Total Synthesis of the Marine Alkaloids (−)-Lepadins A, B, and C Based on Stereocontrolled Intramolecular Acylnitroso-Diels−Alder Reaction

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The first syntheses of (−)-lepadins A and C, as well as a new synthesis of (−)-lepadin B, have been achieved from commercially available (*S*)-malic acid. The methodology is based on an intramolecular hetero-Diels−Alder reaction of the acylnitroso compound, affording the bicyclic oxazino lactam with *trans* selectivity, which was converted to the *cis*-decahydroquinoline via asymmetric enolate hydroxylation followed by intramolecular aldol cyclization. The total syntheses proceed by employing *cis*-decahydroquinoline bearing the (*E*)-iodoalkenyl group as the common key intermediate, which underwent a convergent coupling with the (*E*)-hexenyl unit via a palladium-catalyzed Suzuki cross-coupling reaction for the elaboration of the octadienyl side chain at the C5 position.

Introduction

Lepadin A (**1**) was first isolated in 1991 by Steffan[1] from the tunicate *Clavelina lepadiformis* collected in the North Sea and represents the first example of a decahydroquinoline alkaloid from a marine natural source. Subsequently, the very closely related compounds, lepadins B (**2**) and C (**3**), along with lepadin A have been found in the predatory flatworm *Prostheceraeus villatus* and its tunicate prey *C. lepadiformis*.[2] Both lepadins A (**1**) and B (**2**) have been shown to exhibit significant in vitro cytotoxicity against human cancer cell lines.[2] Although there are no reports of the total synthesis of lepadins A and C, the Toyooka and Takahata group[3] recently published the first total synthesis of the natural enantiomer of lepadin B, which led to confirmation of the proposed relative configuration and established the absolute stereochemistry of this alkaloid as depicted in **2**.

In this study, we report the first syntheses of (−)-lepadins A and C as well as a new synthesis of (−)-lepadin B[4] by a cross-coupling reaction using the *cis*-decahydroquinoline **4** as the common key intermediate, based on retrosynthetic analysis as shown in Figure 1. This method has been effectively coupled to an intramolecular hetero-Diels−Alder reaction of an *N*-acylnitroso compound **7** as a key step for the preparation of **4**.

Results and Discussion

Although there is still no evidence for the absolute configuration of lepadins A and C, it can be inferred that their absolute stereochemistry is the same as that for lepadin B possessing the established absolute configuration since lepadins A, B, and C were found in the same marine source as described above. Thus, disconnection of lepadins (**1**−**3**) between the carbon atoms C2′ and C3′ in the alkadienyl side chain (indicated by the wavy line in Figure 1) should be appropriate for the flexible synthesis of these alkaloids, facilitating a strategy involving convergent coupling between the two fragments

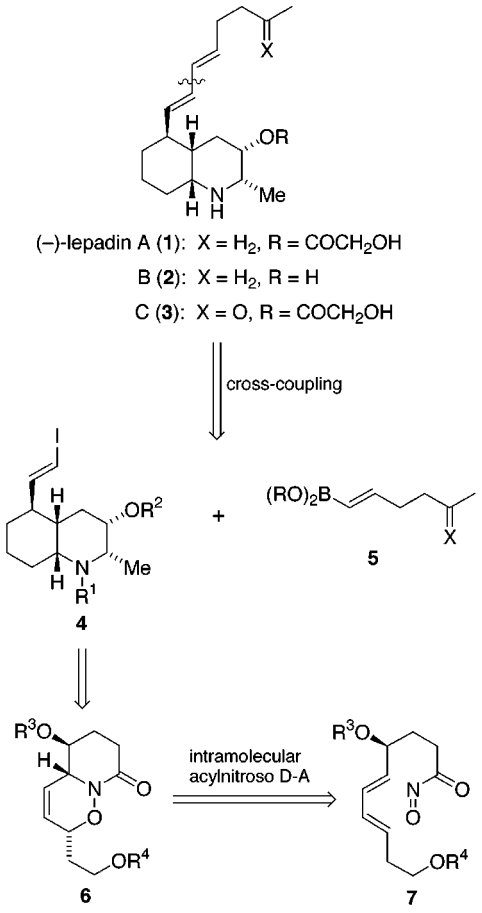

Figure 1. Retrosynthetic analysis of (-)-lepadins A, B, and C.

(1) Steffan, B. *Tetrahedron* **1991**, *47*, 8729−8732.
(2) Kubanek, J.; Williams, D. E.; de Silva, E. D.; Allen, T.; Andersen, R. J. *Tetrahedron Lett.* **1995**, *36*, 6189−6192.
(3) Toyooka, N.; Okumura, M.; Takahata, H. *J. Org. Chem.* **1999**, *64*, 2182−2183.
(4) For a part of a preliminary account on the synthesis of (−)-lepadine B, see: Ozawa, T.; Aoyagi, S.; Kibayashi, C. *Org. Lett.* **2000**, *2*, 2955−2958.

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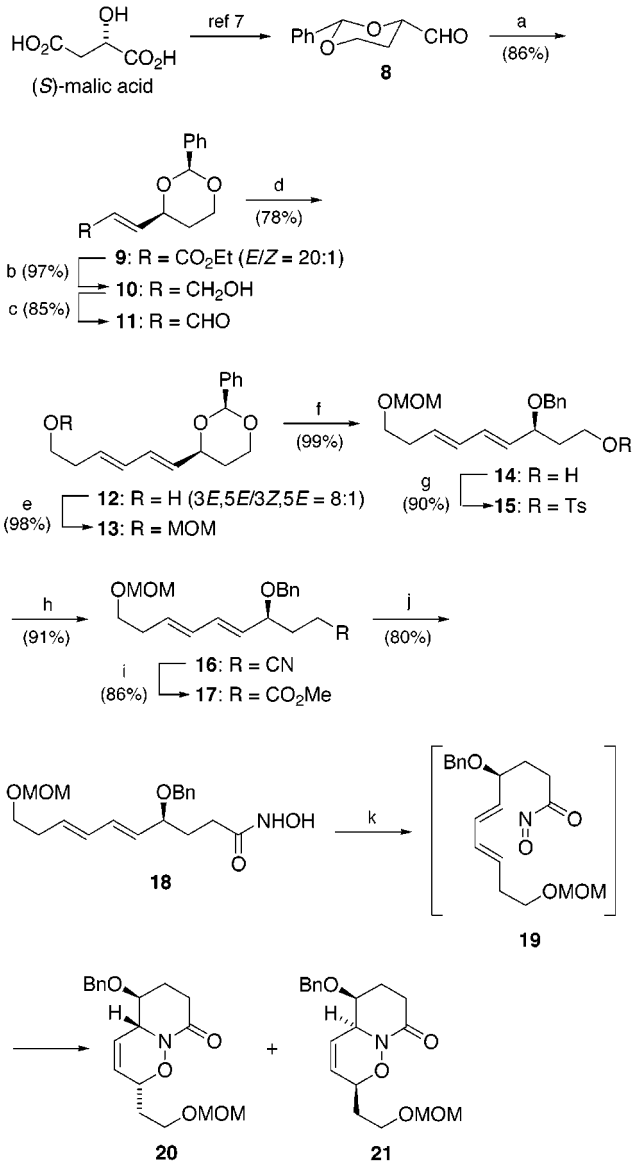
4 and **5** using Suzuki cross-coupling reaction. This strategy revealed the chiral *cis*-decahydroquinoline component **4** as the pivotal common intermediate, which might enantioselectively arise from an intramolecular hetero-Diels−Alder reaction using an *N*-acylnitroso compound **7** as the sole source of chirality.[5]

We have recently demonstrated[6] the utility of enantiopure 2,4-*O*-benzylidene-2,4-dihydroxybutanal (**8**) as a C_3 chiral synthon for the total synthesis of several natural products based on the acylnitroso-Diels−Alder approach. We thus planned to employ the (2*S*)-butanal derivative **8**, conveniently obtained on a large scale from commercially available (*S*)-malic acid,[7] as the simple starting material for the enantiomeric synthesis of the key intermediate **4**, which is a retrosynthetically derived fragment for the coupling shown in Figure 1. According to this scheme, the synthesis started from Horner−Emmons reaction of **8** with $(EtO)_2P(O)CH_2CO_2Et$ (NaH, THF) to give a 20:1 *E*/*Z* mixture of the corresponding α,β-unsaturated ester **9**. Since the reaction conditions employed in this sequence were rather harsh, epimerization at the C4 chiral center was feared to be a problem. However, chiral HPLC analysis described below revealed that no epimerization had occurred during this reaction. The major *E*-isomer of **9** obtained was subjected to DIBAL-H reduction to furnish the alcohol **10**. To test the products' separation on chiral HPLC, the racemic ester and alcohol (±)-**9** and (±)-**10** were prepared from the benzylidene dihydroxybutanal (±)-**8**, using the same procedure as that for its optically active form. Although none of the available columns (Chiralpak AD, Chiralcel OB, or Chiralcel OD) could separate (±)-**9**, (±)-**10** gave a baseline separation on chiral HPLC using a Chiralcel OD column and hexane/*i*-PrOH (9:1) as the eluant. The optical purity of **10** was thus determined to be >99% ee, which confirmed that no appreciable epimerization had occurred during the entire sequence. The resultant alcohol **10** was then underwent MnO_2 oxidation to afford the aldehyde **11**. Subsequent Wittig olefination of **11** with $Ph_3P{=}CH(CH_2)OLi$[9] yielded the desired (3*E*,5*E*)-**12** in 69% yield along with a small amount (9%) of the (3*Z*,5*E*)-isomer. Protection of (3*E*,5*E*)-**12** as its MOM ether followed by reductive ring opening of the benzylidene acetal with DIBAL-H produced the (*E*,*E*)-4,6-nonadienol **14**, which afforded the ester **17** by a sequence involving tosylation, displacement by cyanide, alkaline hydrolysis, and then esterification with diazomethane. Compound **17** was then transformed into the hydroxamic acid **18** (80%) by treatment with hydroxylamine under the alkaline conditions (Scheme 1).

Upon oxidation of **18** with tetrapropylammonium periodate (Pr_4NIO_4) under conventional nonaqueous conditions using $CHCl_3$ at 0 °C (15 min), the in situ generated

Scheme 1[a]



[a] Reagents and conditions: (a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, −20 °C to rt; (b) DIBAL-H, THF, rt; (c) MnO_2, CH_2Cl_2; (d) $Ph_3P^+(CH_2)_3OHI^-$, LiHMDS, THF, 0 °C to rt; (e) MOMCl, *i*-Pr_2NEt, CH_2Cl_2; (f) DIBAL-H, CH_2Cl_2; (g) TsCl, DMAP, Et_3N, CH_2Cl_2; (h) NaCN, DMSO, 50 °C; (i) NaOH, MeOH/H_2O, reflux; (ii) CH_2N_2, Et_2O; (j) $NH_2OH{\cdot}HCl$, KOH, MeOH, 0 °C; (k) Pr_4NIO_4, 0 °C.

Table 1. Intramolecular Acylnitroso Diels−Alder Reaction

entry	solvent	**20**:**21**[a]	yield (%)[b]
1	$CHCl_3$	1.7:1	81
2	MeOH	2.6:1	96
3	H_2O/MeOH (50:1)	3.2:1	88
4	H_2O/acetone (50:1)	4.0:1	78
5	H_2O/THF (50:1)	4.3:1	88
6	H_2O/MeCN (50:1)	4.6:1	93
7	H_2O/DMSO (50:1)	5.6:1	94
8	H_2O/DMF (50:1)	6.6:1	90

[a] Determined by ^1H NMR. [b] Isolated yield of the **20**/**21** mixture.

acylnitroso compound **19** underwent intramolecular [4 + 2] cycloaddition to yield the *trans*- (with respect to C4a and C5) oxazino lactam **20** as a major isomer with very low diastereoselectivity of 1.7:1 (see Table 1, entry 1). The use of methanol as a solvent caused a slight increase (2.6:1) in the trans/cis ratio (entry 2). In our

(5) For a review on our own achievements in the development of the intramolecular acylnitroso-Diels−Alder approach for the synthesis of nitrogen-containing natural products, see: Kibayashi, C.; Aoyagi, S. *Synlett* **1995**, 873−879.

(6) (a) Naruse, M.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1994**, *59*, 1358−1364. (b) Naruse, M.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1994**, *35*, 9213−9216. (c) Naruse, M.; Aoyagi, S.; Kibayashi, C. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1113−1124.

(7) (a) Corcoran, R. C. *Tetrahedron Lett.* **1990**, *31*, 2101−2104. (b) Thiam, M.; Slassi, A.; Chastrette, F.; Amouroux, R. *Synth. Commun.* **1992**, *22*, 83−95.

(8) The reason no epimerization occurs in Wittig reaction of the (2*R*)-enantiomer of **4** has been discussed in the previous publication (ref 6a).

(9) Maryanoff, B. E.; Reitz, A. B.; Duhl-Emswiler, B. A. *J. Am. Chem. Soc.* **1985**, *107*, 217−226.

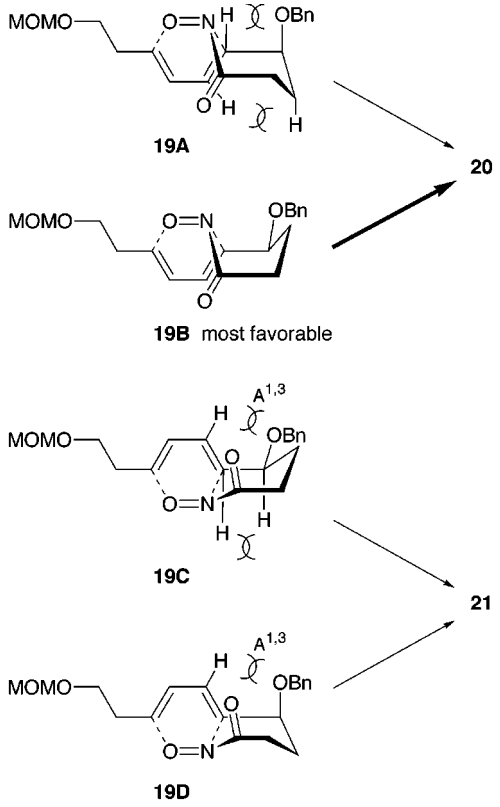


Figure 2. Endo transition state conformers and the resulting products in the intramolecular acylnitroso-Diels−Alder reaction.

earlier study, use of aqueous media for intramolecular Diels−Alder reaction of the acylnitroso compounds effected significant enhancement of the trans selectivity as a result of the hydrophobic effect on a reactant encapsulated in a cavity surrounded by a hydrogen-bonding network of water molecules.[10] Consistent with these observations, on treatment under aqueous conditions, significant enhancement of the trans selectivity was observed (entries 3−8) with the maximum selectivity of 6.6:1 observed using water/DMF (50:1).

The observed trans selectivity can be rationalized according to one of four possible endo transition state conformers **19A**−**D** shown in Figure 2. Of these conformers, **19B** leading to the trans adduct **20** is the most favored one that avoids unfavorable nonbonded interaction.

Catalytic hydrogenation (Pd−C, THF) of the olefin moiety of the *trans*-oxazino lactam **20** gave **22** (Scheme 2). The Davis methodology[11] was then exploited to introduce a hydroxyl group into the C7 position of **22** to form **23**. The sodium enolate of **22**, formed by treatment with NaHMDS (THF, −78 °C), was subjected to oxidation with (±)-2-(phenylsulfonyl)-3-phenyloxaziridine [(±)-PSP][12] followed by protection of the resultant hydroxyl group as the TBDPS ether, affording the oxygenated products **24a** and **24b** with very low diastereoselectivity of 1.1:1 favoring the requisite *S* isomer **24a** (Table 2, entry 1). The stereochemistry of these products was unambiguously assigned on the basis of ^{1}H NMR coupling constants and NOE analyses (Figure 3). When the counterion of the lactam enolate was changed from sodium to lithium, higher diastereoselectivity (3.0:1) was obtained (Table 2, entry 2). While the oxidation of sodium enolate of **22** using (1*R*)-(−)-(10-camphorsulfonyl)oxaziridine [(−)-CS][13] provided only a 1.2:1 ratio of **24a** and **24b**, switching the oxaziridine to antipodal (+)-CS led to a significant increase in the diastereoselectivity (5.0:1) (entries 3 and 4), and in the latter case using (+)-CS, switching from sodium to lithium as the counterion resulted in a further and marked improvement of the selectivity (11:1) (entries 4 and 5) consistent with the above results (entries 1 vs 2). These results revealed that the combination of **22** and the (+)-enantiomer of the oxaziridine CS constituted a matched pair leading to the desired *S* alcohol **23a**. Accordingly, the oxidation was conducted using the matched combination of the lithium enolate of **22** and (1*S*)-(+)-(8,8-dichloro-10-camphorsul-

Scheme 2

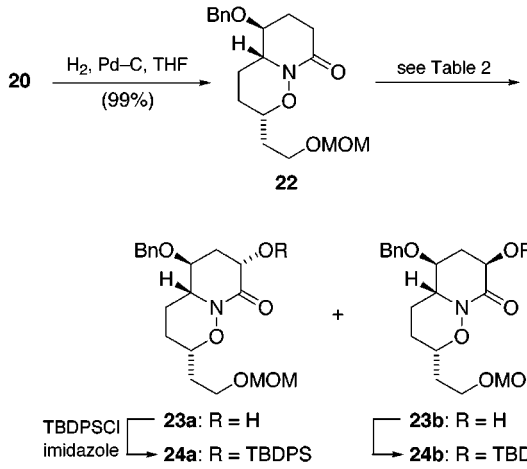
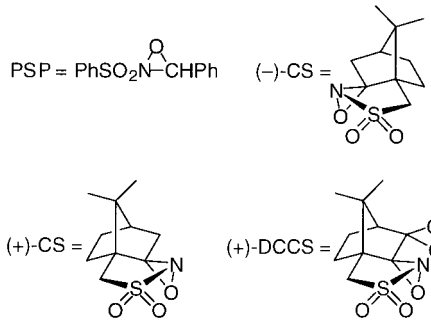


Table 2. α-Hydroxylation of Oxazinolactam 22 with Sulfonyloxaziridines



entry	sulfonyloxaziridine	base	**24a**:**24b**[a]	yield (%)[b]
1	(±)-PSP	NaHMDS	1.1:1	86
2	(±)-PSP	LiHMDS	3.0:1	60
3	(−)-CS	NaHMDS	1.2:1	80
4	(+)-CS	NaHMDS	5.0:1	79
5	(+)-CS	LiHMDS	11:1	84
6	(+)-DCCS	LiHMDS	17:1	91

[a] Determined by ^{1}H NMR. [b] Isolated yield of the **24a**/**24b** mixture.

(10) Naruse, M.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1994**, *35*, 595−598. See also ref 6b and 6c.

(11) Reviews: (a) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703−5742. (b) Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919−934.

(12) Davis, F. A.; Stringer, O. D. *J. Org. Chem.* **1982**, *47*, 1774−1775.

(13) Davis, F. A.; Weismiller, M. C.; Murphy, C. K.; Reddy, R. T.; Chen, B.-C. *J. Org. Chem.* **1992**, *57*, 7274−7285.

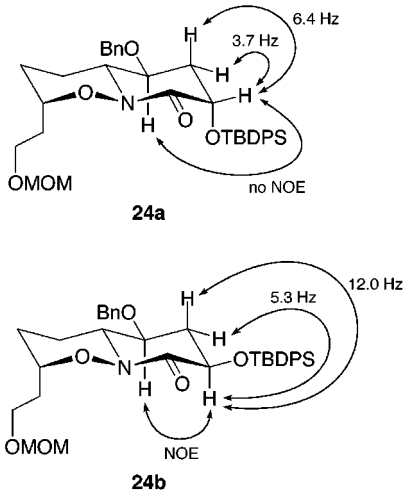


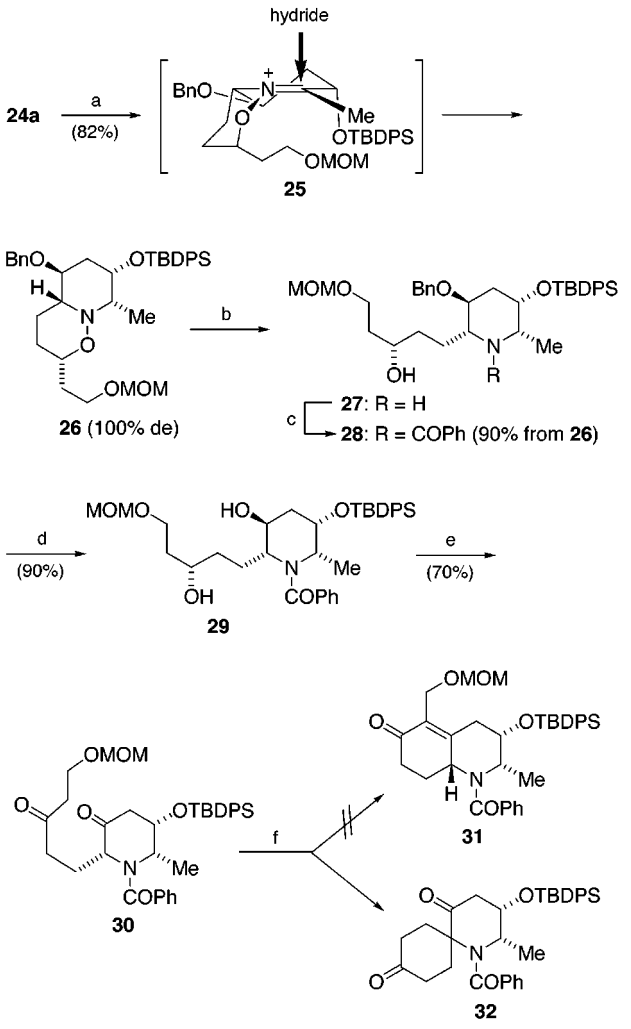
Figure 3. Stereochemical assignments of **24a** and **24b** based on the H−H coupling constants and NOE correlation determined by an NOESY experiment.

fonyl)oxaziridine [(+)-DCCS], resulting in remarkable increase in the diastereoselectivity (17:1) (entry 6).

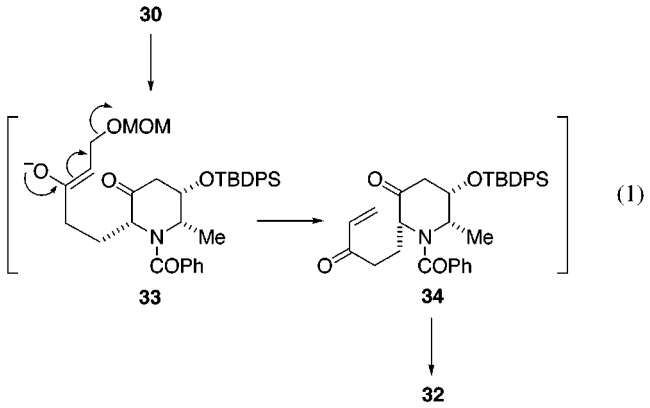
The next step required a stereoselective introduction of the methyl group into C8. This was smoothly accomplished by the tandem Grignard reaction-reduction procedure developed earlier in these laboratories.[14] Therefore **24a** was allowed to react with methylmagnesium bromide followed by $NaBH_3CN$ in acidic medium (AcOH) to give the desired (8*S*)-methylated product **26** as the only stereoisomer (82% overall yield from **24a**) (Scheme 3). The preferential formation of **26** can be interpreted by the more favorable approach of the hydride reagent from the less sterically hindered face of the iminium ion **25**, and in this case the preferred axial attack by the hydride reagent is validated by Stevens' stereoelectronic principle.[15] Reductive cleavage of the N−O bond of **26** (Zn, AcOH) afforded the amino alcohol **27**, which was converted to the diketone **30** by sequential N-benzoylation, catalytic debenzylation, and PCC oxidation. Attempted cyclization of **30** by intramolecular aldol reaction (1 N KOH/MeOH, rt) failed to construct the quinoline framework **31** and instead formed the aza spiro compound **32**. The formation of **32** is probably caused by the initial elimination of the MOM-oxy group of the enolate **33** to give the enone **34** followed by intramolecular Michael addition, as shown in eq 1.

As an alternative to the construction of the quinoline framework, we turned to the intramolecular aldol cyclization using the keto aldehyde as a substrate (Scheme 4). Reductive removal of the secondary hydroxyl group of the above-described amide alcohol **28** was achieved by Barton deoxygenation procedure[16] via the *S*-methyl dithiocarbonate **35** to afford **36**, which was subjected to a three-step sequence of reactions, involving acidic removal of the methoxymethyl group, hydrogenolysis of the benzyl group, and Swern oxidation, to provide the keto aldehyde **39** (67% overall yield from **28**). Intramolecular aldol reaction of **39** under alkaline conditions

Scheme 3[a]



[a] Reagents and conditions: (a) MeMgBr, THF, 0 °C, then $NaBH_3CN$, AcOH, THF, 0 °C; (b) Zn, 90% AcOH, 60 °C; (c) PhCOCl, then 5% KOH; (d) H_2, $Pd(OH)_2$, MeOH; (e) PCC, CH_2Cl_2; (f) 1 N KOH/MeOH, rt.



(1)

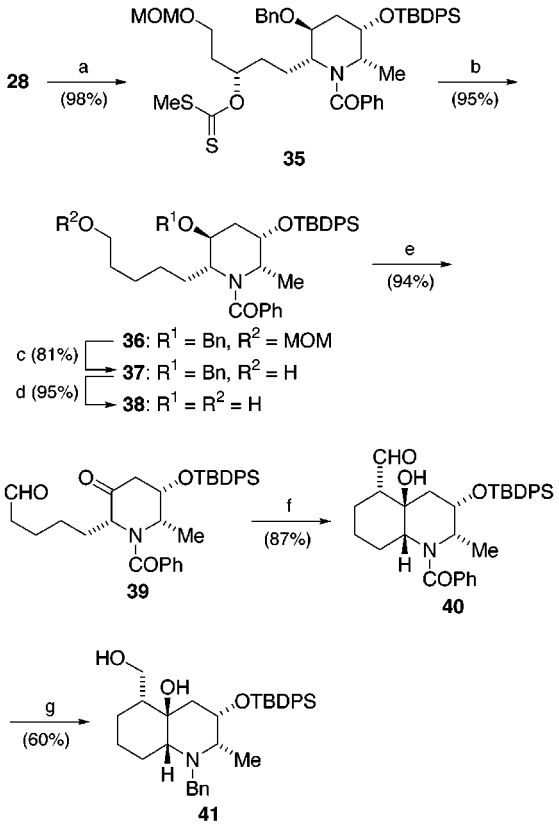
(1 N KOH/MeOH, rt) led to the desired product **40** but in very low yield (10%) accompanied with complex side reactions. However, the use of catalytic amounts of piperidine and acetic acid in refluxing benzene resulted in a clear reaction to form the aldol **40** in much improved yield (87%) as a single diastereomer, the stereochemistry of which was determined by a NOESY experiment (Figure 4) of the amino alcohol **41** derived by DIBAL-H reduction of **40**.

(14) (a) Iida, H.; Watanabe, Y.; Kibayashi, C. *J. Am. Chem. Soc.* **1985**, *107*, 5534−5535. (b) Watanabe, Y.; Iida, H.; Kibayashi, C. *J. Org. Chem.* **1989**, *54*, 4088−4097. (c) Shishido, Y.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 2876−2883. See also ref 6c.

(15) Stevens, R. V. *Acc. Chem. Res.* **1977**, *10*, 193−198.

(16) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574−1585.

Scheme 4[a]



[a] Reagents and conditions: (a) CS_2, NaH, imidazole, then MeI, THF; (b) Bu_3SnH, AIBN, benzene, reflux; (c) PPTS, *t*-BuOH, reflux; (d) H_2, $Pd(OH)_2$, MeOH; (e) $(COCl)_2$, DMSO, Et_3N, −78 → 0 °C; (f) piperidine (0.2 equiv), AcOH (0.2 equiv), benzene, reflux; (g) DIBAL-H, THF, 0 °C.

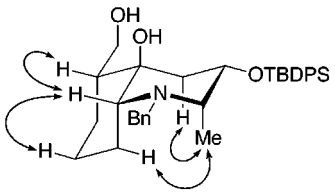
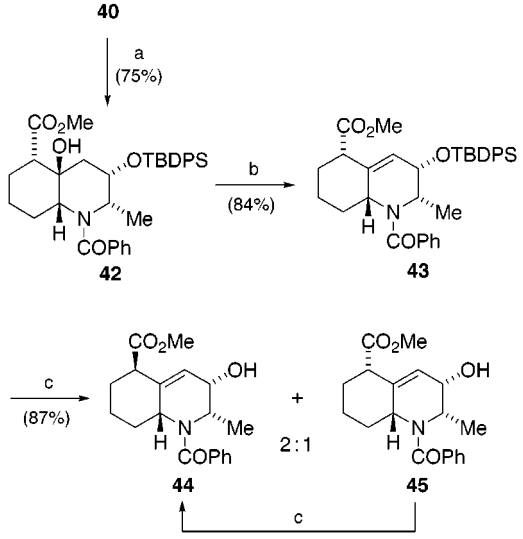


Figure 4. Stereochemical assignment of **41** based on NOE correlation.

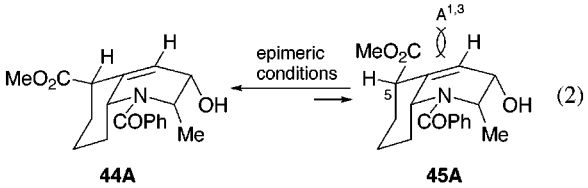
After several failed attempts at dehydration of the aldol **40**, it was converted to the *β*-hydroxyl ester **42** (PDC, then CH_2N_2), which smoothly underwent dehydration with $SOCl_2$ and Et_3N to form via anti elimination the Δ^4-octahydroquinoline **43** as a major product in 84% yield (Scheme 5).[17] Exposure of **43** to Bu_4NF (in THF) at room temperature for 5 days caused both cleavage of the TBDPS ether and epimerization at the labile C5 stereocenter under the reaction conditions to give a 2:1 chromatographically separable mixture of the 5*R*- and the 5*S*-esters **44** and **45** in favor of **44** in 87% total yield.[18] The 5*S*-isomer **45** having undesired C5 chirality could be converted to a 2:1 equilibrium mixture of **44** and **45** by

Scheme 5[a]



[a] Reagents and conditions: (a) (i) PDC, DMF; (ii) CH_2N_2, Et_2O; (b) $SOCl_2$, Et_3N, 0 °C; (c) Bu_4NF, THF, rt, 5 d.

treatment under the same conditions (Bu_4NF, THF, rt, 5 d); in this manner, the conversion of **43** into required **44** could be increased to 77% yield. The observed epimerization of **45** to **44** can be interpreted in terms of more thermodynamically stable **44A**, in which the methoxycarbonyl group orients axial to avoid a 1,3-allylic strain (eq 2).



44A **45A**

With compound **44** in hand, it was converted to the amino alcohol **47** in 87% yield through silylation followed by $LiAlH_4$ reduction of both the methoxycarbonyl and *N*-benzoyl groups (Scheme 6). Catalytic hydrogenation of **47** (5 atm H_2, Pd−C, THF) resulted in exclusive formation of the *cis*-decahydroquinoline **48**. The cis stereochemistry of **48** at the ring juncture was evident from the 2D $^1H-^1H$ NOESY NMR revealing an NOE enhancement between H-4a and H-8a. The stereochemical outcome in this case implies hydroxyl-directed hydrogenation[19] wherein the substrate is bound to the catalyst surface on the same side as the hydroxyl group, resulting in the addition of hydrogen syn to the coordinating moiety. After N-Boc protection of **48** followed by Swern oxidation, the resultant aldehyde **50** was subjected to Takai olefination[20] with CHI_3 and $CrCl_2$ in THF as a single geometric isomer to form (*E*)-alkenyl iodide **51**, which was expected to be the common key intermediate in the synthesis of the lepadin alkaloids.

Subsequent elaboration of the octadienyl side chain was achieved by palladium-catalyzed Suzuki coupling[21]

(17) In this reaction, the formation of a small amount of isomerized dehydration products was observed.

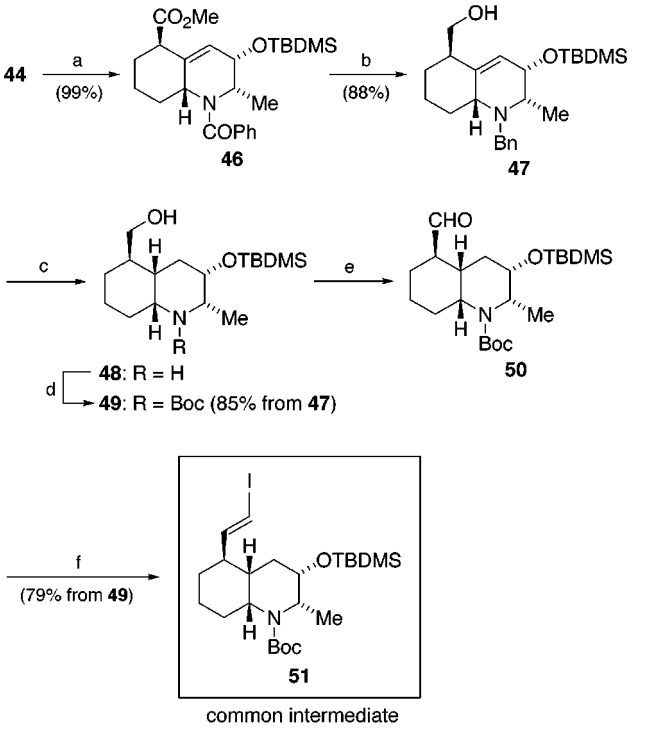
(18) Epimerization of the α-corbomethoxy substituent of **43** also occurred by treatment with sodium methoxide in methanol (rt, 7 h), leading to a 1.7:1 diastereomeric mixture of 5-*epi*-**43** and **43**, but we were unable to effect the separation of these diastereomers by chromatographic method.

(19) For a comprehensive review on heteroatom-directed organic reaction, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370.

(20) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408−7410.

(21) For a recent review, see: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

Scheme 6[a]



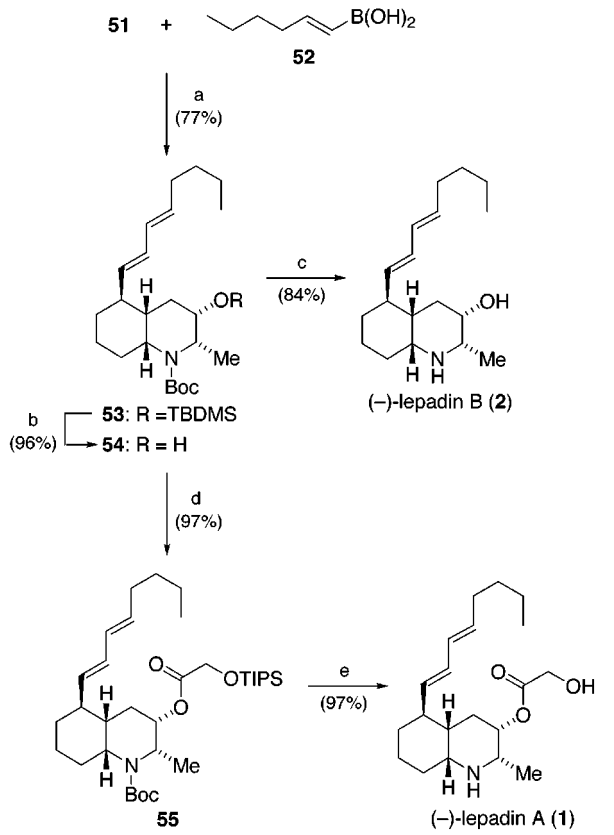
[a] Reagents and conditions: (a) TBDMSCl, imidazole, DMF; (b) $LiAlH_4$, THF, reflux; (c) H_2 (5 atm), Pd-C, THF; (d) $(Boc)_2O$, CH_2Cl_2; (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 → 0 °C; (f) CHI_3, $CrCl_2$, THF.

with (*E*)-hexenyldihydroxyborane [$Pd(PPh_3)_4$, aq KOH, THF, 50 °C] to yield **53** in 77% yield (Scheme 7). The final deprotection of the silyl group (Bu_4NF) followed by the N-Boc group (CF_3CO_2H) provided (−)-lepadin B (**2**), whose trifluoroacetate salt, obtained in a crystalline form, mp 212−214 °C ($CHCl_3$/hexane), exhibited both ^1H and ^{13}C NMR spectra identical with those of the authentic natural sample. Its specific rotation, $[\alpha]^{28}_D$ −84.3 (*c* 0.25, MeOH), was also in agreement with the literature data [$[\alpha]_D$ −96 (MeOH),[1] $[\alpha]^{26}_D$ −92.6 (*c* 0.194, MeOH)[3]].

Alternatively, compound **53** was desilylated to give the alcohol **54**, which was condensed with TIPS-protected glycolic acid by use of DCC in the presence of a catalytic amount of DMAP to form the ester **55**. After removal of the TIPS protecting group with Bu_4NF, N-Boc deprotection was carried out by treatment with CF_3CO_2H; in this case, however, it was accompanied with cleavage of the glycolate ester, resulting in ca. 1:1 mixture of lepadins A (**1**) and B (**2**). Upon treatment with $BF_3{\cdot}Et_2O$ (MeCN, 0 °C), **55** underwent deprotection of the Boc and TIPS groups without ester cleavage to provide (−)-lepadin A (**1**) in 97% yield. The trifluoroacetate salt of the synthetic material had ^1H and ^{13}C NMR spectra that were identical with those of the natural sample, although the optical rotation of the synthetic free base, $[\alpha]^{29}_D$ −55.5 (*c* 0.85, $CHCl_3$), differed in magnitude from the published[2] value $[\alpha]^{26}_D$ −8.5 (*c* 0.002, $CHCl_3$). The discrepancy in the natural lepadin A value may arise from an impurity in the isolated natural sample and/or, presumably, a measurement error due to the very small amount of the sample used for the determination of the optical rotation.

Having achieved the total syntheses of (−)-lepadins A (**1**) and B (**2**) based on the Suzuki cross-coupling, we next directed our efforts toward the coupling reaction using

Scheme 7[a]

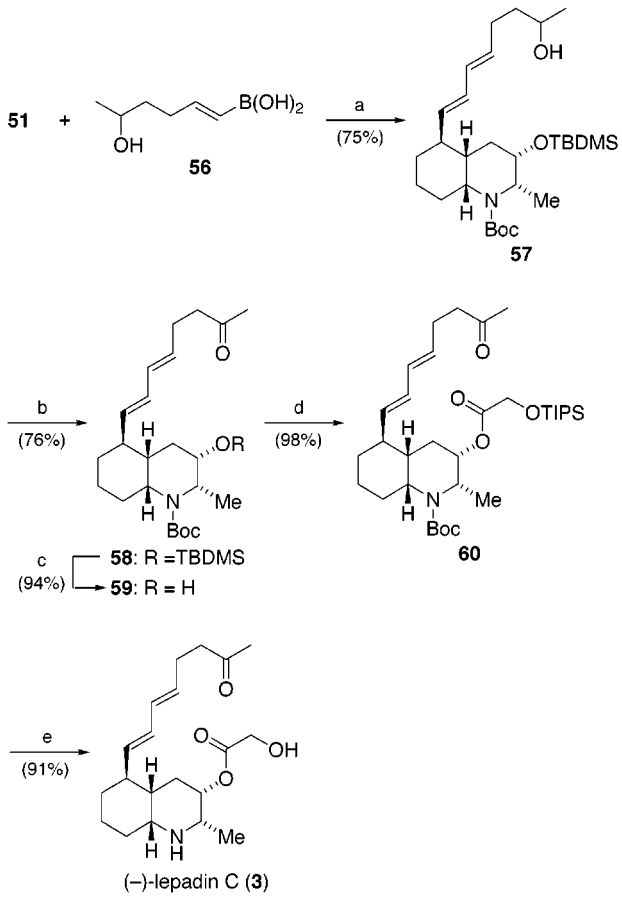


[a] Reagents and conditions: (a) $Pd(PPh_3)_4$ (5 mol%), 2 N aq KOH, THF, 50 °C; (b) Bu_4NF, THF, rt; (c) TFA, CH_2Cl_2; (d) TIPSO-CH_2CO_2H, DCC, DMAP, CH_2Cl_2; (e) $BF_3{\cdot}Et_2O$, MeCN, 0 °C.

the key intermediate **51** that would allow for the synthesis of (−)-lepadin C (**3**). Thus, **51** underwent the coupling with (*E*)-(5-hydroxyhexenyl)dihydroxyborane (**56**) under the Suzuki cross-coupling conditions to produce **57** in 75% yield (Scheme 8). Swern oxidation of **57** followed by desilylation yielded the keto alcohol **59**, which underwent the DCC-DMAP esterification with TIPS protected glycolic acid to give the keto ester **60**. Finally, deprotection of the Boc and TIPS protecting groups was accomplished by treatment with $BF_3{\cdot}Et_2O$ (MeCN, 0 °C) to form (−)-lepadin C (**3**) in 91% yield, whose trifluoroacetate salt possessed both ^1H and ^{13}C NMR spectra identical with those of the trifluoroacetate of the natural product. Although the optical rotation of **3**·CF_3CO_2H, $[\alpha]^{27}_D$ −56.5 (*c* 0.48, MeOH), was found to be considerably higher than the reported[2] value $[\alpha]_D$ −25 (MeOH), the same negative sign and the coincidence of the NMR spectra of synthetic **3** with those of the natural product indicated that the absolute stereochemistry of natural lepadin C is assigned as shown by **3**.

In summary, the first syntheses of (−)-lepadins A and C, as well as a new synthesis of (−)-lepadin B have been achieved from commercially available (*S*)-malic acid. The methodology is based on an intramolecular hetero-Diels−Alder reaction of the acylnitroso compound affording the *trans*-oxazino lactam, which was converted to the *cis*-decahydroquinoline as the common key intermediate. The total syntheses proceed by employing a convergent coupling with the (*E*)-hexenyl unit using palladium-catalyzed Suzuki cross-coupling reaction for the elaboration of the octadienyl side chain.

Scheme 8[a]



[a] Reagents and conditions: (a) $Pd(PPh_3)_4$ (5 mol%), 2 N aq KOH, THF, 50 °C; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 → 0 °C; (c) Bu_4NF, THF; (d) $TIPSOCH_2CO_2H$, DCC, DMAP, CH_2Cl_2; (e) $BF_3{\cdot}Et_2O$, MeCN, 0 °C.

Experimental Section[22]

(2*R*,4a*R*,5*S*)- and (2*S*,4a*S*,5*S*)-5-(Benzyloxy)-2-[2-(methoxymethoxy)ethyl]-4a,5,6,7-tetrahydropyrido[1,2-*b*][1,2]-oxazin-8(2*H*)-one (20 and 21). Typical Procedure. To an ice-cooled, vigorously stirred suspension of solid tetrapropylammonium (meta)periodate (2.89 g, 7.67 mmol) in H_2O (1.35 L) was added a solution of **18** (1.79 g, 5.11 mmol) in DMF (27 mL) by portions. After being stirred at 0 °C for 30 min, the reaction mixture was quenched with solid $Na_2S_2O_3$ (1 g). The mixture was extracted with $CHCl_3$ (3 × 500 mL), and the combined extracts were washed with brine and dried. Concentration in vacuo followed by chromatography ($CHCl_3$/MeOH, 200:1) yielded a 1.6 g (90%) of a mixture of **20** and **21** in a ratio of 6.6:1 (based on ^1H NMR) as a colorless oil. This mixture could be separated by further chromatography (Et_2O/MeOH, 200:1) and the first fractions gave **20** as a colorless oil: $[\alpha]^{23}_D$ −32.0 (*c* 1.38, $CHCl_3$); IR (neat) 1675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.72−1.93 (3H, m), 2.18−2.23 (1H, m), 2.37 (1H, ddd, J = 17.6, 12.1, 5.9 Hz), 2.61 (1H, ddd, J = 17.4, 5.5, 3.2 Hz), 3.36 (3H, s), 3.43 (1H, ddd, J = 10.9, 8.7, 3.5 Hz), 3.70 (1H, td, J = 9.9, 5.2 Hz), 3.90 (1H, ddd, J = 9.7, 8.9, 4.8 Hz), 4.23−4.39 (1H, m), 4.56 and 4.69 (2H, ABq, J = 11.5 Hz), 4.62 and 4.64 (2H, ABq, J = 6.4 Hz), 5.93 (1H, ddd, J = 10.3, 3.6, 2.1 Hz), 6.02 (1H, td, J = 10.3, 1.5 Hz), 7.28−7.49 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2, 28.9, 33.8, 55.3, 60.5, 64.4, 71.6, 76.3, 76.5, 96.7, 124.0, 127.8 (2 carbons), 128.1, 128.6 (2 carbons), 128.8, 137.5, 164.8; CIMS (isobutane) *m*/*z* (relative intensity) 348 (MH^+, 100), 316 (22). Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.56; H, 7.23; N, 3.99.

(22) See Supporting Information for General Procedures section.

The second fractions gave **21** as a colorless oil: $[\alpha]^{23}_D$ +69.8 (*c* 1.30, $CHCl_3$); IR (neat) 1667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.76−1.85 (2H, m), 1.99−2.08 (1H, m), 2.15−2.20 (1H, m), 2.41−2.49 (1H, m), 2.72 (1H, ddd, J = 17.1, 13.2, 6.1 Hz), 3.36 (3H, s), 3.70 (1H, td, J = 9.9, 5.2 Hz), 3.87−3.96 (2H, m), 4.45−4.49 (1H, m), 4.46 and 4.65 (2H, ABq, J = 12.0 Hz), 4.61−4.68 (1H, m), 4.63 and 4.64 (2H, ABq, J = 6.4 Hz), 5.68 (1H, td, J = 10.3, 1.6 Hz), 6.00 (1H, ddd, J = 10.3, 3.9, 2.4 Hz), 7.26−7.48 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3, 28.0, 33.6, 55.3, 60.9, 64.4, 70.9, 73.1, 75.7, 96.6, 123.3, 127.4 (2 carbons), 127.8, 128.5 (2 carbons), 129.0, 137.8, 165.2; EIMS *m*/*z* (relative intensity) 348 (M^+ + 1, 0.04), 316 (M^+ − OMe, 0.5), 302 (3), 286 (1), 174 (5), 140 (15), 91 (100); CIMS (isobutane) *m*/*z* (relative intensity) 348 (MH^+, 100), 316 (26); HRMS (EI) calcd for $C_{18}H_{22}NO_4$ (M^+ − OMe) 316.1549, found 316.1539.

(2*S*,4a*R*,5*S*,7*S*)- and (2*S*,4a*R*,5*S*,7*R*)-5-(Benzyloxy)-7-{[*tert*-butyl(diphenyl)silyl]oxy}-2-[2-(methoxymethoxy)-ethyl]hexahydropyrido[1,2-*b*][1,2]oxazin-8(2*H*)-one (24a and 24b). Typical Procedure. To a stirred, cooled (−78 °C) solution of **22** (1 g, 2.86 mmol) in THF (20 mL) was added a 1.0 M solution of lithium bis(trimethylsilyl)amide in THF (5.72 mL, 5.72 mmol). After 1 h at −78 °C, a solution of (+)-[(8,8-dichlorocamphoryl)sulfonyl]oxaziridine (1.71 g, 5.72 mmol) in THF (17 mL) was slowly added, and stirring was continued for 5 h at the same temperature. The reaction was quenched with saturated aqueous NH_4Cl (30 mL) and then allowed to warm to room temperature, and the layers were separated. The aqueous layer was extracted with $CHCl_3$ (3 × 50 mL), and the combined organic phases were washed with brine, dried, and concentrated in vacuo. Purifcation of the residue by chromatography ($CHCl_3$/MeOH, 200:1) provided an inseparable mixture (1.18 g) of **23a** and **23b** in a ratio of 17:1 (based on ^1H NMR) as a colorless oil. This mixture (1.18 g, 3.23 mmol) was dissolved in DMF (23 mL), and imidazole (1.32 g, 19.4 mmol) and *tert*-butyldiphenylsilyl chloride (2.49 mL, 9.69 mmol) were added. The mixture was stirred at room temperature for 42 h, then quenched with 2 N aqueous HCl, and diluted with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with saturated $NaHCO_3$ (20 mL) and brine and dried. Evaporation of the solvent and chromatography (hexane/AcOEt, 10:1) afforded a mixture (1.57 g, 91%) of **24a** and **24b** as a colorless oil. This mixture was subjected to further chromatography (hexane/AcOEt, 4:1), yielding the 7*R*-product **24b** as a colorless oil: $[\alpha]^{23}_D$ +12.4 (*c* 1.29, $CHCl_3$); IR (neat) 1694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 (9H, s), 1.28−1.40 (1H, m), 1.50−1.60 (2H, m), 1.81 (1H, q, J = 12.0 Hz), 1.91−2.03 (3H, m), 2.19 (1H, ddd, J = 12.1, 5.2, 3.6 Hz), 3.12 (1H, ddd, J = 11.9, 8.7, 3.5 Hz), 3.34 (3H, s), 3.45−3.53 (1H, m), 3.54−3.62 (1H, m), 3.67 (1H, ddd, J = 9.6, 8.5, 5.6 Hz), 3.99 (1H, dd, J = 12.0, 5.3 Hz), 4.20 and 4.46 (2H, ABq, J = 11.7 Hz), 4.28−4.33 (1H, m), 4.59 and 4.62 (2H, ABq, J = 6.4 Hz), 7.15−7.19 (2H, m), 7.16−7.49 (10H, m), 7.72−7.88 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 23.7, 26.4, 26.8, 30.0, 34.9, 55.1, 62.9, 64.6, 66.7, 71.1, 73.8, 75.5, 96.5, 127.5 (2 carbons), 127.6 (2 carbons), 127.9 (2 carbons), 128.3, 128.4 (2 carbons), 129.7, 129.7, 132.9, 134.2, 135.9 (2 carbons), 136.3 (2 carbons), 137.2, 166.8; CIMS (isobutane) *m*/*z* 604 (MH^+, 100). Anal. Calcd for $C_{35}H_{45}NO_6Si$: C, 69.62; H, 7.51; N, 2.32. Found: C, 69.34; H, 7.57; N, 2.29.

Further elution afforded the 7*S*-product **24a** as a colorless oil: $[\alpha]^{23}_D$ +27.5 (*c* 1.26, $CHCl_3$); IR (neat) 1685 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 1.13−1.19 (1H, m), 1.23 (9H, s), 1.28−1.32 (1H, m), 1.33−1.42 (2H, m), 1.43−1.54 (1H, m), 1.61−1.72 (1H, m), 1.79 (1H, ddd, J = 13.4, 6.5, 3.0 Hz), 2.29 (1H, ddd, J = 14.5, 9.9, 4.5 Hz), 3.22 (3H, s), 3.44−3.54 (2H, m), 3.79−3.87 (1H, m), 4.00 and 4.12 (2H, ABq, J = 11.9 Hz), 4.08−4.15 (1H, m), 4.28−4.34 (1H, m), 4.50 (1H, dd, J = 6.4, 3.7 Hz), 4.55 and 4.57 (2H, ABq, J = 6.3 Hz), 7.05−7.14 (4H, m), 7.15−7.29 (7H, m), 7.78−8.07 (4H, m); ^{13}C NMR (100 MHz, C_6D_6) δ 19.3, 24.4, 26.9, 27.1, 30.1, 32.8, 55.3, 62.9, 64.8, 68.9, 71.0, 74.5, 76.2, 96.6, 127.6 (2 carbons), 127.7 (2 carbons), 127.8 (2 carbons), 127.9, 128.5 (2 carbons), 129.9, 129.9, 132.4, 133.9, 135.8 (2 carbons), 136.2 (2 carbons), 137.5, 164.6; CIMS

(isobutane) *m*/*z* 604 (MH^+, 100). Anal. Calcd for $C_{35}H_{45}NO_6Si$: C, 69.62; H, 7.51; N, 2.32. Found: C, 69.47; H, 7.58; N, 2.41.

(2*S*,4a*R*,5*S*,7*S*,8*S*)-5-(Benzyloxy)-7-{[*tert*-butyl(diphenyl)silyl]oxy}-2-[2-(methoxymethoxy)ethyl]-8-methyloctahydropyrido[1,2-*b*][1,2]oxazine (26). To a stirred solution of **24** (2.94 g, 4.87 mmol) in THF (60 mL) was added methylmagnesium bromide (0.92 M solution in THF, 10.6 mL, 9.75 mmol) at 0 °C. After 10 min, the mixture was quenched with 10% aqueous NaOH (40 mL). The layers were separated ,and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined extracts were washed with brine, dried, and concentrated in vacuo to afford the crude enamine (3.62 g), which was immediately dissolved in THF (40 mL) and acidified by a addition of AcOH. To this was added $NaBH_3CN$ (1.61 g, 24.4 mmol) in one portion at 0 °C. After being stirred for 1 h, the mixture was neutralized with 10% aqueous NaOH (40 mL) and extracted with $CHCl_3$ (3 × 30 mL). The combined extracts were washed with brine, dried, and concentrated in vacuo. The residue was purified by chromatography (hexane/AcOEt, 20:1) to afford **26** (2.4 g, 82%) as a colorless oil: $[\alpha]^{22}_D$ +102.4 (*c* 1.41, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (12H, s), 1.24−1.32 (2H, m), 1.51−1.62 (1H, m), 1.67−1.77 (1H, m), 1.82−1.95 (1H, m), 2.07−2.13 (1H, m), 2.17 (1H, dt, J = 12.8, 3.7 Hz), 2.39−2.47 (2H, m), 2.68−2.78 (1H, m), 3.36 (3H, s), 3.54−3.74 (3H, m), 4.01−4.08 (1H, m), 4.09−4.18 (1H, m), 4.20 and 4.27 (2H, ABq, J = 11.3 Hz), 4.63 (2H, s), 7.19−7.33 (5H, m), 7.35−7.48 (6H, m), 7.70−7.80 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7, 19.8, 23.1, 27.2, 28.1, 30.8, 36.8, 55.1, 63.6, 64.9, 69.2, 71.4, 71.7, 72.8, 76.0, 96.5, 127.5 (2 carbons), 127.6 (2 carbons), 127.7 (2 carbons), 127.8, 128.4 (2 carbons), 129.7, 129.8, 134.0, 134.3, 136.1 (2 carbons), 136.2 (2 carbons), 138.5; CIMS (isobutane) *m*/*z* 604 (MH^+, 100). Anal. Calcd for $C_{36}H_{49}NO_5Si$: C, 71.60; H, 8.18; N, 2.32. Found: C, 71.65; H, 8.02; N, 2.40.

(2*S*,3*S*,4a*R*,5*S*,8a*R*)-1-Benzoyl-3-{[*tert*-butyl(diphenyl)silyl]oxy}-4a-hydroxy-2-methyldecahydro-5-quinolinecarbaldehyde (40). A solution of **39** (437 mg, 0.786 mmol), AcOH (9.4 mg, 0.157 mmol), and piperidine (13.4 mg, 0.157 mmol) in benzene (40 mL) was refluxed for 1 h with a Dean−Stark apparatus. After being allowed to cool to room temperature, the mixture was concentrated in vacuo. The resulting oil was purified by chromatography (hexane/AcOEt, 1:1) to give **40** (38.1 mg, 87%) as a colorless oil: $[\alpha]^{24}_D$ +5.20 (*c* 2.23, $CHCl_3$); IR (neat) 3382, 1718, 1614 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, amide rotamer) δ 0.97 and 1.10 (total 9H in 1.5:1 ratio, each br s), 1.27 (3H, d, J = 7.1 Hz), 1.28−1.48 (2H, m), 1.70−1.89 (3H, m), 1.89−2.05 and 2.30−2.39 (total 2H in 1.5:1 ratio, each m), 2.29 (1H, br s), 4.03 and 3.39 (total 1H in 1.5:1 ratio, each br s), 4.41 (1H, quint, J = 5.4 Hz), 4.45−4.57 and 5.10 (total 1H in 1.5:1 ratio, m and br s), 7.19−7.73 (15H, m), 9.66 and 9.45 (total 1H in 1.5:1 ratio, each br s); ^{13}C NMR (100 MHz, $CDCl_3$, amide rotamer) δ 16.8, 18.9, 22.5, 23.7, 26.8 (3 carbons), 30.2, 30.4, 53.5, 57.1, 60.0, 66.3, 72.9, 126.0, 127.5 (2 carbons), 127.6 (4 carbons), 128.4 (2 carbons), 129.0, 129.5, 129.7 (2 carbons), 133.4, 133.5, 135.2, 135.5 (2 carbons), 136.6, 172.8, 204.6; EIMS *m*/*z* (relative intensity) 555 (M^+, 0.1), 498 (M^+ − *t*-Bu, 12), 296 (5), 268 (42), 105 (36); HRMS (EI) calcd for $C_{30}H_{32}NO_4Si$ (M^+ − *t*-Bu) 498.2101, found 498.2086.

Methyl (2*S*,3*S*,5*R*,8a*R*)-1-Benzoyl-3-hydroxy-2-methyl-1,2,3,5,6,7,8,8a-octahydro-5-quinolinecarboxylate (44) and Methyl (2*S*,3*S*,5*S*,8a*R*)-1-Benzoyl-3-hydroxy-2-methyl-1,2,3,5,6,7,8,8a-octahydro-5-quinolinecarboxylate (45). To a stirred solution of **43** (126 mg, 0.222 mmol) in THF (3 mL) was added a 1 M tetrabutylammonium fluoride solution in THF (1.11 mL, 1.11 mmol) at 0 °C. After being stirred at room temperature for 5 d, the mixture was poured into saturated aqueous NH_4Cl (10 mL) and extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with brine, dried, and concentrated in vacuo. Chromatography (hexane/AcOEt, 1:1) of the residue provided a mixture of **44** and **45** (63.2 mg, 87%) in a ratio of 2:1 (based on ^{1}H NMR) as a colorless oil. This mixture was separated by further chromatography (hexane/AcOEt, 1:1), and the first fractions afforded **45** as a colorless oil: $[\alpha]^{25}_D$ −23.4 (*c* 0.82, $CHCl_3$); IR (neat) 3382, 1738, 1612 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, amide rotamer) δ 1.19 (3H, d, J = 6.9 Hz), 1.50−1.73 (3H, m), 1.74−2.02 (3H, m), 2.32 (1H, br s), 3.12 (1H, br s), 3.76 (3H, br s), 4.09 (1H, br s), 4.36 (1H, br s), 4.65 (1H, br s), 5.18 (1H, br s), 7.27−7.45 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$, amide rotamer) δ 14.4, 23.8, 29.5, 32.3, 49.3, 51.6, 51.8, 52.6, 66.4, 119.8, 125.8, 128.5 (2 carbons), 129.2 (2 carbons), 134.6, 136.6, 170.5, 172.8; EIMS *m*/*z* (relative intensity) 330 (M^+ + 1, 21), 311 (13), 296 (98), 270 (23), 215 (5), 182 (24), 147 (83), 104 (100); HRMS (EI) calcd for $C_{19}H_{23}NO_4$ (M^+) 329.1627, found 329.1632.

The second fractions afforded **44** as a colorless oil: $[\alpha]^{25}_D$ −132.4 (*c* 1.24, $CHCl_3$); IR (neat) 3300, 1730, 1604 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, amide rotamer) δ 1.17 (3H, d, J = 6.5 Hz), 1.37−1.80 (4H, m), 1.95 (1H, br s), 2.12−2.47 (2H, m), 3.36−3.42 (1H, m), 3.70 (3H, br s), 4.07 (1H, br s), 4.40 (1H, br s), 4.72 (1H, br s), 5.47 (1H, br s), 7.24−7.41(5H, m); ^{13}C NMR (100 MHz, $CDCl_3$, amide rotamer) δ 14.4, 21.8, 28.8, 32.0, 48.5, 50.2, 52.0, 52.7, 66.1, 124.7, 125.8, 128.4 (2 carbons), 129.1 (2 carbons), 133.8, 136.9, 170.3, 173.3; EIMS *m*/*z* (relative intensity) 329 (M^+, 59), 311 (8), 296 (100), 270 (49), 171 (13), 148 (47), 104 (80); HRMS (EI) calcd for $C_{19}H_{23}NO_4$ (M^+) 329.1627, found 329.1627.

***tert*-Butyl (2*S*,3*S*,4a*S*,5*R*,8a*R*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-5-(hydroxymethyl)-2-methyloctahydro-1(2*H*)-quinolinecarboxylate (49).** To a solution of **47** (69 mg, 4.66 mmol) in THF (4 mL) was added 10% palladium on activated carbon (100 mg), and the resulting suspension was shaken with hydrogen at 5 atm for 18 h. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo to provide 58 mg of crude ((2*S*,3*S*,4a*S*,5*R*,8a*R*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-2-methyldecahydro-5-quinolinyl)methanol **48** as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (3H, s), 0.11 (3H, s), 0.97 (9H, s), 1.17 (2H, qd, J = 12.7, 3.5 Hz), 1.36 (3H, d, J = 5.9 Hz), 1.52−1.66 (4H, m), 1.69−1.95 (4H, m), 2.10−2.23 (2H, m), 2.32 (1H, br s), 3.12 (2H, br d, J = 5.1 Hz), 3.32 (1H, br s), 3.67 (1H, A of ABX, J = 10.8, 2.9 Hz), 3.72 (1H, B of ABX, J = 10.9, 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$,) δ −5.1, −4.2, 16.9, 17.9, 20.5, 25.9, 29.0, 29.9, 32.2, 33.1, 36.9, 56.5, 57.1, 64.6, 67.5.

This product was dissolved in CH_2Cl_2 (2 mL), and triethylamine (28 mg, 0.276 mmol) and di-*tert*-butyl dicarbonate (59 mg, 0.270 mmol) were sequentially added at 0 °C. The mixture was stirred at room temperature for 15 h, diluted with $CHCl_3$ (100 mL), washed with brine, and dried. Evaporation of the solvent followed by purification of the crude material by chromatography (hexane/AcOEt, 4:1) gave **49** (60.8 mg, 85%) as a colorless oil: $[\alpha]^{25}_D$ +6.45 (*c* 1.10, $CHCl_3$); IR (neat) 3440, 1690 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, amide rotamer) δ 0.06 and 0.07 (total 6H in 2:1 ratio, each s), 0.89 and 0.88 (total 9H in 2:1 ratio, each s), 1.12 (3H, d, J = 7.0 Hz), 1.33 (2H, br d, J = 11.2 Hz), 1.45 (9H, s), 147−1.72 (5H, m), 1.74−1.81 (1H, m), 1.84−1.92 (1H, m), 1.96 (1H, q, J = 12.2 Hz), 3.65 (1H, t, J = 7.6 Hz), 3.73 (1H, q, J = 10.4 Hz), 3.79 (1H, ddd, J = 11.0, 6.3, 4.6 Hz), 4.07 and 3.98 (total 1H in 2:1 ratio, each dt, J = 12.5, 4.3 Hz), 4.18 and 4.30 (total 1H in 2:1 ratio, each quint, J = 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, amide rotamer) δ −4.9, −4.7, 15.3 and 14.9 (1 carbon in 2:1 ratio), 18.0, 21.3, 22.6 and 22.5 (1 carbon in 2:1 ratio), 25.8 (3 carbons), 28.0 and 28.7 (1 carbon in 2:1 ratio), 28.4 (3 carbons), 30.4 and 30.6 (1 carbon in 2:1 ratio), 34.6 and 35.0 (1 carbon in 2:1 ratio), 42.6 and 42.8 (1 carbon in 2:1 ratio), 48.9 and 49.9 (1 carbon in 2:1 ratio), 51.4 and 50.6 (1 carbon in 2:1 ratio), 64.0 and 64.3 (1 carbon in 2:1 ratio), 70.7 and 70.4 (1 carbon in 2:1 ratio), 79.4 and 79.3 (1 carbon in 2:1 ratio), 155.1 and 155.2 (1 carbon in 2:1 ratio); EIMS *m*/*z* (relative intensity) 413 (M^+, 3), 357 (5), 341 (10), 312 (10), 299 (100), 282 (30); HRMS (EI) calcd for $C_{22}H_{43}NO_4Si$ (M^+) 413.2961, found 413.2934.

***tert*-Butyl (2*S*,3*S*,4a*S*,5*R*,8a*R*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-5-[(*E*)-2-iodoethenyl]- 2-methyloctahydro-1(2*H*)-quinolinecarboxylate (51).** To a stirred, cooled (−78 °C) solution of oxalyl chloride (102 mg, 0.803 mmol) in CH_2Cl_2 (5 mL) was added dropwise a solution of DMSO (125 mg, 1.60 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred at −78 °C for 30 min followed by dropwise addition of a solution of **49** (167 mg, 0.403 mmol) in CH_2Cl_2 (4 mL). After the mixture was stirred at −78 °C for 1 h, triethylamine (243 mg, 2.40 mmol)

was added, and the mixture was stirred at same temperature for a further 5 min. The mixture was then allowed to warm to room temperature and stirred for 1 h. Saturated aqueous $NaHCO_3$ (10 mL) was added to the mixture, the layers were separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were washed with brine and dried. The solvent was removed in vacuo to provide the aldehyde **50** (195 mg, 117%) as a colorless oil, which was used for next reaction without further purification. Thus a mixture of aldehyde **50** (195 mg, 0.474 mmol) and iodoform (370 mg, 0.940 mmol) in THF (12 mL) was added dropwise to a stirred suspension of chromium(II) chloride (550 mg, 4.48 mmol) in THF (5 mL) at room temperature. After being stirred for 30 min, the mixture was poured into saturated aqueous $NaHCO_3$ (20 mL) and extracted with $CHCl_3$ (3 × 30 mL). The combined organic phases were dried and concentrated in vacuo to give a residual oil, which was purified by chromatography (hexane/AcOEt, 1:1) to afford **51** (168 mg, 79%) as a colorless oil: $[\alpha]^{25}_D$ −34.4 (*c* 1.11, $CHCl_3$); IR (neat) 1687 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, amide rotamer) δ 0.07 and 0.06 (total 6H in 2:1 ratio, each s), 0.89 and 0.88 (total 9H in 2:1 ratio, each s), 1.11 (3H, d, J = 6.9 Hz), 1.34 (2H, dt, J = 12.2, 3.4 Hz), 1.46 (9H, s), 147−1.65 (5H, m), 1.70−1.85 (2H, m), 1.91 (1H, q, J = 12.7 Hz), 2.36 (1H, br s), 3.76 (1H, ddd, J = 10.9, 6.4, 4.3 Hz), 4.10−4.17 and 3.93−3.99 (total 1H in 2:1 ratio, each m), 4.18 and 4.31 (total 1H in 2:1 ratio, each quint, J = 6.6 Hz), 6.10 and 6.13 (total 1H in 2:1 ratio, each d, J = 13.7 Hz), 6.78 and 6.71 (total 1H in 2:1 ratio, each dd, J = 14.4, 7.8, Hz); ^{13}C NMR (125 MHz, $CDCl_3$, amide rotamer) δ −4.9, −4.7, 15.2 and 14.9 (1 carbon in 2:1 ratio), 18.0, 21.1 and 21.2 (1 carbon in 2:1 ratio), 25.4, 25.7 (3 carbons), 27.8, 28.4 (3 carbons), 30.2, 38.5 and 38.3 (1 carbon in 2:1 ratio), 46.7 and 46.4 (1 carbon in 2:1 ratio), 48.8 and 49.6 (1 carbon in 2:1 ratio), 51.4 and 50.5 (1 carbon in 2:1 ratio), 70.5 and 70.2 (1 carbon in 2:1 ratio), 75.6 and 75.4 (1 carbon in 2:1 ratio), 79.3, 149.1, 155.0 and 154.9 (1 carbon in 2:1 ratio); EIMS *m*/*z* (relative intensity) 480 (M^+ + 2 − *t*-Bu, 2), 464 (3), 434 (4), 422 (M^+ + 1 − 2 × *t*-Bu, 100), 392 (9), 378 (5), 308 (5); HRMS (EI) calcd for $C_{15}H_{25}NO_3SiI$ (M^+ + 1 − 2 × *t*-Bu) 422.0648, found 422.0626.

***tert*-Butyl (2*S*,3*S*,4a*S*,5*S*,8a*R*)-3-{[*tert*-Butyl(dimethyl)-silyl]oxy}-2-methyl-5-[(1*E*,3*E*)-1,3-octadienyl]octahydro-1(2*H*)-quinolinecarboxylate (53).** Tetrakis(triphenylphosphin)palladium(0) (14.2 mg, 0.0123 mmol) was added to a solution of **51** (132 mg, 0.246 mmol) in THF (3 mL), and the resulting solution was stirred at room temperature for 5 min. To the solution was added dropwise a solution of hexenyldihydroxyborane **52** (62.9 mg, 0.492 mmol), prepared by a literature procedure[23] from 1-hexyne, in 2 M aqueous KOH (0.74 mL, 1.48 mmol). The mixture was heated at 50 °C for 3 h with stirring and then diluted with $CHCl_3$ (100 mL). The organic phase was washed with brine, dried, and concentrated in vacuo. The resulting crude material was submitted to chromatography (hexane/AcOEt, 40:1) to provide **53** (94 mg, 77%) as a colorless oil: $[\alpha]^{28}_D$ −14.0 (*c* 0.693, $CHCl_3$); IR (neat) 1691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, amide rotamer) δ 0.06 and 0.07 (total 6H in 1.5:1 ratio, each s), 0.69 and 0.88 (total 9H in 1.5:1 ratio, each s), 0.89 (3H, t, J = 6.9 Hz), 1.11 (3H, d, J = 6.9 Hz), 1.28−1.41 (6H, m), 1.49 (9H, s), 1.46−1.63 (5H, m), 1.68−1.82 (2H, m), 1.92 (1H, q, J = 12.2 Hz), 2.02−2.11 (2H, m), 2.29−2.37 (1H, m), 3.76 (1H, quint, J = 5.6 Hz), 4.12−4.17 and 3.97−4.02 (total 1H in 1.5:1 ratio, each m), 4.16 and 4.30 (total 1H in 1.5:1 ratio, each quint, J = 6.7 Hz), 5.56−5.65 (1H, m), 5.82 and 5.74 (total 1H in 1.5:1 ratio, each dd, J = 14.4, 7.6 Hz), 5.95−6.10 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$, amide rotamer) δ -4.8, −4.6, 13.9, 15.3 and 15.0 (1 carbon in 1.5:1 ratio), 18.0, 21.2 and 21.3 (1 carbon in 1.5:1 ratio), 22.2, 25.8 (3 carbons), 26.2 and 26.3 (1 carbon in 1.5:1 ratio), 28.0 and 28.6 (1 carbon in 1.5:1 ratio), 28.5, 30.5 and 30.6 (1 carbon in 1.5:1 ratio), 31.6, 32.3, 39.7 and 39.3 (1 carbon in 1.5:1 ratio), 43.0 and 42.6 (1 carbon in 1.5:1 ratio), 49.1 and 49.9 (1 carbon in 1.5:1 ratio), 51.5 and 50.6 (1 carbon in 1.5:1 ratio), 70.8 and 70.5 (1 carbon in 1.5:1 ratio), 79.2, 130.1 and 130.2 (1 carbon in 1.5:1 ratio), 130.4 and 130.3 (1 carbon in 1.5:1 ratio), 133.2 and 134.4 (1 carbon in 1.5:1 ratio), 134.9 and 134.7 (1 carbon in 1.5:1 ratio), 155.1; EIMS *m*/*z* (relative intensity) 492 (M^+ + 1, 2), 491 (M^+, 3), 436 (4), 391 (6), 378 (13), 334 (5), 295 (8), 57 (100); HRMS (EI) calcd for $C_{29}H_{53}NO_3Si$ (M^+) 491.3795, found 491.3801.

(2*S*,3*S*,4a*S*,5*S*,8a*R*)-2-Methyl-5-[(1*E*,3*E*)-1,3-octadienyl]-decahydro-3-quinolinol [(−)-Lepadin B] (2). To a stirred, cooled (0 °C) solution of **54** (10.8 mg, 0.0286 mmol) in CH_2Cl_2 (0.3 mL) was added trifluoroacetic acid (33, 0.289 mmol), and the solution was stirred at room temperature for 3 h. After evaporation of the solvent, the residue was dissolved in $CHCl_3$ (5 mL), and solid K_2CO_3 (100 mg) was added. The mixture was stirred for 1 h, filtered, and then concentrated in vacuo. Purification of the residual oil by chromatography ($CHCl_3$/MeOH/29% NH_4OH, 60:9:1) yielded (−)-lepadin B (**2**) (6.7 mg, 84%) as a pale yellow oil: $[\alpha]^{30}_D$ −76.8 (*c* 0.78, MeOH); ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 7.1 Hz), 0.97−1.07 (1H, m), 1.13 (3H, d, J = 6.6 Hz), 1.21−1.40 (6H, m), 1.42−1.62 (4H, m), 1.63−1.88 (3H, m), 2.06 (2H, q, J = 6.8 Hz), 2.12 (1H, d, J = 14.6 Hz), 2.62 (1H, qd, J = 11.8, 3.3 Hz), 2.81 (1H, qd, J = 5.1, 1.4 Hz), 2.96 (1H, d, J = 2.6 Hz), 3.55 (1H, d, J = 1.7 Hz), 5.37 (1H, dd, J = 14.9, 8.9 Hz), 5.59 (1H, dt, J = 14.8, 6.9 Hz), 6.00 (1H, dd, J = 14.8, 10.4 Hz), 6.08 (1H, dd, J = 14.9, 10.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 18.3, 20.8, 22.3, 31.6, 32.4, 33.0, 34.2, 38.8, 41.1, 56.2, 56.8, 68.8, 130.4, 131.0, 132.8, 137.1.

The free base **2** obtained above was dissolved in CH_2Cl_2 (2 mL) containing trifluoroacetic acid (4.5 mg, 0.039 mmol), and the solution was concentrated in vacuo to dryness, giving the trifluoroacetate salt of **2** as a white solid. Recrystallization from $CHCl_3$/hexane afforded colorless squares: mp 212−214 °C; $[\alpha]^{28}_D$ −84.3 (*c* 0.25, MeOH); ^1H NMR (500 MHz, MeOH) δ 0.89 (3H, t, J = 7.1 Hz), 1.01−1.10 (1H, m), 1.28−1.39 (4H, m), 1.41 (3H, d, J = 6.7 Hz), 1.56−1.62 (3H, m), 1.62−1.73 (3H, m), 2.06 (2H, q, J = 7.0 Hz), 2.10 (1H, d, J = 13.0 Hz), 2.32 (1H, dd, J = 13.6, 2.7 Hz), 2.81 (1H, qd, J = 11.5, 3.0 Hz), 3.21 (1H, br s), 3.35 (1H, br s), 3.48 (1H, br s), 3.87 (1H, br s), 5.29 (1H, dd, J = 15.1, 8.7 Hz), 5.65 (1H, dt, J = 15.1, 7.0 Hz), 5.99 (1H, dd, J = 15.1, 10.4 Hz), 6.14 (1H, dd, J = 15.1, 10.4 Hz), 7.77 (1H, br s), 9.92 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 14.9, 19.6, 22.3, 29.0, 31.5, 32.4 (2 carbons), 33.1, 37.0, 39.6, 56.7, 57.4, 66.6, 130.0, 132.4, 134.0, 134.4.

(2*S*,3*S*,4a*S*,5*S*,8a*R*)-2-Methyl-5-[(1*E*,3*E*)-1,3-octadienyl]-decahydro-3-quinolinyl Hydroxyacetate [(−)-Lepadin A] (1). To a stirred, cooled (0 °C) solution of **55** (13.8 mg, 0.0233 mmol) in MeCN (0.3 mL) was added boron trifluoride diethyl ether complex (3.6 mg, 0.0253 mmol). After 30 min, additional boron trifluoride diethyl ether complex (3.6 mg, 0.0253 mmol) was added, and the mixture was stirred at 0 °C for an additional 5 h. Then the mixture was directly submitted to chromatography ($CHCl_3$/MeOH/29% NH_4OH, 60:9:1) to afford (−)-lepadin A (**1**) (7.5 mg, 97%) as a pale yellow oil: $[\alpha]^{29}_D$ −55.5 (*c* 0.85, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$/CD_3OD 1:1 v/v) δ 0.91 (3H, t, J = 7.1 Hz), 1.09 (3H, d, J = 6.7 Hz), 1.09−1.13 (1H, m), 1.30−1.41 (5H, m), 1.55−1.72 (5H, m), 1.79−1.84 (1H, m), 2.06 (2H, q, J = 6.9 Hz), 2.18 (1H, d, J = 15.3 Hz), 2.47−2.55 (1H, m), 2.96 (1H, qd, J = 6.7, 2.0 Hz), 3.01 (1H, q, J = 2.8 Hz), 4.22 and 4.25 (2H, ABq, J = 17.0 Hz), 4.93 (1H, q, J = 2.8 Hz), 5.30 (1H, dd, J = 14.5, 8.8 Hz), 5.58 (1H, dt, J = 14.4, 7.2 Hz), 5.92−6.03 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$/CD_3OD 1:1 v/v) δ 14.1, 17.7, 20.9, 22.8, 31.7, 32.1, 32.6, 32.8, 34.6, 38.6, 40.3, 55.3, 55.7, 61.3, 71.7, 130.9, 131.6, 133.3, 136.6, 172.9.

The trifluoroacetate salt of **1** was obtained as a pale yellow oil by treatment with 0.2% trifluoroacetic acid in CH_2Cl_2 followed by concentration to dryness: $[\alpha]^{29}_D$ −53.9 (*c* 0.84, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 7.0 Hz), 1.06 (1H, q, J = 12.0 Hz), 1.27 (3H, d, J = 6.6 Hz), 1.27−1.41 (5H, m), 1.52−1.82 (6H, m), 1.98−2.09 (3H, m), 2.33 (1H, br d, J = 15.0 Hz), 2.81 (1H, qd, J = 11.5, 2.7 Hz), 3.40 (1H, br s), 3.48 (1H, br s), 4.28 and 4.33 (2H, ABq, J = 17.5 Hz), 4.63

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(1H, br s), 5.18 (1H, dd, J = 15.1, 8.9 Hz), 5.21 (1H, br s), 5.62 (1H, dt, J = 15.1, 6.9 Hz), 5.94 (1H, dd, J = 15.1, 10.4 Hz), 6.22 (1H, dd, J = 15.1, 10.4 Hz), 8.38 (1H, br s), 9.50 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.5, 19.4, 22.3, 29.0, 29.8, 31.4, 32.3, 33.4, 36.9, 39.1, 56.3, 56.8, 61.5, 68.2, 129.8, 132.8, 133.5, 134.4, 171.5.

***tert*-Butyl (2*S*,3*S*,4a*S*,5*S*,8a*R*)-3-{[*tert*-Butyl(dimethyl)-siliyl]oxy}-5-[(1*E*,3*E*)-7-hydroxy-1,3-octadienyl]-2-methyloctahydro-1(2*H*)-quinolinecarboxylate (57).** To a stirred solution of **51** (141 mg, 0.263 mmol) in THF (4 mL) was added tetrakis(triphenylphosphin) palladium(0) (15.3 mg, 0.0132 mmol). After 5 min, a solution of 5-hydroxyhexenyldihydroxyborane **56** (75.7 mg, 0.526 mmol), prepared by a literature procedure[24] from 5-hexyn-2-one, in 2 M aqueous KOH (0.790 mL, 1.58 mmol) was added dropwise, and then the mixture was stirred at 50 °C for 3 h. The mixture was diluted with brine (10 mL) and extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. The crude material was submitted to chromatography (hexane/AcOEt, 40:1) to give **57** (100 mg, 75%) as a colorless oil: $[\alpha]^{25}_D$ −12.5 (*c* 0.89, $CHCl_3$); IR (neat) 3443, 1689 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, amide rotamer) δ 0.06 and 0.07 (total 6H in 1.6:1 ratio, each s), 0.89 and 0.88 (total 9H in 1.6:1 ratio, each s), 1.11 (3H, d, J = 6.9 Hz), 1.20 (3H, d, J = 6.2 Hz), 1.30−1.42 (2H, m), 1.45 (9H, s), 1.45−1.66 (7H, m), 1.68−1.82 (2H, m), 1.92 (1H, q, J = 12.2 Hz), 1.99−2.26 (2H, m), 2.29−2.37 (1H, m), 3.76 (1H, ddd, J = 11.2, 6.3, 4.4 Hz), 3.82 (1H, q, J = 6.2 Hz), 4.11−4.17 and 3.96−4.02 (total 1H in 1.6:1 ratio, each m), 4.18 and 4.30 (total 1H in 1.6:1 ratio, each quint, J = 6.6 Hz), 5.53−5.67 (1H, m), 5.83 and 5.76 (total 1H in 1.6:1 ratio, each dd, J = 13.8, 7.6 Hz), 5.98−6.13 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$, amide rotamer) δ -4.8, −4.6, 15.4 and 15.1 (1 carbon in 1.6:1 ratio), 18.0, 21.2 and 21.3 (1 carbon in 1.6:1 ratio), 23.5, 25.8 (3 carbons), 26.1 and 26.2 (1 carbon in 1.6:1 ratio), 28.0 and 28.6 (1 carbon in 1.6:1 ratio), 28.5, 29.0, 30.5 and 30.6 (1 carbon in 1.6:1 ratio), 38.8, 39.7 and 39.3 (1 carbon in 1.6:1 ratio), 43.0 and 42.6 (1 carbon in 1.6:1 ratio), 49.1 and 49.9 (1 carbon in 1.6:1 ratio), 51.5 and 50.6 (1 carbon in 1.6:1 ratio), 67.7, 70.8 and 70.5 (1 carbon in 1.6:1 ratio), 79.3, 129.8 and 129.9 (1 carbon in 1.6:1 ratio), 131.0 and 130.9 (1 carbon in 1.6:1 ratio), 133.2 and 134.4 (1 carbon in 1.6:1 ratio), 135.6 and 135.4 (1 carbon in 1.6:1 ratio), 155.1; EIMS *m*/*z* (relative intensity) 507 (M^+, 8), 451 ($M^+ + 1 - t$-Bu, 13), 407 (100), 364 (8), 350 (25), 301 (6), 256 (8), 214 (26); HRMS (EI) calcd for $C_{25}H_{45}NO_4Si$ ($M^+ + 1 - t$-Bu) 451.3118, found 451.3121.

(2*S*,3*S*,4a*S*,5*S*,8a*R*)-2-Methyl-5-[(1*E*,3*E*)-7-oxo-1,3-octadienyl]decahydro-3-quinolinyl Hydroxyacetate [(−)-Lepadin C] (3). To a stirred, cooled (0 °C) solution of **60** (8.2 mg, 0.0135 mmol) in MeCN (0.2 mL) was added boron trifluoride diethyl ether complex (1.92 mg, 0.0135 mmol). After 30 min, additional boron trifluoride diethyl ether complex (1.92 mg, 0.0135 mmol) was added, and the mixture was stirred at 0 °C for an additional 4 h. Then the mixture was directly submitted to chromatography ($CHCl_3$/MeOH/29% NH_4OH, 60:9:1) to afford (−)-lepadin C (**3**) (4.3 mg, 91%) as a pale yellow oil: $[\alpha]^{28}_D$ −52.0 (*c* 0.19, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01−1.10 (1H, m), 1.07 (3H, d, J = 6.6 Hz), 1.30−1.35 (2H, m), 1.41−1.79 (9H, m), 2.14 (3H, s), 2.15−2.19 (1H, m), 2.32 (1H, q, J = 7.2 Hz), 2.51 (3H, t, J = 7.2 Hz), 2.93−2.97 (1H, m), 2.98 (1H, br s), 4.22 and 4.24 (2H, ABq, J = 16.9 Hz), 4.90−4.92 (1H, m), 5.32 (1H, dd, J = 14.9, 8.8 Hz), 5.52 (1H, dt, J = 14.8, 6.9 Hz), 5.89 (1H, dd, J = 14.9, 10.4 Hz), 5.97 (1H, dd, J = 14.9, 10.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.0, 20.6, 26.7, 30.0, 31.5, 32.6, 34.1, 38.4, 39.9, 43.2, 55.0, 55.5, 60.9, 72.2, 130.4, 130.5, 131.1, 137.4, 173.1, 208.3.

The trifluoroacetate salt of **3** was obtained as a pale yellow oil by treatment with 0.2% trifluoroacetic acid in CH_2Cl_2 followed by concentration to dryness: $[\alpha]^{27}_D$ −56.5 (*c* 0.48, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (1H, q, J = 12.3 Hz), 1.20−1.35 (1H, m), 1.26 (3H, d, J = 6.8 Hz), 1.52−1.80 (7H, m), 2.05 (1H, br d, J = 11.1 Hz), 2.14 (3H, s), 2.26−2.29 (1H, m), 2.32 (2H, q, J = 7.2 Hz), 2.51 (2H, t, J = 7.4 Hz), 2.81 (1H, qd, J = 11.7, 2.9 Hz), 3.39 (1H, q, J = 6.5 Hz), 3.47 (1H, br s), 4.27 and 4.32 (2H, ABq, J = 17.5 Hz), 4.65 (1H, br s), 5.21 (1H, br s), 5.22 (1H, dd, J = 15.2, 8.8 Hz), 5.57 (1H, dt, J = 15.1, 6.9 Hz), 5.97 (1H, dd, J = 15.1, 10.4 Hz), 6.20 (1H, dd, J = 15.1, 10.4 Hz), 9.0 (1H, br s), 9.50 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 19.4, 26.7, 29.0, 29.8, 30.0, 33.3, 36.9, 39.1, 43.1, 56.2, 56.8, 61.4, 68.2, 130.9, 131.8, 132.3, 134.6, 171.5, 208.2.

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Supporting Information Available: Detailed experimental procedures for the preparation of compounds **9**−**18**, **22**, **28**−**30**, **32**, **35**−**39**, **41**−**43**, **46**, **47**, **54**, **55**, and **58**−**60**. Copies of ^{1}H NMR spectra for compounds **1**−**3**, **14**, **21**, **26**, **28**−**30**, **32**, **35**−**49**, **51**, **53**−**55**, and **57**−**60**. This material is available free of charge via the Internet at http://pubs.acs.org.

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