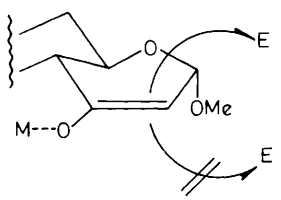
# Facial-selective Carbohydrate-based Aldol Additions

**Kuo-Long Yu and Bert Fraser-Reid***

*Department of Chemistry, Paul M. Gross Laboratory, Duke University, Durham, NC 27706, U.S.A.*

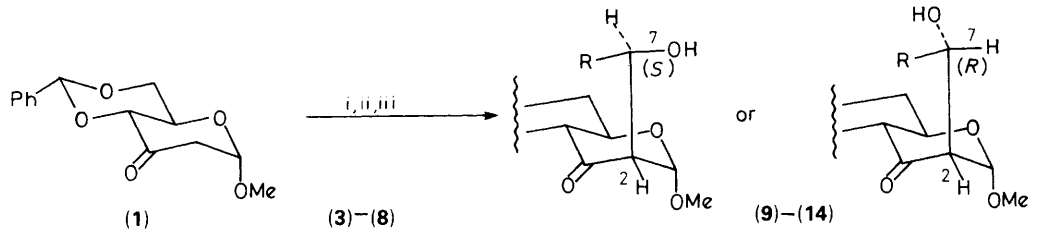
The enolate of the 2-deoxy-3-oxo pyranoside (**1**) undergoes aldol additions from the β-face exclusively, and so stereoselectivity of the reaction apparently relies entirely on control elements in the aldehyde, such as α- or α,β-chelation.

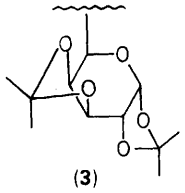
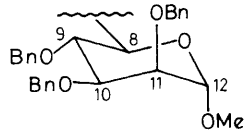
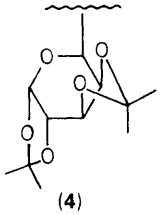
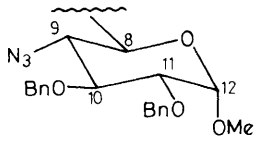
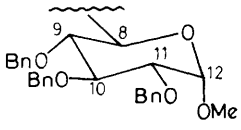
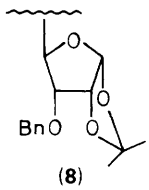
The principle of double stereodifferentiation as it relates to aldol condensation of a chiral aldehyde and a chiral ketone was investigated independently by Heathcock and co-workers[1] and Masamune.[2] The evidence gathered conformed to the expectation that chiral partners display distinct diastereofacial preferences.[3] Thus coupling of 'matched' pairs of reactants led to high diastereoisomeric ratios, whereas with 'mismatched' pairs the selectivity was low. The poor result with the latter is a manifestation of the process occurring *via* the less preferred



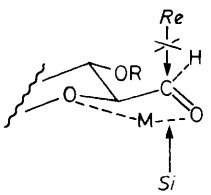

(**2**)

**Table 1.** Some aldol addition reactions of ketone (**1**).[a]

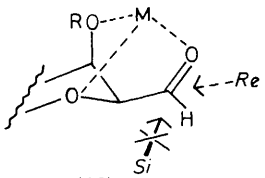



| Aldehydic substrate, R | Product | $J_{2,7}$/Hz | Aldehydic substrate, R | Product | $J_{2,7}$/Hz |
|---|---|---|---|---|---|
|  (3) | (**9**) C-7 (*R*) | 5.6 |  (6) | (**12**) C-7 (*S*) | 11.3 |
|  (4) | (**10a**) (major) C-7 (*S*) | 9.0 |  (7) | (**13**) C-7 (*S*) | 10.8 |
| | (**10b**) (minor) C-7 (*R*) | 4.6 | | | |
|  (5) | (**11**) C-7 (*S*) | 11.0 |  (8) | (**14**) C-7 (*S*) | 8.1 |

[a] The products shown are the only adducts detected chromatographically. Bn = $PhCH_2$. *Reagents*: i, $KN(SiMe_3)_2$; ii, $ZnCl_2$ or $TiCl_4$; iii, RCHO.




(**15**)



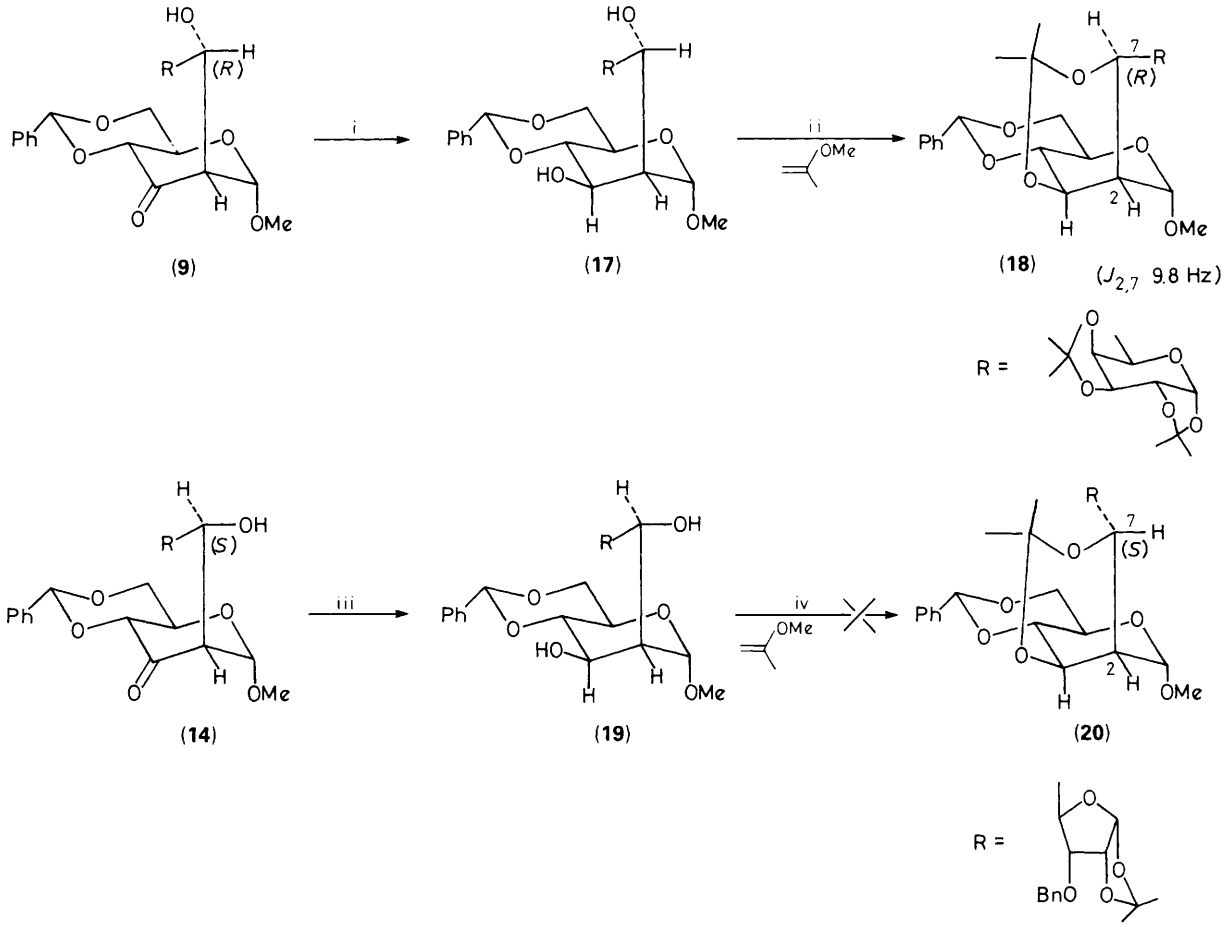

(**16**)

reaction pathway of each partner. But if one of the faces of one partner is totally occluded, then control elements in the other partner can be fully exploited; this may lead to excellent selectivity even for the mismatched pair, because the multiplicative effect of the adverse partners has been obviated. In this manuscript we describe studies relating to this concept.[4]

Our interest in this project arose from our desire to find a convergent strategy[5] for connecting two sugars, which would provide an alternative to our linear pyranosidic homologation[6] route to compounds with multiple contiguous chiral centres. Carbohydrate-derived partners have been used in aldol additions primarily for their properties as chiral templates.[1,5c] However, for some substrates, *e.g.* ketone (**1**), a further dimension exists, which takes advantage of their unique stereoelectronic properties. This is exemplified for the corresponding enolate (**2**), which shows little tendency for elimination of the axial anomeric -OMe.† The latter can therefore be relied upon to steer electrophiles to the β-face,[7] (although *in situ* isomerization is frequently observed).[8] This circumstance, in the case of an aldol condensation, permits attention to be focused entirely on the stereochemical preferences of the aldehyde, and for this we chose to examine the *aldehydo* sugars (**3**)—(**8**).

We were encouraged by previously reported experiments which showed that the enolate (**2**) reacted with the acetonides of D- and L-glyceraldehydes to give homochiral aldol products.[7] Comparable results were also obtained for the more elaborate pair of enantiomorphic aldehydes, (**3**) and (**4**). Thus, with the former, (**9**) was the only product while with the latter, (**10a**) and (**10b**) were given in the ratio 10:1, the isolated yields being 55—65% (Table 1).

† This unusual stability is probably due to the *exo* anomeric effect, which tends to strengthen the glycosidic C–O bond, thereby opposing the pathway for β-elimination.




**Scheme 1.** *Reagents and conditions*: i, DIBAL; ii, camphorsulphonic acid (CSA), $CH_2Cl_2$, 0 °C; iii, as i; iv, CSA, $CH_2Cl_2$, 0 °C to room temp. Bn = $PhCH_2$.

In order to probe the correlation between the C-7 orientation of the products and the resident chiral centre(s) of the aldehydic precursors, aldehydes (**5**)—(**8**) were reacted and the configurations of the products (**11**)—(**13**) were investigated. We found that assignments could be made confidently by using simple $^1H$ n.m.r. spectroscopic measurements. Thus, C-2 axial orientation in all cases was readily apparent from the value $J_{1,2}$ ~0 Hz. The magnitude of $J_{2,7}$ ~11 Hz for (**11**)—(**13**) implied substantial population of the rotamer depicted in Table 1, in which 2-H and 7-H were in the *trans* orientation.‡ In view of this criterion, the value $J_{2,7}$ 8.1 Hz has been interpreted to imply C-7 (*S*) configuration in (**14**).

The validity of such assignments was verified by *X*-ray analysis of crystalline (**10a**). A similar verification has been reported in an earlier study.[7]

The selectivities observed in the adducts (Table 1) imply that each of the aldehydes exercises its stereocontrol independently of the ketone. This remarkable facial selectivity seems to correlate with the alkoxy substitution at the α- and/or β-carbons of the aldehyde, if Cram cyclic models are assumed with α-chelation, as in (**15**), or α,β-chelation, as in (**16**).[9] The results with aldehydes (**3**) and (**4**), as well as for the previously reported[7] glyceraldehyde acetonides, are consistent with the α,β-chelation shown in (**16**). The literature[10] suggests that α-chelation is more important than β-chelation. Accordingly, the aldol reaction of (**1**) with (**5**)—(**8**), to give *anti*-Cram products only, can be rationalized by the α-chelation pattern depicted in (**15**).

The C-3-$sp^2$ centres of simple pyranosides are usually reduced stereoselectively and this also held true for the complex aldol products. Thus reduction of (**9**) and (**14**) with di-isobutylaluminium hydride (DIBAL) affords the equatorial alcohols (**17**) and (**19**), respectively (Scheme 1). The former gave the acetonide (**18**) in which $J_{2,7}$ 9.8 Hz indicated that the protons concerned are in an antiperiplanar orientation, thereby confirming the assignment of (*R*)-configuration made above on the basis of the $J_{2,7}$ values of (**9**) and (**14**) (*vide supra*). In contrast, the diol (**19**) did not undergo acetonide formation. Notably, formation of (**20**) would have caused serious interactions between the furanose and pyranose rings.

The obtainment of (**17**) and (**19**) as homochiral compounds with nine and eight *contiguous* chiral centres, respectively, attests to the potential of this aldol strategy. It is interesting to note that the above rationalization for the C-7 stereocentre when applied to C-6 *aldehydo* pyranosides relies entirely on the orientation of the C-4-(β)-oxygen. C-4-Axial substrates [*e.g.* (**3**) and (**4**)] can form α,β-chelates, but their equatorial counterparts [*e.g.* (**5**) and (**6**)] appear to prefer α-chelation.

‡ Independent support for this conformation came from the $^1H$ n.m.r. spectral signals for the benzylidene methine protons of (**11**) and (**12**), which were shifted upfield by 0.3 p.p.m. (δ 5.3 *vs.* 5.6) compared with the corresponding signal in compound (**1**) and the other aldol products. Models suggested that this effect was due to anisotropic shielding by the C-9 benzyl residue of (**11**) and (**12**), and consistent with this conclusion was the fact that in the corresponding azido derivative, (**13**), the benzylidene methine proton was at the normal position, 5.59 p.p.m.

We are grateful to the National Science Foundation (CHE 8703916) for financial support, and to Dr. Sheetal Handa for preliminary work involving aldehyde (**3**). We thank Dr. Zbigniew Ciunik of Wroclaw University, Poland, for the *X*-ray analysis of (**10a**).

*Received, 1st March 1989; Com. 9/00900K*

## References

1 C. H. Heathcock, C. T. White, J. J. Morrison, and D. Van Derveer, *J. Org. Chem.*, 1981, **46**, 1296.
2 S. Masamune, W. Choy, J. S. Petersen, and L. R. Sita, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 1.
3 D. A. Evans, J. V. Nelson, and T. R. Taber, *Top. Stereochem.*, 1982, **13**, 1; C. H. Heathcock, in 'Asymmetric Synthesis,' ed. J. D. Morrison, Academic Press, New York, 1984, vol. 3, part B, pp. 111—212; T. Mukaiyama, *Org. Reactions*, 1982, **28**, 203.
4 For cases where facial selectivity for one reactant has been biased by steric or other factors, see: D. A. Evans, *Aldrichim. Acta*, 1982, **15**, 23; S. Masamune and W. Choy, *ibid.*, 1982, **15**, 47.
5 For early attempts at convergent synthesis of multiple contiguous chiral centres involving cyclic sugars see: (a) M. Nakata, H. Takao, Y. Ikeyama, T. Sakai, K. Tatsuta, and M. Kinoshita, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 1749; (b) J. A. Secrist and K. D. Barnes, *J. Org. Chem.*, 1980, **45**, 4526; and for *acyclic* sugars (c) S. Hanessian, J. R. Pougny, and I. K. Boessenkool, *J. Am. Chem. Soc.*, 1982, **104**, 6164.
6 B. Fraser-Reid, L. Magdzinski, B. F. Molino, and D. R. Mootoo, *J. Org. Chem.*, 1987, **52**, 4495; B. Fraser-Reid, B. F. Molino, L. Magdzinski, and D. R. Mootoo, *J. Org. Chem.*, 1987, **52**, 4505.
7 S. Handa, R. Tsang, A. T. McPhail, and B. Fraser-Reid, *J. Org. Chem.*, 1987, **52**, 3489; Y. Chapleur, F. Longchambon, and H. Gillier, *J. Chem. Soc., Chem. Commun.*, 1988, 564.
8 R. Tsang and B. Fraser-Reid, *J. Am. Chem. Soc.*, 1986, **108**, 2116; 8102.
9 J. Jurczak, S. Pikul, and T. Bauer, *Tetrahedron*, 1986, **42**, 447.
10 S. V. Frye, E. L. Eliel, and R. Cloux, *J. Am. Chem. Soc.*, 1987, **109**, 1862.