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Ammonium-Directed Oxidation of Cyclic Allylic and Homoallylic Amines

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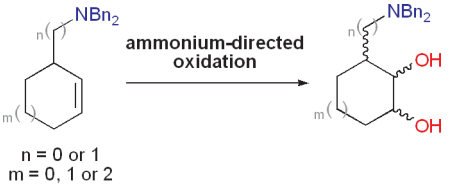

The ammonium-directed olefinic oxidation of a range of cyclic allylic and homoallylic amines has been investigated. Functionalization of a range of allylic 3-(*N*,*N*-dibenzylamino)cycloalk-1-enes with *m*-CPBA in the presence of Cl_3CCO_2H gives exclusively the corresponding *syn*-epoxide for the 5-membered ring (>99:1 dr), the *anti*-epoxide for the 8-membered ring (>99:1 dr), and predominantly the *anti*-epoxide for the 7-membered ring (94:6 dr). Oxidation of the homoallylic amines 3-(*N*-benzylamino)methylcyclohex-1-ene and 3-(*N*,*N*-dibenzylamino)methylcyclohex-1-ene gave, in both cases, the corresponding *N*-protected 1,2-*anti*-2,3-*syn*-3-aminomethylcyclohexane-1,2-diol with high levels of diastereoselectivity (≥90:10 dr). The versatile synthetic intermediates resulting from these oxidation reactions are readily transformed into a range of amino diols.

Introduction

Substrate-directed transformations are valuable synthetic processes.[1] Within this arena, the olefinic oxidation of an allylic alcohol by a peracid (Prileschajew oxidation)[2] under hydrogen-bonded control of the hydroxyl group has been extensively studied[1,3] and utilized.[1] In contrast, oxidations of the corresponding homoallylic substrates have been much less well investigated.[4] We recently reported that the chemo- and diastereoselective oxidation of 3-(*N*,*N*-dibenzylamino)cyclohex-1-ene **1** could be achieved by in situ protection of the amine with either Cl_3CCO_2H or TsOH, followed by treatment with *m*-CPBA.[5] This methodology was utilized to facilitate the synthesis of the diastereoisomeric *syn*- and *anti*-epoxides **2** and **3** and all four diastereoisomers of 3-(*N*,*N*-dibenzylamino)-cyclohexane-1,2-diol **4**−**7** (Figure 1).[6] As part of our ongoing research program concerning the synthesis of the amino diol motif for application in the de novo asymmetric synthesis of unnatural amino sugars and derivatives,[7] we have further

(1) For a review on substrate-directed reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.
(2) Prileschajew, N. *Chem. Ber.* **1909**, *42*, 4811.
(3) Bartlett, P. D. *Rec. Chem. Prog. II* **1950**, 47. Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1957**, 1958. Dryuk, V. G. *Tetrahedron* **1976**, *32*, 2855. Singleton, D. A.; Merrigan, S. R.; Liu, J.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 3385. Houk, K. N.; Liu, J.; DeMello, N. C.; Condroski, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10147. Okovytyy, S.; Gorb, L.; Leszczynski, J. *Tetrahedron Lett.* **2002**, *43*, 4215.
(4) For a discussion of the stereochemistry of epoxidation in some homoallylic cyclohexene alcohols, see: Kočovský, P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1759. For examples concerning the oxidative functionalization of homoallylic substrates, see ref 1 and: Garside, P.; Halsall, T. G.; Hornby, G. M. *J. Chem. Soc. C* **1969**, 716. Ye, D.; Fringuelli, F.; Piermatti, O.; Pizzo, F. *J. Org. Chem.* **1997**, *62*, 3748. de Sousa, S. E.; Kee, A.; O'Brien, P.; Watson, S. T. *Tetrahedron Lett.* **1999**, *40*, 387. Donohoe, T. J.; Mitchell, L.; Waring, M. J.; Helliwell, M.; Bell, A.; Newcombe, N. J. *Org. Biomol. Chem.* **2003**, *1*, 2173.
(5) Aciro, C.; Claridge, T. D. W.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 3751.
(6) Aciro, C.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 3762.
(7) For selected recent examples, see: Cailleau, T.; Cooke, J. W. B.; Davies, S. G.; Ling, K. B.; Naylor, A.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2007**, *5*, 3922. Abraham, E.; Davies, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1655. Abraham, E.; Brock, E. A.; Candela-Lena, J. I.; Davies, S. G.; Georgiou, M.; Nicholson, R. L.; Perkins, J. H.; Roberts, P. M.; Russell, A. J.; Sánchez-Fernández, E. M.; Scott, P. M.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 1665. Davies, S. G.; Durbin, M. J.; Goddard, E. C.; Kelly, P. M.; Kurosawa, W.; Lee, J. A.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Scott, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2009**, *7*, 761. Aciro, C.; Davies, S. G.; Kurosawa, W.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *Org. Lett.* **2009**, *11*, 1333.

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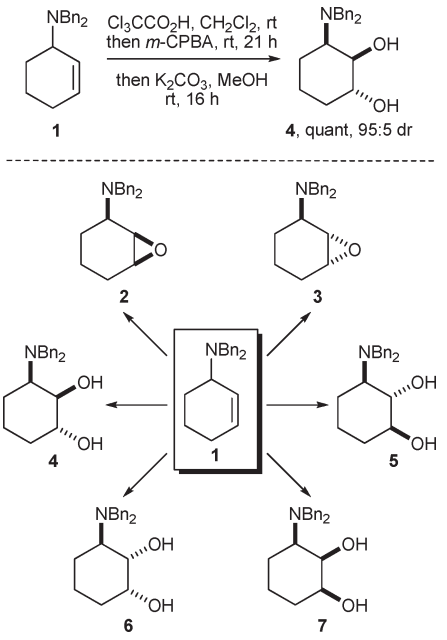


FIGURE 1. Ammonium-directed olefinic oxidation of 3-(*N*,*N*-dibenzylamino)cyclohex-1-ene **1**.

probed the generality of this transformation by application to a range of cyclic allylic and homoallylic amines, as delineated herein.

Results and Discussion

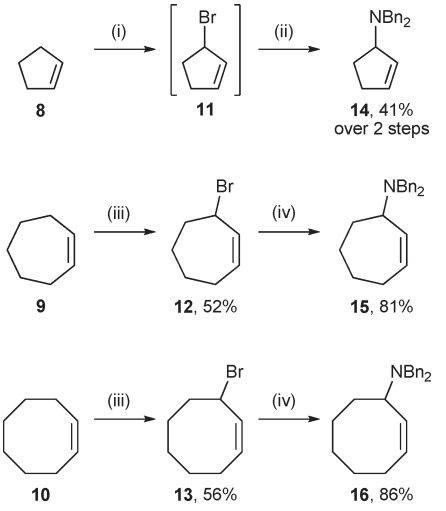
Oxidation of Allylic Amines: Diastereoselective Epoxidation of 3-(*N*,*N*-Dibenzylamino)cycloalk-1-enes. A range of 3-(*N*,*N*-dibenzylamino)cycloalk-1-enes **14**−**16**, comprising 5-, 7-, and 8-membered rings, was prepared via Wohl−Ziegler allylic bromination[8] of the corresponding cycloalkenes **8**−**10** followed by amination with dibenzylamine (Scheme 1).

In order to effect in situ protection of the amines, the formation of the corresponding ammonium species **17**−**19** from amines **14**−**16** in the presence of Cl_3CCO_2H was examined by ^{1}H NMR spectroscopy. Cl_3CCO_2H was added in 1 equiv portions to a solution of the requisite amine **14**−**16** in CD_2Cl_2, and in all cases a pronounced difference in δ_H of the vinylic protons was observed, indicating the time-averaged signal and fast exchange between the amine **14**−**16** and corresponding ammonium **17**−**19**. The difference in chemical shift ($\Delta\delta$) between the values of δ_H for C(1)*H* and C(2)*H* increased with increasing amounts of Cl_3CCO_2H, although a plateau was noted at approximately 4−5 equiv, suggesting the equilibrium lies predominately to the right and the ammonium species **17**−**19** predominate in solution under these conditions. These results suggest that 5 equiv of Cl_3CCO_2H may be sufficient to effect efficient *N*-protonation of **14**−**16** and are in accordance with our analogous study on 3-(*N*,*N*-dibenzylamino)cyclohex-1-ene **1**[5] (Figure 2).

The oxidation of 5-membered ring substrate **14** upon treatment with 5 equiv of Cl_3CCO_2H followed by 1.6 equiv of *m*-CPBA was investigated.[5] After 12 h, a mixture of

(8) Djerassi, C. *Chem. Rev.* **1959**, *71*, 349.

SCHEME 1[a]



[a]Reagents and conditions: (i) NBS (0.25 equiv), $(PhCO_2)_2$ (cat.), CCl_4, reflux, 1 h; (ii) Bn_2NH, 0 °C to rt, 12 h; (iii) NBS (1 equiv), $(PhCO_2)_2$ (cat.), CCl_4, reflux, 1 h; (iv) Bn_2NH, K_2CO_3, 60 °C, 35 h.

products, including *syn*-epoxide **20** and the corresponding ring-opened trichloroacetate adduct **21** in a 62:38 ratio, respectively, was obtained (Scheme 2). This product distribution suggests a slower rate of epoxide ring-opening as compared to the 6-membered ring system,[5] which is consistent with the observed slower rate of ring-opening of cyclopentene oxide versus cyclohexene oxide with a variety of nucleophiles.[9] This may be due in part to relief of torsional strain during a half-chair to chair conformational change in the ring-opening of cyclohexene oxide; during ring-opening of cyclopentene oxide an envelope conformation is retained and no such relief occurs. Optimization of the reaction conditions revealed that using only 1.05 equiv of *m*-CPBA gave *syn*-epoxide **20** as the only product after 3.5 h, and in >99:1 dr, as determined by peak integration of the ^{1}H NMR spectrum of the crude reaction mixture. Purification gave **20** in 99% yield and >99:1 dr. The relative *syn*-configuration within **20** was unambiguously established by single-crystal X-ray analysis. The complete *syn*-diastereoselectivity observed in the epoxidation of the ammonium **17** is in accordance with the very high *syn*-selectivities reported for the peracid epoxidations of cyclopent-2-enol,[10] *N*-(cyclopent-2-enyl)acetamide,[11] *N*-(cyclopent-2-enyl)benzamide,[11b] *N*-(cyclopent-2-enyl)formamide,[12] and *N*-(cyclopent-2-enyl)trichloroacetamide.[13] In these cases, the efficient *syn*-selectivity has been typically ascribed to an intermolecular

(9) (a) For example, see: Iranpoor, N.; Shekarriz, M.; Shiriny, F. *Synth. Commun.* **1998**, *28*, 347. (b) Yoo, D.-W.; Yoo, S.-K.; Kim, C.; Lee, J.-K. *J. Chem. Soc., Dalton Trans.* **2002**, 3931. (c) Iranpoor, N.; Firouzabadi, H.; Aghapour, G.; Nahid, A. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1885. (d) Han, J. H.; Hong, S. J.; Lee, E. Y.; Lee, J. H.; Kim, H. J.; Kwak, H.; Kim, C. *Bull. Korean Chem. Soc.* **2005**, *26*, 1434. (e) Singh, M. C.; Peddinti, R. K. *Tetrahedron Lett.* **2007**, *48*, 7354.

(10) Steyn, R.; Sable, H. Z. *Tetrahedron* **1969**, *25*, 3579. Kočovský, P. *Tetrahedron Lett.* **1988**, *29*, 2475.

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(12) Baldwin, J. E.; Adlington, R. M.; Chondrogianni, J.; Edenborough, M. S.; Keeping, J. W.; Ziegler, C. B. *J. Chem. Soc., Chem. Commun.* **1985**, 816.

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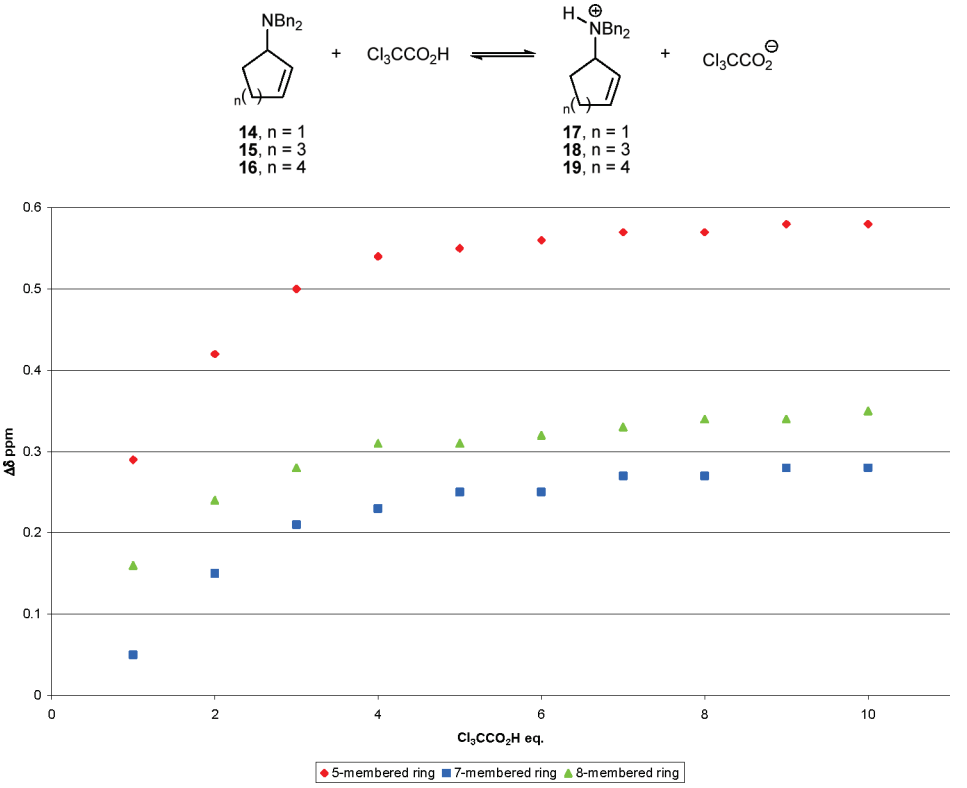
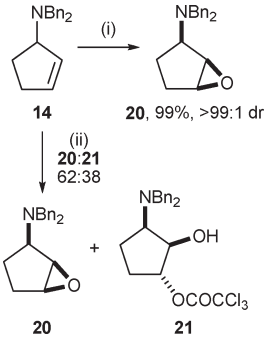


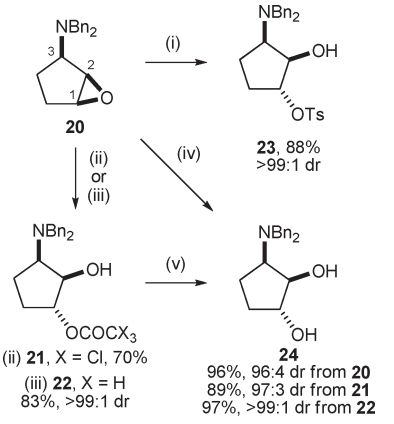
FIGURE 2. Differences in chemical shift ($\Delta\delta$) between C(1)*H* and C(2)*H* upon addition of Cl_3CCO_2H to **14**−**16**.

SCHEME 2[a]



[a]Reagents and conditions: (i) Cl_3CCO_2H (5 equiv), CH_2Cl_2, rt, 5 min, then *m*-CPBA (1.05 equiv), rt, 3.5 h; (ii) Cl_3CCO_2H (5 equiv), CH_2Cl_2, rt, 5 min, then *m*-CPBA (1.6 equiv), rt, 12 h.

SCHEME 3[a]



[a]Reagents and conditions: (i) TsOH (5 equiv), CH_2Cl_2, 40 °C, 4.5 h; (ii) Cl_3CCO_2H (5 equiv), CH_2Cl_2, 40 °C, 12 h; (iii) AcOH, 50 °C, 66 h; (iv) H_2SO_4 (3 M aq), THF, 40 °C, 20 h; (v) K_2CO_3, MeOH, rt, 12 h.

hydrogen bond in the transition state, although minimization of torsional strain may also contribute.[14]

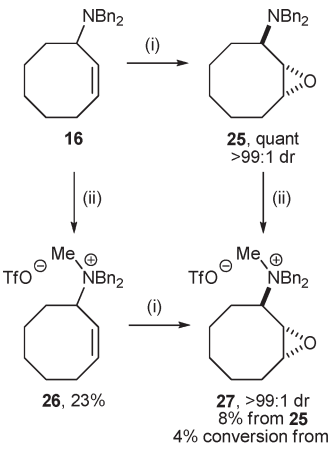
Ring-opening of *syn*-epoxide **20** upon treatment with anhydrous Cl_3CCO_2H at 40 °C gave **21** as the major product (>90%) along with trace amounts of unidentifiable species.

Transesterification of **21** by treatment with K_2CO_3 in MeOH gave **24** in 89% isolated yield and 97:3 dr (Scheme 3). The preferential ring-opening at C(1) of epoxide **20** to give the 1,2-*anti*-2,3-*syn*-diastereoisomer **21** is consistent with the acid-catalyzed ring-opening proceeding via a late (product-like) transition state with substantial carbocationic character at the oxirane carbon undergoing nucleophilic attack.[15] This promotes attack at the C(1)-oxirane carbon where the inductively electron-withdrawing influence of the *N*,*N*-dibenzylammonium group is lower. In order to investigate the

(14) Several instances of *syn*-selective osmylation and epoxidation reactions of 3-substituted cyclopentenes which proceed in the absence of any obvious associative interactions (e.g., hydrogen bonding) in the transition state have been reported; see: (a) Donohoe, T. J.; Blades, K.; Moore, P. R.; Waring, M. J.; Winter, J. J. G.; Helliwell, M.; Newcombe, N. J.; Stemp, G. *J. Org. Chem.* **2002**, *67*, 7946. (b) Ward, S. E.; Holmes, A. B.; McCague, R. *Chem. Commun.* **1997**, 2085. (c) Aggarwal, V. K.; Monteiro, N. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2531. Poli has proposed a model to account for these observations, in which attack on the *syn*-face is favoured due to minimization of torsional strain in the transition state; see: Poli, G. *Tetrahedron Lett.* **1989**, *30*, 7385. Houk has coined the term "torsional steering" for this effect; see: Cheong, P. H.-Y.; Yun, H.; Danishefsky, S. J.; Houk, K. N. *Org. Lett.* **2006**, *8*, 1513.

(15) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737. Addy, J. K.; Parker, R. E. *J. Chem. Soc.* **1963**, 915.

SCHEME 4[a]



[a]Reagents and conditions: (i) Cl_3CCO_2H (5 equiv), CH_2Cl_2, rt, 5 min, then *m*-CPBA (1.05 equiv), rt, 3.5 h; (ii) MeOTf, Et_2O, rt, 2 h.

generality of this regioselectivity, *syn*-**20** was treated with a range of Brønsted acids (aq H_2SO_4, TsOH and AcOH). In each case, ring-opening proceeded preferentially via attack at C(1) to give the corresponding 1,2-*anti*-2,3-*syn*-diastereoisomer as the major product.[16] In the case of 1-acetoxy **22**, the regioselectivity of ring-opening and relative configuration was unambiguously established by single-crystal X-ray analysis of the corresponding HBF_4 salt.[17] Transesterification of **22** with K_2CO_3 in MeOH gave **24** in 97% yield and >99:1 dr, thus confirming the assigned relative configuration within **24**. Ring-opening of epoxide *syn*-**20** with aq H_2SO_4 gave **24** as the major product (96:4 dr), while ring-opening with anhydrous TsOH gave **23** as a single diastereoisomer in 88% isolated yield. The regioselectivity of the ring-opening promoted by TsOH was assigned by analogy to that unambiguously established for ring-opening promoted by aq H_2SO_4, Cl_3CCO_2H, and AcOH (Scheme 3).

Epoxidation of the 8-membered ring substrate **16** gave epoxide *anti*-**25** as the sole product in >99:1 dr and quantitative yield after 3.5 h (Scheme 4). The relative *anti*-configuration within **25** was determined unambiguously by single-crystal X-ray analysis. The observation that epoxide *anti*-**25** is cleanly isolable without competing ring-opening by Cl_3CCO_2H parallels the known, extremely slow intermolecular nucleophilic ring-opening of *cis*-cyclooctene oxide.[18] It has been proposed that the chair-boat conformation of *cis*-cyclooctene oxide presents an extremely hindered approach to nucleophilic attack on the epoxide moiety,[19] though development of transannular and bond-widening strain upon epoxide opening may also contribute. Comparison of the preferred solid-state conformations of both allylic amine **16** and epoxide **25** reveal that both display the characteristic chair-boat conformation,[20] with the *N*,*N*-dibenzylamino group occupying a pseudobowsprit position, which may account for the very slow rate of ring-opening of **25**. Furthermore, the complete *anti*-selectivity (>99:1 dr) in the epoxidation of ammonium **19** parallels the peracid epoxidation of both *cis*-cyclooct-2-en-1-ol[21] and *cis*-cyclooct-2-en-1-yl methyl ether[22] which have also been reported as proceeding with complete *anti*-selectivity, which is usually ascribed to oxidation on the least hindered face of the olefin with the cyclooctene ring in the preferred low energy chair-boat conformation.[20] In order to probe the role of hydrogen bonding in this reaction, *N*-methylammonium triflate species **26** was prepared in 23% yield by treatment of **16** with methyl triflate. Oxidation of **26** under conditions analogous to those employed for oxidation of **16** (1.05 equiv of *m*-CPBA in the presence of 5 equiv of Cl_3CCO_2H) gave 4% conversion to epoxide **27** as the only detectable diastereoisomer. The relative configuration within **27** was unambiguously established by *N*-methylation of **25** upon treatment with methyl triflate, which gave **27** as a single diastereoisomer. These results suggest that an intermolecular hydrogen bond need not be invoked to explain the observed *anti*-selectivity but may be involved in stabilizing the transition state and thereby accelerating the rate of reaction, which is consistent with the relatively close proximity of the *N*,*N*-dibenzylamino group to the *anti*-face of the olefin. In the case of oxidation of **26**, shielding of the *anti*-face by the bulky *N*-methyl-*N*,*N*-dibenzylammonium group, as well as its deactivating electron-withdrawing influence on the olefin, may account for the low reaction conversion.

Attention next turned to oxidation of the 7-membered ring substrate **15**. Under the conditions employed for epoxidation of 5- and 8-membered ring substrates **14** and **16**, respectively, oxidation of **15** gave 88% conversion to a 94:6 mixture of epoxides *anti*-**28**:*syn*-**29**. Chromatographic purification gave the major *anti*-epoxide **28** in 69% yield and >99:1 dr, and the minor *syn*-epoxide **29** in 4% yield and >99:1 dr as crystalline solids (Scheme 5). The relative *anti*-configuration within **28** was assigned unambiguously by single-crystal X-ray analysis. It is notable that unreacted starting material **15** is present after 3.5 h, indicating that the rate of epoxidation of the ammonium **18** is slower than that of the ammoniums **17** and **19**, derived from the 5- and 8-membered ring substrates **14** and **16**, respectively. The epoxidation of cyclohept-2-enol has been reported to proceed with only low levels of *syn*-diastereoselectivity (~2:1 dr) with various peracids.[19,21] These low diastereoselectivities suggest that the 7-membered ring is conformationally ill-defined, consistent with the known conformational lability of cycloheptene itself.[23] This contrasts with the relatively high *anti*-diastereoselectivity observed in the epoxidation of ammonium **18**,

(16) Ring-opening of **20** by TsOH gave **23** as a single diastereoisomer (>99:1 dr). Ring-opening of **20** by aq H_2SO_4 gave a 96:4 ratio of **24**:**35**. Ring-opening of **20** by AcOH gave an 84:6:5:5 mixture of **22** and three other unidentified acetate-containing species [δ_H 4.94 (dd, *J* 7.7, 4.2), 4.97−5.03 (m), 5.29 (dd, *J* 6.2, 2.9)]. Purification of the crude reaction mixture gave **22** in 83% yield and >99:1 dr, while transesterification of the crude reaction mixture gave an 89:11 mixture of **24**:**35**.

(17) A range of Brønsted acids were screened for their ability to promote crystallization of **22** as the corresponding ammonium salt, with HBF_4 giving crystals of suitable quality for X-ray analysis.

(18) See ref 9d and: Iranpoor, N.; Shekarriz, M.; Shiriny, F. *Synth. Commun.* **1998**, *28*, 347. Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421.

(19) Denmark, S. E.; Barsanti, P. A.; Wong, K.-T.; Stavenger, R. A. *J. Org. Chem.* **1998**, *63*, 2428.

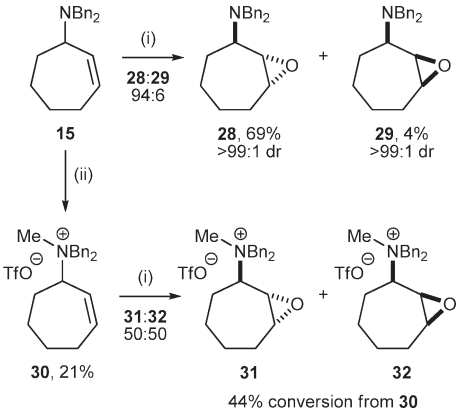
(20) For a discussion of the conformation of cyclooctane derivatives such as *cis*-cyclooctene, see: Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981.

(21) Itoh, T.; Kaneda, K.; Teranishi, S. *Chem. Commun.* **1976**, 421. Cope, A. C.; Keough, A. H.; Peterson, P. E.; Simmons, H. E.; Wood, G. W. *J. Am. Chem. Soc.* **1957**, *79*, 3900.

(22) Chamberlain, P.; Roberts, M. L.; Whitham, G. H. *J. Chem. Soc.* **1970**, 1374.

(23) Leong, M. K.; Mastryukov, V. S.; Boggs, J. E. *J. Mol. Struct.* **1998**, *445*, 149.

SCHEME 5[a]

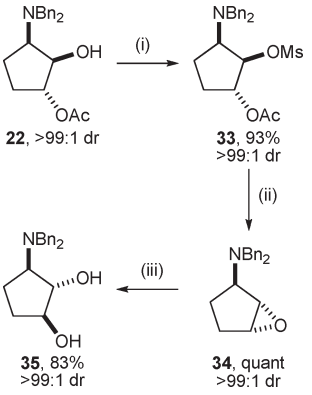


[a]Reagents and conditions: (i) Cl_3CCO_2H (5 equiv), CH_2Cl_2, rt, 5 min, then *m*-CPBA (1.05 equiv), rt, 3.5 h; (ii) MeOTf, Et_2O, rt, 2 h.

suggesting that the sterically demanding *N*,*N*-dibenzylammonium group may be enforcing a more well-defined conformation, which is reflected in the transition state for the epoxidation. In the solid-state structures of both allylic amine **15** and epoxide **28** the 7-membered ring adopts a chair-type conformation, and studies have shown that both cycloheptene[23] and cycloheptene oxide[24] favor this conformation in solution. A comparison of solid-state structures of the allylic amines and the derived *anti*-epoxides in both the 7- and 8-membered ring systems suggests that the origin of the *anti*-selectivity in the formation of epoxide *anti*-**28** may lie in epoxidation on the sterically more accessible face of the olefin. Treatment of **15** with methyl triflate gave the corresponding *N*-methylammonium **30** in 21% yield, with subsequent treatment with 1.05 equiv of *m*-CPBA and 5 equiv of Cl_3CCO_2H giving 44% conversion to a 50:50 mixture of the diastereoisomeric epoxides *anti*-**31** and *syn*-**32**. The relative configuration within *anti*-epoxide **31** was unambiguously established through *N*-methylation of *anti*-epoxide **28**. These observations suggest that, in contrast to the 8-membered ring, an intermolecular hydrogen bond in the oxidation of **15** may not only provide stabilization of the transition state, but also play a crucial role in determining the high facial selectivity of the epoxidation reaction.

The synthetic utility of the epoxide products **20** and **28** was next demonstrated by their elaboration to 3-amino-1,2-diols. In the 5-membered ring system, ring-opening of *syn*-epoxide **20** with aq H_2SO_4 allowed direct access to 1,2-*anti*-2,3-*syn*-*N*,*N*-dibenzylamino diol **24** (vide supra), and it was envisaged that the 1,2-*anti*-2,3-*anti*-diastereoisomer **35** would be available from analogous ring-opening of the corresponding *anti*-epoxide **34**. *anti*-Epoxide **34** was prepared via mesylation of **22** to furnish acetoxy mesylate **33**, followed by treatment with K_2CO_3 in MeOH (Scheme 6). The relative configurations within **33** and **34** were established unambiguously by single-crystal X-ray analysis. Ring-opening of *anti*-epoxide **34** with 3 M aq H_2SO_4 gave **35** in >99:1 dr, with purification giving **35** in 83% yield and >99:1 dr (Scheme 6). The production of **35** as the only diastereoisomer in this reaction is consistent with ring-opening proceeding via preferential attack of H_2O[25] at C(1) where the electron-withdrawing influence of the *N*,*N*-dibenzylammonium moiety is lower.

SCHEME 6[a]



[a]Reagents and conditions: (i) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 2 h; (ii) K_2CO_3, MeOH/THF (7:3), rt, 2 h; (iii) H_2SO_4 (3 M aq), THF, 40 °C, 24 h.

With both the 1,2-*anti*-diastereoisomers of 3-(*N*,*N*-dibenzylamino)cyclopentane-1,2-diol in hand, the 1,2-*syn*-diastereoisomers were targeted. It was envisaged that the 1,2-*syn*-2,3-*anti*-diastereoisomer **39** would be available from acetoxy mesylate **33** utilizing a neighboring group participation reaction originally reported by Winstein et al.[26] Under literature conditions, **33** was suspended in EtOH/H_2O and treated with KOAc which gave a 7:9:84 mixture of the regioisomeric acetates **36** and **37** and dibenzylamine **38**, respectively.[27] When EtOH/H_2O was replaced by AcOH/H_2O (in which **33** proved soluble) a mixture of products, including a 34:12:54 mixture of **36**:**37**:**38**, was obtained.[27] Transesterification of the crude reaction mixture and purification by chromatography gave **39** in 44% yield and >99:1 dr[28] (Scheme 7). The relative configuration within **39** was unambiguously established by single-crystal X-ray analysis of the corresponding 2-methyl-5-nitrobenzenesulfonic acid salt.[29]

A plausible mechanistic rationale for the formation of dibenzylamine **38** in this reaction involves competing ring-opening of the acetoxonium ion intermediate **40** to give

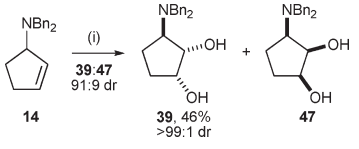
(24) Abraham, R. J.; Castellazzi, I.; Sancassan, F.; Smith, T. A. D. *J. Chem. Soc., Perkin Trans. 2* **1999**, 99.

(25) Alternatively, ring-opening by either HSO_4^- or SO_4^{2-} (followed by hydrolysis) may occur. For a very recent example, see: Cavdar, H.; Saracoglu, N. *Tetrahedron* **2009**, *65*, 985.

(26) Winstein, S.; Hess, H. V.; Buckles, R. E. *J. Am. Chem. Soc.* **1942**, *64*, 2157. Roberts, J. D.; Young, W. G.; Winstein, S. *J. Am. Chem. Soc.* **1942**, *64*, 2796.

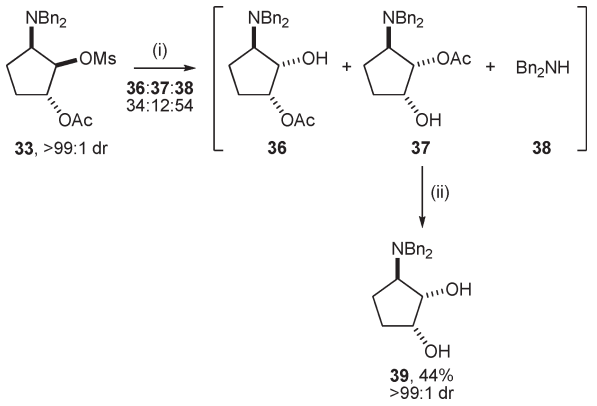
(27) The regiochemistry within **36** and **37** was arbitrarily assigned.

(28) The relative 1,2-*syn*-configurations within **39** and **47** were unambiguously established by dihydroxylation of **14** with OsO_4/NMO, which gave a 91:9 mixture of **39**:**47**. Chromatographic purification gave **39** in 46% yield and >99:1 dr (reagents and conditions: (i) OsO_4 (1 mol %), NMO (3 equiv), acetone/H_2O (4:1), rt, 4 h, then satd aq Na_2SO_3).



(29) A range of Brønsted acids were screened for their ability to promote crystallization of **39** as the corresponding ammonium salt, with 2-methyl-5-nitrobenzenesulfonic acid giving crystals of suitable quality for X-ray analysis.

SCHEME 7[a]



[a]Reagents and conditions: (i) KOAc, AcOH/H_2O (6:1), 80 °C, 18 h; (ii) K_2CO_3, MeOH, rt, 12 h.

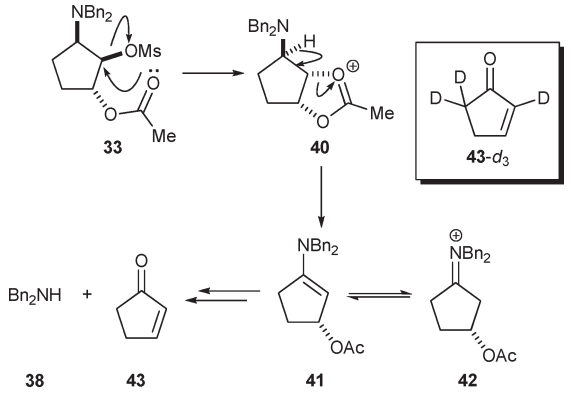


FIGURE 3. Postulated mechanism for the formation of dibenzylamine **38** and cyclopentenone **43**.

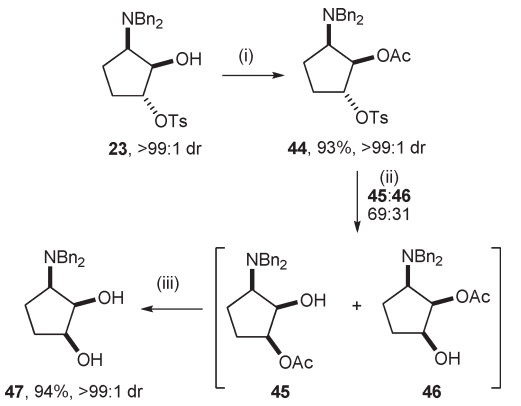
enamine **41**, which may be in equilibrium with iminium **42**; subsequent hydrolysis and $E1_{CB}$-type elimination of AcOH (although not necessarily in that order) gives dibenzylamine **38** and cyclopentenone **43**. Consistent with this hypothesis, when the reaction was carried out in AcOH-d_4/D_2O mixture and analyzed by ^{1}H NMR spectroscopy, the formation of **43**-d_3 was observed. Deuteration at both C(2) and C(5) of **43** potentially arises from tautomerization and deuteration of enamine **41** or the corresponding ketone (Figure 3).

In order to access 1,2-*syn*-2,3-*syn*-**47**, a neighboring group participation strategy was also employed. Thus, acetylation of **23** was followed by exposure of the resultant acetoxy tosylate **44** to Winstein's conditions,[26] affording a 69:31 mixture of regioisomeric acetates **45** and **46**.[30] Subsequent transesterification with K_2CO_3 in MeOH gave **47** in 94% yield as a single diastereoisomer[28] (Scheme 8). This reaction sequence also serves to further confirm the structural assignment of **23**.

With all diastereoisomers of 3-(*N*,*N*-dibenzylamino)-cyclopentane-1,2-diol in hand, *N*-debenzylation to give the diastereoisomers of 3-aminocyclopentane-1,2-diol was investigated. In each case, hydrogenolysis of **24**, **35**, **39**, and **47** mediated by Pearlman's catalyst [$Pd(OH)_2$/C] followed by acidification of the crude reaction mixture with HCl gave the corresponding diastereoisomers of 3-aminocyclopentane-1,2-diol as the hydrochloride salts **48**−**51**, in good yield as

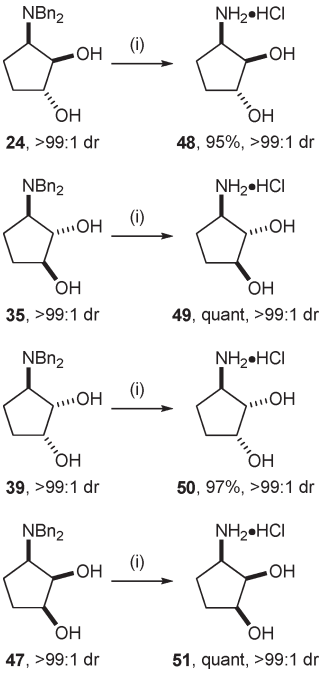
(30) The regiochemistry within **45** and **46** was arbitrarily assigned.

SCHEME 8[a]



[a]Reagents and conditions: (i) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 6 h; (ii) KOAc, EtOH/H_2O (6:1), 80 °C, 6 h; (iii) K_2CO_3, MeOH, rt, 12 h.

SCHEME 9[a]



[a]Reagents and conditions: (i) H_2 (1 atm), $Pd(OH)_2$/C (50% w/w), MeOH, 4 h, rt, then HCl (conc, aq).

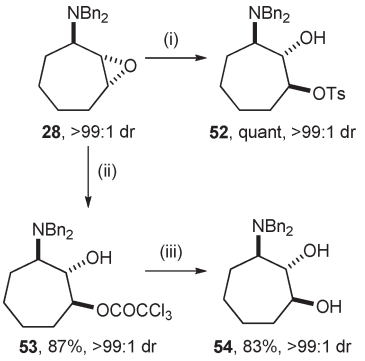
single diastereoisomers. The spectroscopic properties of **48**−**51** were in agreement to those previously reported in the literature[31] (Scheme 9).

Manipulation of *anti*-epoxide **28**, derived from oxidation of the 7-membered substrate **15** was next investigated. Ring-opening of **28** with anhydrous TsOH or anhydrous Cl_3CCO_2H gave the corresponding 1,2-*anti*-2,3-*anti*-diastereoisomers **52** and **53**, resulting from regioselective epoxide opening at C(1), as the major products[32] (Scheme 10).

(31) Whitten, J. P.; McCarthy, J. R.; Whalon, M. R. *J. Org. Chem.* **1985**, *50*, 4399.

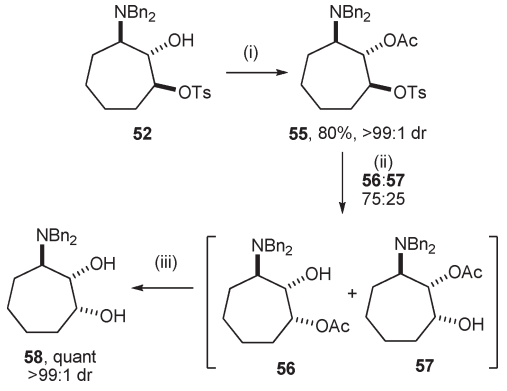
(32) Ring-opening of **28** by anhydrous TsOH gave **52** in >99:1 dr. Ring-opening of **28** by Cl_3CCO_2H gave **53** as the major product (>95%) along with trace amounts of unidentifiable species. Recrystallization of the crude reaction mixture gave **53** in 87% yield and >99:1 dr, while transesterification gave **54** in >95:5 dr.

SCHEME 10[a]



[a]Reagents and conditions: (i) TsOH (5 equiv), CH_2Cl_2, 40 °C, 4.5 h; (ii) Cl_3CCO_2H (5 equiv), CH_2Cl_2, 40 °C, 12 h; (iii) K_2CO_3, MeOH, rt, 12 h.

SCHEME 11[a]



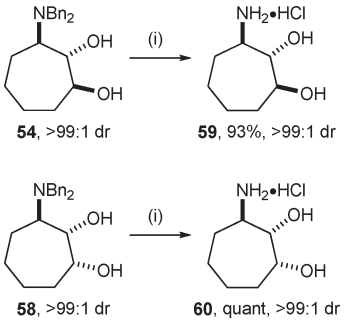
[a]Reagents and conditions: (i) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 18 h; (ii) KOAc, EtOH/H_2O (6:1), 80 °C, 12 h; (iii) K_2CO_3, MeOH, rt, 12 h.

The relative configurations within **52** and **53** were established unambiguously by single-crystal X-ray analysis. Transesterification of **53** gave 1,2-*anti*-2,3-*anti*-**54** in 83% yield as a single diastereoisomer (Scheme 10).

The 1,2-*syn*-2,3-*anti*-diastereoisomer **58** was accessed using the neighboring group participation reaction.[26] Acetylation of **52** provided acetoxy tosylate **55** in >99:1 dr and 80% yield, and treatment with KOAc in EtOH/H_2O gave a 75:25 mixture of hydroxy acetates **56** and **57**.[33] Transesterification of the crude reaction mixture with K_2CO_3 in MeOH gave **58** in quantitative yield and >99:1 dr[34] (Scheme 11).

Catalytic hydrogenolysis of **54** and **58** gave the corresponding diastereoisomers of 3-aminocycloheptane-1,2-diol which were isolated as the hydrochloride salts **59** and **60** in good yield and >99:1 dr in both cases (Scheme 12).

SCHEME 12[a]



[a]Reagents and conditions: (i) H_2 (1 atm), $Pd(OH)_2/C$ (50% w/w), MeOH, 4 h, rt, then HCl (conc, aq).

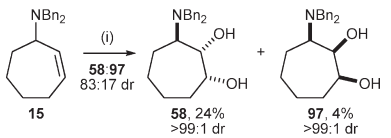
These studies demonstrate that the ammonium-directed oxidation protocol (that has previously been reported by us within a 6-membered ring scaffold)[5,6] is general for the oxidation of a range of cyclic (5-, 7-, and 8-membered ring) allylic amines. In these latter cases, the ring-opening of the intermediate epoxide is sufficiently slow as to allow its isolation by modification of the reaction conditions, and the epoxide products (within the 5- and 7-membered ring systems) are readily derivatized into a range of vicinal amino diol motifs. The extension of this methodology to a more challenging homoallylic system was next probed.

Oxidation of Homoallylic Amines: Diastereoselective Oxidation of *N*-Protected 3-Aminomethylcyclohex-1-enes. 3-Hydroxymethylcyclohex-1-ene **62** and *N*-protected 3-aminomethylcyclohex-1-enes **64** and **65** were prepared from cyclohexene **61**. Treatment of **61** with Schlosser's base[35] followed by paraformaldehyde gave alcohol **62** in 86% yield.[36] Under optimized conditions, treatment of **62** with NBS and triphenylphosphine[37] gave bromide **63** in 74% yield, with subsequent bromide displacement with benzylamine followed by benzylation of the resultant secondary amine **64** with benzyl bromide giving tertiary amine **65** in 53% yield over two steps from **63**[38] (Scheme 13).

The ability of the hydroxyl functionality to enable a diastereoselective oxidation of the olefin within **62** was first investigated. Treatment of alcohol **62** with *m*-CPBA (1.5 equiv) gave a 76:24 mixture of epoxides *syn*-**66** and *anti*-**67**. The major diastereoisomer was assigned the relative *syn*-configuration on the assumption that the reaction proceeds predominantly under hydrogen-bonded substrate control. In support of this hypothesis, protection of the hydroxyl group upon treatment with NaH followed by methyl iodide gave methyl ether **68** which upon oxidation with *m*-CPBA provided a 58:42 mixture of diastereoisomeric epoxides *syn*-**69** and *anti*-**70**. The major product from this reaction was assigned as the *syn*-diastereoisomer **69** by chemical correlation, through *O*-methylation of a 76:24 mixture of *syn*-**66**:*anti*-**67** which gave a 76:24 mixture of *syn*-**69**:*anti*-**70** (Scheme 14).

(33) The regiochemistry within **56** and **57** was arbitrarily assigned.

(34) The relative 1,2-*syn*-configuration within **58** was unambiguously established by dihydroxylation of **15** with OsO_4/NMO, which gave an 83:17 mixture of **58**:**97**. Chromatographic purification gave **58** in 24% yield and >99:1 dr, and **97** in 4% yield and >99:1 dr (reagents and conditions: (i) OsO_4 (1 mol %), NMO (3 equiv), acetone/H_2O (4:1), rt, 4 h, then satd aq Na_2SO_3).



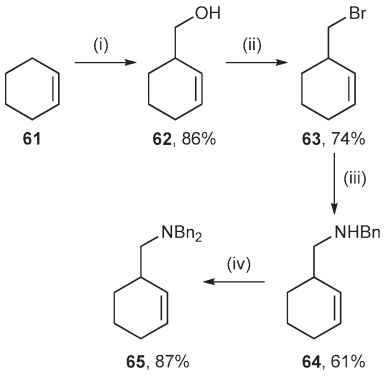
(35) Schlosser, M. *J. Organomet. Chem.* **1967**, *8*, 9.

(36) Clausen, R. P.; Bols, M. *J. Org. Chem.* **2000**, *65*, 2797.

(37) Borcherding, D. R.; Narayanan, S.; Hasobe, M.; McKee, J. G.; Keller, B. T.; Borchardt, R. T. *J. Med. Chem.* **1988**, *31*, 1729.

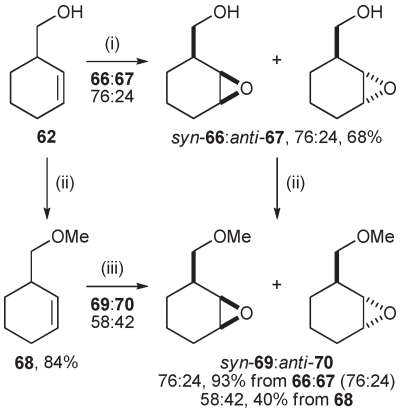
(38) Direct formation of *N*,*N*-dibenzyl-protected amine **65** from bromide **63** via displacement with dibenzylamine was not as efficacious.

SCHEME 13[a]



[a]Reagents and conditions: (i) KO^{t}Bu, BuLi, 0 °C to rt, 18 h, then $(CH_2O)_n$, 60 °C, 3 h; (ii) NBS, PPh_3, CH_2Cl_2, 0 °C to rt, 17 h; (iii) $BnNH_2$, NaI, 50 °C, 20 h; (iv) BnBr, $^i Pr_2NEt$, CH_2Cl_2, 40 °C, 2 h.

SCHEME 14[a]



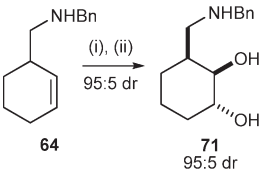
[a]Reagents and conditions: (i) *m*-CPBA, CH_2Cl_2, 0 °C to rt, 1 h; (ii) NaH, MeI, THF/DMF (3:1), rt, 48 h; (iii) *m*-CPBA, CH_2Cl_2, 0 °C to rt, 2.5 h.

The ability of a homoallylic amino substituent to promote diastereoselective oxidation of the olefin within this scaffold was next probed. Oxidation of secondary amine **64** upon treatment with 4 equiv of Cl_3CCO_2H[39] and 1.6 equiv of *m*-CPBA,[5] followed by transesterification with K_2CO_3 in MeOH, gave 1,2-*anti*-2,3-*syn*-*N*-benzylamino diol **71** in 95:5 dr (Scheme 15). Although attempted assignment of the relative configuration within **71** by ^{1}H NMR ^3J coupling constant analysis proved inconclusive, it was subsequently established unambiguously by chemical correlation (vide infra). The level of stereoselectivity in this oxidation process is similar to that observed in the analogous 6-membered ring allylic amine system[5] and is consistent with a highly diastereoselective *syn*-epoxidation under hydrogen bond control, followed by regioselective ring-opening of the protonated intermediate epoxide *syn*-**73** at C(1), in a *trans*-diaxial manner according to the Fürst−Plattner rule,[40] via a chair-like transition state which places the sterically demanding, protonated *N*-benzylaminomethyl group in an equatorial site (Figure 4).

(39) The stoicheiometry of Cl_3CCO_2H or TsOH required to effect the efficient protection of homoallylic amines **64** and **65** was determined in each case by an analogous ^{1}H NMR "titration experiment" as described for allylic amines **14**−**16**.

(40) Fürst, A.; Plattner, P. A. *12th Int. Congress Pure Appl. Chem.* New York, 1951, p 409.

SCHEME 15[a]



[a]Reagents and conditions: (i) Cl_3CCO_2H (4 equiv), CH_2Cl_2, rt, 5 min, then *m*-CPBA (1.6 equiv), rt, 21 h; (ii) K_2CO_3, MeOH, rt, 12 h.

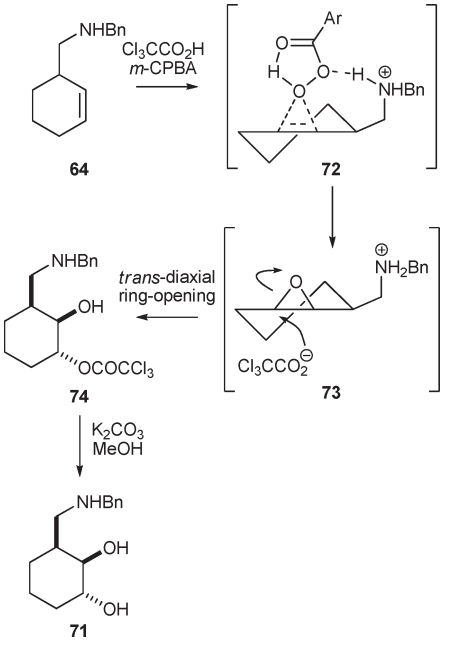
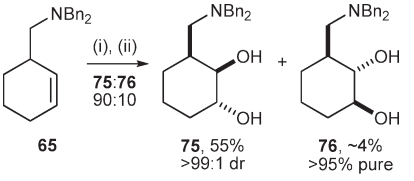


FIGURE 4. Postulated mechanism for the oxidation of **64** with Cl_3CCO_2H and *m*-CPBA.

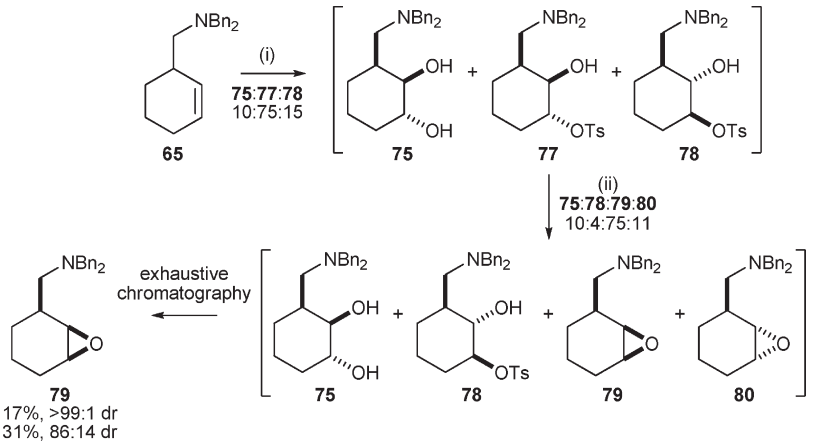
SCHEME 16[a]



[a]Reagents and conditions: (i) Cl_3CCO_2H (5 equiv), CH_2Cl_2, rt, 30 min, then *m*-CPBA (1.5 equiv), rt, 21 h; (ii) K_2CO_3, MeOH, rt, 12 h.

Analogous oxidation of tertiary amine **65** in the presence of 5 equiv of Cl_3CCO_2H[39] gave, after transesterification, a 90:10 mixture of *N*,*N*-dibenzylamino diols **75** and **76**, respectively. Purification via flash column chromatography gave the major diastereoisomer **75** in 55% yield and >99:1 dr and a sample of the minor diastereoisomer **76** (contaminated with trace amounts of unknown impurities) in ~4% yield (Scheme 16). The relative configuration within **75** was unambiguously established by single-crystal X-ray analysis, and the relative configuration within **76** was assigned from ^{1}H NMR ^3J coupling constant analysis of a pure sample (vide infra). There are two possible chair conformations available for **75**: **75A**, which places the *N*,*N*-dibenzylaminomethyl group axial, and **75B**, which places the *N*,*N*-dibenzylaminomethyl group equatorial (Figure 5). Quite clearly, an

SCHEME 17[a]



[a]Reagents and conditions: (i) TsOH (3 equiv), CH_2Cl_2, rt, 30 min, then *m*-CPBA (1.6 equiv), rt, 22 h; (ii) DBU, CH_2Cl_2, 0 °C to rt, 15 h.

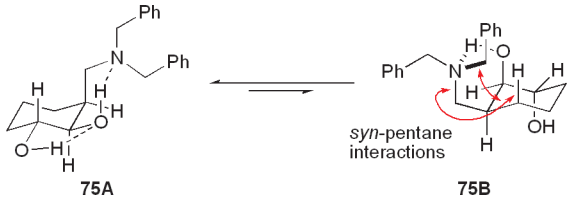
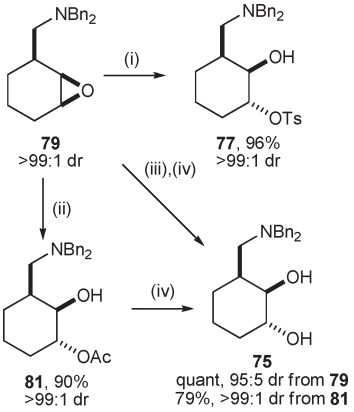


FIGURE 5. Conformations of **75**.

intramolecular hydrogen-bonding network between the C(1)- and C(2)-hydroxyl groups and the nitrogen atom within **75A** can serve to stabilize this conformation.[41] The alternative chair conformation **75B** results in both hydroxyl groups occupying axial sites where formation of one intramolecular hydrogen bond becomes impossible; furthermore, the formation of a hydrogen bond between the axial C(2)-hydroxyl group and the nitrogen atom of the molecule in this conformation results in the *N*,*N*-dibenzylaminomethyl group experiencing unfavorable *syn*-pentane interactions. Within the solid state, **75** exists in conformation **75A**, and an identical conformational preference in solution was inferred from ^{1}H NMR ^3J coupling constant analysis.[42] The stereochemical outcome of the oxidation reaction is consistent with our proposed mechanism for oxidation of secondary amine **64** although, in comparison, the diastereoselectivity of the two-step epoxidation/ring-opening process with tertiary amine **65** is lower.

To probe this observation further, the *syn*- and *anti*-diastereoisomers of the intermediate epoxide were prepared in order that the regioselectivity of their ring-opening could be subsequently investigated. Oxidation of **65** with *m*-CPBA in the presence of 3 equiv of TsOH[39] furnished an approximate 10:75:15 mixture of diol **75** and hydroxy tosylates **77** and **78**,[43] respectively. Presumably, hydroxy tosylates **77** and **78** result from ring-opening of the intermediate *syn*- and *anti*-epoxides **79** and **80** at C(1), respectively (vide infra), while diol **75** results from ring-opening of *syn*-epoxide **79** at C(1) by adventitious water. This implies that the diastereoisomeric ratio of epoxides *syn*-**79**:*anti*-**80** formed in the oxidation of tertiary homoallylic amine **65** with *m*-CPBA in the presence of TsOH is ~85:15. Treatment of the crude reaction mixture (10:75:15, **75**:**77**:**78**) with DBU gave a 10:4:75:11 mixture of diol **75**, hydroxy tosylate **78**, and the diastereoisomeric epoxides *syn*-**79** and *anti*-**80**, respectively. This product distribution is consistent with the elimination of TsOH from **77** being faster than that from **78**; this is presumably a result of ring closure of **77** proceeding via a favored chair-like transition state which places the *N*,*N*-dibenzylaminomethyl moiety in an equatorial position, while ring closure of **78** proceeds either via a disfavored twist-boat-like transition state, or from a disfavored chair conformation with *all* the substituents occupying axial sites. Exhaustive purification of the crude reaction mixture enabled partial separation of the epoxide products, giving a diastereoisomerically pure sample

SCHEME 18[a]



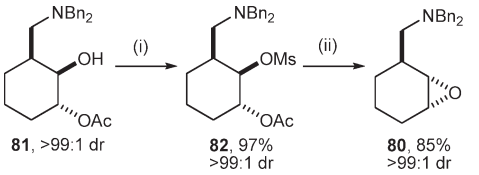
[a]Reagents and conditions: (i) TsOH (3 equiv), CH_2Cl_2, rt, 3 h; (ii) AcOH, rt, 12 h; (iii) Cl_3CCO_2H (5 equiv), CH_2Cl_2, rt, 2 h; (iv) K_2CO_3, MeOH, rt, 12 h.

(41) A "strong" hydrogen bond is observed between C(2)O−H···N, and a "weak" hydrogen bond is observed between C(1)O−H···O−C(2); see: Desiraju, G. R. *The Weak Hydrogen Bond in Structural Chemistry and Biology*; Desiraju, G. R., Steiner, T., Eds.; Oxford University Press: Oxford, 1999; p 13.

(42) The multiplet due to C(2)*H* appears as a doublet of doublets ($J_{2,1}$ 9.1, $J_{2,3}$ 4.6); in addition, it is notable that both O*H* protons are observable, appearing as broad singlets at δ_H 2.55 and 6.75.

(43) The stereo- and regiochemistries within **77** and **78** were subsequently established by comparison with authentic samples prepared via ring-opening of *syn*- and *anti*-epoxides **79** and **80**, respectively.

SCHEME 19[a]



[a]Reagents and conditions: (i) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; (ii) K_2CO_3, MeOH, rt, 12 h.

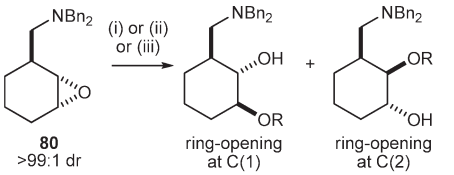
of *syn*-**79** in 17% yield from **65** and a mixed fraction (86:14, **79:80**) in 31% yield from **65** (Scheme 17).

Treatment of diastereoisomerically pure *syn*-epoxide **79** with AcOH gave the C(1) ring-opened product **81** in 95:5 dr, with purification giving **81** in 90% yield and >99:1 dr (Scheme 18). The regioselectivity of ring-opening and relative configuration within **81** were unambiguously determined by single-crystal X-ray analysis. The solid-state conformation of **81** is analogous to that of **75**, with the *N*,*N*-dibenzylaminomethyl group occupying an axial site in order to avoid unfavorable *syn*-pentane interactions when forming an intramolecular hydrogen bond between the C(2)-hydroxyl group and the nitrogen atom. However, ^{1}H NMR ^3J coupling constant analysis was suggestive of the alternative chair conformation which places the bulky *N*,*N*-dibenzylaminomethyl group equatorial being favored in solution. The inability of **81** (versus **75**) to form an additional intramolecular hydrogen bond between the C(1) and C(2) hydroxy groups may account for this difference in conformational preference. Ring-opening of **79** by TsOH gave a single diastereoisomer **77**, with the relative configuration within **77** being assigned by analogy to that unambiguously proven for **81**; ^{1}H NMR ^3J coupling constant analysis, assuming that **77** preferentially adopts a conformation in solution which places the bulky *N*,*N*-dibenzylaminomethyl group equatorial, was supportive of this assignment (Scheme 18). Ring-opening of **79** by Cl_3CCO_2H and transesterification gave diol **75** in 95:5 dr. Additionally, transesterification of hydroxy acetate species **81** (>99:1 dr) gave diol **75** in 79% yield and >99:1 dr (Scheme 18). These results demonstrate that ring-opening of epoxide *syn*-**79** proceeds with very high (≥95:5 dr) levels of regioselectivity for attack at C(1) for a range of acids. This predilection presumably arises due to the ring-opening reaction proceeding preferentially via a chair-like transition state which places the *N*,*N*-dibenzylaminomethyl group equatorial to give the *trans*-diaxial product.[40]

anti-Epoxide **80** was prepared from hydroxy acetate **81** via mesylation to give **82**, isolated in 97% yield after chromatography, and subsequent treatment with K_2CO_3 in MeOH, giving diastereoisomerically pure **80** in 85% yield. ^{1}H NMR ^3J coupling constant analysis of acetoxy mesylate **82** indicated that the favored solution-phase conformation is a chair which places the *N*,*N*-dibenzylaminomethyl group equatorial (Scheme 19).

The regioselectivity observed upon ring-opening of *anti*-epoxide **80** with TsOH, AcOH and Cl_3CCO_2H was investigated. Treatment of **80** with TsOH (3 equiv) gave a 64:36 mixture of hydroxy tosylates **78** and **83**, whilst ring-opening with Cl_3CCO_2H followed by transesterification gave a 56:44 mixture of diols **76** and **75**. (From the 95:5 and 56:44 ratios of C(1):C(2) ring-opened products obtained upon treatment of

SCHEME 20[a]



acid	conditions	R	ratio C(1):C(2)[a]	yield C(1) product %[b]	yield C(2) product %[b]
TsOH	(i)	Ts	64:36	**78**, 57	**83**, 27
Cl_3CCO_2H	(ii)	H	56:44	**76**, 52	**75**, 38
AcOH	(iii)	Ac	29:71[c]	**84**, 2[d]	**85**, 10[d]

[a]Reagents and conditions: (i) TsOH (3 equiv), CH_2Cl_2, rt, 2 h; (ii) Cl_3CCO_2H (5 equiv), CH_2Cl_2, rt, 14 h, then K_2CO_3, MeOH, rt, 12 h; (iii) AcOH, rt, 13 h. [[a]crude; [b]purified, isolated yield of single diastereoisomer (>99:1 dr); [c]reaction proceeded to 82% conversion; [d]a mixed fraction containing both **84** and **85** was also obtained in 68% yield; the combined yield of both products was therefore 80%.]

diastereoisomerically pure *syn*- and *anti*-epoxides **79** and **80**, respectively, with Cl_3CCO_2H, the epoxide ratio resulting from the ammonium-directed oxidation of tertiary amine **65** in the presence of Cl_3CCO_2H can be inferred as ~9:1.) Both of these results indicate that ring-opening at C(1) is marginally preferred. Treatment of **80** with AcOH gave 82% conversion to a 29:71 mixture of C(1):C(2) ring-opened products, hydroxy acetates **84** and **85**, suggesting that ring-opening at C(2) is slightly preferred (Scheme 20). The C(1) and C(2) ring-opened products proved separable by column chromatography in each case. The relative configurations within **76**, **78**, and **83**–**85** were assigned by ^{1}H NMR ^3J coupling constant analyses assuming, in each case, that the preferred conformation in solution was a chair which places the *N*,*N*-dibenzylaminomethyl group equatorial; in the case of **85**, the relative configuration was proven unambiguously by single-crystal X-ray analysis. Within the solid state, **85** preferentially adopts a chair conformation which places the *N*,*N*-dibenzylaminomethyl group equatorial and both the C(1)-hydroxyl and C(2)-acetoxy functionalities axial. This preference is readily accounted for due to the inability of **85** (versus **75** and **81**) to form an intramolecular hydrogen bond to the nitrogen atom. The modest levels of and variation in regioselectivity observed upon ring-opening of *anti*-epoxide **80** with TsOH, AcOH, and Cl_3CCO_2H parallels the observations of Crotti et al. concerning the ring-opening of *anti*-1,2-epoxy-3-benzyloxymethylcyclohexane by a range of nucleophiles.[44] Assuming that *anti*-epoxide **80** exists in solution in one of two possible half-chair conformers, **80A** which has the *N*,*N*-dibenzylaminomethyl group in a pseudoequatorial site, and **80B** which has the *N*,*N*-dibenzylaminomethyl group in a pseudoaxial site, then *trans*-diaxial ring-opening resulting from attack at C(2) of **80A** may be anticipated, since this results in a chair-like transition state with the protonated *N*,*N*-dibenzylaminomethyl group equatorial. However, the necessary approach trajectory of the nucleophile may be hindered by the steric bulk of the amino substituent, thus promoting *trans*-diaxial ring-opening via attack at C(1) of **80B**, giving an alternative chair-like transition state but with the protonated *N*,*N*-dibenzylaminomethyl group in an axial site. Variations in the

(44) Chini, M.; Crotti, P.; Flippin, L. A.; Gardelli, C.; Macchia, F. *J. Org. Chem.* **1992**, *57*, 1713.

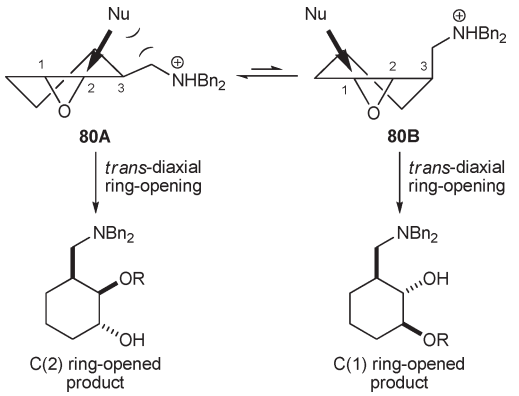
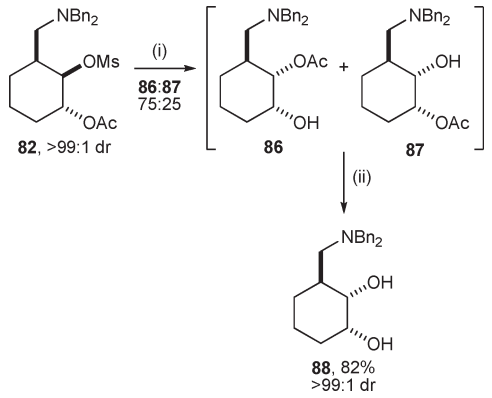


FIGURE 6. Proposed rationale for variation in regioselectivity of ring-opening of epoxide **80** with TsOH, Cl_3CCO_2H, and AcOH.

SCHEME 21[a]



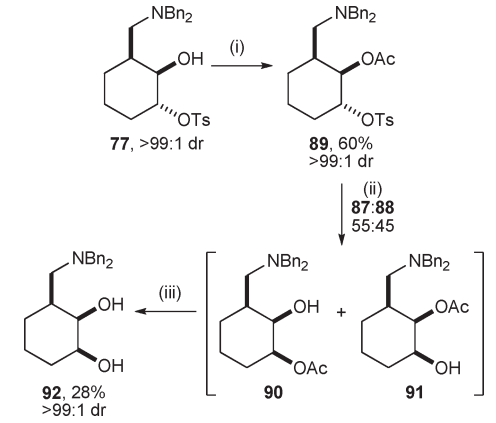
[a]Reagents and conditions: (i) KOAc, EtOH/H_2O (6:1), 80 °C, 12 h; (ii) K_2CO_3, MeOH, rt, 12 h.

regioselectivity of ring-opening with the identity of the nucleophile may therefore be expected[44,45] (Figure 6).

In addition to providing mechanistic insight into this oxidative transformation, these studies also facilitated the preparation of the diastereoisomeric 1,2-*anti*-configured *N*,*N*-dibenzylamino diols **75** and **76**. The corresponding 1,2-*syn*-configured diols were next prepared via the inversion strategy of Winstein, reliant on formation of an acetoxonium intermediate.[26] Treatment of acetoxy mesylate **82** with KOAc in aqueous EtOH at reflux for 12 h afforded a 75:25 mixture of hydroxy acetates **86** and **87**.[46] Transesterification gave **88** as a single diastereoisomer (>99:1 dr) in 82% yield and >99:1 dr[47] after purification (Scheme 21). The relative configuration within **88** was unambiguously established by single-crystal X-ray analysis. In the solid state, both the *N*,*N*-dibenzylaminomethyl group and the C(2)-hydroxyl substituent within **88** are able to adopt equatorial sites within a chair conformation, and an intramolecular hydrogen bond is observed between them. ^{1}H NMR ^3J coupling constant analysis of **88** was indicative of an identical solution-phase conformational preference.

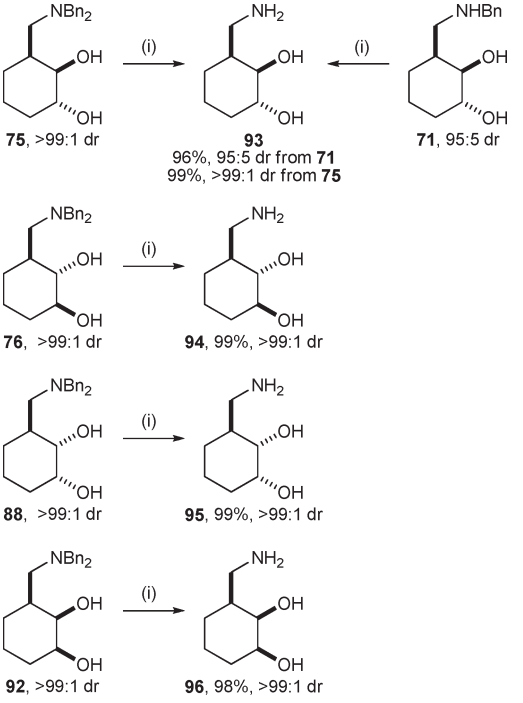
In a similar manner, acetylation of hydroxy tosylate **77** (>99:1 dr) gave acetoxy tosylate **89** in 60% yield, with subsequent treatment with KOAc in aq EtOH giving a 55:45

SCHEME 22[a]



[a]Reagents and conditions: (i) Ac_2O, pyridine, DMAP, CH_2Cl_2, 0 °C to rt, 2 h; (ii) KOAc, EtOH/H_2O (6:1), 80 °C, 12 h; (iii) MeOH, K_2CO_3, rt, 12 h.

SCHEME 23[a]

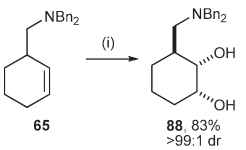


[a]Reagents and conditions: (i) H_2 (1 atm), $Pd(OH)_2$/C (50% w/w), MeOH, 6 h, rt.

(45) Hydrogen-bonded delivery of the conjugate base to C(2) by the protonated *N*,*N*-dibenzylaminomethyl group may also be important in determining the regioselectivity of the ring-opening reaction.

(46) The regiochemistry within **86** and **87** was arbitrarily assigned.

(47) The relative 1,2-*syn*-configuration within **88** was also established by dihydroxylation of **65** with OsO_4/TMEDA, which gave **88** in 83% isolated yield and >99:1 dr (reagents and conditions: (i) OsO_4, TMEDA, CH_2Cl_2, −78 °C, 2 h, then MeOH, HCl, rt, 24 h).



mixture of hydroxy acetates **90** and **91**.[48] Transesterification of this mixture with K_2CO_3 in MeOH gave **92** in 28% yield and >99:1 dr. The relative configurations within **89** and **92** were assigned on the basis of ^{1}H NMR ^3J coupling constant analyses, assuming in each case that the preferred conformation in solution is a chair which places the *N*,*N*-dibenzylaminomethyl group in an equatorial site (Scheme 22).

Hydrogenolysis of *N*-benzylamino diol **71** and *N*,*N*-dibenzylamino diols **75**, **76**, **88**, and **92** gave the corresponding diastereoisomers of 3-aminomethylcyclohexane-1,2-diol **93**−**96** in good yield. Hydrogenolysis of secondary amine **71** (95:5 dr) and tertiary amine **75** gave the same diastereoisomeric product **93**, thus unambiguously confirming the relative configuration within secondary amine **71** (Scheme 23).

Conclusion

In conclusion, the oxidative functionalization of a range of allylic 3-(*N*,*N*-dibenzylamino)cycloalk-1-enes with *m*-CPBA in the presence of Cl_3CCO_2H gives exclusively the corresponding *syn*-epoxide for the 5-membered ring (>99:1 dr), the *anti*-epoxide for the 8-membered ring (>99:1 dr), and predominantly the *anti*-epoxide for the 7-membered ring (94:6 dr). Oxidation of homoallylic amines 3-(*N*-benzylamino)-methylcyclohex-1-ene and 3-(*N*,*N*-dibenzylamino)methylcyclohex-1-ene gave, in both cases, the corresponding *N*-protected 1,2-*anti*-2,3-*syn*-3-aminomethylcyclohexane-1,2-diol with high levels of diastereoselectivity (≥90:10 dr). The versatile synthetic intermediates resulting from these oxidation reactions are readily transformed into a range of amino diols.

Experimental Section

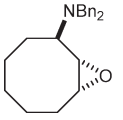
(1*RS*,2*SR*,3*SR*)-1,2-Epoxy-3-(*N*,*N*-dibenzylamino)cyclopentane (20).

Cl_3CCO_2H (31.0 g, 190 mmol) was added to a stirred solution of **14** (10 g, 38.0 mmol) in CH_2Cl_2 (127 mL, 0.3 M with respect to **14**), and the resultant mixture was stirred at rt for 5 min. *m*-CPBA (73%, 9.43 g, 39.9 mmol) was then added in one portion, and the reaction mixture was stirred at rt for 3.5 h. The mixture was diluted with CH_2Cl_2 (100 mL), and satd aq Na_2SO_3 was added until starch−iodide paper indicated no remaining peracid. Saturated aq $NaHCO_3$ (200 mL) was added, and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ (2 × 200 mL) and then dried, filtered through a short plug of silica gel (eluent CH_2Cl_2), and concentrated in vacuo to give **20** in >99:1 dr. Purification via recrystallization (^{i}PrOH) gave **20** as a white crystalline solid. Concentration of the mother liquors and purification of the residue via flash column chromatography (gradient elution, 1%→8% EtOAc in 40−60 °C petroleum ether) gave **20** as a colorless oil that solidified on standing to a white crystalline solid (10.5 g combined, 99%, >99:1 dr): R_f 0.12 (40−60 °C petroleum ether/EtOAc, 96:4); mp 58−60 °C (^{i}PrOH); ν_{max} (KBr) 3084, 3061, 3027, 2951, 2802 (C-H), 1602, 1494, 1453; δ_H (400 MHz, $CDCl_3$) 1.45−1.59 (3H, m, C(4)H_A, C(5)H_2), 2.00−2.11 (1H, m, C(4)H_B), 3.25−3.31 (1H, m, C(3)*H*), 3.34 (1H, app d, *J* 2.7, C*H*, epoxide), 3.47 (1H, app d, *J* 2.7, C*H*, epoxide), 3.74 (2H, d, *J* 14.3, N(C$H_A$$H_B$Ph)$_2$), 3.86 (2H, d, *J* 14.3, N(C$H_A$$H_B$Ph)$_2$), 7.22−7.46 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.9 (*C*(5)), 25.7 (*C*(4)), 53.7, 55.5, 56.4 (*C*(1), *C*(2), N(*C*H_2Ph)$_2$), 61.4 (*C*(3)), 126.8 (*p-Ph*), 128.2, 128.5 (*o*-, *m-Ph*), 140.4 (*i-Ph*); *m*/*z* (ESI$^+$) 280 ([M + H]$^+$, 100); HRMS (ESI$^+$) $C_{19}H_{22}NO^+$ ([M+H]$^+$) requires 280.1696, found 280.1692. Anal. Calcd for $C_{19}H_{21}NO$: C, 81.7; H, 7.6; N, 5.0. Found: C, 81.5; H, 7.7; N, 4.9.

X-ray Crystal Structure Determination for 20. Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite-monochromated Mo Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealized positions. The structure was refined using CRYSTALS.[49]

X-ray crystal structure data for **20** [$C_{19}H_{21}NO$]: M = 558.76, monoclinic, space group $P2_1$, a = 12.444(3) Å, b = 7.8733(16) Å, c = 16.766(3) Å, β = 109.74(3)°, V = 1546.1(6) Å^3, Z = 4, μ = 0.073 mm^{-1}, colorless block, crystal dimensions = 0.2 × 0.2 × 0.2 mm^3. A total of 3651 unique reflections were measured for $5 < \theta < 27$, and 3651 reflections were used in the refinement. The final parameters were wR_2 = 0.214 and R_1 = 0.092 [$I > -3.0\sigma(I)$]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 733891. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

(1*RS*,2*SR*,3*RS*)-1,2-Epoxy-3-(*N*,*N*-dibenzylamino)cyclooctane (25).



Cl_3CCO_2H (26.7 g, 164 mmol) was added to a stirred solution of **16** (10 g, 32.7 mmol) in CH_2Cl_2 (109 mL, 0.3 M with respect to **16**), and the resultant mixture was stirred at rt for 5 min. *m*-CPBA (74%, 8.02 g, 34.4 mmol) was then added in one portion, and the reaction mixture was stirred at rt for 3.5 h. The mixture was diluted with CH_2Cl_2 (100 mL), and satd aq Na_2SO_3 was added until starch−iodide paper indicated no remaining peracid. Saturated aq $NaHCO_3$ (200 mL) was added, and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ (2 × 200 mL) and then dried, filtered through a short plug of silica gel (eluent CH_2Cl_2), and concentrated in vacuo to give **25** as a white crystalline solid (10.4 g, quant, >99:1 dr): mp 104 °C (EtOH); ν_{max} (KBr) 2972, 2926, 2854 (C−H), 1602, 1493, 1454; δ_H (400 MHz, $CDCl_3$) 0.85−0.99 (1H, m, C(8)H_A), 1.11−1.21 (1H, m, CH_2), 1.34−1.61 (5H, m, CH_2), 1.65−1.75 (2H, m, C(4)H_2), 2.10 (1H, app dq, *J* 13.7, 3.9, C(8)H_B), 2.68 (1H, app td, *J* 9.5, 6.7, C(3)*H*), 2.89 (1H, app dt, *J* 10.4, 4.4, C(1)*H*), 3.08 (1H, dd, *J* 9.5, 4.4, C(2)*H*), 3.79 (4H, AB

(48) The regiochemistry within **90** and **91** was arbitrarily assigned.

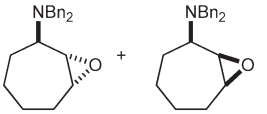
(49) Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *CRYSTALS* **2001**, issue 11, Chemical Crystallography Laboratory, University of Oxford, UK.

system, J_{AB} 13.7, N(CH_2Ph)$_2$), 7.19−7.46 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.2, 25.5, 26.8, 27.1, 31.2 (*C*(4)-*C*(8)), 53.4 (*C*(1)), 54.6 (N(*C*H_2Ph)$_2$), 55.7 (*C*(2)), 55.8 (*C*(3)), 126.7 (*p-Ph*), 128.1, 128.7 (*o-*, *m-Ph*), 140.5 (*i-Ph*); *m*/*z* (ESI$^+$) 322 ([M + H]$^+$, 100); HRMS (ESI$^+$) $C_{22}H_{28}NO^+$ ([M + H]$^+$) requires 322.2165, found 322.2161.

X-ray Crystal Structure Determination for 25. Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite-monochromated Mo Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealized positions. The structure was refined using CRYSTALS.[49]

X-ray crystal structure data for **25** [$C_{22}H_{27}NO$]: M = 642.93, monoclinic, space group $P2_1/c$, a = 14.8507(4) Å, b = 14.8824(4) Å, c = 16.6996(4) Å, β = 94.0401(18)°, V = 3681.67(17) Å^3, Z = 8, μ = 0.070 mm^{-1}, colorless plate, crystal dimensions = 0.2 × 0.2 × 0.3 mm^3. A total of 8288 unique reflections were measured for 5 < θ < 27, and 3748 reflections were used in the refinement. The final parameters were wR_2 = 0.133 and R_1 = 0.151 [$I > 3.0\sigma(I)$]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 733893. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

(1*RS*,2*SR*,3*RS*)- and (1*RS*,2*SR*,3*SR*)-1,2-Epoxy-3-(*N*,*N*-dibenzylamino)cycloheptane (28 and 29).



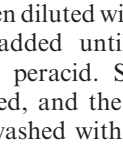
28 29

Cl_3CCO_2H (5.74 g, 35.2 mmol) was added to a stirred solution of **15** (2.05 g, 7.03 mmol) in CH_2Cl_2 (23 mL, 0.3 M with respect to **15**), and the resultant mixture was stirred at rt for 5 min. *m*-CPBA (74%, 1.72 g, 7.38 mmol) was then added in one portion, and the reaction mixture was stirred at rt for 3.5 h. The mixture was diluted with CH_2Cl_2 (25 mL), and satd aq Na_2SO_3 was added until starch−iodide paper indicated no remaining peracid. Saturated aq $NaHCO_3$ (25 mL) was added, and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ (2 × 25 mL) and then dried, filtered through a short plug of silica gel (eluent CH_2Cl_2), and concentrated in vacuo to give a 94:6 mixture of **28**:**29**. Purification via flash column chromatography (gradient elution, 2%→20% Et_2O in 40−60 °C petroleum ether) gave **29** as a colorless oil which solidified on standing to a white crystalline solid (94 mg, 4%, >99:1 dr): R_f 0.28 (40−60 °C petroleum ether:Et_2O, 90:10); mp 54 °C; ν_{max} (film) 3084, 3062, 3027, 2926, 2849, 2803 (C−H), 1603, 1494, 1453; δ_H (400 MHz, $CDCl_3$) 0.59−0.70 (1H, m, CH_2), 1.26−1.65 (4H, m, CH_2), 1.74−1.82 (1H, m, CH_2), 1.84−1.91 (1H, m, CH_2), 2.22−2.31 (1H, m, CH_2), 2.89 (1H, app dd, *J* 11.6, 2.8, C(1)*H*), 3.06 (1H, app t, *J* 5.3, C(3)*H*), 3.35 (1H, dd, *J* 4.8, 1.0, C(2)*H*), 3.59 (2H, d, *J* 13.9, N(CH_AH$_B$Ph)$_2$), 3.90 (2H, d, *J* 13.9, N(CH$_A$$H_B$Ph)$_2$), 7.21−7.42 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 23.4, 24.1, 27.1, 28.0 (*C*(4)-*C*(7)), 53.3 (*C*(3)), 54.3 (N(*C*H_2Ph)$_2$), 58.4 (*C*(1)), 60.7 (*C*(2)), 126.7 (*p-Ph*), 128.1, 128.5 (*o-*, *m-Ph*), 140.4 (*i-Ph*); *m*/*z* (ESI$^+$) 308 ([M + H]$^+$, 100); HRMS (ESI$^+$) $C_{21}H_{26}NO^+$ ([M + H]$^+$) requires 308.2009, found 308.2005. Further elution gave **28** as a colorless oil which solidified on standing to a white crystalline solid (1.49 g, 69%, >99:1 dr): R_f 0.17 (40−60 °C petroleum ether/Et_2O, 90:10); mp 69−70 °C; ν_{max} (KBr) 3084, 3061, 3028, 2926, 2851, 2804 (C−H), 1602, 1494, 1454; δ_H (400 MHz, $CDCl_3$) 1.02−1.12 (1H, m, C(7)H_A), 1.15−1.34 (2H, m, CH_2), 1.60−1.73 (2H, m, C(4)H_2), 1.83−1.92 (2H, m, CH_2), 2.22 (1H, app ddd, *J* 13.7, 6.8, 6.5, C(7)H_B), 2.66 (1H, app dd, *J* 10.4, 7.5, C(3)*H*), 3.00 (1H, ddd, *J* 8.0, 6.5, 5.0, C(1)*H*), 3.24 (1H, dd, *J* 7.5, 5.0, C(2)*H*), 3.77 (4H, AB system, J_{AB} 13.9, N(CH_2Ph)$_2$), 7.21−7.46 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 24.0, 29.3, 29.8, 31.2 (*C*(4)-*C*(7)), 52.7 (*C*(3)), 54.6 (N(*C*H_2Ph)$_2$), 55.6 (*C*(1)), 60.7 (*C*(2)), 126.8 (*p-Ph*), 128.1, 128.8 (*o-*, *m-Ph*), 140.1 (*i-Ph*); *m*/*z* (ESI$^+$) 308 ([M + H]$^+$, 100); HRMS (ESI$^+$) $C_{21}H_{26}NO^+$ ([M + H]$^+$) requires 308.2009, found 308.2006.

X-ray Crystal Structure Determination for 28. Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite-monochromated Mo Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealized positions. The structure was refined using CRYSTALS.[49]

X-ray crystal structure data for **28** [$C_{21}H_{25}NO$]: M = 307.44, monoclinic, space group $P2_1/c$, a = 9.6786(2) Å, b = 15.6935(4) Å, c = 11.6781(4) Å, β = 92.0417(10)°, V = 1772.67(8) Å^3, Z = 4, μ = 0.070 mm^{-1}, colorless block, crystal dimensions = 0.1 × 0.1 × 0.1 mm^3. A total of 4010 unique reflections were measured for 5 < θ < 27, and 1988 reflections were used in the refinement. The final parameters were wR_2 = 0.035 and R_1 = 0.034 [$I > 3.0\sigma(I)$]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 733894. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

(1*RS*,2*RS*,3*SR*)-3-(*N*,*N*-Dibenzylamino)methylcyclohexane-1,2-diol (75).



Dihydroxylation of 65. Cl_3CCO_2H (4.20 g, 25.7 mmol) was added to a stirred solution of **65** (1.5 g, 5.15 mmol) in CH_2Cl_2 (14 mL), and the resultant mixture was stirred at rt for 30 min. *m*-CPBA (70%, 1.90 g, 7.71 mmol) was then added in one portion, and the reaction mixture was stirred at rt for 21 h. The mixture was then diluted with CH_2Cl_2 (20 mL), and satd aq Na_2SO_3 was added until starch−iodide paper indicated no remaining peracid. Saturated aq $NaHCO_3$ (150 mL) was then added, and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ (2 × 100 mL), dried, and concentrated in vacuo. Following the general procedure, transesterification with K_2CO_3 (3.55 g, 25.7 mmol) in MeOH (80 mL) gave **75** in 90:10 dr. Purification via exhaustive flash column chromatography (gradient elution, 7%→60% EtOAc in 30−40 °C petroleum ether) gave **75** as a white solid (916 mg, 55%, >99:1 dr) and a sample of **76** contaminated with trace amounts (< 5%) of unknown impurities (63 mg, ~4%).

Data for **75**: mp 83−85 °C; ν_{max} (film) 3356 (O-H); δ_H (400 MHz, $CDCl_3$) 1.09−1.14 (2H, m, C(5)H_2), 1.26−1.29 (1H, m, C(6)H_A), 1.43−1.49 (2H, m, C(4)H_2), 1.71−1.78 (1H, m, C(6)H_B), 2.20−2.24 (1H, m, C(3)*H*), 2.55−2.60 (1H, br s, O*H*), 2.60−2.70 (2H, m, C(3)CH_2N), 3.07−3.15 (3H, m, C(1)*H*, N(C$H_A$$H_B$Ph)$_2$), 3.36−3.39 (1H, m, C(2)*H*), 4.05−4.09 (2H, m, N(C$H_A$$H_B$Ph)$_2$), 6.78−6.99 (1H, br s, O*H*), 7.27−7.42 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.9 (*C*(5)), 28.5 (*C*(4)), 31.7 (*C*(6)), 33.7 (*C*(3)), 54.7 (C(3)CH_2N), 58.9 (N(*C*H_2Ph)$_2$), 70.6 (*C*(1)), 76.7 (*C*(2)), 127.7 (*p-Ph*), 128.6, 129.6 (*o-*, *m-Ph*), 137.4 (*i-Ph*); *m*/*z* (ESI$^+$) 326 ([M + H]$^+$, 100); HRMS (ESI$^+$) $C_{21}H_{28}NO_2^+$ ([M+H]$^+$) requires 326.2115, found 326.2114.

X-ray Crystal Structure Determination for 75. Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite-monochromated Mo Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealized positions. The structure was refined using CRYSTALS.[49]

X-ray crystal structure data for **75** [$C_{21}H_{27}NO_2$]: M = 325.45, monoclinic, space group $P2_1/n$, a = 10.9893(3) Å, b = 13.7910(3) Å, c = 12.2178(4) Å, β = 102.4024(11)°, V = 1808.44(9) Å^3, Z = 4, μ = 0.076 mm^{-1}, colorless block, crystal dimensions = 0.3 × 0.3 × 0.3 mm^3. A total of 4097 unique reflections were measured for 5 < θ < 27, and 2235 reflections were used in the refinement. The final parameters were wR_2 = 0.037 and R_1 = 0.038 [$I > 3.0\sigma(I)$]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 733901. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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Supporting Information Available: Full details of all experimental procedures, characterization data, copies of ^{1}H and ^{13}C NMR spectra, and crystallographic information files (for structures CCDC 733888-733904). This material is available free of charge via the Internet at http://pubs.acs.org.