Pergamon

*Tetrahedron: Asymmetry* Vol. 5, No. 7, pp. 1161-1162, 1994

0957-4166/94 $7.00+0.00

0957-4166(94)00154-5

# Enantioselective Preparation of a *C₃* Symmetrical Triol

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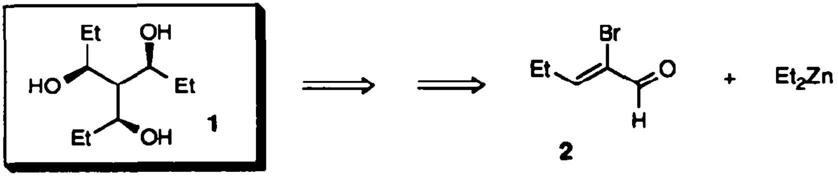
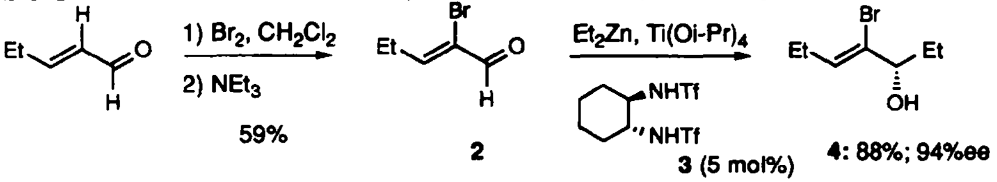
*Summary: The new $C_3$ symmetrical triol 1 has been prepared in optically pure form (> 98 %ee) using a catalytic enantioselective ethylation of a functionalized unsaturated aldehyde in an iterative way and a diastereoselective hydroboration.*

Chiral $C_2$ symmetrical alcohols, amines, thiols or phosphines have found numerous applications as catalyst ligands for asymmetric synthesis.[1] $C_3$ symmetrical ligands have been used far less for asymmetric synthesis,[2] although such auxiliaries should in principle lead to a better stereodifferentiation since the stereochemical information is concentrated in a space of 120 ° compared to 180 ° for a $C_2$ symmetrical ligand. Herein we report a stereoselective synthesis of a new $C_3$ symmetrical triol **1** using a catalytic asymmetric addition of $Et_2Zn$ to an unsaturated α-bromo-aldehyde **2** (eq 1).

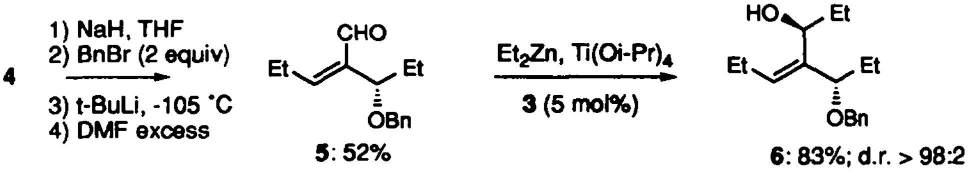


(1)

Recently, we have shown that unsaturated α-bromoaldehydes react with functionalized dialkylzincs with excellent stereoselectivity[3] using (1R, 2R)-1,2-bis(trifluorosulfonamido)cyclohexane **3**[4] (8 mol %) as a catalyst. The treatment of commercially available (E)-2-pentenal successively with $Br_2$ (1 equiv, $CH_2Cl_2$, 0 °C, 5 min) and $Et_3N$ (1.6 equiv, 0 °C) produces after filtration[5] over silica gel the sensitive aldehyde **2** (59 % yield). Catalytic asymmetric addition of $Et_2Zn$ (1.6 equiv) to **2** in the presence of $Ti(Oi\text{-}Pr)_4$ (1.7 equiv) and the catalyst **3** (5 mol%) in toluene (-60 °C, 2 h) affords the (S)-allylic alcohol **4** ($[\alpha]^{25}_D$ = -5.20 (c = 1.68, benzene)) in 88 % yield (50 mmol scale reaction) and 94 %*ee* as determined by $^1H$ NMR analysis of its ester derivative with (S)-(-)-O-acetylmandelic acid[6] (eq 2). The alcohol **4** was protected as a benzyl ether (NaH (1 equiv); BnBr (2 equiv), THF, rt, 12 h; 96 % yield) and converted to the aldehyde **5** via a bromine-lithium exchange using *t*-BuLi (3 equiv, ether, -105 °C) and quenching the resulting alkenyllithium with an excess of DMF (52 % yield). The addition of $Et_2Zn$ to **5** under our standard conditions affords the chiral 1,3-diol derivative **6** ($[\alpha]^{25}_D$ = -46.5 (c = 1.70, benzene); 83 % yield, diastereoselectivity > 98 : 2; eq 3).

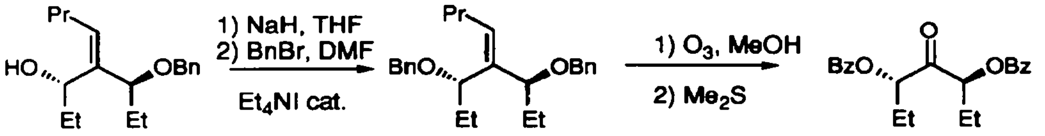


(2)



(3)

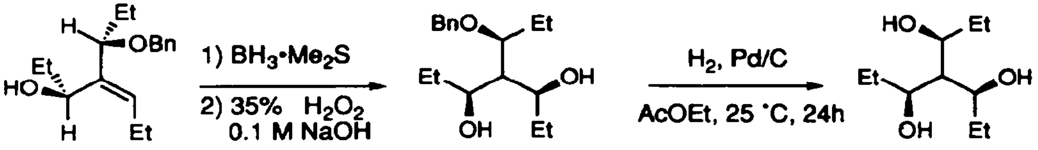
To prove the relative stereochemistry, the alcohol **7** prepared in the same way as **6** was benzylated (NaH, BnBr, THF, $Et_4NI$ cat., rt, 12 h; 83 % yield) and submitted to ozonolysis ($O_3$, MeOH, 4 h) affording the $C_2$ symmetrical ketone **8**[7] ($[\alpha]^{25}_D = +31.82$ (c = 2.20, benzene); 69 % yield; eq 4).



(4)

7 8 9: 69%

Interestingly, the benzyloxy groups of **9** were oxidized to benzoates during the ozonolysis.[8] The hydroboration of **6** with $BH_3 \cdot Me_2S$ (3 equiv, ether, rt, 12 h), followed by oxidation (35 % $H_2O_2$, 0.1 M NaOH, ether, rt, 2h) produces a mixture of two diastereoisomers **10** in the ratio 88:12. The major isomer could be separated by flash-chromatography and isolated in pure form ($[\alpha]^{25}_D = 18.4$ (c = 1.25, benzene); 54 % yield). After removal of the benzyl protecting group ($H_2$(1 atm), Pd/C, rt, 24 h), the triol **1** ($[\alpha]^{25}_D$ : -17.98 (c = 0.98, benzene); 90 % yield) was obtained in pure form as indicated by $^1H$ and $^{13}C$ NMR spectroscopy (eq 5).[9] Applications of **1** and related molecules in asymmetric syntheses are currently underway.



(5)

6 10: 54%; d.r. = 88 : 12 1: 90%

**Acknowledgment.**

We thank the Fonds der Chemischen Industrie, the DFG (SPP "Peroxidchemie") for generous support of this research, BASF AG and Witco (Bergkamen) for generous gift of chemicals.

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9. Spectroscopic data for **1**: $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 4.08 (t, 3H, J = 6.4 Hz), 3.49 (brs, 3H), 1.98 - 1.63 (m, 3H), 1.48 - 1.35 (m, 3H), 1.18 (q, 1H, J = 1.8 Hz), 0.89 (t, 3H, J = 7.4 Hz); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz) $\delta$ 73.55, 45.42, 28.13, 10.72. Anal. Calcd. for $C_{10}H_{22}O_3$: C, 63.12; H, 11.65. Found: C, 63.31; H, 12.00.

(*Received in UK 9 April* 1994)