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A new approach to the C_{28} fatty acid chain of the marine natural products schulzeines B and C: a concise diastereoselective total synthesis of (−)-schulzeine B

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ABSTRACT

An enantioselective approach to the C_{28} fatty acid chain of the marine natural products schulzeines B and C was established based on the L-tartaric acid derived C_4 chiron **11** via successive 1,4-bis-chain elongation reactions and catalytic asymmetric hydrogenation. The chiral tricyclic core **8** was constructed via a diastereoselective Pictet–Spengler cyclization reaction (dr = 89:11) of the L-glutamic acid derived precursor **13**. On this basis, a concise total synthesis of (−)-schulzeine B (**5**) was disclosed.

1. Introduction

Glycosidases play key roles in many biological processes.[1] Many sugar-related natural products, such as azasugars show potent inhibitory activity against glycosidases, and are considered to be promising leads for drug development against metabolites-related diseases.[1] Recently, marine invertebrates have been shown to be a new source of potent α-glucosidase inhibitors.[2] In 2000, two proline-containing macrolide trisulfates penarolide sulfates A_1 (**1**) and A_2 (**2**) were isolated from the marine sponge *Penares* sp. They show potent anti-yeast α-glucosidase activity (IC_{50}=1.2 and 1.5 μg/mL, respectively).[3] Later on, penasulfate A (**3**) (Fig. 1), a pipecolate-containing disulfate was isolated from the same source. It shows ten times more potent than penarolide sulfates A_1 and A_2 against yeast α-glucosidase.[4] Then schulzeines A–C (**4**–**6**), three benzo[*a*]quinolizidine-containing trisulfates were isolated, which exhibit potent inhibitory activities toward yeast α-glucosidase (IC_{50}=48–170 nM) and viral neuraminidase (IC_{50}=60 μM).[5] Noteworthy is that, remarkable inhibitory activities toward α-glucosidase (IC_{50} values of 2.5 and 1.1 μM, respectively) are still retained by the desulfated analogues of schulzeines A and B.[5]

Up to date, the asymmetric total synthesis of penarolide sulfate A_1[6] and schulzeines A–C (**4**–**6**),[7–9] as well as the enantioselective synthesis of the hydroxy acid segment of schulzeines B/C[10] and the 3-aminobenzo[*a*]quinolizidine moiety of schulzeines A–C[11] have been reported. Although Wardrop and Bowen have shown that construction of the tricyclic isoquinoline core by Pictet–Spengler cyclization could reach a 9:1 *cis*/*trans* diastereoselectivity,[9a] however, in all the reported total syntheses of schulzeine B,[7–9] the diastereoselectivities in the construction of the benzo[*a*]quinolizidine core[11] were low, which varied from 1:1 to 2:1.[9b] With a program aiming at the synthesis of glycosidases inhibitors,[12] we now report an efficient and highly diastereoselective synthesis of the C_{28} fatty acid chain of schulzeines B and C, as well as the total synthesis of (−)-schulzeine B via the chiron approach.[13]

2. Results and discussion

Our synthetic approach to schulzeine B (**5**) is displayed retrosynthetically in Scheme 1. As schulzeine B consists of a 3-aminobenzo[*a*]quinolizidine and a C_{28} fatty acid chain, the assembly of two properly protected segments via amide bond formation is the direct and general strategy for its total syntheses.[7–11] For the synthesis of the C_{28} fatty acid chain, a L-tartaric acid-based chiron approach[14] was envisaged. The known tosyl-triflate[15] **11** was chosen as the proper chiron, which includes both the requisite 2,3-diol

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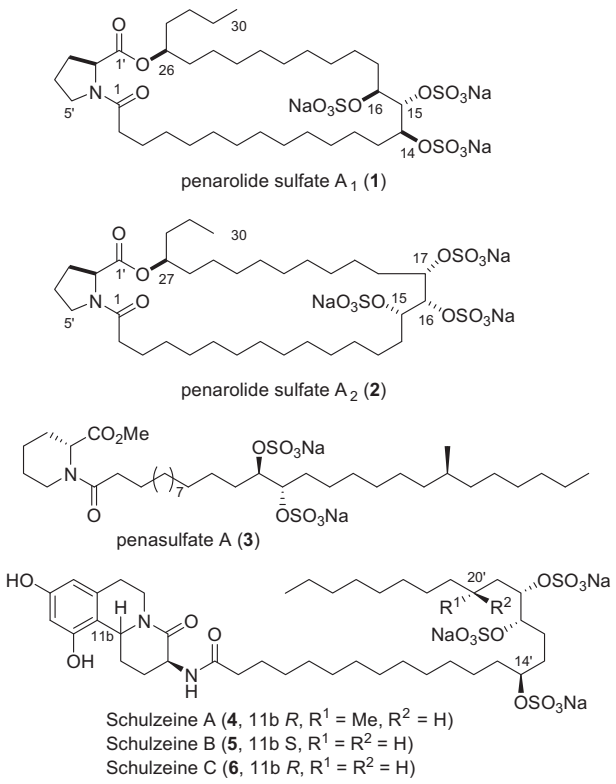
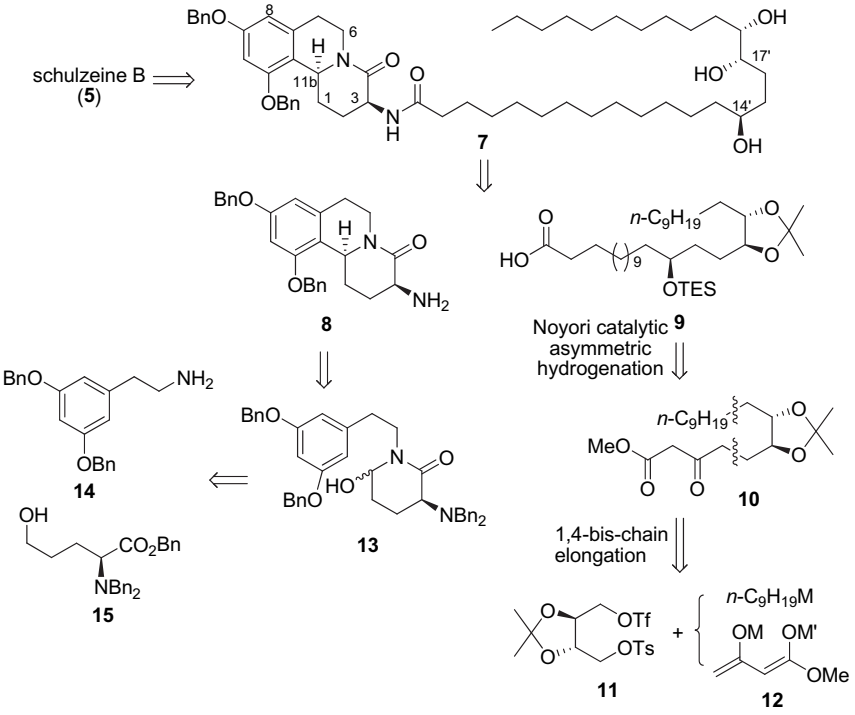


Fig. 1. Marine sulfates exhibiting inhibitory activities toward α-glucosidase.

moiety with *syn*-stereochemistry and 1,4-difunctionalities for a straightforward bis-chain elongation. After coupling with the dienolate **12**, the third carbinolic chiral center could be established by catalytic asymmetric hydrogenation.[8,16] As for the synthesis of the 3-aminobenzo[*a*]quinolizidine moiety, L-glutamic acid-based chiron aproach[7,9,11,17,18] appeared attractive in light of its biogenetic pathway.[5] On the basis of our recent studies on the L-glutamic acid-based synthetic approach to protected 3-amino-6-hydroxy-2-piperidone derivatives,[19] we selected dibenzyl derivative **13** as the precursor for Pictet–Spengler reaction, which could be available from the known compound **14**[7] and **15**.[19] According to recent reports on Pictet–Spengler reactions of *O*,*O*-dimethyl analogue[11] and *N*-Phth protected analogue[9] of **13**, *cis*-diastereoselectivity was expected for Pictet–Spengler reaction of **13**.

The synthesis of the hydroxy acid segment (**9**) of schulzeines B and C started from the known C_4 building block **11**,[15] readily available from L-tartaric acid in 53% overall yield. Treatment of the tosyl triflate **11** with organocopper reagent, generated in situ from 1.1 equiv of Grignard reagent *n*-C_9H_{19}MgBr and a catalytic amount of CuBr, at 0 °C for 1.5 h produced chemoselectively the desired coupling product **16** in 80% yield (Scheme 2). For the second chain elongation, tosylate **16** was treated with the dianion generated in situ from methyl acetoacetate (NaH; *n*-BuLi).[20] Unfortunately the desired γ-alkylation product was not obtained. Considering the success in the similar γ-alkylation with 4,5-bis(iodomethyl)-2,2-dimethyl-1,3-dioxolane,[21] it was envisioned that both electronic and steric hindrance of the tosyl group might be responsible for the failure of the γ-alkylation with tosylate **16**, and replacement of tosyloxy with iodide as the leaving group would be beneficial. Indeed, after converting the tosylate **16** into the corresponding iodide (NaI, DMF), the alkylation proceeded smoothly to give the desired product **10** in 70% yield. Under the catalytic[8,16] asymmetric hydrogenation conditions (0.5 mol % of (*R*)-(BINAP)$RuCl_2$, H_2, 6 atm, MeOH, 70 °C, 20 min), β-ketoester **10** was reduced to give the β-hydroxyester **17** as the only observable diastereomer in 80% yield. The diastereoselectivity of the reduction was estimated to be higher than 95:5 at the limits of the method (NMR). *O*-Protection of the hydroxyl group with TESCl gave compound **18** in 98% yield. Chemoselective reduction of the ester with DIBAL-H at −78 °C yielded the corresponding aldehyde, which reacted with the Wittig reagent, generated in situ from phosphonium salt **19** and KHMDS in THF to produce the *Z*-olefin **20** in 89% overall yield. The geometry of the olefin could not be determined from the ^{1}H NMR data, but



Scheme 1. Retrosynthetic analysis of schulzeine B.