Carbohydrate Research, 123 (1983) C12–C15
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Preliminary communication

Synthesis of a linear, hexahexosyl unit of a high-mannose type of glycan chain of a glycoprotein*

TOMOYA OGAWA**, TOMOO NUKADA, and TOORU KITAJIMA
The Institute of Physical and Chemical Research, Wako-shi, Saitama, 351 (Japan)

(Received August 8th, 1983; accepted for publication, August 18th, 1983)

In 1978, Li *et al.*[2], and, in 1979, Liu *et al.*[3] proposed the structure of the high-mannose type glycan **1**. In 1980, Ugalde *et al.*[4] assigned the stereochemistry of the tri-glucopyranosyl part of **1** as αGlc(1→2)αGlc(1→3)αGlc(1→3) from inhibition experiments with glucosidases. In order to provide synthetic support for the proposed structure **1**, we have studied an approach to a total synthesis of **1** with regio- and stereo-chemical control. According to retrosynthetic considerations, structure **1** was divided into three parts, namely, **2**, **3**, and **4**. Because synthetic routes to the structural equivalents of **2** (ref. 5) and **3** (ref. 6) had already been established, we describe here a synthesis of the linear hexasaccharide **4**. Retrosynthetic considerations indicated that the target structure **4** might be reconstructed from the disaccharide synthons **6**, **7**, and **8**. As the synthetic equivalents **9** (ref. 7) and **10** (ref. 8), corresponding to **6** and **7**, are already available, we first describe the synthesis of **18**, which corresponds to the synthon **8**.

A mixture of allyl 3-*O*-allyl-α- and -β-D-glucopyranoside (**11**), readily obtainable from 3-*O*-allyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, was benzylated, to give **12**, and deallylation of **12** with $PdCl_2$ in aq. AcOH–AcONa (ref. 9) afforded a 61% yield of the tribenzyl ether **13**, $[\alpha]_D$ +29.3°***, as a mixture of the α and β anomer in the ratio of 1:1. Acetylation of **13**, to give **14** (R_F 0.38 in 10:1 toluene–THF), and treatment of **14** with HCl in $Cl(CH)_2Cl$ gave a 70% yield of **15**, R_F 0.50 in 10:1 toluene–THF.

Glycosidation of **16** (ref. 10) with **15** in the presence of $AgOSO_2CF_3$–powdered molecular sieves 4A in $Cl(CH_2)_2Cl$ at −5° afforded a 72% yield of a mixture of **17** and **19** in the ratio of 3:1; for **17**, $\delta_C(CDCl_3)$: 98.7 (C-1b, $^1J_{CH}$ 170.9 Hz), 96.4 (C-1a, $^1J_{CH}$ 168.5 Hz); for **19**, δ_C $(CDCl_3)$: 100.5 (C-1b, $^1J_{CH}$ 153.8 Hz), 97.0 (C-1a, $^1J_{CH}$ 167.2 Hz). In the presence of $Hg(CN)_2 \cdot HgBr_2$, however, glycosidation of **16** (ref. 10) with **15** in $Cl(CH_2)_2Cl$ gave a 79% yield of the α anomer **17**, $[\alpha]_D$ +62.8°. Deacetylation of **17** af-

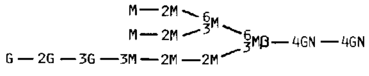
---

*Synthetic Studies on Cell-surface Glycans, Part XXVI. For Part XXV, see ref. 1.

**To whom enquiries should be addressed.

***Values of $[\alpha]_D$ were measured for $CHCl_3$ solutions at 25°, unless noted otherwise. Compounds with $[\alpha]_D$ recorded gave satisfactory data for elemental analyses.

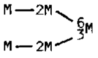
0008-6215/83/$03.00



1

Mβ—4GN—4GN

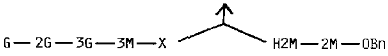
2



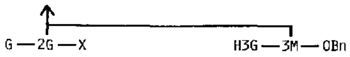
3

G—2G—3G—3M—2M—2M

4

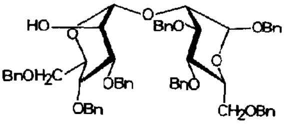


5 **6**



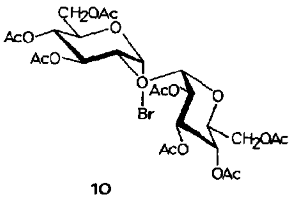
7 **8**

M = α-D-mannopyranosyl
Mβ = β-D-mannopyranosyl
G = α-D-glucopyranosyl
GN = 2-acetamido-2-deoxy-β-D-glucopyranosyl



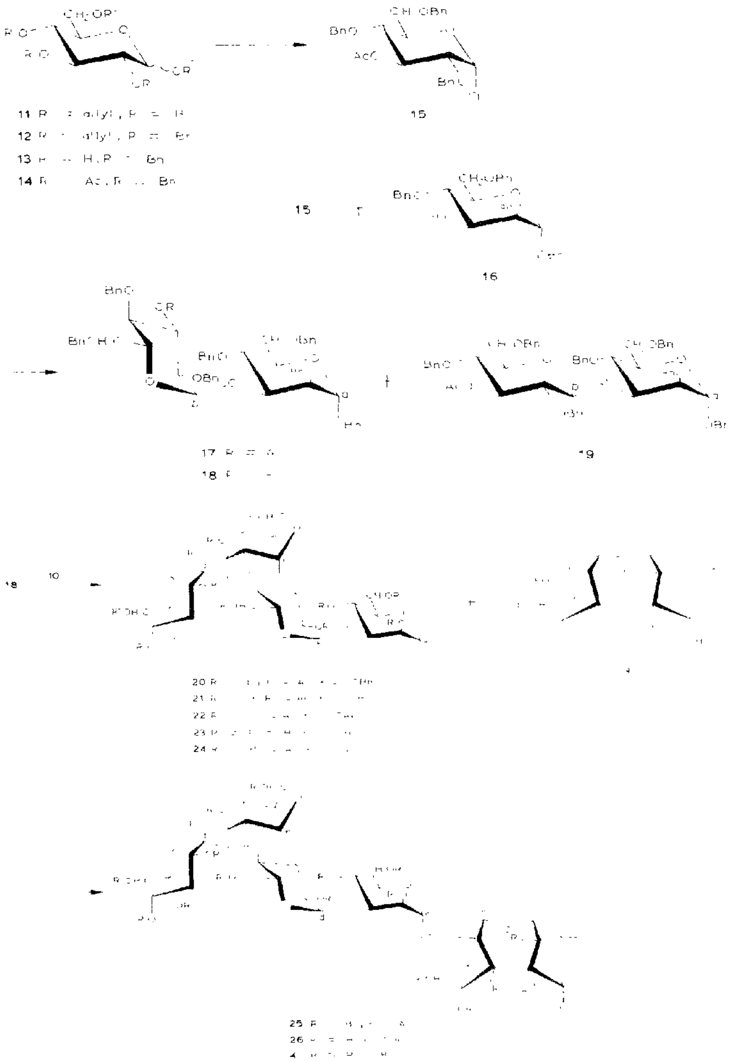
9

Bn = $PhCH_2$



10

forded **18**, $[\alpha]_D$ +56.8°, R_F 0.73 in 3:1 toluene–THF, which was glycosylated with the kojibiosyl donor[8] **10**, $[\alpha]_D$ +219.5°, m.p. 136–138° (Et_2O), in the presence of $AgOSO_2CF_3$–powdered molecular sieves 4A in $Cl(CH_2)_2Cl$, to give a 59% yield of the protected tetrasaccharide **20**, $[\alpha]_D$ +104.4°, R_F 0.50 in 3:1 toluene–THF; δ_C ($CDCl_3$): 98.6 (C-1b, $^1J_{CH}$ 167.2 Hz), 96.2 (C-1a, $^1J_{CH}$ 169.7 Hz), 95.1 (C-1d, $^1J_{CH}$ 174.6 Hz), and 94.8


11 R = allyl, R' = H
12 R = allyl, R' = Bn
13 R = H, R' = Bn
14 R = Ac, R' = Bn
15
15 +
16
17 R = A
18 R =
19
18 + 10
20
21
22
23
24
25
26

(C-1c, $^1J_{CH}$ 175.8 Hz). Debenzylation of **20** by catalytic, hydrogen transfer[11] with 10% Pd–C, HCO_2H, and MeOH for 1 h at 20° gave **21**, and acetylation of **21** afforded a 79% yield of the peracetylated tetrasaccharide **22**, $[\alpha]_D$ +111.5°. Deacetylation of **21** with NaOMe–MeOH gave the free tetrasaccharide **23**: $[\alpha]_D$ +37.5° (H_2O), R_F 0.88 in 1:8:1 AcOH–MeOH–H_2O;δ_H (400 MHz, D_2O): 5.169 (H-1aα, *J* 1.71 Hz), 4.928 (H-1aβ, singlet), 5.199 (H-1d, *J* 3.7 Hz), 5.270 (H-1bβ, *J* 4.4 Hz), 5.281 (H-1bα, *J* 4.6 Hz), and 5.547 (H-1c, *J* 3.4 Hz). Treatment of **22** with HBr–AcOH in CH_2Cl_2 gave tetrasaccharide donor **24**, R_F 0.40 in 3:2 toluene–THF, δ_H 6.31 (H-1a, singlet), which corresponds to the synthon **5**. The reaction of **24** with the mannobiosyl acceptor **9** in the presence of $AgOSO_2CF_3$–powdered molecular sieves 4A in $Cl(CH_2)_2Cl$ for 5 h at 20° afforded a 56% yield of the protected hexasaccharide **25**, $[\alpha]_D$ +75.0°, R_F 0.30 in 5:1 toluene–THF, which was subjected to debenzylation (10% Pd–C, HCO_2H, MeOH) and deacetylation (NaOMe–MeOH), to give the target, linear hexasaccharide **4**: $[\alpha]_D$ +104.8° (H_2O), R_F 0.46 in 1:8:1 AcOH–MeOH–H_2O;δ_H (400 MHz, D_2O): 5.543 (H-1e, d, *J* 3.7 Hz), 5.385 (H-1a, s), 5.311 (H-1b, s), 5.283 (H-1d, d, *J* 3.9 Hz), 5.197 (H-1f, d, *J* 3.7 Hz), and 5.049 (H-1c, d, *J* 1.6 Hz).

In conclusion, a stereoselective synthesis of the linear hexasaccharide **4** was achieved by using the three disaccharide synthons **9**, **10**, and **18**.

ACKNOWLEDGMENTS

We thank Dr. J. Uzawa and Mrs. T. Chijimatsu for recording and measuring the n.m.r. spectra, and Dr. H. Homma and his staff for the elemental analyses. We also thank Mrs. A. Takahashi for her technical assistance.

REFERENCES

1 T. Ogawa, T. Kitajima, and T. Nukada, *Carbohydr. Res.*, 123 (1983) C8–C11.
2 E. Li, I. Tabas, and S. Kornfeld, *J. Biol. Chem.*, 253 (1978) 7762–7770.
3 T. Liu, B. Stetson, S. J. Turco, S. C. Hubbard, and P. W. Robbins, *J. Biol. Chem.*, 254 (1979) 4554–4559.
4 R. A. Ugalde, R. J. Staneloni, and L. F. Leloir, *Eur. J. Biochem.*, 113 (1980) 97–103.
5 T. Ogawa, T. Kitajima, and T. Nukada, *Carbohydr. Res.*, 123 (1983) C5–C7.
6 T. Ogawa, K. Katano, K. Sasajima, and M. Matsui, *Tetrahedron*, 37 (1981) 2779–2786.
7 T. Ogawa and H. Yamamoto, *Carbohydr. Res.*, 104 (1982) 271–283.
8 W. E. Dick, J. E. Hodge, and G. E. Inglett, *Carbohydr. Res.*, 36 (1974) 319–329.
9 T. Ogawa, S. Nakabayashi, and T. Kitajima, *Carbohydr. Res.*, 114 (1983) 225–236.
10 T. Ogawa and H. Yamamoto, unpublished results.
11 B. El Amin, G. M. Anantharamaiah, G. P. Royer, and G. E. Means, *J. Org. Chem.*, 44 (1979) 3442–3444; V. S. Rao and A. S. Perlin, *Carbohydr. Res.*, 83 (1980) 175–177; G. Brieger and T. J. Nestrick, *Chem. Rev.*, 74 (1974) 567–580.