JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

Synthesis of D-*erythro*-Sphinganine through Serine-Derived α-Amino Epoxides

Carlo Siciliano,*[,†] Anna Barattucci,[‡] Paola Bonaccorsi,[‡] Maria Luisa Di Gioia,[†] Antonella Leggio,[†] Lucio Minuti,[§] Emanuela Romio,[†] and Andrea Temperini[∥]

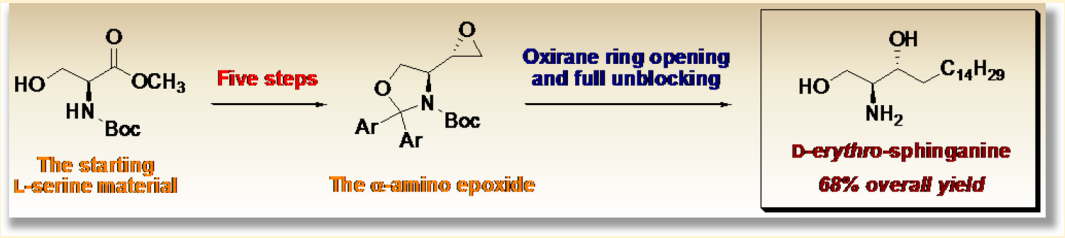
[†]Dipartimento di Farmacia e Scienze della Salute e della Nutrizione, Università della Calabria, Edificio Polifunzionale, I-87030 Arcavacata di Rende (CS), Italy

[‡]Dipartimento di Scienze Chimiche, Università di Messina, Viale F. Stagno d'Alcontres 31, 98166 Messina, Italy

[§]Dipartimento di Chimica, Università di Perugia, Via Elce di Sotto 8, 06123 Perugia, Italy

[∥]Dipartimento di Chimica e Tecnologia del Farmaco, Università di Perugia, Via del Liceo 1, 06123 Perugia, Italy

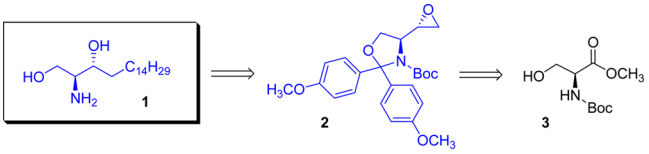
Supporting Information



ABSTRACT: A total synthesis of D-*erythro*-sphinganine [(2*S*,3*R*)-2-aminooctadecane-1,3-diol] starting from commercial *N*-*tert*-butyloxycarbonyl-L-serine methyl ester is described. The approach is based on the completely stereoselective preparation of an α-amino epoxide obtained by treating a protected L-serinal derivative with dimethylsulfoxonium methylide. The oxirane synthon is obtained with an *anti* configuration fitting the (2*S*,3*R*) stereochemistry of the 2-amino-1,3-diol polar head of D-*erythro*-sphinganine. The synthetic procedure afforded the target compound in a 68% overall yield based on the initial amount of the starting L-serine material.

D-*erythro*-Sphinganine [(2*S*,3*R*)-2-aminooctadecane-1,3-diol] (**1**, Scheme 1) is involved in the biosynthesis of

Scheme 1. Retrosynthetic Approach to D-*erythro*-Sphinganine (1)

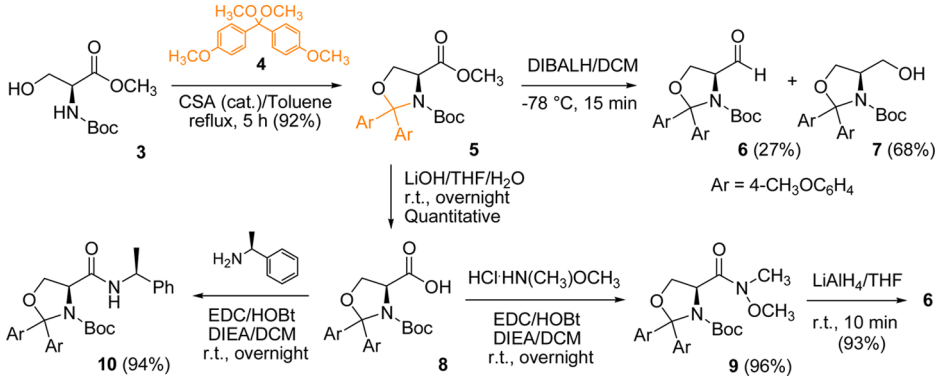


ceramides, sphingomyelin, cerebrosides, and gangliosides, which are ubiquitous components of cell membranes.[1] These compounds regulate signaling, cellular recognition, cell proliferation, growth, differentiation, and apoptosis.[2] D-*erythro*-Sphinganine is also a structural constituent in a large class of biologically active natural products.[3] It inhibits protein kinase C[4] and exerts a potent immunoregulatory activity.[5] A defect of D-*erythro*-sphinganine could determine diabetes, degenerative diseases, and neurological syndromes.[6] The biological role of D-*erythro*-sphinganine justifies the interest in targeting synthetic access to this sphingoid base. Structurally, D-*erythro*-sphinganine (**1**, Scheme 1) features a 2-amino-1,3-diol subunit as polar head inserted in a C_{18} saturated hydrocarbon chain. The 2-NH_2 and 3-OH groups display a reciprocal *anti* configuration, defining a (2*S*,3*R*) stereochemistry of the chiral carbons. The stereoselective synthesis of the 2-amino-1,3-diol subunit by asymmetric approaches[7] is often troublesome. The main drawbacks are low levels of stereoselection and the chromatographic separation of stereoisomers. Otherwise, the use of carbohydrates and serine as chiral pool[8] has been proposed to provide **1** in satisfactory overall yields and high chiral purity. Although most of these routes are of comparable length, they do not show the same level of stereocontrol. The creation of two stereogenic centers in the headgroup with high stereoselectivity is the major difficulty. The total synthesis of **1** proceeds also through a stereoselective nucleophilic addition to the Garner's aldehyde CHO group.[9] The low reactivity of the Garner's aldehyde to Grignard and other aliphatic long-chain organometallic reagents limits the effectiveness of these applications. Moreover, a incomplete stereoselection is observed, and in many cases, the *syn* isomers are preferentially formed, while the opposite *anti* relative stereochemistry is required to build up the backbone of **1**. The use of sacrificial bases to deprotonate a serine-derived Weinreb amide[10] could be used for the preparation of **1**. Nevertheless, these approaches

Received: March 1, 2014
Published: May 7, 2014

dx.doi.org/10.1021/jo500493c | *J. Org. Chem.* 2014, 79, 5320−5326

Scheme 2. Preparation of the L-Serinal Derivative 6



require chromatography to isolate the diastereomers with the appropriate relative configuration. Hence, the preparation of **1** and its stereomers with high levels of stereocontrol is still attractive today because they cannot readily be obtained from natural sources. In the ambit of the synthesis of biologically important compounds,[11] and in a survey of possible approaches that could provide **1**, we have developed a striking stereoselective route to D-*erythro*-sphinganine in which its *anti* configuration could easily be accessible.

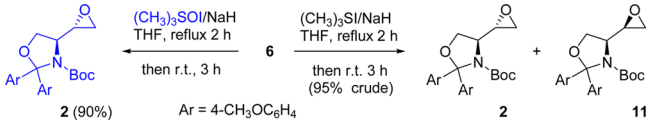
We reasoned that a synthetic strategy to **1** could implicate the preparation of the *anti*-α-amino epoxide **2** (Scheme 1). In this approach, **2** should be obtained by the stereocontrolled epoxidation of a Garner-like aldehyde elaborated from **3** after its protection as a UV-detectable *N*,*O*-acetal. The choice of the 4,4′-dimethoxybenzophenone hemiaminal protection as an alternative to the commonly used acetone hemiaminal moiety as in the Garner's aldehyde was addressed by several considerations. The bulky diaryl chromophore group, removable under mild acid conditions, could also affect the stereoselectivity of the epoxidation. Then, **2** would need only the regioselective oxirane ring opening with a C_{14} organometallic reagent. The protection of **3** as *N*-Boc-*N*,*O*-acetal with two acid-labile groups seemed appealing. In fact, they should globally be cleaved to give the target compound **1** with benefit in terms of total yield. *N*-*tert*-Butyloxycarbonyl-L-serine methyl ester (**3**) was chosen as a source of chirality because both enantiomers are commercially available and inexpensive, and the three functionalities can selectively be manipulated, maintaining the optical integrity of the starting material.

The procedure leading to the serinal intermediate **6** is depicted in Scheme 2. A slightly modified protocol already reported for carbohydrates[12] was applied to obtain **5**. The acid-catalyzed treatment of **3** with the acetal **4** in refluxing toluene afforded **5** in 92% yield and was pure enough to be used in the next step without further purification.

The reactivity of **5** toward hydrides was thus exploited. The preparation of **6** was first attempted by using DIBALH at low temperature. Although reduction of **5** with DIBALH could directly afford **6**, this step was more problematic than expected. In fact, **6** was isolated in unsatisfactory yield (27%) after chromatography, while the serinol **7** was the prevalent product (68%). We concluded that **6** suffered from over-reduction, and this unwanted reaction cannot completely be avoided unless freshly purchased DIBALH is used for the transformation.[13] Therefore, we reasoned that **6** could more conveniently be prepared through the basic hydrolysis of **5** to give the carboxylic acid **8**, precursor of the Weinreb amide **9**. Treatment of the latter with hydrides should generate **6**. The reaction of **5** with lithium hydroxide in THF/water at room temperature[14] gave **8** in an almost quantitative yield, without need for chromatography. The 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide/1-hydroxybenzotriazole (EDC/HOBt)-mediated coupling[15] of **8** to *N*,*O*-dimethylhydroxylamine hydrochloride in DCM at room temperature afforded **9** which was isolated, without chromatography, in 96% yield and high purity as assessed by ^{1}H and ^{13}C NMR spectroscopy. Exposure of **9** to lithium aluminum hydride in THF at room temperature gave exclusively **6** in 93% yield, avoiding chromatography. In this case, no formation of **7** was observed.

We thus envisaged the conversion of **6** into the desired α-amino epoxide **2** (Scheme 3) by using sulfur ylides,[16] a reaction

Scheme 3. Preparation of the *anti*-α-Amino Epoxide 2



well-documented for the Garner's aldehyde.[17] Nevertheless, to the best of our knowledge, the synthesis of **1** through the stereoselective preparation of chiral α-amino epoxides, followed by the oxirane ring opening with long-chain Grignard reagents, has not been attempted yet.

The preparation of **2** was the key step of the procedure. Initially, **6** (1 equiv) was reacted with dimethylsulfonium methylide (1 equiv) in THF at room temperature to give **2** and **11** in 95% crude yield and in an approximately 1:1 ratio, as demonstrated by ^{1}H NMR (Figure 1). No other products were detected. Chemical shifts and proton coupling constants[18] suggested the *anti* and *syn* configurations for **2** and **11**, respectively. The three signals appearing at 2.79, 2.89, and 3.12 ppm were attributable to the *anti*-α-amino epoxide **2** (J = 6.9, 4.0, and 2.6 Hz) and the other three at 2.61, 2.74, and 3.34 ppm to the *syn* isomer **11** (J = 4.7, 4.6, and 2.0 Hz) (Figure 1). This assignment was supported by the comparison with findings already published for a series of similar N-protected α-amino epoxides.[19] In fact, the two *anti* and *syn* diastereomers should show distinguishable resonances for the respective oxirane protons. In accord with the literature, **2** featured better resolved and less spread out signals than for *anti*-α-amino epoxides.

The absence of stereoselection observed for the treatment of **6** with dimethylsulfonium methylide was in stark contrast with the results already reported for Garner's aldehyde.[17] As an alternative, **6** (1 equiv) was reacted with dimethylsulfoxonium

dx.doi.org/10.1021/jo500493c | J. Org. Chem. 2014, 79, 5320−5326

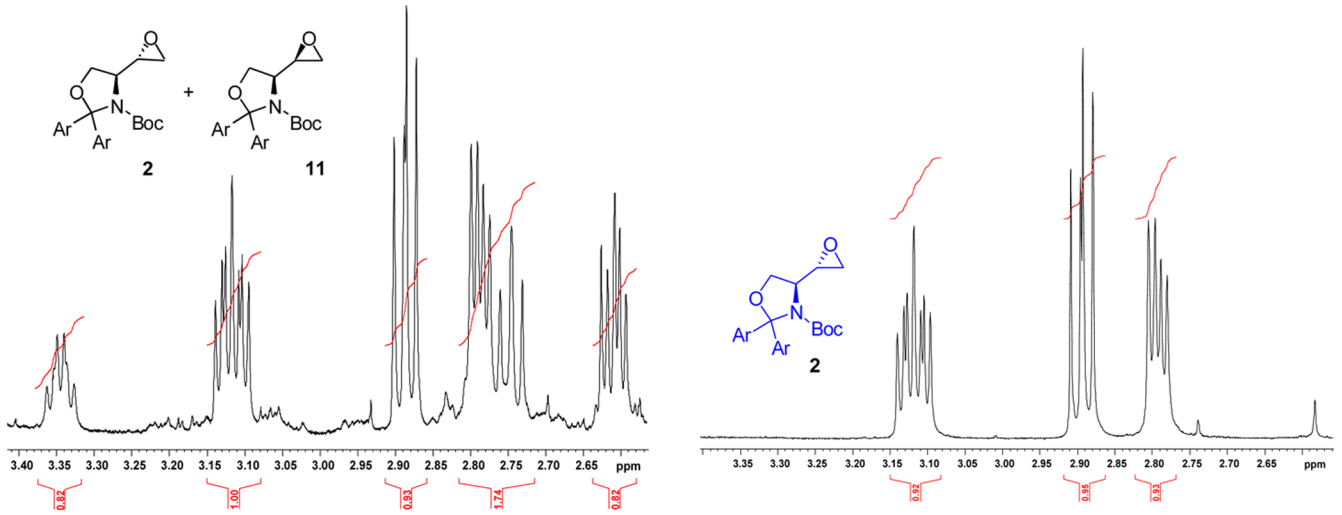
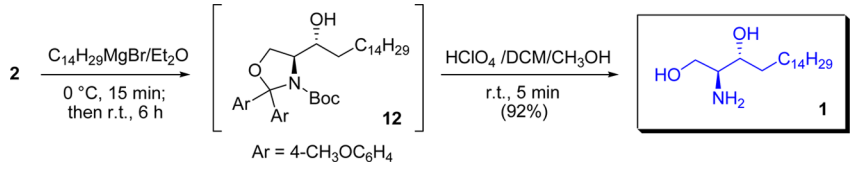
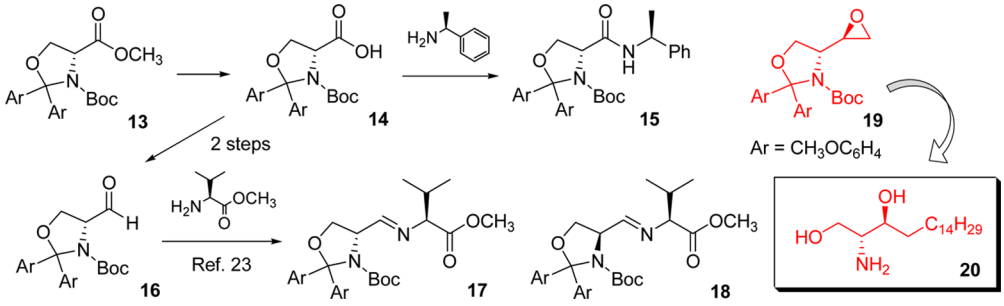


Figure 1. ^{1}H NMR spectral regions of the oxirane protons in **2** and **11** (crude products).

Scheme 4. Nucleophilic Ring Opening of 2 and Global Deprotection of 12 to 1



Scheme 5. Use of *N*-Boc-D-Serine Methyl Ester



methylide (1 equiv) in THF at room temperature. Unpredictably, epoxidation was totally diastereoselective, providing only **2** in 90% yield and high purity, without need for chromatography. The ^{1}H NMR spectrum of **2** displayed a unique series of resonances for the oxirane protons (Figure 1), with chemical shifts identical to those displayed by the mixture of **2** and **11** obtained as described. As a consequence, we postulated the *anti* configuration for **2**, corresponding to the (*S*,*S*) stereochemistry. The ^{1}H NMR spectrum of **2** isolated after the reaction workup did not display signals attributable to **11** within the NMR sensibility limits. Compound **2** was then employed without further purification to produce **1** in two steps (Scheme 4).

Reaction of **2** (1 equiv) with tetradecylmagnesium bromide in Et_2O at room temperature occurred smoothly, and its completion was reached provided that an excess (2 equiv) of the organomagnesium species was used. For simplicity of operation, **12** was recovered by simple trituration of the reaction crude with cold *n*-pentane and used in the next step without further purification. At this level, the complexity of the ^{1}H NMR spectrum in $CDCl_3$ hampered a complete structural assignment, although signals in the spectral window between 3.70 and 4.50 ppm were assumed to be symptomatic of **12**. The elemental composition and the definitive confirmation of the structure of **12** were obtained by ESI-TOF HRMS and MS/MS experiments. With construction of the skeletal framework complete, the solid obtained from trituration was treated with perchloric acid in DCM/CH_3OH at room temperature[20] to globally deprotect **12**. D-*erythro*-Sphinganine (**1**) was isolated in 92 and 68% overall yields, referring to the starting amounts of **2** and **3**, respectively. ^{1}H and ^{13}C NMR spectroscopy in methanol-d_4 gave spectral data in strong agreement with those reported for the same compound synthesized by another route.[21] The *anti* configuration of the 2-amino-1,3-diol frame was indicated by the coupling constant (J = 5.4 Hz) between the H-2 and H-3 protons. Within the limits of NMR techniques, no *syn* diastereomer was detected. The stereochemical outcome of this total synthesis was confirmed by the specific rotation of **1** ($[\alpha]_D$ 7.9, *c* 1.0, CH_3OH) which agreed with the literature values, within the limits of experimental error.[21] NMR spectroscopy and the comparison with already reported data suggested that the configuration of **3** was totally retained in all steps of the procedure. As a consequence, the absolute (2*S*,3*R*) stereochemistry was finally assigned to **1**. This

dx.doi.org/10.1021/jo500493c | J. Org. Chem. 2014, 79, 5320−5326

findings validated also the *anti* configuration previously hypothesized for **2**.

To expand the scope and further exploit the versatility of this procedure, commercial *N*-Boc-D-serine methyl ester was finally used to prepare the α-amino epoxide **19** (Scheme 3), which could be considered a valuable precursor of L-*erythro*-sphinganine (**20**). This isomer appears less attractive than **1** because it does not display the same biological activities as the D-*erythro* form. Nevertheless, a potential high-yielding synthetic access to **20** should be desirable for applications of this compound in studies of biological recognition and response mechanisms.[22] Starting from the D-optical form of serine material, repetition of the synthetic protocol provided **13** and all other expected products in excellent yields and without need for chromatography. Furthermore, compounds **14** and **16** were also successfully used to confirm the retention of configuration during the preparation of **6** and **8** (Scheme 2). Hence, carboxylic acids **8** and **14** were coupled to enantiomerically pure (*S*)-1-methylbenzylamine and converted into the respective diastereomeric amides **10** (Scheme 2) and **15** (Scheme 5). The ^{1}H and ^{13}C NMR analysis of **10** and **15**, as obtained after the reaction workup, displayed such a few evident differences, while spectra of each diastereomer did not show residual resonances attributable to the other one. Thus, lithium hydroxide used in the preparation of **8** and **14** did not affect the configuration of the respective starting serine material. The completely stereoselective and high-yielding synthesis[23] of the diastereomeric (*E*)-imines **17** and **18** (Scheme 5) supplied evidence for the total retention of configuration observed also during the preparation of **6** and **16**. Each imine was the only product recovered from the corresponding preparation, and no traces of the respective diastereomer were detected by ^{1}H NMR analysis of the respective reaction crude. The stereochemistry of the double bond in **17** and **18** was attributed on the basis of the chemical shift values observed for the respective iminic protons, which are less shielded in the *E* isomers and according to literature data.[23] Compound **19** was finally produced in 92% yield and high purity. Epoxidation was totally stereoselective also in this case, as stated by ^{1}H and ^{13}C NMR spectroscopy. Spectroscopic characteristics of **19** were identical to those recorded for **2**, confirming the enantiomeric relationship of the pair of α-amino epoxides.

In conclusion, a new strategy for the satisfying-yield synthesis of the biologically relevant D-*erythro*-sphinganine (**1**) was developed. The procedure was based on the preparation of the *anti*-α-amino epoxide **2** which was obtained through the totally stereoselective epoxidation of the L-serinal derivative **6** with dimethylsulfoxonium methylide. The (*S*,*S*) stereochemistry of **2** was that required for the realization of the 2-amino-1,3-diol scaffold of **1** with the appropriate (2*S*,3*R*) configuration. The procedure is appealing because workup protocols are reduced to a minimum, no chromatography is required to isolate each compound in excellent yields and good purity, and the configuration of the starting serine material is totally maintained. The strategy also showed high potential for the preparation of L-*erythro*-sphinganine, which should be obtained by simply changing the configuration of the starting serine material.

EXPERIMENTAL SECTION

General Experimental. All reagents were used without further purification. All solvents were purified and dried according to standard procedures and freshly distilled before use. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, using $CDCl_3$, DMSO-d_6, or CD_3OD as solvents. For a better resolution of signals, all spectra were recorded at 40 °C. Chemical shifts are reported in parts per million relative to residual solvent ($CDCl_3$: ^{1}H 7.25 ppm, ^{13}C 77.0 ppm; DMSO-d_6: ^{1}H 2.50 ppm, ^{13}C 40.0 ppm; CD_3OD: ^{1}H 3.30 ppm, ^{13}C 49.9 ppm). Coupling constants (*J*) are reported in hertz. ESI-TOF HRMS, GC-MS analysis, MS/MS and MALDI MS spectra were performed under the conditions previously reported.[24] Reactions were monitored by TLC (silica gel 60-F_{254} precoated glass plates), visualizing the spots by a UV lamp (254 nm) and staining with 0.2% ninhydrin. Staining with 20% sulfuric acid in ethanol and charring gave yellow-orange colored spots for all compounds containing the 4,4′-dimethoxybenzophenone hemiaminal protection. Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured in MeOH on a digital polarimeter. All reactions were carried out under an inert atmosphere (dry N_2) in preflamed glassware.

Dimethoxybis(4-methoxyphenyl)methane (4). Trimethyl orthoformate (7.19 mL, 65.7 mmol) and concentrated H_2SO_4 (0.01 mL) were added to a solution of 4,4′-dimethoxybenzophenone (7.07 g, 29.2 mmol) in MeOH (50 mL). The mixture was stirred for 30 h at rt, monitoring the conversion of the starting ketone by TLC. Triethylamine was then added until neutralization, and **4** was recovered by filtration under vacuum. White solid (16.1 g, 85% yield): TLC (eluent AcOEt/petroleum ether 25:75) R_f 0.37; mp 125−127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.09 (s, 6H), 3.77 (s, 6H), 6.81 (d, 4H, *J* = 7.9 Hz), 7.39 (d, 4H, *J* = 7.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.1, 55.2, 102.7, 113.2, 128.0, 132.2, 158.7. Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.56; H, 7.01.

Synthesis of Methyl Esters 5 and 13. A modification of the procedure already published[12] was applied. Acetal **4** (108 mg, 0.374 mmol) was added to a solution of **3** (175 mg, 0.798 mmol) and (1*S*)-(+)-10-canforsulfonic acid (4.25 mg, 0.08 mmol) in toluene (30 mL), and the resulting mixture was refluxed under magnetic stirring for 45 min. Solvent was partially removed under reduced pressure, and another portion of **4** (108 mg, 0.374 mmol) together with fresh solvent (20 mL) was added. After being refluxed for further 45 min, the above operations were repeated and the mixture was refluxed for 5 h (total time). Solvent was removed under reduced pressure to give a solid which was dissolved in Et_2O (15 mL) and partitioned with a 5% aqueous solution of $NaHCO_3$ (15 mL). The aqueous phase was separated and extracted with Et_2O (3 × 20 mL). The organic layers were collected, dried (Na_2SO_4), filtered, and evaporated to dryness under reduced pressure conditions. The oily residue was triturated with Et_2O, and the resulting mother liquor was evaporated to dryness under vacuum to give **5**, which was used in the next step without further purification. White foam (326 mg, 92% yield): TLC (eluent AcOEt/*n*-hexane 30:70) R_f 0.50; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.18 (br s, 9H), 3.72 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 3.89 (m, 1H), 4.11 (dd, 1H, *J* = 9.1, 7.6 Hz), 4.62 (dd, 1H, *J* = 7.5, 4.8 Hz), 6.92 (d, 2H, *J* = 8.0 Hz), 6.90 (d, 2H, *J* = 8.0 Hz), 7.21 (d, 2H, *J* = 8.0 Hz), 7.42 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 28.8, 52.3, 55.1, 59.0, 67.3, 80.7, 98.2, 112.8, 113.7, 129.5, 130.3, 133.1, 152.7, 159.3, 171.2. Anal. Calcd for $C_{24}H_{29}NO_7$: C, 65.00; H, 6.59; N, 3.16. Found: C, 65.18; H, 6.60; N, 3.16. Compound **13** was prepared by the same protocol starting from commercial *N*-Boc-D-Ser-OMe (175 mg, 0.798 mmol) and obtained as a white foam (318 mg, 90% yield). Anal. Calcd for $C_{24}H_{29}NO_7$: C, 65.00; H, 6.59; N, 3.16. Found: C, 64.89; H, 6.58; N, 3.15.

Synthesis of Carboxylic Acids 8 and 14. To a solution of **5** (326 mg, 0.734 mmol) in a THF/H_2O mixture (50:50, v/v; 20 mL) was added LiOH monohydrate (92.4 mg, 2.20 mmol). The resulting homogeneous solution was stirred overnight at room temperature, and the conversion of **5** was monitored by TLC. The organic solvent was removed under reduced pressure, and the aqueous residue was extracted once with Et_2O (5 mL). The aqueous phase was made acidic (pH 2) with solid $NaHSO_4$, extracted with AcOEt (3 × 5 mL), dried (Na_2SO_4), filtered, and evaporated to dryness under reduced pressure conditions to give **8**. White foam (315 mg, quantitative yield): TLC

dx.doi.org/10.1021/jo500493c | J. Org. Chem. 2014, 79, 5320−5326

(eluent AcOEt/*n*-hexane 50:50, with 5 drops of glacial acetic acid) R_f 0.33; ^{1}H NMR (DMSO-d_6) δ 1.18 (br s, 9H), 3.78 (s, 6H), 3.83 (dd, 1H, J = 9.0, 5.2 Hz), 4.10 (dd, 1H, J = 9.0, 7.6 Hz), 4.49 (dd, 1H, J = 7.6, 5.2 Hz), 6.88 (d, 2H, J = 8.0 Hz), 6.90 (d, 2H, J = 8.0 Hz), 7.18 (d, 2H, J = 8.0 Hz), 7.41 (d, 2H, J = 8.0 Hz), 12.4 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 28.3, 55.6, 61.0, 67.9, 79.5, 98.1, 112.8, 113.7, 129.5, 130.9, 133.2, 152.3, 159.2, 173.0. Anal. Calcd for $C_{23}H_{27}NO_7$: C, 64.32; H, 6.34; N, 3.26. Found: C, 64.39; H, 6.33; N, 3.26.

A similar procedure was used to obtain **14** from **13** (300 mg, 0.676 mmol). The product was isolated as a white foam (290 mg, quantitative yield). Anal. Calcd for $C_{23}H_{27}NO_7$: C, 64.32; H, 6.34; N, 3.26. Found: C, 64.28; H, 6.35; N, 3.25.

Synthesis of Weinreb Amide 9. To a solution of **8** (278 mg, 0.647 mmol) in DCM (8 mL) were added HOBt monohydrate (198 mg, 1.29 mmol), EDC hydrochloride (247 mg, 1.29 mmol), and DIEA (0.49 mL, 2.59 mmol). The resulting mixture was stirred for 2 h at rt. A solution of *N*,*O*-dimethylhydroxylamine hydrochloride (78.9 mg, 0.809 mmol) and DIEA (0.49 mL, 2.59 mmol) in DCM (8 mL) was added dropwise. The resulting mixture was stirred overnight at rt, and the conversion of **8** was monitored by TLC. The solvent was evaporated under reduced pressure, and the oily residue was dissolved in AcOEt (6 mL). The organic phase was washed with 5% aqueous $NaHSO_4$ (3 × 5 mL), 5% aqueous $NaHCO_3$ (3 × 5 mL), and once with brine (5 mL), dried (Na_2SO_4), filtered, and evaporated to dryness under reduced pressure conditions to give **9**. Pale yellow viscous oil (293 mg, 96% yield): TLC (eluent AcOEt/*n*-hexane 50:50) R_f 0.59; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.18 (br s, 9H), 3.15 (s, 3H), 3.73 (s, 3H), 3.75 (m, 1H), 3.77 (s, 3H), 3.78 (s, 3H), 4.15 (dd, 1H, J = 9.1, 7.9 Hz), 4.98 (dd, 1H, J = 7.0, 5.6 Hz), 6.88 (d, 2H, J = 8.0 Hz), 6.90 (d, 2H, J = 8.0 Hz), 7.22 (d, 2H, J = 8.0 Hz), 7.51 (d, 2H, J = 8.0 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 28.0, 32.4, 55.5, 55.6, 57.3, 61.8, 66.4, 79.8, 98.1, 112.8, 113.3, 129.6, 130.8, 133.2, 151.7, 152.2, 159.3. Anal. Calcd for $C_{25}H_{32}N_2O_7$: C, 63.54; H, 6.83; N, 5.93. Found: C, 63.51; H, 6.81; N, 5.94.

The same procedure was used to prepare the (*R*) enantiomer of **9** starting from **14** (278 mg, 0.647 mmol). Pale yellow viscous oil (287 mg, 94% yield). Anal. Calcd for $C_{25}H_{32}N_2O_7$: C, 63.54; H, 6.83; N, 5.93. Found: C, 63.59; H, 6.85; N, 5.92.

Synthesis of Serinals 6 and 16 and Serinol 7. *Reduction with DIBALH.* A commercial 1.0 M solution in DCM of diisobutylaluminum hydride (DIBALH; 2.20 mL, 2.20 mmol) was added dropwise to a solution of **5** (280 mg, 0.631 mmol) in DCM (10 mL) at −78 °C. The resulting mixture was stirred for 15 min, then quenched with water (10 mL) and stirred vigorously for further 10 min. After filtration through a short pad of Celite with DCM, the organic phase was separated, washed once with brine (10 mL), dried (Na_2SO_4), filtered, and evaporated to dryness under reduced pressure conditions. Short column flash chromatography of the residue (AcOEt/*n*-hexane 40:60, with the polar component reduced to 1/4) gave **6** (70.4 mg, 27% yield) and **7** (178 mg, 68% yield).

7: Pale yellow viscous oil; TLC (eluent AcOEt/*n*-hexane 40:60) R_f 0.31; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.10 (br s, 9H), 3.49 (m, 1H), 3.65 (m, 1H), 3.77 (s, 3H), 3.78−3.86 (m, 2H), 3.83 (s, 3H), 4.08 (dd, 1H, J = 8.8, 7.1 Hz), 4.50 (br s, 1H), 6.80 (d, 2H, J = 8.0 Hz), 6.86 (d, 2H, J = 8.0 Hz), 7.10 (d, 2H, J = 8.0 Hz), 7.34 (d, 2H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.0, 55.2, 55.3, 60.3, 65.5, 65.7, 81.3, 98.7, 112.9, 113.0, 129.5, 129.6, 132.5, 134.9, 155.0, 159.2. Anal. Calcd for $C_{23}H_{29}NO_6$: C, 66.49; H, 7.04; N, 3.37. Found: C, 66.51; H, 7.06; N, 3.36.

Reduction with $LiAlH_4$. A solution of **9** (500 mg, 1.06 mmol) in THF (5 mL) was treated with $LiAlH_4$ (141 mg, 3.71 mmol) under magnetic stirring at rt. The reaction was monitored by TLC. After 12 min, the conversion of **9** was complete and 5% aqueous $NaHCO_3$ (5 mL) was slowly added to the mixture. The solvent was removed under reduced pressure, and the aqueous residue was extracted with AcOEt (3 × 5 mL). The organic phase was washed once with brine (5 mL), dried (Na_2SO_4), filtered, and evaporated to dryness under vacuum to afford **6**. Pale yellow viscous oil (408 mg, 93% yield): TLC (eluent AcOEt/*n*-hexane 40:60) R_f 0.64; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.21 (br s, 9H), 3.79 (s, 6H), 3.96 (dd, 1H, J = 9.0, 5.5 Hz), 4.14 (dd, 1H, J = 9.0, 7.7 Hz), 4.48 (m, 1H), 6.84 (d, 2H, J = 8.0 Hz), 6.86 (d, 2H, J = 8.0 Hz), 7.22 (d, 2H, J = 8.0 Hz), 7.34 (d, 2H, J = 8.0 Hz), 9.71 (d, 1H, J = 2.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.8, 55.0, 63.8, 65.0, 81.2, 91.7, 98.2, 112.6, 112.7, 128.9, 129.1, 132.5, 132.6, 159.6, 159.7, 199.1. Anal. Calcd for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58; N, 3.39. Found: C, 66.78; H, 6.60; N, 3.39.

The same protocol was used to prepare serinal **16** from the (*R*) enantiomer of **9** (500 mg, 1.06 mmol).

16: Pale yellow viscous oil (395 mg, 90% yield). Anal. Calcd for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58; N, 3.39. Found: C, 67.01; H, 6.59; N, 3.38.

Synthesis of Amides 10 and 15. To a solution of the appropriate carboxylic acid **8** or **14** (180 mg, 0.419 mmol) in DCM (5 mL) were added HOBt monohydrate (128 mg, 0.838 mmol), EDC hydrochloride (161 mg, 0.838 mmol), and DIEA (0.152 mL, 1.68 mmol). The resulting mixture was stirred at room temperature for 2 h before (*S*)-(−)-1-α-methylbenzylamine (0.07 mL, 0.524 mmol) was added. After being stirred at room temperature overnight, the solvent was evaporated under reduced pressure to give a solid residue which was dissolved in AcOEt (10 mL). The organic phase was washed with 5% aqueous $NaHSO_4$ (3 × 5 mL), 5% aqueous $NaHCO_3$ (3 × 5 mL), and once with brine (5 mL), then dried (Na_2SO_4), filtered, and evaporated to dryness under reduced pressure conditions to afford the respective amide **10** or **15**.

10: Pale yellow viscous oil (210 mg, 94% yield); TLC (eluent AcOEt/*n*-hexane 40:60) R_f 0.29; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.15 (s, 9H), 1.40 (d, 3H, J = 7.0 Hz), 3.81 (s, 3H), 3.83 (s, 3H), 4.09−4.21 (m, 2H), 4.61 (m, 1H), 5.11 (quintet, 1H, J = 7.0 Hz), 6.81−6.92 (m, 4H), 7.12 (d, 2H, J = 8.0 Hz), 7.20−7.33 (m. 5H), 7.41 (d, 2H, J = 8.0 Hz), 7.52 (d, 1H, J = 7.0 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 22.0, 28.0, 48.8, 55.2, 61.7, 66.5, 81.5, 98.6, 112.8, 112.9, 125.9, 127.1, 128.5, 129.1, 129.8, 133.2, 142.9, 153.0, 159.5, 159.6, 169.1. Anal. Calcd for $C_{31}H_{36}N_2O_6$: C, 69.90; H, 6.81; N, 5.26. Found: C, 69.83; H, 6.80; N, 5.26.

15: Pale yellow viscous oil (205 mg, 92% yield); TLC (eluent AcOEt/*n*-hexane 40:60) R_f 0.28; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.11 (s, 9H), 1.40 (d, 3H, J = 6.9 Hz), 3.78 (s, 3H), 3.79 (s, 3H), 3.82 (dd, 1H, J = 9.0, 5.6 Hz), 4.08 (dd, 2H, J = 9.0, 7.7 Hz), 4.64 (dd, 1H, J = 7.7, 5.6 Hz), 4.99 (quintet, 1H, J = 6.9 Hz), 6.85 (d, 2H, J = 7.9 Hz), 6.91 (d, 2H, J = 7.9 Hz), 7.18 (d, 2H, J = 7.9 Hz), 7.20−7.36 (m, 5H), 7.50 (d, 2H, J = 7.9 Hz), 7.89 (d, 1H, J = 6.9); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 22.9, 28.1, 48.4, 55.5, 55.6, 61.4, 67.2, 79.8, 98.3, 113.1, 113.6, 126.5, 127.0, 128.3, 129.4, 130.5, 133.2, 144.2, 152.1, 159.4, 159.5, 168.9. Anal. Calcd for $C_{31}H_{36}N_2O_6$: C, 69.90; H, 6.81; N, 5.26. Found: C, 70.05; H, 6.79; N, 5.27.

Synthesis of Imines 17 and 18. A modification of the previously reported procedure was used.[21] The appropriate serinal **6** or **16** (250 mg, 0.605 mmol) was added to a suspension of L-valine methyl ester hydrochloride (117 mg, 0.696 mmol) in DCM (10 mL) containing DIEA (0.076 mL, 1.39 mmol) and anhydrous Na_2SO_4 (25.8 mg, 0.182 mmol). The mixture was stirred at room temperature for 10 min before titanium(IV) isopropoxide (0.358 mL, 1.21 mmol) was added. Magnetic stirring at room temperature was maintained until TLC analysis of the reaction mixture indicated the complete conversion of the starting serinal material. After paper filtration, the solvent was removed under vacuum and the residue was suspended in AcOEt (10 mL). The white precipitate formed was filtered on a short pad of Celite, and the mother liquor was washed once with 5% aqueous $NaHCO_3$ (10 mL). The organic phase was rapidly washed once with 5% aqueous $NaHSO_4$ (10 mL) and once with brine (10 mL), dried (Na_2SO_4), filtered, and evaporated to dryness under reduced pressure conditions to give the respective (*E*)-imine **18** or **17**.

18: Pale yellow viscous oil (283 mg, 89% yield); TLC (eluent AcOEt/*n*-hexane 40:60) R_f 0.74; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82 (d, 3H, J = 6.7 Hz), 0.88 (d, 3H, J = 6.7 Hz), 1.18 (br s, 9H), 2.10 (octet, 1H, J = 6.7 Hz), 3.31 (d, 1H, J = 6.1 Hz), 3.72 (s, 3H), 3.80 (s, 3H), 3.81 (s, 3H), 3.91 (dd, 1H, J = 9.5, 7.0 Hz), 4.11 (dd, 1H, J = 9.5, 4.1 Hz), 4.61 (m, 1H), 6.79−6.90 (m, 4H), 7.18 (d, 2H, J = 7.8 Hz), 7.38 (d, 2H, J = 7.8 Hz), 7.66 (d, 1H, J = 2.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.4, 19.3, 28.0, 34.5, 51.8, 51.9, 55.3, 59.9, 60.3, 65.9, 79.6,

dx.doi.org/10.1021/jo500493c | J. Org. Chem. 2014, 79, 5320−5326

98.3, 112.8, 112.9, 129.5, 129.7, 133.2, 152.6, 159.5, 167.8, 172.2. Anal. Calcd for $C_{29}H_{38}N_2O_7$: C, 66.14; H, 7.27; N, 5.32. Found: C, 66.21; H, 7.29; N, 5.31.

17: Pale yellow viscous oil (271 mg, 85% yield); TLC (eluent AcOEt/*n*-hexane 40:60) R_f 0.72; NMR ($CDCl_3$, 300 MHz) δ 0.82 (d, 3H, J = 6.8 Hz), 0.88 (d, 3H, J = 6.8 Hz), 1.19 (br s, 9H), 2.24 (octet, 1H, J = 6.8 Hz), 3.53 (d, 1H, J = 6.8 Hz), 3.71 (s, 3H), 3.80 (s, 3H), 3.81 (s, 3H), 3.94−4.06 (m, 1H), 4.07−4.18 (m, 1H), 4.76 (m, 1H), 6.80−6.89 (m, 4H), 7.20 (d, 2H, J = 7.9 Hz), 7.38 (d, 2H, J = 7.9 Hz), 7.77 (d, 1H, J = 2.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.4, 19.3, 28.0, 31.5, 51.9, 55.2, 60.7, 66.8, 67.7, 79.6, 98.3, 112.9, 129.5, 129.7, 133.2, 152.6, 159.5, 167.0, 172.0. Anal. Calcd for $C_{29}H_{38}N_2O_7$: C, 66.14; H, 7.27; N, 5.32. Found: C, 66.02; H, 7.28; N, 5.31.

Epoxidation of Serinals 6 and 16. Synthesis of α-Amino Epoxides 2, 11, and 19. *Method A.* Trimethylsulfonium iodide (123 mg, 0.605 mmol) was added to a suspension of NaH (15.2 mg, 0.635 mmol) in THF (10 mL), and the resulting mixture was stirred at 0 °C for 10 min, then at rt for 45 min until complete formation of the ylide.[15] A solution of **6** (250 mg, 0.605 mmol) in THF (10 mL) was added dropwise, and the mixture was stirred at rt for 6 h, monitoring the conversion of **6** by TLC. The mixture was quenched with 5% aqueous $NaHCO_3$ (10 mL), and the organic solvent was removed under vacuum to give an aqueous residue which was diluted with brine (5 mL) and then extracted with AcOEt (3 × 10 mL). The organic layers were collected, dried (Na_2SO_4), filtered, and evaporated to dryness under reduced pressure conditions to afford a crude material which was directly analyzed by ^{1}H NMR. Spectroscopy confirmed the formation of an equimolar mixture of **2** and **11** (246 mg, 95% crude yield): TLC (eluent AcOEt/*n*-hexane 30:70), unique spot, R_f 0.72; ^{1}H NMR (300 MHz, $CDCl_3$), only resonances of the oxirane protons are reported, as obtained from the spectrum recorded for the crude mixture of **2** and **11**, δ 2.61 (dd, 1H, J = 8.9, 4.0 Hz), 2.74 (t, 1H, J = 8.9 Hz), 3.34 (ddd, 1H, J = 4.7, 4.6, 2.0 Hz).

Method B. Trimethylsulfoxonium iodide (133 mg, 0.605 mmol) was added to a stirred suspension of NaH (15.2 mg, 0.635 mmol) in THF (10 mL) at 0 °C. After 10 min, the mixture was refluxed for 2 h, until complete formation of the ylide.[15] After being cooled at rt, a solution of the appropriate serinal **6** or **16** (250 mg, 0.605 mmol) in THF (10 mL) was then added dropwise, and the mixture was stirred at rt for further 12 h, monitoring the conversion of the aldehyde by TLC. The mixture was quenched with 5% aqueous $NaHCO_3$ (10 mL), and the organic solvent was removed under vacuum. The aqueous residue was diluted with brine (5 mL) and then extracted with AcOEt (3 × 10 mL). The organic layers were collected, dried (Na_2SO_4), filtered, and evaporated to dryness under reduced pressure conditions to afford the respective α-amino epoxide **2** or **19**.

2: Pale yellow viscous oil (233 mg, 90% yield); TLC (eluent AcOEt/*n*-hexane 30:70) R_f 0.72; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.19 (s, 9H), 2.79 (dd, 1H, J = 9.1, 2.6 Hz), 2.88 (dd, 1H, J = 9.1, 4.0 Hz), 3.12 (ddd, 1H, J = 6.9, 4.0, 2.6 Hz), 3.76- 3.85 (m, 1H), 3.79 (s, 3H), 3.81 (s, 3H), 3.87 (m, 1H), 4.03 (dd, 1H, J = 6.9, 3.2 Hz), 6.81 (s, 2H, J = 8.0 Hz), 6.86 (s, 2H, J = 8.0 Hz), 7.15 (m, 2H, J = 8.0 Hz), 7.41 (d, 2H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.0, 48.5, 52.6, 55.3, 59.4, 66.0, 80.6, 98.5, 112.9, 129.5, 129.8, 133.3, 133.5, 152.7, 159.4. Anal. Calcd for $C_{24}H_{29}NO_6$: C, 67.43; H, 6.84; N, 3.28. Found: C, 67.38; H, 6.86; N, 3.27.

19: Pale yellow viscous oil (236 mg, 91% yield). Anal. Calcd for $C_{24}H_{29}NO_6$: C, 67.43; H, 6.84; N, 3.28. Found: C, 67.51; H, 6.82; N, 3.29.

Oxirane Ring Opening with Tetradecylmagnesium Bromide. Preparation of D-*erythro*-Sphinganine [(2*S*,3*R*)-2-aminooctadecane-1,3-diol] (1). To a solution of tetradecylmagnesium bromide, prepared from commercial tetradecyl bromide (159 mg, 0.154 mL, 0.562 mmol) and magnesium turnings (13.7 mg, 0.562 mmol) in Et_2O (5 mL), was added dropwise a solution of **2** (120 mg, 0.281 mmol) in Et_2O (5 mL). The resulting mixture was kept under magnetic stirring at 0 °C for 15 min, then warmed to room temperature and stirred for further 6 h. Saturated aqueous NH_4Cl (5 mL) and brine (5 mL) were added, and the mixture was extracted with Et_2O (3 × 10 mL). The organic layers were collected, dried (Na_2SO_4), filtered, and evaporated to dryness under reduced pressure conditions. The residue obtained was dissolved in AcOEt (1 mL) and triturated with cold pentane. The precipitate was separated from the mother liquor, washed rapidly with cold pentane, dried, and directly analyzed by ^{1}H NMR. The structure of **12** was confirmed by MS experiments. The obtained compound was used for the next treatment without further purification.

12 (crude): TLC (eluent AcOEt/*n*-hexane 30:70) R_f 0.81; ESI-TOF HRMS calcd for $C_{38}H_{60}NO_6^+$ 626.4415, found 626.4443.

A slight modification of a previously reported acidolysis procedure[20] was applied to globally deprotect **12**. The crude product isolated from the above treatment was dissolved in DCM (2 mL) and CH_3OH (0.5 mL). A 60% aqueous solution of perchloric acid (0.1 mL) was added, and the reaction mixture was stirred at room temperature for 5 min. Solid Na_2CO_3 was then added portionwise until pH 10. The suspension was filtered through a short pad of Celite (MeOH as eluent), and the mother liquor was evaporated to dryness under reduced pressure conditions. The residue was dissolved in the minimal amount of a 1:2 mixture of CH_3OH/methyl-*tert*-butyl ether and triturated with cold pentane. The precipitate was collected by filtration, washed rapidly once with cold pentane, and dried under vacuum to give D-*erythro*-sphinganine **1**.

1: White powder (79.2 mg, 92% yield, referred to the initial amount of **2**; 68% overall yield, referred to the initial amount of **3**); TLC (eluent AcOEt/*n*-hexane 30:70) R_f 0.80; mp 82−84 °C, $[\alpha]_D$ 7.9, *c* 1.0, CH_3OH), lit.[21] $[\alpha]_D$ 8.1, *c* 1.0, CH_3OH); ^{1}H NMR (CD_3OD, 300 MHz) δ 0.89 (t, 3H, J = 7.0), 1.24−1.46 (m, 26H), 1.52 (m, 2H), 2.70 (ddd, 1H, J = 7.6, 5.4, 4.1 Hz), 3.46 (dd, 1H, J = 10.8, 7.6 Hz), 3.42−3.55 (m, 1H), 3.71 (dd, 1H, J = 10.8, 4.1 Hz), ^{13}C NMR (CD_3OD, 75 MHz) δ 14.4, 23.7, 27.0, 30.1, 33.1, 34.4, 58.2, 64.4, 74.1; MALDI-MS calcd for $C_{18}H_{40}NO_2^+$ 302.3054, found 302.3068. Anal. Calcd for $C_{18}H_{39}NO_2$: C, 71.70; H, 13.04; N, 4.65. Found: C, 71.83; H, 13.08; N, 4.64.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copy of ^{1}H and ^{13}C NMR spectra for compounds **1**, **2**, **4**−**10**, **15**, **17**−**19**. Copy of ^{1}H NMR spectrum of the crude mixture of **2** and **11**. Copy of ^{13}C DEPT135 NMR spectrum of **7**. Copy of ^{1}H NMR and ESI-TOF HRMS and MS/MS spectra of **12** (crude). Copy of MALDI-MS and MS/MS spectra of **1**. Copy of GC-MS analysis of **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: carlo.siciliano@unical.it. Phone: +39 (0)984-493192.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by grants from MIUR (Ministero dell'Istruzione, dell'Università e della Ricerca, ex-60% funds). Prof. Anna Napoli of the Dipartimento di Chimica e Tecnologie Chimiche (CTC), Università della Calabria (Italy), is gratefully acknowledged for mass spectrometric analyses.

■ REFERENCES

(1) (a) Futerman, A. H.; Riezman, H. *Trends Cell Biol.* **2005**, *15*, 312−318. (b) Morales, A.; Fernandez-Checa, J. C. *Mini-Rev. Med. Chem.* **2007**, *7*, 371−382.

(2) (a) Ladish, S.; Li, R.; Olson, E. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 1974−1978. (b) Porcelli, S. A.; Modlin, R. L. *Annu. Rev. Immunol.* **1999**, *17*, 297−329. (c) Veerman, E. C. I.; Valentijn-Benz, M.; van't Hof, W.; Nazmi, K.; van Marle, J.; Amerongen, A. V. N. *Biol. Chem.* **2010**, *391*, 65−71.

(3) (a) Karlsson, A. *Annu. Rev. Biochem.* **1989**, *58*, 309−350. (b) Delgado, A.; Casas, J.; Llebaria, A.; Abad, J. L.; Fabriás, G. *Biochim. Biophys. Acta* **2006**, *1758*, 1957−1977.
(4) Xia, C.; Schümann, J.; Emmanuel, R.; Zhang, Y.; Chen, W.; Zhang, W.; De Libero, G.; Wang, P. G. *J. Med. Chem.* **2007**, *50*, 3489−3496.
(5) Deguchi, H.; Yegneswaran, S.; Griffin, J. H. *J. Biol. Chem.* **2004**, *279*, 12036−12042.
(6) (a) Summers, S. A.; Nelson, D. H. *Diabetes* **2005**, *54*, 591−602. (b) Modrak, D. E.; Gold, D. V.; Goldenberg, D. M. *Mol. Cancer Ther.* **2006**, *5*, 200−208. (c) Kolter, T.; Sandhoff, K. *Biochim. Biophys. Acta* **2006**, *1758*, 2057−2079.
(7) For some selected recent examples, see: (a) Abraham, E.; Davies, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1655−1664. (b) Séguin, C.; Ferreira, F.; Botuha, C.; Chemla, F.; Pérez-Luna, A. *J. Org. Chem.* **2009**, *74*, 6986−6992. (c) Kumar, P.; Dubey, A.; Puranik, V. G. *Org. Biomol. Chem.* **2010**, *8*, 5074−5086. (d) Karjalainen, O. K.; Koskinen, A. M. P. *Org. Biomol. Chem.* **2012**, *10*, 4311−4326. (e) Calder, E. D. D.; Zaed, A. M.; Sutherland, A. *J. Org. Chem.* **2013**, *78*, 7223−7233.
(8) (a) For a comprehensive review, see: Howell, A. R.; So, R. S.; Richardson, S. K. *Tetrahedron* **2004**, *60*, 11327−11347. (b) For a recent literature, see also: Ait-Youcef, R.; Moreau, X.; Greck, C. *J. Org. Chem.* **2010**, *75*, 5312−5315 and references cited therein.
(9) (a) Liang, X.; Andersch, J.; Bols, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2136−2157. (b) Mun, J. Y.; Onorato, A.; Nichols, F. C.; Morton, M. D.; Saleh, A. I.; Welzel, M.; Smith, M. B. *Org. Biomol. Chem.* **2007**, *5*, 3826−3833. (c) Passiniemi, N.; Koskinen, A. M. P. *Beilstein J. Org. Chem.* **2013**, *9*, 2641−2659.
(10) (a) So, R. C.; Ndonye, R.; Izmirian, D. P.; Richardson, S. K.; Guerrera, R. L.; Howell, A. R. *J. Org. Chem.* **2004**, *69*, 3233−3235. (b) Ndonye, R. M.; Izmirian, D. P.; Dunn, M. F.; Yu, K. O. A.; Porcelli, S. A.; Khurana, A.; Kronenberg, M.; Richardson, S. K.; Howell, A. R. *J. Org. Chem.* **2005**, *70*, 10260−10270.
(11) (a) Di Gioia, M. L.; Leggio, A.; Le Pera, A.; Liguori, A.; Napoli, A.; Siciliano, C.; Sindona, G. *J. Org. Chem.* **2003**, *68*, 6416−7421. (b) Di Gioia, M. L.; Leggio, A.; Liguori, A.; Perri, F.; Siciliano, C.; Viscomi, M. C. *Amino Acids* **2010**, *38*, 133−143. (c) De Marco, R.; Di Gioia, M. L.; Leggio, A.; Liguori, A.; Perri, F.; Siciliano, C.; Viscomi, M. C. *Amino Acids* **2010**, *38*, 691−700. (d) De Marco, R.; Di Gioia, M. L.; Liguori, A.; Perri, F.; Siciliano, C.; Spinella, M. *Tetrahedron* **2011**, *67*, 9708−9714. (e) Minuti, L.; Barattucci, A.; Bonaccorsi, P. M.; Di Gioia, M. L.; Leggio, A.; Siciliano, C.; Temperini, A. *Org. Lett.* **2013**, *15*, 3906−3909. (f) Bonaccorsi, P.; Di Gioia, M. L.; Leggio, A.; Minuti, L.; Papalia, T.; Siciliano, C.; Temperini, A.; Barattucci, A. *Beilstein J. Org. Chem.* **2013**, *9*, 2410−2416.
(12) Di Donna, L.; Napoli, A.; Siciliano, C.; Sindona, G. *Tetrahedron Lett.* **1999**, *40*, 1013−1014.
(13) Athanassopoulos, C.; Tzavara, C.; Papaioannou, D.; Sindona, G.; Maia, H. L. S. *Tetrahedron* **1995**, *51*, 2679−2688.
(14) (a) Kaiser, M.; Groll, M.; Siciliano, C.; Assfalg-Machleidt, I.; Weyher, E.; Kohno, J.; Milbradt, A. G.; Renner, C.; Huber, R.; Moroder, L. *ChemBioChem* **2004**, *5*, 1256−1266. (b) Kaiser, M.; Milbradt, A. G.; Siciliano, C.; Assfalg-Machleidt, I.; Machleidt, W.; Groll, M.; Renner, C.; Moroder, L. *Chem. Biodiversity* **2004**, *1*, 161−173.
(15) (a) Papaioannou, D.; Athanassopoulos, C.; Magafa, V.; Karigiannis, G.; Karamanos, N.; Stavropoulos, G.; Napoli, A.; Sindona, G.; Aksnes, D. W.; Francis, G. W.; Aaberg, A. *Acta Chem. Scand.* **1995**, *49*, 103−114. (b) Siciliano, C.; De Marco, R.; Guidi, L. E.; Spinella, M.; Liguori, A. *J. Org. Chem.* **2012**, *77*, 10575−10582. (c) Di Gioia, M. L.; Barattucci, A.; Bonaccorsi, P.; Leggio, A.; Minuti, L.; Romio, E.; Temperini, A.; Siciliano, C. *RSC Adv.* **2014**, *4*, 2678−2686.
(16) (a) Johnson, A. W.; LaCount, R. B. *J. Am. Chem. Soc.* **1961**, *83*, 417−423. (b) Johnson, A. W.; Hruby, V. J.; Williams, J. L. *J. Am. Chem. Soc.* **1964**, *86*, 918−922. (c) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353−1364.
(17) Moore, W. J.; Luzzio, F. A. *Tetrahedron Lett.* **1995**, *36*, 6599−6602.
(18) (a) Ohfune, Y. *Acc. Chem. Res.* **1992**, *25*, 360−366. (b) Hoffman, R. V.; Weiner, W. S.; Maslouh, N. *J. Org. Chem.* **2001**, *66*, 5790−5795.
(19) (a) Barluenga, J.; Baragaña, B.; Concellón, J. M. *J. Org. Chem.* **1995**, *60*, 6696−6699. (b) Albeck, A.; Estreicher, G. I. *Tetrahedron* **1997**, *53*, 5325−5338.
(20) Colacino, E.; Converso, A.; Liguori, A.; Napoli, A.; Siciliano, C.; Sindona, G. *Tetrahedron* **2001**, *57*, 8551−8557.
(21) Cai, Y.; Ling, C.-C.; Bundle, D. R. *Org. Biomol. Chem.* **2006**, *4*, 1140−1146.
(22) Delgado, A.; Casas, J.; Llebaria, A.; Anad, J. L.; Fabriás, G. *ChemMedChem* **2007**, *2*, 580−606.
(23) Leggio, A.; Le Pera, A.; Liguori, A.; Napoli, A.; Romeo, C.; Siciliano, C.; Sindona, G. *Synth. Commun.* **2003**, *33*, 4331−4338 and references cited therein.
(24) (a) Di Gioia, M. L.; Leggio, A.; Le Pera, A.; Liguori, A.; Napoli, A.; Perri, F.; Siciliano, C. *J. Chromatog. A* **2005**, *1066*, 143−148. (b) Mazzotti, F.; Benabdelkamel, H.; Di Donna, L.; Athanassopoulos, C. M.; Napoli, A.; Sindona, G. *J. Mass Spectrom.* **2012**, *47*, 932−939. (c) Furia, E.; Aiello, D.; Di Donna, L.; Mazzotti, F.; Tagarelli, A.; Thangavel, H.; Napoli, A.; Sindona, G. *Dalton Trans.* **2014**, *43*, 1055−1062.