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Chiral Pool Based Efficient Synthesis of the Aminocyclitol Core and Furanoside of (−)- Hygromycin A: Formal Total Synthesis of (−)-Hygromycin A

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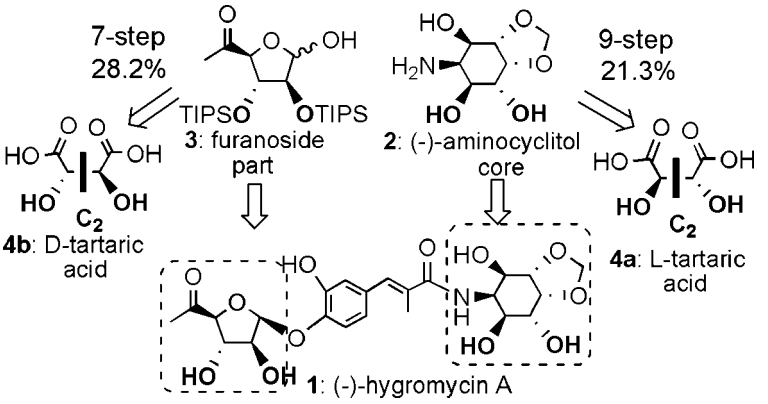
ABSTRACT



A chiral pool based synthetic strategy that leads from the readily available and inexpensive C_2-symmetric tartaric acids to the chiral *O*-isopropylidenebenzooxazole—a convenient precursor to the aminocyclitol core of hygromycin A as well as the chiral γ-disilyloxybutyrolactone—a pivotal intermediate to approach to the furanoside of hygromycin A.

The natural product hygromycin A **1** was shown to have a relatively broad spectrum of activity such as activity against Gram-positive and Gram-negative bacterial and high hemaglutination inactivation activity and high antiterponemal activity (Figure 1).[1] In addition, the aminocyclitol core **2** of hygromycin A has also attracted interest since the discovery that the aminocyclitol unit **2** is critical for the activity of this class of compounds while the furanoside part was not.[2] Despite the promising biological activities and interesting unique structure of hygromycin A, there have been few reports on the synthesis of the structural components of hygromycin A,[3−5] only two reports on the total synthesis of hygromycin A, by

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Donohoe et al.[3a] in 2009 and Ogawa et al.[3c] in 1991, and one report of an efficient synthesis of *C*-2-epihygromycin A by Trost et al.[4] Herein, in contrast to the asymmetric synthesis based upon chiral carbohydrates,[3] Pd-promoted desymmetrization of the racemic conduritol B tetraester,[4] lipase-mediated kinetic resolution of diol,[3,5a,5b] and resolving agent-mediated resolution of racemic mixture,[5c] we report a chiral pool based synthetic strategy that leads from the commercially available and inexpensive C_2-symmetric tartaric acid **4** to the aminocyclitol core **2**[4b,5] and the furanoside part **3**[3a] of hygromycin A.

The ready availability of C_2-symmetric 1,4 diol **7**[6] from the cheap L-tartaric acid **4a** makes it a convenient precursor to a variety of diastereomeric amino alcohols by the choice

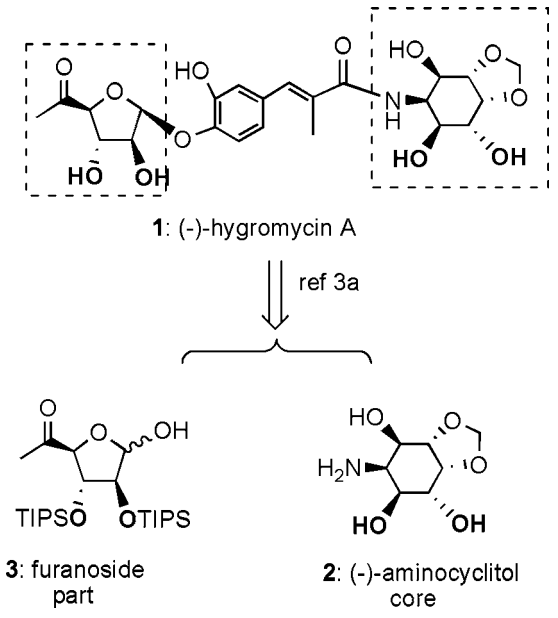
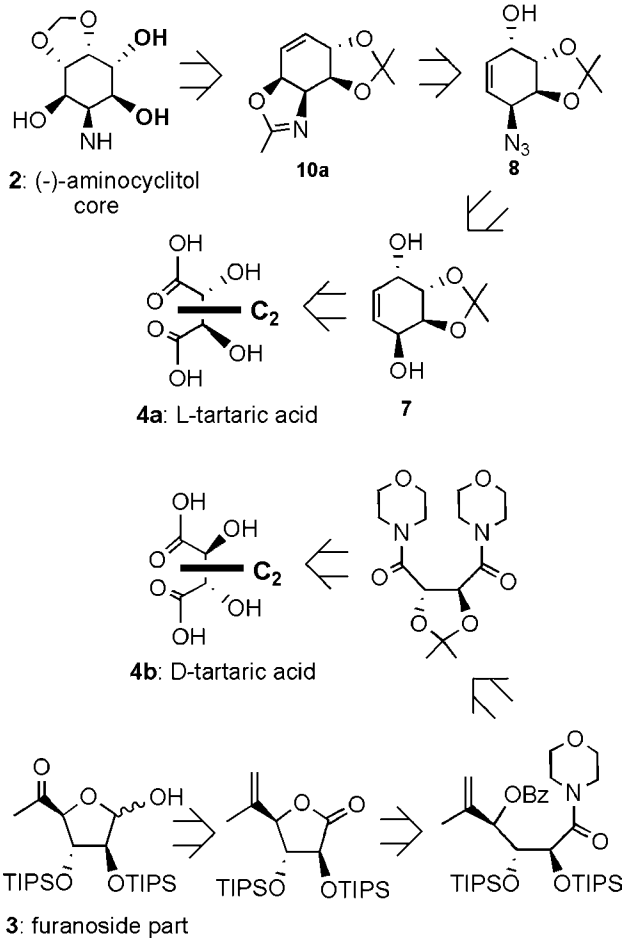


Figure 1. Structures of hygromycin A, (−)-aminocyclitol core **2**, and furanoside part **3**.

of functional group manipulations (Scheme 1). Recently, we have developed the use of the 1,4-diol **7** as a versatile precursor en route to 1,2 and 1,4 *trans*-type azido alcohols and have successfully applied this method in the asymmetric synthesis of (+)-valienamine and other derivatives related to valienamine.[6a] For aminocyclitol core **2**, the primary challenge resides in the installation of the 1,2 *cis*-type amino alcohol unit with complete control of regio- and stereochemistry. Envisioning the oxazoline **10a** as a 1,2 *cis*-type amino alcohol equivalent and a key intermediate to **2** suggests that a new effective strategy toward **2** evolved from two key regio- and stereocontrolled reactions: (1) conversion of the 1,4 *trans* diol **7** to the 1,4 *trans* azido alcohol **8** with net retention of configuration and (2) installation of the oxazoline **10a** via a MsCl-promoted rearrangement of 1,4 *trans*-type acetylamino alcohol **9** derived from **8**.

According to the synthetic blueprint, the synthesis of aminocyclitol **2** began with C_2 symmetric diol **7** derived from L-tartaric acid.[6] Exposure of diol **7** to McMurry reagent ($PhNTf_2$)[7] in DMF at 25 °C in the presence of NaH followed by addition of a solution of sodium azide in EtOH/H_2O at 90 °C to effect the azide-promoted ring-opening of the in situ generated allylic epoxide[6a] with complete control of regio- and stereochemistry afforded 1,4-*trans* azido alcohol **8** in 70% yield. Elaboration of *trans* azido alcohol **8** to acetylamino alcohol **9** was initiated by treatment of **8** with Mg in MeOH at 0 to 25 °C for 4 h followed by addition of Ac_2O/pyridine producing the

Scheme 1. Retrosynthesis of (−)-Aminocyclitol Core **2** and Furanoside Part **3**



acetylamino alcohol **9** in 89% yield (Scheme 2). With enantiopure **9** in hand, attention was then centered upon the conversion of 1,4-acetylamino alcohol into oxazoline **10a**. Surprisingly, the MsCl-promoted cyclization turned out to be challenging. The application of reaction conditions previously described for the cyclization of 1,4-acetylamino

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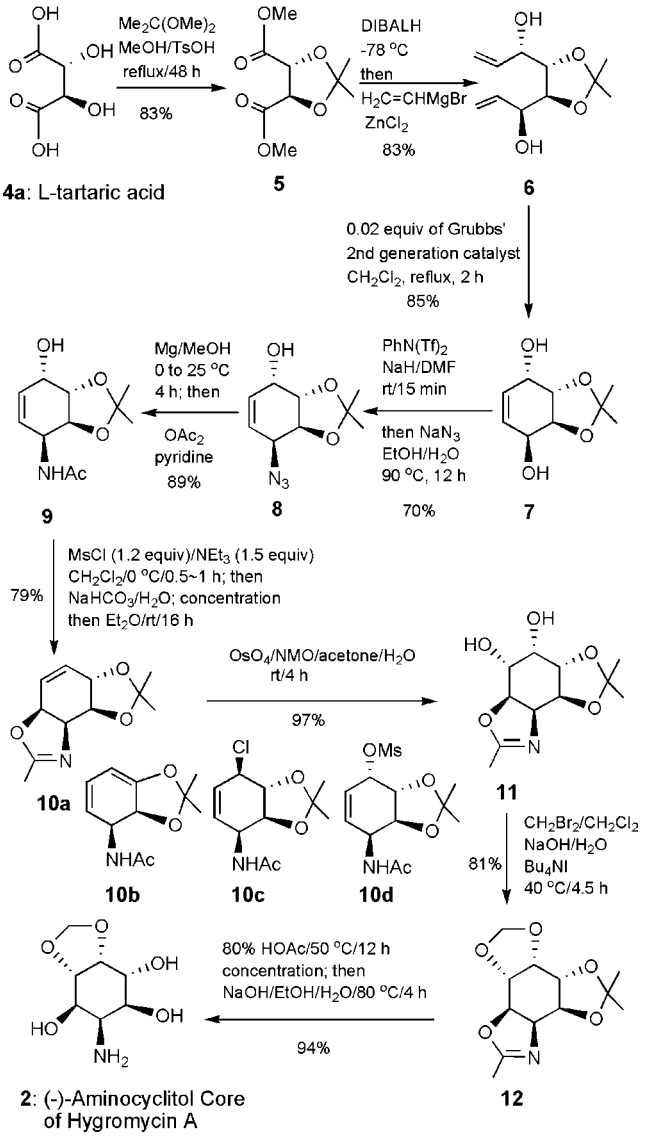
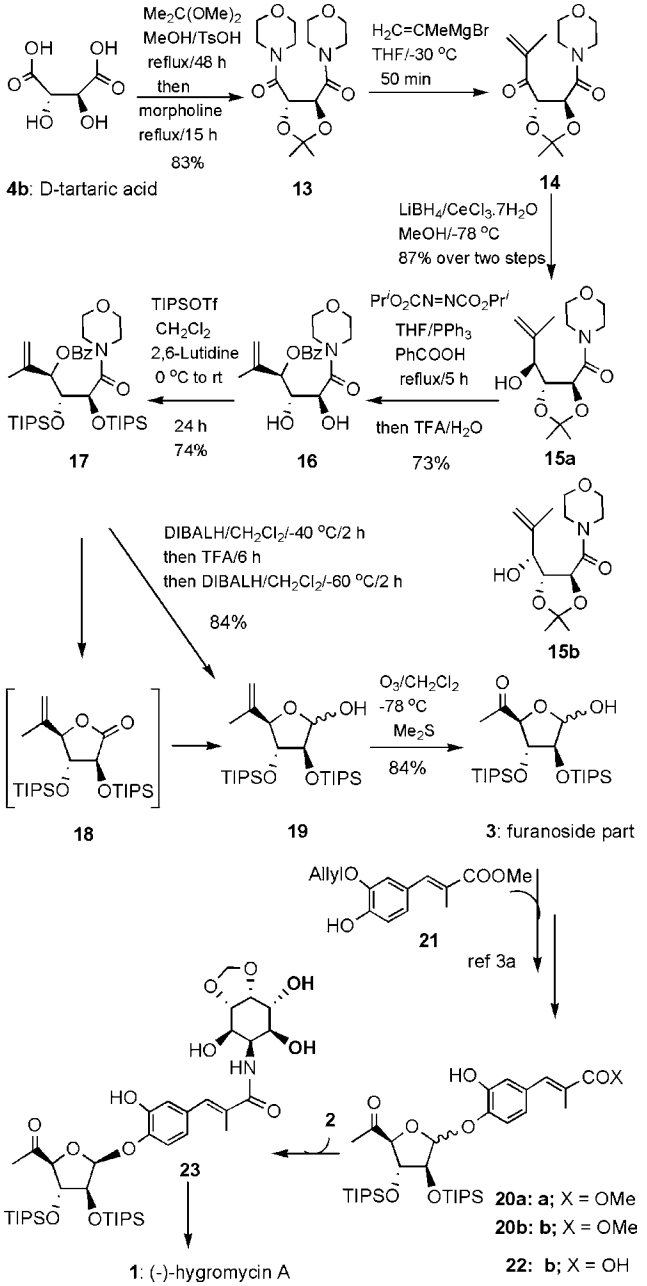
alcohols proved unsuccessful,[8] in that the use of 5 equiv of MsCl and 10 equiv of NEt_3 in CH_2Cl_2 from 0 to 40 °C or in $Cl_2CHCHCl_2$ from 0 to 60 °C led to either extensive decomposition of starting material or a poor yield (~25%) of the desired oxazoline **10a** along with recovered starting material (~15%). The major products isolated were the diene **10b**, the allylic chloride **10c**, and sulfonate **10d**. Fortunately, reducing the amount of MsCl and NEt_3 and lowering the reaction temperature led to gratifying results. Thus, mesylation of **9** using 1.2 equiv of MsCl and 1.5 equiv of NEt_3 in CH_2Cl_2 at 0 °C for 1 h followed by addition of aqueous $NaHCO_3$, concentration, dilution with Et_2O, and stirring at room temperature for 16 h furnished reproducibly the desired cyclization product **10a** in 79% yield. With enantiopure oxazoline **10a** in hand, the stage was set for stereocontrolled introduction of the two hydroxyl groups. Gratifyingly, exposure of **10a** to OsO_4 in acetone–water at 25 °C in the presence of NMO for 4 h smoothly effected the dihydroxylation to afford diol **11** in 97% yield with complete stereoselectivity. Treatment of diol **11** with CH_2Br_2 in CH_2Cl_2 followed by addition of Bu_4NI and $NaOH-H_2O$ at 35 °C and warming to 40 °C over 4.5 h gave the desired methylene acetal **12** in 81% yield. Finally, selective removal of the acetonide and oxazoline was achieved by exposing **12** to 4:1 HOAc-H_2O at 80 °C for 12 h followed by concentration, addition of a solution of NaOH (2.5 equiv) in 4:1 EtOH–H_2O, and stirring at 80 °C for 4 h to afford aminocyclitol core **2** in 94% yield. Comparison of the ^1H and ^{13}C NMR spectra properties to those recorded confirms its identity.[4b,5] Our

Scheme 2. Enantiospecific Synthesis of (−)-Aminocyclitol Core of Hygromycin A



Scheme 3. Enantiospecific Synthesis of the Furanoside of Hygromycin A



$[\alpha]^{20}_D = -26.7$ ($c = 0.6$, H_2O) compares favorably to the literature, $[\alpha]^{20}_D$ −27.2 ($c = 0.45$, H_2O).[5a] This new C_2 chiral pool based synthesis requires only nine steps from commercially available, cheap L-tartaric acid **4a** to give the aminocyclitol core **2** in 21.3% overall yield; this represents not only the shortest approach but also a high-yielding synthesis reported for this aminocyclitol.

Elaboration of C_2-symmetric D-tartaric acid **4b** to the furanoside part **3** of hygromycin A was initiated by treatment of **4b** with acetone dimethyl acetal in MeOH/TsOH at reflux for 48 h followed by addition of morpholine and stirring for an additional 15 h resulting in the efficient formation of desired morpholine amide **13** in 83% yield (Scheme 3).[9] It will be appreciated that the direct coupling of diamide **13** with 2-propenyl Grignard reagent at −30 °C to give the desired γ-keto amide **14** in 95% yield as a single adduct proceeded without complication. Because of its C_2 symmetry before the functional group manipulations, there is no loss in yield due to the formation of diastereomers. With γ-keto amide **14** in hand, the stage was set for chemo-, regio-, and diastereocontrolled reduction of the keto group. After several attempts at reduction with various reducing reagents, such as $NaBH_4$, $Zn(BH_4)_2$, and DIBALH, highly stereoselective reduction of the crude keto amide **14** with a mixture of $LiBH_4$ and $CeCl_3$ in MeOH at −78 °C gave a separable ∼16:1 ratio of **15a**:**15b** in 87% overall yield from diamide **13**. Mitsunobu inversion[10] of the hydroxyl group in **15a** using DIAD, PhCOOH, and PPh_3 in THF at reflux for 5 h followed by in situ removal of the acetonide by addition of TFA−H_2O (9:1) provided diol **16** in 73% yield. Subsequent triisopropylsilyl protection of the diol gave amide **17** in 74% yield. The stage is now set for the five-membered cyclic hemiacetal formation: chemoselective reduction with DIBAL-H at −40 °C in CH_2Cl_2 followed by TFA-promoted γ-butyrolactone formation and in situ reduction of the lactone **18** with DIBAL-H at −60 °C gave 84% yield of the cyclic hemiacetal **19**. Fortunately, by simple modification of the reaction conditions, we found that the two-step reaction sequence from **17** to **19** could be carried out without isolation of any intermediates to deliver the hemiacetal **19** in 84% overall yield in a single vessel. All that now remained to reach the target furanoside part **3** was the oxidative cleavage of the carbon−carbon double bond. Expectedly, ozonolysis of the cyclic hemiacetal **19** and in situ reductive workup with Me_2S proceeded smoothly to give the desired furanoside part **3** in 84% yield. Comparison of the $^1H/^{13}C$ NMR spectral properties to those recorded confirmed its identity.[3a] This new chiral pool based synthesis requires only 7 steps from C_2-symmetric D-tartaric acid **4b** to give the furanoside part **3** in 28.2% overall yield.

Thus, following the protocol of Donohoe, hygromycin A **1** was produced through stereocontrolled glycosylation reaction of **3** with phenol **21** derived from 3,4-dihydroxybenzaldehyde, hydrolysis of methyl ester **20b**, coupling of the aminocyclitol core **2** with **20b**-derived acid **22**, and TIPS-deprotection of the diol in **23** (see the Supporting Information). Comparison of the ^1H and ^{13}C NMR spectra properties to those recorded confirms its identity.[3] Our $[\alpha]^{20}_D$ −143 ($c = 1.2$, H_2O) compares favorably to the literature, $[\alpha]^{20}_D$ −148 ($c = 0.46$, H_2O).[3]

In conclusion, we have developed an efficient and highly stereocontrolled asymmetric synthesis of aminocyclitol core **2** and the furanoside par **3** by a new C_2 chiral pool based synthetic strategy that is unique compared to other previous syntheses of the key intermediates **2** and **3** for the total synthesis of hygromycin A.[3]

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Supporting Information Available. Experimental procedures and characterization data for **2**, **3**, **5**−**9**, **10a**−**c**, **11**, **12**−**14**, **15a**, **16**, **17**, **19**, **20a**,**b**, **22**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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