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CARBOHYDRATE RESEARCH

Synthesis and X-ray crystallographic study of cyclobis-(1 → 2)-α-D-glucopyranosyl peracetate [1]

Vince Pozsgay [a,*], Eric P. Dubois [a], Hermann Lotter [b], András Neszmélyi [c]

[a] *Laboratory of Developmental and Molecular Immunity, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD 20892-2720, USA*

[b] *Institut für Pharmazeutische Biologie, Ludwig-Maximilians-Universität, 29 Karlstrasse, München, D-80333, Germany*

[c] *Central Research Institute for Chemistry of the Hungarian Academy of Sciences, Pusztaszeri ut 59, Budapest, H-1025, Hungary*

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Abstract

Treatment of *O*-(3,4,6-tri-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranosyl)-(1 → 2)-3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate with $BF_3 \cdot Et_2O$ gave a high yield of the peracetate of cyclobis-(1 → 2)-α-D-glucopyranosyl (**6**). Compound **6** crystallizes in the space group $P2_1$ [$a = 6.888(2)$, $b = 24.771(5)$, $c = 9.105(2)$ Å, $\beta = 111.49(2)°$, $Z = 2$] and shows a high degree of symmetry. In **6** the two α-D-glucopyranosyl residues are in a slightly distorted chair conformation. The glucose moieties are interconnected by a 1,4-dioxane moiety which is in a boat conformation, with the anomeric carbon atoms in the bow positions.

Keywords: Cyclic disaccharide; Cyclobisglucosyl; Internal glycosylation; Kojibiose; X-ray analysis

1. Introduction

Cyclic oligosaccharides [2,3] continue to enjoy enormous popularity due to their ability to entrap organic compounds within their cavity, thereby altering such properties as water solubility and stability of the captured molecules [4]. Members of this group of compounds can also act as enzyme mimics [5] and may exhibit catalytic activity [6]. The first synthetic cyclic disaccharide appears to be di-β-ribofuranose 1,5′:1′,5-dianhydride, obtained serendipitously by Bredereck et al. [7] and structurally defined by Jeanloz et al. [8]. The related bis(6-deoxy-β-allofuranose) dianhydride was described by Szarek's group [9]. Cyclic oligomers of other furanoses were also reported, including a xylofuranose dianhydride by Sinaÿ's group [10] and cyclobis-(1 → 2)-α-D-glucofuranosyl by Bock and Pedersen [11]. Kochetkov and co-workers reported the synthesis of cyclobis-(1 → 3)- and (1 → 6)-β-D-galactofuranosyl [12], and the β-(1 → 3)-linked cyclic dimer of D-allofuranoside was described by Köll's group [13]. Dihexulose dianhydride-type cyclic disaccharides have been obtained from 2-hexuloses by HF treat-

* Corresponding author. Tel.: +1(301)402-0036; fax: +1(301)402-9108; e-mail: vipo@helix.nih.gov

[1] For a preliminary disclosure, see ref. [1].

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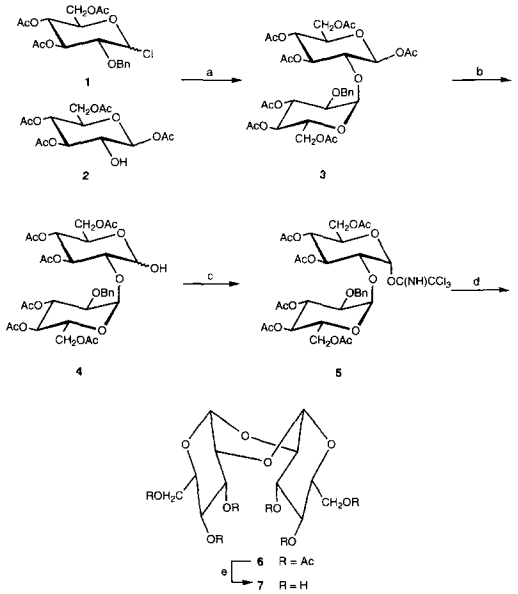
ment [14], and a mixed dianhydride of D-glucose and D-fructose was reported [15]. Glycosylated cyclofructobioses were also synthesized by Defaye and Garcia Fernandez [16]. The formation of the cyclic disaccharide cyclo-[→ 2)-α-D-Gal*p*A-(1 → 2)-β-L-Rha*p*-(1 →] was observed during HF treatment of pectins containing this sequence [17,18]. Cyclobis-(1 → 6)-β-D-glucosyl was prepared by Gagnaire and co-workers by intramolecular glycosylation of gentio-biose and -triose derivatives [19,20]. Recently, Ludewig and Thiem reported the formation of cyclobis-(1 → 2)-α-L-fucosyl in an attempted polymerization reaction [21] and the synthesis of a cyclic dimer of 1-deoxy-D-*threo*-hexulofuranose was also described [22].

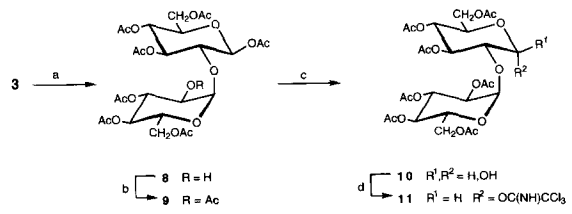
2. Results and discussion

As a new addition to the family of cyclodisaccharides, here we describe a serendipitous synthesis of "cyclokojibiose" (**7**) in which two D-glucose residues are interconnected by α-(1 → 2)-interglycosidic linkages. Additionally, we describe the X-ray crystallographic studies of the per-*O*-acetyl derivative (**6**) of "cyclokojibiose".

In a previous work we reported a stepwise approach to kojidextrins, which are biologically important linear oligosaccharides containing α-(1 → 2)-linked D-glucose residues up to the pentasaccharide length [23]. The synthesis of higher saccharides in this series is a major challenge not only because of the requirement for highly diastereoselective glycosylations necessary to produce the α-interglycosidic linkages but also because of the rapidly decreasing nucleophilicity of the hydroxyl group at the chain link. As an alternative to the stepwise approach, we investigated a blockwise protocol for the synthesis of extended oligosaccharides containing α-(1 → 2)-linked D-glucose residues. Compound **5** was selected as the disaccharide donor which was anticipated to function as an acceptor for the subsequent chain-extension step after removing the *O*-benzyl protecting group. The disaccharide **5** was synthesized as follows (see Scheme 1). Chloride **1** [23] was condensed with the known alcohol **2** [24] under promotion by $AgClO_4$–Ag_2CO_3 to afford the α-linked kojibiose derivative **3** in 70% yield. Selective deblocking (NH_2NH_2–AcOH [25]) of **3** afforded the hemiacetal **4** (94%) which was converted to the α-imidate **5** (87%) under standard conditions [26,27]. Most surprisingly, treatment of the trichloroacetimidate **5** with $BF_3 \cdot Et_2O$ at 0 °C in CH_2Cl_2 under rigorously anhydrous conditions completely transformed compound **5** into a single major product (**6**) that was isolated in 76% yield. In a control experiment the fully acetylated analogue **11**, obtained from **3** by successive hydrogenolysis, acetylation, and conversion to imidate through the hemiacetal underwent no change under identical conditions (see Scheme 2). The structure of **6** was determined as follows. The ammonia chemical-ionization mass spectrum contained the molecular peak at *m/z* 594 ($[M + NH_4]^+$), indicating that the losses from the parent compound **5** (MW for the lowest monoisotopic species 827) exceed that which would correspond to the loss of $CCl_3C(NH)OH$ only by 90 mu. This indicates the loss of a benzyl



Scheme 1. Reagents and conditions: (a) 1.3 equiv **1** $AgClO_4$–Ag_2CO_3, CH_2Cl_2, 0 → 23 °C, 70%; (b) 1.3 equiv NH_2NH_2–AcOH, DMF, 23 °C, 3 h, 94%; (c) Cl_3CCN (excess), 0.6 equiv 1,8-diazabicyclo[5.4.0]undec-7-ene, 0 °C, 1 h, 87%; (d) 5 equiv $BF_3 \cdot Et_2O$, 23 °C, 4 h, 79%; (e) NaOMe (cat), MeOH, 23 °C, 12 h, 80%.



Scheme 2. Reagents and conditions: (a) H_2/Pd–C, EtOH–EtOAc–AcOH, 22 °C, 300 psi, 24 h, 86%; (b) Ac_2O–C_5H_5N, 22 °C, 30 min, 86%; (c) 1.3 equiv NH_2NH_2–AcOH, DMF, 23 °C, 90 min, 66%; (d) Cl_3CCN (excess), 0.6 equiv 1,8-diaza-bicyclo[5.4.0]undec-7-ene, 0 °C, 90 min, 80%.

Table 1
^{1}H chemical shifts (δ) of compounds **6**, **7**, and **12** [a]

Proton	Compound		
	6 [b]	**7** [c]	**12** [b,d]
H-1	5.21	5.33	4.76
H-2	3.99	3.93	3.56
H-3	5.60	4.04	5.43
H-4	4.96	3.52	4.96
H-5	4.27	3.88	3.95
H-6	4.13	3.83	4.26
H-6′	4.39	3.80	4.00

[a] At 500 MHz for **6** and **7**, and at 300 MHz for **12**, at 20 ± 2 °C.
[b] In $CDCl_3$.
[c] In D_2O.
[d] Ref. [28].

Table 2
Three-bond homonuclear H–H coupling constants (Hz) in compounds **6**, **7**, and **12**

Coupling constant	Compound		
	6 [a]	**7** [b]	**12** [a,c]
$J_{1,2}$	3.1	3.3	3.5
$J_{2,3}$	6.8	7.2	10.0
$J_{3,4}$	8.8	8.6	9.6
$J_{4,5}$	7.8	9.5	9.8
$J_{5,6}$	4.8	5.1	4.5
$J_{5,6'}$	2.8	2.7	2.2
$J_{6,6'}$	12.3	12.4	12.2

[a] In $CDCl_3$.
[b] In D_2O.
[c] Ref. [28].

Table 3
^{13}C chemical shifts [a] (δ) of compounds **6**, **7**, and **12**

Carbon	Compound		
	6 [b]	**7** [c]	**12** [b,d]
C-1	90.4	91.2	96.8
C-2	72.8	76.2	76.8
C-3	72.0	74.4	71.9
C-4	67.1	68.8	68.8
C-5	70.8	75.6	67.1
C-6	61.3	61.0	62.1

[a] At 75 MHz, at 20 ± 2 °C.
[b] In $CDCl_3$.
[c] In D_2O.
[d] Ref. [28].

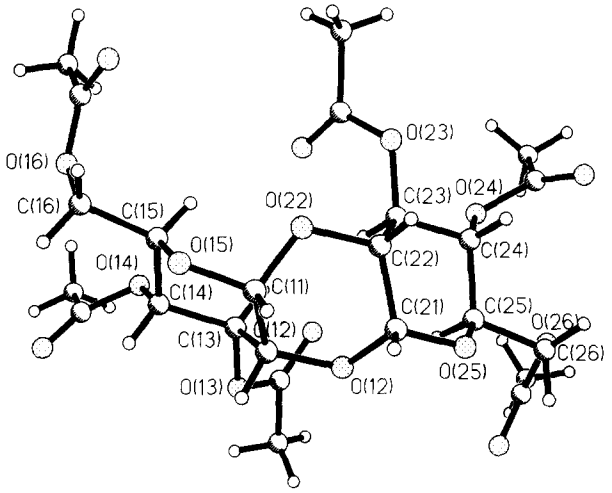


Fig. 1. The perspective view of compound **6**.

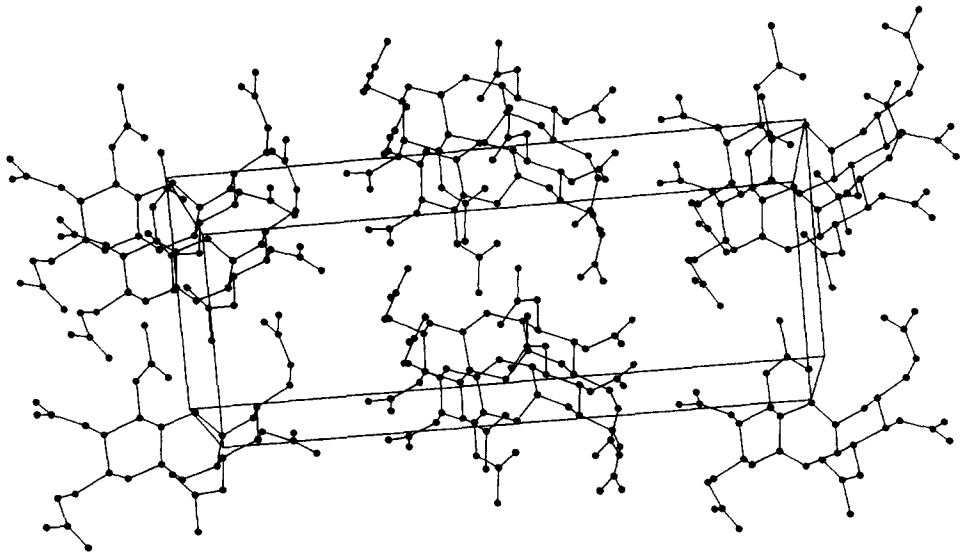


Fig. 2. Unit cell and crystal packing for **6** (hydrogens omitted).

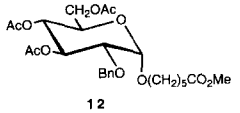
Table 4
Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement coefficients ($Å^2 \times 10^3$) for the non-hydrogen sugar atoms in **6** with standard deviations in parentheses

Atom	x	y	z	U(eq)
C-11	−11454(11)	−5413	−9002(8)	37(3)
C-12	−9746(10)	−5362(4)	−7370(7)	34(3)
C-13	−7587(10)	−5573(4)	−7342(8)	34(3)
C-14	−7861(11)	−6132(4)	−8034(8)	39(2)
C-15	−9418(11)	−6086(4)	−9731(9)	38(3)
C-16	−9891(14)	−6618(4)	−10659(10)	53(3)
C-21	−10844(12)	−4426(4)	−7844(8)	39(3)
C-22	−10805(11)	−4480(4)	−9496(8)	34(3)
C-23	−8673(11)	−4281(4)	−9552(7)	33(3)
C-24	−8200(11)	−3729(4)	−8856(8)	37(3)
C-25	−8048(12)	−3756(4)	−7164(8)	38(3)
C-26	−7596(13)	−3217(4)	−6289(10)	56(4)
O-12	−9412(8)	−4811(3)	−6828(5)	39(2)
O-13	−6144(7)	−5590(3)	−5712(5)	41(2)
O-14	−5768(8)	−6296(3)	−7978(6)	41(2)
O-15	−11447(7)	−5923(3)	−9665(6)	41(2)
O-16	−8113(9)	−6732(4)	−11154(7)	54(2)
O-22	−11078(7)	−5031(3)	−10048(5)	37(2)
O-23	−8878(8)	−4269(3)	−11176(5)	38(2)
O-24	−6133(7)	−3579(3)	−8924(5)	39(2)
O-25	−10121(8)	−3917(3)	−7190(6)	41(2)
O-26	−5328(9)	−3091(4)	−5795(7)	54(2)

group from the molecule. Indeed, the 500-MHz ^{1}H NMR spectrum confirmed the absence of an aromatic group and was consistent with either a monosaccharide having only three *O*-acetyl groups and no other functionalities or with a highly symmetrical saccharidic structure. The position of the H-3 and H-4 signals indicate the presence of acetoxy groups at the corresponding carbon atoms. Examination of the spectral data indicates deviations from the spectral parameters expected of a monosaccharide. A remarkable feature of the ^{1}H NMR spectrum is the unusually low-field position (δ 5.21) of the H-1 signal. While the ^{1}H NMR chemical shifts of the remaining protons in **6** do not deviate significantly from those in reference compound **12** [28], the three-bond H–H coupling constants within the ring are generally smaller in **6**, which appears to indicate a flattened chair conformation for the pyranose rings (see Tables 1 and 2). The unusual environment for the anomeric region is further highlighted by the surprisingly high-field position of the C-1 and C-2 carbon atoms (90.4 and 72.8 ppm, respectively, cf. also Table 3 and the data for **9** in the Experimental Section). Removal of the *O*-acetyl groups (→ **7**) shifted the H-3–6 resonances upfield as expected and led to a general increase of the three-bond H–H coupling constants, which may indicate a somewhat less distorted chair shape for the pyranose rings in **7** relative to **6**.

Table 5
Bond lengths (Å) for **6**, with standard deviations in parentheses

C-11–C-12	1.511(8)	C-11–O-22	1.431(9)
C-12–C-13	1.526(11)	C-11–O-15	1.397(9)
C-13–C-14	1.505(14)	C-12–O-12	1.446(13)
C-14–C-15	1.518(9)	C-13–O-13	1.444(7)
C-15–C-16	1.535(14)	C-14–O-14	1.440(10)
C-21–C-22	1.520(11)	C-15–O-15	1.439(10)
C-22–C-23	1.527(11)	C-16–O-16	1.445(12)
C-23–C-24	1.490(14)	C-21–O-12	1.424(10)
C-24–C-25	1.508(11)	C-21–O-25	1.406(12)
C-25–C-26	1.527(14)	C-22–O-22	1.439(12)
		C-23–O-23	1.435(8)
		C-24–O-24	1.456(10)
		C-25–O-25	1.433(10)
		C-26–O-26	1.450(11)



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The perspective view of **6** determined by X-ray crystallography is shown in Fig. 1, and the unit cell and crystal packing are shown in Fig. 2. Selected

Table 6
Bond angles (degree) for **6**, with standard deviations in parentheses

C-11–C-12–C-13	111.0(6)	C-21–C-22–C-23	111.0(6)
C-12–C-13–C-14	109.7(6)	C-22–C-23–C-24	109.7(7)
C-13–C-14–C-15	106.9(7)	C-23–C-24–C-25	108.6(8)
C-14–C-15–O-15	106.5(7)	C-24–C-25–O-25	107.0(5)
C-15–O-15–C-11	115.2(6)	C-25–O-25–C-21	115.8(7)
O-15–C-11–C-12	112.3(5)	O-25–C-21–C-22	111.8(7)
C-16–C-15–C-14	114.9(8)	C-26–C-25–C-24	114.9(8)
C-16–C-15–O-15	105.0(6)	C-26–C-25–O-25	104.7(7)
O-15–C-11–O-22	106.4(6)	O-25–C-21–O-12	106.2(5)
C-11–O-22–C-22	115.3(5)	C-21–O-12–C-12	115.2(5)
C-11–C-12–O-12	112.4(6)	C-21–C-22–O-22	112.4(7)
C-12–C-11–O-22	110.1(5)	C-22–C-21–O-12	109.5(7)
C-13–C-12–O-12	106.9(6)	C-23–C-22–O-22	107.2(7)

atomic coordinates for non-hydrogen atoms, bond lengths, bond distances, and dihedral angles are listed in Tables 4–7. The 1,4-dioxane ring interconnecting the two glucose residues is in a slightly distorted boat conformation, in which both bow positions are occupied by anomeric carbon atoms. In this regard, **6** differs from a previously reported 1,2′;1′2-dianhydride structure in which two fructose residues are interconnected by a 1,4-dioxane ring in the boat conformation that has the oxygen atoms at the bow positions [29]. Similar observations were made for a dimer of 1-deoxy-β-D-*threo*-hexulofuranose [22], while Kanters et al. reported that the 1,4-dioxane moiety interconnecting two fructose moieties in a pyranose and a furanose form is in a chair conformation [30]. The C–C–O bond angles in the dioxane ring in **6** are in the 110–112° range, i.e. they are close to the C–C–C angle in cyclohexane, which is 111.5°. The C–O–C angles in the dioxane ring and in the glucose rings are near 115°, which is in agree-

Table 7
Selected dihedral angles (degree) for compound **6**

O-12–C-12–C-11–O-15	166.8	O-24–C-24–C-23–O-23	−63.0
O-12–C-12–C-11–O-22	48.5	O-24–C-24–C-23–C-22	178.7
C-13–C-12–C-11–O-15	47.1	C-25–C-24–C-23–O-23	178.7
C-13–C-12–C-11–O-22	−71.2	C-25–C-24–C-23–C-22	60.4
C-21–O-12–C-12–C-11	5.0	O-25–C-25–C-24–C-23	−63.3
C-21–O-12–C-12–C-13	127.0	O-25–C-25–C-24–O-24	−178.8
O-13–C-13–C-12–C-11	−171.1	C-26–C-25–C-24–C-23	−179.2
O-13–C-13–C-12–O-12	66.0	C-26–C-25–C-24–O-24	65.3
C-14–C-13–C-12–C-11	−52.0	C-24–C-25–O-25–C-21	61.8
C-14–C-13–C-12–O-12	−174.9	C-26–C-25–O-25–C-21	−175.7
C-12–C-13–C-14–O-14	179.4	O-26–C-26–C-25–C-24	−79.1
C-12–C-13–C-14–C-15	61.3	O-26–C-26–C-25–O-25	163.7
O-13–C-13–C-14–O-14	−62.9	C-12–O-12–C-21–O-25	−174.2
O-13–C-13–C-14–C-15	179.1	C-12–O-12–C-21–C-22	−53.4
C-13–C-14–C-15–C-16	179.2	C-25–O-25–C-21–O-12	65.1
C-13–C-14–C-15–O-15	−65.1	C-25–O-25–C-21–C-22	−54.2
O-14–C-14–C-15–C-16	64.1	C-23–C-22–O-22–C-11	125.7
O-14–C-14–C-15–O-15	179.8	C-21–C-22–O-22–C-11	3.4
C-14–C-15–C-16–O-16	−78.9	O-23–C-23–C-22–O-22	65.2
O-15–C-15–C-16–O-16	164.4	O-23–C-23–C-22–C-21	−171.6
C-12–C-11–O-15–C-15	−55.0	C-24–C-23–C-22–O-22	−174.8
O-22–C-11–O-15–C-15	65.6	C-24–C-23–C-22–C-21	−51.7
C-14–C-15–O-15–C-11	63.9	O-22–C-22–C-21–O-12	49.6
C-16–C-15–O-15–C-11	−173.9	O-22–C-22–C-21–O-25	167.1
C-22–O-22–C-11–C-12	−52.1	C-23–C-22–C-21–O-12	−70.4
C-22–O-22–C-11–O-15	−174.0	C-23–C-22–C-21–O-25	47.0

ment with the C–O–C angle in phenyl α-D-glucopyranoside (**13**) [31]. The C-21–O-12–C-12–C-11 and the C-21–C-22–O-22–C-11 dihedral angles in the 1,4-dioxane ring are 5° and 3.4°, respectively [2]. The interatomic distances within the glucose residues in **6** are in reasonable agreement with those found for **13**. As expected, the endocyclic C-11–O-15 distance in **6** is shorter than the C-15–O-15 distance [32]. The shortest endocyclic C–C bond in both glucose residues is seen between the C-3 and C-4 atoms. The endocyclic bond angles in **6** differ from the angles in **13** for several pairs of linkages. For example, the average C-3–C-4–C-5 angle in **6** is 107.9°, 4° less than the corresponding angle in **13**. Even larger deviations were seen for the O-15–C-11–O-22 and the C-13–C-12–O-12 angles relative to the corresponding angles in **13**. Similar differences were also found in the endocyclic dihedral angles between **6** and **13**. These differences, together with the NMR parameters, indicate a distorted $^4C_1$ conformation for the pyranose rings. In compound **6** the O-15–C-15 bond is *gauche* to the C-11–O-22 bond and the *exo*-anomeric effect is integrated for the dioxane ring. The anomeric effect is integrated for the pyranose residues, but not the *exo*-anomeric effect: the H-11–C-11–O-22–C-22 torsional angle is 67°, whereas the *exo*-anomeric effect would require this angle to be ca. −60°. In methyl α-D-glucopyranoside, the corresponding angle is indeed −54.4° [33]. In the crystal structures reported [29,30] so far for disaccharide 1,2′;1′2-dianhydrides, the dioxane rings interconnecting the two monosaccharide residues harbor a CH_2 group, and, as molecular models indicate, this part of the molecule appears to be flexible. In these structures the 1,4-dioxane moiety is *spiro*-linked to the rest of the molecule. On the other hand, the anellated structures **6** and **7** appear to be rather rigid. As already discussed by Bock et al. [14], it is likely that the stability of cyclodisaccharides arises from a combination of steric and electronic factors. In compound **6** the anomeric and the *exo*-anomeric effects appear to overcome the unfavorable steric effects imposed by the boat conformation of the central 1,4-dioxane ring. However, the relative contributions of these effects to the stability remain unknown.

The intramolecular cycloglycosylation described here proceeded through a benzyl-protected secondary hydroxyl group. It is important to note that the cycloglycosylations reported earlier either proceeded through intermediates having an unprotected hydroxyl group at the site of the ring closure, or that this site was protected by a highly labile, triphenylmethyl group. To the best of our knowledge ours is the first case of an activated anomeric carbon atom-mediated debenzylation. It is proposed that activation of **5** leads to a reactive intermediate in which the anomeric carbon atom C-11 is in a sterically favorable position to form a covalent bond with the O-22 atom with simultaneous expulsion of the *O*-benzyl group. This group appears critical for the nucleophilicity of the O-22 atom since cycloglycosylation could not be observed for the fully acetylated congener **11**.

3. Experimental

General methods.—All chemicals were commercial grade and were used without purification. Solvents for chromatography were distilled prior to use. Anhydrous solvents were obtained from Aldrich. All glycosylation reactions were carried out under argon in oven-dried glassware. Column chromatography was performed on Silica Gel 60 (0.040–0.063 mm). Melting points were taken on a Meltemp capillary melting point apparatus and are uncorrected. Optical rotations were measured at 23 °C with a Perkin–Elmer Type 341 polarimeter. The ^1H spectra were recorded with a Bruker DMX-500 or a Varian XL-300 spectrometer operating at 500 and 300 MHz. The ^{13}C NMR spectra were recorded on a Varian XL-300 spectrometer at 75.5 MHz. Internal references: Me_4Si (0.000 ppm for ^1H for solutions in $CDCl_3$), acetone (2.225 ppm for ^1H and 31.00 ppm for ^{13}C for solutions in D_2O), MeOH (3.350 ppm for ^1H and 49.63 ppm for ^{13}C for solutions in D_2O), and $CDCl_3$ (77.00 ppm for ^{13}C for solutions in $CDCl_3$). The assignments for the ^{13}C NMR spectra are supported by two-dimensional, heteronuclear correlated spectra. Ammonia was used as the ionizing gas for the chemical-ionization mass spectra (CIMS). Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. Characters A and B refer to individual sugar residues with A standing for the reducing-end unit. A colorless crystal of **6** crystallized from MeOH having a size about $0.4 \times 0.25 \times 0.25$ mm was used for X-ray structural analysis. A total of 1927 independent reflections were measured on a Siemens R3m diffractometer (Ω-scan, scan speed 6–29.5°/min, 2Θ range up to 114°, Ni-filtered Cu K_α radiation). 1845 Reflections were

[2] For the atomic notation, see Fig. 1.

treated as observed with $F > 4\sigma(F)$. An empirical absorption correction was applied to the measurements ($\mu = 1.004$ mm^{-1}). Crystal data: $C_{24}H_{32}O_{16}$, M = 576.5, monoclinic space group $P2_1$, a = 6.888(2), b = 24.771(5), c = 9.105(2) Å, β = 111.49(2)°, $Z = 2$, $D_x = 1.364$ Mg/m^3. The structure was solved by direct methods using SHELXTL [34] and refined initially with isotropic and subsequently anisotropic temperature factors. Hydrogen atoms were calculated from the positions of the heavier atoms to which they are bound. The refinement converged at wR = 5.6% (w = unit weight) for the observed and R = 5.5% for all data [3].

3,4,6-Tri-O-acetyl-2-O-benzyl-α-D-glucopyranosyl-(1 → 2)-1,3,4,6-tetra-O-acetyl-β-D-glucopyranose (**3**).—A mixture of 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-α,β-D-glucopyranosyl chloride (**1**, 5.30 g, 15.2 mmol), 1,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (**2**, 4.90 g, 11.8 mmol), Ag_2CO_3 (4.5 g), and 4 Å powdered molecular sieves (9 g) in dry CH_2Cl_2 (50 mL) was stirred at 23 °C for 1 h, with the exclusion of light, then cooled to 0 °C. $AgClO_4$ (540 mg) was added and the mixture was stirred for 24 h at 23 °C. The mixture was filtered through Celite, and the insoluble material was washed several times with $CHCl_3$. The combined filtrate and washings were washed successively with satd aq $NaHCO_3$ and H_2O, dried (Na_2SO_4), and then concd. The residue was treated with pyridine (7 mL) and Ac_2O (7 mL) at 23 °C. After 12 h the volatiles were removed under reduced pressure. Column chromatography (3:2 hexanes–EtOAc) of the residue afforded **3** (6.0 g, 70%) as a colorless syrup: $[\alpha]_D$ +74° (*c* 0.83); NMR ($CDCl_3$): ^{1}H, δ 7.50–7.25 (m, 5 H, aromatic), 5.79 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1A), 5.30 (2 t, 2 H, H-3A,3B), 5.09 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1B), 5.03 and 4.99 (2 dd, 2 H, J ~9.6–10 Hz, H-4A,4B), 4.59 and 4.53 (2 d, 2 H, J ~12.0 Hz, CH_2 of Bn), 4.35–3.84 (6 H, H-5A,5B,6A,6′A,6B,6′B), 3.81 (dd, 1 H, H-2A), 3.53 (dd, 1 H, $J_{2,3}$ 9.8 Hz, H-2B), 2.09 (6 H), 2.04, 2.03, 2.00, 1.98, and 1.96 (6 s, 21 H, CH_3CO); ^{13}C, δ 170.6–168.8 (*C*=O), 137.4 and 128.6–127.7 (aromatic), 97.8 (C-1B), 92.7 (C-1A), 77.1 (2 C), 74.0, 72.5, 71.3, 68.5, 68.1, and 68.0 (C-2A,2B,3A,3B,4A,4B,5A,5B), 73.2 (*C*H$_2$ of Bn), 61.5 and 61.3 (C-6A,6B), 20.7–20.6 (*C*H$_3$CO); CIMS: *m/z* 744 ([M + NH$_4$]$^+$). Anal. Calcd for $C_{33}H_{42}O_{18}$: C, 54.54; H, 5.83. Found: C, 54.28; H, 5.89.

O-*(3,4,6-Tri-O-acetyl-2-O-benzyl-α-D-glucopyranosyl)-(1 → 2)-3,4,6-tri-O-acetyl-α,β-D-glucopyranose* (**4**).—A mixture of **3** (6.5 g, 8.9 mmol) and hydrazine acetate (1.1 g, 11.9 mmol) in DMF (25 mL) was stirred for 3 h at 23 °C. The soln was dild with EtOAc, washed with H_2O, dried (Na_2SO_4), then concd. Column chromatography (1:1 hexanes–EtOAc) of the residue gave **4** (5.8 g, 94%) as a colorless syrup: NMR ($CDCl_3$): ^{13}C, δ 170.7–169.6 (*C*=O), 136.8, 136.4, and 128.8–128.2 (aromatic), 99.5 [C-1B(β)], 97.2 [C-1B(α)], 96.2 [C-1A(β)], 90.3 [C-1A(α)], 62.0, 61.9, 61.5, and 61.2 (C-6A,6B), 20.8–20.6 (*C*H$_3$CO); CIMS: *m/z* 702 ([M + NH$_4$]$^+$). Anal. Calcd for $C_{31}H_{40}O_{17}$: C, 54.38; H, 5.89. Found: C, 54.09; H, 5.83.

3,4,6-Tri-O-acetyl-2-O-(3,4,6-tri-O-acetyl-2-O-benzyl-α-D-glucopyranosyl)-α-D-glucopyranosyl trichloroacetimidate (**5**).—A soln of **2** (500 mg, 731 μmol) in CH_2Cl_2 (10 mL) was treated at 0 °C with trichloroacetonitrile (2.2 mL, 22.0 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (65 μL, 439 μmol), then stirred at 0 °C for 1 h. Removal of the volatiles, followed by column-chromatographic purification (2:1 hexanes–EtOAc) of the residue, gave **5** (525 mg, 87%) as a colorless syrup: $[\alpha]_D$ +110° (*c* 1.30); NMR ($CDCl_3$): ^{1}H, δ 8.70 (s, 1 H, *H*N=C), 7.42–7.22 (m, 5 H, Ph), 6.57 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1A), 5.52 (dd, 1 H, $J_{3,4}$ 9.6 Hz, H-3A), 5.33 (dd, 1 H, $J_{3,4}$ 9.6 Hz, H-3B), 5.08 (dd, 1 H, $J_{4,5}$ 10.0 Hz, H-4A), 4.94 (dd, 1 H, $J_{4,5}$ 10.0 Hz, H-4B), 4.92 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1B), 4.59 and 4.55 (2 d, 2 H, CH_2 of Bn), 4.32–3.99 (m, 6 H, H-5A,5B,6A,6′A,6B,6′B), 3.88 (dd, 1 H, $J_{2,3}$ 9.8 Hz, H-2A), 3.52 (dd, 1 H, $J_{2,3}$ 9.8 Hz, H-2B), 2.10, 2.07, 2.06, 2.05, 1.97, and 1.94 (6 s, 18 H, CH_3CO); ^{13}C, δ 170.5–169.7 (*C*=O), 160.6 (*C*=NH), 137.6 and 128.6–127.7 (aromatic), 98.4 (C-1B), 93.4 (C-1A), 76.7, 76.6, 71.8, 71.5, 69.8, 68.5, 68.2, and 67.8 (C-2A,3A,4A,5A,2B,3B,4B,5B), 73.4 (*C*H$_2$Ph), 61.5 (C-6A,6B), 20.8–20.6 (*C*H$_3$CO); CIMS: *m/z* 667 [(M − OC(NH)CCl$_3$)$^+$]. Anal. Calcd for $C_{33}H_{40}Cl_3NO_{17}$: C, 47.81; H, 4.86. Found: C, 47.91; H, 4.86.

Cyclobis-(1 → 2)-(3,4,6-tri-O-acetyl-α-D-glucopyranosyl) (**6**).—A mixture of the imidate **5** (250 mg, 302 μmol) and 4 Å powdered molecular sieves (250 mg) in dry CH_2Cl_2 (5 mL) was stirred at 23 °C for 1 h, then cooled to 0 °C. Boron trifluoride etherate (186 μL, 1.5 mmol) was added, and the mixture was stirred for 4 h at 23 °C. Triethylamine (1

[3] Tables of atomic coordinates as well as distances and angles have been deposited at the Cambridge Crystallographic Data Centre. These tables may be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

mL) was added, the mixture was filtered, and then the volatiles removed under reduced pressure. Column chromatography (1:1 hexanes–EtOAc) of the residue gave **6** (138 mg, 79%) as a white solid: mp 129–131 °C (MeOH); $[\alpha]_D$ +139° (*c* 0.87); CIMS: *m/z* 594 ($[M + NH_4]^+$). Anal. Calcd for $C_{24}H_{32}O_{16}$: C, 50.00; H, 5.59. Found: C, 50.10; H, 5.63.

*Cyclobis-(1 → 2)-α-*D*-glucopyranosyl* (**7**).—A soln of **6** (200 mg, 347 μmol) in dry MeOH (5 mL) was treated with a catalytic amount of NaOMe for 12 h at 23 °C. The mixture was neutralized (Dowex 50-X8-100, H^+), filtered, and concd. Column-chromatographic purification (3:1 EtOAc–MeOH) of the residue gave **5** (89 mg, 80%) as a white solid: mp 188–190 °C (MeOH); $[\alpha]_D$ +100° (*c* 0.74); CIMS: *m/z* 342 ($[M + NH_4]^+$). Anal. Calcd for $C_{12}H_{20}O_{10}$: C, 44.45; H, 6.22. Found: C, 44.34; H, 6.30.

*3,4,6-Tri-*O*-acetyl-α-*D*-glucopyranosyl-(1 → 2)-1,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranose* (**8**).—A mixture of **3** (6.0 g, 8.26 mmol), 10% palladium-on-charcoal (~ 500 mg), EtOH (45 mL), EtOAc (45 mL), and AcOH (1 mL) was stirred under hydrogen at 22 °C at 300 psi for 24 h. The usual work-up afforded a solid which was recrystallized from EtOH to afford **8** (4.54 g, 86%) as a crystalline material: mp 164–165 °C; $[\alpha]_D$ +108° (*c* 0.75); NMR ($CDCl_3$): ^{1}H, δ 5.71 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1A), 5.30, 5.08, 5.05, and 5.03 (4 t, 4 H, H-3A,4A,3B,4B), 5.15 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1B), 4.32, 4.24, 4.10, and 4.05 (4 d, 4 H, H-6A,6′A,6B,6′B), 3.94–3.84 (m, 3 H, H-2A,5A,5B), 3.64 (ddd, 1 H, H-2B), 2.17, 2.10, 2.08, 2.06, 2.04, and 2.03 (6 s, 21 H, C*H*$_3$CO); ^{13}C, δ 99.8 (C-1B), 92.9 (C-1A), 77.0, 73.4, 72.7, 72.6, 71.1, 68.8, 68.0, and 67.1 (H-2A,3A,4A,5A,2B,3B,4B,5B), 61.3 (C-6A,6B), 20.7–20.6 (*C*H$_3$CO); CIMS: *m/z* 654 ($[M + NH_4]^+$). Anal. Calcd for $C_{26}H_{36}O_{18}$: C, 49.06; H, 5.70. Found: C, 49.18; H, 5.63.

*2,3,4,6-Tetra-*O*-acetyl-α-*D*-glucopyranosyl-(1 → 2)-1,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranose* (**9**).—A soln of **8** in anhyd pyridine was treated with Ac_2O for 30 min at 22 °C. Removal of the volatiles afforded **9** as a syrup; $[\alpha]_D$ +87° (*c* 0.6); NMR ($CDCl_3$): ^{1}H, δ 5.69 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1A), 5.48 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1B), 5.32 (dd, 1 H, $J_{2,3}$ 10.3, $J_{3,4}$ 9.4 Hz, H-3B), 5.30 (t, 1 H, $J_{2,3} = J_{3,4} = 9.5$ Hz, H-3A), 5.05 (t, 1 H, $J_{4,5}$ 9.5 Hz, H-4B), 5.02 (t, 1 H, $J_{4,5}$ 9.5 Hz, H-4B), 4.75 (dd, 1 H, H-2B), 4.31 (dd, 1 H, $J_{5,6}$ 4.4, $J_{6,6'}$ 12.5 Hz, H-6A), 4.27 (dd, 1 H, $J_{5,6}$ 4.0, $J_{6,6'}$ 12.2 Hz, H-6B), 4.12 (dd, 1 H, $J_{5,6'}$ 2.2 Hz, H-6′B), 4.10 (dd, 1 H, $J_{5,6'}$ 2.2 Hz, H-6′A), 4.01 (ddd, 1 H, H-5B), 3.88 (dd, 1 H, H-2A), 3.85 (ddd, 1 H, H-5A), 2.17, 2.12, 2.08, 2.05, 2.04, 2.03, 2.02, and 2.01 (8 s, 24 H, C*H*$_3$CO); ^{13}C, δ 94.8 (C-1B), 93.1 (C-1A), 74.1 (C-2A), 73.2 (C-3A), 72.4 (C-5A), 70.8 (C-2B), 69.3 (C-3B), 68.1 (C-4A), 67.8 (C-4B,5B), 61.3 and 61.2 (C-6A,6B), 20.8–20.4 (*C*H$_3$CO); CIMS: *m/z* 696 ($[M + NH_4]^+$). Anal. Calcd for $C_{28}H_{38}O_{19}$: C, 49.56; H, 6.54. Found: C, 49.66; H, 6.48.

*2,3,4,6-Tetra-*O*-acetyl-α-*D*-glucopyranosyl-(1 → 2)-3,4,6-tri-*O*-acetyl-α,β-*D*-glucopyranose* (**10**).—A mixture of **9** (1.0 g, 1.47 mmol) and hydrazine acetate (177 mg, 1.92 mmol) in DMF (10 mL) was stirred for 90 min at 23 °C. The soln was dild with EtOAc, washed with H_2O, dried (Na_2SO_4), and concd. Column chromatography (3:2 EtOAc–hexanes) of the residue gave **10** (620 mg, 66%) as a colorless syrup: NMR ($CDCl_3$): ^{13}C, δ 99.5, 96.3, 95.5, and 90.2 [C-1A,1B(β)], 62.0, 61.9, and 61.3 (C-6A,6B), 20.6 (*C*H$_3$CO); CIMS: *m/z* 654 [$(M + NH_4)^+$]. Anal. Calcd for $C_{26}H_{36}O_{18}$: C, 49.06; H, 5.70. Found: C, 49.20; H, 5.81.

*2,3,4,6-Tetra-*O*-acetyl-α-*D*-glucopyranosyl-(1 → 2)-3,4,6-tri-*O*-acetyl-α-*D*-glucopyranosyl trichloroacetimidate* (**11**).—A soln of **10** (550 mg, 865 μmol) in CH_2Cl_2 (10 mL) was treated at 0 °C with trichloroacetonitrile (2.6 mL, 26.0 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (77 μL, 519 μmol), then stirred at 0 °C for 90 min. Removal of the volatiles followed by column-chromatographic purification (1:1 hexanes–EtOAc) of the residue gave **11** (581 mg, 80%) as a colorless syrup: $[\alpha]_D$ +126° (*c* 0.9); NMR ($CDCl_3$): ^{1}H, δ 8.77 (s, 1 H, *H*N=C), 6.54 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1A), 5.54 (dd, 1 H, $J_{3,4}$ 9.6 Hz, H-3A), 5.33 (dd, 1 H, $J_{3,4}$ 9.5 Hz, H-3B), 5.22 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1B), 5.10 (dd, 1 H, $J_{4,5}$ 9.90 Hz, H-4A), 5.05 (dd, 1 H, $J_{4,5}$ 10.0 Hz, H-4B), 4.870 (dd, 1 H, $J_{2,3}$ 10.2 Hz, H-2B), 4.33–4.03 (m, 6 H, H-5A,5B,6A,6′A,6B,6′B), 3.99 (dd, 1 H, $J_{2,3}$ 9.9 Hz, H-2A), 2.11, 2.09, 2.07, 2.05, 2.04, 2.00, and 1.97 (7 s, 21 H, C*H*$_3$CO); ^{13}C, δ 170.6–169.5 (*C*=O), 160.7 (*C*=NH), 96.5 (C-1B), 93.0 (C-1A), 75.8 (C-2A), 71.2, 70.4, 70.0, 69.7, 68.6, 68.0, and 67.8 (C-3A,4A,5A,2B,3B,4B,5B), 61.4 and 61.2 (C-6A,6B), 20.7 (*C*H$_3$CO); CIMS: *m/z* 619 ([M − OC(NH)CCl$_3$]$^+$), 636 ([M − OC(NH)CCl$_3$ + NH$_3$]$^+$). Anal. Calcd for $C_{33}H_{40}Cl_3NO_{17}$: C, 47.81; H, 4.86. Found: C, 47.91; H, 4.86.

4. Note added in proof

After the manuscript was accepted for publication, an excellent review appeared on dihexulose dianhydrides: M. Manley-Harris and G.N. Richards, *Adv.*

Carbohydr. Chem. Biochem., 52 (1997) 207–266. A cyclic disaccharide containing α-(1 → 2)-linked D- and L-fucopyranose residues was also reported: M. Ludewig, D. Lazarevic, and J. Thiem, *Abstracts, 9th European Carbohydrate Symposium, 1997, A55.*

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