Pergamon

*Tetrahedron Letters*, Vol. 35, No. 21, pp. 3625-3628, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0608-Z

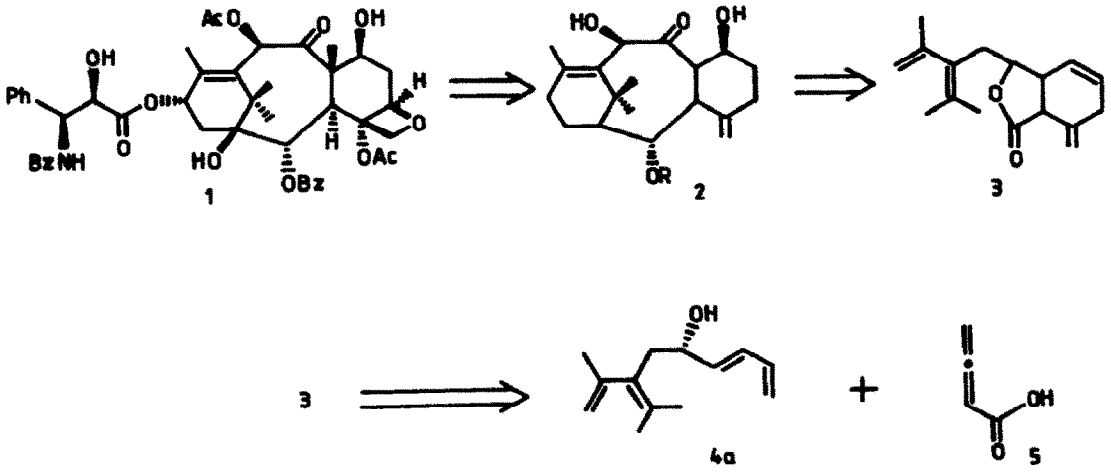
# An Expeditious Approach to the Synthesis of Chiral Butadienyl Alcohols

**Yadav J S*, Srinivas D and Shekharam T**
Indian Institute of Chemical Technology, Hyderabad 500007, India

***Abstract:*** *A highly regioselective reduction of epoxy allylic alcohols to chiral butadienyl alcohols and its application to taxol skeleton is described.*

Antitumour taxoids have always been a constant challenge to organic chemists. Among these classes of natural products, taxol[1] (1) occupies the prominent position not only because of its biological significance,[2] but also its structural complexities. The tough task in its synthesis is the formation of ABC (6+8+6) ring system with an endo conformation. Our strategy towards the synthesis of the tricyclic core of taxol with properly placed functionalities is based on an intramolecular Diels-Alder chemistry. In continuation of our efforts towards the synthesis[4] of taxol skeleton, we have developed an altogether novel method for the preparation of chiral butadienyl alcohol. The utility of suitably substituted butadienyl alcohol **4a** to taxol skeleton is revealed in its retrosynthesis (Scheme 1).

Scheme 1

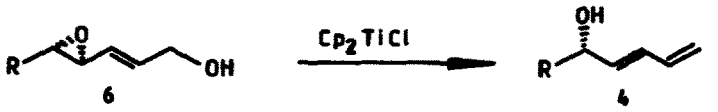



1 2 3 4a

IICT Communication No.3332.

Herein, we demonstrate an expeditious and practical method for the synthesis of chiral butadienyl alcohol of the type 4 by employing our previous protocol[5] i.e. Ti(III) induced regioselective opening of epoxy alcohols (Scheme 2).

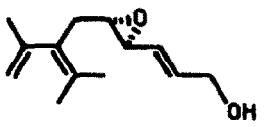
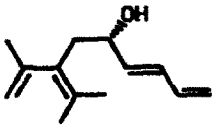
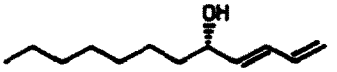
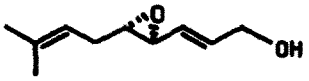
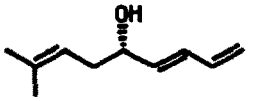
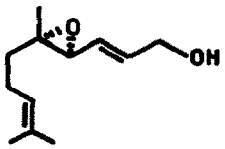
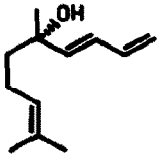
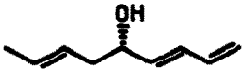
**Scheme 2**




Thus, the chiral epoxy allylic alcohols 6 were treated with two equivalents of $Cp_2TiCl$ in anhydrous THF at room temperarature, 6 was deoxygenated instantaneously to 4 with high regioselectivity and excellent chemical yield.

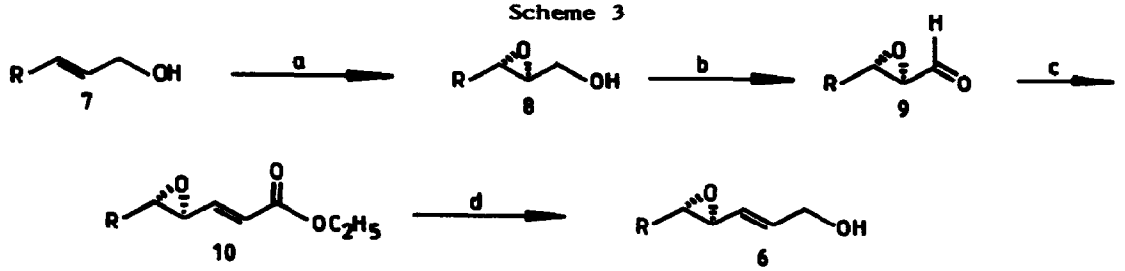
To generalise this method for the dienol synthesis, epoxy allylic alcohols of different types (Table) were successfully converted into corresponding dienols by Ti(III) mediated regioselective reduction.

**Table**

| Entry | Reactant | Product | Yield % |
|---|---|---|---|
| 4a |  |  | 72 |
| 4b |  |  | 90 |
| 4c |  |  | 87 |
| 4d |  |  | 78 |
| 4e |  |  | 82 |

The epoxy allylic alcohols were prepared (Scheme 3) from the corresponding

Scheme 3

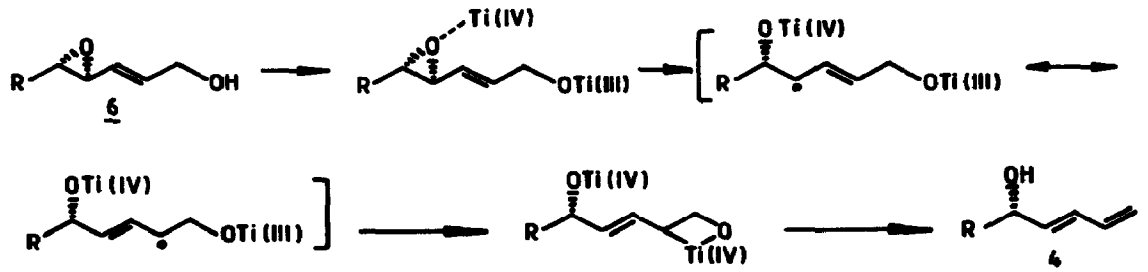


**Reagents:** (a) (+)DET,TIP,t-BHP,4A°MS,DCM,-26°C,6h; (b) $CrO_3$,Py,Celite,4A°MS,DCM, 0°C-5°C; (c) $Ph_3P$=CH-$COOC_2H_5$,Benzene,25°C,6h; (d) DIBAL-H,DCM,-78°C.

allylic alcohol 7 by a four step sequence which includes Sharpless epoxidation,[6] a modified Collin's oxidation,[7a] a two carbon homologation through Wittig olefination[7b] and reduction.

A probable mechanism for the reduction is as shown in Scheme 4. Formation of

scheme 4



the titanium alkoxide and concomitant liberation of HCl with epoxy allyl alcohol is the primary phase, in which a stochiometric amount of $Cp_2TiCl$ is consumed. The allyl radical thus formed participates intramolecularly with the unfilled d orbital of Ti(III) to form a four membered Green's intermediate,[8] which on reductive elimination produces the butadienyl alcohol.

In conclusion, we have developed an efficient method for the synthesis of chiral diene alcohols, valuable intermediates in the natural products synthesis. Synthetic studies on taxol based on above methodology is currently underway in our laboratory.

**Acknowledgement:** This project is generously funded from a grant No.DST/N-USHRF-(138)/86 of PL 480 (NIH) and CSIR, New Delhi.

**References and Notes**

1. Wani, M.C.; Taylor, H.L.; Wall, M.E.; Coggon, P. and McPhail, A.T. *J. Am. Chem. Soc.* **1973**, *93*, 2325.

2. (a) Horwitz, S.B. *Nature* 1979, *277*, 665. (b) Horwitz, S.B. *Trends in Pharmacological Sciences* 1992, *13*, 134.
3. (a) Rehman, A.U. *Studies in Natural Products* 373. (b) Swindell, C.S. *Organic Preparation and Proceedings International* 1991, *23*, 465 and references cited therein. (c) Fallis, A.G. *Tetrahedron Lett.* 1993, *34*, 3367 and references cited therein. (d) Wender, P.A. and Muccario, T.P. *J. Am. Chem. Soc.* 1992, *114*, 5878. (e) Pattenden, G. and Hitchcock, S.A. *Tetrahedron Lett.* 1992, *33*, 4843.(f) Quenean, Y.; Krol, W.J.; Borman, W.G. and Danishefsky, S.J. *J. Org. Chem.* 1992, *57*, 4043. (g) Shea, K.J.; Haffner, C.D. *Tetrahedron Lett.* 1988, *29*, 1367. (h) Bonnet, R.V. and Jenkins, P.R. *J. Chem. Soc.,Chem. Comm.* 1987, 1540. (i) Shea, K.J.; Haffner, C.D.; Gillman, J.W. and Dougherly, T.K. *J. Am. Chem. Soc.* 1986, *108*, 4953.
4. Yadav, J.S. and Ravishankar, R. *Tetrahedron Lett.* 1991, *32*, 2629.
5. Yadav, J.S.; Shekharam, T.; Gadgil, V.R. *J. Chem. Soc.,Chem. Comm.* 1990, 843.
6. Gavo, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, S. and Sharpless, K.B. *J. Am. Chem. Soc.* 1987, *109*, 5763.
7. (a) Corey, E.J.; Clark, D.A.; Goto, G.; Marfat, A.; Mioskowski, C.; Samuelson, B.; Hammerstrom, S. *J. Am. Chem. Soc.* 1980, *102*, 1436, 3663. (b) Yadav, J.S.; Shekharam, T. and Srinivas, D. *Tetrahedron Lett.* 1992, *33*, 7973 and references cited therein.
8. (a) Rajan Babu, T.V. and Nugent, W.A. *J. Am. Chem. Soc.* 1989, *110*, 4525. (b) Nugent, W.A. and Rajan Babu, T.V. *J. Am. Chem. Soc.* 1988, *110*, 8561. (c) Berry, M.; Davies, S.G. and Green, M.L.H, *J. Chem. Soc.,Chem. Comm.* 1978, 99.
9. $^1$H-NMR spectrum of compounds (200 MHz,$CDCl_3$, ) 4b: 0.95 (dt,3H), 1.2-1.6 (m,8H), 4.15 (m,1H), 5.1 (d,1H), 5.2 (d,1H), 5.7 (q,1H), 6.2-6.4 (m,2H), 4a: 1.6 (s,3H), 1.64 (s,3H), 1.7 (s,3H), 2.3 (m,2H), 3.9 (m,1H), 4.55 (s,1H), 4.65 (s,1H), 4.9-5.2 (m,2H), 5.5-5.8 (m,2H), 6.3 (m,1H).

All new compounds are characterized by spectral data and HRMS.

(*Received in UK* 20 *December* 1993; *revised* 7 *March* 1994; *accepted* 24 *March* 1994)