Aldolisation of a Carbohydrate Enolate: Stereochemical Outcome and *X*-Ray Crystal Structure Determination of an Aldol Product†

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Reaction of acetaldehyde and propionaldehyde with the carbohydrate derived enolate (**2**) occurs with excellent diastereofacial selectivity on the enolate but modest facial selectivity on the aldehyde, giving aldols (**4**) and (**5**) in good yield; the major isomer (**4a**) was reduced to the diol (**7**), the structure of which has been determined by *X*-ray crystal structure analysis.

The aldol reaction is a most useful reaction in organic chemistry forming interesting products, often closely related to subunits of natural molecules, which have been biogenetically derived from acetate or propionate pathways. Although it is a well established reaction, its stereochemical course was not investigated until the 1970s, and these studies have given rise to an enormous body of work. This work has been amply studied and reviewed.[1] The importance of enolate geometry[2] as well as the role of the counter ion[3] have been emphasized. Surprisingly, the use of a ketone enolate included in a multichiral array seems to have been little studied. In connection with our programme aimed at the use of carbohydrate enolates in synthesis,[4,5] we decided to study the behaviour of such an enolate in the aldol condensation reaction. A recent report by Tsang *et al.*[6] on this subject prompted us to disclose our results.

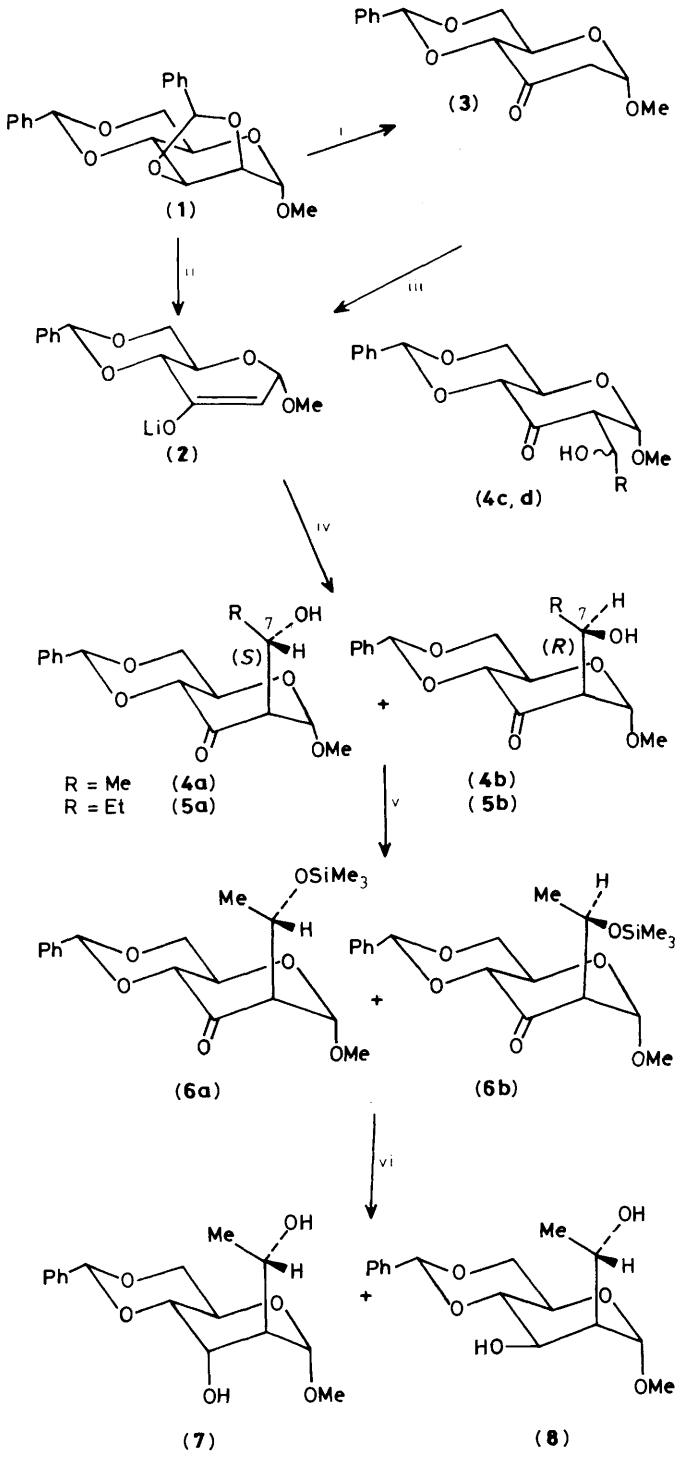
Enolate (**2**), generated from (**1**) on reaction with butyllithium,[7] or from ketone (**3**) by treatment with a lithium amide,[8] was chosen for this study. The enolate (**2**) was known to be stable at −30 °C from our previous work on its stereospecific mono- and di-alkylation.[3] Owing to the fixed *E* geometry of enolate (**2**) and its highly asymmetric environment, one would expect high diastereofacial selectivity and a good *anti*:*syn* ratio in the aldol reaction. We probed this hypothesis using acetaldehyde and propionaldehyde which would give aldols of interest in the synthesis of polyketides related to natural products.[9]

Addition of acetaldehyde or propionaldehyde to enolate (**2**) in tetrahydrofuran (thf) at low temperature gave the aldols (**4**) and (**5**) respectively. Examination of the ^{1}H n.m.r. spectra of crude mixtures of compounds (**4**) or (**5**) showed that they were a mixture of two isomers **a** and **b**, having an axially oriented C-2 chain,‡ resulting from the attack of the aldehyde from the less hindered β side of enolate (**2**). Whereas diastereofacial selectivity was excellent the facial selectivity on the aldehyde was found to be poor. Improvement of that selectivity was attempted using chelating species (zinc or magnesium chloride) and different enolisation systems. The results are summarized in Table 1, and will be discussed below.

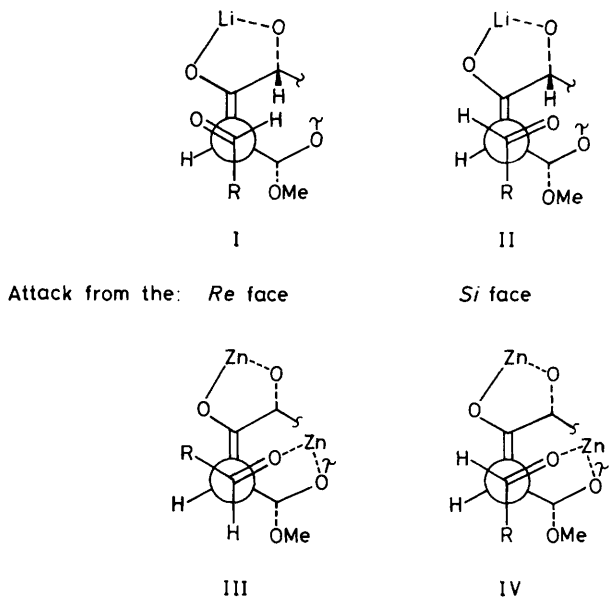
A second problem was to determine the absolute configura-

† Part of this work was presented at the 3rd EURO Carbohydrates Symposium, 1987, Grenoble, France, Abstract B-2-10.

‡ Attempts to isolate the major isomer by column chromatography and/or crystallisation led to epimerisation giving (**4c**) and (**4d**) in significant yield. The use of h.p.l.c. instead of standard chromatography circumvents this problem.



Scheme 1. *Reagents and conditions*: i, BuLi then H_3O^+; ii, BuLi, tetrahydrofuran (thf), −30 °C; iii, $LiNR_2$, thf, −30 °C; iv, RCHO, see Table 1; v, $ClSiMe_3$, NEt_3, CH_2Cl_2, 1 h, room temp.; vi, $NaBH_4$, H_2O, EtOH, then H_3O^+.



Scheme 2

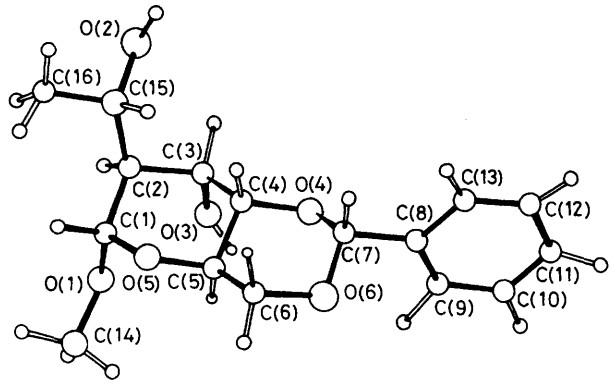


Figure 1. ORTEP diagram of compound (7).

tion at the new stereogenic C-7 centre. Although the coupling constants $J_{2,7}$ were different for the two isomers (7 and 9 Hz) no reasonable conclusions using hydrogen-bonded or non-bonded aldol conformations could be drawn from the ^1H n.m.r. data. Trimethylsilylation of the (**4a**), (**4b**) mixture gave compounds (**6a**) and (**6b**) which were readily separated by column chromatography. ^1H N.m.r. spectra of (**4a**) and (**6a**) or (**4b**) and (**6b**) were very similar, especially the chemical shifts of H-1, H-2 and $J_{2,7}$. In order to synthesise stable compounds and obtain suitable crystals, the trimethylsilyl derivative (**6a**) was reduced with sodium borohydride and subsequently desilylated to give a mixture of C-4 epimeric alcohols (**7**) and (**8**). The structure of (**7**) was determined by *X*-ray crystallographic analysis.§ The (*S*)-configuration at C-7 of (**4a**) could then be deduced from the structure of (**7**).

As shown in Table 1, the *anti*:*syn* ratio, *i.e.* the facial selectivity, induced on the aldehyde is modest. Particularly the use of lithium di-isopropylamide to generate the enolate (**2**)

§ *Crystal data* for (**7**): $C_{16}H_{22}O_6$, M = 310, orthorhombic, space group $P2_12_12_1$, a = 22.692(9), b = 11.231(5), c = 5.691(3) Å, Z = 4, U = 1450.4 Å^3, D_c = 1.42 g cm^{-3}. Data were measured on a Philips PW 1100 four-circle diffractometer using graphite monochromated Cu-K_α radiation in θ–2θ scan mode. No absorption correction was made. The structure was solved by direct methods[1] and full-matrix least-squares refinement using SHELX.[14] All non-hydrogen atoms were considered anisotropic and the hydrogen atoms isotropic. For 1725 unique reflexions [$I \leqslant 3\sigma(I)$] the final R value was 0.073 (R_w = 0.10). Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

Table 1. Condensation of aldehydes RCHO with enolate (**2**).

Entry	Enolization system	Salt added	R	*T*/°C	*t*/min	Products	*anti*:*syn*	% Yield[a]
1	(**1**), BuLi	—	Me	−30	10	(**4a**), (**4b**)	20:10	76
2[b]	(**1**), BuLi	$ZnCl_2$	Me	−78	60	,, ,,	10:26	81
3[b]	(**1**), BuLi	$MgCl_2$	Me	−78	60	,, ,,	10:19	78
4	(**1**), BuLi	—	$MeCH_2$	−30	10	(**5a**), (**5b**)	18:10	72
5[b]	(**1**), BuLi	$ZnCl_2$	$MeCH_2$	−78	60	,, ,,	10:16	66
6[b]	(**1**), BuLi	$MgCl_2$	$MeCH_2$	−78	60	,, ,,	10:20	69
7	(**3**), LDA[c]	—	Me	−30	60	(**4a**), (**4b**)	11:10	70
8	(**3**), LHMDS[d]	—	Me	−30	60	,, ,,	16:10	74
9[e]	(**3**), LHMDS	$ZnCl_2$	Me	−78	60	,, ,,	10:20	64
10	(**3**), LDA	—	$MeCH_2$	−30	60	(**5a**), (**5b**)	10:14	65
11	(**3**), LHMDS	—	$MeCH_2$	−30	60	,, ,,	12:10	45
12[e]	(**3**), LHMDS	$ZnCl_2$	$MeCH_2$	−78	60	,, ,,	10:21	48

[a] Isolated pure compounds. [b] Aldehyde was added at −78 °C and allowed to react at −30 °C within the time indicated. [c] LDA = lithium di-isopropylamide. [d] LHMDS = lithium hexamethyldisilazide. [e] According to ref. 7.

gave a mixture of aldols (*ca.* 1:1). Better results were obtained using butyl lithium or after addition of zinc or

either the *anti* or the *syn* isomers as the major product using different enolization systems. This approach provides interest