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Construction of functionalised medium rings by stereospecific expansions of 2,3-epoxy alcohols under mild conditions

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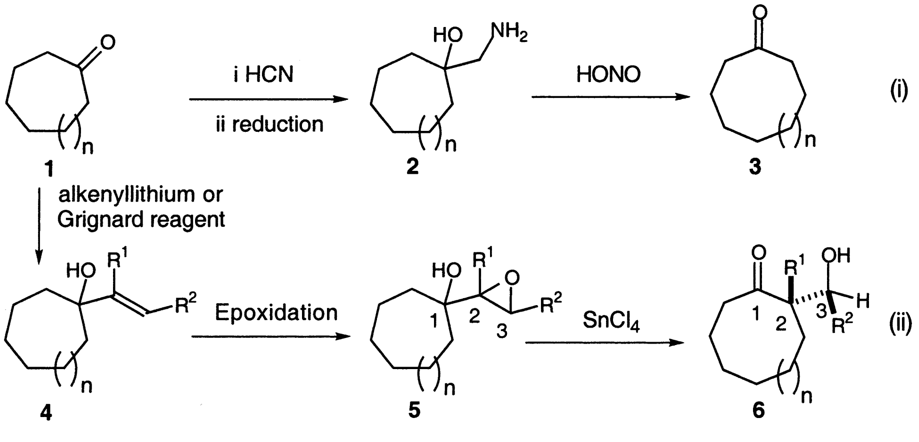
Abstract—Ketones are converted with very high stereocontrol into functionalised medium rings incorporating a β-hydroxy ketone assembly via a ring-expansion mediated by tin(IV) chloride at low temperatures; either the *threo* or the *erythro* aldol products can be obtained. An asymmetric epoxidation permitted a subsequent highly enantiocontrolled semi-pinacol rearrangement. © 2002 Elsevier Science Ltd. All rights reserved.

Carbon-to-carbon migrations have been of continuing importance ever since the pioneering work of Wagner and Meerwein.[1] Ring expansions involving carbon-to-carbon migrations form an important means of access to medium rings and macrocyclic compounds.[2] The Tiffeneau–Demjanov ring expansion, represented by the conversion of amino alcohol **2** into ketone **3**, is a venerable process,[3] but results in no more (if any) stereocentres in the product (e.g. **3**) than in the β-amino alcohol (e.g. **2**), and yields are usually modest. Homologation of ketones by the addition of diazoalkanes[4] (e.g. **1** to **3**) provides a useful alternative route to the Tiffeneau–Demjanov and related procedures, but suffers from the hazards in preparing and handling aliphatic diazoalkanes. Consequently, we sought an alternative ring expansion that would also permit the establishment of new stereocentres of defined configuration. We here report a stereocontrolled rearrangement of epoxy alcohols **5** to give the readily isolable aldol type products **6** (Scheme 1).[5]



Scheme 1. Routes to medium ring ketones.

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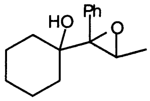
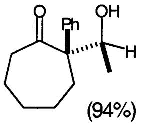
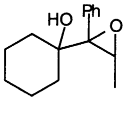
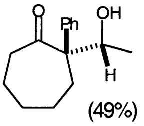
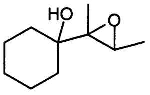
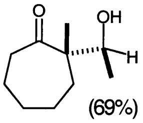
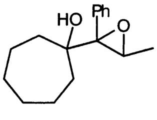
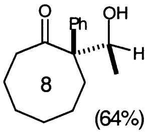
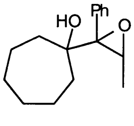
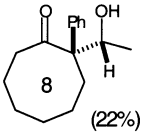
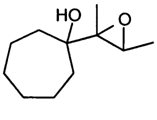
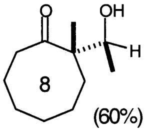
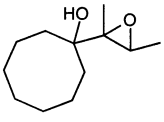
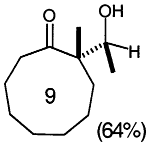
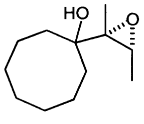
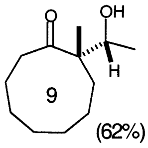
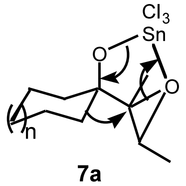
Such 2-(1-hydroxyalkyl)cycloalkanones **6** could in principle be obtained by an aldol addition of R^2CHO to a cycloalkanone, but such aldol condensations have been found to proceed with poor stereocontrol,[6] unlike the present protocol which permits isolation of a single diastereoisomer. This ring expansion has the starting material, ketone **1**, in common with the Tiffeneau–Demjanov procedure, but differs in that the resulting cycloalkanone possesses two newly created stereocentres, one incorporated as part of the ring, and the other adjacent to it, but as part of the α-substituent.

Table 1. Ring expansion of epoxy cycloalkanols using tin(IV) chloride (2.0 mol. equiv.) in dichloromethane

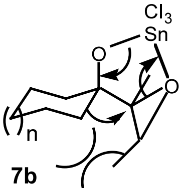
Entry	Epoxy alcohol	Conditions	2-(1-Hydroxyalkyl)cycloalkanone[a]
1.	 **5a**	-78 °C 15 min	 (94%) **6a**
2.	 **5b**	-78 °C 1 h	 (49%) **6b**
3.	 **5c**	-78 °C to -15 °C over 3 h	 (69%) **6c**
4.	 **5d**	-78 °C to 0 °C over 4 h	 (64%) **6d**
5.	 **5e**	-78 °C 15 min	 (22%) **6e**
6.	 **5f**	-78 °C to -15 °C over 2 h	 (60%) **6f**
7.	 **5g**	-78 °C to -65 °C over 2 h	 (64%) **6g**
8.	 **5h**	-78 °C 15 min	 (62%) **6h**

[a] Absolute configurations are depicted for **5h** and **6h**; all other configurations are relative.

Reaction of a cycloalkanone **1** with an alkenyllithium[7] or Grignard reagent[8] afforded the corresponding achiral allylic alcohol **4**.[9] The allylic alcohols **4** were epoxidised with *m*-CPBA (1.5–2.0 equiv.) in chloroform, prior to addition of KF and isolation of the epoxy alcohols **5** by column chromatography. Representative epoxy alcohols **5** were reacted with tin(IV) chloride at low temperatures, and the products of ring expansion were isolated (Table 1). The 2-(1-hydroxyalkyl)-cycloalkanone from each reaction was isolated as a single diastereoisomer; that is consistent with a concerted process involving 1,2-migration with inversion of configuration at the epoxide carbon atom undergoing displacement.[10–12] Such inversion during 1,2-migration of carbon has been repeatedly demonstrated in closely related systems, e.g. where a ring replaces the *cis*-dimethyl groups in **5c**.[10a] Related 1,2-migrations of epoxy alcohols have also been shown to proceed with inversion.[10b,c,11,12] The stereochemistry at the 3-position of **5** (numbering as in eq. (ii) was transmitted intact to the product **6**, but was found to have a marked effect on the yield. For epoxy alcohols **5a**, **5c**, **5d**, **5f**, and **5h**, all of which lack steric bulk at the 3-position that could be proximate to the cycloalkane ring, the yields are satisfactory to excellent. In contrast, a cyclohexanol with a methyl group proximate to the ring gave a much lower yield (49% for **5b**) than did one bearing a 3-methyl group placed distal to the cyclohexyl ring (94% for **5a**). A similar pattern was observed for reactions of the stereoisomers **5d** and **5e**. However, the yields of the cyclononanones **6g** and **6h** are comparable, perhaps indicating that either stereoisomer may be satisfactorily prepared for larger rings. A contributing factor is considered to be the more ready attainment, in a larger ring, with its greater flexibility and smaller non-bonding interactions, of a colinear arrangement of the migrating σ-bond electron density with that of the C–O bond of the epoxide undergoing rupture. Migration facilitated by chelation control[10–12] is as shown for **7a**. The isomer corresponding to **7b** also undergoes migration, though evidently significantly less readily where *n* is less than or equal to two, compared with larger rings.



7a



7b

The feasibility of an enantioselective variant of the ring expansion reaction was probed by repeating entry 8, but with asymmetric epoxidation of the corresponding allylic alcohol[13] (TBHP, 10 mol% Ti(O-^{i}Pr)$_4$, 15 mol% of L-(+)-diethyl tartrate, −20°C to 15°C, 16 h). The enantioenriched **5h** was treated with $SnCl_4$ giving **6h** in 40% ee, corresponding to the enantiopurity of the sample of **5h**. (Ees were determined by splitting of the 3-methyl signals in the ^{1}H NMR spectrum induced by sequential addition of aliquots of Eu(hfc)$_3$ to the corresponding acetates of **5h** and **6h**).

The overall transformation of **1** into **6** corresponds to a formal alkylation (R^1) of the homologous cycloalkanone followed by a completely stereocontrolled aldol addition of R^2CHO (to the same α-carbon atom), an overall process that cannot be readily achieved.[14] In fact, aldol processes involving α-substituted cycloalkanones at the α-position are very limited and usually proceed with little stereoselectivity.[6] Thus, this methodology is useful in furnishing in diastereoisomerically pure form either the *threo* or the *erythro* aldol products (depending solely on whether the *E*- or the *Z*-alkene is used). The formation of a quaternary centre[15] on the cycloalkanone ring is a desirable protocol, useful in the synthesis of natural products.[15]

In conclusion, a stereospecific ring expansion, that can be an asymmetric process, is disclosed that allows medium rings to be assembled with two adjacent stereocentres. This represents a significant advance on previous ring expansions of ketones, and also enhances existing aldol strategies. The scope and synthetic applications of this ring expansion protocol are under investigation.

Acknowledgements

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pressure. The residue was purified by column chromatography to give the β-hydroxyketone **6d** as a colourless oil.

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