

Synthesis of C-Glycosides and C-Disaccharides using Mukaiyama Aldol Reaction in Aqueous Media

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Abstract: We describe here a new strategy for the preparation of C-glycosides and C-disaccharides in the aqueous phase using the Mukaiyama aldol reaction. We first studied the reaction between formyl-2,3,4,6-tetra-*O*-benzyl- β -D-glucopyranoside **1** and the trimethylsilyl enol ether **2** derived from acetophenone. Using Yb(OTf)₃ (10 mol%) as catalyst in a mixture of THF/water at room temperature, the enol adducts were isolated in a high (90%) yield but with a moderate diastereoselectivity. The reaction can also be performed in pure THF leading to a single

diastereoisomer but in a much lower yield (56%). The aldol reaction was then applied to the synthesis of C-disaccharides using the trimethylsilyl enol ether **10** derived from the functionalized ketone **9**. In both the aqueous phase and in anhydrous THF, the reaction can be achieved in high yields giving in each case only two aldol products out of the four possible diastereoisomers.

Keywords: aldol reaction; chemistry in water; C-glycosides; silyl enol ethers; ytterbium

Introduction

C-Glycosides, in which the *exo*-anomeric oxygen atom is replaced by a methylene group, have been the subject of considerable interest in carbohydrate chemistry.^[1] These carbohydrate mimetics, which possess an improved stability toward acid, base, and enzymatic hydrolysis, may display interesting biological activity. Indeed, they may serve as regulators of enzymes (glycosidases and glycosyltransferases that are potential anti-cancer, antiviral, or antidiabetic agents) or as artificial ligands that can be useful in probing cellular interactions. Moreover, despite structural investigations that revealed, most of the time, notable conformational differences between the natural and unnatural glycosides,^[2] a number of studies has shown that the biological properties of C-glycosides are retained and sometimes are even greater.^[3] Consequently, a wide variety of synthetic strategies has been developed for the attachment of carbon-based groups to the anomeric position, in particular in regard to the synthesis of C-disaccharides.^[4,5] For our part, we envisaged a novel approach for the preparation of these compounds using the Mukaiyama aldol reaction in

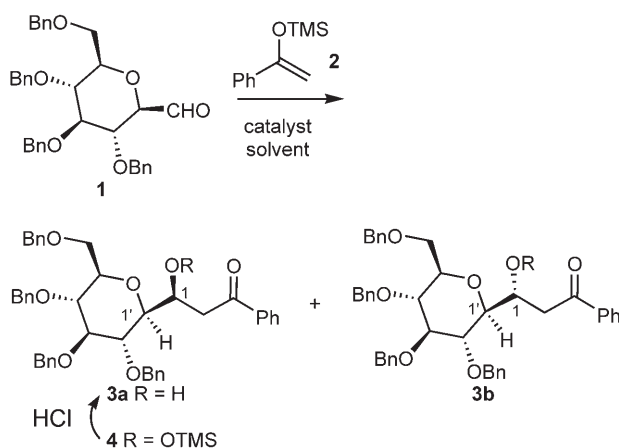
aqueous media between a 1-formyl-C-glycoside for which we have recently reported a convenient approach^[6] and a silyl enol ether. The aldol reaction using silyl enol ethers has been widely used for highly efficient and stereoselective C–C bond formation.^[7] In organic solvents a variety of conditions, particularly the use of Lewis acids or high pressure, are known to promote the nucleophilic process. However, one of us has shown several years ago that the reaction can be performed in water or mixed aqueous solvent without a catalyst, in totally neutral conditions but in moderate yields.^[8] More recently, Kobayashi and co-workers have considerably improved the reaction^[9] in aqueous conditions by showing that water-tolerant Lewis acids, such as Sc(OTf)₃, Y(OTf)₃, lanthanide triflates and salts of Fe(II), Cu(II), Zn(II) and Pb(II) are efficient catalysts and give, in some cases, near quantitative yields of aldol products.^[10] The benefits gained by using such aqueous catalytic systems include easy recovery of the active Lewis acid catalyst,^[11] decreased cost and increased safety. Moreover, water has unique physical and chemical properties such as a high dielectric constant and a high energy density compared

with most organic solvents that allow one to obtain different reactivity and selectivity.^[12]

Results and Discussion

Reaction with the Trimethylsilyl Enol Ether 2 Derived from Acetophenone

We examined first the reaction of the trimethylsilyl enol ether **2** derived from acetophenone with formyl-2,3,4,6-tetra-*O*-benzyl- β -D-glucopyranoside **1**^[6] prepared in a few steps from D-glucose (50% overall yield) (Scheme 1, Table 1). In a preliminary study, we



Scheme 1. Mukaiyama aldol condensation between aldehyde **1** and the trimethylsilyl enol ether **2**.

tested a few of the catalysts described for their efficiency in the Mukaiyama aldol reaction in aqueous media. We first examined the reaction in pure water and we tested $\text{Sc}(\text{DS})_3$ (DS: dodecyl sulfate),^[13] FeCl_3 ^[14] or InCl_3 ^[15] that are known to favorably affect the Mukaiyama aldol reaction in this particular solvent (entries 1, 2, 3). However, in all cases, only traces of the desired aldol compounds were observed. The boron enolate system reported recently by Kobayashi et al. was also tried.^[16] With a catalytic amount of diphenylborinic acid in the presence of a surfactant (SDS) and a Brønsted acid (PhCO_2H), the reaction led to the aldol adducts in 5% yield (entry 4). We then tested $\text{Yb}(\text{OTf})_3$ ^[9] in a mixture of THF/water (4/1) (entry 5). The reaction was carried out with 10 mol% of the catalyst at room temperature and two diastereoisomers **3a** and **3b** were isolated in a 65/35 ratio and in a moderate 42% yield. With $\text{Sc}(\text{OTf})_3$ ^[11b] similar results could be attained (entry 6) but the reaction has to be carried out not only at 65°C but also with a high catalyst loading (20 mol%). We also examined CeCl_3 in a mixture of *i*-PrOH/water (19/1) as described by Juaristi et al.^[17] and the aldol adducts were obtained in a poor 18% yield (entry 7).

From these results, we decided to optimize the reaction conditions with $\text{Yb}(\text{OTf})_3$. As described in entry 5, the reaction was carried out at room temperature with 10 mol% of the catalyst in THF/water. In this case, the reaction was run at a concentration of 0.08M of aldehyde and a large excess of the enol

Table 1. Mukaiyama aldol condensation between aldehyde **1** and enol ether **2** or **10** under various conditions.

Entry	Enol ether (equivs.)	Catalyst (mol%)	Solvent	T [°C], [aldehyde] ($\text{mol}\cdot\text{L}^{-1}$)	Yield [%] ^[a]	<i>dr</i> ^[b]
1	2 (10)	$\text{Sc}(\text{DS})_3$ (20)	H_2O	65, 0.08	traces	–
2	2 (10)	FeCl_3 (10) ^[d]	H_2O	65, 0.08	traces	–
3	2 (3)	InCl_3 (20)	H_2O	rt, 0.16	traces	–
4	2 (10)	Ph_2BOH (10) ^[e]	H_2O	65, 0.16	5	63/37
5	2 (5)	$\text{Yb}(\text{OTf})_3$ (10)	THF/ H_2O	rt, 0.08	42	65/35
6	2 (5)	$\text{Sc}(\text{OTf})_3$ (20)	THF/ H_2O	65, 0.08	42	65/35
7	2 (10)	CeCl_3 (20)	<i>i</i> PrOH/ H_2O	rt, 0.07	18	63/37
8	2 (5)	$\text{Yb}(\text{OTf})_3$ (20)	THF/ H_2O	rt, 0.08	54	68/32
9	2 (5)	$\text{Yb}(\text{OTf})_3$ (30)	THF/ H_2O	rt, 0.08	68	67/33
10	2 (3)	$\text{Yb}(\text{OTf})_3$ (10)	THF/ H_2O	rt, 0.16	90	60/40
11	2 (2)	$\text{Yb}(\text{OTf})_3$ (10)	THF/ H_2O	rt, 0.16	83	65/35
12	2 (3)	$\text{Yb}(\text{OTf})_3$ (5)	THF/ H_2O	rt, 0.16	25	63/37
13	2 (3)	$\text{Yb}(\text{OTf})_3$ (10)	THF	rt, 0.16	56 ^[c]	> 95/5
14	10 (3)	$\text{Yb}(\text{OTf})_3$ (10)	THF/ H_2O	rt, 0.16	55	59/41
15	10 (3)	$\text{Yb}(\text{OTf})_3$ (10)	THF/ H_2O	rt, 0.16	95	59/41
16	10 (3)	$\text{Yb}(\text{OTf})_3$ (20)	THF	rt, 0.16	72 ^[c]	56/44

^[a] Isolated yield following chromatography.

^[b] Determined by ^1H and ^{13}C NMR spectroscopy.

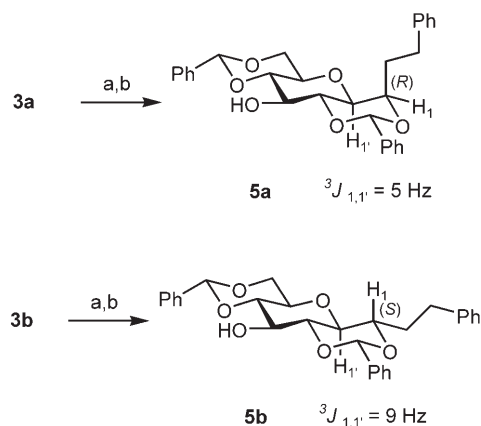
^[c] After acidic treatment.

^[d] The reaction was performed in the presence of sodium dodecyl sulfate (10%) and NaOH (10%).

^[e] The reaction was performed in the presence of sodium dodecyl sulfate (10%) and benzoic acid (1%).

ether **2** (5 equivalents) was necessary to lead to **3a** and **3b** in a moderate yield (42%) that could not be improved at a higher temperature (65°C) or by using sonication.^[8] However, a higher catalyst loading (entries 8 and 9) allowed us to reach yields of up to 68%. The optimal conditions were found when the reaction was carried out at a concentration of 0.16M of aldehyde (entry 10). In this case, 3 equivalents of the enol ether **2** and 10 mol% of Yb(OTf)₃ were required to lead to a mixture of **3a** and **3b** in a 60/40 ratio and 90% yield. The reaction carried out with 2 equivalents of **2** led also to a good 83% yield (entry 11). However, with less catalyst (5 mol%, entry 12) and 3 equivalents of **2**, a poor 25% yield was obtained. For comparison, the same reaction was also performed in pure THF (entry 13). In this case, using 10 mol% of the catalyst and 3 equivalents of **2**, the reaction led to **3a** (in mixture with its *O*-silylated form **4**) as a single diastereoisomer (>95/5) that gave after acidic treatment pure **3a** but in a much lower yield (56%).

In order to determine the absolute configuration of the newly formed stereocenter C-1 in **3a** and in **3b**, the two compounds were independently hydrogenated in the presence of palladium on charcoal in a mixture of EtOH/EtOAc (Scheme 2). The two compounds ob-



Scheme 2. Determination of the absolute configuration of the C-1 center in **3a** and **3b**. *Reagents and conditions:* a) H₂, Pd/C, EtOH/EtOAc. b) PhCH(OMe)₂, CH₃CN, TsOH (**5a**, 55% for 2 steps, **5b**, 77% for 2 steps).

tained were then directly protected with benzylidene groups using benzaldehyde dimethyl acetal in acetonitrile in the presence of a catalytic amount of *p*-toluenesulfonic acid to give **5a** and **5b**. It is worth to be noticed that, under the conditions of the hydrogenolysis step, the carbonyl function α to the phenyl group was also reduced.^[18] The absolute configuration of the C-1 could therefore be deduced from an analysis of the ¹H NMR spectra. Indeed, for **5a**, the coupling constant ³*J*_{1,1'} = 5.0 Hz indicates a *cis* relationship be-

tween H-1' and H-1. Moreover, for **5b** the coupling constant ³*J*_{1,1'} = 9.0 Hz indicates a *trans* diaxial orientation between H-1' and H-1. This implies that the absolute configuration of C-1 for the major aldol adduct **3a** is (*R*) and for the minor **3b**, (*S*).

The better diastereoselectivity observed in pure THF may result from the Cram cyclic chelated model showed in Figure 1.^[7b-c,19] According to this model,

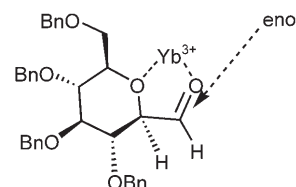


Figure 1. The Cram chelated transition state.

the ytterbium atom may coordinate the carbonyl group and the endocyclic α -oxygen atom of the sugar moiety. Subsequent attack of the nucleophile from the sterically less hindered side of the carbonyl group leads to the predominant formation of the (*R*) isomer **3a**. In contrast, the lower diastereoselectivity observed in the aqueous reaction can presumably be explained by the ratio of chelation-controlled to non-chelation-controlled attack of the nucleophile. Indeed, the presence of water, which is a stronger donor solvent may interfere with the formation of the chelate complex, which is a prerequisite for a high chelation-controlled diastereoselection. In this case, the formation of the minor adduct **3b** may be explained by the Felkin–Anh model depicted in Figure 2.

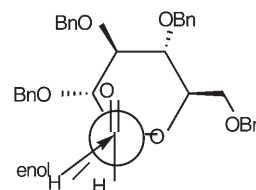
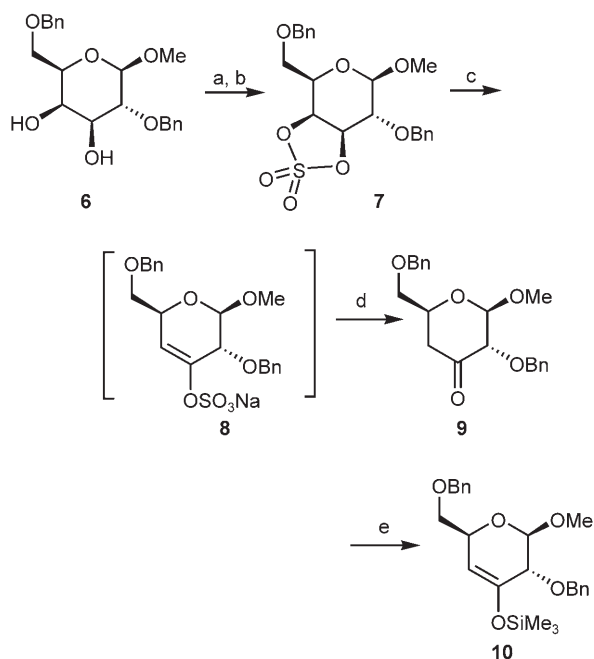


Figure 2. The non-chelated Felkin–Anh model.

Synthesis of C-Disaccharides

The Mukaiyama aldol reaction was then extended to the trimethylsilyl enol ether **10** that should lead to the synthesis of β -(1 $\rightarrow$ 4)-*C*-linked disaccharides. This enol ether **10** derived from ketone **9** can be synthesized from the easily available methyl 2,6-di-*O*-benzyl- β -D-galactopyranoside **6**^[20] (Scheme 3). The diol **6** was first treated with thionyl chloride and triethylamine in dichloromethane to furnish cyclic sulfites as a mixture of diastereoisomers. This step was directly followed by the oxidation procedure described by Gao and Sharpless using the NaIO₄-RuCl₃·H₂O



Scheme 3. Synthesis of the enol ether **10**. *Reagents and conditions:* a) SOCl_2 , NEt_3 , CH_2Cl_2 , 0°C . b) $\text{RuCl}_3 \cdot \text{H}_2\text{O}$ (cat.), NaIO_4 , $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (2/2/3) (**7**, 84% for 2 steps). c) NaOH 10M, DMF, 70°C . d) H_2SO_4 (**9**, 67%). e) LDA , TMSCl , THF, -78°C .

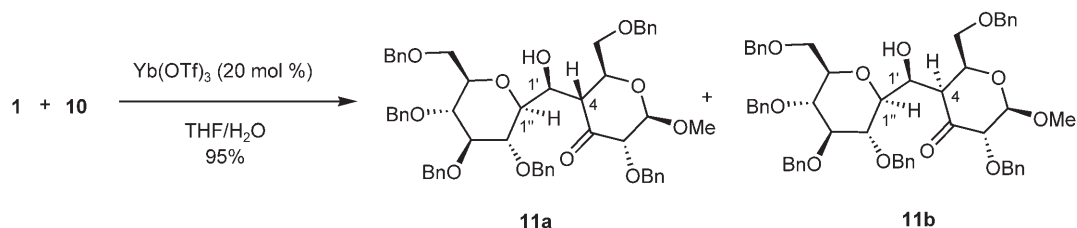
system.^[21] The 3,4-cyclic sulfate **7** obtained in 84% yield was then treated with aqueous sodium hydroxide (10M) in DMF at 70°C .^[22] The elimination process that results from deprotonation at C-3 gave the vinylic sulfate **8** which was hydrolyzed to the corresponding ketone **9** in 67% yield. The kinetic enol ether **10** was then obtained after reaction of LDA in the presence of TMSCl at -78°C in THF. After work-up, **10** was obtained quantitatively and was used without further purification.

We first carried out the aldol condensation between **10** and **1** in aqueous phase using the best conditions that we found previously (Scheme 4, Table 1, entry 14). With 3 equivalents of the enol ether **10** and 10 mol% of $\text{Yb}(\text{OTf})_3$, a mixture of only two aldol adducts **11a** and **11b** in a 59/41 ratio was obtained out of the four possible diastereoisomers but in a moderate 55% yield. However, a higher catalyst loading (20

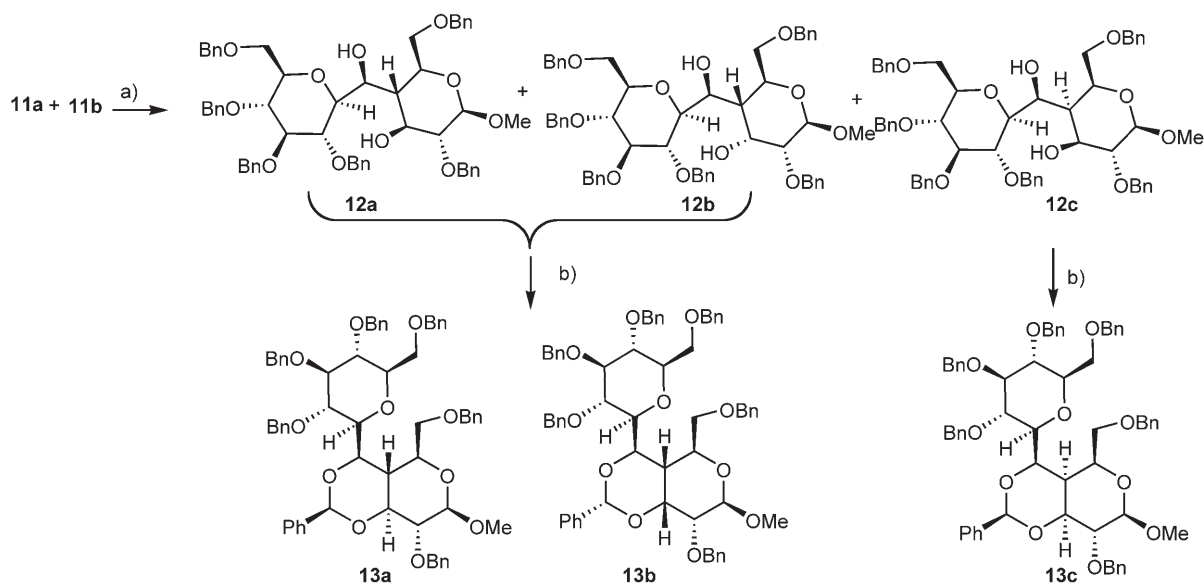
mol%) allowed us to obtain **11a** and **11b** in 95% yield (entry 15). For comparison, the reaction was also conducted in pure THF (entry 16). Using the same conditions (20 mol% of $\text{Yb}(\text{OTf})_3$ and 3 equivalents of **10**), the two enol adducts were obtained in a slightly decreased 72% yield. In this case, compared with the use of water, a similar diastereoselectivity was obtained in contrast to what was observed in the previous case with enol ether **2**.

As we could not separate the two diastereoisomers at this stage, we were not able to determine directly the absolute configuration of the two newly formed stereocenters C-4 and C-1' in **11a** and **11b**. This problem was resolved after treatment of these compounds with sodium borohydride in MeOH at 0°C that led to a mixture of the three diols **12a**, **12b** and **12c** in 94% yield (Scheme 5). After flash chromatography, only **12c** could be separated and was treated with benzaldehyde dimethyl acetal in acetonitrile in the presence of a catalytic amount of *p*-toluenesulfonic acid to give the benzylidene derivative **13c**. The same reaction was carried out with the mixture of **12a** and **12b** to afford the desired separable benzylidene derivatives **13a** and **13b**.

From these three compounds, we could deduce the stereoselectivity of the Mukaiyama aldol reaction between the formyl-2,3,4,6-tetra-*O*-benzyl- β -D-glucopyranoside **1** and the trimethylsilyl enol ether **10** derived from ketone **9** (Figure 3). The stereochemistry of **13a** was assigned on the basis of 3J values ($^3J_{4,1'}=10$, $^3J_{4,5}=10$ and $^3J_{4,3}=10$ Hz) and strong NOE effects between H-1' and both H-3 and the hydrogen atom H-2' of the benzylidene group. From these data, we can conclude that, for this compound, the alkylation at C-4 operated in an equatorial orientation with the C-1' (*R*) configuration. For **13b**, the coupling constants $^3J_{4,5}=10$ Hz, $^3J_{4,3}=2$ Hz and $^3J_{3,2}=2$ Hz indicate an axial H-4 and an equatorial H-3. Moreover, the coupling constant $^3J_{4,1'}=0$ Hz and a NOE effect observed between the hydrogen atom H-2' of the benzylidene group and H-3 but not with H-1' indicate again that the alkylation at C-4 operated in an equatorial orientation with the C-1' (*R*) configuration. These results show that **13a** and **13b** come from the same aldol product **11a**. However, for this compound the reduction of the ketone function is not stereose-



Scheme 4. Synthesis of *C*-disaccharides using Mukaiyama aldol reaction in aqueous media.



Scheme 5. Chemical modifications for the determination of the stereoselectivity of the Mukaiyama aldol reaction between **1** and **10**. *Reagents and conditions:* a) NaBH_4 , MeOH (**12a**, **12b** and **12c**, 94 %). b) $\text{PhCH}(\text{OMe})_2$, TsOH cat. CH_3CN (71 % for **13a** and **13b** and 23 % for **13c**).

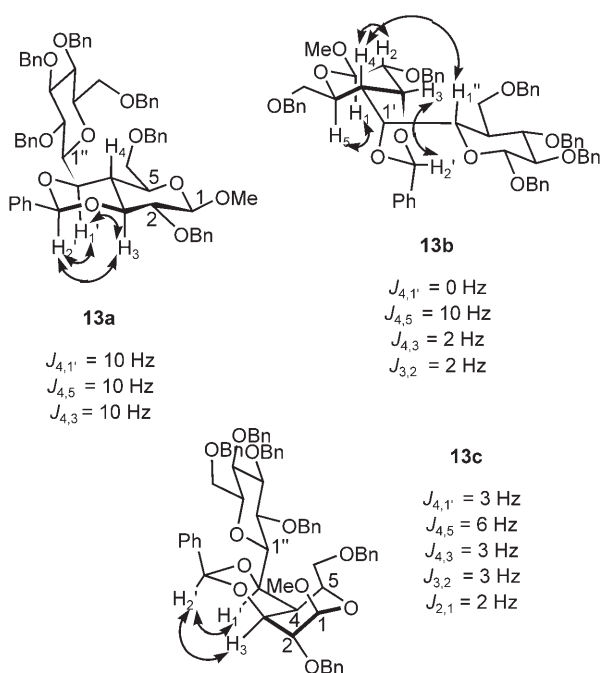


Figure 3. Selected ^1H NMR data and NOEs for **13a**, **13b** and **13c**.

lective leading to the two *C*-disaccharide derivatives [D-Glc- β -(1 $\rightarrow$ 4)-C-D-Glc] **12a** and [D-Glc- β -(1 $\rightarrow$ 4)-C-D-All] **12b** in a 55/45 ratio that can be explain by similarly hindered faces of the ketone, flanked with two equatorial substituents at α -positions on both sides. The stereochemistry of **13c** was also assigned by ^1H NMR analysis. According to the 3J values observed ($^3J_{2,1}=2$, $^3J_{2,3}=3$ and $^3J_{4,3}=3 \text{ Hz}$), the terminal

six-membered ring of **13c** adopts an unusual $^1\text{C}_4$ conformation having H-4 in an axial position and H-3 in an equatorial one. In the six-membered ring formed by the benzylidene derivative, the phenyl group and the glycosyl group coming from the aldehyde, are in equatorial positions. This is confirmed by a strong NOE effect observed between the proton H-2' of the benzylidene group and both H-3 and H-1' that indicate that the absolute configuration of C-1' is (*R*). These results show that **13c** comes from **11b**, i.e., that the alkylation at C-4 operated in an axial orientation. For **11b**, the reduction of the ketone by NaBH_4 is stereoselective, probably because the β face of the ketone is more hindered due to the presence of an axial substituent at C-4 and lead to the *C*-disaccharide derivative [D-Glc- β -(1 $\rightarrow$ 4)-C-D-Gal] **12c**.

In order to confirm the conformation found experimentally for **13c**, different molecular models have been realized.^[23] Whatever the level of calculation, molecular mechanics or semi-empirical calculations, the $^1\text{C}_4$ conformation of the terminal six-membered ring is much more stable than the $^4\text{C}_1$ conformation (10 kcal using MM+ force field). It is also worth noting that the $\langle\text{H}_5\text{C}_5\text{C}_4\text{H}_4\rangle$ dihedral angle is smaller than the other $\langle\text{HCCH}\rangle$ dihedral angles of this ring. For example, with semi-empirical calculation using the AM1 basis, $\langle\text{H}_5\text{C}_5\text{C}_4\text{H}_4\rangle$ dihedral angle was found to be equal to 45° comparing to 56° for the $\langle\text{H}_1\text{C}_1\text{C}_4\text{H}_4\rangle$ dihedral angle. This small value can therefore explain the unusual $^3J_{4,5}=6 \text{ Hz}$ obtained for an axial-equatorial coupling.

Concerning the selectivity of the Mukaiyama reaction between the aldehyde **1** and the sterically hin-

dered enol ether **10**, in the aqueous phase as in anhydrous THF, in contrast to what happened with the smaller enolate **2**, the total selectivity at the C-1' center may be explained by the chelated model depicted in Figure 1, which by far is less sterically demanding than the non-chelated model of Figure 2. In contrast, a low degree of diastereoselection is observed in the C-4 alkylation. This may be attributed to a poor steric control induced by the substituents next to the reactive center (at C-6 and C-2 positions). Thus, the attack of the electrophile could not be preferentially directed to one of the π -faces of the enolate system and therefore yields both equatorial and axial isomers in a 59/41 ratio.

Conclusions

In this paper, we showed that the Mukaiyama aldol reaction in the aqueous phase can be efficiently applied to the preparation of C-glycosides and C-disaccharides starting from easily available formyl-2,3,4,6-tetra-O-benzyl- β -D-glucopyranoside **1**. A first study was carried out with the trimethylsilyl enol ether **2** derived from acetophenone. The best conditions were found using Yb(OTf)₃ (10 mol %) as catalyst in a mixture of water/THF at room temperature leading to the enol adducts in high yield (90 %) but in a moderate diastereoselectivity. The reaction can also be performed in anhydrous THF affording only one diastereoisomer but in a strongly decreased 56 % yield. The aldol reaction was then applied to the synthesis of C-disaccharides using the trimethylsilyl enol ether **10** derived from ketone **9**. In this case, a higher catalyst loading (20 mol %) is needed to reach a high 95 % yield and, in THF as in the aqueous phase, only two enol adducts are obtained out of the four possible diastereoisomers. After chemical modification, we determined the absolute configuration of these two adducts and showed that there is a total selectivity for the nucleophilic attack onto the aldehyde, and a lack of stereoselectivity at the alkylated carbon of the enolate system. With this methodology and after reduction with sodium borohydride, we could access to the three C-disaccharides derivatives [D-Glc- β -(1 $\rightarrow$ 4)-C-D-Glc] **12a**, [D-Glc- β -(1 $\rightarrow$ 4)-C-D-All] **12b** and [D-Glc- β -(1 $\rightarrow$ 4)-C-D-Gal] **12c**. Work is currently in progress in our laboratory to extend this methodology to other enol ethers derived from other sugar moieties.

Experimental Section

All moisture-sensitive reactions were performed under argon using oven-dried glassware. Whenever necessary, solvents were dried and distilled prior to use. Reactions were monitored on TLC (silica gel 60 F₂₅₄). Detection was per-

formed using UV light and/or 5 % sulfuric acid in ethanol, followed by heating. Flash chromatography was performed on silica gel 6–35 μ m.

Synthesis of 1(R)- and 1(S)-1-(2',3',4',6'-Tetra-O-benzyl- β -D-glucopyranosyl)-1-hydroxy-3-phenylpropan-3-one (**3a** and **3b**) using Mukaiyama Aldol Condensation in the Aqueous Phase

To a solution of the aldehyde **1** (140 mg, 0.25 mmol) in a mixture of H₂O/THF (0.3/1.25 mL) was added ytterbium triflate (15 mg, 0.025 mmol) and the silyl enol ether **2** of acetophenone (450 mg, 0.75 mmol). After stirring for one week at room temperature, THF was evaporated and water (10 mL) was added. The aqueous phase was extracted with ethyl acetate (3 $\times$ 10 mL). The combined organic layers were washed with brine (2 $\times$ 10 mL), dried (MgSO₄), filtered and concentrated. Flash chromatography of the crude residue on silica gel (petroleum ether/ethyl acetate = 8/2 to 7/3) gave **3a** (90 mg, 54 %) and **3b** (60 mg, 36 %).

1(R)-1-(2,3',4',6'-Tetra-O-benzyl- β -D-glucopyranosyl)-1-(trimethylsilyl)hydroxy-3-phenylpropan-3-one (**4**)

To a solution of the aldehyde **1** (200 mg, 0.362 mmol) in THF (2.25 mL) was added ytterbium triflate (22 mg, 0.0362 mmol) and the silyl enol ether **2** (209 mg, 1.09 mmol). After stirring for 3 h at room temperature, saturated aqueous NaHCO₃ solution (10 mL) was added and the aqueous phase was extracted with ethyl acetate (3 $\times$ 10 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated. Flash chromatography of the crude residue on silica gel (petroleum ether/ethyl acetate = 8/2 to 7/3) gave **4a** (100 mg, 37 %) and **3a** (46 mg, 19 %).

1(R)-1,2'-O-Benzylidene-1-(4',6'-O-benzylidene- β -D-glucopyranosyl)-1-hydroxy-3-phenylpropane (**5a**)

To a solution of **3a** (100 mg, 0.15 mmol) in a mixture of ethyl acetate/ethanol (1/2, 1.5 mL) was added palladium on charcoal (50 mg). The reaction mixture was stirred for 2 h under a hydrogen atmosphere. After filtration on celite and concentration, the crude residue was dissolved in acetonitrile (1 mL) and benzaldehyde dimethyl acetal (90 μ L, 0.6 mmol) and a catalytic amount of *para*-toluenesulfonic acid (3 mg) were added. After stirring for 1 h at room temperature, the reaction mixture was neutralized with a saturated aqueous NaHCO₃ solution. After addition of water (10 mL), the aqueous phase was extracted with ethyl acetate (3 $\times$ 10 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated. The pure product **5a** (39 mg, 55 %) was obtained after flash chromatography on silica gel (petroleum ether/ethyl acetate = 8/2).

1(S)-1,2'-O-Benzylidene-1-(4',6'-O-benzylidene- β -D-glucopyranosyl)-1-hydroxy-3-phenylpropane (**5b**)

To a solution of **3b** (100 mg, 0.15 mmol) in a mixture of ethyl acetate/ethanol (1/2, 1.5 mL) was added palladium on charcoal (50 mg). After stirring for 2 h under a hydrogen atmosphere, the reaction mixture was filtered and concentrat-

ed. To a solution of the crude residue in acetonitrile (1 mL) were added benzaldehyde dimethyl acetal (90 μ L, 0.6 mmol) and a catalytic amount of *para*-toluenesulfonic acid (3 mg). After stirring for 1 h at room temperature, the reaction mixture was neutralized with a saturated aqueous NaHCO₃ solution. After addition of water (10 mL), the aqueous phase was extracted with ethyl acetate (3 $\times$ 10 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated. The pure product **5b** (77%) was obtained after flash chromatography on silica gel (petroleum ether/ethyl acetate = 8/2).

Methyl 2,6-Di-*O*-benzyl-3,4-sulfuryl- β -D-galactopyranoside (**7**)

To a cooled (0°C) solution of methyl 2,6-*O*-benzyl- β -D-galactopyranoside (**6**; 7 g, 19 mmol) and triethylamine (10.4 mL, 75 mmol) in dichloromethane (37 mL) was added dropwise, over a period of 10 min, a solution of thionyl chloride (2 mL, 28 mmol) in dichloromethane (13 mL). After stirring for 20 min at 0°C, water (100 mL) was added and the aqueous phase was extracted with dichloromethane (3 $\times$ 100 mL). The combined organic layers were washed with water (2 $\times$ 100 mL), brine (2 $\times$ 100 mL) and dried (MgSO₄). After filtration and concentration, the crude residue was dissolved in a mixture of CHCl₃/CH₃CN/H₂O (1/1/1.5, 91 mL) and the solution was cooled to 0°C. Ruthenium trichloride (80 mg, 0.4 mmol) and sodium periodate (8 g, 38 mmol) were added and the solution was stirred for one hour at 0°C. After dilution with dichloromethane (150 mL), the solution was filtered on celite. Water (150 mL) was added and the product was extracted with dichloromethane (3 $\times$ 100 mL). The combined organic layers were washed with a saturated aqueous NaHCO₃ solution (150 mL), brine (150 mL), then dried (MgSO₄), filtered and concentrated. After flash chromatography on silica gel (petroleum ether/ethyl acetate = 8/2), the pure product **7** (7 g, 84%) was obtained as a white solid.

Methyl 2,6-Di-*O*-benzyl-4-deoxy- β -D-erythro-hexopyranosid-3-ulose (**9**)

To a solution of the cyclic sulfate **7** (3.7 g, 8.5 mmol) in DMF (146 mL) was added aqueous NaOH (10M, 7.3 mL, 73 mmol). After stirring for 2 h at 70°C, the reaction mixture was cooled to 0°C before addition of concentrated sulfuric acid until pH 1. After stirring overnight, water (100 mL) was added and the aqueous phase was extracted with ethyl acetate (3 $\times$ 150 mL). The combined organic layers were washed with water (3 $\times$ 150 mL), brine (3 $\times$ 150 mL), then dried (MgSO₄), filtered and concentrated. The ketone **9** (2.02 g, 67%) was obtained as a colorless oil after flash chromatography (petroleum ether/ethyl acetate = 8/2).

Methyl 2,6-Di-*O*-benzyl-4-deoxy-3-trimethylsilyloxy- β -D-erythro-hex-3-enopyranoside (**10**)

To a solution of diisopropylamine (0.52 mL, 3.75 mmol) in THF (7 mL) at 0°C, was added dropwise *n*BuLi (1.6 N in hexane, 2.5 mL, 3.75 mmol). After stirring for 30 min at 0°C, the reaction mixture was cooled to -78°C and TMSCl (0.5 mL, 3.75 mmol) then a solution of ketone **9** (0.9 g,

2.5 mmol) in THF (4 mL) were added. After stirring for 40 min at -78°C, a saturated aqueous NaHCO₃ (10 mL) was added and the aqueous phase was extracted with pentane (3 $\times$ 10 mL). The combined organic layers were washed with brine (2 $\times$ 10 mL), then dried (MgSO₄), filtered and concentrated to afford crude enoxysilane **10**, which was used without further purification.

Methyl 2,6-Di-*O*-benzyl-4-deoxy-4-*C*-[1'(*R*)-1'-(2'',3'',4'',6''-tetra-*O*-benzyl- β -D-glucopyranosyl)-1'-hydroxymethyl]- β -D-ribo-hexapyranosid-3-ulose (**11a**) and Methyl 2,6-Di-*O*-benzyl-4-deoxy-4-*C*-[1'(*R*)-1'-(2'',3'',4'',6''-tetra-*O*-benzyl- β -D-glucopyranosyl)-1'-hydroxymethyl]- β -D-xylo-hexapyranosid-3-ulose (**11b**)

To a solution of aldehyde **1** (246 mg, 0.45 mmol) and ytterbium triflate (56 mg, 0.09 mmol) in a mixture of H₂O/THF (0.26/1.1 mL) was added the enol ether **10** (579 mg, 1.35 mmol). After 4 days at room temperature, the THF was evaporated and water (10 mL) was added. The aqueous phase was extracted with ethyl acetate (3 $\times$ 10 mL) and the combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated. The products **11a** and **11b** (390 mg, 95%) were obtained as a mixture of diastereoisomers after flash chromatography on silica gel (petroleum ether/ethyl acetate = 85/15 to 7/3).

Synthesis of Methyl 2,6-Di-*O*-benzyl-4-deoxy-4-*C*-[1'(*R*)-1'-(2'',3'',4'',6''-tetra-*O*-benzyl- β -D-glucopyranosyl)-1'-hydroxymethyl]- β -D-glucopyranoside (**12a**), Methyl 2,6-Di-*O*-benzyl-4-deoxy-4-*C*-[1'(*R*)-1'-(2'',3'',4'',6''-tetra-*O*-benzyl- β -D-glucopyranosyl)-1'-hydroxymethyl]- β -D-allopyranoside (**12b**) and Methyl 2,6-Di-*O*-benzyl-4-deoxy-4-*C*-[1'(*R*)-1'-(2'',3'',4'',6''-tetra-*O*-benzyl- β -D-glucopyranosyl)-1'-hydroxymethyl]- β -D-galactopyranoside (**12c**)

To a cooled (0°C) solution of the disaccharides **11a** and **11b** (200 mg, 0.22 mmol) in methanol (4 mL) was added sodium borohydride (18 mg, 0.44 mmol). After stirring overnight, an aqueous solution of NH₄Cl was added and the aqueous phase was extracted with ethyl acetate (3 $\times$ 10 mL). The combined organic layers were washed with brine (3 $\times$ 10 mL), dried (MgSO₄), filtered and concentrated before purification by flash chromatography on silica gel (petroleum ether/ethyl acetate = 8/2 to 7/3). Two fractions were obtained, the first one containing **12a** and **12b** (55:45, 102 mg, 51%), the second containing only compound **12c** (87 mg, 43%).

Methyl 2,6-Di-*O*-benzyl-1',3-*O*-benzylidene-4-deoxy-4-*C*-[1'(*R*)-1'-(2'',3'',4'',6''-tetra-*O*-benzyl- β -D-glucopyranosyl)-1'-hydroxymethyl]- β -D-glucopyranoside (**13a**) and Methyl 2,6-Di-*O*-benzyl-1',3-*O*-benzylidene-4-deoxy-4-*C*-[1'(*R*)-1'-(2'',3'',4'',6''-tetra-*O*-benzyl- β -D-glucopyranosyl)-1'-hydroxymethyl]- β -D-allopyranoside (**13b**)

To a solution of a mixture of disaccharides **12a** and **12b** (32 mg, 0.035 mmol) in acetonitrile (1 mL) were added ben-

zaldehyde dimethyl acetal (21 μ L, 0.14 mmol) and a catalytic amount of TsOH (1 mg). After stirring for 2 h, the solution was neutralized with saturated aqueous NaHCO_3 solution and the aqueous phase was extracted with AcOEt (3×10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Flash chromatography of the residue on silica gel (petroleum ether/ethyl acetate = 9/1 to 7/3) gave **13a** (14 mg, 40 %) and **13b** (11 mg, 31 %).

Methyl 2,6-Di-O-benzyl-1',3-O-benzylidene-4-deoxy-4-C-[1'(R)-1'-(2'',3'',4'',6''-tetra-O-benzyl- β -D-glucopyranosyl)-1'-hydroxymethyl]- β -D-galactopyranoside (13c)

To a solution of **12c** (24 mg, 0.026 mmol) in acetonitrile (1 mL) were added benzaldehyde dimethyl acetal (15 μ L, 0.14 mmol) and a catalytic amount of TsOH (1 mg). After stirring for 2 h, the solution was neutralized with saturated aqueous NaHCO_3 solution and the aqueous phase was extracted with AcOEt (3×10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Flash chromatography of the residue on silica gel (petroleum ether/ethyl acetate = 9/1 to 7/3) afforded **13c** (6 mg, 23 %).

Characterization data for all products are given in the Supporting Information.

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