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Towards Glycosyl Inositol Mimics: Stereoselective Synthesis of *C*-α-Glucosyl-inositol Derivatives *via* Diels-Alder Reactions

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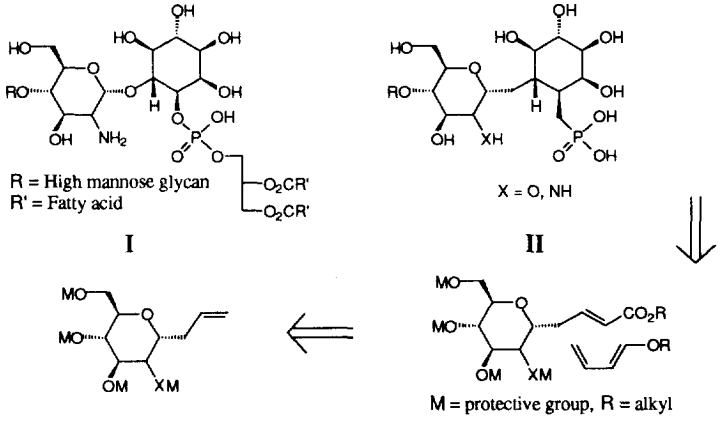
Abstract: The pentafluorophenyl ester of a *C*-glucopyranosidyl-linked olefin has proved to be an efficient chiral dienophile for asymmetric Diels-Alder reactions with *E*-1-acetoxy-1,3-butadiene to give *C*-α-glucosyl-cyclitol derivatives with excellent regioselectivity but fair diastereoselectivity.

The biological role of glycosyl phosphatidyl inositols (GPI) as putative second messengers of insulin[1] and as key structure of protein anchorage system[2] is well recognised. Intracellular GPIs are hydrolysed by a specific phospholipase to glycosyl inositol phosphate which acts as a regulator of enzymes such as pyruvate dehydrogenase, adenylate cyclase and AMPc phosphodiesterase.[3] On the other hand, the anchoring system based on GPI is used by parasites for the coating of their cells with glycoproteins which seem to protect the parasite from host defences[3], and is likely used by the scrapie isoform of the prion protein.[4] Hence it is clear that small molecules able to mimic the second messenger key-role of GPI are of interest for pharmacological studies.[5] The same type of GPI analogues should also play a role as inhibitors of the biosynthesis of the GPI-anchoring system used by parasites such as those responsible for the African sleeping sickness.[6]

As seen from **Scheme 1**, the well conserved basic structure of GPI, **I** is a glucosamine-α-(1→6)-inositol phosphate. Mimics of this molecule, such as **II**, should provide an entry for the elaboration of pharmaceutical tools and potential therapeutics. In connection with this problem, we have explored a route to **II** based on the total synthesis of the inositol ring *via* a Diels-Alder (D.-A.) reaction.[7,8] Given the *C*-disaccharidic structure of **II**, the starting compound should be an allyl α-*C*-glycoside **III** derived from D-glucose *via* **IV**:

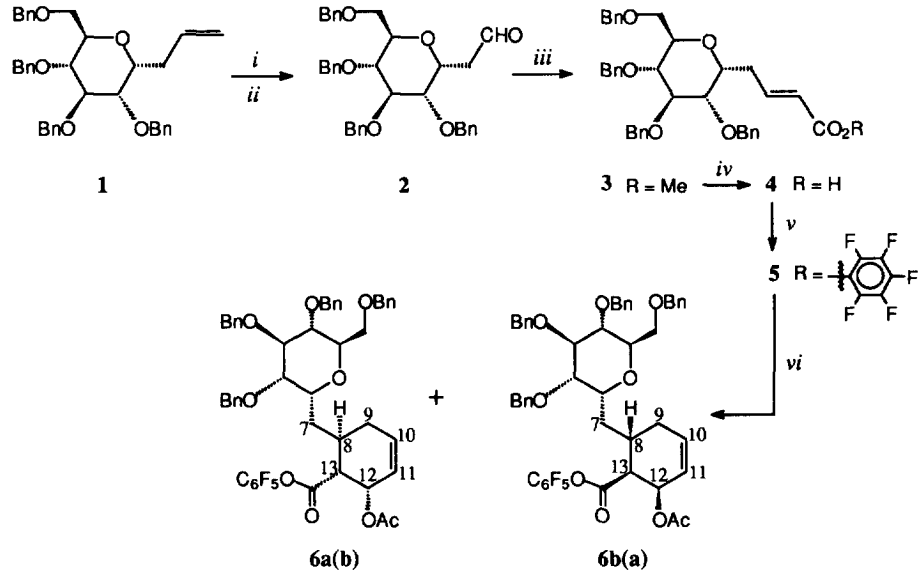


I **II** **IV** **III**

Scheme 1. Retrosynthesis of GPI mimetics from *C*-allyl glucoses

There are numerous examples in the literature of carbohydrates used as chiral auxilliary in D.-A.[9] or hetero D.-A. reactions.[10] However the involvment of *C*-glycosidic appendage in a [4+2] cycloaddition is less

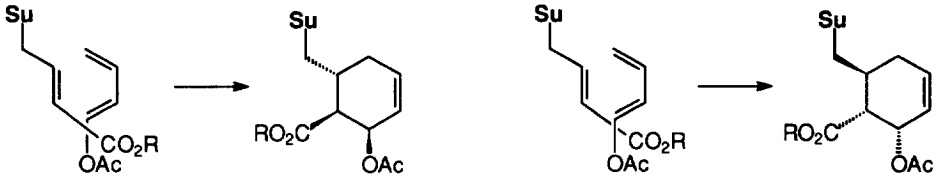
documented.[11] In this letter, we report our first results on a D.-A. reaction between an activated double bond as dienophile and *E*-1-acetoxy-butadiene. Our synthesis started from the known *C*-allyl glycoside **1**[12] which was transformed into the ester **3** (*E*/*Z*=9:1) using standard procedures. These isomers were separated by chromatography but none of them showed interesting reactivity towards oxygenated dienes such as Danishefsky's diene, 1-methoxy or 1-acetoxy-butadiene even at 165°C in xylenes. This poor reactivity could be explained in terms of stereoelectronic effects. In the mean time Kan and Ohfune[13] reported a tremendous improvement in D.-A. reactions by changing the methyl ester for the more active pentafluorophenyl ester. We were pleased to find that this was also true in our case. Thus the saponification of **3** to the corresponding acid **4** followed by dicyclohexylcarbodiimide-mediated coupling with pentafluorophenol[14] gave **5** in 85% overall yield. The [4+2]-cycloaddition of the activated dienophile **5** with an excess of *E*-1-methoxy-1,3-butadiene was almost complete after 4 days at 120°C in toluene in a sealed vessel. A mixture of four partially separable cycloadducts was obtained in 74% yield and a roughly 1:1:1:1 ratio. In the same manner, but after heating **5** for *ca.* six days with a two-fold excess of *E*-1-acetoxy-1,3-butadiene, we successfully isolate besides 43% of unreacted starting material, two major pure fractions, **6a** (17%) and **6b** (17%), and two minor ones (in less than 8% of the products) which were not further investigated.



Scheme 2. Reagents and yields: *i*) O_3, MeOH, -50°C, 4 h; *ii*) PPh_3, -50→ +20°C, 3 h; *iii*) $Ph_3P{=}CHCO_2Me$, ref. THF, 3 h, 84%, 3 steps; *iv*) NaOH 0.04 N / THF, 3 d, 91%; *v*) C_6F_5OH, DCCI, CH_2Cl_2, 0°C, 1.5 h, 93%; *vi*) 1-acetoxy-1,3-butadiene, toluene, 120°C, 6 d, 34%.

Both isolated cycloadducts **6a** and **6b** were diastereomerically pure on the basis of their 400 MHz ^1H NMR spectra measured in $CDCl_3$. The almost complete regioselectivity was obvious from the chemical shifts of H12 (δ 5.65, 5.7) and H13 (δ 3.15, 3.0) respectively. Since the pentafluorophenylester and the sugar moiety will be *trans* to each other due to the starting *E*-geometry of olefin **5**, the relative stereochemistry can be only *trans-trans* or *cis-trans* for H12-H13 and H13-H8. The putative structures **6a** and **6b** are in agreement with the measured vicinal coupling constants $J_{8,13}$ = 12 Hz (*trans*-diaxial orientation), and $J_{12,13}$ which was 4 Hz

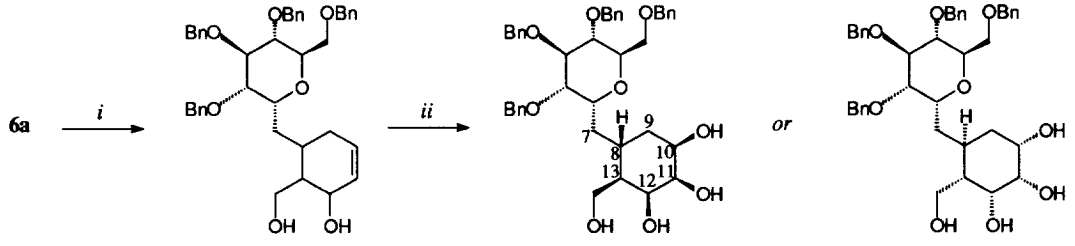
(equatorial-axial *cis* orientation). These results are in full accord with some recent data obtained with the same diene.[7] It was finally concluded that **6a** and **6b** differ only by the absolute configuration of the created asymmetric centres (*vide infra*). This result can be explained in terms of preferred *endo* transition states which led to a *cis*-relationship of the substituants at C12 and C13 in both cases. The 1:1 ratio found in the diastereoisomers **6a** and **6b** indicates the absence of facial selectivity in the studied D.-A. reaction. It is noteworthy to note that *O*-glycosidic dienes exhibited much higher facial selectivity.[8]



R = C_6F_5
Su = 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl

Scheme 3. Two possible *endo*-attacks between dienophile **5** and *E*-1-acetoxy-1,3-butadiene

Crystals, suitable for X-ray crystallographic analysis of compounds **6**, have not yet been obtained. Nevertheless, we explored further chemical transformations *en route* to the cyclitol ring. Complete reduction of **6a** with $LiAlH_4$ afforded the diol **7** in 90% yield. *Cis*-hydroxylation of the double bond using catalytic osmium tetroxide[15] gave two isomers **8a** ($J_{10,11}$ = 4.4 Hz) and **8b** (not represented here) in a 89% overall yield and in a 4:1 ratio. The relative stereochemistry of the five chiral centres of the carbocyclic part in the major compound **8a** was tentatively determined as all *cis*, given the small $J_{11,12}$ = 2.8 Hz in favour of a *cis* orientation of H11 and H12. Hence, the major compound **8a** should be depicted by one of the two following formulas:



7 **8a**

Scheme 4. Reagents and yields: *i*) $LiAlH_4$, THF, 0→20°C, 1.5 h, 84%; *ii*) OsO_4, *N*-methyl morpholine oxide, acetone, water, 20°C, 36 h, **8a** = 69%.

In conclusion, five of the six stereogenic centers present in the *myo*-inositol part of GPI anchors mimic **8a** are installed (*epi* or *allo*-inositol stereo isomers) in a three-step sequence. Hence the use of an active ester, which dramatically improved the yield of the cycloaddition, is an important breakthrough that should be of general use in cycloaddition. Studies aimed at the improvement of the enantioselectivity (*ie* the facial selectivity) on the cycloaddition of sugar dienophiles using for instance chiral butadienes[16] are currently in progress.

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