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Syntheses of Dihydroconduramines (±)-B-1, (±)-E-1, and (±)-F-1 via Diastereoselective Epoxidation of N-Protected 4-Aminocyclohex-2-en-1-ols

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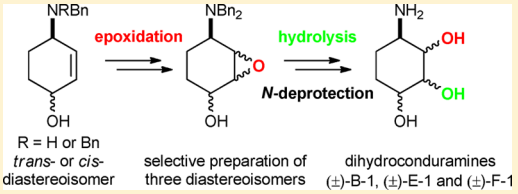
Supporting Information

ABSTRACT: Diastereoselective syntheses of dihydroconduramines (±)-B-1, (±)-E-1, and (±)-F-1 have been achieved from N-protected 4-aminocyclohex-2-en-1-ols via two complementary procedures for epoxidation as the key step. Treatment of either *trans*- or *cis*-4-*N*-benzylaminocyclohex-2-en-1-ol with Cl_3CCO_2H and then *m*-chloroperoxybenzoic acid (*m*-CPBA) resulted in initial formation of the corresponding ammonium species, followed by epoxidation on the face syn to the ammonium moiety exclusively; chemoselective N-benzylation then provided either (1*RS*,2*SR*,3*RS*,4*RS*)- or (1*RS*,2*RS*,3*SR*,4*SR*)-2,3-epoxy-4-*N*,*N*-dibenzylaminocyclohexan-1-ol, respectively. Treatment of either *trans*- or *cis*-4-*N*,*N*-dibenzylaminocyclohex-2-en-1-ol with *m*-CPBA resulted in initial formation of the corresponding *N*-oxide, followed by epoxidation on the face syn to the hydroxyl group exclusively; reduction then provided either (1*RS*,2*RS*,3*SR*,4*RS*)- or an alternative route to (1*RS*,2*RS*,3*SR*,4*SR*)-2,3-epoxy-4-*N*,*N*-dibenzylaminocyclohexan-1-ol, respectively. In all cases, S_N2-type ring opening of these epoxides upon treatment with aqueous H_2SO_4 proceeded by nucleophilic attack with inversion at C(2) preferentially, distal to the in situ formed ammonium moiety. Hydrogenolytic N-deprotection then gave the corresponding dihydroconduramines (±)-B-1, (±)-E-1, and (±)-F-1.



INTRODUCTION

Since the seminal report of Prileschajew in 1909,[1] stereospecific epoxidation of an olefin with a peracid has become a standard part of the organic chemist's synthetic arsenal. Arguably one of the most useful aspects of this reaction is its ability to be directed by an adjacent functional group within the substrate, resulting in a diastereoselective reaction.[2] Perhaps the most well-known example of this phenomenon is the use of an allylic hydroxyl functionality to direct the stereochemical course of epoxidation through formation of a hydrogen bond in the transition state.[3,4] Relatively fewer examples, however, have been reported with ureas,[5] sulfonamides,[6] carbamates,[6−8] amides,[6,7,9−12] or protonated amines[13−15] as the directing groups, with the N−H proton in these systems proposed to act as the hydrogen-bond donor (in the absence of an N−H proton, epoxidation under steric control results).[6,16,17] Within this area, we are currently engaged in a research program concerning the development and deployment of efficient methods to enable the diastereoselective epoxidation of a range of allylic amines.[18] We have reported two complementary methods to effect the formal anti-dihydroxylation of the olefin functionality within 3-*N*,*N*-dibenzylaminocyclohex-1-ene **1** in a diastereodivergent manner.[19,20] Sequential treatment of **1** with Cl_3CCO_2H (5 equiv) and *m*-CPBA (1.6 equiv) was shown to give trichloroacetate ester **4** in 95:5 diastereoisomeric ratio (dr); **4** may be isolated or the crude reaction mixture may be treated with K_2CO_3 in MeOH to give aminodiol **5** in quantitative yield and 95:5 dr (the minor diastereoisomeric product being **9**).[19] This diastereoselectivity is consistent with a mechanism involving initial N-protection by protonation to give the corresponding ammonium species **2**, with subsequent epoxidation proceeding syn to the ammonium moiety, under hydrogen-bonding control. Ring opening then occurs in situ, with high levels of regioselectivity for attack of trichloroacetate anion at C(1), distal to the electron-withdrawing ammonium moiety where its destabilizing electron-withdrawing influence on the transition state is minimized.[21,22] This regioselectivity is also in accordance with the Fürst−Plattner rule.[23] Meanwhile, treatment of **1** with *m*-CPBA (1.5 equiv) gave the corresponding *N*-oxide **6**, which upon further treatment with *m*-CPBA (3 equiv) gave *N*-oxide epoxide **7** in 73:27 dr.[20] This stereochemical outcome is consistent with diastereoselective epoxidation of **6** occurring anti to the *N*-oxide moiety for steric and/or electronic reasons. It was found, however, that addition of Cl_3CCO_2H (10 equiv) to the reaction mixture had a beneficial effect on the diastereoselectivity of this epoxidation reaction, resulting in the production of **7** in 98:2 dr, although under these conditions regioselective ring opening occurred in situ by attack of trichloroacetate anion at C(1), distal to the

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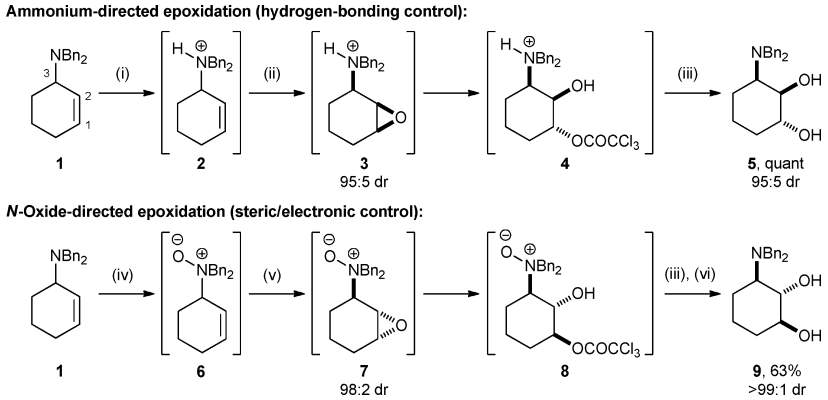
Scheme 1[a]

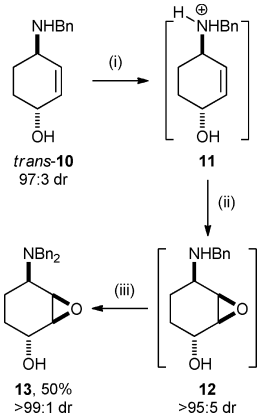


[a]Reagents and conditions: (i) Cl_3CCO_2H (5 equiv), CH_2Cl_2, rt, 5 min. (ii) *m*-CPBA (1.6 equiv), rt, 21 h. (iii) K_2CO_3, MeOH, rt, 16 h. (iv) *m*-CPBA (1.5 equiv), CH_2Cl_2, 0 °C, 30 min. (v) Cl_3CCO_2H (10 equiv), *m*-CPBA (3 equiv), rt, 72 h. (vi) Zn, AcOH, rt, 18 h.

electron-withdrawing (protonated) *N*-oxide moiety, with subsequent treatment with K_2CO_3 in MeOH and finally Zn in AcOH giving aminodiol **9** in 63% isolated yield and >99:1 dr[20] (Scheme 1).

This methodology has been exploited as one of the key steps in the syntheses of a range of natural and nonnatural imino[24,25] and amino[26,27] sugars and other biologically interesting compounds.[28] In continuation of our synthetic endeavors within this area, we became interested in the *trans*- and *cis*-diastereoisomers of N-protected 4-aminocyclohex-2-en-1-ols as substrates for these "ammonium-directed"[19] and "*N*-oxide-directed"[20] epoxidation reactions, in anticipation of being able to develop a means for their diastereodivergent epoxidation. Ring opening of the epoxide products of these reactions would lead to stereodefined 4-amino-1,2,3-triol motifs, which are key structural components in a range of natural and nonnatural products with desirable biological activities. The presence of two potential directing groups within these substrates requires a knowledge of their relative directing abilities for the epoxidation step (the group with higher directing ability is expected to dominate the stereochemical course of the reaction) in order that an appropriate strategy to facilitate a highly diastereoselective reaction can be developed. We have previously established that application of the conditions for "ammonium-directed" epoxidation[19] to secondary *N*-benzyl-protected substrate *trans*-**10** results in formation of a single epoxide product **12** in >95:5 dr.[29] This outcome is due to the far superior directing-group ability of the in situ formed secondary ammonium moiety within **11** over the hydroxyl group, and it demonstrates that a highly diastereoselective reaction is possible in this manifold even when the two directing groups are acting in opposition.[29] Chemoselective N-benzylation of the crude reaction mixture facilitated the isolation of the corresponding *N*,*N*-dibenzyl-protected epoxide **13** in 50% yield from **10** (Scheme 2).[29] We resolved to investigate the behavior of the diastereoisomeric *N*-benzyl-protected substrate *cis*-**15** under the conditions for "ammonium-directed"[19] reaction, as well as epoxidation of the diastereoisomeric *N*,*N*-dibenzyl-protected substrates *trans*-**14** and *cis*-**16** under conditions for "*N*-oxide-directed"[20] reaction. We report herein the results of these studies, which allowed the development of efficient methods for the direct, diastereoselective preparation of three of the four possible diastereoisomers of the intermediate epoxide. Subsequent regioselective ring opening

Scheme 2[a]



[a]Reagents and conditions: (i) Cl_3CCO_2H (10 equiv), CH_2Cl_2, rt, 5 min. (ii) *m*-CPBA (1.6 equiv), rt, 3.5 h. (iii) BnBr, $^iPr_2NEt$, DMAP, CH_2Cl_2, rt, 24 h.

reactions provided the corresponding aminotriols, and final hydrogenolytic N-deprotection gave access to dihydroconduramines (±)-B-1,[30] (±)-E-1,[31,32] and (±)-F-1[33] (Figure 1).

RESULTS AND DISCUSSION

The requisite substrates **14**–**16** for these investigations were prepared from cyclohexa-1,3-diene as previously described.[29] Following the literature procedure for "*N*-oxide-directed"[20] epoxidation, treatment of a solution of *N*,*N*-dibenzyl-protected *trans*-**14** in CD_2Cl_2 with *m*-CPBA (1.5 equiv) and analysis by ^1H NMR spectroscopy after 30 min showed the presence of an approximately 50:50 mixture of two species, assigned as *N*-oxide **17** and *N*-oxide epoxide **18**. Both of these species displayed resonances in their ^1H NMR spectra between ∼4.5 and ∼5 ppm (integrating to a total of four protons), with coupling patterns characteristic of diastereotopic methylene protons of diastereotopic *N*-benzyl groups (AB and AX systems). In order to explore this epoxidation process, a further portion of *m*-CPBA (3 equiv) was added to the reaction mixture. ^1H NMR spectroscopic analysis after a further 8 h revealed complete conversion to *N*-oxide epoxide **18**. Reductive workup (with Na_2SO_3) and chromatographic purification gave the known epoxide **19**[29] in 62% isolated yield. The identity of *N*-oxide epoxide **18** was unambiguously established by

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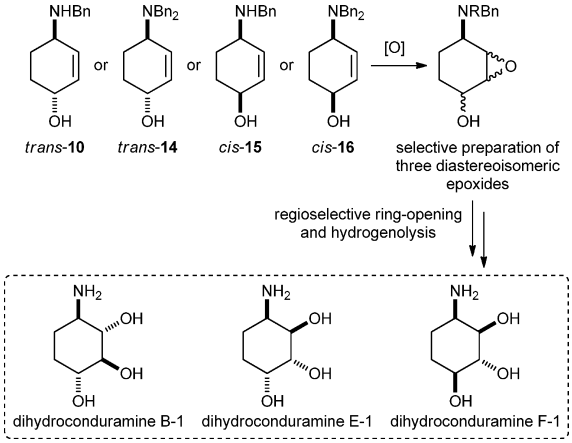
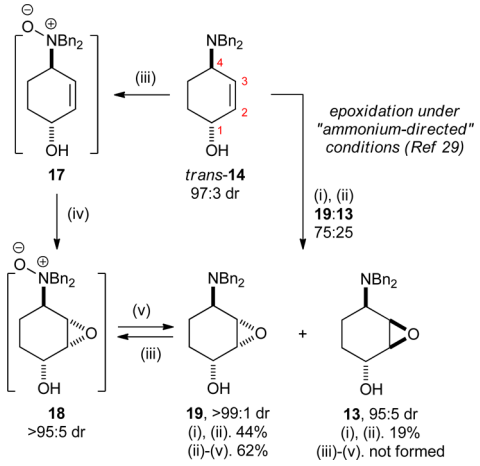


Figure 1. Diastereoselective syntheses of dihydroconduramines B-1, E-1, and F-1 via epoxidation of the *trans*- and *cis*-diastereoisomers of *N*-benzyl- or *N*,*N*-dibenzyl-protected 4-aminocyclohex-2-en-1-ols **10** and **14**–**16** under conditions for "ammonium-directed" or "*N*-oxide-directed" reactions.

treatment of a sample of epoxide **19** in CD_2Cl_2 with *m*-CPBA, which gave a sample of **18** in situ. Thus, the stereochemical outcome of the epoxidation reaction suggests that rapid N-oxidation of **14** is followed by rapid epoxidation of *N*-oxide **17** on the face that is both syn to the hydroxyl group (presumably favored by hydrogen bonding) and anti to the *N*-oxide moiety (presumably favored by the desire to minimize unfavorable steric/electronic interactions). Nonetheless, the high reactivity and high diastereoselectivity elicited upon epoxidation of **17** (even in the absence of Cl_3CCO_2H, in contrast to the behavior of **6**)[20] both suggest that the presence of the hydroxyl group is pivotal in promoting this reaction. It is also instructive to compare the highly diastereoselective outcome of this epoxidation reaction with the previously reported result of treatment of *trans*-**14** under conditions for "ammonium-directed" epoxidation, which gave a 75:25 mixture of epoxides **19** and **13**, respectively, due to the competitive effects of the two directing groups in this case[29] (Scheme 3).

Scheme 3[a]

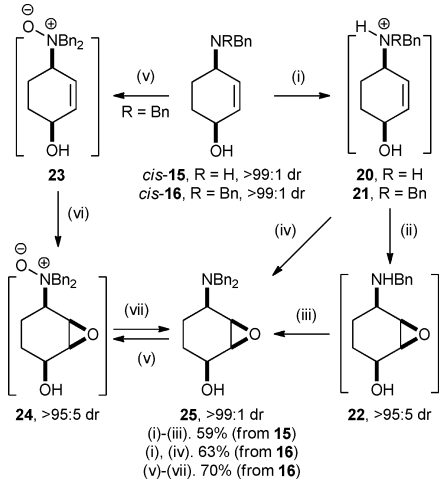


[a]Reagents and conditions: (i) Cl_3CCO_2H (10 equiv), CH_2Cl_2, rt, 5 min. (ii) *m*-CPBA (5 equiv), rt, 3 h. (iii) *m*-CPBA (1.5 equiv), CD_2Cl_2, 0 °C, 30 min. (iv) *m*-CPBA (3 equiv), rt, 8 h. (v) Na_2SO_3.

Epoxidation of *N*-benzyl-protected *cis*-**15** under conditions for "ammonium-directed"[19] reaction was next investigated. Addition of Cl_3CCO_2H (in 1.0 equiv portions) to a 0.36 M solution of **15** (1.0 equiv) in CD_2Cl_2 (monitored by ^1H NMR spectroscopy) formed the corresponding ammonium species **20**, and it was concluded from this experiment that 10 equiv of Cl_3CCO_2H would be required to efficiently protect the nitrogen atom from oxidation within this system.[34] This is consistent with the amount of Cl_3CCO_2H required to protect the diastereoisomeric secondary amine *trans*-**10**.[29] Under conditions analogous to those that we have previously reported to effect epoxidation of ammonium species **2** (i.e., treatment with 1.6 equiv of *m*-CPBA in CH_2Cl_2 at room temperature for 21 h),[19] reaction of **20** gave a complex mixture of products from which epoxide **22** was isolated in only 17% yield and >99:1 dr. The identity of **22**, including its relative configuration, was unambiguously established by single-crystal X-ray diffraction analysis.[35] When the reaction was run for only 3.5 h,[36] epoxide **22** was formed as the major product (in >95:5 dr). In order to facilitate purification, it was found that chemoselective N-benzylation of the crude reaction mixture gave the corresponding *N*,*N*-dibenzylamino epoxide **25**, which was isolated in 59% overall yield from **15**. The identity of **25**, including its relative configuration, was also unambiguously established by single-crystal X-ray diffraction analysis.[35] The stereochemical outcome is consistent with highly diastereoselective epoxidation under hydrogen-bonding direction of either the hydroxyl group or *N*-benzyl ammonium moiety or both. Epoxidation of *N*,*N*-dibenzyl-protected tertiary amine *cis*-**16** under analogous conditions (10 equiv of Cl_3CCO_2H and 5 equiv of *m*-CPBA in CH_2Cl_2 for 21 h)[19] also gave epoxide **25** as a single diastereoisomer (>95:5 dr), which was isolated in 63% yield and >99:1 dr (Scheme 4).

Reaction of *N*,*N*-dibenzyl-protected *cis*-**16** under conditions for "*N*-oxide-directed"[20] epoxidation revealed similar behavior to *trans*-**14**. Treatment of **16** with *m*-CPBA (1.5 equiv) gave an approximately 50:50 mixture of two species, assigned as *N*-oxide **23** and *N*-oxide epoxide **24**. Addition of further *m*-CPBA

Scheme 4[a]



[a]Reagents and conditions: (i) Cl_3CCO_2H (10 equiv), CH_2Cl_2, rt, 5 min. (ii) *m*-CPBA (1.6 equiv), rt, 3.5 h. (iii) BnBr, $^iPr_2NEt$, DMAP, CH_2Cl_2, rt, 24 h. (iv) *m*-CPBA (5 equiv), rt, 21 h. (v) *m*-CPBA (1.5 equiv), CD_2Cl_2, 0 °C, 30 min. (vi) *m*-CPBA (3 equiv), rt, 8 h. (vii) Na_2SO_3.

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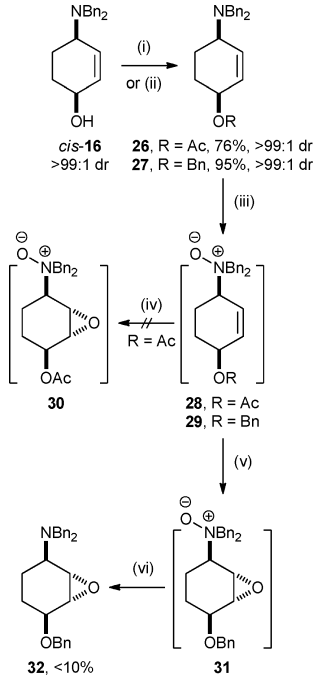
(3 equiv) to the reaction mixture and ^{1}H NMR spectroscopic analysis after a further 8 h showed complete conversion to *N*-oxide epoxide **24**. Reductive workup (with Na_2SO_3) furnished epoxide **25** in 70% isolated yield. The identity of **24** was unambiguously established by treatment of a sample of **25** in CD_2Cl_2 with *m*-CPBA, which gave a sample of **24** in situ. The stereochemical outcome of this epoxidation process is consistent with reaction of **23** being promoted by hydrogen bonding between the hydroxyl group and the oxidant, which overwhelms any steric/electronic effect of the *N*-oxide moiety that might favor epoxidation of the opposite face. Nonetheless, as the favored half-chair conformation of **23** is presumably that which places the sterically demanding *N*-oxide moiety pseudoequatorial, the hydroxyl group would be placed pseudoaxial, and a pseudoaxial hydroxyl group has previously been shown to be only a modest directing group through hydrogen bonding for this transformation in a closely related system.[37] Both the high reactivity and diastereoselectivity observed here are, therefore, noteworthy. Despite the lack of diastereodivergency between reaction under conditions for the "ammonium-directed"[19] epoxidations of *cis*-**15** (and *cis*-**16**), and the "*N*-oxide-directed"[20] epoxidation of *cis*-**16**, the latter procedure offers an alternative and efficient process for preparation of epoxide **25** (Scheme 4).

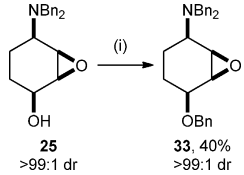
In order to probe further the behavior of *cis*-**16** under the conditions for "*N*-oxide-directed"[20] epoxidation, reaction of the corresponding acetate ester **26** and *O*-benzyl ether **27**, which both lack the capacity for hydrogen bonding through a hydroxyl group, was briefly investigated. Both **26** and **27** were readily prepared from **16** upon treatment with either Ac_2O or NaH/BnBr, respectively. Independent treatment of a solution of either **26** or **27** in CD_2Cl_2 with *m*-CPBA for 30 min gave complete conversion to the corresponding *N*-oxides **28** and **29** only, with no evidence of formation of the corresponding *N*-oxide epoxide species **30** or **31** in either case. Treatment of the sample of **28** with *m*-CPBA (3 equiv) for 24 h resulted in no further reaction; addition of a further portion of *m*-CPBA (3 equiv) and reaction for a further 24 h similarly failed to promote epoxidation, and **28** remained essentially unchanged. Reductive workup resulted in the return of impure starting material **26**. Meanwhile, treatment of **29** with *m*-CPBA (3 equiv) for 24 h gave approximately 25% conversion of **29** to a new species, tentatively assigned as the corresponding *N*-oxide epoxide **31**, alongside the formation of several other unidentified species. Addition of a further portion of *m*-CPBA (6 equiv) and reaction for another 24 h period resulted in formation of a complex mixture of products containing **31** as a major component. Reductive workup and purification unfortunately only allowed isolation of an impure sample of epoxide **32** in <10% yield (Scheme 5). An authentic sample of the diastereoisomeric epoxide **33** was prepared (in 40% yield) via treatment of epoxide **25** with NaH/BnBr, thus supporting the stereochemical assignment of **32**[38] (Scheme 6). The vastly reduced reactivity of both *N*-oxides **28** and **29** (derived from acetate ester **26** and *O*-benzyl ether **27**, respectively) toward epoxidation,[39] as well as the diastereoselectivity of epoxidation of **29**,[38] highlights the importance of the hydroxyl group in promoting reaction of *N*-oxide **23** (derived from **16**) under identical conditions. The differing reactivity of **28** and **29** under these conditions is consistent with the observations of Henbest and Wilson,[3] who noted that the *O*-methyl or *O*-ethyl ethers derived from cyclohex-2-en-1-ol were epoxidized (by peroxybenzoic acid in benzene at 5 °C) approximately 1.5 times

Scheme 5[a]



[a]Reagents and conditions: (i) Ac_2O, DMAP, pyridine, rt, 24 h. (ii) NaH, DMF, 0 °C, 30 min, then BnBr, Bu_4NI, 0 °C to rt, 24 h. (iii) *m*-CPBA (1.5 equiv), CD_2Cl_2, 0 °C, 30 min. (iv) *m*-CPBA (3 equiv), rt, 24 h, then *m*-CPBA (3 equiv), rt, 24 h. (v) *m*-CPBA (3 equiv), rt, 24 h, then *m*-CPBA (6 equiv), rt, 24 h. (vi) Na_2SO_3.

Scheme 6[a]



[a]Reagents and conditions: (i) NaH, DMF, 0 °C, 30 min, then BnBr, Bu_4NI, 0 °C to rt, 24 h.

faster than the corresponding acetate ester derivative. Presumably, an alkoxy functionality is less significantly electron-withdrawing than an acetate ester functionality, which is manifest in greater impedance of the olefin nucleophilicity in the latter case.

In order that its subsequent ring opening could be investigated, Mitsunobu reaction of **19** was used to give access to the C(1)-epimeric epoxide **34**, which was formed as a single diastereoisomer that was isolated in 70% yield (Scheme 7). The identity of **34**, including its relative configuration, was unambiguously established by single-crystal X-ray diffraction analysis.[35]

With samples of all four possible diastereoisomeric epoxides **13**, **19**, **25**, and **34** in hand, attention next turned to the investigation of their ring opening reactions. Treatment of **25** with H_2SO_4 resulted in formation of a single triol **41** in >95:5 dr and in >95% mass return. Chromatographic purification gave **41** in 50% isolated yield and >99:1 dr. The relative configuration within **41** was assigned with the aid of ^{1}H NMR ^3J coupling constant analyses, with the assumption that the favored solution-phase conformation is a chair which places

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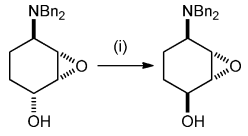
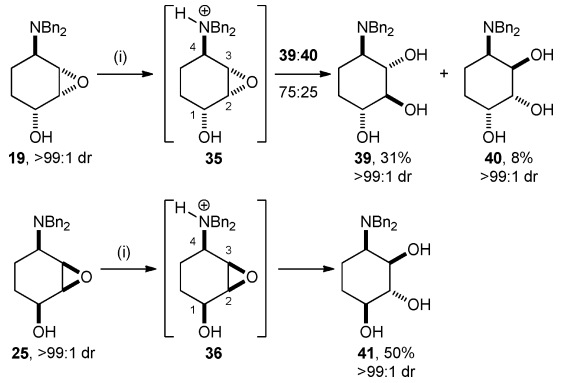
Scheme 7[a]



[a]Reagents and conditions: (i) DEAD, PPh_3, $PhCO_2H$, THF, rt, 16 h, then K_2CO_3, MeOH, rt, 4 h.

the bulky *N*,*N*-dibenzylamino substituent in an equatorial site and is consistent with ring opening of the intermediate ammonium **36** occurring upon regioselective attack of H_2O at C(2). Ring opening of epoxide **19** proceeded with somewhat lower regioselectivity to give a 75:25 mixture of triols **39** and **40**, respectively (>95% mass return), which were isolated in 31% and 8% yield. The relative configuration within **39** was unambiguously established by single-crystal X-ray diffraction analysis[35] while that within **40** was assigned with the aid of ^{1}H NMR ^3J coupling constant analyses, again with the assumption that the favored solution-phase conformation is a chair which places the bulky *N*,*N*-dibenzylamino substituent in an equatorial site; a similar analysis applied to **39** was also supportive of the established configuration. This stereochemical outcome is consistent with attack of H_2O on the intermediate ammonium **35** occurring at both C(2) and C(3) to give the corresponding triols **39** and **40**, respectively (Scheme 8). Under

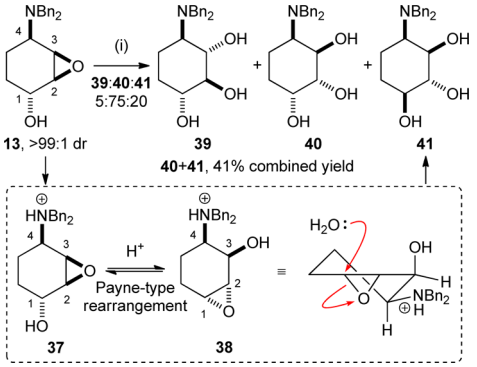
Scheme 8[a]



[a]Reagents and conditions: (i) H_2SO_4, H_2O, dioxane, rt, 12 h.

identical conditions, attempted ring opening of epoxide **34** gave a complex mixture of products, while ring opening of epoxide **13** proceeded to give a 5:75:20 mixture of triols **39**, **40**, and **41**, respectively (>95% mass return). Purification gave a sample of **40** in 14% yield and an 80:20 mixture of **40** and **41** in 27% yield (i.e., **40** and **41** were isolated in a total yield of 41%); triol **39** was not isolated from this reaction. Triols **39** and **40** would arise from direct S_N2-type ring opening of the intermediate epoxide ammonium **37** at C(3) or C(2), respectively, indicating that the ratio of products derived from C(2) versus C(3) attack in this case is 96:4. Formation of triol **41** in this reaction suggests that a competitive Payne-type rearrangement[40] of epoxide ammonium **37** to give epoxide ammonium **38** occurs, and **38** then undergoes regioselective ring opening at C(1), distal to the electron-withdrawing hydroxyl substituent and via a chairlike transition state, in accordance with the Fürst–Plattner rule[23] (Scheme 9). Epoxides **19** and **25** cannot

Scheme 9[a]



[a]Reagents and conditions: (i) H_2SO_4, H_2O, dioxane, rt, 12 h.

undergo an analogous reaction pathway due to the epoxide functionality and hydroxyl group being located on the same face of the six-membered ring scaffold, although this pathway is likely available to epoxide **34** and so may contribute toward the formation of a mixture of products upon its attempted ring opening.

Taken together, and ignoring the alternative Payne-type rearrangement[40] pathway observed with **37**, these results reveal that the ring opening of epoxide ammoniums **35**, **36**, and **37** at C(2) is inherently favored over ring opening at C(3). The primary origin of this selectivity is likely that attack at the carbon atom distal to the in situ formed ammonium moiety is favored in order to minimize its destabilizing inductive electron-withdrawing influence on the transition state,[21,22] irrespective of the relative configuration within the substrate.[41] Nonetheless, the C(1)-epimeric pair of **36** and **37** shows a much higher preference for regioselective ring opening at C(2) than does **35** (>95:5 dr and 94:6 dr, respectively, in the former cases, versus 75:25 dr in the latter). The very high regioselectivity for **36** and **37** parallels the complete regioselectivity observed for ring opening of **3** under identical conditions.[19] This has previously been rationalized by us as arising from reaction of the favored half-chair conformation **3A**, which places the sterically demanding ammonium moiety in a pseudoequatorial site, proceeding via a favored chairlike (rather than disfavored twist-boat-like) transition state (i.e., in accordance with the Fürst-Plattner rule),[23] thus reinforcing the inherent desire to undergo ring opening distal from the ammonium moiety. It is apparent that the introduction of a hydroxyl group in **36** (X = OH, Y = H) or **37** (X = H, Y = OH) plays little or no part in affecting this regioselectivity, which is consistent with ring opening occurring from conformations **36A** and **37A**, respectively (Figure 2).

We have previously observed that ring opening of epoxide **42** proceeds with very high levels of regioselectivity for attack at C(1) of the intermediate epoxide ammonium **43**[42] (Scheme 10). With the apparent desire to undergo ring opening distal to the ammonium moiety being the decisive factor controlling the regioselectivity in this case, this necessitates either ring opening from conformer **43A** (likely the dominant conformer in solution, with the bulky ammonium moiety in a pseudoequatorial position), to traverse an unfavorable twist-boat-like transition state, or ring opening from conformer **43B**, to traverse an unfavorable chairlike transition state with *all* substituents (significantly the bulky ammonium moiety) in pseudoaxial sites. Although the behavior of epoxide ammonium

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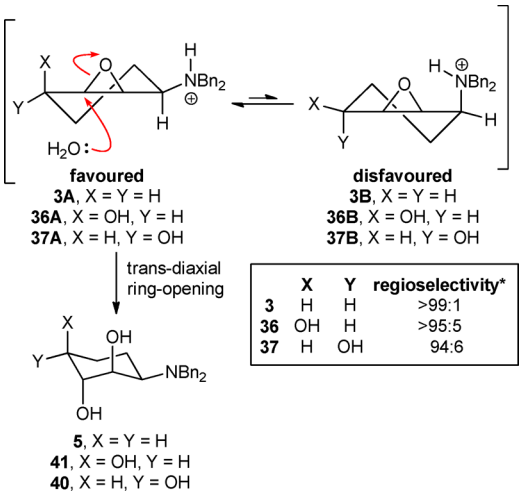
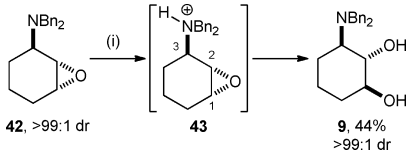


Figure 2. Rationale for regioselectivity of ring opening of epoxide ammoniums **3**, **36**, and **37**. *Regioselectivity refers to the ratio of product resulting from attack at the carbon atom of the epoxide *distal* to the ammonium moiety to product resulting from attack at the carbon atom of the epoxide *proximal* to the ammonium moiety [for **3**, ratio of C(1) vs C(2) attack; for **36** and **37**, ratio of C(2) vs C(3) attack].

Scheme 10[a]



[a]Reagents and conditions: (i) H_2SO_4, H_2O, dioxane, rt, 12 h.

35 under identical conditions shows that the ring opening process is still favored to occur distal to the ammonium moiety, inclusion of an electron-withdrawing heteroatom at C(1) within **35** clearly erodes the dominant effect of the electron-withdrawing ammonium group, meaning that ring opening at C(3) is able to compete in this case (Figure 3).

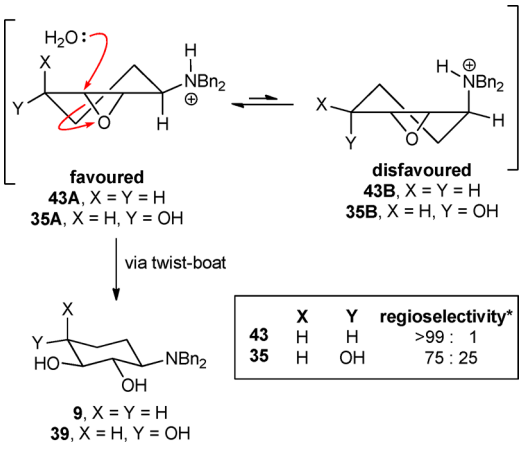
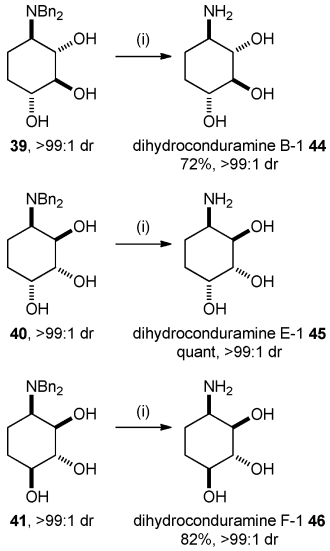


Figure 3. Rationale for regioselectivity of ring opening of epoxide ammoniums **43** and **35**. *Regioselectivity refers to the ratio of product resulting from attack at the carbon atom of the epoxide *distal* to the ammonium moiety to product resulting from attack at the carbon atom of the epoxide *proximal* to the ammonium moiety [for **43**, ratio of C(1) vs C(2) attack; for **35**, ratio of C(2) vs C(3) attack].

With samples of the diastereoisomeric triols **39**–**41** in hand, hydrogenolytic N-deprotection was undertaken. Treatment of **39**–**41** with Pearlman's catalyst [$Pd(OH)_2/C$] under H_2 gave corresponding dihydroconduramines (±)-B-1,[30] (±)-E-1,[31,32] and (±)-F-1[33] (**44**–**46**) in 72% to quantitative yield and as single diastereoisomers in each case. ^{1}H NMR ^3J coupling constant analyses of **44**–**46** were supportive of the assigned relative configurations in each case. Comparison of the ^{1}H and ^{13}C NMR spectroscopic data of these samples of dihydroconduramine (±)-E-1 **45** and dihydroconduramine (±)-F-1 **46** with those previously reported[31−33] showed excellent agreement. Although dihydroconduramine (±)-B-1 **44** has been previously reported,[30] comparison of the spectroscopic data with those of our sample showed only modest agreement. Nonetheless, the stereochemistry of our sample of **44** is secured from single-crystal X-ray diffraction analysis of the precursor **39**. All of these data further confirm the assigned relative configurations within all intermediates (Scheme 11).

Scheme 11[a]



[a]Reagents and conditions: (i) H_2, $Pd(OH)_2/C$, MeOH, rt, 14 h.

CONCLUSION

In conclusion, diastereoselective epoxidation of *N*-protected *trans*- or *cis*-4-aminocyclohex-2-en-1-ols may be achieved by reaction through the corresponding ammonium or *N*-oxide species. Epoxidation of the *N*-benzyl ammonium species proceeds on the face syn to the ammonium moiety, regardless of the relative configuration within the substrate, due to the superior ability of the *N*-benzyl ammonium moiety to direct the stereochemical course of the reaction by hydrogen bonding. Epoxidation of the *N*-oxide species proceeds on the face syn to the hydroxyl group, regardless of the relative configuration of the substrate, indicating that the hydroxyl group is able to direct efficiently the stereochemical course of the reaction by hydrogen bonding, irrespective of the presence of the *N*-oxide moiety. These procedures allow direct preparation of three of the four possible diastereoisomers of 2,3-epoxy-4-*N*,*N*-dibenzylaminocyclohexan-1-ol. Subsequent ring opening of these epoxides upon treatment with aqueous H_2SO_4 proceeds, in all cases, by preferential nucleophilic attack at C(2). This regioselectivity is consistent with ring opening proceeding at

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the carbon atom of the epoxide that is distal to the in situ formed ammonium moiety, in order that its destabilizing electron-withdrawing effect on the transition state is minimized. Hydrogenolytic deprotection of the triol products of these ring opening reactions then furnished the corresponding dihydroconduramines (±)-B-1, (±)-E-1, and (±)-F-1. Further application of this methodology for the synthesis of aminocyclitols is ongoing in our laboratory.

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.[43] *m*-CPBA was supplied as a 70−77% slurry in water and titrated according to the procedure of Swern.[44] Organic layers were dried over Na_2SO_4.

Melting points are uncorrected. IR spectra were recorded by use of an attenuated total reflectance (ATR) module. 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. $^1H-^1H$ correlation spectroscopy (COSY) and $^1H-^{13}C$ heteronuclear multiple quantum coherence (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.[35] Data were collected by use of either graphite monochromated Mo Kα radiation (for **22**, **25**, and **34**) or graphite monochromated Cu Kα radiation (for **39**) 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 by use of CRYSTALS.[45]

(1*RS*,2*RS*,3*SR*,4*RS*)-2,3-Epoxy-4-(*N*,*N*-dibenzylamino)-cyclohexan-1-ol 19. *m*-CPBA (60% by wt, 441 mg, 1.54 mmol) was added to a stirred solution of **14** (300 mg, 1.02 mmol, 97:3 dr) in CD_2Cl_2 (3 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 30 min to give an ∼50:50 mixture of **17** and **18**. Data for **17**: δ_H (400 MHz, CD_2Cl_2) [selected peaks] 1.24−1.34 (1H, m), 1.70−1.82 (1H, m), 2.02−2.10 (1H, m), 2.29−2.36 (1H, m), 4.06−4.13 (1H, m), 4.27−4.36 (1H, m), 4.56 (2H, A_2), 4.63 (1H, d, J = 13.0 Hz), 4.74 (1H, d, J = 13.0 Hz), 5.81−5.86 (1H, m), 5.94−5.99 (1H, m). Further *m*-CPBA (60% by wt, 882 mg, 3.07 mmol) was then added and the resultant mixture was stirred at room temperature for 8 h to give **18** in >95:5 dr: δ_H (400 MHz, CD_2Cl_2) [selected peaks] 1.10−1.20 (1H, m), 1.68−1.80 (2H, m), 2.12−2.22 (1H, m), 2.63 (1H, d, J = 3.5 Hz), 3.26 (1H, dd, J = 3.5, 1.6 Hz), 3.69 (1H, dd, J = 12.5, 6.4 Hz), 3.87 (1H, ddd, J = 10.8, 5.4, 1.6 Hz), 4.56 (1H, d, J = 13.2 Hz), 4.85 (1H, d, J = 13.1 Hz), 4.91 (1H, d, J = 13.1 Hz), 5.04 (1H, d, J = 13.1 Hz). Na_2SO_3 (773 mg, 6.13 mmol) was then added and the reaction mixture was stirred until it solidified (5 min). The resultant mixture was diluted with CH_2Cl_2 (10 mL) and stirred for a further 30 min. Further CH_2Cl_2 (10 mL) was then added and the resultant mixture was washed sequentially with 10% aqueous NaOH (3 × 15 mL) and brine (15 mL) and then dried and concentrated in vacuo to give **19** in >95:5 dr. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O 1:1) gave **19** as a white solid (196 mg, 62%, >99:1 dr):[29] mp 92−95 °C (lit.[29] mp 93−96 °C); δ_H (400 MHz, $CDCl_3$) 1.20−1.28 (1H, m, C(6)H_A), 1.37−1.43 (1H, m, C(5)H_A), 1.72−1.80 (2H, m, C(6)H_B, C(5)H_B), 3.01 (1H, app dd, J = 11.1, 6.0 Hz, C(4)*H*), 3.31−3.32 (1H, m, C(2)*H*), 3.40−3.42 (1H, m, C(3)*H*), 3.66 (2H, d, J = 14.0 Hz, N(C$H_A$$H_B$Ph)$_2$), 3.73 (2H, d, J = 14.0 Hz, N(C$H_A$$H_B$Ph)$_2$), 3.98 (1H, app dd, J = 9.9, 4.8 Hz, C(1)*H*), 7.23−7.41 (10H, m, *Ph*).

(1*RS*,2*RS*,3*SR*,4*SR*)-2,3-Epoxy-4-(*N*-benzylamino)cyclohexan-1-ol 22. *Formation of (RS,SR)-4-(N-Benzylammonio)cyclohex-2-en-1-ol Trichloroacetate **20**.* Cl_3CCO_2H (126 mg, 768 μmol) was added to a solution of **15** (15.6 mg, 77 μmol, >99:1 dr) in CD_2Cl_2 (213 μL, 0.36 M with respect to **15**) to give **20**: δ_H (500 MHz, CD_2Cl_2) 2.05−2.12 (2H, m), 2.24−2.26 (2H, m), 4.10 (1H, app br s), 4.36−4.44 (2H, m), 4.57−4.58 (1H, m), 6.08−6.11 (1H, m), 6.34−6.37 (1H, m), 7.49−7.50 (5H, m), 7.85−7.92 (2H, m).

Epoxidation. Cl_3CCO_2H (667 mg, 4.08 mmol) was added to a stirred solution of **15** (83 mg, 0.41 mmol, >99:1 dr) in CH_2Cl_2 (1.2 mL, 0.36 M with respect to **15**) at room temperature, and the resultant mixture was stirred for 5 min. *m*-CPBA (73% by wt, 154 mg, 0.65 mmol) was subsequently added, and the resultant mixture was stirred for 21 h at room temperature. Saturated aqueous Na_2SO_3 was then added until starch−iodide paper indicated that no *m*-CPBA was present. MeOH (12 mL) and K_2CO_3 (1.13 g, 8.17 mmol) were then added, and the resultant suspension was stirred at room temperature for 4 h before being concentrated in vacuo. H_2O (15 mL) was then added and the mixture was extracted with CH_2Cl_2 (4 × 15 mL). The combined organic extracts were washed with brine (50 mL) and then dried (Na_2SO_4) and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O 1:1) gave **22** as a pale yellow solid (16 mg, 17%, >99:1 dr): mp 81−84 °C; ν_{max} (film) 3315, 2941, 2859, 1602, 1495, 1453; δ_H (400 MHz, $CDCl_3$) 1.46−1.55 (3H, m, C(5)H_2, C(6)H_A), 1.61−1.66 (1H, m, C(6)H_B), 1.81 (1H, br s, O*H*), 2.99 (1H, dt, J = 6.5, 3.0 Hz, C(4)*H*), 3.47 (1H, t, J = 4.0 Hz, C(2)*H*), 3.50−3.52 (1H, dd, J = 4.0, 3.0 Hz, C(3)*H*), 3.95 (2H, app s, NCH_2Ph), 4.02−4.06 (1H, m, C(1)*H*), 7.25−7.40 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 23.3 (*C*(5)), 28.3 (*C*(6)), 50.9 (NCH_2Ph), 51.4 (*C*(4)), 56.7 (*C*(2)), 57.2 (*C*(3)), 65.2 (*C*(1)), 127.1 (*p-Ph*), 128.1, 128.5 (*o,m-Ph*), 140.2 (*i-Ph*); m/z (ESI$^+$) 220 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{18}NO_2^+$ ([M + H]$^+$) requires 220.1332; found 220.1335.

(1*RS*,2*RS*,3*SR*,4*SR*)-2,3-Epoxy-4-(*N*,*N*-dibenzylamino)-cyclohexan-1-ol 25. *Method A (from **15**).* Step 1. Cl_3CCO_2H (4.02 g, 24.6 mmol) was added to a stirred solution of **15** (500 mg, 2.46 mmol, >99:1 dr) in CH_2Cl_2 (6.8 mL, 0.36 M with respect to **15**) at room temperature, and the resultant mixture was stirred at room temperature for 5 min. *m*-CPBA (70% by wt, 970 mg, 3.94 mmol) was subsequently added and the resultant mixture was stirred at room temperature for 3.5 h. Solid Na_2SO_3 (992 mg, 7.87 mmol) was then added, and the resultant suspension was stirred until it solidified (∼5 min). The reaction mixture was then diluted with CH_2Cl_2 (50 mL) and washed with 10% aqueous NaOH (3 × 50 mL). The combined aqueous layers were extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with brine (100 mL) and then dried (Na_2SO_4) and concentrated in vacuo to give **22** in >95:5 dr.

Step 2. BnBr (440 μL, 3.69 mmol), $^iPr_2NEt$ (643 μL, 3.69 mmol), and DMAP (cat.) were added sequentially to a stirred solution of residue **22** from the previous step in CH_2Cl_2 (6.8 mL) at room temperature, and the resultant mixture was stirred at room temperature for 24 h and then diluted with CH_2Cl_2 (50 mL) and washed with H_2O (2 × 50 mL). The combined aqueous washings were extracted with CH_2Cl_2 (100 mL). The combined organic extracts were washed with brine (150 mL) and then dried (Na_2SO_4) and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O 1:1) gave **25** as a white solid (450 mg, 59%, >99:1 dr): mp 81−83 °C; ν_{max} (film) 3417, 2927, 1602; δ_H (400 MHz, $CDCl_3$) 1.27−1.37 (1H, m, C(6)H_A), 1.47−1.54 (1H, m, C(5)H_A), 1.67−1.79 (2H, m, C(5)H_B, C(6)H_B), 2.32 (1H, br s, O*H*), 2.99 (1H, ddd, J = 11.0, 4.7, 1.3 Hz, C(4)*H*), 3.34−3.36 (1H, m, C(2)*H*), 3.52−3.53 (1H, m, C(3)*H*), 3.68 (2H, d, J = 14.0 Hz, N(C$H_A$$H_B$Ph)$_2$), 3.91 (2H, d, J = 14.0 Hz, N(C$H_A$$H_B$Ph)$_2$), 3.98−4.04 (1H, app br s, C(1)*H*), 7.22−7.27 (2H, m, *Ph*), 7.30−7.34 (4H, m, *Ph*), 7.40−7.42 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.6 (*C*(5)), 31.5 (*C*(6)), 54.0 (*C*(2)), 54.6 (N(CH_2Ph)$_2$), 55.1 (*C*(4)), 57.5 (*C*(3)), 63.1 (*C*(1)), 126.9 (*p-Ph*) 128.3, 128.5 (*o,m-Ph*), 140.2 (*i-Ph*); m/z (ESI$^+$) 310 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{24}NO_2^+$ ([M + H]$^+$) requires 310.1802; found 310.1800. $C_{20}H_{23}NO_2$ requires C, 77.6; H, 7.5; N, 4.5; found C, 77.6; H, 7.6; N, 4.5.

*Method B (from **16** via **21**). Formation of (RS,SR)-4-(N,N-Dibenzylammonio)cyclohex-2-en-1-ol Trichloroacetate **21**.* Cl_3CCO_2H (100 mg, 610 μmol) was added to a solution of **16** (17.9 mg, 61 μmol, >99:1 dr) in CD_2Cl_2 (169 μL, 0.36 M with respect to **16**) to give **21**: δ_H (500 MHz, CD_2Cl_2) 1.94−2.00 (1H, m), 2.22−

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2.40 (3H, m), 4.27−4.34 (2H, m), 4.43−4.51 (2H, m), 4.58−4.64 (2H, m), 6.22 (1H, app d, J = 10.4 Hz), 6.44−6.47 (1H, m), 7.43−7.53 (10H, m), 7.99 (1H, m).

Epoxidation. Cl_3CCO_2H (5.57 g, 34.1 mmol) was added to a stirred solution of **16** (1.00 g, 3.41 mmol, >99:1 dr) in CH_2Cl_2 (9.5 mL, 0.36 M with respect to **16**) at room temperature, and the resultant mixture was stirred at room temperature for 5 min. *m*-CPBA (70% by wt, 4.20 g, 17.0 mmol) was subsequently added, and the resultant mixture was stirred at room temperature for 21 h. Solid Na_2SO_3 (4.30 g, 34.1 mmol) was then added, and the resultant suspension was stirred until it solidified (∼5 min). The reaction mixture was then diluted with CH_2Cl_2 (50 mL) and washed with 10% aqueous NaOH (3 × 50 mL). The combined aqueous layers were extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with brine (100 mL) and then dried (Na_2SO_4) and concentrated in vacuo to give **25** in >95:5 dr. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O 1:1) gave **25** as a white solid (664 mg, 63%, >99:1 dr).

*Method C (from **16** via **23**).* *m*-CPBA (60% by wt, 147 mg, 0.51 mmol) was added to a stirred solution of **16** (100 mg, 0.34 mmol) in CD_2Cl_2 (1 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 30 min to give an ∼50:50 mixture of **23** and **24**. Data for **23**: δ_H (400 MHz, CD_2Cl_2) [selected peaks] 1.64−1.74 (1H, m), 1.93−2.01 (1H, m), 2.20−2.28 (1H, m), 2.30−2.40 (1H, m), 4.10−4.14 (1H, m), 4.16−4.22 (1H, m), 4.66 (2H, A_2), 4.77 (1H, d, J = 13.1 Hz), 4.92 (1H, d, J = 13.1 Hz), 5.97−6.04 (1H, m), 6.24 (1H, app d, J = 10.4 Hz). Further *m*-CPBA (60% by wt, 293 mg, 1.02 mmol) was then added, and the resultant mixture was stirred at room temperature for 8 h to give **24** in >95:5 dr: δ_H (400 MHz, CD_2Cl_2) [selected peaks] 1.44−1.55 (1H, m), 1.81−1.90 (1H, m), 1.95−2.04 (1H, m), 2.12−2.24 (1H, m), 3.57 (1H, td, J = 4.3, 1.1 Hz), 3.97 (1H, ddd, J = 10.4, 5.1, 1.1 Hz), 4.09−4.14 (1H, m), 4.22 (1H, app d, J = 4.3 Hz), 4.56 (1H, d, J = 13.1 Hz), 4.62 (2H, A_2), 4.96 (1H, d, J = 13.1 Hz). Na_2SO_3 (258 mg, 2.05 mmol) was then added, and the reaction mixture was stirred until it solidified (5 min). The resultant mixture was diluted with CH_2Cl_2 (1 mL) and stirred for a further 30 min. Further CH_2Cl_2 (10 mL) was then added and the resultant mixture was washed sequentially with 10% aqueous NaOH (3 × 10 mL) and brine (20 mL) and then dried and concentrated in vacuo to give **25** in >95:5 dr. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O 1:1) gave **25** as a white solid (74 mg, 70%, >99:1 dr).

(*RS*,*SR*)-1-Acetoxy-4-(*N*,*N*-dibenzylamino)cyclohex-2-ene 26. Ac_2O (161 μL, 1.70 mmol) and DMAP (cat.) were added sequentially to a stirred solution of **16** (100 mg, 0.34 mmol, >99:1 dr) in pyridine (1.4 mL) at room temperature, and the resultant mixture was stirred at room temperature for 24 h. The resultant solution was diluted with CH_2Cl_2 (5 mL) and washed sequentially with H_2O (2 × 10 mL), saturated aqueous $NaCO_3$ (2 × 10 mL), and brine (10 mL) and then dried (Na_2SO_4) and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O 9:1) gave **26** as a colorless oil (87 mg, 76%, >99:1 dr): ν_{max} (film) 3028, 2943, 1732, 1652, 1603, 1494; δ_H (500 MHz, $CDCl_3$) 1.62−1.69 (1H, m, C(6)H_A), 1.77−1.82 (2H, m, C(5)H_2), 1.92−1.95 (1H, m, C(6)H_B), 2.06 (3H, s, CO*Me*), 3.27−3.31 (1H, m, C(4)*H*), 3.60 (2H, d, J = 14.1 Hz, N(C$H_A$$H_B$Ph)$_2$), 3.75 (2H, d, J = 14.1 Hz, N(C$H_A$$H_B$Ph)$_2$), 5.14 (1H, dt, J = 4.1, 2.4 Hz, C(1)*H*), 5.89−5.92 (1H, m, C(2)*H*), 6.11 (1H, dd, J = 10.1, 1.9 Hz, C(3)*H*), 7.22−7.48 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 18.3 (*C*(5)), 21.4 (CO*Me*), 27.3 (*C*(6)), 54.0 (N(CH_2Ph)$_2$), 54.6 (*C*(4)), 66.3 (*C*(1)), 126.8 (*p-Ph*), 127.0 (*C*(2)), 128.2, 128.5 (*o,m-Ph*), 137.4 (*C*(3)), 140.3 (*i-Ph*), 170.7 (COMe); m/z (ESI$^+$) 336 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{26}NO_2^+$ ([M + H]$^+$) requires 336.1958; found 336.1962.

(*RS*,*SR*)-1-Benzyloxy-4-(*N*,*N*-dibenzylamino)cyclohex-2-ene 27. NaH (60% dispersion in mineral oil, 101 mg, 2.52 mmol) was stirred at room temperature for 20 min in pentane (2 mL). The pentane was then decanted under a stream of argon, and DMF (2 mL) was added. The resultant suspension was cooled to 0 °C, and a solution of **16** (371 mg, 1.26 mmol, >99:1 dr) in DMF (2 mL) was added dropwise. The resultant suspension was stirred at 0 °C for 30 min, after which time BnBr (0.31 mL, 2.52 mmol) and Bu_4NI (cat.) were added sequentially. The resultant mixture was allowed to warm to room temperature, stirred at room temperature for 24 h, and then quenched with H_2O (5 mL). The resultant mixture was extracted with $CHCl_3$ (5 × 10 mL), and the combined organic extracts were washed with brine (2 × 50 mL) and then dried (Na_2SO_4) and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O 19:1) gave **27** as a white solid (460 mg, 95%, >99:1 dr): mp 74−75 °C; ν_{max} (film) 3027, 2935, 2861, 1648, 1603, 1494, 1453; δ_H (400 MHz, $CDCl_3$) 1.46−1.55 (1H, m, C(6)H_A), 1.72−1.77 (1H, m, C(5)H_A), 1.83−1.93 (1H, m, C(5)H_B), 2.01−2.05 (1H, m, C(6)H_B), 3.24−3.28 (1H, m, C(4)*H*), 3.59 (2H, d, J = 14.0 Hz, N(C$H_A$$H_B$Ph)$_2$), 3.76−3.81 (3H, m, C(1)*H*, N(C$H_A$$H_B$Ph)$_2$), 4.55 (1H, d, J = 12.1 Hz, OC$H_A$$H_B$Ph), 4.61 (1H, d, J = 12.1 Hz, OC$H_A$$H_B$Ph), 5.95−6.03 (2H, m, C(2)*H*, C(3)*H*), 7.20−7.41 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.0 (*C*(5)), 26.7 (*C*(6)), 54.0 (N(CH_2Ph)$_2$), 54.9 (*C*(4)), 70.0 (*C*(1)), 70.4 (OCH_2Ph), 126.7, 127.5, 127.6, 128.1, 128.4, 128.6 (*o,m,p-Ph*), 129.0, 135.7 (*C*(2), *C*(3)), 139.0, 140.6 (*i-Ph*); m/z (ESI$^+$) 384 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{30}NO^+$ ([M + H]$^+$) requires 384.2322; found 384.2314.

(*RS*,*SR*)-1-Acetoxy-4-(*N*,*N*-dibenzylamino)cyclohex-2-ene *N*-Oxide 28. *m*-CPBA (60% by wt, 129 mg, 0.45 mmol) was added to a stirred solution of **26** (100 mg, 0.30 mmol, >99:1 dr) in CD_2Cl_2 (1 mL) at 0 °C, and the resultant mixture was stirred for 30 min at 0 °C to give **28**: δ_H (400 MHz, CD_2Cl_2) [selected peaks] 1.66−1.76 (1H, m), 1.99−2.07 (1H, m), 2.10 (3H, s), 2.19 (1H, app qd, J = 13.0, 3.0 Hz), 2.28−2.37 (1H, m), 4.13−4.21 (1H, m), 4.64 (1H, d, J = 12.9 Hz, NC$H_A$$H_B$Ph), 4.73 (1H, d, J = 12.9 Hz, NC$H_A$$H_B$Ph), 4.84 (2H, A_2, NC$H_C$$H_D$Ph), 5.06−5.11 (1H, m), 5.86−5.92 (1H, m), 6.34 (1H, app d, J = 10.6 Hz).

Attempted Preparation of (1*RS*,2*SR*,3*RS*,4*SR*)-1-Benzyloxy-2,3-epoxy-4-(*N*,*N*-dibenzylamino)cyclohexane 32. *m*-CPBA (60% by wt, 112 mg, 0.39 mmol) was added to a stirred solution of **27** (100 mg, 0.26 mmol, >99:1 dr) in CD_2Cl_2 (1 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 30 min at 0 °C to give **29**: δ_H (400 MHz, CD_2Cl_2) [selected peaks] 1.50−1.65 (1H, m), 2.05−2.14 (1H, m), 2.19−2.36 (2H, m), 3.79−3.84 (1H, m), 4.12−4.19 (1H, m), 4.52 (1H, d, J = 11.7 Hz, NC$H_A$$H_B$Ph), 4.56 (1H, d, J = 11.7 Hz, NC$H_A$$H_B$Ph), 4.63 (1H, d, J = 13.2 Hz, NC$H_C$$H_D$Ph), 4.67 (1H, d, J = 13.2 Hz, NC$H_C$$H_D$Ph), 4.79 (2H, app s), 6.00−6.06 (1H, m), 6.25 (1H, app d, J = 10.3 Hz). Further *m*-CPBA (60% by wt, 225 mg, 0.78 mmol) was then added, and the resultant mixture was stirred for 8 h at room temperature to give ∼25% conversion to **31**: δ_H (400 MHz, CD_2Cl_2) [selected peaks] 2.69−2.74 (1H, m), 2.96−3.01 (1H, m), 3.65 (1H, app dd, J = 12.7, 6.1 Hz), 3.91 (1H, app q, J = 2.3 Hz). Further *m*-CPBA (60% by wt, 450 mg, 1.56 mmol) was then added, and the resultant mixture was stirred at room temperature for 24 h. Na_2SO_3 (657 mg, 5.21 mmol) was then added, and the reaction mixture was stirred until it solidified (5 min). The resultant mixture was diluted with CH_2Cl_2 (1 mL) and stirred for a further 30 min. Further CH_2Cl_2 (10 mL) was then added, and the resultant mixture was washed sequentially with 10% aqueous NaOH (3 × 10 mL) and brine (20 mL) and then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O 9:1) gave an impure sample of **32** (<10%, main contaminant *meta*-chlorobenzoic acid). Data for **32**: δ_H (400 MHz, $CDCl_3$) 1.30−1.84 (4H, m, C(5)H_2, C(6)H_2), 3.02 (1H, dd, J = 11.0, 7.0 Hz, C(4)*H*), 3.19−3.23 (1H, m), 3.30−3.33 (1H, app d, J = 3.5 Hz), 3.74 (2H, d, J = 13.9 Hz, N(C$H_A$$H_B$Ph)$_2$), 3.80 (2H, d, J = 13.9 Hz, N(C$H_A$$H_B$Ph)$_2$), 3.93−3.96 (1H, m, C(1)*H*), 4.56 (1H, d, J = 12.0 Hz, OC$H_A$$H_B$Ph), 4.70 (1H, d, J = 12.0 Hz, OC$H_A$$H_B$Ph), 7.22−7.55 (15H, m, *Ph*).

(1*RS*,2*RS*,3*SR*,4*SR*)-1-Benzyloxy-2,3-epoxy-4-(*N*,*N*-dibenzylamino)cyclohexane 33. NaH (60% dispersion in mineral oil, 3 mg, 12 μmol) was stirred at room temperature for 20 min in pentane (0.5 mL). The pentane was then decanted under a stream of argon, and DMF (0.1 mL) was added. The resultant suspension was cooled to 0 °C, and a solution of **25** (18.3 mg, 6.0 μmol, >99:1 dr) in DMF (0.1 mL) was added dropwise. The resultant suspension was stirred at 0 °C for 30 min, after which time BnBr (14 μL, 12 μmol) and Bu_4NI (cat.) were added sequentially. The resultant mixture was

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allowed warm to room temperature, stirred at room temperature for 24 h, and then quenched with H_2O (5 mL). The resultant mixture was extracted with $CHCl_3$ (3 × 8 mL), and the combined organic extracts were washed with brine (10 mL) and then dried (Na_2SO_4) and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O 9:1) gave **33** as a colorless oil (9.2 mg, 40%, >99:1 dr): ν_{max} (film) 3028, 2917, 2849, 1603, 1494, 1264; δ_H (400 MHz, $CDCl_3$) 1.33−1.40 (1H, m, C(6)H_A), 1.46−1.53 (1H, m, C(5)H_A), 1.87−1.97 (2H, m, C(5)H_B, C(6)H_B), 2.98 (1H, ddd, J = 10.2, 5.1, 1.4 Hz, C(4)H), 3.17−3.29 (1H, m, C(2)H), 3.43−3.44 (1H, m, C(3)H), 3.70 (2H, d, J = 14.2 Hz, N(C$H_A$$H_B$Ph)$_2$), 3.78 (1H, dt, J = 6.1, 2.9 Hz, C(1)H), 3.95 (2H, d, J = 14.2 Hz, N(CH$_A$$H_B$Ph)$_2$), 4.64 (1H, d, J = 12.1 Hz, OC$H_A$$H_B$Ph), 4.71 (1H, d, J = 12.1 Hz, OCH$_A$$H_B$Ph), 7.22−7.43 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 16.3 (*C*(6)), 28.2 (*C*(5)), 51.6 (*C*(4)), 54.6 (N(CH_2Ph)$_2$), 54.9 (*C*(2)), 55.1 (*C*(3)), 70.2 (*C*(1)), 70.4 (OCH_2Ph), 126.7, 127.6, 127.8, 128.2, 128.4, 128.5 (*o,m,p-Ph*), 138.4, 140.5 (*i-Ph*); m/z (ESI$^+$) 400 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{29}NNaO_2^+$ ([M + Na]$^+$) requires 422.2091; found 422.2087.

(1*RS*,2*SR*,3*RS*,4*SR*)-2,3-Epoxy-4-(*N*,*N*-dibenzylamino)-cyclohexan-1-ol 34. Diethyl azodicarboxylate (86 μL, 0.55 mmol) was added dropwise via syringe to a stirred solution of **19** (100 mg, 0.33 mmol, >99:1 dr), PPh_3 (169 mg, 0.65 mmol), and $PhCO_2H$ (59 mg, 0.49 mmol) in THF (3.6 mL) at 0 °C. The resultant mixture was allowed to warm to room temperature, stirred at room temperature for 16 h, and then concentrated in vacuo. The residue was dissolved in Et_2O (10 mL) and the resultant solution was washed sequentially with saturated aqueous Na_2SO_3 (3 × 10 mL) and brine (10 mL) and then dried (Na_2SO_4) and concentrated in vacuo. The residue was dissolved in MeOH (10 mL), and K_2CO_3 (223 mg, 1.62 mmol) was added. The resultant suspension was stirred at room temperature for 4 h and then filtered and concentrated in vacuo. The residue was dissolved in Et_2O (10 mL), washed sequentially with H_2O (3 × 10 mL) and brine (10 mL), and then dried (Na_2SO_4) and concentrated in vacuo to give **34** in >99:1 dr. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O 1:1) gave **34** as a colorless oil that solidified to a white solid upon standing (70 mg, 70%, >99:1 dr): mp 111−113 °C; ν_{max} (film) 3420, 3027, 2948, 2804, 1649, 1493, 1453; δ_H (400 MHz, $CDCl_3$) 1.36−1.51 (3H, m, C(5)H_A, C(6)H_2), 1.52−1.74 (2H, m, C(5)H_B, O*H*), 2.94 (1H, app dd, J = 10.9, 6.4 Hz, C(4)H), 3.05 (1H, br s, C(2)H), 3.24 (1H, app d, J = 3.2 Hz, C(3)H), 3.65 (2H, d, J = 13.9 Hz, N(C$H_A$$H_B$Ph)$_2$), 3.71 (2H, d, J = 13.9 Hz, N(CH$_A$$H_B$Ph)$_2$), 4.14−4.18 (1H, m, C(1)H), 7.13−7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.5 (*C*(5)), 25.0 (*C*(6)), 52.5 (*C*(4)), 54.4, 54.7 (*C*(2), N(CH_2Ph)$_2$), 56.1 (*C*(3)), 64.7 (*C*(1)), 127.0 (*p-Ph*), 128.3, 128.4 (*o,m-Ph*), 139.8 (*i-Ph*); m/z (ESI$^+$) 310 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{24}NO_2^+$ ([M + H]$^+$) requires 310.1802; found 310.1813.

(1*RS*,2*SR*,3*SR*,4*RS*)-4-(*N*,*N*-Dibenzylamino)cyclohexane-1,2,3-triol 39. H_2SO_4 (138 μL, 2.59 mmol) and H_2O (2 drops) were added to a stirred solution of **19** (160 mg, 0.52 mmol, >99:1 dr) in 1,4-dioxane (1.5 mL). The resultant mixture was stirred at room temperature for 12 h and then concentrated in vacuo. Saturated aqueous $NaHCO_3$ (2 mL) was added to the residue, and the resultant mixture was extracted with $CHCl_3$/^{i}PrOH (v/v 3:1, 4 × 2 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give a 75:25 mixture of **39** and **40**, respectively. Purification via flash column chromatography (eluent $CHCl_3$/^{i}PrOH, 19:1) gave **39** as a colorless oil that solidified to a white solid upon standing (52 mg, 31%, >99:1 dr): mp 92−94 °C; ν_{max} (film) 3396, 2927, 1494, 1453; δ_H (400 MHz, MeOH-d_4) 0.98−1.10 (1H, m, C(6)H_A), 1.29 (1H, app qd, J = 12.5, 3.5 Hz, C(5)H_A), 1.74−1.88 (2H, m, C(5)H_B, C(6)H_B), 2.34 (1H, ddd, J = 12.5, 10.1, 3.5 Hz, C(4)H), 2.88 (1H, app t, J = 8.8 Hz, C(2)H), 3.17−3.25 (1H, m, C(1)H), 3.32 (1H, dd, J = 10.1, 8.8 Hz, C(3)H), 3.36 (2H, d, J = 13.5 Hz, N(C$H_A$$H_B$Ph)$_2$), 3.74 (2H, d, J = 13.5 Hz, N(CH$_A$$H_B$Ph)$_2$), 7.08−7.24 (10H, m, *Ph*); δ_C (100 MHz, MeOH-d_4) 20.7 (*C*(5)), 31.6 (*C*(6)), 54.9 (N(CH_2Ph)$_2$), 62.5 (*C*(4)), 73.6, 73.8 (*C*(1), *C*(3)), 80.6 (*C*(2)), 128.3 (*p-Ph*), 129.6, 130.2 (*o,m-Ph*), 141.2 (*i-Ph*); m/z (ESI$^+$) 328 ([M + H]$^+$, 100%) HRMS (ESI$^+$) $C_{20}H_{26}NO_3^+$ ([M + H]$^+$) requires 328.1907; found 328.1909. Further elution gave **40** as a colorless oil (13 mg, 8%, >99:1 dr).

(1*RS*,2*RS*,3*RS*,4*RS*)-4-(*N*,*N*-Dibenzylamino)cyclohexane-1,2,3-triol 40. H_2SO_4 (60 μL, 1.13 mmol) and H_2O (2 drops) were added to a stirred solution of **13** (70 mg, 0.23 mmol, >99:1 dr) in 1,4-dioxane (1 mL). The resultant mixture was stirred at room temperature for 12 h and then concentrated in vacuo. Saturated aqueous $NaHCO_3$ (2 mL) was added to the residue, and the resultant mixture was extracted with $CHCl_3$/^{i}PrOH (v/v 3:1, 4 × 2 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give a 5:75:20 mixture of **39**, **40**, and **41**, respectively. Purification via flash column chromatography (eluent $CHCl_3$/^{i}PrOH, 19:1) gave an 80:20 mixture of **40** and **41**, respectively, as a colorless oil (20 mg, 27%). Further elution gave **40** as a colorless oil (10 mg, 14%, >99:1 dr): ν_{max} (film) 3386, 3028, 2938, 1602, 1494, 1453; δ_H (400 MHz, $CDCl_3$/D_2O) 1.49−1.83 (4H, m, C(5)H_2, C(6)H_2), 3.09 (1H, dt, J = 11.3, 3.5 Hz, C(4)H), 3.78 (4H, app s, N(CH_2Ph)$_2$), 3.89−3.97 (1H, m, C(3)H), 4.00 (1H, t, J = 3.8 Hz, C(1)H), 4.15−4.21 (1H, m, C(2)H), 7.19−7.36 (10H, m, *Ph*); δ_C (100 MHz, MeOH-d_4) 21.7 (*C*(5)), 29.1 (*C*(6)), 56.3 (*C*(4)), 56.5 (N(CH_2Ph)$_2$), 69.2 (*C*(1)), 73.9 (*C*(2)), 75.1 (*C*(3)), 127.8 (*p-Ph*), 129.2, 129.9 (*o,m-Ph*), 142.4 (*i-Ph*); m/z (ESI$^+$) 328 ([M + H]$^+$, 100%) HRMS (ESI$^+$) $C_{20}H_{26}NO_3^+$ ([M + H]$^+$) requires 328.1907; found 328.1901.

(1*RS*,2*SR*,3*SR*,4*SR*)-4-(*N*,*N*-Dibenzylamino)cyclohexane-1,2,3-triol 41. H_2SO_4 (146 μL, 2.75 mmol) and H_2O (2 drops) were added to a stirred solution of **25** (170 mg, 0.55 mmol) in 1,4-dioxane (1.5 mL). The resultant mixture was stirred at room temperature for 12 h and then concentrated in vacuo. Saturated aqueous $NaHCO_3$ (2 mL) was added to the residue, and the resultant mixture was extracted with $CHCl_3$/^{i}PrOH (v/v 3:1, 4 × 2 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give **41** in >95:5 dr. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH 9:1) gave **41** as a colorless oil (90 mg, 50%, >99:1 dr): ν_{max} (film) 3386, 3028, 2925, 1602, 1494, 1453; δ_H (400 MHz, MeOH-d_4) 1.54−1.60 (1H, dq, J = 13.0, 3.6 Hz, C(5)H_A), 1.78−1.82 (2H, m, C(6)H_2), 2.11−2.21 (1H, m, C(5)H_B), 3.03 (1H, dt, J = 11.9, 3.6 Hz, C(4)H), 3.72−3.73 (1H, m, C(1)H) overlapping 3.73 (2H, d, J = 14.0 Hz, N(C$H_A$$H_B$Ph)$_2$), 3.85 (1H, t, J = 3.8 Hz, C(2)H), 3.94 (2H, d, J = 14.0 Hz, N(CH$_A$$H_B$Ph)$_2$), 4.09−4.10 (1H, m, C(3)H), 7.17−7.40 (10H, m, *Ph*); δ_C (100 MHz, MeOH-d_4) 16.9 (*C*(5)), 28.2 (*C*(6)), 55.0 (*C*(4)), 55.3 (N(CH_2Ph)$_2$), 70.7 (*C*(1)), 72.1 (*C*(2)), 74.4 (*C*(3)), 126.6 (*p-Ph*), 128.1, 128.7 (*o,m-Ph*), 141.4 (*i-Ph*); m/z (ESI$^+$) 328 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{26}NO_3^+$ ([M + H]$^+$) requires 328.1907; found 328.1907.

(1*RS*,2*SR*,3*SR*,4*RS*)-4-Aminocyclohexane-1,2,3-triol [(±)-Dihydroconduramine B-1] 44. Pd(OH)$_2$/C (20 mg, 50% w/w **39**) was added to a stirred solution of **39** (40 mg, 122 μmol, >99:1 dr) in MeOH (5 mL), and the resultant suspension was stirred at room temperature under H_2 (1 atm) for 14 h. The reaction mixture was then filtered through Celite (eluent MeOH), and the filtrate was concentrated in vacuo to give **44** as a colorless oil (18 mg, 72%, >99:1 dr):[30] δ_H (500 MHz, MeOH-d_4) 1.18−1.42 (2H, m, C(5)H_A, C(6)H_A), 1.79−1.93 (2H, m, C(5)H_B, C(6)H_B), 2.57 (1H, ddd, J = 11.6, 9.4, 4.3 Hz, C(4)H), 3.00 (1H, dd, J = 9.4, 9.1 Hz, C(3)H), 3.11 (1H, dd, J = 9.1, 9.0 Hz, C(2)H), 3.38 (1H, ddd, J = 11.1, 9.0, 4.6 Hz, C(1)H); δ_C (125 MHz, MeOH-d_4) 29.4, 31.3 (*C*(5), *C*(6)), 55.3 (*C*(4)), 74.1, 79.4, 80.0 (*C*(1), *C*(2), *C*(3)).

(1*RS*,2*RS*,3*RS*,4*RS*)-4-Aminocyclohexane-1,2,3-triol [(±)-Dihydroconduramine E-1] 45. Pd(OH)$_2$/C (7 mg, 50% w/w **40**) was added to a stirred solution of **40** (14 mg, 42 μmol, >99:1 dr) in MeOH (0.2 mL), and the resultant suspension was stirred at room temperature under H_2 (1 atm) for 14 h. The reaction mixture was then filtered through Celite (eluent MeOH), and the filtrate was concentrated in vacuo to give **45** as a colorless oil (6 mg, quant, >99:1 dr):[31,32] δ_H (400 MHz, MeOH-d_4) 1.39−1.65 (4H, m, C(5)H_2, C(6)H_2), 3.07 (1H, dt, J = 9.4, 3.3 Hz, C(4)H), 3.74−3.78 (2H, m, C(2)H, C(3)H), 3.83 (1H, dt, J = 8.9, 3.4 Hz, C(1)H).

(1*RS*,2*SR*,3*SR*,4*SR*)-4-Aminocyclohexane-1,2,3-triol [(±)-Dihydroconduramine F-1] 46. Pd(OH)$_2$/C (12 mg, 50% w/w **41**) was added to a stirred solution of **41** (24 mg, 73 μmol, >99:1 dr) in

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MeOH (3 mL), and the resultant suspension was stirred at room temperature under H_2 (1 atm) for 14 h. The reaction mixture was then filtered through Celite (eluent MeOH), and the filtrate was concentrated in vacuo to give **46** as a white solid (9 mg, 82%, >99:1 dr):[33] mp 118−122 °C (lit.[33] mp 120−122 °C); δ_H (400 MHz, MeOH-d_4) 1.50−1.72 (2H, m, C(5)H_A, C(6)H_A), 1.73−1.84 (2H, m, C(5)H_B, C(6)H_B), 3.08−3.20 (1H, m, C(4)H), 3.38−3.63 (3H, m, C(1)H, C(2)H, C(3)H).

■ ASSOCIATED CONTENT

Supporting Information

X-ray crystal structure data for **22**, **25**, **34**, and **39**; ^{1}H NMR spectra for **17**/**18** mixture, **18**, **19**, **21**, **23**/**24** mixture, **24**, **28**, **29**, **45**, and **46**; ^{1}H and ^{13}C NMR spectra for **22**, **25**−**27**, **33**, **34**, **39**−**41**, and **44** (PDF). Crystallographic information files for structures CCDC 1028344−1028347 (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00716.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Prileschajew, N. *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 4811.

(2) For a review of substrate-directed reactions, see Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(3) Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1957**, 1958.

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

(5) Fukushima, D. K.; Smulowitz, M.; Liang, J. S.; Lukacs, G. *J. Org. Chem.* **1969**, *34*, 2702.

(6) O'Brien, P.; Childs, A. C.; Ensor, G. J.; Hill, C. L.; Kirby, J. P.; Dearden, M. J.; Oxenford, S. J.; Rosser, C. M. *Org. Lett.* **2003**, *5*, 4955.

(7) Kocovsky, P.; Stary, I. *J. Org. Chem.* **1990**, *55*, 3236.

(8) Brouillette, W. J.; Saeed, A.; Abuelyaman, A.; Hutchison, T. L.; Wolkowicz, P. E.; McMillin, J. B. *J. Org. Chem.* **1994**, *59*, 4297.

(9) Goodman, L.; Winstein, S.; Boschan, R. *J. Am. Chem. Soc.* **1958**, *80*, 4312.

(10) Lukacs, G.; Fukushima, D. K. *J. Org. Chem.* **1969**, *34*, 2707.

(11) Vince, R.; Daluge, S. *J. Med. Chem.* **1974**, *17*, 578.

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

(13) Asensio, G.; Mello, R.; Boix-Bernardini, C.; Gonzàlez-Núñez, M. E.; Castellano, G. *J. Org. Chem.* **1995**, *60*, 3692.

(14) Edwards, A. S.; Wybrow, R. A. J.; Johstone, C.; Adams, H.; Harrity, J. P. A. *Chem. Commun.* **2002**, 1542.

(15) Aggarwal, V. K.; Fang, G. Y. *Chem. Commun.* **2005**, 3448.

(16) Bäckvall, J.-E.; Oshima, K.; Palermo, R. E.; Sharpless, K. B. *J. Org. Chem.* **1979**, *44*, 1953.

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

(18) For reviews, see (a) Kurosawa, W.; Roberts, P. M.; Davies, S. G. *Yuki Gosei Kagaku Kyokaishi (J. Synth. Org. Chem., Jpn.)* **2010**, *68*, 1295. (b) Davies, S. G.; Fletcher, A. M.; Thomson, J. E. *Org. Biomol. Chem.* **2014**, *12*, 4544.

(19) Aciro, C.; Claridge, T. D. W.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 3751.

(20) Aciro, C.; Davies, S. G.; Kurosawa, W.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *Org. Lett.* **2009**, *11*, 1333.

(21) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737.

(22) Addy, J. K.; Parker, R. E. *J. Chem. Soc.* **1963**, 915.

(23) Fürst, A.; Plattner, P. A. 12th International Congress of Pure and Applied Chemistry: Abstracts of Papers, New York, N.Y. September 10 to 13, 1951; p 409.

(24) Bagal, S. K.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Scott, P. M.; Thomson, J. E. *Org. Lett.* **2010**, *12*, 136.

(25) Bagal, S. K.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Scott, P. M.; Thomson, J. E. *J. Org. Chem.* **2010**, *75*, 8133.

(26) Bagal, S. K.; Davies, S. G.; Fletcher, A. M.; Lee, J. A.; Roberts, P. M.; Scott, P. M.; Thomson, J. E. *Tetrahedron Lett.* **2011**, *52*, 2216.

(27) Csatayová, K.; Davies, S. G.; Ford, J. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2013**, *78*, 12397.

(28) Cresswell, A. J.; Davies, S. G.; Lee, J. A.; Morris, M. J.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2012**, *77*, 7262.

(29) Brennan, M. B.; Davies, S. G.; Fletcher, A. M.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *Aust. J. Chem.* **2015**, *68*, 610.

(30) Łysek, R.; Schütz, C.; Vogel, P. *Helv. Chim. Acta* **2005**, *88*, 2788.

(31) Pandey, G.; Tiwari, K. N.; Puranik, V. G. *Org. Lett.* **2008**, *10*, 3611.

(32) Ahmad, S.; Thomas, L. H.; Sutherland, A. *Org. Biomol. Chem.* **2011**, *9*, 2801.

(33) Łysek, R.; Schütz, C.; Favre, S.; O'Sullivan, A. C.; Pillonel, C.; Krülle, T.; Jung, P. M. J.; Clotet-Codina, I.; Esté, J. A.; Vogel, P. *Bioorg. Med. Chem.* **2006**, *14*, 6255.

(34) Addition of Cl_3CCO_2H to a solution of **15** in CD_2Cl_2 (0.36 M) resulted in a change of chemical shift of the vinylic protons and C(3). The change in chemical shift with increasing amount of Cl_3CCO_2H (versus the free amine) reaches a plateau around 10 equiv, consistent with the ammonium species **20** being predominant under these conditions. This method to determine the amount of Cl_3CCO_2H (or any Brønsted acid) required to efficiently protect the nitrogen atom against oxidation has been shown to give excellent agreement with results derived from experiment (see ref 19).

(35) Full crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 1028344 (**22**), 1028345 (**25**), 1028346 (**34**), and 1028347 (**39**). Copies of these data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(36) Bond, C. W.; Cresswell, A. J.; Davies, S. G.; Kurosawa, W.; Lee, J. A.; Fletcher, A. M.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *J. Org. Chem.* **2009**, *74*, 6735.

(37) Oxidation of *trans*-5-*tert*-butylcyclohex-2-enol has been reported to proceed in 84:16 dr with either peroxybenzoic acid in benzene at 5 °C (ref 4) or *m*-CPBA in CH_2Cl_2 at 0 °C: McKittrick, B. A.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 4895.

(38) The assigned relative configuration within **32** is consistent with epoxidation of *N*-oxide **29** proceeding on the face anti to both the benzyloxy group and *N*-oxide moiety, presumably to minimize unfavourable steric and/or electronic (dipole−dipole) interactions.

(39) The successful epoxidation of a related substrate (i.e., bearing two allylic, nondirecting, heteroatomic groups) has been reported, however, the reaction required refluxing for 3 weeks; see Baran, A.; Balci, M. *J. Org. Chem.* **2009**, *74*, 88.

(40) Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819.

(41) For related examples, see (a) Wolinsky, J.; Thorstenson, J. H.; Killinger, T. A. *J. Org. Chem.* **1978**, *43*, 875. (b) Calvani, F.; Crotti, P.; Gardelli, C.; Pineschi, M. *Tetrahedron* **1994**, *50*, 12999.

(42) Aciro, C.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 3762.

(43) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

(44) Swern, D. *Org. React.* **1953**, *VII*, 392.

(45) Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

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