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A highly efficient and practical method for the synthesis of chiral polyhydroxy diacetylenic alcohols†

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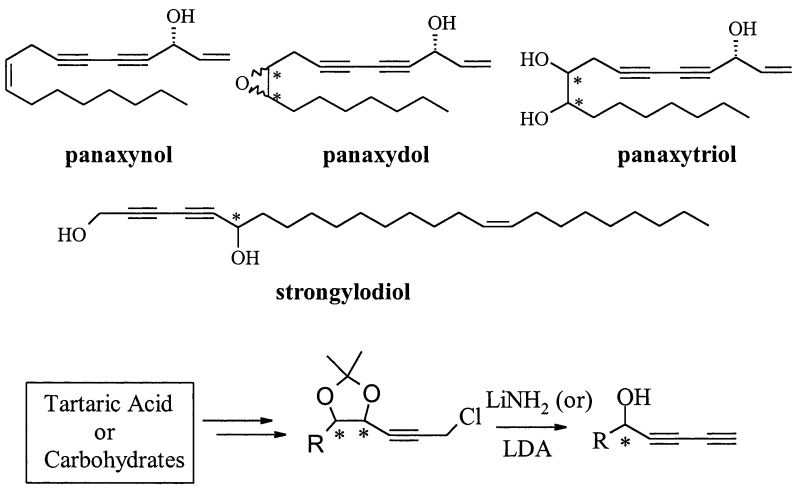
Abstract—An efficient protocol for the synthesis of chiral polyhydroxy diacetylenic alcohols from chiral 4,5-*O*-isopropylidene propargyl chlorides using strong bases is described and is useful for the synthesis of biologically active natural products.

In continuation of our efforts[1–3] towards the total synthesis of biologically active polyunsaturated hydroxy fatty acids, we have developed novel methods for the preparation of enantiomerically enriched building blocks, such as chiral alkynols,[2,4] chlorovinyl alcohols,[5] chlorodienols,[3] and hydroxyenynes.[3] Terminal acetylenic compounds are important precursors for C–C bond formation[6] in the total synthesis of several biologically active natural products. Panaxynol, panaxydol and panxytriol are structurally remarkable diacetylenic alcohol containing natural products isolated from *Panax ginsen*.[7] They are noted for their inhibitory activity on the growth of L-1210, MK-1, B-16, and L-926 cancer cell lines[8] and have been the subject of considerable synthetic efforts.[9] More recently, three new cytotoxic long-chain diacetylenic alcohols, strongylodiols, were isolated from an Okinawan marine sponge.[10] During the course of our studies on the total synthesis of these substances, we have developed a novel methodology for the synthesis of chiral polyhydroxy diacetylenic alcohols from chiral pool carbohydrate precursors.

The details of our findings are presented herein. The salient features of our strategy (Scheme 1) involves initially, the conversion of a polyhydroxy chiral pool precursor (e.g. tartaric acid or a carbohydrate) to 4,5-*O*-isopropylidene propargyl chlorides using standard



Scheme 1.

Keywords: diacetylenic alcohols (diynes); carbohydrate; chemoselective.

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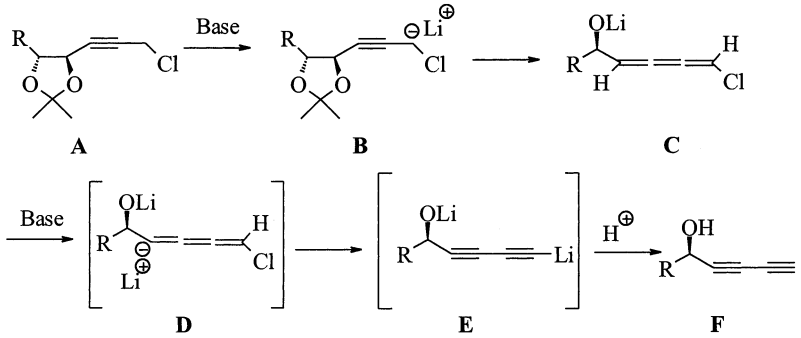
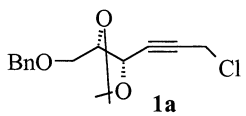
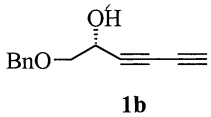
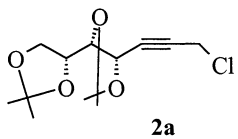
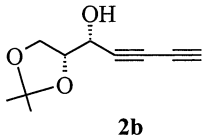
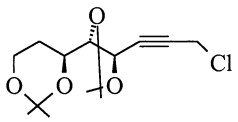
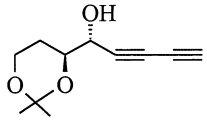
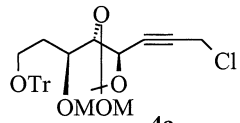
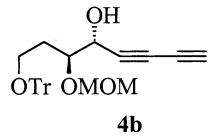
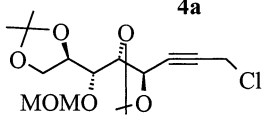
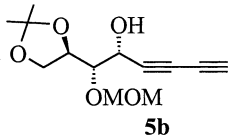
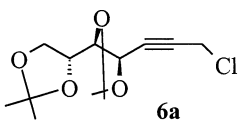
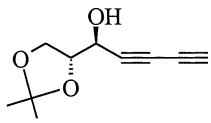
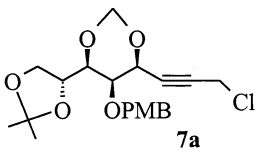
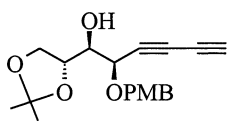
literature procedures[11] and using our earlier approaches to furnish alkynols.[2,4] Finally, these were treated with 3 equiv. of $LiNH_2$ or LDA[14] to afford chiral polyhydroxy diacetylenic alcohols exclusively, in good yields.

A plausible mechanism for the above reaction is shown in Scheme 2, in which the strong base abstracts[12] a proton from **A** followed by elimination of the δ-alkoxy group to form cumulene intermediate **C**, which then



Scheme 2.

Table 1. Preparation of chiral diacetylenic alcohols

Entry	Starting material	Substrate	Product	$[\alpha]_D^{25}$ #	Yield $
1.	L-Tartaric acid	 **1a**	 **1b**	-2.2 (0.52)	82
2.	D-Xylose	 **2a**	 **2b**	-14.12 (0.52)	79
3.	D-Ribose	 **3a**	 **3b**	-7.1 (1.02)	85
4.	D-Ribose	 **4a**	 **4b**	-6.2 (1.00)	81
5.	D-Mannose	 **5a**	 **5b**	+10.9 (0.49)	90
6.	D-Arabinose	 **6a**	 **6b**	+8.3 (1.00)	85
7.	D-Sorbitol	 **7a**	 **7b**	-20.5 (0.50)	75

#: Rotation recorded in $CHCl_3$, concentration in parenthesis

$: Average isolated yield from methods A and B

undergoes dehydrohalogenation and then further deprotonation, resulting in the chiral diacetylenic alcohol **F** after work-up. Our attempts to isolate intermediate **C** failed because of its ability to isomerise.[13]

Taking advantage of readily available sugars, a number of desired 4,5-*O*-isopropylidene propargyl chlorides were prepared in order to generalise and show the versatility of the reaction (Table 1). When these chlorides were treated with bases they underwent a clean transformation to give exclusively diacetylenic alcohols. All new compounds were characterised[14] and found to be enantiomerically pure.[15]

In conclusion, it is worth mentioning that the elimination reaction is highly chemoselective, since the other functionality present in the substrate remains unaffected and that the transformation can be carried out under mild conditions and in high yield. These are very useful synthons that will hopefully find widespread application in the synthesis of biologically active compounds.

Acknowledgements

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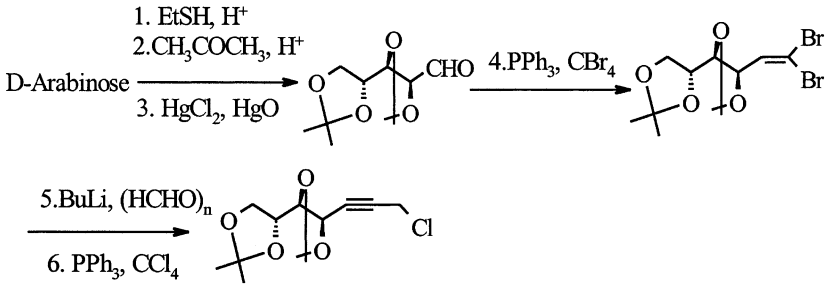

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For example, substrate **6a** was prepared from D-arabinose in six steps in 65% overall yield as described below:
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13. Rutledge, T. F. *Acetylenes and Allenes*; Reinhold: New York, 1969; p. 100.
14. **Typical experimental procedure: Method A**: To a stirred suspension of lithium amide (prepared from 0.039 g, 5.5 mg of Li) in liquid ammonia (20 mL), propargyl chloride **6a** (0.5 g, 1.74 mmol) in THF:HMPA (5:1, 3 mL) was added and stirred for 30 min. The reaction was quenched with solid ammonium chloride (2 g) and excess ammonia was evaporated. The residue was dissolved in water and extracted with ether. The organic layer was washed, dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by flash column chromatography (eluent: 15% ethyl acetate in hexane) to afford diacetylenic alcohol **6b** (0.26 g, 83%) as a colourless oil. **Method B**: To a stirred solution of propargyl chloride **6a** (0.5 g, 1.74 mmol) in THF:HMPA (5:1, 15 mL) at −78°C

was added a freshly prepared solution of LDA (0.59 g, 5.5 mmol) in a dropwise manner and maintained at this temperature for a further 30 min. After completion (as evidenced by TLC), saturated ammonium chloride solution was added and the product was extracted and purified as mentioned above to give **6b** (0.25 g, 79%).

Spectral data for **6b**: $R_f = 0.48$ (25% EtOAc in hexane); $[\alpha]_D^{25}$ +8.3 (*c* 1.0 $CHCl_3$); IR (neat): 3450 (br, OH), 3300 (s, C≡C–H), 2220 (w, C≡C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.42 (s, 3H), 2.11 (s, 1H), 2.20 (brs, 1H), 4.00 (m, 1H), 4.10 (m, 1H), 4.20 (m, 1H), 4.42 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.7, 26.9, 63.9, 64.8, 66.1, 66.5, 69.2, 69.4, 74.5, 111.1; EIMS (*m*/*z*): 165 (M^+-CH_3, 15), 101 (100), 43 (100).

15. The products retained the optical integrity of the substrates as indicated by Mosher's ester studies.