Tetrahedron Letters, Vol. 34, No. 13, pp. 2171-2174, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

CYCLO-GLYCOSYLATION OF (1→4)-LINKED GLYCOHEXAOSES: SYNTHESIS OF CYCLO-LACTOHEXAOSE[1)]

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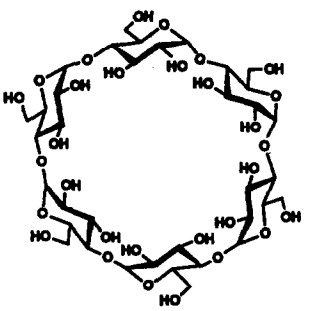
Abstract: Cyclo-glycosylation of (2,3,6-tri-*O*-benzyl-β-D-galactopyranosyl)-{(1→4)-(2,3,6-tri-*O*-benzyl-β-D-glucopyranosyl)-(1→4)-(2,3,6-tri-*O*-benzyl-α-D-galactopyranosyl)}$_2$-(1→4)-(2,3,6-tri-*O*-benzyl-α/β-glucopyranosyl fluoride and subsequent deprotection of the product gave an excellent yield of cyclo-lactohexaose.

In 1985 we first reported[2] a successful cyclo-glycosylation to yield cyclo-α-(1→4)-glucohexaose **1**. Subsequently other examples[2] for the successful synthesis of cyclo-(1→4)-glycohexaoses have been reported besides our own approach[3] to cyclo-α-(1→4)-mannohexaose **2** and related compounds. In the relevant experiments we observed[4] a very low yield (8%) of the cyclo-glycosylation for cyclo-α-(1→4)-mannopentaose **3** in contrast with the high yield (95%) in the case for cyclo-α-(1→4)-mannohexaose **2**. Therefore it may be assumed that, in order to carry out an efficient cyclo-(1→4)-glycosylation, presence of more than six axial interresidual



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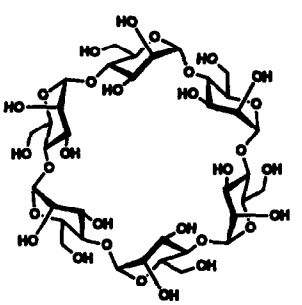

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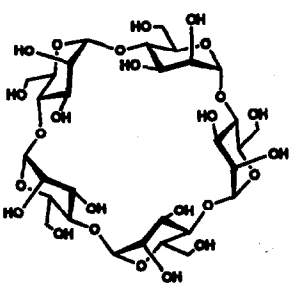

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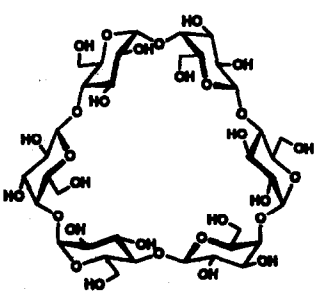

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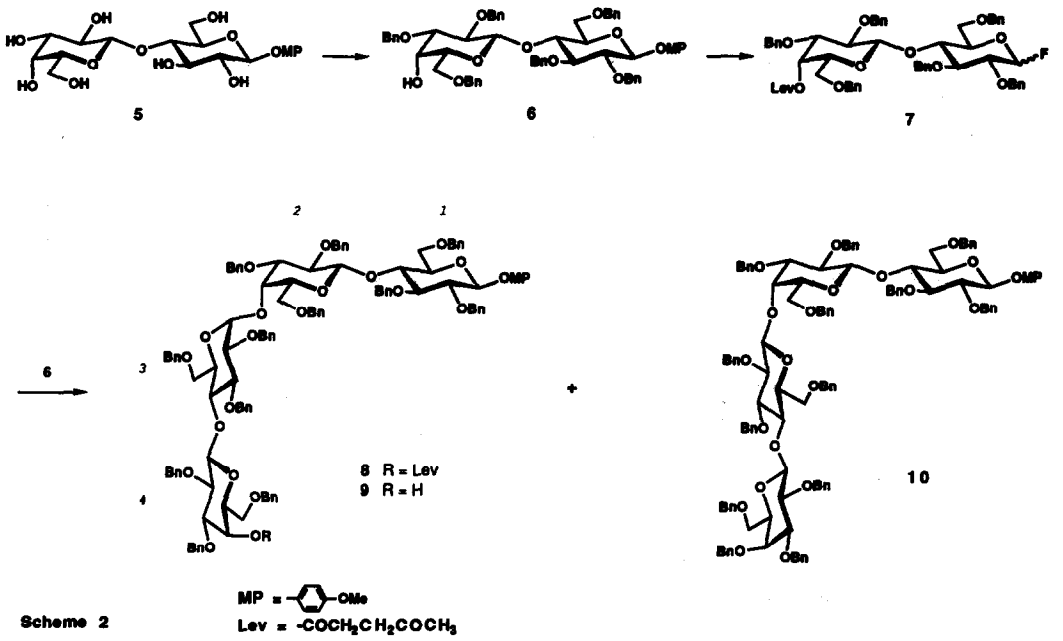
Scheme 1

linkages should be required. Based on this assumption, a trigonally shaped cyclo-α-(1→4)-lactohexaose **4** was designed as a target for our experiments on cyclo-glycosylation.

A key intermediate for the cyclo-glycosylation was designed as fluoride **13** which was synthesized as follows. 4-Methoxyphenyl β-D-lactoside **5**[5] was readily available from octa-*O*-acetyl-β-D-lactose in 2 steps (*1* 4-MeOPhOH, TMSOTf in $(ClCH_2)_2$[6], *2* NaOMe in MeOH, 84% overall). Conversion of **5** into **6**[5] was carried out in 3 steps (*1* $PhCH(OMe)_2$, $TsOH{\cdot}H_2O$ in DMF, *2* BnBr, NaH in DMF, *3* Me_3NBH_3, powdered molecular sieve 4A (MS4A), $AlCl_3$ in THF[7], 69% overall). Compound **6** was then transformed into a glycosyl donor **7**[5] in 3 steps (*1* Lev_2O, DMAP in pyridine[8], *2* CAN in 4:1 MeCN-H_2O[9], *3* diethylaminosulfur trifluoride (DAST) in CH_2Cl_2[10], 68% overall). Glycosylation of **6** with **7** (2 equivalents) in the presence of $Cp_2Zr(ClO_4)_2$[11] and MS4A in Et_2O gave 64% of α-linked product **8**[5] and 22% of β-linked product **10**[5] after separation of the products by silica-gel column chromatography in 200:1 CH_2Cl_2-THF.

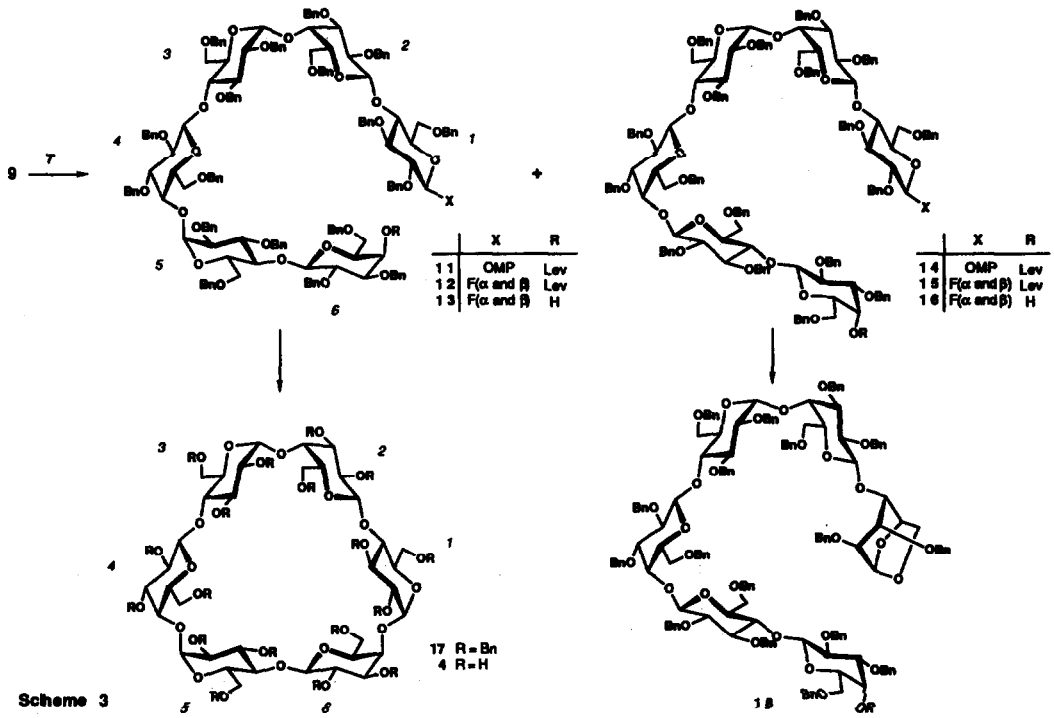


Scheme 2

Treatment of **8** with $NH_2NH_2{\cdot}AcOH$ in 5:1 EtOH-PhMe gave 91% of glycotetraosyl acceptor **9**[5] which was glycosylated with fluoride **7** (2 equivalent) as described for **8** to give 53% of α-linked product **11**[5] and 18% of β-linked product **14**[5] after separation by silica-gel column chromatography in 2:1 hexane-EtOAc. Both **11** and **14** were converted into fluorides **13** (α:β = 1:2) and **16** (α:β = 1:2) in 3 steps (*1* CAN in 4:1:1 MeCN-H_2O-PhMe, *2* DAST in CH_2Cl_2, *3* $NH_2NH_2{\cdot}AcOH$ in 5:1 EtOH-PhMe 69% and 44% overall, respectively).

Having prepared key glycosyl fluorides **13** and **16** crucial cyclo-glycosylations were examined. To a stirred mixture of $Cp_2Zr(ClO_4)_2$ (formed *in situ*) and MS4A in CH_2Cl_2 was added a solution of **13** in CH_2Cl_2 at 0°. After extractive work-up and purification by silica-gel column

chromatography in 10:1 Tolue-EtOAc, 74% of 17[5] was obtained[1,2]. Hydrogenolysis of 17 in the presence of 20% $Pd(OH)_2$-C in 12:1:1 MeOH-EtOAc-H_2O and purification of the product by Biogel P-6 in H_2O afforded a quantitative yield of the target molecule 4[5]. Attempted cycloglycosylation of 16 under the same condition failed and gave 38% of 1,6-anhydro derivative 18[5] besides the hydrolysed hemiacetal.



Scheme 3

In summary, a trigonally shaped cycloglycan 4 containing three molecules of α-(1→4)-linked lactoses was synthesized via highly efficient cyclo-glycosylation of the key fluoride 13.

Acknowledgements. A part of this work was financially supported by a Grant-in-Aid for Scientific Research 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 NMR, Mr. Y. Esumi for FAB-MS, Ms. M. Yoshida and her staff for elemental analyses, and Ms. A. Takahashi for technical assistance.

References and Notes

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5 Physical data for new compounds are given below, values of $[\alpha]_D$ and $\delta_{H,C}$ were measured at 25°±3° for solutions in $CHCl_3$ and $CDCl_3$, respectively, unless noted otherwise. Signal assignment such as 1^3 stands for a proton at C-1 of sugar residue *3*. **4**: $[\alpha]_D$ +40.5° (*c* 0.3, 1:1 MeOH-H_2O); R_F 0.35 in 2:2:1 n-PrOH-MeOH-H_2O; δ_H (D_2O, 60°) 4.967 (d, 3.7 Hz), 4.553 (d, 7.6 Hz); δ_C(D_2O) 104.1 (d, 163 Hz), 101.8 (d, 169 Hz); FAB-MS $(M+Na)^+$ 995. **5**: $[\alpha]_D$ -20° (*c* 0.5, DMF); R_F 0.17 in 3:1 $CHCl_3$-MeOH; δ_H (DMSOd_6) 4.800 (d, 7.6 Hz), 4.228 (d, 7.6 Hz), 3.699 (s, OMe). **6**: $[\alpha]_D$ +4.4° (*c* 1.5); R_F 0.44 in 2:1 hexane-EtOAc; δ_H 4.855 (d, 7.3 Hz), 4.442 (d, 7.6 Hz). **7**: (α:β = 2:3); R_F 0.39 in 20:1 CCl_3-Me_2CO; δ_H 5.562 (d, 2.7 Hz, 4^2), 5.489 (dd, 53.4 and 2.4 Hz, $1^1\alpha$), 5.223 (dd, 53.1 and 6.4 Hz, $1^1\beta$), 4.417 (d, 7.6 Hz, $1^2\beta$), 4.311 (d, 7.9 Hz, $1^2\alpha$), 2.091 (s, Levα), 2.084 (s, Levβ). **8**: $[\alpha]_D$ +27.9° (*c* 1.0); R_F 0.13 in 200:1 CH_2Cl_2-THF; δ_H 5.480 (d, 3.7 Hz, 4^4), 5.055 (d, 3.4 Hz, 1^3), 4.774, 4.449, 4.186 (3d, 7.6 Hz, $1^{1,2,4}$), 2.041 (s, Lev); δ_C 103.1, 102.7 and 102.6 (d, 158-161 Hz, C-$1^{1,2,4}$), 100.6 (d, 169 Hz, C-1^3). **9**: $[\alpha]_D$ +23.7° (*c* 0.7); R_F 0.45 in 6:1 PhMe-EtOAc; δ_H 5.049 (d, 3.5 Hz, 1^3), 4.794, 4.447, and 4.189 (3d, 7.5-8.0 Hz, $1^{1,2,4}$), 3.754 (s, OMe). **10**: $[\alpha]_D$ +18.6° (c 1.4); R_F 0.19 in 200:1 CH_2Cl_2-THF; δ_C 103.1, 102.9, 102.6, and 102.4 (4d, 159-164 Hz). **11**: $[\alpha]_D$ +30.4° (*c* 0.9); R_F 0.31 in 2:1 hexane-EtOAc; δ_H 5.455 (d, 3.7 Hz, 4^6), 5.026 and 4.999 (2d, 3.7 and 3.4 Hz, $1^{3,5}$), 4.788, 4.460, 4.420 and 4.146 (4d, 7.7-7.9 Hz, $1^{1,2,4,6}$), 3.754 (s, OMe), 1.953 (s, Lev); δ_C 103.4, 103.2, 102.7, and 102.7 (d, ~160 Hz, C-$1^{1,2,4,6}$), 100.7 and 100.4 (d, 169 Hz, C-$1^{3,5}$). **12**: (α:β = 1:2); R_F 0.45 in 6:1 PhMe-EtOAc; δ_H 5.466 (d, 3.4 Hz, 4^6), 5.167 (dd, 53.7 and 6.4 Hz, $1^1\beta$), 5.020 and 5.005 (2d, 3.4 Hz, $1^{3,5}$), 4.334 and 4.150 (2d, 7.6 Hz), 2.009 (s, Levα), 1.998 (s, Levβ). **13**: (α:β = 1:2); $[\alpha]_D$ +44.4° (*c* 0.7); R_F 0.39 in 2:1 hexane-EtOAc; δ_H 5.428 (dd, 53.1 and 2.4 Hz, $1^1\alpha$), 5.187 (dd, 53.7 and 6.4 Hz, $1^1\beta$). **14**: $[\alpha]_D$ +28.3° (*c* 2.7); R_F 0.32 in 2:1 hexane-EtOAc; δ_C 103.2, 103.0, 102.7 and 102.5 x 2 (4 d, 160~164 Hz, C-$1^{1,2,4,5,6}$), 100.7 (d, 170 Hz, C-1^3). **15**: (α:β = 2:5); R_F 0.45 in 6:1 PhMe-EtOAc; δ_H 5.580 (d, 2.3 Hz, 4^6), 5.426 (dd, 51.5 and 3.2 Hz, $1^1\alpha$), 5.178 (dd, 52.6 and 5.9 Hz, $1^1\beta$). **16**: (α:β = 2:5); R_F 0.42 in 2:1 hexane-EtOAc; δ_H 5.419 (dd, 53.6 and 3.1 Hz, $1^1\alpha$), 5.180 (dd, 54.0 and 6.1 Hz, $1^1\beta$). **17**: $[\alpha]_D$ +43.8° (*c* 0.3); R_F 0.57 in 2:1 hexane-EtOAc; δ_H 5.024 (3H, d, 2.7 Hz, $1^{1,3,5}$), 3.945 (3H, d, 6.4 Hz, $1^{2,4,6}$); δ_C 103.3 (d, 162 Hz, C-$1^{2,4,6}$) and 101.2 (d, 169 Hz, C-$1^{1,3,5}$); FAB-MS $(M+H)^+$ 2594. **18**: $[\alpha]_D$ +30.1° (*c* 0.3); R_F 0.25 in 2:1 hexane-EtOAc; δ_H 5.414 (s, 1^1), 4.999 (d, 3.7 Hz, 1^3).

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12 The yield of this cycloglycosylation was not optimized.

(Received in Japan 24 November 1992)