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Carbohydrate Research 268 (1995) C1–C6

CARBOHYDRATE RESEARCH

Preliminary communication

Cyclo-glycosylation of a (1 → 4)-linked glycooctaose and glycodecaose: Synthesis of cyclo-*lacto*octaose and cyclo-*lacto*decaose ☆

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Received 24 October 1994; accepted 9 December 1994

Cyclo-glycosylation has successfully afforded a variety of natural and unnatural cyclo-(1 → 4)-linked glycooligosaccharides [1]. In connection with such studies we reported [2] an efficient synthesis of cyclo-*lacto*hexaose **1** in 1993. We now describe the experiments directed toward cyclo-glycosylation of higher homologues of lactooligosaccharides to give cyclo-*lacto*octaose **2** and cyclo-*lacto*decaose **4**.

Immediate precursors for the synthesis of **2** and **4** should be designed as fully benzylated compounds **3** and **5**, which in turn may be obtained by intramolecular glycosylation of a corresponding linear glycosyl fluoride such as **6**. According to this scenario glycosyl fluorides **13** and **19** were designed.

A readily available tetrasaccharide **7** (ref. 2) was converted into glycotetraosyl donor **9** in two steps via hemiacetal **8**: (*i*) $(NH_4)_2Ce(NO_3)_6$ (CAN) in 4:1 MeCN–H_2O [3], (*ii*) DAST [4] in CH_2Cl_2, 82% overall. Compound **9** ($\alpha:\beta$ 1:2) had R_f 0.40 (α anomer) and 0.42 (β anomer) in 2:1 hexane–EtOAc; δ_H 5.440 (dd, 53.1 and 2.8 Hz, H-1$^I\alpha$), 5.183 (dd, 53.4 and 6.4 Hz, H-1$^I\beta$), 2.046 (s, Lev for β), and 2.041 (s, Lev for α). Glycosylation of the reported glycotetraosyl acceptor **10** (ref. 2) with 0.5 equiv of **9** in the presence of $Cp_2Zr(ClO_4)_2$ [5] in Et_2O afforded a 54% yield (calculated based on the donor) of the desired α-linked octasaccharide **11** and a 23% yield of the β-linked

☆ Compounds described with either R_f or $[\alpha]_D$ values gave acceptable combustion analyses. Values for $[\alpha]_D$ and δ_H were measured in $CHCl_3$ and $CDCl_3$, respectively, at ambient temperature, unless noted otherwise. Signal assignment such as H-1^3 stands for H attached to carbon-1 of sugar residue 3.

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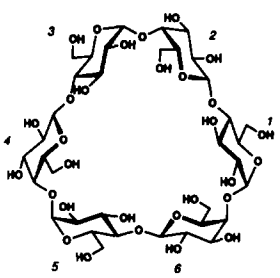
SSDI 0008-6215(94)00372-6



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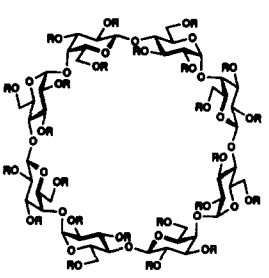

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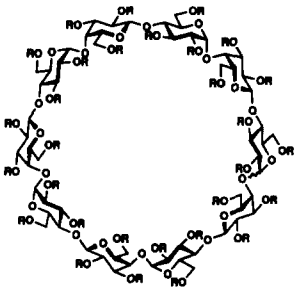
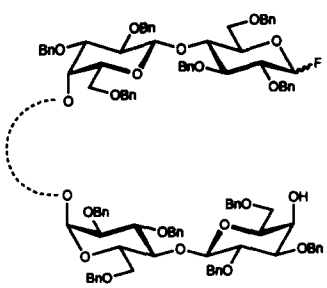
3 R = Bn



4 R = H
5 R = Bn

isomer **14**. Compound **11** had $[\alpha]_D$ +37.0° (*c* 1.5); R_f 0.37 in 6:1 toluene–EtOAc; δ_H 1.930 (s, Lev), 3.740 (s, OMe), 5.006 (d, 3.4 Hz, 2 × H-1), 5.014 (d, 4.0 Hz, H-1); δ_C 99.6, 100.1 and 100.3 (3d, 168–175 Hz, 3 × C-1), 102.6, 102.6, 103.2, 103.3, and 103.5 (5d, 161–164 Hz, 5 × C-1). Compound **14** had $[\alpha]_D$ +34.6° (*c* 2.1); R_f 0.34 in 6:1 toluene–EtOAc; δ_H 3.751 (s, OMe), 5.018 and 5.054 (2d, 3.4 Hz, 2 × H-1); δ_C 100.4 and 100.5 (2d, 172 Hz, 2 × C-1), 102.4, 102.5, 102.6, 102.8, 102.8, and 103.0 (6d, 162 Hz, 6 × C-1). In order to examine the crucial cyclo-glycosylation, both compounds **11** and **14** were converted into fluorides **13** and **15**, respectively, as follows. Treatment of **11** with (*i*) CAN in 4:1:1 MeCN–H_2O–toluene, (*ii*) DAST in CH_2Cl_2, and (*iii*) $NH_2NH_2 \cdot AcOH$ [6] in 1:5 toluene–EtOH afforded a 61% yield of **13** via **12**. Compound **12** ($\alpha:\beta = 1:2$) had R_f 0.40 (α) and 0.44 (β) in 6:1 toluene–EtOAc; δ_H 1.965 (s, Lev), 5.468 (d, 3.4 Hz, H-4^B). Compound **13** ($\alpha:\beta$ 1:2) had R_f 0.44 (α) and 0.48 (β) in 6:1 toluene–EtOAc; δ_H 5.087 (dd, 53.4 and 6.4 Hz, H-1$'\beta$), 5.395 (dd, 53.7 and 2.8 Hz, H = 1$'\alpha$). Similarly, **14** was converted into fluoride **15** in 48% overall yield. Compound **15** ($\alpha:\beta = 1:4$) had R_f 0.46 (α) and 0.49 (β) in 6:1 toluene–EtOAc; δ_H 5.177 (dd, 53.4 and 6.4 Hz, H-1$'\beta$), 5.424 (dd, 54.2 and 2.7 Hz, H-1$'\alpha$). $Cp_2Zr(ClO_4)_2$-promoted cyclo-glycosylation of **13** in Et_2O at 0°C successfully gave a 85% yield of **3** which had R_f 0.52 in 2:1 hexane–EtOAc; $[\alpha]_D$ +17.3° (*c* 1.2); δ_H



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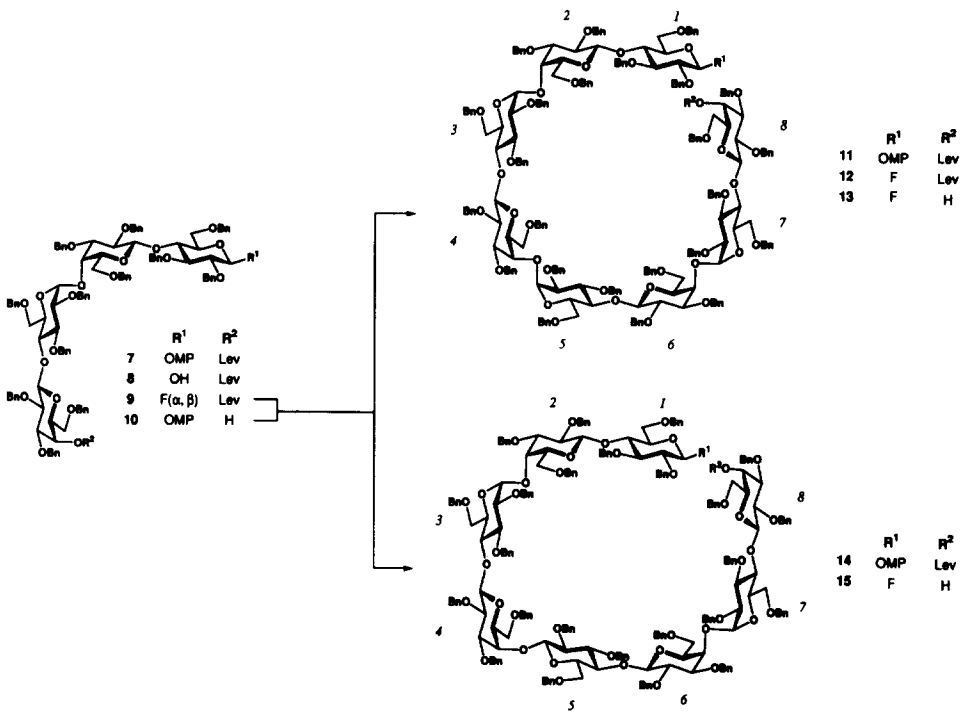
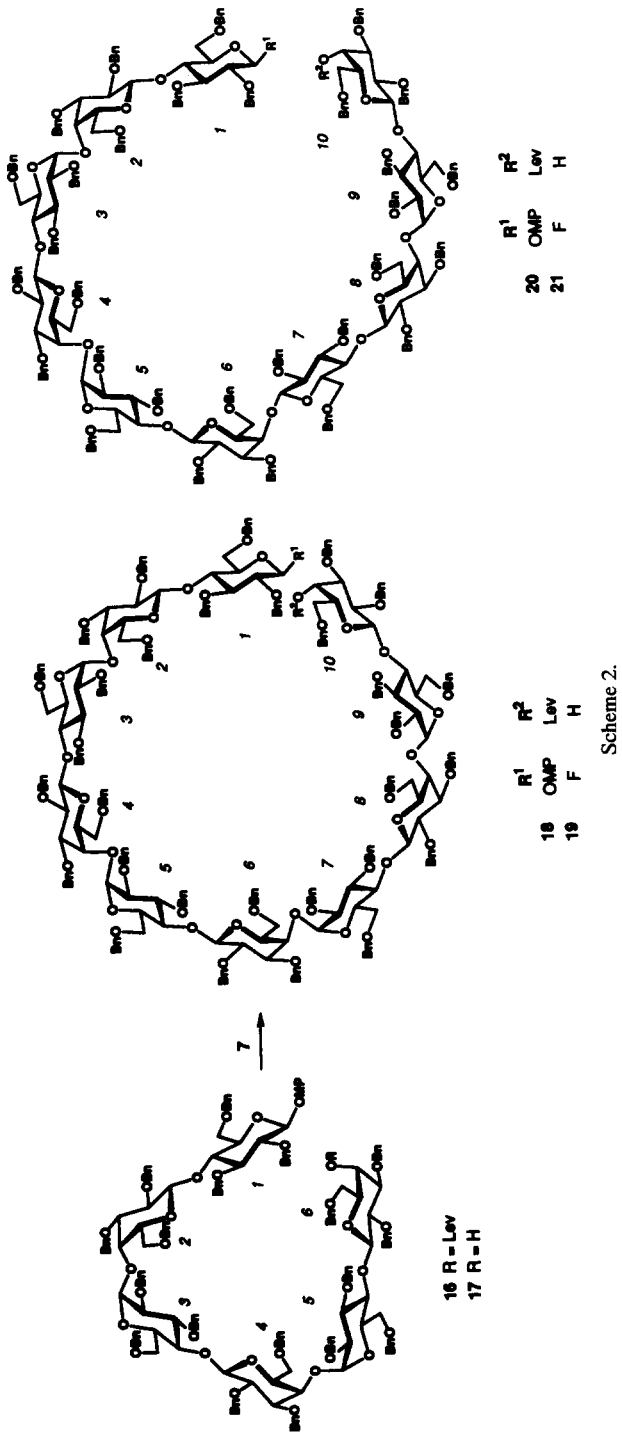


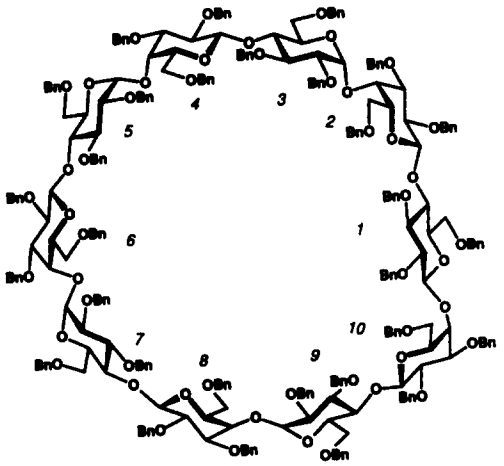
Scheme 1.

4.111 (d, 7.5 Hz, 4 × H-1) and 4.946 (d, 3.3 Hz, 4 × H-1); δ_C 99.0 (d, 174 Hz, 4 × C-1) and 101.4 (d, 162 Hz, 4 × C-1). Catalytic hydrogenolysis of **3** in the presence of $Pd(OH)_2$ in 12:1:1 MeOH–EtOAc–H_2O and purification by a column of Sephadex LH-20 in H_2O quantitatively afforded **2**. Cyclo-*lacto*octaose **2** had R_f 0.48 in 1:1:1 ^{t}BuOH–MeOH–H_2O; $[\alpha]_D$ + 101.9° (*c* 0.5 in 1:1 MeOH–H_2O); δ_H (D_2O) 4.472 (d, 7.6 Hz, 4 × H-1) and 4.916 (d, 4.0 Hz, 4 × H-1); δ_C (D_2O) 100.4 (d, 169 Hz, 4 × C-1) and 102.8 (d, 166 Hz, 4 × C-1); FABMS (negative) 1295 $(M - H)^-$. Attempted cyclo-glycosylation of the fluoride **15**, however, afforded only a 23% of yield an undesired hydrolysis product as well as 12% of a linear octasaccharide having a 1,6-anhydro ring at residue *1*.

$Cp_2Zr(ClO_4)_2$-promoted glycosylation of a glycohexaosyl acceptor **17**; $[\alpha]_D$ +38.4° (*c* 0.8); readily obtainable from known compound **16** (ref. 2), with 0.75 equiv of fluoride **9** in Et_2O afforded, after chromatographic separation, a 32% yield of the desired α-linked product **18** and a 26% of the β isomer **20**. Compound **18** had $[\alpha]_D$ +31.9° (*c* 0.2); R_f 0.34 in 6:1 toluene–EtOAc; δ_H 3.731 (s, Lev), 5.000, 5.015, 5.023, and 5.067 (4d, 3.4–4.0 Hz, 4 × H-1); δ_C 98.9, 99.4, 100.2, and 100.3 (4d, 168–172 Hz, 4 × C-1), 102.6, 102.6, 103.2, 103.2, 103.4, and 103.6 (6d, 160–161 Hz, 6 × C-1). Compound **20** had $[\alpha]_D$ +32.0° (*c* 1.7); R_f 0.37 in 6:1 toluene–EtOAc; δ_C 100.2, 100.6, and 100.6 (3d, 167–170 Hz, 3 × C-1), 102.6, 102.7, 102.7, 103.0, 103.0, 103.2, and 103.5 (7d, 160–161 Hz, 7 × C-1). Decasaccharide **18** was converted as



Scheme 2.



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Scheme 3.

described for **11** and **13** into fluorides **19** in three steps in 53% overall yield. Compound **19** ($\alpha:\beta = 1:2$) had R_f 0.33 (α) and 0.36 (β) in 6:1 toluene–EtOAc; δ_H 5.191 (half of dd, 6.5 Hz, H-1$'\beta$) and 5.479 (dd, 53.1 and 2.5 Hz, H-1$'\alpha$).

Cyclo-glycosylation of fluoride **19** under the same conditions as described above afforded a 51% yield of α-linked cyclo-glycan **5** along with 14% of the β-linked isomer **22**. Compound **5** had $[\alpha]_D$ +33.1° (*c* 0.3); R_f 0.34 in 6:1 toluene–EtOAc; δ_H 4.173 (d, 7.8 Hz, 5 × H-1) and 4.970 (d, 3.4 Hz, 5 × H-1); δ_C 100.2 (5 × C-1) and 103.2 (5 × C-1); FABMS (positive) 4348 $(M + Na)^+$. Compound **22** had R_f 0.39 in 6:1 toluene–EtOAc; δ_H 4.927, 5.045, and 5.080 (3d, 3.1–4.0 Hz, 3 × H-1); FABMS (positive) 4348 $(M + Na)^+$. The cyclo-structure assigned for **22** was confirmed as follows. Compound **20** was transformed into fluoride **21** ($\alpha:\beta = 1:2$), R_f 0.43 (α) and 0.48 (β) in 6:1 toluene–EtOAc, in three steps as described for **18**, in 48% overall yield. The product was then submitted to the cyclo-glycosylation conditions to afford a 34% yield of **22**.

Finally, catalytic hydrogenolysis of **5** in the presence of 20% $Pd(OH)_2/C$ in 40:10:1 MeOH–EtOAc–H_2O and subsequent purification of the product by Sephadex LH-20 in H_2O gave a quantitative yield of cyclo-*lacto*decaose **4** that had R_f 0.28 in 1:1:1 BuOH–MeOH–H_2O; δ_H (1:3 CD_3OD–D_2O at 60°C) 4.496 (d, 7.3 Hz, H-1 for 5 Gal residues), 4.907 (d, 3.9 Hz, H-1 for 5 Glc residues); FABMS (positive) 1643 $(M + Na)^+$. It should be noted that, although from *lacto*octaosyl fluoride **13** a high yield of cyclo-glycan **3** was obtained stereoselectively, a homologous *lacto*decaosyl fluoride **19** afforded a mixture of cyclo-glycan **5** and the β isomer **22** in a ratio of about 4:1.

In summary, cyclo-*lacto*octatose **2** and cyclo-*lacto*decaose **4** were synthesized by employing corresponding linear glycosyl fluorides which may generally be designed as **6** as depicted in Scheme 1.

Acknowledgments

A part of this work was financially supported by a Grant-in-Aid for Scientific Research on Priority Areas No. 05274102 from the Ministry of Education, Science and Culture, and also by the Special Coordination Funds of the Science and Technology Agency of the Japanese Government. We thank Dr. J. Uzawa and Mrs. T. Chijimatsu for the NMR, spectra Mr. Y. Esumi for FABMS determinations, Ms. M. Yoshida and her staff for elemental analyses, and Ms. A. Takahashi for technical assistance.

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