DOI: 10.1002/ejoc.200900889

Reaction Kinetics and Mechanism of Sulfuric Acid-Catalyzed Acetolysis of Acylated Methyl L-Ribofuranosides

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Keywords: Carbohydrates / Acetolysis / Kinetics / Reaction mechanisms / NMR spectroscopy

The mechanism of the sulfuric acid-catalyzed acetolysis of methyl 2,3,5-tri-*O*-acetyl- and methyl 2,3,5-tri-*O*-benzoyl-L-ribofuranosides and the accompanying anomerization of both the starting material and the 1,2,3,5-tetra-*O*-acetyl- and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-L-ribofuranoses formed was investigated. The progress of the reactions was followed by ^{1}H NMR spectroscopy and the rate constants for the reactions were determined for a proposed kinetic model. The role of H^+ and Ac^+ as the catalytically active species was clarified, proving that the anomerization of the acylated methyl furanosides is activated by protonation, while, on the contrary, the anomerization of the 1-*O*-acetyl ribofuranoses is activated by the acetyl cation. The anomerization of the acylated methyl furanosides was verified to be activated on the ring oxygen leading to endocyclic CO-bond rupture while the 1-*O*-acetyl ribofuranoses are activated on the acetyloxy group on C(1) leading to exocyclic cleavage.

Introduction

Acetolysis, as one of the most fundamental chemical reactions in carbohydrate chemistry, was the focus of extensive research from the early 1950s until the late 1960s. During this period, several mechanistic proposals related to the acid-catalyzed acetolysis and the accompanying anomerization of different alkyl glycopyranosides, still accepted today, were established. The early work concerned both the site of anomeric activation,[1,2] as well as the acid species involved in the acetic acid/acetic anhydride mixtures used.[3,4] Miljković has recently investigated the electronic effects influencing the acetolysis of pyranosides.[5] Kaczmarek and co-workers have likewise published on the mechanism of the acetolysis of gluco- and mannopyranosides as a method for degradation of polysaccharides.[6]

During the past 30 years much research has been focused on the synthesis of nucleoside analogues for the use in antiviral therapy and several examples on the modification of both D- as well as L-furanoses have been reported.[7] Since one of the most widely used protocols in nucleoside synthesis involves the use of acylated 1-acetyloxy sugars (the Vorbrüggen glycosylation),[8] the acetolysis of methyl furanosides is a key step in the chemical manipulation of sugars. Nevertheless, only a few mechanistical studies have been carried out on furanoses and most of them cover the acid-catalyzed hydrolysis of alkyl furanosides.[9] Very few investigations exist on the acetolysis of furanoses[10] and even fewer targeting the mechanistical issues.[11]

In the current work, we report our results on the mechanism of the acetolysis and concurrent anomerization of 1,2,3,5-tetra-*O*-acetyl- and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-L-ribofuranoses as followed by in situ ^{1}H NMR spectroscopy. The reactions were carried out in a mixture of acetic acid and acetic anhydride with a catalytic amount of sulfuric acid. The rate constants on the reactions involved have been calculated and are in good agreement with the mechanisms proposed in the present work.

Results and Discussion

Elucidation of Reaction Mechanisms

The acetolysis reactions of methyl 2,3,5-tri-*O*-acetyl-α- (**1**) and -β- (**2**) and the methyl 2,3,5-tri-*O*-benzoyl-α- (**7**) and -β-L-ribofuranosides (**8**) were carried out at 25 °C in a mixture of acetic acid and acetic anhydride (5:4 v/v) containing 0.75% sulfuric acid. The progress of the reactions was monitored by ^{1}H NMR spectroscopy. The chemical shifts of the anomeric signals arising from the different compounds present in the reaction mixture clearly deviate from each other, thus allowing the determination of the relative product concentrations by simple integration of the anomeric signals in the ^{1}H NMR spectra.

Figure 1 adequately illustrates the results obtained during a 48 h run using methyl 2,3,5-tri-*O*-acetyl-α-L-ribofuranoside (**1**) as starting material. An analogous mixture of

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200900889.

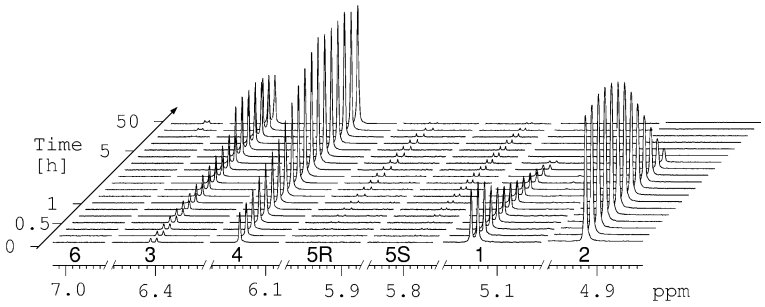


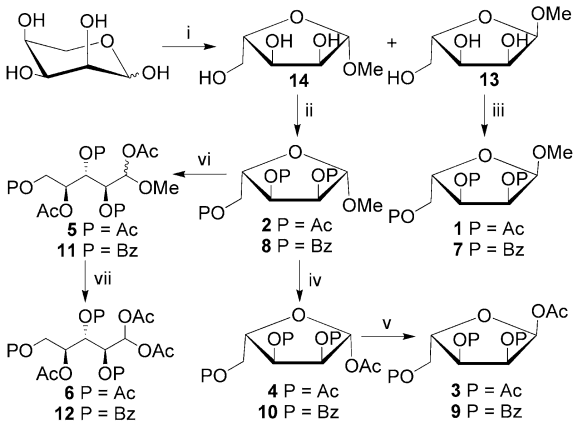
Figure 1. Monitoring of the acetolysis of methyl 2,3,5-tri-*O*-acetyl-α-L-ribofuranoside (**1**) during 48 h at 25 °C in a mixture of acetic acid and acetic anhydride (5:4 v/v) containing 0.75% sulfuric acid. For structures of the compounds, see Scheme 1.

products was obtained when the reactions were carried out starting from compounds **2**, **7** and **8** as well.

All compounds present in the acetolysis reactions were synthesized following slightly modified literature procedures (Scheme 1). First, the methyl α- and β-L-ribofuranosides (**13** and **14**) were synthesized from L-ribose in 26% and 69% yields, respectively.[12] Next, the acetylated methyl L-ribofuranosides **1** and **2**,[13] and their benzoylated analogues **7** and **8** were prepared from the corresponding methyl ribofuranosides by conventional esterification methods.[14] The 1,2,3,5-tetra-*O*-acetyl-β-L-ribofuranose (**4**) and the 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-L-ribofuranose (**10**) were prepared using standard acetolysis conditions and were crystallized from EtOH and *i*PrOH, respectively. Further, portions of compounds **4** and **10** were converted into the corresponding α-anomers **3** and **9** by the use of zinc chloride in acetic anhydride.[15] The isomeric mixture of the acyclic (1*R*)- and (1*S*)-1,2,3,4,5-penta-*O*-acetyl-L-ribose methyl hemiacetals [(1*R*)-**5** and (1*S*)-**5**] and acyclic (1*R*)- and (1*S*)-1,4-di-*O*-acetyl-2,3,5-tri-*O*-benzoyl-L-ribose methyl hemiacetals [(1*R*)-**11** and (1*S*)-**11**] (henceforth labeled as **5** and **11** in the text and Figures) were synthesized from **2** and **8**, respectively. Finally, **5** and **11** were converted into the acyclic 1,1,2,3,4,5-hexa-*O*-acetyl-L-ribose hydrate (**6**) and 1,1,4-tri-*O*-acetyl-2,3,5-tri-*O*-benzoyl-L-ribose hydrate (**12**) as presented in Scheme 1.[16] All compounds prepared were characterized by ^{1}H and 2D NMR spectroscopic techniques (for complete characterization, see the Exp. Section).

Recently, we reported on the acid-catalyzed anomerization of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-L-ribofuranose[17] and hence decided to use the same reaction conditions in the present study in order to enable the utilization of our earlier results in the current experiments. Both the reactions from the acetylated (**1** and **2**) as well as the benzoylated derivatives (**7** and **8**) gave a reaction mixture containing seven compounds: the anomeric methyl furanosides, the anomeric 1-*O*-acetyl furanoses, the isomeric methyl hemiacetals and the fully acylated ribose hydrate. No pyranoses were detected which is in agreement with the kinetically favored formation of five-membered rings.

The time-dependent product distribution for the acetolysis of the acetylated methyl furanosides **1** and **2** is plotted in Figure 2. As seen in the Figure, the acetolysis to afford



Scheme 1. Reagents and conditions: (i) MeOH, H_2SO_4, **13** (26%) and **14** (69%); (ii) CH_2Cl_2, pyridine, AcCl, **2** (69%), CH_2Cl_2, pyridine, BzCl, **8** (89%); (iii) Ac_2O, I_2, **1** (72%), CH_2Cl_2, pyridine, BzCl, **7** (86%); (iv) AcOH, Ac_2O, H_2SO_4, **4** (43%), **10** (49%); (v) Ac_2O, $ZnCl_2$, **3** (8%), **9** (28%); (vi) AcOH, Ac_2O, $ZnCl_2$, **5** (92%), **11** (71%); (vii) AcOH, Ac_2O, H_2SO_4, **6** (77%), **12** (74%).

1-*O*-acetyl-α- (**3**) and β-L-ribofuranose (**4**) is accompanied by a preceding anomerization of the starting material. Since the anomerization is considerably faster than the subsequent acetolysis, an equilibrium mixture containing 25% of the α-anomer (**1**) and 75% of the β-anomer (**2**) is formed, regardless of whether **1** or **2** is used as starting material. It seems likely that the anomerization of the methyl ribofuranosides **1** and **2** in an acetic acid-acetic anhydride mixture takes place via a ring-opening/ring-closing process, as the cleavage of the glycosidic bond would cause the methanol released to compete with acetic acid for the cyclic oxocarbenium ion for the anomerization to proceed (Scheme 3). This assumption is also in agreement with the results obtained on the acid-catalyzed anomerization and hydrolysis of alkyl furanosides suggesting a pathway via acyclic intermediate for methyl furanosides.[9]

The formation of the isomeric acyclic methyl hemiacetals **5** also proceeds via the same acyclic oxocarbenium ion intermediate (**C**). Lindberg proposed that the anomerization and ring-opening is catalyzed by an acetyl cation, from the reaction of acetic anhydride with sulfuric acid, which adds to the ring oxygen and activates the cleavage of the *endo*-cyclic C–O bond followed by ring-closing through nucleo-

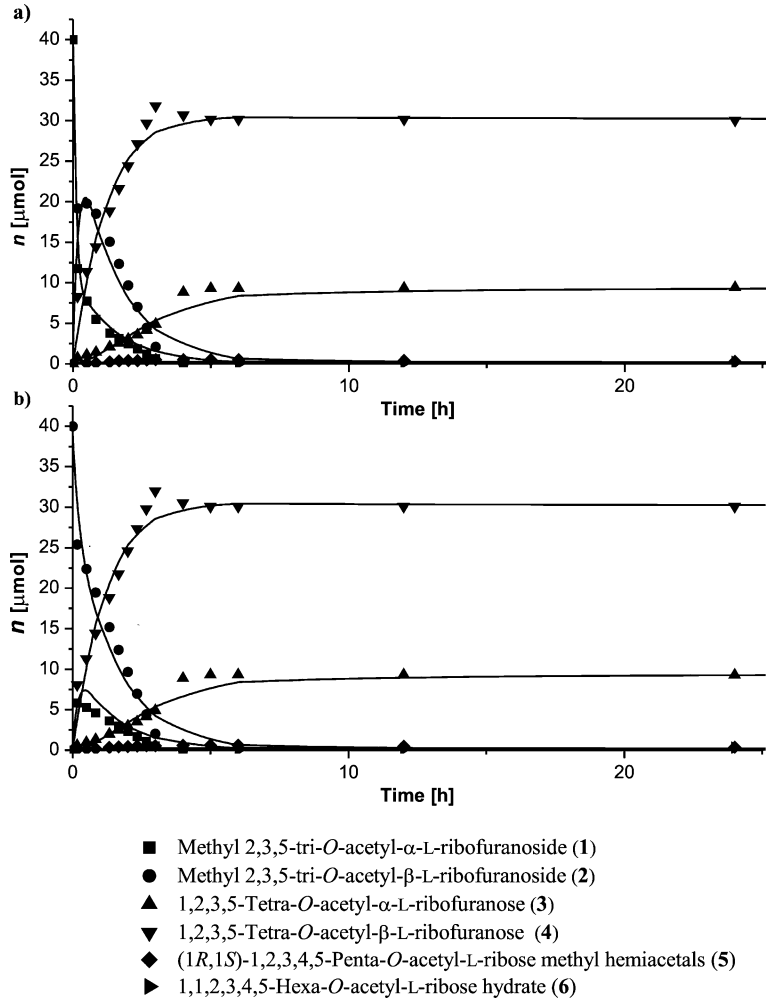


Figure 2. Time-dependent product distribution for the acetolysis of a) methyl 2,3,5-tri-*O*-acetyl-α- (**1**) and b) -β-L-ribofuranoside (**2**) in a 5:4 (v/v) AcOH-Ac_2O mixture catalyzed by 0.75% of H_2SO_4. Experimental and modeled results are presented as symbols and solid lines, respectively.

philic attack by the acetylated oxygen.[3,18] Our previous study evidenced that the ring-opening process takes place via protonation of the ring oxygen and that this acyclic intermediate (**C**) with a free hydroxyl group at C(4) can either ring-close or be acetylated to form the acyclic compound **5**.[17] This proposal is in accordance with the results of Painter[19] and Miljković[5a] indicating that the acetylated oxygen at C(4) is not a strong enough nucleophile for ring-closing.

When **5** was used as starting material for the acetolysis reaction under the same conditions, the acyclic 1,1,2,3,4,5-hexa-*O*-acetyl-L-ribose hydrate (**6**) was formed as the main product while **3** and **4** were obtained in only 1 and 4% yields, respectively. The slow conversion of **5** into **6** under these conditions is also observed in the acetolysis of **1** and **2**. Kaczmarek et al. obtained analogous results from the acetolysis of the fully acetylated D-glucose ethyl and D-mannose methyl hemi-acetals under similar conditions.[6] As the formation of **6** probably proceeds via an acyclic oxocarbenium ion formed after cleavage of methanol, **3** and **4** are expected as the main products if the ring closing would be fast enough even when the oxygen at C(4) is acetylated. The fact that the anomerization of the acetylated methyl ribofuranosides **1** and **2** is much faster than the ring-closing of the acyclic intermediate in the acetolysis of **5** brings further evidence for the proposal that the ring oxygen is protonated prior to endocyclic cleavage in the anomerization reaction. Ring-closing of the fully acetylated acyclic oxocarbenium ion cannot, however, be entirely ruled out, since some formation of furanoses in the acetolysis of **5** was detected (see Supporting Information Figure S2). The rapid anomerization of **1** and **2** nevertheless excludes this from being the main mechanistical pathway.

A widely accepted mechanism for the acid-catalyzed acetolysis of alkyl glycosides in acetic acid-acetic anhydride mixtures presented by Rosenfeld and Ballou suggests that the aglycon part is cleaved as the corresponding acetate.[20] On the contrary, in our present study, the formation of methyl hydrogen sulfate was detected in the early stage of the acetolysis prior to the formation of methyl acetate. This observation suggests that the glycosidic methoxy group is protonated and cleaved off as methanol which immediately

reacts with sulfuric acid to form a sulfate ester. The sulfate ester is then in turn slowly converted to methyl acetate as illustrated in Figure 3.

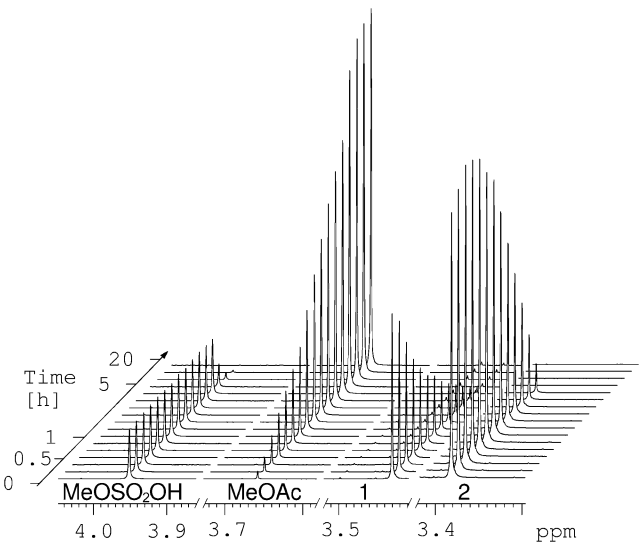
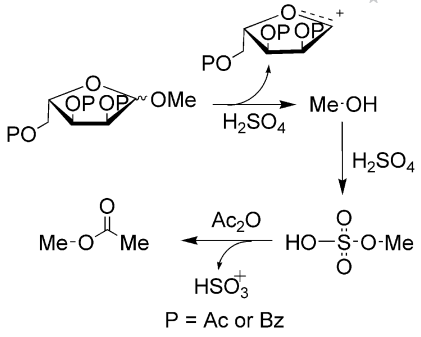


Figure 3. ^{1}H NMR monitoring of methoxy containing compounds during acetolysis of methyl 2,3,5-tri-*O*-acetyl-α-L-ribofuranoside (**1**) during 18 h at 25 °C in a mixture of acetic acid and acetic anhydride (5:4 v/v) containing 0.75% sulfuric acid.

As the concentration of sulfuric acid in the reaction mixture is fairly low, it appears probable that the protonated methoxy group forms an ion pair with sulfuric acid prior to cleavage. The two ions then react to form methyl hydrogen sulfate. Without this kind of coordination it seems rather unlikely that the methanol released would predominantly react with sulfuric acid in the presence of such an excess of acetic anhydride. The amount of methyl sulfate in the reaction mixture remains at a constant level slightly below the total concentration of sulfuric acid as long as unreacted methyl furanosides are present. When all methyl furanosides are consumed the concentration of methyl hydrogen sulfate starts to decrease and is converted to methyl acetate. In the 1940s already, Malm reported that, under similar conditions, sulfuric acid forms sulfate esters with the primary hydroxyl groups of cellulose during the preparation of cellulose acetate and that the sulfate esters then are slowly converted into the final acetate via sulfate acetolysis in the same step.[21] This mechanism was more recently verified by Hyatt and Tindall on monosaccharide model compounds.[22] The formation of sulfate esters of methanol has not earlier been reported in the acetolysis of alkyl glycosides, probably due to the need to follow the reaction in situ in order to be able to detect the methyl hydrogen sulfate formation. A proposed mechanism for the formation of the methyl hydrogen sulfate and the subsequent formation of methyl acetate is hereby presented in Scheme 2.

Based on our findings on the formation of the methyl hydrogen sulfate, we suggest that the acetolysis of the methyl furanosides **1** and **2** occurs via protonation of the exocyclic oxygen followed by methanol cleavage to form a



Scheme 2. Formation of methyl hydrogen sulfate and methyl acetate from the acylated methyl L-ribofuranosides under standard acetolysis conditions.

cyclic oxocarbenium ion intermediate (**I**), which in turn is attacked by acetic acid to give the peracetylated ribofuranoses **3** and **4**. Nevertheless, we do not question the presence of the acetyl cation in this type of acetylating mixtures, neither do we question its role as a catalytically active source. In our previous study,[17] we reported that the acetyl cation is the source of catalytic activity in the anomerization of the benzoylated 1-*O*-acetyl ribofuranoses **9** and **10**. We showed that under various reaction conditions there is no change in the overall reaction path of the anomerization as long as acetic anhydride, the source of the acetyl cation, is present. Furthermore, we showed that the anomerization of **9** and **10** exclusively proceeds via exocyclic cleavage of the glycosidic bond and introduction of a new acetoxy group to the cyclic oxocarbenium ion intermediate.

As seen in Figure 2, the β-anomer **4** is formed much faster than the α-anomer **3** while being formed via the same cyclic intermediate (**I**). Further, it is observed that compound **4** reaches a maximum concentration before equilibrium between the two anomers **3** and **4** is obtained in a 1:3 ratio. This observation can be explained by the formation of a *cis*-fused dioxonium ion intermediate (**J**) via neighboring group participation by the acetoxy group at C(2) after dissociation of the glycosidic bond.[1,23] This results in the intermediate being 1,2-*trans* directing, considering the nucleophilic attack by acetic acid leading to the fast formation of the β-anomer **4**. It is also very likely that the *trans*-1,2-configuration in the acetylated methyl β-ribofuranoside **2** activates the cleavage of the glycosidic bond through neighboring group participation, but as the anomerization of compounds **1** and **2** is evidently faster than the formation of **3** and **4**, this phenomenon is undetectable. When the peracetylated ribofuranoses **3** and **4** are treated under the same acetolysis conditions, anomerization of the starting material is observed giving the same final equilibrium as when the reaction was carried out from **1** or **2**, as presented in the Supporting Information (Figure S1). Further, some formation of the per-acetylated ribose hydrate (**6**) was observed which is in good agreement with the results on the anomerization of the benzoylated ribofuranose acetates **9** and **10** under these conditions.[17]

When the acetolysis reactions were carried out starting from the methyl 2,3,5-tri-*O*-benzoyl-α- (**7**) and β-L-ribofuranoside (**8**), the reaction followed a similar pattern as for the acetylated counterparts **1** and **2**. The time-dependent product distribution for the acetolysis reaction is plotted in Figure 4.

The anomerization of the starting material **7** and **8** leads to an equilibrium mixture with 23% of the α-anomer **7** and 77% of the β-anomer **8** which stays fairly constant during the subsequent acetolysis to compounds **9** and **10**. The anomerization of the benzoylated methyl furanosides **7** and **8** is faster than the analogous anomerization of the acetylated methyl furanosides **1** and **2**. As the anomerization is faster, also the ring-closing of the acyclic oxocarbenium ion intermediate (**C**) has to be faster. This again can be seen as a minor decrease in the formation of the corresponding isomeric acyclic methyl hemiacetals **11** and 1,1-di-*O*-acetyl ribose hydrate **12**. The same trends seen in the formation of the fully acetylated β-anomer **4** are as well seen in the formation of the benzoylated counterpart **10**. The maximum in the concentration of the β-anomer **10** observed before the anomeric equilibrium between **9** and **10** is established is even more distinct in the reactions of the benzoylated methyl furanosides (**7** and **8**). Further, the difference in the formation rate of the 1-acetoxy α-anomer and β-anomer is larger in the benzoylated furanoses **9** and **10** than in the acetylated ones **3** and **4**. These differences could be explained by the bulkiness of the benzoyl group making nucleophilic attack from the α-side more sterically hindered and hence the formation of the β-anomer even more favored. It is, however, not possible to rule out the differences in electronic and solvent effects between the acetyl and benzoyl groups when trying to understand their role as a participating group.

Based on these results, we propose the following mechanism for the anomerization and subsequent acetolysis of the acylated methyl L-ribofuranosides **1**, **2**, **7** and **8** (Scheme 3). We suggest that the anomerization of the starting material is activated by protonation of the ring oxygen leading to *endo* C–O cleavage. When acetylated (as proposed by Lindberg),[18] the C(4) oxygen is not nucleophilic enough for the subsequent ring-closing of **C** to take place. The formation of the acyclic acetyl methyl hemiacetals (**5** and **11**) is a competing reaction with ring-closing and proceeds via acety-

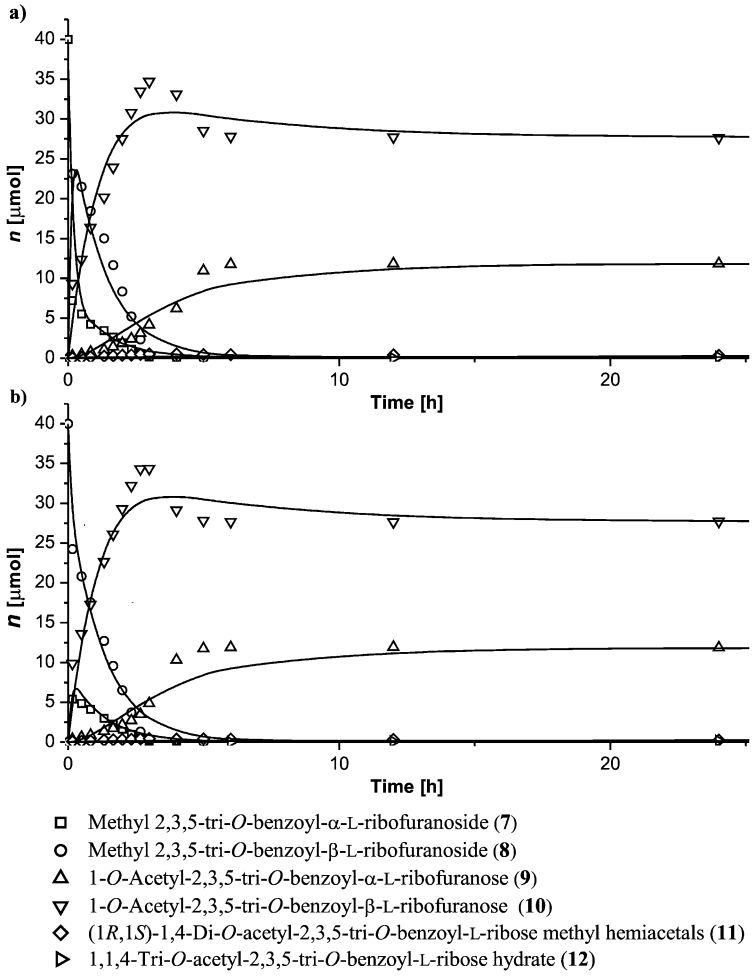
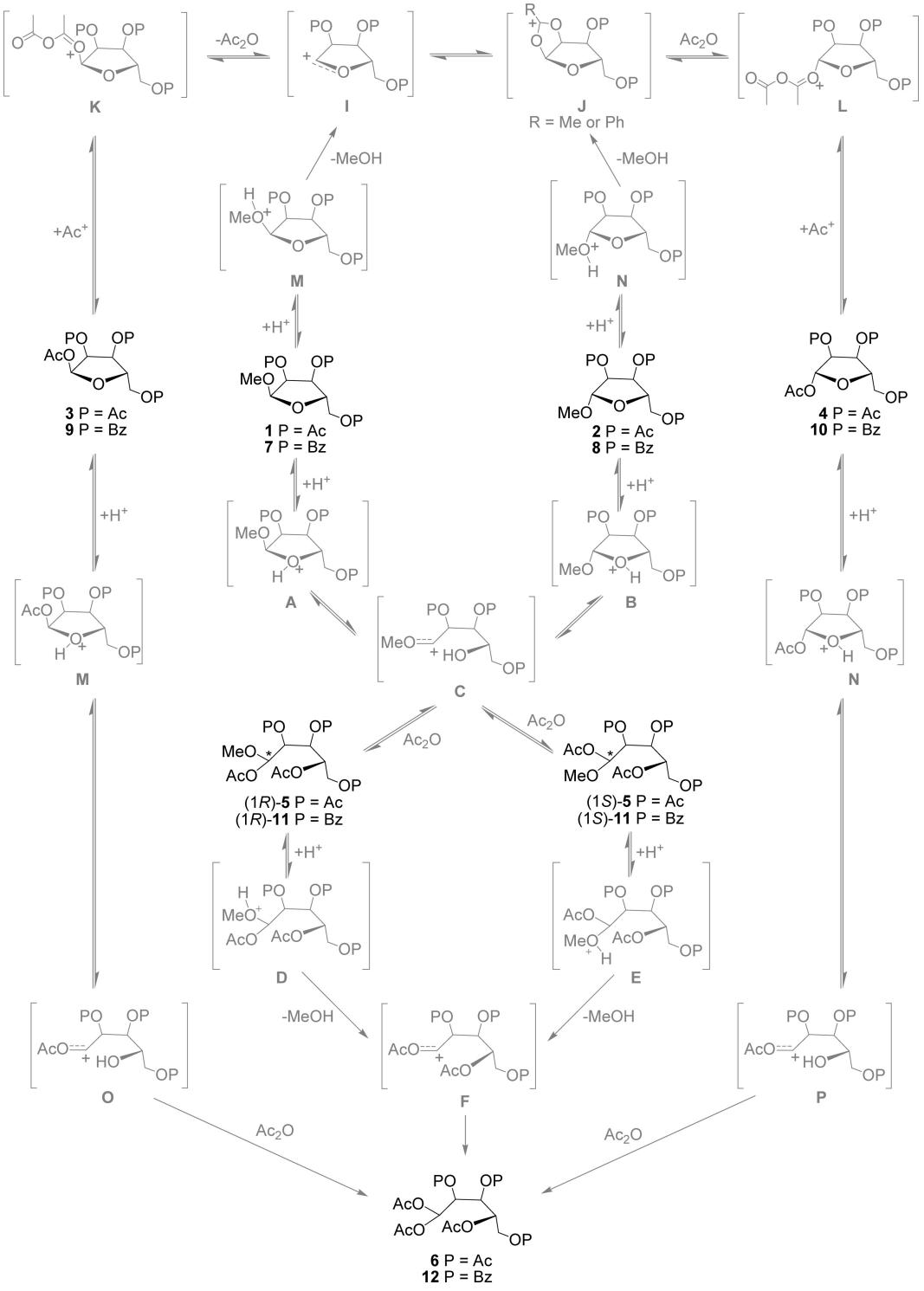


Figure 4. Time-dependent product distribution for the acetolysis of a) methyl 2,3,5-tri-*O*-benzoyl-α- (**7**) and b) -β-L-ribofuranoside (**8**) in a 5:4 (v/v) $AcOH/Ac_2O$ mixture catalyzed by 0.75% of H_2SO_4. Experimental data and calculations are presented as symbols and solid lines, respectively.

lation of the free hydroxyl group at C(4) followed by nucleophilic attack by acetic acid on the acyclic carbenium ion intermediate (**C**). Based on our findings on the formation of methyl hydrogen sulfate, we propose that protonation activates the anomeric methoxy group for *exo* C–O cleavage. The cyclic oxocarbenium intermediate (**I**) formed is stabilized by the formation of a *cis*-fused dioxonium ion intermediate (**J**) via neighboring group participation of the acyl group at C(2). The *cis*-fused intermediate blocks the α-side of the ring and makes the nuclophilic attack by acetic acid from the β-side more feasible.

This participation is possibly also activating the cleavage of methanol from the 1,2-*trans* configured methyl β-ribofuranosides. However, due to fast anomerization, it is im-



Scheme 3. Proposed mechanism for the acid-catalyzed acetolysis of the acetylated (**1** and **2**) and benzoylated (**7** and **8**) methyl L-ribofuranosides.

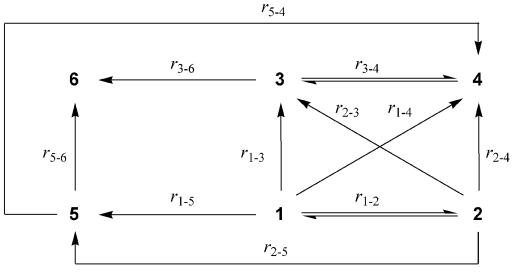
possible to distinguish which one of the anomers is more prone towards *exo*-cyclic cleavage.

Based on our earlier results,[17] we propose a mechanism for the anomerization of 1-*O*-acetylated ribofuranoses (**3**, **4** and **9**,**10**), where the acetyl cation formed in the acetylation media activates the anomeric acetyl group for *exo-cyclic* cleavage. The main pathway for the formation of the fully acylated acyclic L-ribose hydrates (**6** and **12**) proceeds via acetolysis of the acetyl methyl hemiacetals (**5** and **11**), while being also to some extent formed via ring-opening of the 1-*O*-acetylated ribofuranoses (**3**, **4** and **9**,**10**).

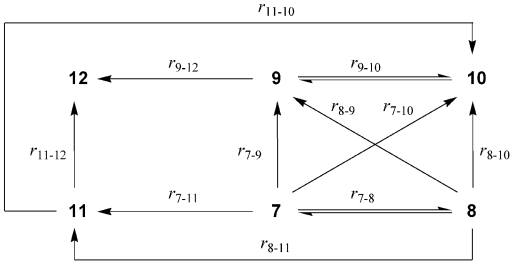
The site of activation is, supposedly, an issue of the relative basicities of the *exo* and *endo* oxygen atoms.[24] The interrelationship of the basicity of the ring oxygen and glycosidic oxygen probably changes when moving from the methyl glycoside to the acetate and this could explain the change in site of activation. This could furthermore explain the differences in H^+ vs. Ac^+ affinities for the oxygens during different stages of the acetolysis reaction. These rather speculative suggestions need, however, further investigation to be confirmed.

Kinetic Calculations

The reactions needed to describe the kinetics of the acetolysis of the acetylated methyl L-ribofuranosides **1** and **2**, as well as for the benzoylated counterparts **7** and **8** are given in Schemes 4 and 5, respectively.



Scheme 4.



Scheme 5.

In order to determine the rate constants for the reactions in Schemes 4 and 5, each containing 11 reactions, the parameter estimation was separated into three parts. Experiments were done starting from the methyl furanosides **1** or **2** and **7** or **8**, the 1-*O*-acetyl furanoses **3** or **4** and **9** or **10** and then finally from the acyclic methyl hemiacetals **5** and **11**. When starting from the 1-*O*-acetyl furanoses the equilibrium between the α- and β-anomer is produced and the acyclic 1,1-*O*-diacetyl ribose hydrates (**6** and **12**) are formed. In this case, reaction rates $r_{3–4}$ and $r_{3–6}$ for the acetylated sugars and reaction rates $r_{9–10}$ and $r_{9–12}$ for the benzoylated ones can be determined. Using the acyclic methyl hemiacetals as starting material produces the 1,1-*O*-diacetyl ribose hydrates (**6** and **12**) and to some extent the α- (**3** and **9**) and β-anomers (**4** and **10**) of the 1-*O*-acetyl furanoses, now $r_{5–6}$ and $r_{5–4}$ for the acetylated and $r_{11–12}$ and $r_{11–10}$ for the benzoylated compounds can be determined. Finally, starting from the acylated methyl ribofuranosides **1** or **2** and **7** or **8** gives the remaining $r_{1–2}$, $r_{1–3}$, $r_{1–4}$, $r_{2–3}$, $r_{2–4}$, $r_{1–5}$ and $r_{2–5}$ for the acetylated sugars and the corresponding reaction rates $r_{7–8}$, $r_{7–9}$, $r_{7–10}$, $r_{8–9}$, $r_{8–10}$, $r_{7–11}$ and $r_{8–11}$ for the benzoylated counterparts (for complete kinetic data see the Supporting Information).

From the kinetic modeling it was found that the reaction rates $r_{1–3}$, $r_{2–3}$ and $r_{2–5}$ for the acetylated derivatives **1** and **2** as well as the reaction rates $r_{7–9}$, $r_{8–9}$ and $r_{8–11}$ for the benzoylated ones **7** and **8** were very low, hence they were set to zero. These results further support that ring-opening only takes place from the α-anomers and that acetolysis of the starting material first gives the 1-*O*-acetylated β-anomers **4** and **10** which subsequently anomerizes to reach the final equilibria. The equilibrium constants for the reactions between the acetylated compounds **3** and **4** and the benzoylated counterparts **9** and **10** were calculated from the experimental data as $K_{3–4} = 3.22$ and $K_{9–10} = 2.33$. For the anomerization of the acylated methyl L-ribofuranosides the equilibrium constants were estimated giving $K_{1–2} = 3.2 \pm 0.1$ and $K_{7–8} = 3.5 \pm 0.1$ for the acetylated and benzoylated sugars, respectively. The anomerization of the benzoylated methyl furanosides **7** and **8** is so fast that equilibrium is immediately reached; therefore the rate constant $k_{7–8}$ was fixed to a large value for the kinetic modeling. The rate constants obtained for the reactions involved in the acetolysis of the acylated methyl L-ribofuranosides **1**, **2** and **7**,**8** are given in Table 1. When the acetylated (**3** and **4**) or benzoylated (**9** and **10**) 1-acetoxy furanoses are treated under the acetolysis conditions we see anomerization of the starting material giving the same final equilibrium as when it is carried out from the acylated methyl furanosides. The rate constants for the formation of the peracetylated ribofuranoses **3** and **4** from these reactions were determined as $k_{4–3} = 2.376 \pm 0.008$ and $k_{3–4} = 7.67 \pm 0.03$, respectively. The corresponding rate constants for the benzoylated sugars **9** and **10** were estimated as $k_{10–9} = 0.918 \pm 0.005$ and $k_{9–10} = 2.14 \pm 0.01$. These rate constants are a tenfold higher than the corresponding constants obtained from the reactions carried out from the acylated methyl furanosides given in Table 1. This further verifies that the sulfuric acid in the acetolysis reactions is converted into the less acidic methyl hydrogen sulfate and which slows down the formation of the 1-acetoxy furanoses **3**, **4** and **9**, **10**.

Table 1. First-order rate constants for the reactions involved in the acid-catalyzed acetolysis of the acetylated (**1** and **2**) and benzoylated (**7** and **8**) methyl L-ribofuranosides at 25 °C in $AcOH/Ac_2O$ (5:4 v/v) with 0.75% of H_2SO_4.

Acetolysis of compounds **1** and **2**		Acetolysis of compounds **7** and **8**	
	k [h^{-1}]		k [h^{-1}]
k_{1-2}	12.7 ± 0.5	K_{7-8}	3.5 ± 0.1[b]
k_{1-3}	0[a]	k_{7-9}	0[a]
k_{1-4}	0[a]	k_{7-10}	0[a]
k_{1-5}	0.023 ± 0.009	k_{7-11}	0.0172 ± 0.0008
k_{2-1}	4.1 ± 0.4	k_{8-7}	[b]
k_{2-3}	0[a]	k_{8-9}	0[a]
k_{2-4}	0.87 ± 0.02	k_{8-10}	1.002 ± 0.004
k_{2-5}	0[a]	k_{8-11}	0[a]
k_{3-4}	0.490 ± 0.002	k_{9-10}	0.249 ± 0.002
k_{3-6}	0.0005 ± 0.00007	k_{9-12}	0.0008 ± 0.0001
k_{4-3}	0.1518 ± 0.0006	k_{10-9}	0.1074 ± 0.0008
k_{4-6}	0[a]	k_{10-12}	0[a]
k_{5-4}	0.0023 ± 0.0002	k_{11-10}	0.00172 ± 0.00001
k_{5-6}	0.0183 ± 0.0002	k_{11-12}	0.0148 ± 0.0001

[a] Rate constants set to 0 based on kinetic modelling. [b] Rate constants k_{7-8} and k_{8-7} were set to a large value due to instantaneous equilibrium between **7** and **8**.

Conclusions

To conclude, new mechanistic and kinetic data on the acid-catalyzed acetolysis for a set of acylated methyl L-ribofuranosides has been obtained. Furthermore, the role of H^+ vs. Ac^+ as the catalytically active source as well as the site of anomeric activation has been discussed. Based on the observed formation of methyl hydrogen sulfate during the acetolysis process it can be deduced that the methyl furanosides are protonated on the exocyclic oxygen and that the aglycon is cleaved off as methanol. The anomerization of the acylated methyl ribofuranosides taking place via a ring-opening/ring-closing process is much faster for the benzoylated compounds than for the acetylated counterparts. Thus, less time is left for the attack by acetic acid on the acyclic oxocarbenium ion intermediate leading to lower formation of acylic side products in the reactions of the benzoylated methyl ribofuranosides. The results reported herein contribute to a better understanding of fundamental reaction mechanisms in carbohydrate chemistry in particular and in organic chemistry in general.

Experimental Section

General Experimental Details: Chemicals were purchased from commercial sources and were used without further purification.

The NMR spectra were recorded using a Bruker Avance 600 MHz spectrometer equipped with a 5 mm inverse *z*-axis fg probe operating at 600.13 MHz for ^1H and 150.92 MHz for ^{13}C. All products were fully characterized with 1D ^1H and ^{13}C NMR spectroscopy in combination with 2D COSY, HMBC and HSQC by using pulse sequences provided by the instrument manufacturer. The NMR spectra were referenced against TMS or the solvent signal. Signal multiplicities and coupling constants are given in parentheses [br = broad unresolved multiplet (^1H NMR)].

HRMS were recorded on a Bruker micrOTOF-Q and EIMS were obtained with Fisons ZabSpec mass spectrometer at 70 eV. Melting points were determined in open glass capillaries and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter equipped with a Na lamp (589 nm) at 24 °C. TLC analyses were performed using silica gel F_{254} precoated aluminum sheets visualized by charring with 25% H_2SO_4 in methanol or UV. Column chromatography was performed using silica gel 60 Å (Merck, 230–400 mesh).

Kinetic Calculations: The kinetics of the acetolysis reactions of the acetylated methyl L-ribofuranosides were described with a first order reversible model for reactions r_{1-2} and r_{3-4}, for the other reactions a first order irreversible model was used. However, it is worth notifying that the rate constants are lumped and do not take into account formation of the possible intermediates. Furthermore, the rate constants k_{1-2}, k_{1-5}, k_{2-4}, k_{3-4}, k_{3-6} and k_{5-6} are apparent, hence implicitly including the concentrations of the catalytically active species which were kept constant during the experiments.

$$r_{1-2} = k_{1-2}(c_1 - c_2 / K_{1-2}) \quad r_{1-3} = k_{1-3}c_1 \quad r_{1-4} = k_{1-4}c_1$$
$$r_{1-5} = k_{1-5}c_1 \quad r_{2-4} = k_{2-4}c_2 \quad r_{2-3} = k_{2-3}c_2$$
$$r_{2-5} = k_{2-5}c_2 \quad r_{3-6} = k_{3-6}c_3 \quad r_{4-3} = k_{4-3}(c_4 - c_3 / K_{4-3})$$
$$r_{5-4} = k_{5-4}c_5 \quad r_{5-6} = k_{5-6}c_5$$

The reactor was described with a batch reactor model and the mass balances for each component were as follows

$$\frac{dc_1}{dt} = -r_{1-5} - r_{1-4} - r_{1-2} - r_{1-3} \qquad \frac{dc_4}{dt} = r_{2-4} + r_{1-4} + r_{5-4} - r_{4-3}$$
$$\frac{dc_2}{dt} = -r_{2-4} - r_{2-3} + r_{1-2} - r_{2-5} \qquad \frac{dc_5}{dt} = r_{1-5} + r_{2-5} - r_{5-6} - r_{5-4}$$
$$\frac{dc_3}{dt} = r_{2-3} - r_{3-6} + r_{4-3} + r_{1-3} \qquad \frac{dc_6}{dt} = r_{3-6} + r_{5-6}$$

For the parameter estimation the following objective function was minimized:

$$Q = \sum_t \sum_i (c_{i,t,\text{exp}} - c_{i,t,\text{model}})^2 w_{i,t}$$

where $c_{i,t,\text{exp}}$ and $c_{i,t,\text{model}}$ are the experimentally recorded concentrations and the concentrations predicted by the model, respectively. The weight factors w_i were set to 1 for all experimental points. The software "Modest" was used to estimate the rate constants and to solve the reactor mass balances. The software minimizes the objective function with the Levenberg–Marquardt method and solves the ODEs describing the reactor model by the backward difference method.[25] The same models were used for the estimation of the kinetics for the benzoylated compounds **7**–**12** as well.

The fit of the model to experimental data of the reactions is presented in Figures 2 and 4 and in the Supporting Information (Figures S7–S16). It can be seen from the figures that the model can describe the experimental data very well. The estimated rate constants are listed in Table 1 and in the Supporting Information (Tables S11–S16).

To evaluate the accuracy of the estimated parameters the MCMC (Markov Chain Monte Carlo) method was used. The method is based on the Bayesian approach. In this method all the uncertainties in the data as well as the modeling results are treated as statistical distributions showing that the parameters were well identified (data given in the Supporting Information).[26]

General Procedures for the Acetolysis Reactions: Compounds **1**–**12** (0.04 mmol) were dissolved in 550 μL of CD_2Cl_2. To this solution

63 μL of a freshly prepared 5:4 (v/v) mixture of AcOH and Ac_2O containing 0.75% H_2SO_4 was added. The reactions were carried out in sealed NMR tubes inside the magnet thermostatted to 25 °C by a Bruker variable temperature unit. ^1H NMR spectra were recorded at different time intervals and the molar concentrations of the products were determined from the integral ratios.

Methyl α- (13) and β-L-Ribofuranoside (14): A solution of L-ribose (5.0 g, 33.3 mmol) in MeOH (100 mL) was treated with H_2SO_4 (0.5 mL). After 4.5 h of stirring at room temperature the reaction was neutralized with Na_2CO_3 (10 g), filtered and evaporated to obtain a mixture of **13** and **14** as a yellowish syrup (5.4 g) in a 3:8 ratio. The anomers were separated by means of column chromatography on a Dowex Monosphere 99 Ca^{2+} column which gave pure **13** (1.4 g, 26%) as a colorless oil: R_f = 0.36 (6:1 $CHCl_3$/MeOH). $[\alpha]_D^{24}$ = –89.9 (*c* = 1.01, H_2O) [ref.[27] $[\alpha]_D^{20}$ = +99 (*c* = 1.8, H_2O) for D-isomer]. ^1H NMR (600.13 MHz, CD_3OD, 25 °C): δ = 4.85 (d, $J_{1,2}$ = 4.5 Hz, 1 H, 1-H), 4.01 (dd, $J_{2,1}$ = 4.5, $J_{2,3}$ = 6.6 Hz, 1 H, 2-H), 3.98 (ddd, $J_{4,3}$ = 3.1, $J_{4,5a}$ = 3.5, $J_{4,5b}$ = 4.2 Hz, 1 H, 4-H), 3.94 (dd, $J_{3,4}$ = 3.1, $J_{3,2}$ = 6.6 Hz, 1 H, 3-H), 3.66 (dd, $J_{5a,4}$ = 3.5, $J_{5a,5b}$ = 12.0 Hz, 1 H, 5_a-H), 3.60 (dd, $J_{5b,4}$ = 4.2, $J_{5b,5a}$ = 12.0 Hz, 1 H, 5_b-H), 3.43 (s, 3 H, 1-OMe) ppm. ^{13}C NMR (150.9 MHz, CD_3OD, 25 °C): δ = 104.8 (C-1), 86.9 (C-4), 73.2 (C-2), 71.4 (C-3), 63.4 (C-5), 55.7 (O*C*H_3) ppm. EIMS calcd. for $C_{15}H_{36}O_5Si_3$ [M^+] 380.1870, found 380.1849.

The pure β-anomer obtained by chromatographic separation was subsequently crystallized from *i*PrOH to give **14** (3.7 g, 69%) as white needles: R_f = 0.36 (6:1 $CHCl_3$/MeOH); m.p. 76–80 °C [ref.[28] 79–80 °C]. $[\alpha]_D^{24}$ = +51.2 (*c* = 1.02, H_2O) [ref.[28] $[\alpha]_D^{20}$ = –50 (*c* = 2.0, H_2O) for D-isomer]. ^1H NMR (600.13 MHz, CD_3OD, 25 °C): δ = 4.75 (s, 1 H, 1-H), 4.03 (dd, $J_{3,2}$ = 4.7, $J_{3,4}$ = 6.9 Hz, 1 H, 3-H), 3.94 (ddd, $J_{4,5a}$ = 3.6, $J_{4,5b}$ = 6.5, $J_{4,3}$ = 6.9 Hz, 1 H, 4-H), 3.87 (d, $J_{2,3}$ = 4.7 Hz, 1 H, 2-H), 3.72 (dd, $J_{5a,4}$ = 3.6, $J_{5a,5b}$ = 11.8 Hz, 1 H, 5_a-H), 3.54 (dd, $J_{5b,4}$ = 6.5, $J_{5b,5a}$ = 11.8 Hz, 1 H, 5_b-H), 3.35 (s, 3 H, 1-OMe) ppm. ^{13}C NMR (150.9 MHz, CD_3OD, 25 °C): δ = 110.0 (C-1), 85.0 (C-4), 76.3 (C-2), 72.8 (C-3), 65.2 (C-5), 55.5 (O*C*H_3) ppm. EIMS calcd. for $C_{15}H_{36}O_5Si_3$ [M^+] 380.1870, found 380.1849.

Methyl 2,3,5-Tri-*O*-acetyl-α-L-ribofuranoside (1): To a suspension of **13** (1.0 g, 6.1 mmol) in Ac_2O (5 mL) was added iodine (200 mg, 0.78 mmol). The reaction was stirred at room temperature for 24 h, then poured into a mixture of crushed ice and saturated aqueous NaS_2O_3 (50 mL) and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic fractions were washed with saturated aqueous Na_2SO_4 (2 × 100 mL), dried with Na_2SO_4 and evaporated to obtain a yellowish oil (1.4 g). Flash column chromatography (silica gel, EtOAc/petroleum ether, 1:5) gave **1** (1.25 g, 72%), as a colorless oil: R_f = 0.46 (1:1 EtOAc/hexane). $[\alpha]_D^{24}$ = –114.9 (*c* = 0.99, MeOH). ^1H NMR (600.13 MHz, $CDCl_3$, 25 °C): δ = 5.16 (dd, $J_{3,4}$ = 3.7, $J_{3,2}$ = 7.4 Hz, 1 H, 3-H), 5.12 (d, $J_{1,2}$ = 4.6 Hz, 1 H, 1-H), 4.96 (dd, $J_{2,1}$ = 4.6, $J_{2,3}$ = 7.4 Hz, 1 H, 2-H), 4.37 (dd, $J_{5a,4}$ = 3.0, $J_{5a,5b}$ = 11.9 Hz, 1 H, 5_a-H), 4.26 (ddd, $J_{4,5a}$ = 3.0, $J_{4,3}$ = 3.7, $J_{4,5b}$ = 4.1 Hz, 1 H, 4-H), 4.20 (dd, $J_{5b,4}$ = 4.1, $J_{5b,5a}$ = 11.9 Hz, 1 H, 5_b-H), 3.43 (s, 3 H, 1-OMe), 2.12 (s, 6 H, 2-OAc, 5-OAc), 2.08 (s, 3 H, 3-OAc) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 25 °C): δ = 170.7 (C=O-5), 170.6 (C=O-3), 170.0 (C=O-2), 101.7 (C-1), 79.6 (C-4), 70.9 (C-2), 69.9 (C-3), 63.6 (C-5), 55.7 (O*C*H_3-1), 20.9 (C*C*H_3-3), 20.7 (C*C*H_3-5), 20.7 (C*C*H_3-2) ppm. EIMS calcd. for $C_{12}H_{17}O_8$ [M^+ – H] 289.0923, found 289.0930.

Methyl 2,3,5-Tri-*O*-acetyl-β-L-ribofuranoside (2): To a cooled (ice bath) solution of compound **14** (2.0 g, 12.2 mmol) in pyridine (7 mL) and CH_2Cl_2 (5 mL) AcCl (3.5 mL, 48.8 mmol) was added drop wise. The ice bath was removed and the reaction was stirred at ambient temperature for 18 h. The excess of AcCl was decomposed by the addition of crushed ice and the mixture was extracted with CH_2Cl_2 (2 × 30 mL). The organic phases were combined and washed with water (2 × 50 mL), 1 M HCl (50 mL), saturated $NaHCO_3$ (50 mL), brine (50 mL) dried with Na_2SO_4 and the solvents evaporated to dryness. The evaporation residue was purified by column chromatography (silica gel, EtOAc/petroleum ether, 4:5) which gave pure **2** (2.4 g, 69%), as a colorless oil: R_f = 0.73 (1:1 EtOAc/hexane). $[\alpha]_D^{24}$ = +16.9 (*c* = 1.05, MeOH) [ref.[29] $[\alpha]_D^{22}$ = +14.6 (*c* = 2.3, MeOH)]. ^1H NMR (600.13 MHz, $CDCl_3$, 25 °C): δ = 5.32 (dd, $J_{3,2}$ = 4.8, $J_{3,4}$ = 6.8 Hz, 1 H, 3-H), 5.22 (d, $J_{2,3}$ = 4.8 Hz, 1 H, 2-H), 4.90 (s, 1 H, 1-H), 4.36 (dd, $J_{5a,4}$ = 3.7, $J_{5a,5b}$ = 11.8 Hz, 1 H, 5_a-H), 4.30 (ddd, $J_{4,5a}$ = 3.7, $J_{4,5b}$ = 5.9, $J_{4,3}$ = 6.8 Hz, 1 H, 4-H), 4.10 (dd, $J_{5b,4}$ = 6.9, $J_{5b,5a}$ = 11.8 Hz, 1 H, 5_b-H), 3.37 (s, 3 H, 1-OMe), 2.11 (s, 3 H, 2-OAc), 2.09 (s, 3 H, 5-OAc), 2.05 (s, 3 H, 3-OAc) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 25 °C): δ = 170.8 (C=O-5), 169.8 (C=O-3), 169.8 (C=O-2), 106.4 (C-1), 78.7 (C-4), 74.8 (C-2), 71.7 (C-3), 64.6 (C-5), 55.4 (O*C*H_3-1), 20.9 (C*C*H_3-5), 20.8 (C*C*H_3-2), 20.7 (C*C*H_3-3) ppm. EIMS calcd. for $C_{12}H_{17}O_8$ [M^+ – H] 289.0923, found 289.0930.

1,2,3,5-Tetra-*O*-acetyl-β-L-ribofuranose (4): A solution of **14** (2.9 g, 17.7 mmol) in glacial AcOH (7.5 mL) and Ac_2O (10 mL) was cooled (ice bath) and H_2SO_4 (0.3 mL) was added. The reaction was stirred at room temperature for 1 h and then again placed on ice bath and a second portion of H_2SO_4 (0.5 mL) was added. The reaction was stirred for two more hours at room temperature and then quenched by the addition of NaOAc (2.5 g). The reaction mixture was evaporated and the brownish residue was dissolved in $CHCl_3$ (50 mL), washed with water (3 × 50 mL), dried with Na_2SO_4 and the solvents evaporated to dryness. The yellow oil (4.2 g) was crystallized from EtOH to afford **5** (2.4 g, 43%) as bright white crystals: R_f = 0.58 (1:1 EtOAc/hexane); m.p. 80–83 °C [ref.[30] 81–83 °C]. $[\alpha]_D^{24}$ = +12.4 (*c* = 1.03, $CHCl_3$) [ref.[31] $[\alpha]_D^{20}$ = +12.1 (*c* = 2.47, $CHCl_3$)]. ^1H NMR (600.13 MHz, $CDCl_3$, 25 °C): δ = 6.17 (br. s, 1 H, 1-H), 5.36 (dd, $J_{3,2}$ = 4.8, $J_{3,4}$ = 6.2 Hz, 1 H, 3-H), 5.34 (dd, $J_{2,1}$ = 0.9, $J_{2,3}$ = 4.8 Hz, 1 H, 2-H), 4.38 (ddd, $J_{4,5a}$ = 3.6, $J_{4,5b}$ = 5.5, $J_{4,3}$ = 6.2 Hz, 1 H, 4-H), 4.34 (dd, $J_{5a,4}$ = 3.6, $J_{5a,5b}$ = 12.1 Hz, 1 H, 5_a-H), 4.15 (dd, $J_{5b,4}$ = 5.5, $J_{5b,5a}$ = 12.1 Hz, 1 H, 5_b-H), 2.13 (s, 3 H, 2-OAc), 2.10 (s, 3 H, 1-OAc), 2.09 (s, 3 H, 5-OAc), 2.08 (s, 3 H, 3-OAc) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 25 °C): δ = 170.5 (C=O-5), 169.7 (C=O-3), 169.4 (C=O-2), 169.0 (C=O-1), 98.2 (C-1), 79.3 (C-4), 74.1 (C-2), 70.5 (C-3), 63.7 (C-5), 21.0 (C*C*H_3-1), 20.7 (C*C*H_3-5), 20.5 (C*C*H_3-2), 20.5 (C*C*H_3-3) ppm. EIMS calcd. for $C_{11}H_{15}O_8$ [M^+ – CH_3CO] 275.0767, found 275.0755.

1,2,3,5-Tetra-*O*-acetyl-α-L-ribofuranose (3): To a solution of $ZnCl_2$ (1.0 g, 7.3 mmol) in Ac_2O (15 mL) 1,2,3,5-tetra-*O*-acetyl-β-L-ribofuranose (**5**) (6.0 g, 18.9 mmol) was added. After 2.5 h stirring at room temperature the reaction was quenched by the addition of 0.7 M NaOAc solution (50 mL). The reaction mixture was extracted with $CHCl_3$ (2 × 25 mL) and the combined organic layers were washed with saturated $NaHCO_3$ (50 mL) and water (2 × 50 mL), dried with Na_2SO_4, concentrated and co-evaporated with EtOH (2 × 10 mL). The obtained syrup was dissolved in EtOH and most of the remaining β-anomer was crystallized and filtered off. The filtrate was evaporated and the yellow oil (1.4 g) was purified by column chromatography (silica gel, EtOAc/petroleum ether, 1:3) to give **6** (500 mg, 8%) as a colorless oil: R_f = 0.58 (1:1 EtOAc/hexane). $[\alpha]_D^{24}$ = –79.2 (*c* = 1.00, $CHCl_3$);. ^1H NMR (600.13 MHz, $CDCl_3$, 25 °C): δ = 6.43 (d, $J_{1,2}$ = 4.4 Hz, 1 H, 1-H), 5.26 (dd, $J_{3,4}$ = 2.8, $J_{3,2}$ = 6.7 Hz, 1 H, 3-H), 5.23 (dd, $J_{2,1}$ = 4.4, $J_{2,3}$ = 6.7 Hz, 1 H, 2-H), 4.44 (ddd, $J_{4,3}$ = 2.8, $J_{4,5a}$ = 3.2, $J_{4,5b}$ = 4.0 Hz, 1 H, 4-H), 4.33 (dd, $J_{5a,4}$ = 3.2, $J_{5a,5b}$ = 12.2 Hz, 1 H, 5_a-H), 4.21 (dd, $J_{5b,4}$ = 4.0, $J_{5b,5a}$ = 12.2 Hz, 1 H, 5_b-H), 2.14 (s, 3 H, 3-OAc), 2.13

(s, 3 H, 1-OAc), 2.11 (s, 3 H, 5-OAc), 2.09 (s, 3 H, 2-OAc) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 25 °C): δ = 170.4 (C=O-5), 170.1 (C=O-3), 169.7 (C=O-1), 169.4 (C=O-2), 94.0 (C-1), 81.6 (C-4), 70.0 (C-2), 69.8 (C-3), 63.3 (C-5), 21.0 (CCH_3-1), 20.8 (CCH_3-5), 20.6 (CCH_3-3), 20.3 (CCH_3-2) ppm. EIMS calcd. for $C_{11}H_{15}O_8$ [M^+ – CH_3CO] 275.0767, found 275.0755.

(1*R*,1*S*)-1,2,3,4,5-Penta-*O*-acetyl-L-ribose Methyl Hemiacetals (5): To a solution of $ZnCl_2$ (1.6 g, 11.7 mmol) in Ac_2O (14 mL) and AcOH (6 mL), methyl 2,3,5-tri-*O*-acetyl-L-ribofuranoside (**2**) (1 g, 3.45 mmol) was added. The reaction was stirred at ambient temperature for 48 h, followed by the addition of ice water (100 mL) to decompose the excess of Ac_2O. The mixture was extracted with $CHCl_3$ (50 mL), the organic layer was dried with Na_2SO_4. Evaporation gave an isomeric mixture of the (1*R*,1*S*)-1,2,3,4,5-penta-*O*-acetyl-L-ribose methyl hemi-acetals (**5**) (1.25 g, 92%, isomeric ratio 4:5), as a pale yellow oil: R_f = 0.58 (1:1 EtOAc/hexane); (major isomer) ^{1}H NMR (600.13 MHz, $CDCl_3$, 25 °C): δ = 5.92 (d, $J_{1,2}$ = 6.0 Hz, 1 H, 1-H), 5.41 (dd, $J_{3,2}$ = 4.9, $J_{3,4}$ = 5.9 Hz, 1 H, 3-H), 5.29 (ddd, $J_{4,5a}$ = 2.8, $J_{4,3}$ = 5.9, $J_{4,5b}$ = 6.2 Hz, 1 H, 4-H), 5.26 (dd, $J_{2,3}$ = 4.9, $J_{2,1}$ = 6.0 Hz, 1 H, 2-H), 4.35 (dd, $J_{5a,4}$ = 2.8, $J_{5a,5b}$ = 12.3 Hz, 1 H, 5_a-H), 4.14 (dd, $J_{5b,4}$ = 6.2, $J_{5b,5a}$ = 12.3 Hz, 1 H, 5_b-H), 3.45 (s, 3 H, 1-OMe), 2.10 (s, 3 H, 4-OAc), 2.10 (s, 3 H, 2-OAc), 2.09 (s, 3 H, 1-OAc), 2.08 (s, 3 H, 3-OAc), 2.06 (s, 3 H, 5-OAc) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 25 °C): δ = 170.7 (C=O-1), 170.6 (C=O-5), 169.8 (C=O-4), 169.4 (C=O-3), 169.4 (C=O-2), 94.9 (C-1), 70.5 (C-2), 69.5 (C-4), 69.1 (C-3), 61.8 (C-5), 57.4 (OCH_3-1), 20.9 (CCH_3-1), 20.9 (CCH_3-4), 20.7 (CCH_3-2), 20.7 (CCH_3-3), 20.7 (CCH_3-5) ppm. (minor isomer) ^{1}H NMR (600.13 MHz, $CDCl_3$, 25 °C): δ = 5.78 (d, $J_{1,2}$ = 4.3 Hz, 1 H, 1-H), 5.43 (dd, $J_{3,4}$ = 4.6, $J_{3,2}$ = 5.8 Hz, 1 H, 3-H), 5.33 (ddd, $J_{4,5a}$ = 3.2, $J_{4,3}$ = 4.6, $J_{4,5b}$ = 7.2 Hz, 1 H, 4-H), 5.29 (covered, 1 H, 2-H), 4.38 (dd, $J_{5a,4}$ = 3.2, $J_{5a,5b}$ = 12.2 Hz, 1 H, 5_a-H), 4.12 (dd, $J_{5b,4}$ = 7.2, $J_{5b,5a}$ = 12.2 Hz, 1 H, 5_b-H), 3.43 (s, 3 H, 1-OMe), 2.15 (s, 3 H, 2-OAc), 2.13 (s, 3 H, 1-OAc), 2.09 (s, 3 H, 3-OAc), 2.08 (s, 3 H, 4-OAc), 2.04 (s, 3 H, 5-OAc) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 25 °C): δ = 170.6 (C=O-1), 170.4 (C=O-5), 169.9 (C=O-4), 169.7 (C=O-2), 169.3 (C=O-3), 95.4 (C-1), 71.2 (C-2), 69.8 (C-4), 69.2 (C-3), 61.7 (C-5), 57.7 (OCH_3-1), 20.9 (CCH_3-1), 20.9 (CCH_3-2), 20.7 (CCH_3-3), 20.7 (CCH_3-5) ppm. EIMS calcd. for $C_{16}H_{24}O_{11}$ [M^+] 392.1319, found 392.1320.

1,1,2,3,4,5-Hexa-*O*-acetyl-aldehydo-L-ribose (6): Compound **5** (1.0 g, 2.5 mmol) was dissolved in a mixture of Ac_2O (17.5 mL) and AcOH (7.5 mL) followed by the addition of concd. H_2SO_4 (0.6 mL). The reaction was left to proceed for 24 h at ambient temperature and subsequently poured on crushed ice to decompose remaining Ac_2O. The mixture was extracted with CH_2Cl_2 (2 × 60 mL), the combined organic layers were successively washed with water (4 × 30 mL) and saturated $NaHCO_3$ (20 mL), dried with Na_2SO_4 and concentrated to give a yellow oil (0.99 g). The oil was analyzed by ^{1}H NMR (250 MHz) in $CDCl_3$ showing the desired product plus 17% of compounds **3** and **4**. Flash column chromatography (EtOAc/petroleum ether, gradient elution) did not improve the purity.

Since the product (**6**) was obtained in no more than 82% purity, only the ^{1}H and ^{13}C NMR resonances and EIMS are reported: ^{1}H NMR (600.13 MHz, $CDCl_3$, 25 °C): δ = 6.97 (d, $J_{1,2}$ = 3.9 Hz, 1 H, 1-H), 5.41 (dd, $J_{2,1}$ = 3.9, $J_{2,3}$ = 6.7 Hz, 1 H, 2-H), 5.38 (dd, $J_{3,4}$ = 4.3, $J_{3,2}$ = 6.7 Hz, 1 H, 3-H), 5.28 (ddd, $J_{4,5a}$ = 3.5, $J_{4,3}$ = 4.3, $J_{4,5b}$ = 6.8 Hz, 1 H, 4-H), 4.34 (dd, $J_{5a,4}$ = 3.5, $J_{5a,5b}$ = 12.1 Hz, 1 H, 5_a-H), 4.12 (dd, $J_{5b,4}$ = 6.8, $J_{5b,5a}$ = 12.1 Hz, 1 H, 5_b-H), 2.15 (s, 3 H, 2-OAc), 2.10 (s, 3 H, 4-OAc), 2.09 (s, 3 H, 1-OAc), 2.09 (s, 3 H, 3-OAc), 2.08 (s, 3 H, 1-OAc), 2.05 (s, 3 H, 5-OAc) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 25 °C): δ = 170.5 (C=O-5), 169.9 (C=O-4), 169.5 (C=O-3), 169.4 (C=O-2), 168.3 (C=O-1), 168.3 (C=O-1), 86.0 (C-1), 69.5 (C-4), 69.3 (C-2), 68.5 (C-3), 61.6 (C-5), 20.8 (CCH_3-2), 20.7 (CCH_3-1), 20.7 (CCH_3-4), 20.6 (CCH_3-1), 20.6 (CCH_3-3), 20.6 (CCH_3-5) ppm. EIMS calcd. for $C_{17}H_{24}O_{12}$ [M^+] 420.1268, found 420.1278.

Methyl 2,3,5-Tri-*O*-benzoyl-α-L-ribofuranoside (7): Compound **13** (2.0 g, 12.2 mmol) was dissolved in pyridine (6 mL) and CH_2Cl_2 (10 mL), the solution was cooled down to 0 °C and BzCl (5.7 mL, 48.8 mmol) was added dropwise. The ice bath was removed and the reaction was stirred at ambient temperature for 20 h. The excess of BzCl was decomposed by the addition of crushed ice and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with water (2 × 200 mL), dried with Na_2SO_4 and the solvents evaporated. The evaporation residue was purified by column chromatography (silica gel, hexane/EtOAc, 10:1) to give **7** (4.99 g, 86%) as a colorless oil: R_f = 0.51 (4:1 petroleum ether/EtOAc). $[\alpha]_D^{24}$ = –85.6 (c = 0.97, $CHCl_3$). ^{1}H NMR (600.13 MHz, $CDCl_3$, 25 °C): δ = 8.10–7.29 (m, 15 H, aromatic), 5.73 (dd, $J_{3,4}$ = 3.6, $J_{3,2}$ = 7.1 Hz, 1 H, 3-H), 5.39 (d, $J_{1,2}$ = 4.5 Hz, 1 H, 1-H), 5.33 (dd, $J_{2,1}$ = 4.5, $J_{2,3}$ = 7.1 Hz, 1 H, 2-H), 4.75 (dd, $J_{5a,4}$ = 3.0, $J_{5a,5b}$ = 11.7 Hz, 1 H, 5_a-H), 4.65 (ddd, $J_{4,5a}$ = 3.0, $J_{4,3}$ = 3.6, $J_{4,5b}$ = 3.8 Hz, 1 H, 4-H), 4.62 (dd, $J_{5b,4}$ = 3.8, $J_{5b,5a}$ = 11.7 Hz, 1 H, 5_b-H), 3.49 (s, 3 H, 1-OMe) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 25 °C): δ = 166.2 (C=O-5), 166.0 (C=O-3), 165.5 (C=O-2), 133.4–128.3 (18C, aromatic), 101.9 (C-1), 79.4 (C-4), 71.8 (C-2), 70.8 (C-3), 64.1 (C-5), 55.8 (OCH_3-1) ppm. EIMS calcd. for $C_{27}H_{23}O_8$ [M^+ – H] 475.1393, found 475.1390.

Methyl 2,3,5-Tri-*O*-benzoyl-β-L-ribofuranoside (8): Compound **8** was prepared from **14** following the same procedure as for the preparation of compound **7**. Purification by column chromatography (silica gel, hexane/EtOAc, gradient elution) gave **8** (5.2 g, 89%). $[\alpha]_D^{24}$ = –58.6 (c = 1.07, $CHCl_3$) [ref.[23] $[\alpha]_D^{25}$ = +58 (c = 0.94, $CHCl_3$) for D-isomer]. ^{1}H NMR (600.13 MHz, $CDCl_3$, 25 °C): δ = 8.10–7.29 (m, 15 H, aromatic), 5.87 (dd, $J_{3,2}$ = 4.9, $J_{3,4}$ = 6.8 Hz, 1 H, 3-H), 5.68 (d, $J_{2,1}$ = 4.9 Hz, 1 H, 2-H), 5.16 (s, 1 H, 1-H), 4.73 (ddd, $J_{4,5a}$ = 4.2, $J_{4,5b}$ = 5.1, $J_{4,3}$ = 6.9 Hz, 1 H, 4-H), 4.72 (dd, $J_{5a,4}$ = 4.2, $J_{5a,5b}$ = 11.8 Hz, 1 H, 5_a-H), 4.53 (dd, $J_{5b,4}$ = 5.1, $J_{5b,5a}$ = 11.8 Hz, 1 H, 5_b-H), 3.42 (s, 3 H, 1-OMe) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 25 °C): δ = 166.3 (C=O-5), 165.4 (C=O-3), 165.3 (C=O-2), 133.4–128.4 (aromatic), 106.4 (C-1), 79.0 (C-4), 75.5 (C-2), 72.4 (C-3), 64.8 (C-5), 55.4 (OCH_3-1) ppm. EIMS calcd. for $C_{27}H_{23}O_8$ [M^+ – H] 475.1393, found 475.1390.

1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-L-ribose (10): To a –15 °C (NaCl/ice) solution of **8** (4 g, 8.4 mmol) in AcOH (7 mL) and Ac_2O (3 mL) concd. H_2SO_4 (450 μL) was slowly added. The ice bath was removed and the reaction stirred at ambient temperature for 4 h. The reaction was quenched by the addition of NaOAc (3 g) followed by the addition of water (5 mL) to decompose remaining Ac_2O. The reaction mixture was concentrated and the residue was dissolved in CH_2Cl_2 (50 mL), washed with water (50 mL) and saturated $NaHCO_3$ (50 mL), dried with Na_2SO_4 and the solvents evaporated. The resulting syrup was crystallized from *i*PrOH to obtain **2** (2.08 g, 49%) as white crystals. The analytical data were in agreement with those reported earlier.[17]

1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-α-L-ribose (9): The 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-α-L-ribose was prepared by conversion of the β-anomer (**10**) following the same procedure as for the preparation of compound **3** but with additional CH_2Cl_2 du to lower solubility in Ac_2O.[15] NMR and EIMS analysis of **9** were in agreement with literature data.[17]

(1*R*,1*S*)-1,4-Di-*O*-acetyl-2,3,5-tri-*O*-benzoyl-L-ribose Methyl Hemiacetals (11): Compound **11** was prepared from **8** following the same procedure as for the preparation of compound **5**.[16] The crude product was purified by column chromatography (silica gel, hexane/EtOAc, gradient elution) which gave **11** (0.78 g, 71%, isomeric ratio 3:1) as a colorless oil. The NMR and EIMS data were in agreement with those reported earlier.[17]

1,1,4-Tri-*O*-acetyl-2,3,5-tri-*O*-benzoyl-L-ribose Hydrate (12): Compound **11** (2.5 g, 4.3 mmol) was dissolved in a mixture of Ac_2O (35 mL) and AcOH (15 mL) followed by the addition of concd. H_2SO_4 (1.2 mL). The reaction was left to proceed for 20 h at ambient temperature before being neutralized with NaOAc (6 g). The remaining Ac_2O was decomposed by the addition of water (80 mL) and the mixture was extracted with $CHCl_3$ (60 mL). The organic layer was successively washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL), dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (silica gel, hexane/EtOAc, 5:1) which gave **3** (1.94 g, 74%) as a colorless oil. NMR and HRMS analysis of **12** were in agreement with earlier reported data.[17]

Supporting Information (see also the footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra of all compounds and complete kinetic data on the different acetolysis experiments.

Acknowledgments

Financial support to J. F. from the Finnish National Glycoscience Graduate School is gratefully acknowledged. The authors also wish to thank Prof. Harri Lönnberg and Dr. Patrik Eklund for the fruitful discussions. We also thank Mr. Markku Reunanen for the EIMS and HRMS analysis.

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Received: August 4, 2009
Published Online: September 24, 2009

