Asymmetric Construction of Optically Active 3-Hydroxyalkyne Functionalities

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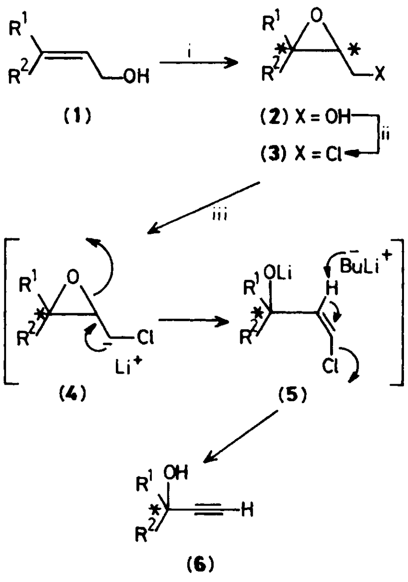
An efficient general method for the construction of optically active 3-hydroxyalkyne functionalities has been developed using optically active α,β-epoxy alcohols readily accessible from non-chiral allyl alcohol precursors.

Optically active 3-hydroxyalkyne functionalities have found a variety of uses in the construction of optically active compounds owing to the chemical nature of the acetylenic bond as well as the directing effect of the hydroxy group on the chiral centre adjacent to the acetylene bond.[1a] Although several synthetic methods have been devised to produce such functionalities,[1] no generally acceptable methods leading to the production of optically active secondary and tertiary 3-hydroxyalkynes from non-chiral precursors have so far been developed. We report herewith an efficient general method producing the optically active secondary and tertiary 3-hydroxyalkyne functionalities using optically active α,β-epoxy alcohols which are readily accessible from non-chiral starting materials by the chiral epoxidation method developed by Sharpless and co-workers.[2]

Treatment of optically active α,β-epoxy alcohols (**2a**—**i**), obtained from allyl alcohols (**1a**—**g**) by the Sharpless chiral epoxidation,[2c] with triphenylphosphine (1.2 equiv.) and an excess of carbon tetrachloride,[3] gave the corresponding α,β-epoxy chlorides (**3a**—**i**) (Scheme 1, Table 1).† Exposure of the chlorides (**3a**—**i**) to n-butyl-lithium (3 equiv.) in tetrahydrofuran (THF) at −35 °C brought about facile formation of the 3-hydroxyalkynes (**6a**—**i**) in one step, presumably *via* a sequence triggered by initial generation of the α-chlorocarbanion (**4**) as shown in Scheme 1. Under these conditions optical integrities introduced in the Sharpless epoxidation were found to be preserved in the acetylenic alcohols which was confirmed by comparison of the ^{1}H n.m.r. (500 MHz)



R^1, R^2 = H, alkyl, Ph

Scheme 1. *Reagents and conditions*: i, di-isopropyl (L)-tartrate (8%), Ti(OPr^i)$_4$ (5%), Bu^{t}OOH (2.0 equiv.), CH_2Cl_2, −20 °C → 0 °C; ii, Ph_3P (1.2 equiv.), CCl_4 (excess), reflux, 4 h; iii, Bu^{n}Li (3.0 equiv.), THF, −35 °C. * Denotes chiral centre.

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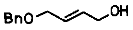
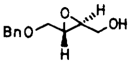
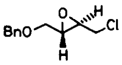
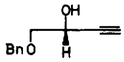
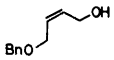
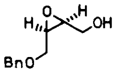
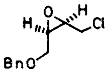
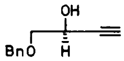
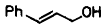
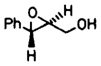
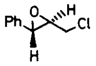
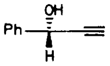
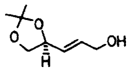
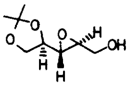
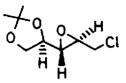
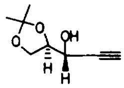
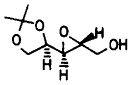
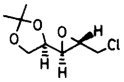
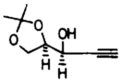
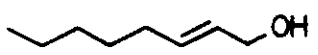
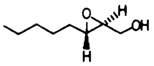
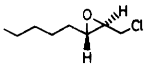
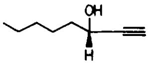
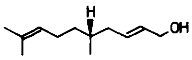
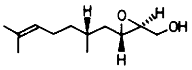
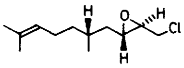
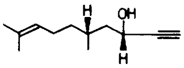
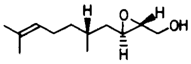
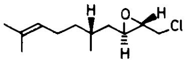
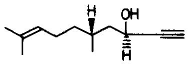
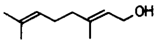
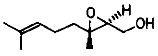
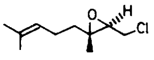
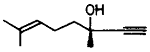
† Satisfactory analytical (combustion and/or high resolution mass) and spectral (i.r., ^{1}H n.m.r., and m.s.) data were obtained for all new compounds.

Table 1. Synthesis of 3-hydroxyalkynes (**6**) from allyl alchols (**1**) (Bn = benzyl).

Entry	Allyl alcohol (**1**)	Epoxy alcohol (**2**) (%; % e.e.)[a]	Epoxy chloride (**3**) (%)	Acetylenic alcohol(**6**) (%; % e.e.)
1	 (**1a**)	 (**2a**) (85;88)	 (**3a**) (91)	 (**6a**) (89;85)
2	 (**1b**)	 (**2b**) (87;73)	 (**3b**) (88)	 (**6b**) (87;75)
3	 (**1c**)	 (**2c**) (76;76)	 (**3c**) (87)	 (**6c**) (74;78)
4	 (**1d**)	 (**2d**) (83;91)	 (**3d**) (83)	 (**6d**) (79;94)
5	(**1d**)	 (**2e**) (73;92)	 (**3e**) (80)	 (**6e**) (87;96)
6	 (**1e**)	 (**2f**) (84;88)	 (**3f**)[b]	 (**6f**) (22[b];87)
7	 (**1f**)	 (**2g**) (76;79)	 (**3g**) (67)	 (**6g**) (97;83)
8	(**1f**)	 (**2h**) (92;75)	 (**3h**) (79)	 (**6h**) (94;74)
9	 (**1g**)	 (**2i**) (95;60)	 (**3i**) (82)	 (**6i**) (84;71[c])

[a] E.e. = enantiomeric excess. [b] Overall yield from (**2f**), (**3f**) could not be isolated as pure product due to its high volatility. [c] Estimated by comparison of specific rotations after conversion into (+)-linalool.

spectra of the α-methoxy-α-trifluoromethylphenylacetate (MTPA) [(*R*)- and (*S*)-] esters between (**2**) and (**6**) [except (**2i**) and (**6i**)]. Although difficulties were encountered in indicating the highly volatile chloride (**3**) (entry 6), the present method generally could be carried out in a facile manner in good overall yield.

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References

1 (a) M. M. Midland, in 'Asymmetric Synthesis,' ed. J. D. Morrison, Academic Press, 1983, vol. 2, part A, pp. 45—69; (b) J. Y. Yadav, M. C. Chander, and B. V. Joshi, *Tetrahedron Lett.*, 1988, **29**, 2737; (c) K. Soai and S. Niwa, *Chem. Lett.*, 1989, 481.

2 (a) B. E. Rossiter, in 'Asymmetric Synthesis,' ed. J. D. Morrison, vol. 5, pp. 194—246; (b) M. G. Finn and K. B. Sharpless, *ibid.*, pp. 247—308; (c) Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, and K. B. Sharpless, *J. Am. Chem. Soc.*, 1987, **109**, 5756, and references cited therein.

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