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## The synthesis of chemical tools for studying sphingolipid metabolism

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Chapter 5

# Synthesis of 6-Hydroxysphingosine and Alpha-Hydroxy Ceramide using a Cross- Metathesis Strategy

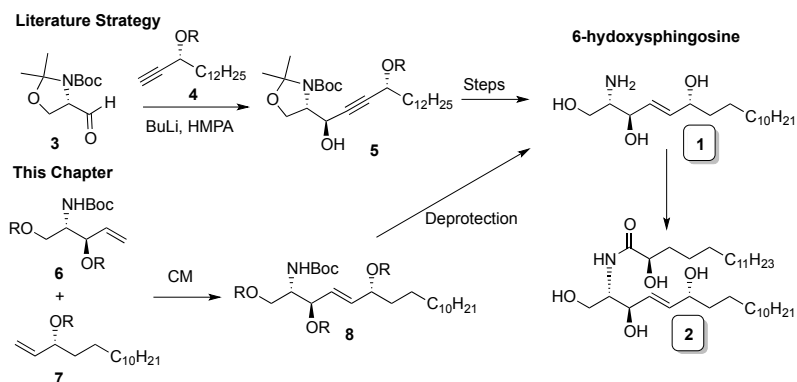
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## 5.1 Introduction

(Glyco)sphingolipids are a family of complex lipids found in all mammalian cells. Besides playing important structural roles as membrane components, they are involved in a multitude of intra- and intercellular signaling events and play a role in many (patho)physiological processes.<sup>[1]</sup> This structurally diverse class of lipids is composed of a sphingosine base, which can be acylated at the nitrogen with a variety of acyl chains.<sup>[2]</sup>

Further structural variation comes from differences in substitution at the primary alcohol group, at which position a large variety of glycans and phosphate groups can be attached. Structural modifications in the sphingosine base are also found. The most recently reported members of the human sphingolipid family, the 6-hydroxyceramides (*e. g.* **2**, Figure 5.1) were discovered in 1989<sup>[3]</sup> and their structure, based on a 6-hydroxysphingosine base (**1**, see Figure 5.1), was fully established in 1994.<sup>[4]</sup> These sphingolipids are important constituents of the human skin, especially the stratum corneum (SC), where they play a role in skin barrier pathologies.<sup>[5]</sup> Authentic samples of these sphingolipids are valuable to study their role in skin physiology processes. Because they are not commercially available and cannot be obtained from natural sources in pure form and sufficient quantity the development of synthetic routes to access these molecules is important.<sup>[6]</sup> To date three reports describing the synthesis of the 6-hydroxysphingosine base have appeared.<sup>[7-9]</sup> These three syntheses all hinge on the diastereoselective nucleophilic attack of an appropriately protected alkyne lipid to (*S*)-Garner aldehyde<sup>10</sup> (**3**, See Figure 5.1), using strongly basic conditions and necessitating a subsequent reduction step.



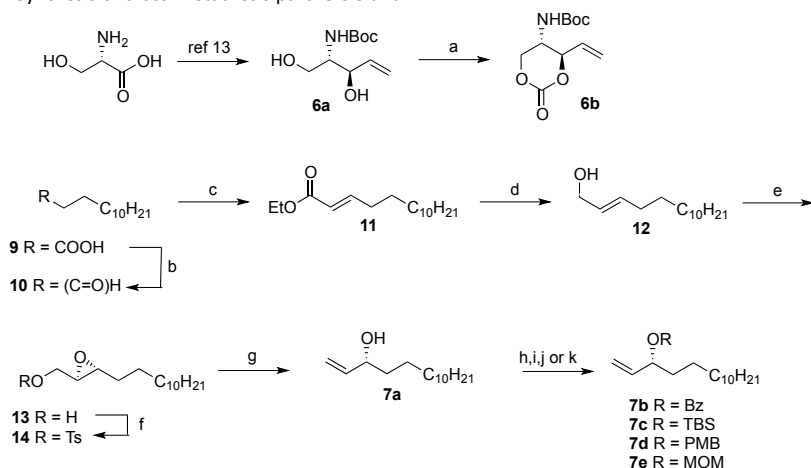
**Figure 5.1** Literature strategy and this chapter.

Chapter 2 describes the assembly of (glyco)sphingolipids using a cross-metathesis (CM) strategy as the key step.<sup>[11-14]</sup> In this approach an allylic sphingosine head is coupled with a long chain alkene (varying in length and carrying different functionalities<sup>[12]</sup> or <sup>13</sup>C labels<sup>[13]</sup>) through the formation of the *E*-double bond. The mild conditions required for this transformation and the broad functional group tolerance make this an attractive strategy and therefore it could be an effective approach to access 6-hydroxysphingosines. To make this strategy successful, difficulties associated with the cross-metathesis of two similar allylic alcohols (Type II or III CM coupling partners)<sup>[15]</sup> had to be overcome. This Chapter describes that CM can be used as a key step in the synthesis of 6-hydroxysphingosine **1** (See Figure 5.1) and, from there, in the synthesis of ceramide **2**.

## 5.2 Results and discussion

The synthesis of the required cross-metathesis partners **6** and **7**, bearing different protecting group patterns is depicted in Scheme 5.1. The sphingosine head **6a** was accessed in six steps from L-serine as previously described by Yamamoto *et al.*<sup>[14]</sup> The long chain allylic alcohol **7** was assembled using a “tellurium transposition” strategy, in which the primary allylic alcohol (**12**) is transformed into the regioisomeric secondary allylic alcohol (**7a**) following a Sharpless asymmetric epoxidation (SAE)-tellurium mediated reductive elimination sequence.<sup>[16]</sup> To this end, the first research objective was to generate the required primary allylic alcohol **12** from tridecanal **10**. Since the commercially available tridecanal did not perform well in the ensuing olefination reaction,

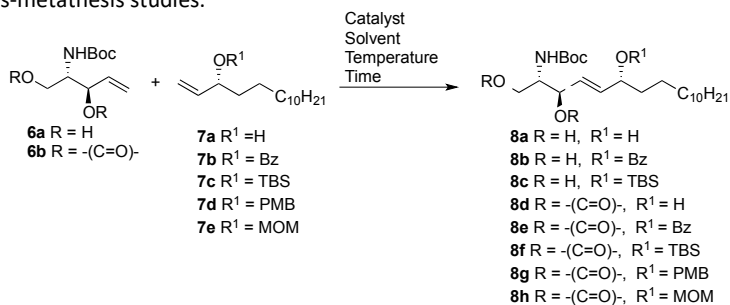
**Scheme 5.1** Synthesis of cross-metathesis partners **6** and **7**.



Reagents and conditions: (a) *N,N*-disuccinimidyl carbonate, DMAP, THF, r.t., 20 h, 76%; (b) oxalyl chloride, DMF, DCM, 0 °C to r.t., 4 h; (ii) *N,O*-dimethylhydroxylamide, DCM, -78 °C to r.t., 20 h, 99% (over two steps); (iii) DIBAL-H, THF, -60 °C, 3 h; (c) (i) diisopropyl (ethoxycarbonylmethyl) phosphonate, *n*-BuLi, r.t., 15 min; (ii) **10**, THF, r.t., 20 h, 77% (over two steps,  $\geq 98\%$ ); (d) DIBAL-H, THF, -78 °C to -60 °C, 3 h, 94%; (e) Ti(*Oi*Pr)<sub>4</sub>, D-(-)-DET, *t*BuOOH, DCM, -19 °C, 5 h, 76% (e.e. 89%); (f) TsCl, Et<sub>3</sub>N, DMAP, DCM, 0 °C to r.t., 20 h, 96%; (g) Te, rongalite, 1 N NaOH, 50 °C, 2 h; (ii) **14**, THF, 0 °C to r.t., 20 h, 90%; (h) Bz<sub>2</sub>O, Et<sub>3</sub>N, DMAP, DCM, 40 °C, 20 h, 89%; (i) TBSCl, Et<sub>3</sub>N, DMAP, DCM, 0 °C to r.t., 20 h, 68%; (j) (i) NaH, DMF, 0 °C, 15 min.; (ii) PMBCl, 0 °C to r.t., 20 h, 87%; (k) MOMCl, DIPEA, DMAP DMF, 0 °C to r.t., 20 h, 94%.

this aldehyde was prepared from tridecanoic acid. Thus, tridecanoic acid was transformed via the acid chloride into the Weinreb amide (99% over two steps), which was reduced to give tridecanal **10**. The aldehyde was immediately used in the ensuing olefination event. The best *E/Z*-selectivity for *trans*-olefin **11** ( $\geq 98\%$  *E*) was achieved using a Horner-Wadsworth-Emmons (HWE) reaction with di-*iso*-propyl (ethoxycarbonylmethyl)phosphonate.<sup>[7]</sup> The Horner-Wittig reaction of tridecanal with (ethoxycarbonylmethyl) triphenylphosphonium bromide, as well as the HWE reaction with di-ethyl (ethoxycarbonylmethyl)phosphonate proceeded with less selectivity (*E/Z* = 9:1 to

95:5). The  $\alpha,\beta$ -unsaturated ester **10** was then reduced to the allylic alcohol **11** with di-*iso*-butylaluminium hydride (DIBAL-H) to set the stage for Sharpless asymmetric epoxidation, which was used to introduce chirality in the molecule. After substantial optimization of this reaction, optimal conditions were found in the use of 13.5 mol% Ti(O*i*Pr)<sub>4</sub>, 17.5 mol% D-(-)-di-ethyltartrate (D-(-)-DET), 2.2 equivalents of *tert*-butylhydroperoxide (*t*BuOOH), and molecular sieves 4Å (1 gram/mol) in dichloromethane at -19 °C. This delivered the chiral epoxide **13** in 79% yield and 89% *ee* (determined from tosylate **14**). Installation of a tosylate function at the primary alcohol allowed for the tellurium mediated reductive elimination reaction. To this end an aqueous solution of Na<sub>2</sub>Te was generated from tellurium and rongalite (HOCH<sub>2</sub>SO<sub>2</sub>Na) in NaOH (aq).<sup>[16]</sup> Addition of **14** to this solution led to the nucleophilic displacement of the primary tosylate by tellurium ion, after which the ensuing epoxide ring opening generates an epitelluride ring that collapses upon exposure to air to give the “transposed” secondary allylic alcohol **7a**. With both allylic alcohols in hand the stage was set for the crucial CM reaction. Generally for a productive CM event, two reaction partners of differing reactivity are required. Grubbs and co-workers<sup>[14]</sup> have divided alkenes in four categories based on their ability to form homodimers in CM reactions. Type I alkenes undergo rapid homodimerization and these can participate in an ensuing CM event. Type II alkenes undergo slow homodimerization leading to homodimers that can participate in CM to a limited extent. Type III alkenes do not form homodimers but they are able to react with type I and II homodimers in a CM. Type IV alkenes are essentially “spectators to cross-metathesis” as they do not display any activity towards the catalyst. For a selective CM, the reaction partners are preferably from different types. The two allylic alcohols at hand are classified as type II CM partners, making the desired CM reaction a challenging process. To discriminate between the reactivity of the alkenes the decision was made to protect the long chain alcohol **7a** (generating a type III CM partner) and mask the hydroxyl group as a benzoyl ester (**7b**), a *tert*-butyldimethylsilyl ether (**7c**), a *para*-methoxybenzyl (PMB) ether (**7d**) or methoxymethyl (MOM) ether (**7e**). The results of the CM reactions are summarized in Table 1. The first attempt, involving diol **6a** and alcohol **7a**, provided the desired CM **8a** product in 23% yield (entry 1). Raising the temperature of this reaction did not lead to an improved reaction (entry 2). Next a CM was attempted with the more electron-poor benzoylated allylic alcohol **7b** in combination with diol **6a**, but this CM was unproductive (entry 3). Similarly the use of silylated CM partner **7c** was to no avail (entry 4). Because modulation of the reactivity of the long chain allylic alcohol proved

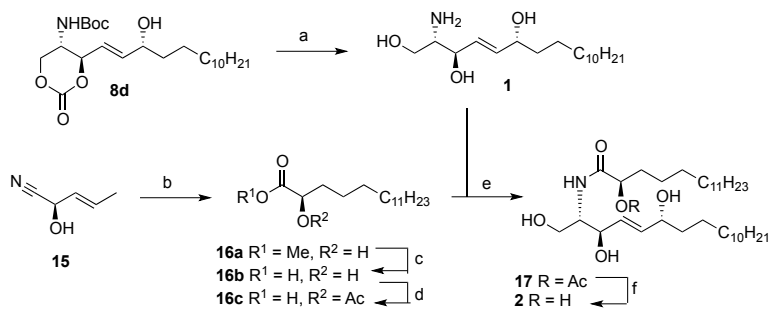
**Table 5.1** Cross-metathesis studies.

entry	<b>6/7</b>	Catalyst <sup>a</sup>	solvent	Temperature (°C)	time (h)	Product (yield) <sup>b</sup>
2	<b>6a/7a</b>	Grubbs II	DCE	80	48	<b>8a</b> (-)
3	<b>6a/7b</b>	Grubbs II	DCM	40	48	<b>8b</b> (-)
4	<b>6a/7c</b>	Grubbs II	DCM	40	48	<b>8c</b> (-)
5	<b>6b/7a</b>	Grubbs II	DCM	40	48	<b>8d</b> (48%)
6	<b>6b/7b</b>	Grubbs II	DCM	40	48	<b>8e</b> (-) <sup>c</sup>
7	<b>6b/7c</b>	Grubbs II	DCM	40	48	<b>8f</b> (-) <sup>c</sup>
8	<b>6b/7d</b>	Grubbs II	DCM	40	48	<b>8g</b> (37%) <sup>c</sup>
9	<b>6b/7e</b>	Grubbs II	DCM	40	66	<b>8h</b> (43%) <sup>c</sup>
10	<b>6b/7a</b>	Grubbs II	DCE	80	48	<b>8d</b> (-)
11	<b>6b/7a</b>	Hoveyda- Grubbs	DCM	40	70	<b>8d</b> (48%)
12	<b>6b/7a</b>	Grubbs II + CuI	Tol.	40	48	<b>8d</b> (78%)
13	<b>6b/7a</b>	Grubbs II + CuI	Et <sub>2</sub> O	r.t.	48	<b>8d</b> (83%)

<sup>a</sup>Reaction conditions: Ratio **6:7** = 3:1; 20 mol % catalyst; 30 mol % (CuI). <sup>b</sup>Yields denote isolated yields after column chromatography. <sup>c</sup>Unreacted cyclic carbonate **6b** as well the protected allylic olefin (**7b**, **7c**, **7d** and **7e**) could be recovered.

unsuccessful, it was decided to protect diol **6** as the cyclic carbonate and to investigate how the resulting **6b** would behave in CM events. The cyclic carbonate group is both strongly electron withdrawing, changing the electronic properties of the alkene, and ties back the functionalities of the groups attached to the alkene, making it more accessible. When the allylic carbonate **6b** and alcohol **7a** were combined in a CM event the desired *E*-alkene **8d** was obtained in an increased yield (48%, entry 5). The use of benzoylated and silylated CM partners **7b** and **7c** again led to unproductive CM reactions (entries 6 and 7). The use of PMB and MOM protected allylic alcohols **7d** and **7e** did deliver the desired CM products **8g** and **8h**, respectively, but in a lower yield than obtained for **8e** (entries 8 and 9). Having established that the most productive CM reaction occurs between carbonate **6b** and alcohol **7a**, this reaction was further optimized. Raising the temperature led to decomposition of the cyclic carbonate and therefore no product was obtained (entry 10). Also different catalytic systems were explored. As the use of the Grubbs-Hoveyda catalyst led to an identical result as compared to the Grubbs II catalyzed CM reaction (entry 11), the next step was to explore the impact of additives on the reaction. As described by Voigtritter *et al.*<sup>[17]</sup>, copper iodide (CuI) can be used to generate a more stable catalyst (due to the iodide), while making the system more reactive because the copper sequesters the phosphine ligands. As shown in entries 12 and 13, the use of this additive proved very successful and alkene **6b** and allylic alcohol **7a** could be fused to provide the desired *E*-alkene **8d** in good yield.

**Scheme 5.2** Synthesis of 6-hydroxysphingosine **1** and  $\alpha$ -hydroxy ceramide **2**.



Reagents and conditions: (a) LiOH, THF/H<sub>2</sub>O (3:1), 0 °C, 3 h; (ii) TFA, DCM, 0 °C, 90 min, 80% over two steps; (b) HCl (g), MeOH, Et<sub>2</sub>O, 0 °C to -20 °C, 20 h, then H<sub>2</sub>O, 48%; (iii) 1-tetradecene, Grubbs 2<sup>nd</sup> generation catalyst, AcOH, DCM, 50 °C, 60 h, 73%; (iii) H<sub>2</sub> (g), Pd/C, EtOAc, r.t., 20 h, 91%; (c) LiOH.H<sub>2</sub>O, THF:MeOH:H<sub>2</sub>O (2:2:1), r.t., 20 h, 99%; (d) Ac<sub>2</sub>O, pyridine, DCM, r.t., 20 h, 97%; (e) EEDQ, EtOH, 50 °C, 20 h, 66%; (f) K<sub>2</sub>CO<sub>3</sub>, DCM/MeOH (4:1), r.t., 2 h, 88%.

Having successfully constructed the 6-hydroxysphingosine backbone, the base was globally deprotected by saponification of the carbonate group and ensuing removal of the Boc protective group using dilute acid at low temperature (0 °C) to give  $\alpha$ -hydroxy ceramide **1**, as depicted in Scheme 5.2. The use of more forceful acidic conditions led to



complex reaction mixtures, presumably as a result of acid catalyzed allylic substitution reactions. The synthesis of the 6-hydroxysphingosine based ceramide **2**, featuring an  $\alpha$ -hydroxyl side chain was finally accomplished as follows. First  $\alpha$ -hydroxy fatty acid **16a** was generated from optically pure cyanohydrin **15**, obtained from crotonaldehyde by the action of almond hydroxynitrilase.<sup>[18]</sup> The cyanohydrin was transformed into the corresponding methyl ester using a Pinner reaction.<sup>[19]</sup> Next a CM reaction of the alkene with 1-tetradecene gave the unsaturated long chain lipid that was reduced and saponified to give the fatty acid **16b**. To condense the  $\alpha$ -hydroxy fatty acid with the 6-hydroxysphingosine, the  $\alpha$ -hydroxy group was first masked with an acetyl group. Activation of acid **16c** with 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ)<sup>[20]</sup> and ensuing condensation then gave acylated ceramide **17**. Final saponification of the acetyl ester completed the synthesis of the target 6-hydroxyceramide **2**.

### 5.3 Conclusion

In conclusion, this Chapter presents a new synthetic route for 6-hydroxysphingosine and its alpha-hydroxy-ceramide counterpart, employing a cross-metathesis (CM) strategy. The crucial CM reaction on which the synthesis hinges unites two similar allylic alcohol alkenes. The use of a cyclic carbonate group to protect the diol system, present in the sphingosine CM partner, with a cyclic carbonate functionality serves two purposes. Firstly, it makes the double bond less electron rich, discriminating it from its designated CM partner, the long chain allylic alcohol. Secondly, it ties back the functional groups on the olefin, making the alkene sterically most accessible for the catalyst and the CM event. In combination with an activated catalyst system (the Grubbs II – CuI reagent pair) this led to an efficient CM connection of the sphingosine head and tail alkenes. The mild conditions required for this connection in conjunction with the straightforward deprotection scheme (mild base followed by mild acid) make the approach versatile and amendable to the use of a variety of CM coupling partners to generate labeled and tagged 6-hydroxysphingosine derived probes for future biochemical studies.<sup>[13,21]</sup>

### 5.4 Experimental section

**General Remarks.** Commercially available reagents and solvents were used as received. DCM and THF were dried and distilled by standard procedures. All moisture-sensitive reactions were carried out under an argon atmosphere. Molecular sieves (3 Å) were flame-dried before use. Column chromatography was carried out with Silica gel 60 (40–63  $\mu$ m mesh). IR spectra are reported in  $\text{cm}^{-1}$ . Optical rotations were measured with an automatic polarimeter (sodium D-line,  $\lambda = 589$  nm). The enantiomeric purity was determined by HPLC analysis using an OD column (hexane/isopropyl alcohol (98:2), 1 mL/min, UV 254 nm). NMR spectra were recorded on a 400 MHz or 850 MHz spectrometer. Chemical shifts are reported as  $\delta$  values (ppm), and were referenced to tetramethylsilane ( $\delta = 0.00$  ppm) directly in  $\text{CDCl}_3$ , or using the residual solvent peak (D<sub>2</sub>O). High-resolution mass spectra were recorded on a LTQ-Orbitrap (Thermo Finnigan) mass spectrometer equipped with an electrospray ion source in positive mode or on a Synapt G2-Si MALDI-TOF mass spectrometer equipped with a 355-nm laser. Samples (1 mL, 100 mM in  $\text{CHCl}_3$ ) were spotted on the MALDI-plate, followed by aqueous silver benzoate (0.5

mL, 10 mM), drying and applying the matrix (2,5-dihydroxybenzoic acid, 0.5 mL, 0.5 M in methanol). A laser frequency of 1000 Hz (power set at 60%) was used.

**tert-Butyl ((4R,5S)-2-oxo-4-vinyl-1,3-dioxan-5-yl)carbamate (6b).** Allylic alcohol **6a** (3.03 g, 13.95 mmol, 1 eq) was dissolved in anhydrous THF (400 mL) under an argon atmosphere. *N,N'*-Disuccinimidyl carbonate (8.93 g, 34.88 mmol, 2.5 eq) and DMAP (4.26 g, 34.88 mmol, 2.5 eq) were added and then left stirring for 20 hours at room. The reaction mixture was concentrated *in vacuo* and purified with silica gel chromatography (30% EtOAc in pentane) giving Cyclic carbonate **6b** (2.57 g, 10.56 mmol, 76%) as a thick, colorless oil.  $R_f = 0.6$  (50% EtOAc in pentane);  $[\alpha]_D = +46.0$  ( $c = 1.0$ ,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.92 (ddd, 1 H,  $J = 16.8, 10.8, 4.4$  Hz, H-4), 5.58 (d, 1 H,  $J = 7.2$  Hz, -NH), 5.50 (dd, 1 H,  $J = 16.8, 1.6$  Hz, H-5<sub>a</sub>), 5.47 (dd, 1 H,  $J = 10.8, 1.6$  Hz, H-5<sub>b</sub>), 5.02 (bs, 1 H, H-3), 4.54 (dd, 1 H,  $J = 11.2, 2.4$  Hz, H-1<sub>a</sub>), 4.31 (bd, 1 H,  $J = 11.2$  Hz, H-1<sub>b</sub>), 3.97 (m, 1 H, H-2), 1.46 (s, 9 H,  $\text{CH}_3\text{-Boc}$ );  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  155.25 (C=O<sub>Boc</sub>), 147.67 (C=O<sub>Carbonate</sub>), 132.50 (C-4), 119.68 (C-5), 81.95 (C-3), 80.87 (C<sub>q</sub>-Boc), 68.15 (C-1), 45.84 (C-2), 28.34 ( $\text{CH}_3\text{-Boc}$ ); IR (neat): 2978, 2932, 1751, 1701, 1165  $\text{cm}^{-1}$ ; HRMS for calculated  $[\text{C}_{11}\text{H}_{18}\text{NO}_5 + \text{H}]^+$ ; 244.11795, found 244.11835.

**Tridecanal (10).** Tridecanoic acid **9** (7.50 g, 35.0 mmol, 1 eq) was dissolved in anhydrous DCM (110 mL) under an argon atmosphere. The solution was cooled to 0°C before adding oxalyl chloride (2 M in DCM, 35 mL, 70 mmol, 2 eq) and DMF (3 drops, cat.). The mixture was stirred for 4 to 5 hours at room temperature. Once gas formation subsided, the reaction mixture was concentrated *in vacuo* and the crude acyl chloride was immediately dissolved in anhydrous DCM (110 mL) under an argon atmosphere. The solution was cooled to -78°C before slowly addition of distilled *N,O*-dimethylhydroxylamine (6.42 mL, 87.5 mmol, 2.5 eq). After 30 minutes the reaction mixture was allowed to reach room temperature and stirred for 20 hours. The reaction mixture was filtered, concentration *in vacuo*, and purified with silica gel chromatography (5% to 10% EtOAc in pentane) giving *N*-methoxy-*N*-methyltridecanamide (8.94 g, 34.74 mmol, 99%) as an oil.  $R_f = 0.3$  (10% EtOAc in pentane);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.68 (s, 3 H, -OCH<sub>3</sub>), 3.18 (s, 3 H, -NCH<sub>3</sub>), 2.41 (t, 2 H,  $J = 7.6$  Hz, H-1), 1.63 (p, 2 H,  $J = 7.6$  Hz, H-2), 1.31 - 1.26 (m, 18 H, H-3 to H-11), 0.88 (t, 3 H,  $J = 6.8$  Hz, H-12);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  175.03 (C=O<sub>Weinreb</sub>), 61.31 (-OCH<sub>3</sub>), 32.30 (-NCH<sub>3</sub>), 32.04 (C-1, CH<sub>2</sub>), 29.79, 29.76 (x2), 29.64, 29.59, 29.56, 29.48 (CH<sub>2</sub> x 7), 24.79 (C-2), 22.82 (CH<sub>2</sub>), 14.25 (C-12); IR (neat): 2922, 2853, 1668  $\text{cm}^{-1}$ ; HRMS calculated for  $[\text{C}_{15}\text{H}_{32}\text{NO}_2 + \text{H}]$ ; 258.24276; found 258.24257.

*N*-methoxy-*N*-methyltridecanamide (2.59 g, 10.05 mmol, 1 eq) was dissolved in anhydrous THF (25 mL) under an argon atmosphere. The solution was cooled to -60 °C followed by addition of diisobutylaluminum hydride (1 M in THF, 12 mL, 12 mmol, 1.2 eq). The reaction mixture was stirred for 3 hours at -60 °C. The reaction was quenched by adding Rochelle salt solution (sat., 20 mL) at -60 °C. The mixture was then allowed to reach room temperature before extracting with EtOAc (2x 150 mL). The combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ , filtrated and concentrated *in vacuo*. The crude tridecanal **10** was collected as an oil, which was used for the next reaction without further purification.  $R_f = 0.7$  (5% EtOAc in pentane);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.76 (t, 1 H,  $J = 1.6$  Hz, -CHO), 2.42 (dt, 2 H,  $J = 7.2, 1.6$  Hz, H-1), 1.63 (p, 2 H,  $J = 7.2$  Hz, H-2), 1.30 - 1.26 (m, 18 H, H-3 to H-11), 0.88 (t, 3 H,  $J = 6.8$  Hz, H-12);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  202.96 (C=O<sub>aldehyde</sub>), 44.03 (C-1), 32.03, 29.76, 29.74, 29.70, 29.55, 29.48, 29.47, 29.28, 22.80, 22.19 (CH<sub>2</sub> x 10), 14.22 (C-12); IR (neat): 3024, 2984, 2941, 1732, 1236  $\text{cm}^{-1}$ .

**Ethyl (E)-pentadec-2-enoate (11).** Diisopropyl (ethoxycarbonylmethyl) phosphonate (3.53 g, 14 mmol, 1.4 eq) was dissolved in anhydrous THF (40 mL) under an argon atmosphere. *n*-Butyllithium (2.5 M in hexanes, 5 mL, 12.5 mmol, 1.25 eq) was added and stirred for 15 minutes at room temperature followed by addition of a solution of crude tridecanal **10** in anhydrous THF (15 mL). The reaction mixture was stirred for 20 hours. The reaction mixture was diluted with  $\text{H}_2\text{O}$  (100 mL) and extracted with  $\text{Et}_2\text{O}$  (3x 100 mL). The combined organic layers were washed with brine, dried over

MgSO<sub>4</sub>, filtrated and concentrated *in vacuo*. The crude product was purified with silica gel chromatography (0-2% EtOAc in pentane). The  $\alpha,\beta$ -unsaturated ester **11** (2.08 g, 7.73 mmol, 77% over 2 steps,  $\geq 98\%$  E) was collected as a light yellow oil.  $R_f = 0.5$  (2% EtOAc in pentane); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.97 (dt, 1 H,  $J = 15.6, 6.8$  Hz, H-4), 5.81 (dt, 1 H,  $J = 15.6, 1.6$  Hz, H-3), 4.18 (q, 2 H,  $J = 7.2$  Hz, H-2), 2.19 (dq, 2 H,  $J = 7.2, 1.2$  Hz, H-5), 1.45 (m, 2 H, H-6), 1.32 – 1.26 (m, 21 H, H-1 and H-7 to H-15), 0.88 (t, 3 H,  $J = 6.8$  Hz, H-16); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  166.89 (C=O), 149.60 (C-4), 121.30 (C-3), 60.21 (C-2), 32.32 (C-5), 32.04, 29.78, 29.76 (x2), 29.65, 29.52, 29.48, 29.28 (CH<sub>2</sub> x 8), 28.14 (C-6), 22.81 (CH<sub>2</sub>), 14.39 (C-1), 14.23 (C-16); IR (neat): 2922, 2853, 1722, 1655, 1179 cm<sup>-1</sup>; HRMS calculated for [C<sub>17</sub>H<sub>33</sub>O<sub>2</sub> + H]<sup>+</sup>: 269.2475, found 269.2475. Spectroscopic data was identical to literature.<sup>[7]</sup>

**(E)-Pentadec-2-en-1-ol (12)**. Ethyl (E)-pentadec-2-enoate **11** (2.39 g, 8.89 mmol, 1 eq) was dissolved in anhydrous THF (45 mL) under an argon atmosphere. The solution was cooled to -78°C followed by addition of diisobutylaluminum hydride (1M in THF, 26.7 mL, 26.7 mmol, 3 eq). The reaction mixture was stirred for 3 hours, slowly warming up to -60°C. The reaction was quenched with NH<sub>4</sub>Cl solution (sat.) at -60°C. The mixture was then allowed to warm to room temperature before adding HCl (5%, 100 mL). The mixture was extracted with Et<sub>2</sub>O (3x 100 mL). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtrated and concentrated *in vacuo*. The crude product was purified with silica gel chromatography (2.5-5% EtOAc in pentane). Allylic alcohol **12** (1.89 g, 8.34 mmol, 94%) was collected as a colorless oil that slowly crystallized into a white solid.  $R_f = 0.3$  (5% EtOAc in pentane): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.73 – 5.59 (m, 2 H, H-2 & H-3), 4.08 (d, 2 H,  $J = 6.0$  Hz, H-1), 2.04 (m, 2 H, H-4), 1.50 (bs, 1 H, -OH), 1.37 (m, 2 H, H-5), 1.32 – 1.26 (m, 18 H, H-6 to H-14), 0.88 (t, 3 H,  $J = 6.8$  Hz, H-15); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  133.75, 128.90 (C-2, C-3), 63.98 (C-1), 32.36 (C-4), 32.06, 29.83, 29.81, 29.79, 29.76, 29.65, 29.50, 29.34, 29.28, 22.83 (CH<sub>2</sub> x 10), 14.26 (C-15); IR (neat): 3292, 2955, 2918, 2849, 1672, 1462 cm<sup>-1</sup>. Spectroscopic data was identical to literature.<sup>[7]</sup>

**((2R,3R)-3-dodecyloxiran-2-yl)methanol (13)**. Activated, powdered molecular sieves (~5 g, 4Å) were added to a flame dried flask with freshly distilled, anhydrous DCM (15 mL) under an argon atmosphere. The suspension was stirred for 10 minutes at room temperature, completely drying DCM in the process. (-)-Diethyl D tartrate (0.15 mL, 0.86 mmol, 0.17 eq) and titanium (IV) isopropoxide (0.2 mL, 0.69 mmol, 0.14 eq) were added to this solution at -19°C. Allylic alcohol **12** (1.13 g, 5.00 mmol, 1 eq) was co-evaporated with toluene (2x) and dissolved in freshly distilled, anhydrous DCM (10 mL). After stirring the titanium-tartrate solution for 30 minutes, the solution of allylic alcohol **12** was added followed by addition of *tert*-butyl hydroperoxide (~5.5 M in decane, 2 mL, 11.0 mmol, 2.2 eq). The reaction mixture was stirred for 5 hours at -19 °C. The reaction was quenched by adding H<sub>2</sub>O (20 mL) at -19 °C. After warming up to room temperature, NaOH (30% in brine, 2.5 mL) was added to hydrolysis of (-)-Diethyl D tartrate. The mixture was stirred for 15 minutes, followed by extraction with DCM (3x 30 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtrated and concentrated *in vacuo*. Remaining *tert*-butyl hydroperoxide was removed by co-evaporation with toluene. The crude product was purified with silica gel chromatography (10-15% EtOAc in pentane). Epoxide **13** (0.92 g, 3.80 mmol, 76%, e.e. = 89% (determined from tosylate **14**) was collected as a white solid. The analytical sample was recrystallized from petroleum ether (40-60%).  $R_f = 0.3$  (20% EtOAc in pentane);  $[\alpha]_D^{25} = +23.4$  ( $c = 1.0$ , CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  3.92 (ddd, 1 H,  $J = 12.4, 5.2, 2.4$  Hz, H-1<sub>a</sub>), 3.63 (ddd, 1 H,  $J = 12.0, 7.2, 4.4$  Hz, H-1<sub>b</sub>), 2.96 (m, 1 H, H-2), 2.92 (m, 1 H, H-3), 1.66 (m, 1 H, -OH), 1.56 (m, 2 H, H-4), 1.44 (m, 2 H, H-5), 1.35 – 1.26 (m, 18 H, H-6 to H-14), 0.88 (t, 3 H,  $J = 6.8$  Hz, H-15); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  61.82 (C-1), 58.51 (C-3), 56.13 (C-2), 32.07 (CH<sub>2</sub>), 31.71 (C-4), 29.81, 29.78 (x2), 29.70, 29.68, 29.55, 29.50 (CH<sub>2</sub> x 7), 26.10 (C-5), 22.84 (CH<sub>2</sub>), 14.28 (C-15); IR (neat): 3252, 2953, 2916, 2870, 2847, 1458, 1248, 868 cm<sup>-1</sup>; HRMS calculated for [C<sub>15</sub>H<sub>31</sub>O<sub>2</sub> + H]<sup>+</sup>: 243.2319, found 243.2321. Spectroscopic data was identical to literature.<sup>[8,22]</sup>

**((2R,3R)-3-dodecyloxiran-2-yl)methyl 4-methylbenzenesulfonate (14).** Epoxide **13** (716 mg, 2.95 mmol, 1 eq)

was dissolved in anhydrous DCM (30 mL) under an argon atmosphere. The solution was cooled to 0 °C followed by addition of *p*-toluenesulfonyl chloride (1.13 g, 5.91 mmol, 2 eq), DMAP (25 mg, 0.2 mmol, cat.) and triethylamine (1.24 mL, 8.86 mmol, 3 eq). The reaction mixture was stirred for 20 hours at room temperature. The reaction was quenched with H<sub>2</sub>O (30 mL). The aqueous layer was extracted with DCM (3x 30 mL). The combined organic layers were washed with H<sub>2</sub>O (2x), dried over MgSO<sub>4</sub>, filtrated and concentrated *in vacuo*. The crude product was purified with silica gel chromatography (2-5% EtOAc in pentane). Tosylate **14** (1.12 g, 2.82 mmol, 96%) was collected as colorless oil that slowly crystallized into a white solid. *R<sub>f</sub>* = 0.3 (5% EtOAc in pentane); [α]<sub>D</sub> = +24.0° (c = 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.00 (ad, 2 H, *J* = 8.4 Hz, H-17), 7.35 (d, 2 H, *J* = 8.0 Hz, H-18), 4.18 (dd, 1 H, *J* = 11.2, 4.0 Hz, H-1<sub>a</sub>), 3.97 (dd, 1 H, *J* = 11.2, 6.0 Hz, H-1<sub>b</sub>), 2.95 (ddd, 1 H, *J* = 6.0, 4.0, 2.0 Hz, H-2), 2.78 (td, 1 H, *J* = 5.6, 2.0 Hz, H-3), 2.45 (s, 3 H, H-20), 1.51 (m, 2 H, H-4), 1.36 (m, 2 H, H-5), 1.32 – 1.25 (m, 18 H, H-6 to H-14), 0.88 (t, 3 H, *J* = 6.8 Hz, H-15); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 145.18 (C-16), 132.86 (C-19), 130.04 (C-18), 128.10 (C-17), 70.34 (C-1), 56.95 (C-3), 54.66 (C-2), 32.05 (CH<sub>2</sub>), 31.43 (C-4), 29.79, 29.77, 29.76, 29.65, 29.61, 29.49, 29.43 (CH<sub>2</sub> x 7), 25.87 (C-5), 22.83 (CH<sub>2</sub>), 21.81 (C-20), 14.27 (C-15); IR (neat): 2953, 2916, 2870, 2849, 1599, 1364, 1177, 829, 808 cm<sup>-1</sup>; HRMS calculated for [C<sub>22</sub>H<sub>37</sub>O<sub>4</sub>S + H]<sup>+</sup>: 397.2407, found 397.2404.

**(R)-pentadec-1-en-3-ol (7a).** Sodium hydroxymethanesulfinate hydrate (6.50 g, 55.0 mmol, 7.3 eq) was dissolved

in NaOH (1M, 150 mL). Argon was purged through the solution before addition of tellurium (powder, -200 mesh, 1.92 g, 15.1 mmol, 2 eq). The reaction mixture was stirred for 2 hours at 50 °C. The purple solution of tellurides was cooled to 0°C followed by slowly addition of a solution of Tosylate **14** (2.99 g, 7.53 mmol, 1 eq) in THF (75 mL). The reaction was stirred for 20 hours at room temperature. The reaction was quenched by bubbling air through the solution. The crude reaction mixture was then filtrated over a pad of Celite and concentrated *in vacuo*. The aqueous layer was extracted with Et<sub>2</sub>O (2x 150 mL). The combined organic layers were washed with H<sub>2</sub>O<sub>2</sub> (3%, 75 mL), sodium thiosulfate (10%) and brine before being dried over MgSO<sub>4</sub>, filtrated and concentrated *in vacuo*. The crude product was purified with silica gel chromatography (5-10% Et<sub>2</sub>O in pentane). Allylic alcohol **7a** (1.54 g, 6.78 mmol, 90%) was collected as a white solid. *R<sub>f</sub>* = 0.4 (20% Et<sub>2</sub>O in pentane); [α]<sub>D</sub> = -7.0° (c = 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.87 (ddd, 1 H, *J* = 16.8, 10.4, 6.4 Hz, H-2), 5.22 (dt, 1 H, *J* = 17.2, 1.2 Hz, H-1<sub>a</sub>), 5.10 (dt, 1 H, *J* = 10.4, 1.2 Hz, H-1<sub>b</sub>), 4.10 (m, 1 H, H-3), 1.69 (bs, 1 H, -OH), 1.52 (m, 2 H, H-4), 1.43 – 1.26 (m, 20 H, H-5 to H-14), 0.88 (t, 3 H, *J* = 6.8 Hz, H-15); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 141.45 (C-2), 114.67 (C-1), 73.45 (C-3), 37.19 (C-4), 32.07, 29.82, 29.80, 29.74, 29.70, 29.51, 25.48, 22.84 (CH<sub>2</sub> x 8), 14.28 (C-15); IR (neat): 3348, 2918, 2853, 1643, 1466 cm<sup>-1</sup>. Spectroscopic data was identical to literature.<sup>[22]</sup>

**(R)-pentadec-1-en-3-yl benzoate (7b).** Allylic alcohol **7a** (325 mg, 1.44 mmol, 1 eq) was dissolved in anhydrous

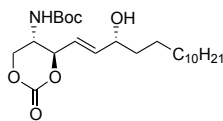
DCM (17 mL) under an argon atmosphere. Benzoic anhydride (974 mg, 4.31 mmol, 3 eq), triethylamine (0.80 mL, 5.74 mmol, 4 eq) and DMAP (17 mg, 0.14 mmol, cat.) were added and the reaction mixture was stirred under reflux for 20 hours. The reaction was quenched by adding NH<sub>4</sub>Cl (sat., 25 mL). The aqueous layer was extracted with Et<sub>2</sub>O (3x 30 mL). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtrated and concentrated *in vacuo*. The crude product was purified with silica gel chromatography (0-2% EtOAc in pentane). The benzoylated product **7b** (424 mg, 1.28 mmol, 89%) was collected as an oil. *R<sub>f</sub>* = 0.8 (10% EtOAc in pentane); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.07 (m, 2 H, H-17), 7.55 (m, 1 H, H-19), 7.44 (m, 2 H, H-18), 5.89 (ddd, 1 H, *J* = 17.2, 10.4, 6.4 Hz, H-2), 5.49 (m, 1 H, H-3), 5.32 (dt, 1 H, *J* = 17.2, 1.2 Hz, H-1<sub>a</sub>), 5.20 (dt, 1 H, *J* = 10.4, 1.2 Hz, H-1<sub>b</sub>), 1.75 (m, 2 H, H-4), 1.46 – 1.25 (m, 20 H, H-5 to H-14), 0.88 (t, 3 H, *J* = 6.8 Hz, H-15); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 165.97 (C=O), 136.75 (C-2), 132.95 (C-19), 130.72 (C-16), 129.70 (C-17), 128.44 (C-18), 166.66 (C-1), 75.50 (C-3), 34.47 (C-4), 32.05, 29.80, 29.77 (x2), 29.70, 29.64, 29.54, 29.49, 25.23, 22.83 (CH<sub>2</sub> x 10), 14.27 (C-15); IR (neat): 3088, 3030, 2922, 2853, 1719, 1267 cm<sup>-1</sup>; HRMS (MALDI-TOF) calculated for [C<sub>22</sub>H<sub>34</sub>O<sub>2</sub> + Ag]<sup>+</sup> 437.1610, found 437.1602.

**(R)-tert-butylidimethyl(pentadec-1-en-3-yloxy)silane (7c).** Allylic alcohol **7a** (259 mg, 1.14 mmol, 1 eq) was dissolved in anhydrous DMF (5 mL) under an argon atmosphere. DMAP (6 mg, 0.05 mmol, cat.) was added and the solution was cooled to 0 °C followed by addition of *tert*-Butyldimethylsilyl chloride (175 mg, 1.16 mmol, 1.02 eq) and triethylamine (0.18 mL, 1.29 mmol, 1.1 eq). The reaction mixture was stirred for 20 hours at room temperature. The reaction was quenched with H<sub>2</sub>O (>50 mL) and extracted with Et<sub>2</sub>O (3x 50 mL). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtrated and concentrated *in vacuo*. The crude product was purified with silica gel chromatography (0% to 2% EtOAc in pentane). The silylated product **7c** was collected as a colorless oil (265 mg, 0.78 mmol, 68%). *R<sub>f</sub>* = 0.4 (pentane); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.79 (ddd, 1 H, *J* = 16.8, 10.4, 6.0 Hz, H-2), 5.12 (dt, 1 H, *J* = 17.2, 1.6 Hz, H-1<sub>a</sub>), 5.01 (dt, 1 H, *J* = 10.4, 1.6 Hz, H-1<sub>b</sub>), 4.07 (m, 1 H, H-3), 1.45 (m, 2 H, H-4), 1.37 – 1.26 (m, 20 H, H-5 to H-14), 0.90 (s, 9 H, CH<sub>3</sub>-*t*Bu), 0.88 (t, 3 H, *J* = 6.8 Hz, H-15), 0.05 (s, 3 H, CH<sub>3</sub>-Si), 0.03 (s, 3 H, CH<sub>3</sub>-Si); <sup>13</sup>C MR (101 MHz, CDCl<sub>3</sub>) δ 142.12 (C-2), 113.48 (C-1), 74.06 (C-3), 38.29 (C-4), 32.10, 29.85, 29.83, 29.82, 29.80, 29.79 (x2), 29.53 (CH<sub>2</sub> x 8), 26.06 (CH<sub>3</sub>-Si-*t*Bu), 25.37, 22.86 (CH<sub>2</sub> x 2), 18.44 (C<sub>q</sub>-Si), 14.29 (C-15), -4.21 (CH<sub>3</sub>-Si), -4.66 (CH<sub>3</sub>-Si); IR (neat): 2955, 2924, 2853, 1252, 1080, 814 cm<sup>-1</sup>; HRMS (MALDI-TOF) calculated for [C<sub>21</sub>H<sub>44</sub>O<sub>2</sub>Si + Ag]<sup>+</sup>: 447.2212, found 447.2229.

**(R)-1-methoxy-4-((pentadec-1-en-3-yloxy)methyl)benzene (7d).** Allylic alcohol **7a** (232 mg, 1.02 mmol, 1 eq) was dissolved in anhydrous DMF (5 mL) under an argon atmosphere. The solution was cooled to 0°C, followed by addition of sodium hydride (60% in mineral oil, 48 mg, 2.0 mmol, 2 eq). After stirring for 15 minutes, 4-methoxybenzyl chloride (0.27 mL, 2.0 mmol, 2 eq) was slowly added to the reaction mixture. The solution was stirred for 20 hours at room temperature. The reaction was quenched by adding NH<sub>4</sub>Cl (sat., 20 mL) drop wise. After quenching, H<sub>2</sub>O (>50 mL) was added and extracted with Et<sub>2</sub>O (2x 100 mL). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtrated and concentrated *in vacuo*. The crude product was purified with silica gel chromatography (0% to 1% Et<sub>2</sub>O in pentane). The PMB-protected product **7d** (309 mg, 0.89 mmol, 87%) was collected as a light yellow oil. *R<sub>f</sub>* = 0.2 (1% Et<sub>2</sub>O in pentane); [α]<sub>D</sub> = +19.0° (*c* = 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.25 (ad, 2 H, *J* = 8.8 Hz, H-18), 6.87 (ad, 2 H, *J* = 8.8 Hz, H-19), 5.72 (ddd, 1 H, *J* = 18.4, 10.4, 8.0 Hz, H-2), 5.21 (dm, 1 H, H-1<sub>a</sub>), 5.18 (dm, 1 H, H-1<sub>b</sub>), 4.52 (d, 1 H, *J* = 11.6 Hz, H-16<sub>a</sub>), 4.28 (d, 1 H, *J* = 11.6 Hz, H-16<sub>b</sub>), 3.80 (s, 3 H, H-21), 3.69 (m, 1 H, H-3), 1.63 (m, 1 H, H-4<sub>a</sub>), 1.46 (m, 1 H, H-4<sub>b</sub>), 1.40 – 1.25 (m, 20 H, H-5 to H-14), 0.88 (t, 3 H, *J* = 6.8 Hz, H-15); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 159.14 (C<sub>q</sub>-PMB), 139.50 (C-2), 131.09 (C<sub>q</sub>-PMB), 129.46 (C-18), 117.00 (C-1), 113.85 (C-19), 80.44 (C-3), 69.80 (C-16), 55.42 (C-21), 35.67 (C-4), 32.08, 29.83, 29.81 (x2), 29.78, 29.75, 29.70, 29.52, 25.54, 22.85 (CH<sub>2</sub> x 10), 14.28 (C-15); IR (neat): 2922, 2853, 1612, 1246, 1038 cm<sup>-1</sup>; HRMS (MALDI-TOF) calculated for [C<sub>17</sub>H<sub>34</sub>O<sub>2</sub> + Ag]<sup>+</sup>: 377.1610, found 377.1598.

**(R)-3-(methoxymethoxy)pentadec-1-ene (7e).** Allylic alcohol **7a** (229 mg, 1.01 mmol, 1 eq) was dissolved in anhydrous DCM (6 mL) under an argon atmosphere. DMAP (16 mg, 0.13 mmol, cat.) was added and the solution was cooled to 0 °C. DIPEA (0.87 mL, 5.0 mmol, 5 eq) and chloromethyl methyl ether (0.34 mL, 4.5 mmol, 4.5 eq) were added. The reaction was stirred for 20 hours at room temperature. The reaction was quenched by adding NH<sub>4</sub>Cl (sat., 20 mL). The reaction mixture was diluted with H<sub>2</sub>O and extracted with DCM (3 x 50 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtrated and concentrated *in vacuo*. The crude product was purified with silica gel chromatography (1-20% Toluene in pentane). The MOM-protected product **7e** (256 mg, 0.95 mmol, 94%) was collected as a light yellow oil. *R<sub>f</sub>* = 0.2 (20% Toluene in pentane); [α]<sub>D</sub> = +50.0 (*c* = 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.66 (ddd, 1 H, *J* = 17.6, 10.4, 7.6 Hz, H-2), 5.19 (dm, 1 H, H-1<sub>a</sub>), 5.16 (dm, 1 H, H-1<sub>b</sub>), 4.70 (d, 1 H, *J* = 6.8 Hz, H-16<sub>a</sub>), 4.53 (d, 1 H, *J* = 6.8 Hz, H-16<sub>b</sub>), 3.97 (m, 1 H, H-3), 3.37 (s, 3 H, H-17), 1.61 (m, 1 H, H-4<sub>a</sub>), 1.49 (m, 1 H, H-4<sub>b</sub>), 1.45 – 1.26 (m, 20 H, H-5 to H-14), 0.88 (t, 3 H, *J* = 6.8 Hz, H-15); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 138.69 (C-2), 117.09 (C-1), 93.83 (C-16), 77.52 (C-3), 55.49 (C-17), 35.58 (C-4), 32.07, 29.82, 29.80 (x2), 29.76, 29.75, 29.70, 29.51, 25.53, 22.83 (CH<sub>2</sub> x 10), 14.25 (C-15); IR (neat): 2924, 2853, 1036 cm<sup>-1</sup>; HRMS (MALDI-TOF) calculated for [C<sub>22</sub>H<sub>34</sub>O<sub>2</sub> + Ag]<sup>+</sup>: 437.1610, found 437.1602.

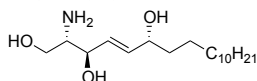
**tert-Butyl ((4R,5S)-4-((R,E)-3-hydroxypentadec-1-en-1-yl)-2-oxo-1,3-dioxan-5-yl)carbamate (8d).** Allylic alcohol



**7a** (24 mg, 0.11 mmol, 1 eq) and cyclic carbonate **6b** (73 mg, 0.30 mmol, 3 eq) were combined and co-evaporated with toluene in a 50 mL round bottom flask. The mixture was dissolved in anhydrous Et<sub>2</sub>O (0.5 mL) under an argon atmosphere. The solution was stirred briefly before addition of second generation Grubbs Catalyst (17 mg, 0.02 mmol, 0.2 eq) and copper (I) iodide (6 mg, 0.03 mmol, 0.3 eq). The reaction

mixture was stirred at room temperature for 48 hours. The reaction mixture was concentrated *in vacuo*. The crude product was purified with silica gel chromatography (20-30% EtOAc in pentane). The metathesized product **8d** was collected as a brown oil that slowly crystallized (39 mg, 0.088 mmol, 83%).  $R_f = 0.4$  (40% EtOAc in pentane);  $[\alpha]_D = +24.4^\circ$  ( $c = 1.0$ , CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.96 (dd, 1 H,  $J = 15.6, 4.8$  Hz, H-5), 5.78 (dd, 1 H,  $J = 15.2, 4.8$  Hz, H-4), 5.53 (d, 1 H,  $J = 7.2$  Hz, -NH), 5.00 (m, 1 H, H-3), 4.55 (bd, 1 H,  $J = 9.6$  Hz, H-1<sub>a</sub>), 4.30 (bd, 1 H,  $J = 10.4$  Hz, H-1<sub>b</sub>), 4.19 (m, 1 H, H-6), 3.94 (bs, 1 H, H-2), 2.41 (bs, 1 H, -OH), 1.51 (m, 2 H, H-7), 1.46 (s, 9 H, CH<sub>3</sub>-Boc), 1.32 – 1.26 (m, 20 H, H-8 to H-17), 0.88 (t, 3 H,  $J = 6.8$  Hz, H-18); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  155.25 (C=O<sub>Boc</sub>), 147.83 (C=O<sub>Carbonate</sub>), 139.19 (C-5), 123.77 (C-4), 81.73 (C-3), 80.93 (C<sub>q</sub>-Boc), 71.32 (C-6), 68.36 (C-1), 46.20 (C-2), 37.16 (C-7), 32.00, 29.76, 29.74 (x2), 29.71, 29.66, 29.61, 29.44 (CH<sub>2</sub> x 8), 28.37 (CH<sub>3</sub>-Boc), 25.44, 22.77 (CH<sub>2</sub> x 2), 14.21 (C-18); IR (neat): 3464, 3352, 2951, 2917, 2850, 1759, 1695, 1190, 1165 cm<sup>-1</sup>; HRMS calculated for [C<sub>19</sub>H<sub>36</sub>NO<sub>4</sub> (M-Boc) +H]<sup>+</sup>: 342.2639, found 342.2641.

**6-Hydroxy sphingosine (1).** Protected 6-hydroxysphingosine **8d** (35 mg, 0.080 mmol) was dissolved in THF/H<sub>2</sub>O

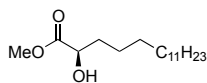


(3:1, 1.5 mL) at room temperature. The solution was cooled to 0°C before addition of lithium hydroxide monohydrate (9 mg, 0.21 mmol, 2.7 eq). The reaction mixture was stirred for 3 hours at 0°C. The reaction mixture was

acidified by addition of Amberlyst. The reaction mixture was filtrated, washed with MeOH/EtOAc and concentrated *in vacuo*. The crude *tert*-Butyl ((2S,3R,6R,E)-1,3,6-trihydroxyoctadec-4-en-2-yl)carbamate was collected as a solid, which was used for the next reaction without further purification.  $R_f = 0.4$  (80% EtOAc in pentane); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.82 (dd, 1 H,  $J = 15.6, 5.2$  Hz, H-5), 5.74 (dd, 1 H,  $J = 15.6, 5.2$  Hz, H-4), 5.46 (d, 1 H,  $J = 8.4$  Hz, -NH), 4.33 (t, 1 H,  $J = 4.6$  Hz, H-3), 4.11 (m, 1 H, H-6), 3.88 (dd, 1 H,  $J = 11.2, 3.6$  Hz, H-1<sub>a</sub>), 3.67 (dd, 1 H,  $J = 11.2, 3.6$  Hz, H-1<sub>b</sub>), 3.60 (m, 1 H, H-2), 1.50 (m, 2 H, H-7), 1.44 (s, 9 H, CH<sub>3</sub>-Boc), 1.28 – 1.26 (m, 20 H, H-8 to H-17), 0.88 (t, 3 H,  $J = 6.8$  Hz, H-18); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  156.55 (C=O<sub>Boc</sub>), 135.66 (C-5), 129.57 (C-4), 80.09 (C<sub>q</sub>-Boc), 73.64 (C-3), 72.03 (C-6), 62.29 (C-1), 55.44 (C-2), 37.35 (C-7), 32.06, 29.83 (x3), 29.80 (x2), 29.76, 29.50 (CH<sub>2</sub> x 8), 28.55 (CH<sub>3</sub>-Boc), 25.70, 22.82 (CH<sub>2</sub> x 2), 14.25 (C-18); HRMS calculated for [C<sub>23</sub>H<sub>45</sub>NO<sub>5</sub>+Na]<sup>+</sup>: 438.3190, found 438.3187.

The crude *tert*-Butyl ((2S,3R,6R,E)-1,3,6-trihydroxyoctadec-4-en-2-yl)carbamate previously described was dissolved in DCM (2.7 mL). The solution was cooled to 0°C before slowly adding TFA (0.3 mL). The solution was stirred for 90 minutes at 0°C. The reaction mixture was diluted with toluene (~20 mL) followed by concentration *in vacuo*. Before complete evaporation of all solvents, the reaction mixture was diluted with toluene 2 more times (2x 20 mL). The crude product was purified with silica gel chromatography (neutralized silica, 5-7.5% MeOH in CHCl<sub>3</sub>). 6-Hydroxy sphingosine **1** was collected as a waxy solid (20 mg, 0.063 mmol, 80% over 2 steps).  $R_f = 0.3$  (30% MeOH in CHCl<sub>3</sub>);  $[\alpha]_D = -9.6^\circ$  ( $c = 0.5$ , MeOH); <sup>1</sup>H NMR (400 MHz, MeOD-*d*<sub>4</sub>)  $\delta$  5.86 (dd, 1 H,  $J = 15.6, 6.0$  Hz, H-5), 5.67 (dd, 1 H,  $J = 15.6, 6.4$  Hz, H-4), 4.37 (t, 1 H,  $J = 5.2$  Hz, H-3), 4.09 (q, 1 H,  $J = 6.0$  Hz, H-6), 3.80 (dd, 1 H,  $J = 11.6, 4.0$  Hz, H-1<sub>a</sub>), 3.70 (dd, 1 H,  $J = 11.6, 8.0$  Hz, H-1<sub>b</sub>), 3.24 (m, 1 H, H-2), 1.51 (m, 2 H, H-7), 1.46 – 1.29 (m, 20 H, H-8 to H-17), 0.90 (t, 3 H,  $J = 6.8$  Hz, H-18); <sup>13</sup>C NMR (101 MHz, MeOD-*d*<sub>4</sub>)  $\delta$  138.26 (C-5), 128.69 (C-4), 72.52 (C-6), 70.43 (C-3), 59.28 (C-1), 58.30 (C-2), 38.27 (C-7), 33.05, 30.77 (x2), 30.74 (x3), 30.45, 26.53, 23.71 (CH<sub>2</sub> x 9), 14.44 (C-18); IR (neat): 3329, 3096, 2953, 2922, 2853, 1668, 1464, 1456, 1435, 1200, 1186, 1136 cm<sup>-1</sup>; HRMS calculated [C<sub>18</sub>H<sub>37</sub>NO<sub>3</sub> +H]<sup>+</sup>: C<sub>18</sub>H<sub>37</sub>NO<sub>3</sub> 316.2846, found 316.2847. Spectroscopic data was identical to literature.<sup>[8]</sup>

**Methyl (R)-2-hydroxyhexadecanoate (16a).** (R,E)-2-hydroxypent-3-enitrile **15** (1.95 g, 20.10 mmol, 1 eq, ee > 99%) was dissolved in anhydrous Et<sub>2</sub>O (25.0 mL) in a flame-dried three necked round bottom flask under an argon atmosphere. Anhydrous MeOH (1.66 mL, 20.98 mmol, 2.0 eq) was added. This solution was purged with dry HCl gas (1.47 g, 40.19 mmol, 2 eq).

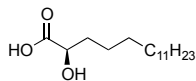


The acidified reaction mixture was stored at -20°C for 20 hours under an argon atmosphere. H<sub>2</sub>O (10 mL) was added and stirring for 40 minutes. The aqueous layer was extracted with EtOAc (3x 40 mL). The combined organic layers were washed with NaHCO<sub>3</sub> (sat., 40 mL) and brine, dried over MgSO<sub>4</sub>, filtrated and concentrated *in vacuo*. The crude product was purified with silica gel chromatography (10% DCM, 10% Et<sub>2</sub>O in pentane, isocratic) giving Methyl (R,E)-2-hydroxypent-3-enoate as a yellow oil (1.26 g, 9.66 mmol, 48%). R<sub>f</sub> = 0.2 (10% DCM, 10% Et<sub>2</sub>O in pentane); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.90 (m, 1 H, H-4), 5.53 (m, 1 H, H-3), 4.61 (d, 1 H, J = 6.4 Hz, H-2), 3.80 (s, 3 H, -OMe), 3.20 (bs, 1 H, -OH), 1.74 (d, 3 H, J = 6.8 Hz, H-5); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 174.26 (C-1), 129.92 (C-4), 127.26 (C-3), 71.48 (C-2), 52.80 (-OMe), 17.74 (C-5); IR (neat): 3439, 2922, 2855, 1732, 1445, 1198 cm<sup>-1</sup>. Spectroscopic data was identical to literature.<sup>[18]</sup>

Methyl (R,E)-2-hydroxypent-3-enoate (1.42 g, 10.94 mmol, 1 eq) was dissolved in anhydrous DCM (6 mL) under an argon atmosphere in a 250 mL round bottom flask. 1-Tetradecene (5.55 mL, 21.88 mmol, 2 eq), acetic acid (63 μL, 1.09 mmol, 0.5 eq) and second generation Grubbs Catalyst (93 mg, 0.11 mmol, 0.05 eq) were added to the reaction mixture. The reaction mixture was stirred for 60 hours at 50 °C. Afterwards, the reaction mixture was concentrated *in vacuo*. The crude product was purified with silica gel chromatography (5% Et<sub>2</sub>O, 10% DCM to 7.5 % Et<sub>2</sub>O, 10% DCM to 10% Et<sub>2</sub>O, 10% DCM in pentane). The metathesized product Methyl (R,E)-2-hydroxyhexadec-3-enoate was collected as a brown oil (2.27 g, 7.99 mmol, 73%). R<sub>f</sub> = 0.2 (10% Et<sub>2</sub>O, 10% DCM in pentane); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.88 (dt, 1 H, J = 14.4, 6.8 Hz, H-4), 5.50 (dd, 1 H, J = 15.2, 6.0 Hz, H-3), 4.61 (d, 1 H, J = 6.0 Hz, H-2), 3.80 (s, 3 H, -OMe), 2.80 (s, 1 H, -OH), 2.06 (q, 2 H, J = 7.2 Hz, H-5), 1.39 (m, 2 H, H-6), 1.35 – 1.26 (m, 18 H, H-7 to H-15), 0.88 (t, 3 H, J = 6.8 Hz, H-16); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 174.44 (C-1), 135.27 (C-4), 125.95 (C-3), 71.58 (C-2), 52.92 (-OMe), 32.29, 32.06, 29.82, 29.80, 29.79, 29.75, 29.60, 29.50, 29.29, 28.96, 22.83 (CH<sub>2</sub> x 11), 14.27 (C-16); IR (neat): 3458, 2922, 2853, 1713, 1466 cm<sup>-1</sup>.

Methyl (R,E)-2-hydroxyhexadec-3-enoate (1.16 g, 4.08 mmol, 1 eq) was dissolved in EtOAc (40 mL) under an argon atmosphere. The solution was purged with argon followed by addition of palladium on carbon (10% loading, 22 mg, 0.2 mmol, 0.05 eq). The mixture was then stirred for 30 minutes under a flow of hydrogen gas and was then left for 60 hours under a hydrogen atmosphere. The mixture was filtered over a pad of Celite and concentration *in vacuo* giving the crude product **16a** as a solid (1.07 g, 3.72 mmol, 91%). R<sub>f</sub> = 0.2 (10% Et<sub>2</sub>O, 10% DCM in pentane); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.19 (dd, 1 H, J = 7.2, 4.4 Hz, H-2), 3.79 (s, 3 H, -OMe), 2.69 (bs, 1 H, -OH), 1.78 (m, 1 H, H-3<sub>a</sub>), 1.63 (m, 1 H, H-3<sub>b</sub>), 1.54 – 1.25 (m, 24 H, H-4 to H-15), 0.88 (t, 3 H, J = 6.8 Hz, H-16); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 176.02 (C-1), 70.62 (C-2), 52.63 (-OMe), 34.57 (C-3), 32.08, 29.84, 29.83, 29.81 (x2), 29.78, 29.70, 29.61, 29.51, 29.45, 24.88, 22.85 (CH<sub>2</sub> x 12), 14.28 (C-16); IR (neat): 3462, 2920, 2853, 1736, 1460, 1215 cm<sup>-1</sup>. HRMS (MALDI-TOF) calculated [C<sub>17</sub>H<sub>34</sub>O<sub>3</sub> + Ag]<sup>+</sup>: 393.1559, found 393.1572.

**α-Hydroxy fatty acid (16b).** Methyl ester **16a** (926 mg, 3.23 mmol, 1 eq) was dissolved in THF/MeOH/H<sub>2</sub>O (2:2:1, 30 mL) at room temperature. Lithium hydroxide monohydrate (420 mg, 10.0 mmol, 3.1 eq) was added and the reaction mixture was stirred for 20 hours at room temperature.



The reaction mixture was quenched by HCl (1M, 15 mL). The aqueous mixture was extracted with EtOAc (3x 75 mL). The combined organic layers were washed with H<sub>2</sub>O (100 mL) and brine, dried over MgSO<sub>4</sub>, filtrated and concentrated *in vacuo*. The crude α-hydroxy fatty acid **16b** was collected as a solid (873 mg, 3.20 mmol, 99%) and was used for the next step without further purification. R<sub>f</sub> = 0.1 (30% EtOAc in pentane); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.28 (dd, 1 H, J = 7.6, 4.4 Hz, H-2), 1.86 (m, 1 H, H-3<sub>a</sub>), 1.71 (m, 1 H, H-3<sub>b</sub>), 1.46 (m, 2 H, H-4), 1.38 – 1.26 (m, 22 H, H-5 to H-15), 0.88 (t, 3 H, J = 6.8 Hz, H-16); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 179.41 (C-1), 70.38 (C-2), 34.36 (C-3), 32.08, 29.84 (x2), 29.81 (x2), 29.79, 29.71, 29.60, 29.52, 29.41 (CH<sub>2</sub> x 10), 24.89 (C-4), 22.85 (CH<sub>2</sub>), 14.29 (C-16); IR (neat): 3445, 2920, 2851, 1732, 1466 cm<sup>-1</sup>.

Spectroscopic data was identical to literature.<sup>[23]</sup>

**(R)-2-Acetoxyhexadecanoic acid (16c).** The crude  $\alpha$ -hydroxy fatty acid **16b** (808 mg, 2.97 mmol, 1 eq) was dissolved in anhydrous DCM (30 mL) under an argon atmosphere at room temperature. Acetic anhydride (4.49 mL, 47.45 mmol, 16 eq) and pyridine (7.45 mL, 92.15 mmol, 31 eq) were added and the reaction mixture was stirred for 20 hours. The reaction was quenched by adding NaHCO<sub>3</sub> (sat. aq., 50 mL). The aqueous layer was extracted with CHCl<sub>3</sub> (2x 50 mL). The combined organic layers were washed with KHSO<sub>4</sub> (0.5 M, 75 mL), dried over MgSO<sub>4</sub>, filtrated and concentrated *in vacuo*. The acetylated product **16c** was collected as a yellow solid (905 mg, 2.88 mmol, 97%), which was used for the next step without further purification.  $R_f = 0.2$  (30% EtOAc in pentane);  $[\alpha]_D = +9.0$  ( $c = 1.0$ , CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  10.61 (bs, 1 H, -COOH), 5.00 (t, 1 H,  $J = 6.4$  Hz, H-2), 2.14 (s, 3 H, CH<sub>3</sub>-Acetyl), 1.86 (m, 2 H, H-3), 1.42 (m, 2 H, H-4), 1.37 – 1.26 (m, 22 H, H-5 to H-15), 0.88 (t, 3 H,  $J = 6.8$  Hz, H-16); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  175.96 (C-1), 170.79 (C=O<sub>Acetyl</sub>), 72.00 (C-2), 32.08 (CH<sub>2</sub>), 31.09 (C-3), 29.83 (x2), 29.80 (x2), 29.76, 29.68, 29.51, 29.49, 29.26 (CH<sub>2</sub> x 9), 25.26 (C-4), 22.85 (CH<sub>2</sub>), 20.73 (CH<sub>3</sub>-acetyl), 14.28 (C-16); IR (neat): 2955, 2916, 2849, 1742, 1722, 1228 cm<sup>-1</sup>. HRMS (MALDI-TOF) calculated [C<sub>18</sub>H<sub>34</sub>O<sub>4</sub> + Ag]<sup>+</sup>: 421.1508, found 421.1516. Spectroscopic data was identical to literature.<sup>[23]</sup>

**(R)-1-Oxo-1-(((2S,3R,6R,E)-1,3,6-trihydroxyoctadec-4-en-2-yl)amino)hexadecan-2-yl acetate (17).** 6-Hydroxy sphingosine **1** (11 mg, 0.035 mmol, 1 eq) and carboxylic acid **16c** (14 mg, 0.045 mmol, 1.3 eq) were dissolved in anhydrous EtOH (1.5 mL) under an argon atmosphere. 2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (17 mg, 0.069 mmol, 2 eq) was added and the reaction mixture was stirred for 20 hours at 50°C. The reaction mixture was concentrated *in vacuo* and purified with silica gel chromatography (0-3% MeOH in CHCl<sub>3</sub>). Acetylated ceramide **17** was collected as a waxy white solid (14 mg, 0.023 mmol, 66%).  $R_f = 0.3$  (5% MeOH in CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.76 (d, 1 H,  $J = 8.0$  Hz, -NH), 5.84 (dd, 1 H,  $J = 15.6, 6.4$  Hz, H-5), 5.73 (dd, 1 H,  $J = 15.6, 5.6$  Hz, H-4), 4.99 (t, 1 H,  $J = 6.4$  Hz, H-2'), 4.37 (t, 1 H,  $J = 4.8$  Hz, H-3), 4.13 (q, 1 H,  $J = 6.4$  Hz, H-6), 3.97 (dd, 1 H,  $J = 11.2, 3.2$  Hz, H-1<sub>a</sub>), 3.89 (m, 1 H, H-2), 3.69 (dd, 1 H,  $J = 11.2, 3.6$  Hz, H-1<sub>b</sub>), 3.24 (bs, 1 H, -OH), 2.86 (bs, 1 H, -OH), 2.16 (s, 3 H, CH<sub>3</sub>-Acetyl), 1.83 (m, 2 H, H-3'), 1.52 (m, 2 H, H-7), 1.37 – 1.26 (m, 44 H, H-8 to H-17 and H-4' to H-15'), 0.88 (t, 6 H,  $J = 6.8$  Hz, H-18 and H-16'); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  170.85, 170.75 (C-1' and C=O<sub>Acetyl</sub>), 136.27 (C-5), 129.50 (C-4), 74.76 (C-2'), 73.55 (C-3), 72.21 (C-6), 61.94 (C-1), 54.20 (C-2), 37.34 (C-7), 32.08 (CH<sub>2</sub>), 31.97 (C-3'), 29.85 (x4), 29.83 (x3), 29.81 (x3), 29.73 (x2), 29.59, 29.51 (x2), 29.41, 25.63, 25.16, 22.84 (CH<sub>2</sub> x 19), 21.10 (CH<sub>3</sub>-Acetyl), 14.27 (C-18 and C-16'); HRMS calculated [C<sub>36</sub>H<sub>69</sub>NO<sub>6</sub> + Na]<sup>+</sup>: 634.5017, found 634.5011.

**Ceramide (2).** Acetylated ceramide **17** (11 mg, 0.018 mmol, 1 eq) was dissolved in DCM/MeOH (4:1, 0.2 mL) under an argon atmosphere. Potassium carbonate (catalytic amount) was added and the reaction mixture was stirred for 2 hours at room temperature. The reaction mixture was acidified by adding Amberlyst 1, followed by filtration and concentration *in vacuo*. The crude product was purified with silica gel chromatography (0- 5% MeOH in CHCl<sub>3</sub>) giving Ceramide **2** as a white solid (9 mg, 0.016 mmol, 88%).  $R_f = 0.5$  (10% MeOH in CHCl<sub>3</sub>); <sup>1</sup>H NMR (850 MHz, CDCl<sub>3</sub>/MeOD-*d*<sub>4</sub>, 9:1)  $\delta$  7.42 (d, 1 H,  $J = 8.5$  Hz, -NH), 5.77 (dd, 1 H,  $J = 15.3, 6.0$  Hz, H-5), 5.66 (dd, 1 H,  $J = 15.3, 6.0$  Hz, H-4), 4.23 (at, 1 H,  $J = 5.1$  Hz, H-3), 4.07 (m, 1 H, H-6), 4.03 (dd, 1 H,  $J = 8.5, 3.4$  Hz, H-2'), 3.85 (m, 1 H, H-2), 3.81 (dd, 1 H,  $J = 12.0, 4.3$  Hz, H-1<sub>a</sub>), 3.69 (dd, 1 H,  $J = 11.9, 2.6$  Hz, H-1<sub>b</sub>), 1.58 – 1.44 (m, 4 H, H-7 and H-3'), 1.41 – 1.26 (m, 44 H, H-8 to H-17 and H-4' to H-15'), 0.88 (t, 6 H,  $J = 6.8$  Hz, H-18 and H-16'); <sup>13</sup>C NMR (214 MHz, CDCl<sub>3</sub>/MeOD-*d*<sub>4</sub>, 9:1)  $\delta$  176.21 (C-1'), 135.79 (C-5), 129.16 (C-4), 72.59 (C-3), 72.18 (C-2'), 71.79 (C-6), 61.45 (C-1), 54.59 (C-2), 37.12 (C-7), 34.37 (C-3'), 31.96, 29.75, 29.73 (x2), 29.72 (x2), 29.71 (x2), 29.70 (x2), 29.68 (x2), 29.66, 29.63, 29.48, 29.40 (x2), 25.60, 22.72 (CH<sub>2</sub> x 19), 14.11 (C-18 and C-16'); IR (neat): 3377, 3264, 2953, 2916, 2849, 1738, 1715, 1651, 1620, 1470, 1074, 1043 cm<sup>-1</sup>; HRMS calculated for [C<sub>34</sub>H<sub>68</sub>NO<sub>5</sub> + H]<sup>+</sup>: 570.5092, found 570.5087.



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# Synthesis of Ceramide-Mimetic Aziridines as Potential Mechanism-Based Enzyme Inhibitors

## 6.1 Introduction

Glucosylceramide (**1**) is the substrate of at least three hydrolases.<sup>[1]</sup> In healthy tissues, glucosylceramide is predominantly processed by lysosomal acid glucosylceramidase (GBA, Figure 6.1) to form glucose (**2**) and ceramide (**3**). Gaucher disease is characterized by genetic impairment of GBA, resulting in glucosylceramide accumulation. Within the lysosomes, elevated glucosylceramide levels can be taken on by acid ceramidase (ACase), which in healthy individuals is responsible for hydrolysis of the amide bond in ceramide to