Tetrahedron Letters,Vol.26,No.13,pp 1643-1646,1985
Printed in Great Britain

0040-4039/85 $3.00 + .00

TANDEM ALDOL ADDITION / ALLYL METAL ADDITION

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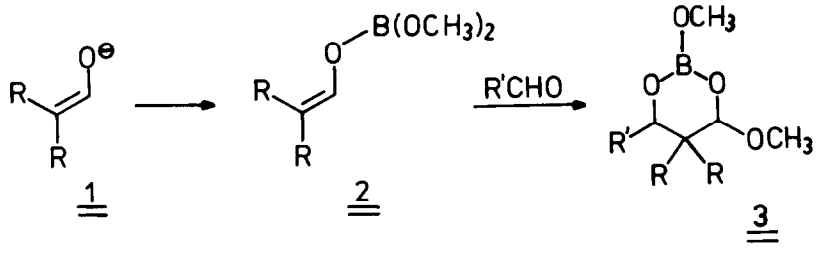
Summary: Addition of the enol borates 2 to aldehydes generated the internally protected aldols 3. These were subjected in situ to an allyl metal addition giving the 1,3-diols 7 or 13. This constitutes a rapid evolution of a carbon skeleton by a highly correlated tandem aldol-addition / allyl metal addition.

A sequence of aldol additions would be the most direct route to products having an 1,3,5-oxygenated carbon chain. Yet the addition of an aldehyde enolate to an aldehyde is an impractical route [1]. Instead, one is forced to use a synthetic equivalent of an aldehyde enolate [2,3] which is added to the acceptor aldehyde. In a subsequent step the resulting hydroxy group is protected and, in the final step, the new aldehyde function is liberated. Among the several reasons that make such a sequence of steps frequently mandatory is the fact that free aldols with an unprotected hydroxyl function form internally various sorts of acetals, which render manipulation and defined reactions highly difficult. Hence, the number of steps involved could be reduced, if the necessary protection of the hydroxyl group could be carried out in situ or, even better, concomitant with the C-C-bond forming step. Our recently discovered aldol addition of enol borates [4] offered a possibility to achieve this goal:



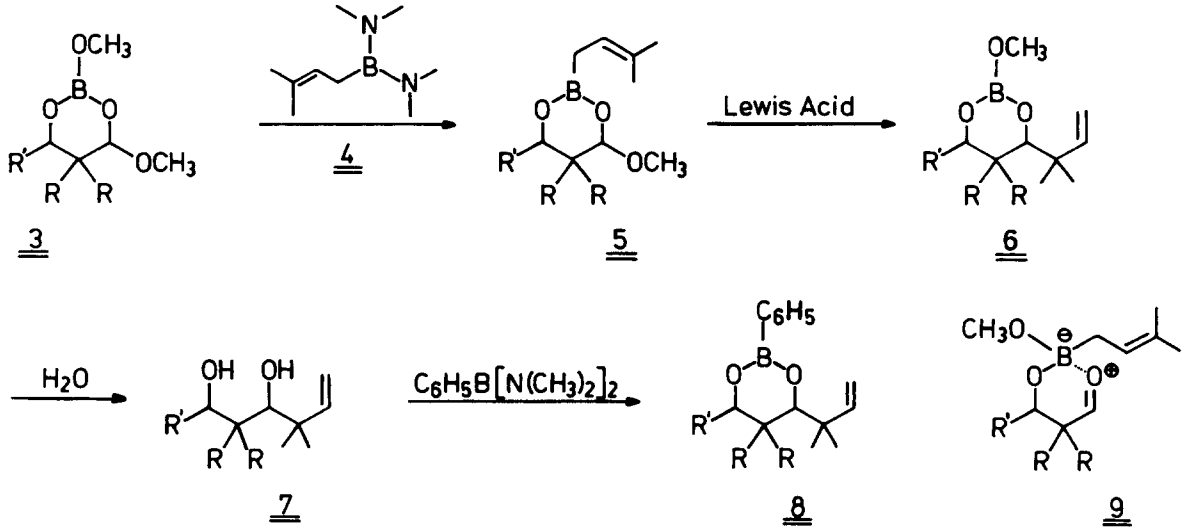
1 2 3

	R	R'
a	H	$C_6H_5CH_2CH_2$
b	H	CH_3
c	H	$(CH_3)_2CH$
d	CH_3	$(CH_3)_2CH$
e	CH_3	$C_6H_5CH_2CH_2$

2,4-Dimethoxy-1,3,2-dioxaborinanes 3 as internally protected aldols:
The enolate of acetaldehyde 1a [5] was borylated at -78 °C with chloro-dimethoxyborane to give the enolborate 2, which polymerized upon warming to room temperature. The enol borate 2 could however be added at low temperatures to representative aldehydes leading to the internally protected aldols 3a, b, c as (2-2,3):1 mixtures of anomeric acetals, which were characterised by their nmr spectra. Similarly, the enolate of isobutyraldehyde [6] was converted into the dioxaborinanes 3d, e. The yield of crude material was generally better than 60 %. Due to their thermal instability and their high tendency towards hydrolysis the dioxaborinanes 3 could not be purified further [7].

In situ allyl metal addition to the dioxaborinanes 3:

The advantage of the internally protected aldols 3 lies in the fact that these are properly set up for further chain extension: Exchange of the crude borate ester 3 in situ with bis(dimethylamino)-prenyl-borane 4 [8] generated the dioxaborinane 5, which was rearranged at room temperature to the borates 6 upon exposure to Lewis acids; cf. the table. The resulting borates 6 were hydrolysed to the diols 7, which were fully characterised as the phenylboronate esters 8. Although this seems to be a lengthy procedure, the over all yields from the enolate 1 to the purified final product 8 usually exceeded 60 %, cf. the table. Thus, this one pot operation constitutes a highly correlated tandem aldol addition/ allyl metal addition, which otherwise would involve five separate steps to the diol 7.

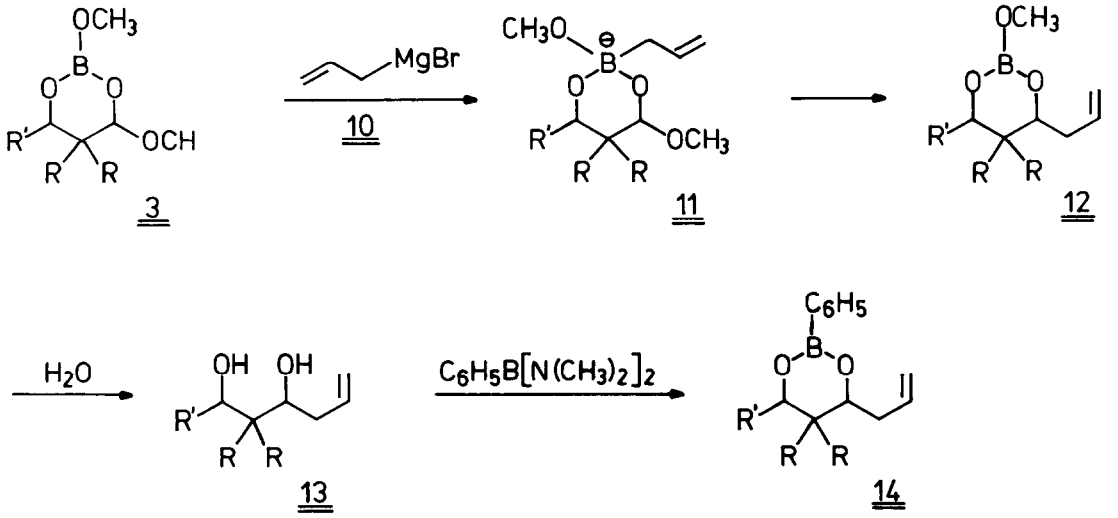


The diols 7 were obtained as (2,3-4):1 mixtures of diastereomers, in which the threo-isomer predominated. The structural assignment is based on the nmr spectra of the cyclic derivative 8. Assignment is also possible directly from the ^{13}C-nmr spectra of the 1,3-diols 7 [9].

The rearrangement 5 → 6 probably rests on a Lewis acid catalysed equilibration of 5 with 9, which is the starting point for an intramolecular allyl metal addition [3,10]. Such an intermediate is also accessible from 3 by addition of other allyl metal species: E.G. reaction of 3 with allyl magnesium bromide led after warming to room temperature and hydrolysis directly to the 1,3-diols 13, which were again characterised as their phenylboronates 14. In this reaction the Lewis acidity of the magnesium counterion is probably sufficient to ionize the ate-complex 11 to an intermediate of type 9. The diastereoselectivity of the Grignard addition is similar to the one recorded above, cf. the table. The overall yields of the diols 13 from the enolate 1 are highly attractive, considering the

Table: In situ conversion of enolates 1 via the dioxaborinanes 3 to the diols 7 and 13

Aldehyde R'=	Enolate 1 R=	Allyl metal compound	Catalyst	% Overall Yield of Diols	threo/ erythro
CH_3	H	$(CH_3)_2C=CH-CH_2-B[N(CH_3)_2]_2$	$FeCl_3$/THF	61	87 : 13
			$Ti(OiPr)_4$/Ether	84	72 : 28
			$ZrCl_4$/THF	72	77 : 23
$(CH_3)_2CH$	H	$(CH_3)_2C=CH-CH_2-B[N(CH_3)_2]_2$	$ZrCl_4$/Ether	98	70 : 30
			$B(OMe)_3$/Ether	96	78 : 22
CH_3	H	$CH_2=CH-CH_2MgBr$	--	62	70 : 30
$(CH_3)_2CH$	H	$CH_2=CH-CH_2MgBr$	--	83	72 : 28
$(CH_2)_2CH$	CH	$CH_2=CH-CH_2MgBr$	--	77	70 : 30
CH_3	H	$(CH_2=CH-CH_2)_4Zr$ [11]	--	76	70 : 30



number of steps it would otherwise take to assemble 13 from an aldehyde, an enolate equivalent and a Grignard reagent.

All in all, the reaction protocol presented here provides a short cut to the usual technique of chain extension using enolate equivalents [12].

Acknowledgement: We would like to thank the Fonds der Chemischen Industrie for support of this study, especially by granting a fellowship to S.F.

Typical procedure: To 10 mmol of the lithium enolate 1 in 50 ml THF under nitrogen were added 11 mmol of chloro-dimethoxy-borane at -78 °C. After 30 min. 11 mmol of the aldehyde were added and the mixture was allowed to reach room temperature. After recooling to -78 °C, 10 mmol of 4 were added under stirring. The mixture was allowed to reach room temperature over 1.5 h and recooled again to -78 °C. One equivalent of the Lewis acid was added and the mixture stirred

at room temperature for 3 h. Hydrolysis with 150 ml of a 0.12 m phosphate buffer (pH = 7) was followed by extraction with 5 x 50 ml ether. The extracts were washed with 20 ml H_2O, dried over Na_2SO_4 and concentrated to give the crude diol 7. 5 - 10 mmol of the crude diol 7 were stirred overnight in 30 ml dry ether with one equivalent of bis(dimethylamino)-phenyl-borane [13] at room temperature. The solvent was removed and the product bulb - to - bulb distilled i.vac. The distillate was taken up in 30 ml CH_2Cl_2 and washed with 50 ml H_2O. The aqueous phase was extracted with 5 x 20 ml of CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated to give the phenylboronate esters 8, or 14, which were fully characterised by elemental analyses and ^{13}C- and ^{1}H-nmr spectra.

3a: ^{13}C-nmr: δ = 21.9, 38.1, 50.0, 54.5, 63.5, 95.4; other diastereomer 22.1, 39.3, 50.1, 54.3, 65.9, 97.2. - 13a: ^{13}C-nmr, threo: δ = 22.1, 22.9, 23.3, 38.9, 41.3, 65.5, 74.4, 113.3, 145.2; erythro: δ = 22.0, 22.7, 24.0, 38.9, 41.5, 69.1, 79.3, 113.4, 145.1. - ^{1}H-nmr (400 MHz, $CDCl_3$): δ = 1.0 (s, 3H), 1.004 (s, 3H), 1.7 (s, broad, 1H), 2.07 (s, broad, 1H), 5.05 (dd, J = 17.5 and 1.4 Hz, 1H), 5.1 (dd, J = 17.5 and 1.4 Hz, 1H); erythro: 1.19 (d, J = 6.2 Hz, 3H), 1.39 (m, 1H), 1.6 (dt, J = 14.4 and 1.9 Hz, 1H), 3.54 (dd, J = 10.7 and 1.9 Hz, 1H), 3.98 (m, 1H), 5.79 (dd, J = 17.5 and 10.8 Hz, 1H); threo: 1.24 (d, J = 6.3 Hz, 3H), 1.52 (m, 2H), 3.64 (t, J = 6.5 Hz, 1H), 4.1 (m, 1H), 5.81 (dd, J = 17.5 and 10.8 Hz, 1H).

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(Received in Germany 14 January 1985)