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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)₃H. 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 homogenous 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 the most economical since L-serine bears the 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's.^{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

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Supporting Information Available Complete description of experimental details and product characterization (19 pages) and photocopies of spectra (66 pages). This material is available free of charge via Internet at <http://pubs.acs.org>.

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 ketones⁸ 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). In order 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 HBBR₂·SMe₂ followed by hydrolysis in the ice-water.⁹ As depicted in Table 1, this cross-coupling showed very good reactivity using 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 yield of ketone in less than 6 hr 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 as solvent 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-serine **6**, the corresponding thiophenyl ester **7** was prepared in excellent yield (89%) and high enantiopurity (ee > 99%) using typical dehydration conditions (DCC/HOBT). Efficient silyl protection of the hydroxyl group of **7** was achieved using TBSCl/Et₃N in CH₂Cl₂. However, HPLC 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,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 minutes 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/H₂O) generated the alcohol **12**, which was used to carry out a diastereoselective chelation-controlled reduction of the ketone using Et₂BOMe/NaBH₄.¹¹ 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** using HCl and the racemization was exacerbated by using TBAF for the desilylation. In order 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)₃H in ethanol¹³ at –78 °C giving alcohol **10** in 96% yield. Subsequent desilylation of **10** produced diol **11** in 99% yield and > 94% diastereomeric purity (¹H 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-sphingosine¹⁵ in 90% yield without epimerization.

Development 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.

Following the reported method,¹⁶ selective phosphorylation of the 1-OH group of **11** using P(OMe)₃/CBr₄/pyridine followed by deprotection of the resulting phosphate ester **17** using a TMSBr-mediated cleavage gives sphingosine-1-phosphate (S1P) **18** 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 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 toolbox 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
(-)-D-erythro-Sphingosine

Scheme 1.
Retrosynthesis.

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

^a. Determined by Chiral HPLC, AS-RH. ^b. Determined by ¹H NMR and chiral HPLC, OD-RH.

Scheme 3. O-Functionalized Derivatives.^a

^a. All starting material stereoprofiles were conserved in the products.

Table 1

The Cross-Coupling.

		$R^1 = \text{TBDMS}$	$R^1 = \text{H}$
entry	R^2	yield (%) ^a	
1	$\text{COC}_{15}\text{C}_{31}$	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 using pure THF as the solvent).