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TETRAHEDRON

Total Syntheses of (+)-Azimic Acid, (+)-Julifloridine, and Proposed Structure of *N*-Methyljulifloridine *via* Cycloaddition of Nitrone to a Chiral Dipolarophile[1]

Toshiko Kiguchi, Mitsuko Shirakawa, Rina Honda, Ichiya Ninomiya, and Takeaki Naito*

Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe 658-8558, Japan

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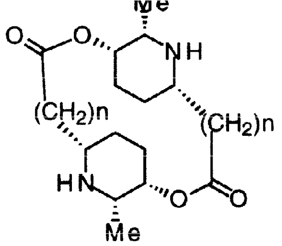
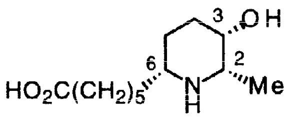
Abstract : A combination of 1,3-dipolar cycloaddition of *Z*-nitrones to the chiral dipolarophile and subsequent ring transformation of the resulting adducts to the piperidinols has provided a new practical synthesis of 2,6-disubstituted 3-piperidinol alkaloids, (+)-azimic acid, (+)-julifloridine, and the proposed structure of *N*-methyljulifloridine. © 1998 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

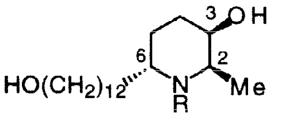
2,6-Disubstituted 3-piperidinols[2] display interesting, naturally occurring structures with three asymmetric centers in the piperidine ring. After the discovery and structure elucidation of a variety of 3-piperidinol alkaloids, much effort has been directed towards efficient and stereoselective synthesis of this unique class of compounds owing to the latent biological activities and ambiguous absolute structures of several compounds in this series.[3] Azimine and carpaine are two of the macrocyclic dilactones consisting of two molecules of the characteristic 2-methyl-3-piperidinol structure with a carboxyl group as a substituent at the C-6 position, designated as azimic[4] and carpamic acids, and these macrocyclic alkaloids were isolated from *Azima tetracantha*.[5] Only carpaine has been biologically evaluated and has exhibited cardiac activity.[2] As the related alkaloids, julifloridine (**2**)[6] and *N*-methyljulifloridine (**3**),[7] were isolated from *Prosopis juliflora* by Ahmad, and the relative stereostructure of **2** was confirmed by the synthesis of its racemate.[8] However, the absolute configuration of **2** remained unclarified. On the other hand, though **3** was proposed to be an *N*-methyl derivative of julifloridine (**2**) based only on ^{1}H and ^{13}C NMR spectral data, neither the interconversion nor total synthesis of **3** was reported. Considering this situation, we undertook to explore a general and



azimine; n = 5
carpaine; n = 7



(+)-azimic acid **1**



julifloridine **2**; R = H
N-methyljulifloridine **3**; R = Me

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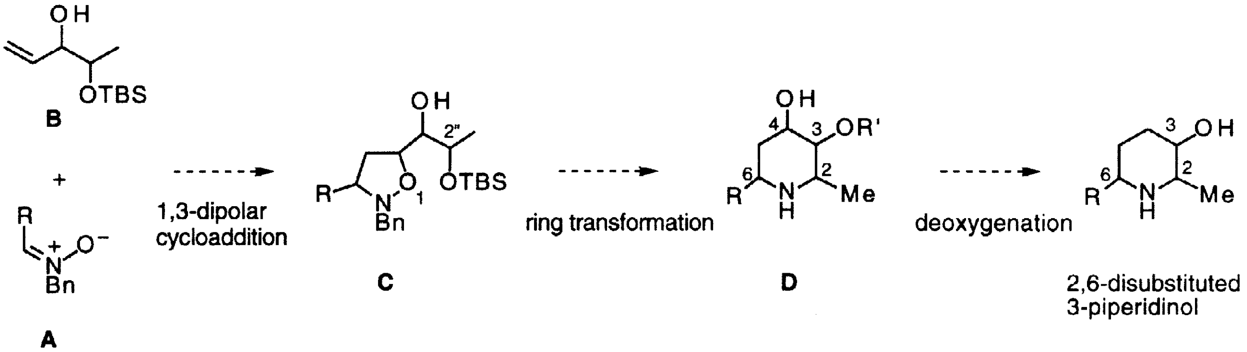
practical synthetic method for 2,6-disubstituted 3-piperidinol for their biological evaluation.

Herein we report in detail a potential method for the synthesis of 2,6-disubstituted 3-piperidinols, (+)-azimic acid (**1**), (+)-julifloridine (**2**), and the proposed structure **3** of *N*-methyljulifloridine.

RESULTS AND DISCUSSION

Synthetic strategy

Though several methods for the stereoselective construction of 2,6-disubstituted 3-piperidinols have been developed,[3] no example of asymmetric synthesis of 2,6-disubstituted 3-piperidinol *via* a route involving the intermolecular 1,3-dipolar cycloaddition of nitrones[9] has appeared to date. In continuation of our synthetic study[10] of natural alkaloids employing the intermolecular cycloaddition of *C,N*-dialkyl nitrone to the chiral olefin as a key reaction, we designed a route to asymmetric construction of 2,6-disubstituted 3-piperidinols as follows. Our synthetic strategy includes the intermolecular 1,3-dipolar cycloaddition of nitrones **A** to dipolarophile **B**, which contains a free hydroxyl group, expecting the known[11] acceleration of the cycloaddition. The following ring transformation of the resulting adducts **C** into the piperidines would proceed *via* SN2 type substitution at the C-2" position in the side chain followed by reductive cleavage of the *N-O* bond. An oxygen atom both at the O-1 position in isoxazolidines **C** and at the C-4 position in the piperidinol **D** is unnecessary for the synthesis of the targets and was therefore, eventually removed by reductive radical reaction.

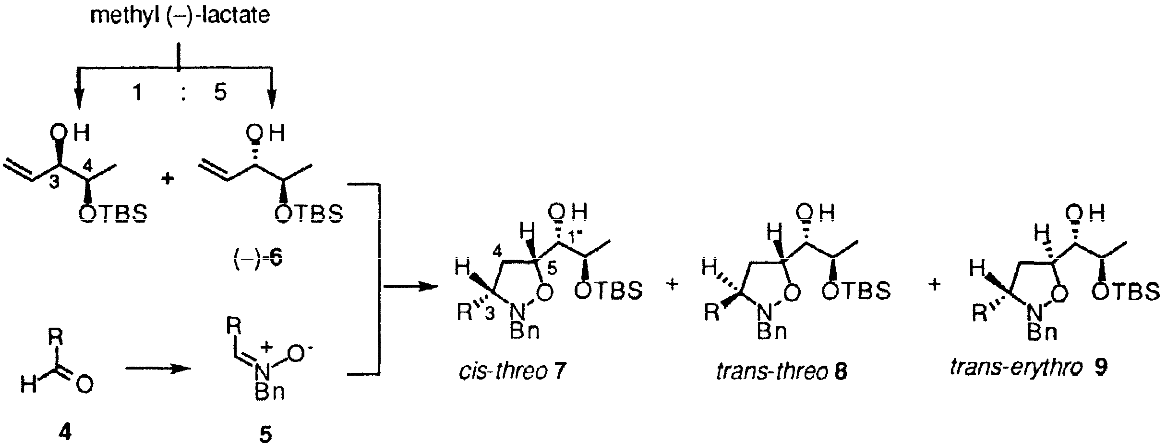


Scheme 1

Total synthesis of (+)-azimic acid

There have been several examples[12] of the synthesis of azimic acid including two asymmetric syntheses. First, we examined the cycloaddition of nitrone **5** to (-)-allyl alcohol **6**.[13] The nitrone **5** was readily prepared by the condensation of methyl 7-oxoheptanoate **4**[14] and *N*-benzylhydroxylamine[15] according to the known method.[16] The geometry of nitrone **5** was suggested to be *Z*-configuration by comparison of ^{1}H NMR spectral data of **5** with those of the known *Z*- and *E*-nitrones.[10,17] The dipolarophile, (-)-allyl alcohol **6** was prepared as a major product from methyl (-)-lactate according to the known procedure.[13] Though the formation of a 5 : 1 mixture of **6** and the isomer was reported, the unambiguous stereostructure of the major isomer, (-)-allyl alcohol **6** has not been reported in the literature.[13] Empirical rules[18] in the ^{1}H NMR of the 1-substituted 3-butene-1,2-diols establish the following two general phenomena. First, a signal due to an allylic proton of the *erythro*-isomer exhibits at lower field than that of the *threo*-congener. Second, *J*-value between two protons at the root of two oxygen atoms in the *erythro*-isomer is smaller than that in the *threo*-

Table 1. 1,3-Dipolar cycloaddition of Z-nitrone **5** to (–)-allyl alcohol **6**



R=$(CH_2)_5COOMe$

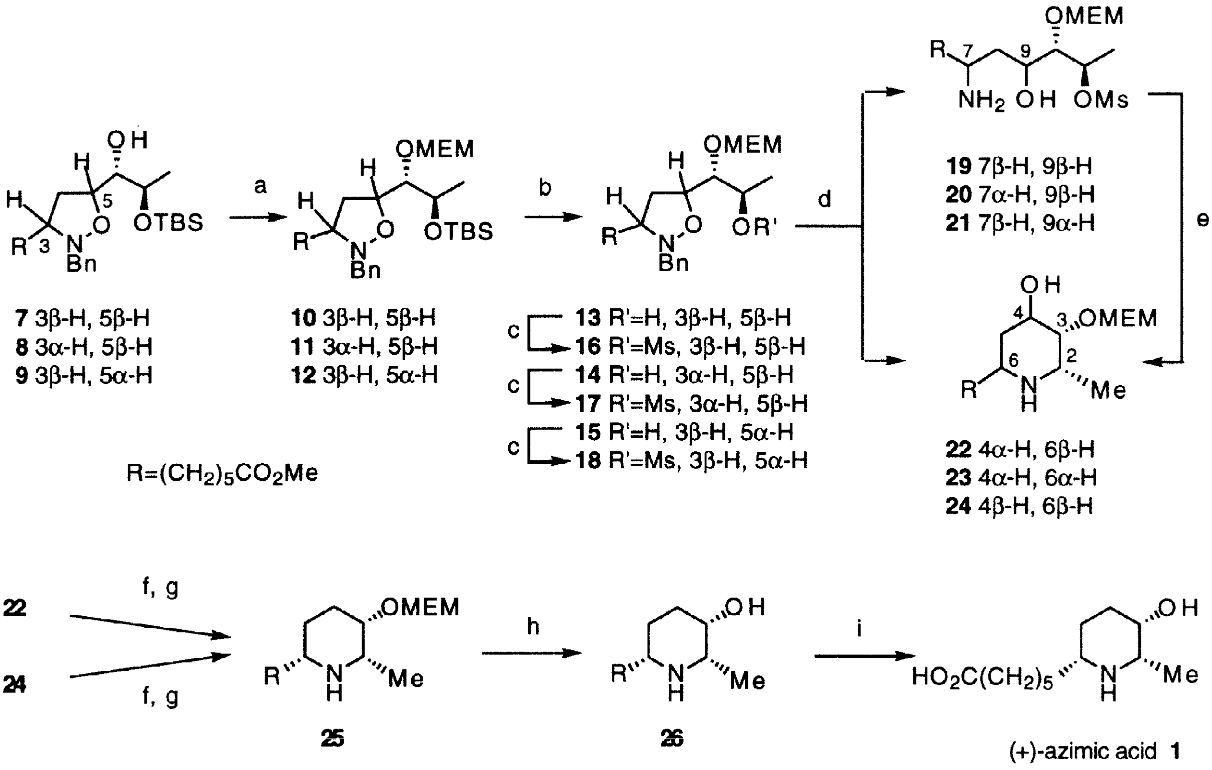
Conditions	Additive	Yield (%) 7	8	9
toluene/Δ, 50h	—	35	37	11
CH_2Cl_2/Δ, 30h	MeMgBr	3	14	—

congener. Thus, comparison of signals due to the allylic protons (δ 3.94 in **6**: δ 3.75 in the isomer) and the *J*-values between 3-H and 4-H (J = 3.5 Hz in **6**: J = 6 Hz in the isomer) clearly revealed that the major isomer **6** and the minor congener are *erythro*- and *threo*-structures, respectively.

Cycloaddition of Z-nitrone **5** to (-)-allyl alcohol **6** in toluene under reflux proceeded smoothly to give a 3.2 : 3.4 : 1 mixture of three adducts **7–9** in 83% combined yield which was separated by repeated medium-pressure liquid chromatography (MPLC). The stereostructures of the adducts **7–9** were tentatively deduced from ^{1}H NMR spectra, particularly the differences in the chemical shifts due to two 4-H. The differences were 0.51 ppm in the *cis*-isomer **7** and 0.07 ppm and 0.39 ppm in the *trans*-isomers **8** and **9**, respectively. We have recently reported that differences in the chemical shifts due to two 4-H in 3,5-disubstituted isoxazolidines are *ca* 0.6 ppm in 3,5-*cis*-compounds and below 0.4 ppm in 3,5-*trans*-compounds.[11] However, the relative configuration between 5-H and 1"-H could not be deduced from the spectral data. The whole stereostructures of all adducts were unambiguously confirmed from the structures of the readily assignable piperidine derivatives which were prepared by ring transformation of the isoxazolidines as shown later.

Our previous study[11] on the 1,3-dipolar cycloaddition of *C, N*-dialkyl nitrone to allyl alcohols has established that the reaction rate and the stereoselectivity are influenced by the form of the hydroxyl group, of which the rate is accelerated and the *trans*-selectivity improves when the magnesium alkoxide (OMgBr)[19] is used. Therefore, we investigated the magnesium-induced cycloaddition of Z-nitrone **5** to (-)-allyl alcohol **6**. (-)-Allyl alcohol **6** was treated with MeMgBr to form the corresponding magnesium alkoxide which was reacted with nitrone **5** in CH_2Cl_2 under reflux to give a 1:4 mixture of two adducts **7** and **8** in 17% combined yield with the recovery of a large amount of **6** (Table 1). Thus, magnesium-induced cycloaddition of Z-nitrone **5** took place with the *trans*-stereoselectivity but in low yield. The *trans-threo* isomer **8** is not suited for the synthesis of (+)-azimic acid **1**. The *threo*-selectivity (products **7** and **8**) observed in both cases of the cycloadditions to either magnesium alkoxide or free alcohol is in accordance with the known results.[20]

Next, we investigated the ring transformation of isoxazolidines **7-9** into the piperidine derivatives. Protection of the hydroxyl group in the adducts **7-9** with the MEM group and deprotection of the silyl group with TBAF gave the alcohols **13-15** in 54-76% yields. Upon treatment with MsCl-pyridine the alcohols **13-15** gave the corresponding mesylates **16-18** which were then treated with hydrogen in the presence of Pearlman's catalyst to give a mixture of the acyclic mesylates **19-21** and the cyclized piperidinols **22-24**. Treatment of the crude hydrogenated products, which would be a mixture of **19-24**, with $NaHCO_3$ in MeOH-H_2O[21] underwent S$_N$2 type substitution at the root of the mesyloxy group in **19-21** leading to the formation of the corresponding piperidinols **22-24** as final products in 62-93 % yields *via* 3 steps. Careful ^{1}H NMR spectral analyses of both **22–24** and the above-mentioned cycloadducts **7–9** firmly established the stereostructures of three isomeric piperidinols **22–24** as shown. Next, two 3,6-*cis*-piperidines **22** and **24** were converted into (+)-azimic acid (**1**). Deoxygenation of the piperidinols **22** and **24** with Bu_3SnH *via* Barton's ester[22] proceeded smoothly to give an identical piperidine **25** in 81-82% yield. Deprotection of the MEM group in **25** was achieved by treatment with $TiCl_4$ to give the piperidinol **26** in 81% yield {**26**•HCl; a powder, mp 160-161°C {lit.[4] mp 164 °C [(+)-methyl azimate•HCl], lit.[12a] mp 153-155 °C [(±)-methyl azimate•HCl]}}. Hydrolysis of the ester group in **26** with KOH-MeOH gave (+)-**1**, which was found to be identical with the authentic sample of (+)-**1** upon comparison of their spectral data,[4] including optical rotation {**1**; mp 217 °C (dec.), $[\alpha]_D$ +7.4 (*c* 0.52, MeOH)[lit.[12b] mp 214-215 °C, $[\alpha]_D$ + 8 (MeOH), lit.[12e] mp 210-214 °C (dec.), $[\alpha]_D$ +7.9 (*c* 1.0, MeOH)]}.

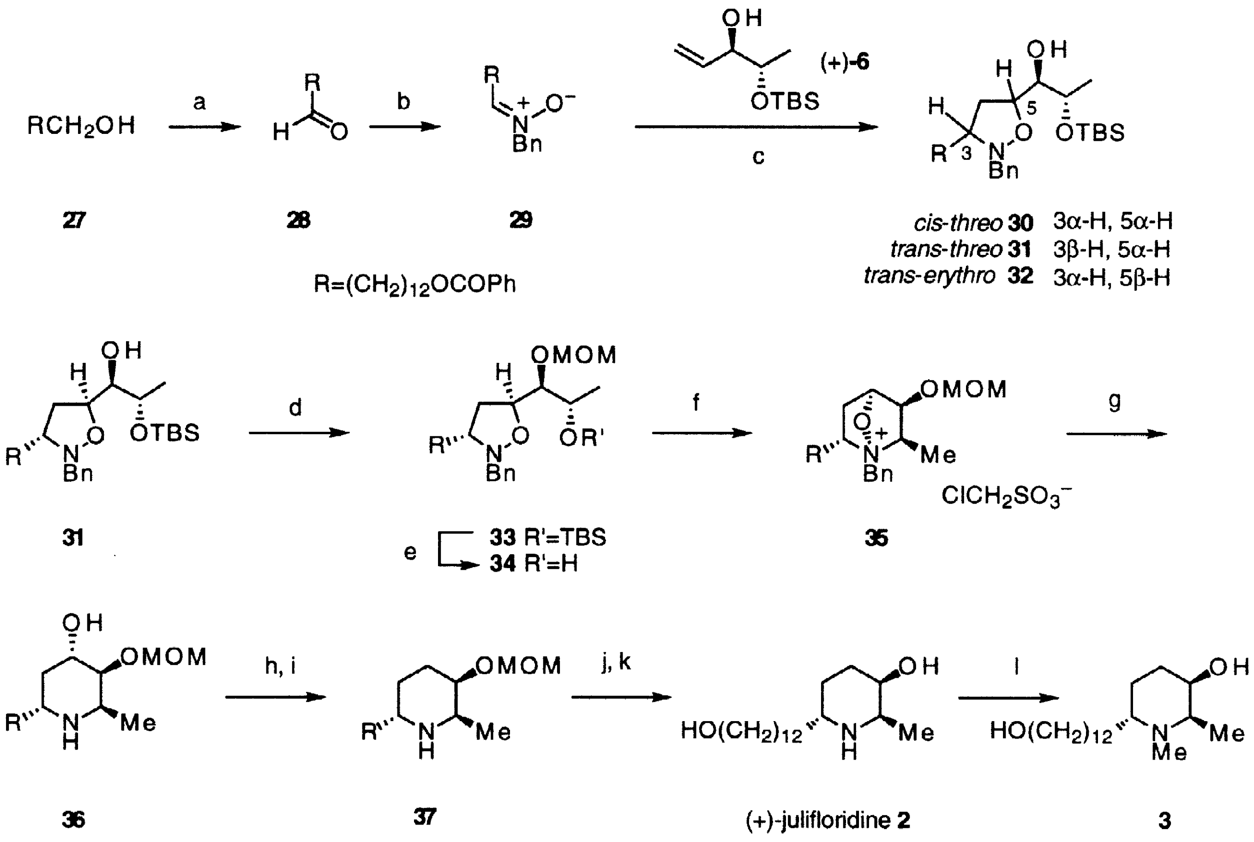


Scheme 2 *Reagents and conditions*; a) MEMCl, $(i\text{-Pr})_2NEt$, CH_2Cl_2, Δ; b) $(n\text{-Bu})_4NF$, THF, Δ; c) MsCl, py., 0 °C; d) 20% $Pd(OH)_2$-C, MeOH, H_2; e) $NaHCO_3$, H_2O-MeOH; f) Im_2CS, THF; g) Bu_3SnH, toluene, Δ; h) $TiCl_4$, CH_2Cl_2, 0 °C; i) KOH, MeOH.

Total syntheses of (+)-julifloridine and proposed structure of N-methyljulifloridine

The newly established synthetic method in this study was successfully applied to the asymmetric synthesis of julifloridine (**2**) and the proposed structure **3** of *N*-methyljulifloridine. Although the absolute configurations of these alkaloids were not established as mentioned above, we used (+)-allyl alcohol **6** as a dipolarophile which is readily available from cheaper methyl (+)-lactate than the (-)-isomer.

The nitrone **29** was prepared by the condensation of *N*-benzylhydroxylamine and 13-benzoyloxytridecanal **28** which is readily available from 1,13-tridecadiol.[23] The geometry of nitrone **29** was suggested to be Z-configuration by the analysis of ^{1}H NMR spectrum.[10,17] Cycloaddition of nitrone **29** to the (+)-allyl alcohol **6** gave a 2.7: 4.4 : 1 mixture of three adducts **30–32** in 57% combined yield. The structures of adducts **30–32** were deduced from comparison of their ^{1}H NMR spectra with those of the adducts **7-9**. The major adduct **31** has the correct stereostructure for the synthesis of julifloridine (**2**) and *N*-methyljulifloridine (**3**) and, therefore, converted into the target compound. Protection of the hydroxyl group in the adduct **31** with the MOM group and deprotection of the silyl group with TBAF gave the alcohol **34** in 59% yield. Nakata[24] have recently reported that the chloromethanesulfonyloxy group is a more efficient leaving group than the methanesulfonyloxy group. Therefore, we employed the chloromethanesulfonyloxy group as a leaving group for the transformation of isoxazolidine **34** into **36**. Treatment of **34** with $ClCH_2SO_2Cl$ gave, as expected, the bicyclic compound **35**, which was successively subjected to catalytic hydrogenolysis with hydrogen in the presence of Pearlman's catalyst to give the piperidinol **36** in 77% yield.



Scheme 3 *Reagents and conditions*; a) PCC, AcONa; b) $PhCH_2NHOH$, molecular sieves; c) toluene, Δ; d) MOMCl, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, Δ; e) $(n\text{-}Bu)_4NF$, THF, Δ; f) $ClCH_2SO_2Cl$, py., 0 °C; g) 20% $Pd(OH)_2$-C, MeOH, H_2; h) Im_2CS, THF; i) Bu_3SnH, toluene, Δ; j) KOH, MeOH; k) HCl, MeOH; l) $NaCNBH_3$, HCHO, MeCN.

Deoxygenation of the piperidinol **36** *via* Barton's ester[22] gave the piperidine **37** in 74% yield. Upon hydrolysis of the ester with KOH-MeOH and deprotection of the MOM group with HCl-MeOH, **37** gave the piperidinol (+)-**2** in 66% yield, mp 85–87.5 °C, $[\alpha]_D$ + 18 (*c* 0.84, MeOH)(lit.[6] mp 82–83 °C) which was found to be identical with the authentic sample of julifloridine (**2**) upon direct comparison of their spectral data.

Next, (+)-julifloridine (**2**) prepared above was methylated with $NaCNBH_3$ and HCHO to give the *N*-methyl derivative **3** in 78% yield. The structure of **3** was established by the careful analysis of ^1H NMR and ^{13}C NMR spectra. Surprisingly, comparison of ^1H and ^{13}C NMR spectra of synthetic piperidinol (–)-**3** with the reported data of natural *N*-methyljulifloridine[7] showed that they are not identical. Therefore, it is clearly concluded that the structure of *N*-methyljulifloridine should be revised.[25]

In conclusion, combination of nitrone cycloaddition to the chiral allyl alcohol **6** and ring transformation of the resulting cycloadducts to piperidines has provided not only a general method for the asymmetric synthesis of 2,6-disubstituted 3-piperidinol alkaloids but also led to unavoidable reinvestigation of the structure determination of *N*-methyljulifloridine (**3**).

EXPERIMENTAL SECTION

General. ^1H NMR spectra were measured using Varian Gemini-200 (200 MHz), Gemini-300 (300 MHz), and VXR-500 (500 MHz) instruments and ^{13}C NMR spectra were measured with Gemini-300 (75 MHz) for solutions in deuteriochloroform unless otherwise stated (tetramethylsilane was used as the internal reference). IR spectra were measured with a Perkin Elmer 1600 FTIR machine and Mass spectra were taken with Hitachi M-4100 instruments. Optical rotations were measured on a Jasco DIP-370 digital polarimeter. Mps were determined with Kofler-type hot-stage apparatus and are uncorrected. All reactions were carried out under nitrogen and the extracts from the reaction mixtures were washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. TLC was performed on precoated silica gel 60F-254 (0.2 mm thick, Merck) and preparative TLC (PLC) on precoated silica gel 60F-254 (0.25 mm thick, Merck), with UV detection at 254 and 300 nm. MPLC was undertaken on a 530-4-10V apparatus (Yamazen) with Lobar größe B (310-25, LiChroprep Si60, Merck) as column adsorbent. Flash column chromatography (FCC) was performed on Silica gel 60 (230–400 mesh, Merck) as column adsorbent. Short column chromatography (SCC) was undertaken on a short glass filter using Silica gel 60 (230–400 mesh, Merck) under reduced pressure. Ether refers to diethyl ether.

Methyl (*Z*)-6-benzyliminoheptanoate *N*-oxide (5). To a stirred mixture of methyl 7-oxoheptanoate **4** (6.65 g, 42 mmol) and molecular sieves 4Å (24 g) in toluene (200 ml) was added *N*-benzylhydroxylamine[15] (4.66 g, 38 mmol). After stirring at room temperature for 2 h, molecular sieves were filtered off. The filtrate was then concentrated and subjected to FCC (AcOEt/hexane 1 : 3 and AcOEt) to give nitrone **5** (7.9 g, 79%) as scales, mp 65–67 °C (ether). IR ($CHCl_3$) 1731 (COO), 1600 (C=N) cm^{-1}. ^1H NMR δ (200 MHz) 7.45–7.33 (5H, m, ArH), 6.63 (1H, t, J = 6 Hz, 1-H), 4.87 (2H, s, CH_2Ph), 3.64 (3H, s, CO_2Me), 2.47 (2H, br q, J = 7 Hz, 2-H_2), 2.27 (2H, t, J = 7 Hz, 6-H_2), 1.72–1.23 (6H, m, 3–5-H_2). Anal Calcd for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.15; H, 8.10; N, 5.16.

(3*S*,4*R*)-(–)-4-[(*tert*-Butyldimethylsilyl)oxy]pent-1-en-3-ol (6). To a stirred solution of (2*R*)-2-

[(*tert*-butyldimethylsilyl)oxy]propanal[13] (3.3 g, 17.5 mmol) in THF (50 ml) was added dropwise vinyl magnesium bromide (1.0 M in THF) (21 ml, 21 mmol) at −60 °C. The mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with ether. The extract was washed with brine, dried and concentrated. The residue was subjected to MPLC (AcOEt/hexane 1 : 8) to afford the major isomer **6** (2.59 g, 68%) and the minor isomer (525 mg, 14%). **6**; an oil. $[\alpha]_D$ − 28 (*c* 2.0, MeOH). ^{1}H NMR δ (200 MHz) 5.74 (1H, ddd, *J* = 17, 10, 6 Hz, 2-H), 5.20 (1H, dt, *J* = 17, 1.5 Hz, 1-H), 5.11 (1H, dt, *J* = 10, 1.5 Hz, 1-H), 3.94 (1H, br q, *J* = 3.5 Hz, 3-H), 3.55 (1H, br qd, *J* = 6, 4 Hz, 4-H), 2.25 (1H, d, *J* = 4 Hz, OH), 1.00 (3H, d, *J* = 6 Hz, Me), 0.82 (9H, s, tBu), 0.00 (6H, s, $SiMe_2$). The minor isomer[13] of **6**; [(3*R*,4*R*)-4-[(*tert*-butyldimethylsilyl)-oxy]pent-1-en-3-ol], an oil. ^{1}H NMR δ (200 MHz) 5.23 (1H, ddd, *J* = 17, 12, 6 Hz, 2-H), 5.23 (1H, dt, *J* = 17, 2 Hz, 1-H), 5.11 (1H, dt, *J* = 12, 1.5 Hz, 1-H), 3.75 (1H, br q, *J* = 6 Hz, 3-H), 3.59 (1H, br quint., *J* = 6 Hz, 4-H), 2.47 (1H, d, *J* = 5 Hz, OH), 1.07 (3H, d, *J* = 6 Hz, Me), 0.81 (9H, s, tBu), 0.00 (6H, s, $SiMe_2$). ^{1}H NMR spectral data of **6** and its isomer were found to be identical with those reported in the literature.[13b]

Cycloaddition of nitrone 5 to olefin (−)-6. A solution of nitrone **5** (5.8 g, 22 mmol) and olefin (−)-**6** (3.8 g, 18 mmol) in toluene (170 ml) was heated to reflux for 60 h. The solvent was evaporated and the residue was subjected to FCC (AcOEt/hexane 1 : 4) to give adducts **7** (2.95 g, 35%), **8** (3.11 g, 37%), **9** (0.93 g, 11%) and recovered olefin (−)-**6** (0.42 g, 11%). **Methyl [3*R*,5*R* (*S*,*R*)]-(−)-2-benzyl-5-[2-[(*tert*-butyldimethylsilyl)oxy]-1-hydroxypropyl]-3-isoxazolidinehexanoate (7)**; a pale yellow oil. $[\alpha]_D$ − 67 (*c* 1.98, MeOH). IR ($CHCl_3$) 3446 (OH) and 1731 (COO) cm^{-1}. ^{1}H NMR δ (200 MHz) 7.42–7.23 (5H, m, ArH), 4.43 (1H, ddd, *J* = 8, 5, 2 Hz, 5-H), 4.03 and 3.73 (2H, ABq, *J* = 13.5 Hz, CH_2Ph), 3.69 (3H, s, CO_2Me), 3.58 (1H, dq, *J* = 8, 6 Hz, 2"-H), 3.10 (1H, br td, *J* = 7.5, 1.5 Hz, 1"-H), 2.79 (1H, br qd, *J* = 7.5, 4.5 Hz, 3-H), 2.57 (1H, dt, *J* = 12, 8 Hz, 4-H), 2.32 (2H, t, *J* = 7.5 Hz, 5'-H_2), 2.06 (1H, ddd, *J* = 12, 7.5, 5 Hz, 4-H), 1.72–1.25 (8H, m, 1'–4'-H_2), 1.19 (3H, d, *J* = 6 Hz, 2"-Me), 0.87 (9H, s, tBu), 0.00 (6H, s, $SiMe_2$). HRMS Calcd for $C_{26}H_{45}NO_5Si$ (M^+): 479.3064. Found: 479.3062. **Methyl [3*S*,5*R*(*S*,*R*)]- (+)-2-benzyl-5-[2-[(*tert*-butyldimethylsilyl)oxy]-1-hydroxypropyl]-3-isoxazolidinehexanoate (8)**; a pale yellow oil. $[\alpha]_D$ + 27 (*c* 1.53, MeOH). IR ($CHCl_3$) 3554 (OH) and 1731 (COO) cm^{-1}. ^{1}H NMR δ (300 MHz) 7.38–7.19 (5H, m, ArH), 4.23 (1H, m, 5-H), 3.99 and 3.82 (2H, ABq, *J* = 13.5 Hz, CH_2Ph), 3.66 (3H, s, CO_2Me), 3.62 (1H, m, 2"-H), 3.21 (1H, td, *J* = 7.5, 3.5 Hz, 1"-H), 2.80 (1H, m, 3-H), 2.28 (2H, t, *J* = 7.5 Hz, 5'-H_2), 2.07 (1H, m, 4-H), 2.00 (1H, dt, *J* = 12, 7 Hz, 4-H), 1.70–1.24 (8H, m, 1'–4'-H_2), 1.18 (3H, d, *J* = 6 Hz, 2"-Me), 0.87 (9H, s, tBu), 0.00 (6H, s, $SiMe_2$). HRMS calcd for $C_{26}H_{45}NO_5Si$ (M^+): 479.3064. Found: 479.3090. **Methyl [3*R*,5*S*(*S*,*R*)]-(−)-2-benzyl-5-[2-[(*tert*-butyldimethylsilyl)oxy]-1-hydroxypropyl]-3-isoxazolidinehexanoate (9)**; a pale yellow oil. $[\alpha]_D$ − 60 (*c* 1.84, MeOH). IR ($CHCl_3$) 3566 (OH) and 1731 (COO) cm^{-1}. ^{1}H NMR δ (500 MHz) 7.30–7.17 (5H, m, ArH), 4.00 (1H, m, 5-H), 3.87 and 3.79 (2H, ABq, *J* = 13 Hz, CH_2Ph), 3.82 (1H, br quint., *J* = 5.5 Hz, 2"-H), 3.60 (3H, s, CO_2Me), 3.49 (1H, t, *J* = 5.5 Hz, 1"-H), 2.76 (1H, m, 3-H), 2.34 (1H, dt, *J* = 12, 7.5 Hz, 4-H), 2.22 (2H, t, *J* = 7.5 Hz, 5'-H_2), 1.95 (1H, ddd, *J* = 12, 8, 6.5 Hz, 4-H), 1.58–1.48 (4H, m, 1', 4'-H_2), 1.33–1.18 (4H, m, 2', 3'-H_2), 1.07 (3H, d, *J* = 6 Hz, 2"-Me), 0.87 (9H, s, tBu), 0.00 (6H, s, $SiMe_2$). HRMS calcd for $C_{26}H_{45}NO_5Si$ (M^+): 479.3064. Found: 479.3063.

Cycloaddition of nitrone 5 to olefin (–)-6 in the presence of EtMgBr. To a stirred solution of **6** (226 mg, 1.04 mmol) in dry CH_2Cl_2 (5 ml) was added EtMgBr (1.04 M in THF) (1 ml, 1.04 mmol) at 0 °C. After stirring at 0 °C for 10 min, a solution of nitrone **5** (275 mg, 0.42 mmol) in CH_2Cl_2 (5 ml) was added and the resulting solution was heated to reflux for 30 h. After being cooled to room temperature, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2. The extract was dried and concentrated and subjected to MCC (AcOEt/hexane 1 : 6) to give *cis*-adduct **7** (15 mg, 3%) and *trans*-adduct **8** (71 mg, 14%). The adducts **7** and **8** were identical with the samples obtained by the cycloaddition of nitrone **5** to olefin (–)-**6** in refluxing toluene upon comparison of their Rf values and ^1H NMR spectra.

Methyl [3*R*,5*R*(*S*,*R*)]-(–)-2-benzyl-5-[2-[(*tert*-butyldimethylsilyl)oxy]-1-[(2-methoxyethoxy)methoxy]propyl]-3-isoxazolidinehexanoate (10). A solution of **7** (1.40 g, 3 mmol), $(i\text{-}Pr)_2NEt$ (7.8 g, 60 mmol) and MEMCl (6.2 g, 18 mmol) in CH_2Cl_2 (48 ml) was heated to reflux for 25 h. The reaction mixture was diluted with CH_2Cl_2, and then washed subsequently with 15% acetic acid, saturated $NaHCO_3$ solution and brine, and the organic layer was dried and concentrated. The residue was subjected to MCC (AcOEt/hexane 1 : 4) to give **10** (1.27 g, 83%) as a pale yellow oil. $[\alpha]_D$ – 43 (c 1.81, MeOH). IR ($CHCl_3$) 1731 (COO) cm^{-1}. ^1H NMR δ (500 MHz) 7.32–7.17 (5H, m, ArH), 4.72 and 4.69 (2H, ABq, J = 7 Hz, OCH_2O), 4.12 (1H, br dt, J = 8.5, 7 Hz, 5-H), 3.87 and 3.81 (2H, ABq, J = 13 Hz, CH_2Ph), 3.78 (1H, qd, J = 6.5, 4 Hz, 2"-H), 3.75, 3.57, 3.52 and 3.35 (each 1H, m, OCH_2CH_2O), 3.62 (3H, s, CO_2Me), 3.46 (1H, dd, J = 7.5, 4 Hz, 1"-H), 3.30 (3H, s, OMe), 2.90 (1H, quint., J = 6.5 Hz, 3-H), 2.36 (1H, dt, J = 12, 7 Hz, 4-H), 2.22 (2H, t, J = 7.5 Hz, 5'-H_2), 1.66 (1H, br dt, J = 12, 8 Hz, 4-H), 1.56–1.49 (4H, m, 1', 4'-H_2), 1.34–1.15 (4H, m, 2', 3'-H_2), 1.11 (3H, d, J = 6.5 Hz, 2"-Me), 0.83 (9H, s, tBu), 0.00 (6H, s, $SiMe_2$). HRMS calcd for $C_{30}H_{53}NO_7Si$ (M^+): 567.3588. Found: 567.3604.

Methyl [3*R*,5*R*(*S*,*R*)]-(–)-2-benzyl-5-[2-hydroxy-1-[(2-methoxyethoxy)methoxy]propyl]-3-isoxazolidinehexanoate (13). A solution of **10** (1.13 g, 2.0 mmol) and TBAF (1.0 M in THF) (2.5 ml, 2.5 mmol) in THF (55 ml) was heated to reflux for 9 h. The solvent was evaporated and the residue was subjected to FCC (AcOEt/hexane 4 : 1) to give **13** (703 mg, 78%) as a yellow oil. $[\alpha]_D$ – 29 (c 1.66, MeOH). IR ($CHCl_3$) 3600–3300 (OH) and 1731 (COO) cm^{-1}. ^1H NMR δ (500 MHz) 7.36–7.23 (5H, m, ArH), 4.68 and 4.65 (2H, ABq, J = 7 Hz, OCH_2O), 4.20 (1H, q, J = 7.5 Hz, 5-H), 3.93 and 3.87 (2H, ABq, J = 13 Hz, CH_2Ph), 3.77 and 3.62 (each 1H, m, OCH_2CH_2O), 3.75 (1H, br qd, J = 6.5, 3.5 Hz, 2"-H), 3.64 (3H, s, CO_2Me), 3.57 (1H, br dd, J = 7, 4 Hz, 1"-H), 3.52 (2H, t, J = 4.5 Hz, OCH_2CH_2O), 3.37 (3H, s, OMe), 2.88 (1H, quint., J = 7Hz, 3-H), 2.45 (1H, dt, J = 12.5, 8 Hz, 4-H), 2.27 (2H, t, J = 7.5 Hz, 5'-H_2), 1.75 (1H, br dt, J = 12, 7 Hz, 4-H), 1.62–1.54 (4H, m, 1', 4'-H_2), 1.40–1.20 (4H, m, 2', 3'-H_2), 1.16 (3H, d, J = 6.5 Hz, 2"-Me). HRMS calcd for $C_{24}H_{39}NO_7$ (M^+): 453.2725. Found: 453.2722.

Methyl (2*S*,3*R*,4*R*,6*R*)-(–)-4-hydroxy-3-[(2-methoxyethoxy)methoxy]-2-methyl-6-piperidinehexanoate (22). To a solution of isoxazolidine **13** (1.06 g, 2.3 mmol) in pyridine (13 ml) was added MsCl (527 mg, 4.6 mmol) at 0 °C and the mixture was stirred at the same temperature for 2 h. The reaction mixture was diluted with H_2O under ice-cooling and extracted with CH_2Cl_2. The extract was washed with saturated $NaHCO_3$ solution, dried and concentrated to give mesylate **16** which was characterized from ^1H NMR spectrum of the crude product; ^1H NMR δ (300 MHz) 7.37–7.20 (5H, m, ArH), 4.81 (1H, qd, *J* = 6.5, 2.5 Hz, 2''-H), 4.69 and 4.62 (2H, ABq, *J* = 7 Hz, OCH_2O), 4.12 (1H, q, *J* = 7.5 Hz, 5-H), 3.92 and 3.80 (2H, ABq, *J* = 13 Hz, CH_2Ph), 3.84 (1H, dd, *J* = 7.5, 2.5 Hz, 1''-H), 3.73 and 3.54 (each 1H, m, OCH_2CH_2O), 3.67 (3H, s, CO_2Me), 3.49–3.44 (2H, m, OCH_2CH_2O), 3.35 (3H, s, OMe), 2.98 (3H, s, Ms), 2.84 (1H, m, 3-H), 2.46 (1H, dt, *J* = 12, 7.5 Hz, 4-H), 2.28 (2H, t, *J* = 7.5 Hz, 5'-H_2), 1.76 (1H, dt, *J* = 12, 7.5 Hz, 4-H), 1.66–1.52 (4H, m, 1', 4'-H_2), 1.41 (3H, d, *J* = 6.5 Hz, 2''-Me), 1.40–1.22 (4H, m, 2', 3'-H_2). A suspension of 20% $Pd(OH)_2$-C (575 mg) in MeOH (10 ml) was stirred under a hydrogen atmosphere at room temperature for 1 h. A solution of the crude mesylate **16** in MeOH (74 ml) was added to a resulting suspension. After stirring under a hydrogen atmosphere at room temperature for 24 h, the reaction mixture was filtered and the filtrate was concentrated. The residue was made alkaline with 1M NaOH solution under ice-cooling and the whole was extracted with CH_2Cl_2. The extract was washed with brine, dried and evaporated to give a mixture of amino alcohol **19** and piperidinol **22**. The structure of **19** was deduced from ^1H NMR spectrum of the crude product; ^1H NMR δ (300 MHz) 4.97 (1H, qd, *J* = 6.5, 4 Hz, 11-H), 3.09 (3H, s, Ms), 1.49 (3H, d, *J* = 6.5 Hz, 11-Me). To a solution of a mixture of **19** and **22** in MeOH (74 ml) was added saturated $NaHCO_3$ solution (28 ml). After stirring at room temperature for 24 h, the reaction mixture was concentrated and diluted with CH_2Cl_2. The organic layer was washed, dried and concentrated. The residue was subjected to SCC (CH_2Cl_2/MeOH 9 : 1) to afford piperidinol **22** (660 mg, 89%) as an oil. $[\alpha]_D$ – 11 (*c* 1.43, MeOH). IR ($CHCl_3$) 3402 (OH) and 1731 (COO) cm^{-1}. ^1H NMR δ (500 MHz) 4.83 and 4.73 (2H, ABq, *J* = 7 Hz, OCH_2O), 4.12 (1H, q, *J* = 3 Hz, 4-H), 3.77–3.69 and 3.58–3.51 (each 2H, m, OCH_2CH_2O), 3.66 (3H, s, CO_2Me), 3.39 (3H, s, OMe), 3.36 (1H, br t, *J* = 2 Hz, 3-H), 3.27 (1H, br q, *J* = 6 Hz, 2-H), 2.98 (1H, m, 6-H), 2.30 (2H, t, *J* = 7 Hz, 5'-H_2), 1.67 (1H, br dt, *J* = 14, 2.5 Hz, 5-Heq), 1.57 (1H, ddd, *J* = 14, 11, 3 Hz, 5-Hax), 1.66–1.28 (8H, m, 1'–4'-H_2), 1.18 (3H, d, *J* = 6.5 Hz, 2-Me). HRMS (CI, isobutane) calcd for $C_{17}H_{33}NO_6$+H(QM^+): 348.2384. Found: 348.2374.

Methyl [3*S*, 5*R*(*S*,*R*)]-(+)-2-benzyl-5-[2-[(*tert*-butyldimethylsilyl)oxy]-1-[(2-methoxyethoxy)methoxy]propyl]-3-isoxazolidinehexanoate (11). According to the procedure described for protection of the hydroxyl group in **7**, treatment of isoxazolidine **8** (370 mg, 0.77 mmol) with MEMCl (575 mg, 4.6 mmol) in the presence of $(i\text{-Pr})_2NEt$ (2.0 g, 15.4 mmol) in CH_2Cl_2 (13 ml) gave **11** (340 mg, 81%) as a pale yellow oil. $[\alpha]_D$ + 27 (*c* 1.17, MeOH). IR ($CHCl_3$) 1731 (COO) cm^{-1}. ^1H NMR δ (300 MHz) 7.40–7.15 (5H, m, ArH), 4.90–4.81 (2H, m, OCH_2O), 4.04 (1H, br q, *J* = 7 Hz, 5-H), 3.91 and 3.86 (2H, ABq, *J* = 13.5 Hz, CH_2Ph), 3.86–3.71 and 3.51–3.38 (each 2H, m, OCH_2CH_2O), 3.64 (3H, s, CO_2Me), 3.62 (1H, m, 2''-H), 3.35 (1H, m, 1''-H), 3.34 (3H, s, OMe), 2.81 (1H, m, 3-H), 2.26 (2H, t, *J* = 7.5 Hz, 5'-H_2), 2.20 (1H, dt, *J* = 12, 8 Hz, 4-H), 1.88 (1H, ddd, *J* = 12, 8, 5 Hz, 4-H), 1.64–1.44 (4H, m, 1', 4'-H_2), 1.40–1.17 (4H, m, 2', 3'-H_2), 1.14 (3H, d, *J* = 6 Hz, 2''-Me), 0.84 (9H, s, tBu), 0.00 (6H, s, $SiMe_2$). HRMS calcd for $C_{30}H_{53}NO_7Si$ (M^+): 567.3588. Found: 567.3604.

Methyl [3*S*,5*R*(*S*,*R*)]-(+)-2-benzyl-5-[2-hydroxy-1-[(2-methoxyethoxy)methoxy]propyl]-3-isoxazolidinehexanoate (14). According to the procedure described for the synthesis of **13**, treatment of isoxazolidine **11** (1.3 g, 2.3 mmol) with TBAF (1.0 M in THF)(2.3 ml, 2.3 mmol) in THF (63 ml) gave the crude product. It was subjected to SCC (AcOEt/hexane 1 : 3 and AcOEt/hexane 1 : 1) to give **14** (721 mg, 70%) as a pale yellow oil. $[\alpha]_D$ + 47 (*c* 1.72, MeOH). IR ($CHCl_3$) 3454 (OH) and 1731 (COO) cm^{-1}. ^1H NMR δ (300 MHz) 7.38–7.21 (5H, m, ArH), 4.83 (2H, s, OCH_2O), 4.12 (1H, br q, *J* = 7.5 Hz, 5-H), 3.92 (2H, s, CH_2Ph), 3.89–3.80 and 3.74–3.65 (each 2 H, m, OCH_2CH_2O), 3.79 (1H, dqd, J = 9, 6.5, 3 Hz, 2''-H), 3.66 (3H, s, CO_2Me), 3.59 (1H, dd, J = 6.5, 3 Hz, 1''-H), 3.38 (3H, s, OMe), 3.54 (1H, br d, J = 9 Hz, OH), 2.90 (1H, m, 3-H), 2.28 (2H, t, J = 7.5 Hz, 5'-H_2), 2.24 (1H, dt, J = 12, 8 Hz, 4-H), 1.91 (1H, ddd, J = 12, 7.5, 5 Hz, 4-H), 1.65–1.47 (4H, m, 1', 4'-H_2), 1.42–1.21 (4H, m, 2', 3'-H_2), 1.17 (3H, d, J = 6.5 Hz, 2''-Me). HRMS calcd for $C_{24}H_{39}NO_7$ (M^+): 453.2725. Found: 453.2724.

Methyl (2*S*,3*R*,4*R*,6*S*)-(–)-4-hydroxy-3-[(2-methoxyethoxy)methoxy]-2-methyl-6-piperidinehexanoate (23). According to the procedure described for mesylation of **13**, treatment of isoxazolidine **14** (307 mg, 0.68 mmol) with MsCl (156 mg, 1.36 mmol) in pyridine (4 ml) gave the crude product. It was subjected to SCC (AcOEt/hexane 1 : 1) to give mesylate **17** (286 mg, 79%) as an oil; ^1H NMR δ (300 MHz) 7.38–7.20 (5H, m, ArH), 4.89 and 4.82 (2H, ABq, J = 7 Hz, OCH_2O), 4.75 (1H, qd, J = 6.5, 4 Hz, 2''-H), 4.07 (1H, q, J = 5.5 Hz, 5-H), 3.94 and 3.83 (2H, ABq, J = 13.5 Hz, CH_2Ph), 3.79 (1H, dd, J = 5.5, 4 Hz, 1''-H), 3.78–3.51 and 3.55–3.50 (each 2H, m, OCH_2CH_2O), 3.67 (3H, s, CO_2Me), 3.38 (3H, s, OMe), 2.86 (1H, m, 3-H), 2.83 (3H, s, Ms), 2.34 (1H, br dt, J = 12, 7 Hz, 4-H), 2.29 (2H, t, J = 7.5 Hz, 5'-H_2), 1.95 (1H, br ddd, J = 12, 7.5, 6 Hz, 4-H), 1.68–1.52 (4H, m, 1', 4'-H_2), 1.43 (3H, d, J = 6.5 Hz, 2''-Me), 1.42–1.23 (4H, m, 2', 3'-H_2). According to the procedure described for the synthesis of **22**, catalytic hydrogenation of mesylate **17** (286 mg, 0.54 mmol) in MeOH (22 ml) in the presence of 20% $Pd(OH)_2$-C (170 mg) gave a mixture of amino alcohol **20** and piperidinol **23**. The structure of **20** was characterized from ^1H NMR spectrum of the crude product; ^1H NMR δ (300 MHz) 4.93 (1H, qd, J = 6.5, 4 Hz, 11-H), 3.07 (3H, s, Ms), 1.46 (3H, d, J = 6.5 Hz, 11-Me). A solution of a mixture of **20** and **23** in MeOH (19 ml) and saturated $NaHCO_3$ solution (8 ml) was heated to reflux for 10 h. After evaporation of the solvent, the residue was diluted with CH_2Cl_2. The organic layer was washed, dried and concentrated and the residue was subjected to SCC (AcOEt/MeOH 19 : 1) to afford **23** (141 mg, 78%) as an oil. $[\alpha]_D$ – 46 (*c* 0,89, MeOH). IR ($CHCl_3$) 3441 (OH) and 1731 (COO) cm^{-1}. ^1H NMR δ (500 MHz) 4.79 and 4.76 (2H, ABq, J = 7 Hz, OCH_2O), 3.80 and 3.69 (each 1H, m, OCH_2CH_2O), 3.71 (1H, ddd, J = 11, 8.5, 5 Hz, 4-H), 3.63 (3H, s, CO_2Me), 3.53 (2H, t, J = 4.5 Hz, OCH_2CH_2O), 3.42–3.37 (2H, m, 2, 3-H), 3.36 (3H, s, OMe), 2.82 (1H, m, 6-H), 2.27 (2H, t, J = 7 Hz, 5'-H_2), 2.03 (1H, ddd, J = 13, 5, 3 Hz, 5-Heq), 1.63–1.56 (4H, m, 1', 4'-H_2), 1.36–1.26 (4H, m, 2', 3'-H_2), 1.11 (3H, d, J = 7 Hz, 2-Me), 1.06 (1H, br dt, J = 13, 11.5 Hz, 5-Hax). HRMS calcd for $C_{17}H_{33}NO_6$ (M^+): 347.2306. Found: 347.2314.

Methyl [3*R*,5*S*(*S*,*R*)]]-(–)-2-benzyl-5-[2-[(*tert*-butyldimethylsilyl)oxy]-1-[(2-methoxyethoxy)methoxy]propyl]-3-isoxazolidinehexanoate (12). According to the procedure described for protection of the hydroxyl group in **7**, treatment of isoxazolidine **9** (444 mg, 0.93 mmol) with MEMCl (700 mg, 5.6 mmol) in the presence of $(i\text{-}Pr)_2NEt$ (2.4 g, 18.6 mmol) in CH_2Cl_2 (15 ml) gave the crude product. It was subjected to MCC ($CHCl_3/Et_2O$ 8 : 1) to afford **12** (346 mg, 66%) as a pale yellow oil. $[\alpha]_D$ – 59 (*c* 2.76, MeOH). IR ($CHCl_3$) 1732 (COO) cm^{-1}. ^1H NMR δ (300 MHz) 7.33–7.15 (5H, m, ArH), 4.87 and 4.80 (2H, ABq, J = 7 Hz, OCH_2O), 4.03 (1H, br q, J = 6.5 Hz, 5-H), 3.87 and 3.79 (2H, ABq, J = 13.5 Hz, CH_2Ph), 3.89 (1H, qd, J = 6, 3.5 Hz, 2''-H), 3.79–3.62 (2H, m, OCH_2CH_2O), 3.63 (3H, s, CO_2Me), 3.56 (1H, dd, J = 5, 3.5 Hz, 1''-H), 3.52 (2H, t, J = 4.5 Hz, OCH_2CH_2O), 3.36 (3H, s, OMe), 2.77 (1H, m, 3-H), 2.41 (1H, dt, J = 12, 7.5 Hz, 4-H), 2.24 (2H, t, J = 7.5 Hz, 5'-H_2), 1.91 (1H, ddd, J = 12, 8, 6 Hz, 4-H), 1.64–1.43 (4H, m, 1', 4'-H_2), 1.38–1.16 (4H, m, 2', 3'-H_2), 1.09 (3H, d, J = 6 Hz, 2''-Me), 0.83 (9H, s, tBu), 0.00 (6H, s, $SiMe_2$). HRMS calcd for $C_{30}H_{53}NO_7Si$ (M^+): 567.3588. Found: 567.3587.

Methyl [3*R*,5*S*(*S*,*R*)]-(−)-2-benzyl-5-[2-hydroxy-1-[(2-methoxyethoxy)methoxy]propyl]-3-isoxazolidinehexanoate (15). According to the procedure described for the synthesis of **13**, treatment of isoxazolidine **12** (130 mg, 0.23 mmol) with TBAF (1.0 M in THF) (0.35 ml, 0.35 mmol) in THF (6 ml) gave the crude product. It was subjected to SCC (AcOEt/hexane 1 : 3 and AcOEt/hexane 1 : 1) to give **15** (86 mg, 82%) as a pale yellow oil. $[\alpha]_D$ − 45 (*c* 1.46, MeOH). IR ($CHCl_3$) 3461 (OH) and 1731 (COO) cm^{-1}. ^1H NMR δ (300 MHz) 7.35–7.23 (5H, m, ArH), 4.86 and 4.81 (2H, ABq, *J* = 7 Hz, OCH_2O), 4.04 (1H, br q, *J* = 6 Hz, 5-H), 3.92 (1H, m, 2"-H), 3.92 and 3.84 (2H, ABq, *J* = 13.5 Hz, CH_2Ph), 3.85 and 3.71 (each 1H, m, OCH_2CH_2O), 3.67 (3H, s, CO_2Me), 3.62 (1H, dd, *J* = 5.5, 3 Hz, 1"-H), 3.57 (2H, t, *J* = 4.5 Hz, OCH_2CH_2O), 3.39 (3H, s, OMe), 3.08 (1H, br s, OH), 2.83 (1H, m, 3-H), 2.39 (1H, dt, *J* = 12, 7 Hz, 4-H), 2.28 (2H, t, *J* = 7.5 Hz, 5'-H_2), 2.01 (1H, ddd, *J* = 12, 8, 6 Hz, 4-H), 1.65–1.51 (4H, m, 1', 4'-H_2), 1.40–1.23 (4H, m, 2', 3'-H_2), 1.16 (3H, d, *J* = 6.5 Hz, 2"-Me). HRMS calcd for $C_{24}H_{39}NO_7$ (M^+): 453.2725. Found: 453.2718.

Methyl (2*S*,3*R*,4*S*,6*R*)-(+)-4-hydroxy-3-[(2-methoxyethoxy)methoxy]-2-methyl-6-piperidinehexanoate (24). According to the procedure described for mesylation of **13**, treatment of isoxazolidine **15** (167 mg, 0.37 mmol) with MsCl (85 mg, 0.74 mmol) in pyridine (2.2 ml) gave the crude product. It was subjected to SCC (AcOEt/hexane 1 : 1) to give mesylate **18** (187 g, 95%) as an oil; ^1H NMR δ (300 MHz) 7.42–7.22 (5H, m, ArH), 4.96 (1H, qd, *J* = 6.5, 2.5 Hz, 2"-H), 4.90–4.81 (2H, m, OCH_2O), 4.05 (1H, br q, *J* = 6.5 Hz, 5-H), 3.94 and 3.84 (2H, ABq, *J* = 13.5 Hz, CH_2Ph), 3.87 (1H, dd, *J* = 6, 2.5 Hz, 1"-H), 3.79–3.73 and 3.60–3.52 (each 2H, m, OCH_2CH_2O), 3.66 (3H, s, CO_2Me), 3.39 (3H, s, OMe), 2.99 (3H, s, Ms), 2.85 (1H, m, 3-H), 2.45 (1H, dt, *J* = 12, 7 Hz, 4-H), 2.28 (2H, t, *J* = 7.5 Hz, 5'-H_2), 2.05 (1H, dt, *J* = 12, 7.5 Hz, 4-H), 1.66–1.52 (4H, m, 1', 4'-H_2), 1.39 (3H, d, *J* = 6.5 Hz, 2"-Me), 1.40–1.22 (4H, m, 2', 3'-H_2). According to the procedure described for the synthesis of **22**, catalytic hydrogenation of mesylate **18** (187 mg, 0.35 mmol) in MeOH (12 ml) in the presence of 20% $Pd(OH)_2$-C (93 mg) gave a mixture of amino alcohol **21** and piperidinol **24**. The structure of **21** was characterized from ^1H NMR spectrum of the crude product; ^1H NMR δ (300 MHz) 4.93 (1H, qd, *J* = 6.5, 3 Hz, 11-H), 3.39 (3H, s, Ms), 1.46 (3H, d, *J* = 6.5 Hz, 11-Me). A solution of a mixture of **21** and **24** in MeOH (12 ml) and saturated $NaHCO_3$ solution (4.6 ml) was stirred at room temperature for 24 h. Work-up described for the synthesis of **22** gave **24** (122 mg, 98%) as an oil. $[\alpha]_D$ + 7 (*c* 1.02, MeOH). IR ($CHCl_3$) 3443 (OH) and 1732 (COO) cm^{-1}. ^1H NMR δ (500 MHz) 4.95 and 4.69 (2H, ABq, *J* = 7 Hz, OCH_2O), 3.94 and 3.69 (each 1H, m, OCH_2CH_2O), 3.67 (3H, s, CO_2Me), 3.58–3.55 (2H, m, OCH_2CH_2O), 3.53 (1H, ddd, *J* = 11, 5, 4 Hz, 4-H), 3.48 (1H, br s, $W_{1/2}$ = 5.5 Hz, 3-H), 3.39 (3H, s, OMe), 2.73 (1H, qd, *J* = 6.5, 1 Hz, 2-H), 2.54 (1H, m, 6-H), 2.30 (2H, t, *J* = 7.5 Hz, 5'-H_2), 1.76 (1H, br dt, *J* = 12, 3 Hz, 5-Heq), 1.68–1.28 (8H, m, 1'–4'-H_2), 1.23 (1H, br q, *J* = 12 Hz, 5-Hax), 1.12 (3H, d, *J* = 6.5 Hz, 2-Me). HRMS (CI, isobutane) calcd for $C_{17}H_{33}NO_6$ +H(QM^+): 348.2384. Found: 348.2373.

Methyl (2*S*,3*S*,6*R*)-(+)-3-[(2-methoxyethoxy)methoxy]-2-methyl-6-piperidinehexanoate (25). Preparation from piperidinol **22**: A solution of piperidinol **22** (125 mg, 0.36 mmol) and thiocarbonyldiimidazole (128 mg, 0.72 mmol) in THF (2 ml) was heated to reflux for 4 h, and the solvent was evaporated. ^{1}H NMR spectrum of the crude reaction mixture indicated that **22** was converted completely to the corresponding thioester; ^{1}H NMR δ (300 MHz) 5.82 (1H, q, J = 3 Hz, 4-H). To a solution of Bu_3SnH (314 mg, 1.08 mmol) in refluxing toluene (23 ml) was added dropwise slowly a solution of the crude product in toluene (6 ml) and the mixture was heated to reflux for 4 h. The solvent was evaporated and the residue was diluted with MeCN. The MeCN layer was extracted with hexane for removal of stannyl compound. The MeCN layer was concentrated and subjected to SCC (AcOEt/MeOH 9 : 1) to give **25** (97 mg, 82%) as an oil. $[\alpha]_D$ + 18 (c 1.92, MeOH). IR ($CHCl_3$) 3420 (OH) and 1731 (COO) cm^{-1}. ^{1}H NMR δ (500 MHz) 4.80 and 4.73 (2H, ABq, J = 7 Hz, OCH_2O), 3.81–3.68 and 3.57–3.53 (each 2H, m, OCH_2CH_2O), 3.66 (3H, s, CO_2Me), 3.63 (1H, m, $W_{1/2}$ = 6 Hz, 3-H), 3.39 (3H, s, OMe), 2.92 (1H, br q, J = 5.5 Hz, 2-H), 2.68 (1H, m, 6-H), 2.08 (1H, br dq, J = 13.5, 4.5 Hz, 4-Heq), 1.67–1.59 (4H, m, 1', 4'-H_2), 1.55 (1H, m, 5-Heq), 1.51–1.39 (1H, m, 4-Hax, 5-Hax), 1.39–1.27 (4H, m, 2', 3'-H_2), 1.24 (3H, d, J = 6.5 Hz, 2-Me). HRMS (CI, isobutane) calcd for $C_{17}H_{33}NO_5$ +H (QM^+): 332.2435. Found: 332.2406.

Preparation from piperidinol **24:** According to the procedure described above, treatment of piperidinol **24** (60 mg, 0.17 mmol) and thiocarbonyldiimidazole (61 mg, 0.34 mmol) in THF (1 ml) gave the crude thioester; ^{1}H NMR δ (300 MHz) 5.63 (1H, ddd, J = 12, 4.5, 3 Hz, 4-H). To a solution of Bu_3SnH (76 mg, 0.26 mmol) in refluxing toluene (13 ml) was added dropwise slowly a solution of the crude product in toluene (3 ml) and the mixture was heated to reflux for 5 h. Work-up described above gave **25** (45 mg, 81%). ^{1}H NMR spectra and R_f value of **25** were identical with those of **25** prepared from **22**.

Methyl (2*S*,3*S*,6*R*)-3-hydroxy-2-methyl-6-piperidinehexanoate (26). To a solution of **25** (130 mg, 0.39 mmol) in CH_2Cl_2 (1.4 ml) was added $TiCl_4$ (223 mg, 1.17 mmol) at 0 °C and the mixture was stirred at the same temperature for 4 h. The reaction mixture was washed with saturated $NaHCO_3$ solution, and the organic layer was dried and concentrated and the residue was subjected to PTLC (CH_2Cl_2/MeOH/28% NH_4OH 9 : 1 : 0.04) to give **26** (95 mg, 81%) as an oil. ^{1}H NMR δ (300 MHz) 3.69 (3H, s, CO_2Me), 3.61 (1H, m, $W_{1/2}$ = 6.5 Hz, 3-H), 2.84 (1H, qd, J = 6.5, 1.5 Hz, 2-H), 2.61 (1H, m, 6-H), 2.31 (2H, t, J = 7 Hz, 5'-H_2), 1.94 (1H, br dq, J = 10.5, 3 Hz, 4-Heq), 1.69–1.24 (11H, m, 4-Hax, 5-H_2, 1"–4"-H_2), 1.18 (3H, d, J = 6.5 Hz, 2-Me). HRMS calcd for $C_{13}H_{25}NO_3$ (M^+): 243.1833. Found: 243.1840.

26•Hydrochloride; a powder, mp 160-161 °C {lit.[4] mp 164°C [(+)-methyl azimate•hydrochloride], lit.[12a] mp 153–155°C [(±)-methyl azimate•hydrochloride]}. IR (nujol) 3344 (OH) and 1732 (COO) cm^{-1}. ^{1}H NMR δ (500 MHz, D_2O) 3.99 (1H, m, $W_{1/2}$ = 6 Hz, 3-H), 3.70 (3H, s, CO_2Me), 3.32 (1H, qd, J = 6.5, 1.5 Hz, 2-H), 3.15 (1H, m, 6-H), 2.41 (2H, t, J = 7.5 Hz, 5'-H_2), 1.99 (1H, dq, J = 14, 3 Hz, 4-Heq), 1.89 (1H, dq, J = 14, 3.5 Hz, 5-Heq), 1.77 (1H, tdd, J = 14, 4, 2.5 Hz, 4-Hax), 1.71–1.55 (5H, m, 5-Hax, 1', 4'-H_2), 1.49–1.31 (4H, m, 2', 3'-H_2), 1.30 (3H, d, J = 6.5 Hz, 2-Me). HRMS calcd for $C_{13}H_{25}NO_3$ (M^+ – HCl): 243.1833. Found: 243.1849. The IR and ^{1}H NMR spectra of **26**•hydrochloride were found to be identical with those of methyl azimate•hydrochloride obtained from natural azimine[4] and synthetic racemate.[12a]

(+)-Azimic acid (1). A solution of **26** (4.7 mg, 0.02 mmol) in 10% KOH-MeOH (0.1 ml) was stirred at room temperature for 20 h. The reaction mixture was acidified to pH 6-7 with 1% HCl and concentrated. The residue was dissolved in MeOH and the insoluble material was filtered off. The filtrate was concentrated to give **1** in quantitative yield as a powder (MeOH), mp 217 °C (dec.). $[\alpha]_D$ + 7.4 (c 0.52, MeOH). [lit.[12b]

mp 214–215 °C. $[\alpha]_D$ + 8 (MeOH), lit.[12e] mp 210-214 °C (dec.), $[\alpha]_D$ + 7.9 (*c* 1.0, MeOH)]. IR (nujol) 1649, 1555 (COO^- and NH_2^+) cm^{-1}. ^1H NMR δ (500 MHz, CD_3OD) 3.87 (1H, m, $W_{1/2}$ = 7 Hz, 3-H), 3.24 (1H, qd, *J* = 6.5, 1.5 Hz, 2-H), 3.05 (1H, m, 6-H), 2.21 (2H, t, *J* = 7 Hz, 5'-H_2), 1.95 (1H, m, 4-Heq), 1.84–1.22 (11H, m, 4-Hax, 5-H_2, 1'–4'-H_2), 1.33 (3H, d, *J* = 6.5 Hz, 2-Me). HRMS calcd for $C_{12}H_{23}NO_3$ (M^+): 229.1677. Found: 229.1689. The IR and ^{1}H NMR spectra of **1** were found to be identical with those of synthetic azimic acid **1**.[12]

13-(Benzoyloxy)tridecanol (27). To a solution of 1,13-tridecadiol[23] (4.04 g, 18.7 mmol) and Et_3N (2.25g, 22 mmol) in CH_2Cl_2 (170 ml) was added dropwise a solution of benzoyl chloride (2.67 g, 19 mmol) in CH_2Cl_2 (20 ml) at room temperature, and the mixture was stirred at the same temperature for 24 h. After evaporation of the solvent, the residue was diluted with Et_2O. The organic layer was washed, dried and concentrated. The residue was subjected to FCC (AcOEt/hexane 1 : 4) to gave **27** (3.23 g, 54%) as crystals, mp 40–41 °C (hexane). IR ($CHCl_3$) 3628 (OH) and 1713(COO) cm^{-1}. ^1H NMR δ (200 MHz) 8.05 (2H, br d, *J* = 7 Hz, ArH), 7.55 (1H, br t, *J* = 7 Hz, ArH), 7.44 (2H, br t, *J* = 7 Hz, ArH), 4.32 (2H, t, *J* = 6.5 Hz, CH_2OCO), 3.64 (2H, t, *J* = 6.5 Hz, CH_2OH), 1.76 (2H, br quint., *J* = 6.5 Hz, CH_2CH_2OCO), 1.56 (2H, br quint., *J* = 6.5 Hz, CH_2CH_2OH), 1.43–1.27 (19H, m, OH and $(CH_2)_9$). HRMS calcd for $C_{20}H_{32}O_3$ (M^+): 320.2350. Found: 320.2330.

(*Z*)-*N*-[13-(Benzoyloxy)tridecanylidene]benzylamine *N*-oxide (29). To a suspension of PCC (7.91g, 36.7 mmol) and AcONa (5.47 g, 66.7 mmol) in CH_2Cl_2 (300 ml) was added dropwise a solution of alcohol **27** (5.35 g, 16.7 mmol) in CH_2Cl_2 (100 ml) at room temperature, and the mixture was stirred at the same temperature for 2 h. After evaporation of the solvent, the residue was suspended with Et_2O and filtered through Celite. The filtrate was concentrated to give unstable aldehyde **28**; ^1H NMR δ (200 MHz) 9.78 (1H, t, *J* = 2 Hz, CHO), 4.32 (2H, t, *J* = 7 Hz, CH_2OCO), 2.40 (2H, td, *J* = 6, 2 Hz, CH_2CHO). To a stirred mixture of the crude aldehyde **28** (4.99 g, 15.7 mmol) and molecular sieves 4Å (8.8 g) in toluene (90 ml) was added *N*-benzylhydroxylamine[11] (1.93 g, 15.7 mmol). After stirring at room temperature for 2 h, molecular sieves were filtered off. The filtrate was concentrated to give nitrone **29** (3.41 g, 48%) as crystals, mp 87–88.5 °C (Et_2O). IR($CHCl_3$) 1713(COO) and 1602(C=N) cm^{-1}. ^1H NMR δ (200 MHz) 8.04 (2H, br d, *J* = 7 Hz, ArH), 7.59–7.39 (8H, m, ArH), 6.63 (1H, t, *J* = 6 Hz, CH=N), 4.89 (2H, s, CH_2Ph), 4.32 (2H, *J* = 7 Hz, CH_2OCO), 2.48 (2H, br q, *J* = 6 Hz, CH_2CH=N), 1.76 (2H, br quint., *J* = 7 Hz, CH_2CH_2OCO), 1.47–1.25 (18H, m, $(CH_2)_9$). HRMS calcd for $C_{27}H_{37}NO_3$ (M^+): 423.2771. Found: 423.2788.

Cycloaddition of nitrone 29 to olefin (+)-6. A solution of nitrone **29** (3.5 g, 8 mmol) and olefin (+)-**6**[$[\alpha]_D$ + 28 (*c* 2.0, MeOH)] (1.4 g, 6.38 mmol) in toluene (170 ml) was heated to reflux for 48 h. The solvent was evaporated and the residue was subjected to FCC and MCC (AcOEt/hexane 1 : 8) to give adducts **30** (0.8 g, 19%), **31** (1.3 g, 31%) and **32** (0.3 g, 7%). **[3*S*,5*S* (*R*,*S*)]-(+)-3-[12-(Benzoyloxy)-dodecanyl)]-2-benzyl-α-[1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-5-isoxazolidinemethanol (30)**; a pale yellow oil. $[\alpha]_D$ + 56 (*c* 1.15, MeOH). IR ($CHCl_3$) 1713 (COO) cm^{-1}. ^1H NMR δ (300 MHz) 8.08 (2H, br d, *J* = 8 Hz, ArH), 7.59 (1H, br t, *J* = 8 Hz, ArH), 7.45 (2H, br t, *J* = 8 Hz, ArH), 7.40–7.21 (5H, m, ArH), 4.43 (1H, m, 5-H), 4.34 (2H, br t, *J* = 6 Hz, CH_2OCO), 4.05 and 3.71 (2H, ABq, *J* = 12 Hz, CH_2Ph), 3.67 (1H, br s, OH), 3.58 (1H, m, 2"-H), 3.10 (1H, m, 1"-H), 2.77 (1H, m, 3-H), 2.58

(1H, dt, J = 10, 7 Hz, 4-H), 2.08 (1H, ddd, J = 10, 7, 4 Hz, 4-H), 1.79 (2H, br quint., J = 6 Hz, CH_2CH_2OCO), 1.66–1.24 (20H, m, $(CH_2)_{10}$), 1.20 (3H, d, J = 6 Hz, 2"-Me), 0.87 (9H, s, tBu), 0.00 (6H, s, $SiMe_2$). HRMS calcd for $C_{38}H_{61}NO_5Si$ (M^+): 639.4316. Found: 639.4311. **[3*R*,5*S*(*R*,*S*)]-(–)-3-[12-(Benzoyloxy)dodecanyl]-2-benzyl-α-[1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-5-isoxazolidinemethanol (31)**; a pale yellow oil. $[\alpha]_D$ – 30 (*c* 1.7, MeOH). IR ($CHCl_3$) 1715 (COO) cm^{-1}. ^1H NMR δ (300 MHz) 8.05 (2H, br d, J = 8 Hz, ArH), 7.55 (1H, br t, J = 8 Hz, ArH), 7.42 (2H, br t, J = 8 Hz, ArH), 7.40–7.20 (5H, m, ArH), 4.31 (2H, br t, J = 6 Hz, CH_2OCO), 4.25 (1H, m, 5-H), 4.01 and 3.82 (2H, ABq, J = 13.5 Hz, CH_2Ph), 3.62 (1H, m, 2"-H), 3.21 (1H, br td, J = 7, 4 Hz, 1"-H), 2.78 (1H, m, 3-H), 2.32 (1H, dt, J = 12, 7 Hz, 4-H), 2.13 (1H, br s, OH), 2.07 (1H, m, 4-H), 1.76 (2H, br quint., J = 6 Hz, CH_2CH_2OCO), 1.65–1.20 (20H, m, $(CH_2)_{10}$), 1.19 (3H, d, J = 6 Hz, 2"-Me), 0.87 (9H, s, tBu), 0.00 (6H, s, $SiMe_2$). HRMS calcd for $C_{38}H_{61}NO_5Si$ (M^+): 639.4316. Found: 639.4322. **[3*S*,5*S*(*R*,*S*)]-(+)-3-[12-(Benzoyloxy)dodecanyl]-2-benzyl-α-[1-[(*tert*-butyldimethylsilyl)-oxy]ethyl]-5-isoxazolidinemethanol (32)**; a pale yellow oil. $[\alpha]_D$ + 32 (*c* 2.75, MeOH). IR ($CHCl_3$) 1715 (COO) cm^{-1}. ^1H NMR δ (300 MHz) 8.00 (2H, br d, J = 8 Hz, ArH), 7.48 (1H, br t, J = 8 Hz, ArH), 7.38 (2H, br t, J = 8 Hz, ArH), 7.32–7.18 (5H, m, ArH), 4.25 (2H, br t, J = 6 Hz, CH_2OCO), 4.00 (1H, m, 5-H), 3.92–3.70 (3H, m, 2”-H, CH_2Ph), 3.49 (1H, br t, J = 5.5 Hz, 1"-H), 2.77 (1H, m, 3-H), 2.34 (1H, dt, J = 12, 7 Hz, 4-H), 2.22 (1H, br s, OH), 1.95 (1H, br dt, J = 12, 7 Hz, 4-H), 1.70 (2H, br quint., J = 6 Hz, CH_2CH_2OCO), 1.60–1.10 (20H, m, $(CH_2)_{10}$), 1.06 (3H, d, J = 6 Hz, 2"-Me), 0.82 (9H, s, tBu), 0.00 (6H, s, $SiMe_2$). HRMS calcd for $C_{38}H_{61}NO_5Si$ (M^+): 639.4316. Found: 639.4308.

[3*R*,5*S*(*R*,*S*)]-(–)-3-[12-(Benzoyloxy)dodecanyl]-2-benzyl-5-[2-[(*tert*-butyldimethylsilyl)-oxy]-1-[(methoxymethoxy)propyl]]isoxazolidine (33). A solution of isoxazolidine **31** (727 mg, 1.14 mmol), MOMCl (275 mg, 3.4 mmol) and (i-Pr)$_2$NEt (1.8 g, 14 mmol) in CH_2Cl_2 (7 ml) was heated to reflux for 10 h. Then after another MOMCl (275 mg, 3.4 mmol) and (i-Pr)$_2$NEt (1.8 g, 14 mmol) were added and the mixture was heated to reflux for a further 20h. The reaction mixture was diluted with CH_2Cl_2, and then washed subsequently with 15% acetic acid, saturated $NaHCO_3$ solution and brine, and the organic layer was dried and concentrated. The residue was subjected to FCC (AcOEt/hexane 1 : 8) to give **33** (648 mg, 82%) as a pale yellow oil. $[\alpha]_D$ – 34 (*c* 2.35, MeOH). IR ($CHCl_3$) 1715 (COO) cm^{-1}. ^1H NMR δ (300 MHz) 8.03 (2H, br d, J = 8 Hz, ArH), 7.52 (1H, br t, J = 8 Hz, ArH), 7.42 (2H, br t, J = 8 Hz, ArH), 7.38–7.20 (5H, m, ArH), 4.79 and 4.74 (2H, ABq, J = 7 Hz, OCH_2O), 4.30 (2H, t, J = 7 Hz, CH_2OCO), 4.05 (1H, m, 5-H), 3.93 and 3.86 (2H, ABq, J = 13.5 Hz, CH_2Ph), 3.83 (1H, m, 2"-H), 3.45 (1H, br dd, J = 6, 4 Hz, 1"-H), 3.35 (3H, s, OMe), 2.81 (1H, m, 3-H), 2.21 (1H, br dt, J = 12, 8 Hz, 4-H), 1.90 (1H, m, 4-H), 1.74 (2H, br quint., J = 7 Hz, CH_2CH_2OCO), 1.60–1.20 (20H, m, $(CH_2)_{10}$), 1.14 (3H, d, J = 6 Hz, 2"-Me), 0.87 (9H, s, tBu), 0.00 (6H, s, $SiMe_2$). HRMS calcd for $C_{40}H_{65}NO_6Si$ (M^+): 683.4578. Found: 683.4575.

[3*R*,5*S*(*R*,*S*)]-3-[12-(Benzoyloxy)dodecanyl]-2-benzyl-α-(methoxymethoxy)-β-methyl-5-isoxazolidineethanol (34). According to the procedure described for the synthesis of **13**, treatment of isoxazolidine **33** (1.02 g, 1.5 mmol) with TBAF (1.0 M in THF)(1.6 ml, 1.6 mmol) in THF (41 ml) gave the crude product which was subjected to SCC (AcOEt/hexane 1 : 3 and AcOEt/hexane 2 : 3) to give **34** (604 mg, 71%) as a pale yellow oil. IR ($CHCl_3$) 1713 (COO) cm^{-1}. ^1H NMR δ (300 MHz) 8.08 (2H, br d, J = 8

Hz, ArH), 7.57 (1H, br t, *J* = 8 Hz, ArH), 7.45 (2H, br t, *J* = 8 Hz, ArH), 7.43–7.20 (5H, m, ArH), 4.76 and 4.73 (2H, ABq, *J* = 8 Hz, OCH_2O), 4.32 (2H, br t, *J* = 6 Hz, CH_2OCO), 4.18 (1H br q, *J* = 9 Hz, 5-H), 3.98 and 3.88 (2H, ABq, *J* = 13 Hz, CH_2Ph), 3.85 (1H, m, 2"-H), 3.50 (1H, br dd, *J* = 8, 5 Hz, 1"- H), 3.42 (3H, s, OMe), 3.08 (1H, br s, OH), 2.88 (1H, m, 3-H), 2.27 (1H, dt, *J* = 12, 7 Hz, 4-H), 1.95 (1H, m, 4-H), 1.80–1.20 (22H, m, $(CH_2)_{11}$), 1.19 (3H, d, *J* = 6 Hz, 2"-Me). HRMS calcd for $C_{34}H_{51}NO_6Si$ (M^+): 569.3714. Found: 569.3724.

(2*R*,3*S*,4*S*,6*R*)-(+)-6-[12-(Benzoyloxy)dodecanyl]-3-(methoxymethoxy)-2-methyl-4-piperidinol (36). According to the procedure described for mesylation of **13**, treatment of isoxazolidine **34** (192 mg, 0.34 mmol) with $ClCH_2SO_2Cl$ (284 mg, 0.5 mmol) in pyridine (2 ml) at 0 °C for 2h gave quaternary salt **35**; ^1H NMR δ (200 MHz) 5.78 and 4.66 (2H, ABq, *J* = 14.5 Hz, CH_2Ph), 4.60 and 4.54 (2H, ABq, *J* = 8 Hz, OCH_2O), 4.32(2H, br t, *J* = 7 Hz, CH_2OCO), 4.18 (1H, br q, *J* = 9 Hz, 5-H), 4.38 (2H, s, SCH_2Cl), 3.35 (3H, s, OMe), 1.67 (3H, d, *J* = 7 Hz, 2"-Me). A solution of crude quaternary salt **35** in MeOH (8 ml) was catalytically hydrogenated over 20% $Pd(OH)_2$-C (100 mg) under a hydrogen atmosphere at room temperature. After 10 h, another 20% $Pd(OH)_2$-C (100 mg) was carefully added and the mixture was stirred for a further 5 h. Then the catalyst was filtered off and the filtrate was concentrated. The residue was made alkaline with 1M NaOH solution under ice-cooling and the whole was extracted with CH_2Cl_2. The extract was washed with brine, dried and evaporated and the residue was subjected to SCC (AcOEt and MeOH/AcOEt 5 : 95) to afford piperidine **36** (122 mg, 77%) as an oil. $[\alpha]_D$ + 6 (*c* 1.32, MeOH). IR ($CHCl_3$) 1713 (COO) cm^{-1}. ^1H NMR δ (300 MHz) 8.04 (2H, br d, *J* = 8 Hz, ArH), 7.54 (1H, br t, *J* = 8 Hz, ArH), 7.45 (2H, br t, *J* = 8 Hz, ArH), 4.73 (2H, s, OCH_2O), 4.31 (2H, t, *J* = 6 Hz, CH_2OCO), 3.75 (1H, ddd, *J* = 11, 9, 5 Hz, 4-H), 3.50–3.35 (2H, m, 5, 6-H), 3.43 (3H, s, OMe), 2.85 (1H, m, 6-H), 2.06 (1H, ddd, *J* = 13, 5, 3 Hz, 3-Heq), 1.76 (2H, quint, CH_2CH_2OCOAr), 1.50–1.20 (20H, m, $(CH_2)_{10}$), 1.16 (3H, d, *J* = 7 Hz, 2-Me), 1.10 (1H, q, *J* = 12 Hz, 3-Hax). HRMS calcd for $C_{27}H_{45}NO_5$ (M^+):463.3295. Found: 463.3287.

(2*R*,3*R*,6*R*)-6-[12-(Benzoyloxy)dodecanyl]-3-(methoxymethoxy)-2-methylpiperidine (37). According to the procedure described for thiocarbonylation of **22**, a solution of piperidinol **36** (161 mg, 0.35 mmol) and thiocarbonyldiimidazole (123 mg, 0.7 mmol) in THF (2 ml) was heated at 60°C for 4 h. ^1H NMR spectrum of the crude product indicated that **36** was converted completely to the corresponding thioester; ^1H NMR δ (300 MHz) 5.75 (1H, br td, *J* = 10, 7 Hz, 4-H). To a solution of Bu_3SnH (304 mg, 1.04 mmol) in refluxing toluene (19 ml) was added dropwise slowly a solution of the crude product in toluene (10 ml) and the mixture was heated to reflux for 5 h. Work-up described for the synthesis of **25** gave **37** (115 mg, 74%) after SCC ($MeOH/CH_2Cl_2$ 5 : 95) as an oil. IR ($CHCl_3$) 1713 (COO) cm^{-1}. ^1H NMR δ (300 MHz) 8.04 (2H, br d, *J* = 8 Hz, ArH), 7.57 (1H, br t, *J* = 8 Hz, ArH), 7.45 (2H, br t, *J* = 8 Hz, ArH), 4.70 and 4.64 (2H, ABq, *J* = 8 Hz, OCH_2O), 4.32 (2H, t, *J* = 6 Hz, CH_2OCO), 3.69 (1H, br dt, *J* = 9, 4 Hz, 3-H), 3.37 (3H, s, OMe), 3.29 (1H, m, 2-H), 2.81 (1H, m, 6-H), 2.20–1.20 (27H, NH, 4-H_2, 5-H_2, $(CH_2)_{11}$), 1.18 (3H, d, *J* = 7 Hz, 2-Me). HRMS calcd for $C_{27}H_{45}NO_4$ (M^+): 447.3334. Found: 447.3346.

(+)-Julifloridine (2). A solution of piperidine **37** (50 mg, 0.11 mmol) in MeOH (3 ml) and 10% KOH solution (0.5 ml) was stirred at room temperature for 2 h. The solvent was evaporated and the residue was diluted with CH_2Cl_2. The organic layer was washed, dried and concentrated to give a crude product. ^{1}H NMR spectrum of the crude product indicated that **37** was converted completely to the corresponding alcohol; ^{1}H NMR δ (300 MHz) 4.69 and 4.63 (2H, ABq, *J* = 8 Hz, OCH_2O), 3.67 (1H, m, 3-H), 3.62 (2H, t, *J* = 6 Hz, CH_2OCO), 3.36 (3H, s, OMe), 3.25 (1H, m, 2-H), 2.75 (1H, m, 6-H), 1.12 (3H, d, *J* = 7 Hz, 2-Me). To a solution of this crude product in MeOH (2 ml) was added conc. HCl (0.2 ml), and the mixture was stirred at room temperature for 2 h. After evaporation of the solvent, the residue was dissolved in H_2O and made alkaline with 10% NaOH solution under ice-cooling and the whole was extracted with CH_2Cl_2. The extract was dried and evaporated to give (+)-julifloridine (**2**) (22 mg, 66%) as crystals (Et_2O/AcOEt), mp 85–87.5 °C. $[\alpha]_D$ + 18 (*c* 0.84, MeOH). (lit.[6] mp 82–83 °C) ^{1}H NMR δ (300 MHz) 3.69 (1H, br dt, *J* = 8.5, 3.5 Hz, 3-H), 3.64 (2H, t, *J* = 7 Hz, CH_2OH), 3.14 (1H, qd, *J* = 6.5, 3 Hz, 2-H), 2.85 (1H, m, 6-H), 2.00–1.10 (26H, m, 4-H_2, 5-H_2, $(CH_2)_{11}$), 1.11 (3H, d, *J* = 6.5 Hz, 2-Me). ^{13}C NMR δ (75 MHz) 69.04, 63.04, 50.03, 49.74, 32.81, 32.73, 29.64–29.39, 27.57, 26.59, 25.72, 15.72. HRMS calcd for $C_{18}H_{37}NO_2$ (M^+): 299.2823. Found: 299.2808. The IR ^{1}H, and ^{13}C NMR spectra of **2** were found to be identical with those of natural julifloridine **2**.[6]

(2*R*,3*R*,6*R*)-(–)-6-(12-Hydroxydodecanyl)-1,2-dimethyl-3-piperidinol (3) (*N*-Methyl julifloridine). To a solution of **2** (22 mg, 0.74 mmol) and formalin (37%) (0.05 ml) in MeCN (0.3 ml) were added $NaCNBH_3$ (11 mg) and acetic acid (0.006 ml) at room temperature. After stirring at the same temperature for 2 h, the reaction mixture was concentrated and the residue was diluted with Et_2O. The organic layer was washed with saturated $NaHCO_3$ solution, dried and concentrated. The residue was subjected to PTLC (CH_2Cl_2/MeOH/NH_4OH 9 : 1 : 0.04) to afford *N*-methyl derivative **3** (18 mg, 78%) as crystals. $[\alpha]_D$ – 20 (*c* 0.6, $CHCl_3$). ^{1}H NMR δ (300 MHz) 3.73 (1H, br dt, *J* = 7, 3 Hz, 3-H), 3.63 (2H, t, *J* = 7 Hz, CH_2OH), 2.92 (1H, br qd, *J* = 7, 3 Hz, 2-H), 2.59 (1H, m, 6-H), 2.35 (3H, s, NMe), 1.98–1.10 (26H, m, 4-H_2, 5-H_2, $(CH_2)_{11}$), 1.07 (3H, d, *J* = 7 Hz, 2-Me). ^{13}C NMR δ (75 MHz) 69.23, 62.99, 58.15, 57.88, 39.33, 32.80, 29.88–29.42, 26.95, 26.68, 25.75, 11.10. HRMS calcd for $C_{19}H_{39}NO_2$ (M^+): 313.2979. Found: 313.2961.

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