Graphical Abstract

Stereoselective Cycloaddition of 1-glucosyl-1,3-butadienes with *tert*-Butyl-2*H*-azirine-3-carboxylate, Glyoxylates and Imines

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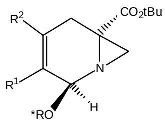
Glucose diene derivatives have been reacted with a 2*H*-azirine, glyoxylates and imines to form bicyclic structures of type **5**, disaccharides **7** and tetrahydroquinolines **10**.



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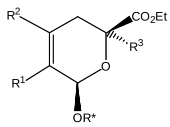

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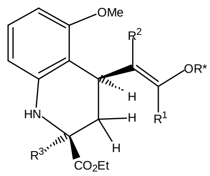

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Stereoselective Cycloaddition of 1-glucosyl-1,3-butadienes with *tert*-Butyl 2*H*-azirine-3-carboxylate, Glyoxylates and Imines

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Abstract- Glucosyl dienes **1** have been reacted with the achiral 2*H*-azirine **4** and with glyoxylates, forming fused structures of type **5** and disaccharide-like compounds **7** with good to excellent selectivity. Glucosyl dienes **1** participated as dienophiles in reactions with Schiff bases derived from anilines forming isoquinolines **10** and **11**. The diastereoselectivity of this reaction is poor.

Keywords: cycloaddition, 1,3-butadienes, 2*H*-azirines, glyoxylates, imines.

Dienes of type **1** have been used by Stoodley and co-workers in Diels-Alder reactions with carbon dienophiles; they showed facial selectivity with cyclic[1] and acyclic[1,2] dienophiles.

More recently diene **1** (R^1= Me, R^2= Me_3SiO) has also been combined with *tert*-butyl 2*H*-azirine-3-carboxylate and the reaction proved to be completely diastereoselective.[3] This result prompted us to broaden the scope of the reaction to other less reactive glucose-bound dienes **1**. Since cycloadducts of a similar type would be expected to be formed with activated imines and with activated carbonyl compounds such as ethyl glyoxylate and diethyl ketomalonate, these reagents were also used as dienophiles to evaluate the reactivity and the selectivity of the reactions.

The dienes **1** can be easily obtained by a condensation reaction between the enolate **2** and 1-bromo-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose **3**, followed by transformation of a C=O bond into a C=C bond by a Wittig reaction,[2] according to Scheme 1.

The azirine **4** formed *in situ* by pyrolysis of *tert*-butyl α-azidoacrylate in toluene[3] was reacted

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with the sugar dienes **1a-1c** at 50 - 55 ºC for 1.5 h. The reaction solutions were concentrated and the residual oils subjected to dry flash chromatography giving the adducts **5a-5c** as single isomers in moderate to good yields (42-89%). The structure **5** is assigned on the basis that it will be formed by *endo* cycloaddition of 2*H*-azirine **4** to the less hindered face of diene **1**, in its *s-cis* form, conformer **a** (more stable than conformer **b**)[2] (Figure 1). 2*H*-Azirine-3-carboxylates have shown before to participate in *endo* cycloadditions with carbodienes[4,5] and with 2-azadienes.[6] The stereochemistry of products was confirmed by X-ray diffraction spectroscopy. On the contrary, reactions of 2*H*-azirine-3-carboxylates with furan and 1,3-diphenylisobenzofuran are controlled by a thermodynamic process due to the easy reversibility of cycloaddition giving *exo* products.[7] On the other hand, Stoodley[2] has also showed that the glucosyl diene **1** (R^1= Me, R^2= Me_3SiO) undergoes *endo* addition to benzoquinone, based on X-ray diffraction spectrum of the product. The chemical shift of H-2 in compounds **5** (δ_H= 5.11 - 5.29 p.p.m.) is in accordance with the H-2 chemical shift (δ_H= 5.26 p.p.m.) in compound **6**, described to be obtained by an *endo* cycloaddition.[3] Besides, the stereochemistry of compound **7a**, obtained by combination of diene **1b** and ethyl glyoxylate was unequivocally shown to be formed by an *endo* approach of the dienophile to the diene, as discussed later. The ^{1}H NMR spectrum of compound **7a** showed H-2 with a chemical shift of 5.34 consistent with the chemical shifts obtained for H-2 in compounds **5**. A feature of the ^{1}H NMR spectra of compounds **5** is the zero geminal coupling of the methylene protons in the three membered ring moiety, which is known to be characteristic of 1-azabicyclo[4.1.0]heptenes reported in literature.[8]

Reaction of dienes **1b** and **1c** with diethyl ketomalonate and ethyl glyoxylate took place in the absence of catalyst after stirring for 1-5 days at room temperature. The reaction mixtures were concentrated to an oil, which ^{1}H NMR showed to be essentially pure samples consisting of a mixture of two diastereomers in ratios of 85 : 15 for **7a** and **7c** and 82 : 18 for **7b**. Major isomers were isolated pure (**7b** and **7c**) or almost pure (**7a**) by flash chromatographic separation. It was not possible to determine the ratio of isomers in the case of **7d** since the ^{1}H NMR signals of isomers overlap in the spectrum, although ^{13}C NMR show two sets of signals for two very similar compounds. Also, the two isomers of **7d** could not be separated by flash chromatography (Scheme 3).

The NOESY spectrum of compound **7a** showed that H-2 and H-6 were close in space. This

result led us to the conclusion that the cycloaddition between the ethyl glyoxylate and the diene **1b** was *endo*, the approach being from the less hindered face of conformer **a** (Figure 1).
Reactions of imines **8** with the diene **1b** in the presence of BF_3 etherate surprisingly do not produce the expected Diels-Alder products **9**. Instead the Schiff bases **8** functioned as the 4π components and the sugar-diene **1b** as the 2π component to give the tetrahydroquinolines **10** and **11** (Scheme 4). This kind of reaction has been reported in the literature, where Schiff bases derived from anilines act as dienes, namely with electron rich enol ethers in the presence of BF_3 etherate.[9] The products were obtained in moderate yields (36 - 43%) after flash chromatography. The isomeric ratio in the crude products is 7 : 3 for **10a**/**11a** and 5.4 : 4.6 for **10b**/**11b**. The major isomers (**10a** and **10b**) could be enriched by flash chromatography to 85:15 in both cases (Scheme 4).
Since the more stable conformations of the glucose diene **1b** are the *s-trans* forms,[2] it is rather likely that the cycloaddition of the imine **8** to **1b** occurs to the *s-trans* conformers. Diastereomers are formed by an *endo* approach of diene **8** to the less hindered face of conformer **a** and **b** giving respectively the major and the minor tetrahydroquinoline isomers **10** and **11**, according to Figure 2.
The ^{1}H NMR spectrum of the major isomer **10a** shows H-2 as a doublet of doublets coupling to one H-3 proton with an antiperiplanar vicinal coupling of 10.8 Hz, and to the other with a equatorial-axial coupling of 3.3 Hz. H-4 is also a doublet of doublets with J = 11.1 Hz and 5.4 Hz. Unfortunately the two protons H-3 appear as two multiplets at 300 MHz. In the spectrum of compound **10b** H-4 displays a similar pattern to H-4 in compound **10a** (doublet of doublets with J = 11.1 and 5.4 Hz) and the two H-3 protons show a geminal coupling (13.5 Hz) and a vicinal coupling of 5.4 Hz in one proton and 11.1 Hz in the other. Thus the spatial arrangement of protons H-2 and H-4 in compound **10a** is *cis*. This is consistent with an *endo* transition state for these Diels-Alder reactions. The poor diastereoselectivity of these reactions is probably connected with the distance between the sugar chiral unit and the active centres in the molecule of **1b** in the Diels-Alder reaction.

We have thus broadened the scope of cycloaddition between electrophilic azirines and sugar dienes of type **1**. The literature does not refer to reactions between imines and glucosyl dienes **1**. We found them not to be reactive enough in the absence of catalyst, but capable of taking part in Diels-Alder cycloadditions as a 4π component in the presence of $BF_3.Et_2O$. Activated carbonyl compounds were also combined with dienes of type **1** for the first time. The reactions occur in the absence of a catalyst at room temperature. The products were obtained with good diastereoselectivity and can be looked upon as potential disaccharides after minor chemical transformations.

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Table 1. [1]H NMR key assignments for compounds **5** **(**$CDCl_3$, chemical shifts in p.p.m., *J* in Hertz)

Compound	**H-2**	**R[1]**	**R[2]**	**H-5**	**H-7**	**$CO_2{}^tBu$**
5a	5.29(br s, 1H)	5.47(dm, 1H, *J*10.8)	5.73-5.77 (m, 1H)	2.64(br m, 2H)	1.95(s, 1H) 1.97(s, 1H)	1.50(s, 9H)
5b	5.15(br s, 1H)	1.65(d, 3H, *J*1.2)	5.40(br m,1H)	2.62(br m, 2H)	1.92(s, 2H)	1.49(s, 9H)
5c	5.11(br s, 1H)	1.65(s, 3H)	1.59(s, 3H)	2.48(d, 1H, *J*18.0) 2.64(d, 1H, *J*18.0)	1.85(s, 1H) 1.88(s, 1H)	1.49(s, 9H)

Table 2. [1]H NMR key assignments for compounds **7** **(**$CDCl_3$, chemical shifts in p.p.m., *J* in Hertz)

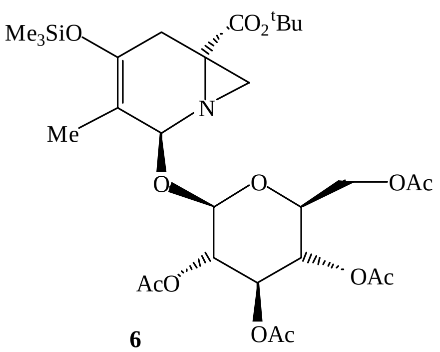
Com-pound	**H-2**	**R[1]**	**R[2]**	**H-5**	**R[3]**	**CO_2Et**
7a a)	5.34 (br s,1H)	1.68(d, 3H, *J*1.5)	5.69 (br m, 1H)	2.36(dm, 2H)	4.33(dd, 1H, *J*7.8 and 5.1)	1.30(t, 3H, *J*7.2)
7b b)	5.54 (br s,1H)	1.69(d, 3H, *J*1.5)	5.70(br m, 1H)	2.81(dm, 1H) 2.46(dm, 1H)	1.27(t, 3H, *J*7.2)	1.27(t, 3H, *J*7.2)
7c	5.49 (br s,1H)	1.74 (s, 3H)	1.64(s, 3H)	2.44(br d, *J*16.8) 2.71(br d,*J*16.8)	1.27 (t, 3H, *J*7.2); 4.18-4.28 (m, 4H)	1.28 (t, 3H, *J*7.2)
7d c)	-----	-----	-----	------	-----	---

a) $CO_2\underline{CH_2}$ show up together with the two glucose 6´ protons (4.30-4.14, m, 4H).
b) the two $CO_2\underline{CH_2}$ show up together with one of the glucose 6´H (4.17-4.31, m, 5H).
c) was not possible to assign signals for protons, neither to obtain the diastereomeric ratio on the basis of [1]H NMR.

Table 3. ^{1}H NMR key assignments for compounds **10 (**$CDCl_3$, chemical shifts in p.p.m., *J* in Hertz)

Com-pound	**N-H**	**R^1**	**CO_2Et**	**H-3**	**H-4**	**5-Me**	**H-6**	**OMe**	**Ar**
10a[a)]		4.03(dd, *J*10.5 and 2.7)	1.31 (t, *J*6.9)	2.28-2.2 (m, 1H) 2.08-2.0 (m, 1H)	3.49(dd, *J*11.1 and 5.4)	1.44 (s, 3H)	6.28(br d, *J*1.2)	3.72 (s,3H)	6.7-6.5 (m, 3H)
10b[b)]	4.64 (br s,1H)	1.29(t, 3H, *J*7.0)	1.22(t, 3H, *J*7.0)	2.53(dd, 1H, *J*13.5 and 5.4) 2.16(dd, 1H, *J*13.5 and 11.1)	3.45(dd, 1H, *J*11.1 and 5.4)	1.46 (d, 3H, *J*1.0)	6.24(br s, 1H)	3.71 (s,3H)	6.66-6.62 (br m, 2H) 6.53-6.50 (br m, 1H)

a) $CO_2\underline{CH_2}$ show up together with glucose the two 6´protons (4.34-4.12, m, 4H).
b) the two $CO_2\underline{CH_2}$ show up together with the two glucose 6´protons (4.35-4.12, m, 6H).



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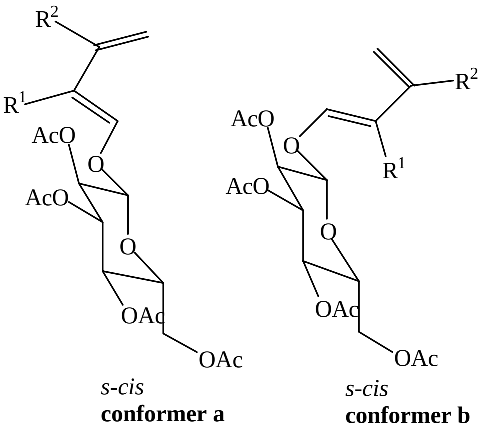


Fig. 1 Conformer **a** and **b** of the *s-cis* form of diene **1**.

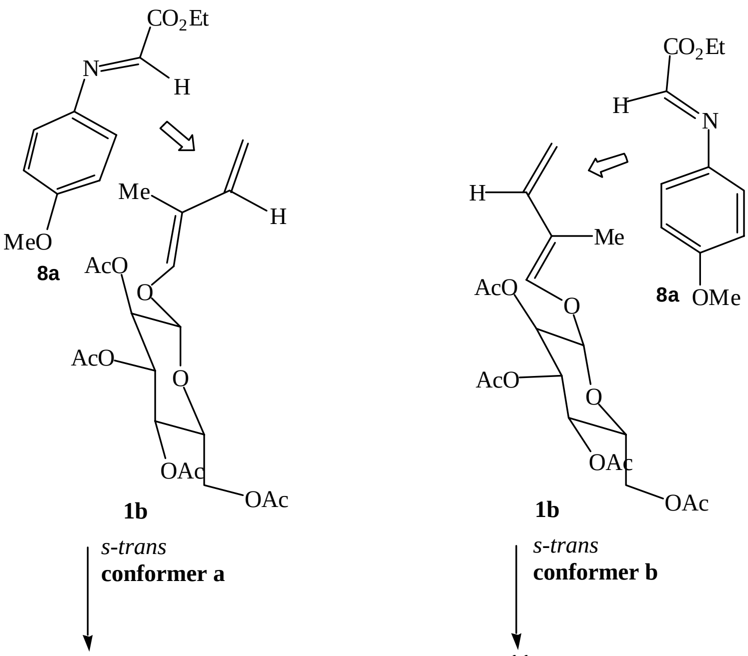
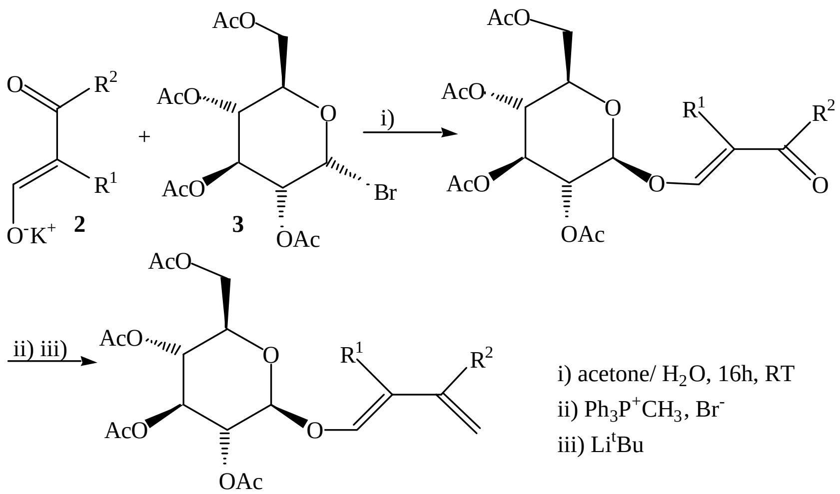
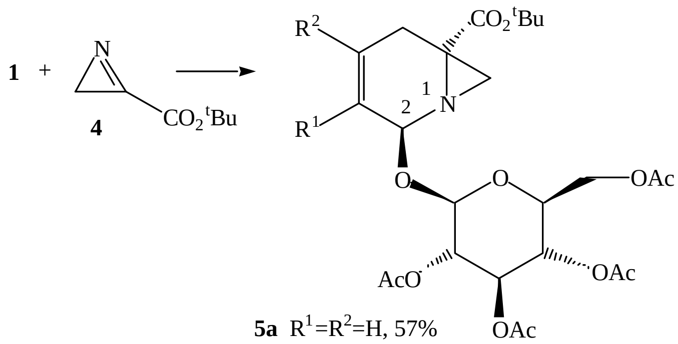


Fig. 2 Direction of approach of imine **8a** to the *s-trans* form of diene **1** in the conformer **a** and **b**.



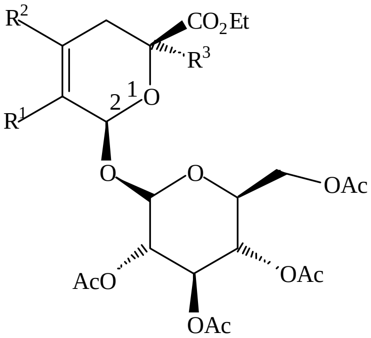
1a R^1=R^2=H
1b R^1=Me, R^2=H
1c R^1=R^2=Me

Scheme 1



5a R^1=R^2=H, 57%
5b R^1=Me, R^2=H, 42%
5c R^1=R^2=Me, 89%

Scheme 2



	η (%)	isomeric ratio	η (%) major isomer[b]
7a R^1=Me, R^2=R^3=H	81[a]	85:15	40[c]
7b R^1=Me, R^2=H, R^3=CO_2Et	79[a]	82:18	31[d]
7c R^1=R^2=Me, R^3=CO_2Et	63[a]	85:15	36[d]
7d R^1=R^2=Me, R^3=H	74	--[e]	--[f]

a) after flash chromatography;

b) partially separated by flash chromatography;

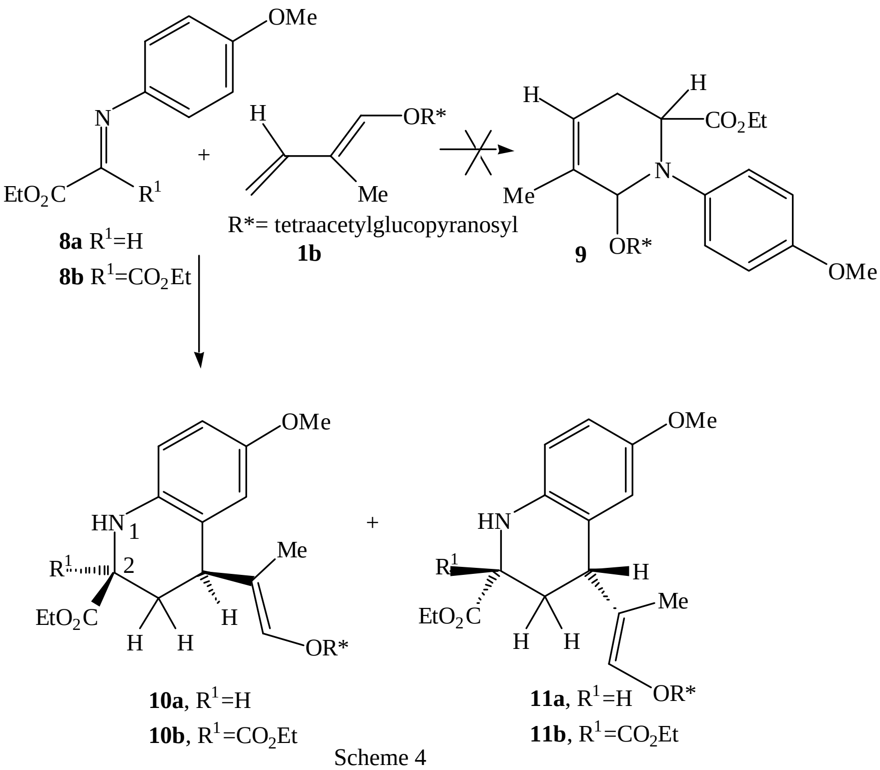
c) isolated major isomer > 90%;

d) isolated major isomer, pure sample;

e) it was not possible to assign signals for protons, neither to obtain the diastereomeric ratio on the basis of ^{1}H NMR due to signals overlaping;

f) it was not possible to separate the diastereomers by flash chromatography.

Scheme 3



Scheme 4