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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

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Abstract: We report here the syntheses of *cis*- and *trans*-2,6-disubstituted piperidines using chiral 1-aza-4-oxabicyclo[4.3.0]nonane synthon **1**, which shows high reactivity toward nucleophilic attack at its C-5 position. Bicyclic compounds resembling synthon **1** were transformed to *cis*- and *trans*-2,6-disubstituted piperidine derivatives *via* reactions with various Grignard reagents in a stereospecific manner. Using this methodology, (+)-solenopsin A (**2b**) and both enantiomers of isosolenopsin A (**3a** and **3b**) were synthesized in an enantioselective manner from a single enantiomeric source. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: Bicyclic heterocyclic compounds; Grignard reactions/reagents; Piperidines; Solenopsin A.

1. INTRODUCTION

There has been significant interest in solenopsins (i.e., solenopsin A (**2a**), B and C along with the corresponding *cis* derivatives isosolenopsin A (**3a**), B and C), the major components of the non-proteinaceous venom of the fire ant *Solenopsis* (Myrmicinae), ever since their structures were determined by MacConnell and co-workers in 1970.[1] These fire ant alkaloids exhibit cytotoxic, hemolytic, necrotic, antibacterial, insecticidal and antifungal activities.[2] Their *cis-trans* isomerism, combined with their simple structures and bioactive potency, make them an ideal target for testing the stereoselectivity of numerous reactions. Although the absolute stereochemistry of natural solenopsins was not unambiguously resolved until Braekman and co-workers[3] confirmed the *R*-configuration of the methyl moiety in 1994, there are currently 30 different synthetic routes for solenopsins, 10 of which exist in optically active forms. The methods used to prepare the parent 2,6-disubstituted piperidine ring structure include catalytic or chemical reduction of the corresponding pyridine derivatives,[1] intramolecular cyclization of olefins or aminoketones,[4–7] alkylation of pyridinium salts or piperidinic derivatives,[8–11] Beckmann rearrangement of oxime sulfonates,[12] and cycloaddition.[13]

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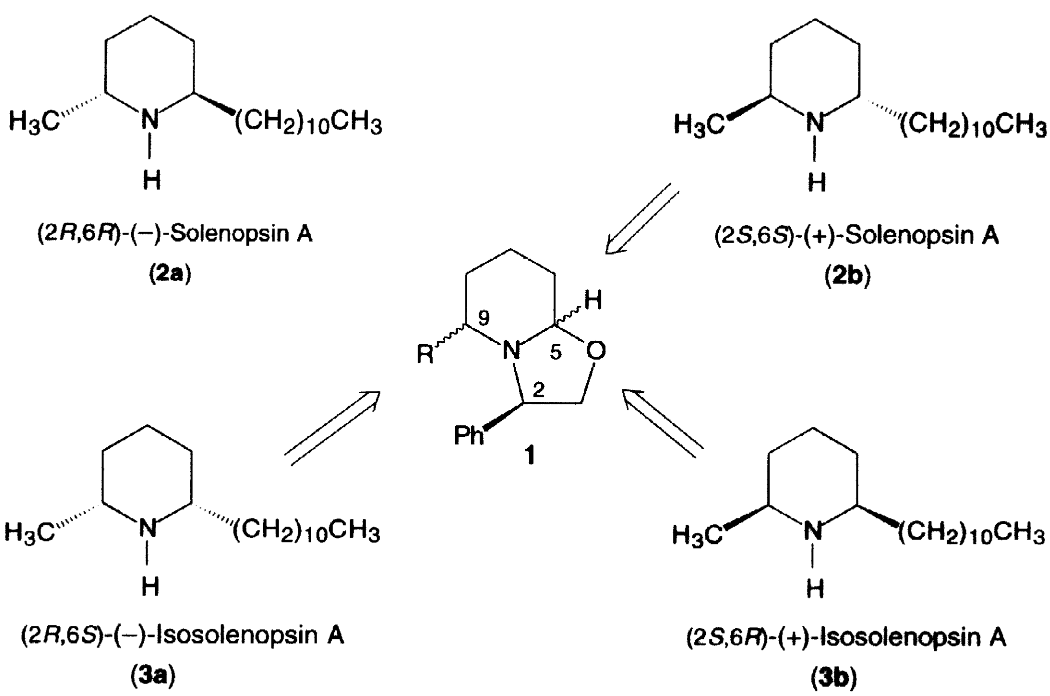
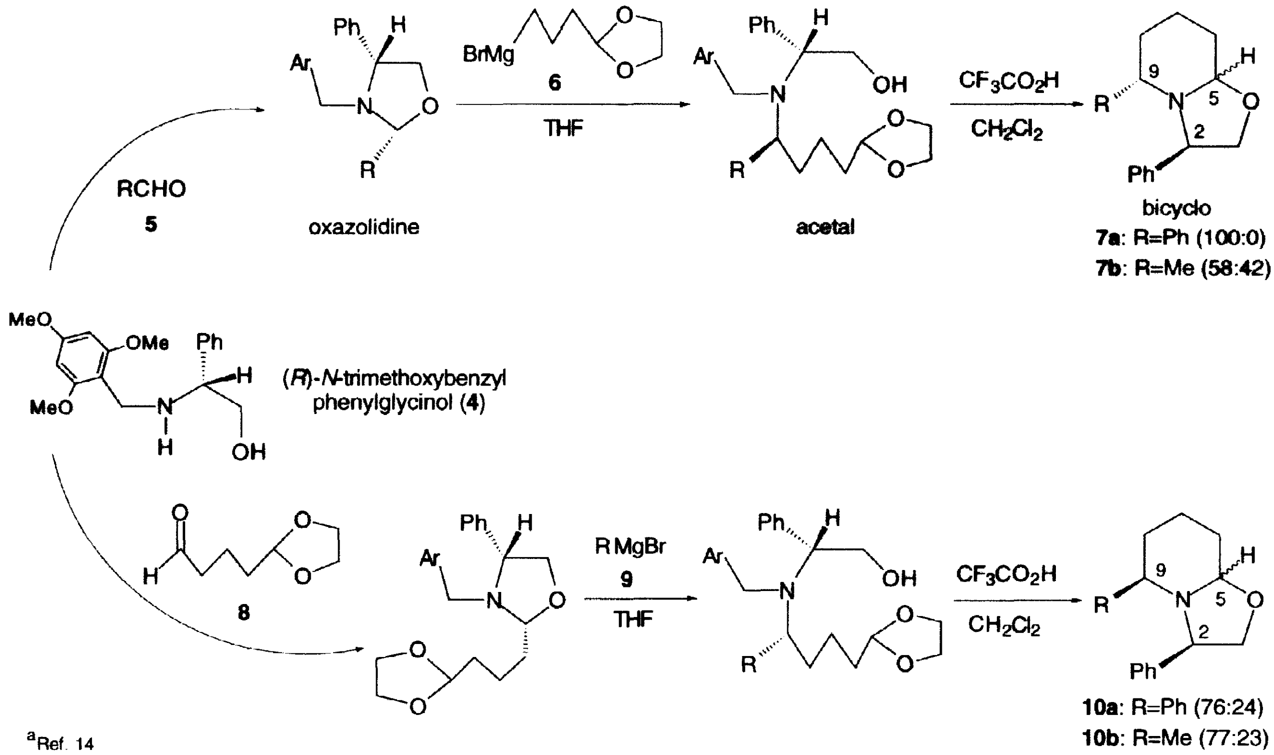


Chart 1

In a recent publication,[14] we described the syntheses of 2-substituted and 2,6-disubstituted piperidines using the chiral 1-aza-4-oxabicyclo[4.3.0]nonane synthon **1**, which shows high reactivity toward nucleophilic attack at its C-5 position. Stereocontrol over both of the α positions of the piperidine derivatives depends on both the stereochemistry and the steric nature of the C-2 and C-9 substituents of **1**. Although this procedure has been successfully applied to the syntheses of enantiopure 2-alkyl- and *cis*-2,6-dialkylpiperidine alkaloids, such as the α-pipecoline enantiomers,[14] (−)-sedamine,[15] and pinidine enantiomers,[16] the synthesis of the respective *trans* isomers gave poor results due to poor stereoselectivity. To investigate the role of *cis-trans* isomerism in the preparation of *cis*- and *trans*-2,6-dialkyl piperidines with a reasonable yield, we have extended our previous work to the reaction of bicyclic compounds resembling synthon **1** with various Grignard reagents in a stereospecific manner. Using this methodology, unnatural (+)-solenopsin A (**2b**) and both enantiomers of isosolenopsin A (natural **3a** and unnatural **3b**) were synthesized in an enantioselective manner.

2. RESULTS AND DISCUSSION

In a preliminary study,[14] both of the C-9 diastereomers of synthon **1** were prepared in three steps from the readily available, enantiomerically pure amino alcohol (*R*)-*N*-(2,4,6-trimethoxybenzyl)phenylglycinol (**4**), which acts as a chiral auxiliary as depicted in Scheme 1. As the C-9 substituents, we chose a methyl group to represent an aliphatic substituent and a phenyl group to represent an aromatic substituent. The stereochemistry at C-9 is established through the chiral 1,3-oxazolidine derivative intermediate,[17] which can provide the required stereoselectivity. By changing the functional groups of both the aldehydes (**5** and **8**) and Grignard reagents (**6** and **9**), the desired compounds **7a,b** and **10a,b** were obtained, with some of them as inseparable mixtures of C-5 epimers.



Scheme 1[a]

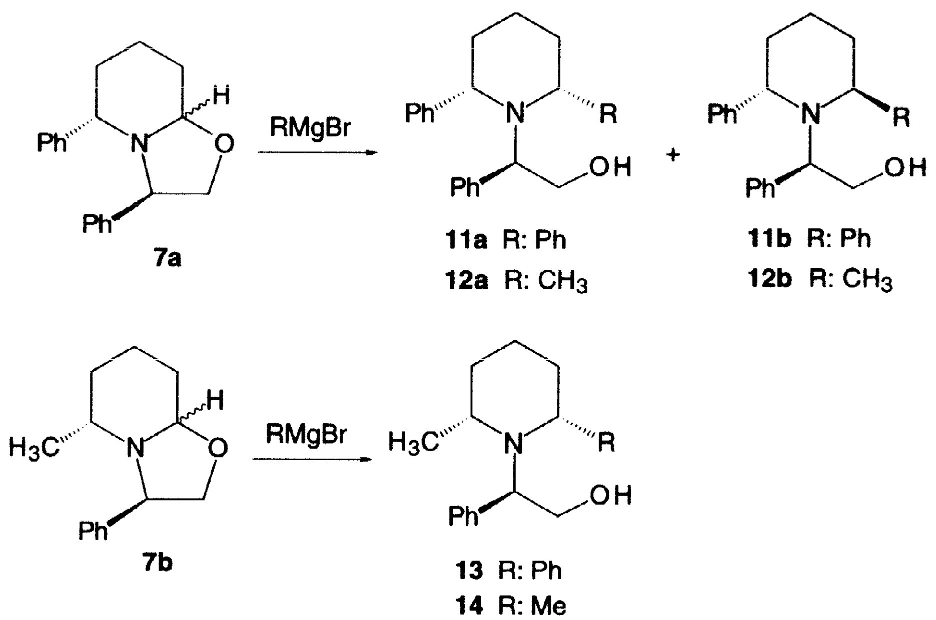
As part of our initial studies, the asymmetric reactions of bicyclic compounds **7** and **10** were carried out by adding three equivalents of Grignard reagents to a THF solution of the bicyclic compounds. Compounds **7a** and **10a** gave the *cis* and *trans* isomers of piperidine derivatives, respectively, upon reaction with phenylmagnesium bromide. However, both **7b** and **10b** predominantly gave the *cis* isomer of piperidine derivatives in the reaction with methylmagnesium bromide.[14] The preceding experiment and the current effort to achieve high stereoselectivity of the *trans* isomer, by reacting bicyclic **10b** with various Grignard reagents, as well as the stereoelectronic mechanism are decribed below.

2.1. Asymmetric reaction of synthon **7a,7b** *with Grignard reagents*

First, the asymmetric reaction of **7a** with phenylmagnesium bromide was performed to predominantly give the *cis* isomer **11a**, a piperidine derivative with a phenyl moiety at both of its α-carbons, in excellent yield, as depicted in Table 1. Similarly, the bicyclic synthon **7b** with a methyl group at C-9 was treated with methylmagnesium bromide to completely give the *cis*-α,α'-dimethylpiperidine derivative (**14**) in moderate yield.[14] We then reacted bicyclic compound **7a** with methylmagnesium bromide to give almost exclusively the *cis* isomer **12a**, and reacted **7b** with phenylmagnesium bromide to give only the *cis* isomer **13**, both in excellent yield.

This outcome reveals the mechanism involved in controlling the stereoselective attack of the methyl or phenyl function of the Grignard reagents toward the C-5 position of the starting bicyclic 7**a** or **7b**. As shown in Table 1, the C-5 diasteromerically pure bicyclic **7a** give a mixture of the *cis-trans* isomers of the piperidine derivatives **11a+11b** (82:18) and **12a+12b** (97:3). On the other hand, the C-5 diastereomeric mixture of **7b** give only the *cis* isomer of the piperidine derivatives **13** and **14**. The diastereoselectivity of this reaction can be explained by assuming that the Grignard reagent approaches the oxygen atom of the 1,3-oxazolidine ring of the bicyclic compound to give a favorable intermediate iminium salt, as suggested in the reaction of 1,3-oxazolidine itself with a Grignard reagent.[16,17]

Table 1. Stereoselective Reactions of **7a/7b** with Grignard Reagents[a]



Substrate	Grignard reagent[b]	Yield[c], %	Product	ratio[d] cis : trans
7a	PhMgBr	100	**11a+11b**	82 : 18
7a	CH_3MgBr	94	**12a+12b**	97 : 3
7b	PhMgBr	96	**13**	100 : 0
7b	CH_3MgBr	82	**14**	100 : 0

[a]Reactions were generally performed in THF at rt for 40 h. [b]Three equiv. of Grignard reagents were used. [c]Yield of total product obtained after column chromatography. [d]Ratio determined by ^{1}H-NMR.

The stereochemical course of the Grignard addition to the 1,3-oxazolidine, which is widely known as a masked imine derivative, has been well clarified.[18] Similarly, the stereoselectivity of the Grignard addition to a piperidinium ion intermediate leading to α, α'-disubstituted piperidine presumably originates from a stereoselective effect. By way of explanation, we can examine the case of the Grignard addition to bicyclic **7a**, as shown in Figure 1. Due to strong $A^{(1,2)}$ strain[19] between the α-phenyl group and the *N*-phenylethyl group of iminium ion **I-A**, the α-phenyl group occupies the axial position through half-chair conformation **I-B**. The Grignard reagent stereoelectronically prefers the axial attack[5,20,21] on **I-B** to give the *cis*-2,6-diphenylpiperidine derivative **11a** as the major product. The emergence of *trans* isomer **11b** (minor product) is due to steric hindrance between the bulky α-phenyl group of **I-B** and the attacking Grignard reagent, which raises the possibility of Grignard attack from the opposite direction (equatorial attack) to a limited extent. This is consistent with the results of the Grignard addition to bicyclic **7b**, the small α-methyl moiety of which provides less steric hindrance for the stereoelectronically preferred axial attack, and thus gives the *cis* isomer as the sole product (**13** and **14**).

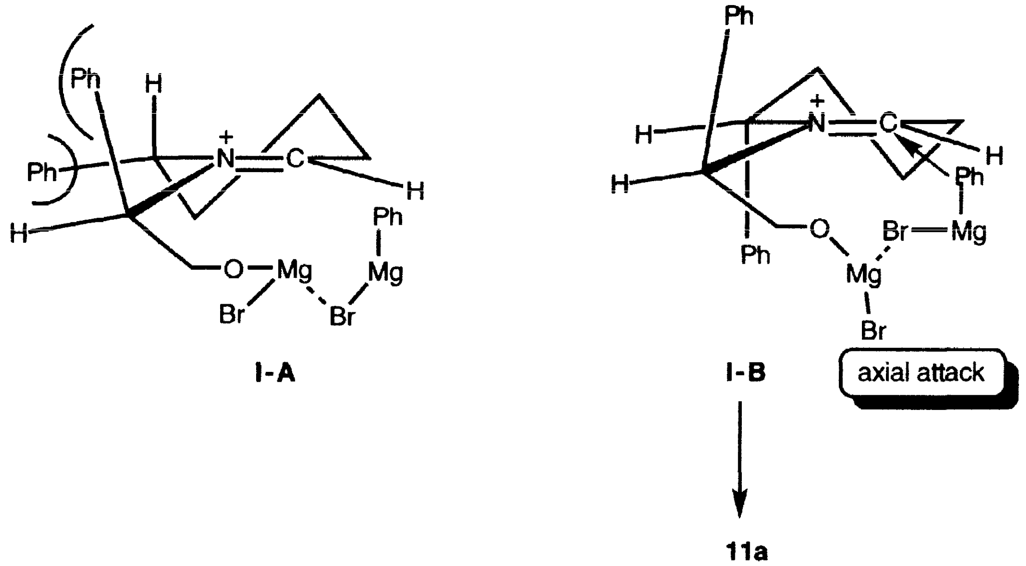


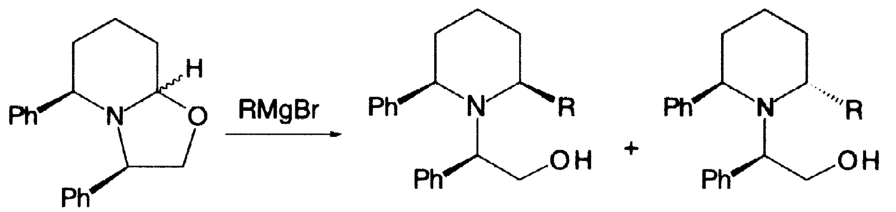
Figure 1

2.2. Asymmetric reaction of synthon **10a**,**10b** *with Grignard reagents*

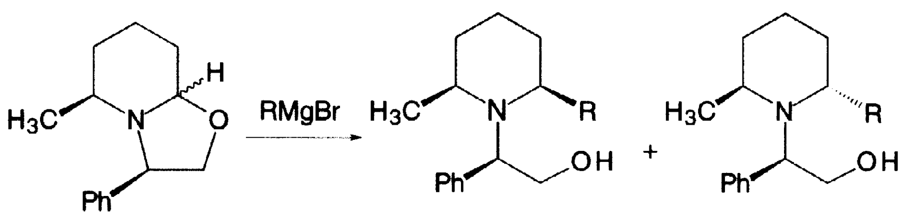
Based on the finding that the 1-aza-4-oxabicyclo[4.3.0]nonane synthon bearing an (*S*)-phenyl or (*R*)-methyl moiety at C-9 mainly gave the *cis*-α,α'-dialkylpiperidine derivatives in the nucleophilic Grignard addition, we applied a similar reaction to bicyclic compounds bearing C-9 moieties with opposite configurations; i.e., (*R*)-phenyl and (*S*)-methyl (**10a** and **10b**, respectively), as depicted in Table 2. The diastereofacial addition of phenylmagnesium bromide to bicyclic **10a** gave the *trans* isomer of the α,α'-diphenylpiperidine derivative **15** in good yield. Analogously, the addition of methylmagnesium bromide to bicyclic **10b** gave a mixture of the *cis* isomer **17a** and the *trans* isomer **17b** in a ratio of 62:38, respectively, in very good yield.[14] This previous result prompted us to confirm the relation between the nature of the functionality at C-9 and *cis-trans* isomerism by reacting **10a** with methylmagnesium bromide to almost exclusively give the *trans* isomer **16** in moderate yield, and the reaction of **10b** with phenylmagnesium bromide gave the *trans* isomer **16** as the major product in excellent yield.

The *cis-trans* isomeric outcome of these nucleophilic additions varies depending upon the nature of the functionality at the stereogenic center C-9. This phenomenon can be explained as shown in Figure 2. As in the mechanism described in Figure 1, the piperidinium intermediate **II** for Grignard addition to **10a** takes a half-chair conformation with an α-phenyl group at the axial position. The Grignard reagent can then attack the piperidinium intermediate from either direction. The bulkiness of the α-phenyl substituent[22] hinders the axial attack of the Grignard reagent (**II-A**), and prefers the less sterically hindered equatorial attack (**II-B**) to give only the *trans* isomer **15**. The steric hindrance that leads to the equatorial attack is also produced by the phenyl function of the Grignard reagent, as shown in the reaction of **10b** with phenylmagnesium bromide to predominantly give the *trans* isomer **16**. On the other hand, such hindrance is minimized for the stereoelectronically preferred axial attack of **10b** by methylmagnesium bromide to give the *cis* isomer **17a** as the major product.

Table 2. Stereoselective Reactions of **10a/10b** with Grignard Reagents[a]



10a **13** R: CH_3 **15** R: Ph; **16** R: CH_3



10b

12a R: Ph
17a R: CH_3
18a R: CH_3CH_2
19a R: $H_2C{=}CH$
20a R: HC≡C

16 R: Ph
17b R: CH_3
18b R: CH_3CH_2
19b R: $H_2C{=}CH$
20b R: HC≡C

Substrate	Grignard reagent	Yield, %	Product	ratio cis : trans
10a	PhMgBr	91	**15**	0 : 100
10a	CH_3MgBr	86	**13+16**	7 : 93
10b	PhMgBr	96	**12a+16**	13 : 87
10b	CH_3MgBr	97	**17a+17b**	62 : 38
10b	CH_3CH_2MgBr	93	**18a+18b**	53 : 47
10b	$H_2C{=}CHMgBr$	94	**19a+19b**	24 : 76
10b	HC≡CMgBr	87	**20a+20b**	3 : 97

[a]All conditions were generally similar to those mentioned in Table 1.

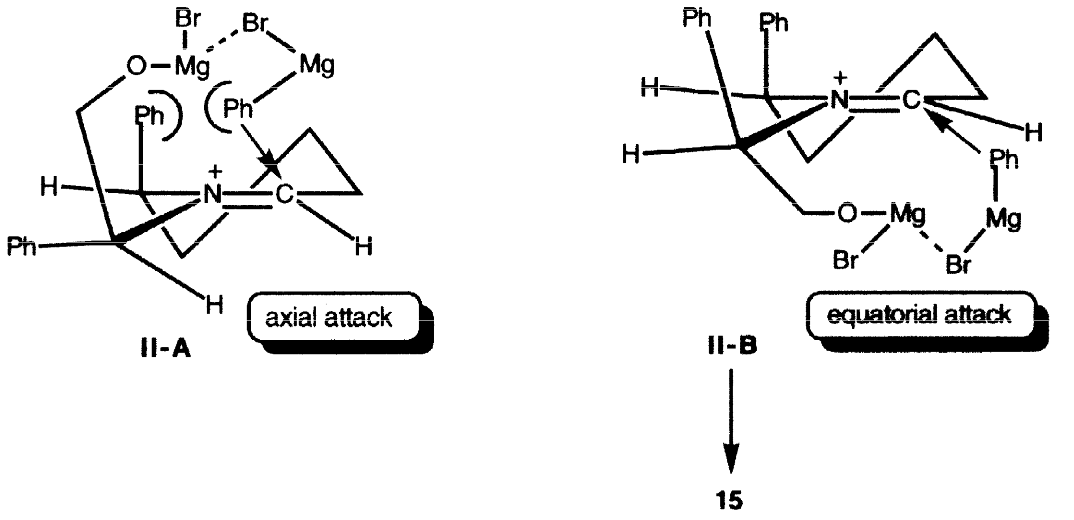


Figure 2

While the stereochemical outcome of the Grignard addition to **10a** was unequivocally clarified as described above, **10b** gave us a great opportunity to explore its reaction with various Grignard reagents. For the next experiment, we considered that despite the effect of the bulkiness of phenylmagnesium bromide, the C=C bond of the phenyl function of the Grignard reagent plays a predominant role in *cis-trans* isomerism. First, ethylmagnesium bromide was added to **10b** to produce equal proportions of the *cis* isomer **18a** and the *trans* isomer **18b** in good yield. We then used the same procedure with vinylmagnesium bromide to give a 24:76 ratio of the *cis* isomer **19a** and the *trans* isomer **19b** in good yield. Under the same conditions, ethynylmagnesium bromide was used to give the *trans* isomer **20b** almost exclusively and in moderate yield.

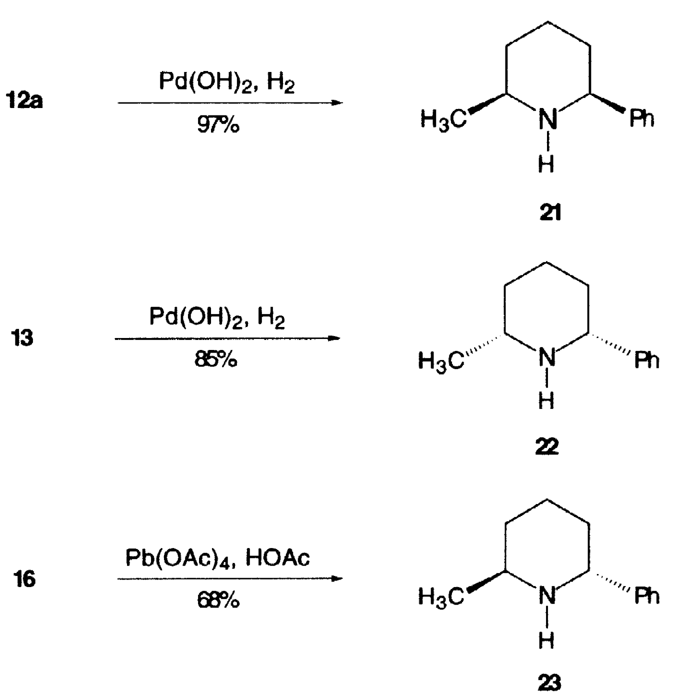


Chart 2

Surprisingly, however, there is a linear correlation between the number of bonds within the 2-membered alkyl function of the Grignard reagent and the *trans* isomer. Accordingly, the choice of Grignard reagent was found to be crucial for obtaining the *trans* isomer in good yield in these reactions. We do not yet know why Grignard reagents with double and triple bonds enhance the proportion of the *trans* isomer. The alkenyl and alkynyl character of Grignard reagents based on the HSAB principle, as suggested by Yamaguchi and co-workers,[8] has been taken into consideration.

2.3. Determination of the stereochemistry of the resulting piperidine derivatives

We successfully prepared *cis*- and *trans*-2,6-dialkylpiperidine in a simple and concise manner from a single enantiomeric source. The piperidine derivatives obtained in this work were determined as follows. The absolute stereochemistries of **12a**, **13** and **16**, all of which are 2-methyl-6-phenylpiperidine derivatives that could be derived from two different bicyclic sources, were determined by cross-checking their NMR spectra. In addition, **12a** and **13** were subjected to hydrogenolysis using a palladium hydroxide catalyst to give the enantiomeric pair **21**, $[\alpha]^{24}_{D}$ −35.6 (*c* 1.38, $CHCl_3$), and **22**, $[\alpha]^{24}_{D}$ +35.2 (*c* 1.26, $CHCl_3$), in moderate to good yield. Compound **16** was subjected to oxidative cleavage using lead tetraacetate in acetic acid to give the enantiomer **23**, $[\alpha]^{24}_{D}$ +33.4 (*c* 1.25, $CHCl_3$), in moderate yield (Chart 2).

The stereochemistries of the *cis-trans* isomers **19a** and **19b**, which have a vinyl side chain, were established by NOE experiments, the more important details of which are summarized in Figure 3. With the stereochemistries of **19a** and **19b** in hand, we carried out the hydrogenation of **19b** using a platinum oxide catalyst to provide a single enantiomer whose NMR spectra are consistent with those of the *trans* isomers **18b**. Next, the hydrogenation of the *trans* isomers **20b** using the Lindlar catalyst gave **19b**.

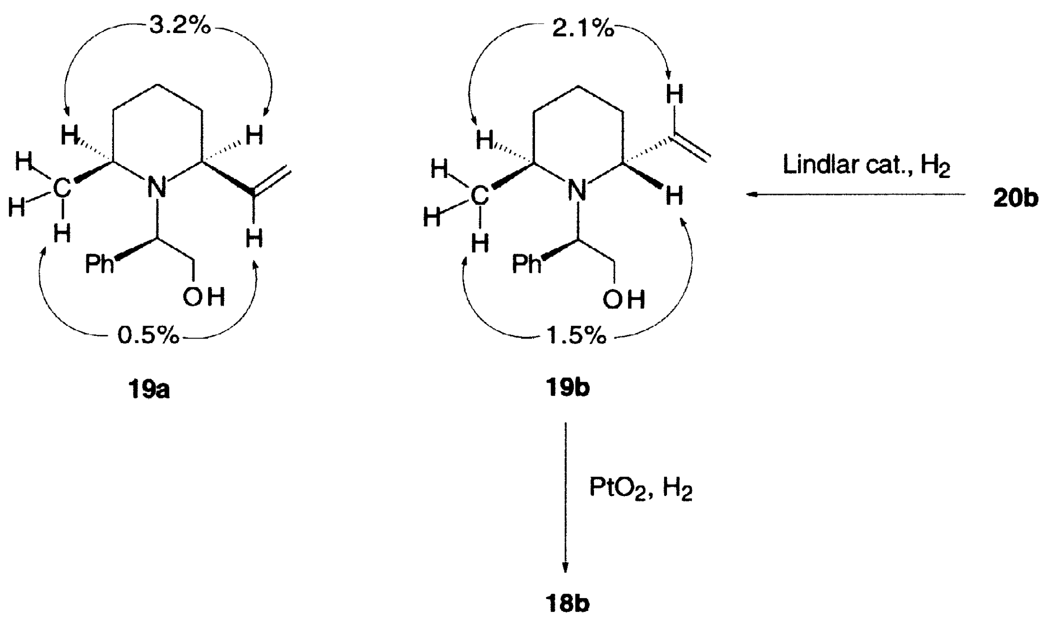
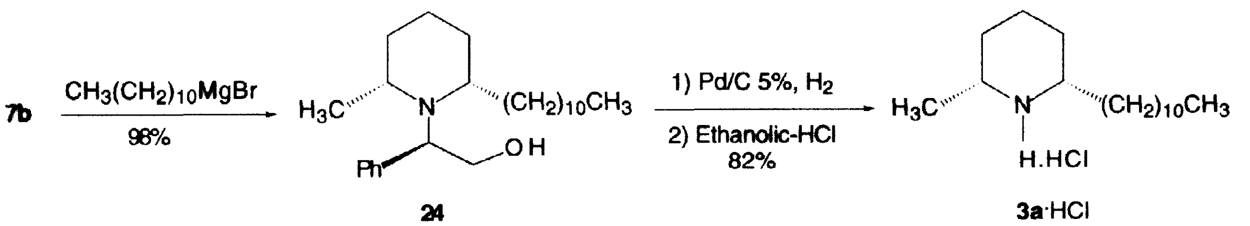


Figure 3

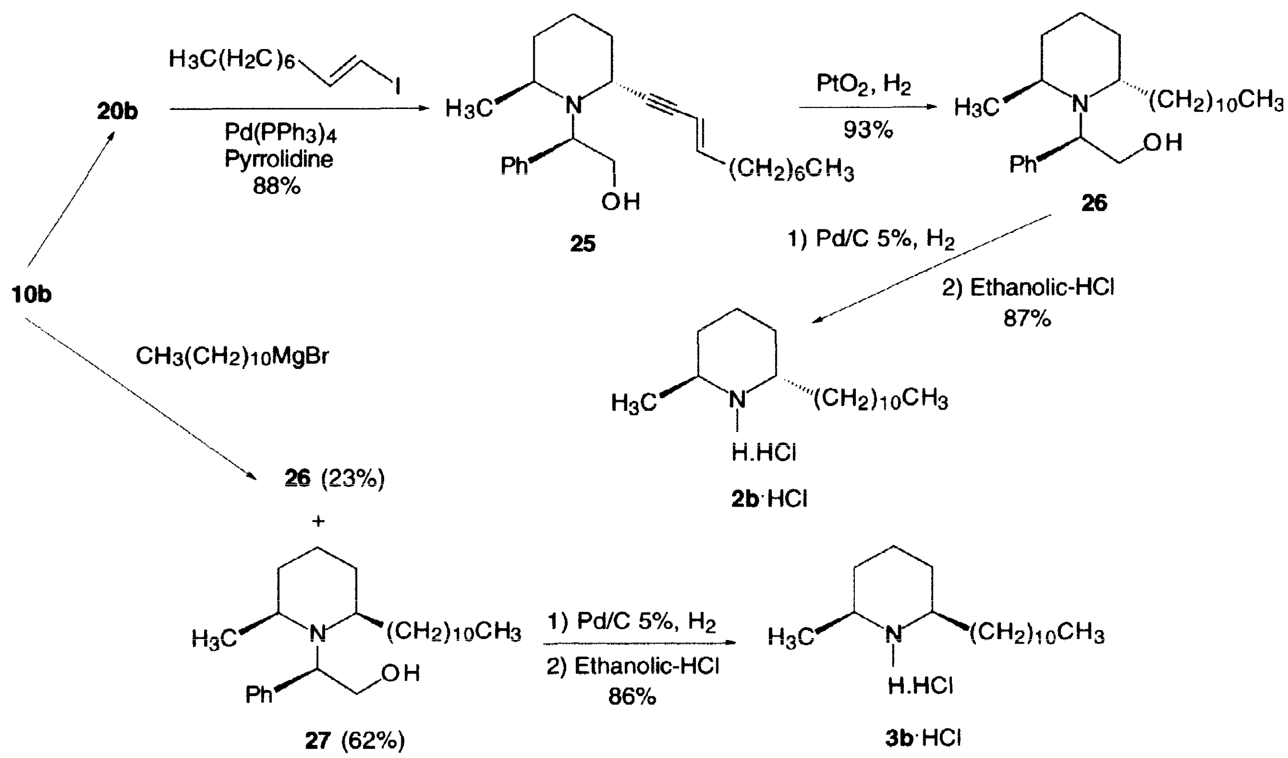
2.4. Enantioselective synthesis of (+)-solenopsin A (**2b**) *and both enantiomers of isosolenopsin A* (**3a** *and* **3b**)

We applied our findinds to the synthesis of (−)-isosolenopsin A (**3a**), beginning with Grignard addition to bicyclic **7b** to give the diasteromerically pure piperidine **24** in 98% yield (Scheme 2). After reductive cleavage of the chiral auxiliary over 5% palladium on carbon under a hydrogen atmosphere, followed by ethanolic-hydrochloric acidification, (−)-isosolenopsin A hydrochloride (**3a**·HCl) was obtained as colorless crystals, mp 152–153 ℃ (CH_2Cl_2–ether) (lit.[1] mp 154–155 ℃); $[\alpha]^{24}_D$ +10.0 (*c* 1.1, $CHCl_3$) (lit.[3] (+)-isosolenopsin A hydrochloride: $[\alpha]^{20}_D$ −10.3 (*c* 1.3, $CHCl_3$)) in 82% yield.



Scheme 2

The same route was successfully used to prepare (+)-isosolenopsin A (**3b**) through the reaction of bicyclic **10b** with the correct Grignard reagent to give a diastereomeric mixture, from which the desired *cis* isomer **27** was easily separated in 62% yield. A similar elimination of the *N*-functionality, and acidification of the resulting secondary amine gave (+)-isosolenopsin A hydrochloride (**3b**·HCl) as colorless crystals, mp 152–153 ℃ (CH_2Cl_2–ether) (lit.[1] mp 154–155 ℃); $[\alpha]^{24}_D$ −10.1 (*c* 1.0, $CHCl_3$) (lit.[3] $[\alpha]^{20}_D$ −10.3 (*c* 1.3, $CHCl_3$)) in 86% yield.



Scheme 3

The synthesis of (+)-solenopsin A (**2b**) was achieved starting from **20b**, which was derived as above from **10b**. The 11-membered aliphatic side chain was built up by introducing readily available (*E*)-1-iodo-1-nonene[23] to **20b**, using tetrakis(triphenylphosphine)palladium catalysis,[24] to give the unsaturated piperidine **25** in 88% yield. The subsequent stage is critical because migration of the double bond during the palladium on carbon catalytic hydrogenation causes a loss of configuration. Based on the Wasserman procedure,[5] the unsaturated side chain was first hydrogenated with platinum oxide to give the saturated piperidine **26** in 93% yield, and this was followed by hydrogenolytic cleavage of the chiral appendage and salt formation to yield the (+)-solenopsin A hydrochloride (**2b**·HCl) as colorless crystals, mp 151–152 ℃ (CH_2Cl_2–ether) (lit.[10] mp 146 ℃); $[\alpha]^{24}_D$ +8.0 (*c* 1.3, $CHCl_3$) (lit.[10] $[\alpha]^{20}_D$ +7.5 (*c* 1.3, $CHCl_3$)) in 87% yield.

3. CONCLUSION

We have developed a simple procedure for the enantioselective preparation of *cis*- and *trans*-2,6-dialkylpiperidine derivatives *via* Grignard addition to 1-aza-4-oxabicyclo[4.3.0]nonane derivatives. Although the mechanism that exclusively provides the *trans* isomer is still unclear, this procedure was successfully applied to the synthesis of (+)-solenopsin A (**2b**) in 29% overall yield in seven steps from the chiral auxiliary **4**. We also achieved the enantioselective synthesis of (–)-isosolenopsin A (**3a**) in 49% overall yield in five steps, and of (+)-isosolenopsin A (**3b**) in 25% overall yield in five steps, from a single enantiomeric source (**4**). We are confident that this methodology may be applicable to the enantioselective synthesis of numerous 2,6-disubstituted piperidine alkaloids.

4. EXPERIMENTAL SECTION

General procedures

Melting points were measured without correction. The ^1H NMR and ^{13}C NMR spectra were run in $CDCl_3$ unless otherwise noted. All chemical shifts are reported as δ values (ppm) relative to TMS and residual $CDCl_3$ as internal standards on 270 Mhz and 500 Mhz spectrometer. IR spectra were recorded on a JASCO FT/IR-200, and major absorptions are listed in cm^{-1}. Mass spectra and High-resolution mass spectra were recorded on a JEOL JMS 600 spectrometer in the chemical ionization (CI) with isobutane and electron impact (EI) methods. Optical rotations were performed on a JASCO DIP-1000; concentrations reported are in g/100 mL. Column chromatography was performed on silica gel (45~75 mm, Wakogel C-300). The THF was distilled over potassium metal. All other solvents and reactants were of the best commercial grade available and used without further purification unless noted.

Reaction of the bicyclic compounds with Grignard reagents

To a stirred solution of bicyclic compound (**7a**, **7b**, **10a**, **10b**)[14] in THF (10 mL) was added dropwise a solution of Grignard reagent (3 equiv). After being stirred at 10–20℃ for 2 d, the reaction mixture was quenched with water and the organic solution was decanted from the insoluble solid. The residue was extracted with ether (2 x 10 mL), then the organic extracts were combined, dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator to give a crude product or a diastereomeric mixture of 2,6-disubstituted piperidine derivative (**12a**, **13**, **16**, **18a**, **18b**, **19a**, **19b**, **20b**, **24**, **27**). The crude product or diastereomeric mixture was subjected to column chromatography on silica gel using appropriate solvent as eluent to give the requisite compound in purity.

(2S,6S,1'R)-N-(2-Hydroxy-1-phenylethyl)-2-methyl-6-phenylpiperidine (**12a**)

A 3 mol/L solution of methylmagnesium bromide in THF was added to **7a** to give a diastereomeric mixture (97:3) of **12a+12b** in 94% yield. Separation by column chromatography on silica gel with CH_2Cl_2–MeOH (50:1) gave **12a** and **12b**. Major product: **12a**, colorless crystals (from hexane), mp 77–78 °C. $[\alpha]^{24}_D$ −162.8 (*c* 1.13, $CHCl_3$). ^1H NMR δ 1.26–1.48 (m, 3 H), 1.27 (d, 3 H, *J* = 6.4 Hz), 1.60–1.76 (m, 3 H), 2.83 (m, 1 H), 3.46 (br s, 1 H), 3.52 (dd, 1 H, *J* = 2.5, 6.3 Hz), 3.86 (t, 1 H, *J* = 7.2 Hz), 3.93–4.04 (m, 2 H), 7.24–7.47 (m, 10 H). ^{13}C NMR δ 21.18, 23.83, 32.40, 35.20, 50.48, 61.76, 62.03, 64.82, 127.17, 127.39, 127.82, 128.13, 128.64, 128.77, 136.99, 145.16. EIMS *m/z* (relative intensity): 295 $[M]^+$ (3), 264 $[M - CH_2OH]^+$ (100). IR ($CHCl_3$): 3440 (OH) cm^{-1}. Anal. Calcd for $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.43; H, 8.66; N, 4.78.

(2R,6R,1'R)-N-(2-Hydroxy-1-phenylethyl)-2-methyl-6-phenylpiperidine (**13**)

A 1 mol/L solution of phenylmagnesium bromide in THF was added to **7b** to give a single diastereomer of **13** in 96% yield. Purification by column chromatography on silica gel with CH_2Cl_2–MeOH (50:1) gave the pure **13** as an almost colorless oil. $[\alpha]^{24}_D$ +49.7 (*c* 1.15, $CHCl_3$). ^1H NMR δ 1.22–1.78 (m, 6 H), 1.23 (d, 3 H, *J* = 5.9 Hz), 2.69 (br s, 1 H), 3.07 (m, 1 H), 3.38 (t, 1 H, *J* = 9.4 Hz), 3.50–3.58 (m, 2 H), 4.28 (dd, 1 H, *J* = 6.3, 9.4 Hz), 7.12–7.38 (m, 10 H). ^{13}C NMR δ 23.11, 23.72, 35.38, 36.86, 55.06, 60.64, 62.14, 62.77, 126.93, 127.01, 127.63, 127.74, 127.96, 128.57, 139.30, 145.69. EIMS *m/z* (relative intensity): 295 $[M]^+$ (3), 264 $[M - CH_2OH]^+$ (100). IR ($CHCl_3$): 3400 (OH) cm^{-1}. Anal. Calcd for $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.15; H, 8.52; N, 4.75.

(2S,6R,1'R)-N-(2-Hydroxy-1-phenylethyl)-2-methyl-6-phenylpiperidine (**16**)

A 3 mol/L solution of methylmagnesium bromide in THF was added to **10a** to give a diastereomeric mixture (7:93) of **13+16** in 86% yield. Separation by column chromatography on silica gel with CH_2Cl_2–MeOH (50:1) gave **13** and **16**. Major product: **16**, colorless oil. $[\alpha]^{24}_D$ −92.2 (*c* 1.31, $CHCl_3$). ^1H NMR δ 1.18–1.31 (m, 2 H), 1.29 (d, 3 H, *J* = 6.9 Hz), 1.49–1.75 (m, 4 H), 2.38 (br s, 1 H), 3.34 (m, 1 H), 3.54 (m, 1 H), 3.83–3.93 (m, 2 H), 4.29 (br d, 1 H, *J* = 8.9 Hz), 7.23–7.44 (m, 10 H). ^{13}C NMR δ 18.48, 20.11, 29.96, 30.28, 47.79, 57.38, 60.68, 60.78, 126.94, 127.21, 128.19, 128.24, 128.48, 128.68, 140.77, 143.17. EIMS *m/z* (relative intensity): 295 $[M]^+$ (3), 264 $[M - CH_2OH]^+$ (100). IR ($CHCl_3$): 3390 (OH) cm^{-1}. Anal. Calcd for $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.17; H, 8.53; N, 4.58.

(2R,6S,1'R)- and (2S,6S,1'R)-N-(2-Hydroxy-1-phenylethyl)-2-ethyl-6-methylpiperidine (**18a** and **18b**)

A 1 mol/L solution of ethylmagnesium bromide in THF was added to **10b** to give a diastereomeric mixture (53:47) of **18a+18b** in 93% yield. Separation by column chromatography on silica gel with CH_2Cl_2–MeOH (50:1) gave **18a** and **18b**. Major product: **18a**, colorless oil. $[\alpha]^{24}_D$ −18.8 (*c* 1.09, $CHCl_3$). ^1H NMR δ 0.73 (t, 3 H, *J* = 7.4 Hz), 1.13 (d, 3 H, *J* = 6.9 Hz), 1.22–1.72 (m, 8 H), 2.68 (m, 1 H), 2.94 (br s, 1 H), 3.16 (m, 1 H), 3.72 (dd, 1 H, *J* = 5.6, 10.4 Hz), 3.86 (dd, 1 H, *J* = 7.6, 10.4 Hz), 4.01 (dd, 1 H, *J* = 5.6, 7.6 Hz), 7.24–7.34 (m, 5 H). ^{13}C NMR δ 11.90, 15.80, 20.66, 26.10, 27.54, 30.43, 47.65, 58.27, 61.83, 65.93, 127.47, 128.29, 128.38, 140.20. EIMS *m/z* (relative intensity): 247 $[M]^+$ (3), 216 $[M - CH_2OH]^+$ (44). IR ($CHCl_3$): 3420 (OH) cm^{-1}. Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.71; H, 10.30; N, 5.68. Minor product: **18b**, colorless oil. $[\alpha]^{24}_D$ −19.9 (*c* 1.27, $CHCl_3$). ^{1}H NMR δ 0.77–1.12 (m, 4 H), 0.95 (t, 3 H, *J* = 7.4 Hz), 1.27 (d, 3 H, *J* = 6.9 Hz), 1.31–1.77 (m, 4 H), 2.99 (m, 1 H), 3.33 (m, 1 H), 3.46 (dd, 1 H, *J* = 5.6, 10.4 Hz), 3.86 (t, 1 H, *J* = 10.4 Hz), 4.20 (dd, 1 H, *J* = 5.6, 10.4 Hz), 7.24–7.39 (m, 5 H). ^{13}C NMR δ 11.83, 20.20, 20.60, 25.48, 25.93, 29.90, 48.52, 54.10, 58.96, 60.33, 127.47, 128.29, 129.17, 141.20. EIMS *m/z* (relative intensity): 247 $[M]^+$ (9), 216 $[M - CH_2OH]^+$ (100). IR ($CHCl_3$): 3430 (OH) cm^{-1}. Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.66; H, 10.26; N, 5.50.

(2S,6S,1'R)- and (2R,6S,1'R)-N-(2-Hydroxy-1-phenylethyl)-2-ethenyl-6-methylpiperidine (**19a** and **19b**)

A 1 mol/L solution of vinylmagnesium bromide in THF was added to **10b** to give a diastereomeric mixture (24:76) of **19a+19b** in 94% yield. Separation by column chromatography on silica gel with CH_2Cl_2–EtOAc (5:1) gave **19a** and **19b**. Major product: **19b**, colorless oil. $[\alpha]^{24}_D$ −20.2 (*c* 1.30, $CHCl_3$). ^{1}H NMR δ 1.08–1.34 (m, 4 H), 1.21 (d, 3 H, *J* = 6.8 Hz), 1.42–1.51 (m, 2 H), 2.85 (br s, 1 H), 3.30 (m, 1 H), 3.66 (dd, 1 H, *J* = 6.1, 10.6 Hz), 3.70 (m, 1 H), 3.89 (dd, 1 H, *J* = 9.1, 10.6 Hz), 4.24 (dd, 1 H, *J* = 6.1, 9.1 Hz), 5.13–5.20 (m, 2 H), 6.07 (ddd, 1 H, *J* = 5.9, 9.4, 11.2 Hz), 7.23–7.38 (m, 5 H). ^{13}C NMR δ 19.62, 19.74, 28.57, 30.84, 48.46, 55.45, 60.42, 61.34, 115.21, 127.32, 128.25, 128.91, 140.79, 141.01. EIMS *m/z* (relative intensity): 245 $[M]^+$ (4), 214 $[M - CH_2OH]^+$ (100). IR ($CHCl_3$): 3400 (OH) cm^{-1}. Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.07; H, 9.53; N, 5.49. Minor product: **19a**, colorless oil. $[\alpha]^{24}_D$ −71.9 (*c* 1.05, $CHCl_3$). ^{1}H NMR δ 1.06 (d, 3 H, *J* = 6.3 Hz), 1.20–1.69 (m, 6 H), 2.61 (m, 1 H), 3.20 (br s, 1 H), 3.44 (dt, 1 H, *J* = 2.6, 8.9 Hz), 3.75 (dd, 1 H, *J* = 6.3, 10.1 Hz), 3.92 (t, 1 H, *J* = 10.1 Hz), 4.44 (dd, 1 H, *J* = 6.3, 10.1 Hz), 5.10–5.22 (m, 2 H), 5.87 (ddd, 1 H, *J* = 8.9, 10.1, 17.3 Hz), 7.24–7.38 (m, 5 H). ^{13}C NMR δ 21.45, 21.94, 29.65, 33.77, 34.57, 51.33, 61.89, 64.75, 115.67, 127.17, 128.09, 128.14, 138.49, 142.65. EIMS *m/z* (relative intensity): 245 $[M]^+$ (3), 214 $[M - CH_2OH]^+$ (100). IR ($CHCl_3$): 3420 (OH) cm^{-1}. Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 77.98; H, 9.63; N, 5.52.

(2R,6S,1'R)-N-(2-Hydroxy-1-phenylethyl)-2-ethynyl-6-methylpiperidine (**20b**)

A 0.5 mol/L solution of ethynylmagnesium bromide in THF was added to **10b** to give a diastereomeric mixture (3:97) of **20a+20b** in 87% yield. Separation by column chromatography on silica gel with hexane–EtOAc (5:1) gave **20a** and **20b**. Major product: **20b**, pale yellow oil. $[\alpha]^{24}_D$ +122.5 (*c* 1.22, $CHCl_3$). ^{1}H NMR δ 1.21 (d, 3 H, *J* = 6.3 Hz), 1.48–1.85 (m, 6 H), 2.39 (d, 1 H, *J* = 2.0 Hz), 3.35 (m, 1 H), 3.70 (m, 1 H), 4.26–4.67 (m, 3 H), 7.22–7.45 (m, 5 H). ^{13}C NMR δ 20.72, 21.30, 31.77, 36.09, 45.57, 50.48, 61.06, 61.38, 73.24, 85.61, 126.86, 128.13, 128.22, 140.95. EIMS *m/z* (relative intensity): 243 $[M]^+$ (4), 212 $[M - CH_2OH]^+$ (100). IR ($CHCl_3$): 3400 (OH), 3300 (C≡CH) cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.79; H, 8.56; N, 5.69.

(2R,6S,1'R)-N-(2-Hydroxy-1-phenylethyl)-2-methyl-6-undecylpiperidine (**24**)

A solution of undecylmagnesium bromide in THF, prepared *in situ* from Mg turnings and 1-bromoundecane, was added to **7b** to give a single diastereomer of **24**. Purification by column chromatography on silica gel with CH_2Cl_2–EtOAc (1:1) gave **24** as a colorless oil in 98% yield. $[\alpha]^{24}_D$ +10.2 (*c* 1.1, $CHCl_3$). ^{1}H NMR δ 0.88 (t, 3 H, *J* = 7.3 Hz), 1.06 (d, 3 H, *J* = 6.1 Hz), 1.13–1.62 (m, 10 H), 1.26 (br s, 16 H), 2.83 (m, 1 H), 2.95 (br s, 1 H), 3.01 (m, 1 H), 3.70 (dd, 1 H, J = 5.5, 10.4 Hz), 3.79 (dd, 1 H, J = 7.3, 10.4 Hz), 4.00 (dd, 1 H, J = 5.5, 7.3 Hz), 7.26–7.33 (m, 5 H). ^{13}C NMR δ 14.09, 15.66, 20.10, 22.66, 26.20, 28.13, 29.33, 29.62 (4 C), 29.86, 31.14, 31.89, 34.27, 50.59, 53.07, 61.76, 65.14, 127.47, 128.28, 128.43, 139.90. EIMS *m/z* (relative intensity): 373 $[M]^+$ (7), 342 $[M - CH_2OH]^+$ (79). IR ($CHCl_3$): 3400 (OH) cm^{-1}. Anal. Calcd for $C_{25}H_{43}NO$: C, 80.37; H, 11.60; N, 3.75. Found: C, 80.19; H, 11.75; N, 3.62.

(2S,6R,1'R)-N-(2-Hydroxy-1-phenylethyl)-2-methyl-6-undecylpiperidine (**27**)

A solution of readily available undecylmagnesium bromide in THF was added to **10b** to give a pale yellow oil as a diastereomeric mixture of **26**+**27**. Separation and purification by column chromatography on silica gel with CH_2Cl_2–EtOAc (1:1) gave **27** as a colorless oil in 62% yield. $[\alpha]^{24}_D$ −41.2 (*c* 2.28, $CHCl_3$). ^{1}H NMR δ 0.88 (t, 3 H, J = 6.7 Hz), 0.96 (m, 1 H), 1.13 (d, 3 H, J = 6.7 Hz), 1.21–1.62 (m, 15 H), 1.26 (br s, 10 H), 2.74 (m, 1 H), 3.16 (m, 1 H), 3.72 (dd, 1 H, J = 5.5, 10.4 Hz), 3.83 (dd, 1 H, J = 7.3, 10.4 Hz), 3.99 (dd, 1 H, J = 5.5, 7.3 Hz), 7.25–7.33 (m, 5 H). ^{13}C NMR δ 14.11, 15.71, 20.47, 22.67, 27.78, 28.14, 29.34, 29.59 (2 C), 29.63 (2 C), 29.82, 30.46, 31.90, 33.42, 47.82, 56.82, 61.89, 66.02, 127.53, 128.32, 128.46, 140.06. EIMS *m/z* (relative intensity): 373 $[M]^+$ (5), 342 $[M - CH_2OH]^+$ (22). IR ($CHCl_3$): 3400 (OH) cm^{-1}. HRMS Calcd for $C_{25}H_{43}NO$: 373.3347. Found: 373.3354.

(2S,6S)-2-Methyl-6-phenylpiperidine (**21**)

A solution of **12a** in MeOH (10 mL) was hydrogenated under 1 atm pressure of hydrogen with palladium hydroxide on carbon (Pearlman's catalyst) at rt for 12 h. After the catalyst was removed through Celite, the organic solution was concentrated in vacuo to give a pale yellow oil. Filtration through silica gel with CH_2Cl_2–MeOH (20:1) gave piperidine **21** as a colorless oil in 97% yield. $[\alpha]^{20}_D$ −35.6 (*c* 1.38, $CHCl_3$). ^{1}H NMR δ 1.11 (d, 3 H, J = 6.3 Hz), 1.17 (m, 1 H), 1.38–1.91 (m, 6 H), 2.81 (m, 1 H), 3.66 (dd, 1 H, J = 2.6, 10.6 Hz), 7.20–7.40 (m, 5 H). ^{13}C NMR δ 23.01, 25.33, 33.78, 34.18, 53.15, 62.44, 126.68, 126.92, 128.28, 145.42. EIMS *m/z* (relative intensity): 175 $[M]^+$ (43), 160 $[M - CH_3]^+$ (100). HRMS Calcd for $C_{25}H_{43}NO$: 175.1361. Found: 175.1344.

(2R,6R)-2-Methyl-6-phenylpiperidine (**22**)

A solution of **13** in MeOH (10 mL) was hydrogenated under 1 atm pressure of hydrogen with palladium hydroxide on carbon (Pearlman's catalyst) at rt for 12 h. After the catalyst was removed through Celite, the organic solution was concentrated in vacuo to give a pale yellow oil. Filtration through silica gel with CH_2Cl_2–MeOH (20:1) gave the secondary amine **22** as a colorless oil in 85% yield. $[\alpha]^{20}_D$ +35.2 (*c* 1.26, $CHCl_3$). ^{1}H NMR δ 1.11 (d, 3 H, J = 6.3 Hz), 1.17 (m, 1 H), 1.38–1.91 (m, 6 H), 2.81 (m, 1 H), 3.65 (dd, 1 H, J = 2.5, 10.5 Hz), 7.20–7.39 (m, 5 H). ^{13}C NMR δ 23.01, 25.32, 33.76, 34.16, 53.15, 62.44, 126.68, 126.93, 128.29, 145.40. EIMS *m/z* (relative intensity): 175 $[M]^+$ (42), 160 $[M - CH_3]^+$ (100). HRMS Calcd for $C_{25}H_{43}NO$: 175.1361. Found: 175.1371.

(2S,6R)-2-Methyl-6-phenylpiperidine (**23**)

To a solution of **16** in glacial acetic acid (10 mL) was added lead tetraacetate (1.5 equivalent). After the reaction mixture was stirred at 60°C for 14 h, it was quenched with the addition of water (20 mL) and 1 N sodium hydroxide solution (40 mL), respectively. The resulted basic mixture was extracted with ether (3 x 15 mL), the organic extracts were combined and concentrated *in vacuo* to give a yellow oil. The crude oil was subjected to column chromatography on silica gel with CH_2Cl_2–MeOH (20:1) to give **23** as a colorless oil in 68% yield. $[\alpha]^{20}_D$ +33.4 (*c* 1.25, $CHCl_3$). ^{1}H NMR δ 1.21 (d, 3 H, *J* = 6.6 Hz), 1.40 (m, 1 H), 1.56–1.87 (m, 6 H), 3.29 (m, 1 H), 4.04 (dd, 1 H, *J* = 3.7, 7.5 Hz), 7.18–7.39 (m, 5 H). ^{13}C NMR δ 19.77, 19.90, 31.28, 33.27, 47.24, 54.10, 126.60, 126.68, 128.28, 145.05. EIMS *m/z* (relative intensity): 175 $[M]^+$ (36), 160 $[M - CH_3]^+$ (100). HRMS Calcd for $C_{25}H_{43}NO$: 175.1361. Found: 175.1360.

(2S,6R,1'R)-N-(2-Hydroxy-1-phenylethyl)-2-methyl-6-[(E)-undec-3-en-1-ynyl]piperidine (**25**)

To a stirred solution of (*E*)-1-iodo-1-nonene (1.77 g, 7.0 mmol) and tetrakis(triphenylphosphine)-palladium (400 mg, 0.346 mmol) in pyrrolidine (5 mL), under an argon atmosphere, was added a solution of **20b** (1.42 g, 5.84 mmol) in pyrrolidine (5 mL). After stirring at rt for 12 h, the mixture was hydrolyzed with a saturated aqueous solution of ammonium chloride and extracted with ether. The organic extract was dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. Filtration through silica gel with hexane–EtOAc (10:1) gave **25** as a pale yellow oil (1.88 g, 88%). $[\alpha]^{24}_D$ +213.8 (*c* 1.28, $CHCl_3$). ^{1}H NMR δ 0.89 (t, 3 H, *J* = 6.9 Hz), 1.20 (d, 3 H, *J* = 6.4 Hz), 1.19–1.62 (m, 8 H), 1.28 (br s, 8 H), 1.76 (m, 1 H), 2.03 (br s, 1 H), 2.10 (m, 1 H), 3.35 (m, 1 H), 3.76 (m, 1 H), 4.25–4.36 (m, 3 H), 5.51 (ddd, 1 H, *J* = 1.6, 3.3, 15.8 Hz), 6.14 (dt, 1 H, *J* = 7.0, 15.8 Hz), 7.21–7.36 (m, 3 H), 7.44 (d, 2 H, *J* = 7.4 Hz). ^{13}C NMR δ 14.04, 20.95, 21.26, 22.60, 28.66, 29.07, 29.08, 31.72, 32.06, 33.02, 36.19, 46.26, 50.45, 61.17, 61.50, 84.33, 89.16, 108.99, 126.75, 128.13, 128.17, 141.02, 144.47. EIMS *m/z* (relative intensity): 367 $[M]^+$ (1), 336 $[M - CH_2OH]^+$ (100). IR ($CHCl_3$): 3410 (OH) cm^{-1}. Anal. Calcd for $C_{25}H_{37}NO$: C, 81.69; H, 10.15; N, 3.81. Found: C, 81.52; H, 10.18; N, 3.75.

(2S,6S,1'R)-N-(2-Hydroxy-1-phenylethyl)-2-methyl-6-undecylpiperidine (**26**)

A solution of **25** (0.40 g, 1.088 mmol) in benzene (10 mL) and glacial acetic acid (0.02 mL) was hydrogenated under 1 atm pressure of hydrogen with platinum oxide catalyst (15 mg) at rt for 3 h. After the catalyst was removed through Celite, the organic solution was concentrated on a rotary evaporator to give a pale yellow oil. Purification by column chromatography on silica gel with hexane–EtOAc (10:1) gave **26** as a colorless oil (0.38 g, 93%). $[\alpha]^{24}_D$ −1.5 (*c* 1.52, $CHCl_3$). ^{1}H NMR δ 0.72–1.12 (m, 4 H), 0.88 (t, 3 H, *J* = 6.7 Hz), 1.14–1.74 (m, 12 H), 1.23 (d, 3 H, *J* = 6.7 Hz), 1.28 (s, 10 H), 3.06 (m, 1 H), 3.32 (m, 1 H), 3.43 (dd, 1 H, *J* = 5.5, 10.4 Hz), 3.85 (t, 1 H, *J* = 10.4 Hz), 4.18 (dd, 1 H, *J* = 5.5, 10.4 Hz), 7.26–7.34 (m, 5 H). ^{13}C NMR δ 14.10, 20.27, 20.66, 22.67, 26.37, 27.43, 29.34, 29.66 (4 C), 29.89 (2 C), 31.90, 33.02, 48.50, 52.50, 58.96, 60.32, 127.48, 128.31, 129.21, 141.29. EIMS *m/z* (relative intensity): 373 $[M]^+$ (8), 342 $[M - CH_2OH]^+$ (45). IR ($CHCl_3$): 3400 (OH) cm^{-1}. Anal. Calcd for $C_{25}H_{43}NO$: C, 80.37; H, 11.60; N, 3.75. Found: C, 80.28; H, 11.60; N, 3.62.

(2R,6S)-(−)-Isosolenopsin A hydrochloride (**3a**·HCl)

To a solution of **24** in MeOH (10 mL) was added 5% palladium on carbon, and hydrogenated under 1 atm pressure of hydrogen at rt for 12 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated after addition of a few drops of ethanolic–HCl. To the resultant white solid was added ether, the insoluble part was separated and recrystallized from CH_2Cl_2–ether to give (−)-isosolenopsin A hydrochloride (**3a**·HCl) as colorless crystals in 82% yield, mp 152–153 °C. $[\alpha]^{24}_D$ +10.0 (*c* 1.1, $CHCl_3$). ^{1}H NMR δ 0.88 (t, 3 H, $J = 6.7$ Hz), 1.24 (br s, 18 H), 1.58 (d, 3 H, $J = 6.7$ Hz), 1.64 (br s, 3 H), 1.74–1.99 (m, 4 H), 2.16 (m, 1 H), 2.89 (m, 1 H), 3.07 (m, 1 H), 9.06 (br s, 1 H), 9.44 (br s, 1 H). ^{13}C NMR δ 14.12, 22.68, 23.11, 24.89, 26.00, 29.35, 29.60 (3 C), 29.66, 29.84, 31.91, 32.28, 34.44, 37.46, 52.48, 57.14. EIMS *m/z* (relative intensity): 253 $[M]^+$ (18), 238 $[M - CH_3]^+$ (61).

(2S,6R)-(+)-Isosolenopsin A hydrochloride (**3b**·HCl)

To a solution of **27** in MeOH (10 mL) was added 5% palladium on carbon, and hydrogenated under 1 atm pressure of hydrogen at rt for 12 h. After work-up and recrystallization procedure in the same manner as described for **3a**·HCl, the (+)-isosolenopsin A hydrochloride (**3b**·HCl) was obtained as colorless crystals in 86% yield, mp 152–153 ℃. $[\alpha]^{24}_D$ −10.1 (*c* 1.0, $CHCl_3$). ^{1}H NMR δ 0.88 (t, 3 H, $J = 6.7$ Hz), 1.24 (br s, 18 H), 1.57 (d, 3 H, $J = 6.7$ Hz), 1.71 (br s, 3 H), 1.74–1.99 (m, 4 H), 2.14 (m, 1 H), 2.89 (m, 1 H), 3.08 (m, 1 H), 9.02 (br s, 1 H), 9.42 (br s, 1 H). ^{13}C NMR δ 14.11, 22.68, 23.09, 24.87, 25.99, 29.34, 29.60 (3 C), 29.66, 29.83, 31.91, 32.26, 34.42, 37.44, 52.49, 57.14. EIMS *m/z* (relative intensity): 253 $[M]^+$ (22), 238 $[M - CH_3]^+$ (65).

(2S,6S)-(+)-Solenopsin A hydrochloride (**2b**·HCl)

To a solution of **26** in MeOH (10 mL) was added 5% palladium on carbon, and hydrogenated under 1 atm pressure of hydrogen at rt for 12 h. After work-up and recrystallization procedure in the same manner as described for **3a**·HCl, the (+)-solenopsin A hydrochloride (**2b**·HCl) was obtained as colorless crystals in 87% yield, mp 151–152 ℃. $[\alpha]^{24}_D$ +8.0 (*c* 1.3, $CHCl_3$). ^{1}H NMR δ 0.88 (t, 3 H, $J = 6.7$ Hz), 1.25 (br s, 19 H), 1.48 (d, 3 H, $J = 6.7$ Hz), 1.58–1.82 (m, 4 H), 1.87–2.18 (m, 3 H), 3.27 (m, 1 H), 3.54 (m, 1 H), 9.35 (br s, 2 H). ^{13}C NMR δ 14.08, 19.53, 21.21, 22.66, 26.43, 29.32, 29.60 (3 C), 29.63, 29.76, 30.75, 31.88, 32.95, 34.03, 45.79, 50.80. EIMS *m/z* (relative intensity): 253 $[M]^+$ (9), 238 $[M - CH_3]^+$ (72).

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