Special Issue Article

Journal of Physical Organic Chemistry

Received: 23 April 2013, Revised: 14 June 2013, Accepted: 3 July 2013, Published online in Wiley Online Library: 14 August 2013

(wileyonlinelibrary.com) DOI: 10.1002/poc.3183

Reactions of nitrogen nucleophiles with enantiopure cyclohexenyl electrophiles: a stereo- and regio- selective study†‡

Derek R. Boyd[a]*, Narain D. Sharma[a], Tayeb Belhocine[a], John F. Malone[a], Stuart T. McGregor[a], Jordan Atchison[a], Peter A. B. McIntyre[a] and Paul J. Stevenson[a]*

The reactions of enantiopure cyclohexene epoxides and *trans*-1,2-bromoacetates, derived from the corresponding substituted benzene *cis*-dihydrodiol metabolites, with nitrogen nucleophiles, were examined and possible mechanisms proposed. An initial objective was the synthesis of new 1,2-aminoalcohol enantiomers as potential chiral ligands and synthetic scaffolds for library generation. These apparently simple substitution reactions proved to be more complex than initially anticipated and were found to involve a combination of different reaction mechanisms.

Allylic *trans*-1,2-azidohydrins were prepared by Lewis acid-catalysed ring-opening of cyclic vinyl epoxides with sodium azide *via* an S_N2 mechanism. On heating, these *trans*-1,2-azidohydrins isomerized to the corresponding *trans*-1,4-azidohydrins *via* a suprafacial allyl azide [3,3]-sigmatropic rearrangement mechanism. Conversion of a 1,2-azidohydrin to a 1,2-azidoacetate moved the equilibrium position in favour of the 1,4-substitution product. Allylic *trans*-1,2-bromoacetates reacted with sodium azide at room temperature to give C-2 and C-4 substituted products. A clean inversion of configuration at C-2 was found, as expected, from a concerted S_N2-pathway. However, substitution at C-4 was not stereoselective and resulted in mixtures of 1,4-*cis* and 1,4-*trans* products. This observation can be rationalized in terms of competitive S_N2 and S_N2' reactions allied to a [3,3]-sigmatropic rearrangement. *cis*-1,2-Azidohydrins and *cis*-1,2-azidoacetates were much more prone to rearrange than the corresponding *trans*-isomers.

Reaction of the softer tosamide nucleophile with *trans*-1,2-bromoacetates resulted, predominantly, in C-4 substitution *via* a *syn*-S_N2' mechanism. One application of the reaction of secondary amines with allylic cyclohexene epoxides, to give *trans*-1,2-aminoalcohols, is in the synthesis of the anticholinergic drug vesamicol, *via* an S_N2 mechanism.

Supporting information may be found in the online version of this paper.

Keywords: dihydrodiols; vinyl epoxides; bromoacetates; S_N2, S_N2'; sigmatropic rearrangement mechanisms

INTRODUCTION

Mutant strains of the bacterium *Pseudomonas putida*, *e.g.* 39/D or UV4, and *Escherichia coli* recombinant bacterial strains, *e.g.* JM109(pDTG601) or CL-4 t, each containing the toluene dioxygenase enzyme (TDO), can catalyse the *cis*-dihydroxylation of a wide range of monocyclic aromatic substrates **1**, in both regio- and stereo-selective manner. The resulting highly functionalized *cis*-dihydrodiols **2** (Scheme 1) have enormous potential as chiral building blocks in organic synthesis.[1,2] A major advantage of this biocatalytic route is that these processes are easily and cheaply scaled to give large quantities (multigram to kilogram) of enantiopure monocyclic arene *cis*-1,2-dihydrodiols **2**, *e.g.* R = Cl (**2a**), Br (**2b**), and Ph (**2c**). To date, these compounds have been extensively used in the synthesis of homochiral natural products, including alkaloids,[2–5] and of novel chiral ligands required for transition metal catalysis.[6,7a-d] The unsubstituted alkene bond in these *cis*-dihydrodiol bioproducts **2** can be regioselectively reduced by catalytic hydrogenation to give the much more stable, and easier to handle, *cis*-tetrahydrodiol precursors **3**, *e.g.* R = Cl (**3a**), Br (**3b**), and Ph (**3c**) and ultimately their electrophilic derivatives **4** and **5**.[6,8]

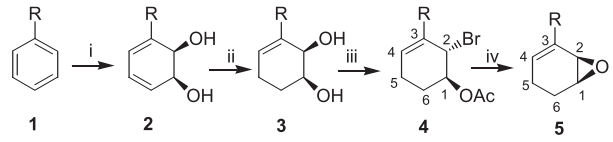
In this context, we became interested in activating, and indirectly replacing, the allylic hydroxyl group in *cis*-tetrahydrodiols **3** with nitrogen nucleophiles *via* electrophilic compounds of type **4** and **5**. This was initially considered as a possible route to a new range of monocyclic 1,2-aminoalcohols. It was, however, recognized that, in general, the reaction of nucleophiles with allylic electrophiles may be more complex due to a number of factors. For compounds **4** and **5** (Scheme 1), a regiochemical issue arises, as there are two possible electrophilic positions for

* *Correspondence to: Paul Stevenson and Derek Boyd, School of Chemistry and Chemical Engineering, Queen's University, Belfast, BT9 5AG, UK. E-mail: p.stevenson@qub.ac.uk, dr.boyd@qub.ac.uk*

† *This article is dedicated to the memory of Professor Rory A. More O' Ferrall, an excellent scientist and a wonderful friend.*

‡ *This article is published in Journal of Physical Organic Chemistry as a Special issue: In Memoriam edited by Michael Page (University of Huddersfield, Chemistry, Queensgate, Huddersfield, HD1 3DH, United Kingdom).*

a *D. R. Boyd, N. D. Sharma, T. Belhocine, J. F. Malone, S. T. McGregor, J. Atchison, P. A. B. McIntyre, P. J. Stevenson*
School of Chemistry and Chemical Engineering, Queen's University, Belfast, BT9 5AG, UK

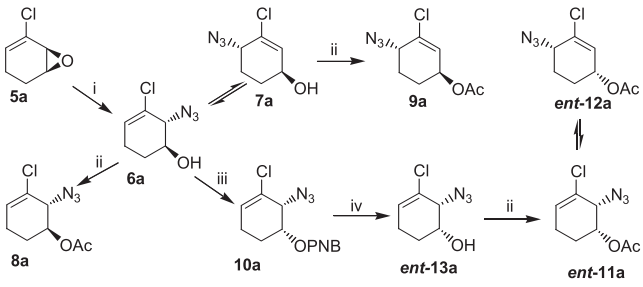


Scheme 1. Synthesis of compounds **2–5**

nucleophilic attack resulting in direct substitution (C-2) or indirect substitution with allylic rearrangement (C-4, Scheme 2). Furthermore, there are stereochemical issues where the nucleophile can add either *syn* or *anti* with respect to the leaving group. If the C-2 substitution proceeds *via* an S_N2 mechanism, then inversion of configuration is expected. Substitution *via* an S_N1 pathway may lead to loss of stereochemical integrity at C-2 (with either inversion or retention of configuration), and the delocalized allylic carbocation (C-2/C-4) may react at either position with no stereoelectronic preference again leading to mixtures of diastereoisomers. If C-4 substitution is a true bimolecular process, in which the nucleophile approaches the alkene first, then this reaction is classically described as S_N2'.[9] In the case of an acyclic allyl electrophile undergoing an S_N2' reaction, the nucleophile adds *syn* with respect to the leaving group, with the electrophile reacting from either an *s-cis* or *s-trans* conformation; this conformational flexibility adds further complexity to any stereochemical analysis of the reaction. Reactions of allylic electrophiles with organometallic reagents may result in allylic rearrangement, with formal *anti*-addition of the alkyl group, but it is unlikely that these reactions proceed *via* a concerted S_N2' mechanism.[10] The detailed mechanisms for these processes are undoubtedly multistep, involving organometallic intermediates. There is continuing intense interest in the development of new chiral ligands for reactions of this type involving both achiral and racemic allylic electrophiles[11] leading to chiral products with high *ee* values. In this context, the current study of the structure/stereochemistry of products, and possible mechanisms involved in the reactions of nitrogen nucleophiles with the chiral electrophilic cycloalkenes **4** and **5**, was undertaken.

RESULTS AND DISCUSSION

The potential of enantiopure arene *cis*-1,2-diol scaffolds **2** and **3**, derived from our continuing biotransformation programme on substituted arenes **1**, as precursors of a new range of monocyclic 1,2-aminoalcohol ligands, was examined. This would ideally involve cleanly substituting an allylic leaving group with a range of nitrogen nucleophiles in a predictable stereo- and regioselective fashion. Extensive studies have previously been carried out on ring-opening reactions of cyclohexenyl epoxides and mesylate displacements with nitrogen nucleophiles including azides.[12] In most cases, the products of such reactions have been successfully employed in the early stages of complex organic synthetic sequences thus indicating that these reactions generally proceed in an efficient manner.



Scheme 2. Substitution reaction of epoxide **5a** with sodium azide and rearrangement products

(i) Synthesis of *trans*-bromoacetates 4a–c and epoxides 5a–c

The previously described biotransformation of chlorobenzene **1a**, bromobenzene **1b**, and biphenyl **1c**, using whole cells of *P. putida* UV4, gave the corresponding relatively unstable *cis*-dihydrodiol metabolites **2a–c** which were found to readily dehydrate to give phenols.[13] This prompted the synthesis of the corresponding substituted cyclohexenes **3a–c**, **4a–c**, and **5a–c** as more stable derivatives. Regioselective catalytic hydrogenation of the unsubstituted alkene double bond gave the corresponding *cis*-tetrahydrodiols **3a–c** (Scheme 1).[14] Chemoselective activation of diols **3a–c** was readily accomplished using Maddock's reagent (1-bromocarbonyl-1-methylethyl acetate)[15] and gave *trans*-bromoacetates **4a–c**.[14] Using sodium methoxide as base, treatment of compounds **4a–c**, gave the corresponding vinyl epoxides **5a–c**.[14] The new phenyl-substituted compounds **3c–5c** were synthesized and characterized while compounds **2a–c**, **3a**, **3b**, **4a**, **4b**, **5a**, and **5b** had been reported earlier and were available for this study.[14] Cyclic compounds **4** and **5** were considered as ideal substrates for studying subsequent stereo- and regio-selective reactions, as all the possible products of these reactions were readily identified and distinguished by NMR spectroscopy. Furthermore, for geometrical reasons, all of the compounds studied adopted *s-cis* conformations, which greatly simplified subsequent stereochemical analysis. As larger quantities of *cis*-dihydrodiols **2a** and **2b** and their derivatives, **3a**, **3b**, **4a**, **4b**, **5a**, and **5b**, were available from our earlier studies, they provided the major focus of the current programme.

(ii) Reaction of sodium azide with epoxide 5a

The C-2 substitution chemistry of electrophilic epoxide **5a** using nitrogen nucleophiles was examined first. As expected, treatment of epoxide **5a** with sodium azide in methanol containing zinc chloride gave predominantly *trans*-azidohydrin **6a** (Scheme 2).

However, a more careful ^{1}H-NMR spectroscopic analysis of the products from epoxide **5a** showed that partial rearrangement of 1,2-azidohydrin **6a** to the 1,4-isomer **7a** was occurring slowly at room temperature in deuteriated chloroform during the course of one day. On subsequent heating in $CDCl_3$, further isomerization took place to give an equilibrium mixture of compounds **6a**:**7a** (75:25). A similar reaction of sodium azide with epoxide **5a** in hot DMF again occurred to give virtually the same product mixture of azidohydrins **6a**:**7a** (73:27).

It is well known that allylic azides are prone to undergo facile thermal [3,3]-sigmatropic rearrangements. This rearrangement was first observed by Vander Werf[16] and studied in detail by Winstein.[17] With acyclic substrates, this reaction proceeds at room temperature thus limiting its use in synthesis, unless the alkene is anchored by additional conjugation,[18] steric strain,[19]

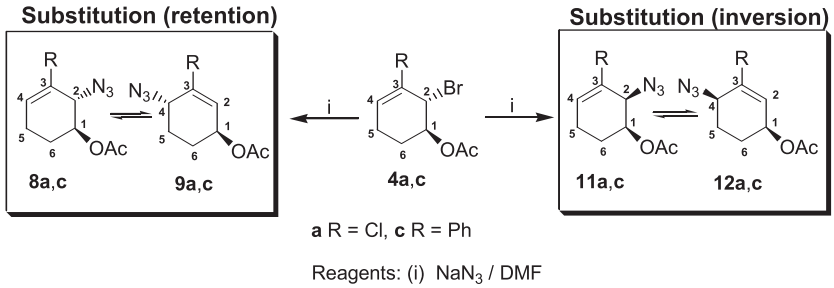
Journal of Physical Organic Chemistry

or when one of the azides can be chemoselectively removed from the equilibrium.[20] Recent theoretical studies indicate that allylic azidohydrins have a lower activation energy for rearrangement due to intramolecular hydrogen bonding between the alcohol and the azide.[21] However, for cyclic alkenes, the rearrangement is much less facile and, with the exception of studies by Trost,[22] Berchtold[23], and more recently Chang[24] this rearrangement reaction has remained largely unused in synthesis. Cyclohexadiene azidoacetates show no tendency to rearrange as this would result in loss of conjugation.[25] Indeed, six- membered ring allylic azides have been routinely used in organic synthesis, without the report of competing rearrangement,[26] have been recrystallized from chloroform,[27] and have survived heating at 50 °C for 24 h.[28] Furthermore, heterocyclic nine-membered ring allylic azidohydrins can be heated to 130 °C for 2 h without rearrangement.[29] Conditions for the zinc chloride-catalysed epoxide ring-opening, using sodium azide, were sufficiently mild to suppress the subsequent sigmatropic rearrangement making *trans*-azidohydrin **6a** suitable as a substrate for further synthetic manipulation.

Alcohols **6a** and **7a** were acylated to give acetates **8a** and **9a**, respectively (Scheme 2). These authentic samples were required later for comparison with the potential products arising from azide substitution of the allylic bromine present in *trans*-bromoacetate **4a**, (Scheme 3). It is interesting to note that the equilibrium ratio favouring 1,2-azidoalcohol **6a** over 1,4-azidoalcohol **7a** (75:25) was different with 1,2-azidoacetate **8a** and 1,4-azidoacetate **9a** (50:50). The configuration at the C-1 position of the *trans* azidoalcohol **6a** was inverted using the Mitsunobu reaction[30]; this proceeded cleanly and gave *cis* 1,2-azido *p*-nitrobenzoate **10a**. However, this compound also rearranged very slowly on standing to give a mixture of 1,2- and 1,4-azido *p*-nitrobenzoates. Hydrolysis of *p*-nitrobenzoyl ester **10a** to give azidohydrin *ent*-**13a** followed by acylation gave a mixture of authentic samples of *cis*-azido acetates *ent*-**11a** and *ent*-**12a**; thermal equilibration of this mixture gave a slight excess of 1,4-isomer *ent*-**12a** over 1,2-isomer *ent*-**11a** (58:42, Table 1, entry 1).

(iii) Reaction of sodium azide with *trans*-bromoacetates 4a and 4c

It is noteworthy that the reaction of sodium azide with epoxide **5a**, initially, yielded the corresponding azide product **6a**, from substitution with inversion of configuration at C-2 (Scheme 2, Table 1 entry 5). A facile isomerization process then occurred to give a second isomeric product **7a**, *via* a suprafacial allyl azide [3,3]-sigmatropic rearrangement (Table 1 entry 6). A more comprehensive ^{1}H-NMR spectroscopic study of the structure and stereochemistry of products obtained from the reaction of the azide nucleophile with the electrophilic *trans*-bromoacetate **4a** was required as four isomeric products were obtained at 60 °C (Table 1, entry 1).



Scheme 3. Substitution/rearrangement reactions of compounds **4a** and **4c** with sodium azide

Table 1. Relative proportions of substitution (Substit) and rearrangement (Rearrr.) products obtained with inversion (Inver.) or retention (Retent.) of configuration from nucleophilic nitrogen attack of substrates (Sub.) **4a–c** and **5a–c**

Entry	Sub	Nucleophile	Temp.	Substit. Inver. (%)	Rearr. Inver. (%)	Rearr. Retent. (%)	Substit. Retent. (%)
1	**4a**	NaN_3	60 °C	**11a** (25)	**12a** (35)	**9a** (20)	**8a** (20)
2	**4a**	NaN_3	25 °C	**11a** (45)	**12a** (44)	**9a** (11)	[a]
3	**4c**	NaN_3	60 °C	**11c** (24)	**12c** (32)	**9c** (21)	**8c** (23)
4	**4c**	NaN_3	25 °C	**11c** (43)	**12c** (50)	**9c** (7)	[a]
5	**5a**	NaN_3	25 °C	**6a** (100)			
6	**5a**	NaN_3	60 °C	**6a** (75)	**7a** (25)		
7	**5b**	NaN_3	25 °C	**6b** (100)			
8	**4b**	NaNHTs	60 °C			**19b**	
9	**4c**	NaNHTs	60 °C			**19c**	
10	**5a**	Morpholine	25 °C	**20a**			
11	**5b**	4-Phenyl piperidine	25 °C	**21b**			

[a]isomer not observed by proton NMR spectroscopy

When sodium azide reacted with bromoacetate **4a**, in DMF at 60 °C, this resulted in an inseparable mixture of four isomeric products **8a**, **9a**, **11a**, and **12a**, (Scheme 3, Table 1 entry 1), whose structures were mainly based on ^{1}H-NMR analysis and comparison with the previously prepared authentic samples of **8a**, **9a**, *ent*-**11a**, and *ent*-**12a** (Scheme 2). It should be noted that compounds *ent*-**11a** and *ent*-**12a** (Scheme 2) are spectroscopically indistinguishable from their respective opposite enantiomers **11a** and **12a** (Scheme 3). To complicate matters further, the 1,2-substitution products **8a** and **11a** were in equilibrium with the 1,4-substitution products **9a** and **12a**, obtained *via* a suprafacial allyl azide [3,3]-sigmatropic rearrangement mechanism as previously demonstrated in (Scheme 2).

In Figure 1-i is presented an expansion of the ^{1}H-NMR spectrum of the mixture of isomers (**8a, 9a, 11a**, and **12a**). It shows the signals for the H-2 proton of the C-2 substitution products **11a** (d, δ 4.21, 25%) and **8a** (d, δ 3.93, 20%) and also the H-4 proton for the allylic rearranged products **12a** (t, δ 3.96, 35%) and **9a** (t, δ 4.03, 20%). The formal C-2 substitution products **11a** and **8a** (H-2, doublets) were also readily distinguished from the C-4 substitution products **12a** and **9a** (H-4, apparent triplets) by the different multiplicity patterns. At 300 MHz, there was little overlap of the chemical shifts for each of these proton signals which were used to quantify the ratio of components of the mixture by ^{1}H-NMR spectroscopy (Table 1). A corresponding analysis was carried out on the vinyl proton signals, but this suffered from multiplet overlap. The authentic samples of these compounds, required for comparison with these isomers, and for independently establishing the position of equilibrium, were previously prepared as outlined in Scheme 2.

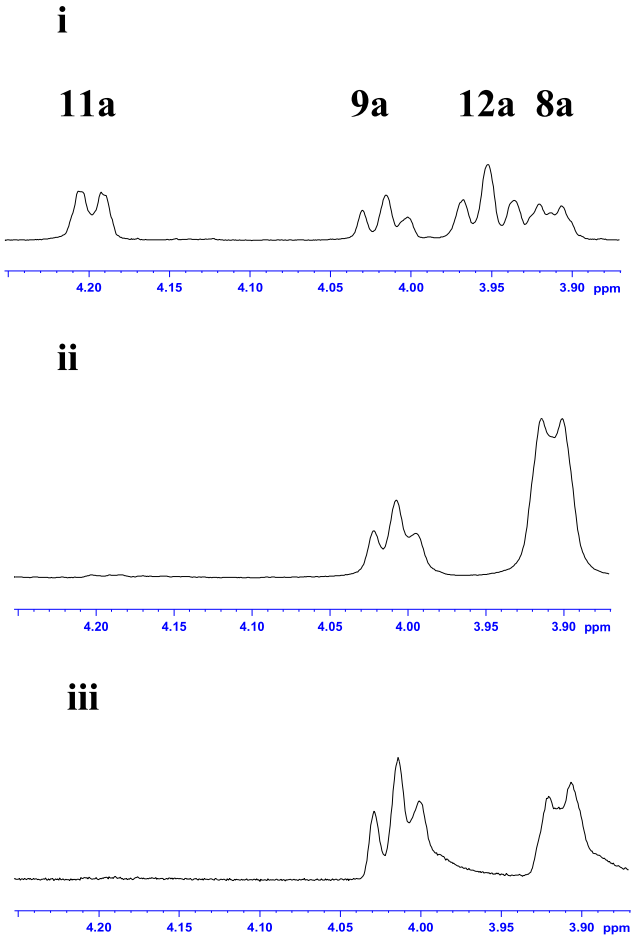


Figure 1. In Figures 1-i, 1-ii, and 1-iii are presented the characteristic signals of ^{1}H-NMR spectra which show: (i) the H-2 signal for isomers **8a** and **11a** and the H-4 signal for isomers **9a** and **12a**, (ii) in the authentic samples, the H-2 signal in compound **8a** and the H-4 signal in compound **9a**, and (iii) H-2 and H-4 signals for compounds **8a** and **9a** after equilibrium was established

Figure 1-ii shows a mixture of independently synthesized authentic samples of compounds **8a**:**9a** (71:29). Figure 1-iii shows the same sample after equilibrium had been established (50:50) after two weeks at room temperature. It is clear that in the crude reaction mixture, using *trans*-bromoacetate **4a** as electrophile, equilibrium was established between compounds **8a** and **9a**. Likewise, equilibrium was established between compounds **11a** and **12a** under conditions used for the substitution reaction. The ratio of isomeric products **11a**:**12a** (42:58, Table 1 entry 1) was close to the independently confirmed equilibrium ratio with a small but distinct preference for the allylic rearranged product **12a**.

The relevant coupling constants of all four isomers **8a**, **9a**, **11a**, and **12a** that could potentially give useful information on both preferred conformations and configurations are listed in Table 2. In cyclohexene, the ring inversion barrier between half chair conformers (5.3 kcal mol^{-1}) is much lower than the corresponding value for cyclohexane (11 kcal mol^{-1}), making the unsaturated ring much more flexible. Figure 2 shows half chair conformations of compounds **8a**, **9a**, **11a**, and **12a**. Theoretical optimized models of both half chair forms of cyclohexenes **8aX/8aY** and **9aX/9aY, 11aX/11aY**, and **12aX/12aY**, respectively, were generated using Density Function Theory BLYP 6-31*. It is known that this level of theory is insufficient to calculate the accurate free energies of the half chair conformers;[31] nevertheless, it does give some indication of the relevant dihedral angles in each half chair conformer.

In compound **11a**, proton H-1 has a large diaxial coupling constant $J_{1,6a}$ of 11.2 Hz. This value provides strong evidence for conformer homogeneity with the acetate group occupying an equatorial position with conformer **11aX** being dominant. The azide group was pseudoaxial, as confirmed by an axial/equatorial coupling constant of $J_{1,2}$ of 4.1 Hz.

The ^{1}H-NMR spectrum of *trans*-azidoacetate **8a** provided information on both relative configuration and preferred conformation. For 1,2-azidoacetate **8a** proton H-2 was a doublet with a

Table 2. ^{1}H-NMR coupling constants for compounds **8a, 9a, 11a, 12a, 19b**, and **19c**

Entry	Compound	$J_{1,2}$	$J_{1,6a}$	$J_{1,6e}$	$J_{4,5a}$	$J_{4,5e}$
1	**11a**	4.1	11.2	4.1		
2	**12a**		7.3	3.3	4.7	4.7
3	**9a**		4.5	4.3	4.3	4.3
4	**8a**	4.2	4.7	4.7		
5	**19b**	6.9[a]	4.1	4.1	4.3	4.3
6	**19c**		3.8	3.8	[b]	[b]

[a] $J_{4,NH}$
[b] Peak was too broad to extract coupling constants

Journal of Physical Organic Chemistry

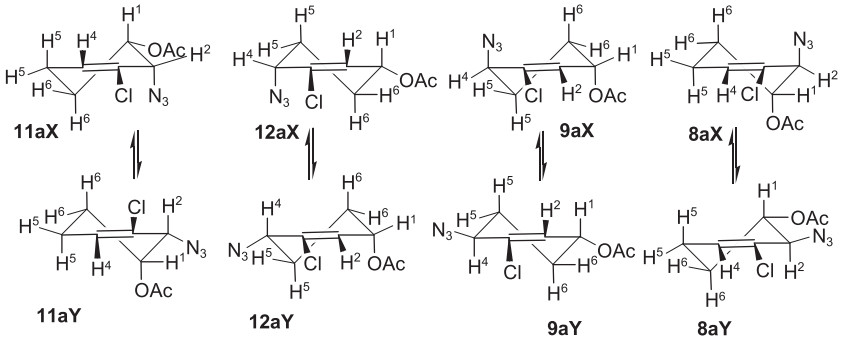


Figure 2. Half chair conformers of substituted cyclohexenes **8aX/8aY**, **9aX/9aY**, **11aX/11aY**, and **12aX/12aY**

coupling constant of 4.2 Hz. Molecular modelling, using Density Function Theory with BPY-6-31* suggested a dihedral angle between protons H-1 and H-2 of 71° in conformer **8aX** and 168° for conformer **8aY**. Ignoring the effect of electronegativity of the nitrogen and oxygen substituents, this equates to coupling constants of 2.8 Hz and 12.5 Hz, respectively. If the observed coupling constant is the weighted average of both conformers **8aX** and **8aY**, then clearly the weighting lies heavily in favour of conformation **8aX**. Proton H-1 was an apparent quartet, *J* 4.7 Hz, confirming that proton H-1 of the major conformer **8aX** occupied an equatorial position with no substantial diaxial coupling to H-6.

For the rearranged products **9a** and **12a**, both azide and acetate groups occupy allylic positions and are thus designated as pseudo axial and pseudo equatorial which made the detailed analysis of their ^{1}H-NMR spectra more difficult. For 1,4-azidoacetate **9a**, protons, H-1 and H-4 were apparent triplets, *J* 4.3 and 4.3 Hz, respectively, suggesting that these protons were largely pseudoequatorial and that conformer **9aX** was dominant. In compound **12a**, $J_{1,6a}$ was substantially larger than $J_{4,5}$ indicating that the conformer ratio was marginally weighted towards conformation **12aX**, (Figure 2). Based on the coupling constant values for all four azidoacetate isomers (**8a**, **9a**, **11a**, and **12a**), the dominant half chair conformers (**8aX**, **9aX, 11aX**, and **12aX**) existed with the azide group occupying a pseudoaxial position. In both *cis* (**11a** and **12a**) and *trans* azidoacetates (**8a** and **9a**), the azido group adopted the correct position to undergo an allylic [3,3]-sigmatropic rearrangement. However, *cis*-isomer **11a** is much more labile than the *trans*-isomer **8a** and rapidly equilibrates, to give predominantly the 1,4-azidoacetate **12a**, even on storage in the refrigerator. It is not clear why the *trans*-azidoacetates are less prone to undergo sigmatropic rearrangement than the *cis*-azidoacetates. The origin of this differential reactivity may be stereoelectronic in nature.

The earlier reaction of sodium azide with *trans*-bromoacetate **4a**, to yield the four isomeric products **8a**, **9a**, **11a**, and **12a** (Scheme 3), was repeated using compound **4c**, and similar results were obtained by ^{1}H-NMR analysis (Table 1). Thus, two *cis*-azidoacetates **11c** (δ 4.58, d, H-2, 43%) and **12c** (δ 4.37, t, H-4, 50%), along with a minor amount of *trans*-azidoacetate **9c** (δ 4.48, t, H-4, 7%), were observed at room temperature, while a mixture of *cis*-isomers **11c** (24%) and **12c** (32%), and both *trans*-isomers **9c** (δ 4.48, t, H-4, 21%) and **8c** (δ 4.37, d, H-2, 23%) was obtained when the reaction was carried out at 60 °C. The structures of each of the eight *cis*- and *trans*-azidoacetates, found to be present in the inseparable mixtures obtained from *trans*-bromoacetates **4a** or **4c** (Scheme 3), were mainly assigned following extensive ^{1}H-NMR spectroscopic analysis (Table 2).

(iv) Possible mechanisms to account for the formation of azidoacetates 8, 9, 11, and 12 from the corresponding *trans*-bromoacetates 4

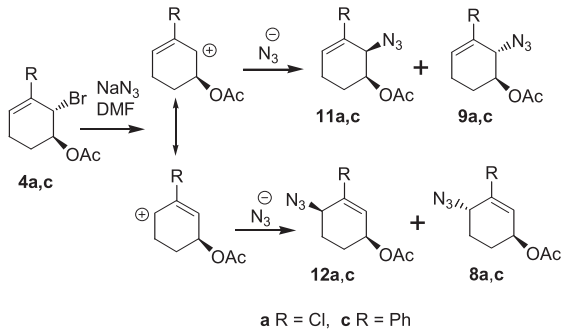
Several possible mechanisms could be involved in the formation of compounds **8a**, **9a**, **11a**, and **12a** from compound **4a**. A pathway, proceeding *via* a stepwise dissociative C-2-N bond cleavage followed by a subsequent C-4-N or C-2-N recombination is unlikely, as on heating pure azidoacetate **11a**, it equilibrated to a mixture of isomers **11a**:**12a** (1:2) with no sign of the potential dissociation products **9a** and **8a**. The formation of C-2 substitution product **11a** and the C-4 substitution product **9a** could, in principle, result from S_N2 and *syn*-selective S_N2' displacements, respectively, from compound **4a**. Thermal sigmatropic rearrangements of azidoacetates **9a** and **11a** would then give azidoacetates **8a** and **12a**, respectively (Scheme 3). At 60 °C, the proportion of substitution with inversion products **11a**/**12a** was higher (60%) compared to substitution with retention of configuration products **9a**/**8a** (40%), Table 1 entry 1. Repeating the reaction at room temperature (Table 1 entry 2) had a profound effect on the product ratio and gave predominantly the inversion products **11a** and **12a** (89%) along with a small amount of compound **9a** (11%). Since compound **8a** was *not* observed at this lower temperature, therefore compound **9a** was not derived from compound **8a** in this instance. A similar product distribution of compounds **8c**, **9c**, **11c**, and **12c** was observed from the reaction of bromoacetate **4c** with sodium azide (Table 1, entries 3 and 4).

Formation of all the isomeric azidoacetates **8**, **9**, **11**, and **12** from bromoacetates **4** could also, in principle, occur *via* an S_N1 reaction mechanism involving carbocation intermediates (Scheme 4). However, since none of the substitution products, with retention of configuration, **8a** and **8c**, are observed at room temperature (Table 1, entries 2 and 4), the involvement of an S_N1 mechanism seems less likely. Our preferred explanation for the observed distribution of azidoacetates **8**, **9**, **11**, and **12**, is that; (i) compound **11** formed *via* an S_N2 mechanism, (ii) compound **12** by a suprafacial [3,3]-sigmatropic rearrangement of **11**, (iii) compound **8** by an S_N2' mechanism, and (iv) compound **9** also by a [3,3]-sigmatropic rearrangement of compound **8**. At lower temperature, the rearrangement linking *trans*-azidoacetates **9** and **8** was not observed but occurred for *cis*-azidoacetates **11** and **12** which were much more labile.

(v) X-ray crystal structure analysis of derivatives 14c, 16c, 17c, and 18c obtained from azidoacetates 11c, 8c, 9c and 12c respectively

The earlier study of interconverting isomeric azidoacetate products was totally based on ^{1}H-NMR analyses of the inseparable mixtures. Therefore, the possibility of forming and separating crystalline derivatives from azidoacetates **8c**, **9c**, **11c**, and **12c**, which might be suitable for X-ray crystallography, and the resulting unequivocal determination of structure and relative stereochemistry, was also investigated. As part of our earlier unpublished efforts, to synthesize the alkaloid epibatidine from *cis*-diols **2b** and **2c**,[2–4] attempts were made to characterize the products (**8c**, **9c**, **11c**, and **12c**) through the formation of their derivatives. In order to solve the problem of product equilibration, the azide groups present in compounds **8c**, **9c**, **11c**, and **12c** were reduced with trimethyl phosphine, using a Staudinger reaction. The resulting aminoacetates (from compounds **8c**, **9c**, and **12c**) were then converted directly to tosamide acetates and hydrolysed to yield alcohols **16c**, **17c**, and **15c**, (Scheme 5). Suitable crystalline samples of the alcohol derivatives, **14c**, **16c**, **17c**, and acetate **18c**, were finally obtained for X-ray crystallographic analysis by an extensive combination of methods including: (i) utilization of enriched mixtures of compounds, *e.g.* **11c** and **12c**, formed at room temperature, or **8c** and **9c**, found at elevated temperatures, (ii) flash column and multiple elution preparative layer chromatography (PLC), and (iii) fractional crystallization. Compounds **15c**, **16c**, and the acetate derivative **18c** had previously been synthesized during an earlier model approach to the synthesis of racemic epibatidine, but were not characterized by X-ray crystallography.[32] On the basis of NMR spectroscopy, these compounds were found to be indistinguishable from our samples of derivatives **15c**, **16c**, and acetate **18c**, obtained by rearrangement during an alternative model approach to the synthesis of individual enantiomers of epibatidine. Isolation of *cis*-aminoacetamide **14c**, where the *O*-acetyl group initially formed had migrated to the NH_2 group, confirmed that azide **11c** was indeed a reaction product.

Single crystal X-ray analyses of acetate **18c** (Figure 4-i), alcohols **14c** (Figure 3), **16c** (Figure 4-ii), and **17c** (Figure 4-iii)



Scheme 4. Substitution/rearrangement reactions of compounds **4a** and **4c**

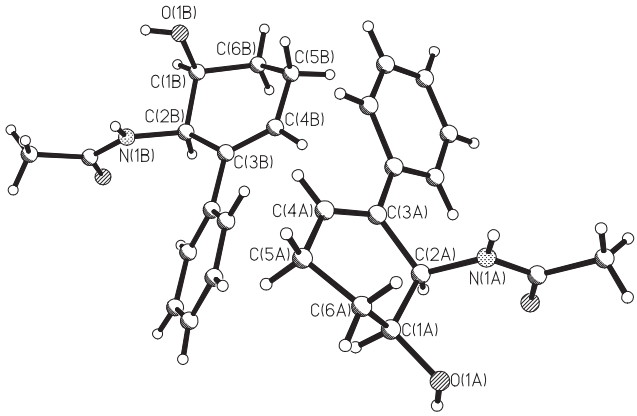
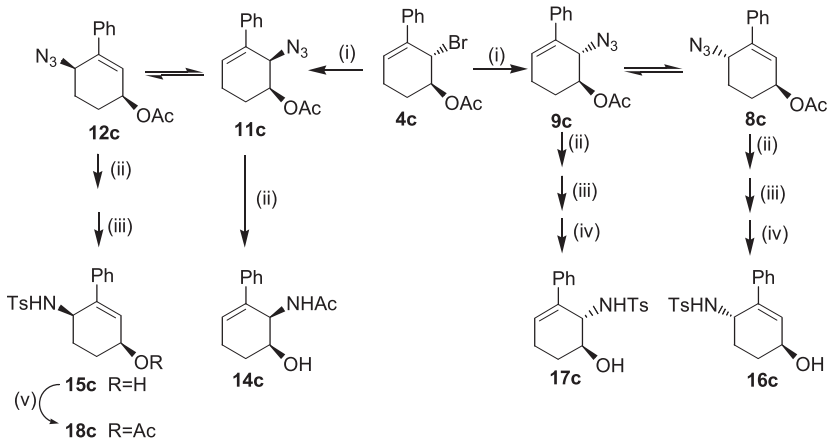


Figure 3. The crystallographic asymmetric unit of hydroxyamide **14c** showing different molecular conformations



Scheme 5. Reactions of bromoacetate **4c** with sodium azide to yield azidoacetates **8c**, **9c**, **11c**, and **12c** and conversion to the crystalline derivatives **16c**, **17c**, **14c**, and **18c** respectively

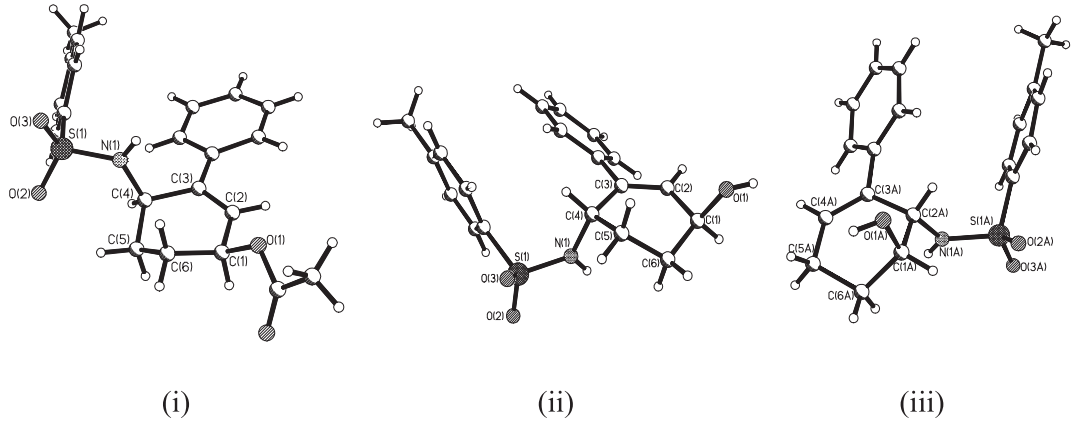


Figure 4. X-ray structures of compounds (i) **18c**, (ii) **16c**, and (iii) **17c**

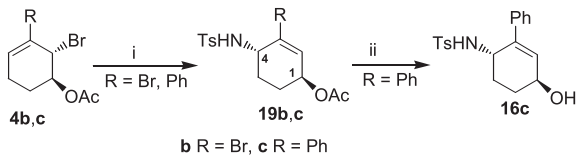
confirmed their structures, relative configurations and preferred conformations. In compound **14c**, there were two crystallographically independent molecules in the asymmetric unit, each having a half-chair conformation of the cyclohexene ring (Figure 3). One molecule had the OH group axial and the NHAc group pseudoequatorial, while, conversely, the other had the OH equatorial and the NHAc group pseudoaxial. Structures **18c**, **16c**, and **17c** were present as single conformations only, and in each case, the allylic NHTs group was pseudoaxial (Figure 4-i, 4-ii, and 4-iii).

For crystalline compound **18c**, the NHTs and OAc groups were pseudoaxial and pseudoequatorial, respectively, and as expected, with more $A_{1,2}$ strain[33] coming from the phenyl group than the alkene hydrogen atom (Figure 4-i). Interestingly, for tosamide **16c**, derived from the *trans* rearranged product **8c**, both alcohol and tosyl groups were *trans*-pseudodiaxial (Figure 4-ii). In compound **17c**, the tosamide and alcohol groups adopted a *trans*-axial/pseudoaxial conformation (Figure 4-iii).

Crystal structures, shown in Figures 3 and 4-i, 4-ii, and 4-iii are consistent with the earlier conclusions from NMR spectroscopy that the preferred solution conformations for compounds **8c**, **9c**, **11c**, and **12c** were correct and complement the results obtained from the detailed ^{1}H-NMR analyses of compounds **8a**, **9a**, **11a**, and **12a**. They also support the assumption that the allylic azide can readily access the pseudoaxial position preferred for a subsequent sigmatropic rearrangement.

(vi) Reaction of sodium tosamide with bromoacetates 4b,c

Reaction of bromoacetates **4b**,**c** with sodium tosamide gave compounds **19b**,**c** as the only identified products (Scheme 6, Table 1, entries 8 and 9). The structure of ester **19c** (Scheme 6) was confirmed by hydrolysis to give alcohol **16c**, a known compound,[30] unambiguously assigned by X-ray crystallography



Reagents: (i) NaNHTs/ H_2NTs/ DMSO; (ii) K_2CO_3 / MeOH-H_2O

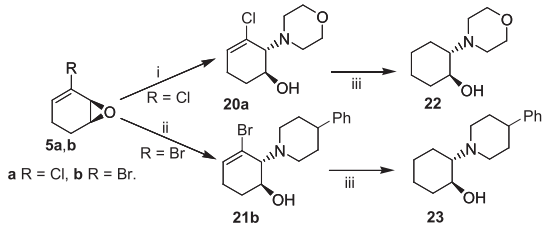
Scheme 6. Reactions of bromoacetates **4b**,**c** with sodium tosamide

(Figure 4-ii). It was evident, from the ^{1}H-NMR spectra of compounds **19b**,**c** that a rearrangement with retention of configuration had occurred, as the C-2 alkene protons were both doublets. The ^{1}H-NMR spectrum of **19b** was sufficiently resolved to extract the more important coupling constants. Proton H-1 appeared as an apparent quartet with coupling constant *J* 4.1 Hz and proton H-4 was a doublet of triplets with coupling constants *J* 6.9, 4.3 Hz (Table 2, entry 5). The large coupling constant value of *J* 6.9 Hz was due to coupling with the NH of the tosamide. Comparing these values with those for the corresponding *trans*- and *cis*-azidoacetates (**12a**, Table 2, entries 2 and 3) strongly inferred that the OAc and NHT groups in azidoacetate **19b** were *trans* and both occupied pseudoaxial positions.

It was interesting to find that changing the *N*-nucleophile from sodium azide (Schemes 3 and 5) to the softer nucleophile NaNHTs (Scheme 6) reversed the preferred regioselectivity of the reaction, and stereoselectively gave the allylic rearrangement products **19b** and **19c**, probably *via* an S_N2' mechanism.

Finally, reaction of epoxides **5a**,**b** with the secondary amines, morpholine and 4-phenyl piperidine, under mild Lewis acid catalysis, resulted in a ring-opening reaction at the allylic C-2 position and gave *trans*-1,2-aminoalcohols **20a** and **21b** (Scheme 7, Table 1, entries 10 and 11). Catalytic hydrogenolysis of the carbon halogen bonds, followed by hydrogenation of the resulting alkenes, gave *trans*-aminoalcohols **22** and **23**. This synthetic approach provided one enantiomer of the racemic anti-cholinergic drug vesamicol[34] **23**, in four steps, from *cis*-tetrahydrodiol **3a** with an overall yield of 56%.

A stated objective of this programme was to synthesize a new range of cyclohexene *cis*-1,2-aminoalcohols, from the corresponding cyclohexene *cis*-dihydrodiols **2**, by a generally applicable and



Reagents: (i) Morpholine / $ZnCl_2$-MeOH; (ii) 4-Phenyl piperidine / $ZnCl_2$-MeOH; (iii) H_2, Pd-C, Et_3N

Scheme 7. Reactions of epoxides **5a**,**b** with cyclic amines

simple route. This objective could not be achieved due to the mechanistic complexity discussed herein. However, preliminary studies have shown that some of the azides produced can be reduced to the corresponding cyclohexene 1,2-aminoalcohols, albeit *via* a multistep approach.

CONCLUSION

It was demonstrated that cyclic allylic epoxides react with a range of *N*-nucleophiles to give both C-2 and or C-4 substitution products. Good C-2 regioselectivity and *trans*-stereoselectivity was obtained in reactions of vinyl epoxides with sodium azide at room temperature under mild Lewis acid conditions. Uncatalysed reactions, at elevated temperatures, led to mixtures of *trans* C-2 and C-4 substituted products which equilibrated *via* an [3,3]-allylazide rearrangement mechanism. Sterically hindered secondary amines reacted, exclusively at the C-2 position of vinylic epoxides, under mild Lewis acid catalysis conditions, to give *trans*-1,2 aminoalcohols, including a useful precursor to the drug vesamicol.

Treatment of *trans*-1,2-bromoacetates with sodium azide at room temperature led mainly to C-2 and C-4 *cis*-azidoacetates *via* an S_N2 reaction. The small amount of C-4 *trans*-azidoacetate formed can be attributed to a minor competing S_N2' pathway. This stereochemical study provides the first hard evidence that azide does participate in S_N2' reactions. At an elevated temperature, a mixture of four (*cis* and *trans* 1,2- and 1,4-azidoacetate) isomers was formed. The *cis*-azidoacetates were more prone to rearrange than the corresponding *trans*-isomers, *via* a [3,3]-sigmatropic rearrangement mechanism. Reactions of sodium tosamide with *trans*-1,2-bromoacetates gave, predominantly, *trans*-C-4 substitution products *via* an S_N2' mechanism.

The formation, and structural/stereochemical assignments, of azidoalcohol and azidoacetate products, obtained from reactions of allylic epoxides and *trans*-1,2-bromoacetates with sodium azide, have been rationalized in terms of S_N2, S_N2' and [3,3]-sigmatropic rearrangement mechanisms.

EXPERIMENTAL

^{1}H- and ^{13}C-NMR spectra were recorded on Bruker Avance 400, DPX-300, and DRX-500 instruments. Chemical shifts (δ) are reported in ppm relative to $SiMe_4$, and coupling constants (J) are given in Hz. Mass spectra were recorded at 70 eV, on a VG Autospec Mass Spectrometer, using a heated inlet system. Accurate molecular weights were determined by the peak matching method, with perfluorokerosene as the standard. Flash chromatography and PLC were performed on Merck Kieselgel type 60 (250–400 mesh) and $PF_{254/366}$ plates, respectively. Merck Kieselgel type 60 F_{254} analytical plates were employed for TLC. A Perkin Elmer 341 polarimeter was used for optical rotation ($[\alpha]_D$) measurements.

3-Chlorocyclohex-3-ene-1,2-dio1 **3a**, 3-bromocyclohex-3-ene-1,2-diol **3b**, '(1*S*, 2*R*)-2-bromo-3-chlorocyclohex-3-enyl acetate **4a**, (1*S*, 2*R*)-2, 3-dibromocyclohex-3-enyl acetate **4b**, 2-chloro-7-oxabicyclo[4.1.0]hept-2-ene **5a**, 2-bromo-7-oxabicyclo[4.1.0]hept-2-ene **5b**, and 3-phenyl-2-(*p*-toluenesulfonamido)cyclohex-2-enyl acetate **18c** were available from earlier studies.[4,14]

(1S,2R)-3-Phenylcyclohex-3-ene-1,2-diol ***3c***

A solution of biphenyl-*cis*-dihydrodiol **2c** (10.00 g, 0.05 mol) in ethyl acetate (100 mL) was stirred for 4 h in the presence of 3% Pd/C (0.2 g) under an atmosphere of hydrogen, at ambient temperature and pressure. The catalyst was filtered off and the filtrate concentrated to give a crude sample of hydrogenated product **3c** (10.0 g, 99% yield). Purification by column chromatography (EtOAc:hexane, 1:1), yielded a white solid; mp 92–94 °C (from EtOAc); (lit, mp 90–92 °C)[35]; $[\alpha]_D$ −83 (c 0.9, $CHCl_3$) (lit., $[\alpha]_D$ −86 (c 1.1, $CHCl_3$)[35]; δ_H (300 MHz; $CDCl_3$) 2.2–2.5 (4 H, m, H-5, H-6), 4.66–4.70 (1 H, m, H-1), 4.53–4.61 (1 H, m, H-2), 6.17–6.19 (1 H, m, H-4), 7.25–7.40 (5 H, m, Ar); δ_C (125 MHz; $CDCl_3$) 22.95, 25.32, 68.22, 70.10, 126.30, 127.69, 128.27, 133.90, 137.67, 143.07.

(1S,2S)-2-Bromo-3-phenylcyclohex-3-enyl acetate ***4c***

1-Bromocarbonyl-l-methylethylacetate (14.0 g, 0.07 mol) was added to a stirred solution of tetrahydrodiol **3c** (11.54 g, 0.06 mol) in dry acetonitrile (100 mL) at 0 °C. After stirring the reaction mixture for 3 h, it was partially concentrated, diluted with diethyl ether (100 mL), and washed with 2.5% aqueous $NaHCO_3$ solution (2 × 50 mL). The organic layer was dried over (Na_2SO_4) and concentrated under reduced pressure to give unstable bromoacetate **4c** (15.8 g, 90%) as a pale orange oil. As this product was found to decompose at ambient temperature, it was stored at low temperature or used for the next step without purification; (Found M^+ 294.0252 $C_{14}H_{15}S^{79}BrO_2$ requires 294.0255); υ_{max}/cm^{-1} 1739 (C = O); δ_H (500 MHz; $CDCl_3$) 1.98 (1 H, m, H-6a), 2.07 (3 H, s, Me), 2.39 (2 H, m, H-5), 2.47 (1 H, m, H-6b), 5.01 (1 H, br, s, H-2), 5.49 (1 H, m, H-1), 6.25 (1 H, m, H-4), 7.35 (5 H, m, Ar); δ_C (125 MHz; $CDCl_3$) 21.07, 21.55, 21.96, 46.30, 72.91, 126.10, 128.08, 128.31, 128.62, 128.89, 129.59, 135.62, 139.62, 170.70; *m/z* (EI) 294 (M^+ ^{79}Br, 5%), 296 (M^+ ^{81}Br, 5%), 215 (90), 172 (100).

2-Phenyl-7-oxa-bicyclo[4.1.0]hept-2-ene ***5c***

Sodium methoxide (5.0 g, in excess) was added to a solution of crude bromoacetate **4c** (5.00 g, 0.017 mol) in dry ether (100 mL), and the reaction mixture was stirred overnight. The inorganic salts were filtered off, and the solution was concentrated under reduced pressure. Purification by flash chromatography (EtOAc: hexane, 0.5:9.5) yielded the titled compound **5c** (2.33 g, 80%) as a colourless viscous oil; $[\alpha]_D$ +112 (c 0.14, $CHCl_3$); (Found: M^+ 172.0888 $C_{12}H_{12}O$ requires 172.0888); δ_H (500 MHz; $CDCl_3$) 1.59 (2 H, m, H-5), 2.26 (2 H, m, H-4), 3.64 (2 H, m, H-1 and H-6), 6.17–6.19 (1 H, m, H-3), 7.25–7.40 (5 H, m, Ar); δ_C (125 MHz; $CDCl_3$) 21.03, 21.10, 55.71, 64.30, 125.42, 126.18, 127.52, 128.81, 135.69, 139.49; *m/z* (EI) 172 (M^+, 100%).

(1S,2R)-2-Azido-3-chlorocyclohex-3-enol ***6a***

Sodium azide (0.62 g, 9.58 mmol) and zinc chloride (1.54 g, 9.58 mmol) were added to a solution of chloroepoxide **5a** (0.50 g, 3.83 mmol) in MeOH (20 mL). The reaction mixture was stirred at room temperature overnight, filtered through a pad of celite and the filtrate concentrated under reduced pressure. The crude product obtained was purified by flash chromatography (Et_2O:hexane, 1:1) to give the titled compound **6a** (0.53 g, 80%); $[\alpha]_D$ +110 (c 1.63, $CHCl_3$); (Found: M^+ 173.0352 $C_6H_8ON_3^{35}Cl$ requires 173.0356); υ_{max}/cm^{-1} (KBr) 3372 (O-H), 2096 (N_3); δ_H (500 MHz; $CDCl_3$) 1.74 (1 H, m, H-6), 1.86 (1 H, m, H-6'), 2.18 (1 H, m, H-5), 2.25 (1 H, m, H-5'), 3.85 (1 H, d, *J* 5.4, H-2), 3.88 (1 H, ddd, *J* 8.6, 5.4, 3.0, H-1), 6.06 (1 H, dd, *J* 4.7, 2.9, H-4); δ_C (125 MHz; $CDCl_3$) 23.13, 26.63, 67.83, 71.27, 128.47, 129.68; *m/z* (EI) 175 (M^+ ^{37}Cl, 2%), 173 (M^+ ^{35}Cl, 7%), 146 (26), 144 (78), 133 (20), 132 (28), 131 (81), 130 (75), 129 (72), 120 (17), 118 (73), 116 (82),103 (64),101 (100), 97 (13), 95 (54).

Isomerization of (1*S*,2*R*)-2-azido-3-chlorocyclohex-3-enol 6a to yield (1*S*,4*S*)-*trans*-4-azido-3-chlorocyclohex-2-enol 7a and synthesis of their *trans*-azidoacetate derivatives 8a and 9a

On heating a sample of pure **6a** in $CDCl_3$ at 50 °C for 4 h, new peaks appeared which were attributed to the rearranged product **7a**. An equilibrium mixture of **6a:7a** of 75:25 was established. Important peaks for identifying rearranged product **7a** in the mixture are: δ_H (300 MHz; $CDCl_3$) 6.07 (1 H, d, *J* 4.6, H-2), 4.25(1 H, m, H-1), and 3.93 (1 H, t, *J* 4.9, H-4).

When the reaction of epoxide **5a** with sodium azide was repeated in DMF solution at 60 °C, an equilibrated mixture of azidohydrin **6a** and

the isomeric azido alcohol **7a** (73:27) was also obtained. The mixture of isomers **6a** and **7a** could not be separated by chromatography.

*(1S,2R)-2-Azido-3-chlorocyclohex-3-enyl acetate **8a***

Acetic anhydride (0.60 mL, 6.36 mmol) was added to azidohydrin **6a** (0.04 g, 0.23 mmol) in dry pyridine solution (0.4 mL). The reaction mixture was allowed to stir overnight at room temperature. The pyridine was removed by coevaporation with toluene under vacuum (3 × 10 mL). The crude sample of azidoacetate **8a** was purified by flash chromatography (Et_2O:hexane, 1:1); R_F 0.75 to give the titled compound (0.04 g, 81%); (Found: $(M+NH_4)^+$ 233.0800 $C_8H_{14}ClN_4O_2$ requires 233.0800); υ_{max}/cm^{-1} (KBr) 2103 (N_3), 1743 (C = O); δ_H (300 MHz; $CDCl_3$) 1.84 (2 H, m, H-6 and H-6′), 2.09 (3 H, s, Me), 2.24 (2 H, m, H-5 and H-5′), 3.93 (1 H, d, *J* 4.2 H-2), 5.03 (1 H, q, *J* 4.7, H-1), 6.12 (1 H, t, *J* 4.3, H-4); δ_C (75 MHz; $CDCl_3$) 21.43, 22.69, 22.97, 63.63, 72.14, 127.31, 129.94, 170.41.

*(1S,4S)-4-Azido-3-chlorocyclohex-2-enyl acetate **9a***

On heating a sample of (1*S*,2*R*)-2-azido-3-chlorocyclohex-3-enyl acetate **8a** in $CDCl_3$ at 50 °C for 4 h, an inseparable equilibrium mixture of **8a**:**9a** (1:1) was obtained. From this, the relevant NMR spectroscopic data for compound **9a** could be extracted. δ_H (300 MHz; $CDCl_3$) 1.75 (2 H, m, H-6 and H-6′), 1.93 (2 H, m, H-5 and H-5′), 2.05 (3 H, s, Me), 4.03 (1 H, t, *J*, 4.3, H-4), 5.26 (1 H, dt, *J* 4.7, 4.3, H-1), 6.14 (1 H, d, *J* 4.5, H-2); δ_C (75 MHz; $CDCl_3$) 23.87, 26.37, 30.08, 60.95, 67.00, 127.78, 136.96, 170.61.

*(1R,2R)-2-Azido-3-chlorocyclohex-3-enyl 4′-nitrobenzoate **10a***

Diethyldiazocarboxylate (0.6 mL, 3.4 mmol) was added dropwise to an ice-cooled solution of triphenylphosphine (1.0 g, 3.7 mmol) and (1*S*,2*R*)-2-azido-3-chlorocyclohex-3-eno1 **6a** (0.50 g, 2.88 mmol) in THF (10 mL) containing 3A molecular sieves. After stirring the solution at room temperature for 30 min, *p*-nitrobenzoic acid (0.60 g, 3.5 mmol) was added, and the solution was stirred overnight. The molecular sieves were filtered off, and the solvent removed under reduced pressure. The crude *p*-nitrobenzoate was purified by flash chromatography (40% Et_2O in hexane) to yield a white crystalline solid (0.64 g, 69%); mp 88–90 °C; $[\alpha]_D$ +60 (c 0.67, $CHCl_3$); υ_{max}/cm^{-1} (KBr) 2090 (N_3), 1717 (C = O); Found: M^+ 322.2057 $C_{13}H_{11}O_4N_3^{35}Cl$ requires 322.2054); δ_H (500 MHz; $CDCl_3$) 1.99 (2 H, m, H-4, H-4′), 2.35 (2 H, m, H-5, H-5′), 4.36 (1 H, d, *J* 4.3, H-2), 5.34 (1 H, dt, *J* 11.5, 4.3, H-1), 6.11 (1 H, dd, *J* 4.8, 3.5, H-4), 8.27 (2 H, m, Ar-H), 8.32 (2 H, m, Ar-H); *m/z* (EI) 322 (M^+, 1%), 312 (9), 310 (7), 293 (24), 269, (23), 252 (19), 217 (33), 194 (36), 155 (100), 146 (57), 132 (34), 130 (78), 120 (81), 110 (52), 96 (26), 82 (7), 59 (7). Compound **10a** was used directly after synthesis, as on storage in the refrigerator, within one day, the rearranged product was found to be present to the extent of 25%. Distinctive ^{1}H-NMR data for the rearrangement product in the mixture: δ_H (500 MHz; $CDCl_3$) 4.05 (1 H, t, *J* 4.8, H-4), 5.56 (1 H, m, H-1), 6.18 (1 H, d, *J* 3.8, H-2).

*(1R,2R)-2-Azido-3-chloro-3-cyclohex-3-enol ent-**13a***

(1*R*,2*R*)-2-Azido-3-chloro-cyclohex-3-enyl 4′-nitrobenzoate **10a** (0.11 g, 0.34 mmol) was dissolved in MeOH:H_2O (20:1) mixture, and potassium carbonate (0.12 g, 0.85 mmol) was added to the solution. The reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure, and water (50 mL) was added and extracted with ethyl acetate (4 × 25 mL), dried over sodium sulfate, and concentrated. The crude azidohydrin product *ent*-**13a**, was purified by flash chromatography (Et_2O:hexane, 1:4) (56 mg, 95%); $[\alpha]_D$ +85 (c 1.98, $CHCl_3$); (Found: M^+ 173.0353 $C_6H_8ON_3^{35}Cl$ requires 173.0356); δ_H (300 MHz; $CDCl_3$) 1.74 (1 H, m, H-6), 1.85 (1 H, m, H-6′), 2.18 (2 H, m, H-5, H-5′), 3.97 (1 H, m, H-1), 4.14 (1 H, d, *J* 4.2, H-2), 6.09 (1 H, t, *J* 3.0, H-4); *m/z* (EI) 175 (M^+ ^{37}Cl, 2%), 173 (M^+ ^{35}Cl, 7%), 146 (15), 144 (10), 133 (7), 131 (24), 130 (16), 128 (33), 117 (44), 110 (100), 103 (34), 101 (61), 93 (45), 82 (83), 67 (54), 55 (45).

Synthesis of (1*R*,2*R*)-2-azido-3-chlorocyclohex-3-enyl acetate *ent*-11a and (1*R*,4*S*)-4-azidochlorocyclohex-2-enyl acetate *ent*-12a from (1*R*,2*R*)-2-azido-3-chlorocyclohex-3-enol *ent*-13a

Acetic anhydride (0.1 mL, 1.06 mmol) was added to an equilibrated solution of (1*R*,2*R*)-2- azido-3-chlorocyclohex-3-enol *ent*-**13a** (40 mg, 0.23 mmol) in dry pyridine (0.5 mL). The reaction mixture was stirred overnight at room temperature. The excess of pyridine was removed by coevaporation with toluene under vacuum. Purification of the isomeric mixture of compounds *ent*-**11a** and *ent*-**12a** was achieved by flash chromatography and PLC (Et_2O:hexane, 2:1), but the isomers were not separated. (36 mg, 72%); υ_{max}/cm^{-1} (KBr) 2100 (N_3), 1745 (C = O); (Found: $(M+Na)^+$ 238.0353 $C_8H_{10}ClN_3NaO_2$ requires 238.0354).

*(1R,2R)-2-Azido-3-chlorocyclohex-3-enyl acetate ent-**11a***

δ_H (300 MHz; $CDCl_3$) 1.7–1.83 (2 H, m, H-6 and H-6′), 2.13 (3 H, s, Me), 2.18–2.29 (2 H, m, H-5 and H-5′), 4.21 (1 H, d, *J* 4.1, H-2), 5.05 (1 H, dt, *J* 11.2, 4.1, H-1), 6.04 (1 H, dd, *J* 4.0, 4.9, H-4); δ_C (75 MHz; $CDCl_3$) 21.27, 22.15, 24.48, 63.28, 72.05, 128.83, 129.66, 170.66.

*(1R,2S)-4-Azido-3-chlorocyclohex-2-enyl acetate ent-**12a***

δ_H (300 MHz; $CDCl_3$) 1.84–1.97 (2 H, m, H-6 and H-6′), 1.97–2.05 (2 H, m, H-5 and H-5′), 2.06 (3 H, s, Me), 3.96 (1 H, t, *J* 4.7, H-4), 5.26 (5 H, m, H-1), 6.07 (1 H, d, *J* 3.5, H-2); δ_C (75 MHz; $CDCl_3$) 21.48, 24.17, 27.45, 60.83, 68.71, 127.57, 135.71, 170.83.

Synthesis and X-ray crystal structure analysis of (1*S*,2*R*)-2-acetamido-3-phenylcyclohex-3-enol 14c, (1*S*,4*R*)-3-phenyl-4-(*p*-toluenesulfonamido)cyclohex-2-enol 15c and (1*S*,4*S*)-3-phenyl-4-(*p*-toluenesulfonamido)cyclohex-2-enol 16c and (1*S*,2*S*)-3-phenyl-2-(*p*-toluenesulfonamido)cyclohex-2-enyl acetate 17c from (1*S*,2*S*)-2-bromo-3-phenylcyclohex-3-enyl acetate 4c

Sodium azide (1.41 g, 0.025 mol) was added to a stirred solution of crude bromoacetate **4c** (5.0 g, 0.017 mol) in dry DMF (50 mL), and the reaction mixture was stirred at 70 °C overnight. After quenching with water (50 mL), the cooled reaction mixture was extracted with ethyl acetate (2 × 50 mL). The organic layer was washed with water (3 × 50 mL) and concentrated under reduced pressure to give an inseparable mixture of products whose ^{1}H-NMR spectrum was consistent with compounds **8c** (δ 4.37, d, H-2), **9c** (δ 4.88, t, H-4) **11c** (δ 4.58, d, H-2), and **12c** (δ 4.37, t, H-4) being the major components. The crude mixture of azidoacetates was dissolved in THF/H_2O (9:1, 100 mL), and a trimethylphosphine solution in THF (1 M, 27 mL) was added, and the mixture stirred for 1.5 h at 0 °C, then 3 h at room temperature. The acetamide **14c** was separated from the mixture of azido alcohol intermediates. Tosyl chloride (3.67 g, 0.19 mmol) followed by sodium hydroxide (20 mL, 2 M) was added, and the mixture stirred overnight at room temperature. The solvent was evaporated under reduced pressure, and flash chromatography (EtOAc: hexane, 1:1) gave compounds **15c–17c**. Acetylation of compound **15c** to yield compound **18c** was carried out under similar conditions used earlier for azido alcohol **13a**.

*(1S,2R)-2-Acetamido-3-phenylcyclohex-3-enol **14c***

White crystalline solid; mp 120–121 °C; $[\alpha]_D$ −43 (c 0.3, $CHCl_3$); (Found: M^+ 231.1258 $C_{14}H_{17}O_2N$ requires 231.1259); υ_{max}/cm^{-1} 1157, 1727; δ_H (500 MHz; $CDCl_3$) 1.85 (1 H, ddd, *J* 9.3, 7.8, 4.4, H-6), 2.01 (1 H, m, H-6′), 2.09 (3 H, s, Me), 2.22–2.42 (2 H, m, H-5, H-5′), 3.92 (l H, m, H-2), 4.98 (1 H, ddd, *J* 7.2, 4.7, 2.7, H-2), 6.03 (l H, t, *J* 3.5, H-4), 7.25–7.40 (5 H, m, Ar).

*Crystal data for **14c***

$C_{14}H_{17}N_1O_2$, *M* = 231.3, monoclinic, *a* = 5.187(2), *b* = 18.111(8), *c* = 13.491 (6) Å, β = 91.88(1)^0, *U* = 1266.6(10) Å^3, *T* = 293(2) K, *Mo-Kα* radiation,

$\lambda = 0.71073$ Å, space group $P2_1$ (no. 4), $Z = 4$, $F(000) = 496$, $D_x = 1.213$ g cm^{-3}, $\mu = 0.081$ mm^{-1}, Bruker SMART CCD area detector diffractometer, φ/ω scans, $3.0° < 2\theta < 50.0°$, measured/independent reflections: 10946/4270, $R_{int} = 0.064$, direct methods solution, full-matrix least squares refinement on F_o^2, anisotropic displacement parameters for non-hydrogen atoms; hydrogen atoms located in a difference Fourier synthesis but included at positions calculated from the geometry of the molecules using the riding model, with isotropic vibration parameters. $R_1 = 0.085$ for 2531 data with $F_o > 4\sigma(F_o)$, 312 parameters, $\omega R_2 = 0.185$ (all data), GoF = 1.11, $\Delta\rho_{min,max} = -0.35/0.34$ e Å^{-3}. CCDC 930363.

(1S,4R)-3-Phenyl-4-(p-toluenesulfonamido)cyclohex-2-enol **15c**

White crystalline solid; mp 158–159 °C; (lit., mp 155–156 °C)[32]; $[\alpha]_D$ −43 (c 0.3, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 1.79 (1 H, m, H-6), 2.02 (1 H, m, H-6′), 2.24 (1 H, m H-7), 2.33 (1 H, m H-7′), 2.44 (3 H, s, CH_3), 4.17 (1 H, dt *J* 6.4, 3.1, H-4), 4.26 (1 H, bm, H-1), 5.08 (1 H, d, *J* 6.7, NH), 6.0 (1 H, d, *J* 2.7, H-2), 6.97 (2 H, d, *J* 8.1, Ar), 7.12 (5 H, m, Ar), 7.5 (2 H, d, *J* 8.1, Ar); δ_C (125 MHz; $CDCl_3$) 21.49, 26.49, 27.89, 49.18, 66.94, 126.27, 126.96, 127.54, 128.29, 129.47, 133.46, 137.12, 137.97, 138.11, 143.06.

(1S,4S)-3-Phenyl-4-(p-toluenesulfonamido)cyclohex-2-enol **16c**

White crystalline solid; mp 193–194 °C; (lit., mp 190–192 °C)[32]; $[\alpha]_D$ −25 (c 1.0, $CHCl_3$); physical spectroscopic properties in good agreement with literature values[32]; δ_H (500 MHz; $CDCl_3$) 1.72 (l H, m, H-6), 2.06 (3 H, m, H-5, H-5′, H-6′), 2.42 (3 H, s, Me), 4.27 (l H, m, H-4), 4.34 (1 H, m, H-4), 6.08 (1 H, d, *J* 4.0, H-2), 6.95 (2 H, d, *J* 7.2, Ar), 7.09 (2 H, m, Ar), 7.19 (3 H, m, Ar), 7.52 (2 H, d, *J* 8.2, Ar)

Crystal data for **16c**

$C_{19}H_{21}N_1O_3S_1$, $M = 343.4$, monoclinic, $a = 8.9058(4)$, $b = 10.5644(5)$, $c = 9.1348(4)$ Å, $\beta = 91.233(1)^0$, $U = 859.24(7)$ Å^3, $T = 293(2)$ K, *Mo-Kα* radiation, $\lambda = 0.71073$ Å, space group $P2_1$ (no. 4), $Z = 2$, $F(000) = 364$, $D_x = 1.327$ g cm^{-3}, $\mu = 0.205$ mm^{-1}, Bruker SMART CCD area detector diffractometer, φ/ω scans, $4.5° < 2\theta < 56.6°$, measured/independent reflections: 10031/3853, $R_{int} = 0.020$, direct methods solution, full-matrix least squares refinement on F_o^2, anisotropic displacement parameters for non-hydrogen atoms; all hydrogen atoms located in a difference Fourier synthesis but included at positions calculated from the geometry of the molecules using the riding model, with isotropic vibration parameters. $R_1 = 0.045$ for 3697 data with $F_o > 4\sigma(F_o)$, 219 parameters, $\omega R_2 = 0.123$ (all data), GoF = 1.05, $\Delta\rho_{min,max} = -0.31/0.54$ e Å^{-3}. Flack parameter $x = 0.02(6)$ establishes the absolute configuration as (*1S,4S*). CCDC 930365

(1*S*,2*S*)-3-Phenyl-2-(*p*-toluenesulfonamido)cyclohex-2-enyl acetate 17c

Crystal data for **17c**

$C_{19}H_{21}N_1O_3S_1$, $M = 343.4$, monoclinic, $a = 9.087(4)$, $b = 19.996(9)$, $c = 10.177(5)$ Å, $\beta = 91.922(7)^0$, $U = 1848.3(14)$ Å^3, $T = 293(2)$ K, *Mo-Kα* radiation, $\lambda = 0.71073$ Å, space group $P2_1$ (no. 4), $Z = 4$, $F(000) = 728$, $D_x = 1.234$ g cm^{-3}, $\mu = 0.191$ mm^{-1}, Bruker SMART CCD area detector diffractometer, φ/ω scans, $4.0° < 2\theta < 45.0°$, measured/independent reflections: 13528/4788, $R_{int} = 0.102$, direct methods solution, full-matrix least squares refinement on F_o^2, anisotropic displacement parameters for non-hydrogen atoms; hydrogen atoms included at positions calculated from the geometry of the molecules using the riding model, with isotropic vibration parameters. $R_1 = 0.137$ for 3349 data with $F_o > 4\sigma(F_o)$, 437 parameters, $\omega R_2 = 0.361$ (all data), GoF = 1.19, $\Delta\rho_{min,max} = -0.49/0.38$ e Å^{-3}. The asymmetric unit contains two crystallographically independent molecules which do not differ significantly. CCDC 930366.

(1S,4R)-3-Phenyl-4-(p-toluenesulfonamido)cyclohex-2-enyl acetate **18c**

NMR spectra in agreement with literature values.[32] δ_H (500 MHz; $CDCl_3$) 1.90–1.75 (2 H, m, H-6, H-6′), 2.10 (3 H, s, Me), 2.23 (2 H, m, H-5, H-5′), 2.44 (3 H, s, Me), 4.23 (1 H, m, 1 H-4), 4.50 (1 H, d, *J* 6.1, NH), 5.34 (1 H, m, H-1), 5.92 (1 H, d, *J* 3.0, H-2), 6.95 (2 H, d, *J* 8.5, Ar), 7.12 (5 H, m, Ar), 7.50 (2 H, d, *J* 8.3, Ar).

Crystal data for **18c**

$C_{21}H_{23}N_1O_4S_1$, $M = 385.5$, monoclinic, $a = 8.482(3)$, $b = 5.598(2)$, $c = 20.839$ (8) Å, $\beta = 99.469(7)^0$, $U = 976.1(6)$ Å^3, $T = 293(2)$ K, *Mo-Kα* radiation, $\lambda = 0.71073$ Å, space group $P2_1$ (no. 4), $Z = 2$, $F(000) = 408$, $D_x = 1.312$ g cm^{-3}, $\mu = 0.192$ mm^{-1}, Bruker SMART CCD area detector diffractometer, φ/ω scans, $2.0° < 2\theta < 50.0°$, measured/independent reflections: 7650/3372, $R_{int} = 0.082$, direct methods solution, full-matrix least squares refinement on F_o^2, anisotropic displacement parameters for non-hydrogen atoms; hydrogen atoms located in a difference Fourier synthesis but included at positions calculated from the geometry of the molecules using the riding model, with isotropic vibration parameters. $R_1 = 0.111$ for 1509 data with $F_o > 4\sigma(F_o)$, 247 parameters, $\omega R_2 = 0.345$ (all data), GoF = 1.03, $\Delta\rho_{min,max} = -0.28/0.47$ e Å^{-3}. CCDC 930364.

(1S,4S)-3-Bromo-4-(p-toluenesulfonamido)cyclohex-2-enyl acetate **19b**

NaNHTs (0.92 g, 4.8 mmol) and $TsNH_2$ (0.27 g, 1.6 mmol) were added to a solution of (1*S*,2*R*)-bromoacetate **4b** (0.95 g, 3.2 mmol) in DMSO and the mixture heated at 60 °C overnight. The mixture was diluted with ethyl acetate and washed with brine, dried (Na_2SO_4), and concentrated. Purification of the crude product by column chromatography (EtOAc: hexane, l:1) furnished the titled compound **19b** as a clear oil (0.72 g, 63%); R_F 0.52 (EtOAc:hexane, 1:1); (Found: $(M+1)^+$ 388.0218; $C_{15}H_{19}BrNO_4S$ requires 388.0213); δ_H (500 MHz; $CDCl_3$) 1.74 (1 H, m, H-5), 1.95 (2 H, m, H-5′, H-6), 2.02 (3 H, s, Me), 2.10 (1 H, m, H-6′), 2.43 (3 H, s, Me), 3.90 (1 H, dt *J* 7.5, 4.1, H-4), 5.14 (1 H, q, *J* 4.3, H-1), 5.84 (1 H, d, *J* 7.5, N-H), 6.23 (1 H, d, *J* 4.6, H-2), 7.30 (2 H, d, *J* 6.8, Ar), 7.79 (2 H, d, *J* 6.8, Ar); δ_C (125 MHz; $CDCl_3$) 21.02, 21.57, 23.18, 27.70, 54.89, 67.46, 127.35, 127.45, 129.62, 132.14, 137.00, 143.70, 170.30; *m/z* (CI) 390 [$(M+1)^+$, ^{81}Br, 40%], 388 [$(M+1)^+$, ^{79}Br, 47%], 329 (36), 327 (33), 174 (30), 172 (53), 155 (34), 91 (100), 65 (36).

(1S,4S)-3-Phenyl-4-(p-toluenesulfonamido)cyclohex-2-enyl acetate **19c**

NaNHTs (1.0 g, 5.1 mmol) and H_2NTs (0.29 g, 1.7 mmol) were added to a solution of bromoacetate **4c** (1.0 g, 3.4 mmol) in DMSO (20 mL), and the reaction mixture was heated at 55 °C overnight. The cooled mixture was diluted with EtOAc (100 mL) and washed with brine containing 2% NaOH (3 × 50 mL) and saturated NH_4Cl solution (75 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by flash chromatography (pentane:EtOAc gradient 90:10 → 40:60) to afford compound **19c** (1.1 g, 84%) as a white needles; mp 152–153 °C (from EtOAc) (lit., mp 135 °C)[32]; $[\alpha]_D$ −35 (c 1.0, $CHCl_3$); υ_{max}/cm^{-1} 1157, 1255, 1729; δ_H (500 MHz; $CDCl_3$) 1.80 (l H, m, H-5), 2.01 (3 H, s, Me), 2.05 (3 H, m, H-5′, H-6, H-6′), 2.44 (3 H, s, Me), 4.30 (1 H, m, H-4), 4.55 (1 H, d, *J* 6.5, NH), 5.34 (1 H, q, *J* 3.8, H-l), 6.07 (1 H, d, *J* 4.2, H-2), 6.97 (2 H, d, *J* 7.2, Ar), 7.09 (2 H, m, Ar), 7.19 (3 H, m, Ar), 7.53 (2 H, d, *J* 8.2, Ar).

(1S,4S)-3-Phenyl-4-(p-toluenesulfonamido)cyclohex-2-enol **16c**

To a solution of compound **19c** (0.60 g, 1.54 mmol) in MeOH:H_2O (15 mL, 4:1) was added potassium carbonate (0.22 g, 1.60 mmol), and the reaction was stirred overnight at room temperature. The solvents were evaporated under reduced pressure and the crude product recrystallized from MeOH/H_2O to give compound **16c** as white crystals (0.47 g, 90%);

mp 193–194 °C (lit., mp 190–192 °C)[32]; $[\alpha]_D$ −25 (c 1.0, $CHCl_3$); (Found: M^+ 343.1248 $C_{19}H_{21}NO_3S$ requires 343.1242); υ_{max}/cm^{-1} 1014, 1158; δ_H (500 MHz; $CDCl_3$) 1.71 (l H, m, H-5), 2.08 (3 H, m, H-5′, H-6, H-6′), 2.46 (3 H, s, Me), 4.27 (2 H, m, H-4, NH), 4.34 (1 H, m, H-1), 6.10 (1 H, d, *J* 4.1, H-2), 6.99 (2 H, d, *J* 7.2, Ar), 7.09 (2 H, m, Ar), 7.19 (3 H, m, Ar), 7.50 (2 H, dm, *J* 8.2, Ar); *m/z* (LSIMS) 343 (M^+, 25%).

(1S,2R)-3-Chloro-2-morpholinylcyclohex-3-enol ***20a***

A solution of chloroepoxide **5a** (0.34 g, 2.61 mmol) and morpholine (0.23 mL, 2.61 mmol) in MeOH (25 mL) containing $ZnCl_2$ (18 mg, 0.13 mmol) was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the crude product purified by PLC (EtOH) to furnish compound **20a**; (0.44 g, 76%); $[\alpha]_D$ +10 (c 0.93, $CHCl_3$); (Found: M^+ 217.0868 $C_{10}H_{16}O_2N^{35}Cl$ requires 217.0870); δ_H (500 MHz; $CDCl_3$); 1.64 (1 H, m, H-6), 1.99 (1 H, m, H-6′), 2.13 (2 H, m, H-5, H-5′), 2.29 (2 H, m, CH_2), 3.04 (2 H, m, CH_2), 3.13 (1 H, d, *J* 5.8, H-2), 3.69 (5 H, m, 2xCH_2, H-1), 5.92 (1 H, s, H-4); δ_C (125 MHz; $CDCl_3$) 24.24, 28.23, 50.15, 68.42, 68.73, 72.62, 129.77; *m/z* (EI) 219 (M^+, ^{37}Cl, 10%), 217 (M^+, ^{35}Cl, 32%), 175 (30), 173 (100), 160 (10), 158 (28), 144 (14), 142 (40), 138 (17), 80 (27), 67 (11).

(1S,2R)-3-Bromo-2-(4′-phenylpiperin-1′-yl)cyclohex-3-enol ***21b***

Zinc chloride (6 mg, 0.043 mmol) was added to a solution of bromoepoxide **5b** (0.15 g, 0.86 mmol) and 4-phenylpiperidine (0.14 g, 0.86 mmol) in methanol (25 mL) and the reaction mixture stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the crude product purified by PLC (Et_2O:hexane, 3:7) to give compound **21b** as a colourless oil (0.2 g, 70%); $[\alpha]_D$ +12.5 (c 0.16, $CHCl_3$); (Found: M^+ 335.0882 $C_{17}H_{22}ONBr$ requires 335.0885); δ_H (500 MHz; $CDCl_3$) 1.71 (3 H, m, H-6, H-9, H-11), 1.88 (2 H, m, H-9′, H-11′), 2.05 (1 H, m H-6′), 2.13 (2 H, m, H-5, H-5′), 2.57 (1 H, m, H-10), 2.94 (3 H, m, H-8′, H-12, H-12′), 3.28 (1 H, d, *J* 5.8, H-2), 3.43 (1 H, t, *J* 10.8, H-8), 3.76 (1 H, m, H-1), 6.18 (1 H, s, H-4), 7.22 (3 H, m, ArH), 7.31 (2 H, t, *J* 7.5, ArH); δ_C (125 MHz; $CDCl_3$) 25.97, 28.41, 34.95, 35.58, 43.94, 46.28, 54.35, 60.83, 69.33, 73.83, 122.55, 126.55, 127.27, 128.83, 133.60, 146.85, 171.56; *m/z* (EI) 337 (M^+ ^{81}Br, 8%) 335 (M^+ ^{79}Br 13%), 334 (22), 292 (82), 290 (79), 212 (100), 117 (17), 108 (37), 104 (19), 91 (30), 80 (32), 67 (23).

(1S,2S)-2-Morpholinylcyclohexanol ***22***

To a solution of (1*S*,2*R*)-3-chloro-2-morpholinyl-cyclohex-3-enol **20a** (0.33 g, l.22 mmol), in EtOH (10 mL) containing Et_3N (0.1 mL), was added 10% Pd-C (10 mg), and the reaction mixture stirred overnight under a hydrogen atmosphere. The catalyst was filtered off and the crude product purified by PLC (0.5% NH_3 in EtOH) to yield compound **22** as a white crystalline solid (0.27 g, 94%); (Found: M^+ 185.1418 $C_{10}H_{19}O_2N$ requires 185.1415); δ_H (500 MHz; $CDCl_3$) 0.98 (4 H, m, H-4, H-4′, H-5, H-5′), 1.53 (3 H, m, H-2, H-3, H-3′), 1.90 (2 H, m, H-6, H-6′), 2.19 (2 H, m, H-7, H-10), 2.48 (2 H, m, H-7′, H-10′), 3.14 (1 H, dt, *J* 4.7, 10, H-1), 3.47 (4 H, m, H-8, H-8′, H-9, H-9′); *m/z* (EI) 185 (M^+, 28%), 126 (98), 86 (100).

(1S,2S)-2-(4′-Phenylpiperidin-1′-yl)cyclohexanol ***23***

(1*S*,2*R*)-3-Bromo-2-(4′-phenylpiperin-l′-yl)cyclohex-3-enol **21b** (0.15 g, 0.45 mmol) was converted into (1*S*,2*S*)-2-(4′-phenylpiperidin-l′-yl) cyclohexanol following the catalytic hydrogenation procedure used for the synthesis of compound **22**. The crude product was purified by crystallization (CH_2Cl_2) to yield the aminoalcohol **23** a white crystalline solid (0.10 g, 92%); mp 239–241 °C; $[\alpha]_D$ +26 (c 1.03, EtOH); (Found: M^+ 259.1933 $C_{17}H_{25}ON$ requires 259.1936); δ_H (500 MHz; $CDCl_3$) 1.34 (8 H, m, H-3, H-3′, H-4, H-4′, H-5, H-5, H-6, H-6′), 1.81 (1 H, m, H-7), 1.91 (1 H, m, H-7′), 2.07(1 H, m, H-11), 2.22 (1 H, m, H-11′), 2.65 (1 H, m, H-9), 3.07 (2 H, dt, *J* 11.0, 2.4, H-8, H-10), 3.30 (1 H, t, *J* 10.5, H-2), 3.71 (2 H, m, H-8′, H-10′), 3.83 (1 H, td, *J* 4.6, 0.8, H-1), 7.27 (3 H, m, ArH), 7.32 (2 H, m, ArH); δ_C (125 MHz; $CDCl_3$) 24.39, 24.89, 25.10, 30.95, 31.17, 35.31, 49.05, 53.31, 69.83, 71.47, 127.27, 127.63, 129.28; *m/z* (EI) 259 (M^+, 1%), 248 (35%), 232 (34), 172 (31), 155 (42), 154 (65), 130 (38), 128 (38), 115 (42), 105 (36), 91 (25), 77 (20).

REFERENCES

[1] a) D.A. Widdowson, D.W. Ribbons, S.D. Thomas, *Janssen Chimica Acta* **1990**, *8*, 3; b) H.A.J. Carless, S.S. Malik, *Tetrahedron-Asymmetry* **1992**, *3*, 1135; c) G.N. Sheldrake, *Chirality in Industry*, Wiley Ltd, Chichester, **1992**, d) S.M. Resnick, K. Lee, D.T. Gibson, *J. Indus. Microbiol.* **1996**, *17*, 438; e) D.R. Boyd, G.N. Sheldrake, *Nat. Prod. Rep.* **1998**, *15*, 309; f) T. Hudlicky, D. Gonzalez, D.T. Gibson, *Aldrichim. Acta.* **1999**, *11*, 236; g) D.R. Boyd, N.D. Sharma, C.C.R. Allen, *Curr. Opin. Biotechnol.* **2001**, *12*, 564; h) R.A. Johnson, *Org Reactions* **2004**, *63*, 117; i) D.R. Boyd, T.D.H. Bugg, *Org. Biomol. Chem.* **2006**, *4*, 181; j) T. Hudlicky, J.W. Reed, *Chem. Soc. Rev.* **2009**, *38*, 3117; k) M.A. Khan, J.P. Lowe, A.L. Johnson, A.J.W. Stewart, S.E. Lewis, *Chem. Commun.* **2011**, *47*, 215; l) D. Bon, B. Lee, M.G. Banwell, I.A. Cade, *Chim. Oggi* **2012**, *30*, 22.

[2] J. Duchek, D.R. Adams, T. Hudlicky, *Chem. Rev.* **2011**, *111*, 4223.

[3] a) T.A. Reekie, M.G. Banwell, A.C. Willis, *J. Org. Chem.* **2012**, *77*, 10773; b) D. Bon, M.G. Banwell, J.S. Ward, A.C. Willis, *Tetrahedron* **2013**, *69*, 1363; c) N. Gao, X.H. Ma, L. Petit, B.D. Schwartz, M.G. Banwell, A.C. Willis, I.A. Cade, A.D. Rae, *Aust. J. Chem.* **2013**, *66*, 30; d) B.D. Schwartz, L.V. White, M.G. Banwell, A.C. Willis, *J. Org. Chem.* **2011**, *76*, 8560; e) B.D. Schwartz, M.G. Banwell, I.A. Cade, *Tetrahedron Lett.* **2011**, *52*, 4526; f) L.V. White, B.D. Schwartz, M.G. Banwell, A.C. Willis, *J. Org. Chem.* **2011**, *76*, 6250; g) D.R. Adams, C. Aichinger, J. Collins, U. Rinner, T. Hudlicky, *Synlett* **2011**, 1188; h) V. Semak, T.A. Metcalf, M.A.A. Endoma-Arias, P. Mach, T. Hudlicky, *Org. Biomol. Chem.* **2012**, *10*, 4407; i) V. Varghese, T. Hudlicky, *Synlett* **2013**, 369; j) S. Vshyvenko, J. Scattolon, T. Hudlicky, A.E. Romero, A. Kornienko, D. Ma, I. Tuffley, S. Pandey, *Can. J. Chem.* **2012**, *90*, 932; k) L. Werner, A. Machara, B. Sullivan, I. Carrera, M. Moser, D.R. Adams, T. Hudlicky, J. Andraos, *J. Org. Chem.* **2011**, *76*, 10050; l) M.A.A. Endoma-Arias, T. Hudlicky, *Tetrahedron Lett.* **2011**, *52*, 6632; m) J. Duchek, T.G. Piercy, J. Gilmet, T. Hudlicky, *Can. J. Chem.* **2011**, *89*, 709; n) M.J. Palframan, G. Kociok-Kohn, S.E. Lewis, *Chem.-Eur. J.* **2012**, *18*, 4766; o) M.J. Palframan, G. Kociok-Kohn, S.E. Lewis, *Org. Lett.* **2011**, *13*, 3150; p) D.R. Boyd, N.D. Sharma, C.A. Acaru, J.F. Malone, C.R. O'Dowd, C.C.R. Allen, P.J. Stevenson, *Org. Lett.* **2010**, *12*, 2206.

[4] D.R. Boyd, N.D. Sharma, M. Kaik, P.B.A. McIntyre, P.J. Stevenson, C.C. R. Allen, *Org. Biomol. Chem.* **2012**, *10*, 2774.

[5] D.R. Boyd, N.D. Sharma, J.G. Carroll, P.L. Loke, C. O' Dowd, C.C.R. Allen, *RSC Adv.* **2013**, 11, DOI: 10.1039/c3ra42026d

[6] D.R. Boyd, M. Bell, K.S. Dunne, B. Kelly, P.J. Stevenson, J.F. Malone, C. C.R. Allen, *Org. Biomol. Chem.* **2012**, *10*, 1388.

[7] a) D.R. Boyd, N.D. Sharma, M. Kaik, M. Bell, M.V. Berberian, P.B.A. McIntyre, B. Kelly, C. Hardacre, P.J. Stevenson, C.C.R. Allen, *Adv. Syn. Cat.* **2011**, *353*, 2455; b) D.R. Boyd, N.D. Sharma, L. Sbircea, D. Murphy, J.F. Malone, S.L. James, C.C.R. Allen, J.T.G. Hamilton, *Org. Biomol. Chem.* **2010**, *8*, 1081; c) D.R. Boyd, N.D. Sharma, L. Sbircea, D. Murphy, T. Belhocine, J.F. Malone, S.L. James, C.C.R. Allen, J.T.G. Hamilton, *Chem. Commun.* **2008**, 5535; d) D.R. Boyd, N.D. Sharma, N.I. Bowers, P.A. Goodrich, M.R. Groocock, A.J. Blacker, D.A. Clarke, T. Howard, H. Dalton, *Tetrahedron-Asymmetry* **1996**, *7*, 1559.

[8] D.R. Boyd, N.D. Sharma, N.M. Llamas, C.R. O'Dowd, C.C.R. Allen, *Org. Biomol. Chem.* **2007**, *5*, 2267.

[9] T. Borrmann, W.D. Stohrer, *Ann.* **1996**, 1593; b) W.D. Stohrer, *Angew. Chem. Int. Ed Engl.* **1983**, *22*, 613; c) R.M. Magid, *Tetrahedron* **1980**, *36*, 1901.

[10] J.A. Marshall, *Chem. Rev.* **1989**, *89*, 1503.

[11] a) G. Jindal, R.B. Sunoj, *Chem. -Eur. J.* **2012**, *18*, 7045; b) D. Grassi, A. Alexakis, *Org. Lett.* **2012**, *14*, 1568; c) J.B. Langlois, D. Emery, J. Mareda, A. Alexakis, *Chemical Science* **2012**, *3*, 1062; d) J.B. Langlois, A. Alexakis, *Angew. Chem. Int. Ed Engl.* **2011**, *50*, 1877; e) M. Fananas-Mastral, B. ter Horst, A.J. Minnaard, B. Feringa, *Chem. Commun.* **2011**, *47*, 5843; f) J.B. Langlois, A. Alexakis, *Adv. Syn. Cat.* **2011**, *352*, 447; g) E.R. Bartholomew, S.H. Bertz, S. Cope, M. Murphy, C.A. Ogle, *J. Am. Chem. Soc.* **2008**, *130*, 11244; h) A. Alexakis, J.E. Backvall, N. Krause, O. Pamies, M. Dieguez, *Chem. Rev.* **2008**, *108*, 2796.

[12] a) M.G. Banwell, N. Haddad, T. Hudlicky, T.C. Nugent, M.F. Mackay, S. L. Richards, *J. Chem. Soc., Perkin Trans. 1* **1997**, 1779; b) T. Hudlicky, H. Luna, H.F. Olivo, C. Anderson, T. Nugent, J.D. Price, *J. Chem. Soc.,*

Perkin Trans. 1 **1993**, 535; c) J.T. Kohrt, J.X. Gu, C.R. Johnson, *J. Org. Chem.* **1998**, *63*, 5088.
[13] a) J.S. Kudavalli, S.N. Rao, D.E. Bean, N.D. Sharma, D.R. Boyd, P.W. Fowler, S. Gronert, S.C.L. Kamerlin, J.R. Keeffe, R.A. More O' Ferrall, *J. Am. Chem. Soc.* **2012**, *134*, 14056; b) D.R. Boyd, J. Blacker, B. Byrne, H. Dalton, M.V. Hand, S.C. Kelly, R.A. More O' Ferrall, S.N. Rao, N.D. Sharma, G.N. Sheldrake, *J. Chem. Soc., Chem. Commun.* **1994**, 313.
[14] D.R. Boyd, N.D. Sharma, V. Ljubez, P.K.M. McGeehin, P.J. Stevenson, M. Blain, C.C.R. Allen, *Org. Biomol. Chem.* **2013**, 3020.
[15] A.R. Mattocks, *J. Chem. Soc. 1964*, **1918**.
[16] C.A. Vander Werf, R.Y. Heisler, W.E. McEwen, *J. Am. Chem. Soc.* **1954**, *76*, 1231.
[17] A. Gagneux, S. Winstein, W.G. Young, *J. Am. Chem. Soc.* **1960**, *82*, 5965.
[18] a) J.S. Panek, M. Yang, I. Muler, *J. Org. Chem.* **1992**, *57*, 4063; b) P.H. Lu, C.S. Yang, B. Devendar, C.C. Liao, *Org. Lett.* **2012**, *12*, 2642; c) G. Cardillo, S. Fabbroni, L. Gentilucci, R. Perciaccante, F. Piccinelli, A. Tolomelli, *Org. Lett.* **2005**, *7*, 533; d) G. Righi, L.S. Manni, P. Bovicelli, R. Pelagalli, *Tetrahedron Lett.* **2011**, *52*, 3895; e) P.S. Reddy, V. Ravi, B. Sreedhar, *Tetrahedron Lett.* **2010**, *51*, 4037; f) J.D. Ha, S.Y. Kim, S.J. Lee, S.K. Kang, J.H. Ahn, S.S. Kim, J.K. Choi, *Tetrahedron Lett.* **2004**, *45*, 5969.
[19] a) S. Lauzon, F. Tremblay, D. Gagnon, C. Godbout, C. Chabot, C. Mercier-Shanks, S. Perreault, H. DeSeve, C. Spino, *J. Org. Chem.* **2008**, *73*, 6239; b) D. Gagnon, S. Lauzon, C. Godbout, C. Spino, *Org. Lett.* **2005**, *7*, 4769.
[20] a) R.Z. Liu, O. Gutierrez, D.J. Tantillo, J. Aube, *J. Am. Chem. Soc.* **2012**, *134*, 6528; b) A.K. Feldman, B. Colasson, K.B. Sharpless, V.V. Fokin, *J. Am. Chem. Soc.* **2005**, *127*, 13444; c) D. Craig, J.W. Harvey, A.G. O'Brien, A.J.P. White, *Org. Biomol. Chem.* **2011**, *9*, 7057.
[21] A. Jabbari, *Org. Chem. J.* **2010**, *1*, 6.
[22] B.M. Trost, S.R. Pulley, *Tetrahedron Lett.* **1995**, *36*, 8737.
[23] M.J. McManus, G.A. Berchtold, D.M. Jerina, *J. Am. Chem. Soc.* **1985**, *107*, 2977.
[24] Y.K. Chang, H.J. Lo, T.H. Yan, *Org. Lett.* **2009**, *11*, 4278.
[25] M.A. Khan, M.F. Mahon, J.P. Lowe, A.J.W. Stewart, S.E. Lewis, *Chem. - Eur. J.* **2012**, *18*, 13480.
[26] a) T.L. Shih, W.S. Kuo, Y.L. Lin, *Tetrahedron Lett.* **2004**, *45*, 5751; b) S.T. Murphy, J.R. Bencsik, C.R. Johnson, *Org. Lett.* **1999**, *1*, 1483; c) R. Lysek, S. Favre, P. Vogel, *Tetrahedron* **2007**, *63*, 6558; d) M.A.L. Podeschwa, O. Plettenburg, H.J. Altenbach, *Org. Biomol. Chem.* **2003**, *1*, 1919; e) Y.S. Lai, M. Stamper, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2147.
[27] O. Block, G. Klein, H.J. Altenbach, D.J. Brauer, *J. Org. Chem.* **2000**, *65*, 716.
[28] H.B. Guo, G.A. O'Doherty, *Org. Lett.* **2006**, *8*, 1609.
[29] M. Cakmak, P. Mayer, D. Trauner, *Nat. Chem.* **2011**, *3*, 543.
[30] O. Mitsunobu, *Synthesis* **1981**, 1.
[31] a) S. Grimme, *Angew. Chem. Int. Ed Engl.* **2006**, *45*, 4460; b) D.S. Ribeiro, R. Rittner, *J. Org. Chem.* **2003**, *68*, 6780.
[32] A. Palmgren, A.L.E. Larsson, J.E. Backvall, P. Helquist, *J. Org. Chem.* **1999**, *64*, 836.
[33] F. Johnson, *Chem. Rev.* **1968**, *68*, 375.
[34] H. Varoqui, J.D. Erickson, *J. Biol. Chem.* **1996**, *44*, 27229.
[35] H. Yagi, D.M. Jerina, *J. Am. Chem. Soc.* **1975**, *97*, 3185.