An Enantioselective Synthesis of (−)-Allosamidin by Asymmetric Desymmetrization of a Highly Functionalized *meso*-Epoxide

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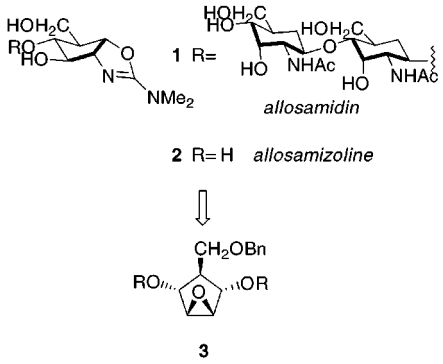
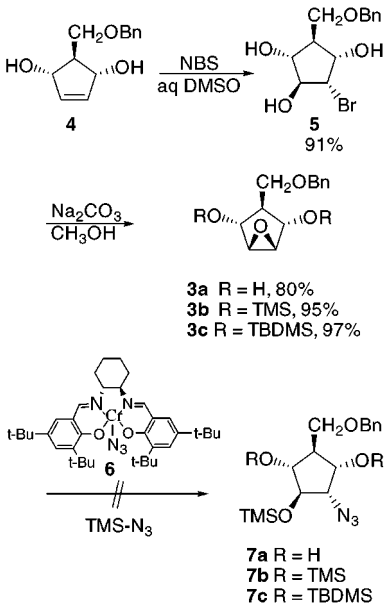
Chitin is a major component of insect cuticle and fungal cell wall and one of nature's most abundant polysaccharides.[1] Since chitin-processing enzymes play an integral role in insect cuticle and fungal wall assemblies,[2] the development of chitinase inhibitors could lead to potential insecticides[3] and fungicides[4] that would be nontoxic to humans. At present, only two classes of naturally occurring chitinase inhibitors are known: the allosamidins[5] and the styloguanidines.[6]

Allosamidins constitute a novel family of pseudotrisaccharides represented by structure **1** and have attracted considerable attention because of their potent and selective activity against insect chitinases.[7] Several successful syntheses of **1**[8−11] and its core aminocyclopentitol, allosamizoline **2**,[12−18] have been achieved. Our previously reported synthesis of (±)-**2** relied on the azidolysis of an electron-deficient, pentasubstituted *meso*-epoxycyclopentane.[17] Recently, Martinez et al. described an asymmetric ring opening (ARO) of simple *meso*-epoxides using trimethylsilyl azide ($TMSN_3$)[19] in which bimetallic catalysis[20] was observed using (salen)-Cr^{III} complexes. Here we describe an efficient enantioselective synthetic route to allosamidin (−)-**1** from more highly functionalized *meso*-epoxides of general structure **3** (Scheme 1), for which the published ARO procedures are ineffective. In probing the importance of adjacent substituents, our findings shed light on the role of electronic and steric effects in bimetallic catalysis and extend the utility of the Jacobsen reaction in constructing bioactive aminocyclitols and other densely functionalized, stereochemically complex systems.

Scheme 1



Scheme 2



Addition of HOBr to the known[21] 4-benzyloxymethyl-3,5-dihydroxycyclopentene **4** (Scheme 2) afforded bromotriol **5** (91%), which could be cyclized in base to *meso*-epoxydiol **3a** (Na_2CO_3, CH_3OH, rt, 20 h, 80%). When solutions of **3a** in ether or THF were reacted with $TMSN_3$ in the presence of chromium ((*R*,*R*)-salen) complex **6**, rapid silylation occurred leading to **3b**, but none of desired azidoether **7b** was observed. Reaction of **3a**, **3b**, and the corresponding bis(*tert*-butyldimethylsilyl) ether **3c** with varying amounts of $TMSN_3$ and catalyst **6** under a broad range of conditions generated no trace of the desired azidocyclopentitol derivatives, returning only the unreacted epoxydisilyl ethers **7b** or **7c**.

Whereas reactive epoxides normally deaggregated and solubilized **6** in solvents such as *tert*-butyl methyl ether (TBME),[20] epoxide **3b** failed to dissolve the catalyst, even when heated. Reasoning that the adjacent silyl ether groups in **3b** were large enough to deflect the catalyst-delivered

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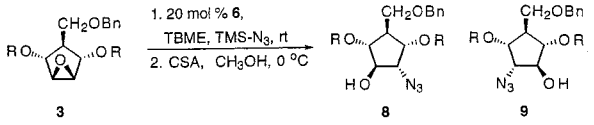
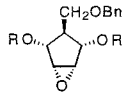
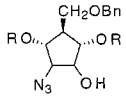
Table 1. ARO Azidolysis of Functionalized *meso*-Epoxides Catalyzed by (Salen)CrN_3



3 8 9

meso-Epoxide (% yield from **6**)	Catalyst, Conditions	Product (% yield, 2 steps)	Enantiomeric Excess
3d R = Bn (62%)	*R,R*-**6** 2 d	(+)-**8d** R = Bn (>95%)	98[a]
3d	*S,S*-**6** 6 d	(-)-**9d** (92%)	97.2[a]
3e R = Vr (69%)	*R,R*-**6** 10 d	(+)-**8e** R = Vr (97%)	94[a]
3e	*S,S*-**6** 10 d	(-)-**9e** (99%)	96.4[a]
3f R = Et (64%)	*R,R*-**6** rt, 8 d	(+)-**8f** (60%)	60[b]
3g R = Ac (38%)	*S,S*-**6** 10 d	no reaction	-----
 **10a** R = Vr (35% from **4**)	*S,S*-**6** 20 d	 (-)-**11a** (R = Vr) (85%)	80[b]
10b R = TBDMS (70% from **4**)	*R,R*-**6** 6 d	no reaction	-----

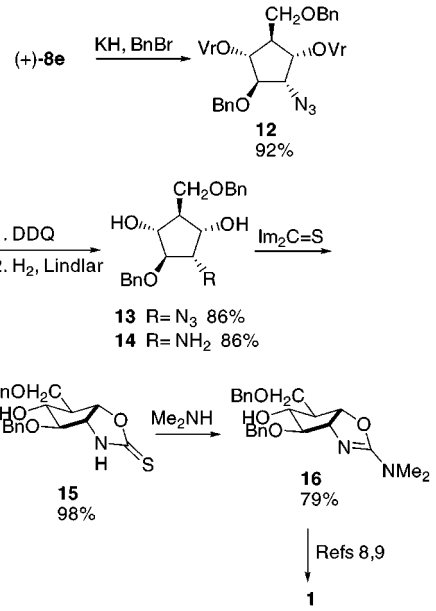
[a] Chiral HPLC analysis. [b] Mosher ester analysis.

nucleophile and sufficiently electron-withdrawing (via p-π to d-π stabilization) to influence the complexation of epoxide with **6**, we examined several different ethers. Epoxydiol **3a** was therefore transformed under standard conditions (KH, THF, 0 °C) using benzyl bromide, veratryl (3,4-dimethoxybenzyl) bromide, and ethyl iodide to the corresponding benzyl, veratryl (Vr), and ethyl ethers, **3d**−**f**.

When O-benzylated epoxide **3d** was dissolved in TBME and treated with (*R*,*R*)-**6**, the mixture rapidly became homogeneous at room temperature. After addition of $TMSN_3$, a new product appeared that was identified after premature workup and hydrolysis as (+)-**8d** (Table 1). The desired azido alcohol was formed in 56% yield (>95% based on recovered SM) and 98% ee based on chiral reversed-phase HPLC.[22] Using the enantiomeric catalyst (*S*,*S*)-**6**, **3d** was completely converted to (−)-**9d** with comparable ee after 6 d at room temperature (Table 1, entry 2).

Other entries in Table 1 confirmed the role of catalyst involvement both in complexation and nucleophile delivery. ARO azidolysis of the corresponding bis-veratryl ether **3e** proceeded in excellent yield and high ee, but was somewhat slower, perhaps because of competing catalyst complexation with the aryl ether oxygens. Reaction of the corresponding bis-ethyl ether **3f** was equally slow, but significantly less enantioselective. Diacetate **3g**, with its strong inductively withdrawing ester protecting groups, was completely inert to ring opening. ARO azidolysis of *syn*-epoxydiether **10a**, prepared from **4** by peracid-mediated epoxidation[21] and veratrylation, proceeded very slowly, but *trans*-azido alcohol **11a** was obtained in good yield and respectable ee. While nucleophilic approach in this case was unhindered, the ether protecting groups in **10a** apparently retarded complexation of the epoxide with catalyst. No ARO azidolysis was observed with the much more hindered bis-TBDMS ether **10b**.

Scheme 3



With its easily differentiated benzyl and veratryl ethers, key intermediate azido alcohol (+)-**8e** led to a formal total synthesis of (−)-allosamidin as shown in Scheme 3. Benzylation of (+)-**8e** under standard conditions gave **12**. Oxidative deprotection of the veratryl groups in **12** using DDQ afforded **13** (86%). Using Lindlar's catalyst, the azide group in **13** could be hydrogenolyzed to amine **14** (86%). Upon treatment with 1,1′-thiocarbonyldiimidazole, **14** formed thiocarbamate **15** (98%), which, when condensed with dimethylamine, gave (−)-allosamizoline derivative **16** in 79% yield. All spectroscopic and chiroptical data for **16** were identical with literature values.[8,9]

The enantioselective synthesis of **16** represents a formal synthesis of (−)-**1**, and a significant improvement (nine steps, 94% ee, 25% overall yield from **4**) in what were the shortest (nine steps, 6.9%)[8] and highest-yielding (12 steps, 11.7%)[10] prior syntheses of this key intermediate. Moreover, by developing a solution to the ARO azidolysis of highly functionalized *meso*-epoxides, our work expands the potential for use of such intermediates in organic synthesis.

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Supporting Information Available: Procedures for the synthesis of **16** from **4** and supporting characterization data.

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