Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 2311–2314
Tetrahedron Letters

$ZrCl_4$ mediated cross-cyclization between epoxides and homoallylic alcohols: synthesis of 4-chlorotetrahydropyran derivatives☆

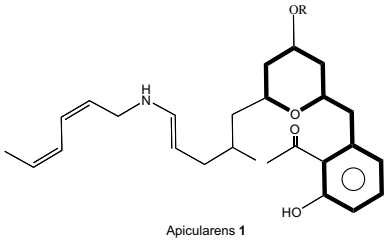
J. S. Yadav, K. Rajasekhar and M. S. R. Murty*

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500007, India

Received 20 September 2004; revised 28 January 2005; accepted 1 February 2005

Abstract—Epoxides undergo cross-cyclization with homoallylic alcohols in the presence of zirconium tetrachloride under mild conditions to afford the corresponding tetrahydropyran derivatives in excellent yields.

The benzyl tetrahydropyran fragment is a common core structure in a number of natural products such as the apicularens[1] **1**. The apicularens possess highly cytotoxic activity and are potent inhibitors of human tumour cell lines such as those originating from kidney, lung and cervia. They are particularly interesting therapeutic leads since they are extremely specific for a novel target, selectively toxic towards cancer cells and are highly amenable to chemical modification. Despite their wide range of pharmacological activities, the synthesis of benzyl substituted tetrahydropyrans has received little attention. The synthesis of tetrahydropyran derivatives by various methods has been reported in the literature.[2] However, the development of an efficient and versatile catalytic method for the construction of the benzyl tetrahydropyran core structure would still be useful. $ZrCl_4$ has been used for various epoxide ring-opening reactions giving the products in good yield.[3] Herein, we describe zirconium tetrachloride mediated cross-cyclization between aryl-substituted epoxides and homoallylic alcohols for the formation of tetrahydropyran derivatives.

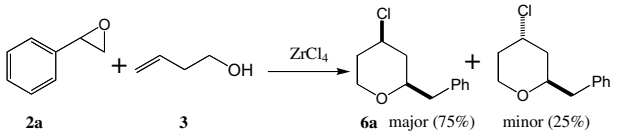


Apicularens **1**

The required epoxides were prepared by epoxidation of the corresponding olefins.[4] When a mixture of styrene epoxide and 3-buten-1-ol was stirred with zirconium tetrachloride in dry methylene chloride at room temperature, the disappearance of the starting materials was observed by TLC over 2 h. After work-up, the crude product was separated by column chromatography over silica gel. The ^1H NMR spectrum showed clean formation of the two isomers of benzyl tetrahydropyran derivative **6a**. By comparing the spectroscopic data with the literature values, the major product was shown to have the *cis* stereochemistry[2] (Scheme 1).

The formation of *trans*-2,3,4-trisubstituted tetrahydropyrans **7** and *cis*-2,3,4-trisubstituted tetrahydropyrans **8** was achieved by the reaction of epoxides with the corresponding *E*/*Z*-homoallylic alcohols in the presence of $ZrCl_4$ (Scheme 2).

Similarly, various epoxides reacted smoothly with homoallylic alcohols to give the tetrahydropyran derivatives in high yields ranging from 80% to 95% (Table 1). Treatment of epoxides with *cis*-3-nonen-1-ol afforded



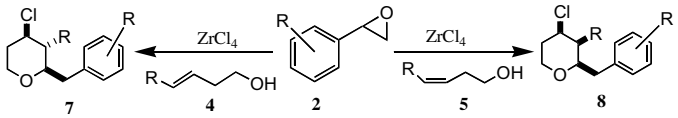
2a **3** **6a** major (75%) minor (25%)

Scheme 1.

☆ IICT communication number: 040924.

* Corresponding author. Tel.: +91 40 27193434; fax: +91 40 27160512; e-mail: msrmurty@iict.res.in

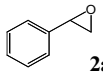
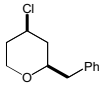
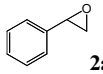
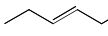
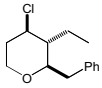
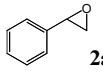
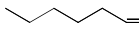
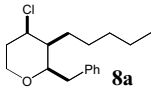
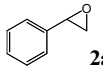
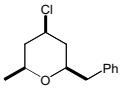
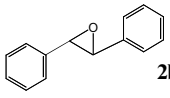
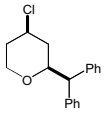
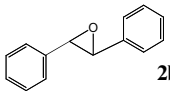
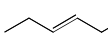
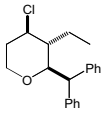
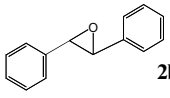
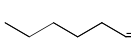
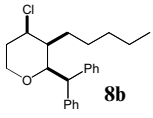
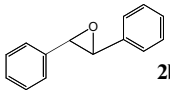
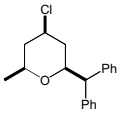
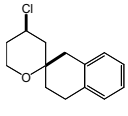
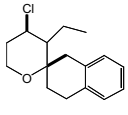
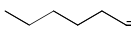
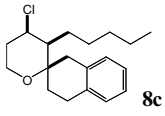
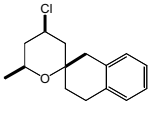
0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.02.013



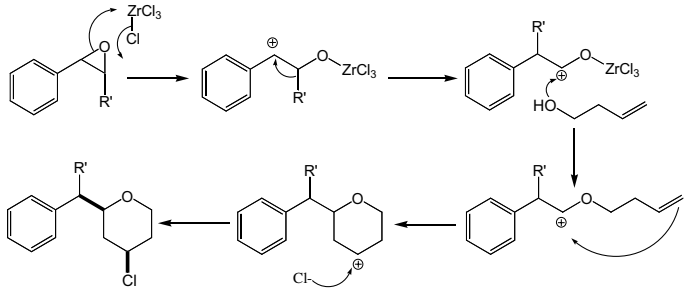
Scheme 2.

the corresponding 2,3,4-trisubstituted tetrahydropyran with the *cis–cis* configuration, as the major product, whereas *trans*-3-hexen-1-ol gave the 2,3,4-trisubstituted tetrahydropyran with the *trans–trans* configuration as

Table 1. Zirconium tetrachloride mediated cross-cyclization of epoxides and homoallylic alcohols

Entry	Epoxide	Alcohol	Products[a]	Yield (%)[b,c]
a	 **2a**	 **3**	 **6a** (*cis*/*trans* 3:1)	95
b	 **2a**	 **4a**	 **7a**	90
c	 **2a**	 **5a**	 **8a**	82
d	 **2a**	 **3a**	 **9a**	95
e	 **2b**	 **3**	 **6b**	87
f	 **2b**	 **4a**	 **7b**	92
g	 **2b**	 **5a**	 **8b**	80
h	 **2b**	 **3a**	 **9b**	90
i	 **2c**	 **3**	 **6c**	92
j	 **2c**	 **4a**	 **7c**	87
k	 **2c**	 **5a**	 **8c**	84
l	 **2c**	 **3a**	 **9c**	92

[a] All the products were characterized by ^{1}H NMR, IR and mass spectroscopy.
[b] Isolated and optimized yields.
[c] The minor isomers of trisubstituted THP products were not isolated.



Scheme 3. Proposed mechanism for the $ZrCl_4$ mediated tetrahydropyran formation.

the dominant product.[5] We also carried out the reaction with cyclic epoxides such as 1,2-dihydronaphthalene oxide **2c** to give spiro-tetrahydropyran derivatives[6] **6c**–**9c**. The stereochemistry of **7c** was not established due to the complexity of the ^{1}H NMR spectrum.

The assignment of the stereochemistry of **9a** was based on the coupling constants of the protons at the C_2, C_4 and C_6 positions. The coupling constants of the proton on the carbon bearing the benzyl group (2-H) ($J = 11.15$ Hz) the proton on the carbon bearing the methyl group (6-H) ($J = 11.89$ Hz) and the proton on the carbon bearing the halide group (4-H) ($J = 4.46$ and 11.15 Hz) in the ^{1}H NMR spectrum were consistent with the benzyl, methyl and the halide groups being *cis* and equatorial.

As reported, the formation of **6b**–**9b** was achieved by migration of the aromatic group whereas **6a**–**9a** and **6c**–**9c** were formed by the migration of hydrogen (Scheme 3). We also carried out the formation of tetrahydropyrans by the reaction between aldehydes and homoallylic alcohols[7] and the same products were obtained as those from the cross-cyclization between epoxides and homoallylic alcohols in the presence of $ZrCl_4$.

In summary, we have described a simple and highly efficient protocol for the preparation of benzyl tetrahydropyran derivatives through the cross-cyclization between epoxides and homoallylic alcohols using zirconium tetrachloride.

General procedure: to a stirred solution of 3-buten-1-ol (144 mg, 2 mmol) and styrene oxide (360 mg, 3 mmol) in dry methylene chloride (20 mL) was added zirconium tetrachloride (932 mg, 4 mmol) at room temperature. The mixture was stirred under a nitrogen atmosphere for 2 h. After work-up, the solution was concentrated and the crude mixture was separated by column chromatography over silica gel (ethyl acetate–hexane, 3:7). The diastereomers of **6a** were obtained in a 3:1 ratio.

Compound **6c**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.85–7.00 (m, 4H), 4.10–4.20 (m, 1H), 3.80 (dd, $J = 2.05$, 2.73 Hz, 1H), 3.65 (dd, $J = 2.05$, 2.73 Hz, 1H), 2.84–2.97 (m, 1H), 2.68–2.76 (s, 2H), 2.55–2.64 (m, 1H), 1.96–2.16 (m, 2H), 1.56–1.92 (m, 4H). EIMS: *m*/*z*: 236 (25) M^+, 201 (80), 129 (55), 104 (100), 91 (35), 55 (70). Anal. Calcd for $C_{14}H_{17}ClO$ (236.74): C, 71.03; H, 7.24. Found: C, 71.46; H, 7.32.

Compound **7b**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.18–7.38 (m, 10H), 4.20 (m, 1H), 3.95–4.05 (m, 2H), 3.80 (dd, $J = 7.33$, 9.53 Hz, 1H), 3.20–3.30 (m, 1H), 2.00–2.10 (m, 1H), 1.80–1.90 (m, 2H), 1.65–1.75 (m, 2H), 1.00 (t, $J = 7.33$ Hz, 3H). EIMS: *m*/*z*: 314 (10) M^+, 278 (15), 249 (15), 179 (40), 167 (15), 147 (50), 105 (100), 77 (80), 41 (60). Anal. Calcd for $C_{20}H_{23}ClO$ (314.85): C, 76.30; H, 7.36. Found: C, 76.62; H, 7.72.

Compound **7c**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.85–7.10 (m, 4H), 3.84–4.00 (m, 2H), 3.72–3.84 (m, 1H), 2.80–2.92 (s, 2H), 2.64–2.80 (m, 2H), 2.08–2.32 (m, 2H), 1.50–1.92 (m, 5H), 1.00 (t, $J = 7.34$ Hz, 3H). EIMS: *m*/*z*: 264 (10) M^+, 229 (30), 141 (15), 129 (20), 104 (30), 82 (40), 41 (100). Anal. Calcd for $C_{16}H_{21}ClO$ (264.79): C, 72.57; H, 7.99. Found: C, 72.93; H, 8.22.

Compound **8c**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.85–7.20 (m, 4H), 3.70–4.09 (m, 2H), 3.60–3.70 (m, 1H), 2.50–3.00 (m, 3H), 2.18–2.32 (m, 2H), 1.87–2.15 (m, 2H), 1.10–1.60 (m, 10H), 0.85 (t, $J = 6.79$ Hz, 3H). EIMS: *m*/*z*: 306 (15) M^+, 271 (15), 230 (10), 202 (30), 169 (25), 129 (50), 69 (50), 57 (80), 43 (100). Anal. Calcd for $C_{19}H_{27}ClO$ (306.87): C, 74.36; H, 8.87. Found: C, 74.64; H, 9.15.

Compound **9a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10–7.30 (m, 5H), 3.80–4.00 (m, 1H), 3.30–3.50 (m, 2H), 2.95 (dd, $J = 5.95$, 13.38 Hz, 1H), 2.65 (dd, $J = 6.69$, 13.38 Hz, 1H), 2.05 (dt, $J = 2.23$, 12.63 Hz, 2H), 1.40–1.60 (m, 2H), 1.20 (d, $J = 5.95$ Hz, 3H). EIMS: *m*/*z*: 224 (10) M^+, 150 (15), 133 (100), 97 (30), 69 (85), 41 (35). Anal. Calcd for $C_{13}H_{17}ClO$ (224.73): C, 69.48; H, 7.62. Found: C, 69.56; H, 7.87.

Compound **9b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10–7.30 (m, 10H), 3.85–4.00 (m, 3H), 3.40–3.50 (m, 1H), 2.10 (dt, $J = 1.49$, 2.23 Hz, 1H), 1.92 (dt, $J = 1.49$, 2.23 Hz, 1H), 1.40–1.56 (m, 2H), 1.18 (d, $J = 6.69$ Hz, 3H). EIMS: *m*/*z*: 300 (10) M^+, 166 (45), 134 (100), 98 (25), 69 (70), 41 (30). Anal. Calcd for $C_{19}H_{21}ClO$ (300.82): C, 75.86; H, 7.04. Found: C, 76.15; H, 7.23.

Compound **9c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.90–7.00 (m, 4H), 4.15–4.25 (m, 1H), 3.65–3.85 (m, 1H), 2.50–3.00 (m, 4H), 2.00–2.10 (m, 2H), 1.40–1.90 (m,

4H), 1.17 (d, J = 5.95 Hz, 3H). EIMS: m/z: 250 (15) M^+, 216 (100), 215 (20), 129 (25), 104 (50), 91 (10), 42 (10). Anal. Calcd for $C_{15}H_{19}ClO$ (250.76): C, 71.84; H, 7.64. Found: C, 71.95; H, 7.85.

Acknowledgements

K.R.S. thanks CSIR, New Delhi for the award of a fellowship.

References and notes

1. Kunze, B.; Jansen, R.; Sasse, F.; Hofle, G.; Reichenbach, H. *J. Antibiot.* **1998**, *51*, 1075.
2. (a) Li, J.; Li, C.-J. *Tetrahedron Lett.* **2001**, *42*, 793; (b) Yadav, J. S.; Reddy, B. V. S.; Venugopal, Ch.; Srinivas, R.; Ramalingam, T. *Synth. Commun.* **2002**, *32*, 1803; (c) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. S.; Niranjan, N.; Prasad, A. R. *Eur. J. Org. Chem.* **2003**, 1779.
3. (a) Giovanni, V.; Stephen, B.; Jamal, E. M.; Marcella, B.; Guiseppe, Z. *Tetrahedron Lett.* **2002**, *43*, 2687; (b) Chakraborti, A. K.; Kondaskar, A. *Tetrahedron Lett.* **2003**, *44*, 8315.
4. Paquette, L. A.; Barrett, J. H. *Org. Synth.* **1969**, *49*, 62.
5. (a) Yang, X. F.; Li, C. J. *Tetrahedron Lett.* **2000**, *41*, 1321; See also: (b) Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217.
6. For related compounds, see: (a) Dongwei, C.; David, T.; Shi, Y. J.; Thomas, R. V.; Robert, A. R.; Alan, W. D. *Tetrahedron Lett.* **1993**, *34*, 3243; (b) Rechard, J. B.; Christopher, D. G.; Stephane, G. R. G.; John, D. H.; Mark, B. H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1925.
7. (a) Viswanathan, G. S.; Yang, J.; Li, C. J. *Org. Lett.* **1999**, *1*, 993; (b) Ranu, B. C.; Jana, U. *J. Org. Chem.* **1998**, *63*, 8212.