A general, efficient and stereospecific route to sphingosine, sphinganines, phytosphingosines and their analogs

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Received 17th November 2005, Accepted 4th January 2006
First published as an Advance Article on the web 26th January 2006
DOI: 10.1039/b516333a

Sphingosine, sphinganines and phytosphingosines and their analogs were synthesized by an aldol condensation between an iminoglycinate bearing a (+)-(1*R*,2*R*,5*R*)-2-hydroxy-3-pinanone group as chiral auxiliary and an appropriate aldehyde. All condensations proceeded with excellent enantioselectivity to generate the (2*S*,3*R*)-D-*erythro* structures in good yields.

Introduction

Sphingosines, sphinganines (dihydrosphingosines) and phytosphingosines are common long-chain structural constituents of sphingolipids. This class of lipid is unusual because they bear a small positive charge at neutral pH as a consequence of intramolecular hydrogen bonding.[1] This property enables them to cross membranes or move between membranes with ease. The sphingolipids are essential components of the plasma membrane of eukaryotic cells, where they are typically found in the outer leaflet. Although particularly abundant in mammalian cells, they are also present in bacteria and fungi,[2] plants[3] and marine organisms.[4] In addition to their structural functions, they are also involved in various biological activities and play critical roles in many physiological processes, including modulation of immune response, signalling and cellular recognition.[5] Sphingosine and sphinganine can both strongly inhibit protein kinase C[6] and their ceramide derivatives are potent stimulators of the mammalian immune system.[7] Phytosphingosine is a potential heat stress signal in yeast cells,[8] and some of its derivatives exhibit important physiological activities. For example, KRN7000, an α-galactosylphytosphingosine derivative isolated from a marine sponge, binds to CD1d protein on antigen presenting cells and is a powerful immunostimulant of natural killer T (NKT) cells.[9] Recognition of the glycolipid-CD1d complex by NKT cells results in the production of several cytokines such as interferon-γ (IFN-γ) and interleukins (IL)-12 and -4.

Due to their biological significance, as well as the complication of isolation from natural sources in homogeneous form, a great deal of effort has been devoted to the synthesis of this class of compounds.[10] Despite their structural diversity, sphingoid bases share a common (2*S*,3*R*)-D-*erythro* amino alcohol moiety. Of all the methodologies, strategies based on diastereoselective asymmetric synthesis are the most challenging. Solladié-Cavallo and Koessler[11] were the first to achieve the diastereoselective synthesis of natural sphingosine using an aldol condensation strategy. These authors employed a titanium enolate derived from an iminoglycinate bearing a (+)-(1*R*,2*R*,5*R*)-2-hydroxy-3-pinanone group as chiral auxiliary. When condensing with (*E*)-2-hexadecenal the desired (2*S*,3*R*)-D-*erythro* structure was elegantly constructed in just one step and was found to be the only diastereoisomer isolated.

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This methodology was subsequently used by Li *et al*. to synthesize the deuterium and tritium labelled sphingosines,[12] and by Shioiri and Irako to prepare sulfobacin A.[13] Vo-Hoang *et al*. recently reported minor modifications for the synthesis of the natural sphingosine.[14] To the best of our knowledge this methodology has not been used to synthesize other sphingoid derivatives.

We were interested in extending Solladié-Cavallo's methodology as a general route to synthesize other members of the sphingoid family such as the truncated sphingosine (**1**),[15] sphinganines (**2a–c**), phytosphingosine (**3**) and even its 4-epimer (**4**) (Fig. 1). This appeared attractive since the stereo and enantiomeric outcome of the aldol condensation should be dictated by the (+)-(1*R*,2*R*,5*R*)-2-hydroxy-3-pinanone auxiliary while the stereochemistry of the aldehydes should have little effect.

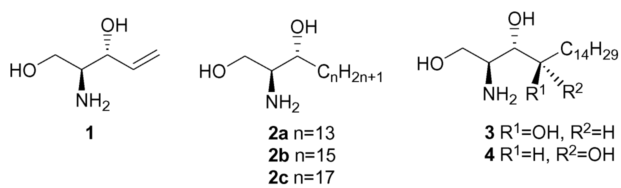
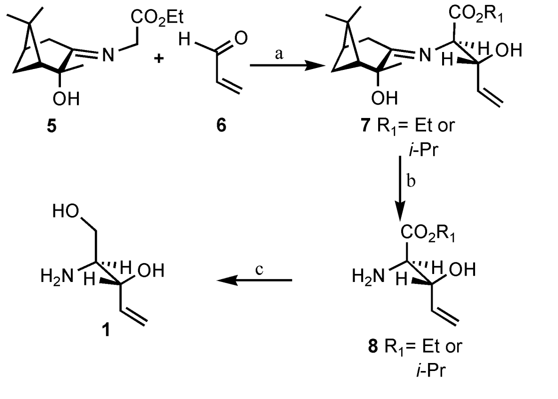


Fig. 1

Results and discussions

In research that targets ganglioside based cancer vaccines, we have designed a truncated sphingosine **1**[15] as a versatile aglycone for the synthesis of glycolipid, tumour-associated antigens.[16] Compound **1** conserves the (2*S*,3*R*)-D-*erythro* element found in natural sphingosine, while permitting flexible carbohydrate epitope–protein conjugation strategies *via* either the amino group or the double bond. In addition, the terminal double bond allows the transformation of oligosaccharides bearing **1** into the natural oligosaccharide bearing 18-carbon ceramide through a metathesis reaction with 1-pentadecene.[17,15b,c] We have designed a highly efficient process to prepare **1** on a large scale from 1,2-*O*-isopropylidene-α-D-glucofuranose.[15a] As seen in Scheme 1, compound **1** can be prepared *via* Solladié-Cavallo's route by condensing iminoglycinate **5** with acrolein **6**.

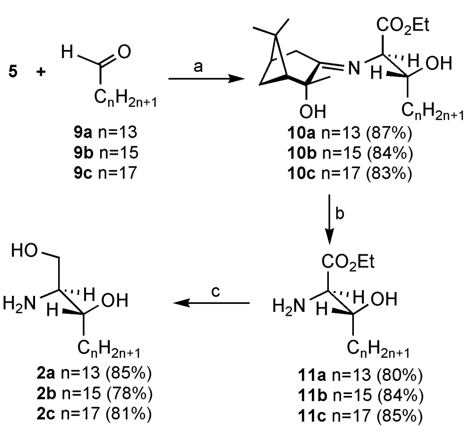
The literature reports the preparation of iminoglycinate **5** by condensation of (+)-(1*R*,2*R*,5*R*)-2-hydroxy-3-pinanone with ethyl glycinate.[18] When the aldol condensation with acrolein was first carried out using $ClTi(OPr\text{-}i)_3$ and NEt_3 as reagents, a 1:1 mixture



Scheme 1 *Reagents and conditions:* (a) $ClTi(OEt)_3$, NEt_3, CH_2Cl_2, 0 °C, 72% or $ClTi(OPr\text{-}i)_3$, NEt_3, CH_2Cl_2, 0 °C, 70%; (b) 1N HCl, THF, 82%; (c) 2M $LiBH_4$, THF–MeOH, 74%.

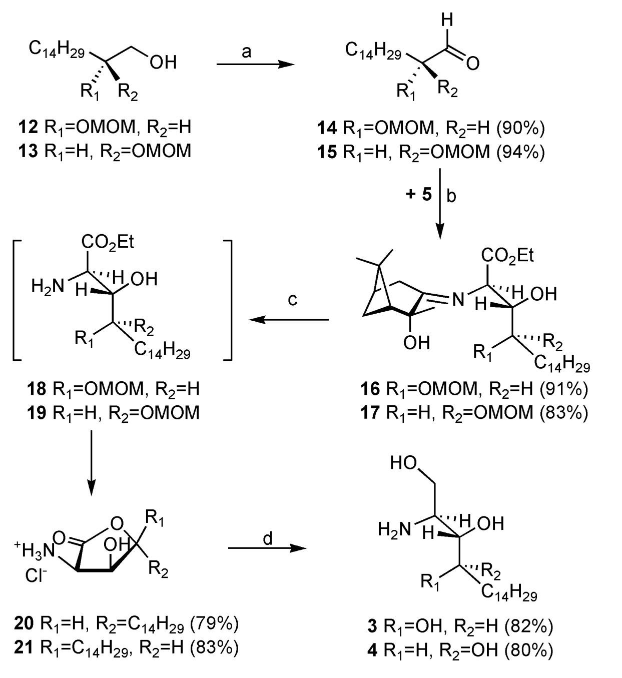
of ethyl and isopropyl esters was obtained due to a partial exchange of the ethoxy group in the glycinate ester with the isopropoxy group of the reagent. This exchange was also reported in Solladié-Cavallo's original publication.[11] However, the desired adducts **7** (R^1 = Et, and *i*-Pr), were obtained in 70% yield and each was found to be the only diastereoisomer by NMR spectroscopy. To simplify the analysis, we also performed the reaction using NEt_3 and $ClTi(OEt)_3$ (which still contained ~10% $ClTi(OPr\text{-}i)_3$) and as expected, adduct **7** (R^1 = Et) was obtained in 72% yield, as the major product, as detected by NMR spectroscopy. No 1,4-Michael addition products were observed in either case (R^1 = Et or *i*-Pr). The ethyl and isopropyl adducts **7** were both smoothly hydrolyzed in 1 M HCl in THF to yield **8** in 82% yield. Furthermore, the chiral auxiliary was recovered and could be recycled to prepare the iminoglycinate **5**. The free amino-ester **8** (Et or *i*-Pr) was reduced with $LiBH_4$ in a mixture of methanol and THF at room temperature to afford the desired truncated sphingosine analogue **1** in 74% yield.

This strategy was applied to the asymmetric syntheses of sphinganines (Scheme 2). In the literature, sphinganines are normally prepared from the hydrogenation of expensive sphingosines,[19] carbohydrates,[20] or L-serine[21] in six or more steps. However, using the strategy shown in Scheme 2, various sphinganines with different aliphatic chain lengths were successfully prepared in a concise manner. Treating the iminoglycinate **5** with three aldehydes (**9a–c**) in the presence of $ClTi(OEt)_3$ and NEt_3, the corresponding aldol adducts (**10a–c**) were obtained in yields that ranged from 83 to 87%. NMR spectroscopy revealed that only one diastereoisomer was obtained in each case. Imines (**10a–c**) were hydrolyzed under acidic conditions to afford intermediate amines **11a–c** in high yields (80–85%); and once again, the chiral auxiliary was recovered. Final reductions using $LiAlH_4$ in refluxing THF gave the desired sphinganines (**2a–c**) in 78–85%.



Scheme 2 *Reagents and conditions:* (a) $ClTi(OEt)_3$, NEt_3, CH_2Cl_2, 0 °C; (b) 1N HCl, THF; (c) $LiAlH_4$, THF, reflux.

Following the success in the syntheses of truncated sphingosine **1** and sphinganines **2a–c**, the D-*ribo*- and L-*lyxo*-phytosphingosines were the logical synthetic targets for extension of the methodology. Phytosphingosines differ from sphingosines and sphinganines by an additional stereocenter at C-4. Like sphinganines and sphingosines, the chemical synthesis of phytosphingosines usually employs carbohydrates[22] or amino acids[23] as starting materials, and a few syntheses are based on asymmetric synthesis.[24] In order to prepare phytosphingosine **3** and its 4-epimer **4**, aldehydes **14** and **15** are required. We chose to use the methoxymethyl group (MOM) for protection of the α-hydroxyl group, because this group is acid-sensitive and can be easily removed during the hydrolysis of the imine linkage. The two aldehydes were prepared from **12** and **13** by Dess–Martin oxidation.[25] Both **12** and **13** were synthesized from the commercially available 1-hexadecene according to known literature procedures (Scheme 3).[24e,26]



Scheme 3 *Reagents and conditions:* (a) Dess–Martin periodinane, CH_2Cl_2, Py, RT; (b) $ClTi(OEt)_3$, NEt_3, CH_2Cl_2, 0 °C; (c) 1N HCl, THF, RT; (d) $LiAlH_4$, THF, reflux.

Condensation of the aldehydes **14** and **15** with **5** proceeded well to give **16** and **17** in excellent yields (83–91%) and high diastereoselectivity. As predicted, the stereochemistry at the α-position of the aldehydes did not influence the stereo- and enantioselectivity of the aldol condensation. Treatment of **16** or **17** with 1N HCl smoothly cleaved both the imine and the MOM protecting group; intermediates **18** and **19** spontaneously lactonized to afford **20** and **21**, and were isolated as the hydrochloride salt in 83 and 79% yield. The stereochemistry of the lactones was confirmed by comparing the coupling patterns and the $^3J_{2,3}$ coupling constants with literature data.[24e] Finally, both lactones were reduced with $LiAlH_4$ in refluxing THF to give the desired D-*ribo*-phytosphingosine (**3**) and its 4-epimer, L-*lyxo*-phytosphingosine (**4**) in 82 and 80% yields. The overall yield from 1-hexadecene was greater than 45% in both cases.

The stereochemistry of the synthesized sphingoids was determined by NMR spectroscopy. For example, for compound **1**, in methanol-d_4, H-2 appeared as a ddd pattern at 2.77 ppm, with $J_{1a,2} \sim 4.5$ Hz, $J_{1b,2} \sim 6.8$ Hz and $J_{2,3} \sim 6.4$ Hz. H-3 also appeared as a ddd pattern, with $J_{3,4} \sim 6.1$ Hz. This is in agreement with the coupling patterns of the corresponding protons of the natural sphingosine, as reported in the literature.[11] It is also consistent with a similar compound prepared by another route.[15a] For sphinganine derivatives **2a–c**, phytosphingosine **3** and its 4-epimer **4**, unfortunately, most of the literature NMR data were recorded in pyridine-d_5, DMSO-d_6 or chloroform-d. In these solvents, due to complications resulting from coupling with the attached hydroxyl proton as well as aggregation in some solvents (such as chloroform-d) most of the key protons appear either as broad resonances or as multiplets. Rarely were coupling constants for these protons reported. We discovered all these compounds gave well resolved NMR spectra in methanol-d_4. With the suppression of coupling to the hydroxyl protons, most of the key coupling constants could be extracted. For example, for sphinganine **2b**, the H-2 resonated at 2.70 ppm as a ddd and H-3 at 3.49 as a ddd, with $J_{1a,2} \sim 4.2$ Hz, $J_{1b,2} \sim 7.6$ Hz and $J_{2,3} \sim 5.4$ Hz; for phytosphingosine **3**, the H-2 appeared as a ddd at 2.94 ppm, H-3 as a dd at 3.33 ppm and H-4 as a ddd at 3.51 ppm, with $J_{1a,2} \sim 4.2$ Hz, $J_{1b,2} \sim 6.6$ Hz, $J_{2,3} \sim 5.7$ Hz and $J_{3,4} \sim 7.8$ Hz; in addition, for the phytosphingosine 4-epimer **4**, H-2 appeared as a ddd at 2.93 ppm, H-3 as a dd at 3.32 ppm and H-4 as a ddd at 3.67 ppm, with $J_{1a,2} \sim 4.2$ Hz, $J_{1b,2} \sim 7.0$ Hz, $J_{2,3} \sim 7.0$ Hz and $J_{3,4} \sim 2.7$ Hz. That the compounds have the same (2*S*,3*R*)-D-*erythro* configuration is supported by the observation that similar $J_{2,3}$ coupling constants (5.4–7.0 Hz) were observed for the newly formed C2–C3 linkages when comparing to **1** ($J_{2,3} \sim 6.4$ Hz). Optical rotations were also consistent with literature reports.

Conclusion

We have demonstrated that the (2*S*,3*R*)-D-*erythro* amino alcohol structures, commonly found in a wide range of sphingoid bases, can be synthesized in very good yields with high diastereoselectivity by an aldol condensation between the titanium enolate derived from an iminoglycinate that bears the (+)-(1*R*,2*R*,5*R*)-2-hydroxy-3-pinanone group as chiral auxiliary, and the appropriate aldehydes. This methodology has been shown to be practical, highly versatile and amenable to the synthesis of structurally more elaborate compounds related to sphingolipids.

Experimental

General methods

Optical rotations were measured with a Perkin-Elmer 241 polarimeter for samples in a 10 cm cell at 22 ± 2 °C. Specific rotations $[\alpha]_D$ are given in units of 10^{-1} deg cm^2 g^{-1}. Analytical TLC was performed on Silica Gel 60-F_{254} (Merck, Darmstadt) with detection by quenching of fluorescence and/or by charring with 5% sulfuric acid in water. All commercial reagents were used as supplied. $Ti(OEt)_4$ was purchased from Aldrich, and contains ~15% $Ti(OPr\text{-}i)_4$. $ClTi(OEt)_3$ (containing ~10% $ClTi(OPr\text{-}i)_3$) was prepared from $Ti(OEt)_4$ and CH_3COCl according to a known procedure.[11] Column chromatography was performed on Silica Gel 60 (Silicycle, Ontario). ^{1}H NMR spectra were recorded at 300, 500, or 600 MHz. First order proton chemical shifts δ_H are referenced to either residual $CHCl_3$ (δ_H 7.24 ppm, $CDCl_3$), $CDHCl_2$ (δ_H 5.30 ppm, CD_2Cl_2) or residual CD_2HOD (δ_H 3.30 ppm, CD_3OD), or internal acetone (δ_H 2.225 ppm, D_2O). ^{13}C NMR spectra are reported to the second decimal; although it is expected that the reproducibility of chemical shifts will only be accurate to one tenth of a ppm, the reported data often include resonances separated by less than 0.1 ppm. Organic solutions were dried with anhydrous Na_2SO_4 prior to concentration under vacuum at <40 °C (bath). Microanalyses and electrospray mass spectra were performed by the analytical services of this department.

General procedure A: aldol condensation

To a solution of iminoglycinate **5** (6.0 mmol) in anhydrous CH_2Cl_2 (4 mL) was added a solution of $ClTi(OEt)_3$ (15.0 mmol) in anhydrous CH_2Cl_2 (8 mL) at 0 °C under argon; followed by the addition of Et_3N (3.5 mL), a solution of the aldehyde (6.6 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 5–6 h, and quenched by addition of brine (30 mL). The mixture was diluted with CH_2Cl_2 (20 mL) and the organic phase was separated; the aqueous phase was extracted with more CH_2Cl_2 (2 × 50 mL), and organic layers were combined, dried and concentrated. Chromatography on silica gel (pretreated with 15% Et_3N in eluent) afforded the desired compounds.

For the condensation with acrolein, we also employed $ClTi(OPr\text{-}i)_3$ as reagent in a similar fashion (not shown in the experimental section). Ethyl and isopropyl esters were obtained as a 1:1 mixture of single diastereoisomers in 70% yield.

General procedure B: acid hydrolysis of imines

The imines (4.6 mmol) were dissolved in a mixture of 1.0 N HCl (32 mL) and THF (8 mL) and the mixture was stirred for 3 days at room temperature. The mixture was extracted with Et_2O (2 × 20 mL), and the organic phase containing mainly the auxiliary was evaporated. The aqueous phase was neutralized to pH 8 with a solution of sat. $NaHCO_3$, and extracted with CH_2Cl_2 until no more desired compounds could be detected by TLC. The combined extracts were dried and concentrated. Column chromatography on silica gel gave the desired amino esters.

General procedure C: reduction of the amino esters

Reduction with $LiAlH_4$. To a solution of amino ester (1.5 mmol) in anhydrous THF (35 mL) at 0 °C, was added $LiAlH_4$ (15 mmol) in small portions under argon; the mixture was heated at reflux for 3 days. The reaction was cooled and the mixture was filtered through a thin pad of silica gel using CH_2Cl_2–MeOH–NH_4OH (100:15:2) as eluent. After concentration, the residue was purified by column chromatography to provide the desired sphingoids.

Reduction with $LiBH_4$. To a solution of amino ester (2.5 mmol) in methanol (15 mL) was added dropwise a solution of 2 M $LiBH_4$ in THF (7.5 mL, 15 mmol) at room temperature. The reaction was continued for 3 days and concentrated. The residue was loaded onto a thin pad of silica gel and eluted with CH_2Cl_2–MeOH–NH_4OH (100:15:2) to afford the crude product. After concentration, the residue was purified by column chromatography to give the desired sphingoids.

General procedure D: oxidation with Dess–Martin periodinane (DMP)

To a suspension of DMP (8.0 mmol) in anhydrous CH_2Cl_2 (45 mL), was added pyridine (1.5 mL); the resulting slurry was stirred until all the reagents dissolved. A solution of alcohol (7.9 mmol) in anhydrous CH_2Cl_2 (20 ml) was added dropwise and the reaction was continued at room temperature for 5 h. A solution of sat. brine (20 ml) and sat. Na_2SO_3 (20 ml) was added and the organic phase was separated; the aqueous phase was extracted with more CH_2Cl_2 (3 × 50 ml), and the organic extracts were combined, washed with water (1 × 100 ml) and brine (1 × 40 ml), dried and evaporated. The desired aldehydes were obtained after column chromatography.

Ethyl {1*R*-[1α,2β,3(2*R*,3*R*),5α]}-3-hydroxy-2-[(2-hydroxy-2,6,6-trimethylbicyclo [3,1,1]hept-3-ylidene)amino]-4-pentenoate (7). This compound was prepared according to the general procedure **A** using ClTi(OEt)$_3$ as reagent. Compound **7** was obtained as a single diastereoisomer by chromatography on silica gel (eluent: hexane–EtOAc 4:1) and was found to contain ~10% isopropyl ester. Yield 72%. R_f: 0.43 (hexane–EtOAc 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz): δ_H 5.88 (ddd, 1H, J = 17.0, 10.5, 6.2 Hz), 5.38 (ddd, 1H, J = 17.0, 1.5, 1.5 Hz), 5.22 (ddd, 1H, J = 10.6, 1.5, 1.5 Hz), 4.62 (dd, 1H, J = 6.3, 6.3 Hz), 4.15–4.25 (m, 3H), 3.22 (broad s, 1H), 2.56 (dd, 1H, J = 18.0, 3.0 Hz), 2.53 (ddd, 1H, J = 18.0, 2.6, 2.6 Hz), 2.47 (broad s, 1H), 2.34 (ddd, 1H, J = 10.7, 6, 6, 2.3 Hz), 2.08 (dd, 1H, J = 5.9, 5.9 Hz), 2.03 (ddd, 1H, J = 6.0, 6.0, 3.0 Hz), 1.54 (d, 1H, J = 10.7 Hz), 1.50 (s, 3H), 1.33 (s, 3H), 1.24 (t, 3H, J = 7.1 Hz), 0.87 (s, 3H); for the isopropyl ester, all signals overlap with the ethyl ester except the signal at 5.05 (sept, 1H, J = 6.5 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 180.66, 169.94, 136.50, 116.99, 76.71, 73.77, 67.00, 61.14, 50.22, 38.60, 38.39, 34.15, 28.18, 27.95, 27.26, 22.74, 14.13. HRMS m/z calc'd for $C_{17}H_{28}NO_4$ (M + H$^+$): 310.2018; found 310.2018.

Ethyl (2*R*,3*R*)-2-amino-3-hydroxy-4-pentenoate (8). This compound was prepared according to the general procedure **B**. Compound **8** (containing trace amounts of isopropyl ester) was obtained by chromatography on silica gel (eluent: CH_2Cl_2–CH_3OH–NH_4OH 100:2.5:1). Yield: 82%. R_f: 0.27 (CH_2Cl_2–MeOH–NH_4OH 100:5:1). ^{1}H NMR (CD_3OD, 500 MHz): δ_H 5.73 (ddd, 1H, J = 16.7, 10.5, 6.5 Hz), 5.33 (ddd, 1H, J = 17.0, 1.6, 1.6 Hz), 5.21 (ddd, 1H, J = 10.5, 1.5, 1.5 Hz), 4.39 (dddd, 1H, J = 5.2, 5.2, 1.4, 1.4 Hz), 4.19 (dq, 1H, J = 10.8, 7.2 Hz), 4.16 (dq, 1H, J = 10.8, 7.2 Hz), 3.61 (d, 1H, J = 5.0 Hz), 1.26 (t, 3H, J = 7.0 Hz); ^{13}C NMR (CD_3OD, 125 MHz): δ_C 173.16, 135.57, 117.33, 72.63, 61.18, 58.45 14.178. HRMS m/z calc'd for $C_7H_{14}NO_3$ (M + H$^+$): 160.0974; found 160.0974. Anal. calc'd for $C_7H_{13}NO_3$: C, 52.82; H, 8.23; N, 8.80; found: C, 52.92,; H, 8.36; N, 8.31%.

(2*S*,3*R*)-2-Aminopent-4-ene-1,3-diol (1). This compound was prepared according to the general procedure **C** using $LiBH_4$ as reducing reagent. Compound **1** was obtained as a single diastereoisomer by chromatography on silica gel (eluent: CH_2Cl_2–CH_3OH–NH_4OH 100:10:1). Yield 74%. $[\alpha_{25}^{D}]$: +18.5° (c 0.75, MeOH). R_f: 0.27 (CH_2Cl_2–MeOH–NH_4OH 100:20:1). ^{1}H NMR (CD_3OD, 500 MHz): δ_H 5.90 (ddd, 1H, J = 17.0, 10.5, 6.5 Hz), 5.30 (ddd, 1H, J = 17.0, 1.6, 1.6 Hz), 5.21 (ddd, 1H, J = 10.5, 1.6, 1.6 Hz), 4.03 (dddd, 1H, J = 6.2, 6.1, 1.3, 1.3 Hz), 3.60 (dd, 1H, J = 10.9, 4.5 Hz), 3.50 (dd, 1H, J = 10.9, 6.9 Hz), 2.77 (ddd, 1H, J = 6.8, 6.4, 4.5 Hz); ^{13}C NMR (CD_3OD, 125 MHz): δ_C 139.34, 117.08, 75.33, 64.24, 57.80. HRMS m/z calc'd for $C_5H_{11}NO_2Na$ (M + Na$^+$): 140.0682; found 140.0680. Anal. calc'd for $C_5H_{11}NO_2$: C, 51.26; H, 9.46; N, 11.96; found: C, 51.28,; H, 9.57; N, 11.36%.

Ethyl {1*R*-[1α,2β,3(2*R*,3*R*),5α]}-3-hydroxy-2-{(2-hydroxy-2,6,6-trimethylbicyclo[3,1,1]hept-3-ylidene)amino}hexadecanoate (10a). This compound was prepared according to the general procedure **A** using ClTi(OEt)$_3$ as reagent. Compound **10a** (containing trace amounts of isopropyl ester) was obtained as a single diastereoisomer by chromatography on silica gel (eluent: hexane–EtOAc 6:1). Yield: 87%. R_f: 0.29 (hexane–EtOAc 4:1). ^{1}H NMR ($CDCl_3$, 600 MHz): δ_H 4.19 (dq, 2H, J = 7.2, 2.8 Hz), 4.11 (d, 1H, J = 6.3 Hz), 4.07 (m, 1H), 3.01 (br s, 1H), 2.58 (dd, 1H, J = 18.0, 3.0 Hz), 2.53 (ddd, 1H, J = 18.0, 2.5, 2.5 Hz), 2.35 (dddd, 1H, J = 10.7, 6.0, 6.0, 2.3 Hz), 2.09 (dd, 1H, J = 5.9, 5.8 Hz), 2.04 (ddd, 1H, J = 6.0, 5.9, 3.0 Hz), 1.55 (d, 1H, J = 10.7 Hz), 1.50 (s, 3H), 1.33 (s, 3H), 1.25 (t, 3H, J = 7.1 Hz), 1.25–1.50 (m, 24H), 0.88 (t, 3H, J = 7.0 Hz), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 180.37, 170.59, 76.74, 72.62, 67.07, 61.12, 50.13, 38.64, 38.42, 34.10, 32.78, 31.92, 29.68–29.61 (7C), 29.34, 28.31, 28.03, 27.29, 25.52, 22.80, 22.68, 14.16, 14.10. HRMS m/z calc'd for $C_{28}H_{52}NO_4$ (M + H$^+$): 466.3891; found 466.3893.

Ethyl {1*R*-[1α,2β,3(2*R*,3*R*),5α]}-3-hydroxy-2-{(2-hydroxy-2,6,6-trimethylbicyclo[3,1,1]hept-3-ylidene)amino}octadecanoate (10b). This compound was prepared according to general procedure **A** using ClTi(OEt)$_3$ as reagent. Compound **10b** (containing trace amounts of isopropyl ester) was obtained as a single diastereoisomer by chromatography on silica gel (eluent: hexane–EtOAc 6:1). Yield: 84%. R_f: 0.34 (hexane–EtOAc 4:1). ^{1}H NMR ($CDCl_3$, 600 MHz): δ_H 4.15 (dq, 2H, J = 7.2, 2.3 Hz), 4.09 (d, 1H, J = 6.0 Hz), 4.04 (m, 1H), 3.22 (br s, 1H), 2.53 (dd, 1H, J = 18.0, 2.5 Hz), 2.49 (ddd, 1H, J = 18.0, 2.5, 2.5 Hz), 2.32 (dddd, 1H, J = 10.8, 6.0, 5.9, 2.3 Hz), 2.06 (dd, 1H, J = 5.9, 5.9 Hz), 2.01 (ddd, 1H, J = 6.0, 5.9, 3.0 Hz), 1.52 (d, 1H, J = 10.7 Hz), 1.48 (s, 3H), 1.30 (s, 3H), 1.24 (t, 3H, J = 7.2 Hz), 1.25–1.50 (m, 28H), 0.85 (t, 3H, J = 6.8 Hz), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 180.43, 170.54, 76.75, 72.65, 67.09, 61.10, 50.14, 38.64, 38.42, 34.06, 32.78, 31.92, 29.69–29.62 (9C), 29.35, 28.29, 28.02, 27.28, 25.55, 22.79, 22.68, 14.15, 14.10. HRMS m/z calc'd for $C_{30}H_{56}NO_4$ (M + H$^+$): 494.4204; found 494.4202.

Ethyl {1*R*-[1α,2β,3(2*R*,3*R*),5α]}-3-hydroxy-2-{(2-hydroxy-2,6,6-trimethylbicyclo[3,1,1]hept-3-ylidene)amino}icosanoate (10c). This compound was prepared according to the general procedure **A** using ClTi(OEt)$_3$ as reagent. Compound **10c** (containing trace amounts of isopropyl ester) was obtained as a single diastereoisomer by chromatography on silica gel (eluent: hexane–EtOAc 6:1). Yield: 83%. R_f: 0.34 (hexane–EtOAc 4:1). ^{1}H NMR

($CDCl_3$, 500 MHz): δ_H 4.17 (dq, 2H, $J = 7.1, 2.0$ Hz), 4.10 (d, 1H, $J = 6.1$ Hz), 4.07 (m, 1H), 3.20 (br s, 1H), 2.57 (dd, 1H, $J = 18.0, 2.8$ Hz), 2.50 (ddd, 1H, $J = 18.0, 2.5, 2.5$ Hz), 2.33 (dddd, 1H, $J = 10.8, 6.0, 5.9, 2.3$ Hz), 2.06 (dd, 1H, $J = 5.9, 5.9$ Hz), 2.02 (ddd, 1H, $J = 5.9, 5.8, 2.8$ Hz), 1.52 (d, 1H, $J = 10.9$ Hz), 1.50 (s, 3H), 1.31 (s, 3H), 1.22 (t, 3H, $J = 7.2$ Hz), 1.25–1.50 (m, 32H), 0.88 (t, 3H, $J = 7.0$ Hz), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 180.35, 170.55, 76.66, 72.61, 67.05, 61.08, 50.13, 42.90, 38.60, 38.40, 34.07, 32.76, 31.90, 29.33–29.67 (11C), 28.27, 28.03, 27.26, 25.52, 22.77, 22.65, 14.13, 14.08. HRMS *m/z* calc'd for $C_{32}H_{60}NO_4$ ($M + H^+$): 522.4517; found 522.4519.

Ethyl (2*R*,3*R*)-2-amino-3-hydroxyhexadecanoate (11a). This compound was prepared according to the general procedure **B**. Compound **11a** was obtained by chromatography on silica gel (eluent: Et_2O–CH_3OH 25:1). Yield: 80%. R_f: 0.31 (Et_2O–MeOH 20:1). $[\alpha]_{25}^{D}$: −7.4 (*c* 0.50, MeOH). ^{1}H NMR (CD_3OD, 600 MHz): δ_H 4.33 (dq, 1H, $J = 10.8, 7.1$ Hz), 4.29 (dq, 1H, $J = 10.8, 7.1$ Hz), 4.04 (d, 1H, $J = 3.3$ Hz), 3.99 (ddd, 1H, $J = 9.0, 3.7, 3.7$ Hz), 1.59 (m, 1H), 1.50 (m, 1H), 1.32 (t, 3H, $J = 7.1$ Hz), 1.25–1.40 (m, 22H), 0.89 (t, 3H, $J = 7.0$ Hz); ^{13}C NMR (CD_3OD, 125 MHz): δ_C 168.34, 70.74, 63.54, 58.96, 33.63, 33.07, 30.85, 30.79, 30.77, 30.75, 30.68, 30.57, 30.46, 30.42, 26.91, 23.73, 14.44, 14.43. HRMS *m/z* calc'd for $C_{18}H_{38}NO_3$ ($M + H^+$): 316.2846; found 316.2845. Anal. calc'd for $C_{18}H_{37}NO_3$: C, 61.43; H, 10.88; N, 3.98; found: C, 61.47; H, 11.07; N, 3.73%.

Ethyl (2*R*,3*R*)-2-amino-3-hydroxyoctadecanoate (11b). This compound was prepared according to the general procedure **B**. Compound **11b** was obtained by chromatography on silica gel (eluent: Et_2O–CH_3OH 25:1). Yield: 84%. R_f: 0.34 (Et_2O–MeOH 20:1). $[\alpha]_{25}^{D}$: −9.6 (*c* 0.57, MeOH). ^{1}H NMR (CD_3OD, 600 MHz): δ_H 4.32 (dq, 1H, $J = 10.8, 7.2$ Hz), 4.28 (dq, 1H, $J = 10.8, 7.2$ Hz), 4.04 (d, 2H, $J = 3.3$ Hz), 3.99 (ddd, 1H, $J = 8.7, 5.0, 3.3$ Hz), 1.59 (m, 1H), 1.50 (m, 1H), 1.32 (t, 3H, $J = 7.2$ Hz), 1.25–1.40 (m, 26H), 0.89 (t, 3H, $J = 7.0$ Hz); ^{13}C NMR (CD_3OD, 125 MHz): δ_C 168.32, 70.73, 63.54, 58.95, 33.64, 33.07, 30.79–30.43 (10C), 26.92, 23.72, 14.45 (2C). HRMS *m/z* calc'd for $C_{20}H_{42}NO_3$: 344.3159 ($M + H^+$); found 344.3159. Anal. calc'd for $C_{20}H_{41}NO_3$: C, 63.21; H, 11.14; N, 3.69; found: C, 63.31; H, 11.25; N, 3.48%.

Ethyl (2*R*,3*R*)-2-amino-3-hydroxyicosanoate (11c). This compound was prepared according to the general procedure **B**. Compound **11c** was obtained by chromatography on silica gel (eluent: Et_2O–CH_3OH 25:1). Yield: 85%. R_f: 0.35 (Et_2O–MeOH 20:1). $[\alpha]_{25}^{D}$: −6.8 (*c* 0.6, MeOH). ^{1}H NMR (CD_3OD, 600 MHz): δ_H 4.27 (dq, 1H, $J = 10.8, 7.2$ Hz), 4.23 (dq, 1H, $J = 10.8, 7.2$ Hz), 3.87 (ddd, 1H, $J = 9.0, 8.9, 3.8$ Hz), 3.76 (d, 1H, $J = 3.8$ Hz), 1.52–1.60 (m, 2H), 1.30 (t, 3H, $J = 7.2$ Hz), 1.25–1.40 (m, 30H), 0.89 (t, 3H, $J = 7.0$ Hz); ^{13}C NMR (CD_3OD, 125 MHz): δ_C 174.37, 74.37, 61.98, 60.37, 33.81, 33.07, 30.90–30.47 (12C), 27.02, 23.74, 14.56, 14.44. HRMS *m/z* calc'd for $C_{22}H_{46}NO_3$ ($M + H^+$): 372.3472; found 372.3471. Anal. calc'd for $C_{22}H_{45}NO_3$: C, 64.75; H, 11.36; N, 3.43; found: C, 64.78; H, 11.43; N, 3.27%.

(2*S*,3*R*)-2-Aminohexadecane-1,3-diol (2a). This compound was prepared according to the general procedure **C** using $LiAlH_4$ as reducing reagent. Compound **2a** was obtained by chromatography on silica gel (eluent: CH_2Cl_2–CH_3OH–NH_4OH 100:10:1). Yield: 85%. $[\alpha]_{25}^{D}$: +8.7 (*c* 1.0, MeOH). R_f: 0.21 (CH_2Cl_2–MeOH–NH_4OH 100:10:2). ^{1}H NMR (CD_3OD, 600 MHz): δ_H 3.72 (dd, 1H, $J = 10.9, 4.2$ Hz), 3.50 (ddd, 1H, $J = 8.0, 5.5, 3.0$ Hz), 3.46 (dd, 1H, $J = 10.9, 7.6$ Hz), 2.71 (ddd, 1H, $J = 7.6, 5.4, 4.2$ Hz), 1.52 (m, 2H), 1.25–1.45 (m, 22H), 0.9 (t, 3H, $J = 7.0$ Hz); ^{13}C NMR (CD_3OD, 125 MHz): δ_C 74.03, 64.30, 58.15, 34.40, 33.07, 30.82–30.75 (8C), 27.03, 23.73, 14.42. HRMS *m/z* calc'd for $C_{16}H_{36}NO_2$ ($M + H^+$): 274.2741; found 274.2743. Anal. calc'd for $C_{16}H_{35}NO_2$: C, 70.28; H, 12.90; N, 5.12; found: C, 69.65; H, 12.91; N, 5.04%.

(2*S*,3*R*)-2-Aminooctadecane-1,3-diol (2b). This compound was prepared according to the general procedure **C** using $LiAlH_4$ as reducing reagent. Compound **2b** was obtained by chromatography on silica gel (eluent: CH_2Cl_2–CH_3OH–NH_4OH 100:10:1). Yield: 78%. $[\alpha]_{25}^{D}$: +8.1 (*c* 1.0, MeOH). lit.[21] $[\alpha]_{25}^{D}$: +1.83 (*c* 1.0, pyridine), lit.[24e] $[\alpha]_{25}^{D}$: +5.7 (*c* 2.74, $CHCl_3$–MeOH 4:1). R_f: 0.41 (CH_2Cl_2–MeOH–NH_4OH 100:20:2). ^{1}H NMR (CD_3OD, 600 MHz): δ_H 3.72 (dd, 1H, $J = 10.9, 4.2$ Hz), 3.49 (ddd, 1H, $J = 8.0, 5.5, 3.0$ Hz), 3.46 (dd, 1H, $J = 10.9, 7.6$ Hz), 2.70 (ddd, 1H, $J = 7.6, 5.4, 4.2$ Hz), 1.52 (m, 2H), 1.25–1.45 (m, 26H), 0.9 (t, 3H, $J = 7.0$ Hz); ^{13}C NMR (CD_3OD, 125 MHz): δ_H 74.07, 64.37, 58.15, 34.41, 33.07, 30.08–30.75 (10C), 27.04, 23.73, 14.43. HRMS *m/z* calc'd for $C_{18}H_{40}NO_2$ ($M + H^+$): 302.3054; found 302.3055. Anal. calc'd for $C_{18}H_{39}NO_2$: C, 71.70; H, 13.04; N, 4.65; found: C, 71.46; H, 12.95; N, 4.58%.

(2*S*,3*R*)-2-Aminoicosane-1,3-diol (2c). This compound was prepared according to the general procedure **C** using $LiAlH_4$ as reducing reagent. Compound **2c** was obtained by chromatography on silica gel (eluent: CH_2Cl_2–CH_3OH–NH_4OH 100:10:1). Yield: 81%. $[\alpha]_{25}^{D}$: +6.5 (*c* 0.9, $CHCl_3$–MeOH 4:1). R_f: 0.19 (CH_2Cl_2–MeOH–NH_4OH 100:10:2). ^{1}H NMR (CD_3OD, 600 MHz): δ_H 3.72 (dd, 1H, $J = 10.9, 4.2$ Hz), 3.49 (ddd, 1H, $J = 8.0, 5.5, 3.0$ Hz), 3.46 (dd, 1H, $J = 10.9, 7.6$ Hz), 2.70 (ddd, 1H, $J = 7.5, 5.4, 4.2$ Hz), 1.53 (m, 2H), 1.25–1.44 (m, 30H), 0.9 (t, 3H, $J = 7.0$ Hz); ^{13}C NMR (CD_3OD, 125 MHz): δ_H 74.11, 64.37, 58.15, 34.41, 33.07, 30.78–30.50 (12C), 27.039, 23.74, 14.43. HRMS *m/z* calc'd for $C_{20}H_{44}NO_2$ ($M + H^+$): 330.3366; found 330.3363. Anal. calc'd for $C_{20}H_{43}NO_2$: C, 72.89; H, 13.15; N, 4.25; found: C, 72.56; H, 13.04; N, 4.16%.

(2*R*)-2-Methoxymethoxyhexadecanal (14). This compound was prepared according to the general procedure **D**. Compound **14** was obtained by chromatography on silica gel (eluent: hexane–EtOAc 20:1). Yield: 90%. $[\alpha]_{25}^{D}$: +24.7 (*c* 1.0, $CHCl_3$). R_f: 0.51 (hexane–EtOAc 6:1). ^{1}H NMR (CD_2Cl_2, 500 MHz): δ_H 9.58 (d, 1H, $J = 2.0$ Hz), 4.70 (d, 1H, $J = 7.0$ Hz), 4.68 (d, 1H, $J = 7.0$ Hz), 3.85 (ddd, 1H, $J = 6.6, 5.6, 2.0$ Hz), 3.39 (s, 3H), 1.64 (m, 2H), 1.41 (m, 2H), 1.20–1.35 (m, 22H), 0.89 (t, 3H, $J = 7.0$ Hz); ^{13}C NMR (CD_2Cl_2, 125 MHz): δ_C 203.28, 97.15, 82.86, 56.12, 32.32, 30.37, 30.08–29.75 (9C), 25.21, 23.08, 14.26. HRMS *m/z* calc'd for $C_{18}H_{36}O_3Na$ ($M + Na^+$): 323.2562; found: 323.2564. Anal. calc'd for $C_{18}H_{36}O_3$: C, 71.95; H, 12.08; found: C, 71.83; H, 12.19%.

(2*S*)-2-Methoxymethoxyhexadecanal (15). This compound was prepared according to the general procedure **D**. Compound **15** was obtained by chromatography on silica gel (eluent: hexane–EtOAc 20:1). Yield: 94%. $[\alpha]_{25}^{D}$: −24.3 (*c* 0.9, $CHCl_3$). R_f: 0.50 (hexane–EtOAc 6:1). ^{1}H NMR (CD_2Cl_2, 500 MHz): δ_H 9.58 (d, 1H, $J = 2.0$ Hz), 4.70 (d, 1H, $J = 7.0$ Hz), 4.68 (d, 1H, $J = 7.0$ Hz), 3.86 (ddd, 1H, $J = 7.6, 5.6, 2.2$ Hz), 3.39 (s, 3H), 1.62–1.68 (m, 2H), 1.40 (m, 2H), 1.25–1.35 (m, 22H), 0.89 (t, 3H, $J = 7.0$ Hz); ^{13}C NMR (CD_2Cl_2, 125 MHz): δ_C 203.28, 97.15, 82.84, 56.12, 32.32, 30.37, 30.08–29.75 (9C), 25.21, 23.08, 14.26. HRMS m/z calc'd for $C_{18}H_{36}O_3Na$ (M + Na$^+$): 323.2562; found: 323.2561. Anal. calc'd for $C_{18}H_{36}O_3$: C, 71.95; H, 12.08; found: C, 71.62; H, 12.14%.

Ethyl {1*R*-[1α,2β,3(2*R*,3*R*,4*R*),5α]}-3,4-dihydroxy-2-{(2-hydroxy-2,6,6-trimethylbicyclo[3,1,1] hept-3-ylidene)amino}octadecanoate (16). This compound was prepared according to the general procedure **A** using ClTi(OEt)$_3$ as reagent. Compound **16** (containing trace amounts of isopropyl ester) was obtained as a single diastereoisomer by chromatography on silica gel (eluent: hexane–EtOAc 6:1). Yield: 91%. R_f: 0.31 (hexane–EtOAc 3:1). ^{1}H NMR ($CDCl_3$, 600 MHz): δ_H 4.78 (d, 1H, J = 6.7 Hz), 4.58 (d, 1H, J = 6.8 Hz), 4.24–4.30 (m, 2H), 4.17 (dt, 2H, J = 7.1, 0.9 Hz), 3.67 (dt, 1H, J = 8.5, 3.2 Hz), 3.41 (s, 3H), 3.23 (br s, 1H), 2.58 (broad s, 2H), 2.32 (ddd, 1H, J = 10.7, 6.0, 5.8 Hz), 2.06 (dd, 1H, J = 6.0, 5.9 Hz), 2.02 (ddd, 1H, J = 6.0, 5.9, 3.0 Hz), 1.58–1.70 (m, 2H), 1.52 (d, 1H, J = 10.7 Hz), 1.47 (s, 3H), 1.33 (s, 3H), 1.25 (t, 3H, J = 7 Hz), 1.25–1.30 (m, 24H), 0.88 (t, 3H, J = 7.0 Hz), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 180.27, 170.21, 96.45, 78.92, 76.71, 73.82, 64.63, 61.07, 55.81, 50.23, 38.64, 38.43, 34.13, 31.91, 30.23, 29.77–29.35 (7C), 28.26, 28.02, 27.27, 25.36, 22.78, 22.67, 14.16, 14.09. HRMS m/z calc'd for $C_{32}H_{60}NO_6$ (M + H$^+$): 554.4421; found 554.4423.

Ethyl {1*R*-[1α,2β,3(2*R*,3*R*,4*R*),5α]}-3,4-dihydroxy-2-{(2-hydroxy-2,6,6-trimethylbicyclo[3,1,1] hept-3-ylidene)amino}octadecanoate (17). This compound was prepared according to the general procedure **A** using ClTi(OEt)$_3$ as reagent. Compound **17** (containing trace amounts of isopropyl ester) was obtained as a single diastereoisomer by chromatography on silica gel (eluent: hexane–EtOAc 6:1). Yield: 83%. R_f: 0.32 (hexane–EtOAc 3:1). ^{1}H NMR ($CDCl_3$, 600 MHz): δ_H 4.66 (d, 1H, J = 6.4 Hz), 4.63 (d, 1H, J = 6.4 Hz), 4.31 (d, 1H, J = 8.2 Hz), 4.20 (quint, 2H, J = 7.0 Hz), 4.12 (quint, 1H, J = 7.1 Hz), 3.57 (ddd, 1H, J = 8, 5.9, 2 Hz), 3.37 (s, 3H), 3.01 (broad s, 1H), 2.66 (dd, 1H, J = 8.2, 2.8 Hz), 2.58 (ddd, 1H, J = 8.1, 2.5, 2.5 Hz), 2.34 (dddd, 1H, J = 10.7, 6.0, 5.8, 2.5 Hz), 2.08 (dd, 1H, J = 5.9, 5.9 Hz), 2.03 (ddd, 1H, J = 6.0, 5.9, 2.9 Hz), 1.74 (m, 1H), 1.64 (m, 1H), 1.52 (d, 1H, J = 10.7 Hz), 1.48 (s, 3H), 1.32 (s, 3H), 1.24 (t, 3H, J = 7.0 Hz), 1.25–1.30 (m, 24H), 0.88 (t, 3H, J = 7.0 Hz), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 180.48, 170.99, 96.55, 77.94, 76.67, 73.43, 64.98, 61.18, 60.37, 55.86, 50.21, 38.62, 38.42, 34.01, 31.91, 31.06, 29.78–29.35 (8C), 28.26, 27.97, 27.28, 25.58, 22.81, 22.68, 14.18, 14.10. HRMS m/z calc'd for $C_{32}H_{59}NO_6Na$ (M + Na$^+$): 576.4240; found 576.4239.

(2*R*,3*R*,4*R*)-2-Amino-3-hydroxyoctadecane-1,4-lactone hydrochloride (20). This compound was prepared according to the general procedure **B**. Compound **20** was obtained as a single diastereoisomer by chromatography on silica gel (eluent: CH_2Cl_2–CH_3OH–NH_4OH 100:2.5:1). Yield: 79%. R_f: 0.27 (CH_2Cl_2–MeOH–NH_4OH 100:5:2). ^{1}H NMR (CD_3OD, 600 MHz): δ_H 4.47 (d, 1H, J = 6.2 Hz), 4.45 (d, 1H, J = 7.4 Hz), 4.36 (d, 1H, J = 5.3 Hz), 1.8 (quint, 2H, J = 7.5 Hz), 1.24–1.50 (m, 24H), 0.89 (t, 3H, J = 7.0 Hz). ^{13}C NMR (CD_3OD, 125 MHz): δ_C 172.67, 89.78, 70.54, 52.15, 33.07, 32.91, 30.78, 30.77, 30.75, 30.74, 30.67, 30.57, 30.26, 26.60, 23.74, 14.43. HRMS m/z calc'd for $C_{18}H_{36}NO_3$ (M + H$^+$): 314.2690; found 314.2691. Anal. calc'd for $C_{18}H_{35}NO_3$: C, 68.97; H, 11.25; N, 4.47; found: C, 68.69; H, 11.36; N, 4.43%.

(2*R*,3*R*,4*S*)-2-Amino-3-hydroxyoctadecane-1,4-lactone hydrochloride (21). This compound was prepared according to the general procedure **B**. Compound **21** was obtained as a single diastereoisomer by chromatography on silica gel (eluent: CH_2Cl_2–CH_3OH–NH_4OH 100:2.5:1). Yield: 83%. R_f: 0.26 (CH_2Cl_2–MeOH–NH_4OH 100:5:2). ^{1}H NMR (CD_3OD, 600 MHz): δ_H 4.52 (ddd, 1H, J = 5.2, 2.6, 2.6 Hz), 4.50 (dd, 1H, J = 5.2, 5.0 Hz), 4.43 (d, 1H, J = 5.0 Hz), 1.82 (m, 1H), 1.72 (m, 1H), 1.48 (m, 2H), 1.25–1.40 (m, 22H), 0.89 (t, 3H, J = 7.0 Hz); ^{13}C NMR (CD_3OD, 125 MHz): δ_C 172.91, 84.93, 69.52, 54.40, 33.07, 30.87, 30.84, 30.78, 30.76, 30.72, 30.66, 30.60, 30.57, 30.46, 29.32, 26.33, 23.73, 14.43. HRMS m/z calc'd for $C_{18}H_{36}NO_3$ (M + H$^+$): 314.2690; found 314.2694. Anal. calc'd for $C_{18}H_{35}NO_3HCl$: C, 61.78; H, 10.37; N, 4.00; found: C, 61.50; H, 10.66; N, 3.74%.

(2*S*,3*R*,4*R*)-2-Aminooctadecane-1,3,4-triol (D-*ribo*-phytosphingosine) (3). This compound was prepared according to the general procedure **C** using $LiAlH_4$ as reducing reagent. Compound **3** was obtained by chromatography on silica gel (eluent: CH_2Cl_2–CH_3OH–NH_4OH 100:10:1). Yield 82%. $[\alpha]^D_{25}$: +7.6 (c 0.7, pyridine); lit.[22i] $[\alpha]^D_{24}$: +8.7 (c 0.8, pyridine); lit.[22j] $[\alpha]^D_{23}$: +8.5 (c 0.9, pyridine). R_f: 0.13 (CH_2Cl_2–MeOH–NH_4OH 100:10:2). ^{1}H NMR (CD_3OD, 500 MHz): δ_H 3.75 (dd, 1H, J = 10.9, 4.2 Hz), 3.56 (dd, 1H, J = 10.9, 6.6 Hz), 3.51 (ddd, 1H, J = 8.3, 8.0, 3.0 Hz), 3.33 (dd, 1H, J = 7.8, 5.6 Hz), 2.94 (ddd, 1H, J = 6.4, 5.7, 4.2 Hz), 1.73 (m, 1H), 1.55 (m, 1H), 1.25–1.40 (m, 24H), 0.9 (t, 3H, J = 7.0 Hz); ^{13}C NMR (CD_3OD, 125 MHz): δ_C 76.51, 74.51, 64.21, 55.70, 34.78, 33.08, 30.95–30.48 (9C), 26.61, 23.74, 14.44. HRMS m/z calc'd for $C_{18}H_{40}NO_3$ (M + H$^+$) 318.3002; found 318.3001. Anal. calc'd for $C_{18}H_{39}NO_3$: C, 68.09; H, 12.38; N, 4.41; found: C, 67.45; H, 12.53; N, 4.29%.

(2*S*,3*R*,4*S*)-2-Aminooctadecane-1,3,4-triol (L-*lyxo*-phytosphingosine) (4). This compound was prepared according to the general procedure **C** using $LiAlH_4$ as reducing reagent. Compound **4** was obtained by chromatography on silica gel (eluent: CH_2Cl_2–CH_3OH–NH_4OH 100:10:1). Yield: 80%. $[\alpha]^D_{25}$: −10.0 (c 1.0, pyridine); lit.[24e] $[\alpha]^D_{25}$: −7.4 (c 0.9, pyridine); lit.[22i] $[\alpha]^D_{23}$: −6.2 (c 1.0, pyridine). R_f: 0.14 (CH_2Cl_2–MeOH–NH_4OH 100:10:2). ^{1}H NMR (CD_3OD, 600 MHz): δ_H 3.76 (dd, 1H, J = 10.9, 4.2 Hz), 3.67 (ddd, 1H, J = 7.7, 4.8, 2.7 Hz), 3.52 (dd, 1H, J = 10.9, 7.0 Hz), 3.32 (dd, 1H, J = 7.0, 2.7 Hz), 2.93 (ddd, 1H, J = 7.0, 7.0, 4.3 Hz), 1.45–1.59 (m, 2H), 1.25–1.40 (m, 24H), 0.9 (t, 3H, J = 7.0 Hz); ^{13}C NMR (CD_3OD, 125 MHz): δ_C 75.31, 72.34, 64.71, 55.65, 34.64, 33.07, 30.86–30.46 (9C), 27.05, 23.73, 14.42. HRMS m/z calc'd for $C_{18}H_{40}NO_3$ (M + H$^+$): 318.3002; found 318.3002. Anal. calc'd for $C_{18}H_{39}NO_3$: C, 68.09; H, 12.38; N, 4.41; found: C, 67.70; H, 12.57; N, 4.33%.

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