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Versatile Synthetic Method for Sphingolipids and Functionalized Sphingosine Derivatives via Olefin Cross Metathesis

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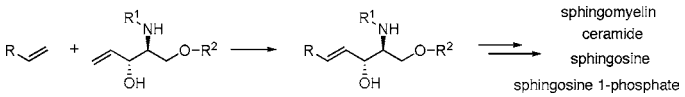
ABSTRACT



A highly efficient and versatile method for the synthesis of various sphingolipids, such as sphingomyelin, ceramide, sphingosine, sphingosine 1-phosphate, and functionalized sphingosine derivatives, was established by two types of combinations of the olefin cross metathesis reaction. One reaction was between the same olefin part and appropriate amino alcohols, which were prepared starting from *N*-Boc-L-serine, and the other was between appropriate olefins and the same amino alcohol.

Sphingolipids, such as sphingomyelin **1**, ceramide **2**, sphingosine **3**, and sphingosine 1-phosphate **4**, are regarded as lipid secondary messengers in mammalian cells and cell membranes, as shown in Figure 1, and are now accepted to play an important role in signal transduction and molecular recognition processes in cell membranes.[1] Meanwhile, sphingomyelin **1** is known as a major component to form a raft domain, which is proposed as a particular organism in a mammalian cell membrane to efficiently transmit various biological signals.[2] Thus, a great deal of attention has been devoted to studies of the biological processes regulated by sphingolipids, and hence an efficient method for the synthesis of these sphingolipids along with their various kinds of analogues is strongly desired.

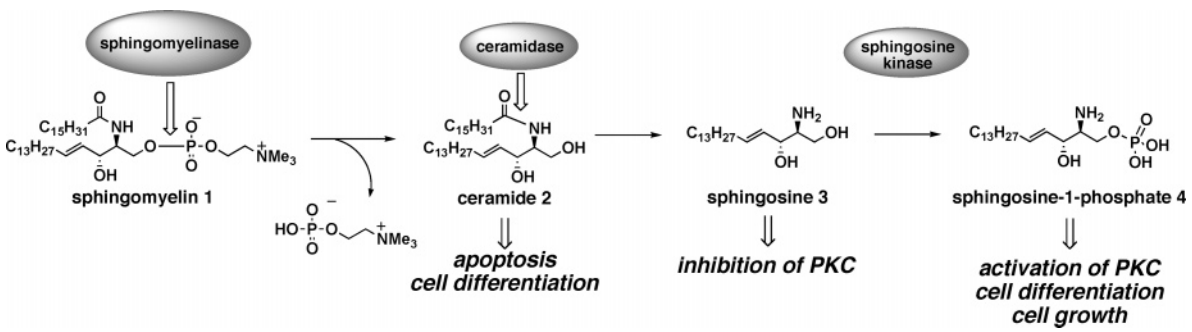


Figure 1. Metabolic pathway of sphingolipids.

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In the course of our study on sphingolipid synthesis, we previously reported the syntheses of not only various sphingolipids, such as natural sphingomyelin, ceramide, sphingosine, sphingosine 1-phosphate, and their short chain analogues,[3] but also fluorescence[4] and photoaffinity labeled sphingolipids.[5] During synthetic studies of these sphingolipid derivatives, including those possessing fluorescence and photoaffinity groups in the backbone skeleton, a further convenient and versatile method for providing them has been strongly required. Then, we investigated the olefin cross metathesis reaction[6] between 1-pentadecene and disubstituted olefines having amino alcohol functions, which were prepared starting from our chiral oxazolidinone ester.[7] At nearly the same time, two groups independently reported the synthesis of sphingosine **3**[8] and ceramide **2**[9] by utilizing an olefin cross metathesis reaction. One used monosubstituted olefin with chiral oxazoridinone alcohol prepared from divinylcarbinol,[8] and the other used monosubstituted olefin with protected aminodiol prepared from D-tartrate.[9] However, the reported procedures including our results did not show the essential versatility of this very attractive olefin cross metathesis method. In this paper, we disclose highly efficient and versatile syntheses of sphingomyelin **1**, ceramide **2**, sphingosine **3**, and sphingosine 1-phosphate **4** from common olefin part **A** and appropriate amino alcohol part **B** by olefin cross metathesis as a simple and practical procedure. Furthermore, we disclose that the olefin cross metathesis method is also effective for the preparation of fluorescence and photoaffinity labeled sphingosine derivatives **28** and **29** (Figure 2).

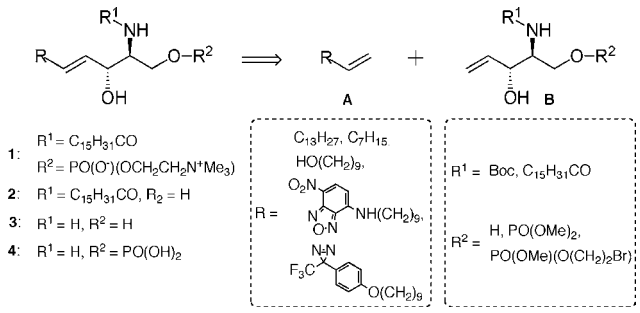
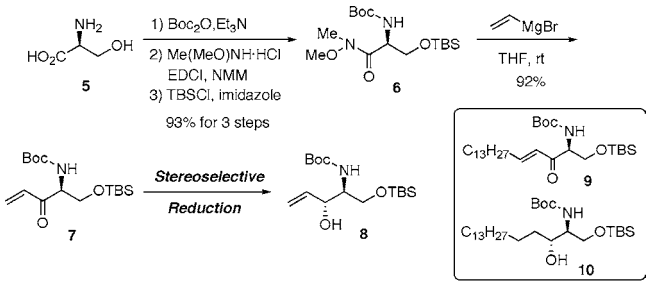
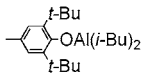


Figure 2. Versatile synthetic method for sphingolipids and derivatives.

Substrate **B** for the olefin cross metathesis was synthesized starting from L-serine **5** through intermediary alcohol **8**, as shown in Table 1. Thus, *tert*-butoxycarbonyl protection of **5**, followed by the Weinreb amide formation,[10] and the protection of the primary hydroxyl group produced **6** in excellent yield in three steps without column chromatography. Introduction of a vinyl group with the Grignard reagent provided vinyl ketone **7** in 92% yield. Then, *anti*-selective reduction of obtained α,*β*-unsaturated ketone **7** was investigated (Table 1). Although lithium aluminumhydride reduction gave the corresponding alcohol in 82% yield, stereoselectivety was 3:2 of *anti*- and *syn*-derivatives by ^{1}H NMR (entry 1). Treatment with L-Selectride and diisobutylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide[11] (entries 2 and 3) gave unsatisfactory results. Diisobutylaluminum hydride treatment gave product in 49% yield, whose stereoselectivity was 14:1 (entry 4). Gratifyingly, when lithium tri-*tert*-butoxyaluminohydride was employed in ethanol at −78 °C,[3d,12] the desired *anti*-product **8** was obtained in 96% yield as a sole stereoisomer. It is noteworthy that under the same reaction conditions, the reduction of enone **9**, obtained from **7** and 1-pentadecene **16** by olefin cross metathesis, unexpectedly afforded the corresponding saturated alcohol **10** with *anti*-stereochemistry that resulted from 1,4-addition followed

Table 1. Preparation of Intermediate **8**



entry	reagent	solvent	yield (%)[a]	*anti* : *syn*
1	$LiAlH_4$	THF	82%	3 : 2
2	L-Selectride	THF	decompose	———
3		toluene	7%	4 : 1
4	DIBAL	toluene	49%	14 : 1
5	$LiAl(Ot\text{-}Bu)_3H$	EtOH	96%	*anti* only

[a] Isolated yields.

(1) For recent reviews on signal transduction mediated by sphingolipids, see: (a) *Sphingolipid Metabolism and Signaling Minireview Series*; Smith, W. L., Merrill, A. H., Jr., Eds.; *J. Biol. Chem.* **2002**, *277*, 25841. (b) Cremesti, A. E.; Goni, F. M.; Kolesnick, R. *FEBS Lett.* **2002**, *531*, 47 and references therein.

(2) (a) Suzuki, A.; Igarashi, Y. *Protein Nucleic Acid Enzyme* **2002**, *47*, 315. (b) Simons, K.; Ikonen, E. *Science* **2000**, *290*, 1721. (c) Simons, K.; Ikonen, K. *Nature* **1997**, *387*, 569 and references therein.

(3) (a) Hakogi, T.; Monden, Y.; Taichi, M.; Iwama, S.; Fujii, S.; Ikeda, K.; Katsumura, S. *J. Org. Chem.* **2002**, *67*, 4839. (b) Hakogi, T.; Taichi, M.; Katsumura, S. *Org. Lett.* **2003**, *5*, 2801. (c) Hasegawa, H.; Yamamoto, T.; Hatano, S.; Hakogi, T.; Katsumura, S. *Chem. Lett.* **2004**. *33*, 1592. (d) Hakogi, T.; Fujii, S.; Morita, M.; Ikeda, K.; Katsumura, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2141. (e) Hakogi, T.; Yamamoto, T.; Fujii, S.; Ikeda, K.; Katsumura, S. *Tetrahedron Lett.* **2006**, *47* 2627.

(4) Hakogi, T.; Shigenari, T.; Katsumura, S.; Sano, T.; Kohno, T.; Igarashi, Y. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 661.

(5) Shigenari, T.; Hakogi, T.; Katsumura, S. *Chem. Lett.* **2004**, *33*, 594.

(6) (a) Grubbs, R. H. *Handbook of Metathesis*; Wiley-VCH: Germany, 2003. (b) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900 and references therein.

(7) Katsumura, S.; Kondo, A.; Han, Q. *Chem. Lett.* **1991**, *1*, 1245.

(8) Torssell. S.; Somfai, P. *Org. Biomol. Chem.* **2004**, *2*, 1643.

(9) Rai, A. N.; Basu, A. *Org. Lett.* **2004**, *6*, 2861.

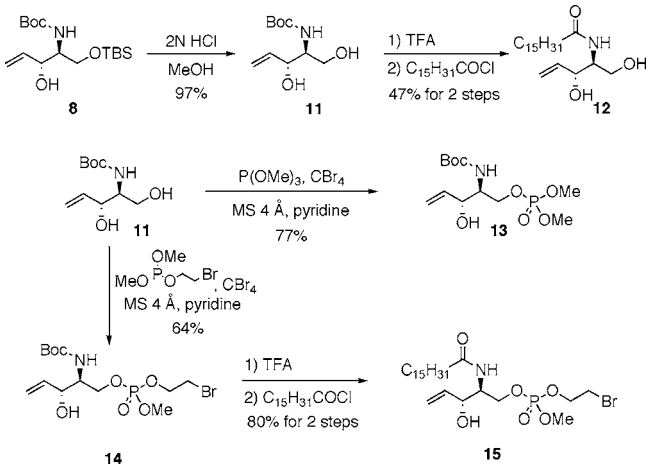
(10) So, R. C.; Ndonye, R.; Izmirian, D. P.; Richardson, S. K.; Guerrera, R. L.; Howell, A. R. *J. Org. Chem.* **2004**, *69*, 3233.

(11) (a) Murakami, M.; Iwama, S.; Fujii, S.; Ikeda, K.; Katsumura, S. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1725. (b) Iguchi, S.; Nakai, H.; Hayashi, M.; Yamamoto, H. *J. Org. Chem.* **1979**, *44*, 1363.

by stereoselective reduction in 96% yield along with a small amount of desired unsaturated alcohol **17**.

Allyl alcohol **8**, a synthetic precursor of sphingosine, was transformed into amino alcohol segments **11**−**15** of sphingolipid synthesis by olefin cross metathesis protocol (segment **B**) (Scheme 1). Thus, removing the protecting group at the

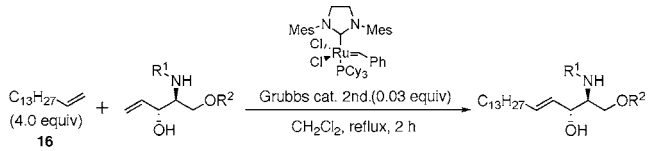
Scheme 1. Preparation of Substrates of Olefin Cross Metathesis Reaction

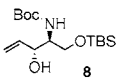
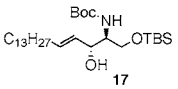
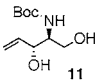
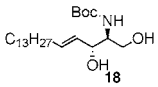
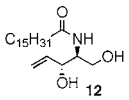
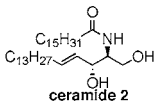
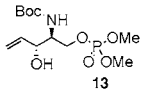
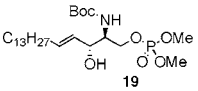
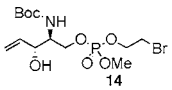
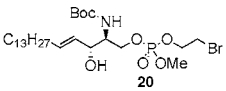
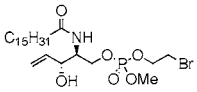
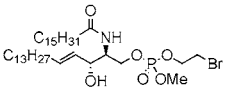


primary hydroxyl group of **8** produced diol **11** in 97% yield, which is also a synthetic precursor of sphingosine. Exchanging the Boc group of **11** into an acyl group afforded **12** in 47% yield, a precursor of ceramide. Treatment of **11** with trimethylphosphite and carbon tetrabromide[3d,13] in pyridine at −15 °C produced dimethylphosphate **13** in 77% yield, a precursor of sphingosine 1-phosphate. Furthermore, reaction of **11** with 2-bromoethyl dimethylphosphite[3d] produced the corresponding allyl alcohol **14** in 64% yield, which was transformed into **15** by acylation. Both **14** and **15** were synthetic precursors of sphingomyelin. Thus, amino alcohol derivatives **8** and **11**−**15** were easily prepared and used as the substrates of the olefin cross metathesis reaction. Another segment **A**, 1-pentadecene **16**, was synthesized by the Swern oxidation of commercially available 1-tetradecanol followed by the Wittig olefination.

With substrates **8** and **11**−**15** in hand, the cross metathesis coupling reaction between substrate **8**, **11**−**15**, and olefin **16** was examined (Table 2). After detailed investigation, we found the following suitable conditions. Thus, substrate **8** was stirred with 4 equiv of olefin **16** and 0.03 equiv of Grubbs catalyst second generation in dichloromethane for 2 h at reflux. The reaction proceeded smoothly, and desired coupling product **17** was obtained in 72% yield as sole (*E*)-stereoisomer, and the homocoupling product of **8** was not observed in its ^{1}H NMR.[14] When we used the catalyst at 0.01 equiv under the same reaction condition, desired **17** was

Table 2. Olefin Cross Metathesis Reaction

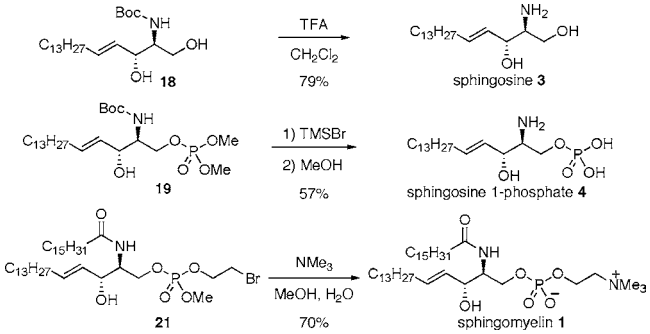


substrate	product	yield (%)[a]
 **8**	 **17**	72% 75% (*E* : *Z* = 15 : 1)[b]
 **11**	 **18**	58%
 **12**	 **ceramide 2**	56%
 **13**	 **19**	76%
 **14**	 **20**	70%
 **15**	 **21**	55%

[a] Isolated yields. [b] A quantity of 0.01 equiv of Grubbs catalyst was used.

successfully obtained in 75% yield as a mixture of *E*:*Z* = 15:1. Diol **11** also produced desired coupling product **18** in 58% yield, which was easily transformed to sphingosine **3** by trifluoroacetic acid treatment in 79% yield (Scheme 2).

Scheme 2. Syntheses of Sphingolipids



N-Acyl diol **12** directly afforded ceramide **2** in 56% yield by the same coupling procedure. This is a simple and practical synthesis of ceramide **2**. Phosphate **13** also succeeded in coupling to produce **19**, which was treated with

(12) Hofmann, R. V.; Maslouh, N. Lee, F.-C. *J. Org. Chem.* **2002**, *67*, 1045.

(13) (a) Szulc, Z. M.; Hannun, Y. A.; Bielawska, A. *Tetrahedron Lett.* **2000**, *41*, 7821. (b) Oza, V. B.; Corcoran, R. C. *J. Org. Chem.* **1995**, *60*, 3680.

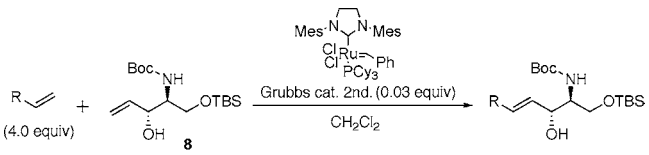
(14) The olefin **16** that was recovered as a mixture with its dimer could be used for the cross metathesis coupling reaction. The ratio of olefin **16** in the mixture was determined by ^{1}H NMR.

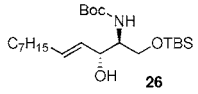
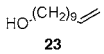
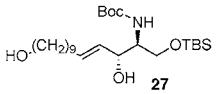
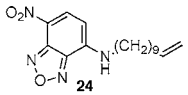
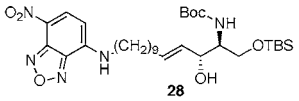
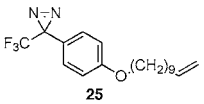
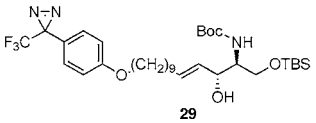
bromotrimethylsilane in acetonitrile to afford sphingosine 1-phosphate **4** in 57% yield. Furthermore, phosphates **14** and **15**, which are amino alcohol segments for olefin cross metathesis, expectedly afforded desired coupling products **20** and **21** in 70% and 55% yield, respectively. Treatment of **21** with Me_3N in MeOH produced sphingomyelin **1** in 70% yield. Thus, sphingomyerin **1**, ceramide **2**, sphingosine **3**, and sphingosine 1-phospate **4** were simply and easily synthesized from L-serine by the olefin cross metathesis method.

The next attempts was a synthesis of the backbone skeleton having various functional groups at the terminal. In this case, compound **8** was fixed as amino alcohol part **B**, and compounds **22**−**25** were used as olefin part **A** (Table 3). Compound **22** was obtained from octanal by the Wittig reaction, and fluorescence and photoaffinity labeled olefins **24** and **25** were prepared from commercially available alcohol **23** by a previously reported procedure.[4,5] Olefin cross metathesis reactions between **8** and **22**−**25** were employed under the same reaction conditions as **16** with **8** and **11**−**15**, respectively. The results are listed in Table 3. The reaction of hydroxyl compound **23** and fluorescence labeled compound **24** with amino alcohol **8** afforded coupling products **27** and **28** in 76% and 57% yield, respectively. In the case of photoaffinity labeled olefin **25**, although this olefin gradually decomposed at the reflux temperature of CH_2Cl_2, the coupling reaction at room temperature produced the desired product **29** in 58% yield along with decomposed products. Thus, the olefin cross metathesis method is actually effective and versatile for providing various kinds of sphingolipid derivatives.

In conclusion, we synthesized various sphingolipids including sphingomyelin **1**, ceramide **2**, sphingosine **3**, and sphingosine 1-phosphate **4** by utilization of the olefin cross metathesis reaction between 1-pentadecene **16** and amino alcohol derivatives **8** and **11**−**15**, which were derived starting from L-serine through intermediate **8** by vinyl group introduction followed by highly *anti*-stereoselective reduction as key steps. The olefin cross metathesis method was also effective for providing functionalized sphingolipid derivatives.

Table 3. Olefin Cross Metathesis Reaction between **8** and Some Olefin Parts **A**



olefin	product	yield (%)[a]
 **22**	 **26**	55%
 **23**	 **27**	76%
 **24**	 **28**	57%
 **25**	 **29**	58%[b]

[a] Isolated yields. [b] Reaction was proceeded under room temperature for 30 min.

Acknowledgment. This work was partly supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: General method and optical rotation; ^{1}H NMR, IR, and MS data; and spectra of the corresponding compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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