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Synthesis of Cytotoxic Aza Analogues of Jaspine B

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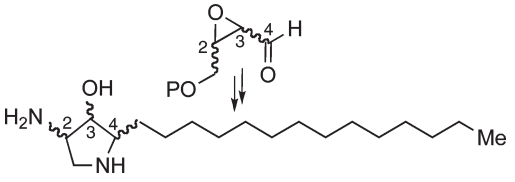

A straightforward access to pyrrolidine-based analogues of jaspine B was developed. Five stereoisomers were prepared including the all-*cis* derivatives presenting the configuration of the natural anhydrophytosphingosine. The synthesis of the latter relied on an original Staudinger-type cyclization process. The compounds were evaluated regarding their ability to alter tumor cells' viability and to interfere with the metabolism of sphingolipids.

Sphingolipids represent a wide family of bioactive lipids.[1] They are key mediators of fundamental cell-signaling processes related to tumorigenicity and cancer progression.[2] In balance with the "tumor-promoting" sphingosine-1-phosphate, the pro-apoptotic ceramide lies at the center of a metabolic manifold. In cancer cells, this "tumor-suppressing lipid" is rapidly converted into sphingomyelin (an abundant plasma membrane component) or glucosylceramide (involved in chemoresistance of cancer cells). Inhibiting the enzymatic pathways responsible for this accelerated consumption of ceramide is thus expected to enhance the susceptibility of cancer cells to apoptosis.[3]

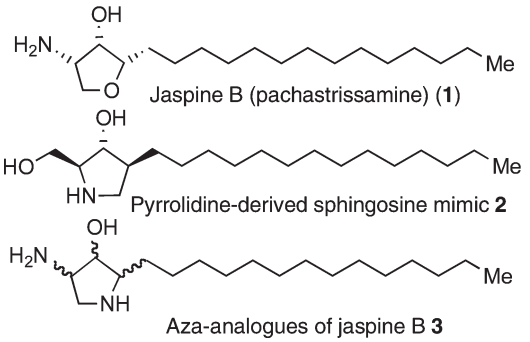

FIGURE 1. Structures of the sphingomyelin synthase inhibitor jaspine B (**1**), the pyrrolidine-based glucosylceramide synthase inhibitor **2** and the targeted aminopyrrolidines **3**.

We recently identified jaspine B (**1**) as a new structural archetype for the development of sphingomyelin synthase inhibitors (Figure 1).[4] On the other hand, we designed pyrrolidine-derived sphingosine mimics such as **2** with potent glucosylceramide synthase inhibitory activity.[5] Both chemical series display a marked pro-apoptotic behavior in melanoma cells, correlated with an increased intracellular ceramide concentration.

In search for new sphingolipid analogues interfering with ceramide metabolism in cancer cells, we envisioned merging the structural frameworks of **1** and **2**.[6] Such structural hybridation would lead to novel pyrrolidine-based jaspine B derivatives **3**. Altered ionization state and hydrogen-bond donor/acceptor capacity of such analogues may indeed modulate their pharmacological profiles. We report here our results concerning the enantioselective syntheses of these derivatives and their first biological evaluations.

Syntheses of 2-alkyl-4-amino-3-hydroxy pyrrolidine such as **3** are scarce.[7] Our synthetic approach relied on the use of an enantioenriched α,β-epoxyaldehyde as a precursor of the four-carbon head unit of the targeted structures (Scheme 1).[8] We planned that the all-*cis* aminopyrrolidines **6** could be accessed from a (2*R*,3*S*,4*S*)-*anti*-epoxyamine **4**. Early introduction of the lipophilic chain with creation of the (4*S*) stereogenic center was envisioned by means of the *anti*-selective alkylation of an intermediate imine.[9] A carbonatation/intramolecular cyclization sequence would in turn invert the configuration at C-3 while leaving a free hydroxyl group at

(1) (a) Hirabayashi, Y.; Igarashi, Y.; Merrill, A. H. J. *Sphingolipid Biology*; Springer-Verlag: Tokyo, 2006. (b) Hannun, Y. A.; Obeid, L. M. *Nat. Rev. Mol. Cell Biol.* **2008**, *9*, 139–150.

(2) (a) Ogretmen, B.; Hannun, Y. A. *Nat. Rev. Cancer* **2004**, *4*, 604–616. (b) Ségui, B.; Andrieu-Abadie, N.; Jaffrézou, J.-P.; Benoist, H.; Levade, T. *Biochim. Biophys. Acta* **2006**, *1758*, 2104–2120.

(3) (a) Lin, C. F.; Chen, C. L.; Lin, Y. S. *Curr. Med. Chem.* **2006**, *13*, 1609–1616. (b) Modrak, D. E.; Gold, D. V.; Goldenberg, D. M. *Mol. Cancer Ther.* **2006**, *5*, 200–208. (c) Morales, A.; Fernandez-Checa, J. C. *Mini-Rev. Med. Chem.* **2007**, *7*, 371–382.

(4) (a) Salma, Y.; Lafont, E.; Therville, N.; Carpentier, S.; Bonnafe, M. J.; Levade, T.; Génisson, Y.; Andrieu-Abadie, N. *Biochem. Pharmacol.* **2009**, *78*, 477–485. (b) Salma, Y.; Ballereau, S.; Ladeira, S.; Andrieu-Abadie, N.; Génisson, Y. *Org. Biomol. Chem.* **2010**, *8*, 3227–3243.

(5) (a) Faugeroux, V.; Génisson, Y.; Andrieu-Abadie, N.; Colie, S.; Levade, T.; Baltas, M. *Org. Biomol. Chem.* **2006**, *4*, 4437–4439. (b) Rives, A.; Génisson, Y.; Faugeroux, V.; Zedde, C.; Lepetit, C.; Chauvin, R.; Saffon, N.; Andrieu-Abadie, N.; Colie, S.; Levade, T.; Baltas, M. *Eur. J. Org. Chem.* **2009**, 2474–2489.

(6) For a review of sphingolipids metabolism modulators: Delgado, A.; Casas, J.; Llebaria, A.; Abad, J. L.; Fabrias, G. *ChemMedchem* **2007**, *2*, 580–606.

(7) Boto, A.; Hernandez, D.; Hernandez, R. *Tetrahedron Lett.* **2009**, *50*, 3974–3977.

(8) For the use of such epoxyaldehydes in the synthesis of iminosugars see: Ayad, T.; Genisson, Y.; Baltas, M.; Gorrichon, L. *Chem. Commun.* **2003**, 582–583. Ayad, T.; Génisson, Y.; Baltas, M. *Org. Biomol. Chem.* **2005**, *3*, 2626–2631.

(9) For the use of a related vinylation in the synthesis of iminosugars see: Ayad, T.; Génisson, Y.; Baltas, M.; Gorrichon, L. *Synlett* **2001**, 866–868.

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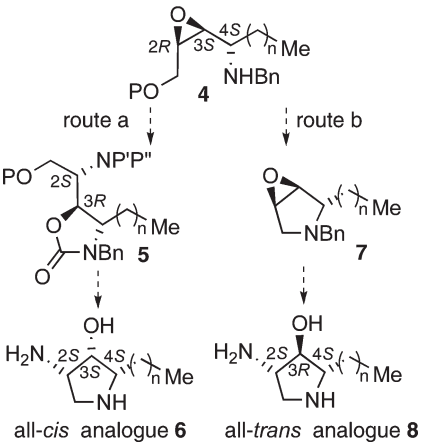
SCHEME 1. General Synthetic Approach to all-*cis* and all-*trans* Pyrrolidine-Based Jaspine B Analogues 6 and 8

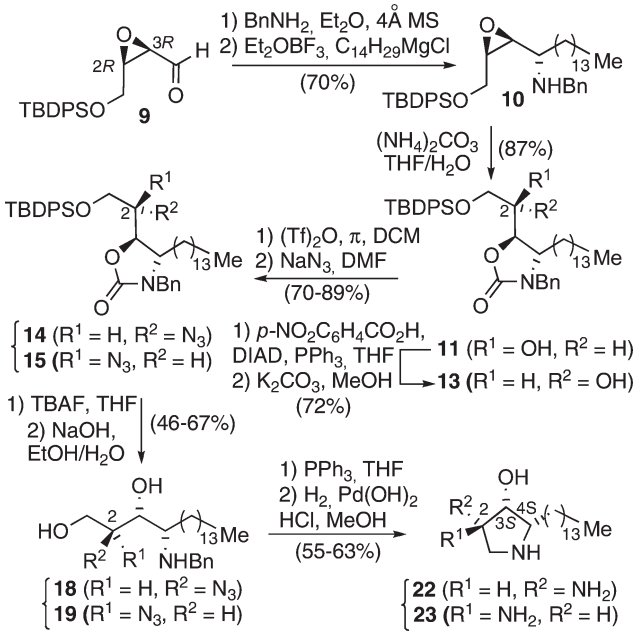


C-2 (route a).[10] Introduction of a nitrogenated group with inversion of configuration in this position, leading to **5**, would set the stage for the construction of the all-*cis* pyrrolidine ring of **6**. Variation of this route via epimerization at C-2 would also give ready access to *trans*−*cis* aminopyrrolidine derivatives (*vide infra*). On the other hand, preparation of all-*trans* analogues **8** would rely on the regioselective oxirane opening of epoxypyrrolidine intermediates **7** (route b).[11] Finally, preparation of another set of steroisomers was planned starting from enantiomeric epoxide precursors.

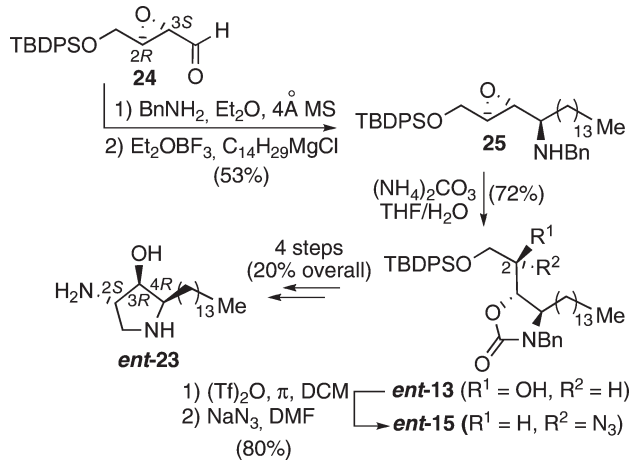
The assembling of the C_{18} skeleton thus relied on the preparation of epoxyamine **10** (Scheme 2). The (2*R*,3*R*)-*cis*-epoxyaldehyde **9**[10] was first treated with benzylamine, and the resulting imine was reacted without isolation with tetradecyl magnesium bromide in the presence of Et_2OBF_3. The unstable *anti*-epoxyamine **10** was isolated as a single diatereoisomer in 70% yield. Treatment of the latter with ammonium carbonate smoothly delivered oxazolidinone **11** in good yield. At this stage, the choice of the nitrogenated group was decisive. The presence of a nucleophilic amine was anticipated to interfere with the final cyclization process while the phtalimide moiety proved labile under preliminary saponification attempts. The use of an azido group was thus considered. Azide **14** was prepared in good yield from secondary alcohol **11** via the corresponding triflate. Desilylation of the primary hydroxyl group followed by carefully monitored saponification led to the linear azido aminoalcohol **18** in 74% yield (based on the starting material recovering, bsmr, at 63% of conversion).

Appel[12] and Mitsunobu reactions[13] are two complementary processes to prepare hydroxylated pyrrolidine from linear aminopolyols. Fast trapping of the Ph_3P by the vicinal azido group was however expected here. We thus thought of exploiting the 1,2-azidoalcohol moiety in **18** to activate the primary hydroxyl group. After some optimization, it was found that treatment of **18** with one equivalent of Ph_3P at 50 °C in

SCHEME 2. Synthesis of Aminopyrrolidines 22 and 23



SCHEME 3. Synthesis of Aminopyrrolidine *ent*-23



THF gratifyingly delivered the corresponding amino pyrrolidine **20** in 78% yield (Scheme 4).[14] Finally, hydrogenolysis of the *N*-benzyl group gave the targeted all-*cis* (2*S*,3*S*,4*S*) jaspine B analogue **22** (Scheme 2).

We also used this route to prepare *trans*−*cis* analogues **23** (Scheme 2). The secondary hydroxyl group in **11** was epimerized to give **13**. The diastereoisomeric azido aminoalcohol **15** obtained after desilylation and saponification of **13** was treated with Ph_3P under the previous conditions to give the desired aminopyrrolidine in 87% yield. The *trans*−*cis* (2*R*,3*S*,4*S*) pyrrolidine-based jaspine B analogue **23** was obtained after a final hydrogenation step. In order to further illustrate the flexibility of our approach, we targeted the *trans*,*cis* pyrrolidine enantiomer of **23** from the *trans*-epoxide precursor **24**,[10] thus avoiding the epimerization step (Scheme 3).

(10) Ayad, T.; Faugeroux, V.; Génisson, Y.; Andre, C.; Baltas, M.; Gorrichon, L. *J. Org. Chem.* **2004**, *69*, 8775–8779.

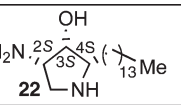
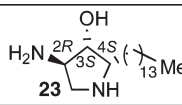
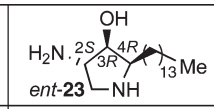
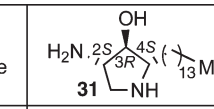
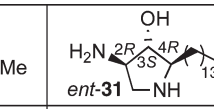
(11) For an in-depth study of this oxirane opening reaction see ref 5b.

(12) (a) Appel, R. *Angew. Chem., Int. Ed.* **1975**, *14*, 801–811. (b) Casiraghi, G.; Rassu, G.; Spanu, P.; Pinna, L.; Ulgheri, F. *J. Org. Chem.* **1993**, *58*, 3397–3400. (c) Razavi, H.; Polt, R. *J. Org. Chem.* **2000**, *65*, 5693–5706.

(13) (a) Veith, U.; Schwardt, O.; Jäger, V. *Synlett* **1996**, 1181–1183. (b) Schwardt, O.; Veith, U.; Gaspard, C.; Jager, V. *Synthesis-Stuttgart* **1999**, 1473–1490.

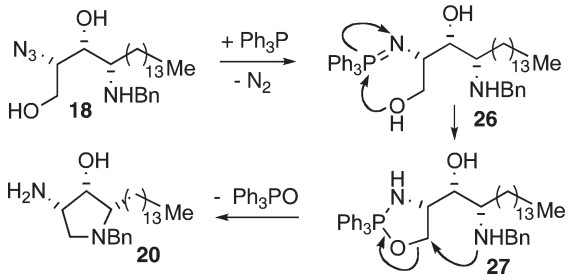
(14) The structural assignment of the cyclisation products as pyrolidines was based on NMR analyses. HMBC experiments on **21**, the *N*-Bn precursor of **23**, showed a ^3J correlation between the benzylic methylene protons and the C-1 (sphingolipid numbering), thus indicating an N−C-1 connection.

TABLE 1. Cytotoxicity of 22, 23, *ent*-23, 31 and *ent*-31 toward Cancer Cells (MTT Experiments, see Supporting Information)

Compounds	 **22**	 **23**	 *ent*-**23**	 **31**	 *ent*-**31**
IC_{50} (B16 cells)[a]	2.9 μM	5.0 μM	6.1 μM	2.9 μM	3.6 μM
IC_{50} (A375 cells)[b]	2.6 μM	/	5.7 μM	2.5 μM	2.5 μM
IC_{50} (WM115 cells)[c]	2.4 μM	/	3.6 μM	2.7 μM	2.4 μM

[a] 1.1 μM for natural jaspine B. [b] 4.7 μM for natural jaspine B. [c] 2.4 μM for natural jaspine B.

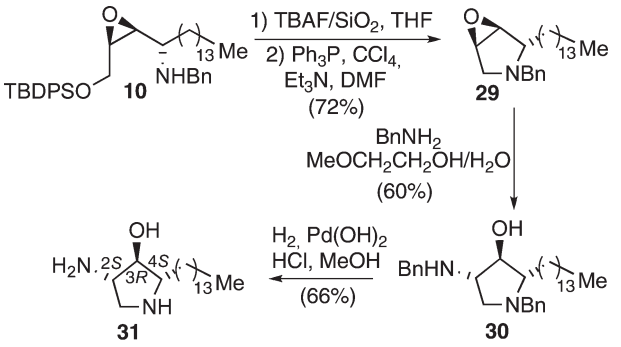
SCHEME 4. Proposed Mechanism for the Staudinger-Type Cyclization/Reduction Process



The Grignard reagent addition onto the intermediate epoxyimine delivered the expected *anti*-epoxyamine **25** in 53% isolated yield (*anti*/*syn* 80:20, based on the ^{1}H NMR of the crude reaction mixture). The oxazolidinone *ent*-**13** was then directly obtained by mean of the carbonatation/intramolecular cyclization sequence. The rest of the sequence leading to the jaspine B analogue *ent*-**23** paralleled the one used for the preparation of its enantiomer. The X-ray diffraction analysis of a crystalline sample of the oxazolidinone *ent*-**17** allowed us to assign the final (2*S*,3*R*,4*R*) configuration in this series (see Supporting Information).

The synthesis of the three aminopyrrolidines **22**, **23** and *ent*-**23** thus relied on an original Ph_3P-promoted cyclization/reduction of azido aminoalcohols to aminohydroxy pyrrolidines. A Staudinger-type mechanism may be proposed for this transformation (Scheme 4).[15] From **18**, the formation of iminophosphorane **26** would lead to oxazophospholidine **27** through intramolecular trapping by the vicinal primary alcohol. Such a pathway is reminiscent to the phosphine-promoted aziridine formation introduced by Zwanenburg and coll..[16] However, the presence of the secondary amine would allow here formation of the pyrrolidine ring, concomitant with the reduction of the azido group and liberation of Ph_3PO, yielding **20**.[17] Noteworthy, this transformation offers a direct entry to the important 3-amino-4-hydroxy-

SCHEME 5. Synthesis of all-*trans* Aminopyrrolidine 31



pyrrolidine framework present in several 5-membered ring iminosugars including potent inhibitors of the lysosomal catabolism of glycosphingolipids.[18]

The epoxypyrrolidine intermediate **29** required for the preparation of the all-*trans* aminopyrrolidines was obtained in 72% yield through desilylation of **10** and Appel cyclization (Scheme 5). We then took advantage of a regio- and stereocontrolled oxirane-opening reaction to introduce the nitrogenated group in the correct location and configuration. Thus, treatment of the epoxypyrrolidine **29** with benzylamine in methoxyethanol/water at 65 °C smoothly led to the formation of aminopyrrolidine **30**, isolated in 77% yield as a single isomer. A final hydrogenolysis delivered the targeted (2*S*,3*R*,4*S*) jaspine B analogue **31**.

The enantiomeric (2*R*,3*S*,4*R*) jaspine B *ent*-**31** analogue was obtained through a similar sequence starting from the (2*S*,3*S*)-*cis*-epoxyaldehyde *ent*-**9**. Crystallographic analysis of the epoxypyrrolidine *ent*-**29** allowed confirmation of its structure (see Supporting Information).

The ability of aminopyrrolidines **22**, **23**, *ent*-**23**, **31**, and *ent*-**31** to inhibit tumor cells growth was evaluated in various melanoma cell lines (Table 1). All compounds showed a dose-dependent effect with IC_{50} in the low micromolar range. In murine B16 cells, the pyrrolidine **22**, presenting the all-*cis* configuration of the parent natural compound, as well as the all-*trans* derivatives **31** and *ent*-**31** displayed an IC_{50} inferior to 4 μM. This trend was also observed in human A375 and WM115 cells were the aza analogues **22**, **31** and *ent*-**31** proved as cytotoxic as the natural jaspine B with IC_{50} values around 2.5 μM.

To determine whether the cytotoxic aminopyrrolidines **22** and **31** affect sphingomyelin synthesis, as we previously reported for the natural jaspine B, we next evaluated the changes in the sphingolipid pattern in B16 cells treated for 6 h by jaspine B aza analogues.[4a] We observed that **22** and **31** elicited an increase in [^{3}H]sphingosine-labeled ceramide content, whereas the level of radiolabeled sphingomyelin decreased as compared to untreated control cells (see Supporting

(15) For a review on the Saudinger reaction see: Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353–1406.

(16) (a) Legters, J.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett*. **1989**, *30*, 4881–4884. (b) Thijs, L.; Porskamp, J. J. M.; Vanloon, A. A. W. M.; Derks, M. P. W.; Feenstra, R. W.; Legters, J.; Zwanenburg, B. *Tetrahedron* **1990**, *46*, 2611–2622. (c) Legters, J.; Thijs, L.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 1–15. For a related process see: (d) Chun, J.; He, L. L.; Byun, H. S.; Bittman, R. *J. Org. Chem*. **2000**, *65*, 7634–7640.

(17) The generation of Ph_3PO was monitored by ^{31}P NMR with the appearance of a signal at δ = 29.3 ppm in $CDCl_3$.

(18) For recent studies see: (a) Rountree, J. S. S.; Butters, T. D.; Wormald, M. R.; Dwek, R. A.; Asano, N.; Ikeda, K.; Evinson, E. L.; Nash, R. J.; Fleet, G. W. J. *Tetrahedron Lett*. **2007**, *48*, 4287–4291. (b) Choubdar, N.; Bhat, R. G.; Stubbs, K. A.; Yuzwa, S.; Pinto, B. M. *Carbohydr. Res*. **2008**, *343*, 1766–1777. (c) Curtis, K. L.; Evinson, E. L.; Handa, S.; Singh, K. *Org. Biomol. Chem*. **2007**, *5*, 3544–3553. (d) Rountree, J. S. S.; Butters, T. D.; Wormald, M. R.; Boomkamp, S. D.; Dwek, R. A.; Asano, N.; Ikeda, K.; Evinson, E. L.; Nash, R. J.; Fleet, G. W. J. *ChemMedChem* **2009**, *4*, 378–392.

Information). These effects were comparable with those produced by the natural jaspine B.

In conclusion, *C*-alkyl aminopyrrolidines embedding a sphingolipid-like C_{18} carbon skeleton were designed as aza analogues of jaspine B. Five stereoisomers were prepared and an original Ph_3P-promoted cyclization/reduction of azido aminoalcohols to aminohydroxypyrrolidines was developed. All compounds displayed cytotoxicity against various melanoma cells with a potency comparable to that of the parent natural compound for the all-*cis* compound **22** and the all-*trans* derivatives **31** and *ent*-**31**. The active aza analogues **22** and **31** were shown to impair the conversion of ceramide into sphingomyelin in B16 cells, as the natural jaspine B.

Experimental Section

(2*S*,3*R*,4*S*)-2-Azido-4-(benzylamino)octadecane-1,3-diol (18). NaOH (68.0 mg, 1.7 mmol) was added to a solution of oxazolidinone **16** (76.7 mg, 0.17 mmol) in a 8:2 EtOH/H_2O mixture (3.5 mL). The reaction mixture was heated at 85 °C for 6 h before being cooled to room temperature. The mixture was extracted three times with EtOAc and the combined extracts were concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (PE/EtOAc 80:20, 0.8% NH_4OH) to give **18** (49.5 mg, 74% bsmr at 63% of conversion) as a colorless oil. $[\alpha]_D^{25}$ +25.1 (*c* 1.1; $CHCl_3$); IR (neat) 3436 (O−H), 2099 (N_3) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, ^3J = 6.7 Hz, 3H), 1.20−1.40 (m, 24H), 1.54−1.67 (m, 2H), 2.76 (td, ^3J = 6.4 Hz, ^3J = 2.5 Hz, 1H), 3.05 (brs, 2H), 3.35 (pseudoq, $^3J \approx {}^3J \approx {}^3J \approx 5.7$ Hz, 1H), 3.54 (dd, ^3J = 6.4 Hz, ^3J = 2.6 Hz, 1H), 3.81 (AB system, ^2J = 12.6 Hz, $\delta a - \delta b$ = 47.4 Hz, 2H), 3.86 (AB part of an ABX, ^2J = 11.6 Hz, ^3J = 5.9 Hz, ^3J = 4.7 Hz, $\delta a - \delta b$ = 45.6 Hz, 2H), 7.25−7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.7, 26.1, 29.3−29.7 (9C), 31.9, 32.2, 52.3, 57.7, 61.9, 65.2, 72.6, 127.5, 128.4, 128.6, 139.1; MS (ES): *m*/*z* = 433 (100) [M + H^+]. HRMS (ESI^+): calcd for $C_{25}H_{45}N_4O_2$ 433.3543, found 433.3547.

(2*S*,3*S*,4*S*)-4-Amino-1-benzyl-2-tetradecylpyrrolidin-3-ol (20). Triphenylphosphine (42.0 mg, 0.16 mmol) was added to a solution of azidoalcohol **18** (67.2 mg, 0.16 mmol) in anhydrous THF (1.6 mL). The mixture was allowed to react at 50 °C for 16 h. The THF was then evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (EtOAc/MeOH, 95:5; 1.6% NH_4OH) to give **20** (47.1 mg, 78%) as a colorless oil. $[\alpha]_D^{25}$ +65.8 (*c* 1.8; $CHCl_3$); IR (neat) 3430 (O−H), 1604 (N−H) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, ^3J = 6.7 Hz, 3H), 1.18−1.38 (m, 24H), 1.47−1.69 (m, 2H), 2.29−2.40 (m, 2H), 2.59 (dd, ^2J = 10.2 Hz, ^3J = 3.6 Hz, 1H), 3.10 (d, ^2J = 13.2 Hz, 1H), 3.27−3.32 (m, 1H), 3.92 (pseudot, $^3J \approx {}^3J \approx$ 5.4 Hz, 1H), 4.00 (d, ^2J = 13.2 Hz, 1H), 7.18−7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 26.6, 28.1, 29.3−30.1 (8C), 30.1, 31.9, 51.4, 57.9, 60.1, 68.2, 71.6, 126.9, 128.1, 128.7, 139.1; MS (ES): *m*/*z* = 389 (100) [M + H^+]; HRMS (ESI^+): calcd for $C_{25}H_{45}N_2O$ 389.3532, found. 389.3518.

(2*S*,3*S*,4*S*)-4-amino-2-tetradecylpyrrolidin-3-ol (22). Twenty percent $Pd(OH)_2/C$ (11.1 mg, 23% w/w) and 12 N HCl aqueous solution (1−2 drops) were successively added to a solution of *N*-benzylpyrrolidine **20** (47.1 mg, 0.12 mmol) in MeOH (1.2 mL). The flask was purged with N_2 and then loaded with H_2 (10−12 bar). The mixture was stirred at room temperature until disappearance of the starting material (24−90 h). The catalyst was then removed by filtration through Celite and the filtrate evaporated to dryness. The residue was taken up in 2:1 MeOH/water (3 mL) and Dowex 50WX8−200 ion-exchange resin (1.44 g) was added. After being stirred for 1 h, the resin was successively filtered and washed with water and MeOH. A 3 M ammonium hydroxide solution was then added (6 mL) and the suspension was stirred for 1 h before being filtered and rinsed with a 3 M ammonium hydroxide solution (60 mL). The resulting solution was evaporated to dryness under reduced pressure. The crude product was purified by flash column chromatography on silica gel (MeOH/EtOH/NH_4OH/CH_2Cl_2, 6:12:6:76) to give **22** (24.6 mg, 70%) as a white amorphous solid. $[\alpha]_D^{25}$ +18.8 (*c* 1.3; MeOH); IR (neat) 3321 (O−H), 1601 (N−H) cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 0.90 (t, ^3J = 6.7 Hz, 3H), 1.25−1.44 (m, 24H), 1.47−1.68 (m, 2H), 2.63 (dd, ^2J = 10.8 Hz, ^3J = 9.2 Hz, 1H), 2.94 (td, ^3J = 7.0 Hz, ^3J = 2.8 Hz, 1H), 3.06 (dd, ^2J = 10.8 Hz, ^3J = 8.6 Hz, 1H), 3.35 (pseudotd, $^3J \approx {}^3J \approx 8.8$ Hz, ^3J = 4.0 Hz, 1H), 3.79 (pseudotd, $^3J \approx {}^3J \approx 9.0$ Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 14.5, 23.8, 28.1, 30.6−30.9 (10C), 31.1, 33.1, 51.6, 56.7, 64.0, 73.8; MS (ES): *m*/*z* = 299 (100) [M + H^+]; HRMS (ESI^+): calcd for $C_{18}H_{39}N_2O$ 299.3062, found 299.3054.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds; copies of ^{13}C NMR spectra for **10**−**23**, **25**; crystallographic data for *ent*-**17** and *ent*-**29**; experimental procedures and graphs for biological evaluations. This material is available free of charge via the Internet at http://pubs.acs.org.