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STEREOCHEMICAL VARIATIONS IN AQUEOUS CYCLOADDITIONS USING GLYCO-ORGANIC SUBSTRATES AS A CONSEQUENCE OF CHEMICAL MANIPULATIONS ON THE SUGAR MOIETY.+

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Summary

Chemical modifications of the sugar moiety in dienyl glycosides allowed us to rationalize the stereochemistry of our aqueous cycloadditions using glyco-organic substrates. In this way, several dienyl glucosides having benzyl group in 2 or 6 position of the sugar gave a stereofacial selectivity which could be anticipated. Finally, aqueous cycloaddition of 2-methyl butadienyl α-D-glucoside with methacrolein gave a mixture of adducts in which the major diastereoisomer (endo-Re) was obtained in 78% yield resulting from a 18:82 stereofacial selectivity and a 20:1 endo-exo ratio.

Introduction

Diels-Alder reactions continue to promote intensive research in order to get reaction conditions as smooth as possible along with an increased selectivity. In this respect, we have shown recently[1] that the use of glycoorganic compounds allowed us to perform [4+2] cycloadditions in water as solvent, with a fair rate enhancement in comparison with organic solvents, and an asymmetric induction giving rise to chiral adducts in pure enantiomeric form after cleavage of the sugar moiety by acidic hydrolysis, or in a better way, using glycosidase in neutral conditions at room temperature. In this type of cycloaddition, the sugar, in the same time, induces chirality and water solubility of the starting materials, giving rise to a virtually complete endoselectivity, and a rate enhancement of the

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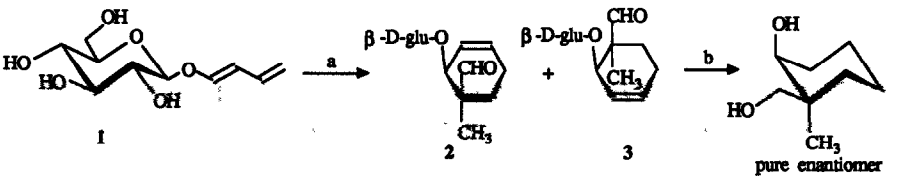
reaction, due to the hydrophobic effect[1-3]. In these preliminary studies, we used, as a model, glycoorganic compounds derived from glucose[4] as depicted in scheme 1.

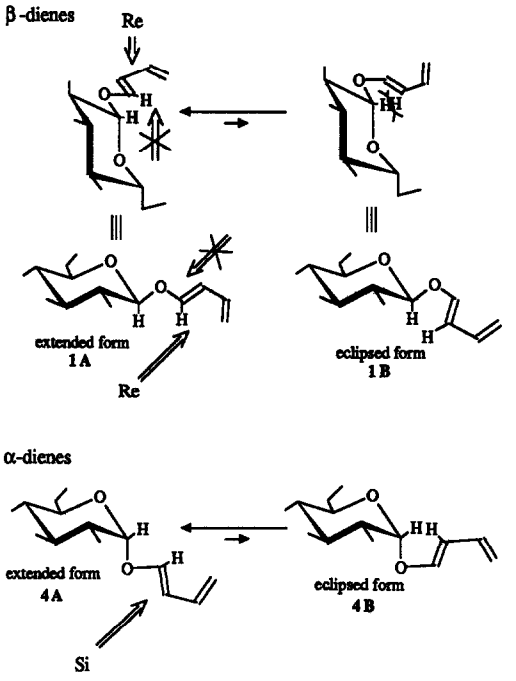
SCHEME 1



a. methacrolein, H_2O, 3.5 hrs, 20°C. b. Ac_2O, Pyridine; separation of the two diastereoisomers; $NaBH_4$; H_2/Pd; H_2SO_4 1N, 100°C, 4 hrs.

From the β-diene **1**, the reaction leads to a mixture of the diastereoisomers **2** and **3** in a 60:40 ratio. The determination of the absolute stereochemistry of the major adduct **2** allowed us to propose a rationale for the stereochemical course of the reaction. Diene **1** may react by way of the two conformers **1A** and **1B** (figure 1) where in both cases, the butadiene ether moiety is planar and perpendicular to the endocyclic C-O bond, due to the exoanomeric effect[5].

FIGURE 1



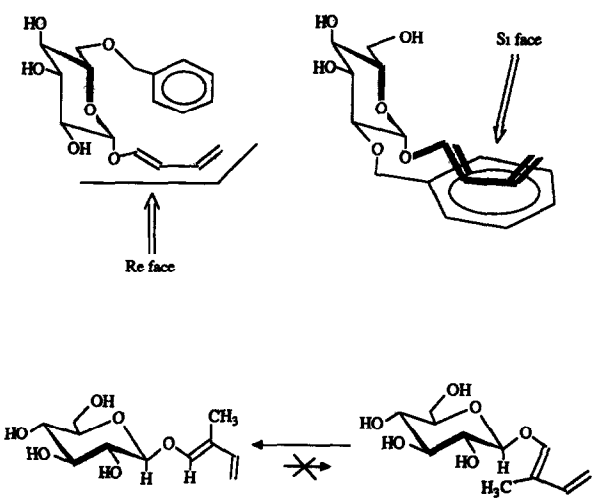
We have shown that the major diastereoisomer we get in the cycloaddition results from an approach of the dienophile onto the Re-face of the diene, that is from the top face in the conformer **1A** or the bottom face in the conformer **1B** (the absolute configuration of the face is defined with reference to the prochiral carbon atom C-1' linked to the oxygen atom).

Quite obviously, the first case must be energetically favored, as the extended conformation **1A** must be prefered to the eclipsed conformation **1B**. Moreover, the top face is the less hindered side of the diene unit as the approach from the bottom face implies a syn 1-3 interaction with the C-O endocyclic bond in the sugar.

Similar features have been observed by Stoodley for a similar but bis-oxygenated diene linked to peracetylated glucose, where the conformation in the solid state, as proved by X-ray crystallography, corresponds to the s-trans conformer of **1A**[4b]. Moreover, these observations were strenghtened by the fact that, in the case of the diene with the α anomeric configuration **4**, we observed in the cycloaddition a reversal of the π-facial selectivity. The major diastereoisomer still resulted from an approach of the dienophile from the same side with reference to the glucose unit, that is the side of the hydroxyl group in the 2-position, but in this case, this corresponds to the Si face of the diene unit in the extended conformation **4A**. The modest π-facial selectivity (~ 20% d.e.) observed in both cases (diene **1** or **4**) can result either from an insufficient dissymmetry between the two π-faces of the diene (as a result of the chirality of the sugar) in the conformer **1A** or **4A**, or from a too low energy barrier between the two conformers **1A** and **1B** for the β diene or **4A** and **4B** for the α diene.

The object of this communication is to show that it is possible to modulate the stereochemical outcome of the cycloaddition by chemical manipulations on the sugar moiety to modify or increase the dissymmetry of the diene unit, and to measure the importance of the conformational equilibrium onto the stereochemistry of the reaction.

FIGURE 2



First, we describe the influence of a benzyl protecting group at O-2 (the less hindered side) or at O-6 (the more hindered side). Due to hydrophobic effect, one can expect that the use of water as the solvent must enhance the interaction between the phenyl ring and the diene unit as shown in figure 2.

Second, to measure the contribution of the two conformers **1A**, **1B** or **4A**, **4B** in the cycloaddition, we prepared similar dienes bearing a methyl group at C-2' of the diene unit, which must improve the equilibrium shift in favor of the extended conformation for obvious steric reasons.

Results and discussion

A. Preparation of dienes 15 and 16 bearing a benzyl group at O-2. (Scheme 2)

Starting from a mixture of the known allyl-3-O-allyl-D-glucopyranoside[6] 5 (α+β), acetalation gave the new allyl-3-O-allyl-4,6-O-benzylidene-D-glucopyranoside 6 (α+β) as an anomeric mixture. For purposes of characterization, the two anomers were separated by silica gel chromatography affording 6α (53%) and 6β (18%). In fact, a mixture of 6 (α+β) could be directly treated with HNa and BnBr in THF to afford a mixture of 7 (α+β), from which the two allyl groups were isomerized to propenyl groups by tBuOK in DMSO before acidic hydrolysis which provided the known 2-O-benzyl glucose 9 (α+β)[7]. The mixture of 9 (α+β) was peracetylated in usual manner, to give 10 (α+β)[8]. The bromide[8] 11 was obtained by treatment with HBr 30% in AcOH. It reacted as already described[1] for diene 1 with the sodium salt of malonaldehyde[9] in DMSO, to give the unsaturated aldehyde 12 with no concomittent formation of the α anomer. Wittig olefination with salt-free methylene triphenyl phosphorane at -78°C afforded the pure β diene 13 (90%) whereas the reaction conducted at room temperature gave a mixture of the dienes 13 and 14 in a 1.5:1 ratio.

This anomerization during Wittig reaction occurred on the unsaturated aldehyde as the β-diene is stable under the Wittig conditions. We suppose that the anomerization occurred through an addition elimination mechanism of the phosphorane onto the α,β-unsaturated aldehyde leading to the sugar having a free 1-OH which rearranged to the more stable α anomer before recombination. This mechanism is supported by the fact that during the reaction, a transient spot visible under U.V. light appeared on TLC chromatography (certainly the α aldehyde) before the appearance of the α-diene 14. In the case of 6-O-benzyl derivatives, this has been firmly demonstrated as we had in hand the unsaturated aldehyde with the α configuration, which allowed us to confirm the formation of α aldehyde from pure β aldehyde (vide infra).

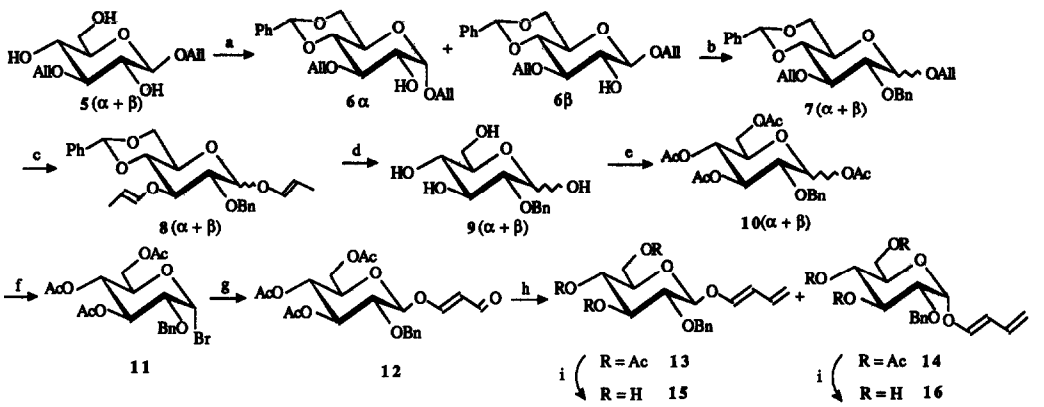
Moreover, this assumption gains some support in considering the 2'-methyl substituted unsaturated aldehyde 30, which, under the same conditions, leads to the α anomer to a lower extent due to the electron donor character of the methyl group which thwarts the Michael addition of the phosphorane.

Finally, the pure dienes 15 and 16 were obtained in a quantitative yield respectively from the peracetylated dienes 13 and 14 after alkaline hydrolysis (NEt_3, MeOH, H_2O).

All the free dienes are homogeneous in TLC (AcOEt-iPrOH, H_2O, 8:2:1)

and gave correct ^1H NMR spectra. They were not further characterized and they were used directly for the cycloaddition.

SCHEME 2 : syntheses of 2-O-benzyl dienes.



a. PhCHO, $ZnCl_2$; b. BnBr, HNa, THF; c. tBuOK, DMSO, 1hr, 50°C; d. H_2SO_4 5N, acetone, 80°C, 16hrs; e. Ac_2O, Pyr.; f. HBr, AcOH; g $NaHC(CHO)_2$, DMSO, 20°C, 16hrs; h. $Ph_3P{=}CH_2$, THF-Toluene; i. NEt_3-MeOH-H_2O (1:8:1), 20°C, 16hrs.

B. Preparation of dienes 27 and 28 bearing a benzyl group at O-6.(Scheme 3)

Starting from the triol 1,2-isopropylidene-α-D-glucofuranose **17**[10] selective benzylation was performed through the stannylene procedure, giving rise to the already known compound **18**[11] in a 77% yield. This method proved to be much more efficient that the method already described.[11]

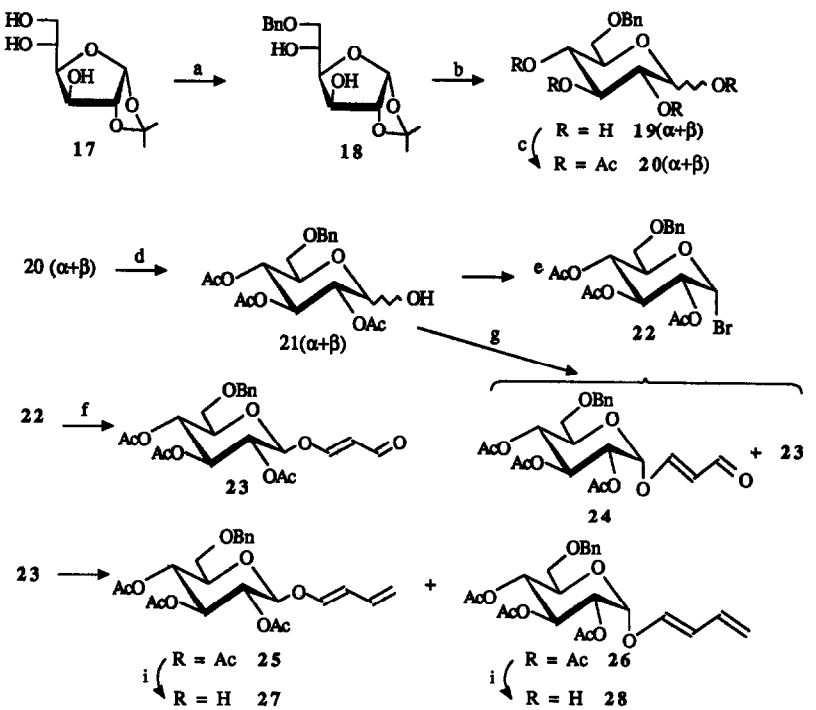
Acidic hydrolysis (DOW $50H^+$) followed by peracetylation (Ac_2O, pyridine) afforded **20**[12] (α+β) as an anomeric mixture. At this stage, it was impossible to get cleanly the bromide **22** using the usual HBr 30% in AcOH. In fact in this case, hydrolysis of the primary benzyl ether occurred to a large extent. So we turned to Vilsmeier type reaction using oxalyl bromide in CH_2Cl_2[13] with a catalytic amount of DMF. First selective deprotection of the anomeric hydroxyl group from **20** (α+β) was performed with hydrazine acetate[14] to give **21** (α+β) from which the crude bromide **22** was obtained as an unstable oil. It was directly used for the preparation of the aldehyde **23** by reaction with the sodium salt of malonaldehyde in DMSO. **23** was obtained in a 34% yield from **21**.

Alternatively and in a better way, a mixture of aldehydes **23** and **24** could be obtained directly from **21** through an addition-elimination mechanism onto the 3-tosyloxy acrolein which was prepared in situ from the sodium salt of malonaldehyde and tosyl chloride[15]. The unsaturated aldehydes **23** and **24** were obtained in 79% yield in a 1:2 ratio. Wittig

olefination from the β aldehyde **23** at -78°C gave the crystalline β diene **25** in 70% yield without anomerization.

The α-diene **26** was obtained as for the diene **25** except that in this case the reaction must be conducted at room temperature. Silica gel chromatography afforded in the order of elution diene **26** (51%) followed by the diene **25** (29%). In this case, evidence for the intermediate formation of aldehyde **24** was obtained by comparison with an authentic sample of aldehyde **24**, obtained directly from compound **21** (α+β). Finally the free dienes **27** and **28** were obtained in a quantitative yield respectively from the peracetylated dienes **25** and **26** by alkaline hydrolysis (NEt_3, MeOH, H_2O). These dienes were homogeneous in TLC (AcOEt-iPrOH-H_2O, 8:2:1) and gave correct ^1H NMR spectra. They were used directly for the cycloadditions.

SCHEME 3 : Syntheses of 6-O-benzyl dienes.

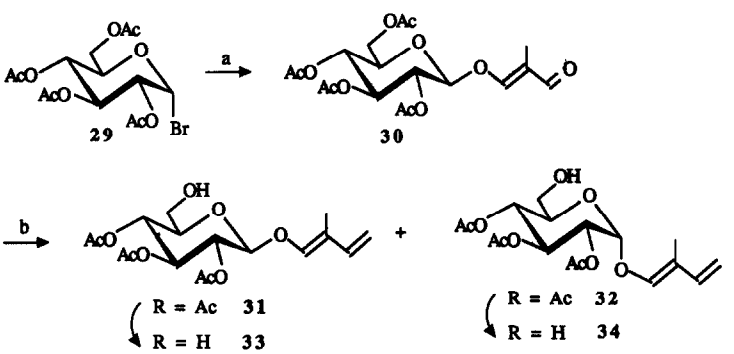


a. Bu_2SnO, BnBr, $Br^-N^+Bu_4$, Toluene; b. Dow. 50 H^+, 80°C, 2h; c. Ac_2O, Pyr.,
d. NH_2NH_2, AcOH, DMF, 60°C, 1h; e. $(COBr)_2$, DMF, CH_2Cl_2; f. $NaCH(CHO)_2$, DMSO;
g. TsO-CH=CH-CHO, HNa; h. $Ph_3P{=}CH_2$, THF, Toluene; i. NEt_3-MeOH-H_2O (1:8:1), 20°C,16h

C. Preparation of dienes 33 and 34 bearing a methyl group at C-2' of the diene unit. (Scheme 4)

The corresponding unsaturated aldehyde **30** was prepared from the easily available acetobromoglucose **29** using the sodium salt of methyl malonaldehyde[16] in 48% yield without chromatography. Wittig olefination as above gave, at -78°C, the peracetylated diene **31** in 74% yield, whereas at room temperature, a mixture of α **32** and β **31** anomers was obtained in which the β isomer predominates. In fact, in this case, the α and β dienes were obtained in a 1:2.5 ratio. Alkaline hydrolysis gave the free dienes **33** and **34** in a quantitative yield. The E stereochemistry of the dienes **33** and **34** (and in consequence, that of the aldehyde **30** and the dienes **31** and **32**) rely upon the fact that they exhibit a similar reactivity toward methacrolein than the unmethylated dienes **1** and **4**. Actually, Z isomers of similar dienes were shown to be unreactive in cycloaddition.[15]

SCHEME 4 : Syntheses of 2'-Methyl dienes



a. $Na(CH_3)C(CHO)_2$, DMSO; b. $Ph_3P{=}CH_2$, THF, Toluene; c. NEt_3-MeOH-H_2O (1:8:1), 16h, 20°C

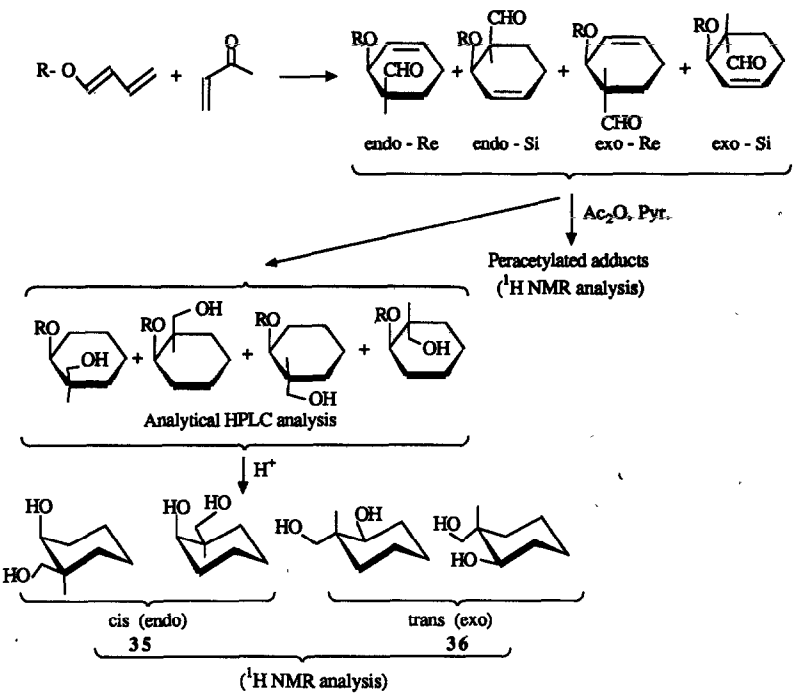
D. Stereochemical course of the cycloadditions. (Scheme 5)

For each of the dienes, the cycloaddition was performed in water using methacrolein as dienophile, as already described[1] for dienes **1** and **4**. Since the dienes are prochiral, Diels Alder addition may provide four diastereoisomers which are called endo-Re, endo-Si, exo-Re and exo-Si, according to the endo or exo transition state and the absolute configuration of the face of the diene which is attacked.

In the case of the 2-O-benzyl and 6-O-benzyl diene, the stereochemical outcome of the reaction was determined from the crude mixture obtained after cycloaddition. Sequential treatment with $NaBH_4$ and H_2/Pd/C gave a

mixture which could be directly compared with the result of cycloadditions of the parent diene **1** and **4** treated in the same conditions. At this stage, analytical HPLC gave the ratio of the two major isomers (endo-Re and endo-Si). The endo-exo ratio was determined after removal of the sugar moiety by acidic hydrolysis affording a mixture of cis and trans diols which was analyzed by ^{1}H NMR spectroscopy. Alternatively, ^{1}H NMR analysis of the mixture of peracetylated adduct allowed us to confirm the stereochemistry of the reaction, by comparison of the aldehyde resonance signals.

SCHEME 5 : Determination of the stereochemical outcome of the cycloadditions



In the case of the dienes **33** and **34**, bearing a methyl group at C-2', the stereochemical outcome of the reaction was determined by ^{1}H NMR spectroscopy of the mixture obtained after evaporation of the aqueous phase after cycloaddition and peracetylation. At this stage, the mixture of the four diastereoisomers gave a correct elemental analysis.

We anticipate that the methyl group on a sp^2 carbon atom must not change the overall conformation of the four adducts and in fact, because of a great similarity, the comparison of the chemical shifts of the aldehydic protons with those of the adducts obtained from all the other dienes, for which the configurations were known, allowed us to determine the

stereochemical outcome of the reaction. Indeed, as shown in table 1, the resonance signals for endo-Re diastereoisomers are in each case more deshielding in comparison with the endo-Si adducts. A similar comparison related to the resonance signals of the methyl group and of the anomeric proton of the sugar leads to the same attribution. The results of all the cycloadditions are summarized in table 2.

Table 1.

^{1}H NMR Chemical shifts of CHO in the peracetylated adducts (% in the mixture).

Starting dienes	endo-Re	endo-Si	exo-Re	exo-Si
α dienes				
4	9.73 (34)	9.61 (59)	9.51 (2)	9.44 (5)
6-O-Bn (**28**)	9.77 (27)	9.65 (68)	9.52 (1.5)	9.47 (3.5)
2-O-Bn (**16**)	9.80 (53)	9.76 (40)	9.53 (4)	9.47 (3)
Me (**34**)	9.71 (17)	9.62 (78)	9.51 (1)	9.43 (4)
β dienes				
1	9.60 (100)		9.48 (tr)	9.42 (tr)
6-O-Bn (**27**)	9.72 (66)	9.66 (29)	9.49 - (5) -	9.48
2-O-Bn (**15**)	9.84 (32)	9.74 (61)	9.55 - (7) -	9.53
Me (**33**)	9.64 (66)	9.62 (30)	9.50 - (4) -	9.49

Table 2.

Stereochemistry of the cycloaddition in water of methacrolein with various dienes.

diene	Yield (%)	T (°C)	t (h)	Re:Si (endo)	endo:exo	Ref
β dienes						
1	90	20	3.5	60:40	100:0	1
6-O-Bn (**27**)	86	40	17	69:31	95:5	
2-O-Bn (**15**)	95	40	17	34:66	93:7	
Me (**33**)	96	20	20	69:31	96:4	
α dienes						
4	78	20	6	36:64	93:7	1
6-O-Bn (**28**)	85	40	17	28:72	95:5	
2-O-Bn (**16**)	97	40	17	57:43	93:7	
Me (**34**)	92	20	20	18:82	95:5	

Beside the reversal of the facial selectivity between α and β dienes in each case (substituted or unsubstituted dienes), the salient features for both cases α and β are :

1) the reversal of the face selectivity when the favored face was hindered with a benzyl group at O-2 of the sugar;

2) the enhanced facial selectivity when the already disfavored face was hindered with a benzyl group at O-6 of the sugar;

3) a methyl group at C-2' of the diene unit has a much more significant effect in the α series than in the β one, which indicates that the participation of the eclipsed conformer in the cycloaddition is more important in the former case.

Conclusion

The use of sugar to induce chirality in organic reactions is still an uncommon process. However, sugar is certainly the cheapest source of chiral carbon atom, if not too much energy is expended to keep only few of the asymmetric centers as chiral synthons. In our methodology using glycoorganic substrates, the sugar is used as a whole, limiting in the same time the number of steps in the synthesis. We have shown that we are able to achieve chiral synthesis under very smooth conditions (room temperature, neutral) by controlling the asymmetric induction provided by the sugar, after facile chemical manipulations, by taking advantage of the great versatility of carbohydrate chemistry. Moreover, it must be noted that sugars give very crystalline compounds allowing purification of the major diastereoisomer without chromatography. Of course, such a strategy implies that the sugar must be easily removed at the most appropriate moment in the synthesis. In this respect, we have shown[1] that the sugar could be removed either by enzymatic hydrolysis when the compounds are still water-soluble, or by acidic hydrolysis at any stage of the synthesis. Finally, in the method described herein, the best result was obtained with the α diene **34** bearing a methyl group at C-2'. In this case, among the four possible adducts, one diastereoisomer was obtained in 78% yield resulting from a 20:1 endo-exo ratio and a 82:18 facial selectivity ratio. These results bring up the method among the best uncatalyzed asymmetric Diels-Alder reactions and we are currently using this aqueous methodology for natural product synthesis.

Experimental Section.

General considerations.

When the temperature of a reaction is not specified, it was conducted at room temperature. Preparative chromatographic separations were performed on silica gel (Merck 60) columns, with the eluents given in brackets and monitoring of the effluent by thin-layer chromatography on silica gel plates. Spots were visualized by ultra-violet light or by spraying with 10% H_2SO_4 in EtOH. Melting points were measured on a Reichert hot stage apparatus and are uncorrected. Optical rotations were measured at 20°C with a Roussel-Jouan electronic digital micropolarimeter. Proton ^1H NMR spectra were recorded at 250 MHz with a Bruker AM250 spectrometer. NMR chemical shifts are expressed in parts per million downfield from internal tetramethyl-silane. Coupling constants (J) are given in hertz with splitting patterns designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Elemental analyses were performed by the Service Central de Microanalyse du CNRS. Analytical HPLC was performed with a Waters system using a differential refractometer as detector and inverse phase C_{18} 5 μ column.

General procedure for Wittig olefinations.

This reaction was conducted either at -78°C to give only β dienes or at room temperature, affording a mixture of α and β dienes. To a solution of the aldehyde in anhydrous THF was added dropwise a 0.6 M solution of methylene triphenylphosphorane in toluene. When the reaction was conducted at -78°C, the mixture was then allowed to warm to -20°C before beeing poured in a CH_2Cl_2 and phosphate buffer (pH 7) mixture. When the reaction was conducted at room temperature, the solution was directly poured in the CH_2Cl_2-buffer mixture. The organic layer was washed with water, dried (Na_2SO_4), filtered on a 2-in plug of Florisil and evaporated. Silica gel chromatography (Et_2O - CH_2Cl_2 - hexane, 1:1:4) gave either only the β diene or, in order of elution, the α diene followed by the β diene.

General procedure for deacetylation of peracetylated dienes.

A solution of peracetylated diene (10 mmol) in a NEt_3 - MeOH - H_2O (1:8:1, 100 mL mixture was stirred overnight at room temperature . The resultant clear solution was then coevaporated under vacuum several times until the odorless residue (free from triethylammonium salts) reached a constant weight. The crude water soluble dienes obtained in a quantitative yield were homogeneous in TLC (AcOEt - iPrOH - H_2O, 8:2:1) and gave correct ^1H NMR spectra. They were used for cycloaddition without further purification.

Allyl-3-O-allyl-4,6-O-benzylidene-α and β-D-glucopyranoside (6α and 6β).

$ZnCl_2$ (20 g, 146 mmol) was added to a solution of 5 (α+β) (38 g, 146 mmol) in benzaldehyde (200 mL). After 24 h at room temperature, cold water (600 mL) was added and the mixture was extracted with CH_2Cl_2 (2 x 200 mL). The combined organic layers were washed with $NaHCO_3$ (10%) and water, and dried over Na_2SO_4. The solution was concentrated in vacuo to remove most of the benzaldehyde. At this stage, the oil crystallized (CH_2Cl_2 - Et_2O - hexane) to yield 35 g (69%) of a mixture of compound 6 (α+β) in a 76:24 ratio as judged by ^1H NMR. Alternatively, silica gel chromatography (toluene - Et_2O, 8:2) gave in the order of elution pure 6β followed by 6α.

6α : m.p. 130-132°C $[\alpha]_D^{20}$ +110° (c 3, CH_2Cl_2); ^1H NMR ($CDCl_3$, 250 MHz) δ 2.54 (brs, 1 OH), 3.56 (t, J = 9 Hz, 1 H, H_3), 3.68 (dd, J = 9, 3.5 Hz, 1 H, H_2), 3.72 (t, J = 10 Hz, 1 H, H_{6ax}), 3.76 (t, J = 9.5 Hz, 1 H, H_4), 3.87 (dt, J = 9.5, 9.5, 4.5 Hz, 1 H, H_5), 4.25 (m, 4 H, $OCH_2CH=CH_2$), 4.27 (dd, J = 10, 4.5 Hz, 1 H, H_{6eq}), 4.93 (d, J = 3.5 Hz, 1 H, H_1), 5.25 (m, 4 H, $OCH_2CH=CH_2$), 5.54 (s, 1 H, PhCH-), 5.94 (m, 2 H, $OCH_2CH=CH_2$), 7.30-7.52 (m, 5 H, Ph). Anal. Calcd for $C_{19}H_{24}O_6$: C : 65.50, H : 6.94, O : 27.55; found : C : 65.65, H : 6.99, O : 27.81.

6β : m.p. 146.5-147.5°C; $[\alpha]_D^{20}$ = -49.9° (c 2.2, CH_2Cl_2); ^1H NMR ($CDCl_3$, 250 MHz) δ 2.65 (brs, 1 OH), 3.43 (dt, J = 10, 10, 5 Hz, 1 H, H_5), 3.52-3.68 (m, 3 H, H_2, H_3, H_4), 3.79 (t, J = 10 Hz, 1 H, H_{6ax}), 4.30 (m, 4 H, $OCH_2CH=CH_2$), 4.33 (dd, J = 10, 5 Hz, 1 H, H_{6eq}), 4.46 (d, J = 7.5 Hz, 1 H, H_1), 5.28 (m, 4 H, $OCH_2CH=CH_2$), 5.55 (s, 1 H, PhCH-), 5.96 (m, 2 H, $OCH_2CH=CH_2$), 7.33-7.53 (m, 5 H, Ph). Anal. Calcd for $C_{19}H_{24}O_6$: C : 65.50, H : 6.94, O : 27.55; found : C : 65.58, H : 7.07, O : 27.80.

(E)(prop-2-enal)-3-yl 2-O-benzyl-3,4,6-tri-O-acetyl-β-D-glucopyranoside (aldehyde **12**).

NaH (60% in mineral oil, 1.24 g, 31 mmol) was added portionwise to a solution of **6** (α+β) (9 g, 25.8 mmol) and benzyl bromide (3.7 mL, 31 mmol) in anhydrous THF (50 mL). This mixture was cautiously warmed until no hydrogen gas evolved, and left under reflux for 14 h. After addition of water, the mixture was extracted with CH_2Cl_2 (2 x 150 mL). The combined organic layers were washed with water, dried (Na_2SO_4) and evaporated. Silica gel chromatography (AcOEt - hexane, 1:4) of the residue gave allyl-3-O-allyl-2-O-benzyl-4,6-benzylidene-α and β-D-glucopyranoside **7** (α+β) which crystallized from hexane (10.3 g, 91%). The mixture **7** (α+β) (10 g, 22.8 mmol) was then heated at 50°C with tBuOK (6 g) in DMSO (60 mL). After 1 h, the solution was diluted with water and extracted with ether (4 x 100 mL). The combined organic layers were washed with water, dried (Na_2SO_4) and evaporated. The residue was then stirred in refluxing 2.5 N H_2SO_4 in 50% aqueous acetone (100 mL). After 16 h, neutralization with barium carbonate followed by filtration of insoluble salts, evaporation and silica gel chromatography (AcOEt - iPrOH - H_2O, 17:2:1) afforded 4 g (65%) of 2-O-benzyl-D-glucopyranose[7] **9** (α+β) as a syrup, which was treated with acetic anhydride (25 mL) in pyridine (40 mL) at room temperature for 24 h. Coevaporation with toluene yielded 6 g (92%) of the mixture of 1,3,4,6-tetra-O-acetyl-2-O-benzyl-D-glucopyranose[8] **10** (α+β). To a cooled (8°C) solution of **10** (α+β) (6 g, 13.7 mmol) in glacial acetic acid (14 mL), HBr (33% in AcOH, 14 mL) was added dropwise and the mixture was stirred for 3 h. Then the reaction mixture was diluted with CH_2Cl_2,[8] washed with iced water and iced $KHCO_3$ (10%), dried (Na_2SO_4) and evaporated. Crude residue was immediately treated with the sodium salt of malonaldehyde (3.8 g, 40 mmol) in DMSO (50 mL) and allowed to stand overnight at room temperature. After dilution with water, the reaction mixture was extracted with ether (2 x 100 mL). The combined organic layers were washed with water, dried (Na_2SO_4), and evaporated. Silica gel chromatography of the residue (Et_2O - hexane, 2:1) gave 3.14 g (51%) of aldehyde **12** which crystallized (ether - hexane).

12 : m.p. 93-95°C $[\alpha]_D^{20}$ = +13.6° (c 1, CH_2Cl_2); ^1H NMR ($CDCl_3$, 250 MHz) δ 1.97, 2.05, 2.10 (3 s, 9 H, 3 Ac), 3.67 (dd, J = 9.5, 7.5 Hz, 1 H, H_2), 3.82 (ddd, J = 10, 5, 2 Hz, 1 H, H_5), 4.13 (dd, J = 13, 2 Hz, 1 H, H_6), 4.30 (dd, J = 13, 5 Hz, 1 H, $H_{6'}$), 4.63 (d, J = 11 Hz, 1 H, CH_2Ph), 4.76 (d, J = 11 Hz, 1 H, CH_2Ph), 4.95 (d, J = 7.5 Hz, 1 H, H_1), 5.03 (t, J = 10 Hz, 1 H, H_4), 5.23 (t, J = 9.5 Hz, 1 H, H_3), 5.83 (dd, J = 13, 8 Hz, 1 H, $H_{2'}$), 7.23-7.41 (m, 6 H, Ph, $H_{3'}$), 9.46 (d, J = 8 Hz, 1 H, $H_{1'}$). Anal. Calcd for $C_{22}H_{26}O_{10}$: C : 58.66, H : 5.82, O : 35.52; found C : 58.18, H : 5.76, O : 35.77.

(E)buta-1,3-dienyl 2-O-benzyl-3,4,6-tri-O-acetyl-β-D-glucopyranoside (diene **13**).

Following the general procedure for Wittig olefination at -78°C, **12** (0.8 g, 1.77 mmol) in THF (20 mL) was treated with methylene triphenylphosphorane (2.8 mmol) to give 0.72 g (91%) of crystalline (ether-hexane) diene **13**.

13 : m.p. 103-104°C $[\alpha]_D^{20}$ = +22.1° (c 1.2, CH_2Cl_2); ^1H NMR ($CDCl_3$, 250 MHz) δ 1.94, 2.03, 2.08 (3 s, 9 H, 3 Ac), 3.56 (dd, J = 9, 7.5 Hz, 1 H, H_2), 3.74 (ddd, J = 10, 5, 2 Hz, 1 H, H_5), 4.10 (dd, J = 13, 2 Hz, 1 H, H_6), 4.28 (dd, J = 13, 5 Hz, 1 H, $H_{6'}$), 4.59 (d, J = 11 Hz, 1 H, CH_2Ph), 4.76 (d, J = 7.5 Hz, 1 H, H_1), 4.82 (d, J = 11 Hz, 1 H, CH_2Ph), 4.96 (brd, J = 10 Hz, 1 H, $H_{4''}$), 5.00 (t, J = 10 Hz, 1 H, H_4), 5.11 (brd, J = 17 Hz, 1 H, $H_{4'}$), 5.18 (t, J = 10 Hz, 1 H, H_3), 5.88 (dd, J = 12, 10 Hz, 1 H, $H_{2'}$), 6.22 (dt,

J = 17, 10, 10 Hz, 1 H, $H_{3'}$), 6.59 (d, J = 12 Hz, 1 H, $H_{1'}$), 7.22-7.38 (m, 5 H, Ph). Anal.Calcd for $C_{23}H_{28}O_9$: C : 61.59, H : 6.29, O : 32.11; found : C : 61.25, H : 6.36, O : 32.36.

(E)buta-1,3-dienyl 2-O-benzyl-3,4,6-tri-O-acetyl-α-D-glucopyranoside (diene **14**).

Following the general procedure for Wittig olefination at room temperature, **12** (1 g, 2.2 mmol) in THF (10 mL) was treated with methylene triphenylphosphorane (3.5 mmol) to give 0.38 g (38%) of crystalline (ether - hexane) diene **14** and 0.55 g (55%) of diene **13**.

14 : m.p. 98-100°C $[\alpha]_D^{20}$ +135° (c 1.25, CH_2Cl_2); ^1H NMR ($CDCl_3$, 250MHz) δ 2.02, 2.03 and 2.06 (3 s, 9 H, 3 Ac), 3.63 (dd, J = 9,5, 3 Hz, 1 H, H_2), 3.94 (ddd, J = 9.5, 4, 2 Hz, 1 H, H_5), 4.02 (dd, J = 12, 2 Hz, 1 H, H_6), 4.25 (dd, J = 12, 4 Hz, 1 H, $H_{6'}$), 4.58 (d, J = 12 Hz, 1 H, CH_2Ph), 4.66 (d, J = 12 Hz, 1 H, CH_2Ph), 4.93 (brd, J = 10 Hz, 1 H, $H_{4''}$), 4.99 (t, J = 9.5 Hz, 1 H, H_4), 5.06 (d, J = 3 Hz, 1 H, H_1), 5.09 (brd, J = 16 Hz, 1 H, $H_{4'}$), 5.48 (t, J = 9.5 Hz, 1 H, H_3), 5.91 (dd, J = 10.5, 10 Hz, 1 H, $H_{2'}$), 6.19 (dt, J = 17, 10.5, 10.5 Hz, 1 H, $H_{3'}$), 6.46 (d, J = 10.5 Hz, 1 H, $H_{1'}$), 7.32 (m, 5 H, Ph). Anal. Calcd for $C_{23}H_{28}O_9$: C : 61.59, H : 6.29, O : 32.11; found : C : 61.43, H : 6.28, O : 32.21.

6-O-benzyl-1,2-isopropylidene-α-D-glucofuranose[11] **18**.

A mixture of the triol **17**[10] (19 g, 86 mmol) and Bu_2SnO (26 g, 103 mmol) in toluene was refluxed overnight with azeotropic removal of water. Then, tetrabutylammonium bromide (14 g, 43 mmol) and benzyl bromide (14.3 mL, 120 mmol) were added and the mixture was refluxed for 20 h. The solution was concentrated in vacuo, and silica gel chromatography (first hexane then hexane - AcOEt, 1:2) afforded 20.4 g (77%) of 6-O-benzyl-1,2-isopropylidene-α-D-glucofuranose[11] **18** which crystallized from a CH_2Cl_2 - hexane mixture (m.p. 76.5 - 78.5°C (litt.[11] 78.5-79°C). ^1H NMR ($CDCl_3$, 250 MHz) δ 1.33 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3), 3.07 (d, J = 4 Hz, 1 H, OH), 3.47 (d, J = 2.5 Hz, 1 H, OH), 3.63 (dd, J = 9, 5 Hz, 1 H, H_6), 3.76 (dd, J = 9, 3 Hz, 1 H, $H_{6'}$), 4.09 (dd, J = 6, 2.5 Hz, 1 H, H_4), 4.13-4.25 (m, 1 H, H_5), 4.34 (t, J = 2.5 Hz, 1 H, H_3), 4.53 (d, J = 3 Hz, 1 H, H_2), 4.58 (s, 2 H, CH_2Ph), 5.95 (d, J = 3 Hz, 1 H, H_1), 7.23-7.42 (m, 5 H, Ph).

(E)(prop-2-enal)3-yl 6-O-benzyl-3,4,6-tri-O-acetyl-β-D-glucopyranoside (aldehyde **23**).

A mixture of the diol[11] **18** (9.3 g, 30 mmol) and resin Dowex 50 H^+ 200-400 mesh (3 g) in water (60 mL) was stirred at 80°C for 2 h. Filtration and evaporation gave 6.7 g (83%) of crystalline (AcOEt) 6-O-benzyl-D-glucose **19** (α+β), which was allowed to stand overnight in a mixture of Ac_2O (15 mL) and pyridine (30 mL) at room temperature. Coevaporation several times with toluene led to 10 g (92%) of the crystalline (CH_2Cl_2 - Et_2O - hexane) 6-O-benzyl 1,2,3,4 tetra-O-acetyl D-glucopyranose[12] **20** (α+β). To a solution of **20** (α+β) (21.8 g, 50 mmol) in anhydrous DMF (40 mL), hydrazine acetate[14] (5.6 g, 60 mmol) was added. After 1 h at 60°C, the mixture was allowed to cool to room temperature, diluted with ether, washed with water and dried (Na_2SO_4). Evaporation gave 16.2 g (82%) of **21** (α+β) as a pale yellow oil.

To a mixture of **21** (α+β) (1.2 g, 3 mmol) and DMF (1 mL) in CH_2Cl_2 (5 mL), a 2 M solution of oxalyl bromide[13] (2.25 mL, 4.5 mmol) in CH_2Cl_2 was added dropwise. After 5 min at room temperature, the mixture was poured in iced water. The organic layer was then washed with iced $KHCO_3$ (10%) and iced water, dried (Na_2SO_4) and evaporated. The crude residue was immediately dissolved in DMSO (5 mL) and sodium salt of malonaldehyde (0.94 g, 10 mmol) was added. The mixture was allowed to stand at room temperature for 30 min and then diluted with water and extracted with ether (2 x 50 mL). The combined organic layers were washed with water, dried (Na_2SO_4) and evaporated. Silica gel chromatography (Et_2O) afforded 0.46 g (34%) of the aldehyde **23** which crystallized from a mixture of ether and hexane.

23 : 103-104°C $[\alpha]_D^{20}$ +1° (c 1.2, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 1.93, 2.02, 2.07 (3

s, 9 H, 3 Ac), 3.59 (m, 2 H, H_6, $H_{6'}$), 3.79 (ddd, J = 9, 4, 2 Hz, 1 H, H_5), 4.47 (d, J = 11 Hz, 1 H, CH_2Ph), 4.57 (d, J = 11 Hz, 1 H, CH_2Ph), 4.98 (d, J = 7 Hz, 1H, H_1), 5.20 (m, 3 H, H_2, H_3, H_4), 5.82 (dd, J = 12, 7 Hz, 1 H, $H_{2'}$), 7.32 (m, 6 H, Ph, $H_{3'}$), 9.42 (d, J = 7 Hz, 1 H, $H_{1'}$). Anal. Calcd for $C_{22}H_{26}O_{10}$: C : 58.66, H : 5.81, O : 35.52; found : C : 58.33, H : 5.82, O : 35.01.

(E)(prop-2-enal)-3-yl 6-O-benzyl-2,3,4,tri-O-acetyl-α and β-D-glucopyranoside (aldehydes 23 and 24).

A solution of tosylchloride[15] (1.15 g, 6 mmol), 18-C-6 crown ether (0.264 g, 1 mmol) and sodium salt of malonaldehyde (1.41 g, 15 mmol) in THF (20 mL) was stirred at room temperature until TLC (Et_2O - hexane, 2:1) showed that all tosyl chloride had reacted (c.a. 1 h). At this moment a solution of 21 (α+β) (1.18 g, 3 mmol) in THF (4 mL) was added and the mixture was warmed to 60°C before adding portionwise HNa (60% in mineral oil, 0.16 g, 4 mmol). After 2 h at 60°C, the mixture was filtered through a 2 in. plug of celite, diluted with ether, washed with phosphate buffer (pH 7) and water, dried (Na_2SO_4) and evaporated. Silica gel chromatography (Et_2O - hexane, 3:1) afforded in order of elution the α aldehyde 24 (0.72 g, 54%) which crystallized neat when refrigerated and the β aldehyde 23 (0.33 g, 25%).

24 : m.p. 66.5-68°C, $[\alpha]_D^{20}$ +175° (c 2.1, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 1.93, 2.04 and 2.08 (3 s, 9 H, 3 Ac), 3.53 (m, 2 H, H_6, $H_{6'}$), 3.93 (dt, J = 10, 3, 3 Hz, H_5), 4.44 (d, J = 11 Hz, 1 H, CH_2Ph), 4.57 (d, J = 11 Hz, 1 H, CH_2Ph), 5.04 (dd, J = 10, 3 Hz, 1 H, H_2), 5.27 (t, J = 10 Hz, 1 H, H_4), 5.53 (t, J = 10 Hz, 1 H, H_3), 5.60 (d, J = 3 Hz, 1 H, H_1), 5.90 (dd, J = 12, 7 Hz, 1 H, $H_{2'}$), 7.32 (m, 6 H, Ph, $H_{3'}$), 9.37 (d, J = 7 Hz, 1 H, $H_{1'}$). Anal. Calcd. for $C_{22}H_{26}O_{10}$: C : 58.66, H : 5.81, O : 35.52; found : C : 57.94, H : 5.82, O : 34.89.

(E)buta-1,3-dienyl 6-O-benzyl-2,3,4-tri-O-acetyl-β-D-glucopyranoside (diene 25).

Following the general procedure for Wittig olefination at -78°C, 23 (0.23 g, 0.51 mmol) in THF (3 mL) was treated with methylene triphenylphosphorane (0.87 mmol) to give 0.16 g (70%) of crystalline (hexane) diene 25.

25 : m.p. 60-62°C $[\alpha]_D^{20}$ +9,2° (c 1.2, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 1.93; 2.01 and 2.04 (3s, 9 H, 3 Ac), 3.59 (m, 2 H, H_6, $H_{6'}$), 3.75 (m, 1 H, H_5), 4.49 (d, J = 11 Hz, 1 H, CH_2Ph), 4.56 (d, J = 11 Hz, 1 H, CH_2Ph), 4.77 (d, J = 7 Hz, 1 H, H_1), 4.93 (brd, J = 9.5 Hz, 1 H, $H_{4''}$), 5.06 (brd, J = 17 Hz, 1 H, $H_{4'}$), 5.12 (m, 2 H, H_2, H_4), 5.23 (t, J = 9 Hz, 1 H, H_3), 5.83 (t, J = 11 Hz, 1 H, $H_{2'}$), 6.18 (dt, J = 17, 11, 11 Hz, 1 H, $H_{3'}$), 6.59 (d, J = 11 Hz, 1 H, $H_{1'}$), 7.30 (m, 5 H, Ph). Anal. Calcd for $C_{23}H_{28}O_9$: C : 61.59, H : 6.29; found : C : 60.86, H : 6.21.

(E)buta-1,3-dienyl 6-O-benzyl-2,3,4-tri-O-acetyl-α-D-glucopyranoside (diene 26).

Following the general procedure for Wittig olefination at room temperature, 23 (225 mg, 0.5 mmol) was treated with methylene triphenylphosphorane (0.75 mmol) to give 114 mg (51%) of the crystalline (ether-hexane) α diene 26 and 66 mg (29%) of the β diene 25.

26 : m.p. 90-91°C; $[\alpha]_D^{20}$ +151° (c 1.66, CH_2Cl_2); ^1H NMR ($CDCl_3$, 250 MHz) δ 1.92, 2.01 and 2.07 (3s, 9 H, 3 Ac), 3.53 (m, 2 H, H_6, $H_{6'}$), 3.94 (dt, J = 9.75, 3.25, 3.25 Hz, 1 H, H_5), 4.44 (d, J = 11.5 Hz, 1 H, CH_2Ph), 4.58 (d, J = 11.5 Hz, 1 H, CH_2Ph), 4.93 (brd, J = 10.5 Hz, 1 H, $H_{4''}$), 4.95 (dd, J = 10, 3.75 Hz, 1 H, H_2), 5.10 (brd, J = 16.5 Hz, 1 H, $H_{4'}$), 5.22 (t, J = 9.75 Hz, 1 H, H_4), 5.38 (d, J = 3.75 Hz, 1 H, H_1), 5.53 (t, J = 9.5 Hz, 1 H, H_3), 5.93 (t, J = 11 Hz, 1 H, $H_{2'}$), 6.20 (dt, J = 16.5, 10.5, 10.5 Hz, 1 H, $H_{3'}$), 6.51 (d, J = 11 Hz, 1 H, $H_{1'}$), 7.32 (m, 5 H, Ph). Anal. Calcd for $C_{23}H_{28}O_9$: C : 61.59 H : 6.29 O : 32.11; found : C :61.44 H : 6.07 O : 31.99.

(E)(2-methyl-prop-2-enal)3-yl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (aldehyde **30**).

A solution of acetobromoglucose (16.7 g, 40.6 mmol) and the sodium salt of 2-methylmalonaldehyde[16] (9 g, 83 mmol) in anhydrous DMSO (100 mL) was stirred for 1.5 h at room temperature. The reaction mixture was then diluted with water, and extracted with Et_2O-CH_2Cl_2 (9:1, 2 x 200 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. Crystallization (CH_2Cl_2-Et_2O) afforded 8.1 g (48%) of aldehyde **30**.

30 : m.p. 155-156°C $[\alpha]_D^{20}$ -21° (c 1.5, CH_2Cl_2); ^1H NMR ($CDCl_3$, 250 MHz) δ 1.68 (d, J = 1 Hz, 3 H, Me), 2.05, 2.06, 2.08 and 2.10 (4 s, 12 H, 4 Ac), 3.88 (ddd, J = 9.5, 4.2, 2 Hz, 1 H, H_5), 4.18 (dd, J = 12.5, 2 Hz, 1 H, H_6), 4.32 (dd, J = 12.5, 4.2 Hz, 1 H, $H_{6'}$), 5.02 (d, J = 7 Hz, 1 H, H_1), 5.15-5.30 (m, 3 H, H_2, H_3, H_4), 7.13 (brs, 1 H, $H_{3'}$), 9.31 (s, 1 H, $H_{1'}$). Anal. Calcd for $C_{18}H_{24}O_{11}$: C: 51.92, H : 5.81, O : 42.27; found : C : 51.88, H : 5.98, O : 42.54.

(E)2-methyl-buta-1,3-dienyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (diene **31**).

Following the general procedure for Wittig olefination at -78°C, **30** (0.21 g, 0.5 mmol) in THF (7 mL) was treated with methylene triphenylphosphorane (0.72 mmol) to give 0.153 g (74%) of the crystalline (CH_2Cl_2-Et_2O-hexane) β diene **31**.

31 : m.p. 120.5-122°C $[\alpha]_D^{20}$ -28° (c 1, CH_2Cl_2); ^1H NMR ($CDCl_3$, 250 MHz) δ 1.68 (d, J = 1 Hz, 3 H, Me), 2.03, 2.04, 2.06 and 2.18 (4 s, 12 H, 4 Ac), 3.78 (ddd, J = 9.5, 4, 2.2 Hz, 1 H, H_5), 4.13 (dd, J = 13, 2.2 Hz, 1 H, H_6), 4.30 (dd, J = 13.4 Hz, 1 H, $H_{6'}$), 4.76 (d, J = 7.8 Hz, 1 H, H_1), 4.93 (d, J = 10.5 Hz, 1 H, $H_{4''}$), 5.09 (d, J = 17 Hz, 1 H, $H_{4'}$), 5.10-5.30 (m, 3 H, H_2, H_3, H_4), 6.24 (dd, J = 17, 10.5 Hz, 1 H, $H_{3'}$), 6.38 (brs, 1 H, $H_{1'}$). Anal. Calcd for $C_{19}H_{26}O_{10}$: C : 55.07, H : 6.32, O : 38.61; found : C : 55.16, H : 6.55, O : 38.85.

(E)2-methyl-buta-1,3-dienyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside (diene **32**).

Following the general procedure for Wittig olefination at room temperature, **30** (0.21 g, 0.5 mmol) in THF (7 mL) was treated with methylene triphenylphosphorane (0.72 mmol) to give 0.048 g (23%) of the crystalline (Et_2O-hexane) α diene **32** and 0.122 g (59%) of the β diene **31**.

32 : m.p. 68.5-69.5°C $[\alpha]_D^{20}$ +149° (c 1, CH_2Cl_2); ^1H NMR ($CDCl_3$, 250 MHZ) δ 1.81 (d, J = 1.5 Hz, 3 H, Me), 2.035, 2.05, 2.07 and 2.08 (4 s, 12 H, 4 Ac), 3.99 (ddd, J = 10, 4, 2.2 Hz, 1 H, H_5), 4.10 (dd, J = 12, 2.2 Hz, 1 H, H_6), 4.25 (dd, J = 12, 4 Hz, 1 H, $H_{6'}$), 4.96 (dd, J = 9.5, 3.6 Hz, 1 H, H_2), 4.97 (d, J = 10 Hz, 1 H, $H_{4''}$), 5.10 (t, J = 9.5 Hz, 1 H, H_4), 5.11 (d, J = 17 Hz, 1 H, $H_{4'}$), 5.33 (d, J = 3.6 Hz, 1 H, H_1), 5.55 (t, J = 10 Hz, 1 H, H_3), 6.26 (dd, J = 17, 10 Hz, 1 H, $H_{3'}$), 6.30 (brs, 1 H, $H_{1'}$). Anal. Calcd for $C_{19}H_{26}O_{10}$: C: 55.07, H : 6.32, O : 38.61; found : C : 55.11, H : 6.31, O : 38.71.

General procedure for aqueous cycloadditions.

To a 0.1-0.5 M solution of water-soluble diene in water was added 4 equivalents of methacrolein. After a few hours (3.5-20), the mixture was evaporated and used without further purification either for peracetylation, or reduction followed by hydrogenation.

General procedure for peracetylation of adduct mixtures.

The mixture of adducts directly obtained from evaporation of the water solution is stirred overnight at room temperature in a 2:1 mixture of pyridine - Ac_2O (the reaction is conducted at a c.a. 0.1 M concentration). Coevaporation with toluene afforded a residue which was analyzed by ^1H NMR spectroscopy.

General procedure for reduction and hydrogenation of adducts mixtures.

The crude mixture of adducts of aqueous cycloaddition was treated with $NaBH_4$ (1.25 eq) in 95% aqueous ethanol at room temperature. After 15 min, evaporation provided a residue which was chromatographed on a silica gel column (AcOEt-iPrOH-H_2O, 47:2:1) to give a mixture of the reduced adducts in c.a. 90% yield. This mixture was then hydrogenated (Pd/C 10%, H_2 7 atm, r.t., 24 h, 0.1 M in EtOH). Filtration through a 2 in. plug of celite gave quantitatively hydrogenated and debenzylated adducts. These mixtures were analyzed without further purification by analytical HPLC (C_{18}, H_2O-MeOH, 70:30).

General procedure for the obtention of diols 35 (cis) and 36 (trans).

A 0.2 M solution of the crude mixture of reduced and hydrogenated adducts in 1 N H_2SO_4 was stirred 5 h at 100°C. After neutralization with $KHCO_3$ (10%), the solution was extracted with AcOEt (6 x 30 mL). The combined organic layers were washed with water, dried (Na_2SO_4) and evaporated. Silica gel chromatography (Et_2O-hexane, 2:1) provided a mixture of cis and trans diols **35** and **36** already described[1b] which was analyzed by ^1H and ^{13}C NMR spectroscopy.

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