

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

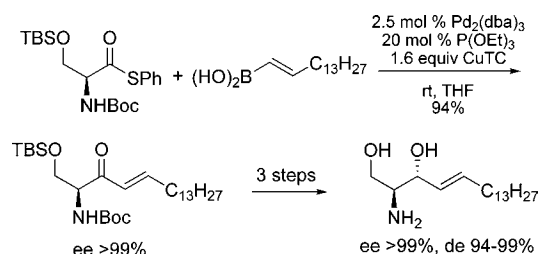
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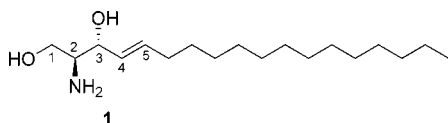
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## ABSTRACT



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  $\text{LiAl}(\text{O}-t\text{-Bu})_3\text{H}$ . 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



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

controlling cell growth, maturity, survival, and death, sphingolipids show promising efficacy for the control of cancer and other proliferative diseases.<sup>1</sup> The related *N*-acylsphingosines (ceramides) are already widely used in the cosmetic

industry as active ingredients to improve skin cell cohesion.<sup>2</sup> 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.<sup>1a,3</sup> Of these, those using the inexpensive amino acid serine as the starting material are

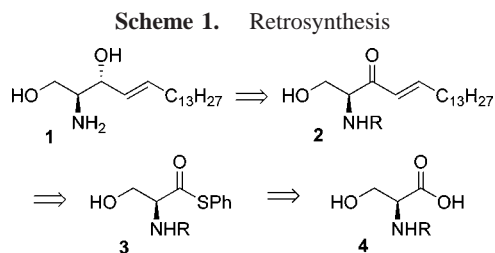
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the most economical since L-serine bears the C-1 hydroxyl group and the C-2 chiral center of sphingosine. However, synthetic methods using serine can sometimes be complicated by the ease with which the  $\alpha$  stereocenter of derivatives of the 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)<sup>4</sup> gave enol or ynone derivatives in 95–98% ee.<sup>4,5</sup> 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.<sup>6</sup> 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.<sup>3a,7</sup> 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<sup>8</sup> 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-



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<sub>2</sub>·SMe<sub>2</sub> followed by hydrolysis in ice–water.<sup>9</sup> 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

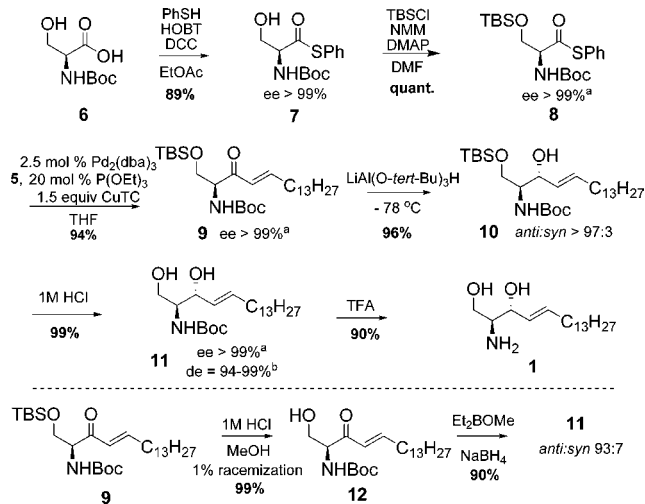
entry	R <sup>2</sup>	yield (%) <sup>a</sup>	
		R <sup>1</sup> = TBDMS	R <sup>1</sup> = H
1	COC <sub>15</sub> C <sub>31</sub>	60	37
2	Cbz	78	40
3	Trityl	0 <sup>b</sup>	0 <sup>b</sup>
4	Boc	94	75 <sup>c</sup>
5	Fmoc	73	32

<sup>a</sup> Isolated yield. <sup>b</sup> Starting material was recovered. <sup>c</sup> 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



<sup>a</sup> Determined by chiral HPLC, AS-RH. <sup>b</sup> Determined by <sup>1</sup>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<sub>3</sub>N in CH<sub>2</sub>Cl<sub>2</sub>. However, HPLC

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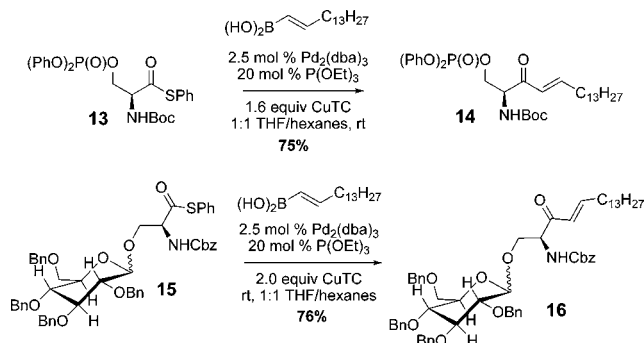
analyses showed a significant racemization (ca. 20%) of product **8**. Assuming that an intramolecular hydrogen bonding interaction of the 1-O(H)⋯HNBoc portion of serine thiophenyl ester **7** may decrease the nucleophilicity of the 1-OH,<sup>10</sup> DMAP was added and DMF was used as the solvent to 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  $\alpha,\beta$ -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<sub>2</sub>O) generated the alcohol **12**, which was used to carry out a diastereoselective chelation-controlled reduction of the ketone by using Et<sub>2</sub>BOMe/NaBH<sub>4</sub>.<sup>11</sup> The resulting *N*-protected  $\alpha$ -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)<sup>12</sup> of **9** was observed by employing LiAl(*tert*-butoxy)<sub>3</sub>H in ethanol<sup>13</sup> at -78 °C giving alcohol **10** in 96% yield. Subsequent desilylation of **10** produced diol **11** in 99% yield and >94% diastereomeric purity (<sup>1</sup>H NMR). HPLC and LC-MS showed high enantiopurity for each of the diastereomers (ee >99%).<sup>14</sup> 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<sup>15</sup> 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<sup>a</sup>



<sup>a</sup> All starting material stereoprofiles were conserved in the products

Following the reported method,<sup>16</sup> selective phosphorylation of the 1-OH group of **11** with P(OMe)<sub>3</sub>/CBr<sub>4</sub>/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.<sup>17</sup> 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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(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.

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