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Enantioselective synthesis of (−)-barrenazines A and B

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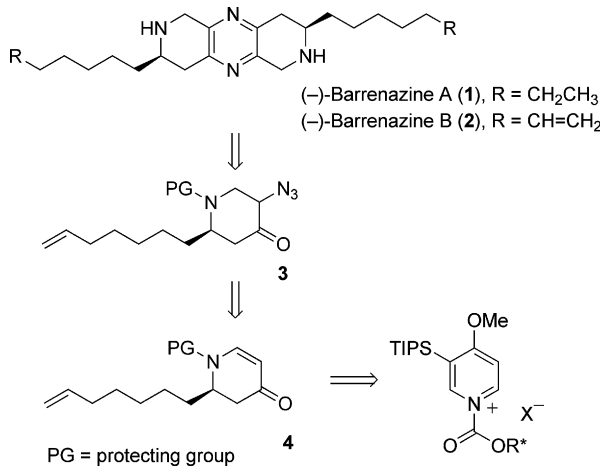
Abstract—A short enantioselective synthesis of barrenazines A and B is described. Barrenazines A and B are prepared following a common synthetic route in nine steps (19% overall yield) and eight steps (21% overall yield), respectively, from readily available 4-methoxy-3-(triisopropylsilyl)pyridine. The synthesis relies on a highly diastereoselective nucleophilic addition of a Grignard reagent to a chiral acylpyridinium salt, a radical azidation of a silyl enol ether and the assembly of the pyrazine ring by reductive dimerization of a functionalized 5-azidopiperidin-4-one.

Barrenazines A (**1**) and B (**2**) are novel cytotoxic alkaloids isolated by Kashman et al. from an unidentified tunicate collected from the Barren Islands (Madagascar) in 2003.[1] They form part of a mixture of compounds obtained from this tunicate, some of them with undetermined structure, with a common and unique C_2-symmetrical heterocyclic skeleton of 1,2,3,4,5,6,8,9-octahydrodipyrido[3,4-*b*:3′,4′-*e*]pyrazine bearing different side chains (Scheme 1). Barrenazine A presents mild cytotoxic activity against LOVO-DOX colon carcinoma and, in a mixture with other unidentified congeners from the same tunicate, a wider biological activity which includes cytotoxic activity against LN-caP prostate carcinoma and K-562 leukemia cells. Structurally related tetrahydropyridinopyrazine derivatives also exhibit a variety of biological activities, and there are other biologically active symmetrical and unsymmetrical natural products containing the 1,4-pyrazine ring, such as the antitumoral cephalostatins[2] and ritterazines,[3] and the antibiotic pelagiomicins[4] and palythazins.[5] The extraordinary biological activities associated with natural products containing the pyrazine motif, together with the novel C_2-symmetric heterocyclic core of the barrenazines, have attracted our interest in their synthesis.[6] Herein, we report a short and versatile enantioselective synthesis of (−)-barrenazines A and B.



Scheme 1. Retrosynthetic analysis for barrenazines.

For the synthesis of barrenazines A and B we devised a common synthetic route depicted in Scheme 1. Taking into account the C_2 symmetry axis present in barrenazines, we considered the assembly of the novel octahydrodipyridopyrazine skeleton by reductive dimerization of 5-azidopiperidin-4-one **3** furnished with the side chain of barrenazine B, which should be easily converted to barrenazine A. The synthesis of **3** is proposed from the chiral enantiomerically pure 2,3-dihydropyridin-4(1*H*)-one **4** by means of a tandem 1,4-reduction/enolate trapping by electrophilic amination reaction. The required dihydropyridinone **4** could be prepared, accordingly with the well-established method of Comins,[7] by stereoselective nucleophilic addition of a Grignard reagent to a chiral acylpyridinium salt (Scheme 1). This approach

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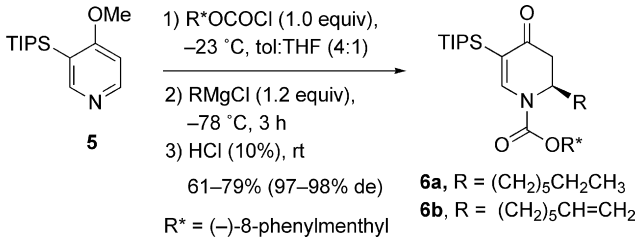
has been shown to be a useful strategy in the stereocontrolled synthesis of a variety of enantiopure dihydropyridinones, and has been already applied to the synthesis of natural products.[7a,8] Indeed, during the development of this work, we learned that this reaction was also chosen by Focken and Charette to achieve the first stereoselective synthesis of barrenazines.[9,10]

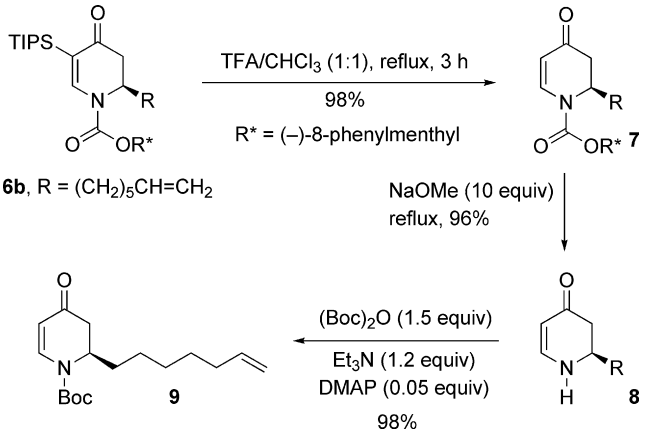
Our synthesis began with the stereoselective synthesis of dihydropyridinones by Grignard nucleophilic addition to chiral acylpyridinium salts. In line with the findings of Comins, for the synthesis of the enantiopure dihydropyridinone **4** we chose 4-methoxy-3-(triisopropylsilyl)pyridine (**5**),[7b] the (−)-8-phenylmenthyl carbamate as the chiral auxiliary, and Grignard reagents bearing the aliphatic side chain of the barrenazines. In our first experiment, the addition of chloro(heptyl)magnesium (1.2 equiv) in ether to the chiral acylpyridinium salt preformed from **5** (1.0 equiv) and (−)-8-phenylmenthyl chloroformate (1.0 equiv) in toluene/THF (4:1) afforded, after acidic work up (HCl 10%), dihydropyridinone **6a** in 79% yield as the only diastereoisomer detected by ^{1}H NMR (Scheme 2). Additional HPLC analysis revealed a 99:1 diastereomeric ratio (98% de). When the reaction was performed with the Grignard reagent derived from 7-chlorohept-1-ene, dihydropyridinone **6b** was obtained in 61% yield and 97% de. The relative configuration of the dihydropyridinones was assigned, based on Comins's precedents, by ^{1}H NMR.[7b] Dihydropyridinones **6a** and **6b** showed the chemical shifts of H-2 and H-6, at 2.65–2.78 ppm (m) and 7.73 ppm (s), respectively, which should correspond to the major diastereoisomer when (−)-8-phenylmenthyl is used as the chiral auxiliary. Further support for this assignment was provided by the final conversion into natural barrenazines.

With the enantiomerically rich dihydropyridinone **6b** in hand, we proceeded further in our synthetic route with the cleavage of the triisopropylsilyl group and the removal of the chiral auxiliary to prevent undesired side reaction products. Protodesilylation of **6b** with a 1:1 mixture of trifluoroacetic acid/chloroform gave **7** in 98% yield (Scheme 3). Methanolysis of **7** with sodium methoxide afforded **8** as a crystalline solid in 96% yield. The enantiopure dihydropyridinone **8** was then protected as a *t*-butoxycarbonyl carbamate by treatment with $(Boc)_2O$ (1.5 equiv) and Et_3N (1.2 equiv)/DMAP (0.05 equiv), affording the corresponding *N*-Boc-derivative **9** in 98% yield.

At this stage of the synthesis, we attempted the direct conversion of 2,3-dihydropyridinone **9** to the required



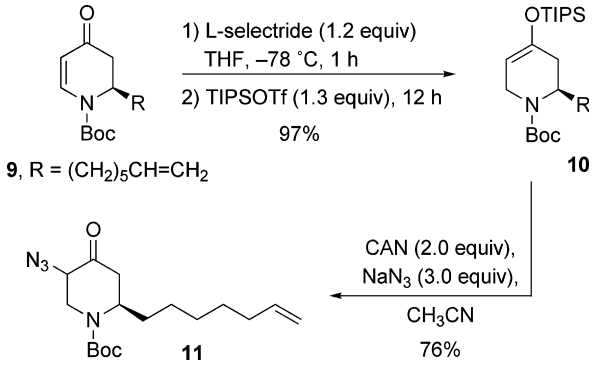
Scheme 2. Stereoselective synthesis of dihydropyridinones **6a** and **6b**.



Scheme 3. Synthesis of dihydropyridinone **9**.

α-azido ketone **11** in a one-step tandem 1,4-reduction/enolate trapping by azidation reaction. This approach should avoid the problems of regioselectivity derived of a two-step procedure. Although the electrophilic amination of enolates is a known reaction, to the best of our knowledge, tandem 1,4-addition-enolate amination reactions have not been reported yet.[11] After considerable efforts, the reaction of 2,3-dihydropyridinone **9** with several 1,4-reducing reagents such as L-Selectride, or lithium in ammonia, followed by the addition of different aminating reagents, such as azodicarboxylates or sulfonyl azides, gave the desired 1,4-reduction product.

Based on these results, we considered an alternative route based on trapping the enolate resulting from 1,4-reduction of **9** as a silyl enol ether, followed by radical azidation of the silyl enol ether with sodium azide and ceric ammonium nitrate (CAN).[12] The reaction of 2,3-dihydropyridinone **9** with L-Selectride (1.2 equiv) in THF at −78 °C followed by the addition of TIPSOTf (1.3 equiv) afforded triisopropylsilyl enol ether **10** in 97% yield (Scheme 4). Subsequently, the treatment of **10** with NaN_3 (3.0 equiv) and CAN (2.0 equiv) in acetonitrile at −20 °C gave the desired α-azido ketone **11** in 76% yield. In this reaction, we observed that careful tuning of the NaN_3 and CAN amounts, and rapid purification, was crucial for obtaining α-azido ketone **11** in good yield.



Scheme 4. Synthesis of α-azido ketone **11**.