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A novel stereoselective synthesis of pachastrissamine (jaspine B) starting from 1-pentadecanol

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Abstract—A novel stereoselective synthesis of pachastrissamine (jaspine B), starting from commercially available 1-pentadecanol is described. Sharpless asymmetric dihydroxylation and a chelation controlled vinyl Grignard reaction are the key steps in this synthetic strategy.

1. Introduction

Pachastrissamine **I** (Fig. 1), a naturally occurring novel anhydrophytosphingosine derivative, has recently been isolated from the Okinawan marine sponge Pachastrissa sp.[1] Another research group has reported the isolation of the same natural product from a different marine sponge, *Jaspis* sp. and named it as jaspine B.[2] Jaspine B hydrochloride displayed a remarkable bioactivity ($IC_{50} = 0.24\ \mu M$) against the A549 human lung carcinoma cell line using the ATPlite assay and represented the most potent anticancer agent on this cell line yet isolated from the Jaspis genus.[1,3] Jaspine B represents the first example of an anhydrophytosphingosine structural feature in a natural product. Pachastrissamine possesses three contiguous stereogenic centers and is structurally similar to the open

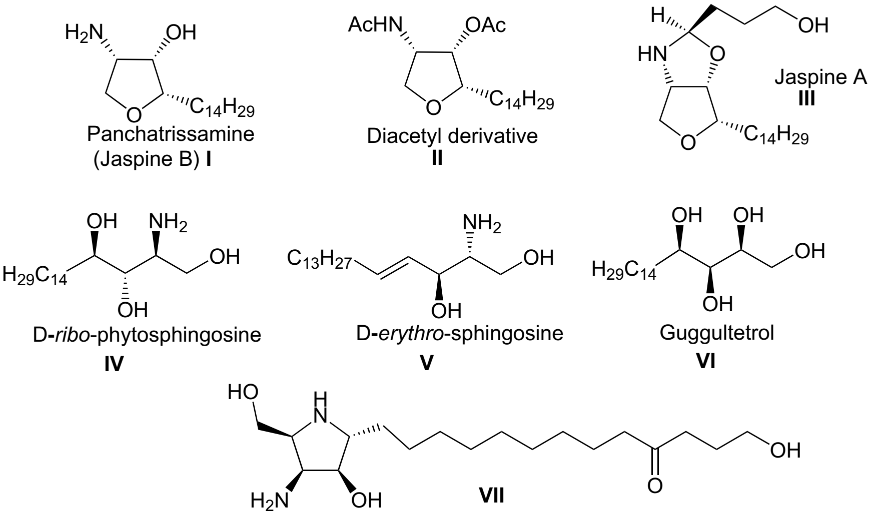

Figure 1.

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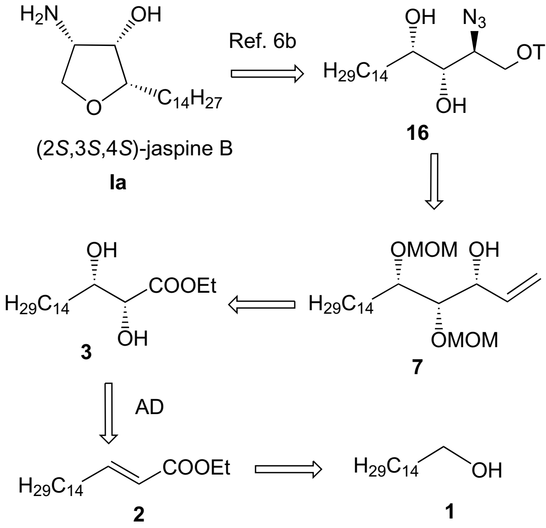
chain sphingolipid D-*ribo*-phytosphingosine **IV**. Interestingly, guggultetrol **VI**, a naturally occurring lipid isolated from the gum-resin of the tree *Commiphoru mukul* (*guggulu*), known in Ayurveda, the Indian traditional system of medicine, for the treatment of arthritis, inflammation, obesity, and disorders of lipid metabolism closely resembles the sphigolipid phytosphingosine **IV**.[4] The impressive biological activity and the novel structural features encouraged us to undertake a stereoselective synthesis of this interesting natural product. In the interest of evaluating the biological and pharmacological properties of these compounds, it was necessary to obtain sufficient quantities by chemical synthesis. Most of the total syntheses known for jaspine B derive the asymmetry from the chiral pool of starting materials[5,6] such as xylose, glucose, and Garner's aldehyde. Even though the synthesis of jaspine B, as reported by Overkleeft and co-workers[5d] involved only three steps, the starting material D-*ribo*-phytosphingosine itself has to be prepared from 3,4,6-tri-*O*-acetyl-D-galactal in nine steps, and is thus highly expensive and less widely available. Moreover, some of the literature methods for the synthesis of jaspine B involve expensive catalysts such as Grubb's catalyst[5b] and unnatural (−)-diethyl tartrate.[5e]

To the best of our knowledge, there has been no synthetic report which describes asymmetric synthesis of jaspine B, starting from 1-pentadecanol, which is achiral. However, most recently two contemporary synthetic protocols for the preparation of jaspine B starting from different achiral starting materials have been reported.[7] As a part of our ongoing project for the asymmetric synthesis of biologically active compounds,[8] we herein report a novel route to the synthesis of jaspine B **I**, starting from the commercially available, and inexpensive achiral starting material 1-pentadecanol **1**, for the first time.

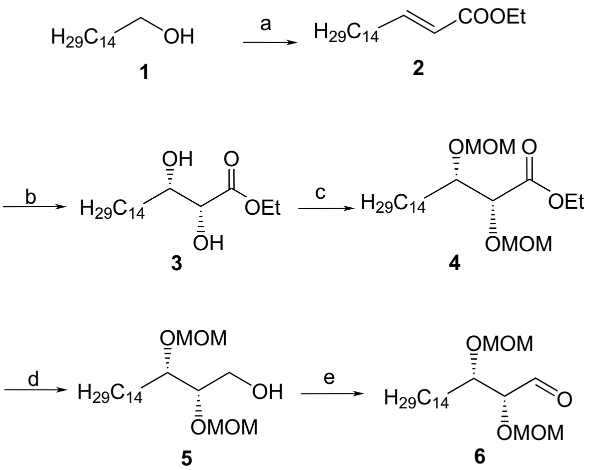
2. Results and discussion

The Sharpless asymmetric dihydroxylation can be envisioned as a powerful tool offering considerable opportunities for synthetic manipulation.[9] Sharpless asymmetric dihydroxylation and a chelation controlled vinyl Grignard reaction are the key steps of our synthetic strategy and are shown in Scheme 1. We envisioned that azido diol **16** could be prepared from terminal olefin **7**, which in turn could be prepared from diol **3** after suitable protection via a chelation controlled vinyl Grignard reaction. Diol **3** itself could be prepared by Sharpless asymmetric dihydroxylation of an α,β-unsaturated olefin ester **2**, which in turn could be obtained from the commercially available 1-pentadecanol **1**.

1-Pentadecanol **1** after subjection to oxidation with PCC, followed by a Wittig olefin reaction, furnished *trans*-α,β-unsaturated ester **2** in 92% yield. Olefin **2** was treated with osmium tetroxide and potassium ferricyanide as a co-oxidant in the presence of a $(DHQ)_2PHAL$ ligand under asymmetric dihydroxylation (AD) conditions[9] to give diol **3** in 88% yield and 97% ee.[10] Treatment of the diol with MOMCl in the presence of DIPEA gave the di MOM derivative **4**, which on reduction with DIBAL-H resulted in alcohol **5** in 96% yield. Alcohol **5** was oxidized with IBX to afford aldehyde **6**. Due to the unstable nature of aldehyde **6**, it was immediately taken to the next step as such without further purification (Scheme 2).



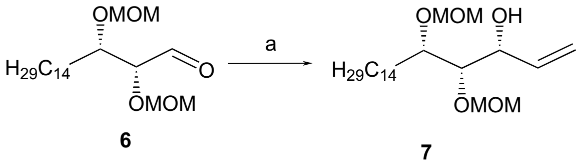
Scheme 1. Retrosynthetic approach to (2*S*,3*S*,4*S*)-jaspine B **I**.



Scheme 2. Synthesis of intermediate **6** (Sharpless dihydroxylation method as a key step). Reagents and conditions: (a) (i) PCC, dry DCM, 0 °C, 3 h, (ii) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 4 h, 92%; (b) $(DHQ)_2PHAL$, K_2CO_3, $K_3[Fe(CN)]_6$, $MeSO_2NH_2$, OsO_4 (0.1 M sol in toluene), *t*-BuOH/H_2O (1:1), 0 °C, 24 h, 88%; (c) MOMCl, dry DCM, DIPEA, 0 °C to rt, overnight, 96%; (d) DIBAL-H, dry DCM, −10 °C, 1 h, 96%; (e) IBX, EtOAc, reflux, 3 h.

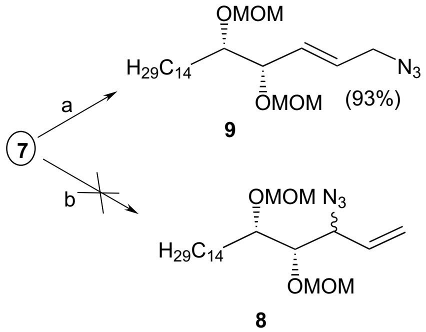
To create a third stereogenic center with the required stereochemistry, a chelation controlled vinyl Grignard reaction[11] was performed (Scheme 3).

Thus, the crude aldehyde **6** was subjected to a vinylation reaction using vinyl magnesium bromide in the presence of $MgBr_2{\cdot}Et_2O$ at −78 °C to furnish the *syn*-isomer (allylic alcohol **7**) in 89% yield with high diastereomeric excess (de = >95%) as judged by ^1H and ^{13}C NMR spectroscopic analysis.



Scheme 3. Chelation controlled vinyl Grignard reaction. Reagents and conditions: (a) vinyl magnesium bromide, $MgBr_2\cdot OEt_2$, dry THF, −78 °C, 45 min, 89%.

Allylic alcohol **7** was mesylated using MsCl in the presence of Et_3N after which nucleophilic displacement with sodium azide furnished the terminal azide **9** in only 93% yield. Also, the one-pot azide formation conducted in DMF medium under the standard conditions (DMF/CCl_4 (7:1), TPP, NaN_3, 75 °C, 12 h) resulted in no reaction (96% of **7** was recovered from the reaction medium) as shown in Scheme 4.



Scheme 4. Reagents and conditions: (a) (i) MsCl, dry CH_2Cl_2, Et_3N, 0 °C, 3 h, (ii) NaN_3, dry DMF, 65 °C, 12 h, 93%; (b) DMF/CCl_4 (7:1), PPh_3, NaN_3, 75 °C, 12 h.

Thus, allyl alcohol **7** was benzylated to give the terminal olefin **10** in 87% yield. Olefin **10** was subjected to oxidative cleavage[12] followed by reduction with $NaBH_4$ in MeOH to afford terminal alcohol **11** in 82% yield, which was protected as the MOM ether using MOMCl to furnish MOM-protected alcohol **12** in 94% yield and subsequently the benzyl moiety of **12** was deprotected with 5% Pd/C in methanol to give the secondary alcohol **13** in 96% yield. The secondary alcohol **13** was tosylated using TsCl in the presence of Et_3N and subsequently a nucleophilic displacement with sodium azide furnished the required azide **14** in 83% yield (Scheme 5).

Deprotection of the MOM groups followed by mono-tosylation furnished tosyl derivative **16**. The spectral and analytical data of **16** are in conformity with the reported data in the literature.[6b] Compound **16** was subjected to cyclization and subsequent reduction, by employing the literature procedure[6b] to furnish jaspine B **I** with all the desired stereocenters (88% yield from 16, Scheme 6).

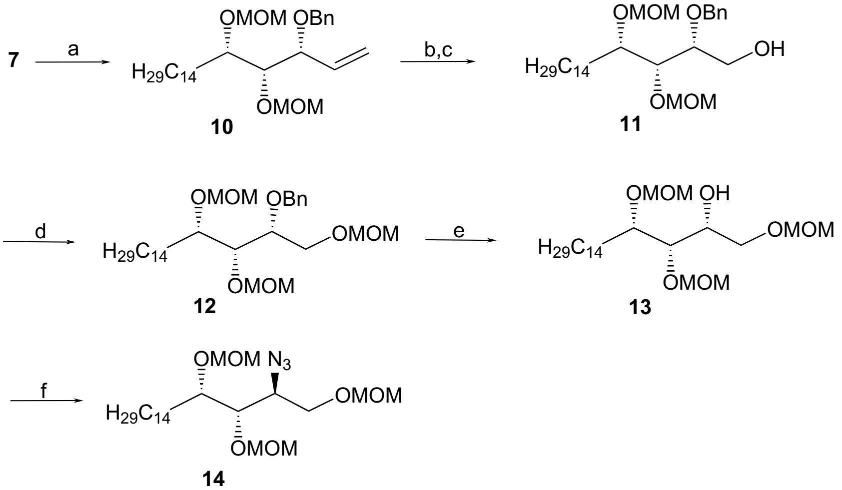
3. Conclusion

In conclusion, a novel total synthesis of jaspine B, with high enantioselectivity starting from an achiral molecule has been developed, in which two of the stereogenic centers were established by Sharpless asymmetric dihydroxylation, and the third stereogenic center was established by a chelation controlled vinyl Grignard reaction to afford jaspine B **I** with the required stereochemistry.

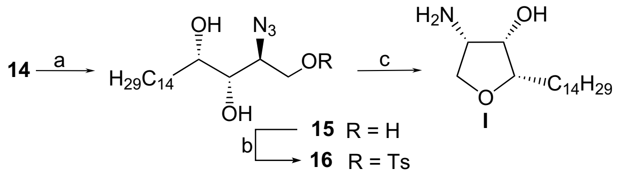
4. Experimental

4.1. General experimental

Solvents were purified and dried by standard procedures prior to use; petroleum ether with boiling range 60–80 °C was used for column chromatography. Optical rotations were measured using sodium D line on a JASCO-P-1020-



Scheme 5. Synthesis of intermediate **14**. Reagents and conditions: (a) BnBr, NaH, THF, 0 °C, 4 h, 87%; (b) (i) OsO_4 (0.1 M sol in toluene), *t*-BuOH/THF/H_2O (3:2:1), NMO, overnight, (ii) $NaIO_4$, $NaHCO_3$, water, rt, 3 h; (c) $NaBH_4$, MeOH, 0 °C to rt, 1 h, 82% from **10**; (d) MOMCl, dry DCM, DIPEA, 0 °C to rt, 6 h, 94%; (e) H_2/Pd–C, MeOH, rt, overnight, 96%; (f) (i) TsCl, dry CH_2Cl_2, Et_3N, DMAP (cat.), 0 °C to rt, 3 h, (ii) NaN_3, dry DMF, 95 °C, 14 h, 83%.



Scheme 6. Synthesis of (2*S*,3*S*,4*S*)-jaspine B **I**. Reagents and conditions: (a) aq HCl, THF, 0 °C to rt, 5 h; (b) *p*-tosyl chloride, CH_2Cl_2, DMAP, 0 °C to rt, 4 h, 80% from **14**; (c) Ref. 6b.

polarimeter under standard conditions. Infrared spectra were recorded on Perkin Elmer FTIR spectrometer. Enantiomeric excesses were measured using either chiral HPLC or by comparison with the specific rotation. Elemental analyses were carried out with a Carlo Erba CHNS–O EA 1108 Elemental analyzer. All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried glassware (110 °C), which was cooled under argon. Column chromatography was performed using silica gel (100–200 mesh size and 230–400 mesh size for flash column chromatography) and TLC was carried out using aluminum sheets precoated with silica gel 60F254 (Merck). All chemicals used were reagent grade procured commercially and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 200/400 spectrometer by using TMS as an internal standard. Infra red spectra were recorded with ATI MATT-SON RS-1 FTIR spectrometer. MS analyses were performed on a Peseiex API QSTAR Pulsar with an electrospray ionization mass spectrometer (LC–MS), using MeOH as a solvent (*m*/*z*, fragentor 70 V).

4.1.1. Synthesis of *trans*-2-heptadecenoic acid ethyl ester 2.

To an ice cold solution of 1-pentadecanol **1** (8.0 g, 35 mmol) in dry CH_2Cl_2 was charged PCC (11.32 g, 52.5 mmol) and the reaction mixture was stirred at 0 °C for 3 h. The organic solvent was evaporated in vacuo and to the residue obtained was charged 100 mL of diethyl ether, stirred at rt for 15 min and filtered through a short neutral alumina bed. The organic solvent was dried over anhyd Na_2SO_4 and concentrated in vacuo. The crude aldehyde (1-pentadecanal) obtained was used as such for the next step without further purification.

To a solution of (ethoxycarbonylmethylene)triphenylphosphorane (14.67 g, 42.23 mmol) in dry benzene (120 mL) was added a solution of the above aldehyde in dry benzene (100 mL). The reaction mixture was refluxed for 4 h. It was then concentrated and purified by silica gel column chromatography using petroleum ether/EtOAc (9.5:0.5) as eluent to afford the α,β-unsaturated olefin (9.55 g, 92%) as a colorless oily liquid; IR ($CHCl_3$): 3133, 3020, 2927, 2855, 1732, 1515, 1466, 1389, 1215, 1030, 759, 670 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.81 (t, $J = 7.0$ Hz, 3H), 1.18 (br s, 24H), 1.23 (t, $J = 7.2$ Hz, 3H), 1.33–1.42 (m, 2H), 2.06–2.17 (m, 2H), 4.06 (q, $J = 7.2$ Hz, 2H), 5.69 (td, $J = 15.1$, 1.6 Hz, 1H), 6.88–6.97 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2, 14.3, 22.7, 28.0, 29.2, 29.4, 29.5, 29.6 (several overlapping peaks), 31.9, 32.2, 60.1, 121.2, 149.6, 166.8. Anal. Calcd for $C_{19}H_{36}O_2$: C, 76.97; H, 12.24. Found: C, 76.88; H, 12.31.

4.1.2. Synthesis of (2*R*,3*S*)-2,3-dihydroxyheptadecanoic acid ethyl ester 3.

To a mixture of $K_3[Fe(CN)]_6$ (15.99 g, 48.55 mmol), K_2CO_3 (6.70 g, 48.55 mmol) and $(DHQ)_2PHAL$ (13.6 mg, 1 mol %), in *t*-BuOH–H_2O (1:1, 80 mL) cooled to 0 °C, was added OsO_4 as a 0.1 M solution in toluene (0.70 mL, 0.4 mol %) followed by methanesulfonamide (1.54 g, 16.2 mmol). After stirring for 30 min at 0 °C, the (*E*)-α,β-unsaturated ester **2** (4.80 g, 16.19 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid Na_2SO_3 (22 g). Stirring was continued for 60 min and the solution was extracted with EtOAc (3 × 25 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (3:2) to afford the diol **3** (4.71 g, 88%) as a colorless solid; mp 56–58 °C; $[\alpha]_D^{25} = -7.1$ (*c* 0.8, $CHCl_3$). IR ($CHCl_3$): 3400, 3133, 3020, 2927, 2855, 1732, 1515, 1466, 1389, 1215, 1030, 759, 670 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.81 (t, $J = 7.0$ Hz, 3H), 1.18 (br s, 24H), 1.23 (t, $J = 7.2$ Hz, 3H), 1.49–1.57 (m, 2H), 2.0 (br s, 2H), 3.78 (dt, $J = 7.1$, 2.1 Hz, 1H), 4.01 (dd, $J = 2.1$ Hz, 1H), 4.17 (q, $J = 7.2$ Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 22.6, 25.7, 29.3, 29.5 (several overlapping peaks), 29.6, 31.9, 33.7, 61.9, 72.6, 73.1, 173.7. Anal. Calcd for $C_{19}H_{38}O_4$: C, 69.05; H, 11.59. Found: C, 69.12; H, 11.50.

4.1.3. Synthesis of (2*R*,3*S*)-2,3-bis(methoxymethoxy)-heptadecanoic acid ethyl ester 4.

To a CH_2Cl_2 solution of protected diol **3** (4.50 g, 13.62 mmol) was charged into a flame dried RB flask under argon atmosphere. DIPEA (9.5 mL, 54.48 mmol) was charged slowly over 5 min at rt and then 3.20 mL of MOMCl (42.22 mmol, 3.1 equiv) was slowly added to the reaction mixture at to 0 °C over a period of 10 min. The reaction was stirred at rt for about 12 h and quenched with 20 mL of water. The organic layer was separated, dried over anhyd Na_2SO_4 and concentrated in vacuo. The residue obtained was purified by silica gel column chromatography using petroleum ether/EtOAc (20:1) to give 5.47 g of **4** as a pale yellow liquid in 96% yield. $[\alpha]_D^{25} = +43.6$ (*c* 1.0, $CHCl_3$). IR ($CHCl_3$): 2927, 2855, 1748, 1466, 1370, 1216, 1153, 1112, 1032, 759, 667 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.81 (t, $J = 7.1$ Hz, 3H), 1.18 (br s, 24H), 1.23 (t, $J = 7.2$ Hz, 3H), 1.55–1.59 (m, 2H), 3.28 (s, 3H), 3.34 (s, 3H), 3.83–3.92 (m, 1H), 4.10–4.18 (m, 3H), 4.59 (d, $J = 2.4$ Hz, 2H), 4.66 (d, $J = 3.2$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 14.2, 22.7, 25.4, 29.3, 29.5, 29.6 (several overlapped peaks), 30.9, 31.9, 55.7, 56.2, 60.9, 76.8, 78.4, 96.4, 96.5, 171.0. Anal. Calcd for $C_{23}H_{46}O_6$: C, 65.99; H, 11.08. Found: C, 65.90; H, 11.15.

4.1.4. Synthesis of (2*S*,3*S*)-2,3-bis(methoxymethoxy)heptadecan-1-ol 5.

To a solution of **4** (5.30 g, 12.66 mmol) in dry CH_2Cl_2 (75 mL) at −10 °C was added dropwise DIBAL-H (19 mL, 18.98 mmol, 1.0 M solution in toluene) through a syringe. The reaction mixture was allowed to warm to room temperature over 1 h, then re-cooled to

0 °C and treated with saturated solution of sodium/potassium tartrate. The solid material was filtered through a pad of Celite and concentrated in vacuo. Silica gel column chromatography of the crude product (residue) using petroleum ether/EtOAc (10:3) as eluent gave alcohol **5** (4.58 g, 96%) as a colorless oil. $[\alpha]_D^{25} = -10.5$ (*c* 1.0, $CHCl_3$). IR (neat, ν_{max}): 3300, 3019, 2957, 2928, 2856, 1463, 1378, 1261, 1216, 1099, 1026, 838, 759, 669 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.81 (t, $J = 7.1$ Hz, 3H), 1.18 (br s, 24H), 1.55–1.59 (m, 2H), 1.88 (br s, 1H), 3.34 (s, 3H), 3.37 (s, 3H), 3.59–3.67 (m, 4H), 4.61–4.72 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 22.7, 25.8, 29.3, 29.5, 29.6 (several overlapping peaks), 30.4, 31.9, 55.8, 55.9, 62.7, 78.4, 82.4, 96.8, 97.7. Anal. Calcd for $C_{21}H_{44}O_5$: C, 66.98; H, 11.78. Found: C, 66.89; H, 11.87.

4.1.5. Synthesis of (3*R*,4*S*,5*S*)-4,5-bis(methoxymethoxy)-nonadec-1-en-3-ol 7. A mixture of 4.10 g of alcohol **5** (10.89 mmol) and 4.57 g of IBX (16.34 mmol) in 40 mL of EtOAc was refluxed for about 3 h. The reaction mixture was filtered off and washed with excess of EtOAc. The solvent was evaporated from the filtrate in vacuo to afford the crude aldehyde **6** which was then, directly taken to the next step without any further purification.

The crude aldehyde **6** dissolved in CH_2Cl_2 under argon was added via cannula to a stirred suspension of $MgBr_2 \cdot Et_2O$ at 0 °C. After stirring for 10 min, the flask was cooled to −78 °C and vinyl magnesium bromide (11 mL, 10.89 mmol; purchased from Aldrich as 1.0 M solution in THF) was added slowly at −78 °C and the reaction was stirred further at this temperature for 45 min. The solvent was then removed in vacuo, after which the residue was diluted with CH_2Cl_2 and allowed to warm to 0 °C. Then, the reaction mixture was diluted with saturated aq NH_4Cl and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (10:1) as eluent gave *syn*-isomer of the allylic alcohol **7** as a pale yellow viscous oil (3.90 g, 89%). $[\alpha]_D^{25} = +1.85$ (*c* 0.56, $CHCl_3$). IR (neat): ν_{max} 3450, 3019, 2927, 2855, 1466, 1378, 1216, 1030, 761, 669 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.81 (t, $J = 7.1$ Hz, 3H), 1.18 (br s, 24H), 1.55–1.59 (m, 2H), 1.8 (br s, 1H), 3.06 (dd, $J = 4.4$ Hz, 1H), 3.33 (s, 3H), 3.37 (s, 3H), 3.58–3.66 (m, 1H), 4.21–4.28 (m, 1H), 4.61–4.76 (m, 4H), 5.13 (td, $J = 1.6$, 10.3 Hz, 1H), 5.30 (td, $J = 1.53$, 11 Hz, 1H), 5.81–5.97 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 22.7, 25.7, 29.3, 29.5 (several overlapping peaks), 29.6, 30.9, 31.9, 55.9, 56.3, 71.8, 78.4, 83.7, 96.7, 98.5, 116.3, 137.7. LC–MS (ESI-TOF) *m*/*z*: 425.04 (M+Na).

4.1.6. Synthesis of *trans*-(4*S*,5*S*)-1-azido-4,5-bis-(methoxymethoxy)-2-nonadecene 9. To the CH_2Cl_2 solution of **7** (250 mg, 0.621 mmol) under argon, Et_3N (0.18 mL, 1.24 mmol) was added slowly at rt. The reaction flask was cooled to 0 °C and mesyl chloride (0.06 mL, 0.714 mmol) was added. The reaction mixture was stirred at 10 °C for about 2 h and quenched with 2 mL of water. The organic solvent was separated, dried over anhyd Na_2SO_4, concentrated in vacuo and the residue obtained was dissolved in 2 mL of DMF. To this, NaN_3 (0.049 g, 0.745 mmol) was added and the reaction mixture was heated to 65 °C under an argon atmosphere for about 12 h. Then, the reaction mixture was concentrated to half of its volume in vacuo, the residue obtained was dissolved in 10 mL of EtOAc and washed with brine solution. The organic solvent was separated, dried over Na_2SO_4 and concentrated in vacuo. The crude product was then purified by silica gel column chromatography using petroleum ether/EtOAc (9.5:0.5) to afford 0.247 g of azide **9** as a pale yellow oily compound (93%). $[\alpha]_D^{25} = +8.25$ (*c* 0.15, $CHCl_3$). IR (neat): ν_{max} 2959, 2927, 2855, 2103, 1262, 1216, 1150, 1098, 1027, 760, 669 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.81 (t, $J = 7.1$ Hz, 3H), 1.18 (br s, 24H), 1.45–1.57 (m, 2H), 3.30 (s, 3H), 3.33 (s, 3H), 3.47–3.55 (m, 1H), 3.73 (d, $J = 4.6$ Hz, 2H), 4.08 (t, $J = 5.1$ Hz, 1H), 4.51 (d, $J = 6.8$ Hz, 1H), 4.60–4.70 (m, 3H), 5.69–5.74 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.7, 25.5, 29.4, 29.6 (several overlapping peaks), 29.7, 30.7, 31.4, 31.9, 36.5, 52.3, 55.7, 55.8, 79.8, 94.3, 96.9, 127.0, 132.2, 162.5.

4.1.7. Synthesis of 1-(((3*R*,4*R*,5*S*)-4,5-bis(methoxymethoxy)-nona-dec-1-en-3-yloxy)methyl)benzene 10. To the DMF solution of the allyl alcohol **7** (3.80 g, 9.44 mmol) under argon, 0.680 g of NaH (50% assay, 14.16 mmol) was added slowly at 0 °C. The reaction mixture was then stirred at room temperature for 30 min, after which it was again cooled to 0 °C. To this was added slowly the DMF solution of BnBr (1.3 mL of BnBr in 5 mL of DMF, 10.86 mmol), tetra *n*-butylammonium iodide (0.348 g, 0.94 mmol) and the stirring was further continued for 4 h at the same temperature. The reaction mixture was quenched with the addition of cold water at 0 °C and was concentrated to half of its volume in vacuo. To this was charged diethyl ether and the mixture was stirred well for 10 min. The organic layer was separated, dried over Na_2SO_4 and concentrated in vacuo. The crude product was then purified by silica gel column chromatography using petroleum ether/EtOAc (20:1) to afford 4.05 g of terminal olefin **10** in 87% of yield. $[\alpha]_D^{25} = -2.10$ (*c* 0.80, $CHCl_3$). IR ($CHCl_3$): 3019, 2927, 2854, 1466, 1215, 1150, 1099, 1027, 927, 757, 669 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.81 (t, $J = 7.1$ Hz, 3H), 1.18 (br s, 24H), 1.45–1.57 (m, 2H), 3.23 (s, 3H), 3.34 (s, 3H), 3.49 (m, 2H), 3.92–4.00 (m, 1H), 4.27 (d, $J = 10.5$ Hz, 1H), 4.42–4.53 (m, 1H), 4.57 (d, $J = 2.1$ Hz, 1H), 4.60 (s, 2H), 4.67 (d, $J = 6.9$ Hz, 1H), 4.84 (d, $J = 10.5$ Hz, 1H), 5.26 (d, $J = 3.8$ Hz, 1H), 5.70–5.88 (m, 1H), 7.24 (br s, 5H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 22.7, 25.3, 29.3, 29.6 (several overlapping peaks), 29.7, 31.1, 31.9, 55.8, 56.2, 70.6, 78.4, 80.5, 81.0, 96.9, 98.4, 118.8, 127.5, 127.7, 127.9, 128.3, 135.4, 138.2. Anal. Calcd for $C_{30}H_{52}O_5$: C, 73.13; H, 10.64. Found: C, 73.22; H, 10.73.

4.1.8. Synthesis of (2*R*,3*R*,4*S*)-2-(benzyloxy)-3,4-bis-(methoxymethoxy)-octadecan-1-ol 11. The oxidative cleavage of the terminal olefin **10** (3.50 g, 7.08 mmol) was performed using standard conditions[12] to afford the crude aldehyde (3.01 g) as a pale yellow liquid. IR ($CHCl_3$): 2925, 2854, 1732, 1455, 1377, 1212, 1151, 1102, 1029, 918, 734, 698 cm^{-1}. The crude aldehyde obtained was used as such in the next step without further purification.

To the methanolic solution of the above crude aldehyde, $NaBH_4$ (250 mg, 7.08 mmol) was added at 0 °C. The reaction mixture was further stirred at rt for 1 h and was concentrated to half of its volume in vacuo. Then, the reaction mixture was quenched with brine solution and the product was extracted with diethyl ether (3 × 25 mL). The combined organic phases were dried over Na_2SO_4 and concentrated to give the crude alcohol, which was then purified by silica gel column chromatography using petroleum ether/EtOAc (7:1) to afford 2.89 g of pure alcohol **11** as a pale yellow oily liquid (82% yield for two steps). $[\alpha]_{D}^{25} = -15.5$ (*c* 2.0, $CHCl_3$). IR ($CHCl_3$): 3459, 3018, 2926, 2854, 1466, 1455, 1215, 1150, 1101, 1027, 919, 758, 668 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.81 (t, $J = 7.1$ Hz, 3H), 1.18 (br s, 24H), 1.51–1.60 (m, 2H), 3.30 (s, 3H), 3.36 (s, 3H), 3.59–3.77 (m, 5H), 4.51–4.73 (m, 6H), 7.26 (br s, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.7, 25.2, 29.3, 29.5, 29.6 (several overlapping peaks) 29.7, 30.7, 31.9, 55.9, 56.2, 60.8, 72.9, 78.4, 79.1, 79.3, 96.9, 98.8, 128.0, 128.4, 138.0. LC–MS (ESI-TOF) *m*/*z*: 518.86 (M+Na).

4.1.9. Synthesis of 1-(((2*R*,3 *R*,4*S*)-1,3,4-tris(methoxymethoxy)-octadecan-2-yloxy)methyl)benzene 12. To the CH_2Cl_2 solution containing **11** (1 g, 2.0 mmol) under an argon atmosphere, DIPEA (0.70 mL, 4.0 mmol) was charged at rt and then MOMCl (1.8 mL, 2.2 mmol) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at rt for about 6 h and quenched with 0.5 mL of cold water. The organic layer was separated, dried over anhyd Na_2SO_4 and concentrated in vacuo. The residue obtained was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) to give 1.02 g of **12** as a colorless oily liquid in 94% yield. $[\alpha]_{D}^{25} = +5$ (*c* 0.5, $CHCl_3$). IR ($CHCl_3$): 2925, 2854, 1466, 1261, 1213, 1151, 1106, 1034, 919, 801, 698, 734 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.81 (t, $J = 6.9$ Hz, 3H), 1.10–1.26 (m, 24H), 1.45–1.48 (m, 2H), 3.30 (s, 6H), 3.34 (s, 3H), 3.60–3.76 (m, 5H), 4.52–4.84 (m, 8H), 7.16–7.33 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.7, 25.5, 29.3, 29.6 (several overlapping peaks), 29.8, 30.9, 31.9, 55.3, 55.9, 56.2, 67.6, 73.1, 77.9, 78.6, 96.6, 96.8, 98.5, 127.6, 128.0, 128.3, 138.4. LC–MS (ESI-TOF) *m*/*z*: 562.83 (M+Na).

4.1.10. Synthesis of (2*R*,3*S*,4*S*)-1,3,4-tris(methoxymethoxy)-octa-2-decanol 13. To a solution of **12** (0.760 g, 1.41 mmol) in MeOH (10 mL) were added a catalytic amount of 5% Pd/C and the reaction mixture was stirred at room temperature under a hydrogen atmosphere (1 atm balloon pressure) for 12 h. The reaction mixture was then filtered through a pad of Celite and the solvent was removed under reduced pressure to give the crude product, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (8:2) as eluent to give **13** (0.608 g, 96%) as a pale yellow oil. $[\alpha]_{D}^{25} = -2.3$ (*c* 1.6, $CHCl_3$). IR ($CHCl_3$): 3400, 3019, 2926, 1519, 1031, 909, 758, 669, 625 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.82 (t, $J = 6.9$ Hz, 3H), 1.19 (br s, 24H), 1.54–1.59 (m, 2H), 2.10 (br s, 1H), 3.32 (br s, 6H), 3.37 (s, 3H), 3.56–3.60 (m, 2H), 3.64–3.69 (m, 2H), 3.88–3.93 (m, 1H), 4.61 (d, $J = 5.2$ Hz, 2H), 4.64–4.75 (m, 3H), 4.82 (d, $J = 6.5$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.7, 25.7, 29.3, 29.6 (several overlapping peaks), 29.7, 30.6, 31.9, 55.4, 55.9, 56.2, 69.7, 70.0, 78.3, 80.1, 96.6, 97.0, 98.4. LC–MS (ESI-TOF) *m*/*z*: 473.21 (M+Na).

4.1.11. Synthesis of (2*S*,3*S*,4*S*)-2-azido-1,3,4-tris-(methoxymethoxy)-octadecane 14. To a solution of **13** (0.550 g, 1.22 mmol) in dry CH_2Cl_2 (4 mL) at 0 °C were added Et_3N (0.2 mL, 1.47 mmol), *p*-tosyl chloride (254 mg, 1.33 mmol), and DMAP (3 mg, 2 mol %). The reaction mixture was stirred at room temperature for 3 h and then poured into DCM/H_2O mixture. The organic phase was separated and the aqueous phase extracted with DCM (3 × 10 mL). The combined organic phase was washed with water, brine, dried over Na_2SO_4, and concentrated to a white solid, which was dissolved in dry DMF (3 mL). To this, NaN_3 (0.099 g, 1.52 mmol) was added and the reaction mixture was heated to 95 °C under an argon atmosphere for about 14 h, and then cooled to room temperature. The reaction mixture was concentrated to half of its volume in vacuo. The residue obtained was dissolved in 8 mL of EtOAc and washed with brine solution. The organic solvent was separated, dried over Na_2SO_4 and concentrated in vacuo to furnish crude azide **14**, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (9:1) as eluent to give **14** as a yellow oil (0.482 g, 83%). $[\alpha]_{D}^{25} = +7$ (*c* 0.5, $CHCl_3$); IR ($CHCl_3$): 2927, 2103, 1519, 1030, 910, 756, 669, 625 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.81 (t, $J = 7.2$ Hz, 3H), 1.19 (br s, 24H), 1.52–1.61 (m, 2H), 3.32 (s, 6H), 3.37 (s, 3H), 3.60–3.92 (m, 5H), 4.60–4.75 (m, 6H). ^{13}C NMR (200 MHz, $CDCl_3$): δ 14.1, 22.7, 25.7, 29.3, 29.6 (several overlapping peaks), 29.7, 30.6, 31.9, 55.4, 55.9, 56.2, 67.1, 69.7, 78.3, 80.1, 96.6, 97.0, 98.4. Anal. Calcd for $C_{24}H_{49}N_3O_6$: C, 60.60; H, 10.38; N, 8.83. Found: C, 60.52; H, 10.44; N, 8.90.

4.1.12. Synthesis of (2*S*,3*S*,4*S*)-2-azido-3,4-bis-(dihydroxy)-octadecyl-4-methylbenzenesulfonate 16. To a solution of **14** (0.470 g, 0.99 mmol) in THF (4 mL) was added 10% aq HCl (4 mL) at 10 °C and stirred at room temperature for 5 h. The reaction mixture was quenched by the addition of saturated solution of $NaHCO_3$ and extracted with ethyl acetate (3 × 10 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated in vacuo to afford the crude azidotriol **15** as a residue. The residue obtained was used as such without further purification in the next step.

To a solution of the above crude azidotriol **15** in CH_2Cl_2 (5 mL) was added Et_3N (0.3 mL) and *p*-toluenesulphonyl chloride (0.188 g, 0.99 mmol) at 0 °C and stirred at room temperature for 4 h. The reaction mixture was quenched by the addition of water (5 mL), extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated to give the product, which was then purified by silica gel column chromatography using EtOAc/petroleum ether (3.5:6.5) to afford 0.393 g of pure tosylated derivative **16** as a white solid (80% yield for two steps). Mp 64–65 °C; $[\alpha]_{D}^{25} = +14$ (*c* 0.45, $CHCl_3$) {lit.[6b] $[\alpha]_{D}^{25} = +15$ (*c* 0.4, $CHCl_3$)}; The spectral and analytical data were in good agreement with that of reported in the literature.[6b] Anal. Calcd for $C_{25}H_{43}N_3O_5S$: C, 60.33;

H, 8.71; N, 8.44; S, 6.44. Found: C, 60.39; H, 8.78; N, 8.38; S, 6.37.

4.1.13. Synthesis of pachastrissamine (jaspine B) I. The spectral and analytical data of **I** are in good conformity with the reported values.[5e] $[\alpha]_D^{25} = +17.7$ (*c* 0.40, EtOH) [lit.[1] +18 (*c* 0.1, EtOH)]; amorphous solid; IR ($CHCl_3$): 3350, 2926, 1469, 1030, 726 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 0.87 (t, $J = 7.2$ Hz, 3H), 1.25–1.39 (m, 24H), 1.57–1.66 (m, 2H), 2.10 (br s, 3H), 3.49–3.53 (m, 1H), 3.63–3.67 (m, 1H), 3.69–3.75 (m, 1H), 3.84–3.88 (m, 1H), 3.89–3.94 (m, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 14.1, 22.7, 25.7, 29.3, 29.6 (several overlapping peaks), 29.7, 30.6, 31.9, 54.4, 71.8, 72.3, 83.2. Anal. Calcd for $C_{18}H_{37}NO_2$: C, 72.19; H, 12.45; N, 4.68. Found: C, 72.26; H, 12.51; N, 4.62.

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