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Efficient stereodivergent synthesis of *erythro*- and *threo*-sphingosines: unprecedented reversal of the stereochemistry in the addition

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Abstract—A convenient diastereoselective synthesis of D-*erythro*- and L-*threo*-sphingosine derivatives is described. L-Serine-derived aldehyde (Garner's aldehyde) (**2**) was treated with 1-alkenyl-zirconocene chlorides (**3**) in the presence of $ZnBr_2$ in THF to give the natural *erythro*-(*anti*-) isomers with high diastereoselectivity (*anti*/*syn*=12–20:1). In contrast, reaction of **2** with 1-alkenyl-ethyl-zinc, prepared from **3** and Et_2Zn, in CH_2Cl_2 gave the unnatural *threo*-(*syn*-) isomers predominantly (*anti*/*syn*=1:12–15).

1. Introduction

Sphingolipids, e.g. sphingomyelin, cerebrosides, and gangliosides, are ubiquitous membrane components of eukaryotic cells and are involved in many essential biological processes such as cell growth, cell differentiation, and adhesion.[1] Common to this diverse group of natural products is a sphingoid base bearing a long aliphatic chain and a polar 2-amino-1,3-diol head group. The most abundant sphingoid base in nature is D-*erythro*-C_{18}-sphingosine [(2*S*,3*R*,4*E*)-2-aminooctadec-4-ene-1,3-diol, **1**]. Sphingolipid metabolites such as sphingosine and ceramide are emerging as a novel class of lipid second messengers.[2] Sphingosine is a potent inhibitor of protein kinase C,[3] and ceramide has been found to play a crucial role in cell regulation and in programmed cell death (apoptosis) (Fig. 1).[4]

Because of their biological significance as well as the difficulty of isolation from natural sources in homogeneous form, considerable efforts have been devoted to the synthetic studies of sphingolipids and a number of synthetic methods of **1** have been reported since 1950's.[5]

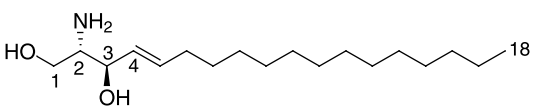

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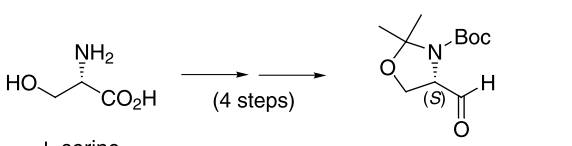
Figure 1. D-*erythro*-C_{18}-sphingosine.

Conceptually, one of the most straightforward strategies for the enantioselective synthesis of D-*erythro*-sphingosine **1** would be the addition of a 1-alkenyl nucleophile to a suitably protected L-serine-derived aldehyde (serinal). Earlier syntheses[6] based on this strategy, however, met with serious problems such as low yield,[6a] poor diastereoselectivity,[6b] and/or loss of enantiomeric purity during the addition reaction, presumably due to the instability of the serinal derivatives as well as the modest nucleophilicity of the alkenylating agent (alkenyl-aluminum). In 1984, Garner succeeded in preparing a configurationally stable serinal **2** (*N*-Boc-*N*,*O*-isopropylidene-L-serinal=Garner's aldehyde) from L-serine[7] (Scheme 1). This aldehyde and the closely related ones have been widely employed as chiral building blocks for the synthesis of natural products bearing 1,2-amino-alcohol or 2-amino-1,3-diol subunit.[8] In 1988, four research groups independently reported[9] efficient syntheses of sphingosine **1** from the aldehyde **2** via addition of 1-pentadecynyllithium to **2** with high *anti*-diastereoselectivity (*anti*/*syn*=8:1[9b] to 15:1[9d]). Herold[9a] further investigated the effect of additives and found that the *anti*-selectivity increased to 20:1 in the presence of HMPA, a



L-serine (*S*)-Garner's aldehyde

2

Scheme 1.

Keywords: sphingosine; addition reactions; diastereoselection; zirconium and compounds.

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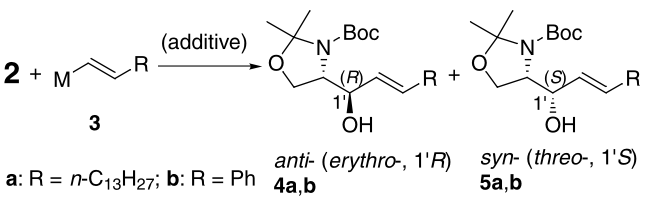


Scheme 2. Addition of (*E*)-1-alkenyl metals **3** to Garner's aldehyde **2**.

cation complexing agent, whereas the selectivity was reversed to *syn*-selective (*anti*/*syn*=1:20) by adding 1 equiv. of $ZnBr_2$ in Et_2O. These methods have been widely applied to the synthesis of natural and unnatural sphingolipid derivatives.[10] For the sphingosine synthesis, however, this type of alkyne-addition method requires an additional step, that is, reduction of the triple bond to an (*E*)-olefin with Red-Al[9a] or lithium/liq. NH_3.[9d]

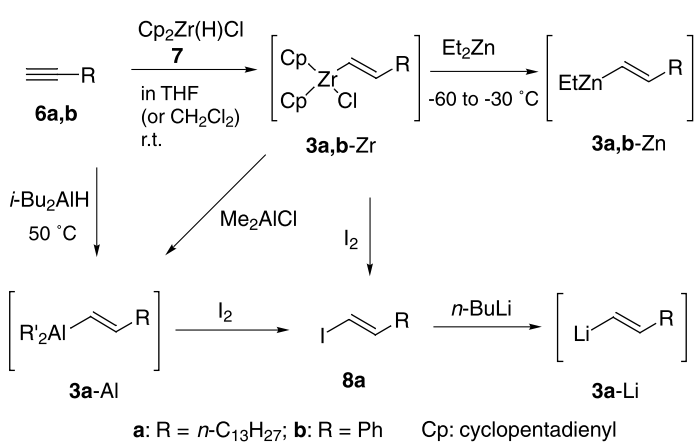
Compared with the alkynylation mentioned above, less attention has been paid to the alkenylation of Garner's aldehyde **2** (Scheme 2). Coleman et al. investigated the addition reactions of simple vinyl metals (**3**, R=H, M=Li, MgBr, ZnCl) to **2** and found that the *anti*/*syn* ratio of the adducts (**4**/**5**) ranged from 5:1 to 1:6 depending on the metals, additives, and solvents.[11] However, 1-(*E*)-alkenyllithiums (R≠H) or the Grignard counterparts[12] have rarely been employed for the sphingosine synthesis because, in addition to their tedious preparations,[13] the yield and the stereoselectivity in the addition are usually lower[14] than those of 1-alkynyl-lithiums. To our knowledge, addition reactions using other alkenyl-metals have been reported from four laboratories. Garner et al. observed that the reaction of **2** with 1-pentadecenyl-alane (**3a**, M=Al(*i*-Bu)$_2$) gave the adducts with modest *syn*-selectivity (**4a/5a**=1:2).[9b] Soai et al. reported that the reaction of 1-pentadecenylethyl-zinc (**3a**, M=ZnEt) with **2** in the presence of 2-(dibutylamino)ethanol afforded **4a/5a** in 50% combined yield in a ratio of 7.3:1, the highest *anti*-selectivity to date.[15a] Suzuki et al. reported that the reaction of 1-octenylzirconocene chloride (**3**, R=*n*-C_6H_{13}, M=$ZrCp_2Cl$) with **2** in the presence of $AgAsF_6$ gave the corresponding allylic alcohols in 70% yield as a 1:1 diastereomeric mixture.[15b] Very recently, Fürstner et al. found that the rhodium-catalyzed addition of 1-octenylboronic acid [**3**, R=*n*-C_6H_{13}, M=$B(OH)_2$] to **2** gives the adducts in 78% yield with *anti*-selectivity (*anti*/*syn*=82:18).[15c] Therefore, improvements in both the stereoselectivity[16] and the yield are still necessary for practical synthesis.

Here we disclose our results on the stereoselective additions of 1-alkenyl metals, most of which were prepared via hydrozirconation of 1-alkynes, to Garner's aldehyde to develop an efficient direct synthesis of *erythro*- and *threo*-sphingosines.[17–19]

2. Results and discussion

We focused our attention on 1-(*E*)-alkenylzirconocene species, since they are readily formed by hydrozirconation[20] of terminal alkynes **6** with zirconocene chloride hydride (Schwartz reagent) **7** in a regio and stereo-specific manner (Scheme 3). In general, hydrozirconation of 1-alkynes with $Cp_2Zr(H)Cl$ proceeds more rapidly than hydroalumination with DIBAL-H, and more importantly, the former reaction tolerates the presence of certain functional groups such as ethers, silyl ethers, and *t*-butyl esters. Although addition of alkenylzirconocenes to aldehydes is sluggish, the reaction is accelerated either by adding a catalyst (Ag-salts,[15b,21a] $ZnBr_2$[21b]) or by transmetalation with dialkylzinc[21c] to afford (*E*)-allylic alcohols in fair to high yields. Besides, methyllithium has been reported to promote the addition by generating a reactive alkyne–zirconocene complex.[21d]

The aldehyde **2** was prepared from *N*-Boc-L-serine in three steps according to an improved procedure by Taylor et al.,[22] or was obtained from a commercial source. The results of the reaction of **2** with 1-pentadecenyl metals **3a** are summarized in Table 1. We first examined the addition of 1-pentadecenyl-lithium (**3a**, M=Li), prepared from **8a**[13] with butyllithium, to **2** at low temperatures in THF (entry 1). Although the *syn*-isomer **5a** was slightly more polar than the *anti*-isomer **4a** on TLC as reported by Garner,[9b] it was difficult to separate these isomers by silica gel chromatography. In addition, the starting aldehyde **2** had a similar R_f value to the adducts **4a/5a**. In the work-up procedure, the crude extraction mixture was treated with $NaBH_4$ to reduce the unreacted aldehyde to the more polar primary alcohol. The ^1H NMR spectrum of the product mixture **4a/5a** in



Scheme 3. Preparation of 1-alkenyl metals from 1-alkynes.

Table 1. Addition of (*E*)-1-pentadecenyl metals **3a** to Garner's aldehyde **2**

Entry	M[a]	Additive (mol%[b])	Solvent	Conditions	Yield[c] (%)		
					4a/5a	Ratio[d]	**2**[e]
1	Li		THF	−70 to −40°C	41	5:1	30
2	$Cp_2Zr(Cl)$	AgOTf (15)	CH_2Cl_2	0°C to rt, 6 h	30	1:1	40
3	$Cp_2Zr(Cl)$	$ZnBr_2$ (50)	THF	0°C to rt, 24 h	74	12:1	11
4	$Cp_2Zr(Cl)$	$ZnBr_2$ (25)	THF	0°C to rt, 24 h	70	20:1	8
5	$Cp_2Zr(Cl)$	$ZnBr_2$ (100)	THF	0°C to rt, 20 h	73	5:1	5
6	$Cp_2Zr(Cl)$	$ZnBr_2$ (50)	CH_2Cl_2	0°C to rt, 20 h	81	5:1	
7	$Cp_2Zr(Cl)$	$Zn(OTf)_2$ (50)	THF	0°C to rt, 24 h	48	1.1:1	33
8	$Cp_2Zr(Cl)$	$Zn(OTf)_2$ (45)	CH_2Cl_2	0°C to rt, 24 h	78	2:1	
9	EtZn		CH_2Cl_2	−30 to 0°C, 1 h	84	1:15	
10	EtZn		THF	−20°C to rt, 18 h	67	12:1	19
11	Me_2Al		CH_2Cl_2	−20°C to rt	77	1:1.5	
12	$Cp_2Zr(Me)$		THF	−30°C to rt, 2 h	28	1.8:1	42

[a] Alkenyl-metals used were 1.8–2.0 equiv. to **2**.
[b] Relative to **2**.
[c] Isolated yield after chromatography.
[d] Ratio determined by ^{1}H NMR.
[e] The yield of reduced primary alcohol.

C_6D_6 at 75°C[†] revealed the *anti*/*syn* ratio to be=5:1 from the integration of the diastereotopic (C-1′) protons [**4a**: δ 4.31 (br s) vs **5a**: δ 4.41 (t, *J*=7 Hz)].[15a] This *anti*/*syn* ratio is in accordance with those reported for the addition of vinyllithium,[11] vinylmagnesium bromide,[23a] and aryllithiums,[23b,c] indicating that the addition would occur mainly via a non-chelated Felkin–Anh transition state.

We then investigated the reaction of 1-(*E*)-pentadecenylzirconocene chloride (**3a**-Zr), prepared from 1-pentadecyne **6a** and $Cp_2Zr(H)Cl$ **7**,[24] with **2**. Following the protocol of Suzuki,[21a] a catalytic amount of silver trifluoromethanesulfonate (AgOTf) was added to a mixture of **2** and **3a**-Zr (2 equiv. to **2**) in CH_2Cl_2 (entry 2). This reaction provided a 1:1 mixture of **4a/5a** in low yield (not optimized). The lack of stereoselectivity is consistent with the precedent[15b] mentioned above. Next, according to the protocol of Srebnik,[21b] $ZnBr_2$ (50 mol% to **2**) was added to a mixture of **2** and **3a**-Zr in THF (entry 3). The addition reaction was very slow at 0°C, but gradually proceeded at room temperature to afford the adducts in 74% yield along with the primary alcohol (11%) after treatment with $NaBH_4$. The ^{1}H NMR analysis showed that *anti*-**4a** was the major product with high diastereoselectivity (12:1). The *anti*-selectivity increased to 20:1 by using a reduced amount (25 mol%) of $ZnBr_2$, whereas it decreased to 5:1 with 100 mol% of $ZnBr_2$. When the reaction was carried out in CH_2Cl_2 instead of THF, the addition proceeded more rapidly to give the adducts in better yield, albeit with a slightly diminished selectivity (entry 6). We found the addition was promoted by $Zn(OTf)_2$, but the stereoselectivities were low (entries 7 and 8).

Then according to the protocol of Wipf,[21c] an equimolar amount of Et_2Zn (1.0 M solution in hexane) was added to a solution of **3a**-Zr in CH_2Cl_2 at −40°C to generate 1-pentadecenyl-ethyl-zinc (**3a**-Zn) via transmetalation, then **2** was added (entry 9). The reaction proceeded smoothly below 0°C giving the adducts in high yield with high *syn*-selectivity (*anti*/*syn*=1:15). When this Et_2Zn-mediated reaction was carried out in THF, the *anti*/*syn* ratio was entirely reversed to *anti*-selective (entry 10). In the case of transmetalation with Me_2AlCl[25] in CH_2Cl_2, both isomers were obtained with modest *syn*-selectivity (entry 11). When MeLi was used for replacing the chloride with methyl group following the protocol of Maier,[21d] the adducts were obtained in low yield with modest *anti*-selectivity (entry 12).

The enantiomeric purities of the *anti*-rich (entry 4) and the *syn*-rich (entry 9) products were determined by their optical rotations, which agreed well with those reported,[9b] as well as by NMR analysis of their Mosher esters[26] prepared by condensation with (*S*)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (*S*-MTPA). The ^{1}H NMR spectrum of the each Mosher ester showed no diastereomeric peak from the antipode,[‡] indicating that essentially no racemization occurred during the reaction.

We then examined the reaction of **2** with (*E*)-β-styryl-metals **3b** derived from phenylacetylene **6b** and Schwartz reagent **7**. The addition products **4b/5b**[17h,27] were easily detected on TLC by their UV absorption at 254 nm, but they were also inseparable by silica gel chromatography. The structures and the ratio of the adducts were determined by NMR analyses.[§] The results are summarized in Table 2. $ZnBr_2$ catalyzed addition of **3b**-Zr in THF predominantly gave the *anti*-isomer **4b** (entry 1), whereas *syn*-isomer **5b** was major in CH_2Cl_2 (entry 2). Addition of β-styryl-ethylzinc (**3b**-Zn), generated in situ from **3b**-Zr with Et_2Zn, to **2** in CH_2Cl_2 predominantly afforded the *syn*-isomer **5b** (entry 3). However, Et_2Zn-mediated reaction carried out in THF gave a complex mixture, which contained the adducts **4b/5b** in only ca. 5% yield (entry 4). Thus, the stereochemical

[†] This type of oxazolidine-carbamate exists as a pair of rotamers that interconvert slowly at 25°C, thereby the ^{1}H NMR spectrum shows doubling and line broadening of certain resonances.

[‡] Racemic *anti*- and *syn*-adducts were prepared from racemic Garner's aldehyde, which was prepared by treatment of **2** with DBU in CH_2Cl_2, by the same procedures as above, and they were treated with (*S*)-MTPA to give the 1:1 diastereomeric Mosher esters, respectively.

[§] Distinguishable proton signals: C1′–H: **4b** δ 4.40 (s-like) vs **5b** δ 4.60 (t); C3′–H: **4b** δ 6.72 (d) vs **5b** δ 6.62 (d); *t*-Bu (9H): **4b** δ 1.32 (s) vs **5b** δ 1.39 (s).

Table 2. Addition of (*E*)-β-styryl-metals **3b** to Garner's aldehyde **2**

Entry	M[a]	Additive (mol%[b])	Solvent	Conditions	Yield[c] (%)		
					4b/5b	Ratio[d]	**2**[e]
1	$Cp_2Zr(Cl)$	$ZnBr_2$ (50)	THF	0°C to rt, 24 h	58	15:1	14
2	$Cp_2Zr(Cl)$	$ZnBr_2$ (25)	CH_2Cl_2	0°C to rt, 3 h	87	1:4.5	
3	EtZn		CH_2Cl_2	−30 to 0°C, 1 h	86	1:12	
4	EtZn		THF	−20°C to rt, 16 h	ca. 5[f]	3:1	

[a] Alkenyl-metals used were 1.8–2.0 equiv. to **2**.
[b] Relative to **2**.
[c] Isolated yield after chromatography.
[d] Ratio determined by ^1H NMR.
[e] The yield of reduced primary alcohol.
[f] Contaminated with byproducts.

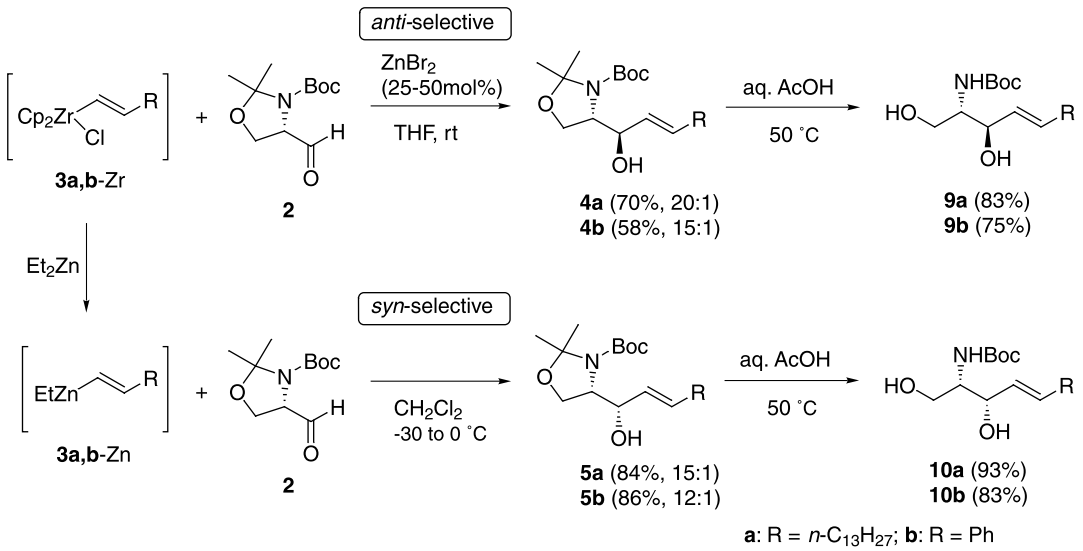
results of entries 1 and 3 are consistent with those observed for the additions of **3a**-Zr and **3a**-Zn under otherwise identical conditions, respectively. (Scheme 4)

There have been a number of studies[8,28] on the addition of organometallic reagents to the aldehyde **2**. The stereochemical outcome of these reactions has been generally rationalized that the *anti*-isomers are formed via the Felkin–Anh transition state, whereas the *syn*-isomers are formed via a cyclic chelate between the aldehyde carbonyl and the Boc carbonyl groups. However, the stereoselectivity has been shown to be rather reagent dependent, and both chelated and non-chelated processes can occur concomitantly. To our knowledge, the reaction mechanism of the $ZnBr_2$ catalyzed addition of alkenylzirconocenes remains unclear,[21b,29] and no precedent exists for the addition to α-chiral aldehydes. In our cases, $ZnBr_2$ catalyzed additions in THF afforded the non-chelation controlled *anti*-adducts **4a**,**b** predominantly and the *anti*-selectivity slightly decreased with the increase of $ZnBr_2$. These results suggest that zinc bromide in THF would interact preferably with **3**-Zr rather than with the serinal **2** and excess $ZnBr_2$ may form a chelate with **2**. The *syn*-selective addition of **3a**,**b**-Zn in CH_2Cl_2 can be explained by a chelated transition model of **2** with zinc or by a coordinated delivery model.[11] However, high *anti*-selectivity is also observed in the addition of **3a**-Zn in THF (entry 10) or in toluene.[15a] Therefore it has been clearly indicated that the stereoselectivity in the additions of alkenylzirconocene-zinc reagents (for both $ZnBr_2$ and Et_2Zn) to **2** is strongly dependent on the solvent employed. The high selectivities observed here may be attributed to the steric bulk of the zirconocene moiety.

The *N*,*O*-isopropylidene acetal of **4a**,**b** and **5a**,**b** was selectively cleaved with aqueous acetic acid to give the known *N*-Boc sphingosines **9a**,**b** and **10a**,**b** in good to high yields (Scheme 4). These *N*-Boc derivatives except **9b** were recrystallized to remove the minor diastereomer and showed spectral and physical data identical with those reported.[9a,10b,30]

3. Conclusion

We have developed a practical, highly diastereoselective synthesis of both D-*erythro*- and L-*threo*-sphingosines from Garner's aldehyde **2** with 1-alkenyl nucleophiles prepared via hydrozirconation. The enantiomeric L-*erythro*- and D-*threo*-sphingosines should be accessible from D-serine by the same procedures. This diastereodivergent approach has been applied to the synthesis of phenyl-substituted sphingosine analogues. Since hydrozirconation is compatible with some functional groups, this protocol would also be applicable to the synthesis of sphingosine analogues



Scheme 4. Diastereodivergent synthesis of *N*-Boc sphingosine derivatives from **2** and alkenyl-zirconocenes (**3**-Zr).

bearing a functionalized hydrophobic backbone. Syntheses of other sphingoid bases using this protocol are in progress and will be reported in due course.

4. Experimental

4.1. General

Melting points were determined with a Yanaco melting point apparatus MP-500D and are uncorrected. Optical rotations were measured with a JASCO DIP-1000 polarimeter and $[\alpha]_D$ values are given in 10^{-1} deg. cm^2 g^{-1}. ^{1}H NMR spectra were recorded at 270 MHz on a JEOL JNM-GSX-270 spectrometer for solutions in $CDCl_3$ or C_6D_6, and chemical shifts (δ) are reported in ppm relative to internal tetramethylsilane (δ 0.00), residual $CHCl_3$ (δ 7.26), or C_6HD_5 (δ 7.15). ^{13}C NMR spectra were recorded at 67.8 MHz and chemical shifts (δ) are reported in ppm relative to $CDCl_3$ (δ 77.0), or C_6D_6 (δ 128.0). Elemental analyses and high-resolution mass spectrometry (HRMS) were performed in the analytical section in this Institute (AIST). Thin layer chromatography (TLC) and column chromatography were performed on Merck pre-coated silica gel 60F_{254} plates and silica gel (Kanto Chemicals, neutral, 100–210 μm), respectively. Schwartz reagent **7** and Et_2Zn (1.0 M in hexane) were purchased from Fluka, and Garner's aldehyde **2** and 1-pentadecyne **6a** were purchased from Tokyo Kasei (TCI).

4.1.1. *tert*-Butyl (4*S*)-4-[(1*R*,2*E*)-1-hydroxy-2-hexadecenyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (4a). To an ice-cooled stirred suspension of $Cp_2Zr(H)Cl$ **7** (260 mg, 1.0 mmol) in THF (1 mL) under argon was added 1-pentadecyne **6a** (210 mg, 1.0 mmol) in THF (1.4 mL), and the mixture was stirred at room temperature for 1 h, and then cooled to 0°C. To the resulting orange solution was added the aldehyde **2** (116 mg, 0.5 mmol) in THF (1.4 mL) followed by $ZnBr_2$ (60 mg, 0.25 mmol, dried under vacuum for 1 h before use), and the mixture was stirred for 24 h at room temperature. The mixture was diluted with AcOEt (10 mL) and aq. potassium sodium (+)-tartrate (10 mL), and stirred for 10 min. The resulting suspension was filtered off and washed thoroughly with AcOEt (10 mL). The combined filtrate and washings were transferred into a separatory funnel, and successively washed with H_2O and brine. The aqueous phase was extracted with AcOEt (2×20 mL), and the combined organic layers were dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the residue was dissolved in THF (3 mL) and methanol (1 mL), and treated with $NaBH_4$ (10 mg, 0.25 mmol). After 30 min, AcOH (20 mg, 0.33 mmol) was added, and the mixture was concentrated and purified by silica gel chromatography (eluting with hexane–AcOEt mixture, 7:1→5:1→4:1) to afford 163 mg (74%) of **4a** containing a small amount of **5a** (12:1 ratio by ^{1}H NMR) as a colorless oil: $[\alpha]_D^{24}=-28.7$ (*c* 0.84, $CHCl_3$) [lit.[9b] $[\alpha]_D=-28$ (*c* 0.65, $CHCl_3$)]; ^{1}H NMR data (C_6D_6, 75°C) were fully consistent with those reported;[9b] ^{13}C NMR (C_6D_6, 75°C)[31] δ 14.1, 23.0, 24.4, 26.8, 28.4, 29.6, 29.7, 29.9, 30.0, 30.1, 32.3, 32.8, 62.8, 64.9, 73.7, 80.1, 94.6, 130.2, 132.6; HRMS (CI) calcd for $C_{22}H_{40}NO_3$ (M−*t*-BuO)$^+$ 366.3008, found 366.2982. Further elution with hexane–AcOEt (2:1→1:1) gave the primary alcohol (13 mg, 11%).

4.1.2. *tert*-Butyl (4*S*)-4-[(1*R*,2*E*)-1-hydroxy-3-phenyl-2-propenyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (4b). This compound was prepared as described for **4a**, using phenylacetylene **6b** (82 mg, 0.80 mmol), **7** (210 mg, 0.81 mmol), **2** (93 mg, 0.40 mmol), and $ZnBr_2$ (46 mg, 0.2 mmol). Column chromatographic purification (hexane/AcOEt=3:1) gave 77 mg (58%) of **4b** containing a small amount of **5b** (15:1 ratio by ^{1}H NMR) as a colorless oil: $[\alpha]_D^{24}=-47.0$ (*c* 2.40, $CHCl_3$); ^{1}H NMR (C_6D_6, 75°C) δ 1.32 (s, 9H), 1.42 (s, 3H), 1.58 (s, 3H), 3.67 (dd, *J*=6.6, 9.0 Hz, 1H), 3.81 (d-like, *J*=9.0 Hz, 1H), 4.01 (br s, 1H), 4.40 (br s, 1H), 6.23 (dd, *J*=5.6, 15.9 Hz, 1H), 6.72 (d, *J*=15.9 Hz, 1H), 7.01 (m, 1H), 7.11 (m, 2H), 7.29 (m, 2H); ^{13}C NMR (C_6D_6, 75°C)[31] δ 24.4, 26.9, 28.4 (3C), 62.8, 65.1, 74.1, 80.4, 94.7, 126.9 (2C), 128.6, 128.7 (2C), 130.1, 131.3, 137.8; HRMS calcd for $C_{19}H_{28}NO_4$ (M+H)$^+$ 334.2020, found 334.1990. Further elution with hexane–AcOEt (2:1→1:1) gave the primary alcohol (13 mg, 14%).

4.1.3. *tert*-Butyl (4*S*)-4-[(1*S*,2*E*)-1-hydroxy-2-hexadecenyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (5a). To an ice-cooled stirred suspension of $Cp_2Zr(H)Cl$ **7** (260 mg, 1.0 mmol) in CH_2Cl_2 (1 mL) under argon was added 1-pentadecyne **6a** (210 mg, 1.0 mmol) in CH_2Cl_2 (1.4 mL), and the mixture was stirred at room temperature for 1 h, and then cooled to −40°C. To the resulting yellow solution was added 1.0 M solution in hexane Et_2Zn (1 mL, 1.0 mmol) followed by the aldehyde **2** (116 mg, 0.5 mmol) in CH_2Cl_2 (1.4 mL), and the mixture was allowed to warm to 0°C. The mixture was diluted with AcOEt (10 mL) and aq. sodium potassium tartrate (10 mL). The products were purified as described for **4a** to give 185 mg (84%) of **5a** containing a small amount of **4a** (15:1 ratio by ^{1}H NMR) as a colorless oil: $[\alpha]_D^{24}=-37.8$ (*c* 0.84, $CHCl_3$) [lit.[9b] $[\alpha]_D=-39$ (*c* 0.25, $CHCl_3$); ^{1}H NMR data (C_6D_6, 75°C) were fully consistent with those reported;[9b] ^{13}C NMR (C_6D_6, 75°C)[31] δ 14.1, 23.0, 24.3, 27.2, 28.5, 29.5, 29.6, 29.7, 29.9, 30.00, 30.03, 30.1, 32.3, 32.7, 62.4, 64.7, 74.6, 80.3, 94.5, 130.5, 134.0; HRMS calcd for $C_{26}H_{50}NO_4$ (M+H)$^+$: 440.3742, found 440.3652.

4.1.4. *tert*-Butyl (4*S*)-4-[(1*S*,2*E*)-1-hydroxy-3-phenyl-2-propenyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (5b).[27b] This compound was prepared as described for **4b**, using phenylacetylene **6b** (103 mg, 1.0 mmol), **7** (265 mg, 1.0 mmol), 1.0 M Et_2Zn solution (1.0 mL, 1.0 mmol), and **2** (135 mg, 0.60 mmol). Column chromatographic purification (hexane/AcOEt=3:1) gave 177 mg (86%) of **5b** containing a small amount of **4b** (12:1 ratio by ^{1}H NMR) as a colorless oil: $[\alpha]_D^{24}=-89.1$ (*c* 1.48, $CHCl_3$); ^{1}H NMR (C_6D_6, 75°C) δ 1.39 (s, 9H), 1.42 (s, 3H), 1.59 (s, 3H), 3.67 (dd, *J*=6.3, 9.3 Hz, 1H), 3.94 (dd, *J*=2.0, 9.3 Hz, 1H), 4.02 (dt, *J*=2.0, 6.4 Hz, 1H), 4.60 (t, *J*=6.7 Hz, 1H), 6.22 (dd, *J*=7.1, 15.9 Hz, 1H), 6.62 (d, *J*=15.9 Hz, 1H), 7.00–7.15 (m, 3H), 7.26 (m, 2H); ^{13}C NMR (C_6D_6, 75°C)[31] δ 24.3, 27.1, 28.5 (3C), 62.5, 64.5, 74.4, 80.4, 94.6, 127.0 (2C), 127.1, 128.8 (2C), 128.9, 129.9, 132.7; HRMS calcd for $C_{19}H_{28}NO_4$ (M+H)$^+$ 334.2020, found 334.1962.

4.1.5. *tert*-Butyl (1*S*,2*R*,3*E*)-*N*-[2-hydroxy-1-(hydroxymethyl)-3-heptadecenyl]carbamate (9a). The alcohol **4a** (145 mg, 0.33 mmol) was dissolved in acetic acid (0.9 mL) and water (0.1 mL), and the mixture was stirred at 50°C for 5 h. The mixture was concentrated and co-evaporated with heptane (2×1 mL). The residue was purified by silica gel chromatography (eluting with hexane–AcOEt mixture, 2:1→1:1) to afford the *N*-Boc sphingosine **9a** (110 mg, 83%) as a colorless solid: mp 65–67°C, $[\alpha]_D^{24}=-1.4$ (*c* 1.25, $CHCl_3$) [lit.[9a] mp 64–65°C, $[\alpha]_D^{25}=-1.4$ (*c* 1.1, $CHCl_3$)]; ^1H and ^{13}C NMR data ($CDCl_3$) were fully consistent with those reported;[9d] Anal. Calcd for $C_{23}H_{45}NO_4$: C, 69.13; H, 11.35; N, 3.51. Found: C, 69.27; H, 11.38; N, 3.49.

4.1.6. *tert*-Butyl (1*S*,2*S*,3*E*)-*N*-[2-hydroxy-1-(hydroxymethyl)-3-heptadecenyl]carbamate (10a). In a manner similar to that described for **9a**, compound **10a** was obtained from **5a** in 93% yield as a colorless oil, which was recrystallized from hexane to afford a colorless solid: mp 58–60°C; $[\alpha]_D^{24}=-0.7$ (*c* 1.6, $CHCl_3$) [lit.[9a] mp 58–59°C; $[\alpha]_D^{24}=-0.4$ (*c* 1.0, $CHCl_3$)]; ^1H NMR ($CDCl_3$) δ 0.88 (t, *J*=6.6 Hz, 3H), 1.26 (s, 20H), 1.35 (m, 2H), 1.45 (s, 9H), 2.04 (q, *J*=6.7 Hz, 2H), 2.61 (d, *J*=3.2 Hz, 1H), 2.68, (br, 1H), 3.62 (dq, *J*=4.2, 8.3 Hz, 1H), 3.79 (t-like, *J*=5.0 Hz, 2H), 4.34 (m, 1H), 5.17 (d, *J*=7.8 Hz, 1H), 5.51 (tdd, *J*=1.2, 6.6, 15.5 Hz, 1H), 5.75 (dtd, *J*=1.0, 6.7, 15.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 28.3 (3C), 29.1, 29.2, 29.3, 29.5, 29.58, 29.63, 29.7 (3C), 31.9, 32.3, 55.5, 64.4, 73.5, 79.7, 128.9, 134.1, 156.6; Anal. Calcd for $C_{23}H_{45}NO_4$: C, 69.13; H, 11.35; N, 3.51. Found: C, 69.43; H, 11.41; N, 3.40.

4.1.7. *tert*-Butyl (1*S*,2*R*,3*E*)-*N*-[2-hydroxy-1-(hydroxymethyl)-4-phenyl-3-butenyl]carbamate (9b). In a manner similar to that described for **9a**, compound **9b** was obtained from **4b** in 75% yield as a colorless semi-solid: $[\alpha]_D^{24}=+6.5$ (*c* 1.05, $CHCl_3$) [lit.[10b] $[\alpha]_D=+5.12$ (*c* 1.23, $CHCl_3$)]; ^1H NMR ($CDCl_3$) δ 1.40 (s, 9H), 3.50 (br, 2H), 3.72 (dd, *J*=3.5, 12.0 Hz, 1H), 3.75 (m, 1H), 3.95 (dd, *J*=4.4, 12.0 Hz, 1H), 4.49 (m, 1H), 5.46 (d, *J*=7.1 Hz, 1H), 6.24 (dd, *J*=6.1, 16.1 Hz, 1H), 6.66 (d, *J*=16.1 Hz, 1H), 7.20–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 28.3 (3C), 55.5, 62.3, 74.2, 79.9, 126.5 (2C), 127.7, 128.5 (3C), 131.7, 136.3, 156.3; HRMS calcd for $C_{16}H_{24}NO_4$ $(M+H)^+$ 294.1705, found 294.1645.

4.1.8. *tert*-Butyl (1*S*,2*S*,3*E*)-*N*-[2-hydroxy-1-(hydroxymethyl)-4-phenyl-3-butenyl]carbamate (10b). In a manner similar to that described for **9a**, compound **10b** was obtained from **5b** in 83% yield as a colorless solid: mp 112–114°C; $[\alpha]_D^{24}=+11.3$ (*c* 1.32, $CHCl_3$) [lit.[10b] $[\alpha]_D=+8.61$ (*c* 1.37, $CHCl_3$)]; ^1H NMR ($CDCl_3$) δ 1.40 (s, 9H), 2.80 (br, 1H), 3.06 (d, *J*=3.4 Hz, 1H), 3.75 (m, 1H), 3.85 (t-like, 2H), 4.60 (m, 1H), 5.24 (d, *J*=8.3 Hz, 1H), 6.27 (dd, *J*=6.1, 15.9 Hz, 1H), 6.67 (d, *J*=15.9 Hz, 1H), 7.20–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 28.3 (3C), 55.5, 64.1, 73.3, 79.9, 126.6 (2C), 127.8, 128.5 (2C), 128.7, 131.6, 136.4, 156.5; Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.41; H, 7.66; N, 4.75.

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