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SYNTHESES OF 1-*O*-ACYLALDOSE DERIVATIVES *via* THE CORRESPONDING *O*-GLYCOSYLPSEUDOUREAS*

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ABSTRACT

A series of 1-*O*-acylaldose derivatives was prepared in good yield through the reaction of 1,3-dialkyl-*O*-glycosylpseudoureas with carboxylic acids.

INTRODUCTION

1,2,3-Trialkylpseudoureas have been prepared[2] by treating an alcohol with a carbodiimide in the presence of copper(I) chloride [Cu(I)Cl]. On the other hand, the pseudoureas are well known to give the corresponding esters, ethers, and sulfides on reaction with carboxylic acids, phenols, and thiophenols, respectively[3]. Successive to a communication[4] on the reaction of *O*-glycosylpseudoureas with a variety of nucleophiles, we reported[5] the nucleophilic substitution reactions, with a series of phenols, of a pseudourea derivative, obtained from 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose (**1**), bearing no protecting group to exert an anchimeric effect, and proved that the reaction proceeds through an SN2 mechanism, to give the corresponding phenyl β-D-glucopyranoside derivatives in good yields[5]. We now describe, in detail, the reaction of *O*-glycosylpseudoureas with carboxylic acids.

RESULTS AND DISCUSSION

*Synthesis of 1-*O*-acyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoses.* — Treatment of **1** (2.0 mmol) with dicyclohexylcarbodiimide (**2**) (6.0 mmol) in the presence of copper(I) chloride (0.02 mmol) by fusion for 0.5 h at 80–85° gave the corresponding *O*-D-glucopyranosylpseudourea derivative (**4**), according to a method reported[5]. Compound **4** thus obtained was dissolved in 1,2-dimethoxyethane (DME), and treated with a carboxylic acid; the results thus obtained are summarized in Table I.

An equimolar reaction with benzoic acid (**10**) (Entry 3) gave the corresponding 1-benzoate (**19**) (62% yield), but reaction with 3 molar equivalents of **10** gave the product in 88% yield; the recovery of **1** decreased from 30 to 5% as the proportion

*Partial Protection of Carbohydrate Derivatives, Part 11. For Part 10, see ref. 1.

TABLE I

REACTIONS AT 20–25° OF CARBOXYLIC ACIDS WITH *O*-(2,3,4,6-TETRA-*O*-BENZYL-D-GLUCOPYRANOSYL)-PSEUDOUREA, RESULTING FROM THE FUSION OF **1** WITH **2**[a]

Entry	*Carboxylic acid (mmol)*	*Reaction time (h)*	*1-O-Acyl sugar derivative*				*Recovered* **1** *(%)*
				Yield (%)	$\alpha:\beta$[b]	*β anomer*[c]	
1	**6** (6.0)	1	**15**	82	7:43	n.d.[d]	10
2	**8** (6.0)	1	**17**	n.d.	1:4	15	n.d.
3	**10** (2.0)	1	**19**	62	n.d.	53	30
4	**10** (6.0)	1	**19**	88	3:22	70	5
5[e]	**10** (6.0)	1	**19**	89	7:43	70	7
6	**11** (2.2)	0.5	**20**	80	n.d.	n.d.	11
7	**11** (6.0)	0.5	**20**	88	4:21	n.d.	6

[a]A melt resulting from fusion of **1** (2.0 mmol) with **2** (6.0 mmol) in the presence of Cu(I)Cl (0.02 mmol) for 0.5 h at 80–85°, with stirring, was treated with a carboxylic acid (2.0–6.0 mmol) in DME under the conditions given in the Table. [b]The ratios were calculated in terms of the area ratios of H-1 signals, due to the 1-*O*-acyl derivatives, in the ^{1}H-n.m.r. spectra. [c]These yields are of the β anomers isolated by crystallization. [d]Not determined. [e]Prior to the reaction, the Cu(I)Cl was removed.

of **10** was increased. The stereoselectivity in the formation of the β anomer was, moreover, high ($\alpha:\beta$ = 3:17). Copper(I) chloride was found scarcely to affect the reaction of **4** with **10** (Entry 5); removal of the catalyst after the formation reaction of **4** brought about no difference in the yield of **19**, or in the ratio of the anomers.

The reaction with the strongly acidic *p*-nitrobenzoic acid (**11**) was effectively induced, despite use of an equimolar proportion and a short reaction-time (0.5 h), to give the corresponding 1-(*p*-nitrobenzoate) in 80% yield (Entry 6). Even the reaction with acetic acid (**6**) gave the corresponding 1-acetate (**15**) in good yield (Entry 1); this reaction was also induced smoothly in M aqueous acetic acid–dichloromethane at 0°, to give **15** (76% isolated yield; $\alpha:\beta$ = 7:43), in addition to recovered **1** (24%). The reaction with *N*-benzoylglycine (**8**) (Entry 2) similarly gave the expected 1-*O*-(*N*-benzoylglycyl) derivative (**17**); however, it underwent undesirable decomposition during chromatography on silica gel, and thus was subjected to repeated recrystallization (to remove contaminant), giving only a 15% yield of the β anomer.

Subsequently, the reaction in chloroform was examined; **1** was treated with **2** (1.1 mol) in chloroform in the presence of a catalytic amount of copper(I) chloride for 2 days at room temperature, and the resulting solution was treated with 1.1 mol of a carboxylic acid for 1 h. The results thus obtained are summarized in Table II, together with those given by use of diisopropylcarbodiimide (**3**), instead of **2**, for the reaction; the reactions of carboxylic acids **6–14** gave the corresponding 1-*O*-acyl derivatives **15–23** (67–89% yield).

Among these reactions, the yields of **20** and **21** were comparatively lower than those of the others (Entries 9 and 11), but were found to be improvable by

TABLE II

REACTIONS OF 1-*O*-ACYL-2,3,4,6-TETRA-*O*-BENZYL-D-GLUCOPYRANOSES WITH CARBOXYLIC ACIDS IN CHLOROFORM, BY USE OF **2** OR **3** AS THE COUPLING AGENT[a]

Entry	*Carboxylic acid*	1-O-*Acyl sugar derivative*				*Properties of β anomers*									*Properties of α anomers*		*Recovered* **1** *(%)*
			Yield (%)	*α:β*[b]	*β*[c]	*M.p.*[d] *(°C)*	$[\alpha]_D^{22}$ *(degrees) (c 1.0, $CHCl_3$)*	ν_{max}^{KBr} *(cm^{-1}) (C=O)*	*^{1}H-N.m.r. (H-1)* δ	*^{1}H-N.m.r. (H-1)* $J_{1,2}$ *(Hz)*	*Molecular formula*	*Elemental analyses*[e] *(%)* C	H	N	*^{1}H-N.m.r. (H-1)* δ	*^{1}H-N.m.r. (H-1)* $J_{1,2}$ *(Hz)*	
1†	6	**15**	89	7:43	—	n.d.[b] (*lit.*[5], syrup)	n.d.[f]	n.d.	5.63(d)	7.1					6.35(d)	3.3	8
2†	7	**16**	82	1:4	57	87.5–88.5(H)	−14	1739	5.67(d)	7.0	$C_{39}H_{43}O_7$	75.13 (74.97	7.11 7.10)		6.42(d)	2.8	13
3†	8	**17**	n.d.	19:81	21	133.5–134.5(M)	−5	1770 1649	5.71(d)	6.2	$C_{43}H_{43}NO_8$	73.58 (73.58	6.21 6.18	2.04 2.00)	6.40(d)	3.0	n.d.
4†	9	**18**	87	1:4	55	89.5–91(M)	+14	1760 1719	5.84(d)	7.0	$C_{44}H_{45}NO_9$	72.21 (72.21	6.18 6.20	1.69 2.03)	6.38(d)	2.4	9
5†	10	**19**	83	23:78	69	95–95.5(C) [*lit.*[6] 96.7–97.2(C),	−23 −23]	1742	5.91(dd)	5.5 2.2					6.57(d)	3.0	14
6§,[h]	11	**20**	70	3:17	n.d.	97–98(H) [*lit.*[5] 96–98,	−29 −27]	1740	5.93(dd)	5.0 1.8[g]					6.63(d)	3.0	6
7§,[i]	11	**20**	85	29:71	44												
8§	12	**21**	67	4:21	43	97–97.5(H)	−28	1749	5.89(d)	6.7	$C_{41}H_{39}NO_9$	71.12 (71.39	5.60 5.70	1.88 2.03)	6.58(d)	2.8	8
9§	13	**22**	81	n.d.	58	107.5–109(M)	−12	1695	5.90(dd)	5.5 2.0[g]	$C_{41}H_{40}O_8$	74.43 (74.53	6.50 6.10)		n.d.	n.d.	9
10§	14	**23**	78	37:63	39	87.5–88(M)	−19	1726	5.93(d)	7.0	$C_{42}H_{42}O_7$	76.78 (76.57	6.47 6.43)		6.63(d)	3.0	11

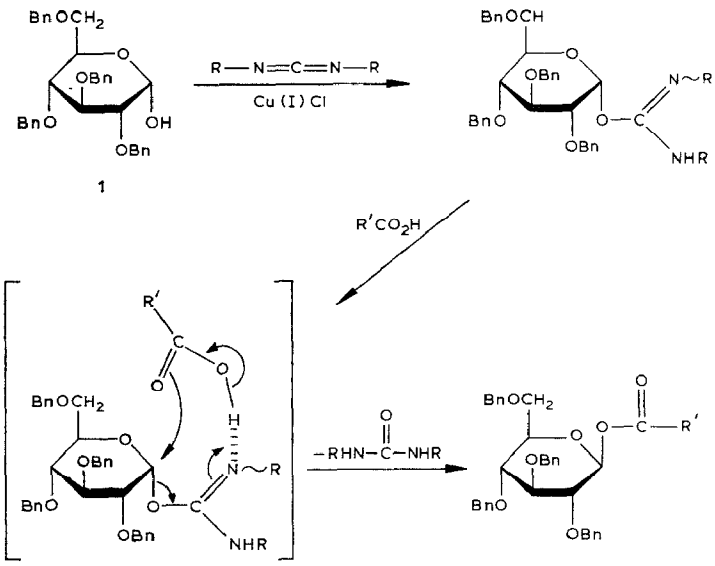
[a]A solution of **1** (2.0 mmol), **2**† or **3**§ (2.2 mmol), and Cu(I)Cl (0.02 mmol) in chloroform (2 mL) was stirred for 2 days at 20–25°, after which a carboxylic acid (2.2 mmol) was added, and the mixture was stirred for 1 h at 20–25°. [b]These ratios were estimated in terms of the area-ratios of the H-1 signals, of the 1-*O*-acyl derivatives, in the ^{1}H-spectra. [c]These yields are of β anomers isolated crystalline. [d]C, H, and M (in parentheses) denote cyclohexane, hexane, and methanol, respectively. [e]Found, no parentheses; Calculated, in parentheses. [f]Not determined. [g]These coupling constants are of long-range couplings. [h]Properties of the corresponding α anomer: m.p. 126–127° (M), $[\alpha]_D^{22}$ +77° (*c* 1.0, $CHCl_3$), ν_{max}^{KBr} 1732 cm^{-1} (C=O) (*lit.*[7] m.p. 127–129°, $[\alpha]_D$ +73°). [i]Following the preparation of pseudourea **5**, DME (2 mL, as the solvent) and then **11** were added.

addition of DME as the solvent prior to the reaction with the carboxylic acids (see Entry 10; from 70 to 85% yield). Incidentally, the anomer ratio in the mixtures of the 1-*O*-acyl derivatives **15–23** obtained was, by and large, 1 : 4, which is similar to those obtained in the phenyl glycoside synthesis.

Incidentally, 1-*O*-acylation of **1** performed traditionally gave an anomeric mixture composed mainly of α anomer or a 1 : 1 mixture of the anomers[6,7]. Recently, however, the corresponding β anomers have been prepared from the reactions of 1-*O*-lithio derivatives, obtained by treatment of **1** with butyllithium in benzene, with an acyl chloride[8], or of the tributyltin alkoxide of **1** with an acyl chloride[9], although attention must always be paid to exclusion of moisture when these methods are used. In contrast, in the present instance, the whole procedure can be performed, in a one-flask operation, regardless of any moisture; this procedure is thus promising as a simple method for the preparation of 1-*O*-acyl-β-aldose derivatives.

The reaction mechanism involved may be assumed to be as follows: the resulting intermediary 1,3-dialkyl-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)pseudoureas (**4** and **5**, respectively) have been proved to be mainly composed of the corresponding α anomers[5]. Moreover, all of the resulting 1-*O*-acyl derivatives contain a preponderance of the corresponding β anomers. Therefore, the reaction is assumed to proceed *via* the mechanism depicted in Scheme 1, which is similar to that proposed for the reaction of *O*-alkylpseudoureas with carboxylic acids.

*Synthesis of 1-*O*-acyl-2,3 : 5,6-di-*O*-isopropylidene-*D*-mannofuranoses.* — 1-*O*-Acylation of 2,3 : 5,6-di-*O*-isopropylidene-α-D-mannofuranose (**24**) was successively investigated in terms of the corresponding pseudourea. The resulting 1,3-diisopropyl-



Scheme 1

TABLE III

SYNTHESIS OF 1-*O*-ACYL-2,3:5,6-DI-*O*-ISOPROPYLIDENE-D-MANNOFURANOSES IN CHLOROFORM SOLUTION BY USE OF THE PSEUDOUREA PREPARED[a] FROM **24** AND **3**

Entry	*Conditions for the 1st stage*				*Conditions for the 2nd stage*			*1-O-Acyl derivative*					*Yield(%) of* **31**	*Recovered* **24** *(%)*
	24 *(mmol)*	**3** *(mmol)*	*Cu(I)Cl (mmol)*	*Time (days)*	*Carboxylic acid (mmol)*		*Time (days)*	*Yield (%) of α anomer*		*Yield (%) of β anomer*		*α:β*		
1	2.0	4.4	0.02	15	**6**	4.4	2	**25**	25	**26**	41	19:31	—	10
2	2.0	4.4	0.02	15	**10**	4.4	2	**27**	27	**28**	73	23:77	—	5
3[b]	2.0	4.4	0.02	15	**11**	4.4	2	**29**	31	***00***	46	41:59	—	13
4	2.0	2.2	0.2	5	**6**	2.2	2	**25**	22	**26**	55	29:71	3	16
5	2.0	2.2	0.2	5	**10**	2.2	2	**27**	16	**28**	63	1:4	—	11
6	2.0	2.2	0.2	5	**10**	2.2	1/24	**27**	28	**28**	55	17:33	—	8
7[b]	2.0	2.2	0.2	5	**11**	2.2	2	**29**	13	***00***	60	9:41	5	12

[a]All reactions in the 1st and 2nd stage were performed at 20–25°, except for the 2nd stage in Entry 6, which was conducted under reflux. [b]After the 1st-stage reaction of **24** with **3**, DME was added to the resulting mixtures.

TABLE IV

PROPERTIES OF 1-*O*-ACYL-2,3:5,6-DI-*O*-ISOPROPYLIDENE-D-MANNOFURANOSES

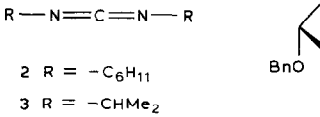
Compound	*M.p.*[a] *(°C)*	$[\alpha]_D^{22}$ *(degrees) (c, CHCl₃)*	ν_{max}^{KBr} *(cm⁻¹) (C=O)*	*¹H-N.m.r. data*				*Elemental analysis*						
				H-1		*CMe₂*	*Others*	*Molecular formula*	*Calc. (%)*			*Found (%)*		
				δ	$J_{1,2}$ *(Hz)*	*δ*	*δ, J (Hz)*		*C*	*H*	*N*	*C*	*H*	*N*
25	syrup	+76 (1.5)	1742	6.12(s)		1.33, 1.35, 1.45, 1.47	2.07(s) [$COCH_3$]	$C_{14}H_{22}O_7$	55.62	7.34		55.77	7.28	
26	74–75(H)	+52 (1.2)	1742	5.85(dd)	2.6 1.3[b]	1.38, 1.38, 1.45, 1.53	2.17(s) [$COCH_3$]	$C_{14}H_{22}O_7$	55.62	7.34		55.68	7.19	
27	127–128(H)	+26 (1.6)	1722	6.38(s)		1.38, 1.38, 1.47, 1.52		$C_{19}H_{24}O_7$	62.62	6.64		52.38	6.62	
28	syrup	+8 (2.0)	1725	6.13(d)	3.5	1.37, 1.40, 1.47, 1.47		$C_{19}H_{24}O_7$	62.62	6.54		62.38	6.66	
29	165–166(H)	+125 (2.5)	1732	5.70(s)		1.38, 1.38, 1.40, 1.52	7.08(d), 8.02(d), *J* 9.0 [$COC_6H_4NO_2$]	$C_{19}H_{23}NO_9$	55.74	5.66	3.42	55.68	5.65	3.40
30	121–121.5(B–H)	−74 (1.9)	1725	6.15(d)	4.5	1.42, 1.42, 1.45, 1.47	8.27(s) [$COC_6H_4NO_2$]	$C_{19}H_{23}NO_9$	55.74	5.66	3.42	55.97	5.61	3.43
31[c]	103–104(B–C)	+20 (1.0)	1705	6.07(d)		1.36, 1.37, 1.45, 1.45	1.17(d), *J* 6.0 [$CH(CH_3)_2$]	$C_{16}H_{27}NO_7$	55.64	7.88	4.06	55.54	7.80	3.90

[a]B, C, and H (in parentheses) denote benzene, cyclohexane, and hexane, respectively. [b]This coupling constant is of a long-range coupling. [c]These data are for the β anomer of **31**.

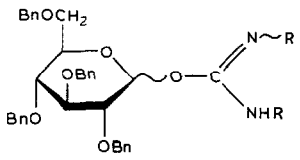
O-(2,3 : 5,6-di-*O*-isopropylidene-D-mannofuranosyl)pseudourea (**32**), prepared from **24** by treatment with **3** in the presence of a catalytic amount of Cu(I)Cl, was then treated with a variety of carboxylic acids; the results thus obtained, the conditions used, and the properties of all of the products are summarized in Tables III and IV.

The corresponding α and β anomers were separated by chromatography on a column of silica gel. Their ratios obtained by the use of **24** (2.0 mmol), **3** (4.4 mmol), and Cu(I)Cl (0.02 mmol) for the first-stage reaction, and of carboxylic acids (4.4 mmol) for the second-stage reaction, were from 2:3 to 1:4; the stereoselectivity was lower, compared with that observed in the reactions of **1** (Entries 1–3). As may be seen from Entries 4, 5, and 7, however, increase in the amount of Cu(I)Cl, up to 0.2 mmol, and decrease in that of **3**, down to 2.2 mmol, for the first-stage reaction, improved the stereoselectivity to 1:4. Performance of the second-stage reaction in chloroform under reflux, on the other hand, lowered the selectivity to $\alpha:\beta$ = 17:33.

Confronted with these results, we were interested in examining the i.r. and ^{1}H-n.m.r. spectra of the reaction intermediate **32**. The i.r. spectrum contained the

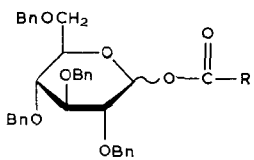


2 R = $-C_6H_{11}$
3 R = $-CHMe_2$

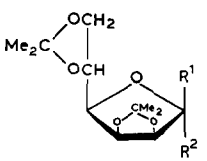


4 R = $-C_6H_{11}$
5 R = $-CHMe_2$

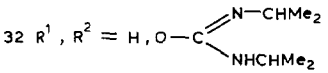
6 $MeCO_2H$
7 Me_3CCO_2H
8 $PhCONHCH_2CO_2H$
9 $PhCH_2OCONHCH_2CO_2H$
10 $PhCO_2H$
11 p-$O_2NC_6H_4CO_2H$
12 o-$O_2NC_6H_4CO_2H$
13 o-$HOC_6H_4CO_2H$
14 o-$MeC_6H_4CO_2H$



15 R = $-Me$
16 R = $-CMe_3$
17 R = $-CH_2NHCOPh$
18 R = $-CH_2NHCO_2CH_2Ph$
19 R = $-Ph$
20 R = $-C_6H_4NO_2$-p
21 R = $-C_6H_4NO_2$-o
22 R = $-C_6H_4OH$-o
23 R = $-C_6H_4Me$-o



24 R^1 = H, R^2 = OH
25 R^1 = H, R^2 = OCOMe
26 R^1 = OCOMe, R^2 = H
27 R^1 = H, R^2 = OCOPh
28 R^1 = OCOPh, R^2 = H
29 R^1 = H, R^2 = $OCOC_6H_4NO_2$-p
30 R^1 = $OCOC_6H_4NO_2$-p, R^2 = H
31 R^1, R^2 = H, $OCONHCHMe_2$



specific absorption band for the C=N double bond at 1650 cm^{-1}, regardless of the amount of **3** used (1.1 or 2.2 mol. equiv.). On the other hand, in the anomeric-proton region of the ^{1}H-n.m.r. spectrum were observed two singlet proton-signals, at δ 6.07 and 6.30, both of which could be assumed to arise from the geometrical isomers with respect to the double bond of the α anomers. The area ratios of these signals, however, varied, depending on the amount of **3** used, *i.e.*, ~1:6 and ~1:2 on using 2.2 and 1.1 mmol of **3**, respectively, although correlation of the anomer ratio with those present in the resulting 1-acylates is difficult to assess.

1-*O*-(Isopropylcarbamoyl)-2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**31**) was isolated in low yield (see Entries 4 and 7).

It is thus concluded that carbodiimides are useful for the condensation of aldose derivatives having OH-1 free with carboxylic acids through use of one-flask procedures.

EXPERIMENTAL

General methods. — Melting points were determined with a Yanagimoto micro melting-point apparatus and are uncorrected. Optical rotations were measured with a Hitachi PO-B polarimeter. T.l.c. was performed on precoated plates (thickness 0.20 mm) of silica gel 60 F_{254} (Merck) with 9:1 benzene–acetone, and detection of spots was effected with sulfuric acid. Column chromatography was performed on Wakogel C-300 (Wako Pure Chemical Ind., Ltd.) and in a prepacked column, size B (Merck). Solvent proportions used for elution are given in volume per volume. Elemental analyses were made with a Perkin–Elmer 240-002 instrument. Dicyclohexylcarbodiimide (**2**) was purchased from Wako Pure Chemical Ind., Ltd., and diisopropylcarbodiimide (**3**) from Nakarai Chemicals. I.r. spectra were recorded with a Hitachi 285 spectrometer. ^{1}H-N.m.r. spectra were recorded with a Varian T-60 instrument, for solutions in chloroform-*d* with tetramethylsilane as the internal standard.

2,3,4,6-Tetra-O-*benzyl*-α-D-*glucopyranose* (**1**). — The product (**1**), prepared according to the method reported by Glaudemans and Fletcher[7], had m.p. 151–152° (methanol) [lit.[7] m.p. 151–152° (methanol)].

Reactions of carboxylic acids with the pseudourea **4** *resulting from the fusion of* **1** *with* **2**. — A mixture of **1** (1.080 g, 2.0 mmol) and **2** (1.240 g, 6.0 mmol) was fused for 0.5 h at 80–85° in the presence of Cu(I)Cl (2 mg, 0.02 mmol), with stirring. The resulting mixture was cooled to room temperature, mixed with DME (5 mL), and the solution treated with a carboxylic acid (**6**, **10**, and **11**, respectively; 2.0–6.0 mmol) for 1 h at 20–25°, except in the reaction in Entries 6 and 7 (0.5 h). After the reaction, the mixture was stirred with M oxalic acid in acetone (5 mL), with stirring, for 1 h, and insoluble 1,3-dicyclohexylurea was filtered off. The filtrate was mixed with chloroform (20 mL), washed successively with M aqueous sodium hydroxide solution (20 mL) and water (20 mL), dried (anhydrous sodium sulfate), and evaporated to a syrup which was chromatographed on a column of silica gel (25 g); elution

with 1% of acetone in 1:1 (v/v) benzene–cyclohexane gave the corresponding 1-acylates (**15**, **19**, and **20**, respectively), and the eluate having 4% of acetone in the solvent system gave recovered **1**. The ratios of the anomers were estimated by ^{1}H-n.m.r. spectroscopy, after which, the corresponding β anomers were isolated by crystallization. In the case of Entry 5, the melt resulting from fusion of **1** with **2** in the presence of Cu(I)Cl was dissolved in chloroform (20 mL), and the solution was washed successively with M aqueous ammonia (20 mL) and water (20 mL), dried (anhydrous sodium sulfate), and evaporated to a syrup which was treated with benzoic acid (**10**) in DME.

For the reaction with *N*-benzoylglycine (**8**), the syrup obtained by the processing was first checked for its anomeric ratio, and then chromatographed on a column of silica gel (20 g), and the fractions containing 1-*O*-(*N*-benzoylglycyl)-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**17**), obtained by elution with 1:12:12 (v/v) acetone–benzene–cyclohexane, were combined and evaporated. The crystalline residue was recrystallized five times from methanol, giving the β anomer. The results are summarized in Table I.

Reaction of aqueous acetic acid with the pseudourea prepared by fusion of **1** *with* **2**. — The melt resulting from fusion of **1** with **2** as in the preceding experiment was dissolved in chloroform (5 mL), and the solution was stirred with M aqueous acetic acid solution (5 mL) for 2 h at 0°. The same processing as before gave 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**15**; 885 mg, 76% yield; $\alpha:\beta$ = 7:43), as well as recovered **1** (260 mg, 24%).

Reactions of carboxylic acids with the pseudoureas **4** *and* **5**, *respectively, prepared from* **1** *and* **2** *in chloroform*. — A solution of **1** (1.080 g, 2.0 mmol) and **2** (455 mg, 2.2 mmol) or **3** (280 mg, 2.2 mmol) in ethanol-free chloroform (2 mL) was stirred for 2 days at room temperature in the presence of Cu(I)Cl (2 mg, 0.02 mmol); then a carboxylic acid (**6–14**, respectively) was added, and the mixture was stirred for 1 h at room temperature. The precipitated urea derivative was filtered off, and the filtrate was evaporated to a syrup, which was then similarly chromatographed on a column of silica gel (20 g). Thus, the yields, and ratios of anomers, in the resultant mixtures, and the yields of β anomer isolated crystalline were obtained.

Owing to its low solubility in chloroform, the reaction of *p*-nitrobenzoic acid (**11**) was performed in a modified procedure as follows. To the solution of **5**, prepared from **1** and **3**, was added **11** (370 mg, 2.2 mmol), and the solution was stirred for 1 h at room temperature. Processing as already described, followed by chromatography, afforded the corresponding 1-(*p*-nitrobenzoate) (**20**; 1.175 g, 85% yield). The anomers of **20** were separated by flash column-chromatography on a LOBAR column (size B; 310 × 25 mm) of LiChroprep Si-60 (Merck) with 1:12:12 (v/v) acetone–benzene–cyclohexane under 2 atm., giving the β anomer (550 mg, 40%), a mixture of the anomers (450 mg, 33%), and the α anomer (140 mg, 10% yield). The results thus obtained, and some properties of the resulting anomers, are summarized in Table II.

*2,3:5,6-Di-*O*-isopropylidene-α-*D*-mannofuranose* (**24**). — Compound **24** was

prepared from D-mannose according to the method reported by Schmidt[12]; m.p. 122–123°; lit.[13] m.p. 122–123°.

Reactions of carboxylic acids with the pseudourea **32** *prepared from* **24** *and* **3**. — A solution of **24** (520 mg, 2.0 mmol) and **3** (560 mg, 4.4 mmol) in chloroform was stirred in the presence of Cu(I)Cl (2 mg, 0.02 mmol) for 15 days at room temperature, after which was added a carboxylic acid (**6**, **10**, and **11**, respectively; 4.4 mmol) and the mixture was stirred for 2 days at room temperature.

The reaction of **11** was performed after addition of DME (2 mL). After the reaction, a M solution of oxalic acid in acetone (3 mL) was added, and the mixture was stirred for 1 h at room temperature. The precipitated urea derivative was filtered off, and the filtrate was mixed with chloroform (20 mL), washed successively with M aqueous solution of sodium hydroxide (20 mL) and water (20 mL), dried (anhydrous sodium sulfate) and evaporated to a syrup which was chromatographed on a column of silica gel (30 g). Elution with chloroform afforded the corresponding α anomer (**25**, **27**, and **29**) and β anomer (**26**, **28**, and **30**), in turn, and elution with 1:99 methanol–chloroform afforded recovered **24**.

Shortening of the reaction time for the preparation of the pseudourea from 15 to 5 days, and conducting the reaction with the carboxylic acid for 2 days at room temperature, or under reflux in chloroform for 1 h, followed by the same processing and chromatography as before, gave, in turn, 1-*O*-(isopropylcarbamoyl)-2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**31**), α anomer, and then the β anomer (and **24**).

The results thus obtained are summarized in Table III, and the properties of the products are given in Table IV.

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