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Formation of tetrahydrofurans *via* a 5-*endo-tet* cyclization of aziridines – synthesis of (−)-pachastrissamine†

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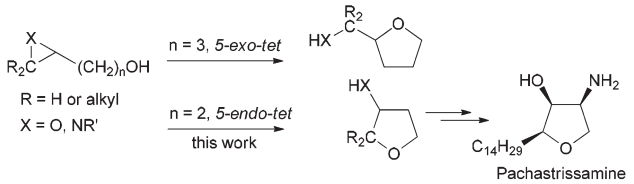
The formation of tetrahydrofurans from 2-hydroxyalkyl-oxirane or aziridine is reported. The *5-endo-tet* cyclization/ring opening of aziridine proceeded smoothly to give tetrahydrofurans (THFs) under mild conditions. In contrast, the corresponding process of oxirane was unsuccessful and a sequence of S_N2 substitution/cyclization was required to form THFs. The application of the process to prepare *ent*-(−)-pachastrissamine is described.

Introduction

Tetrahydrofurans (THFs) are often found in natural products and bioactive compounds.[1,2] Among the many synthetic methods developed to prepare tetrahydrofurans, applying oxiranes (epoxides) as the building blocks for THFs is a frequently adopted approach.[3] This approach is popular because many optically active oxiranes are commercially available or efficiently prepared by Sharpless asymmetric epoxidation (SAE),[4] and their transformations to other functionalities, including THFs, have highly conserved regio- and stereochemistry. Most of the reported cyclizations involving epoxides to THFs utilize the kinetically favourable 5-*exo-tet* cyclization,[3,5] and the corresponding process for aziridine, the *N*-analogue of oxiranes, has also been reported.[6] On the other hand, applying the unfavourable 5-*endo-tet* cyclization to prepare heterocycles has been less explored. Recently several groups reported that the intramolecular, 5-*endo-tet* cyclization of oxiranes can be synthetically useful, while the competing 5- or 6-*exo-tet* processes are absent (Scheme 1).[7] We noticed that the 5-*endo-tet* cyclization/ring opening of the oxirane derived from the C_2 symmetrical (3*R*,4*R*)-1,5-hexadiene-3,4-diol (**1**)[8] may be an attractive approach to prepare the substituted THFs such as pachastrissamine (jaspine B), a phytosphingosine derived, natural marine product with anti-cancer activity.[9] Recent studies showed that its cytotoxicity to melanoma cells is due to the inhibition of sphingosine and related protein kinases.[10] The high levels of biological activity and relatively simple structure of pachastrissamine has received substantial attention.[11] Here, we report our attempts to synthesize pachastrissamine, and we find that the unusual intramolecular, 5-*endo-tet* cyclization/ring opening of aziridines can be an efficient process by which to generate THFs.



Scheme 1 Intramolecular 5-*exo*- and 5-*endo-tet* cyclization and its application to pachastrissamine.

Results and discussion

Applying Sharpless asymmetric epoxidation to the allylic alcohol **2**, derived from mono-*tert*-butyldimethylsilyl (TBS)-protected diene-diol **1**, generated the oxirane **3** (Scheme 2). The stereochemistry of **3** is consistent with a previous report[12] and the general reaction model for SAE.[13] The remaining hydroxyl group was further protected by a methoxymethyl (MOM) group. After the removal of the TBS protective group with fluoride, cross metathesis (CM) was performed to elongate the carbon skeleton and generate **5**. Hydrogenation with Pd/C provided the saturated compound **6**, which allowed us to study the formation of THF by 5-*endo-tet* cyclization. However, we were unable to produce any product with the THF moiety, such as compound **7**, under various reaction conditions, including those previously reported.[7,14] The successful formation of THF from 4-chloroalcohols recently reported by Britton's group inspired us to adopt a similar strategy

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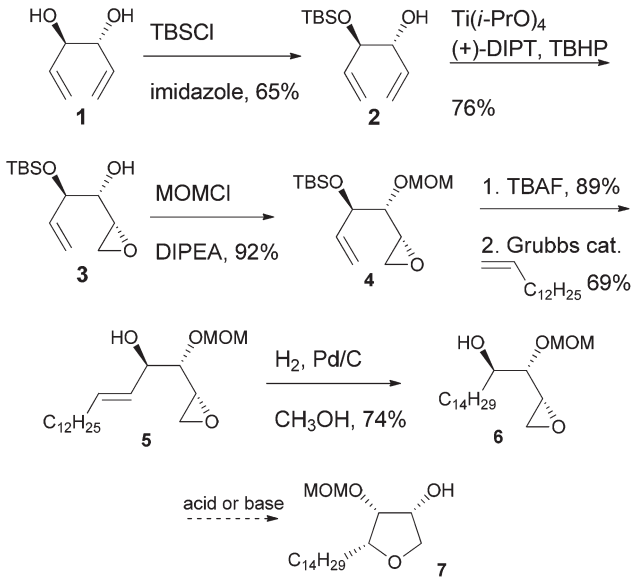
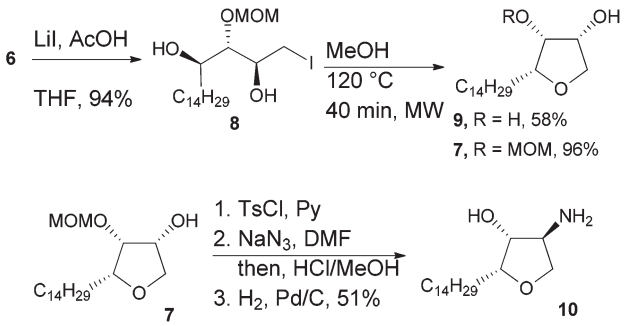
†Electronic supplementary information (ESI) available: Copies of the ^{1}H NMR and ^{13}C NMR spectra for the new compounds. See DOI: 10.1039/c3ob40797g



Scheme 2 Initial attempt to form THF.

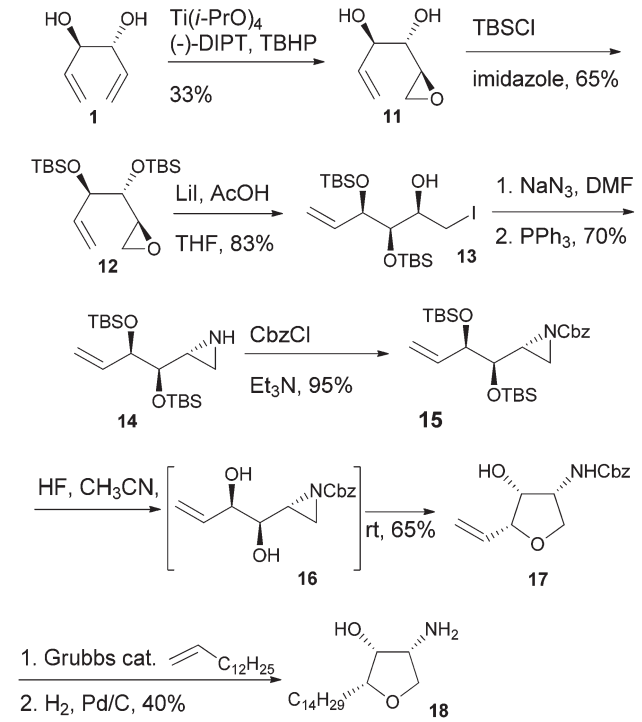


Scheme 3 Synthesis of (2*R*,3*R*,4*S*)-isomer of pachastrissamine (**10**).

(Scheme 3).[15] Thus, epoxide **6** was converted to the iodide **8**, and the formation of THF **9** was achieved under microwave irradiated thermal conditions (in methanol, 40 minutes at 120 °C). Later, the addition of propylene oxide removed the byproduct, hydrogen iodide, and provided the product **7**, whose MOM group remained intact.[16,17] The sequence of tosylation, nucleophilic substitution with sodium azide, deprotection, and reduction provided the (2*R*,3*R*,4*S*)-isomer of pachastrissamine.[11*l*]

Although the ring opening of epoxide by LiI and the subsequent intramolecular S_N2 reaction yielded the THF moiety,[15] we still looked for substrates suitable for 5-*endo-tet* cyclization to allow direct preparation of THF. Since one of the C–N bonds is replaced with the thermodynamically more stable C–O bond during the ring opening of aziridine to THF (Scheme 1),[18] we suspected that the corresponding ring opening of aziridine should be more feasible than that of oxirane.

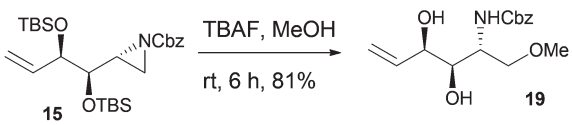
Thus, the stereochemically inverted (2*S*)-oxirane **11** was prepared from the diene-diol **1** according to the report by Takano's group (Scheme 4).[19] Both hydroxyl groups were then protected with the *tert*-butyldimethylsilyl (TBS) group to give **12**, and the oxirane was converted to aziridine **14** after the



Scheme 4 Synthesis of *ent*-(−)-pachastrissamine.

sequence of iodination (**13**) and Staudinger type reaction.[20] We noticed that the aziridine moiety could not be generated when the diol **11** was protected as an acetonide. The amino group of **14** was further masked with a benzyloxycarbonyl (Cbz) group to give the carbamate **15**. To our delight, the cyclization of **15** occurred simultaneously during the HF-promoted deprotection of the TBS groups and provided the desired THF **17** at room temperature. The total synthesis of *ent*-(−)-pachastrissamine (**18**) was achieved after the sequence of cross metathesis with 1-tetradecene, subsequent hydrogenation of the resulting alkene and hydrogenolysis of the Cbz protecting group. The natural (+)-pachastrissamine could be prepared by the same approach using the known (3*S*,4*S*)-1,5-hexadiene-3,4-diol[21] and (+)-DIPT.

Further studies on the cyclization process found that an acidic condition is required. When the aziridine **15** was treated with the basic tetrabutylammonium fluoride (TBAF), the ring-opening product **19**, derived from the addition of methanol, was obtained (eqn (1)). To our knowledge, only two reports have described the intramolecular 5-*endo-tet* cyclization of aziridines.[22] In both cases, the reaction sites for the nucleophilic attack of the hydroxyls are tertiary carbons under Lewis-acid catalyzed conditions. Here, we provide an example that the ring opening occurred at the less substituted carbon.



(1)

Conclusions

In conclusion, applying the 5-*endo-tet* cyclization of oxiranes and aziridines to prepare natural products with a tetrahydrofuran moiety, such as pachastrissamine, is reported. Although this approach was unsuccessful for the oxirane **6**, the alternative sequence of iodination and intramolecular S_N2 reaction at elevated temperature generated THF **7**, leading to the synthesis of (2*R*,3*R*,4*S*)-isomer of pachastrissamine. The 5-*endo-tet* cyclization of aziridine **15**, on the other hand, went smoothly in HF/acetonitrile at room temperature, and the synthesis of *ent*-(−)-pachastrissamine was achieved in eight steps. These results suggest that the 5-*endo-tet* cyclization/ring opening of aziridines may be a synthetically useful process.

Experimental section

(3*R*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)hexa-1,5-dien-3-ol (2)

tert-Butyldimethylsilyl chloride (TBSCl, 1.58 g, 10.5 mmol) was added to the solution of diene-diol **1** (1 g, 8.76 mmol), imidazole (895 mg, 13.1 mmol) and dichloromethane (50 mL) at 0 °C. The reaction mixture was heated to reflux for 16 h, quenched with water (30 mL) and extracted with diethyl ether (40 mL × 3). The combined organic layers were washed with $HCl_{(aq.)}$ (0.1 N, 50 mL) and sat. $NaCl_{(aq.)}$, dried with $Na_2SO_{4(s)}$, filtered and concentrated. The crude product was further purified by column chromatography (SiO_2, EtOAc–hexanes, 1 : 9; R_f 0.6) to give **2** (1.20 g, 5.25 mmol, 60%) as a colorless oil. $[\alpha]_D^{20}$ +8.94 (*c* 2.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.03 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 2.53 (s, 1H, *J* = 4.5 Hz), 3.91–3.97 (m, 2H), 5.14–5.32 (m, 4H), 5.73–5.86 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.1, 25.8, 75.6, 77.4, 116.4, 117.0, 136.9, 137.7; IR (neat): 3465 (br), 3080 (w), 2930 (m), 2857 (m), 1245 (m), 836 (m), 777 (m) cm^{-1}; HRMS (ESI) calcd for $[M + Na]^+$ ($C_{12}H_{24}NaO_2Si$) 251.1443, found 251.1440.

(1*R*,2*R*)-2-(*tert*-Butyldimethylsilyloxy)-1-((*R*)-oxiran-2-yl)but-3-en-1-ol (3)

Compound **2** (1.0 g, 4.38 mmol) in dichloromethane (3 mL) was added to the suspension of (+)-diisopropyl L-tartrate (1.30 mL, 6.14 mmol), titanium tetraisopropoxide (1.49 g, 5.26 mmol), molecular sieves (3 Å, 1.33 g) and dichloromethane (25 mL) at −30 °C. After stirring for 1 h, *tert*-butyl hydroperoxide (3 M in toluene, 2.60 mL, 7.89 mmol) was added to the above solution at −30 °C. The reaction mixture was stirred at −20 °C for another 72 h, quenched with a solution of ferrous sulfate heptahydrate (1.46 g, 5.26 mmol), citric acid (505 mg, 2.63 mmol) and water (15 mL). The mixture was stirred at −20 °C for another 1 h, warmed to rt, filtered, and the filtrate was extracted with dichloromethane (20 mL × 3). The combined organic layers were washed with sat. $NaCl_{(aq.)}$ (20 mL), dried with $Na_2SO_{4(s)}$, filtered and concentrated. The crude product was further purified by column chromatography (SiO_2, EtOAc–hexanes, 1 : 5; R_f 0.31) to give **3** (816 mg, 3.34 mmol, 76%) as a light yellow oil. $[\alpha]_D^{20}$ +12.8 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.06 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 2.35 (br, 1H), 2.72–2.80 (m, 2H), 2.98–3.02 (m, 1H), 3.30–3.33 (m, 1H), 4.27–4.30 (m, 1H), 5.18–5.21 (d, 1H, *J* = 10.5 Hz), 5.26–5.32 (d, 1H, *J* = 17.1 Hz), 5.83–5.94 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.1, −4.3, 18.1, 25.8, 45.5, 51.9, 74.1, 74.7, 116.6, 137.4; HRMS (ESI) calcd for $[M + Na]^+$ ($C_{12}H_{24}O_3SiNa$) 267.1392, found 267.1397.

(5*R*,6*R*)-8,8,9,9-Tetramethyl-5-((*R*)-oxiran-2-yl)-6-vinyl-2,4,7-trioxa-8-siladecane (4)

Chloromethyl methyl ether (617 mg, 7.66 mmol) was added to the solution of epoxide **3** (936 mg, 3.83 mmol), *N*,*N*-diisopropylethylamine (1.50 g, 11.5 mmol) and dichloromethane (9 mL) at 0 °C. The reaction mixture was heated to reflux for 16 h, cooled to rt, $NaHCO_{3(aq.)}$ (3 wt%, 20 mL) was added, and extracted with dichloromethane (10 mL × 3). The combined organic layers were dried with $Na_2SO_{4(s)}$, filtered and concentrated. The crude product was further purified by column chromatography (SiO_2, EtOAc–hexanes, 1 : 9; R_f 0.56) to give **4** (1.01 g, 3.51 mmol, 92%) as a light yellow oil. $[\alpha]_D^{20}$ +51.9 (*c* 1.23, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.04 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 2.67–2.74 (m, 2H), 3.07–3.10 (m, 1H), 3.31 (s, 3H), 3.48–3.51 (m, 1H), 4.28–4.32 (m, 1H), 4.56–4.58 (d, *J* = 6.6 Hz, 1H), 4.62–4.64 (d, *J* = 6.6 Hz , 1H), 5.12–5.15 (d, 1H, *J* = 10.5 Hz), 5.24–5.30 (d, 1H, *J* = 17.1 Hz), 5.85–5.96 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.1, −4.7, 18.2, 25.8, 44.9, 50.6, 55.4, 74.4, 78.2, 96.8, 115.8, 137.2; HRMS (ESI) calcd for $[M + Na]^+$ ($C_{14}H_{28}O_4SiNa$) 311.1655, found 311.1656.

(*E*,1*S*,2*R*)-1-(Methoxymethoxy)-1-((*R*)-oxiran-2-yl)hexadec-3-en-2-ol (5)

Tetrabutylammonium fluoride (TBAF, 1 Min THF, 5 mL, 5 mmol) was added to the solution of **4** (962 mg, 3.33 mmol) and THF (30 mL). The reaction mixture was stirred at rt for 4 h, diluted with water (20 mL) and extracted with diethyl ether (20 mL × 3). The combined organic layers were dried with $Na_2SO_{4(s)}$, filtered and concentrated. The residue was purified by column chromatography (SiO_2, EtOAc–hexanes, 1 : 1; R_f 0.40) to give (1*S*,2*R*)-1-(methoxymethoxy)-1-((*R*)-oxiran-2-yl)but-3-en-2-ol (515 mg, 2.96 mmol, 89%) as a light yellow oil. $[\alpha]_D^{20}$ +9.08 (*c* 1.04, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.45 (br, 1H), 2.75–2.82 (m, 2H), 3.06–3.10 (m, 1H), 3.35 (s, 3H), 3.33–3.37 (m, 1H), 4.22–4.26 (m, 1H), 4.60–4.62 (d, *J* = 6.6 Hz, 1H), 4.69–4.71 (d, *J* = 6.6 Hz , 1H), 5.22–5.26 (d, 1H, *J* = 10.5 Hz), 5.36–5.42 (d, 1H, *J* = 17.1 Hz), 5.88–5.99 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 45.4, 50.6, 55.7, 73.4, 79.2, 96.6, 116.6, 136.8; HRMS (ESI) calcd for $[M + Na]^+$ ($C_8H_{14}O_4Na$) 197.0790, found 197.0793.

A solution of the above alcohol (382 mg, 2.19 mmol), 1-tetradecene (1.73 g, 8.77 mmol), Grubbs catalyst, 2nd generation (56 mg, 3 mol%) and dichloromethane (33 mL) was heated to reflux for 2 h under an atmosphere of nitrogen. The reaction mixture was concentrated, and the residue was purified by column chromatography (SiO_2, EtOAc–hexanes, 1 : 5; R_f 0.23) to give **5** (514 mg, 1.50 mmol, 69%) as a light brown oil. $[\alpha]_D^{20}$ −3.62 (*c* 0.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.83–0.88

(t, J = 6.6 Hz, 3H), 1.23 (br, 20H), 2.01–2.08 (m, 2H), 2.47–2.49 (d, J = 5.1 Hz, 1H), 2.73–2.79 (m, 2H), 3.04–3.07 (m, 1H), 3.34–3.38 (m, 4H), 4.13–4.17 (m, 1H), 4.61–4.63 (d, J = 6.6 Hz, 1H), 4.70–4.72 (d, J = 6.6 Hz, 1H), 5.49–5.57 (dd, J = 6.8 Hz, 15.5 Hz, 1H), 5.74–5.84 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 22.7, 29.0, 29.2, 29.3, 29.5, 29.6, 31.9, 32.3, 45.1, 50.8, 55.8, 73.5, 79.6, 96.8, 128.2, 134.4; HRMS (ESI) calcd for $[M + Na]^+$ ($C_{20}H_{38}O_4Na$) 365.2668, found 365.2674.

(1*S*,2*R*)-1-(Methoxymethoxy)-1-(oxiran-2-yl)hexadecan-2-ol (6)

A suspension of **5** (514 mg, 1.50 mmol), palladium on carbon (10 wt%, 80 mg) and methanol (10 mL) was stirred for 40 min at rt under hydrogen (1 atm). The suspension was filtered and concentrated. The crude product was further purified by column chromatography (SiO_2, EtOAc–hexanes, 1 : 5; R_f 0.23) to give **6** (381.0 mg, 0.75 mmol, 74%) as a colorless solid. M.p. 38.0–40.0 °C; $[\alpha]_D^{20}$ −4.91 (c 1.04, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.83–0.88 (t, J = 6.6 Hz, 3H), 1.23 (br, 24H), 1.51–1.56 (m, 2H), 2.72–2.74 (dd, J = 2.7 Hz, 5.1 Hz, 1H), 2.80–2.83 (dd, J = 2.7 Hz, 5.1 Hz, 1H), 3.02–3.06 (m, 1H), 3.20–3.23 (dd, J = 4.5 Hz, 6.0 Hz, 1H), 3.37 (s, 3H), 3.67–3.73 (m, 1H), 4.60–4.62 (d, J = 6.6 Hz, 1H), 4.73–4.75 (d, J = 6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 22.7, 25.6, 29.3, 29.6, 31.9, 33.3, 45.8, 50.8, 55.8, 72.4, 79.6, 96.6; HRMS (ESI) calcd for $[M + Na]^+$ ($C_{20}H_{40}O_4Na$) 367.2824, found 367.2819.

(2*S*,3*S*,4*R*)-1-Iodo-3-(methoxymethoxy)octadecane-2,4-diol (8)

The solution of **6** (150 mg, 0.44 mmol), lithium iodide (117.0 mg, 0.87 mmol), acetic acid (56 μL, 1.31 mmol) and THF (2.6 mL) was stirred at rt for 16 h. Sat. $NaCl_{(aq.)}$ (5 mL) was added to the reaction mixture and extracted with ethyl acetate (10 mL × 3). The combined organic layers were dried with $Na_2SO_{4(s)}$, filtered and concentrated. The crude product was further purified by column chromatography (SiO_2, EtOAc–hexanes, 1 : 3; R_f 0.77) to give **8** (194 mg, 0.41 mmol, 94%) as a colorless solid. M.p. 43.0–45.0 °C; $[\alpha]_D^{20}$ +13.9 (c 0.81, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82–0.87 (t, J = 6.9 Hz, 3H), 1.22 (br, 24H), 1.50 (br, 2H), 2.63 (br, 1H), 3.28–3.34 (m, 1H), 3.40–3.46 (m, 4H), 3.50–3.53 (m, 2H), 3.78 (br, 2H), 4.66–4.68 (d, J = 6.6 Hz, 1H), 4.76–4.78 (d, J = 6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.1, 14.1, 22.6, 25.8, 29.3, 29.5, 29.6, 31.9, 33.3, 56.2, 71.5, 71.7, 82.4, 97.8.

(2*R*,3*R*,4*R*)-2-Tetradecyltetrahydrofuran-3,4-diol (9)

The solution of **8** (36.0 mg, 0.076 mmol) and methanol (0.8 mL) in a sealed tube was heated to 120 °C in a microwave oven (CEM Discover, 50 W) for 40 min. After cooling to rt, the reaction mixture was diluted with ethyl acetate (10 mL) and washed with sat. $NaCl_{(aq.)}$ (5 mL). The organic layer was separated, dried with $Na_2SO_{4(s)}$, filtered and concentrated. The crude product was further purified by column chromatography (SiO_2, EtOAc–hexanes, 1 : 3; R_f 0.32) to give **9** (13.2 mg, 0.044 mmol, 58%) as a colourless solid. M.p. 97.0–99.0 °C; $[\alpha]_D^{20}$ −13.1 (c 0.63, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.83–0.87 (t, J = 6.9 Hz, 3H), 1.23 (br, 24H), 1.59–1.66 (m, 2H), 2.46 (br, 1H), 2.66 (br, 1H), 3.63–3.72 (m, 2H), 3.81–3.86 (dd, J = 6.6 Hz, 9.6 Hz, 1H), 4.04 (br, 1H), 4.36–4.38 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 22.7, 26.1, 29.0, 29.3, 29.6, 29.7, 31.9, 72.0, 72.2, 72.4, 81.9.

(3*R*,4*R*,5*R*)-4-(Methoxymethoxy)-5-tetradecyltetrahydrofuran-3-ol (7)

The solution of **8** (36.0 mg, 0.076 mmol), propylene oxide (18 μL, 0.26 mmol) and methanol (0.8 mL) in a sealed tube was heated to 120 °C in a microwave oven (CEM Discover, 50 W) for 40 min. After cooling to rt, the reaction mixture was diluted with ethyl acetate (10 mL) and washed with sat. $NaCl_{(aq.)}$ (5 mL). The organic layer was separated, dried with $Na_2SO_{4(s)}$, filtered and concentrated. The crude product was further purified by column chromatography (SiO_2, EtOAc–hexanes, 1 : 3; R_f 0.58) to give **7** (25 mg, 0.073 mmol, 96%) as a colorless solid. M.p. 73.0–75.0 °C; $[\alpha]_D^{20}$ −3.70 (c 0.99, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.83–0.86 (t, J = 6.9 Hz, 3H), 1.22 (br, 24H), 1.58–1.65 (m, 2H), 2.91–2.93 (d, J = 7.2 Hz, 1H), 3.42 (s, 3H), 3.67–3.83 (m, 3H), 4.01–4.04 (m, 1H), 4.29–4.32 (m, 1H), 4.66–4.68 (d, J = 6.6 Hz, 1H), 4.75–4.77 (d, J = 6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 22.7, 26.3, 29.3, 29.7, 31.9, 56.2, 71.8, 72.2, 79.4, 80.6, 97.7; HRMS (ESI) calcd for $[M + Na]^+$ ($C_{20}H_{40}O_4Na$) 367.2824, found 367.2834.

(2*R*,3*R*,4*S*)-4-Amino-2-tetradecyltetrahydrofuran-3-ol (10)

p-Toluenesulfonyl chloride (238 mg, 1.25 mmol) was added to the solution of **7** (43 mg, 0.13 mmol) and pyridine (1 mL) at 0 °C. The reaction mixture was stirred in a 50 °C oil bath for 16 h, sat. $NaHCO_{3(aq.)}$ (2 mL) was added and extracted with dichloromethane (5 mL × 3). The combined organic layers were dried with $Na_2SO_{4(s)}$, filtered and concentrated. The crude product was further purified by column chromatography (SiO_2, EtOAc–hexanes, 1 : 5; R_f 0.58) to give the tosylate (60 mg, 0.12 mmol, 96%) as a light yellow oil. $[\alpha]_D^{20}$ −31.8 (c 0.80, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82–0.87 (t, J = 6.9 Hz, 3H), 1.22 (br, 24H), 1.57–1.60 (m, 2H), 2.42 (s, 3H), 3.34 (s, 3H), 3.75–3.81 (m, 3H), 4.11–4.14 (t, J = 4.5 Hz, 1H), 4.58–4.60 (d, J = 6.9 Hz, 1H), 4.66–4.68 (d, J = 6.9 Hz, 1H), 4.89–4.95 (m, 1H), 7.31–7.33 (d, J = 8.1 Hz, 2H), 7.75–7.78 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 21.6, 22.7, 25.9, 29.2, 29.3, 29.5, 29.6, 31.9, 56.1, 68.1, 75.7, 78.4, 80.0, 96.7, 127.8, 129.9, 133.3, 145.1; HRMS (ESI) calcd for $[M + Na]^+$ ($C_{27}H_{46}O_6SNa$) 521.2913, found 521.2921.

A solution of the above tosylate (29 mg, 0.058 mmol), sodium azide (38 mg, 0.58 mmol) and DMF (1 mL) was stirred in a 100 °C oil bath for 16 h. After cooling to rt, the reaction mixture was diluted with ethyl acetate (5 mL) and washed with sat. $NaCl_{(aq.)}$ (2 mL). The organic layer was separated, concentrated, and methanol (4.3 mL) and $HCl_{(aq.)}$ (3 M, 1.3 mL) were added to the residue. The solution was stirred at 55 °C for 5 h and concentrated. The crude product was further purified by column chromatography (SiO_2, EtOAc–hexanes, 1 : 5; R_f 0.31) to give (2*R*,3*R*,4*S*)-4-azido-2-tetradecyltetrahydrofuran-3-ol

(14 mg, 0.043 mmol, 74%) as a colourless solid. M.p. 54.0–56.0 °C; $[\alpha]_D^{20}$ +6.30 (*c* 0.68, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.83–0.88 (t, *J* = 6.9 Hz, 3H), 1.23 (br, 24H), 1.51–1.66 (m, 2H), 1.74 (br, 1H), 3.62–3.67 (dd, *J* = 2.7 Hz, 9.9 Hz, 1H), 3.76–3.82 (m, 1H), 3.99–4.05 (m, 2H), 4.16–4.21 (dd, *J* = 5.7 Hz, 9.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 22.7, 26.2, 28.2, 29.4, 29.5, 29.7, 31.9, 67.6, 70.0, 76.4, 81.1; HRMS (FAB) calcd for $[M + H]^+$ ($C_{18}H_{36}N_3O_2$) 326.2808, found 326.2808.

A suspension of the azido-alcohol (12 mg, 0.037 mmol), palladium on carbon (10 wt%, 4 mg) and TFA–methanol (1% v/v, 4 mL) was stirred for 5 h at rt under hydrogen (1 atm). The suspension was filtered, neutralized with $NaHCO_{3(s)}$ and concentrated. The crude product was further purified by column chromatography (SiO_2, methanol–dichloromethane–ammonium hydroxide, 10 : 90 : 1; R_f 0.37) to give **10** (8.0 mg, 0.027 mmol, 72%) as a colorless solid.[11l] M.p. 86.0–88.0 °C; $[\alpha]_D^{20}$ −5.1 (*c* 0.15, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.84–0.87 (t, *J* = 6.9 Hz, 3H), 1.23 (br, 24H), 1.55–1.67 (m, 5H), 3.37–3.39 (dd, *J* = 2.5 Hz, 9.0 Hz, 1H), 3.47 (br, 1H), 3.80 (br, 1H), 3.86–3.89 (m, 1H), 4.18–4.21 (dd, *J* = 6.0 Hz, 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1, 22.7, 26.4, 28.5, 29.4, 29.5, 29.6, 29.7, 29.7, 29.8, 31.9, 59.9, 73.7, 79.8, 80.7; HRMS (FAB) calcd for $[M + H]^+$ ($C_{18}H_{38}NO_2$) 300.2897, found 300.2664.

(1*S*,2*R*)-1-((*S*)-Oxiran-2-yl)but-3-ene-1,2-diol (11)

Diene-diol **1** (1.0 g, 8.76 mmol) in dichloromethane (6 mL) was added to the solution of (−)-diisopropyl D-tartrate (1.80 mL, 8.76 mmol), titanium tetraisopropoxide (2.6 mL, 8.76 mmol) and dichloromethane (50 mL) at −30 °C. After stirring for 1 h, *tert*-butyl hydroperoxide (3 M in toluene, 4.38 mL, 13.14 mmol) was added to the above solution at −30 °C. The reaction mixture was stirred at −20 °C for another 10 h, and quenched with a solution of ferrous sulfate heptahydrate (1.46 g, 5.26 mmol), citric acid (505 mg, 2.63 mmol) and water (15 mL). The mixture was stirred at −20 °C for another 1 h, warmed to rt, filtered, and the filtrate was extracted with dichloromethane (25 mL × 3). The combined organic layers were washed with sat. $NaCl_{(aq.)}$ (20 mL), dried with $Na_2SO_{4(s)}$, filtered and concentrated. The crude product was further purified by column chromatography (SiO_2, EtOAc–hexanes, 1 : 1; R_f 0.16) to give **11** (376 mg, 2.89 mmol, 33%) as a light yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.72–2.79 (m, 2H), 2.86 (br, 1H), 2.90 (br, 1H), 3.08–3.12 (m, 1H), 3.43 (s, 1H), 4.17 (t, *J* = 6.5 Hz, 1H), 5.23–5.42 (m, 2H), 5.82–5.93 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 44.6, 52.4, 73.2, 74.6, 118.2, 136.3; HRMS (EI+) calcd for $[M + H]^+$ ($C_6H_{11}O_3$) 131.0708, found 131.0708.

(5*R*,6*R*)-2,2,3,3,8,8,9,9-Octamethyl-5-((*S*)-oxiran-2-yl)-6-vinyl-4,7-dioxa-3,8-disiladecane (12)

tert-Butyldimethylsilyl chloride (TBSCl, 0.87 g, 5.76 mmol) was added into the solution of **11** (0.30 g, 2.30 mmol), imidazole (471 mg, 6.92 mmol) and dichloromethane (50 mL) at 0 °C. The reaction mixture was heated to reflux for 16 h, quenched with water (30 mL) and extracted with diethyl ether (20 mL × 3). The combined organic layers were dried with $Na_2SO_{4(s)}$, filtered and concentrated. The crude product was further purified by column chromatography (SiO_2, EtOAc–hexanes, 1 : 15; R_f 0.78) to give **12** (752 mg, 2.10 mmol, 91%) as a colourless oil. $[\alpha]_D^{20}$ +36.2 (*c* 1.12, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.039 (q, 12H), 0.89 (d, *J* = 3.6 Hz, 18H), 2.63 (t, *J* = 3.8 Hz, 1H), 2.74 (t, *J* = 3.7 Hz, 1H), 2.91 (d, *J* = 2.7 Hz, 1H), 3.20 (t, *J* = 5.6 Hz, 1H), 4.13 (s, 1H), 5.15 (d, *J* = 10.5 Hz, 1H), 5.28 (d, *J* = 17.1, 1H), 5.99–6.10 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −2.95, 18.1, 25.7, 25.8, 44.9, 53.1, 75.3, 77.7, 115.2, 136.8; HRMS (ESI) calcd for $[M + Na]^+$ ($C_{18}H_{38}O_3Si_2Na$) 381.2257; found 381.2253.

(2*R*,3*R*,4*R*)-3,4-Bis((*tert*-butyldimethylsilyl)oxy)-1-iodohex-5-en-2-ol (13)

The solution of **12** (700 mg, 1.95 mmol), lithium iodide (522.47 mg, 3.91 mmol), acetic acid (335 μL, 5.86 mmol) and THF (15 mL) was stirred at rt for 6 h. Sat. $NaCl_{(aq.)}$ (20 mL) was added to the reaction mixture and extracted with ethyl acetate (20 mL × 3). The combined organic layers were dried with $Na_2SO_{4(s)}$, filtered and concentrated. The crude product was further purified by column chromatography (SiO_2, EtOAc–hexanes, 1 : 15; R_f 0.62) to give **13** (788 mg, 1.62 mmol, 83%) as a light yellow oil. $[\alpha]_D^{20}$ +16.6 (*c* 0.605, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.059 (q, 12H), 0.87 (d, *J* = 18.3 Hz, 18H), 2.76 (d, *J* = 6.3 Hz, 1H), 3.18 (q, 2H), 3.84 (t, *J* = 3 Hz, 2H), 4.13–4.16 (m, 1H), 5.15 (d, *J* = 10.5 Hz, 1 Hz), 5.23 (d, *J* = 17.1 Hz, 1H), 5.92–6.01 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −2.95, 9.7, 18.0, 18.2, 25.8, 25.9, 69.6, 74.6, 115.6, 136.5; HRMS (ESI) calcd for $[M + Na]^+$ ($C_{18}H_{39}IO_3Si_2Na$) 509.1380, found 509.1374.

(*R*)-2-((5*R*,6*R*)-2,2,3,3,8,8,9,9-Octamethyl-6-vinyl-4,7-dioxa-3,8-disiladecan-5-yl)aziridine (14)

A solution of **13** (500 mg, 1.03 mmol), sodium azide (334 mg, 5.15 mmol) and DMF (30 mL) was stirred in a 40 °C oil bath for 16 h. The reaction mixture was diluted with ethyl acetate (30 mL) and washed with sat. $NaCl_{(aq.)}$ (20 mL). The organic layer was separated, dried with $Na_2SO_{4(s)}$, filtered and concentrated. The crude product was further purified by column chromatography (SiO_2, EtOAc–hexanes, 1 : 15; R_f 0.62) to give the azide (409 mg, 1.02 mmol, 99%) as a colorless oil. $[\alpha]_D^{20}$ +29 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.04 (q, 12H), 0.89 (t, *J* = 9.5 Hz, 18H), 2.53 (d, *J* = 5.7 Hz, 1H), 3.25 (q, 2H), 3.62 (t, *J* = 4.4 Hz, 1H), 3.86–3.93 (m, 1H), 4.16–4.19 (m, 1H), 5.14–5.29 (m, 2H), 5.94–6.05 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −2.95, 18.0, 18.1, 25.8, 25.9, 53.9, 69.3, 74.0, 74.5, 115.6, 136.4; HRMS (ESI) calcd for $[M + H]^+$ ($C_{18}H_{40}N_3O_3Si_2$) 402.2608, found 402.2611.

A solution of the above azide (300 mg, 0.75 mmol), triphenylphosphine (294 mg, 1.12 mmol) and toluene (35 mL) was heated to reflux for 6 h. Diethyl ether (20 mL), was added to the reaction mixture filtered and concentrated. The crude product was further purified by column chromatography (SiO_2, EtOAc–hexanes, 1 : 5; R_f 0.61) to give **14** (188 mg, 0.53 mmol,

70%) as a colorless oil. $[\alpha]_D^{20}$ +16.9 (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.05 (d, *J* = 3.9 Hz, 12H), 0.87 (d, *J* = 10.5 Hz, 18H), 1.45 (t, *J* = 5.5 Hz, 1H), 1.58 (d, *J* = 3 Hz, 1H), 2.13 (s, 1H), 3.62 (s, 1H), 4.19 (t, *J* = 4.7 Hz, 1H), 5.09–5.27 (m, 2H), 5.88–5.99 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −2.95, 18.0, 18.1, 22.0, 25.7, 25.8, 30.4, 75.9, 115.4, 137.1; HRMS (ESI) calcd for $[M + H]^+$ ($C_{18}H_{40}NO_2Si_2$) 358.2598, found 358.2591.

(*R*)-Benzyl 2-((5*R*,6*R*)-2,2,3,3,8,8,9,9-octamethyl-6-vinyl-4,7-dioxa-3,8-disiladecan-5-yl)aziridine-1-carboxylate (15)

Benzyl chloroformate (77.94 μL, 0.55 mmol) was added to the solution of **14** (130 mg, 0.36 mmol), triethylamine (101.47 μL, 0.73 mmol) and dichloromethane (5 mL) at 0 °C. The reaction mixture was stirred at rt for 16 h, quenched with sat. $NaHCO_{3(aq.)}$ (2 mL), extracted with dichloromethane (10 mL × 3). The combined organic layers were dried with $Na_2SO_{4(s)}$, filtered and concentrated. The crude product was further purified by column chromatography (SiO_2, EtOAc–hexanes, 1 : 9; R_f 0.60) to give **15** (168 mg, 0.34 mmol, 95%) as a light yellow oil. $[\alpha]_D^{20}$ +43.2 (*c* 0.65, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.08 (q, 12H), 0.91 (d, *J* = 11.1 Hz, 18H), 1.62 (s, 1H), 2.17 (d, *J* = 6.3 Hz, 1H), 2.24 (d, *J* = 3.9 Hz, 1H), 2.77–2.81 (m, 1H), 3.99 (q, *J* = 1.5 Hz, 1H), 5.09–5.19 (m, 3H), 5.26–5.33 (m, 1H), 5.90–6.00 (m, 1H), 7.34–7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −2.9, 18.0, 25.7, 27.6, 37.7, 67.6, 71.5, 74.8, 115.1, 127.7, 128.0, 128.4, 136.1, 136.4, 163.7; HRMS (FAB) calcd for $[M + H]^+$ ($C_{26}H_{46}O_4NSi_2$) 492.2965, found 492.2974.

Benzyl ((3*R*,4*R*,5*R*)-4-hydroxy-5-vinyltetrahydrofuran-3-yl)-carbamate (17)

Hydrofluoric acid (48 wt% in H_2O, 163 μL, 4.50 mmol) was added to the solution of **15** (30 mg, 0.06 mmol) and acetonitrile (1.5 mL). The reaction mixture was stirred at rt for 16 h, quenched with sat. $NaHCO_{3(aq.)}$ (2 mL), and extracted with ethyl acetate (3 mL × 3). The combined organic layers were washed with sat. $NaCl_{(aq.)}$ (2 mL), dried with $Na_2SO_{4(s)}$, filtered and concentrated. The crude product was further purified by column chromatography (SiO_2, methanol–dichloromethane, 1 : 9; R_f 0.76) to give **17** (10.3 mg, 0.04 mmol, 65%) as a light yellow oil. $[\alpha]_D^{20}$ −9.7 (*c* 0.35, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.45–3.63 (m, 1H), 3.75–3.79 (m, 1H), 3.91–3.98 (m, 1H), 4.02–4.15 (m, 1H), 2.24 (s, 1H), 5.10 (d, *J* = 9 Hz, 2H), 5.25–5.45 (m, 3H), 5.78–5.93 (m, 1H), 7.34–7.35 (br, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 70.1, 72.4, 74.3, 82.4, 94.9, 118.9, 128.2, 128.3, 128.5, 134.1, 136.5, 171.2; HRMS (ESI) calcd for $[M - H]^-$ ($C_{14}H_{16}NO_4$) 262.1079, found 262.1079.

ent-(−)-Pachastrissamine (18)

The solution of **17** (10 mg, 0.038 mmol), 1-tetradecene (37 mg, 0.038 mmol), Grubbs catalyst, 2nd generation (3.2 mg, 3.7 μmol) and dichloromethane (3 mL) was heated to reflux for 3 h under a nitrogen atmosphere. The reaction mixture was concentrated, and TFA–methanol (1% v/v, 4 mL) and palladium on carbon (10 wt%, 4 mg) were added to the residue. The suspension was stirred for 16 h at rt under hydrogen (1 atm). The suspension was filtered, acidified with $HCl_{(aq.)}$ (2 N, 5 mL) and washed with dichloromethane (2 mL × 3). The aqueous layer was basified with $NaOH_{(aq.)}$ (5 N), and extracted with dichloromethane (2 mL × 3). The combined organic layers were dried with $Na_2SO_{4(s)}$, filtered and concentrated. The crude product was further purified by column chromatography (SiO_2, methanol–dichloromethane–ammonium hydroxide, 10 : 90 : 1; R_f 0.37) to give *ent*-(−)-pachastrissamine (4.5 mg, 0.015 mmol, 40%) as a colorless solid.[11f] M.p. 89.0–91.0 °C; $[\alpha]_D^{20}$ −7.0 (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 3.51 (q, 1H), 3.62 (q, 1H), 3.72 (q, 1H), 3.82 (q, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1, 21.7, 22.0, 22.7, 28.5, 29.1, 29.7, 30.0, 31.4, 31.9, 52.7, 69.8, 70.7, 81.1.

Benzyl ((2*R*,3*R*,4*R*)-3,4-dihydroxy-1-methoxyhex-5-en-2-yl)-carbamate (19)

Tetrabutylammonium fluoride trihydrate (79 mg, 0.25 mmol) was added to the solution of **15** (15 mg, 0.03 mmol) and methanol (0.75 mL). The reaction mixture was stirred at rt for 16 h, quenched with sat. $NaHCO_{3(aq.)}$ (1 mL), and extracted with ethyl acetate (2 mL × 3). The combined organic layers were washed with sat. $NaCl_{(aq.)}$ (1 mL), dried with $Na_2SO_{4(s)}$, filtered and concentrated. The crude product was further purified by column chromatography (SiO_2, ethyl acetate–hexanes, 1 : 1; R_f 0.64) to give **19** (7.2 mg, 0.24 mmol, 81%) as a light yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.33 (s, 3H), 3.34–3.51 (m, 2H), 3.64–3.69 (t, *J* = 7.9 Hz, 1H), 3.78–3.82 (q, 1H), 4.18–4.19 (d, *J* = 3 Hz, 1H), 5.10 (s, 2H), 5.23–5.26 (d, *J* = 9 Hz, 1H), 5.43–5.51 (t, *J* = 12.5 Hz, 1H), 5.82–5.93 (m, 1H), 7.34 (s, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.4, 59.2, 70.7, 71.0, 72.8, 116.7, 128.2, 128.4, 128.6, 136.7, 157.4; HRMS (ESI) calcd for $[M + H]^+$ ($C_{14}H_{16}NO_4$) 262.1498, found 296.1505.

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