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

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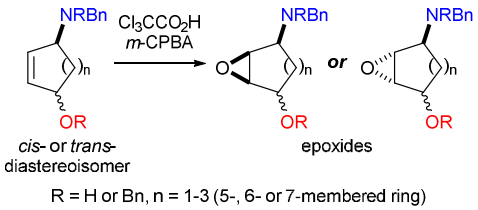
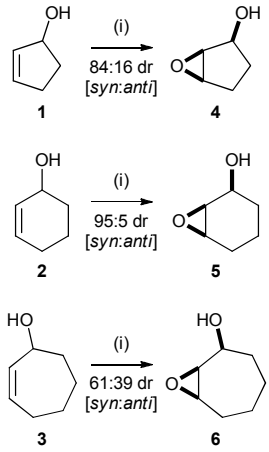


ABSTRACT: The diastereoselectivities and rates of epoxidation (upon treatment with Cl_3CCO_2H then *m*-CPBA) of a range of *cis*- and *trans*-4-aminocycloalk-2-en-1-ol derivatives (containing five-, six- and seven-membered rings) have been investigated. In all cases where the two potential directing 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 > NBn_2), 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 rationalised by the drive to minimise 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 disfavouring 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, whilst 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 reaction[3] 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 CH_2Cl_2 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] whilst higher levels of diastereoselectivity are observed for five-membered ring substrate **1**[7] and six-membered ring substrate **2**[8] (Scheme 1).

SCHEME 1[a]

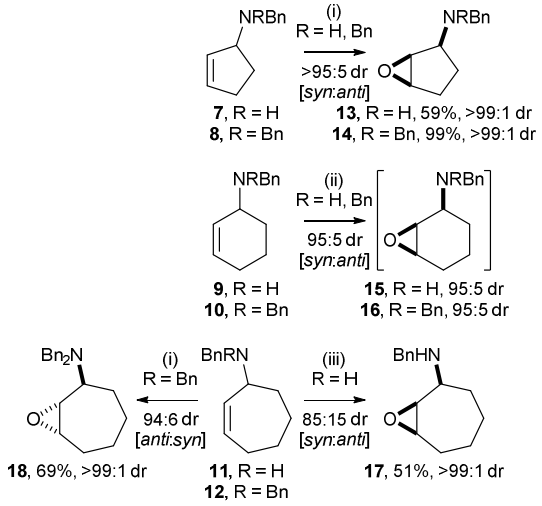


[a]Reagents and Conditions: (i) *m*-CPBA, CH_2Cl_2, 0 °C, 24 h.

We have investigated the related epoxidation of a range of chiral allylic amines, reliant on a strategy involving initial treatment with a strong Brønsted acid (e.g., Cl_3CCO_2H, F_3CCO_2H, TsOH, HBF_4) to effect protonation of the nitrogen atom, and hence offer protection against *N*-oxidation.[9] The N–H proton of the resultant ammonium moiety is capable of acting as a hydrogen-bond donor to direct epoxidation upon addition of a peracid (e.g., *m*-CPBA, F_3CCO_3H) 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 5.0 equiv of Cl_3CCO_2H then 1.05 or 1.6 equiv of *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**) upon treatment 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 favoured 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.[5,6] In contrast, epoxidation of **12** gave *anti*-epoxide **18** in 94:6 dr (88% conversion).[11,16] This outcome is anomalous on two counts when compared to **3** and **11**: firstly, it is significantly more diastereoselective, and secondly, it proceeds on the face *anti* to the directing group. We have previously rationalized these observations[11,16] 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 conformation[17] (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 face in this conformer (Scheme 2).[11,14]

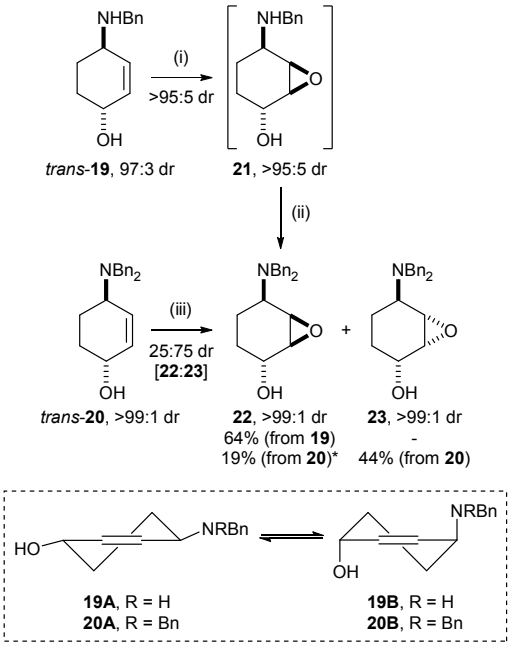
SCHEME 2[a]



[a]Reagents and Conditions: (i) Cl_3CCO_2H (5.0 equiv), *m*-CPBA (1.05 equiv), CH_2Cl_2, rt, 3.5 h; (ii) Cl_3CCO_2H (5.0 equiv), *m*-CPBA (1.6 equiv), CH_2Cl_2, rt, 21 h; (iii) Cl_3CCO_2H (5.0 equiv), *m*-CPBA (2.5 equiv), CH_2Cl_2, rt, 20 min.

We have recently explored the epoxidations of *N*-benzyl- and *N*,*N*-dibenzyl-protected *trans*-4-aminocyclohex-2-en-1-ol **19** and **20**.[18,19] 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 pseudo-equatorial 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*-benzylation 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 > NBn_2[18,19] (Scheme 3).

SCHEME 3[a]

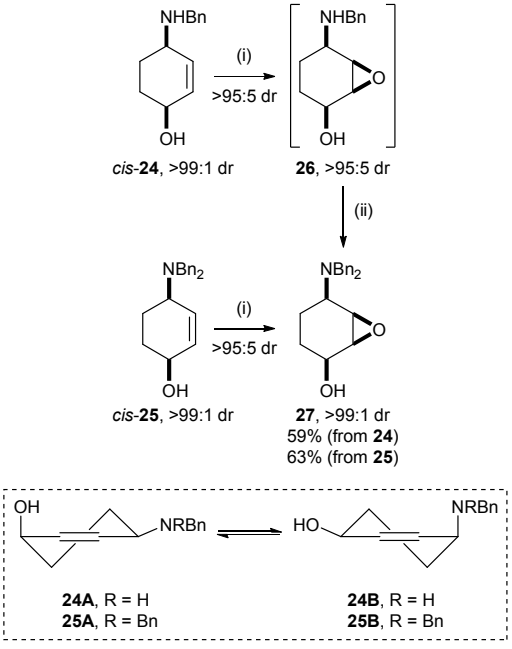


[a]Reagents and Conditions: (i) Cl_3CCO_2H (10 equiv), *m*-CPBA (5.0 equiv), CH_2Cl_2, rt, 30 min; (ii) BnBr, $^iPr_2NEt$, DMAP, CH_2Cl_2, rt, 24 h; (iii) Cl_3CCO_2H (10 equiv), *m*-CPBA (5.0 equiv), CH_2Cl_2, rt, 3.5 h. * Sample isolated in 95:5 dr [**22**:**23**].

The epoxidations of the diastereoisomeric compounds *cis*-**24** and *cis*-**25** were also explored.[19] 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 was thus isolated in 59% yield from **24** and 63% yield from **25** (Scheme 4). These results are

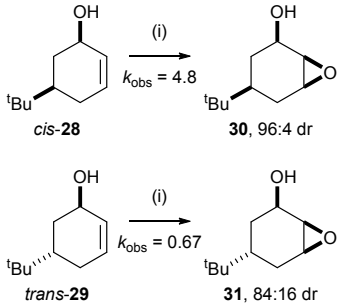
consistent with the epoxidation being directed by either the hydroxyl group or the ammonium moiety, or indeed both. However, the relative contributions from hydrogen-bonding to either of the two potential directing groups cannot be easily dissected; a matter that can be further complicated by issues 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 pseudo-equatorial hydroxyl group was significantly better than a pseudo-axial one as a directing group:[20] for *trans*-**29** (pseudo-axial 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** (pseudo-equatorial 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).

SCHEME 4[a]



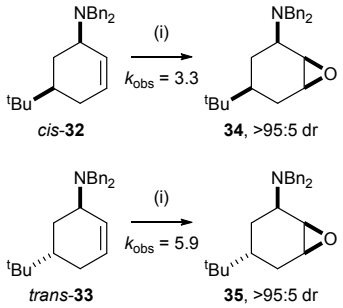
[a]Reagents and Conditions: (i) Cl_3CCO_2H (10 equiv), *m*-CPBA (5.0 equiv), CH_2Cl_2, rt, 21 h; (ii) BnBr, $^iPr_2NEt$, DMAP, CH_2Cl_2, rt, 24 h.

SCHEME 5[a]



[a]Reagents and Conditions: (i) $PhCO_3H$, C_6H_6, 5 °C. *k* values given in units of 10^3 dm^3 mol^{-1} s^{-1}.

SCHEME 6[a]



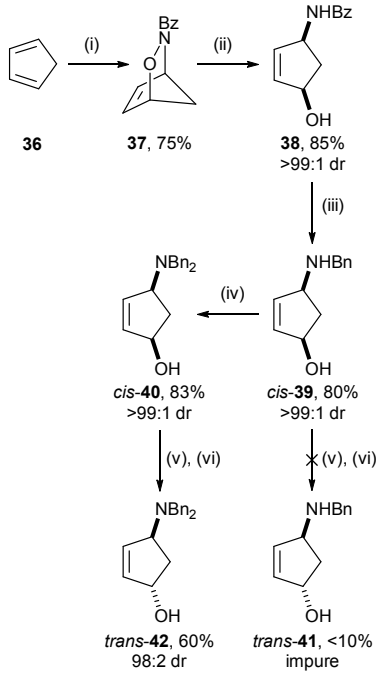
[a]Reagents and Conditions: (i) Cl_3CCO_2H, *m*-CPBA, CH_2Cl_2, rt, 21 h, then K_2CO_3, MeOH, rt, 16 h. *k* values given in units of 10^4 dm^3 mol^{-1} s^{-1}.

As part of our ongoing research program concerning the synthesis of biologically significant molecules containing an aminotriol moiety, we proposed to investigate the behaviour 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 Bu_4NIO_4) 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 $LiAlH_4$ then gave *cis*-**39** in 80% yield and >99:1 dr. Chemoselective *N*-benzylation of *cis*-**39** was achieved using BnBr/^{i}Pr_2NEt, 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).

SCHEME 7[a]

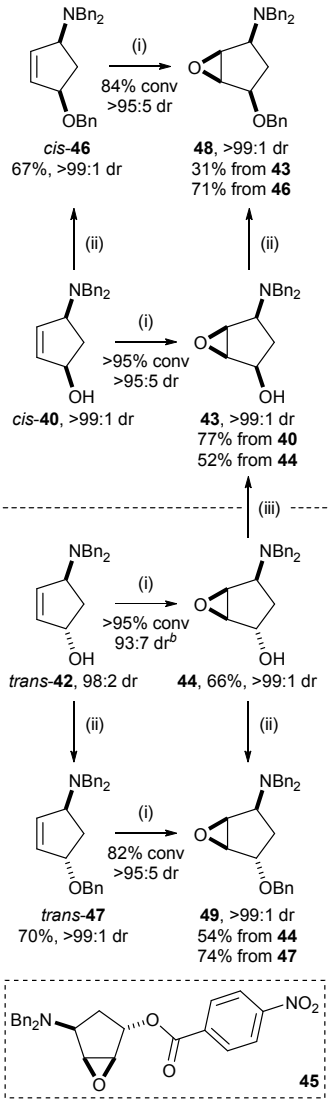


[a]Reagents and Conditions: (i) PhCONHOH, Bu_4NIO_4, MeOH, rt, 1 h; (ii) Na/Hg, Na_2HPO_4, MeOH, −10 °C then rt, 16 h; (iii) $LiAlH_4$, THF, reflux, 16 h; (iv) BnBr, $^iPr_2NEt$, DMAP, CH_2Cl_2, rt, 24 h; (v) PPh_3, $PhCO_2H$, DEAD, PhMe, 0 °C, 1 h, then rt, 16 h; (vi) K_2CO_3, MeOH, rt, 4 h.

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" procedure[10] was used to determine the number of equivalents of Cl_3CCO_2H required to efficiently protect *cis*-**40** against *N*-oxidation. In this experiment, Cl_3CCO_2H was added in 1.0 equiv portions to a 0.36 M solution of *cis*-**40** in CD_2Cl_2 and the solution was analysed by ^1H NMR spectroscopy. The resultant differences in chemical shifts ($\Delta\delta$) 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 7.0 equiv of Cl_3CCO_2H. 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 Cl_3CCO_2H throughout these investigations. Treatment of *cis*-**40** with 10 equiv of Cl_3CCO_2H 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**)[11] 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**.[23] 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; particularly it was hoped that this might provide some insight into the relative importance of the amino moiety versus the hydroxyl group in promoting diastereoselective epoxidation of *cis*-**40**. 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 behaviour of the 'parent' system **8** under analogous conditions which results in formation of the corresponding *syn*-epoxide **14** exclusively).[11] Epoxidations of *cis*-**40** and *cis*-**46** reveal that epoxidation on the *syn*-face of the olefin of (proximal to both heteroatoms) is favoured 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).

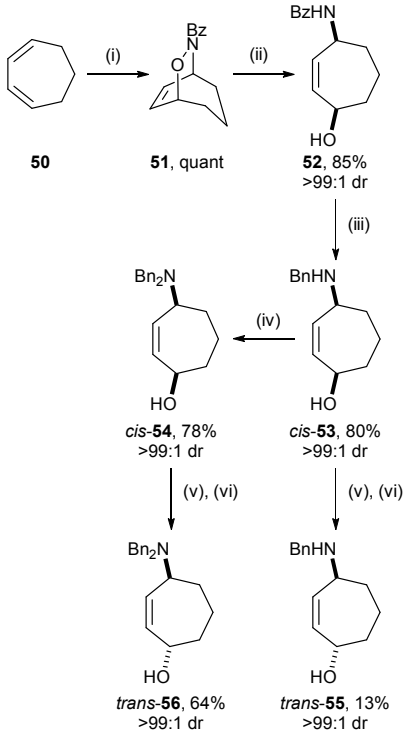
SCHEME 8[a]



[a]Reagents and Conditions: (i) Cl_3CCO_2H (10 equiv), *m*-CPBA (2.0 equiv), CH_2Cl_2, rt, 16 h; (ii) NaH, THF, 0 °C, 30 min, then BnBr, Bu_4NI, rt, 24 h; (iii) PPh_3, $PhCO_2H$, DEAD, PhMe, 0 °C, 1 h, then rt, 16 h. [b]Diastereoisomeric ratio is for the diastereoisomeric epoxides derived from epoxidation of *trans*-**42**; the fate of the 2% of *cis*-**40** in the starting material was not determined.

The requisite seven-membered ring substrates **53**–**56** were prepared from 1,3-cycloheptadiene **50** via a directly analogous route to that used for the preparation of the corresponding five-membered ring substrates **39**–**42**. Initially, following the previously reported route,[24] treatment of 1,3-cycloheptadiene **50** with (in situ generated) PhCONO gave bicycle **51** in quantitative yield,[24] and sequential reduction using sodium amalgam then $LiAlH_4$ gave *cis*-**53** in 68% yield (over two steps from **51**).[24] The relative configuration of *cis*-**53** was unambiguously confirmed by single crystal X-ray diffraction analysis.[23] Chemoselective *N*-benzylation of *cis*-**53** delivered *cis*-**54** in 78% yield. Mitsunobu reaction of *N*,*N*-dibenzyl-protected *cis*-**54** gave *trans*-**56** in 64% yield and >99:1 dr, and although the analogous reaction of *N*-benzyl-protected *cis*-**53** proceeded with similar inefficiency to the corresponding reaction of *cis*-**39** in the five-membered ring series, in this case *cis*-**55** was isolated as a pure sample, albeit in only 13% yield (Scheme 9).

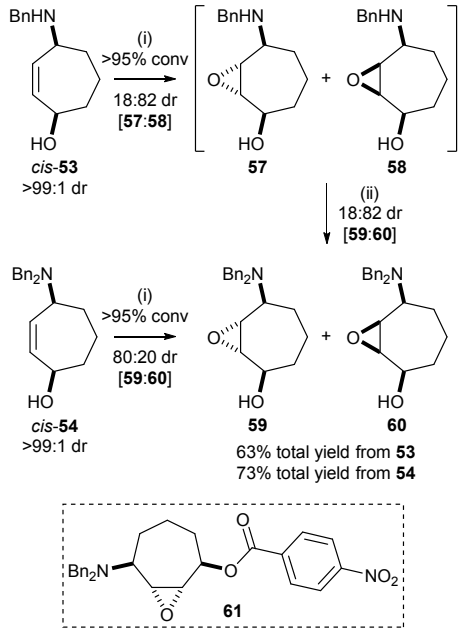
SCHEME 9[a]



[a]Reagents and Conditions: (i) PhCONHOH, Bu_4NIO_4, $CHCl_3$, DMF, rt, 3 h; (ii) Na/Hg, Na_2HPO_4, MeOH, –10 °C then rt, 16 h; (iii) $LiAlH_4$, THF, reflux, 16 h; (iv) BnBr, $^iPr_2NEt$, DMAP, CH_2Cl_2, rt, 48 h; (v) PPh_3, $PhCO_2H$, DEAD, PhMe, 0 °C, 1 h, then rt, 16 h; (vi) K_2CO_3, MeOH, rt, 4 h.

Epoxidation of *N*,*N*-dibenzyl-protected *cis*-**54** upon treatment of 10 equiv of Cl_3CCO_2H[25] and 1.05 equiv of *m*-CPBA in CH_2Cl_2 at rt for 3.5 h (i.e., analogous to the optimized conditions for the 'parent' system **12**)[11] 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/^{i}Pr$_2$NEt, which resulted in chemoselective *N*-benzylation to give an 18:82 mixture of the corresponding *N*,*N*-dibenzyl-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).

SCHEME 10[a]

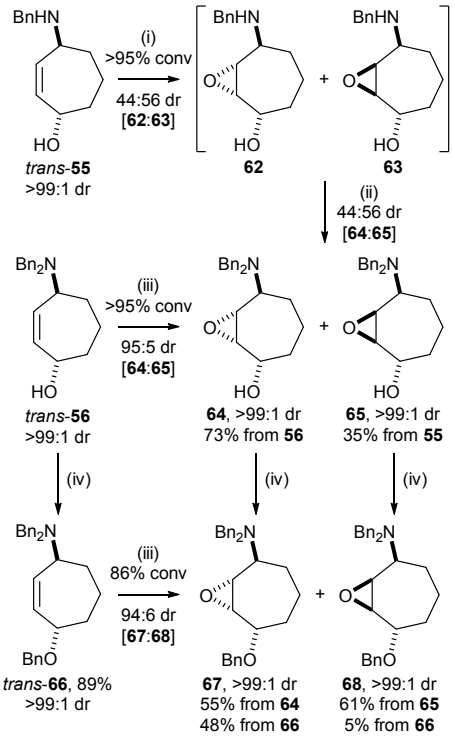


[a]Reagents and Conditions: (i) Cl_3CCO_2H (10 equiv), *m*-CPBA (3.0 equiv), CH_2Cl_2, rt, 3.5 h; (ii) BnBr, $^iPr_2NEt$, DMAP, CH_2Cl_2, rt, 24 h.

Epoxidation of the *trans*-diastereoisomers under the same conditions revealed that epoxidation of *N*,*N*-dibenzyl-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. Chemoselective *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 diastereoisomerically 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

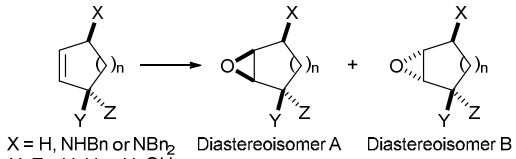
ring-opened species) as the major products for all of the seven-membered ring substrates is entirely consistent with the behaviour of the 'parent' systems **11** and **12** under analogous conditions.[11]

SCHEME 11[a]



[a]Reagents and Conditions: (i) Cl_3CCO_2H (10 equiv), *m*-CPBA (3.0 equiv), CH_2Cl_2, rt, 2 h; (ii) BnBr, $^iPr_2NEt$, DMAP, CH_2Cl_2, rt, 24 h; (iii) Cl_3CCO_2H (10 equiv), *m*-CPBA (3.0 equiv), CH_2Cl_2, rt, 3.5 h; (iv) NaH, THF, 0 °C, 30 min, then BnBr, Bu_4NI, rt, 24 h.

The rates of these 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_3CCO_2H and 1.6 equiv of *m*-CPBA) used for each substrate for the sake of simplicity (full conversion to the epoxide products not being necessary for determination of reaction rate). In each case, Cl_3CCO_2H was added to a 0.36 M solution of the substrate in CD_2Cl_2 at 298 K. This resulted in formation of the corresponding ammonium ion which displayed characteristic resonances in the olefinic region of its ^{1}H 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,[26] gave the second-order rate constants (k_{obs}) 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] whilst 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).



	n	X	Y	Z	dr (A:B)	k_{obs}	k_{rel}[a]
cis-**40**	1	NBn_2	OH	H	>95: 5	4.9	8
8	1	NBn_2	H	H	>95: 5	61	100
trans-**42**	1	NBn_2	H	OH	93: 7	6.0	10
1	1	H	H	OH	16:84[b]	-	-
cis-**24**	2	NHBn	OH	H	>95: 5	37	10
9	2	NHBn	H	H	95: 5	360	100
trans-**19**	2	NHBn	H	OH	>95: 5	38	11
2	2	H	H	OH	5:95[b]	-	-
cis-**25**	2	NBn_2	OH	H	>95: 5	0.9	12
10	2	NBn_2	H	H	95: 5	7.3	100
trans-**20**	2	NBn_2	H	OH	25:75	2.7	37
2	2	H	H	OH	5:95[b]	-	-
cis-**53**	3	NHBn	OH	H	82:18	28	16
11	3	NHBn	H	H	85:15	180	100
trans-**55**	3	NHBn	H	OH	56:44	39	22
3	3	H	H	OH	39:61[b]	-	-
trans-**56**	3	NBn_2	H	OH	5:95	6.7	30
12	3	NBn_2	H	H	6:94	22	100
cis-**54**	3	NBn_2	OH	H	20:80	13	59
3	3	H	OH	H	61:39[b]	-	-

FIGURE 1. Selected rate constants, relative rate constants and diastereoselectivities for epoxidations of cycloalk-2-en-1-ols, *N*-protected cycloalk-2-en-1-amine derivatives and *N*-protected 4-aminocycloalk-2-en-1-ol derivatives. For ease of comparison, reactions are grouped into sub-sets of four: (i) epoxidation of co-operative substrate; (ii) epoxidation of 'parent' allylic amine substrate (i.e., ammonium-directed reaction); (iii) epoxidation of competitive substrate; (iv) epoxidation of 'parent' allylic alcohol substrate (i.e., hydroxyl-directed reaction); as such, values for cyclohex-2-en-1-ol **2** and cyclohept-2-en-1-ol **3** are listed twice. [a] k_{rel} values are listed within each sub-set of reactions; in each case the relative rate of the ammonium-directed reaction (i.e., epoxidation of **8**, **9**, **10**, **11** or **12**) is set at $k_{rel} = 100$. [b] Result of Teranishi *et al.* (Ref 5). k_{obs} values given in units of 10^4 dm^3 mol^{-1} s^{-1}.

As with the six-membered ring substrates 6-NHBn *trans*-**19** and 6-NBn_2 *trans*-**20**, 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-NBn_2 *trans*-**42**, 7-NBn_2 *cis*-**54** and 7-NHBn *trans*-**55** are less diastereoselective than those of the corresponding 'parent' systems **8** and **11** and **12**, possessing only one potential directing group.[27] The diastereoselectivity of epoxidation of 5-NBn_2 *trans*-**42** suggests that the order of directing group proficiency in the five-membered ring system is: NBn_2 > OH. This is in contrast to the corresponding ranking established (from the diastereoselectivity of the epoxidation of 6-NBn_2 *trans*-**20**) for the six-membered ring system: OH > NBn_2. As the two possible envelope conformations (**42A** and **42C**) of 5-NBn_2 *trans*-**42** place the *N*,*N*-dibenzylammonium moiety and hydroxyl group in geometrically non-equivalent 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 proficiencies 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-NBn_2 *trans*-**42** proceeding from conformation **42A** to give **44** (as observed experimentally) proceeds via a favoured boatlike

transition state with reduction in torsional strain, most significantly between C(3)-proton and the pseudo-equatorial C(4)-ammonium group. In contrast, epoxidation of 5-NBn_2 *trans*-**42** proceeding from conformation **42C** to give **44** proceeds via a disfavoured chairlike transition state with increase of torsional strain, most significantly between the C(2)-proton and pseudo-equatorial C(1)-hydroxyl group[11,14,15] (Figure 3). The combination of conformational differences affecting ability to form a hydrogen-bond with the oxidant, and the drive to minimise torsional strain may therefore be responsible for the apparently higher directing group proficiency of the *N*,*N*-dibenzylammonium moiety versus the hydroxyl group in this case.

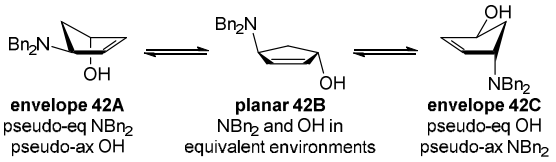


FIGURE 2. Representative conformers of 5-NBn_2 *trans*-**42**.

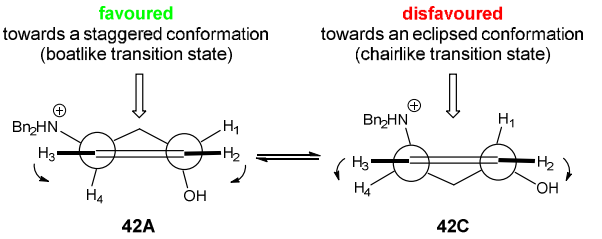


FIGURE 3. Model to rationalise facial selectivity of epoxidation of 5-NBn_2 *trans*-**42** proceeding from conformation **42A**, based upon minimisation of torsional strain in transition state.

The diastereoselectivities of the epoxidations of 7-NBn_2 *cis*-**54** and 7-NHBn *trans*-**55** suggests that the order of directing group proficiency in the seven-membered ring system is: NBn_2 > NHBn > OH. This is again in contrast to the ranking established from the diastereoselectivities of the epoxidations of 6-NHBn *trans*-**19** and 6-NBn_2 *trans*-**20** for the six-membered ring system: NHBn >> OH > NBn_2. The presence of two relatively non-sterically 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; *syn*:*anti*) and cyclohept-2-en-1-ol **3** (61:39 dr; *syn*:*anti*) suggest modest directing proficiencies in this system; if the two are able to operate largely independently, a mixture of products slightly favouring 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-NBn_2 **12** has been shown to favour a seven-membered chair conformation with the bulky *N*,*N*-dibenzylammonium moiety occupying a pseudo-

equatorial 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; *anti*:*syn*).[11] It seems likely that 7-NBn_2 *cis*-**54** would show a similar conformational preference and favour **54A** (Figure 4), with epoxidation of the least sterically encumbered face in this conformation again 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-NBn_2 *cis*-**54** in which the hydroxyl group is optimally placed to effect hydrogen-bonding delivery of the oxidant to the *syn* face are energetically disfavoured. 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 proficiency of the *N*,*N*-dibenzylammonium moiety in this case.

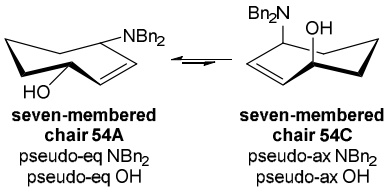


FIGURE 4. Representative conformers of 7-NBn_2 *cis*-**54**.

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-NBn_2 *cis*-**40**, 6-NHBn *cis*-**24**, 6-NBn_2 *cis*-**25**, 7-NHBn *cis*-**53** and 7-NBn_2 *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 alone[25] 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 non-sterically 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-NBn_2 *cis*-**40** and 7-NBn_2 *trans*-**56** undergo epoxidation with the same levels of diastereoselectivity as the corresponding *O*-benzyl ethers 5-NBn_2 *cis*-**46** and 7-NBn_2 *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-NBn_2 *trans*-**42**, 6-NHBn *trans*-**19**, 6-NBn_2 *trans*-**20**, 7-NHBn *trans*-**55** and 7-NBn_2 *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*-dibenzylammonium 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, this was proposed to be the result of reduction of torsional strain in the transition state being coupled with assistance from hydrogen-bonding with a pseudo-equatorial ammonium moiety. Meanwhile in the seven-membered ring it was proposed that the *N*,*N*-dibenzylammonium moiety, being able to mimic the effects of a conformational lock, enforces a well-defined conformational preference on the otherwise mobile seven-membered ring, disfavouring 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 syntheses of aminopolyols 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 Na_2SO_4. 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–^{13}C HMQC analyses were used to establish atom connectivity. Accurate mass measurements were run on a MicroTOF instrument internally calibrated with polyalanine.

X-ray Crystal Structure Determination.[23] 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 idealised positions. The structure was refined using CRYSTALS.[30]

(1*RS*,4*SR*)-4-(*N*-Benzylamino)cyclopent-2-en-1-ol 39. A solution of **38**[22] (5.34 g, 26.3 mmol, >99:1 dr) in THF (270 mL) at rt was added via cannula to a stirred solution of powdered $LiAlH_4$ (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 (eluent Et_2O). 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; ν_{max} (film) 3285, 3060, 3028, 1642, 1598; δ_H (400 MHz, $CDCl_3$) 1.46-1.52 (1H, m, C(5)H_A), 2.54-2.61 (1H, m, C(5)H_B), 3.69-3.71 (1H, m, C(4)*H*), 3.81-3.83 (2H, m, NCH_2Ph), 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*); δ_C (100 MHz, $CDCl_3$) 39.8 (*C*(5)), 41.3 (N*C*H_2Ph), 61.7 (*C*(1)), 75.5 (*C*(4)), 127.1, 128.3, 128.5 (*o*,*m*,*p*-*Ph*), 135.5, 136.0 (*C*(2), *C*(3)), 139.8 (*i*-*Ph*); *m/z* (ESI^+) 190 ($[M+H]^+$, 96%), 172 ($[M–OH]^+$, 100%); HRMS (ESI^+) $C_{12}H_{16}NO^+$ ($[M+H]^+$) requires 190.1226; found 190.1234.

(1*RS*,4*SR*)-4-(*N*,*N*-Dibenzylamino)cyclopent-2-en-1-ol 40. BnBr (1.78 mL, 15.0 mmol), $^iPr_2NEt$ (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 CH_2Cl_2 (100 mL) at rt and the resultant mixture was stirred at rt for 24 h, then washed with H_2O (2 × 100 mL). The combined aqueous washings were extracted with CH_2Cl_2 (200 mL) and the combined organic extracts were washed with brine (300 mL), then dried and concentrated in vacuo. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:1) gave **40** as a yellow solid (2.32 g, 83%, >99:1 dr); mp 52-54 °C; ν_{max} (film) 3385, 1642, 1598, 1494, 1453; δ_H (400 MHz, $CDCl_3$) 0.87-0.91 (1H, m, C(5)H_A), 2.41-2.49 (1H, m, C(5)H_B), 3.46-3.49 (2H, d, *J* 14.0, N(CH_AH$_B$Ph)$_2$), 3.72 (2H, d, *J* 14.0, N(CH$_A$$H_B$Ph)$_2$), 3.83-3.92 (1H, m, C(4)*H*), 4.69-4.72 (1H, m, C(1)*H*), 5.88-5.90 (1H, m, C*H*=CH), 5.95-5.98 (1H, m, CH=C*H*), 7.21-7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 34.3 (*C*(5)), 54.6 (N(*C*H$_2$Ph)$_2$), 54.6 (*C*(4)), 64.0 (*C*(1)), 126.8, 128.2, 128.7, (*o*,*m*,*p*-*Ph*), 135.0, 136.4 (*C*(2), *C*(3)), 140.1 (*i*-*Ph*); *m/z* (ESI$^+$) (ESI$^+$) 280 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{22}NO^+$ ([M+H]$^+$) requires 280.1696; found 280.1705.

(1*RS*,4*RS*)-4-(*N*,*N*-Dibenzylamino)cyclopent-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), PPh_3 (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 Et_2O (100 mL) and the resultant solution was washed sequentially with satd aq Na_2CO_3 (3 × 100 mL) and brine (100 mL), then dried and concentrated in vacuo. The residue was dissolved in MeOH (100 mL) and K_2CO_3 (6.91 g, 50.0 mmol) was added. The resultant suspension was stirred at rt for 4 h, then filtered and concentrated in vacuo. The residue was dissolved in Et_2O (100 mL) and the resultant solution was washed sequentially with H_2O (3 × 100 mL) and brine (100 mL), then dried and concentrated in vacuo. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et_2O, 1:1) gave **42** as a pale yellow oil (1.67 g, 60%, 98:2 dr); ν_{max} (film) 3300, 2982, 2935, 1602; δ_H (400 MHz, $CDCl_3$) 1.57-1.68 (1H, m, O*H*), 1.77 (1H, ddd, *J* 14.3, 7.9, 2.7, C(5)H_A), 2.24 (1H, ddd, *J* 14.3, 7.5, 4.5, C(5)H_B), 3.43 (2H, d, *J* 13.9, N(CH_AH$_B$Ph)$_2$), 3.63 (2H, d, *J* 13.9, N(CH$_A$$H_B$Ph)$_2$), 4.27-4.31 (1H, m, C(4)*H*), 4.94-4.96 (1H, m, C(1)*H*), 5.95-5.97 (1H, m, C*H*=CH), 6.01-6.03 (1H, m, CH=C*H*), 7.19-7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 34.4 *C*(5), 54.4 (N(*C*H$_2$Ph)$_2$), 65.1 (*C*(4)), 76.6 (*C*(1)), 127.0, 128.2, 128.6 (*o*,*m*,*p*-*Ph*), 135.4, 137.1 (*C*(2), *C*(3)), 140.0 (*i*-*Ph*); *m/z* (ESI$^+$) 280 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{22}NO^+$ ([M+H]$^+$) requires 280.1696; found 280.1701.

(1*RS*,2*RS*,3*SR*,4*SR*)-2,3-Epoxy-4-(*N*,*N*-dibenzylamino)cyclopent-1-ol 43. Cl_3CCO_2H (2.36 g, 14.4 mmol) was added to a stirred solution of **40** (401 mg, 1.44 mmol, >99:1 dr) in CH_2Cl_2 (4.0 mL, 0.36 M w.r.t. **40**) at rt and the resultant solution was stirred at rt for 5 min. *m*-CPBA (72% by wt, 690 mg, 2.88 mmol) was added and the resultant suspension was stirred at rt for 16 h. Na_2SO_3 (726 mg, 5.76 mmol) was added and

the resultant suspension was stirred until it solidified (~5 min). The resultant mixture was diluted with CH_2Cl_2 (20 mL) and washed with 10% aq NaOH (3 × 20 mL). The combined aqueous washings were extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine (100 mL), dried and concentrated in vacuo to give >95% conversion to **43** in >95:5 dr. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et_2O, 1:1) gave **43** as a white solid (347 mg, 77%, >99:1 dr); mp 74-76 °C; ν_{max} (film) 3406, 3028, 2947, 2804, 1603, 1494, 1453, 1256; δ_H (400 MHz, $CDCl_3$) 1.41 (1H, ddd, *J* 12.3, 10.1, 8.2, C(5)H_A), 1.77 (1H, br s, O*H*), 1.98 (1H, ddd, *J* 12.3, 7.5, 7.3, C(5)H_B), 3.19 (1H, ddd, *J* 10.1, 7.3, 1.0, C(4)*H*), 3.41 (1H, dd, *J* 3.0, 1.5, C(2)*H*), 3.52-3.53 (1H, d, *J* 3.0, 1.0, C(3)*H*), 3.66 (2H, d, *J* 14.5, N(CH_AH$_B$Ph)$_2$), 3.88 (2H, d, *J* 14.5, N(CH$_A$$H_B$Ph)$_2$), 4.03-4.07 (1H, m, C(1)*H*), 7.23-7.27 (2H, m, *Ph*), 7.33 (4H, app t, 7.4, *Ph*), 7.40 (4H, d, 7.4, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.4 (*C*(5)), 55.2 (N(*C*H$_2$Ph)$_2$), 55.9 (*C*(2)), 56.7 (*C*(3)), 58.3 (*C*(4)), 71.1 (*C*(1)), 126.9 (*p-Ph*), 128.3, 128.5 (*o,m-Ph*), 139.9 (*i-Ph*); *m/z* (ESI$^+$) 296 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{21}NNaO_2^+$ ([M+Na]$^+$) requires 318.1465; found 318.1470.

(1*RS*,2*SR*,3*RS*,4*RS*)-2,3-Epoxy-4-(*N*,*N*-dibenzylamino)cyclopent-1-ol 44. Cl_3CCO_2H (585 mg, 3.58 mmol) was added to a stirred solution of **42** (100 mg, 0.358 mmol, 98:2 dr) in CH_2Cl_2 (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, 172 mg, 0.72 mmol) was added and the resultant suspension was stirred at rt for 16 h. Na_2SO_3 (180 mg, 1.43 mmol) was added and the resultant suspension was stirred until it solidified (~5 min). The resultant mixture was diluted with CH_2Cl_2 (5 mL) and washed with 10% aq NaOH (3 × 5 mL). The combined aqueous washings were extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were washed with brine (25 mL), dried and concentrated in vacuo to give >95% conversion to **44** in 93:7 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 1:1) gave **44** as a white solid (41 mg, 66%, >99:1 dr); mp 83-85 °C; ν_{max} (film) 3406, 3028, 2947, 2804, 1602, 1494, 1453, 1251; δ_H (400 MHz, $CDCl_3$) 1.52 (1H, br s, OH), 1.62 (1H, dd, *J* 13.8, 7.7, C(5)H_A), 1.74-1.81 (1H, m, C(5)H_B), 3.31 (1H, app d, *J* 2.6, C(2)*H*), 3.53 (1H, app d, *J* 2.6 C(3)*H*), 3.60-3.64 (1H, m, C(4)*H*), 3.69-3.72 (2H, m, N(CH_AH$_B$Ph)$_2$), 3.79-3.82 (2H, m, N(CH$_A$$H_B$Ph)$_2$), 4.38 (1H, app d, *J* 5.5, C(1)*H*), 7.22-7.25 (2H, m, *Ph*), 7.34 (4H, app t, *J* 7.3 *Ph*) 7.40-7.41 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 29.6 (*C*(5)), 55.5 (*C*(2)), 55.5 (N(*C*H$_2$Ph)$_2$), 55.9 (*C*(3)), 59.4 (*C*(4)), 70.5 (*C*(1)), 126.9 (*p-Ph*), 128.2, 128.5 (*o,m-Ph*), 140.0 (*i-Ph*); *m/z* (ESI$^+$) 296 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{22}NO_2^+$ ([M+H]$^+$) requires 296.1645; found 296.1644.

(1*RS*,2*SR*,3*RS*,4*RS*)-1-(*p*-Nitrobenzoyloxy)-2,3-epoxy-4-(*N*,*N*-dibenzylamino)cyclopentane 45. *p*-Nitrobenzoyl chloride (67 mg, 0.37 mmol) and DMAP (3 mg, 0.02 mmol) were added sequentially to a stirred solution of **44** (60 mg, 0.20 mmol, >99:1 dr) in pyridine (1 mL) at rt. The resultant solution was stirred at rt for 16 h then diluted with CH_2Cl_2 (5 mL). The resultant solution was washed sequentially with

sat. aq. $NaHCO_3$ (5 mL), sat. aq. citric acid (2 × 5 mL) and brine (2 × 5 mL), dried and concentrated in vacuo to give **45** as a pale yellow solid (60 mg, 67%, >99:1 dr); mp 98-102 °C; ν_{max} (ATR) 3029, 2803, 1726, 1527, 1270; δ_H (400 MHz, $CDCl_3$) 1.79 (1H, dd, *J* 7.8, 14.3, C(5)H_A), 1.91 (1H, ddd, *J* 5.7, 9.9, 14.5, C(5)H_B), 3.46 (1H, d, *J* 2.6, C(2)*H*), 3.52 (1H, d, *J* 1.8, C(3)*H*), 3.59 (1H, t, *J* 9.3, C(4)*H*), 3.64 (2H, d, *J* 14.0, N(C$H_A$$H_B$Ph)$_2$), 3.77 (2H, d, *J* 14.0, N(C$H_A$$H_B$Ph)$_2$), 5.44 (1H, d, *J* 5.6, C(1)*H*), 7.13-7.39 (10H, m, *Ph*), 7.99-8.04 (2H, m, *Ar*), 8.17-8.21 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 26.7 (*C*(5)), 53.1 (*C*(2)), 55.4 (N*C*H_2Ph), 56.1 (*C*(3)), 59.7 (*C*(4)), 74.5 (*C*(1)), 123.5 (*Ar*), 127.0 (*p-Ph*), 128.3, 128.5 (*o*,*m-Ph*), 130.8 (*Ar*), 135.1, 139.7 (*i-Ph*, *Ar*), 150.6 (*Ar*), 164.0 (*C*=O); *m/z* (ESI^+) 445 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{25}N_2O_5^+$ ($[M+H]^+$) requires 445.1758; found 445.1746.

(1*RS*,4*SR*)-1-Benzyloxy-4-(*N*,*N*-dibenzylamino)cyclopent-2-ene 46. NaH (60% dispersion in mineral oil, 84 mg, 2.1 mmol) was stirred at rt for 20 min in pentane (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_4NI (12 mg, 0.10 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 (5 mL). The resultant mixture was extracted with $CHCl_3$ (5 × 20 mL) and the combined organic extracts were washed with brine (2 × 50 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 9:1) gave **46** as a colourless oil (263 mg, 67%, >99:1 dr); ν_{max} (film) 3061, 3028, 2919, 2850, 1733, 1603, 1494, 1454; δ_H (400 MHz, $CDCl_3$) 1.81 (1H, dt, *J* 13.6, 5.5, C(5)H_A), 2.38 (1H, dt, *J* 13.6, 7.7 C(5)H_B), 3.50 (2H, d, *J* 14.2, N(C$H_A$$H_B$Ph)$_2$), 3.78 (2H, d, *J* 14.2, N(C$H_A$$H_B$Ph)$_2$), 3.90 (1H, t, *J* 6.8, C(4)*H*), 4.46 (1H, dd, *J* 7.5, 5.2, (C(1)*H*), 4.58 (1H, d, *J* 11.9, OC$H_A$$H_B$Ph), 4.60 (1H, d, *J* 11.9, OC$H_A$$H_B$Ph), 5.96-6.00 (2H, m, C(2)*H*, C(3)*H*), 7.21-7.41 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 31.2 (*C*(5)), 54.6 (N(*C*H_2Ph)$_2$), 63.7 (*C*(4)), 70.9 (O*C*H_2Ph), 82.1 (*C*(1)), 126.7, 127.5, 127.8, 128.2, 128.4, 128.6 (*o*,*m*,*p-Ph*), 132.8, 136.4 (*C*(2), *C*(3)), 138.7, 140.3 (*i-Ph*); *m/z* (ESI^+) 370 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{28}NO^+$ ($[M+H]^+$) requires 370.2165; found 370.2161.

(1*RS*,4*RS*)-1-Benzyloxy-4-(*N*,*N*-dibenzylamino)cyclopent-2-ene 47. NaH (60% dispersion in mineral oil, 80 mg, 2.0 mmol) was stirred at rt for 20 min in pentane (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 **42** (279 mg, 1.00 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 (0.24 mL, 2.0 mmol) and Bu_4NI (12 mg, 0.10 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 (5 mL). The resultant mixture was extracted with $CHCl_3$ (5 × 20 mL) and the combined

organic extracts were washed with brine (2 × 50 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 9:1) gave **47** as a colourless oil (258 mg, 70%, >99:1 dr); $C_{26}H_{27}NO$ requires C, 84.5; H, 7.4; N, 3.8%; found C, 84.4; H, 7.3; N, 3.8%; ν_{max} (film) 3061, 3028, 2932, 2833, 2799, 1746, 1603, 1494, 1453; δ_H (400 MHz, $CDCl_3$) 1.91-1.97 (1H, m, C(5)H_A), 2.12-2.19 (1H, m, C(5)H_B), 3.44 (2H, d, *J* 13.9, N(C$H_A$$H_B$Ph)$_2$), 3.63 (2H, d, *J* 13.9, N(C$H_A$$H_B$Ph)$_2$), 4.28-4.32 (1H, m, C(4)*H*), 4.48-4.57 (2H, m, OCH_2Ph), 4.74-4.77 (1H, m, C(1)*H*), 6.03-6.08 (2H, m, C(2)*H*, C(3)*H*), 7.22-7.39 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 31.1 (*C*(5)), 54.4 (N(*C*H_2Ph)$_2$), 65.2 (*C*(4)), 70.8 (O*C*H_2Ph), 83.5 (*C*(1)), 126.8, 127.5, 127.7, 128.2, 128.4, 128.6 (*o*,*m*,*p*-*Ph*), 133.1, 137.7 (*C*(2), *C*(3)), 138.6, 140.0 (*i*-*Ph*); *m/z* (ESI^+) 370 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{28}NO^+$ ($[M+H]^+$) requires 370.2165; found 370.2165.

(1*RS*,2*RS*,3*RS*,4*RS*)-1-Benzyloxy-2,3-epoxy-4-(*N*,*N*-dibenzylamino)cyclopentane 48. *Method A. O-Benzylation of **43**.* NaH (60% dispersion in mineral oil, 4 mg, 0.1 mmol) was stirred at rt for 20 min in pentane (0.5 mL). The pentane was then decanted under a stream of argon, and THF (0.5 mL) was added. The resultant suspension was cooled to 0 °C and a solution of **43** (32 mg, 0.11 mmol, >99:1 dr) in THF (0.5 mL) was added dropwise. The resultant suspension was stirred at 0 °C for 30 min, after which time BnBr (20 μL, 0.20 mmol) and Bu_4NI (1 mg, 0.01 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), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 4:1) gave **48** as a colourless oil (13 mg, 31%, >99:1 dr); ν_{max} (film) 3029, 2918, 2850, 1604, 1494, 1257; δ_H (400 MHz, $CDCl_3$) 1.64 (1H, ddd, *J* 11.9, 10.2, 8.5, C(5)H_A), 1.91 (1H, dt, *J* 11.9, 7.3, C(5)H_B), 3.18 (1H, app dd, *J* 10.1, 7.3, C(4)*H*), 3.44 (1H, dd, *J* 2.9, 1.0, C(2)*H*), 3.51 (1H, d, *J* 2.9, C(3)*H*), 3.71 (2H, d, *J* 14.2, N(C$H_A$$H_B$Ph)$_2$), 3.82-3.86 (1H, m, C(1)*H*), 3.92 (2H, d, *J* 14.2, N(C$H_A$$H_B$Ph)$_2$), 4.61-4.68 (2H, m, OC$H_2$Ph), 7.24-7.44 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 23.0 (*C*(5)), 53.4 (*C*(2)), 55.2 (N(*C*H_2Ph)$_2$), 55.6 (*C*(3)), 57.9 (*C*(4)), 71.3 (O*C*H_2Ph), 76.8 (*C*(1)), 126.9, 127.7, 127.8, 128.3, 128.5, 128.5 (*o*,*m*,*p*-*Ph*), 138.1, 140.0 (*i*-*Ph*); *m/z* (ESI^+) 386 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{28}NO_2^+$ ($[M+H]^+$) requires 386.2115; found 386.2115.

*Method B. Epoxidation of **46**.* Cl_3CCO_2H (359 mg, 2.19 mmol) was added to a stirred solution of **46** (81 mg, 0.22 mmol, >99:1 dr) in CH_2Cl_2 (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. Na_2SO_3 (111 mg, 0.88 mmol) was added and the resultant suspension was stirred until it solidified (~5 min). The resultant mixture was diluted with CH_2Cl_2 (5 mL) and washed with 10% aq

NaOH (3 × 5 mL). The combined aqueous washings were extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were washed with brine (25 mL), dried and concentrated in vacuo to give 82% conversion to **48** in >95:5 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 4:1) gave **48** as a colourless oil (60 mg, 71%, >99:1 dr).

(1*RS*,2*SR*,3*RS*,4*RS*)-1-Benzyloxy-2,3-epoxy-4-(*N*,*N*-dibenzylamino)cyclopentane 49. *Method A. O-Benzylation of **44**.* NaH (60% dispersion in mineral oil, 8 mg, 0.2 mmol) was stirred at rt for 20 min in pentane (0.5 mL). The pentane was then decanted under a stream of argon, and THF (0.5 mL) was added. The resultant suspension was cooled to 0 °C and a solution of **44** (30 mg, 0.10 mmol, >99:1 dr) in THF (0.5 mL) was added dropwise. The resultant suspension was stirred at 0 °C for 30 min, after which time BnBr (24 μL, 0.20 mmol) and Bu_4NI (1 mg, 0.01 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), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 6:1) gave **49** as a colourless oil (21 mg, 54%, >99:1 dr); ν_{max} (film) 3062, 3028, 2890, 2803, 1602, 1494, 1453, 1256; δ_H (400 MHz, $CDCl_3$) 1.62-1.70 (1H, m, C(5)H_A), 1.79-1.85 (1H, m, C(5)H_B), 3.39 (1H, app d, *J* 2.4, C(2)*H*), 3.53 (1H, app d, *J* 2.4, C(3)*H*), 3.63-3.67 (1H, m, C(4)*H*), 3.70-3.73 (2H, m, N(C$H_A$$H_B$Ph)$_2$), 3.81-3.84 (2H, m, N(C$H_A$$H_B$Ph)$_2$), 4.13 (1H, app d, *J* 5.6, C(1)*H*), 4.48-4.51 (1H, m, OC$H_A$$H_B$Ph), 4.56-4.58 (1H, m, OC$H_A$$H_B$Ph), 7.23-7.43 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.4 (*C*(5)), 54.2 (*C*(2)), 54.2 (N(*C*H_2Ph)$_2$), 56.3 (*C*(3)), 59.8 (*C*(4)), 71.6 (O*C*H_2Ph), 77.6 (*C*(1)), 126.8, 127.7, 127.8, 128.2, 128.5 (*o*,*m*,*p*-*Ph*), 138.0, 140.1 (*i*-*Ph*); *m/z* (ESI^+) 386 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{28}NO_2^+$ ($[M+H]^+$) requires 386.2115; found 386.2111.

*Method B. Epoxidation of **47**.* Cl_3CCO_2H (340 mg, 2.08 mmol) was added to a stirred solution of **47** (77 mg, 0.21 mmol, >99:1 dr) in CH_2Cl_2 (0.60 mL, 0.36 M w.r.t. **47**) at rt and the resultant solution was stirred at rt for 5 min. *m*-CPBA (75% by wt, 101 mg, 0.42 mmol) was added and the resultant suspension was stirred at rt for 16 h. Na_2SO_3 (106 mg, 0.84 mmol) was added and the resultant suspension was stirred until it solidified (~5 min). The resultant mixture was diluted with CH_2Cl_2 (5 mL) and washed with 10% aq NaOH (3 × 5 mL). The combined aqueous washings were extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were washed with brine (25 mL), dried and concentrated in vacuo to give 82% conversion to **49** in >95:5 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 6:1) gave **49** as a colourless oil (59 mg, 74%, >99:1 dr).

(1*RS*,4*SR*)-4-(*N*-Benzylamino)cyclohept-2-en-1-ol 53. A solution of **52**[24] (427 mg, 1.73 mmol, >99:1 dr) in THF (37 mL) at rt was added via cannula to a stirred solution of powdered $LiAlH_4$ (319 mg,

8.40 mmol) in THF (18 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 (~2 g) was then added portionwise, followed by addition of satd. aq. sodium potassium tartrate (40 mL). The resultant mixture was stirred vigorously at rt for 2 h, then filtered through Celite (eluent Et_2O). The organic layer was washed with brine (100 mL), dried and concentrated in vacuo. Purification via flash column chromatography (eluent EtOAc) gave **53** as a white solid (322 mg, 80%, >99:1 dr);[23] mp 107-109 °C; δ_H (400 MHz, $CDCl_3$) 1.58-2.36 (6H, m, C(5)H_2, C(6)H_2, C(7)H_2), 3.31 (1H, td, *J* 6.6, 1.9, C(4)*H*), 3.70-3.82 (2H, m, NCH_2Ph), 4.22 (1H, td, *J* 6.6, 1.7, C(1)*H*), 5.92 (1H, dd, *J* 11.3, 6.6, C*H*=CH), 6.22 (1H, dd, *J* 11.3, 6.6, CH=C*H*), 7.25-7.36 (5H, m, *Ph*).

(1*RS*,4*SR*)-4-(*N*,*N*-Dibenzylamino)cyclohept-2-en-1-ol 54. BnBr (410 μL, 3.45 mmol), $^iPr_2NEt$ (601 μL, 3.45 mmol) and DMAP (28 mg, 0.23 mmol) were added sequentially to a stirred solution of **53** (500 mg, 2.30 mmol, >99:1 dr) in CH_2Cl_2 (23 mL) at rt and the resultant solution was stirred at rt for 24 h, then washed with H_2O (2 × 25 mL). The combined aqueous washings were extracted with CH_2Cl_2 (50 mL) and the combined organic extracts were washed with brine (75 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 4:1) gave **54** as a yellow solid (550 mg, 78%, >99:1 dr); mp 48-50 °C; ν_{max} (film) 3387, 3028, 2927, 1603, 1493, 1453; δ_H (400 MHz, $CDCl_3$) 1.45-2.07 (7H, m, C(5)H_2, C(6)H_2, C(7)H_2, O*H*), 3.21-3.22 (1H, m, C(4)*H*), 3.57-3.61 (2H, m, N(C$H_A$$H_B$Ph)$_2$), 3.69-3.72 (2H, m, N(CH$_A$$H_B$Ph)$_2$), 4.20-4.21 (1H, m, C(1)*H*), 5.80-5.83 (1H, m, C*H*=CH), 5.94-5.97 (1H, m, C*H*=CH), 7.27-7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.0, 29.1, 36.4, (*C*(5), *C*(6), *C*(7)), 53.8 (N(*C*H$_2$Ph)$_2$), 58.9 (*C*(4)), 71.9 (*C*(1)), 126.8 (*p-Ph*), 128.2, 128.6 (*o*,*m-Ph*), 133.4, 137.1 (*C*(2), *C*(3)), 139.9 (*i-Ph*); *m/z* (ESI$^+$) 308 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{26}NO^+$ ([M+H]$^+$) requires 308.2009; found 308.2006.

(1*RS*,4*RS*)-4-(*N*-Benzylamino)cyclohept-2-en-1-ol 55. DEAD (40% wt solution in PhMe, 1.79 mL, 3.93 mmol) was added dropwise via syringe pump over 1 h to a stirred solution of **53** (502 mg, 2.31 mmol, >99:1 dr), PPh_3 (1.21 g, 4.62 mmol) and benzoic acid (423 mg, 3.47 mmol) in PhMe (18 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 Et_2O (20 mL) and the resultant solution was washed sequentially with satd aq Na_2CO_3 (3 × 20 mL) and brine (20 mL), then dried and concentrated in vacuo. The residue was dissolved in MeOH (6 mL) and K_2CO_3 (1.60 g, 11.6 mmol) was added. The resultant suspension was stirred at rt for 4 h, then filtered and concentrated in vacuo. The residue was dissolved in Et_2O (20 mL) and the resultant solution was washed sequentially with H_2O (3 × 20 mL) and brine (20 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent EtOAc) gave **55** as a colourless oil (65 mg, 13%, >99:1 dr); ν_{max} (film) 3355, 3025, 2930, 2858, 1651, 1603, 1495, 1453; δ_H (400 MHz, $CDCl_3$) 1.61-

1.87 (6H, m, C(5)H_2, C(6)H_2, C(7)H_2), 3.42-3.44 (1H, m, C(4)*H*), 3.76-3.83 (2H, m, NCH_2Ph), 4.47-4.50 (1H, m, C(1)*H*), 5.75-5.82 (2H, m, C(2)*H*, C(3)*H*), 7.24-7.34 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.8, 32.4, 35.3 (*C*(5), *C*(6), *C*(7)), 51.4 (N*C*H_2Ph), 55.6 (*C*(4)), 69.9 (*C*(1)), 127.0 (*p-Ph*), 128.2, 128.4 (*o*,*m-Ph*), 134.8, 135.9 (*C*(2), *C*(3)), 140.4 (*i-Ph*); *m/z* (ESI^+) 497 (100%), 218 ($[M+H]^+$, 80%); HRMS (ESI^+) $C_{14}H_{20}NO^+$ ($[M+H]^+$) requires 218.1539; found 218.1537.

(1*RS*,4*RS*)-4-(*N*,*N*-Dibenzylamino)cyclohept-2-en-1-ol 56. DEAD (40% wt solution in PhMe, 1.23 mL, 2.69 mmol) was added dropwise over 1 h to a stirred solution of **54** (487 mg, 1.58 mmol, >99:1 dr), PPh_3 (831 mg, 3.17 mmol) and benzoic acid (290 mg, 2.38 mmol) in PhMe (12 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 Et_2O (20 mL) and washed sequentially with sat. aq. Na_2SO_3 (3 × 20 mL) and brine (20 mL), dried and concentrated in vacuo. The residue was dissolved in MeOH (5 mL) and K_2CO_3 (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 Et_2O (20 mL) and washed sequentially with H_2O (3 × 20 mL) and brine (20 mL), dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 4:1) gave **56** as a white solid (312 mg, 64%, >99:1 dr); mp 56-58 °C; ν_{max} (film) 3356, 3026, 2934, 1646, 1602, 1493, 1454; δ_H (400 MHz, $CDCl_3$) 1.44 (1H, d, *J* 3.79, O*H*), 1.54-1.61 (2H, m, C(5)H_A, C(7)H_A), 1.70-1.82 (3H, m, C(6)H_2, C(7)H_B), 2.02-2.09 (2H, m, C(5)H_B), 3.36 (1H, ddd, *J* 8.1, 5.2, 2.4, C(4)*H*), 3.5 (2H, d, *J* 14.0, N(C$H_A$$H_B$Ph)$_2$), 3.74 (2H, d, *J* 14.0, N(C$H_A$$H_B$Ph)$_2$), 4.39-4.41 (1H, m, C(1)*H*), 5.77-5.82 (1H, m, C(3)*H*), 5.89-5.92 (1H, m, C(2)*H*), 7.21-7.40 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.9 (*C*(6)), 26.6 (*C*(5)), 35.0 (*C*(7)), 53.8 (N(*C*H_2Ph)$_2$), 56.9 (*C*(4)), 69.1 (*C*(1)), 126.8 (*p-Ph*), 128.2, 128.5 (*o*,*m-Ph*), 135.5, 136.0 (*C*(2), *C*(3)), 140.3 (*i-Ph*); *m/z* (ESI^+) 308 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{26}NO^+$ ($[M+H]^+$) requires 308.2009; found 308.2006.

(1*RS*,2*SR*,3*RS*,4*SR*)- and (1*RS*,2*RS*,3*SR*,4*SR*)-2,3-Epoxy-4-(*N*,*N*-dibenzylamino)cyclohept-1-ol 59 and 60. *Method A. via Epoxidation of **53**. Step 1.* Cl_3CCO_2H (376 mg, 2.30 mmol) was added to a stirred solution of **53** (50 mg, 0.23 mmol, >99:1 dr) in CH_2Cl_2 (0.64 mL, 0.36 M w.r.t **53**) 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. Na_2SO_3 (174 mg, 1.38 mmol) was added and the resultant suspension was stirred until it solidified (~5 min). The resultant mixture was diluted with CH_2Cl_2 (5 mL) and washed with 10% aq. NaOH (3 × 5 mL). The combined aqueous washings were extracted with CH_2Cl_2 (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. BnBr (41 μL, 0.35 mmol), $^{i}Pr_2NEt$ (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 CH_2Cl_2 (2.3 mL) at rt and the resultant solution was stirred at rt for 24 h, then washed with H_2O (2 × 5 mL). The combined aqueous washings were extracted with CH_2Cl_2 (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/Et_2O, 3:2) gave **60** as a colourless oil (44 mg, 53%, >99:1 dr); ν_{max} (film) 3384, 2932, 2851, 1603, 1494, 1453, 1264; δ_H (500 MHz, $CDCl_3$) 0.73-0.83 (1H, m, C(6)H_A), 1.51-1.59 (2H, m, C(5)H_A, C(7)H_A), 1.74-1.78 (2H, m, C(6)H_B, C(7)H_B), 1.84-1.89 (1H, m, C(5)H_B) 2.85-2.88 (1H, m, C(4)*H*), 3.20 (1H, app d, *J* 5.1, C(2)*H*), 3.89 (1H, dd, *J* 5.1, 1.0, C(3)*H*), 3.58 (2H, d, *J* 14.0, N(CH_AH$_B$Ph)$_2$), 3.82-3.89 (3H, m, C(1)*H*, N(CH$_A$$H_B$Ph)$_2$), 7.22-7.26 (2H, m, *Ph*), 7.30-7.33 (4H, m, *Ph*), 7.38 (4H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 23.0 (*C*(6)), 23.7 (*C*(5)), 33.9 (*C*(7)), 54.1 (N(*C*H$_2$Ph)$_2$), 57.9 (*C*(4)), 58.5 (*C*(2)), 58.5 (*C*(3)), 72.0 (*C*(1)), 126.8 (*p-Ph*), 128.2, 128.5 (*o*,*m-Ph*), 140.0, (*i-Ph*); *m/z* (ESI$^+$) 346 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{25}NNaO_2^+$ ([M+Na]$^+$) requires 346.1778; found 346.1773. Further elution gave a 53:47 mixture of **59** and **60** as a colourless oil (8 mg, 10%).

*Method B. Epoxidation of **54**.* Cl_3CCO_2H (2.66 g, 16.3 mmol) was added to a stirred solution of **54** (500 mg, 1.63 mmol, >99:1 dr) in CH_2Cl_2 (4.5 mL, 0.36 M w.r.t **54**) at rt and the resultant solution was stirred at rt for 5 min. *m*-CPBA (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 (1.23 g, 9.77 mmol) was added and the resultant suspension was stirred until it solidified (~5 min). The resultant mixture was diluted with CH_2Cl_2 (5 mL) and washed 10% aq. NaOH (3 × 5 mL). The combined aqueous washings were extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were washed with brine (50 mL), dried and concentrated in vacuo to give an 80:20 mixture of **59** and **60**. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 3:2) gave a 23:77 mixture of **59** and **60** as a colourless oil (89 mg, 17%). Further elution gave an 82:18 mixture of **59** and **60** as a colourless oil (275 mg, 52%). Further elution gave **59** as a colourless oil (20 mg, 4%, 95:5 dr); ν_{max} (film) 3406, 3062, 2929, 2854, 1602, 1494, 1453, 1260; δ_H (400 MHz, $CDCl_3$) 1.27-1.33 (1H, m, C(6)H_A), 1.52-1.88 (5H, m, C(5)H_2, C(6)H_B, C(7)H_2), 2.47 (1H, app dd, *J* 10.6, 7.5, C(4)*H*), 3.04 (1H, t, *J* 5.5, C(2)*H*), 3.32 (1H, dd, *J* 7.5, 5.5, C(3)*H*), 3.39-3.44 (1H, m, C(1)*H*), 3.70-3.73 (2H, m, N(CH_AH$_B$Ph)$_2$), 3.78-3.81 (2H, m, N(CH$_A$$H_B$Ph)$_2$), 7.21-7.41 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.5, 29.8, 33.9 (*C*(5), *C*(6), *C*(7)), 54.0 (*C*(3)), 54.3 (N(*C*H$_2$Ph)$_2$), 58.5 (*C*(2)), 60.9 (*C*(4)), 73.4 (*C*(1)), 126.9 (*p-Ph*), 128.2, 128.8 (*o*,*m-Ph*), 139.6, (*i-Ph*); *m/z* (ESI$^+$) 346 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{25}NNaO_2^+$ ([M+Na]$^+$) requires 346.1778; found 346.1778.

(1*RS*,2*SR*,3*RS*,4*SR*)-1-(*p*-Nitrobenzoyloxy)-2,3-epoxy-4-(*N*,*N*-dibenzylamino)cycloheptane 61. *p*-Nitrobenzoyl chloride (246 mg, 1.33 mmol) and DMAP (9 mg, 0.07 mmol) were added sequentially to a stirred solution of **59** (215 mg, 0.66 mmol, 82:18 dr) in pyridine (2.6 mL) at rt. The resultant solution was stirred at rt for 16 h then diluted with CH_2Cl_2 (10 mL). The resultant solution was washed sequentially with sat. aq. $NaHCO_3$ (10 mL), sat. aq. citric acid (2 × 10 mL) and brine (2 × 10 mL), dried and concentrated in vacuo to give **61** in 82:18 dr. Purification via flash column chromatography (eluent PhMe/Et_2O, 15:1) gave **61** as a white solid (248 mg, 79%, 93:7 dr). Recrystallisation gave an analytical sample of **61** (>99:1 dr); mp 154-156 °C; ν_{max} (film) 3029, 2930, 2856, 1725, 1607, 1494, 1454, 1271; δ_H (500 MHz, $CDCl_3$) 1.43-1.51 (1H, m, C(6)H_A), 1.58-1.66 (1H, m, C(5)H_A), 1.68-1.76 (1H, m, C(7)H_A), 1.91-1.97 (3H, m, C(5)H_B, C(6)H_B, C(7)H_B), 2.56 (1H, dd, *J* 11.0, 7.6, C(4)*H*), 3.30-3.32 (1H, m, C(2)*H*), 3.40 (1H, dd, *J* 7.6, 5.3, C(3)*H*), 3.73-3.76 (2H, m, N(C$H_A$$H_B$Ph)$_2$), 3.82-3.85 (2H, m, N(C$H_A$$H_B$Ph)$_2$), 4.64 (1H, ddd, *J* 11.9, 6.2, 1.7, C(1)*H*), 7.23-7.42 (10H, m, *Ph*), 8.21-8.23 (2H, m, *Ar*), 8.29-8.31 (2H, m, *Ar*); δ_C (125 MHz, $CDCl_3$) 25.5 (*C*(6)), 30.0 (*C*(5)), 31.5 (*C*(7)), 53.8 (*C*(3)), 54.5 (N*C*H_2Ph), 55.4 (*C*(2)), 61.5 (*C*(4)), 77.8 (*C*(1)), 123.5 (*Ar*), 127.0 (*p-Ph*), 128.2, 128.7 (*o*,*m-Ph*), 130.8 (*Ar*), 135.5, 139.5 (*i-Ph*, *Ar*), 150.6 (*Ar*), 163.7 (*C*=O); *m/z* (ESI$^+$) 473 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{29}N_2O_5^+$ ([M+H]$^+$) requires 473.2071; found 473.2065.

(1*RS*,2*RS*,3*SR*,4*RS*)- and (1*RS*,2*SR*,3*RS*,4*RS*)-2,3-Epoxy-4-(*N*,*N*-dibenzylamino)cyclohept-1-ol 64 and 65. *Method A. via Epoxidation of **55**. Step 1.* Cl_3CCO_2H (376 mg, 2.30 mmol) was added to a stirred solution of **55** (50 mg, 0.23 mmol, >99:1 dr) in CH_2Cl_2 (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. Na_2SO_3 (174 mg, 1.38 mmol) was added and the resultant suspension was stirred until it solidified (~5 min). The resultant mixture was diluted with CH_2Cl_2 (5 mL) and washed with 10% aq. NaOH (3 × 5 mL). The combined aqueous washings were extracted with CH_2Cl_2 (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 **63** (60 mg).

Step 2. BnBr (41 μL, 0.35 mmol), $^iPr_2NEt$ (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 CH_2Cl_2 (2.3 mL) at rt and the resultant solution was stirred at rt for 24 h, then washed with H_2O (2 × 5 mL). The combined aqueous washings were extracted with CH_2Cl_2 (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/Et_2O, 4:1) gave **65** as a colourless oil (29 mg, 35%, >99:1 dr); ν_{max} (film) 3357, 3030, 2927, 2854, 1496, 1454; δ_H (400 MHz, $CDCl_3$) 1.08-1.90 (6H, m, C(5)H_2,

C(6)H_2, C(7)H_2), 3.04 (1H, dd, *J* 11.8, 2.6, C(4)*H*), 3.09 (1H, m, C(2)*H*), 3.41 (1H, d, *J* 3.4, C(3)*H*), 3.59 (2H, d, *J* 14.2, N(C$H_A$$H_B$Ph)$_2$), 3.87 (2H, d, *J* 14.2, N(CH$_A$$H_B$Ph)$_2$), 4.51-4.44 (1H, m, C(1)*H*), 7.21-7.40 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 18.7 (*C*(6)), 23.3 (*C*(5)), 32.5 (*C*(7)), 54.3 (N(*C*H$_2$Ph)$_2$), 54.9 (*C*(2)), 57.9 (*C*(4)), 60.6 (*C*(3)), 69.8 (*C*(1)), 126.8 (*p-Ph*), 128.2, 128.5 (*o*,*m-Ph*), 140.1, (*i-Ph*); *m/z* (ESI$^+$) 346 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{25}NNaO_2^+$ ([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*-CPBA (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 (1.23 g, 9.77 mmol) was added and the resultant suspension was stirred until it solidified (~5 min). The resultant mixture was diluted with CH_2Cl_2 (5 mL) and washed 10% aq. NaOH (3 × 5 mL). The combined aqueous washings were extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were washed with brine (50 mL), dried and concentrated in vacuo to give a 95:5 mixture of **64** and **65**. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 4:1) gave **64** as a white solid (48 mg, 73%, >99:1 dr); mp 92-94 °C; ν_{max} (film) 3443, 1494, 1453, 1260; δ_H (400 MHz, $CDCl_3$) 1.36-1.44 (1H, m, C(6)H_A), 1.53-1.66, 1.75-1.82 (4H, m, C(5)H_2, C(6)H_B, C(7)H_A), 1.90-1.98 (1H, m, C(7)H_B), 2.93 (1H, m, C(4)*H*), 3.06 (1H, t, *J* 4.7, C(2)*H*), 3.35-3.37 (1H, m, C(3)*H*) 3.68-3.71 (2H, m, N(C$H_A$$H_B$Ph)$_2$), 3.76-3.80 (2H, m, N(CH$_A$$H_B$Ph)$_2$), 4.25-4.28 (1H, m, C(1)*H*), 7.22-7.45 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.0 (*C*(6)), 30.0, 30.2 (*C*(7), (*C*(5)), 54.4 (*C*(2)), 54.6 (N(*C*H$_2$Ph)$_2$), 56.9 (*C*(3)), 58.8 (*C*(4)), 65.1 (*C*(1)), 126.9 (*p-Ph*), 128.2, 128.7 (*o*,*m-Ph*), 139.8 (*i-Ph*); *m/z* (ESI$^+$) 324 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{26}NO_2^+$ ([M+H]$^+$) requires 324.1958; found 324.1955.

(1*RS*,4*RS*)-1-Benzyloxy-4–(*N*,*N*-dibenzylamino)cyclohept-2-ene 66. NaH (60% dispersion in mineral oil, 20 mg, 0.50 mmol) was stirred at rt for 20 min in pentane (1 mL). The pentane was then decanted under a stream of argon, and THF (1 mL) was added. The resultant suspension was cooled to 0 °C and a solution of **56** (76 mg, 0.25 mmol, >99:1 dr) in THF (1 mL) was added dropwise. The resultant suspension was stirred at 0 °C for 30 min, after which time BnBr (60 μL, 0.50 mmol) and Bu_4NI (1 mg, 0.01 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 (1 mL). The resultant mixture was extracted with $CHCl_3$ (5 × 5 mL) and the combined organic extracts were washed with brine (2 × 10 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 24:1) gave **66** as a colourless oil (88 mg, 89%, 99:1 dr); ν_{max} (film) 3027, 2933, 2859, 1649, 1603, 1494, 1454; δ_H (400 MHz, $CDCl_3$) 1.52-1.68 (2H, m, C(5)H_A, C(6)H_A), 1.74-1.88 (3H, m, C(6)H_B, C(7)H_2), 2.01-2.05 (1H, m, C(5)H_B), 3.46-3.49 (1H, m, C(4)*H*), 3.53 (2H, d, *J* 14.2, N(C$H_A$$H_B$Ph)$_2$), 3.72 (2H, d, *J* 14.2, N(CH$_A$$H_B$Ph)$_2$), 4.11-4.12 (1H, m,

(C(1)*H*), 4.44-4.53 (2H, m, OCH_2Ph), 5.87-5.91 (1H, m, C(2)*H*), 5.98-6.02 (1H, m, C(3)*H*), 7.21-7.40 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.4 (*C*(6)), 26.9 (*C*(5)), 31.4 (*C*(7)), 53.8 (N(*C*H_2Ph)$_2$), 57.4 (*C*(4)), 70.1 (O*C*H_2Ph), 75.2 (*C*(1)), 126.7, 127.4, 127.6, 128.2, 128.3, 128.5 (*o*,*m*,*p-Ph*), 133.2 (*C*(3)), 136.7 (*C*(2)), 138.8, 140.4 (*i-Ph*); *m/z* (ESI^+) 398 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{28}H_{32}NO^+$ ($[M+H]^+$) requires 398.2478; found 398.2478.

(1*RS*,2*RS*,3*SR*,4*RS*)- and (1*RS*,2*SR*,3*RS*,4*RS*)-1-Benzyloxy-2,3-epoxy-4-(*N*,*N*-dibenzylamino)cycloheptane 67 and 68. *Method A. O-Benzylation of* ***64****.* NaH (60% dispersion in mineral oil, 6.8 mg, 0.17 mmol) was stirred at rt for 20 min in pentane (1 mL). The pentane was then decanted under a stream of argon, and THF (1 mL) was added. The resultant suspension was cooled to 0 °C and a solution of **64** (27 mg, 0.083 mmol, >99:1 dr) in THF (0.5 mL) was added dropwise. The resultant suspension was stirred at 0 °C for 30 min, after which time BnBr (20 μL, 0.17 mmol) and Bu_4NI (1 mg, 0.01 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), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 9:1) gave **67** as a colourless oil (17 mg, 55%, >99:1 dr); ν_{max} (film) 3029, 2929, 2851, 1602, 1494, 1453; δ_H (400 MHz, $CDCl_3$) 1.44-1.67 (4H, m, C(5)H_A, C(6)H_2, C(7)H_A), 1.77-1.88 (2H, m, C(5)H_B, C(7)H_B), 3.02 (1H, dd, *J* 4.6, 3.4, C(2)*H*), 3.17-3.22 (1H, m, C(4)*H*), 3.28 (1H, dd, *J* 6.1, 4.6, C(3)*H*), 3. 75 (4H, s, N(*C*H_2Ph)$_2$), 3.95 (1H, ddd, *J* 7.9, 3.4, 1.4, C(1)*H*), 4.43 (1H, d, *J* 12.1, OC$H_A$$H_B$Ph), 4.63 (1H, d, *J* 12.1, OC$H_A$$H_B$Ph), 7.16-7.21, 7.25-7.30, 7.40-7.42 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.2 (*C*(5)), 28.8 (*C*(7), 29.7 (*C*(6)), 54.7 (N(*C*H_2Ph)$_2$), 54.8 (*C*(2)), 55.6 (*C*(3)), 58.4 (*C*(4)), 71.3 (O*C*H_2Ph), 73.4 (*C*(1)), 126.8, 127.1, 127.2, 128.1, 128.2, 128.7 (*o*,*m*,*p-Ph*), 138.8, 140.0 (*i-Ph*); *m/z* (ESI^+) 415 (100%), 414 ($[M+H]^+$, 95%); HRMS (ESI^+) $C_{28}H_{32}NO_2^+$ ($[M+H]^+$) requires 414.2428; found 414.2429.

Method B. O-Benzylation of ***65****.* NaH (60% dispersion in mineral oil, 3.7 mg, 0.092 mmol) was stirred at rt for 20 min in pentane (0.5 mL). The pentane was then decanted under a stream of argon, and THF (0.5 mL) was added. The resultant suspension was cooled to 0 °C and a solution of **65** (15 mg, 0.046 mmol, >99:1 dr) in THF (0.5 mL) was added dropwise. The resultant suspension was stirred at 0 °C 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), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30-40 °C petroleum ether/Et_2O, 9:1) gave **68** as a colourless oil (12 mg, 61%, >99:1 dr); ν_{max} (film)

3030, 2962, 2919, 1603, 1494, 1454; δ_H (500 MHz, $CDCl_3$) 1.14-1.27 (1H, m, C(6)H_A), 1.41-1.52 (3H, m, C(5)H_A, C(6)H_B, C(7)H_A), 1.84-1.97 (2H, m, C(5)H_B, C(7)H_B), 3.12-3.13 (1H, m, C(4)*H*), 3.14-3.15 (1H, m, C(2)*H*), 3.39 (1H, d, *J* 4.4, C(3)*H*), 3.59 (2H, d, *J* 14.0, N(CH_AH$_B$Ph)$_2$), 3.87 (2H, app d, *J* 14.0, N(CH$_A$$H_B$Ph)$_2$), 4.19 (1H, t, *J* 5.1, (C(1)*H*), 4.40 (1H, d, *J* 12.0, OCH_AH$_B$Ph), 4.58 (1H, d, *J* 12.0, OCH$_A$$H_B$Ph), 7.19-7.23, 7.25-7.33, 7.38-7.40 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 19.1 (*C*(6)), 23.1 (*C*(5)), 28.1 (*C*(7)), 54.0 (*C*(4)), 54.3 (N(*C*H$_2$Ph)$_2$), 57.5 (*C*(2)), 60.7 (*C*(3)), 70.8 (O*C*H$_2$Ph), 76.4 (*C*(1)), 126.7, 127.4, 127.6, 128.2, 128.4, 128.6 (*o*,*m*,*p*-*Ph*), 138.3, 140.2 (*i*-*Ph*); *m/z* (ESI$^+$) 436 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{31}NNaO_2^+$ ([M+Na]$^+$) requires 436.2247; found 436.2251.

Method C. Epoxidation of ***66****.* Cl_3CCO_2H (376 mg, 2.30 mmol) was added to a stirred solution of **66** (71 mg, 0.23 mmol, >99:1 dr) in CH_2Cl_2 (0.64 mL, 0.36 M w.r.t **66**) 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. Na_2SO_3 (174 mg, 1.38 mmol) was added and the resultant suspension was stirred until it solidified (~5 min). The resultant mixture was diluted with CH_2Cl_2 (5 mL) and washed with 10% aq. NaOH (3 × 5 mL). The combined aqueous washings were extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried and concentrated in vacuo to give 86% conversion to a 94:6 mixture of **67** and **68**, respectively. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 9:1) gave **68** as a colourless oil (4 mg, 5%, >99:1 dr). Further elution gave **67** as a colourless oil (36 mg, 48%, >99:1 dr).

Kinetics Experiments. Cl_3CCO_2H (10 equiv) was added to a solution of the requisite substrate (1.0 equiv, 1.0 mmol) in CD_2Cl_2 (0.36 M w.r.t. substrate). After five minutes, *m*-CPBA (1.6 equiv) was quickly added to the solution and the ^{1}H NMR spectrum (16 scans) of an aliquot of the resultant solution was recorded immediately and then at regular intervals, without removal of the sample from the NMR spectrometer.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra, and crystallographic information file (for structures CCDC 1562293–1562296). This material is available free of charge via the Internet at http://pubs.acs.org.

† Deceased.

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[28] The rates of epoxidation of 6-NHBn *trans*-**19** and 6-NHBn *cis*-**24** are actually very similar, which may be linked to the *N*-benzylammonium moiety promoting rapid epoxidation of the *syn* face in the six-membered

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