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# REDUCTIVE CLEAVAGES OF α,β-ALKYNYL ACETALS. NEW ROUTE TO OPTICALLY PURE PROPARGYLIC ALCOHOLS

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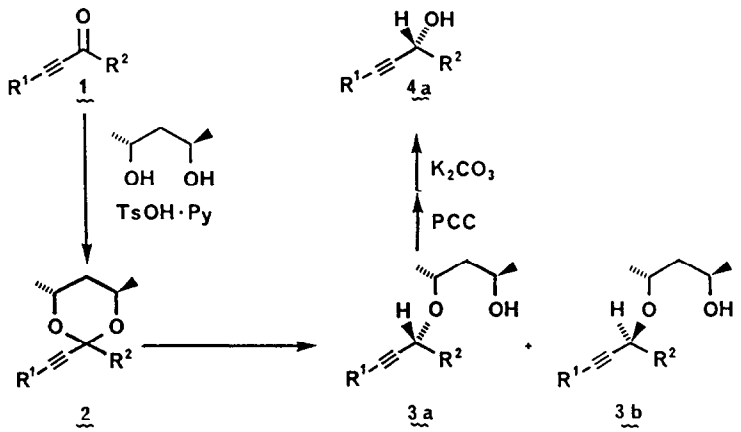
**ABSTRACT** Optically pure propargylic alclhols are obtained by the reductive cleavages of chiral α,β-alkynyl acetals with organoaluminum reagent followed by removal of chiral auxiliary.

The optically active propargylic alcohol has been recognized as an important synthetic intermediate of a variety of natural products including insect pheromones,[1a] alkaloids,[1b] prostagrandins,[1c] steroids[1d] and Vitamin E and K.[1e] Asymmetric reduction of the α,β-alkynyl ketone is a general synthetic method for the preparation of this class of compound.[2] However, there still exists a need for new methods where the greater stereoselectivity is prerequisites for success.

**Scheme 1.**



We have recently reported the selective reductive cleavages of chiral acetals using organoaluminum reagents (e.g. $Br_2AlH$, $Cl_2AlH$, DIBAH).[3] With this new procedure at hand, optically active aliphatic alcohols were prepared highly selectively. The same method seems to be effective for the preparation of the optically active propargylic alcohol, which is the subject of the present paper. The new process is illustrated in Scheme 1.

The acetals 2 were prepared from the corresponding ketone 1 and (-)-(2R,4R)-2,4-pentanediol[4] in moderate to excellent yields.[3] Experimental details of the cleavage of the acetal and the removal of the chiral auxiliary are as follows: To a solution of the acetal 2 (0.5 mmol; $R^1$ = Bu, $R^2$ = Me) in dichloromethane (3 mL) was added diisobutylaluminum hydride (DIBAH, 3 mL of an 1 M hexane solution) at 0 °C. After being stirred for 1 h, the mixture was poured into ice cold dilute hydrochloric acid and the product was extracted with ether twice. The organic layers were dried over anhydrous sodium sulfate, concentrated in vacuo, and passed through a short path column chromatography on silica gel to give the crude oil in 90% yield. Gc analysis of this product showed two peaks with the ratio of 3a:3b=96/4. The separation of diastereoisomers was effected by column chromatography on silica gel to afford the pure 3a: $R_f$ 0.42 using hexane-ethyl acetate, 5:1 (3b: $R_f$ 0.52). Oxidation of 3a thus obtained, was carried out with pyridinium chlorochromate (1.0 mmol) in dichloromethane (3 mL) at room temperature for 14 h. The mixture was poured into saturated aqueous sodium bisulfite (10 mL) and stirred for 1 h. The product was extracted with ether repeatedly and the dried organic layers were concentrated in vacuo to give the crude oil which was subsequently treated with potassium carbonate (0.7 g) in methanol (5 mL) at room temperature for 2 h. Usual extractive workup, concentration in vacuo and chromatography on silica gel (hexane-ether, 10:1) furnished the pure (R)-3-octyn-2-ol (4, $R^1$ = Bu, $R^2$ = Me) in 71 % yield from 3a as a colorless liquid: $[\alpha]^{24}_D$ +39.11 (c 1.63, ether).[1a]

Some of our results are listed in Table 1. Both DIBAH and $Br_2AlH$ were equally effective for the cleavage of the alkynyl acetal. It should be noted that the carbinol 4 shows (R)-configuration. Thus, sterically less hindered alkynyl group should occupy the axial position in the six-membered transition state 5 as shown below. Therefore, the internal consistency of all our previous results is maintained.[3]

The new process showed several unique advantages including (1) high stereospecificity, (2) easy separation of the trace isomer after reductive cleavage,[5] (3) readily availavility of the starting pentanediol.[4] Thus, the generality of the method described herein as a route for the stereocontrolled synthesis of optically active propargylic alcohol is evident.

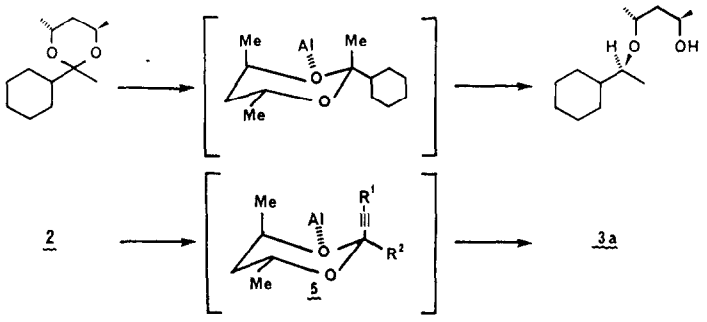



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Table 1. Reduction of $\alpha,\beta$-alkynyl acetals[a]

| 1 | | hydride reagent (equiv) | conditions[b] °C, h | 3 | | 4a[d] |
|---|---|---|---|---|---|---|
| $R^1$ | $R^2$ | | | yield (%) | ratio[c] 3a:3b | $[\alpha]_D$ (Confign) |
| Bu | Me | DIBAH (2) | 0, 6 | 68 | 85:15 | |
| | | DIBAH (4) | 0, 1 | 80 | 93:7 | |
| | | DIBAH (6) | 0, 1 | 90 | 96:4 | +39.11[e] (R) |
| | | $Br_2AlH$ (2) | -20, 5 | 53 | 50:50 | |
| | | $Br_2AlH$ (4) | -20, 3 | 99 | 68:32 | |
| | | $Br_2AlH$ (6) | -20, 3 | 100 | 93:7 | |
| Bu | Et | DIBAH (4) | 0, 1 | 93 | 97:3 | +21.60[f] |
| | | $Br_2AlH$ (6) | -20, 5 | 98 | 98:2 | |
| Me | $^iBu$ | $Br_2AlH$ (6) | -20, 4 | 99 | 98:2 | +15.08[g] (R) |
| Ph | Me | DIBAH (6) | 0, 2 | 86 | 90:10 | |
| | | $Br_2AlH$ (6) | -20, 2 | 92 | 90:10 | +36.68[h] (R) |
| Ph | Et | $Br_2AlH$ (6) | -20, 2 | 99 | 95:5 | +21.97[i] |
| Me | $^cHex$ | $Br_2AlH$ (6) | -20, 1 | 98 | 99:1 | |

[a] Reduction of the chiral acetal was carried out as described in text. [b] The reaction with DIBAH was carried out in dichloromethane and with $Br_2AlH$ in ether. [c] The ratio was determined by gc on a 25m PEG-HT capillary column. [d] The optical purity of 4a was confirmed to be >99% by gc analysis after the transformation to the corresponding (+)-MTPA ester. [e] (c 1.63, ether) at 24°C; Reported $[\alpha]^{23}_D$ +33.0° (c 1.62, ether) in 84% ee, see ref. 1a. [f] (c 1.03, ether) at 26°C. [g] (c, 2.47, $CHCl_3$) at 24°C; Reported $[\alpha]^{25}_D$ +13.48° (c 4.9, $CHCl_3$) see ref. 2a. [h] (c, 0.81, $CHCl_3$) at 21°C; Reported $[\alpha]^{25}_D$ +51.8 (neat) see ref. 2b. [i] (c 1.27, ether) at 21°C.

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