Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 37–41

Stereochemical Prins cyclization: electronic versus steric effects on the synthesis of 2,4,6-trisubstituted tetrahydropyran rings

Kok-Ping Chan, Ai-Hua Seow and Teck-Peng Loh*

Division of Chemistry and Chemical Biology, Nanyang Technological University, Singapore 637616, Singapore

Received 6 October 2006; revised 26 October 2006; accepted 2 November 2006
Available online 21 November 2006

Abstract—A convenient approach towards the synthesis of both *syn*- and *anti*-2,4,6-chlorotetrahydropyrans has been developed. The electronic and steric influences on the stereochemistry of the Prins cyclized products were investigated based on the substituents of the homoallylic alcohol.

Functionalized pyran ring systems feature widely in a vast array of biologically active natural products[1] (Fig. 1). There are several methods[2] available to synthesize 2,6-disubstituted tetrahydropyran (THP) rings. Of these methods, the Prins cyclization[3] offers a convenient and direct synthesis from easily attainable homoallylic alcohols and aldehydes.

However, this method is mainly confined to the formation of 2,6-*syn*-tetrahydropyranyl products, whereas, convenient methodologies for the *anti*-isomers[4] of THP rings are still not widely established. This is possibly attributable to the preferred formation of the more favourable chair-like transition state from the oxonium ion due to a severe 1,3-diaxial interaction (Scheme 1).

Panek[5] has demonstrated an elegant synthesis of *anti*-2,6-tetrahydropyrans using TMSOTf catalyzed Prins cyclizations of enantiomerically pure *anti*-hydroxycrotyl and allylsilanes. Several mechanistic pathways[6] have been proposed, attributing the formation of the 2,6-*anti*-configuration to the β-directing effects of the silyl

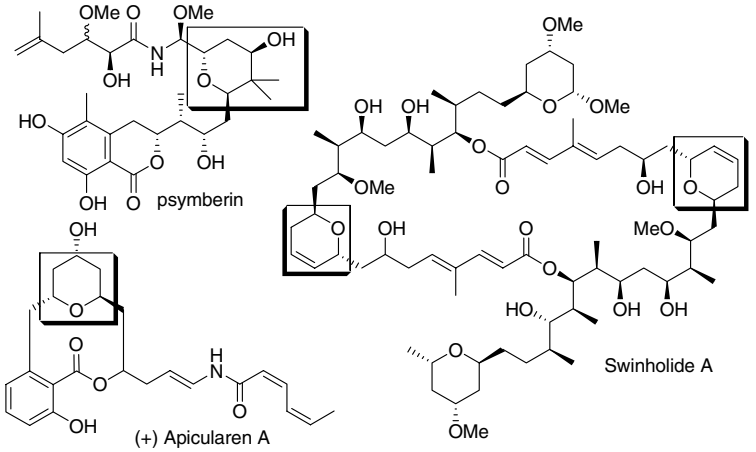
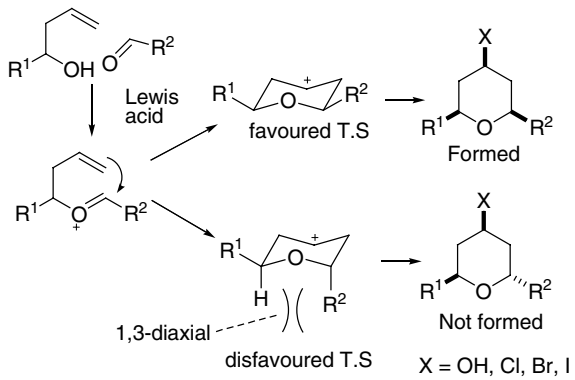


Figure 1. Examples of natural products possessing *anti*-2,6-tetrahydropyrans.

Keywords: Prins cyclization; *anti*-Tetrahydropyran; Lone-pair inductive effect.
* Corresponding author. Tel.: +65 6316 8899; fax: +65 6791 1961; e-mail: teckpeng@ntu.edu.sg

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.11.023

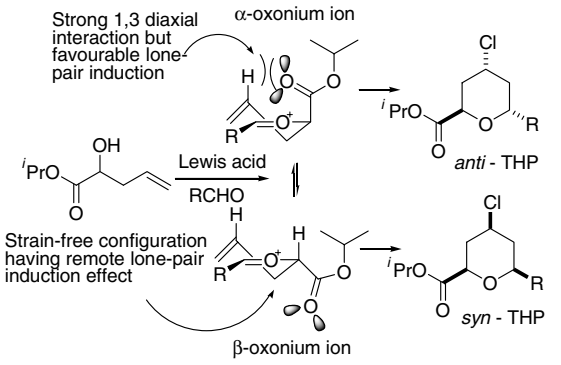


Scheme 1. Formation of the *syn*-THP ring.

moiety in the cyclic transition state. Unfortunately, the synthesis of the α-silyl-homoallylic alcohol is often tedious and low yielding. Therefore, we investigated a more direct and sustainable method to obtain 2,6-*anti*-THP rings based on stereochemical and steric considerations. In this letter, we demonstrate a new strategy to obtain 2,6-*anti*-THP rings using homoallyllic-α-hydroxy esters in an indium triflate catalyzed Prins cyclization with moderate selectivities.

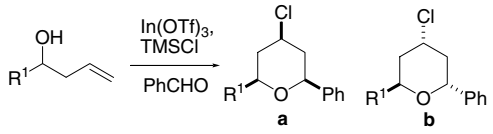
From our previous work, the indium-based Lewis acid[7] catalyzed Prins cyclization yields predominantly the *syn*-4-halo-2,6-disubstituted THP product.[3i,j] We envisaged that with an electron rich moiety on the homoallylic alcohol adopting the β-position, the inductive effect exerted may be able to stablize the oxonium cation in the conventional chair-like transition state (Scheme 2). Hence, various homoallylic alcohols were subjected to catalytic Prins cyclization with an aldehyde. The results are summarized in Table 1.

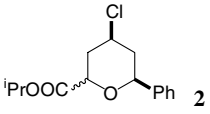
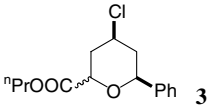
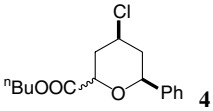
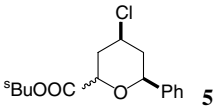
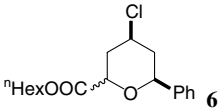
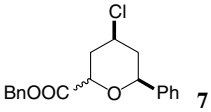
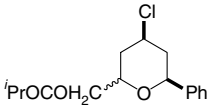
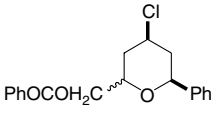
We were delighted to establish several findings. Firstly, the inductive effect of the *iso*-propyl ester group (entry 1) yielded a 1:1 diastereomeric mixture of the *syn*- and *anti*-4-chloro-2,6-trisubstituted THPs. A variation of the temperature from −78 to 40 °C had no apparent effect on the yields and diastereoselectivities. In addition, neither the chain length nor the bulkiness of the R-group improved the selectivity. Interestingly, only the *syn*-isomer was isolated when the benzoyl ester (entry 8) and the *sec*-butyl ester (entry 7) underwent Prins



Scheme 2. Electronic inductive effects on oxonium cations.

Table 1. Prins cyclization of substituted homoallylic alcohols with benzaldehyde



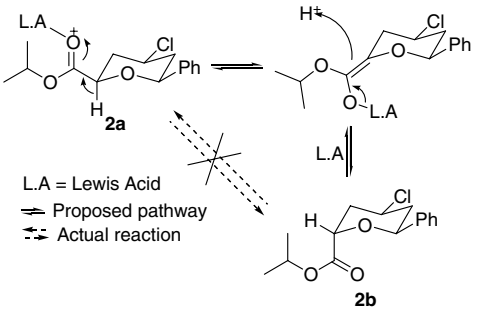
Entry	R^1	Product	Yield[a] (%)	
			a	b
1	–COO^{i}Pr **1**	 **2**	32	32
2	–COO^{n}Pr	 **3**	27	27
3	–COO^{n}Bu	 **4**	36	35
4	–COO^{s}Bu	 **5**	32	34
5	–COO^{n}Hex	 **6**	24	24
6	–COOBn	 **7**	26	25
7	–CH_2OCO^iPr	 **8**	65	—
8	–CH_2OCOPh	 **9**	69	—

[a] In most cases, a small amount (approximately 3–8%) of the 2,6-*syn*-2,4-*anti*-chloro-THP isomer (**2c**, Scheme 4) was isolated. These are not taken into consideration in the computation of the overall yield.

cyclization with benzaldehyde. This gave us an understanding on the importance of the 1,2-carbonyl lone pair[8] in the formation of *anti*-tetrahydropyran rings.

The possibility of *anti*-2,6-THP ring formation via Lewis acid-catalyzed formation of an *exocyclic* enolate was also investigated (Scheme 3). No enolization was observed on the separate treatment of **2a** or **2b** with In(OTf)$_3$ and TMSCl at 0 °C. This result showed that the formation of the *anti*-THP product was not likely to be attributed to the isomerization of the 2,6-*syn*-isomer or vice versa.

Homoallylic alcohol **1** was reacted with various aldehydes as shown in Table 2. The results were satisfactory



Scheme 3. Possible enolization of α-ester THPs in the presence of a Lewis acid.

with moderate yields and equivalent diastereomeric ratios. The isomers were easily separable using flash column chromatography.

A plausible mechanism for the diversity of isomers formed is proposed (Scheme 4). Competition exists between the electronically favoured transition state T.S.1 and the sterically preferred T.S.2. The latter leads to the conventional *syn*-isomer **2a** while T.S.1 leads to *anti*-isomer **2b**. In both cases, axial nucleophilic attack by the external chloride at the 4-position is prevented. The formation of axial 4-chloro-THP product **2c** is likely to proceed via a less stable boat transition state T.S.3, thus accounting for its comparatively lower yield.

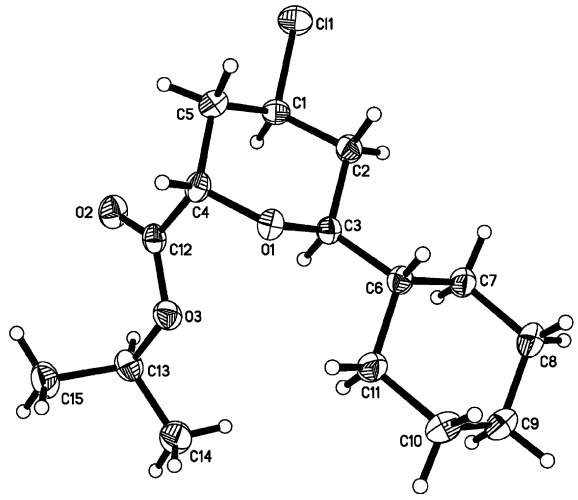
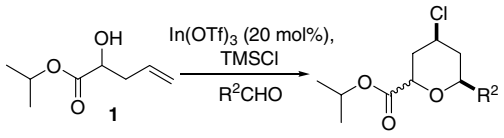
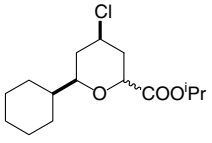
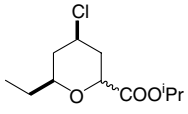
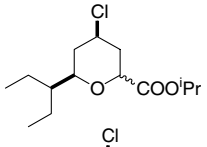
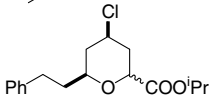
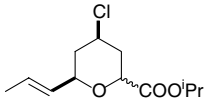


Figure 2. X-ray crystal structure[9] of (2,6-*anti*)-isopropyl-4-chloro-6-cyclohexyl-tetrahydro-2*H*-pyran-2-carboxylate, *anti*-**10**.

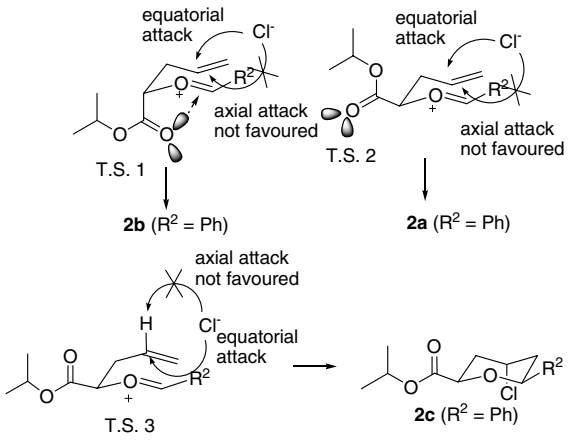
Similarly, the sterically unstable boat-like T.S.4 equilibrates rapidly to form the bicyclo-carbocation T.S.5, where equatorial attack by chloride collapses the structure back to the *anti*-2,6-THP ring. Such a pathway evidently indicates the strong electronic interaction of the ester moiety with the oxonium ion. Interestingly, the formation of **2e** was not observed, indicating that preferential adoption of T.S.1 or T.S.5 (Scheme 5).

Table 2. Prins cyclization[a] of **1** with various aldehydes

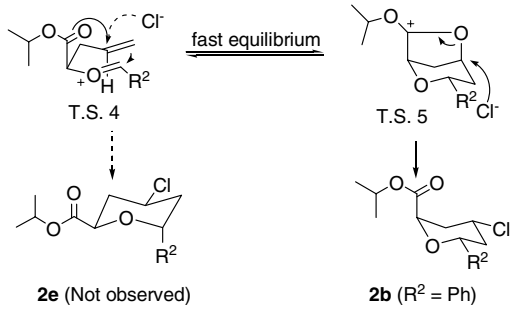


Entry	R^2	Product	Overall yield (%)	dr (*syn*/*anti*)
9	–Cyclohexyl	 **10**[b]	56	50:50
10	–Ethyl	 **11**	62	50:50
11	–3-Pentyl	 **12**	57	44:56
12	$-(CH_2)_2Ph$	 **13**	62	50:50
13	–CH=CH–CH_3	 **14**	58	51:49

[a] Reactions were carried out at 0 °C in 0.1 M CH_2Cl_2 solution.
[b] The X-ray crystal structure of *anti*-**10** is shown in Figure 2.



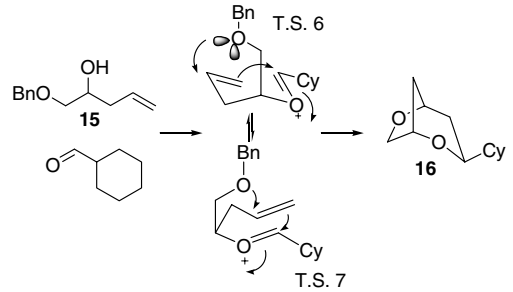
Scheme 4. Possible mechanisms for the formation of the *syn*- and *anti*-products in Table 1.



Scheme 5. Alternative mechanistic proposal following a bicyclic acetal-carbocation pathway.

A comparison between a benzyl ester (Table 1, entry 6), a benzoyl ester (Table 1, entry 8) and a benzylic alcohol R-group also provided interesting insight for our postulate. In the case of the benzyloxy homoallylic alcohol **15** (Scheme 6), the benzylic group adopted the axial position such that the lone pairs on the oxygen offered strong inductive effects in both T.S 6 and T.S 7. A competing sterically favourable 2,6-equatorial mechanism also exists, hence equimolar amounts of bicyclo-dioxo product **16** and the respective *syn*-isomer were obtained. This reinforced the concept of lone pair electronic effects on stablizing the oxonium ion.

In conclusion, the electronic and steric effects of α-homoallylic alcohol esters in Prins cyclization to form



Scheme 6. Mechanistic interpretation for the formation of a bicyclic-dioxo product.

both *syn*- and *anti*-2,4,6-trisubstituted THP rings have been investigated. The substrates afforded moderate yields of both products, which were easily separated by flash column chromatography. Further improvements in yields and selectivity, together with applications of this method for the synthesis of biologically active natural products are in progress.

Acknowledgements

We thank the Nanyang Technological University and the Biomedical Research Council (Research Grant No. M47110002 and M47110003) for generous financial support. Kok-Ping Chan thanks the Agency of Science, Technology and Research for a post-graduate scholarship.

Supplementary data

Experimental procedures and characterization data for the compounds are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.11.023.

References and notes

1. Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH Weiheim, 1996.
2. Some examples of tetrahydropyran ring formation include: (a) Vares, L.; Rein, T. *J. Org. Chem.* **2002**, *67*, 7226; (b) Semmelhack, M. F.; Kim, C. R.; Dobler, W.; Meier, M. *Tetrahedron Lett.* **1989**, *30*, 4925; (c) Clarke, P. A.; Martin, W. H. C. *Org. Lett.* **2002**, *4*, 4527; (d) Martin, V. S.; Nuñez, M. T.; Ramirez, M. A.; Soler, M. A. *Tetrahedron Lett.* **1990**, *31*, 763; (e) Sekido, M.; Aoyagi, K.; Nakamura, H.; Kabuto, C.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 7142; (f) Andrews, W. J.; Evans, P. A. *Tetrahedron Lett.* **2005**, *46*, 5625; (g) Rancourt, J.; Burke, S. D. *J. Am. Chem. Soc.* **1991**, *113*, 2335.
3. Selected references on Prins cyclization: (a) Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 913; (b) Wei, Z. Y.; Li, S. J.; Wang, D.; Chan, T. H. *Tetrahedron Lett.* **1987**, *28*, 3441; (c) Yang, J.; Viswanathan, G. S.; Li, C. J. *Tetrahedron Lett.* **1999**, *40*, 1627; (d) Patterson, B.; Marumoto, S.; Rychnovsky, S. D. *Org. Lett.* **2003**, *5*, 3163; (e) Wei, Z. Y.; Li, S. J.; Wang, D.; Chan, T. H. *J. Org. Chem.* **1989**, *54*, 5768; (f) Coppi, L.; Ricci, A.; Taddei, M. *Tetrahedron Lett.* **1987**, *28*, 973; (g) Perron, F.; Albizati, K. F. *J. Org. Chem.* **1987**, *52*, 4128; (h) Rychnovsky, S. D.; Hu, Y.; Ellsworth, B. *Tetrahedron Lett.* **1998**, *39*, 7271; (i) Chan, K. P.; Loh, T. P. *Tetrahedron Lett.* **2004**, *45*, 8387; (j) Chan, K. P.; Loh, T. P. *Org. Lett.* **2005**, *7*, 4491.
4. (a) Ohmi, M.; Ueda, A.; Uenishi, J. *Tetrahedron: Asymmetry* **2005**, *16*, 1299; (b) Lian, Y.; Litvinas, N. D.; Jenkins, A. T.; Burnette, D. C.; Hinkle, R. J. *Tetrahedron* **2005**, *61*, 11679.
5. (a) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2000**, *7*, 3231; (b) Huang, H.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9836; (c) Su, Q.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425.
6. (a) Roush, W. R.; Dilley, G. J. *Synlett* **2001**, 955; (b) Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3426; (c) Lolkerma, L. D. M.; Semeyn, C.; Ashek, L.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1994**, *50*, 7129.

7. (a) Loh, T. P.; Chua, G. L. *Chem. Commun.* **2006**, 2739; (b) Loh, T.-P. In *Science of Synthesis*; Yamamoto, H., Ed.; Georg ThiemeVerlag Stuttgart: New York, 2004; p 413.
8. For interactions of carbonyl lone pairs, refer to: (a) Roush, W. R.; Walts, A. E.; Lee, K. H. *J. Am. Chem. Soc.* **1985**, *107*, 8186; (b) Gung, B. W.; Xue, X.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 10692.
9. CCDC 617598 contains the supplementary crystallographic data for this letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.