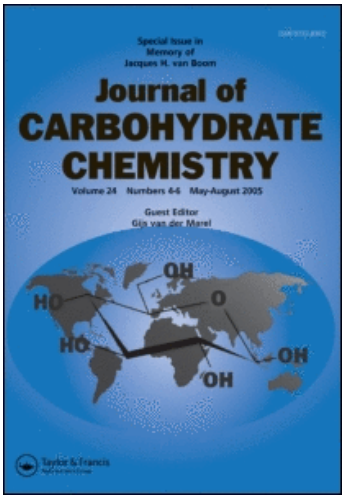


Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Stereocontrolled Synthesis of 6'-Deoxy-6'-Fluoro Derivatives of Methyl α-Sophoroside, α-Laminaribioside, α-Kojibioside and α-Nigeroside

Pavol Kováč[a]; Cornelis P. J. Glaudemans[a]
[a] NIDDK, National Institutes of Health, Bethesda, MD, U.S.A.

To cite this Article Kováč, Pavol and Glaudemans, Cornelis P. J.(1988) 'Stereocontrolled Synthesis of 6'-Deoxy-6'-Fluoro Derivatives of Methyl α-Sophoroside, α-Laminaribioside, α-Kojibioside and α-Nigeroside', Journal of Carbohydrate Chemistry, 7: 2, 317 — 335
To link to this Article: DOI: 10.1080/07328308808058928
URL: http://dx.doi.org/10.1080/07328308808058928

J. CARBOHYDRATE CHEMISTRY, 7(2), 317-335 (1988)

STEREOCONTROLLED SYNTHESIS OF 6'-DEOXY-6'-FLUORO DERIVATIVES OF METHYL α-SOPHOROSIDE, α-LAMINARIBIOSIDE, α-KOJIBIOSIDE AND α-NIGEROSIDE

Pavol Kováč and Cornelis P. J. Glaudemans

NIDDK, National Institutes of Health
Bethesda, MD 20892 (U.S.A.)

Received September 7, 1987 - Final Form November 8, 1987

ABSTRACT

Sequential tritylation, benzoylation and detritylation of D-glucose, followed by resolution of the crude product by chromatography gave crystalline 1,2,3,4-tetra-*O*-benzoyl-α- (**1**) and β-D-glucopyranose (**2**). Compound **1**, **2**, and the corresponding methyl α-glycoside **5** were treated with dimethylaminosulfur trifluoride (methyl DAST) to give, respectively, the 6-deoxy-6-fluoro derivatives **3**, **4**, and **6**. Crystalline 2,3,4-tri-*O*-benzoyl-6-deoxy-6-fluoro-α-D-glucopyranosyl chloride (**10**) could be obtained from either **3**, **4**, or **6** by reaction with dichloromethyl methyl ether in the presence of anhydrous zinc chloride. Silver trifluoromethanesulfonate-promoted reaction of **10** with methyl 2-*O*-(**9**) and 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**8**) gave the corresponding, β-linked disaccharides in high yield. Subsequent deprotection afforded the 6'-deoxy-6'-fluoro derivatives of methyl α-sophoroside (**13**) and methyl 6'-deoxy-6'-fluoro-α-laminaribioside (**16**). Condensation of **8** and **9** with 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl chloride in the presence of silver perchlorate was highly stereoselective and produced the α-linked disaccharides **17** and **21**, respectively, in excellent yield. Deacetylation of **17** and **21**, followed by fluorination of the resulting alcohols **18** and **22** with methyl DAST and subsequent hydrogenolysis, gave 6'-deoxy-6'-fluoro derivatives of methyl α-kojibioside and methyl α-nigeroside **20** and **24**, respectively.

INTRODUCTION

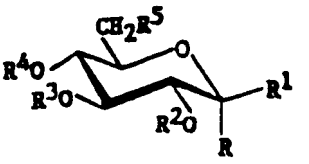
We have published extensively on a novel method of subsite mapping of monoclonal anti-polysaccharide antibodies using as ligands

specifically fluorinated oligosaccharides.[1] In addition, this laboratory has studied the spacial accessibility of antibody combining sites by the use of ligands bearing substituents posessing large molecular volumes at defined positions.[2,3] Having completed our work on monoclonal antigalactans we are now engaged in similar work on an antidextran known to bind only to the non-reducing end of α-(1→6)-linked glucopyranans.[4,5] In order to probe the spacial accessibility of a terminal α-D-glucosyl-binding subsite in this antibody we needed a number of methyl α-D-glucopyranosides bearing large substituents at *O*-2 and *O*-3, themselves incapable of binding. We have found *that* subsite to require a 6-OH group in the glucosyl group it is to bind, as methyl 6-deoxy-6-fluoro-α-D-glucopyranoside shows no measurable affinity for the studied antibody.[6] Thus, if methyl α-D-glucosides are to be constructed bearing large non-binding substituents, the substituent of choice is a 6-deoxyfluoro D-glucopyranosyl group. The syntheses of four compounds of this class are reported here. The binding studies - including those on the compounds prepared here - will be reported in the near future.[6]

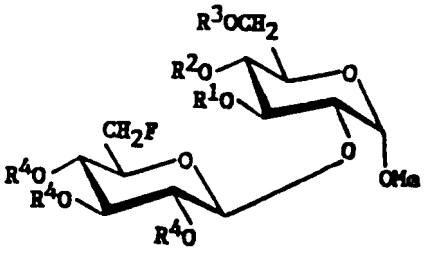
RESULTS AND DISCUSSION

To prepare the title oligosaccharides **13**, **16**, **20**, and **24** methyl 3-*O*- (**8**) and 2-*O*-benzyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**9**) were used as nucleophiles in the coupling reactions. Compounds **8** and **9** were prepared as described[7] and they were characterized by ^{13}C NMR data, which were subsequently used as an aid in the interpretation of ^{13}C NMR spectra of the synthesized disaccharides.

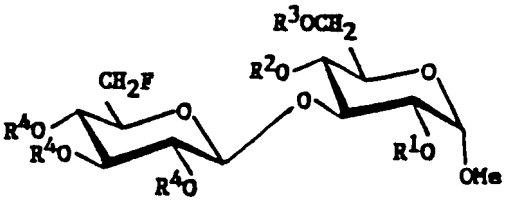
The preparation of the described derivatives of sophorose and laminaribiose required a glycosyl halide derived from 6-deoxy-6-fluoro-D-glucose, containing at C-2 a group capable of anchimeric assistance in the displacement of the halogen atom at C-1. It has been previously shown[8,9] that benzoylated glycosyl halides, when used as glycosyl donors in a silver trifluoromethanesulfonate (triflate) promoted glycosidation reaction, give higher yields of oligosaccharides than their acetylated counterparts. Therefore, rather than using the known[10] 2,3,4-tri-*O*-acetyl-6-deoxy-6-fluoro-α-D-glucopyranosyl bromide, we prepared the related, benzoylated glycosyl halide **7**. This crystalline glycosylating reagent can be readily obtained by treatment of either of the benzoyl



	R	R^1	R^2	R^3	R^4	R^5
1	OBz	H	Bz	Bz	Bz	OH
2	H	OBz	Bz	Bz	Bz	OH
3	OBz	H	Bz	Bz	Bz	F
4	H	OBz	Bz	Bz	Bz	F
5	OMe	H	Bz	Bz	Bz	OH
6	OMe	H	Bz	Bz	Bz	F
7	Cl	H	Bz	Bz	Bz	F
8	OMe	H	H	Bn	—PhCH—	
9	OMe	H	Bn	H	—PhCH—	
10	Cl	H	Bn	Bn	Bn	OAc



	R^1	R^2	R^3	R^4
11	Bn	—PhCH—		Bz
12	Bn	—PhCH—		H
13	H	H	H	H



	R1	R^2	R^3	R^4
14	Bn	—PhCH—		Bz
15	Bn	—PhCH—		H
16	H	H	H	H

derivatives **1**, **2** or **5** with dimethylaminosulfur trifluoride (methyl DAST), followed by cleavage of the substituent at C-1 with dichloromethyl methyl ether- (DCMME) -zinc chloride reagent.[11] We have pointed out the advantage of the use of methyl DAST over DAST in some related fluorinations.[12] While we have previously described in detail[12] the preparation and characterization of the glycoside **5**, the benzoyl derivative **1** has not been referred to in the literature. Compound **2** was used by Fügedi and Garegg[13,14] as a nucleophile in an oligosaccharide synthesis but the compound was not fully characterized. Our preparations of **1** and **2** were obtained by slight modification of the procedure described[14] for the preparation of **2**, that is, tritylation[15] of D-glucose was followed by conventional benzoylation, detritylation,[16] and purification by chromatography. Both compounds **1** and **2** were obtained crystalline, and they were characterized by ^{1}H and ^{13}C NMR data (Tables 1 and 2).

For economic reasons, an excess of the synthetically more valuable chloride **7** was not used in the condensation with **8** and **9**. Also, to avoid possible loss of the acid-labile *O*-benzylidene group during condensations under acidic conditions,[8,9] the reactions of **7** with **8** or **9** catalyzed by silver triflate were carried out in the presence of more base than would be necessary to neutralize all triflic acid to be liberated. The yield of the fully protected, fluorinated disaccharides **11** and **14** from equimolar amounts of reactants was ~90% in each case. We have in the past confirmed[9,17] findings of others[8] that base-deficient conditions in the silver triflate-catalyzed glycosidation reactions are favorable for the formation of oligosaccharides (rather than orthoesters). The high yields of **11** and **14** obtained under the conditions described above show that the base deficient conditions are not always necessary, and confirm again[8,18] that there are no general optimum conditions for glycosidation reactions. Subsequent debenzoylation (Zemplén) and hydrogenolysis of **11** and **14** (in the presence of palladium-on-charcoal catalyst) yielded the desired methyl α-glycosides of 6'-deoxy-6'-fluoro-sophorose (**13**) and 6'-deoxy-6'-fluoro-laminaribiose (**16**), respectively.

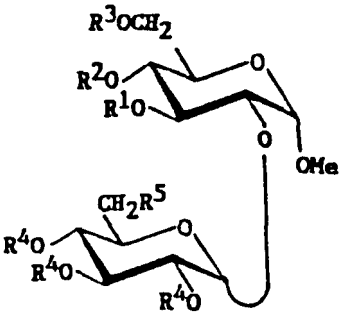
We have previously obtained[12] (1→6)-α-linked gluco-oligosaccharides in high yields when 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-

glucopyranosyl chloride was used as the glycosyl donor in the silver perchlorate-promoted glycosylation reaction.[19] We explored the same approach here in order to obtain derivatives **17** and **21**, for eventual conversion into the wanted disaccharides **20** and **24**. Under the aforementioned conditions, the reactions of the chloride **10** with nucleophiles **8** and **9** were fast, simple to perform, high yielding, and the target oligosaccharides **17** and **21**, respectively, were virtually the only products formed. Crystalline compound **21** could be obtained from the crude product in high yield without chromatography. Pure ether was originally[19] recommended as the best reaction medium to achieve high α-(*cis*)-stereoselectivity. Due to a poor solubility of the nucleophile **8** in ether, the reaction of **8** with **10** was carried out in a dichloromethane-ether mixture, which did not appear to affect the stereoselectivity of the reaction. Each of the obtained disaccharide derivatives **17** and **21** was deacetylated and the respectively formed compounds **18** and **22** were treated with methyl DAST. The main products of the fluorination reactions, **19** and **23**, respectively, were isolated by chromatography, and subsequent hydrogenolysis afforded the desired derivatives **20** and **24**.

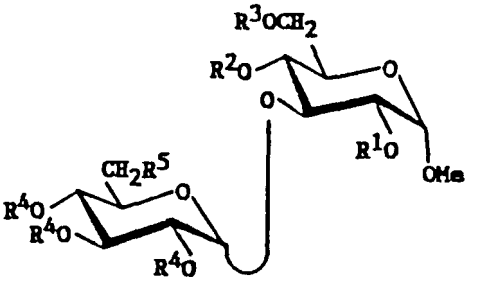
The reactions of the 6'-hydroxy derivatives **18** and **22** with methyl DAST gave the respective fluorinated compounds **19** and **23** in good yield, but also yielded a side product in each case. When DAST was used-rather then methyl DAST - the same by products were formed (TLC). The ammonia CI MS of both these by-products showed a peak at *m/z* 900 ($[M + 18]^+$), suggesting that they had identical structural features. The by-product isolated from the reaction of the (1→3)-linked disaccharide **22** with DAST was obtained crystalline. The structure of this material is currently being investigated.

EXPERIMENTAL

General methods.— Melting points were determined on a Kofler hot-stage. Unless otherwise stated, optical rotations were measured at 22 °C (c ~1), using a Perkin-Elmer automatic polarimeter, Model 241 MC. Thin-layer chromatography (TLC) on glass slides precoated with silica gel (Analtech or Whatmann) and preparative chromatography on columns of silica gel (Merck, cat. No. 9385) was performed with solvent mixtures of



	R^1	R^2	R^3	R^4	R^5
17	Bn	—PhCH—		Bn	OAc
18	Bn	—PhCH—		Bn	OH
19	Bn	—PhCH—		Bn	F
20	H	H	H	H	F



	R^1	R^2	R^3	R^4	R^5
21	Bn	—PhCH—		Bn	OAc
22	Bn	—PhCH—		Bn	OH
23	Bn	—PhCH—		Bn	F
24	H	H	H	H	F

appropriately adjusted polarity consisting of *A*. carbon tetrachloride-ethyl acetate, *B*. toluene-ethyl acetate, and *C*. carbon tetrachloride-acetone. Detection was effected by charring with 5% (v/v) sulfuric acid in ethanol. ^{1}H and ^{13}C NMR chemical shifts (Tables 1-3) are reported relative to that of tetramethylsilane, except for compounds **13**, **16**, **20**, and **24**, the ^{13}C NMR spectra of which were taken for solutions in D_2O (internal standard, methanol, δ_{MeOH} *vs.* δ_{TMS} 49.0 ppm). The instrument used was a Varian XL 300 spectrometer. Where required, proton-signal assignments (Table 1) were supported by homonuclear selective decoupling experiments. Unless otherwise stated, carbon-signal assignments (Tables 2 and 3) were made by mutual comparison of the spectra using as aids the assigned spectra of 1,2,3,4,6-penta-*O*-benzoyl-α- and β-D-glucopyranose,[20] related[12,21] mono- and oligosaccharides, and of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside.[22] Signals of secondary carbons were identified by DEPT experiments. Ammonia CI mass spectra were obtained employing a Finnigan 10151 D spectrometer. Methyl-DAST and DAST were purchased from Aldrich Chemical Company, and used as supplied. Tetrafluoroboric acid (aqueous, ~50%) was purchased from Fluka Chemical Company. Silver trifluoromethanesulfonate, a product of Aldrich Chemical company, was dried at 100 °C/0.1 mm Hg for 8 h. Palladium-on-charcoal catalyst was a product of Engelhardt Industries. Solutions in organic solvents were dried with anhydrous sodium sulfate and, unless otherwise stated, concentrated at 40 °C/15 mm Hg.

1,2,3,4-Tetra-*O*-benzoyl-α- (1) and β-D-glucopyranose (2).— A mixture of D-glucose (3.6 g, 20 mmol), N,N-dimethylaminopyridine (122 mg, 1 mmol), triethylamine (5 mL) and triphenylchloromethane (6.2 g, 22 mmol) in DMF (20 mL) was stirred at 25 °C for 24 h. Pyridine (60 mL) was added, the mixture was cooled to -20 °C and benzoyl chloride (18.6 mL, 160 mmol) was added. Cooling was discontinued and, after 4 h, TLC (solvent *A*) showed that the reaction was complete. Four products were present. The two showing lower R_f values were indistinquishable from authentic[23,24] samples of 1,2,3,4,6-penta-*O*-benzoyl-α- and β-D-glucopyranose, and resulted from incomplete tritylation of D-glucose. The mixture was processed conventionally, and tetrafluoroboric acid[16] (8 mL) was added to a solution of the crude product in acetonitrile (100 mL). After 10 min at room temperature, the mixture was neutralized with

TABLE 1. ^{1}H NMR (300 MHz) Chemical Shifts (δ, ppm) and ^{1}H-^{1}H Coupling Constants (Hz) for Compounds 1-9[a,b]

	H-1 $J_{1,2}$	H-2 $J_{2,3}$	H-3 $J_{3,4}$	H-4 $J_{4,5}$	H-5 $J_{5,6a}$;$J_{5,6b}$	H-6a[c] $J_{6a,6b}$	H-6b	Me
1	6.81d 3.8	5.61 dd 10.0	6.31 t 10.0	5.67 t 10.0	4.28 ddd 2.0;4.0	3.83 dd 12.5	3.72 dd	
2	6.25 d 8.3	5.83 dd 10.0	6.07 t 10.0	5.63 t 9.5	4.05 ddd 1.5;4.5	3.88 dd 12.5	3.72 dd	
3[d]	6.87 d 3.7	5.66 dd 10.0	6.33 t 10.0	5.77 t 10.0	4.75 ——	——	4.40	
4[e]	6.29 d 8.2	5.85 dd 9.3	6.05 t 9.5	5.71 t 9.7	4.25- 4.18 m	6.47 ddd 10.6	4.59 ddd	
5[f]	5.25 d 3.5	5.50 dd 10.0	6.59 t 10.0	5.80 t 10.0	4.01 ddd 2.5;4.5	3.75 dd 12.0	3.65 dd	3.10 s
5	5.35 ——	5.25 m	6.22 t 10.0	5.54 t 10.0	4.09 ddd 2.5;4.5	3.83 dd 13.0	3.72 dd	3.49 s
6[g]	5.30 ——	5.22 m	6.17 m	5.55 t 10.0	4.26 qt 3.5;3.5	4.58 dd *h*	4.58 dd	
6[g,h,i]	5.20 d 3.8	5.43 dd 10.0	6.57 t 10.0	5.76 t 10.0	4.00- 4.22 m	4.31 dd	4.31 dd	

	H-1 $J_{1,2}$	H-2 $J_{2,3}$	H-3 $J_{3,4}$	H-4 $J_{4,5}$	H-5 $J_{5,6a};J_{5,6b}$	H-6a[c] $J_{6a,6b}$	H-6b	Me
7	6.57 d 3.9	5.46 dd 10.0	6.26 t 10.0	5.72 t 10.0	4.76	———	4.50 m	
8[j,k]	4.77 d 3.6	4.31	———	———	———	———	3.60 m	3.42 s
9[l,m]	4.59 d 3.6	3.45 dd[n] 9.0	4.13 bt 9.0	3.47 bt[o] 10.5	3.80 dt 4.5;10.0	4.24 dd 10.0	3.68 t	3.35 s

[a]Measured at 25 °C for solutions in $CDCl_3$. [b]Peak multiplicities: d, doublet; t, triplet; q, quartet; b, broad. [c]Proton resonating at lower field is denoted H-6a. [d]$J_{F,6a}$ 47.2 Hz, $J_{F,6b}$ not determined due to overlapping of signals; [e]$J_{F,6a}$ 47.1 Hz; $J_{F,6b}$ 46.9 Hz. [f]Data obtained for a solution in C_6D_6 containing a drop of CD_3OD taken from ref. 12. [g]$J_{F,5}$ 23 Hz, $J_{F,6a}$ = $J_{F,6b}$ 47 Hz. [h]$J_{H\text{-}6a,6b}$ not observed. [i]Data for a solution in C_6D_6. [j]CHPh: δ 5.55. [k]CH_2Ph: δ 4.95 and 4.78, ^2J 11.5 Hz. [l]CHPh: δ 5.49. [m]CH_2Ph: δ 4.77 and 4.67, ^2J 12.2 Hz. [n]Overlapped with the signal of H-4. [o]Overlapped with the signal of H-2.

TABLE 2. ^{13}C NMR Chemical Shifts[a] (δ, ppm) for Compounds 1-10.

	C-1	C-2	C-3	C-4	C-5	C-6	Me
1	90.12	70.47[b]	70.20[b]	68.90	72.78	60.89	
2	92.79	70.88	72.68	69.12	75.61	60.98	
3[c]	89.97	70.35	70.35	68.02	71.30	80.90	
4[d]	92.64	70.75	72.76	68.27	73.99	80.86	
5[e]	97.19	72.02	70.20	69.59	69.84	61.12	55.65
6[f]	97.09	71.94	70.32	68.46	68.59	81.50	55.73
7[g]	90.45	71.57	69.76	67.33	71.68	80.49	
8[h]	99.91	72.43	78.86	81.94	62.58	69.01	55.35
9[i]	98.65	79.60	70.36	81.40	62.02	68.98	55.35
10[e,j]	92.86	79.83	81.27	76.06	71.82	62.29	

[a]Spectra measured in $CDCl_3$ at 25 °C. [b]The assignment may be reversed. [c]$J_{F,6}$ 176.8; $J_{F,5}$ 19.3; $J_{F,4}$ 4.8 Hz. [d]$J_{F,6}$ 176.9; $J_{F,5}$ 19.5; $J_{F,4}$ 6.4 Hz. [e]Data taken from ref. 12. [f]$J_{F,6}$ 175.0; $J_{F,5}$ 18.5; $J_{F,4}$ 9.4 Hz. [g]$J_{F,6}$ 177.2; $J_{F,5}$ 16.4; $J_{F,4}$ 6.4 Hz. [h]CHPh: δ 101.29. [i]CHPh: δ 101.93. [j]CH_2Ph: δ 75.85, 75.15, and 72.89 ppm.

triethylamine, concentrated and chromatographed (solvent *B*). The material eluted first was crystallized from carbon tetrachloride-hexane to give **2** (3.6 g, 30%), mp 179-183 °C (from 2-propanol), $[\alpha]_D$ -15°, lit.[13], mp 179-181 °C, $[\alpha]_D$ -15°, lit.[14], mp 183-184 °C, $[\alpha]_D$ -15°.

Continuing elution gave **1** (3 g, 25%), mp 85-87 °C, $[\alpha]_D$ +114.3° (dimorphous: material showing mp 141-142 °C, obtained in certain experiments, showed the same spectral characteristics).

Anal. Calcd for $C_{34}H_{28}O_{10}$: C, 68.45; H, 4.73. Found: C, 68.31; H, 4.78.

An intermediate, mixed fraction (0.6 g, 5%) was also obtained. Total yield, 60%.

TABLE 3. ^{13}C NMR Chemical Shifts[a] (δ, ppm) for Compounds 11-24.

	C-1	C-2	C-3	C-4	C-5	C-6	Me
11[b]	100.26	80.89	77.30	82.02	62.15	69.10	55.59
	102.10	73.02[c]	71.38[c]	68.73	73.23	81.61	
12[d]	100.27	80.23	77.68	83.04	62.39	69.26	55.57
	104.58	73.94	77.02	69.30	74.82	82.20	
13[e]	98.93	80.89	72.00	69.55	71.35	60.27	54.90
	103.96	73.26	75.49	68.47	74.38	82.35	
14[f]	98.91	77.86	79.78[c]	79.33[c]	62.25	68.93	55.22
	100.89	73.23[c]	72.27[c]	68.78	72.83	81.26	
15[g]	98.39	78.92[h]	79.01[h]	80.50[h]	62.58	68.89	55.31
	104.49	73.23	76.41	68.95	74.80	81.86	
16[i]	99.26	70.79	83.14	68.17	71.49	60.64	55.09
	103.16	73.51	75.47	68.55	74.50	82.26	
17[j]	97.22	76.81[k]	74.55	82.55[l]	62.52	69.01	54.97
	94.31	79.28	81.94[l]	77.23[k]	68.70	62.25	
18[m]	97.32	76.94[k]	74.70	82.50[l]	62.27	69.03	55.01
	94.62	79.44	81.97[l]	77.45[k]	70.88	61.38	
19[n]	97.28	76.88	74.70	82.59[k]	62.26	69.03	55.03
	94.71	79.21	81.83[k]	76.82	69.82	81.83	
20[o]	96.90[k]	76.17	71.44[h]	69.75	71.32[h]	60.67	54.96
	96.71[k]	71.57[h]	72.67	68.47	70.88	82.21	
21[p]	98.46	72.79[h]	77.84[h]	82.83[k]	61.86	69.20	55.32
	95.94	78.74[h]	81.66[k]	77.05[h]	68.41	62.79	
22[q]	98.50	72.96[h]	78.04	82.87[k]	61.87	69.21	55.35
	96.14	79.01[h]	81.62[k]	77.34[h]	70.60	61.50	
23[r]	98.11	72.78[h]	78.83[h]	82.63[k]	61.67	69.00	55.15
	96.03	78.62[h]	81.27[k]	76.50	69.47	81.51	
24[s]	99.58[k]	70.22[c]	79.88	69.91[c]	71.45[l]	60.48	55.09
	99.26[k]	71.72[l]	72.88	68.46	70.73	82.22	

1,2,3,4-Tetra-*O*-benzoyl-6-deoxy-6-fluoro-α-D-glucopyranose (3).— Methyl-DAST (0.39 mL, 4 mmol) was added at -10 °C to a solution of **1** (0.6 g, 1 mmol) in 1,2-dimethoxyethane (5 mL). Cooling was terminated, and the mixture was stirred at 65 °C for 1 h. TLC (solvent *A* and *B*) then showed that little of **1** remained and that one major product was formed. After cooling (-10 °C), methanol (1 mL) was added, the mixture was concentrated and the residue was partitioned between dichloromethane and saturated, aqueous sodium hydrogen carbonate solution. The organic phase was dried, concentrated, and the residue was chromatographed to give **3** (0.49 g, 82%), mp 154-155 °C (from ether), $[\alpha]_D$ +132.5°.

Anal. Calcd for $C_{34}H_{27}FO_9$: C, 68.22; H, 4.54; F, 3.11. Found: C, 68.22; H, 4.54; F, 3.11.

1,2,3,4-Tetra-*O*-benzoyl-6-deoxy-6-fluoro-β-D-glucopyranose (4).— Compound **2**, when treated as described above for the preparation of **3**, afforded **4** in 85% yield, mp 184-186 °C (from acetone-methanol, $[\alpha]_D$-16.5°.

---

[a]Spectra recorded at 25 °C for solutions in $CDCl_3$, except for compounds **13**, **16**, **20**, and **24**, the spectra of which were taken in D_2O; the second row of data for each compound refers to the non-reducing D-glucosyl group. [b]*C*HPh: δ 101.37, *C*H_2Ph: δ 74.52; $J_{F,6'}$ 175.6, $J_{F,5'}$ 19.5, $J_{F,4'}$ 6.8 Hz. [c]The assignments in the same row may be reversed. [d]*C*HPh: δ 101.57, *C*H_2Ph: δ 75.29; $J_{F,6'}$ 173.1, $J_{F,5'}$ 18.6, $J_{F,4'}$ 6.4 Hz. [e]$J_{F,6'}$ 168.0, $J_{F,5'}$ 17.6, $J_{F,4'}$ ~2Hz. [f]*C*HPh: δ 101.18, *C*H_2Ph δ 74.01; $J_{F,6'}$ 175.8, $J_{F,5'}$ 19.6, $J_{F,4'}$ 5.7 Hz. [g]*C*HPh: δ 101.21, *C*H_2Ph: δ 75.10; $J_{F,6'}$ 173.3, $J_{F,5'}$ 18.3, $J_{F,4'}$ 8.0 Hz. [h]Tentative assignment. [i]$J_{F,6'}$ 168.0, $J_{F,5'}$ 17.4, $J_{F,4'}$ 5.6 Hz. [j]*C*HPh: δ 101.26, *C*H_2Ph: δ 75.69, 75.60, 74.93, 72.93; *C*H_3CO: δ 20.79. [k,l]The assignment may be reversed. [m]*C*HPh: δ 101.27, *C*H_2Ph: δ 75.70, 75.64, 74.93, 73.03. [n]*C*HPh: δ 101.29, *C*H_2Ph: δ 75.68, 75.14 (2C), 73.11. $J_{F,6'}$ 172.1, $J_{F,5'}$ 17.6, $J_{F,4'}$ 7.9 Hz. [o]$J_{F,6'}$ 167.5, $J_{F,5'}$ 17.4, $J_{F,4'}$ 6.4 Hz. [p]*C*HPh: δ 102.29, *C*H_2Ph: δ 75.60, 74.73, 73.03, 70.95, *C*H_3CO: δ 20.81. [q]*C*HPh: δ 102.22, *C*H_2Ph: δ 75.52, 74.85, 73.37, 71.17. [r]*C*HPh: δ 101.99, *C*H_2Ph: δ 75.34, 74.87, 72.94, 71.01; $J_{F,6'}$ 169.0, $J_{F,5'}$ 17.2, $J_{F,4}$ 7.8 Hz. [s]$J_{F,6'}$ 167.0, $J_{F,5'}$ 16.6 Hz.

Anal. Calcd for $C_{34}H_{27}FO_9$: C, 68.22; H, 4.54; F, 3.17. Found: C, 68.16; H, 4.75; F, 3.33.

Methyl 2,3,4-Tri-*O*-benzoyl-6-deoxy-6-fluoro-α-D-glucopyranoside (6).— Compound 5[12] when treated as described for the preparation of **3** and **4**, afforded **6** in 87% yield, mp 145-146 °C (from methanol), $[\alpha]_D$ +52.7°.

Anal. Calcd for $C_{28}H_{25}FO_8$: C, 66.13; H, 4.95; F: 3.73. Found: C, 66.19; H, 5.08; F, 3.63.

2,3,4-Tri-*O*-benzoyl-6-deoxy-6-fluoro-α-D-glucopyranosyl chloride (7).— a) Freshly fused zinc chloride (~70 mg) was added to a solution of **6** (0.51 g, ~1 mmol) in DCMME (1.5 mL), and the mixture was stirred, with the exclusion of moisture at 80 °C (bath) in a round-bottomed flask equipped with a small dry-ice condenser. When TLC (solvent *B*) showed that only a trace of the starting material remained (6 h), the dark solution was diluted with toluene, concentrated, and the residue was chromatographed (solvent *A*) to give **7** (0.38 g, 75%). The solid formed on standing was recrystallized from isopropyl ether (twice) to give a material with a mp 108-109 °C and $[\alpha]_D$ +75.5°.

Anal. Calcd for $C_{27}H_{22}ClFO_7$: C, 63.22 H, 4.32; Cl, 6.91; F, 3.70. Found: C, 62.95; H, 4.48; Cl, 6.97; F, 3.60.

b) When each of compounds **3** and **4** was treated at 65 °C (bath) with a mixture of alcohol-free chloroform-DCMME (1:1, 2 mL/mmoL) in the presence of freshly fused zinc chloride (~30 mg/mmol), the chloride **7** was obtained in 85-90% yield, following purification of the crude product by chromatography.

Methyl *O*-(2,3,4-Tri-*O*-benzoyl-6-deoxy-6-fluoro-β-D-glucopyranosyl)-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (11).— Crystalline glycosyl chloride **7** (1.02 g, 2 mmol) was added at room temperature to a stirred mixture of the nucleophile **8** (0.74 g, 2 mmol), 2,4,6-trimethylpyridine (0.264 mmol) and silver trifluoromethanesulfonate (0.616 g, 2.4 mmol). After 16 h, when TLC showed that the reaction was complete and that one major product was formed, the mixture was filtered. The filtrate was washed with aqueous sodium thiosulfate. The organic phase was dried and concentrated and the residue was chromatographed to give the major product **11** as a white foam (1.57 g, 93%), $[\alpha]_D$ -8.2°.

Anal. Calcd for $C_{48}H_{45}FO_{13}$: C, 67.91; H, 5.34; F, 2.23. Found: C, 67.63; H, 5.43; F, 2.26.

Methyl *O*-(6-Deoxy-6-fluoro-β-D-glucopyranosyl)-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (12).— Methanolic sodium methoxide (M, 1 mL) was added to a warm solution of **11** (1.1 g) in methanol (50 mL). The solution was heated at 50 °C for 1 h and then left at room temperature overnight. The separated crystalline product was collected by filtration and washed successively with cold methanol and ether, to give **12** (0.59 g, 84%), mp 239-240° and $[\alpha]_D$ -16.3° (c 0.5, pyridine), after crystallization from 2-methoxyethanol-ethanol.

Anal. Calcd for $C_{27}H_{33}FO_{10}$: C, 60.43; H, 6.20; F, 3.54. Found: C, 60.32; H, 6.16; F, 3.51.

Methyl *O*-(6-Deoxy-6-fluoro-β-D-glucopyranosyl)-(1→2)-α-D-glucopyranoside (Methyl 6'-Deoxy-6'-fluoro-α-sophoroside) (13).— A mixture of **12** (0.35 g) and palladium-on-charcoal catalyst (0.2 g) in 2-methoxyethanol (50 mL) was stirred in a hydrogen atmosphere for 16 h. The mixture was concentrated, and the solid residue was crystallized from methanol-acetone to give pure **13** (208 mg, 90%), mp 271-273 °C, $[\alpha]_D$ +70.6°.

Anal. Calcd for $C_{13}H_{23}FO_{10}$: C, 43.57; H, 6.47; F, 5.30. Found: C, 43.51; H, 6.42; F, 5.16.

Methyl *O*-(2,3,4-Tri-*O*-benzoyl-6-deoxy-6-fluoro-β-D-glucopyranosyl)-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (14).— Crystalline compound **7** (1.026 g, 2 mmol) was added at room temperature to a stirred mixture of the nucleophile **9** (744 mg, 2 mmol), silver triflate (0.616 g, 2.4 mmol) and 2,4,6-trimethyl-pyridine (0.27 mL, 2.04 mmol) in dichloromethane (15 mL). The mixture was stirred for 2 h at room temperature and TLC (solvent *B*) showed that the reaction was complete, and that one major product was formed. The mixture was processed as described for the preparation of **11** and chromatographed (solvent *B*), to give **14** as a white foam (1.52 g, 89.8%), $[\alpha]_D$ -34°.

Anal. Calcd for $C_{48}H_{45}FO_{13}$: C, 67.91; H, 5.34; F, 2.23. Found: C, 68.14; H, 5.46; F, 2.08.

Methyl *O*-(6-Deoxy-6-fluoro-β-D-glucopyranosyl)-(1→3)-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (15).— Methanolic M sodium methoxide was added to a hot solution of **14** (1 g) in methanol (80 mL) until a strongly alkaline solution was obtained. After 16 h at room temperature, the mixture was processed conventionally, and

crystallization from ethanol gave pure **15** (0.55 g, 87%), mp 204-205 °C, $[\alpha]_D$ +21.6°.

Anal. Calcd for $C_{27}H_{33}FO_{10}$: C, 60.43; H, 6.20; F, 3.54. Found: C, 59.98; H, 6.38; F, 3.63.

Methyl *O*-(6-Deoxy-6-fluoro-β-D-glucopyranosyl)-(1→3)-α-D-glucopyranoside (Methyl 6'-Deoxy-6'-fluoro-α-laminaribioside) (16).— A solution of **15** (0.5 g) in methanol (50 mL) was stirred in a hydrogen atmosphere overnight at room temperature in the presence of palladium-on-charcoal catalyst (0.25 g). After conventional processing, the amorphous compound **16** was obtained as a colorless foam, $[\alpha]_D$ +78°.

Methyl *O*-(6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (17).— A solution of **10** (1.22 g, 2.4 mmol) in dry ether (9 mL) was added to a solution of **8** (0.745 g, 2 mmol) and 2,4,6-trimethylpyridine (0.33 mL, 2.5 mL) in dichloromethane (10 mL). The solution was cooled to -5 °C and a solution of silver perchlorate in ether (0.08 M, 33.75 mL, 2.7 mmol) was added with stirring. Cooling was discontinued and, after 5 min of reaction time, TLC (solvent *C*) showed that no glycosyl chloride **10** remained and that only a trace of the nucleophile **8** was present. The mixture was filtered, the filtrate was concentrated and the solution of the residue in dichloromethane was washed with aqueous sodium thiosulfate solution. The organic phase was dried, concentrated, and the crude product was chromatographed. First obtained was material which showed slightly faster chromatographic mobility than the major product. Based on ^{13}C NMR spectroscopy this material was assigned the structure of the β-linked condensation product, methyl O-(6-O-acetyl-2,3,4-tri-O-benzyl-β-D-glucopyranosyl)-(1→2)-3-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside (32 mg, 1.8%), δ 104.41 (C-1'), 101.35 (*C*HPh), 100.33 (C-1), 84.64 (C-3'), 82.77 (C-4), 81.86 (C-2'), 78.99 (C-2), 78.00 (C-3), 77.37 (C-4'), 75.66, 74.99, 74.59 (C, 2C, C, 4 x CH_2HPh), 72.42 (C-5'), 69.20 (C-6), 63.09 (C-6'), 62.16 (C-5), 55.31 (Me).

Eluted next was the desired, α-linked disaccharide **17** (1.55 g, 91.4%), $[\alpha]_D$ +38.5°.

Anal. Calcd for $C_{50}H_{54}O_{12}$: C, 70.90; H, 6.42. Found: C, 71.14; H, 6.47.

Methyl *O*-(2,3,4-Tri-*O*-benzyl-α-D-glucopyranosyl)-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (18).— The α-linked disaccharide **17** (12.5 g) was dissolved in hot toluene (10 mL) and hot methanol (80 mL) was added, followed by M methanolic sodium methoxide, until a strongly alkaline solution was obtained. The solution was allowed to cool and it was kept at room temperature overnight. TLC (solvent *B*) showed that the reaction was complete and that a single product was formed. The solution was neutralized with solid carbon dioxide, concentrated, and the residue was partitioned between dichloromethane and water. The organic phase was concentrated and the residue was crystallized from toluene-ether, to give pure **18** (1.3 g, 92%), mp 184-185 °C, $[\alpha]_D$ +43°.

Anal. Calcd for $C_{48}H_{52}O_{11}$: C, 71.62; H, 6.51. Found: C, 71.73; H, 6.56.

Methyl *O*-(2,3,4-Tri-*O*-benzyl-6-deoxy-6-fluoro-α-D-glucopyranosyl)-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (19).— Methyl DAST (6 ml) was added onto compound **18** (1.9 g) and the reaction vessel was placed in an oil bath, preheated to 50 °C. The temperature was raised to 90 °C and samples (~10 μL) of the stirred mixture were periodically withdrawn, added to cold (-20 °C) methanol (~200 μL) containing a drop of pyridine, and the composition of the reaction mixture was checked by TLC (solvent *B*). After 2 h, TLC showed that some starting material remained but prolonged reaction time did not change the situation. Two major products were formed; the one showing faster chromatographic mobility greatly predominated. The mixture was cooled (-20 °C), pyridine (5 mL) was added, followed by dropwise addition of methanol into the cooled and stirred solution. The semisolid mixture was dissolved in dichloromethane (50 mL) and poured into aqueous sodium hydrogen carbonate solution contained in a separatory funnel. When effervescence ceased, the organic phase was separated, dried, concentrated at 70 °C/0.1 mmHg, and the residue was chromatographed, to give the major product **19** (1.5 g, 78.9%), m.p.178-179 °C (from dichloromethane-methanol), $[\alpha]_D$ +35°, ammonia CI MS, m/z 824 $[M + NH_4]^+$.

Anal. Calcd for $C_{48}H_{51}FO_{10}$: C, 71.44; H, 6.37; F, 2.35. Found: C, 71.44; H, 6.49; F, 2.47.

Further elution gave the by-product showing slower chromatographic mobility, NH_4 CI MS m/z 900 $([M + 18)]^+$.

Methyl *O*-(6-Deoxy-6-fluoro-α-D-glucopyranosyl)-(1→2)-α-D-glucopyranoside (Methyl 6'-Deoxy-6'-fluoro-α-kojibioside) (20).— A suspension of **19** (1 g) and palladium-on-charcoal catalyst (0.5 g) in 2-methoxyethanol (50 mL) was stirred in a hydrogen atmosphere. When the uptake of hydrogen ceased, the mixture was processed conventionally, and the solid obtained was crystallized from aqueous methanol (twice), to give pure **20** (416 mg, 93.6%), mp 269.5-270 °C, $[\alpha]_D$ +197°.

Anal. Calcd for $C_{15}H_{23}FO_{10}$: C, 43.57; H, 6.47; F, 5.30. Found: C, 43.63; H, 6.64; F, 5.61.

Methyl *O*-(6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (21).— The nucleophile **9** (1.86 g, 5 mmol) and the glycosyl chloride **10** (3.3 g, 6.45 mmol) were allowed to react in the manner described for the preparation of **17**. The crude product solidified on concentration of the solution. Crystallization from dichloromethane-ethanol (twice) gave pure **21** (3.4 g, 80%), mp 178-179 °C, $[\alpha]_D$ +60°. The mother liquor was chromatographed (solvent *A*) to give a further amount of **21** (0.5 g, total yield, 92%).

Anal. Calcd for $C_{50}H_{54}O_{12}$: C, 70.90; H, 6.42. Found: C, 71.04; H, 6.45.

Methyl *O*-(2,3,4-Tri-*O*-benzyl-α-D-glucopyranosyl)-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (22).— The α-linked disaccharide derivative **21** was deacetylated in the manner described for the preparation of **18**, to give pure **22** in a virtually theoretical yield. The amorphous, white solid showed an $[\alpha]_D$ of +57°.

Anal. Calcd for $C_{48}H_{52}O_{11}$: C, 71.62; H, 6.51. Found: C, 71.48; H, 6.52.

Methyl *O*-(2,3,4-Tri-*O*-benzyl-6-deoxy-6-fluoro-α-D-glucopyranosyl)-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (23).— Compound **22** (0.8 g) was wetted with methyl DAST (4 mL). The mixture was stirred at room temperature and when a clear solution was obtained the temperature was raised to 90°. After ~2 h, when the composition of the mixture stabilized (TLC, solvent *B*), the mixture was worked up as described for the preparation of **19**. Chromatography gave first the desired, fluorinated compound **23** (0.54 g, 68%), mp 62-63 °C (from dichloromethane-methanol), $[\alpha]_D$ +50°.

Anal. Calcd for $C_{48}H_{51}FO_{10}$: C, 71.44; H, 6.37; F, 2.35. Found: C, 71.04; H, 6.40; F, 2.40.

Continued elution gave the slower moving by-product showing mp 171-172 °C (from ether-hexane), $[\alpha]_D$ +61.5°, NH_3 CI MS, *m/z* 900 ($[M + 18]^+$).

Methyl *O*-(6'-Deoxy-6'-fluoro-α-D-glucopyranosyl)-(1→3)-α-D-glucopyranoside (Methyl 6'-Deoxy-6'-fluoro-α-nigeroside) (24).— Compound **23**, when subjected to hydrogenolysis under the conditions described for the preparation of **20**, afforded **24** in a virtually theoretical yield. After crystallization from methanol (twice), compound **24** showed mp 193-195 °C and $[\alpha]_D$ +212.5°.

Anal. Calcd for $C_{13}H_{23}FO_{10}$: C, 43.57; H, 6.47; F, 5.30. Found: C, 43.43; H, 6.34; F, 5.48.

REFERENCES

1. C. P. J. Glaudemans and P. Kováč, *ACS Symposium Series*, in press.
2. G. Ekborg, Y. Ittah, and C. P. J. Glaudemans, *Mol. Immun.*, **20** 235 (1983).
3. C. P. J. Glaudemans, E. Zissis, and M. E. Jolley, *Carbohydr. Res.*, **40** 129 (1975).
4. J. Cisar, E. A. Kabat, M. M. Dorner, and S. Liao, *J. Exp. Med.*, **142** 435 (1975).
5. L. G. Bennet, and C. P. J. Glaudemans, *Carbohydr. Res.*, **72** 315 (1975).
6. C. P. J. Glaudemans, P. Kovác, and A. Rao, *Biochemistry*, to be published.
7. T. Ogawa and T. Kaburagi, *Carbohydr. Res.*, **103** 53 (1982).
8. P. J. Garegg and T. Norberg, *Acta Chem. Scand.*, B, **33** 116 (1979).
9. P. Kováč, C. P. J. Glaudemans, W. Guo, and T. C. Wong, *Carbohydr. Res.*, **149** 229 (1985).
10. E. M. Bessel, A. B. Foster, J. H. Westwood, L. D. Hall, and R. N. Johnson, *Carbohydr. Res.*, **19** 39 (1971).
11. H. Gross, I. Farkas, and R. Bognár, *Z. Chem.*, **18** 201 (1978).
12. P. Kováč, V. Sklenář, and C. P. J. Glaudemans, *Carbohydr. Res.*, **175** (1988) 201-213.
13. P. Fügedi and P. J. Garegg, *Carbohydr. Res.*, **149** C9 (1986).
14. P. Fügedi, W. Birberg, P. J. Garegg, and A. Pilotti, *Carbohydr. Res.*, **164** 297 (1987).

15. S. K. Chandhary and O. Hernandez, *Tetrahedron Lett.*, 95 (1979).

16. R. Albert, K. Dax, R. Pleschko, and A. E. Stütz, *Carbohydr. Res.*, **137** 282 (1985).

17. P. Kováč, R. B. Taylor, and C. P. J. Glaudemans, *J. Org. Chem.*, **50** 5323 (1985).

18. H. Paulsen, *Angew. Chem., Int. Ed. Engl.*, **21** 155 (1982).

19. K. Igarashi, J. Irisawa, and T. Honma, *Carbohydr. Res.*, **39** 213 (1975).

20. N. B. D'Accorso, I. M. E. Thiel, and M. Schüller, *Carbohydr. Res.*, **124** 177 (1983).

21. J. H. Bradbury and G. A. Jenkins, *Carbohydr. Res.*, **126** 125 (1984).

22. E. Conway and R. D. Guthrie, *Tetrahedron Lett.*, 4879 (1972).

23. A. Levene and G. M. Meyer, *J. Biol. Chem.*, **76** 513 (1928).

24. E. Fischer and K. Freudenberg, *Ber.*, **45** 2709 (1912).