Ammonium-directed dihydroxylation: metal-free synthesis of the diastereoisomers of 3-aminocyclohexane-1,2-diol†

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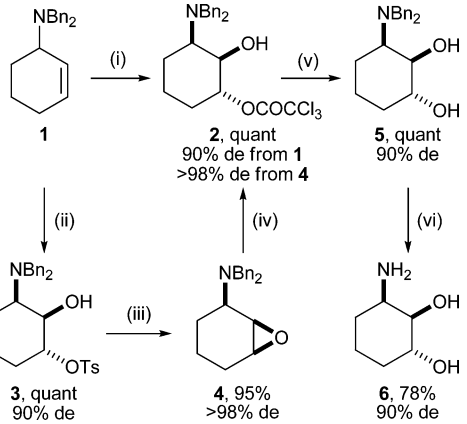
The ammonium-directed, metal-free oxidation of 3-(*N*,*N*-dibenzylamino)cyclohex-1-ene with *m*CPBA in the presence of either trichloroacetic acid or tosic acid has been used as the key step to facilitate the synthesis of all the diastereoisomers of 3-aminocyclohexane-1,2-diol, in >98% de in each case.

Introduction

The vicinal amino diol motif is ubiquitous throughout organic chemistry due to the prevalence of this moiety in natural products and a variety of other biologically and pharmaceutically important compounds.[1] As such, a range of methodologies for the synthesis of this unit in both racemic and homochiral forms has been developed, with arguably the most common methods being based upon dihydroxylation or epoxidation of an allylic amine[2] (or equivalent),[3] or aminohydroxylation[4] or epoxidation[5] of an allylic alcohol. In the preceding manuscript, we reported the development of an ammonium-directed, metal-free dihydroxylation protocol.[6] Treatment of 3-(*N*,*N*-dibenzylamino)cyclohex-1-ene **1** with trichloroacetic acid followed by *m*CPBA furnished 1,2-*anti*-2,3-*syn*-1-trichloroacetoxy-2-hydroxy-3-(*N*,*N*-dibenzylamino)cyclohexane **2** in 90% de, consistent with initial ammonium-directed (hydrogen-bonded) epoxidation occurring on the face of the olefin *syn* to the 3-*N*,*N*-dibenzylamino group, with subsequent epoxide opening occurring exclusively at the C(1)-position. In order to corroborate this mechanistic proposal, treatment of **1** with tosic acid (TsOH) followed by *m*CPBA gave 1,2-*anti*-2,3-*syn*-1-*p*-toluenesulfonyloxy-2-hydroxy-3-(*N*,*N*-dibenzylamino)cyclohexane **3** in 90% de, which underwent base-catalysed elimination of TsOH to give *syn*-epoxide **4**, isolated in >98% de. Subsequent ring-opening of **4** with Cl_3CCO_2H furnished **2** with complete regio- and stereocontrol. Transesterification of **2** (90% de) upon treatment with methanolic K_2CO_3 gave **5** in 90% de. Hydrogenolytic deprotection afforded the corresponding primary amino diol **6** in 78% yield and 90% de (Scheme 1).

It was anticipated that this transformation could be applied as the key step to facilitate the synthesis of all the diastereoisomers of 3-aminocyclohexane-1,2-diol **6–9** (Fig. 1), utilising **3** and **4** as the key intermediates. We have previously communicated a method to effect some of these transformations,[7] although the methods described were not found to be the most robust, reproducible or generally applicable and we therefore describe herein our full investigations into the development and application of a reliable experimental protocol.



Scheme 1 *Reagents and conditions*: (i) Cl_3CCO_2H (5 eq), *m*CPBA, DCM rt, 21 h, then $NaHCO_3$ (0.1 M, aq); (ii) TsOH (3 eq), *m*CPBA, DCM, rt, 21 h, then $NaHCO_3$ (0.1 M, aq); (iii) DBU, DCM, rt, 24 h; (iv) Cl_3CCO_2H, DCM, rt, 16 h, then $NaHCO_3$ (0.1 M, aq); (v) K_2CO_3, MeOH, rt, 16 h; (vi) $Pd(OH)_2/C$, H_2 (1 atm), MeOH, rt, 24 h.

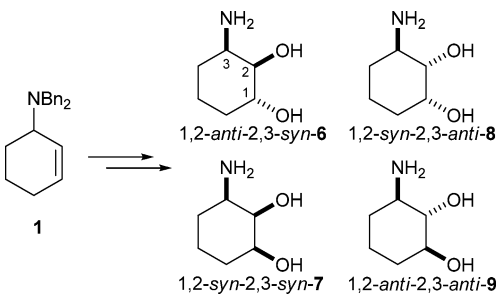


Fig. 1 The diastereoisomers of 3-amino-cyclohexane-1,2-diol **6–9**.

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Results and discussion

Preparation of 1,2-*syn*-2,3-*syn*-3-(*N*,*N*-dibenzylamino)cyclohexane-1,2-diol

Initial studies focused on the synthesis of 1,2-*syn*-2,3-*syn*-**11** from 1,2-*anti*-2,3-*syn*-**3**, *via* C(2)-acetylation and subsequent inversion of configuration at C(1), employing a neighbouring group participation reaction first described by Winstein *et al.*,[8] to give the corresponding 1,2-*syn*-2,3-*syn* relationship (Fig. 2).

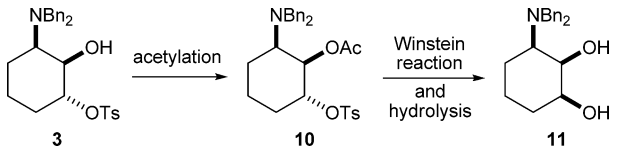
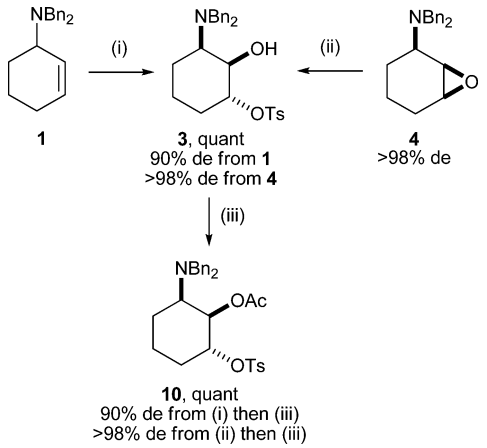


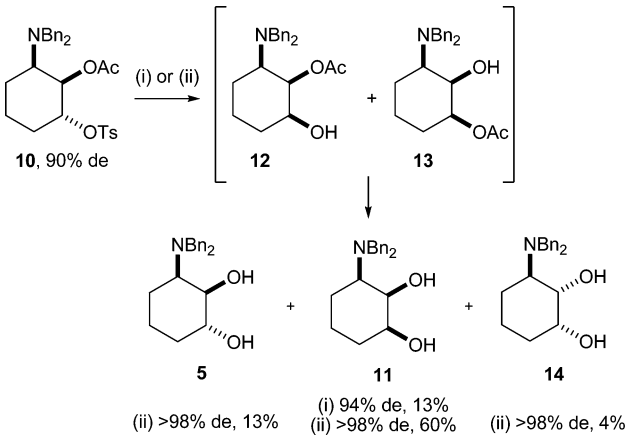
Fig. 2 Proposed strategy for the synthesis of **11**.

Acetylation of **3** (90% de, generated from TsOH promoted, ammonium-directed oxidation of **1** with *m*CPBA) gave **10** in 90% de and quantitative yield. Alternatively, treatment of *syn*-epoxide **4** (>98% de) with TsOH followed by Ac_2O gave **10** in quantitative yield and >98% de (Scheme 2).



Scheme 2 *Reagents and conditions*: (i) TsOH (3 eq), *m*CPBA (1.6 eq), DCM, rt, 21 h, then $NaHCO_3$ (0.1 M, aq); (ii) TsOH, DCM, rt, 16 h, then $NaHCO_3$ (0.1 M, aq); (iii) Ac_2O, DMAP, DCM–pyridine (1 : 1), rt, 24 h, then $NaHCO_3$ (0.1 M, aq).

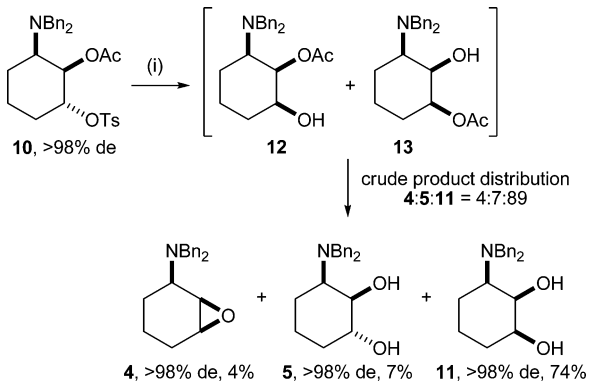
In order to effect a Winstein reaction, **10** (90% de) was subjected to reflux in EtOH–H_2O (6 : 1), and gave a complex mixture of products which, after transesterification with MeOH/K_2CO_3 and column chromatography, gave a 97 : 3 mixture of **11**:**5** (94% de) in 13% yield. Modification of the experimental procedure by addition of $CaCO_3$ also gave a complex mixture of products, although transesterification followed by column chromatography allowed access to **11** in >98% de and an improved 60% yield, along with the diastereoisomers **5** in >98% de and 13% yield, and **14** in >98% de and 4% yield (Scheme 3). The observation of the diastereoisomeric diol **5** in this reaction protocol is indicative of a competing reaction pathway: plausibly **5** arises from acetate hydrolysis of **10** under the basic reaction conditions and subsequent *syn*-epoxide formation followed by *trans*-diaxial ring-opening with hydroxide. 1,2-*syn*-2,3-*anti*-**14** can be envisaged as originating from a Winstein reaction on



Scheme 3 *Reagents and conditions*: (i) EtOH–H_2O (6 : 1), reflux, 48 h, then K_2CO_3, MeOH, rt, 16 h; (ii) EtOH–H_2O (6 : 1), $CaCO_3$, reflux, 48 h, then K_2CO_3, MeOH, rt, 16 h.

the minor 1,2-*anti*-2,3-*anti*-diastereoisomer present in the starting material (*vide infra*).

An alternative procedure reported by Winstein *et al.*[8] was therefore investigated. Treatment of **10** (>98% de) in EtOH–H_2O (6 : 1) with KOAc (1.5 eq) at reflux gave a mixture of products, containing the regioisomeric monoacetates **12** and **13**. Transesterification of this mixture upon treatment with K_2CO_3 in MeOH gave a 4:7:89 mixture of **4**:**5**:**11**. After column chromatography the major product **11** was isolated in >98% de and 74% yield, along with *syn*-epoxide **4** in >98% de and 4% yield, and **5** in >98% de and 7% yield. The stereochemistry within **11** was assigned by a combination of ^{1}H NMR NOE and ^3J coupling constant analyses, assuming that in solution **11** resides preferentially in a chair conformation with the *N*,*N*-dibenzylamino group occupying an equatorial site[9] (Scheme 4).



Scheme 4 *Reagents and conditions*: (i) EtOH–H_2O (6 : 1), KOAc, reflux, 48 h, then K_2CO_3, MeOH, rt, 16 h.

Preparation of 1,2-*anti*-2,3-*anti*-3-(*N*,*N*-dibenzylamino)cyclohexane-1,2-diol

With the 2,3-*syn*-stereoisomeric combinations of 3-(*N*,*N*-dibenzylamino)cyclohexane-1,2-diol **5** and **11** in hand, the preparation of the corresponding 2,3-*anti*-stereoisomers was pursued. It was proposed that the ring-opening of *syn*-epoxide **4** with acetic acid would give **15**. Subsequent activation of the C(2)-hydroxyl as

a leaving group, followed by base-promoted acetate hydrolysis, was then anticipated to facilitate the preparation of *anti*-epoxide **17**. Subsequent acid-promoted epoxide opening was then predicted to give **18** (Fig. 3).

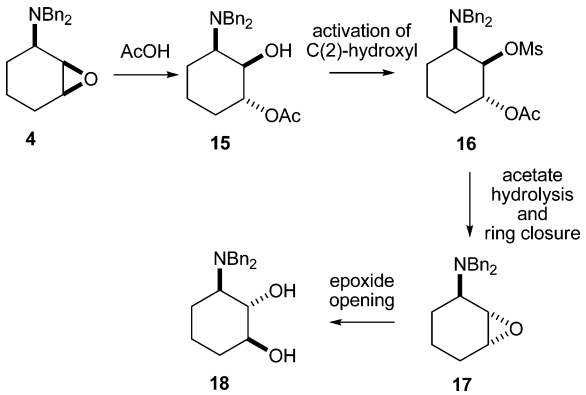
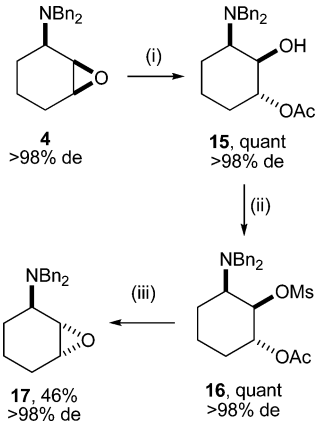


Fig. 3 Proposed strategy for the synthesis of **18**.

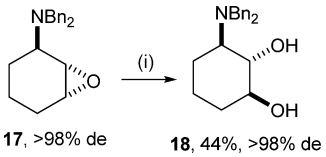
Although treatment of **4** with 10% AcOH (aq) in DCM at rt returned predominantly starting material, with only a trace of the desired ring-opened product (<2%), upon exposure to neat AcOH (5 eq) at 50 °C followed by 0.1 M aq $NaHCO_3$, **15** was furnished in >98% de and quantitative yield. The regiochemistry of epoxide opening, and hence the relative stereochemistry within **15**, was assigned by analogy to that observed during the ring-opening of **4** with Cl_3CCO_2H and TsOH;[6] ^{1}H NMR NOE data obtained on **15** supported this assignment. With **15** in hand, studies focused on the conversion of the C(2)-hydroxyl group to a leaving group. Initial attempts to synthesise the corresponding tosylate *via* treatment with TsCl at either rt or 50 °C, or Ts_2O at 50 °C, were all unsuccessful and returned starting material in each case. Presumably, steric hindrance from the 3-*N*,*N*-dibenzylamino substituent has a pronounced effect in these reactions. While attempted mesylation of **15** at rt generated an intractable mixture of products, mesylation at −78 °C gave 34% conversion to the desired product **16** and at −42 °C, 84% conversion was obtained. Consequently mesylation at −10 °C was attempted, giving **16** in >98% de and quantitative yield. Transesterification of **16** promoted concomitant ring closure, giving *anti*-epoxide **17** in >98% de, which was isolated in >98% de and 46% yield after column chromatography (Scheme 5).

The regioselectivity of ring-opening of *anti*-epoxide **17** upon treatment with a range of Brønsted acids was next investigated as it was predicted that this would facilitate the preparation of the desired 1,2-*anti*-2,3-*anti* relative stereochemistry. It was also anticipated that this would unambiguously establish the nature of the minor diastereoisomeric products observed in studies into the ammonium-directed oxidation protocol, reported in the preceding paper.[6] Thus, in order to access **18** directly, **17** was treated with H_2SO_4 ($pK_a1 = -9$)[10] in 1,4-dioxane, with ring-opening proceeding with complete regio- and diastereocontrol to give **18** in >98% de and 44% yield after basification and column chromatography. ^{1}H NMR NOE and ^3J coupling constant analyses were supportive of the assigned configuration of **18** (Scheme 6).

Subsequent investigations into the ring-opening of **17** with a range of acids revealed that the regioselectivity [ring-opening at C(1) *versus* C(2)] is highly dependent on the strength of the

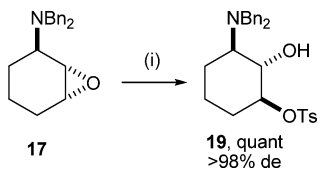


Scheme 5 *Reagents and conditions*: (i) AcOH, 50 °C, 24 h, then $NaHCO_3$ (0.1 M, aq); (ii) MsCl, DMAP, Et_3N, DCM, −10 °C, 48 h; (iii) K_2CO_3, MeOH, rt, 16 h.



Scheme 6 *Reagents and conditions*: (i) H_2SO_4, 1,4-dioxane, rt, 16 h, then $NaHCO_3$ (0.1 M, aq).

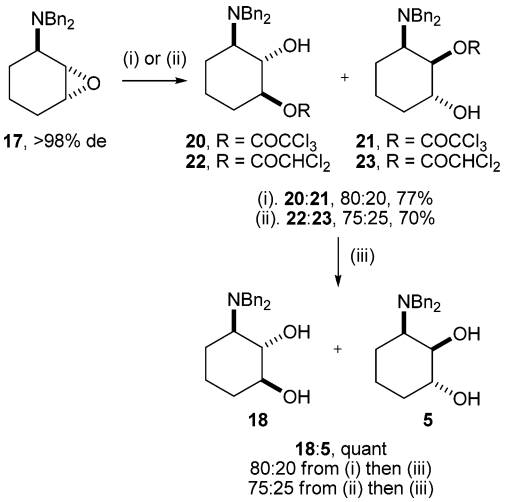
Brønsted acid employed, with the complete C(1)-regioselectivity (as observed with H_2SO_4) being eroded with decreasing strength of the acid. Upon treatment of **17** (>98% de) with TsOH ($pK_a = -6.5$)[10] complete regio- and diastereocontrol was observed giving, after basification, **19** in >98% de and quantitative yield. The relative stereochemistry within **19** was assigned by a combination of ^{1}H NMR NOE and ^3J coupling constant analyses[11] (Scheme 7).



Scheme 7 *Reagents and conditions*: (i) TsOH, DCM, rt, 16 h, then 0.1 M $NaHCO_3$ (aq).

Treatment of **17** (>98% de) with Cl_3CCO_2H (pK_a 0.65)[10] followed by basification gave an 80 : 20 mixture of **20** and **21** in quantitative combined yield. The minor product **21** was assigned as arising from regioisomeric ring-opening of **17** at C(2) based on ^{1}H NMR analysis, which indicated the presence of a multiplet corresponding to C(2)*H* at δ_H 5.36–5.42 ppm: this high δ_H value is not consistent with the presence of the hydroxyl substituent but rather indicates the more electron withdrawing trichloroacetoxy substituent at C(2). Ring-opening of **17** (>98% de) with Cl_2CHCO_2H (pK_a 1.29),[10] gave a 75:25 mixture of **22** and **23** after basification. The minor product **23** exhibited a complex multiplet at δ_H 5.46-5.51 ppm for C(2)*H*, indicating the presence of the dichloroacetoxy substituent at C(2). In both cases the identity of the major 1,2-*anti*-2,3-*anti*-diastereoisomers **20** and **22** was established on the basis of ^{1}H NMR NOE and ^3J coupling constant analyses.[12] The isomeric composition of **20**:**21**

and **22**:**23** was supported by transesterification of the mixtures, which generated 80 : 20 and 75 : 25 diastereoisomeric mixtures of **18**:**5**, respectively (Scheme 8).



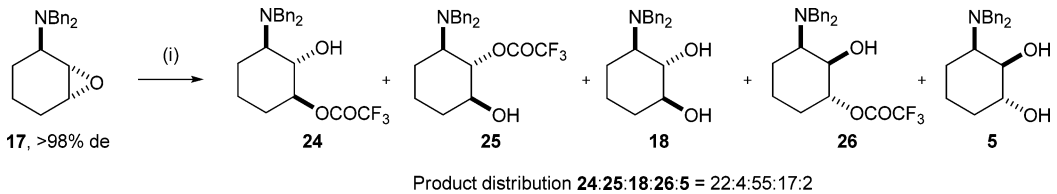
Scheme 8 *Reagents and conditions*: (i) Cl_3CCO_2H, DCM, rt, 16 h, then $NaHCO_3$ (0.1 M, aq); (ii) Cl_2CHCO_2H, DCM, rt, 16 h, then $NaHCO_3$ (0.1 M, aq); (iii) K_2CO_3, MeOH, rt, 16 h.

The ring-opening of *anti*-epoxide **17** with F_3CCO_2H (pK_a = –0.25)[10] was next investigated and gave, after basification, a 22 : 4 : 55 : 17 : 2 mixture of **24**:**25**:**18**:**26**:**5**, respectively (Scheme 9).

^{1}H NMR analysis was used to elucidate the identities of the components of this mixture. **24** was spectroscopically identical to the minor diastereoisomeric product observed upon F_3CCO_2H-promoted ammonium-directed oxidation of tertiary allylic amine **1**.[6] **25** exhibited a complex multiplet at δ_H 5.07–5.14 ppm for C(2)*H* and plausibly originates from an acyl-transfer reaction of **24**, due to the lability of the trifluoroacetyl group under the reaction conditions. **26** was identical by ^{1}H NMR spectroscopic analysis to the major diastereoisomeric product observed upon F_3CCO_2H-promoted ammonium-directed oxidation of **1**, and presumably originates from an acyl-transfer reaction of isomer **27**, where **27** is generated from ring-opening of **17** at C(2). The absence of **27** and the presence of **26** in this mixture may reflect an equilibrium distribution of these species. The observation of diols **18** and **5** is presumably the result of partial trifluoroacetate ester hydrolysis of **24**, **25** and **26** upon aqueous work-up (Fig. 4).

The isomeric composition of this mixture was supported by transesterification, giving an 81 : 19 (*i.e.* [**24**+**25**+**18**]:[**26**+**5**] = 81 : 19) mixture of diastereoisomeric diols **18**:**5** (Scheme 10).

Finally, ring-opening of **17** with AcOH (pK_a 4.76)[10] was investigated, and gave a 44 : 36 : 11 : 9 mixture of **28**:**29**:**30**:**31** respectively (Scheme 11). The stereochemical assignment of 1,2-*anti*-2,3-*anti*-**28** was made by chemical correlation to the corresponding diol **18**, whilst **30** and **31** were identical to the products of a Winstein reaction on mesylate **16** (*vide infra*). 1,2-*anti*-2,3-*syn*-**29** exhibited a complex multiplet at δ_H 3.09–3.16 ppm for C(1)*H* and a complex multiplet at δ_H 5.17–5.22 ppm for C(2)*H*. Thus, the regioselectivity of the ring-opening process is reflected in the ratio of **28** and **29** (*i.e.* the ratio of products resulting from opening at C(1) *versus* C(2) is approximately 1.25 : 1). The observation of the minor 1,2-*syn*-2,3-*anti* products **30** and **31** in this case could support a competing pathway which traverses an aziridinium intermediate **33**, giving rise to monoacetate **31** which may be able to undergo acyl-transfer to give a mixture of **30** and **31** (Fig. 5).[13] This is consistent with observations reported in the preceding manuscript that attempted AcOH-promoted ammonium-directed oxidation of tertiary allylic amine **1** does not result in efficient protonation of the nitrogen atom.[6]



Scheme 9 *Reagents and conditions*: (i) F_3CCO_2H, DCM, rt, 16 h, then $NaHCO_3$ (0.1 M, aq).

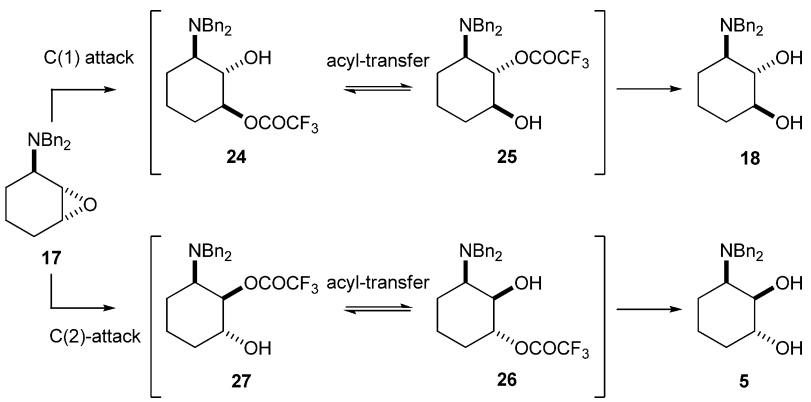
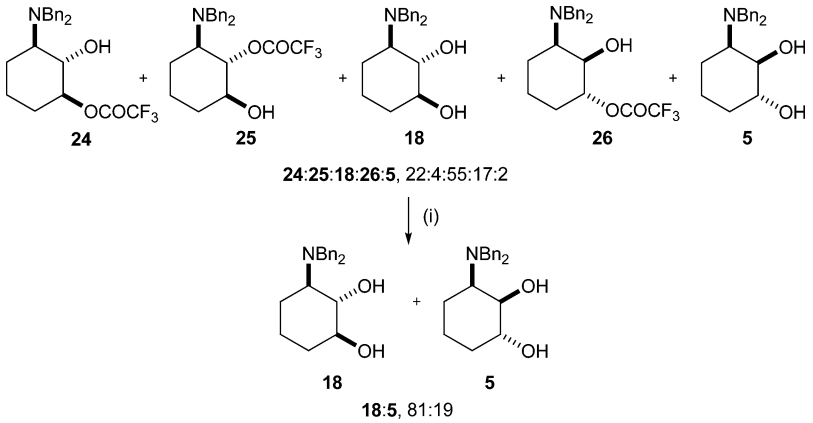
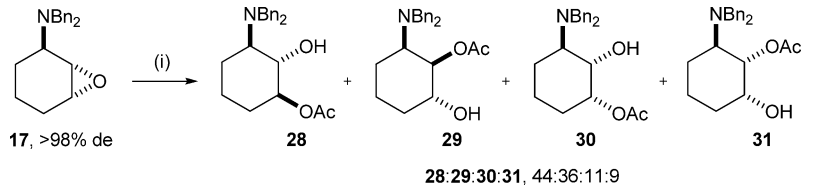


Fig. 4 Ring-opening of **17** upon treatment with F_3CCO_2H.



Scheme 10 *Reagents and conditions*: (i) K_2CO_3, MeOH, rt, 16 h.



Scheme 11 *Reagents and conditions*: (i) AcOH, DCM, 50 °C, 24 h, then $NaHCO_3$ (0.1 M, aq).

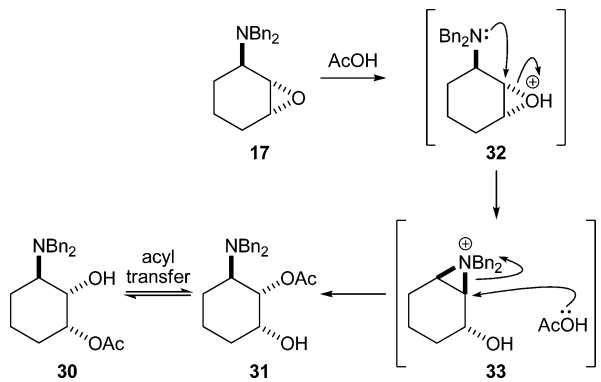
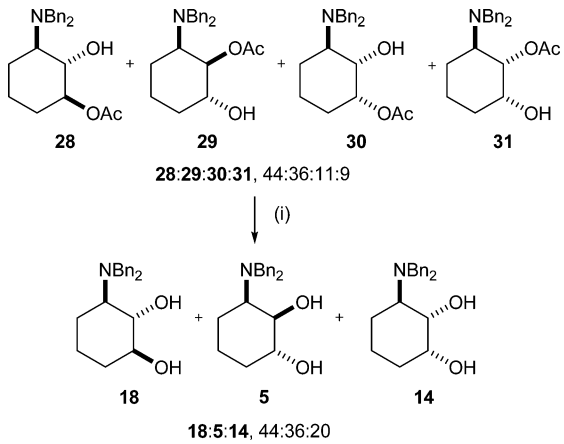


Fig. 5 Postulated mechanism for the formation of **30** and **31** upon ring-opening of **17** with AcOH.



Scheme 12 *Reagents and conditions*: (i) K_2CO_3, MeOH, rt, 16 h.

The isomeric composition of the mixture was confirmed by subsequent transesterification of the mixture of **28**:**29**:**30**:**31** to give a 44 : 36 : 20 mixture of **18**:**5**:**14** (Scheme 12).

These results are in contrast to ring-openings of *syn*-epoxide **4**, which proceed exclusively at C(1) regardless of the strength of the Brønsted acid employed, as rationalised in the preceding manuscript.[6] The regioselectivity observed upon ring-opening of **17** in the case of strong acids such as H_2SO_4 or TsOH, however, is consistent with attack at C(1) being favoured electronically. The ring-opening of epoxides in Brønsted acidic conditions is known to proceed *via* a late transition state:[14] the oxirane carbon atom undergoing nucleophilic attack possesses considerable carbocationic character, which presumably favours nucleophilic attack at C(1) where the effects of the electron-withdrawing *N*,*N*-dibenzylammonium moiety are minimised. C(1) attack on epoxide ammonium **32** presumably occurs in the favoured conformation **32A**, resulting in a twist-boat-like transition state. The alternative attack on C(1), with the epoxide ammonium in conformation **32B**, is presumably disfavoured on steric grounds due to the requirement of the large *N*,*N*-dibenzylammonium group to occupy a pseudo-axial position. However, with decreasing acid strength, attack at C(2) with the epoxide in the favoured conformation **32A** competes, with ring-opening proceeding *via* a chair-like transition state to give the *trans*-diaxial product, in accordance with the Fürst–Plattner rule[15] (Fig. 6).

With the highly diastereoselective synthesis of 1,2-*anti*-2,3-*anti*-**18** achieved, the concluding 1,2-*syn*-2,3-*anti* arrangement was tackled.

Preparation of 1,2-*syn*-2,3-*anti*-3-(*N*,*N*-dibenzylamino)cyclohexane-1,2-diol

It was envisaged that inversion of the configuration at C(2) of 1,2-*anti*-2,3-*syn*-**16** *via* a Winstein protocol would give access to the 1,2-*syn*-2,3-*anti* relationship. Thus, application of the Winstein

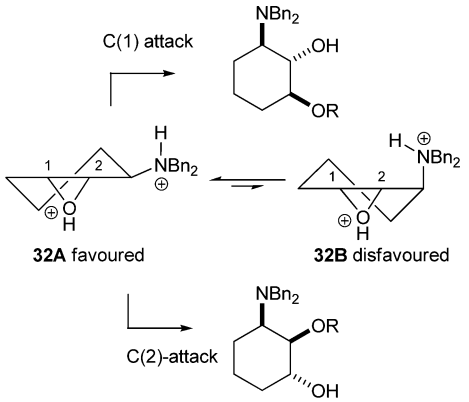
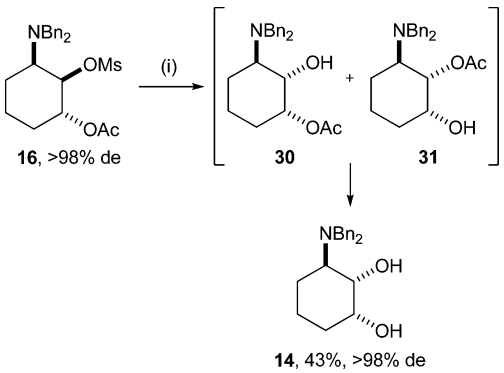


Fig. 6 Ring-opening of **17** in the presence of acid [R = conjugate base of the Brønsted acid].

protocol to **16** gave a mixture containing regioisomeric monoacetates **30** and **31**. Subsequent transesterification gave **14** in >98% de and 43% yield (Scheme 13). ^{1}H NMR NOE and ^{3}J coupling constant analyses of **14** facilitated initial assignment of the relative stereochemistry, and this was subsequently unambiguously proven by single-crystal X-ray analysis† (Fig. 7).



Scheme 13 *Reagents and conditions*: (i) EtOH–H_2O (6 : 1), KOAc, reflux, 48 h, then K_2CO_3, MeOH, rt, 16 h.

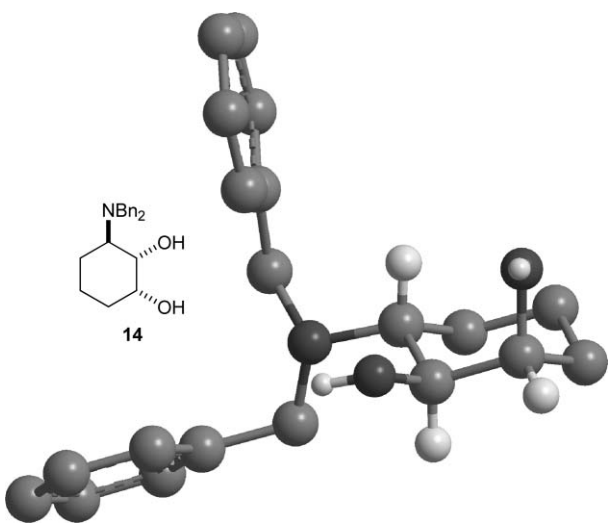
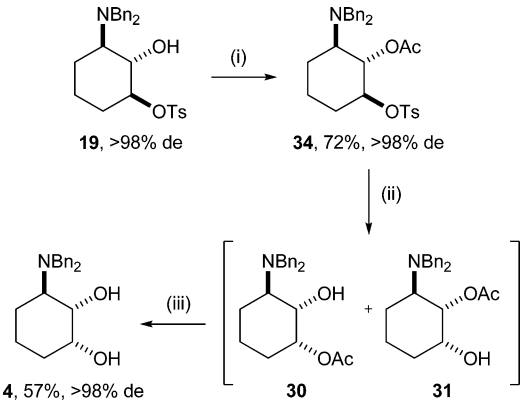


Fig. 7 Chem 3D representation of the X-ray crystal structure of **14** (some H atoms omitted for clarity).

In an alternative preparation of **14** it was predicted that, under Winstein conditions, **19** (prepared from ring-opening of **17** with TsOH) could be used to access the 1,2-*syn*-2,3-*anti* relationship, which would also serve to further corroborate the assigned relative stereochemistry. In accordance with this hypothesis, acetylation of **19** liberated **34** in >98% de and 72% yield. Treatment of **34** with KOAc in EtOH–H_2O generated a mixture containing the regioisomeric monoacetates **30** and **31**. Transesterification of this mixture with K_2CO_3 in MeOH provided **14** as a single diastereoisomer in 57% yield, with identical spectroscopic properties to that prepared from mesylate **16** (Scheme 14).



Scheme 14 *Reagents and conditions*: (i) Ac_2O, DMAP, DCM–pyridine (1 : 1), rt, 24 h, then $NaHCO_3$ (0.1 M, aq); (ii) EtOH–H_2O (6 : 1), KOAc, reflux, 72 h; (iii) K_2CO_3, MeOH, rt, 16 h.

N-Deprotection: Synthesis of the diastereoisomers of 3-aminocyclohexane-1,2-diol

With samples of 3-(*N*,*N*-dibenzylamino)cyclohexane-1,2-diols **11**, **14** and **18** in hand, hydrogenolytic deprotection to the parent amino diols was investigated. By analogy to the hydrogenolysis of **5** (90% de) to **6** reported in the preceding paper, treatment of **5**, **11**, **14** or **18** (>98% de in each case) with $Pd(OH)_2$/C under 1 atm of H_2 gave the corresponding diastereoisomer of 3-aminocyclohexane-1,2-diol **6–9** in >98% de and good to excellent yield (Scheme 15).

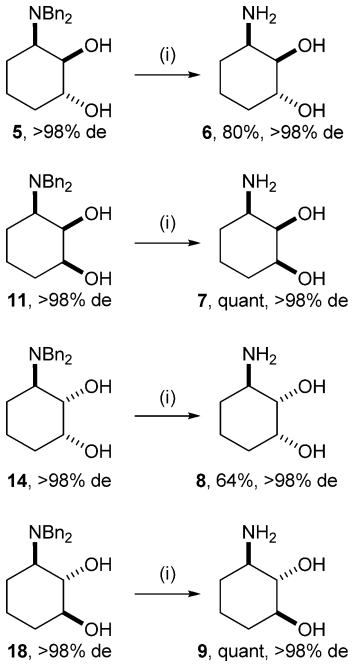
Conclusion

In conclusion, in this manuscript we have demonstrated that the highly diastereoselective, ammonium-directed oxidation of 3-(*N*,*N*-dibenzylamino)cyclohex-1-ene facilitates the stereoselective synthesis of the four diastereoisomers of 3-aminocyclohexane-1,2-diol, in >98% de in each case (Scheme 16). A full evaluation of the scope and limitations of this metal-free dihydroxylation protocol, the development of an enantioselective variant, and the application of this methodology toward amino carbohydrate synthesis are currently under investigation within our laboratory.

Experimental

General experimental

Reactions involving moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame-dried and cooled

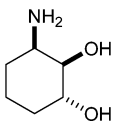


Scheme 15 *Reagents and conditions*: (i) $Pd(OH)_2/C$, H_2 (1 atm), MeOH, rt, 24 h.

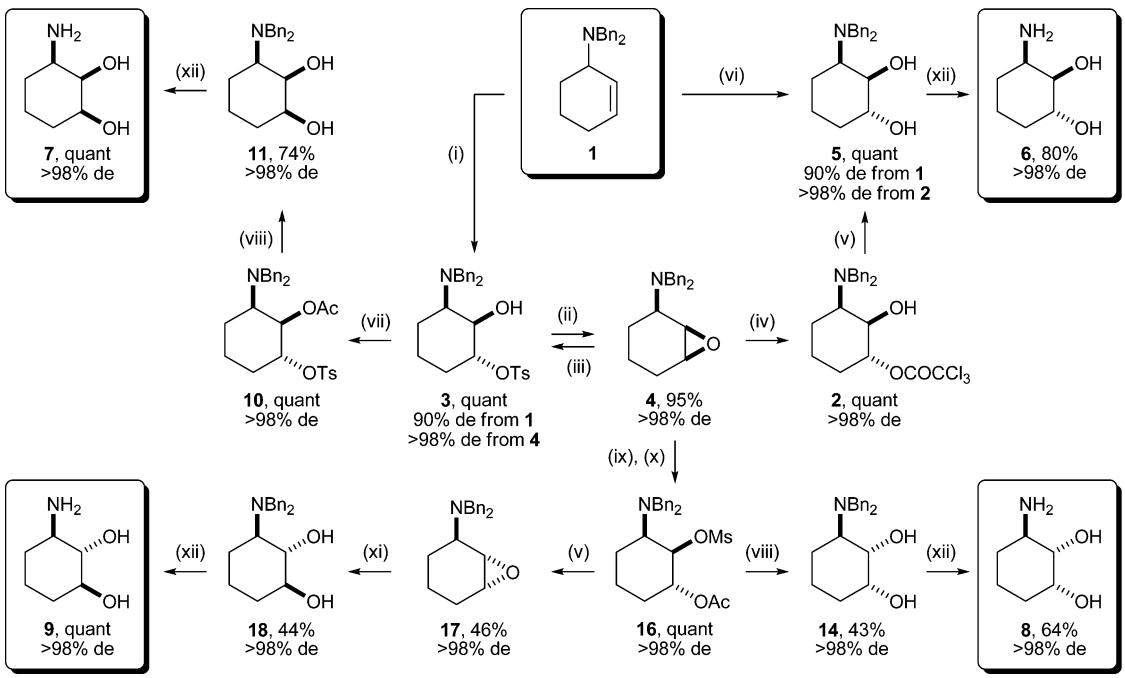
under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[16] Water was purified by an Elix® UV-10 system. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed either on Kieselgel 60 silica on a glass column, or on a Biotage SP4 automated flash column chromatography platform.

Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (film) or a KBr disc (KBr), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. Low-resolution mass spectra were recorded on either a VG MassLab 20-250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass.

(1*RS*,2*RS*,3*RS*)-3-Aminocyclohexane-1,2-diol 6



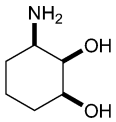
$Pd(OH)_2/C$ (78 mg) was added to a vigorously stirred solution of **5** (157 mg, 0.50 mmol) in degassed MeOH (2 mL) and the resultant suspension was stirred at rt under H_2 (1 atm) for 24 h.



Scheme 16 *Reagents and conditions*: (i) TsOH (3 eq), *m*CPBA, DCM rt, 21 h, then $NaHCO_3$ (0.1 M, aq); (ii) DBU, DCM, rt, 24 h; (iii) TsOH, DCM, rt, 16 h, then $NaHCO_3$ (0.1 M, aq); (iv) Cl_3CCO_2H, DCM, rt, 16 h, then $NaHCO_3$ (0.1 M, aq); (v) K_2CO_3, MeOH, rt, 16 h; (vi) Cl_3CCO_2H (5 eq), *m*CPBA, DCM, rt, 21 h, then K_2CO_3, MeOH, rt, 16 h; (vii) Ac_2O, DMAP, DCM–pyridine (1 : 1), rt, 24 h, then $NaHCO_3$ (0.1 M, aq); (viii) EtOH–H_2O (6 : 1), KOAc, reflux, 48 h, then K_2CO_3, MeOH, rt, 16 h; (ix) AcOH, 50 °C, 24 h, then $NaHCO_3$ (0.1 M, aq); (x) MsCl, DMAP, Et_3N, DCM, –10 °C, 48 h; (xi) H_2SO_4, 1,4-dioxane, rt, 16 h, then $NaHCO_3$ (0.1 M, aq); (xii) $Pd(OH)_2/C$, H_2 (1 atm), MeOH, rt, 24 h.

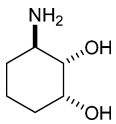
The suspension was then filtered through a pad of Celite (eluent MeOH) and the filtrate was concentrated *in vacuo* to give **6** as a pale yellow solid (53 mg, 80%, >98% de); mp 115–116 °C; ν_{max} (KBr) 3355 (O–H), 2936, 2867 (C–H); δ_H (400 MHz, d_4-MeOH) 1.34–1.46 (1H, m, C(6)H_A), 1.47–1.66 (4H, m, C(4)H_2, C(5)H_2), 1.74–1.87 (1H, m, C(6)H_B), 3.02–3.12 (1H, m, C(3)*H*), 3.52 (1H, dd, *J* 5.3, 3.3, C(2)*H*), 3.74–3.82 (1H, m, C(1)*H*); δ_C (100 MHz, d_4-MeOH) 18.6, 29.2 (*C*(4), *C*(5)), 47.4 (*C*(6)), 49.9 (*C*(3)), 70.0 (*C*(1)), 74.2 (*C*(2)); *m*/*z* (ESI$^+$) 132 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_6H_{14}NO_2^+$ ([M + H]$^+$) requires 132.1019; found 132.1022.

(1*RS*,2*SR*,3*SR*)-3-Aminocyclohexane-1,2-diol 7



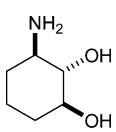
$Pd(OH)_2$/C (121 mg) was added to a vigorously stirred solution of **11** (243 mg, 0.78 mmol) in degassed MeOH (2 mL) and the resultant suspension was stirred at rt under H_2 (1 atm) for 24 h. The suspension was then filtered through a pad of Celite (eluent MeOH) and the filtrate was concentrated *in vacuo* to give **7** as a colourless oil (103 mg, quant, >98% de); ν_{max} (film) 3385 (O–H), 2941, 2867 (C–H); δ_H (400 MHz, d_4-MeOH) 1.11–1.76 (6H, m, C(4)H_2, C(5)H_2, C(6)H_2), 2.59–2.74 (1H, m, C(3)*H*), 3.46–3.59 (1H, m, C(1)*H*), 3.75–3.81 (1H, m, C(2)*H*); δ_C (100 MHz, d_4-MeOH) 21.0, 27.6, 28.2 (*C*(4), *C*(5), *C*(6)), 52.2 (*C*(3)), 71.8 (*C*(1)), 73.2 (*C*(2)); *m*/*z* (ESI$^+$) 132 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_6H_{14}NO_2^+$ ([M + H]$^+$) requires 132.1019; found 132.1020.

(1*RS*,2*SR*,3*RS*)-3-Aminocyclohexane-1,2-diol 8



$Pd(OH)_2$/C (25 mg) was added to a vigorously stirred solution of **14** (54 mg, 0.17 mmol) in degassed MeOH (2 mL) and the resultant suspension was stirred at rt under H_2 (1 atm) for 24 h. The suspension was then filtered through a pad of Celite (eluent MeOH) and the filtrate was concentrated *in vacuo* to give **8** as a white solid (14 mg, 64%, >98%); mp 134–135 °C; ν_{max} (KBr) 3384 (O–H), 2940, 2871 (C–H); δ_H (400 MHz, d_4-MeOH) 1.14–1.27 (1H, m, C(4)H_A), 1.44–1.57 (2H, m, C(5)H_A, C(6)H_A), 1.63–1.78 (1H, m, C(5)H_B), 1.79–1.97 (2H, m, C(4)H_B, C(6)H_B), 2.92–3.03 (1H, m, C(3)*H*), 3.21 (1H, dd, *J* 9.6, 3.1, C(2)*H*), 4.00 (1H, app q, *J* 3.0, C(1)*H*); δ_C (100 MHz, d_4-MeOH) 18.7 (*C*(5)) 31.4 (*C*(6)), 32.2 (*C*(4)), 50.4 (*C*(3)), 67.0 (*C*(1)), 77.3 (*C*(2)); *m*/*z* (ESI$^+$) 132 ([M + H]$^+$, 55%); HRMS (ESI$^+$) $C_6H_{14}NO_2^+$ ([M + H]$^+$) requires 132.1019; found 132.1022.

(1*RS*,2*RS*,3*SR*)-3-Aminocyclohexane-1,2-diol 9



$Pd(OH)_2$/C (55 mg) was added to a vigorously stirred solution of **18** (110 mg, 0.35 mmol) in degassed MeOH (2 mL) and the resultant suspension was stirred at rt under H_2 (1 atm) for 24 h. The suspension was then filtered through a pad of Celite (eluent MeOH) and the filtrate was concentrated *in vacuo* to give **9** as a white solid (47 mg, quant, >98% de); mp 45–46 °C; ν_{max} (KBr) 3356 (O–H), 2934, 2868 (C–H); δ_H (400 MHz, d_4-MeOH) 1.25–1.46 (3H, m, C(4)H_A, C(5)H_A, C(6)H_A), 1.71–1.81 (1H, m, C(5)H_B), 1.88–2.02 (2H, m, C(4)H_B, C(6)H_B), 2.75 (1H, app td, *J* 10.3, 3.7, C(3)*H*), 3.12 (1H, app t, *J* 9,2, C(2)*H*), 3.30–3.43 (1H, m, C(1)*H*); δ_C (100 MHz, d_4-MeOH) 21.3 (*C*(5)), 30.5, 32.9 (*C*(4), *C*(6)), 54.6 (*C*(3)), 73.6 (*C*(1)), 78.6 (*C*(2)); *m*/*z* (ESI$^+$) 132 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_6H_{14}NO_2^+$ ([M + H]$^+$) requires 132.1019; found 132.1022.

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oxidation of tertiary allylic amine **1**, thus confirming unambiguously the nature of the minor diastereoisomer in this process; see ref. 6.
12 The major diastereoisomers **20** and **22** were spectroscopically identical to the minor diastereoisomeric products observed upon Cl_3CCO_2H- and Cl_2CHCO_2H-promoted ammonium-directed oxidation of tertiary allylic amine **1** respectively, thus confirming unambiguously the nature of the minor diastereoisomers in these processes; see ref. 6.
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