LIMITED DIASTEREOSELECTIVITY ON ADDITION OF Y-ALKOXY-Z-ALLYLBORONATES TO ALDEHYDES

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<u>Summary</u>: Addition of $Z-\gamma-alkoxy-allylboronates <math>\frac{2}{2}$ to aldehydes leads to the homoallylalcohols $\frac{3}{2}$ and $\frac{4}{2}$. Increased steric bulk both on the aldehyde part or the allylboronates causes a decrease in diastereoselectivity. The stereochemistry of the addition is established by a novel synthesis of exo-brevicomine.

In a preceding communication ¹⁾ we reported the diastereoselective addition of E- and Z- γ -methoxy-allylboronates, e.g. $\frac{2}{2}$ to aldehydes. By this reaction a carbon chain is extended providing hydroxy- and methoxy-groups as new appendages. Whereas hydroxyl functions are useful in all kinds of natural product syntheses, the utility of methoxy groups is limited. We therefore became interested in allylboronates, such as $\frac{2}{2}$ and $\frac{2}{2}$, carrying protected hydroxy groups in the γ -position. These can be generated from the known derivatives $\underline{1}\underline{b}$ and $\underline{1}\underline{c}$ of allyl alcohol ³⁾ following the route previously described for the preparation of $\underline{2}\underline{a}$ ¹⁾. Since the starting materials are readily available we did not optimize the yields.

 $\frac{n - BuLi}{R'O} \xrightarrow{HO} \frac{HO}{HO} \xrightarrow{HO} \xrightarrow{HO}$

The addition of $\frac{2}{2}$ and $\frac{2}{2}$ to aldehydes neat (2-14 d 25° or 4-12 h 60° C) was followed by workup with either triethanolamine in ether or filtration over Alox giving the homoallylalcohols $\frac{3}{2}$ and $\frac{4}{2}$, cf. Table.

R'O R'O	RCHO	N(CH ₂ C	H ₂ OH) ₃) +)R' 3		 R' 4
2					3		•
	<u>3</u> a∕ <u>4</u> a		<u>3</u> <u>b</u> / <u>4</u> <u>b</u>		<u>3</u> ⊆/4⊆		
Aldehyde	yield १	ratio	yield %	ratio	yield %	ratio	
C ₆ H ₅ CHO	86	>95:< 5	82	>95:< 5	93	94: 6	
СН₃СНО	85	93: 7	89	92: 8	86	88:12	
CH ₃ CH ₂ CHO	94	92: 8	88	89: 11	88	80:20	
(CH ₃) ₂ CHCHO	94	89: 11	90	80: 20	57	68:32	

The data reveal an unexpected decrease in diastereoselectivity with both increasing bulk of the γ -substituent in the allylboronate and the residue R of the aldehyde. This effect (although small) could already be recognized in the reactions of $\underline{2a}$, cf. table. It should be noted that this decrease in diastereo= selectivity is peculiar to the Z-configurated series, since the E- γ -methoxy= allylboronate added to isobutyraldehyde with a selectivity of >98:<2¹⁾.

We feel that these variations in diastereoselectivity can be rationalized in the context of the cyclic transition state models developed for aldol additions $^{4,5)}$. The high diastereoselectivity encountered when both R and R' are small must result from the fact that transition state $\underline{6}$ is ≥ 2 kcal more stable than transition state $\underline{5}$. This is the difference between the destabilizing 1,3-diaxial interaction between the R-group and the oxygen on boron in $\underline{5}$ and the destabili= zing gauche interaction between the R-group and the R'O-residue of the allyl= boronates in transition state $\underline{6}$. It is seen that increasing the bulk of R' selectively destabilizes transition state $\underline{6}$, so that more of the reaction adopts transition state $\underline{5}$. It is less obvious that an increase in the bulk of R should also favour transition state $\underline{5}$.



A similar inspection of the transition states for the addition of the E- γ -alkoxy-allylboronates (not depicted) makes it clear that an increase in steric bulk of the reactands would destabilize both transition states, but predominantly the one with the axial R-group. Hence in the E-series increasing bulk should lead to an increased diastereoselectivity as observed ¹⁾.

It becomes clear that uniform diastereoselectivity is not granted. Even the structural assignment of the homoallylalcohols $\frac{3}{2}$ and $\frac{4}{2}$ by analogy from similar studies ^{1,6)} may be incorrect in cases of significant steric hindrance. Hence we felt it necessary to establish rigorously the relative configuration of the adduct in one such reaction. We chose the addition of $\frac{2}{2}c$ to the ketoaldehyde $\frac{7}{2}$ ⁷⁾, since the adduct $\frac{8}{2}$ could easily be converted to the racemic brevicomins, the relative configurations of which are known ⁸⁾.



After addition of $\underline{2}\underline{c}$ to $\underline{7}$ the crude adduct $\underline{8}$ was cyclized with perchloric acid in ether during workup to give the dehydro-brevicomine $\underline{9}$ with an exo-/endoratio of 94:6. Reduction of the double bond (KOOC-N=N-COOK, AcOH, CH₃OH) yielded (<u>+</u>)-brevicomine, the main component of which was identified as the exo-isomer by comparison of the ¹H-NMR-spectrum with the published data ⁸. This established that the addition of $\underline{2}\underline{c}$ to $\underline{7}$ proceeded predominantly via transition state $\underline{6}$; following the normal pattern of stereoselectivity.

In the case of the brevicomins isomeric purity is more important than enantiomeric purity, since the unnatural enantiomer is not an inhibitor of pheromone activity ⁹⁾. For that matter, the residual amount of endo-isomer in $\underline{10}$ could be removed by selective hydrogenolysis ¹⁰⁾. Although the present synthesis of the exo-isomer is not the shortest one reported ¹¹⁾, it constitutes a novel convergent and stereoselective approach.

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