SYNTHETIC APPLICATION OF CHIRAL 4-METHOXY-2-OXAZOLIDINONE SYNTHONS TO 2-AMINO ALCOHOLS OF BIOLOGICAL INTEREST‡

Tadao Ishizuka, Kohei Morooka, Seigo Ishibuchi, and Takehisa Kunieda*

Faculty of Pharmaceutical Sciences, Kumamoto University,
5-1 Oe-honmachi, Kumamoto 862, Japan

Abstract- The versatility as chiral synthons of (4*S*, 5*S*)- and (4*R*, 5*R*)-5-allyl-4-methoxy-2-oxazolidinones, readily obtainable from 3-[(1*S*)-2-*exo*-alkoxy-1-apocamphanecarbonyl]-2-oxazolone, is demonstrated by the facile stereospecific conversions to (2*R*, 3*S*)-3-amino-2-hydroxy-3-phenylpentanoic acid, (2*R*, 3*R*, 5*E*, 7*E*)-2-amino-5,7-tetradecadien-3-ol and (2*S*, 3*R*)-dihydrosphingosine.

The 2-amino alcohol skeleton is an important structural unit found in a substantial number of bioactive compounds such as peptidic enzyme inhibitors,[1] amino sugar antibiotics[2] and alkaloids as well as synthetic drugs. Most of the strategies reported for stereocontrolled construction of the unit appear of limited use in terms of synthetic versatility. We previously explored the synthetic potential of the simple heterocycle, 2-oxazolone, as a building block, to present a promising methodology of versatile use for chiral synthesis of 2-amino alcohols.[3] It has hence been disclosed that electrophilic additions of Br_2 and PhSeCl to the 2-oxazolone smoothly proceed with throughly reversed diastereoselectivity to permit facile preparation of both enantiomers of *trans*-5-allyl-4-methoxy-2-oxazolidinones (**3** and **5**) from the same chiral source (Scheme 1).[4] The optically active 2-oxazolidinones, obtained as the versatile intermediates, could be successfully converted to the hydroxy amino acids, key components of bioactive peptides, such as pepstatin and amastatin.[5]

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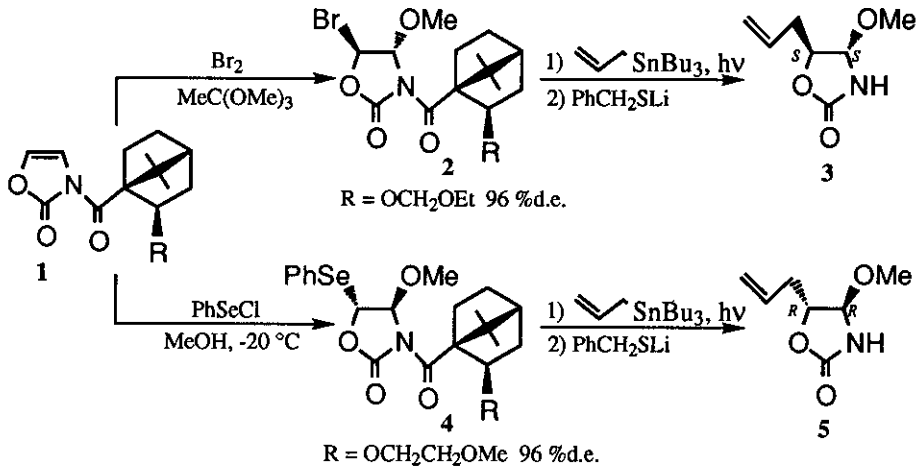
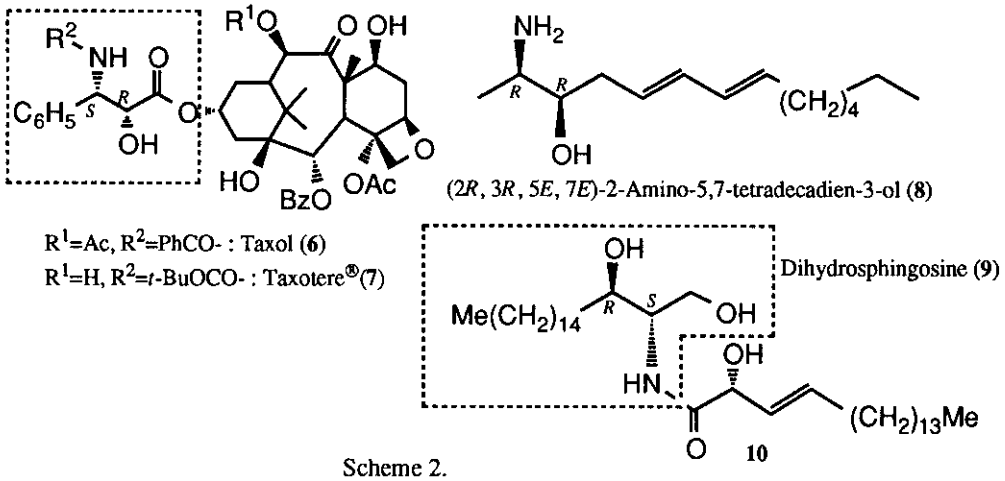
‡ This paper is dedicated to the late Prof. Yoshio Ban.



Scheme 1.

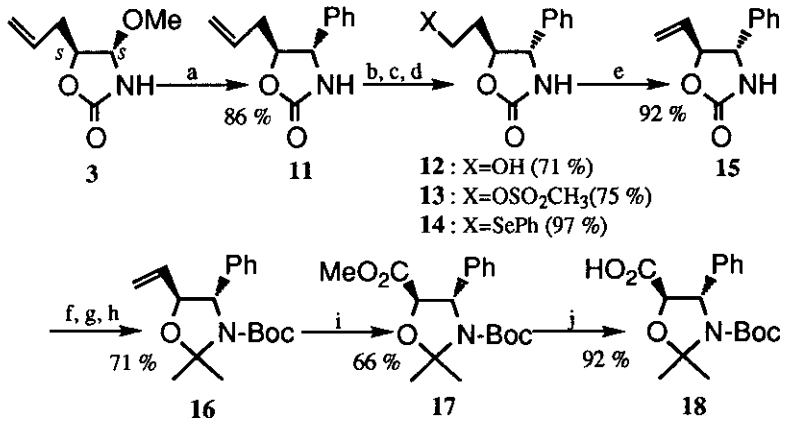
This paper describes further application of the readily available 2-oxazolidinone synthons (**3**) and (**5**) to stereospecific syntheses of (2*R*, 3*S*)-3-amino-2-hydroxy-3-phenylpentanoic acid and the long-chain 2-amino alcohols, (2*R*, 3*R*, 5*E*, 7*E*)-2-amino-5,7-tetradecadien-3-ol and (2*S*, 3*S*)- and (2*S*, 3*R*)-dihydrosphingosines, of biological interest. On the basis of the stereochemistry involved, the amino alcohol (**8**) was prepared from (4*R*, 5*R*)-5-allyl-4-methoxy-2-oxazolidinone (**5**), while the enantiomer (**3**) was used as a common synthetic intermediate for the rest compounds.



Scheme 2.

(2*R*, 3*S*)-3-Amino-2-hydroxy-3-phenylpentanoic Acid.

This hydroxy amino acid is a key compound of promising *anti*-tumor agents, taxol[6] (**6**) and Taxotere®[7] (**7**), and has long been good target for synthetic challenge.[8]



a : PhCuCNMgBr, BF_3• OEt ; b : O_3, $NaBH_4$; c : $MeSO_2Cl$, NEt_3, DMAP;
d : PhSeNa ; e : MCPBA, D ; f : $(Boc)_2O$, DMAP ; g : Cs_2CO_3, MeOH;
h : dimethoxypropane, TsOH, 80 °C ; i : O_3, NaOMe ; j : LiOH

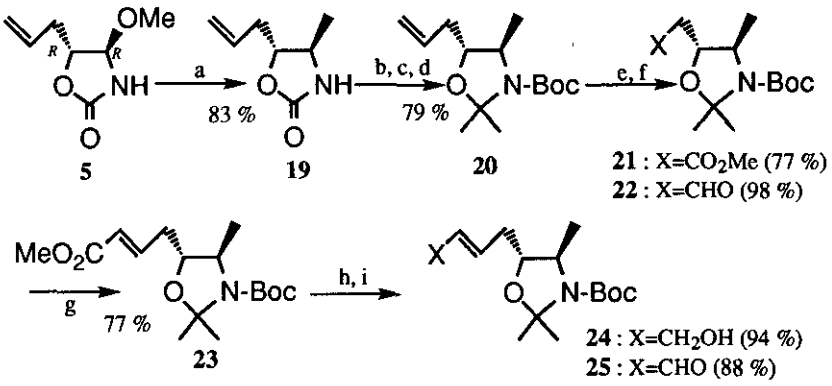
Scheme 3.

The 4-phenylation of (4*S*, 5*S*)-5-allyl-4-methoxy-2-oxazolidinone (**3**) with phenyl cyanocuprate[9] in the presence of BF_3•OEt_2 gave (4*S* ,5*S*)-5-allyl-4-phenyl-2-oxazolidinone (**11**) with full retention of configuration of which the allyl group was smoothly converted to the vinyls by the conventional procedures involving the oxidative elimination of the selenide (**14**). Conversion to the 1,3-oxazolidine ring and subsequent ozonolysis of the vinyl group gave a reasonable yield of protected (2*R*, 3*S*)-carboxylic acid (**18**), which served as the side-chain precursor of taxol and its family (Scheme 3).[10]

(2*R*, 3*R*)-2-Amino-5,7-tetradecadien-3-ol.

The long-chain 2-amino-5,7-tetradecadien-3-ol (**8**), structurally resembling the biomembrane constituent sphingosines, has been isolated from a marine sponge[11] and found to inhibit fungal growth.

By virtually the same procedures as mentioned above, (4*R*, 5*R*)-5-allyl-4-methoxy-2-oxazolidinone (**5**) was converted *via* (4*R*, 5*R*)-5-allyl-4-methyl-2-oxazolidinone (**19**) to the 2-(5-oxazolidine)acetaldehyde (**22**) which reacted with methyl (triphenylphosphoranylidene)acetate to yield the (2*E*)-butenoate (**23**) exclusively. Subsequent reduction with diisobutylaluminum hydride (DIBAL) and the Swern oxidation afforded a good yield of the protected (2*E*, 5*R*, 6*R*)-6-amino-5-hydroxy-2-heptenal derivative (**25**), of which conversion to **8** was previously reported (Scheme 4).[12]

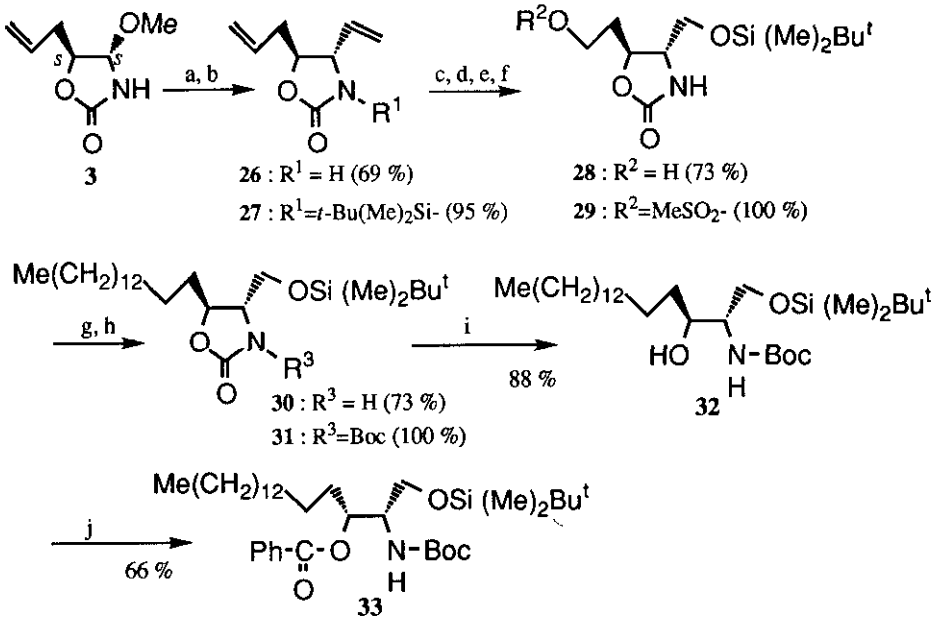


a : MeCuCNMgBr, BF_3• OEt_2 ; b : $(Boc)_2O$, DMAP ; c : Cs_2CO_3, MeOH ;
d : dimethoxypropane, TsOH ; e : MeCN-CCl_4-H_2O, $NaIO_4$, $RuCl_3$; f : DIBAL;
g : Ph_3P=$CHCO_2Me$; h : DIBAL ; i : $(COCl)_2$, DMSO, NEt_3

Scheme 4.

***threo*- and *erythro*-Dihydrosphingosines.**

Dihydrosphingosine, a family of long-chain amino alcohols sphingosines,[13] has been isolated from natural sources as a constituent of biologically important ceramides and cerebrosides.[14]



a : $(CH_2$=$CH)_2CuCN(MgBr)_2$, BF_3•OEt ; b : TBDMSiCl / BuLi ; c : O_3 / MeOH;
d : $NaBH_4$; e : NaH / DMF ; f : $MeSO_2Cl$, NEt_3, DMAP ; g : $[Me(CH_2)_{12}]_2CuMgBr$;
h : $(Boc)_2O$, DMAP ; i : Cs_2CO_3 / MeOH ; j : $PhCO_2H$, PPh_3, EtO_2N=NCO_2Et

Scheme 5

Both *threo*- and *erythro*-isomers of dihydrosphingosine were synthesized from (4*S*, 5*S*)-5-allyl-4-methoxy-2-oxazolidinone (**3**), as outlined in Scheme 5.

Olefinic bonds of 3-silyl-5-allyl-4-vinyl-2-oxazolidinone (**27**), prepared in a way similar to that mentioned above, were simultaneously cleaved to give exclusive formation of *O*-monoprotected 2-oxazolidinone (**28**) by ozonolysis, followed by successive treatment with sodium hydride. Intramolecular *N*→*O* migration of the silyl group resulted in highly regioselective differentiation of the resulting primary diol. Elongation at the 5-substituent with long-chain alkyl cuprate yielded *threo*-dihydrosphingosine (**32**), which was smoothly converted to *erythro*-(2*S*, 3*R*)-derivative (**33**) *via* the configurational inversion of the hydroxy group by Mitsunobu reaction.

In conclusion, chiral 4-methoxy-2-oxazolidinones readily available have a high synthetic potential as the new electrophilic building block for a variety of optically active 2-amino alcohols.

EXPERIMENTAL

Melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. ^{1}H-Nmr spectra were recorded in $CDCl_3$, unless otherwise specified, at 400 and 270 MHz on JEOL GX400 and JEOL EX270 instruments, respectively, using tetramethylsilane as the internal standard. Optical rotations were measured with a JASCO DIP-370 polarimeter. Mass spectroscopic data were obtained with the JEOL DX303HF spectrometer. Column chromatography was performed using silica gel 60 (70-230 mesh, Merck). All solvents were distilled before use : THF over Na / benzophenone, CH_2Cl_2 and benzene over CaH_2, CCl_4 over P_2O_5 and MeOH over MeONa.

(4*S*, 5*S*)-5-Allyl-4-phenyl-2-oxazolidinone (11)

A mixture of LiCl (3.60 g, 84.8 mmol, dried at 150 °C for 1 h under vacuum), CuCN (3.80 g, 42.4 mmol) and PhMgBr (56 ml, 38.6 mmol, 0.69 M in THF) was stirred in THF (48 ml) under argon atmosphere at -30 °C for 1 h. After successive addition of **3** (1.52 g, 9.6 mmol, dissolved in 24 ml of THF) and BF_3•OEt_2 (2.4 ml, 19.3 mmol), the mixture was further stirred at -30 °C for 12 h. The reaction was quenched by addition of saturated NH_4Cl solution (30 ml) and AcOEt (150 ml) was added. The organic layer was washed with satd. NH_4Cl solution (30 ml x 5) and NaCl solution (30 ml x 3) and dried over Na_2SO_4. Concentration in vacuo followed by chromatography (CH_2Cl_2 : AcOEt = 9 : 1) yielded **11** as colorless crystals (1.69 g, 86 %) : mp 106°C (from hexane / CH_2Cl_2) ; $[\alpha]_D^{25}$ -46.0° (c 1.00, $CHCl_3$) ; ^{1}H-nmr (400 MHz) δ : 2.52-2.55 (2H, m), 4.40 (1H, q, J=6.2 Hz), 4.57 (1H, d, J=6.2 Hz), 5.20-5.25 (2H, m), 5.74-5.85 (2H, m), 5.96 (1H, br), 7.26-7.43 (5H, m) ; Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92 ; H, 6.45 ; N, 6.89. Found : C, 70.89 ; H, 6.56 ; N, 6.86.

(4*S*, 5*S*)-5-(2-Hydroxy)ethyl-4-phenyl-2-oxazolidinone (12)

Ozone was bubbled through a solution of **11** (1.69 g, 8.3 mmol) in MeOH (38 ml) at -78 °C until the solution turned to blue. Sodium borohydride (31.5 g, 83.3 mmol) was added to the solution. After stirring at 0 °C for 1 h,

the mixture was acidified with citric acid (16.01 g, 83.3 mmol) and extracted with CH_2Cl_2 (50 ml x 3). The extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2 : AcOEt = 3 : 2) yielded **12** (1.22 g, 71 %) as colorless crystals : mp 124 °C (from AcOEt) ; $[\alpha]_D^{24}$ -40.3° (c 1.00, MeOH) ; ^{1}H-nmr (400 MHz / acetone-d_6) δ : 2.04-2.06 (2H, m), 3.65-3.77 (2H, m), 4.44 (1H, q, J=6.2 Hz), 4.68 (1H, dd, J=1.1, 6.2 Hz), 7.00 (1H, br), 7.32-7.46 (5H, m) ; Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76 ; H, 6.32 ; N, 6.76. Found : C, 63.71 ; H, 6.41 ; N, 6.88.

(4*S*, 5*S*)-5-(2-Methanesulfonyloxy)ethyl-4-phenyl-2-oxazolidinone (13)

A solution of **12** (1.22 g, 5.9 mmol), methanesulfonyl chloride (1.4 ml, 17.6 mmol), NEt_3 (2.4 ml, 17.6 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (0.72 g, 5.9 mmol) in THF (85 ml) was stirred at room temperature for 1 h. The mixture was passed through a silica gel-packed short column with AcOEt as the eluent and the eluate was evaporated *in vacuo*. Chromatography (CH_2Cl_2 : AcOEt = 4 : 1) gave **13** as colorless crystals (1.26 g, 75 %) : ^{1}H-Nmr (270 MHz / acetone-d_6) δ : 2.25-2.33 (2H, m), 3.07 (3H, s), 4.33-4.47 (3H, m), 4.72 (1H, dd, J=1.1, 6.4 Hz), 7.07 (1H, br), 7.32-7.48 (5H, m).

(4*S*, 5*S*)-5-(2-Phenylselenenyl)ethyl-4-phenyl-2-oxazolidinone (14)

A mixture of sodium hydride (0.21 g, 8.8 mmol) and diphenyl diselenide (0.36 g, 4.8 mmol) in THF (9 ml) was refluxed under argon atmosphere for 1 h. After addition of **13** (1.26 g, 4.4 mmol), the mixture was stirred at 0 °C for 1 h. It was passed through a silica gel pad with AcOEt as the eluent and the eluate was concentrated *in vacuo*. Chromatography (CH_2Cl_2 : hexane = 1 : 1 to CH_2Cl_2 : AcOEt = 4 : 1) yielded **14** as colorless crystals (1.47 g, 92 %) : ^{1}H-Nmr (270 MHz) δ : 1.98-2.23 (2H, m), 2.82-3.13 (2H, m), 4.44-4.51 (2H, m), 5.67 (1H, br), 7.20-7.42 (5H, m).

(4*S*, 5*S*)-4-Phenyl-5-vinyl-2-oxazolidinone (15)

To **14** (1.47 g, 4.3 mmol) in CH_2Cl_2 (22 ml), *m*-chloroperbenzoic acid (0.95 g, 5.5 mmol) dissolved in CH_2Cl_2 (45 ml) was dropwise added at 0 °C. The whole mixture was refluxed for 30 min and cooled thereafter AcOEt (100 ml) was added and the mixture was worked up in a usual way. Evaporation of the solvent followed by chromatography (CH_2Cl_2 : hexane = 9 : 1 to CH_2Cl_2 : AcOEt = 19 : 1) gave **15** as colorless crystals (0.74 g, 92 %) : mp 68-69°C (from CCl_4) ; $[\alpha]_D^{28}$ -0.4° (c 1.00, $CHCl_3$) ; ^{1}H-nmr (400 MHz) δ : 4.60-4.61 (1H, m), 4.68-4.72 (1H, m), 5.29-5.36 (1H, m), 5.94-6.02 (1H, m), 6.23 (1H, br), 7.31-7.42 (5H, m) ; HRms Calcd for $C_{11}H_{11}NO_2$ (M^+): m / z 189.0790, Found : m / z 189.0809.

(4*S*, 5*S*)-3-*tert*-Butoxycarbonyl-4-phenyl-5-vinyl-2-oxazolidinone

Compound (**15**) (0.63 g, 3.3 mmol) was treated with di-*tert*-butyl dicarbonate (1.44 g, 6.6 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (0.49 g, 4.0 mmol) in THF (33 ml) at room temperature for 12 h. Evaporation *in vacuo* followed by column chromatography (CH_2Cl_2) yielded (4*S*, 5*S*)-3-*tert*-butoxycarbonyl-4-phenyl-5-vinyl-2-oxazolidinone as colorless crystals (0.72 g, 92 %) : mp 79-79.5°C (from hexane) ; $[\alpha]_D^{29}$ +1.6° (c 1.00, $CHCl_3$) ; ^{1}H-nmr(400 MHz) δ : 1.27 (9H, s), 4.65-4.69 (1H, m), 4.83 (1H, d, J =5.5 Hz), 5.37-5.42 (2H, m), 5.92-

6.00 (1H, m), 7.27-7.42 (5H, m) ; Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42 ; H, 6.62 ; N, 4.84. Found : C, 66.41 ; H, 6.64 ; N, 4.81 ; HRms Calcd for $C_{16}H_{19}NO_4$ (MH+) : m / z 289.1314, Found : m / z 289.1329.

(3*S*, 4*S*)-4-*tert*-Butoxycarbonylamino-4-phenyl-1-buten-3-ol

A solution of (4*S*, 5*S*)-3-*tert*-butoxycarbonyl-4-phenyl-5-vinyl-2-oxazolidinone (0.86 g, 3.0 mmol) in MeOH (30 ml) was treated with cesium carbonate (0.48 g, 1.5 mmol) at room temperature for 12 h. The mixture was passed through a short sillica gel column with AcOEt as the eluent and the eluate was concentrated under reduced pressure. Column chromatography (hexane : AcOEt = 3 : 1) gave (3*S*, 4*S*)-4-*tert*-butoxycarbonylamino-4-phenyl-1-buten-3-ol as colorless crystals (0.72 g, 92 %) : mp 59° C (from hexane) : $[\alpha]_D^{30}$ -0.2° (c 1.00, $CHCl_3$) ; ^{1}H-nmr (400 MHz) δ : 1.41 (9H, s), 2.30 (1H, br), 4.36 (1H, br), 4.70 (1H, br), 5.20 (1H, dt, J=1.5, 10.6 Hz), 5.31-5.36 (2H, m), 5.81-5.90 (1H, m), 7.25-7.37 (5H, m) : Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42 ; H, 8.04 ; N, 5.32. Found : C, 68.12 ; H, 8.07 ; N, 5.33.

(4*S*, 5*S*)-3-*tert*-Butoxycarbonyl-2,2-dimethyl-4-phenyl-5-vinyloxazolidine (16)

A solution of (3*S*, 4*S*)-4-*ert*-butoxycarbonylamino-4-phenyl-1-buten-3-ol (0.68 g, 2.6 mmol) and 2,2-dimethoxypropane (0.7 ml, 5.7 mmol) in benzene (10 ml) was refluxed for 1 h in the presence of *p*-toluenesulfonic acid hydrate (0.005 g, 0.03 mmol). Et_2O (90 ml) was added to the mixture and the ether layer was dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2) gave **16** as a colorless oil (0.73 g, 93 %) : $[\alpha]_D^{27}$ +58.0° (c 1.01, $CHCl_3$) ; ^{1}H-nmr (400 MHz) δ : 1.03 (9H, s), 1.72 (3H, s), 1.74 (3H, s), 4.25 (1H, t, J=7.7 Hz), 4.35 (1H, br), 5.19-5.23 (2H, m), 5.83-5.91 (1H, m), 7.20-7.34 (5H, m) ; HRms Calcd for $C_{18}H_{28}NO_3$ (MH^+): m / z 304.1913, Found : m / z 304.1945.

Methyl (4*S*, 5*R*)-3-*tert*-butoxycarbonyl-2,2-dimethyl-4-phenyl-5-oxazolidinecarboxylate (17)

Ozone was passed through a CH_2Cl_2 (4 ml) solution of **16** (0.16 g, 0.53 mmol) and NaOMe (1 ml, 2.5 mmol, 2.5 M in MeOH) at -78 °C until the mixture turned blue. Et_2O (90 ml) was added to the mixture and the organic layer was washed with satd. NaCl solution (30 ml x 3). Evaporation *in vacuo* followed by column chromatography (hexane : AcOEt = 9 : 1) gave **17** as a colorless oil (0.12 g, 66 %) : $[\alpha]_D^{23}$ -9.2° (c 1.00, $CHCl_3$) ; ^{1}H-nmr (400 MHz) δ : 1.13 (9H, s), 1.70(3H, s), 1.78 (3H, s), 3.80 (3H, s), 4.48 (1H, d, J=5.5 Hz), 5.07 (1H, br), 7.26-7.36 (5H, m) ; HRms Calcd for $C_{18}H_{26}NO_5$ (MH^+): m / z 336.1811, Found : m / z 336.1792.

(4*S*, 5*R*)-3-*tert*-Butoxycarbonyl-2,2-dimethyl-4-phenyl-2-oxazolidine-5-carboxylic acid (18)

The ester (**17**) (0.06 g, 0.17 mmol) was treated with $LiOH{\cdot}H_2O$ (0.07 g, 1.7 mmol) in aqueous MeOH (20 ml) at room temperature for 1 h. The aqueous layer was acidified with citric acid, and extracted with AcOEt (30 ml x 3). The extracts were washed with satd. NaCl solution (30 ml x 3) and dried over Na_2SO_4. Removal of the solvent yielded **18** as colorless crystals (0.05 g, 92 %) : mp 133°C (from hexane) [lit.,[9] mp 137°C] ; $[\alpha]_D^{27}$ +4.6° (c 1.05 $CHCl_3$) [lit.,[9] $[\alpha]_D^{20}$ +5.3° (c 1.1 $CHCl_3$)] ; ^{1}H-nmr (400 MHz) δ : 1.15 (9H, s), 1.73 (3H, s), 1.79 (3H, s), 4.53 (1H, d, J=5.5Hz), 5.09 (1H, br), 7.26-7.37 (5H, m), 7.49 (1H, br) ; Anal. Calcd for $C_{17}H_{23}NO_5$

: C, 63.54; H, 7.21; N, 4.36. Found : C, 63.50; H, 7.31 ; N, 4.35 ; HRms Calcd for $C_{17}H_{24}NO_5$ (MH+): m / z 322.1655, Found : m / z 322.1667.

(4*R*, 5*R*)-5-Allyl-4-methyl-2-oxazolidinone (19)

To LiCl (2.24 g, 52.8 mmol, dried at 150 °C for 1 h under vacuum) and CuCN (2.36 g, 26.4 mmol) in THF (30 ml), MeMgBr (25 ml, 24 mmol, 0.96 M in THF) was added at -30 °C under argon atmosphere and the mixture was stirred at -30 °C for 1 h. After successive addition of **5** (0.94 g, 6.0 mmol, dissolved in 15 ml of THF) and BF_3•OEt_2 (1.4 ml, 12 mmol), the mixture was further stirred at -30 °C for 12 h. Usual work-up gave **19** as a colorless oil (0.70g, 83 %) : $[\alpha]_D^{22}$ +55.8° (c 1.00, $CHCl_3$) ; ^{1}H-nmr (270 MHz) δ : 1.26 (3H, d, J =6.2 Hz), 2.39-2.54 (2H, m), 3.60-3.66 (1H, m), 4.16 (1H, q, J =6.2 Hz), 5.16-5.22 (2H, m), 5.73-5.84 (1H, m), 6.37 (1H, br) ; HRms Calcd for $C_7H_{11}NO_2$: m / z 141.0797, Found : m / z 141.0790.

(4*R*, 5*R*)-5-Allyl-3-*tert*-butoxycarbonyl-4-methyl-2-oxazolidinone

Compound (**19**) (0.70 g, 5.0 mmol) was treated with di-*tert*-butyl dicarbonate (2.16 g, 9.9 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (0.73 g, 6.0 mmol) in THF (50 ml) at room temperature for 12 h. Usual work-up gave (4*R*, 5*R*)-5-allyl-3-*tert*-butoxycarbonyl-4-methyl-2-oxazolidinone as a colorless oil (1.15 g, 96 %) : ^{1}H-Nmr (270 MHz) δ : 1.40 (3H, d, J=6.3 Hz), 1.54 (9H, s), 2.38-2.51 (2H, m), 3.98 (1H, dq, J=3.6, 6.3 Hz), 4.08 (1H, dt, J=3.6, 6.3 Hz), 5.18-5.25 (2H, m), 5.68-5.83 (1H, m).

(4*R*, 5*R*)-5-*tert*-Butoxycarbonylamino-1-hepten-4-ol

A solution of (4*R*, 5*R*)-5-allyl-3-*tert*-butoxycarbonyl-4-methyl-2-oxazolidinone (1.15 g, 4.8 mmol) and cesium carbonate (0.78 g, 2.4 mmol) in MeOH (53 ml) was stirred at room temperature for 12 h. Subsequent work-up gave (4*R*, 5*R*)-5-(*tert*-butoxycarbonylamino)-1-hepten-4-ol as a colorless oil (0.85 g, 82 %) : $[\alpha]_D^{26}$ +16.0°C (c 1.01, $CHCl_3$) ; ^{1}H-nmr (270MHz) δ : 1.19 (3H, d, J=6.22 Hz), 1.44 (9H, s), 1.80 (1H, br), 2.17-2.35 (2H, m), 3.55-3.67 (2H, m), 4.77 (1H, br), 5.12-5.17 (2H, m), 5.82-5.86 (1H, m) ; ms (FAB) : m / z 216 (MH+).

(4*R*, 5*R*)-5-Allyl-3-*tert*-butoxycarbonyl-2,2,4-trimethyloxazolidine (20)

A solution of (4*R*, 5*R*)-5-*tert*-butoxycarbonylamino-1-hepten-4-ol (0.57 g, 2.7 mmol) and 2,2-dimethoxypropane (0.71 ml, 5.9mmol) in benzene (10 ml) was refluxed in the presence of *p*-toluenesulfonic acid hydrate (0.005 g, 0.003 mmol) for 1 h. Usual work-up gave **20** (0.68 g, 100 %) as a colorless oil : $[\alpha]_D^{26}$ -15.8° (c 1.01, $CHCl_3$) ; ^{1}H-nmr (270 MHz) δ : 1.28 (3H, d, J=6.2 Hz), 1.47 (12H, s), 1.58 (3H, s), 2.36 (2H, t, J =6.2 Hz), 3.42-3.64 (1H, m), 3.75 (1H, q, J =6.2 Hz), 5.09-5.16 (2H, m), 5.78-5.87 (1H, m) ; ms (FAB) : m / z 256 (MH^+).

(4*R*, 5*R*)-3-*tert*-Butoxycarbonyl-2,2,4-trimethyl-5-methoxycarbonylmethyloxazolidine (21)

To a mixture of **20** (0.15 g, 0.6 mmol), MeCN (1 ml), CCl_4 (1 ml), H_2O (2 ml), $NaIO_4$ (1.84 g, 8.6 mmol) and $RuCl_3$•H_2O (0.001 g, 0.013 mmol) were added and the whole mixture was stirred at room temperature for 48 h. After addition of saturated $NaHCO_3$ aqueous solution (30 ml), mixture was washed with Et_2O (30 ml x 3). The aqueous layer was acidified with citric acid and extracted with Et_2O (30 ml x 3). The extract was washed with satd. NaCl solution (30 ml x 3), dried over Na_2SO_4 and evaporated *in vacuo*. Treatment of residue with

diazomethane (Et_2O solution) was followed by column chromatography (CH_2Cl_2 : AcOEt = 9 : 1) to give the methyl ester (**21**) as a colorless oil (0.13 g, 77 %): $[\alpha]_D^{23}$ -6.0° (c 0.50, $CHCl_3$) ; ^{1}H-nmr (270 MHz) δ : 1.32 (3H, d, J =6.3 Hz), 1.47 (9H, s), 1.51 (3H, s), 1.57 (3H, s), 2.60-2.63 (2H, m), 3.65 (1H, br), 3.71 (3H, s), 4.10-4.19 (1H, m).

(4*R*, 5*R*)-3-*tert*-Butoxycarbonyl-2,2,4-trimethyl-5-oxazolidineacetaldehyde (22)

To **21** (0.13 g, 0.45 mmol) in toluene (9 ml), diisobutylaluminum hydride (0.5 ml, 0.51 mmol, 1.02 M in toluene) was added at -78 °C under argon atmosphere. The mixture was stirred for 1 h, and then poured into an aqueous citric acid solution. Extraction with Et_2O (30 ml x 3) followed by column chromatography (CH_2Cl_2 : AcOEt = 7 : 3) yielded **22** as a colorless oil (0.11 g, 98 %) : $[\alpha]_D^{23}$ -6.9°(c 1.01, $CHCl_3$) ; ^{1}H-nmr (270 MHz) δ : 1.33 (3H, d, J=6.3 Hz), 1.47 (9H, s), 1.51 (3H, s), 1.57 (3H, s), 2.55-2.85 (2H, m), 3.60 (1H, br), 4.19-4.22 (1H, m), 9.81 (1H, s).

Methyl (2*E*)-4-[(4*R*, 5*R*)-3-*tert*-butoxycarbonyl-2,2,4-trimethyl-5-oxazolidine]-2-butenoate (23)

The aldehyde (**22**) (0.11 g, 0.43 mmol) was treated with methyl (triphenylphosphoranylidene)acetate (0.22 g, 0.66 mmol) in benzene (6.1 ml) at 55 °C for 15 h. The mixture was passed through a celite pad with pentane as the eluent and the eluant was concentrated *in vacuo*. Column chromatography (hexane : AcOEt = 19 : 1) gave **23** as a colorless oil (0.11 g, 77%) : $[\alpha]_D^{25}$ +5.4° (c 1.01, $CHCl_3$) ; ^{1}H-nmr (270 MHz) δ : 1.29 (3H, d, J =6.3 Hz), 1.47 (12H, s), 1.57 (3H, s), 2.50 (2H, t, J =6.3 Hz), 3.54 (1H, br), 3.74 (3H, s), 3.81 (1H, dd, J=6.3, 12.2 Hz), 5.93 (1H, d, J=15.8 Hz), 6.91-7.02 (1H, m).

(2*E*, 4*R*, 5*R*)-3-*tert*-Butoxycarbonyl-5-(4-hydroxy-2-butenyl)-2,2,4-trimethyloxazolidine (24)

The ester (**23**) (0.11 g, 0.34 mmol) was reduced with disobutylaluminum hydride (0.66ml, 0.68 mmol, 1.02M in toluene) in toluene (9 ml) at -78 °C under argon atmosphere for 1 h. Usual work-up followed by column chromatography (hexane : AcOEt = 4 : 1 to 3 : 1) yielded **24** as a colorless oil (0.09 g, 94 %) : $[\alpha]_D^{24}$ -5.4° (c 1.00, $CHCl_3$) ; ^{1}H-nmr (270 MHz) δ : 1.28 (3H, d, J =6.3 Hz), 1.47 (12H, s), 1.58 (3H, s), 2.34-2.28 (2H, m), 3.55 (1H, br), 3.74 (1H, q, J=6.3 Hz), 4.02-4.19 (2H, m), 5.68-5.76 (2H, m).

(2*E*)-4-[(4*R*, 5*R*)-3-*tert*-Butoxycarbonyl-2,2,4-trimethyl-5-oxazolidine]-2-butenal (25)

To oxalyl chloride (0.08 ml, 0.64 mmol) and dimethyl sulfoxide (0.13 ml, 1.9 mmol) in CH_2Cl_2 (6 ml), **24** (0.09 g, 0.32 mmol) was added at room temperature and the mixture was stirred for 1 h. After addition of NEt_3 (0.61 ml, 4.4 mmol), the reaction was quenched with H_2O (10 ml). The mixture was extracted with Et_2O (30 ml x 3) and the extract was washed with satd. NaCl solution (30 ml x 3) and dried over Na_2SO_4. Evaporation *in vacuo* followed by column chromatography (hexane : AcOEt = 19 : 1 to 4 : 1) gave **25** as a colorless oil (0.08 g, 88 %) : $[\alpha]_D^{24}$ +17.4° (c 1.00, $CHCl_3$) [lit.,[11] $[\alpha]_D^{24}$ +18.7° (c 1.01, $CHCl_3$) ; ^{1}H-nmr (270MHz) δ : 1.31 (3H, d, J=6.3Hz), 1.48 (9H, s), 1.50 (3H, s), 1.58 (3H, s), 2.59-2.66 (2H, m), 3.57 (1H, br), 3.82-3.89 (1H, m), 6.17-6.26 (1H, m), 6.87 (1H, dt, J=6.9, 15.8Hz), 9.54 (1H, d, J =7.9Hz).

(4*S*, 5*S*)-5-Allyl-4-vinyl-2-oxazolidinone (26)

To CuCN (1.95 g, 21.7 mmol) suspended in THF (27 ml), vinylmagnesium bromide (44.3 ml, 43.4 mmol, 0.98 M in THF) was added at -30 °C under argon atmosphere. The mixture was stirred for 1 h. **3** (0.85 g, 5.4 mmol, dissolved in 13.6 ml of THF) and BF_3•OEt_2 (1.3 ml, 10.9 mmol) were added. After stirring at -30 °C for 15 h, satd. NH_4Cl solution (100 ml) was added and the mixture was extracted with AcOEt (100 ml x 3). Column chromatography (CH_2Cl_2) yielded **26** as a colorless oil (0.57 g, 69 %) : $[\alpha]_D^{29}$ -75.1° (c 1.03, $CHCl_3$) ; ^{1}H-nmr (400 MHz) δ : 2.51 (2H, t, J=6.2 Hz), 4.03 (1H, ddd, J=0.7, 6.2, 7.3 Hz), 4.28 (1H, dd, J=6.2, 12.5 Hz), 5.17-5.33 (4H, m), 5.74-5.86 (2H, m), 6.26 (1H, br) ; HRms Calcd for $C_8H_{11}NO_2$: m / z 153.0788, Found : m / z 153.0790.

(4*S*, 5*S*)-5-Allyl-3-*tert*-butyldimethylsilyl-4-vinyl-2-oxazolidinone (27)

To **26** (0.18 g, 1.2 mmol) in THF (5 ml) were added BuLi (0.84 ml, 1.3 mmol, 1.56 M in hexane) and *tert*-butyldimethylchlorosilane (0.27 g, 1.78 mmol) at -78 °C. After stirring at room temperature for 11 h, the mixture was passed through a short silica gel column with CH_2Cl_2 as the eluent and the eluate was evaporated *in vacuo*. Column chromatography (CH_2Cl_2) gave **27** as a colorless oil (0.30 g, 95 %) : $[\alpha]_D^{27}$ -35.9° (c 1.07, $CHCl_3$) ; ^{1}H-nmr (400 MHz) δ: 0.24 (3H, s), 0.28 (3H, s), 0.97 (9H, s), 2.37-2.51 (2H, m), 3.89 (1H, dd, J=3.3, 8.4 Hz), 4.17 (1H, dt, J=3.3, 6.2 Hz), 5.15-5.22 (4H, m), 5.73- 5.89 (2H, m).

(4*S*, 5*S*)-4-*tert*-Butyldimethylsilyloxymethyl-5-(2-hydroxyethyl)-2-oxazolidinone (28)

Ozone was passed through a MeOH solution of **27** (0.54 g, 2 mmol) at -78 °C until the mixture turned blue. Sodium borohydride (0.77 g, 20.3 mmol) was added to the solution and the whole was stirred at 0 °C for 1 h. Usual work-up gave a crude stirring product. To the crude oil dissolved in DMF (10 ml) was added NaH (0.20 g, 5.1 mmol, 60 % in oil). After stirring at room temperature for 2 h, the reaction was quenched by addition of satd. NH_4Cl solution (4 ml) and AcOEt (200 ml). The organic layer was washed with satd. NaCl solution (50 ml x 2), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2 : AcOEt = 1 : 1) yielded **28** as colorless crystals (0.41 g, 73 %) : mp 114-116 °C (from CH_2Cl_2 / hexane) ; $[\alpha]_D^{28}$ -59.9° (c 1.16, $CHCl_3$) ; ^{1}H-nmr (400 MHz) δ: 0.08 (6H, s), 0.89 (9H, s), 1.70-2.10 (3H, m), 3.61-3.67 (3H, m), 3.81-3.86 (2H, m), 4.48-4.54 (1H, m), 5.68 (1H, br) ; Anal. Calcd for $C_{12}H_{25}NO_4Si$: C, 52.33; H, 9.15; N, 5.09. Found : C, 52.54; H, 9.28; N, 5.18.

(4*S*, 5*S*)-4-*tert*-Butyldimethylsilyloxymethyl-5-(2-methanesulfonyloxyethyl)-2-oxazolidinone (29)

To methanesufonyl chloride (0.28 g, 2.4 mmol), NEt_3 (0.17 ml, 1.2 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (0.099 g, 0.81 mmol) in THF (12 ml) was added **28** (0.22 g, 0.81 mmol). After stirring at room temperature for 1 h, the mixture was passed through a short silica gel column with AcOEt as the eluent and the eluate was evaporated *in vacuo*. Column chromatography (CH_2Cl_2 : AcOEt =8 : 2) gave **29** as a colorless oil (0.29 g, 100 %) : $[\alpha]_D^{28}$ -65.1° (c 1.07, $CHCl_3$) ; ^{1}H-nmr (400 MHz) δ : 0.08 (6H, s), 0.89 (9H, s), 2.12-2.19 (2H, m), 3.04 (3H, s), 3.56-3.65 (3H, m), 4.34-4.45 (2H, m), 4.46-4.53 (1H, m), 5.79 (1H, br).

(4*S*, 5*S*)-4- *tert*-Butyldimethylsilyloxymethyl-5-pentadecyl-2-oxazolidinone (30)

To a suspension of CuI (1.35 g, 7.1 mmol) in THF (13 ml), $Me(CH_2)_{12}MgBr$ (25.8 ml, 14.2 mmol, 0.55 M in THF) was added at -30 °C under argon atmosphere and the mixture was stirred for 2 h. After addition of **29** (0.29 g, 0.82 mmol, dissolved in 4 ml of THF) and subsequent stiring at -30 °C for 15 h, usual work-up followed by column chromatography (CH_2Cl_2 : AcOEt = 95 : 5 to 7 : 3) gave **30** as colorless crystals (0.26 g, 73 %) : mp 53-53.5 °C (from hexane) ; $[\alpha]_D^{28}$ -40.7° (c 1.21, $CHCl_3$) ; ^{1}H-nmr (400 MHz) δ : 0.066 (6H, s), 0.89 (9H, s), 0.89 (3H, t, J=2.6 Hz), 1.17-1.80 (28H, m), 3.50-3.54 (1H, m), 3.59 (2H, d, J=5.5 Hz), 4.25-4.30 (1H, m), 5.69 (1H, br) ; Anal. Calcd for $C_{25}H_{51}NO_3Si$: C, 67.97; H, 11.64; N, 3.17. Found : C, 68.02; H, 11.79; N, 3.26.

(4*S*, 5*S*)-3-*tert*-Butoxycarbonyl-4-(*tert*-butyldimethylsilyloxymethyl)-5-pentadecyl-2-oxazolidinone (31)

A solution of **30** (0.22 g, 0.49 mmol), di-*tert*-butyl dicarbonate (0.22 g, 0.99 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (0.03 g, 0.25 mmol) in THF (4.8 ml) was stirred at room temperature for 15 h. Concentration of the mixture *in vacuo* followed by column chromatography (CH_2Cl_2) yielded **31** as a colorless oil (0.27 g, 100 %) : $[\alpha]_D^{26}$ +2.2° (c 0.91, $CHCl_3$) ; ^{1}H-nmr (400 MHz) δ : 0.05 (3H, s), 0.06 (3H, s), 0.88 (9H, s), 0.88 (3H, t, J=2.9 Hz), 1.11-1.74 (28H, m), 1.49 (9H, s), 3.64-3.70 (1H, m), 3.75-3.82 (2H, m), 4.30-4.36 (1H, m).

***N*-*tert*-Butoxycarbonyl-1-*O*-*tert*-butyldimethylsilyl-L-*threo*-dihydrosphingosine (32)**

Compound (**31**) (170 mg, 0.32 mmol) was treated with Cs_2CO_3 (51 mg, 0.16 mmol) in MeOH (3.2 ml) at room temperature for 15 h to give **32** as a colorless oil (99 mg, 61 %), in addition to the starting material (**31**) (43 mg, 31 %) : $[\alpha]_D^{25}$ -2.23° (c 1.35, $CHCl_3$) ; ^{1}H-nmr (400 MHz) δ : 0.08 (6H, s), 0.88 (3H, t, J=7.0 Hz), 0.90 (9H, s), 1.25-1.67 (28H, m), 3.32 (1H, br), 3.53 (1H, br), 3.80-3.82 (1H, m), 3.90-3.93 (2H, m), 5.19 (1H, brd, J=8.8 Hz).

3-*O*-Benzoyl-*N*-*tert*-butoxycarbonyl-1-*O*-*tert*-butyldimethylsilyl-D-*erythro*-dihydrosphingosine (33)

To a solution of **32** (71 mg, 0.15 mmol), triphenylphosphine (140 mg, 0.52 mmol) and benzoic acid (64 mg, 0.52 mmol) in benzene (0.8 ml) was added diethyl azodicarboxylate (91 mg, 0.52 mmol, dissolved 0.5 ml of benzene) and the whole mixture was stirred at 80 °C for 15 h. Evaporation *in vacuo* followed by column chromatography (AcOEt : hexane = 1 : 9) yielded **33** (41 mg, 46 % (66 % based on the unrecovered **32**)) as a colorless oil in addition to **32** (21 mg, 30 %) : $[\alpha]_D^{27}$ +19.0° (c 0.58, $CHCl_3$) ; ^{1}H-nmr (400 MHz) δ : 0.02 (6H, s), 0.89 (9H, s), 0.91 (3H, t, J=3.3 Hz), 1.23-1.80 (28H, m), 1.46 (9H, s), 3.69 (1H, dd, J=4.0, 10.3 Hz), 3.76 (1H, dd, J=4.0, 10.3 Hz), 3.98 (1H, br), 4.94 (1H, d, J=10.3 Hz), 5.22 (1H, br), 7.46 (2H, t, J=7.3Hz), 7.58 (1H, t, J= 7.3 Hz), 8.05 (2H, d, J=7.3 Hz).

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