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ASYMMETRIC INDUCTION FROM A TETRAHYDROPYRANYL GROUP ON ADDITION OF TETRAHYDROPYRANYL-OXY-(Z)-ALLYLBORONATES TO ALDEHYDES

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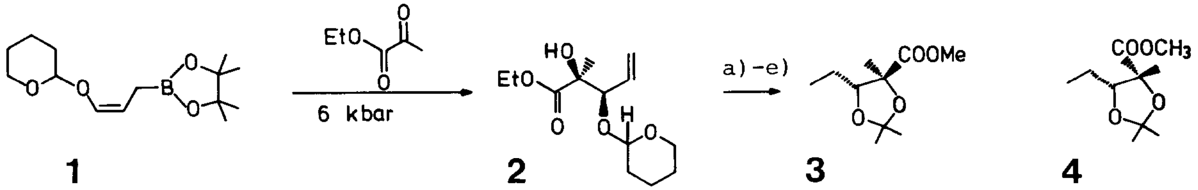
Abstract: A novel type of asymmetric induction originating from the chiral center of a THP protecting group was observed. The induction amounted to a 14:1 diastereoselection on addition of 1 to ethyl pyruvate. Selectivities of 3:1 to 13:1 were observed on addition of 5 to various aldehydes.

Being interested in the generation of macrolide building blocks such as 4 [1), we considered their preparation by an aldol type addition [2) to ethyl pyruvate. Of the various γ-alkoxy-allylboronates [3,4) the THP derivatives, such as 1 show the highest diastereoselectivity on addition to aldehydes. Hoping that this might hold for the addition to ketones as well, we prepared the pinacol ester 1 by metalation (n-BuLi/TMEDA) of allyl THP ether followed by borylation with $ClB[N(CH_3)_2]_2$ (56%) and esterification with pinacol (91%). 1 (Z/E=>95:<5 by ^{13}C nmr) reacted with ethyl pyruvate (80 hr, 45°, petr.ether) under 6 kbar pressure to give 85% of an adduct mixture (13:1.0:1.4 by capill.g.c.). The relative configuration of the major diastereomer 2 was secured by converting the crude adducts to a 90:10 mixture of the racemates of the known [1) esters 3 and 4, reflecting the syn/anti selectivity in the reaction of 1.

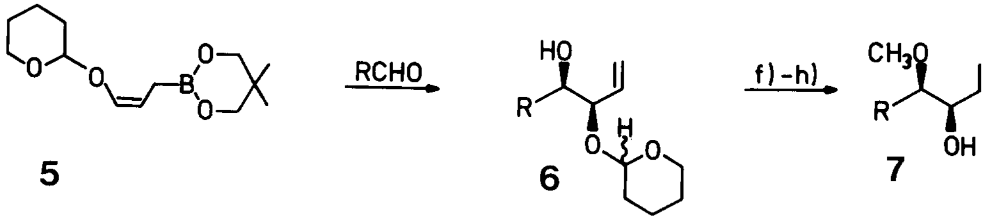


1 2 3 4

a) H_2/Pt, 83%; b) TsOH,CH_3OH, 82%; c) TsOH,$(CH_3)_2CO$, 98%; d) KOH,CH_3OH, 96%; e) CH_2N_2,Et_2O, 87%.

Remarkably this reaction led to a predominant diastereomer also with respect to the chiral center of the THP group as evidenced from the ^{13}C nmr spectrum. This suggests that a substantial (14:1) asymmetric induction originated from the THP-group. In order to evaluate the scope of this effect, we examined briefly the reaction of 5 prepared as above, with some representative aldehydes (48 hr, r.t.,neat).

The adducts 6 were isolated [3] in 70-80% yield with diastereoselectivities ranging from 93:7 for R= Ph over 80:20 for R= Et or iPr to 78:22 for R= Me. In order to verify that these numbers reflect the extent of asymmetric induction from the THP group and not an incomplete syn/anti-selectivity, 6 (R= Et), was transformed into 7, which was obtained in a diastereomeric purity of >95%. Since stereohomogeneous 7 resulted from a pair of diastereomers 6, the latter must be epimeric at the THP-center only.



f) CH_3I,KOH,DMSO, 82%; g) H_2/Pt, 70%; h) TsOH,CH_3OH, 79%.

While the chirality of the THP group is usually considered to be a nuisance in the synthesis of compounds containing other stereocenters, the observations documented here and similarly made by Wuts [5] show that this feature could be highly useful for asymmetric synthesis. We therefore hope to exploit this effect by the development of useful chiral THP protecting groups.

Prof. Wuts kindly informed us [5] that he made similar observations and that he was able to synthesize exo-brevicomin of 75% o.p. utilizing a chiral THP inductor.

^{13}C nmr data: 1: 18,6; 24,7; 25,2; 29,7; 61,6; 83,1; 98,0; 103,0; 141,6. 2, major diastereomer: 14,1; 19,1; 21,4; 24,7; 30,4; 61,5; 62,3; 76,8; 84,7; 99,1; 119,4; 134,0; 175,2. 6, R= Et, major diastereomer: 9,9; 19,8; 25,2; 25,4; 30,7; 63,0; 74,6; 83,2; 99,5; 117,7; 136,5. Minor diastereomer: 9,7; 19,9; 25,6; 74,6; 81,0; 96,0; 119,3; 135,0. 7, R= Et: 9,1; 10,0; 22,2; 26,1; 57,9; 73,4; 84,8.

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