JOC*Article*

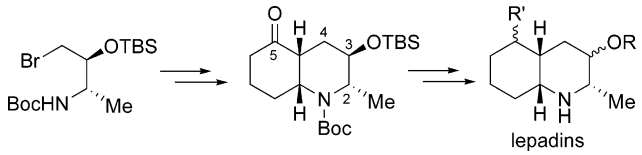
Facile Entry to Substituted Decahydroquinoline Alkaloids. Total Synthesis of Lepadins A−E and H

Xiaotao Pu and Dawei Ma*

State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

madw@mail.sioc.ac.cn

Received May 25, 2006



Condensation of a L-alanine derived δ-bromo-β-silyloxy-propylamine with 1,3-cyclohexadione followed by alkylative cyclization produces a bicyclic enone. Diastereoselective Pt/C-catalyzed hydrogenation of this enone in HOAc provides a 5-oxo-*cis*-fused decahydroquinoline. Wittig olefination of this decahydroquinoline and subsequent epimerization of the resulting 5-formyl intermediate gives rise to a 5-β-formyl decahydroquinoline exclusively. In a parallel procedure, Peterson reaction of this decahydroquinoline and subsequent hydrogenation of the generated 5-exo-olefin provides a decahydroquinoline with a 5-α-substituent predominantly. For these two diastereoselective processes, using the intermediates without *N*-protection as the substrates is essential because the corresponding *N*-Boc intermediates give poor diastereoselectivity. The intermediate with β-form side chain is further converted into lepadins A−C via carbon chain elongation, while the intermediate with α-form side chain is transformed into lepadins D, E, and H and corresponding 5′-epimers via connection with two sulfones generated from two Sharpless epoxidation products. By comparison of the rotations and NMR data, the stereochemistry of lepadins D, E, and H is assigned as 2*S*,3*R*,4a*S*,5*S*,8a*R*,5′*R*.

Introduction

Lepadins belong to an increasing alkaloid family with over 60 members that contain a decahydroquinoline moiety with either cis or trans configuration. The first member of this family named pumiliotoxin C, was isolated from skin extracts of the Panamanian poison-frog *Dendrobates pumilio* in 1969.[1] Since then about 50 2,5-disubstituted decahydroquinolines have been isolated from similar species.[2] Their interesting structures and biological activities have attracted numerous synthetic efforts during the past decades.[3] In 1991, Steffan reported the discovery of lepadin A (**1a**) (Figure 1), a 2,3,5-trisubstituted decahydroquinoline, from the tunicate *Clavelina lepadiformis* in the North Sea.[4] Four years later, from the same species and other sources, lepadins B (**1b**) and C (**1c**) were isolated.[5] These compounds have been found to possess significant in vitro cytotoxicity against several human cancer cell lines.[5] Recently, two groups independently discovered the other members of lepadin family. Lepadins D−F were isolated by Wright and co-workers from a new *Didemnum* species collected from the Great Barrier Reef,[6] while lepadins F−H were found by Carroll and co-workers from *Aplidium tabascum* Kott.[7] The major structural difference of these new members with lepadins A−C is the substituents and their stereochemistry at the 5-position. These disparities could influence their biological activities, as preliminary biological studies revealed that lepadins D−F had low cytotoxicity but significant and selective antiplasmodinium and antitrypanosomal

(1) Daly, J. W.; Tokuyama, T.; Habermehl, G.; Karle, I. L.; Witkop, B. *Liebigs Ann. Chem.* **1969**, *729*, 198.
(2) For a review, see Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556.
(3) For selected examples, see the following: (a) Sklenicka, H. M,; Hsung, R. P.; McLaughlin, M. J.; Wei, L.; Gerasyuto, A. I.; Brennessel, W. B. *J. Am. Chem. Soc.* **2002**, *124*, 10435. (b) Weymann, M.; Schultz-Kukula, M.; Kunz, H. *Tetrahedron Lett.* **1998**, *39*, 7835. (c) Naruse, M.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1994**, *35*, 9213.
(4) Steffan, B. *Tetrahedron* **1991**, *47*, 8729.
(5) Kubanek, J.; Williams, D. E.; de Silva, E. D.; Allen, T.; Anderson, R. J. *Tetrahedron Lett.* **1995**, *36*, 6189.
(6) Wright, A. D.; Goclik, E.; König, G. M.; Kaminsky, R. *J. Med. Chem.* **2002**, *45*, 3067.
(7) Davis, R. A.; Carroll, A. R.; Quinn, R. J. *J. Nat. Prod.* **2002**, *65*, 454.

10.1021/jo061070c CCC: $33.50
Published on Web 07/20/2006

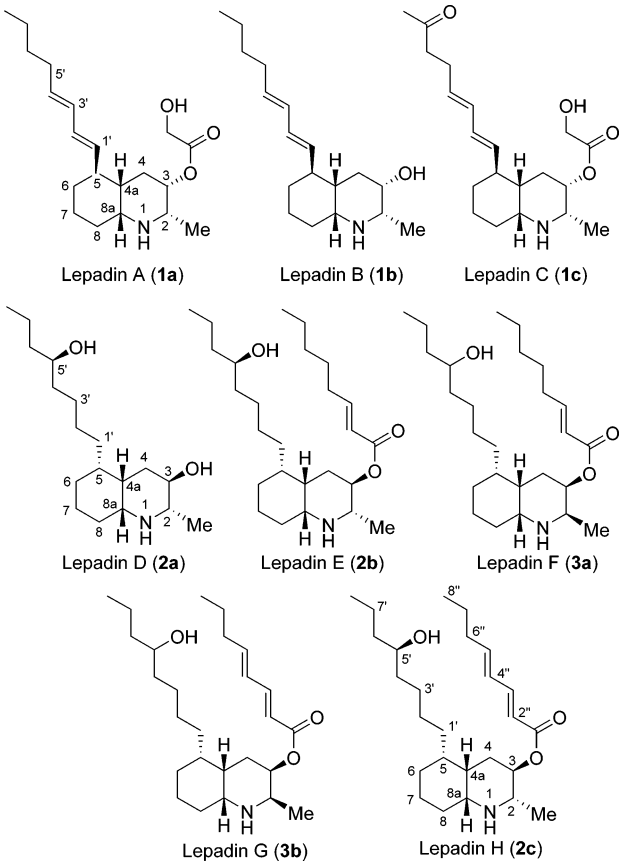


FIGURE 1. Structures of lepadins A−H.

activity.[6] These findings suggested that these compounds might serve as new lead structures for the development of novel antimalarial drugs. In addition, a recent report revealed that lepadin B could block neuronal nicotinic acetylcholine receptors with IC_{50} values of 0.7−0.9 μM.[8] However, further pharmacological research on these alkaloids is hampered by lack of materials. Consequently a facile route to these alkaloids or their analogues is highly required.

Prior to our synthetic studies,[9] three groups had disclosed their efforts toward the assembly of lepadins A−C. The first total synthesis of lepadin B was achieved by Toyooka group,[10] in which an intramolecular aldol type of cyclization of the piperidine derivative **4** was used as the key step (Figure 2). On the basis of stereocontrolled intramolecular acylnitroso-Diels−Alder reaction of **6**, Kibayashi and co-workers developed another protocol to lepadin B and elaborated lepadins A and C first.[11] The common feature of these two routes is using intramolecular aldol reaction (from **4** or **5**) to build the left cyclohexane ring, which required lengthy reaction sequences and therefore greatly reduced the synthetic efficiency. In 2002, Zard described a short formal route to racemic lepadin B,[12] but many more steps would obviously be necessary if applied to enantioselective synthesis. Quite recently, Bonjoch and Mena

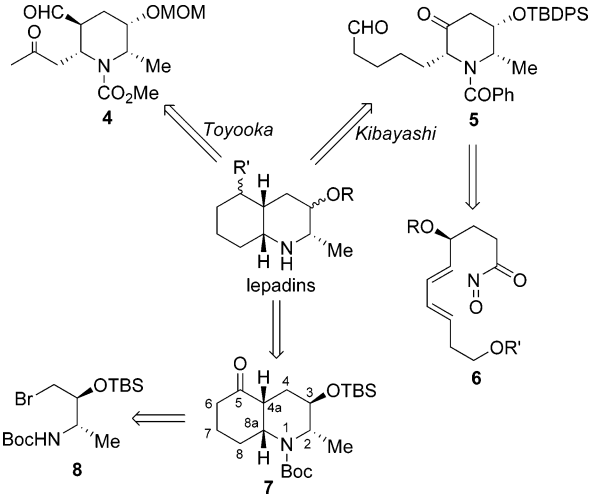
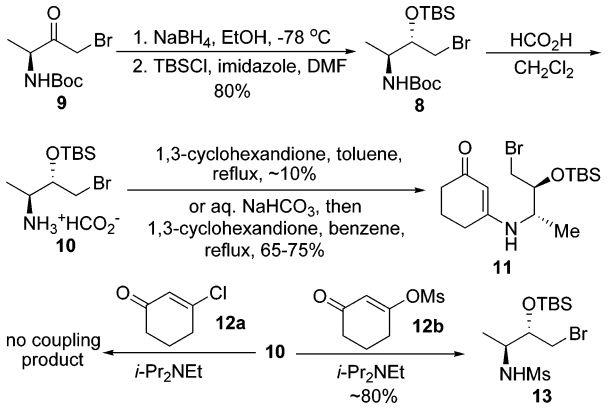


FIGURE 2. Retrosynthetic analysis of lepadins.

SCHEME 1



demonstrated their attempts[13] to lepadins by aminocyclization of 2-(3-aminoalkyl)cyclohexenones. Herein we wish to describe that most of the lepadins could be assembled through intermediate **7** via stereoselective introduction of both α- and β-form side chains into its C5 position. The preparation of the ketone **7** could be accomplished by condensation of an amine liberated from bromide **8** with 1,3-cyclohexadione and subsequent alkylative cyclization. Together with the total syntheses of lepadins D, E and H, their stereochemistry was fully established.

Results and Discussion

As outlined in Scheme 1, our synthesis started from ketone **9**, a known intermediate prepared from L-alanine.[14] Reduction of **9** with $NaBH_4$ in ethanol at −78 °C followed by protection of the resultant alcohol with TBSCl afforded the bromide **8** in 80% yield. Removal of Boc-protecting group in **8** with formic acid produced amine **10** as a formic acid salt. Initially, condensation of this salt with 1,3-cyclohexadione was attempted. However, this reaction only worked in refluxed toluene, giving the desired product **11** in about 10% yield. After some experimentation, we found that reaction of a free amine generated from **10** with 1,3-cyclohexandione proceeded well to afford **11** in 65−75% yields. Noteworthy is that attempts to

(8) Tsuneki, H.; You, Y.; Toyooka, N.; Sasaoka, T.; Nemoto, H.; Dani, J. A.; Kimura, I. *Biol. Pharm. Bull.* **2005**, *28*, 611.

(9) Part of the result has been reported as a communication, see Pu, X.; Ma, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4222.

(10) (a) Toyooka, N.; Okumura, M.; Takahatam, H. *J. Org. Chem.* **1999**, *64*, 2182. (b) Toyooka, N.; Okumura, M.; Takahatam, H.; Nemoto, H. *Tetrahedron* **1999**, *55*, 10673.

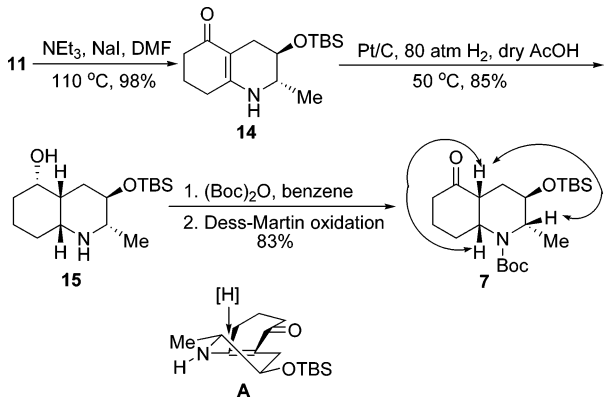
(11) (a) Ozawa, T.; Aoyagi, S.; Kobayashi, C. *Org. Lett.* **2000**, *2*, 2955. (b) Ozawa, T.; Aoyagi, S.; Kobayashi, C. *J. Org. Chem.* **2001**, *66*, 3338.

(12) Kalai, C.; Tate, E.; Zard, S. Z. *Chem. Commun.* **2002**, 1430.

(13) Mena, M.; Bonjoch, J. *Tetrahedron* **2005**, *61*, 8264.

(14) Rotella, P. D. *Tetrahedron Lett.* **1995**, *36*, 5453.

SCHEME 2

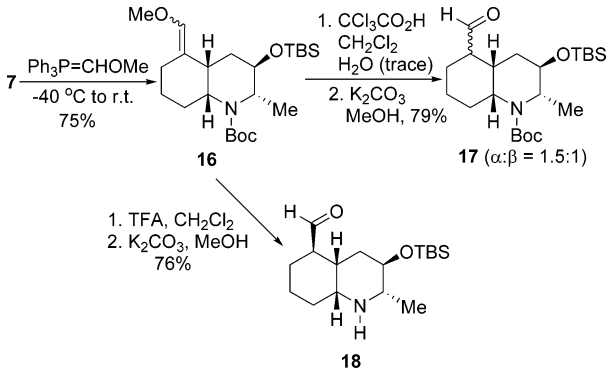


obtain **11** via reacting **10** with vinyl chloride **12a** or vinyl mesylate **12b** failed because of no reaction or isolation of sulfonamide **13**.[15]

Alkylative cyclization of **13** was accomplished at 110 °C in DMF under the action of triethylamine and sodium iodide to produce enone **14** in 98% yield (Scheme 2). Adding sodium iodide to this reaction system was important for excellent yield, as only 67% yield was observed in the absence of sodium iodide. The next planned step was diastereoselective hydrogenation of the C−C double bond of **14**. On the basis of our previous observation[16] we envisaged that a stereoelectronic controlled axial addition of hydrogen would occur from the *Re* face of the more stable conformation **A**, thereby giving the desired C-4a and C-8a stereochemistry for synthesizing lepadins A−E and H. This step was challenging as evidenced from that no reaction occurred using PtO_2, Rh/C, and Rh/Al_2O_3 as the catalysts, and only 23% conversion was obtained in the presence of Pt/Al_2O_3. Fortunately, when this reaction was conducted under the catalysis of Pt/C in dry acetic acid at 80 atm and 50 °C, hydrogenated product **15** was isolated in 85% yield as a single isomer. Next, protection of **15** with $(Boc)_2O$ and subsequent Dess−Martin oxidation provided the designed intermediate **7**. After NOESY studies of **7**, we were gratified to notice that it has an expected (4a*R*,8a*R*)-configuration.

With the ketone **7** in hand, we next tried to install suitable *β*-form side chains at its C-5, which were required for assembling lepadins A−C (Scheme 3). Accordingly, olefination of **7** via a Wittig reaction provided enol ether **16**, which was selectively hydrolyzed with trichloroacetic acid in methylene chloride containing trace water to give aldehyde **17**.[17] By ^1H NMR determination it was found that there existed inseparable diastereomers in a ratio of 1:1.3. Treatment of this mixture with K_2CO_3 in methanol did not give an enhanced ratio (1:1.5), which indicated that two isomers might have similar stability by taking the conformations **B** and **C** respectively (Figure 3). At this stage we considered to remove the *N*-Boc group in **17** to get aldehyde **18**. On the basis of Booth's studies,[18] we realized that the favored conformations would be **D** and **E** for **18** and its 5-epimer. The stronger 1,5-strain displayed in **E** would make conformer **D** more stable, thereby affording *β*-form aldehyde

SCHEME 3



18 exclusively. As we expected, after cleavage of the Boc group in **17** with TFA selectively, and subsequent treatment with K_2CO_3 in methanol, aldehyde **18** was isolated as a single isomer.

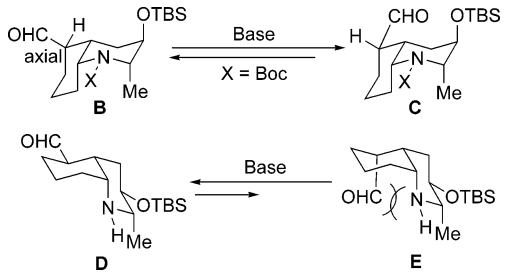


FIGURE 3. Conformation analysis of aldehydes **17** and **18**.

The assembly of lepadins A and B was depicted in Scheme 4. Initially, extension of the C-1′ to C-8′ from the aldehyde **18** was attempted by employing the Kocienski−Julia coupling reaction.[19] Although there have appeared several reports that (*E*,*E*)-dienes were exclusively obtained when allyl substituted PT-sulfones were used,[20] we found that reaction of PT-sulfone **19** with the aldehyde **18** gave only (*E*,*Z*)-diene **20** in 90% yield. The reason for this stereoselectivity is unclear yet. At this stage we moved our attention to the Emmons−Wadsworth−Honer reaction.[21] To our delight, coupling of **18** with an anion generated from phosphonate **21** produced the desired *E*,*E*-diene **22** in greater than 95% selectivity. The remaining task now for finishing the synthesis was inversion of the C-3 stereocenter. We decided to perform it via an oxidation/reduction strategy. As a result, protection of **22** with $(Boc)_2O$, cleavage of the silyl ether with TBAF, and subsequent Dess−Martin oxidation yielded ketone **23**. Reduction of **23** with $NaBH_4$ gave the corresponding alcohol as a single diastereomer, which was treated with TFA to furnish lepadin B as its TFA salt. In a parallel procedure, the alcohol that resulted from **23** was esterified with TBS-protected 2-hydroxyacetic acid to furnish lepadin A, after deprotection with boron trifluoride diethyl etherate.

(15) (a) Kowalski, C. J.; Fields, K. W. *J. Org. Chem.* **1981**, *46*, 197. (b) Clark, R. D.; Heathcock, C. H. *Synthesis* **1974**, 47.

(16) Pu, X.; Ma, D. *J. Org. Chem.* **2003**, *68*, 4400.

(17) Harrington, P. E.; Stergiades, I. A.; Erickson, J.; Makriyannis, A.; Tius, M. A. *J. Org. Chem.* **2000**, *65*, 6576.

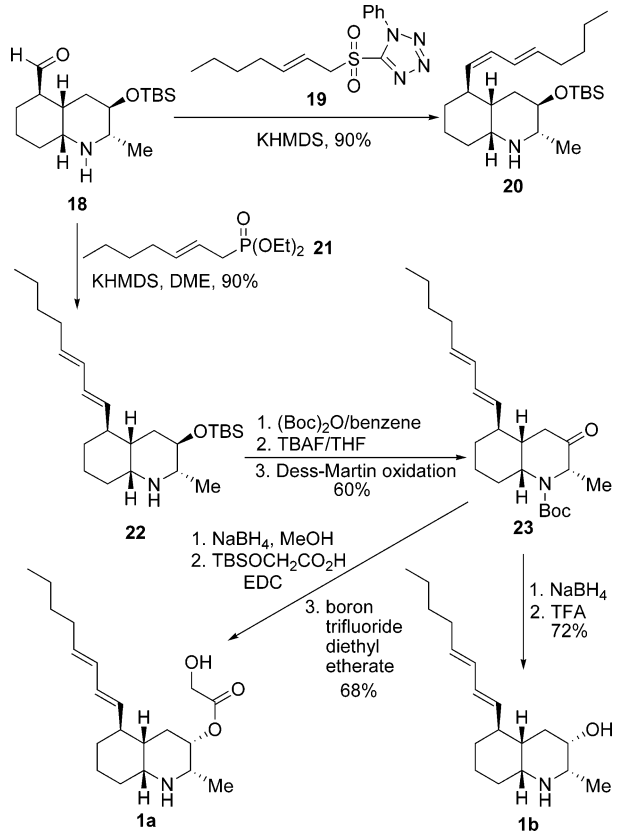
(18) (a) Booth, H.; Bostock, A. H. *J. Chem. Soc., Perkin Trans. 2* **1972**, 615. (b) Booth, H.; Griffiths, D. V. *J. Chem. Soc., Perkin Trans. 2* **1975**, 111.

(19) For a review, see Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563.

(20) (a) Williams, D. R.; Cortez, G. S.; Bogen, S. L.; Rojas, C. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4612. (b) Shimizu, T.; Masuda, T.; Hiramoto, K.; Nakata, T. *Org. Lett.* **2000**, *2*, 2153. (c) Takano, D.; Nagamitsu, T.; Ui, H.; Shiomi, K.; Yamaguchi, Y.; Masuma, R.; Kuwajima, I.; Omura, S. *Org. Lett.* **2001**, *3*, 2289.

(21) For recent examples, see (a) Trost, B. M.; Gunzner, J. L.; Dirat, O.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 10396. (b) Boeckman, R. K., Jr.; Weinder, C. H.; Perni, R. B.; Napier, J. J. *J. Am. Chem. Soc.* **1989**, *111*, 8036.

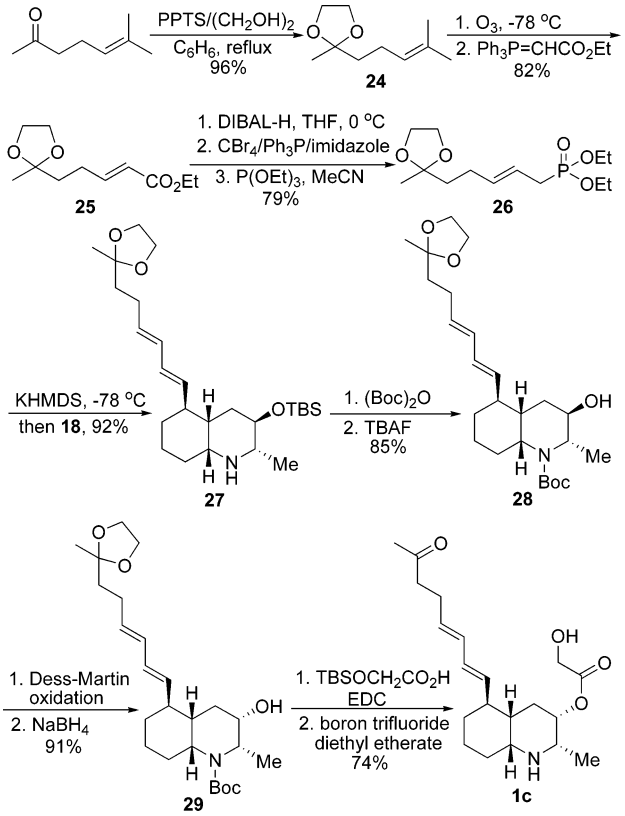
SCHEME 4



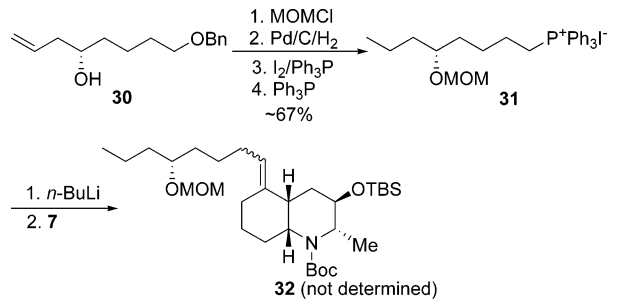
For synthesis of lepadin C, a phosphonate with a functional group at its C-6′ position should be prepared. As shown in Scheme 5, commercial available 6-methyl-5-hepten-2-one was selected for this purpose. After protection of this ketone with 1,2-ethanediol to afford **24**, ozonolysis of the C−C double bond was conducted to give an aldehyde, which was subjected to Wittig olefination to deliver ester **25**. Reduction of **25** with DIBAL-H and subsequent bromination with CBr_4/PPh_3 provided an allyl bromide, which was reacted with triethyl phosphite to give the desired phosphonate **26**. Next, treatment of **26** with KHMDS followed by trapping the resultant anion with the aldehyde **18** produced diene **27** in 92% yield. Protection of **27** with $(Boc)_2O$ and then cleavage of the silyl ether provided alcohol **28**. Finally, inversion of the C-3 stereochemistry via oxidation/reduction afforded alcohol **29** in 90% yield, which was connected with TBS-protected 2-hydroxyacetic acid, and then treated with boron trifluoride diethyl etherate, to furnish lepadin C in 74% yield.

After success in elaboration of lepadins A−C, we next explored synthesizing lepadins D, E, and H from the intermediate **7**. The first task for us was to introduce the α-form side chain into C-5 of the ketone **7**. We planned to reach this goal via a stereoselective hydrogenation of an exo-alkene derived from **7**. Obviously, Wittig olefination of **7** with **31**, a phosphonium salt prepared from homoallyl alcohol **30** in four steps, was quite attractive because it would give the desired molecules in a very convergent manner. As a result, reaction of **31** with **7** mediated with *n*-BuLi was conducted. However, no olefination products were isolated under various reaction conditions (Scheme 6). Considering that the enol ether **16** had been obtained via a similar Wittig reaction, we thought that the ylide generated from **31** might be too hindered to attack the ketone **7**, and therefore

SCHEME 5



SCHEME 6



other olefination methods were attempted. To our delight, when the Peterson reaction[22] was employed, the desired olefin **33** was isolated as a mixture of *E*- and *Z*-isomers in 98% yield (Scheme 7). Direct Pt/C-catalyzed hydrogenation of **33** in dry acetic acid gave a diastereomer mixture **34** in a ratio of 3:1. Switch of the catalyst to Pd/C, Rh/C, and Raney-Ni or changing solvents could not enhance the ratio greatly. However, we were pleased to observe that hydrogenation of **35**, a derivative of **33** without the *N*-Boc group, produced **36** in a highly diastereoselective manner (>95% de). By X-ray crystal studies of **37**, a tosylation product of **17**, we confirmed that the side chain at C-5 was in the α-form.

The above two stereochemical courses might be rationalized as that different steric hindrances, met by hydride, attack in two favored conformations **F** and **G** as depicted in Figure 4. When X was Boc, the preferred conformer might be **F** because there existed larger steric interaction between the Boc group and two equatorial groups at the 2 and 8a positions in conformer

(22) Shimoji, K.; Taguchi, H.; Oshima, K.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 1620.

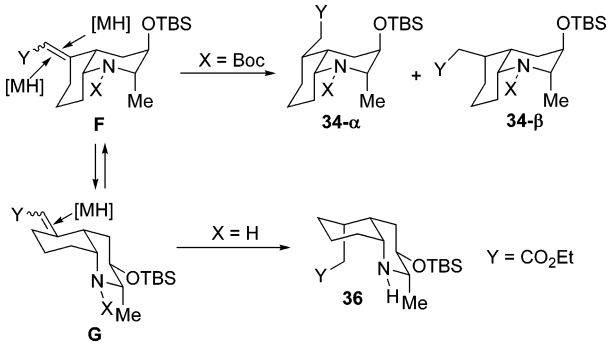
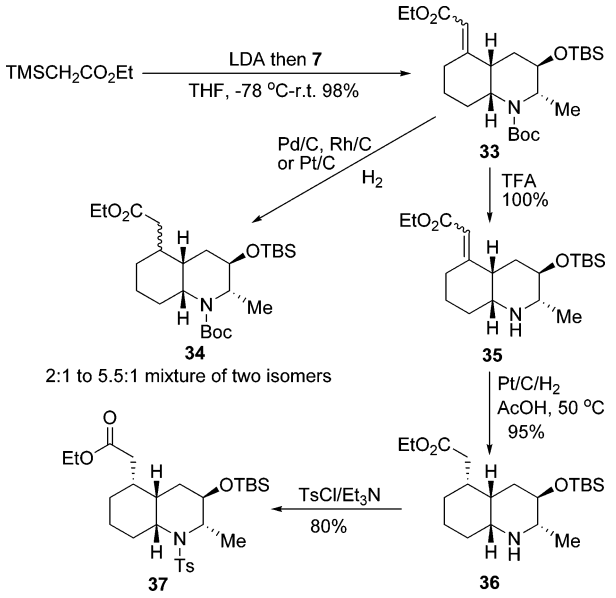


FIGURE 4. Stereochemical course for hydrogenation of olefins **33** and **35**.

SCHEME 7

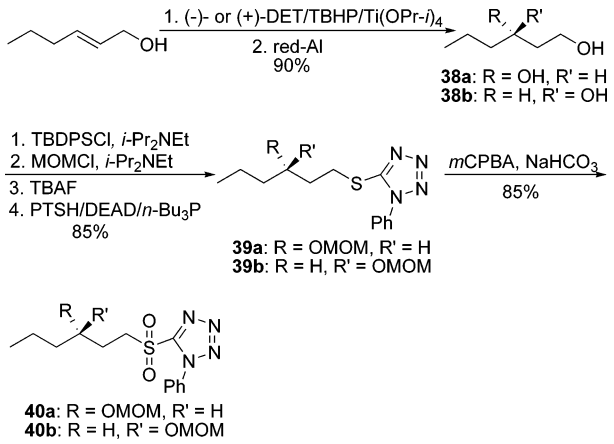


G. The steric difference for both *Re* or *Si* faces of the olefin moiety in conformer **F** might be limited and thereby give a mixture of 34-α and 34-*β*. In contrast, the steric hindrance of the *Re* face of the olefin moiety in conformer **G** was larger than that of the *Si* face. Thus, exclusive formation of **36** was observed.

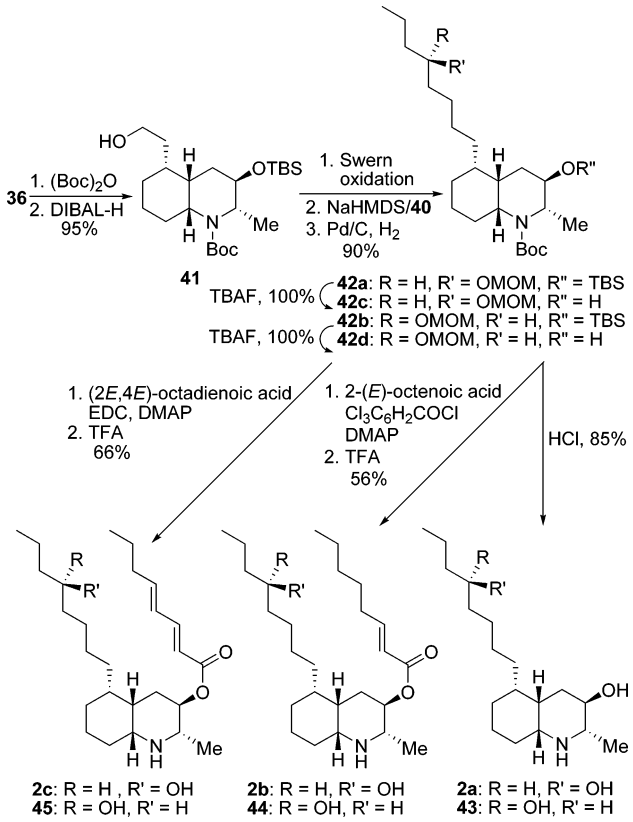
To elongate the side chain of **36** to finish the synthesis of lepadins D, E, and H, both (*R*)- and (*S*)-sulfones **40** were prepared, which provided a chance to establish the C-5′ stereochemistry of these natural products. The reaction sequence for this preparation was shown in Scheme 8. By tuning the chiral ligands in Sharpless epoxidation, both (*R*)- and (*S*)-diols **38** were obtained. Selective protection of the primary hydroxy group in **38** with TBDPSCl and subsequent treatment with MOMCl afforded a silyl ether, which was deprotected with TBAF, and then subjected to Mitsunobu reaction with BTSH to give thioethers **39**.[23] Oxidation of **39** with mCPBA produced **40** in 85% yield.

The completion of lepadins D, E, and H was depicted in Scheme 9. Protection of **36** with $(Boc)_2O$ followed by reduction with DIBAL afforded alcohol **41**, which was oxidized to aldehyde, coupled with sulfones **40**, and hydrogenated over Pd/C

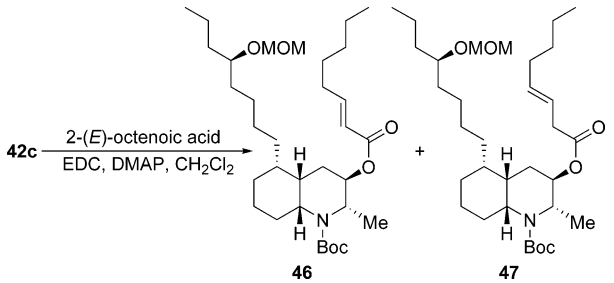
SCHEME 8



SCHEME 9



SCHEME 10



to produce decahydroquinolines **42a** and **42b**. After deprotection of the silyl ethers **42a** and **42b** with TBAF, alcohols **42c** and **42d** were isolated, which were further treated with HCl to afford **2a** and its 5′-epimer **43**, respectively. Moreover, acylation of **42c** and **42d** with 2-(*E*)-octenoic acid ($Cl_3C_6H_2COCl$/*i*-$PrNEt_2$)[24]

(23) (a) D'Souza, L. J.; Sinha, S. C.; Lu, S.; Keinan, E.; Sinha, S. C. *Tetrahedron* **2001**, *57*, 5255. (b) Blackemore, P. A.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett.* **1998**, 26.

or (2*E*,4*E*)-octadienoic acid (EDC/DMAP),[25] and followed by deprotection with TFA furnished **2b**, **44**, **2c**, and **45**, respectively. Noteworthy is that when esterification of **42c** was conducted with 2-(*E*)-octenoic acid in the presence of EDC and DMAP, migration of C−C double bond occurred to give a mixture of α,*β*-unsaturated ester **46** and *β*,*γ*-unsaturated ester **47**. The formation of **47** might go through a vinylketene intermediate derived from 2-(*E*)-octenoic acid. Similar unexpected isomerization was also noticed by Danishefsky and coworkers during the synthesis of migrastatin.[26] We solved this problem by using the Yamaguchi procedure.[24] However, the sequence for adding reagents was essential as no migration took place only when DMAP was introduced after alcohol.

Although both NMR spectra and optical rotation for **2a** and **43**, **2b** and **44**, or **2c** and **45** were very close, marked difference of **2c** and **45** in ^{1}H NMR at δ 1.2−1.5 clearly showed that **2c** but not **45** had all-identical data with those reported for lepadin H. Furthermore, the hydrochloride salt of **2a** showed $[\alpha]^{20}_D = -12$ (*c* 1.0 MeOH), which was close to that reported for hydrochloride salt of lepadin D ($[\alpha]^{20}_D = -14$ (*c* 0.2 MeOH)), while hydrochloride salt of **43** had relatively big difference in rotation ($[\alpha]^{20}_D = -5.7$ (*c* 0.9 MeOH)). Therefore, we concluded that the absolute configuration for lepadins D, E, and H was 2*S*,3*R*,4a*S*,5*S*,8a*R*,5′*R*.

In summary, we have developed an efficient and divergent strategy for access of lepadins together with a concise synthesis of lepadins A−C and the first total synthesis and establishment of all stereochemistry of lepadins D, E, and H. The key elements in this approach included a concise elaboration of the cis fused decahydroquinoline via condensation of a L-alanine derived *γ*-bromo-*β*-silyloxy-propylamine with 1,3-cyclohexadione and introducing 5α and 5*β* side carbon chains via diastereoselective hydrogenation of a 5-*exo*-olefine and epimerization of a 5-formyl intermediate, respectively. The possible stereochemical courses for the latter two processes were discussed, which should be valuable for decahydroquinoline chemistry. Noteworthy, for assembly of lepadins A−C, more than 5% yields were obtained by using less than 21 linear steps from *N*-Boc-L-alanine, which is more efficient when compared with the previous two protocols.[10,11] These results should prompt further studies on the synthesis and biological testing of these compounds and their analogues.

Experimental Section

(2*S*,3*R*)-3-(2-Cyclohexenon-3-yl)amino-2-(*tert*-butyldimethylsilyloxy)butyl Bromide 10. To an ice-cooled solution of bromide **8** (3.82 g, 10 mmol) in 50 mL of CH_2Cl_2 was added 50 mL of formic acid dropwise. After the mixture was warmed to room temperature and then stirred for about 4 h, the solution was concentrated in vacuo. The residue was diluted with saturated sodium bicarbonate solution and then stirred for 5 min. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine and dried over $MgSO_4$. After removal of solvent, the residue was dried under vacuum to give crude free amine.

A mixture of the above amine and cyclohexadione (1.6 g, 15 mmol) in 10 mL of benzene was placed in a flask equipped with a Dean−Stark dehydration trap. The mixture was heated to gently reflux for about 4 h and then cooled to room temperature. After saturated sodium bicarbonate solution was added, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give yellow-orange oil, which was purified via chromatography, eluting with 1:1:0.02 ethyl acetate/petroleum ether/MeOH to afford 2.4 g (65%) of **10**. $[\alpha]^{17}_D$ +2.7 (*c* 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, amide rotamer): δ −0.11 (s, 3H), −0.03 (s, 3H), 0.91 (s, 9H), 1.12 (d, J = 6.3 Hz, 3H), 1.90 (m, 2H) 2.3 (m, J = 6.3, 7.2 Hz, 4H), 3.10 and 3.31 (dd, J = 4.8, 10.5 Hz, 2H in 3:1 ratio), 3.75 and 3.89 (dt, J = 2.5, 5.1 Hz, 1H in 3:1 ratio) 3.99 (dq, J = 2.7, 6.2 Hz, 1H), 4.61 (bd, J = 6.9 Hz, 1H), 5.15 and 5.18 (s, 1H in 3:1 ratio). ^{13}C NMR (75 MHz, $CDCl_3$, amide rotamer): δ −4.0, −4.7, 12.4, 12.1, 18.0, 21.9, 25.8, 32.6, 36.4, 44.2, 48.9, 49.1, 71.6, 72.0, 97.2, 162.5, 197.4. IR (neat): 3269, 1604 cm^{-1}. ESI-MS: *m*/*z* 376 $(M + H)^+$. ESI-HRMS calcd for $C_{16}H_{30}NO_2BrSi$ $(M + H)^+$: requires, 376.1295; found, 376.1301.

Alkylative Cyclization of 10. To a solution of compound **10** (1.22 g, 3.2 mmol) in anhydrous DMF (degassed) was added NaI (2.44 g, 16 mmol). The resultant mixture was heated under argon for about 0.5 h at 80 °C before Et_3N (0.53 mL, 3.8 mmol) was slowly added via syringe. The reaction temperature was slowly raised to 110 °C, and the stirring was continued for about 10 h. The cooled solution was evaporated under reduced pressure, and the residue was partitioned between brine and ethyl ether. The organic layer was separated, and the aqueous layer was extracted with ethyl ether. The combined organic layers were dried over $MgSO_4$, and the solvent was removed in vacuo. The residue was purified via chromatography, eluting with 1:1:0.02 ethyl acetate/petroleum ether/MeOH to yield 920 mg (98%) of **14**. $[\alpha]^{18}_D$ −196.8 (*c* 0.24, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.05 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 1.21 (d, J = 6.6 Hz, 3H), 1.90 (ddd, J = 6.3, 7.2, 6.0 Hz, 2H), 2.11 (dd, J = 9.3, 15.6 Hz, 1H), 2.31 (q like, J = 6.0, 7.0 Hz, 4H), 2.71 (dd, J = 7.7, 15.1 Hz, 1H) 3.11 (dq, J = 6.6, 6.8 Hz, 1H), 3.50 (ddd, J = 6.4, 8.1, 9.0 Hz, 1H), 4.50 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.8, −4.1, 18.0, 18.9, 21.6, 25.8, 28.8, 28.9, 36.5, 53.4, 70.5, 103.5, 158.2, 194.7. IR (neat): 3271, 1665, 1571 cm^{-1}. EI-MS: *m*/*z* 295 (M^+), 280, 238, 222, 164, 146, 115. HRMS calcd for $C_{16}H_{29}NO_2Si$ (M^+): requires, 295.1948; found, 295.1929.

(2*S*,3*R*,4a*S*,5*S*,8a*R*)-2-Methyl-3-(*tert*-butyldimethylsilyloxy)-5-hydroxy-decahydroquinoline 15. A solution of **14** (1.2 g, 4 mmol) in glacial acid (20 mL) was hydrogenated over platinum on charcoal (5% Pt, 1.2 g) at 50 °C and 80 atm for 12 h. It was then filtered through Celite, and the filtrate was concentrated and diluted with saturated aqueous $NaHCO_3$. The aqueous layer was extracted several times with ethyl acetate, and the combined organic layers were dried over $MgSO_4$. The solution was concentrated, and the residue was purified via chromatography, eluting with 10:1 ethyl acetate/MeOH to give 1.0 g (86%) of **15** as a colorless oil. $[\alpha]^{18}_D$ −53.6 (*c* 1.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.07 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 1.22 (d, J = 6.2 Hz, 3H), 1.4 (m, 2H), 1.6 (m, 3H), 1.68 (m, 2H), 1.98 (m, 2H), 2.03 (dd, J = 5.8, 15.1 Hz, 1H), 2.71 (dq, J = 3.9, 6.0 Hz, 1H), 3.20 (m, 2H), 3.91 (m, 2H), 4.11 (ddd, J = 4.2, 5.7, 13.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.6, −3.8, 14.4, 18.0, 19.4, 25.9, 31.4, 33.8, 39.1, 39.9, 56.3, 59.5, 71.5, 72.1. IR (neat): 3366, 1712 cm^{-1}. ESI-MS: *m*/*z* 300 $(M + H)^+$. ESI-HRMS calcd for $C_{16}H_{33}NO_2Si$ $(M + H)^+$: requires, 300.2367; found, 300.2353.

(2*S*,3*R*,4a*S*,8a*R*)-1-(*tert*-Butyloxycarbonyl)-2-methyl-3-(*tert*-butyldimethylsilyloxy)-5-oxo-decahydroquinoline 7. To a solution of the alcohol **15** (1.0 g, 3.3 mmol) in 20 mL of anhydrous CH_3CN were sequentially added $(Boc)_2O$ (1.33 g, 6.1 mmol) and K_2CO_3 (45 mg, 0.3 mmol). The resultant mixture was heated to gently reflux under argon for 72 h. After water was added to quench the reaction, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried

(24) (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989. (b) Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1990**, *31*, 6367.

(25) Evans, D. A.; Carter, P. H.; Carreira, E. M.; Prunet, J. A.; Charette, A. B.; Lautens, M. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2354.

(26) Gaul, C.; Njardarson, J. T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 6042.

over $MgSO_4$ and evaporated in vacuo to give a crude carbamate, which was pure enough to be used for next step.

To a solution of the above carbamate in 25 mL of CH_2Cl_2 was added Dess−Martin reagent (1.68 g, 4.1 mmol) dropwise at room temperature. After the resultant mixture was stirred for about 5 h, saturated sodium bicarbonate solution was added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to give a colorless oil, which was purified via chromatography, eluting with 10:1 ethyl acetate/petroleum ether to afford 1.0 g (86%) of **7**. $[\alpha]^{15}_D$ −35.2 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.87 (s, 9H), 1.18 (d, J = 7.2 Hz, 3H), 1.44 (s, 9H), 1.61 (m, 2H), 1.78 (ddd, J = 3.2, 12.7, 12.9 Hz, 1H), 1.92 (m, 2H), 1.93 (ddd, J = 2.1, 11.2, 11.3 Hz, 1H), 2.31 (ddd, J = 6.0, 5.4, 15.0 Hz, 2H), 3.11 (dt, J = 4.9, 13.5 Hz, 1H), 3.81 (m, 1H), 4.11 (q, J = 7.1 Hz, 1H), 4.30 (dt, J = 4.9, 12.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.2, −4.9, 17.9, 19.4, 21.7, 25.6, 26.6, 27.5, 28.3, 38.1, 44.7, 51.4, 52.5, 67.9, 79.5, 155.0, 212.8. IR (neat): 2975, 1711, 1676 cm^{-1}. ESI-MS: *m*/*z* 420 (M + Na)$^+$. ESI-HRMS calcd for $C_{21}H_{39}NNaO_4Si$ (M + Na)$^+$: requires 420.2541; found, 420.2541.

(2*S*,3*R*,4a*S*,5*R*,8a*R*)-2-Methyl-3-(*tert*-butyldimethylsilyloxy)-5-formyl-decahydroquinoline 18. To a solution of the enol ether **16** (177 mg, 0.42 mmol) in 50 mL of CH_2Cl_2 at room temperature were added wet trichloroacetic acid (653.6 mg, 4 mmol) and 1 drop of water. After the starting material was consumed as monitored by TLC, saturated sodium bicarbonate was added to quench this reaction. The aqueous layer was extracted several times with ethyl acetate, and the combined organic layers were washed with brine and dried over $MgSO_4$. After being concentrated and dried under vacuum, the crude aldehyde was obtained.

To a solution of the above crude product in 50 mL of dry CH_2Cl_2 was added trifluoroacetic acid (2.5 mL) dropwise at room temperature. The reaction was carefully monitored by TLC and quenched with a saturated methanolic K_2CO_3. After removal of the solvent under reduced pressure, the residue was dissolved in 20 mL of methanol. To this solution was added K_2CO_3 (200 mg, 1.5 mmol). After the resultant mixture was stirred at room temperature for about 10 h, it was evaporated, and the residue was triturated with water and extracted with ethyl acetate. The organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was allowed to pass a short column of silica gel to afford 97 mg (76%) of aldehyde **18** as an unstable product, which was used immediately. $[\alpha]^{17}_D$ −48.8 (*c* 0.36, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.03 (s, 3H), 0.05 (s, 3H), 0.87 (s, 9H), 1.13 (dq, J = 1.8, 10.1 Hz, 1H), 1.33 (d, J = 6.2 Hz, 3H), 1.61 (m, 4H), 2.11 (m, 4H), 2.92 (dq, J = 2.4, 6.1 Hz, 1H), 3.11 (t, J = 12.1 Hz, 1H), 3.41 (m, 1H), 3.71 (ddd, J = 4.5, 6.1, 6.6 Hz, 1H), 9.61 (d, J = 3.6 Hz, 1H). IR (neat): 1720, 1681 cm^{-1}. EI-MS: *m*/*z* 311 (M$^+$) 296, 282, 254, 240, 180, 150, 124, 101. HRMS calcd for $C_{17}H_{34}NO_2Si$ (M + H)$^+$: requires, 312.2341; found, 312.2353.

(2*S*,3*R*,4a*S*,5*R*,8a*R*)-2-Methyl-3-(*tert*-butyldimethylsilyloxy)-5-((1′*E*,3′*E*)-octadien-1-yl)decahydroquinoline 22. To a solution of hept-2-enyl-phosphonic acid diethyl ester **21** (150 mg, 0.64 mmol) in 2 mL of DME was added KHMDS (1 M in THF, 0.65 mL) dropwise by a syringe at −78 °C over 20 min. The resultant solution was stirred for 0.5 h before a solution of the aldehyde **18** (50 mg, 0.16 mmol) in 2 mL of DME was added dropwise via syringe over 10 min. The reaction mixture was maintained at −78 °C for 6 h and then allowed to slowly warm to room temperature. The resultant solution was diluted with ether before saturated ammonium chloride was added. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography, eluting with 1:10 ethyl acetate/petroleum ether to give 57 mg (92%) of **22**. $[\alpha]^{20}_D$ −23.5 (*c* 1.95, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.03 (s, 3H), 0.05 (s, 3H), 0.86 (s, 9H), 0.89 (t, J = 7.2 Hz, 3H), 1.06 (dd, J = 2.7, 12.3 Hz, 1H), 1.13 (d, J = 6.1 Hz, 3H), 1.21−1.70 (m, 12H), 1.98 (m, 1H), 2.07 (q, J = 6.6 Hz, 2H), 2.41 (m, J = 2.4, 11.8 Hz, 1H), 2.42 (br s, 1H), 2.56 (dq, J = 2.7, 6.0 Hz, 1H), 3.01 (br d, J = 1.1 Hz, 1H), 3.28 (ddd, J = 4.5, 6.0, 6.7 Hz, 1H), 5.26 (dd, J = 9.1, 14.1 Hz, 1H), 5.54 (dt, J = 6.6, 14.2 Hz, 1H), 5.96 (dd, J = 7.2, 15.0 Hz, 1H), 6.02 (dd, J = 5.4, 14.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.8, −4.2, 13.8, 17.9, 19.1, 20.2, 22.0, 25.8, 29.6, 31.7, 32.1, 33.6, 37.2, 39.3, 41.7, 54.7, 59.6, 70.5, 129.9, 130.6, 132.7, 135.9. IR (neat): 1716, 1413 cm^{-1}. EI-MS: *m*/*z* 391 (M$^+$), 376, 348, 334, 260, 214, 188. HRMS calcd for $C_{24}H_{46}NOSi$ (M$^+$): requires, 391.3256; found, 391.3242.

(2*S*,4a*S*,5*R*,8a*R*)-1-(*tert*-Butyloxycarbonyl)-2-methyl-3-oxo-5-((1′*E*,3′*E*)-octadien-1-yl)decahydroquinoline 23. To a solution of **22** (50 mg, 0.15 mmol) in anhydrous benzene were sequentially added $(Boc)_2O$ (160 mg, 0.73 mmol) and K_2CO_3 (2 mg, 0.015 mmol). The resultant solution was heated to gently reflux under argon for 72 h. After water was added to quench the reaction, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give a colorless oil, which was purified via chromatography, eluting with 1:100 ethyl acetate/petroleum ether to give a crude carbamate. This crude product was dissolved in anhydrous THF (2 mL), and then TBAF (2 M in THF, 0.76 mL) was added via syringe at room temperature. The reaction mixture was stirred for 72 h, and then partitioned between ether and saturated ammonium chloride. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by chromatography, eluting with 1:5 ethyl acetate/petroleum ether to give an alcohol (45 mg, 82%).

To a solution of the above alcohol (31 mg, 0.082 mmol) in 1 mL of CH_2Cl_2 was added Dess−Martin reagent (52.4 mg, 0.123 mmol) dropwise at room temperature. The resultant solution was stirred for about 5 h before saturated sodium bicarbonate was added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified via chromatography, eluting with 1:15 ethyl acetate/petroleum ether to afford 23 mg (76%) of **23**. $[\alpha]^{15}_D$ −21 (*c* 0.42, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, J = 7.5 Hz, 3H), 1.21−1.60 (m, 9H), 1.35 (d, J = 7.2, 3H), 1.47 (s, 9H), 1.76 (m, J = 3.9, 5.1 Hz, 1H), 2.11 (q like, J = 6.6, 7.2 Hz, 2H), 2.25 (m, 2H), 2.73 (dd, J = 4.8, 16.2 Hz, 1H), 4.35 (q like, J = 6.9 Hz, 1H), 4.4 (m, 1H), 5.62 (dt, J = 6.6, 14.1 Hz, 1H), 5.75 (dd, J = 6.9, 14.7 Hz, 1H), 6.02 (dd, J = 7.2, 15.1 Hz, 1H), 6.02 (dd, J = 6.0, 15.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 20.1, 20.9, 22.2, 24.8, 27.5, 28.4, 31.4, 32.2, 38.4, 38.7, 41.6, 48.7, 58.3, 80.2, 130.1, 130.9, 133.1, 133.9, 154.1, 209.5. IR (neat): 1719, 1692, 1400 cm^{-1}. ESI-MS: *m*/*z* 376 (M + H)$^+$. HRMS calcd for $C_{23}H_{38}NO_3$ (M + H)$^+$: requires, 376.2832; found, 376.2846.

Lepadin B (1b). To a solution of **23** (20 mg, 0.053 mmol) in anhydrous methanol was added $NaBH_4$ (2 mg) at −40 °C with stirring. After being stirred at this temperature for 1 h, the mixture was neutralized with 0.5 N HCl, and extracted with $CHCl_3$. The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give a colorless oil, which was dissolved in 1 mL dry CH_2Cl_2 before trifluoroacetic acid (0.06 mL) was added. The mixture was stirred until the starting material disappeared monitored by TLC, and then saturated methanolic K_2CO_3 was added to quench the reaction. After the mixture was stirred for 5 h, it was concentrated, and the residue was chromatographed eluting with 5:1:0.06 ethyl acetate/MeOH/NH_4OH to afford 10 mg (73%) of **1b**, which was treated with trifluoroacetic acid to give its salt for analysis. $[\alpha]^{15}_D$ −82 (*c* 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (t, J = 7.0 Hz, 3H), 1.06 (m, 1H), 1.29−1.37 (m, 4H), 1.39 (d, J = 6.7 Hz, 1H), 1.56−1.66 (m, 5H), 1.74 (d like, J = 13.4 Hz, 1H), 2.06 (q, J = 6.9 Hz, 2H), 2.10 (d, J = 9.5 Hz, 1H), 2.31 (d, J = 13.9 Hz, 1H), 2.78 (q like, J = 11.0 Hz, 1H), 3.35 (br s, 1H), 3.49 (br s, 1H) 3.89 (br s, 1H), 4.14 (br s, 1H), 5.30 (dd, J =

8.6, 15.1 Hz, 1H), 5.64 (dt, J = 6.9, 15.1 Hz, 1H), 5.99 (dd, J = 10.0, 15.1 Hz, 1H), 6.11 (dd, J = 10.5, 15.2 Hz, 1H), 7.47 (br s, 1H), 9.70 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 14.9, 19.5, 22.3, 28.9, 31.4, 32.1, 32.3, 33.0, 36.9, 39.6, 56.8, 57.5, 66.5, 129.9, 132.3, 134.0, 134.3. IR (neat): 3389, 1450 cm^{-1}. ESI-MS: m/z 278 $(M + H)^+$.

Lepadin A 1a. Following the procedure for reduction of **23** mentioned above, the corresponding alcohol was obtained. This alcohol (26 mg, 0.07 mmol) was dissolved in 1 mL of anhydrous CH_2Cl_2 before $TMSOCH_2CO_2H$ (26.6 mg, 0.14 mmol), DMAP (1 mg, 0.1 mmol), and EDC (30 mg, 0.15 mmol) were added sequentially at 0 °C. The mixture was warmed to room temperature and stirred for about 12 h. After water was added to quench the reaction, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give a colorless oil, which was purified via chromatography, eluting with 1:30 ethyl acetate/petroleum ether to give an ester (36 mg, 90%), which was dissolved in 1.5 mL of dry CH_2Cl_2. To this solution was added $F_3B{\cdot}OEt_2$ (7.2 mg, 0.05 mmol) at 0 °C. The resultant solution was stirred at room temperature until the starting material disappeared monitored by TLC. Saturated methanolic $NaHCO_3$ was added to quench the reaction, and then stirring was continued for 1 h. After removal of the solvents via rotavapor, the residue was purified by chromatography (1:2:0.02 MeOH/EtOAc/NH_4OH as eluent) to afford 15.6 mg (76%) of **1a**, which was transformed into its trifluoroacetic acid salt for analysis. $[\alpha]^{30}_D$ −50.7 (*c* 0.2, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, J = 7.0 Hz, 3H), 1.06 (m, 1H), 1.29−1.42 (m, 4H), 1.33 (d, J = 6.9 Hz, 3H), 1.56−1.75 (m, 5H), 2.0−2.10 (q like, J = 6.9, 9.1 Hz, 3H), 2.32 (d, J = 13.6 Hz, 1H), 2.77 (br s, 1H), 2.80 (m, 1H), 3.39 (br s, 1H) 3.47 (br s, 1H), 4.33 (br m, 2H), 5.25 (dd, J = 8.6, 15.1 Hz, 1H), 5.27 (br s, 1H), 5.62 (dt, J = 7.0, 15.1 Hz, 1H), 5.95 (dd, J = 10.0, 15.2 Hz, 1H), 6.11 (dd, J = 10.5, 15.2 Hz, 1H), 7.42 (br, 1H), 9.92 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 14.8, 19.4, 22.2, 28.9, 29.6, 31.3, 32.2, 32.8, 36.9, 39.5, 56.7, 57.4, 61.0, 68.5, 129.9, 132.7, 133.2, 134.6, 171.5. ESI-MS: m/z 336 $(M + H)^+$.

(2*S*,3*S*,4a*S*,5*R*,8a*R*)-1-(*tert*-Butyloxycarbonyl)-2-methyl-3-hydroxy-5-((1′*E*,3′*E*)-7,7-ethylenedioxy-octadien-1-yl)decahydroquinoline 29. To a solution of **28** (41 mg, 0.094 mmol) in 1 mL of CH_2Cl_2 were added $NaHCO_3$ (118 mg, 1.4 mmol) and Dess−Martin reagent (60.5 mg, 0.141 mmol) at room temperature. The resultant mixture was stirred for about 0.5 h before saturated sodium bicarbonate was added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified via chromatography, eluting with 1:15 ethyl acetate/petroleum ether to yield a crude ketone.

To a solution of the above ketone (31 mg, 0.072 mmol) in anhydrous methanol was added $NaBH_4$ (1.8 mg) at −40 °C. After being stirred at this temperature for 0.6 h, the mixture was neutralized with 0.1 N HCl and then extracted with $CHCl_3$. The combined organic layers were dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified via chromatography, eluting with 5:1 ethyl acetate/petroleum ether to afford 28 mg (91% for two steps) of **29**. $[\alpha]^{30}_D$ −2.8 (*c* 0.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, amide rotamer): δ 1.17 (d, J = 6.6 Hz, 3H), 1.33 (s, 3H), 1.47 (s, 9H), 1.46−1.78 (m, 9H), 1.74 (dd like, J = 7.9, 6.2 Hz, 2H), 1.84 (m, 1H), 1.92 (q, J = 9.6, 12 Hz, 1H), 2.20 (dd like, J = 6.9, 6.6 Hz, 2H), 3.86 (m, 1H), 3.96 (dd like, J = 3.5, 4.0 Hz, 4H), 4.00−4.17(m, 1H), 4.32 (m, 1H), 5.60 (m, 1H), 5.82 (m, 1H), 6.01 (m, 1H), 6.06 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, amide rotamer): δ 21.1, 21.2, 22.6, 23.9, 26.1, 27.2, 28.4, 29.6, 29.9, 38.6, 38.7, 40.2, 49.1, 53.9, 64.6, 70.1, 79.4, 109.8, 130.1, 130.4, 132.5, 135.0, 155.1. IR (neat): 3428, 1681 cm^{-1}. ESI-MS: m/z 436 $(M + H)^+$. HRMS calcd for $C_{25}H_{42}NO_5$ $(M + H)^+$: requires, 436.3063; found, 436.3068.

Lepadin C 1c. To an ice cooled solution of **29** (28 mg, 0.064 mmol) in anhydrous CH_2Cl_2 were sequentially added $TMSOCH_2CO_2H$ (26.6 mg, 0.14 mmol), DMAP (1 mg, 0.1 mmol), and EDC (30 mg, 0.15 mmol). The mixture was warmed to room temperature and then stirred for about 12 h. After water was added to quench the reaction, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give crude ester, which was dissolved in 1.5 mL of dry CH_2Cl_2. To this solution was added $F_3B{\cdot}OEt_2$ (8.5 mg, 0.06 mmol) at 0 °C. The resultant solution was stirred at room temperature until the starting material disappeared monitored by TLC. Saturated methanolic $NaHCO_3$ was added to quench the reaction, and then stirring was continued for 1 h. After removal of the solvents via rotavapor, the residue was purified by chromatography (1:2:0.02 MeOH/EtOAc/NH_4OH as eluent) to afford 16.5 mg (74%) of **1c**, which was transformed into its trifluoroacetic acid salt for analysis. $[\alpha]^{30}_D$ −60.3 (*c* 0.3, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (m, 1H), 1.26 (d, J = 6.7 Hz, 3H), 1.60−1.79 (m, 6H), 2.06 (m, 1H), 2.15 (s, 3H), 2.27 (m, 1H), 2.33 (q like, J = 6.6 Hz, 2H), 2.52 (t, J = 7.8 Hz, 2H), 2.80 (m, 1H), 3.39 (q, J = 7.0 Hz, 1H), 3.48 (br s, 1H), 4.09 (br s, 1H), 4.30 (m, 2H), 5.24 (br s, 1H), 5.26 (dd, J = 10.5, 14.7 Hz, 1H), 5.57 (dt, J = 6.9, 15.1 Hz, 1H), 5.97 (dd, J = 10.3, 15.1 Hz, 1H), 6.15 (dd, J = 10.5, 15.5 Hz, 1H), 7.39 (br, 1H), 9.74 (br, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.0, 19.6, 26.7, 29.1, 29.8, 33.0, 33.4, 37.0, 39.9, 43.1, 57.0, 57.6, 61.5, 68.2, 130.9, 131.5, 132.4, 134.7, 171.5, 208.2. ESI-MS: m/z 350 $(M + H)^+$.

(2*S*,3*R*,4a*S*,5*S*,8a*R*)-2-Methyl-3-(*tert*-butyldimethylsilyloxy)-5-(ethoxy-carbonyl)methyldecahydroquinoline 36. A solution of **35** (370 mg, 1.01 mmol) in glacial acid (20 mL) was hydrogenated over platinum on charcoal (5%, 200 mg) at room temperature and 1 atm for 6 h before it was filtered through Celite. The filtrate was concentrated and then diluted with saturated $NaHCO_3$. The aqueous layer was extracted several times with ethyl acetate, and the combined organic layers were washed with brine and dried over $MgSO_4$. The solution was concentrated and the residue was purified via chromatography, eluting with 2:1:0.01 ethyl acetate/petroleum ether/methanol to give 351 mg (95%) of **36** as a colorless oil. $[\alpha]^{15}_D$ +10.1 (*c* 0.25, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.03 (s, 3H), 0.05 (s, 3H), 0.85 (s, 9H), 1.11 (d, J = 6.9 Hz, 3H), 1.22 (t with m, J = 7.2 Hz, 3H), 1.41 (m, 2H), 1.55 (m, 1H), 1.66 (m, 2H), 1.78 (m, 2H), 1.85 (br s, 1H), 2.15 (m, 2H), 2.31 (dd, J = 5.4, 14.9 Hz, 1H), 2.45 (dd, J = 10.1, 14.6 Hz, 1H), 2.65 (dq like, J = 3.9, 4.2 Hz, 1H), 2.91 (dq like, J = 4.2, 4.3 Hz, 1H), 3.50 (q like J = 5.5 Hz, 1H), 4.12 (dq like, J = 2.8, 7.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.9, −4.4, 14.1, 17.8, 20.4, 21.0, 25.7, 28.2, 30.2, 31.4, 35.3, 35.6, 38.2, 54.6, 55.8, 59.9, 71.7, 173.4; IR (neat): 3421, 1735, 1675 cm^{-1}. ESI-MS: m/z 370 $(M + H)^+$. HRMS calcd for $C_{20}H_{40}NO_3Si$ $(M + H)^+$: requires, 370.2775; found, 370.2772.

(2*S*,3*R*,4a*S*,5*S*,8a*R*)-1-Tosyl-2-methyl-3-(*tert*-butyldimethylsilyloxy)-5-(ethoxycarbonyl)methyldecahydroquinoline 37. To an ice cooled solution of **36** (19 mg, 0.053 mmol) in 1 mL of anhydrous CH_2Cl_2 were sequentially added NEt_3 (0.023 mL, 0.16 mmol) and TsCl (30.1 mg, 0.158 mmol). The mixture was warmed to room temperature and then stirred for about 4 h. After water was added to quench the reaction, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and then evaporated in vacuo. The residue was purified via chromatography, eluting with 1:30 ethyl acetate/petroleum ether to give 21 mg (75%) of **37**. $[\alpha]^{15}_D$ −9.2 (*c* 0.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.01 (s, 3H), 0.02 (s, 3H), 0.82 (s, 9H), 1.01 (dq like, J = 3.0, 9.3 Hz, 1H), 1.22 (t, J = 7.2 Hz, 3H), 1.21−1.40 (m, 3H), 1.72 (m, 3H), 1.90 (m, 2H), 2.18 (m, 2H), 2.41 (s, 3H), 3.50 (dt, J = 3.4, 7.5 Hz 1H), 3.81 (m, J = 1.0 1H), 4.05 (dq, J = 3.9, 4.5, 1H), 4.10 (dq like, J = 2.8, 7.0 Hz, 2H), 7.21 (d, J = 7.4 Hz, 2H), 7.8 (d, J = 7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.53, −5.48, 13.7, 17.7, 20.9, 21.4, 22.1, 24.6, 25.3, 25.7, 28.8, 30.8, 36.5, 38.1, 55.2, 55.3, 59.8, 69.2, 126.6, 128.8, 138.2, 142.0, 172.1. IR (neat): 3421, 1735, 1675

cm^{-1}. ESI-MS: *m*/*z* 524 (M + H)$^+$. HRMS calcd for $C_{27}H_{45}NO_5SSiNa$ (M + Na)$^+$: requires, 546.2680; found, 546.2696.

(2*S*,3*R*,4a*S*,5*R*,8a*R*)-1-(*tert*-Butyloxycarbonyl)-2-methyl-3-(*tert*-butyl-dimethylsilyloxy)-5-(2′-hydroxyethyl)decahydroquinoline 41. To a solution of **37** (500 mg, 1.36 mmol) in 15 mL of anhydrous benzene were sequentially added $(Boc)_2O$ (1.8 g, 8 mmol) and K_2CO_3 (19 mg, 0.13 mmol). The resultant mixture was heated at reflux under argon for 72 h. After water was added to quench the reaction, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give a colorless oil, which was purified via chromatography, eluting with 1:40 ethyl acetate/petroleum ether to afford a crude carbamate, which was reduced with DIBAL (4.1 mmol) in THF at −40 °C. After completion of this reaction, methanol and saturated seignette salt solution were sequentially added at the same temperature, and then the solution was allowed to warm to room-temperature overnight. The organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography, eluting with 1:10 ethyl acetate/petroleum ether to give 512 mg (90% for two steps) of **41**. $[\alpha]^{18}_D$ −8.9 (*c* 0.26, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ −0.01 (s, 3H), 0.01 (s, 3H), 0.83 (s, 9H), 0.98 (dq like, *J* = 2.7, 12.6 Hz, 1H), 1.21−1.50 (m, 8H), 1.07 (d, *J* = 7.2 Hz, 3H), 1.41 (s, 3H), 1.65 (m, 3H), 2.35 (br d, *J* = 10.1 Hz, 1H), 3.63 (d, *J* = 6.9 Hz, 2H), 3.72 and 3.78 (m, 1H in 1: 2 ratio due to rotamer), 3.88 and 4.05 (m and dt, *J* = 5.1, 10.2 Hz, 2H in 2:1 ratio due to rotamer). ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.2, −4.9, 17.9, 20.0, 21.5, 25.3, 25.67, 27.12, 27.85, 28.36, 30.9, 36.2, 36.15, 53.0, 53.7, 60.7, 69.5, 78.9, 155.4. IR (neat): 3490, 1687 cm^{-1}. ESI-MS: *m*/*z* 428 (M + H)$^+$. HRMS (ESI) calcd for $C_{23}H_{45}NO_4SiNa$ (M + Na)$^+$: requires, 450.3010; found, 450.3027.

(2*S*,3*R*,4a*S*,5*S*,8a*R*,5′*R*)-1-(*tert*-Butyloxycarbonyl)-2-methyl-3-(*tert*-butyl-dimethylsilyloxy)-5-(5′-methoxymethoxyoctan-1-yl)-decahydroquinoline 42a. A precooled solution of DMSO (212.8 μL) in dry CH_2Cl_2 was added to a solution of oxalyl chloride (128.6 μL, 1.5 mmol) in dry CH_2Cl_2 at −78 °C. After stirring for 10 min, the alcohol **41** (320 mg, 0.75 mmol) in CH_2Cl_2 was added dropwise within 10 min, and the mixture was stirred at this temperature for additional 1 h. Then NEt_3 (0.83 mL, 6 mmol) was added, and the cooling bath was removed. After the reaction mixture was warmed to room temperature, brine was added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give the crude aldehyde (320 mg, 100%).

To a solution of sulfone **40a** (250 mg, 0.7 mmol) in 2 mL of THF was added dropwise NaHMDS (2 M in THF, 0.35 mL, 0.7 mmol) at −78 °C. The mixture was stirred for 30 min, and then a solution of the above aldehyde (140 mg, 0.35 mmol) in THF was added. After stirring was continued for 3 h at −78 °C, the reaction mixture was allowed to warm to room temperature. Then brine was added to quench the reaction, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give a colorless oil, which was purified via chromatography, eluting with 1:30 ethyl acetate/petroleum ether to give the crude coupling product. After this product was dissolved in methanol (40 mL), 10 mg of 10% palladium on charcoal was added. The resultant mixture was stirred under hydrogen atmosphere at room temperature and ordinary pressure for 6 h. After Pd/C was filtered off, the filtrate was concentrated, and the residue was purified via chromatography, eluting with 1:30 ethyl acetate/petroleum ether to give 166 mg (90% for three steps) of **42a** as a colorless oil. $[\alpha]^{19}_D$ −7.4 (*c* 0.38, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.02 (s, 3H), 0.04 (s, 3H), 0.86 (s, 9H), 0.95 (t and m, *J* = 7.3 Hz, 4H), 1.10 (d, *J* = 7.2 Hz, 3H), 1.21−1.50 (m, 12H), 1.44 (s, 9H), 1.61−1.72 (m, 3H), 2.41 (br d, *J* = 13.8 Hz, 1H), 3.38 (s, 3H), 3.74 (pent, *J* = 5.2 Hz, 1H), 3.76 and 3.78 (m, 1H in 1: 2 ratio due to rotamer), 3.88 and 4.05 (m and dt, *J* = 5.1, 10.2 Hz, 2H in 2:1 ratio due to rotamer), 4.65 (s, 2H). IR (neat): 1689, 1465 cm^{-1}. ESI-MS: *m*/*z* 556 (M + H)$^+$. HRMS (ESI) calcd for $C_{31}H_{61}NO_5SiNa$ (M + Na)$^+$: requires, 578.4211; found, 578.4194.

(2*S*,3*R*,4a*S*,5*S*,8a*R*,5′*S*)-1-(*tert*-Butyloxycarbonyl)-2-methyl-3-(*tert*-butyl-dimethylsilyloxy)-5-(5′-methoxymethoxyoctan-1-yl)-decahydroquinoline 42b. Following the same procedure from **41a** to **42a**, **42b** was obtained from **41b** in 89% yield. $[\alpha]^{19}_D$ −12.9 (*c* 0.25, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.02 (s, 3H), 0.04 (s, 3H), 0.86 (s, 9H), 0.92 (t and m, *J* = 6.9 Hz, 4H), 1.10 (d, *J* = 7.2 Hz, 3H), 1.21−1.50 (m, 10H), 1.44 (s, 9H), 1.63−1.71 (m, 3H), 2.42 (br d, *J* = 13.8 Hz, 1H), 3.38 (s, 3H), 3.54 (pent, *J* = 5.2 Hz, 1H), 3.75 and 3.79 (m, 1H in 1: 2 ratio due to rotamer), 3.88 and 4.05 (m and dt, *J* = 5.1, 10.2 Hz, 2H in 2:1 ratio due to rotamer), 4.65 (s, 2H). IR (neat): 1689, 1465 cm^{-1}. ESI-MS: *m*/*z* 556 (M + H)$^+$. HRMS (ESI) calcd for $C_{31}H_{61}NO_5SiNa$ (M + Na)$^+$: requires, 578.4211; found, 578.4194.

(2*S*,3*R*,4a*S*,5*S*,8a*R*,5′*R*)-1-(*tert*-Butyloxycarbonyl)-2-methyl-3-hydroxy-5-(5′-methoxymethoxyoctan-1-yl)decahydroquinoline 42c. To a solution of **42a** (166 mg, 0.3 mmol) in anhydrous THF (3 mL) was added TBAF (1 M in THF, 0.9 mL, 0.9 mmol) via syringe at room temperature. This reaction mixture was stirred for 72 h and then diluted with ether before addition of water. The organic layer was separated, and the aqueous layer was extracted with ethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography, eluting with 1/5 ethyl acetate/petroleum ether to give 136 mg of **42c** (100%). $[\alpha]^{19}_D$ +2.5 (*c* 1.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, *J* = 7.2 Hz, 3H), 0.97 (q, *J* = 11.4 Hz, 1H), 1.16 (d, *J* = 7.2 Hz, 3H), 1.21−1.50 (m, 16H), 1.46 (s, 9H), 1.65 (q like, *J* = 13.8 Hz, 3H), 2.25 (m, 3H), 3.38 (s, 3H), 3.53 (p, *J* = 5.3 Hz, 1H), 3.81 and 3.86 (narrow m, 1H in 1: 2 ratio due to rotamer), 3.86 and 4.12 (m and dt, *J* = 7.2, 12.3 Hz, 2H in 2:1 ratio due to rotamer), 4.60 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, amide rotamers): δ 14.0, 14.2, 18.4, 19.8, 20.2, 20.5, 20.7, 20. 8, 25.3, 25.5, 26.8, 27.1, 27.2, 27.8, 28.4, 28.5, 28.8, 30.7, 30.8, 33.1, 33.3, 34.1, 36.6, 39.7, 52.9, 53.4, 53.6, 54.6, 55.4, 68.8, 69.1, 73.1, 79.3, 95.2, 155.5, 155.6. IR (neat): 3458, 1687, 1666 cm^{-1}. ESI-MS: *m*/*z* 464 (M + Na)$^+$. HRMS (ESI): calcd for $C_{25}H_{47}NO_5Na$, 464.3346 (M + Na)$^+$; found, 464.3352.

(2*S*,3*R*,4a*S*,5*S*,8a*R*,5′*S*)-1-(*tert*-Butyloxycarbonyl)-2-methyl-3-hydroxy-5-(5′-methoxymethoxyoctan-1-yl)decahydroquinoline 42d. Following the same procedure as mentioned above, **42d** was obtained from **42b**: $[\alpha]^{19}_D$ +1.9 (*c* 1.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, *J* = 7.2 Hz, 3H), 0.95 (q, *J* = 12 Hz, 1H), 1.11 (d, *J* = 7.2 Hz, 3H), 1.21−1.51 (m, 16H), 1.41 (s, 9H), 1.65 (q like, *J* = 13.5, 12.6 Hz, 3H), 2.23 (m, 3H), 3.33 (s, 3H), 3.49 (pent, *J* = 5.8 Hz, 1H), 3.77 and 3.82 (narrow m, 1H in 1:2 ratio due to rotamer), 3.86 and 4.12 (m and dt, *J* = 7.2, 12.3 Hz, 2H in 2:1 ratio due to rotamer), 4.60 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, amide rotamers): δ 14.2, 18.4, 19.8, 20.2, 20.5, 20.7, 20.8, 25.3, 25.4, 26.7, 26.9, 27.1, 27.3, 27.7, 28.3, 28.5, 30.6, 30.7, 33.1, 33.3, 34.1, 36.6, 39.5, 39.7, 52.8, 53.4, 53.5, 54.5, 55.4, 68.7, 69.0, 79.1, 79.2, 95.2, 155.4, 155.5. IR (neat): 3459, 1687 cm^{-1}. ESI-MS: *m*/*z* 464 (M + Na)$^+$. HRMS (ESI): calcd for $C_{25}H_{47}NO_5Na$, 464.3346 (M + Na)$^+$; found, 464.3360.

Lepadin D 2a. To a solution of **42c** (25 mg, 0.057 mmol) in 5 mL methanol (degassed) was added 5 drops of concentrated HCl. The resultant solution was heated at reflux under argon for 5 h. Then the mixture was quenched with a solution of K_2CO_3 in methanol and stirred for additional 5 h. After removal of the solvent in vacuo, the residue was chromatographed, eluting with 1:5:0.6 MeOH/ethyl acetate/NH_4OH to afford the free amine **2a** (15 mg, 85%). $[\alpha]^{19}_D$ +2.4 (*c* 0.62, MeOH). ^{1}H NMR (300 MHz, CD_3OD): δ 1.01 (t, *J* = 7.0 Hz, 3H), 1.17 (q like, *J* = 11.7, 12.0 Hz,

1H), 1.28 (d, J = 6.6 Hz, 3H), 1.35−1.62 (m, 17H), 1.65 (q like, J = 4.0, 12.0 Hz, 1H), 1.78 (m, 1H), 1.91 (ddd, J = 13.8, 13.8, 5.4 Hz, 1H), 2.38 (dq like, J = 4.2, 12.3 Hz, 1H), 2.90 (dq, J = 6.0, 6.9 Hz, 1H), 2.99 (ddd, J = 5.1, 6.0, 11.1 Hz, 1H), 3.60 (m, 1H), 3.70 (q like, J = 4.2, 4.8, 5.1 Hz, 1H). ^{13}C NMR (75 MHz, CD_3OD): δ 14.5, 19.9, 20.3, 25.6, 25.8, 27.1, 28.4, 28.5, 31.3, 34.0, 34.5, 38.4, 40.4, 40.8, 53.6, 55.8, 72.1, 72.2. IR (neat): 3336, 1463 cm^{-1}. ESI-MS: m/z 298 (M + H)$^+$.

5′-Epimer of Lepadin D 43. Following the same procedure as mentioned above, **43** was obtained from **42d**. $[\alpha]^{19}_D$ +5.8 (c 0.32, MeOH). ^{1}H NMR (300 MHz, CD_3OD): δ 1.02 (t, J = 7.0 Hz, 3H), 1.16 (q like, J = 11.7, 12.0 Hz, 1H), 1.28 (d, J = 6.6 Hz, 3H), 1.35−1.58 (m, 17H), 1.65 (q like, J = 4.0, 12.0 Hz, 1H), 1.78 (m, 1H), 1.89 (ddd, J = 13.8, 13.8, 5.4 Hz, 1H), 2.37 (dq like, J = 4.2, 12.3 Hz, 1H), 2.91 (dq, J = 6.0, 6.9 Hz, 1H), 2.99 (ddd, J = 5.1, 6.0, 11.1 Hz, 1H), 3.62 (m, 1H), 3.70 (q like, J = 4.2, 4.8, 5.1 Hz, 1H). ^{13}C NMR (75 MHz, CD_3OD): δ 14.5, 20.0, 20.2, 25.6, 25.6, 27.1, 28.4, 28.5, 31.0, 33.9, 34.5, 38.4, 40.4, 40.8, 53.6, 55.9, 71.9, 72.1. IR (neat): 3336, 1463 cm^{-1}. ESI-MS: m/z 298 (M + H)$^+$.

Hydrochloride Salts of 2a and 43. The free bases obtained above were dissolved in methanolic hydrochloride (about 1 M) and stirred for 30 min. Then solvent was evaporated in vacuo to give the hydrochloride salts of **2a** and **43**, respectively. Salt of **2a**: $[\alpha]^{19}_D$ −12 (c 1.0, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ 0.92 (t, J = 7.1 Hz, 3H), 1.11 (q like, J = 11.7, 12.3, 12.4 Hz, 1H), 1.28−1.52 (m, 17H), 1.43 (d, J = 7.2 Hz, 3H), 1.59 (br d, J = 14.3 Hz, 1H), 1.85−1.91 (m, J = 14.2, 6.8, 11.6 Hz, 3H), 2.55 (d like, J = 10.3 Hz, 1H), 3.37 (m, J = 4.2, 6.6 Hz, 1H), 3.41 (dq like, J = 2.2, 6.2 Hz, 1H) 3.51 (m, 1H), 3.91 (narrow m, 1H). ^{13}C NMR (100 MHz, CD_3OD): δ 14.8, 17.7, 20.2, 21.8, 26.2, 27.2, 27.6, 27.9, 28.2, 31.3, 34.3, 38.6, 40.4, 41.0, 55.7, 57.4, 68.3, 72.4. ESI-MS: m/z 298 (M + H)$^+$. Salt of **43**: $[\alpha]^{19}_D$ −5.7 (c 0.9, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ 0.91 (t, J = 7.1 Hz, 3H), 1.12 (q like, J = 11.7, 12.3, 12.1 Hz, 1H), 1.30−1.52 (m, 17H), 1.43 (d, J = 7.2 Hz, 3H), 1.59 (br d, J = 14.3 Hz, 1H), 1.85−1.91 (m, 3H), 2.55 (d like, J = 11 Hz, 1H), 3.38 (m, J = 5.2 Hz, 1H), 3.41 (q like, J = 6.2 Hz, 1H) 3.51 (m, 1H), 3.90 (narrow m, 1H). ^{13}C NMR (100 MHz, CD_3OD): δ 14.8, 17.7, 20.2, 21.8, 26.2, 27.2, 27.6, 27.9, 28.3, 31.3, 34.3, 38.6, 40.5, 41.0, 55.7, 57.4, 68.3, 72.4. ESI-MS: m/z 298 (M + H)$^+$.

Lepadin E 2b. To a stirred solution of 2-(*E*)-octenoic acid (41.8 mg, 0.3 mmol) in benzene (2 mL) were added *i*-Pr_2NEt (77 μL, 0.45 mmol) and $Cl_3C_6H_2COCl$ (111 mg, 0.44 mmol). After alcohol **42c** (65 mg, 0.147 mmol) was added in benzene, the mixture was stirred for 30 min. Then a solution of DMAP (48.6 mg) in benzene was added dropwise for 20 min, and the resulting solution was stirred for 8 h before it was partitioned between ether and brine. The organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography, eluting with 1/40 ethyl acetate/petroleum ether to give the ester, which was dissolved in 2 mL dry CH_2Cl_2 before trifluoroacetic acid (2 mL) was added dropwise at room temperature. After the starting material disappeared monitored by TLC, the mixture was quenched with saturated methanolic $NaHCO_3$ and then stirred for an additional 5 h. After removal of the solvent, the residue was chromatographed, eluting with 1:2:0.02 MeOH/ethyl acetate/NH_4OH to afford 2b (34 mg, 56% in two steps). $[\alpha]^{19}_D$ −5.3 (c 1.2, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (t, J = 7.0 Hz, 3H), 0.93 (t, J = 6.6 Hz, 3H), 1.09 (q like, J = 11.3, 12.3, 12.4 Hz, 1H),, 1.17 (d, J = 6.9 Hz, 3H), 1.21 (m, 1H) 1.25−1.53 (m, 22H), 1.66 (m, 2H), 1.77 (br s, 1H), 1.59 (ddd, J = 4.2, 12.0, 11.3 Hz, 1H), 2.17 (m, 1H), 2.20 (q like, J = 7.0, 7.3, 7.4 Hz, 2H), 2.91 (ddd, J = 4.0, 4.3, 10.5 Hz, 1H), 3.04 (dq like, J = 6.5, 6.3, 6.0 Hz, 1H) 3.58 (narrow m, J = 4.0 Hz, 1H), 4.78 (ddd, J = 4.6, 4.8, 4.6 Hz, 1H), 5.84 (d, J = 15.6 Hz, 1H), 6.99 (dt, J = 6.9, 15.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 14.1, 18.8, 21.0, 22.4, 23.1, 25.7, 27.2, 27.4, 27.6, 31.3, 31.4, 32.1, 32.8, 34.0, 37.5, 38.9, 39.6, 50.6, 54.6, 71.5, 73.7, 121.3, 149.6, 166.3. IR (neat): 3411, 1718, 1655 cm^{-1}. UV λ_{max} (MeOH): 211 nm (ϵ 13502). ESI-MS: m/z 422 (M + H)$^+$.

5′-Epimer of Lepadin E 44. Following the same procedure as mentioned above, **44** was obtained from **42d**. $[\alpha]^{19}_D$ −5.5 (c 0.5, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90 (t, J = 7.0 Hz, 3H), 0.93 (t, J = 6.6 Hz, 3H), 1.10 (q like, J = 11.3, 12.3, 12.4 Hz, 1H), 1.17 (d, J = 6.9 Hz, 3H), 1.20 (m, 1H) 1.28−1.54 (m, 22H), 1.66 (m, 2H), 1.75 (br, 1H), 1.59 (ddd, J = 4.2, 12.0, 11.3 Hz, 1H), 2.18 (m, 1H), 2.20 (q like, J = 7.0, 7.3, 7.4 Hz, 2H), 2.92 (ddd, J = 4.0, 4.4, 10.4 Hz, 1H), 3.04 (dq like, J = 6.5, 6.3, 6.0 Hz, 1H) 3.59 (narrow m, J = 4.3 Hz, 1H), 4.77 (ddd, J = 4.6, 4.8, 4.6 Hz, 1H), 5.84 (d, J = 15.6 Hz, 1H), 6.99 (dt, J = 6.9, 15.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 14.1, 18.8, 21.0, 22.4, 23.2, 23.6, 25.8, 27.3, 27.5, 27.6, 31.3, 31.5, 32.2, 32.8, 34.1, 37.5, 38.9, 39.7, 50.8, 54.6, 71.5, 73.7, 121.4, 149.6, 166.3. IR (neat): 3317, 1717, 1655 cm^{-1}. UV λ_{max} (MeOH): 209 nm (ϵ 13983). ESI-MS: m/z 422 (M + H)$^+$.

Lepadin H 2c. To an ice-cooled solution of compound **42c** (45 mg, 0.102 mmol) in anhydrous CH_2Cl_2 were sequentially added DMAP (36.5 mg 0.3 mmol), (2*E*,4*E*)-octadienoic acid (39 mg, 0.3 mmol), and EDC (62 mg). The mixture was warmed to room temperature and stirred for about 12 h. After water was added to quench the reaction, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give a colorless oil which was purified via chromatography, eluting with 1/40 ethyl acetate/petroleum ether to give ester. This product was dissolved in 1.5 mL of dry CH_2Cl_2, and then trifluoroacetic acid (1.5 mL) was added dropwise at room temperature. After the starting material disappeared monitored by TLC, the mixture was quenched with saturated methanolic $NaHCO_3$ and then stirred for an additional 5 h. After removal of the solvent, the residue was chromatographed, eluting with 1:2:0.02 MeOH/ethyl acetate/NH_4OH to afford **2c** (29 mg, 68% in two steps). $[\alpha]^{19}_D$ +9.5 (c 1.25, CH_2Cl_2). ^{1}H NMR (500 MHz, C_6D_6): δ 0.76 (t, J = 7.4 Hz, 3H), 0.93 (t, J = 7.0 Hz, 3H), 1.07 (m, 2H), 1.12 (d, J = 6.9 Hz, 3H), 1.18 (m, 1H), 1.20 (q like, J = 7.4, 7.3 Hz 2H), 1.24 (m, 2H), 1.32−1.42 (m, 11H), 1.49 (m, 1H), 1.56 (m, 1H), 1.60 (m, 1H), 1.68 (m, 1H), 1.75 (ddd, J = 4.0, 4.3, 10.5 Hz, 1H), 1.82 (ddd, J = 7.1, 7.1, 7.2 Hz, 1H), 2.23 (ddd, J = 4.5, 4.7, 9.8 Hz, 2H), 2.85 (br s, 2H), 2.96 (ddd, J = 4.8, 4.0 9.5 Hz, 1H), 3.12 (dq like, J = 6.3, 6.0 Hz, 1H) 3.52 (m, 1H), 4.99 (ddd, J = 4.9, 5.0, 5.0 Hz, 1H), 5.82 (dt, J = 7.0, 15.2 Hz, 1H), 5.98 (dd, J = 11.9, 15.4 Hz, 1H), 6.01 (d, J = 15.4 Hz, 1H), 7.60 (dd, J = 10.8, 15.4 Hz, 1H). ^{13}C NMR (125 MHz, C_6D_6): δ 13.7, 14.4, 19.3, 19.8, 22.1, 22.7, 22.9, 26.0, 27.6, 28.0, 30.8, 32.9, 34.1, 35.1, 38.1, 38.9, 40.3, 52.3, 55.1, 71.1, 73.3, 120.1, 129.0, 144.3, 145.6, 166.5. IR (neat): 3406, 1675 cm^{-1}. UV λ_{max} (MeOH): 264 nm (ϵ 24000). ESI-MS: m/z 420 (M + H)$^+$.

5′-Epimer of Lepadin H 45. Following the same procedure as mentioned above, **45** was obtained from **42d**. $[\alpha]^{19}_D$ +11.3 (c 1.3, CH_2Cl_2). ^{1}H NMR (500 MHz, C_6D_6): δ 0.76 (t, J = 7.4 Hz, 3H), 0.93 (t, J = 6.9 Hz, 3H), 1.06 (m, 2H), 1.20−1.29 (m, 6H), 1.32−1.43 (m, 9H), 1.48 (m, J = 8 Hz, 1H), 1.49 (m, 1H), 1.56 (m, 1H), 1.60 (m, 1H), 1.72 (m, 1H), 1.75 (ddd, J = 4.0, 4.3, 10.5 Hz, 1H), 1.82 (ddd, J = 7.1, 7.1, 7.2 Hz, 1H), 2.23 (ddd, J = 5.0, 4.4, 9.4 Hz, 2H),, 2.99 (ddd, J = 4.7, 4.5 9.5 Hz, 1H), 3.01 (br, 2H), 3.12 (dq like, J = 6.1, 6.0 Hz, 1H), 3.51 (m, 1H), 4.99 (ddd, J = 4.7, 4.7, 4.8 Hz, 1H), 5.84 (dt, J = 7.0, 15.2 Hz, 1H), 5.98 (dd, J = 11.9, 15.4 Hz, 1H), 6.01 (d, J = 15.4 Hz, 1H), 7.60 (dd, J = 10.8, 15.4 Hz, 1H). ^{13}C NMR (125 MHz, C_6D_6): δ 13.7, 14.4, 19.3, 19.6, 22.1, 22.7, 22.8, 26.2, 27.8, 28.1, 30.6, 32.9, 34.2, 35.1, 38.2, 38.9, 40.3, 52.3, 55.1, 71.2, 73.2, 120.1, 129.0, 144.3, 145.7, 166.5. IR (neat): 3406, 1675 cm^{-1}. UV λ_{max} (MeOH): 264 nm (ϵ 23168). ESI-MS: m/z 420 (M + H)$^+$.

Acknowledgment. The authors are grateful to the Chinese Academy of Sciences, National Natural Science Foundation of China (Grant 20321202) and Science and Technology Commission of Shanghai Municipality (Grants 02JC14032 and 03XD14001) for their financial support.

Supporting Information Available: Experimental for preparing compounds **8**, **16**, **27**, **28**, **33**, and **35**, and copies of ^{1}H NMR and ^{13}C NMR spectrum for key intermediates and final products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO061070C