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Total Synthesis of Cytotoxic Anhydrophytosphingosine Pachastrissamine (Jaspine B)

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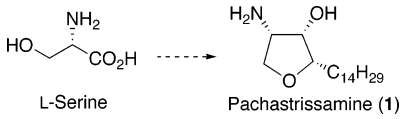
ABSTRACT



Starting from L-serine, a stereoselective synthesis of pachastrissamine, a structurally novel anhydrosphingosine derivative, is reported in this Letter.

Pachastrissamine (**1**, Figure 1), a naturally occurring novel anhydrosphingosine derivative, has been isolated recently from the Okinawan marine sponge *Pachastrissa* sp.[1] Shortly thereafter, another research group reported the isolation of the same natural product from a different marine sponge, *Jaspis* sp., and named it as jaspine B.[2] The all-*syn* trisubstituted tetrahydrofuran structural framework and the (2*S*,3*S*,4*S*) absolute configuration of pachastrissamine (and jaspine B) was assigned on the basis of high-resolution NMR, mass spectral analysis, and chemical derivatization studies. Pachastrissamine represents the first example of an anhydrosphingosine structural feature in a natural product. In anticancer assays, this novel sphingosine derivative exhibited submicromolar cytotoxic activity against several human cancer cell lines.[1,2] The impressive biological activity, novel structural features, and the lack of any total synthesis/structure−activity relationship (SAR) studies on pachastrissamine encouraged us to undertake a stereoselective total synthesis of this interesting natural product. Accordingly, starting from the natural amino acid L-serine and following the strategy as shown below (Figure 1), we report herein a total synthesis of pachastrissamine.

Enantiopure aminobutenolide **3**, easily obtainable from L-serine by a recently developed method from our laboratories,[3] represents the key chiral template for our desired synthesis. We envisioned that deprotection of the *N*,*O*-acetonide linkage of **3** and subsequent Michael addition of the resulting primary hydroxy group into the β-carbon of the butenolide will result in the bicyclic lactone **2** as shown (Figure 1). Stereselective formation of the *cis*-fused bicyclic system **2** is predicted as a result of the highly unfavorable ring strain associated with the alternative *trans*-ring junction between the two five-membered rings. Standard functional group transformations involving the right-hand side lactone moiety is expected to complete the synthesis of the desired

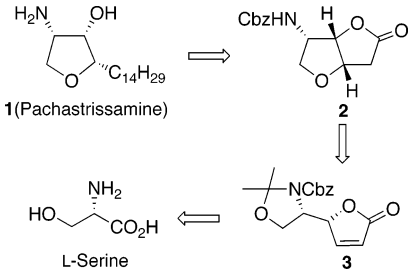


Figure 1. Pachastrissamine and retrosynthetic analysis.

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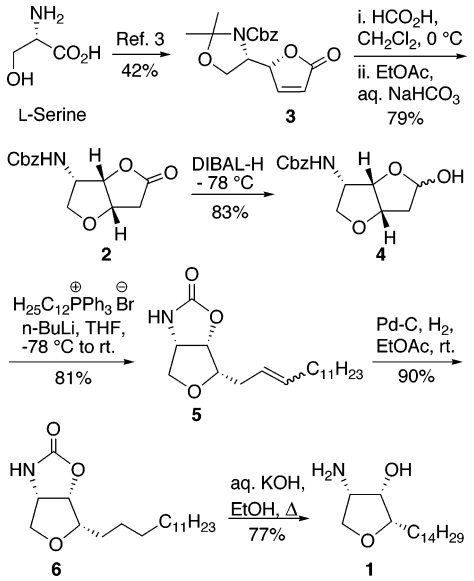
all-*syn* tetrahydrofuran natural product **1**. Details of the studies thus undertaken are described below.

Starting from L-serine and following a recently developed protocol,[3] the chiral lactone **3** (Scheme 1) was prepared in

Scheme 1



42% overall yield. Attempted hydrolysis of the *N*,*O*-acetonide linkage of **3**, followed by treatment of the crude product with aqueous bicarbonate, directly afforded the bicyclic lactone **2** as the only product. The assigned stereochemistry and the all-*syn* relationship between the three contiguous asymmetric centers as present in **2** were confirmed on the basis of NOE studies.

As per our expectations, the favorable energetics involved in the *cis*-fused [5,5] bicyclic ring forming reaction during the above intramolecular Michael addition contributed to the exclusive formation of product **2**. Toward introduction of the required tetradecyl side chain, the carbonyl group of the lactone **2** was partially reduced to afford the lactol derivative **4**. Standard Wittig olefination of the lactol with a C-12 alkyl donor resulted in the incorporation of an inseparable mixture of *E*- and *Z*-isomers of the corresponding C-14 olefinic side chain. Interestingly, the C_3-secondary oxyanion, generated during the opening of the lactol, underwent spontaneous intramolecular addition to the favorably disposed C_4-*N*Cbz-carbonyl group, resulting in the concomitant formation of the cyclic carbamate-protected tetrahydrofuran derivative **5**. Hydrogenation of the side chain double bond uneventfully afforded the desired saturated derivative **6** in high yield. Finally, alkaline hydrolysis of the cyclic carbamate culminated in an efficient synthesis of pachastrissamine (**1**). The spectral and analytical data of **1** were in good conformity with the reported values,[2] thereby confirming its structural and stereochemical integrity.

In conclusion, utilizing a chiral pool strategy involving serine, the stereoselective total synthesis of a structurally unique bioactive anhydrosphingosine natural product has been achieved. A key step in the synthesis involves the facile formation of the bicyclic lactone **2** via an intramolecular conjugate addition process. Interestingly, the tetrahydrofurofuranone structural core as present in **2** is found in several natural products such as goniofufurones,[4] lactonamycin,[5] delesserine,[6] dilaspirolactone,[7] etc. Consequently, development of methods for the efficient construction of similar structural frameworks and their further application is an active area of research.[8] Additionally, as demonstrated in the present research, the bicyclic lactone core of **2** can be utilized as a versatile synthon toward accessing variously substituted chiral tetrahydrofurans, a frequently encountered heterocyclic core of considerable biological importance.[9] It is expected that, besides achieving an efficient total synthesis of pachastrissamine, possible application of the strategy and the approach described in the present study will also be of potential use toward rapid synthesis of functionalized tetrahydrofurans of contemporary interest.[10]

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Supporting Information Available: Full experimental procedures, characterization data of all new products, and copies of NMR (^{1}H and ^{13}C) spectra of compounds **2**, **4**, **5**, **6**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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