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Stereocontrolled synthesis of cytotoxic anhydrosphingosine pachastrissamine by using [3.3] sigmatropic rearrangement of allyl cyanate

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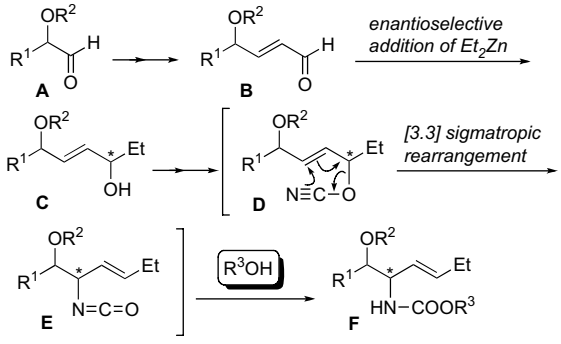
ABSTRACT

A new route for the synthesis of the cytotoxic anhydrosphingosine pachastrissamine has been developed. [3.3] Sigmatropic rearrangement of an allyl cyanate was employed to construct the allyl amine moiety in **2** from the chiral C-4 unit **3**. Oxidative cleavage of the double bond in **2**, followed by THF ring formation furnished the target pachastrissamine.

1. Introduction

The chiral 1,2-amino alcohol moieties represent important structural motifs owing to their ubiquity in natural products and pharmaceuticals. For example, this structural component is found in a variety of amino sugars, peptide antibiotics, and glycosidase inhibitors.[1] Moreover, chiral 1,2-amino alcohols have been employed as both chiral auxiliaries and ligands to control absolute stereochemistry in a number of asymmetric syntheses.

As part of continuing studies aimed at the development and applications of [3.3] sigmatropic rearrangement reactions of allyl cyanates,[2] we discovered an efficient methodology for construction of 1,2-amino alcohols that is based on a protocol for stereoselective allyl amine synthesis[3] (Scheme 1). Starting with a chiral α-alkoxy aldehyde **A**, α,β-unsaturated aldehyde **B** is prepared by using the standard method. Enantioselective addition of diethylzinc (Et_2Zn) to aldehyde **B** furnishes an allyl alcohol **C** stereoselectively. It should be noted that facially selective addition of Et_2Zn to the aldehyde moiety in **B** takes place at a position, which is remote from the preexisting chiral center. Allyl alcohol **C** is then transformed into the allyl cyanate **D**, which then undergoes [3.3] sigmatropic rearrangement to afford allyl isocyanate **E** in a process that is attended by a high degree of 1,3-chirality transfer. The well organized, six-membered transition state for the sigmatropic reaction enables a predictably high level of stereocontrol for the C–O to C–N transfer across the allylic system. Consequently, a stereogenic center bearing nitrogen functionality is introduced at a position adjacent to the stereocenter containing R^2O group with a high degree of stereochemical control. Treatment of the resultant allyl isocyanate **E** with an alcohol (R^3OH) gives rise to the 1,2-amino alcohol **F** as an appropriately protected carbamate.



Scheme 1.

To demonstrate the applicability of this protocol in natural product synthesis, we designed a strategy for the preparation of the novel anhydrosphingosine, pachastrissamine.

2. Background

In 2002, Higa and his co-workers reported the isolation and characterization of pachastrissamine (**1**) from the Okinawan marine sponge *Pachastrissa* sp. (Fig. 1).[4] Subsequently, Debitus isolated this substance from the marine sponge *Jaspis*, collected in Vanuatu and gave it the name jaspine B.[5] It has been shown that **1** has cytotoxic activity against P388, A549, T29, and MEL28 cell lines at IC_{50} level of 0.001 mg/ml. The structure of pachastrissamine (**1**) is characterized by the presence of a tetrahydrofuran (THF) ring possessing cis-oriented tetradecanyl, hydroxy, and

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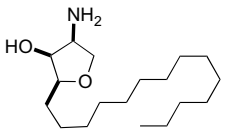


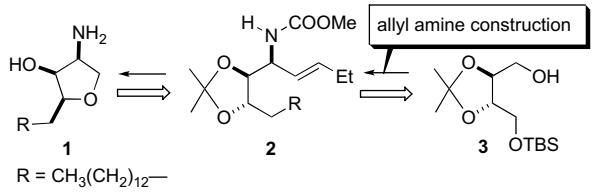
pachastrissamine (jaspine B) (**1**)

Figure 1.

amino groups. Its interesting biological activity coupled with its simple structure stimulated the interest of chemists and, thus far, more than 10 independent syntheses describing synthetic studies related to pachastrissamine have appeared between 2005 and 2007.[6]

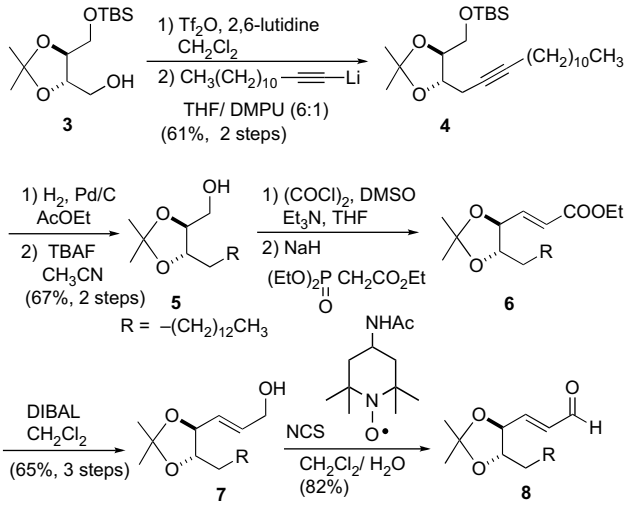
3. Results and discussion

A retrosynthetic analysis of pachastrissamine (**1**) is shown in Scheme 2. It was envisioned that the general protocol outlined in Scheme 1 could be used to construct the allyl amine moiety in intermediate **2** starting with the chiral C-4 unit found in **3**. Oxidative cleavage of double bond in **2** followed by THF ring construction would then furnish a key precursor to **1**.



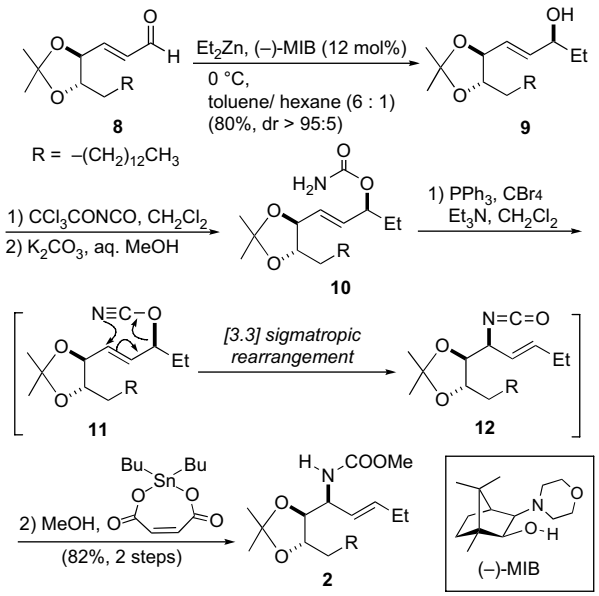
Scheme 2.

Preparation of intermediate **2** started with **3**, which was prepared from L-tartaric acid by employing known procedures[7] (Scheme 3). Treatment of **3** with triflic anhydride in the presence of 2,6-lutidine gave the corresponding triflate, which subsequently underwent S_N2 displacement to furnish **4** (61%, 2 steps) when treated with lithium acetylide[8] in a mixture of THF and DMPU (6:1).[9] Catalytic hydrogenation of the triple bond in **4** followed by deprotection of the silyl ether with tetra-*n*-butylammnoium fluoride provided **5** in 67% yield. Transformation of **5** into α,β-unsaturated aldehyde **8** was carried out by using a standard set of reactions involving (i) one-pot Swern oxidation–Horner–Wadsworth–Emmons olefination,[10] (ii) DIBAL reduction of the resulting ester **6**, and (iii) nitroxido-catalyzed oxidation of **7** using NCS as the primary oxidant (two-phase system CH_2Cl_2–H_2O).[11]



Scheme 3.

The next task in the route to pachastrissamine (**1**) is the construction of allyl amine moiety involving elaboration of an allylic alcohol **9** using enantioselective addition of Et_2Zn (Scheme 4). Initially, the Soai protocol, using diphenyl(1-methylpyrrolidin-2-yl)methanol (DPMPM) as a chiral ligand, was investigated for the conversion of **8** to **9**.[12] Unfortunately, reaction of the aldehyde in **8** with Et_2Zn in cyclohexane at 0 °C in the presence of DPMPM was capricious, giving **9** in variable low yields (0–24%). We next explored use of the Nugent method,[13] which employs the β-amino alcohol ligand, 3-*exo*-morpholinoisoborneol (MIB), and a toluene–hexane mixture as solvent. By using the reported reaction conditions (1 M solution of aldehyde **8** in a 1:2 toluene–hexane), poor yields (30–36%) of **9** were obtained. After experimentation, we found that the yield of this process is improved by using increased amounts of toluene in the solvent mixture. Importantly, enantioselective addition of Et_2Zn to a 0.08 M solution of aldehyde **8** in the presence of 12 mol % (−)-MIB in a mixture of toluene and hexane (6:1) at 0 °C for 24 h led to generation of the allylic alcohol **9** in an 80% yield and a dr >95:5.[14] The stereochemistry of **9** was initially assigned based on the empirical rule and finally confirmed by using the Mosher–Kusumi MTPA ester analysis method, which showed that the configuration of secondary alcohol center in **9** is *S*.[15]

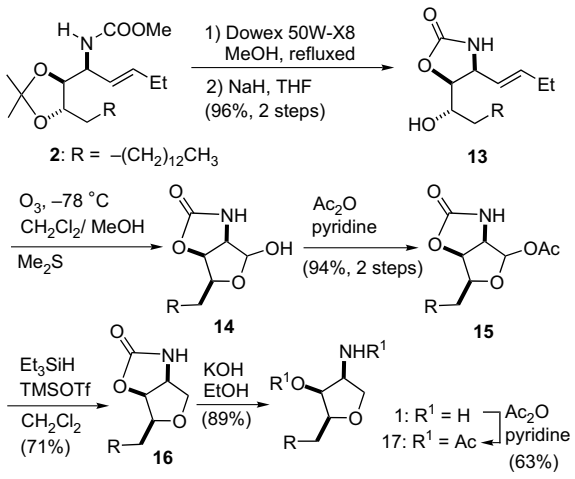


Scheme 4.

With the allyl alcohol **9** in hand, we next turned attention to the preparation of the allyl amine intermediate **2**. Treatment of **9** with trichloroacetyl isocyanate followed by hydrolysis with potassium carbonate in aqueous methanol gave the allyl carbamate **10**. Dehydration of **10** with triphenylphosphine, carbon tetrabromide, and triethylamine at −20 °C generated the allyl cyanate **11**, which spontaneously underwent [3.3] sigmatropic rearrangement to afford the allyl isocyanate **12**. In order to avoid hydrolysis of the isocyanate group caused by aqueous workup, the reaction mixture was treated in situ with methanol in the presence of dibutyltin maleate.[16] After workup and chromatographic purification, methyl carbamate **2** was isolated in 82% yield from **9** as a crystalline material. At this stage, the minor diastereomer arising from the Et_2Zn addition reaction was removed by recrystallization.

The intermediate allylic amine **2**, which contains all three of the stereogenic centers found in pachastrissamine, was then subjected

to a route for construction of the THF ring in the target (Scheme 5). Deprotection of the acetonide group in **2** with Dowex 50W-X8 in refluxing MeOH followed by treatment of the resulting diol with sodium hydride in THF provided the carbamate **13** in 96% yield. Ozonolysis of the alkene moiety in **13** in a mixture of CH_2Cl_2–MeOH at −78 °C followed by reductive workup with dimethyl sulfide gave rise to the lactol **14**. Unexpectedly, this lactol is quite stable under reduction conditions (excess sodium borohydride in refluxing methanol for 4 days).[17] Consequently, lactol **14** was transformed into the acetate **15**, which was reduced with triethylsilane in the presence of trimethylsilyl triflate in CH_2Cl_2 to furnish **16** in 66% yield (3 steps). Finally, cleavage of the oxazoline ring in **16** with potassium hydroxide in ethanol followed by silica gel chromatography afforded pachastrissamine (**1**) in 89% yield. To our surprise, the ^1H and ^{13}C NMR data of the synthetic material were not identical to those reported previously. However, when a CH_2Cl_2 solution of the synthetic material was treated with aqueous 1 M NaOH followed by concentration, it produced a residue, which has ^1H and ^{13}C NMR spectra that match those reported by Kim for pachastrissamine.[6g] Further confirmation was achieved by preparation and analysis of the diacetate **17**.[18]



Scheme 5.

In summary, a new route for the synthesis of the marine natural product pachastrissamine has been developed. The 1,2-amino alcohol moiety found in pachastrissamine was efficiently constructed by a combination of enantioselective addition of Et_2Zn catalyzed with (−)-MIB and 1,3-chirality transfer using an allyl cyanate [3.3] sigmatropic rearrangement.

4. Experimental

4.1. General information

Melting points were recorded on a micro melting point apparatus and are not corrected. Optical rotations were measured at the sodium D line with a 100 mm path length cell, and are reported as follows: $[\alpha]_D^T$ (concentration (g/100 ml), solvent). Infrared spectra are reported in wave number (cm^{-1}). ^1H NMR data are reported with the solvent resonance as the internal standard relative to chloroform (δ 7.27) and methanol (δ 3.31) as follows; chemical shift (δ), multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broadened, m=multiplet), coupling constants (J in Hz), and integration. ^{13}C NMR chemical shifts (δ) are recorded in parts per million (ppm) relative to $CDCl_3$ (δ 77.0) and CD_3OD (δ 49.0) as internal standards. High-resolution mass spectra (HRMS) are reported in m/z. Reactions were run under atmosphere of argon when the reactions were sensitive to moisture or oxygen. Dichloromethane was dried over molecular sieves 3 Å. Pyridine and triethylamine were stocked over anhydrous KOH. All other commercially available reagents were used as received.

4.2. Synthesis of pachastrissamine

*4.2.1. tert-Butyl(((4S,5S)-2,2-dimethyl-5-(tetradec-2-ynyl)-1,3-dioxolan-4-yl)methoxy)dimethylsilane (**4**)*

To a solution of alcohol **3** (5.00 g, 18 mmol) and 2,6-lutidine (10.5 ml, 90 mmol) in CH_2Cl_2 (72.0 ml) at −78 °C was added trifluoromethanesulfonic anhydride (3.25 ml, 23 mmol). After being stirred at −78 °C for 2 h, the reaction mixture was diluted with Et_2O and then washed with 1 M $KHSO_4$, H_2O, aqueous $NaHCO_3$, and brine. After being dried over Na_2SO_4, the solution was concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (AcOEt/hexane 1:9) to afford the corresponding triflate (7.03 g, 96%) as a yellow oil.

To a solution of 1-tridecyne (7.15 ml, 30 mmol) in THF (72.0 ml) at −20 °C was added *n*-BuLi (1.65 M in hexane, 16.7 ml, 27 mmol). After being stirred at room temperature for 30 min, *N*,*N*-dimethylpropylene urea (DMPU) (24.0 ml) was added. The reaction mixture was cooled to −20 °C, and a solution of triflate (7.03 g 17 mmol) in THF (72.0 ml) was added via syringe over 10 min. After being stirred at −20 °C for 20 min, aqueous solution of NH_4Cl was added, and the separated aqueous layer was extracted with Et_2O. The combined organic extracts were washed with saturated aqueous $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (hexane, Et_2O/hexane 1:30 and Et_2O/hexane 1:15) to afford alkyne **4** (4.77 g, 64%) as a yellow oil. $[\alpha]_D^{25}$ −1.70 (*c* 1.00, MeOH); IR (KBr) ν_{max}=2927, 2856 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.07 (s, 6H), 0.87 (t, J=7.0, 3H), 0.89 (s, 9H), 1.25 (br s, 18H), 1.38 (s, 3H), 1.41 (s, 3H), 1.46 (m, 2H), 2.13 (tt, J=7.0, 2.5, 2H), 2.52 (quint, J=2.5, 2H), 3.75–3.79 (m, 2H), 3.86–3.99 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.26, −5.19, 14.2, 18.5, 18.9, 22.8, 23.4, 26.0, 27.2, 27.3, 29.0, 29.3, 29.4, 29.6, 29.7, 32.0, 63.7, 64.0, 75.3, 76.3, 78.7, 80.8, 82.6, 109.0; HRMS (ESI): m/z calcd for $C_{26}H_{51}N_4O_3Si$ $(M+H)^+$ 439.3607, found 439.3643.

*4.2.2. ((4S,5S)-2,2-Dimethyl-5-tetradecyl-1,3-dioxolan-4-yl)methanol (**5**)*

A mixture of alkyne **4** (9.32 g, 21 mmol), palladium on carbon (10%, 932 mg) in AcOEt (210 ml) was stirred vigorously under hydrogen atmosphere for 2 h. The reaction mixture was filtered through a pad of Super Cell and the filtrate was concentrated under reduced pressure to provide the product (9.80 g), which was dissolved in CH_3CN (210 ml), and then treated with a solution of tetrabutylammonium fluoride (1.0 M in THF, 24.5 ml, 24.5 mmol) at room temperature. The reaction mixture was heated at 60 °C for 1 h and then concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (AcOEt/hexane 1:9, 1:5, and 1:3) to afford alcohol **5** (4.62 g, 67%). $[\alpha]_D^{26}$ −18.2 (*c* 1.00, $CHCl_3$); IR (KBr) ν_{max}=3513, 2914, 2849 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, J=7.0, 3H), 1.25 (br s, 24H), 1.40 (s, 3H), 1.41 (s, 3H), 1.56 (m, 2H), 2.07 (t, J=6.0, 1H), 3.56–3.89 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 22.6, 25.9, 27.0, 27.3, 29.3, 29.4, 29.5, 29.6, 31.8, 33.0, 62.0, 76.8, 81.5, 108.5. Anal. Calcd for $C_{20}H_{40}O_3$: C, 73.12; H, 12.27; O, 14.61. Found: C, 73.14; H, 12.35.

*4.2.3. (E)-Ethyl 3-((4S,5S)-2,2-dimethyl-5-tetradecyl-1,3-dioxolan-4-yl)acrylate (**6**)*

To a stirred solution of oxalyl chloride (1.50 ml, 17 mmol) in THF (30 ml) at −78 °C was added dimethyl sulfoxide (3.00 ml, 42 mmol). After being stirred at −78 °C for 30 min, a solution of alcohol **5** (2.50 g, 7.60 mmol) in THF (7.0 ml) was added. After

stirring at −78 °C for 30 min, the reaction mixture was treated with triethylamine (7.90 ml, 57 mmol). After being stirred at −78 °C for 45 min, the solution was allowed to warm to room temperature.

A second flask is charged with sodium hydride (60% dispersion in mineral oil, 852 mg, 21.3 mmol). The mineral oil was removed by washing with hexane, allowing the sodium hydride to settle and withdrawing the supernatant solvent with a pipette. THF (16.5 ml) was added and the suspension was cooled to −20 °C. Ethyl diethyl phosphonoacetate (4.50 ml, 22.6 mmol) was added and then allowed to warm to room temperature. After 30 min, the reaction mixture was recooled to −78 °C.

A solution of the first flask was added to the solution in the second flask via syringe. The first flask was washed with THF (16.5 ml), and then washings were added to the second flask. After stirring at −78 °C for 15 min, the solution was allowed to warm to room temperature and then stirred for 3 h. The reaction mixture was poured into saturated aqueous solution of NH_4Cl and extracted with three portions of 1:1 ether/hexane. The combined organic extracts were washed with saturated aqueous solution of NH_4Cl, saturated aqueous sodium bicarbonate, brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (AcOEt/hexane 1:8) to afford α,β-unsaturated ester **6** (2.56 g, 85%) exclusively as a yellow oil. $[\alpha]_D^{23}$ −11.8 (*c* 1.00, $CHCl_3$); IR (KBr) ν_{max}=2985, 2924, 1725, 1661 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, *J*=7.0, 3H), 1.25 (br s, 24H), 1.28 (t, *J*=7.0, 3H), 1.40 (s, 3H), 1.43 (s, 3H), 1.58 (m, 2H), 3.73 (m, 1H), 4.13 (m, 1H), 4.20 (q, *J*=7.0, 2H), 6.11 (dd, *J*=15.5, 1.0, 1H), 6.86 (dd, *J*=15.5, 6.0, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 14.3, 22.8, 26.1, 26.7, 27.4, 29.4, 29.5, 29.6, 29.7, 32.0, 32.2, 60.6, 80.3, 80.7, 109.4, 122.8, 144.3, 166.1. Anal. Calcd for $C_{24}H_{44}O_4$: C, 72.68; H, 11.18; O, 16.14. Found: C, 72.47; H, 11.28.

4.2.4. (E)-3-((4S,5S)-2,2-Dimethyl-5-tetradecyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (**7**)

To a solution of α,β-unsaturated ester **6** (2.56 g, 6.45 mmol) in CH_2Cl_2 (33 ml) cooled to −20 °C was added DIBAL (0.94 M in hexane, 20.0 ml, 18.9 mmol). After stirring at −20 °C for 60 min, the reaction was quenched by the addition of MeOH and aqueous potassium sodium (+)-tartrate tetrahydrate solution. After stirring at room temperature for 30 min, the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by silica gel chromatography (AcOEt/hexane 1:5 and 1:3) to afford allyl alcohol **7** (1.73 g, 76%) as a colorless oil. $[\alpha]_D^{26}$ −7.2 (*c* 1.00, $CHCl_3$); IR (KBr) ν_{max}=3413, 2985, 2924, 2854 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.83 (t, *J*=7.0, 3H), 1.21 (br s, 12H), 1.36 (s, 3H), 1.37 (s, 3H), 1.49 (m, 2H), 1.98 (br s, 1H), 3.63 (m, 2H), 3.97 (t, *J*=8.0, 1H), 4.12 (br s, 2H), 5.65 (ddt, *J*=15.5, 7.5, 1.5, 1H), 5.92 (dt, *J*=15.5, 5.0, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 22.7, 26.2, 27.0, 27.3, 29.4, 29.6, 29.7, 31.9, 32.0, 62.7, 80.9, 81.8, 108.5, 128.0, 134.2. Anal. Calcd for $C_{22}H_{42}O_3$: C, 74.52; H, 11.94; O, 13.54. Found: C, 74.23; H, 11.85.

4.2.5. (E)-3-((4S,5S)-2,2-Dimethyl-5-tetradecyl-1,3-dioxolan-4-yl)acrylaldehyde (**8**)

To a solution of alcohol **7** (1.34 g, 3.77 mmol) dissolved in a mixture of CH_2Cl_2 (37.0 ml) and aqueous solution (37.0 ml) of $NaHCO_3$ (0.5 M) and K_2CO_3 (0.05 M) were added 4-acetamido-TEMPO (160 mg, 0.75 mmol) and tetra-*n*-butylammonium chloride (210 mg, 0.75 mmol). After vigorously stirring at room temperature for 20 min, *N*-chlorosuccinimide (1.76 g, 13.2 mmol) was added. After being stirred at room temperature for 17 h, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (AcOEt/hexane 1:9) to afford α,β-unsaturated aldehyde **8** (1.08 g, 82%) as a yellow oil, which was immediately used for the enantioselective addition of diethylzinc. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, *J*=6.5, 3H), 1.25 (br s, 24H), 1.42 (s, 3H), 1.46 (s, 3H), 1.58 (m, 2H), 2.07 (t, *J*=6.0, 1H), 3.77 (td, *J*=8.0, 4.5, 1H), 4.27 (td, *J*=7.5, 1.5, 1H), 6.37 (ddd, *J*=10.5, 7.5, 1.0, 1H), 6.75 (dd, *J*=10.5, 5.5, 1H), 9.60 (d, *J*=7.5, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 22.8, 26.0, 26.7, 27.3, 29.4, 29.5, 29.6, 29.7, 29.8, 32.0, 32.3, 80.3, 80.7, 109.8, 132.8, 152.7, 193.1.

4.2.6. (S,E)-1-((4S,5S)-2,2-Dimethyl-5-tetradecyl-1,3-dioxolan-4-yl)pent-1-en-3-ol (**9**)

To a solution of aldehyde **8** (146 mg, 0.41 mmol) and (−)-MIB (12 mg, 0.05 mmol) in toluene (5.0 ml) cooled to −20 °C was added a solution of diethylzinc (1.0 M in hexane, 0.82 ml, 0.82 mmol) dropwise over 20 min. The reaction mixture was kept at 0 °C for 24 h and then quenched with saturated aqueous $NaHCO_3$. The separated aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Silica gel chromatography of the residue (AcOEt/hexane 1:7) gave allyl alcohol **9** (117 mg, 80%) as a colorless oil, which was analyzed by ^{13}C NMR to determine the diastereoselectivity to be 98:2. $[\alpha]_D^{24}$ −4.7 (*c* 1.00, $CHCl_3$); IR (KBr) ν_{max}=3428, 2984, 2924, 2854 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, *J*=7.0, 3H), 0.94 (t, *J*=7.5, 3H), 1.25 (br s, 12H), 1.40 (s, 3H), 1.41 (s, 3H), 1.57 (m, 2H), 3.67 (m, 1H), 4.00 (t, *J*=7.5, 1H), 5.66 (ddd, *J*=10.5, 7.5, 1.0, 1H), 5.84 (ddd, *J*=10.5, 5.5, 0.5, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.6, 14.2, 22.8, 26.2, 27.0, 27.4, 29.4, 29.6, 29.7, 29.8, 30.0, 32.0, 73.2, 80.9, 81.9, 108.5, 127.6, 133.7.

4.2.7. Methyl (S,E)-1-((4S,5S)-2,2-dimethyl-5-tetradecyl-1,3-dioxolan-4-yl)pent-2-enylcarbamate (**2**)

To a solution of allyl alcohol **9** (370 mg, 0.96 mmol) in CH_2Cl_2 (6.0 ml) cooled to 0 °C was added trichloroacetyl isocyanate (0.23 ml, 1.97 mmol). After stirring at 0 °C for 30 min, the solution was concentrated under reduced pressure. The resulting residue was dissolved in a mixture of MeOH (6.0 ml) and 1 M aqueous potassium carbonate (4.8 ml), and then was stirred at room temperature for 24 h. The aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (AcOEt/hexane 1:5) to afford carbamate **10** (323 mg, 87%) as a white solid.

To a solution of carbamate **10** (445 mg, 1.04 mmol), triphenylphosphine (668 mg, 2.61 mmol), and triethylamine (0.87 ml, 6.27 mmol) in CH_2Cl_2 (5.0 ml) at −20 °C was added a solution of carbon tetrabromide (970 mg, 2.92 mmol) in CH_2Cl_2 (5.0 ml) dropwise. After being stirred at −20 °C for 30 min, di-*n*-butyltin maleate (36 mg, 0.10 mmol) and MeOH (0.10 ml) were added. The resulting reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 12 h, the mixture was diluted with Et_2O, washed with 1 M $KHSO_4$, water, saturated aqueous $NaHCO_3$, and brine, and dried over anhydrous Na_2SO_4. Concentration under reduced pressure gave the residue, which was purified by silica gel chromatography (AcOEt/hexane 1:7 and 1:5) to afford methyl carbamate **2** (427 mg, 94%) as a white powder. Further purification was carried out by recrystallization from ether and hexane to afford an analytically pure sample (207 mg): mp 44–45 °C. $[\alpha]_D^{21}$ −18.4 (*c* 1.00, $CHCl_3$); IR (KBr) ν_{max}=3341, 2917, 2851, 1694, 1537, 1240 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, *J*=6.5, 3H), 0.99 (t, *J*=7.5, 3H), 1.25 (br s, 12H), 1.34 (s, 3H), 1.38 (s, 3H), 1.55 (m, 2H), 2.07 (quint, *J*=7.5, 2H), 3.67 (s, 3H), 3.73 (m, 2H), 4.17 (br, 1H), 5.02 (br, 1H), 5.46 (dd, *J*=15.5, 7.5, 1H), 5.73 (dt, *J*=15.5, 6.0, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.4, 14.2, 22.8, 25.4, 26.0, 26.9, 27.5, 29.4, 29.5, 29.7, 29.8, 32.0, 33.2, 52.2, 54.2, 77.9, 83.0, 108.6, 124.2,

136.6, 156.3; HRMS (ESI): *m*/*z* calcd for $C_{26}H_{50}NO_4$ $(M+H)^+$ 440.3740, found 440.3720.

4.2.8. (4S,5S)-4-((E)-But-1-enyl)-5-((S)-1-hydroxypentadecyl)-oxazolidin-2-one (**13**)

A suspension of methyl carbamate **2** (207 mg, 0.47 mmol) and Dowex 50W-X8 (8.0 ml) in MeOH (5.0 ml) was vigorously stirred at reflux for 14 h. The reaction mixture was filtered and then concentrated under reduced pressure to give the crude residue, which was purified by recrystallization from ether and hexane to provide diol (185 mg, 99%) as a white powder: mp 84–86 °C. $[\alpha]_D^{20}$ −2.06 (*c* 1.50, MeOH); IR (KBr) ν_{max}=3737, 2915, 2848, 1704, 1534 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 0.90 (t, *J*=6.5, 3H), 1.00 (t, *J*=7.5, 3H), 1.29 (br s, 12H), 1.49 (m, 2H), 2.07 (quint, *J*=7.5, 2H), 3.33 (m, 1H), 3.53 (m, 1H), 3.63 (s, 3H), 4.15 (t, *J*=6.5, 1H), 5.51 (dd, *J*=15.5, 6.5, 1H), 5.70 (dt, *J*=15.5, 6.5, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 13.9, 14.4, 23.7, 26.4, 26.7, 30.4, 30.7, 30.8, 33.0, 34.3, 52.5, 56.6, 71.9, 76.1, 127.3, 135.8, 159.0; HRMS (ESI): *m*/*z* calcd for $C_{23}H_{45}NaNO_4$ $(M+Na)^+$ 422.3246, found 422.3264.

To a solution of the diol (103 mg, 0.25 mmol) in THF (2.0 ml) was added NaH (60% dispersion in mineral oil, 20 mg add, 0.51 mmol) at room temperature. After stirring at room temperature for 8 h, acetic acid (0.1 ml, 0.16 mmol) was added. Concentration under reduced pressure provided the residue, which was purified by silica gel chromatography (AcOEt/hexane 1:1) to afford oxazolidinone **13** (91 mg, 97%) as a white solid: mp 104–106 °C. $[\alpha]_D^{22}$ −17.0 (*c* 1.00, $CHCl_3$); IR (KBr) ν_{max}=3640, 3124, 2918, 2851, 1763, 1698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, *J*=6.5, 3H), 1.00 (t, *J*=7.5, 3H), 1.25 (br s, 24H), 1.48 (m, 2H), 2.08 (m, 2H), 3.72 (m, 1H), 4.31 (t, *J*=8.5, 1H), 4.44 (dd, *J*=8.0, 5.0, 1H), 5.26 (br, 1H), 5.60 (dd, *J*=15.0, 8.5, 1H), 5.77 (dt, *J*=15.0, 6.5, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.3, 14.2, 22.7, 25.3, 25.4, 29.4, 29.5, 29.6, 29.7, 32.0, 32.9, 57.5, 69.9, 82.3, 123.9, 138.9, 159.0; HRMS (ESI): *m*/*z* calcd for $C_{22}H_{42}NO_3$ $(M+H)^+$ 368.3165, found 368.3172.

4.2.9. (3aR,6S,6aS)-2-Oxo-6-tetradecylhexahydrofuro[3,4-d]oxazol-4-yl acetate (**15**)

Ozone was passed into a solution of the oxazolidinone **13** (84 mg, 0.23 mmol) in a mixture of CH_2Cl_2 (9.3 ml) and MeOH (4.7 ml) at −78 °C for 1 h. After purging with nitrogen, dimethyl sulfide (0.25 ml, 3.40 mmol) was added at −78 °C. After being allowed to warm up to room temperature, the mixture was quenched with saturated aqueous $NaHCO_3$. The separated aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude lactol **14** (93 mg), which was dissolved in a mixture of pyridine (2.0 ml) and acetic anhydride (30 μl, 0.31 mmol). After stirring at 0 °C for 11 h, the mixture was quenched with saturated aqueous $NaHCO_3$. The separated aqueous layer was extracted with Et_2O. The combined organic extracts were washed with saturated aqueous NH_4Cl, water, saturated aqueous $NaHCO_3$, and brine, and dried over anhydrous Na_2SO_4. Concentration under reduced pressure gave the residue, which was purified by silica gel chromatography (AcOEt/hexane 1:1 and 2:1) to give the acetate **15** (82 mg, 94% in two steps, a 4:1 diastereomeric mixture).

4.2.10. Pachastrissamine carbamate (**16**)

To a solution of acetate **15** (15 mg, 0.039 mmol) and triethylsilane (1.0 M solution in CH_2Cl_2, 0.20 ml, 0.20 mmol) in CH_2Cl_2 (0.15 ml) at −20 °C was added TMSOTf (1.0 M solution in CH_2Cl_2, 0.090 ml, 0.090 mmol). The solution was allowed to warm to 0 °C and stirring was continued for 20 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude residue, which was purified by silica gel chromatography (AcOEt/hexane 2:1) to afford pachastrissamine carbamate **16** (9 mg, 71%): mp 124–126 °C. $[\alpha]_D^{20}$ +54.8 (*c* 0.50, $CHCl_3$); IR (KBr) ν_{max}=2923, 2848, 1758, 1722 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, *J*=7.0, 3H), 1.25–1.48 (br s, 24H), 1.78 (m, 2H), 3.52 (m, 2H), 3.94 (d, *J*=10.0, 1H), 4.38 (dd, *J*=7.5, 4.0, 1H), 4.97 (dd, *J*=7.5, 4.0, 1H), 5.45 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 22.8, 26.1, 28.2, 29.5, 29.6, 29.7, 29.8, 32.0, 57.1, 73.5, 77.4, 81.0, 83.4, 159.0; HRMS (ESI): *m*/*z* calcd for $C_{19}H_{36}NO_3$ $(M+H)^+$ 326.2695, found 326.2675.

4.2.11. Pachastrissamine (**1**)

A solution of the carbamate **16** (10 mg, 0.030 mmol) in ethanol (1.0 ml) and aqueous potassium hydroxide (1.0 M solution in H_2O, 1.0 ml) was refluxed for 10 h. The reaction mixture was concentrated and the resultant residue was purified by silica gel chromatography ($CHCl_3$/MeOH/aq NH_4OH=95:6:1 and 95:10:1) to afford pachastrissamine (**1**) as a white solid (8 mg, 89%).

The resultant pachastrissamine (**1**) (8 mg) was dissolved in CH_2Cl_2 (5.0 ml) and then treated with 1 M aqueous NaOH. The separated aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over K_2CO_3 and then concentrated to afford **1**, ^1H and ^{13}C NMR of which was immediately measured: mp 89–91 °C (mp 89–91 °C reported by Overkleeft[6c]). $[\alpha]_D^{23}$ +18.6 (*c* 1.00, MeOH) {$[\alpha]_D^{23}$ +19.7 (*c* 0.50, MeOH) reported by Kim[6g]}; IR (KBr) ν_{max}=3342, 2921, 2850, 1471 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, *J*=7.0, 3H), 1.25–1.43 (br s, 24H), 1.66 (m, 2H), 2.02 (br s, 3H), 3.51 (dd, *J*=8.5, 7.0, 1H), 3.65 (dt, *J*=7.0, 5.1, 1H), 3.73 (dt, *J*=6.6, 3.4, 1H), 3.87 (dd, *J*=4.8, 3.4, 1H), 3.92 (dd, *J*=8.2, 7.5, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 22.8, 26.4, 29.5, 29.7, 29.8, 29.9, 32.0, 54.4, 71.9, 72.5, 83.3; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{38}NO_2$ $(M+H)^+$ 300.2903, found 300.2878.

4.2.12. 2-Acetamido-3-O-acetyl-1,4-anhydro-(2S,3S,4S)-1,3,4-octadecanetriol (**17**)

Pachastrissamine (**1**) (10 mg, 0.033 mmol) was dissolved in a mixture of pyridine (0.20 ml) and acetic anhydride (50 μl, 0.52 mmol). After stirring at room temperature for 11 h, the mixture was quenched with saturated aqueous $NaHCO_3$. The separated aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with saturated aqueous NH_4Cl, water, saturated aqueous $NaHCO_3$, and brine, and dried over anhydrous Na_2SO_4. Concentration under reduced pressure gave the residue, which was purified by silica gel chromatography (AcOEt/hexane 4:1) to give the acetate **17** (8 mg, 63%): mp 111–113 °C. $[\alpha]_D^{23}$ −23.5 (*c* 0.40, $CHCl_3$); {$[\alpha]_D^{22}$ −22.6 (*c* 1.00, $CHCl_3$) reported by Overkleeft[6c]}; IR (KBr) ν_{max}=2920, 2851, 1740, 1646, 1560, 1471, 1375, 1228, 1059 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, *J*=6.8, 3H), 1.24 (br s, 24H), 1.49 (m, 2H), 1.98 (br s, 3H), 2.15 (br s, 3H), 3.59 (dd, *J*=8.0, 1H), 3.90 (m, 1H), 4.07 (t, *J*=8.0, 1H), 4.81 (qd, *J*=8.0, 5.4, 1H), 5.38 (dd, *J*=5.4, 3.4, 1H), 5.62 (d, *J*=8.5, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 20.8, 22.8, 23.3, 26.1, 29.4, 29.6, 29.7, 29.8, 32.0, 51.4, 70.1, 73.7, 81.3, 169.9, 170.0; HRMS (ESI): *m*/*z* calcd for $C_{22}H_{41}NaNO_4$ $(M+Na)^+$ 406.2933, found 406.2928.

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Supplementary data

Spectral data for all relevant compounds are provided. This material is available free of charge via the Internet. Supplementary

data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.09.036.

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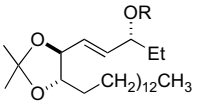
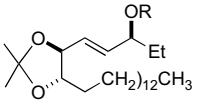
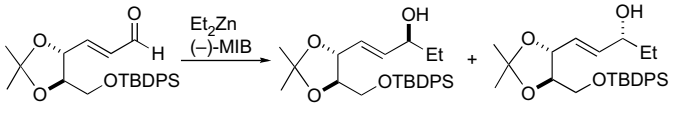


i: R = H
ii: R = Ac, Bz or (*R*)-MTPA



iii: R = Ac, Bz or (*R*)-MTPA

Determination of the diastereoselectivity based on proton-decoupled ^{13}C NMR spectrum assumed that each carbon in **9** and **i** has similar spin-lattice relaxation time and the NOE effect associated with decoupling. To confirm this assumption, we checked similar examples shown below. In this reaction, the products (a mixture of **v** and **vi**) were transformed into the corresponding acetates. ^{1}H NMR analysis determined the diastereoselectivity to be 96:4, which is consistent to the ratio (95:5) derived from the ^{13}C NMR data of **v** and **vi**. We thank Ken Okumura for these experiments.



iv **v** **vi**

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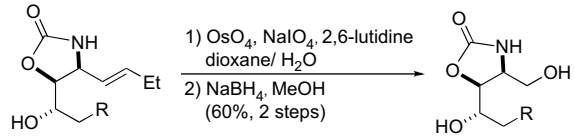
17. Our initial route to **16** involved oxidative cleavage of the alkene moiety in **13** with sodium periodate and a catalytic amount of osmium tetroxide in the presence of 2,6-lutidine (Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217–3219). In this case, the subsequent reduction of the resultant products with sodium borohydride in methanol occurred smoothly to afford the diol **i** in 60% yield over two steps.



13 **i**

18. Melting point and specific rotation of the synthetic pachastrissamine (**1**): mp 89–91 °C (lit.[6c] mp 89–91 °C); $[\alpha]_D^{23}$ +18.6 (*c* 1.00, MeOH) (lit.[6g] $[\alpha]_D^{23}$ +19.7 (*c* 0.50, MeOH)). Diacetate **17**: $[\alpha]_D^{23}$ −23.5 (*c* 0.40, $CHCl_3$) (lit.[6c] $[\alpha]_D^{22}$ −22.6 (*c* 1.00, $CHCl_3$)). ^{1}H NMR spectra of our diacetate **17** match those reported by Davies. See Ref. 6q.