Diastereoselective Anionic and Radical Conjugate Addition on a Chiral Enone: a Route to Multichiral Arrays

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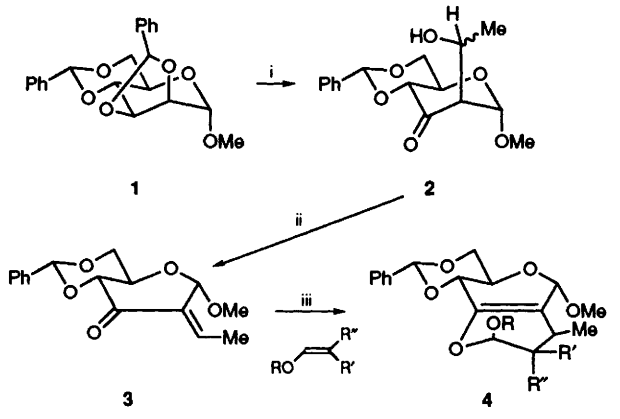
1,4 Addition of several alkyl groups using cuprates and radicals on a conformationally biased chiral enone **3** derived from carbohydrate is described, showing essentially identical diastereoselection in anionic and radical processes and a dramatic influence of the alkyl group size on the sense of 1,2-asymmetric induction.

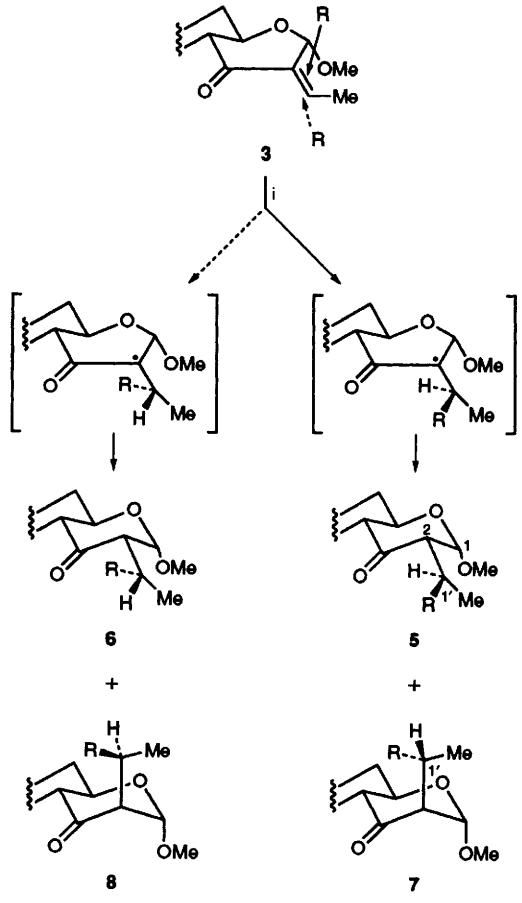
The use of cyclic systems as templates for the stereoselective construction of multichiral arrays is well recognised. This concept has been and is widely used in carbohydrate chemistry for the regio- and stereo-specific modification of five- and six-membered rings. However, the drawback of this approach *vs.* acyclic stereoselection is the limited number of chiral centres available on the sugar ring. A solution to this problem has been provided by the so-called 'pyranosidic homologation'.[1–4] A second ring is fused to the basic pyranose ring and allows a new set of chiral centres to be established. We have developed such an approach using hetero Diels–Alder reaction between vinyl ethers and a carbohydrate enone **3**,[5] readily available from **1** *via* aldol **2** through our carbohydrate enolate methodology.[6,7] We report here the acyclic diastereoselective conjugate addition on enone **3** expecting a high degree of 1,2-asymmetric induction because of the highly asymmetric surrounding and the conformational bias of the sugar template. For that purpose, we decided to explore anionic and radical 1,4-addition of several suitable alkyl groups.[8]

The Michael addition of cuprates generated from different alkyllithium and copper iodide on enone **3** was first explored.[9] Condensation of lithium dimethylcuprate (entry 1) proceeded with a high diastereoselection at C-2, giving the two expected compounds **5a** and **7a** as a 9:1 mixture in favour of the equatorial derivative (2*S*). Because of the formation of two chiral centres, reaction with other cuprates gave four isomers, as seen from the ^{1}H NMR spectra which showed several sets of protons. Depending on the stereochemistry at C-2 (carbohydrate numbering), the H-1 signal appeared as a doublet when H-1 and H-2 were in a *cis* relationship (equatorial alkyl chain), or as a singlet when H-1 and H-2 were in a *trans* relationship (axial alkyl chain). Thus, integration of the different H-1 and/or H-2 ^{1}H NMR signals allowed a rapid evaluation of the crude diastereoisomeric mixture. The stereochemistry at the new stereogenic centre C-1′ has not been rigorously established but was tentatively assigned as *S*, assuming that attack likely occurred from the less hindered β face of the bicyclic system, on the basis of the stereochemical course of the hetero Diels–Alder reaction which proceeded exclusively along this way.[5] As seen from the results (Table 1), good diastereoisomeric excesses were observed for primary and secondary alkyl groups (entries 1–5). In these instances, the alkyl chain was in an equatorial orientation ($J_{1,2}$ 5 Hz) in the major product. However, the introduction of tertiary alkyl residue, led to a reversal of the selectivity at C-2, the major product resulting from the protonation from the α face of the sugar ring (see below).

Activated olefins are efficient radical traps as demonstrated by several reports.[10–13] Recent studies on the stereoselectivities of radical reactions have drawn attention,[14–19] and major achievements in 1,2-asymmetric induction have been reported.§ Thus an alternate, more versatile route using the 1,4 addition of radicals on the enone **3** was explored. The standard tin method was chosen for radical generation starting from readily available halides and using AIBN as a radical initiator.† The results of this study are summarized in Table 1 (entries 7–20). The expected products were obtained in moderate to good yields. Several observations are worthy of note. (1) The observed diastereoselectivities are very close to



Scheme 1 *Reagents and conditions*: i, BuLi, THF, −40 °C then MeCHO, ref. 7; ii, MsCl, pyridine; iii, Eu(fod)$_3$, ref. 5



Scheme 2 *Reagents and conditions*: i, RX, Bu_3SnH, AIBN, benzene, reflux

Table 1 Conjugate addition of cuprates and radicals on enone **3**

	Reagent	Method[a] conditions	Products 5–8	R =	5 + 6/7 + 8 2*S*:2*R* ratio[b]	5 + 7/6 + 8 1′*S*:1′*R* ratio[b]	Yield/ (%)[c]
1	Me_2CuLi	A, 0 °C	**a**	Me[d]	90:10	—	69
2	Bu^n_2CuLi	A, −80 °C	**b**	Bu	95:5	89:11	65
3	Bu^n_2CuLi	A, −30 °C	**b**	Bu	88:12	80:20	55
4	Bu^s_2CuLi	A, 0 °C	**c**	Bu[e]	68:32	76:24	50
5	Bu^t_2CuLi	A, −30 °C	**d**	Bu[t]	30:70	85:15[f]	30
6	Ph_2CuLi	A, 0 °C	**e**	Ph	95:5	80:20	49
7	EtI	B, 60 °C	**f**	Et	86:14	66:34	62
8	Bu^nI	B, reflux	**b**	Bu^n	87:13	68:32	60
9	Bu^sI	B, reflux	**c**	Bu[e]	69:31	78:22	58
10	Bu^tBr	B, reflux	**d**	Bu[t]	30:70	81:19[f]	35
11	*tert*-Pentyl	B, reflux	**g**	*tert*-Pentyl	27:73	89:11[f]	30
12	$PhCH_2Br$	B, reflux	**h**	$PhCH_2$	87:13	63:37	47
13	$C_6H_{13}Br$	B, reflux	**i**	C_6H_{13}	89:11	73:27	68
14	$C_8H_{17}I$	B, reflux	**j**	C_8H_{17}	86:14	77:23	58
15	$C_{10}H_{21}Br$	B, reflux	**k**	$C_{10}H_{19}$	86:14	66:33	48
16	$C_{12}H_{25}Br$	B, reflux	**l**	$C_{12}H_{25}$	85:15	72:28	43
17	$BrCH_2CH_2CN$	B, reflux	**m**	CH_2CH_2CN	90:10	82:18	58
18	$BrCH_2CO_2Me$	B, reflux	**n**	CH_2CO_2Me	81:19	52:48	54
19	$BrCH_2CH(OEt)_2$	B, reflux	**o**	$CH_2CH(OEt)_2$	83:17	57:43	47
20	$BrCH_2CH_2OEt$	B, reflux	**p**	CH_2CH_2OEt	83:17	56:44	48

[a] Method A: R_2CuLi (2 equiv.) in diethyl ether; Method B: RX (7 equiv.), AIBN, benzene, heating. [b] Measured on the crude mixture of **5–8** by integration of NMR signals. [c] Refers to pure isolated compounds (as a mixture of **5–8**). [d] Compounds **5** and **6** as well as **7** and **8** are the same in this case (no stereogenic centre at C-1′). [e] In this case a third stereogenic centre was formed without asymmetric induction. *f* Only compounds **5**, **6** and **7** are detected in this case. It should be also noted that because of the presence of the tertiary R group the nomenclature of the stereochemistry at C1′ switch from *R* to *S* and *vice-versa*.

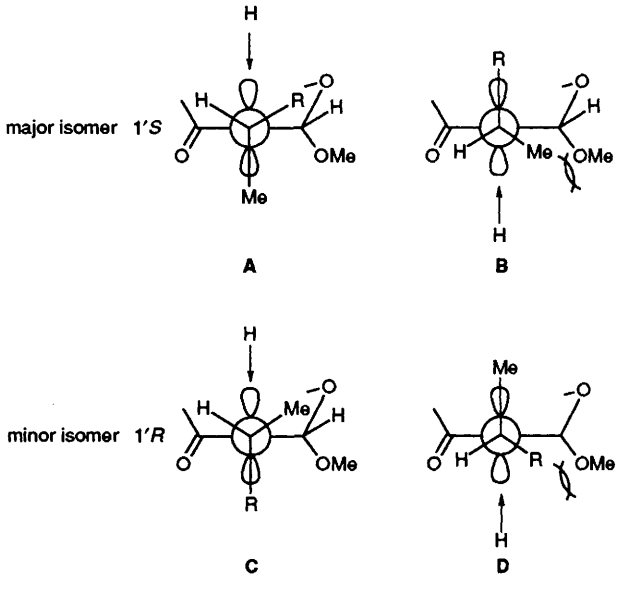


Fig. 1 Models of conformers for hydrogen capture of the intermediate α-keto radicals

those observed in the anionic reactions case, thus 1,4 addition of anions or radicals to enone **3** follow the same stereochemical course. (2) The same complete reversal of the stereoselectivity at C-2 is observed in the reaction of Bu^t_2CuLi (entry 5) and *tert*-butyl radical (entry 10). This is also true for *tert*-pentyl radicals (entry 11). (3) Almost no selectivity at C-1′ is observed using α-oxygenated primary radicals.

The observed diastereoselectivities could be explained using recently proposed models for the 1,2-asymmetric induction in radical reactions.[14,16c,17–19] The stereochemistry at C-2 is controlled, in principle, by hydrogen transfer to the C-2 carbon atom, but hydrogen transfer to the oxygen atom cannot be excluded. This would give the same enol, and subsequent tautomerisation would give identical products distribution for both systems. The absence of such a mechanism has been elegantly demonstrated, by deuterium labelling, in the protonation/reduction of chiral acyclic esters by Hart[17] and by Curran.[18] Although we did not check this point, it is likely that the same is true for ketones. Thus, only conformers of the carbon centred intermediate radicals in their ground state will be considered (Fig. 1). The most likely conformers are those in which 1,3 allylic strain is minimal.[20] In the major 1′*S* isomer, with primary or secondary R substituents, conformer **A** should be preferred, in order to minimize non-bonding interactions between the methyl group and the aglycon oxygen. Provided that the R group is not too sterically demanding, hydrogen capture occurs from the less hindered β face.‡ As seen from molecular models, when R is a *tert*-butyl group, one of its methyl should point upward, impeding approach of the hydrogen donor from the β face, thus hydrogen abstraction and even protonation is more rapid on conformer **B**. Molecular models also show that destabilising interactions between R and H-1 may exist in conformer **A** when R becomes too large, thus conformer **B** is favoured and hydrogen abstraction occurs from the α face. For the minor isomer 1′*R*, conformer **C** is favoured especially when R is tertiary again because of steric interactions between R and the aglycon oxygen in conformer **D**. Thus, for this isomer again, hydrogen abstraction or protonation will occur mainly from the β face. When R is a tertiary alkyl group, conformer **D** is strongly disfavoured and hydrogen capture should occur exclusively on conformer **C**. This could explain why only one axial isomer (compounds **7d**, **7g**, respectively) was detected.

The lack of stereoselectivity using α oxygenated radicals is by far more difficult to explain at the present time. One might assume that the addition of this radical should be reversible and this process would give a *Z*–*E* mixture of olefin **3** thus a mixture of products would result from a subsequent radical addition. However, the reversibility of the addition of such radicals is not known. Moreoever, in our case, stabilised benzyl radical, which is known to add reversibly to olefins, behaves like primary alkyl radicals in terms of diastereoselection at C-1′ (compare entries 12 and 15). Another explanation could be unfavourable interactions between the incoming α-oxygenated radical and the oxygenated olefins in terms of

stereoelectronic repulsions. This point remains to be clarified, perhaps on more simple models.

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Footnotes

† Typical run for radical addition: a solution of **3** and the alkyl halide (7 equiv.) in degassed benzene containing a catalytic amount of AIBN as initiator was refluxed and a solution of tributyltinhydride (3 equiv.) in benzene was added dropwise using a motor-driven syringe. The heating was continued (Table 1) until the reaction was completed, the solvent was then evaporated and the crude residue was analysed by ^{1}H NMR spectroscopy. Pure compounds were obtained after purification on a silica gel column.

‡ Improvements of the selectivity at C-2 may be obtained using aglycons bulkier than methyl. However, the result of this change should be rather poor, the steric hindrance being essentially due to oxygen because of *exo* anomeric effect which tends to orientate the O–C bond of the aglycon antiperiplanar to the C-1–C-2 bond. It is likely that the presence of a sulfur or a substituted carbon atom (*e.g.* Bu^t) in place of algycon oxygen should be required to induce a better C-2 selectivity. For recent reports on the *trans* selectivity of hydrogen capture of carbon–carbon bond formation on a cyclic α-keto *tert*-butoxyl radical (see ref. 19).

§ *Note added in proof.* A paper by Giese *et al.* on the stereoselectivity of cyclic enolate radicals appeared while this work was under evaluation; see: B. Giese, W. Damm, T. Witzel and H. G. Zeitz, *Tetrahedron Lett.*, 1993, **34**, 7053.

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