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Enantioselective Synthesis of Sphingadienines and Aromatic Ceramide Analogs‡

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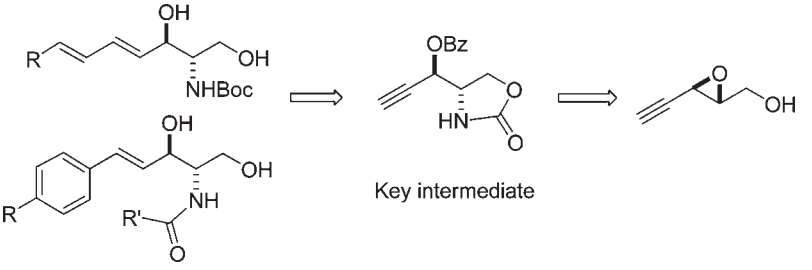
ABSTRACT



A new approach to the synthesis of sphingoid bases has been developed. The strategy is based on Sonogashira coupling of a chiral acetylenic carbamate that can be prepared in enantiomerically enriched form from 2,3-epoxy-4-pentyn-1-ol, which is readily accessible by Sharpless asymmetric epoxidation. Several *N*-Boc-sphingadienines and aromatic ceramide analogs have been synthesized.

Glycosphingolipids are constituents of eukaryotic cell membranes[1] and play important roles in many physiological processes.[2] The basic components of these lipids are called *sphingosines* and have a characteristic 2-amino-1,3-diol fragment with a 2*S*,3*R* (*D-erythro*) configuration[3] (Figure 1). Ceramides are fatty acid sphingosine amides and have been implicated in the regulation of cell growth and differentiation, inflammation, and apoptosis.[4] Ceramides have been implicated in many physiological events.[5] The C(4)−C(5) *trans* double bond in the sphingoid base may be crucial for the biological activities of ceramides. Sphingosines are potent inhibitors of protein Kinase C.[6] There is growing interest in the development of sphingosine analogs. For instance, sphingosines with aromatic substituents in the side chain[7] are stronger sphingosine kinase inhibitors relative to their corresponding parent compounds.[8] Sphingadienines, which have two double bonds in the hydrocarbon chain, are less abundant sphingoid bases.[9] Over the past few years, ceramide analogs with

‡ Dedicated to Prof. Rafael Suau (Universidad de Málaga), in memoriam.

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enhanced antitumor activity have been proposed as a potential new class of chemotherapeutic agents.[10]

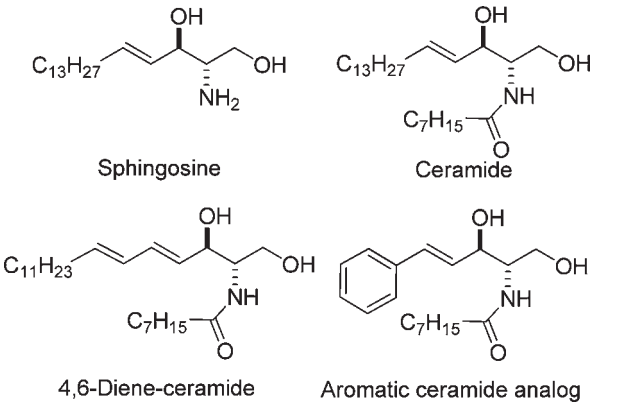


Figure 1. Biologically important sphingolipids.

Most synthetic approaches to sphingoid alkaloids[11−14] are based on the diastereoselective addition of organometallic nucleophiles to Garner's aldehyde or equivalent compounds, which entail forming the C3−C4 bond or ring closing metathesis (forming the C4−C5 bond). Contrariwise, we envisioned that a novel and convenient route to these compounds would be through coupling of aryl or vinyl halides to the acetylenic carbamates **I** to form the C5−C6 bond. To date, few precedents of alkyne-aminodiol synthons have been described.[15] Adequately protected compounds **I** would be accessible from the known acetylenic epoxy alcohol **1**, which can be prepared in any configuration by Sharpless asymmetric epoxidation of the commercially available (*E*)-2-penten-4-yn-1-ol. Herein we describe the enantioselective synthesis of aromatic sphingosine analogs and sphingadienines using this approach (Figure 2).

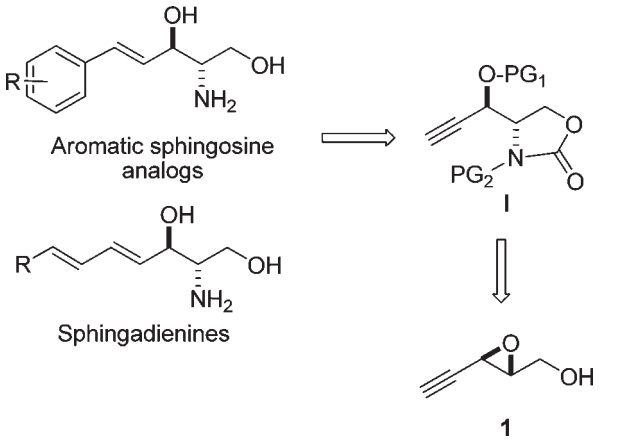
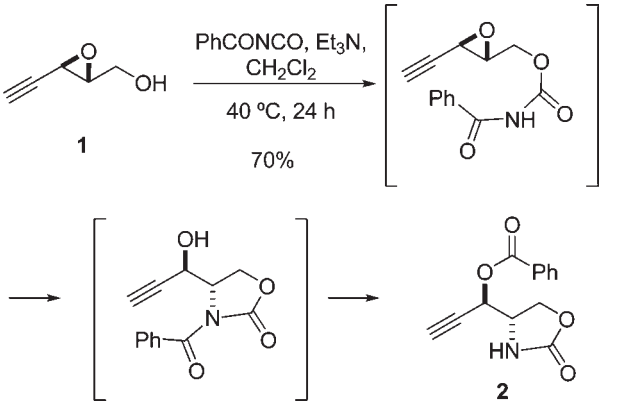


Figure 2. Retrosynthetic analysis of sphingadienines and aromatic sphingosine analogs.

We obtained the epoxy alcohol **1**[16] by Sharpless epoxidation[17] of commercial (*E*)-2-penten-4-yn-1-ol in moderate yield and 90% ee. Treatment of this compound with benzoyl isocyanate afforded, somewhat surprisingly, benzoate **2** in good yield.[18] In this case, the carbamate formation, the intramolecular epoxide ring opening, and the subsequent *trans*-acylation took place in a one-pot reaction (Scheme 1). Benzoate **2** is a very convenient chiral aminodiol synthon, since both chiral centers are clearly defined and all functional protecting groups would be easily deprotected by simple hydrolysis.

Scheme 1. Preparation of the Acetylenic Carbamate **2**, Key Intermediate of Our Approach



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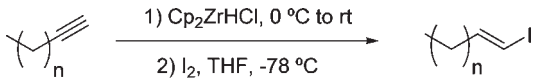
Preparation of the long-chain (*E*)-vinyl iodides **4** from the corresponding aldehydes via the Takai reaction has been described.[19] However, in our hands, the yields were moderate and the reaction was not completely stereoselective. Conversely, hydrozirconation of the acetylenes **3** using Schwartz's reagent[20] followed by iodine treatment afforded the (*E*)-vinyl iodides **4** in high yield with full stereoselectivity (Scheme 2).

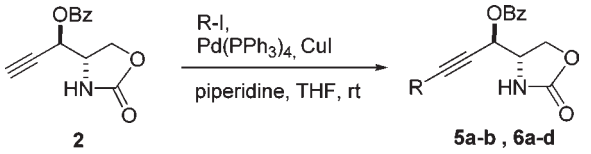
Scheme 2. Preparation of the (*E*)-Vinyl Iodides **4**



3a, n = 10	84%	**4a**, n = 10
3b, n = 6	74%	**4b**, n = 6

The Sonogashira coupling[21] of carbamate **2** using either vinyl iodide **4a** or **4b**, or using aryl iodides proceeded in good yields under the standard reaction conditions (Table 1).

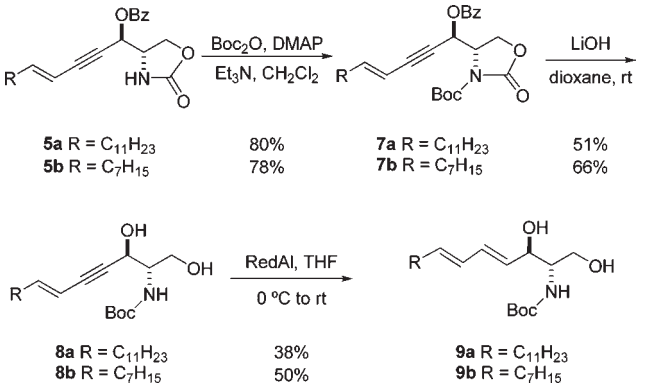
Table 1. Sonogashira Reactions of the Carbamate **2**



entry	R-I	product.	yield
1	$C_{13}H_{25}$-I (**4a**)	**5a**	75%
2	C_9H_{17}-I (**4b**)	**5b**	75%
3	Ph	**6a**	82%
4	MeO-Ph-I	**6b**	80%
5	^{t}Bu-Ph-I	**6c**	84%
6	*n*-C_7H_{15}-Ph-I	**6d**	80%

The functional group protection scheme of the enynes **5** was easily changed by treatment with Boc_2O and subsequent chemoselective basic hydrolysis (using lithium hydroxide) to afford the *N*-Boc-enynes **8**. Gratifyingly, these enynes were converted into the corresponding *N*-Boc-sphingadienines **9** by Red-Al (sodium bis(2-methoxyethoxy)aluminum hydride)[22] reduction of the propargylic triple bond (Scheme 3). Deprotection of the Boc group, however, proved to be difficult, and to date we have not been able to perform it in a reasonable yield. The Boc-sphingadienines have been thus prepared in five steps (8−14% overall yield) from epoxy alcohol **1**.

Scheme 3. Functional Group Manipulation of the Enynes **5** and Subsequent Reduction To Afford the *N*-Boc-Protected Sphingadienines **9**

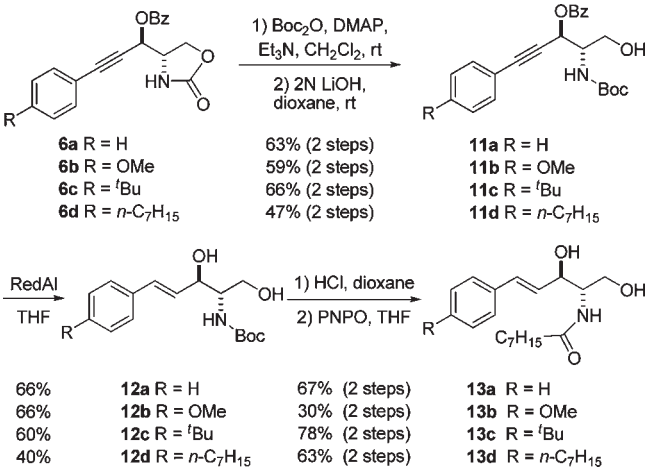


5a R = $C_{11}H_{23}$	80%	**7a** R = $C_{11}H_{23}$	51%
5b R = C_7H_{15}	78%	**7b** R = C_7H_{15}	66%

8a R = $C_{11}H_{23}$	38%	**9a** R = $C_{11}H_{23}$
8b R = C_7H_{15}	50%	**9b** R = C_7H_{15}

We also prepared several aromatic analogs of ceramides using an analogous sequence. First, *N*-Boc-protection of the aromatic carbamates **6** gave *N*-Boc carbamates **10** in excellent yields. Subsequent basic hydrolysis afforded the *N*-Boc protected aminodiols **11**. Then, Red-Al reduction of the triple bond in compounds **11** afforded the allyl alcohols **12** in moderate yields. Finally, acid deprotection of the *tert*-butoxycarbamate, followed by amide formation with *n*-alkyl *p*-nitrophenyl octanoate (PNPO), yielded the desired ceramide analogs **13** (Scheme 4). These ceramide analogs have been thus prepared in seven steps (7−18% overall yield) from epoxy alcohol **1**.

Scheme 4. Transformation of Aromatic Carbamates **6** into the Aromatic Ceramide Analogs **13**[a]



6a R = H	63% (2 steps)	**11a** R = H	
6b R = OMe	59% (2 steps)	**11b** R = OMe	
6c R = ^{t}Bu	66% (2 steps)	**11c** R = ^{t}Bu	
6d R = *n*-C_7H_{15}	47% (2 steps)	**11d** R = *n*-C_7H_{15}	

66%	**12a** R = H	67% (2 steps)	**13a** R = H
66%	**12b** R = OMe	30% (2 steps)	**13b** R = OMe
60%	**12c** R = ^{t}Bu	78% (2 steps)	**13c** R = ^{t}Bu
40%	**12d** R = *n*-C_7H_{15}	63% (2 steps)	**13d** R = *n*-C_7H_{15}

[a] PNPO = *para*-nitrophenyl octanoate.

In summary, *N*-Boc-protected sphingadienines and several aromatic analogs of ceramides have been synthesized

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from a common acetylenic precursor in a very straightforward way. Our approach has two main advantages: first, all the chiral centers are defined in the key intermediate, and second, the acetylenic coupling offers high synthetic versatility for the preparation of structurally diverse derivatives.

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Supporting Information Available. Experimental procedures and characterization data for compounds **1**–**2**, **4**–**13**; ^{1}H /^{13}C NMR spectra of compounds **2** and **5**–**13**. This material is available free of charge via the Internet at http://pubs.acs.org.