Hetero Diels–Alder Reactions in Carbohydrate Chemistry: A New Strategy for Multichiral Arrays Synthesis

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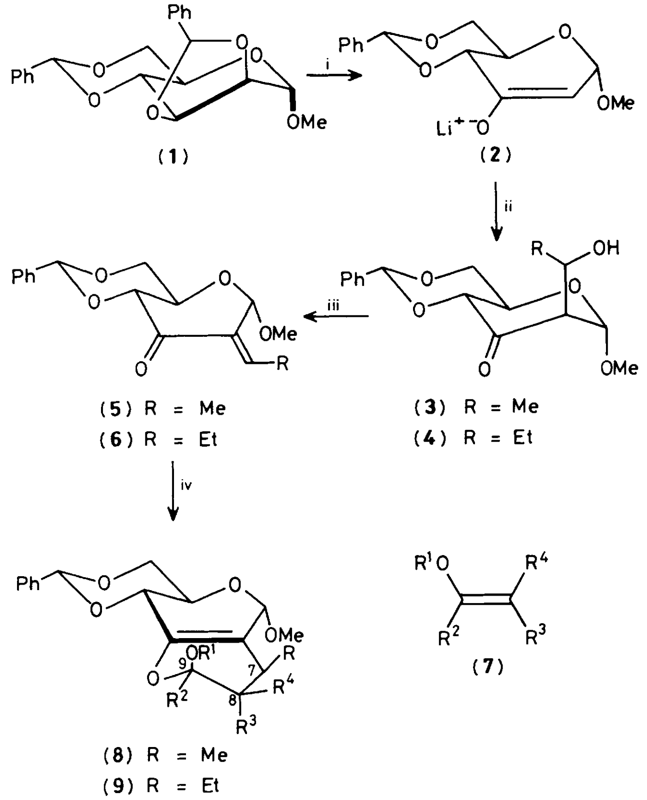
Hetero Diels–Alder reactions of α,β-unsaturated ketones (**5**) and (**6**) derived from carbohydrates with enol ethers (**7**) led to the formation of fused dihydropyrans with complete stereospecificity and creation of chiral centres on the newly formed template.

The use of cyclic systems as templates for the construction of multichiral arrays is well recognized. Five, six, and seven membered rings allow stereo- and regio-specific reactions which are widely used in carbohydrate chemistry for furanose and pyranose chemical modifications. However the major drawback of this 'cyclic approach' *vs.* 'acyclic stereoselection' is the limited number of chiral centres available on the ring. In this context the concept of 'pyranosidic homologation' first introduced by Fraser-Reid[1] is of interest for the synthesis of long chain multichiral arrays. In this approach a pyranose ring serves as a template for the construction of a second fused pyranose ring thus allowing stereospecific creation of new chiral centres on this new framework. In connection with our ongoing programme aimed at the use of carbohydrate enolates



	R^1	R^2	R^3	R^4
a;	Et	H	H	H
b;	Me	Me	H	H
c;	Et	H	H	Me
d;	Et	H	Me	H

Scheme 1. *Reagents and conditions:* i, BuLi, tetrahydrofuran, −30 °C; ii, RCHO, −30 °C; iii, methanesulphonyl chloride, pyridine, room temp.; iv, (7), see Table 1.

in synthesis,[2] we propose in this communication a new path to pyranosidic homologation using a hetero Diels–Alder reaction.

The enolate (**2**) prepared by treatment of (**1**) with butyllithium[3] underwent *in situ* aldolisation with acetaldehyde and propionaldehyde giving aldols (**3**) and (**4**) as mixtures of isomers in 70—80% yield.[4] Treatment with methanesulphonyl chloride in pyridine gave a single α,β-unsaturated ketone of (*E*) configuration, (**5**) and (**6**) respectively, in 75% yield. This heterodienic system was found to be very reactive in Diels–Alder reactions with inverse electron demand.[5,6] Electron rich alkenes such as enol ethers (**7**) acted as dienophiles in the presence of Eu(fod)$_3$ (fod = 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionate) as the catalyst according to the recent method of Danishefsky *et al.*[7] In every case a single isomer was isolated in excellent yield. The results obtained with ketones (**5**) and (**6**) are summarized in Table 1.†

Table 1. Dihydropyrans obtained from ketones (**5**) and (**6**).

Starting material	Reagent	Product	Solvent) (reflux)	Yield/ %	M.p./ °C	$[\alpha]_D^{20}$ (*c* 0.5, CHCl$_3$)/°
(**5**)	(**7a**)	(**8a**)	(**7a**)	74	184	+5
(**5**)	(**7b**)	(**8b**)	(**7b**)	72	150	+36
(**5**)	(**7c**)	(**8c**)	Hexane	78	129	+9
(**5**)	(**7d**)	(**8d**)	Hexane	87	145	+1.5
(**6**)	(**7a**)	(**9a**)	(**7a**)	68	170	−26
(**6**)	(**7b**)	(**9b**)	(**7b**)	65	98	+89
(**6**)	(**7c**)	(**9c**)	Hexane	90	139	−1
(**6**)	(**7d**)	(**9d**)	Hexane	80	86	+0.8

Structures of (**8**) and (**9**) were determined on the basis of spectral data in the light of literature data on related systems,[6e,f] which confirmed mechanistical assumptions. Thus we assumed the reaction took place from the less hindered side of the dienic system, securing the stereochemistry at C-7. As pointed out by numerous authors *endo* attack of the enol ether was the most favoured owing to LUMO–HOMO interactions between the carbonyl group and the vinyl ether.[5,8] Further we assumed that the most favoured conformation of the newly formed dihydropyran ring would be that having the aglycon in an axial orientation owing to the anomeric effect. Thus coupling constants between 9-H and 8-,8′-H (3 Hz) suggested an equatorial orientation of 9-H, whereas those between 7-H and 8-, 8′-H (4.5, 6.5 Hz) were in favour of a pseudo equatorial orientation of R.

The observed stereospecificity with enol ethers (**7a**) and (**7b**) prompted us to study the reaction of vinyl ethers (**7c**) and (**7d**). A (*Z*)/(*E*) mixture (65:35) gave a 1:1 mixture of (**8c**) and (**8d**) in agreement with a lower reactivity of the (*Z*) isomer already found in such reactions.[6b] Pure enol ethers (**7c**) or (**7d**) gave a single product on reaction with (**5**) and (**6**). As expected, the (*Z*) isomer gave compound (**8c**) and (**9c**) with a *cis* relationship between Me at C-8 and OEt at C-9 whereas the (*E*) isomer gave (**8d**) and (**9d**). Thus, one can ensure complete stereocontrol of both the C-7 and C-8 stereochemistry.

In summary, this new approach allows the formation of a 'satellite pyranose'[1] bearing two new chiral centres. Proper choices of substituents and reactants will permit the synthesis of long chain multichiral arrays present in a number of natural products.

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† In a typical experiment, ketones (**5**) and (**6**) (1 mmol.) were suspended in the enol ether (**7**), (5 ml) or in a hexane–enol ether mixture (5 ml, 6 mmol.), the catalyst Eu(fod)$_3$ (5% mol.) was added, and the mixture refluxed until no starting material remained (t.l.c. monitoring). The solvent was removed *in vacuo* and products (**8**) and (**9**) were purified by column chromatography.