wish to report the synthesis of nitrone **4** in enantiomerically pure form, which has not been reported before, and its elaboration to the fire ant venom constituent (+)-solenopsin-A^{12} *via* [3+2] cycloaddition.[21-23]

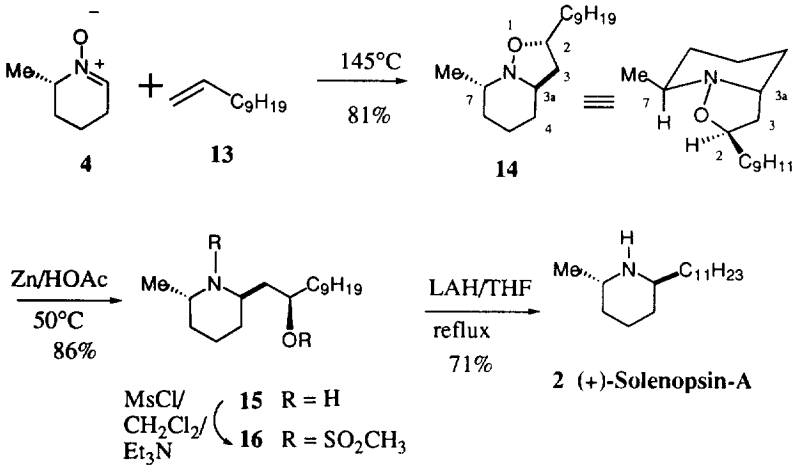
The synthesis of the nitrone **4** is described in Scheme 2. N-Cbz-*L*-alanine methyl ester (**6**) was converted to the corresponding aldehyde **7** by treatment with diisobutylaluminum hydride according to the

Scheme 2



reported procedure.[24] Wittig reaction of **7** with the commercially available phosphonium salt **8** mediated by potassium *tert*-butoxide yielded the *cis*-alkene **9**.[25] Palladium catalyzed reduction of compound **9** effected N-deprotection with concomitant reduction of the double bond to give the free amine **10**. Treatment of the amine **10** with excess of benzoyl peroxide in the presence of potassium carbonate at room temperature gave the corresponding hydroxylamine benzoate **11**.[26] Saponification of compound **11** using lithium hydroxide gave the free hydroxylamine derivative **12** which upon treatment with 2N HCl in dioxane yielded the nitrone **4**. The crude nitrone **4** was unstable and was immediately used in the subsequent step without further purification.

Scheme 3



Nitrone **4** was elaborated to (+)-solenopsin-A as shown in Scheme 3 following Carruthers' protocol which was used in the racemic series.[20] Reaction of nitrone **4** with excess of undec-1-ene at 145°C for 45 min gave the isoxazolidine **14** in 81% yield. The relative stereochemistry of isoxazolidine **14** was established based NOE studies. Strong NOE was observed between protons at C_2 and C_7. Additionally, the methyl substituent at C_7 showed no NOE to the C_2 or C_3 protons. This NOE pattern suggests an axial orientation of C_7 proton in close proximity to the C_2 hydrogen as represented in structure **14** in which the C_7 methyl bears a *trans* relationship to the isoxazolidine ring and the relative stereochemistry at C_2 results from an *exo* mode of cycloaddition. None of the other three diastereomers of **14** (not shown), would explain such an NOE pattern. The *trans* mode of addition was further corroborated by elaboration of intermediate **14** to (+)-solenopsin-A as described below.

Reductive cleavage of the isoxazolidine **14** with zinc and acetic acid gave the amino alcohol **15** which was converted to the bis-mesyl derivative **16**. Lithium aluminum hydride reduction of compound **16** gave (+)-solenopsin-A (**2**) which showed ^{1}H and ^{13}C NMR spectra[20] as well as optical rotation[27] in close agreement with literature values. Treatment of a solution of (+)-solenopsin-A in dichloromethane with hydrochloric acid in ether (1 N) gave the corresponding hydrochloride salt as white crystals which melted at 140-143°C (lit.,[12] 146°C) and showed optical rotation identical to that reported ($[\alpha]_D^{20}$ = +7.5 (c = 1.3, $CHCl_3$); lit.,[12] $[\alpha]_D^{20}$ = +7.5 (c = 1.3, $CHCl_3$)).

In conclusion, an enantiospecific synthesis of nitrone **4** was achieved from commercially available N-Cbz-*L*-alanine methyl ester in approximately 34% overall yield. This method should be applicable for the synthesis of analogous nitrones of desired chirality starting from suitable amino acids. The potential synthetic utility of nitrone **4** in the enantioselective synthesis of *trans*-2,5-disubstituted piperidine alkaloids has been demonstrated by the total synthesis of (+)-solenopsin-A (**2**). Future studies will be addressed towards the application of this approach in the enantioselective synthesis of (+)-himbacine (**1**).

EXPERIMENTAL

General Procedures: ^{1}H NMR spectra were recorded on a Varian Gemini 400 (400 MHz) spectrometer using $CHCl_3$ as an internal standard (δ 7.270). ^{13}C NMR spectra were recorded on a Varian 400 (100 MHz) spectrometer using chloroform-*d* (δ 77.0) as an internal standard. Infrared spectra were recorded on a Genesis Series FT IR spectrophotometer. Optical rotations were measured on a Perkin Elmer 243 B or a Jasco DIP-140 polarimeter. Tetrahydrofuran (THF) was distilled over sodium-benzophenone under argon, and halogenated solvents were used as purchased without further purification. Mass spectra were obtained on a VG-ZAB-SE, HP-MS-Engine, or JEOL-HX-110 mass spectrometer using chemical ionization or fast atom bombardment ionization technique. High resolution mass spectra (FAB) were obtained on a VG-ZAB-SE spectrometer by peak matching against appropriate standards.

Phenylmethyl [(*Z*)-4-(1,3,-dioxan-2-yl)-1-(*S*)-methyl-2-butenyl]carbamate (9). To a solution of N-Cbz-*L*-alanine methyl ester (5.10 g, 21.5 mmol) in dichloromethane (200 ml), cooled under nitrogen in a dry ice-acetone bath, was added dropwise over 1 h, *via* syringe pump, a solution of diisobutylaluminum hydride in dichloromethane (1.0 M, 32.3 mmol). After completion of addition, the reaction mixture was stirred at -78°C for 30 min. The reaction was quenched by addition of 1 N HCl (50 ml). The mixture was warmed to room temperature, layers were separated and the organic layer was washed with 1 N HCl (50 ml) and water (2 x 50 ml). The organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the aldehyde **7** (4.35 g, 98%) which was used in the subsequent step without further purification.

To a mixture of phosphonium bromide **8** (Aldrich) (13.3 g, 29.0 mmol) and potassium *tert*-butoxide (3.30 g, 29.0 mmol), under nitrogen, was added tetrahydrofuran (130 ml). The suspension was stirred at room temperature for 1 h and a solution of the crude aldehyde from above in THF (50 ml) was added slowly over 10 min. The reaction mixture was stirred at room temperature for 40 min and poured into saturated aqueous ammonium chloride (200 ml). The mixture was extracted with ether (3 x 100 ml). The organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (600 g; eluent: 10% ethyl acetate in hexane) to afford alkene **9** as a single isomer (4.71 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, J = 6.7 Hz, 3 H), 1.31 (d, J = 13.4 Hz, 1 H), 2.06 (m, 1 H), 2.46 (m, 2 H), 3.74 (t, J = 12.2 Hz, 2 H), 4.08 (m, 1 H), 4.47 (m, 1 H), 4.56 (m, 1H), 4.70 (d, J = 6.0 Hz, 0.3 H), 4.80 (m, 0.7 H), 5.08 (s, 2 H), 5.40 (dd, J = 8.7 Hz, 10.6 Hz, 1 H), 5.52 (dq, J = 10.6 Hz, 5.5 Hz, 1 H), 7.25 - 7.39 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 25.6, 33.5, 44.6, 66,4, 66.9 (2 carbons), 101.2, 124.9, 128.0 (3 carbons), 128.4 (3 carbons), 133.9, 161.2. MS (CI), m/e 306 $(M+1)^+$, 230. IR (neat) 1714 cm^{-1}. HRMS (FAB): Calcd for $C_{17}H_{24}NO_4$ $(M+H)^+$, m/e 306.1705; found: m/e 306.1703. $[\alpha]_D^{24}$ = +34.9 (c = 0.61, $CHCl_3$).

α(*S*)-Methyl-1,3-dioxane-2-butanamine (10). To a solution of compound **9** (3.76 g, 12.3 mmol) in ethanol/ethyl acetate (2:1, v/v, 60 ml) was added 10% palladium on carbon (500 mg). The reaction mixture was hydrogenated at 60 psi for 45 min. The suspension was filtered and the filtrate was concentrated to give the free amine **10** (2.13 g, 100 %) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (d, J = 6.3 Hz, 3 H), 1.30 - 1.46 (m, 5 H), 1.56 - 1.62 (m, 2 H), 1.98 - 2.12 (m, 1 H), 2.88 - 2.94 (m, 1 H), 3.03 (br s, 2 H), 3.74 (dt, J = 12.3 Hz, 2.5 Hz, 2 H), 4.08 (dd, = 6.8 Hz, 1.2 Hz, 2 H), 4.51 (t, J = 5.2 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 23.8, 25.8, 35.1, 39.9, 46.8, 86.8 (2 carbons), 102.1. MS (CI), m/e 174 $(M+H)^+$, 98. HRMS (FAB): Calcd for $C_9H_{20}NO_2$ $(M+H)^+$, m/e 174.1494; found: m/e 174.1492. $[\alpha]_D^{24}$ = +53.8 (c = 0.47, $CHCl_3$).

N-(Benzoyloxy)-α(*S*)-methyl-1,3-dioxane-2-butanamine (11). To a solution of compound **10** (4.30 g, 24.9 mmol) in chloroform (600 ml), under nitrogen, was added potassium carbonate (30 g, 217 mmol). The suspension was stirred for 15 min and benzoyl peroxide (Aldrich) (45.0 g, 185.9 mmol) was added slowly over 10 min. The reaction mixture was stirred at room temperature for 4.5 h and filtered. The filtrate was concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (900 g; eluent: 25% ethyl acetate in hexane) to afford compound **11** (5.0 g, 69%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, J = 6.4 Hz, 3 H), 1.31 (d, J = 13.4 Hz, 1 H), 1.38 - 1.72 (m, 8 H), 2.00 - 2.15 (m, 1 H), 3.18 - 3.28 (m, 1 H), 3.74 (t, J = 8.0 Hz, 2 H), 4.09 (dd, J = 5.2 Hz, 1.2 Hz, 2 H), 4.52 (t, J = 5.0 Hz, 1 H), 7.43 (t, J = 7.6 Hz, 2 H), 7.59 (t, J = 7.2 Hz, 1 H), 8.01 (d, J = 7.2 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 20.4, 25.8, 33.8, 35.1, 56.7, 66.9 (2 carbons), 102.0, 128.5 (3 carbons), 129.3 (2 carbons), 133.3, 163.3. MS

(CI), m/e 294 $(M+1)^+$, 218, 172. HRMS (FAB): Calcd for $C_{16}H_{24}NO_4$ $(M+H)^+$, m/e 294.1705; found: m/e 294.1690. $[\alpha]_D^{20} = -3.0$ (c = 0.37, CH_2Cl_2).

N-Hydroxy-α(*S*)-methyl-1,3-dioxane-2-butanamine (12). To a solution of compound **11** (4.4 g, 15 mmol) in THF/methanol (48 ml; 1:1, v/v), under nitrogen, was added aqueous 2 M lithium hydroxide (48 ml). The reaction mixture was stirred at room temperature for 30 min. The mixture was diluted with ether (50 ml), layers were separated and the aqueous phase was extracted with ether (3 x 50 ml). The combined organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure to afford the hydroxylamine **12** as a semi-solid (2.25 g, 79%). MP 46 - 47°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, J = 6.4 Hz, 3 H), 1.16 - 1.59 (m, 7 H), 1.90 - 2.07 (m, 1 H), 2.85 - 2.95 (m, 1 H), 3.69 (dt, J = 12.3 Hz, 2.2 Hz, 2 H), 4.04 (dd, J = 4.9 Hz, 4.0 Hz, 2 H), 4.46 (t, J = 5.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 20.4, 25.8, 33.5, 35.3, 57.1, 66.9, 66.9, 102.1. MS (FAB), m/e 190 $(M+H)^+$, 188. HRMS (FAB): Calcd for $C_7H_{20}NO_3$ $(M+H)^+$, m/e 190.1443; found: m/e 190.1438. $[\alpha]_D^{24} = +3.0$ (c = 0.12, $CHCl_3$).

3a(*R*)-Hexahydro-7(*S*)-methyl-2(*S*)-nonyl-2H-isoxazolo[2,3-a]pyridine (14). To a solution of hydroxylamine **12** (420 mg, 2.2 mmol) in dioxane/water (4:1, v/v; 1.0 ml) was added 4 M HCl in dioxane (2.0 ml). The reaction mixture was stirred at room temperature for 1 h. Aqueous sodium hydroxide (10%) was added to the reaction mixture to bring the pH to 12. The mixture was diluted with dioxane (5 ml) and concentrated to dryness. The residue was suspended in dichloromethane (20 ml) and stirred vigorously. The suspension was dried over magnesium sulfate, filtered and concentrated to give the nitrone **4** as an oil (218 mg, 87%) which was used immediately.

The above residue was mixed with 2 ml of undec-1-ene under argon. The mixture was heated in a sealed tube at 145°C for 45 min. The reaction mixture was cooled and directly chromatographed on silica gel (30 g) eluting with 10% ethyl acetate in hexane to give compound **14** (0.421 g, 81% based on **4**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (dd, J = 5.2 Hz, 5.3 Hz, 3 H), 1.12 (d, J = 6.0 Hz, 3 H), 1.14 - 1.50 (m, 20 H), 1.50 - 1.68 (m, 2 H), 1.67 - 1.83 (m, 1 H), 1.91 - 2.02 (m, 1 H), 2.29 (q, J = 10.9 Hz, 1 H), 2.55 - 2.68 (m, 1 H), 3.50 - 3.51 (m, 1 H), 4.24 - 4.31 (m, 1 H). ^{13}C NMR (100 Hz, $CDCl_3$) δ 7.1, 11.8, 13.5, 15.7, 18.5, 18.9, 22.3, 22.5, 22.6, 22.7, 24.9, 25.7, 28.3, 28.5, 46.5, 53.0, 69.5. MS (CI), m/e 268 $(M+H)^+$. HRMS (FAB): Calcd for $C_{17}H_{34}NO$ $(M+H)^+$, m/e 268.2640; found: m/e 268.2636. $[\alpha]_D^{24} = +26.4$ (c = 0.30, MeOH).

6(*S*)-Methyl-α(*S*)-nonyl-2(*R*)-piperdineethanol (15). To a solution of isoxazolidine **14** (0.83 g, 3.1 mmol) in 50% aqueous acetic acid (20 ml) was added zinc dust (1.3 g, 20 mmol). The suspension was heated at 70°C for 3.25 h and cooled to room temperature. The reaction mixture was filtered and the filtrate extracted with ether (20 ml). The aqueous phase was basified with aqueous sodium hydroxide (10%) and

extracted with dichloromethane (3 x 50 ml). The dichloromethane layer was dried over potassium carbonate and concentrated under reduced pressure to give the aminoalcohol **15** as an oil (720 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (dd, J = 5.9 Hz, 7.1 Hz, 3 H), 1.12 (d, J = 6.7 Hz, 3 H), 1.26 - 1.70 (m, 24 H), 1.83 - 1.92 (m, 1 H), 3.15 - 3.20 (m, 1 H), 3. 23 - 3.28 (m, 1 H), 3.80 - 3.85 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 19.3, 20.0, 22.6, 26.1, 29.3, 29.5, 29.6, 29.7, 31.1, 31.8, 32.2, 37.4, 38.1, 46.0, 47.6, 69.6. MS (CI), m/e 270 $(M+H)^+$. HRMS (FAB): Calcd for $C_{17}H_{36}NO$ $(M+H)^+$, m/e 270.2797; found: m/e 270.2791. $[\alpha]_D^{20}$ = -13.9 (c = 0.30, MeOH).

(+)-Solenopsin-A. To a solution of aminoalcohol **15** (260 mg, 0.95 mmol) and triethylamine (0.5 ml) in dichloromethane (5 ml), cooled under argon in a bath at -25 °C, was added methanesulfonyl chloride (320 mg, 2.8 mmol) dropwise over 5 min. After completion of addition, the reaction mixture was stirred at -25°C for 2 h and quenched by addition of 1 N HCl (10 ml). The reaction mixture was extracted with dichloromethane (2 x 20 ml). The organic phase was dried over magnesium sulfate and concentrated *in vacuo* to give the bis-mesylate as an oil. The residue was dissolved in THF (10 ml) and lithium aluminum hydride (220 mg, 5.7 mmol) was added. The reaction mixture was refluxed for 16 h under argon. The mixture was cooled to room temperature and quenched by careful dropwise addition of 1 N sodium hydroxide (10 ml). The mixture was extracted with ether (3 x 15 ml). The combined organic phase was dried over potassium carbonate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (10 g; eluent: methanol: dichloromethane:ammonium hydroxide = 5:94:1, volume ratio) to afford (+)-solenopsin-A (171 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 6.7 Hz, 3 H), 1.06 (d, J = 6.6 Hz, 3 H), 1.18 - 1.63 (m, 27 H), 2.80 - 2.90 (m, 1 H), 3.01 - 3.10 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 19.5, 21.1, 22.7, 26.4, 29.3, 29.6 (4-CH_2), 29.8, 30.6, 31.9, 32.8, 33.9, 45.8, 50.8. MS (CI) m/e 254 $(M+H)^+$. HRMS (FAB): Calcd for $C_{17}H_{36}N$ $(M+H)^+$, m/e 254.2848; found, m/e 254.2847. $[\alpha]_D^{24}$ = +2.5 (c = 3.0, $CHCl_3$); lit.,[27] $[\alpha]_D^{20}$ = +2.5 (c = 3.0, $CHCl_3$). Treatment of a solution of (+)-solenopsin-A in dichloromethane with HCl in ether (1 N) gave (+)-solenopsin-A hydrochloride salt as white crystals which melted at 141-143°C (lit.,[12] 146°C). $[\alpha]_D^{20}$ = +7.5 (c = 1.3, $CHCl_3$); lit.,[12] $[\alpha]_D^{20}$ = +7.5 (c = 1.3, $CHCl_3$).

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