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Synthesis of a cycloheptaose consisting of (1 → 4)-linked 7-amino-6,7-dideoxy-α-D-*gluco*-heptopyranosyl units: A new analog of cyclomaltoheptaose

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ABSTRACT

Approaches to chain extension at the C-6 positions in cyclomaltoheptaose (**1**) were examined with the aim of producing novel β-cyclodextrin analogs composed of heptose or hepturonic acid units. Iron carbonyl-mediated methoxycarbonylation, and nucleophilic displacement by cyanide, in the fully acetylated heptakis(6-deoxy-6-iodo) and heptakis(6-*O*-mesyl) derivates of **1**, respectively, were unsuccessful, as were similar reactions attempted with the newly synthesized, analogous allyl-protected derivatives of **1**. However, reaction of unprotected heptakis(6-deoxy-6-iodo)cyclomaltoheptaose with lithium cyanide in *N*,*N*-dimethylformamide afforded a high yield of the corresponding heptakis(6-cyano-6-deoxy) compound, namely, cyclohepta-(1 → 4)-(6-deoxy-α-D-*gluco*-heptopyranosid)urononitrile, catalytic hydrogenation of which gave the title compound, cyclo-(1 → 4)-(7-amino-6,7-dideoxy-α-D-*gluco*-heptopyrano)heptaose, isolated as its peracetyl derivative.

INTRODUCTION

In continuation of our work[1] on chemical modification of cyclomaltoheptaose (β-cyclodextrin, **1**), which had provided new, convenient procedures for the preparation of the heptakis-6-deoxy derivative **2**, we decided to prepare a number of other derivatives specifically and uniformly modified at the 6-positions. Targets of particular interest were chain-elongated analogs of **1** constituted of 6-deoxyheptopyranosyl units (such as **3** or **4**) and 6-deoxyheptopyranosyluronic acid units (for example, **5**). We recently synthesized novel trehalose-type disaccharides of this kind from α,α-trehalose by use of various chain-elongation procedures[2], and

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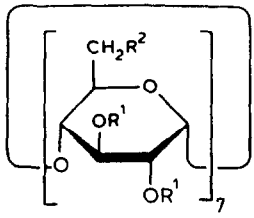

1 R^1 = H, R^2 = OH

2 R^1 = R^2 = H

3 R^1 = H, R^2 = CH_2OH

4 R^1 = H, R^2 = CH_2NH_2

5 R^1 = H, R^2 = CO_2H

6 R^1 = Ac, R^2 = I

7 R^1 = H, R^2 = $OSiMe_2t$-Bu

8 R^1 = Ac, R^2 = $OSiMe_2t$-Bu

9 R^1 = Ac, R^2 = OH

10 R^1 = Ac, R^2 = OTf

11 R^1 = Ac, R^2 = OMs

12 R^1 = Ac, R^2 = OTs

13 R^1 = Ac, R^2 = Cl

14 R^1 = Ac, R^2 = SCN

15 R^1 = all, R^2 = $OSiMe_2t$-Bu

16 R^1 = all, R^2 = OH

17 R^1 = all, R^2 = OMs

18 R^1 = all, R^2 = I

19 R^1 = H, R^2 = I

20 R^1 = H, R^2 = CN

21 R^1 = Ac, R^2 = CN

22 R^1 = Bz, R^2 = CN

23 R^1 = Ac, R^2 = CH_2NHAc

became interested in examining whether this chemistry can be extended to cyclomalto-oligosaccharides. Cyclo-oligosaccharides composed of heptoses appear to be unknown.

The vast literature (for an extensive review see ref. 3) on chemical modification of cyclodextrins contains several references to the fact that regioselective and complete protection of all primary hydroxyl groups by standard procedures is difficult to achieve. For example, full *O*-tritylation of **1** proved impossible[4], and although selective, heptamolar 6-methanesulfonylation[4,5] and 6-*p*-toluenesulfonylation[4–6] were claimed, regioisomeric uniformity of the products has not been established and, at least for the case of tosylation, has been disputed[7,8]. Even with the more selective mesitylsulfonyl chloride, the desired heptakis-6-sulfonate was not the sole product formed[7]. On the other hand, direct selective persubstitution of the HO-6 groups in **1** by azido[8], bromo[1,9], iodo[1], and phenylthio[1] substituents have been achieved with high yields. Another recent advance was primary-selective *tert*-butyldimethylsilylation in **1**, efficiently conducted either in *N*,*N*-dimethylformamide in the presence of imidazole[10], or better still, in pyridine[11]. (In the former system, secondary hydroxyl groups may also undergo silylation[12].)

RESULTS AND DISCUSSION

Targeting first the homologous cycloheptaose **5**, which consists of 6-deoxy-α-D-*gluco*-heptopyranosyluronic acid residues, we attempted to apply the iron carbonyl method[2,13] of chain extension to heptakis(2,3-di-*O*-acetyl-6-deoxy-6-iodo)cyclomaltoheptaose[1] (**6**). The procedure involves reaction of a terminal halide or tosylate with sodium dicarbonylcyclopentadienyliron, followed by oxidative carbonyl insertion in, and solvolysis of, the sugar–iron complex engendered. Product yields had been high (70–90%) with monosaccharides[13], and lower but still adequate (42%) with trehalose[2] as substrates, but the method failed completely when applied to **6**. Although this compound reacted rapidly with the reagent under the same conditions, as indicated by TLC, no identifiable product could be isolated. Probably the steric requirements of the $Fe(CO)_2Cp^-$ anion prevented complete and effective substitution around the cyclodextrin torus.

We then turned to the second method which had proved successful[2] in the case of trehalose, namely, nucleophilic substitution of terminal sulfonic ester groups by cyanide ion, followed by elaboration of carboxyl groups from the generated nitrile functions. This approach led to nitriles after some initial difficulties were overcome. First, we intended to employ the hitherto unknown heptakis(trifluoromethanesulfonate) (**10**) of heptakis (2,3-di-*O*-acetyl)cyclomaltoheptaose (**9**), as the 6,6′-ditriflates of acetyl- and benzyl-protected trehalose had been amenable to facile cyanide displacement under mild conditions. Compound **9** is readily obtained by *tert*-butyldimethylsilylation of **1** as already mentioned, followed by peracetylation[10b,11c] of the silyl ether **7** (to give **8**) and subsequent desilylation[10b] with boron trifluoride etherate, with each of these steps affording yields in the 80–90% range. Unfortunately, several attempts at triflation of **9** failed to produce the desired **10** in pure, isolable form; the product appeared rather unstable and prone to decomposition during processing. We therefore considered the known, crystalline heptamesylate[4,5] **11** or the corresponding heptatosylate **12** (if obtainable) as alternative, though intrinsically less-reactive, candidates for cyanide displacement. Whereas **11** could be prepared without problem by mesylation[10b] of **9** (yield, 91%), the analogous tosylation was not straightforward. When **9** was treated with a large excess of tosyl chloride in pyridine (containing 4-dimethylaminopyridine as a catalyst) during three days at room temperature, a product showing a single spot in TLC was obtained, but its ^1H and ^{13}C NMR spectra and elemental analysis gave evidence of incomplete tosylation. When the reaction was performed at 60° for 40 h, the product isolated in 92% yield was the known heptakis(2,3-di-*O*-acetyl-6-chloro-6-deoxy)cyclomaltoheptaose (**13**), previously obtained[10b] from the mesylate **11** by displacement with lithium chloride. Direct replacement of a hydroxyl group by a chloro substituent under similar conditions of tosylation has been observed before[14].

In the event, we tried mesyloxy displacement in **11** by potassium cyanide and found that it occurred only under forcing conditions (in *N*,*N*-dimethylformamide

solution at 60°), under which far-reaching decomposition took place, probably as a consequence of simultaneous *O*-deacetylation induced by the cyanide. In aqueous acetonitrile solution at room temperature, where *O*-deacetylation should not be significant[2], cyanide was ineffective for displacement. By contrast, treatment of **11** with potassium thiocyanate in *N*,*N*-dimethylformamide for 12 h at 100° gave an 85% yield of crystalline heptakis(2,3-di-*O*-acetyl-6-deoxy-6-thiocyanato)cyclomaltoheptaose (**14**). The thiocyanate ion is a considerably weaker base than the cyanide ion, and this result complements earlier observations[4,5,10b] that high-yielding displacements in **11** with such weakly basic nucleophiles as chloride, bromide, iodide, and azide ions can be achieved without compromising the *O*-acetyl protecting groups.

It was hoped that the difficulties just mentioned might be circumvented by using a substrate bearing resistant protecting groups for cyanide displacement, and the per-2,3-*O*-allyl heptamesylate **17** was chosen. This was prepared by treatment of the silyl ether **7** with allyl bromide and sodium hydride, desilylation of the resulting tetradeca-*O*-allyl derivative **15** to give the crystalline heptol **16**, and mesylation to provide **17** in 60% overall yield. In addition, the corresponding, perallylated heptakis-6-deoxy-6-iodo compound **18** was synthesized as a alternative substrate, by applying the previously elaborated[1], Vilsmeier-type iodination to **16**. Several attempts were made to achieve displacement in **17** and **18**, using potassium, sodium, or lithium cyanide under various conditions, but again, none was successful. However, it was then discovered (ironically, after all these labors) that the readily available[1], unprotected heptakis(6-deoxy-6-iodo)cyclomaltoheptaose (**19**) reacts well with lithium cyanide in *N*,*N*-dimethylformamide, to furnish the desired cyclohepta(6-deoxy-α-D-*gluco*-heptopyranosid)urononitrile (**20**) in high yields (74% after 26 h at 45°, 87% after 72 h at ~30°). The crystalline nitrile, which was converted into its per-*O*-acetyl (**21**) and per-*O*-benzoyl (**22**) derivatives by standard procedures, constitutes the first example of a cyclooligosaccharide composed of a hepturonic acid derivative.

Hydrogenation of the nitrile functions was difficult. Thus, reduction of **20** with lithium borohydride in the presence of trimethoxyborane[15], attempted in pyridine solution because of insolubility of **20** in the preferred solvents (ether or oxolane)[15], led to complex mixtures of products, as did reduction of **22** with sodium trifluoroacetoxyborohydride[16] in oxolane. More successful was catalytic hydrogenation of **20** over platinum. The reaction was slow (10 days at room temperature and 4.5 atm H_2), and it also gave a mixture of products, peracetylation and chromatography of which afforded a modest yield (23%) of crystalline cyclo-(1 → 4)-(7-acetamido-2,3-di-*O*-acetyl-6,7-dideoxy-α-D-*gluco*-heptopyrano)heptaose (**23**), the first cyclodextrin analog composed of heptose units.

EXPERIMENTAL

General methods.—Unless otherwise noted, the following solvent combinations (v/v) were used for thin-layer and column chromatography on silica gel: (*A*)

30:5:4 EtOAc–MeOH–H_2O; EtOAc–hexanes, (*B*) 20:1, (*C*) 10:1, (*D*) 1:1, and (*E*) 1:20; (*F*) 1:9 EtOH–benzene; MeOH–$CHCl_3$, (*G*) 1:5, (*H*) 1:7, (*I*) 1:9, and (*J*) 1:99. Melting points were determined in capillaries with an electrothermal apparatus and are uncorrected. The $[\alpha]_D$ values refer to room temperature.

Heptakis(2,3-di-O-acetyl)cyclomaltoheptaose (**9**).—β-Cyclodextrin (**1**) was dried to constant weight at 110° over P_4O_{10} in vacuo, and *tert*-butyldimethylsilylated in dry pyridine (freshly distilled from CaH_2) essentially according to Fügedi[11c], except that 8.5 instead of 7.7 mol equiv of the trialkylchlorosilane was employed. The chromatographically purified silyl ether **7** (yields, 80–85%) had mp 314–318° (dec), $[\alpha]_D$ +107° (*c* 1, $CHCl_3$); lit.[11c] mp 314–318° (dec), $[\alpha]_D$ +105 and[10b] mp 299–302°, $[\alpha]_D$ +113°. For complete acetylation of **7**, treatment[11c] with Ac_2O and pyridine for 1 day at 60° was not entirely sufficient (TLC) in our hands, but subsequent heating for 4 h at[10b] 100° led to completion, and amorphous peracetate **8**, purified by chromatography, was obtained in yields of 90% in several experiments; $[\alpha]_D$ +81.5° (*c* 1.2, $CHCl_3$), lit.[10b] +82° and[11c] +83°.

Compound **8** (1.60 g) was dissolved in CH_2Cl_2 (20 mL) and desilylated at room temperature by addition of $BF_3 \cdot Et_2O$ (2 mL) following the procedure of Takeo et al.[10b] Complete replacement of the fast-moving **8** by **9** (R_F 0.3) was noted after 4 h (TLC with solvent *A*). The mixture was diluted with CH_2Cl_2 (80 mL) and washed sequentially with ice–water, satd aq $NaHCO_3$, and water (50 mL of each). The dried (Na_2SO_4) organic phase was evaporated and the residue subjected to flash chromatography on SiO_2 with solvent *G*, to give crystalline **9** (0.92 g, 81%), mp 208–212°, $[\alpha]_D$ +114° (*c* 0.6, $CHCl_3$), lit.[10b] mp 184–186°, $[\alpha]_D$ +115°; ^1H NMR (300 MHz, $CDCl_3$ at 55°): δ 5.33 (dd, $J_{3,4}$ 8.4, $J_{2,3}$ 9.7 Hz, H-3), 5.11 (d, $J_{1,2}$ 3.9 Hz, H-1), 4.78 (dd, $J_{1,2}$ 3.9, $J_{2,3}$ 9.7 Hz, H-2), 4.24 (br, OH), 4.1–3.8 (m, 3 H, H-5,6,6′), 3.75 (~ t, $J_{3,4}+J_{4,5}$ 17.8 Hz, H-4), 2.05 and 2.03 (2 s, 3 H each, 2 OAc); ^{13}C NMR (75.43 MHz, $CDCl_3$): δ 170.4 and 169.1 (2 CO), 96.5 (C-1), 76.2 (C-4), 72.4, 71.2, 70.7 (C-2,3,5), 61.4 (C-6), 20.7 and 20.6 (2 MeCO). The ^{13}C values were slightly higher, by 0.1–1.5 (average, 0.6) ppm than those obtained[10b] at 22.6 MHz from a $(CD_3)_2SO$ solution.

Anal. Calcd for $C_{70}H_{98}O_{49}$ (1723.5): C, 48.78; H, 5.73. Found: C, 48.64; H, 5.84.

Heptakis(2,3-di-O-acetyl-6-O-methylsulfonyl)cyclomaltoheptaose (**11**).—Compound **9** was mesylated essentially as described[10b], with minor procedural modifications. Methanesulfonyl chloride (1 mL) was added dropwise, at 0°, to a solution of **9** (0.50 g) in dry pyridine (15 mL). The mixture was kept for 2 h at 0° and 20 h at room temperature, whereafter a single product spot (R_F 0.4) was seen in TLC (solvent *F*). Water (1 mL) was then added, and after 15 min the mixture was poured into ice–water. The precipitate was washed with water and dissolved in $CHCl_3$ (50 mL), and the solution was washed with 5% HCl (100 mL), aq $NaHCO_3$ (100 mL), and water, dried, and evaporated. The crude product was passed through a short column of SiO_2 with solvent *B*, to give crystalline **11** (0.60 g, 91%), mp 210–213°, $[\alpha]_D$ +110.3° (*c*, 0.6, $CHCl_3$); lit.[4] mp 165°, $[\alpha]_D$ +114 ± 2°, and[10b] amorphous, $[\alpha]_D$ +108°. ^1H NMR (300 MHz, $CDCl_3$): δ 5.34 (dd, $J_{3,4}$ 8.5, $J_{2,3}$ 9.8

Hz, H-3), 5.12 (d, $J_{1,2}$ 3.7 Hz, H-1), 4.78 (dd, $J_{1,2}$ 3.7, $J_{2,3}$ 9.9 Hz, H-2), 4.60 and 4.15 (2 m, 2 and 1 H, H-5,6,6'), 3.78 (dd, $J_{3,4}$ 8.5, $J_{4,5}$ 9.3 Hz, H-4), 3.09 (s, 3 H, $MeSO_3$), 2.05 and 2.03 (2 s, 3 H each, 2 OAc), in reasonable agreement with reported[10b] 90-MHz data; ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 170.6 and 169.5 (2 CO), 96.6 (C-1), 75.9 (C-4), 70.1, 70.1, 69.4 (C-2,3,5), 68.3 (C-6), 37.1 ($MeSO_3$), and 20.5 (2 MeCO), in good accord with reported[10b] 22.6-MHz data.

Anal. Calcd for $C_{77}H_{112}S_7O_{63}$ (2270.2): C, 40.74, H, 4.97; S, 9.89. Found: C, 40.64; H, 5.02; S, 10.06.

Attempted heptamolar tosylation of **9**.—*(a) Reaction at room temperature.* To a solution of **9** (200 mg) in dry pyridine (15 mL) containing a catalytic amount of 4-dimethylaminopyridine was added a large excess of *p*-toluenesulfonyl chloride (930 mg, 6 mol equiv). The mixture was kept for 3 days at room temperature, whereafter a single product spot (R_F 0.45) was seen in TLC (solvent *F*, double irrigation). A separate experiment had indicated no change to occur after prolonged storage. Conventional processing, and purification of the product by passage through a short column of SiO_2 by means of solvent *B*, gave a crystalline tosylate (245 mg) whose microanalytical data for C and S (found: C, 50.86; H, 5.23; S, 7.76) lay between those calculated for a heptakis(tosylate) (C, 50.99; H, 5.04; S, 8.01) and a hexakis(tosylate) (C, 50.79; H, 5.10; S, 7.26). Although ^{13}C NMR (50.3 MHz, $CDCl_3$) did not show a signal for CH_2OH (expected near δ 61.0), there were six signals in the δ 70.2–68.8 range (C-2,3,5) instead of the three expected for a uniformly substituted product, and the C-1 signal (δ 96.2) also had a small companion (δ ~96.3). The remaining resonances were at δ 170.4 and 169.4 (2 CO), 145.2, 132.5, 130.0, and 128.1 (arom.), 75.3 (C-4), 21.4 (Me of Ts), and 20.5 (2 MeCO). The ^1H NMR spectrum showed resonances for the tosyl group (δ 7.75, 7.30, and 2.40) which integrated to slightly less than 7 H as measured against the 6-proton integral for the signals (δ 1.98 and 1.95) of the two OAc groups per glucose unit. Moreover, the tosyl CH_3 was not a clean singlet, and the main resonances for the sugar ring protons (δ 4.15–3.55) were accompanied by some minor signals, indicating that the compound was not uniformly substituted.

*(b) Formation of heptakis(2,3-di-*O*-acetyl-6-chloro-6-deoxy)cyclomaltoheptaose* (**13**). When **9** (50 mg) and TsCl (230 mg) in dry pyridine (5 mL) containing a catalytic amount of 4-dimethylaminopyridine were heated for 40 h at 60° and the mixture was conventionally worked up, the crude product was homogeneous in TLC (solvent *F*). After purification on a short column of SiO_2 using solvent *C*, crystalline **13** (50 mg, 92%) was obtained, mp 180–182°, $[\alpha]_D$ +104° (*c* 1, $CHCl_3$); lit.[10b] mp 179–182° $[\alpha]_D$ +102°; ^1H NMR (300 MHz, $CDCl_3$): δ 5.31 (t, $J_{2,3}+J_{3,4}$ 17.8 Hz, H-3), 5.17 (d, $J_{1,2}$ 3.5 Hz, H-1), 4.79 (dd, $J_{1,2}$ 3.5, $J_{2,3}$ 9.9 Hz, H-2), 4.2–3.75 (m, 4 H, H-4,5,6,6'), 2.08 and 2.06 (2 s, 3 H each, 2 OAc); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 170.6 and 169.5 (2 CO), 96.4 (C-1), 77.0 (C-4), 70.7, 70.3, 70.1 (C-2,3,5), 44.3 (C-6), and 20.5 (2 MeCO).

*Heptakis(2,3-di-*O*-acetyl-6-deoxy-6-thiocyanato)cyclomaltoheptaose* (**14**).—A solution of **11** (60 mg) and KSCN (200 mg) in dry *N*,*N*-dimethylformamide (3 mL)

was heated for 12 h at 90–100°. The cooled mixture was diluted with water (25 mL) and extracted with 1:1 toluene–EtOAc (50 mL). The extract was washed with water (2 × 25 mL), dried (Na_2SO_4), and evaporated to a solid that was passed through a short column of SiO_2 with EtOAc as the eluent, to afford crystalline **14** (45 mg, 85%), mp 194–196°, $[\alpha]_D$ +116° (*c* 0.65, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.27 (dd, $J_{3,4}$ 7.7, $J_{2,3}$ 9.3 Hz, H-3), 5.10 (d, $J_{1,2}$ 3.8 Hz, H-1), 4.86 (dd, $J_{1,2}$ 3.8, $J_{2,3}$ 9.4 Hz, H-2), 4.28 (m, H-5), 3.77 (dd, $J_{5,6}$ 2.8, $J_{6,6'}$ 13.0 Hz, H-6), 3.63 (dd, $J_{3,4}$ 7.6, $J_{4,5}$ 9.1 Hz, H-4), 3.22 (dd, $J_{5,6'}$ 8.9, $J_{6,6'}$ 13.0 Hz, H-6'), 2.10 and 2.04 (2 s, 3 H each, 2 OAc); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 170.6 and 169.4 (2 CO), 112.3 (–S–CN; by contrast, –N=C=S resonates[17] near 131), 97.2 (C-1), 79.9 (C-4), 70.5, 69.8, 69.6 (C-2, 3, 5), 35.7 (C-6), and 20.5 (2 MeCO).

Anal. Calcd for $C_{77}H_{91}N_7O_{42}S_7$ (2011.1): C, 45.99; H, 4.56; N, 4.88; S, 11.16. Found: C, 46.09; H, 4.54; N, 5.00; S, 10.97.

*Heptakis(2,3-di-*O*-allyl-6-*O*-*tert*-butyldimethylsilyl)cyclomaltoheptaose* (**15**).—To a chilled (0°) solution of silyl ether **7** (2.30 g; see under preparation of **9**) in dry *N*,*N*-dimethylformamide (70 mL) was added NaH (2.5 g of a 60% oil immersion, rinsed with hexane), and the mixture was stirred under exclusion of moisture for 2 h at 0° and overnight at room temperature. Allyl bromide (13 mL) was then added, and stirring was continued for 2 days. The excess of NaH was decomposed by addition of a small amount of MeOH, and the mixture was concentrated to dryness at 60° (bath temperature) under reduced pressure. A solution of the residue in $CHCl_3$ (100 mL) was washed successively with water, aq $NaHCO_3$, and water, then dried, and evaporated. Column chromatography of the crude product, using solvent *E* as the eluent, yielded syrupy **15** that was dried in vacuo to a brittle glass (2.50 g, 82%), $[\alpha]_D$ +76.4° (*c* 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, assignments aided by COSY): δ 6.06–5.85 (2 m, partially overlapping, 1 H each, 2 –CH=), 5.28–5.21 (narrow m and dd, 1 H each, H-3 of 2 allyl groups), 5.17 (d, $J_{1,2}$ 3.6 Hz, H-1), 5.08 (center of 2 dd, 1 H each, H-3' of 2 allyl groups), 4.49 and 4.23 (2 dd, 1 H each, O–CH_2– of 1 allyl group), 4.16–4.12 (m, 3 H, H-6 and O–CH_2– of 1 allyl group), 3.80 (t, $J_{3,4} = J_{4,5} = 9$ Hz, H-4), 3.70 (t, $J_{2,3} + J_{3,4}$ 18.2 Hz, H-3), 3.56 (center of 4 lines spaced ~ 10 Hz, 2 H, H-5,6'), 3.20 (dd, $J_{1,2}$ 3.5, $J_{2,3}$ 9.5 Hz, H-2), 0.85 (s, Me_3C), −0.01 and −0.013 (2 s, $SiMe_2$); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 136.4 and 135.4 (2 –CH=), 116.6 and 115.9 (2 H_2C=), 98.2 (C-1), 80.1, 79.3, 77.8 (C-2,3,4), 74.6 and 72.0 (2 allylic O–CH_2), 72.1 (C-5), 62.2 (C-6), 25.7 (*Me*$_3$C), 18.0 (Me_3CSi), −5.1 and −5.5 (Me_2Si).

Anal. Calcd for $C_{126}H_{224}O_{35}Si_7$ (2495.7): C, 60.63; H, 9.05. Found: C, 60.66; H, 8.97.

*Heptakis(2,3-di-*O*-allyl)cyclomaltoheptaose* (**16**).—A mixture of **15** (1.10 g) in oxolane (30 mL) and M Bu_4NF in oxolane (5 mL) was boiled under reflux for 1.5 h, after which a single product spot (R_F 0.4) was seen in TLC (solvent *H*, triple irrigation). The solvent was evaporated and the residue taken up in $CHCl_3$ (100 mL) and washed with water (3 × 50 mL). Evaporation of the dried (Na_2SO_4) solution and column chromatography of the residue with $CHCl_3$ followed by

solvent *I* as eluents gave syrupy **16** (726 mg, dried in a high vacuum), $[\alpha]_D$ +116° (*c* 0.8, $CHCl_3$). An analytical sample was solidified by trituration with ether, and dried for 8 h at 110°; it then analyzed as a trihydrate, and on this basis the yield of **16** was ~94%. ^1H NMR (300 MHz, $CDCl_3$, assignments aided by COSY): δ 6.00–5.82 (complex m, 2 H, 2 –CH=), 5.29–5.08 (2 m, 4 H, 2 H_2C=), 5.05 (d, H-1), 4.7 (b s, exchangeable, OH), 4.31 (center of 2 dd, 1 H each, *J* 5.6 and 12.5 Hz, O–CH_2– of 1 allyl group), 4.12 narrow m, 2 H, O–CH_2– of 1 allyl group), 3.93 (narrow m, H-6), 3.77 (narrow m, 2 H, H-5,6′), 3.68 (t, $J_{2,3}+J_{3,4}$ 17.3 Hz, H-3), 3.54 (t, $J_{3,4}+J_{4,5}$ 16.9 Hz, H-4), and 3.33 (dd, $J_{1,2}$ 3.7, $J_{2,3}$ 9.2 Hz, H-2); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 136.1 and 135.2 (2 –CH=), 116.8 and 115.8 (2 H_2C=), 98.5 (C-1), 79.7, 79.6, 78.8 (C-2,3,4), 74.2 and 72.0 (2 allylic O – CH_2), 72.4 (C-5), and 61.35 (C-6).

Anal. Calcd for $C_{84}H_{126}O_{35} \cdot 3H_2O$ (1749.9): C, 57.65; H, 7.60. Found: C, 57.62; H, 7.42.

Heptakis(2,3-di-O-allyl-6-O-methylsulfonyl)cyclomaltoheptaose (**17**).—Methanesulfonyl chloride (0.6 mL) was added at −10° to a solution of **16** (300 mg) in dry pyridine (15 mL), which was then kept overnight at 5°, diluted with $CHCl_3$, washed sequentially with 5% HCl, aq $NaHCO_3$, and water, and evaporated to dryness with addition of several portions of toluene. The crude product was purified by column chromatography (solvent *J*), to give crystalline **17** (311 mg, 79%), mp 186–188° (dec), $[\alpha]_D$ + 93° (*c* 0.5 $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, assignments aided by COSY): δ 6.02–5.82 (complex m, 2 H, 2 –CH=), 5.31–5.07 (complex m, 5 H, 2 CH_2=, and H-1 at δ 5.11), 4.54 (~ s, 2 H, H-6,6′), 4.44 and 4.23 (2 dd, *J* 5.5 and 12.2 Hz, 1 allylic O–CH_2–), 4.15 (narrow m, 2 H, 1 allylic O–CH_2–), 3.90 (d with broadened lines, $J_{4,5}$ 9.1 Hz, H-5, weakly coupled with H-6,6′), 3.67 (sept, 2 H, H-3,4), 3.33 (dd, $J_{1,2}$ 3.6, $J_{2,3}$ 9.3 Hz, H-2), 3.05 (s, 3 H, $MeSO_3$); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 135.9 and 134.9 (2 –CH=), 117.3 and 116.0 (2 CH_2=), 98.9 (C-1), 79.2, 79.0, 78.6 (C-2,3,4), 74.4 and 72.3 (2 allylic O–CH_2), 69.4 (C-5,6), and 36.8 ($MeSO_3$).

Anal. Calcd for $C_{91}H_{140}O_{49}S_7 \cdot 10H_2O$ (2422.6): C, 45.11; H, 6.66; S, 9.26. Found: C, 45.11; H, 6.65; S, 9.23.

Heptakis(2,3-di-O-allyl-6-deoxy-6-iodo)cyclomaltoheptaose (**18**).—To a stirred solution of PPh_3 (7.06 g, dried over P_4O_{10}) in dry *N*,*N*-dimethylformamide (40 mL) was added I_2 (6.83 g) in small portions, followed after 1 h by **16** (2.4 g). The mixture was stirred overnight under N_2 at 60–70°, after which it showed a major (R_F 0.31) and a minor (R_F 0.23) spot in TLC (CH_2Cl_2). After concentration in vacuo to a small volume, the mixture was diluted with CH_2Cl_2, washed successively with aq $Na_2S_2O_3$ solution, aq $NaHCO_3$, and water, dried, and evaporated. Flash chromatography (with CH_2Cl_2) of the residue gave amorphous **18** (1.96 g, 56%), $[\alpha]_D$ +76.3° (*c* 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$; assignments aided by COSY): δ 5.90 (12-line m, 2 H, 2 –C=), 5.31–5.07 (m, 5 H; 2 H_2C=, and d for H-1 at δ 5.17), 4.45 and 4.20 (2 dd, 1 H each, *J* 5.4 and 12.1 Hz, 1 allylic O–CH_2–), 4.16 (narrow m, 2 H, 1 allylic O–CH_2–), 3.80–3.50 (m, 5 H, H-3,4,5,6,6′),

and 3.33 (dd, $J_{1,2}$ 3.6, $J_{2,3}$ 9.6 Hz, H-2); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 135.6 and 134.8 (2 –CH=), 117.2 and 115.9 (2 H_2C=), 98.2 (C-1), 83.0 (C-4), 79.1, 78.7 (C-2,3), 74.4 and 72.2 (2 allylic O – CH_2), 70.1 (C-5), and 10.2 (C-6).

The compound was stable only under refrigeration; it developed a brown discoloration on storage at room temperature.

*Cyclohepta(1 → 4)-(6-deoxy-α-*D*-gluco-heptopyranosid)uronitrile* [**20**, *heptakis(6-cyano-6-deoxy)cyclomaltoheptaose*].—A solution of heptakis(6-deoxy-6-iodo)cyclomaltoheptaose[1] (**19**, 2.0 g) in 0.5 M LiCN in *N,N*-dimethylformamide (40 mL; Aldrich Chemical Co.) was kept for 1 day at 45°, then poured into water (850 mL). The fine suspension of the precipitate formed was allowed to settle overnight, and then filtered to give solid **20** that was washed with water and dried over P_4O_{10} in vacuo (yield 930 mg, 74%). Another experiment, using the same amounts of reagents, was conducted for 3 days at room temperature (28–30°) and gave 1.10 g (87%) of crystalline **20**, mp 276–278° (dec), $[\alpha]_D$ +138° (*c* 0.7, DMF); IR: ν_{max}^{KBr} 3369 (OH), 2257 (CN) cm^{-1}; ^{13}C NMR (75.4 MHz, Me_2SO-d_6): δ 118.0 (CN), 102.0 (C-1), 85.2 (C-4), 72.1, 71.7, 66.9 (C-2,3,5), and 20.5 (C-6). However, the crude **20** so obtained contained some inorganic impurity, presumably Li_2CO_3, as suggested by microanalytical data. A sample was purified by reprecipitation (DMF–water) and dried at room temperature in a high vacuum over P_4O_{10}; it then analyzed correctly as a tetrahydrate inclusion complex, showed an unchanged decomposition point, and had $[\alpha]_D$ +169° (*c* 0.7, DMF).

Anal. Calcd for $C_{49}H_{63}N_7O_{28} \cdot 4H_2O$ (1270.1): C, 46.33; H, 5.63; N, 7.72. Found: C, 46.18; H, 5.37; N, 7.99.

In later experiments, **20** was obtained free from ash by pouring the mixture into dilute HCl instead of water.

*Cyclohepta(1 → 4)-(2,3-di-*O*-acetyl-6-deoxy-α-*D*-gluco-heptopyranosid)urono-nitrile* (**21**).—Crude nitrile **20** obtained from 1.00 g of **19** was treated with Ac_2O (5 mL), pyridine (5 mL), and a catalytic amount of 4-dimethylaminopyridine during 30 h at room temperature. The mixture was concentrated with additions of MeOH, taken up in $CHCl_3$, washed successively with 5% HCl, aq $NaHCO_3$, and water, dried (Na_2SO_4), and brought to dryness. The crude product was crystallized from EtOH to give pure **21** (660 mg, 70.4% based on **19**), mp 200–205°, $[\alpha]_D$ +117° (*c* 1, $CHCl_3$); IR: ν_{max}^{KBr} 3481 and 1634 (weak) for H_2O, 2257 (CN), and 1750 (ester CO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.26 (dd, $J_{3,4}$ 8.0, $J_{2,3}$ 9.6 Hz, H-3), 5.11 (d, $J_{1,2}$ 3.8 Hz, H-1), 4.90 (dd, $J_{1,2}$ 3.8, $J_{2,3}$ 9.6 Hz, H-2) 4.20 (m, H-5), 3.70 (~ t, $J_{3,4} \approx J_{4,5} \approx 8.5$ Hz, H-4), 3.00 (m, 2 H, H-6,6'), 2.05 and 2.03 (2 s, 3 H each, 2 OAc); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 170.3 and 169.6 (2 CO), 117.3 (CN), 96.7 (C-1), 79.5 (C-4), 70.0, 69.6, 67.6 (C-2,3,5), 22.2 (C-6), 20.8 and 20.7 (2 MeCO). The analytical sample was dried in vacuo over P_4O_{10} at room temperature but still retained water as inclusion complex.

Anal. Calcd for $C_{77}H_{91}N_7O_{42} \cdot 5H_2O$ (1876.6): C, 49.28; H, 5.43; N, 5.22. Found: C, 49.03; H, 5.00; N, 4.98.

*Cyclohepta(1 → 4)-(2,3-di-*O*-benzoyl-6-deoxy-α-*D*-gluco-heptopyranosid)urono-*

nitrile (**22**).—Crude nitrile **20** obtained from 180 mg of **19** was dissolved in dry pyridine (5 mL) containing a catalytic amount of 4-dimethylaminopyridine, and treated overnight at room temperature with BzCl (0.8 mL). The mixture was poured into ice–water, the product extracted with CH_2Cl_2, and the extract washed with aq $NaHCO_3$, 5% HCl, aq $NaHCO_3$ again, and water, dried, and evaporated. Column chromatography (solvent *D*) of the crude product yielded pure **22** (194 mg, 77.3%), mp 220–225°, $[\alpha]_D$ +80° (*c* 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.5–7.0 (10 H, arom.), 5.92 (dd, $J_{3,4}$ 8.8, $J_{2,3}$ 10.1 Hz, H-3), 5.52 (d, $J_{1,2}$ 4.0 Hz, H-1), 5.12 (dd, $J_{1,2}$ 3.9, $J_{2,3}$ 10.2 Hz, H-2), 4.61 (m, H-5), 4.00 ($\sim$ t, $J_{3,4} \approx J_{4,5} = 9$ Hz, H-4), 3.31 and 3.20 (centers of 2 dd, AB system, $J_{5,6}$ 3.2, $J_{5,6'}$ 7.2, $J_{6,6'}$ 17.3 Hz, H-6,6′); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 165.8 and 164.6 (2 CO), 134–128 region (Ph), 117.4 (CN), 97.3 (C-1), 80.1 (C-4), 71.0, 70.7, 68.1 (C-2,3,5), and 22.7 (C-6).

Anal. Calcd for $C_{147}H_{119}O_{42}N_7$ (2655.5): C, 66.48; H, 4.52; N, 3.69. Found: C, 65.98; H, 4.58; N, 3.67.

*Cyclo(1 → 4)-(7-acetamido-2,3-di-*O*-acetyl-6,7-dideoxy-α-*D*-gluco-heptopyrano)-heptaose* (**23**).—A suspension of PtO_2 (140 mg) in water (50 ml) and M HCl (20 mL) was prehydrogenated, compound **20** (200 mg) was added, and hydrogenation was continued for 10 days at 4.5 atm H_2. The catalyst was filtered off over Celite and washed well with water, and the combined filtrate and washings were concentrated to give a residue which was treated with Ac_2O (10 mL) and pyridine (5 mL) for 2 days at room temperature. Concentration of the mixture and column chromatography (solvent *G*) of the crude product gave fractions (R_F 0.8 and 0.7, TLC with solvent *G*) containing mixtures of unidentified products, followed by a fraction (R_F 0.6) of **23**, isolated as a white, crystalline solid (88 mg, 23%), mp 183–186°, $[\alpha]_D$ +38° (*c* 1, $CHCl_3$); IR: ν_{max}^{Nujol} 3400–3150 (NH, H_2O), 1752 (ester CO), 1647 and 1559 (amide I and II) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.80 (bs, NH), 5.14 (dd, $J_{2,3}$ 8.8, $J_{3,4}$ 7.8 Hz, H-3), 5.00 (d, $J_{1,2}$ 3.7 Hz, H-1), 4.75 (dd, $J_{1,2}$ 3.7, $J_{2,3}$ 8.8 Hz, H-2), 3.94 (broadened t, $J_{4,5} \approx J_{5,6} \approx 8$, $J_{5,6'} \approx 1$ Hz, H-5), 3.60 (m, 1 H, H-7), 3.38 (dd, $J_{3,4} \approx J_{4,5} \approx 7.8$ Hz, H-4), 3.09 (m, 1 H, H-7′), 2.30 (m, 1 H, H-6), 2.06, 2.00, and 1.97 (3 s, 3 H each, 3 Ac), and 1.75 (m, 1 H, H-6′); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 171.8, 170.7, and 169.4 (3 CO), 97.4 (C-1), 81.4 (C-4), 70.6, 69.9, 69.9 (C-2,3,5), 36.5 (C-7), 31.5 (C-6), 22.82 (MeCOO) and 22.80 (MeCONH).

Anal. Calcd for $C_{91}H_{133}N_7O_{49} \cdot 6H_2O$ (2217.1): C, 49.29; H, 6.59. Found: C, 49.46; H, 6.66.

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