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Total Synthesis of (+)-Monomorine I via Nitrone Cycloaddition Route

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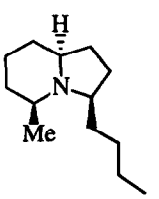
Key Words: nitrone; 1,3-dipolar cycloaddition; chiral allylic ether; inside alkoxy effect; (+)-monomorine I

*Abstract: An enantioselective total synthesis of (+)-monomorine I (1) is described. The key feature of the synthesis is the asymmetric 1,3-dipolar cycloaddition of the prochiral nitrone 9 with the chiral (S)-allylic ether 8 as a dipolarophile, which provides stereoselectively the C-3,C-5-*trans*-isoxazolidine 10 with the correct relative and absolute stereochemistry suitable for the synthesis of (+)-monomorine I.*

The indolizidine alkaloids constitute an exceptionally large class of natural products which have attracted a vast amount of interests of synthetic organic chemists in many years because of their significant biological activities.[1] In continuation of a study in our laboratory on developing synthetic entries into optically active simple indolizidine alkaloids,[2] we have been interested in the development of the chiral approach to (+)-monomorine I (1). (+)-Monomorine I, isolated from Pharaoh's ant



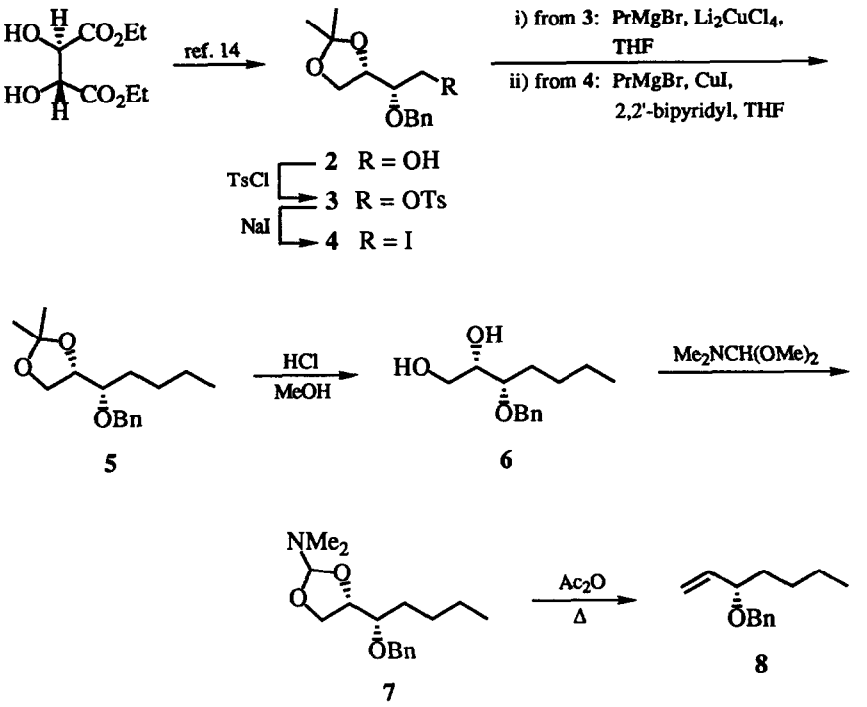
(+)-Monomorine I (1)

Monomorium pharaonis as a major alkaloidal component,[3] is the first example of indolizidine alkaloids found in the animal kingdom; the compound constitutes, together with other alkaloids found in thief ants, *Solenopsis* species, a rare group of arthropod alkaloids having the indolizidine skeleton.[4] Due to its trail-following activity as well as the unique structural feature, **1** has been subject of extensive synthetic efforts which have culminated in numerous syntheses of racemic monomorine I.[5] The first chiral synthesis of the unnatural (–)-enantiomer of monomorine I (**1**) was reported by Husson's group,[6] which permitted the absolute stereochemistry of the natural monomorine I be that shown for **1**. After Husson's synthesis, the chiral synthesis of natural (+)-monomorine I (**1**) has so far been by four groups including us.[7,8] In this paper we describe an alternative chiral synthesis of (+)-monomorine I (**1**).[9] The key feature of our approach is an asymmetric 1,3-dipolar cycloaddition of a prochiral nitrone with a chiral alkene possessing an allylic oxygen at a chiral center.

RESULTS AND DISCUSSION

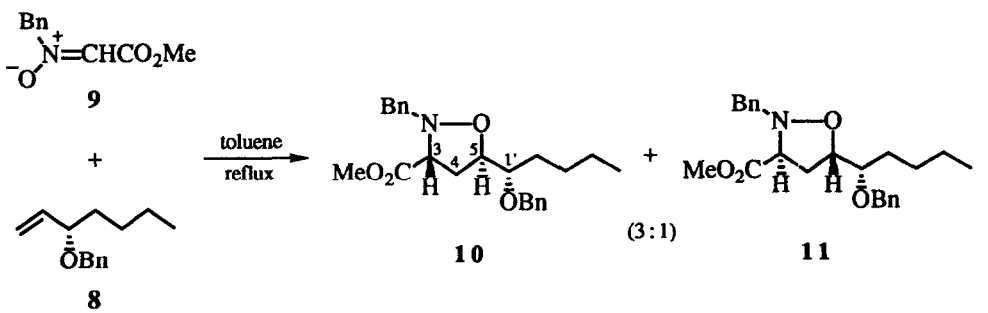
Asymmetric cycloadditions of nitrones and its application to natural product syntheses[10] have been focus of recent synthetic investigations with increasing frequency. In particular, asymmetric cycloadditions involving the use of chiral nitrones bearing chiral substituents either at carbon[10d-j, 11] or at nitrogen[10k-q, 12] have been extensively explored. In contrast, the use of chiral dipolarophiles, however, have received only limited study.[13] Therefore we initiated investigations aimed at the nitrone cycloaddition reaction by using a chiral allylic ether as a dipolarophile. Toward this end, the L-threitol derivative **2**, prepared from diethyl L-tartrate in 3 steps according to the known method,[14] was transformed into (3*S*)-3-benzyloxy-1-heptene (**8**) as outlined in Scheme 1. Thus, the tosylate **3**, obtained from **2** (97%), was converted to the iodide **4** (96%) with NaI in methyl ethyl ketone. Treatment of **4** with PrMgBr in the presence of catalytic amounts of 2,2'-bipyridyl and copper(I) iodide afforded the (2*S*,3*S*)-heptanetriol (**5**); however, this reaction was unsatisfactory, because the yield was inconstant and sometimes very low, ranging from 20% to 70%. When the same process was carried out with the tosylate **3** by using dilithium tetrachlorocuprate (Li_2CuCl_4) as a catalyst remarkable improvement was achieved, providing **5** in 87% yield. After removal of the isopropylidene group under acidic conditions, the resulting diol **6** was treated with *N*,*N*-dimethylformamide dimethyl acetal to afford the 2-dimethylamino-1,3-dioxolane **7**, which subsequently underwent elimination by heating with acetic anhydride[15] to form the allylic ether **8** in 68% overall yield from **5**.[16]

The (*S*)-allylic ether **8** was allowed to react with the nitrone **9** (*E*/*Z* equilibrium mixture), generated by condensation of methyl glyoxylate with *N*-benzylhydroxylamine,[17] in refluxing toluene to give a 3:1 mixture of the C-3, C-5-*trans*-isoxazolidines **10** and **11** in 76% yield in favor of the desired diastereomer **10**. In this reaction, accompanying formation of a small amount of a mixture of C-3, C-5-



Scheme 1

cis-isoxazolidines, probably resulted from exo addition of the *Z* nitrone (*Z*)-**9**, was observed. It is known that the nitrone **9** exists in a *Z* form in a crystalline state and in *E*/*Z* equilibrium (*E*/*Z* = 1.6) in $CDCl_3$, however the *E*/*Z* ratio in $CDCl_3$ is not necessarily reflected on the ratio of the trans/cis ratio of the cycloadducts.[17]



The trans stereochemistry of the C-3 and C-5 substituents in both products **10** and **11** was verified based on 2D NOESY analysis and NOE difference experiments (Fig. 1) that showed 5.6% and 7.0% NOE enhancements between H_a and H_b, and H_c and H_d, respectively, for **10**. Similarly, 10.8% and 10.9% enhancements were observed between H_a and H_b, and H_c and H_d, respectively, for **11**. Whereas, both in **10** and **11**, no NOE's were observed between H_a and H_c, and also between H_b and H_d, thus proving the trans relationship of H_a (C-3) and H_d (C-5).

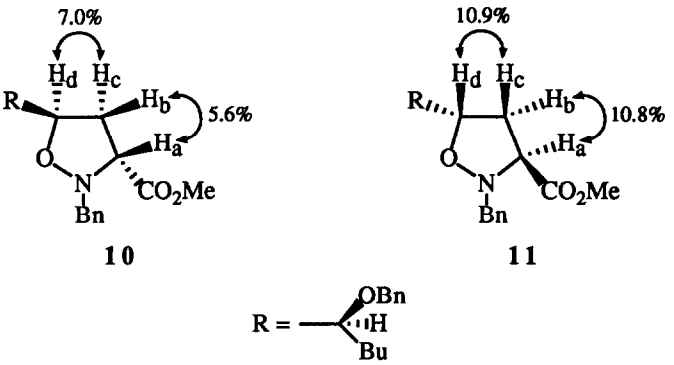


Fig. 1. NOE differences observed for the C-3, C-5-*trans*-isoxazolidines **10** and **11**.

Both the *trans*-adducts **10** and **11** must arise from an exo transition state involving the *E* nitrone (*E*)-**9**. Another pathway involving a *Z*-endo transition state, which also leads to **10** and **11**, would be less favored, since there is no potential for secondary orbital overlap to favor the endo transition state,[18] but is there steric congestion developed in this transition state. In the trans pair, the preferential diastereomer **10** formed as a result of the *re* face approach at the prochiral nitrone (*E*)-**9** in the exo manner can be rationalized according to Houk's stereoelectronic concept.[19] In electrophilic attack on, and electrophilic cycloaddition to an allylic ether, the π system suffers electron deficient. Thus, in the allylic ether **8**, the σ-donating butyl group adapts a position anti to stabilize the transition state, which an

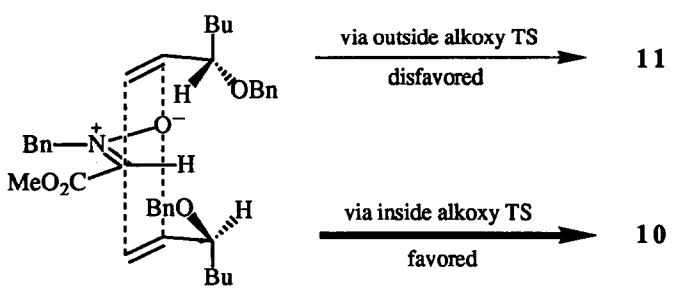
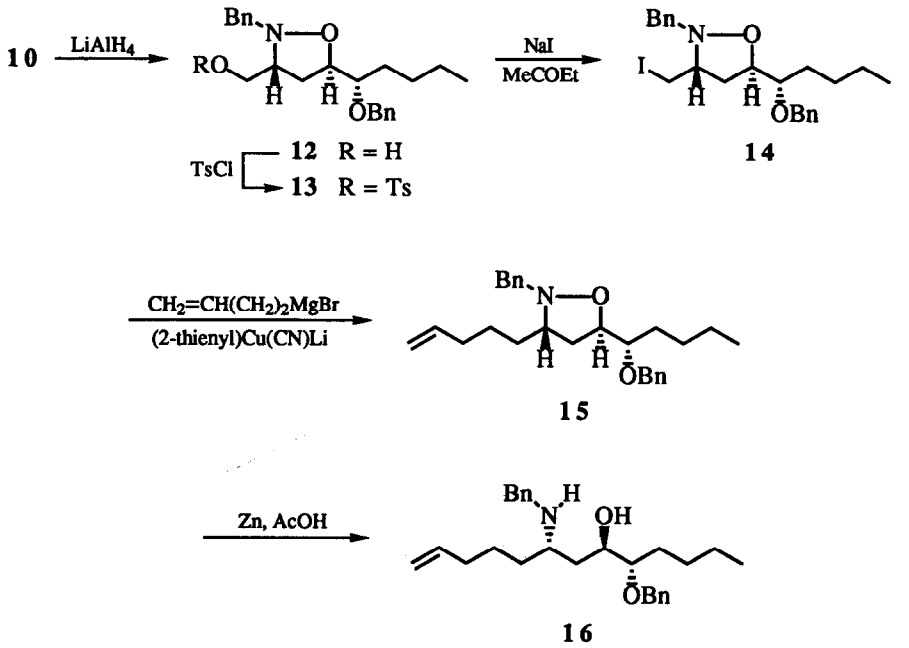


Fig. 2. Cycloaddition of the prochiral nitrone (*E*)-**9** with the chiral allylic ether **8**.

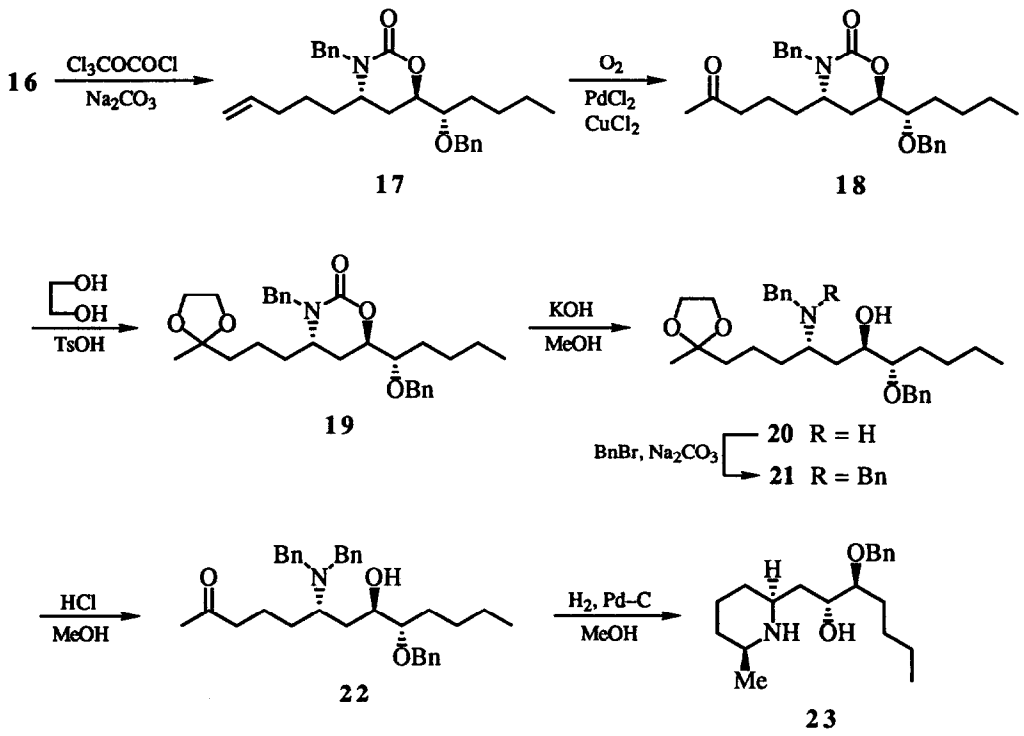
antiperiplanar approach (Fig. 2). In this case, when the alkoxy group (BnO) occupies an "inside" position, electron withdrawal from the π system due to σ^*_{CO}/π overlap is minimized, and the transition permits an antiperiplanar approach (Fig. 2). In this case, when the alkoxy group (BnO) occupies an "inside" position, electron withdrawal from the π system due to σ^*_{CO}/π overlap is minimized, and the transition state would be stabilized to lead to **10** with the C-5, C-1'-*erythro* stereochemistry. The alternative approach involving "outside" alkoxy conformation leading to the C-5, C-1'-*threo* isomer **11** would be less favorable.[20]

The C-3, C-1'-*erythro*-isoxazolidine **10** was transformed into the iodide **14** in 74% overall yield by sequential treatment with $LiAlH_4$, TsCl, and NaI (Scheme 2). Grignard coupling reaction of **14** was carried out with 3-butenylmagnesium bromide in the presence of 2,2'-bipyridyl and copper(I) iodide, in a similar manner to that described above for **5**, to give **15**, which was, however, low in yield (31%).[21] Much higher yield was obtained when employed the higher-order mixed organocuprate[22] derived from 3-butenylmagnesium bromide and lithium 2-thienylcyanocuprate, leading to **15** in 90% yield. Resulting **15** was converted to the amino alcohol **16** by reductive N–O bond cleavage with zinc in aqueous acetic acid.



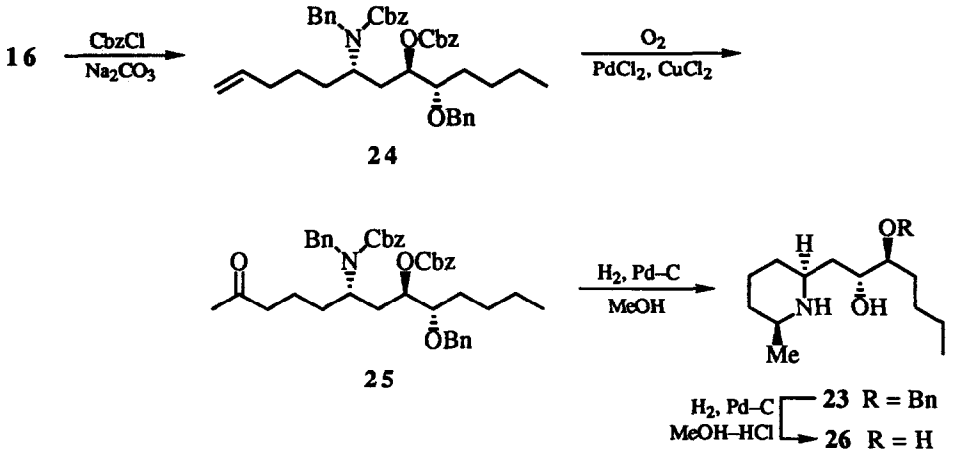
Scheme 2

We next attempted to prepare the 2,6-*cis*-piperidine derivative **23** which was expected to be utilized as the key intermediate for the synthesis of monomorine I. Both amino and hydroxy groups of **16** was protected as the cyclic carbamate **17** (84%) with trichloromethyl chloroformate, which was then oxydized via Wacker process[23] using O_2 and catalytic $PdCl_2$ and $CuCl_2$ to give the ketone **18** in 89% yield (Scheme 3). After ketalization, resulting **19** was converted to **22**[24] by hydrolysis (KOH, MeOH), N-benzylation ($PhCH_2Br$, Na_2CO_3), and deketalization (HCl, MeOH) in 57% overall yield. On hydrogenolysis (H_2, Pd–C, MeOH) of the ketone **22**, deprotection and simultaneous cyclization (via iminium ion) occurred to generate the 2,6-*cis*-piperidine **23** (70%) as a single isomer.



Scheme 3

Preparation of the key intermediate **23** which possesses the proper enantiogenic centers and carbon framework for utilization in the synthesis of monomorine I was thus established. However, this route is lengthy and encumbered by extensive protection group manipulations. Therefore, with the amino alcohol **16** in hand, we explored a more convenient short route to **23** as outlined in Scheme 4. Thus, both secondary amine and alcohol of **16** was protected by the benzyloxycarbonyl groups with $PhCH_2OCOCl$ to give **24** (79%). After oxidation of **24** via the Wacker process (91% yield), catalytic hydrogenolysis of the resultant ketone **25** over palladium on carbon in methanol led to intramolecular

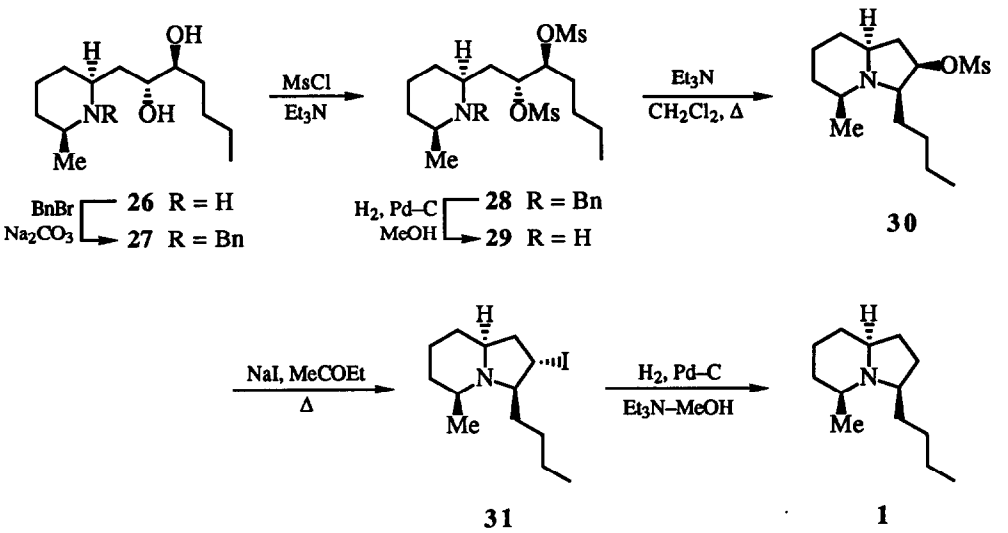


Scheme 4

reductive cyclization to **23**. The subsequent hydrogenolysis in an acidic medium (H_2, Pd–C, HCl–MeOH) resulted in deblocking of the benzyl ether, furnishing the dihydroxy piperidine **26**.[25]

Compound **26** was, without isolation, subsequently subjected to N-protection by the benzyl group to give **27** (52% overall yield from **25**) and two hydroxy groups in **27** was mesylated (Scheme 5). Removal of the benzyl protective group of the resultant dimesylate **28** (76%) by catalytic hydrogenolysis furnished **29**, which was immediately cyclized by heating with triethylamine in dichloromethane to afford **30** as a single diastereomeric product (66% overall yield from **28**). Finally, **30** was converted to (+)-monomorine I (**1**) in 58% overall yield by means of nucleophilic displacement (NaI) followed by reductive deiodination (H_2, Pd–C, Et_3N, MeOH). The synthetic material was identical in all respects with an authentic material of (+)-monomorine I previously prepared in this laboratory.[7]

We have demonstrated the synthetic utility of an asymmetric 1,3-dipolar cycloaddition of a prochiral nitrone by using a chiral allylic ether as a dipolarophile for the synthesis of (+)-monomorine I. Further work to investigate asymmetric 1,3-dipolar cycloaddition using various chiral allylic ethers and its application to the synthesis of nitrogenous natural products are currently being carried out in our laboratory.



Scheme 5

EXPERIMENTAL SECTION

General Procedures

Melting points (uncorrected) were determined by using a Yanagimoto micro melting points apparatus. Optical rotations were measured with a JASCO DIP-360 digital polarimeter in a 1-dm cell. IR spectra were determined on a Perkin-Elmer 1710 FTIR spectrometer. ^1H and ^{13}C NMR spectra were taken at 400 MHz, and 100 MHz, respectively on a Bruker AM-400 spectrometer. ^1H chemical shifts are expressed relative to $CHCl_3$ at δ 7.26 and ^{13}C chemical shifts relative to $CDCl_3$ at δ 77.1. Mass spectra were obtained with a Hitachi RMU-7L double-focusing mass spectrometer at 70 eV. TLC was run on Wako precoated silica gel 70FM plates. Merck silica gel 60 (230–400 mesh) and aluminium oxide 90 (basic, activity I, 70–230 mesh) were used for column chromatography.

2-O-Benzyl-3,4-O-isopropylidene-1-O-p-tolylsulfonyl-L-threitol (3)

To an ice bath-cooled, stirred mixture of **2** (8.00 g, 31.7 mmol) and *N,N*-dimethylaminopyridine (5.82 g, 47.6 mmol) in CH_2Cl_2 (60 mL) was added dropwise a solution of *p*-tolylsulfonyl chloride (7.26 g, 38.1 mmol) in CH_2Cl_2 (40 mL) over a period of 30 min. Then the ice bath was removed and the mixture was stirred for 2 h and diluted with CH_2Cl_2 (100 mL). The solution was washed with water, dried ($MgSO_4$), and evaporated. The crude product was purified by column chromatography on silica gel (hexane–ethyl acetate, 7:1) to give **3** (12.4 g, 97%) as a colorless oil: $[\alpha]^{28}_D$ +11.1° (*c* 0.95,

$CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.30 (3 H, s), 1.35 (3 H, s), 2.44 (3 H, s), 3.67–3.71 (1 H, m), 3.75 (1 H, dd, J = 8.5, 6.6 Hz), 3.93 (1 H, dd, J = 8.5, 6.6 Hz), 4.10 (1 H, dd, J = 10.6, 6.3 Hz), 4.17 (1 H, dd, J = 11.7, 6.6 Hz), 4.18 (1 H, dd, J = 10.6, 4.0 Hz), 4.60 and 4.67 (2 H, AB q, J = 11.8 Hz), 7.27–7.34 (5 H, m, including 2 H, d, J = 8.3 Hz at δ 7.26), 7.77 (2 H, d, J = 8.3 Hz); MS *m/z* (relative intensity) 407 (M^+ + 1, 0.2), 391 (4), 133 (13), 101 (39), 91 (100), 65 (8). Anal. calcd for $C_{21}H_{26}O_6S$: C, 62.05; H, 6.45. Found: C, 62.05; H, 6.43.

[4S,4(1S)]-4-(1-Benzyloxy-2-iodoethyl)-2,2-dimethyl-1,3-dioxolane (4)

To a solution of **3** (24.6 g, 60.5 mmol) in 2-butanone (300 mL) was added NaI (36.3 g, 242 mmol) and the mixture was heated at 80 °C for 3 h. Ether (500 mL) was added to the reaction mixture and the mixture was filtered through a pad of Celite. The filtrate was washed with 5% aqueous $Na_2S_2O_3$ and then water. The ether solution was dried over $MgSO_4$ and evaporated affording an oily residue, which was purified by column chromatography on silica gel (hexane–ethyl acetate, 20:1) to give **4** (21.1 g, 96%) as a colorless oil: $[\alpha]^{27}_D$ –8.60° (*c* 1.97, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.44 (3 H, s), 1.67 (3 H, s), 3.19 (1 H, dd, J = 10.6, 6.8 Hz), 3.33 (1 H, dd, J = 10.6, 4.8 Hz), 3.57 (1 H, dt, J = 6.8, 4.8 Hz), 3.78 (1 H, dd, J = 8.4, 6.6 Hz), 4.00 (1 H, dd, J = 8.4, 6.6 Hz), 4.33 (1 H, dt, J = 6.6, 5.2 Hz), 4.70 and 4.77 (2 H, AB q, J = 11.5 Hz), 7.29–7.43 (5 H, m); MS *m/z* (relative intensity) 362 (M^+, 0.03), 347 (2), 177 (3), 134 (4), 133 (2), 101 (86), 91 (100). Anal. calcd for $C_{14}H_{19}IO_3$: C, 46.43; H, 5.29. Found: C, 46.68; H, 5.37.

[4S,4(1S)]-4-[1-(Benzyloxy)pentyl]-2,2-dimethyl-1,3-dioxolane (5). Method A. From 4

To a mixture of CuI (460 mg, 2.42 mmol), 2,2'-dipyridyl (378 mg, 2.42 mmol), and THF (13 mL) was added a solution of **4** (8.76 g, 24.2 mmol) in THF (13 mL). The resultant mixture was stirred and cooled to –20 °C and *n*-propylmagnesium bromide in THF (43 mL), prepared from 1-bromopropane (10.4 g, 84.6 mmol) and Mg (2.06 mg, 84.6 mmol), was added under Ar. After the mixture was stirred at room temperature for another 1 h, it was quenched with saturated aqueous NH_4Cl (120 mL) and filtered through a Celite pad. The organic phase was separated and the aqueous phase was extracted with ether. The combined organic phases were washed with water, dried ($MgSO_4$), and evaporated. The crude product was purified by column chromatography on silica gel (hexane–ethyl acetate, 70:1) to give **5** (4.71 g, 70%) as a colorless oil: $[\alpha]^{26}_D$ –41.5 ° (*c* 1.21, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.89 (3 H, t, J = 7.2 Hz), 1.26–1.50 (6 H, m, including two 3 H, s at δ 1.38 and 1.45), 3.43 (1 H, ddd, J = 7.9, 6.5, 3.6 Hz), 3.69 (1 H, dd, J = 8.1, 7.5 Hz), 3.99 (1 H, dd, J = 8.1, 6.5 Hz), 4.22 (1 H, dt, J = 7.5, 6.5 Hz), 4.63 and 4.77 (2 H, AB q, J = 11.7 Hz), 7.25–7.39 (5 H, m); MS *m/z* (relative intensity) 279 (M^+ + 1, 0.03), 278 (M^+, 0.05), 220 (5), 177 (11), 134 (20), 101 (49), 92 (22), 91 (100). Anal. calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.51; H, 9.52.

Method B. From 3

To a stirred solution of **3** (5.00 g, 12.3 mmol) in THF (10 mL) were added a solution of *n*-propylmagnesium bromide in THF (20 mL), prepared from 1-bromopropane (3.79 g, 30.8 mmol) and Mg (747 mg, 30.8 mmol), and then a 0.1 M solution of Li_2CuCl_4 (0.74 mL, 0.074 mmol) in THF at –78 °C under Ar. The mixture was stirred at –78 °C for 1.5 h and allowed to warm to room temperature, and stirring was continued at ambient temperature for 65 h. The reaction was quenched with saturated aqueous NH_4Cl (100 mL) and filtered through a Celite pad. The organic phase was separated and the aqueous phase was extracted with ether. The combined organic phases were washed with water, dried ($MgSO_4$), and evaporated. The crude product was chromatographed on silica gel (hexane–ethyl acetate, 70:1) to give **5** (2.99 g, 87%).

(2S,3S)-3-Benzyloxy-1,2-heptanediol (6)

A stirred solution of **5** (1.01 g, 3.63 mmol) in MeOH (15 mL) including 6 N HCl (3 mL) was heated at 55 °C for 1 h. The reaction mixture was concentrated in vacuo to give an oily residue, which was neutralized with saturated aqueous Na_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with brine, dried ($MgSO_4$), and evaporated. The crude product was chromatographed on silica gel (hexane–ethyl acetate, 3:1) to give **6** (0.85 g, 98%) as a colorless oil: $[\alpha]^{20}_D$ +36.6 ° (*c* 0.54, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.92 (2 H, t, *J* = 7.1 Hz), 1.29–1.43 (4 H, m), 1.55–1.72 (2 H, m), 2.27 (1 H, br s), 2.63 (1 H, br s), 3.47 (1 H, dd, *J* = 10.8, 5.8 Hz), 3.58–3.71 (3 H, m), 4.48 and 4.67 (2 H, AB q, *J* = 11.4 Hz), 7.28–7.38 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 14.1, 23.0, 27.4, 30.0, 64.2, 72.3, 72.9, 79.9, 128.0 (3 carbons), 128.6 (2 carbons), 138.2; MS *m/z* (relative intensity) 239 (M^+ + 1, 0.7), 177 (20), 107 (7), 92 (25), 91 (100). Anal. calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.19; H, 9.32.

(3S)-3-Benzyloxy-1-heptene (8)

A solution of **6** (10.5 g, 44.0 mmol) in *N,N*-dimethylformamide dimethylacetal (40 mL) was stirred for 1.5 h at 70 °C and the reaction mixture was evaporated to dryness in vacuo to give the 2-dimethylamino-1,3-dioxolane **7** as an oil, which was dissolved in acetic anhydride (20 mL) and refluxed for 1 h. The reaction mixture was poured into ice water (10 mL), neutralized with saturated aqueous Na_2CO_3, and extracted with CH_2Cl_2. The extract was washed with water, dried ($MgSO_4$), and evaporated. The residual oil was purified by column chromatography on silica gel (hexane–benzene, 15:1) to give **8** (6.30 g, 70%) as a colorless oil: $[\alpha]^{22}_D$ –39.8° (*c* 0.65, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.89 (3 H, t, *J* = 7.1 Hz), 1.25–1.44 (4 H, m), 1.46–1.54 (1 H, m), 1.62–1.71 (1 H, m), 3.72 (1 H, dd, *J* = 13.9, 6.9 Hz), 4.39 and 4.56 (2 H, AB q, *J* = 11.9 Hz), 5.20 (1 H, ddd, *J* = 17.1, 1.8, 0.9 Hz), 5.22 (1 H, ddd, *J* = 10.5, 1.8, 0.7 Hz), 5.74 (1 H, ddd, *J* = 17.1, 10.5, 7.8 Hz), 7.25–7.37 (5 H,

m); MS *m/z* (relative intensity) 204 (M^+, 0.09), 147 (33), 107 (6), 92 (32), 91 (100), 77 (6), 65 (17). Anal. calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.83. Found: C, 82.04; H, 9.88.

Cycloaddition Reaction of the Nitrone 9 with 8

A toluene (20 mL) solution including **8** (905 mg, 4.43 mmol) and **9** (940 mg, 4.87 mmol) was refluxed for 14 h. After evaporation of the solvent, the residual oil was chromatographed on silica gel (hexane/ethyl acetate, 20:1). The first fraction contained a mixture of two products (170 mg, 10%) which was considered to be the cis adducts, methyl [3*S*,5*R*,5(1*S*)]- and [3*R*,5*S*,5(1*S*)]-5-[1-(benzyloxy)pentyl]isoxazolidine-3-carboxylates. Separation of this mixture by silica gel column chromatography was difficult, however, careful HPLC on silica gel (hexane–ethyl acetate, 4:1) provided the [3*S*,5*R*,5(1*S*)]-isomer as the major cis product: $[\alpha]^{20}_D$ –49.8 ° (*c* 0.15, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.86 (3 H, t, *J* = 7.1 Hz), 1.21–1.52 (6 H, m), 2.61–2.68 (2 H, m), 3.57 (3 H, s), 3.60 (1 H, dd, *J* = 11.3, 5.2 Hz), 3.72 (1 H, dd, *J* = 8.4, 6.0 Hz), 3.95 and 4.12 (2 H, AB q, *J* = 12.9 Hz), 4.26 (1 H, dt, *J* = 7.3, 5.1 Hz), 4.56 and 4.66 (2 H, AB q, *J* = 11.5 Hz), 7.24–7.39 (10 H, m).

The second fraction contained methyl [3*R*,5*R*,5(1*S*)]-*N*-benzyl-5-[1-(benzyloxy)pentyl]isoxazolidine-3-carboxylate (**10**) (1.01 g, 57%) as a colorless oil: $[\alpha]^{20}_D$ +53.3 ° (*c* 0.83, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.87 (3 H, t, *J* = 7.1 Hz), 1.22–1.56 (6 H, m), 2.43 (1 H, ddd, *J* = 12.2, 7.7, 6.5 Hz), 2.59 (1 H, ddd, *J* = 12.2, 9.0, 7.7 Hz), 3.55 (1 H, dd, *J* = 9.0, 6.5 Hz), 3.60 (1 H, dt, *J* = 7.5, 3.1 Hz), 3.66 (3 H, s), 4.05 and 4.09 (2 H, AB q, *J* = 13.5 Hz), 4.17 (1 H, dt, *J* = 7.7, 3.1 Hz), 4.57 and 4.68 (2 H, AB q, *J* = 11.6 Hz), 7.24–7.40 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.8, 27.8, 32.1, 33.4, 52.2, 62.2, 66.8, 73.4, 78.1, 80.6, 127.6 (2 carbons), 127.8 (2 carbons), 128.3 (2 carbons), 128.4 (2 carbons), 129.6 (2 carbons), 136.5, 139.0, 171.3; MS *m/z* (relative intensity) 397 (M^+, 4.5), 339 (28), 338 (100), 233 (4), 232 (30), 220 (5), 191 (5), 181 (19), 178 (14), 120 (28), 106 (20), 91 (100); HRMS calcd for $C_{24}H_{31}NO_4$ (M^+) 397.2252, found 397.2237.

The third fraction contained methyl [3*S*,5*S*,5(1*S*)]-*N*-benzyl-5-[1-(benzyloxy)pentyl]isoxazolidine-3-carboxylate (**11**) (335 mg, 19%) as a colorless oil: $[\alpha]^{20}_D$ –68.0° (*c* 0.49, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (3 H, t, *J* = 7.2 Hz), 1.24–1.57 (6 H, m), 2.26 (1 H, dt, *J* = 12.4, 8.8 Hz), 2.47 (1 H, ddd, *J* = 12.4, 7.3, 5.4 Hz), 3.39 (1 H, m), 3.56 (1 H, dd, *J* = 9.1, 5.4 Hz), 3.66 (3 H, s), 4.08 and 4.13 (2 H, AB q, *J* = 13.3 Hz), 4.26 (1 H, dd, *J* = 14.1, 7.8 Hz), 4.55 and 4.65 (2 H, AB q, *J* = 11.5 Hz), 7.22–7.40 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.7, 27.7, 31.0, 35.1, 52.2, 62.1, 66.3, 72.7, 79.8, 80.4, 127.5 (2 carbons), 128.0 (2 carbons), 128.2 (2 carbons), 128.3 (2 carbons), 129.6 (2 carbons), 136.4, 138.8, 171.3.

[3R,5R,5(1S)]-N-Benzyl-5-[1-(benzyloxy)pentyl]-3-(hydroxymethyl)isoxazolidine (12)

To a stirred, ice–cooled suspension of $LiAlH_4$ (609 mg, 16.1 mmol) in ether (20 mL) was added a solution of **10** (5.32 g, 13.4 mmol) in ether (30 mL). After being stirred at room temperature for 14 h,

the reaction mixture was quenched with water and filtered through a Celite pad. The filtrate was washed with water and dried over $MgSO_4$. Evaporation of the solvent followed by silica gel chromatography (hexane–ethyl acetate, 7:1) afforded **11** (4.57 g, 96%) as a colorless oil, which was crystallized on standing at 5 °C for several days: mp 46.0–48.5 °C; $[\alpha]^{22}_D$ +43.1° (*c* 3.10, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.87 (3 H, t, *J* = 7.0 Hz), 1.24–1.55 (6 H, m), 2.10 (1 H, ddd, *J* = 12.3, 7.4, 4.5 Hz), 2.23 (1 H, br s), 2.46 (1 H, dt, *J* = 12.3, 8.7 Hz), 3.17 (1 H, ddd, *J* = 13.6, 8.7, 4.5 Hz), 3.50 (2 H, br d, *J* = 5.4 Hz), 3.59 (1 H, dt, *J* = 7.4, 4.2 Hz), 3.97 and 4.06 (2 H, AB q, *J* = 13.3 Hz), 4.07 (1 H, unresolved), 4.60 and 4.69 (2 H, AB q, *J* = 11.5 Hz), 7.22–7.55 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.8, 27.7, 31.7, 32.1, 62.4, 62.6, 66.2, 73.2, 78.9, 81.2, 127.5, 127.6, 127.8 (2 carbons), 128.4 (2 carbons), 128.5 (2 carbons), 129.1 (2 carbons), 137.4, 139.0; MS *m/z* (relative intensity) 369 (M^+, 2), 339 (24), 338 (99), 232 (25), 181 (19), 149 (6), 91 (100). Anal. calcd for $C_{23}H_{31}NO_3$: C, 74.76; H, 8.46; N, 3.79. Found: C, 75.01; H, 8.67; N, 3.96.

[3R,5R,5(1S)]-N-*Benzyl-5-[1-(benzyloxy)pentyl]-3-[[(*p*-tolylsulfonyl)oxy]-methyl]isoxazolidine (13)*

To an ice–cooled stirred mixture of **12** (4.57 g, 12.9 mmol), *N,N*-dimethylaminopyridine (1.57 g, 12.9 mmol), and diisopropylethylamine (1.66 g, 12.9 mmol) in CH_2Cl_2 (30 mL) was added dropwise a solution of *p*-tolylsulfonyl chloride (2.94 g, 15.4 mmol) in CH_2Cl_2 (20 mL). After the mixture was stirred at room temperature for 1.5 h, it was diluted with CH_2Cl_2 (50 mL), washed with water, and dried ($MgSO_4$). The solvent was evaporated to give a crude product, which was chromatographed on silica gel (hexane–ethyl acetate, 15:1) to give **13** (6.53 g, 97%) as a colorless oil: $[\alpha]^{24}_D$ +42.2° (*c* 1.83, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.86 (3 H, t, *J* = 7.0 Hz), 1.22–1.48 (6 H, m), 1.95 (1 H, ddd, *J* = 12.5, 7.3, 5.3 Hz), 2.38–2.48 (1 H, m, including 3 H, s at δ 2.44), 3.24 (1 H, ddd, *J* = 11.6, 8.4, 6.1 Hz), 3.55 (1 H, dt, *J* = 7.3, 3.7 Hz), 3.92–4.00 (5H, m), 4.64 and 4.56 (2 H, AB q, *J* = 11.5 Hz), 7.23–7.36 (12 H, m), 7.75 (2 H, d, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0, 21.7, 22.8, 27.7, 32.1, 32.2, 62.4, 63.2, 70.4, 73.4, 78.3, 80.3, 127.4, 127.6, 127.8 (2 carbons), 128.0 (2 carbons), 128.3 (2 carbons), 128.4 (2 carbons), 129.2 (2 carbons), 130.0 (2 carbons), 137.1, 138.9, 145.0; MS *m/z* (relative intensity) 523 (M^+, 0.14), 261 (7), 217 (14), 216 (18), 176 (31), 146 (39), 120 (100), 107 (91), 106 (99), 105 (56).

[3R,5R,5(1S)]-N-*Benzyl-5-[1-(benzyloxy)pentyl]-3-(iodomethyl)isoxazolidine (14)*

To a solution of **13** (3.93 g, 7.50 mmol) in 2-butanone (65 mL) was added NaI (9.0 g, 60 mmol) and the mixture was heated at 75 °C for 5.5 h. Ether (350 mL) was added to the reaction mixture and the mixture was filtered through a Celite pad. The filtrate was washed with 5% aqueous $Na_2S_2O_3$ and then water. The organic phase was dried over $MgSO_4$ and evaporated, affording an oily residue, which was purified by column chromatography on silica gel (hexane–ethyl acetate, 70:1) to give **14** (2.89 g, 80%) as a colorless oil: $[\alpha]^{23}_D$ +37.2° (*c* 1.60, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.87 (3 H, t, *J* =

7.1 Hz), 1.23–1.53 (6 H, m), 2.10 (1 H, ddd, J = 12.4, 7.8, 4.8 Hz), 2.54 (1 H, dt, J = 12.4, 7.8 Hz), 3.01–3.13 (1 H, m, including two 2 H, d, J = 7.6 Hz at δ 3.04 and 3.11), 3.58 (1 H, dt, J = 7.5, 3.5 Hz), 3.95 and 4.00 (2 H, AB q, J = 13.3 Hz), 4.10 (1 H, dt, J = 7.8, 3.5 Hz), 4.59 and 4.70 (2 H, AB q, J = 11.6 Hz), 7.25–7.38 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 7.6, 14.1, 22.8, 27.8, 32.1, 36.3, 62.1, 66.3, 73.4, 78.4, 80.0, 127.6 (2 carbons), 127.8 (2 carbons), 128.4 (2 carbons), 128.5 (2 carbons), 129.2 (2 carbons), 137.0, 139.0; MS *m/z* (relative intensity) 479 (M^+, 6), 388 (5), 373 (7), 353 (3), 352 (14), 339 (23), 338 (94), 261 (10), 260 (100), 246 (36), 232 (40), 181 (21), 146 (19), 120 (43), 106 (33). Anal. calcd for $C_{23}H_{30}INO_2$: C, 57.62; H, 6.31; N, 2.92. Found: C, 57.79; H, 6.24; N, 2.90.

[3S,5R,5(1S)]-N-Benzyl-5-[1-(benzyloxy)pentyl]-3-(4-pentenyl)isoxazolidine (15)

To a stirred 0.25 M solution of lithium 2-thienylcyanocuprate (48.4 mL, 12.1 mmol) in THF was added a solution of 3-butenylmganesium bromide, prepared from 4-bromobutene (1.63 g, 12.1 mmol) and Mg (294 mg, 12.1 mmol), in THF (6 mL) at –78 °C under Ar. The mixture was stirred at –78 °C for 15 min and then at room temperature for 1.5 h. The reaction mixture was recooled to –78 °C and a solution of **14** (2.90 g, 6.05 mmol) in THF (6 mL) was added to this. The mixture was stirred at –78 °C for 15 min, at 0 °C for 1.5 h, and then at room temperature for 18 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (60 mL) at 0 °C and the mixture was stirred at room temperature until the aqueous phase turned blue. After filtration through a Celite pad, the filtrate was extracted with ether. The ether extracts were washed with water, dried ($MgSO_4$), and evaporated. Silica gel chromatography (hexane–ethyl acetate, 80:1) provided **15** (2.21 g, 90%) as a colorless oil: $[\alpha]^{23}_D$ +77.9° (*c* 2.62, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.86 (3 H, t, J = 7.1 Hz), 1.23–1.60 (10 H, m), 1.90 (1 H, dt, J = 11.9, 7.5 Hz), 1.99–2.06 (2 H, m), 2.44 (1 H, dt, J = 11.9, 7.4 Hz), 2.83 (1 H, s), 3.57 (1 H, dt, J = 7.5, 3.8 Hz), 3.84 and 3.98 (2 H, AB q, J = 13.6 Hz), 4.07 (1 H, br s), 4 58 and 4.72 (2 H, AB q, J = 11.5 Hz), 4.92–5.01 (2 H, m), 5.57 (1 H, ddt, J = 17.0, 10.2, 6.7 Hz), 7.22–7.43 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.8, 25.9, 27.8, 32.1, 32.5, 33.8, 35.3, 61.9, 65.6, 73.3, 78.9, 80.1, 114.7, 127.2, 127.5, 127.8 (2 carbons), 128.2 (2 carbons), 128.3 (2 carbons), 129.2 (2 carbons), 137.9, 138.5, 139.2; MS *m/z* (relative intensity) 407 (M^+, 5), 337 (11), 338 (47), 231 (5), 232 (30), 230 (9), 189 (14), 188 (100), 181 (21), 140 (8), 106 (38); HRMS calcd for $C_{27}H_{37}NO_2$ (M^+) 407.2824, found 407.2809.

(5S,6R,8S)-8-(Benzyl)amino-5-benzyloxy-6-hydroxy-12-tridecene (16)

To a stirred solution of **15** (3.20 g, 7.85 mmol) in AcOH–THF–water (2:1:1) (160 mL) was added Zn dust (1.5 g, 22.9 mmol) at 60 °C and the resulting suspension was stirred at the same temperature for 30 min. To this mixture was added Zn dust (1.5 g, 22.9 mmol) again and the mixture was stirred at 60 °C for another 2 h. After removal of the excess of Zn by filtration, the filtrate was

neutralized with saturated aqueous Na_2CO_3 and extracted with $CHCl_3$. The extracts were washed with water, dried ($MgSO_4$), and evaporated to give a residual oil, which was chromatographed on silica gel (hexane–ethyl acetate, 7:1) to afford **16** (2.90 g, 90%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.93 (3 H, t, J = 7.1 Hz), 1.29–1.65 (11 H, m), 1.95 (1 H, ddd, J = 14.6, 9.4, 3.4 Hz), 2.06 (2 H, q, J = 6.8 Hz), 2.98 (1 H, ddd, J = 11.9, 6.6, 3.4 Hz), 3.39 (1 H, dd, J = 11.2, 5.4 Hz), 3.72 and 3.92 (2 H, AB q, J = 12.8 Hz), 3.98 (1 H, ddd, J = 9.4, 5.4, 2.7 Hz), 4.64 and 4.68 (2 H, AB q, J = 11.5 Hz), 4.94–5.04 (2 H, m), 5.79 (1 H, ddt, J = 17.0, 10.2, 6.8 Hz), 7.24–7.49 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 14.2, 23.0, 25.6, 27.7, 30.4, 31.6, 33.0, 33.7, 51.4, 55.8, 71.5, 72.7, 82.7, 114.9, 127.3, 127.4, 127.8 (2 carbons), 128.3 (3 carbons), 128.4, 128.6 (2 carbons), 138.4, 139.3, 139.6; MS *m/z* (relative intensity) 410 (M^+ + 1, 3), 409 (M^+, 1), 341 (4), 340 (19), 322 (6), 318 (6), 232 (14), 189 (8), 188 (56), 146 (4), 106 (17), 92 (17), 91 (100); HRMS calcd for $C_{27}H_{39}NO_2$ (M^+) 409.2980, found 409.2969.

[4S,6R,6(1S)]-N-Benzyl-6-[1-(benzyloxy)pentyl]-4-(4-pentenyl)-3,4,5,6-tetrahydro-1,3-oxazin-2-one (17)

To an ice bath-cooled, stirred mixture of a solution of **16** (903 mg, 2.20 mmol) in CH_2Cl_2 (10 mL) and saturated aqueous Na_2CO_3 (8 mL) was added dropwise trichloromethyl chloroformate (13.1 g, 6.60 mmol) over a period of 30 min. After being stirred at room temperature for 2 h, the mixture was cooled to 0 °C and 30% ammonia water (4 mL) was added. The resultant mixture was stirred for 15 min at ambient temperature and the organic phase was separated. The aqueous phase was extracted with $CHCl_3$ and the combined organic phases were washed with water and dried over $MgSO_4$. Evaporation of the solvent followed by column chromatography on silica gel (hexane–ethyl acetate, 15:1) gave **17** (805 mg, 84%) as a colorless oil: $[\alpha]^{22}_D$ –55.1° (c 0.55, $CHCl_3$); IR (neat) 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (3 H, t, J = 7.0 Hz), 1.25–1.62 (9 H, m), 1.72–1.78 (1 H, m), 1.90 (2 H, m), 2.05 (2 H, dt, J = 13.2, 6.6 Hz), 3.23 (1 H, m), 3.69 (1 H, dt, J = 7.7, 3.8 Hz), 4.04 (1 H, d, J = 15.3 Hz), 4.37 (1 H, dt, J = 13.4, 9.6 Hz), 4.46 and 4.73 (2 H, AB q, J = 11.3 Hz), 5.00 (2 H, m), 5.18 (1 H, d, J = 15.3 Hz), 5.74 (1 H, ddt, J = 16.9, 10.4, 6.6 Hz), 7.24–7.38 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.8, 25.4, 25.5, 27.7, 30.8, 31.7, 33.3, 50.6, 52.5, 73.8, 76.4, 80.2, 115.4, 127.6, 127.7, 127.8 (2 carbons), 128.0 (2 carbons), 128.4 (2 carbons), 128.7 (2 carbons), 137.3, 137.8, 138.5, 153.9; MS *m/z* (relative intensity) 435 (M^+, 1.8), 344 (1.6), 322 (5), 300 (4), 258 (9), 233 (12), 232 (75), 188 (10), 92 (32), 91 (100). Anal. calcd for $C_{28}H_{37}NO_3$: C, 77.20; H, 8.56; N, 3.22. Found: C, 76.80; H, 8.61; N, 3.22.

[4S,6R,6(1S)]-N-Benzyl-6-[1-(benzyloxy)pentyl]-4-(4-oxopentyl)-3,4,5,6-tetrahydro-1,3-oxazin-2-one (18)

To a mixture of $PdCl_2$ (164 mg, 0.925 mmol), $CuCl_2$ (124 mg, 0.925 mmol), and dimethylformamide (6 mL) containing water (1 mL) was added a solution of **17** (805 mg, 1.85 mmol) in dimethylformamide (4 mL). After the mixture was stirred at 50 °C with bubbling of oxygen for 4 h, benzene (80 mL) was added to this mixture. The resulting suspension was filtered through a Celite pad and the filtrate was washed with water, dried ($MgSO_4$), and evaporated to dryness. The crude residue was purified by silica gel chromatography (hexane–ethyl acetate, 4:1) to give **18** (745 mg, 89%) as a colorless oil: IR (neat) 1693, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, t, J = 7.1 Hz), 1.30–1.61 (9 H, m), 1.70 (1 H, m), 1.92 (2 H, m), 2.12 (3 H, s), 2.42 (2 H, t, J = 6.6 Hz), 3.22 (1 H, dt, J = 13.0, 3.7 Hz), 3.69 (1 H, dt, J = 7.7 3.8 Hz), 4.05 (1 H, d, J = 15.2 Hz), 4.37 (1 H, dt, J = 7.7, 4.1 Hz), 4.23 and 4.72 (2 H, AB q, J = 11.2 Hz), 5.15 (1 H, d, J = 15.3 Hz), 7.24–7.49 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.1, 22.8, 25.3, 27.7, 30.1, 30.8, 31.8, 42.9, 50.6, 52.6, 73.8, 76.5, 80.2, 127.6, 127.8, 127.9 (2 carbons), 128.1 (2 carbons), 128.5 (2 carbons), 128.8 (2 carbons), 137.2, 138.6, 153.9; MS *m/z* (relative intensity) 451 (M^+, 1.5), 360 (2.3), 275 (6), 274 (11), 248 (11), 205 (14), 204 (100), 146 (18), 106 (10).

[4S,6R,6(1S)]-N-*Benzyl-6-[1-(benzyloxy)pentyl]-4-[(4,4-ethylenedioxy)pentyl]-3,4,5,6-tetrahydro-1,3-oxazin-2-on (19)*

A mixture of **18** (745 mg, 1.65 mmol), ethylene glycol (195 mg, 3.15 mmol), and *p*-TsOH (10 mg) in benzene (20 mL) was refluxed through a Soxhlet extractor packed with Molecular Sieves (3A) for 14 h. After evaporation of the solvent, the residue was dissolved in ether (20 mL). The solution was washed with saturated aqueous $NaHCO_3$ and then water, and dried over $MgSO_4$. Evaporation of the solvent followed by chromatography on silica gel (hexane–ethyl acetate, 5:1) gave **19** (732 mg, 89%) as a colorless oil: $[\alpha]^{26}_D$ –46.6° (*c* 0.34, $CHCl_3$); IR (neat) 1451, 1694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (3 H, t, J = 7.1 Hz), 1.22–1.66 (11 H, m, including 3 H, s at δ 1.27), 1.71–1.80 (1 H, m), 1.91 (2 H, unresolved), 3.23 (1 H, dt, J =13.1, 3.7 Hz), 3.69 (1 H, dt, J = 7.5, 3.7 Hz), 3.82–3.95 (4 H, m), 4.05 (1 H, d, J = 15.4 Hz), 4.37 (1 H, dt, J = 7.5, 4.2 Hz), 4.63 and 4.72 (2 H, AB q, J = 11.2 Hz), 5.15 (1 H, d, J = 15.4 Hz), 7.23–7.37 (10 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.7, 22.8, 23.7, 25.5, 27.7, 30.9, 32.6, 38.7, 50.6, 52.7, 64.7 (2 carbons), 73.8, 76.5, 80.3, 109.7, 127.6, 127.7, 127.8 (2 carbons), 128.1 (2 carbons), 128.5 (2 carbons), 128.7 (2 carbons), 137.3, 138.6, 153.9; MS *m/z* (relative intensity) 496 (M^+ + 1, 1.2), 495 (M^+, 1.4), 480 (2.6), 450 (1.2), 404 (2), 366 (2), 322 (11), 318 (18), 249 (17), 248 (100), 190 (8), 146 (17), 115 (18). Anal. calcd for $C_{30}H_{41}NO_5$: C, 72.70; H, 8.34; N, 2.82. Found: C, 72.52; H, 8.31; N, 2.87.

(6S,8R,9S)-6-(Benzylamino)-9-(benzyloxy)-2,2-ethylenedioxy-8-hydroxytridecane (20)

A stirred mixture of **19** (300 mg, 0.610 mmol), EtOH (5 mL), and saturated aqueous KOH (1.5 mL) was heated at 100 °C. After 14 h, a mixture of EtOH (0.3 mL) and saturated aqueous KOH (0.1

mL) was added to the reaction mixture and the resulting mixture was heated at 100 °C for an additional 1 h to complete the reaction. After concentration in vacuo, the residue was treated with water (8 mL) and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water, dried ($MgSO_4$), and evaporated. Purification by silica gel chromatography (hexane–ethyl acetate, 3:1) gave **20** (214 mg, 75%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.90 (3 H, t, J = 7.1 Hz), 1.24–1.64 (13 H, m, including 3 H, s at δ 1.28), 1.94 (1 H, ddd, J = 14.6, 9.5, 3.4 Hz), 2.97 (1 H, unresolved), 3.37 (1 H, dd, J = 11.3, 5.1 Hz), 3.70 (1 H, 1/2 AB q, J = 12.8 Hz), 3.85–3.99 (5 H, m, including 1 H, 1/2 AB q, J = 12.8 Hz), 4.61 and 4.66 (2 H, AB q, J =11.5 Hz), 7.23–7.37 (10 H, m).

(6S,8R,9S)-6-(Dibenzylamino)-9-(benzyloxy)-2,2-ethylenedioxy-8-hydroxytridecane (21)

A stirred mixture of **20** (292 mg, 0.620 mmol), dimethylformamide (5 mL), benzylbromide (139 mg, 0.810 mmol), and Na_2CO_3 (131 mg, 1.24 mmol) was heated at 100 °C. After 2 h, the mixture was poured into ice water (20 mL) and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by chromatography on silica gel (hexane–ethyl acetate, 15:1) to give **21** (300 mg, 87%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.89 (3 H, t, J = 7.1 Hz), 1.18–1.87 (14 H, m, including 3 H, s at δ 1.28), 2.79 (1 H, dt, J = 6.4, 4.1 Hz), 2.88–2.95 (1 H, br m), 3.36 and 3.84 (4 H, AB q, J = 13.1 Hz), 3.84–3.98 (5 H, m), 4.29 and 3.36 (2 H, AB q, J = 11.4 Hz), 4.36 (1 H, s), 7.23–7.40 (15 H, m).

(6S,8R,9S)-6-(Dibenzylamino)-9-(benzyloxy)-8-hydroxytridecan-2-one (22)

A stirred solution of **21** (300 mg, 0.54 mmol) in MeOH (4 mL) and 6 N HCl (0.4 mL) was heated at 80 °C for 1 h. The mixture was concentrated in vacuo and the residue was neutralized with saturated aqueous Na_2CO_3. The reaction mixture was extracted with $CHCl_3$. The extracts were washed with water, dried ($MgSO_4$), and evaporated. Purification by chromatography on silica gel (hexane–ethyl acetate, 15:1) to give **22** (241 mg, 87%) as a colorless oil: IR (neat) 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (3 H, t, J = 7.1 Hz), 1.14–1.67 (10 H, m), 1.74–1.85 (2 H, m), 2.09 (3 H, s), 2.37 (2 H, t, J = 7.1 Hz), 2.80 (1 H, dt, J = 6.4, 4.0 Hz), 2.87 (1 H, tt, J = 10.0, 3.4 Hz), 3.33 and 3.80 (4 H, AB q, J = 13.1 Hz), 3.85 (1 H, s), 4.16 (1 H, s), 4.23 and 4.38 (2 H, AB q J =11.5 Hz), 7.23–7.37 (15 H, m).

[2S,2(2R),2(3S),6S]-2-[3-(Benzyloxy)-2-hydroxyheptyl]-6-methylpiperidine (23)

A mixture of **22** (238 mg, 0.460 mmol) and 10% palladium on carbon (200 mg) in MeOH (5 mL) was stirred under hydrogen for 6 h. Filtration and evaporation provided an oily residue, which was purified by chromatography on silica gel ($CHCl_3$–MeOH, 100:1) followed by recrystallization from $CHCl_3$–hexane to afford **23** (103 mg, 70%) as colorless needles: mp 143–144 °C; $[\alpha]^{23}_D$ +21.4° (*c* 2.42, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (3 H, t, J = 7.1 Hz), 1.14 (3 H, d, J = 6.4 Hz), 1.24–1.83 (13

H, m), 2.10 (1 H, ddd, J = 15.0, 10.0, 3.2 Hz), 2.63 (1 H, dt, J = 21.1, 6.4 Hz), 3.26 (1 H, dt, J = 10.6, 3.2 Hz), 3.55 (1 H, dt, J = 7.7, 4.2 Hz), 4.09 (1 H, quint, J = 3.7 Hz), 4.59 and 4.62 (2 H, AB q, J = 11.1 Hz), 5.98 (2 H, br s), 7.23–7.36 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.0, 22.9, 23.2, 28.0, 29.1, 30.5, 30.7, 35.6, 53.8, 56.2, 69.0, 73.4, 83.2, 127.8, 128.2 (2 carbons), 128.5 (2 carbons), 138.7; MS *m/z* (relative intensity) 320 (M^+ + 1, 0.3), 319 (M^+, 0.2), 318 (0.9), 304 (3.4), 262 (0.6), 230 (4), 228 (36), 213 (4), 212 (4), 198 (2), 196 (4), 154 (4), 143 (9), 142 (100), 124 (3), 112 (12).

*(5S,6R,8S)-8-[*N*-Benzyl-*N*-[(benzyloxy)carbonyl]amino]-5-(benzyloxy)-6-[[(benzyloxy)carbonyl]-oxy]-12-tridecene (24)*

To an ice bath-cooled, stirred mixture of a solution of **16** (1.10 g, 2.68 mmol) in CH_2Cl_2 (8 mL) and 3.5 N Na_2CO_3 (8 mL) was added benzyloxycarbonyl chloride (1.37 g, 8.04 mmol). The mixture was stirred at 0 °C for 30 min and then at room temperature for 2.5 h. The organic phase was separated and the aqueous phase was extracted with $CHCl_3$. The combined organic phases were washed with water, dried ($MgSO_4$), and evaporated. The residual oil was chromatographed on silica gel (hexane–ethyl acetate, 30:1) to give **24** (1.44 g, 79%) as a colorless oil: $[\alpha]^{25}_D$ +24.4° (*c* 1.26, $CHCl_3$); IR (neat) 1699, 1745 cm^{-1}; MS *m/z* (relative intensity) 677 (M^+, 2), 586 (4), 543 (11), 542 (31), 525 (6), 480 (6), 456 (23), 434 (8), 413 (23), 412(65), 390 (11), 323 (25), 322 (100), 279 (20), 278 (80), 258 (8), 240 (32), 236 (32), 214(8), 196 (13), 181(46), 133 (17), 107 (27). Anal. calcd for $C_{43}H_{51}NO_6$: C, 76.19; H, 7.58; N, 2.07. Found: C, 76.15; H, 7.58; N, 2.01.

*(6S,8R,9S)-6-[*N*-Benzyl-*N*-[(benzyloxy)carbonyl]amino]-9-benzyloxy-8-[(benzyloxy)carbonyl]-oxytridecan-2-one (25)*

In a manner similar to that described above for the preparation of **18**, **24** (200 mg, 0.295 mmol) was oxidized to give **25** (185 mg, 91%) as a colorless oil: $[\alpha]^{26}_D$ +23.7° (*c* 1.09, $CHCl_3$); IR (neat) 1697, 1745 cm^{-1}; MS *m/z* (relative intensity) 693 (M^+, 0.3), 602 (3), 558 (19), 557 (48), 496 (7), 456 (24), 413 (25), 412 (75), 339 (23), 338 (98), 295 (252), 294 (100), 240 (32), 236 (43), 204 (17), 181 (52). Anal. calcd for $C_{43}H_{51}NO_7$: C, 74.43; H, 7.41; N, 2.02. Found: C, 74.39; H, 7.42; N, 1.86.

*[2S,2(2R),2(3S),6S]-*N*-Benzyl-2-[2,3-(dihydroxy)heptyl]-6-methylpiperidine (27)*

A mixture of **25** (600 mg, 0.865 mmol) and 10% palladium on carbon (600 mg) in MeOH (6 mL) was stirred under hydrogen for 30 min. This process led to the formation of **23**, which was confirmed by isolation of a part of the reaction product by usual working up. To the reaction mixture so obtained was added 10% palladium on carbon (200 mg) and 2 drops of 10% HCl and the hydrogenation was further continued for another 2 h. Filtration and evaporation provided the HCl salt of [2*S*,2(2*R*),2(3*S*),6*S*]-2-[2,3-(dihydroxy)heptyl]-6-methylpiperidine (**26**) as an oily residue, a part of

which was treated with aqueous Na_2CO_3, worked up, and purified by passing through a short column of silica gel ($CHCl_3$–MeOH, 30:1) to give a pure sample of **26** as a colorless oil (turned yellow by standing): $[\alpha]^{21}_D$ +12.3° (*c* 0.47, $CHCl_3$); IR (neat) 3357 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (3 H, t, *J* = 7.1 Hz), 1.23–1.58 (7 H, m, including 3 H, d, *J* = 6.4 Hz at δ 1.49), 1.61–1.93 (6 H, m), 2.07 (1 H, ddd, *J* = 14.9, 9.1, 2.8 Hz), 3.06–3.18 (1 H, m), 3.34–3.44 (1 H, m), 3.66 (1 H, dt, *J* = 8.0, 3.7 Hz), 3.99 (1 H, dt, *J* = 9.1, 3.7 Hz).

The crude HCl salt of **26** thus obtained was immediately dissolved in dimethylformamide (2.5 mL). To this solution was added Na_2CO_3 (275 mg, 2.60 mmol) and benzyl bromide (178 mg, 1.04 mmol) and the mixture was heated at 70 °C for 6 h. After addition of toluene (100 mL), the mixture was filtered through Celite and the filtrate was washed with brine and dryed ($MgSO_4$). Concentration in vacuo and chromatography on silica gel ($CHCl_3$–MeOH, 100:1) gave **27** (144 mg, 52% from **25**) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.89 (3 H, t, *J* = 7.1 Hz), 1.17–1.83 (15 H, m, including 3 H, d, *J* = 7.1 Hz at δ 1.24), 2.35 (1 H, dt, *J* = 12.8, 2.7 Hz), 2.52 (1 H, br s), 2.88 (1 H, unresolved), 3.52 (1 H, dt, *J* = 8.1, 4.0 Hz), 3.87–3.93 (1 H, unresolved), 3.94 and 4.09 (2 H, AB q, *J* = 15.7 Hz), 7.23–7.35 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.5, 22.9, 23.6, 28.4, 29.5 (2 carbons), 31.3, 33.5, 52.1, 55.4, 58.1, 71.9, 74.2, 127.1, 128.2 (2 carbons), 129.6 (2 carbons), 137.6; MS *m/z* (relative intensity) 319 (M^+, 2.1), 304 (13), 232 (15), 189 (64), 188 (100), 172 (8), 92 (22), 91 (99), 69 (20); HRMS calcd for $C_{19}H_{30}NO_2$ (M^+ – Me) 304.2276, found 304.2258.

[2S,2(2R),2(3S),6S]-N-Benzyl-2-[[2,3-di(methanesulfonyl)oxy]heptyl]-6-methylpiperidine (28)

To a stirred and cooled (–20 °C) mixture of **27** (217 mg, 0.679 mmol) and triethylamine (550 mg, 5.43 mmol) in CH_2Cl_2 (5 mL) was added methanesulfonyl chloride (311 mg, 2.72 mmol) and the resulting mixture was stirred at –20 °C for 10 min. The mixture was quenched with ice water (5 mL) and diluted with CH_2Cl_2 (5 mL). The organic phase was separated and washed with water, dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel (hexane–ethyl acetate, 15:1) followed by recrystallization from $CHCl_3$–hexane, affording **28** (247 mg, 76%) as colorless plates: mp 141–143 °C; $[\alpha]^{25}_D$ +31.9° (*c* 0.31, CHCl3); ^1H NMR ($CDCl_3$) δ 0.77 (3 H, t, *J* = 7.1 Hz), 0.97–1.39 (9 H, m, including, 3 H, d, *J* = 6.8 Hz at δ 1.08), 1.57–1.61 (4 H, m), 1.85 (1 H, dd, *J* = 8.6, 3.2 Hz), 2.88 (1 H, q, *J* = 6.8 Hz), 2.96 (1 H, br s), 3.03 (3 H, s), 3.21 (3 H, s), 3.58 and 3.72 (2 H, AB q, *J* = 17.2 Hz), 4.67 (2 H, m), 7.19–7.40 (5 H, m); MS *m/z* (relative intensity) 475 (M^+, 0.1), 460 (3.4), 268 (1.5), 232 (8), 187 (13), 188 (100), 187 (21), 164 (5), 163 (30), 135 (13). Anal. calcd for $C_{22}H_{37}NO_6S_2$: C, 55.55; H, 7.84; N, 2.94. Found: C, 55.57; H, 7.99; N, 2.83.

(2R,3R,5S,9S)-3-Butyl-2-(methanesulfonyl)oxy-5-methylindorizidine (30)

A mixture of **28** (228 mg, 0.479 mmol) and 10% palladium on carbon (200 mg) in dioxane (8 mL) was stirred under hydrogen for 14 h. After filtration, MeOH (4 mL) and then fresh 10% palladium

on carbon (200 mg) were added to the filtrate and the mixture was further hydrogenated for another 6 h, resulting in completion of de-N-benzylation. Filtration and evaporation provided the crude HCl salt of **29**, which was without purification dissolved in CH_2Cl_2 (8 mL) and triethylamine (97 mg, 0.958 mmol) was added to this solution. The resulting mixture was refluxed for 8 h and diluted with CH_2Cl_2 (25 mL). The CH_2Cl_2 solution was washed with brine, dried ($MgSO_4$), and evaporated. The obtained crude material was purified by silica gel chromatography (hexane–ethyl acetate, 7:1) to give **30** (91 mg, 66%) as a colorless solid: mp 47–47.5 °C; $[\alpha]^{25}_D$ –15.1° (*c* 0.27, CHCl3); ^{1}H NMR ($CDCl_3$) δ 0.91 (3 H, t, *J* = 7.2 Hz), 1.15 (3 H, d, *J* = 6.3 Hz), 1.19–1.81 (13 H, m), 2.06 (1 H, br s), 2.23 (1 H, m), 2.30 (1 H, ddd, *J* = 12.0, 7.4, 4.7 Hz), 2.71 (1 H, dt, *J* = 8.7, 2.3 Hz), 3.00 (3 H, s), 5.08 (1 H, dd, *J* = 15.9, 8.1 Hz); MS *m/z* (relative intensity) 289 (M^+, 1.3), 288 (0.8), 274 (21), 234 (15), 233 (34), 232 (100), 210 (47), 194 (11), 178 (11), 164 (24), 136 (60), 122 (15). Anal. calcd for $C_{14}H_{27}NO_3S$: C, 58.10; H, 9.40; N, 4.84. Found: C, 58.16; H, 9.58; N, 4.68.

(+)-Monomorine I (1)

To a solution of **30** (76 mg, 0.26 mmol) in 2-butanone (5 mL) was added NaI (394 mg, 2.63 mmol) and the mixture was refluxed for 4 h. Ether (60 mL) was added to the reaction mixture and the resulting suspension was filtrated through a pad of Celite. After evaporation, the residue was passed through a short column of silica gel. Eluting with hexane–ethyl acetate (10:1) afforded (2*S*,3*R*,5*S*,9*S*)-3-butyl-2-iodo-5-methylindorizidine (**31**) as a pale yellow oil, which was dissolved in MeOH (4 mL). To this solution of **31** were added triethylamine (20 mg, 0.20 mmol) and 10% palladium on carbon (35 mg) and the mixture was hydrogenated for 3 h. Filtration and evaporation provided an oily residue, which was purified by chromatography on aluminum oxide (hexane–$CHCl_3$, 2:1) to give (+)-**1** (30 mg, 58%) as a colorless oil: $[\alpha]^{24}_D$ +33.3° (*c* 0.39, hexane) [lit.[7] $[\alpha]^{20}_D$ +34.8° (*c* 1.02, hexane)]. The spectral (IR, ^{1}H and ^{13}C NMR, and mass) characteristics as well as TLC behavior of this product were identical with those of authentic (+)-monomorine I.[7]

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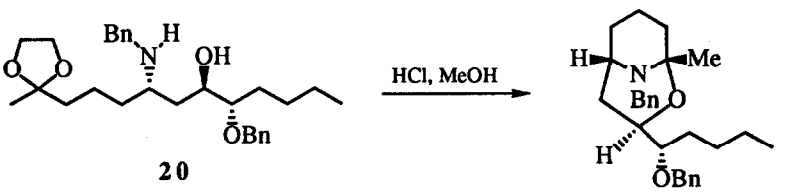
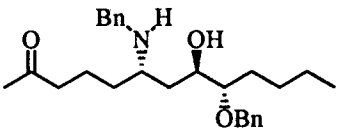


20 i

25. For the conversion of **25** to **26**, if the hydrogenolysis of **25** was conducted in an acidic medium at the initial stage in the synthetic sequence, there would be a fear of unfavorable formation of the bicyclic *N,O*-ketal i (see ref. 24), incapable of undergoing reductive cyclization to **23**, through the initial deblocking of the N- and O-benzyloxycarbonyl groups of **25** generating ii followed by spontaneous intramolecular ketalization under the reaction conditions.



ii