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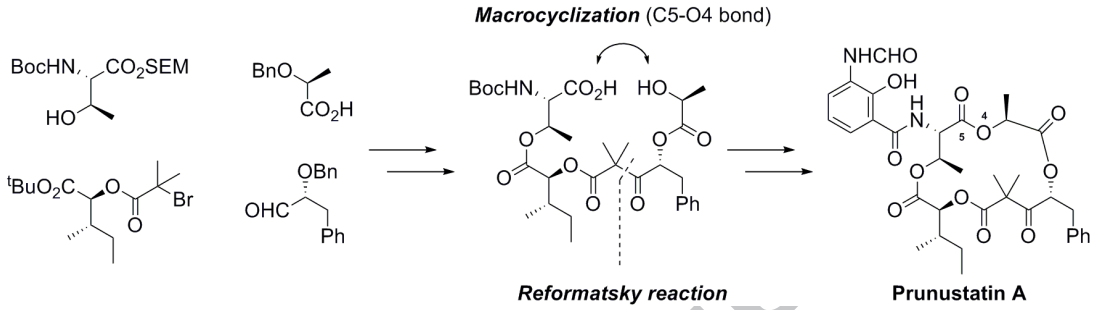

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First total synthesis of prunustatin A

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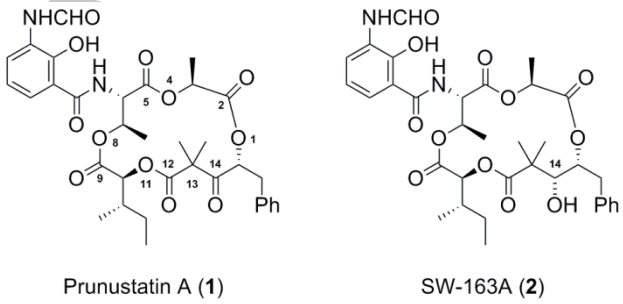
ABSTRACT

In this study, we achieved the first total synthesis of natural prunustatin A (**1**), a novel inhibitor of glucose-regulated protein 78 (GRP78) expression. A key feature included a 15-membered ring macrocyclization, which was successfully accomplished by employing Shiina macrolactonization using 2-methyl-6-nitrobenzoic anhydride (MNBA) and 4-dimethylaminopyridine (DMAP).

Prunustatin A (**1**) has been isolated from *Streptomyces Violaceoniger* 4521-SVS3 as a novel inhibitor of glucose-regulated protein 78 (GRP78) expression.[1,2] The absolute structure of **1** was determined by Shin-ya *et al.* in 2007 (Fig. 1).[3] The structure of **1** closely resembles that of neoantimycin family SW-163A (**2**),[3] including a 15-membered macrocycle and 4 ester groups.

GRP78 acts as a molecular chaperone in the endoplasmic reticulum (ER) to promote protein folding. Recently, it was reported that GRP78 contributes to tumor growth, resistance of cancer cells to chemotherapy, and hypoglycemic stress in solid tumors.[4] GRP78 is also utilized as a novel predictive biomarker to guide physicians in choosing the appropriate treatment for patients.[5] Recent discoveries about the role of GRP78 expression in cancer cells have led to the development of new therapeutic approaches targeted against cancer. In this letter, we report the first total synthesis of prunustatin A (**1**) to confirm its absolute stereochemistry.



Prunustatin A (**1**) SW-163A (**2**)

Figure 1. Structure of prunustatin A (**1**) and SW-163A (**2**).

Our retrosynthetic analysis of compound **1** is shown in Scheme 1. We decided to construct the 15-membered ring by using macrolactonization of precursor **5**, which would be prepared from esterification of compounds **6** and **7**. The strategy for the construction of the 15-membered ring involve a key step, i.e., selection of the O4–C5 bond from four cyclized points (O1–C2, O4–C5, O8–C9, and O11–C12) as appropriate macrocyclization in precursor **5**, based on a conformational search and molecular dynamics (MD) simulations using MOE.[6] Firstly we calculated conformations against four precursors corresponding to cyclized points (O1–C2, O4–C5, O8–C9, and O11–C12) with LowModeMD method. Secondary we selected each the most stable conformation, and then conducted MD simulations for 2 ns at 320K against four precursors having the most stable conformation respectively. In this simulation, tetrahydrofuran molecules were soaked within 20Å of the center of a compound to set up a virtual macrocyclization reaction condition. The calculated simulations confirmed that the shortest distance of O4–C5 was 1.35Å, and the result would be more promising than other bonds.[7] Following, compound **6** was expected to be obtained by the Reformatsky reaction of bromide **9** and α-benzyloxyaldehyde **10**, followed by esterification of β-ketoester **8** and alcohol **7**.

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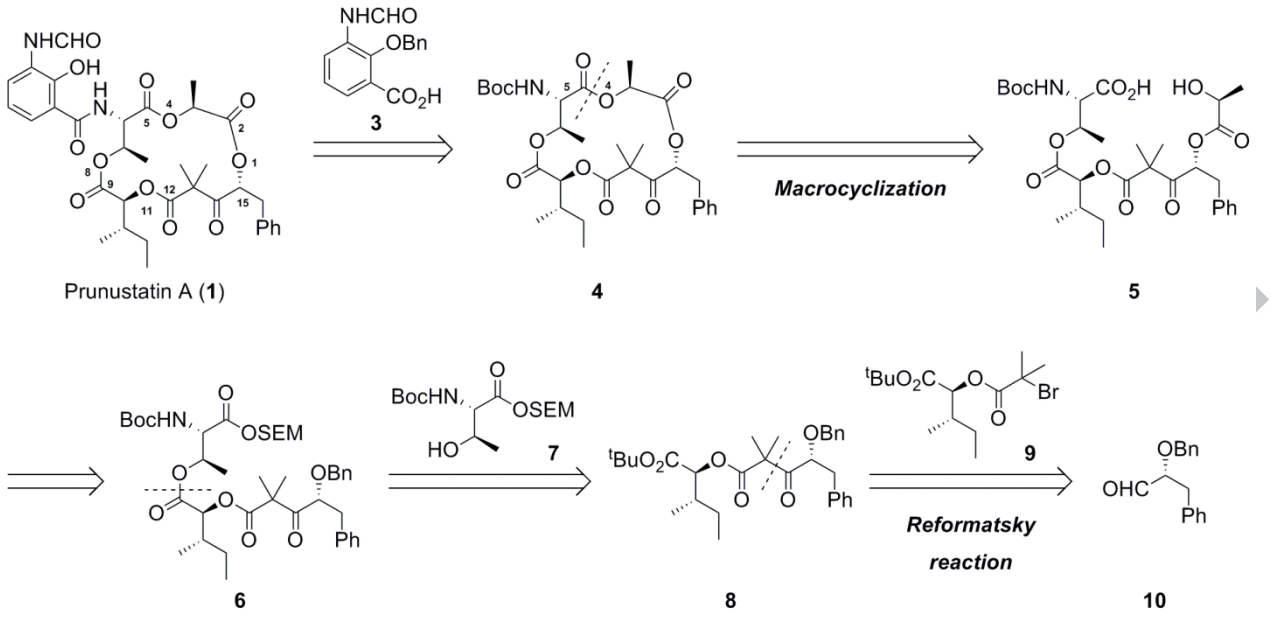
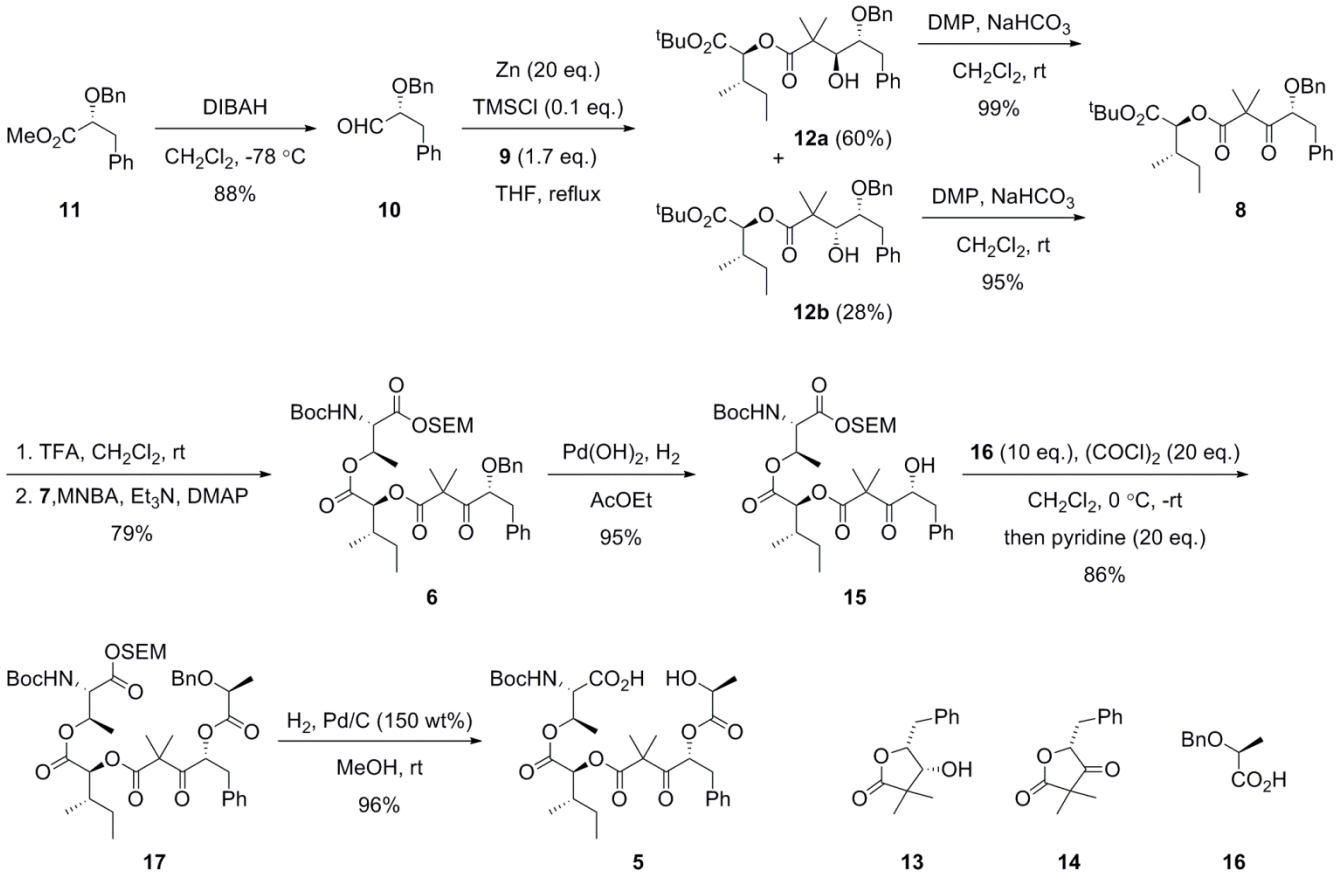


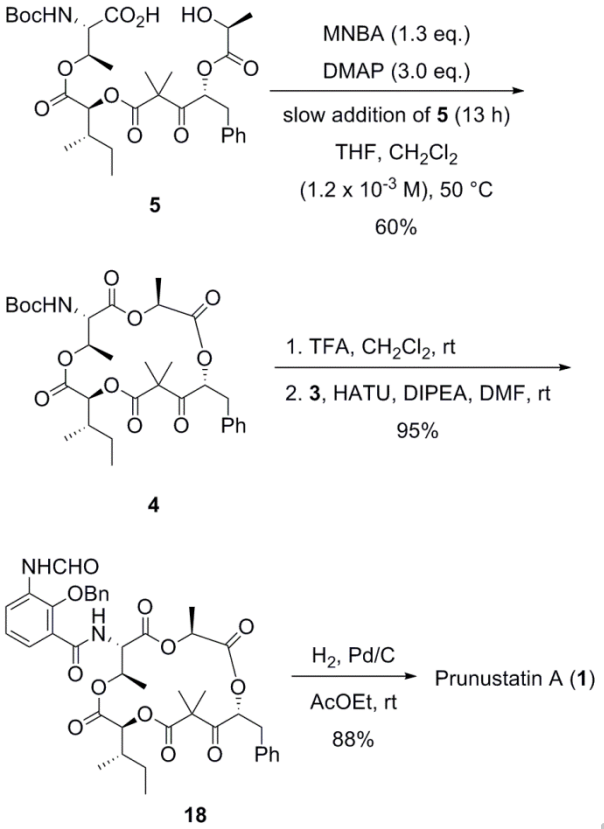
Scheme 1. Retrosynthetic analysis of Prunustatin A.

The Reformatsky reaction of bromide **9**[8] and α-benzyloxyaldehyde **10**,[9] prepared from methyl α-benzyloxyphenyllactate **11**[10] by reduction with diisobutylaluminium hydride (DIBAL-H) in 88% yield, afforded two alcohols *S*-isomer (**12a**) and *R*-isomer (**12b**) in 60% and 28% yield, respectively. Each stereochemistry was determined by conversion of **12b**[3, 11] to the lactone **13**. The next oxidation of both **12a** and **12b** using Dess–Martin periodinane (DMP) obtained the same product **8** in high yield (99% and 95%). In the preliminary study, deprotection of the benzyl group in **8** was attempted. However, the desired alcohol was not obtained. In this reaction, 5-membered lactone **14** was produced exclusively. This was probably because the lactonization proceeded by the proximity of O1 to C12 under the Thorpe–Ingold effect of dimethyl substituents on C13.[12] The introduction of *S*-benzyloxylactate **16** at O1 was conducted after modification of *tert*-butylester of **8**. *tert*-Butylester in **8** was deprotected by trifluoroacetic acid (TFA); subsequently, the esterification



Scheme 2. Synthesis of the precusor **5**.

reaction of the L-threonine derivative **7**,[13] possessing an 2-



Scheme 3. Total synthesis of prunustatin A (**1**).

(trimethylsilyl)ethoxymethyl (SEM) group, with 2-methyl-6-nitrobenzoic anhydride (MNBA), triethylamine, and 4-dimethylaminopyridine (DMAP) afforded **6** in 79% yield. The benzyl group of **6** was removed using Pearlman's catalyst to provide **15** in 95% yield. First, an esterification reaction of **15** using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) or *N,N′*-carbonyldiimidazole (CDI) was attempted. The desired **17** was not obtained, although 5-membered lactone **14** was observed. Meanwhile, an esterification reaction of **15** using an excess amount of acid chloride of *S*-benzyloxylactate **16**[14] afforded **17** in 86% yield without the production of lactone **14**. Deprotection of the benzyl group in **17** achieved by hydrogenation with a stoichiometric amount of palladium on carbon afforded the macrocyclization precursor **5** in 96% yield, in which cleavage of the SEM ether took place simultaneously[15] (Scheme 2).

Although a large number of methods are available for macrolactonization reactions, those most commonly employed include the Corey–Nicolaou,[16] Yamaguchi,[17] and Shiina[18] lactonization procedures. Firstly compound 5 was subjected to macrolactonization under Yamaguchi's condition, however, the product was only diolide. In this study, macrocyclization of **5** was smoothly achieved by treatment with MNBA and DMAP at 50°C under high dilution (1.2×10^{-3} M) and slow addition (13 h) of **5**, affording **4** in 60% yield. After deprotection of **4**, condensation of the amine derivative with 3-aminosalycilic moiety **3**[19] using *O*-(7-azabenzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate (HATU) afforded **18** in 95% yield. Finally, reductive removal of the benzyl group using palladium on carbon provided prunustatin A (**1**) in 88% yield (Scheme 3). The spectral data (^{1}H and ^{13}C NMR) of the synthetic **1** were identical to those reported for the natural product **1**.[1,3] The specific rotation of the synthetic **1** ($[\alpha]_D^{28}$ +35.2, *c* 0.21, chloroform) agreed with natural sample ($[\alpha]_D^{27}$ +21.2, *c* 0.01, chloroform).[1] Thus, the first total synthesis of prunustatin A (**1**) was achieved in 11 synthetic steps from the known aldehyde **10**.

In conclusion, we successfully performed the first total synthesis of prunustatin A (**1**) via the Reformatsky reaction followed by macrocyclization with Shiina's protocol. The macrocyclization precursor was successfully selected by studying its conformation on the basis of molecular dynamics. The bioactivity of prunustatin A is currently being investigated.

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Supplementary data

Supplementary data associated with this article can be found in the online version.

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