



A Highly Efficient Practical Method for the Synthesis of Chiral Polyhydroxy-(E,E)-1-Chlorodienols and (E)-5-Hydroxy Enynes

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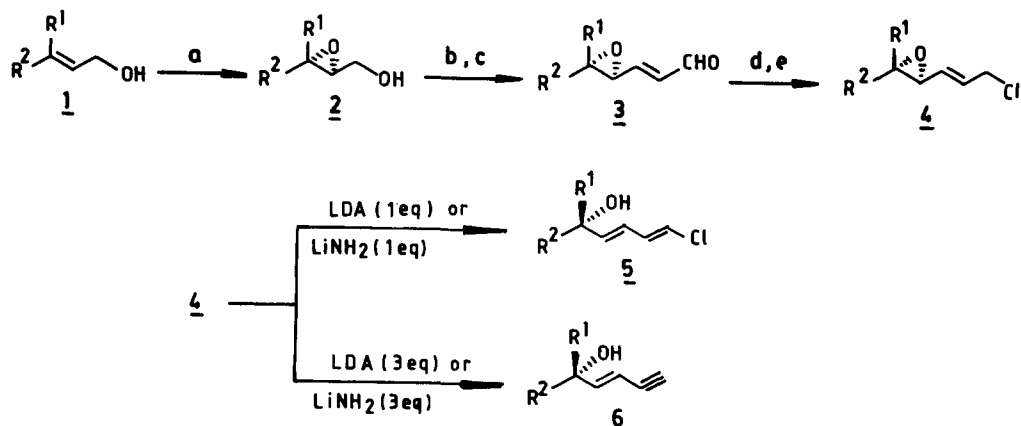
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Abstract : An efficient protocol for the synthesis of chiral polyhydroxy-(E, E)-1-chlorodienols and (E)-5-hydroxy enynes from chiral 4,5-epoxy trans allyl chlorides and 4,5-O-isopropylidene allyl chlorides is described by using stoichiometric amount of LiNH_2 or LDA in HMPA : THF (1 : 5) useful in the synthesis of biologically active natural products. © 1997 Elsevier Science Ltd.

Our continued interest^{1,2} on the synthesis of biologically active polyunsaturated hydroxy fatty acids has culminated in the development of novel methods for the preparation of enantiomerically enriched building blocks such as chiral alkynols^{2,3} and chlorovinyl alcohols⁴. The stereospecific C-C bond formation⁵ with the terminal acetylenic functionality under palladium catalyst forms one of the most distinctive features of recent discoveries and has increased greatly their utility. As a part of our on going research it was considered of interest to augment our earlier work⁶ for the synthesis of optically pure chlorodienols and hydroxy enynes and these intermediates can be utilized in the synthesis of leukotrienes,^{7,8} lipoxins^{7,8}, 5- HETE⁹, alkaloids¹⁰, prostaglandins¹¹, pyrethroids¹², steroids¹³ and others^{14,15}. Therefore we report a simple single step methodology for the synthesis of polyhydroxy-(E, E)-1-chlorodienols and (E)-5-hydroxy enynes derived from epoxy allyl chlorides and chiral pool carbohydrate precursors, and the details of our findings are described herein.

The salient features of our strategy involves initially the conversion of prochiral allyl alcohol **1** into chiral epoxy allyl chloride **4**. The final and novel reaction is the treatment of **4** with stoichiometric amount of LDA in HMPA : THF (1:5) at -78°C or LiNH_2 at -33°C (**Scheme 1**), (**entry 1-5**).

Scheme 1

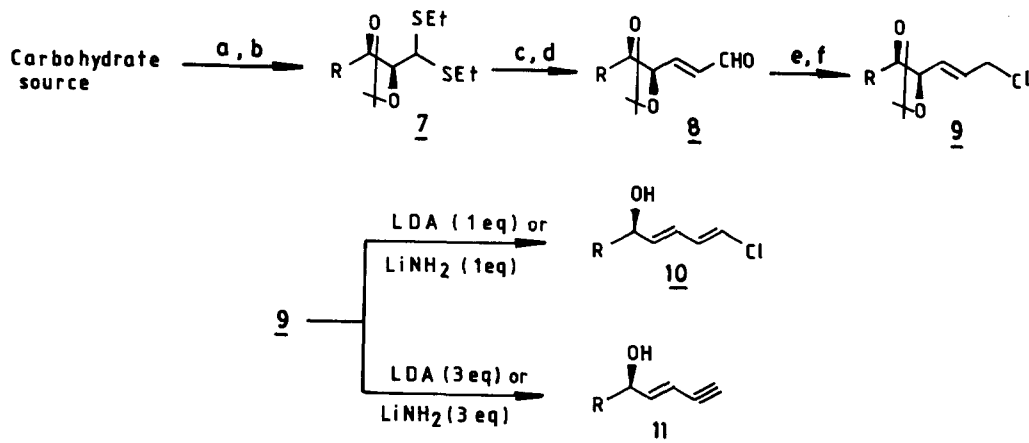


Reagents: (a) TBHP, TIP, (+)DIPT, mol. sieves 4A^o, (85-95%); (b) CrO₃·2Pyrs, CH₂Cl₂, (80-85%); (c) Ph₃P=CH-CHO, C₆H₆, RT, (70-85%); (d) NaBH₄, CeCl₃, MeOH, (90-95%); (e) Ph₃P, CCl₄, NaHCO₃, (80-85%).

Thus when trans epoxy allylchloride **4** was treated with 1 eq. of LDA in HMPA : THF (1:5) at -78°C or LiNH₂ at -33°C, it underwent elimination reaction to give **5** exclusively in quantitative yields. Similarly when 3 eq. of LDA or LiNH₂ was used, **6** were obtained exclusively.

In addition as mentioned earlier chiral centre can also be derived directly from the carbohydrate chiral pool¹⁶ to generate the polyhydroxy chlorodienols and enynes as delineated in scheme 2, (entry 6,7).

Scheme 2

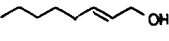
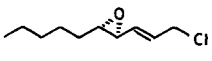
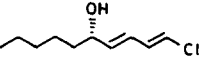
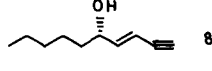
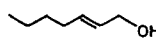
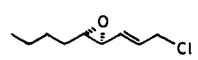
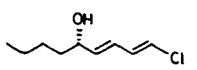
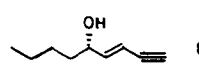

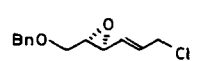
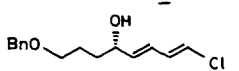
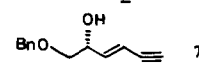
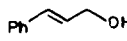
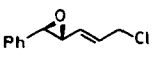
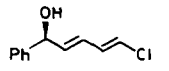
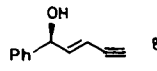
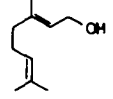
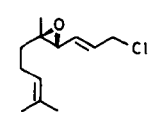
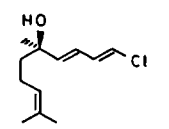
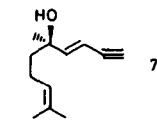
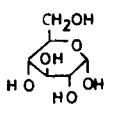
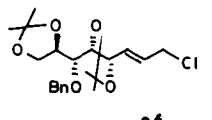
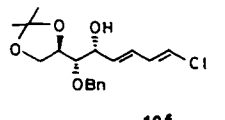
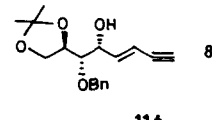
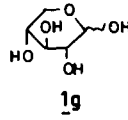
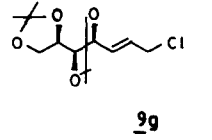
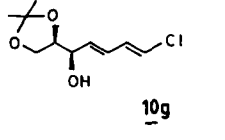
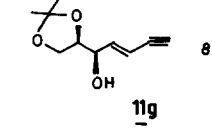


Reagents: (a) EtSH, HCl, (75-80%); (b) Acetone, H₂SO₄, CuSO₄, (75-80%); (c) HgCl₂, HgO, Acetone, (70-80%); (d) Ph₃P=CH-CHO, C₆H₆, RT, (70-85%); (e) NaBH₄, CeCl₃, MeOH, (90-95%); (f) Ph₃P, CCl₄, NaHCO₃, (80-90%).

Taking advantage of the readily available sugars like D-glucose and D-xylose the desired 4,5-O-isopropylidene trans allyl chlorides were prepared by reported method and when treated with LDA or LiNH₂, it underwent clean transformation to give exclusively corresponding polyhydroxy-(E, E)-chlorodienols and enynes. Under similar conditions described above all the new compounds thus prepared were confirmed

by ^1H , ^{13}C NMR and spectroscopic studies¹⁷, and were found to be optically pure.¹⁸ In order to generalize and show the versatility of the reaction, different epoxy allyl chlorides, and 4,5-O-isopropylidene allyl chlorides were prepared (Table 1) and tested the above mentioned reaction and they underwent smooth transformation to give enantiomerically pure final products in quantitative yields.

Table 1 Preparation of (E, E) chlorodienols and hydroxy enynes

Entry	Starting materials	Reactants	Products		Yield %	
			Chlorodienols (A)	Hydroxy enynes (B)	A	B
1	 1a	 4a	 5a	 6a	82	85
2	 1b	 4b	 5b	 6b	81	83
3	 1c	 4c	 5c	 6c	79	81
4	 1d	 4d	 5d	 6d	83	82
5	 1e	 4e	 5e	 6e	75	73
6	 1f	 9f	 10f	 11f	81	83
7	 1g	 9g	 10g	 11g	84	85

For entries 1, 2 (+) DIPT and for entries 3-5 (-) DIPT were used.

In conclusion it is pertinent to mention that the elimination reaction is highly chemoselective in both the carbohydrate precursor and epoxy chlorides, since the other isopropylidene group and other functionality present in the substrate remains unaffected and the ease with which these transformations can be carried out under mild conditions in high chemical and optical yields will find a great deal of application in the asymmetric synthesis.

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17. Selected NMR data for some compound **10f**. ¹H NMR (CDCl₃, 200MHz) : δ 1.31 (s, 3H); 1.45 (s, 3H); 2.61-2.71 (d, 1H, J=8.51Hz); 3.51-3.40 (dd, 1H, J=4.25, 7.65, Hz); 3.79-3.90 (m, 1H); 3.97-4.09 (m, 1H); 4.10-4.24 (m, 1H); 4.25-4.38 (m, 1H); 4.63-4.7 (d, 2H, J=4.25 Hz); 5.85-5.98 (dd, 1H, J=6.43, 16.30 Hz); 5.99 -6.65 (d, 1H, J=8.58 Hz); 2.24-2.37 (dd, 1H, J=8.58, 12.87 Hz); 6.65-6.82 (dd, 1H, J=10.72, 16.73 Hz); 7.21-7.40 (m, 5 H). ¹³C NMR (CDCl₃, 50 MHz); δ 25.3, 25.8, 66.7, 71.1, 74.2, 75.8, 76.3, 80.7, 81.8, 109.3, 110.0, 128.1, 128.2, 128.5, 137.4, 144.3; [α]_D²⁴ +50.7° (c 3.15, CHCl₃).
- 11f** ¹H NMR (CDCl₃, 200MHz) : δ 1.30 (s, 3 H); 1.45 (s, 3H); 2.70 (d, 1H, J= 8.99 Hz); 2.85 (br s, 1H); 3.47-3.56 (dd, 1H, J = 4.08, 8.17 Hz); 3.75-3.85 (dd, 1H, J=6.13, 8.58 Hz); 3.98-4.21 (m, 2H); 4.28-4.40 (m, 1H); 4.65 (s, 2 H); 5.75-5.89 (d, 1H, J=16.35 Hz); 6.28-6.44 (dd, 1H, J=5.31, 16.35 Hz); 7.21-7.41 (m, 5H). ¹³C NMR (CDCl₃, 50 MHz); δ 25.3, 26.7, 66.4, 71.4, 74.3, 76.0, 81.0, 109.1, 118.7, 124.5, 128.0, 128.3, 128.4, 128.9, 136.3, 137.6; [α]_D²⁴ +15.7° (c 1.8, CHCl₃).
18. The opening products retained the optical integrity of the substrates as indicated by Mosher's ester studies.