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Formal synthesis of schulzeines B and C

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ABSTRACT

A formal synthesis of schulzeines B and C, marine natural products with inhibitory effect against α-glucosidase, has been achieved. The key reactions of the synthesis are *N*-acyliminium ion cyclization, Sharpless asymmetric dihydroxylation, olefin cross metathesis, and asymmetric allylboration.

1. Introduction

Schulzeines A–C (**1**–**3**) are marine natural products isolated from Japanese sponge, *Penares schulzeii*.[1] These natural products exhibit potent activity against α-glucosidase, an enzyme, which plays pivotal roles in carbohydrate metabolism and cell cycle.[1,2] This intriguing biological activity renders them potential leads for medicinal investigation for treatment of various diseases, such as diabetes, cancers, and viral infections. There have been several synthetic studies[3] of these natural products resulting in three total syntheses of schulzeines B and C[4,5] and one total synthesis of schulzeine A.[5] We have reported a synthesis of the 9,11-dimethyl ether of the tricyclic core of schulzeines utilizing *N*-acyliminium ion cycliaztion.[3a,b] Herein we present a formal synthesis of schulzeines B and C featuring *N*-acyliminium ion cyclization, Sharpless asymmetric dihydroxylation, asymmetric allylboration and olefin cross metathesis as key reactions (Fig. 1).

Our retrosynthetic analysis of schulzeines, as shown in Scheme 1, divides the molecule into two major subunits, namely, the tricyclic core **4** and 28-carbon fatty acid side chain **5**. The tricyclic core **4** could be obtained from intramolecular cyclization of *N*-acyliminium ion **6**, which in turn could be prepared from arylethylamine **7** and benzylated glutamic acid **8**. The 28-carbon fatty acid side chain would be constructed from benzyl 11-dodecenoate (**9**)[6] and C12–C28 subunit **10** via olefin cross metathesis. The

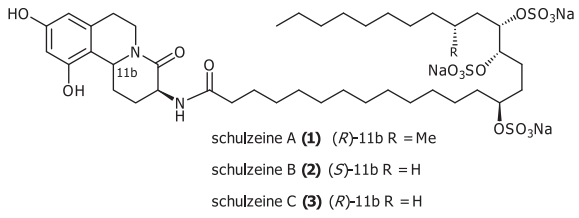

Fig. 1. Schulzeines A–C.

subunit **10** possessing three stereogenic centers at C14, 17, and 18 would be derived from asymmetric allylboration of C14-aldehyde **11**. The C17–18 protected diol functionality could be installed by Sharpless asymmetric dihydroxylation of alkene **12**.

2. Results and discussion

Synthesis of the tricyclic core **4** began with known 2-(3,5-dibenzyloxyphenyl)ethylamine (**7**),[7] prepared in five steps from 3,5-dihydroxybenzoic acid (Scheme 2). This amine was coupled with L-glutamic acid derivative **8** to give amide **13** in good yield. Treatment of this amide with lithium aluminum hydride gave imide **14**.[8] DIBAL-H reduction of the imide occurred selectively at the less hindered carbonyl group to give hydroxylactam **15**.[9] Subsequent treatment of this compound with TMSOTf yielded the protected tricyclic core **16** of schulzeines as an inseparable mixture of two diastereomers at C11b. This mixture was converted into *N*-Boc-carbamates **17a** and **17b** (ca. 3:1) and the two diastereomers were readily separable by flash chromatography and their

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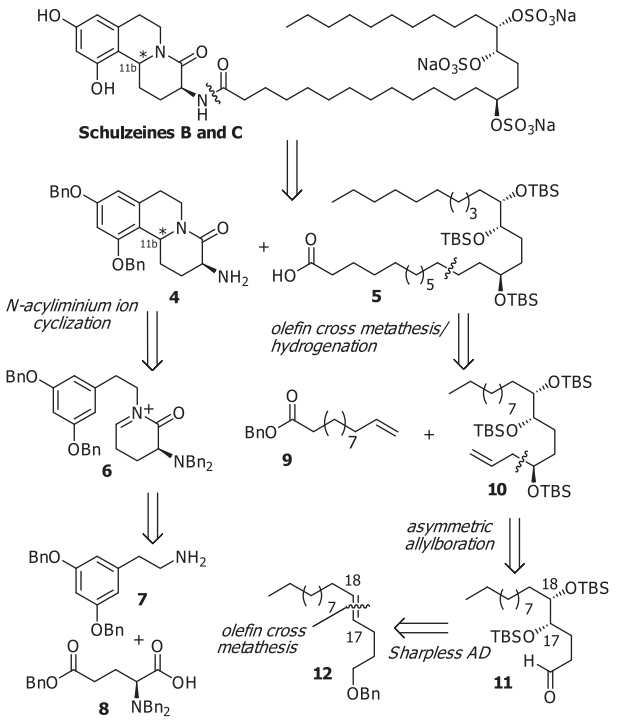
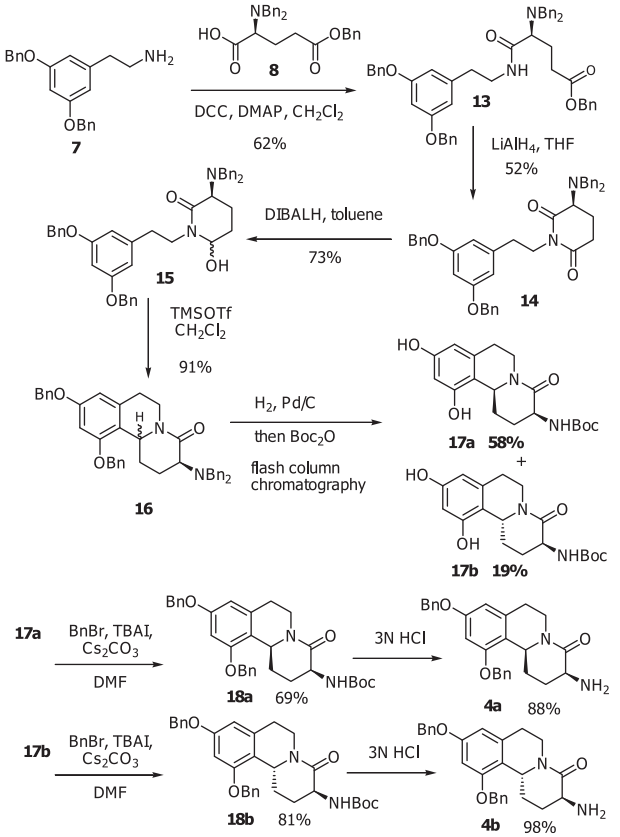


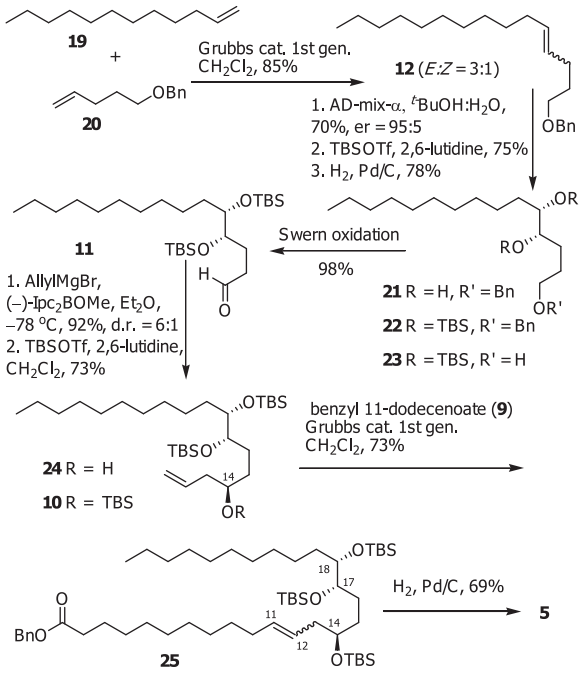
Scheme 1. Retrosynthetic analysis of schulzeines B and C.

configurations at C11b were assigned based on NOESY experiments and comparison of NMR results with a related dimethoxy derivative whose configuration has been confirmed by X-ray crystal analysis.[10,3b] The separated diastereomers were then re-protected as dibenzyl ether **18a** and **18b** and the *N*-Boc-carbamate was removed to give the desired tricyclic core **4a** and **4b** of schulzeines.

The synthesis of C28-fatty acid side chain commenced with olefin cross metathesis of 1-dodecene (**19**) and benzyl-4-pentenyl ether (**20**) in the presence of Grubbs' first generation catalyst (Scheme 3).[11] The product was obtained as a mixture of *E*/*Z* olefin **12** (ca. 3:1) and was treated with AD-mix-α to yield diol **21**.[12] The diol was obtained from Sharpless asymmetric dihydroxylation of *E*-olefin and was separated from the mixture of unreacted mixture of olefin, which had an increased ratio of *Z*-isomer. The diol was protected as bis-TBS ether **22** and the benzyl ether was subsequently removed to give primary alcohol **23**. The alcohol was oxidized to give aldehyde **11** using Swern oxidation and subsequent asymmetric allylboration using Brown's conditions[13] gave the homoallylic alcohol **24** with the desired (*R*)-configuration in a diastereomeric ratio of 6:1. This sets up the stereogenic center at C14 of the 28-carbon fatty acid side chain. The homoallylic alcohol was protected as TBS ether **10**, which subsequently underwent olefin cross metathesis with benzyl 11-dodecenoate (**9**)[6] to give a mixture of inconsequential *E*/*Z* alkene product **25** possessing the full carbon skeleton of C28-fatty acid side chain of schulzeines B and C. Treatment of this mixture with hydrogen gas and palladium on activated carbon resulted in simultaneous reduction of the olefin and hydrogenolysis of the benzyl ester. The resulting 28-carbon fatty acid side chain **5** with the correct absolute configuration of 14*S*, 17*S*, and 18*S* was therefore in hand for coupling with the tricyclic core **4** of schulzeines.



Scheme 2. Synthesis of the tricyclic core **4**.



Scheme 3. Synthesis of the 28-carbon fatty acid side chain **5**.

With both key fragments in hand we proceeded to the coupling of the tricyclic core **4a** or **4b** and the C28-fatty acid side chain **5** (Scheme 4). Amide **26** was obtained from the coupling in good yield in the presence of DCC and DMAP in CH_2Cl_2. The tris-TBS ether was removed using 1 N HCl to furnish the corresponding triol **27**. These advanced intermediates are in common with those in two previously reported syntheses of schulzeines B and C and our spectral data match perfectly with those reported results.[4] Thus a formal synthesis of schulzeines B and C was achieved with the remaining steps for the completion of the synthesis of the natural products being sulfate formation and debenzylation using the reported procedure.[4]