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Diastereoselective Formation of Pyruvylated Glycosides from Partly Protected Sugars and Methyl Pyruvate

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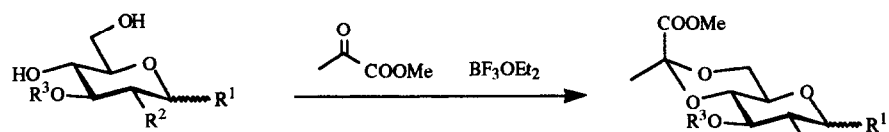
Abstract: Various partly protected sugars (*gluco-, manno-, and galactopyranosides*) were acetalized with methyl pyruvate in moderate to good yield with BF_3-etherate as the condensing reagent. Thus, (1-methoxycarbonyl)ethylidene glycosides were obtained diastereoselectively.

Pyruvic acid acetals (*i.e.* 1-carboxyethylidene groups) are present in many bacterial oligo- and polysaccharides. Due to the negative charge and the chiral center provided by the pyruvate acetal these important non-carbohydrate groups influence the immunological properties of the saccharides[1-5]. In particular, (S)-configurated 1-carboxyethylidene groups are found in the 4,6-*O*-positions of D-Glc*p*, D-Man*p*, D-Glc*p*NAc, and D-Man*p*NAc, and (R)-configurated in D-Gal*p*[6,7]. 3,4-*O*-(1-Carboxyethylidene) groups are present in the (S)-configuration in D-Gal*p*[6] and L-Rha*p*[8-10], and the 2,3-*O*-positions are pyruvylated in D-Gal*p*[11] and D-GlcA[12,13]. For the construction of higher pyruvate acetal-containing oligosaccharides efficient diastereoselective methods are therefore required for the synthesis of the respective pyruvylated monosaccharide building blocks.

Of the various procedures developed so far for the introduction of a pyruvate acetal to distinct positions of a sugar derivative[14-25], none uses the direct condensation of a sugar diol with alkyl pyruvates although this would be apparently the most straightforward approach. It has been noted[21,23,24] that all attempts for the latter direct acetalisation were unsuccessful due to the sluggish reaction of alkyl pyruvates with alcohols. However, it has been shown[2] that methyl β-D-glucopyranoside does react with methyl pyruvate, to give a diastereomeric mixture of the corresponding pyruvate acetals in a small yield. We now found that under carefully optimized conditions BF_3-etherate catalyzes the formation of the title compounds **2** from partly protected glycosides **1** and methyl pyruvate. TLC of the reaction mixture revealed that initially a mixture of the diastereomeric acetals was formed. Under the acidic conditions, however, the thermodynamically less stable isomers rearranged to the thermodynamically favoured ones which were finally isolated as the sole products. For 4,6-*O*-acetals this were the isomers having an axial methoxycarbonyl group [*i.e.* (S)-isomers for D-Glc*p* and D-Man*p* and (R)-isomers for D-Gal*p* derivatives]. Similar results also have been obtained previously for other acetalisation procedures of alkyl pyruvates[25-27].

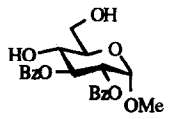
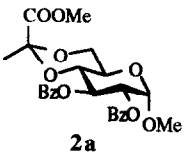
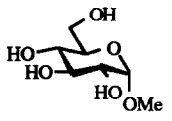
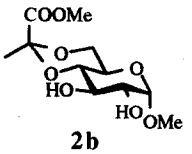
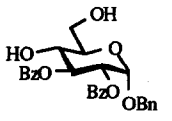
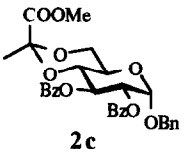
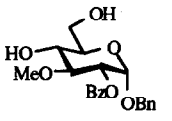
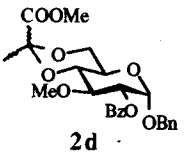
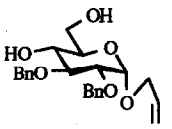
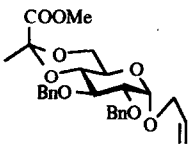
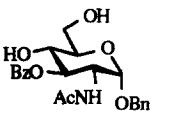
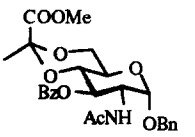
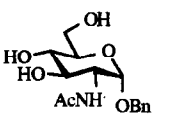
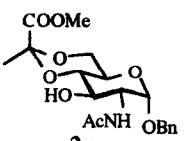


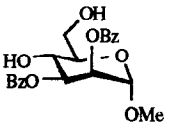
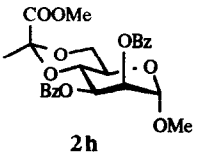
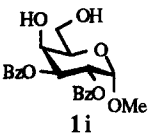
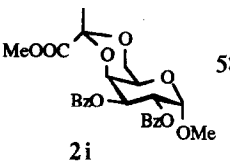
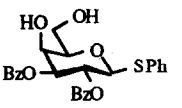
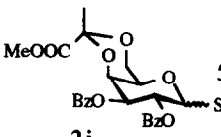
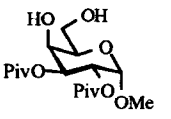
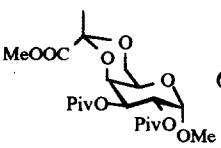
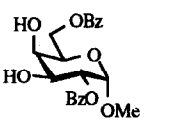
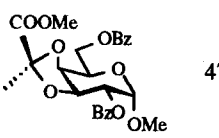
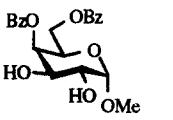
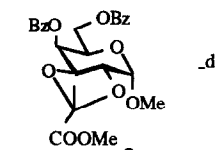
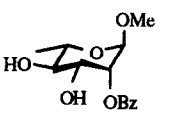
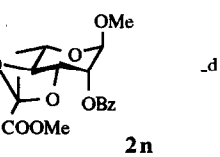
1: R^1, R^2, R^3 see table

2

In a typical example, a solution of compound **1** (1.0 mmol), methyl pyruvate (2.0 mmol) and BF_3-etherate (2.0 mmol) in CH_2Cl_2 (1.0 ml) was stirred at room temperature under Ar for 24 h. The mixture was neutralized by addition of pyridine, diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$, dried and concentrated. The residue was chromatographed on silica gel with CCl_4-acetone (5:1), to give compound **2**. The results for the acetalisation of several glycosides **1** are presented in the table.

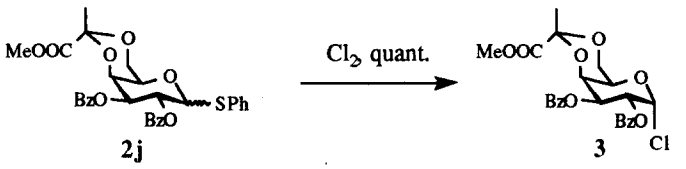
Table. Condensation of D-glycopyranosides **1** with methyl pyruvate under BF_3-catalysis[28].

entry	starting material 1	product 2	yield
1	 **1a**	 **2a**	65%
2	 **1b**	 **2b**	40%
3	 **1c**	 **2c**	52%
4	 **1d**	 **2d**	36%[a]
5	 **1e**	 **2e**	45%
6	 **1f**	 **2f**	83%
7	 **1g**	 **2g**	65%

entry	starting material 1	product 2	yield
8	 **1h**	 **2h**	43%
9	 **1i**	 **2i**	58%
10	 **1j**	 **2j**	58%[b]
11	 **1k**	 **2k**	65%
12	 **1l**	 **2l**	47%[c]
13	 **1m**	 **2m**	-[d]
14	 **1n**	 **2n**	-[d]

[a](S)-**2d** : (R)-**2d** = 56 : 44. [b]α-**2j** : β-**2j** = 52 : 48. [c](S)-**2l** : (R)-**2l** = 73 : 27. [d]Complete decomposition.

The configuration of the pyruvate acetal in all compounds **2** was unambiguously assigned by carbon NMR spectroscopy. For 4,6-*O*-(1-methoxycarbonyl)ethylidene-D-glucopyranosides **2a-g** (entries 1-7) and D-mannopyranoside **2h** (entry 8) the methyl group of the pyruvate acetal resonated at 24-26 ppm, characteristic for the (S)-configuration[15,17]. In the D-*galacto* series (entries 9-11), the methyl group showed also peaks at 24-26 ppm, and thus, the (R)-configuration for the acetal group in **2i-k**[15]. Methyl 2,6-di-*O*-benzoyl-α-D-galactopyranoside (**1l**) furnished a diastereomeric mixture of the corresponding 3,4-*O*-acetal **2l** (entry 12) that could not be separated by simple chromatography. Unfortunately, the convenient method presented here was not suitable for the preparation of pyruvate acetals of glycoside derivatives having two adjacent hydroxyls in the *trans-diequatorial* conformation (entries 13, 14). The resulting 2,3-*O*- and 3,4-*O*-acetals of methyl D-galactoside **2m** and L-rhamnoside **2n**, respectively were not stable under the acidic conditions needed for the condensation. It also should be noted that alkyl β-D-glycosides gave complex mixtures when treated under the conditions described here. This was due to extensive anomerisation and transacetalisation/transesterification[26] with methyl pyruvate during the acetalisation. Even 1-thio-galactoside **1j** (entry 10), usually anomerically stable under acidic conditions[26], was prone to anomerisation and gave a mixture of the corresponding (S)-pyruvylated D-galactosides **2j**. However, both anomers **2j** were converted smoothly by Cl_2, without separation, into 2,3-di-*O*-benzoyl-4,6-*O*-(1-methoxycarbonyl)ethylidene-α-D-galactopyranosyl chloride **3**. Compound **3** was previously obtained[26] from **2i** and has been shown to be suitable for silver salt promoted glycosylations.



In summary, the method presented here for the diastereoselective preparation of (1-methoxycarbonyl)ethylidene-glycosyl derivatives for oligosaccharide synthesis is a convenient and easy to perform alternative to the more complex procedures published previously.

Acknowledgment

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28. Compounds **2a**[24,25], **2b**[14], **2c**[26], **2d**[25], **2f**[25], **2h**[25], **2i**[25], and **3**[25] showed physical data identical to those reported previously. All new compounds gave satisfactory elemental analyses. Compound **2e** m.p. (n-hexane) 94°C; $[\alpha]_D$=+52.6° (*c*=0.4, $CHCl_3$); ^{1}H-NMR ($CDCl_3$), δ=6.00-5.58 (m, 1H, -C*H*=CH_2), 5.36-5.21 (m, 2H, -CH=C*H*$_2$), 4.97, 4.78 (2 d, 2H, CH_2Ph, J=11.2), 4.81, 4,62 (2 d, 2H, CH_2Ph, J=12.1), 4.71 (d, 1H, H-1, $J_{1,2}$=3.8), 4.20-4.12 (m, 1H, C*H*$_2$CH=CH_2), 4.04-4.00 (m, 1H, C*H*$_2$CH=CH_2), 3.98-3.91 (m, 2H, H-5,6a), 3.82 (s, 3H, $COOCH_3$), 3.76 (dd, 1H, H-6b, $J_{5,6a}$=4.5, $J_{6a,6b}$=10.1), 3.66 (t, 1H, H-4, $J_{3,4}$=10.1, $J_{4,5}$=10.1), 3.46 (dd, 1H, H-2), $J_{2,3}$=9.4), 3.40 (t, 1H, H-3), 1.56 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$), δ=133.6 (-*C*H=CH_2), 118.3 (-CH=*C*H_2), 99.1 (C_{acetal}), 96.8 (C-1), 78.8, 78.7, 78.3 (C-2,3,4), 74.7, 73.8 (CH_2Ph), 68.5 (-*C*H_2CH=CH_2), 65.5 (C-6), 61.9 (C-5), 52.7 (OCH_3), 25.5 (CH_3). **2g** $[\alpha]_D$=+79° (*c*=0.1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$), δ=5.82 (bd, 1H, NH, $J_{NH,2}$=8.8), 4.87 (d, 1H, H-1, $J_{1,2}$=3.8), 4.72, 4.48 (2 d, 2H, CH_2Ph, J=11.8), 4.17 (ddd, 1H, H-2, $J_{2,3}$=10.1), 3.98 (dd, 1H, H-6a, $J_{5,6a}$=3.8, $J_{6a,6b}$=9.3), 3.97-3.71 (m, 2H, H-5,6b), 3.85 (s, 3H, OCH_3), 3.67 (t, 1H, H-4, $J_{3,4}$=9.8, $J_{4,5}$=9.8), 3.40 (t, 1H, H-3), 3.04 (bs, 1H, OH), 1.99 (s, 3H, CH_3CO), 1.57 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$), δ=99.4 (C_{acetal}), 97.2 (C-1), 78.0 (C-4), 70.5 (C-3), 70.0 (CH_2Ph), 65.2 (C-6), 62.3 (C-5), 53.9 (OCH_3), 52.9 (C-2), 25.4 (CH_3), 23.3 (CH_3CO). β-**2j** $[\alpha]_D$=+44° (*c*=1.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ=5.74 (t, 1H, H-2, $J_{1,2}$=$J_{2,3}$=9.9), 5.22 (dd, 1H, H-3, $J_{3,4}$=3.4), 4.92 (d, 1H, H-1), 4.56 (dd, 1H, H-4, $J_{4,5}$=2.8), 4.20 (dd, 1H, H-6a, $J_{5,6a}$=1.5, $J_{6a,6b}$=12.8), 4.02 (dd, 1H, H-6b, $J_{5,6b}$=1.7), 3.64 (s, 3H, OCH_3), 3.64-3.67 (m, 1H, H-5), 1.53 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ=98.6 (C_{acetal}), 85.6 (C-1), 73.9 (C-4), 69.1, 69.0 (C-2,3), 67.0 (C-5), 65.3 (C-6), 52.4 ($COOCH_3$), 25.6 (CH_3). α-**2j** $[\alpha]_D$=+125.3° (*c*=0.9, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ=6.23 (d, 1H, H-1, $J_{1,2}$=5.5), 6.01 (dd, 1H, H-2, $J_{2,3}$=10.8), 5.55 (dd, 1H, H-3, $J_{3,4}$=3.5), 4.65 (d, 1H, H-4, $J_{4,5}$=2.9), 4.29 (s, 1H, H-5), 4.09 (dd, 1H, H-6a, $J_{5,6a}$=1.8, $J_{6a,6b}$=13.1), 4.00 (dd, 1H, H-6b, $J_{5,6b}$=1.6), 3.68 (s, 3H, OCH_3), 1.55 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ=98.8 (C_{acetal}), 86.0 (C-1), 69.8 (C-4), 69.6, 68.0 (C-2,3), 65.3 (C-6), 62.4 (C-5), 52.5 ($COOCH_3$), 25.7 (CH_3). **2k** $[\alpha]_D$=+80° (*c*=0.2, $CHCl_3$); ^{1}H-NMR ($CDCl_3$), δ=5.27 (dd, 1H, H-3, $J_{2,3}$=10.5, $J_{3,4}$=3.5), 5.15 (dd, 1H, H-2, $J_{1,2}$=3.5), 5.04 (d, 1H, H-1), 4.32 (bdd, 1H, H-4, $J_{4,5}$<1), 4.01 (bd, 2H, H-6a,6b), 3.76 (s, 3H, $COOCH_3$), 3.64 (bd, 1H, H-5), 3.39 (s, 3H, OCH_3), 1.56 (s, 3H, CH_3), 1.22, 1.19 (2 s, 18H, $CH_3^{Piv.}$); ^{13}C-NMR ($CDCl_3$), δ=98.6 (C_{acetal}), 97.8 (C-1), 69.1, 68.2, 67.6 (C-2,3,4), 65.2 (C-5), 61.1 (C-6), 55.8 (OCH_3), 52.4 ($COOCH_3$), 38.8, 38.7 ($C_{Piv.}$), 27.0 ($CH_3^{Piv.}$), 25.8 (CH_3). **2l** ^{1}H-NMR ($CDCl_3$), significant peaks δ=5.38 (dd, 1H, H-2 (S)-**2l**, $J_{1,2}$=3.6, $J_{2,3}$=8.2), 5.17 (dd, 1H, H-2 (R)-**2l**, $J_{1,2}$=3.6, $J_{2,3}$=7.6), 5.04 (d, 1H, H-1 (S)-**2l**), 5.03 (d, 1H, H-1 (R)-**2l**), 1.59 (S, 3H, CH_3 (S)-**2l**), 1.27 (s, 3H, CH_3 (R)-**2l**); ^{13}C-NMR ($CDCl_3$), significant peaks δ=106.1 (C_{acetal} (S)-**2l**), 105.8 (C_{acetal} (R)-**2l**), 97.2 (C-1), 29.3 (CH_3 (S)-**2l**), 23.4 (CH_3 (R)-**2l**).

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