Facial selectivity in the cycloaddition of heterodienes to carbohydrate cyclic ketene acetals. A novel synthesis of disaccharide derivatives

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Carbohydrate ketene acetals derived from mannopyranose and glucopyranose are shown to serve as electron-rich dienophiles in facially selective, Lewis acid-catalyzed inverse electron demand hetero-Diels–Alder reactions.

The inverse electron demand hetero-Diels–Alder reaction of electron-rich dienophiles with electron-poor enones and enals has been established as a useful method for the stereospecific construction of 3,4-dihydro-2*H*-pyran analogues.[1,2] These intermediates have been transformed easily into synthetically useful carbohydrates, and their structural components have been found to be present in a host of natural products.[2–4]

We recently reported the synthesis of carbohydrate cyclic ketene acetals.[5] Herein, we describe studies that demonstrate the ability of this intrinsically asymmetric class of compounds to serve as electron-rich dienophiles in facially selective, Lewis acid-catalyzed inverse electron demand hetero-Diels–Alder reactions.

To establish the use of carbohydrate cyclic ketene acetals as dienophiles in hetero-Diels–Alder reactions, the mannopyranose (**1**) and glucopyranose (**2**) derivatives[5] were each treated with acrolein (1.2 equiv.) in CH_2Cl_2 at ambient temperature. No reaction occurred in the absence of a Lewis acid, even at 220 °C. However, after 19 h in the presence of Yb(fod)$_3$[6] (0.05 equiv.), the crude product derived from **1** was obtained as a *ca.* 5 : 1 mixture of diastereomers (**3a** and **3b**), as judged by integration of the vinylic proton resonances (Scheme 1). The cycloadduct **3a** was isolated after silica gel chromatography as a single regio- and stereo-isomer in *ca.* 80–85% yield.‡ Analogously, after 72 h the cycloadduct **4** was isolated as a single regio- and stereo-isomer (**4a** or **4b**), albeit in much lower yield (24%), from the glucopyranose derivative **2**. The specific orthoester isomer obtained must reflect both the intrinsic *endo : exo* Diels–Alder selectivity, with the obvious exception of products derived from acrolein, as well as the facial selectivity of addition to the asymmetric dienophile.[7]

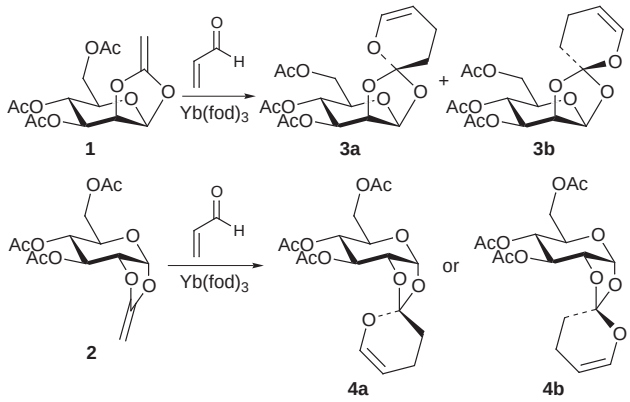
Extensive studies have been conducted to demonstrate the high degree of asymmetric induction in Diels–Alder reactions of 1-oxabuta-1,3-diene analogues with electron-rich dienophiles.[8,9] Boger and Robarge have reported on the pressure-promoted reaction of methyl (*E*)-4-phenyl-2-oxobut-3-enoate (**5a**, Table 1) with a wide range of electron-rich dienophiles to provide cycloadducts that exhibit *endo : exo* Diels–Alder selectivities of 4–9 : 1.[8] Similarly, Tietze has recently utilized several asymmetric 1-oxabuta-1,3-dienes derived from chiral oxazolidinones in which large *endo* Diels–Alder selectivities have been obtained.[9] *exo* Diels–Alder selectivities can be achieved by a judicious choice of Lewis acid catalyst.

In an attempt to provide insight into the stereoselectivity of [4+2] cycloadditions with carbohydrate cyclic ketene acetals, mannopyranose derivative **1** was treated with 1-oxabuta-1,3-diene analogues **5a**–**5d** in the presence of Yb(fod)$_3$ (Table 1).§ Achiral heterodienes **5a** and **5b** exhibited excellent reactivity with **1** in CH_2Cl_2 at ambient temperature, cleanly providing the [4 + 2] cycloadducts **6a**/**7a** and **6b**/**7b** in 97 and 80% yields, respectively.¶ Each analogue was isolated as an *ca.* 1 : 1 mixture of diastereomers; similar results were obtained with Eu(hfc)$_3$. Compounds **6a**/**7a** (as a 1.2 : 1 mixture; *cf.* Table 1) were converted to (*R*)-phenylsuccinic acid *via* a two step procedure to establish the (*S*)-phenyl configuration of the cycloadduct.‖ Therefore, **6a**/**7a**, being a diastereomeric mixture of cyclic *endo*- and *exo*-orthoesters, but having the phenyl substituents with the same absolute configuration, must be derived from a facially controlled orientation of the diene **5a**. Specifically, the cycloaddition of a **5a** with **1** proceeds *via* an *exo* Diels–Alder selective process with attack of the diene onto the back face of the dienophile and an *endo* Diels–Alder selective process with attack onto the front face (*cf.* Table 1).[13]

To further enhance the stereoselectivity of the cycloaddition, **1** was treated with **5c** and **5d** in the presence of Yb(fod)$_3$. The use of asymmetric dienes **5c** and **5d** did provide a more diastereoselective route to [4 + 2] cycloadducts (Table 1). The crude cycloadducts **6c**/**7c** were obtained in 81% yield as a 5.3 : 1 mixture of diastereomers. Likewise, cycloadducts **6d**/**7d** were obtained as a 32 : 1 mixture of diastereomers. Cycloadducts **6c**/**7c** and **6d**/**7d** were determined to be cyclic *endo*-orthoesters by NOESY experiments, thereby establishing the (*R*)-orientation of the spiro-linkage (*i.e.* the same as in **3a**). Presumably this reflects addition of the heterodienes to the ketene acetal from the more hindered face.

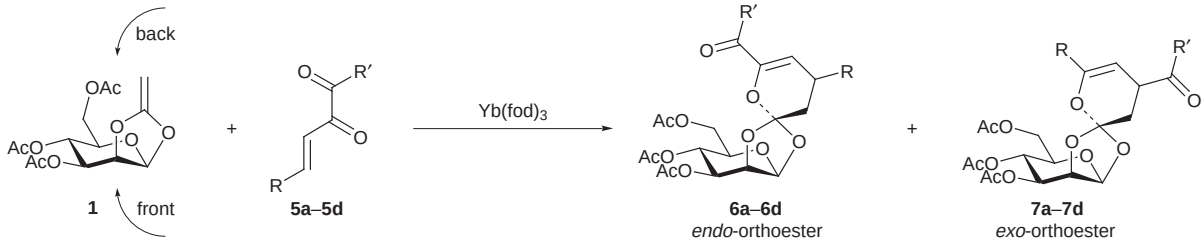
The ability of [4 + 2] cycloadducts derived from carbohydrate cyclic ketene acetals to provide uniquely substituted *O*-glycosides was assessed using cycloadducts **6a**/**7a** and **6d**/**7d**. Treatment with $BF_3{\cdot}OEt_2$ (1.0 equiv.) and Et_3SiH (1.0 equiv.) in dry benzene provided the corresponding β-D-mannopyranosides **9**/**10** and **11**, respectively. Compounds **9**/**10** derived from a 1 : 1 mixture of cyclic *endo*- and *exo*-orthoesters, were also obtained as a diastereomeric mixture of acetals in 54% yield. Compound **11** was obtained as a pure regio- and stereo-isomer in 40% yield; the absolute stereochemistry of the stereocenter produced in the Et_3SiH reduction was defined by the known[14] stereoselective hydride transfer.

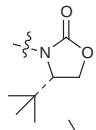
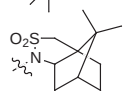
The facially and *exo* selective hetero-Diels–Alder reaction described herein constitutes the novel use of a carbohydrate as a scaffold to direct the stereochemistry of formation of a second carbohydrate (precursor).



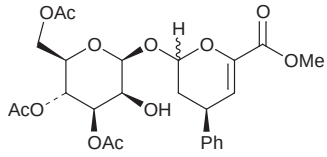
Scheme 1

Table 1 Results of Diels–Alder reactions



Series	R	R′	Solvent	*T*/°C	Diastereoselectivity[a]	Yield (%)[b]
a	Ph	OMe	CH_2Cl_2	25	1.2:1	97
b	OEt	OEt	CH_2Cl_2	25	1:1	80
c	Ph		Benzene	Reflux	5.3:1[c,d]	81
d	Ph		Benzene	Reflux	32:1[d]	50

[a] Determined by ^{1}H NMR spectroscopy by integration of the vinyl proton resonances. The absolute stereochemistry at the allylic carbon was established explicitly for **6a**/**7a** and **6c**/**7c**. [b] Isolated yields of purified cycloadduct after chromatography on SiO_2. [c] After extensive chromatography on SiO_2, the product was obtained as an almost pure compound, albeit in low yield (13%) from **1**. [d] The *endo*-orthoester is the major product.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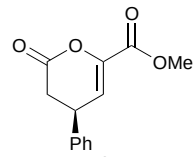
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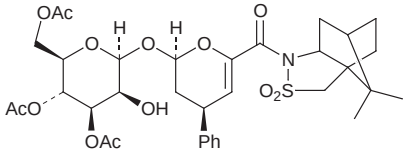
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Notes and References

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‡ Cycloadducts **3a** and **4** were each isolated as oils and characterized by ^{1}H NMR spectroscopy. Each analogue exhibited resonances in the range δ 4.81–4.87 (m) and 6.16–6.19 (d, *J* 6). Additionally, the regioisomers indicated in the scheme were identified by analysis of the allylic resonances (δ 2.25–2.30).

§ The β,γ-unsaturated α-keto esters **5a** (M. Reimer, *J. Am. Chem. Soc.*, 1924, 46, 783) and **5b** (W. Trowitzsch, *Z. Naturforsch., Teil B*, 1977, **32**, 1068) were prepared as described. Heterodiene **5c** was prepared by acylation of lithiated 4-*tert*-butyloxazolidin-2-one[10] with the appropriate α-keto acid chloride by a standard procedure in 43% yield. Analogously, heterodiene **5d** was prepared from lithiated (1*S*)-(−)-camphor-2,10-sultam in 81% yield.[11]

¶ Compounds **6a**/**7a**–**6d**/**7d** were characterized by ^{1}H NMR spectroscopy; especially diagnostic was the resonance in the range δ 5.88–6.24.

‖ Compounds **6a**/**7a** were treated with $BF_3{\cdot}OEt_2$ (2.0 equiv.) and Et_3SiH (1.0 equiv.) in benzene[12] to provide the lactone **8** in 61% yield. Optical rotation for **8**: $[\alpha]_D^{22}$ −47.2 (*c* 1.0, CH_2Cl_2). The enantiopurity of **8** was established by ^{1}H NMR studies conducted with Eu(hfc)$_3$; the enantiopurity exceeded 95%. Ozonolysis of **8**, followed by acid hydrolysis, provided (*R*)-phenylsuccinic acid which was confirmed by comparison with a commercial sample.

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