Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 87–93

TETRAHEDRON: *ASYMMETRY*

Stereoselective synthesis of (+)-spectaline

Yiu-Suk Lee,[a] Yong-Ho Shin,[a] Yong-Hyun Kim,[a] Kee-Young Lee,[a] Chang-Young Oh,[a] Sung-Jae Pyun,[a] Hyun-Ju Park,[a] Jin-Hyun Jeong[b] and Won-Hun Ham[a,*]

[a]*College of Pharmacy, SungKyunKwan University, Suwon 440-746, Korea*
[b]*College of Pharmacy, Kyung Hee University, Seoul 130-701, Korea*

Received 7 October 2002; accepted 21 November 2002

Abstract—Our synthesis of (+)-spectaline revealed that the methodology involving diastereoselective palladium(0)-catalyzed oxazoline formation and intramolecular reductive amination by catalytic hydrogenation of an oxazoline is an effective method for the asymmetric synthesis of natural products possessing complex functionalized piperidine cores.

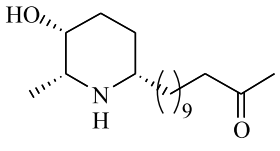
1. Introduction

Piperidine alkaloids are widespread in nature and many compounds of this family exhibit interesting biological activity.[1] All *cis*-2,6-disubstituted 3-piperidinols such as cassine **1**[2] and spectaline **2**[3] are members of this family that have been the subjects of synthetic studies. Over the past several years, we have been investigating the stereocontrolled synthesis of the *trans*-oxazoline ring via the highly stereoselective intramolecular cyclization of acyclic allylic and homoallylic amides having a benzoyl substituent as an *N*-protecting group in the presence of tetrakis(triphenylphosphine) palladium(0) and base (K_2CO_3).[4] More recently, the *trans*-oxazoline has been applied successfully to the synthesis of (+)-preussin **3**,[5] a potent antifungal agent possessing a pyrrolidine skeleton. We have now explored this strategy as an efficient route to the *cis*-2,6-disubstituted piperidin-3-ol skeleton, a core found in a number of biologically active compounds. Herein, we report the stereoselective synthesis of (+)-spectaline **2**, a potent antifungal agent possessing a piperidinol skeleton (Fig. 1).

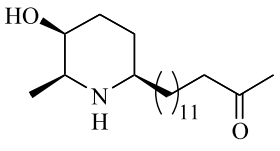
Our approach to the piperidinol skeleton, shown retrosynthetically in Scheme 1, is focused on the utilization of oxazoline **6** as a building block to generate the vicinal amino alcohol stereochemistry of the spectaline and the stereoselective intramolecular cyclization of oxazoline **4** by the sequential unmasking of the oxazoline and intramolecular reductive amination under hydrogenolysis conditions.

2. Results and discussion

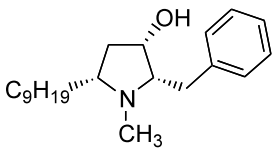
The synthesis of oxazoline **6** began with L-*N*-benzoyl serinol **7** as shown in Scheme 2. Oxidation of alcohol **7** with Dess–Martin periodinane[4b,6] gave the corresponding aldehyde without racemization,[4b,6b] which was reacted with vinylmagnesium bromide in THF at 0°C to afford the corresponding allyl alcohol **8** as a ca. 1.1:1 mixture of *syn*/*anti* isomer (^{1}H NMR) in 75% yield.[7] Acetylation of the hydroxyl group yielded the sec-



(-)-Cassine 1



(+)-Spectaline 2

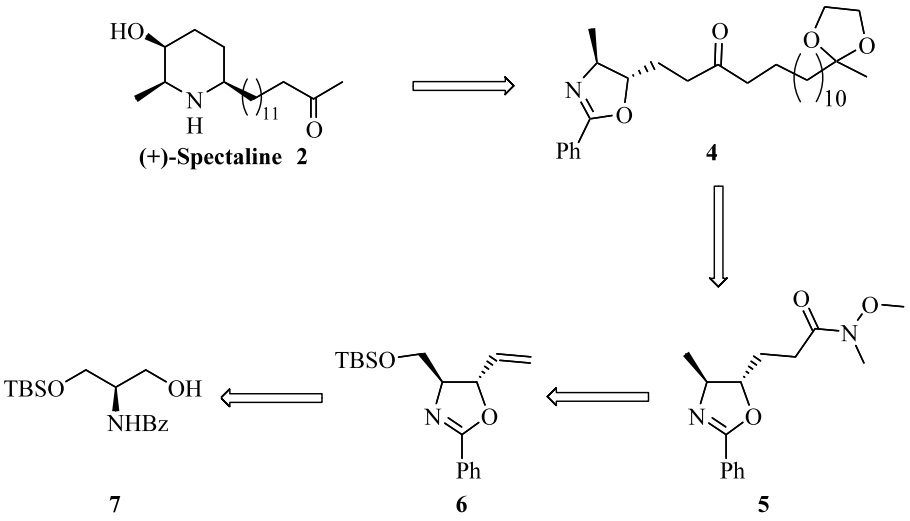


(+)-Preussin 3

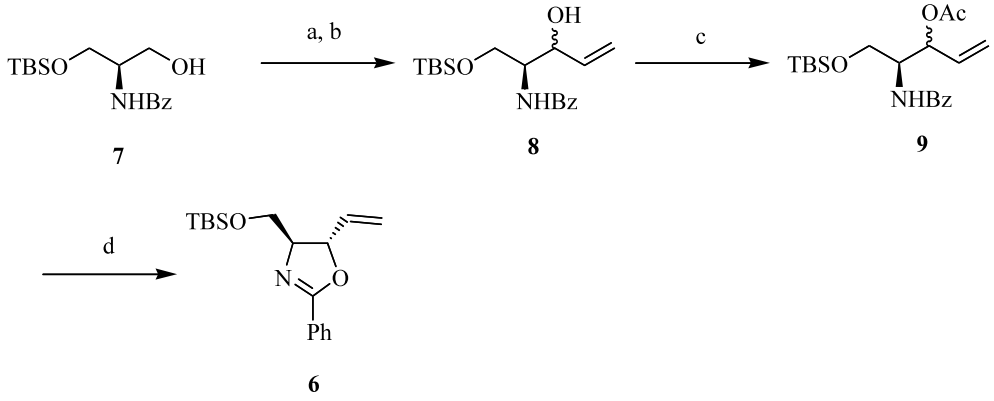
Figure 1.

* Corresponding author. Tel.: +82 331 290 7706; fax: +82 331 292 8800; e-mail: whham@speed.skku.ac.kr

0957-4166/03/$ - see front matter
PII: S0957-4166(02)00794-2



Scheme 1. Retrosynthesis of (+)-spectaline.



Scheme 2. *Reagents and conditions*: (a) Dess–Martin periodinane, CH_2Cl_2, rt; (b) vinylmagnesium bromide, THF, 0°C, 75% for two steps; (c) Ac_2O, Pyri, DMAP, CH_2Cl_2, rt, 99%; (d) $Pd(Ph_3P)_4$, K_2CO_3, CH_3CN, reflux, 75%.

ondary allylic acetate **9**. The standard oxazoline ring formation reaction ($Pd(PPh_3)_4$, K_2CO_3, in CH_3CN) of secondary allylic acetate **9** gave the desired *trans*-oxazoline **6** in good yield (75%) as a single isomer.

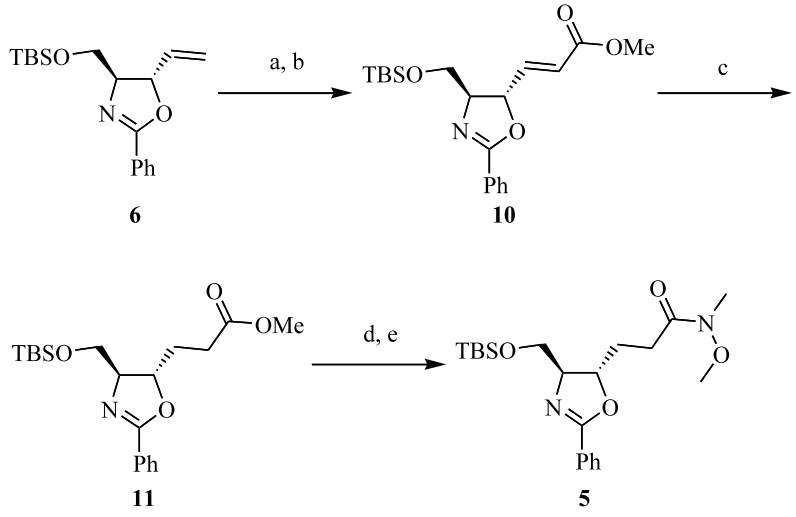
The *trans*-oxazoline **6** was converted into the α,β-unsaturated methyl ester **10** in 86% yield in two steps via ozonolysis and subsequent Horner–Wardworth–Emmons reaction. 1,4-Reduction[8] of **10** with copper bromide, Red-Al and 2-butanol gave the saturated methyl ester **11** in 82% yield. Hydrolysis of **11** with LiOH gave the corresponding acid which was converted to its Weinreb amide[9] **5** via DCC-mediated condensation with *N*,*O*-dimethylhydroxylamine in 76% yield over two steps (Scheme 3).

The conversion of **5** to **12** was accomplished by a three step sequence: Removal of the TBDMS group with tetrabutylammonium fluoride (TBAF) followed by iodination and subsequent reduction of the resulting iodide with tri-*n*-butyltin hydride gave the corresponding amide **12** in 74% overall yield in three steps. Treatment of **12** with Grignard reagent, which was prepared from **13**,[10] provided ketone **4** in 70% yield. Fortunately, the resulting ketone **4** could be directly converted to (+)-spectaline **2** as a single isomer by means of a one-pot procedure for a multi-reaction. Thus, unmasking of the oxazoline followed by intramolecular reductive amination[11] of the resulting amine and deprotection of terminal ketone occurred consecutively by simple treatment of 20% $Pd(OH)_2$ in AcOH/MeOH (1:9) under H_2 atmosphere (70 psi) for 24 h in 70% yield (Scheme 4).

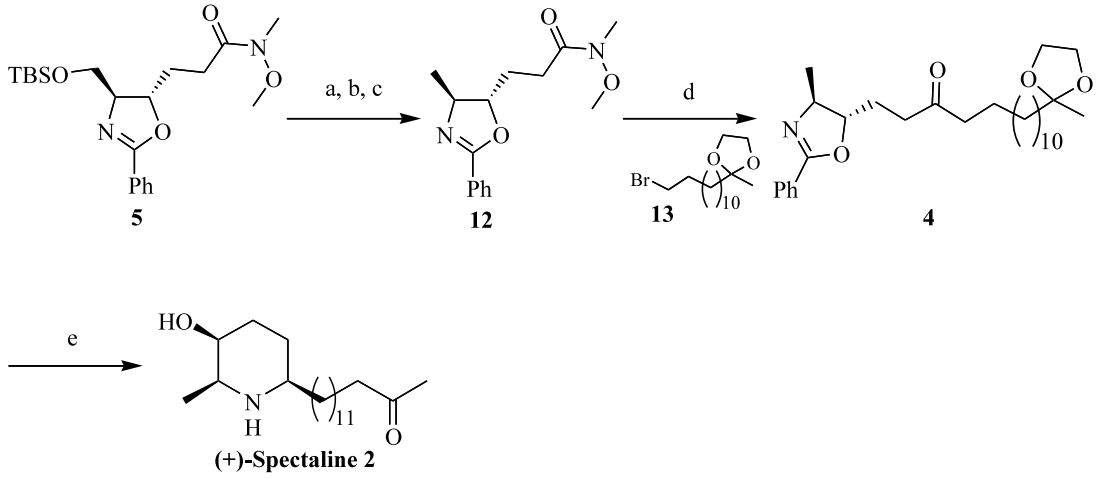
Not even a trace of the C-2 epimer could be detected. The stereochemistry may be attributed to the steric hindrance by which the catalytic hydrogenation occurs from the less hindered site (α-face) of intermediate **A** and **B** (Fig. 2). The physicochemical properties of (+)-spectaline obtained from the present synthesis were in complete agreement with those reported in the literature. ($[\alpha]_D^{25}$ +8.8 (*c* 1.3, $CHCl_3$) [lit.[3c] $[\alpha]_D^{26}$ +9.0 (*c* 1.3, $CHCl_3$)]).

3. Conclusion

In summary, we report a new asymmetric synthetic method for (+)-spectaline from oxazoline. This synthe-



Scheme 3. *Reagents and conditions*: (a) O_3, MeOH, −78°C then DMS; (b) $(MeO)_2POCH_2CO_2Me$, LiCl, DBU, CH_3CN, 86% for two steps; (c) CuBr, Red-Al, 2-butanol, THF, 82%; (d) LiOH, THF/H_2O, rt; (e) $NH(CH_3)OCH_3{\cdot}HCl$, DCC, HOBT, Et_3N, CH_2Cl_2, 76% for two steps.



Scheme 4. *Reagents and conditions*: (a) TBAF, THF, 0°C; (b) PPh_3, I_2, Imidazole, CH_3CN/Et_2O; (c) Bu_3SnH, AIBN, PhH/MeOH, reflux 74% for three steps; (d) **13**, Mg, THF, 0°C, 70%; (e) 20% $Pd(OH)_2/C$, 70 psi H_2, MeOH/AcOH (9:1), 70%.

sis revealed that the methodology involving diastereoselective palladium(0)-catalyzed oxazoline formation and piperidine formation by catalytic hydrogenation of oxazoline is effective for the asymmetric synthesis of natural products possessing complex functionalized piperidine subunits.

4. Experimental

4.1. General methods

Melting points were determined with a capillary apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP 1020 digital polarimeter. ^1H NMR spectra were recorded at 400 or 500 MHz in $CDCl_3$ unless specified otherwise. ^{13}C NMR spectra were recorded at 100 or 125 MHz in $CDCl_3$ unless specified otherwise. Chemical shifts are reported as δ values in ppm relative to $CHCl_3$ (7.26) in $CDCl_3$. IR spectra were measured on an Nicolet 205 FT-IR spectrometer. The high resolution mass spectra were recorded at 70 eV ionizing voltage; ammonia was used for chemical ionization (CI). Flash chromatography was executed with Merck Kiesegel 60 (230–400 mesh). Tetrahydrofuran (THF) and diethylether (Et_2O) were distilled over sodium and benzophenone (indicator). Methylene chloride (CH_2Cl_2) was shaken with concentrated sulfuric acid, dried over potassium carbonate, and distilled. Commercially available compounds were used without further purification.

4.2. (−)-*N*-[(1*S*,2*S*)-2-Hydroxy-1-(*tert*-butyldimethyl silanyloxymethyl)-3-butenyl]-benzamide, 8

To a stirred solution of **7** (3.10 g, 10.02 mmol) in CH_2Cl_2 (20 mL) at 0°C under argon was added Dess–Martin periodinane (6.32 g, 15.03 mmol), and stirring

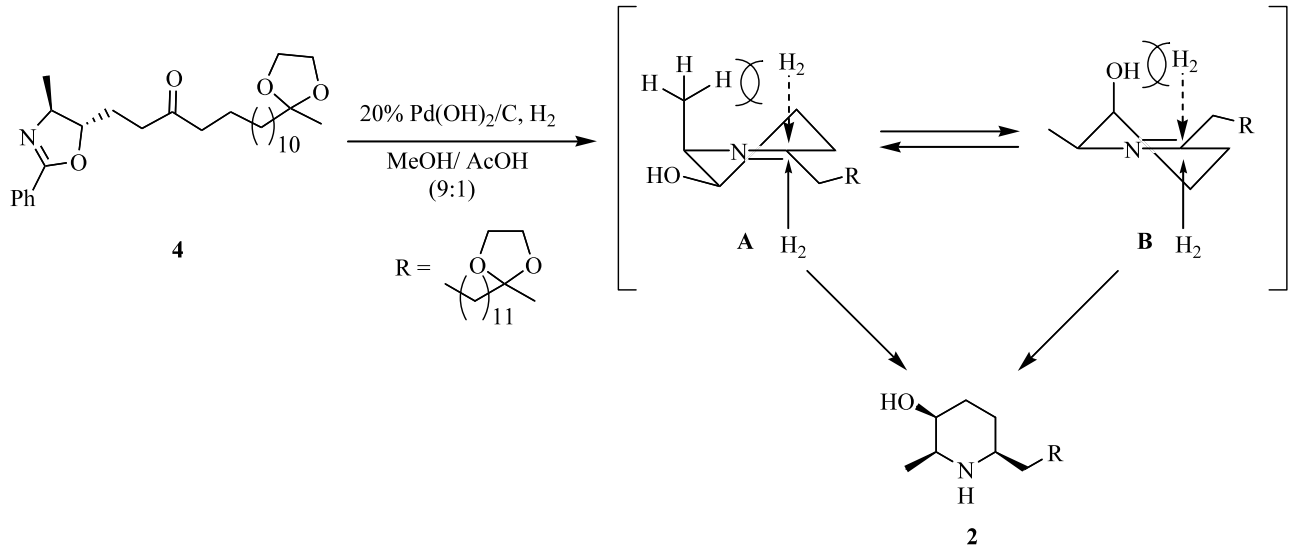


Figure 2.

was allowed to continue for 2 h at 25°C, after which time TLC analysis indicated complete reaction. The reaction mixture was diluted with Et_2O (100 mL) and poured into saturated aqueous $NaHCO_3$ solution (200 mL) containing $Na_2S_2O_3$ (16.6 g, 105.1 mmol, 10.5 equiv.). The mixture was stirred to dissolve the solid, and the layers were separated. The ethereal layer was washed with saturated $NaHCO_3$ (100 mL) and with water (100 mL), dried with $MgSO_4$. The filtrate was concentrated in vacuo to give crude aldehyde. This aldehyde was immediately employed in the next step without further purification. To a stirred solution of crude aldehyde (1.0 mmol) in THF (50 mL) at −78°C, was added a solution of vinylmagnesium bromide (1.0 M in THF, 50.1 mL). After being stirred for 1 h, the reaction mixture was washed with saturated aqueous NH_4Cl (20 mL×2), brine (20 mL×2), dried with Na_2SO_4 and evaporated in vacuo. Purification by silica gel chromatography (ethyl acetate/hexane = 1/10) gave **8** (2.52 g, 96%); colorless oil; $[\alpha]_D^{24}$ +8.3 (*c* 1.0, $CHCl_3$); IR (neat) 3427, 2930, 2857, 1643 cm^{-1}; ^1H NMR (500 MHz) δ 0.064–0.10 (d, 6H), 0.91 (s, 9H), 3.62 (s, 1H), 3.99–4.01 (dd, J = 2.5, 4.0 Hz, 2H), 4.16 (m, 1H), 4.64 (m, 1H), 5.21 (dt, J = 1.5, 11.0 Hz, 1H), 5.39 (dt, J = 1.5, 15.5 Hz, 1H), 5.88 (ddd, J = 6.0, 11.0, 15.5 Hz, 1H), 6.79 (d, J = 7.5 Hz, 1H), 7.43–7.52 (m, 3H), 7.76–7.78 (m, 2H); ^{13}C NMR (125 MHz) δ −5.33, 18.37, 26.04, 53.74, 65.36, 73.83, 116.47, 127.15, 128.86, 131.84, 134.60, 137.54, 167.91; HRMS (EI, 70 eV) calcd for $C_{18}H_{29}NO_3Si$ 335.1917, found 335.1917.

4.3. (−)-*N*-((1*S*,2*S*)-2-Acetoxy-1-(*tert*-butyldimethylsilanyloxymethyl)-3-butenyl)-benzamide, 9

To a stirred solution of **8** (350 mg, 1.04 mmol) in CH_2Cl_2 (4 mL) were added acetic anhydride (0.11 mL, 1.42 mmol), pyridine (0.093 mL, 1.42 mmol), and stirring was allowed to continue for 12 h. The reaction mixture was washed with 1N HCl (20 mL×2), saturated aqueous $NaHCO_3$ solution (20 mL×2), brine (20 mL×2), dried with Na_2SO_4, and evaporated in vacuo. Purification by silica gel chromatography (ethyl acetate/hexane = 1/15) gave **9** (389 mg, 99%); colorless oil; $[\alpha]_D^{24}$ +8.4 (*c* 1.0, $CHCl_3$); IR (neat) 3322, 2931, 2857, 1745, 1646 cm^{-1}; ^1H NMR (500 MHz) δ 0.036–0.060 (d, 6H), 0.91 (s, 9H), 1.58 (s, 3H), 3.69 (dd, J = 3.0, 10.0 Hz, 1H), 3.82 (dd, J = 5.5, 10.0 Hz, 1H), 4.39 (m, 1H), 5.31 (dt, J = 1.0, 11.0 Hz, 1H), 5.37 (dt, J = 1.0, 17.5 Hz, 1H), 5.67 (m, 1H), 5.88 (ddd, J = 6.5, 11.0, 17.5 Hz, 1H), 6.49 (d, J = 9.5 Hz, 1H), 7.43–7.52 (m, 3H), 7.74–7.75 (m, 2H); ^{13}C NMR (125 MHz) δ −5.35, 18.42, 21.34, 26.03, 53.55, 62.00, 73.86, 119.41, 127.07, 128.93, 131.85, 133.71, 134.61, 167.25, 170.63; HRMS (EI, 70 eV) calcd for $C_{20}H_{31}NO_4Si$ 377.2022, found 377.2027.

4.4. (4*S*,*trans*)-4,5-Dihydro-4-(*tert*-butyl-dimethylsilanyloxymethyl)-2-phenyloxazoline, 6

To a stirred solution of **9** (400 mg, 1.06 mmol) and K_2CO_3 (439 mg, 3.178 mmol) in CH_3CN (20 mL) was added $Pd(PPh_3)_4$ (6.12 mg, 0.053 mmol) under N_2. The resulting mixture was heated under reflux for 24 h, whereupon it was allowed to cool to rt and was filtered through a pad of silica, which was then evaporated under reduced pressure to give crude product. Purification by silica gel chromatography (ethyl acetate/hexane = 1/20) gave **6** (252 mg, 75%); colorless oil; $[\alpha]_D^{25}$ −3.7 (*c* 1.0, $CHCl_3$); IR (neat) 2930, 2857, 1650 cm^{-1}; ^1H NMR (500 MHz) δ 0.04–0.076 (d, 6H), 0.86 (s, 9H), 3.69 (dd, J = 7.0, 10.0 Hz, 1H), 3.94 (dd, J = 4.0, 10.0 Hz, 1H), 4.06 (ddd, J = 4.0, 5.5, 7.0 Hz, 1H), 5.02 (dd, J = 5.5, 6.5 Hz, 1H), 5.21 (dt, J = 1.5, 10.5 Hz, 1H), 5.36–5.40 (dt, J = 1.5, 17.0 Hz, 1H), 5.96 (ddd, J = 6.5, 10.5, 17.0 Hz, 1H), 7.39–7.48 (m, 3H), 7.95–7.97 (m, 2H); ^{13}C NMR (125 MHz) δ −5.08, 26.04, 64.95, 74.33, 83.31, 116.62, 128.02, 128.54, 131.59, 137.00, 164.11; HRMS *m*/*e* calcd for $C_{18}H_{27}NO_2Si$ 318.1889, found 318.1880.

4.5. (2*E*)-3-((4*S*,*trans*)-4,5-Dihydro-4-(*tert*-butyl-dimethylsilanyloxymethyl)-2-phenyloxazol-5-yl)-acrylic acid methyl ester, 10

Oxazoline **6** (2.0 g, 6.30 mmol) was dissolved in dry methanol (50 mL) and cooled to −78°C. Pass ozonied oxygen until the reaction is complete. The reaction mixture was quenched with $(CH_3)_2S$ (0.93 mL, 12.6 mmol) and allowed to warm to rt. The solvents were evaporated under reduced pressure. The crude aldehyde was immediately employed in the next step without further purification. To a stirred solution of LiCl (320 mg, 7.56 mmol) in CH_3CN (80 mL) were added trimethylphosphonoacetate (1.09 mL, 7.56 mmol), 8-diazabicyclo[5,4,0]undec-7-ene (DBU) (0.942 mL, 6.30 mmol) and stirring was allowed to continue for 1 h. The crude aldehyde in CH_3CN (20 mL) was added and the reaction mixture was stirred for 2 h. The reaction mixture was poured into H_2O (30 mL), extracted with EtOAc (100 mL). The organic extract was washed with brine, dried with Na_2SO_4 and evaporated in vacuo. Purification by silica gel chromatography (ethyl acetate/hexane = 1/6) gave **10** (2.03 g, 85.8%); colorless oil; $[\alpha]_D^{24}$ +53.9 (*c* 1.0, $CHCl_3$); IR (neat) 2954, 2857, 1729, 1653 cm^{-1}; ^1H NMR (500 MHz) δ 0.04–0.08 (d, 6H), 0.87 (s, 9H), 3.68 (dd, J = 7.0, 10.0 Hz, 1H), 3.75 (s, 3H), 3.97 (dd, J = 4.0, 10.0 Hz, 1H), 4.14 (dt, J = 4.0, 6.5 Hz, 1H), 5.19 (dd, J = 1.5, 6.5 Hz, 1H), 6.10 (dt, J = 1.5, 15.5 Hz, 1H), 7.00 (dd, J = 5.0, 15.5 Hz, 1H), 7.41–7.51 (m, 3H), 7.95–7.96 (m, 2H); ^{13}C NMR (125 MHz) δ −5.10, 18.44, 26.00, 52.04, 64.85, 74.35, 80.94, 120.84, 127.48, 128.57, 128.67, 131.91, 145.92, 164.03, 166.67; HRMS *m*/*e* calcd for $C_{20}H_{29}NO_4Si$ 376.1944, found 376.1953.

4.6. 3-((4*S*,*trans*)-4,5-Dihydro-4-(*tert*-butyl-dimethyl-silanyloxymethyl)-2-phenyloxazol-5-yl)-propionic acid methyl ester, 11

To a stirred solution of cuprous bromide (1.53 g, 10.65 mmol) and Red-Al (6.39 mL, 21.30 mmol) in THF (30 mL) at −78°C, was added 2-butanol (4.4 mL, 47.93 mmol) all at once, followed by a solution of **10** (1.0 g, 2.66 mmol) in THF (10 mL). After 10 min at −78°C, the reaction mixture was stirred at −20°C for 4 h. The reaction mixture was quenched with 1N HCl (20 mL), extracted with Et_2O. The organic extract was washed with brine, dried with Na_2SO_4, and evaporated in vacuo. Purification by silica gel chromatography (ethyl acetate/hexane = 1/6) gave **11** (828 mg, 82.4%); colorless oil; $[\alpha]_D^{24}$ −15.7 (*c* 1.0, $CHCl_3$); IR (neat) 2953, 2857, 1741, 1649 cm^{-1}; ^1H NMR (500 MHz) δ 0.034–0.079 (d, 6H), 0.86 (s, 9H), 2.02 (m, 2H), 2.53 (m, 2H), 3.58 (dd, J = 7.0, 10.0 Hz, 1H), 3.68 (s, 3H), 3.91 (dd, J = 4.0, 10.0 Hz, 1H), 3.94 (m, 1H), 4.61 (dd, J = 6.0, 12.5 Hz, 1H), 7.39–7.48 (m, 3H), 7.91–7.93 (m, 2H); ^{13}C NMR (125 MHz) δ −5.13, 18.47, 26.06, 30.08, 30.85, 51.94, 65.30, 73.51, 82.24, 128.04, 128.48, 128.53, 131.60, 164.12, 173.61; HRMS *m*/*e* calcd for $C_{20}H_{31}NO_4Si$ 378.2101, found 378.2094.

4.7. 3-((4*S*,*trans*)-4,5-Dihydro-4-(*tert*-butyl-dimethyl-silanyloxymethyl)-2-phenyloxazol-5-yl)-*N*-methoxy-*N*-methyl-propionamide, 5

To a stirred solution of **11** (600 mg, 1.59 mmol) in THF/H_2O (2.5:1, 10 mL) was added LiOH (333 mg, 7.94 mmol), and stirring was allowed to continue for 2 h. The reaction mixture was diluted with EtOAc and washed with brine, dried with $MgSO_4$, and evaporated in vacuo. The crude acid was immediately employed in the next step without further purification. The crude acid (570 mg), *N*,*O*-dimethylhydroxylamine hydrochloride (167.8 mg, 1.72 mmol), and triethylamine (0.24 mL, 1.72 mmol) were dissolved in CH_2Cl_2 (20 mL) and cooled to 0°C. *N*-Hydroxybenzotriazole (HOBt) (232 mg, 1.72 mmol), DCC (324 mg, 1.57 mmol) were added and the reaction mixture was stirred for 12 h. The reaction mixture was filtered to remove dicyclohexylurea and concentrated. The resulting slurry was diluted with EtOAc and washed with 1N HCl, saturated aqueous $NaHCO_3$ solution, brine, dried with Na_2SO_4, and evaporated in vacuo. Purification by silica gel chromatography (ethyl acetate/hexane = 2/1) gave **5** (491 mg, 76%); colorless oil; $[\alpha]_D^{24}$ −32.2 (*c* 1.0, $CHCl_3$); IR (neat) 2931, 2857, 1669 cm^{-1}; ^1H NMR (500 MHz) δ 0.027–0.076 (d, 6H), 0.86 (s, 9H), 2.03 (m, 2H), 2.63 (brs, 2H), 3.18 (s, 3H), 3.61 (dd, J = 7.0, 10.0 Hz, 1H), 3.90 (s, 3H), 3.92 (dd, J = 4.0, 10.0 Hz, 1H), 3.97 (ddd, J = 4.0, 6.0, 7.0 Hz, 1H), 4.64 (dd, J = 6.0, 7.0 Hz, 1H), 7.38–7.47 (m, 3H), 7.92–7.94 (m, 2H); ^{13}C NMR (125 MHz) δ −5.11, 18.46, 26.05, 27.86, 30.52, 61.44, 65.24, 73.46, 82.42, 128.19, 128.40, 128.48, 131.51, 164.12; HRMS *m*/*e* calcd for $C_{21}H_{34}N_2O_4Si$ 407.2366, found 407.2362.

4.8. 3-((4*S*,*trans*)-4,5-Dihydro-4-methyl-2-phenyloxazol-5-yl)-*N*-methoxy-*N*-methyl propionamide, 12

To a stirred solution of **5** (1.0 g, 2.46 mmol) in THF (10 mL) at 0°C was added Bu^n_4NF (1.0 M solution in THF, 2.71 mL, 2.71 mmol). The reaction mixture was stirred at rt for 1 h. The reaction was quenched with saturated aqueous NH_4Cl, extracted with Et_2O followed by washing with brine, dried with $MgSO_4$ and evaporated in vacuo. Purification by silica gel chromatography (ethyl acetate/hexane = 3/1) gave primary alcohol (680 mg, 94%); white solid; $[\alpha]_D^{23}$ −83.5 (*c* 1.0, $CHCl_3$); mp 111 ~ 112°C; IR (KBr) 3214, 2917, 2866, 1651 cm^{-1}; ^1H NMR (500 MHz) δ 2.09 (m, 2H), 2.67 (m, 2H), 3.20 (s, 3H), 3.71 (s, 3H), 3.88 (m, 2H), 4.03 (ddd, J = 4.0, 5.0, 7.0 Hz, 1H), 4.62 (ddd, J = 5.0, 8.0, 12.0 Hz, 1H), 7.40–7.49 (m, 3H), 7.93–7.95 (m, 2H); ^{13}C NMR (125 MHz) δ 27.82, 30.16, 32.48, 61.53, 64.78, 73.63, 81.76, 127.83, 128.55, 128.58, 131.79; HRMS *m*/*e* calcd for $C_{15}H_{20}N_2O_4$ 293.1501, found 293.1527.

To a stirred solution of primary alcohol (600 mg, 2.05 mmol) in CH_3CN/Et_2O (3:5, 5.7 mL) were added triphenylphosphine (1.4 g, 5.34 mmol), imidazole (381 mg, 5.60 mmol) followed by portionwise of iodine (1.49 g, 5.88 mmol) at 0°C. The reaction mixture was stirred at rt for 4 h. Dilution with Et_2O followed by washing with saturated aqueous $Na_2S_2O_3$ (20 mL), saturated

aqueous $CuSO_4$ (20 mL), brine, dried with $MgSO_4$ and evaporated in vacuo. Purification by silica gel chromatography (ethyl acetate/hexane = 1/1) gave iodide (743 mg, 90%); yellow oil; IR (neat) 2962, 1777, 1646 cm^{-1}; ^1H NMR (500 MHz) δ 2.04 (m, 2H), 2.68 (m, 2H), 3.19 (s, 3H), 3.20 (dd, J = 7.0, 10.0 Hz, 1H), 3.48 (dd, J = 4.0, 10.0 Hz, 1H), 3.71 (s, 3H), 4.09 (ddd, J = 3.5, 4.0, 5.5 Hz, 1H), 4.51 (ddd, J = 5.5, 8.5, 10.0 Hz, 1H), 7.41–7.51 (m, 3H), 7.94–7.95 (m, 2H); ^{13}C NMR (125 MHz) δ 10.72, 27.77, 29.94, 30.52, 61.53, 72.35, 80.88, 127.76, 128.64, 128.66, 131.98, 164.59; HRMS m/e calcd for $C_{15}H_{19}N_2O_3$ 403.0519, found 403.0511.

To a stirred solution of iodide (945 mg, 2.35 mmol) and azobis (isobutyronitrile) (386 mg, 2.35 mmol) in benzene/MeOH (5:1, 8.8 mL) was added tri-n-butyltin hydride (1.26 mL, 4.7 mmol), and the reaction mixture was heated under reflux for 1 h. The solvents were removed under reduced pressure. Purification by silica gel chromatography (ethyl acetate/hexane = 1/1) gave **12** (390 mg, 87.5%); white–yellow oil; $[\alpha]_D^{25}$ −53.9 (c 1.0, $CHCl_3$); IR (neat) 2965, 2929, 1648 cm^{-1}; ^1H NMR (400 MHz) δ 1.36 (d, J = 6.5 Hz, 3H), 1.97 (m, 1H), 2.08 (m, 1H), 2.65 (m, 2H), 3.20 (s, 3H), 3.82 (s, 3H), 3.95 (dd, J = 6.5, 7.0 Hz, 1H), 4.28 (ddd, J = 4.0, 7.0, 8.5 Hz, 1H), 7.46–7.56 (m, 3H), 7.92–7.95 (m, 2H); ^{13}C NMR(125 MHz) δ 21.60, 27.93. 29.84, 61.50, 67.53, 86.18, 128.32, 128.40, 128.52, 131.45, 162.82; HRMS m/e calcd for $C_{15}H_{20}N_2O_3$ 277.1552, found 277.1567.

4.9. 2-(12-Bromododecyl)-2-methyl-1,3-dioxolane, 13

To a stirred solution of 1,10-dibromodecane (1.54 g, 5.13 mmol) in THF (3 mL) at rt was added dropwise dilithium tetrachlorocuprate solution (15.4 mL, 0.1 M). Grignard reagent 20.5 mL, which was prepared from 2-(2-bromoethyl)-2-methyl-1,3-dioxolane and magnesium turning, was added dropwise and the reaction mixture was stirred for 2 h. The reaction mixture was washed with saturated aqueous NH_4Cl, brine, dried with $MgSO_4$ and evaporated in vacuo. Purification by silica gel chromatography (ethyl acetate/hexane = 1/30) gave **13** (900 mg, 52%); colorless oil; ^1H NMR (500 MHz) δ 1.27–1.43 (br m, 20H), 1.56 (s, 3H), 1.85 (t, 2H), 3.40 (t, 2H), 3.94 (m, 4H); ^{13}C NMR (125 MHz) δ 23.97, 24.37, 28.43, 29.03, 29.69, 29.77, 29.80, 29.84, 29.85, 30.13, 33.09, 34.36, 39.50, 64.86, 110.46; HRMS m/e calcd for $C_{16}H_{31}BrO_2$ 335.1586, found 335.1597.

4.10. 3-((4*S*,*trans*)-4,5-Dihydro-4-methyl-2-phenyloxazol-5-yl)-heptadecan-3-one-16-ethylenacetal, 4

Under an Ar atmosphere magnesium turning (729 mg, 30 mmol) were treated with 5 mL of a solution of **13** (9.21 g, 30 mmol) in dry THF (30 mL). After addition of 2 drops of 1,2-dibromoethane the reaction started and the remaining solution was added dropwise. Then a solution of **12** (1.54 g, 5.13 mmol) in dry THF (50 mL) was added dropwise at 0°C and the reaction mixture was stirred for 2 h. the reaction mixture was washed with saturated aqueous NH_4Cl, brine, dried with $MgSO_4$ and evaporated in vacuo. Purification by silica gel chromatography (ethyl acetate/hexane = 1/3) gave **4** (162 mg, 70%); colorless oil; $[\alpha]_D^{23}$ −21.0 (c 1.0, $CHCl_3$); IR (neat) 2927, 2852, 1709, 1649 cm^{-1}; ^1H NMR (400 MHz) δ 1.26–1.40 (br m, 22H), 1.56–1.65 (m, 2H), 1.90 (m, 1H), 2.01 (m, 1H), 2.43 (t, J = 9.6 Hz, 2H), 2.61 (t, J = 9.8 Hz, 2H), 3.92 (m, 5H), 4.21 (ddd, J = 4.0, 7.0, 8.0 Hz, 1H), 7.38–7.47 (m, 3H), 7.91–7.94 (m, 2H); ^{13}C NMR (125 MHz) δ 21.59, 23.92, 24.31, 28.83, 29.37, 29.42, 29.59, 29.66, 29.75, 29.78, 29.80, 29.81, 30.04, 38.30, 39.45, 43.20, 43.99, 64.79, 67.45, 86.00, 128.18, 128.36, 128.49, 131.46, 162.72, 210.25; HRMS m/e calcd for $C_{29}H_{45}NO_4$ 472.3427, found 472.3436.

4.11. (+)-Spectaline, 2

A solution of **4** (366 mg, 0.78 mmol) in AcOH/MeOH (1:9, 10 mL), to which was added 366 mg of 20% $Pd(OH)_2$, was vigorously shaken under 75 psi H_2 for 24 h at ambient temperature. The mixture was then filtered through a pad of silica and concentrated in vacuo. Purification by column chromatography over silica gel ($CHCl_3$/ EtOH = 100:1) gave (+)-spectaline, **2** (158 mg, 70%); white solid; $[\alpha]_D^{26}$ +8.8 (c 1.3, $CHCl_3$); mp 59 ~ 61°C; IR (KBr) 3283, 2916, 2848, 1706 cm^{-1}; ^1H NMR (500 MHz) δ 1.12 (d, J = 6.5 Hz, 3H), 1.25–1.39 (br, 21H), 1.47–1.57 (br m, 4H), 1.90 (br m, OH, NH), 2.13 (s, 3H), 2.41 (t, J = 7.5 Hz, 2H), 2.50–2.54 (m, 1H), 2.79 (qd, J = 7.0, 1.0 Hz, 1H), 3.56 (br s, 1H); ^{13}C NMR (125 MHz) δ 18.54, 24.10, 25.84, 26.01, 29.41, 29.63, 29.68, 29.81, 29.83, 29.87, 29.93, 29.98, 30.08, 32.15, 36.75, 44.05, 56.15, 57.53, 68.03, 209.64; HRMS m/e calcd for $C_{20}H_{39}NO_2$ 326.3059, found 326.3070.

Acknowledgements

This study was supported by a grant of the Korea Health 21 R&D Project, Ministry of Health and Welfare, Republic of Korea (01-PJ1-PG1-01CH13-0002).

References

1. (a) Strunz, G. M.; Findlay, J. A. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1986; Vol. 26, p. 89; (b) Jones, T. H.; Blum, M. S.; Robertsson, H. G. *J. Nat. Prod.* **1990**, *53*, 429 and references cited therein.
2. (a) Highet, R. J. *J. Org. Chem.* **1964**, *29*, 471–474; (b) Highet, R. J.; Highet, P. F. *J. Org. Chem.* **1966**, *31*, 1275–1276; (c) Rice, W. Y., Jr.; Coke, J. L. *J. Org. Chem.* **1966**, *31*, 1010–1012. Synthesis: (d) Oetting, J.; Holzkamp, J.; Meyer, H. H.; Pahl, A. *Tetrahedron: Asymmetry* **1997**, *8*, 477–484 and references cited therein.
3. (a) Christofidis, I.; Welter, A.; Jadot, J. *Tetrahedron* **1977**, *33*, 977–979. Synthesis: (b) Momose, T.; Toyooka, N. *Tetrahedron Lett.* **1993**, *34*, 5785–5786; (c) Momose, T.; Toyooka, N.; Jin, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2005–2013; (d) Toyooka, N.; Yoshida, Y.; Yotsui, Y.; Momose, T. *J. Org. Chem.* **1999**, *64*, 4914–4919.
4. (a) Lee, K. Y.; Kim, Y. H.; Park, M. S.; Ham, W. H. *Tetrahedron Lett.* **1998**, *39*, 8129–8132; (b) Lee, K. Y.; Kim, Y. H.; Park, M. S.; Ham, W. H. *J. Org. Chem.* **1999**, *64*, 9450–9458.

5. Lee, K. Y.; Kim, Y. H.; Oh, C. Y.; Ham, W. H. *Org. Lett*. **2000**, *2*, 4041–4042.
6. (a) Dess, D. B.; Martin, J. C. *J. Org. Chem*. **1983**, *48*, 4155–4156; (b) Meyers, A. G.; Zhong, B.; Movassaghi, M.; Kung, D. W.; Lanman, B. A.; Kwon, S. *Tetrahedron Lett*. **2000**, *41*, 1359–1362.
7. Denis, J.-N.; Correa, A.; Greene, A. E. *J. Org. Chem*. **1991**, *56*, 6939–6942.
8. (a) Suh, Y.-G.; Jung, J.-K.; Kim, S.-A.; Shin, D.-Y.; Min, D.-H. *Tetrahedron Lett*. **1997**, *38*, 3911–3914; (b) Takao, K.; Nigawara, Y.; Nishino, E.; Takagi, I.; Maeda, K.; Tadano, K.; Ogawa, S. *Tetrahedron* **1994**, *50*, 5681–5704.
9. (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett*. **1981**, *22*, 3815–3818; (b) Fehrentz, J.-A.; Castro, B. *Synthesis* **1983**, 676–678.
10. (a) Tamura, M.; Kochi, J. *Synthesis* **1971**, 303–304; (b) Fujisawa, T.; Sato, T.; Kawara, T.; Noda, A. *Tetra -hedron Lett*. **1982**, *31*, 3193–3194; (c) Paquette, L. A.; Galemmo, R. A., Jr.; Caille, J.-C.; Valpey, R. S. *J. Org. Chem*. **1986**, *51*, 686–695; (d) Volkmann, R. A.; Davis, J. T.; Meltz, C. N. *J. Org. Chem*. **1983**, *48*, 1767–1769.
11. (a) Sunazuka, T.; Nagamitsu, T.; Matsuzaki, K.; Tanaka, H.; Omura, S.; Smith, A. B., III. *J. Am. Chem. Soc*. **1993**, *115*, 5302; (b) Nagamitsu, K.; Sunazuka, T.; Tanaka, H.; Omura, S.; Sprengeler, P. A.; Smith, A. B., III. *J. Am. Chem. Soc*. **1996**, *118*, 3584–3590; (c) Soucy, F.; Grenier, L.; Behnke, M. L.; Destree, A. T.; McCormack, T. A.; Adams, J.; Plamondon, L. *J. Am. Chem. Soc*. **1999**, *121*, 9967–9976.