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Enantioselective Synthesis of Jaspine B (Pachastrissamine) and Its C-2 and/or C-3 Epimers

Josep Llaveria,[a] Yolanda Díaz,[a] M. Isabel Matheu,*[a] and Sergio Castillón*[a]

Dedicated to Professor Cármen Nájera on the occasion of her 60th birthday

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Jaspine B and its C-2 and/or C3 epimers have been enantioselectively prepared from butadiene monoepoxide through a synthetic procedure consisting of allylic amination by palladium-catalyzed dynamic kinetic asymmetric transformation, cross metathesis, and stereoselective dihydroxylation as key steps.

Introduction

Jaspine B, also known as pachastrissamine (**1**; Figure 1), is a cyclic anhydrosphingosine isolated by Higa and co-workers in 2002 from the marine sponge Pachastrissa sp. (family Calthropellidae), which is found in the Okinawan islands.[1] Simultaneously, Debitus and co-workers[2] reported the isolation of jaspine B from the marine sponge Jaspis sp. This compound has shown submicromolar cytotoxic activity against P388, A549, MT29 and MEL28, MDA231, and HeLa and CNE cell lines, indicating potential usage in various cancer treatments.[2–4] This biological activity could act in synergy with classical antitumor molecules, as has been shown for phytosphingosine.[5]

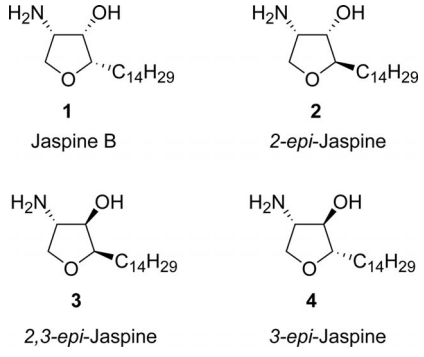
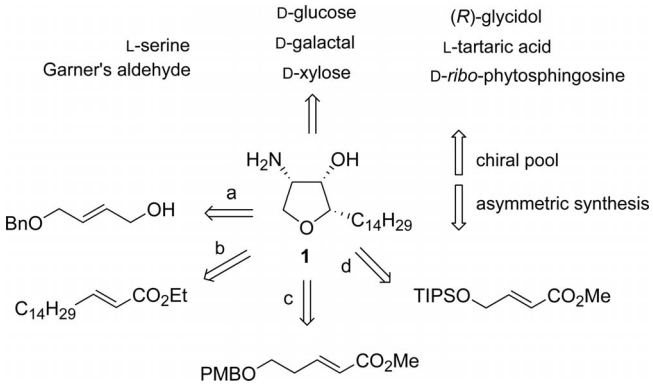


Figure 1. Jaspine B (**1**) and its isomers **2**–**4**.

Since its isolation in 2002, and in view of its interesting biological activity, different synthetic methods have been reported for the total synthesis of aspine B (**1**),[6] its isomers **2**–**4**, and other analogues (Scheme 1). Thus, jaspine B and its derivatives have been prepared by using starting materials from the chiral pool, such as L-serine,[7] Garner's aldehyde,[8–11] D-xylose,[4,12,13] D-glucose,[13–15] tri-*O*-benzyl-D-galactal,[16] D-*ribo*-phytosphingosine,[3,17,18] (*R*)-glycidol,[19] and L-tartaric acid[20,21] (Scheme 1).



Scheme 1. Published approaches to jaspine B.

A few enantioselective catalytic procedures have been reported that are based on: (i) Sharpless asymmetric epoxidation of 4-benzyloxy-(2*E*)-butene-1-ol (Scheme 1a),[22] (ii) Sharpless asymmetric dihydroxylation of ethyl (2*E*)-heptadecenoate (Scheme 1b),[23] and (iii) methyl (2*E*)-5-*p*-methoxybenzyloxy-2-pentanoate (Scheme 1c).[24] Recently, an asymmetric organocatalytic method that uses a proline-catalyzed aldol[25] or oxidation[26] reaction as a key step and a diastereoselective synthesis based on the tandem conjugate

[a] Departament de Química Analítica i Química Orgànica, Facultat de Química, Universitat Rovira i Virgili, C/Marcel.lí Domingo s/n, 43007 Tarragona, Spain
Fax: 34-977-558446
E-mail: sergio.castillon@urv.cat

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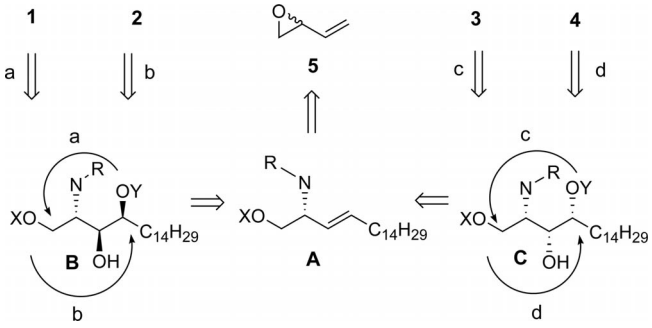
addition of a chiral lithium amide to a triisopropylsilyloxy-α,β-unsaturated methyl ester followed by enolate oxidation have been described (Scheme 1d).[27]

Results and Discussion

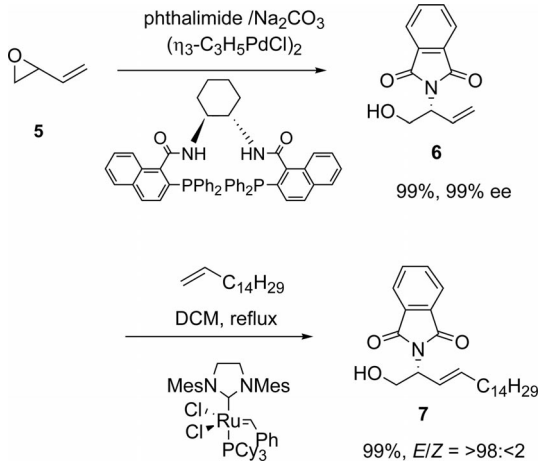
Herein we report a catalytic enantioselective route to the synthesis of jaspine B (**1**) and its epimers **2**–**4** (Figure 1), starting from racemic butadiene monoepoxide (**5**). In the proposed retrosynthesis, compounds **1**–**4** can be obtained from common intermediate **A** (Scheme 2), which in turn can be obtained from **5** by an enantioselective palladium-catalyzed allylic amination, followed by a cross-metathesis reaction with a ruthenium catalyst.



Scheme 2. Retrosynthetic route to jaspine B (**1**) and its isomers **2**–**4**.

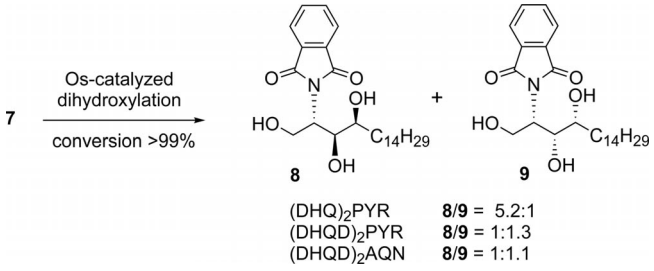
The strategy to **1**–**4** consists of performing the diastereoselective dihydroxylation of **A** to afford intermediates **B** and **C**, from which compounds **1**–**4** can be obtained by cyclization involving routes a–d (Scheme 2).

Initially, butadiene monoepoxide (**5**) was treated with phthalimide in the presence of Pd/(*S*,*S*)-DACH-naphthyl to afford 2-*N*-phthalimido-3-buten-1-ol (**6**; Scheme 3) in excellent yield and enantioselectivity through a palladium-catalyzed DYKAT (dynamic kinetic asymmetric transformation) process described by Trost.[28] Compound **6** was treated with an excess amount of 1-hexadecene in the presence of the second generation Grubbs catalyst to afford compound **7** in excellent yield (99%) and stereoselectivity, with only the *E* isomer being detected by ^{1}H NMR spectroscopy.



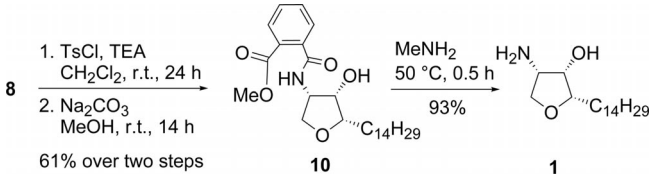
Scheme 3. Synthesis of compound **7** from racemic butadiene monoepoxide (**5**).[29]

We have described the substrate-controlled dihydroxylation of compound **7** by using osmium catalysis, which provides a separable mixture of **8** and **9** in a 3.3:1 ratio.[29] The diastereomeric ratio was further improved by using $(DHQ)_2PYR$ as a ligand. Under these conditions, the reaction was quantitative, and the ratio **8/9** was improved to 5.2:1, which allowed the isolation of compound **8** in an 80% yield over three steps (Scheme 4). To promote the formation of mismatched product **9**, from which isomers **3** and **4** can be obtained, the pseudoenantiomeric ligands $(DHQD)_2$-PYR and $(DHQD)_2AQN$ were tested in the osmium-catalyzed dihydroxylation reaction. Both ligands afforded a mixture of products **8** and **9** with excellent conversion (>98%), and an **8/9** ratio of 1:1.3 was obtained when $(DHQD)_2PYR$ was used. This allowed the recovery of compound **9** in a 47% yield (Scheme 4).



Scheme 4. Synthesis of compounds **8** and **9** by osmium-catalyzed dihydroxylation.

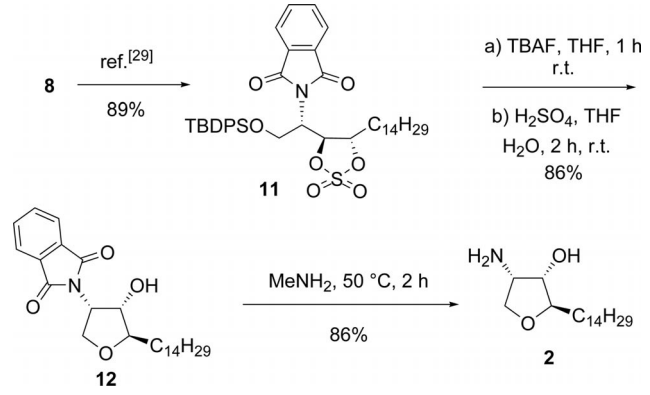
With **8** in hand, two strategies were studied to obtain jaspine B and its C-2 epimer (*epi*-Jaspine). One pathway was based on a cyclization involving a leaving group at the primary hydroxy group (OX, Scheme 2a). Thus, when compound **8** was treated with TsCl in TEA/DMAP, the isolated tosyl derivative was obtained in a 42% yield, together with the cyclization product in 25% yield. However, when the crude reaction product was treated with Na_2CO_3 in methanol, tetrahydrofuran derivative **10** was obtained in a 61% yield over two steps as a consequence of intramolecular tosylate displacement[3,17,19] and partial methanolysis of the phthalimido group (Scheme 5). The phthalimido group was then removed by treatment with $MeNH_2$ to afford jaspine B (**1**)[3,19,27a] in 93% yield.



Scheme 5. Synthesis of jaspine B (**1**) from triol **8**.

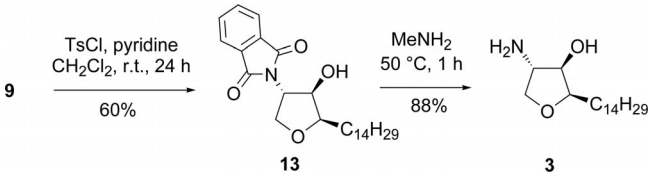
The second strategy involved a reverse cyclization reaction, where the leaving group is now present at the C-4 position (OY, Scheme 2b) and the 1-OH is the nucleophile (X =

H, Scheme 2b). The 3,4-cyclic sulfate was selected as the leaving group. The primary hydroxy group in **8** was protected as a *tert*-butyldimethylsilyl ether in 89% yield. Reaction with thionyl chloride followed by oxidation with RuO_4 and $NaIO_4$ afforded sulfate **11** in quantitative yield (Scheme 6). Treatment of reactive sulfate **11** with TBAF in THF at room temperature afforded protected tetrahydrofuran **12** in 86% yield over two steps through desilylative cyclization and hydrolysis of the sulfate group. The 4-*exo*-cyclization product was not detected in the reaction mixture by ^1H NMR spectroscopy, as described by Kim et al.[18] After deprotection of the phthalimido group, 2-*epi*-jaspine B (**2**)[3,7,27] was obtained in 86% yield (Scheme 6).



Scheme 6. Synthesis of *2-epi*-jaspine B (**2**) from triol **8**.

A similar strategy was followed to obtain C-2 and C-3 epimers **3** and **4** from the corresponding diastereoisomer **9** (Scheme 2, routes c and d). Thus, compound **9** was treated with TsCl in CH_2Cl_2/pyridine to directly afford cyclization product **13** in a 60% yield. Then, the phthalimido protecting group was removed by reaction with methylamine to provide **3**[3,11] in an 88% yield (Scheme 7).



Scheme 7. Synthesis of 2,3-*epi*-jaspine (**3**) from **9**.

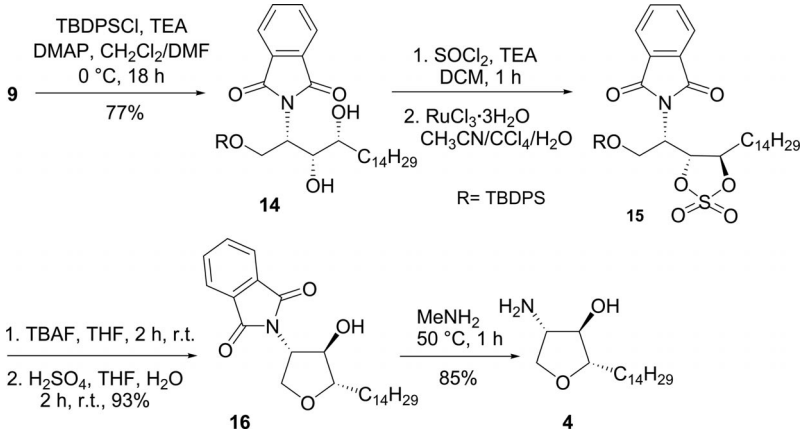
The synthesis of 3-*epi*-jaspine B (**4**)[3,11] was carried out by initial silylation of **9** to give **14**, which was then treated with $SOCl_2$ and RuO_4 to afford cyclic sulfate **15**. Compound **15** was treated with TBAF in THF at room temperature to afford protected tetrahydrofuran **16** through desilylative cyclization and sulfate hydrolysis in 93% yield over two steps. Cyclization to give the oxetane was not detected by ^1H NMR spectroscopy. Finally, removal of the phthalimido group with methylamine afforded compound **4** in 85% yield (Scheme 8).

Conclusions

In conclusion, we have developed a short and efficient divergent enantioselective catalytic method to synthesize the natural anhydrosphingosine jaspine B (Pachastrissamine, **1**) and three of its 2-, 3-, and 2,3-epimers (i.e., **2**–**4**) from racemic butadiene monoepoxide. Jaspine B was synthesized in a 54% overall yield, and compounds **2**, **3**, and **4** were obtained in 55, 36, and 24% yield, respectively. A similar methodology using the enantiomeric ligand (*R*,*R*)-DACH-naphthyl could be used to obtain the corresponding enantiomers.

Experimental Section

General Methods: All chemicals were reagent grade and used as supplied unless otherwise specified. HPLC-grade dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), and dimethylformamide (DMF) were dried by using a solvent purification system (Pure SOLV system-4). ^1H and ^{13}C NMR spectra were recorded with a Varian Mercury VX 400 (400 and 100.6 MHz, respectively) or Varian 400-MR spectrometer in $CDCl_3$ as solvent, with chemical shifts (δ) referenced to internal standards $CDCl_3$ (δ = 7.26 ppm for ^1H; δ = 77.23 ppm for ^{13}C) or Me_4Si as an internal reference (δ = 0.00 ppm). 2D correlation spectra (gCOSY, NOESY, gHSQC, gHMBC) were visualized by using VNMR program (Varian). MS (ESI) were run with an Agilent 1100 Series LC–MSD instrument. Optical rotations were measured at room temperature with a Perkin–Elmer 241 MC apparatus with 10-cm cells. IR spectra were recorded with a JASCO FTIR–600 plus Fourier Transform Infrared Spectrometer ATR Specac Golden Gate. Melting points were



Scheme 8. Synthesis of 3-*epi*-jaspine B (**4**) from **9**.

determined with a Reichert apparatus. Optical rotations were measured at 598 nm with a Jasco DIP-370 digital polarimeter by using a 100-mm cell. Reactions were monitored by TLC carried out on 0.25 mm E. Merck silica gel 60 F254 glass or aluminum plates. Developed TLC plates were visualized under a short-wave UV lamp (250 nm) and by heating plates that were dipped in ethanol/H_2SO_4 (15:1) and basic solution of potassium permanganate. Flash column chromatography was carried out by using forced flow of the indicated solvent on Merck silica gel 60 (230–400 mesh). Radial chromatography was performed on 1- or 2-mm plates of Kieselgel 60 PF254 silica gel, depending on the amount of product. Flash column chromatography (FCC) was performed by using flash silica gel (32–63 μm) and employing a solvent polarity correlated with TLC mobility.

(2*S*,3*S*,4*S*)-4-(2-Methylbenzoate)carbamoyl-2-tetradecyltetrahydrofuran-3-ol (10): Compound **8** (276 mg, 0.6 mmol) was dissolved in anhydrous dichloromethane (5 mL) and triethylamine (0.3 mL, 2.2 mmol). Then, DMAP (7 mg, 0.06 mmol) and tosyl chloride (206 mg, 1.1 mmol) were added, and the mixture was stirred for 22 h at room temperature. The crude was acidified with HCl aqueous solution (10%) and then the organic layer was washed with aqueous solution of $NaHCO_3$ and brine. The organic layer was dried with anhydrous $MgSO_4$, and the solvent was removed under vacuum. Then, Na_2CO_3 (125 mg, 1.5 mmol) was added, and the mixture was dissolved in anhydrous methanol and it was stirred for 20 h at room temperature. The solvent was removed under vacuum, and the crude was directly purified by silica gel chromatography (hexanes/ethyl acetate, 7:3) to afford **10** as a white solid (165 mg, 61%). $[\alpha]_D^{25}$ = –8.3 (*c* = 0.25, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 3453, 3279, 2970, 2922, 2852, 2361, 1727, 1633, 1547, 1464, 1292, 772 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.97 (d, $^3J_{H,H}$ = 7.6 Hz, 1 H, Ar), 7.58 (t, $^3J_{H,H}$ = 7.6 Hz, 1 H, Ar), 7.49 (t, $^3J_{H,H}$ = 7.6 Hz, 1 H, Ar), 7.44 (d, $^3J_{H,H}$ = 7.6 Hz, 1 H, Ar), 6.13 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, NH), 4.72 (tdd, $^3J_{H,H}$ = 8.4, 8.0, 4.0 Hz, 1 H, 4-H), 4.43 (dd, $^3J_{H,H}$ = 4.0, 3.6 Hz, 1 H, 3-H), 4.13 (dd, $^3J_{H,H}$ = 8.4, 8.0 Hz, 1 H, 5-H), 3.91 (s, 3 H, OCH_3), 3.87 (td, $^3J_{H,H}$ = 6.8, 3.6 Hz, 1 H, 2-H), 3.72 (dd, $^3J_{H,H}$ = 8.4, 8.0 Hz, 1 H, 5′-H), 3.13 (br. s, 1 H, OH), 1.70 (m, 2 H), 1.45–1.25 (m, 24 H, alkyl chain), 0.88 (t, $^3J_{H,H}$ = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.2, 167.0, 138.7, 132.7, 130.4, 129.7, 127.6, 82.6, 70.9, 69.2, 54.4, 52.9, 31.9, 29.8, 29.7, 29.6, 29.5, 29.4, 29.0, 26.2, 22.7, 14.2 ppm. HMRS (ESI): calcd. for $C_{27}H_{43}NO_5SNa^+$ 484.3039; found 484.3048.

(2*S*,3*S*,4*S*)-4-Amino-2-tetradecyltetrahydrofuran-3-ol [Pachastrissamine or Jaspine B (1)]: Compound **10** (23 mg, 0.051 mmol) was dissolved in an aqueous solution of $MeNH_2$ (40%, 0.15 mmol), and the resulting mixture was stirred in an open flask for 1 h at 50 °C). The reaction was allowed to cool to room temperature, and methylamine was removed, first by bubbling argon through the reaction mixture for 30 min and then by placing the mixture under vacuum for 1 h. The crude was purified by silica gel chromatography (CH_2Cl_2/MeOH/NH_4OH, 96:3:1) to afford **1** as a white solid (13 mg, 93%). $[\alpha]_D^{25}$ = +7.7 (*c* = 0.6, $CHCl_3$) {ref.[3] $[\alpha]_D^{25}$ = +8.7 (*c* = 1.1, CH_3Cl); ref.[19] $[\alpha]_D^{25}$ = +9.0 (*c* = 1.5, CH_3Cl); ref.[2] $[\alpha]_D^{25}$ = +7.0 (*c* = 0.1, CH_3Cl); ref.[27a] $[\alpha]_D^{25}$ = +6.5 (*c* = 0.45, CH_3Cl)}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.86 (dd, $^3J_{H,H}$ = 8.5, 7.2 Hz, 1 H, 5-H), 3.80 (dd, $^3J_{H,H}$ = 4.8, 3.4 Hz, 1 H, 3-H), 3.66 (td, $^3J_{H,H}$ = 7.2, 3.4 Hz, 1 H, 2-H), 3.60 (dt, $^3J_{H,H}$ = 7.2, 4.8 Hz, 1 H, 4-H), 3.45 (dd, $^3J_{H,H}$ = 8.5, 7.2 Hz, 1 H, 5-H), 1.80 (br. s, 3 H, NH_2 and OH), 1.65–1.52 (m, 2 H), 1.38–1.18 (m, 24 H, alkyl chain), 0.81 (t, $^3J_{H,H}$ = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 83.4, 72.5, 71.9, 54.4, 32.1, 30.0, 29.9, 29.8, 29.6, 26.5, 26.5, 22.9, 14.5 ppm. HMRS (ESI): calcd. for $C_{18}H_{38}NO_2^+$ 300.2903; found 300.3000.

(2*R*,3*S*,4*S*)-4-*N*-Phthalimido-2-tetradecyltetrahydrofuran-1-ol (12): To a solution of sulfate **11** (0.09 mmol) dissolved in anhydrous THF (1 mL) was dropwise added TBAF (1 M in THF, 117 mL, 0.117 mmol). The solution was stirred for 2 h at room temperature and then a drop of water and H_2SO_4 were added to the solution. The mixture was stirred at room temperature for another 2 h, and the crude was then washed with an aqueous solution of $NaHCO_3$ and brine. The organic layer was dried with anhydrous $MgSO_4$, and the solvent was removed under vacuum. The crude was purified by silica gel chromatography (hexanes/ethyl acetate, 7:3) to afford **12** as a white solid (33 mg, 86%). $[\alpha]_D^{25}$ = +8.3 (*c* = 0.6, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 3300, 2958, 2920, 2895, 1704, 1392, 1280, 720 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.85 (dd, *J* = 5.4, 3.2 Hz, 2 H, Ar), 7.74 (dd, *J* = 5.4, 3.2 Hz, 2 H, Ar), 4.95 (dd, $^3J_{H,H}$ = 8.0, 5.6 Hz, 1 H, 3-H), 4.91 (dt, $^3J_{H,H}$ = 8.4, 8.0 Hz, 1 H, 4-H), 4.59 (t, $^3J_{H,H}$ = 8.4 Hz, 1 H, 5-H), 4.21 (dd, $^3J_{H,H}$ = 8.4, 8.0 Hz, 1 H, 5′-H), 4.15 (td, $^3J_{H,H}$ = 7.6, 5.6 Hz, 1 H, 2-H), 1.68–1.62 (m, 2 H), 1.57 (s, 1 H, OH), 1.34–1.25 (m, 24 H, alkyl chain), 0.86 (t, $^3J_{H,H}$ = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 168.1, 134.4, 131.6, 123.6, 82.5, 75.7, 66.3, 50.7, 33.6, 32.1, 29.9, 29.8, 29.7, 25.8, 22.9, 20.7, 14.4 ppm. HMRS (ESI): calcd. for $C_{16}H_{39}NO_4Na^+$ 452.2777; found 452.2765.

(2*R*,3*S*,4*S*)-4-Amino-2-tetradecyltetrahydrofuran-3-ol [2-*epi*-Jaspine (2)]: Compound **12** (25 mg, 0.055 mmol) was dissolved in aqueous solution of $MeNH_2$ (0.2 mmol, 0.2 mL, 40%), and the resulting mixture was stirred in an open flask for 1.5 h at 50 °C. The reaction was cooled to room temperature, and methylamine was removed, first by bubbling argon through the reaction mixture for 30 min and then by placing the mixture under vacuum for 1 h. The crude was purified by silica gel chromatography (CH_2Cl_2/MeOH/NH_4OH, 96:3:1) to afford **2** as a white solid (13 mg, 86%). $[\alpha]_D^{25}$ = +9.1 (*c* = 0.1, $CHCl_3$) {ref.[7] $[\alpha]_D^{25}$ = +9.6 (*c* = 0.11, CH_3Cl); ref.[27a] $[\alpha]_D^{25}$ = +11.7 (*c* = 0.65, CH_3Cl); ref.[3] $[\alpha]_D^{25}$ = +14.8 (*c* = 0.97, CH_3Cl)}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.12 (dd, $^3J_{H,H}$ = 9.1, 6.8 Hz, 1 H, 5-H) 3.61 (m, 2 H, 3-H, 2-H), 3.45 (m, 1 H, 4-H), 3.40 (dd, $^3J_{H,H}$ = 9.1, 6.8 Hz 1 H,5′-H), 2.10–1.49 (m, 5 H, NH_2, OH, CH_2), 1.34–1.25 (m, 24 H, alkyl chain), 0.86 (t, $^3J_{H,H}$ = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 85.5, 74.5, 73.4, 52.7, 32.1, 30.0, 29.9, 29.8, 29.6, 26.5, 22.9, 14.4 ppm. HMRS (ESI): calcd. for $C_{18}H_{38}NO_2^+$ 300.2903; found 300.2910.

(2*R*,3*R*,4*S*)-4-*N*-Phthalimido-2-tetradecyltetrahydrofuran-3-ol (13): Alcohol **9** (200 mg, 0.44 mmol) and tosyl chloride (92 mg, 0.48 mmol) were dissolved in anhydrous dichloromethane (1 mL), and the solution was cooled to 0 °C. Pyridine (1 mL) was added, and the mixture was stirred at 0 °C for 1 h. Then, the mixture was warmed to room temperature for 10 h, tosyl chloride (40 mg, 0.24 mmol) was added, and the mixture was stirred for another 10 h. The mixture was treated with HCl aqueous solution (10%), the aqueous layer was washed with dichloromethane, and the combined organic layers were washed with $NaHCO_3$ saturated aqueous solution and brine. The organic layer was dried with anhydrous $MgSO_4$, and the solvent was removed under vacuum. The mixture was purified by radial chromatography (hexanes/ethyl acetate, 7:3) to afford **13** as a white solid (190 mg, 60%). $[\alpha]_D^{25}$ = +11.5 (*c* = 1.6, CH_2Cl_2). FTIR (neat): $\tilde{\nu}$ = 3350, 2963, 2910, 2845, 1697, 1392, 720 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.78 (dd, *J* = 5.2, 3.0 Hz, 2 H, Ar), 7.67 (dd, *J* = 5.2, 3.0 Hz, 2 H, Ar), 4.67 (ddd, $^3J_{H,H}$ = 7.6, 6.0, 1.6 Hz, 1 H, 3-H), 4.53 (m, 1 H, 4-H), 4.25–4.20 (m, 2 H, 5-H and 5′-H), 3.56 (t, $^3J_{H,H}$ = 6.8 Hz, 1 H, 2-H), 2.27 (d, $^3J_{H,H}$ = 6.0 Hz, 1 H, OH), 1.70–1.60 (m, 2 H), 1.41–1.25 (m, 24 H, alkyl chain), 0.792 (t, $^3J_{H,H}$ = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 168.2, 134.5, 131.9, 123.6, 82.9, 76.4, 67.6, 59.8. 32.1, 30.0, 29.9, 29.8, 26.6, 28.7, 26.4, 22.9, 14.3 ppm.

HMRS (ESI): calcd. for $C_{26}H_{39}NO_4Na^+$ 452.2777; found 452.2779.

(2*R*,3*R*,4*S*)-4-Amino-2-tetradecyltetrahydrofuran-3-ol [C-2,C-3-*epi*-Jaspine B (3)]: Compound **13** was dissolved in aqueous solution of $MeNH_2$ (0.17 mmol, 15 mL, 40%), and the resulting mixture was stirred in an open flask for 1 h at 50 °C. The reaction is allowed to cool to room temperature, and methylamine was removed, first by bubbling argon through the reaction for 30 min and then by placing the mixture under vacuum for 1 h. The crude was purified by silica gel chromatography (CH_2Cl_2/MeOH/NH_4OH, 96:4:1) to afford **3** as a white solid (17 mg, 88%). $[\alpha]_D^{25}$ = –0.7 (*c* = 1.0, CH_3Cl) {ref.[3] $[\alpha]_D^{25}$ = –2.5 (*c* = 0.7, CH_3Cl); ref.[11] $[\alpha]_D^{25}$ = –1.11 (*c* = 0.99, CH_3Cl)}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.22 (dd, $^3J_{H,H}$ = 9.4, 5.6 Hz, 1 H, 5-H), 3.89 (dt, $^3J_{H,H}$ = 7.2, 3.6 Hz, 1 H, 4-H), 3.82–3.79 (m, 1 H, 3-H), 3.49–3.47 (m, 1 H, 2-H), 3.38 (dd, $^3J_{H,H}$ = 9.4, 3.6 Hz, 1 H, 5-H), 1.62–1.52 (m, 5 H), 1.33–1.25 (m, 24 H, alkyl chain), 0.87 (t, $^3J_{H,H}$ = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 80.9, 80.0, 74.0, 60.1, 32.1, 30.0, 29.9, 29.8, 29.7, 29.6, 28.7, 26.6, 22.9, 14.4 ppm. HMRS (ESI): calcd. for $C_{18}H_{37}NO_2Na^+$ 322.2722; found 322.2720.

(2*S*,3*R*,4*R*)-1-*tert*-Butyldiphenylsilyloxy-2-*N*-phthalimidooctadecane-3,4-diol (14): Alcohol **9** (107 mg, 0.24 mmol) was dissolved in dichloromethane (2 mL) and DMF (0.5 mL). DMAP (1.5 mg, 0.012 mmol) and triethylamine (0.1 mL, 0.6 mmol) were added, and then the solution was cooled to 0 °C and TBDPSCl (0.07 mL, 0.3 mmol) was added dropwise. After 1 h, the mixture was warmed to room temperature and it was stirred for 18 h, at which point TLC showed complete conversion. The crude was quenched with a NH_4Cl aqueous saturated solution, the aqueous layer was washed with dichloromethane, and the combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. The solvent was removed under vacuum, and the crude was purified by radial chromatography (hexanes/ethyl acetate, 6:4) to afford **14** as a colorless oil (163 mg, 77%). $[\alpha]_D^{25}$ = –20.2 (*c* = 0.9, CH_3Cl). FTIR (neat): $\tilde{\nu}$ = 3424, 3123, 2924, 2853, 2361, 1706, 1465, 1430, 1389, 1213, 1111, 751 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.85 (dd, *J* = 5.4, 3.2 Hz, 2 H, Ar), 7.75 (dd, *J* = 5.4, 3.2 Hz, 2 H, Ar), 7.61 (dd, *J* = 8.0, 1.4 Hz, 2 H, Ar), 7.51 (dd, *J* = 8.0, 1.4 Hz, 2 H, Ar), 7.41–7.32 (m, 4 H, Ar), 7.27 (t, *J* = 8.0 Hz, 2 H, Ar), 4.77 (ddd, $^3J_{H,H}$ = 8.8, 5.8, 3.2 Hz, 1 H, 2-H), 4.17 (dd, $^3J_{H,H}$ = 10.8, 5.8 Hz, 1 H, 1-H), 4.15 (dd, $^3J_{H,H}$ = 10.8, 8.8 Hz, 1 H, 1′-H), 4.08 (m, 1 H, 3-H), 3.91–3.88 (m, 1 H, 4-H), 3.55 (br. s, 1 H, OH), 1.93 (br. s, 1 H, OH), 1.43–1.38 (m, 2 H), 1.25–1.22 (m, 24 H, alkyl chain), 0.89 (t, $^3J_{H,H}$ = 6.8 Hz, 3 H), 0.89 [s, 9 H, $(CH_3)_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 169.5 135.9, 135.7, 134.4, 133.2, 133.1, 132.0, 130.0, 129.9, 127.9, 127.9, 123.7, 75.4, 72.7, 60.8, 54.6, 32.6, 32.1, 29.9, 29.8, 29.7, 29.6, 26.8, 25.8, 22.9, 19.1, 14.3 ppm. HRMS (ESI): calcd. for $C_{42}H_{59}NO_5SiNa^+$ 708.4060; found 708.4021.

(2*S*,3*R*,4*R*)-1-(*tert*-Butyldiphenylsilyloxy)-2-*N*-phthalimido-3,4-*O*-sulfuryloctadecane (15): To a solution of diol **14** (0.16 g, 0.23 mmol) in dichloromethane (2 mL) was added triethylamine (90 μL, 0.68 mmol) and thionyl chloride (20 μL, 0.27 mmol) at 0 °C. After stirring for 40 min, the reaction mixture was poured into brine and extracted with ethyl acetate. The organic layer was dried with anhydrous $MgSO_4$ and concentrated in vacuo. The crude was dried in vacuo for one night and then dissolved in $CCl_4/CH_3CN/H_2O$ (1:1:1 mL). $RuCl_3{\cdot}3H_2O$ (6 mg, 0.011 mmol) and $NaIO_4$ (0.14 g, 0.68 mmol) were added. After 2.5 h, no starting material was observed by TLC. The reaction mixture was diluted with AcOEt and washed with a saturated solution of Na_2SO_3, and the organic layer was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to afford compound **15** as a beige oil, which was not purified and directly used in the next reaction. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.87 (dd, *J* = 5.6, 3.2 Hz, 2 H, Ar), 7.80 (dd, *J* = 5.6, 3.0 Hz, 2 H, Ar), 7.50 (d, *J* = 6.6 Hz, 2 H, Ar), 7.45 (d, *J* = 6.6 Hz, 2 H, Ar), 7.41–1.36 (m, 4 H, Ar), 7.30 (t, *J* = 8.0 Hz, 2 H, Ar), 5.92 (dd, $^3J_{H,H}$ = 11.4, 5.0 Hz, 1 H, 3-H), 4.86 (ddd, $^3J_{H,H}$ = 11.4, 5.0, 2.8 Hz, 1 H, 4-H), 4.76 (ddd, $^3J_{H,H}$ = 8.6, 5.0, 4.2 Hz, 1 H, 2-H), 4.16 (dd, $^3J_{H,H}$ = 10.6, 8.6 Hz, 1 H, 1-H), 3.95 (dd, $^3J_{H,H}$ = 10.6, 4.2 Hz, 1 H, 1′-H), 1.52–1.39 (m, 2 H), 1.28–1.15 (m, 24 H, alkyl chain), 0.88 (t, $^3J_{H,H}$ = 6.8 Hz, 3 H), 0.58 [s, 9 H, Si-$(CH_3)_3$] ppm. ^{13}C NMR (100 MHz, 25 °C): δ = 168.5, 135.6, 134.9, 132.5, 131.6, 130.2, 130.1, 128.2, 128.0, 124.0, 85.6, 79.8, 61.4, 51.0, 32.1, 30.1, 29.9, 29.8, 29.7, 29.6, 29.3, 28.9, 27.9, 26.9, 26.7, 25.9, 25.0, 22.9, 19.1, 14.4 ppm. HMRS (ESI): calcd. for $C_{42}H_{57}NO_7SNa^+$ 770.3523; found 770.3551.

(2*S*,3*R*,4*S*)-4-*N*-Phthalimido-2-tetradecyltetrahydrofuran-3-ol (16): To a solution of **15** (0.052 mmol) dissolved in anhydrous dichloromethane (2 mL) was added a solution of TBAF (1 M in THF, 57 mL, 0.057 mmol). The solution was stirred for 2 h at room temperature and then a drop of water and H_2SO_4 were added to the solution. The mixture was stirred at room temperature for another 2 h, and the crude was then washed with an aqueous solution of $NaHCO_3$ and brine. The crude was purified by radial chromatography (hexanes/ethyl acetate, 5:2) to afford **16** as a white solid (20 mg, 92%). $[\alpha]_D^{25}$ = +8.9 (*c* = 1.4, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 3530, 3414, 2952, 2915, 2848, 2361, 2334, 1695, 1467, 1397, 720 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.81 (dd, *J* = 5.6, 3.2 Hz, 2 H, Ar), 7.71 (dd, *J* = 5.6, 3.2 Hz, 2 H, Ar), 4.64 (ddd, $^3J_{H,H}$ = 8.6, 8.0, 7.6 Hz, 1 H, 4-H), 4.53 (dd, $^3J_{H,H}$ = 7.6, 6.8 Hz, 1 H, 3-H), 4.24 (dd, $^3J_{H,H}$ = 8.8, 8.6 Hz, 1 H, 5-H), 4.12 (dd, $^3J_{H,H}$ = 8.8, 8.0 Hz, 1 H, 5′-H), 3.75 (td, $^3J_{H,H}$ = 7.6, 4.8 Hz, 1 H, 2-H), 2.74 (br. s, 1 H, OH), 1.77–1.68 (m, 2 H), 1.53–1.24 (m, 24 H, alkyl chain), 0.86 (t, $^3J_{H,H}$ = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 168.6, 134.5, 131.9, 123.6, 83.4, 77.8, 67.2, 59.3, 33.3, 32.1, 29.9, 29.8, 29.7, 29.6, 26.0, 22.9, 14.3 ppm. HMRS (ESI): calcd. for $C_{26}H_{39}NO_4Na^+$ 452.2777; found 452.2763.

(2*S*,3*R*,4*S*)-4-Amino-2-tetradecyltetrahydrofuran-3-ol [3-*epi*-Jaspine B (4)]: Compound **16** (36 mg, 0.085 mol) was dissolved in an aqueous solution of $MeNH_2$ (0.20 mmol, 0.25 mL, 40%) and the resulting mixture was stirred in an open flask for 1 h at 50 °C. The reaction was allowed to cool at room temperature, and methylamine was removed, first by bubbling argon through the reaction for 30 min and then by placing the mixture under vacuum for 1 h. The crude was purified by silica gel chromatography (CH_2Cl_2/MeOH/NH_4OH, 96:4:1) to afford **4** as a white solid (30 mg, 85%). $[\alpha]_D^{25}$ = –1.8 (*c* = 0.8, $CHCl_3$) {ref.[3] $[\alpha]_D^{25}$ = –3.8 (*c* = 0.7, $CHCl_3$); ref.[11] $[\alpha]_D^{25}$ = –1.55 (*c* = 0.4, $CHCl_3$)}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.00 (dd, $^3J_{H,H}$ = 9.2, 6.0 Hz, 1 H, 5-H), 3.59–3.56 (m, 3 H, 5′–H, 3-H, 4-H), 3.29 (ddd, $^3J_{H,H}$ = 8.0, 4.4, 3.6 Hz, 1 H, 2-H), 1.94 (br. s, 3 H, NH_2 and OH), 1.68–1.57 (m, 2 H), 1.49–1.14 (m, 24 H, alkyl chain), 0.87 (t, $^3J_{H,H}$ = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 85.1, 83.7, 73.7, 60.4, 34.0, 31.9, 29.7, 29.6, 29.5, 29.4, 26.1, 22.7, 14.1 ppm. HMRS (ESI): calcd. for $C_{18}H_{38}NO_2^+$ 300.2903; found 300.2906.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra of compounds **1**–**4** and **10**–**16**.

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[1] I. Kuroda, M. Musman, I. I. Ohtani, T. Ichiba, J. Tanaka, D. Garcia-Gravalos, T. Higa, *J. Nat. Prod.* **2002**, *65*, 1505–1506.
[2] V. Ledroit, C. Debitus, C. Lavaud, G. Massiot, *Tetrahedron Lett.* **2003**, *44*, 225–228.
[3] D. Canals, D. Mormeneo, G. Fabriàs, A. Llebaria, J. Casas, A. Delgado, *Bioorg. Med. Chem.* **2009**, *17*, 235–241.
[4] J. Liu, Y. Du, X. Dong, S. Meng, J. Xiao, L. Cheng, *Carbohydr. Res.* **2006**, *341*, 2653–2687.
[5] Y. Salma, E. Lafont, N. Therville, S. Carpentier, M.-J. Bonnafé, T. Levade, Y. Génisson, N. Andrieu-Abadie, *Biochem. Pharmacol.* **2009**, *78*, 477–485.
[6] E. Abraham, S. G. Davies, P. M. Roberts, A. J. Russel, J. E. Thomson, *Tetrahedron: Asymmetry* **2008**, *19*, 1027–1047.
[7] P. Bhaket, K. Morris, C. S. Stauffer, A. Datta, *Org. Lett.* **2005**, *7*, 875–876.
[8] M. Passiniemi, A. M. P. Koskinen, *Tetrahedron Lett.* **2008**, *49*, 980–983.
[9] N. Sudhakar, A. R. Kumar, A. Prabhakar, B. Jagadeesh, B. V. Rao, *Tetrahedron Lett.* **2005**, *46*, 325–327.
[10] a) S. Inuki, Y. Yoshimitsu, S. Oishi, N. Fujii, H. Ohno, *J. Org. Chem.* **2010**, *75*, 3831–3842; b) S. Inuki, Y. Yoshimitsu, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2009**, *11*, 4478–4481.
[11] Y. Yoshimitsu, S. Inuki, S. Oishi, N. Fujii, H. Ohno, *J. Org. Chem.* **2010**, *75*, 3843–3846.
[12] Y. Du, J. Liu, R. J. Linhardt, *J. Org. Chem.* **2006**, *71*, 1251–1253.
[13] S. Chandrasekhar, B. Tiwari, S. J. Prakash, *ARKIVOC* **2006**, *11*, 155–161.
[14] C. V. Ramana, A. G. Giri, S. B. Suryawanshi, R. G. Gonnade, *Tetrahedron Lett.* **2007**, *48*, 265–268.
[15] G. Jayachitra, N. Sudhakar, R. K. Anchoori, R. Vankateswara, S. Roy, R. Banerjee, *Synthesis* **2010**, *1*, 115–119.
[16] L. V. R. Reddy, P. V. Reddy, A. K. Shaw, *Tetrahedron: Asymmetry* **2007**, *18*, 542–546.
[17] R. J. B. H. N. Van der Berg, T. J. Boltje, C. P. Verhagen, R. E. J. N. Litjens, G. A. Van der Marel, H. S. Overkleeft, *J. Org. Chem.* **2006**, *71*, 836–839.
[18] T. Lee, S. Lee, Y. S. Kwak, D. Kim, S. Kim, *Org. Lett.* **2007**, *9*, 429–932.
[19] C. Ribes, E. Falomir, M. Carda, J. A. Marco, *Tetrahedron* **2006**, *62*, 5421–5425.
[20] Y. Ichikawa, K. Matsunaga, T. Masuda, H. Kotsuki, K. Nakano, *Tetrahedron* **2008**, *64*, 11313–11318.
[21] a) K. R. Prasad, A. Chandrakumar, *J. Org. Chem.* **2007**, *72*, 6312–6315; b) G. Reddipalli, M. Venkataiah, M. K. Mishra, N. W. Fadnavis, *Tetrahedron: Asymmetry* **2009**, *20*, 1802–1805.
[22] a) Y. Génisson, L. Lamandé, Y. Salma, N. Andrieu-Abadie, C. André, M. Baltas, *Tetrahedron: Asymmetry* **2007**, *18*, 857; b) Y. Salma, S. Ballereau, C. Maaliki, S. Ladeira, N. Andrieu-Abadie, Y. Génisson, *Org. Biomol. Chem.* **2010**, *8*, 3227–3243.
[23] K. Venkatesan, K. V. Srinivasan, *Tetrahedron: Asymmetry* **2008**, *19*, 209–215.
[24] T. Yakura, S. Sato, Y. Yoshimoto, *Chem. Pharm. Bull.* **2007**, *55*, 1284–1286.
[25] D. Enders, V. Terteryan, J. Palecek, *Synthesis* **2008**, *14*, 2278–2282.
[26] H. Urano, M. Enamoto, S. Kuwahara, *Biosci. Biotechnol. Biochem.* **2010**, *74*, 152–157.
[27] a) E. Abraham, J. I. Candela-Lena, S. G. Davies, M. Georgiou, R. L. Nicholson, P. M. Roberts, A. J. Russell, E. M. Sánchez-Fernández, A. D. Smith, J. E. Thomson, *Tetrahedron: Asymmetry* **2007**, *18*, 2510–2513; b) E. Abraham, E. A. Brock, J. I. Candela-Lena, S. G. Davies, M. Georgiou, R. L. Nicholson, J. H. Perkins, P. M. Roberts, A. J. Russell, E. M. Sánchez-Fernández, P. M. Scott, A. D. Smith, J. E. Thomson, *Org. Biomol. Chem.* **2008**, *6*, 1665–1673.
[28] a) B. M. Trost, D. B. Horne, M. J. Woltering, *Angew. Chem. Int. Ed.* **2003**, *42*, 5987–5990; b) B. M. Trost, R. C. Nunt, R. C. Lemoine, T. L. Calkins, *J. Am. Chem. Soc.* **2000**, *122*, 5968–5976; c) B. M. Trost, D. B. Horne, M. J. Woltering, *Chem. Eur. J.* **2006**, *12*, 6607–6620.
[29] J. Llaveria, Y. Díaz, M. I. Matheu, S. Castillón, *Org. Lett.* **2009**, *11*, 205–208.

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