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High-Yielding Synthesis of Sphingoid-Type Bases

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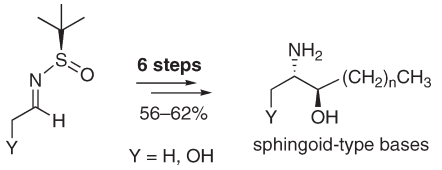

An efficient methodology for the synthesis of sphingoid-type bases is reported. It involves the stereoselective addition of a racemic 3-alkoxy allenylzinc to enantiopure *N*-*tert*-butylsulfinyl imines and a cross-metathesis reaction as the key steps. It has been successfully applied to the syntheses of sphinganine and naturally occurring bioactive related compounds, among which the hydrolysis product of clavaminol H and two spisulosines. All of these compounds have been prepared in six steps from *N*-*tert*-butylsulfinyl imines in high overall yields (> 56%).

Introduction

Sphingoid-type bases are long-chain 1,2-amino alcohols that are found in a number of bioactive natural products. For instance, ceramides,[1] which are composed of a sphingoid base linked by an amide bond to a fatty alkyl chain (Figure 1), exert a wide range of biological functions in relation to cellular signaling by triggering apoptosis and activating various protein kinase cascades. Ceramides are especially present in relatively high levels in the outermost layer of skin (as much as 50% of the total lipids).[2] Sphingolipids (Figure 1), which are composed of a polar headgroup (sugar, phosphate, or sulfate) linked to a ceramide, constitute another class of biologically important compounds. They possess diverse biological roles such as antitumor,[2] immunostimulatory, and immunosuppressive activities,[3] as well as neuronal proliferation[4] and protein kinase activity modulation.[5] In all of these compounds, sphingosine is the most prevalent sphingoid base and is biogenetically derived from enzymatic oxidation of sphinganine (Figure 1).[6] Because of the biological importance of ceramides and sphingolipids, numerous methods for the preparation of sphinganine and its derivatives have been reported in the literature from both carbohydrate and non-carbohydrate sources.[7]

Simple long-chain 1,2-amino alkanols can also exhibit remarkable biological activities. This is the case for some

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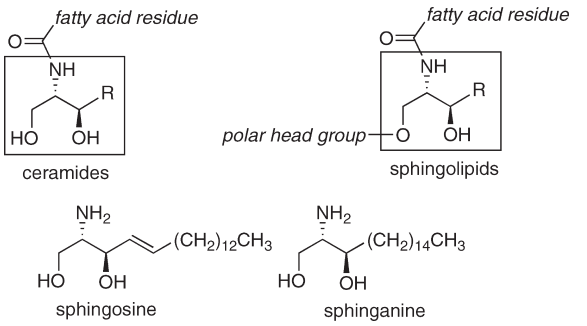


FIGURE 1. Structure of ceramides, sphingolipids, sphingosine, and sphinganine.

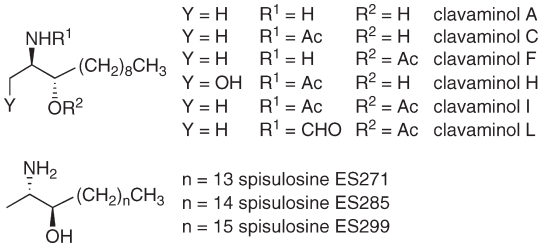
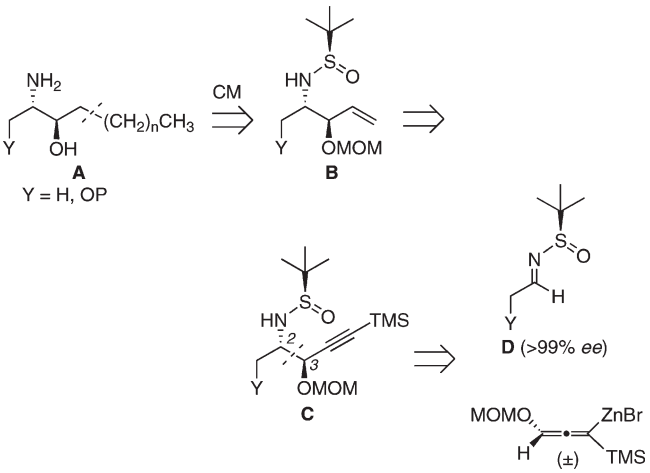


FIGURE 2. Structures of some representative clavaminols and spisulosines.

of clavaminols A−N (Figure 2), 14 new marine sphingoid-type compounds extracted from the Mediterranean ascidian *Clavelina phlegraea*, which possess cytotoxic properties against lung, breast, and gastric carcinoma cell lines by activating the apoptic machinery.[8]

Similarly, spisulosine ES285 (Figure 2) was found off the coasts of Japan and isolated in submilligram amounts (400 μg) from 35 (1.9 kg) edible clams *Spisula polynyma* (i.e., in 0.021% yield based on wet weight of clams).[9b,c] This compound has been demonstrated to possess specific long-lasting antitumor *in vitro* and *in vivo* cytotoxic activity against various tumor cell lines with selectivity (down to the nanomolar range) for certain human solid tumors such as colon, mammary, pancreas, ovary, breast, lung, kidney, pharynx, liver, and stomach tumors.[9] Studies have shown that this simple 1,2-amino alkanol, as well as a number of related compounds, exhibit an unusual type of bioactivity by triggering an atypical cell death program.[10] Because of their biological properties, natural and non-natural compounds of this type constitute highly promising antitumor agents.[11]

SCHEME 1. Proposed Retrosynthesis of Sphingoid-Type Bases



In this paper, we would like to report an efficient strategy for the asymmetric synthesis of long-chain 1,2-amino alkanols using a methodology developed in our group to access diastereo- and enantiomerically pure 1,2-amino alcohol derivatives.[12] This methodology involves the stereoselective reaction of enantiopure *N-tert*-butylsulfinyl imines[13] with racemic 3-(methoxymethoxy)-1-trimethylsilyl allenylzinc bromide and has been already successfully applied to natural product syntheses.[14]

We reasoned that long-chain 1,2-amino alkanols **A** could be obtained by subjecting intermediates **B** to cross-metathesis with the appropriate terminal alkenes and further functionalization of the resulting compounds (Scheme 1). Intermediates **B** could be obtained from *anti*-(2*S*,3*R*)-1,2-sulfinylamidoalkyl ethers **C** by desilylation at the acetylenic position followed by the semihydrogenation of the C−C triple bond. Regarding compounds **C**, they could be prepared by the stereoselective reaction of the corresponding enantiopure *N-tert*-butylsulfinyl imines **D** with racemic 3-(methoxymethoxy)allenylzinc bromide.

In this strategy, the two sterogenic centers would be created in the first step through a high dynamic kinetic

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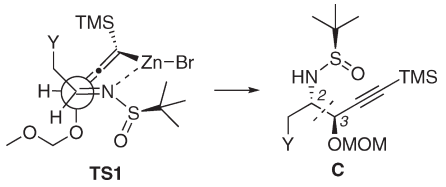
SCHEME 2. Postulated Transition State for the Formation of *anti*-(2*S*,3*R*)-Sulfinylamidoalkyl Ether C



resolution process. The required (2*S*,3*R*) stereochemistry can be anticipated from the reaction transition state **TS1** wherein the (a*R*)-enantiomer of the racemic allenylzinc approaches from the *re* face of (R_S)-*N*-*tert*-butylsulfinyl imines **D** (Scheme 2), as demonstrated by our previous studies[12] and corroborated by the successful application of our methodology to the asymmetric syntheses of several natural products in enantiomerically pure form.[14]

The versatility of this strategy is exemplified hereafter by the high-yielding syntheses of two spisulosines, i.e., spisulosines ES285 (Y = H, n = 14) and ES271 (Y = H, n = 13), of sphinganine (Y = OH, n = 14), and of the bioactive hydrolysis product of clavaminol H (Y = OH, n = 7).

Results and Discussion

Synthesis of Spisulosines. We first planned to synthetize the naturally occcuring marine bioactive spisulosine ES285, a long-chain 1,2-amino alkanol. Our synthesis then began with the reaction between *N*-*tert*-butylsulfinyl imine **1**, easily prepared with an *E*:*Z* ratio of 97:3 from enantiopure commercially or easily synthetically available (R_S)-*N*-*tert*-butylsulfinyl amide[13] and racemic allenylzinc (±)-**2**. Slow addition of **1** over a period of 45 min to an excess of (±)-**2** (4 equiv, Et_2O, −80 °C) allowed a high dynamic kinetic resolution to take place giving, after acidic workup, the desired acetylenic *anti*-(2*S*,3*R*)-sulfinylamidoalkyl ether **3** (Scheme 3). As seen from the ^{1}H NMR spectrum of the crude product, a high stereoselectivity was attained since only two diastereomers were formed in a 93:7 ratio. Purification by silica gel chromatography afforded adduct **3** in 94% yield, accompanied with an inseparable unidentified minor isomer (93:7 dr).

Further treatment of **3** with TBAF (1 equiv, THF, 0 °C, 15 min) resulted in the clean protodesilylation of the acetylenic position. The resulting crude product was subjected to semihydrogenation (1 atm H_2, 5% acetone−hexane, 20 °C, 4 h)[14a] in the presence of Lindlar palladium catalyst (20 wt % of Pd) and 3,5-dithia-1,2-octanediol (4 wt %). Intermediate **4** was thus obtained in high purity (> 95% by ^{1}H NMR) as a mixture of two isomers (91:9 dr) and could be engaged in the next step without further purification (Scheme 3).

At this stage, we expected to obtain the internal alkene derivative **5** by subjecting **4** to cross-metathesis[15,16] with 1-pentadecene. To the best of our knowledge, only one example of cross-metathesis reaction on substrates presenting a sulfinylamido moiety has been reported to date.[17] To our pleasure, product **4** could be readily converted into compound **5**, as an *E*-isomer exclusively as indicated by the ^{1}H NMR coupling constants ^3J of 15.5 Hz between the two ethylenic protons, upon reaction with 1-pentadecene (4 equiv) in the presence of Grubbs II catalyst (Scheme 3). Noteworthy, the reaction occurred smoothly (CH_2Cl_2, 60 h, 40 °C), and its completion was reached provided that 12 mol % of Grubbs II catalyst was used in three subsequent additions (3 × 4 mol %) separated by periods of 20 h. This suggested that the ruthenium species was deactivated in the reaction medium, probably by its coordination to the *N*-*tert*-butylsulfinyl moiety, as previously reported for the Hoveyda−Blechert catalyst in the cross-metathesis of *N*-*tert*-butylsulfinyl homoallylamines with methyl vinyl ketone.[17] The same phenomenon was also observed by us and others in ring-closing metathesis involving similar substrates.[14a,18] Under these conditions, compound **5** was therefore isolated in 72% overall yield (three steps from **3**) after silica gel chromatography. One minor product arising from cross-metathesis of the alkene with the minor isomer of **4** (itself obtained during the addition step) was easily separated and isolated by flash chromatography in 7% yield.

The target molecule spisulosine ES285 was finally readily obtained after acidic removal of the *N*-*tert*-butylsulfinyl auxiliary concomitant with MOM-ether deprotection using dry HCl (5 equiv, MeOH, 65 °C, 1 h). The crude material was directly subjected to hydrogenation on Pd/C (1 atm H_2, MeOH, 20 °C, 20 h). Simple filtration of the catalyst through a pad of Celite then afforded spisulosine ES285 with high purity (> 95% by ^{1}H NMR) as a white solid in 93% overall yield (Scheme 3). An analytically pure sample of this compound could be obtained by further silica gel chromatography. Worthy of note, the obtained compound exhibited ^{1}H and ^{13}C NMR spectra in CD_3OD (at 400 and 100 MHz, respectively) in accordance with those reported[9c] for spisulosine ES285 (at 500 and 100 MHz, respectively). By contrast, due to the insolubility of our product in $CDCl_3$, we could not determined its optical rotation in this solvent. Thus, we were not able to compare the optical rotation measured for our product [($[\alpha]^{20}_D$ +5.2 (*c* 0.36, MeOH)] with the only value reported in the literature for spisulosine ES285 [($[\alpha]^{26}_D$ +24.9 (*c* 1, $CHCl_3$)].[9c] Differences were also found in the melting points (mp 115−116 °C vs 66−67 °C[9c]). Although the origin of the problem is not clear, both the acidity of $CDCl_3$ and the final mode of purification may be invoked to explain the differences in the data.

Thus, spisulosine ES285 has been prepared in six steps from *N*-*tert*-butylsulfinyl imine **1** in 62% overall yield. Spisulosine ES271, a non-natural sphingoid-type base also highly active against prostate cancer, sarcomas, and melanomas,[9a] could similarly be prepared from intermediate **3** (Scheme 3) by (i) protodesilylation, semihydrogenation, and subsequent cross-metathesis with 1-tetradecene (giving **6** in 67% yield over the three steps) and finally (ii) acidic treatment and hydrogenation (giving spisulosine ES271 in 92% yield over the two steps). Spisulosine ES271 was thus isolated as a white solid in 58% overall yield from **1**. Its spectral

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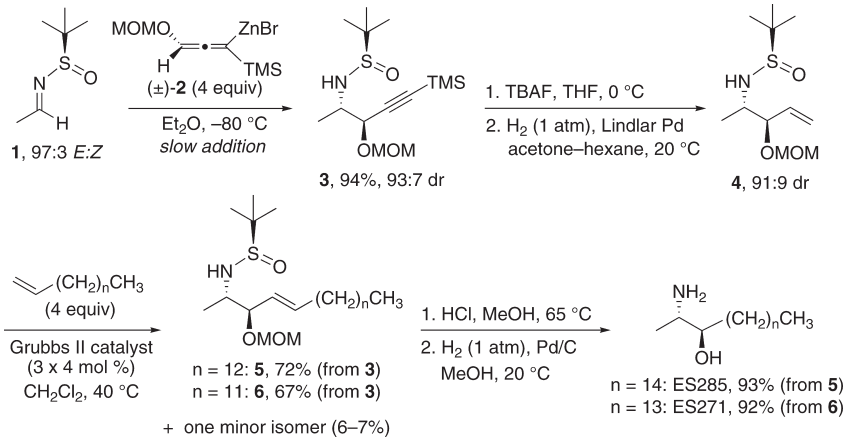
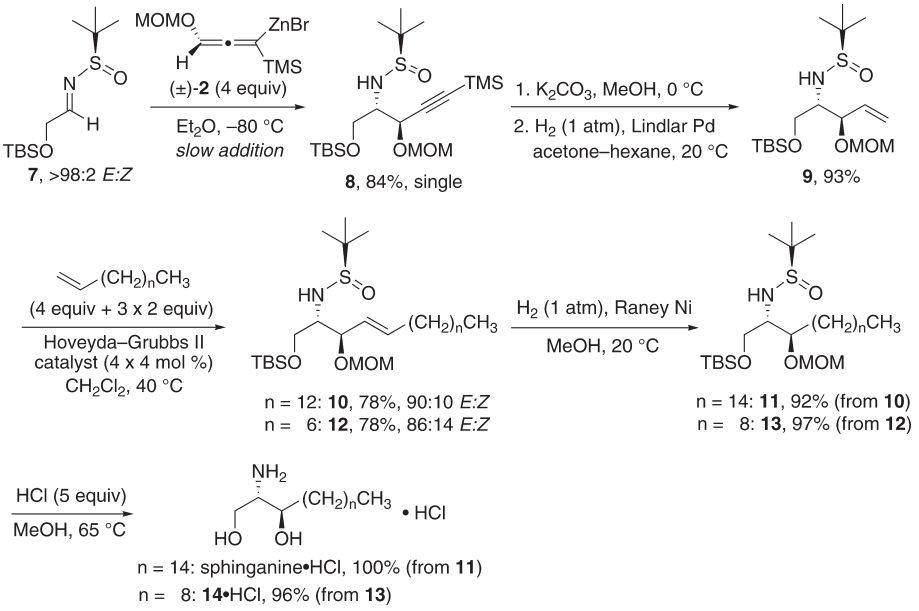
SCHEME 3. Synthesis of Spisulosines



SCHEME 4. Syntheses of Sphinganine and the Hydrolysis Product of Clavaminol H



and physical data [$([\alpha]^{20}_{D}$ +8.1 (*c* 0.32, MeOH), mp 117−119 °C)], which were not reported so far, were similar to those of spisulosine ES285.

Syntheses of Sphinganine and the Hydrolysis Product of Clavaminol H. Sphinganine is the enzymatic biosynthetic precursor of sphingosine, the most prevalent sphingoid base of sphingolipids.[6] It could be prepared following a similar methodology by employing (as starting material) α-alkoxy (*E*)-*N*-*tert*-butylsulfinyl imine **7**, readily available in diastereo- and enantiomerically pure form in three steps from glycerol.[14a,19] In this case, *anti*-(2*S*,3*R*)-sulfinylamidoalkyl ether **8** was obtained as a single isomer in 84% yield through the slow addition of **7** to racemic allenylzinc (±)-**2** (4 equiv, Et_2O, −80 °C). Subsequent desilylation of the acetylenic position with methanolic K_2CO_3 (5 equiv, MeOH, 0 °C, 2 h) and semihydrogenation of the C−C triple bond under the conditions described above then afforded compound **9** in 93% overall yield (Scheme 4).

The formation of the internal alkene derivative **10** was attempted by subjecting **9** to cross-metathesis with 1-pentadecene under the optimized conditions described above in the syntheses of spisulosines. Surprisingly, when the reaction was conducted with 1-pentadecene (4 equiv) in the presence of up to 16 mol % of Grubbs II catalyst, added as before in four subsequent portions, no reaction occurred in CH_2Cl_2 at 40 °C. However, we were delighted to find that using Hoveyda−Grubbs II catalyst allowed the metathesis reaction to take place smoothly under these conditions. This time, the completion of the reaction was reached provided that 16 mol % of the catalyst and 1-pentadecene (10 equiv) were used in four subsequent additions (3 × 4 mol % of the catalyst and 4 equiv followed by 3 × 2 equiv of the alkene) separated by periods of 20 h. Under these optimized conditions, internal alkene **10** was obtained in 78% yield after silica gel flash chomatography (Scheme 4). It was isolated as an inseparable 90:10 *E*:*Z* mixture in favor of the *E* isomer as evidenced by the coupling constant ^3J of 15.5 Hz between the two ethylenic protons. It is worthy of note that all attempts to

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decrease the amount of Hoveyda−Grubbs II catalyst failed. More particularly, carrying out the reaction with 8 mol % of catalyst in toluene at 100 °C resulted only in degradation.

To reach the tri-protected sphinganine derivative **11**, we envisioned to carry out the hydrogenation of the alkene moiety. Both Pd/C or the Wilkinson catalyst under H_2 (1 atm) failed to produce **11**, starting material **10** being quantitatively recovered. Fortunately, when running the reaction with Raney nickel (MeOH, 20 °C, 22 h), the desired product **11** was obtained in 92% yield after rapid filtration over silica gel. In the last step, upon treatment with dry HCl (5 equiv, MeOH, 65 °C, 2 h), *N*-*tert*-butylsulfinyl auxiliary was removed and the two ether functions were deprotected giving quantitatively the sphinganine hydrochloride salt after removal of the solvent under vacuum (Scheme 4). The physical and spectroscopic data of the obtained salt [($[\alpha]^{20}_D$ +10.0 (*c* 0.06, MeOH), mp 89−90 °C)] were in good agreement with those previously reported for this product [($[\alpha]^{26}_D$ −8.6 (*c* 1, MeOH) for the (2*S*,3*R*)-antipode, mp 90−92 °C)].[20]

The sphinganine hydrochloride salt was then prepared in six steps with 56% overall yield from *N*-*tert*-butylsulfinyl imine **7**. The same methodology was successfully applied to the first synthesis of the hydrolysis product of clavaminol H (see Figure 2). Although clavaminol H itself exhibits no significant bioactive activity, its hydrolysis product **14** has been very recently shown to be selectively cytotoxic in gastric carcinoma.[8a] This compound could be prepared, as its hydrochloride salt **14**·HCl, from intermediate **9** (Scheme 4) by (i) cross-metathesis with 1-nonene (giving **12** in 78% yield as a 86:14 *E*:*Z* mixture), (ii) hydrogenation of the alkene moiety (giving **13** in 97% yield), and finally (iii) acidic deprotection (giving **14**·HCl in 96% yield). Following this methodology, **14**·HCl has been obtained as a colorless oil in six steps with 57% overall yield from *N*-*tert*-butylsulfinyl imine **7**.

Conclusion

In conclusion, we have disclosed an efficient and versatile strategy for the high-yielding asymmetric synthesis of sphingoid-type bases involving the stereoselective addition of a racemic 3-alkoxy allenylzinc to a *N*-*tert*-butylsulfinyl imine and a cross-metathesis reaction as the key steps. Following this strategy, spisulosines ES285 and ES271, two new promising highly potent antitumoral agents, have been prepared in six steps and only two chromatographic purifications from readily available enantiopure (R_S,*E*)-*N*-ethylidene-2-methylpropane-2-sulfinamide in 62% and 58% overall yields, respectively. This strategy has been extended to the synthesis of sphinganine, the biosynthetic precursor of sphingosine, and that of the selective cytotoxic hydrolysis product of clavaminol H. Here again, these two compounds have been efficiently obtained in six steps and only three chromatographic purifications from readily available enantiopure (R_S,*E*)-*N*-[2-(*tert*-butyldimethylsiloxy)ethylidene)]-2-methylpropane-2-sulfinamide in 56% and 57% overall yields, respectively.

Experimental Section

(−)-(R_S)-*N*-{(1*S*,2*R*)-2-(Methoxymethoxy)-1-methyl-4-[(trimethylsilyl)but-3-ynyl)]}-2-methylpropane-2-sulfinamide (3). Under a nitrogen atmosphere, at −80 °C, to a stirred solution of 3-[(methoxymethoxy)prop-1-ynyl]trimethylsilane[21] (3.04 mL, 16.00 mmol) and TMEDA (0.24 mL, 1.60 mmol) in anhydrous Et_2O (120 mL) was added dropwise *s*-BuLi (1.3 M in cyclohexane−hexane 92/8, 12.30 mL, 16.00 mmol). The resulting clear orange mixture was stirred for 1 h at −80 °C, and then a 1 M ethereal solution of $ZnBr_2$ (16.00 mL, 16.00 mmol) was added. The resulting white slurry of allenylzinc (±)-**2** was stirred at −80 °C for an additionnal 20 min before imine **1** (97:3 *E*:*Z* ratio, 588 mg, 4.00 mmol) in anhydrous Et_2O (16 mL) was added over a period of 45 min. After completion of the addition, the mixture was stirred for an additional 15 min at −80 °C. Then, 1 M HCl solution (80 mL) was added, and the mixture was warmed to room temperature. The layers were separated, and the aqueous one was extracted with Et_2O (3 × 80 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (25 mL), water (2 × 25 mL), and brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The residual oil was purified by flash chromatography on silica gel (30% to 50% EtOAc−cyclohexane) to produce the desired compound **3** (1.20 g, 94%) as a pale yellow viscous oil (mixture of isomers in a 93:7 ratio). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.94 (d, J = 6.8 Hz, 1H), 4.64 (d, J = 6.6 Hz, 1H for the *minor isomer*), 4.62 (d, J = 6.8 Hz, 1H), 4.34 (d, J = 4.6 Hz, 1H for the *minor isomer*), 4.29 (d, J = 7.7 Hz, 1H), 3.63−3.55 (m, 1H), 3.42−3.39 (m, 1H), 3.39 (s, 3H), 1.42 (d, J = 8.6 Hz, 3H), 1.23 (s, 9H), 0.19 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 101.4, 94.3, 92.4, 70.7, 56.04, 56.02, 55.7, 22.5, 18.5, −0.3; IR 3210, 2956, 2897, 2823, 2173, 1455, 1025, 840, 759 cm^{-1}; HRMS (ESI) $C_{14}H_{30}O_3NSSi$ [M + H]$^+$ 320.1710, found 320.1711; $[\alpha]^{20}_D$ −127.0 (*c* 1.14, $CHCl_3$).

(−)-(R_S)-*N*-[(1*S*,2*R*,*E*)-2-(Methoxymethoxy)-1-(methylhept-dec-3-enyl)]-2-methylpropane-2-sulfinamide (5). To a stirred solution of **3** (1.12 g, 3.50 mmol) in THF (35 mL), at 0 °C, was added TBAF (1 M in solution in THF, 3.70 mL, 3.70 mmol). The mixture was stirred for 15 min at 0 °C, and then H_2O (35 mL) was added. After warming to room temperature, the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine (35 mL), dried over $MgSO_4$, and concentrated in vacuo to give a brownish viscous oil (873 mg).

The oil was taken up in a mixture of hexane (120 mL) and acetone (6 mL). To the solution were added Lindlar palladium (3.49 g, i.e., 20 wt % of Pd) and 3,5-dithia-1,2-octanediol (35 mg, 4 wt %). The flask was then flushed with H_2 (3×). After 4 h of stirring at 20 °C under 1 atm of H_2, the reaction mixture was filtered through a pad of Celite, and the catalyst was rinsed with EtOAc. Removal of the solvents in vacuo gave compound **4** (883 mg, ∼100%) as a yellow oil (mixture of isomers in a 91:9 ratio), which was used in the next step without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (ddd, J = 16.9, 10.7, and 7.2 Hz, 1H), 5.31 (m, 2H), 4.71 (d, J = 6.3 Hz, 1H for the *minor isomer*), 4.70 (d, J = 6.9 Hz, 1H), 4.59 (d, J = 6.8 Hz, 1H), 4.58 (d, J = 6.3 Hz, 1H for the *minor isomer*), 4.02 (dd, J = 7.2 and 4.0 Hz, 1H), 3.45−3.33 (m, 2H), 3.39 (s, 3H), 1.32 (d, J = 6.6 Hz, 3H), 1.23 (s, 9H).

Under an argon atmosphere, to a stirred solution of crude **4** (371 mg, 1.49 mmol) and 1-pentadecene (1.62 mL, 6.00 mmol) in anhydrous CH_2Cl_2 (12 mL) was added at 40 °C Grubbs II catalyst (3 × 51 mg, 3 × 0.06 mmol) in three portions separated by periods of 20 h. After the solution was cooled to room temperature, removal of the solvent in vacuo gave a dark oil, which was purified by flash chromatography on silica gel (50% EtOAc−cyclohexane) to yield first the minor isomer (44 mg, 7%) and then the title compound **5** (464 mg, 72%) as a brown

(20) Ibuka, T.; Nakai, K.; Akaji, M.; Tamamura, H.; Fujii, N. *Tetrahedron* **1996**, *52*, 11739.

(21) [3-(Methoxymethoxy)prop-1-ynyl]trimethylsilane was prepared from propargyl alcohol by silylation at the acetylenic position (see: Jones, T. K.; Denmark, S. E. *Org. Synth.* **1985**, *64*, 182) followed by treatment of the resulting product with an excess of dimethoxymethane in $CHCl_3$ in the presence of an excess of P_2O_5.

oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (td, J = 15.5 and 6.8 Hz, 1H), 5.28 (dd, J = 15.5 and 8.1 Hz, 1H), 4.70 (d, J = 6.8 Hz, 1H), 4.52 (d, J = 6.8 Hz, 1H), 3.95 (dd, J = 8.1 and 3.7 Hz, 1H), 3.42−3.30 (m, 2H), 3.37 (s, 3H), 2.05 (q, J = 6.8 Hz, 2H), 1.31 (d, J = 6.6 Hz, 3H), 1.45−1.30 (m, 22H), 1.21 (s, 9H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 126.3, 93.5, 80.6, 56.4, 55.8, 55.4, 32.3, 31.8, 29.60, 29.59, 29.57, 29.51, 29.35, 29.27, 29.1, 29.0, 22.6, 22.5, 17.9, 14.0; IR 3222, 2922, 2852, 1667, 1457, 1031 cm^{-1}; HRMS (ESI) $C_{24}H_{49}O_3NNaS$ [M + Na]$^+$ 454.3325, found 454.3323; $[\alpha]^{20}_D$ −67.8 (*c* 0.86, $CHCl_3$).

(+)-(2*S*,3*R*)-2-Aminooctadecan-3-ol (Spisulosine ES285). Under a nitrogen atmosphere, to a stirred solution of **5** (431 mg, 1.00 mmol) in absolute MeOH (10 mL), at 20 °C, was added dry HCl (4 M in solution in 1,4-dioxane, 1.25 mL, 5.00 mmol). The mixture was refluxed for 1 h. After warming to room temperature, the solvent was removed in vacuo. The residue was partitioned between EtOAc (100 mL) and saturated aqueous $NaHCO_3$ solution (40 mL). The layers were separated, and the aqueous one was extracted with EtOAc (5 × 40 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo to give a brown solid (310 mg).

The solid was taken up in absolute MeOH (35 mL) and 10% Pd/C (155 mg, i.e., 5 wt % of Pd) was added. The flask was flushed with H_2 (3×). After 20 h of stirring at 20 °C under 1 atm of H_2, the reaction mixture was filtered through a pad of Celite, and the catalyst was rinsed with EtOAc. Removal of the solvents in vacuo gave spisulosine ES285 (266 mg, 93%) as a white solid. An analytically pure sample could be obtained by silica gel flash chromatography (5% to 20% MeOH−CH_2Cl_2). ^{1}H NMR (400 MHz, CD_3OD) δ 3.72 (m, 1H), 3.29 (dq, J = 6.8 and 2.9 Hz, 1H), 1.61−1.27 (m, 28H), 1.24 (d, J = 6.8 Hz, 3H), 0.93 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 72.6, 53.5, 34.9, 33.9, 31.7, 31.6, 31.5, 31.3, 27.9, 24.6, 15.3, 13.1; IR 3390, 2997, 2916, 2849 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{40}ON$ [M + H]$^+$ 286.3104, found 286.3108; mp 115−116 °C; $[\alpha]^{20}_D$ +5.2 (*c* 0.36, MeOH).

(−)-(*R*$_S$)-*N*-[(1*S*,2*R*,*E*)-2-(Methoxymethoxy)-1-(methylhexadec-3-enyl)]-2-methylpropane-2-sulfinamide (6). The same procedure as for **5** was followed using crude **4** (373 mg, 1.50 mmol) and 1-tetradecene (1.65 mL, 6.00 mmol) in the cross-metathesis step. Flash chromatography on silica gel (50% EtOAc−cyclohexane) yielded first the minor isomer (38 mg, 6%) and then the title compound **6** (416 mg, 67%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 (td, J = 15.5 and 6.7 Hz, 1H), 5.27 (ddt, J = 15.5, 8.1, and 1.4 Hz, 1H), 4.66 (d, J = 6.8 Hz, 1H), 4.49 (d, J = 6.8 Hz, 1H), 3.92 (dd, J = 8.1 and 3.5 Hz, 1H), 3.41−3.32 (m, 2H), 3.34 (s, 3H), 2.03 (q, J = 6.6 Hz, 2H), 1.28 (d, J = 6.4 Hz, 3H), 1.45−1.30 (m, 20H), 1.17 (s, 9H), 0.85 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 126.3, 93.8, 80.7, 56.4, 55.9, 55.5, 32.3, 31.9, 29.63, 29.61, 29.56, 29.4, 29.3, 29.13, 29.06, 22.65, 22.62, 18.0, 14.1; IR 3211, 2922, 2853, 1667, 1457, 1032 cm^{-1}; HRMS (ESI) $C_{23}H_{47}O_3NNaS$ [M + Na]$^+$ 440.3169, found 440.3167; $[\alpha]^{20}_D$ −66.6 (*c* 0.95, $CHCl_3$).

(+)-(2*S*,3*R*)-2-Aminoheptadecan-3-ol (Spisulosine ES271). The same procedure as for spisulosine ES285 was followed from **6** (393 mg, 0.94 mmol) to give spisulosine ES271 (235 mg, 92%) as a white solid. An analytically pure sample could be obtained by silica gel flash chromatography (5% to 20% MeOH−CH_2Cl_2). ^{1}H NMR (400 MHz, CD_3OD) δ 3.76 (m, 1H), 3.31 (dq, J = 6.8 and 2.8 Hz, 1H), 1.63−1.44 (m, 3H), 1.32 (m, 23H), 1.24 (d, J = 6.8 Hz, 3H), 0.93 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 72.3, 53.2, 34.8, 33.8, 31.54, 31.52, 31.48, 31.44, 31.39, 31.2, 27.7, 24.5, 15.2, 12.8; IR 3369, 3153, 2914, 2849 cm^{-1}; HRMS (ESI) $C_{17}H_{38}ON$ [M + H]$^+$ 272.2948, found 272.2946; mp 117−119 °C; $[\alpha]^{20}_D$ +8.1 (*c* 0.32, MeOH).

(−)-(*R*$_S$)-*N*-{(1*S*,2*R*)-1-[(*tert*-Butyldimethylsiloxy)methyl]-2-(methoxymethoxy)-4-(trimethylsilyl)but-3-ynyl}-2-methylpropane-2-sulfinamide (8). The same procedure as for **3** was followed using imine **7**[14a,19] (1.94 g, 7.00 mmol). Flash chromatography on silica gel (20% EtOAc−cyclohexane) yielded the title compound **8** (2.64 g, 84%) as as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.94 (d, J = 6.6 Hz, 1H), 4.62 (d, J = 6.6 Hz, 1H), 4.48 (d, J = 6.6 Hz, 1H), 3.98 (ABX system, J = 10.1 and 3.3 Hz, 1H), 3.89 (d, J = 9.1 Hz, 1H), 3.78 (ABX system, J = 10.1 and 5.4 Hz, 1H), 3.54−3.47 (m, 1H), 3.40 (s, 3H), 1.26 (s, 9H), 0.92 (s, 9H), 0.17 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 102.0, 94.3, 92.1, 66.2, 62.6, 60.9, 56.3, 55.7, 25.8, 22.7, 18.1, −0.2, −5.4, −5.6; $[\alpha]^{20}_D$ −63.8 (*c* 0.76, $CHCl_3$). Anal. Calcd for $C_{20}H_{43}NO_4SSi_2$: C, 53.41; H, 9.64; N, 3.11. Found: C, 53.38; H, 9.43; N, 3.07.

(−)-(*R*$_S$)-*N*-{(1*S*,2,*E*)-1-[(*tert*-Butyldimethylsiloxy)methyl]-2-(methoxymethoxy)but-3-enyl}-2-methylpropane-2-sulfinamide (9). At 0 °C, K_2CO_3 (4.06 g, 29.40 mmol) was added in one portion to a stirred solution of **8** (2.64 g, 5.88 mmol) in absolute MeOH (30 mL). After 2 h of stirring at 0 °C, water (15 mL) was added, and the solution was warmed to room temperature. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 45 mL). The combined organic layers were washed with water (2 × 20 mL) and brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo.

The residual yellow oil (2.23 g) was taken up in a mixture of hexane (200 mL) and acetone (10 mL). To the resulting solution were added 5% Lindlar Pd (8.92 g, i.e., 20 wt % of Pd) and 3,5-dithia-1,2-octanediol (89 mg, 4 wt %). The flask was flushed with H_2 (3×). After 4 h of stirring at 20 °C under 1 atm of H_2, the reaction mixture was filtered through a pad of Celite, and the catalyst was rinsed with EtOAc. Removal of the solvents in vacuo gave an orange oil which was purified by flash chromatography on silica gel (30% EtOAc−cyclohexane) to yield the title compound **9** (2.07 g, 93%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (ddd, J = 17.1, 9.5 and 7.4 Hz, 1H), 5.32−5.29 (m, 1H), 5.29−5.23 (m, 1H), 4.69 (AB system, J = 6.6 Hz, 1H), 4.55 (AB system, J = 6.6 Hz, 1H), 4.11 (t, J = 7.4 Hz, 1H), 3.97 (ABX system, J = 10.0 and 3.3 Hz, 1H), 3.81 (d, J = 9.6 Hz, 1H), 3.78 (ABX system, J = 10.0 and 4.4 Hz, 1H), 3.37 (s, 3H), 3.36−3.31 (m, 1H), 1.20 (s, 9H), 0.91 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 119.3, 94.1, 76.4, 62.5, 60.7, 56.1, 55.6, 25.8, 22.7, 18.1, −5.4, −5.5; HRMS (ESI) calcd for $C_{17}H_{38}NO_4SSi$ [M + H]$^+$ 380.2285, found 380.2287; $[\alpha]^{20}_D$ −68.2 (*c* 0.93, $CHCl_3$).

(−)-(*R*$_S$)-*N*-{(1*S*,2,*E*)-1-[(*tert*-Butyldimethylsiloxy)methyl]-2-(methoxymethoxy)heptadec-3-enyl}-2-methylpropane-2-sulfinamide (10). Under an argon atmosphere, to a stirred solution of **9** (190 mg, 0.50 mmol) and 1-pentadecene (0.54 mL, 2.00 mmol) in anhydrous CH_2Cl_2 (9 mL) was added Hoveyda−Grubbs II catalyst (12 mg, 0.02 mmol). After 20 h of stirring at 40 °C, Hoveyda−Grubbs II catalyst (3 × 12 mg, 3 × 0.02 mmol) and 1-pentadecene (3 × 0.27 mL, 3 × 1.00 mmol) were added in three subsequent portions separated by periods of 20 h. After the last addition, the mixture was stirred for an additional 6 h and then cooled to room temperature. Removal of the solvent in vacuo gave a dark oil which was purified by flash chromatography on silica gel (50% EtOAc−cyclohexane) to yield the title compound **10** (223 mg, 78%) as a brown oil (mixture of *E*:*Z* isomers in a 90:10 ratio). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (td, J = 15.4 and 6.9 Hz, 1H), 5.28 (dd, J = 15.4 and 8.3 Hz, 1H), 4.73 (d, J = 6.6 Hz, 1H), 4.68 (d, J = 6.6 Hz, 1H for the *minor Z-isomer*), 4.53 (d, J = 7.9 Hz, 1H), 4.51 (d, J = 6.6 Hz, 1H for *minor Z-isomer*), 4.09 (t, J = 7.4 Hz, 1H), 3.98 (dd, J = 9.9 and 3.3 Hz, 1H), 3.83−3.78 (m, 2H), 3.38 (s, 3H), 3.38−3.30 (m, 1H), 2.06 (q, J = 6.9 Hz, 2H), 1.38−1.23 (m, 22H), 1.22 (s, 9H), 0.95 (s, 9H for the *minor Z-isomer*), 0.94 (s, 9H), 0.91 (t, J = 7.2 Hz, 3H), 0.14 (s, 3H for the *minor Z-isomer*), 0.13 (s, 3H), 0.11 (s, 3H for the *minor Z-isomer*), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 136.0 (*minor Z-isomer*), 127.2, 127.0

(*minor Z-isomer*), 94.5, 76.9, 62.6, 62.4 (*minor Z-isomer*), 61.0 (*minor Z-isomer*), 60.8, 55.9, 55.5, 55.4 (*minor Z-isomer*), 32.3, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 29.0, 25.80, 25.77 (*minor Z-isomer*), 22.62, 22.57 (*minor Z-isomer*), 18.10, 18.05 (*minor Z-isomer*), 14.0, −5.46, −5.50; IR 3271, 2924, 2853, 1666, 1464, 1254, 1155, 1078, 1029, 834, 778 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{63}NNaO_4SSi$ $[M + Na]^+$ 584.4140, found 584.4125; $[\alpha]^{20}_D$ −63.0 (*c* 1.04, $CHCl_3$).

(−)-(*R*$_S$)-*N*-{(1*S*,2*R*)-1-[(*tert*-Butyldimethylsiloxy)methyl]-2-(methoxymethoxy)heptadecanyl}-2-methylpropane-2-sulfinamide (11). To a solution of alkene **10** (655 mg, 1.17 mmol) in absolute MeOH (40 mL) was added Raney Ni (a spatula). The flask was flushed with H_2 (3×). After 20 h of stirring at 20 °C under 1 atm of H_2, the reaction mixture was filtered through a short pad of silica gel eluting with 30% EtOAc−cyclohexane. The solvents were removed, and the residue was filtered through a short pad of silica gel eluting with EtOAc. Removal of the solvent gave the title compound **11** (603 mg, 92%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71 (AB system, J = 6.7 Hz, 1H), 4.66 (AB system, J = 6.7 Hz, 1H), 3.96−3.89 (m, 2H), 3.84 (ABX system, J = 9.9 and 4.2 Hz, 1H), 3.67−3.61 (m, 1H), 3.41 (s, 3H), 3.38−3.30 (m, 1H), 1.69−1.64 (m, 2H), 1.28 (s, 26H), 1.24 (s, 9H), 0.93 (s, 9H), 0.90 (t, J = 7.2 Hz, 3H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 96.9, 78.0, 62.7, 59.6, 55.8, 55.7, 31.9, 31.3, 29.8, 29.7, 29.64, 29.62, 29.58, 29.3, 25.8, 24.4, 22.64, 22.61, 18.1, 14.1, −5.5; IR 3290, 2923, 2853, 1464, 1253, 1079, 1035, 835, 778 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{65}NNaO_4SSi$ $[M + Na]^+$ 586.4296, found 586.4282; $[\alpha]^{20}_D$ −7.2 (*c* 1.03, $CHCl_3$).

(+)-(2*S*,3*R*)-2-Aminooctadecane-1,3-diol Hydrochloride (Sphinganine·HCl). Under an argon atmosphere, at 20 °C, to a stirred solution of **11** (114 mg, 0.20 mmol) in absolute MeOH (5 mL) was added dropwise HCl (4 M in solution in 1,4-dioxane, 0.25 mL, 1.00 mmol). After 2 h of stirring at 65 °C, the solvents were removed under vacuo to give sphinganine·HCl (68 mg, 100%) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 3.87 (ABX system, J = 11.6 and 3.9 Hz, 1H), 3.84−3.78 (m, 1H), 3.73 (ABX system, J = 11.6 and 8.5 Hz, 1H), 3.23 (dt, J = 8.5 and 4.0 Hz, 1H), 1.61−1.46 (m, 3H), 1.45−1.26 (m, 25H), 0.93 (t, J = 7 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 71.4, 59.9, 59.6, 35.2, 34.1, 31.84, 31.81, 31.78, 31.75, 31.6, 31.5, 28.1, 24.8, 14.5; IR 3334, 3050, 2917, 2848, 1058 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{40}NO_2$ $[M + H]^+$ 302.3054, found 302.3045; mp 89−90 °C; $[\alpha]^{20}_D$ +10.0 (*c* 0.06, MeOH).

(−)-(*R*$_S$)-*N*-{(1*S*,2,*E*)-1-[(*tert*-Butyldimethylsiloxy)methyl]-2-(methoxymethoxy)undec-3-enyl}-2-methylpropane-2-sulfinamide (12). The same procedure as for **10** was followed from **9** (152 mg, 0.400 mmol), 1-nonene (0.270 mL, 1.600 mmol then 3 × 0.140 mL, 3 × 0.800 mmol) and Hoveyda−Grubbs II catalyst (4 × 10 mg, 4 × 0.016 mmol). Flash chromatography on silica gel (30% EtOAc−cyclohexane) yielded the title compound **12** (149 mg, 78%) as a brown oil (mixture of *E*:*Z* isomers in a 86:14 ratio). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (td, J = 15.3 and 6.8 Hz, 1H), 5.31 (ddt, J = 15.3, 8.3 and 1.3 Hz, 1H), 4.73 (d, J = 6.6 Hz, 1H), 4.68 (d, J = 6.6 Hz, 1H for the *minor Z-isomer*), 4.53 (d, J = 7.9 Hz, 1H), 4.51 (d, J = 6.6 Hz, 1H for the *minor Z-isomer*), 4.10 (t, J = 7.4 Hz, 1H), 3.98 (dd, J = 9.9 and 3.4 Hz, 1H), 3.83−3.78 (m, 2H), 3.41−3.31 (m, 1H), 3.38 (s, 3H), 2.06 (q, J = 6.8 Hz, 2H), 1.46−1.29 (m, 10H), 1.22 (s, 9H), 0.94 (s, 9H for the *minor Z-isomer*), 0.95 (s, 9H), 0.91 (t, J = 7.0 Hz, 3H), 0.14 (s, 3H for the *minor Z-isomer*), 0.13 (s, 3H), 0.11 (s, 3H for the *minor Z-isomer*), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 127.2, 93.5, 75.9, 62.6, 60.8, 56.0, 55.5, 32.4, 31.8, 29.2, 29.1, 29.0, 25.8, 22.65, 22.62, 18.10, 14.0, −5.43, −5.46; IR 3303, 2953, 2926, 2855, 1686, 1464, 1254, 1155, 1078, 1028, 834, 777 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{51}NNaO_4SSi$ $[M + Na]^+$ 500.3200, found 500.3183; $[\alpha]^{20}_D$ −51.4 (*c* 0.73, $CHCl_3$).

(−)-(*R*$_S$)-*N*-{(1*S*,2*R*)-1-[(*tert*-Butyldimethylsiloxy)methyl]-2-(methoxymethoxy)undecanyl}-2-methylpropane-2-sulfinamide (13). The same procedure as for **11** was followed from **12** (127 mg, 0.270 mmol) to give the title compound **13** (125 mg, 97%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71 (AB system, J = 6.6 Hz, 1H), 4.65 (AB system, J = 6.6 Hz, 1H), 3.96−3.87 (m, 2H), 3.83 (ABX system, J = 9.9 and 4.2 Hz, 1H), 3.67−3.60 (m, 1H), 3.40 (s, 3H), 3.38−3.31 (m, 1H), 1.69−1.50 (m, 2H), 1.40−1.18 (m, 22H), 0.92 (s, 9H), 0.90 (t, J = 6.9 Hz, 3H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 96.9, 78.0, 62.7, 59.6, 55.9, 55.8, 31.9, 31.3, 29.8, 29.59, 29.56, 29.3, 25.9, 24.5, 22.6, 18.2, 14.1, −5.5; IR 3293, 2952, 2925, 2854, 1464, 1253, 1078, 1035, 834, 778 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{53}NNaO_4SSi$ $[M + Na]^+$ 502.3357, found 502.3341; $[\alpha]^{20}_D$ −7.5 (*c* 0.62, $CHCl_3$).

(−)-(1*S*,2*R*)-2-Aminododecane-1,3-diol Hydrochloride (Hydrochloride Salt of the Hydrolysis Product of Clavaminol H, 14·HCl). The same procedure as for sphinganine·HCl was followed from **13** (123 mg, 0.25 mmol) to give the title compound **14**·HCl (62 mg, 96%) as a colorless oil. ^{1}H NMR (400 MHz, CD_3OD) δ 3.87 (ABX system, J = 11.6 and 4.0 Hz, 1H), 3.84−3.79 (m, 1H), 3.73 (ABX system, J = 11.6 and 8.8 Hz, 1H), 3.23 (m, 1H), 1.63−1.45 (m, 3H), 1.45−1.23 (m, 13H), 0.93 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 71.1, 59.7, 59.3, 35.0, 33.9, 31.5, 31.4, 31.2, 27.8, 24.5, 15.3; IR 3327, 3043, 2952, 2918, 2849, 1055 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{28}NO_2$ $[M + H]^+$ 218.2115, found 218.2112; $[\alpha]^{20}_D$ −6.0 (*c* 0.10, MeOH).

Supporting Information Available: General informations, experimental procedures for compounds **1** and **7**, ^{1}H and ^{13}C spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.