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Asymmetric Synthesis of Sphinganine and Clavaminol H

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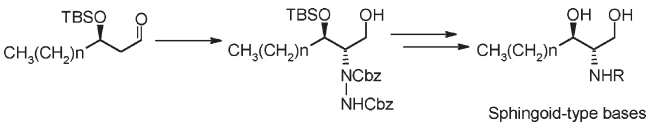


An efficient enantioselective synthesis of sphinganine and clavaminol H is reported. These sphingoid-type bases were obtained from commercially available fatty acids using highly enantioselective Ru-catalyzed hydrogenation and organocatalytic electrophilic amination reactions to create the stereogenic centers.

Sphingoid bases or related long-chain amino alcohols are common subunits present in a large class of biologically active natural products.[1] Among these sphingoids, sphinganine is known to be an important precursor in the biosynthesis of ceramides or sphingolipids (for example, sphingomyelin, cerebrosides, or gangliosides) which play important roles in cell regulation, cell growth modulation, and signal transmission.[2] Sphinganine itself found to be an inhibitor of protein kinase C.[3] As a consequence, several methods for the synthesis of sphinganine were reported in the literature.[4]

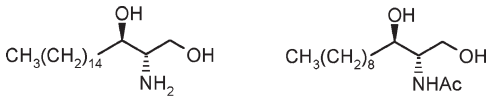
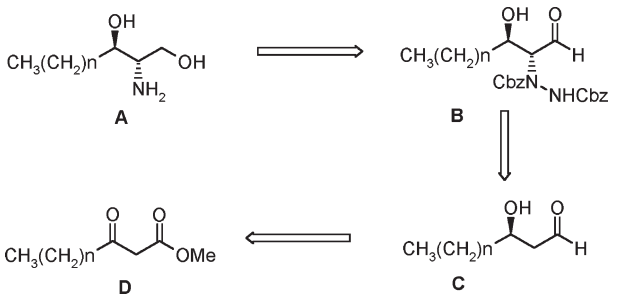


FIGURE 1. Structure of sphinganine and clavaminol H.

SCHEME 1. Proposed Retrosynthesis of Sphingoids



In 2007 and 2009, a new family of sphingoid-type bases, called clavaminols, have been extracted from the Mediterranean ascidian *Clavelina phlegraea*. Some of these news compounds possess cytotoxic properties against lung, breast, and gastric carcinoma cell lines by activating the apoptic machinery.[5]

Among these molecules, clavaminol H (Figure 1) presents a structure similar to sphinganine and differs only by the length of the alkyl chain. This product did not exhibit significant biological activity, but the corresponding hydrolysis has showed cytotoxic activities against gastric carcinoma cell lines.[5b] To our knowledge, only one synthesis of the hydrolysis product of clavaminol H was recently described in the literature.[4a]

In this paper, we report a general approach to the long-chain 2-amino 1,3-diol. In our ongoing program toward electrophilic amination,[6] we recently reported an efficient access to the enantioenriched 2-amino 1,3-diol moiety based on asymmetric α-amination of chiral β-hydroxy aldehydes catalyzed by proline.[7] We envisioned applying this strategy to the synthesis of two sphingoid-type bases, sphinganine and clavaminol H.

We proposed that 2-aminoalkane-1,3-diols **A** could be obtained from the intermediates **B**. *anti*-α-Hydrazino β-hydroxy aldehydes **B** could be synthesized stereoselectively by organocatalytic electrophilic amination of β-hydroxy esters **C**. Intermediates **C** could be prepared enantioselectively by Ru-catalyzed asymmetric hydrogenation of β-keto esters **D** followed by the reduction of the ester moiety (Scheme 1).

(1) Pruett, S. T.; Bushnev, A.; Hagedorn, K.; Adiga, M.; Haynes, C. A.; Sullards, M. C.; Liotta, D. C.; Merrill, H. M., Jr. *J. Lipids Res.* **2008**, *49*, 1621.

(2) (a) Hannun, Y. A.; Bell, R. M. *Science* **1989**, *243*, 500. (b) Kolter, T.; Sandhoff, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 1532. (c) Brodesser, S.; Sawatzki, P.; Kolter, T. *Eur. J. Org. Chem.* **2003**, 2021. (d) Liao, J.; Tao, J.; Lin, G.; Liu, D. *Tetrahedron* **2005**, *61*, 4715.

(3) Schwartz, G. K.; Jiang, J.; Kelsen, D.; Albino, A. P. *J. Nat. Cancer Inst.* **1993**, *85*, 402.

(4) For recent references on the synthesis of sphinganine derivatives, see: (a) Seguin, C.; Ferreira, F.; Botuha, B.; Chemla, F.; Perez-Luna, A. *J. Org. Chem.* **2009**, *74*, 6986. (b) Cai, Y.; Ling, C. C.; Bundle, D. R. *Org. Biomol. Chem.* **2006**, *4*, 1140. (c) Zhong, Y.-W.; Dong, Y.-Z.; Fang, K.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2005**, *127*, 11956. (d) Howell, A. R.; So, R. S.; Richardson, S. K. *Tetrahedron* **2004**, *60*, 11327. (e) Torssell, S.; Somfai, P. *J. Org. Chem.* **2005**, *70*, 10260. (f) Kokatla, H. P.; Sagar, R.; Vankar, Y. D. *Tetrahedron Lett.* **2008**, *49*, 4728. (g) Mun., J.; Onorato., A.; Nichols., F. C.; Morton., M. D.; Saleh., A. I.; Welzel., M.; Smith, M. B. *Org. Biomol. Chem.* **2007**, *5*, 3826. (h) So, R. C.; Douglas, R. N.; Izmirian, P.; Richardson, S. K.; Guerrera, R. L.; Howell, A. R. *J. Org. Chem.* **2004**, *69*, 3233. (i) Enders, D.; Müller-Hüwen, A. *Eur. J. Org. Chem.* **2004**, 1732. (j) Abraham, E.; Davies, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1655. (k) Tian, Y.-S.; Joo, J.-E.; Pham, V.-T.; Lee, K.-Y.; Ham, W.-H. *Arch. Pharmacal Res.* **2007**, *30*, 167.

(5) (a) Aiello, A.; Fattorusso, E.; Giordano, A.; Menna, M.; Navarrete, C.; Muñoz, E. *Bioorg. Med. Chem.* **2007**, *15*, 2920. (b) Aiello, A.; Fattorusso, E .; Giordano, A.; Menna, M.; Navarrete, C.; Muñoz, E. *Tetrahedron* **2009**, *65*, 4384.

(6) (a) Kalch, D.; De Rycke, N.; Moreau, X.; Greck, C. *Tetrahedron Lett.* **2009**, *50*, 492. (b) Ait-Youcef, R.; Kalch, D.; Moreau, X.; Thomassigny, C.; Greck, C. *Lett. Org. Chem.* **2009**, *6*, 377. (c) For either diastereoselective or organocatalylic electrophilic α-amination, see: Greck, C.; Drouillat, B.; Thomassigny, C. *Eur. J. Org. Chem.* **2004**, 1377. Thomassigny, C; Prim, D; Greck, C. *Tetrahedron Lett.* **2006**, 1117.

(7) Ait-Youcef, R.; Sbargoud, K.; Moreau, X.; Greck, C. *Synlett* **2009**, *18*, 3007.

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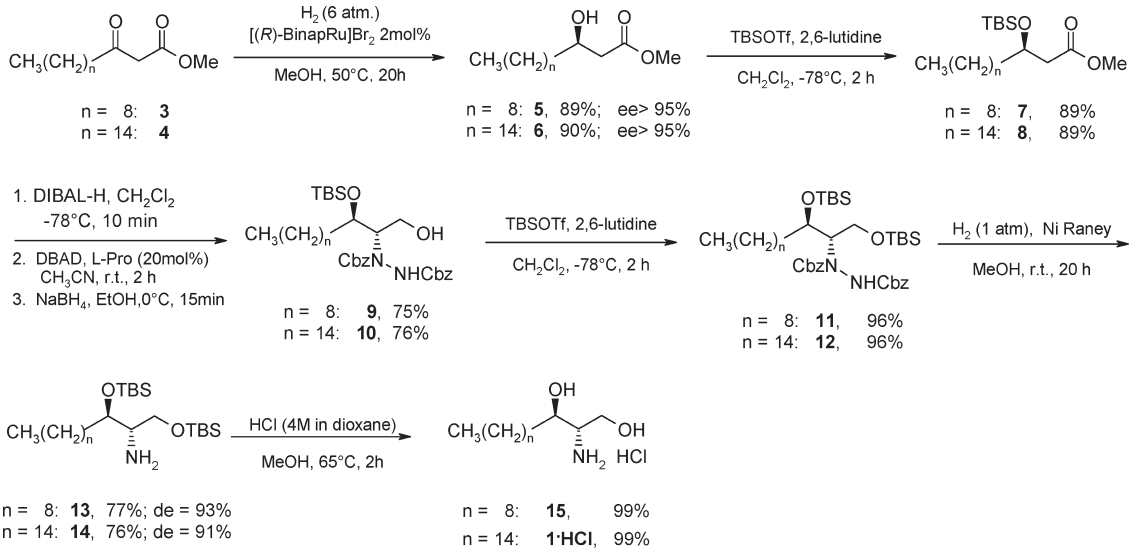
SCHEME 2. Syntheses of Sphinganine and the Hydrolysis Product of Clavaminol H Hydrochloride Salts

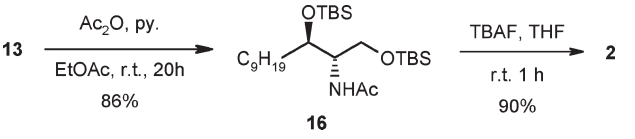


Starting from commercially available decanoic and palmitic acids and employing a procedure described by Masamune,[8] we first synthesized the long-chain β-keto esters **3** and **4** with good yields of 80%. Asymmetric Ru-catalyzed hydrogenation of these intermediates was achieved in the presence of 2 mol % of [(*R*)-BinapRu]Br_2 under mild conditions: under 6 atm of hydrogen and at 50 °C. The β-hydroxy esters **5**[9] and **6**[10] were isolated in high yields of 89% and 90%, respectively, and excellent enantioselectivities (ee $>$95%).[11] They were converted to their *tert*-butyldimethylsilyl ethers under classical conditions, and the corresponding O-protected β-hydroxy esters **7** and **8** were obtained in good yields (Scheme 2).

Following our recent report dealing with organocatalytic α-amination of protected β-hydroxy aldehydes,[7] the reduction of the ester moieties of compounds **7** and **8** was performed at −78 °C using diisobutylaluminium hydride to produce the corresponding O-protected β-hydroxy aldehydes which were engaged directly in this transformation. The reaction was conducted in the presence of L-proline (20 mol %) and dibenzyl azodicarboxylate (1.5 equiv) as a source of electrophilic nitrogen in CH_3CN at room temperature. After completion of the reaction (2 h), $NaBH_4$ and EtOH were added to reduce the aldehyde functionality. Monoprotected α-hydrazino 1,3-diols **9** and **10** were isolated in good yields of 75% and 76%, respectively, for the three steps. At this stage, the diastereomeric excesses could not be determinated precisely by NMR analysis.[12] They have been measured unambiguously on the O,O-diprotected amino diols **13** and **14**.

The regeneration of the amine and alcohol functionalities would afford the target molecules. Unfortunately, heterogeneous hydrogenation to remove the benzyl carbamate and to cleave the hydrazine bond failed, and the protection of the primary alcohol of **9** and **10** as the *tert*-butyldimethylsilyl ether was necessary. The silylation step was quantitative; the compounds **11** and **12** were isolated in 96% yield after flash chromatography. They were then submitted to hydrogenolysis using Raney-Ni in MeOH at room temperature. Under these conditions, the free amines **13** and **14** were obtained in 77% and 76% yields, respectively, and excellent levels of diastereoselectivities *anti*/*syn* $>$ 95:5.[13]

SCHEME 3. Completion of Clavaminol H Synthesis



Finally, acidic removal of the silyl ether afforded quantitatively the hydrolysis product of clavaminol H and sphinganine as their hydrochloride salts **15** and **1·HCl**, respectively. The physical and spectroscopic data of **15** and **1·HCl** were in agreement with those described in the literature for the same products.[4a]

To complete the synthesis of clavaminol H, the amine of the compound **13** was acetylated to give the compound **16** in 86% yield. In the last step, the silyl ethers were deprotected using tetrabutylammonium fluoride (1 M in hexanes) to regenerate the 1,3-diol. After flash chromatography, clavaminol H (**2**) was isolated in 90% yield (Scheme 3).

In conclusion, we have developed an efficient method for the asymmetric synthesis of sphingoid-type bases involving enantioselective catalytic hydrogenation of β-keto ester in presence of chiral ruthenium complex and organocatalytic electrophilic α-amination of aldehyde as key steps. Sphinganine and the hydrolysis product of clavaminol H as their hydrochloride salts, **1·HCl** and **15**, were prepared efficiently in eight steps with overall yields of 43% and 44%, respectively, from the corresponding long-chain β-keto esters **3** and **4**. We described the first synthetic access to clavaminol H (**2**) in nine steps with an overall yield of 34%.

(8) Brooks, D. W.; Lu, L. D. L.; Masamune., S. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 72.
(9) Utaka, M.; Watabu, H.; Higashi, H.; Sakai, T.; Tsuboi, S.; Torii., S. *J. Org. Chem.* **1990**, *55*, 3917.
(10) Ratovelomanana-Vidal, V.; Girard, C; Touati, R.; Tranchier, J. P.; Ben Hassine, B.; Genêt, J. P. *Adv. Synth. Catal.* **2003**, *345*, 261.
(11) The enantiomeric excesses were determined by ^{1}H NMR analysis of the crude product using (+)-Eu(tfc)$_3$.
(12) HPLC analysis was also uneffective because the diastereomers of compounds **9** and **10** were unseparable.
(13) The diastereoisomeric excess was determined by ^{1}H NMR analysis.

Experimental Section

General Procedure for Hydrogenation Reaction at Atmospheric Pressure. A solution of the β-keto ester **3** (500 mg, 2.18 mmol) or **4** (500 mg, 1.60 mmol) was diluted in degassed methanol (4 mL). This solution was canulated into a Schlenk tube and degassed by three cycles of vacuum/argon. The mixture was added to the in situ generated catalyst (2 mol % [(*R*)-BinapRu]Br_2[10] in a glass vessel and placed under argon. The argon atmosphere was replaced with 6 atm of hydrogen, and the mixture was heated to 50 °C. The solvent was evaporated under vacuum, and the β-hydroxy esters were purified on a short pad of silica using a pentane/Et_2O = 8/2 mixture.

Methyl (*R*)-3-hydroxydodecanoate (5): yield 445 mg (89%); white solid; mp 28−29 °C (lit.[9] mp 26−28 °C); $[\alpha]^{25}_D = -21.4$ (*c* 0.9, $CHCl_3$) [lit.[9] $[\alpha]^{25}_D = -21.1$ (*c* 1.5, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, *J* = 6.9 Hz, 3H), 1.25 (s, 14H), 1.46 (m, 2H), 2.43 (m, 2H), 3.69 (s, 3H), 3.98 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.4, 67.9, 51.6, 41.0, 36.4, 31.8, 29.5, 29.4, 29.4, 29.2, 25.4, 22.6, 14.0.

Methyl (*R*)-3-hydroxyoctadecanoate (6): yield 450 mg (90%); white solid; mp 57−58 °C (lit.[10] mp 55−56 °C); $[\alpha]^{25}_D = -15.9$ (*c* 0.9, $CHCl_3$) [lit.[10] $[\alpha]^{25}_D = -15.5$ (*c* 1.0, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, *J* = 6.9 Hz, 3H), 1.25 (s, 28H), 1.47 (m, 2H), 2.46 (m, 2H), 3.71 (s, 3H), 3.99 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.4, 67.9, 51.6, 41.0, 36.5, 31.9, 29.6, 29.6, 29.6, 29.5, 29.5, 29.4, 29.3, 25.4, 22.6, 14.0.

General Procedure for Formation of Silyl Ethers. To a stirred solution of alcohol (2 mmol) in dry CH_2Cl_2 (10 mL) cooled to −78 °C were added 2,6-lutidine (4 mmol) and *tert*-butyldimethylsilyl triflate (3 mmol). After 2 h of stirring at −78 °C, MeOH (3 mL) was added, and the solution was warmed to room temperature. The organic layers were evaporated under vacuum, and the residue was purified by flash chromatography on silica (pentane/ether = 9/1).

Methyl (*R*)-3-(*tert*-butyldimethylsilyloxy)dodecanoate (7): yield 406 mg (89%); colorless oil; $[\alpha]^{25}_D = -13.2$ (*c* 1.0, $CHCl_3$); IR (ATR, cm^{-1}) 2953, 2926, 2850, 1734, 1469, 1250, 1069, 834; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.05 (s, 3H), 0.86 (s, 12H), 1.26 (s, 14H), 1.43−1.52 (m, 2H), 2.42 (d br., *J* = 6.9 Hz, 2H), 3.66 (s, 3H), 4.12 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.3, 69.4, 51.3, 42.5, 37.6, 31.8, 29.6, 29.5, 29.5, 29.2, 25.7, 25.6, 24.9, 22.6, 17.9, 14.0, −2.9, −4.5, −4.8. Anal. Calcd for $C_{19}H_{40}O_3Si$: C, 66.22; H, 11.70. Found: C, 65.92; H, 11.88.

Methyl (*R*)-3-(*tert*-butyldimethylsilyloxy)octadecanoate (8): yield 556 mg (89%); colorless oil; $[\alpha]^{25}_D = -16.9$ (*c* 1.0, $CHCl_3$); IR (ATR, cm^{-1}) 2923, 2846, 1742, 1452, 1252, 1078, 843; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.06 (s, 3H), 0.86 (s, 12H), 1.25 (s, 26H), 1.43−1.50 (m, 2H), 2.44 (d br, *J* = 6.9 Hz, 2H), 3.66 (s, 3H), 4.12 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.3, 69.5, 51.3, 42.5, 37.6, 31.9, 29.7, 29.6, 29.5, 29.3, 25.7, 25.7, 25.6, 24.9, 22.6, 18.0, 17.9, 14.1, −2.9, −4.5, −4.8. Anal. Calcd for $C_{25}H_{52}O_3Si$: C, 70.03; H, 12.22. Found: C, 70.03; H, 12.41.

(2*S*,3*R*)-2-(*N*,*N*′-Bis(benzyloxycarbonyl)hydrazino)-1,3-bis-(*tert*-butyldimethylsilyloxy)dodecane (11): yield 1179 mg (96%); colorless oil; $[\alpha]^{25}_D = -4.9$ (*c* 0.9, $CHCl_3$); IR (ATR, cm^{-1}) 2947, 2924, 2858, 2165, 2017, 1978, 1710, 1476, 1254, 1216, 1083, 830; ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.01 (s, 12H), 0.84 (s, 21H), 1.02−1.63 (m, 16H), 3.37−4.00 (m, 3H), 4.11−4.39 (m, 1H), 5.16−5.54 (m, 4H), 6.16−6.59 (s, 1H), 7.21−7.48 (m, 10H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 157.6, 156.9, 156.6, 156.1, 135.9, 135.7, 135.5, 128.6, 128.5, 128.3, 128.2, 128.1, 127.9, 127.6, 71.1, 70.7, 68.4, 67.6, 67.6, 67.4, 67.3, 62.0, 61.2, 33.6, 33.4, 31.8, 29.9, 29.5, 29.1, 22.6, 17.8, 14.1, −4.1, −5.1, −5.6, −5.7. Anal. Calcd for $C_{40}H_{68}N_2O_6Si_2$: C, 65.89; H, 9.40; N, 3.84. Found: C, 66.09; H, 9.64; N, 3.99.

(2*S*,3*R*)-2-(*N*,*N*′-Bis(benzyloxycarbonyl)hydrazino)-1,3-bis-(*tert*-butyldimethylsilyloxy)octadecane (12): yield 1341 mg (96%); colorless oil; $[\alpha]^{25}_D = -5.9$ (*c* 0.5, $CHCl_3$); IR (ATR, cm^{-1}) 2944, 2922, 2855, 2161, 2013, 1974, 1704, 1471, 1255, 1218, 1082, 834; ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.07−0.10 (m, 12H), 0.84−0.90 (m, 21H), 1.09−1.31 (m, 28H), 3.46−4.01 (m, 3H), 4.12−4.40 (m, 1H), 5.04−5.29 (m, 4H), 6.19−6.52 (s, 1H), 7.20−7.46 (m, 10H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 157.7, 156.9, 156.6, 156.1, 135.9, 135.7, 135.5, 128.6, 128.5, 128.4, 128.4, 128.2, 128.2, 128.0, 127.6, 127.6, 71.0, 70.7, 68.4, 67.9, 67.6, 67.4, 61.2, 61.2, 33.6, 33.4, 31.9, 30.0, 29.6, 29.6, 29.5, 29.3, 22.6, 17.9, 14.1, 14.0, −4.0, −4.1, −4.9, −5.0, −5.5, −5.6. Anal. Calcd for $C_{46}H_{80}N_2O_6Si_2$: C, 67.93; H, 9.91; N, 3.44. Found: C, 68.21; H, 10.14; N, 3.61.

General Procedure for the Organocatalytic α-Amination. To a solution of **7** or **8** (1.72 mmol) in CH_2Cl_2 (10 mL) was added DIBAL-H (1.80 mmol, 1 M in hexane) at −78 °C. The mixture was stirred for 30 min, and then MeOH (1 mL) and HCl (1 N) (3 mL) were added, and the solution was stirred during 30 min at rt. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water and then brine, dried over $MgSO_4$, and concentrated in vacuo. The crude aldehyde was immediately dissolved in MeCN (10 mL). To this solution were added dibenzyl azodicarboxylate (1.14 mmol) and L-proline (0.22 mmol) at rt. The reaction mixture was stirred during 2 h at this temperature. The mixture was then treated with EtOH (10 mL) and NaBH4 (40 mg) and was stirred for 5 min at 0 °C. The reaction was worked up with aq NH_4Cl solution and EtOAc. The organic layers were dried ($MgSO_4$), filtered, and concentrated. The resulting crude product **9** or **10** was purified by flash chromatography on silica (pentane/Et_2O = 8/2).

(2*S*,3*R*)-2-(*N*,*N*′-Bis(benzyloxycarbonyl)hydrazino)-3-(*tert*-butyldimethylsilyloxy)dodecanol (9): yield 803 mg (76%); colorless oil; $[\alpha]^{25}_D = -12.2$ (*c* 0.4, $CHCl_3$); IR (ATR, cm^{-1}) 3482, 3282, 2915, 2848, 1726, 1679, 1526, 1429, 1259, 1055, 836; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.004−0.04 (m, 6H), 0.87 (s, 12H), 1.12−1.44 (m, 16H), 3.50−4.12 (m, 4H), 4.31−4.47 (m, 1H), 5.15−5.31 (m, 4H), 6.54 (s, 1H), 7.24−7.38 (m, 10H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 158.8, 158.1, 156.8, 155.6, 135.7, 135.4, 134.9, 128.6, 128.5, 128.4, 128.2, 128.1, 127.7, 71.1, 70.5, 68.7, 68.1, 67.8, 63.2, 59.8, 34.4, 34.1, 31.8, 30.3, 29.6, 29.5, 29.3, 25.7, 23.1, 22.6, 17.9, 14.1, −4.1, −4.8. Anal. Calcd for $C_{34}H_{54}N_2O_6Si$: C, 66.41; H, 8.85; N, 4.56. Found: C, 66.31; H, 8.81; N, 4.47.

(2*S*,3*R*)-2-(*N*,*N*′-Bis(benzyloxycarbonyl)hydrazino)-3-(*tert*-butyldimethylsilyloxy)octadecanol (10): yield 925 mg (77%); colorless oil; $[\alpha]^{25}_D = -5.6$ (*c* 0.3, $CHCl_3$); IR (ATR, cm^{-1}) 3509, 3278, 2919, 2857, 1723, 1684, 1530, 1418, 1321, 1259, 1066, 835; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.006−0.05 (m, 6H), 0.87 (s, 12H), 1.02−1.53 (m, 28H), 3.47−4.21 (m, 4H), 4.22−4.56 (m, 1H), 5.08−5.34 (m, 4H), 6.57 (s, 1H), 7.23−7.46 (m, 10H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 158.7, 158.3, 156.8, 155.5, 135.7, 135.6, 134.9, 134.9, 128.6, 128.5, 128.4, 128.3, 128.1, 127.7, 127.6, 71.2, 70.5, 68.6, 68.5, 68.4, 68.1, 67.8, 63.2, 60.1, 34.3, 34.0, 31.9, 31.8, 29.8, 29.6, 29.6, 29.3, 25.7, 25.6, 23.2, 22.6, 17.8, 14.0, −4.1, −4.8. Anal. Calcd for $C_{40}H_{66}N_2O_6Si$: C, 68.73; H, 9.52; N, 4.01. Found: C, 68.71; H, 9.62; N, 3.96.

General Procedure for the Conversion of Hydrazino Diols into the Corresponding Amino Diols. To a stirred solution of hydrazino diols **11** or **12** (0.30 mmol) in anhydrous MeOH (5.0 mL) were added AcOH (5 drops) and Raney-Ni (ca. 200 mg, prewashed with anhydrous MeOH). The reaction mixture was degassed under vacuum and saturated with hydrogen (by an H_2-filled balloon) three times. The suspension was stirred at room temperature for 20 h under a slightly positive pressure of hydrogen and then filtered off through a pad of Celite. The solvent were evaporated under vacuum, and the residue was purified by flash chromatography on silica (pentane/ether = 8/2) to give **13** or **14** as an oil.

(2*S*,3*R*)-2-Amino-1,3-(di-*tert*-butyldimethylsilyloxy)dodecane (13): yield 102 mg (77%); colorless oil; $[\alpha]^{25}_D = -0.6$ (*c* 1.0,

$CHCl_3$); IR (ATR, cm^{-1}) 2955, 2924, 2851, 2126, 1758, 1721, 1478, 1246, 1080, 846; ^1H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 12H), 0.84 (s, 21H), 1.20 (s, 14H), 1.37 (m, 2H), 2.82 (m, 1H,), 3.38 (ABX system, J = 10.0 and 7.7 Hz, 1H), 3.56−3.70 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 73.6, 64.8, 56.5, 32.3, 31.8, 29.8, 29.6, 29.5, 29.2, 25.9, 25.8, 25.0, 22.6, 18.4, 18.0, 14.1, −4.3, −4.5, −5.3, −5.4. Anal. Calcd for $C_{24}H_{55}NO_2Si_2$: C, 64.65; H, 12.43; N, 3.14. Found: C, 65.04; H, 12.25; N, 3.11.

(2*S*,3*R*)-2-Amino-1,3-bis(*tert*-butyldimethylsilyloxy)octadecane (14): yield 120 mg (76%); colorless oil; $[\alpha]^{25}_D = -5.7$ (*c* 1.0, $CHCl_3$); IR (ATR, cm^{-1}) 2954, 2927, 2853, 2124, 1757, 1719, 1476, 1248, 1082, 844; ^1H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 12H), 0.84 (s, s21H), 1.19 (s, 26H), 1.45 (m, 2H), 2.89 (m, 1H,), 3.45 (ABX system, J = 10.0 and 7.3 Hz, 1H), 3.56−3.70 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 73.6, 64.8, 56.4, 32.3, 31.9, 29.9, 29.8, 29.8, 29.6, 29.6, 29.6, 29.7, 29.6, 29.3, 25.8, 25.8, 25.7, 24.9, 22.6, 18.2, 18.0, 14.1, −4.3, −4.5, −5.3, −5.4. Anal. Calcd for $C_{30}H_{67}NO_2Si_2$: C, 67.98; H, 12.74; N, 2.64. Found: C, 67.88; H, 12.78; N, 2.63.

(1*S*,2*R*)-2-Aminododecane-1,3-diol Hydrochloride (15). Under an argon atmosphere, a stirred solution of **13** (15 mg, 0.033 mmol) in absolute MeOH (2 mL) was prepared. HCl (4 M in solution in 1,4-dioxane, 0.171 mmol) was then added dropwise. After 2 h of stirring at 65 °C, the solvents were removed in vacuo to give **15** (8 mg, 99%) as a colorless oil: $[\alpha]^{25}_D = -5.8$ (*c* 0.9, MeOH) [lit.[4a] $[\alpha]^{20}_D = -6.0$ (*c* 0.1, MeOH)]; IR (ATR, cm^{-1}) 3340, 2907, 2842, 1499, 1055; ^1H NMR (300 MHz, CD_3OD) δ 0.84 (t, J = 6.9 Hz, 3H), 1.24−1.42 (m, 13H), 1.44−1.59 (m, 3H), 3.19 (dt, J = 8.4 and 4.1 Hz, 1H), 3.70 (ABX system, J = 11.5 and 8.4 Hz, 1H), 3.73−3.82 (m, 1H), 3.84 (ABX system, J = 11.5 and 4.2 Hz, 1H); ^{13}C NMR (300 MHz, CD_3OD) δ 71.1, 59.6, 59.2, 35.0, 33.9, 31.5, 31.4, 31.3, 27.8, 24.5, 15.2; HRMS (ESI) calcd for $C_{12}H_{28}NO_2$ $[M + H]^+$ 218.2120, found 218.2117.

(+)-(2*S*,3*R*)-2-Aminooctadecane-1,3-diol Hydrochloride (1·HCl). The same procedure as for **15** was followed from **14** (25 mg, 0.047 mmol) to give **1·HCl** (16 mg, 100%) as a white solid: mp 90−91 °C (lit.[4a] mp 89−90 °C); $[\alpha]^{25}_D = +9.8$ (*c* 0.4, MeOH) [lit.[4a] $[\alpha]^{20}_D = +10.0$ (*c* 0.06, MeOH)]; IR (ATR, cm^{-1}) 3340, 2911, 2842, 1468, 1055; ^1H NMR (300 MHz, CD_3OD) δ 0.84 (t, J = 6.9 Hz, 3H), 1.24−1.42 (m, 25H), 1.44−1.59 (m, 3H), 3.19 (dt, J = 8.4 and 4.1 Hz, 1H), 3.70 (ABX system, J = 11.5 and 8.4 Hz, 1H), 3.73−3.82 (m, 1H), 3.84 (ABX system, J = 11.5 and 4.2 Hz, 1H); ^{13}C NMR (300 MHz, CD_3OD) δ 71.3, 59.6, 59.5, 35.2, 34.1, 31.9, 31.8, 31.6, 31.5, 31.5, 31.4, 28.1, 24.8, 15.5; HRMS (ESI) calcd for $C_{18}H_{40}NO_2$ $[M + H]^+$ 302.3059, found 302.3058.

***N*-((2*S*,3*R*)-1,3-Bis(*tert*-butyldimethylsilyloxy)dodecan-2-yl)-acetamide (16).** To a solution of **13** (33 mg, 0.074 mmol) in pyridine (0.3 mL) was added Ac_2O (0.15 mL), and the reaction mixture was stirred at rt for 18 h. The solvent was removed by evaporation under vacuum, and the residue was purified by flash chromatography on silica (pentane/EtOAc = 9/1) to give **16** (31 mg, 86%) as a colorless oil: $[\alpha]^{25}_D = +2.2$ (*c* 0.5, $CDCl_3$); IR (ATR, cm^{-1}) 2954, 2926, 2855, 1644, 1097, 833; ^1H NMR (300 MHz, $CDCl_3$) δ 0.00−0.11 (m, 12H), 0.89 (s, 21H), 1.16−1.57 (m, 16H), 1.97 (s, 3H), 3.64 (ABX system, J = 10.4 and 5.0 Hz, 1H), 3.75 (ABX system, J = 10.4 and 5.4 Hz, 1H), 3.83 (q, J = 6.6 Hz, 1H), 3.96−4.06 (m, 1H), 5.56 (d, J = 8.4 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.3, 71.7, 60.9, 53.7, 33.7, 31.8, 29.8, 29.5, 29.2, 25.8, 25.8, 25.7, 24.8, 23.5, 22.6, 18.2, 18.0, 14.1, −4.2, −4.6, −5.3, −5.5. Anal. Calcd for $C_{26}H_{57}NO_3Si_2$: C, 64.00; H, 11.78; N, 2.87. Found: C, 64.28; H, 11.94; N, 3.02.

Clavaminol H (2). To a solution of **16** (18 mg, 0.036 mmol) in THF (0.5 mL) at 0 °C was added TBAF (0.05 mL), and the reaction mixture was stirred at rt for 1 h. The solvent was removed by evaporation under vacuum, and the residue was purified by flash chromatography on silica (EtOAc/MeOH = 95/5) to give **2** (9 mg, 90%) as a colorless oil: $[\alpha]^{25}_D = +3.0$ (*c* 0.6, $CHCl_3$) [lit.[5b] $[\alpha]^{25}_D = +3.19$ (*c* 0.0013, MeOH)]; IR (ATR, cm^{-1}) 3274, 2907, 2849, 1715, 1364, 1221; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 6.9 Hz, 3H), 1.26 (s, 13H), 1.47−1.58 (m, 3H), 2.05 (s, 3H), 2.73 (s br., 2H), 3.70−3.90 (m, 3H), 4.03 (dq, J = 8.3 and 2.7 Hz, 1H), 6.45 (d, J = 7.0 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.6, 74.3, 62.4, 53.8, 34.6, 32.0, 29.6, 29.4, 29.3, 26.1, 23.5, 22.8, 22.7, 14.2; HRMS (ESI) calcd for $C_{14}H_{29}NO_3Na$ $[M + Na]^+$ 282.2045, found 282.2050.

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Supporting Information Available: General experimental methods and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.