Stereoselective Total Syntheses of the Racemic Form and the Natural Enantiomer of the Marine Alkaloid Lepadiformine via a Novel *N*-Acyliminium Ion/Allylsilane Spirocyclization Strategy

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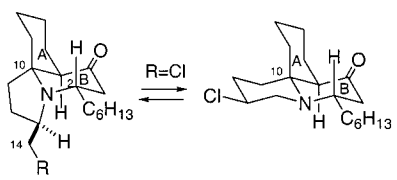
Received February 14, 2002

Stereoselective total syntheses of the racemic form and the natural enantiomer of the tricyclic marine alkaloid lepadiformine (**6**) have been accomplished using a novel intramolecular spirocyclization of an *N*-acyliminium ion with an allylsilane to form the A/C rings as the key step. Introduction of the hydroxymethyl group at C-13 of the racemic spirocycle **11** was achieved using our methodology for oxidative radical-based remote functionalization of *o*-aminobenzamides, followed by copper-catalyzed addition of Grignard reagent **16** to the *N*-acyliminium ion intermediate derived from **15**. Subsequent Tamao oxidation of silane **17** then afforded the requisite hydroxymethyl compound **19**, which was converted to the dimethyl acetal **25** via hydroformylation followed by aldehyde protection. Hydrolysis of the benzamide moiety of **25** and subsequent protection of the primary alcohol gave amino acetal **27**. The synthesis was concluded from **27** by a four-step procedure: acid-catalyzed ring closure, amino nitrile formation, introduction of the hexyl chain by a Grignard reaction to an iminium salt, and removal of the *O*-benzyl protecting group to give (±)-lepadiformine (**6**). The enantioselective total synthesis of **6** started from known optically pure bromide **37**, derived from (*S*)-pyroglutamic acid, and followed a similar sequence involving the key spirocyclization of *N*-acyliminium ion **42**. This synthesis has established the absolute configuration of naturally occurring lepadiformine to be 2(*R*),5(*S*),10(*S*),13(*S*).

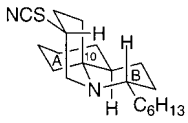
In a series of papers published in the 1990s, Blackman et al. reported the isolation of a small group of interesting, structurally related tricyclic alkaloids from the marine ascidian *Clavelina cylindrica*, collected at various sites off the eastern coast of Tasmania.[1] The most abundant of these alkaloids are cylindricines A (**1**) and B (**3**), whose structures and relative stereochemistry were unambiguously established by X-ray crystallography. These two compounds slowly form a 3:2 equilibrium mixture upon standing in solution, presumably interconverting through an aziridinium intermediate.[1a] Subsequent investigations led to the characterization of several other minor congeneric compounds having the cylindricine A pyrroloquinoline framework and relative stereochemistry but differing in the functionality at C-14 such as cyclidricine C (**2**) and/or having an *n*-butyl rather than a hexyl group at C-2. One additional compound in the cylindricine B pyridoquinoline series was also isolated.[1c,2] If one focuses on the A/B ring fusion in these alkaloids, all members can be considered *cis*-1-azadecalin derivatives.



1 R=Cl cylindricine A
2 R=OH cylindricine C

3 cylindricine B

More recently, a related compound, fasicularin, was isolated from the stalked green ascidian *Neptheis fasicularis* collected in Pohnpei (Micronesia).[3] The constitution of this new alkaloid was established by a series of NMR and NOE experiments that led to the assignment of the structure and relative stereochemistry depicted by **4**, thus putting the compound in the cylindricine B pyridoquinoline alkaloid series, but epimeric at the C-10 quaternary center (i.e., a *trans*-1-azadecalin A/B ring system) and lacking the C-4 oxygenation usually found in the cylindricines. Fasicularin is also of considerable interest due to its biological activity against a DNA repair-deficient strain of yeast, as well as its cytotoxicity against Vero cells.



4 fasicularin

In 1994, the Biard group reported the isolation of another alkaloid of this general class, lepadiformine, from the tunicate *Clavelina lepadiformis* (Muller) collected in the Mediterranean near Tunisia and from *Clavelina moluccensis* (Sluiter) obtained near the Djibouti coast.[4]

(1) (a) Blackman, A. J.; Li, C.; Hockless, D. C. R.; Skelton, B. W.; White, A. H. *Tetrahedron* **1993**, *49*, 8645. (b) Li, C.; Blackman, A. J. *Aust. J. Chem.* **1994**, *47*, 1355. (c) Li, C.; Blackman, A. J. *Aust. J. Chem.* **1995**, *48*, 955.

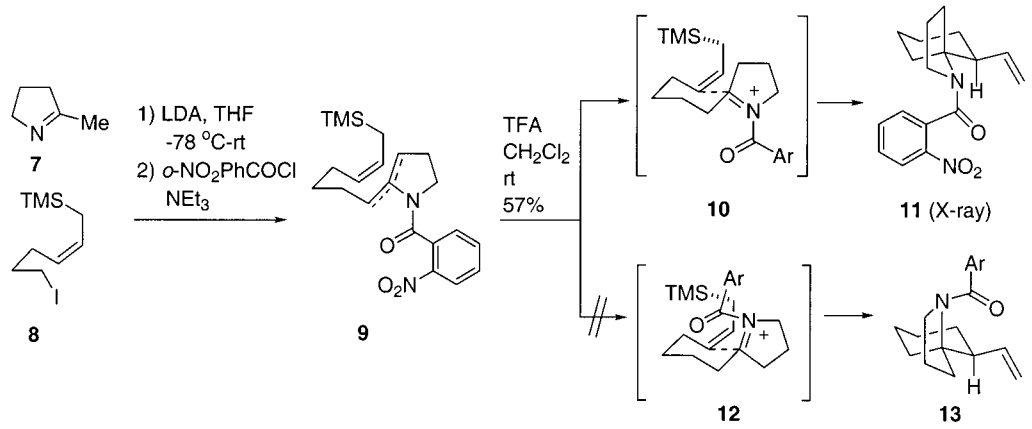
(2) For synthetic work on the cylindricines, see: Snider, B. B.; Liu, T. *J. Org. Chem.* **1997**, *62*, 5630. Molander, G. A.; Ronn, M. *J. Org. Chem.* **1999**, *64*, 5183. Liu, J. F.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 8263.

(3) Patil, A. D.; Freyer, A. J.; Reichwein, R.; Carte, B.; Killmer, L. B.; Faucette, L.; Johnson, R. K.; Faulkner, D. J. *Tetrahedron Lett.* **1997**, *38*, 363.

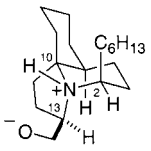
(4) Biard, J. F.; Guyot, S.; Roussakis, C.; Verbist, J. F.; Vercauteren, J.; Weber, J. F.; Boukef, K. *Tetrahedron Lett.* **1994**, *35*, 2691.

10.1021/jo0201070 CCC: $22.00
Published on Web 04/24/2002

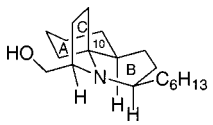
Scheme 1



Lepadiformine was reported to have moderate in vitro cytotoxic activity against several tumor cell lines,[4] as well as various cardiovascular effects in vivo and in vitro.[5] On the basis of primarily NMR spectroscopic data, lepadiformine was initially formulated as having the pyrroloquinoline constitution **5** related to the cylindricine A *cis*-azadecalin series of ascidian alkaloids. It was also proposed on the basis of spectral analysis that the compound existed in the very unusual zwitterionic structure shown. Initially, lepadiformine was reported to have a D-line rotation of zero; however these data have recently been reacquired, and the alkaloid actually has a small positive rotation ($[\alpha]_D^{25}$ +4.6 (*c* 1.28, $CHCl_3$)), although the absolute configuration was indeterminate.[6] In 1999, we demonstrated by total synthesis that the putative structure **5** does not represent lepadiformine (nor is **5** a zwitterion).[7] Moreover, Pearson and co-workers synthesized the other three diastereomers of structure **5** at C-2 and C-13, showing that none of these compounds corresponds to the natural product, and suggested that lepadiformine might in fact be in the fasicularin *trans*-1-azadecalin stereochemical series.[8]



5 (original lepadiformine structure)



6 lepadiformine

As part of a project on the total synthesis of fasicularin (**4**), Kibayashi and co-workers prepared some pyrroloquinoline compounds related to lepadiformine and found one that corresponded to the alkaloid. It was also conclusively proven by X-ray crystal analysis that lepadiformine is indeed a *trans*-1-azadecalin with the relative configuration and conformation shown in structure **6**.[9,10] Interestingly, the natural product exists with the B ring as a boat, thereby having the hexyl group in an equatorial position. In addition, it was shown that the natural material isolated by Biard is actually the hydrochloride salt of **6** rather than a zwitterion as originally postulated.

With the structure of lepadiformine now secure, we decided to turn to a completely new synthetic approach to this interesting alkaloid since our nitrone-based strategy leading to structure **5** could not be modified to produce the requisite *trans*-1-azadecalin.[7] The plan was to effect a novel intramolecular spirocyclization of an *N*-acyliminium ion with an allylsilane to generate the spirocyclic A/C ring system and attendant stereochemistry of lepadiformine (**6**), followed by construction of the B ring.[11] In this paper, we provide the details of this work, which has led to a total synthesis of racemic lepadiformine and has now also been applied in an enantioselective synthesis of the alkaloid that has allowed us to assign its absolute configuration.[12,13]

The synthesis began with commercially available 2-methyl-1-pyrroline (**7**), which was metalated with LDA[14] and then exposed to the known, easily prepared (*Z*)-allylsilane iodide **8**[15] to give an alkylated imine (Scheme 1). This material was then treated in situ with *o*-nitrobenzoyl chloride/triethylamine to afford enamides **9** as a mixture of double-bond isomers. Without purification, compound **9** was treated with 10 equiv of trifluoroacetic acid in methylene chloride at room temperature to afford a single, crystalline spirocyclization product **11** in 57% overall yield based on imine **7**.[16] The structure

(5) Juge, M.; Grimaud, N.; Biard, J. F.; Sauviat, M. P.; Nabil, M.; Verbist, J. F.; Petit, J. Y. *Toxicon* **2001**, *39*, 1231.

(6) Biard, J. F. Personal communication.

(7) Werner, K. M.; De los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem*. **1999**, *64*, 686. Werner, K. M.; De los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem*. **1999**, *64*, 4865.

(8) Pearson, W. H.; Barta, N. S.; Kampf, J. W. *Tetrahedron Lett.* **1997**, *38*, 3369. Pearson, W. H.; Ren, Y. *J. Org. Chem*. **1999**, *64*, 688.

(9) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc*. **2000**, *122*, 4583.

(10) For another recent total synthesis of racemic fasicularin, see: Maeng, J.-H.; Funk, R. L. *Org. Lett*. **2002**, *4*, 331.

(11) (a) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. (b) Hiemstra, H.; Speckamp, W. N. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1988; Vol. 32, p 271. (c) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 1047. (d) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.

(12) For a preliminary account of portions of this work, see: Sun, P.; Sun, C.; Weinreb, S. M. *Org. Lett*. **2001**, *3*, 3507. Taken in part from: Sun, P. Ph.D. Thesis, The Pennsylvania State University, University Park, PA, 2001.

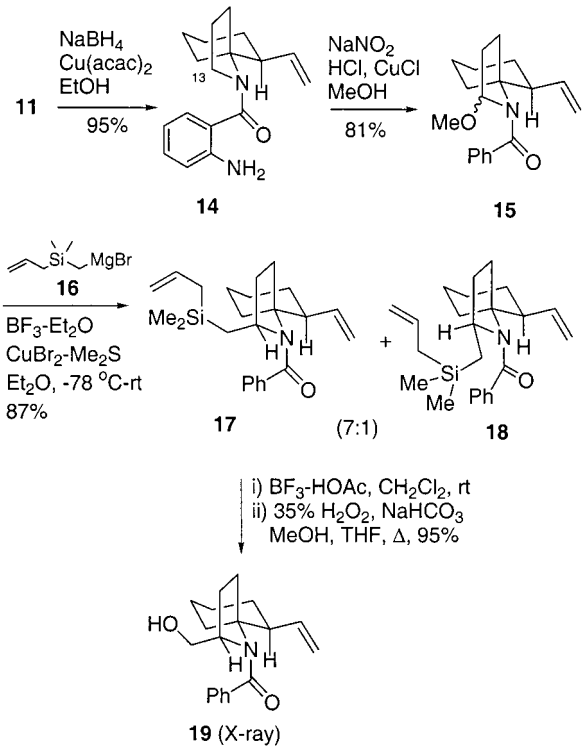
(13) For an elegant total synthesis of racemic lepadiformine, see: Maeng, J.-H.; Funk, R. L. *Org. Lett*. **2001**, *3*, 3511.

(14) For C-alkylations of metalated endocyclic imines, see: (a) Gramain, J.-C.; Husson, H.-P.; Troin, Y. *J. Org. Chem*. **1985**, *50*, 5517. (b) Evans, D. A. *J. Am. Chem. Soc.* **1970**, *92*, 7593. (c) Houk, K. N.; Strozier, R. W.; Rondan, N. G.; Fraser, R. R.; Chauqui-Offermanns, N. *J. Am. Chem. Soc*. **1980**, *102*, 1426.

(15) Hiemstra, H.; Sno, M. H. A. M.; Vijn, R. J.; Speckamp, W. N. *J. Org. Chem*. **1985**, *50*, 4014.

(16) For some related imine spirocyclizations, see: Tanner, D.; Hagberg, L. *Tetrahedron* **1998**, *54*, 7907. Evans, D. A.; Thomas, E. W.; Cherpeck, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 3695. David, M.; Dhimane, H.; Vanucci-Bacque, C.; Lhommet, G. *Heterocycles* **2001**, *55*, 941.

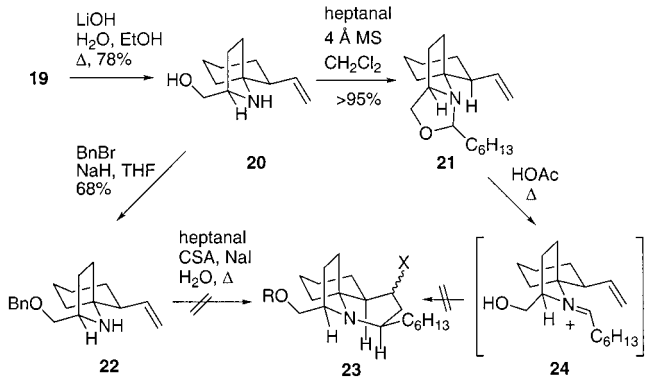
Scheme 2



and conformation of this product was determined by X-ray crystallography to be as shown.[17] This cyclization undoubtedly occurs via a reactive *N*-acyliminium ion,[11] which we believe cyclizes through the preferred conformation **10** having both the allylsilane and *N*-acylimine groups quasi-equatorial. The alternative conformation **12**, which would lead to diastereomer **13**, is probably destabilized relative to **10** by a steric interaction between the bulky quasi-axial *N*-acyl group and the axial hydrogens of the newly forming six-membered ring.

Having efficiently prepared the A/C-ring spirocycle **11**, we next turned to introduction of the hydroxymethyl group at C-13 of the alkaloid. The intent was to make use of our methodology for oxidative remote functionalization of *o*-aminobenzamides in effecting this transformation.[18] Therefore, *o*-nitrobenzamide **11** was first reduced to the *o*-amino compound **14** with sodium borohydride catalyzed by $Cu(acac)_2$[19] (Scheme 2). Subsequent exposure of amine **14** to sodium nitrite/HCl in methanol containing a catalytic amount of cuprous chloride led to the formation of the desired α-methoxybenzamide **15** in good yield. Treatment of **15** with a hydroxymethyl carbanion equivalent, the cuprate derived from Grignard reagent **16**,[20,21] in the presence of boron trifluoride etherate, provided a chromatographically separable 7:1 mixture of alkylation products **17** and **18** in high yield. The desired major product **17** presumably arises via

Scheme 3



nucleophilic attack of the organometallic reagent from the least congested face of the *N*-acyliminium salt derived from α-methoxybenzamide **15**. Tamao oxidation[20] of **17** then cleanly afforded the hydroxymethyl compound **19**, whose stereochemistry was confirmed by X-ray analysis.[17]

The initial strategy for construction of the B ring of the alkaloid was based upon a Mannich-like cyclization. Thus, we hoped to generate an (*E*)-iminium ion like **24**, which would be expected cyclize in a 6-endo process with the alkene moiety via a chairlike transition state to afford a tricycle **23** having the desired C-2 configuration (Scheme 3).[22,23] Hydrolysis of benzamide **19** with aqueous lithium hydroxide gave amino alcohol **20**, which on treatment with heptanal afforded oxazolidine **21** in high yield. Unfortunately, all attempts to rearrange **21** to tricyclic amine **23** under acidic conditions failed, with only starting material or amino alcohol **20** being recovered. Alternatively, amino alcohol **20** was first protected as the benzyl ether **22**, which was exposed to heptanal under the conditions developed by Overman for related olefin Mannich cyclizations.[23] However, once again, only starting material was recovered, rather than the desired cyclization product **23** (X = I). It might be noted that the Overman Mannich cyclizations of alkenes have only been effected with formaldehyde-derived iminium salts.[24] It is possible that the iminium compounds generated from higher aldehydes are not sufficiently electrophilic to participate in this process.

In view of the failure of the Mannich annulation approach, we turned to another methodology for elaboration of the remaining B ring. Therefore, alkene **19** was first hydroformylated[25] and the resulting aldehyde was immediately protected as the dimethyl acetal **25** (Scheme 4). Basic hydrolysis of the benzamide group of **25** then afforded the amino alcohol **26** in excellent yield. Although we had hoped to complete the total synthesis without having to resort to protecting the primary alcohol group of **26**, this proved to be unworkable.[26] Therefore, alcohol **26** was next converted to the benzyl ether **27**. Upon treatment with *p*-toluenesulfonic acid, amino acetal **27** cyclized to enamine **28**, which proved to be rather

(17) We are grateful to Dr. Louis Todaro (Hunter College, CUNY) for the X-ray analyses of compounds **11** and **19**. Data has been deposited with the Cambridge Crystallographic Data Centre (**11**: CCDC 177 834; **19**: CCDC 177 835).

(18) (a) Han, G.; McIntosh, M. C.; Weinreb, S. M. *Tetrahedron Lett.* **1994**, *35*, 5813. (b) Han, G.; LaPorte, M. G.; McIntosh, M. C.; Weinreb, S. M.; Parvez, M. *J. Org. Chem.* **1996**, *61*, 9483. (c) Chao, W.; Weinreb, S. M. *Tetrahedron Lett.* **2000**, *41*, 9199.

(19) Hanaya, K.; Muramatsu, T.; Kudo, H.; Chow, Y. L. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2409.

(20) Tamao, K.; Ishida, N. *Tetrahedron Lett.* **1984**, *25*, 4249.

(21) Wistrand, L.-G.; Skrinjar, M. *Tetrahedron* **1991**, *47*, 573.

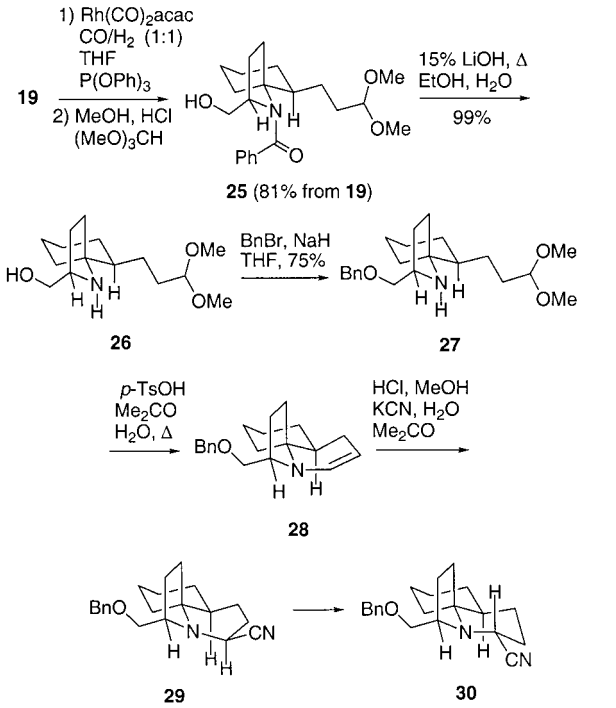
(22) Cf.: Rischke, H.; Wilcock, J. D.; Winterfeldt, E. *Chem. Ber.* **1973**, *106*, 3105. Bohlmann, F.; Winterfeldt, E. *Chem. Ber.* **1960**, *93*, 1956. Demailly, G.; Solladie, G. *Tetrahedron Lett.* **1977**, 1885.

(23) McCann, S. F.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6107.

(24) Some examples do exist of Overman Mannich cyclizations with higher aldehydes involving alkynes. We thank Professor Overman for providing this information.

(25) Ojima, I.; Tsai, C.-Y.; Tzamarioudaki, M.; Bonafoux, D. *Org. React.* **2000**, *56*, 1.

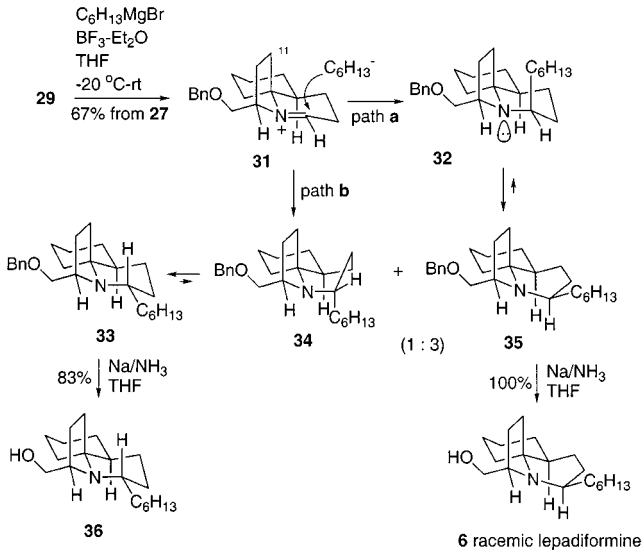
Scheme 4



unstable and could not be purified by chromatography. A few attempts were made to C-alkylate this enamine directly (e.g., allyltrimethylsilane, TFA; TFA, and then hexylmagnesium bromide, CuBr·Me_2S), but none of the desired products could be detected. Alternatively, enamine **28** could be converted to α-amino nitrile **29**, which showed somewhat better stability than the enamine. The nitrile is formed initially as a kinetic product to which we have tentatively assigned the stereostructure shown in **29**. Upon standing in solution, nitrile **29** slowly isomerizes to the thermodynamically more stable stereoisomer, which we expect is epimer **30**.

We next investigated the possibility of introducing the C-2 hexyl chain by treating the crude kinetic amino nitrile **29** with commercially available hexylmagnesium bromide under various reaction conditions. The optimum yield and stereoselectivity was eventually achieved using the Grignard reagent in the presence of boron trifluoride etherate in THF, which produced a 3:1 mixture of the desired alkylation product **35** along with its C-2 epimer **33** (56% overall total yield from amino acetal **27**) (Scheme 5).[27] The results of this reaction can be rationalized on the basis of the stereoelectronic principles outlined by Stevens[28] via antiperiplanar addition of the Grignard reagent to intermediate iminium salt **31** from the preferred "axial" direction (path **a**), which would lead to an initial chair **32**. This compound then undergoes conformational inversion to the more stable lepadiformine B ring boat conformation **35**. Attack on the iminium species **31** from the opposite ("equatorial") face (path **b**) will initially produce an unfavorable B ring boat **34**, which ring-flips to the more stable chair conformer **33** having an equatorial C-2 hexyl group. In simpler ring systems, path **a** is ordinarily highly preferred over path **b**.[27,28] However, in the case of iminium compound **31**, a developing severe 1,3-diaxial interaction between the incoming nucleophile and the bridge carbon (C-11) is probably responsible for the lower than normal stereoselectivity in the alkylation step.

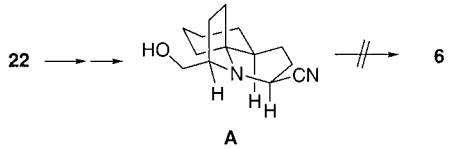
Scheme 5



To complete the total synthesis, cleavage of the benzyl ether group from compound **35** using sodium/liquid ammonia afforded racemic lepadiformine (**9**) in high yield. Both the synthetic alkaloid **6** and its HCl salt have spectral data identical to those of authentic material.[29] Similarly, the epimer **33** could be deprotected to afford 2-*epi*-lepadiformine (**36**).[9]

The next goal of this program was to attempt to extend the basic strategy outlined here to achieve an enantioselective total synthesis of lepadiformine. Toward this end, known bromide **37**[30] derived from inexpensive (*S*)-pyroglutamic acid was chosen as the starting material (Scheme 6). We decided that it would be prudent to use as sterically bulky a group as possible to block one face of the system in the key spirocyclization step (vide infra), and therefore bromide **37** was first converted to the phenyldimethylsilyl derivative **38**. The lactam **38** was then converted to the *N*-Cbz compound **39**. Iodide (*Z*)-allylsilane **40**, prepared from the known corresponding alcohol,[31] was transformed to the lithium species with *tert*-butyllithium and was added to Cbz lactam **39**. Without purification, adduct **41** was exposed to boron trifluoride acetic acid complex in methylene chloride to provide spirocycle **43** as a single stereoisomer in 52% overall yield based upon **39**. As we had anticipated, this cyclization involves selective attack by the allylsilane

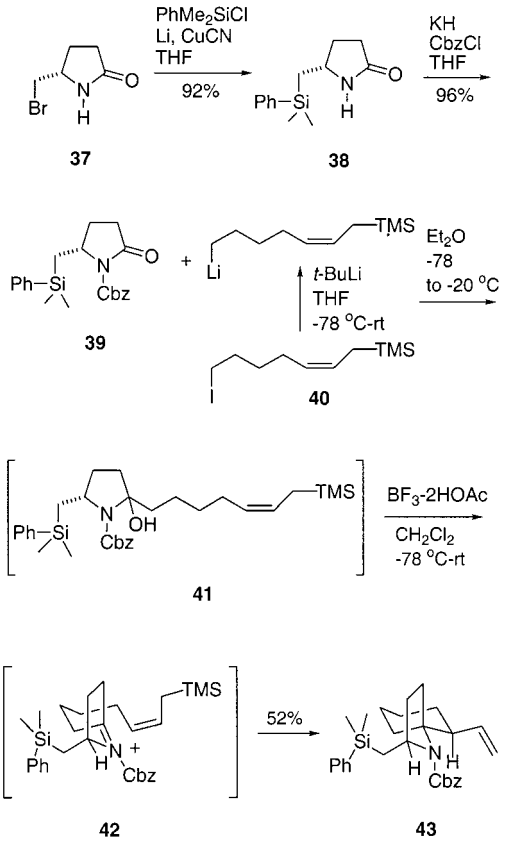
(26) Amino alcohol **26** could in fact be converted to tricyclic alcohol nitrile **A** as was done for benzyl-protected compound **27** (cf. Scheme 4), but all attempts to alkylate this compound with organometallic reagents to directly produce lepadiformine (**6**) failed.



(27) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, *55*, 4688.
(28) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289.

(29) We thank Professor J. F. Biard for copies of the proton and carbon NMR spectra, as well as a sample of natural lepadiformine. We are also grateful to Professor Raymond L. Funk for NMR spectra of synthetic (±)-lepadiformine free base and the corresponding hydrochloride salt.[13]
(30) Misun, M.; Pfaltz, A. *Helv. Chim. Acta* **1996**, *79*, 961.
(31) Tietze, L. F.; Ruther, M. *Chem. Ber.* **1990**, *123*, 1387.

Scheme 6



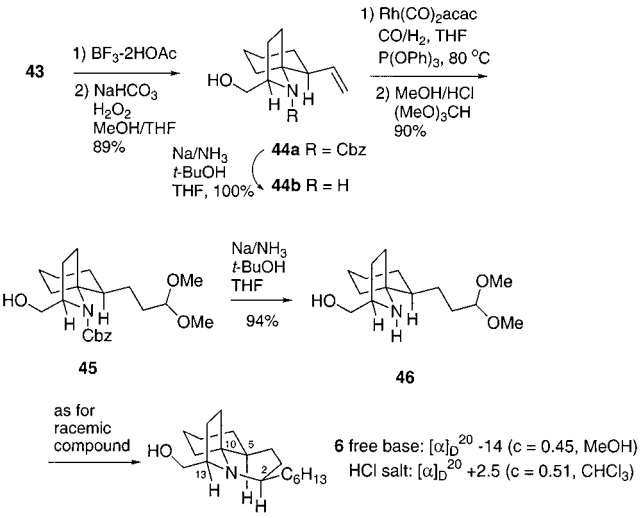
onto the less encumbered face of *N*-acyliminium ion **42**. The stereochemistry of intermediate **43** was proven by its eventual conversion into lepadiformine (vide infra).

To continue the synthesis, the silyl group of **43** was converted to the primary alcohol **44** by a Tamao oxidation (Scheme 7). Since the Cbz compounds **43** and **44a** show mixtures of carbamate rotamers in their NMR spectra, the product **44a** was cleaved to amino alcohol **44b** for characterization purposes (see Experimental Section). The alkene moiety of **44a** could then be cleanly hydroformylated,[25] and the aldehyde that was produced was transformed to the dimethyl acetal **45**. Removal of the Cbz group by a dissolving metal reduction yielded the amino alcohol **46**, which was identical in all respects except for optical rotation to the racemic material **26** (cf. Scheme 4). Using exactly the same methodology applied in the racemic series (vide supra), we converted amino alcohol **46** in five steps to enantiomerically pure lepadiformine (**6**).

The hydrochloride salt of synthetic **6** showed a small positive D-line rotation ($[\alpha]_D^{20}$ +2.5 (*c* 0.51, $CHCl_3$)) similar to that of natural material (vide supra).[6,29,32] However, since the magnitude of the rotation is so small, a more reliable comparison with the natural product was done by NMR analysis. Therefore, racemic lepadiformine, the natural alkaloid, and the synthetic enantiomerically pure material were all converted to their corresponding Mosher esters using the (*R*)-Mosher acid. The proton and ^{19}F NMR spectra of the Mosher ester of racemic lepadiformine showed most resonances to be doubled (see Supporting Information). In the case of the Mosher esters

(32) The D-line rotation of natural lepadiformine free base has not been reported.

Scheme 7



derived from natural lepadiformine and our synthetic enantiomerically pure alkaloid, sharp single resonances were observed. Portions of the ^1H NMR spectra of these derivatives are shown in Figure 1. It can be clearly seen from the figure that our synthetic material in fact corresponds to the natural enantiomer. Therefore the absolute configuration of naturally occurring lepadiformine (**6**) has been established to be 2(*R*),5(*S*),10(*S*),13(*S*) as indicated in the structure.

In summary, we have successfully completed a total synthesis of racemic lepadiformine (**6**) that utilizes as key steps a novel stereoselective spirocyclization of an *N*-acyliminium ion with an allylsilane, followed by an application of our radical-based remote amide oxidation methodology for generation of *N*-acyliminium compounds, which allows efficient introduction of the C-13 hydroxymethyl group. The spirocyclization strategy has also been extended to an enantioselective total synthesis of the alkaloid starting from an (*S*)-pyroglutamic acid derivative. This synthesis has now definitively proven the absolute configuration of lepadiformine to be as shown in structure **6**.

Experimental Section

(2-Nitrophenyl)-(6-vinyl-1-azaspiro[4.5]dec-1-yl)methanone (11). To a solution of diisopropylamine (813 μL, 5.80 mmol) in 12 mL of THF was added *n*-BuLi (2.2 M in hexanes, 2.64 mL) at −78 °C. The reaction mixture was warmed to 0 °C and stirred for 10 min. The mixture was then cooled to −78 °C, and neat 2-methyl-1-pyrroline (**7**, 95% purity, 401 mg, 4.83 mmol) was added dropwise. The resulting mixture was stirred for 1 h at −78 °C, followed by the addition of iodide (*Z*)-allylsilane **8** (1.50 g, 5.31 mmol). The mixture was gradually warmed to room temperature over 1 h and kept at that temperature for an additional 2 h. To the reaction mixture was then added triethylamine (2.0 mL, 14.5 mmol) and 2-nitrobenzoyl chloride (90% purity, 2.13 mL, 14.5 mmol). The resulting reaction mixture was stirred for an additional 15 min at room temperature, diluted with brine (20 mL), and extracted with Et_2O. The organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was filtered through a short column of neutral alumina (containing 5% H_2O), eluting with EtOAc/hexanes (1:2).

To a solution of crude enamides **9** in CH_2Cl_2 (125 mL) at −78 °C were added flame-dried 4 Å molecular sieves (∼2 g) and trifluoroacetic acid (3.73 mL, 48.3 mmol). The reaction mixture was gradually warmed to room temperature over 1.5 h. The reaction mixture was stirred for an additional 1.5 h at

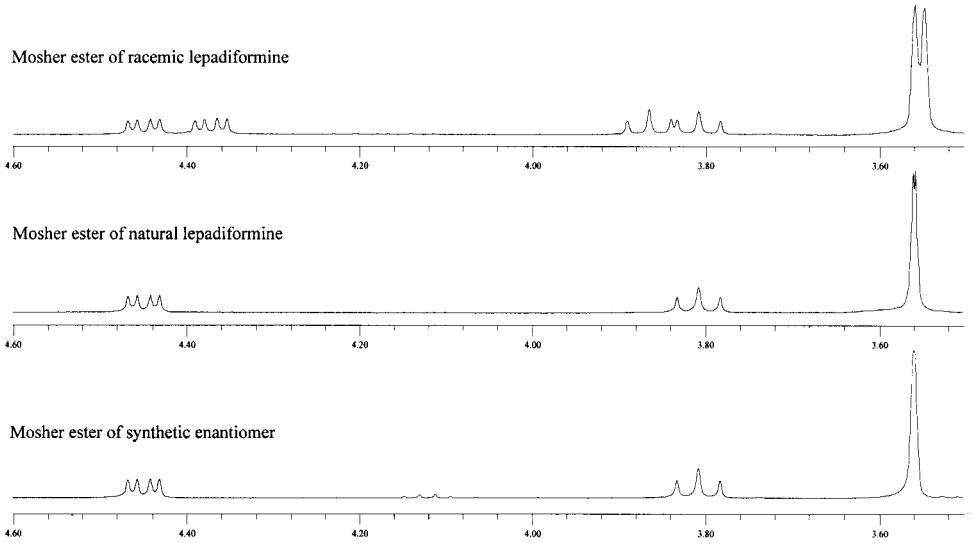


Figure 1. Portions of the ^{1}H NMR spectra (400 MHz, $CDCl_3$) of the (*R*)-Mosher esters of racemic and natural lepadiformine (**6**) and its synthetic enantiomer.

room temperature, diluted with saturated aqueous $NaHCO_3$ (100 mL), and extracted with CH_2Cl_2. The organic extracts were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:2 EtOAc/hexanes) to afford spirocyclic amide **11** (860 mg, 57% from 2-methyl-1-pyrroline) as a white solid. Recrystallization of the purified product from CH_2Cl_2 gave single crystals suitable for X-ray analysis: mp 83−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 8.3 Hz, 1 H), 7.66 (td, J = 7.5 Hz, 1.0 Hz, 1 H), 7.50 (td, J = 8.4, 1.4 Hz, 1 H), 7.22 (dd, J = 7.6, 1.2 Hz, 1 H), 5.95 (br s, 1 H), 5.20−5.15 (m, 2 H), 3.70 (ddd, J = 11.3, 7.3, 3.4 Hz, 1 H), 3.18−3.05 (m, 2 H), 2.81 (td, J = 12.4, 4.1 Hz, 1 H), 2.04−1.97 (m, 1 H), 1.93−1.87 (m, 1 H), 1.77−1.71 (m, 6 H), 1.43−1.24 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 144.2, 139.6, 135.3, 134.5, 129.1, 127.7, 124.5, 115.6, 69.4, 51.0, 44.0, 32.3, 31.0, 28.9, 24.9, 23.7, 23.3; CIMS (APCI+) (relative intensity) 315.2 (MH^+, 100), 149.1 (21); HRMS (APCI+) calcd for $C_{18}H_{23}N_2O_3$ (MH^+) 315.1709, found 315.1694.

(2-Aminophenyl)-(6-vinyl-1-azaspiro[4.5]dec-1-yl)-methanone (14). To a solution of amide **11** (1.010 g, 3.21 mmol) in anhydrous ethanol (20 mL) was added a catalytic amount of $Cu(acac)_2$ (168 mg, 0.642 mmol) and $NaBH_4$ (365 mg, 9.64 mmol) under argon. The reaction mixture was stirred for 3 h at room temperature and then diluted with water (10 mL). The mixture was extracted with CH_2Cl_2. The organic extracts were dried over K_2CO_3 and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:2 EtOAc/hexanes) to afford *o*-aminobenzamide **14** (863 mg, 95%) as a white solid: mp 105−106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10−7.05 (m, 2 H), 6.70−6.66 (m, 2 H), 5.88 (ddd, J = 17.5, 10.4, 7.7 Hz, 1 H), 5.18−5.10 (m, 2 H), 4.23 (br s, 2 H), 3.73 (br t, J = 8.2 Hz, 1 H), 3.36−3.31 (m, 2 H), 2.87 (td, J = 12.7, 4.1 Hz, 1 H), 1.93−1.89 (m, 2 H), 1.76−1.66 (m, 5 H), 1.55−1.28 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 144.0, 139.6, 129.7, 126.8, 124.4, 117.5, 116.4, 115.8, 69.2, 51.7, 43.8, 33.0, 30.6, 29.0, 25.0, 24.0, 23.3; CIMS (APCI+) (relative intensity) 285.2 (MH^+, 45), 149.1 (25), 120.1 (100); HRMS (APCI+) calcd for $C_{18}H_{25}N_2O$ (MH^+) 285.1967, found 285.1952.

(2-Methoxy-6-vinyl-1-azaspiro[4.5]dec-1-yl)phenylmethanone (15). To a solution of *o*-aminobenzamide **14** (436 mg, 1.54 mmol) and $NaNO_2$ (159 mg, 2.31 mmol) in anhydrous MeOH (30 mL) was added HCl/MeOH (1 N, 8.6 mL) dropwise over 5 min at 0 °C. After the reaction was stirred at this temperature for an additional 40 min, 4 Å molecular sieves (~600 mg) were added and the resulting mixture was stirred for 5 min. CuCl (15 mg, 0.15 mmol) was then added, and the mixture was stirred at 18 °C for 1.5 h. The reaction was quenched with NaOMe (466 mg, 8.6 mmol), and the mixture was diluted with saturated aqueous $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2. The organic extracts were dried over K_2CO_3 and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:9 EtOAc/MeOH) on neutral alumina (containing 8% H_2O) to afford a diastereomeric mixture (ratio = 3:1) of α-methoxybenzamides **15** (372 mg, 81%) as a colorless liquid: IR (film) 2927, 1636, 1445, 1389, 1070 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.36 (m, 5 H), 6.12 (ddd, J = 17.0, 10.7, 6.0 Hz, 0.25 H), 5.75 (ddd, J = 18.6, 10.3, 8.5 Hz, 0.75 H), 5.15−5.04 (m, 2 H), 3.69 (m, 1 H), 2.91 (s, 2.25 H), 2.83 (s, 0.75 H), 2.23 (m, 1 H), 1.89−1.38 (m, 12 H); HRMS (ESI+) calcd for $C_{19}H_{26}NO_2$ (MH^+) 300.1964, found 300.1975.

{2-[(Allyldimethylsilanyl)-methyl]-6-vinyl-1-azaspiro-[4.5]dec-1-yl}-phenyl-methanone (17). To a solution of $CuBr{\cdot}Me_2S$ (331 mg, 1.61 mmol) in Et_2O (4 mL) was added Grignard reagent **16** (2.1 M in Et_2O, 767 μL) at −50 °C. After 30 min at that temperature, the reaction mixture was cooled to −78 °C and neat $BF_3{\cdot}OEt_2$ (228 mg, 1.61 mmol) was added. After being kept at −78 °C for 5 min, the reaction mixture was transferred via a cannula into a solution of amide **15** (96 mg, 0.32 mmol) in THF (5 mL). The mixture was stirred at −78 °C for 3 h and then allowed to warm to room temperature over 1 h. The reaction mixture was diluted with saturated aqueous NH_4Cl (10 mL) and extracted with Et_2O. The organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:9 EtOAc/hexanes) to afford a 7:1 ratio of diastereomers allylsilane **17** (93 mg, 76%) and allylsilane **18** (13 mg, 11%). **Allylsilane 17**: IR (film) 2925, 1627, 1397 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.36−7.29 (m, 5 H), 5.78 (ddd, J = 17.9, 9.8, 8.6 Hz), 5.47 (dq, J = 17.9, 8.3 Hz, 1 H), 5.15−5.07 (m, 2 H), 4.75−4.67 (m, 2 H), 3.98 (dd, J = 12.1 6.3 Hz, 1 H), 3.69 (br t, J = 8.0 Hz, 1 H), 3.01 (td, J = 13.1, 3.2 Hz, 1 H), 2.23−2.18 (m, 1 H), 1.93−1.57 (m, 6 H), 1.45−1.15 (m, 6 H), 0.91−0.83 (m, 1 H), 0.67−0.63 (m, 1 H), −0.31 (s, 3 H), −0.42 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7. 139.9, 139.8, 134.2, 128.5, 128.3, 126.1, 115.4, 113.1, 68.8, 58.6, 42.6, 37.9, 31.2, 30.4, 29.6, 24.9, 24.4, 23.9, 23.1, −3.4, −4.0; HRMS (APCI+) calcd for $C_{24}H_{36}NOSi$ (MH^+) 382.2566, found 382.2577. **Allylsilane 18**: IR (film) 2924, 1625, 1398 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.20 (m, 5 H), 5.92 (ddd, J = 17.2, 11.1, 6.9 Hz, 1 H), 5.45 (dddd, J = 17.4, 8.4, 8.4, 8.4 Hz, 1 H), 5.12−5.06 (m, 2 H), 4.73−4.64 (m, 2 H), 3.91 (dd, J = 12.0, 5.6 Hz, 1 H), 3.80 (br t, J = 8.4 Hz, 1 H), 2.66 (td, J = 10.9, 3.4 Hz, 1 H), 1.86−1.70 (m, 6 H), 1.52−1.30 (m, 4 H), 1.19−1.10 (m, 3 H), 0.74 (dd, J = 14.4, 12.6 Hz, 1 H), 0.47 (d, J = 14.5 Hz, 1 H), −0.35 (s, 3 H), −0.48 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 140.2, 140.0, 134.3, 128.2, 128.1, 125.7, 115.1, 112.9,

69.9, 57.5, 43.8, 31.3, 28.5, 28.2, 26.7, 25.0, 24.0, 23.3, 23.1, −3.4, −4.0; HRMS (ESI+) calcd for $C_{24}H_{36}NOSi$ (MH^+) 382.2566, found 382.2559.

(2-Hydroxymethyl-6-vinyl-1-azaspiro[4.5]dec-1-yl)-phenylmethanone (19). To a solution of allylsilane **17** (140 mg, 0.37 mmol) in CH_2Cl_2 (5 mL) was added BF_3·2AcOH (150 μL, 0.73 mmol) at room temperature. After 15 min, the mixture was diluted with saturated aqueous $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to give the fluorosilane: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.30 (m, 5 H), 5.78 (dt, J = 17.9, 9.9 Hz, 1 H), 5.17−5.08 (m, 2 H), 4.07 (dd, J = 11.8, 6.3 Hz, 1 H), 3.68 (t, J = 8.6 Hz, 1 H), 3.01 (t, J = 12.4 Hz, 1 H), 2.32−2.21 (m, 1 H), 1.90−0.67 (m, 12 H), −0.06 (d, J = 7.5 Hz, 3 H), −0.29 (d, J = 7.6 Hz, 3 H).

To a solution of the above fluorosilane in a mixture of MeOH (5 mL) and THF (5 mL) was added $NaHCO_3$ (16 mg, 0.20 mmol) at room temperature. After 15 min, H_2O_2 (35 wt % solution in water, 500 μL) was added to the reaction mixture. After being refluxed overnight, the mixture was diluted with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:1 EtOAc/hexanes) to afford alcohol **19** (89 mg, 95%) as a white solid. Recrystallization from EtOAc/CH_2Cl_2 provided X-ray quality crystals: mp 169−170 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.27 (m, 5 H), 5.77 (dt, J = 17.4, 8.9 Hz, 1 H), 5.14−5.09 (m, 2 H), 3.86 (dd, J = 13.0, 7.2 Hz, 1 H), 3.61 (br t, J = 7.7 Hz, 1 H), 3.20−3.09 (m, 2 H), 2.89 (td, J = 13.0, 3.5 Hz, 1 H), 2.29 (br s, 1 H), 2.18 (br t, J = 7.2 Hz, 1 H), 1.84−1.67 (m, 6 H), 1.46−1.24 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 139.7, 139.2, 128.7, 128.3, 126.1, 115.7, 69.6, 63.6, 62.3, 42.7, 37.4, 30.9, 29.8, 25.8, 24.9, 23.9; CIMS (APCI+) (relative intensity) 300.1 (MH^+, 100); HRMS (APCI+) calcd for $C_{19}H_{26}NO_2$ (MH^+) 300.1963, found 300.1958.

[6-(3,3-Dimethoxypropyl)-2-hydroxymethyl-1-azaspiro-[4.5]dec-1-yl]-phenylmethanone (25). To a solution of olefin **19** (76 mg, 0.25 mmol) in THF (5 mL) were added $Rh(CO)_2$(acac) (4 mg, 0.015 mmol) and $P(OPh)_3$ (7 μL, 0.025 mmol) under argon. The reaction mixture was transferred to a glass reaction vessel with a flat bottom, long narrow neck, and open top and subsequently placed in a stainless steel autoclave. The reaction was carried out at 60 °C and 4 atm (initial pressure at 20 °C) of CO and H_2 (1:1) for 6 h with stirring. After the autoclave was cooled to room temperature, the gases were released and the reaction mixture was concentrated under reduced pressure.

To a solution of the crude aldehyde in dry MeOH (3 mL) were added trimethyl orthoformate (139 μL, 1.27 mmol) and HCl/MeOH (1 N, 50 μL) at room temperature. After 10 min, the mixture was diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (3:1 EtOAc/hexanes) to afford acetal **25** (77 mg, 81%) as a white solid: mp 96−97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36 (br s, 5 H), 4.36 (t, J = 5.2 Hz, 1 H), 3.97 (br m, 1 H), 3.26 (s, 3 H), 3.25 (s, 3 H), 3.38−3.18 (m, 2 H), 2.86 (t, J = 10.1 Hz, 2 H), 2.12 (t, J = 10.3 Hz, 1 H), 1.88−1.02 (m, 15 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 139.3, 128.9, 128.4, 126.1, 104.4, 70.6, 64.0, 62.5, 53.2, 52.1, 38.5, 37.6, 30.5, 30.1, 29.1, 25.8, 25.5, 24.7, 24.0; HRMS (ESI+) calcd for $C_{22}H_{34}NO_4$ (MH^+) 376.2488, found 376.2466.

[6-(3,3-Dimethoxypropyl)-1-azaspiro[4.5]dec-2-yl]-methanol (26). To a solution of amide **25** (250 mg, 0.666 mmol) in a mixture of H_2O (22 mL) and EtOH (11 mL) was added LiOH·H_2O (3.25 g, 77.5 mmol) at room temperature. After being refluxed for 7 days, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (5:100:1.5 MeOH/$CHCl_3$/NH_4OH) to afford amino alcohol **26** (179 mg, 99%) as a colorless liquid: IR (film) 3360, 2932, 2856, 1447, 1126, 1071 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.34 (t, J = 5.4 Hz, 1 H), 3.49 (dd, J = 9.7, 3.5 Hz, 1 H), 3.30 (s, 3 H), 3.28 (s, 3 H), 3.37−3.25 (m, 2 H), 2.50 (br s, 2 H), 1.74−1.00 (m, 17 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.6, 64.8, 64.3, 59.7, 53.0, 52.2, 46.5, 40.7, 30.9, 28.7, 27.9, 24.5, 24.3, 24.1; CIMS (APCI+) (relative intensity) 272.2 (MH^+, 100), 240.2 (MH^+ − OMe, 28), 208.2 (14); HRMS (APCI+) calcd for $C_{15}H_{29}NO_3$ (MH^+) 272.2226, found 272.2244.

2-Benzyloxymethyl-6-(3,3-dimethoxypropyl)-1-azaspiro-[4.5]decane (27). To a suspension of NaH (60% w/w in mineral oil, 50 mg, 1.24 mmol) in THF (12 mL) at −8 °C were added the above amino alcohol **26** and BnBr (147 μL, 1.24 mmol). The reaction mixture was stirred at room temperature for 3 days, diluted with water, and extracted with CH_2Cl_2. The organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (100:3:1.5 $CHCl_3$/MeOH/NH_4OH) to afford the benzyl ether **27** (169 mg, 75%) as a colorless oil: IR (film) 2927, 2856, 1654, 1451, 1125, 1075 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25−7.16 (m, 5H), 4.44 (dd, J = 12.2, 14.0 Hz, 2H), 4.30 (t, J = 5.0 Hz, 1H), 3.37 (dddd, J = 4.0, 4.0, 3.9, 3.4 Hz, 1H), 3.31−3.22 (m, 3H), 3.23 (s, 3H), 3.22 (s, 3H), 1.76−0.89 (m, 17 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 128.1, 127.4, 127.3, 104.7, 74.2, 72.9, 64.7, 58.6, 52.7, 52.2, 47.4, 40.6, 30.9, 30.0, 29.0, 28.5, 24.7, 24.3; HRMS (APCI+) calcd for $C_{22}H_{36}NO_3$ (MH^+) 362.2695, found 362.2691.

3-Benzyloxymethyl-5-hexyldecahydropyrrolo[2,1-j]-quinoline (35). To a solution of amino acetal **27** (34 mg, 0.0968 mmol) in a mixture of acetone (3 mL) and H_2O (2 mL) was added p-TsOH·H_2O (22 mg, 0.116 mmol) at room temperature. The resulting reaction mixture was stirred at reflux for 3.0 h, diluted with saturated aqueous $NaHCO_3$ (5 mL), and extracted with CH_2Cl_2. The organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to afford the unstable enamine **28** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.24 (m, 5H), 5.78 (d, J = 7.9 Hz, 1H), 4.55 (ABq, J = 12.2 Hz, 2H), 4.56 (dt, J = 4.4, 7.3 Hz, 1H), 3.52 (dd, J = 7.6, 9.2 Hz, 1H), 3.39 (dd, J = 6.2, 9.2 Hz, 1H), 3.32−3.22 (m, 1H), 2.07−1.12 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.1, 138.6, 128.2, 127.5, 127.4, 100.9, 76.4, 73.1, 65.3, 64.5, 41.5, 37.1, 26.1, 25.34, 25.30, 25.2, 23.6.

The above enamine **28** was dissolved in acetone (0.4 mL) and water (4 mL) at room temperature. KCN (54 mg, 0.968 mmol) and 1 N HCl in MeOH (97 μL, 0.097 mmol) were added to the reaction mixture. The solution was stirred at room temperature for 2.5 h, diluted with saturated aqueous $NaHCO_3$ (5 mL), and extracted with CH_2Cl_2. The organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to afford the amino nitrile **29** as a colorless oil: IR (film) 2929, 2858, 2244 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.22 (m, 5H), 4.54 (ABq, J = 12.1 Hz, 2H), 4.16 (dd, J = 3.8, 8.2 Hz, 1H), 3.70 (dd, J = 5.4, 9.0 Hz, 1H), 3.44 (m, 1H), 3.34 (dd, J = 7.1, 9.0 Hz, 1H), 2.20 (m, 1H), 2.00 (m, 1H), 1.87−1.08 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 128.3, 127.6, 127.5, 121.3, 76.1, 73.1, 67.7, 63.4, 50.1, 40.6, 39.4, 30.7, 27.4, 26.6, 26.1, 26.0, 23.8, 22.9; HRMS (APCI+) calcd for $C_{21}H_{29}N_2O$ (MH^+) 325.2280, found 325.2275.

Amino Nitrile 30: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 4.56 (ABq, J = 12.0, 32.8 Hz, 2H), 3.85 (dd, J = 3.5, 5.8 Hz, 1H), 3.35−3.44 (m, 2H), 3.08 (m, 1H), 2.20−1.04 (m, 17H); HRMS (APCI+) calcd for $C_{21}H_{29}N_2O$ (MH^+) 325.2280, found 325.2285.

The above cyanide **29** was dissolved in dry THF (4 mL) and cooled to −20 °C, and 2.0 M $C_6H_{13}MgBr$ in Et_2O (339 μL, 0.678 mmol) and BF_3·Et_2O (25 μL, 0.19 mmol) were added dropwise. The reaction mixture was allowed to warm to room temperature slowly and stirred overnight (∼12 h). The reaction mixture was diluted with 1 N NaOH and extracted with CH_2Cl_2. The organic extracts were dried with K_2CO_3 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (100:20:1.5 hexanes/EtOAc/conc NH_4OH) to give a 3:1 mixture of diastereomers **35** and **33** (25 mg, 67% from **27**). The two diastereomers were separated by preparative TLC (20:100:5 Et_2O/hexanes/TEA) to give **35** (19 mg, 50%) and **33** (6 mg, 17%). **Major Diaste-**

reomer 35: pale yellow oil; IR (film) 2927, 2856, 1090 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31−7.22 (m, 5H), 4.49 (s, 2H), 3.54 (dd, J = 4.1, 8.6 Hz, 1H), 3.27−3.26 (m, 1H), 3.13−3.03 (m, 2H), 2.02−1.96 (m, 1H), 1.67−0.99 (m, 26 H), 0.86 (t, J = 6.5 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 138.8, 128.3, 127.6, 127.4, 77.9, 73.2, 70.6, 67.6, 57.6, 53.7, 41.4, 37.9, 34.4, 31.9, 31.0, 29.6, 29.3, 28.1, 27.7, 26.4, 24.5, 24.0, 22.6, 14.1; HRMS (ESI+) calcd for $C_{26}H_{42}NO$ (MH^+) 384.3266, found 384.3236. **Minor Diastereomer 33**: colorless oil; IR (film) 2926, 2856, 1099 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.31−7.23 (m, 5H), 4.52 (ABq, J = 12.1 Hz, 2H), 3.61 (dd, J = 6.0, 9.0 Hz, 1H), 3.59 (t, J = 8.8 Hz, 1H), 3.10−3.06 (m, 1H), 2.14−2.10 (m, 2H), 1.83−1.01 (m, 26 H), 0.85 (t, J = 6.6 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 138.8, 128.3, 127.5, 127.4, 77.6, 73.1, 67.5, 65.3, 62.7, 43.6, 38.8, 37.4, 32.0, 31.4, 31.0, 29.7, 27.1, 26.5, 26.4, 26.0, 24.9, 23.7, 22.7, 14.1; HRMS (ESI+) calcd for $C_{26}H_{42}NO$ (MH^+) 384.3266, found 384.3277.

(±)-Lepadiformine (6). To a solution of the above alkylation product **35** (18 mg, 0.0470 mmol) in THF (2 mL) and NH_3 (10 mL) at −78 °C was added sodium metal (∼5 mg). The color of the reaction solution changed to dark blue. The reaction mixture was stirred at −78 °C for 1 h and quenched with NH_4Cl (solid). The mixture was slowly warmed to room temperature with occasional replacement of the evaporating NH_3 with THF. The resulting solution was made basic with 1 N aqueous NaOH and extracted with CH_2Cl_2. The organic extracts were dried with K_2CO_3 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (100:5:1.5 $CHCl_3$/MeOH/concd NH_4OH) to give (±)-lepadiformine free base (**6**, 14 mg, 100%) as a colorless oil: IR (film) 3412, 2931, 2857 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.37−3.30 (m, 2H), 3.19 (d, J = 8.1 Hz, 1H), 3.13−3.10 (m, 1H), 1.78−1.13 (m, 27H), 1.04−0.97 (m, 1H), 0.85 (t, J = 6.6 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 67.4, 62.4, 58.4, 53.3, 40.2, 38.3, 34.1, 31.8, 30.5, 29.6, 28.2, 27.7, 27.6, 26.3, 24.3, 23.3, 22.7, 22.6, 14.0; HRMS (ESI+) calcd for $C_{19}H_{36}NO$ (MH^+) 294.2797, found 294.2789.

The above oil was dissolved in 2 mL of MeOH containing 1% 1 N aqueous HCl, and the solution was evaporated in vacuo to give the hydrochloride salt of (±)-lepadiformine as a white solid: ^1H NMR (360 MHz, $CDCl_3$) δ 10.14 (br s, 1H), 5.23 (br s, 1H), 4.17 (d, J = 13.5 Hz, 1H), 3.61−3.70 (m, 3H), 2.49 (m, 1H), 2.38 (m, 1H), 2.16 (m, 2H), 2.02−2.08 (m, 2H), 1.90−1.97 (m, 2H), 1.65−1.82 (m, 5H), 1.24−1.55 (m, 13H), 0.98−1.08 (m, 1H), 0.86 (t, J = 6.6 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 77.2, 63.5, 59.9, 58.7, 36.2, 33.7, 31.6, 30.8, 29.9, 29.0, 26.5, 26.4, 24.9, 24.3, 23.2, 22.6, 22.4, 19.2, 14.0; HRMS (ESI+) calcd for $C_{19}H_{36}NO$ ($M - Cl^+$) 294.2797, found 294.2789.

(5-Hexyldecahydropyrrolo[2,1-j]quinolin-3-yl)-methanol (36). To a solution of the alkylation product **33** (11 mg, 0.0287 mmol) in THF (2 mL) and NH_3 (10 mL) at −78 °C was added sodium metal (∼5 mg). The color of the reaction solution changed to dark blue. The mixture was stirred at −78 °C for 1 h, and the reaction was quenched with NH_4Cl (solid). The mixture was slowly warmed to room temperature with occasional replacement of the evaporating NH_3 with THF. The resulting solution was made basic with 1 N aqueous NaOH and extracted with CH_2Cl_2. The organic extracts were dried with K_2CO_3 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (100:5:1.5 $CHCl_3$/MeOH/conc NH_4OH) to give **36** (7 mg, 83%) as a colorless oil: IR (film) 3402, 2926, 2857 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.50 (dd, J = 5.8, 10.3 Hz, 1H), 3.32−3.28 (m, 1H), 3.11−3.08 (m, 1H), 2.20−2.19 (m, 1H), 1.93−1.88 (m, 2H), 1.71−1.10 (m, 26H), 0.85 (t, J = 6.6 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 66.7, 66.3, 64.9, 60.4, 41.8, 39.4, 38.0, 31.9, 31.2, 29.5, 27.7, 27.0, 26.3, 25.9, 25.85, 24.4, 23.9, 22.6, 14.1; HRMS (ESI+) calcd for $C_{19}H_{36}NO$ (MH^+) 294.2797, found 294.2818.

(5*S*)-5-[(Dimethylphenylsilanyl)-methyl]-pyrrolidin-2-one (38). To a stirred mixture of lithium shot (4.345 g, 626 mmol) in THF (100 mL) under argon at 0 °C was added dropwise a solution of dimethylphenylsilyl chloride (17.53 mL, 104 mmol) in 25 mL of dry THF, and the mixture was warmed to room temperature. After stirring for 16 h, the red solution was added to a suspension of CuCN (4.675 g, 52 mmol) in 500 mL of dry THF under argon at 0 °C and the mixture was stirred for 30 min. A solution of bromide **37**[30] (2.891 g, 16.2 mmol) in 40 mL of dry THF was added to the mixture at −40 °C over 2 h, and then the mixture was stored in a freezer (−20 °C) overnight (about 19 h). To the solution was added 30 mL of saturated NH_4Cl. The mixture was stirred for 1 h and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography on silica gel (gradient from 2:1 EtOAc/hexanes to 5:1 EtOAc/MeOH) to provide **38** as a colorless oil (3.503 g, 92%): $[\alpha]^{20.0}_D$ −22.3 (*c* 1, EtOH); IR (film) 3222, 3069, 2954, 1694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49−7.47 (m, 2H), 7.46−7.34 (m, 3H), 6.17 (br s, 1H), 3.72 (tt, J = 7.0, 7.1 Hz, 1H), 2.26−2.20 (m, 2H), 1.58−1.51 (m, 1H), 1.20 (dd, J = 5.7, 14.4 Hz, 1H), 1.02 (dd, J = 8.6, 14.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 137.9, 133.4, 129.4, 128.0, 52.0, 30.8, 30.5, 24.9, −2.4, −2.5; HRMS (APCI+) calcd for $C_{13}H_{19}NOSi$ (MH^+) 234.1314, found 234.1314.

(2*S*)-2-[(Dimethylphenylsilanyl)-methyl]-5-oxopyrrolidine-1-carboxylic Acid Benzyl Ester (39). Potassium hydride in mineral oil (35%, 4.008 g, 34.98 mmol) was prewashed with dry hexane and dried under high vacuum. THF (20 mL) was added, followed by lactam **38** (3.407 g, 14.60 mmol) in 50 mL of THF by cannula at 0 °C. The mixture was stirred at 0 °C for 5 min and room temperature for 50 min. The solution was then recooled to 0 °C and benzyl chloroformate (3.287 mL, 21.90 mmol) was added. The reaction mixture was stirred at room temperature for 4 h and diluted with CH_2Cl_2. The mixture was washed with saturated sodium bicarbonate and water, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography on silica gel (25−50% EtOAc/hexanes) to provide the *N*-Cbz lactam **39** (5.130 g, 96%) as a pale yellow oil: $[\alpha]^{20.0}_D$ −33.9 (*c* 1, EtOH); IR (film) 2955, 1788, 1748, 1714 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.48−7.36 (m, 10H), 5.31 (d, J = 12.2 Hz, 1H), 5.22 (d, J = 12.3 Hz, 1H), 4.30 (ddt, J = 11.8, 8.2, 2.2 Hz, 1H), 2.55 (ddd, J = 17.8, 10.5, 9.1 Hz, 1H), 2.37 (ddd, J = 17.8, 9.3, 3.2 Hz, 1H), 2.05−1.94 (m, 1H), 1.54−1.50 (m, 2H), 1.09 (dd, J = 11.9, 14.1 Hz, 1H), 0.32 (s, 3H), 0.317 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.8, 151.1, 137.7, 135.3, 129.3, 128.5, 128.4, 128.3, 128.0, 67.8, 56.1, 31.1, 24.8, 22.1, −2.5, −2.7; HRMS (APCI+) calcd for $C_{21}H_{25}NO_3Si$ (MH^+) 368.1682, found 368.1704.

(2*Z*)-(7-Iodohept-2-enyl)-trimethylsilane (40). To a solution of triphenylphosphine (5.629 g, 21.46 mmol) in CH_2Cl_2 were added imidazole (2.922 g, 42.93 mmol) and iodine (5.462 g, 21.46 mmol) at 0 °C. After stirring the mixture for 30 min, 7-trimethylsilanylhept-5-en-1-ol [31](2.000 g) in CH_2Cl_2 (10 mL) was added dropwise. The resulting mixture was warmed to room temperature and stirred for 1.5 h. Brine was added, and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexanes) to provide iodide **40** (2.694 g, 85%) as a colorless oil: IR (film) 3005, 2953, 16545 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.42−5.35 (m, 1H), 5.26−5.20 (m, 1H), 3.17 (t, J = 7.1 Hz, 2H), 1.99 (q, J = 7.0 Hz, 2H), 1.83 (p, J = Hz 2H), 1.48−1.38 (m, 4H), −0.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 126.6, 126.1, 33.2, 30.5, 25.9, 18.5, 7.1, −1.8; HRMS (ESI+) calcd for $C_{10}H_{21}ISi$ (MH^+) 297.0536, found 297.0560.

(2*S*,5*S*)-2-[(Dimethylphenylsilanyl)-methyl]-6-vinyl-1-azaspiro[4.5]decane-1-carboxylic Acid Benzyl Ester (43). To a stirred solution of iodide **40** (2.10 g, 7.07 mmol) in 11 mL of Et_2O at −78 °C was added dropwise 1.7 M *t*-BuLi in pentane (8.53 mL, 14.5 mmol). The reaction mixture was kept at −78 °C for 40 min and slowly warmed to room temperature over 30 min. The solution was kept at room temperature for 0.5 h, cooled to −78 °C, and transferred by cannula to a solution of Cbz lactam **39** (1.30 mg, 3.54 mmol) in 8 mL of THF at −78 °C. The mixture was slowly warmed to −20 °C over 4 h, and the reaction was quenched by a solution of saturated $NaHCO_3$. The aqueous layer was extracted with Et_2O; the combined organic layers were dried over Na_2SO_4 and concentrated, and the residue was dried in vacuo.

The residue was diluted with dry CH_2Cl_2 (65 mL) and then cooled to −78 °C. Flame-dried 4 Å molecular sieves (~6 g) were added followed by BF_3·2AcOH (983 μL, 7.08 mmol). The mixture was kept at −78 °C for 1 h and warmed to room temperature overnight. The reaction mixture was diluted with saturated sodium bicarbonate solution and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography on silica gel (10−25% EtOAc/hexanes) to provide spirocycle **43** as a pale yellow oil (828 mg, 52%) (4:1 mixture of rotamers): $[\alpha]^{20.0}_D$ −13.0 (*c* 1, EtOH); IR (film) 2930, 2857, 1746, 1694 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.21−7.05 (m, 10H), 5.40 (ddd, *J* = 17.3, 7.5, 7.2 Hz, 1H), 5.05−4.82 (m, 2H), 4.67−4.62 (m, 2H), 4.05 (m, 0.2H), 3.90 (dd, *J* = 7.9, 10.9 Hz, 0.8H), 3.10 (m, 0.8H), 2.75 (m, 0.2H), 2.50 (dt, *J* = 3.5, 13.2 Hz, 0.8H), 2.15 (m, 0.2H), 1.78 (m, 1H), 1.50−1.03 (m, 11H), 0.74 (dd, *J* = 11.9, 14.1 Hz, 1H), 0.13 (s, 0.6H), 0.11 (s, 0.6H), 0.0 (s, 2.4H), −0.02 (s, 2.4H); ^{13}C NMR (75 MHz, d_8-toluene) δ 152.8, 140.6, 140.2, 139.8, 139.1, 139.0, 138.1, 137.7, 137.4, 134.0, 133.8, 114.8, 114.7, 68.0, 67.3, 66.5, 66.0, 58.0, 56.7, 45.2, 43.3, 40.2, 39.0, 32.2, 31.2, 30.5, 30.2, 30.1, 29.4, 25.7, 25.5, 24.8, 24.5, −2.4, −2.6. ^1H NMR (70 °C, 300 MHz, d_8-toluene) δ 7.17−6.97 (m, 10H), 5.57 (ddd, *J* = 17.5, 7.3, 7.1 Hz, 1H), 5.07−4.42 (m, 4H), 4.26 (br s, 1H), 3.65 (br s, 1H), 2.90 (br s, 1H), 1.65−0.85 (m, 12H), 0.21 (br s, 6H); HRMS (APCI+) calcd for $C_{28}H_{37}NO_2Si$ (MH^+) 448.2672, found 448.2672.

2-Hydroxymethyl-6-vinyl-1-azaspiro[4.5]decane-1-carboxylic Acid Benzyl Ester (44a). To a solution of the above silane **43** (116 mg, 0.259 mmol) in CH_2Cl_2 (5 mL) was added BF_3·2AcOH (108 μL, 0.777 mmol) at room temperature. After 15 min, the mixture was diluted with saturated aqueous $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to give the fluorosilane.

To a solution of the above fluorosilane in a mixture of MeOH (5 mL) and THF (5 mL) was added $NaHCO_3$ (109 mg, 1.30 mmol) at room temperature. After 15 min, H_2O_2 (35 wt % solution in water, 275 μL) was added to the reaction mixture. After being refluxed overnight, the mixture was diluted with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (4:1 EtOAc/hexanes) to afford alcohol **44a** as a colorless oil (76 mg, 89%) (1:1 mixture of rotamers): $[\alpha]^{20.0}_D$ −31.9 (*c* 1, EtOH); IR (film) 3401, 2928, 2858, 1682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.26 (m, 5H), 5.71−5.58 (m, 1H), 5.19−5.02 (m, 2H), 4.96−4.77 (m, 2H), 4.14−4.00 (m, 1H), 3.67−3.54 (m, 1.5H), 3.47−3.41 (dd, *J* = 7.3, 10.4 Hz, 0.5H), 3.20 (m, 0.5H), 3.06−3.03 (m, 0.5H), 2.61−2.52 (m, 0.5H), 2.33−2.25 (m, 0.5H), 2.12−2.00 (m, 1H), 1.91−1.09 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 153.3, 139.5, 138.9, 136.9, 136.1, 128.4, 128.3, 128.0, 127.7, 127.6, 115.4, 115.0, 69.0, 68.8, 67.2, 66.8, 66.0, 64.3, 62.9, 60.8, 44.8, 43.0, 38.2, 37.8, 31.4, 31.1, 29.2, 29.0, 26.1, 25.1, 24.9, 23.9; HRMS (APCI+) calcd for $C_{20}H_{27}NO_3$ (MH^+) 330.2069, found 330.2071.

(6-Vinyl-1-azaspiro[4.5]dec-2-yl)-methanol (44b). To a solution of the above alcohol **44a** (3 mg, 0.009 mmol) in THF (2 mL), *t*-BuOH (0.5 mL), and NH_3 (~8 mL) at −78 °C was added sodium metal (~5 mg). The color of the reaction solution slowly changed to dark blue. The reaction mixture was stirred at −78 °C for 10 min; the reaction was quenched with saturated aqueous NH_4Cl, and the mixture was slowly warmed to room temperature. The mixture was basified with 1 N aqueous NaOH and extracted with CH_2Cl_2. The organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (100:5:1 CH_2Cl_2/MeOH/concentrated NH_4OH) to give the amino alcohol **44b** (2 mg, 100%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 5.85−5.76 (m, 1H), 5.10−5.05 (m, 2H), 3.46 (dd, *J* = 4.0, 10.0 Hz, 1H), 3.34−3.28 (m, 1H), 3.24 (dd, *J* = 6.0, 10.0 Hz, 1H), 2.43 (br s, 2H), 2.02−1.98 (m, 1H), 1.75−1.54 (m, 8H), 1.31−1.27 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 116.4, 64.5, 64.3, 59.0, 51.7, 41.3, 30.5, 30.1, 28.0, 24.8, 24.3.

6-(3,3-Dimethoxypropyl)-2-hydroxymethyl-1-azaspiro-[4.5]decane-1-carboxylic Acid Benzyl Ester (45). To a solution of olefin **44a** (419 mg, 1.27 mmol) in THF (6 mL) were added $Rh(CO)_2$(acac) (20 mg, 0.076 mmol) and $P(OPh)_3$ (100 μL, 0.38 mmol) under argon. The round-bottomed flask was subsequently placed in a stainless steel autoclave. The reaction was carried out at 60 °C and 4 atm (initial pressure at 20 °C) of CO and H_2 (1:1) for 6 h with stirring. After the autoclave was cooled to room temperature, the gases were released and the reaction mixture was concentrated under reduced pressure.

To a solution of the above crude aldehyde in dry MeOH (6 mL) was added trimethyl orthoformate (696 μL, 6.36 mmol) and HCl/MeOH (1 N, 254 μL) at room temperature. After 50 min, the mixture was diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (30−50% EtOAc/hexanes) to afford acetal **45** as a colorless oil (466 mg, 90%) (1:1 mixture of rotamers): $[\alpha]^{20.0}_D$ −45.1 (*c* 1, EtOH); IR (film) 3418, 2930, 1682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.26 (m, 5H), 5.17 (ABq, *J* = 12.3, 25.5 Hz, 1H), 5.09 (ABq, *J* = 12.3, 25.5 Hz, 1H), 4.26 (t, *J* = 5.6 Hz, 0.5H), 4.20 (m, 0.5H), 4.10 (m, 0.5H), 3.94 (m, 0.5H), 3.64 (m, 1.5H), 3.47 (m, 0.5H), 3.25 (s, 1.5H), 3.24 (s, 1.5H), 3.22 (s, 1.5H), 3.21(s, 1.5H), 2.51−2.49 (m, 1H), 2.24−2.17 (m, 1H), 2.04−0.84 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 153.1, 137.0, 136.3, 128.5, 128.0, 127.8, 127.78, 104.4, 104.36, 69.7, 69.2, 67.3, 67.2, 66.1, 64.5, 63.2, 60.9, 52.6, 52.4, 52.1, 41.7, 39.5, 38.4, 38.2, 31.0, 30.8, 30.4, 30.2, 29.2, 26.1, 25.7, 25.6, 25.0, 24.8, 24.1, 24.0; HRMS (ESI+) calcd for $C_{23}H_{36}NO_5$ (MH^+) 406.2593, found 406.25933.

[6-(3,3-Dimethoxypropyl)-1-azaspiro[4.5]dec-2-yl]-methanol (46). To a solution of the above alcohol **45** (40 mg, 0.099 mmol) in THF (2 mL), *t*-BuOH (0.2 mL), and NH_3 (~8 mL) at −78 °C was added sodium metal (~10 mg). The color of the reaction solution slowly changed to dark blue. The reaction mixture was stirred at −78 °C for 10 min, and the reaction was quenched with saturated aqueous NH_4Cl. The mixture was slowly warmed to room temperature, made basic with 1 N aqueous NaOH, and extracted with CH_2Cl_2. The organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (100:5:1 $CHCl_3$/MeOH/concentrated NH_4OH) to give the amino alcohol **46** (25 mg, 94%) as a colorless oil, having spectral data identical to those of the racemic compound **26**: $[\alpha]^{20.0}_D$ −42.2 (*c* 1, EtOH).

Enantiomers **27**, **35**, and **6** and the HCl salt of **6** were prepared as described for the racemic compounds and had spectral data identical to those of corresponding racemates. **27**: $[\alpha]^{20.0}_D$ −30.7 (*c* 1, EtOH). **35**: $[\alpha]^{20.0}_D$ −22.3 (*c* 0.61, MeOH). **6** free base: $[\alpha]^{20.0}_D$ −14.0 (*c* 0.45, MeOH). **6** HCl salt: $[\alpha]^{20.0}_D$ +2.5 (*c* 0.51, $CHCl_3$).

Acknowledgment. We are grateful to the National Institutes of Health (CA-34303) for financial support of this research.

Supporting Information Available: Copies of NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0201070