

# Concise and Enantioselective Synthesis of the Aminocyclitol Core of Hygromycin A

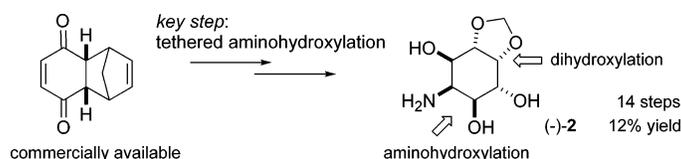
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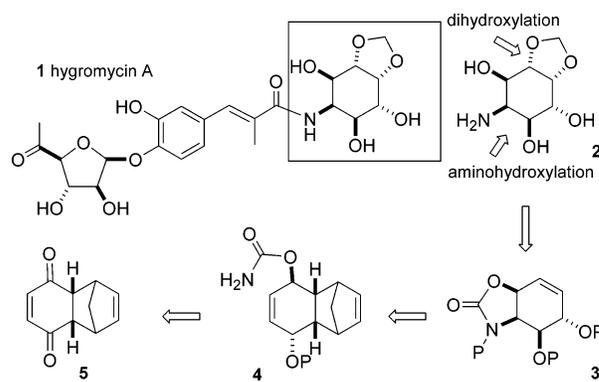
## ABSTRACT



Stereoselective aminohydroxylation and dihydroxylation using osmium(VIII) oxidants enabled the short and efficient synthesis of the aminocyclitol core of hygromycin A. In addition to allowing the selective introduction of the heteroatoms N and O, the use of osmium (via an osmate ester) as a protecting group for a 1,2-glycol is also reported. This tactic allowed efficient differentiation of otherwise equivalent hydroxyl groups and allowed us to complete the synthesis in short order (14 steps) and excellent overall yield (12%).

Hygromycin A **1** is an antibiotic first isolated from the fermentation broth of *Streptomyces hygrosopicus* in 1953 (Figure 1).<sup>1</sup> It was identified as having a broad spectrum of activity against both Gram-positive and Gram-negative bacteria. Its mode of action is peptidyl transferase inhibition, sharing a binding site on the ribosome with chloramphenicol.<sup>2</sup> More recent studies on **1** have shown that it also has hemagglutination inactivation activity, plus high antirepental activity.<sup>3</sup> This has led to renewed interest in hygromycin A as a treatment for mucohemorrhagic diseases, the control of which is of economic importance to farmers.

A series of semisynthetic modifications to **1** were made by a group from Pfizer in the mid-1990s and revealed that the aminocyclitol was critical for the activity of the compound while the furanoside unit was not.<sup>4</sup>



**Figure 1.** Retrosynthesis of the aminocyclitol core of hygromycin A.

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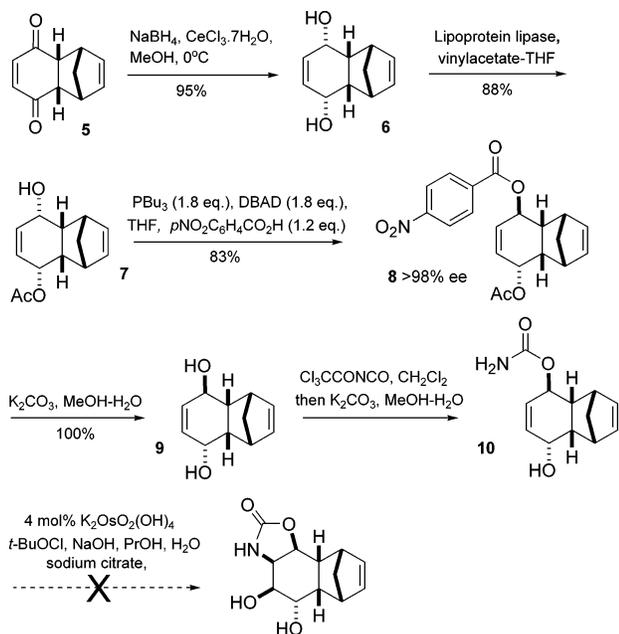
<sup>‡</sup> Eli Lilly and Company, Ltd.

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Scheme 1



To date, there has been only one total synthesis of hygromycin A, completed by Ogawa and co-workers in 1989.<sup>5</sup> However, the aminocyclitol unit of the natural product has also been prepared by Trost (en route to a synthesis of C-2 epihygromycin A),<sup>6</sup> and some formal synthetic work has been published by Arjona.<sup>7</sup>

A short and efficient synthesis of the key inositol subunit **2** was envisaged that would test some directed oxidation methodology developed within the group (Figure 1). Our unique approach would rely upon two key stereoselective reactions: (i) the facially selective dihydroxylation of intermediate **3** and (ii) the regio- and stereoselective tethered aminohydroxylation (TA) reaction of allylic carbamate **4**.<sup>8</sup>

Thus, the commercially available diketone **5** was converted into masked cyclohexadiene **7** in two steps, 84% yield, and 98% ee (of known absolute configuration) following the protocol of Ogasawara (Scheme 1).<sup>9</sup>

Inversion of the alcohol **7** under Mitsunobu conditions and ester hydrolysis furnished *trans*-diol **9** in good yield (the ee

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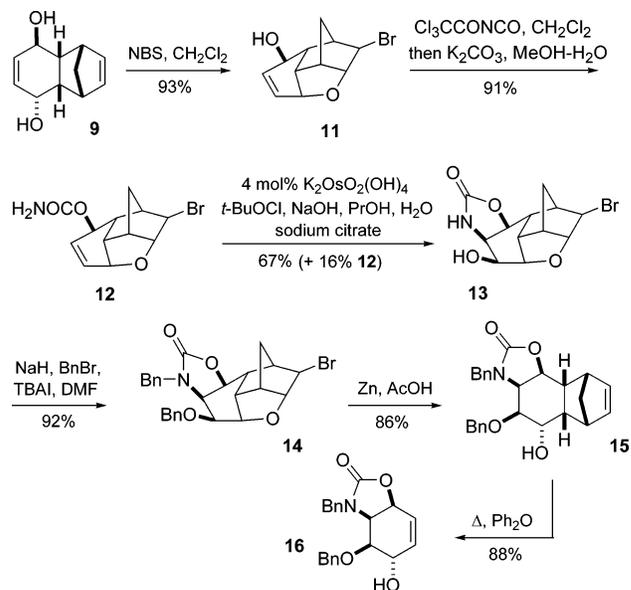
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Scheme 2



of intermediate **8** was conveniently measured by HPLC). However, our initial attempts to introduce the amino alcohol functionality onto C-2/3 using the tethered aminohydroxylation of carbamate **10** failed and returned starting material in each case (protection of the free hydroxyl group did not improve the situation). Analysis of a model of **9** and **10** led us to postulate that the pseudoaxial nature of the carbamate within **10** was responsible for the failure to oxidize the alkene unit.<sup>10</sup>

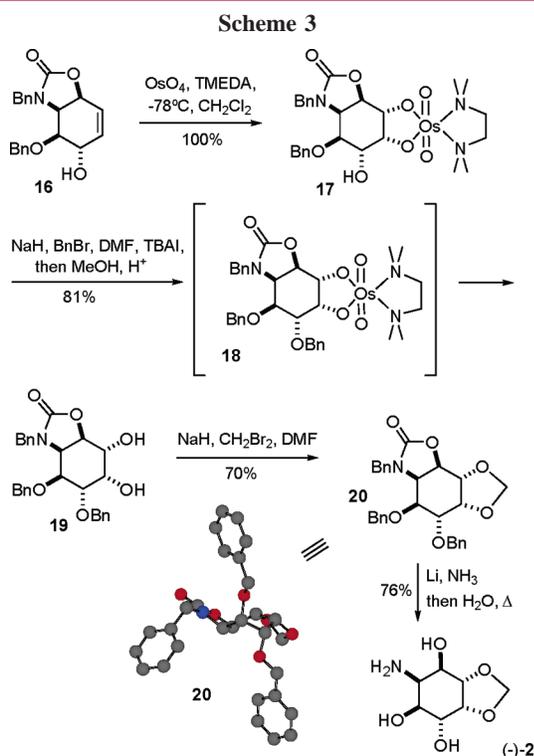
Therefore, the conformation of the TA precursor was altered by formation of a temporary bridge between the two carbocyclic rings using an ether oxygen link (Scheme 2). The ethereal linkage within **11** acts as a “drawstring”, imposing greater strain throughout the molecule while pulling the alcohol closer to a (more desirable) pseudo-equatorial position.<sup>11</sup> If the model predicted above is correct, this may permit a TA reaction to occur.

Compound **9** was reacted with NBS, forming bromoether **11** in 93% yield; after carbamate formation (**12**), it was possible to try the key oxidation again. Pleasingly, carbamate **12** reacted smoothly under modified TA conditions<sup>12</sup> furnishing **13** in 67% yield (with 16% recovered starting material). As expected from previous work, this reaction showed complete regio- and stereoselectivity.<sup>8</sup>

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(10) Subsequent studies with allylic carbamates axially disposed on a six-membered ring have supported this hypothesis: it is presumed that the reaction fails because orbitals on the oxidant cannot overlap correctly with the  $\pi$ -system of the alkene. The fact that high (syn) stereoselectivity is observed during the TA reaction of chiral acyclic allylic carbamates is also consistent with a strict stereoelectronic constraint on the reaction. Donohoe, T. J.; Johnson, P. D.; Pye, R. J.; Keenan, M. *Org. Lett.* **2004**, *6*, 2583.

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Next, the OH and NH groups were benzyl protected (**14**), the ether bridge removed (Zn, AcOH), and a retro Diels–Alder reaction performed on **15** to produce alkene **16** in good overall yield.

To complete the synthesis, a diastereoselective dihydroxylation of **16** was required, followed immediately by a regioselective protection of the two new hydroxyl groups as a methylene acetal (Scheme 3).

Protection of the C-4 hydroxyl group of **16** prior to dihydroxylation was required in order to allow regioselective acetal formation afterward. However, such protection led to a series of compounds that underwent a nonstereoselective dihydroxylation reaction. Moreover, the oxidation was also low yielding and sluggish (a similar problem had beset Ogawa's original synthesis).<sup>5</sup>

As a solution, it was decided to use the hydroxyl group at C-4 to perform a directed dihydroxylation using the mixture of OsO<sub>4</sub>/TMEDA (a reagent we developed some years ago).<sup>13</sup>

(12) Modified conditions involving the use of sodium citrate as a ligand for osmium increase the yield of the TA and also improve the workup. For the original report on the use of citrate in the dihydroxylation reaction, see: Dupau, P.; Epple, R.; Thomas, A. A.; Fokin, V. V.; Sharpless, K. B. *Adv. Synth. Catal.* **2002**, *344*, 421.

The advantages of this reagent are (i) that the complex is very reactive; (ii) hydrogen bonding control with OsO<sub>4</sub>/TMEDA is well established and so the correct stereoselectivity should ensue; (iii) the initial product of osmylation is a stable osmate ester<sup>13</sup> that could conceivably be used as a protected form of the glycol.

The results in Scheme 3 show that this key dihydroxylation of **16** worked as planned and furnished osmate ester **17** as the sole product in quantitative yield. Moreover, it was possible to exploit the stability of osmate ester **17** and use it as a glycol protecting group: compound **17** was easily benzylated to give **18** (which could be isolated if required), and the reaction was quenched with acidic methanol to release the osmium from the glycol and form **19**. This two-step procedure (**16**→**19**) solved all the problems of poor reactivity and stereo- and regioselectivity that had previously arisen.

Finally, all that remained was formation of the methylene acetal **20**<sup>5</sup> (the stereochemistry of this fully protected aminocyclitol was confirmed by X-ray crystallography<sup>14</sup>) and then one-pot deprotection of the benzyl groups and oxazolidinone under conditions reported by Trost.<sup>6</sup> The data (<sup>1</sup>H/<sup>13</sup>C NMR and specific rotation) for the final compound (–)-**2** was a good match with that reported in the literature.

To conclude, a new synthesis of the key inositol portion of hygromycin A is reported that proceeds in 14 steps and 12% overall yield; this represents the highest yielding route reported for this compound. The key reactions in this sequence were the tethered aminohydroxylation reaction and directed dihydroxylation, both of which were completely stereoselective. Moreover, the novel idea of using an osmate ester as a protecting group for a 1,2-glycol is one that may find further use in organic synthesis.

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**Supporting Information Available:** Experimental procedures and analytical and spectroscopic characterization of all starting materials and products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(14) Crystallographic data for compound **20** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 249567. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; E-mail: [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk)).