Supporting Information

Stereochemically Reliable Derivation to Pachastrissamine and its 2-epi-Congener via Oxazolidinone Precursors, of an Established Starting Material, N-Boc-Protected Phytosphingosine

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I. Materials and Methods

General Methods:

Except as otherwise indicated, reactions were carried out under an argon atmosphere in flame- or oven-dried glassware. In aqueous work-up, all organic solutions were dried over sodium sulfate or magnesium sulfate, and filtered prior to rotary evaporation at water aspirator pressure. Reactions were monitored by thin layer chromatography (TLC) with 0.25-mm E. Merck precoated silica gel plates (Kieselgel 60F\textsubscript{254}, Merck). Spots were detected by viewing under a UV light, colorizing with charring after dipping in anisaldehyde solution with acetic acid and sulfuric acid and MeOH, or in KMnO\textsubscript{4} solution with sulfuric acid and ethanol, or ceric ammonium molybdate solution with sulfuric acid and ethanol. Silica gel for flash chromatography (particle size 0.040-0.063 mm) was supplied by E. Merck. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise noted.
Materials:

Commercial reagents and solvents were used as received with the following exceptions. All solvents were freshly purified and dried by standard techniques just before use. Diethyl ether (Et₂O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone. Dichloromethane (CH₂Cl₂) from freshly opened bottles were stored over 4Å molecular sieves and used without purification.

Instrumentation:

¹H and ¹³C spectra were recorded on a Bruker AMX-500 (500 MHz), a Bruker advance 400 (400 MHz), or JEOL JNM-LA 300 (300 MHz) spectrometer. Chemical shifts are reported as δ value relative to internal chloroform (δ 7.26 for ¹H and δ 77.0 for ¹³C). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, coupling constant in Hz, and assignment. Infrared (IR) spectra were measured on a Perkin-Elmer 1600 FT-IR spectrometer referenced to a polystyrene standard. Data are represented as follows: frequency of the absorption (cm⁻¹), intensity of absorption (s = strong, m = medium, w = weak, br = broad), and assignment (where appropriate). Low and High resolution mass spectra were recorded using fast atom bombardment (FAB). High resolution mass spectra (HRMS) were also recorded using FAB.

(4S,5S)-4-(trityloxy)methyl)-5-[(R)-1-(mesyloxy)-pentadecyl]oxazolidin-2-one (11).

To a solution of 10 (100 mg, 0.17 mmol) in pyridine (3 mL) at room temperature was added mesyl chloride (27 µL, 0.34 mmol). The reaction mixture was stirred for 12 h at room temperature, then quenched by the slow addition of water. The aqueous layer was extracted with EtOAc, and the organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel, using hexanes–EtOAc (2:1) as elutant, provided 11 (106 mg, 95%) as a slightly yellow oil. [α]⁺²⁴° D -13.1 (c 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 0.87 (t, J = 6.3 Hz, 3H), 1.12–1.47 (m, 24H), 1.48–1.76 (m, 2H), 2.76 (s, 3H), 3.28 (dd, J = 7.8, 9.9 Hz, 1H), 3.38 (dd, J = 3.9, 9.9 Hz, 1H), 4.06 (dt, J = 4.1, 7.6 Hz,
1H), 4.72 (dd, J = 5.0, 8.0 Hz, 1H), 4.78–4.86 (m, 1H), 5.72–5.90 (m, 1–NH); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): δ 14.1, 22.6, 24.4, 29.1, 29.27, 29.30, 29.47, 29.53, 29.60, 29.62, 30.6, 31.9, 38.6, 54.6, 62.2, 77.7, 79.0, 87.6, 127.4, 128.0, 128.2, 128.5, 143.0, 157.9; IR (CHCl\(_3\)): \(\lambda_{\text{max}}\) 3267, 2925, 2853, 1763, 1598, 1491, 1448, 1358, 1220, 1176 (cm\(^{-1}\)); HRMS (FAB) calcd for C\(_{19}\)H\(_{36}\)NO\(_3\) 664.3672 ([M+H]\(^{+}\)), found 664.3636.

\((4S,5S)-4\)-(hydroxymethyl)-5-((R)-1-hydroxypentadecyl)oxazolidin-2-one (12).

![Conversion reaction diagram]

To a solution of 10 (100 mg, 0.17 mmol) in toluene (3 mL) and methanol (1 mL) was added BF\(_3\)-OEt\(_2\) (43 μL, 0.34 mmol) at room temperature. The reaction mixture was stirred for 12 h at room temperature, then quenched by the slow addition of a saturated NaHCO\(_3\) solution. The aqueous layer was extracted with EtOAc, and the organic layer was washed with brine, dried over Na\(_2\)SO\(_4\), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel, using hexanes–EtOAc (1:1) as eluant, provided 12 (53 mg, 90%) as a white solid. [\(\alpha\)]\(^{24}\)_D –39.9 (c 0.5, CHCl\(_3\)); \(^1\)H NMR (CDCl\(_3\)–CD\(_3\)OD 1:3, 400 MHz): δ 0.87 (t, J = 6.2 Hz, 3H), 1.26–1.48 (m, 24H), 1.49–1.62 (m, 1H), 1.65–1.78 (m, 1H), 3.66 (dd, J = 5.1, 11.4 Hz, 1H), 3.77 (dd, J = 5.6, 11.4 Hz, 1H), 3.83–3.92 (m, 2H), 4.32–4.40 (m, 1H); \(^{13}\)C NMR (CDCl\(_3\)–CD\(_3\)OD 1:3, 75 MHz): δ 15.2, 24.3, 26.5, 31.0, 31.29, 31.32, 31.34, 33.6, 35.9, 58.0, 62.0, 69.9, 82.9, 162.1; IR (CHCl\(_3\)): \(\lambda_{\text{max}}\) 3340, 2917, 2850, 1717, 1691, 1054, 941, 705 (cm\(^{-1}\)); HRMS (FAB) calcd for C\(_{19}\)H\(_{37}\)NO\(_4\) 344.2801 ([M+H]\(^{+}\)), found 344.2815.

\((3aS,6S,6aS)-6\)-tetradecyltetrahydrofuro[3,4-d]oxazol-2(3H)-one (3).

![Conversion reaction diagram]

To a solution of 11 (80 mg, 0.12 mmol) in toluene (3 mL) and MeOH (1 mL) was added BF\(_3\)-OEt\(_2\) (30 μL, 0.24 mmol) at room temperature. The reaction mixture was
stirred for 12 h at room temperature, then quenched by the slow addition of a saturated NaHCO₃ solution. The aqueous layer was extracted with EtOAc, and the organic layer was washed with brine, dried with Na₂SO₄, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel, using CH₂Cl₂–MeOH (15:1) as eluant, provided 3 (35 mg, 90%) as a white solid. [α]²⁴_D +57.5 (c 0.5, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 0.86 (t, J = 6.8 Hz, 3H), 1.18–1.48 (m, 24H), 1.67–1.82 (m, 2H), 3.45–3.54 (m, 2H), 3.93 (d, J = 10.5 Hz, 1H), 4.35 (dd, J = 4.1, 7.7 Hz, 1H), 4.93 (dd, J = 3.8, 7.4 Hz, 1H), 6.09 (br s, 1–NH); ¹³C NMR (75 MHz, CDCl₃): δ 14.1, 22.7, 26.0, 28.1, 29.3, 29.47, 29.54, 29.61, 29.63, 29.65, 31.7, 50.1, 57.1, 63.9, 73.3, 77.2, 159.3; IR (CHCl₃): λ_max 3330, 3240, 2952, 2925, 2847, 1759, 1720, 1463, 1406, 1321 (cm⁻¹); HRMS (FAB) calcd for C₁₉H₁₆NO₃ 326.2695 ([M+H]⁺), found 326.2706.

(3aS,6R,6aS)-6-tetradecyltetrahydrofuro[3,4-d]oxazol-2(3H)-one (4).

To a solution of 12 (200 mg, 0.60 mmol) in pyridine (10 mL) were added DMAP (5 mg, 0.05 mmol) and p-toluenesulfonyl chloride (335 mg, 1.75 mmol) at room temperature. The reaction mixture was refluxed for 12 h and cooled to room temperature, then quenched by the slow addition of water. The aqueous layer was extracted with EtOAc, and the organic layer was washed with brine, and dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel, using CH₂Cl₂–MeOH (10:1) as eluant, provided 4 (36 mg, 94%) as a white solid. [α]²⁴_D +8.2 (c 0.5, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 0.86 (t, J = 6.8 Hz, 3H), 1.19–1.55 (m, 26H), 3.75 (dd, J = 2.5, 10.2 Hz, 1H), 3.92 (dd, J = 4.9, 10.2 Hz, 1H), 4.01–4.06 (m, 1H), 4.30–4.34 (m, 1H), 4.69 (dd, J = 2.3, 8.1 Hz, 1H), 5.63 (br s, 1–NH); ¹³C NMR (75 MHz, CDCl₃): δ 14.1, 22.7, 25.4, 29.27, 29.35, 29.45, 29.51, 29.61, 29.64, 29.7, 30.6, 31.9, 56.3, 63.0, 72.6, 77.2, 84.0, 84.2, 158.7; IR (CHCl₃): λ_max 3249, 2954, 2920, 2850, 1758, 1728, 1703, 1469, 1408, 1250 (cm⁻¹); HRMS (FAB) calcd for C₁₉H₁₆NO₃ 326.2695 ([M+H]⁺), found 326.2674.

(2S,3S,4S)-4-amino-2-tetradecyltetrahydrofuran-3-ol (1).
To a solution of 3 (20 mg, 0.06 mmol) in EtOH (1 mL) was added an aqueous KOH solution (1.0 M in H₂O, 1 mL) at room temperature. The reaction mixture was refluxed for 12 h and cooled to room temperature, then evaporated and dried with MeOH (5 mL x 3) and toluene (5 mL x 3) in azeotrope. Purification of the residue by flash column chromatography on silica gel, using CH₂Cl₂/MeOH/NH₄OH (100:10:1) as eluent, provided 1 as a white solid (13.3 mg, 72%). [α]²³D +23.2 (c 1.0, MeOH); ¹H NMR (CDCl₃, 300 MHz): δ 0.87 (t, J = 6.6 Hz, 3H), 1.24–1.60 (m, 26H), 2.13 (br s, 3H), 3.39 (dd, J = 6.9, 8.4 Hz, 1H), 3.45 (m, 1H), 3.60 (dd, J = 5.1, 10.8 Hz, 1H), 3.62 (m, 1H), 4.11 (dd, J = 6.0, 8.4 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ 14.1, 22.7, 25.9, 29.4, 29.5, 29.6, 29.7, 31.9, 33.7, 32.7, 73.1, 74.8, 85.2; IR (CH₃Cl): λmax 3420, 2917, 2851, 1474 (cm⁻¹); HRMS (FAB) calcd for C₁₆H₃₈O₂N (M + H⁺) 300.2903, found 300.2923.

(2R,3S,4S)-4-amino-2-tetradecyltetrahydrofuran-3-ol (2).

To a solution of 4 (20 mg, 0.06 mmol) in EtOH (1 mL) was added an aqueous KOH solution (1.0 M in H₂O, 1 mL) at room temperature. The reaction mixture was refluxed for 12 h and cooled to room temperature, then evaporated and dried with MeOH (5 mL x 3) and toluene (5 mL x 3) in azeotrope. Purification of the residue by flash column chromatography on silica gel, using CH₂Cl₂/MeOH/NH₄OH (100:10:1) as eluent, provided 2 as a white solid (13.3 mg, 72%). [α]²⁴D +38.4 (c 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 0.86 (t, J = 6.8 Hz, 3H), 1.15–1.34 (m, 22H), 1.35–1.47 (m, 2H), 1.48–1.62 (m, 2H), 3.35–3.41 (m, 1H), 3.41–3.50 (m, 1H), 3.55–3.62 (m, 2H), 4.11 (J = 6.4, 8.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 14.1, 22.7, 25.9, 29.4, 29.56, 29.59, 29.66, 29.67, 31.9, 33.7, 52.6, 73.2, 74.8, 77.2, 85.2, 85.2; IR (CHCl₃): λmax 3336, 3277, 3096, 2952, 2916, 2849, 1739, 1596, 1469, 1370 (cm⁻¹); HRMS (FAB) calcd for
C_{19}H_{36}NO_{3} 300.2824 ([M+H]^+), found 300.2892.
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\section*{Contents}

\begin{itemize}
\item[$^{1}$H NMR and $^{13}$C NMR spectra of compound 11 S2-S3
\item[$^{1}$H NMR and $^{13}$C NMR spectra of compound 12 S4-S5
\item[$^{1}$H NMR and $^{13}$C NMR spectra of compound 3 S6-S7
\item[$^{1}$H NMR and $^{13}$C NMR spectra of compound 4 S8-S9
\item[$^{1}$H NMR and $^{13}$C NMR spectra of compound 1 S10-S11
\item[$^{1}$H NMR and $^{13}$C NMR spectra of compound 2 S12-S13
\end{itemize}
(+)-2-epi-Pachastrissamine (2)