Probing Competitive and Co-operative Hydroxyl and Ammonium Hydrogen-Bonding Directed Epoxidations

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## Supporting Information

### ABSTRACT:
The diastereoselectivities and rates of epoxidation (upon treatment with Cl₃CCO₂H then m-CPBA) of a range of cis- and trans-4-aminocycloalk-2-en-1-ol derivatives (containing five-, six-, and seven-membered rings) have been investigated. In all cases where the two potential directing groups can promote epoxidation on opposite faces of the ring scaffold, evidence of competitive epoxidation pathways, promoted by hydrogen-bonding to either the in situ formed ammonium moiety or the hydroxyl group, was observed. In contrast to the relative directing group abilities already established for the six-membered ring system (NHBn ≫ OH > NBn₂), an N,N-dibenzylammonium moiety appeared more proficient than a hydroxyl group at directing the stereochemical course of the epoxidation reaction in a five- or seven-membered system. In the former case, this was rationalized by the drive to minimize torsional strain in the transition state being coupled with assistance from hydrogen-bonding to the ammonium moiety. In the latter case, this was ascribed to the steric bulk of the ammonium moiety disfavoring conformations in which hydrogen-bonding to the hydroxyl group results in direction of the epoxidation to the syn face. In cases where the two potential directing groups can promote epoxidation on the same face of the ring scaffold, an enhancement of epoxidation diastereoselectivity was not observed, while introduction of a second, allylic heteroatom to the substrate results in diminishment of the rate of epoxidation in all cases. Presumably, reduction of the nucleophilicity of the olefin by the second, inductively electron-withdrawing heteroatom is the dominant factor, and any assistance to the epoxidation reaction by the potential to form hydrogen-bonds to two directing groups rather than one is clearly unable to overwhelm it.

### INTRODUCTION

The ability to both accurately predict and be able to exert total control over the stereochemical outcome of a given reaction might be considered a Holy Grail of organic synthesis.¹,² As such, a substrate-directed reaction³ is an attractive means to achieve a diastereoselective transformation. In these processes the substrate is equipped with some structural feature that is able to influence the stereochemical course of the reaction. Perhaps one of the earliest and most widely recognized examples of this tactic is the diastereoselective epoxidation of a chiral allylic alcohol with a peracid, the stereochemical outcome of which is rationalized by invoking a hydrogen-bond between the allylic hydroxyl group "donor" and the peracid "acceptor" in the transition state.⁴ Teranishi et al. have reported the diastereoselectivities of epoxidation of the homologous series of cycloalk-2-en-1-ols 1–3 upon treatment with m-CPBA in CH₂Cl₂ at 0 °C for 24 h:⁵ diastereoselective epoxidation of the syn face occurs in each case, with the levels of diastereoselectivity being dependent on the ring size. Epoxidation of seven-membered ring substrate 3 proceeds with only modest diastereoselectivity,⁶ while higher levels of diastereoselectivity are observed for five-membered ring substrate 1⁷ and six-membered ring substrate 2⁸ (Scheme 1).

We have investigated the related epoxidation of a range of chiral allylic amines, reliant on a strategy involving initial treatment with a strong Bronsted acid (e.g., Cl₃CCO₂H, F₃CCO₂H, TsOH, HBF₄) to effect protonation of the nitrogen atom, and hence offer protection against N-oxidation.⁹ The proton of the resultant ammonium moiety is capable of acting as a hydrogen-bond donor to direct epoxidation upon addition

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Scheme 1

| Reagents and conditions: (i) m-CPBA, CH₂Cl₂, 0 °C, 24 h. |
| Reagents: F₃CCO₂H, TsOH, HBF₄ |

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of a peracid (e.g., m-CPBA, F₂CCO₂H) to the proximal face of the olefin. For example, treatment of N-benzyl- or N,N-
dibenzyl-protected cycloalk-2-en-1-amine derivatives 7–12 with Cl₃CCO₂H then m-CPBA gave the corresponding epoxides 13–18.¹⁰⁻¹³ The stereochemical outcome of the epoxidation was influenced not only by the ring size but also by the nature of the amino substituent, although in all cases the amino substituent provided equivalent or better diastereoselectivity of epoxidation than the analogous hydroxyl group. The five- and six-membered ring substrates 7–10 underwent epoxidation on the face syn to the amino substituent (regardless of its identity) with very high levels of diastereoselectivity (≥95:5 dr), leading to the corresponding syn-epoxides 13–16.¹⁰⁻¹³ This sense of diastereoselectivity is in accord with that elicited during the epoxidations of both of the corresponding allylic alcohols (cyclopent-2-en-1-ol 1 and cyclohex-2-en-1-ol 2) under epoxidation with a range of peracids,⁷,⁸ and is consistent with hydrogen-bonding between the in situ formed ammonium ion and the oxidant resulting in delivery of the latter to the proximal face. In the five-membered ring substrates 7 and 8, the syn-selectivity may also be inherently favored by minimization of torsional strain in the transition state.¹¹,¹⁴,¹⁵ Within the seven-membered ring substrates, epoxidation of 11 gave syn-epoxide 17 in 85:15 dr.¹⁶ This is consistent with the diastereoselectivity elicited upon epoxidation of cyclohept-2-en-1-ol 3 with a range of peracids, which proceeds to give the syn-epoxide 6 in ~2:1 dr.²,⁶ In contrast, epoxidation of 12 gave anti-epoxide 18 in 94:6 dr (88% conversion).¹³,¹⁶,¹⁷ This outcome is anomalous on two counts when compared to 3 and 11: first, it is significantly more diastereoselective, and second, it proceeds on the face anti to the directing group. We have previously rationalized these observations¹¹,¹⁶ as the result of the N,N-dibenzylammonium moiety playing two distinct roles: (i) its large steric bulk enforces a well-defined seven-membered chair conformation¹⁷ (as present in the X-ray crystal structures of 12, the corresponding HBr salt 12-HBr and epoxide 18) upon the otherwise conformationally promiscuous seven-membered ring;¹⁷ (ii) hydrogen-bonding between the ammonium moiety and the peracid assists in epoxidation of the proximal (anti) face in this conformer (Scheme 2).*¹³,¹⁴

We have recently explored the epoxidations of N-benzyl- and N,N-dibenzyl-protected trans-4-aminocyclohex-2-en-1-ol 19 and 20.¹⁴,¹⁹ These are privileged structures within which the relative directing abilities of the various substituents may be evaluated, as in either of the possible half-chair conformations (19A/20A and 19B/20B) of the six-membered rings, the allylic amino (and hence in situ formed ammonium) moiety and the allylic hydroxyl group are located in identical environments (e.g., both pseudoequatorial in the ground states 19A and 20A). Epoxidation of N-benzyl-protected trans-19 resulted in complete diastereoselectivity (>95:5 dr) for production of epoxide 21 (i.e., epoxidation exclusively on the face of the olefin syn to the in situ formed ammonium moiety); N-benzylolation of the crude reaction mixture gave 22 in 64% yield. This result suggests that the N-benzylammonium moiety is superior to the hydroxyl group as a directing group. In contrast, epoxidation of N,N-dibenzyl-protected trans-20 gave a separable 25:75 mixture of epoxides 22 and 23, respectively (i.e., the major product 23 results from epoxidation on the face of the olefin syn to the hydroxyl group), suggesting that the hydroxyl group is a better directing group than the N,N-dibenzylammonium moiety in an identical environment. From the results of these studies, it followed that the order of directing group ability is NHBN > OH > NBn₂ (Scheme 3).

The epoxidations of the diastereoisomeric compounds cis-24 and cis-25 were also explored.¹⁵ In these cases, the corresponding epoxides 26 and 27 were obtained as the exclusive products, which result from reaction on the face syn to both the amino (ammonium) moiety and the hydroxyl group, as may be expected; in the former case N-benzylation of the crude reaction mixture to facilitate purification gave 27, which

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**Scheme 2**

Reagents and conditions: (i) Cl₃CCO₂H (5.0 equiv), m-CPBA (1.05 equiv), CH₂Cl₂, rt, 3.5 h; (ii) Cl₃CCO₂H (5.0 equiv), m-CPBA (1.6 equiv), CH₂Cl₂, rt, 21 h; (iii) Cl₃CCO₂H (5.0 equiv), m-CPBA (2.5 equiv), CH₂Cl₂, rt, 20 min.

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**Scheme 3**

Reagents and conditions: (i) Cl₃CCO₂H (10 equiv), m-CPBA (5.0 equiv), CH₂Cl₂, rt, 30 min; (ii) BnBr, iPr₂NEt, DMAP, CH₂Cl₂, rt, 24 h; (iii) Cl₃CCO₂H (10 equiv), m-CPBA (5.0 equiv), CH₂Cl₂, rt, 3.5 h. *Sample isolated in 95:5 dr [22:23].
was thus isolated in 59% yield from 24 and 63% yield from 25 (Scheme 4). These results are consistent with the epoxidation being directed by either the hydroxyl group or the ammonium moiety, or indeed both. However, the relative contributions from hydrogen-bonding to either of the two potential directing groups cannot be easily dissected; a matter that is further complicated by issues of geometry, as the two potential directing groups now do not occupy identical environments in either of the possible half-chair conformations of the six-membered rings (24A/25A and 24B/25B). The dependence of reaction diastereoselectivity (as well as rate) on conformation is known in the epoxidations of related six-membered ring substrates. For example, Whitham et al. investigated epoxidation of the diastereoisomers of 5-tert-butylcyclohex-2-en-1-ol (cis-28 and trans-29) and found that a pseudoequatorial hydroxyl group was significantly better than a pseudoequatorial one as a directing group:20 for trans-29 (pseudoequatorial hydroxyl group) the diastereoselectivity was 84:16 (syn:anti) with a relative rate of reaction on the face syn to the hydroxyl group of 1.0, whereas for cis-28 (pseudoequatorial hydroxyl group) the diastereoselectivity was 94:6 (syn:anti) with a relative rate of reaction on the face syn to the hydroxyl group of 8.2 (Scheme 5). A related (albeit much more subtle) effect was noted when we investigated epoxidation of the diastereoisomers of N,N-dibenzyl-5-tert-butylcyclohex-2-en-1-amine (cis-32 and trans-33):10 for cis-32 the diastereoselectivity was >95:5 (syn:anti) with a relative rate of reaction on the face syn to the ammonium moiety of 1.0 whereas for trans-33 the diastereoselectivity was >95:5 (syn:anti) with a relative rate of reaction on the face syn to the ammonium moiety of 1.8 (Scheme 6).

As part of our ongoing research program concerning the synthesis of biologically significant molecules containing an aminotriol moiety, we proposed to investigate the behavior of the diastereoisomers of the corresponding N-benzyl- and N,N-dibenzyl-protected 4-aminocyclopent-2-en-1-ols and 4-aminocyclohept-2-en-1-ols (i.e., containing five- and seven-membered rings, respectively) under these epoxidation conditions, and the results of these investigations are reported herein.

## RESULTS AND DISCUSSION

The requisite five-membered ring substrates were prepared from cyclopentadiene 36. The synthesis began with conversion of 36 into 38 following previously reported procedures:21,22 a [4+2]-cycloaddition of 36 with PhCONO (generated in situ from the oxidation of benzhydroxamic acid by Bu4NIO4) gave bicycle 37 in 75% yield,21 and subsequent N–O bond cleavage upon treatment of 37 with sodium amalgam gave 38 in 85% yield and >99:1 dr.22 Reduction of 38 using LiAlH4 then gave cis-39 in 80% yield and >99:1 dr. Chemoselective N-benzylation of cis-39 was achieved using BnBr/Pr3NEt, which gave cis-40 in 83% yield and >99:1 dr. Unfortunately, attempted Mitsunobu reaction of cis-39 resulted in the formation of a complex mixture of products from which only an impure sample of trans-41 could be isolated in <10% yield. However, Mitsunobu reaction of cis-40 gave access to trans-42 in 60% isolated yield and 98:2 dr (Scheme 7).

With diastereoisomeric N,N-dibenzyl-protected cis-40 and trans-42 in hand, investigations into the diastereoselectivities of their epoxidations were undertaken. Our “NMR titration” procedure10 was used to determine the number of equivalents of Cl3CCO2H required to efficiently protect cis-40 against N-oxidation. In this experiment, Cl3CCO2H was added in 1.0 equiv portions to a 0.36 M solution of cis-40 in CD2Cl2 and the solution was analyzed by 1H NMR spectroscopy. The resultant differences in chemical shifts (Δδ) of C(1)H, C(2)H and C(3)H (which were easily discernible) versus the free amine were determined. These differences showed a plateau around...
However, in order for a more direct comparison of the results with those of the corresponding six-membered substrates trans-20 and cis-25 to be made, it was decided to employ 10 equiv of Cl₃CCO₂H throughout these investigations. Treatment of cis-40 with 10 equiv of Cl₃CCO₂H then 1.05 equiv of m-CPBA for 3.5 h at rt (i.e., analogous to the optimized conditions for the "parent" system 8) resulted in only 44% conversion to epoxide 43 (in >95:5 dr). Using 2.0 equiv of m-CPBA over 16 h, however, gave >95% conversion to 43 (in >95:5 dr), which was isolated in 77% yield and >99:1 dr. Meanwhile, epoxidation of trans-42 (98:2 dr) under the same conditions gave >95% conversion to epoxide 44 in 93:7 dr, with purification giving 44 in 66% yield and >99:1 dr. Both the gross structure and relative configuration of 44 were unambiguously established by single crystal X-ray diffraction analysis of the corresponding p-nitrobenzoate derivative 45. Mitsunobu reaction of 44 gave 43, thus unambiguously establishing both the gross structure and relative configuration of the latter. The effect of O-protection on the diastereoselectivities of these epoxidation reactions was also probed in order to assess the importance of hydrogen-bonding to the hydroxyl group in these transformations. The corresponding O-benzyl ethers cis-46 and trans-47 were duly prepared from cis-40 (>99:1 dr) and trans-42 (98:2 dr) upon treatment with NaH and BnBr. Epoxidation of cis-46 (>99:1 dr) resulted in 84% conversion to epoxide 48 in >95:5 dr, which was isolated in 71% yield and >99:1 dr. The relative configuration of 48 was unambiguously established by correlation to 43: treatment of 43 with NaH/BnBr gave 48. Meanwhile, epoxidation of trans-47 (>99:1 dr) resulted in 82% conversion to epoxide 49 in >95:5 dr, which was isolated in 74% yield and >99:1 dr. The relative configuration of 49 was unambiguously established by correlation to 44: treatment of 44 with NaH/BnBr gave 49. The formation of epoxides 43, 44, 48, and 49 (rather than formation of ring-opened species) as the major products of all of these reactions is entirely consistent with the behavior of the "parent" system 8 under analogous conditions which results in formation of the corresponding syn-epoxide 14 exclusively. Epoxidations of cis-40 and cis-46 reveal that epoxidation on the syn-face of the olefin of (proximal to both heteroatoms) is favored even when the oxygen atom is incapable of acting as a hydrogen-bond donor. Although the increase in diastereoselectivity upon epoxidation of trans-47 (>95:5 dr) as compared to trans-40 (93:7 dr) is consistent with formation of the minor diastereoisomeric product being the result of a hydroxyl-directed pathway, steric effects may also contribute (Scheme 8).

The requisite seven-membered ring substrates 53−56 were prepared from 1,3-cycloheptadiene 50 via a directly analogous scheme.

Scheme 7"
Epoxidation of the trans-diastereoisomers under the same conditions revealed that epoxidation of N,N-dibenzy1-protected trans-56 proceeded to >95% conversion to give a 95:5 mixture of epoxides 64 and 65, respectively. These species proved separable by chromatography, allowing isolation of 64 in 73% yield and >99:1 dr, although 65 was not isolated in this case. The gross structure and relative configuration of 64 were unambiguously established by single crystal X-ray diffraction analysis.23 In order to provide some insight into the relative importance of the amino moiety versus the hydroxyl group in promoting diastereoselective epoxidation, the corresponding O-benzyl ether trans-66 was prepared from trans-56 upon treatment with NaH and BnBr. Subsequent epoxidation of trans-66 (>99:1 dr) resulted in 86% conversion to a 94:6 mixture of epoxides 67 and 68 (i.e., the same level of diastereoselectivity as trans-56, within experimental error). Meanwhile, epoxidation of N-benzyl-protected trans-55 under these conditions resulted in >95% conversion (within 2 h) to a 44:56 mixture of epoxides 62 and 63, respectively. Chemo-selective N-benzylation of the crude reaction mixture was performed as before, which gave a 44:56 mixture of epoxides 64 and 65, respectively, from which a sample of diastereoisomer-

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**Scheme 9**

(i) BzNH, CHCl3, DMF, rt, 3 h; (ii) Na/Hg, Na2HPO4, MeOH, 90 °C then rt, 16 h; (iii) LiAlH4, THF, reflux, 16 h; (iv) BnBr, Pr2NEt, DMAP, CH2Cl2, rt, 48 h; (v) PPh3, PhCO2H, DEAD, PhMe, 0 °C, 1 h then rt, 16 h; (vi) K2CO3, MeOH, rt, 4 h.

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Reagents and conditions: (i) PhCONHOH, Bu4NIO4, CHCl3, DMF, reflux, 16 h; (ii) BnBr, Pr2NEt, DMAP, CH2Cl2, rt, 48 h; (iii) PPh3, PhCO2H, DEAD, PhMe, 0 °C, 1 h; (iv) K2CO3, MeOH, rt, 4 h.

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Epoxidation of N,N-dibenzy1-protected cis-54 upon treatment of 10 equiv of Cl3CCO2H25 and 1.05 equiv of m-CPBA in CH2Cl2 at rt for 3.5 h (i.e., analogous to the optimized conditions for the “parent” system 12)25 gave 69% conversion to an 80:20 mixture of epoxides 59 and 60, respectively. Use of 3.0 equiv of m-CPBA resulted in >95% conversion to the 80:20 mixture of epoxides 59 and 60; chromatography enabled their partial separation, and 59 and 60 were isolated in 73% total yield. The gross structure and relative configuration of 59 were unambiguously established by single crystal X-ray diffraction analysis of the corresponding p-nitrobenzoate derivative 61.23 The gross structure of 60 was assigned on the basis of NMR spectroscopic analyses and its relative configuration was thence assigned by reference to that unambiguously established for 59, i.e., on the basis that 60 is the only alternative diastereoisomer resulting from the epoxidation of cis-54. Meanwhile, epoxidation of N-benzyl-protected cis-53 under the same conditions gave >95% conversion to an 18:82 mixture of epoxides 57 and 58, respectively. In order to facilitate purification, the crude reaction mixture was treated with BnBr/Pr2NEt, which resulted in chemo-selective N-benzylation to give an 18:82 mixture of the corresponding N,N-dibenzy1-protected epoxides 59 and 60, which were again partially separated by chromatography and isolated in 63% total yield (over two steps from cis-53). This correlation also unambiguously established the gross structures and relative configurations of both 57 and 58 (Scheme 10).
cally pure 65 was isolated in 35% yield (over two steps from *trans*-55) and an 86:14 mixture of 64 and 65 in 16% combined yield (over two steps from *trans*-55). This allowed the gross structure of 65 to be confirmed by a combination of NMR spectroscopic analyses and thus, following the same rationale as before, its relative configuration was assigned from that of 64. The relative configurations of 67 and 68 were unambiguously established by correlation to the corresponding epoxides 67 and 68 upon their O-benzylation using NaH/BnBr (Scheme 11). As with the analogous five-membered ring substrates, the formation of epoxides (rather than formation of ring-opened species) as the major products for all of the seven-membered ring substrates is entirely consistent with the behavior of the "parent" systems 11 and 12 under analogous conditions.

The rates of the epoxidation reactions of the five-membered ring substrates 40 and 42, and the seven-membered ring substrates 53–56 were next determined using our previously reported procedure,16 with the same condition set (10 equiv of *Cl*₂CO₂H and 1.6 equiv of *m*-CPBA) used for each substrate for the sake of simplicity (full consumption of starting material not being necessary for determination of reaction rate). In each case, *Cl*₂CO₂H was added to a 0.36 M solution of the substrate in CD₂Cl₂ at 298 K. This resulted in formation of the corresponding ammonium ion which displayed characteristic resonances in the olefinic region of its ¹H NMR spectrum, corresponding to C(2)H and C(3)H which were distinct from other resonances in the spectrum and so easy to monitor. The decay in intensity of these signals was monitored upon addition of *m*-CPBA to the NMR tube. Analysis of the data so generated, by application of the integrated form of the second order rate law,20 gave the second-order rate constants (*k*₉₀) for the epoxidation reactions of 40, 42, and 53–56. The rate constants of the epoxidation reactions of six-membered ring substrates 19 and 20 have already been determined,18 while the rate constants for the (previously reported) epoxidations of six-membered ring substrates 24 and 25 were determined here, in an analogous manner, to give a more complete picture of the results across the ring systems (Figure 1).

**Scheme 11**

"Reagents and conditions: (i) Cl₂CO₂H (10 equiv), *m*-CPBA (3.0 equiv), CH₂Cl₂, rt, 2 h; (ii) BnBr, Pr₃NEt, DMAP, CH₂Cl₂, rt, 24 h; (iii) Cl₂CO₂H (10 equiv), *m*-CPBA (3.0 equiv), CH₂Cl₂, rt, 3.5 h; (iv) NaH, THF, 0 °C, 30 min, then BnBr, Bu₄NI, rt, 24 h.

As with the six-membered ring substrates 6-NHBn, 7-NHBn, 8-NBn₂, and 9-NBn₂, evidence of competitive ammonium-directed and hydroxyl-directed epoxidation pathways are noted in the five- and seven-membered ring substrates where the two established, individual directing group preferences would result in epoxidation being directed to opposite faces of the olefin, depending on which group acts as the directing group: i.e., the epoxidations of 5-NBn₂, 24, 7-NBn₂, cis-54, and 7-NBn₂, 55 are less diastereoselective than those of the corresponding "parent" systems 8 and 11 and 12, possessing only one potential directing group. The diastereoselectivity of epoxidation of 5-NBn₂, 42 suggests that the order of directing group proficiency in the five-membered ring system is NBn₂ > OH. This is in contrast to the corresponding ranking established (from the diastereoselectivity of the epoxidation of 6-NBn₂, 20) for the six-membered ring system, where OH > NBn₂. As the two possible envelope conformations (42A and 42B) of the parent 6-NHBn would be the major contributors to the observed diastereoselectivity, the observed diastereoselectivity of the epoxidation of 5-NBn₂, 42 suggests that with an increase in ring size, the relative efficiency of the ammonium-directed epoxidation pathway decreases. However, the data do not allow for a clear conclusion as to the relative efficiencies of the two pathways. Further studies are ongoing involving the use of *N*-acyl protected cycloalk-2-en-1-amine substrates.
of 5-NBn2, trans-42 place the N,N-dibenzylammonium moiety and hydroxyl group in geometrically nonequivalent environments, with only the very high energy conformation 42B with the ring completely planar placing them in geometrically equivalent environments (Figure 2), it is plausible that the difference in the observed directing group efficiencies are the result of subtle constraints of geometry, analogous to the effects already evidenced in six-membered ring systems.10,20 Furthermore, epoxidation of 5-NBn2, trans-42 proceeding from conformation 42A to give 44 (as observed experimentally) proceeds via a favored boatlike transition state with reduction in torsional strain, most significantly between C(3)-proton and the pseudoequatorial C(4)-ammonium group. In contrast, epoxidation of 5-NBn2, trans-42 proceeding from conformation 42C to give 44 proceeds via a disfavored chairlike transition state with increase of torsional strain, most significantly between the C(2)-proton and pseudoequatorial C(1)-hydroxyl group11,14,15 (Figure 3). The combination of conformational differences affecting ability to form a hydrogen-bond with the oxidant, and the drive to minimize torsional strain may therefore be responsible for the apparently higher directing group efficiency of the N,N-dibenzylammonium moiety versus the hydroxyl group in this case.

The diastereoselectivities of the epoxidations of 7-NBn2 cis-54 and 7-NHBn trans-55 suggests that the order of directing group efficiency in the seven-membered ring system is NBn2 > NHBn > OH. This is again in contrast to the ranking established from the diastereoselectivities of the epoxidations of 6-NHBn trans-19 and 6-NBn2 trans-20 for the six-membered ring system: NHBn ≫ OH > NBn2. The presence of two relatively nonstERICally demanding substituents within 7-NHBn trans-55 likely results in a certain degree of conformational promiscuity (which is known for cycloheptene)17 with several possible reactive conformations, which satisfy the geometric requirements for efficient hydrogen-bonding to either the N-benzylammonium moiety or hydroxyl group, being accessible and so allowing the two hydrogen-bonding directed epoxidation processes to compete effectively with each other. The diastereoselectivities of epoxidation of the "parent" seven-membered ring substrates 7-NHBn 11 (85:15 dr; sym:anti) and 7-NBn2 cis-54 (61:39 dr; sym:anti) suggest modest directing efficiencies in this system; if the two are able to operate largely independently, a mixture of products slightly favoring epoxide 63 (resulting from direction from the N-benzylammonium moiety, the superior directing group) may be expected, as observed experimentally (56:44 dr). Meanwhile, the "parent" system 7-NBn2 12 has been shown to favor a seven-membered chair conformation with the bulky N,N-dibenzylammonium moiety occupying a pseudoequatorial position in the solid state, with epoxidation of this conformation proceeding on the most sterically accessible face being assisted by hydrogen bonding and leading to high diastereoselectivity (94:6 dr; cis:anti).11 It seems likely that 7-NBn2 cis-54 would show a similar conformational preference and favor 54A (Figure 4), with epoxidation of the least sterically encumbered face in this conformation being assisted by hydrogen-bonding to the ammonium moiety or indeed, given the geometrically similar environments in this conformation, the hydroxyl group. With the bulky N,N-dibenzylammonium moiety acting akin to conformational lock, it may be that conformations of 7-NBn2 cis-54 in which the hydroxyl group is optimally placed to effect hydrogen-bonding delivery of the oxidant to the syn face are energetically disfavored. A combination of these factors may be responsible for formation of epoxide 59 as the major product (80:20 dr), and hence the apparent enhancement of the directing group efficiency of the N,N-dibenzylammonium moiety in this case.

In the substrates where the two established, individual directing group preferences would result in epoxidation being directed to the same face of the olefin, regardless of which group acts as the directing group (i.e., 5-NBn2 cis-40, 6-NHBn cis-24, 6-NBn2 cis-25, 7-NHBn cis-53, and 7-NBn2 trans-56), the observed diastereoselectivities are higher than those of the respective "parent" allylic alcohol 1–3 and ostensibly the same as those of the respective "parent" allylic amine 8–12. Although in most cases the diastereoselectivities of the latter epoxidation process is at or beyond the limit of detection, the diastereoselectivity of epoxidation of 7-NHBn 11 (85:15 dr), resulting from direction by the ammonium moiety alone25 and falling well within the limits of detection, is not enhanced by the presence of the hydroxyl group within 7-NHBn cis-53 (82:18 dr) and in this instance at least, the effect is unlikely due to a lack of conformational freedom given that seven-membered rings with nonstERICally demanding substituents are involved.17 It may be that it is simply not feasible for both directing groups to form hydrogen-bonds to the peracid oxidant simultaneously. The observation that 5-NBn2 cis-40 and 7-NBn2 trans-56 undergo epoxidation with the same levels of diastereoselectivity as the corresponding O-benzyl ethers 5-NBn2 cis-46 and 7-NBn2 trans-56 demonstrates that hydrogen-bonding to the hydroxyl group is not prerequisite for the high diastereoselectivity observed in these instances. The reaction rates of all of these systems are lower than those of the...
corresponding "parent" allylic amine 8–12 (and, in fact, are also lower than for the diastereoisomeric substrates 5-NBn2, trans-42, 6-NHbN trans-19, 6-NBn2, trans-20, 7-NHBn trans-55, and 7-NBn cis-54,28 which may be due to steric/electrostatic repulsive effects, geometrical restrictions imposed on hydrogen-bonding, or indeed both). It is apparent, however, that the incorporation of a second, allylic heteroatom into the substrate retards the epoxidation reaction for all of the five-, six-, and seven-membered ring substrates examined in this study when compared to the corresponding "parent" system. The diminishment of the nucleophilicity of the olefin by introduction of the second inductively electron-withdrawing heteroatom is clearly the dominant factor here, and any assistance to the epoxidation reaction by the potential ability to form hydrogen-bonds to two directing groups rather than one is clearly unable to overwhelm it.

**CONCLUSION**

In conclusion, in the epoxidations of a range of diastereoisomeric, N-protected 4-aminocycloalk-2-en-1-ols containing five-, six-, and seven-membered rings, evidence of competitive epoxidation pathways, promoted by hydrogen-bonding to either the in situ formed ammonium moiety or the hydroxyl group, are observed in those systems within which the two potential directing groups can promote epoxidation on the opposite faces of the olefin, depending upon which acts as the directing group. In the five- and seven-membered ring substrates, an N,N-dibenzylationmmonium moiety appears more efficacious than a hydroxyl group at promoting a diastereoselective reaction in comparison to the corresponding six-membered ring substrate. In the five-membered ring it was proposed to be the result of reduction of torsional strain in the transition state being coupled with assistance from hydrogen-bonding with a pseudoequatorial ammonium moiety. Meanwhile in the seven-membered ring it was proposed that the N,N-dibenzylationmmonium moiety, being able to mimic the effects of a conformational lock, enforces a well-defined conformational preference on the otherwise mobile seven-membered ring, disfavoring conformations within which the hydroxyl group is optimally placed to promote hydrogen-bonded delivery of the oxidant to the syn face. In a system within which the two potential directing groups can promote epoxidation on the same face of the ring scaffold, an enhancement of epoxidation diastereoselectivity was not observed. The introduction of a second, allylic heteroatom to the substrate results in diminishment of the rate of epoxidation in all cases, indicating that the diminishment of the nucleophilicity of the olefin by inductive electron-withdrawing effect of the second heteroatom is the dominant factor, and any assistance to the epoxidation reaction by the potential to form hydrogen-bonds to two directing groups rather than one is clearly unable to overwhelm it. It is hoped that the results from these studies will be instructive for the future design of synthetics of aminopoloyls of biological interest.

**EXPERIMENTAL SECTION**

**General Experimental Details.** Reactions involving moisture-sensitive reagents were carried out under a nitrogen atmosphere using standard vacuum line techniques and glassware that was flame-dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.29 Organic layers were dried over Na2SO4. Flash column chromatography was performed on Kieselgel 60 silica.

Melting Points Are Uncorrected. IR spectra were recorded as a thin film on NaCl plates (film), as a KBr disc (KBr), or using an ATR module (ATR). Selected characteristic peaks are reported in cm−1. NMR spectra were recorded in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. 1H−1H COSY and 1H−13C HMBC analyses were used to establish atom connectivity. Accurate mass measurements were run on a MicroTOF instrument internally calibrated with polyaniline.

**X-ray Crystal Structure Determination.**29 Data were collected using either graphite monochromated Cu-Kα radiation (for 53) or graphite monochromated Mo-Kα radiation (for 45, 61, and 64) via 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.30

**1(8R,4S,R)-4-(N-Benzylamino)cyclopropane-2- en-1-ol 39.** A solution of 38(35.4 g, 26.3 mmol, >99:1 dr) in THF (270 mL) at rt was added via cannula to a stirred solution of powdered LiAlH4 (4.89 g, 129 mmol) in THF (170 mL) at rt. The resultant solution was heated at reflux for 16 h, then allowed to cool to rt and then further cooled to 0 °C. Crushed ice (~20 g) was then added portionwise, followed by addition of satd. aq. sodium potassium tartrate (200 mL). The resultant mixture was stirred vigorously at rt for 2 h, then filtered through Celite (eluena EtO). The organic layer was washed with brine (500 mL), dried and concentrated in vacuo to give 39 as a yellow solid (3.98 g, 80%, >99:1 dr); mp 43–45 °C; υmax (film) 3285, 3600, 3028, 1642, 1598; δH (400 MHz, CDCl3) 1.60–1.52 (2H, m, C(5)H2), 2.54–2.61 (1H, m, C(5)H), 3.69–3.71 (1H, m, C(4)H), 3.81–3.83 (2H, m, NCH2Ph), 4.67–4.68 (1H, m, C(1)H), 5.94–5.99 (2H, m, C(2)H, C(3)H), 7.25–7.33 (5H, m, Ph); δC (100 MHz, CDCl3) 39.8 (C(5)), 41.3 (NCH2Ph), 61.7 (C(1)), 75.5 (C(4)), 127.1, 128.3, 128.5 (omH-Ph), 135.5, 136.0 (C(2)), 139.8 (i-Ph); m/z (ESI+) 190 [M+H]+, 196, 172 ([M−OH]−, 100%); HRMS (ESI+) C19H16NO+ [M+H]+ requires 190.1226; found 190.1234.

**1(8R,4S,R)-4-(N-Benzylamino)cyclopropane-2 en-1-ol 40.** BNBr (1.78 mL, 15.0 mmol), Py(NEt2)2 (2.61 mL, 15.0 mmol) and DMAP (122 mg, 1.00 mmol) were added sequentially to a stirred solution of 39 (1.89 g, 10.0 mmol, >99:1 dr) in CH2Cl2 (100 mL) at rt and the resultant mixture was stirred at rt for 24 h, then washed with H2O (2 x 100 mL). The combined aqueous washings were extracted with CH2Cl2 (200 mL) and the combined organic extracts were washed with brine (300 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluena 30–40 °C petrol/EtO, 1:1) gave 40 as a yellow solid (2.32 g, 83%, >99:1 dr); δH (400 MHz, CDCl3) 1.46 (3H, t (J=7 Hz), C(5)H3), 2.61–2.69 (1H, m, C(5)H2), 3.46–3.49 (2H, m, NCH2Ph), 4.72 (1H, m, C(1)H), 5.98–6.00 (1H, m, C(2)H, C(3)H), 7.21–7.40 (10H, m, Ph); δC (100 MHz, CDCl3) 34.3 (C(5)), 54.6 (N(CH2Ph)4), 54.6 (C(4)), 64.0 (C(4)), 126.8, 128.2, 128.7, 135.0, 136.4 (C(2), C(3)), 140.1 (i-Ph); m/z (ESI+) 280 [M+H]+, 100%; HRMS (ESI+) C19H16NO+ [M+H]+ requires 280.1696; found 280.1705.

**1(8R,4S,R)-4-(N-Benzylamino)cyclopropane-2 en-1-ol 42.** DEAD (40 wt% solution in PhMe, 7.74 mL, 17.0 mmol) was added dropwise via syringe pump over 1 h to a stirred solution of 40 (2.79 g, 10.0 mmol, >99:1 dr), PPh3 (5.25 g, 20.0 mmol) and benzoic acid (1.83 g, 15.0 mmol) in PhMe (100 mL) at 0 °C. The resultant solution was allowed warm to rt and stirred at rt for a further 16 h, then concentrated in vacuo. The residue was dissolved in EtO (100 mL) and the resultant solution was washed sequentially with satd aq Na2CO3 (3 x 100 mL) and brine (100 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluena 30–40 °C petrol/EtO, 1:1) gave 42 as a pale
yellow oil (1.67 g, 60%, 98.2 dr); δ<sub>vmax</sub> (film) 3300, 2982, 2935, 1602; δ<sub>1</sub> (400 MHz, CDCl<sub>3</sub>) 1.57–1.68 (1H, m, OH), 1.77 (1H, ddd, J 1.4, 7.9, 2.7, C(S)<sub>Ph</sub>), 2.24 (1H, ddd, J 1.4, 7.5, 4.5, C(S)<sub>Ph</sub>), 3.43 (2H, d, J 13.9, N(CH<sub>2</sub>Ph)<sub>2</sub>), 3.63 (2H, d, J 13.9, N(CH<sub>2</sub>Ph)<sub>2</sub>), 4.11–4.21 (1H, m, C(4)<sub>H</sub>), 4.94–4.96 (1H, m, C(1)<sub>H</sub>), 5.95–5.97 (1H, m, CH<sub>olefin</sub>), 6.01–6.03 (1H, m, CH<sub>olefin</sub>), 7.19–7.40 (10H, m, Ph); δ<sub>1</sub> (400 MHz, CDCl<sub>3</sub>) 14.4 (C(1)<sub>H</sub>), 54.4 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 54 (C(2)<sub>H</sub>), 76.6 (C(1)), 127.0, 128.2, 128.6 (m,p<sub>Ph</sub>), 134.5, 137.1 (C(2)), 130.0 (i-P<sub>Ph</sub>); m/z (ESI<sup>+</sup>) 280 [M+H]<sup>+</sup>*, 100%; HRMS (ESI<sup>+</sup>) C<sub>29</sub>H<sub>34</sub>N<sub>2</sub>O<sub>2</sub> requires 418.2645; found 418.2644.

(1R,5R,2S,3R,4S)-2,3-Epoxy-4-(N,N-dibenzylamino)cyclopentene-1-ol 43. Cl<sub>2</sub>CC=O-H (2.36 g, 14.4 mmol) was added to a stirred solution of 42 (100 mg, 0.358 mmol, 98.2 dr) in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL, 0.36 M w.r.t. 42) at rt and the resultant solution was stirred at rt for 5 min. m-CPBA (72% by wt, 72 mg, 0.28 mmol) was added and the resultant suspension was stirred at rt for 16 h. Na<sub>2</sub>SO<sub>3</sub> (180 mg, 1.44 mmol, >99:1 dr) in CH<sub>2</sub>Cl<sub>2</sub> (4.0 mL) was added sequentially. The resultant mixture was allowed to warm to rt and the resultant solution was stirred at rt for 16 h. Na<sub>2</sub>SO<sub>3</sub> (180 mg, 1.44 mmol, >99:1 dr) in CH<sub>2</sub>Cl<sub>2</sub> (4.0 mL) was added sequentially. The resultant mixture was stirred at rt for 20 min in pentane (0.5 mL). The pentane was then decanted under a stream of argon, and THF (5 mL) was added. The resultant suspension was cooled to 0 °C and a solution of 40 (300 mg, 1.07 mmol, >99:1 dr) in THF (5 mL) was added dropwise. The resultant suspension was stirred at 0 °C for 30 min, after which time BnBr (0.26 mL, 2.1 mmol) and Bu<sub>4</sub>Ni (12 mg, 0.04 mmol) were added sequentially. The resultant mixture was allowed to warm to rt and stirred at rt for 24 h, then quenched with H<sub>2</sub>O (5 mL). The resultant mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and the combined organic extracts were washed with brine (5 mL), dried and concentrated in vacuo to give >90% conversion to 44 in >95:5 dr. Purification via flash column chromatography (eluent 30–40 °C pentol/EtO<sub>2</sub>2, 1:1) gave 44 as a white solid (347 mg, 77%, >99:1 dr); mp 74–76 °C; δ<sub>vmax</sub> (film) 3406, 3028, 2947, 2804, 1603, 1494, 1455, 1256; δ<sub>1</sub> (400 MHz, CDCl<sub>3</sub>) 1.14 (1H, ddd, J 12.3, 10.1, 8.2, C(1)<sub>H</sub>), 1.77 (1H, br, s, OH), 1.98 (1H, ddd, J 12.3, 7.5, 7.3, C(S)<sub>Ph</sub>), 3.19 (1H, ddd, J 10.1, 7.3, 1.0, C(4)<sub>H</sub>), 3.41 (1H, dd, J 3.0, 1.5, C(2)<sub>H</sub>), 3.52–3.53 (1H, d, J 3.0, 1.0, C(3)<sub>H</sub>), 3.66 (2H, d, J 14.5, N(CH<sub>2</sub>Ph)<sub>2</sub>), 3.88 (2H, d, J 14.5, N(CH<sub>2</sub>Ph)<sub>2</sub>), 4.03–4.07 (1H, m, C(1)<sub>H</sub>), 7.23–7.27 (2H, m, Ph), 7.33 (4H, app t, 7.4, Ph), 7.40 (4H, d, J 7.4, Ph); δ<sub>1</sub> (100 MHz, CDCl<sub>3</sub>) 26.4 (C(5)), 55.2 (N(CH<sub>2</sub>Ph)<sub>2</sub>), 55.9 (C(2)), 65.7 (C(3)), 88.3 (C(4)), 71.1 (C(1)), 126.9 (p-P<sub>Ph</sub>), 128.3, 128.5 (m-p<sub>Ph</sub>), 139.9 (i-P<sub>Ph</sub>); m/z (ESI<sup>+</sup>) 294 ([M+H]<sup>+</sup>*, 100%); HRMS (ESI<sup>+</sup>) C<sub>29</sub>H<sub>33</sub>NH<sub>3</sub>O requires 418.2645; found 418.2644.
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Method B: Epoxidation of 46 (35 mg, 2.19 mmol) was added to a stirred solution of 46 (81 mg, 0.22 mmol, >99:1 dr) in CH₂Cl₂ (0.61 mL, 0.36 M w.r.t. 46) at rt and the resultant solution was stirred at rt for 5 min. m-CPBA (75% by wt, 103 mg, 0.44 mmol) was added and the resultant suspension was stirred at rt for 16 h. Na₂SO₄ (111 mg, 0.88 mmol) was added and the resultant suspension was stirred until it solidified (~5 min). The resultant mixture was diluted with CH₂Cl₂ (5 mL) and washed with 10% aq NaOH (3 × 5 mL). The combined aqueous washings were extracted with CH₂Cl₂ (2 × 5 mL). The combined organic extracts were washed with brine (25 mL). The combined aqueous washings were extracted with CH₂Cl₂ (2 × 25 mL). The combined organic washes were extracted with CH₂Cl₂ (50 mL) and the combined organic extracts were washed with brine (75 mL) and then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum/Et₂O 1:1) gave 44 as a colorless oil (13 mg, 31%, >99:1 dr); δₑₓ (film) 3029, 2981, 2850, 1604, 1494, 1257; δ₁ (400 MHz, CDCl₃) 1.64 (1H, dd, J 1.9, 7.3, C(5)H₃), 3.18 (1H, app d, J 10.1, 7.3, C(4)H), 3.44 (1H, dd, J 2.9, 1.0, C(2)H₂), 3.51 (1H, d, J 2.9, C(3)H), 3.71 (2H, d, J 14.2, N(CH₂Ph)₂), 3.82–3.86 (1H, m, C(2)H), 3.92 (2H, d, J 14.2, N(CH₂Ph)₂), 4.61–4.68 (2H, m, OCH₂Ph), 7.24–7.44 (15H, m, Ph); δₑₓ (100 MHz, CDCl₃) 23.0 (C(5)), 53.4 (C(2)), 52.5 (N(CH₂Ph)₂), 56.5 (C(5)), 57.5 (C(4)), 71.3 (OCH₂Ph), 7.68 (C(1)), 126.9, 127.7, 128.7, 128.3, 128.5 (o-mg-Ph), 138.1, 140.0 (i-Ph); m/z (EST) 386 ([M+H]+, 100%); HRMS (EST) C₂₃H₂₅NO+ ([M+H]+) requires 386.2115; found 386.2115.

sequentially with sat. aq. Na₂SO₄ (3 × 20 mL) and brine (20 mL), dried and concentrated in vacuo. The residue was dissolved in MeOH (5 mL) and K₂CO₃ (1.09 g, 7.92 mmol) was added. The resultant suspension was stirred at rt for 4 h, then filtered and concentrated in vacuo. The residue was dissolved in Et₂O (20 mL) and washed sequentially with H₂O (3 × 20 mL) and brine (20 mL), dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et₂O, 4:1) gave a 56 as a white solid (312 mg, 64%, >99:1 dr); mp 56–58 °C; tₘᵋᵢₜ (film) 3356, 3026, 2934, 1646, 1602, 1493, 1454; δ₁H (400 MHz, CDCl₃) 1.41 (1H, d, J 3.9, OH), 1.54–1.61 (2H, m, C(5)H₂, C(7)H₂), 1.70–1.82 (3H, m, C(6)H₃), C(7)H₂), 2.02–2.09 (2H, m, C(5)H₂), 3.36 (1H, ddd, J 8.1, 5.2, 2.4, C(4)H), 3.5 (2H, d, J 14.0, N(CH₂Ph₇), 3.74 (2H, d, J 14.0, N(CH₂Ph₇), 4.39–4.41 (1H, m, C(1)H)), 5.72–5.82 (1H, m, C(3)H), 5.89–5.92 (1H, m, C(2)H), 7.21–7.40 (9H, m, Ph), δ₂C (100 MHz, CDCl₃) 20.9 (C(6)), 26.6 (C(5)), 35.0 (C(5)), 53.8 (N(CH₂Ph₇), 56.9 (C(4)), 69.1 (C(11)), 126.5 (p-Ph), 128.2, 128.5 (p-Ph), 133.5, 136.0 (C(2), C(3)), 140.3 (z-Ph); m/z (ESI²) 308 ([M+H]+, 100%); HRMS (ESI²) C₂H₁₂N₂O₄⁺ requires 346.1778; found 346.1778.

(1RS,2S,3SR,4SR)-1-(p-Nitrobenzoyloxy)-2,3-Epoxy-4-(N-dibenzyldimino)cylohept-1-ol 59 and 60. Method A via Epoxidation of 53. Step 1. CI₂COC₂H₇ (376 mg, 2.30 mmol) was added to a stirred solution of 53 (50 mg, 0.23 mmol, >99:1 dr) in CH₂Cl₂ (2 × 5 mL) and the resultant solution was stirred at rt for 5 min. m-CPBA (69% by wt, 173 mg, 0.69 mmol) was added and the resultant suspension was stirred at rt for 3.5 h. Na₂SO₄ (174 mg, 1.38 mmol) was added and the resultant suspension was stirred until it solidified (~5 min). The resultant mixture was diluted with CH₂Cl₂ (5 mL) and washed with 10% aq. NaOH (3 × 5 mL). The combined aqueous washings were extracted with CH₂Cl₂ (2 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried and concentrated in vacuo to give an 18:82 mixture of 57 and 58 (62 mg).

Step 2. Br₃Sn (41 µL, 0.35 mmol), Ph₃P (60 µL, 0.35 mmol) and DMAP (2 mg, 0.02 mmol) were added sequentially to a stirred solution of the residue from the previous step (62 mg) in CH₂Cl₂ (2 × 5 mL) at rt and the resultant solution was stirred at rt for 24 h, then washed with H₂O (2 × 5 mL). The combined aqueous washings were extracted with CH₂Cl₂ (10 mL) and the combined organic extracts were washed with brine (20 mL), dried and concentrated in vacuo to give an 18:82 mixture of 59 and 60. Purification via flash column chromatography (eluent 30–40 °C petrol/Et₂O, 2:3) gave 60 as a colorless oil (44 mg, 53%, >99:1 dr); tₘᵋᵢₜ (film) 3384, 2930, 2856, 1725, 1607, 1494, 1454, 1271; δ₁H (500 MHz, CDCl₃) 1.43–1.51 (1H, m, C(6)H₃), 1.58–1.66 (1H, m, C(5)H₃), 1.68–1.76 (1H, m, C(7)H₃), 1.91–1.97 (3H, m, C(5)H₃, C(6)H₃, C(7)H₃), 2.56 (1H, d, J 11.0, 7.6, C(4)H), 3.0–3.32 (1H, m, C(2)H), 3.40 (1H, d, J 7.6, 5.3, C(3)H), 3.73–3.76 (2H, m, N(CH₂Ph₇), 3.82–3.85 (2H, m, N(CH₂Ph₇), 4.64 (1H, ddd, J 11.9, 6.2, 1.7, C(1)H₃), 7.23–7.42 (10H, m, Ph), 8.21–8.23 (2H, m, Ar), 8.29–8.31 (2H, m, Ar); δ₂C (125 MHz, CDCl₃) 25.5 (C(6)), 30.0 (C(5)), 31.5 (C(7)), 33.8 (C(5)), 54.5 (N(CH₂Ph₇), 55.4 (C(4)), 61.5 (C(5)), 77.8 (C(11)), 123.5 (Ar), 127.0 (p-Ph), 128.2, 128.7 (o-Ph), 130.8 (Ar), 135.5, 139.5 (p-Ph, Ar), 150.6 (Ar), 163.7 (C=O); m/z (ESI²) 473 ([M+H]+, 100%); HRMS (ESI²) C₂H₁₂N₂O₄⁺ requires 473.2071; found 473.2065.

(1RS,2S,3SR,4SR)-1-(p-Nitrobenzoyloxy)-2,3-Epoxy-4-(N-dibenzyldimino)cylohept-1-ol 64 and 65. Method A via Epoxidation of 55. Step 1. CI₂COC₂H₇ (376 mg, 2.30 mmol) was added to a stirred solution of 55 (50 mg, 0.23 mmol, >99:1 dr) in CH₂Cl₂ (0.64 mL, 0.36 M w.r.t. 55) at rt and the resultant solution was stirred at rt for 5 min. m-CPBA (69% by wt, 173 mg, 0.69 mmol) was added and the resultant suspension was stirred at rt for 3.5 h. Na₂SO₄ (174 mg, 1.38 mmol) was added and the resultant suspension was stirred until it solidified (~5 min). The resultant mixture was diluted with CH₂Cl₂ (5 mL) and washed with 10% aq. NaOH (3 × 5 mL). The combined aqueous washings were extracted with CH₂Cl₂ (2 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried and concentrated in vacuo to give a 44:56 mixture of 62 and 60 (60 mg).

Step 2. Br₃Sn (41 µL, 0.35 mmol), Ph₃P (60 µL, 0.35 mmol) and DMAP (2 mg, 0.02 mmol) were added sequentially to a stirred solution of the residue from the previous step (60 mg) in CH₂Cl₂ (2.3 mL) at rt and the resultant solution was stirred at rt for 24 h, then washed with H₂O (2 × 5 mL). The combined aqueous washings were extracted with CH₂Cl₂ (10 mL) and the combined organic extracts were washed with brine (20 mL), dried and concentrated in vacuo to give a 44:56 mixture of 64 and 65. Purification via flash column chromatography (eluent 30–40 °C petrol/Et₂O, 4:1) gave 65 as a colorless oil (29 mg, 55%, >99:1 dr); tₘᵋᵢₜ (film) 3357, 3030, 2927, 2854, 1496, 1454; δ₁H (400 MHz, CDCl₃) 1.08–1.90 (9H, m, C(5)H₃, C(6)H₃, C(7)H₃), 3.04 (1H, d, J 11.8, 2.6, C(4)H₃), 3.09 (1H, m, C(5)H₃, C(7)H₃), 3.91 (1H, d, J 13.1, 10.3, C(6)H₃), 3.75 (8H, m, N(CH₂Ph₇), 3.87 (2H, d, J 14.2, N(CH₂Ph₇), 4.51–4.44 (1H, m, C(1)H), 7.21–7.40 (10H, m, Ph); δ₂C (125 MHz, CDCl₃) 18.7 (C(6)), 23.3 (C(5)), 32.5 (C(7)), 54.3 (N(CH₂Ph₇), 54.9 (C(2)), 57.9 (C(4)), 60.6 (C(3)), 69.8 (C(11)), 126.8 (p-Ph), 128.2, 128.5 (o-Ph), 140.1, (r-Ph); m/z (ESI²) 473 ([M+Na]+, 100%);
HRMS (ESI+) C_{12}H_{22}NNaO_{4}^+ ([M+Na]^+) requires 346.1778; found 346.1777.

**Method B: Epoxidation of 56.** Cl_3CCO_2H (2.66 g, 16.3 mmol) was added to a stirred solution of 56 (500 mg, 1.63 mmol, >99:1 dr) in CH_2Cl_2 (4.5 mL, 0.36 M w.r.t. 56) at rt and the resultant solution was stirred at rt for 5 min. m-CBPA (69% by wt, 1.22 g, 4.89 mmol) was added and the resultant suspension was stirred at rt for 3.5 h. Na_2SO_3 (15 mg, 0.046 mmol) was added and the resultant suspension was stirred until it solidified (<5 min). The resultant mixture was diluted with CHCl_3 (5 mL) and washed 10%aq. NaOH (3 × 5 mL). The combined aqueous washings were extracted with CHCl_3 (2 × 15 mL).

**Method C: Epoxidation of 56.** Cl_3CCO_2H (10 equiv) was added to a stirred solution of 56 (76 mg, 0.25 mmol, >99:1 dr) in THF (1 mL) and the combined organic extracts were washed with brine (2 × 5 mL) and dried. The resultant mixture was washed with brine (2 × 5 mL), dried and concentrated in vacuo to give a 95:5 mixture of 64 and 65.

**Method B: O-Benzylolation of 56.** NaH (60% dispersion in mineral oil, 0.02 mmol) was stirred at rt for 30 min, after which time BnBr (11 µL, 0.092 mmol) and Bu_4NI (0.5 mg, 0.001 mmol) were added sequentially. The resultant mixture was allowed to warm to rt and stirred at rt for 24 h, then quenched with H_2O (0.5 mL). The resultant mixture was extracted with CHCl_3 (5 × 2 mL) and the combined organic extracts were washed with brine (2 × 5 mL), dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/ Et_2O, 4:1) gave 56 as a white solid (48 mg, 73%>99:1 dr); mp 92–94 °C; δ_{max} (film) 3434, 1493, 1453, 1385, 1334, 1303, 1293, 1261, 1239, 1219, 1217, 1211, 1176, 1128, 1128, 1045, 966, 929, 874, 814, 663, 616, 598, 547, 513, 488, 473, 438, 423, 396, 377, 359, 345, 322, 290, 276, 258, 243, 228, 208, 186, 170, 158, 139, 122, 107, 91, 79, 63, 47 (ν_max = 3443, 1494, 1453, 1260, 1176, 1128, 1045, 966, 929, 874, 814, 663, 616, 598, 547, 513, 488, 473, 438, 423, 396, 377, 359, 345, 322, 290, 276, 258, 243, 228, 208, 186, 170, 158, 139, 122, 107, 91, 79, 63, 47).

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X-ray crystallographic data for compounds 45 (CCDC 1562293), 53 (CCDC 1562294), 61 (CCDC 1562295), and 64 (CCDC 1562296) (CIF)
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Notes
The authors declare no competing financial interest.

1Deceased.

■ REFERENCES

(13) In the cases of the six-membered ring substrates 9 and 10, in situ ring-opening of the epoxides 15 and 16 occurs, giving the corresponding trichloroacetate esters or diols after workup. For purposes of comparison, however, 15 and 16 are shown in Scheme 1. For a discussion of the relative rates of ring-opening of epoxides 13–18, see: ref 11.