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Rhizobial Saccharides 2. Selective Synthesis of Both Diastereomers of 4,6-*O*-Pyruvylated D-Glycopyranosides[1]

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Abstract: Both diastereomers of 4,6-*O*-pyruvylated glycosides *S*- and *R*-**2** were selectively prepared from the corresponding 4,6-unprotected glycosides **1** by acetalation of the latter with methyl pyruvate and BF_3-diethylether complex. In acetonitrile as the solvent, the thermodynamically favoured diastereomers having an axial-oriented methoxycarbonyl group are formed preferentially. In methyl pyruvate as the solvent, the diastereomers having an equatorial-oriented methoxycarbonyl group are the main products and the diastereoselectivity of the acetalation is influenced by the protecting groups at positions 2-O and 3-O of the starting glycosides **1**.

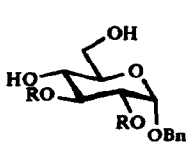
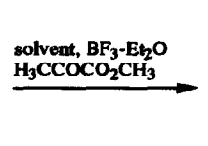
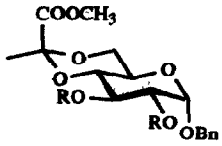
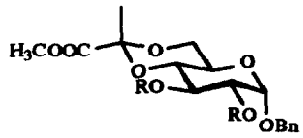
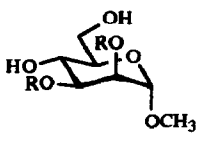
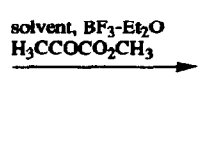
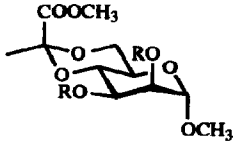
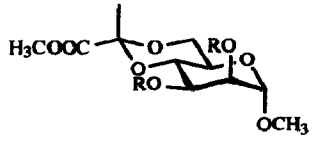
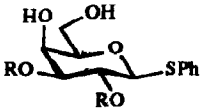
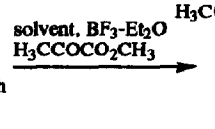
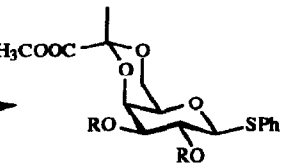
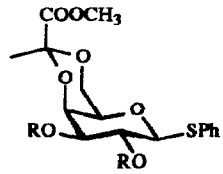
4,6-*O*-Pyruvylated hexopyranosyl [4,6-*O*-(1-carboxyethylidene)-D-glycopyranosyl] residues are found in many bacterial polysaccharides. Most prominently, 4,6-*O*-pyruvylated D-mannosyl residues are frequently detected in *Klebsiella* bacteria[2] and 4,6-*O*-pyruvylated D-glucosyl and D-galactosyl residues in *Rhizobium* bacteria[3]. As far as determined by NMR spectroscopy of bacterial saccharides[4] all 4,6-*O*-pyruvylated glycosyl residues contain a thermodynamically favoured[2e,5] *axial*-oriented carboxyl group at the pyruvate acetal moiety. Since pyruvic acid acetals as non-carbohydrate substituents of bacterial polysaccharides are immunodominant groups[6] and the interaction of 4,6-*O*-pyruvylated hexoyranoses with lectins depends on the stereochemistry of the acetal carbon of the pyruvate acetal group[7] diastereoselective syntheses are required in order to provide sufficient material for further studies of protein-interactions with pyruvate acetal-containing saccharides. This appears to be especially important for the agriculturally significant *Rhizobium* species because much controversy is found in the literature whether the pyruvylated polysaccharides of these bacteria are involved in species-specific infection mechanisms with their leguminous hosts[8].

Of the various procedures developed so far for the preparation of pyruvylated monosaccharides[5,9] the direct acetalation[1,5b,d] of partially protected glycosides with methyl pyruvate opens up the possibility to prepare selectively both diastereomers of 4,6-*O*-(1-carboxyethylidene)-D-glycopyranosides by the proper choice of the reaction conditions for the acetalation step. Results of this approach are now communicated here.

Table 1 summarises the results of the BF_3-diethylether-catalysed condensation of some 2,3-*O*-protected alkyl and phenyl 1-thio D-glycopyranosides **1** with methyl pyruvate in different solvents to give the corresponding 4,6-*O*-[1-(methoxycarbonyl)ethylidene]-D-glycopyranosides **2**[10,11]. For comparison, also some examples for pyruvylations in dichloromethane[5b] are added.

In general, all condensations in acetonitrile as the solvent proceed faster (2 h) than in dichloromethane (24 h) that was previously used for pyruvylations[5b,d]. This is due to the better stabilisation of the cationic intermediate by acetonitrile during acetalation of methyl pyruvate[5d]. However, following the course of the condensation by tlc revealed that in dichloromethane a mixture of both diastereomers *R*-**2** and *S*-**2** is initially formed that slowly isomerises during the reaction period of 24 h into the thermodynamically more stable isomer (*i.e.* *S*-**2** in the *gluco* and *manno* series and *R*-**2** in the *galacto* series). In contrast, in cation-stabilising acetonitrile as the solvent only the thermodynamically favoured diastereomer is detected in the course of the condensation probably due to the formation of nitrilium ions that enables the acetalation to proceed highly diastereoselective. Similar observations are described for pyruvate acetals of aliphatic diols[12].

Table 1. Condensation of D-glycosides **1** with methyl pyruvate under different reaction conditions[a].

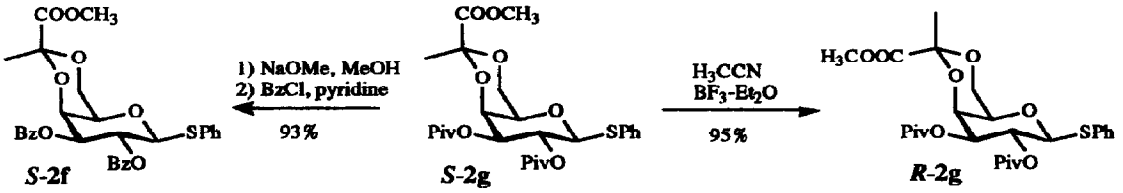
entry	start. mat. 1	solvent	thermodyn. favoured 2		kinetically favoured 2	
		solvent, BF_3-Et_2O $H_3CCOCO_2CH_3$ 		+		
1	**1a** R = Piv	H_3CCN	***S*-2a** R = Piv	69%	***R*-2a** R = Piv	traces
2		methyl pyruvate		11%		33%
3	**1b** R = Bz	CH_2Cl_2	***S*-2b** R = Bz	52%[b]	***R*-2b** R = Bz	0%[b]
4		H_3CCN		86%		0%
5		methyl pyruvate		29%		34%
6	**1c** R = ClAc[c]	H_3CCN	***S*-2c** R = ClAc[c]	78%	***R*-2c** R = ClAc[c]	0%
7		methyl pyruvate		27%		39%
		solvent, BF_3-Et_2O $H_3CCOCO_2CH_3$ 		+		
8	**1d** R = Bz	CH_2Cl_2	***S*-2d** R = Bz	43%[b]	***R*-2d** R = Bz	0%[b]
9		H_3CCN		81%		traces
10	**1e** R = Piv	H_3CCN	***S*-2e** R = Piv	60%	***R*-2e** R = Piv	traces
11		methyl pyruvate		41%		35%
		solvent, BF_3-Et_2O $H_3CCOCO_2CH_3$ 		+		
12	**1f** R = Bz	CH_2Cl_2	***R*-2f** R = Bz	58%[b,d]	***S*-2f** R = Bz	0%[b]
13		H_3CCN		91%[e]		0%[e]
14		methyl pyruvate		37%[f]		37%[f]
15	**1g** R = Piv	H_3CCN	***R*-2g** R = Piv	77%	***S*-2g** R = Piv	0%
16		methyl pyruvate		0%		95%

a: Reactions in H_3CCN were performed at room temp. for 2 h; those in methyl pyruvate for 0.1-0.5 h until all starting material had reacted[10]. b: Taken from ref. 5b. c: ClAc = chloroacetyl. d: A 52:48 mixture of α:β anomers is formed[5b]. e: Taken from ref. 5d. f: An unseparable mixture of diastereomers is formed.

In the D-gluco (entries 1-7) and D-manno series (entries 8-11) a complete diastereocontrol of the acetal formation is found for condensations in acetonitrile. In all cases, the thermodynamically favoured *S*-**2** are obtained as the sole products. In contrast, when methyl pyruvate is used as the solvent both diastereomeric pyruvate acetals are formed in variable ratios (~1:1 for entries 5,7, 11 and 1:3 for entry 2). Although the diastereoselectivity is not significantly governed by the protecting group at positions 2 and 3 of the starting diols **1**, preparative useful ratios of *S*-**2** and *R*-**2** are obtained for pivaloyl groups (entries 2 and 11). The separation of the respective diastereomers is easily achieved by a single chromatography.

In the D-galacto series (entries 12-16), however, a dramatic influence of the protecting group is observed. The 2,3-*O*-benzoylated galactoside **1f** yields a 1:1 mixture of the respective pyruvate acetals **2f** in methyl pyruvate (entry 14) whereas the corresponding 2,3-*O*-pivaloylated galactoside **1g** is diastereoselectively acetalated to give *S*-**2g** almost quantitatively[10] (entry 16). The strong dependence of the selectivity of the acetalation from the protecting group may be due to a steric hindrance of the *cis*-orientation of 3-*O* and 4-*O* in D-galactosides that favours the formation of the kinetically controlled diastereomer *S*-**2g** having an *equatorial* carboxylate group. In D-glucosides and D-mannosides, steric factors are less operative since 3-*O* and 4-*O* are *trans-diequatorial* here. Compound *S*-**2g** is also easily converted by subsequent depivaloylation (Zemplén) and rebenzoylation (BzCl, pyridine) into *S*-**2f** (93%) which could not be obtained in pure form from the 2,3-*O*-benzoylated galactoside **1f** (entry 14).

That *S*-**2g** is in fact the kinetically favoured diastereomer despite the steric influence of the 3-*O*-pivaloyl group is demonstrated by its conversion to the thermodynamically stable isomer *R*-**2g**. Treatment of *S*-**2g** in acetonitrile with BF_3-diethylether complex for 2 h at room temp. gives *R*-**2g** in 95% yield. The found equilibrium mixture of *S*-**2g** and *R*-**2g** of >5:95 is in good agreement with previously performed AM 1 calculations in the D-gluco series[5a] that revealed a 2.3 kcal/mol higher stability for diastereomeric pyruvylated glycosides with an *axial*-oriented carboxylate group.



In summary, the selective pyruvylation of simple glycoside diols **1** presented here opens up a preparatively easy entry to both diastereomers of 4,6-*O*-[1-(methoxycarbonyl)ethylidene]-D-glycopyranosides that are useful for the construction of higher oligosaccharides *via* the respective pyruvylated glycosyl donors[5].

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References and Notes

1. For part 1 see: E. Eckhardt, T. Ziegler, *Carbohydr. Res.*, **1994**, in press.
2. (a) Jones, D. N. M.; Sanders, J. K. M. *J. Chem. Soc, Chem. Commun.*, **1989**, 167-169. (b) Dutton, G. G. S.; Yang, M. T. *Can. J. Chem.*, **1973**, *51*, 1826-1832. (c) Elsässer-Beile, U.; Friebolin, H.; Stirm, S. *Carbohydr. Res.*, **1978**, *65*, 245-249. (d) Gromus, B. J.; Wheat, R. W. *J. Bacteriol.*, **1971**, *108*, 1304-1309. (e) Okutani, K.; Dutton, G. G. S. *Carbohydr. Res.*, **1980**, *86*, 259-271. (f) Dutton, G. G. S.; Parolis, H.; Parolis, L. A. S. *Carbohydr. Res.*, **1986**, *152*, 249-259 and ref. therein.

3. (a) Cremers, H. C. J. C.; Stevens, K.; Lugtenberg, B. J. J.; Wijffelman, C. A.; Batley, M.; Redmond, J. W.; Breedvelt, M. W.; Zevenhuizen, L. P. T. M. *Carbohydr. Res.*, **1991**, *218*, 185-200. (b) Dudman, W. F.; Franzén, L.-E.; McNeil, M.; Darvill, A. G.; Albersheim, P. *Carbohydr. Res.*, **1983**, *117*, 169-183 and ref. therein. (c) Gil-Serrano, A.; González-Jiménez, I.; Tejero-Mateo, P.; Sanchez del Junco, A.; Megias, M.; Romero-Vázquez, M. J. *Carbohydr. Res.*, **1992**, *225*, 169-174 and ref. therein. (d) Navarini, L.; Cesàro, A.; Ross-Murphy, S. B. *Carbohydr. Res.*, **1992**, *223*, 227-234. (e) Amemura, A.; Harada, T. *Carbohydr. Res.*, **1983**, *112*, 85-93. (f) Levery, S. B.; Zhan, H.; Lee, C. C.; Leigh, J. A.; Hakomori, S.-i. *Carbohydr. Res.*, **1991**, *210*, 339-347 and ref. therein. (g) Hollingsworth, R. I.; Dazzo, F. B.; Hallenga, K.; Musselman, B. *Carbohydr. Res.*, **1988**, *172*, 97-112 and ref. therein.
4. (a) Garegg, P. J.; Lindberg, B.; Kvarnström, I. *Carbohydr. Res.*, **1979**, *77*, 71-78. (b) Garegg, P. J.; Jansson, P.-E.; Lindberg, B.; Lindh, F.; Lönngren, J.; Kvarnström, I.; Nimmich, W. *Carbohydr. Res.*, **1980**, *78*, 127-132. (c) Gorin, P. A. J.; Mazurek, M.; Duarte, H. S.; Iacomini, M.; Duarte, J. H. *Carbohydr. Res.*, **1982**, *100*, 1-15. (d) Jones, D. N. M.; Sanders, J. K. M. *Carbohydr. Res.*, **1990**, *208*, 15-21. (e) Jansson, P.-E.; Lindberg, J.; Widmalm, G. *Acta Chem. Scand.*, **1993**, *47*, 711-715.
5. (a) Ziegler, T.; Eckhardt, E.; Herold, G. *Liebigs Ann. Chem.*, **1992**, 441-451. (b) Ziegler, T.; Eckhardt, E.; Herold, G. *Tetrahedron Lett.*, **1992**, *33*, 441-451. (c) Ziegler, T.; Eckhardt, E.; Neumann, K.; Birrault, V. *Synthesis.*, **1992**, 1013-1017. (d) Ziegler, T.; Eckhardt, E.; Strayle, J.; Herzog, H. *Carbohydr. Res.*, **1994**, *253*, 167-183.
6. (a) Dudman, W. F.; Heidelberger, M. *Science*, **1969**, *164*, 954-955. (b) Kabat, E. A.; Liao, J.; Bretting, H.; Franklin, E. C.; Geltner, D.; Frangione, B.; Koshland, M. E.; Shyong, J.; Osserman, E. F. *J. Exp. Med.*, **1980**, *152*, 979-995. (c) Rao, A. S.; Kabat, E. A.; Nimmich, W.; Osserman, E. F. *Mol. Immunol.*, **1982**, *19*, 609-618. (d) Rao, A. S.; Liao, J.; Kabat, E. A.; Osserman, E. F.; Harboe, M.; Nimmich, W. *J. Biol. Chem.*, **1984**, *259*, 1018-1026.
7. (a) Hind, C. R. K.; Collins, P. M.; Renn, D.; Cook, R. B.; Caspi, D.; Baltz, M. L.; Pepys, M. B. *J. Exp. Med.*, **1984**, *159*, 1058-1069. (b) Hind, C. R. K.; Collins, P. M.; Pepys, M. B. *Biochim. Biophys. Acta*, **1984**, *802*, 148-150. (c) Hind, C. R. K.; Collins, P. M.; Baltz, M. L.; Pepys, M. B. *Biochem. J.*, **1985**, *255*, 107-111.
8. (a) Werner, D. *Pflanzliche und mikrobielle Symbiosen*, Thieme Verlag, Stuttgart, **1987**. (b) Gray, J. X.; Rolfe, B. G. *Mol. Microbiol.*, **1990**, *4*, 1425-1431. (c) Zevenhuizen, L. P. T. M. in Dawes, E. D. (ed.), *Novel Biodegradable Microbial Polymers*, Kluwer Academic Publ., Netherlands, **1990**, pp. 387-402. (d) Verma, D. P. S. *Plant Cell*, **1992**, *4*, 373-382.
9. (a) Gorin, P. A. J.; Ishikawa, T. *Can. J. Chem.*, **1967**, *45*, 521-532. (b) Hashimoto, H.; Hiruma, K.; Tamura, J.-i. *Carbohydr. Res.*, **1988**, *177*, c9-c12. (c) Lipták, A.; Szabó, L. *Carbohydr. Res.*, **1988**, *184*, c5-c8. (d) Lipták, A.; Szabó, L. *J. Carbohydr. Chem.*, **1989**, *8*, 629-644. (e) Collins, P. M.; McKinnon, A. C.; Manro, A. *Tetrahedron Lett.*, **1989**, *30*, 1399-1400. (f) Aspinall, G. O.; Ibrahim, I. H.; Khare, N. K. *Carbohydr. Res.*, **1990**, *200*, 247-256.
10. In a typical procedure, BF_3-diethylether (2.4 ml, 19 mmol) was added at room temp. to a suspension of compound **1 g** (4.40 g, 10 mmol) in methyl pyruvate (40 ml) wherupon dissolution of the educt ocurred. The solution was stirred at room temp. until tlc indicated the complete conversion of the educt to a single faster moving product (10 min.). The mixture was poured onto aq. $NaHCO_3$ solution and extracted with CH_2Cl_2. Evaporation of the solvent and recrystallisation of the residue from acetone/n-hexane gave compound ***S*-2 g** (5.0 g, 95%). For physical data of new compounds 2 see ref. 11.
11. All new compounds 2 gave satisfactory elemental analyses. ***S*-2a**: oil, $[\alpha]_D$ +122.4° (1.0, $CHCl_3$); ^{13}C-NMR ($CDCl_3$): δ 95.8 (C-1), 68.5 (C-2), 70.9 (C-3), 75.7 (C-4), 62.1 (C-5), 65.4 (C-6), 52.6 ($COOCH_3$), 25.3 (CH_3), 99.3 (C_{acetal}); ***R*-2a**: mp. 141°C, $[\alpha]_D$ +98.9° (0.6, $CHCl_3$), ^{13}C-NMR ($CDCl_3$): δ 95.9 (C-1), 69.0 (C-2), 71.7 (C-3), 72.5 (C-4), 53.6 (C-5), 63.2 (C-6), 52.9 ($COOCH_3$), 17.8 (CH_3), 98.4 (C_{acetal}); ***S*-2c**: oil, $[\alpha]_D$ +133.2° (0.4, $CHCl_3$), ^{13}C-NMR ($CDCl_3$): δ 95.3 (C-1), 70.7 (C-2), 72.5 (C-3), 74.8 (C-4), 62.2 (C-5), 65.2 (C-6), 52.8 ($COOCH_3$), 25.2 (CH_3), 99.4 (C_{acetal}); ***R*-2c**: oil, $[\alpha]_D$ +83.7° (1.0, $CHCl_3$), ^{13}C-NMR ($CDCl_3$): δ 95.4 (C-1), 70.8 (C-2), 71.4 (C-3), 72.8 (C-4), 63.2 (C-5), 62.9 (C-6), 53.0 ($COOCH_3$), 18.0 (CH_3), 98.2 (C_{acetal}); ***S*-2e**: oil, $[\alpha]_D$ +55.5° (0.7, $CHCl_3$), ^{13}C-NMR ($CDCl_3$): δ 99.5 (C-1), 73.2, 69.9, 67.5, 63.2 (C-2,3,4,5), 65.4 (C-6), 52.3 ($COOCH_3$), 25.3 (CH_3), 99.6 (C_{acetal}); ***R*-2e**: mp. 113-114°C, $[\alpha]_D$ -1.2° (0.7, $CHCl_3$), ^{13}C-NMR ($CDCl_3$): δ 99.7 (C-1), 69.9, 69.2, 67.9, 64.2 (C-2,3,4,5), 63.3 (C-6), 52.8 ($COOCH_3$), 17.9 (CH_3), 98.2 (C_{acetal}); ***S*-2f**: mp. 141°C, $[\alpha]_D$ +156.8° (0.7, $CHCl_3$), ^{13}C-NMR ($CDCl_3$): δ 86.4 (C-1), 73.7, 70.9, 67.7, 67.1 (C-2,3,4,5), 64.7 (C-6), 52.9 ($COOCH_3$), 22.0 (CH_3), 97.4 (C_{acetal}); ***R*-2g**: mp. 149°C, $[\alpha]_D$ -0.7° (0.5, $CHCl_3$), ^{13}C-NMR ($CDCl_3$): δ 86.0 (C-1), 72.7, 68.8, 65.7, 68.8 (C-2,3,4,5), 65.3 (C-6), 52.4 ($COOCH_3$), 25.7 (CH_3), 98.5 (C_{acetal}); ***S*-2g**: mp. 170°C, $[\alpha]_D$ +61.6° (1.4, $CHCl_3$), ^{13}C-NMR ($CDCl_3$): δ 86.3 (C-1), 72.6, 70.5, 66.5, 66.5 (C-2,3,4,5), 64.4 (C-6), 52.8 ($COOCH_3$), 21.2 (CH_3), 97.2 (C_{acetal}).
12. (a) Bailey, W. F.; Eliel, E. L. *J. Amer. Chem. Soc.*, **1974**, *96*, 1798-1806. (b) Suemune, H.; Tanaka, N.; Sakai, K. *Chem. Pharm. Bull.*, **1990**, *38*, 3155-3157.

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