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A Versatile Enantioselective Synthesis of Barrenazines†

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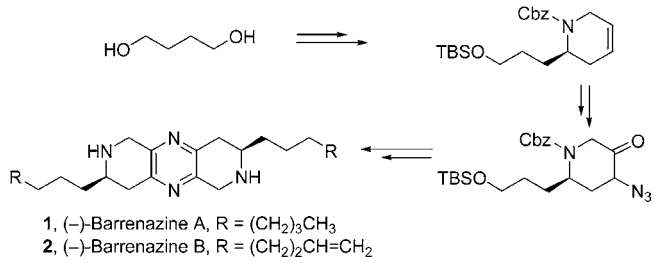
ABSTRACT



1, (−)-Barrenazine A, R = $(CH_2)_3CH_3$
2, (−)-Barrenazine B, R = $(CH_2)_2CH{=}CH_2$

A versatile enantioselective total synthesis of barrenazines A and B has been accomplished from 1,4-butanediol. The key steps of the synthesis are a sequential allylboration/ring-closing metathesis for the construction of the tetrahydropyridine ring and the preparation of a functionalized 4-azidopiperidin-5-one through a stereoselective epoxidation and regioselective ring-opening reaction. The C_2-symmetrical pyrazine skeleton of barrenazines was prepared by dimerization of the azidopiperidinone, and the carbon side chain was completed by copper-catalyzed reactions using Grignard reagents.

Barrenazines are novel marine cytotoxic alkaloids isolated from an unidentified tunicate collected at the Barren Islands (Madagascar) by Kashman et al. in 2003.[1] These compounds present a C_2 symmetric structure that consists of a central pyrazine ring condensed with two piperidine cycles, two stereogenic centers, and different heptyl carbon side chains. The low natural appearance of barrenazines has limited the structural identification and biological evaluation to only two members of the family, barrenazines A (**1**) and B (**2**). Barrenazine A exhibits cytotoxic activity against LOVO−DOX colon carcinoma and, in a mixture with other unidentified congeners from the same tunicate, a wider biological activity that includes cytotoxic activity against LN-caP prostate carcinoma and K-562 leukemia cells.[1]

Hitherto, several research groups have pursued the synthesis of barrenazines, and two independent total syntheses have been reported. In 2006, Focken and Charette[2] published the first enantioselective synthesis, and later on, our group reported the total synthesis of barrenazines A and B.[3] In both cases, the carbon side chain was introduced in an early step of the synthesis through diastereoselective nucleophilic Grignard addition to a chiral pyridinium salt.[4] An unsuccessful biomimetic approach to barrenazine A using aspartic acid as the starting material has also been reported.[5] In this letter, we report a new and versatile enantioselective synthesis of barrenazines A and B.

The synthetic strategy was based on the preparation of the C_2-symmetrical tricyclic pyrazine core of barrenazines

† This work is dedicated to Professor Amos B. Smith, III, University of Pennsylvania, on the occasion of his 65th birthday.

(1) Chill, L.; Aknin, M.; Kashman, Y. *Org. Lett.* **2003**, *5*, 2433–2435.

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(4) (a) Comins, D. L.; Joseph, S. P.; Hong, H.; Al-awar, R. S.; Foti, C. J.; Zhang, Y.; Chen, X.; LaMuyon, D. H.; Guerra-Weltzien, M. *Pure Appl. Chem.* **1997**, *69*, 477–481. (b) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719–4728. (c) Comins, D. L.; Goehring, R. R.; Joseph, S. P.; O'Connor, S. *J. Org. Chem.* **1990**, *55*, 2574–2576.

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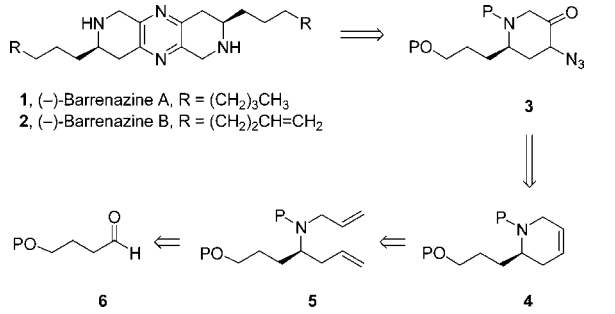
prior to the completion of the side chain to facilitate the synthesis of analogues (Scheme 1). The construction of the

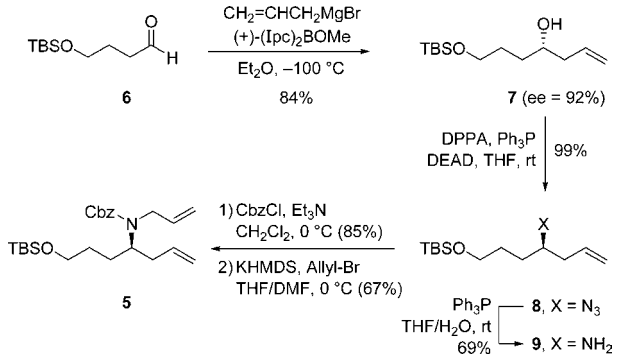
Scheme 1. Retrosynthetic Analysis of Barrenazines A and B



hexahydrodipyridopyrazine skeleton was proposed by reductive dimerization of a conveniently functionalized 4-azidopiperidin-5-one **3**,[6] which could be prepared from the tetrahydropyridine **4** through epoxidation and regioselective nucleophilic epoxide opening using the azide ion as a nucleophile. For the construction of the tetrahydropyridine ring, we devised a synthetic strategy based on a sequential enantioselective aldehyde allylation and ring-closing metathesis.[7]

Our synthesis started with the preparation of the known *tert*-butyldimethylsilyl ether of 4-hydroxybutyraldehyde (**6**) from 1,4-butanediol (Scheme 2).[8] The enantioselective

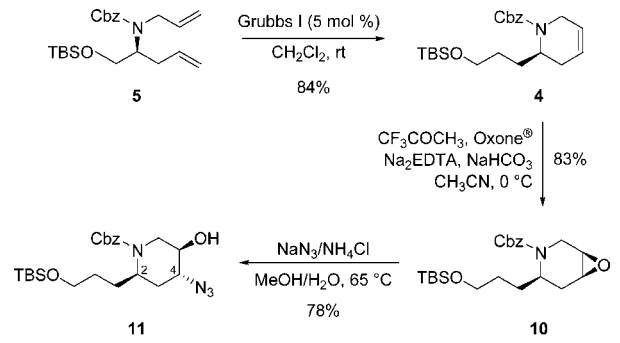
Scheme 2. Synthesis of the *N*-Allyl Amine **5**



Brown allylation of **6** using allyl magnesium bromide and (+)-$(Ipc)_2$BOMe at −100 °C provided the homoallylic alcohol **7** in good yield and with high enantioselectivity (84%, 92% ee).[9] The reaction of **7** under Mitsunobu conditions using diphenyl phosphoryl azide (DPPA) provided the azide **8** in quantitative yield.[10] Under Staudinger conditions, **8** was cleanly reduced to amine **9** with aqueous Ph_3P in 69% yield.[11] At this point, the primary amine **9** was protected to favor the selective introduction of the allyl group and to perform the olefin metathesis. The reaction of **9** with benzyloxycarbonyl chloride (CbzCl) and Et_3N in CH_2Cl_2 at 0 °C and subsequent allylation provided the desired tertiary *N*-allyl amine **5** in good overall yield (Scheme 2).

The ruthenium-catalyzed ring-closing metathesis[12] of **5** using Grubbs I catalyst [5 mol %, $(Cy_3P)_2RuCl_2CHPh$] afforded tetrahydropyridine **4** at rt in 84% yield (Scheme 3). It is interesting to note that the metathesis reaction failed on compound **5** protected as the *p*-methoxybenzylamine, with starting material recovered unalterated.[13]

Scheme 3. Synthesis of the Azido Alcohol **11**



With tetrahydropyridine **4** in hand, we pursued the synthesis of the α-azido ketone **3** through an epoxidation, nucleophilic opening, and oxidation sequence. A successful strategy should require a highly regioselective epoxide opening to avoid the formation of a mixture of regioisomeric pyrazines during the dimerization step.[14] Initially, the reaction of **4** with *m*-CPBA under several sets of reaction conditions provided epoxide **10** with low yields and conversions. Alternatively, the epoxidation using the methyl (trifluoromethyl)dioxirane, generated in situ from trifluoroacetone and

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(9) The enantiomeric excess was determined in the corresponding MTPA esters of **7** by ^{19}F NMR. For further details see Supporting Information.

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(12) For a comprehensive treatment of the metathesis reaction, see: *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003. For leading references in the metathesis reaction, see: (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490–4527. (b) Donohoe, T. J.; Orr, A. J.; Bingham, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 2664–2670. (c) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243–251.

(13) Fu, G. C.; Neguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856–9857.

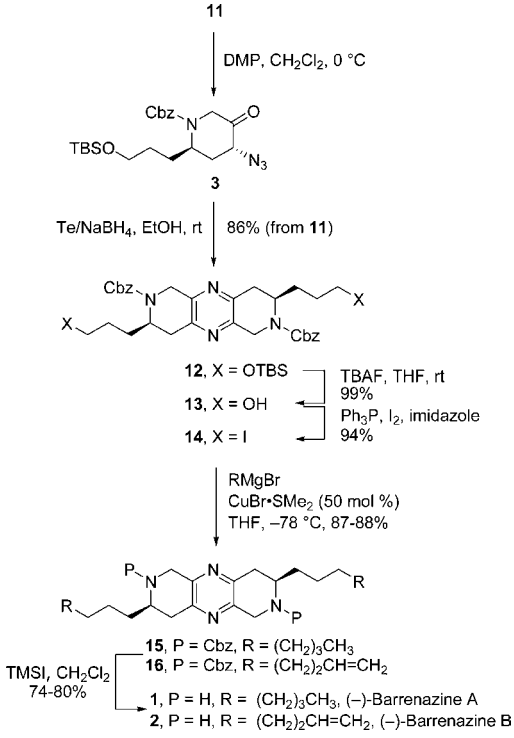
(14) It is worth noting that either of the pure regioisomeric azido ketones should provide the same dimeric pyrazines.

Oxone at 0 °C,[15] afforded **10** in high yield and stereoselectivity (83%, 96:4). It seems that the high stereoselectivity observed is controlled by the steric hindrance produced by the Cbz group.[16]

The reaction of epoxide **10** with sodium azide at 65 °C during 12 h gave the azido alcohol **11** in 78% yield in a regio- and stereoselective manner as a single stereoisomer (Scheme 3). The regiochemistry of the reaction can be explained by the preferred diaxial epoxide opening (Fürst−Platter rule)[17] and was determined by 2D NMR experiments (HMBC) based on the correlation observed between H-2 and C-4. The stereochemistry of **11** was assigned on the basis of the coupling constants in the ^{1}H NMR spectra.[18]

The next step was the conversion of **11** into the corresponding α-azido ketone **3**, which is suitable for reductive dimerization through self-condensation of the corresponding α-amino ketone.[6] The oxidation of azido alcohol **11** with Dess-Martin periodinane[19] (DMP) gave the desired 4-azidopiperidin-5-one **3** as the only reaction product, although this compound proved to be unstable to the chromatographic purification. Unfortunately, the reduction of azide **3** with aqueous Ph_3P and the spontaneous self-condensation of the resulting amino ketone only produced the symmetrical pyrazine **12** in low yields. Alternatively, the reaction using reduced tellurium ($Te/NaBH_4$) in EtOH at rt afforded the symmetrical pyrazine **12** as a single product by ^{1}H NMR in 86% overall yield (from **11**, Scheme 4).[20]

Scheme 4. Synthesis of Barrenazines A and B



Once the tricyclic pyrazine core of the barrenazines had been prepared, we proceeded to explore the completion of the heptyl carbon side chain by copper-catalyzed cross-coupling reactions using Grignard reagents.[21] For this purpose, the two TBS ethers of **12** were cleaved with TBAF at rt to give diol **13** (99% yield), which was in turn converted into the diiodide **14** by treatment with Ph_3P, I_2, and imidazole (94% yield, Scheme 4). The reaction of **14** with *n*-butylmagnesium bromide at −78 °C under copper(I) catalysis (50 mol %) gave the dicoupling product **15** (Cbz-protected barrenazine A) in excellent yield (88%). Analogously, the reaction using 3-butenylmagnesium bromide, under the same reaction conditions, provided the Cbz-protected barrenazine B (**16**) in similar yield. Finally, treatment of **15** and **16** with TMSI at 0 °C furnished synthetic (−)-barrenazine A and (−)-barrenazine B in 80% and 74% yield, respectively.

In summary, a novel and versatile enantioselective synthesis of (−)-barrenazine A and (−)-barrenazine B has been accomplished from 1,4-butanediol. The key steps of the synthesis are a sequential allylboration/ring-closing metathesis strategy for the construction of the tetrahydropyridine ring and the preparation of a functionalized 4-azidopiperidin-5-one through a stereoselective epoxidation and regioselective ring-opening reaction. The C_2-symmetrical pyrazine skeleton of barrenazines was prepared by reductive dimerization of an α-azido ketone with reduced tellurium, and the carbon side chain was completed by copper-catalyzed coupling reactions using Grignard reagents. The synthesis and biological evaluation of new derivatives of barrenazines A and B modified at the side chain are in progress.

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Supporting Information Available: Experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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