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Highly Diastereoselective Bis-Hydroxylation of the Amino-deoxy-Conduritol C Ring System. A Formal Synthesis of the Aminocyclitol Moiety of the Antibiotic Hygromycin A.

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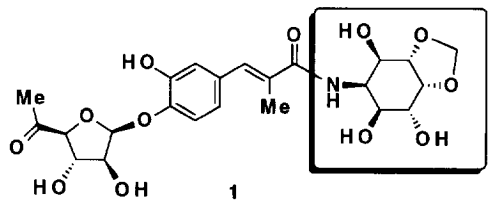
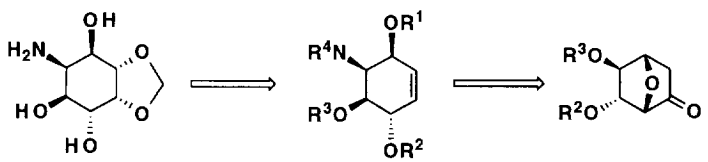
Abstract: *A formal synthesis of the aminocyclitol fragment of the antibiotic Hygromycin A is reported using, as a key step, a highly diastereoselective bis-hydroxylation of an amino-deoxy-conduritol C derivative, easily accesible from an 7-oxanorbornenic derivative which in turn can be synthesised from furan.*

Hygromycin A **1** is an antibiotic produced by cultures of several types of *Streptomyces*[1] and it is widely used against both Gram-positive and Gram-negative bacterias[2]. A fragment of the antibiotic posseses a unique aminocyclitol structure assigned as an amino-deoxy-*neo*-inositol derivative **2**. Recent structure-activity relationship studies[3] have shown that the presence of the aminocyclitol moiety in synthetic analogs is crucial for the antibacterial activity.



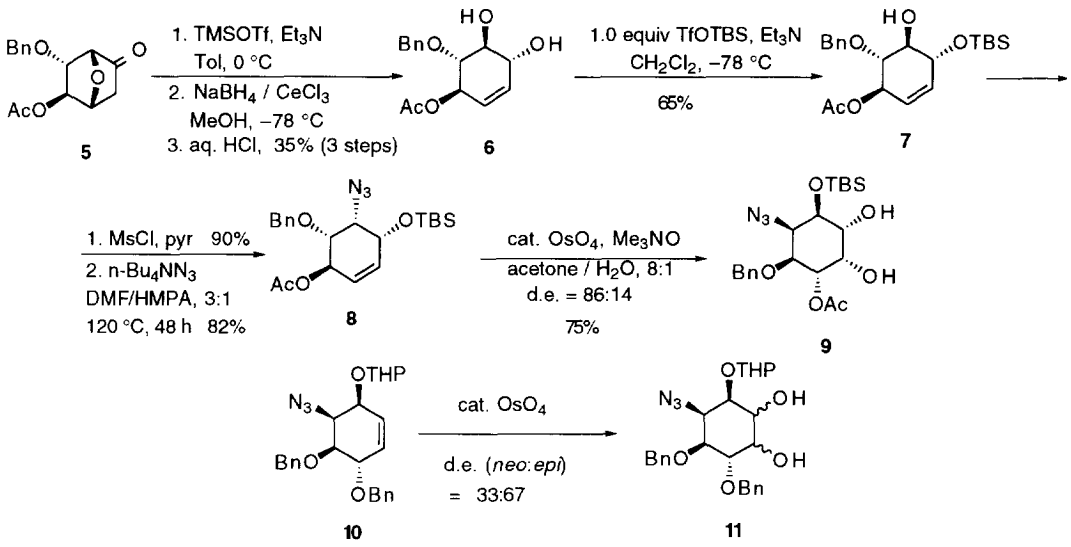
1

In 1991 Ogawa et al. reported the total synthesis of the antibiotic[4] from D-glucose. The key step for its preparation was the osmylation of an amino-deoxy-conduritol C derivative **3** which, not surprisingly, afforded a mixture of diols, under 13 different conditions, varying from 50:50 to 66:34 and attack favouring the less hindered face.



2 **3** **4**

We envisioned that the presence of two allylic ethers (R_1 = THP vs. R_2 = Bn) in Ogawa's substrate was the reason for the poor selectivity encountered and this fact prompted us to design a short and convenient route to a direct precursor of **2** starting from a 7-oxanorbornenic system[5] **4** suitable for introducing the appropiate directing group R_2.



From the acetate **5** previously prepared from furan in a sequence of six steps[6,7], compound **6**[8] was prepared by consecutive ring opening, Luche's reduction[9] and appropriate protection of the allylic position as TBS ether[10]. Inversion of the mesylated hydroxyl group at C_3 was then carried out using *n*-Bu_4NN_3[11]. Finally, the catalytic bis-hydroxylation of azido compound **8** (similar substrate to **10**, prepared by Ogawa) afforded a 86:14 mixture of *neo*:*epi* azido-deoxy-inositols favoring the *syn* attack to the acetate group, **9**. It is worth mentioning that a related azido compound **10** prepared by Ogawa afforded a *neo*:*epi* 33:67 mixture of **11** favoring the undesired *epi* stereochemistry[4].

In summary, the synthetic potential of the stereoelectronic control in the osmium-catalysed bis-hydroxylation of doubly O-allylic substituted cyclohexene derivatives has been efficiently applied to the synthesis of the aminocyclitol component of Hygromycin A derivatives. In this latter case an important improvement to the previous total synthesis is reported.

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7. Although the synthesis has been performed in racemic version, compound **5** is available in homochiral form in multigran scale. See: Black, K. A.; Vogel, P. *Helv. Chim. Acta* **1984**, *67*, 1612-1615.
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