Probing the mechanism of Prins cyclisations and application to the synthesis of 4-hydroxytetrahydropyrans

Conor S. Barry,[a] Nick Bushby,[b] John R. Harding,[b] Rachael A. Hughes,[a] Gregory D. Parker,[a] Richard Roe[a] and Christine L. Willis*[a]

Received (in Cambridge, UK) 1st April 2005, Accepted 19th May 2005
First published as an Advance Article on the web 16th June 2005
DOI: 10.1039/b504562b

Trapping intermediates on the Prins cyclisation pathway with carbon-based nucleophiles has given further insight into factors affecting the acid-mediated reactions of homoallylic alcohols with aldehydes, enabling the design of efficient syntheses of 4-hydroxy-2,6-disubstituted tetrahydropyrans.

Substituted tetrahydropyrans are common structural features of an array of biologically active natural products and many incorporate an alcohol (or sugar) at C-4. A valuable approach to the synthesis of these heterocycles is the acid-promoted Prins-type cyclisation of an oxycarbenium ion generated *in situ*, for example, from reaction of a homoallylic alcohol with an aldehyde or from a homoallylic acetal or α-acetoxy ether.[1] Various reaction conditions have been employed to prepare C-4 oxygenated tetrahydropyrans.[2] In many cases they are formed in high yield and with good stereocontrol, incorporating an equatorial hetero-atom at the C-4 position. Interestingly, the selective introduction of an axial bromide has been achieved recently.[3]

The mechanism of the Prins cyclisation is not simple and there is good evidence for the participation of oxonia-Cope rearrangements.[4] In addition, Alder and co-workers have proposed that cyclisation proceeds *via* a delocalised cationic intermediate.[5] In this paper we report our recent investigations which have led to a deeper understanding of Prins-type cyclisations which facilitate the design of synthetic routes to 4-hydroxytetrahydropyrans.

We have reported that treatment of benzylic homoallylic alcohols with aldehydes in the presence of $BF_3{\cdot}OEt_2$, AcOH and TMSOAc gave up to 4 products depending upon the electron density of the aromatic ring.[6] The isolated species include the desired 4-acetoxytetrahydropyran **1**, symmetrical tetrahydropyran **2** arising from an allyl exchange process, homoallylic acetate **3** and the parent benzaldehyde **4** (Fig. 1). The proposed reaction mechanism involves oxycarbenium ion **A** which may undergo an oxonia-Cope rearrangement to give **B**; both **A** and **B** may be intermediates to the required tetrahydropyran **1**. Alternatively, fragmentation of **B** leads to an allyl exchange process giving aldehyde **4** and a new homoallylic alcohol **5** with an alkyl side-chain. Reaction of **5** with the parent aldehyde gives symmetrical tetrahydropyran **2**. Furthermore a benzylic carbocation is implicated in the formation of acetate **3**.

The first goal was to gain further evidence for the proposed mechanism (Fig. 1) by trapping the putative intermediates **A**, **B** and **C** and homoallylic acetals were selected as simple precursors to the charged intermediates. Rychnovsky has shown that Bu_3SnH or Et_3SiH can be used as hydride sources in trapping experiments and our studies began using analogous conditions.[4a] Thus, treatment of the electron-rich methoxyethoxymethyl (MEM) ethers **6a** and **6b** with $BF_3{\cdot}OEt_2$ in the presence of Et_3SiH gave solely the deoxygenated species **7a** and **7b** in 83% and 99% yield respectively (Scheme 1).

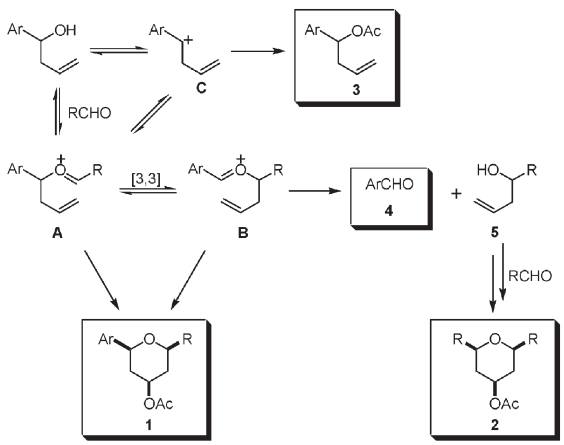
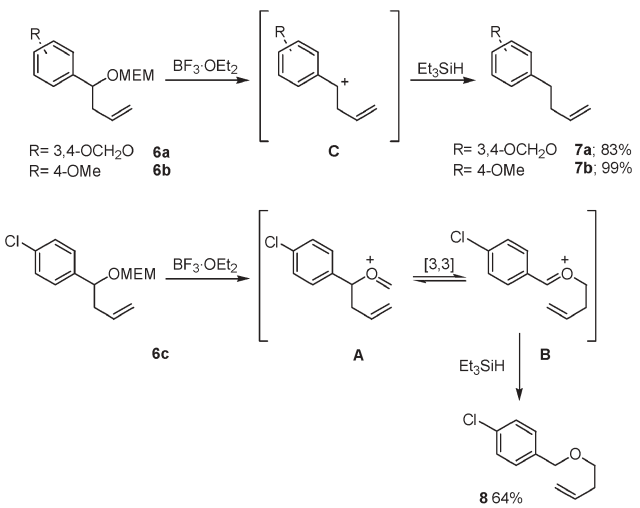


Fig. 1 Proposed mechanistic pathway for the reaction of a benzylic homoallylic alcohol with RCHO, AcOH, TMSOAc and $BF_3{\cdot}OEt_2$.



Scheme 1 Hydride reduction of intermediates **A**, **B** and **C**.

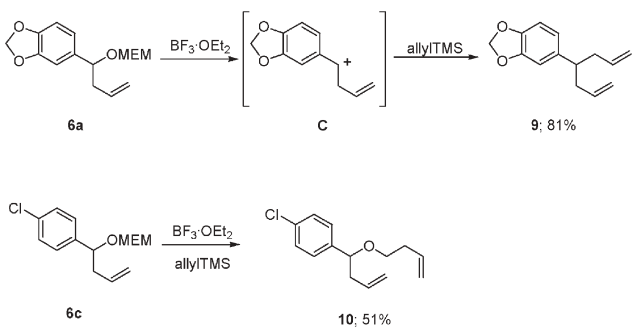
[a]*School of Chemistry, University of Bristol, Cantock's Close, Bristol, UK BS8 1TS. E-mail: chris.willis@bristol.ac.uk*
[b]*AstraZeneca UK Ltd., Mereside, Alderley Park, Macclesfield, UK SK10 4TG*

In contrast, under identical conditions the more electron-deficient analogue **6c** gave allyl ether **8** in 64% yield. These results are in accord with the mechanism shown in Fig. 1. In the case of the 3,4-methylenedioxy and 4-methoxy species **6a** and **6b**, the benzylic carbocation **C** is stabilised by the electron-rich aromatic ring and reduction gives **7**, whereas with the 4-chloro derivative **6c**, in which a benzylic cation is less favoured, the pathway *via* the oxycarbenium ions (**A** and **B**) predominates. Reduction occurs on the more stabilised oxycarbenium ion **B** (in conjugation with the aromatic ring) giving ether **8**. In neither case was there evidence for the formation of tetrahydropyrans.[7] Similar results were obtained using $BF_3{\cdot}OEt_2$-promoted reactions in the presence of carbon-based nucleophiles. Reaction of the electron-rich substrate **6a** with allylTMS and $BF_3{\cdot}OEt_2$ gave diene **9** in 81% yield *via* attack on the benzylic carbocation (Scheme 2), whereas with the electron-deficient 4-chloro derivative **6c**, ether **10** was isolated in 51% yield.

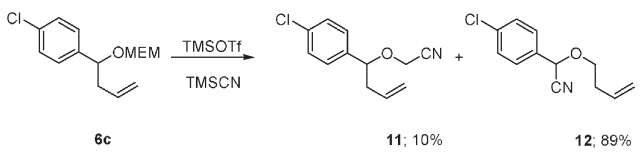
Formation of **10** gives no indication as to whether or not an oxonia-Cope rearrangement is occurring as the product from oxycarbenium ions **A** or **B** with allylTMS would be the same. Thus TMS cyanide was examined as an alternative carbon-based nucleophile (Scheme 3). Homoallylic acetal **6c** was treated with TMS triflate and TMS cyanide to yield a 1:9 mixture of isomeric cyanides **11** and **12**, confirming that in this case an oxonia-Cope rearrangement preferentially occurs prior to formation of the new carbon–carbon bond.

Having probed the acid-promoted reaction of benzylic homoallylic acetals with carbon-based nucleophiles, next trapping of oxycarbenium ions derived from aliphatic homoallylic acetals was investigated (Scheme 4). Treatment of the homoallylic MEM derivative **13** with $AlMe_3$ gave a 1:2 mixture of ethers **14** and **15**, albeit in a disappointing 42% overall yield, whilst with $BF_3{\cdot}OEt_2$ and allylTMS, ether **16** was isolated in 40% yield as approximately a 1:1 mixture of diastereomers.

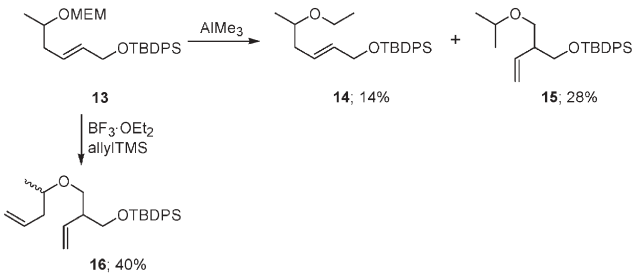
Armed with further evidence for the proposed intermediates **A**–**C** (Fig. 1), further factors which may influence the utility of Prins cyclisations for the synthesis of 4-hydroxytetrahydropyrans were considered. Based on our understanding of the mechanism



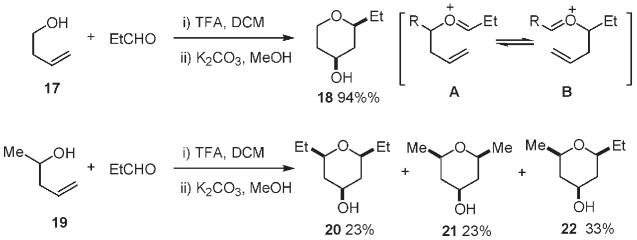
Scheme 2 Allyl trapping of intermediates **A**, **B** and **C**.



Scheme 3 Cyanide trapping of oxycarbenium ion intermediates **A** and **B**.



Scheme 4 Reactions of aliphatic homoallylic acetals.



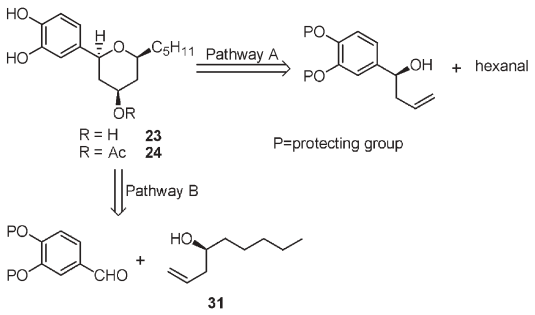
Scheme 5 Cyclisation of a primary and secondary homoallylic alcohol.

and theoretical calculations, it would be predicted that in the acid-promoted reaction of homoallylic primary alcohol **17** with propanal, an oxonia-Cope rearrangement would not be favoured (Scheme 5).

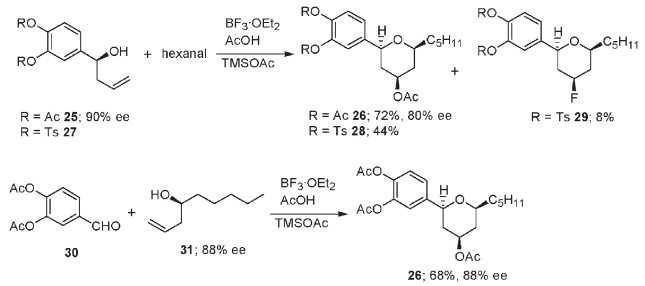
The initially formed oxycarbenium ion (**A**, R = H) is more stable than the unsubstituted oxycarbenium ion **B** by 9.6 kcal mol^{-1} (by semi-empirical energy minimisations calculated using Spartan™12) and the disubstituted tetrahydropyran should be formed cleanly. Indeed this proved to be the case and treatment of **17** with propanal and TFA gave tetrahydropyran **18** in 94% yield following hydrolysis of the initially formed trifluoroacetate (Scheme 5). In contrast, in the case of the secondary alcohol **19**, the two oxycarbenium ions **A** and **B** (R = CH_3) are of similar energy (**A** was calculated to be just 0.42 kcal mol^{-1} more stable using Spartan™12), thus an oxonia-Cope rearrangement and subsequent allyl transfer reaction may occur leading to a mixture of products. As expected, treatment of **19** with propanal and TFA indeed gave, after hydrolysis, two symmetrical tetrahydropyrans **20** and **21** arising from allyl transfer processes as well as the unsymmetrical tetrahydropyran **22**.

Whilst oxycarbenium ion stability is important, the outcome of the reaction of a homoallylic alcohol and aldehyde under acidic conditions may be influenced by further factors including the nature of the acid and nucleophile. For example, Rychnovsky has shown that reaction of 3-phenyl-3-hydroxybut-1-ene and 3-phenylpropanal with $BF_3{\cdot}Et_2O$ and AcOH gave a mixture of 4 products, whereas with $SnBr_4$ a cleaner reaction occurred, giving the 4-bromotetrahydropyran as the major product in 77% yield.[1f]

We have reported[8] the use of a Prins cyclisation (pathway A, where P = Ac, Scheme 6) to construct the tetrahydropyran core of catechols **23** and **24** isolated from extracts of the woody plant, *Plectranthus sylvestris* (*Labiatae*).[9] Treatment of (*S*)-homoallylic alcohol **25** (90% ee) with hexanal in the presence of $BF_3{\cdot}OEt_2$, AcOH and TMSOAc gave the required tetrahydropyran **26** in 72% yield as a single diastereomer but with some loss of enantiopurity (80% ee) (Scheme 7).



Scheme 6 Retrosynthetic analysis of catechols **23** and **24**.



Scheme 7 Construction of framework of catechols **23** and **24**.

Based on the further insight into the mechanism of Prins reactions gained in the investigations described herein, we returned to the synthesis of catechols **23** and **24**. It was apparent that if the tetrahydropyran core was to be constructed *via* pathway A (Scheme 6), then the aromatic ring of the benzylic homoallylic alcohol would need to be more deactivated than in diacetate **25**. Thus the ditosylate **27** was investigated. Treatment of **27** with hexanal under the $BF_3{\cdot}OEt_2$-promoted cyclisation conditions gave 4-acetoxytetrahydropyran **28** as a single diastereomer in 44% yield along with the corresponding 4-fluoro derivative **29** (8%) and recovered starting material **25** (41%) (Scheme 7). All attempts to convert ditosylate **28** to the required catechols **23** and **24** were unsuccessful, leading to decomposition.[10]

Thus the retrosynthetic analysis of catechols **23** and **24** was reconsidered (Scheme 6). In pathway B, the homoallylic alcohol **31** now has a simple alkyl side-chain which is less able to stabilise a carbocation than the benzylic analogue and hence it was predicted that tetrahydropyran **26** should be formed with no loss of stereochemical integrity. In addition, the initially formed oxycarbenium ion would be stabilised by conjugation with the aromatic ring and thus an oxonia-Cope rearrangement would be disfavoured. Using 3,4-diacetoxybenzaldehyde **30** and racemic alcohol under the standard $BF_3{\cdot}OEt_2$-mediated conditions gave tetrahydropyran **26** in 68% yield (Scheme 7). (*S*)-Homoallylic alcohol **31**, was prepared in 91% yield by treatment of hexanal with allylmagnesium chloride and (+)-DIPC1.[11] Reaction of **31** (88% ee as determined by chiral GC) with hexanal under the standard conditions gave the required tetrahydropyran **26** (88% ee) with no loss of stereochemical purity. Hydrolysis of the acetates in **26** as previously reported gave a short and efficient route for the syntheses of the natural products **23** and **24**.[8] Thus by judicious choice of the components for the Prins cyclisation, the synthesis of the catechols was achieved with excellent stereocontrol and with no loss of enantiopurity of the starting homoallylic alcohol.

In conclusion, we have shown that oxycarbenium ion intermediates **A** and **B** (Fig. 1) in Prins cyclisations may be trapped with carbon-based nucleophiles (allylTMS, TMSCN and $AlMe_3$). In addition, in the case of electron-rich benzylic homoallylic alcohols the proposed benzylic carbocation **C** may be trapped with either a hydride source or allylTMS. A deeper understanding of the mechanism of the Prins cyclisation has enabled a more effective route to the enantioselective synthesis of catechols **23** and **24** to be achieved. Armed with this further knowledge of factors affecting the outcome of Prins-type cyclisations, the design of efficient strategies to the synthesis of complex tetrahydropyrans will be possible.

We are grateful to AstraZeneca UK Ltd, the University of Bristol and EPSRC for funding to CSB, RAH and GDP and to Professor R. W. Alder for valuable assistance with molecular modelling and calculations.

Notes and references

1 Examples of Prins cyclisations include: (*a*) M. J. Cloninger and L. E. Overman, *J. Am. Chem. Soc.*, 1999, **121**, 1092; (*b*) S. D. Rychnovsky, Y. Hu and B. Ellsworth, *Tetrahedron Lett.*, 1998, **39**, 7271; (*c*) E. H. Al-Mutairi, S. R. Crosby, J. Darzi, J. R. Harding, R. A. Hughes, C. D. King, T. J. Simpson, R. W. Smith and C. L. Willis, *Chem. Commun.*, 2001, 835; (*d*) D. J. Dixon, S. V. Ley and E. W. Tate, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1829; (*e*) D. J. Hart and C. E. Bennett, *Org. Lett.*, 2003, **5**, 1499; (*f*) J. E. Dalgard and S. D. Rychnovsky, *J. Am. Chem. Soc.*, 2004, **126**, 15662.

2 For examples of the introduction of an oxygen-containing nucleophile at C-4 see: (*a*) W.-C. Zhang and C.-J. Li, *Tetrahedron*, 2000, **56**, 2403; (*b*) S. D. Rychnovsky and C. R. Thomas, *Org. Lett.*, 2000, **2**, 1217; (*c*) C. St. J. Barry, S. R. Crosby, J. R. Harding, R. A. Hughes, C. D. King, G. D. Parker and C. L. Willis, *Org. Lett.*, 2003, **5**, 2429; (*d*) S. A. Kozmin, *Org. Lett.*, 2001, **3**, 755; (*e*) M. Nishizawa, T. Shigaraki, H. Takao and H. T. Imagawa, *Tetrahedron Lett.*, 1999, **40**, 1153.

3 R. Jasti, J. Vitale and S. D. Rychnovsky, *J. Am. Chem. Soc.*, 2004, **126**, 9904.

4 Examples of oxonia-Cope rearrangements include: (*a*) S. D. Rychnovsky, S. Marumoto and J. J. Jaber, *Org. Lett.*, 2001, **3**, 3815; (*b*) W. R. Roush and G. J. Dilley, *Synlett*, 2001, 955; (*c*) C. M. Gasparki, P. M. Herrinton, L. E. Overman and J. P. Wolfe, *Tetrahedron Lett.*, 2000, **41**, 9431; (*d*) T.-P. Loh, Q.-Y. Hu and L.-T. Ma, *J. Am. Chem. Soc.*, 2001, **123**, 2450; (*e*) C. Semeyn, R. H. Blaauw, H. Hiemstra and W. N. Speckamp, *J. Org. Chem.*, 1997, **62**, 3426; (*f*) H. B. Huang and J. S. Panek, *J. Am. Chem. Soc.*, 2000, **122**, 9836.

5 R. W. Alder, J. N. Harvey and M. T. Oakley, *J. Am. Chem. Soc.*, 2002, **124**, 4960.

6 S. R. Crosby, J. R. Harding, C. D. King, G. D. Parker and C. L. Willis, *Org. Lett.*, 2002, **4**, 577.

7 Interestingly, using α-acetoxy ethers, Rychnovsky and co-workers observed the formation of tetrahydropyrans when using $Et_3SiH/BF_3{\cdot}Et_2O$ conditions,[4a] albeit in low yields.

8 S. R. Crosby, J. R. Harding, C. D. King, G. D. Parker and C. L. Willis, *Org. Lett.*, 2002, **4**, 3407.

9 M. Juch and P. Ruedi, *Helv. Chim. Acta*, 1997, **80**, 436.

10 An aromatic tosylate has been used in Prins cyclisations in the synthesis of centrolobine: S. Marumoto, J. J. Jaber, J. P. Vitale and S. D. Rychnovsky, *Org. Lett.*, 2002, **4**, 3919.

11 H. C. Brown, K. S. Bhat and R. S. Randad, *J. Org. Chem.*, 1987, **52**, 319.

12 *Spartan*, Wavefunction, Inc., Irvine, CA.