ORGANIC LETTERS

2002
Vol. 4, No. 10
1719−1722

Synthesis of D-*erythro*-Dihydrosphingosine and D-*xylo*-Phytosphingosine from a Serine-Derived 1,5-Dioxaspiro[3.2]hexane Template

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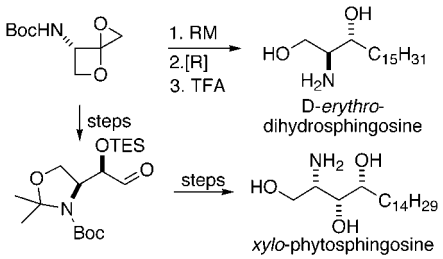
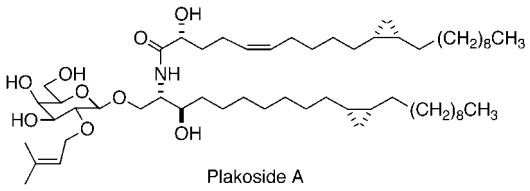
Received February 26, 2002

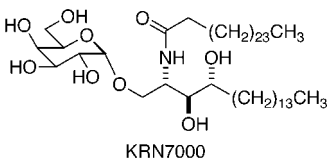
ABSTRACT



A serine-derived 1,5-dioxaspiro[3.2]hexane template is shown to be a useful precursor for both aminodiol and aminotriol sphingoid bases by its conversion to D-*erythro*-dihydrosphingosine and D-*xylo*-phytoshingosine.

Interest in glycosphingolipids has increased in recent years, in part due to the recognition that they 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] One of the most challenging aspects of synthesizing glycosphingolipids is the construction of the sphingoid base, the aminodiol or aminotriol, portion of the molecules. We have been interested in exploiting the reactivity and level of functionality housed in 1,5-dioxaspiro[3.2]hexanes,[8] a class of compounds whose preparation we pioneered.[9] We felt that serine-derived

(1) Merrill, A. H.; Sweeley, C. C. In *Biochemistry of Lipids, Lipoproteins and Membranes*; Vance, D. E., Vance, J., Eds.; Elsevier: Amersterdam, 1996; Vol. 31, pp 309−339.
(2) Hannum, Y. A. *Sphingolipid-Mediated Signal Transduction*; R. G. Landes Company: Austin, 1997.
(3) Porcelli, S. A.; Modlin, R. L. *Annu. Rev. Immunol.* **1999**, *17*, 297−329.
(4) Nicolaou, K. C.; Li, J.; Zenke, G. *Helv. Chim. Acta* **2000**, *83*, 1977−2006.
(5) Costantino, V.; Fattorusso, E.; Mangoni, A.; Di Rosa, M.; Ianaro, A. *J. Am. Chem. Soc.* **1997**, *119*, 12465−12470.
(6) Kawano, T.; Cui, J.; Koezuka, Y.; Toura, I.; Kaneko, Y.; Motoki, K.; Ueno, H.; Nakagawa, R.; Sato, H.; Kondo, E.; Koseki, H.; Taniguchi, M. *Science* **1997**, *278*, 1626−1629.
(7) Morita, M.; Motoki, K.; Akimoto, K.; Natori, T.; Sakai, T.; Sawa, E.; Yamaji, K.; Koezuka, Y.; Kobayashi, E.; Fukushima, H. *J. Med. Chem.* **1995**, *38*, 2176−2187.
(8) Howell, A. R.; Ndakala, A. J. *Org. Lett.* **1999**, *1*, 825−827.

10.1021/ol0200448 CCC: $22.00
Published on Web 04/18/2002

dioxaspirohexane **1** represented a versatile and novel template for the construction of diverse sphingoid bases, as illustrated in Figure 1.[10] In this Letter, the utility of **1** is demonstrated

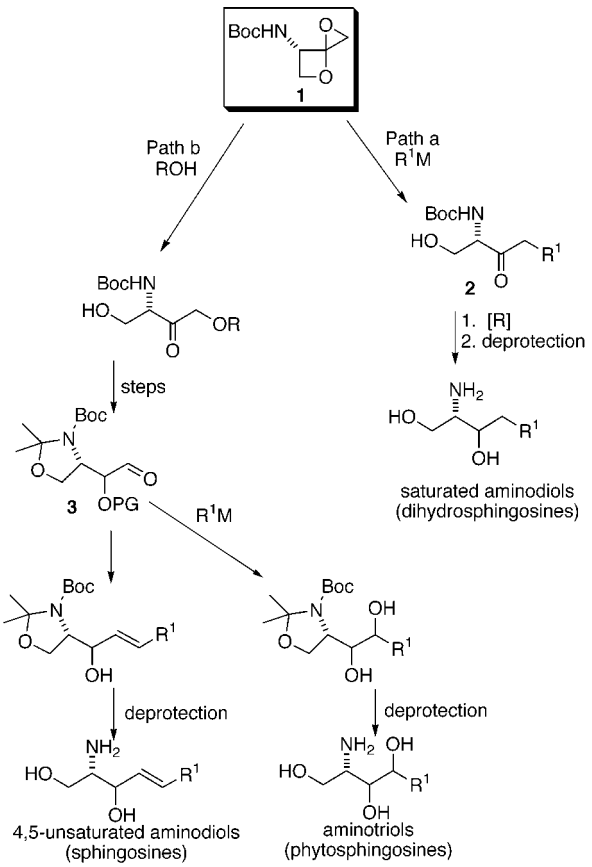


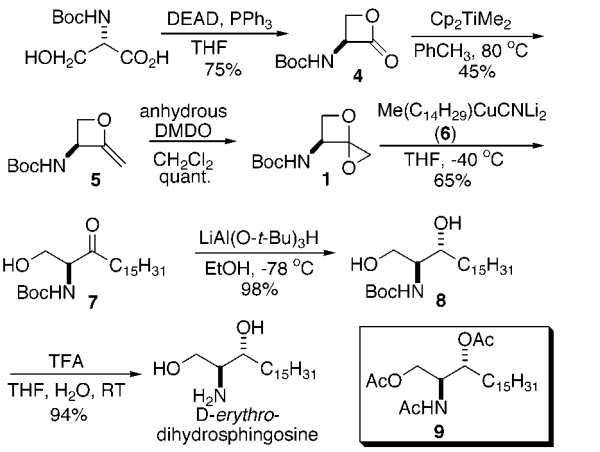
Figure 1. General strategy for sphingoid base synthesis from **1**.

by its conversion to D-*erythro*-dihydrosphingosine and D-*xylo*-phytosphingosine.

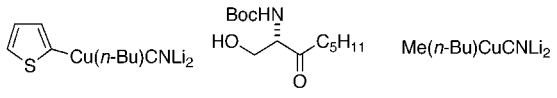
Our route to dioxaspirohexane **1** is shown in Scheme 1. We have previously described the preparation of this compound.[9] Thus, β-lactone **4** was secured from the protected serine under Mitsunobu conditions, as described by Vederas.[11] Methylenation provided **5**. Oxidation with dimethyldioxirane (DMDO) was quantitative and clean, and **1**[12] was used without further purification.

We felt that ring-opening of **1** by an appropriate organometallic reagent represented a particularly straightforward

Scheme 1



entry to aminodiol sphingoid bases (see Figure 1, path a). The ketones **2** produced by such reactions would need only stereoselective reduction and deprotection to provide dihydrosphingosines. To illustrate this, we prepared D-*erythro*-dihydrosphingosine, as shown in Scheme 1. Our first goal was to ascertain the appropriate organometallic reagent to effect the conversion of **1** to **7**. Not surprisingly, reaction of **1** with either organolithium or Grignard reagents led to complex mixtures, since the initial ketonic products appeared to be at least as reactive as **1**. Organocuprates are reported to be more effective than organomagnesium or organolithium reagents in opening oxiranes.[13,14] Reaction of **1** with the mixed higher order thienylcuprate **10**[15] gave **11** in 24% yield. When the mixed higher order alkyl cuprate **12** was used,[16] **11** was isolated in 43% yield. Gratifyingly, when mixed alkyl



cuprate **6** was employed, ketone **7** was isolated in 65% yield (Scheme 1). Stereoselective reduction of **7** with lithium tris(*tert*-butoxy)aluminum hydride[17] provided solely the *erythro*-diastereomer **8** in excellent yield, and treatment with TFA gave D-*erythro*-dihydrosphingosine. This was converted to the corresponding known triacetate **9** to confirm its identity.

We envisaged that both sphingosines and phytosphingosines could be procured from a protected aldehyde, such as

(9) Ndakala, A. J.; Howell, A. R. *J. Org. Chem.* **1998**, *63*, 6098−6099.

(10) Approaches to sphingosines (Koskinen, P. M.; Koskinen, A. M. P. *Synthesis* **1998**, 1075−1091. Curfman, D.; Liotta, D. *Methods Enzymol.* **2000**, *311*, 391−440) and phytosphingosines (Howell, A. R.; Ndakala, A. J. *Curr. Org. Chem.*, in press) have been recently reviewed. For recent syntheses of dihydrosphingosines, see: (a) Hertweck, C.; Sebek, P.; Svatos, A. *Synlett* **2001**, 1965−1967. (b) Fernandes, R. A.; Kumar, P. *Eur. J. Org. Chem.* **2000**, 3447−3449. (c) Azuma, H.; Tamagaki, S.; Ogino, K. *J. Org. Chem.* **2000**, *65*, 3538−3541. (d) Fernandes, R. A.; Kumar, P. *Tetrahedron: Asymmetry* **1999**, *10*, 4797−4802. (e) Villard, R.; Fotiadu, F.; Buono, G. *Tetrahedron: Asymmetry* **1998**, *9*, 607−611. (f) Hoffman, R. V.; Tao, J. *J. Org. Chem.* **1998**, *63*, 3979−3985.

(11) Pansare, S. V.; Arnold, L. D.; Vederas, J. C. *Org. Synth.* **1992**, *70*, 10−17.

(12) Compound **1** was isolated as a mixture of diastereomers (95/5). The identity of the major diastereomer is not known. Evidence (see ref 9) suggests that diastereoselectivity is largely sterically controlled. It is noteworthy that the diastereomeric ratio is inconsequential for the subsequent transformations of **1** in the applications described in this Letter.

(13) Lipshutz, B. H. *Synthesis* **1987**, 325−341.

(14) Posner, G. H. *Org. React.* **1975**, *22*, 253−400.

(15) Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945−948.

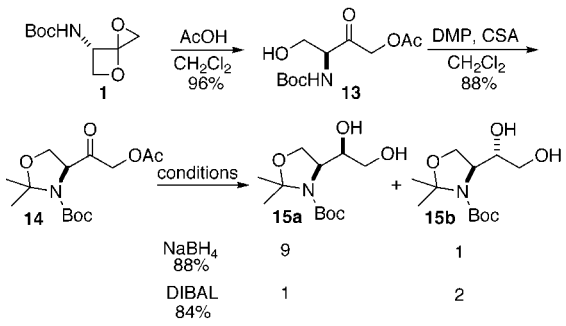
(16) Lipshutz, B. H.; Kozlowski, J. A.; Wilhelm, R. S. *J. Org. Chem.* **1984**, *49*, 3943−3949.

(17) Hoffman, R. V.; Maslouh, N.; Cervantes-Lee, F. *J. Org. Chem.* **2002**, *67*, 1045−1056.

3 (see Figure 1, path b). Such a species could undergo either olefination to yield sphingosines or provide phytosphingosines by reaction with an appropriate nucleophile. Obviously, in either case, diastereoselective control of reactions of **3** is crucial for the versatility of the template. Because of our interest in KRN7000, we decided to examine the utility of **1** as a precursor for phytosphingosines.

We had previously found that a variety of heteroatom nucleophiles opened 1,5-dioxaspirohexanes at the unhindered epoxide carbon to give α-functionalized-β′-hydroxyketones.[8] Acetic acid was employed to cleave **1** to ketol **13** (Scheme 2), because we had found the acetate functionality to be labile

Scheme 2



under the reductive conditions employed in converting **14** to **15**. Acetonide protection of **13** provided **14**. Initially, sodium borohydride was used to reduce **14** in very good yield (88%). The conversion of 2-methyleneoxetane **5** to diol **15** could be conducted without purification of the intermediates in an overall yield of 64%.

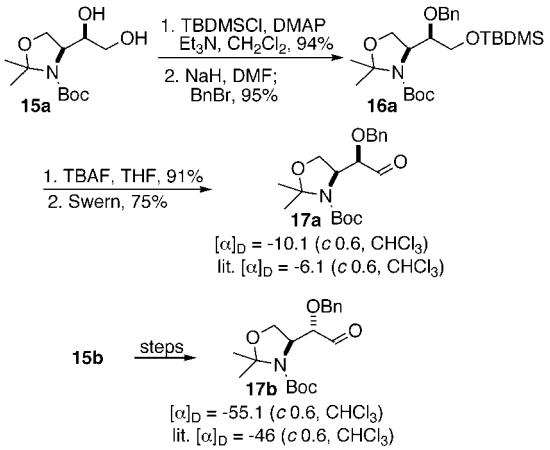
The reduction of **14** with sodium borohydride was stereoselective (diastereomeric ratio 9:1), and the diastereomers could be separated by careful chromatography. The C-2 epimer could be procured stereoselectively (2:1) with DIBAL. To unambiguously assign the absolute stereochemistry, compounds **15a** and **15b** were converted to known protected aldehydes **17a** and **17b**.[18] The sequence for the transformation of **15a** to **17a** is shown in Scheme 3. The optical rotation and the correlation of NMR spectroscopic data established that **15a** had the absolute stereochemistry shown at C-2. This was confirmed by the synthesis and characterization of **17b**.

Diastereomer **15a** was used to examine conditions for the preparation of a sphingoid base (see Scheme 4). Conversion to aldehyde **19** was based on literature precedent for selective oxidation of primary silyl (TMS or TES) protected alcohols in the presence of secondary silyl alcohols.[19] Thus, bis-TES protection provided **18**, which was oxidized under Swern conditions to aldehyde **19**. A nucleophilic addition of tetradecylmagnesium chloride to **19** at −10 °C provided a mixture of diastereomeric diols (major isomer **20a**: vide infra

(18) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *J. Org. Chem.* **1990**, *55*, 1439−1446.

(19) Rodriguez, A.; Nomen, M.; Spur, B. W.; Godfroid, J. J. *Tetrahedron Lett.* **1999**, *40*, 5161−5164.

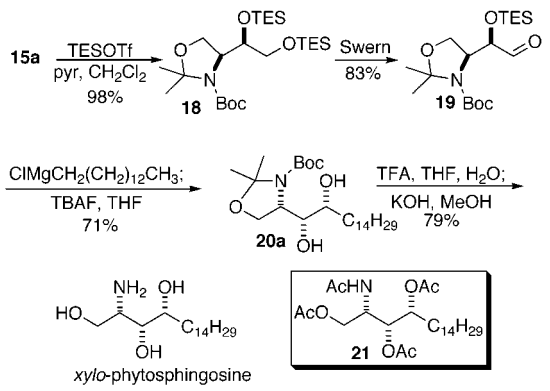
Scheme 3



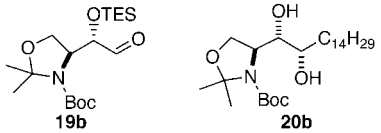
for discussion of determination of relative stereochemistry) in 71% yield. Due to conformational complications caused by restricted inversion at the nitrogen, the diastereomeric ratio could not be determined by ^{1}H NMR. However, global deprotection of the mixture with TFA/H_2O, followed by tetraacetylation, allowed us to ascertain the diastereomeric ratio (7:2) by ^{1}H NMR. An attempt to improve the diastereoselectivity by running the reaction at a lower temperature (−78 °C) was hampered by the reduced solubility of the Grignard reagent at temperatures below −20 °C. Nevertheless, when the Grignard reagent was added slowly to a solution of the aldehyde in THF at −78 °C and the resulting mixture was left to warm slowly to rt, the diastereoselectivity improved to 15:2. However, the yield was lower (61%).

Deprotection of **20** with TFA/H_2O, followed by treatment with KOH and recrystallization, provided *xylo*-phytosphingosine in 79% yield. Tetraacetylation gave **21**. The stereochemical outcome of the nucleophilic addition to aldehyde **19** was determined by comparison of the specific rotation and other physical data of tetraacetate **21** with the literature values of the four diastereomeric tetraacetates of 2*S*-phytosphingosine.[20] This assignment also confirmed our previous assignment of a *syn* stereochemistry to diol **15a**.

Scheme 4



The stereochemical outcome of the nucleophilic addition to aldehyde **19** can be ascribed to a significant level of chelate controlled addition of the Grignard reagent.[21] These results suggest that the C2 epimer of aldehyde **19** (**19b**) should provide predominantly the *lyxo*-diastereomer **20b**. Thus, alternative strategies will be required to access *ribo*- and *arabino*-phytosphingosine, and approaches to these compounds via **1** are under investigation.



In summary, we have shown that serine-derived dioxaspirohexane **1** can be readily converted to dihydrosphingosine and *xylo*-phytosphingosine. We believe that these preliminary results demonstrate that **1** represents a template of considerable potential for the preparation of biologically important dihydrosphingosines, phytosphingosines, and sphingosines, and further studies are underway to exploit this building block and expand its utility.

Acknowledgment. Helpful discussions with Nina Berova, Robert V. Hoffman, Bruce Lipshutz, and Robin Polt are gratefully acknowledged. A.R.H. thanks the NSF for a CAREER Award.

Supporting Information Available: Experimental procedures and characterization data, as well as copies of high-resolution ^{1}H and C ^{13}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.

OL0200448

(20) Shirota, O.; Nakanishi, K.; Berova, N. *Tetrahedron* **1999**, *55*, 13643−13658.

(21) Eliel and Frye and co-workers have shown (see: Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778−1784) that the addition of Grignard reagents to α-siloxy ketones proceeds via chelated transition states to varying degrees. However, there is evidence that TES ethers can participate in chelatation to a significant extent. Due to competing steric effects of the bulky BOC-protected oxazolidine and the TES ether, it would be anticipated that an open transition state would afford low levels of diastereoselectivity. The lower diastereoselectivity at −10 °C in comparison to that at −78 °C can be attributed to the reaction proceeding through a mixture of chelated and open transition states with reaction through the chelated intermediate predominating to a greater extent at the lower temperature.