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A Diels–Alder strategy to 1,4-glycosidically linked monocarba-disaccharides

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Abstract

A concise synthesis of the β-1,4-linked monocarba-disaccharide, 4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3,6-tetra-*O*-acetyl-5a-carba-α-L-idopyranose **10**, using an asymmetric Diels–Alder reaction of maleic anhydride and the glucosylated diene **1** to construct the carbocyclic ring is described.

Keywords: asymmetric synthesis; Diels–Alder reactions; carbohydrate mimetics.

Carba-sugars (also referred to as pseudo-sugars) are compounds in which the ring oxygen of a furanoid or pyranoid sugar is replaced by a methylene group.[1] Because of their structural similarity to the parent carbohydrates they are expected to possess interesting biological activities. Indeed, carba-α-D-galactopyranose—a naturally occurring pseudo-monosaccharide—is endowed with antibiotic properties, carba-β-DL-glucopyranose is as sweet as D-glucose and carba-α-DL-glucopyranose is effective in inhibiting glucose-stimulated release of insulin and has islet glucokinase activity.[1,2] Many synthetic routes have been developed for the synthesis of pseudo-monosaccharides in racemic and enantiomerically pure forms.[1,3] However, relatively little attention has been focused on the elaboration of monocarba-disaccharides (disaccharides containing one carba-sugar residue). In such compounds, the sugar and carba-sugar units may be joined by either acetal[4] or ether linkages.[5]

Our aim was to provide an alternative approach to acetal-linked monocarba-disaccharides where the glycosylation pattern was established at the outset of the synthesis. The strategy relies on an asymmetric Diels–Alder reaction of analogues of Danishefsky's diene bearing carbohydrate auxiliaries with maleic anhydride to construct the glycosylated carbocycle. The ready availability of such dienes and the high diastereofacial selectivities that they exhibit in their cycloaddition reactions with cyclic dienophiles[6] make them attractive as a starting point in a

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direct synthesis of glycosylated pseudo-sugars and cyclitols. Using this approach we were able to synthesise a 1,3-glycosidically linked amino monocarba-disaccharide, 3-*O*-(β-D-glucopyranosyl)-4-acetamido-2,4-dideoxy-5a-carba-β-L-lyxopyranose[7] and 3-*O*-(β-D-glucopyranosyl)-4-*epi*-shikimate.[8] We now report chemistry which allows the direct synthesis of a fully substituted monocarba-disaccharide possessing a 1,4-glycosylation pattern.

Our strategy is based upon the premise that modification of the carbocyclic ring of the glycosylated cycloadducts formed in the reaction with maleic anhydride could result in the direct synthesis of a variety of 1,4-linked monocarba-disaccharides. An overview of the transformations required from a generalised cycloadduct is given in Fig. 1.

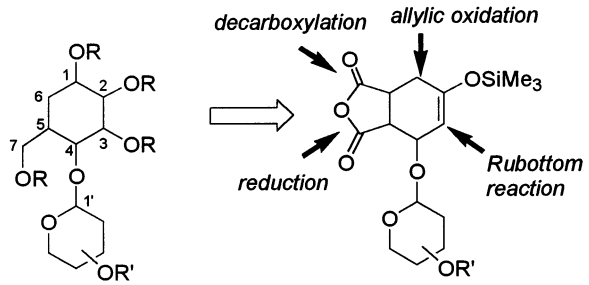
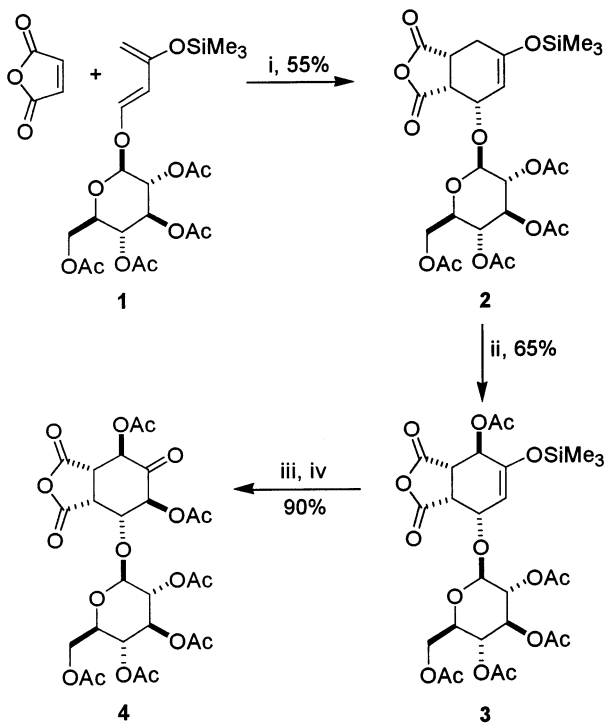


Figure 1.

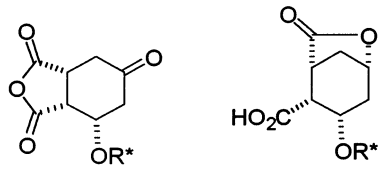
Reaction of the diene **1** (68 mmol scale) with maleic anhydride and subsequent treatment of the crude reaction product with diethyl ether gave the cycloadduct **2** in 55% yield (Scheme 1).



Scheme 1. *Reagents and conditions*: (i) C_6H_6, rt; (ii) $Pb(OAc)_4$, CH_2Cl_2, Δ; (iii) dimethyldioxirane, Me_2CO–CH_2Cl_2; (iv) Ac_2O, $HClO_4$

The introduction of the acetoxyl group at C-1 without hydrolysis of the silyl enol ether moiety was achieved by an allylic oxidation of compound **2** with lead(IV) acetate[9] in boiling dichloromethane to give the acetate **3** (65%). Unfortunately, attempts to hydroxylate the C-3 position using a Rubottom reaction,[10] by treatment of the silyl enol ether moiety with MCPBA, failed. However, reaction of **3** with dimethyldioxirane and subsequent treatment of the crude product with acetic anhydride and a catalytic amount of perchloric acid gave the diacetoxy ketone **4** in 90% yield.

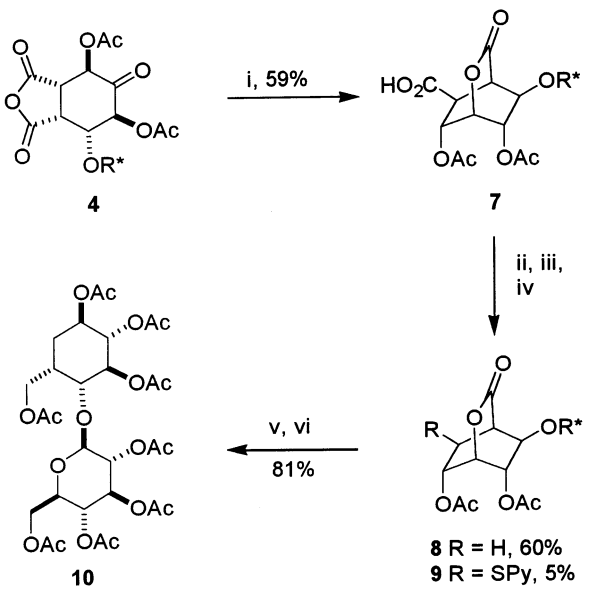
With the successful introduction of oxygen functionality at C-1 and C-3, attention was turned to differentiation of the carboxyl groups of the anhydride. In an earlier model study directed at the synthesis of 1,3-linked amino monocarba-disaccharides, it was found that treatment of the ketone **5** with sodium cyanoborohydride resulted in the formation of the γ-lactonic acid **6**.[7]



5 **6**

(R* = tetra-*O*-acetyl-β-D-glucopyranosyl)

In the present study, an analogous reduction of the diacetoxy ketone **4** gave the δ-lactonic acid **7** as the exclusive product[†] (Scheme 2). The decarboxylation of the C-6 carboxylic acid



4 **7** **10**

(R* = tetra-*O*-acetyl-β-D-glucopyranosyl)

Scheme 2. *Reagents and conditions*: (i) $NaBH_3CN$, HOAc; (ii) $(COCl)_2$, DMF, THF; (iii) 1-hydroxypyridinethione, sodium salt; (iv) ^{t}BuSH, *hv*, 5 min; (v) $LiAlH_4$, THF, Δ; (vi) Ac_2O, py

[†] It can be rationalised that the δ-lactone is preferentially formed because a severe 1,3-diaxial interaction between the acetoxyl substituents of the carbocyclic ring destabilises the transition state leading to the γ-lactone.

moiety was achieved using Barton's methodology.[11] Thus, in a one-pot reaction, treatment of **7** in THF with oxalyl chloride and DMF, the sodium salt of 1-hydroxypyridine-2-thione and 2-methyl-2-propanethiol gave, after brief irradiation with a broad spectrum tungsten lamp, the decarboxylated product **8** and the sulphide **9** in 60 and 5% yields, respectively. Lithium aluminium hydride reduction of **8** followed by acetylation gave the protected monocarba-disaccharide, 4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3,6-tetra-*O*-acetyl-5a-carba-α-L-idopyranose **10**.[12]

The substitution pattern and stereochemistry about the carbocyclic ring of **10** was confirmed by a single crystal X-ray crystallographic study.[13] The crystal structure, depicted in Fig. 2, clearly showed that the carba-sugar possessed the L-*ido* configuration and, in the solid state, adopted the $^4C_1$ chair conformation with the C-5 acetoxymethyl group in an axial orientation.‡

In summary, we have developed a concise synthesis of a 1,4-linked monocarba-disaccharide **10** in six steps utilising an asymmetric Diels–Alder cycloaddition of the readily available glycosidic diene **1** and maleic anhydride to form the glycosylated carbocyclic ring. Oxygen functionality at C-1, C-2, and C-3 of the carbocyclic ring was introduced with high stereoselectivities. The availability of a wide range of glycosylated dienes makes this methodology attractive for the synthesis of monocarba-disaccharides and related products and further work is underway to vary the stereochemistry of the substituents of the carba-sugar residue.

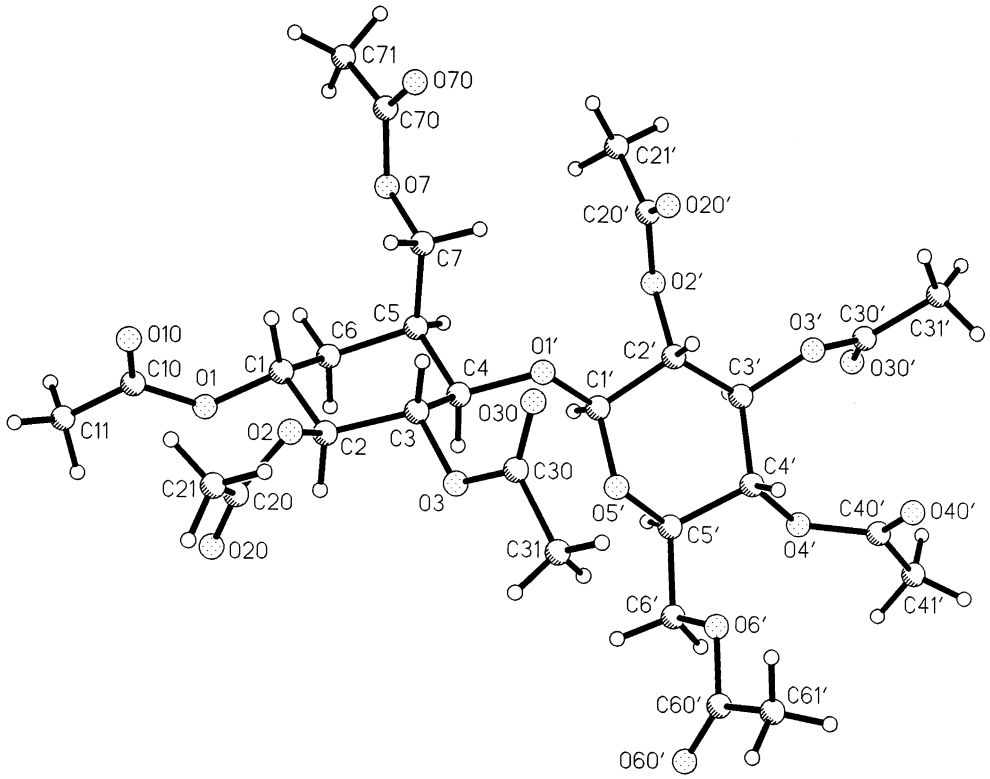


Figure 2. Molecular structure of **10**

‡ The ^{1}H NMR spectrum of **10** indicates that in deuteriochloroform the carbocyclic ring adopts a distorted $^4C_1$ conformation. H-3 resonates at δ 5.39 as an apparent triplet with coupling constants $J_{3,2} = J_{3,4} = 4.5$ Hz: thus, using the Karplus equation, $\phi(H_3–C_3–C_2–H_2) = \phi(H_3–C_3–C_4–H_4) = 135°$.

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12. Data for compound **10**: mp 116–118°C, $[\alpha]_D$ −26.0 (*c* 0.4, CH_2Cl_2), ν_{max} cm^{-1}/KBr inter alia: 1749 (OAc); δ_H (300 MHz, $CDCl_3$): 1.58–1.66 (1H, m, H-5a), 1.99, 2.01, 2.04, 2.06, 2.07, 2.08, and 1.99–2.08 (25H, 6×s and 1×1H m, 8×OAc and H-5a), 2.37–2.48 (1H, m, H-5), 3.74 (1H, ddd, *J* 2.5, 5.0, and 10.0 Hz, H-5′), 3.81 (1H, t, *J* 4.5 and 4.5 Hz, H-4), 3.96 (1H, dd, *J* 7.0 and 11.0 Hz, H-6), 4.02 (1H, dd, *J* 7.5 and 11.0 Hz, H-6), 4.06 (1H, dd, *J* 2.0 and 12.5 Hz, H-6′), 4.29 (1H, dd, *J* 5.0 and 12.5 Hz, H-6′), 4.60 (1H, d, *J* 8.0 Hz, H-1′), 4.88–4.94 (2H, m, H-2 and -2′), 4.99–5.06 (2H, m, H-1 and -4′), 5.17 (1H, t, *J* 9.5 and 9.5 Hz, H-3′), and 5.39 (1H, t, *J* 4.5 and 4.5 Hz, H-3); *m*/*z* (FAB, +ve): 699 (MNa^+, 2%), (677 MH^+, 3%) and 331 ($C_{14}H_{19}O_9^+$, 60%); Found: C, 51.5; H, 5.8%. $C_{29}H_{40}O_{18}$ requires: C, 51.48; H, 5.96%.

13. Crystal data: $C_{29}H_{40}O_{18}$ colourless triangular prism, 0.2×0.2×0.6 mm, triclinic, space group $P\bar{1}$, $a=5.733(1)$, $b=12.061(1)$, $c=13.414(2)$ Å, $\alpha=67.43(1)$, $\beta=78.29(2)$, $\gamma=83.17(2)°$, $U=837.8(2)$ Å^3, $Z=1$, $\mu=0.113$ mm^{-1}. Data were collected at 150 K on a Siemens P4 four circle diffractometer using graphite-monochromated Mo Kα radiation. 3626 independent reflections were collected in the range $5<2\theta<48°$ and the 3626 independent reflections were used in the structural analysis. The structure was solved by direct methods (SHELXS-86)[14] and refined against all F^2 data (SHELXL-93) to $R_1=0.044$ (for $2608F>4\sigma(F)$; $wR_2=0.103$ and goodness-of-fit = 0.89 for all $3626F^2$; 377 parameters; oxygen and non-ring carbon anisotropic; absolute structure was known due to the presence of the D-glucopyranose residue). Atomic coordinates, thermal parameters, and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). Any request to the CCDC for this material should quote the full literature citation and the deposition number CCDC 145071.
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