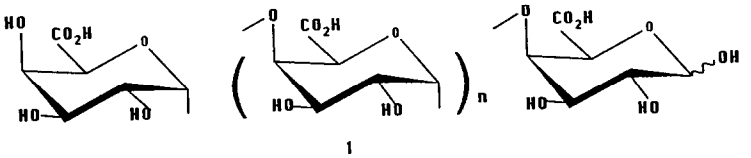
Tetrahedron Letters,Vol.28,No.24,pp 2731-2734,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

A HIGHLY EFFICIENT, PRACTICAL, AND STEREOSELECTIVE APPROACH TO THE SYNTHESIS OF α 1 ⟶ 4 LINKED GALACTOOLIGOSACCHARIDES[1]

Yoshiaki Nakahara* and Tomoya Ogawa*
RIKEN (The Institute of Physical and Chemical Research).
Wako-shi, Saitama, 351-01, Japan

Abstract: Exclusive formation of α1⟶4 linked galactopyranosyl oligosaccharides could be achieved by employing glycosyl fluorides. The observed diastereofacial selectivity was explained in terms of the nucleophilic attack of glycosyl acceptors toward convex face of the glycosyl fluorides.

The available approaches[2] to the synthesis of an α-linked galactobiose unit have been developed mainly in connection with the synthetic studies on oligosaccharides of either blood group B antigens or globo series glycosphingolipids such as p^k and Forssman antigens. In this paper we describe a remarkably efficient approach to the synthesis of α1⟶4 linked galactooligosaccharides. Galactopyranosyl fluorides **2**~**8** as well as the glycosyl acceptors **9**~**12** are designed, so that their characteristic feature of protective groups should be transfered into the glycosylation products, which in turn may be regarded as key intermediates for the total synthesis of oligogalacturonides **1** with phytoalexin eliciting activity[3]. Among these fluorides, compounds **3**, **4**, **7**, and **8** were found to give exclusively α-D glycosides.



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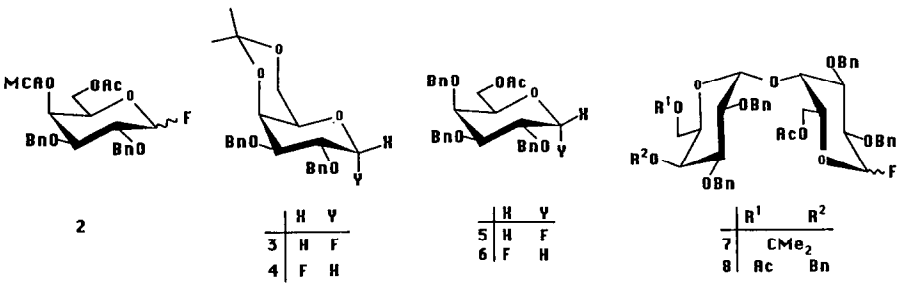
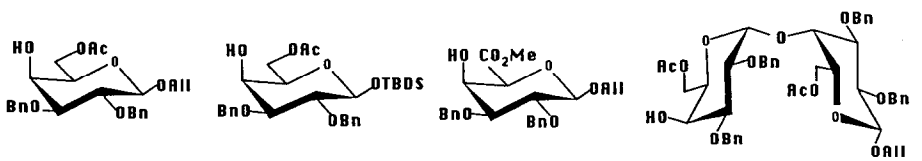


2

	H	Y
3	H	F
4	F	H

	H	Y
5	H	F
6	F	H

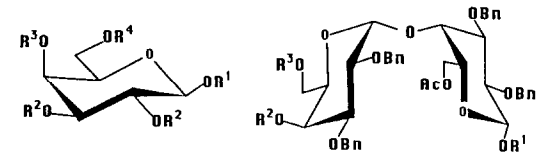
	R^1	R^2
7	CMe_2	
8	Ac	Bn



9 **10** **11** **12**

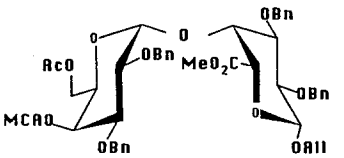
The glycosyl donors were prepared as follows. Selective acetylation followed by chloroacetylation of **13** (ref.1) gave a 62% yield of **14**, $[\alpha]_D$ +41.6° (c 1.4)[4] which was converted via desilylation by HF•pyridine[5] and fluorination with DAST[6] in THF into **2** in 73%

yield as an anomeric mixture of α:β=1:3, 2α-anomer: δ_C 105.9 ($^1J_{CF}$ 228.3 Hz, C-1); 2β-anomer: δ_C 109.7 ($^1J_{CF}$ 217.3 Hz, C-1)[7]. The α and β-D-galactopyranosyl fluorides **3** and **4** were prepared in 89% yield (**3**:**4**=1.3:1) from corresponding hemiacetal[1] by treatment with DAST, **3**:$[\alpha]_D$ +27.1° (c 1.4), δ_H 5.64 (dd, 1 H, J 2.7 and 53.6 Hz, H-1); **4**: m.p. 120-121°, $[\alpha]_D$ +27.7° (c 0.5), δ_H 5.16 (dd, 1 H, J 7.0 and 53.1 Hz, H-1). Compound **17**, $[\alpha]_D$ -33.3° (c 0.6), (ref.8), available from **15** in 48% yield by a conventional way, was acetylated to **18**, $[\alpha]_D$ -26.3° (c 1.1), which, by two step deallylation[9]: 1) $Rh(PPh_3)_3Cl$, and 2) $HgCl_2$, HgO, aq.acetone, and then by fluorination with DAST in THF, was converted into fluorides **5** and **6** in a ratio of 9:11; **5**: $[\alpha]_D$ +1.2° (c 0.5), δ_H 5.52 (dd, 1 H, J 2.7 and 53.5 Hz, H-1); **6**: m.p. 70°, $[\alpha]_D$ +11.3° (c 0.3), δ_H 5.19 (dd, 1 H, J 6.6 and 52.7 Hz, H-1). The galactobiosyl donor **7** (α:β=3:7), $\delta_H(\alpha)$ 5.66 (dd, 1 H, J 2.8 and 55.2 Hz); $\delta_H(\beta)$ 5.18 (dd, 1 H, J 6.6 and 53.2 Hz) were prepared in 90% yield from **22** (Table 1) through desilylation[10] with Bu_4NF-AcOH in THF followed by fluorination. Another galactobiosyl donor **8** (α:β=3:7), $\delta_H(\alpha)$ 5.62 (dd, 1 H, J 2.8 and 54.7 Hz); $\delta_H(\beta)$ 5.20 (dd, 1 H, J 5.9 and 52.7 Hz) was prepared in 92% yield from **23** (Table 1).



	R^1	R^2	R^3	R^4
13	TBDPS	Bn	H	H
14	TBDPS	Bn	MCA	Ac
15	All	H	H	H
16	All	Bn	H	H
17	All	Bn	Bn	H
18	All	Bn	Bn	Ac

	R^1	R^2	R^3
19	All	MCA	Ac
20	All	CMe_2	
21	All	H	H
22	TBDPS	CMe_2	
23	All	Bn	Ac
24	TBDPS	Bn	Ac



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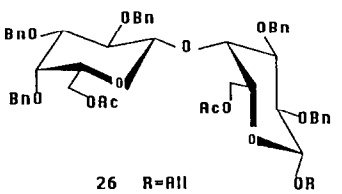
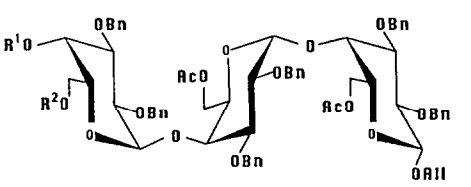


26 R=All
27 R=TBDPS



	R^1	R^2
28	CMe_2	
29	H	H
30	Bn	Ac

Bn = $CH_2C_6H_5$, All = $CH_2CH=CH_2$, MCA = $COCH_2Cl$, TBDPS = $Si(C_6H_5)_2Bu^t$

The glycosyl acceptors **9**, m.p. 91.5-92°, $[\alpha]_D$ +0.8° (c 0.8) and **10**, $[\alpha]_D$ +29.8° (c 0.9), were obtained by selective acetylation of diols **16** and **13** (ref.1), respectively. The preparation of the glycosyl acceptor **11** has already been reported[1]. The galactobiosyl glycosyl acceptor **12**, $[\alpha]_D$ +36.7° (c 0.8), was readily prepared either from **19** (Table 1) by dechloroacetylation or from **21** (Table 1) by monoacetylation.

Having prepared the designed glycosyl donors and acceptors, their reactions[11] were now examined and the results are summarized in Table 1. The fluoride **2** reacted smoothly with the glycosyl acceptor **9**, to give exclusively α1⟶4 linked product **19** in high yield (entry 1). However, the glycosylation of the galacturonide glycosyl acceptor **11** with the same glycosyl donor **2** gave exclusively α -linked product **25** but only in moderate yield (entry 2), manifesting the lower reactivity of 4-hydroxyl group in **11**. The tribenzyl fluorides **5** and **6**

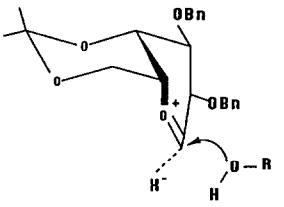
were then separately reacted with the glycosyl acceptors **9**, and **10**, resulting in the formation of a mixture of α and β-linked proudcts in a ratio of about 4:1 to 9:1 in high yields. No significant influence of the anomeric configuration of the glycosyl fluorides to the stereochemical outcome of glycosylation was observed (entry 7,8, and 9). Note that change of the protective group at 4-OH of the glycosyl donor from electronegative chloroacetyl (**2**) to benzyl group (**5** and **6**) was not in favor of the formation of α-D glycosylation product, even though in the case of insoluble silver salt promoted glycosylations such effect of substituent was observed[12].

The use of isopropylidene fluorides **3** and **4** was proved quite efficient to obtain exclusively α-linked product **20**, but the isopropylidene group of **20** was hydrolysed during work-up to give diol **21** as a major product (entry 3 and 4), unless pyridine was added prior to the work-up (entry 5 and 6). The glycosyl donor **4** was also reacted smoothly with galactobiosyl glycosyl acceptor **12** to give again exclusively α1⟶4 linked galactotriose product **28** (entry 10).

Table 1 The Results of Glycosylation Reactions

entry	donor	acceptor	don./acc.	solvent[a]	temp.(°C)	time(h)	yield(%)	product and physical data
1	**2**	**9**	1.16	A	-15~r.t.	20	83	**19**:$[\alpha]_D$ +57.9°(c 0.6), δ_C100.5 ($^1J_{CH}$169.7Hz),103.1($^1J_{CH}$159.9 Hz)
2	**2**	**11**	1.16	A	-15~r.t.	20	42	**25**:$[\alpha]_D$ +47.3°(c 1.3), δ_H 5.11 (d, 1 H, J 3.4 Hz)
3[b]	**3**	**9**	1.21	B	-15~r.t.	20	9	**20**:δ_H 1.33 (s, 3 H), 1.43 (s, 3 H, 2.04 (3H, s)
						21	62	**21**:$[\alpha]_D$ +39.1°(c 1.8), δ_C 100.5 ($^1J_{CH}$168.5Hz), 103.1($^1J_{CH}$156.3Hz)
4[b]	**4**	**9**	1.21	B	-15~r.t.	20	4	**20**
							74	**21**
5[c]	**3**	**10**	1.42	A	-20	1.5	84	**22**:$[\alpha]_D$ +71.8°(c 1.5), δ_C 98.2 ($^1J_{CH}$152.6Hz), 100.5($^1J_{CH}$169.7Hz)
6[c]	**4**	**10**	1.44	C	-20~-10	3	77	**22**
7	**5**	**9**	1.28	A	-20~r.t.	4	87	**23**:$[\alpha]_D$ +27.1°(c 1.1), δ_C 100.2 ($^1J_{CH}$168.5Hz), 103.0($^1J_{CH}$158.7Hz)
							9	**26**:$[\alpha]_D$ +7.4°(c 0.8), δ_C 102.9 ($^1J_{CH}$158.7Hz), 103.2($^1J_{CH}$158.7Hz)
8	**5**	**10**	1.30	A	-15~5	4	79	**24**:$[\alpha]_D$ +40.0°(c 0.8), δ_C 98.1 ($^1J_{CH}$152.6Hz), 100.0($^1J_{CH}$168.5Hz)
							16	**27**
9	**6**	**10**	1.30	A	-15~0	2.5	78	**24**
							18	**27**:$[\alpha]_D$ +17.3° (c 0.6), δ_C 98.1 ($^1J_{CH}$160.5Hz), 102.8($^1J_{CH}$ 156.3Hz)
10[c,d]	**4**	**12**	1.40	B	-15	6	81	**29**:$[\alpha]_D$ +41.9°(c 0.9), δ_C 99.6($^1J_{CH}$ 169.7Hz), 99.7($^1J_{CH}$169.7Hz), 102.8 ($^1J_{CH}$159.9Hz)
11[c,d]	**7**	**9**	0.84	A	-15~r.t.	7	68	**29**
12	**8**	**9**	0.76	C	-15~r.t.	4	89	**30**:$[\alpha]_D$ +31.5°(c 0.4), δ_C 99.6 ($^1J_{CH}$ 167.2Hz), 99.8($^1J_{CH}$167.2Hz), 102.9 ($^1J_{CH}$160.5Hz)

a) Solvent A : Et_2O, B: 10:1 Et_2O-toluene, and C: dichloroethane. b) Pyridine was not added prior to the work-up. c) Pyridine was added prior to the work-up. d) Compound **28** was directly converted into compound **29** and characterized.



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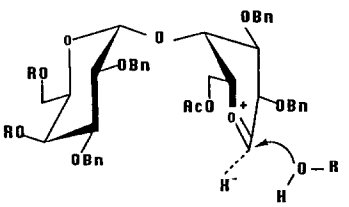

32

Finally, the galactobiosyl glycosyl donors **7** and **8** were examined. The reaction of the anomeric mixture of either **7** or **8** with the glycosyl acceptor **9** yielded the desired α-linked products **28** and **30**, respectively, with remarkable stereoselectivity. No β-linked product was detected either by tlc or ^{1}H-n.m.r. The stereoselectivity observed in the case of the glycosyl donors **3**, **4**, **7** and **8** may reasonably be explained by the nucleophilic attack of a hydroxyl group of the glycosyl acceptor on the intermediate "intimate ion pair"[13] such as **31** and **32** from the convex face which in the case of **32** is defined by exo-anomeric effect[14].

In conclusion, a highly efficient and practical approach to the linear α1⟶4 linked galactooligosaccharides was developed by employing galactopyranosyl fluorides.

Acknowledgment. We thank Dr. J. Uzawa and Mrs. T. Chijimatsu for recording and measuring the NMR spectra and Dr. H. Yamazaki and his staff for the elemental analyses. We also thank Ms. A. Takahashi and Ms. K. Moriwaki for their technical assistance.

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(Received in Japan 14 March 1987)