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Preliminary communication

A new and efficient synthesis of pyruvate acetals of hexopyranosides

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Pyruvic acid acetals (1-carboxyethylidene acetals) linked to aldohexopyranosyl residues are known to occur in a number of polysaccharides. These include agar[1], and exocellular[2] and capsular polysaccharides[3]. Pyruvic acid is most often linked to O-4 and O-6 of such hexoses as D-glucose, D-mannose, D-galactose, and 2-acetamido-2-deoxy-D-glucose, and is also found linked to such vicinal atoms as O-3 and O-4 of D-galactose and L-rhamnose, and O-2 and O-3 of D-glucuronic acid.

Pyruvic acid acetals of hexopyranosides were first synthesized by Gorin and Ishikawa[4] by acetalation with 1-acetoxy-2-propanone in the presence of acid, followed by platinum–oxygen oxidation. However, the total yields from these two steps were not satisfactory for preparative purposes[5]. In the study described in this communication, the method[6] of acetal formation between a ketone and a trimethylsilyl ether of a diol in the presence of trimethylsilyl triflate was successfully applied to synthesis of the pyruvate acetals of several hexopyranosides, using *tert*-butyldimethylsilyl ethers of diols. Among them, the 4,6-acetals of α-D-mannopyranosides and the 3,4-acetals of α-D-galactopyranosides were synthesized for the first time.

The carbonyl function in a carboxylic ester can form the acetal, giving the orthoester, as proved in the synthesis of glycosylideneglycoses[7], including such orthosomycin antibiotics as[8] destomycin C. However, in acetalations with pyruvate, only the keto function reacts, to give the desired pyruvate acetals as depicted in Scheme 1.

Methyl 2,3-di-*O*-benzyl-α-D-hexopyranosides of the *gluco* (**3**) *manno* (**5**)†, and *galacto* (**7**) configurations and methyl 2,6-di-*O*-benzyl-α-D-galactopyranoside (**10**) were silylated with *tert*-butylchlorodimethylsilane and imidazole in *N,N*-di-

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†The diol **5** was prepared in 75% yield from the known methyl 4,6-di-*O*-allyl-α-D-mannopyranoside[7] by conventional benzylation and *O*-deallylation.

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3 R = H
4 R = Me_3CMe_2Si

5 R = H
6 R = Me_3CMe_2Si

7 R^1 = R^2 = H
8 R^1 = H, R^2 = Me_3CMe_2Si
9 R^1 = Me_3Si, R^2 = Me_3CMe_2Si

10 R^1 = R^2 = H
11 R^1 = Me_3CMe_2Si, R^2 = H
12 R^1 = Me_3CMe_2Si, R^2 = Me_3Si

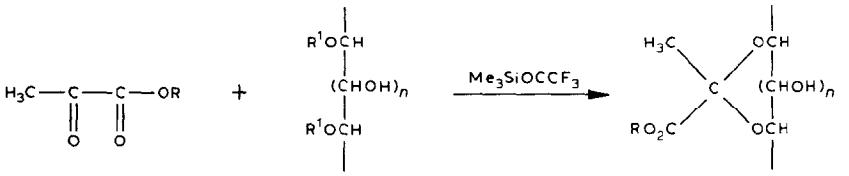
13 (R) R^1 = CO_2Et, R^2 = Me
13 (S) R^1 = Me, R^2 = CO_2Et

14 (R) R^1 = CO_2Et, R^2 = Me
14 (S) R^1 = Me, R^2 = CO_2Et
15 (S) R^1 = Me, R^2 = CO_2Bn

16 (R) R^1 = CO_2Et, R^2 = Me
16 (S) R^1 = Me, R^2 = CO_2Et

17 (R) R^1 = CO_2Et, R^2 = Me
17 (S) R^1 = Me, R^2 = CO_2Et

methylformamide. Although the first two 4,6-diols gave the corresponding 4,6-di-*O*-(*tert*-butyldimethylsilyl) derivatives (**4** and **6**), both in quantitative yield, the latter two gave only the mono-*O*-(*tert*-butyldimethylsilyl) derivatives, **8** and **11**, respectively. Successive treatment of these monosilyl ethers with chlorotrimethylsilane afforded mixed di-*O*-silyl derivatives **9** and **12** in ~90% yields. These four disilyl ethers were sufficiently stable during chromatographic purification on silica gel, or during removal of imidazole by extraction with water.



Scheme 1

A typical acetalation procedure is as follows. To a solution of a silyl ether (**4, 6, 9,** or **12**; 1 mmol) and pyruvate [**1** or **2** (ref. 9), 2 mmol] in dichloromethane or diethyl ether (1 mL) was added trimethylsilyl triflate (0.4 mmol) at −20°, and the mixture was kept at −5° or +3° for a few days at the same temperature. The results are summarized in Table I. When ethyl pyruvate (**1**) was used, the total yields of the two stereoisomers possible due to the asymmetric acetal carbon atom were ~60% for all silyl ethers tested, irrespective of the solvent. In the cases of the 4,6-di-*O*-silyl ethers having *gluco* (**4**) and *galacto* (**9**) configurations, stereoselectivity was not observed (in both solvents), giving **13** and **16**, respectively, as an ~1:1 mixture of the (*R*) and (*S*) isomers. However, the *manno* isomer **6** of the 4,6-disilyl ether and the *galacto* isomer **12** of the 3,4-disilyl ether gave mainly the (*S*)-isomers,

TABLE I

ACETALATION REACTIONS

Pyruvate	*Disilyl ether*	*Solvent*	*Temp. (°)*	*Time (d)*	*Product*	*Yield*	
						(R)	(S)
1	**4**	CH_2Cl_2	−5	2	**13**	31	24
1	**4**	Et_2O	−5	3	**13**	18	28
1	**6**	CH_2Cl_2	−5	3	**14**	0	60
1	**6**	Et_2O	−5	5	**14**	28	34
2	**6**	CH_2Cl_2	+3	2	**15**	0	22
2	**6**	Et_2O	+3	5	**15**	0	25
1	**9**	CH_2Cl_2	−5	3	**16**	32	33
1	**9**	Et_2O	−5	2	**16**	36	27
1	**12**	CH_2Cl_2	−5	1	**17**	20	42
1	**12**	Et_2O	−5	2	**17**	19	35

TABLE II

^1H- AND ^{13}C-N.M.R. CHEMICAL SHIFTS[a] OF ACETALIC METHYL GROUP

Compounds	$\delta\ ^1H$		$\delta\ ^{13}C$	
	(R)	(S)	(R)	(S)
13	1.67	1.55	17.88	25.46
14	1.72	1.52	17.88	25.62
15		1.57		25.62
16	1.62	1.76	26.00	20.37
17	1.58	1.65	23.35	25.90

[a]In $CDCl_3$ at 100 MHz.

14(*S*) and **17**(*S*). Furthermore, in the case of the *manno* isomer, a remarkable solvent effect was observed; that is, in dichloromethane, only **14**(*S*) was obtained (in 60% yield). On the other hand, in the case of benzyl pyruvate (**2**), the acetalation proceeded slowly. Although the coupling of **2** with **6**, even at a higher temperature (+3°), gave the acetal **15** in lower yields, the (*S*)-isomer was formed exclusively.

The configuration of the acetal carbon atom was determined by ^1H- and ^{13}C-n.m.r. chemical shifts of the acetalic methyl groups (see Table II), in comparison with those previously reported[4,5]. It was proved that the 4,6-acetal of the *manno* configuration showed a difference in the chemical shifts of isomeric pairs similar to those for the corresponding *gluco* and *galacto* isomers.

Thus, the pyruvate acetal formation described herein should be practical for introduction of this immunologically important function into such oligosaccharides as repeating units of exocellular and capsular polysaccharides.

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