Aminodiols via Stereocontrolled Oxidation of Methyleneaziridines

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Supporting Information

ABSTRACT: A highly diastereoselective Ru-catalyzed oxidation/reduction sequence of bicyclic methyleneaziridines provides a facile route to complex 1-amino-2,3-diol motifs. The relative anti stereochemistry between the amine and the vicinal alcohol are proposed to result from 1,3-bischelation in the transition state by the C1 and C3 heteroatoms.

Aminodiols are ubiquitous in a host of bioactive molecules and natural products (Figure 1). Popular approaches to these motifs often employ starting materials from the chiral pool or utilize the ring-opening of chiral epoxy alcohols with amine nucleophiles. These strategies work well when the target aminodiol is relatively simple, but accessing more complex and densely substituted motifs can be difficult. While the dihydroxylation of chiral allylic amines addresses this challenge to some extent, high loadings of OsO4 and variable dr are drawbacks.

Our group has developed new methods that introduce three new \( \text{sp}^3 \) carbon–heteroatom bonds into an allene in a sterecontrolled manner. Rapid access to \( \text{C–Nu/C–N/C–E} \) stereotriad structures containing three contiguous chiral carbons, \( \text{Ic} \), from homoallenic sulfamates is enabled through the intermediacy of bicyclic methyleneaziridines \( \text{Ia} \). This method offers diversity in the choices for the Nu and E groups of \( \text{Ic} \) but restricts the placement of nitrogen to the central carbon of the stereotriad. The utility of allene oxidation could be expanded if amine-containing stereotriads of other substitution patterns could be accessed. Herein, we report a highly diastereoselective formation of \( \text{C–N/C–O/C–O} \) (NOO) triads from simple homoallenic carbamates.

The initial step of our strategy employs allene aziridination to a methyleneaziridine \( \text{IIa} \) (Scheme 1). The bicyclic nature of \( \text{IIa} \) was expected to promote dihydroxylation to a hemiaminal \( \text{IIb} \) in high dr. Unraveling of \( \text{IIb} \) to a 1,3-hydroxyaminated ketone \( \text{IIc} \), followed by reduction, would yield either \( \text{IId} \) or \( \text{IIe} \), depending on the nature of the reductant.

We initially attempted to use homoallenic sulfamates as substrates, but aziridine ring-opening prior to reaction of the exocyclic double bond was problematic. Treatment of homoallenic carbamate \( \text{Ia} \) (Table 1) with OsO4 and NMO gave no reaction; however, a 1 mol % loading of RuCl3 in the presence of NaIO4 as the terminal oxidant (“flash dihydroxylation”) cleanly provided the desired ketone \( \text{2aE} \) (IIc, Scheme 1 for general structure). The key to achieving excellent conversion and minimizing oxidative cleavage was to employ CeCl3 as an additive. Under these conditions, the ketone \( \text{2aE} \) was obtained as a single diastereomer, indicating excellent facial selectivity in the dihydroxylation. Immediate reduction of the ketone with NaBH4 in MeOH yielded the 1-amino-2,3-diol \( \text{3aE} \) in >20:1 dr (Table 1, entry 1).

The scope of the reaction was investigated (Table 1). In all cases, the 1-amino-2,3-diol was obtained in >20:1 dr, with both

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aryl (entries 1−3) and alkyl (entries 4−8) groups tolerated at C3 of the substrate. The presence of an EWG on the arene decreased the yield but did not impact the dr (Table 1, compare entry 3 to entries 1 and 2). The 1-amino-2,3-diols obtained from E methyleneaziridines contained the 1,2-anti:2,3-syn stereochemistry, as verified by X-ray crystallography of 3cE. The structures of 3aE and 3bE were assigned by analogy to 3cE (Supporting Information). The anti relationship between the

Table 1. Stereocontrolled Transformation of gem-Dimethyl Bicyclic Methyleneaziridines to NOO Stereotriads

| Entry | R1, R2 | E:Z | Yield | α | Major Product |
|-------|--------|-----|-------|---|---------------|
| 1     | Ph, Me | 3aE | 94%   | >20:1 | 3bE |
| 2     | tol, Me | 7b | 70:30 | 84% | 7c |
| 3     | 4-CF3C6H4 | 3cE | 73% | >20:1 | 3d |
| 4     | Me, Me | 3e | 70:30 | 57% | 3f |

Table 2. Expanding the Scope of NOO Stereotriad Synthesis

| Entry | R1, R2, R3 | E:Z | Yield | α | Major Ketone (from E) | Major Products (from E) | Yield | dr |
|-------|------------|-----|-------|---|------------------------|-------------------------|-------|----|
| 1     | C6H11, Me, H | 5a | 98%   | >20:1 | 7a | 80% | 5.7:1 |
| 2     | 'Bu, Me, H | 5b | 55% | >20:1 | 7b | 96% | 7.2:1 |
| 3     | Et, Me, H | 5c | 66% | 2.3:1 | 7c | 50% | 8.3:1 |
| 4     | Pr, Pr, H | 5d | 96% | >20:1 | 7d | 88% | 6.1:1 |
| 5     | - (CH2)2-, H | 5e | 79% | >20:1 | 7e | 98% | 8.9:1 |
| 6     | C6H11, Me, Me | 5f | 80% | >20:1 | 7f | 98% | 6.6:1 |
C1 amine and the C2 alcohol was also observed when C3 was achiral (entries 4 and 5). When the two substituents at C3 of the allene were very similar, the mixtures of E and Z methyleneaziridines were difficult to separate (entries 6–8). However, the reaction could be carried out on the 70:30 E/Z mixtures and the resulting isomers separated to give the diastereomeric triads 3f−hE and 3f−hZ in excellent dr (E shown). Separating ketones 2gE and 2gZ and independently subjecting them to reduction clearly showed the dr of the reduction was >20:1. The relative stereochimistries of both 3gE and 3gZ were verified by X-ray crystallography as 1,2-anti:2,3-syn (Supporting Information) for 3gE and 1,2-anti:2,3-anti for 3gZ.

The 1,3-disubstituted methyleneaziridine 1i (entry 9) was challenging, as overoxidation to the diketone using Ru catalysis was problematic.7 Increasing the amount of CeCl3 improved the selectivity for 2i, but at the cost of conversion. The use of a full equivalent of CeCl3 and portionwise addition of 3.0 equiv of NaI/acetate gave a 66% yield of the desired product with minimal overoxidation.

To expand the reaction scope and shed light on the factors responsible for stereocontrol in the ketone reduction, methyleneaziridines lacking the gem-dimethyl group were explored (Table 2). These compounds were susceptible to ring-opening when the conditions described in Table 1 were employed. Substitution of AcOH or H2SO4 for CeCl3 as the additive improved both the conversions and the yields in the dihydroxylation.

Oxidation of E-4a (Table 2, entry 1) gave the ketone 5a in 98% yield as a single diastereomer. Reduction of 5a with NaBH4 in MeOH gave the 1,2-anti:2,3-syn stereoisomer 7a in 80% yield (verified by X-ray crystallography) and 5.7:1 dr, along with the minor isomer 8a. The dialkyl-substituted methyleneaziridines 4b and 4c were not easily separable, but the diastereomers could be resolved at either the ketone or the 1-amino-2,3-diol stage to give the products in dr of 7:1–8:3:1 (entries 2 and 3). Substrates with identical substituents at C3 (entries 4 and 5) exhibited a 1,2-anti relationship between the C1 amine and the C2 alcohol.

The unexpected stereochemical outcomes were initially puzzling. While Felkin–Anh and Crand chelation models are often invoked to explain stereochemical outcomes in the addition of nucleophiles to α-substituted carbonyls, control when a ketone is flanked by two different potential chelating groups is poorly understood.8,9 We propose the −NH and the −OH of ketones of the general form 9 (Figure 2) participate in 1,3-bis-chelation to give a trans decalin-type intermediate 10. Reduction of the ketone from the top face should be favored to yield the 1,2-anti:2,3-syn relationship observed in the products. To determine how well this hypothesis fit our data, the reduction of ketones of several substitution patterns were examined more closely. In the case of 3iE and 3iZ, formed from the E and Z stereoisomers of 2f, an anti relationship between C1 and C2 was noted in both of the products (Table 1, entry 6 and Figure 2, A and B), ruling out stereocontrol of the reduction by C3. The observed results could be rationalized either by our proposed model or by assuming that the amine at C1 is responsible for controlling the reduction outcome. If C1 were solely responsible for stereocontrol of the reduction, the removal of a substituent from C3 of 2i (Table 1, entry 9 and Figure 2, C) would not be expected to influence the dr. However, we found that the dr of 3iE decreased to 2.2:1 using NaBH4 in MeOH. Switching to a less polar solvent and a lower temperature increased the dr, while substitution of Zn(BH4)2 for NaBH4 restored the dr to 7.9:1 with a 1,2-anti relationship as verified by X-ray crystallography. Chelation control through the C3 oxygen would be expected to yield the 1,2-syn:2,3-anti triad; thus, we propose that a tighter transition state exists in C when M = Zn (van der Waal radius of Zn = 0.88 Å), as compared to M = Na (Na = 1.16 Å), leads to an increase in dr.

In conclusion, rapid and diastereoselective conversion of homoallenic carbamates to 1-amino-2,3-diols has been achieved. Stereoselectivity in the reduction of the α,α′-substituted ketones depends on the specific substitution pattern of the substrate but often exhibits dr > 10:1. Coupled with our previous observations that the axial chirality of an allene can be transferred to point chirality, this protocol permits rapid access to densely functionalized, enantioenriched aminodiols.

**ASSOCIATED CONTENT**

Supporting Information

Experimental procedures and full characterizations are available for all new compounds. X-ray crystallographic data is available for compounds 3cE, 3gE, 3gZ, 7aE, and 3iE (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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