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A Concise and Scalable Synthesis of High Enantiopurity (−)-D-*erythro*-Sphingosine Using Peptidyl Thiol Ester−Boronic Acid Cross-Coupling

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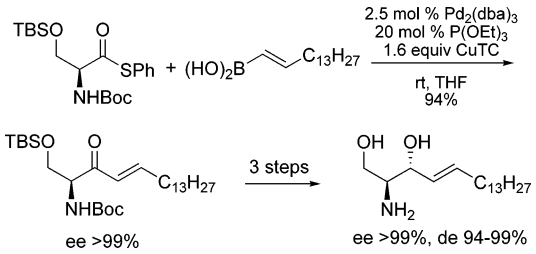
ABSTRACT



A short and efficient synthesis of high enantiopurity (−)-D-*erythro*-sphingosine has been achieved in 71% yield over 6 steps from *N*-Boc-L-serine. The key steps are high yield, racemization-free, palladium-catalyzed, copper(I)-mediated coupling of the thiophenyl ester of *N*-Boc-*O*-TBS L-serine with *E*-1-pentadecenyl boronic acid and the highly diastereoselective reduction of the resulting peptidyl ketone with LiAl(O-*t*-Bu)$_3$H. By using this concise route (−)-D-*erythro*-sphingosine can be prepared on large scale and in high enantio- and diastereopurity (ee >99%, de up to 99%).

Sphingolipids are derived from the common base structure sphingosine (**1**, Figure 1). As important messengers for controlling cell growth, maturity, survival, and death, sphingolipids show promising efficacy for the control of cancer and other proliferative diseases.[1] The related *N*-acylsphingosines (ceramides) are already widely used in the cosmetic industry as active ingredients to improve skin cell cohesion.[2] Given their broad biological activities and the difficulty of acquiring homogeneous forms of sphingolipids from natural sources, the chemical synthesis of sphingosine has been a valuable quest. To date more than 50 syntheses of sphingosine have been disclosed.[1a,3] Of these, those using the inexpensive amino acid serine as the starting material are

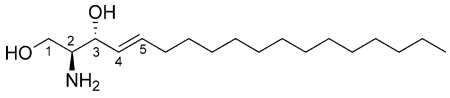


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Figure 1. Structure of (−)-D-*erythro*-sphingosine.

(1) (a) Milstien, S.; Spiegel, S. *Cancer Cell* **2006**, *9*, 148−150. (b) Ogretmen, B.; Hannun, Y. A. *Nat. Rev. Cancer* **2004**, *4*, 604−616. (c) Smith, W. L.; Merrill, A. H., Jr. *J. Biol. Chem.* **2002**, *277*, 25841−25842. (d) Spiegel, S.; Milstien, S. *Nature Rev. Mol. Cell Biol.* **2003**, *4*, 397−407.

(2) Philippe, M.; Garson, J. C.; Gilard, P.; Hocquaux, M.; Hussler, G.; Leroy, F.; Mahieu, C.; Semeria, D.; Vanlerberghe, G. *Int. J. Cosmet. Sci.* **1995**, *17*, 133−146.

(3) For recent syntheses see: (a) Merino, P.; Jimenez, P.; Tejero, T. *J. Org. Chem.* **2006**, *71*, 4685−4688. (b) Rai, A. N.; Basu, A. *Org. Lett.* **2004**, *6*, 2861−2863. (c) Lu, X.; Cseh, S.; Byun, H.-S.; Tigyi, G.; Bittman, R. *J. Org. Chem.* **2003**, *68*, 7046−7050.

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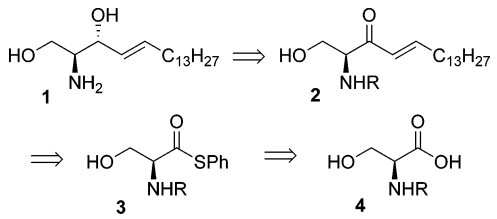
the most economical since L-serine bears the C-1 hydroxyl group and the C-2 chiral center of sphingosine. However, synthetic methods using serine can sometimes be complicated by the ease with which the α stereocenter of derivatives of the amino acid is racemized under both acidic and basic condition. While high enantiomeric excesses are routinely reported (95−98%), few methods are able to deliver sphingosine in >99% enantiomeric excess. For example, the addition of alkenyl- or alkynyllithium reagents to a protected serine-derived aldehyde (Garner aldehyde)[4] gave enol or ynol derivatives in 95−98% ee.[4,5] A modified Horner−Wadsworth−Emmons reaction on a serine-derived ketophosphonate does provide a mild and epimerization-free protocol to produce the C4−C5 *trans* alkene.[6] Recently, Basu introduced a cross-metathesis method to build the *trans* only alkene under very mild conditions, but a large excess of one olefin must be incorporated to avoid homo metathesis of the substrate.[3a,7] Herein is reported a short, simple, and scalable synthesis of high enantiopurity (−)-D-*erythro*-sphingosine that uses, in the key step, our recently disclosed racemization-free synthesis of peptidyl ketones[8] by the palladium-catalyzed, copper(I)-mediated, non-basic coupling of peptidyl thiol esters and boronic acids.

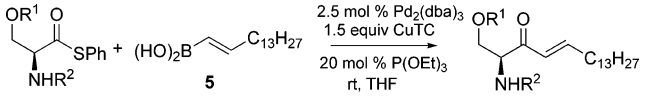
The key to generating high enantiopurity sphingosine from L-serine is the efficient construction of enone **2** without racemization (Scheme 1). To utilize this strategy, the cross-

Scheme 1. Retrosynthesis



couplings of a series of *N*-protected serine thiophenyl esters and *trans*-1-pentadecenyl boronic acid **5** were initially studied. *trans*-1-Pentadecenyl boronic acid **5** was prepared by hydroboration of 1-pentadecyne with $HBBr_2{\cdot}SMe_2$ followed by hydrolysis in ice−water.[9] As depicted in Table 1, this cross-coupling showed very good reactivity with use of a typical selection of amino protecting groups, except for the hindered trityl group. Of the protected thiol esters studied, mono *N*-Boc-*O*-TBS serine thiophenyl ester gave the highest

Table 1. The Cross-Coupling



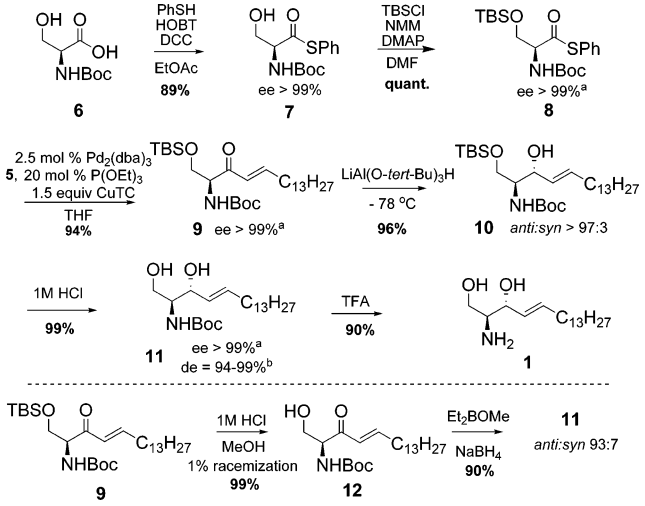
		yield (%)[a]	
entry	R^2	R^1 = TBDMS	R^1 = H
1	$COC_{15}C_{31}$	60	37
2	Cbz	78	40
3	Trityl	0[b]	0[b]
4	Boc	94	75[c]
5	Fmoc	73	32

[a] Isolated yield. [b] Starting material was recovered. [c] THF/hexane (1:1) used as solvent (30% yield with pure THF as the solvent).

yield of ketone in less than 6 h at rt (94%). Without protection of the 1-OH group of *N*-Boc-Ser-SPh, a satisfactory yield of the ketone was obtained (75%) by carrying out the reaction in THF/hexanes (1:1). In pure THF the product yield was only 30%. HPLC comparisons of the reaction products with the corresponding racemic mixtures demonstrated that no racemization of the ketone product had occurred.

N-Boc-*O*-TBS serine thiophenyl ester was used as the preferred substrate to carry out a total synthesis of (−)-D-*erythro*-sphingosine. The complete route is illustrated in Scheme 2. Starting from commercially available *N*-Boc-L-

Scheme 2. A Concise Synthesis of (−)-D-*erythro*-Sphingosine



[a] Determined by chiral HPLC, AS-RH. [b]Determined by ^{1}H NMR and chiral HPLC, OD-RH.

serine **6**, the corresponding thiophenyl ester **7** was prepared in excellent yield (89%) and high enantiopurity (ee >99%) by using typical dehydration conditions (DCC/HOBT). Efficient silyl protection of the hydroxyl group of **7** was achieved by using TBSCl/Et_3N in CH_2Cl_2. However, HPLC

(4) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361−2364.
(5) Dondoni, A.; Perrone, D. *Org. Synth.* **2000**, *77*, 64−77.
(6) (a) Koskinen, A. M. P.; Krische, M. J. *Synlett* **1990**, 665−666. (b) Koskinen, P. M.; Koskinen, M. P. *Method Enzymol.* **1999**, *311*, 458−479. (c) Chung, S.-K.; Lee, J.-M. *Tetrahedron*: *Asymmetry* **1999**, *10*, 1441−1444.
(7) For other examples of sphingosine syntheses by cross-metathesis see: (a) Chang, C.-W.; Chen, Y.-N.; Adak, A. K.; Lin, K.-H.; Tzou, D.-L. M.; Lin, C.-C. *Tetrahedron* **2007**, *63*, 4310−4318. (b) Yamamoto, T.; Hasegawa, H.; Hakogi, T.; Katsumura, S. *Org. Lett.* **2006**, *8*, 5569−5572. (c) Torssell, S.; Somfai, P. *Org. Biomol. Chem.* **2004**, *2*, 1643.
(8) Yang, H.; Li, H.; Wittenberg, R.; Egi, M.; Huang, W.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 1132−1140.
(9) Brown, H. C.; Bhat, N. G.; Somayaji, V. *Organometallics* **1983**, *2*, 1311−1316.

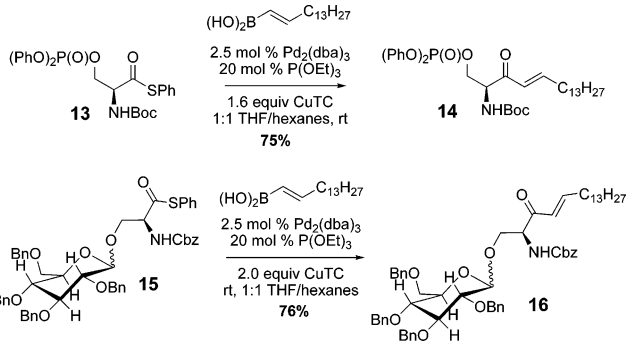
analyses showed a significant racemization (ca. 20%) of product **8**. Assuming that an intramolecular hydrogen bonding interaction of the 1-O(H)···HNBoc portion of serine thiophenyl ester **7** may decrease the nucleophility of the 1-OH,[10] DMAP was added and DMF was used as the solvent to achieve a higher rate of silylation. Although significantly improved, 2% racemization could not be avoided under these reaction conditions. Finally, employing *N*-methyl morpholine rather than triethylamine furnished the requisite silylated product **8** in less than 30 min without racemization (ee >99%).

The subsequent cross-coupling of thiol ester **8** and boronic acid **5** delivered peptidyl ketone **9** in high yield (94%). HPLC analyses demonstrated that high enantiopurity (ee >99%) was maintained and no *E*/*Z* isomerization of the α,*β*-unsaturated ketone was observed throughout the course of the reaction and the workup procedure.

In seeking a method for the asymmetric reduction of enone **9**, desilylation of **9** (HCl in MeOH/H_2O) generated the alcohol **12**, which was used to carry out a diastereoselective chelation-controlled reduction of the ketone by using $Et_2BOMe/NaBH_4$.[11] The resulting *N*-protected α-amino alcohol **11** was produced with very good *anti* selectivity (*anti:syn* > 93:7). However, 1% racemization had occurred during the desilylation of **9** with HCl and the racemization was exacerbated by using TBAF for the desilylation. To avoid racemization, the ketone reduction was performed before the desilylation step. Excellent *anti* diastereoselective reduction (>97:3)[12] of **9** was observed by employing LiAl(*tert*-butoxy)$_3$H in ethanol[13] at −78 °C giving alcohol **10** in 96% yield. Subsequent desilylation of **10** produced diol **11** in 99% yield and >94% diastereomeric purity (^{1}H NMR). HPLC and LC-MS showed high enantiopurity for each of the diastereomers (ee >99%).[14] A simple recrystallization from isopropyl ether/hexane (1:1) improved the diastereomeric purity of **11** to 99%. A final *N*-deprotection with TFA yielded (−)-D-*erythro*-sphingosine[15] in 90% yield without epimerization.

Extension of this synthesis of D-*erythro*-sphingosine will give easy access to hundreds of sphingolipid related natural products. Note, for example, that this mild cross-coupling method shows a high tolerance for phosphate (Scheme 3, **13** → **14**) and glycoside functionality (Scheme 3, **15** → **16**) attached to the 1-hydroxyl of the serine thiol ester.

Scheme 3 *O*-Functionalized Derivatives[a]



[a] All starting material stereoprofiles were conserved in the products

Following the reported method,[16] selective phosphorylation of the 1-OH group of **11** with $P(OMe)_3/CBr_4$/pyridine followed by deprotection of the resulting phosphate ester with a TMSBr-mediated cleavage gives sphingosine-1-phosphate (S1P) in 62% yield.

In summary, a concise total synthesis (6 steps, 71% overall yield from *N*-Boc-L-serine) of high enantiopurity (−)-D-*erythro*-sphingosine and sphingosine-1-phosphate has been achieved by using a key thiol ester and boronic acid cross-coupling for the critical bond-forming step.[17] This method not only establishes a rapid, mild, and efficient synthesis of sphingosine, but also provides a powerful tool for rapidly building a family of sphingosine-related lipids. Future work will demonstrate the versatility of the thiol ester−boronic coupling for the construction of various amino acid-derived sphingosine analogues.

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Supporting Information Available: Complete description of experimental details and product characterization and photocopies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Szabo, L.; Li, Y.; Polt, R. *Tetrahedron Lett.* **1991**, *32*, 585−588.
(11) Chen, K. M.; Hardtmann, G.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155−158.
(12) Ratio was determined by ^{1}H NMR.
(13) Hoffman, R. V.; Najib, M.; Cervantes-Lee, F. *J. Org. Chem.* **2002**, *67*, 1045−1056.
(14) LC-MS showed 4 isomers of **11** with the same mass weight based on the synthetic route with a racemic mixture of **9**.
(15) (−)-D-*erythro*-Sphingosine was characterized as its triacetate derivative. See the Supporting Information.
(16) (a) Szulc, Z. M.; Hannun, Y. A.; Bielawska, A. *Tetrahedron Lett.* **2000**, *41*, 7821−7824. (b) Murakami, T.; Furusawa, K.; Tamai, T.; Yoshikaib, K.; Nishikawa, M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1115−1119.
(17) Yang, H.; Liebeskind, L. S. U.S. Prov. Patent Appl. 60/842,624, September 6, 2006.