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

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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 7⁶ from the cheap L-tartaric acid **4a** makes it a convenient precursor to a variety of diastereometric 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 regioand 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

Org. Lett., Vol. 14, No. 23, 2012

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 (PhNTf₂)⁷ in DMF at 25 °C in the presence of NaH followed by addition of a solution of sodium azide in EtOH/H₂O 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 Ac₂O/pyridine producing the





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 NEt₃ in CH₂Cl₂ from 0 to 40 °C or in Cl₂CHCHCl₂ from 0 to 60 °C led to either extensive decomposition of starting material or a poor yield ($\sim 25\%$) of the desired oxazoline 10a along with recovered starting material ($\sim 15\%$). The major products isolated were the diene 10b, the allylic chloride 10c, and sulfonate 10d. Fortunately, reducing the amount of MsCl and NEt₃ and lowering the reaction temperature led to gratifying results. Thus, mesylation of 9 using 1.2 equiv of MsCl and 1.5 equiv of NEt₃ in CH₂Cl₂ at 0 °C for 1 h followed by addition of aqueous NaHCO₃, concentration, dilution with Et₂O, 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 OsO4 in acetone-water at

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



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 CH₂Br₂ in CH₂Cl₂ followed by addition of Bu₄NI and NaOH–H₂O 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-H₂O at 80 °C for 12 h followed by concentration, addition of a solution of NaOH (2.5 equiv) in 4:1 EtOH–H₂O, and stirring at 80 °C for 4 h to afford aminocyclitol core **2** in 94% yield. Comparison of the ¹H and ¹³C NMR spectra properties to those recorded confirms its identity.^{4b,5} Our



 $[\alpha]^{20}{}_{\rm D} = -26.7 (c = 0.6, H_2O)$ compares favorably to the literature, $[\alpha]^{20}{}_{\rm D} -27.2 (c = 0.45, H_2O)$.^{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 NaBH₄, Zn(BH₄)₂, and DI-BALH, highly stereoselective reduction of the crude keto amide 14 with a mixture of LiBH₄ and CeCl₃ in MeOH at -78 °C gave a separable ~16:1 ratio of **15a:15b** in 87% overall vield from diamide 13. Mitsunobu inversion¹⁰ of the hydroxyl group in 15a using DIAD, PhCOOH, and PPh₃ in THF at reflux for 5 h followed by in situ removal of the acetonide by addition of TFA-H₂O (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 Me₂S proceeded smoothly to give the desired furanoside part 3 in 84% yield. Comparison of the ¹H/¹³C 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 ¹³C 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.

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The authors declare no competing financial interest.