Highly Regioselective α-Addition of Alkynyl and Alkenyl Grignard Reagents to 1-Alkoxycarbonylpyridinium Salts and Its Application to Synthesis of 1-Azabicycloalkanes and (±)-Solenopsin A

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Nucleophilic addition of a variety of alkynyl and alkenyl Grignard reagents to 1-methoxycarbonylpyridinium chloride takes place at the α-position in a highly regioselective manner to give 2-substituted 1-methoxycarbonyl-1,2-dihydropyridines exclusively, while, with alkyl Grignard reagents, a lack of the regioselectivity is observed. These results may be explained by the HSAB principle. The high α-regioselectivity is preserved in the cases of 2-substituted pyridines as well, giving 2,6-disubstituted 1,2-dihydropyridines exclusively, which can be transformed stereoselectively into *cis*- and *trans*-2,6-dialkylated piperidines. These highly regioselective α-alkynylations of 1-methoxycarbonylpyridinium salts are exploited in synthesis of 1-azabicycloalkanes as well as (±)-solenopsin A.

Nucleophilic addition of organometallic reagents to 1-acylpyridinium salts has been utilized to prepare 2- and 4-substituted 1,2- and 1,4-dihydropyridines, which have proved to be valuable synthetic intermediates for nitrogen heterocycles.[1] The regioselectivity of these reactions has been of critical importance in synthetic and mechanistic points of view. There have been several organometallic reagents which favor the γ-attack on 1-acylpyridinium salts; organocopper reagents,[2] trialkylalkynylborates,[3] enol silyl ethers,[4] and titanium enolates[5] produce regioselectively the 4-substituted 1,4-dihydropyridines.

On the other hand, only a few organometallics, i.e. Grignard[6] and organocadmium reagents,[6e] have been reported to predominantly attack on the α-position. The regioselectivity of these reactions, however, is apparently biased, because 4- and/or 3-substituted pyridines have been used as the starting material in most of the cases.

Then, we have examined the reaction of 1-methoxycarbonylpyridinium chloride itself with a variety of Grignard reagents and found that the regioselectivity is highly dependent on the nature of Grignard reagent. Thus, with alkyl Grignard reagents, 4-alkyl-1,4- and 2-alkyl-1,2-dihydropyridines are produced in variable ratios, uncovering a lack of the regioselectivity.[7,8]

In this report we describe that alkynyl and alkenyl Grignard reagents add to the α-position of the pyridinium salt in a highly regioselective manner to afford 2-substituted 1,2-dihydropyridines exclusively and that this methodology provides an easy access to the synthesis of 1-azabicycloalkanes as well as 2,6-dialkylated piperidines.[9]

Results and Discussion

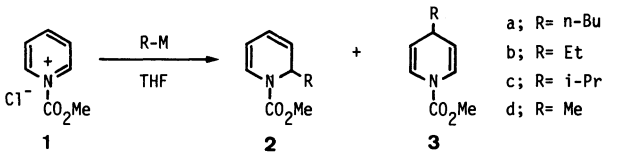
When we reexamined the reaction of 1-methoxycarbonylpyridinium chloride (**1**) with butylmagnesium

Table 1. Reactions of 1-Methoxycarbonylpyridinium Chloride (**1**) with Alkyl Grignard Reagents and Other Organometallic Reagents

Entry	R	M	Temp °C	Method[a]	Yield[b] %	Ratio(2/3)[c]
1	*n*-Bu	MgBr	0	A	41	78/22[d]
2	*n*-Bu	MgBr	−78	A	99	67/33
3	*n*-Bu	MgBr	−78	B	79	60/40
4	*n*-Bu	MgCl	−78	A	86	67/33
5	Me	MgI	0	A	54	92/8
6	Et	MgBr	−78	A	51	57/43
7	*i*-Pr	MgBr	−78	A	99	37/63
8	*n*-Bu	ZnCl[e]	0	A	99	19/81
9	*n*-Bu	Li	−78	B	f)	
10	*n*-Bu	$Cu \cdot BF_3$	−78	B		0.5/99.5[g]

a) Method A: Methyl chloroformate was added to a mixture of pyridine and organometallic reagent in THF. Method B: **1** was preformed before adding organometallic reagent. b) Combined yield. c) Determined by GLC and/or ^1H NMR. d) A small amount of 5-butyl-5-nonanol was obtained. e) Prepared by adding $ZnCl_2$ to *n*-BuMgBr. f) Pentanoic anhydride was obtained. g) Taken from Ref. 2b.

bromide in THF at 0 °C according to the Fraenkel method,[6a] we found that 2-butyl-1-methoxycarbonyl-1,2-dihydropyridine (**2a**) and 4-butyl-1-methoxycarbonyl-1,4-dihydropyridine (**3a**) were produced in a ratio of 78:22, along with a small amount of 5-butyl-5-nonanol. The reaction conducted at −78 °C gave again a mixture of **2a** and **3a** in a ratio of 67:33. Since these results were inconsistent with that of Fraenkel et al., who reported the exclusive formation of **2a**, we decided to investigate the reaction of **1** with a couple of alkyl Grignard reagents as well as other organometallic reagents in more detail (Scheme 1, Table 1).



1 2 3

Scheme 1.

Table 1 evidently demonstrates that the regioselectivity is dependent on the character of metals. It has been suggested that the regioselectivity of the attack on the pyridinium cation by nucleophiles may be explained by the HSAB principle[10,11] (Fig. 1); with such relatively hard nucleophiles as hydroxide and amide ions the preferential α-attack (an arrow b) is observed, while with such soft ones as cyanide and enolate ions an attack on the γ-position (an arrow a) is predominant.[11] The above reactions with the organometallic reagents may be rationalized in the same context; the very soft organocopper reagents almost exclusively attack at the γ-position, as has been recently suggested by Akiba et al. (Entry 10).[2b,2c] The organozinc reagent, which is slightly harder than organocopper reagent, reveals a slightly less γ-selectivity (Entry 8). With harder alkyl Grignard reagents, both of α- and γ-attack occur in variable ratios (Entries 1—7). Furthermore, we have found that much harder organolithium reagent gives pentanoic anhydride exclusively (Entry 9), probably through the attack on the carbonyl moiety, the hardest position of the pyridinium salt (an arrow c in Fig. 1).

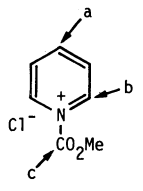
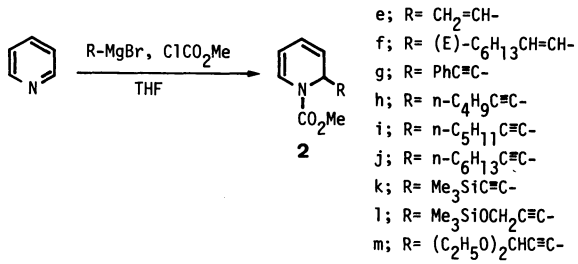


Fig. 1. Three possible positions attacked by nucleophiles.

While the above results led to the conclusion that alkyl Grignard reagents generally showed no appreciable α-regioselectivity, we were interested in that, among alkyl Grignard reagents, methyl Gignard reagent showed more than the 90% of the α-addition (Entry 5). We have thought that this is because the α-regioselectivity is enhanced by harder methyl group than other alkyl ones. Accordingly, in order to obtain 2-substituted 1,2-dihydropyridine selectively which may be a potential intermediate for alkaloid synthesis,[1] we have next examined the reaction of **1** with alkynyl as well as alkenyl Grignard reagents, considering that these organic moieties are supposed to be harder than alkyl ones (Scheme 2). The results are summarized in Table 2. As is shown in Table 2, the α-regioselectivity is far better than the expected; with a variety of alkynyl and alkenyl Grignard reagents the α-attack takes place exclusively to afford 2-alkynyl- and 2-alkenyl-1,2-dihydropyridines in good to excellent yields.[12,13]



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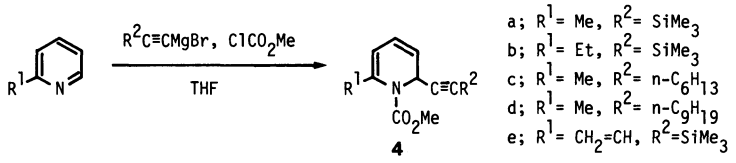
Scheme 2.

Tabe 2. Reactions of **1** with Alkynyl and Alkenyl Grignard Reagents[a]

Entry	R	Yield[b,c] %
1	CH_2=CH-	81
2	(*E*)-*n*-C_6H_{13}CH=CH-	71[d]
3	PhC≡C-	98
4	*n*-C_4H_9C≡C-	97
5	*n*-C_5H_{11}C≡C-	93
6	*n*-C_6H_{13}C≡C-	93
7	Me_3SiC≡C-	99
8	Me_3SiOCH$_2$C≡C-	98
9	$(EtO)_2$CHC≡C-	87

a) All reaction were carried out by Method A at 0° C, unless otherwise noted. b) Isolated yield. c) The α-regioselectivity was shown to be >98% by GLC and/or ^{1}H NMR analysis in all of the cases. d) The reaction was conducted at −40 °C.

To our further delight, it has been found that the above high α-regioselectivity is completely preserved in the reactions of 2-substituted pyridines (Scheme 3). The results are summarized in Table 3. Thus, reactions of 2-methyl- or 2-ethylpyridine with alkynyl Grignard reagents in the presence of methyl chloroformate proceeded in a highly regioselective manner to give exclusively 2,6-disubstituted 1-methoxycarbonyl-1,2-dihydropyridines, in spite of their steric congestion.[14]



Scheme 3.

Table 3. Reactions of 2-Substituted 1-Methoxycarbonylpyridinium Chlorides with Alkynyl Grignard Reagents[a)]

Entry	R^1	R^2	Yield[b)] %
1	Me	$SiMe_3$	79
2	Et	$SiMe_3$	66
3	Me	n-C_6H_{13}	73
4	Me	n-C_9H_{19}	79
5	CH_2=CH-	$SiMe_3$	26

a) All reactions carried out by Method A at 0 °C.
b) Isolated yield.

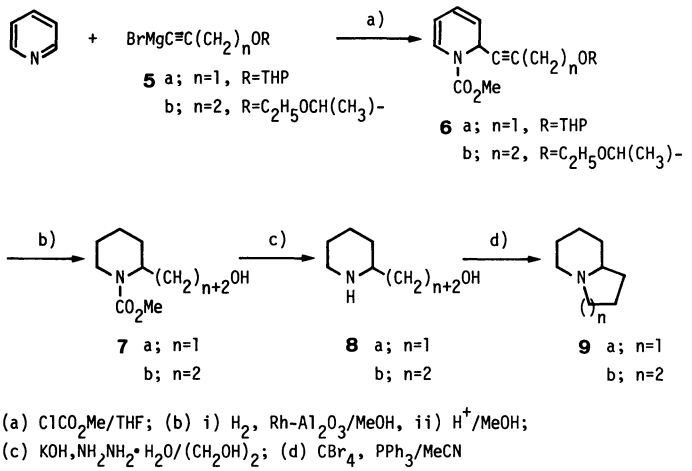
Synthesis of Indolizidine and Quinolizidine through Highly Regioselective α-Alkynylation of Pyridinium Salt. Indolizidine and quinolizidine skeletons are incorporated in a number of alkaloids and much effort has been made for constructing these systems.[15)] We describe here an application of the above reactions to synthesis of 1-azabicycloalkanes (Scheme 4).

Reactions of pyridine with alkynyl Grignard reagents possessing protected hydroxyl group **5** in the presence of methyl chloroformate gave exclusively 1-methoxycarbonyl-2-alkynyl-1,2-dihydropyridines (**6a** and **6b**), which were successively hydrogenated on Rh-Al_2O_3 and deprotected to afford 2-(3-hydroxypropyl)- and 2-(4-hydroxybutyl)piperidine derivatives (**7a** and **7b**), respectively, in good yields. Demethoxycarbonylation[16)] of **7**, followed by cyclization of the resulting amino alcohols (**8a** and **8b**) with PPh_3 and CBr_4,[17)] furnished indolizidine (**9a**) and quinolizidine (**9b**), respectively.

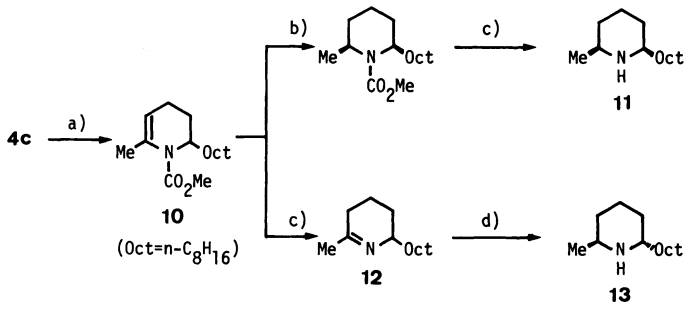
Synthesis of *cis*- and *trans*-2,6-Dialkylated Piperidines and (±)-Solenopsin A via 1-Methoxycarbonyl-2,6-disubstituted-1,2-dihydropyridines. 2,6-Dialkylated piperidines constitute the principal structure of a number of piperidine alkaloids.[18,19)] Accordingly, we next examined the stereoselective transformation of 2,6-disubstituted 1-methoxycarbonyl-1,2-dihydropyridine obtained above into *cis*- and *trans*-2,6-dialkylated piperidines and an application of this sequence to synthesis of (±)-solenopsin A, a piperidine alkaloid isolated from the venom of the fire ant.[20,21)]

At first we have found that careful hydrogenation of **4c** over 5% Pd-C can give a partially hydrogenated, crucial intermediate, 2,6-dialkylated 1,2,3,4-tetrahydropyridine (**10**) in 83% yield. Further hydrogenation of **10** over Pd-black, followed by demethoxycarbonylation with iodotrimethylsilane,[22)] afforded *cis*-2-methyl-6-octylpiperidine (**11**) exclusively (Scheme 5).

On the other hand, a cyclic imine (**12**) could be obtained, when **10** was demethoxycarbonylated with iodotrimethylsilane. According to the Yamamoto's elegant method for stereoselective reduction of this type of cyclic imine,[21a)] **12** was reduced by lithium tetrahydroaluminate in THF at −78 °C to afford *trans*-2-methyl-6-octylpiperidine (**13**), along with a small amount of the cis-isomer **11** (**13**:**11**=78:22).

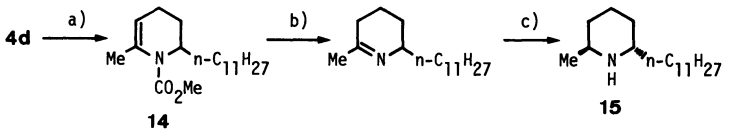


Scheme 4.



(a) H_2, Pd-C/MeOH; (b) H_2, Pd/MeOH; (c) $Me_3SiI/CHCl_3$; (d) $LiAlH_4$/THF, -78°C

Scheme 5.



(a) H_2, Pd-C/MeOH; (b) $Me_3SiI/CHCl_3$; (c) $LiAlH_4$, Me_3Al/THF, -78°C

Scheme 6.

Thus, it has been shown that 2,6-disubstituted 1,2-dihydropyridine is a versatile precursor for *cis*- and *trans*-2,6-dialkylated piperidines.[23]

Consequently, the above sequence has been applied to the regio- and stereoselective synthesis of (±)-solenopsin A, *trans*-2-methyl-6-undecylpiperidine (Scheme 6). Careful hydrogenation of **4d** over 5% Pd-C in methanol gave 1,2,3,4-tetrahydropyridine derivative (**14**). Demethoxycarbonylation of **14** followed by reduction with lithium tetrahydroaluminate in the presence of trimethylaluminium[21a] afford (±)-solenopsin A (**15**) in 90% yield based on **14**, along with a small amount of its epimer. Thus, the present route provides one of the most practical and efficient method for the synthesis of (±)-solenopsin A (43% overall yield in 4 steps from 2-methylpyridine).[24]

Experimental

All the temperatures were uncorrected. The IR spectra were obtained on a Hitachi 215 or JASCO IR-810 spectrometer. The mass spectra were taken by using a Hitachi RMS-4 mass spectrometer. The ^1H and ^{13}C NMR spectra were obtained on Varian EM-390 and CFT-20 or JEOL FX-90Q spectrometers, Me_4Si being chosen as the internal standard. Analytical GLC were carried out on a Shimadzu GC-4C gas chromatography with 10% SE-30, 10% HVSG, or 10% PEG-20M on Chromsorb W columns. The microanalyses were performed by Kyoto University Elemental Analysis Center. All the reactions were carried out under Ar atmosphere, otherwise noted. THF was distilled from benzophenone ketyl before use.

General Procedure for the Reaction of 1-Methoxycarbonylpyridinium Chloride (1) with Alkyl Grignard Reagents. Method A. To a mixture of butylmagnesium bromide (5 mL, 2.0 M†, 10.0 mmol) and pyridine (0.396 g, 5.0 mmol) in THF (7.5 mL) was added methyl chloroformate (0.473 g, 5.0 mmol) at −78 °C. The reaction mixture was stirred for 5 h and quenched by adding water (0.75 mL) at that temp. The mixture was poured onto water and extracted with CH_2Cl_2. The organic layer was washed with brine and dried (Na_2SO_4). The solvent was evaporated and the residue was passed through a short silica-gel column eluting with CH_2Cl_2 to give a mixture of **2a**[3a] and **3a**[2a] (0.966 g, 99%). The ratio of **2a** to **3a** was 67:33 by GLC analysis.

Method B. To a solution of pyridine (0.396 g, 5.0 mmol) in THF (20 mL) were added methyl chloroformate (0.473 g, 5.0 mmol) at 0 °C. The mixture was stirred for 1 h and cooled to −78 °C. To this mixture was added butylmagnesium bromide (10.0 mmol in 15 mL of THF) and the reaction mixture was stirred for 5 h. The usual work-up gave a mixture of **2a** and **3a** (0.767 g, 79%). The ratio of **2a** to **3a** was 59:41 by GLC analysis.

The reactions of **1** with other alkyl Grignard reagents were conducted in a similar manner to the above. The yields and the ratios are described in Table 1.[2a]

Reaction of 1 with Butyllithium. To a mixture of **1**, prepared from pyridine (0.158 g, 2.0 mmol) and methyl chloroformate (0.189 g, 2.0 mmol), in THF (6 mL) was added *n*-BuLi (0.64 mL, 1.56 M, 1.0 mmol) in hexane at −78 °C. After 15 min, water (0.5 mL) was added to the mixture. The usual work-up gave valeric anhydride (0.091 g, 98%).

General Procedure for the Reaction of 1 with Alkenyl and Alkynyl Grignard Reagents. To a mixture of pyridine

† 1 M=1 mol dm^{-3}.

(0.211 g, 2.7 mmol) and alkenyl or alkynyl Grignard reagent (2.7—5.0 mmol) in THF (6—10 mL) was added a solution of methyl chloroformate (0.230 g, 2.4 mmol) in THF (2 mL) dropwise under ice-cooling. After 30 min, the mixture was poured onto 1 M aq NH_4Cl and extracted with CH_2Cl_2. The organic solution was washed with water and dried (Na_2SO_4). The solvent was evaporated and the residue was passed through a short silica-gel column eluting with CH_2Cl_2 to give **2**. The yield of each product is described in Table 2.

1-Methoxycarbonyl-2-vinyl-1,2-dihydropyridine (2e): MS *m/z* (%) 165 (M^+, 36), 138 (100); IR (neat): 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ=6.68 (br d, 1H, *J*=6 Hz), 4.66—6.02 (m, 7H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$) δ=169.7 (s), 134.6 (d), 125.2 (d), 122.0 (d), 120.5 (d), 115.1 (t), 105.4 (d), 54.1 (d), 53.1 (q). Found: C, 65.45; H, 6.81%. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71%.

1-Methoxycarbonyl-2-[(*E*)-1-octenyl]-1,2-dihydropyridine (2f): MS *m/z* (%) 249 (M^+, 11), 138 (100); IR (neat): 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ=6.65 (br d, 1H, *J*=6 Hz), 6.00—7.00 (m, 6H), 3.76 (s, 3H), 1.89—2.50 (br m, 2H), 1.08—1.70 (m, 8H), 0.88 (t, 3H, *J*=7 Hz); ^{13}C NMR ($CDCl_3$) δ=154.0 (s), 126.4 (d), 125.2 (d), 121.4 (d), 120.9 (d), 105.3 (d), 105.1 (d), 52.9 (q), 50.2 (d), 32.2 (t), 31.8 (t), 29.9 (t), 29.1 (t), 22.7 (t), 14.0 (q). Found: C, 72.38; H, 9.46%. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30%.

1-Methoxycarbonyl-2-phenylethynyl-1,2-dihydropyridine (2g): MS *m/z* (%) 239 (M^+, 100); IR (neat): 2200, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ=7.15—7.50 (m, 5H), 6.60—7.15 (br, 1H), 5.18—6.12 (m, 4H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$) δ=153.9 (s), 131.9 (2d), 128.3 (d), 128.2 (2d), 125.1 (d), 122.8 (s), 122.3 (d), 118.7 (d), 105.5 (d), 86.7 (s), 83.2 (s), 53.4 (q), 44.3 (d). Found: C, 75.06; H, 5.73%. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48%.

1-Methoxycarbonyl-2-(1-hexynyl)-1,2-dihydropyridine (2h): MS *m/z* (%) 219 (M^+, 79), 218 (74), 79 (100); IR (neat): 2000, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ=6.66 (br d, 1H, *J*=6 Hz), 5.10—5.98 (m, 4H), 3.78 (s, 3H), 1.97—2.25 (m, 2H), 1.10—1.62 (m, 4H), 0.82 (t, 3H, *J*=7 Hz); ^{13}C NMR ($CDCl_3$) δ=153.9 (t), 125.0 (d), 121.7 (d), 119.7 (d), 105.3 (d), 83.9 (s), 77.9 (s), 53.3 (q), 44.0 (d), 30.8 (t), 21.9 (t), 18.5 (t), 13.5 (q). Found: C, 71.13; H, 7.98%. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81%.

1-Methoxycarbonyl-2-(1-heptynyl)-1,2-dihydropyridine (2i): MS *m/z* (%) 263 (M^+, 83), 262 (100); IR (neat): 2200, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ=6.67 (br d, 1H, *J*=6 Hz), 5.07—6.00 (m, 4H), 3.79 (s, 3H), 1.92—2.25 (m, 2H), 1.10—1.61 (m, 6H), 0.87 (t, 3H, *J*=7 Hz); ^{13}C NMR ($CDCl_3$) δ=154.0 (s), 125.0 (d), 121.6 (d), 119.7 (d), 105.3 (d), 84.0 (s), 77.8 (s), 53.3 (q), 44.0 (d), 31.1 (t), 28.3 (t), 22.2 (t), 18.8 (t), 13.9 (q). Found: C, 72.14; H, 8.29%. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21%.

1-Methoxycarbonyl-2-(1-octynyl)-1,2-dihydropyridine (2j): MS *m/z* (%) 247 (M^+, 100); IR (neat): 2245, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ=6.68 (br d, 1H, *J*=7 Hz), 5.15—6.00 (m, 4H), 3.78 (s, 3H), 1.98—2.27 (m, 2H), 1.10—1.60 (m, 8H), 0.88 (t, 3H, *J*=7 Hz); ^{13}C NMR ($CDCl_3$) δ=153.9 (s), 125.1 (d), 121.7 (d), 119.7 (d), 105.3 (d), 84.0 (s), 77.9 (s), 53.3 (q), 44.0 (d), 31.4 (t), 28.6 (t), 28.5 (t), 22.6 (t), 18.9 (t), 14.0 (q). Found: C, 72.58; H, 8.61%. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.66%.

1-Methoxycarbonyl-2-trimethylsilylethynyl-1,2-dihydropyridine (2k): MS *m/z* (%) 235 (M^+, 67), 234 (66), 73 (100); IR (neat): 2160, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ=6.65 (br d, 1H, *J*=7 Hz), 5.17—6.00 (m, 4H), 3.77 (s, 3H), 0.15 (s, 9H); ^{13}C NMR ($CDCl_3$) δ=153.9 (s), 125.2 (d), 122.3 (d), 118.9 (d), 105.5 (d), 102.9 (s), 87.8 (s), 53.4 (q), 44.5 (d), 0.0 (q). Found: C, 61.19; H, 7.26%. Calcd for $C_{12}H_{17}NO_2Si$: C, 61.24; H, 7.28%.

1-Methoxycarbonyl-2-(3-trimethylsilyloxy-1-propynyl)-1,2-dihydropyridine (2l): MS *m/z* (%) 265 (M^+, 81), 73 (100); IR (neat): 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ=6.63 (br d, 1H, *J*=6 Hz), 5.03—5.95 (m, 4H), 4.16 (s, 2H), 3.69 (s, 3H), 0.06 (s, 9H); ^{13}C NMR ($CDCl_3$) δ=153.4 (s), 124,8 (d), 122.0 (d), 118.2 (d), 105.1 (d), 82.3 (s), 81.4 (s), 53.1 (q), 50.9 (t), 43.5 (d), −0.5 (q). Found: C, 58.65; H, 7.15.% Calcd for $C_{13}H_{19}NO_3Si$: C, 58.84; H, 7.22%.

1-Methoxycarbonyl-2-(3,3-diethoxy-1-propynyl)-1,2-dihydropyridine (2m): MS *m/z* (%) 265 (M^+, 35), 138 (100); IR (neat): 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ=6.68 (br d, 1H, *J*=7 Hz), 5.22—6.07 (m, 4H), 5.20 (s, 1H), 3.80 (s, 3H), 3.31—3.75 (m, 4H), 1.20 (t, 6H, *J*=7 Hz); ^{13}C NMR ($CDCl_3$) δ=157.5 (s), 125.0 (d), 122.7 (d), 118.1 (d), 105.5 (d), 91.3 (d), 82.6 (s), 78.5 (s), 60.8 (2t), 53.5 (q), 43.6 (d), 15.1 (2q). Found: C, 63.12; H, 7.36%. Calcd for $C_{14}H_{13}NO_4$: C, 63.38; H, 7.22%.

General Procedure for the Reactions of 2-Substituted 1-Methoxycarbonylpyridinium Salts with Alkynyl Grignard Reagents. To a mixture of 2-substituted pyridine (5.3 mmol) and alkynylmagnesium bromide, prepared from the corresponding alkyne (2.7 mmol) and ethylmagnesium bromide (2.7 mmol), in THF (17 mL) was slowly added a solution of methyl chloroformate (0.255 g, 2.7 mmol) in THF (6 mL) over 1.5 h under ice-cooling. The mixture was stirred for 1.5 h and poured onto 10% aq NH_4Cl. The usual work-up and the subsequent short-column chromatography on silica-gel eluting with CH_2Cl_2 gave **4**. The yield of each product is described in Table 3.

1-Methoxycarbonyl-6-methyl-2-trimethylsilylethynyl-1,2-dihydropyridine (4a): mp 63.2—64.0 °C; MS *m/z* (%) 249 (M^+, 86), 174 (100); IR (nujol): 2150, 1715, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ=5.29—5.96 (m, 4H), 3.64 (s, 3H), 2.07 (s, 3H), 0.07 (s, 9H); ^{13}C NMR ($CDCl_3$) δ=154.3 (s), 135.3 (s), 123.5 (d), 120.1 (d), 112.2 (d), 103.2 (s), 87.4 (s), 53.1 (q), 45.0 (d), 21.6 (q), 0.1 (q). Found: C, 62.63; H, 7.66%. Calcd for $C_{13}H_{19}NO_2Si$: C, 62.61; H, 7.68%.

1-Methoxycarbonyl-6-ethyl-2-trimethylsilylethynyl-1,2-dihydropyridine (4b): MS *m/z* (%) 263 (M^+, 69), 234 (100); IR (neat): 2175, 1720, 845 cm^{-1}; ^1H NMR ($CDCl_3$) δ=5.41—5.71 (m, 4H), 3.94 (s, 3H), 2.01—3.04 (m, 2H), 1.04 (t, 3H, *J*=7 Hz), 0.11 (s, 9H); ^{13}C NMR ($CDCl_3$) δ=154.3 (s), 140.8 (s), 123.6 (d), 120.8 (d), 111.6 (d), 102.8 (s), 87.5 (s), 53.1 (q), 45.1 (d), 27.5 (t), 12.5 (q), 0.0 (q). Found: C, 63.58; H, 8.06%. Calcd for $C_{14}H_{21}NO_2Si$: C, 63.84; H, 8.04%.

1-Methoxycarbonyl-6-methyl-2-(1-octynyl)-1,2-dihydropyridine (4c): MS *m/z* (%) 261 (M^+, 100); IR (neat): 2220, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ=5.36—5.94 (m, 4H), 3.73 (s, 3H), 2.15 (s, 3H), 1.90—2.28 (m, 2H), 1.05—1.57 (m, 8H), 0.85 (t, 3H, *J*=7 Hz); ^{13}C NMR ($CDCl_3$) δ=154.4 (s), 135.1 (s), 122.7 (d), 120.7 (d), 111.8 (d), 83.4 (s), 77.5 (s), 52.9 (q), 44.5 (d), 31.4 (t), 28.7 (t), 28.4 (t), 22.6 (t), 21.5 (q), 18.9 (t), 14.0 (q). Found: C, 73.50; H, 9.11%. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87%.

1-Methoxycarbonyl-6-methyl-2-(1-undecynyl)-1,2-dihydropyridine (4d): MS *m/z* (%) 303 (M^+, 100); IR (neat): 2220, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ=5.37—5.97 (m, 4H), 3.75 (s,

3H), 2.17 (s, 3H), 2.00—2.40 (m, 2H), 1.07—1.70 (m, 14H), 0.87 (t, 3H, J=7 Hz); ^{13}C NMR ($CDCl_3$) δ=154.4 (s), 135.0 (s), 122.7 (d), 120.6 (d), 111.8 (d), 83.4 (s), 77.3 (s), 53.0 (q), 44.3 (d), 32.0 (t), 29.6 (t), 29.3 (t), 29.2 (t), 28.8 (t), 28.7 (t), 22.8 (t), 21.5 (q), 18.8 (t), 14.1 (q). Found: C, 75.18; H, 9.92%. Calcd for $C_{19}H_{29}NO_2$: C, 75.20; H, 9.63%.

1-Methoxycarbonyl-2-trimethylsilylethynyl-6-vinyl-1,2-dihydropyridine (4e): MS m/z (%) 261 (M^+, 77), 202 (100); IR (neat): 2170, 1710, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=4.92—6.45 (m, 7H), 3.64 (s, 3H), 0.04 (s, 9H); ^{13}C NMR ($CDCl_3$) δ=154.8 (s), 136.3 (s), 134.1 (d), 128.5 (d), 123.6 (d), 114.3 (t), 113.7 (d), 102.2 (s), 88.5 (s), 53.1 (q), 45.1 (d), 0.0 (q). Found: C, 64.19; H, 7.35%. Calcd for $C_{14}H_{19}NO_2Si$: C, 64.33; H, 7.33%.

1-Methoxycarbonyl-2-(3-hydroxypropyl)piperidine (7a). To a mixture of pyridine (1.242 g, 12.6 mmol) and 3-(2-tetrahydropyranyloxy)propynylmagnesium bromide, prepared from tetrahydro-2-(2-propynyloxy)-2*H*-pyran (1.396 g, 9.97 mmol) and ethylmagnesium bromide (6.0 mL, 1.88 M, 11.3 mmol), in THF (20 mL) was added a solution of methyl chloroformate (1.000 g, 10.5 mmol) in THF (10 mL) slowly over 1.5 h under ice-cooling. The mixture was stirred for 2 h, poured onto 10% aq NH_4Cl, and extracted with CH_2Cl_2. The organic solution was washed with water and brine, and dried (Na_2SO_4). The solvent was evaporated to give almost pure **6a**: ^{1}H NMR ($CDCl_3$) δ=6.76 (br d, 1H, J=7 Hz), 5.20—6.21 (m, 4H), 4.80 (br s, 1H), 4.27 (s, 2H), 3.83 (s, 3H), 3.47—4.02 (m, 2H), 1.30—1.97 (m, 6H); ^{13}C NMR ($CDCl_3$) δ=153.7 (s), 124.8 (d), 122.0 (d), 118.2 (d), 105.1 (d), 96.6 (d), 83.2 (t), 78.6 (s), 61.8 (t), 54.2 (t), 53.4 (q), 43.6 (d), 30.3 (t), 25.5 (t), 19.1 (t). Without purification, **6a** was dissolved in dry MeOH (15 mL) and completely hydrogenated over 5% Rh-Al_2O_3 (0. 20 g) under 8 kg cm^{-2} pressure of H_2. After the catalyst was removed by filtration through Celite, the solvent was evaporated. The residue was dissolved in dry MeOH (10 mL) and to this solution was added Amberlyst H-15 (0.15 g). The mixture was stirred at 45 °C for 1 h and Amberlyst H-15 was removed by filtration. The solvent was evaporated and the residue was purified through bulb-to-bulb distillation to give **7a** (1.621 g, 81%): Bp 110—120 °C/80 Pa; MS m/z (%) 201 (M^+, 4), 142 (100); IR (neat): 3450, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.83—4.50 (m, 2H), 3.68 (s, 3H), 3.53—3.83 (m, 2H), 2.63—3.10 (m, 1H), 2.53 (s, 1H), 1.20—1.90 (m, 10H); ^{13}C NMR ($CDCl_3$) δ=156.3 (s), 61.8 (t), 52.4 (q), 50.8 (d), 39.1 (t), 29.5 (t), 28.7 (t), 26.1 (t), 25.7 (t), 19.0 (t).

1-Methoxycarbonyl-2-(4-hydroxybutyl)piperidine (7b). To a mixture of pyridine (1.27 g, 12.9 mmol) and 4-(1-ethoxyethoxy)-1-butynylmagnesium bromide, prepared from 4-(1-ethoxyethoxy)-1-butyne (1.43 g, 10.1 mmol) and ethylmagnesium bromide (7.8 mL, 1.42 M, 11.1 mmol), in THF (20 mL) was added a solution of methyl chloroformate (1.00 g, 10.5 mmol) in THF (10 mL) slowly over 1.5 h under ice-cooling. The mixture was stirred for 2 h and the usual work-up gave **6b**: ^{1}H NMR ($CDCl_3$) δ=6.80 (br d, 1H, J=7 Hz), 5.38—6.13 (m, 4H), 4.75 (q, 1H, J=6 Hz), 3.83 (s, 3H), 3.36—3.80 (m, 4H), 2.43 (t, 2H, J=6 Hz), 1.30 (d, 3H, J=6 Hz), 1.13 (t, 3H, J=6 Hz); ^{13}C NMR ($CDCl_3$) δ=153.6 (s), 124.7 (d), 121.7 (d), 119.2 (d), 105.3 (d), 99.5 (d), 80.6 (s), 78.6 (s), 63.1 (t), 60.8 (t), 53.3 (q), 43.6 (d), 20.5 (t), 19.7 (q), 15.3 (q). Without purification, **6b** was hydrogenated in a similar manner to the above. In this case, 1-ethoxyethyl group was removed during this hydrogenation. Purification through bulb-to-bulb distillation gave **7b** (1.61 g, 75%): Bp 110—130 °C/67 Pa; IR (neat): 3400, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.80—4.33 (m, 2H), 3.65 (s, 3H), 3.57 (t, 2H, J=6 Hz), 2.60—3.07 (m, 2H), 1.10—1.83 (m, 12H); ^{13}C NMR ($CDCl_3$) δ=156.4 (s), 62.4 (t), 52.4 (q), 50.7 (d), 39.1 (t), 32.6 (t), 29.4 (t), 28.4 (t), 25.7 (t), 22.5 (t), 19.0 (t).

2-(3-Hydroxypropyl)piperidine (8a). A mixture of **7a** (0.699 g, 3.5 mmol), KOH (5.11 g), and 100% $NH_2NH_2 \cdot H_2O$ (0.85 mL) in ethylene glycol (26 mL) was heated under reflux for 1.5 h. The reaction mixture was poured onto water and extracted with CH_2Cl_2. The organic solution was washed with 30% aq NaOH and dried (Na_2SO_4). The solvent was evaporated to give almost pure **8a** (0.473 g, 95%): MS m/z (%) 143 (M^+, 9), 142 (100); ^{1}H NMR ($CDCl_3$) δ=3.57 (s, 2H), 3.53 (t, 2H, J=6 Hz), 2.90—3.20 (m, 1H), 2.30—2.77 (m, 2H), 0.93—1.90 (m, 14H); ^{13}C NMR ($CDCl_3$) δ=62.6 (t), 56.9 (d), 46.6 (t), 35.9 (t), 32.2 (t), 30.4 (t), 26.6 (t), 24.8 (t).

2-(4-Hydroxybutyl)piperidine (8b). A mixture of **7b** (0.263 g, 1.2 mmol), KOH (1.80 g), and 100%$NH_2NH_2 \cdot H_2O$ (0.3 mL) in ethylene glycol (9 mL) was heated under reflux for 1.5 h. The similar work-up to the above gave almost pure **8b** (0.179 g, 93%): ^{1}H NMR ($CDCl_3$) δ=3.55 (t, 2H, 6 Hz), 2.84—3.20 (m, 1H), 2.80 (br s, 2H), 2.27—2.77 (m, 2H), 0.97—1.90 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ=61.5 (t), 56.8 (d), 47.0 (t), 37.0 (t), 32.9 (t), 32.8 (t), 26.4 (t), 24.8 (t), 22.2 (t).

Indolizidine (9a). A solution of **8a** (0.258 g, 1.8 mmol), PPh_3 (0.890 g, 3.3 mmol), and CBr_4 (1.320 g, 4.0 mmol) in dry CH_3CN (18 mL) was stirred at room temp overnight. The mixture was poured onto 10% aq HCl and washed with AcOEt. The aqueous layer was basified by adding 2 M aq NaOH and K_2CO_3, and extracted with ether. The organic layer was dried (K_2CO_3) and the solvent was evaporated. The residue was purified through bulb-to-bulb distillation (80 °C/6000 Pa) to give **9a** (0.130 g, 58%): Picrate, mp 229—231.5 °C (lit,[25] 233—234 °C); ^{1}H NMR ($CDCl_3$) δ=2.90—3.23 (m, 2H), 1.03—2.63 (m, 13H); ^{13}C NMR ($CDCl_3$) δ=64.4 (d), 54.3 (t), 53.2 (t), 31.1 (t), 30.6 (t), 25.6 (t), 24.7 (t), 20.7 (t).

Quinolizidine (9b). A solution of **8b** (0.164 g, 1.04 mmol), PPh_3 (0.520 g, 2.00 mmol), and CBr_4 (0.770 g, 2.33 mmol) in dry CH_3CN (11 mL) was heated under reflux for 2 h. The similar work-up to the above and purification through bulb-to-bulb distillation (80 °C/2666 Pa) gave **9b**: Picrate, mp 195—198 °C (lit,[26] 198—199 °C); ^{1}H NMR ($CDCl_3$) δ=2.60—2.97 (m, 2H), 0.90—2.23 (m, 15H); ^{13}C NMR ($CDCl_3$) δ=63.0 (d), 56.7 (t), 33.6 (t), 26.0 (t), 24.7 (t).

1-Methoxycarbonyl-6-methyl-2-octyl-1,2,3,4-tetrahydropyridine (10). A mixture of **4c** (0.783 g, 3.0 mmol) and 5% Pd-C (0.157 g) in dry MeOH (30 mL) was stirred under atmospheric pressure of H_2. The reaction was carefully monitored by TLC. As soon as the starting material disappeared, the reaction was stopped. The catalyst was removed by filtration through Celite and the solvent was evaporated. The residue was passed through a short silica-gel column eluting with hexane-CH_2Cl_2 (4:1) to give **10** (0.667 g, 83%): MS, m/z (%) 267 (M^+, 34), 196 (100); IR (neat): 1710 cm^{-1} ^{1}H NMR ($CDCl_3$) δ=4.85 (br s, 1H), 4.35 (br s, 1H), 3.66 (s, 3H), 2.00 (s, 3H), 1.10—2.10 (m, 18H), 0.87 (t, 3H, J=6 Hz); ^{13}C NMR ($CDCl_3$) δ=154.4 (s), 132.9 (s), 111.7 (d), 52.7 (d), 52.3 (q), 32.0 (t), 31.7 (t), 29.9 (t), 29.7 (t), 29.4 (t), 26.5 (t), 26.0 (t), 22.7 (t), 22.7 (q), 19.6 (t), 14.1 (q). Found: C, 75.18; H, 9.92%. Calcd for $C_{16}H_{29}NO_2$: C, 75.20; H, 9.63%.

***cis*-2-Methyl-6-octylpiperidine (11).** A mixture of **10** (0.203 g, 0.76 mmol) and Pd-black (0.02 g) in dry MeOH (5 mL) was stirred under atmospheric pressure of H_2 for 20 h. The catalyst was removed by filtration through Celite and the solvent was evaporated. The residue (0.126 g) was dissolved in dry $CHCl_3$ (2.0 mL) and to this solution was added iodotrimethylsilane (0.10 mL, 0.6 mmol). The reaction mixture was stirred at 50—60 °C for 3 h and then, after addition of MeOH (0.06 mL), at room temp for 0.5 h. The mixture was condensed under reduced pressure, diluted with 0.1 M aq NaOH, and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and the solvent was evaporated to give **11** (0.103 g, 64%), which was identical with the authentic **11** prepared by a different route (vide infra).

***trans*-2-Methyl-6-octylpiperidine (13).** To a mixture of **10** (0.134 g, 0.50 mmol) in dry $CHCl_3$ (2.0 mL) was added iodotrimethylsilane (0.10 mL, 0.60 mmol). The mixture was stirred at 50—60 °C for 1.5 h and then, after addition of MeOH (0.06 mL), at room temp for 0.5 h. The mixture was condensed under reduced pressure, diluted with 0.1 M aq NaOH, and extracted with CH_2Cl_2. The solvent was evaporated to give a imine (**12**) (0.103 g): IR (neat): 1655 cm^{-1}. To a suspension of $LiAlH_4$ (0.475 g, 12.5 mmol) in THF (8.0 mL) was added a solution of **12** (0.103 g) in THF (8.0 mL) at −78 °C. The mixture was stirred at −78 °C for 1 h, −45 °C for 1 h, −20 °C for 1 h, and 0 °C for 1 h. The usual work-up and column chromatography on alumina eluting with ether gave **13**, along with a small amount of **11** (0.081 g, 70%, **13**:**11**=78:22 by GLC analysis).

Preparation of 11 and 13 by MacConell's Method.[22] To a mixture of 2,6-dimethylpyridine (2.15 g, 20 mmol) in ether (20 mL) was added PhLi in ether (17 mL, 1.33 M, 22 mmol) and the mixture was heated at reflux for 15 min. To this solution was added heptyl bromide (3.59 g, 20 mmol) over 30 min and the mixture was heated at reflux for 1 h. Usual work-up and distillation gave 2-methyl-6-octylpyridine (2.78 g, 68%). To a solution of 2-methyl-6-octylpyridine (0.48 g, 2.3 mmol) in dry EtOH (100 mL) was added Na (5.00 g, 217 mmol) in portionwise under reflux for 5 h. Usual work-up gave a mixture of **11** and **13** (0.412 g, 85%, 69:31 by GLC analysis), each of which was separated by column chromatography on alumina eluting with pentane–ether (9:1 to 0:10). **11**: MS *m/z* (%) 211 (M^+, 1), 98 (100); IR (neat): 1320 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.30—2.80 (m, 2H), 1.14—1.86 (m, 21H), 1.03 (d, 3H, J=6 Hz), 0.87 Hz (t, 3H, J=6 Hz); ^{13}C NMR ($CDCl_3$) δ=57.4 (d), 52.7 (d), 37.7 (t), 34.8 (t), 32.6 (t), 32.0 (t), 29.7 (t), 26.1 (t), 25.1 (t), 23.2 (q), 22.7 (t), 14.1 (q). **13**: MS *m/z* (%) 211 (M^+, 1), 98 (100); IR (neat): 1320 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.70—3.14 (m, 2H), 1.15—1.80 (m, 21H), 1.04 (d, 3H, J=6 Hz), 0.86 (t, 3H, J=6 Hz); ^{13}C NMR ($CDCl_3$) δ=51.1 (d), 46.1 (d), 34.4 (t), 33.3 (t), 32.0 (t), 31.1 (t), 29.9 (t), 29.7 (t), 29.4 (t), 26.6 (t), 22.7 (t), 21.3 (q), 19.8 (t), 14.1 (q).

1-Methoxycarbonyl-6-methyl-2-undecyl-1,2,3,4-tetrahydropyridine (14). A mixture of **4d** (0.303 g; 1.0 mmol) and 5% Pd–C (0.060 g) in dry MeOH (10 mL) was stirred under atmospheric pressure of H_2. The reaction was followed by GLC. After **4d** disappeared, the catalyst was removed by filtration through Celite and the solvent was evaporated. The residue was chromatographed on silica gel. Elution by hexane–CH_2Cl_2 (4:1) gave **14** (0.185 g, 60%): MS *m/z* (%) 309 (M^+, 31), 196 (100); IR (neat): 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ=4.87 (br s, 1H), 4.35 (br s, 1H), 3.69 (s, 3H), 2.02 (s, 3H), 1.07—2.07 (m, 24H), 0.87 (t, 3H, J=6 Hz); ^{13}C NMR ($CDCl_3$) δ=155.3 (s), 132.6 (s), 111.7 (d), 52.5 (q), 52.4 (d), 32.0 (t), 29.7 (6t), 29.4 (t), 26.4 (t), 25.8 (t), 22.7 (t), 22.7 (q), 19.5 (t), 14.1 (q). Found: C, 73.74; H, 11.40%. Calcd for $C_{19}H_{35}NO_2$: C, 74.06; H, 11.81%.

(±)-Solenopsin A, *trans*-2-Methyl-6-undecylpiperidine (15). To a mixture of **14** (0.155 g, 0.50 mmol) in dry $CHCl_3$ (2.0 mL) was added iodotrimethylsilane (0.10 mL, 0.60 mmol). The mixture was stirred at 50—60 °C for 1 h and, after addition of MeOH (0.06 mL), at room temp for 10 min. The solvent was evaporated and diluted with CH_2Cl_2. The solution was washed with 0.1 M aq NaOH and dried (Na_2SO_4). The solvent was evaporated and the residue was dissolved in THF (8.0 mL). This solution was added to a suspension of $LiAlH_4$ (0.133 g, 3.5 mmol) in THF (8.0 mL) at −78 °C. To this mixture was added trimethylaluminium in hexane (3.5 mL, 1.0 M, 3.5 mmol) and the mixture was stirred at −78 °C and warmed gradually to room temp over 2 h. Usual work-up and column chromatography on alumina eluting with ether gave **15** (0.113 g, 90%), which was shown to contain the cis-isomer (10%) by GLC analysis.[27] **15**: IR (neat): 1370 cm^{-1} (weak); ^1H NMR ($CDCl_3$) δ=2.70—3.13 (m, 2H), 1.13—1.87 (m, 27H), 1.05 (d, 3H, J=6 Hz), 0.87 (t, 3H, J=6 Hz); ^{13}C NMR ($CDCl_3$) δ=50.9 (d), 45.9 (d), 34.1 (t), 33.0 (t), 31.9 (t), 30.7 (t), 29.8 (t), 29.7 (t, 5C), 29.4 (t, 2C), 26.5 (t), 22.7 (t), 21.2 (q), 19.6 (t), 14.1 (q).

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23) It should be noted that reductions of 2,6-dialkylated pyridines give exclusively or predominantly *cis*-2,6-dialkylated piperidines.[19,20]

24) Another route which also starts from 2-methylpyridine provides (±)-solenopsin A in 28% overall yield in 7 steps.[21b]

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