Total Synthesis of D-*lyxo*-Phytosphingosine and Formal Synthesis of Pachastrissamine via a Chiral 1,3-Oxazine

Yu Mu,[a] Ji-Yeon Kim,[a] Xiangdan Jin,[a] Seok-Hwi Park,[a] Jae-Eun Joo,[b] Won-Hun Ham*[a]

[a] School of Pharmacy, Sungkyunkwan University, Suwon 440-746, Republic of Korea

[b] Yonsung Fine Chemicals Co., Ltd., 129-9 Suchon-ri, Jangan-myeon, Hwaseong-si, Gyeonggi-do 445-944, Republic of Korea
Fax +82(31)2928800; E-mail: whham@skku.edu

Received: 27.03.2012; Accepted after revision: 14.05.2012

Abstract: Concise and efficient syntheses of D-*lyxo*-phytosphingosine and pachastrissamine were achieved utilizing a chiral oxazine. The key features in these strategies are the stereoselective intramolecular oxazine formation catalyzed by palladium(0), and intermolecular olefin cross-metathesis.

Key words: palladium catalysis, sphingolipids, stereoselective synthesis, cross-coupling, natural products

The sphingolipids are distributed ubiquitously in the membranes of eukaryotic cells and have been demonstrated to regulate biological processes.[1] One of the most important sphingolipids, phytosphingosines, have been widely distributed in plants, fungi, yeasts, mammalian tissues, and marine organism. They consist of a base, bearing a long aliphatic chain (an 18-carbon atom) and a polar 2-amino-1,3,4-triol head group. Phytosphingosines and their glycosylated derivatives exhibit significant immunostimulatory and antitumor properties.[2,3] Phytosphingosines with other chain lengths, as well as different stereochemistries of the amino and hydroxy groups, are also known and bioactive to various degrees.[4] Because of its promising biological activities and its three contiguous stereocenters, much effort has been devoted to the development of the syntheses of D-*lyxo*-phytosphingosine (**1**) (see Figure 1) and other stereoisomers, such as D-*lyxo*-, D-*xylo*- and D-*arabino*-phytosphingosine.[5,6]

(+)-Pachastrissamine (**2**) (see Figure 1), a potent cytotoxic agent possessing a tetrahydrofuran skeleton, was isolated from the Okinawa marine sponge, *Pachastrissa sp.* (family calthropellidae), by Higa et al. in 2002.[7] Subsequently, the Debitus research group reported the isolation of the same natural product from a different marine sponge, *Jaspis sp.,* and named as jaspine B.[8] Pachastrissamine **2** represents the first example of a cyclic anhydrosphingosine structural feature as a natural product. It was reported to possess the 2*S*,3*S*,4*S* absolute configuration and is structurally similar to that of the open chain sphingolipid D-*ribo*-phytosphingosine. A number of synthetic approaches[6a,9,10] have been reported due to its novel tetrahydrofuran structure and its promising biological activity.[11]

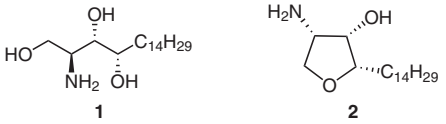
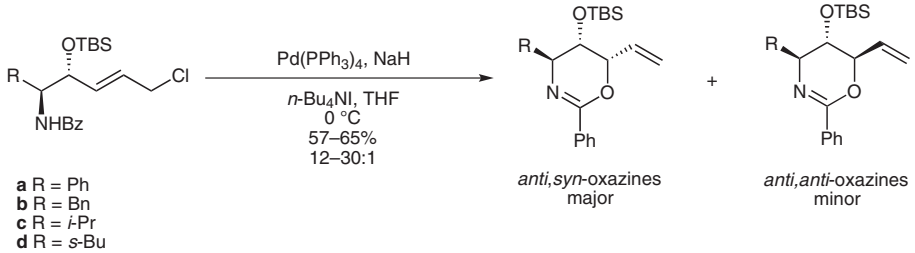


Figure 1 Structures of D-*lyxo*-phytosphingosine (**1**) and pachastrissamine (**2**)

On the basis of our previous research,[12] as shown in Scheme 1, we anticipated that the palladium(0)-catalyzed oxazine formation of a γ-allyl benzamide, having a benzoyl substituent as an N-protection group in the presence of $Pd(PPh_3)_4$, NaH, and *n*-Bu_4NI might proceed with high stereoselectivity. The bulkiness of protecting group on the secondary alcohols is responsible for controlling the diastereoselectivity of oxazine ring formation. This process efficiently adjusted stereochemistry and provided simultaneous protection for the nearly generated hydroxy group.

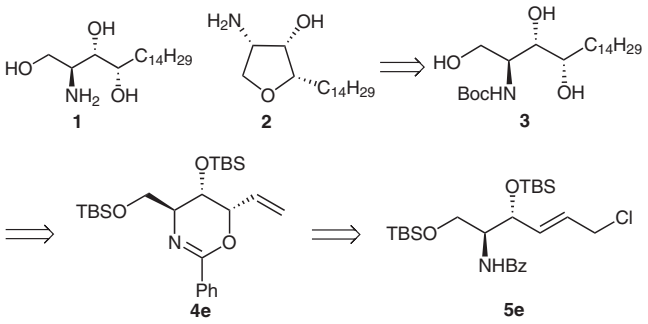
As shown in Scheme 2, our retrosynthetic analysis suggested that D-*lyxo*-phytosphingosine (**1**) and pachastrissamine (**2**) could be easily synthesized from *N*-Boc triol **3**.



Scheme 1 Oxazine formation from 1,2-*anti*-amino alcohol derivatives

SYNTHESIS 2012, 44, 2340–2346
Advanced online publication: 26.06.2012
DOI: 10.1055/s-0031-1289813; Art ID: SS-2012-F0314-OP

N-Boc triol **3** could be synthesized by ring cleavage of oxazine under Schotten–Baumann reaction of **4e**. We envisioned that the intramolecular palladium(0)-catalyzed oxazine formation of benzamide **5e** would generate the oxazine **4e**, bearing a pendant vinyl group, that could be elaborated to the alkene via an olefin cross-metathesis reaction.



Scheme 2 Retrosyntheses of D-*lyxo*-phytosphingosine (**1**) and pachastrissamine (**2**)

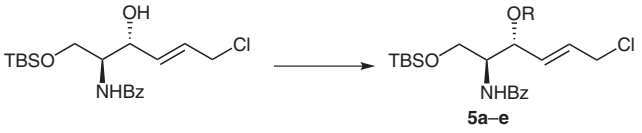
In our laboratory, we have been exploring the utility of enantiopure oxazine, as a chiral building block, for the stereocontrolled synthesis of natural products.[12,13] As part of this program, we have now developed a novel strategy for concise syntheses of D-*lyxo*-phytosphingosine (**1**) and pachastrissamine (**2**). Here we describe the novel asymmetric syntheses of D-*lyxo*-phytosphingosine (**1**) and pachastrissamine (**2**) that utilize an oxazine as a chiral building block.

The synthesis of **1** and **2**, commenced with *N*-benzoyl-L-serine methyl ester (**6**).[12] Treatment of **6** with *N*,*O*-dimethylhydroxylamine in the presence of trimethylaluminum readily converted the ester **6** into the corresponding Weinreb amide in 94% yield. Reaction of this Weinreb amide with vinyltin and MeLi in THF at –78 °C gave the α,β-unsaturated ketone **7** in 86% yield (Scheme 3). Chelation-controlled hydride reduction of amino ketone **7** with lithium tri-*tert*-butoxyaluminum hydride in ethanol at –78 °C gave *anti*-amino alcohol as the major compound in good yield with excellent stereoselectivity (*anti*/*syn* = 10:1, as determined by ^{1}H NMR analysis). Protection of *anti*-amino alcohol with TBSCl afforded the cyclization precursor **5e** in excellent yield (Scheme 3).

Different cyclization precursors **5a**–**e** were simply prepared under the reaction conditions shown in Table 1.

The reaction of **5e**, which has *tert*-butyldimethylsilyl as the protecting group, with NaH and *n*-Bu_4NI in the presence of $Pd(PPh_3)_4$ in THF at 0 °C afforded the *anti*,*syn*-oxazine **4e** as the major product along with a minor amount of *anti*,*anti*-oxazine product **4e′**. The diastereoselectivity was improved to >30:1 with TBS protecting group on the secondary alcohol. It is clear from this experiment that steric bulkiness of the protecting group highly influences the level of diastereoselectivity (Table 2).

Table 1 Cyclization Precursors Prepared



5a–e

Product	R	Reagents	Temp (°C)	Time (h)	Yield (%)[a]
5a	Me	MeI, NaH, THF	0	2	73
5b	Bn	BnBr, NaH, THF	r.t.	2	70
5c	$MeOCH_2$	MOMCl, Et_3N, CH_2Cl_2	0–r.t.	24	80
5d	BOM	BOMCl, Et_3N, CH_2Cl_2	0	24	76
5e	TBS	TBSCl, imidazole, DMF	r.t.	2	93

[a] Yields refer to the isolated products.

The stereochemistries of the oxazines obtained above were elucidated by ^{1}H NMR spectroscopy. The relative configuration of each diastereomer of the oxazine products, obtained after the silica gel column separation, was determined by a comparison of their coupling constants (Figure 2). The small coupling constant of $J_{5,6}$ = 4.0 Hz, as in *anti*,*syn*-oxazine **4e**, was caused by the axial-equatorial relationship between the two adjacent protons in six-membered rings. The large coupling constant of $J_{5,6}$ = 8.8 Hz, as in *anti*,*anti*-oxazine **4e′**, was typically due to the diaxial relationship between the two adjacent protons in six-membered rings.

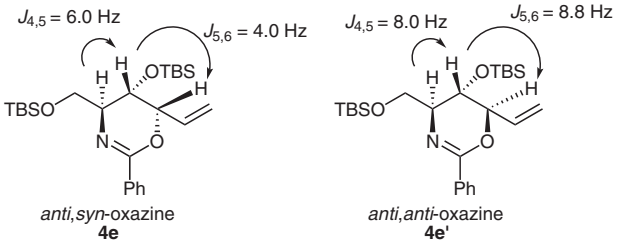
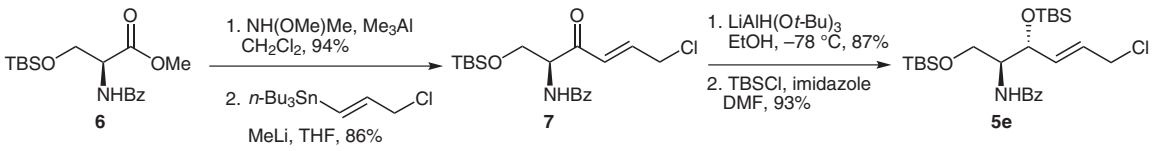
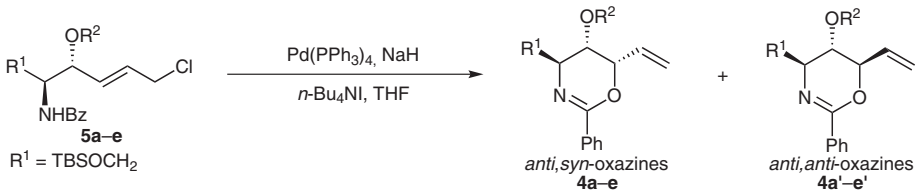


Figure 2 ^{1}H NMR ($CDCl_3$) coupling constants of oxazines



Scheme 3 Synthesis of **5** from l-serine

Table 2 Oxazine Formation Catalyzed by Pd(0)[a]



R^2	Substrate	Temp (°C)	Time (h)	Yield of **4** (%)[b]	Ratio (*anti*,*syn*/*anti*,*anti*)[c]
Me	**5a**	0	5	51	2:1
Bn	**5b**	0	5	52	6:1
MOM	**5c**	0	5	71	9:1
BOM	**5d**	0	5	69	13:1
TBS	**5e**	0	5	65	>30:1

[a] Reaction conditions: $Pd(PPh_3)_4$ (0.2 equiv), NaH (2 equiv), *n*-Bu_4NI (1 equiv), and THF.
[b] Yield refers to the isolated and mixed products.
[c] Ratio was determined by ^1H NMR analysis of *anti*,*syn*-oxazines and *anti*,*anti*-oxazines.

In addition, the coupling constant of the newly generated chiral center (H_5-H_6) of **4e** has similar values of 2.5–4.0 Hz, when compared to those of the previously reported *syn*,*syn*-oxazine compounds.[13] In contrast, the coupling constant of the newly generated chiral center (H_5-H_6) of **4e′** has the same values of 7.5–9.0 Hz, as the *syn*,*anti*-isomer.

The assignment of relative configuration was confirmed by observation of the larger NOE enhancement for *anti*,*syn*-oxazine **4e** and *anti*,*anti*-oxazine **4e′** as shown in Figure 3. In the *anti*,*syn*-oxazine case, for compound **4e**: there are 9.60% NOE between H_5 and H_6, 3.94% between H_5 and H_4, but no NOE effects between H_4 and H_6. In the *anti*,*anti*-oxazine case, for compound **4e′**: there are 2.75% NOE between H_5 and H_6, 2.00% between H_5 and H_4, and 5.99% between H_4 and H_6.

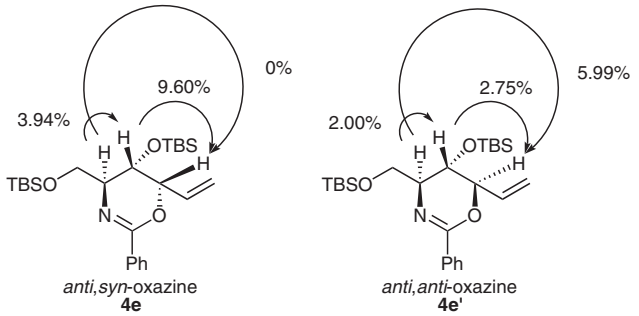
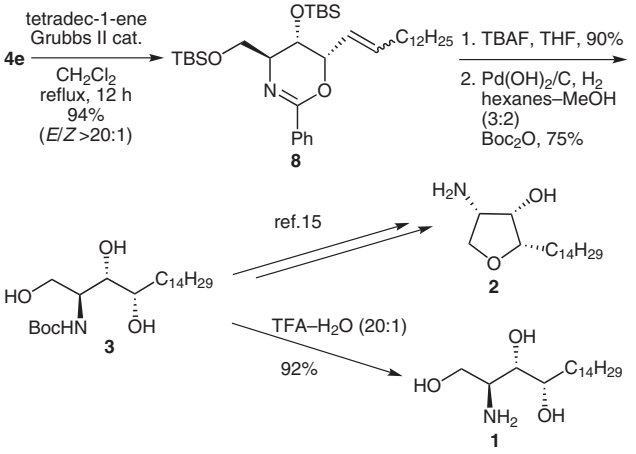


Figure 3 Observed NOEs in oxazines

The olefin cross-metathesis of **4e** with tetradec-1-ene in the presence of 5 mol% Grubbs II catalyst yielded compound **8** in high yield (94%), with *E*/*Z* >20:1 regioseletivity (^1H NMR).[14] Deprotection of the disilyl ether of oxazine **8** with tetrabutylammonium fluoride gave a diol. The diol was converted into the known compound **3** by treatment with $Pd(OH)_2$/C under 70 psi of H_2 at ambient temperature in the presence of $(Boc)_2O$ in 75% yield. The optical rotation of *N*-Boc triol **3**, $[\alpha]_D^{25}$ –8.9 (*c* 0.9, $CDCl_3$), compared to the reported value, $[\alpha]_D^{25}$ –8.3 (*c* 1.0, $CDCl_3$),[15] confirmed the identity of the absolute configuration. Since *N*-Boc-triol **3** was employed as an intermediate in the synthesis of pachastrissamine (**2**) by the Marco group,[15] this sequence represents a formal synthesis of the **2**.



Scheme 4 Syntheses of D-*lyxo*-phytosphingosine (**1**) and pachastrissamine (**2**)

The final product **1** was easily obtained by a simple acid hydrolysis with trifluoroacetic acid–water (20:1) of *N*-Boc-triol **3**. After vacuum evaporation of excess TFA, neutralization with aqueous $NaHCO_3$ and extraction with EtOAc, D-*lyxo*-phytosphingosine (**1**) was isolated in 92% yield, by flash chromatography on silica gel. Optical and spectroscopic data were in excellent agreement with those reported in the literature.[6]

A previous paper from our laboratory described[12] a new procedure for the highly stereoselective formation of an oxazine ring. Further, the bulkiness of alcohol protecting groups predominantly controls the diastereoselectivity of oxazine ring formation. On the basis of these results, we applied the asymmetric synthetic method of D-*lyxo*-phytosphingosine (**1**) and pachastrissamine (**2**) utilizing the chiral oxazine **4e**. The key features in these strategies are the stereoselective intramolecular oxazine formation catalyzed by palladium(0) and intermolecular olefin cross-metathesis. The net results were the syntheses from a linear sequence of five steps from **6** in 27.0% overall yield for *N*-Boc triol **3**, which has previously been transformed to pachastrissamine (**2**) in three steps,[15] and to D-*lyxo*-phytosphingosine (**1**) in 24.8% overall yield in six steps .

Optical rotations were measured on a polarimeter in the solvent specified. ^{1}H and ^{13}C NMR spectra were obtained from Cooperative Center for Research Facilities in Sungkyunkwan University on FT-NMR 125 or 500 MHz spectrometers. Chemical shifts values are reported in parts per million relative to TMS or $CDCl_3$ as an internal standard and coupling constants in hertz. IR spectra were recorded on a FTIR spectrometer. Mass spectral data were obtained from the Korea Basic Science Institute (Daegu) on Jeol JMS 700 high-resolution mass spectrometer. Flash chromatography was carried out using mixtures of EtOAc and hexane as eluents. Unless otherwise noted, all nonaqueous reactions were done under an argon atmosphere with commercial grade reagents and solvents. THF was distilled over Na and benzophenone (indicator). CH_2Cl_2 was distilled from CaH_2.

(*S*,*E*)-*N*-[1-(*tert*-Butyldimethylsilyloxy)-6-chloro-3-oxohex-4-en-2-yl]benzamide (7)

Formation of Weinreb Amide: To a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (867 mg, 8.89 mmol) in CH_2Cl_2 (10 mL) was added Me_3Al (4.45 mL of a 2 M solution in hexane, 8.89 mmol) at 0 °C (**Caution**: CH_4 evolution). The mixture was stirred for 30 min at r.t. Subsequently, a solution of *N*-benzoyl-O-TBS-L-serine methyl ester (**6**; 1.00 g, 2.96 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The mixture was stirred at r.t. for 1 h, after which time TLC analysis (eluent: EtOAc–hexanes, 1:2) indicated completion of the reaction. The reaction mixture was cooled to 0 °C and carefully quenched with aq 10% sodium potassium tartrate (2.20 mL). After stirring for 1 h at r.t., the resulting suspension was filtered through a Celite pad and washed with CH_2Cl_2 (20 mL). The filtrate was concentrated in vacuo to give the crude product, which upon purification by column chromatography on silica gel gave the corresponding Weinreb amide (987 mg, 91%) as a colorless oil; R_f = 0.30 (EtOAc–hexanes, 1:2); $[\alpha]_D^{25}$ +41.15 (*c* 1.0, $CHCl_3$).

IR (neat): 3326, 2931, 2857, 1644, 1111 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.02–0.05 (m, 6 H), 0.92 (s, 9 H), 3.29 (s, 3 H), 3.83 (s, 3 H), 3.96 (dd, *J* = 4.5, 10.0 Hz, 1 H), 4.06 (dd, *J* = 4.5, 10.0 Hz, 1 H), 5.25 (m, 1 H), 7.09 (d, *J* = 7.5 Hz, 1 H), 7.44–7.52 (m, 3 H), 7.83–7.85 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 0.02, 0.05, 23.76, 31.31, 57.48, 67.06, 68.73, 132.62, 134.07, 137.13, 139.26, 172.43.

HRMS-FAB: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{31}N_2O_4Si$: 367.2053; found: 367.2050.

Conversion of the Weinreb Amide into the Amino Ketone 7: Vinyltin (1.50 g, 4.09 mmol) was dissolved in anhyd THF (10 mL) and cooled to –78 °C. MeLi (1.6 M solution in hexane, 2.60 mL, 4.09 mmol) was added dropwise. The mixture was stirred for 30 min at the same temperature. Subsequently, a solution of the above Weinreb amide (0.50 g, 1.36 mmol) in anhyd THF (5 mL) was added dropwise and the stirring was allowed to continue for 30 min, after which time TLC analysis (eluent: EtOAc–hexanes, 1:2) indicated completion of the reaction. The reaction was quenched by sat. aq NH_4Cl (10 mL) and then warmed to r.t. The layers were separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ (20 mL), brine (20 mL), dried ($MgSO_4$), and filtered. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography to give the amino ketone **7** (447 mg, 86%) as a colorless oil; R_f = 0.6 (EtOAc–hexanes, 1:2); $[\alpha]_D^{25}$ +56.19 (*c* 1.6, $CHCl_3$).

IR (neat): 3412, 2932, 1643, 1521, 1255, 974 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.034–0.089 (m, 6 H), 0.87–0.91 (m, 9 H), 4.02 (dd, *J* = 4.5, 10.2 Hz, 1 H), 4.26 (dd, *J* = 3.0, 4.5 Hz, 1 H), 4.27 (dd, *J* = 1.8, 5.7 Hz, 2 H), 5.06–5.11 (m, 1 H), 6.67 (ddd, *J* = 1.5, 1.8, 15.3 Hz, 1 H), 7.03–7.08 (m, 1 H), 7.11 (d, *J* = 3.0 Hz, 1 H), 7.47–7.60 (m, 3 H), 7.86–7.89 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.34, –5.32, 18.28, 25.95, 42.97, 59.67, 63.28, 127.29, 127.46, 128.36, 128.88, 132.02, 134.16, 141.50, 167.13, 195.89.

HRMS-FAB: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{29}ClNO_3Si$: 382.1605; found: 382.1602.

***N*-{(5*R*,6*S*)-5-[(*E*)-3-Chloroprop-1-enyl]-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-yl}benzamide (5e)**

Intermediate Amino Alcohol: To a solution of the amino ketone **7** (365 mg, 0.96 mmol) in EtOH (10 mL) was added $LiAlH(Ot\text{-}Bu)_3$ (1 N solution in THF, 1.92 mL, 1.92 mmol) at –78 °C. After stirring the reaction mixture at the same temperature for 2 h, 10% aq citric acid (10.00 mL) was added. The resulting mixture was warmed to r.t. and extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to give the crude product. Column chromatography on silica gel gave the intermediate amino alcohol (323 mg, 0.84 mmol, 87% yield, ratio *anti*/*syn* >10:1 by ^{1}H NMR) as a colorless oil; R_f = 0.3 (EtOAc–hexanes, 1:1); $[\alpha]_D^{25}$ +7.95 (*c* 1.0, $CHCl_3$).

IR (neat): 3346, 2953, 2858, 1639, 1534, 1487, 1253, 1076, 712 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.076–0.13 (m, 6 H), 0.92–0.95 (m 9 H), 3.91 (dd, *J* = 3.0, 10.5 Hz, 1 H), 3.99–4.03 (m, 1 H), 4.05 (d, *J* = 3.0, 5.4 Hz, 1 H), 4.12 (d, *J* = 6.0 Hz, 2 H), 4.15–4.25 (m, 1 H), 4.47–4.44 (m, 2 H), 5.87–6.10 (m, 2 H), 6.97 (d, *J* = 8.1 Hz, 1 H), 7.42–7.59 (m, 3 H), 7.78–7.85 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.38, –5.35, 18.30, 54.03, 63.38, 73.74, 127.17, 127.99, 128.80, 128.91, 131.98, 134.32, 134.41, 167.86.

HRMS-FAB: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{31}ClNO_3Si_2$: 384.1762; found: 384.1759.

*Formation of **5e***: Imidazole (64 mg, 0.94 mmol) and *tert*-butyldimethylchlorosilane (141 mg, 0.94 mmol) were added to a stirred solution of the above alcohol (300 mg, 0.78 mmol) in DMF (8.0 mL) at r.t. And stirring for 6 h, the reaction mixture was quenched with H_2O (8 mL), and extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and evaporated in vacuo. Purification by silica gel chromatography gave **5e** (363 mg, 93%) as a colorless oil; R_f = 0.3 (EtOAc–hexanes, 1:8); $[\alpha]_D^{25}$ +13.61 (*c* 1.0, $CHCl_3$) (Table 1).

IR (neat): 3298, 2942, 2857, 1638, 1538, 1253, 1087, 838 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.06–0.11 (m, 12 H), 0.91–0.93 (m, 18 H), 3.71 (dd, *J* = 4.9, 10.2 Hz, 1 H), 3.98–4.07 (m, 2 H), 4.17–4.20 (m, 1 H), 4.44 (t, *J* = 6.4 Hz, 1 H), 5.83–5.87 (m, 1 H), 5.92 (dd, *J* = 6.5, 15.3 Hz, 1 H), 6.34 (d, *J* = 8.6 Hz, 1 H), 7.42–7.45 (m, 2 H), 7.49–7.52 (m, 1 H), 7.72–7.74 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.29, –5.09, –4.70, –3.84, 18.32, 18.42, 25.88, 26.05, 26.10, 31.17, 44.44, 55.46, 61.25, 72.20, 126.94, 128.18, 128.81, 131.63, 135.05, 135.45, 167.24.

HRMS-FAB: *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{45}ClNO_3Si_2$: 498.2627; found: 498.2624.

Oxazine Formation; (4*S*,5*S*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-4-[(*tert*-butyldimethylsilyloxy)methyl]-2-phenyl-6-vinyl-5,6-dihydro-4*H*-1,3-oxazine (4e) and (4*S*,5*S*,6*R*)-5-(*tert*-Butyldimethylsilyloxy)-4-[(*tert*-butyldimethylsilyloxy)methyl]-2-phenyl-6-vinyl-5,6-dihydro-4*H*-1,3-oxazine (4e′); Typical Procedure

NaH (321 mg, 8.03 mmol, 60% in mineral oil) and *n*-Bu_4NI (1.48 g, 4.01 mmol) were added to a stirred solution of the silyl ether **5e** (2.00 g, 4.01 mmol) in anhyd THF (80 mL) at 0 °C. After stirring for 5 min, $Pd(PPh_3)_4$ (928 mg, 0.80 mmol) was added to the mixture and stirring was allowed to continue for 5 h at the same temperature. The reaction mixture was filtered through a pad of silica gel and the filtrate was evaporated under reduced pressure to give the crude product. Purification by silica gel chromatography gave a mixture of *anti*,*syn*/*anti*,*anti* **4e** and **4e′** (1.20 g, 65%, ratio *anti*,*syn*/*anti*,*anti* >30:1 by ^{1}H NMR) as a colorless oil (Table 2).

4e

R_f = 0.5 (EtOAc–hexanes, 1:20); $[\alpha]_D^{25}$ –37.24 (*c* 1.0, $CHCl_3$).

IR (neat): 2940, 2860, 1661, 1245, 1115, 836, 777 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.08–0.20 (m, 12 H), 0.88–0.96 (m, 18 H), 3.47 (dd, *J* = 3.0, 5.0, 8.0 Hz, 1 H), 3.83 (dd, *J* = 5.0, 10.0 Hz, 1 H), 4.02 (dd, *J* = 3.0, 10.0 Hz, 1 H), 4.21 (dd, *J* = 4.0, 7.0 Hz, 1 H), 4.80 (ddd, *J* = 2.0, 4.0, 7.0 Hz, 1 H), 5.35 (ddd, *J* = 1.0, 2.0, 7.0 Hz, 1 H), 5.40 (ddd, *J* = 1.0, 2.0, 13.0 Hz, 1 H), 6.10 (ddd, *J* = 5.0, 10.5, 17.0 Hz, 1 H), 7.38–7.47 (m, 3 H), 8.01–8.04 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.04, –4.99, –4.51, –4.35, 18.27, 18.55, 26.00, 26.13, 26.27, 59.62, 64.13, 65.35, 75.93, 117.54, 127.62, 128.21, 130.59, 133.72, 133.79, 154.43.

HRMS-FAB: *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{44}NO_3Si_2$: 462.2860; found: 462.2862.

4e′

R_f = 0.5 (EtOAc–hexanes, 1:20); $[\alpha]_D^{25}$ –28.41 (*c* 1.0, $CHCl_3$).

IR (neat): 3356, 2946, 2833, 1663, 1451, 1030, 836, 780, 671 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.05 (s, 3 H), 0.11 (s, 3 H), 0.12 (s, 3 H), 0.17 (s, 3 H), 0.87 (s, 9 H), 0.93 (s, 9 H), 3.43 (dd, *J* = 2.85, 2.85, 8.55 Hz, 1 H), 3.90 (t, *J* = 8.55 Hz, 1 H), 3.94–4.02 (m, 2 H), 4.40 (dd, *J* = 6.5, 8.5 Hz, 1 H), 5.38 (dt, *J* = 1.5, 10.5 Hz, 1 H), 5.53 (dt, *J* = 1.5, 17.5 Hz, 1 H), 6.03 (ddd, *J* = 6.5, 10.5, 17.5 Hz, 1 H), 7.33–7.42 (m, 3 H), 7.97–8.01 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.05, –4.90, –4.20, –3.40, 18.39, 18.55, 26.05, 26.20, 62.80, 63.10, 66.28, 79.39, 119.10, 127.70, 128.19, 130.60, 133.21, 135.19, 154.70.

HRMS-FAB: *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{44}NO_3Si_2$: 462.2860; found: 462.2861.

(4*S*,5*S*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-4-[(*tert*-butyldimethylsilyloxy)methyl]-2-phenyl-6-[(*E*)-tetradec-1-enyl]-5,6-dihydro-4*H*-1,3-oxazine (8)

To a solution of **4e** (1.03 g, 2.24 mmol) in CH_2Cl_2 (50 mL) was added tetradec-1-ene (1.24 mL, 4.48 mmol) and Grubbs II catalyst (95 mg, 0.11 mmol) at r.t. After stirring the reaction mixture for 8 h under reflux, the solvent was removed in vacuo to give the crude product (*E*/*Z* >20:1 by ^{1}H NMR). Column chromatography on silica gel gave pure **8** (1.33 g, 94%) as a colorless oil; R_f = 0.5 (EtOAc–hexanes, 1:20); $[\alpha]_D^{25}$ –33.79 (*c* 1.0, $CHCl_3$).

IR (neat): 2927, 2857, 1657, 1462, 1115, 839, 776 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.07–0.18 (m, 12 H), 0.90–0.99 (m, 21 H), 1.33–1.45 (m, 20 H), 2.02–2.03 (m, 1 H), 2.14 (q, *J* = 6.9 Hz, 1 H), 3.50–3.55 (m, 1 H), 3.81 (dd, *J* = 5.1, 5.4 Hz, 1 H), 4.03 (dd, *J* = 3.6, 9.9 Hz, 1 H), 4.17 (m, 1 H), 4.72–475 (m, 1 H), 5.41–5.46 (m, 1 H), 5.69–5.86 (m, 2 H), 7.38–7.49 (m, 3 H), 7.98–8.03 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.02, –4.99, –4.47, –4.33, 14.38, 18.30, 22.96, 26.03, 26.09, 26.14, 29.22, 29.44, 29.47, 29.64, 29.75 (several overlapped peaks), 29.81, 29.84, 29.88, 29.93, 29.97, 32.20, 32.70, 32.88, 59.86, 64.33, 65.76, 75.94, 125.53, 127.63, 128.12, 130.13, 130.48, 130.59, 133.98, 134.97, 154.88.

HRMS-FAB: *m*/*z* [M + H]$^+$ calcd for $C_{37}H_{68}NO_3Si_2$: 630.4738; found: 630.4734.

***tert*-Butyl (2*S*,3*S*,4*S*)-1,3,4-Trihydroxyoctadecan-2-yl-carbamate (3)**

Intermediate Diol: To a stirred solution of **8** (1.33 g, 2.10 mmol) in THF (20 mL) at 0 °C was added *n*-Bu_4NF (1.0 M solution in THF, 4.42 mL, 4.42 mmol). The reaction mixture was stirred at r.t. for 1 h. The reaction was quenched with sat. aq NH_4Cl (15 mL) and extracted with EtOAc (3 × 15 mL). the combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and evaporated in vacuo. Purification of the residue by silica gel chromatography gave the intermediate diol (0.79 g, 90%) as a white solid; R_f = 0.20 (EtOAc–hexanes, 1:1); $[\alpha]_D^{25}$ –42.19 (*c* 1.0, $CHCl_3$).

IR (neat): 3327, 2198, 2851, 2357, 1639, 1246, 1059, 499 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 6.7 Hz, 3 H), 1.30–1.46 (m, 20 H), 2.13 (dt, *J* = 6.6, 14.0 Hz, 2 H), 3.58 (dd, *J* = 5.4, 11.7 Hz, 1 H), 3.83–3.99 (m, 3 H), 4.41–4.51 (m, 1 H), 4.82–4.85 (m, 1 H), 5.58–5.69 (m, 1 H), 5.80–5.96 (m, 1 H), 7.39–7.52 (m, 3 H), 7.93–8.01 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.33, 22.91, 29.31, 29.49, 29.58, 29.72, 29.83, 29.88, 29.90, 29.92, 32.15, 32.59, 68.56, 68.71, 73.76, 75.47, 127.22, 128.47, 128.57, 128.65, 128.71, 131.77, 135.49, 165.69.

HRMS-FAB: *m*/*z* [M + H]$^+$ calcd for $C_{25}H_4NO_3$: 402.3008; found: 402.3008.

*Conversion of the Diol into Carbamate **3***: A solution of the above diol (300 mg, 0.64 mmol) in a 3:2 mixture of hexane and MeOH (10 mL) was stirred at r.t. for 12 h under an atmosphere of H_2 in the presence of a catalytic quantity of 20% $Pd(OH)_2$ on charcoal (60 mg) and Boc_2O (562 mg, 2.58 mmol). The catalyst was then removed by filtration through Celite, and the solvents were evaporated under reduced pressure. The resulting residue was purified by silica gel chromatography to afford Boc-carbamate **3** (235 mg, 75%) as a white solid; mp 131–133 °C; R_f = 0.3 (EtOAc–hexanes, 2:1); $[\alpha]_D^{25}$ –8.9 (*c* 0.9, $CDCl_3$).

IR (neat): 3338, 2921, 2853, 1670, 1539, 1460, 1249, 1172, 1047 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.0 Hz, 3 H), 1.20–1.40 (br m, 26 H), 1.47 (s, 9 H), 1.58–1.68 (m, 2 H), 2.59–2.64 (br s, 1 H, CH_2OH), 3.39–3.41 (m, 1 H), 3.51–3.55 (m, 1 H), 3.62–3.63 (m, 1 H), 3.75 (dd, *J* = 4.0, 11.0 Hz, 1 H), 4.06 (d, *J* = 10.8 Hz, 1 H), 5.21 (br d, *J* = 8.7 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.31, 22.90, 26.29, 28.54, 29.57, 29.76, 29.83, 29.87, 29.91, 32.14, 33.00, 53.72, 62.24, 69.91, 73.12, 80.63, 157.40.

HRMS-FAB: *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{48}NO_5$: 418.3532; found: 418.3528.

(2*S*,3*S*,4*S*)-2-Aminooctadecane-1,3,4-triol (D-*lyxo*-Phytosphingosine, 1)

Triol **3** (26 mg, 0.06 mmol) was dissolved in CF_3CO_2H–H_2O (20:1, 1.2 mL) and the solution was vigorously stirred at r.t. for 2 h. Excess CF_3CO_2H was removed under reduced pressure, the aqueous layer was neutralized with aq $NaHCO_3$, and extracted with EtOAc (4 × 5 mL). The combined organic layers were dried (Na_2SO_4) and evaporated at reduce pressure. The crude residue was purified by silica gel

chromatography eluting with $CHCl_3$–MeOH–NH_4OH, 40:10:1 to afford **1** (18.2 mg, 92%) as a white solid; mp 104.5–105.5 °C; R_f = 0.27 ($CHCl_3$–MeOH–NH_4OH, 40:10:1); $[\alpha]_D^{25}$ –6.4 (*c* 1.0, pyridine) {Lit.[11b] $[\alpha]_D^{25}$ –6.7 (*c* 0.9, pyridine)}.

IR (neat): 3344, 2920, 2934, 2526, 1452, 1114, 1001, 693 cm^{-1}.

^1H NMR (500 MHz, pyridine-d_5): δ = 0.81 (t, *J* = 7.0 Hz, 3 H), 1.20–1.35 (m, 22 H), 1.48–1.58 (m, 1 H), 1.64–1.73 (m, 1 H), 1.82–1.90 (m, 1 H), 1.93–2.10 (m, 1 H), 3.84 (ddd, *J* = 4.5, 6.5, 11.0 Hz, 1 H), 4.15 (dd, *J* = 2.5, 6.5 Hz, 1 H), 4.26–4.29 (m, 1 H), 4.30–4.38 (m, 2 H).

^{13}C NMR (125 MHz, pyridine-d_5): δ = 14.22, 22.88, 26.64, 29.56, 29.87, 29.93, 30.01, 30.17, 32.07, 34.48, 56.65, 63.63, 72.02, 74.08.

HRMS-FAB: *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{40}NO_3$: 318.3008; found: 318.3006.

Acknowledgment

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (S-2011-0948-000) & Yonsung Fine Chemicals Corporations. The Global Ph.D. Fellowship grant to S.H.P. is gratefully acknowledged.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

Primary Data for this article are available online and can be cited using the following DOI: 10.4125/pd0031th. The primary data set includes FIDs and associated files for the ^1H and ^{13}C NMR spectra as well as NOE experiments.

References

(1) (a) Merrill, A. H. Jr.; Sandhoff, K. *Sphingolipid Metabolism and Cell Signaling,* In *Biochemistry of Lipids, Lipoproteins, and Membranes*; Vance, D. E.; Vance, J. E., Eds.; Elsevier: New York, **2002**, 373. (b) Merrill, A. H. Jr.; Sweeley, C. C. In *Biochemistry of Lipids, Lipoproteins, and Membranes*; Vance, D. E.; Vance, J. E., Eds.; Elsevier: Amsterdam, **1996**, 309.

(2) (a) Morita, M.; Motoki, K.; Akimoto, K.; Natori, T.; Sakai, T.; Sawa, E.; Yamaji, K.; Koezuka, Y.; Kobayashi, E.; Fukushima, H. *J. Med. Chem.* **1995**, *38*, 2176. (b) Kobayashi, E.; Motoki, K.; Uchida, T.; Fukushima, H.; Koezuka, Y. *Oncol. Res.* **1995**, *7*, 529. (c) Kawano, T.; Cui, J.; Koezuka, Y.; Toura, I.; Kaneko, Y.; Motoki, K.; Ueno, H.; Nakagawa, R.; Sato, H.; Kondo, E.; Koseki, H.; Taniguchi, M. *Science* **1997**, *278*, 1626. (d) Miyamoto, K.; Miyake, S.; Yamamura, T. *Nature* **2001**, *413*, 531.

(3) (a) Kobayashi, E.; Motoki, K.; Yamaguchi, Y.; Uchida, T.; Fukushima, H.; Koezuka, Y. *Bioorg. Med. Chem.* **1996**, *4*, 615. (b) Zanolari, B.; Friant, S.; Funato, K.; Sutterlin, C.; Stevenson, B. J.; Riezman, H. *EMBO J.* **2000**, *19*, 2824.

(4) For recent reviews of phytosphingosines, see: (a) Morales-Serna, J. A.; Llaveria, J.; Diaz, Y.; Matheu, M. I.; Castillón, S. *Curr. Org. Chem.* **2010**, *14*, 2483. (b) Liao, J.; Tao, J.; Lin, D. *Tetrahedron* **2005**, *61*, 4715. (c) Howell, A. R.; Ndakala, A. J. *Curr. Org. Chem.* **2002**, *6*, 365.

(5) For more recent syntheses of phytosphingosines, see: (a) Perali, R. S.; Mandava, S.; Chalapala, S. *Tetrahedron* **2011**, *67*, 9283. (b) Rao, G. S.; Rao, B. V. *Tetrahedron Lett.* **2011**, *52*, 4861. (c) Martinkova, M.; Gonda, J.; Pomikalova, K.; Kozisek, J.; Kuchar, J. *Carbohydr. Res.* **2011**, *346*, 1728. (d) Ballereau, S.; Abadie, N. A.; Saffon, N.; Génisson, Y. *Tetrahedron* **2011**, *67*, 2570. (e) Liu, Z.; Byun, H. S.; Bittman, R. *J. Org. Chem.* **2010**, *75*, 4356. (f) Raghavan, S.; Krishnaiah, V. *J. Org. Chem.* **2010**, *75*, 748. (g) Dubey, A.; Kumar, P. *Tetrahedron Lett.* **2009**, *50*, 3425. (h) Pandey, G.; Tiwari, D. K. *Tetrahedron Lett.* **2009**, *50*, 3296.

(6) For recent syntheses of D-*lyxo*-phytosphingosine, see: (a) Rao, G. S.; Rao, B. V. *Tetrahedron Lett.* **2011**, *52*, 6076. (b) Lee, Y. M.; Baek, D. J.; Kim, S. W.; Kim, D. J.; Kim, S. H. *J. Org. Chem.* **2011**, *76*, 408. (c) Abraham, E.; Brock, E. A.; Candela-Lena, J. I.; Davies, S. G.; Georgiou, M.; Nicholson, R. L.; Perkins, J. H.; Roberts, P. M.; Russell, A. J.; Sanchez-Fernandez, E. M.; Scott, P. M.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 4668. (d) Kim, S.; Lee, N.; Lee, S.; Lee, T.; Lee, Y. M. *J. Org. Chem.* **2008**, *73*, 1379.

(7) Kuroda, I.; Musman, M.; Ohtani, I. I.; Ichiba, T.; Tanaka, J.; Garcia Gravalos, D.; Higa, T. *J. Nat. Prod.* **2002**, *65*, 1505.

(8) Ledroit, V.; Debitus, C.; Lavaud, C.; Massiot, G. *Tetrahedron Lett.* **2003**, *44*, 225.

(9) For reviews on pachastrissamine syntheses, see: (a) Ballereau, S.; Baltas, M.; Genisson, Y. *Curr. Org. Chem.* **2011**, *15*, 953. (b) Abraham, E.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *Tetrahedron: Asymmetry* **2008**, *19*, 1027.

(10) For recent syntheses of pachastrissamine, see: (a) Zhao, M.-L.; Zhang, E.; Gao, J.; Zhang, Z.; Zhao, Y.-T.; Qu, W.; Liu, H.-M. *Carbohydr. Res.* **2012**, *351*, 126. (b) Cruz-Gregorio, S.; Espinoza-Rojas, C.; Quintero, L.; Sartillo-Piscil, F. *Tetrahedron Lett.* **2011**, *52*, 6370. (c) Passiniemi, M.; Koskinen, A. M. P. *Org. Biomol. Chem.* **2011**, *9*, 1774. (d) Lee, H. J.; Lim, C. M.; Hwang, S. H.; Jeong, B. S.; Kim, S. H. *Chem.–Asian J.* **2011**, *6*, 1943. (e) Llaveria, J.; Diaz, Y.; Matheu, M. I.; Castillon, S. *Eur. J. Org. Chem.* **2011**, 1514. (f) Yoshimitsu, Y.; Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2010**, *75*, 3843. (g) Vichare, P.; Chattopadhyay, A. *Tetrahedron: Asymmetry* **2010**, *21*, 1983. (h) Urano, H.; Enomoto, M.; Kuwahara, S. *Biosci. Biotechnol., Biochem.* **2010**, *74*, 152. (i) Inuki, S.; Yoshimitsu, Y.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2010**, *75*, 3831. (j) Inuki, S.; Yoshimitsu, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2009**, *11*, 4478. (k) Canals, D.; Mormeneo, D.; Fabrias, G.; Llebaria, A.; Casas, J.; Delgado, A. *Bioorg. Med. Chem.* **2009**, *17*, 235.

(11) (a) Salma, Y.; Lafont, E.; Therville, N.; Carpentier, S.; Bonnafe, M.-J.; Levade, T.; Genisson, Y.; Andrieu-Abadie, N. *Biochem. Pharmacol.* **2009**, *78*, 477. (b) Canals, D.; Mormeneo, D.; Fabrias, G.; Llebaria, A.; Casas, J.; Delgado, A. *Bioorg. Med. Chem.* **2009**, *17*, 235.

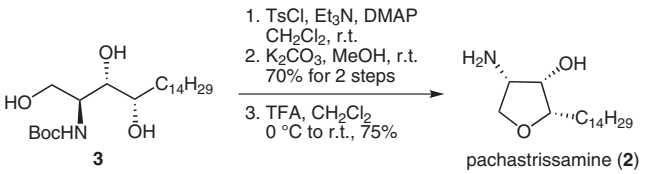
(12) (a) Kim, J. Y.; Mu, Y.; Jin, X. D.; Park, S. H.; Pham, V. T.; Song, D. K.; Lee, K. Y.; Ham, W. H. *Tetrahedron* **2011**, *67*, 9426. (b) Pham, V. T.; Joo, J. E.; Lee, K. Y.; Kim, T. W.; Mu, Y.; Ham, W. H. *Tetrahedron* **2010**, *66*, 2123.

(13) (a) Joo, J. E.; Pham, V. T.; Tian, Y. S.; Chung, Y. S.; Lee, K. Y.; Ham, W. H. *Org. Biomol. Chem.* **2008**, *6*, 1498. (b) Joo, J. E.; Lee, K. Y.; Pham, V. T.; Ham, W. H. *Eur. J. Org. Chem.* **2007**, 1586. (c) Joo, J. E.; Lee, K. Y.; Pham, V. T.; Tian, Y. S.; Ham, W. H. *Org. Lett.* **2007**, *9*, 3627.

(14) (a) Schwab, P. E.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100. (b) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247. (c) Love, J. A.; Sanford, M. S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 10103. (d) Lombardo, M.; Capdevila, M. G.; Pasi, F.; Trombini, C. *Org. Lett.* **2006**, *8*, 3303. (e) Singh, O. V.; Kampf, D. J.; Han, H. *Tetrahedron Lett.* **2004**, *45*, 7239. (f) Perali, R. S.; Mandava, S.; Chalapala, S. *Tetrahedron* **2011**, *67*, 9283. (g) Tian, Y. S.;

Joo, J. E.; Pham, V. T.; Lee, K. Y.; Ham, W. H. *Arch. Pharm. Res.* **2007**, *30*, 167. (h) Pham, V. T.; Joo, J. E.; Tian, Y. S.; Oh, C. Y.; Ham, W. H. *Arch. Pharm. Res.* **2007**, *30*, 22.

(15) The synthesis of pachastrissamine (**2**) was achieved in three steps from *N*-Boc-triol **3**: Ribes, C.; Falomir, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2006**, *62*, 5421.



Scheme 5 Synthesis of pachastrissamine (**2**) from *N*-Boc-triol **3**

