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TETRAHEDRON

Total Syntheses of (+)-Azimic Acid, (+)-Julifloridine, and Proposed Structure of N-Methyljulifloridine via Cycloaddition of Nitrone to a Chiral Dipolarophile¹

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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-piperidinols² 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 azimic⁴ 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 ¹H and ¹³C NMR spectral data, neither the interconversion nor total synthesis of 3 was reported. Considering this situation, we undertook to explore a general and



0040-4020/98/\$ - see front matter © 1998 Elsevier Science Ltd. All rights reserved. *PII*: S0040-4020(98)01012-6 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 nitrones⁹ has appeared to date. In continuation of our synthetic study¹⁰ 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 known¹¹ 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.



Total synthesis of (+)-azimic acid

There have been several examples¹² 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-benzylhydroxylamine¹⁵ according to the known method.¹⁶ The geometry of nitrone 5 was suggested to be Z-configuration by comparison of ¹H 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 rules¹⁸ in the ¹H 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

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 mediumpressure liquid chromatography (MPLC). The stereostructures of the adducts 7–9 were tentatively deduced from ¹H 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 study¹¹ 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 CH₂Cl₂ 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 Znitrone 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 NaHCO₃ in MeOH- H_2O^{21} underwent SN2 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 ¹H 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 Bu₃SnH via Barton's ester²² proceeded smoothly to give an identical piperidine 25 in 81-82% yield. Deprotection of the MEM group in 25 was achieved by treatment with TiCl₄ to give the piperidinol 26 in 81% yield {26•HCl; a powder, mp 160-161℃ {lit.⁴ mp 164 ℃ [(+)-methyl azimate•HCl], lit.^{12a} mp 153-155 ℃ [(±)-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, $(i-Pr)_2NEt$, CH_2Cl_2 , Δ ; b) $(n-Bu)_4NF$, THF, Δ ; c) MsCl, py., 0 °C; d) 20% Pd(OH)₂-C, MeOH, H₂; e) NaHCO₃, H₂O-MeOH; f) Im₂CS, THF; g) Bu₃SnH, toluene, Δ ; h) TiCl₄, CH₂Cl₂, 0 °C; i) KOH, MeOH.

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 ¹H 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 ¹H 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. Nakata²⁴ 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 ClCH₂SO₂Cl 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) PhCH₂NHOH, molecular sieves; c) toluene, Δ ; d) MOMC1, (*i*-Pr)₂NEt, CH₂Cl₂, Δ ; e) (*n*-Bu)₄NF, THF, Δ ; f) ClCH₂SO₂Cl, py., 0 °C; g) 20% Pd(OH)₂-C, MeOH, H₂; h) Im₂CS, THF; i) Bu₃SnH, toluene, Δ ; j) KOH, MeOH; k) HCl, MeOH; l) NaCNBH₃, HCHO, MeCN.

Deoxygenation of the piperidinol 36 via Barton's ester²² 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 NaCNBH₃ 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 ¹³C NMR spectra. Surprisingly, comparison of ¹H and ¹³C NMR spectra of synthetic piperidinol (-)-**3** with the reported data of natural *N*-methyljulifloridine⁷ 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 ¹³C 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-benzylhydroxylamine¹⁵ (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 (CHCl₃) 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, CH₂Ph), 3.64 (3H, s, CO₂Me), 2.47 (2H, br q, J = 7 Hz, 2-H₂), 2.27 (2H, t, J = 7 Hz, 6-H₂), 1.72–1.23 (6H, m, 3–5-H₂). Anal Calcd for C₁₅H₂₁NO₃: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.15; H, 8.10; N, 5.16.

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

[(tert-butyldimethylsily]oxy]propanal¹³ (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 NH₄Cl 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. $[\alpha]_D - 28 (c 2.0, MeOH)$. ¹H 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, SiMe₂). The minor isomer¹³ of 6; [(3R,4R)-4-[(tert-butyldimethylsily])-oxy]pent-1-en-3-ol], an oil. ¹H NMR δ (200 MHz) 5.23 (1H, ddd, J = 17, 12, 6 Hz, 2-H), 5.23 (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, dt, J = 5 Hz, OH), 1.07 (3H, d, J = 6 Hz, Me), 0.81 (9H, s, tBu), 0.00 (6H, s, SiMe₂). ¹H 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 [3R,5R (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 (CHCl₃) 3446 (OH) and 1731 (COO) cm⁻¹. ¹H 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, CH₂Ph), 3.69 (3H, s, CO₂Me), 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'-H₂), 2.06 (1H, ddd, J = 12, 7.5, 5 Hz, 4-H), 1.72–1.25 (8H, m, 1'–4'-H₂), 1.19 (3H, d, J = 6 Hz, 2"-Me), 0.87 (9H, s, tBu), 0.00 (6H, s, SiMe₂). HRMS Calcd for C₂₆H₄₅NO₅Si (M⁺): 479.3064. Found: 479.3062. Methyl [3S,5R(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 (CHCl₃) 3554 (OH) and 1731 (COO) cm⁻¹. ¹H NMR δ (300 MHz) 7.38–7.19 (5H, m, ArH), 4.23 (1H, m, 5-H), 3.99 and 3.82 $(2H, ABq, J = 13.5 Hz, CH_2Ph), 3.66 (3H, s, CO_2Me), 3.62 (1H, m, 2"-H), 3.21 (1H, td, J = 7.5, 3.5 Hz, CH_2Ph), 3.66 (3H, s, CO_2Me), 3.62 (1H, m, 2"-H), 3.21 (1H, td, J = 7.5, 3.5 Hz, CH_2Ph), 3.66 (3H, s, CO_2Me), 3.62 (1H, m, 2"-H), 3.21 (1H, td, J = 7.5, 3.5 Hz, CH_2Ph), 3.61 (1H, td, J = 7.5, 3.5 Hz, CH_2Ph)$ 1"-H), 2.80 (1H, m, 3-H), 2.28 (2H, t, J = 7.5 Hz, 5'-H₂), 2.07 (1H, m, 4-H), 2.00 (1H, dt, J = 12, 7 Hz, 4-H), 1.70–1.24 (8H, m, 1'–4'-H₂), 1.18 (3H, d, J = 6 Hz, 2"-Me), 0.87 (9H, s, tBu), 0.00 (6H, s, SiMe₂). HRMS calcd for $C_{26}H_{45}NO_5Si(M^+)$: 479.3064. Found: 479.3090. Methyl [3R,5S(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 (CHCl₃) 3566 (OH) and 1731 (COO)

cm⁻¹. ¹H 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, CH₂Ph), 3.82 (1H, br quint., J = 5.5 Hz, 2"-H), 3.60 (3H, s, CO₂Me), 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'-H₂), 1.95 (1H, ddd, J = 12, 8, 6.5 Hz, 4-H), 1.58–1.48 (4H, m, 1', 4'-H₂), 1.33–1.18 (4H, m, 2', 3'-H₂), 1.07 (3H, d, J = 6 Hz, 2"-Me), 0.87 (9H, s, tBu), 0.00 (6H, s, SiMe₂). HRMS calcd for C₂₆H₄₅NO₅Si (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 NH₄Cl 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 R_f values and ¹H NMR spectra.

Methyl [3R, 5R(S,R)]-(-)-2-benzyl-5-[2-[(tert-butyldimethylsilyl)oxy]-1-[(2-methoxy-

ethoxy)methoxy]propyl]-3-isoxazolidinehexanoate (10). A solution of 7 (1.40 g, 3 mmol), (*i*-Pr)₂NEt (7.8 g, 60 mmol) and MEMCl (6.2 g, 18 mmol) in CH₂Cl₂ (48 ml) was heated to reflux for 25 h. The reaction mixture was diluted with CH₂Cl₂, and then washed subsequently with 15% acetic acid, saturated NaHCO₃ 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 (CHCl₃) 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, OCH₂O), 4.12 (1H, br dt, J = 8.5, 7 Hz, 5-H), 3.87 and 3.81 (2H, ABq, J = 13 Hz, CH₂Ph), 3.78 (1H, qd, J = 6.5, 4 Hz, 2"-H), 3.75, 3.57, 3.52 and 3.35 (each 1H, m, OCH₂CH₂O), 3.62 (3H, s, CO₂Me), 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'-H₂), 1.66 (1H, br dt, J = 12, 8 Hz, 4-H), 1.56–1.49 (4H, m, 1', 4'-H₂), 1.34–1.15 (4H, m, 2', 3'-H₂), 1.11 (3H, d, J = 6.5 Hz, 2"-Me), 0.83 (9H, s, tBu), 0.00 (6H, s, SiMe₂). HRMS calcd for C₃₀H₅₃NO₇Si (M⁺): 567.3588. Found: 567.3604.

Methyl [3*R*, 5*R*(*S*, *R*)]-(-)-2-benzyl-5-[2-hydroxy-1-[(2-methoxyethoxy)methoxy]propyl]-3isoxazolidinehexanoate (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 (CHCl₃) 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, OCH₂O), 4.20 (1H, q, J = 7.5 Hz, 5-H), 3.93 and 3.87 (2H, ABq, J = 13 Hz, CH₂Ph), 3.77 and 3.62 (each 1H, m, OCH₂CH₂O), 3.75 (1H, br qd, J = 6.5, 3.5 Hz, 2"-H), 3.64 (3H, s, CO₂Me), 3.57 (1H, br dd, J = 7, 4 Hz, 1"-H), 3.52 (2H, t, J = 4.5 Hz, OCH₂CH₂O), 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'-H₂), 1.75 (1H, br dt, J = 12, 7 Hz, 4-H), 1.62–1.54 (4H, m, 1', 4'-H₂), 1.40–1.20 (4H, m, 2', 3'-H₂), 1.16 (3H, d, J = 6.5 Hz, 2"-Me). HRMS calcd for C₂₄H₃₉NO₇ (M⁺): 453.2725. Found: 453.2722.

Methyl (2S, 3R, 4R, 6R)-(-)-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 H₂O under ice-cooling and extracted with CH₂Cl₂. The extract was washed with saturated NaHCO₃ 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,

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qd, J = 6.5, 2.5 Hz, 2"-H), 4.69 and 4.62 (2H, ABq, J = 7 Hz, OCH₂O), 4.12 (1H, q, J = 7.5 Hz, 5-H), 3.92 and 3.80 (2H, ABq, J = 13 Hz, CH₂Ph), 3.84 (1H, dd, J = 7.5, 2.5 Hz, 1"-H), 3.73 and 3.54 (each 1H, m, OCH₂CH₂O), 3.67 (3H, s, CO₂Me), 3.49–3.44 (2H, m, OCH₂CH₂O), 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'-H₂). 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 CH₂Cl₂. 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 NaHCO3 solution (28 ml). After stirring at room temperature for 24 h, the reaction mixture was concentrated and diluted with CH2Cl2. The organic layer was washed, dried and concentrated. The residue was subjected to SCC (CH₂Cl₂/MeOH 9 : 1) to afford piperidinol 22 (660 mg, 89%) as an oil. $[\alpha]_D - 11$ (c 1.43, MeOH). IR (CHCl₃) 3402 (OH) and 1731 (COO) cm⁻¹. ¹H NMR δ (500 MHz) 4.83 and 4.73 (2H, ABq, J = 7 Hz, OCH₂O), 4.12 (1H, q, J = 3 Hz, 4-H), 3.77–3.69 and 3.58– 3.51 (each 2H, m, OCH₂CH₂O), 3.66 (3H, s, CO₂Me), 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'-H₂), 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'-H₂), 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 [3S, 5R(S,R)]-(+)-2-benzyl-5-[2-[(tert-butyldimethylsilyl)oxy]-1-[(2-methoxy-

ethoxy)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*-Pr)₂NEt (2.0 g, 15.4 mmol) in CH₂Cl₂ (13 ml) gave 11 (340 mg, 81%) as a pale yellow oil. $[\alpha]_D + 27 (c \ 1.17, MeOH)$. IR (CHCl₃) 1731 (COO) cm⁻¹. ¹H NMR δ (300 MHz) 7.40–7.15 (5H, m, ArH), 4.90–4.81 (2H, m, OCH₂O), 4.04 (1H, br q, J = 7 Hz, 5-H), 3.91 and 3.86 (2H, ABq, J = 13.5 Hz, CH₂Ph), 3.86–3.71 and 3.51–3.38 (each 2H, m, OCH₂CH₂O), 3.64 (3H, s, CO₂Me), 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'-H₂), 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'-H₂), 1.40–1.17 (4H, m, 2', 3'-H₂), 1.14 (3H, d, J = 6 Hz, 2"-Me), 0.84 (9H, s, tBu), 0.00 (6H, s, SiMe₂). HRMS calcd for C₃₀H₅₃NO₇Si (M⁺): 567.3588. Found: 567.3604.

Methyl [3S, 5R(S, R)]-(+)-2-benzyl-5-[2-hydroxy-1-[(2-methoxyethoxy)methoxy]propyl]-3isoxazolidinehexanoate (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 (CHCl₃) 3454 (OH) and 1731 (COO) cm⁻¹. ¹H NMR δ (300 MHz) 7.38–7.21 (5H, m, ArH), 4.83 (2H, s, OCH₂O), 4.12 (1H, br q, J = 7.5 Hz, 5-H), 3.92 (2H, s, CH₂Ph), 3.89–3.80 and 3.74–3.65 (each 2 H, m, OCH₂CH₂O), 3.79 (1H, dqd, J = 9, 6.5, 3 Hz, 2"-H), 3.66 (3H, s, CO₂Me), 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'-H₂), 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'-H₂), 1.42–1.21 (4H, m, 2', 3'-H₂), 1.17 (3H, d, J = 6.5 Hz, 2"-Me). HRMS calcd for C₂₄H₃₉NO₇ (M⁺): 453.2725. Found: 453.2724.

Methyl (2S, 3R, 4R, 6S) - (-)-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, OCH₂O), 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, CH₂Ph), 3.79 (1H, dd, J = 5.5, 4 Hz, 1"-H), 3.78-3.51 and 3.55-3.50 (each 2H, m, OCH₂CH₂O), 3.67 (3H, s, CO₂Me), 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'-H₂), 1.95 (1H, br ddd, J = 12, 7.5, 6 Hz, 4-H), 1.68–1.52 (4H, m, 1', 4'-H₂), 1.43 (3H, d, J = 6.5 Hz, 2"-Me), 1.42–1.23 (4H, m, 2', 3'-H₂). 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 NaHCO₃ solution (8 ml) was heated to reflux for 10 h. After evaporation of the solvent, the residue was diluted with CH₂Cl₂. 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 (CHCl₃) 3441 (OH) and 1731 (COO) cm⁻¹. ¹H NMR δ (500 MHz) 4.79 and 4.76 (2H, ABq, J = 7 Hz, OCH₂O), 3.80 and 3.69 (each 1H, m, OCH₂CH₂O), 3.71 (1H, ddd, J = 11, 8.5, 5 Hz, 4-H), 3.63 (3H, s, CO₂Me), 3.53 (2H, t, J = 4.5 Hz, OCH₂CH₂O), 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'-H₂), 2.03 (1H, ddd, J = 13, 5, 3 Hz, 5-Heq), 1.63-1.56 (4H, m, 1', 4'-H₂), 1.36-1.26 (4H, m, 2', 3'-H₂), 1.11 (3H, d, J = 7 Hz, 2-Me), 1.06 (1H, br dt, J = 7 Hz, 2-Me), 1.06 (1H 13, 11.5 Hz, 5-Hax). HRMS calcd for C₁₇H₃₃NO₆ (M⁺): 347.2306. Found: 347.2314.

Methyl [3R, 5S(S,R)]-(-)-2-benzyl-5-[2-[(tert-butyldimethylsilyl)oxy]-1-[(2-methoxy-

ethoxy)methoxy]propy]-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 $(i-Pr)_2NEt$ (2.4 g, 18.6 mmol) in CH₂Cl₂ (15 ml) gave the crude product. It was subjected to MCC (CHCl₃/Et₂O 8 : 1) to afford 12 (346 mg, 66%) as a pale yellow oil. $[\alpha]_D - 59$ (c 2.76, MeOH). IR (CHCl₃) 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, OCH₂O), 4.03 (1H, br q, J = 6.5 Hz, 5-H), 3.87 and 3.79 (2H, ABq, J = 13.5 Hz, CH₂Ph), 3.89 (1H, qd, J = 6, 3.5 Hz, 2"-H), 3.79–3.62 (2H, m, OCH₂CH₂O), 3.63 (3H, s, CO₂Me), 3.56 (1H, dd, J = 5, 3.5 Hz, 1"-H), 3.52 (2H, t, J = 4.5 Hz, OCH₂CH₂O), 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'-H₂), 1.91 (1H, ddd, J = 12, 8, 6 Hz, 4-H), 1.64–1.43 (4H, m, 1', 4'-H₂), 1.38–1.16 (4H, m, 2', 3'-H₂), 1.09 (3H, d, J = 6 Hz, 2"-Me),

0.83 (9H, s, tBu), 0.00 (6H, s, SiMe₂). 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]-3isoxazolidinehexanoate (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 (CHCl₃) 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, OCH₂O), 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, CH₂Ph), 3.85 and 3.71 (each 1H, m, OCH₂CH₂O), 3.67 (3H, s, CO₂Me), 3.62 (1H, dd, J = 5.5, 3 Hz, 1"-H), 3.57 (2H, t, J =4.5 Hz, OCH₂CH₂O), 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'-H₂), 2.01 (1H, ddd, J = 12, 8, 6 Hz, 4-H), 1.65–1.51 (4H, m, 1', 4'-H₂), 1.40–1.23 (4H, m, 2', 3'-H₂), 1.16 (3H, d, J = 6.5 Hz, 2"-Me). HRMS calcd for C₂₄H₃₉NO₇ (M⁺): 453.2725. Found: 453.2718.

Methyl (2S, 3R, 4S, 6R)-(+)-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, OCH₂O), 4.05 (1H, br q, J = 6.5 Hz, 5-H), 3.94 and 3.84 (2H, ABq, J = 13.5 Hz, CH₂Ph), 3.87 (1H, dd, J = 6, 2.5 Hz, 1"-H), 3.79-3.73 and 3.60-3.52 (each 2H, m, OCH₂CH₂O), 3.66 (3H, s, CO₂Me), 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'-H₂), 2.05 (1H, dt, J = 12, 7.5 Hz, 4-H), 1.66–1.52 (4H, m, 1', 4'-H₂), 1.39 (3H, d, J = 6.5 Hz, 2"-Me), 1.40-1.22 (4H, m, 2', 3'-H₂). 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 ${}^{1}H$ 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 NaHCO3 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 (CHCl₃) 3443 (OH) and 1732 (COO) cm⁻¹. ¹H NMR δ (500 MHz) 4.95 and 4.69 (2H, ABq, J = 7 Hz, OCH₂O), 3.94 and 3.69 (each 1H, m, OCH₂CH₂O), 3.67 (3H, s, CO₂Me), 3.58-3.55 (2H, m, OCH₂CH₂O), 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'-H₂), 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 (2S, 3S, 6R)-(+)-3-[(2-methoxy)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. ¹H NMR spectrum of the crude reaction mixture indicated that **22** was converted completely to the corresponding thioester; ¹H NMR δ (300 MHz) 5.82 (1H, q, J = 3 Hz, 4-H). To a solution of Bu₃SnH (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. [α]_D + 18 (c 1.92, MeOH). IR (CHCl₃) 3420 (OH) and 1731 (COO) cm⁻¹. ¹H NMR δ (500 MHz) 4.80 and 4.73 (2H, ABq, J = 7 Hz, OCH₂O), 3.81–3.68 and 3.57–3.53 (each 2H, m, OCH₂CH₂O), 3.66 (3H, s, CO₂Me), 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'-H₂), 1.55 (1H, m, 5-Heq), 1.51–1.39 (1H, m, 4-Hax, 5-Hax), 1.39–1.27 (4H, m, 2', 3'-H₂), 1.24 (3H, d, J = 6.5 Hz, 2-Me). HRMS (CI, isobutane) calcd for C₁₇H₃₃NO₅ +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; ¹H NMR δ (300 MHz) 5.63 (1H, ddd, J = 12, 4.5, 3 Hz, 4-H). To a solution of Bu₃SnH (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%). ¹H NMR spectra and R_f value of 25 were identical with those of 25 prepared from 22.

Methyl (2S, 3S, 6R)-3-hydroxy-2-methyl-6-piperidinehexanoate (26). To a solution of 25 (130 mg, 0.39 mmol) in CH₂Cl₂ (1.4 ml) was added TiCl₄ (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 NaHCO₃ solution, and the organic layer was dried and concentrated and the residue was subjected to PTLC (CH₂Cl₂/MeOH/28% NH₄OH 9 : 1 : 0.04) to give 26 (95 mg, 81%) as an oil. ¹H NMR δ (300 MHz) 3.69 (3H, s, CO₂Me), 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'-H₂), 1.94 (1H, br dq, J = 10.5, 3 Hz, 4-Heq), 1.69–1.24 (11H, m, 4-Hax, 5-H₂, 1"-4"-H₂), 1.18 (3H, d, J = 6.5 Hz, 2-Me). HRMS calcd for C₁₃H₂₅NO₃ (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 [(\pm)-methyl azimate•hydrochloride]}. IR (nujol) 3344 (OH) and 1732 (COO) cm⁻¹. ¹H NMR δ (500 MHz, D₂O) 3.99 (1H, m, W_{1/2} = 6 Hz, 3-H), 3.70 (3H, s, CO₂Me), 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'-H₂), 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'-H₂), 1.49–1.31 (4H, m, 2', 3'-H₂), 1.30 (3H, d, J = 6.5 Hz, 2-Me). HRMS calcd for C₁₃H₂₅NO₃ (M⁺ – HCl): 243.1833. Found: 243.1849. The IR and ¹H NMR spectra of **26**•hydrochloride were found to be identical with those of methyl azimate•hydrochloride obtained from natural azimine⁴ 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.). [α]_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 NH₂⁺) cm⁻¹. ¹H NMR δ (500 MHz, CD₃OD) 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'-H₂), 1.95 (1H, m, 4-Heq), 1.84–1.22 (11H, m, 4-Hax, 5-H₂, 1'-4'-H₂), 1.33 (3H, d, J = 6.5 Hz, 2-Me). HRMS calcd for C₁₂H₂₃NO₃ (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-tridecadiol²³ (4.04 g, 18.7 mmol) and Et₃N (2.25g, 22 mmol) in CH₂Cl₂ (170 ml) was added dropwise a solution of benzoyl chloride (2.67 g, 19 mmol) in CH₂Cl₂ (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 Et₂O. 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 (CHCl₃) 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, CH₂OCO), 3.64 (2H, t, J = 6.5 Hz, CH₂OH), 1.76 (2H, br quint., J = 6.5 Hz, CH₂CH₂OCO), 1.56 (2H, br quint., J = 6.5 Hz, CH₂CH₂OH), 1.43-1.27 (19H, m, OH and (CH₂)₉). HRMS calcd for C₂₀H₃₂O₃ (M⁺): 320.2350.

(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 CH₂Cl₂ (300 ml) was added dropwise a solution of alcohol 27 (5.35 g, 16.7 mmol) in CH₂Cl₂ (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 Et₂O 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, CH₂OCO), 2.40 (2H, td, J = 6, 2 Hz, CH₂CHO). 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-benzylhydroxylamine¹¹ (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 (Et₂O). IR(CHCl₃) 1713(COO) and 1602(C=N) cm⁻¹. ¹H NMR δ (200 MHz) 8.04 (2H, br d, J = 7 Hz, CH₂OCO), 2.48 (2H, br q, J = 6 Hz, CH₂CH=N), 1.76 (2H, br quint., J = 7 Hz, CH₂CH₂OCO), 1.47-1.25 (18H, m, (CH₂)₉). HRMS calcd for C₂₇H₃₇NO₃ (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[[α]_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%). [3S,5S (R,S)]-(+)-3-[12-(Benzoyloxy)-dodecanyl)]-2-benzyl- α -[1-[(tert-butyldimethylsilyl)oxy]ethyl]-5-isoxazolidinemethanol (30); a pale yellow oil. [α]_D + 56 (c 1.15, MeOH). IR (CHCl₃) 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, CH₂OCO), 4.05 and 3.71 (2H, ABq, J = 12 Hz, CH₂Ph), 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, CH₂CH₂OCO), 1.66–1.24 (20H, m, (CH₂)₁₀), 1.20 (3H, d, J = 6 Hz, 2"-Me), 0.87 (9H, s, tBu), 0.00 (6H, s, SiMe₂). HRMS calcd for C₃₈H₆₁NO₅Si (M⁺): 639.4316. Found: 639.4311. [3R,5S(R,S)]-(-)-3-[12-(Benzoyloxy)dodecany]-2-benzyl- α -[1-[(tert-butyldimethylsily])oxy]ethyl]-5-

isoxazolidinemethanol (31); a pale yellow oil. $[α]_D - 30$ (*c* 1.7, MeOH). IR (CHCl₃) 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, CH₂OCO), 4.25 (1H, m, 5-H), 4.01 and 3.82 (2H, ABq, J = 13.5 Hz, CH₂Ph), 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, CH₂CH₂OCO), 1.65–1.20 (20H, m, (CH₂)₁₀), 1.19 (3H, d, J = 6 Hz, 2"-Me), 0.87 (9H, s, tBu), 0.00 (6H, s, SiMe₂). HRMS calcd for C₃₈H₆₁NO₅Si (M⁺): 639.4316. Found: 639.4322. [3S, 5S(R,S)]-(+)-3-[12-(Benzoyloxy)dodecany]-2-benzyl-α-[1-[(*tert*-butyldimethylsilyl)-oxy]ethyl]-5-isoxazolidinemethanol (32); a pale yellow oil. $[α]_D + 32$ (*c* 2.75, MeOH). IR (CHCl₃) 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, CH₂OCO), 4.00 (1H, m, 5-H), 3.92–3.70 (3H, m, 2"-H, CH₂Ph), 3.49 (1H, br t, J = 12, 7 Hz, 4-H), 1.70 (2H, br quint., J = 6 Hz, CH₂CH₂OCO), 1.60–1.10 (20H, m, (CH₂)₁₀), 1.06 (3H, d, J = 6 Hz, 2"-Me), 0.82 (9H, s, tBu), 0.00 (6H, s, SiMe₂). HRMS calcd for C₃₈H₆₁NO₅Si (M⁺): 639.4316. Found: 639.4308.

[3R,5S(R,S)]-(-)-3-[12-(Benzoyloxy)dodecanyl]-2-benzyl-5-[2-[(tert-butyldimethylsilyl)-

oxy]-1-[(methoxymethoxy)propy]]]isoxazolidine (33). A solution of isoxazolidine 31 (727 mg, 1.14 mmol), MOMCl (275 mg, 3.4 mmol) and (*i*-Pr)₂NEt (1.8 g, 14 mmol) in CH₂Cl₂ (7 ml) was heated to reflux for 10 h. Then after another MOMCl (275 mg, 3.4 mmol) and (*i*-Pr)₂NEt (1.8 g, 14 mmol) were added and the mixture was heated to reflux for a further 20h. The reaction mixture was diluted with CH₂Cl₂, and then washed subsequently with 15% acetic acid, saturated NaHCO₃ 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 (CHCl₃) 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, OCH₂O), 4.30 (2H, t, *J* = 7 Hz, CH₂OCO), 4.05 (1H, m, 5-H), 3.93 and 3.86 (2H, ABq, *J* = 13.5 Hz, CH₂Ph), 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, CH₂CH₂OCO), 1.60–1.20 (20H, m, (CH₂)₁₀), 1.14 (3H, d, *J* = 6 Hz, 2"-Me), 0.87 (9H, s, tBu), 0.00 (6H, s, SiMe₂). HRMS calcd for C₄₀H₆₅NO₆Si (M⁺): 683.4578. Found: 683.4575.

[3R, 5S(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 (CHCl₃) 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, OCH₂O), 4.32 (2H, br t, J = 6 Hz, CH₂OCO), 4.18 (1H br q, J = 9 Hz, 5-H), 3.98 and 3.88 (2H, ABq, J = 13 Hz, CH₂Ph), 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, (CH₂)₁), 1.19 (3H, d, J = 6 Hz, 2"-Me). HRMS calcd for C₃₄H₅₁NO₆Si (M⁺): 569.3714. Found: 569.3724.

(2R, 3S, 4S, 6R)-(+)-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 ClCH₂SO₂Cl (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, CH₂Ph), 4.60 and 4.54 (2H, ABq, J = 8 Hz, OCH₂O), 4.32(2H, br t, J = 7 Hz, CH₂OCO), 4.18 (1H, br q, J = 9 Hz, 5-H), 4.38 (2H, s, SCH₂Cl), 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. $[\alpha]_{\rm D}$ + 6 (c 1.32, MeOH). IR (CHCl₃) 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, OCH₂O), 4.31 (2H, t, J = 6 Hz, CH₂OCO), 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, CH₂CH₂OCOAr), 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 C₂₇H₄₅NO₅ (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 Bu₃SnH (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/CH₂Cl₂ 5 : 95) as an oil. IR (CHCl₃) 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, OCH₂O), 4.32 (2H, t, J = 6 Hz, CH₂OCO), 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-H₂, 5-H₂, (CH₂)₁₁), 1.18 (3H, d, J = 7 Hz, 2-Me). HRMS calcd for C₂₇H₄₅NO₄ (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 CH₂Cl₂. The organic layer was washed, dried and concentrated to give a crude product. ¹H NMR spectrum of the crude product indicated that **37** was converted completely to the corresponding alcohol; ¹H NMR δ (300 MHz) 4.69 and 4.63 (2H, ABq, J = 8 Hz, OCH₂O), 3.67 (1H, m, 3-H), 3.62 (2H, t, J = 6 Hz, CH₂OCO), 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 H₂O and made alkaline with 10% NaOH solution under ice-cooling and the whole was extracted with CH₂Cl₂. The extract was dried and evaporated to give (+)-julifloridine (**2**) (22 mg, 66%) as crystals (Et₂O/AcOEt), mp 85–87.5 °C. [α]_D + 18 (c 0.84, MeOH). (lit.⁶ mp 82–83 °C) ¹H NMR δ (300 MHz) 3.69 (1H, br dt, J = 8.5, 3.5 Hz, 3-H), 3.64 (2H, t, J = 7 Hz, CH₂OH), 3.14 (1H, qd, J = 6.5, 3 Hz, 2-H), 2.85 (1H, m, 6-H), 2.00–1.10 (26H, m, 4-H₂, 5-H₂, (CH₂)₁₁), 1.11 (3H, d, J = 6.5 Hz, 2-Me). ¹³C 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 C₁₈H₃₇NO₂ (M⁺): 299.2823. Found: 299.2808. The IR ¹H, and ¹³C NMR spectra of **2** were found to be identical with those of natural julifloridine **2**.⁶

(2R, 3R, 6R)-(-)-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 NaCNBH₃ (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 Et₂O. The organic layer was washed with saturated NaHCO₃ solution, dried and concentrated. The residue was subjected to PTLC (CH₂Cl₂/MeOH/NH₄OH 9 : 1 : 0.04) to afford *N*-methyl derivative 3 (18 mg, 78%) as crystals. $[\alpha]_D - 20$ (*c* 0.6, CHCl₃). ¹H NMR δ (300 MHz) 3.73 (1H, br dt, *J* = 7, 3 Hz, 3-H), 3.63 (2H, t, *J* = 7 Hz, CH₂OH), 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-H₂, 5-H₂, (CH₂)₁₁), 1.07 (3H, d, *J* = 7 Hz, 2-Me). ¹³C 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 C₁₉H₃₉NO₂ (M⁺): 313.2979. Found: 313.2961.

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