

An efficient asymmetric synthesis of Enigmols (1-deoxy-5-hydroxysphingoid bases), an important class of bioactive lipid modulators

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Abstract

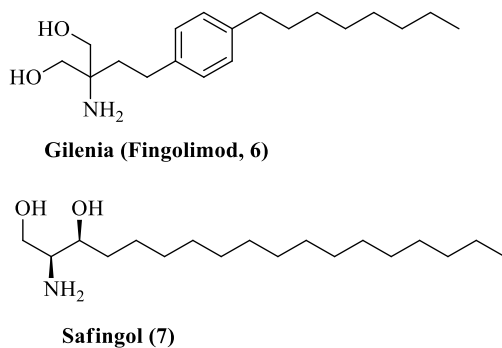
An enantioselective synthesis of the four 2*S*-diastereomers of enigmol (2-amino-octadecane-3,5-diols) from *L*-alanine is reported. The procedure described is robust, highly stereoselective at each step, and suitable for preparation of gram quantities of material.

Keywords: Enigmols, sphingolipids, boron enolates, aldol reaction, 1-deoxysphingoid bases

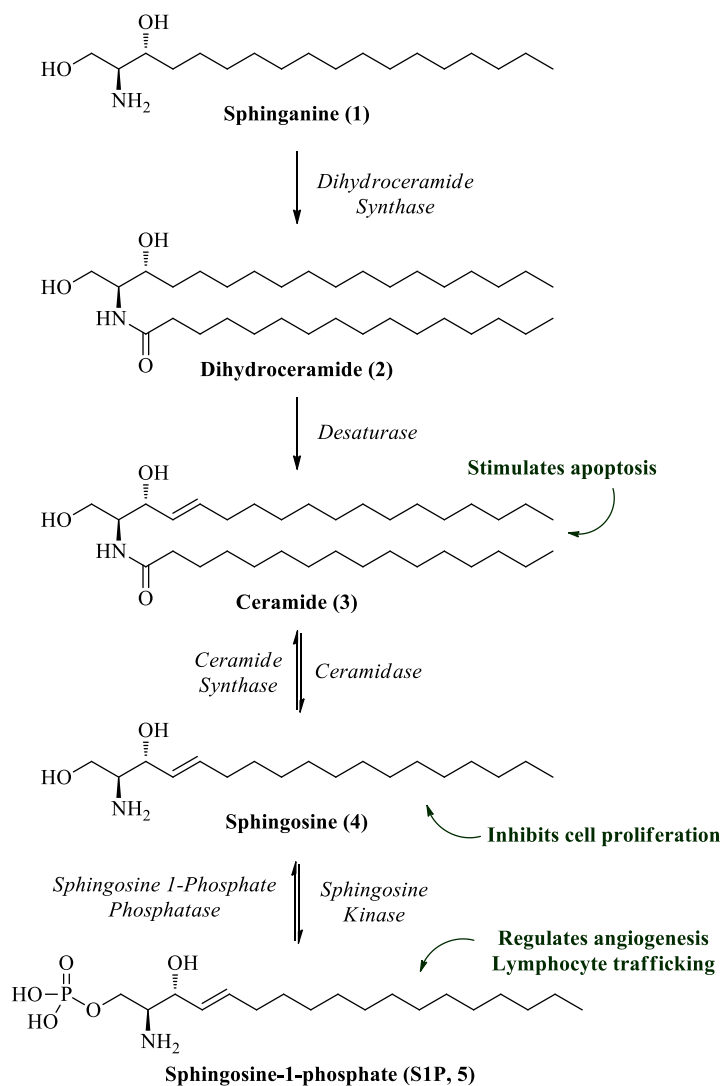
Introduction

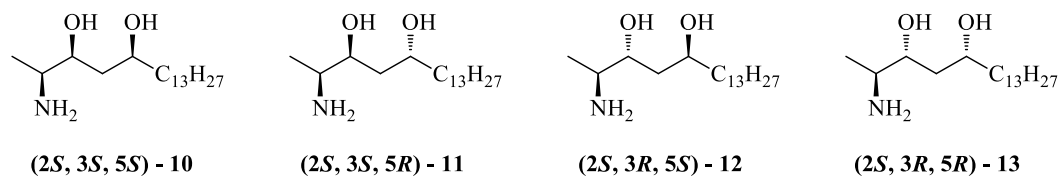
Sphingolipids (ceramides, sphingomyelins, cerebrosides, gangliosides, *etc.*) are a structurally diverse class of complex membrane lipids, composed of long-chain 2-amino-1,3-diols (sphingoid bases), amide-linked fatty acids, and numerous phosphoric acid and carbohydrate polar head groups, connected to the primary hydroxyl. Studies performed over the past two decades have shown that the low molecular weight sphingolipid metabolites (ceramide **3**, sphingosine **4**, sphingosine 1-phosphate (S1P, **5**)) are involved in many critical signaling pathways that regulate, *inter alia*, cell growth, cell differentiation and apoptosis.¹ Furthermore, sphingolipids function as modulators for growth factor receptors and as second messengers for a growing list of agonists.^{1,2}

Sphingolipid modulators are now emerging as potential therapeutics, and the first candidates targeting S1P signaling have just begun to come on to the market. For example, the Novartis-developed drug candidate Gilenia (previously Fingolimod) **6** just received FDA approval. This compound is a potent S1P antagonist and has shown to be beneficial to patients having relapsing multiple sclerosis in clinical studies. Similarly, safinol **7**, an unnatural sphinganine diastereomer and potent sphingosine kinase inhibitor, has been shown to provide some benefit in breast cancer patients when used topically.⁵

**Figure 1**

During the early stages of our own sphingolipid modulator program, we were intrigued by the apparent bifurcation in the biological functions of the sphingolipid biosynthesis products shown in Scheme 1.

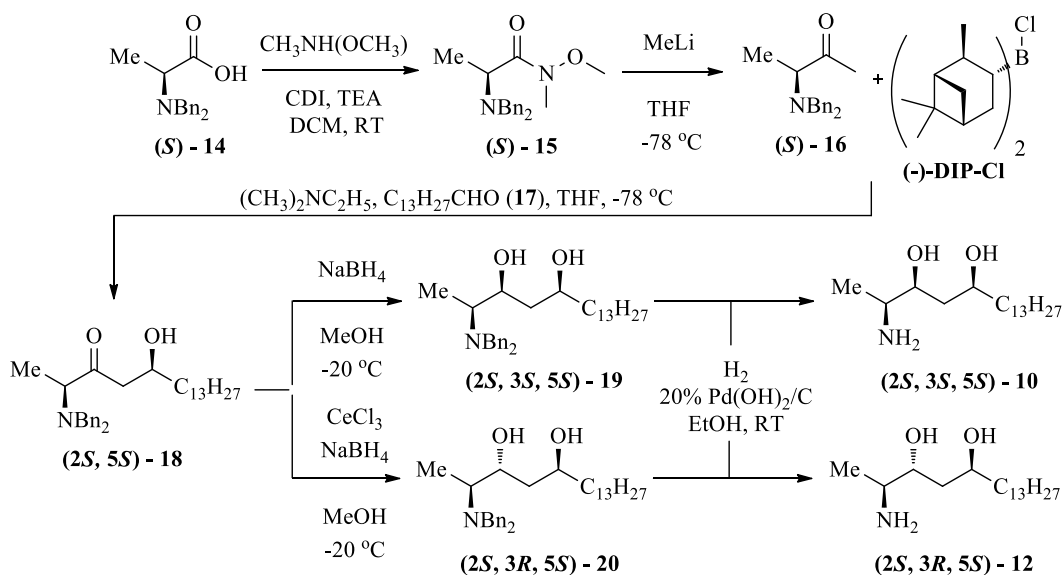
**Scheme 1**

**Figure 3**

In the early 1990's, we performed the first total synthesis of the four *2S*-enigmol diastereomers **10-13** as simplified structural analogs of Fumonisin B₁, starting from *L*-alanine.⁹ While this route served its purpose, a more efficient synthesis was required to prepare larger quantities of each compound. Herein, we describe a scalable synthesis of *2S,3S,5S*-enigmol **10** and its C-3 and C-5 diastereomers **11-13**. The synthesis is centered around a highly diastereoselective boron-mediated aldol reaction, which is a modification of a methodology developed in our lab, between (*S*)-3-(dibenzylamino)butan-2-one **16** (derived from *L*-alanine) and tetradecanal **17**.¹⁰ Interest in this series of compounds is evident by recent publications describing the synthesis of 1-deoxy-5-hydroxy sphingoid bases.¹¹

Results and Discussion

The synthesis of the enigmols drew from the chiral pool, starting from *L*-alanine. Conversion into (*S*)-3-(*N,N*-dibenzyl)-alanine **14** was accomplished following literature procedures.¹² Further manipulation of **14** to obtain the methyl ketone (*S*)-3-(dibenzylamino)butan-2-one **16** was achieved in two steps *via* the intermediate Weinreb amide in nearly quantitative yield, a significant improvement over direct conversion of the carboxylic acid.^{10b}

**Scheme 2**

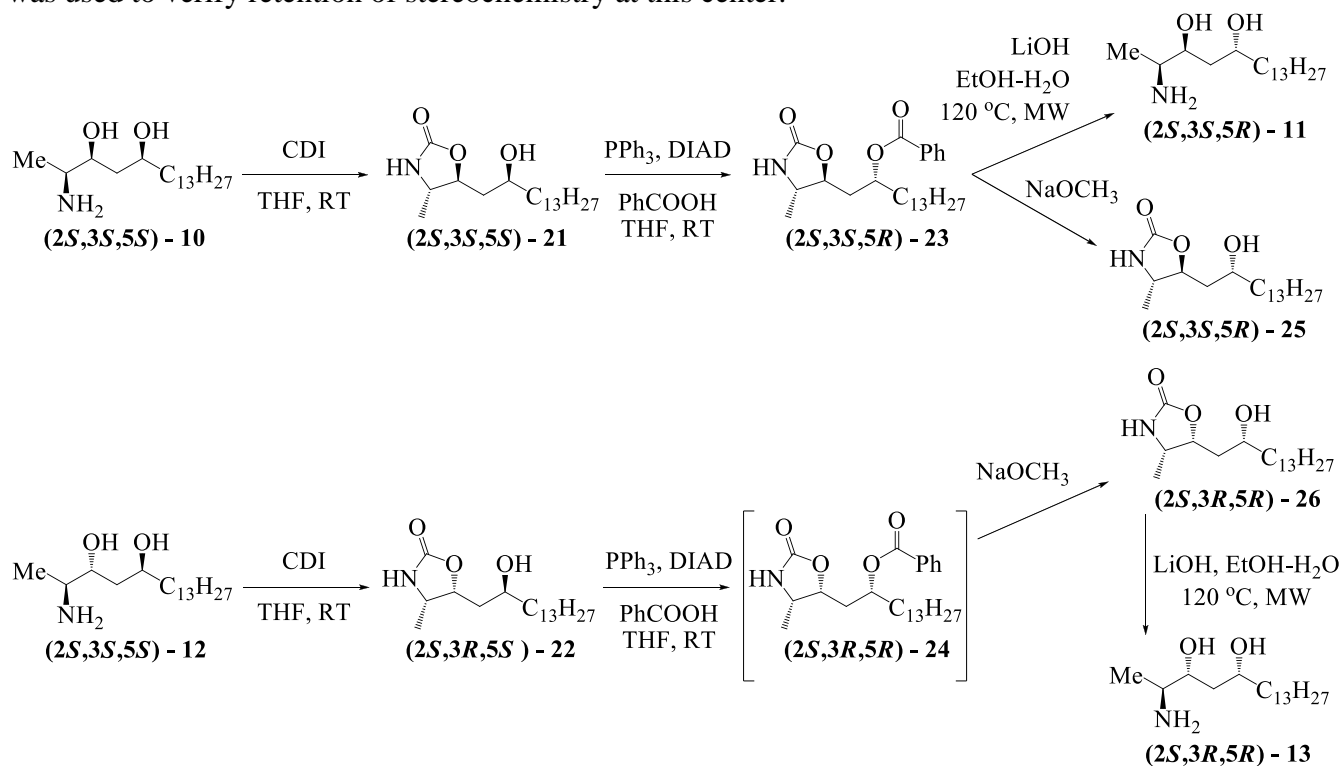
The aldol reaction of ketone **16** with tetradecanal **17** in the presence of (-)-diisopinocampheyl chloroborane ((-)-DIP-Cl) provided the corresponding (2*S*,5*S*)-keto derivative **18** exclusively. The extremely high diastereoselectivity (the 5*R* product is not observed) of this aldol reaction is driven by the bulky *N,N*-dibenzyl substituent at C-2, a somewhat counterintuitive finding when using a chiral boron reagent. However, the same stereochemistry (5*S*) was observed independent of boron-ligand chirality. Reduction of ketone **18** with sodium borohydride proceeded smoothly to give (2*S*,3*S*,5*S*)-aminodiol **19** without the observed formation of other products. To gain access to the inverse reduction product, Luche conditions were used, producing a 4:1 mixture of the anti **20** to syn **19** 1,3-diol, which could be easily separated by flash chromatography. The enigmols **10** and **12** were then obtained from **19** and **20** following standard hydrogenolysis conditions with Pearlman's catalyst under 1 atmosphere of hydrogen.

In the early stages of development, the aldol chemistry between methyl ketone **16** and tetradecanal **17**^{10b} proved to be quite versatile for small-scale synthesis. However, when we attempted to utilize this approach on a gram scale, we observed partial- to total- loss of optical activity. The degree to which optical activity was reduced was substrate- and batch- dependent. After careful investigation it became apparent that the methyl ketone **16** and the 3-keto-derivative **18** are prone to racemization at C-2 under chromatographic conditions (on silica or neutral alumina). This conclusion was reinforced by the observation that initial fractions of methyl ketone **16** on silica gel produced a clear oil that had a greater specific rotation than later fractions, which had no optical rotation and became solid after drying. The epimerization of compound **18** occurred more slowly on silica than **16**, and this process could be further retarded by neutralizing the silica with 1% triethylamine. To circumvent this problem, we developed a synthetic route to the methyl ketone **16** through the Weinreb amide **15**, which obviated the need for purification and therefore racemization, before using **16** in the aldol reaction. Also, reduction of **18** was performed immediately after simple work-up, also avoiding racemization. The methyl ketone **16** can be stored at -20 °C without racemization for several months. Chiral chromatography was used to verify that enantiopure methyl ketone **16** yielded only one enantiomer of *N,N*-dibenzyl-enigmol **19** after two consecutive steps without isolation of the intermediate compound **18** (>99.8% *ee*, HPLC).

Access to the remaining two 5*R*- diastereomers was accomplished by performing a Mitsunobu inversion at that center. First, the free base **10** was regioselectively converted to oxazolidinone **21** with carbonyldiimidazole, tying up the C-2 and C-3 functionality. Next, the hydroxyl group at C-5 was inverted using standard conditions. Finally, microwave irradiation with lithium hydroxide at 120 °C for 1.5 hours gave the corresponding (2*S*,3*S*,5*R*)-amino-diol **11**.¹³ Similar reaction conditions were used to convert **12** into **13**.

To confirm the absolute stereochemistry of the enigmol diastereomers, two methods were utilized. First, the oxazolidinone intermediates **21**, **22**, **25**, and **26**¹⁴ were converted into their corresponding C-5 Mosher esters and analyzed by NMR spectroscopy¹⁵ to confirm stereochemistry before (*S*) and after (*R*) Mitsunobu inversion.¹⁶ Next, the relative stereochemistry of the C-3/C-5 1,3-diols was confirmed using Rychnovsky's acetonide methodology with ¹³C-

NMR analysis.¹⁷ The *syn*- (2*S*,3*S*,5*S*)- acetonide showed resonances at 98.4, 30.6, and 19.7 ppm, and the *anti*- (2*S*,3*R*,5*S*)-acetonide showed resonances at 100.3, 24.9, and 24.8 ppm. Finally, the (*S*)- stereochemistry at C-2 was derived from the starting material *L*-alanine, and chiral HPLC was used to verify retention of stereochemistry at this center.



Scheme 3

Conclusions

Using the synthetic methodology described above, we have successfully prepared all four 2*S*-enigmol diastereomers. Although others have attempted to synthesize the enigmol amino-diol headgroup *via* a boron-mediated aldol reaction,^{11d} this is the first example of a high yielding, completely diastereoselective application. In addition, we have successfully prepared (2*S*,3*S*,5*S*)- and (2*S*,3*R*,5*S*)-enigmols in gram quantities for biological evaluation, proving the scalability and reproducibility of our procedure.

Experimental Section

General. All reactions were run under inert atmosphere unless otherwise stated. All chemicals used were purchased from Sigma-Aldrich Chemical Co. and used without further purification, unless otherwise stated. All solvents termed “dry” were dried via a Glass Contour solvent

purification system (SG Water, USA LLC). All melting points were obtained on a 200W MelTemp apparatus and are uncorrected. ^1H NMR spectra were obtained on a 400 MHz Varian Spectrometer, referenced to residual solvent or to TMS. ^{13}C NMR spectra were taken on a 100 MHz Varian Spectrometer referenced to the solvent carbon signal. Elemental analyses were performed by Atlantic Microlab, Inc (Norcross, GA). Infrared absorption spectra were obtained on a Thermo Scientific Nicolet 370 FT-IR spectrophotometer via the Smart Orbit Attenuated Total Reflectance accessory. High-resolution mass spectrometry was performed by the Emory University Mass Spectrometry Center (Dr. Fred Strobel). Optical rotation was measured on a Perkin Elmer 341 Polarimeter. Merck Silica Gel 60 TLC plates were used to monitor the reactions. Chiral HPLC was performed on a Varian ProStar using a Chiral Technologies Inc ChiralPak® AD-H (0.46cm x 25cm) column, 1 mL/min with isocratic conditions of 90:10 hexanes to isopropanol. TLC plates were visualized with: UV, 4% aq. H_2SO_4 , Ninhydrin, or KMnO_4 . Flash column chromatography was done with a Teledyne ISCO CombiFlash Companion automated flash column system unless otherwise specified. Microwave reactions were performed in a Biotage Initiator microwave synthesizer.

(2S)-2-Dibenzylamino-propionic acid benzyl ester. Prepared as reported in the literature¹² in 68% yield. $[\alpha]_{\text{D}}^{24}$ -97.6 °(c 1.1, ethyl acetate); ^1H NMR (400 MHz, CDCl_3) δ 7.45 - 7.25 (m, 15 H), 5.28 (d, J = 12.5 Hz, 1 H), 5.20 (d, J = 12.5 Hz, 1 H), 3.89 (d, J = 14.1 Hz, 2 H), 3.69 (d, J = 14.1 Hz, 2 H), 3.62 (q, J = 7.0 Hz, 1 H), 1.40 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.7, 140.0 (2 C), 136.2, 128.7 (6 C), 128.4 (6 C), 127.0 (3 C), 66.2, 56.3, 54.5, 15.1. Lit. $[\alpha]_{\text{D}}^{20}$ -91.8 °(c 1, ethyl acetate).¹⁸

(2S)-2-Dibenzylamino-propionic acid (14). Prepared by the literature procedure¹² in 97% yield. $[\alpha]_{\text{D}}^{24}$ -50 °(c 5.3, MeOH); ^1H NMR (400 MHz, CDCl_3) δ 7.35 - 7.25 (m, 10 H), 3.92 (d, J = 13.4 Hz, 2 H), 3.71 (d, J = 13.4 Hz, 2 H), 3.58 (q, J = 7.0 Hz, 1 H), 1.40 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.9, 136.6, 129.3, 128.9, 128.3, 57.9, 54.6, 11.7; HRMS (ESI) m/z 270.14912 (theoretical for $\text{C}_{17}\text{H}_{19}\text{NO}_2+\text{H}$: 270.14886). Lit. $[\alpha]_{\text{D}}^{20}$ -44.9 °(c 2.0, MeOH).¹⁹

(2S)-2-Dibenzylamino-*N*-methoxy-*N*-methylpropanamide (15). Synthesized by the method reported in the literature.²⁰ 1,1'-Carbonyldiimidazole (12.33 g, 76.04 mmol) was added at 0 °C to a stirring solution of (2S)-2-dibenzylamino-propionic acid **14** (10.25 g, 38.06 mmol) in dry dichloromethane (DCM, 130 mL). After 50 minutes, a heterogeneous mixture of *N,O*-dimethylhydroxylamine hydrochloride (7.42 g, 76.1 mmol) and triethylamine (Et_3N , 10.6 mL, 76.1 mmol) in dry DCM (75 mL) was added, and the mixture was stirred at 0 °C for 1 hour, and then allowed to warm to room temperature overnight. The reaction mixture was taken into diethyl ether (Et_2O), washed with 1 M HCl, saturated sodium bicarbonate, brine, dried over magnesium sulfate, and concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2 , hexane: ethyl acetate) to yield a clear oil (12.7 g), which was recrystallized from hexane to give the desired compound as a colorless crystalline product (11.70 g, 98%). R_f = 0.48 (2:1 hexane: ethyl acetate); mp 59 – 60 °C; IR (ν_{max} , cm^{-1}): 3067, 3024, 2980, 2942, 2862, 2841, 2820, 1650, 1451, 1364, 1161, 1141, 1073, 993, 748, 731, 697, 645,

616; $[\alpha]_{\text{D}}^{24} = +19.8$ (c 2.1, CHCl_3); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.38 (d, $J = 7.3$ Hz, 4 H), 7.31 (t, $J = 7.4$ Hz, 4 H), 7.22 (d, $J = 7.3$ Hz, 2 H), 4.00 - 3.78 (m, 5 H), 3.3 - 3.1 (m, 6 H), 1.35 (d, $J = 7.0$ Hz, 3 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 175.5, 140.5, 128.7, 128.1, 126.8, 60.8, 54.5, 52.2, 31.8, 14.0; HRMS (ESI) m/z 313.19114 (theoretical for $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}_2 + \text{H}$: 313.19105); Anal. Calcd. for $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}_2$: C, 73.05; H, 7.74; N, 8.97. Found: C, 73.04; H, 7.66; N, 8.99. Lit. mp = 58 °C; $[\alpha]_{\text{D}}^{20} = +19.5$ (c 1.0, DCM).²¹

(S)-3-(Dibenzylamino)butan-2-one (16). Methylolithium (66.8 mL of 1.6 M in Et_2O , 107 mmol) was slowly added to a stirred solution of (S)-2-dibenzylamino-N-methoxy-N-methylpropanamide **15** (11.6 g, 37.3 mmol) in dry tetrahydrofuran (THF, 300 mL) at -78 °C over a period of 45 minutes. The resulting solution was stirred for another 30 minutes. The reaction was quenched with saturated ammonium chloride and extracted with Et_2O (3 L). The ether solution was then washed with water, brine, dried over magnesium sulfate, and concentrated *in vacuo* to yield the methyl ketone **16** as a pale yellow oil (9.89 g, 99%), which was used in the next step without additional purification. $R_f = 0.42$ (9:1 hexanes: ethyl acetate); mp = 43 – 44 °C; IR (ν_{max} , cm^{-1}): 3024, 2872, 2841, 2810, 1709, 1493, 1454, 1381, 1348, 1187, 1145, 1071, 1029, 968, 744, 729, 699, 594, 499, 460; $[\alpha]_{\text{D}}^{24} -55.4$ (c 3.2, CHCl_3); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.39 (d, $J = 7.2$ Hz, 4 H), 7.34 (t, $J = 8.0$ Hz, 4 H), 7.26 (t, $J = 6.8$ Hz, 2 H), 3.70 (d, $J = 13.6$ Hz, 2 H), 3.45 (d, $J = 13.6$ Hz, 2 H), 3.36 (q, $J = 6.8$ Hz, 1 H), 2.23 (s, 3 H), 1.16 (d, $J = 6.8$ Hz, 3 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 211.2, 139.5, 128.9, 128.6, 127.4, 63.1, 54.8 (2 C), 27.9, 7.2; HRMS (ESI) m/z 268.16985 (theoretical for $\text{C}_{18}\text{H}_{21}\text{NO} + \text{H}$: 268.16959); Anal. Calcd. for $\text{C}_{18}\text{H}_{21}\text{NO}$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.76; H, 7.93; N, 5.30%.

Tetradecanal (17). Pyridinium chlorochromate (37.7 g, 175 mmol) and Celite (37.7 g) were mixed in DCM (200 mL). To this mixture was added a solution of tetradecanol (25.0 g, 117 mmol) in DCM (165 mL) over a 90 minute period *via* addition funnel. Reaction mixture was stirred for 1 hour at which point all the starting material had been completely consumed. The mixture was passed through a silica plug and the product was eluted with DCM to give a clear colorless oil (22.6 g, 91%). Tetradecanal was stored at -20 °C. Before use, tetradecanal trimers were cracked by short path distillation under vacuum (0.2 mm Hg at 110 – 130 °C, matching reported literature values).²²

(2S,5S)-2-(Dibenzylamino)-5-hydroxyoctadecan-3-one (18). To a stirred solution of (-) DIP-Cl (50-65 wt.% in hexanes, 10.4 mL, 14.0 mmol) in dry THF (45 mL), was added dimethyl ethylamine (4.86 mL, 44.9 mmol) dropwise at room temperature. The reaction mixture was then cooled to -30 °C, and a solution of (S)-3-(dibenzylamino)butan-2-one **16** (3.00 g, 11.2 mmol) in dry THF (21 mL) was added dropwise over a 15 minute period at -30 °C. The resulting mixture was stirred for an additional 1.5 hours at -30 °C and then cooled to -78 °C. A solution of freshly distilled tetradecanal **17** (4.77 g, 22.4 mmol) in dry THF (31 mL) was then added dropwise over the next 2 hours. The mixture was kept at -78 °C overnight, at which point no starting material remained. The reaction mixture was quenched by the addition of a phosphate buffer (45 mL, pH = 7) over 3 minutes at -20 °C, and stirring was continued over the next hour while the reaction was allowed to warm to room temperature. The mixture was then cooled to -20 °C, and hydrogen

peroxide (30% solution in water, 0.9 mL, 9 mmol) was added dropwise to the stirred mixture. After stirring for an additional hour, the reaction mixture was diluted with Et₂O (1.5 L), washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* (theoretical yield = 5.38 g, crude mass = 14.3 g). This compound was immediately used in next step without further purification or analysis. $R_f = 0.59$ (4:1 hexanes: ethyl acetate); $[\alpha]_D^{24} = -36.9$ (c 2.7, CHCl₃), -55.9 (c 2.7, MeOH);²³ HRMS (ESI) m/z 480.38360 (theoretical for C₃₂H₄₉NO₂+H: 480.38492).

(2S,3S,5S)-2-(Dibenzylamino)octadecane-3,5-diol (19). To a stirred solution of crude 3-keto-derivative **18** (theoretically 5.38 g, 11.2 mmol) in methanol (70 ml) at -20 °C was added granulated sodium borohydride (770 mg, 18.8 mmol) in 3 portions, and the resulting mixture was stirred for 1 hour at -20 °C, then allowed to warm to 0 °C. The reaction mixture was then quenched by the dropwise addition of glacial acetic acid (4 ml, 59 mmol), concentrated under vacuum, and the resulting residue was diluted with Et₂O, washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate and concentrated under vacuum to give the crude product as an oil (11.0 g). The crude reaction mixture was subjected to sublimation at 0.2 mm Hg at 50 °C for 24 hours to remove pinene byproducts derived from DIP-Cl, and the remaining oil (8.4 g) was purified by flash chromatography (SiO₂, hexanes: ethyl acetate, both containing 2% triethylamine) to yield dibenzylaminodiol **19** as a waxy solid (4.62 g, 86%). $R_f = 0.54$ (4:1 hexanes: ethyl acetate); IR (ν_{max} , cm⁻¹): 3400, 3030, 2921, 2851, 1453, 1378, 1301, 1142, 1301, 1097, 1058, 1028, 841, 745, 731, 697; $[\alpha]_D^{24} = +32.4$ (c 1.5, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.35 - 7.21 (m, 10 H), 4.73 (bs, 1 H), 4.01 (bs, 1 H), 3.80 (m, 1 H), 3.79 (d, $J = 13.3$ Hz, 2 H), 3.63 (dt, $J = 7.9, 2.5$ Hz, 1 H), 3.28 (d, $J = 13.0$ Hz, 2 H), 2.53 (m, 1 H), 1.81 (d, $J = 14.0$ Hz, 1 H), 1.68 (m, 1 H), 1.5 - 1.2 (m, 24 H), 1.2 - 1.0 (m, 2 H), 0.99 (d, $J = 6.7$ Hz, 3 H), 0.90 (t, $J = 7.0$ Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 140.1, 129.1, 128.5, 127.2, 71.3, 70.0, 57.1, 54.8, 39.3, 37.8, 32.1, 29.9 (2 C), 29.6 (6 C), 26.0, 22.9, 14.3, 8.7; HRMS (ESI) m/z 482.39942 (theoretical for C₃₂H₅₁NO₂+H: 482.39926); Anal. Calcd. for C₃₂H₅₁NO₂: C, 79.78; H, 10.67; N, 2.91. Found: C 79.70; H 10.70; N 2.91%.

(2S,3R,5S)-2-(Dibenzylamino)octadecane-3,5-diol (20). To a stirred solution of crude 3-keto derivative **18** (theoretically 5.38 g, 11.2 mmol) in MeOH (225 mL) at -20 °C was added cerium (III) chloride heptahydrate (8.46 g, 22.7 mmol). The mixture was stirred for 20 minutes at -20 °C, followed by addition of granulated sodium borohydride (850 mg, 22.5 mmol) in 9 portions of ~100 mg each with continued stirring until no starting material remained. The resulting mixture was quenched by the dropwise addition of glacial acetic acid (~2 mL), and the resulting mixture was concentrated *in vacuo*, diluted with Et₂O, and neutralized with saturated sodium bicarbonate. The solids were then filtered off, and the organic layer was isolated and washed with water, brine, dried over magnesium sulfate, and concentrated under vacuum to give the crude product as an oil (12.4 g). After this material was subjected to sublimation at 0.2 mm Hg at 50 °C for 24 hours to remove pinene byproducts derived from DIP-Cl, the remaining oil (7.5 g) was purified by flash chromatography (SiO₂, hexanes: ethyl acetate, both containing 2% triethylamine) to yield **20** as a waxy colorless solid (3.60 g, 67%). Compound **19** was also isolated as a waxy colorless solid (761 mg, 11%). $R_f = 0.27$ (4:1 hexanes: ethyl acetate); IR (ν_{max} , cm⁻¹): 3317, 2918, 2849, 1493,

1469, 1452, 1367, 1110, 1064, 1027, 996, 728, 696; $[\alpha]_D^{24} = +20.5$ (c 2.2, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.35 - 7.21 (m, 10 H), 3.89 (dt, *J* = 7.9, 2.5 Hz, 1 H), 3.74 (d, *J* = 13.3 Hz, 2 H), 3.61 (m, 1 H), 3.41 (d, *J* = 14.6 Hz, 2 H), 3.10 (bs, 1 H), 2.73 (m, 1 H), 2.32 (bs, 1 H), 1.77 (m, 1 H), 1.63 (m, 1 H), 1.5 - 1.2 (m, 23 H), 1.13 (d, *J* = 6.7 Hz, 3 H), 0.87 (t, *J* = 7.0 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 140.1, 129.1, 128.5, 127.2, 71.3, 70.0, 57.1, 54.8 (2 C), 39.3, 37.8, 32.1, 29.9 (2 C), 29.6 (6 C), 26.0, 22.9, 14.3, 8.7; HRMS (ESI) *m/z* 482.39942 (theoretical for C₃₂H₅₁NO₂+H: 482.39926); Anal. Calcd. for C₃₂H₅₁NO₂: C, 79.78; H, 10.67; N, 2.91. Found: C 79.97; H 11.16; N 2.69%.

(2*S*,3*S*,5*S*)-2-Aminooctadecane-3,5-diol (10). *N,N*-Dibenzyl-*S,S,S*-enigmol **19** (299 mg, 620 μmol) and Pearlman's catalyst (wet, 160 mg, 0.23 mmol) were taken up in ethanol (190 proof, 250 mL). The heterogeneous solution was then evacuated and purged with hydrogen gas (1 atm.). The resulting mixture was stirred vigorously for 3.5 hours at which point no starting material remained, and the mixture was filtered over Celite. The solvent was then evaporated under reduced pressure, and the white powdery solid obtained was washed with hexanes to remove any impurities (163 mg, 87%). *R_f* = 0.40 (45:10:1 CHCl₃:MeOH:ammonium hydroxide (aq. 25%)), and 0.49 (20:5:2:1 CHCl₃:MeOH:acetic acid:water); mp = 64 – 65 °C; IR (*v*_{max}, cm⁻¹): 3402, 3328, 2917, 2847, 1596, 1463, 1325, 1170, 1142, 1120, 1075, 1020, 984, 919, 845, 818, 721, 607; $[\alpha]_D^{24} = +3.3$ (c 1.6, CHCl₃), -10.6 (c 1.6, MeOH); ¹H NMR (400 MHz, CD₃OD) δ 3.86 (m, 1 H), 3.46 (m, 1 H), 2.75 (quintet, *J* = 6.1 Hz, 1 H), 1.64 (dt, *J* = 14.3, 2.4 Hz, 1 H), 1.55 - 1.35 (m, 5 H), 1.35 - 1.20 (m, 22 H), 1.08 (d, *J* = 6.7 Hz, 3 H), 0.88 (t, *J* = 7.0 Hz, 3 H); ¹³C NMR (100 MHz, CD₃OD) δ 72.2 (2 C), 51.8, 40.5, 38.2, 32.1, 29.9 (7 C), 29.7, 25.7, 22.9, 21.1, 14.3; HRMS (ESI) *m/z* 302.30550 (theoretical for C₁₈H₃₉NO₂+H: 302.30590); Anal. Calcd. for C₁₈H₃₉NO₂: C, 71.70; H, 13.01; N, 4.65. Found: C 71.76; H 13.26; N 4.64%.

(2*S*,3*R*,5*S*)-2-Aminooctadecane-3,5-diol (12). *N,N*-Dibenzyl-*S,R,S*-enigmol **20** (2.69 g, 5.58 mmol) and Pearlman's catalyst (wet, 1.44 g, 2.05 mmol) were taken up in ethanol (190 proof, 250 mL). The heterogeneous solution was then evacuated and purged with hydrogen gas (1 atm.). The resulting mixture was stirred vigorously for 3.5 hours at which point no starting material remained, and the mixture was filtered over Celite. The solvent was then evaporated *in vacuo*, and the crude product was purified by flash chromatography (SiO₂, 84:15:1 DCM: MeOH: ammonium hydroxide (aq. 25%)) to yield **12** as a white powder (1.57 g, 93%). *R_f* = 0.20 (84:15:1 DCM: MeOH: ammonium hydroxide (aq. 25%)), and 0.46 (20:5:2:1 CHCl₃:MeOH:acetic acid: water); mp = 86 – 92 °C; IR (*v*_{max}, cm⁻¹): 3331, 2916, 2849, 1581, 1555, 1469, 1403, 1389, 1302, 1045, 1021, 718, 674; $[\alpha]_D^{24} = +17.7$ (c 0.85, MeOH); ¹H NMR (400 MHz, CD₃OD) δ 3.80 - 3.70 (m, 2 H), 2.83 (m, 1 H), 1.51 - 1.35 (m, 6 H), 1.26 (m, 22 H), 1.05 (d, *J* = 6.7 Hz, 3 H), 0.87 (t, *J* = 7.0 Hz, 3 H); ¹³C NMR (100 MHz, CD₃OD) δ 72.9, 69.4, 52.9, 41.2, 39.5, 33.2, 31.0 (7 C), 30.7, 27.0, 23.9, 17.2, 14.6; HRMS (ESI) *m/z* 302.30551 (theoretical for C₁₈H₃₉NO₂+H: 302.30590); Anal. Calcd. for C₁₈H₃₉NO₂ + 0.75•H₂O: C, 68.63; H, 12.96; N, 4.45. Found: C 68.74; H 12.50; N 4.28%.

(4*S*,5*S*)-5-((*S*)-2-Hydroxypentadecyl)-4-methyloxazolidin-2-one (21). To a stirred solution of (*2S*,3*S*,5*S*)-enigmol **10** (167 mg, 554 μmol) in dry THF (15 mL) was added a solution of 1,1'-

carbonyldiimidazole (121 mg, 401 μmol) in dry THF (2 mL), dropwise, at 0 °C. After addition was complete, the reaction was allowed to warm to ambient temperature over 3.5 hours. The reaction mixture was quenched by addition of MeOH and the solvents were evaporated under reduced pressure. The crude material was purified by flash chromatography (SiO_2 , hexanes: ethyl acetate) to give a white solid (156 mg, 86%). $R_f = 0.48$ (9:1:1, CHCl_3 :MeOH:acetone); mp = 87 – 88 °C; IR (ν_{max} , cm^{-1}): 3224, 2918, 2849, 1720, 1469, 1428, 1388, 1330, 1072, 1030, 960, 719; $[\alpha]_{\text{D}}^{24} = -31.8$ ° (c 1.5, MeOH); ^1H NMR (400 MHz, CDCl_3) δ 4.31 (m, 1 H), 3.83 (m, 1 H), 3.68 (m, 1 H), 2.10 (m, 1 H), 1.89 (m, 1 H), 1.80 (m, 1 H), 1.55 - 1.40 (m, 3H), 1.26 (m, 23 H), 0.89 (t, $J = 7.0$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.1, 82.9, 69.3, 54.0, 41.2, 37.3, 32.1, 29.9 (4 C), 29.8 (3 C), 29.6, 25.7, 22.9, 20.5, 14.3; HRMS (ESI) m/z 328.28480 (theoretical for $\text{C}_{19}\text{H}_{37}\text{NO}_3 + \text{H}$: 328.28519); Anal. Calcd. for $\text{C}_{19}\text{H}_{37}\text{NO}_3 \cdot 0.25 \text{H}_2\text{O}$: C, 68.73; H, 11.38; N, 4.22. Found: C 68.95; H 11.41; N 4.21%.

(R)-1-((4S,5S)-4-Methyl-2-oxazolidin-5-yl)pentadecan-2-yl benzoate (23). This compound was synthesized by the method reported in literature.²⁴ To a solution of oxazolidinone **21** (610 mg, 1.86 mmol) in dry THF (10 mL) was added triphenylphosphine (1.46 g, 5.55 mmol) and benzoic acid (1.12 g, 9.16 mmol) at 0 °C. The resultant mixture was allowed to stir at 0 °C for 15 minutes, to which diisopropyl azodicarboxylate (1.90 mL, 9.16 mmol) was added. After 1 hour at 0 °C, the mixture was then diluted with Et_2O , washed with the aqueous saturated sodium bicarbonate, brine, dried over magnesium sulfate, and concentrated *in vacuo* to give the crude product (4.9 g). The resulting material was taken into hexanes and filtered, then concentrated and purified by flash chromatography (SiO_2 , hexanes: ethyl acetate) to yield **23** as an off-white powder (736 mg, 92%). $R_f = 0.40$ (1:1 hexanes: ethyl acetate); mp = 61 – 62 °C; IR (ν_{max} , cm^{-1}): 3276, 2919, 2850, 1731, 1712, 1273, 1229, 1109, 1069, 1023, 707, 673; $[\alpha]_{\text{D}}^{24} = -42.4$ ° (c 1.1, CHCl_3), -45.4 ° (c 1.1, MeOH); ^1H NMR (400 MHz, CDCl_3) δ 8.04 (m, 2 H); 7.58 (m, 1 H); 7.46 (m, 2 H); 5.37 (bs, 1 H), 5.30 (m, 1 H), 4.24 (m, 1 H), 3.62 (m, 1 H), 2.06 (m, 2 H), 1.75 (m, 2 H), 1.4 - 1.2 (m, 25 H), 0.88 (t, $J = 7.0$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.2, 159.2, 133.2, 130.4, 129.7, 128.6, 81.3, 72.1, 54.1, 39.3, 32.1, 29.8 (4 C), 29.7 (4 C), 29.5, 25.3, 22.9, 20.5, 14.3; HRMS (ESI) m/z 432.30999 (theoretical for $\text{C}_{26}\text{H}_{41}\text{NO}_4 + \text{H}$: 432.10830).

(4S,5S)-5-((R)-2-Hydroxypentadecyl)-4-methyloxazolidin-2-one (25). To a solution of oxizolidinone-benzoate **23** (112 mg, 260 μmol) in MeOH (5 mL) was added sodium methoxide (1 mL, 30% solution in MeOH) and the resulting mixture was stirred for 3 hours at room temperature, neutralized with glacial acetic acid, and concentrated *in vacuo*. The resulting residue was dissolved in Et_2O , washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate, and concentrated under vacuum. The remaining residue was washed with hexanes to yield **25** as a white powder (70 mg, 82%). $R_f = 0.48$ (9:1:1, CHCl_3 :MeOH:acetone); mp = 112 – 114 °C; IR (ν_{max} , cm^{-1}): 3298, 3123, 2921, 2850, 1717, 1467, 1407, 1250, 1068, 1012, 912, 773, 728, 693, 647; $[\alpha]_{\text{D}}^{24} = -42.5$ ° (c 1.0, CHCl_3) and -50.2 ° (c 1.0, MeOH); ^1H NMR (400 MHz, CDCl_3) δ 4.41 (m, 1 H), 3.90 (m, 1 H), 3.60 (m, 1 H), 1.82 (m, 1 H), 1.65 (m, 1 H), 1.55 - 1.40 (m, 3H), 1.26 (m, 24 H), 0.88 (t, $J = 7.0$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.4, 81.6, 68.0, 54.2, 41.7, 38.3, 32.1, 29.9 (4 C), 29.8 (2 C), 29.7, 29.6, 25.7, 22.9, 20.3, 14.3;

HRMS (ESI) m/z 328.28438. (theoretical for $C_{19}H_{37}NO_3+H$: 328.28462). Anal. Calcd. for $C_{19}H_{37}NO_3 + 0.50 \cdot H_2O$: C, 67.81; H, 11.38; N, 4.16. Found: C 67.77; H 10.95; N 4.02%.

(2S,3S,5R)-2-Amino-octadecane-3,5-diol (11). The benzoate ester **23** (624 mg, 1.45 mmol) and lithium hydroxide monohydrate (380 mg, 9.01 mmol) were dissolved in a mixture of ethanol and water (10:1, 30 mL), and the mixture was subject to microwave irradiation at 120 °C for 1.5 hours (~3 bar). The reaction mixture was allowed to cool to room temperature, concentrated under vacuum and diluted with Et_2O . The organic phase was washed with water, brine, dried over magnesium sulfate, and concentrated under vacuum. The crude product was then purified by flash chromatography (SiO_2 , $CHCl_3$: MeOH: ammonium hydroxide (aq., 25%), 100:10:1) to afford **11** as a white powder (202 mg, 46%). R_f = 0.30 (45:10:1 $CHCl_3$:MeOH:ammonium hydroxide (aq. 25%)), and 0.48 (20:5:2:1 $CHCl_3$:MeOH:acetic acid: water); mp = 63 – 68 °C; IR (ν_{max} , cm^{-1}): 3367, 3289, 2917, 2849, 1675, 1467, 1378, 1202, 1135, 1068, 1018, 992, 841, 800, 721; $[\alpha]_D^{24}$ = -12.9 (c 2.0, MeOH), -4.83 (c 2.9, $CHCl_3$); 1H NMR (500 MHz, CD_3OD , 60 °C) δ 3.80 (m, 1 H), 3.72 (dt, J = 6.8, 1.6 Hz, 1 H), 3.10 (quintet, J = 6.8 Hz, 1 H), 1.54 (m, 2 H), 1.45 (m, 2 H), 1.28 (m, 22 H), 1.26 (d, J = 5.0 Hz, 3 H), 0.89 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (75.5 MHz, d_6 -DMSO) δ 72.3, 67.7, 51.4, 40.5, 37.9, 31.6, 29.4 (7 C), 29.0, 25.4, 22.3, 17.5, 13.0; HRMS (ESI) m/z 302.30515 (theoretical for $C_{18}H_{39}NO_2+H$: 302.30590).

(4S,5R)-5-((S)-2-Hydroxypentadecyl)-4-methyloxazolidin-2-one (22). To a stirred solution of (2S,3R,5S)-enigmol **12** (263 mg, 872 μ mol) in THF (40 mL) was added a solution of 1,1'-carbonyldiimidazole (1.15 g, 3.81 mol) in dry THF (20 mL), dropwise, at 0 °C. After addition was complete, the reaction was allowed to warm to ambient temperature and the mixture was stirred for 16 hours. The reaction mixture was quenched by addition of MeOH and 1N HCl (2 mL). The solution was diluted with Et_2O , washed with the aqueous saturated sodium bicarbonate, brine, dried over magnesium sulfate, and concentrated *in vacuo* to give the crude product. The material was washed with hexanes to afford the product as a white solid (177 mg, 55%). R_f = 0.43 (9:1:1, $CHCl_3$:MeOH:acetone); mp = 99 – 101 °C; IR (ν_{max} , cm^{-1}): 3345, 3234, 2954, 2919, 2848, 1734, 1716, 1466, 1417, 1392, 1380, 1235, 1101, 1067, 1055, 987, 961, 946, 746, 724, 665, 617, 572; $[\alpha]_D^{24}$ = +34.0 (c 1.8, MeOH), +29.0 (c 1.7, $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) δ 4.93 (ddd, J = 10.7, 7.6, 2.4 Hz, 1 H), 3.96 (m, 1 H), 3.94 (m, 1 H), 2.15 (d, J = 4.0 Hz, 1 H), 1.82 (m, 1 H), 1.50 (m, 4 H), 1.24 (m, 20 H), 1.18 (d, J = 6.7 Hz, 3 H), 0.86 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 76.9, 68.2, 51.2, 38.4, 36.7, 32.1, 29.9 (4 C), 29.8 (3 C), 29.6, 25.7, 22.9, 16.4, 14.3; HRMS (ESI) m/z 328.28497 (theoretical for $C_{19}H_{37}NO_3+H$: 328.28462). Anal. Calcd. for $C_{19}H_{37}NO_3$: C, 69.68; H, 11.39; N, 4.28. Found: C 69.48; H 11.50; N 4.24%.

(4S,5R)-5-((R)-2-Hydroxypentadecyl)-4-methyloxazolidin-2-one (26). This compound was synthesized by the method reported in literature.²⁴ To a solution of the oxazolidinone **22** (192 mg, 568 μ mol) in dry THF (5 mL) was added triphenylphosphine (466 mg, 1.76 mmol) and benzoic acid (360 mg, 2.93 mmol) at 0 °C. The resulting mixture was allowed to stir at 0 °C for 15 minutes, to which diisopropyl azodicarboxylate (610 μ L, 2.93 mmol) was added. After 3.5 hour at 0 °C, the mixture was diluted with Et_2O , washed with the aqueous saturated sodium

bicarbonate, brine, dried over magnesium sulfate, and concentrated *in vacuo* to give the crude product (1.6 g). This material was taken up in hexanes and filtered. The filtrate was concentrated, and the material ((*R*)-1-((4*S*,5*R*)-4-methyl-2-oxazolidin-5-yl)pentadecan-2-yl benzoate) **24** was dissolved in MeOH (25 mL), to which sodium methoxide (3 mL, 30% solution in MeOH) was added. The mixture was allowed to stir for 3 hours at room temperature, neutralized with glacial acetic acid, and concentrated under vacuum. The resulting residue was then dissolved in Et₂O, washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate and concentrated *in vacuo*. Purification was achieved with flash chromatography (SiO₂, hexanes: ethyl acetate) to give an off- white powder (85 mg, 44%). *R*_f = 0.43 (9:1:1, CHCl₃:MeOH:acetone); mp = 74 – 75 °C; IR (*v*_{max}, cm⁻¹): 3564, 3266, 2916, 2849, 1746, 1707, 1472, 1419, 1386, 1349, 1259, 1246, 1229, 1073, 1052, 1043, 1022, 1012, 994, 946, 850, 718, 674, 568; [α]_D²⁴ = +8.7 °(c 0.6, CHCl₃), ¹H NMR (400 MHz, CDCl₃) δ 5.94 (s, 1 H), 4.78 (m, 1 H), 3.93 (m, 1 H), 3.82 (m, 1 H), 2.27 (bs, 1 H), 1.89 (m, 1 H), 1.72 (dt, *J* = 14.3, 3.4 Hz, 1 H), 1.55 - 1.40 (m, 3 H), 1.25 (m, 21 H), 1.17 (d, *J* = 6.4 Hz, 3 H), 0.88 (t, *J* = 7.0 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 159.7, 79.1, 70.1, 51.4, 37.4, 36.5, 32.1, 29.8 (7 C), 29.6, 25.7, 22.9, 16.4, 14.3; HRMS (ESI) *m/z* 328.28448 (theoretical for C₁₉H₃₇NO₃+H: 328.28462).

(2*S*,3*R*,5*R*)-2-Amino-octadecane-3,5-diol (13). The oxazolidinone **26** (80 mg, 244 μmol) and lithium hydroxide monohydrate (104 mg, 2.48 mmol) were dissolved in a mixture of ethanol and water (20:3, 15 mL), and the mixture was subject to microwave irradiation at 120 °C for 1.5 hours (~3 bar). The reaction mixture was allowed to cool to room temperature, concentrated *in vacuo* and diluted with Et₂O. The organic phase was washed with water, brine, dried over magnesium sulfate, and concentrated *in vacuo*. The crude product was then purified by flash chromatography (SiO₂, 100:10:1 CHCl₃: MeOH: ammonium hydroxide (aq., 25%)) to afford **13** as a white powder (33 mg, 45%). *R*_f = 0.35 (45:10:1 CHCl₃:MeOH:ammonium hydroxide (aq. 25%)), and 0.49 (20:5:2:1 CHCl₃:MeOH:acetic acid: water); mp = 80 – 82 °C; IR (CDCl₃ solution, *v*_{max}, cm⁻¹): 3450, 2890, 2820, 1690, 1470, 1370, 1325, 1200, 1085, 1060, 1030, 1010; [α]_D²⁴ = +9.3 °(c 1.7, MeOH), +4.1 °(c 1.7, CHCl₃); ¹H NMR (500 MHz, *d*₆-DMSO, 80 °C) δ 3.63 (m, 1 H), 3.40 (quintet, *J* = 4.1 Hz, 1 H), 3.07 (m, 4 H), 2.71 (ddd, *J* = 6.6, 4.6, 1.9 Hz, 1 H), 1.50 (dt, *J* = 14.0, 3.9 Hz, 1 H), 1.39 (dd, *J* = 14.0, 8.1 Hz, 1 H), 1.38 (m, 4 H), 1.26 (m, 20 H), 0.92 (d, *J* = 6.5 Hz, 3 H), 0.86 (t, *J* = 6.8 Hz, 3 H); ¹³C NMR (75.5 MHz, CDCl₃) δ 74.5, 71.7, 50.7, 38.3, 37.5, 31.9, 29.7, 29.5 (5 C), 29.4 (2 C), 25.6, 22.7, 16.8, 14.1; HRMS (ESI) *m/z* 302.30449 (theoretical for C₁₈H₃₉NO₂+H: 302.30590).

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14. (a) To simplify the discussion, we kept the numbering of carbon atoms in oxazolidinones the same as the parent enigmols. (b) While attempting to determine relative stereochemistry between C2 and C3 by NOE in the oxazolidinones (**21,22,25,26**), we observed that the exocyclic methyl group appeared as a doublet at ~1.18 ppm in the (2*S*,3*S*) trans-diastereomers (**21,25**). However, the corresponding resonance in the (2*S*,3*R*) cis-diastereomers (**22,26**) was obscured by the large alkyl chain signal at 1.26 ppm.
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23. Optical rotation reported here was obtained from purifying a small portion by chromatography (SiO₂, hexanes: ethyl acetate, both containing 2% triethylamine). The reported value is for initial fractions only as later fractions displayed lower values (due to slow racemization on the column). See Discussion for details.
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