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Synthesis of Novel Polyyne Analogues of Sphingoid Base via an Iterative Acetylene Homologation Sequence

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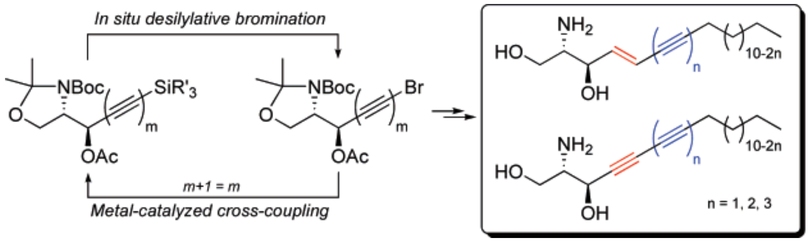
ABSTRACT



The first syntheses of polyyne-containing sphingoid base analogues were achieved by employing our iterative strategy that uses a two-step acetylene homologation sequence. In this process, a bromoalkyne is homologated by one acetylene unit through a Pd-catalyzed cross-coupling with a TIPS-protected acetylene and a subsequent in situ AgF-mediated desilylative bromination. Repeating this homologation sequence followed by cross-coupling with the long-chained terminal acetylene provides access to the polyyne framework in good overall yields.

Sphingolipids are a structurally diverse class of compounds, considered to be composed of three principal moieties: a sphingoid base, an amide-linked fatty acid, and a polar head group. They are important components of the plasma membranes of essentially all eukaryotic cells.[1] The main structural role of sphingolipids in membranes is the regulation of the fluidity and subdomain structure of the lipid bilayer. In addition to their structural functions, they also play critical roles in many fundamental biological processes. For example, sphingolipid metabolites, such as ceramide, sphingosine-1-phosphate, and sphingosine-1-phosphocholine, act as second messengers that regulate diverse cellular processes including apoptosis, cell senescence, the cell cycle, and cellular differentiation.[2]

Due to their obvious biological significance, natural sphingolipids have been attractive and popular targets for synthetic chemists over the last few decades.[3] Moreover, the design and syntheses of various sphingolipid analogues and mimetics have progressed, because nonnatural sphingolipids could also be useful in the investigation of biological functions of sphingolipids and provide opportunities for modulating cellular processes. Among the three moieties of sphingolipids, sphingoid bases have been the primary subject for structural modification, since they are intrinsically bioactive and are the fundamental backbone of the other sphingolipids. Sphingoid bases are long-chain aliphatic compounds typically possessing a 2-amino-1,3-diol functionality. A large number of structurally interesting nonnatural sphingoid bases have appeared in the literature.[4] However, to the best of our knowledge, there has been no literature precedent relating to the synthesis of sphingoid base analogues containing two or more conjugated acetylene units in the long chain. Conjugated diyne and polyyne units are

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(1) Merrill, A. H., Jr.; Sandhoff, K. Sphingolipids: Metabolism and Cell Signaling. In *Biochemistry of Lipids, Lipoprotein, and Membranes*; Vance, D. E., Vance, J. E., Eds.; Elsevier: New York, 2002; pp 373−407.

(2) For a good review with citations, see: (a) Kester, M.; Kolesnick, R. *Pharmacol. Res.* **2003**, *47*, 365−371. (b) Rosen, H.; Liao, J. *Curr. Opin. Chem. Biol.* **2003**, *7*, 461−468.

(3) For recent reviews, see: (a) Liao, J.; Tao, J.; Lin, G.; Liu, D. *Tetrahedron* **2005**, *61*, 4715−4733. (b) Howell, A. R.; So, R. C.; Richardson, S. K. *Tetrahedron* **2004**, *60*, 11327−11347. (c) Curfman, C.; Liotta, D. *Methods Enzymol.* **1999**, *311*, 391−440. (d) Koskinen, P. M.; Koskinen, A. M. P. *Synthesis* **1998**, 1075−1091.

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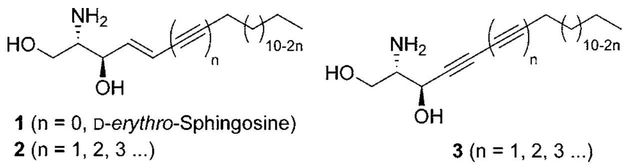
found in numerous natural products that exhibit a variety of interesting biological activities.[5] Furthermore, they continue to attract widespread interest because of their unusual electronic and structural properties.[6]

As part of our ongoing research on the preparation of sphingolipid analogues and libraries, we became particularly interested in a synthesis of polyyne-containing sphingoid bases. We envisaged that the incorporated rigid polyyne moiety in the sphingoid base could alter the physicochemical properties of the sphingolipid, thereby affecting biological behaviors that would be useful in the sphingolipid research. Herein, we wish to report a novel approach that allows the efficient synthesis of the polyyne-containing sphingoid bases of general structures **2** and **3** (Figure 1), in which conjugated triple bonds are incorporated near the 2-amino-1,3-diol functionality and the alkyl chain lengths are 18 carbon atoms, identical with sphingosine **1**.

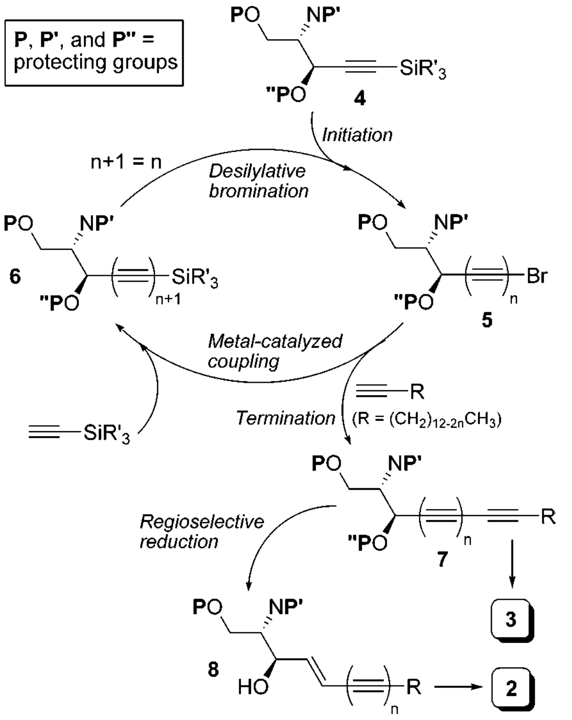


1 (n = 0, D-*erythro*-Sphingosine)
2 (n = 1, 2, 3 ...)
3 (n = 1, 2, 3 ...)

Figure 1. Chemical structures of compounds **1**, **2**, and **3**.

We predicted that the major challenge associated with their preparation was the often unstable nature of polyyne compounds.[5,6] Futhermore, the terminal diynes and higher polyynes required as synthetic intermediates for acetylenic coupling reaction are usually highly sensitive molecules that are prone to rapid decomposition. We felt that this expected instability could be circumvented by the employment of our recently developed iterative strategy,[7] which avoids the complications encountered with isolating sensitive terminal alkynes. Our iterative strategy entailed a two-step acetylene homologation sequence, namely, in situ desilylative bromination of alkynylsilanes followed by cross-coupling with a trialkylsilylacetylene.

Scheme 1. Iterative Protocol for Synthesis of the Polyyne-Containing Sphingoid Bases **2** and **3**



Scheme 1 depicts a general outline of our iterative protocol for the synthesis of the target compounds. We envisioned that the bromoalkyne **5** ($n = 1$), derived from alkynylsilane **4**, could be homologated by one acetylene unit through cross-coupling with the trialkylsilylacetylene and subsequent in situ desilylative bromination of **6** to give bromodiyne **5** ($n = 2$). Repeating this two-step homologation sequence would generate the homologated product, bromopolyyne **5** ($n \geq 3$). Then, cross-coupling of **5** with a long-chained terminal acetylene, followed by removal of the protecting groups of the resulting polyyne **7** would afford the desired polyyne-containing sphingoid base **3**. In this process, the number of incorporated acetylene units could vary depending on the number of homologation cycles. Furthermore, the regioselective reduction of the $\Delta^{4,5}$-triple bond of **7** to the corresponding *trans* double bond of **8** would allow the preparation of the triple bonds containing sphingosine analogue **2**.

Our synthesis started with (*S*)-Garner's aldehyde **9**[8] as the chiral synthon to prepare the target compounds. Indeed, Garner's aldehyde has received considerable attention due to its inherent 2-amino-1,3-diol functionality in the synthesis of sphingosine and its derivatives.[9] Lithium triisopropylsilylacetylide addition to **9** in the presence of HMPA in THF at −78 °C proceeded with very high diastereoselectivity (dr >20:1), similar to the previous work of Herold,[10] to give *erythro*-isomer **10** in 93% yield (Scheme 2). At this stage, it

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(4) For selected recent examples, see: (a) Oldendorf, J.; Haufe, G. *Eur. J. Org. Chem.* **2006**, 4463−4472. (b) Waschowski, V.; Giannis, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 827−830. (c) Dougherty, A. M.; McDonald, F. E.; Liotta, D. C.; Moody, S. J.; Pallas, D. C.; Pack, C. D.; Merrill, A. H. *Org. Lett.* **2006**, *8*, 649−652. (d) Hillaert, U.; Van Calenbergh, S. *Org. Lett.* **2005**, *7*, 5769−5772. (e) Wiseman, J. M.; McDonald, F. E.; Liotta, D. C. *Org. Lett.* **2005**, *7*, 3155−3157. (f) Lu, X.; Arthur, G.; Bittman, R. *Org. Lett.* **2005**, *8*, 1645−1648. (g) Sawatzki, P.; Kolter, T. *Eur. J. Org. Chem.* **2004**, 3693−3700. (h) Triola, G.; Fabriàs, G.; Casas, J.; Llebaria, A. *J. Org. Chem.* **2003**, *68*, 9924−9932. (i) De Jonghe, S.; Lamote, I.; Venkataraman, K.; Boldin, S. A.; Hillaert, U.; Rozenski, J.; Hendrix, C.; Busson, R.; De Keukeleire, D.; Van Calenbergh, S.; Futerman, A. H.; Herdewijn, P. *J. Org. Chem.* **2002**, *67*, 988−996. (j) Chun, J.; He, L.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **2000**, *65*, 7634−7640.

(5) For a recent review, see: Shi Shun, A. L. K.; Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 1034−1057.

(6) (a) Ginsburg, E. J.; Gorman, C. B.; Grubbs, R. H. In *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, Germany, 1995. (b) *Acetylene Chemistry*: *Chemistry, Biology and Material Science*; Diederich, F., Stang, P. J., Tykwinski, R. R., Eds.; Wiley-VCH: Weinheim, Germany, 2005.

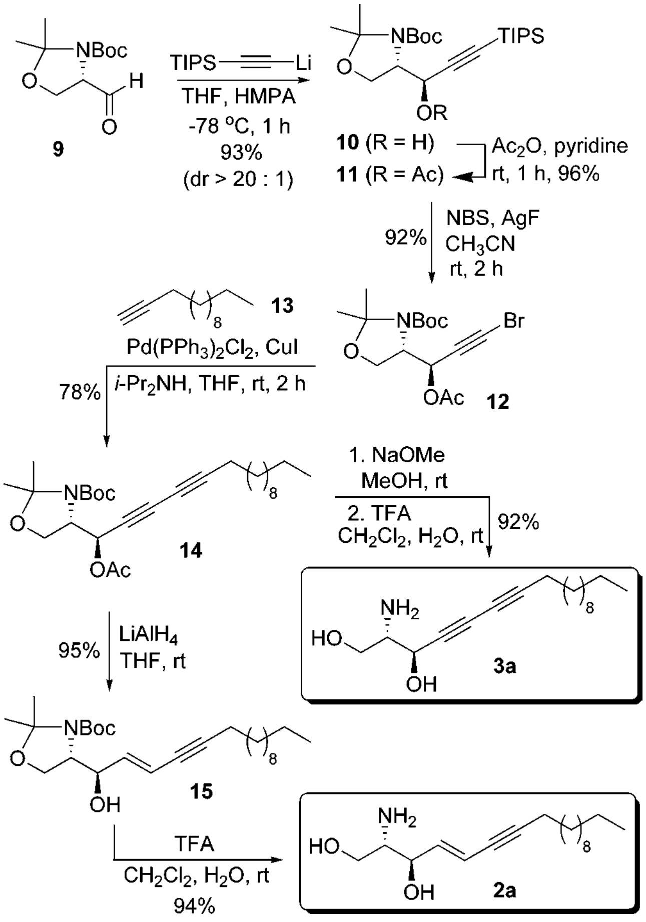
(7) Kim, S.; Kim, S.; Lee, T.; Ko, H.; Kim, D. *Org. Lett.* **2004**, *6*, 3601−3604.

(8) (a) Garner, P.; Park, J. M. *Organic Syntheses*; Wiley: New York, 1998; Collect. Vol. IX, pp 300−305.

(9) For selected recent examples, see: (a) Lu, X.; Bittman, R. *J. Org. Chem.* **2005**, *70*, 4746−4750. (b) Murakami, T.; Hirono, R.; Furusawa, K. *Tetrahedron* **2005**, *61*, 9233−9241. Also see ref 4g−j.

(10) Herold, P. *Helv. Chim. Acta* **1988**, *71*, 354−362.

Scheme 2. Synthesis of Diyne and Enyne Analogues of Sphingoid Base

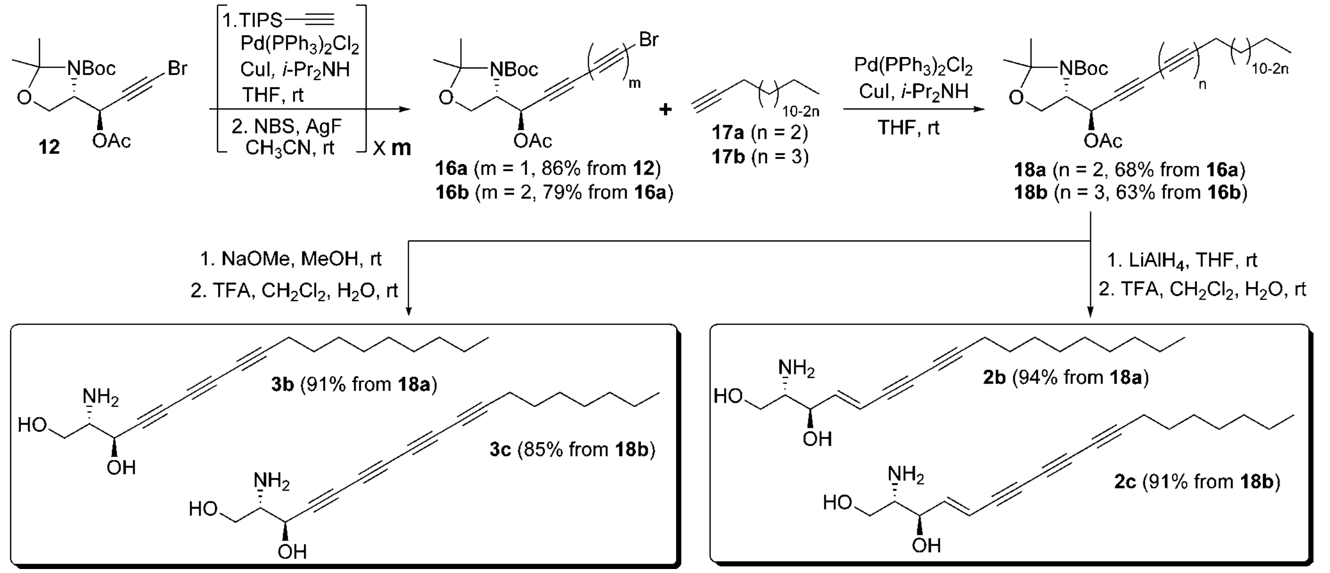


was desirable to protect the free hydroxyl group of **10** for the efficient transformation of triisopropylsilyl (TIPS)-protected acetylene into bromoacetylene. This was accomplished by treating compound **10** with Ac_2O to furnish **11** in 96% yield. Under our recently developed in situ AgF-mediated desilylative bromination conditions,[7,11] TIPS-protected acetylene **11** was smoothly converted to the bromoacetylene **12** in very high yield (92%).

Prior to the two-step acetylene homologation sequence, we undertook the cross-coupling of bromoacetylene **12** with a slight excess (1.2 equiv) of the long-chain terminal acetylene **13**. Under the modified Sonogashira conditions ($Pd(PPh_3)_2Cl_2$, CuI, diisopropylamine, THF),[12] the desired cross-coupling product **14** was obtained in 78% yield along with 7% of a homocoupling byproduct.[13] Removal of the acetate protecting group of **14** with NaOMe/MeOH followed by concomitant hydrolysis of the acetonide and the *N*-Boc protecting groups with TFA in CH_2Cl_2/H_2O gave the diyne analogue **3a** in high overall yield (92%). On the other hand, treatment of **14** with $LiAlH_4$ in THF effected the regioselective reduction of the $\Delta^{4,5}$-triple bond to *trans* double bond and concomitant removal of the acetate protecting group to afford hydroxy enyne **15** in excellent yield (95%). Subsequently, removal of the acetonide as well as the *N*-Boc protecting groups with TFA in CH_2Cl_2/H_2O afforded the triple bond containing sphingosine analogue **2a** in 94% yield.

After achieving the synthesis of simple diyne **3a** and enyne **2a** analogues of sphingoid base, we then investigated the synthesis of the higher polyyne-containing analogues as shown in Scheme 3. We encountered no difficulties when converting bromoacetylene **12** into bromodiyne **16a** through our two-step acetylene homologation sequence. The palladium-catalyzed cross-coupling of **12** with TIPS-acetylene provided TIPS-diyne in 90% yield,[14] and the subsequent AgF-mediated desilylative bromination afforded bromodiyne **16a** successfully in 95% yield. We performed the second iteration in the same manner to obtain bromotriyne **16b** in 79% overall yield from **16a**. The obtained bromodiyne **16a** and bromotriyne **16b** were cross-coupled respectively with

Scheme 3. Synthesis of Polyyne-Containing Analogues of Sphingoid Base



the long-chain terminal acetylenes **17a** and **17b** under the above-mentioned Sonogashira conditions to give triyne **18a** (68%) and tetrayne **18b** (63%) in that order. In these cases, homocoupling products were also isolated as byproducts from the reaction mixtures (11% from **16a** and ca. 10% from **16b**).[15]

Removal of all of the protecting groups in compounds **18a** and **18b** as described above furnished the desired higher polyyne analogues of sphingoid base **3b** and **3c** in 91% and 85% overall yields, respectively. Analogous to the preparation of **2a**, a two-step sequence, viz., regioselective reduction of the $\Delta^{4,5}$-triple bond and acidic hydrolysis, transformed the triyne **18a** and tetrayne **18b** into the corresponding polyyne-containing analogues of sphingosine **2b** and **2c** in 94% and 91% overall yields, respectively.[16]

In summary, we have presented a novel approach that allows the efficient synthesis of polyyne-containing sphingoid base analogues. Our methodology features a repetitive acetylene homologation that provides access to the polyyne framework in good yield. A special advantage of our approach is the possibility of preparing different polyyne base analogues by terminating the sequence with different terminal acetylenes or other types of coupling partners that allows control of the chain length as well as the diversification of lipid tail. We believe that this versatile and efficient synthetic method could be of value in the development of novel sphingoid base analogues for sphingolipid research. The above and other polyyne analogues are now being evaluated for biological activity and the details will be reported in due course.

Acknowledgment. This work was supported by the Korea Science and Engineering Foundation (KOSEF) through the National Research Laboratory Program funded by the Ministry of Science and Technology (M10500000055-06J0000-05510). Two of the authors (Y.M.L. and J.C.) were supported financially by the second stage of the BK21 project for Applied Pharmaceutical Life Science Research Division.

Supporting Information Available: Full experimental procedures and analytical data of compounds; copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **2a−c**, **3a−c**, **12**, **16a**, and **16b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Lee, T.; Kang, H. R.; Kim, S.; Kim, S. *Tetrahedron* **2006**, *62*, 4081−4085.

(12) Sonogashira, K. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley, New York, 2002; Vol. 1, pp 493−549.

(13) The formation of homocoupling products during the cross-coupling reaction has been observed earlier. For reviews, see: (a) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979−2017. (b) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632−2657.

(14) Under the condition studied, the cross-coupling reaction between **12** and trimethylsilyl (TMS) acetylene gave a complex mixture of products, including the expected cross-coupled TMS-diyne (55%) and the corresponding terminal diyne (17%) that does not contain TMS group.

(15) The homocoupled byproducts were unstable to prolonged exposure to silica gel, to air, and to light. Particularly noteworthy is that the carefully isolated hexayne, derived from **16b**, decomposed rapidly at room temperature under air.

(16) All of the obtained analogues are stable at room temperature for at least a week.