Efficient Synthesis of a Styryl Analogue of (2*S*,3*R*,4*E*)-*N*^{2}-Octadecanoyl-4-tetradecasphingenine *via* Cross-Metathesis Reaction

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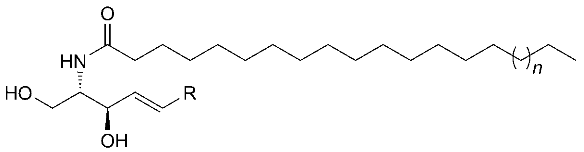
The first total synthesis of sphingolipid (2*S*,3*R*,4*E*)-*N*^{2}-octadecanoyl-4-tetradecasphingenine (**1a**), a natural sphingolipid isolated from Bombycis Corpus 101A, and of its styryl analogue **1b** was achieved in good overall yield (*Schemes 1* and *2*). The key step involved the installation with (*E*) stereoselectivity of a long lipophilic chain or phenyl group on allyl alcohol derivative **3** *via* a cross-metathesis reaction (→ **5a** or **5b**). The *N*-Boc protected **3** was easily accessible from (*S*)-*Garner* aldehyde.

Introduction. – Sphingolipids are important structural and functional components of plasma membrane of essentially all eukaryotic cells. Structurally sphingolipids are considered to be composed of three principle moieties: a sphingoid base, an amide-linked fatty acid, and a polar head group. The most common sphingoid base in almost all eukaryotic cells is (2*S*,3*R*,4*E*)-2-aminooctadec-4-ene-1,3-diol, known as D-*erythro* sphingosine. Several sphingolipid key metabolites such as sphingosine, ceramide, sphingosine 1-phosphate have emerged over the last decade as a family of signaling molecules [1] which regulates many fundamental and diverse cell processes, including cell recognition, cell proliferation, adhesion, and apoptosis [2], and are known to play a critical role in higher-order physiological processes [3]. Moreover, it has been recently shown that sphingolipids are also implied in some of the most common human diseases like diabetes, *Alzheimer*'s disease, and cancer [4].

Besides the natural sphingolipids, their analogues have also been evaluated for various biological activities [5]. In particular, ceramide analogues synthesized by the incorporation of a phenyl and substituted-phenyl group into the sphingoid moiety have been found to be biologically active [6]. Recently, new aromatic ceramide analogues with alkylsulfonamido chains have been evaluated for cytotoxic activities against human-tumor cell lines [7].

Lee and co-workers [8] have isolated (2*S*,3*R*,4*E*)-*N*^{2}-octadecanoyl-4-tetradecasphingenine (**1a**) and (2*S*,3*R*,4*E*)-*N*^{2}-eicosanoyl-4-tetradecasphingenine (**1c**; *Fig.*) along with two other sphingolipids from Bombycis Corpus 101A and evaluated their neurotrophic effects by examining PC12 cell neurite outgrowth. Bombycis Corpus 101A has been used in Korean traditional medicine to treat palsy, headache, convulsion, and speech problem induced by stroke and tremor [9].

Due to the biological significance of the sphingosine and its derivatives and their limited availability in pure form from natural sources, considerable efforts have been devoted towards developing efficient methods for their synthesis [10]. These



1a $R = Me(CH_2)_8$, $n = 1$
1b $R = Ph$, $n = 1$
1c $R = Me(CH_2)_8$, $n = 3$
1d $R = Ph$; $n = 3$

Figure. *Natural sphingolipids and their styryl analogues*

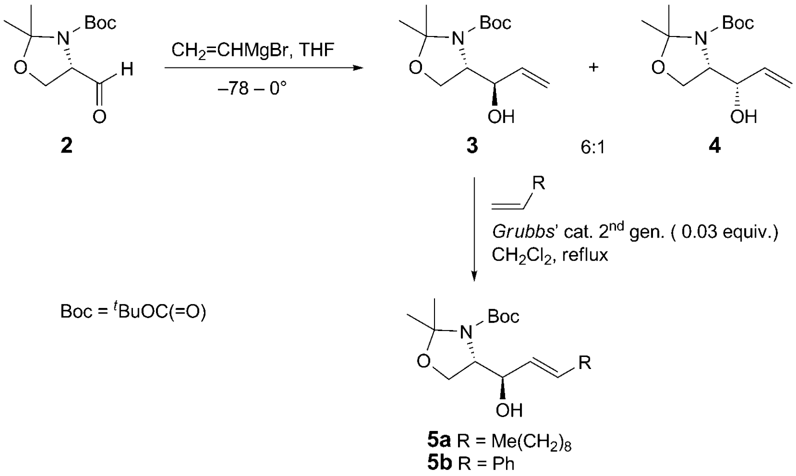
compounds have been synthesized by various routes, but mainly from compounds of the chiral pool, particularly amino acids (L-serine) [11] and carbohydrates [12]. Asymmetric synthesis has been achieved *via Sharpless* asymmetric epoxidation [13], dihydroxylation reaction [14], use of chiral auxiliaries [15], and organo catalytic procedures [16].

The configurationally stable *Garner* aldehyde (=*tert*-butyl 4-formyl-2,2-dimethyloxazolidine-3-carboxylate) [17][18] has received considerable attention as chiral synthon for the stereoselective synthesis of sphingosine and its derivatives due to its inherent 2-amino-1,3-diol subunit which is the main backbone of sphingolipids. Procedures were developed, wherein the alkene configuration, the C(3) stereogenic center, and the C(4)–C(5) bond with desired chain length were efficiently installed on *Garner* aldehyde-derived intermediates mainly *via* stereoselective addition of (alk-1-ynyl) [5a][5b][6d][6e] and (alk-1-enyl)metals [6a][6b][19][20], asymmetric α-chloroallylboration [21], cross-metathesis [19][22], and *Wittig* reaction [23]. The procedures used for the synthesis of aromatic and substituted analogues include nucleophilic addition of lithium phenylacetylide [6d][6e], substituted lithium phenylacetylides, and [(*E*)-β-styryl]metals derived from phenylacetylene to the *Garner* aldehyde and *via* asymmetric aldol reaction [7].

In the present work, the olefin cross-metathesis reaction employing second-generation *Grubbs*' catalyst, which is compatible with a wide range of functionalities [11d][12c][15b], was utilized for the synthesis of sphingolipids and their derivatives. The long aliphatic chains installed *via* olefin cross-metathesis on sphingosine and its derivatives were shown to generate the newly formed C=C bond with (*E*) configuration, and both the yield and stereoselectivity can be improved in this reaction by increasing the reactant/substrate alkene ratio and reaction time [24]. To the best of our knowledge, no sphingolipid styryl analogues have been synthesized *via* cross-metathesis reaction of *Garner* aldehyde-derived substrates.

Results and Discussion. – In this study, we have carried out a novel total synthesis of the sphingolipid (2*S*,3*R*,4*E*)-*N*^{2}-octadecanoyl-4-tetradecasphingenine (**1a**) and of its styryl analogue **1b** starting from (*S*)-*Garner* aldehyde. The key step involved the synthesis of *tert*-butyl oxazolidine-3-carboxylate (=*N*-Boc-oxazolidine) intermediates **5a** and **5b** with exclusive (*E*) configuration *via* a cross-metathesis reaction of Boc-protected allyl alcohol derivative **3**, with corresponding terminal alkenes as shown in *Scheme 1.*

Scheme 1. *Synthesis of* tert-*Butyl Oxazolidine-3-carboxylate Intermediates* **5a** *and* **5b**

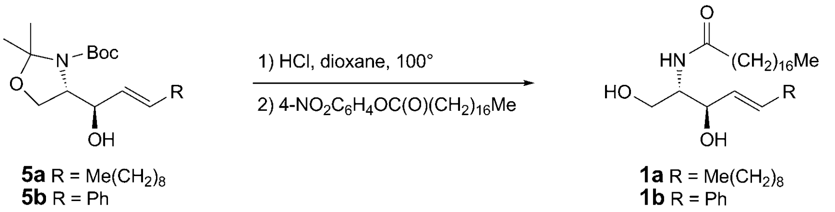


Stereoselective addition of CH_2=CHMgBr to (*S*)-*Garner* aldehyde **2** afforded a 6 : 1 mixture of 4-(1-hydroxyallyl)oxazolidine-3-carboxylates **3** and **4**, which were separated by column chromatography, and the absolute configuration (1′*R*,4*S*) was assigned to **3** in correlation to the optical rotation and spectral data reported in [25]. The cross-metathesis reaction of **3** with 4 equiv. of undec-1-ene in the presence of 0.03 equiv. of *Grubbs*' second-generation catalyst [21] in dry CH_2Cl_2, followed by purification by column chromatography, afforded *tert*-butyl oxazolidine-3-carboxylate intermediate **5a** (69%). The exclusive (*E*) configuration was confirmed by the ^{1}H-NMR data ($J = 15.2$ and 6.0 Hz for CH=C*H*CH_2, and $J = 15.2$ and 7.3 Hz for C*H*=CHCH_2). Under similar reaction conditions, 1-hydroxyallyl derivative **3** was treated with styrene (= ethenylbenzene) and, on subsequent purification, afforded oxazolidine-3-carboxylate intermediate **5b** (65%). The exclusive (*E*) configuration was again confirmed by the ^{1}H-NMR spectrum ($J = 15.4$ and 4.1 Hz for CH=C*H*Ph, and $J = 15.8$ Hz for C*H*=CHPh). To the best of our knowledge, this is the first report utilizing the cross-metathesis reaction for the synthesis of an aromatic analogue of natural sphingolipid **1a**.

Deprotection of the Boc group and oxazolidine moiety of **5a** and **5b** with 1M HCl in dioxane [6c] followed by *N*-acylation with 4-nitrophenyl octadecanoate afforded crude **1a** and **1b**, respectively, in 57% and 59% yield after column chromatography (*Scheme 2*).

All synthesized compounds were analyzed by NMR, IR, and mass spectroscopy, and their optical rotation was determined. The analytical data of compound **1a** was in agreement with that reported in [8]. The overall yield of **1a** and **1b** starting from (*S*)-*Garner* aldehyde was 27.5 and 26.8%, respectively. Following the same synthetic route, the syntheses of (2*S*,3*R*,4*E*)-*N*^{2}-eicosanoyl-4-tetradecasphingenine (**1c**) and of its styryl analogue **1d** were also achieved with high stereoselectivity.

Scheme 2. *Deprotection and* N-*Acylation of* tert-*Butyl Oxazolidine-3-carboxylate Intermediates* **5a** *and* **5b**



Conclusion. – We undertook the stereoselective and efficient novel synthesis of natural sphingolipid **1a** and of its styryl analogue **1b** by means of a cross-metathesis reaction for installing the long-aliphatic-chain and phenyl group, respectively, on 1-hydroxyallyl derivative **3**, the latter being obtained from L-serine-derived (*S*)-*Garner* aldehyde **2**. It is a general method for the synthesis of related sphingolipids and their styryl analogues with high stereoselectivity and in good overall yield.

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Experimental Part

General. All reactions were carried out under N_2 in oven-dried glassware. All solvents were dried as reported in the literature prior to use. TLC: Silica-gel precoated (*60 F_{254}*; *Merck*) glass plates. Column chromatography (CC): silica gel (SiO_2, 60–120 mesh; *Merck*). M.p.: *Veego*-540 apparatus; uncorrected. Optical rotations: *Perkin-Elmer 241* polarimeter; at the Na_D line. IR Spectra: *Perkin-Elmer-RX-1* FT-IR spectrometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker-Avance-II* 400 MHz spectrometer; in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, J in Hz. MS: *Waters-Micromass-q-Tof* micro spectrometer; in m/z (rel. %).

tert-*Butyl (4*S*)-4-[(1*R*,2*E*)-1-Hydroxydodec-2-en-1-yl]-2,2-dimethyloxazolidine-3-carboxylate* (**5a**). The *N*-Boc-protected allyl alcohol derivative **3** [25] (220 mg, 0.85 mmol) and undec-1-ene (528 mg, 3.42 mmol) were dissolved in dry CH_2Cl_2 (8.0 ml), and the resulting soln. was degassed. *Grubbs*' second-generation catalyst (21.8 mg, 0.026 mmol) was added to the mixture under N_2, and the mixture was heated to reflux for 5 h (TLC monitoring). The solvent was evaporated and the crude product purified by CC (SiO_2, hexane/AcOEt 8.8 : 1.2): **5a** (224 mg, 68%). Colorless oil. $[\alpha]_D^{25} = -26.9$ ($c = 1$, $CHCl_3$). IR (neat): 3452, 2975, 2854, 1710, 1670, 1465, 1454, 1390, 1365, 1255, 1170. ^1H-NMR (400 MHz): 0.88 (*t*, $J = 7$, 3 H); 1.25–1.62 (*m*, 29 H); 2.03 (*q*, $J = 6.7$, 2 H); 3.84–4.18 (*m*, 5 H including OH); 5.44 (*dd*, $J = 15.2$, 6.0, 1 H); 5.75 (*dt*, $J = 15.2$, 7.3, 1 H). ^{13}C-NMR (100 MHz): 14.1; 22.6; 24.6; 26.2; 28.9; 29.1; 29.2; 29.3; 29.4; 29.5; 31.8; 32.3; 62.2; 65.1; 74.0; 80.9; 94.3; 128.2; 133.3; 154.1. EI-MS: 406.4 (100, $[M + Na]^+$). Anal. calc. for $C_{22}H_{41}NO_4$ (383.56): C 68.88, H 10.77, N 3.65, O 16.68; found: C 68.83, H 10.74, N 3.62, O 16.70.

tert-*Butyl (4*S*)-4-[(1*R*,2*E*)-1-Hydroxy-3-phenylprop-2-en-1-yl]-2,2-dimethyloxazolidine-3-carboxylate* (**5b**). As described for **5a**, with **3** (196 mg, 0.76 mmol), styrene (317 mg, 3.0 mmol), CH_2Cl_2 (7.0 ml), and *Grubbs*' second-generation catalyst (19.4 mg, 0.023 mmol) for 4.5 h. CC (SiO_2, hexane/AcOEt 8.5 : 1.5) afforded **5b** (165 mg, 65%). Colorless oil. $[\alpha]_D^{25} = -45.5$ ($c = 2.0$, $CHCl_3$). IR (neat): 3440, 3059, 2975, 2854, 1710, 1668, 1465, 1383, 1367, 1255, 1172. ^1H-NMR (400 MHz): 1.44–1.62 (*m*, 15 H); 3.95–4.24 (*m*, 4 H including OH); 4.44 (br. *s*, 1 H); 6.23 (*dd*, $J = 15.4$, 4.1, 1 H); 6.68 (*d*, $J = 15.8$, 1 H); 7.20–7.26 (*m*, 1 H); 7.28–7.32 (*m*, 2 H); 7.36–7.40 (*m*, 2 H). ^{13}C-NMR (100 MHz): 24.4; 26.5; 28.3; 62.3; 65.0; 75.2; 81.7; 94.5; 126.4; 127.4; 128.5; 130.9; 132.9; 136.8; 154.2. EI-MS: 356.3 (100, $[M + Na]^+$).

Anal. calc. for $C_{19}H_{27}NO_4$ (333.42): C 68.44, H 8.16, N, 4.20, O 19.20; found: C 68.38, H 8.11, N 4.15, O 19.11.

*(2*S*,3*R*,4*E*)-*N^2*-Octadecanoyl-4-tetradecasphingenine* (= *N-[(1*S*,2*R*,3*E*)-2-Hydroxy-1-(hydroxymethyl)tridec-3-en-1-yl]octadecanamide*; **1a**). A soln. of **5a** (90 mg, 0.23 mmol) in 1M HCl (3 ml) and dioxane (3 ml) was heated at 100° with stirring for 1 h under N_2. The mixture was cooled to r.t. and neutralized with 1M NaOH (3 ml). The product was extracted with AcOEt (4 × 15 ml), and the combined org. layers were washed with brine and dried (Na_2SO_4). Removal of the solvent provided crude sphingosine as a yellowish solid, which was dissolved in dry THF (4 ml), and 4-nitrophenyl octadecanoate (189 mg, 0.46 mmol) was added at r.t. The mixture was stirred for 48 h and concentrated. Purification by CC (SiO_2, $CHCl_3$/MeOH 9.7 : 0.3) afforded **1a** (67.8 mg, 57%). White solid. M.p. 71.4–71.9°. $[\alpha]^{25}_{D} = -3.1$ ($c = 0.1$, $CHCl_3$). IR: 3340, 2922, 2847, 1654, 1462, 1050. ^{1}H-NMR (400 MHz): 0.86 (*t*, *J* = 7.1, 6 H); 1.25–1.45 (*m*, 42 H); 1.63 (br. *s*, 2 H); 2.04 (*q*, *J* = 6.7, 2 H); 2.22 (*t*, *J* = 7.4, 2 H); 2.78 (br. *s*, 2 H); 3.70–3.91 (*m*, 3 H); 4.30 (br. *s*, 1 H); 5.52 (*dd*, *J* = 15.2, 4.0, 1 H); 5.77 (*dd*, *J* = 15.1, 7.8, 1 H); 6.36 (*d*, *J* = 7.2, 1 H). ^{13}C-NMR (100 MHz): 14.1; 22.7; 25.6; 29.1; 29.3; 29.5; 29.7; 31.9; 32.3; 36.8; 54.6; 62.4; 74.5; 128.8; 134.2; 174.1. EI-MS: 510.7 (7, $[M + H]^+$), 532.6 (42, $[M + Na]^+$). Anal. calc. for $C_{32}H_{63}NO_3$ (509.84): C 75.39, H 12.45, N 2.74, O 9.41; found: C 75.29, H 12.38, N 42.69, O 9.36.

*(2*S*,3*R*,4*E*)-2-(Octadecanoylamino)-5-phenylpent-4-ene-1,3-diol* (= *N-[(1*S*,2*R*,3*E*)-2-Hydroxy-1-(hydroxymethyl)-4-phenylbut-3-en-1-yl]octadecanamide*; **1b**). As described for **1a**, with **5b** (70 mg, 0.21 mmol), 1M HCl (2.5 ml), and dioxane (2.5 ml) (at 100° for 0.5 h); then with 1M NaOH (5 ml) and AcOEt (4 × 15 ml); then with THF (4 ml) and 4-nitrophenyl octadecanoate (170 mg, 0.42 mmol) for 36 h. Purification by CC (SiO_2, $CHCl_3$/MeOH 9.6 : 0.4) afforded **1b** (56.8 mg, 59%). White solid. M.p. 73.5–74.1°. $[\alpha]^{25}_{D} = -2.98$ ($c = 0.2$, $CHCl_3$). IR: 3444, 3340, 2922, 2847, 1645, 1462, 1050. ^{1}H-NMR (400 MHz): 0.88 (*t*, *J* = 7, 3 H); 1.22–1.29 (*m*, 28 H); 1.56–1.63 (*m*, 2 H); 2.19–2.23 (*t*, *J* = 7.2, 2 H); 3.45 (br. *s*, 1 H); 3.67–3.74 (*m*, 2 H including OH); 3.96–4.0 (*m*, 2 H); 4.52 (*t*, *J* = 4.3, 1 H); 6.25 (*dd*, *J* = 15.9, 5.9, 1 H); 6.68 (*d*, *J* = 15.5, 1 H); 7.22–7.37 (*m*, 5 H).^{13}C-NMR (100 MHz): 14.1; 22.7; 25.8; 29.2; 29.4; 29.7; 31.9; 36.8; 54.6; 62.3; 74.3; 126.5; 127.9; 128.4; 128.6; 131.8; 136.2; 174.3. EI-MS: 482.6 (42, $[M + Na]^+$). Anal. calc. for $C_{29}H_{49}NO_3$ (459.70): C 75.66, H 10.74, N 3.04, O 10.44; found: C 75.67, H 10.67, N 3.01, O 10.25.

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