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# Synthesis of Virtually Enantiopure Aminodiols with Three Adjacent Stereogenic Centers by Epoxidation and Ring-Opening

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**A virtually complete enantioselective synthesis of 3-amino-1,2-diols with three consecutive stereocenters was accomplished by a sequential cascade of two kinetic resolutions, which features a Sharpless or Hafnium-catalyzed asymmetric epoxidation and a subsequent W-catalyzed aminolysis. Enantiopure products with up to > 99.9 % ee and > 99.9:0.1 dr were obtained and could serve as potential building blocks for pharmaceutical or biological significant molecules.**

Synthesizing compounds with complete enantiopurity has been a paramount challenge in organic chemistry, especially with pharmaceutical drugs or biologically important molecules. Many such compounds[1] have 3-amino-1,2-diol motifs in the backbone, including the antitumor aminocyclopentitol pactamycin, proteasome inhibitor TMC-95A, immunosuppressant antibiotic myriocin, riboflavin (vitamin B2) and hydrogenase coenzyme F420 (Figure 1). The aminodiol moieties in these compounds have generally been accessed by dihydroxylation or epoxidation[2] followed by nucleophilic ring-opening[3] .

Although the kinetic resolution of secondary allylic alcohols has been extensively studied since the emergence of Sharpless epoxidation, there is no efficient system for the kinetic resolution of substituted 2,3-epoxy alcohols. In fact, previous efforts on its asymmetric catalysis are often limited to terminal or *meso* epoxides.[4] Despite our group's recent developments that provided a catalytic regio- and enantioselective aminolysis of 2,3-epoxy alcohols using a tungsten/bis(hydroxamic acid) system[4], only primary alcohols have been demonstrated as substrates. Here we report a two-step combined epoxidation/ring-opening methodology[5] starting with a secondary allylic alcohol. This reaction sequence (Scheme 1, top) was shown to generate virtually enantiopure functionalized 3-amino-1,2-diols with three stereogenic centers, an important step forward from the two stereogenic centers in the previous paper.

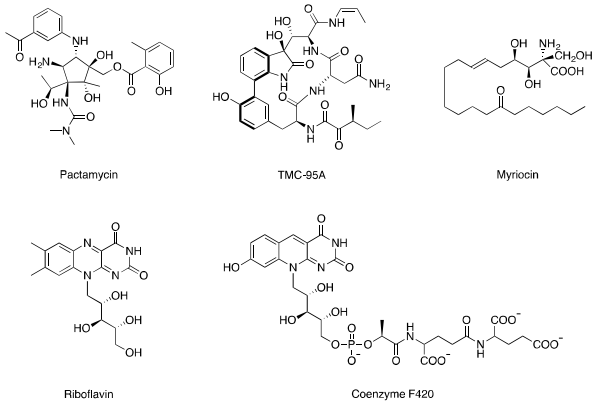
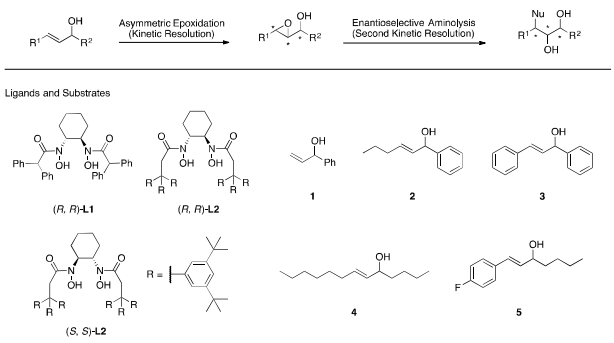



**Figure 1** Potential synthetic targets such as pactamycin, TMC-95A, myriocin, riboflavin and coenzyme F420.




**Scheme 1** Top: Two-step combined epoxidation/ring-opening strategy for the synthesis of aminodiols with three-stereogenic centers. Bottom: Ligands and substrates for reaction screening.

Distinct advantages are associated with a two-step kinetic resolution strategy. In the usual kinetic resolution of a racemic mixture, enantioselectivity erodes with reaction progression and

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plunges after about 50% conversion. (Figure 2, left)[6] Thus, kinetic resolution is perceived as inefficient in comparison with a normal asymmetric reaction of a prochiral substrate, which exhibits a constant enantioselectivity[6] However, in a two-step system, the second kinetic resolution starts with a non-racemic mixture. And if the two resolution steps have matched stereoselectivity (i.e. the more abundant product of the first step is also the kinetically favored substrate in the second step), the product can maintain exceptional enantiopurity up to high conversion (Figure 2, right), since the favored substrate's higher concentration and greater rate constant act in synergy. The enhanced enantioselectivity (often more than 99.9 %) would be extremely valuable to the pharmaceutical industry.

With respect to catalysis in our particular reaction, the hydroxyl group in the secondary allylic alcohol can serve as the directing group for both asymmetric epoxidation and aminolysis, alleviating the complexity of pre-functionalization and post-treatment. Our combination of two kinetic resolutions for constructing three adjacent stereogenic centers in the molecules is unprecedented to the best of our knowledge.

$$seletivity = k_{rel} = \frac{\ln\left[\frac{(R_o + S_o)(1 + c - ee \cdot c) + (R_o - S_o)}{2R_o}\right]}{\ln\left[\frac{(R_o + S_o)(1 + ee \cdot c - c) - (R_o - S_o)}{2S_o}\right]}$$

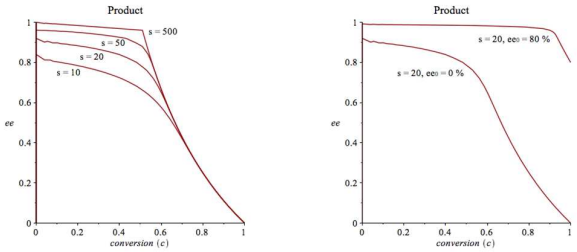
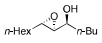
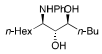
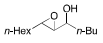
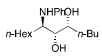
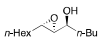
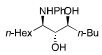
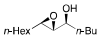
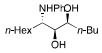
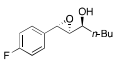
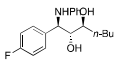



**Figure 2.** Top: Equation of $k_{rel}$ (selectivity) as a function of *ee* and conversion (*c*), with known values of $R_0$, and $S_0$. (Refer to SI for derivation of equation) Bottom left: Plots of ee (product) vs. conversion when $ee_0$ = 0 % (racemic mixture), with varying selectivity (500, 50, 20 and 10). Bottom right: Plot of ee (product) vs. conversion when $ee_0$ = 0 % (racemic mixture) and 80 % (non-racemic), both with a selectivity of 20.

**Table 1** Reaction screening of substrates and catalyst system.

| Entry | Substrate | Epoxide | Epoxidation Method | Time | Results[i] | Aminodiol | Aminolysis Method | Time | Results[i] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **1** |  | a[a] | 15 h | 48 % yield<br>98 : 2 dr<br>98 % ee |  | e[e] | 24 h | 69 % yield<br>99.5 : 0.5 dr<br>99.6 % ee |
| 2 | **2** |  | a[a] | 2 h | 50 % yield<br>> 99.8 : 0.2 dr<br>92 % ee |  | e[e] | 48 h | 94 % yield<br>99.9 : 0.1 dr<br>99.9 % ee |
| 3 | **2** |  | b[b] | 2 h | 50 % yield<br>dr and ee n.d. |  | f[f] | 48 h | 86 % yield<br>> 99.9 : 0.1 dr<br>> 99.9 % ee |
| 4 | **2** |  | *m*CPBA | overnight | 56 % yield |  | e[e] | 24 h | 44 % yield<br>> 95:5 dr<br>96 % ee |
| 5 | **3** |  | a[a] | 3 h | 39 % yield<br>17:1 dr<br>96 % ee |  | e[e] | 20 h | 81 % yield<br>> 99.5 :0.5 dr<br>98.8 % ee |
| 6 | **3** |  | a[a] | 3 h | 39 % yield<br>17:1 dr<br>96 % ee |  | f[f] | 20 h | 41 % yield<br>> 99 :1 dr<br>94.8 % ee |
| 7 | **4** |  | c[c] | 20 h | 35 % yield<br>dr and ee n.d. |  | W(OEt)$_6$<br>(racemic) | 24 h | 81:19 dr<br>93 % ee |
| 8 | **4** |  | *m*CPBA | overnight | 69 % yield |  | e[e] | 24 h | 16 % yield<br>6:94 dr<br>58 % ee |
| 9 | **4** |  | a[a][g] | 25 min | 44 % yield<br>98:2 dr |  | e[e] | 4 d | 33 % yield<br>>99.9 % ee |
| 10 | **4** |  | d[d][g] | 15 h(0°C)<br>+3 h(r.t.) | 56 % yield<br>1:2 dr |  | f[f][h] | 48 h | 52 % yield<br>91 % ee |
| 11 | **5** |  | a[a][g] | 3 h | 49 % yield<br>93:7 dr |  | e[e] | 4 d | 38 % yield<br>91 % ee |

Asymmetric epoxidation methods: [a] $Ti(OiPr)_4$/(+)-DIPT/TBHP/substrate = 0.1/0.12/0.7/1, 3Å MS (30 wt %), -20 °C in $CH_2Cl_2$. [b] $Ti(OiPr)_4$/(-)-DIPT/TBHP/substrate = 0.1/0.12/0.7/1, 3Å MS (30 wt %), -20 °C in $CH_2Cl_2$. [c] $WO_2(acac)_2$/(*R*,*R*)-**L2**/NaCl/$H_2O_2$/substrate = 0.025/0.03/0.5/1.5/1, r.t. in $CH_2Cl_2$. [d] $Hf(OtBu)_4$/(*R*,*R*)-**L1**/MgO/CHP/substrate =

0.05/0.055/0.2/1/1, 0 °C in toluene. Enantioselective aminolysis methods: [e] $W(OEt)_6$/(*S,S*)-**L2**/$H_2O_2$/aniline/substrate = 0.05-0.2/0.06-0.24/0.2/1/1.5, 55 °C in THF. [f] $W(OEt)_6$/(*R,R*)-**L2**/$H_2O_2$/aniline/substrate = 0.05-0.2/0.06-0.24/0.2/1/1.5, 55 °C in THF. [g] major diastereomer isolated for ring-opening step. [h] aniline/substrate = 0.5 :1 [i] dr in anti : syn. [j] dr in anti, anti : syn, anti

We started by examining our two-step methodology on a few model substrates (compounds **1**-**5** in Scheme 1) for optimization. Screening of previously established systems $WO_2(acac)_2$/(*R,R*)-**L2**, $VO(iPr)_3$/(*R,R*)-**L1**, $Hf(OtBu)_4$/(*R,R*)-**L1** and $Ti(OiPr)_4$/(+)-DIPT was performed on the epoxidation of these secondary allylic alcohols. We began with the recent developed $WO_2(acac)_2$/(*R,R*)-**L2**[7] on substrates **1** and **2**; the reaction of **1** gave substantial amount of the ketone whereas **2** gave exclusively the double-bond rearranged products. $VO(iPr)_3$/(*R,R*)-**L1** catalyst system was attempted subsequently, as well as Sharpless epoxidation with $Ti(OiPr)_4$/(+)-DIPT[8] (entry 2); the latter exhibit a much better efficiency with 50% yield, 99.8:0.2 diastereoselectivity, and 92 % enantioselectivity. This system also works well for substrates **1** (entry 1), **3** (entry 5), **4** (entry 9) and **5** (entry 11). $Hf(OtBu)_4$/(*R,R*)-**L1**, on the other hand gave the *syn*-epoxy alcohol for **4** as the major diastereomer, which differs from all the other systems. (entry 10)

In the subsequent enantioselective aminolysis of 2, 3-epoxy alcohols, only the $W(OEt)_6$/**L2** approach[4] was attempted, given the scarcity of existing methods. Since all of the known tungsten-catalyzed epoxide-opening reactions proceeded with complete C3 regioselectivity via $S_N2$ mechanism[4,9], the theoretical outcome of the combined sequence is four product stereoisomers. Remarkably, when the racemic epoxide of **2** was exposed to asymmetric ring-opening conditions with aniline, a high selectivity for one out of the four was observed with 96% ee and >95:5 dr. (entry 4) In tandem with the stereoselective epoxidation, the enantiopurity of final product **2ae** was boosted to 99.9 % ee and 99.9:0.1 dr (entry 2), and its absolute configuration was determined by X-ray crystallography as (1*S*,2*R*,3*R*)-1-phenyl-3-(phenyl-amino)hexane-1,2-diol. A comparison between $W(OEt)_6$/(*S,S*)-**L2** (entry 5, where ee was enhanced) and $W(OEt)_6$/(*R,R*)-**L2** (entry 6, where ee dropped) suggested that the former matches in enantioselectivity, while diastereoselectivity remained unperturbed.

Interestingly, an unusual stereochemical outcome of the reaction sequence was observed for substrates **4** and **5**. When W- and Ti-catalyzed epoxidation was combined with W-catalyzed aminolysis, a mismatch in diastereoselectivity was observed. Two experiments (entries 7 and 8), each with only one asymmetric step revealed that W-catalyzed epoxidation gave the *anti*-epoxy alcohol while W-catalyzed aminolysis preferred the *syn*-epoxy alcohol. Hf-catalyzed epoxidation, surprisingly, showed a preference for *syn*-epoxy alcohol, and provided access to 1,2,3-*syn, anti*-amino diols (entry 10), which was unusual in the literature.

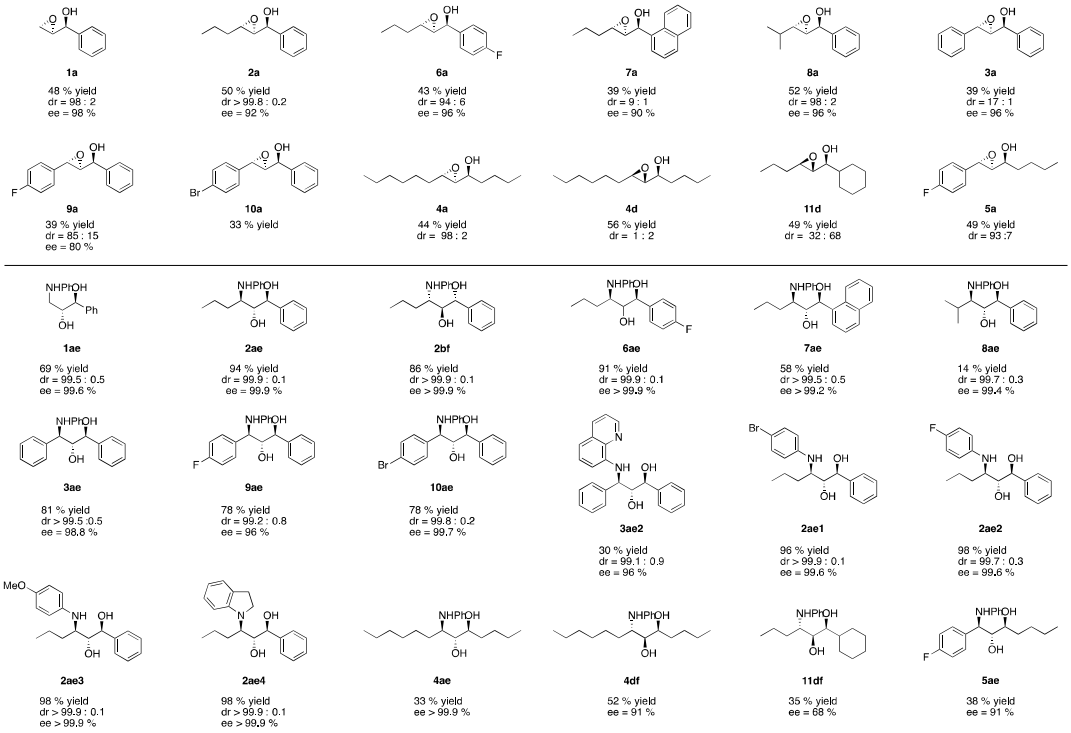



**Figure 4** Substrate scope of the combined system of titanium-catalyzed or hafnium catalyzed asymmetric epoxidation and tungsten-catalyzed ring-opening. Letter a, b, c, d, e, f represents methods used in Table 1, for example **1ae** denotes substrate 1 was subject to epoxidation by method a and ring-opening by method e. (Refer to SI for details) Yield refers to yield for each individual step, not overall yield.

To explore the substrate scope of our system, different substrates and amine nucleophiles were evaluated and excellent stereochemical outcomes were obtained for most of them (Figure 4). Generally, reactions with these substrates proceed with 69 % to 98 % yield, 98.8-99.9 % ee and 99.5:0.5-99.9:0.1 dr. Starting from the model substrate **2**, we varied the structure of $R_1$ (**8ae**) and $R_2$ (**6ae** and **7ae**), and all gave remarkable stereoselectivity, though low yield was obtained from the more hindered compound **8** bearing an isopropyl group. Derivatives from substrate **3** gave high yields (**9ae** and **10 ae**), but **9ae** gave relatively lower enantioselectivity of 96 %. Variations on the nucleophilic amine, such as substituted aniline (**2ae1**, **2ae2** and **2ae3**) and secondary amine (**2ae4**) all proceeded smoothly with exceptionally high yield and stereoselectivity, while heterocyclic amine (**3ae2**) encountered lower reactivity and selectivity. Reversing the enantiomeric identity of both catalysts to $Ti(OiPr)_4$/(-)-DIPT and $W(OEt)_6$/(*R*,*R*)-**L2** provided the anticipated product **2bf**, the enantiomer of **2ae**. The reactions with **4ae** and **5ae** were much slower as anticipated due to a mismatch in diastereoselectivity, nevertheless products were generated with good enantioselectivity.

These remarkable results presented a route to virtually enantiopure 3-amino-1,2-diols by cascade of an asymmetric epoxidation with a tungsten-catalyzed aminolysis. The products synthesized in this paper (up to >99.9% ee and >99.9:0.1 dr) are significant since this level of enantiopurity (>99.9 % ee) is rare in the literature but are of great importance to the pharmaceutics given the ubiquity of the aminodiol motif in many drug candidates.

## Conclusions

In summary, we have accomplished the highly enantioselective synthesis of aminodiols with three stereocenters by combining a $Ti(OiPr)_4$/(+)-DIPT or $Hf(OtBu)_4$/(*R*,*R*)-**L1** catalyzed asymmetric epoxidation with a subsequent enantioselective aminolysis using $W(OEt)_6$ /(*S*,*S*)-**L2**, with up to > 99.9 % ee and > 99.9:0.1 dr. This sequential approach, which tolerates a broad substrate scope and various amines, provides access to pharmaceutical or biological significant molecules.

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## Notes and references

1 For total synthesis of complex molecules containing 3-amino-1,2-diols motif: a) J. T. Malinowski, R. J. Sharpe, J. S. Johnson, *Science* **2013**, *340*, 180–182; b) B. K. Albrecht, R. M. Williams, *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 11949–11954; c) M. Inoue, H. Sakazaki, H. Furuyama, M. Hirama, *Angew. Chem. Int. Ed. Engl.* **2003**, *42*, 2654–2657.

2 For reviews on asymmetric epoxidation: a) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1; b) Katsuki, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, **1999**; Vol. 2, p 621; c) McGarrigle, E. M.; Gilheany, D. G. *Chem. Rev.* **2005**, *105*,1563 ; d) Xia, Q.-H.; Ge, H.-Q.; Ye, C.-P.; Liu, Z.-M.; Su,K.-X. *Chem. Rev.* **2005**, *105*, 1603; e) Wong, O. A.; Shi, Y. *Chem. Rev.* **2008**, *108*, 3958
For examples on asymmetric epoxidation of allylic alcohols: a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974; b) Zhang, W.; Basak, A.; Kosugi, Y.; Hoshino, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2005**,*44*, 4389; c) Egami, H.; Ogama, T.; Katsuki, T. *J. Am. Chem. Soc.* **2010**, *132*, 5886; d) Olivares-Romero, J. L.; Li, Z.; Yamamoto, H. *J. Am. Chem. Soc.* **2013**, *135*, 3411;

3 For reviews and examples on regioselective ring opening of 2,3-epoxy alcohols: a) R. M. Hanson, *Chem. Rev.* **1991**, *91*, 437–475; b) P. C. A. Pena, S. M. Roberts, *Curr. Org. Chem.* **2003**, *7*, 555–571. c) M. Caron, K. B. Sharpless, *J. Org. Chem.* **1985**, 50, 1557 – 1560; d) C. H. Behrens, K. B. Sharpless, *J. Org. Chem.* **1985**, *50*, 5696 – 5704; e) S. Y. Ko, K. B. Sharpless, *J. Org. Chem.* **1986**, *51*, 5413 – 5415; f) M. Caron, P. R. Carlier, K. B. Sharpless, *J. Org. Chem.* **1988**, *53*, 5185 – 5287; g) M. Onaka, K. Sugita, H. Takeuchi, Y. Izumi, *J. Chem. Soc. Chem. Commun.* **1988**, 1173 – 1174; h) T. K. Chakraborty, G. V. Reddy, *Tetrahedron Lett.* **1991**, *32*, 679 – 682; i) M. Canas, M. Poch, X. Verdaguer, A. Moyano, M. A. Pericàs, A. Riera, *Tetrahedron Lett.* **1991**, *32*, 6931 – 6934; j) M. Chini, P. Crotti, L. A. Flippin, C. Gardelli, E. Giovani, F. Macchia, M. Pineschi, *J. Org. Chem.* **1993**, *58*, 1221 – 1227; k) R. Martín, G. Islas, A. Moyano, M. A. Pericàs, A. Riera, *Tetrahedron* **2001**, *57*, 6367 – 6374; l) M. Sasaki, K. Tanino, M. Miyashita, *Org. Lett.* **2001**, *3*, 1765 – 1767; m) M. Sasaki, K. Tanino, A. Hirai, M. Miyashita, *Org. Lett.* **2003**, *5*, 1789 – 1791; n) M. Pastó, B. Rodríguez, A. Riera, M. A. Pericàs, *Tetrahedron Lett.* **2003**, *44*, 8369 – 8372; o) Y. Tomata, M. Sasaki, K. Tanino, M. Miyashita, *Tetrahedron Lett.* **2003**, *44*, 8975 – 8977; p) K. Surendra, N. S. Krishnaveni, K. R. Rao, *Synlett* **2004**, 506 – 510.

4 C. Wang, H. Yamamoto, *Angew. Chem. Int. Ed. Engl.* **2014**, *53*, 13920–13923.

5 For reviews on combined asymmetric catalysis: a) L. Fransson, C. Moberg, *ChemCatChem* **2010**, *2*, 1523–1532; b) T. R. Hoye, J. C. Suhadolnik, *J. Am. Chem. Soc.* **1985**, *107*, 5312–5313; c) S. L. Schreiber, T. S. Schreiber, D. B. Smith, *J. Am. Chem. Soc.* **1987**, *109*, 1525–1529; d) W. R. Roush, J. A. Straub, M. S. VanNieuwenhze, *J. Org. Chem.* **1991**, *56*, 1636–1648; e) M. I. Klauck, S. G. Patel, S. L. Wiskur, *J. Org. Chem.* **2012**, *77*, 3570–3575; f) S. Xu, C.-T. Lee, G. Wang, E.-i. Negishi, *Chem. Asian J.* **2013**, *8*, 1829–1835.

6 J. M. Keith, J. F. Larrow, E. N. Jacobsen, *Adv. Synth. Catal.* **2001**, *343*, 5–26.

7 C. Wang, H. Yamamoto, *J. Am. Chem. Soc.* **2014**, *136*, 1222–1225.

8 Y. Gao, J. M. Klunder, R. M. Hanson, H. Masamune, S. Y. Ko, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.

9 C. Wang, H. Yamamoto, *J. Am. Chem. Soc.* **2014**, *136*, 6888–91.

10 The absolute stereochemistry of **2ae** was assigned by X-ray crystallography and comparison with literature (see Supporting Information). The stereochemistry of the remaining amino diols was assigned by analogy.