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Straightforward Synthesis of Sphinganines via a Serine-derived Weinreb Amide

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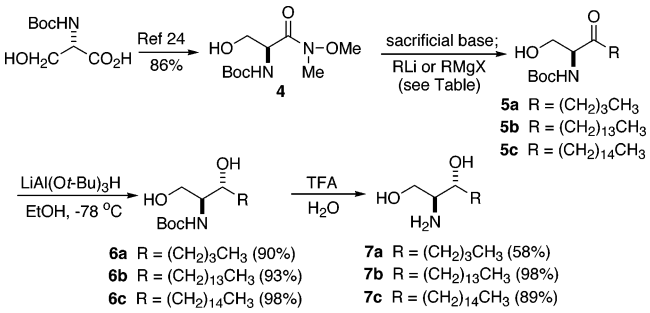
Abstract: Sphinganines can be synthesized in just three steps from easily prepared serine-derived Weinreb amide **4**. Pre-deprotonation of the acidic (N−H and O−H) protons of **4** allows for its efficient conversion to amino ketones **5**. Such ketones can be selectively reduced to either *erythro*- or *threo*-sphinganines. Partially protected sphinganines **11** are also readily accessible in five steps from **4**. Thus, Weinreb amide **4** represents one of the most versatile templates described to date for sphinganine synthesis.

We are interested in glycosphingolipids because of their ability to modulate immune responses.[1−3] For example, the β-galactosyl ceramide, plakoside A, isolated from the marine sponge *Plakortis simplex*, was found to be a noncytotoxic immunosuppressant.[4,5] On the other hand, KRN7000, an α-galactosyl ceramide identified from SAR studies at Kirin Brewery, has been shown to be a potent activator of the immune system.[6,7] The preparation of the sphingoid base represents one of the major challenges in the synthesis of glycosphingolipids. We recently described the exploitation of serine-derived 1,5-dioxaspiro-[3.2]hexane **3** as a template for the construction of both aminodiol and aminotriol sphingoid bases, illustrated by the conversion of **3** to D-*erythro*-dihydrosphingosine and D-*xylo*-phytosphingosine (Figure 1).[8] In this paper, we describe a more direct route to dihydrosphingosines (sphinganines) from serine-derived Weinreb amide **4**. This approach (Scheme 1) represents one of the most versatile, convenient, and direct methods reported to date for the preparation of sphinganines.

Literature syntheses of sphinganines are not as abundant as those for sphingosines (which have a double bond at C4 of the sphingoid base),[9] although it is obvious that sphinganines are available in only one step from the corresponding sphingosines by reduction. Sphinganines have been synthesized from sugars,[10,11] from the amino acid, serine,[12−17] and from racemic precursors by a variety of asymmetric strategies.[18−22] In general, the most common and straightforward syntheses exploit serine derivatives, with routes from serine to the sphinganines generally being six or more steps. By contrast, our current approach to sphinganines **7** is a four-step, three-purification procedure from commercially available Boc-serine (Scheme 1).

SCHEME 1



Our initial plan for enhancing the efficiency of sphinganine synthesis was to circumvent the modest methylenation yield in our previous approach (i.e., conversion of **1** to **2**) by directly reacting lactone **1**, available in one step from Boc-serine,[23] with a Grignard or lithium reagent. Not unexpectedly, even with sub-stoichiometric amounts of the organometallic reagent, yields were low, and the product ketones were contaminated with difficult to separate tertiary alcohols. However, lactone **1** could be converted in high yield to Weinreb amide **4**. A literature search revealed that **4** could be prepared directly from Boc-serine.[24] In fact, using the method described, no purification of **4** was required. When **4** was treated with excess *n*-BuLi (3.5 equiv) at −78 °C, ketone **5a** was isolated in 67% yield. Reaction with excess, commercially available tetradecylmagnesium chloride

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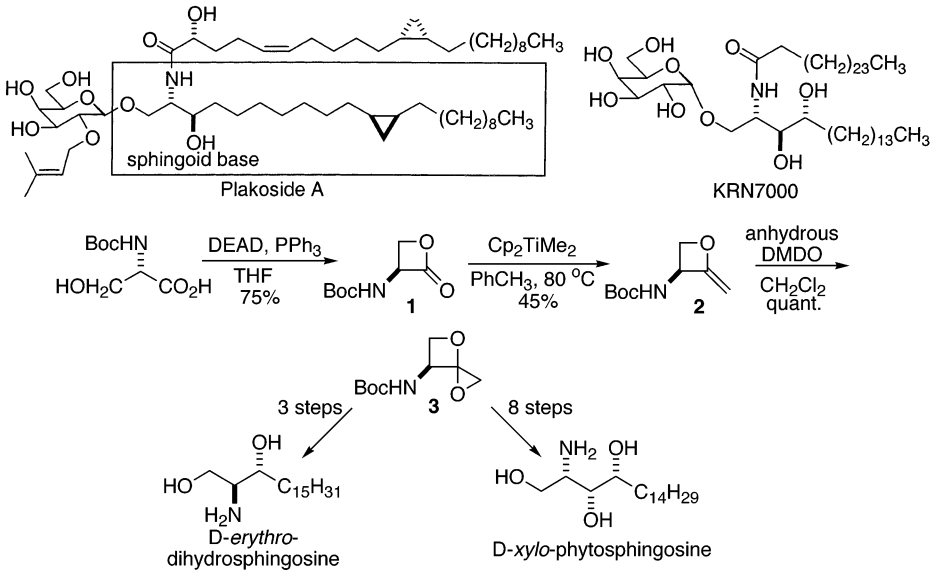
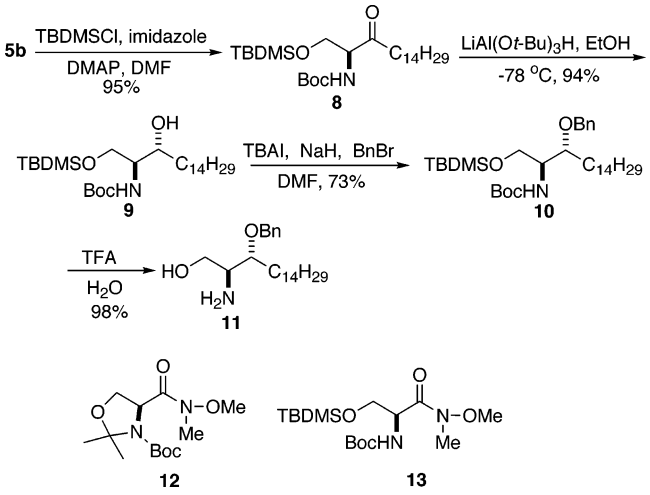


FIGURE 1. Sphingoid bases from serine-derived 1,5-dioxaspiro[3.2]hexane **3**.

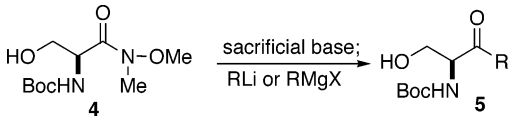
SCHEME 2



provided **5b** in 53% yield. However, the use of multiple equivalents of expensive or difficult to prepare organometallic reagents would be unacceptable. For our program of synthesizing glycosphingolipids, we had examined the use of a sacrificial lithium base (*t*-BuLi, 1.2 equiv) with partially protected Weinreb amide **13** (see Scheme 2). Subsequent addition of tetradecyllithium at −78 °C, followed by warming to rt, provided **8** in 44% yield. A recent report of the use of sacrificial Grignard reagents with Weinreb amides possessing Boc-amide substituents[25] prompted us to examine similar conditions with **4**, and herein, we report our straightforward approach to free and partially protected sphinganines **7** and **11**.

Weinreb amide **4** was treated with 2.0 equiv of either *n*-BuMgCl or *s*-BuMgCl at −15 °C, followed by the addition of the nucleophile. The solutions were then warmed to room temperature and stirred for 4 h. The results are shown in Table 1. The use of either *n*-BuMgCl

TABLE 1. Reactions of Serine-Derived Weinreb Amide 4 with Sacrificial Bases and Organometallic Reagents



entry	sacrificial base	RM (equiv)	product	% yield
1	*n*-BuMgCl	*n*-BuMgCl (1.2)	**5a**	69
2	*s*-BuMgCl	*n*-BuMgCl (1.2)	**5a**	71
3	*s*-BuMgCl	*n*-BuMgCl (1.9)	**5a**	82
4	*s*-BuMgCl	*n*-BuLi (1.2)	**5a**	80
5	*n*-BuLi	*n*-BuLi (1.2)	**5a**	70
6	*n*-BuMgCl	*n*-$C_{14}H_{29}$MgCl (1.2)	**5b**	63
7	*s*-BuMgCl	*n*-$C_{14}H_{29}$MgCl (1.2)	**5b**	70
8	*s*-BuMgCl	*n*-$C_{14}H_{29}$MgCl (1.9)	**5b**	78
9	*n*-BuLi	*n*-$C_{14}H_{29}$MgCl (1.2)	**5b**	66
10	*s*-BuMgCl	*n*-$C_{15}H_{31}$MgBr (1.2)	**5c**	73
11	*s*-BuMgCl	*n*-$C_{15}H_{31}$Li (1.2)	**5c**	<10[a]
12	*n*-BuLi	*n*-$C_{15}H_{31}$Li (1.2)	**5c**	12[a]

[a] See text.

or *s*-BuMgCl as the sacrificial base provided similar yields of product (entries 1 vs 2 and 6 vs 7). Unlike the outcomes observed in the studies of Liu et al.,[25] use of an organolithium agent as a sacrificial base did not give substantially lower yields (entries 4 vs 5 and 7 vs 9). Extended reaction times did not improve the yields. Higher yields were achieved with more nucleophile. Because of obvious concerns about alternative ketone products, we chose not to employ more than 2 equiv of the sacrificial base. Mass balance could be accounted for by recovered Weinreb amide **4**. When the deprotonation and nucleophilic addition were conducted at 0 °C, no product was isolated.

Unsatisfactory results were obtained with pentadecyllithium (entries 11 and 12), prepared from pentadecyliodide and excess *t*-BuLi, as desribed by Bailey and Punzalan.[26] Long-chain lithium reagents generated by the Bailey procedure can be used with compound **13** when the reaction is run at a lower temperature (−50 °C).

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The results shown in Table 1 demonstrate that predeprotonation of Weinreb amide **4** with an inexpensive sacrificial base provides efficient access to aminoketone precursors of sphinganines. The protocol is simple and avoids the use of large excesses of Grignard or lithium reagents that might be costly or difficult to prepare. As previously shown by Hoffman,[27] diastereoselective reduction of the protected aminoketones **5** is readily achieved, and deprotection completes the synthesis of the sphinganines **7**.

In glycosylations of ceramides it is common for the OH groups, other than the OH donor at C1 of the sphingoid base, to be protected. Differential protection of C1 and C3 of the sphingoid base can be achieved conveniently by protecting ketones **5**. For example, ketone **5b** was protected as the corresponding silyl ether **8** (Scheme 2). The reduction of **8** was highly stereoselective (only one diastereomer was observed in ^{1}H NMR's of crude reaction mixtures), and the hydroxyl group at C3 of **9** was benzylated. Both the silyl protecting group and the Boc-amide were cleaved upon treatment of **10** with aqueous TFA, providing the monoprotected sphinganine **11** efficiently.

In theory, the use of a sacrificial base would be unnecessary if **4** were converted to ketal **12**. Our results with **12** were consistent with those reported by Guanti and co-workers[28] in that, surprisingly, **12** did not react with long-chain organometallic reagents. It was also noteworthy that the silyl ether **13**, derived from **4** in high yield (94%), could be converted to ketone **8** with the use of only 1 equiv of a sacrificial base. However, we found that **8** (and the corresponding C-18 homolog) prepared by this procedure was contaminated with a small amount of an inseparable (and as yet unidentified) impurity.

In conclusion, sphinganines are found in an increasing variety of biologically important molecules. Weinreb amide **4**, readily accessible from serine, represents a versatile template for the efficient preparation of either unprotected or partially protected sphinganines. The use of a sacrifical Grignard or lithium reagent circumvents the need for full protection.

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Supporting Information Available: Experimental procedures and characterization data, as well as copies of high-resolution ^{1}H and ^{13}C NMR spectra for those new compounds for which elemental analyses are not reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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