Enantioselective Total Synthesis of the Macrocyclic Spermidine Alkaloid (−)-Oncinotine

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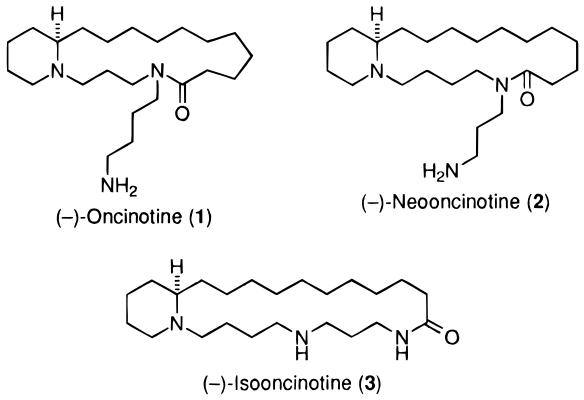
The macrocyclic spermidine alkaloid (−)-oncinotine (**1**), isolated from *Oncinotis nitida* (Apocynaceae), was synthesized enantioselectively for the first time based on intramolecular iminium ion cyclization utilizing enantiomerically pure (2*S*)-*N*-[(benzyloxy)carbonyl]-2-piperidineacetaldehyde (**8**) as a chiral starting material. The required **8** was derived from the *erythro* adduct **16**, which was obtained by diastereoselective 1,3-dipolar cycloaddition between 2,3,4,5-tetrahydropyridine 1-oxide (**4**) and (3*S*)-3-[(*tert*-butyldiphenylsilyl)oxy]-4-methyl-1-pentene (**15**). Wittig condensation of **8** with [8-(methoxycarbonyl)octyl]triphenylphosphonium iodide (**21**) followed by saponification provided the chiral piperidine moiety **23**, which was coupled with the *N*-propyl-1,4-butanediamine segment **29** by using diethoxyphosphoryl cyanide in the presence of triethylamine to afford the tertiary amide **30**. Conversion of **30** to the aldehyde **34** via desilylation and Swern oxidation, followed by hydrogenation over a palladium hydroxide catalyst under high dilution led to in situ formation of the transient iminium ion **35**, which was further hydrogenated to form **33** in a single operation. Subsequent removal of the Boc protecting group resulted in (−)-oncinotine (**1**).

Introduction

(−)-Oncinotine (**1**), (−)-neooncinotine (**2**), and (−)-isooncinotine (**3**), isolated from the stem bark of *Oncinotis nitida* (Apocynaceae),[1,2] are a group of isomeric polyamine alkaloids which are characterized by macrocyclic lactams containing the biogenetic base spermidine.[3] Since oncinotine (**1**) and neooncinotine (**2**) are not easily separated, whereas isolation of isooncinotine (**3**) can be readily achieved, pure oncinotine was obtained by treating the natural mixture of **1** and **2** with potassium *tert*-butoxide; under these conditions neooncinotine can be completely converted into isooncinotine with oncinotine unchanged.[2] Degradation and spectroscopic analysis established the structures of these three bicyclic spermidine alkaloids. In these structure elucidation studies the absolute configuration of the alkaloids was deduced to be *R* as depicted in structures **1**−**3** by means of the CD measurement by relating the degradation product to (*R*)-(−)-*N*-methylconiine.[2] These three alkaloids have been synthesized in racemic form by Hesse, Schmid, and coworkers,[4,5] and more recently a new synthetic route to racemic oncinotine has been reported by Hesse et al.[6] However, no report on the chiral synthesis of these spermidine alkaloids has appeared.

We have recently demonstrated[7] that 1,3-dipolar cycloaddition of chiral allyl ethers **5** to a cyclic nitrone **4** proceeds with erythro (with respect to C-2−O and C-1′−O) selectivity due to an "inside alkoxy effect" to afford the cycloadducts **6** as major isomer, which can be converted to (*R*)-(−)-coniine (**9**) via enantiomerically pure (2*S*)-*N*-[(benzyloxy)carbonyl]-2-piperidineacetaldehyde (**8**) (Scheme 1). In this paper we detail the first enantioselective total synthesis of (−)-oncinotine (**1**) utilizing **8** as a chiral starting material based on a new approach involving macrocyclization to the 17-membered ring by intramolecular N-alkylation via an iminium ion intermediate.[8] Our synthesis unambiguously confirmed the absolute configuration of (−)-oncinotine to be 17*R* as earlier proposed.



Results and Discussion

The construction of macrocyclic lactam rings has been a pivotal object in the total synthesis of macrocyclic lactam alkaloids, which in many cases has been performed by intramolecular amidation.[3,9] As outlined in Scheme 2, our synthetic strategy toward the framework

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(1) Badawi, M. M.; Guggisberg, A.; van den Broek, P.; Hesse, M.; Schmid, H. *Helv. Chim. Acta* **1968**, *51*, 1813.

(2) Guggisberg, A.; Badawi, M. M.; Hesse, M.; Schmid, H. *Helv. Chim. Acta* **1974**, *57*, 414.

(3) For reviews of macrocyclic spermidine alkaloids, see: (a) Matsuyama, H. *Yuki Gosei Kagaku Kyokaishi* **1981**, *39*, 1151. (b) Wasserman, H. H.; Wu, J. S. *Heterocycles* **1982**, *17*, 581. (c) Guggisberg, A.; Hesse, M. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: Orlando, 1983; Vol. 22, Chapter 3, p 85.

(4) Schneider, F.; Bernauer, K.; Guggisberg, A.; van den Broek, P.; Hesse, M; Schmid, H. *Helv. Chim. Acta* **1974**, *57*, 434.

(5) Guggisberg, A.; van den Broek, A.; Hesse, M.; Schmid, H.; Schneider, F.; Bernauer, K. *Helv. Chim. Acta* **1976**, *59*, 3013.

(6) Bienz, S.; Guggisberg, A.; Walchli, R.; Hesse, M. *Helv. Chim. Acta* **1988**, *71*, 1708.

(7) Ito, M.; Maeda, M.; Kibayashi, C. *Tetrahedron Lett.* **1992**, *33*, 3765. For inside alkoxy effect in the nitrone cycloaddition, see also: Ito, M.; Kibayashi, C. *Tetrahedron Lett.* **1991**, *32*, 1659.

(8) For a preliminary account of this work, see: Ina, H.; Ito, M.; Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1995**, 1015.

(9) For a recent review of ring closure methods in the synthesis of macrocyclic natural products, see: Meng, Q.; Hesse, M. *Top. Curr. Chem.* **1992**, *161*, 107.

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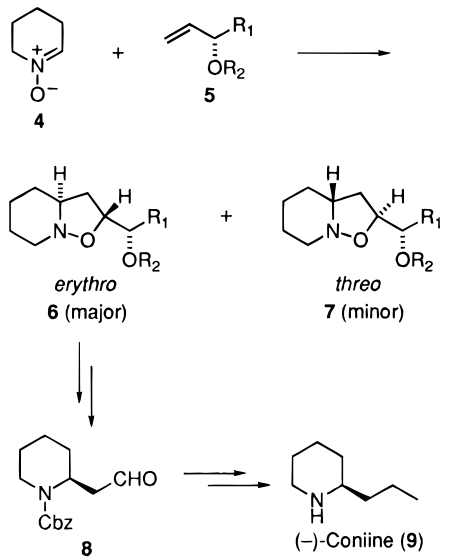
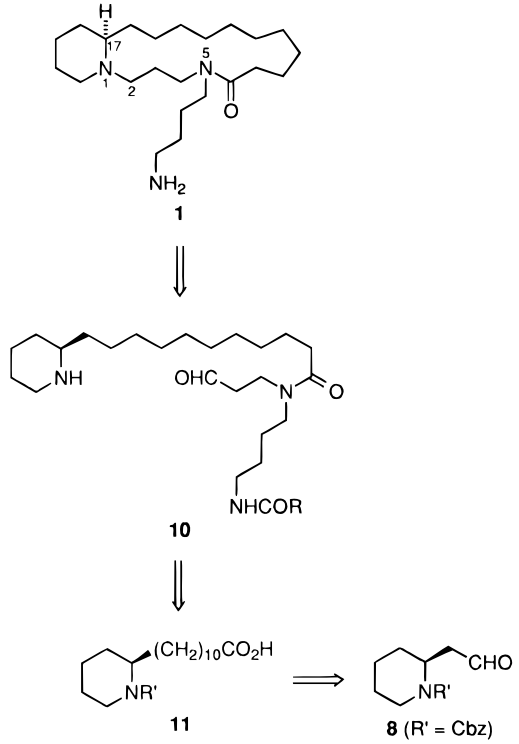
Scheme 1



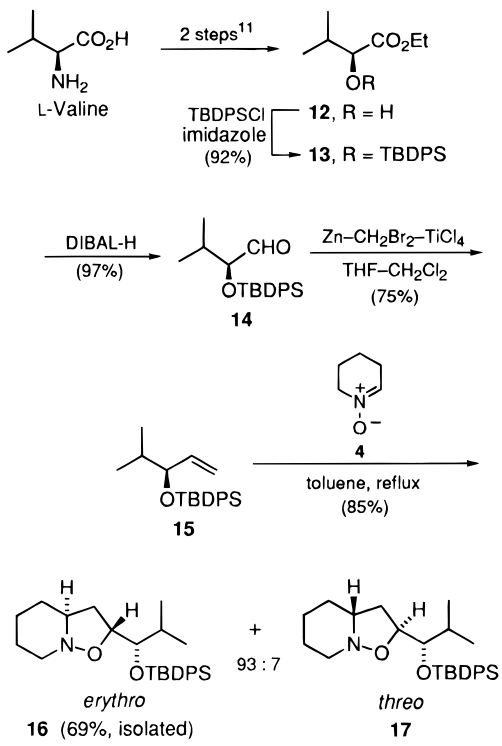
Scheme 2



of (−)-oncinotine (**1**) is based upon a disconnection of the carbon−nitrogen bond between C-2 and N-1 of the 17-membered lactam ring. This disconnective analysis illustrates the crucial intramolecular iminium ion cyclization step for macrocyclic lactam formation which has previously been developed in this laboratory for the synthesis of the monocyclic spermidine alkaloid dihydroperiphyline.[10] Precursor **10**, with two interacting sites for facile iminium ion formation, can be obtained from (*S*)-2-piperidineacetaldehyde (**8**) which is available according to the nitrone cycloaddition protocol described above in Scheme 1.

Prior studies[7] in this laboratory on the nitrone cycloaddition with chiral allyl ethers demonstrated that the erythro selectivity was remarkably dependent upon the size of the alkyl substituent attached to the allylic chiral center. On the basis of this protocol, we employed as a dipolarophile the (*S*)-allyl ether **15** bearing the isopropyl group which provides the increased erythro selectivity as well as better yield for cycloaddition. The preparation of **15** (see Scheme 3) began with ethyl (*S*)-2-hydroxy-3-methylbutanoate (**12**), prepared in two steps ($NaNO_2$, H_2SO_4, and then esterification) from L-valine.[11] After the hydroxy group of **12** was protected as the *tert*-butyldiphenylsilyl ether, the resulting ester **13** was subjected to reduction with DIBALH providing the aldehyde **14** in 89% overall yield. To avoid racemization of the chiral center adjacent to the formyl group, methylenation of **14** was performed under mild, nonbasic conditions.[12] Thus, a dichloromethane solution of **14** was treated with a THF solution of the $Zn-CH_2Br_2-TiCl_4$ reagent[13] to give the (*S*)-allyl ether **15** in 75% yield. When heated with an excess of 2,3,4,5-tetrahydropyridine 1-oxide (**4**)[14] in toluene, **15** underwent [3 + 2] cycloaddition to afford a 93:7 mixture (determined by HPLC) of the *erythro* and *threo* bicyclic oxazolidines **16** and **17** in favor of **16** in 85% combined yield. This mixture was separated by column chromatography on silica gel, and the pure *erythro* isomer **16** was obtained in 69% yield. The NMR analysis showed that compound **16** exists as a 4.5:1 mixture of two conformers at ambient temperature, probably due to pyramidal inversion at the ring nitrogen.

Scheme 3



The silyl protecting group in **16** was subsequently removed to yield **18** (86% yield) which was also found to exist as a 2:1 conformational mixture (by NMR analysis). Hydrogenolytic cleavage of the N−O bond in **18** with hydrogen and a palladium(II) chloride catalyst at 6.5 atm

(10) Kaseda, T.; Kikuchi, T.; Kibayashi, C. *Tetrahedron Lett.* **1989**, *30*, 4539.

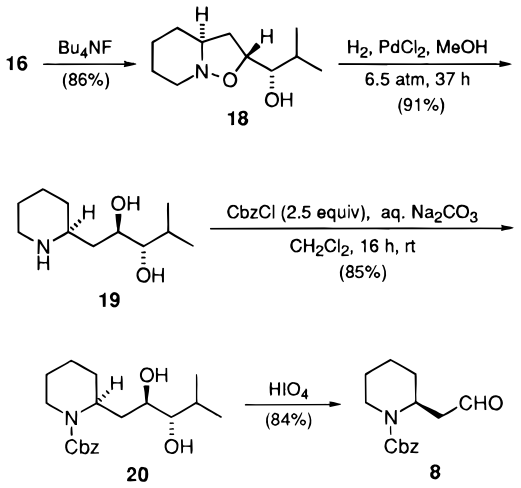
(11) Vigneron, J. P.; Dhaenens, M.; Horeau, A. *Tetrahedron* **1977**, *33*, 507.

(12) Cf. Ito, M.; Kibayashi, C. *Synthesis* **1993**, 137.

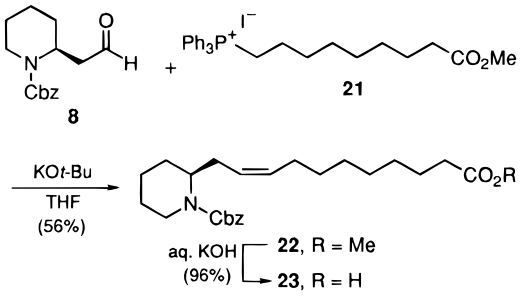
(13) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, 2417.

(14) Prepared according to: Murahashi, S.; Shiota, T. *Tetrahedron Lett.* **1987**, *28*, 5223.

Scheme 4



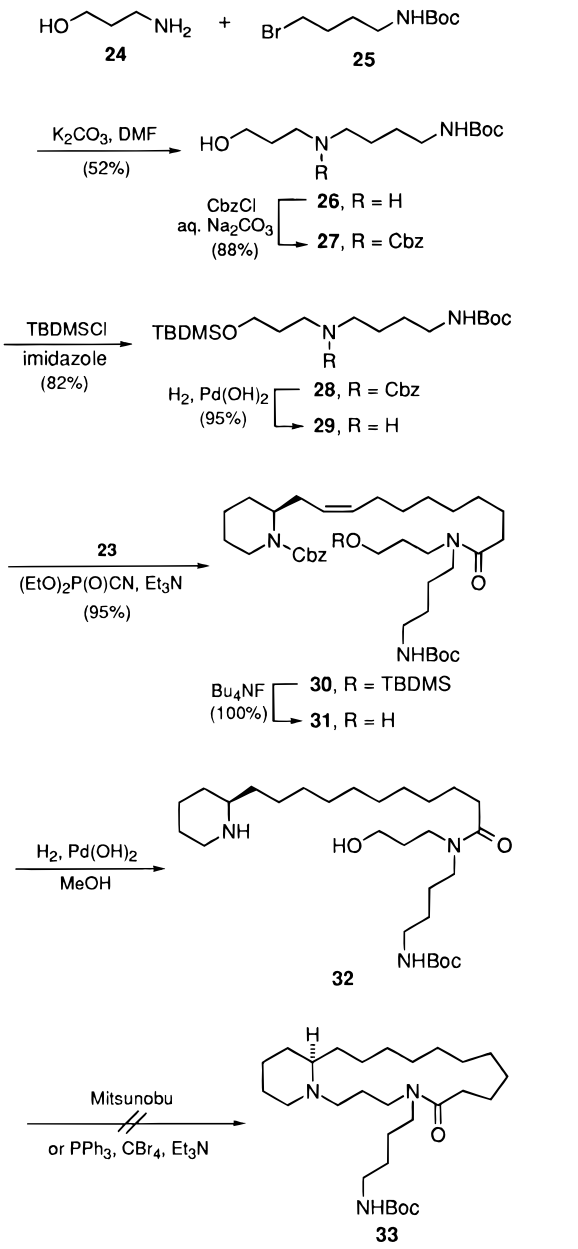
Scheme 5



provided the amino alcohol **19**, which was converted to the benzyl carbamate **20** (77% yield from **18**) by treatment with 2.5 equiv of benzyl chloroformate in aqueous Na_2CO_3 and subsequent ester hydrolysis by prolonged stirring of the reaction mixture. Cleavage of the glycol in **20** by oxidation with periodic acid resulted in the aldehyde **8** in 84% yield (Scheme 4).

The nine-carbon homologation was performed by Wittig condensation of **8** with [8-(methoxycarbonyl)octyl]-triphenylphosphorane (from the phosphonium salt **21** and *t*-BuOK)[15] followed by saponification with KOH in methanol which afforded the unsaturated carboxylic acid **23** in 54% overall yield (Scheme 5). To construct the spermidine moiety, the *N*-propyl-1,4-butanediamine segment was prepared via a straightforward sequence as shown in Scheme 6. Thus, N-alkylation of 3-amino-1-propanol (**24**) with *N*-Boc protected 4-bromobutylamine **25** produced **26** in 52% yield, which immediately underwent N-protection with benzyl chloroformate to yield the carbamate **27** (88% yield). Subsequent silylation of the alcohol function followed by hydrogenolytic removal of the Cbz group over palladium hydroxide converted **27** to **29** in 78% overall yield. This *N*-propyl-1,4-butanediamine segment **29** was coupled with the chiral piperidine **23** by using diethoxyphosphoryl cyanide[16] in the presence of triethylamine in DMF to furnish the tertiary amide **30** in 95% yield. In an attempt to construct the 17-membered framework of oncinotine by intramolecular N-alkylation, **30** was desilylated to give **31**, which was converted by catalytic hydrogenation to the amino alcohol **32**, a linear bifunctional precursor. This amino alcohol was immediately treated under Mitsunobu conditions[17]

Scheme 6

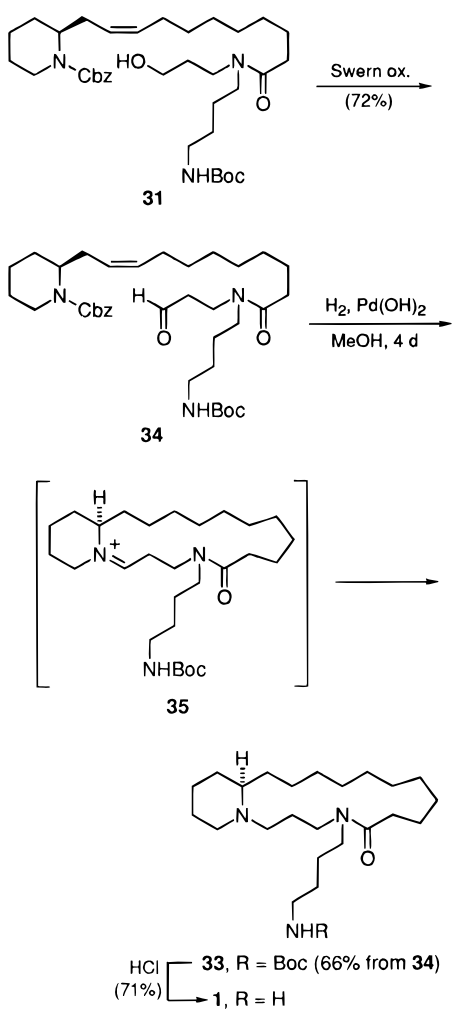


or an intramolecular N-alkylation procedure utilizing PPh_3−CBr_4.[18] However, these and other attempted C−N coupling methods under high dilution were all sluggish and did not result in the desired *N*-Boc oncinotine (**33**).

For an alternative solution to macrocyclic ring formation, we envisaged to utilize a bifunctional precursor with amino and formyl groups in the molecule, which can readily combine to generate an iminium ion. Accordingly, the alcohol **31** was converted to the aldehyde **34** in 72% yield by oxidation with the Swern reagent.[19] Compound **34** was then treated with hydrogen over a palladium hydroxide catalyst under high dilution (4×10^{-3} M in MeOH) conditions. As shown in Scheme 7 during this reaction, hydrogenation of the alkene and deprotection of the amine took place, leading to in situ formation of the transient iminium ion **35**, which was further hydrogenated to form **33** in a single operation in 66% yield. The synthesis was completed by removal of the Boc

(15) Gunn, B. P. *Heterocycles* **1985**, *23*, 3061.
(16) Yamada, S.; Kasai, Y.; Shioiri, T. *Tetrahedron Lett.* **1973**, 1595.
(17) Mitsunobu, O. *Synthesis* **1981**, 1.
(18) Shishido, Y.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 2876.
(19) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

Scheme 7



protecting group. Thus, treatment of **33** with methanolic HCl resulted in (−)-oncinotine (**1**) in 71% yield. The synthetic material had optical rotations, $[\alpha]^{26}_D$ −28.7° (*c* 2.6, $CHCl_3$) and $[\alpha]^{26}_D$ −32.7° (*c* 2.1, MeOH), and spectral data (IR and MS) consistent with those recorded[1,2] for the natural alkaloid ($[\alpha]_D$ −29° ($CHCl_3$) and $[\alpha]_D$ −33° (MeOH)). Furthermore, the ^1H and ^{13}C NMR spectra of the hydrochloride salt **1**·2HCl of the synthetic sample were identical with those of the hydrochloride salt of racemic oncinotine.[6]

In summary, the first chiral total synthesis of (−)-oncinotine utilizing enantioselectively prepared **8** has been accomplished, confirming the previously assigned absolute configuration of natural alkaloid. The required chiral center in the piperidine fragment (C-17 in oncinotine) could be set by diastereoselective nitrone 1,3-dipolar cycloaddition with the (*S*)-allyl ether **15** as a dipolarophile. The central 17-membered macrocyclic framework was efficiently achieved based on an iminium ion cyclization of the reactive linear precursor possessing amino and formyl groups at both the ends, which was generated from **34** during catalytic hydrogenation. This iminium ion cyclization strategy should prove useful as a means for preparing other macrocyclic spermidine alkaloids.

Experimental Section

General Procedures. Melting points are uncorrected. Optical rotations were measured on a digital polarimeter in a 1-dm cell. IR spectra were recorded on an FTIR instrument. ^1H NMR spectra were run at 300, 400, or 500 MHz. ^{13}C NMR spectra were determined at 75, 100, or 125 MHz. Chemical shifts were reported in δ scale relative to $CHCl_3$ as an internal reference (7.26 ppm for ^1H and 77.0 ppm for ^{13}C), unless otherwise indicated. MeOH (3.35 ppm for ^1H and 49.0 ppm for ^{13}C), DOH (4.75 ppm for ^1H), and dioxane (67.4 ppm for ^{13}C) were occasionally used as internal references. Peak assignments of ^{13}C NMR spectra were confirmed by DEPT experiments. Mass spectra were measured at 70 eV. HPLC analyses were performed using a Sim-pak silica gel column (6.0 × 150 mm) with detection at 254 nm and hexane−EtOAc (3:1) as eluent at flow rate of 1 mL/min. TLC was performed on precoated silica gel 60 F 254 plates (Merck) and silica gel 60 (230−400 mesh) (Merck) was used for column chromatography. Microanalyses were carried out by the Microanalytical Laboratory at Tokyo University of Pharmacy & Life Science.

Ethyl (2*S*)-2-[(*tert*-Butyldiphenylsilyl)oxy]-3-methylbutanoate (13). To a solution of ethyl (2*S*)-2-hydroxy-3-methylbutanoate (**12**)[11] (2.22 g, 15.2 mmol) in DMF (20 mL) were added imidazole (1.24 g, 18.2 mmol) and *tert*-butyldiphenylsilyl chloride (5.00 g, 18.2 mmol), and the mixture was stirred at 80 °C. After being stirred for 7 h, the mixture was diluted with water (60 mL) and extracted with CH_2Cl_2 (3 × 60 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Column chromatography on silica gel (hexane) gave **13** (5.40 g, 92%) as a colorless oil: $[\alpha]^{26}_D$ −37.4° (*c* 1.47, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.93 (3H, d, J = 6.7 Hz), 0.95 (3H, d, J = 6.7 Hz), 1.12 (9H, s), 1.04 (3H, t, J = 7.2 Hz), 2.03 (1H, d quint, J = 6.7, 4.7 Hz), 3.83 (2H, dq, J = 7.2, 4.0 Hz), 4.06 (1H, d, J = 4.7 Hz), 7.32−7.45 (6H, m), 7.63−7.70 (4H, m); ^{13}C NMR ($CDCl_3$) δ 14.1, 17.6, 18.7, 19.7, 27.1 (3 carbons), 33.5, 60.2, 77.8, 127.4 (2 carbons), 127.6 (2 carbons), 129.7, 129.8, 133.7, 135.8, 136.0 (2 carbons), 136.2 (2 carbons), 172.6; CIMS (isobutane) *m*/*z* (rel intensity) 384 (M^+, 0.13), 307 (100). Anal. Calcd for $C_{23}H_{32}O_3Si$: C, 71.83; H, 8.39. Found: C, 71.72; H, 8.33.

(2*S*)-2-[(*tert*-Butyldiphenylsilyl)oxy]-3-methylbutanal (14). To a stirred, cold (−85 °C) solution of **13** (211 mg, 0.584 mmol) in Et_2O (5 mL) under Ar was added via syringe a 0.94 M solution of DIBALH (0.64 mL, 0.60 mmol) in hexane, and stirring was continued at −85 °C. After 6 h, the mixture was quenched by addition of water (0.5 mL) and allowed to warm to rt. The precipitate was removed by filtration through a Celite pad and thoroughly rinsed with Et_2O, and the filtrate was washed with brine and dried ($MgSO_4$). After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane) to give **14** (181 mg, 97%) as a colorless oil: $[\alpha]^{26}_D$ −35.1° (*c* 1.30, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.94 (3H, d, J = 6.9 Hz), 0.95 (3H, d, J = 6.9 Hz), 1.13 (9H, s), 2.01 (1H, d quint, J = 6.9, 4.3 Hz), 3.86 (1H, dd, J = 4.3, 2.1 Hz), 7.34−7.46 (6H, m), 7.62−7.65 (4H, m), 9.54 (1H, d, J = 2.1 Hz); ^{13}C NMR ($CDCl_3$) δ 17.1, 18.4, 19.6, 27.1 (3 carbons), 32.6, 82.4, 127.8 (4 carbons), 130.0 (2 carbons), 133.8, 135.9 (5 carbons), 204.5.

(3*S*)-3-[(*tert*-Butyldiphenylsilyl)oxy]-4-methyl-1-pentene (15). To a stirred, cold (−40 °C) suspension of the Zn−CH_2Br_2−$TiCl_4$ reagent in THF (16 mL), prepared from zinc dust (1.84 g, 28.1 mmol), dibromomethane (1.59 g, 9.15 mmol), and $TiCl_4$ (1.28 g, 6.75 mmol), according to the literature,[13] was added a solution of **14** (2.31 g, 6.78 mmol) in CH_2Cl_2 (25 mL) under Ar, and the mixture was stirred at rt for 2 h. After dilution of the mixture with hexane (20 mL), a suspension of Na_2CO_3 (30 g) in water (20 mL) was added to the mixture and stirring was continued for an additional 2 h at rt. The solid was filtered and rinsed with Et_2O (100 mL). The filtrate was washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane−EtOAc, 100:1) to give **15** (1.73 g, 75%) as a colorless oil: $[\alpha]^{28}_D$ +22.8° (*c* 0.18, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.79 (3H, d, J = 6.9 Hz), 0.85 (3H, d, J = 6.8 Hz), 1.07 (9H, s), 1.71 (1H, m), 3.96 (1H, t, J = 6.9 Hz), 4.88 (1H, d, J = 17.3 Hz), 4.96 (1H, d, J = 10.4 Hz), 5.77 (1H, ddd, J = 17.3, 10.4, 6.9 Hz), 7.32−7.43 (6H, m), 7.65−7.70 (4H, m); ^{13}C NMR ($CDCl_3$) δ 17.0, 18.3, 19.5, 27.1 (3 carbons), 34.3, 79.7, 115.7, 127.3 (2 carbons), 127.4 (2 carbons), 129.4, 129.5, 134.6, 136.0 (2 carbons), 136.1 (3 carbons), 138.2; CIMS (isobutane) *m*/*z*

(rel intensity) 339 ($M^+ + 1$, 0.4), 281 (100). Anal. Calcd for $C_{22}H_{30}OSi$: C, 78.05; H, 8.93. Found: C, 78.05; H, 9.02.

Cycloaddition Reaction of the Nitrone 4 with the (*S*)-Allyl Ether 15. A solution containing **4** (2.51 g, 25.4 mmol) and **15** (857 mg, 2.54 mmol) in toluene (25 mL) was refluxed under Ar for 14 h. The mixture was diluted with benzene (30 mL), washed with brine, and dried ($MgSO_4$). After removal of the solvent by evaporation, the product was purified by silica gel chromatography (hexane−AcOEt, 20:1) to yield an oily mixture (942 mg, 85%) of [2*R*,2(1*S*),3a*S*]-2-[1-[(*tert*-butyldiphenylsilyl)oxy]-2-methylpropyl]-3,3a,4,5,6,7-hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine (**16**) and [2*R*,2(1*S*),3a*R*]-2-[1-[(*tert*-butyldiphenylsilyl)oxy]-2-methylpropyl]-3,3a,4,5,6,7-hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine (**17**) in a 93:7 ratio (by HPLC analysis), which was separated by further chromatography on a silica gel column (hexane−EtOAc, 40:1). The first fractions contained **17** (44 mg, 4%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.89 (3H, d, J = 7.0 Hz), 0.92 (3H, d, J = 7.0 Hz), 1.05 (9H, s), 1.23−1.78 (8H, m), 1.94 (1H, m), 2.07 (1H, m), 2.29 and 2.56 (total 1H in 3.5:1 ratio, each m), 2.87 and 3.29 (total 1H in 1:3.5 ratio, m and br s, respectively), 3.72 (1H, m), 4.01 (1H, q, J = 7.0 Hz), 7.34−7.44 (6H, m), 7.69−7.77 (4H, m); ^{13}C NMR ($CDCl_3$) for the major conformer δ 16.9, 18.6, 23.7, 24.7, 27.2 (3 carbons), 29.1, 29.7, 31.7, 39.7, 55.3, 67.3, 76.2, 80.6, 127.8 (4 carbons), 129.7 (2 carbons), 134.9 (2 carbons), 136.2 (2 carbons), 136.3 (2 carbons); for the minor conformer δ 19.1, 19.9, 23.7, 24.7, 27.2 (3 carbons), 29.1, 29.7, 32.0, 39.7, 55.3, 67.3, 76.2, 80.6, 127.4 (2 carbons), 127.5 (2 carbons), 129.4, 129.5, 134.4, 135.3, 136.2 (2 carbons), 136.3 (2 carbons).

The second fractions yielded **16** (765 mg, 69%) as a colorless oil: $[\alpha]^{25}_D$ +11.7° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.74 (3H, d, J = 7.0 Hz), 0.84 (3H, d, J = 7.0 Hz), 1.08 (9H, s), 1.10−1.18 (7H, m), 1.87 (1H, br d, J = 13.1 Hz), 2.08 (1H, dd, J = 17.6, 8.3 Hz), 2.33 (1H, ddd, J = 11.3, 6.5, 4.8 Hz), 2.41 and 2.63 (total 1H in 4.5:1 ratio, ddd, J = 12.0, 9.1, 2.8 Hz and br t, J = 11.4 Hz, respectively), 3.03 and 3.41 (total 1H in 1:4.5 ratio, br d, J = 11.4 Hz and br d, J = 9.1 Hz, respectively), 3.73 and 3.80 (total 1H in 1:4.5 ratio, br s and t, J = 2.8 Hz, respectively), 4.06 and 4.37 (total 1H in 4.5:1 ratio, dt, J = 8.4, 4.1 Hz and br s, respectively), 7.32−7.44 (6H, m), 7.68−7.78 (4H, m); ^{13}C NMR ($CDCl_3$) for the major conformer δ 17.6, 18.4, 19.8, 24.0, 25.0, 27.3 (3 carbons), 29.6, 32.3, 36.6, 54.9, 66.7, 76.9, 77.6, 127.4 (2 carbons), 127.5 (2 carbons), 129.6, 129.7, 134.1, 134.8, 136.1 (2 carbons), 136.3 (2 carbons); for the minor conformer δ 18.1, 18.7, 19.8, 24.3, 25.5, 27.3 (3 carbons), 32.0, 32.6, 49.8, 60.2, 66.7, 76.9, 78.6, 127.4 (2 carbons), 127.5 (2 carbons), 129.6, 129.7, 134.1, 134.8, 136.1 (2 carbons), 136.3 (2 carbons); EIMS *m*/*z* (rel intensity) 437 (M^+, 13), 380 (23), 281 (11), 253 (16), 239 (17), 199 (40), 183 (28), 100 (100). Anal. Calcd for $C_{27}H_{39}NO_2Si$: C, 74.09; H, 8.98; N, 3.20. Found: C, 73.72; H, 8.92; N, 3.14.

[2*R*,2(1*S*),3a*S*]-2-(1-Hydroxy-2-methylpropyl)-3,3a,4,5,6,7-hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine (18). To a stirred solution of **16** (1.70 g, 3.89 mmol) in THF (30 mL) was added a 1.0 M solution of tetrabutylammonium fluoride (15.5 mL, 15.5 mmol) in THF, and the mixture was stirred under Ar at 45 °C for 1.5 h. After evaporation of the solvent in vacuo, the residue was dissolved in Et_2O (100 mL) and the solution was washed with brine and dried ($MgSO_4$). Removal of the solvent and purification by silica gel chromatography (hexane−EtOAc, 3:1) gave **18** (665 mg, 86%) as a colorless oil: $[\alpha]^{25}_D$ +38.9° (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.89 (3H, d, J = 6.8 Hz), 1.02 (3H, d, J = 6.6 Hz), 1.15−1.50 (3H, m), 1.57−2.15 (6H, m), 2.24 (1H, unresolved), 2.45 and 2.85 (total 1H in 2:1 ratio, br t, J = 9.3 Hz and br s, respectively), 3.04 and 3.44 (total 2H in 1:5 ratio, each br s), 4.14 and 4.42 (total 1H in 2:1 ratio, br dd, J = 5.1, 4.1 Hz and br s, respectively); ^{13}C NMR ($CDCl_3$) for the major conformer δ 18.8 (2 carbons), 23.9, 24.9, 29.6, 30.8, 34.3, 55.2, 67.7, 75.9, 77.6; for the minor conformer δ 19.2, 19.7, 23.0, 25.9, 29.6, 30.8, 31.1, 50.1, 60.6, 77.7, 78.0; EIMS *m*/*z* (rel intensity) 199 (M^+, 11), 156 (3), 100 (100). Anal. Calcd for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03. Found: C, 66.03; H, 10.55; N, 6.83.

[2*S*,2(2*R*),2(3*S*)]-*N*-[(Benzyloxy)carbonyl]-2-(2,3-dihydroxy-4-methylpentyl)piperidine (20). A mixture of **18** (1.36 g, 6.83 mmol), $PdCl_2$ (140 mg), and MeOH (40 mL) was hydrogenated at 6.5 atm for 37 h. After filtration of the catalyst, the solvent was evaporated in vacuo to give [2*S*,2-(2*R*),2(3*S*)]-2-(2,3-dihydroxy-4-methylpentyl)piperidine (**19**) (1.25 g, 91%) as a colorless oil, which was dissolved in CH_2Cl_2 (15 mL), and a solution of Na_2CO_3 (3.30 g, 31.1 mmol) in water (25 mL) was added. This mixture was stirred and cooled (0 °C), and a solution of benzyl chloroformate (2.67 g, 15.6 mmol) in CH_2Cl_2 (15 mL) was added dropwise. After continuation of stirring at rt for 14 h, water (15 mL) was added and the organic layer was separated. The aqueous layer was extracted with $CHCl_3$ (3 × 20 mL), and the combined organic layers were washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane−EtOAc, 6:1) to yield **20** (1.77 g, 85%) as a colorless oil: $[\alpha]^{26}_D$ −24.4° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.83 (3H, d, J = 6.8 Hz), 0.98 (3H, d, J = 6.6 Hz), 1.37−1.84 (8H, m), 2.06 (1H, t, J = 13.4 Hz), 2.20 (1H, br s), 2.76 (1H, dt, J = 13.4, 2.4 Hz), 3.36 (2H, br s), 4.08 (1H, br d, J = 12.4 Hz,), 4.34 (1H, br s), 4.50 (1H, br d, J = 12.4 Hz), 5.12 and 5.20 (2H, br AB q, J = 10.4 Hz), 7.37−7.38 (5H, m); ^{13}C NMR ($CDCl_3$) δ 18.6, 19.1, 19.3, 25.5, 29.7, 30.3, 39.5, 47.4, 67.6, 68.0, 79.3, 127.9, 128.2 (2 carbons), 128.6 (2 carbons), 136.7, 157.0; EIMS *m*/*z* (rel intensity) 336 ($M^+ + 1$, 0.1), 262 (2), 218 (20), 174 (41), 128 (10), 91 (100); CIMS *m*/*z* (rel intensity) 336 ($M^+ + 1$, 9), 91 (100). Anal. Calcd for $C_{19}H_{29}NO_4$: C, 68.02; H, 8.72; N, 4.18. Found: C, 67.73; H, 8.76; N, 4.21.

(2*S*)-*N*-[(Benzyloxy)carbonyl]-2-(formylmethyl)piperidine (8). A mixture of **20** (576 mg, 1.72 mmol), periodic acid (588 mg, 2.58 mmol), THF (4 mL), and H_2O (4 mL) was stirred at 0 °C for 2 h. The reaction mixture was extracted with Et_2O (4 × 10 mL), and the combined extracts were washed with water, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (hexane−EtOAc, 8:1) gave **8** (376 mg, 84%) as a colorless oil: $[\alpha]^{20}_D$ −40.9° (*c* 6.5, $CHCl_3$); IR (neat) 2940, 2862, 1724, 1695, 1498, 1471, 1423, 1354, 1319, 1262, 1213, 1176, 1143, 1076, 1055, 1030, 1015, 766, 738, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.37−1.77 (6H, m), 2.60 (1H, ddd, J = 15.6, 6.9, 2.1 Hz), 2.75 (1H, ddd, J = 15.6, 8.0, 2.9 Hz), 2.85 (1H, br t, J = 12.6 Hz), 4.07 (1H, br d, J = 13.2 Hz), 4.92 (1H, br s), 5.12 (2H, s), 7.29−7.40 (5H, m), 9.70 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 18.3 (CH_2), 24.7 (CH_2), 28.2 (CH_2), 39.1 (CH_2), 43.9 (CH_2), 45.7 (CH), 66.6 (CH_2), 127.3 (CH), 127.5 (2 × CH), 128.0 (2 × CH), 136.2 (C), 154.6 (C), 199.9 (CH); EIMS *m*/*z* (rel intensity) 261 (M^+, 1.6), 233 (11), 218 (11), 174 (55), 126 (20), 108 (15), 92 (30), 91 (100). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.85; H, 7.36; N, 5.31.

Methyl [11(2*S*)]-11-[2-[*N*-[(Benzyloxy)carbonyl]piperidinyl]]-9-undecenoate (22). To a cooled (0 °C), stirred mixture of **8** (830 mg, 3.18 mmol), [8-(methoxycarbonyl)octyl]-triphenylphosphonium iodide (**21**)[15] (3.20 g, 5.72 mmol), and THF (35 mL) was added under Ar potassium *tert*-butoxide (535 mg, 4.77 mmol). After stirring for 20 min at 0 °C, an aqueous saturated solution of NH_4Cl (20 mL) was added and stirring was continued for an additional 30 min at the same temperature. To this mixture was added Et_2O (150 mL), and the separated organic phase was washed with brine and dried ($MgSO_4$). Concentration followed by column chromatography on silica gel (hexane−EtOAc, 20:1) gave **22** (739 mg, 56%) as a colorless oil: $[\alpha]^{26}_D$ −40.6° (*c* 2.0, $CHCl_3$); IR (neat) 2931, 2855, 1739, 1698, 1498, 1422, 1343, 1319, 1259, 1205, 1171, 1089, 1045, 733, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 (9H, br s), 1.56−1.63 (7H, m), 2.00 (2H, br q, J = 6.6 Hz), 2.23−2.39 (2H, m), 2.29 (2H, t, J = 7.6 Hz), 2.86 (1H, td, J = 13.2, 2.3 Hz), 3.66 (3H, s), 4.06 (1H, br d, J = 11.6 Hz), 4.31 (1H, br s), 5.11 and 5.13 (2H, AB q, J = 12.5 Hz), 5.23−5.34 (1H, m), 5.35−5.44 (1H, m), 7.29−7.36 (5H, m); ^{13}C NMR ($CDCl_3$) δ 18.9 (CH_2), 24.9 (CH_2), 25.5 (CH_2), 27.4 (CH_2), 27.5 (CH_2), 27.6 (CH_2), 29.07 (2 × CH_2), 29.14 (CH_2), 29.5 (CH_2), 34.1 (CH_2), 39.4 (CH_2), 50.9 (CH), 51.4 (CH_3), 66.8 (CH_2), 125.7 (CH), 127.7 (CH), 127.8 (2 × CH), 128.4 (2 × CH), 132.0 (CH), 137.0 (C), 155.5 (C), 174.3 (C); EIMS *m*/*z* (rel intensity) 384 (M^+ − OMe, 0.9), 280 (1.3), 277 (1.2), 218 (44), 174 (100). Anal. Calcd for $C_{25}H_{37}NO_4$: C, 72.26; H, 8.79; N, 3.37. Found: C, 72.25; H, 8.98; N, 3.36.

[11(2*S*)]-11-[2-[*N*-(Benzyloxy)carbonyl]piperidyl]]-9-

undecenoic Acid (23). A mixture of **22** (880 mg, 2.12 mmol), 3 N KOH (2 mL), and MeOH (10 mL) was stirred at rt for 5 h. After neutralization with 1 N HCl, the mixture was extracted with EtOAc (4 × 20 mL). The extracts were washed with water, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (hexane−EtOAc, 2:1) gave **23** (816 mg, 96%) as a colorless oil: $[\alpha]^{28}_D$ −41.3° (*c* 1.1, $CHCl_3$); IR (neat) 3173, 3011, 2932, 2856, 1733, 1699, 1668, 1426, 1345, 1320, 1261, 1240, 1212, 1173, 1148, 1091, 1074, 1046, 733, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (9H, br s), 1.59−1.66 (7H, m), 1.99−2.03 (2H, m), 2.24−2.42 (2H, m), 2.35 (2H, t, J = 7.5 Hz), 2.86 (1H, td, J = 13.3, 2.6 Hz), 4.06 (1 H, br d, J = 2.0 Hz), 4.31 (1H, br s), 5.11 and 5.14 (2H, AB q, J = 12.5 Hz), 5.26−5.34 (1H, m), 5.38−5.47 (1H, m), 7.33−7.38 (5H, m); ^{13}C NMR ($CDCl_3$) δ 18.9 (CH_2), 24.6 (CH_2), 25.4 (CH_2), 27.3 (CH_2), 27.4 (CH_2), 27.6 (CH_2), 28.9 (CH_2), 29.0 (CH_2), 29.1 (CH), 29.5 (CH_2), 34.0 (CH_2), 39.4 (CH_2), 50.9 (CH), 66.9 (CH_2), 125.7 (CH), 127.7 (CH), 127.8 (2 × CH), 128.3 (2 × CH), 131.9 (CH), 136.9 (C), 155.5 (C), 179.5 (C); EIMS m/z (rel intensity) 402 (M^+ + 1, 0.2), 356 (3), 218 (46), 174 (100). Anal. Calcd for $C_{24}H_{35}NO_4$: C, 71.79; H, 8.79; N, 3.49. Found: C, 71.79; H, 8.80; N, 3.46.

***N*-[(Benzyloxy)carbonyl]-*N*-[4-[(*tert*-butoxycarbonyl)-amino]butyl]-*N*-(3-hydroxypropyl)amine (27).** A mixture of 1-bromo-4-[(*tert*-butoxycarbonyl)amino]butane (**25**) (1.95 g, 77.3 mmol), K_2CO_3 (2.14 g, 154.6 mmol), 3-amino-1-propanol (**24**) (581 mg, 77.3 mmol), and DMF (10 mL) was stirred under Ar at 90 °C for 3 h. The mixture was poured into ice−water (70 mL) and extracted with EtOAc (4 × 40 mL). The combined organic layers were washed with water, dried ($MgSO_4$), and concentrated in vacuo. Rapid chromatography on a short column of silica gel ($CHCl_3$−MeOH−NH_4OH, 40:9:1) gave *N*-[4-[(*tert*-butoxycarbonyl)amino]butyl]-*N*-(3-hydroxypropyl)-amine (**26**) (991 mg, 52%) as a colorless oil. A solution of Na_2CO_3 (657 mg, 6.20 mmol) in water (8 mL) was added to a solution of **26** (763 mg, 3.10 mmol) in CH_2Cl_2 (12 mL), and the mixture was cooled (0 °C) and stirred. To this was added dropwise a solution of benzyl chloroformate (634 mg, 3.72 mmol) in CH_2Cl_2 (4 mL) and stirring was continued at 0 °C. After 30 min, water (10 mL) was added and the organic layer was was separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc−hexane, 1:1) to yield **27** (1.04 g, 88%) as a colorless oil: IR (neat) 3354, 3033, 2936, 1685, 1526, 1480, 1426, 1391, 1367, 1253, 1210, 1171, 1062, 913, 866, 770, 753, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38−1.58 (4H, m), 1.43 (9H, s), 1.66−1.76 (2H, m), 3.06−3.10 (2H, m), 3.22 (2H, br t, J = 7.1 Hz), 3.41 (2H, br t, J = 5.9 Hz), 3.53−3.63 (2H, m), 4.61 (1H, br s), 5.13 (2H, s), 7.34 (5H, s); ^{13}C NMR ($CDCl_3$) for the major rotamer δ 25.6 (CH_2), 27.3 (CH_2), 28.3 (3 × CH_3), 30.5 (CH_2), 39.9 (CH_2), 43.3 (CH_2), 46.5 (CH_2), 58.4 (CH_2), 67.2 (CH_2), 79.1 (C), 127.8 (2 × CH_2), 128.0 (CH), 128.4 (2 × CH_2), 136.5 (C), 155.9 (C), 157.2 (C); for the minor rotamer δ 25.1 (CH_2), 27.3 (CH_2), 28.3 (CH_3, 3 carbons), 31.5 (CH_2), 39.9 (CH_2), 43.3 (CH_2), 47.1 (CH_2), 59.5 (CH_2), 67.0 (CH_2), 79.1 (C), 127.8 (CH, 2 carbons), 128.0 (CH), 128.4 (CH, 2 carbons), 136.5 (C), 155.9 (C), 157.2 (C); EIMS m/z (rel intensity) 380 (M^+, 0.5), 279 (30), 263 (20), 235 (15), 188 (58), 114 (100). Anal. Calcd for $C_{20}H_{32}N_2O_5$: C, 63.14; H, 8.48; N, 7.36. Found: C, 63.02; H, 8.56; N, 7.30.

***N*-[(Benzyloxy)carbonyl]-*N*-[4-[(*tert*-butoxycarbonyl)-amino]butyl]-*N*-[3-[(*tert*-butyldimethylsilyl)oxy]propyl]-amine (28).** To a solution of **27** (870 mg, 2.29 mmol) in DMF (10 mL) were added imidazole (390 mg, 5.73 mmol) and *tert*-butyldimethylsilyl chloride (415 mg, 2.75 mmol). The mixture was stirred at rt for 14 h, diluted with water (70 mL), and extracted with EtOAc (4 × 40 mL). The extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Column chromatography on silica gel (hexane−EtOAc, 10:1) gave **28** (928 mg, 82%) as a colorless oil: IR (neat) 3358, 2931, 2858, 1701, 1520, 1474, 1423, 1390, 1366, 1253, 1214, 1175, 1100, 1007, 837, 776, 736, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (6H, s), 0.87 (9H, s), 1.33−1.60 (4H, m), 1.43 (9 H, s), 1.65−1.78 (2H, m), 3.04−3.12 (2H, m), 3.29 (4H, br q, J = 7.5 Hz), 3.56−3.63 (2H, m), 5.11 (2H, s), 7.33 (5H, s); ^{13}C NMR ($CDCl_3$) for the major rotamer δ −5.6 (2 × CH_3), 17.9 (C), 25.6 (CH_2), 25.6 (3 × CH_3), 27.1 (CH_2), 28.2 (3 × CH_3), 31.7 (CH_2), 39.9 (CH_2), 43.8 (CH_2), 47.1 (CH_2), 60.1 (CH_2), 66.5 (CH_2), 78.6 (C), 127.5 (CH), 127.6 (2 × CH), 128.2 (2 × CH), 136.7 (C), 155.7 (2 × C); for the minor rotamer δ −5.6 (2 × CH_3), 17.9 (C), 25.1 (CH_2), 25.6 (3 × CH_2), 27.1 (CH_2), 28.2 (3 × CH_2), 31.0 (CH_2), 39.9 (CH_2), 44.4 (CH_2), 46.6 (CH_2), 60.1 (CH_2), 66.5 (CH_2), 78.6 (C), 127.5 (CH), 127.6 (2 × CH), 128.2 (2 × CH), 136.7 (C), 155.7 (2 × C); CIMS (isobutane) m/z (rel intensity) 495 (M^+ + 1, 8), 439 (62), 420 (14), 395 (100), 380 (24), 337 (22), 273 (21), 161 (12), 144 (13), 114 (13). Anal. Calcd for $C_{26}H_{46}N_2O_5Si$: C, 63.12; H, 9.37; N, 5.66. Found: C, 63.14; H, 9.47; N, 5.60.

***N*-[4-[(*tert*-Butoxycarbonyl)amino]butyl]-*N*-[3-[(*tert*-butyldimethylsilyl)oxy]propyl]amine (29).** A mixture of **28** (5.16 g, 10.4 mmol), $Pd(OH)_2$ (780 mg), and MeOH (40 mL) was hydrogenated at atmospheric pressure for 30 min. After removal of the catalyst by filtration, the filtrate was concentrated in vacuo to give **29** (3.57 g, 95%) as a colorless oil: IR (neat) 3343, 2932, 2858, 1698, 1525, 1473, 1463, 1391, 1365, 1253, 1176, 1099, 1006, 837, 815, 777, 662 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.03 (3H, s), −0.02 (3H, s), 0.81 (3H, s), 0.82 (6H, s), 1.37 (11H, s), 1.43−1.46 (2H, m), 1.63 (2H, br t, J = 6.3 Hz), 2.52−2.56 (2H, m), 2.61 (2H, td, J = 6.9, 1.4 Hz), 3.05−3.34 (2H, m), 3.61 (2H, td, J = 6.1, 1.5 Hz), 5.06 (1H, br s); ^{13}C NMR ($CDCl_3$) δ −5.5 (2 × CH_3), 18.1 (C), 25.8 (3 × CH_3), 27.4 (CH_2), 27.8 (CH_2), 28.3 (3 × CH_3), 32.7 (CH_2), 40.4 (CH_2), 47.2 (CH_2), 49.6 (CH_2), 61.7 (CH_2), 78.6 (C), 155.9 (C); EIMS m/z (rel intensity) 369 (M^+, 44), 315 (17), 304 (37), 300 (18), 247 (82), 215 (20), 202 (42), 187 (43), 145 (21), 132 (36), 101 (33), 75 (27), 57 (100). This material was used immediately without purification for the next reaction.

[11(2*S*)]-*N*-[4-[(*tert*-Butoxycarbonyl)amino]butyl]-*N*-[3-[(*tert*-butyldimethylsilyl)oxy]propyl]-11-[2-[*N*-(benzyloxy)-carbonyl]piperidyl]-9-undecenamide (30). A mixture of **23** (2.01 g, 5.00 mmol), **29** (2.70 g, 7.50 mmol), triethylamine (1.52 g, 15.0 mmol), diethoxyphosphoryl cyanide[16] (1.05 g, 6.00 mmol), and DMF (18 mL) was stirred under Ar at rt for 14 h. After addition of H_2O (200 mL), the mixture was extracted with Et_2O (4 × 100 mL). The combined organic layers were washed with water, dried ($MgSO_4$), and concentrated in vacuo. Chromatography of the residue on silica gel (hexane−EtOAc, 2:1) gave **30** (3.53 g, 95%) as a colorless oil: $[\alpha]^{26}_D$ −20.8° (*c* 4.5, $CHCl_3$); IR (neat) 3346, 3005, 2930, 2856, 1700, 1642, 1520, 1455, 1423, 1390, 1364, 1343, 1319, 1257, 1173, 1143, 1096, 1044, 1007, 969, 837 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (3H, s), 0.04 (3H, s), 0.87 (3H, s), 0.88 (6H, s), 1.28 (9H, br s), 1.42 (6H, s), 1.43 (3H, s), 1.47−1.76 (14H, m), 1.91−2.01 (3H, m), 2.23−2.34 (4H, m), 2.84 (1H, td, J = 13.3, 2.0 Hz), 3.11 (2H, br d, J = 5.8 Hz), 3.22−3.38 (3H, m), 3.60 (2H, t, J = 5.8 Hz), 4.05 (1H, br d, J = 11.9 Hz), 4.30 (1H, br s), 5.05 and 5.13 (2H, AB q, J = 12.5 Hz), 5.23−5.31 (1H, m), 5.35−5.43 (1H, m), 7.30−7.34 (5H, m); ^{13}C NMR ($CDCl_3$) δ (rotamers) 5.64, 5.56, 17.9, 18.0, 18.7, 24.8, 25.2, 25.6, 25.7, 26.1, 27.1, 27.2, 27.4, 28.2, 28.9, 29.0, 29.2, 29.4, 30.7, 31.8, 32.8, 39.1, 39.8, 39.9, 42.8, 44.3, 44.9, 47.7, 50.6, 59.4, 60.5, 66.48, 66.54, 78.5, 125.4, 127.4, 127.5, 128.1, 131.8, 136.8, 155.2, 155.8, 172.4, 172.7; EIMS m/z (rel intensity) 743 (M^+, 8), 668 (5), 608 (7), 525 (18), 500 (10), 467 (16), 342 (12), 218 (48), 174 (100). Anal. Calcd for $C_{42}H_{73}N_3O_6Si$: C, 67.79; H, 9.89; N, 5.65. Found: C, 67.76; H, 10.10; N, 5.62.

[11(2*S*)]-*N*-[4-[(*tert*-Butoxycarbonyl)amino]butyl]-*N*-(3-hydroxypropyl)-11-[2-[*N*-(benzyloxy)carbonyl]piperidyl]-9-undecenamide (31). To a stirred solution of **30** (2.86 g, 3.84 mmol) in THF (30 mL) was added a 1.0 M solution of tetrabutylammonium fluoride (9.2 mL, 9.2 mmol) in THF. After being stirred at rt for 2 h, the mixture was diluted with EtOAc (100 mL), washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane−EtOAc, 1:1) to yield **31** (2.42 g, 100%) as a colorless oil: $[\alpha]^{26}_D$ −20.5° (*c* 4.7, $CHCl_3$); IR (neat) 3356, 2931, 2856, 1696, 1625, 1526, 1425, 1390, 1365, 1319, 1258, 1172, 1074, 1047, 734, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (9H, br s), 1.42 (9H, s), 1.45−1.70 (11H, m), 1.96−2.00 (3H, m), 2.22−2.38 (2H, m), 2.30 (2H, t, J = 7.6 Hz), 2.84 (1H, td, J = 13.8, 2.3 Hz), 3.12 (2H, t, J = 6.3 Hz), 3.14 (2H, t, J =

6.6 Hz), 3.28−3.38 (1H, m), 3.42−3.50 (3H, m), 4.02−4.10 (2H, m), 4.29 (1H, br s), 5.08 and 5.12 (2H, AB q, J = 12.5 Hz), 5.22−5.31 (1H, m), 5.35−5.43 (1H, m), 7.30−7.34 (5H, m); ^{13}C NMR ($CDCl_3$) δ (rotamers) 18.8, 24.7, 25.3, 25.5, 25.9, 27.2, 27.4, 27.5, 28.3, 29.0, 29.2, 29.3, 29.5, 30.2, 31.7, 32.8, 32.9, 39.3, 39.7, 41.4, 44.6, 45.1, 47.4, 50.7, 57.9, 59.1, 66.7, 79.1, 125.6, 127.6, 127.7, 128.2, 131.8, 136.8, 155.4, 155.9, 173.0, 174.3; EIMS m/z (rel intensity) 529 ($M^+ + 1 - (CH_3)_3COCO$, 33), 512 (26), 479 (12), 440 (12), 426 (27), 422 (16), 412 (100). Anal. Calcd for $C_{36}H_{59}N_3O_6$: C, 68.65; H, 9.44; N, 6.67. Found: C, 68.68; H, 9.62; N, 6.59.

[11(2*S*)]-*N*-[4-[(*tert*-Butoxycarbonyl)amino]butyl]-*N*-(2-formylethyl)-11-[2-[*N*-[(benzyloxy)carbonyl]piperidyl]]-9-undecenamide (34). To a stirred, cold (−78 °C) solution of oxalyl chloride (142 mg, 1.12 mmol) in CH_2Cl_2 (2 mL) was added via syringe a solution of dimethyl sulfoxide (175 mg, 2.24 mmol) in CH_2Cl_2 (2 mL), and the mixture was stirred at −78 °C for 1 h. To this mixture was added dropwise a solution of **31** (353 mg, 0.560 mmol) in CH_2Cl_2 (2 mL) over a period of 5 min, and stirring was continued at −78 °C. After 2 h, triethylamine (340 mg, 3.36 mmol) was added to the reaction mixture, and the mixture was allowed to warm to rt. Addition of water (30 mL) and extraction with CH_2Cl_2 (4 × 30 mL) afforded a CH_2Cl_2 solution, which was washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was subjected to silica gel column chromatography (EtOAc−hexane, 1:1) to give **34** (253 mg, 72%) as a colorless oil: $[\alpha]^{27}_D$ −28.9° (c 2.6, $CHCl_3$); IR (neat) 3346, 2931, 2856, 1695, 1635, 1525, 1424, 1390, 1365, 1319, 1259, 1172, 1090, 1046, 1005, 764, 735, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 (9H, br s), 1.43 (9H, s), 1.46−1.63 (10H, m), 1.96−2.01 (3H, m), 2.22−2.34 (4H, m), 2.70−2.89 (3H, m), 3.11−3.85 (2H, m), 3.29 (2H, br t, J = 7.4 Hz), 3.6 (2H, t, J = 6.5 Hz), 4.03−4.07 (1H, m), 4.30 (1H, br s), 5.09 and 5.13 (2H, AB q, J = 12.4 Hz), 5.23−5.31 (1H, m), 5.35−5.44 (1H, m), 7.30−7.35 (5H, m), 9.77 (1H, t, J = 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ (rotamers) 18.6, 24.5, 24.9, 25.1, 26.0, 27.0, 27.2, 27.3, 28.1, 28.8, 28.9, 29.0, 29.2, 32.6, 32.8, 39.0, 39.5, 39.9, 40.3, 42.6, 42.9, 44.8, 48.0, 50.5, 66.4, 78.7, 125.4, 127.3, 127.4, 128.0, 131.6, 136.7, 155.1, 155.7, 172.3, 172.8, 199.2, 200.5; EIMS m/z (rel intensity) 554 ($M^+ - (CH_3)_3CO$, 42), 549 (14), 526 (20), 510 (42), 498 (100), 592 (24). Anal. Calcd for $C_{36}H_{57}N_3O_6$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.70; H, 9.35; N, 6.65.

17(*R*)-5-[4-[(*tert*-Butoxycarbonyl)amino]butyl]-1,5-diazabicyclo[15.4.0]henicosan-6-one (33). A mixture of **34** (146 mg, 0.233 mmol), $Pd(OH)_2$ (40 mg), and MeOH (58 mL) was stirred in an atmosphere of hydrogen at atmospheric pressure for 4 days. After filtration of the catalyst, the solvent was evaporated in vacuo and purification of the residue by column chromatography on silica gel ($CHCl_3$−MeOH−NH_4OH, 500:9:1) gave **33** (74 mg, 66%) as a colorless oil: $[\alpha]^{27}_D$ −18.9° (c 4.8, $CHCl_3$); IR (neat) 3331, 2930, 2857, 2106, 1709, 1636, 1525, 1458, 1390, 1365, 1270, 1252, 1174, 1043, 1005, 870, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.17−1.80 (31H, m), 1.37 (9H, s), 2.12−2.88 (6H, m), 3.04−3.26 (4H, m), 3.28−3.37 (2H, unresolved), 4.75 (1H, br s); ^{13}C NMR ($CDCl_3$) δ (rotamers) 22.3, 23.55, 23.60, 23.8, 24.2, 24.4, 24.6, 24.8, 24.9, 25.3, 25.7, 26.0, 26.3, 26.4, 26.6, 26.7, 26.9, 26.97, 27.04, 27.3, 27.4, 27.7, 27.8, 27.85, 28.3, 29.0, 30.1, 30.5, 32.2, 32.4, 39.9, 40.0, 42.9, 45.2, 46.4, 47.2, 50.6, 51.0, 51.3, 52.3, 59.9, 60.4, 78.8, 79.0, 155.9, 172.7, 173.0; EIMS m/z (rel intensity), 479 (M^+, 10), 406 (5), 123 (100), 112 (78); HRMS calcd for $C_{28}H_{53}N_3O_3$ (M^+) 479.4087, found 479.4106.

17(*R*)-5-(4-Aminobutyl)-1,5-diazabicyclo[15.4.0]henicosan-6-one ((−)-Oncinotine) (1). To a cooled (0 °C), stirred MeOH (3 mL) solution of **33** (248 mg, 0.653 mmol) was added 3 N HCl (3 mL) and stirring was continued at rt for 3 h. After concentration of the mixture in vacuo, the residue was dissolved in H_2O (16 mL), made basic (pH 10) with K_2CO_3, and extracted with $CHCl_3$ (5 × 16 mL). The combined organic phases were washed with water, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by column chromatography on silica gel ($CHCl_3$−MeOH−NH_4OH, 200:9:1) gave **1** (140 mg, 71%) as a colorless oil: $[\alpha]^{26}_D$ −28.7° (c 2.6, $CHCl_3$), $[\alpha]^{26}_D$ −32.7° (c 2.1, MeOH); IR (CCl_4) 3584, 3369, 2929, 2856, 1636, 1461, 1378, 1320, 1231, 1126, 1045, 823 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.21−1.72 (32H, m), 2.12−2.39 (5H, m), 2.49−2.61 (1H, m), 2.67 (2H, dt, J = 4.1, 6.8 Hz), 2.72−2.84 (1H, m), 3.08−3.26 (3H, m), 3.35 (1H, dt, J = 13.4, 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ (rotamers) 23.1, 23.6, 23.6, 23.8, 24.3, 24.8, 24.9, 25.0, 25.4, 25.6, 25.8, 26.4, 26.6, 26.7, 26.8, 27.0, 27.1, 27.3, 27.7, 27.9, 28.1, 30.0, 30.2, 30.5, 30.8, 30.9, 32.4, 32.5, 41.8, 43.1, 45.5, 46.5, 47.5, 50.7, 51.3, 51.8, 52.4, 60.0, 172.7, 172.9; EIMS m/z (rel intensity) 379 (M^+, 20), 350 (10), 150 (34), 137 (14), 123 (100), 112 (57), 98 (50), 84 (47) 70 (52); HRMS calcd for $C_{23}H_{45}N_3O$ (M^+) 379.3563, found 379.3574.

A part of the synthetic sample was converted to the hydrochloride salt (**1**·2HCl) by treatment with concentrated HCl−MeOH followed by evaporation in vacuo as a colorless oil: ^{1}H NMR (CD_3OD) δ 1.20−2.35 (30H, m), 2.40−2.51 (2H, m), 3.01 (2H, br s), 3.12−3.35 (5H, m), 3.40−3.64 (4H, m); ^{1}H NMR (D_2O) δ 1.26−2.00 (30H, m), 2.32−2.46 (2H, m), 2.95 (2H, br s), 3.02−3.18 (5H, m), 3.30−3.51 (4H, m); ^{13}C NMR (CD_3OD) δ (rotamers) 19.6, 22.2, 22.4, 23.1, 23.6, 23.7, 24.0, 24.26, 24.32, 24.6, 25.0, 25.1, 25.3, 25.37, 25.42 25.7, 25.9, 26.0, 26.7, 26.8, 27.1, 27.2, 27.5, 27.6, 27.7, 27.8, 27.85, 27.93, 28.0, 28.1, 28.2, 28.3, 28.4, 28.5, 28.7, 28.8, 28.9, 29.6, 30.1, 30.8, 33.0, 40.3, 40.4, 40.5, 43.6, 43.9, 46.6, 48.3, 51.1, 51.2, 51.36, 51.45, 52.7, 54.9, 61.9, 62.3, 64.7, 64.9, 176.2, 176.5, 176.7; ^{13}C NMR (D_2O) δ dioxane (rotamers) 19.2, 22.4, 22.5, 23.0, 23.2, 23.7, 24.0, 24.2, 24.4, 24.9, 25.1, 25.2, 25.3, 25.4, 25.5, 26.0, 26.2, 26.3, 26.4, 27.0, 27.1, 27.3, 27.5, 27.7, 27.9, 28.0, 28.2, 28.3, 28.4, 28.7, 29.1, 29.7, 30.2, 30.6, 33.3, 33.4, 40.5, 43.6, 43.7, 46.4, 46.45, 46.5, 48.8, 49.3, 50.3, 50.4, 51.3, 51.5, 53.6, 55.2, 61.5, 62.0, 64.6, 64.7, 177.1, 177.2, 178.0, 178.2.

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