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Stereoselective Divergent Synthesis of Four Diastereomers of Pachastrissamine (Jaspine B)

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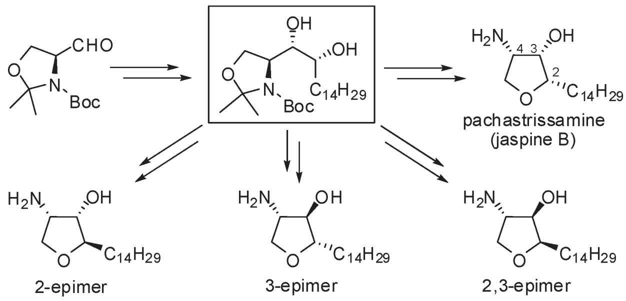

A divergent short synthesis of four diastereomers of pachastrissamine was achieved. Natural pachastrissamine was synthesized through bis-tosylation of the common intermediate and cyclization. 2-*epi*-Pachastrissamine was obtained by monotosylation and spontaneous cyclization of D-*ribo*-phytosphingosine derivative. By use of regio- and stereospecific ring-opening reaction of the orthoester assisted by a Boc group as a key step, 3-*epi*- and 2,3-*epi*-pachastrissamines were synthesized. The three stereogenic centers of all the diastereomers were constructed by using Garner's aldehyde as the sole chiral source.

In 2002, pachastrissamine (**1**) (Figure 1), the first naturally occurring anhydrophytosphingosine derivative, was isolated from the Okinawan marine sponge *Pachastrissa* sp.[1a] Shortly thereafter, a French research group isolated the same compound from the Vanuatuan marine sponge *Jaspis* sp. and named the compound jaspine B.[1b] Pachastrissamine exhibits marked submicromolar cytotoxicity against several cancer cell lines.[1] Due to its impressive biological activity, and simple and unique structure, several total syntheses of pachastrissamine (**1**) have been reported,[1d,2,3] including our synthesis based on bis-cyclization of bromoallene,[2s] whereas less attention was given to its epimers **2**−**4**. Actually, 2-*epi*- (**2**), 3-*epi*- (**3**), and 2,3-*epi*-pachastrissamine (**4**) have been synthesized by Delgado[1d] and, limited to **2**, by Overleeft et al.[2c,k,m,r]

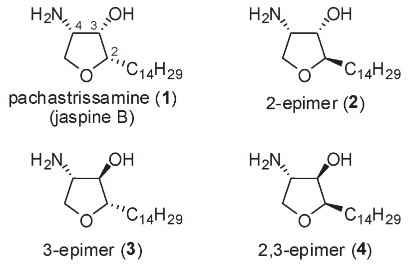

FIGURE 1. Pachastrissamine and its diastereomers.

There is significant interest concerning the molecular mechanisms of cell death induced by pachastrissamine. Abadie et al. indicated that pachastrissamine inhibits sphingomyelin synthase and thus increases the intracellular ceramide level, inducing apoptotic cell death by a caspase-dependent pathway.[1c] Delgado and co-workers reported that the potency of cytotoxicity is dependent on the stereochemistry of the tetrahydrofuran moiety.[1d] In view of elucidating the effect of the stereochemistry on the biological activity as well as the structure−activity relationship of pachastrissamine including its stereochemistry, a useful synthetic route with a high stereoselectivity and divergency is required. This synthetic route should also aid in the production of pachastrissamine derivatives with potentially more potent anticancer activities. Herein, we report a stereoselective and divergent short synthesis of four pachastrissamine diastereomers from a single intermediate.

(1) (a) Kuroda, I.; Musman, M.; Ohtani, I.; Ichiba, T.; Tanaka, J.; Garcia-Gravalos, D.; Higa, T. *J. Nat. Prod.* **2002**, *65*, 1505–1506. (b) Ledroit, V.; Debitus, C.; Lavaud, C.; Massoit, G. *Tetrahedron Lett.* **2003**, *44*, 225–228. (c) Salma, Y.; Lafont, E.; Therville, N.; Carpentier, S.; Bonnafé, M. J.; Levade, T.; Génisson, Y.; Abadie, N. A. *Biochem. Pharmacol.* **2009**, *78*, 477–485. (d) Canals, D.; Mormeneo, D.; Fabriàs, G.; Llebaria, A.; Casas, J.; Delgado, A. *Bioorg. Med. Chem.* **2009**, *17*, 235–241.

(2) For previous syntheses, see: (a) Sudhakar, N.; Kumar, A. R.; Prabhakar, A.; Jagadeesh, B.; Rao, B. V. *Tetrahedron Lett.* **2005**, *46*, 325–327. (b) Bhaket, P.; Morris, K.; Stauffer, C. S.; Datta, A. *Org. Lett.* **2005**, *7*, 875–876. (c) van den Berg, R.; Boltje, T.; Verhagen, C.; Litjens, R.; Vander Marel, G.; Overkleeft, H. *J. Org. Chem.* **2006**, *71*, 836–839. (d) Du, Y.; Liu, J.; Linhardt, R. J. *J. Org. Chem.* **2006**, *71*, 1251–1253. (e) Liu, J.; Du, Y.; Dong, X.; Meng, S.; Xiao, J.; Cheng, L. *Carbohydr. Res.* **2006**, *341*, 2653–2657. (f) Ribes, C.; Falomir, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2006**, *62*, 5421–5425. (g) Lee, T.; Lee, S.; Kwak, Y. S.; Kim, D.; Kim, S. *Org. Lett.* **2007**, *9*, 429–432. (h) Reddy, L. V. R.; Reddy, P. V.; Shaw, A. K. *Tetrahedron: Asymmetry* **2007**, *18*, 542–546. (i) Ramana, C. V.; Giri, A. G.; Suryawanshi, S. B.; Gonnade, R. G. *Tetrahedron Lett.* **2007**, *48*, 265–268. (j) Prasad, K. R.; Chandrakumar, A. *J. Org. Chem.* **2007**, *72*, 6312–6315. (k) Abraham, E.; Candela-Lena, J. I.; Davies, S. G.; Georgiou, M.; Nicholson, R. L.; Roberts, P. M.; Russell, A. J.; Snchez-Fernndez, E. M.; Smith, A. D.; Thomson, J. E. *Tetrahedron: Asymmetry* **2007**, *18*, 2510–2513. (l) Yakura, T.; Sato, S.; Yoshimoto, Y. *Chem. Pharm. Bull.* **2007**, *55*, 1284–1286. (m) Abraham, E.; Brock, E. A.; Candela-Lena, J. I.; Davies, S. G.; Georgiou, M.; Nicholson, R. L.; Perkins, J. H.; Roberts, P. M.; Russell, A. J.; Snchez-Fernndez, E. M.; Scott, P. M.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 1665–1673. (n) Passiniemi, M.; Koskinen, A. M. P. *Tetrahedron Lett.* **2008**, *49*, 980–983. (o) Venkatesan, K.; Srinivasan, K. V. *Tetrahedron: Asymmetry* **2008**, *19*, 209–215. (p) Enders, D.; Terteryan, V.; Palecek, J. *Synthesis* **2008**, 2278–2282. (q) Ichikawa, Y.; Matsunaga, K.; Masuda, T.; Kotsuki, H.; Nakano, K. *Tetrahedron* **2008**, *64*, 11313–11318. (r) Reddipalli, G.; Venkataiah, M.; Mishra, M. K.; Fadnavis, N. W. *Tetrahedron: Asymmetry* **2009**, *20*, 1802–1805. (s) Inuki, S.; Yoshimitsu, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2009**, *11*, 4478–4481. (t) Jayachitra, G.; Sudhakar, N.; Ravi Kumar Anchoori, B.; Venkateswara, R.; Sayantani, R.; Rajkumar, B. *Synthesis* **2010**, 115–119.

(3) For a review, see: Abraham, E.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *Tetrahedron: Asymmetry* **2008**, *19*, 1027–1047.

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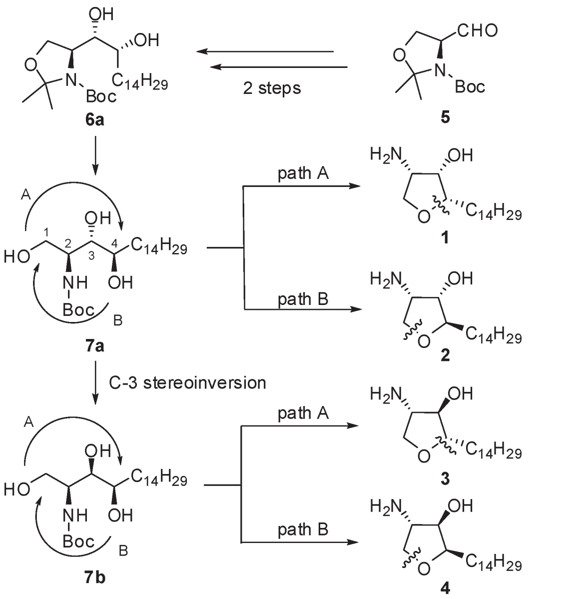
SCHEME 1. Strategy for Stereoselective Divergent Synthesis of Four Pachastrissamine Diastereomers

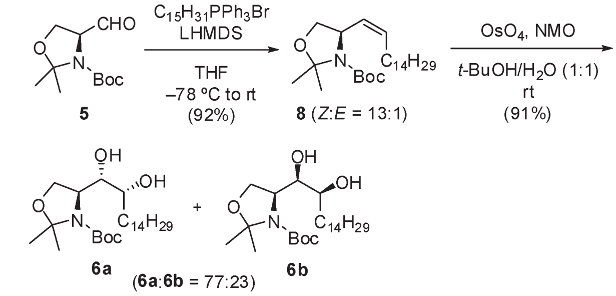


Our synthetic plan is depicted in Scheme 1. We envisaged diol **6a**,[4] which can be easily prepared from Garner's aldehyde **5**[5] in two steps, as a common intermediate for the synthesis of all the diastereomers.[6] Thus, the removal of the acetonide of **6a** would furnish the D-*ribo*-phytosphingosine derivative **7a**, which could be converted into **7b** by stereoinversion at C-3. We expected that these amino triol derivatives **7a** and **7b** would be good precursors of **1**–**4**: conversion of the C-4 hydroxy group in **7a** or **7b** into a leaving group would lead to nucleophilic attack by the C-1 hydroxy group to give **1** or **3** (Scheme 1, path A). Conversely, nucleophilic cyclization by use of the C-1 hydroxy group as the leaving group would give **2** or **4** (Scheme 1, path B). The key to the success of this strategy would be the efficient stereoinversion of **7a** at C-3 and the regioselective activation/cyclization at C-4 (path A).

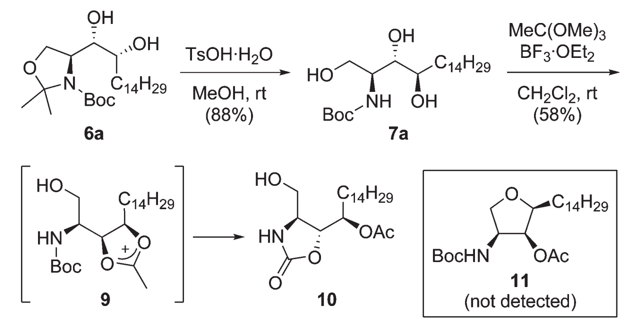
Preparation of the requisite diol **6a** was already described by Ogino and co-workers.[4] We synthesized **6a** by use of a slightly modified protocol for improvement of the yields in each step (Scheme 2). Garner's aldehyde was converted into the (*Z*)-olefin **8** in 92% yield with 13:1 selectivity by treatment with a phosphonium ylide derived from $C_{15}H_{31}PPh_3Br$.[4] In good accordance with Ogino's observation, dihydroxylation of **8** with OsO_4 in the presence of *N*-methylmorphorine *N*-oxide gave a diastereomeric mixture of the diol **6a** and **6b**, which can be separated by column chromatography.

With the common intermediate **6a** in hand, we first examined synthesis of natural pachastrissamine (**1**) (Scheme 3). The acetonide group was removed by using a catalytic amount of $TsOH \cdot H_2O$ in MeOH to give the triol **7a**. We then tried to construct the desired tetrahydrofuran core by orthoester-mediated tetrahydrofuran formation, a related reaction of the

SCHEME 2. Preparation of the Common Intermediate 6a



SCHEME 3. Unsuccessful Tetrahydrofuran Formation via Orthoester



2-azide-1,3,4-triol derivative reported by Overkleeft et al.[2c,7] Unfortunately, when **7a** was treated under the same reaction conditions as reported, we obtained oxazolidinone **10** in 58% yield,[8] formed by participation of a carbamate in the intramolecular nucleophilic reaction instead of the C-1 hydroxy group. However, this reaction clearly shows a potential strategy for regioselective inversion at the C-3 position (vide infra).

We next examined regioselective protection of the C-3 hydroxy group of **6a**. We expected that the formation of the oxazolidinone of type **13** would be useful for this purpose (Scheme 4). However, the reaction of **6a** with *t*-BuOK in THF selectively promoted oxazinanone formation leading to **12**. Other basic conditions were also ineffective.[9,10]

We decided to utilize bis-tosylate **14** as a cyclization precursor (Scheme 5). The diol **6a** was converted into the corresponding bis-tosylate **14** with TsCl, Et_3N, and $Me_3N \cdot HCl$.[11] Treatment of **14** with $TsOH \cdot H_2O$ in MeOH at 70 °C successfully produced the desired tetrahydrofuran **15** in

(4) Azuma, H.; Tamagaki, S.; Ogino, K. *J. Org. Chem.* **2000**, *65*, 3538–3541. They synthesized (*Z*)-**8** in 66% yield ($C_{15}H_{31}PPh_3Br$, LHMDS, −78 °C) and **6a** and **6b** in 55% and 19% respective yield (cat. OsO_4, NMO, *t*-BuOH/H_2O).

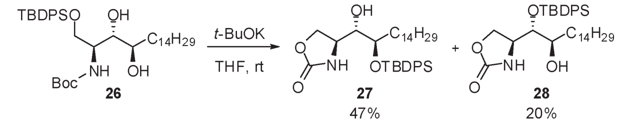
(5) (a) Garner, P. *Tetrahedron Lett.* **1984**, *25*, 5855–5858. (b) Campbell, A. D.; Raynham, T. M.; Taylor, R. J. K. *Synthesis* **1998**, 1707–1709.

(6) For the synthesis of pachastrissamine derivatives from Garner's aldehyde, see refs 2a 2n, and 2s.

(7) For the pioneering work on the Lewis acid-mediated THF ring formation of triol derivatives via orthoester formation, see: Zheng, T.; Narayan, R. S.; Schomaker, J. M.; Borhan, B. *J. Am. Chem. Soc.* **2005**, *127*, 6946–6947.

(8) Formation of unidentified byproduct was observed. Protection of the primary hydroxy group as silyl ether (**18**, Scheme 7) suppressed formation of the side products to give **20** in excellent yield.

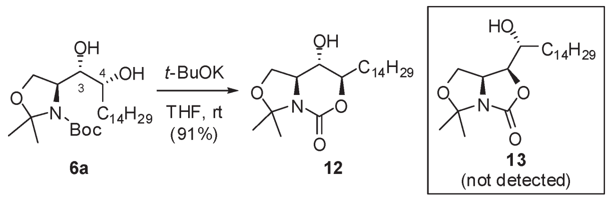
(9) The reaction of the corresponding silyl ether **26** with *t*-BuOK gave the silyl migration products **27** and **28** (see the Supporting Information).



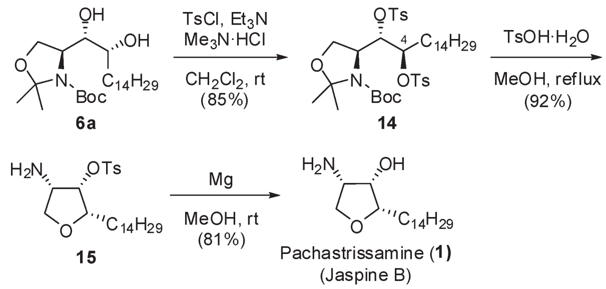
(10) A related oxazinanone formation was reported; see: Komatsu, Y.; Ikishima, H.; Okuyama, A.; Nakamura, M.; Kotsuki, H. *Synth. Org. Chem. Jpn.* **2009**, *67*, 65–75.

(11) Tanabe, Y.; Yamamoto, H.; Yoshida, Y.; Miyawaki, T.; Utsumi, N. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 297–300.

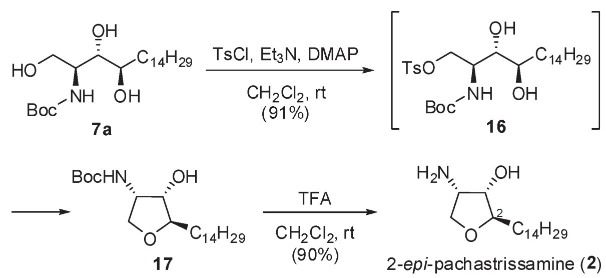
SCHEME 4. Unsuccessful Protection of 3-OH by Oxazolidinone Formation



SCHEME 5. Synthesis of Pachastrissamine (1)



SCHEME 6. Synthesis of 2-*epi*-Pachastrissamine (2)



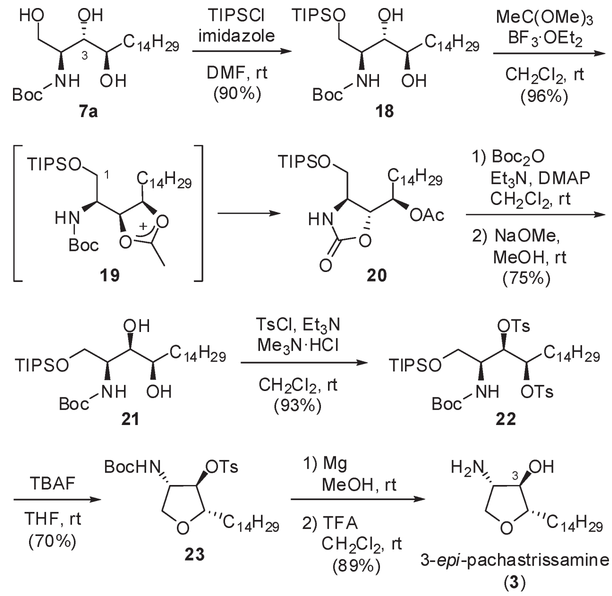
92% yield. This reaction proceeds through initial removal of acetonide and Boc groups followed by intramolecular nucleophilic displacement at the C-4 position.[12] Pachastrissamine (**1**) was obtained by the cleavage of the tosyl group with Mg in MeOH.

2-*epi*-Pachastrissamine (**2**) was then prepared in analogy with the reported procedure (Scheme 6).[1d,2c] Regioselective tosylation of the primary hydroxy group of the D-*ribo*-phytosphingosine derivative **7a** prompted spontaneous cyclization to give the tetrahydrofuran derivative **17**. Removal of the Boc group with TFA provided the desired product, 2-*epi*-pachastrissamine (**2**).

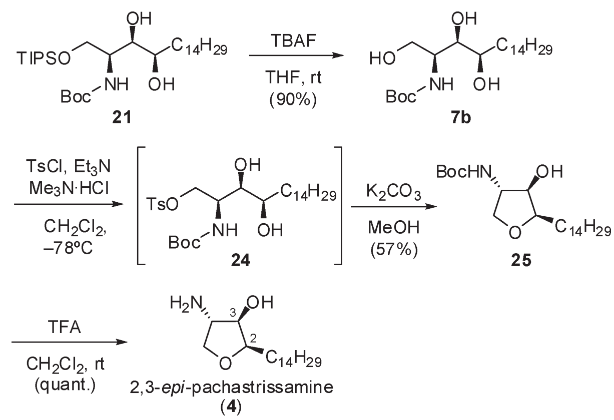
Next, the synthesis of 3-*epi*-pachastrissamine (**3**) was attempted, which requires regioselective inversion of the C-3 stereogenic center. We envisioned that this challenging issue can be addressed by foregoing the regio- and stereospecific ring-opening reaction of the orthoester assisted by the neighboring Boc-amide group, followed by loss of isobutene and decarbonylation under basic conditions (Scheme 3). The primary hydroxy group of **7a** was protected by using TIPSCl in the presence of imidazole to give the silyl ether **18** (Scheme 7). Reaction of **18** with $MeC(OMe)_3$ in the presence of a catalytic amount of $BF_3 \cdot OEt_2$ in CH_2Cl_2 directly afforded the desired oxazolidinone **20** in excellent yield, through orthoester formation

(12) For a related THF formation under acidic conditions, see: Armin, B.; Jens, H.; Jacques, W.; Henri, B. K. *J. Org. Chem.* **1993**, *58*, 6814–6817.

SCHEME 7. Synthesis of 3-*epi*-Pachastrissamine (3)



SCHEME 8. Synthesis of 2,3-*epi*-Pachastrissamine (4)



followed by regioselective nucleophilic attack of the Boc oxygen toward C-3. Protection of the carbamate nitrogen of **20** with Boc_2O and alcoholysis of the oxazolidinone successfully provided **21**, the C-3 epimer of **18**. Similar to the synthesis of **1** (Scheme 3), bis-tosylation, desilylation, and tetrahydrofuran formation promoted by TBAF afforded the desired tetrahydrofuran **23**. Finally, successive removal of the tosyl and Boc groups led to 3-*epi*-pachastrissamine (**3**).[1d]

The final stage was set for the synthesis of 2,3-*epi*-pachastrissamine **4** (Scheme 8).[1d] The silyl ether of **21** was cleaved with TBAF in THF to give the cyclization precursor **7b**. Selective monotosylation of the primary hydroxy group followed by base treatment afforded tetrahydrofuran **25**. Finally, the Boc group was removed with TFA in CH_2Cl_2 to give 2,3-*epi*-pachastrissamine (**4**). The spectroscopic data and optical rotation of all diastereomers **1**−**4** were in good agreement with those reported previously.[1−3]

In conclusion, we have developed a stereoselective divergent synthesis of four pachastrissamine diastereomers using Garner's aldehyde as the sole chiral pool. Further research including biological assays and structure−activity relationships are currently underway and will be reported elsewhere.

Experimental Section

***tert*-Butyl (*S*)-4-[(1*S*,2*R*)-1,2-Bis(tosyloxy)hexadecyl]-2,2-dimethyloxazolidine-3-carboxylate (14).** To a stirred solution of **6a** (293 mg, 0.640 mmol) in CH_2Cl_2 (1.3 mL) were added Et_3N (887 μL, 6.40 mmol), TsCl (610 mg, 3.20 mmol), and $Me_3N\cdot HCl$ (61 mg, 0.638 mmol) at room temperature. After stirring for 2 d at this temperature, the whole was extracted with CH_2Cl_2. The extract was washed with saturated NH_4Cl and brine, then dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (10:1) to give **14** as a colorless oil (417 mg, 85% yield): $[\alpha]^{25}_D$ −21.7 (*c* 0.84, $CHCl_3$); IR (neat) 1689 (C=O), 1365 (OSO_2), 1176 (OSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.08−1.33 (m, 26H), 1.44 (s, 6H), 1.49 (s, 9H), 2.41 (s, 3H), 2.43 (s, 3H), 3.84 (dd, *J* = 9.2, 6.9 Hz, 1H), 3.93 (dd, *J* = 9.2, 2.9 Hz, 1H), 4.05 (m, 1H), 4.68 (m, 1H), 5.21 (m, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 21.5 (2C), 22.6, 25.1 (2C), 28.4 (3C), 28.9, 29.2, 29.3, 29.4, 29.6 (4C), 29.7 (3C), 31.9, 56.5, 63.5, 80.1, 80.8, 82.8, 94.0, 127.9 (4C), 128.2 (4C), 129.7 (2C), 134.1 (2C), 144.7; HRMS (FAB) calcd for $C_{40}H_{63}NNaO_9S_2$ (MNa^+) 788.3842, found 788.3835.

(2*S*,3*S*,4*S*)-4-Amino-2-tetradecyltetrahydrofuran-3-yl 4-Methylbenzenesulfonate (15). To a stirred solution of **14** (92 mg, 0.120 mmol) in MeOH (4.0 mL) was added $TsOH\cdot H_2O$ (23 mg, 0.121 mmol) at 70 °C. After stirring for 8 h at this temperature, the mixture was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with $CHCl_3$−MeOH−28% NH_4OH (95:4:1) to give **15** as a white solid (50 mg, 92% yield): mp 65−66 °C; $[\alpha]^{25}_D$ +18.2 (*c* 1.85, $CHCl_3$); IR (neat) 1362 (OSO_2), 1175 (OSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.02−1.32 (m, 26H), 1.32−1.48 (m, 2H), 2.46 (s, 3H), 3.43 (dd, *J* = 8.6, 8.6 Hz, 1H), 3.72 (ddd, *J* = 8.6, 8.6, 4.6 Hz, 1H), 3.88 (ddd, *J* = 4.6, 4.6, 4.0 Hz, 1H), 3.99 (dd, *J* = 8.6, 8.6 Hz, 1H), 4.85 (dd, *J* = 4.6, 4.6 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.83 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 21.5, 22.6, 25.8, 29.3, 29.4, 29.5 (2C), 29.6 (5C), 29.8, 31.9, 55.3, 71.3, 81.1, 84.2, 127.8 (2C), 129.9 (2C), 133.9, 145.0; HRMS (FAB) calcd for $C_{25}H_{44}NO_4S$ (MH^+) 454.2986, found 454.2982.

(2*S*,3*S*,4*S*)-4-Amino-2-tetradecyltetrahydrofuran-3-ol (Pachastrissamine) (1). To a stirred mixture of **15** (54 mg, 0.119 mmol) in MeOH (2.4 mL) was added Mg (58 mg, 2.39 mmol) at room temperature. After stirring for 1.5 h at this temperature, the mixture was concentrated under reduced pressure, then the residue was diluted with CH_2Cl_2, washed with 2 N NaOH, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give a white solid, which was purified by flash chromatography over silica gel with $CHCl_3$−MeOH−28% NH_4OH (95:4:1) to give **1** as a white solid (29 mg, 81% yield): mp 95−97 °C; $[\alpha]^{25}_D$ +14.8 (*c* 0.57, EtOH), [lit.[3] $[\alpha]_D$ +13.3−19.0 (EtOH)]; IR (neat) 3341 (NH and OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.20−1.49 (m, 24H), 1.59−1.73 (m, 2H), 1.80−2.20 (br s, 2H), 3.52 (dd, *J* = 8.5, 7.1 Hz, 1H), 3.60−3.70 (m, 1H), 3.73 (ddd, *J* = 7.1, 7.1, 3.4 Hz, 1H), 3.87 (dd, *J* = 4.6, 3.4 Hz, 1H), 3.92 (dd, *J* = 8.5, 7.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 26.3, 29.3, 29.4, 29.6 (6C), 29.7, 29.8, 31.9, 54.3, 71.8, 72.4, 83.2. Anal. Calcd for $C_{18}H_{37}NO_2$: C, 72.19; H, 12.45; N, 4.68. Found: C, 72.40; H, 12.18; N, 4.39.

(*R*)-{(4*S*,5*R*)-2-Oxo-4-[(triisopropylsilyloxy)methyl]oxazolidin-5-yl}pentadecyl Acetate (20). To a stirred solution of **18** (352 mg, 0.614 mmol) in CH_2Cl_2 (61 mL) were added $MeC(OMe)_3$ (460 μL, 3.68 mmol) and $BF_3\cdot OEt_2$ (15 μL, 0.122 mmol) at 0 °C, then the mixture was stirred for 1.5 h at room temperature. The mixture was quenched by addition of MeOH at 0 °C, and concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane−EtOAc (4:1) to give **20** as a colorless oil (318 mg, 96% yield): $[\alpha]^{25}_D$ −25.5 (*c* 0.81, $CHCl_3$); IR (neat) 3305 (NH), 1746 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.05 (d, *J* = 5.7 Hz, 18H), 1.08−1.14 (m, 2H), 1.22−1.37 (m, 24H), 1.63−1.75 (m, 3H), 2.10 (s, 3H), 3.61−3.67 (m, 1H), 3.67−3.73 (m, 2H), 4.44 (dd, *J* = 4.6, 3.4 Hz, 1H), 5.00 (ddd, *J* = 6.9, 6.9, 3.4 Hz, 1H), 5.95 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.8, 14.0, 17.8 (6C), 20.8, 22.6 (3C), 25.2, 29.2, 29.3, 29.4, 29.5, 29.6 (6C), 29.9, 55.5, 65.0, 73.3, 78.7, 159.0, 170.6; HRMS (FAB) calcd for $C_{30}H_{60}NO_5Si$ (MH^+) 542.4235, found 542.4241.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.