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Synthesis of Pachastrissamine from Phytosphingosine: A Comparison of Cyclic Sulfate vs an Epoxide Intermediate in Cyclization

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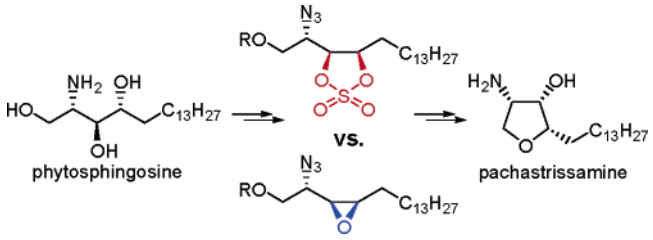
ABSTRACT



The syntheses of the cytotoxic natural product pachastrissamine and its unnatural 4-*epi*-congener were accomplished starting from a natural phytosphingosine. The relatively unstrained cyclic sulfate intermediate smoothly underwent the 5-*endo* cyclization to yield the 2,3,4-trisubstituted tetrahydrofuran ring system of pachastrissamine. The corresponding epoxy alcohol afforded the 4-*epi*-congener via a tosylate-mediated double inversion process.

Pachastrissamine (**1**, Figure 1) is an anhydrophytosphingosine derivative, which was initially isolated from a marine sponge *Pachastrissa* sp. in 2002 by Higa and co-workers.[1] Soon after, the same compound was isolated from a different marine sponge *Jaspis* sp. and named jaspine B by Debitus and co-workers.[2] This marine natural product exhibits a high cytotoxic activity against various tumor cell lines in vitro.[1,2]

Pachastrissamine possesses three contiguous stereogenic centers in the tetrahydrofuran core. The three substituents on the tetrahydrofuran ring of **1** are also observed identically on the C-2 to C-4 carbon frame of the typical sphingoid base D-*ribo*-phytosphingosine (**2**, Figure 1). The hydroxyl group at C-4 of **2** possesses the opposite absolute configuration, and it indicates that **2** is very likely the biosynthetic precursor to pachastrissamine (**1**) via an intramolecular O-alkylation with inversion of the stereochemistry at C-4.

The novel structural features and interesting biological activity of pachastrissamine have prompted extensive syn-

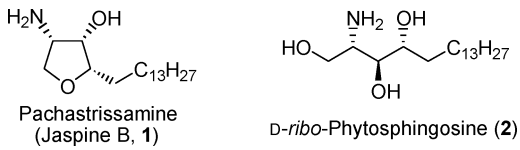


Figure 1. Chemical structures of compounds **1** and **2**.

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thetic efforts from a number of laboratories.[3,4] Most of the reported synthetic approaches have utilized simple chiral building blocks, such as serine and xylose, as the starting materials. The structurally more related **2** has also served as a starting material for the synthesis of **1**.[3e]

We recently reported a practical preparative route of D-*erythro*-sphingosine synthesis from the low-cost phytosphingosine **2** via the cyclic sulfate intermediate **3** in Figure 2.[5] We envisioned that the cyclic sulfate **3** could also serve

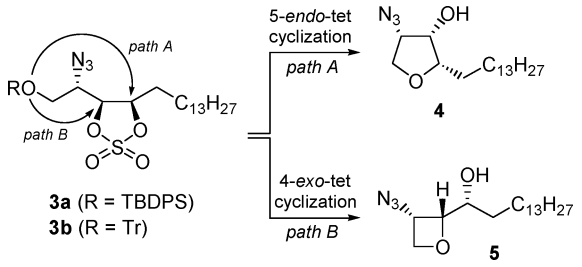


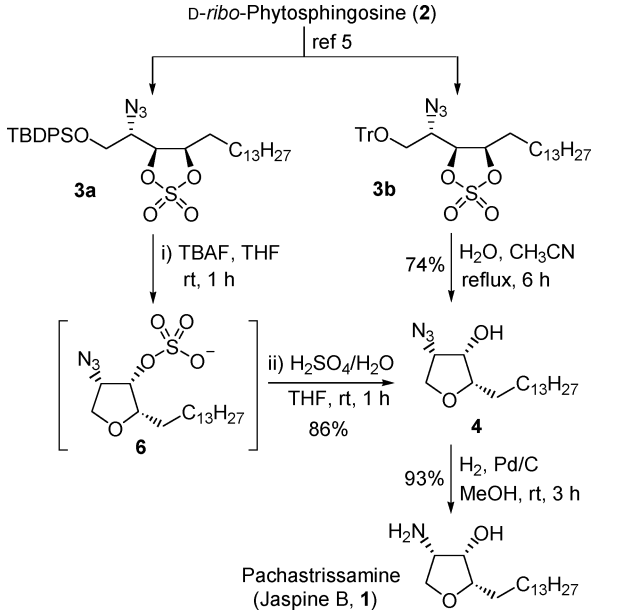
Figure 2. Intramolecular opening of cyclic sulfate **3**.

as a key intermediate for the synthesis of pachastrissamine via a 5-*endo* cyclization. Herein, we wish to report our studies on this subject.

Cyclic sulfate is like epoxide but much more reactive,[6] and many synthetic applications have appeared in the literature due to its beneficial properties.[7] Cyclic sulfates have been used as intramolecular O-alkylation substrates for the construction of tetrahydrofuran rings.[8] The ring opening of cyclic sulfate **3** may occur in either a 4-*exo*-tet or 5-*endo*-tet fashion as shown in Figure 2. The 5-*endo* cyclization would result in the formation of the desired 2,3,4-trisubstituted tetrahydrofuran ring system of pachastrissamine. Although the intramolecular cyclization of tetrahedral systems generally proceeds via an *exo*-cyclization pathway,[9] Sharpless has demonstrated that the relatively unstrained cyclic sulfate could permit 5-*endo* cyclization in preference to 4-*exo* cyclization.[8d]

With these perspectives, we set out to study the transformation of cyclic sulfate **3** into pachastrissamine (**1**). Cyclic sulfate **3** was easily prepared from D-*ribo*-phytosphingosine (**2**) in high overall yield as described in our previous work.[5] Because it has been reported that 1-*O*-silyl-2,3-cyclic sulfate can be directly converted to 1,2-epoxy-3-sulfate upon deprotection of the silyl protecting group,[10] we anticipated that the in situ desilylative cyclization of **3a** would lead to the formation of the desired tetrahydrofuran core. To our delight, the reaction of cyclic sulfate **3a** with *n*-Bu_4NF (TBAF) in THF at room temperature led, after hydrolysis of the resulting sulfate ester intermediate **6** with aqueous sulfuric acid, to the formation of the desired *endo*-cyclization product **4** as the only detectable isomer in 86% yield (Scheme 1). No *exo*-

Scheme 1. Synthesis of Pachastrissamine (**1**)



cyclization product **5** was detected in the crude ^{1}H NMR spectra. The relative stereochemistry of **4** was determined by its conversion to the final natural product **1** as discussed later.

Alternatively, the trityl ether **3b** was able to afford the same cyclized product **4** as a single isomer (74% yield) by refluxing in CH_3CN with 50 equiv of H_2O (Scheme 1). The free alcohol **4** was isolated directly from the reaction instead of the sulfate ester intermediate **6**, presumably due to the autocatalytic hydrolysis process in the course of the reaction.[11]

The azide moiety of **4** was reduced to an amine by hydrogenation in the presence of Pd/C in MeOH to give a

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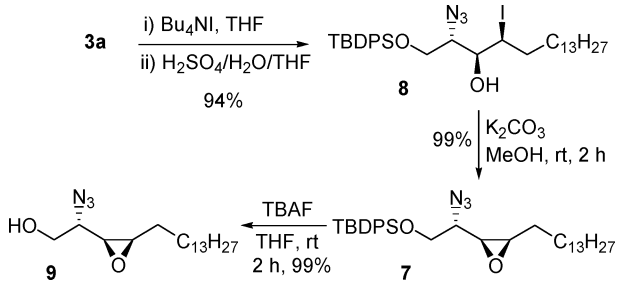
(10) Ko, S. Y.; Malik, M.; Dickinson, A. F. *J. Org. Chem.* **1994**, *59*, 2570−2576.

(11) The similar cyclization and autocatalytic hydrolysis of sulfate ester have been described previously. See ref 8c.

93% yield of pachastrissamine (**1**), a white solid. The analytical and spectroscopic data of both the synthetic **1** and its diacetate derivative[12] were identical to those reported, thereby confirming the 5-*endo* cyclization of **3** with accompanied inversion of the stereochemistry at C-4.

Although cyclic sulfates and epoxides are often regarded as synthetic equivalents, they display different chemical behaviors in many cases, particularly in terms of selectivity in ring-opening reactions with nucleophiles.[7] Therefore, we were interested in comparing the chemistry of cyclic sulfate **3** with that of the corresponding epoxide. The epoxide **7** was obtained from the cyclic sulfate **3a** in high overall yield in the following manner. The regioselective nucleophilic ring opening of the cyclic sulfate **3a** by iodide in THF followed by an acidic hydrolysis of the intermediate *O*-sulfate provided the iodo alcohol **8** as the single regioisomer in 94% yield.[5] Treatment of the iodo alcohol **8** with K_2CO_3 in MeOH afforded the desired epoxide **7** in nearly quantitative yield (Scheme 2).

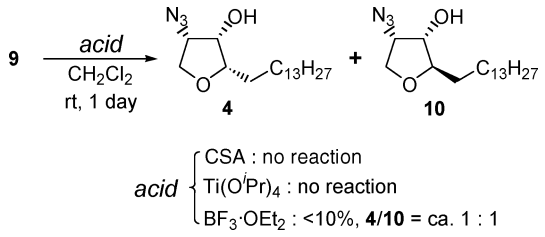
Scheme 2. Synthesis of Epoxdes **7** and **9**



With the epoxide **7** in hand, we investigated the intramolecular cyclization. Unlike the corresponding cyclic sulfate **3a**, the epoxide **7** did not undergo the spontaneous desilylative cyclization upon treatment with TBAF at room temperature. Instead, the epoxy alcohol **9** was obtained in nearly quantitative yield (Scheme 2). The formation of the tetrahydrofuran product was not detected even at elevated temperatures. This can be ascribed to the relatively lower reactivity of epoxide compared to that of cyclic sulfate in ring-opening reactions under the basic reaction conditions. Our attempts at accomplishing the possible 5-*endo* or 4-*exo* cyclization of the epoxy alcohol **9**, using various bases such as NaH, NaOMe, and KHMDS, were not successful and provided either unreacted starting material or decomposed material without forming any detectable cyclized products.

Because the Lewis acid catalyzed intramolecular cyclization of epoxy alcohols is the general and popular method for constructing cyclic ethers,[13] the epoxy alcohol **9** was subjected to the acid-catalyzed cyclization conditions. Upon exposure of **9** to a catalytic amount of camphorsulfonic acid (CSA) or $Ti(O^iPr)_4$ in CH_2Cl_2 at room temperature, only unreacted starting material was recovered. On the other hand, the treatment of **9** with a catalytic amount of $BF_3{\cdot}Et_2O$ (0.1 equiv) in CH_2Cl_2 at room temperature for 1 day led to rather complex mixtures of products containing an inseparable mixture of the all-*syn* tetrahydrofuran ring product **4** and its 4-*epi*-congener **10** in ca. 1:1 ratio in very low yield (<10%) (Scheme 3). No oxetane product was detected by careful ^1H

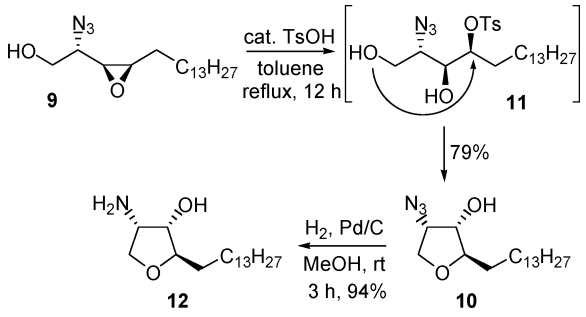
Scheme 3. Acid-Catalyzed Intramolecular Cyclization of Epoxy Alcohol **9**



NMR analysis of the reaction mixture. The low yield obtained was possibly due to adventitious hydrolysis of the epoxide or other undetermined reactions. More systematic studies would be needed to elucidate the cause of the scrambled stereochemistry at C-4 of 5-*endo* cyclized products. However, these observed results were not surprising in view of the generally accepted disfavored 5-*endo*-tet cyclization mode and denote the unfavorable 5-*endo* ring closures of epoxy alcohol **9**.

Interestingly, treatment of **9** with a catalytic amount of *p*-toluenesulfonic acid (TsOH, 0.1 equiv) in refluxing toluene produced the 4-*epi*-isomer **10** as the only detectable product in 79% yield (Scheme 4). The stereochemical outcome of

Scheme 4. Synthesis of *epi*-Pachastrissamine (**12**)



this reaction can be explained by reasoning that initial opening of the epoxide ring of **9** with TsOH could provide the α-hydroxy tosylate **11**,[14] which was followed by displacement of the tosylate by the terminal hydroxyl group to

(12) The spectroscopic data of pachastrissamine diacetate were reported in the literature. See refs 1, 2, 3a, and 3e.

(13) (a) Narayan, R. S.; Borhan, B. *J. Org. Chem.* **2006**, *71*, 1416−1429. (b) Koert, U. *Synthesis* **1995**, 115−132. (c) Mukai, C.; Sugimoto, Y.-i.; Ikeda, Y.; Hanaoka, M. *J. Chem. Soc., Chem. Commun.* **1994**, 1161−1162. (d) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309−3362.

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give rise to the tetrahydrofuran ring closure with a net retention of the stereochemistry. Indeed, we were able to isolate the rather unstable α-hydroxy tosylate intermediate **11** from the reaction mixture when the reaction was performed at room temperature with 1.2 equiv of TsOH, which is a strong support for the proposed mechanism. To our knowledge, the direct one-pot oxacyclic ring formation from epoxy alcohol via a tosylate-mediated double inversion process has not yet appeared in the literature, and we believe our result could constitute the first example. The relative stereochemistry of **10** was later confirmed by its conversion to 4-*epi*-pachastrissamine (**12**) by hydrogenation in the presence of Pd/C in MeOH (94%). The 4-*epi*-pachastrissamine (**12**) is known in the literature as a derivative of a plant metabolite,[15] of which the absolute stereochemistry has been determined by synthesis in a later work.[16]

In conclusion, here we describe a synthesis of the cytotoxic natural product pachastrissamine and its unnatural 4-*epi*-congener from natural phytosphingosine. We found that a relatively unstrained cyclic sulfate intermediate **3** smoothly converted to the all-*syn* tetrahydrofuran ring product via a 5-*endo* cyclization mode, whereas the corresponding epoxy alcohol cyclized in only poor yield and selectivity principally due to the unfavorable energetics of 5-*endo* ring closures. This study offered an opportunity for direct comparison of cyclic sulfate vs epoxide in intramolecular substitution with an oxygen nucleophile and showed cyclic sulfate is superior to epoxide in 5-*endo* cyclization to afford the substituted tetrahydrofuran. In addition, we observed the tosylate-mediated direct one-pot tetrahydrofuran ring formation of epoxy alcohol with double inversion. We believe this hitherto unreported process might increase the repertoires of chemical transformations of epoxy alcohol after further studies.

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Supporting Information Available: Full experimental procedures and analytical data of compounds and copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **1**, **4**, **7**, and **9**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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